ABSTRACT

A Methodology for Chemoselective Carbonyl Ylide Formation, Total Synthesis of (±)-Aspergilline A, Cyclopiamide A and Speradine E and Progress Toward the Total Synthesis of (±)-Isopalhinine A

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In 2001, the total synthesis of (±)-epoxysorbicillinol was completed by Wood and coworkers. This work featured as the key step a Rh(II) catalyzed carbonyl ylide formation and subsequent dipolar cycloaddition of a diazomalonate to yield a highly functionalized oxabicyclic intermediate. In efforts to render the synthesis enantioselective, a method for chemoselective carbonyl ylide formation was devised; this culminated in the formal enantioselective synthesis of (+)-epoxysorbicillinol in 2005. The methodology utilized in this synthesis centered around electronic differentiation of the diazomalonate's esters to induce chemoselective carbonyl ylide formation. Having established a methodology for chemoselective carbonyl ylide formation, the substrate scope was expanded and steric differentiation of the diazomalonate's esters explored.

Aspergilline A was isolated from *Aspergillus versicolor* in 2014 by Hu and Gao and was shown to exhibit moderate biological activity against several human cancer cell lines. The compound bears several intriguing structural features including a 6/5/6/5/5/5 fused ring system which contains an oxindole moiety and a substituted tetramic acid. In

synthesizing this compound our strategy relied upon two key steps. The first was a single step conversion of a propargyl amine into to a pyrrolinone through the action of an ammonium enolate and the second was a formal [3+2] dipolar cycloaddition between an imidate and a cyclopropenone derived all carbon 1, 3 dipole. Ultimately this work resulted in the sixteen step total synthesis of (±)-aspergilline A. Additionally, two other related natural products cyclopiamide A and speradine E were synthesized by diverting intermediates accessed during the aspergilline A synthesis.

In 2013, the Lycopodium alkaloid isopalhinine A was isolated from *Palhinhaea cernua* by Zhao and coworkers. To date, the compound has not been shown to exhibit any biological activity. Despite its lack of known biological activity, the compound does possess a variety of synthetically challenging structural features, including a 5/6/6/6/7 fused ring system which contains an isotwistane and a cycloheptane hemiaminal. In devising a synthetic strategy, we settled upon two key synthetic transformations; an allene Nazarov cyclization to construct the central cyclopentanone core and a late stage titanium mediated 6-*exo*-trig cyclization and subsequent deoxygenation to complete construction of the isotwistane.

A Methodology for Chemoselective Carbonyl Ylide Formation, Total Synthesis of (±)-Aspergilline A, Cyclopiamide A and Speradine E and Progress Towards the Total Synthesis of (±)-Isopalhinine A

by

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LIST OF ABBREVIATIONS

Ac	acetyl
AIBN	2,2'-azobis(2-methylpropionitrile)
Ar	aromatic
Bu	n-butyl
Cat.	catalyst
CO	carbon monoxide
COSY	correlation spectroscopy
DBB	4,4-di-*t*-butylphenyl
DCE	dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-p-benzoquinone
DEPT	distortionless enhancement by polarization transfer
DIBAL-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine (aka Hünig's base)
DMAP	4-(dimethylamino)pyridine
DMB	2,4-dimethoxybenzyl
DMDO	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	dimethyl sulfoxide
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
Hex	hexanes
HFIP	hexafluoroisopropanol
HMBC	heteronuclear multiple-bond correlation
HMPA	hexamethylphosphoramide
HOBt	hydroxybenzotriazole
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation *hv* irradiation by light
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamine
LiHMDS	lithium bis(trimethylsilyl)amide
MM2	molecular mechanics 2
MOM	methoxymethyl acetal
Me	methyl

MeCN	acetonitrile
MS	molecular sieves
NCI	National Cancer Institute
NIH	National Institute of Health
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
Ph	phenyl
PIFA	phenyliodonium bis(trifluoroacetate)
PLE	pig liver esterase
PTSA	4-toluenesulfonic acid
RT	room temperature
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
TFE	trifluoroethanol
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
Ts	4-toluenesulfonyl
UV	ultra violet

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that total synthesis research often brings. Collin, I have enjoyed the past few months of sitting next to you in the office, I am honestly saddened that we could not get to know each other better. Additionally, your constant, thorough surveying of the literature always amazes me; it inspires me to do the same. I am confident that you will expediently accomplish the total synthesis of isopalhinine A. Ricky, your constant lightheartedness is always refreshing in the lab, I have never seen someone dance in excitement over an argon balloon! I am also saddened to not have the opportunity to spend more time with you. I know you feel things are a struggle at the moment but due to your constant effort, once you have established your chemical skills…as John has said about you, your work will then bear only "pure results". Miyu, meeting you strongly defined the later part of my time in the Wood group, I am so grateful to have you in my life, I am so happy to have gone to Japan with you and to have enjoyed so many fun and exciting experiences together. Things may be difficult in the future but I am hopeful that we will work through them.

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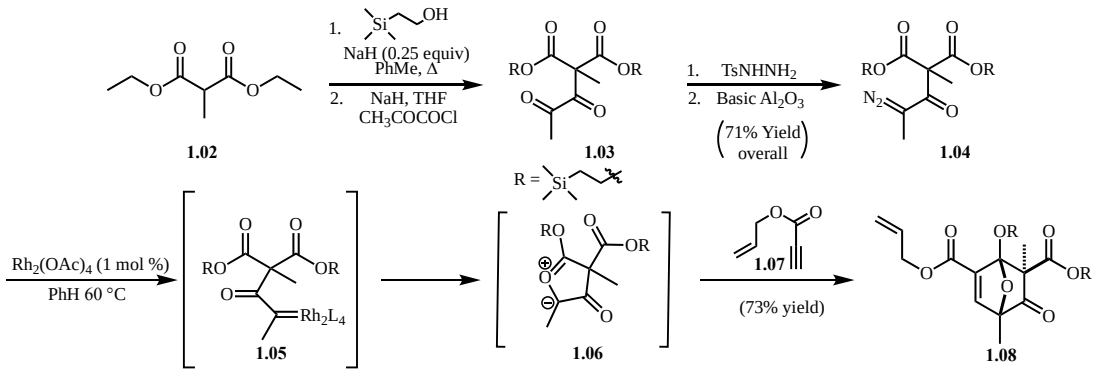
CHAPTER ONE

Origins and Background of the Chemoselective Carbonyl Ylide Methodology

1.1 Total Synthesis of (±)-Epoxysorbicillinol and Formal Synthesis of (+)-Epoxysorbicillinol

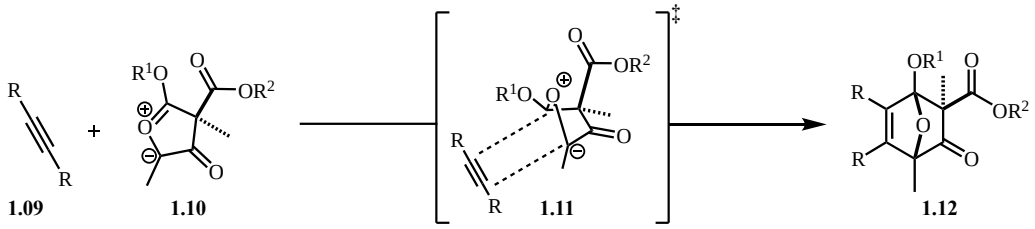
1.1.1 Racemic Synthesis – 2001

The Vertinoid polyketide epoxysorbicillinol (**1.01**, Scheme 1.3) was isolated in 1998 from *Trichoderma longibrachiatum* by Crews *et al.* and at the time no bioactivity was reported.[1] The Wood group then became interested in targeting this molecule due to its intriguing structural features. Eventually, Wood *et al.* were able to accomplish the racemic total synthesis of epoxysorbicillinol (Schemes 1.1 and 1.3) in 2001 utilizing a key rhodium-catalyzed carbonyl ylide formation and subsequent dipolar cycloaddition to access a highly versatile oxabicyclic (**1.08**) intermediate.[2] The synthesis commenced from commercially available diethyl methyl malonate **1.02**; transesterification with 2-(trimethylsilyl)ethanol in the presence of substoichiometric sodium hydride followed by acylation with pyruvoyl chloride yielded acylated malonate **1.03**. Subsequent



Scheme 1.1. Racemic epoxysorbicillinol – key oxabicycle

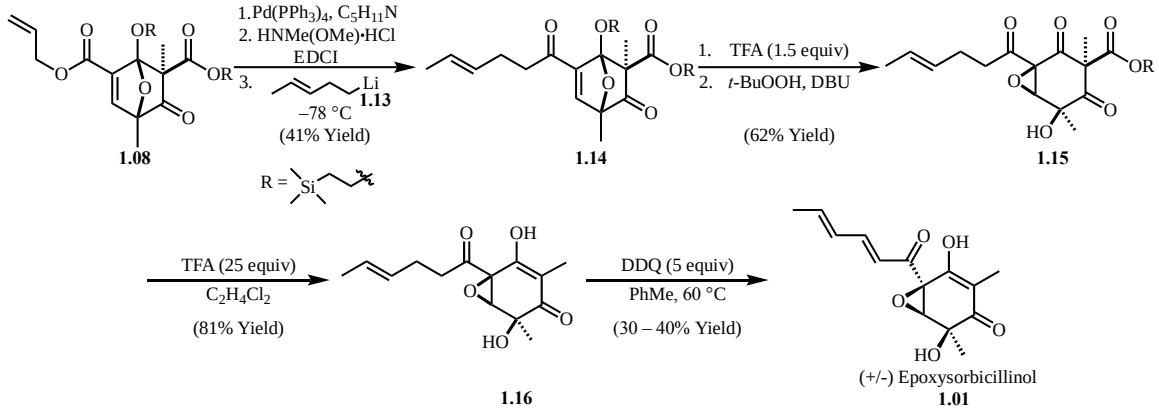
treatment with tosyl hydrazide and elimination by action of basic alumina provided diazomalonate **1.04** in an excellent 71% yield overall! Exposure of **1.04** to catalytic rhodium acetate in benzene at 60 °C in the presence of allyl propiolate **1.07** furnished the desired oxabicyclic compound in 73% yield as a single diastereomer. The origin of the diastereoselectivity was surmised by rudimentary MM2 calculations and is depicted in Scheme 1.2. The intermediate carbonyl ylide **1.10** present in this synthesis bears an α-face methyl group and a β-face ester (Scheme 1.2). It is believed that the β-face ester directs



Scheme 1.2. Origin of diastereoselectivity

approach of the dipolarophile to the less sterically hindered face as shown in transition state **1.11**. Dipolar cycloaddition then generates an oxabicyclic compound (**1.12**) in which the bridging oxygen and remaining ester reside on the β-face of the molecule. Having accessed the key oxabicyclic intermediate, it was eventually found that seven additional synthetic transformations were needed to access the natural product (Scheme 1.3). De-allylation of the allyl ester **1.08** by catalytic palladium tetrakis followed by Weinreb amide formation and subsequent 1,2 addition of 3-pentenyllithium (**1.13)** selectively into the Weinreb amide provided ketone **1.14** in 41% overall yield. The strategic use of 3-pentenyllithium (**1.13**) rather than an organolithium reagent which bore the full unsaturation present in the sorbyl side chain of the natural product is of note. The authors cited the need for selective

epoxidation in subsequent steps as well as the prevention of unwanted polymerization as the reasons for utilizing 3-pentenyllithium (**1.13**). Acetal cleavage was then effected by TFA and selective epoxidation of the enone induced by *t*-BuOOH giving epoxyketone **1.15**. Finally, what remained was installation of



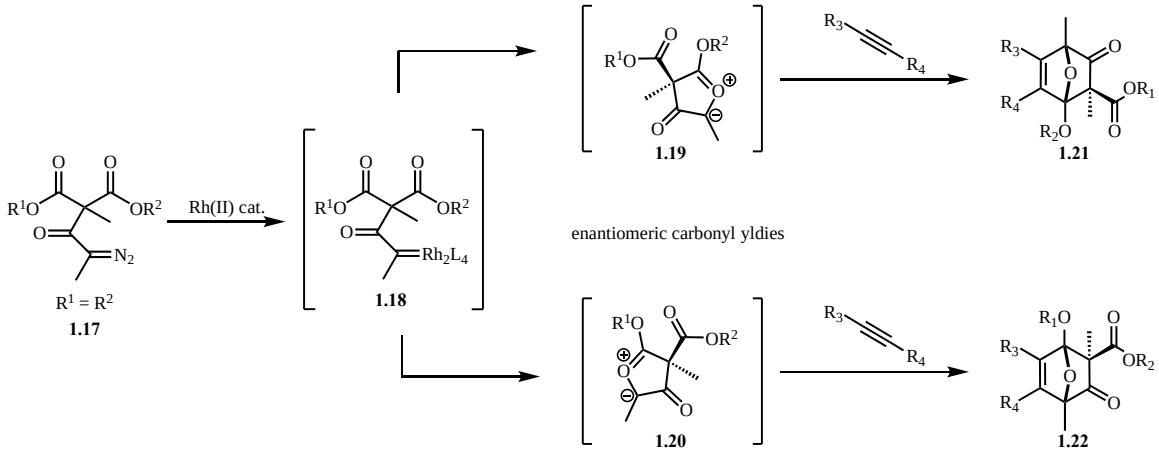
Scheme 1.3. Completion of racemic epoxysorbicillinol

the unsaturation present in the side chain and decarboalkoxylation of the remaining ester. The sequence of events proved critical. Initial exposure to DDQ effected the desired dehydrogenation in good yield but, subsequent exposure to TFA gave the natural product in unacceptably poor yield. Simply reversing the order of events provided (±)-epoxysorbicillinol **1.01** in workable yields in thirteen steps from commercially available materials.

1.1.2 Enantioselective Formal Synthesis – 2005

Having achieved the racemic synthesis of epoxysorbicillinol (**1.01**), a strategy was devised to access the natural product as a single enantiomer. In considering the racemic synthesis, it quickly became obvious that an enantioselective synthesis could be achieved

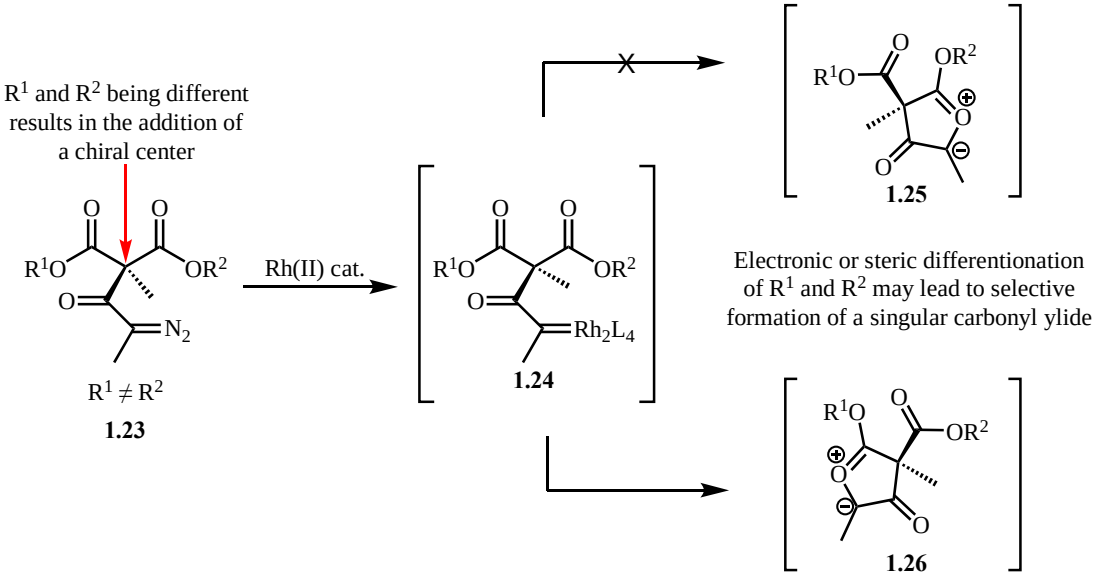
if a single enantiomer of the key oxabicyclic compound could be accessed. With the established diastereoselectivity of the dipolar cycloaddition in mind, it became clear that two additional constraints would need to be placed on the reaction to allow for the access of a single enantiomer of the oxabicyclic compound.[3] In the racemic synthesis, both esters of the diazomalonate precursor were equivalent, and thereby enantiotopic. The dipolar-cycloaddition led to a mixture of enantiomers of the oxabicyclic compounds (**1.21**, **1.22**) due to the formed enantiomeric carbonyl ylide intermediates (**1.19**, **1.20**, Scheme 1.4).



Scheme 1.4. Enantiomeric carbonyl ylides

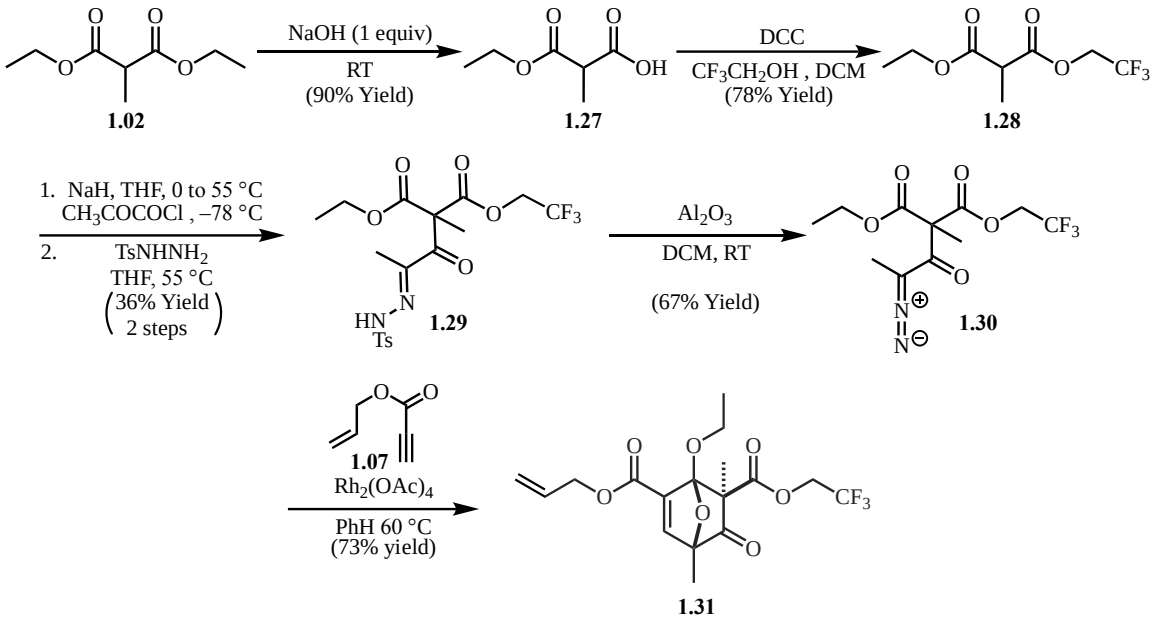
Thus, the first constraint needed to be control of which ester participated in carbonyl ylide formation, e.g. chemoselective carbonyl ylide formation. It was envisioned that this could be achieved either through electronic or steric differentiation of the esters in malonate (**1.23**, Scheme1.5). Differentiating the esters results in the addition of a chiral center at the diazomalonate's (**1.23**) central carbon, and therefore generation of a racemic mixture of carbonyl ylides. As such, the second constraint needed to be the setting of the stereocenter

present at the central carbon of the differentiated malonate prior to chemoselective carbonyl ylide formation and subsequent dipolar cycloaddition. With these constraints



Scheme 1.5. Chemoselective carbonyl ylide formation

in place, a single enantiomer of the oxabicyclic compound would be accessed and could be elaborated to a single enantiomer of epoxysorbicillinol (**1.54**, Scheme 1.9). Prior to focusing on the enantioselective synthesis of epoxysorbicillinol, Wood endeavored to prove the concept by establishing a viable means of chemoselective carbonyl ylide formation. In considering the options, the electronic differentiation of the malonate's esters appeared the most intriguing. To that end, electronically differentiated ethyl trifluoroethyl diazomalonate (**1.30**, Scheme 1.6) was accessed from diethyl methyl malonate **1.02**. As illustrated, partial saponification with sodium hydroxide followed by Steglich esterification with trifluoroethanol provided malonate **1.28**. Acylation with pyruvoyl chloride, condensation with tosyl hydrazide and subsequent exposure to base supplied dipolar cycloaddition precursor **1.30**. With access to this electronically differentiated

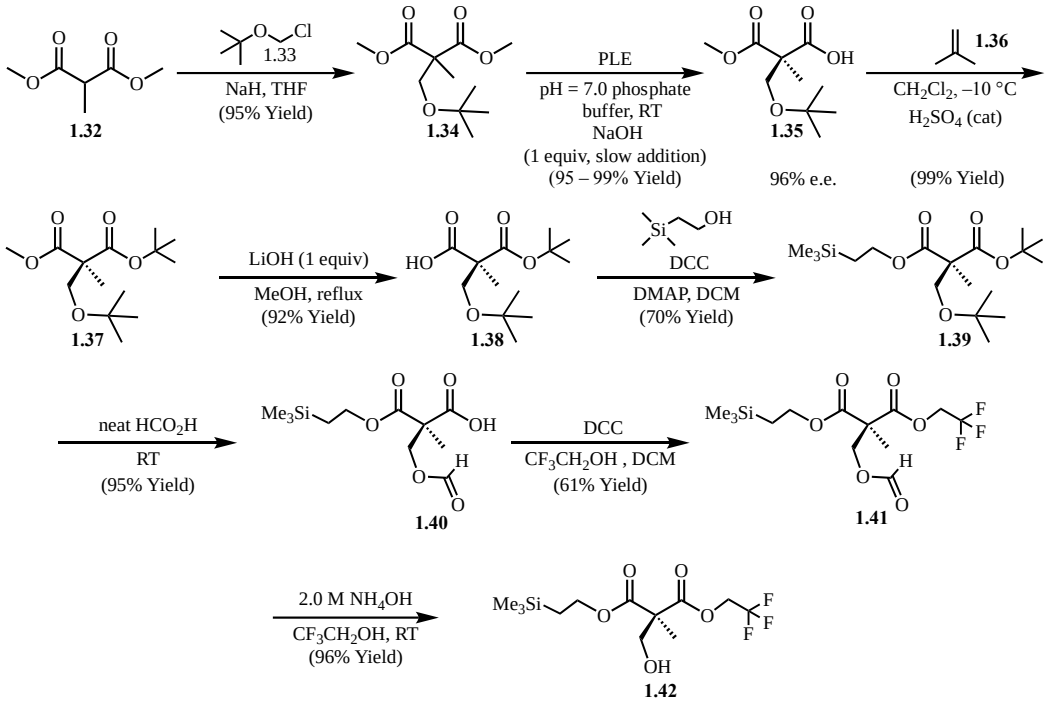


Scheme 1.6. Electronic differentiation proof of concept

diazomalonate achieved, the compound was heated to 60 °C in the presence of allyl propiolate **1.07** and rhodium acetate, furnishing the oxabicyclic compound **1.31** (as a mixture of enantiomers). The obtained oxabicyclic compound **1.31** was generated through the intermediacy of a carbonyl ylide formed selectively from the electron rich ethyl ester. Having observed the viability of electronic differentiation for chemoselective carbonyl ylide formation the stage was set for application toward the enantioselective synthesis of epoxysorbicillinol (**1.54**).

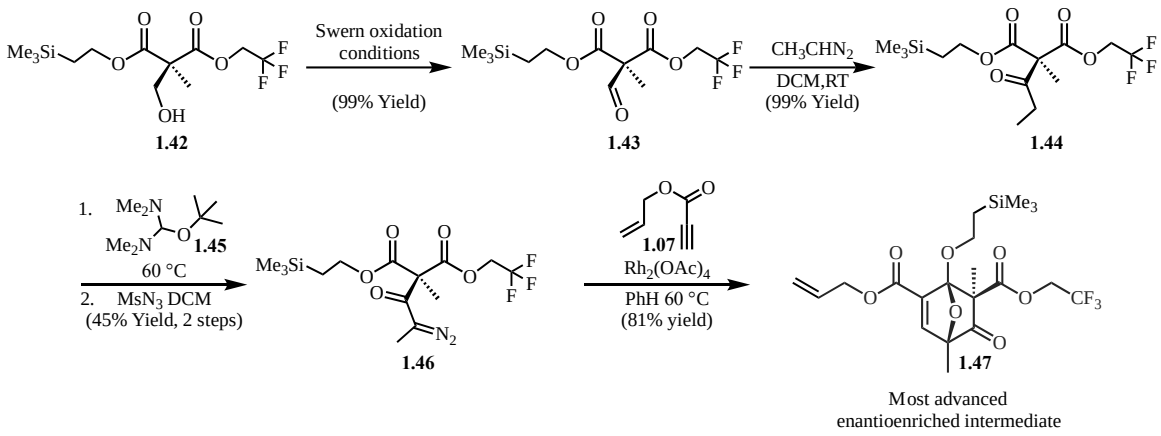
The formal enantioselective synthesis of (+)-epoxysorbicillinol commenced from commercially available dimethyl methyl malonate.[4] Deprotonation with sodium hydride followed by quenching with *t*-butoxy chloromethyl ether gave ether **1.34** (Scheme 1.7). Following precedent from Keese and coworkers [5], pig liver esterase and sodium hydroxide in a pH = 7 phosphate buffer provided half acid **1.35** in 96% e.e. With the enantioenriched

half acid in hand a route to the enantioenriched diazomalonate was established and the synthesis continued. To this end, acid **1.35** was converted to the corresponding *t*-butyl



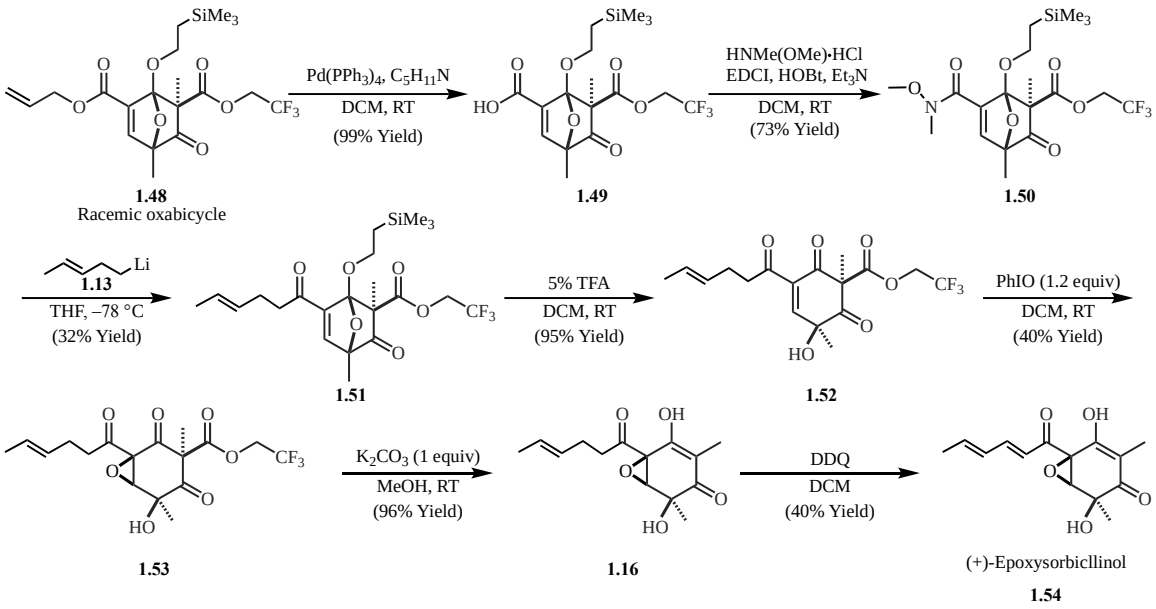
Scheme 1.7. Synthesis of enantioenriched malonate **1.42**

ester (**1.37**) which, upon saponification of the methyl ester and Steglich esterification with 2-(trimethylsilyl)ethanol gave malonate **1.39**. Exposure of **1.39** to neat formic acid removed both *t*-butyl groups and resulted in esterification of the primary alcohol to furnish formate **1.40**. A second Steglich esterification in the presence of trifluoroethanol gave the electronically differentiated malonate **1.41**. Cleavage of the formate ester was achieved by a 2M solution of NH_4OH in trifluoroethanol to give primary alcohol **1.42**. **1.42** was exposed to Swern oxidation conditions to produce aldehyde **1.43** which, upon further treatment with diazoethane provided ethyl ketone **1.44** (Scheme 1.8). Extensive exploration eventually resulted in the discovery that heating of **1.44** with Bredereck's



Scheme 1.8. Synthesis of Enantioenriched Oxabicycle **1.47**

reagent **1.45** [(*t*-butoxybis(dimethylamino)methane] at 60 °C followed by exposure to mesyl azide provided the diazomalonate cyclization precursor **1.46**.[6] Treatment of **1.46** with rhodium acetate in the presence of allyl propiolate **1.07** in benzene at 60 °C furnished enantioenriched oxabicyclic compound **1.47** in 81% yield. At this stage, once again only seven synthetic steps were required to access (+)-epoxysorbicillinol. Due to lack of material this final sequence was only performed in the racemic series (i.e., on **1.48**, the racemic version of oxabicycle **1.47**, Scheme 1.9). Palladium (0) induced de-allylation provided carboxylic acid **1.49** which was converted to the Weinreb amide. Selective 1,2-addition of 3-pentenyllithium **1.13** was followed by acetal cleavage with 5% TFA in DCM furnishing enone **1.52**. Unfortunately, epoxidation under conditions developed in the previous racemic synthesis with *t*-BuOOH failed to give the desired epoxide. Instead, it was discovered that epoxidation could be effected by action of iodosobenzene upon enone **1.52** to provide epoxide **1.53** in 40% yield. Finally, decarboalkoxylation with methanolic potassium carbonate and dehydrogenation by DDQ completed the formal synthesis of



Scheme 1.9. Formal enantioselective epoxysorbicillinol synthesis

(+)-epoxysorbicillinol **1.54** with the oxabicyclic compound **1.47** as the final enantioenriched compound accessed in the synthesis.

1.2 Conclusion

The total synthesis of (±)-epoxysorbicillinol and formal the synthesis of (+)-epoxysorbicillinol allowed for the development and establishment of a proof of concept for chemoselective carbonyl ylide formation through electronically differentiation of the malonate substrate's esters. With this knowledge, this chemistry would be expanded to a full methodology, exploring both substrate scope as well as steric differentiation of the diazomalonate's esters. The development and scope of the methodology will be discussed in chapter two.

1.3 References and Notes

[1] Sperry, S.; Samuels, G. J.; Crews, P. *J. Org. Chem.* **1998**, *63*, 10011.

[2]Wood, J. L.; Thompson, B.D.; Yusuff, N.; Pflum, D. A.; Matthäus, M. S. P. *J. Am. Chem. Soc.* **2001**, *123*, 2097.

[3]Chiral rhodium catalysis was an option for the enantioselective formal synthesis of epoxysorbicillinol. In light of the possible novelty of a method which chemoselectively forms a carbonyl ylide it was decided that chiral rhodium catalysis would not be utilized for the enantioselective synthesis.

[4] Lee, C.-W. The Formal Asymmetric Synthesis of (+)-Epoxysorbicillinol. Ph.D. Thesis, Yale University, New Haven, CT, 2005.

[5]Keese, R.; Luyten, M.; Muller, S.; Herzog, B. *Helv. Chim. Acta.* **1987**, *70*, 1250.

[6] Bredereck, H.; Simchem, G.; Rebsdat, S.; Kantlehner, W.; Horn, P.; Wahl, R.; Hoffman, H.; Grieshaben, P. *Chem. Ber.* **1968**, *101*, 41.

CHAPTER TWO

Chemoselective Carbonyl Ylide Formation Through Electronic Differentiation of the Esters of Diazomalonates Exploration of Steric Differentiation for Chemoselective Carbonyl Ylide Formation.

2.1 Background

Rhodium(II) induced carbonyl ylide formation and subsequent dipolar cycloadditions have been established as highly valuable and versatile synthetic methodologies for the synthesis of complex molecular targets (Figure 2.1).[1] Beginning

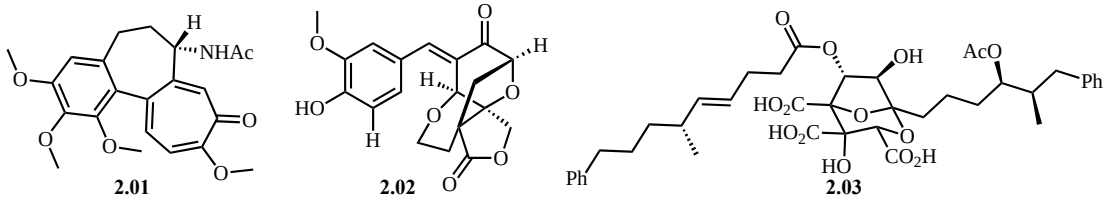
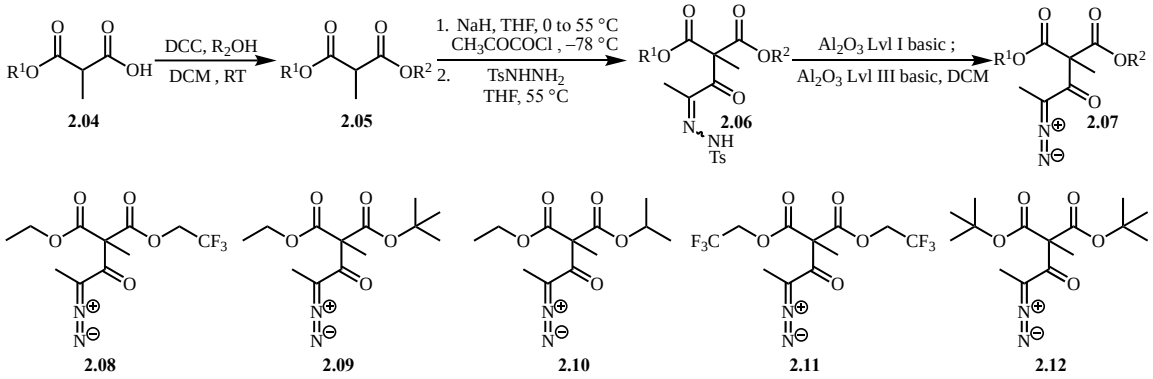


Figure 2.1. Complex molecular targets accessed through carbonyl ylide chemistry

with the seminal work of Bien *et al.*,[2] this chemistry has been extensively studied and was quickly applied to the synthesis of natural product targets; most notably by the groups of Padwa and Hashimoto. Interestingly, apart from our group's exploration of chemoselective carbonyl ylide formation no other reports of such a phenomenon have been disclosed. Drawing upon the knowledge gained from our group's syntheses of epoxysorbicillinol, we set out to further explore substrates for their potential to undergo chemoselective carbonyl ylide formation. Specifically, we aimed to explore the viability of steric differentiation, while also expanding the scope of the previously described electronic differentiation.

2.1.1 Substrate Synthesis

Following the synthetic route established in the epoxysorbicillinol synthesis we accessed a variety of electronically and sterically differentiated diazomalonates (Scheme 2.1).[3] In general, beginning with a known half acid **2.04**, Steglich esterification with an appropriate alcohol gave the electronically or sterically differentiated methyl malonates **2.05** which were acylated with pyruvoyl chloride and condensed with tosyl hydrazide. The



Scheme 2.1. Substrate synthesis

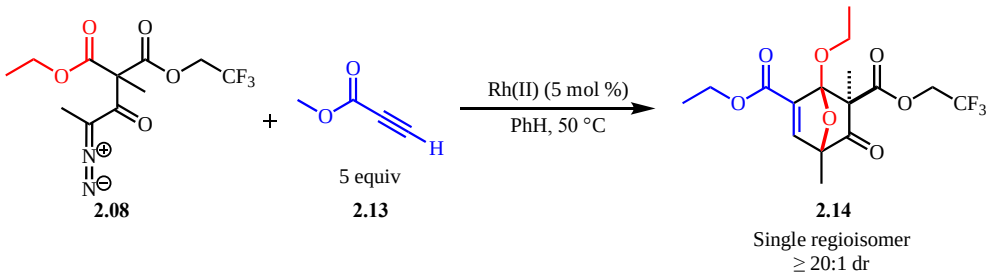
tosyl hydrazones (**2.06**) were then converted through exposure to basic alumina to the requisite dipolar cycloaddition precursors **2.07**. Ultimately, five different substrates were accessed. The electronically differentiated ethyl trifluoroethyl diazomalonate **2.08**, the sterically differentiated ethyl *t*-butyl (**2.09**) and ethyl 2-propyl diazomalonates (**2.10**) and the control substrates bis-trifluoroethyl (**2.11**) and bis-*t*-butyl diazomalonates (**2.12**).

2.1.2 Catalyst Screening and Optimization

Reaction optimization was briefly performed using the electronically differentiated diazomalonate **2.08**. The reaction conditions established in the epoxysorbicillinol syntheses were used as a point reference for this methodology (Table 2.1). It was

discovered that prolonged reaction times of about 24 hours as well as five equivalents of the dipolarophile reaction partner **2.13** resulted in consistently higher yields. A quick survey of rhodium catalysts then led to the conclusion that relatively electron poor complexes such as those bearing perfluorobutyrate or trifluoroacetate ligands would not promote the desired transformation. Alternatively, relatively electron rich complexes with acetate or octanoate ligands generated the desired oxabicyclic compound **2.14** in up to 71% yield. Ultimately, rhodium acetate was chosen as the optimal catalyst due to ease of purification. Simple filtration of the reaction mixture containing rhodium acetate

Table 2.1. Reaction optimization



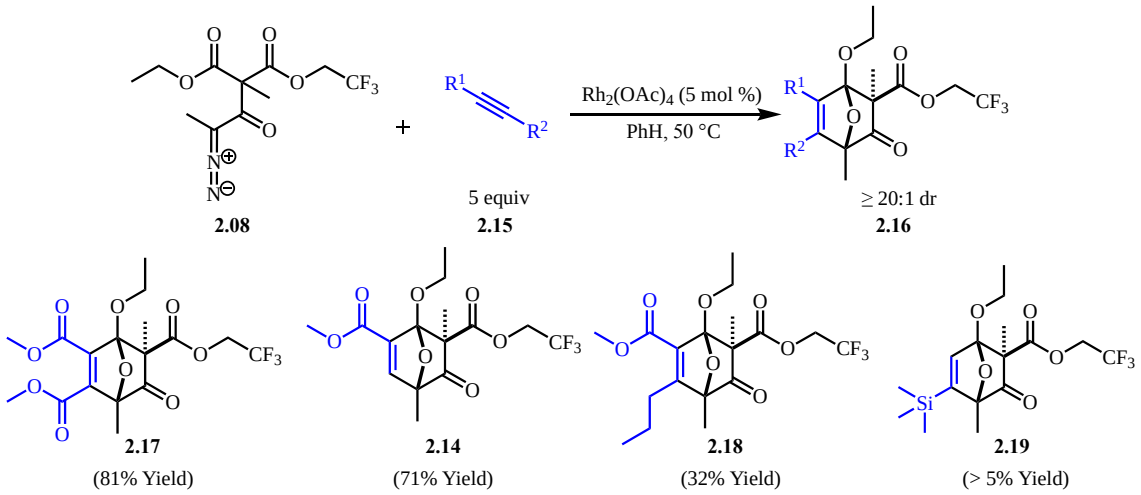
2.08 **2.13** **2.14**
Single regioisomer
≥ 20:1 dr

Entry	Rh(II) Cat.	Time	Yield
1	$Rh_2(OAc)_4$	12h	58%
2	$Rh_2(OAc)_4$	24h	71%
3	$[Rh[Oct]_2]_2$	24h	71%
4	$[Rh[TFA]_2]_2$	24h	0%
5	$[Rh(pfb)_2]_2$	24h	0%

through celite® removed the catalyst; whereas the greater solubility of rhodium octanoate in organic solvents led to its co-elution with the desired oxabicyclic compounds resulting in the isolation of green oils. Optimal reaction conditions were thus defined as 5 mol % of rhodium acetate in benzene at 50 °C with five equivalents of the dipolarophile for 24 hours.

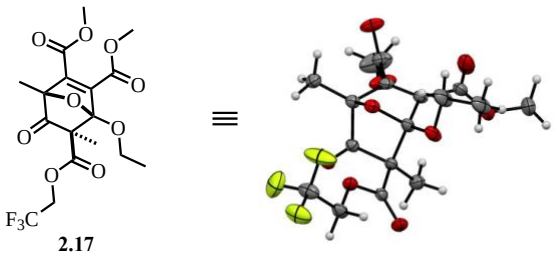
2.1.3 Dipolarophile Scope – Electronically Differentiated Malonate

With optimized reaction conditions in hand, a quick survey of reaction scope in terms of dipolarophile reaction partner was performed (Scheme 2.2). As precedented, the carbonyl ylides acted as type one dipoles.[4] Type one dipoles are nucleophilic having high



Scheme 2.2. Dipolarophile scope expansion

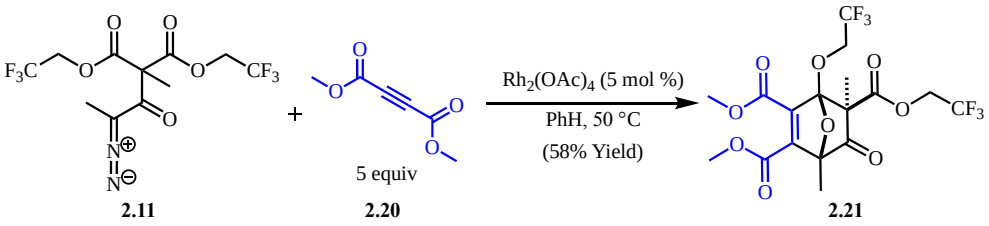
lying HOMO's which react with the LUMO of the dipolarophile. Due to this phenomenon, relatively electron poor dipolarophiles, such as dimethyl acetylene dicarboxylate and methyl propiolate, proved to be viable reaction partners, yielding the corresponding oxabicyclic compounds (**2.17**, **2.14** Scheme 2.2) in good to excellent yields with complete regiochemical control. As the dipolarophile became increasingly electron rich, and thereby the energy of its LUMO raised, the yield gradually diminished. Thus, poor yield was observed with methyl hexynoate (**2.18**) and trace yield with TMS acetylene (**2.19**). Compound **2.17** was crystalline, allowing for confirmation of the structure through X-ray crystallographic analysis. As depicted in Figure 2.2, the X-ray structure reaffirmed the chemoselectivity of carbonyl ylide formation; showing that in fact the electron poor



2.17

Figure 2.2 X-ray structure of **2.17**

trifluoroethyl ester had not participated in carbonyl ylide formation. Whether this apparent lack of reactivity was due to the incapability of the trifluoroethyl ester to participate in ylide formation or was simply due to preferential formation of the ylide from the more electron rich ethyl ester was explored through a control experiment. To this end, bis-trifluoroethyl diazomalonate **2.11** (Scheme 2.3) was subjected to the optimized reaction conditions in the presence of dimethyl acetylene dicarboxylate **2.20** and was shown to be a competent reaction partner, providing oxabicyclic compound **2.21** in modest yield. This therefore suggested that in the case of ylide formation by diazomalonate **2.08**, that the more electron rich ethyl ester out competed the trifluoroethyl ester for ylide formation.

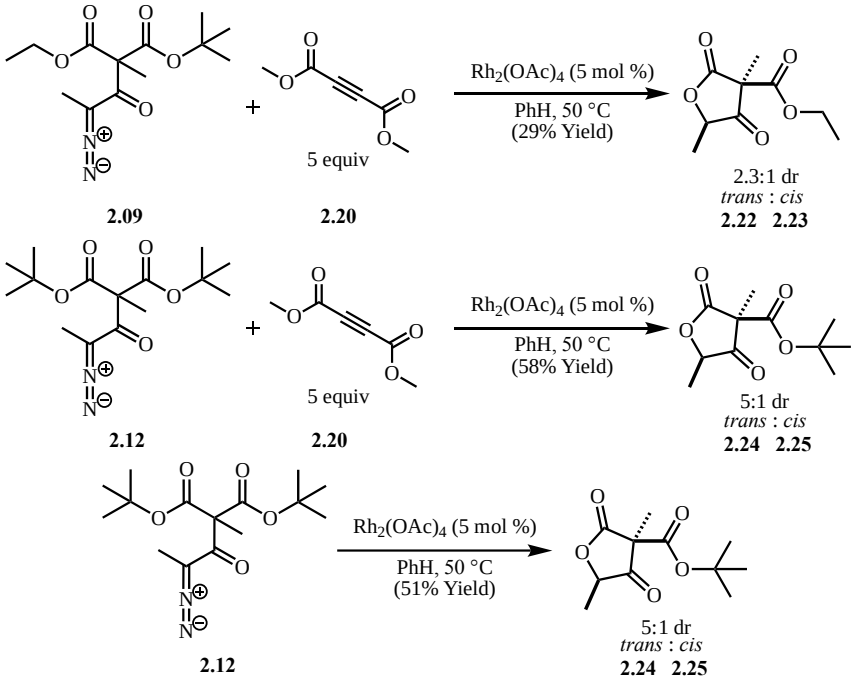


2.11 **2.20** **2.21**

Scheme 2.3. Viability of trifluoroethyl ester in ylide formation

2.1.4 Sterically Differentiated Malonates

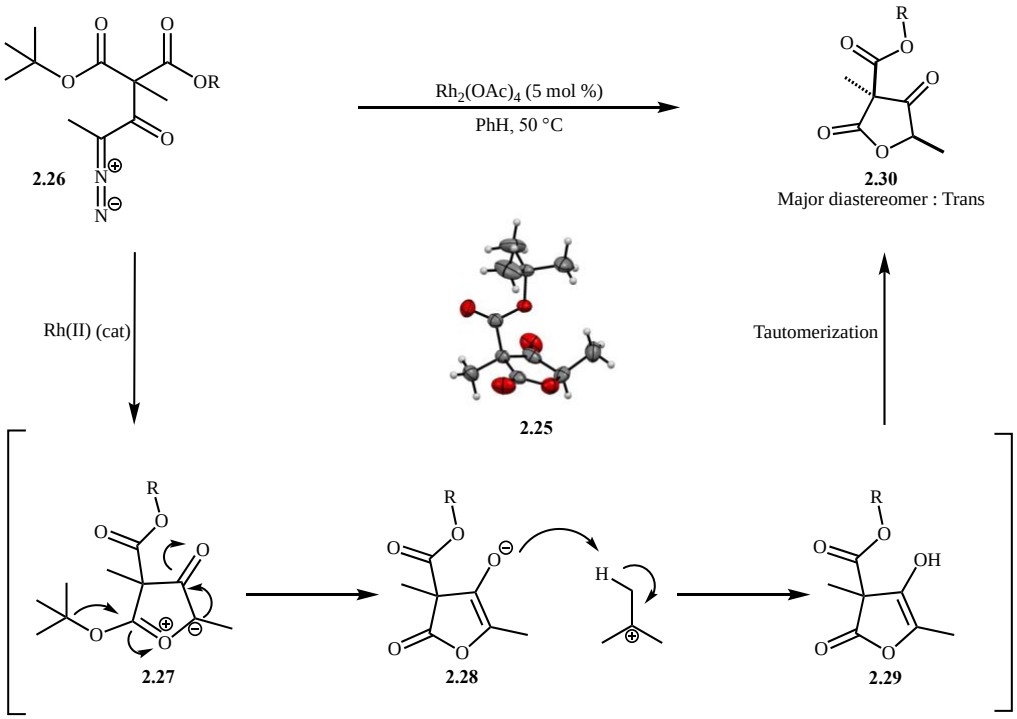
To explore the viability of steric differentiation for chemoselective carbonyl ylide formation ethyl *t*-butyl diazomalonate **2.09** was exposed to the reaction conditions in the presence of dimethyl acetylene carboxylate **2.20**. Surprisingly, this substrate failed to engage the dipolarophile and furnished tetronic acids (**2.22**/**2.23**) instead of the expected oxabicycle (Scheme 2.4). Preforming the same reaction with the bis-*t*-butyl substrate also



Scheme 2.4. Tetronic acid formation

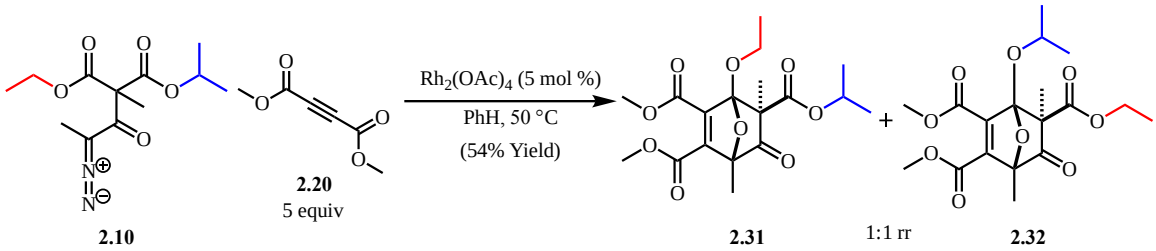
resulted in only tetronic acid products (**2.24** and **2.25**). As anticipated, removal of the dipolarophile reaction partner did not inhibit the formation of the observed tetronic acids. This reactivity was unprecedented for carbonyl ylides and is likely driven by the facile loss of *t*-butyl cation (see mechanism Scheme 2.5), suggesting the generality of this transformation in the presence of *t*-butyl esters. The structure of tetronic acid **2.25** was

confirmed by X-ray analysis. In addition to confirming this new reactivity, this compound's structure gives insight to the aforementioned (section 1.1.1) origin of cycloaddition diastereoselectivity as the ester depicted in the crystal structure clearly blocks one face of the tetronic acid and by analogy the intermediate carbonyl ylide involved in these reactions.



Scheme 2.5. Mechanistic proposal for tetronic acid formation

Though this unprecedented reactivity was intriguing, it did not reveal whether or not steric differentiation was a viable method for chemoselective carbonyl ylide formation. To explore this, ethyl 2-propyl diazomalonate **2.10** was exposed to the reaction conditions (Scheme 2.6). Unfortunately, a 1:1 mixture of structural isomers was obtained, suggesting that steric differentiation was ineffective for chemoselective carbonyl ylide formation.



Scheme 2.6. Steric differentiation of diazomalonate

2.2 Conclusion

In conclusion the scope of chemoselective carbonyl ylide formation through electronic differentiation of diazomalonates has been further explored. Additionally, steric differentiation was found to be unsuitable for selective ylide generation. Interestingly, these latter efforts revealed that carbonyl ylide forming reactions using *t*-butyl esters is an efficient method for the synthesis of tetronic acids.[3]

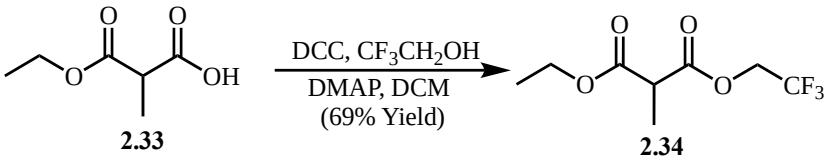
2.3 Experimental

2.3.1 General

Unless otherwise stated, all reactions were performed in oven-dried glassware under a nitrogen atmosphere, using reagents as received from the manufacturers. The reactions were monitored by thin-layer chromatography (TLC) using Silicycle glass-backed extra hard layer, 60 Å plates (indicator F-254, 250 μM). Tetrahydrofuran, dichloromethane and benzene were dried using a solvent purification system manufactured by SG Water U.S.A., LLC. Manual flash chromatography was performed using the indicated solvent systems with Silicycle SiliaFlash® P60 (230–400 mesh) silica gel as the stationary phase. Flash Chromatography on a Teledyne RF+UV-Vis Ms Comp MPLC was performed using the indicated solvent systems, and Teledyne RediSep® Rf normal phase

disposable columns of the indicated size and at the indicated flow rate. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on a Bruker Ascend™ 400 autosampler or Bruker Ascend™ 600 autosampler. Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual solvent resonance and coupling constants (J) are reported in hertz (Hz). IR spectra were recorded on Bruker Platinum-ATR IR spectrometer using a diamond window and all stretches are reported in cm^{-1}. High Resolution mass spectra (HRMS) were obtained in the Baylor University Mass Spectrometry Center on a Thermo Scientific LTQ Orbitrap Discovery spectrometer using +ESI and reported for the molecular ion ($M+H^{+}$ & $M+Na^{+}$) Single crystal X-ray diffraction data were collected on a Bruker Apex II-CCD detector using Mo-Kα radiation **(**λ = 0.71073 Å). Crystals were selected under oil, mounted on micromounts then immediately placed in a cold stream of N_2. Structures were solved and refined using SHELXTL.[5]

*Preparation of Electronically Differentiated Malonate **2.34***

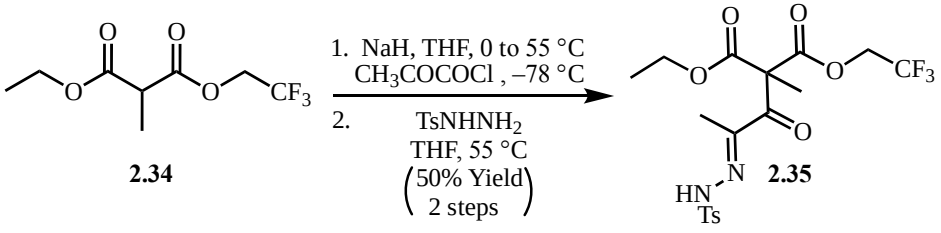


2.33 **2.34**

Carboxylic acid **2.33** (6 g, 41.06 mmol) was added to a 250 mL round bottom flask and dissolved in dry DCM (90 mL). Then trifluoroethanol (6.8 g, 68 mmol, 4.95 mL) and DMAP (390 mg, 3.2 mmol) were added. Following this N,N'-dicyclohexylcarbodiimide (11.397 g, 55.23 mmol) was added portion-wise to the reaction flask. The solution was left to stir for 12 hours during which N,N'-dicyclohexylurea precipitated. The mixture was filtered to remove N,N'-dicyclohexylurea and the filtrate extracted twice with 50 mL of 1 M HCl and twice more with 50 mL of saturated sodium bicarbonate. The organic layer was

filtered again to remove any additional N, N'-dicyclohexylurea that precipitated during the work-up. The organic layer was then dried over sodium sulfate and most of the solvent removed under reduced pressure. The remaining organic layer was then cooled in a dry ice acetone bath to facilitate N,N'-dicyclohexylurea precipitation and it was once again filtered. The remainder of the solvent was removed under reduced pressure and the crude product was purified by flash chromatography using silica gel and a gradient beginning at 3:97 ethyl acetate: hexanes and progressing to 1:9 ethyl acetate: hexanes. This yielded 6.5 g (69%) of **2.34** as a light clear oil. R_f = 0.33 (5% EtOAc/hexanes), $KMnO_4$; **^{1}H NMR** (400 MHz, Chloroform-d) δ 4.56 – 4.47 (m, 2H), 4.23 – 4.15 (m, 2H), 3.53 (q, J = 7.3 Hz, 1H), 1.45 (d, J = 7.3 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 169.25, 168.83, 122.85 (q, J = 277.3 Hz), 61.91, 60.91 (q, J = 36.7 Hz), 45.88, 14.02, 13.53. **+ESI-HRMS** m/z: calc'd for (M+Na^+) $C_8H_{11}F_3O_4Na^+$ = 251.05071, found $C_8H_{11}O_4F_3Na^+$ = 251.05025 **FTIR (Neat)**: 2988, 2949, 1767, 1736, 1457, 1413, 1382, 1279, 1158, 1084.8, 1049, 1021, 975, 863, 839, 632, 558, 446.

*Preparation of Tosyl Hydrazone **2.35***

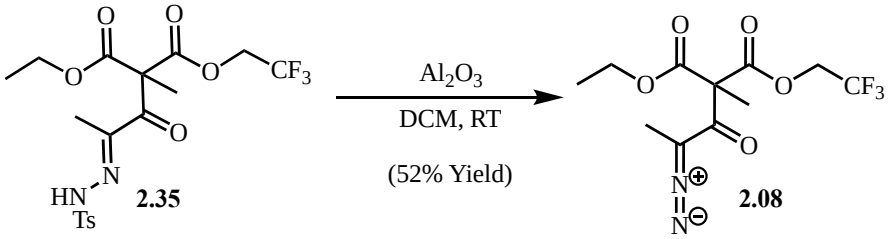


To a round bottom flask was added malonate ester **2.34** (1.0 g, 4.38 mmol) and dry THF (19 mL). The reaction solution was then cooled in an ice water bath and let stir for ten minutes. Then sodium hydride (200 mg, 5 mmol) as a 60% dispersion in mineral oil was added portion wise. After addition of the sodium hydride was complete the solution

was allowed to stirred for five minutes and then heated to 55 °C (oil bath temperature) for 1 hour. After heating was complete the reaction mixture was allowed to cool to RT, then cooled to –78 °C using a dry ice acetone bath and allowed to stir for ten minutes at –78 °C. Following this pyruvoyl chloride (0.46 mL, 6.05 mmol) was added. Upon addition of the acyl chloride the solution turned bright yellow and thickened. The reaction mixture was allowed to stir for an additional twenty minutes at –78 °C and then slowly allowed to warm up to RT over twenty minutes. It was then quenched with 5 mL 1M HCl and 30 mL diethyl ether were added. The organic layer was washed twice with 25 mL water, and the aqueous layers were combined and extracted with 25 mL diethyl ether. The organic layers were then combined and washed twice with 25 mL brine and dried over 9:1 sodium and magnesium sulfate mixture. The solvent was then evaporated under reduced pressure to give a clear yellow oil that was re-dissolved in dry THF (19 mL). To this solution was added tosyl hydrazide (0.819 g, 4.4 mmol) at RT. The solution was then heated for 15 hours at 55 °C (oil bath temperature), cooled to room temperature and allowed to stir for an additional hour. The solvent was evaporated under reduced pressure. Flash chromatography was performed using an MPLC and a solvent gradient beginning at 0% ethyl acetate: hexanes and progressing to 35% ethyl acetate: hexanes. A 40-gram column with the flow rate set at 25 mL/min was used. The reaction yielded 1.023 g (50%) of tosyl hydrazone **2.35**. An analytically pure sample was obtained by taking the purest fraction from the column and used for characterization. R_f = 0.21 (35% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, DMSO-*d*6) δ 11.88 (br s, 1H), δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.1 Hz, 2H), 4.78 – 4.66 (m, 1H), 4.63 – 4.50 (m, 1H), 4.09 – 3.94 (m, 2H), 2.43 (s, 3H), 1.93 (s, 3H), 1.53 (s, 3H), 1.07 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, DMSO-*d*6) δ 190.71, 166.74, 166.34,

146.35, 144.27, 135.53, 129.77, 127.60, 123.13 (q, *J* = 277.3 Hz), 63.25, 61.73, 60.78 (q, *J* = 35.4 Hz), 21.04, 19.80, 13.49, 10.88 **+ESI-HRMS** m/z: calc'd for ($M+Na^+$) $C_{18}H_{21}F_3N_2O_7SNa^+$ = 489.09193, found $C_{18}H_{21}O_7N_2F_3NaS^+$= 489.0917 **FTIR (Neat):** 3216, 2982 1766, 1740, 1697, 1599, 1450, 1411, 1352, 1285, 1255, 1168, 1114, 1087, 1036, 1020, 974, 886, 715, 661, 547, 461. *Note: For the synthesis of pyruvoyl chloride see reference #6

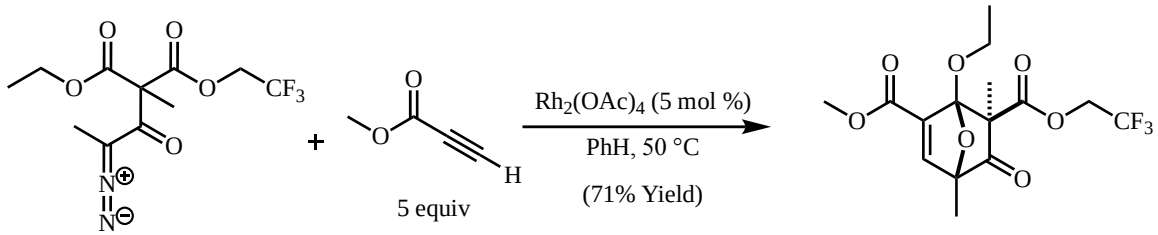
*Preparation of Diazomalonate **2.08***



Tosyl hydrazone **2.35** (1.02 g, 2.19 mmol) was added to a 50 mL round bottom flask and dissolved in dry DCM (22.5 mL). Then Al_2O_3 (2.81 g, 27.5 mmol) Brockmann LVL I were added, the flask was wrapped in foil and the reaction mixture was allowed to stir for 18.5 hours. The mixture slowly became yellow in color. Following this an additional 2.81 g (27.5 mmol) of Al_2O_3 Brockmann LVL III were added and the mixture stirred for an additional three hours after which the reaction mixture was poured directly into a fritted filter filled with 41.7 g of Brockmann LVL III Al_2O_3 and the compound was eluted using DCM. Analytically pure material was obtained by silica gel flash chromatography using a gradient beginning at 0% ethyl acetate: hexanes progressing to 10% ethyl acetate: hexanes. This yielded 338.8 mg (52% yield) of the desired diazo compound **2.08** as a bright yellow oil. R_f = 0.24 (15% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, Chloroform-d) δ 4.62 (dq, J = 12.6, 8.3 Hz, 1H), 4.51 (dq, J = 12.6, 8.3 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 2.02 (s,

3H), 1.74 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 167.51, 166.71, 122.66 (q, J = 277.3 Hz), 65.02, 63.07, 61.58 (q, J = 37.1 Hz), 18.98, 13.87, 9.90. **+ESI-HRMS** m/z: calc'd for ($M+Na^+$) $C_{11}H_{13}F_3N_2O_5Na^+$ = 333.06743, found $C_{11}H_{13}F_3N_2O_5Na^+$ = 333.06766 **FTIR (Neat)**: 2986, 2949, 2077, 1736, 1621, 1449, 1411.9, 1380, 1331, 1284, 1247, 1164, 1105, 1018, 975, 862, 649.

*Preparation of Oxabicyclic Compound **2.14***

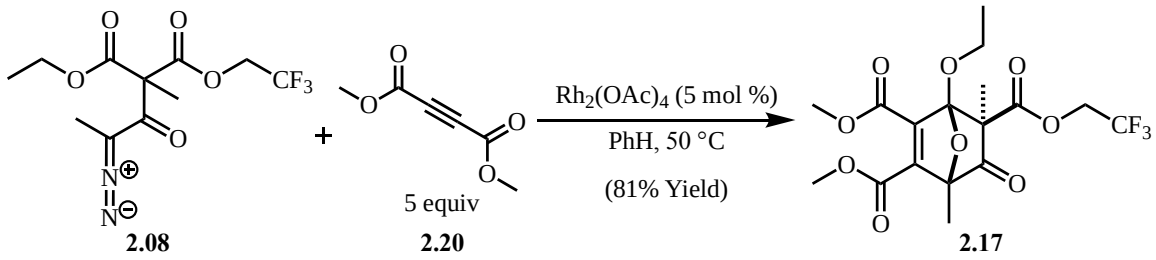


2.08 **2.13** **2.14**

To an oven dried 1.5-dram vial was added a stir bar, diazomalonate **2.08 (**50.9 mg, 0.164 mmol), dry benzene (1.5 mL) and methyl propiolate (0.075 mL, 0.843 mmol). The reaction vial was then evacuated of air and backfilled with nitrogen three times. Rhodium acetate dimer (3.5 mg, 5 mol %) was then added to the reaction vial and the vial purged with a stream of nitrogen. The reaction mixture was stirred for 10 minutes at RT then warmed to 50 °C in a preheated aluminum heating block for 24 hours. After 24 hours the reaction mixture was filtered through Celite® to remove the rhodium catalyst and the Celite® washed with benzene. The solvent was then evaporated under reduced pressure and the crude reaction mixture purified by flash chromatography using 1:4 ethyl acetate: hexanes yielding 43.6 mg (71% yield) of the desired oxabicycle (**2.14**) as a clear viscous oil*. The sample used for the characterization spectra was obtained by preparative TLC using 0.5% ethyl acetate in toluene or from the purest fraction of the column. R_f = 0.2 (15% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.12 (s, 1H), 4.64 – 4.53 (m,

1H), 4.50 – 4.39 (m, 1H), 3.96 – 3.87 (m, 1H), 3.82 (s, 3H), 3.75 – 3.65 (m, 1H), 1.64 (s, 3H), 1.37 (s, 3H), 1.26 (t, J = 7.0 Hz, 3H). **^{13}C NMR** (151 MHz, Chloroform-d) δ 203.37, 167.05, 162.07, 147.66, 143.72, 122.78 (q, J = 277.4 Hz), 113.16, 86.35, 63.16, 61.05 (q, J = 37.0 Hz), 54.00, 52.47, 17.88, 15.12, 12.48 (d, J = 1.9 Hz). **+ESI-HRMS** m/z: calc'd for ($M+Na^+$) $C_{15}H_{17}F_3O_7Na^+$ = 389.08186, found $C_{15}H_{17}F_3O_7Na^+$ = 389.08215 **FTIR (Neat)**: 2988, 2944, 1776,1752, 1725, 1612, 1439, 1385, 1333, 1269, 1227, 1157, 1119, 1075, 1041, 1005, 974, 893, 760. *Note: this oxabicycle often co-eluted with a small amount of a known reaction by-product formed by cyclotrimerization of the alkyne, yield reported was corrected to take into account the minor impurity.

*Preparation of Oxabicyclic Compound **2.17***

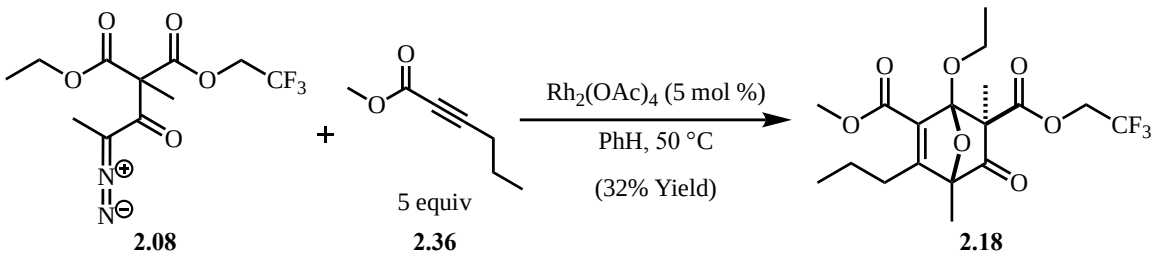


2.08 **2.20** **2.17**

To an oven dried 1.5-dram vial was added a stir bar, diazomalonate **2.08** (50.8 mg, 0.164 mmol), dry benzene (1.5 mL) and dimethyl acetylenedicarboxylate (0.1 mL, 0.813 mmol). The reaction vial was then evacuated of air and backfilled with nitrogen three times. Rhodium acetate dimer (3.5 mg, 5 mol %) was then added to the vial and the vial purged with a stream of nitrogen. The reaction mixture was stirred for 10 minutes at RT then warmed to 50 °C in a preheated aluminum heating block for 24 hours. After 24 hours the reaction mixture was filtered through Celite® to remove the rhodium catalyst and the Celite® washed with benzene. The solvent was then evaporated under reduced pressure and the crude reaction mixture purified by flash chromatography using a gradient beginning at

1:19 ethyl acetate: hexanes progressing to 3:22 ethyl acetate: hexanes yielding 56.3 mg (80.9% yield) of the desired oxabicycle **2.17** as a clear viscous oil which crystallizes under vacuum.* An analytically pure sample and crystals for X-ray crystallographic analysis were obtained by vapor diffusion using ethyl acetate as the solvent and hexanes as the precipitant. R_f = 0.14 (15% EtOAc/hexanes), UV; **^{1}H NMR** (600 MHz, Chloroform-d) δ 4.61 (dq, J = 12.6, 8.3 Hz, 1H), 4.42 (dq, J = 12.6, 8.3 Hz, 1H), 3.96 (dq, J = 9.6, 7.0 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.79 (dq, J = 9.4, 7.0 Hz, 1H), 1.69 (s, 3H), 1.45 (s, 3H), 1.25 (t, J = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 201.56, 166.65, 161.88, 161.83, 145.91, 145.32, 122.75 (q, J = 277.2 Hz), 112.92, 86.97, 63.67, 61.17 (q, J = 37.0 Hz), 53.99, 53.05, 53.04, 17.65, 15.13, 11.49. **+ESI-HRMS** m/z: calc'd for ($M+Na^+$) $C_{17}H_{19}F_3O_9Na^+$ = 447.08789, found $C_{17}H_{19}F_3O_9Na^+$ = 447.08765 **FTIR (Neat)**: 2988, 2959, 1783, 1731, 1640, 1439, 1386, 1372, 1329, 1311, 1275, 1167, 1124, 1053, 1030, 1004, 978. *Note: crystallization for the viscous oil occurs if the solvent used was ethyl acetate. Usually an oil emerges from other solvents.

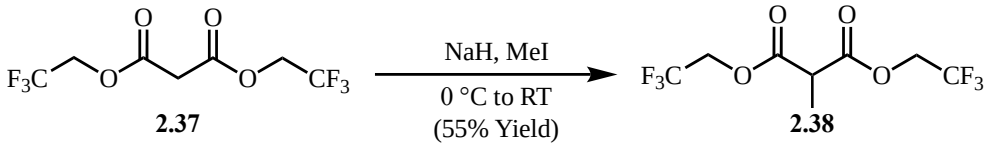
*Preparation of Oxabicyclic Compound **2.18***



To an oven dried 1.5-dram vial was added a stir bar, the diazomalonate **2.08 (**50.1 mg, 0.161 mmol), dry benzene (1.5 mL) and methyl hexynoate (0.11 mL, 0.822 mmol). The reaction vial was then evacuated of air and backfilled with nitrogen three times. Rhodium acetate dimer (3.5 mg, 5 mol%) was then added to the vial and the vial purged with a stream of nitrogen. The reaction mixture was stirred for 10 minutes at RT then warmed to 50 °C in a preheated aluminum heating block for 24 hours. After 24 hours the reaction mixture was filtered through Celite® to remove the rhodium catalyst and the Celite® washed with benzene. The solvent was then evaporated under reduced pressure and the crude reaction mixture purified by flash chromatography with toluene as the eluent. This yielded 21 mg (32% yield) of the desired oxabicycle **2.18** as a clear oil. R_f = 0.27 (15% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, Chloroform-d) δ 4.59 (dq, J = 12.6, 8.3 Hz, 1H), 4.42 (dq, J = 12.6, 8.3 Hz, 1H), 3.90 – 3.84 (m, 1H), 3.82 (s, 3H) 3.62 (dq, J = 9.4, 7.0 Hz, 1H), 2.73 (ddd, J = 12.7, 10.0, 6.5 Hz, 1H), 2.41 (ddd, J = 12.7, 9.7, 5.5 Hz, 1H), 1.61 (s, 3H), 1.53 – 1.42 (m, 1H), 1.38 (s, 3H), 1.36 – 1.28 (m, 1H), 1.23 (t, J = 7.0 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H).**^{13}C NMR** (151 MHz, Chloroform-d) δ 204.69, 167.34, 163.48, 163.41, 134.97, 122.82 (q, J = 277.5 Hz), 112.37, 88.52, 62.56, 60.99 (q, J = 36.9 Hz), 54.59, 51.94, 28.62, 21.34, 18.00, 15.18, 14.44, 11.05. **+ESI-HRMS** m/z: calc'd for (M+Na^+) $C_{18}H_{23}F_3O_7Na^+$ = 431.12936, found $C_{18}H_{23}F_3O_7Na^+$ = 431.12906 **FTIR (Neat)**:

2968, 2941, 1775, 1753, 1717, 1632, 1448, 1438, 1411, 1384, 1371, 1329, 1285, 1238, 1167, 1137, 1121, 1039, 980.

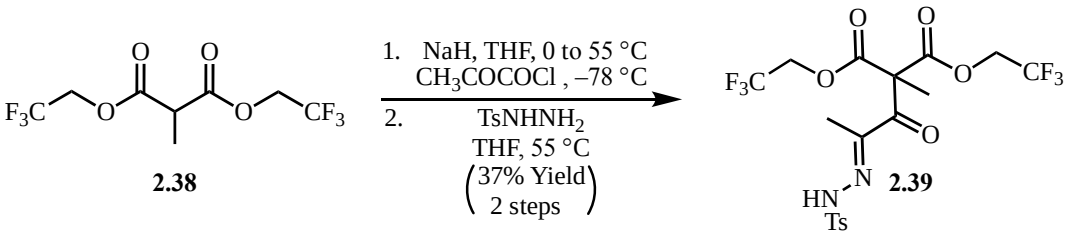
*Preparation of Bis-Trifluoroethyl Methyl Malonate **2.38***



To a flame dried round bottom flask was added malonate **2.37 (**283 mg, 1.05 mmol) and dry THF (10 mL). This solution was cooled to 0 ℃ using an ice bath and to this was added NaH (50 mg,1.25 mmol) as a 60% dispersion in mineral oil. The solution was allowed to stir at 0 ℃ for fifteen minutes and then methyl iodide (0.072 mL, 1.16 mmol) was added dropwise over five minutes. The reaction was stirred for an additional fifteen minutes at 0 ℃ and then the ice bath removed and the reaction allowed to warm up to room temperature and stir overnight. The reaction was then quenched with 1 mL ammonium chloride. Ethyl acetate was added and the reaction was washed with deionized water twice. The water washes were extracted twice with ethyl acetate and the organic layers combined and washed twice with brine. The organic layer was then dried over sodium sulfate and the solvent removed under reduced pressure. The compound was then purified by flash chromatography using 1:12 ethyl acetate: hexanes. This yielded 162.7 mg, (55% yield) of **2.38** as a clear oil. R_f = 0.23 (5% EtOAc/hexanes), $KMnO_4$; **^{1}H NMR** (400 MHz, Chloroform-d) δ 4.58 – 4.48 (m, 4H), 3.67 (q, J = 7.3 Hz, 1H), 1.52 (d, J = 7.3 Hz, 3H) **^{13}C NMR** (151 MHz, Chloroform-d) δ 122.70 (q, J = 277.2 Hz), 61.24 (q, J = 37.1 Hz), 45.42, 13.48. **+ESI-HRMS** m/z: calc'd for ($M+Na^+$) $C_8H_8F_6O_4Na^+$ = 305.02245, found

$C_8H_8F_6O_4Na^+$ = 305.02191 **FTIR (Neat)**: 2982, 2954, 1756, 1458, 1413, 1277, 1157, 1087, 973, 916, 842, 652. *Note: For the synthesis of **2.37** see reference #7

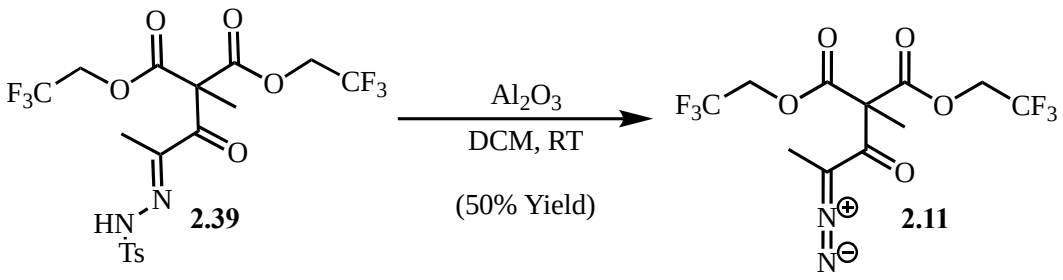
*Preparation of Tosyl Hydrazone **2.39***



Malonate ester **2.38** (500 mg, 1.78 mmol) was dissolved in dry THF (11 mL). The reaction solution was then cooled in an ice water bath and let stir for ten minutes. Then NaH (85 mg, 2.1 mmol) as a 60% dispersion in mineral oil were added portion wise. After addition of the NaH was complete the solution was allowed to stirred for five minutes and then heated to 55 °C (oil bath temperature) for one hour. After heating was complete the reaction mixture was allowed to cool to RT, then cooled to –78 °C using a dry ice acetone bath and allowed to stir for ten minutes at –78 °C. Following this pyruvoyl chloride (0.21 mL, 2.76 mmol) was added. Upon addition of the acyl chloride the solution turned bright yellow and thickened. The reaction mixture was allowed to stir for an additional twenty minutes at –78 °C and then slowly allowed to warm up to RT over twenty minutes. It was then quenched with 3 mL 1M HCl and 12 mL diethyl ether were added. The organic layer was washed twice with 12 mL water, and the aqueous layers were combined and extracted with an additional 12 mL of diethyl ether. The organic layers were then combined and washed twice with 20 mL of brine and dried over sodium and magnesium sulfate. The solvent was then evaporated under reduced pressure to give a clear yellow oil which was re-dissolved in dry THF (11 mL). To this solution was added tosyl hydrazide (0.331 g,1.78

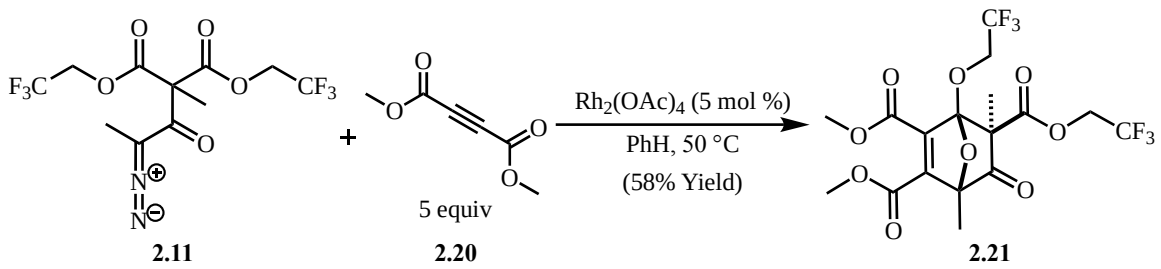
mmol) at RT. The reaction was then heated for 20 hours at 55 °C (oil bath temperature). It was then allowed to cool to RT and the solvent evaporated under reduced pressure. Flash chromatography was performed on the crude material using an MPLC and a gradient beginning at 0% ethyl acetate: hexanes and progressing to 20% ethyl acetate: hexanes. A 12-gram column with a flow rate of 30 mL/min was used. This gave 343.4 mg (37%) of **2.39** as a clear glassy solid. An analytically pure sample was taken from a pure fraction of the column and used for characterization. **^{1}H NMR** (600 MHz, DMSO-d6) δ 12.05 (br s, 1H), 7.78 (d, J = 7.8 Hz, 2H), 7.49 (d, J = 7.9 Hz, 2H), 4.76 – 4.67 (m, 2H), 4.67 – 4.57 (m, 2H), 2.43 (s, 3H), 1.93 (s, 3H), 1.55 (s, 3H). **^{13}C NMR** (101 MHz, DMSO-d6) δ 189.83, 165.57, 145.84, 144.32, 135.47, 129.76, 127.56, 122.95 (q, J = 277.1 Hz), 63.04, 61.06 (q, J = 35.9 Hz), 20.98, 19.71, 10.75. **+ESI-HRMS** m/z: calc'd for ($M+Na^+$) $C_{18}H_{18}F_6N_2O_7SNa^+$= 543.06366, found $C_{18}H_{18}F_6N_2O_7SNa^+$ = 543.06580 **FTIR (Neat)**: 3214, 2923, 2855, 1776, 1758, 1699, 1599, 1452,1412, 1378, 1352, 1286, 1244, 1168, 1118, 1087, 1037, 974, 899, 842, 816, 713, 547, 494.

*Preparation of Diazomalonate **2.11***



Tosyl hydrazone **2.39** (0.247 g, 0.475 mmol) was added to a 75 mL pear shaped flask and dissolved in dry DCM (4 mL). Then of Al_2O_3 (0.52 g, 5.1 mmol) Brockmann LVL I was added, the flask was wrapped in foil and the reaction mixture was allowed to stir for 13 hours. The mixture slowly became yellow in color. Following this an additional 0.52 g (5.1 mmol) of Al_2O_3 Brockmann LVL III were added and the mixture stirred for an additional 6 hours. The mixture was then poured into a fritted filter filled with Brockmann LVL III Al_2O_3 and the compound eluted using DCM. The material was purified by silica gel flash chromatography using a 5% ethyl acetate: hexanes. This yielded 86.5 mg (50% yield) of the desired diazo compound **2.11** as a bright yellow oil. **^{1}H NMR** (400 MHz, Chloroform-d) δ 4.68 – 4.48 (m, 4H), 2.03 (s, 3H), 1.80 (s, 3H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 166.04, 122.51 (q, J = 277.3 Hz), 64.85, 61.87 (q, J = 37.4 Hz), 18.79, 9.80. **+ESI-HRMS** m/z: calc'd for ($M+H^+$): $C_{11}H_{11}F_6N_2O_5^+$= 365.05722, found $C_{11}H_{11}F_6N_2O_5^+$ = 365.05679 **FTIR (Neat)**: 2080, 1756, 1626, 1452, 1412, 1285, 1240, 1169, 1111, 1025, 977, 652.

*Preparation of Oxabicyclic Compound **2.21***

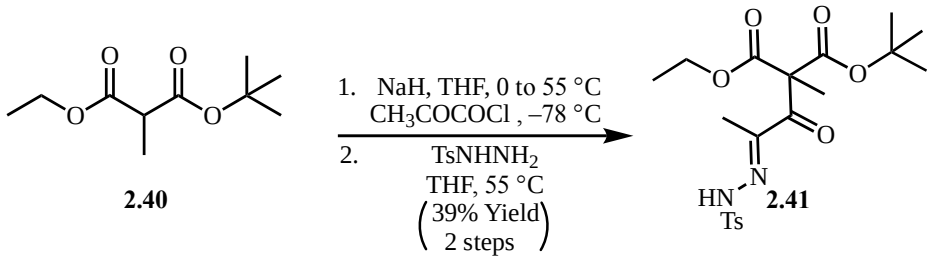


To an oven dried 1.5-dram vial was added a stir bar, the diazomalonate **2.11** (59.4 mg, 0.162 mmol), dry benzene (1.5 mL) and dimethyl acetylenedicarboxylate (0.1 mL, 0.813 mmol). The reaction vial was then evacuated of air and backfilled with nitrogen three times and then rhodium acetate dimer (3.5 mg, 5 mol %) was added to the vial and the vial purged with a stream of nitrogen. The reaction mixture was stirred for 10 minutes at RT then warmed to 50 °C in a preheated aluminum heating block for 24 hours. After 24 hours the reaction mixture was filtered through Celite® to remove the rhodium catalyst and the Celite® washed with benzene. The solvent was then evaporated under reduced pressure and the crude reaction mixture purified by flash chromatography using a gradient beginning at 5:95 ethyl acetate: hexanes progressing to 15:85 ethyl acetate: hexanes. This yielded 45.3 mg (58% yield) of the product (**2.21**) as a clear viscous oil that quickly crystalizes. An analytically pure sample and crystals for X-ray crystallographic analysis were obtain by vapor diffusion using dichloromethane as the solvent and pentane as the precipitant. R_f = 0.16 (15% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, Chloroform-d) δ 4.57 (dq, J = 12.6, 8.2 Hz, 1H), 4.41 (dq, J = 12.6, 8.2 Hz, 1H), 4.33 – 4.17 (m, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 1.72 (s, 3H), 1.48 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-d) δ 199.78, 165.79, 161.40, 161.10, 146.52, 143.72, 122.88 (q, J = 277.0 Hz), 122.65 (q, J = 277.2 Hz), 111.86, 87.86, 63.96 (q, J = 36.7 Hz),

61.51 (q, J = 37.1 Hz), 53.70, 53.32, 53.23, 17.46, 11.32. **+ESI-HRMS** m/z: calc'd for ($M+Na^+$) $C_{17}H_{16}F_6ONa^+$= 501.05962, found $C_{17}H_{16}F_6ONa^+$ = 501.05957 FTIR (Neat): 2962, 1786, 1729, 1640, 1439, 1388, 1282, 1245, 1157, 1125, 1074, 1032, 1004, 978, 839, 802, 787, 712.

*Preparation of Tosyl Hydrazone **2.41***

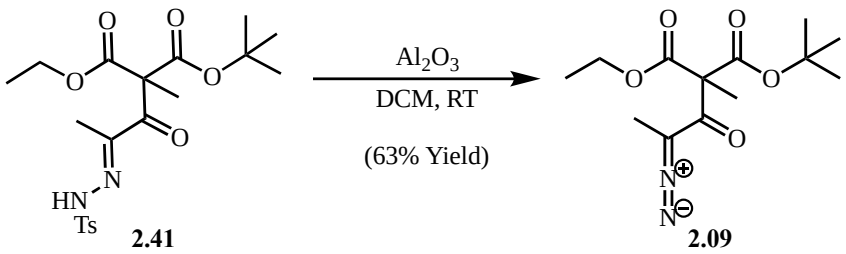


Malonate ester **2.40** (651 mg, 3.22 mmol) was dissolved in dry THF (13 mL). The reaction solution was then cooled in an ice water bath and let stir for ten minutes. Then sodium hydride (151 mg, 3.77 mmol) as a 60% dispersion in mineral oil was added portion wise. After addition of the sodium hydride was complete the solution was allowed to stir for five minutes, warmed to RT and then heated to 55 °C (oil bath temperature) for one hour. After heating was complete the reaction mixture was allowed to cool to RT, then it was cooled to –78 °C using a dry ice acetone bath and allowed to stir for at –78 °C for ten minutes. After which, pyruvoyl chloride (0.34 mL, 4.4 mmol) was added. Upon addition of the acyl chloride the solution turned bright yellow and thickened. The reaction mixture was allowed to stir for an additional twenty minutes at –78 °C and then slowly allowed to warm up to RT over ten minutes. It was then quenched with 5 mL water and 25 mL diethyl ether were added. The organic layer was washed twice with 5 mL water, and the aqueous layers were combined and extracted with 25 mL diethyl ether. The organic layers were then

combined and washed twice with 25 mL of brine and dried over sodium and magnesium sulfate. The solvent was then evaporated to give a clear yellow oil which was re-dissolved in dry THF (13 mL). To this solution was added tosyl hydrazide (605 mg, 3.26 mmol) at RT. The reaction was then heated for 18 hours at 55 °C (oil bath temperature). The solution was allowed to cool to room temperature and the solvent evaporated under reduced pressure. Flash chromatography was performed on the crude material using an MPLC and a gradient beginning at 0% ethyl acetate: hexanes and progressing to 20% ethyl acetate: hexanes. A 24-gram column with a flow rate of 35 mL/min was used. This gave 547.8 mg (39%) of the product (**2.41**) as a clear glassy solid. An analytically pure sample was taken from a pure fraction of the column and used for characterization. R_f = 0.39 (35% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.09 (br s, 1H), δ 7.86 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 7.9 Hz, 2H),4.17 – 4.04 (m, 2H), 2.43 (s, 3H), 1.92 (s, 3H), 1.57 (s, 3H), 1.35 (s, 9H), 1.15 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 191.55, 168.40, 166.71, 146.94, 145.13, 134.60, 130.03, 128.70, 82.81, 64.56, 61.81, 27.84, 21.78, 20.21, 14.02, 9.71. **+ESI-HRMS** m/z: calc'd for ($M+Na^+$) $C_{20}H_{28}N_2O_7SNa^+$= 463.15149, found $C_{20}H_{28}N_2O_7SNa^+$ = 463.15161. **FTIR (Neat)**: 3217, 2981, 1750, 1732, 1693, 1598, 1454, 1396, 1370, 1352, 1258, 1169, 1114, 1086, 1035, 884, 848, 816, 714, 662, 569, 548.

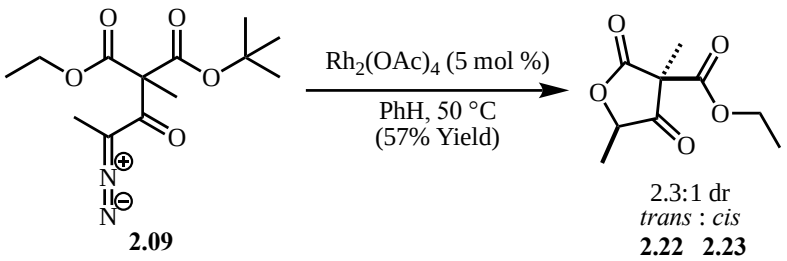
*Note: For the synthesis of **2.40** see reference #8

*Preparation of Diazomalonate **2.09***



Tosyl hydrazone **2.41** (1 g, 2.27 mmol) was added to a 75 mL pear shaped flask and dissolved in dry DCM (4 mL). Then Al_2O_3 (2.96 g, 29.0 mmol) Brockmann LVL I was added, the flask was wrapped in foil and the reaction mixture was allowed to stir for 16 hours. The mixture slowly became yellow in color. Then an additional 3.09 g (30.3 mmol) of Al_2O_3 Brockmann LVL III were added and the mixture stirred for an additional hour. The mixture was then poured into a fritted filter filled with Brockmann LVL III Al_2O_3 and eluted using DCM. The material was purified by silica gel flash chromatography using a 5% ethyl acetate: hexanes. This yielded 463 mg (63% yield) of desired diazo compound **2.09** as a bright yellow oil. **^{1}H NMR** (400 MHz, Chloroform-d) δ 4.24 (qd, J = 7.1, 0.9 Hz, 2H), 2.01 (s, 3H), 1.65 (s, 3H), 1.47 (s, 9H), 1.29 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 168.48, 167.04, 83.48, 65.98, 62.38, 27.83, 19.14, 14.06, 9.99. **+ESI-HRMS** m/z: calc'd for ($M+Na^+$) $C_{13}H_{20}N_2O_5Na^+$= 307.12699, found $C_{13}H_{20}N_2O_5Na^+$ = 307.12674 **FTIR (Neat)**: 2981, 2938, 2078, 1730, 1626, 1450, 1371, 1330, 1163, 1112, 1021, 845.

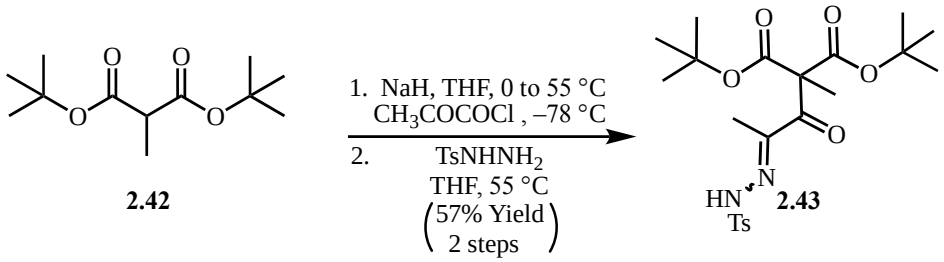
*Preparation of Tetronic acids **2.22, 2.23***



To an oven dried 1.5-dram vial was added a stir bar the diazomalonate **2.09 (**46.3 mg, 0.163 mmol), and 1.5 mL of dry benzene. The reaction vial was then evacuated of air and backfilled with nitrogen three times. Rhodium acetate dimer (3.5 mg, 5 mol %) was then added to the reaction vial and the vial purged with a stream of nitrogen. The reaction mixture was stirred for 10 minutes at RT then warmed to 50 °C in a preheated aluminum heating block for 24 hours. After 24 hours the reaction mixture was filtered through Celite® to remove the rhodium catalyst and the Celite® washed with benzene. The solvent was then evaporated under reduced pressure and the crude reaction mixture purified by flash chromatography using a gradient beginning at 0% ethyl acetate: hexanes and progressing to 5% ethyl acetate: hexanes. This yielded 18.6 mg (57%) of tetronic acids **2.22** and **2.23** as a mix of diastereomers and as a clear oil. The Crude NMR showed that the reaction gave what appears to be a mixture of diastereomers in a 2.3:1 ratio. The major isomer was the trans isomer with respect to the methyl groups and was used for characterization. Full characterization of the minor isomer was not possible due to difficulty of purification. A crude proton NMR showing the mixture of diastereomers is included with the spectra R_f = 0.1 (5% EtOAc/hexanes), $KMnO_4$; **^{1}H NMR** (600 MHz, Chloroform-d) δ 4.87 (q, J = 7.1 Hz, 1H), 4.29 – 4.19 (m, 2H), 1.64 (d, J = 7.0 Hz, 3H), 1.59 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, Chloroform-d) δ 205.82, 170.95, 163.86, 81.52, 63.53, 55.60,

17.32, 16.53, 13.98. +ESI-HRMS m/z: calc'd for ($M+Na^+$) $C_9H_{12}O_5Na^+$= 223.05824, found $C_9H_{12}O_5Na^+$ = 223.05771 **FTIR (Neat)**: 2990, 2942, 1807, 1760, 1450, 1378, 1330, 1261, 1219, 1126, 1099, 1079, 1014, 992.

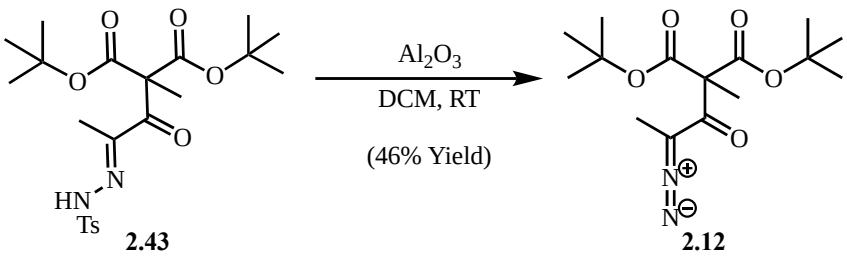
*Preparation of Tosyl Hydrazone **2.42***



Malonate ester **2.42** (0.503 g, 2.18 mmol) was dissolved in dry THF (9 mL). The reaction solution was then cooled in an ice water bath and let stir for ten minutes. Then sodium hydride (100 mg, 2.50 mmol) as a 60% dispersion in mineral oil was added portion wise. After addition of the sodium hydride was complete the solution was allowed to warm to room temperature and then heated to 55 °C (oil bath temperature) for 80 minutes. After heating was complete the reaction mixture was allowed to cool to RT, then it was cooled to –78 °C using a dry ice acetone bath and allowed to stir for ten minutes at –78 °C. Following this pyruvoyl chloride (0.26 mL, 3.4 mmol) was added. Upon addition of the acyl chloride the solution turned bright yellow and thickened. The reaction mixture was allowed to stir for an additional twenty minutes at –78 °C and then slowly allowed to warm up to room temperature and left to stir for 30 minutes. It was then quenched with 3 mL water and 15 mL diethyl ether were added. The organic layer was washed twice with 3 mL of water, and the aqueous layers were combined and extracted with 15 mL diethyl ether. The organic layers were then combined, and washed with brine and dried over sodium and

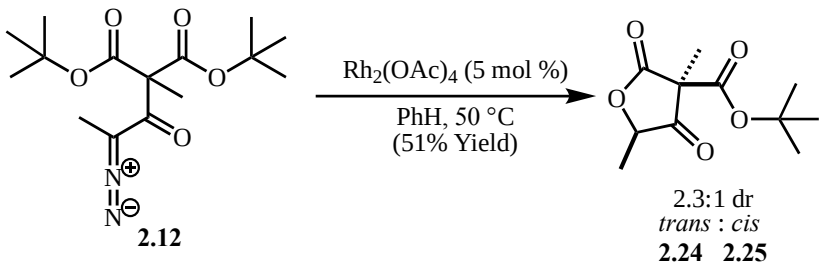
magnesium sulfate. The solvent was then evaporated under reduced pressure and dry THF (9 mL) added. To the solution was added tosyl hydrazide (420 mg, 2.26 mmol) at RT and the solution heated for 21.5 hours at 55 °C (oil bath temperature). It was then cooled to room temperature and the solvent removed under reduced pressure. Flash chromatography was performed on the crude material using an MPLC and a gradient beginning at 0% ethyl acetate: hexanes and progressing to 20% ethyl acetate: hexanes. A 24-gram column with a flow rate of 30 mL/min was used. This gave 585 mg (57% yield) of the product (**2.43**) as a clear glassy solid and as mixture of E and Z isomers which were both carried on through the reaction sequence. A sample containing only the desired compounds as a mixture of E and Z isomers was taken from the purest fraction of the column and used for characterization. **^{1}H NMR** (400 MHz, Acetone-d6) δ 10.11 (br s, 2H), 9.12 (broad s, 1H), δ 7.82 (d, J = 8.4 Hz,4H), 7.76 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 7.9 Hz, 4H), 7.38 (d, J = 7.9 Hz, 2H), 2.43 (s, 6H), 2.41 (s, 3H), 1.98 (s, 6H), 1.94 (s, 3H), 1.49 (s, 6H), 1.43 (s, 3H), 1.42 (s, 18H), 1.39 (s, 36H). (Integration value of *t*-butyl groups of major isomer set to 36 protons.) **^{13}C NMR** (151 MHz, Chloroform-d) δ 191.97, 168.71, 166.97, 153.53, 147.71, 145.20, 144.21, 135.36, 134.51, 130.07, 129.62, 128.66, 128.03, 82.55, 82.42, 65.74, 63.45, 27.88, 21.78, 21.72, 20.19, 19.47, 15.06, 9.95. **+ESI-HRMS** m/z: calc'd for ($M+Na^+$) $C_{22}H_{32}N_2O_7SNa^+$= 491.18279, found $C_{22}H_{32}N_2O_7SNa^+$ = 491.18369 **FTIR (Neat)**: 3214, 2979, 2934, 1746, 1727, 1691, 1598, 1455, 1394, 1369, 1256, 1165.2, 1121, 1085, 1035, 910, 885, 846, 814, 713, 662, 547. *Note: For the synthesis of **2.42** see reference #9

*Preparation of Diazomalonate **2.12***



Tosyl hydrazone **2.43** (700 mg E and Z mixture, 1.5 mmol) was added to a round bottomed flask and dissolved in dry DCM (15 mL). Then Al_2O_3 (1.87 g, 18.3 mmol) Brockmann LVL I was added, the flask was wrapped in foil and the reaction mixture was allowed to stir for 14.5 hours. The mixture slowly became yellow in color. Then an additional 1.87 g (18.3 mmol) of Al_2O_3 Brockmann LVL III were added and the reaction mixture stirred for an additional 1.5 hours. The mixture was then poured into a fritted filter filled with Brockmann LVL III Al_2O_3 and the compound eluted using DCM. The material was purified by silica gel flash chromatography using 10% ethyl acetate in hexanes. This yielded 213.1 mg (46% yield) of the desired diazo compound **2.12** as a bright yellow oil which upon cooling in the fridge solidified to a bright yellow solid. **^{1}H NMR** (400 MHz, Chloroform-d) δ 2.02 (s, 3H), 1.61 (s, 3H), 1.48 (s, 18H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 167.29, 83.17, 66.71, 27.91, 19.31, 10.05. **+ESI-HRMS** m/z: calc'd for ($M+Na^+$) $C_{15}H_{24}N_2O_5Na^+$= 335.15829, found $C_{15}H_{24}N_2O_5Na^+$ = 335.15793 **FTIR (Neat)**: 2978, 2926, 2854, 2079, 1724, 1622, 1457, 1394, 1369, 1328, 1277, 1255, 1161, 1117, 1020, 939, 845, 799, 738, 571, 527, 468.

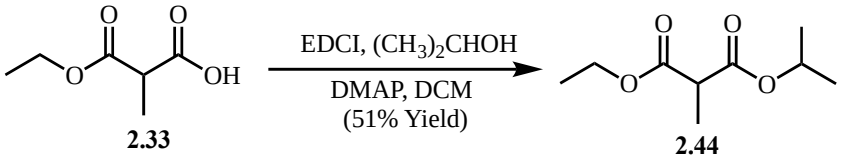
*Preparation of Tetronic acids **2.24**, **2.25***



To an oven dried 1.5-dram vial was added a stir bar, the diazomalonate **2.12** (47.7 mg, 0.153 mmol) and dry benzene (1.4 mL). The reaction vial was then evacuated of air and backfilled with nitrogen three times. Rhodium acetate dimer (3.5 mg, 5 mol %) was then added to the reaction mixture and the vial purged with a stream of nitrogen. The reaction mixture was stirred for 10 minutes at RT then warmed to 50 °C in a preheated aluminum heating block for 24 hours. After 24 hours the reaction mixture was filtered through Celite® to remove the rhodium catalyst and the Celite® washed with benzene. The solvent was then evaporated under reduced pressure and the crude reaction mixture purified by flash chromatography using a gradient beginning at 0% ethyl acetate: hexanes and progressing to 5% ethyl acetate: hexanes. This yielded 17.8 mg (51% yield) of the tetronic acids **2.24** and **2.25** as a mixture of diastereomers and as a clear viscous oil that slowly crystalizes. Crude NMR showed that the reaction appeared to give the mixture of diastereomers in a 5:1 ratio. The major isomer was determined by X-ray crystallographic analysis to be the trans isomer with respect to the methyl groups. An analytically pure sample and crystals for X-ray crystallographic analysis of the major diastereomer were obtained by vapor diffusion using dichloromethane as the solvent and pentane as the precipitant. Due to difficulty of purification the minor diastereomer was not fully characterized. A crude proton NMR showing the mixture of diastereomers is included with

the spectra. R_f = 0.15 (5% EtOAc/hexanes), $KMnO_4$;**^{1}H NMR** (400 MHz, Chloroform-d) δ 4.83 (q, J = 7.0 Hz, 1H), 1.63 (d, J = 7.0 Hz, 3H), 1.53 (s, 3H), 1.45 (s, 9H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 206.39, 171.40, 162.72, 85.15, 81.39, 56.49, 27.88, 17.28, 16.49. **+ESI-HRMS** m/z: calc'd for ($M+Na^+$) $C_{11}H_{16}O_5Na^+$= 251.08954, found $C_{11}H_{16}O_5Na^+$ = 251.08911 **FTIR (Neat)**: 2983, 2941, 1806, 1759, 1478, 1451, 1396, 1372, 1260, 1234, 1154, 1124, 1098, 1077, 994.

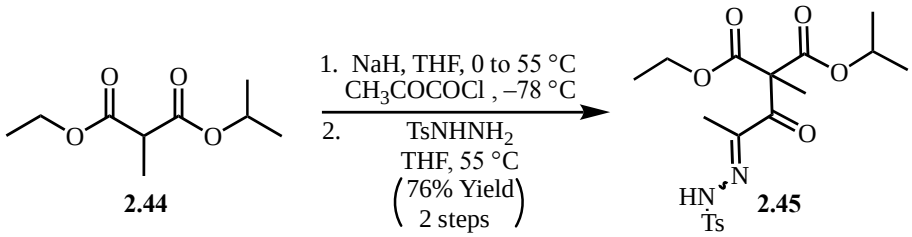
*Preparation of Malonate **2.33***



Carboxylic acid **2.33** (1.1 g, 7.6 mmol) was added to a round bottom flask and dissolved in dry DCM (18 mL). To this solution was added 2-propyl alcohol (1 mL 13.06 mmol), DMAP (77.6 mg, 0.64 mmol) and N-(3- Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (1.65 g, 8.61 mmol). The solution was left to stir for 11.5 hours. The crude reaction mixture was washed three times with 35 mL 1M HCL and the combined aqueous washes extracted once with 35 mL DCM. The combined organic layers were then washed twice with 35 mL saturated sodium bicarbonate, once with 70 mL of brine and dried over sodium sulfate. The solvent was then removed under reduced pressure. This yielded 734.5 mg (51% yield) of product **2.44** as a clear oil. No further purification was performed. **^{1}H NMR** (400 MHz, Chloroform-d) δ 5.05 (hept, J = 6.3 Hz, 1H), 4.25 – 4.13 (m, 2H), 3.38 (q, J = 7.3 Hz, 1H), 1.40 (d, J = 7.3 Hz, 3H), 1.29 – 1.21 (m, 9H overlap of a doublet and a triplet). **^{13}C NMR** (101 MHz, Chloroform-d) δ 170.40, 169.86, 68.94, 61.41, 46.54, 21.70, 14.22, 13.62. **+ESI-HRMS** m/z: calc'd for ($M+Na^+$) $C_9H_{16}O_4Na^+$ =

211.09463, found $C_9H_{16}O_4Na^+$ = 211.09419 **FTIR (Neat)**: 2983, 1748, 1728, 1456, 1376, 1321, 1219, 1163, 1094, 1036, 936, 902, 867, 828.

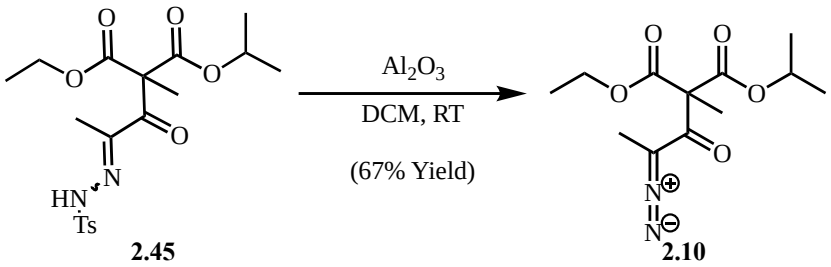
*Preparation of Tosyl Hydrazone **2.45***



Malonate ester **2.44** (962 mg, 5.11 mmol) was added to a 50 mL round bottom flask and dissolved in dry THF (21.5 mL). The reaction solution was then cooled in an ice water bath and let stir for ten minutes. Then sodium hydride (240 mg, 6.0 mmol) as a 60% dispersion in mineral oil was added portion wise. After addition of the sodium hydride was complete the solution was allowed to stirred for five minutes, warmed to RT and then heated to 55 °C (oil bath temperature) for 1.5 hours. After heating was complete the reaction mixture was allowed to cool to RT, it was cooled to –78 °C using a dry ice acetone bath and allowed to stir for ten minutes at –78 °C. After which pyruvoyl chloride (0.53 mL, 7.0 mmol) was added. Upon addition of the acyl chloride the solution turned bright yellow and thickened. The reaction mixture was stirred for an additional twenty minutes at –78 °C and then slowly allowed to warm up to RT over thirty minutes. It was then quenched with water and 20 mL diethyl ether were added, and the organic layer then washed twice with water. The aqueous layers were combined and extracted with diethyl ether. The organic layers were then combined and washed twice with brine and dried over sodium and magnesium sulfate. The solvent was then evaporated to give a clear yellow oil which was re-dissolved in dry THF (21.5 mL). To this solution was added tosyl hydrazide (953 mg,

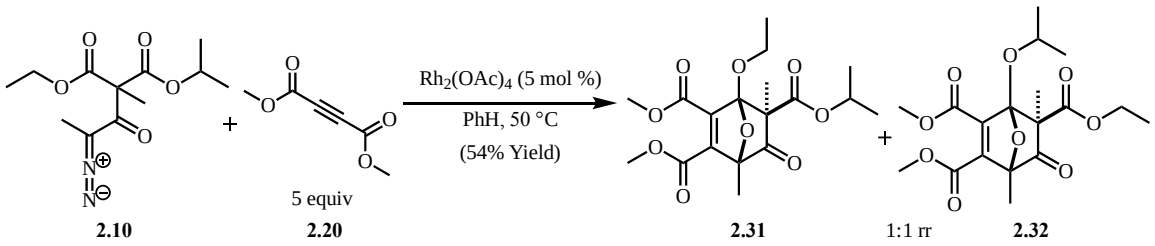
5.2 mmol) at RT and the solution heated for 16 hours at 55 °C (oil bath temperature). It was then allowed to cool to RT and the solvent evaporated under reduced pressure. Flash chromatography was performed on the crude material using an MPLC and a gradient beginning at 0% ethyl acetate: hexanes and progressing to 35% ethyl acetate: hexanes. A 24-gram column with a flow rate of 35 mL/min was used. This gave 1.66 g (76%) of product **2.45** as a clear glassy solid. An analytically pure sample for characterization was taken from purest fraction of the column. R_f = 0.32 (35% EtOAc/hexanes), UV;**^{1}H NMR** (400 MHz, Chloroform-d) δ 8.02 (br s, 1H), δ 7.87 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 4.96 (p, J = 6.3 Hz, 1H), 4.20 – 4.05 (m, 2H), 2.44 (s, 3H), 1.91 (s, 3H), 1.61 (s, 3H), 1.19 – 1.07 (m, 9H doublet and triplet overlapping). **^{13}C NMR** (151 MHz, Chloroform-d) δ 191.31, 168.17, 167.42, 146.47, 145.13, 134.55, 129.99, 128.67, 69.68, 63.85, 62.01, 21.82, 21.49, 21.43, 20.16, 13.99, 9.59. **+ESI-HRMS** m/z: calc'd for ($M+Na^+$) $C_{19}H_{26}N_2O_7SNa^+$ = 449.13584, found $C_{19}H_{26}N_2O_7SNa^+$ = 449.13519 **FTIR (Neat)**: 3205, 2983, 1751, 1731, 1693, 1598, 1452, 1375, 1265, 1170, 1101, 1035, 904, 816, 715, 662, 547.

*Preparation of Diazomalonate **2.10***



Tosyl hydrazone **2.45** (1.66 g, 3.88 mmol) was added to a pear shaped flask and dissolved in of dry DCM (39 mL). Then Al_2O_3 (5.17 g, 50.7 mmol) Brockmann LVL I were added, the flask was wrapped in foil and the reaction mixture was allowed to stir for 13.5 hours. The mixture slowly became yellow in color. Then an additional 5.17 g (50.7 mmol) of Al_2O_3 Brockmann LVL III were added and the mixture stirred for an additional three hours. The mixture was then poured onto a fritted filter filled with Brockmann LVL III Al_2O_3 and the compound eluted using DCM. The material was purified by silica gel flash chromatography using 1:9 ethyl acetate: hexanes as the eluent. This yielded 698 mg (67% yield) of the desired diazo compound **2.10** as a bright yellow oil. R_f = 0.24 (15% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, Chloroform-d) δ 5.09 (septet, 1H), 4.25 (qd, J = 7.1, 1.5 Hz, 2H), 2.02 (s, 3H), 1.68 (s, 3H), 1.32 – 1.22 (m, 9H doublet and triplet overlapping). **^{13}C NMR** (101 MHz, Chloroform-d) δ 168.30, 167.65, 70.41, 65.29, 62.52, 21.55, 19.08, 14.05, 10.02. **+ESI-HRMS** m/z: calc'd for ($M+Na^+$) $C_{12}H_{18}N_2O_5Na^+$ = 293.11134, found $C_{12}H_{18}N_2O_5Na^+$ = 293.11096 **FTIR (Neat)**: 2984, 2940, 2075, 1726, 1620, 1449, 1376, 1326, 1252, 1226, 1182, 1096, 1017.

*Preparation of Oxabicyclic Compounds **2.31**, **2.32***



To an oven dried 1.5-dram vial was added a stir bar, the of diazomalonate **2.10 (**44.1 mg, 0.163 mmol), dry benzene (1.5 mL) and dimethyl acetylenedicarboxylate (0.1mL (0.81 mmol). The reaction vial was then evacuated of air and backfilled with nitrogen three times and then rhodium acetate dimer (3.5 mg, 5 mol %) was added to the reaction mixture and the vial purged with a stream of nitrogen. The reaction mixture was stirred for ten minutes at RT then warmed to 50 °C in a preheated aluminum heating block for 24 hours. After 24 hours the reaction mixture was filtered through Celite® to remove the rhodium catalyst and the Celite® washed with benzene. The solvent was then evaporated under reduced pressure and the crude reaction mixture purified by flash chromatography using an MPLC. A 4-gram column set to a flow rate of 18 mL/min with a gradient beginning at 0% ethyl acetate: hexanes and progressing to 5% ethyl acetate: hexanes was used. This yielded 34.2 mg (54% yield) of oxabicyclic products **2.31**, **2.32** as a 2:1 mixture of isomers. The crude proton NMR showed a mixture of isomers in a 1:1 ratio. R_f = 0.19 (15% EtOAc/hexanes), UV; **^{1}H NMR** (600 MHz, Chloroform-d) δ 5.03 (p, J = 6.3 Hz, 1H), 4.27 – 4.18 (m, 5H), 4.17 – 4.09 (m, 2H), 4.00 – 3.93 (m, 1H), 3.84 (s, 7H), 3.83 (s, 4H), 3.82 (s, 3H), 3.81 (s, 7H), 1.69 (s, 6H), 1.68 (s, 3H), 1.41 (s, 6H), 1.39 (s, 3H), 1.27 – 1.19 (m, 33H). (Pentet proton of minor isomer set to an integration of 1.) **^{13}C NMR** (151 MHz, Chloroform-d) δ 203.18, 202.84, 167.94, 167.43, 162.58, 162.08 (d, J = 3.7 Hz), 161.83,

147.62, 145.85, 145.70, 144.43, 113.52, 113.12, 86.80, 86.66, 72.09, 69.61, 63.41, 61.82, 54.33, 53.93, 53.01, 52.98, 52.88, 23.95, 23.19, 21.69, 21.65, 17.90, 17.67, 15.37, 14.25, 11.80, 11.54. **+ESI-HRMS** m/z: calc'd for ($M+Na^+$) $C_{18}H_{24}O_9Na^+$ = 407.13180, found $C_{18}H_{24}O_9Na^+$ = 407.13235 **FTIR (Neat)**: 2983, 2956, 1778, 1730, 1638, 1438, 1327, 1249, 1129, 1107, 1049, 1007.

2.4 References

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CHAPTER THREE

Total Syntheses of (±)-Aspergilline A, Cyclopiamide A and Speradine E

3.1 Isolation and Bioactivity of (±)-Aspergilline A, Cyclopiamide A, and Speradine E

3.1.1 The Cyclopiazonic Acid Family of Natural Products

Aspergilline A **3.01**, cyclopiamide A **3.02** and speradine E **3.03** (Figure 3.1) are considered to be cyclopiazonic acid-type natural products, specifically falling under the cyclopiazonic acid oxindole sub class.[1] α-Cyclopiazonic acid (CPA **3.04**) was isolated

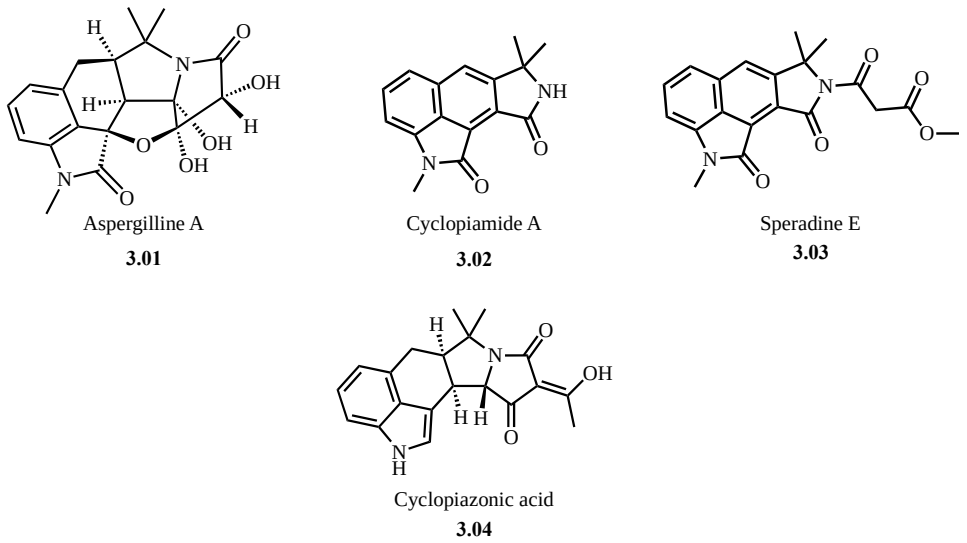


Figure 3.1 CPA type natural products

from *Penicillium cyclopium* in 1968 by Holzapfel and was found to be cytotoxic through its disruption of calcium ion flux in the cell.[2,3] CPA has been observed in various foods including cheeses, milk, meats and grains.[1] Despite its presence in various foods, poisoning by CPA is rare and has not been explicitly identified in humans.[3,4] Specifically, CPA is a

reversible inhibitor of sarco/endoplasmic reticulum Ca^{2+}-ATPase. Disruption of this membrane Ca^{2+} pump causes an imbalance between cytosolic and endoplasmic reticulum calcium ion concentrations. This calcium ion concentration is critical in controlling cell differentiation, death and proliferation; its disruption eventually leads to cell death.[1,3] Interestingly, CPA is a selective inhibitor of Ca^{2+}-ATPase showing no specific inhibition of kidney or brain Na^+/K^+ -ATPase or gastric H^+/K^+-ATPase.[4]

3.1.2 Aspergilline A - Isolation and Bioactivity

Aspergilline A (**3.01**) was isolated in 2014 from the *Aspergillus versicolor* by Hu and Gao.[5] The *Aspergillus versicolor* fungus was cultivated on a potato dextrose agar for seven days at room temperature. Agar plugs were placed into 250 mL Erlenmeyer flasks containing 100 mL of potato dextrose broth and cultured for 5 days at room temperature. Fermentation was then performed in 200 Fernback flasks; each contained 100 g of rice,120 mL of deionized water and which had been inoculated with 5 mL of the cultured broth. After 45 days at room temperature the fermented substrate was extracted with methanol to yield 560g of crude material. After flash chromatography and HPLC purification this yielded, 25.6 mg of Aspergilline A.

The aspergillines (**3.01**, **3.05** – **3.08** Figure 3.2) are considered highly oxygenated derivatives of the natural product cyclopiazonic acid (**3.04**). Though the biogenic origin of CPA is known,[2] that of the aspergillines has not been identified. The gene cluster for the biosynthesis of CPA has been identified in *Aspergillus flavus* and *Aspergillus oryzae* and the biogenic pathway elucidated. Feeding studies with radiolabeled substrates along with degradation studies showed that CPA was constructed biosynthetically from a tryptophan, a dimethylallyl diphosphate and two acetate units.[3]

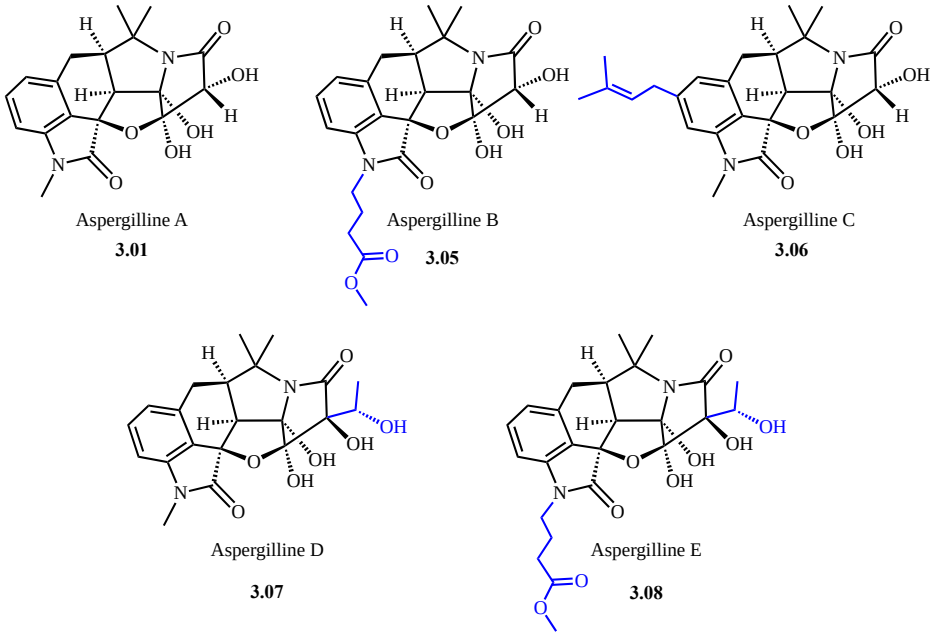


Figure 3.2 Aspergilline family

Aspergilline A, along with the other members of the family (Figure 3.2) were shown to be cytotoxic against several human cancer cell lines in the low micromolar range (Table 3.1). Specifically, the aspergillines possess moderate biological activity against A549 lung

Table 3.1 IC_{50} values (in μM) of the aspergillines

Compound	A549	NB4	MCF7	PC3	SHSY5Y
3.01	1.2	3.8	1.5	2.6	3.4
3.05	>10	7.2	4.5	2.6	5.4
3.06	2.8	1.2	3.6	2.8	1.5
3.07	1.5	2.2	2.9	4.2	3.6
3.08	2.8	4.7	6.5	>10	8.2

epithelial carcinoma, NB4 promyelocytic leukemia, MCF7 breast adenocarcinoma, PC3 prostate cancer and SHSY5Y neuroblastoma cancer cell lines. Aspergilline A is the most

potent congener overall.[5] At this current juncture no mechanism of action for the aspergillines' cytotoxicity has been elucidated.

3.1.3 Cyclopiamide A –Isolation

Cyclopiamide A (**3.02**, Figure 3.3) is a tetracyclic indole alkaloid which bears a core structure similar to a core structural fragment present in aspergilline A (red highlight **3.01** Figure 3.3). Cyclopiamide A was isolated in 1990 by Holzapfel and coworkers from *Penicillium cyclopium*.[6] The fungus was grown on crushed maize seeds and the culture

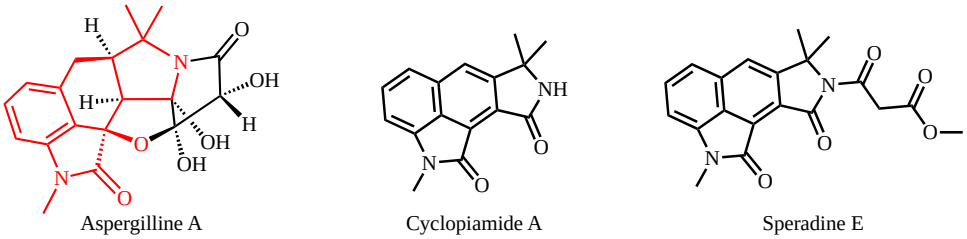


Figure 3.3 Common tetracyclic core structure

media was dried and milled prior to being extracted with chloroform/methanol. The extract was dissolved in HCl (aq) and washed with chloroform. After neutralization the aqueous layer was extracted with chloroform and the extract present in the organic layer purified by flash silica gel chromatography and sephadex to give cyclopiamide A (**3.02**, Figure 3.3). To date, no notable bioactivity has been reported for this compound.

3.1.4 Speradine E –Isolation and Biological activity

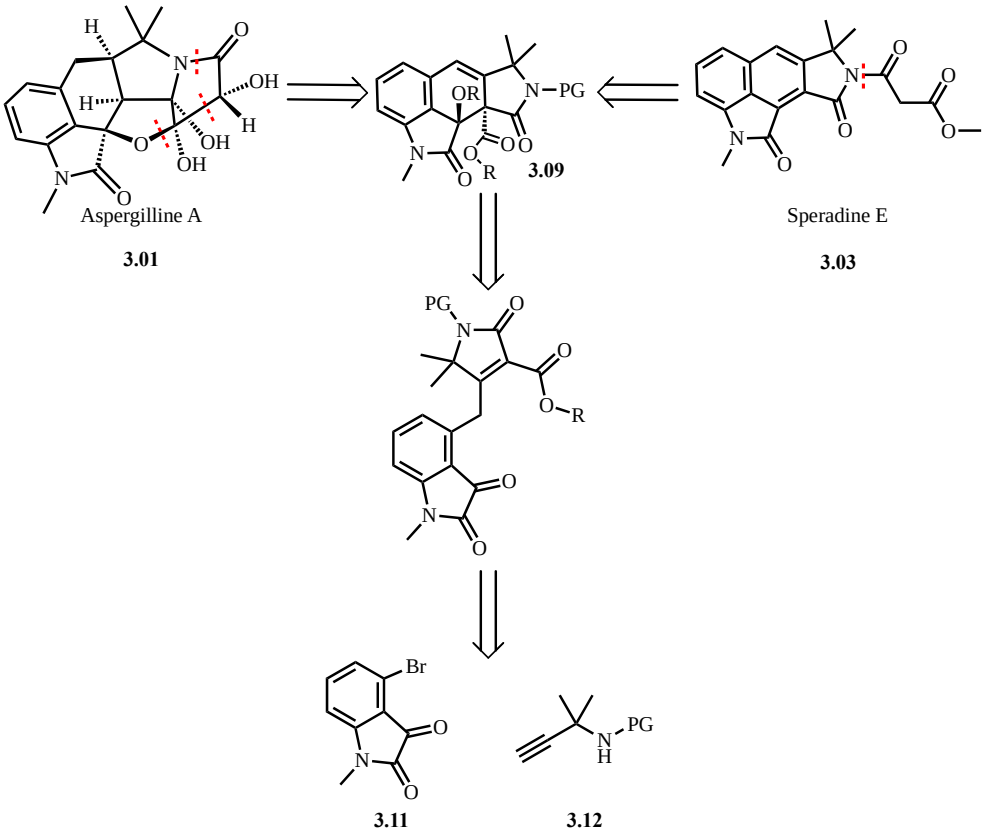
Speradine E (**3.03**, Figure 3.3) is a tetracyclic indole alkaloid differing in structure from cyclopiamide A **3.02** only by a pendant methyl β-keto ester on the free amide's nitrogen. Speradine E was isolated from the fungus *Aspergillus oryzae* by Chen and Zhang

in 2014.[7] The fungus was cultured in 1 L conical flasks containing a liquid medium of yeast extract, mannitol, maltose, glucose, monosodium glutamate, mono basic potassium hydrogen phosphate and magnesium sulfate heptahydrate in sea water. After 30 days the culture broth was filtered through a cheese cloth and the filtrate extracted with ethyl acetate. The filter cake was extracted with acetone and the solvent removed to give an aqueous extract. The aqueous extract was then extracted with ethyl acetate and all ethyl acetate extracts combined and the solvent removed. This gave a crude extract (42.3 g) which was purified by silica gel chromatography, size exclusion chromatography (sephadex) and semi-preparative HPLC to give 3.2 mg of speradine E (**3.03**); It was then found that speradine E (**3.03**) exhibited weak cytotoxicity against HeLa cells with an IC_{50} value of 200 μM.

3.2 Total Synthesis of Aspergilline A, Cyclopiamide A and Speradine E via a Unified Strategy

3.2.1 A General Unified Approach

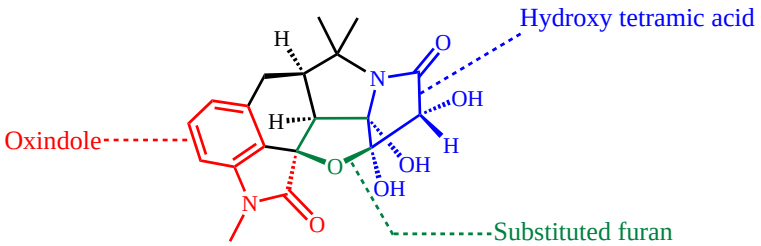
As depicted earlier in this chapter (Figure 3.3) aspergilline A (**3.01)**, cyclopiamide A (**3.02**) and speradine E (**3.03**) bear a similar tetracyclic core structure. During the course of our work on the total synthesis of aspergilline A it became apparent that a unified strategy could be developed for the synthesis of these three natural products. Considering this, we devised a general retrosynthetic plan (Scheme 3.01) wherein both aspergilline A (**3.01)** and speradine E (**3.03**) would be accessed from a common tetracyclic ester (**3.09**). Tetracycle **3.09** would then be derived from a pyrrolinone compound (**3.10**) through an intramolecular aldol reaction; Finally, we envisioned that the pyrrolinone would be accessed in a few steps from a protected propargyl amine (**3.12**) and a bromoisatin (**3.11**).



Scheme 3.01 Unified synthetic strategy

3.2.2 Aspergilline A: Evolution of Strategy and Total Synthesis

Other than our work on aspergilline A, no total synthesis or progress towards this family of natural products has been reported. The closest congener to be prepared by total synthesis is the simpler cyclopiazonic acid, which to date has been produced in both total and formal syntheses several times.[8] Although aspergilline A possesses somewhat interesting biological activity, our interest was piqued by its complex structural features which include a daunting 6/5/6/5/5/5 fused ring system, a hydroxy tetramic acid moiety, a hemi ketal, a hemi aminal and an oxindole moiety (Figure 3.4).

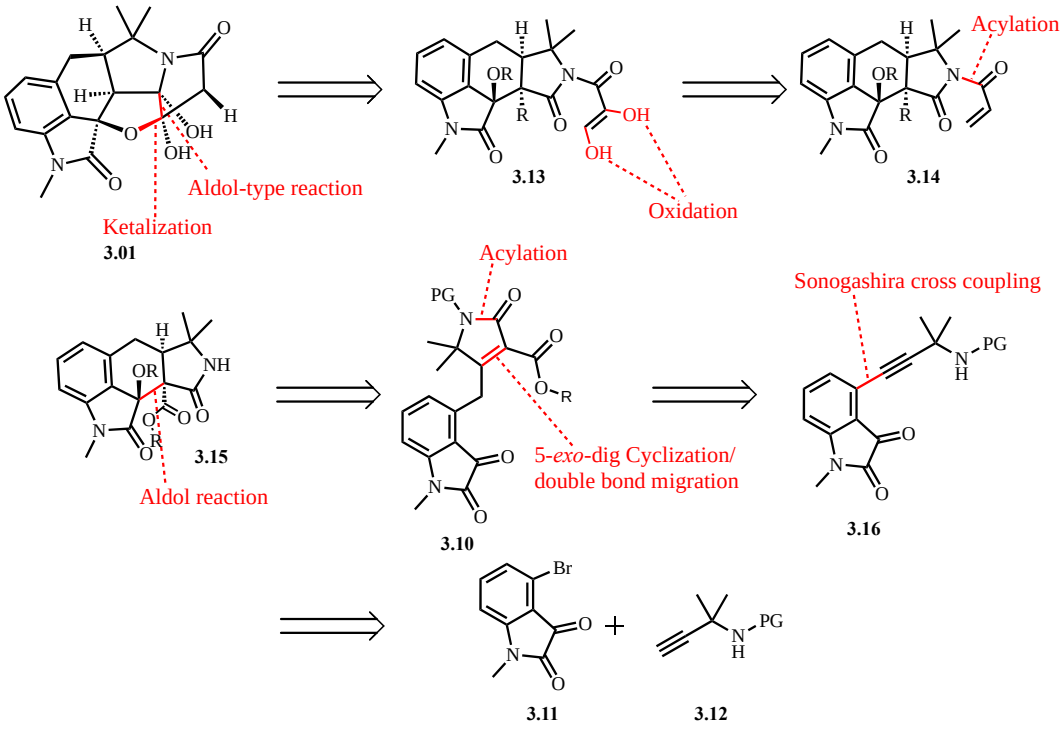


Aspergilline A

3.01

Figure 3.4 Salient features of aspergilline A

During our synthetic studies of aspergilline A, a number of strategies were explored, all of which diverted from a key tetracyclic amide **3.15** (Scheme 3.02). In the initial retrosynthetic strategy, we envisioned accessing aspergilline A through a late stage intramolecular aldol reaction and ketal formation from ene-diol **3.13** (Scheme 3.02). **3.13** could be accessed by oxidation of the alkene of acrylimide **3.14**, which itself could be derived from key tetracyclic amide **3.15** through acylation with acryloyl chloride. A reduction and intramolecular aldol reaction of pyrrolinone **3.10** would construct amide **3.15**. Pyrrolinone **3.10** would in turn be accessed from propargyl amine **3.16** by an acylation/ 5-*exo*-dig cyclization /double bond migration sequence. Finally, we envisioned that propargyl amine **3.16** would come about through a Sonogashira cross coupling of bromoisatin **3.11** and propargyl amine **3.12**. In the forward sense, we began with commercially available bromoisatin **3.19**. Methylation of **3.19** with methyl iodide gave bromoisatin **3.11** (Scheme 3.03). The Sonogashira cross coupling was then explored. Initial optimization was done with propargyl amine **3.17** (Table 3.2) but subsequently, due to the predicted need of an amide protecting group, dimethoxybenzyl protected propargyl amine **3.20** was chosen for utilization in the synthesis. Although reaction conditions for these

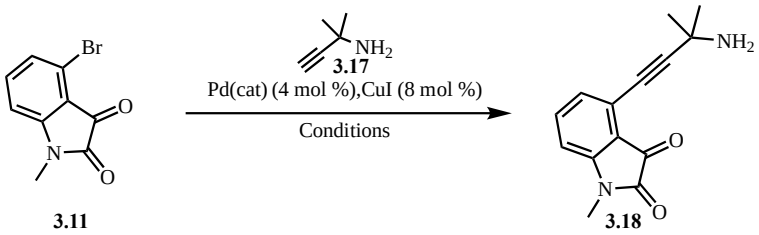


Scheme 3.02 Retrosynthetic analysis I

exact substrates were not known, similar Sonogashira cross coupling reactions utilizing propargyl amine **3.17** were precedented.[9] On the basis of this literature, we chose our initial reaction conditions to be 4 mol % of $Pd(Cl)_2(PPh_3)_2$, 8 mol % CuI, 8 mol % $P(Cy)_3$, 1.2 equiv of Cs_2CO_3, in a 2.75:1 mixture of Hünig's base: diglyme at 130 °C for two hours. This resulted in a poor 12% yield due to decomposition of the product under the reaction conditions (Entry 1, Table 3.2). During the course of the optimization we discovered several interesting facets to this reaction, the most interesting of which was that rapid addition of several equivalents of the propargyl amine substrate **3.17** appeared to complex the copper catalyst inducing apparent 1,2 addition of the alkyne into the isatin's ketone. A solvent screen revealed toluene to be an effective solvent for this transformation. Additionally, it was noted that a reduction in temperature led to less decomposition. After further exploration, the optimum reaction conditions were chosen to be 4 mol % of

$Pd(PPh_3)_4$, 8 mol % CuI, 1.2 equiv of Cs_2CO_3, 2 equiv of Hünig's in toluene at 70 °C with slow addition of the propargyl amine reaction partner and a reaction time of three hours. These conditions yielded a 95% yield of the desired cross coupling product **3.18**. Applying these conditions to the dimethoxybenzyl protected propargyl amine substrate gave cross

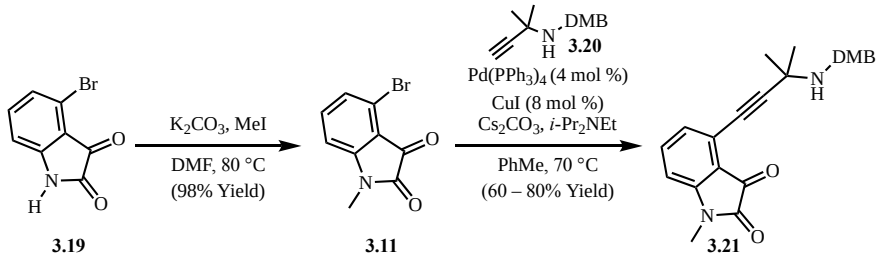
Table 3.2 Sonogashira cross coupling optimization



Catalyst	Base	Solvent	Ligand	Temperature	Time	Yield
$Pd(Cl)_2(PPh_3)_2$	Cs_2CO_3 (1.2 equiv)	2.75:1 DIPEA:diglyme	$P(Cy)_3$ (8 mol%)	130 °C	2 h	12%
$Pd(Cl)_2(PPh_3)_2$	Cs_2CO_3 (1.2 equiv)	2.75:1 DIPEA:diglyme	$P(Cy)_3$ (12 mol%)	105 °C	1 h 45min	43%
$Pd(PPh_3)_4$	Cs_2CO_3 (1.2 equiv)	2.75:1 DIPEA:diglyme	–	105 °C	1 h	30%
$Pd(PPh_3)_4$	Cs_2CO_3 (1.2 equiv) DIPEA (2 equiv)	DMF	–	70 °C	1 h	31%
$Pd(PPh_3)_4$	Cs_2CO_3 (1.2 equiv) DIPEA (2 equiv)	MeCN	–	70 °C	1 h	58%
$Pd(PPh_3)_4$	Cs_2CO_3 (1.2 equiv) DIPEA (2 equiv)	Toluene	–	70 °C	1 h	32%
$Pd(PPh_3)_4$	Cs_2CO_3 (1.2 equiv) DIPEA (2 equiv)	Toluene	–	70 °C	3 h	95%

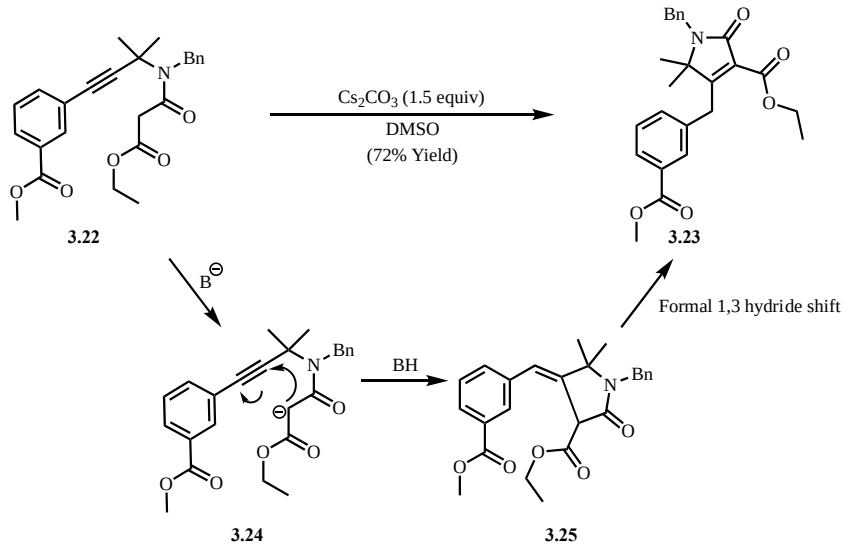
coupling product **3.21** in an acceptable 60 – 80 % yield (Scheme 3.03). Carrying **3.21** forward we sought to apply work from Arcadi and Marinelli.[10] Precedent from Arcadi and

Marinelli had shown that acylation of aryl propargyl amines with a malonyl chloride and subsequent exposure to cesium carbonate in DMSO gave pyrrolinones (**3.23** Scheme 3.04)



Scheme 3.03 Methylation and Sonogashira cross coupling

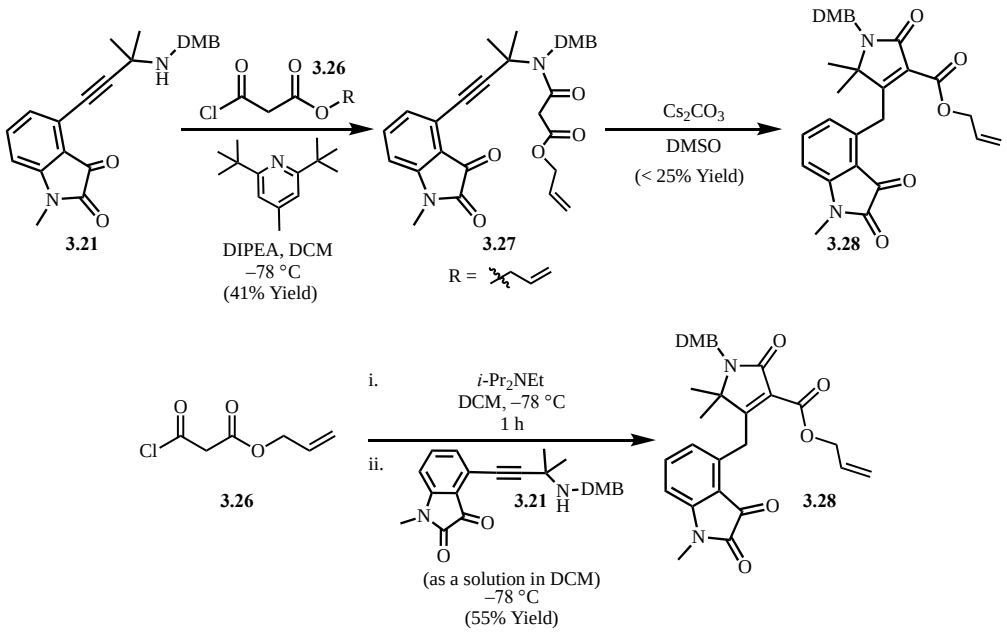
in high yields, presumably through a 5-*exo*-dig cyclization and subsequent double bond migration. In applying this chemistry, we exposed propargyl amine **3.21** to allyl malonyl chloride **3.26** to give malonamide **3.27**. Reaction of **3.27** with Cs_2CO_3 in DMSO gave pyrrolinone **3.28** but in poor yield (< 25%)



Scheme 3.04 Pyrrolinone formation – Arcadi & Marinelli

(Scheme 3.05). All attempts to optimize this reaction failed to increase the yield. While examining these reactions we were surprised to find that from the acylation reactions with

malonyl chlorides small amounts of the pyrrolinone were formed directly! A survey of the literature showed this to be an unprecedented transformation. Hoping to capitalize on this observation we sought to optimize the initial acylation reaction to give the pyrrolinone directly. To shed light on the reaction pathway a series of experiments were performed to determine exactly how the pyrrolinone was forming. It was initially thought that the intermediate malonamide **3.27** under the influence of excess Hünig's may be deprotonated, thereby inducing the 5-*exo*-dig cyclization and double bond migration. However, performing the reaction employing excess Hünig's base only returned starting material. Considering next the possibility of malonamide activation by ammonium salts present



Scheme 3.05 Unprecedented pyrrolinone formation

in the reaction, we exposed the malonamide **3.27** to Hünig's hydrochloride salt in the presence of excess Hünig's base; this once again resulted in only returned starting material. Re-exposing the malonamide **3.27** to the initial acylation reaction conditions also resulted

in no product formation. With these results in mind we began considering the possibility that a ketene was being generated *in situ* through the reaction of the tertiary amine and the acyl chloride. Eventually, we discovered that premixing the malonyl chloride with excess Hünig's base at –78 °C then slowly adding the propargyl amine substrate (**3.21**) afforded up to 55% yield of the desired pyrrolinone **3.28** (Scheme 3.05). To further examine this reaction, we performed React IR studies with methyl malonyl chloride (Figure 3.5).

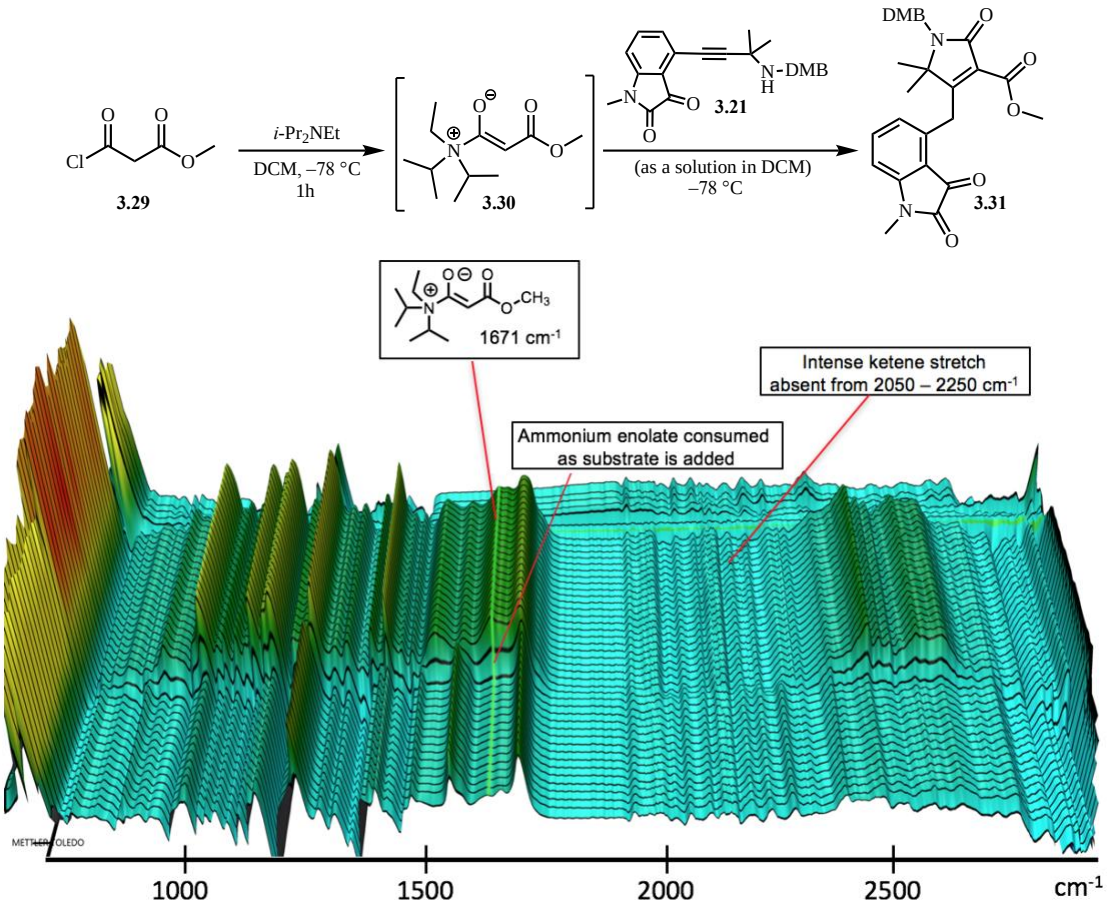
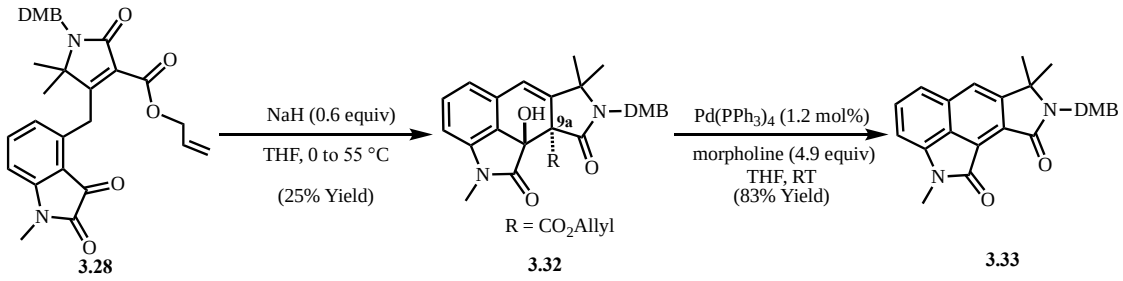


Figure 3.5 React IR data indicating ammonium enolate

We were intrigued to observe that no ketene was forming in this reaction as the characteristic intense stretch between 2050 – 2250 cm^{-1} was absent.[11] In addition to this, the lack of a stretch between 1790 – 1820 cm^{-1} indicated that no acyl ammonium species

was present in the reaction mixture![12] This led us to conclude that the likely active species generated under these reaction conditions was an ammonium enolate. IR stretches for ammonium enolates are reported in the literature with stretches in the 1600 – 1750 cm^{-1} range; enolates are also known to produce IR stretches between 1600 – 1700 cm^{-1}.[13,14] These values correlate well to the observed IR-stretch 1671 cm^{-1}. What is peculiar is that the reported ammonium enolates were observed to decompose upon warming above 160K (–113.15 °C) while it appeared that our enolate species was stable at –78 °C for over an hour. Upon addition of the propargyl amine substrate **3.21** to the React IR reaction vessel, the stretch at 1671 cm^{-1}quickly vanished suggesting consumption of the ammonium enolate intermediate.

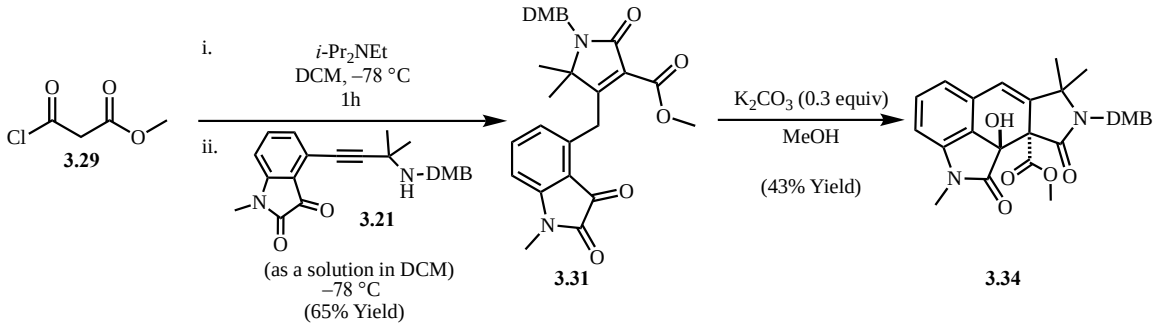
With a viable means of accessing the desired pyrrolinone substrates, we turned our attention to preparing the key tetracyclic amide. Intramolecular aldol cyclization of pyrrolinone **3.28** was induced by sodium hydride, to give tetracyclic allyl ester **3.32** as a single diastereomer in low yield but with large amounts of recovered starting material (Scheme 3.06). Hoping then to install the hydrogen atom at C9a we exposed allyl ester



Scheme 3.06 Aromatization of allyl ester

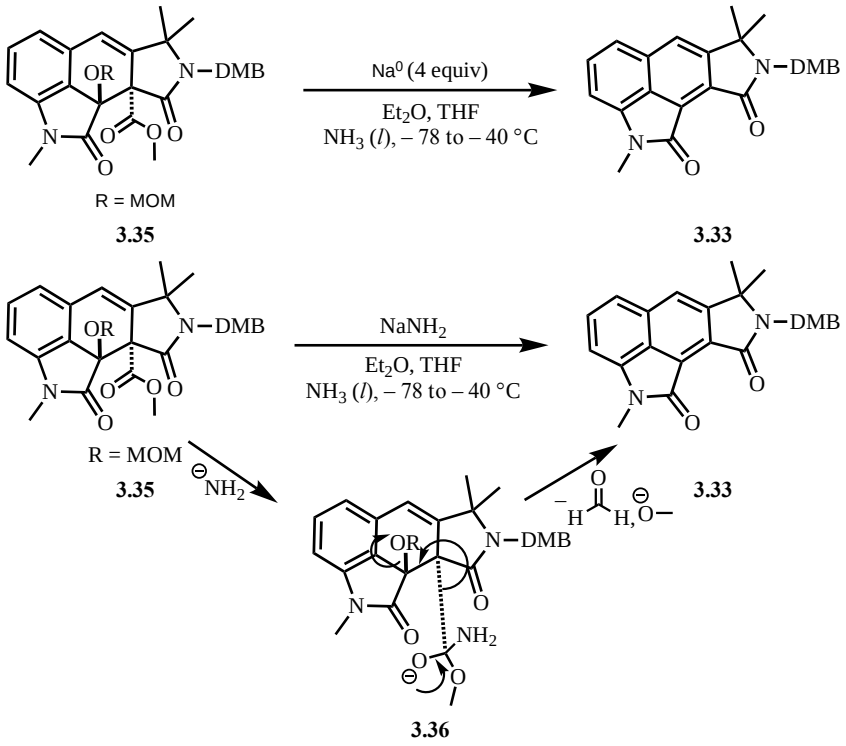
3.32 to catalytic palladium tetrakis. We were puzzled on observing the formation of a bright yellow compound, which was later determined to be aromatized compound **3.33**.

Mechanistically, it appears that de-allylative decarboxylation occurred followed by hydroxy group elimination. Though unexpected, we were excited by the potential of quickly elaborating this intermediate to cyclopiamide A and speradine E. Prior to exploring these latter possibilities we directed our efforts at avoiding aromatization and explored the possibility of reducing the trisubstituted alkene prior to decarboxylation. Given that the planned reduction would not be compatible with the allyl ester in **3.32** we prepared the corresponding tetracyclic methyl ester (**3.34**) through an analogous sequence (Scheme 3.07). Unfortunately, reduction of the trisubstituted alkene in **3.34** failed under a variety



Scheme 3.07 Tetracyclic methyl ester synthesis

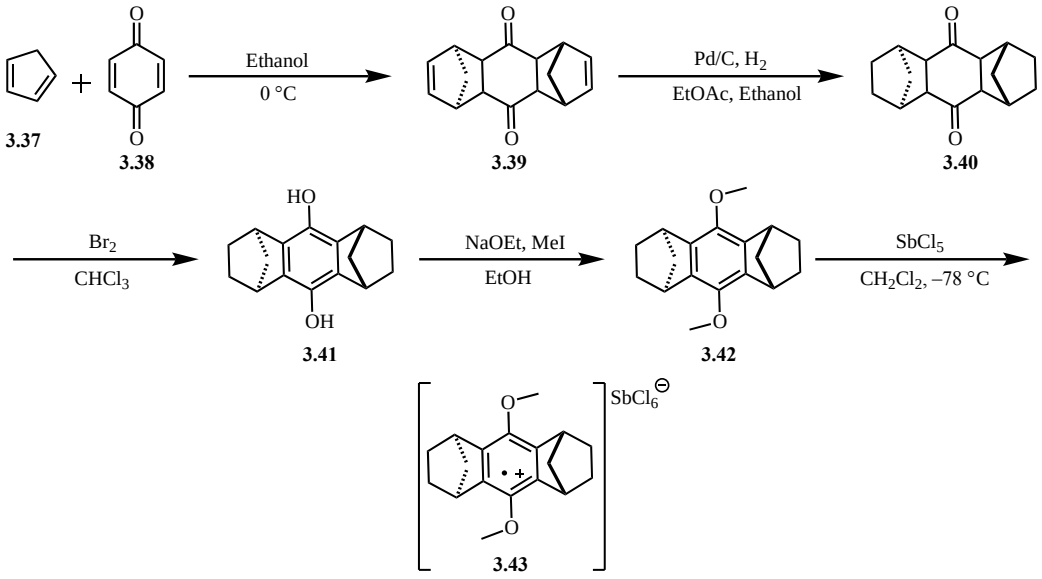
of conditions, including both ionic reduction and hydrogen atom transfer conditions. Application of Birch reduction conditions on a MOM protected variant (**3.35**) of tetracyclic ester **3.34** surprisingly also lead to aromatized compound **3.33**. This was later determined to be due to *in situ* generated sodium amide, which presumably generates the illustrated tetrahedral intermediate (**3.36**) en route to the aromatized compound (Scheme 3.08). Any products other than **3.33** obtained from these Birch reductions reactions appeared to be the result of over reduction of the initially formed aromatized compound **3.33**. Attempts to use ammonia-free conditions with lithium DBB in THF also lead to aromatization.



Scheme 3.08 Sodium amide-induced aromatization of **3.35**

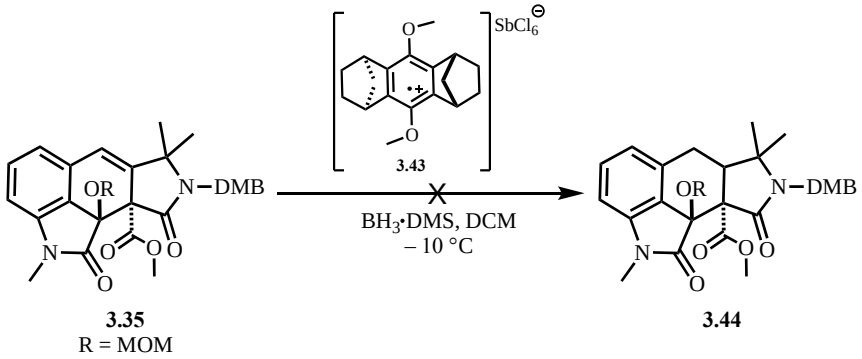
In fact, attempts to reduce the methyl ester of **3.32** with $NaBH_4$ in the presence of calcium chloride also lead to compound **3.33**!

A promising lead for the reduction of highly sterically hindered alkenes was found in an unusual dimethoxyanthracenium hexachloroantimonate radical cation (**3.43**), which was colloquially named orange CRET by the authors. This radical cation in the presence of borane dimethyl sulfide complex, was precedented to reduce hindered tetrasubstituted alkenes such as biadamantylidene![15] Wishing to explore this chemistry, the radical cation was synthesized according to a literature procedure; beginning from cyclopentadiene **3.37** and benzoquinone **3.38** a Diels-Alder reaction in cold ethanol gave dione **3.39** (Scheme 3.09).[16] The alkenes of **3.39** were then reduced via catalytic hydrogenation with palladium on carbon. Bromine-induced aromatization was followed by methylation of the resultant



Scheme 3.09 Literature preparation of orange CRET **3.40**

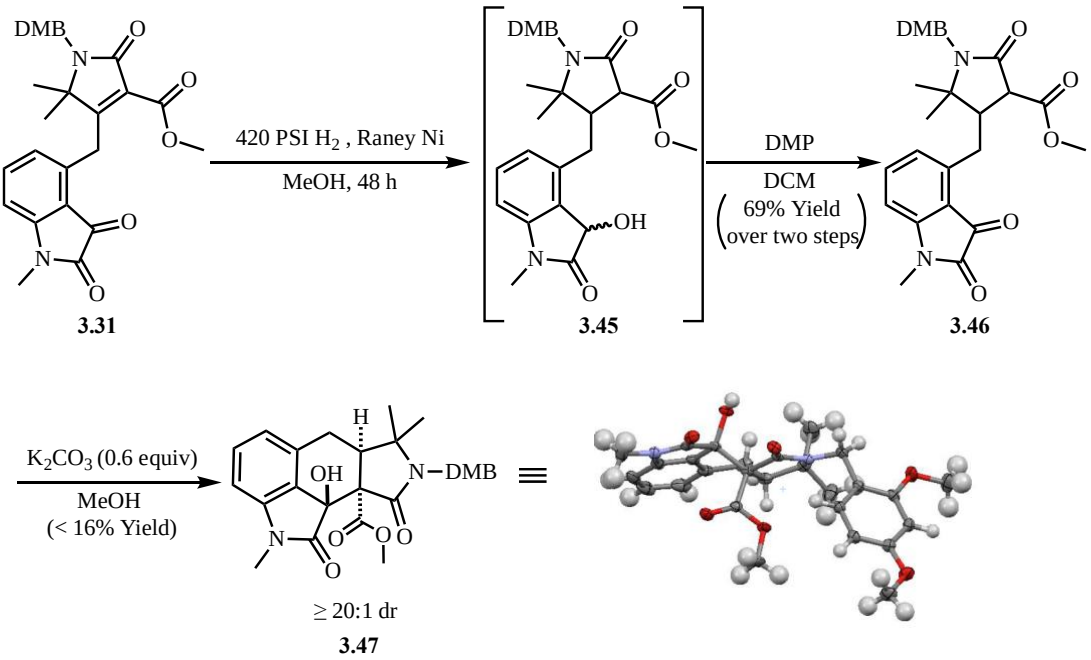
hydroquinone with methyl iodide to give dimethyl ether **3.42**. Subsequent exposure to antimony pentachloride provided orange CRET **3.43**. Reduction of the trisubstituted alkene was once again attempted. In the event tetracycle **3.35** was exposed to a mixture of orange CRET and borane dimethyl sulfide complex. The orange red color of the radical cation bleached indicating reaction completion, but no desired product was obtained. Unfortunately, numerous trials utilizing radical cation **3.43** were attempted but all gave returned starting material or decomposition. More conventional catalytic hydrogenation



Scheme 3.10 Attempted alkene reduction by orange CERT

conditions were also explored. Heterogeneous hydrogenation catalysts failed to provide the desired product from **3.34** except in the case of palladium on carbon at 1150 PSI of H_2. Reaction under the latter conditions for two days gave a 40% conversion of the starting alkene **3.34** to the reduced product. This suggested that prolonged reaction times of up to a week were needed for complete reduction at this pressure. Considering the need to perform this reaction on decagram scale, prolonged high pressure hydrogenation appeared impractical and dangerous.

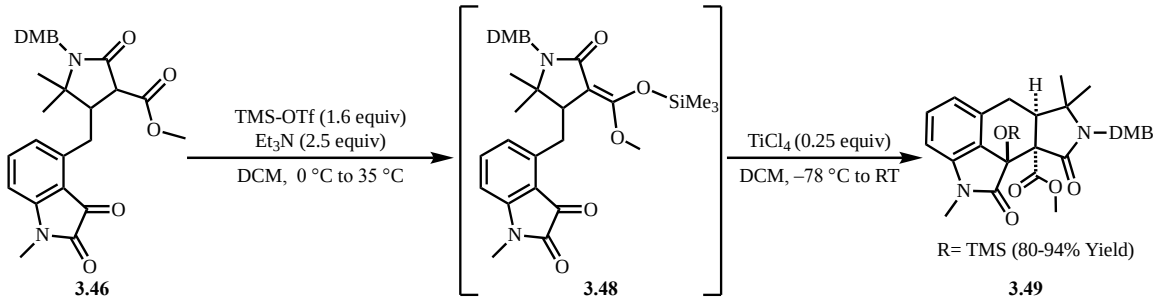
We surmised that the difficulty in reducing the alkene of **3.34** and **3.35** was due to the two adjacent quaternary centers. We therefore believed that reduction at the pyrrolinone stage may proceed under milder conditions (Scheme 3.11). Indeed, exposing pyrrolinone **3.31** to Raney nickel at 420 PSI gave the reduced product **3.45**. Unfortunately, it appeared



Scheme 3.11 Accessing reduced tetracycle 3.46

in this reaction that the isatin's ketone was reduced to the alcohol prior to reduction of the alkene. Thus, the crude pyrrolidone **3.45** was then exposed to DMP to give isatin **3.46**.

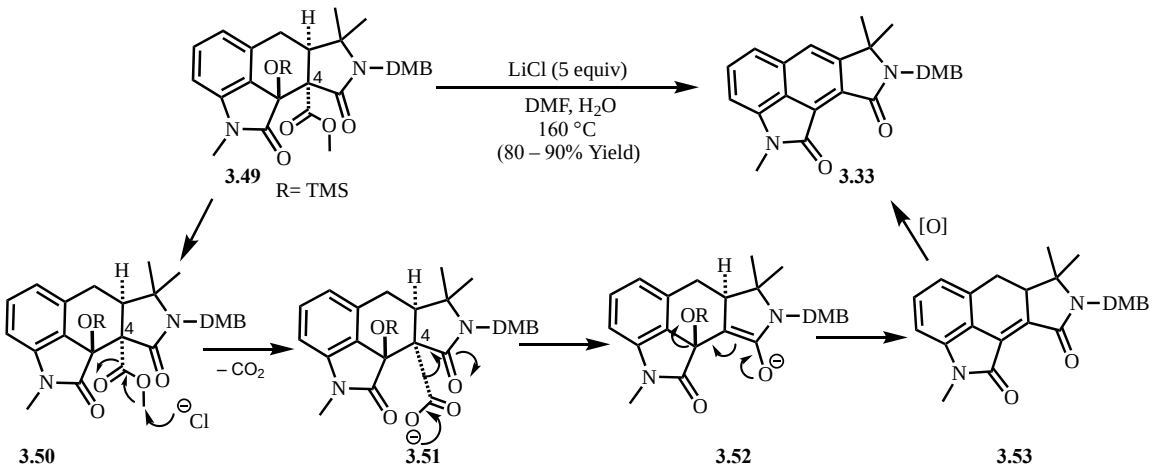
Treatment of **3.46** with methanolic potassium carbonate induced an intramolecular aldol cyclization furnishing reduced tetracycle **3.47** in very low yield. The relative stereochemistry of **3.47** was confirmed by X-ray analysis. A screening of various bases and solvents failed to increase the yield of the tetracyclic product (**3.47**). Persuaded that competing retro-aldol reaction was the cause of our observed low yields, we turned to a Mukaiyama aldol reaction in an effort to avoid anionic reaction intermediates (Scheme 3.12). Gratifyingly, silyl ketene acetal formation followed by exposure to titanium tetrachloride gave reduced tetracyclic ester **3.49** in high yield! TMS group deprotection under acidic conditions provided material which was spectroscopically identical to **3.47**, confirming the relative stereochemistry depicted. With the reduced tetracycle now in hand



3.46 **3.48** **3.49**

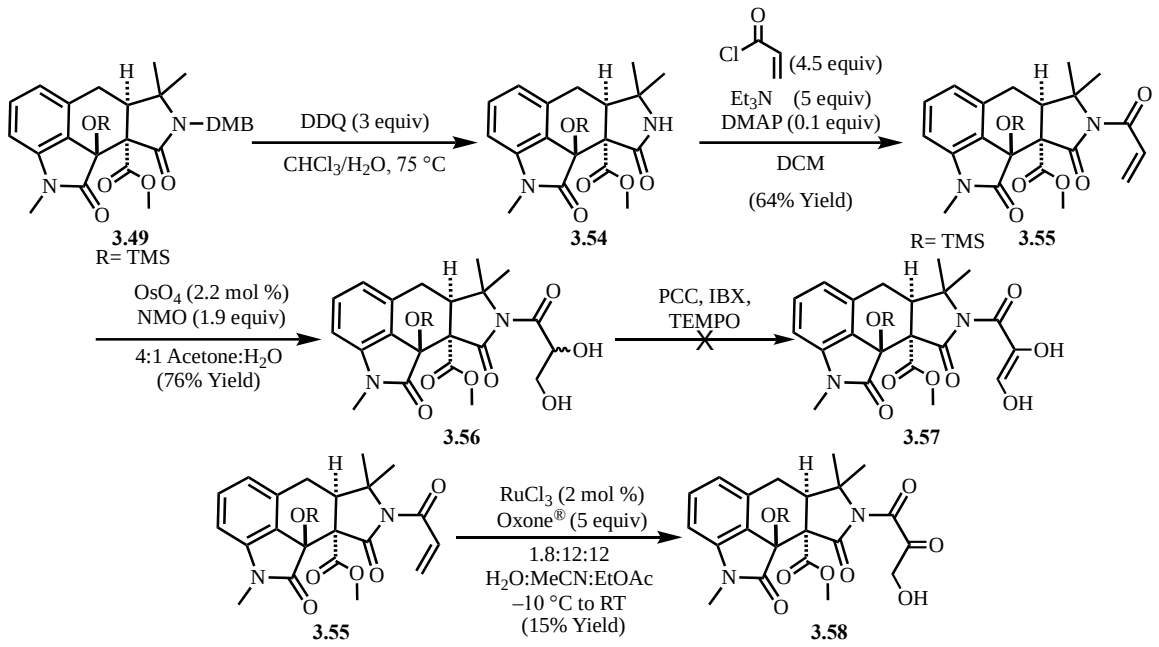
Scheme 3.12 Mukaiyama aldol

we once again sought to remove the ester and install the methine at C4. Surprisingly, Krapcho decarboxylation conditions yielded the previously observed aromatized compound **3.33** (Scheme 3.13). Given this result, we opted to leave decarboxylation at C4 until the latter end of the synthesis hoping that the methyl ester would act as a protecting group, preventing deleterious aromatization.

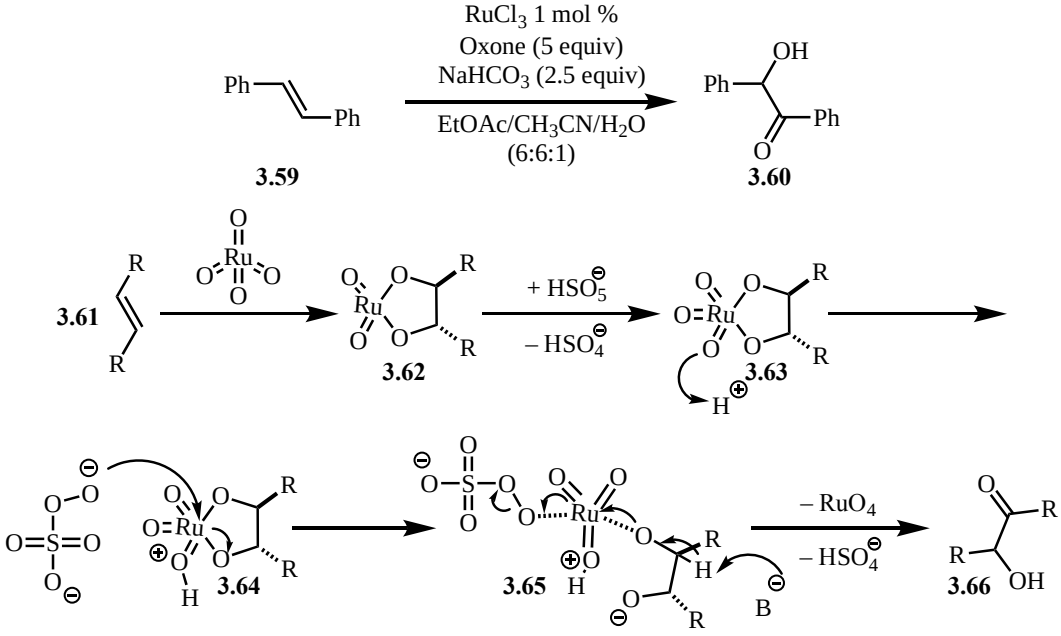


Scheme 3.13 Plausible mechanism for Krapcho induced aromatization

Having decided to delay decarboalkoxylation, we began setting the stage for introducing the penultimate ring (Scheme 3.14). To this end, the DMB protecting group in **3.49** was removed by exposure to DDQ. Acylation of the derived tetracyclic amide intermediate (**3.54**) with acryloyl chloride provided requisite acrylimide **3.55** which was found to smoothly undergo dihydroxylation with catalytic osmium tetroxide to furnish diol **3.56**. Unfortunately attempts to further oxidize **3.56** to the ene diol failed under a variety of conditions. In seeking an alternative for oxidation of **3.55** we became intrigued by a ruthenium-based method reported by Plietker and were gratified to find these latter conditions capable of converting **3.55** to acyloin **3.58** (via *in situ* generated ruthenium tetroxide, Scheme 3.15).[17] Unfortunately, numerous attempts to optimize this transformation never resulted in yields beyond 15%. In addition to this, the acyloin product was unstable, hydrolyzing back to amide **3.54** upon exposure to silica gel. Attempts to effect the tautomerization to **3.57** and the subsequent cyclization cascade to access the hexacyclic core under acidic conditions also resulted in hydrolysis back to the amide.



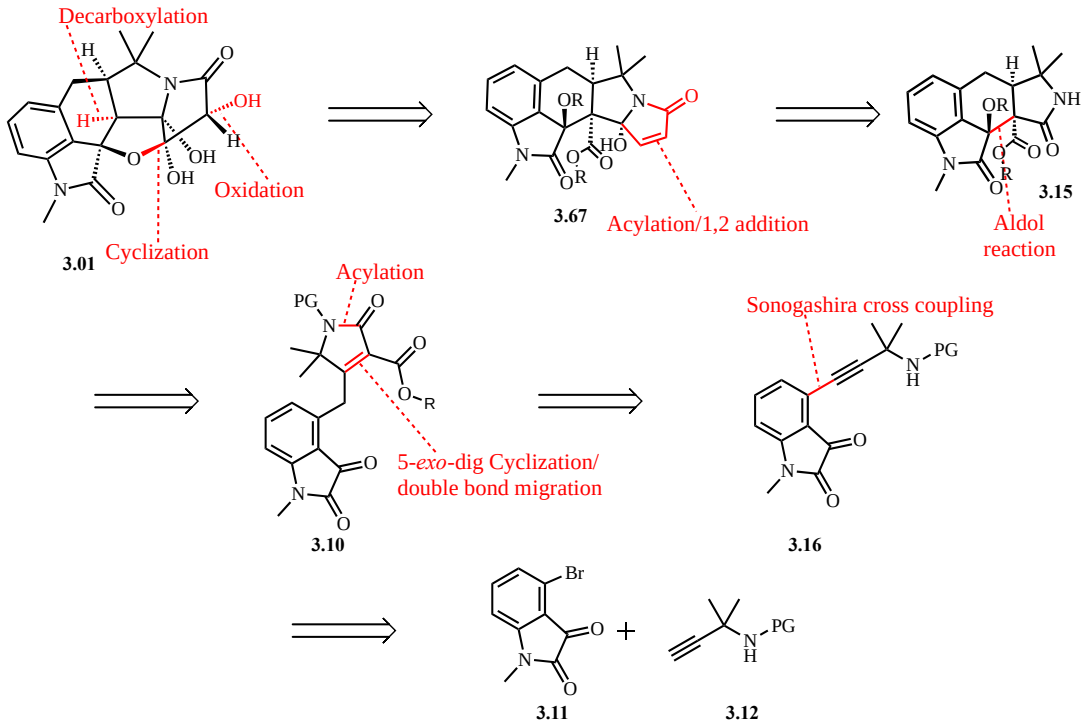
Scheme 3.14 Attempted synthesis of key ene-diol intermediate



Scheme 3.15 Precedent and plausible mechanism adapted from Plietker

Observing that early incorporation of all the oxidation present in the tetramic acid moiety leads to unstable intermediates, we revised the approach and, as illustrated in Scheme 3.16,

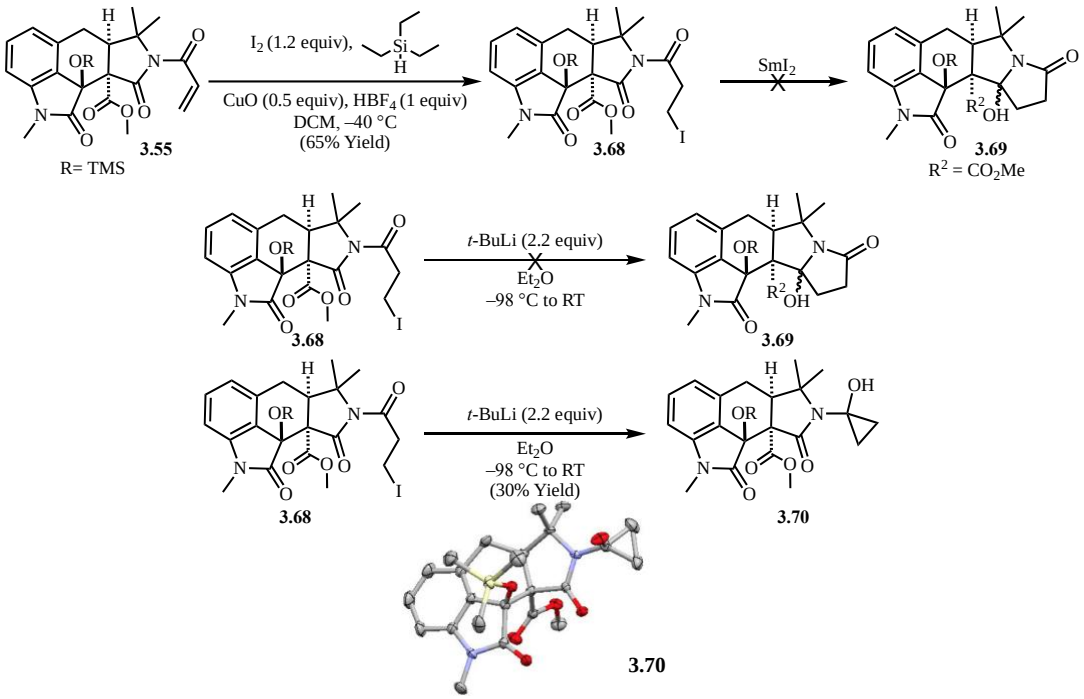
targeted hemiaminal **3.67** (Scheme 3.16). Accessing aspergilline A via this latter route would require the late stage decarboxylation, hemiacetal formation and oxidation of pentacyclic intermediate **3.67**. Pentacycle **3.67** was seen as accessible from tetracyclic amide **3.15** by acylation with acryloyl chloride and subsequent cyclization by intramolecular addition into the imide's carbonyl.



Scheme 3.16 Retrosynthetic analysis II

As illustrated in Scheme 3.17, implementation of this modified route began with the conversion of acrylimide **3.55** to β-iodo compound **3.68** (Scheme 3.17).[18] Cyclization of **3.68** to the corresponding hemiaminal was then attempted under the influence of samarium diiodide. Unfortunately, neither radical generating conditions nor samarium mediated Barbier-type conditions gave the desired cyclization product.[19] Exposure of **3.68** to samarium diiodide often resulted in a complex mixture of 10 – 15 different compounds.

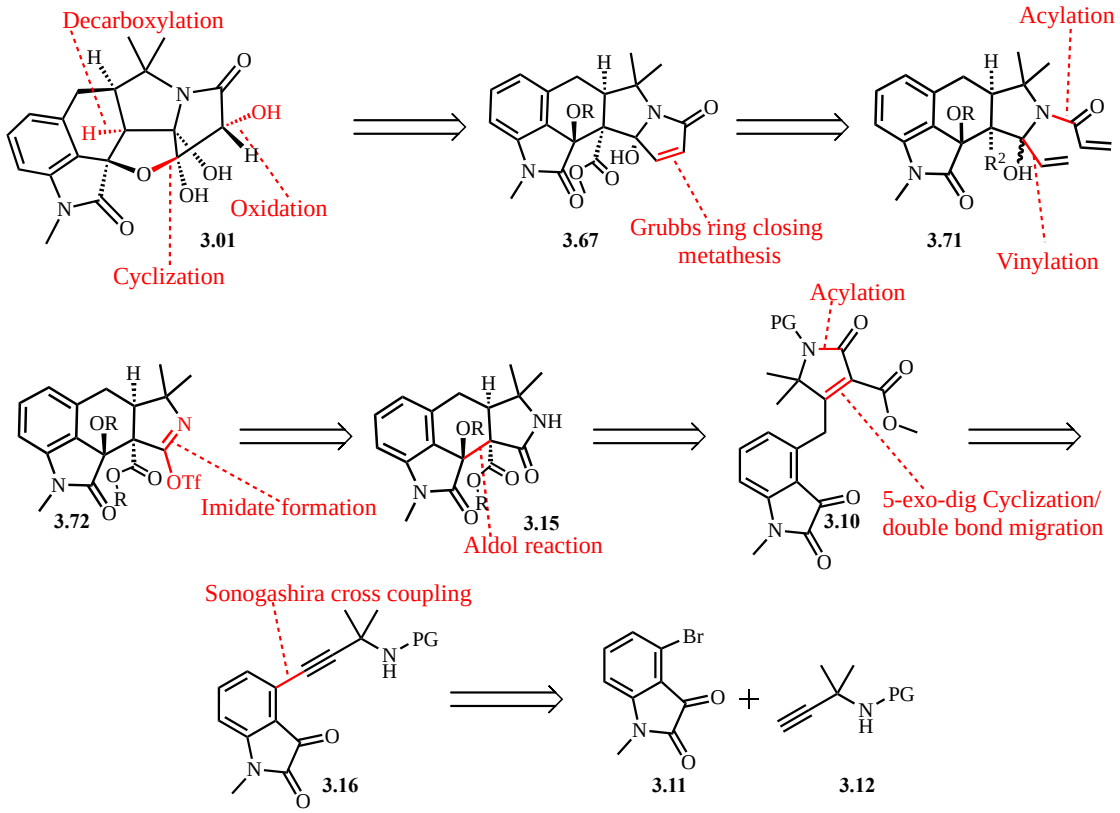
Exploring lithium halogen exchange chemistry, we generated what we initially believed to be a desired pentacyclic intermediate **3.69**. Upon further examination of 1D and 2D NMR data we became suspicious of the assigned structure and sought confirmation via X-ray analysis. Fortunately we were able to obtain crystals of suitable quality to provide a low resolution structure. Surprisingly, this analysis showed that in fact cyclopropyl hemiaminal **3.70** had been produced. This unexpected result is likely the due to the confirmation of the starting imide, wherein due to the adjacent gem dimethyl group, the exocyclic carbonyl is rotated out of plane. An out of the plane rotation would deconjugate the carbonyl from the nitrogen atom's lone pair and substantially enhance electrophilicity.



Scheme 3.17 Unexpected cyclopropyl hemiaminal formation

Thwarted by unstable ene-diol intermediates and the unexpected formation of a cyclopropyl hemiaminal, we again revised the synthetic strategy to obviated the need for nucleophilic addition to the imide carbonyl (Scheme 3.18). As illustrated in Scheme 3.18,

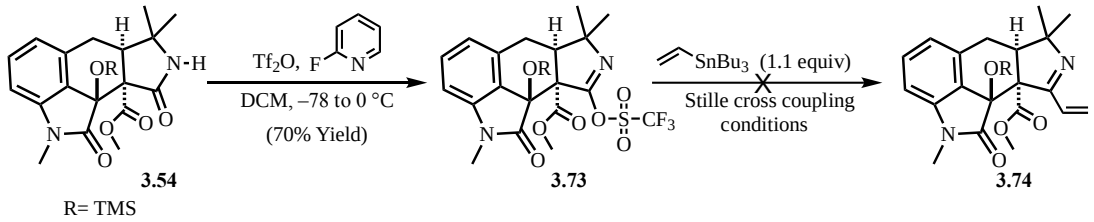
in this third generation approach aspergilline A was again seen to arise via late stage decarboxylation, hemiketal formation and oxidation; however, in this approach the end-game would commence from pentacyclic intermediate **3.67**, which would be accessed from diene **3.71** via a Grubbs ring-closing metathesis reaction. In turn, imidoyl triflate **3.72** would be used to construct **3.71** through a vinylation reaction followed by acylation with acryloyl chloride and subsequent reaction of an intermediate acyliminium with water. Once again, the imidoyl triflate **3.72** would be accessed from key tetracyclic amide **3.15**. In essence, this strategy sought to construct the elusive five membered ring which had been the downfall of previous strategies by building it from the amide carbonyl (**3.15**) around to the nitrogen atom.



Scheme 3.18 Retrosynthetic analysis III

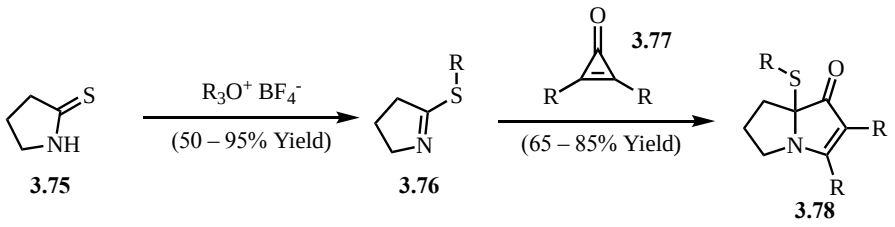
In the forward sense, amide **3.54** was treated with triflic anhydride in the presence of 2-fluoropyridine to provide imidoyl triflate **3.73** (Table 3.3).[20] Stille cross coupling conditions were then applied in hopes of inducing the desired vinylation reaction. As outlined a number of reaction conditions failed to provide even a trace of the desired product. In fact, it appeared that at temperatures above 60 °C triflate migration from oxygen to nitrogen was occurring. Attempts to utilize a Sonogashira cross coupling or addition of a vinyl organometallic reagent followed by triflate elimination also proved difficult.

Table 3.3 Screening of Stille cross coupling conditions



Catalyst	Additive	Solvent	Ligand	Temperature	Yield of **3.62**
$Pd_2(dba)_3$	CuI (1.2 equiv)	NMP	$AsPh_3$	RT to 60 °C	0%
$Pd_2(dba)_3$	CuI (1.2 equiv)	NMP	Tris-(2-furyl)P	RT to 60 °C	0%
$Pd(t\text{-}Bu_3P)_2$	CuI 1.2 (equiv)	NMP		RT to 60 °C	0%
$Pd(Cy_3P)_2$	CuI (1.2 equiv)	NMP		RT to 60 °C	0%
$Pd_2(dba)_3$		NMP	$AsPh_3$	RT to 85 °C	0%
$Pd_2(dba)_3$		NMP	Tris-(2-furyl)P	RT to 85 °C	0%
$Pd(t\text{-}Bu_3P)_2$		NMP		RT to 85 °C	0%
$Pd(Cy_3P)_2$		NMP		RT to 85 °C	0%
Pd/C		NMP		RT to 140 °C	0%
Pd/C	LiCl (3 equiv)	NMP		RT to 140 °C	0%
Pd/C	LiF (2 equiv)	NMP		RT to 140 °C	0%
$Pd(PPh_3)_4$	LiCl (3 equiv)	THF		RT to 125 °C	0%
$Pd(PPh_3)_4$		DMF		RT to 120 °C	0%

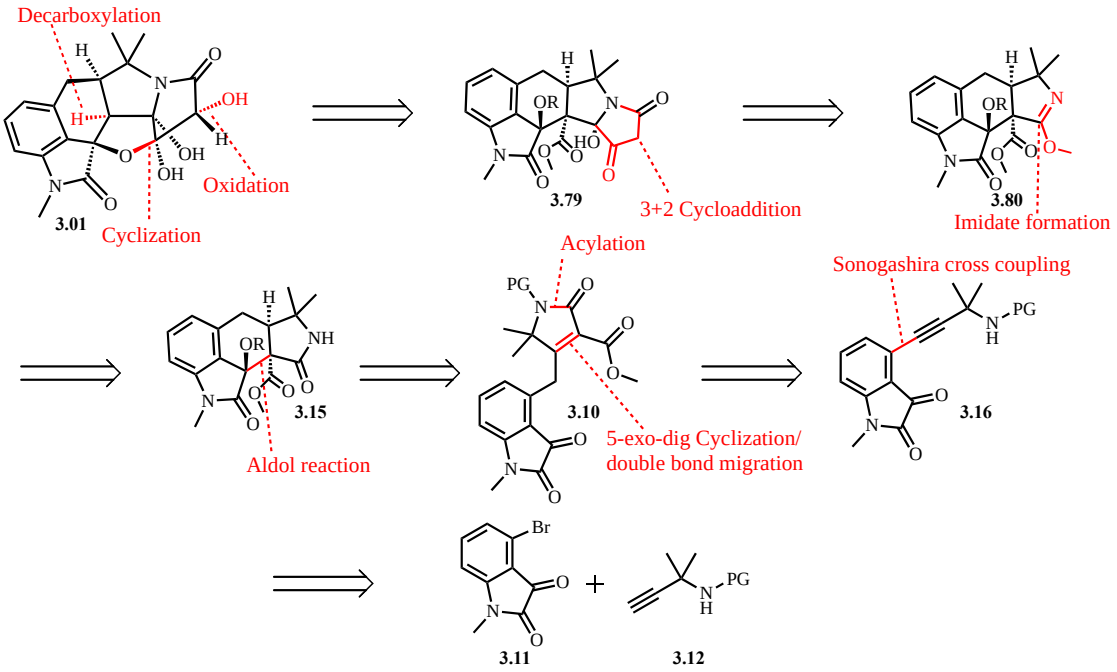
Concurrent with exploring the vinylation approach, we were also considering a more efficient strategy wherein the penultimate ring would derive from a dipolar cycloaddition of an intermediate imidate with an all-carbon 1,3 dipole, thus simultaneously forming the two bonds required for the annulation. It is perhaps worth noting that from a strategic perspective, the annulation of imidates is not a particularly obvious approach and thus our redirecting the synthesis in this fashion is an example of how strategies often evolve in unforeseen ways. In this particular case, it was clearly the preparation of imidoyl triflate **3.73** that had us thinking along these lines. A survey of the literature quickly revealed that all-carbon 1,3 dipoles were scarcely utilized and that the most practical version of such a dipole was cyclopropenone and its derivatives (Scheme 3.19). Precedent from Hemming disclosed that exposure of thioimidates (**3.76**) to cyclopropenone derivatives (**3.77**) in acetonitrile furnished 5,5 fused ring systems which mapped well onto our natural product and also bore desirable oxidation.[21]



Scheme 3.19 All-carbon 1,3-dipole – precedent from Hemming

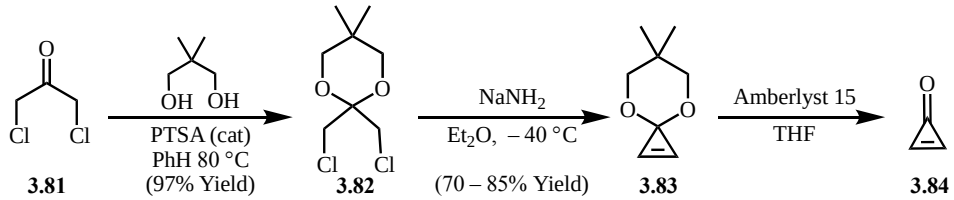
Changing our retrosynthetic analysis again, we sought to construct aspergilline A through the intermediacy of pentacycle **3.79** (Scheme 3.20) via late stage decarboxylation, hemiketal formation and oxidation. We believed **3.79** could be derived from methyl imidate **3.80** through a formal dipolar cycloaddition with parent cyclopropenone **3.84**

(Scheme 3.21). Finally, **3.80** would derive from tetracyclic amide **3.15** by exposure to a hard methylating agent.



Scheme 3.20 Retrosynthetic analysis IV

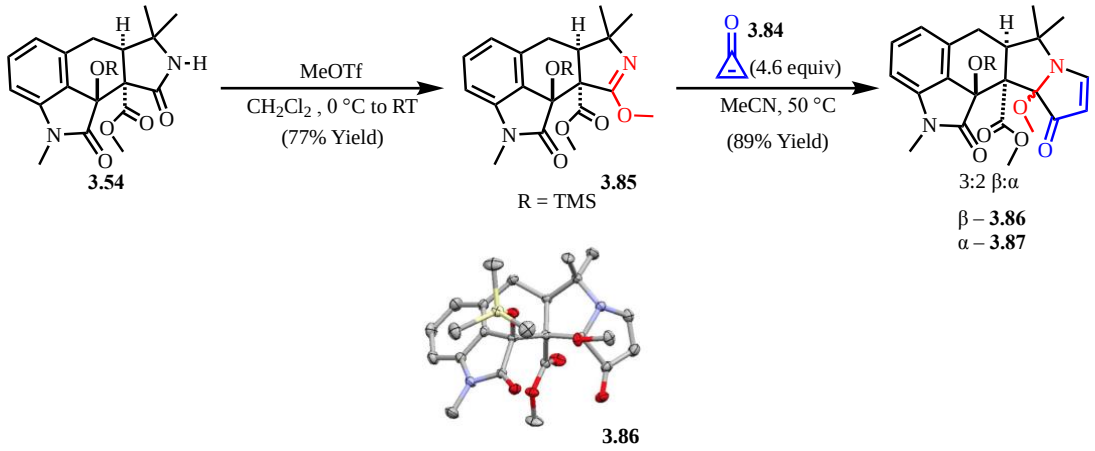
Eager to apply this alluring methodology, we prepared parent cyclopropenone **3.84** according to known methods (Scheme 3.21).[22] Transformation of amide **3.54** to methyl



Scheme 3.21 Literature synthesis of cyclopropenone

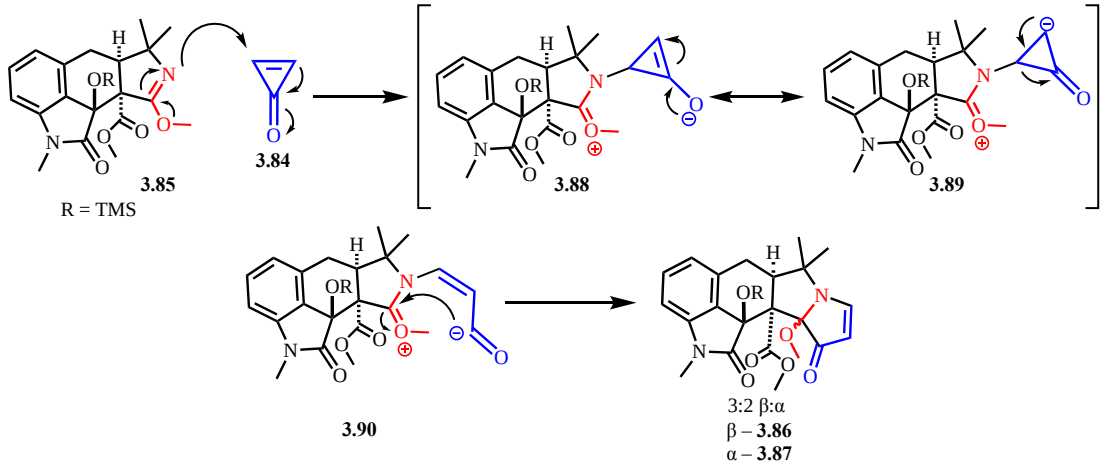
imidate **3.85** was achieved by the portion wise addition of ~45 equivalents of methyl triflate without the addition of base (Scheme 3.22). With both components of the dipolar cycloaddition in hand, the stage was set for the cyclization. To this end, methyl imidate

3.85 was dissolved in acetonitrile and warmed in the presence of 4.6 equivalents of cyclopropenone **3.84**. To our delight we found that this reaction smoothly produced



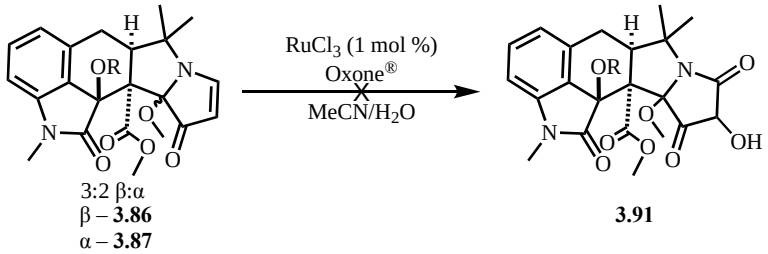
Scheme 3.22 [3+2] Dipolar-cycloaddition

the sought after pentacycle as an inconsequential (3:2 β:α, **3.86**: **3.87**) mixture of diastereomers in 89% yield. The diastereomer bearing the β-face methoxy group was confirmed by X-ray crystallographic analysis. A plausible mechanism for this reaction is depicted in Scheme 3.23 and is an adaption of a mechanism put forth by Hemming.[22]



Scheme 3.23 Plausible mechanism of formal [3+2] dipolar-cycloaddition

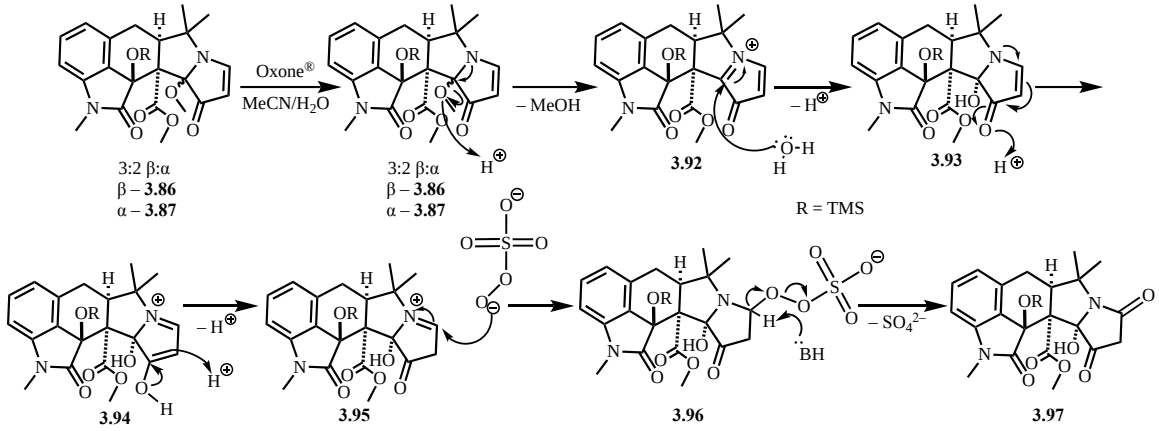
Initially seeking to elaborate the vinylogous amides of **3.86** and **3.87** directly to a hydroxy tetramic acid (**3.91**) we applied the chemistry developed by Plietker, a variation of which we had earlier utilized to synthesize acyloin **3.58** (Scheme 3.24) .[19] We were



Scheme 3.24 Attempted hydroxy tetramic acid synthesis

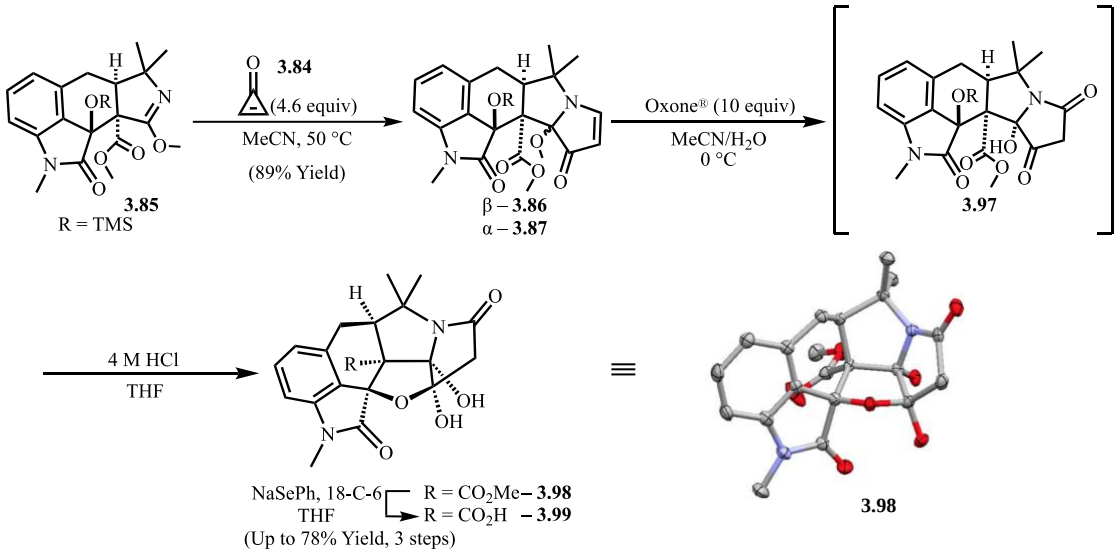
surprised to observe that instead of hydroxy tetramic acid formation, the reaction provided the tetramic acid **3.97** as a single diastereomer; furthermore, the methoxy group was replaced by a hydroxy group (Scheme 3.25). Consulting the literature, we were excited to find that the direct transformation of a vinylogous amide to a tetramic acid was without precedent! Exploring the reaction further it was discovered that ruthenium trichloride was unnecessary for conversion of the vinylogous amide to tetramic acid **3.97**; instead solely Oxone® in acetonitrile/water solution was sufficient. Curiously, we also observed that a 1:1 mole ratio of sodium bicarbonate to Oxone® inhibited the reaction. Although this reaction was not studied in detail, we propose here a plausible mechanism based on our observations (Scheme 3.25). In the event, we speculate that initial acid induced displacement of the methoxy group by water precedes protonation of the vinylogous amide **3.93** to give enol **3.94**. Tautomerization and attack by peroxymonosulfate would furnish an intermediate peroxymonosulfate ester (**3.96**) which, upon base promoted alpha-elimination

of sulfate would deliver the observed tetramic acid (**3.97**). the possibility of further functionalization of **3.97** remained. To this end, α- hydroxylation of tetramic acid



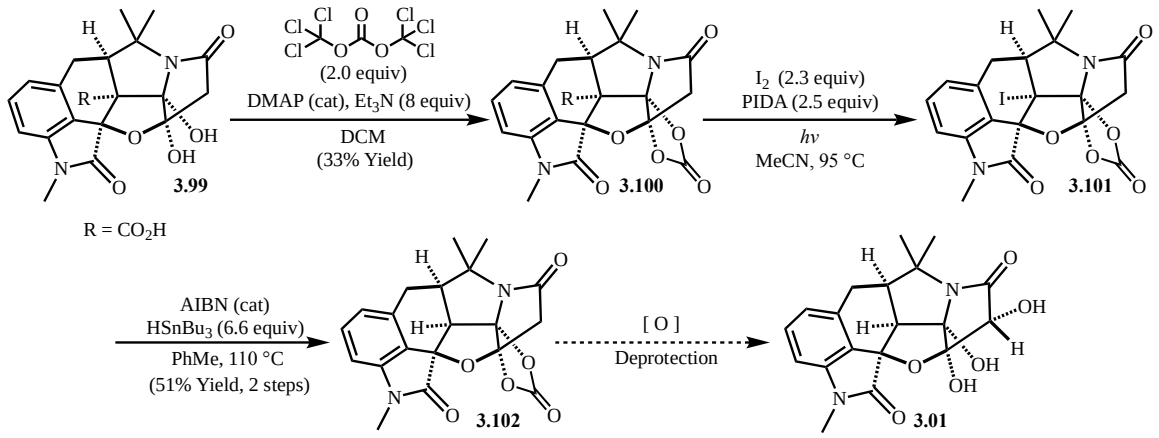
Scheme 3.25 Plausible mechanism for tetramic acid formation

3.97 was attempted with PIFA in DCM. Crude mass and NMR appeared to indicate that an oxidation had occurred, but the obtained compound was viciously unstable, quickly decomposing in the NMR tube prior to retrieval of the sample.[23] Observing the instability of the oxidized material we opted to forego the final oxidation until the end of the synthesis. At this stage we also deduced that the tetramic acid (**3.97**) partially decomposed on silica gel during purification; thus we carried the tetramic acid crude through to the next step. As illustrated in Scheme 3.26, crude **3.97** was exposed to acidic desilylation conditions to reveal the tertiary alcohol which promptly cyclized providing hexacyclic ester **3.98**, a crystalline solid which proved amenable to X-ray analysis (Scheme 3.26). It should be noted that the tetramic acid formation and ketalization reactions were quite peculiar. To



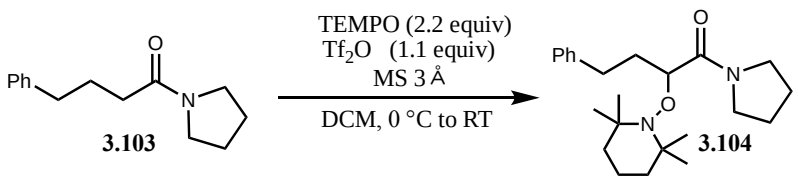
Scheme 3.26 Hexacycle formation

obtain reproducibly high yields of the tetramic acid, the water co-solvent/reactant had to be added slowly by syringe pump while the reaction mixture was kept cold. Perplexingly, crude NMR spectra of tetramic acid **3.97** revealed what often appeared to be a very complex mixture of products. That complex mixture of products when exposed to acidic conditions inexplicably funneled almost entirely to the single observed hexacyclic ester **3.98**. With **3.98** in hand, all that remained for the completion of the total synthesis was decarboxylation and appending of the final hydroxy group. Sodium phenyl selenide in the presence of 18-crown-6 smoothly de-methylated the ester revealing the carboxylic acid (**3.99**), which was obtained in up to 78% yield over three steps.[24] Decarboxylation attempts with the hydroxy groups unprotected proved fruitless. Protection of the hydroxy groups as the cyclic carbonate was then effected by triphosgene to give **3.100** (Scheme 3.27). Iodinative decarboxylation followed by radical dehalogenation proceeded in 51% yield to furnish decarboxylated product **3.102**. Finally, all that remained to complete the synthesis



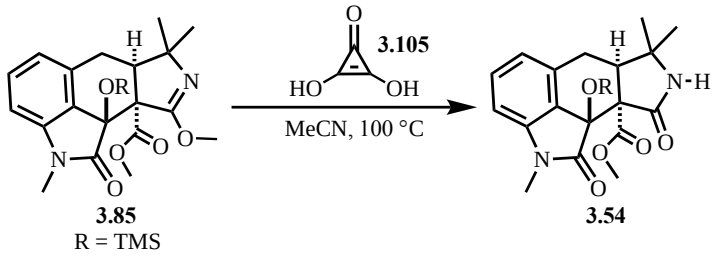
Scheme 3.27 Failed late stage hydroxylation

was carbonate deprotection and installation of the remaining hydroxy group. Disappointingly, conventional enolate oxidation conditions utilizing Davis oxaziridine, *m*-CPBA, DMDO, oxygen and triethyl phosphite or Rubottom-type oxidations failed to install the final hydroxy group. Deprotonation followed by quenching with a deuterium source at low temperature affirmed that **3.102** was not tolerant of strong bases such as LDA. Unconventional conditions developed by the Maulide group utilizing triflic anhydride and TEMPO to install α-oxidation were also explored (Scheme 3.28), but were found to be ineffective.[25] Unable to install the final hydroxy group at this stage we attempted to perform the dipolar cycloaddition with deltic acid **3.105** in hopes of installing all the needed oxidation at once (Scheme 3.29). Heating with deltic acid proved nugatory, resulting in



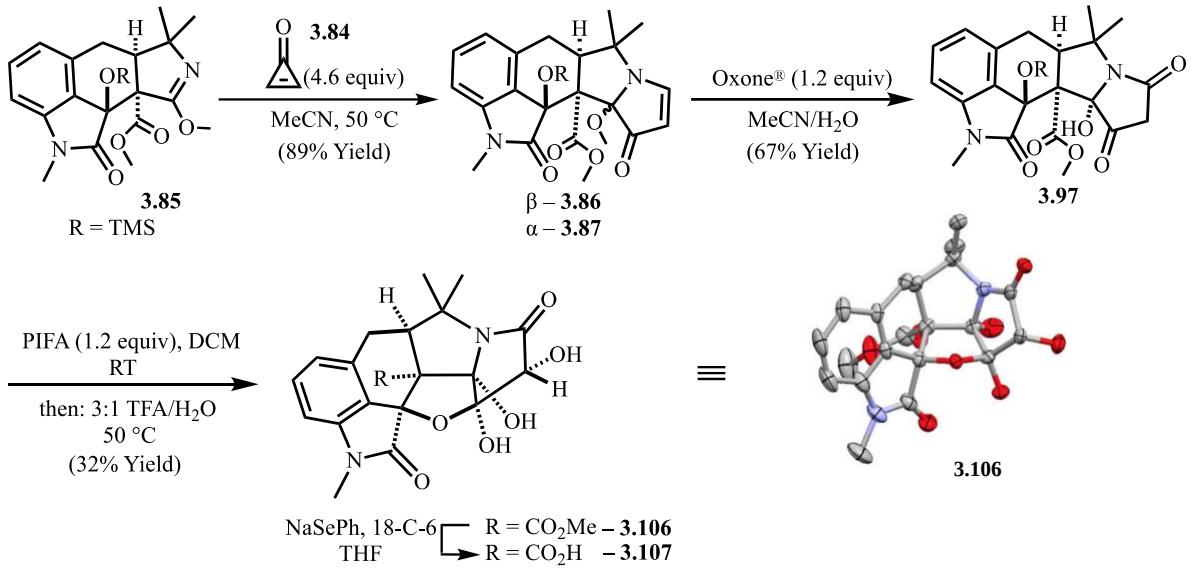
Scheme 3.28 Representative example of Maulide α-oxidation of amides

reversion of the methyl imidate **3.85** to amide **3.54**. With this result it appeared that no obvious avenue forward was left except for the installation of the hydroxy group at the tetramic acid stage.



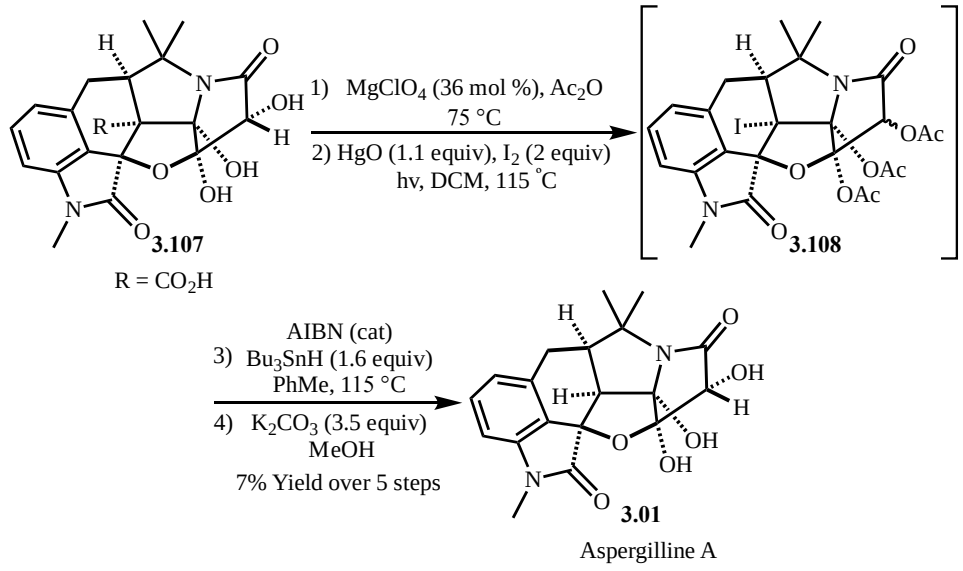
Scheme 3.29 Attempted cycloaddition with deltic acid

Tetramic acid **3.97,** now purified by silica gel chromatography, was exposed once again to PIFA in DCM (Scheme 3.30). Previous experience with this reaction had revealed that the hydroxy tetramic acid intermediate was highly susceptible to oxidation by atmospheric oxygen. Due to this observation, upon completion of the PIFA oxidation a solution of TFA:H_2O (3:1v/v) was degassed via freeze-pump-thaw and added to the reaction mixture followed by immediate warming to 55 °C. The acidic conditions once again revealed the tertiary alcohol which immediately participated in hemiketal formation to give hexacyclic ester **3.106** with all desired hydroxy groups present as a crystalline solid amenable to X-ray analysis. Luckily, the cyclized material was not prone to decomposition when exposed to atmospheric oxygen, which allowed us to proceed forward with the completion of the synthesis. At this stage we employed the previously developed condition and deesterified **3.106** with sodium phenyl selenide to give carboxylic acid **3.107**. Peracetylation of **3.107** with acetic anhydride and catalytic magnesium perchlorate



Scheme 3.30 Installation of the final hydroxy group

(Scheme 3.31) was followed by iodinative decarboxylation under Hunsdiecker-type conditions to furnish iodide **3.108**. Radical dehalogenation of crude

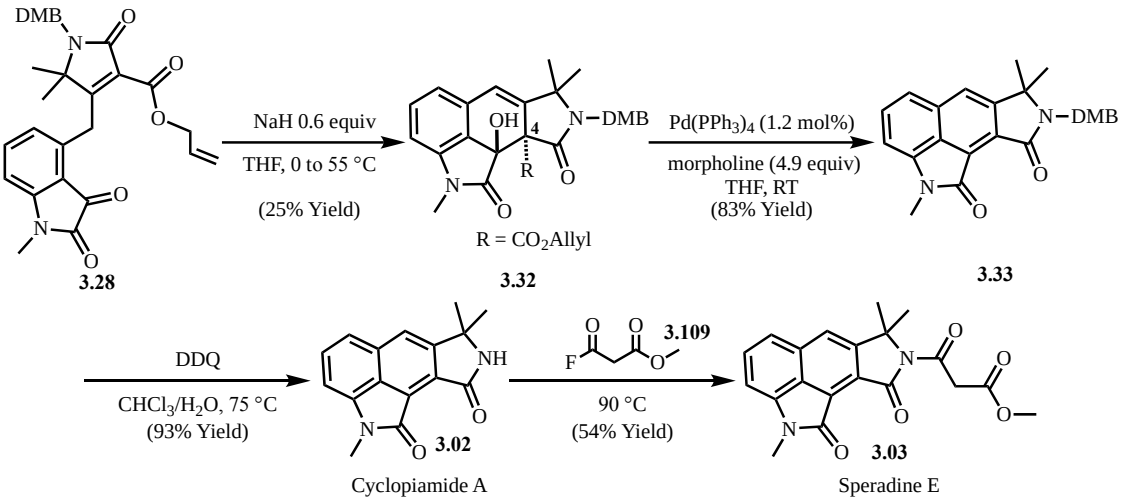


Scheme 3.31 Total synthesis of aspergilline A

3.108 followed by exposure to methanolic potassium carbonate then delivered the natural product aspergilline A **3.01** in 7% yield over the final five steps.[26]

3.2.2 Total Synthesis of Cyclopiamide A and Speradine E

Having contended with aromatization early on during the aspergilline A synthesis, we were eager to utilize this initially unwanted reactivity to our advantage. Thus, tetracycle **3.32**, which had been synthesized through intramolecular aldol reaction of **3.28**, was exposed to catalytic palladium(0) to induce aromatization through a de-allylative decarboxylation and subsequent hydroxide elimination (Scheme 3.32). The DMB group



Scheme 3.32 Total synthesis of cyclopiamide A and speradine E

of **3.33** was then removed under the same conditions utilized in the aspergilline A synthesis to give in 93% yield cyclopiamide A **3.02**. To access speradine E a methyl β-keto ester had to be appended. Literature precedent revealed that such a transformation was not trivial.[6] In fact, the acylation of cyclopiamide A had been attempted by the isolation chemists without success. After attempting conventional acylation conditions with methyl malonyl chloride, as well as more forceful deprotonation with LDA or *t*-BuLi and exposure to

methyl malonyl chloride, we turned to acyl fluoride chemistry. Acyl fluorides are precedented in the peptide coupling literature to be useful in preforming coupling reactions in cases where the amine or carboxylic acid substrate may be sterically hindered.[27] Believing that the gem dimethyl group present in the substrate was hindering acylation we exposed it to freshly prepared, neat methyl malonyl fluoride at 90 °C and were delighted to find that the reaction provided speradine E **3.03** in 54% yield.

3.3 Conclusion

In conclusion the first total syntheses of aspergilline A, cyclopiamide A and speradine E were accomplished in 16, 6 and 7 steps, respectively. The most notable features of the aspergilline synthesis include: a direct conversion of a propargyl amine **3.21** to a pyrrolinone **3.30**, the first utilization in a total synthesis of a cyclopropenone all-carbon 1,3 dipole in a reaction with an imidate, and a novel conversion of a vinylogous amide directly to a tetramic acid. The cyclopiamide A and speradine E total synthesis were marked by the utilization of a de-allylative decarboxylation/elimination/aromatization sequence to give the aromatic tetracyclic core structure. Finally, due to the reported bioactivity of these compounds samples of cyclopiamide A **3.02**, hexacyclic ester **3.98** and hexacyclic acid **3.99** were submitted for screening to the NIH national cancer institute. The compounds were screened against 60 cancer cell lines and the data is detailed in appendix F. Overall the compounds showed no strong inhibition of cancer cell growth at 0.01 mM. We acknowledge the NIH National Cancer Institute for their work in screening these compounds.

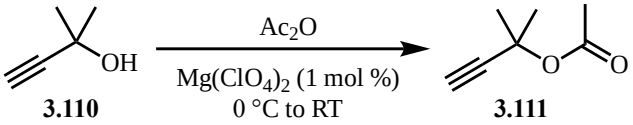
3.4 Experimental

3.4.1 General

Unless otherwise stated, all reactions were performed in flame dried glassware under a nitrogen atmosphere, using reagents as received from the manufacturers. The reactions were monitored and analytical samples purified by normal phase thin-layer chromatography (TLC) using Millipore glass-backed 60 Å plates (indicator F-254, 250 μM) or by using Sigma Aldrich glass-backed 60 Å reverse phase C-18 fully end-capped plates (fluorescent indicator, 250 μM). Tetrahydrofuran, dichloromethane, acetonitrile, and toluene were dried using a solvent purification system manufactured by SG Water U.S.A., LLC. Manual flash chromatography was performed using the indicated solvent systems with Silicycle SiliaFlash® P60 (230–400 mesh) silica gel as the stationary phase. Flash Chromatography on a Teledyne RF+UV-Vis Ms Comp MPLC was performed using the indicated solvent systems, and Teledyne RediSep® Rf normal phase disposable columns of the indicated size and at the indicated flow rate. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III 300, a Bruker AscendTM 400 autosampler or a Bruker AscendTM 600 autosampler. Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual solvent resonance and coupling constants (J) are reported in hertz (Hz). NMR peak pattern abbreviations are as follows: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, at = apparent triplet, q = quartet, ABq = AB quartet, m = multiplet. NMR spectra were calibrated relative to their respective residual NMR solvent peaks, $CDCl_3$ = 7.26 ppm (^{1}H NMR)/ 77.16 ppm (^{13}C NMR), DMSO = 2.50 ppm (^{1}H NMR)/ 39.52 ppm (^{13}C NMR), MeOD = 3.31 ppm (^{1}H NMR) MeCN = 1.94 ppm (^{1}H NMR)/118.26 ppm (^{13}C NMR). IR spectra were recorded on Bruker Platinum-ATR IR spectrometer using a diamond window

and the stretches reported in cm^{-1}. High Resolution mass spectra (HRMS) were obtained in the Baylor University Mass Spectrometry Center on a Thermo Scientific LTQ Orbitrap Discovery spectrometer using +ESI or –ESI and reported for the molecular ion ($[M+H]^+$ & $[M+Na]^+$ or $[M-H]^-$ respectively) Single crystal X-ray diffraction data were collected on a BrukerApex II-CCD detector using Mo-Kα radiation (λ = 0.71073 Å). Crystals were selected under oil, mounted on micromounts then placed in a cold stream of N_2. Structures were solved and refined using SHELXTL.[29]

*Preparation of Propargyl Acetate **3.111***

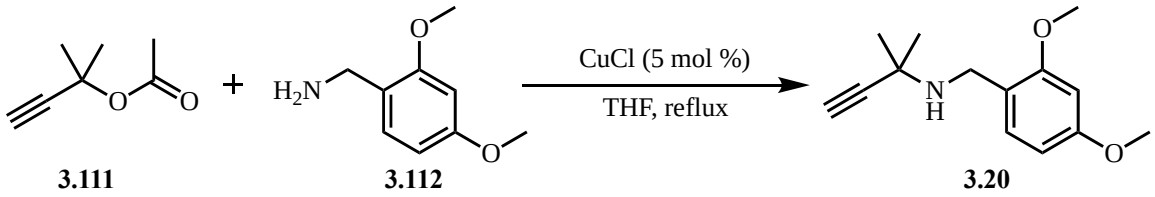


3.110 **3.111**

A flame dried 500 mL round bottomed flask was charged with magnesium perchlorate (1.63 g, 7.3 mmol, 0.01 equiv) and acetic anhydride (73.7 mL, 775 mmol, 1.04 equiv). The solution was cooled in an ice water bath and the propargyl alcohol **3.110** (72 mL, 743.0 mmol, 1 equiv) was added dropwise over forty minutes. The solution was then allowed to stir in the ice bath for ten minutes and then warmed to room temperature. Stirring was continued at room temperature for an additional one hour and ten minutes. During this time the reaction color turned a light brown and the solution became cloudy. To the reaction was added 500 mL Et_2O and the reaction mixture washed twice with 500 mL of 0.1 M $NaHCO_3$. The organic layer was dried over sodium sulfate and the solvent removed by rotary evaporation. The compound was used as is for the next step without further purification. This gave 86.6 grams (92.1% yield) of the propargyl acetate **3.111** as a pale yellow oil.[2] **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 2.53 (s, 1H), 2.03 (s, 3H), 1.68

(s, 6H).**^{13}C NMR** (101 MHz, Chloroform-*d*) δ 169.6, 84.9, 72.3, 71.7, 29.0, 22.0. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_7H_{10}O_2Na^+$ = 149.05785, found $C_7H_{10}O_2Na^+$ = 149.05725 **FTIR (Neat)** 3289, 2991, 2942, 1741, 1469, 1432, 1366, 1233, 1197, 1132, 1046, 1015, 965, 940, 844 cm^{-1}. *Notes: The reaction is strongly exothermic. The reaction color varies, often darker yellow or brown is observed if the reaction warms too strongly during the addition of the propargyl alcohol, but this does not significantly impact the purity of the product which is obtained.

*Preparation of Propargyl Amine **3.20***

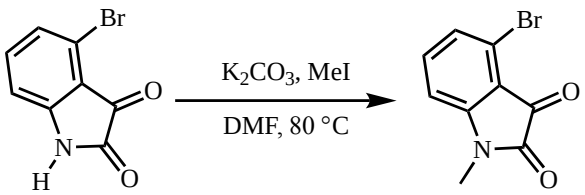


3.111 **3.112** **3.20**

To a flame dried 2L round bottomed flask was added the propargyl acetate **3.111** (50 g, 396.3 mmol, 1 equiv), dry THF (800 mL), cuprous chloride (1.96 g, 19.8 mmol, 0.05 equiv) and dimethoxy benzyl amine **3.112** (100 mL, 666 mmol, 1.68 equiv). The flask was evacuated and back filled with nitrogen twice. A reflux condenser was attached, and the system was evacuated and back filled with nitrogen an additional two times. The reaction mixture was then heated to reflux for four hours and 30 minutes. The reaction flask was then removed from the heat and allowed to cool for ten minutes. The reaction mixture was then poured into a separatory funnel which contained 250 mL of 2M HCl. deionized water and diethyl ether were added and the organic layer was extracted with the HCl solution. The aqueous layer was removed and the organic layer extracted again with an additional 250 mL 2M HCl. The aqueous phases were combined and washed twice with diethyl ether.

The combined aqueous phases were then neutralized with 600 mL 2M NaOH and then extracted four times with diethyl ether. The organic layer was dried over magnesium sulfate and the solvent removed by rotary evaporation. The residue was purified by flash column chromatography using a gradient beginning at 0% ethyl acetate in hexanes and progressing to 20% ethyl acetate in hexanes (all eluent solvents contained triethyl amine in a 100:1 ratio solvent: triethyl amine). The fractions containing the desired product were combined and evaporated to give a light yellow crystalline solid which was then triturated with 50 mL of 10% diethyl ether in hexanes this yielded 58.1 grams (63.1% Yield) of dimethoxy benzyl protected propargyl amine **3.20** as a white crystalline solid.[3] R_f = 0.43 (40% EtOAc/hexanes), UV; **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.19 (d, *J* = 8.4 Hz, 1H), 6.44 – 6.42 (m, 2H), 3.81 (s, 3H), 3.80 (s, 2H), 3.79 (s, 3H), 2.34 (s, 1H), 1.43 (s, 6H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 160.2, 158.7, 130.5, 121.3, 104.1, 98.7, 89.3, 69.8, 55.5, 55.5, 49.9, 43.8, 29.7. **+ESI-HRMS** m/z: calc'd for $[M+H]^+$ $C_{14}H_{20}NO_2^+$ = 234.14940, found $C_{14}H_{20}NO_2^+$ = 234.14874. **FTIR (Neat)** 3313, 3191, 2973, 2935, 2835, 1613, 1587, 1507, 1464, 1434, 1418, 1383, 1367, 1333, 1286, 1264, 1209, 1179, 1155, 1126, 1070, 1045, 1029, 920, 837, 798, 718 cm^{-1}.

*Methyl Bromoisatin **3.11***

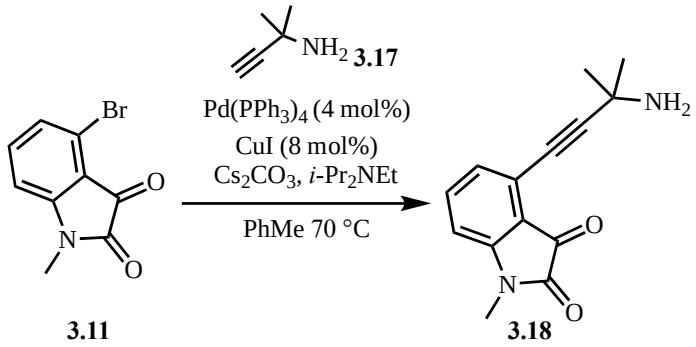


3.19 **3.11**

To an oven dried 1 L round bottomed flask was added bromoisatin **3.19** (63 g, 279 mmol, 1 equiv), dry DMF (350 mL), potassium carbonate (57.8 g, 418 mmol, 1.5 equiv) and then iodomethane (52 mL, 835 mmol, 3 equiv). The mixture was stirred for ten minutes at room temperature and then warmed to 80 ºC for five hours and ten minutes. The reaction mixture was then allowed to cool to room temperature and a 10% solution of hexanes in DCM was added. The reaction solution was poured into a separatory funnel and washed with deionized water several times. The aqueous washes were combined and extracted with DCM twice. The organic layers were then combined and washed three times with water and once with half saturated brine solution. The organic layer was dried over sodium sulfate and the solvent removed by rotary evaporation. The solid residue was then filtered through a sintered glass filter funnel and washed several times with water. The bright orange solid was held under high vacuum until all traces of DMF were removed to give 63 grams (94% Yield) of the *N*-methylated bromo isatin **3.11** as a free flowing orange solid. R_f = 0.55 (90% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.54 (t, J = 8.0 Hz, 1H), 7.28 (d, J = 8.2, 1H), 7.13 (d J = 7.8, 1H), 3.13 (s, 3H).**^{13}C NMR** (101 MHz, DMSO-d_6) δ 180.8, 157.5, 153.2, 138.6, 127.2, 119.1, 116.1, 109.7, 26.1.+**ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_9H_6BrNO_2Na^+$ = 261.94796, 263.94581 found $C_9H_6BrNO_2Na^+$ = 261.94733,

263.94528 FTIR **(Neat)** 3077, 1741, 1729, 1596, 1580, 1481, 1453, 1349, 1303, 1287, 1208, 1164, 1116, 1039, 867, 782 cm^{-1}.

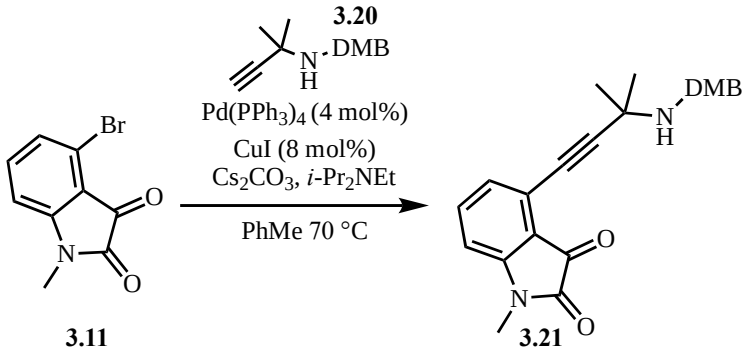
*Preparation of Propargyl Amine **3.18***



To a dry round bottomed flask was added bromo isatin **3.11** (250 mg,1.04 mmol), tetrakis triphenyl phosphine palladium (48 mg, 0.042 mmol), CuI (16 mg,0.084 mmol), cesium carbonate (408 mg,1.25 mmol), toluene (12.5 mL) and Hünig's base (375 μL, 2.20 mmol). Then propargyl amine **3.17** (150 μL,1.43 mmol) was added. After 40 minutes an additional 50 μL of **3.17** (0.475 mmol) were added. After an additional hour 30 μL of **3.17** (0.285 mmol) were added the reaction was then poured into half saturated brine and the reaction mixture extracted with diethyl ether until most of the color was removed from the aqueous layer. The combined organic layer was then extracted twice with 1 M HCl and the combined aqueous extracts were washed three times with diethyl ether. The aqueous extract was then neutralized with solid sodium bicarbonate and extracted several times with ethyl acetate. The combined organic layers were dried over sodium sulfate and the solvent removed under reduced pressure to give 238 mg (94% Yield) of cross coupling product **3.18** as a red solid. R_f = 0.34 (20% MeOH/DCM), UV; **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.50 (t, J = 7.9 Hz, 1H), 7.06 (d, J = 7.9 Hz, 1H), 6.79 (d, J = 7.9 Hz, 1H), 3.24 (s, 3H),

1.54 (s, 6H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 181.3, 158.1, 151.4, 137.4, 127.3, 122.4, 117.5, 109.0, 106.4, 76.5, 46.2, 31.3, 26.4. **+ESI-HRMS** m/z: calc'd for $[M+H]^+$ $C_{14}H_{15}N_2O_2^+$ = 243.11335 found $C_{14}H_{15}N_2O_2^+$ = 243.11296. **FTIR (Neat)** 3355, 2975 2932, 1734, 1588, 1490, 1456, 1360, 1305, 1277, 1201, 1165, 1066, 991, 871, 822, 789, 714, 695 cm^{-1}.

*Preparation of Propargyl Isatin **3.21***

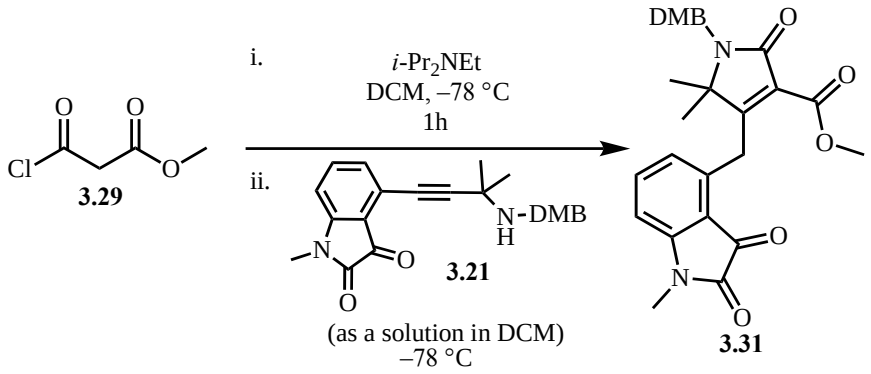


A 2 L round bottom flask was charged with the bromo isatin **S6** (20 g, 83.3 mmol, 1.0 equiv), tetrakis triphenyl phosphine palladium (3.852 g, 3.333 mmol, 0.036 equiv), CuI (1.268 g, 6.66 mmol, 0.08 equiv), 20 g crushed and activated 4Å MS, cesium carbonate (32.56 g, 99.97 mmol, 1.19 equiv), and the propargyl amine **3.20** (29.155 g, 124 mmol, 1.49 equiv). The flask was evacuated and backfilled with nitrogen then dry toluene (950 mL) was added, followed by Hünig's base (26 mL, 149 mmol, 1.78 equiv). The reaction was then placed in a preheated 85 °C oil bath. Successive slow addition of additional propargyl amine **3.20** was required for the reaction to proceed to completion without the formation of side products. After 1 hour and 15 minutes 7.5 g (32.1 mmol, 0.39 equiv) of propargyl amine **3.20** dissolved in 40 mL toluene was added by cannula. 40 minutes later 7.5g (32.1 mmol, 0.39 equiv) of the propargyl amine **3.20** dissolved in 40 mL toluene was

added by cannula. 30 minutes later 7.5g (32 mmol, 0.39 equiv) of propargyl amine **3.20** dissolved in 40 mL toluene was added by cannula. 50 minutes later 10 g (43 mmol, 0.52 equiv) of propargyl amine **3.20** dissolved in 50 mL toluene added by cannula. 40 minutes later 10 g (43 mmol, 0.52 equiv) of propargyl amine **3.20** dissolved in 50 mL toluene was added by cannula. 30 minutes later 10 g (43 mmol, 0.52 equiv) of propargyl amine **3.20** dissolved in 50 mL toluene was added by cannula. 50 minutes later 10 g (43 mmol, 0.52 equiv) of propargyl amine **3.20** dissolved in 50 mL toluene was added by cannula. After an additional 30 minutes the reaction was removed from the heat and allowed to cool for 30 minutes. A half saturated brine solution was added to a separatory funnel followed by the reaction mixture. Ethyl acetate was added and the organic layer was washed twice with half saturated brine (including what it was originally poured into) then extracted with 1.75 M HCl 2x (1000 mL total volume) followed by 200 mL 1 M HCl. The acidified aqueous layer was then washed several times with diethyl ether. The aqueous layer was then neutralized with solid $NaHCO_3$. The neutralized aqueous layer was then extracted several times with ethyl acetate followed by drying of the organic layer over sodium sulfate and removal of the solvent by rotary evaporation. The reaction was purified by MPLC, it was purified in two batches using a gradient beginning at 0% ethyl acetate in hexanes and progressing to 70% ethyl acetate in hexanes both eluents contained ~ 1% triethyl amine. This yielded 23.6 g (72% yield) of the coupled product **3.21** as a red orange solid. Also, 51.8 g of the propargyl amine **3.20** starting material were recovered. R_f = 0.4 (90% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.50 (t, *J* = 7.9 Hz, 1H), 7.24 (d, *J* = 8.9 Hz, 1H), 7.10 (dd, *J* = 7.9, 0.8 Hz, 1H), 6.80 (d, *J* = 7.9, 0.8 Hz, 1H), 6.47 – 6.39 (m, 2H), 3.94 (s, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.25 (s, 3H), 1.57 (s, 6H).**^{13}C NMR** (101

MHz, Chloroform-*d*) δ 181.1, 160.1, 158.8, 158.2, 151.4, 137.2, 130.8, 127.8, 122.7, 121.5, 117.5, 108.7, 104.7, 104.1, 98.8, 78.5, 55.5, 55.5, 50.9, 44.0, 29.4, 26.4.+**ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{23}H_{24}N_2O_4Na^+$ = 415.16338, found $C_{23}H_{24}N_2O_4Na^+$ = 415.16306. **FTIR (Neat)** 2970, 2935, 2838, 1736, 1588, 1508, 1456, 1418, 1360, 1305, 1289, 1207, 1157, 1127, 1065, 1038, 920, 833, 788, 695 cm^{-1}.

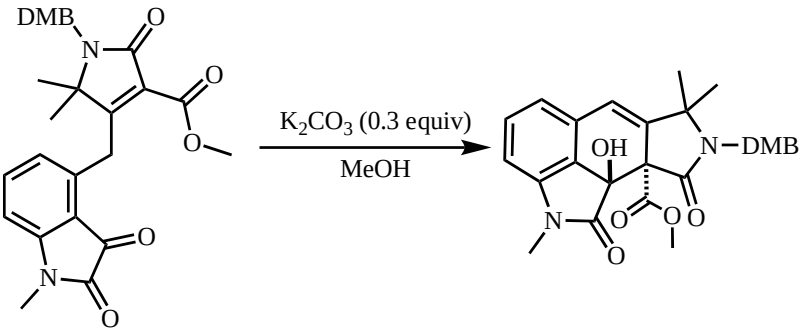
*Preparation of Methyl Pyrrolinone **3.31***



To a flame dried 1 L round bottomed flask was added Hünig's base (36.6 mL, 210 mmol 7.5 equiv) and dry DCM (350 mL), the solution was then cooled to –78 °C in a dry ice/acetone bath. To the Hünig's base solution was then dropwise added methyl malonyl chloride **3.29** (10.4 mL, 97.2 mmol, 3.5 equiv) and the solution stirred for 1 hour. The substrate **3.21** (11 g, 28 mmol, 1 equiv), which had been placed in a flame dried 500 mL round bottomed flask and dissolved in dry DCM (130 mL) was then transferred by slow addition through cannula to the flask containing the Hünig's base/acyl chloride solution. After cannulation the reaction mixture was allowed to stir for an additional 40 minutes at –78 °C and subsequently was quenched with 50 mL of 1M $NaHCO_3$. The dry ice acetone/bath was removed and the flask was allowed to warm slightly. The mixture was then transferred to a separatory funnel and extracted several times with DCM. The organic

layer was dried over sodium sulfate and solvent removed by rotary evaporation. The residue was purified by MPLC using a 330-gram column with a flow rate of 200 mL/min. A gradient from 0% ethyl acetate in hexanes to 90% ethyl acetate in hexanes was used. this yielded 7.8 g (56.5% Yield) of pyrrolinone **3.31** as an orange foam. R_f = 0.34 (90% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.45 (t, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.44 – 6.37 (m, 2H), 4.57 (s, 2H), 4.50 (s, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 3.77 (s, 3H), 3.24 (s, 3H), 1.10 (s, 6H). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 184.1, 170.9, 165.8, 163.8, 160.3, 157.9, 157.6, 151.9, 139.6, 138.4, 131.0, 126.0, 124.5, 119.0, 115.1, 108.4, 104.7, 98.3, 65.9, 55.5, 55.5, 52.4, 35.8, 26.9, 26.4, 23.6. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{27}H_{28}N_2O_7Na^+$ = 515.17942, found $C_{27}H_{28}N_2O_7Na^+$ = 515.17914 **FTIR (Neat)** 2949, 2839, 1737, 1685, 1604, 1508, 1463, 1436, 1398, 1360, 1326, 1294, 1265, 1208, 1157,1110, 1056, 1035, 916, 896, 835, 788, 730, 646 cm^{-1}. *Notes: Often evaporation from ethyl acetate gives an orange viscous oil, dissolving this oil in DCM followed by rotary evaporation gives an orange foam. The yield decreases on larger scales, up to 3 g scale the reaction gives 65% yield. Often the compound has trace impurities after column chromatography, this does not appear to significantly impact the next steps. An analytically pure sample was obtained by prep TLC using 75:25 ethyl acetate: hexanes.

*Preparation of Tetracyclic Methyl Ester **3.34***

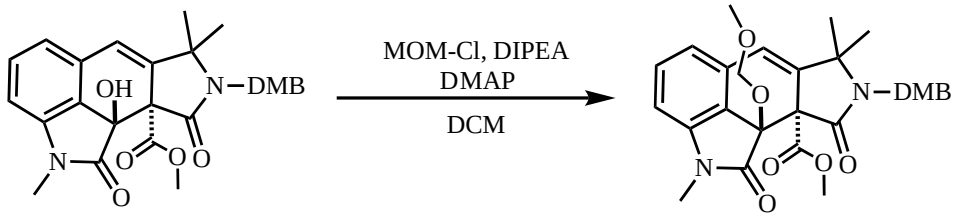


3.31 **3.34**

Pyrrolinone **3.31** (764 mg, 1.55 mmol) was placed into a dry round bottom flasked equipped with a stir bar. Dry methanol (13 mL) was added. The reaction flask was then cooled in an ice water bath and potassium carbonate (64.4 mg, 0.047 mmol) was added. The ice bath was then removed and the solution warmed to room temperature. Over ten minutes the reaction color slowly darkened, changing from orange to emerald green. After 45 minutes of reaction time the flask was placed in a 50 ^{o}C oil bath and warmed for 35 minutes and then quenched with 8 mL of 0.5M ammonium chloride (enough ammonium chloride is added until the orange color returns). Brine and DCM were added. The reaction mixture was then extracted five times with DCM and the organic layer dried over sodium sulfate. The solvent was removed under reduced pressure and the residue triturated with ~30% ethyl acetate: hexane mixture. This gave 330 mg (43% Yield) of tetracyclic ester **3.34** as an amorphous white to yellow solid; 300 mg of starting material were recovered from the trituration solution. R_f = 0.25 (90% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.37 (d, J = 8.2 Hz, 1H), 7.25 (t, J = 7.8 Hz, 1H), 6.78 (d, J = 7.7 Hz, 1H), 6.68 (d, J = 7.8 Hz, 1H), 6.56 (s, 1H), 6.44 – 6.38 (m, 2H), 4.71 (d, J = 15.7 Hz, 1H), 4.51 (d, J = 15.8 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.55 (s, 3H), 3.23 (s, 3H), 1.47 (s, 3H), 1.35 (s, 3H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 175.5, 167.0, 166.3, 160.2, 157.5, 144.8,

144.7, 131.6, 131.2, 130.4, 123.6, 119.2, 118.8, 118.8, 108.3, 104.5, 98.3, 71.3, 64.1, 62.6, 55.5, 53.0, 36.4, 28.0, 26.7, 26.3. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{27}H_{28}N_2O_7Na^+$ = 515.17942, found $C_{27}H_{28}N_2O_7Na^+$ = 515.17883 **FTIR (Neat)** 3370, 2938, 2838, 1731, 1692, 1645, 1615, 1592, 1508, 1473, 1435, 1406, 1369, 129, 1264, 1238, 1207, 1155, 1127, 1035, 1022, 969, 966, 934, 901, 881, 833, 782, 730 cm^{-1}.

*Preparation of MOM Protected Tetracycle **3.35***

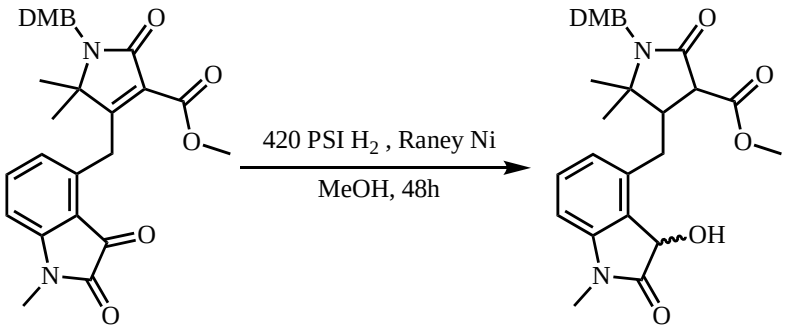


3.34 **3.35**

To a dry round bottomed flask was added tetracycle **3.34** (150 mg, 0.304 mmol), DMAP (9.1 mg, 0.074 mmol) and dry DCM (3 mL). The solution was then cooled in an ice bath and Hünig's base (1 mL, 5.7 mmol) was added. To this mixture was added dropwise MOM-Cl (280 μL, 3.7 mmol) after 25 minutes the ice bath was removed. After five hours and additional 1 mL of Hünig's base (5.7 mmol) was added, the reaction cooled in an ice bath and 280 μL of MOM-Cl (3.7 mmol) added dropwise over several minutes, then the reaction allowed to warm to room temperature. After nine hours, the reaction was once again cooled in an ice bath and 0.5 mL Hünig's base (2.85 mmol) was added followed by 280 μL of MOM-Cl (3.7 mmol). The reaction was allowed to warm to room temperature and the reaction monitored by TLC; upon TLC indicating completion, the reaction mixture was worked up by adding to brine (to the brine had been added a few drops of sodium bicarbonate) and extracting with DCM several times. The combined organic layers were

dried over sodium sulfate and the solvent removed under reduced pressure. The residue was purified by MPLC using a 12-gram column and a gradient which began at 0% ethyl acetate in hexanes and progressed to 95% ethyl acetate in hexanes this yielded 116.1 mg (72% Yield) of **3.35** as an orange glassy solid. R_f = 0.26 (90% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.42 (d, *J* = 8.4 Hz, 1H), 7.24 (t, *J* = 7.8 Hz, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 7.4 Hz, 1H), 6.47 (s, 1H), 6.41 (d, *J* = 2.4 Hz, 1H), 6.37 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.66 – 4.48 (m, 4H), 3.83 (s, 3H), 3.77 (s, 3H), 3.53 (s, 3H), 3.26 (s, 3H), 3.22 (s, 3H), 1.39 (s, 6H). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 173.4, 166.7, 165.5, 160.0, 157.3, 147.3, 145.6, 131.9, 130.3, 121.5, 119.3, 118.2, 118.1, 107.8, 104.4, 98.0, 93.0, 75.1, 63.6, 62.6, 56.6, 55.5, 55.4, 52.9, 36.2, 28.5, 26.7, 26.5. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{29}H_{32}N_2O_8Na^+$ = 559.20564, found $C_{29}H_{32}N_2O_8Na^+$ = 559.20514. **FTIR (Neat)**: 2936, 2838, 2246, 1732, 1695, 1644, 1614, 1590, 1508, 1472, 1436, 1402, 1368, 1301, 1262, 1235, 1207, 1153, 1127, 1103, 1075, 1026, 985, 996, 913, 877, 855, 833, 782, 727, 645, 571 cm^{-1}

*Preparation of Pyrrolidone **3.45***

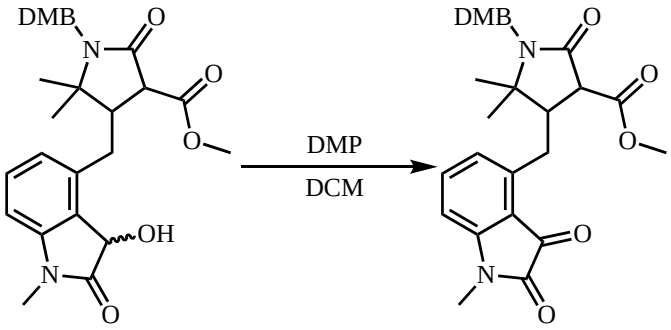


3.31 **3.45**

Into a parr bomb's steel reaction vessel was added pyrrolinone **3.31** (20 g, 40.6 mmol, 1 equiv), methanol (175 mL) and several large spatulas full of Raney® nickel slurry. The vessel was loaded into the parr bomb and was then subjected to 420 PSI H_2 pressure for 48 hours. The reaction was monitored by NMR and periodically extra Raney® nickel was added until the reaction was complete as indicated by NMR. The solution was quickly filtered through a glass fritted filter and the reaction vessel and glass filter washed several times with methanol and acetone. This gave 17.2 g (85% Yield) of pyrrolidone **3.45** (white to yellow solid) as an inconsequential mixture of diastereomers which was carried on to the next step without further purification. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.25 – 7.16 (m, 3H), 6.88 – 6.82 (m, 1.5H), 6.70 – 6.61 (m, 1.5H), 6.47 – 6.35 (m, 3H), 5.15 (d, *J* = 5.5 Hz, 0.4 H minor diastereomer), 5.11 (d, *J* = 6.2 Hz, 1H major diastereomer), 4.52 – 4.31 (m, 3H), 3.82 (s, 3H major diastereomer), 3.81 (s, 1.6 H minor diastereomer), 3.77 (s, 3H major diastereomer), 3.77 (s, 2H minor diastereomer), 3.48 (d, *J* = 11.3 Hz, 1.4 H), 3.29 (s, 3H major diastereomer), 3.14 (s, 5H), 2.91 – 2.78 (m, 2H), 2.63 (at, *J* = 12.3 Hz, 1H), 1.34 (s, 3H major diastereomer), 1.24 (s, 1.6H minor diastereomer), 1.09 (s, 1.4 H minor diastereomer), 1.07 (s, 3H major diastereomer).**^{13}C NMR** (101 MHz, Chloroform-*d*) δ 176.3, 176.3, 171.3, 170.8, 169.4, 169.1, 160.1, 157.5, 157.4, 144.3, 144.2, 137.5, 137.0,

130.0, 130.0, 129.9, 129.8, 125.4, 125.3, 124.6, 119.0, 118.9, 107.0, 106.9, 104.5, 104.5, 98.4, 69.7, 69.6, 62.5, 62.3, 55.5, 55.4, 55.4, 53.6, 53.5, 52.4, 52.3, 49.5, 49.1, 36.8, 31.5, 31.1, 26.5, 25.8, 25.6, 21.3, 21.1.**+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{27}H_{32}N_2O_7Na^+$ = 519.21072, found $C_{27}H_{32}N_2O_7Na^+$ = 519.21072 **FTIR (Neat)** 3368, 3054, 2950, 2839, 1707, 1682, 1608, 1590, 1507, 1467, 1435, 1407, 1368, 1294, 1263, 1207, 1157, 1128, 1116, 1030, 1007, 961, 935, 922, 863, 834, 782, 732, 701, 656 cm^{-1}. *Notes: The reaction frequently stalls, as such NMR monitoring of aliquots is critical. If the reaction stalls extra Raney® nickel should be added until the reaction is complete as indicated by NMR. In total an estimated 33.4 g of wet Raney nickel slurry was added over seven additions for the described reaction. Under these reaction conditions the isatin's ketone is reduced first. The reaction time varies between 48 – 72 h. The ratio of diastereomers varies between reactions, in the provided spectra it appears in the crude as ~ 2:1 mixture.

*Preparation of Isatin **3.46***

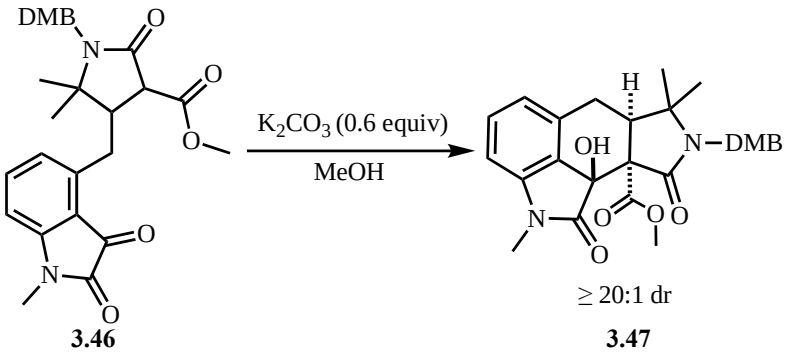


3.45 **3.46**

Two iterations of the same reaction were run simultaneously. The reactions were combined for work up and purification. To a flame dried round bottom flask was added pyrrolidone **3.45** (9.25 g, 18.6 mmol, 1 equiv) dry DCM (180 mL) and Dess-Martin periodinane (15.8 g, 37.2 mmol, 2 equiv). The reaction mixture was stirred for four hours

at room temperature and then both reactions were poured into a separatory funnel which contained 110 mL of saturated sodium bicarbonate solution. The reactions were washed with this solution. Half saturated brine was then used to wash the organic layer and the combined aqueous layers re-extracted several times with DCM. The organic layers were combined and dried over sodium sulfate and the solvent then removed by rotary evaporation. The compound was purified by column chromatography MPLC using 330-gram column with a flow rate of 200 mL/min. A gradient which began at 0% ethyl acetate in hexanes and progressed to 80% ethyl acetate in hexanes was used for purification. This gave 15.0 grams (81% Yield) of isatin **3.46** as an orange foam. R_f = 0.19 (90% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.45 (t, *J* = 7.8 Hz, 1H), 7.15 (d, *J* = 8.1 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 6.48 – 6.36 (m, 2H), 4.41 (ABq, *J* = 15.7 Hz, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 3.40 (s, 3H), 3.37 – 3.25 (m, 2H), 3.23 (s, 3H), 2.83 – 2.68 (m, 2H), 1.40 (s, 3H), 1.08 (s, 3H).**^{13}C NMR** (101 MHz, Chloroform-*d*) δ 183.7, 170.4, 169.1, 160.1, 158.0, 157.5, 152.1, 141.9, 137.7, 129.9, 125.8, 118.8, 115.5, 108.4, 104.5, 98.4, 62.5, 55.5, 55.4, 53.3, 52.3, 49.4, 36.9, 31.1, 26.4, 25.5, 21.4. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{27}H_{30}N_2O_7Na^+$ = 517.19507, found $C_{27}H_{30}N_2O_7Na^+$ = 517.19470 **FTIR (Neat)** 2970, 2946, 2839, 1734, 1686, 1606, 1508, 1462, 1436, 1407, 1359, 1301, 1263, 1208, 1161, 1128, 1063, 1032, 1007, 919, 839, 789, 728, 697 cm^{-1}. *Notes: The reaction solution turns orange upon addition of the Dess-Martin periodinane. Upon rotary evaporation of the crude material, a white solid sometimes precipitates. The precipitate is filtered away from the product before column chromatography.

*Preparation of Reduced Tetracycle **3.47***

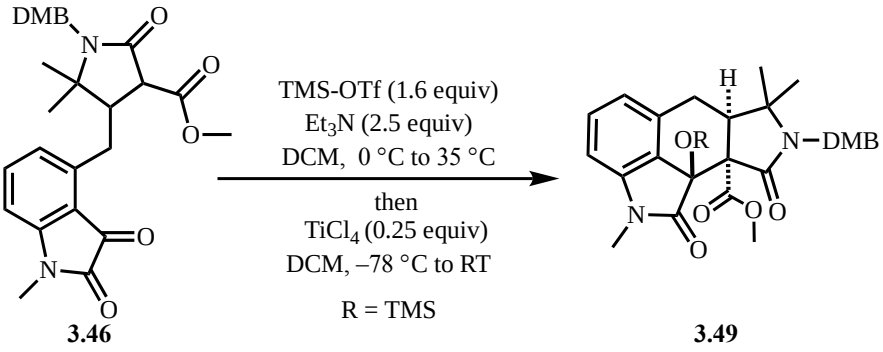


3.46 **3.47**

Pyrrolidone **3.46** (29 mg, 0.059 mmol) was dissolved in dry methanol (0.5 mL) and (2 mg, 0.014 mmol) of potassium carbonate were added. The reaction was stirred at room temperature for 30 minutes then an additional 2 mg (0.014 mmol) of potassium carbonate were added. After 45 minutes the reaction was quenched with 0.5 mL saturated ammonium chloride and deionized water was added. The mixture was then extracted several times with DCM and the solvent dried over sodium sulfate. The solvent was removed under reduced pressure and the residue purified by preparative TLC using 95% ethyl acetate: 5% hexanes as the eluent system. This gave 4.6 mg (16% Yield) of the desired tetracyclic material **3.47** (yellow - green film) and 7.6 mg of recovered starting material. R_f = 0.25 (90% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, Acetonitrile-d3) δ 7.35 – 7.27 (m, 2H overlaps), 6.90 (d, J = 7.7 Hz, 1H), 6.79 (d, J = 7.8 Hz, 1H), 6.53 (d, J = 2.4 Hz, 1H), 6.48 (dd, J = 8.5, 2.4 Hz, 1H), 4.54 – 4.41 (m, 2H), 3.86 (s, 3H), 3.77 (s, 3H), 3.49 (s, 3H), 3.13 (s, 3H), 2.93 – 2.79 (m, 2), 2.63 (dd, J = 11.6, 6.3 Hz, 1H), 1.26 (s, 3H), 1.17 (s, 3H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 176.2, 171.9, 169.1, 160.2, 157.5, 143.7, 136.0, 131.0, 130.1, 126.0, 120.4, 118.9, 106.6, 104.6, 98.4, 73.1, 63.7, 61.7, 55.6, 55.5, 54.1, 53.0, 36.9, 28.8, 27.7, 26.6, 23.9. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{27}H_{30}N_2O_7Na^+$ = 517.19507, found $C_{27}H_{30}N_2O_7Na^+$ = 517.19452. **FTIR (Neat)** 3398,

2952, 2839, 1731, 1681, 1614, 1591, 1508, 1456, 1437, 1414, 1372, 1298, 1262, 1208, 1157, 1127, 1081, 1033, 916, 834, 782, 730, 646 cm^{-1}.

*Preparation of Reduced Tetracycle **3.49***

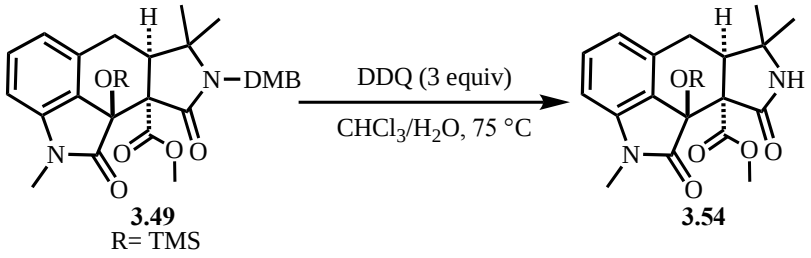


3.46 **3.49**

Three iterations of this reaction were run simultaneously and combined for work up and purification. Pyrrolidone **3.46** (3.5 g, 7.07 mmol, 1 equiv) was dissolved in dry DCM (70 mL) and triethyl amine was added (2.5 mL, 18 mmol, 2.5 equiv). The reaction was placed in an ice bath and TMS-OTf (2.05 mL, 11.3 mmol, 1.6 equiv) was added slowly over five minutes. Ten minutes later the reaction was removed from the ice bath and warmed to RT then to 40 °C and stirred for two hours and five minutes. The reaction was then allowed to cool to RT and the solvent was removed under reduced pressure by rotary evaporation. The residue was placed under high vacuum and the reaction flask evacuated and back filled with nitrogen. Dry DCM (60 mL) was added to the residue, following this the solution was cooled to –78 °C in a dry ice/acetone bath for five minutes and 1M $TiCl_4$ in DCM (1.76 mL, 1.76 mmol, 0.25 equiv) was added and the reaction stirred for 50 minutes followed by warming to RT and stirring for an additional 30 minutes. The three reactions were then poured into a separatory funnel which contained 300 mL of 0.05 M $NaHCO_3$. The organic layer was washed with the bicarbonate solution. The aqueous layer

was then extracted several times with DCM and the combined organic layers dried over sodium sulfate. The solvent was removed by rotary evaporation, upon evaporation or sitting after concentration a white precipitate formed which was filtered prior to loading the residue onto a column for chromatography. The residue was purified by MPLC using a 220-gram column with a flow rate of 150 mL/min. A gradient which began at 0% ethyl acetate in hexanes and progressed 70% ethyl acetate in hexanes was used for purification. This gave 9.2 g (76% Yield) of tetracycle **3.49** as a light peach coloured foam. R_f = 0.1 (60% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.28 (t, *J* = 7.7 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 6.84 (dd, *J* = 7.7, 5.1 Hz, 2H), 6.56 (d, *J* = 2.3 Hz, 1H), 6.43 (dd, *J* = 8.5, 2.3 Hz, 1H), 4.35 (s, 2H), 3.84 (s, 3H), 3.74 (s, 3H), 3.46 (s, 3H), 3.11 (s, 3H), 2.97 – 2.73 (m, 3H), 1.30 (s, 3H), 1.16 (s, 3H), -0.19 (s, 9H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 174.6, 171.2, 167.5, 159.8, 157.2, 143.4, 135.4, 130.9, 130.8, 126.8, 120.2, 120.1, 105.9, 104.7, 98.0, 74.3, 66.0, 61.7, 55.5, 55.5, 52.9, 50.4, 36.4, 29.9, 26.7, 26.3, 24.2, 1.0. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{30}H_{38}N_2O_7SiNa^+$ = 589.23460, found $C_{30}H_{38}N_2O_7SiNa^+$ = 589.23474. **FTIR (Neat)** 2954, 1736, 1688, 1612, 1590, 1508, 1477, 1437, 1410, 1372, 1332, 1298, 1252, 1207, 1156, 1113, 1072, 1040, 918, 867, 843, 781, 754, 729, 644 cm^{-1}. *Notes: During work up an emulsion forms. The yield for this reaction ranges from 75 – 90%.

*Preparation of Secondary Amide **3.54***



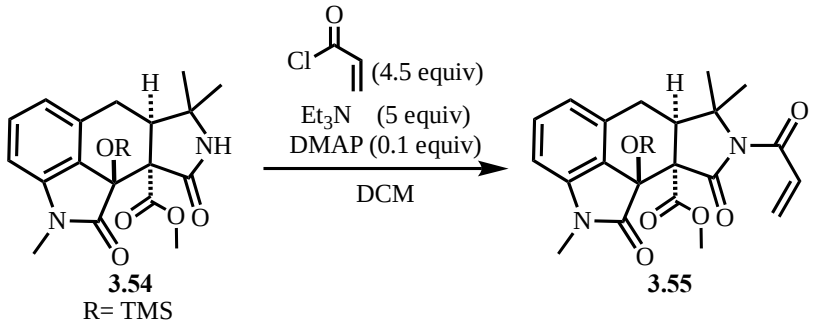
3.49
R= TMS

3.54

To a sealed tube was added tetracycle **3.49** (500 mg, 0.882 mmol, 1 equiv), $CHCl_3$ (9 mL) and H_2O (0.13 mL). Then 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (300 mg, 1.32 mmol, 1.5 equiv) was added. the reaction vessel was then purged with nitrogen, the tube sealed and placed in a pre-heated 75 °C oil bath. After 45 minutes the reaction vessel was removed from the oil bath and allowed to cool for ten minutes. An additional 300 mg (1.32 mmol, 1.5 eq) of DDQ were added and the reaction vessel purged with nitrogen, sealed and then placed in the 75 °C oil bath for an additional hour. After the hour the reaction vessel was removed from the heat and allowed to cool for ten minutes. To the reaction was then added DCM, and the solution poured into a separatory funnel. The organic layer was washed several times with 0.1M $NaHCO_3$ (280 mL total volume), The aqueous layers were combined and re-extracted with DCM several times. The combined organic layers were then dried over magnesium sulfate and the solvent removed by rotary evaporation. The compound was purified by MPLC on a 24-gram column with a flow rate of 35 mL/min. using a gradient which began at 0% ethyl acetate in hexanes and was stepped up to 1:1 ethyl acetate/hexanes then stepped up to pure ethyl acetate and then stepped up once more to 10% methanol in ethyl acetate (the flow rate for the last step in the gradient was increased to 50 mL/min). This gave 265.5 mg (72% Yield) of the secondary amide product **3.54** as an orange foam. R_f = 0.16 (90% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, DMSO-d_6) δ

8.18 (s, 1H), 7.25 (t, *J* = 7.7 Hz, 1H), 6.82 (at, *J* = 7.2 Hz, 2H), 3.41 (s, 3H), 3.09 (s, 3H), 2.92 – 2.69 (m, 3H), 1.33 (s, 3H), 1.25 (s, 3H), -0.20 (s, 9H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 173.7, 170.7, 167.1, 142.7, 135.2, 130.6, 125.9, 120.0, 105.9, 73.6, 66.5, 55.8, 52.3, 50.6, 31.7, 26.2, 26.0, 25.3, 0.7. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{21}H_{28}N_2O_5SiNa^+$ = 439.16652, found $C_{21}H_{28}N_2O_5SiNa^+$ = 439.16650 **FTIR (Neat)** 3210, 3061, 2956, 2898, 1731, 1702, 1637, 1611, 1478, 1434, 1388, 1370, 1333, 1299, 1205, 1236, 1197, 1154, 1115, 1082, 1054, 1017, 983, 961, 922, 869, 843, 806, 780, 752, 730, 697 cm^{-1}. *Notes: The reaction time is critical for this reaction, prolonging the reaction time leads to decomposition. DDQ impurities can often carry over even after several washes with 0.1 M $NaHCO_3$, washing once with half saturated $NaHCO_3$ may be effective for removing persistent DDQ impurities. During work up often an emulsion forms, if this is the case using 10:1 0.1M $NaHCO_3$: brine helps to resolve this issue. The free amide **3.54** is not stable on silica gel, especially in the presence of methanol, quick column purification is essential for high yield. The compound may be obtained as an orange foam, a cream colored solid or a brown amorphous solid depending on the amount of DDQ impurities which were carried through the work up. Very slight DDQ impurities impart a significant amount of colouration.

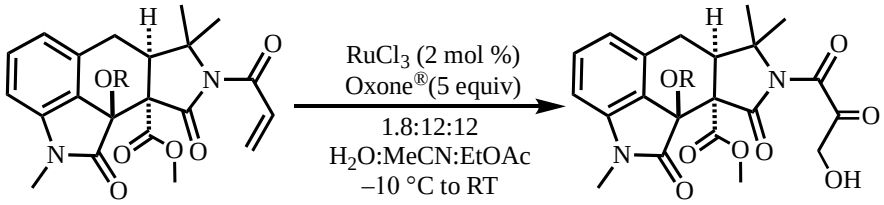
*Preparation of Acrylimide **3.55***



Amide **3.54** (139 mg, 0.33 mmol), DMAP (4.0 mg, 0.033 mmol) and Et_3N (232 μL, 1.66 mmol) were dissolved in dry DCM (3.3 mL). Acryloyl chloride (122 μL,1.50 mmol) was then added and the reaction allowed to stir for 1 hour and 15 minutes and then poured into a separatory funnel which contained basified brine (a few drops of saturated sodium bicarbonate had been added to it). The mixture was then extracted several times with DCM and the organic layers combined. The organic layer was then washed with 0.5 M HCl (aq) and the aqueous acid solution back extracted three times with DCM. The combined organic layers were dried over sodium sulfate and the solvent removed under reduced pressure. The residue was then purified by MPLC using a 4-gram column at a flow rate of 18 mL/min with a gradient elution system which began at 0% ethyl acetate in hexanes and progressed to 55% ethyl acetate in hexanes over nine minutes. The gradient was held at 55% for three additional minutes. This gave 97 mg (62% Yield) of the desired product **3.55** as a waxy white solid. R_f = 0.25 (40% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.29 (t, J = 7.7 Hz, 1H), 7.20 (dd, J = 16.9, 10.4 Hz, 1H), 6.82 (d, J = 7.7 Hz, 1H), 6.68 (d, J = 7.7 Hz, 1H), 6.40 (dd, J = 16.9, 1.8 Hz, 1H), 5.76 (dd, J = 10.4, 1.8 Hz, 1H), 3.54 (s, 3H), 3.22 (s, 3H), 3.04 (dd, J = 13.2, 9.5 Hz, 1H), 2.92 – 2.74 (m, 2H), 1.74 (s, 3H), 1.65 (s, 3H), -0.12 (s, 9H). **^{13}C NMR** (151 MHz, Chloroform-d) δ 174.2, 170.1, 169.9, 168.0,

143.3, 135.0, 131.7, 131.4, 129.2, 126.0, 120.5, 106.2, 74.3, 66.2, 63.9, 53.2, 50.3, 30.5, 26.7, 26.2, 22.7, 0.8. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{24}H_{30}N_2O_6SiNa^+$ = 493.17708, found $C_{24}H_{30}N_2O_6SiNa^+$ = 493.17679. **FTIR (Neat)** 2958, 1737, 1668, 1612, 1478, 1402, 1373,1309, 1252, 1219, 1178, 1153, 1112, 1080, 1041, 1022, 963, 925, 862, 844, 795, 781, 753, 703 cm^{-1}.

*Preparation of Acyloin **3.58***



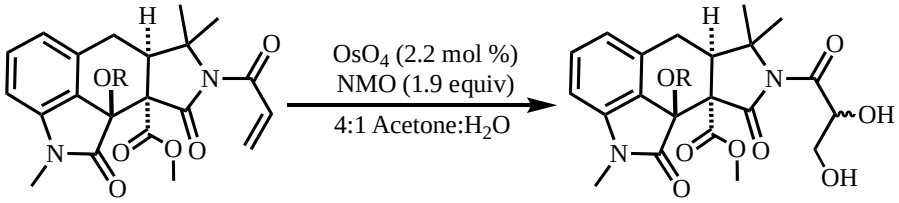
3.55
R= TMS

3.58

Acrylimide **3.55** (5 mg, 0.01 mmol) was added to a vial which contained a 1.8:12:12 solution of H_2O:MeCN:EtOAc (0.12 mL), and was cooled in an ice acetone bath. Then 0.1 M $RuCl_3$ in H_2O solution (1 μL, 0.0001 mmol) Oxone® (7.6 mg, 0.025 mmol), and sodium bicarbonate (2.1 mg, 0.025 mmol) were added. After this was added an additional 7.5 mg of Oxone® (0.024 mmol) and 1 μL of the 0.1 M $RuCl_3$ solution (0.0001 mmol). The reaction was allowed warm to room temperature and was stirred overnight. The reaction mixture was then diluted with ethyl acetate and washed with half saturated brine. The aqueous layer was back extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate and the solvent removed under reduced pressure. The residue was loaded onto a TLC plate for prep TLC and was eluted with 75% ethyl acetate in hexanes to give 0.8 mg (15% yield) of **3.58** as a white solid. R_f = 0.51 (90% EtOAc/hexanes), UV; **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.32 (t, *J* = 7.7 Hz, 1H), 6.87 (d, *J* = 7.7 Hz, 1H), 6.71

(d, *J* = 7.7 Hz, 1H), 4.59 – 4.43 (m, 2H), 3.57 (s, 3H), 3.21 (s, 3H), 3.08 (dd, *J* = 13.9, 10.1 Hz, 1H), 3.00 (dd, *J* = 10.1, 7.8 Hz, 1H), 2.83 (dd, *J* = 13.9, 7.8 Hz, 1H), 1.76 (s, 3H), 1.71 (s, 3H), -0.08 (s, 9H).**^{13}C NMR** (151 MHz, Chloroform-*d*) δ 197.4, 174.2, 172.1, 169.7, 168.9, 143.3, 134.7, 131.7, 125.4, 120.8, 106.6, 74.3, 66.3, 65.5, 63.5, 53.6, 51.4, 29.3, 26.7, 26.0, 22.4, 0.8. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{24}H_{30}N_2O_8SiNa^+$ = 525.16691, found $C_{24}H_{30}N_2O_8SiNa^+$ = 525.16644. **FTIR (Neat)** 3449, 3339, 2957, 2927, 2854, 1736, 1696, 1638, 1612, 1478,1436, 1387, 1370, 1314, 1253, 1198, 1156, 1113, 1079, 1043, 1024, 960, 922, 866, 846, 816, 805, 782, 753, 740, 688, 637.

*Preparation of Diol **3.56***



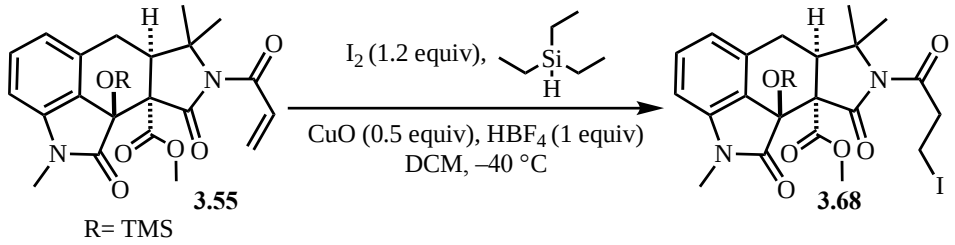
3.55
R= TMS

3.56

Acrylimide **3.55** (152 mg, 0.322 mmol) and NMO (45.6 mg, 0.389 mmol) were dissolved in 4:1 acetone: H_2O solution (3.2 mL). Subsequently a 0.01 M solution of osmium tetroxide (0.06 mmol) in *t*-butanol was added. After 14 h and 50 minutes to the reaction was added 25 mg of NMO (0.21 mmol) and 100 μL of a 0.01 M solution of osmium tetroxide in (0.01 mmol) in *t*-butanol was added. After 8 hours and 25 minutes the reaction was quenched with 0.1M sodium bisulfite and extracted several times with ethyl acetate and once with DCM. The organic layers were combined and dried over sodium sulfate. The solvent was then removed under reduced pressure. The residue was purified by MPLC on a 4-gram silica column using a gradient beginning at 0% ethyl acetate in

hexanes and progressing to 75% ethyl acetate in hexanes at a flow rate of 18 mL/min. This gave 123 mg (76% Yield) of the desired product **3.56** (compounds were characterized as a 1:0.68 mixture of diastereomers, the gem dimethyl resonance for the major diastereomer was chosen to integrate to six protons) as a pale yellow foam which was used in the next step as a mixture of diastereomers. Diastereomer 1 R_f = 0.33 (90% EtOAc/hexanes), UV; diastereomer 2 R_f = 0.24 (90% EtOAc/hexanes), UV; **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.33 – 7.27 (m, 1.7H), 6.84 (d, *J* = 7.7 Hz, 1.7H), 6.69 (d, *J* = 7.7 Hz, 1.7H), 3.97 – 3.75 (m, 5H), 3.57 (s, 3H), 3.55 (s, 1.9H), 3.21 (s, 5H), 3.10 – 3.02 (m, 1.7H), 2.94 (dd, *J* = 9.9, 8.1 Hz, 1H), 2.87 (dd, *J* = 10.0, 7.9 Hz, 0.7H), 2.83 – 2.77 (m, 1.7H), 1.78 (s, 2H), 1.69 (d, *J* = 1.5 Hz, 6H), 1.61 (s, 2H), -0.09 – -0.11 (m, 15H).**^{13}C NMR** (151 MHz, Chloroform-d) δ 176.2, 175.9, 174.1, 174.0, 170.4, 170.2, 169.5, 169.5, 143.4, 143.3, 134.8, 134.7, 131.6, 125.8, 125.7, 120.6, 120.5, 106.3, 106.3, 74.4, 74.2, 73.6, 73.3, 66.2, 66.2, 65.0, 65.0, 64.3, 63.8, 53.3, 53.3, 50.5, 50.2, 30.6, 29.3, 26.7, 26.3, 25.6, 22.8, 22.5, 0.9, 0.8. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{24}H_{32}N_2O_8SiNa^+$ = 527.18256, found $C_{24}H_{32}N_2O_8SiNa^+$ = 527.18243. **FTIR (Neat)** 3492, 2956, 1737, 1706, 1637, 1613, 1478, 1371, 1304, 1252, 1211, 1154, 1111,1081, 1042, 1024, 962, 920, 865, 846, 780, 729, 646 cm^{-1}.

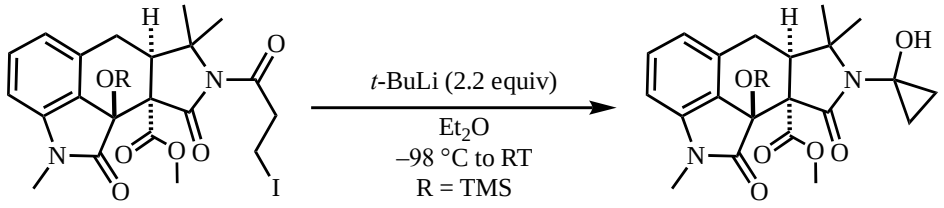
*Preparation of Iodide **3.68***



To a dry vial was added CuO (17.2 mg, 0.0216 mmol) and 50% tetrafluoroboric acid in diethyl ether (67 μL, 0.49 mmol) and dry DCM (2.2 mL); they were allowed to stir for five minutes. Subsequently, the reaction vial was cooled in a dry ice/acetonitrile bath. Then iodine (138 mg, 0.542 mmol), acrylimide **3.55 (**215 mg, 0.457 mmol) and of triethyl silane (284 μL, 1.78 mmol) were sequentially added. The reaction was allowed to stir for 3.5 h then DCM and water were added. The reaction solution was washed with the water. The aqueous layer was back extracted with DCM and the organic layers combined and dried over magnesium sulfate and the solvent removed under reduced pressure. The residue was then purified by MPLC using a 12-gram silica gel column and a gradient which began at 0% ethyl acetate in hexanes and progressed to 45% ethyl acetate in hexanes. A flow rate of 30 mL/min was used. This gave 198 mg (73% Yield) of iodide **3.68** (viscous pale yellow oil). R_f = 0.25 (40% EtOAc/hexanes), UV; **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.29 (t, *J* = 7.7 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 6.69 (d, *J* = 7.7 Hz, 1H), 3.68 (dt, *J* = 18.0, 6.4 Hz, 1H), 3.64 – 3.51 (m, 1H), 3.55 (s, 3H), 3.45 – 3.36 (m, 2H), 3.22 (s, 3H), 3.04 (dd, *J* = 14.0, 9.9 Hz, 1H), 2.87 (dd, *J* = 9.9, 8.0 Hz, 1H), 2.79 (dd, *J* = 13.9, 8.1 Hz, 1H), 1.74 (s, 3H), 1.65 (s, 3H), -0.09 (s, 9H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 174.1, 173.5, 169.9, 169.8, 143.3, 134.9, 131.4, 125.9, 120.5, 106.2, 74.3, 66.2, 64.4, 53.3, 50.1, 43.0, 30.2, 26.7, 26.0, 22.8, 0.9, -2.7. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{24}H_{31}IN_2O_6SiNa^+$ =

621.08938, found $C_{24}H_{31}IN_2O_6SiNa^+$ = 621.08893 FTIR neat 2956, 1740, 1703, 1638, 1613, 1478, 1366, 1303, 1252, 1215, 1153, 1113, 1079, 1042,1022, 925, 867, 845, 780, 753, 731 cm^{-1}.

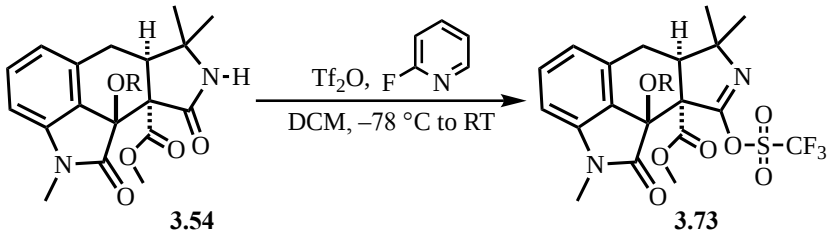
*Preparation of Cyclopropyl Hemiaminal **3.70***



Iodide **3.68** (10.8 mg, 0.018 mmol) was dissolved in dry diethyl ether (0.35 mL) and the reaction cooled in a methanol liquid nitrogen bath. Slowly was then added 1.65 M solution of *t*-BuLi (24 μL, 0.040 mmol). After 45 minutes the reaction was moved to a dry ice acetone bath and allowed to stir for 25 minutes, then allowed to warm up to room temperature. The reaction was quenched with 0.1 mL acetic acid after a total reaction time of 1 h and 40 minutes. Deionized water was then added and the reaction mixture extracted several times with DCM. The organic layers were combined and dried over sodium sulfate and the solvent removed by rotary evaporation. The residue was purified by prep TLC utilizing ethyl acetate as the eluent. This gave 2.6 mg (31% Yield) of the cyclopropyl hemiaminal **3.70** as a yellow - orange film. R_f = 0.21 (90% EtOAc/hexanes), UV; **^{1}H NMR** (600 MHz, Acetonitrile-d_3) δ 7.29 (t, *J* = 7.7 Hz, 1H), 6.85 (d, *J* = 7.7 Hz, 1H), 6.74 (d, *J* = 7.7 Hz, 1H), 3.43 (s, 3H), 3.13 (s, 3H), 2.89 – 2.78 (m, 3H), 1.54 (s, 3H), 1.51 (s, 3H), 1.16 – 1.12 (m, 1H), 1.08 – 1.00 (m, 3H), -0.20 (s, 9H). **^{13}C NMR** (151 MHz, Acetonitrile-d_3) δ 175.5, 172.1, 169.3, 144.0, 136.7, 131.8, 127.2, 121.2, 106.8, 75.2, 66.0, 63.8, 62.5, 53.0, 51.1, 32.2, 26.8 (d, *J* = 3.9 Hz), 25.8, 15.1, 14.7, 0.7. **+ESI-HRMS** m/z: calc'd for

$[M+Na]^+$ $C_{24}H_{32}N_2O_6SiNa^+$ = 495.19273, found $C_{24}H_{32}N_2O_6SiNa^+$ = 495.19235. **FTIR (Neat)** 3427, 2955, 1735, 1638, 1612, 1478, 1372, 1298, 1251, 1198, 1153, 1112, 1078, 1042, 1021, 965, 926, 868, 845,781, 754 cm^{-1}.

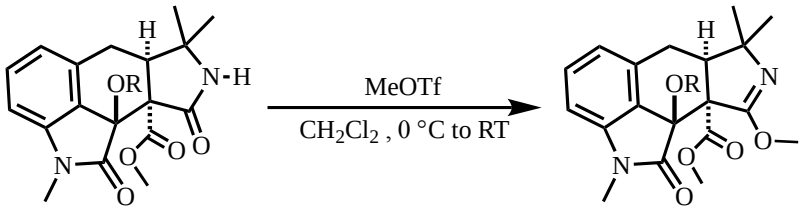
*Preparation of Imidoyl Triflate **3.73***



To a dry round bottomed flask was added amide **3.54** (180 mg, 0.432 mmol), dry DCM (9.8 mL) and 2-fluoropyridine (54 μL, 0.063 mmol). The reaction flask was cooled in a dry ice acetone bath and triflic anhydride (107 μL, 0.636 mmol) was added. After one hour the reaction flask was transferred to a cooling bath containing 1:1 2-propanol: H_2O and dry ice (~ –35 ^oC) and stirred for one hour and 15 minutes. The reaction was then placed in an ice bath and 10 μL of additional triflic anhydride (0.059 mmol) were added and after 10 minutes the reaction was allowed to warm to room temperatures and quenched with 25:75:1 ethyl acetate: hexanes: triethyl amine. The material was then flushed through a silica plug utilizing the same solvent system. This gave 166 mg (70% Yield) of **3.73** as a white solid. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.29 (t, *J* = 7.7 Hz, 1H), 6.83 (d, *J* = 7.7 Hz, 1H), 6.69 (d, *J* = 7.7 Hz, 1H), 3.59 (s, 3H), 3.19 (s, 3H), 2.97 (dd, *J* = 13.0, 9.9 Hz, 1H), 2.83 – 2.64 (m, 2H), 1.46 (s, 3H), 1.40 (s, 3H), -0.10 (s, 9H). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 174.5, 169.2, 155.0, 143.6, 135.7, 131.3, 125.7, 120.6, 119.5 (q, J = 320.1 Hz), 106.4, 73.5, 70.7, 70.2, 56.7, 53.2, 31.5, 27.1, 26.6, 25.8, 0.6. **+ESI-HRMS** m/z:

calc'd for $[M+Na]^+$ $C_{22}H_{27}F_3N_2O_7SSiNa^+$ = 571.11580, found $C_{22}H_{27}F_3N_2O_7SSiNa^+$ = 571.11505. **FTIR (Neat)** 2958, 2921, 2850, 1739, 1697, 1614, 1478, 1417, 1371, 1254, 1230, 1206, 1134, 1074, 1042, 1014, 959, 929, 901, 867, 847, 812, 797, 764, 611, 588 cm^{-1}.

*Preparation of Imidate **3.85***



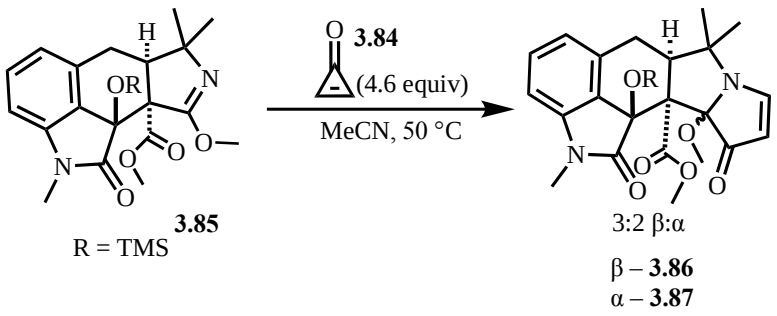
3.54
R = TMS

3.85

Into a flame dried round bottomed flask was added secondary amide **3.54** (900 mg, 2.16 mmol, 1 equiv) and dry DCM (22 mL). This solution was cooled in an ice bath then methyl triflate (3.6 mL, 32 mmol, 14.7 equiv) was added over 15 min, the ice bath was immediately removed and the reaction stirred for 30 minutes while warming to room temperature. After the 30 minutes the reaction was cooled again in an ice bath an additional 2.7 mL (24 mmol, 11.1 equiv) of MeOTf were added over 17 minutes. The ice bath was immediately removed and the reaction was allowed to warm to room temperature. After 30 minutes the reaction was cooled in an ice bath and additional 3.6 mL (32 mmol, 14.7 equiv) of methyl triflate were added over 18 minutes the reaction was once again immediately removed from the ice bath. The reaction was then stirred for 40 minutes then cooled in the ice bath and 1 mL (8.8 mmol, 4.1 equiv) additional of methyl triflate was added and the ice bath once again removed. Ten minutes later the reaction was once again cooled in an ice bath and quenched with a mixture containing 20 mL DCM, 15 mL triethyl amine, and 10.5

mL H_2O. Immediately following the quench was added 7 grams of silica gel and the mixture stirred for one hour and 40 minutes. After the one hour and 40 minutes the mixture was filtered through a pad of silica, and eluted with a 70:30:1 ethyl acetate: hexanes: triethyl amine solution. The eluent solution was placed into a separatory funnel and washed with 150 mL of a 10:1 deionized water: saturated sodium bicarbonate solution. The aqueous layer was extracted with DCM then once more with ethyl acetate. The organic layer was dried over sodium sulfate and the solvent removed by rotary evaporation. The residue was purified by column chromatography using an MPLC with a 12-gram column at a flow rate of 30 mL/min. A gradient which began at 0% ethyl acetate in hexanes and progressed to 50% ethyl acetate in hexanes was used for purification (all solvents for chromatography contained ~ 1% triethyl amine). This gave 702 mg (76% Yield) of imidate **3.85** as a crystalline white solid. R_f = 0.6 (50% EtOAc/hexanes), UV; **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.25 (t, J = 7.7 Hz, 1H), 6.82 (at, J = 7.8 Hz, 2H), 3.69 (s, 3H), 3.42 (s, 3H), 3.08 (s, 3H), 2.82 – 2.69 (m, 3H), 1.31 (s, 3H), 1.22 (s, 3H), -0.20 (s, 9H).**^{13}C NMR** (151 MHz, Chloroform-d) δ 175.1, 171.0, 164.4, 143.2, 136.4, 130.6, 126.6, 120.3, 105.8, 73.9, 70.9, 67.8, 56.1, 56.0, 52.7, 32.5, 26.9, 26.8, 26.4, 0.8.**+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{22}H_{30}N_2O_5SiNa^+$ = 453.18217, found $C_{22}H_{30}N_2O_5SiNa^+$= 453.18173. **FTIR (Neat)** 2955, 1730, 1667, 1637, 1611, 1477, 1437, 1374, 1318, 1297, 1249, 1193, 1153, 1116, 1065, 1041, 1016, 983, 968, 943, 920, 900, 868, 842, 802, 775, 752, 731, 702, 647 cm^{-1}. Notes: Addition of all the methyl triflate over a single 45-minute period resulted in significantly lower yields.

*Preparation of Pentacycle Diastereomeric Mixture **3.86** & **3.87***

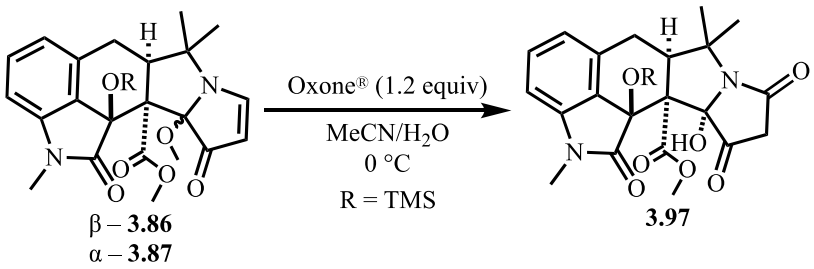


Three of these reactions were run simultaneously, then combined for work up and purification. To a flame dried round bottomed flask was added imidate **3.85** (1.1 g, 2.27 mmol, 1 equiv), dry MeCN (25 mL) and cyclopropenone **3.84** (834 mg, 10.4 mmol, 4.58 equiv) as a 67.4% by weight mixture of cyclopropenone in neopentyl glycol (as determined by quantitative NMR). The reaction flask was then purged with nitrogen and stirred for five minutes at room temperature. The reaction was then placed in a pre-heated 50 ^{o}C oil bath for five hours. After five hours 228 mg (2.84 mmol, 1.25 eq) additional cyclopropenone (**3.71**) solution was added and the reaction heated at 50 ^{o}C for an additional 35 minutes. The reactions were combined and poured into a separatory funnel containing deionized water. DCM was then added and the reaction mixture extracted several times with DCM. The combined organic layers were dried over sodium sulfate and the solvent then removed by rotary evaporation. The residue was purified by MPLC on an 80-gram column using a flow rate of 60 mL/min and a gradient which began at 0% ethyl acetate in hexanes and progressed to 85% ethyl acetate in hexanes (all solvents contained ~1% triethyl amine). This gave 3.31 grams (89% Yield) of **3.86** & **3.87** as an inconsequential mixture of diastereomers. The compound ranges in appearance from a white foam to a light peach coloured foam. If glycol remained in the product mixture it was removed by

dissolving the product in chloroform and washing several times with deionized water. Slightly higher yield was observed on smaller scales for this reaction. Crystals for X-ray analysis were grown by vapor diffusion, pentane into DCM solution of the compound. R_f = 0.27 (75% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.96 (d, *J* = 3.9 Hz, 1H major diastereomer), 7.78 (d, *J* = 4.0 Hz, 0.70 H minor diastereomer), 7.21 (t, *J* = 7.7 Hz, 0.78 H minor diastereomer), 7.14 (t, *J* = 7.7 Hz, 1H major diastereomer), 6.80 (d, *J* = 7.7 Hz, 0.71 H minor diastereomer), 6.72 (d, *J* = 7.7 Hz, 1H major diastereomer), 6.53 (d, *J* = 5.2 Hz, 1H major diastereomer), 6.51 (d, *J* = 5.2 Hz, 0.73 H minor diastereomer), 5.25 (d, *J* = 3.9 Hz, 0.73 H minor diastereomer), 5.02 (d, *J* = 3.9 Hz, 1H major diastereomer), 3.93 (at, *J* = 9.4, 8.4 Hz, 0.81 H minor diastereomer), 3.45 (dd, *J* = 10.0, 8.2 Hz, 1H major diastereomer), 3.30 (s, 2H minor diastereomer), 3.25 (s, 3H major diastereomer), 3.25 (s, 3H major diastereomer), 3.17 (s, 3H major diastereomer), 3.08 (s, 2H minor diastereomer), 3.07 (s, 2H minor diastereomer), 2.93 – 2.80 (m, 3H), 2.66 (dd, *J* = 14.0, 8.3 Hz, 1H), 1.59 (s, 3H major diastereomer), 1.53 (s, 3H major diastereomer), 1.51 (s, 2H minor diastereomer), 1.49 (s, 2H minor diastereomer), -0.12 (s, 9H major diastereomer), -0.15 (s, 6H minor diastereomer). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 200.4, 194.5, 173.9, 173.7, 170.9, 168.1, 164.3, 161.8, 141.9, 141.7, 137.1, 134.5, 131.6, 130.4, 128.6, 125.0, 120.9, 120.3, 105.4, 105.4, 102.2, 101.2, 99.9, 97.2, 76.1, 68.3, 67.2, 62.8, 60.9, 57.4, 54.3, 52.6, 52.6, 51.4, 50.2, 34.5, 27.1, 26.4, 26.4, 26.3, 26.3, 23.8, 23.3, 1.0. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{25}H_{32}N_2O_6SiNa^+$ = 507.19273, found $C_{21}H_{28}N_2O_5SiNa^+$ = 507.19275. **FTIR (Neat)** 2952, 2249, 1734, 1689, 1635, 1609, 1532, 1477, 1434, 1399, 1373, 1329, 1298, 1247, 1135, 1117, 1081, 1056, 1042, 1015, 992, 951, 909, 872, 840, 800, 774, 752, 723, 644 cm^{-1}. *Notes: The cyclopropenone used for this

procedure was obtained using the same method delineated in the references of Nakamura et al.,[3] with the exception that none of the intermediates were distilled, we found that the material obtained at each step was adequately pure without purification. Additionally, the cyclopropenone was also not distilled (as described by Breslow et al.[4]) due to excessive decomposition. Instead of distillation, the cyclopropenone/neopentyl glycol viscous oil mixture obtained from the last step of Nakamura et al.'s procedures was placed in a –20 °C freezer overnight. After standing in the freezer the neopentyl glycol crystallizes. Slight warming then allows for decantation of a solution now enriched in cyclopropenone. The percent by weight of cyclopropenone was then determined by quantitative NMR and the stoichiometry for the reaction calculated accordingly. The excess neopentyl glycol often caused an emulsion to form during work up of this reaction.

*Preparation of Tetramic Acid **3.97***

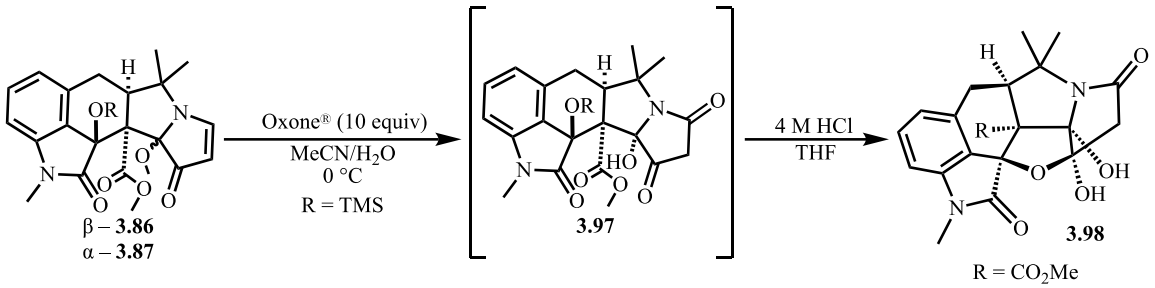


To a round bottom flasked was added pentacycle **3.86** & **3.87** (300 mg, 0.62 mmol, 1 equiv) the flask was evacuated and back filled with nitrogen three times and dry MeCN (15 mL) was added. The solution was cooled in an ice bath then Oxone® (209 mg, 0.679 mmol, 1.1 equiv) was added. The flask was then purged with nitrogen. To the reaction mixture was then introduced water (11.2 mL) by syringe pump over one hour. The reaction mixture was then allowed to stir for an additional four hours and twenty minutes then 10

mg (0.033 mmol, 0.05 equiv) of additional Oxone® were added and the reaction stirred for an additional 30 minutes. The reaction mixture was then poured into a separatory funnel which contained deionized water. The aqueous layer was extracted several times with DCM and then several times with ethyl acetate. The organic layers were combined and dried over sodium sulfate. The solvent was removed by rotary evaporation and the residue purified by MPLC on a 12-gram column using a flow rate of 30 mL/min. A gradient elution which began at 0% ethyl acetate in hexanes and progressed to 75% ethyl acetate in hexanes was used for purification. This gave 202 mg (67% Yield) of tetramic acid **3.97** as a single diastereomer (beige solid). R_f = 0.21 (75% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.30 (t, *J* = 7.7 Hz, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 4.01 (d, *J* = 21.1 Hz, 1H), 3.70 (dd, *J* = 9.7, 7.8 Hz, 1H), 3.30 (s, 3H), 3.12 (s, 3H), 3.10 – 2.99 (m, 2H), 2.94 (dd, *J* = 15.1, 9.6 Hz, 1H), 1.85 (s, 3H), 1.64 (s, 3H), -0.07 (s, 9H).**^{13}C NMR** (151 MHz, Chloroform-*d*) δ 201.9, 175.1, 168.1, 167.1, 141.9, 138.4, 132.2, 124.1, 121.8, 106.1, 95.4, 75.6, 69.5, 63.3, 52.7, 52.1, 44.5, 34.0, 26.6, 26.2, 22.8, 0.9. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{24}H_{30}N_2O_7SiNa^+$ = 509.17200, found $C_{24}H_{30}N_2O_7SiNa^+$ = 509.17160. **FTIR (Neat)** 3460, 3423, 2953, 1778, 1721, 1702, 1686, 1605, 1475, 1437, 1389, 1367, 1307, 1253, 1190, 1155, 1129, 1112, 1088, 1029, 1014, 954, 870, 846, 778, 751, 736, 618, 598 cm^{-1}. *Note: an analytically pure sample was obtained by prep TLC eluting twice: the first time with 65% ethyl acetate in hexanes and the second time with 75% ethyl acetate in hexanes. Despite the low solubility in various organic solvents, methanol should not be used in any quantity to dissolve the compound in preparation for loading it onto silica gel, this will lead to almost complete de-silylation and cyclization to

form the lactol ring during chromatography. Crystals for X-ray analysis were grown by slow evaporation of DCM/$CDCl_3$ solution of the compound.

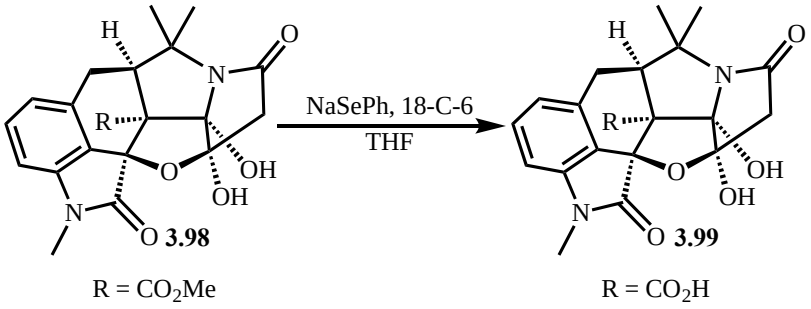
*Preparation of Hexacyclic Ester **3.98***



To a round bottomed flask was added 1.24 grams of vinylogous amides **3.86** & **3.87** (2.6 mmol), Oxone® (76 mg, 24.7 mmol) and MeCN (64 mL). The reaction flask was cooled in an ice bath and deionized water (39 mL) as added over 1h and 45 minutes using a syringe pump. The reaction was stirred for an additional 3h and 40 minutes and then to the reaction was added ethyl acetate with vigorous stirring. The solution was then allowed to warm up and extracted several times with ethyl acetate and several times with DCM the combined organic layers were then dried over sodium sulfate and the solvent removed by rotary evaporation. The crude tetramic acid **3.97** was then dissolved in THF (38 mL) and 31 mL of 4 M HCl (aq) was added at room temperature. The flask was purged with N_2 and the solution was heated to 32 ^oC after 16 h and 25 minutes 9 mL of additional 4 M HCl (aq) was added and the reaction warmed to 37 ^oC for 1.5 h. Brine and water were added and the reaction mixture was extracted three times with ethyl acetate to give 859 mg (81% Yield) of hexacyclic ester **3.98** which was used for the next step without further purification. R_f = 0.51 (90% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.35 (t, J = 7.8 Hz, 1H), 6.95 (d, J = 7.7 Hz, 1H), 6.73 (d, J = 7.8 Hz, 1H), 6.36 (s, 1H),

6.21 (s, 1H), 3.53 (s, 3H), 3.20 (s, 3H), 2.97 (d, J = 17.6 Hz, 1H), 2.85 – 2.62 (m, 4H), 1.77 (s, 3H), 1.57 (s, 3H). **^{13}C NMR** (151 MHz, Chloroform-d) δ 177.6, 172.7, 171.6, 143.0, 136.6, 132.2, 122.2, 122.2, 108.8, 107.1, 104.5, 85.4, 67.1, 63.9, 62.3, 53.2, 43.8, 30.3, 28.8, 26.9, 22.5. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{21}H_{22}N_2O_7Na^+$ = 437.13247, found $C_{21}H_{22}N_2O_7Na^+$ = 437.13247. **FTIR (Neat)** 3365, 2927, 1710, 1695, 1642, 1618, 1499, 1478, 1395, 1371, 1295, 1240,1180, 1154, 1136, 1090, 1044, 1022, 996, 886, 792, 730, 698, 675, 648, 617 cm^{-1}.

*Preparation of Hexacyclic Acid **3.99***

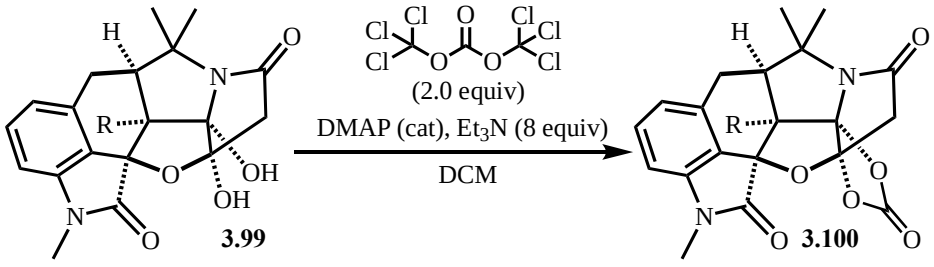


R = CO_2Me R = CO_2H

To a dry round bottomed flask was added sodium hydride (256 mg, 9.60 mmol, degreased assuming 90%) and dry THF (20 mL). Then selenophenol (0.99 mL, 9.3 mmol) was added followed shortly after by 18-C-6 (168 mg, 0.064 mmol) the solution was stirred for 30 minutes then hexacyclic ester **3.98** (500 mg, 1.2 mmol) was added and the solution stirred at room temperature for 1 hour and 40 minutes. The reaction was then quenched by the addition of 8 mL of a 1:10 TFA:THF solution. To the acidic solution was then added 20% saturated sodium bicarbonate solution until the solution was basic. Brine was then added and several chloroform washes used to remove excess selenophenol. An additional wash with minimal DCM was performed then TFA was added to acidify the solution, once acidic the solution was extracted several times with a 3:1 chloroform: isopropanol mixture.

The combined organic layers were dried over sodium sulfate and the solvent removed by rotary evaporation and residual isopropanol removed under a stream of nitrogen. The entire work up process was repeated again on the crude residue which was after the second work up procedure triturated several times with chloroform to give 350 mg (72% Yield) of hexacyclic acid **3.99** (white amorphous solid). **^{1}H NMR** (400 MHz, Methanol-d_4) δ 7.36 (t, *J* = 7.7 Hz, 1H), 6.99 (d, *J* = 7.8 Hz, 1H), 6.86 (d, *J* = 7.9 Hz, 1H), 3.18 (s, 3H), 2.94 – 2.85 (m, 2H), 2.71 – 2.51 (m, 3H), 1.71 (s, 3H), 1.61 (s, 3H). **^{13}C NMR** (151 MHz, Deuterium Oxide) δ 178.8, 178.1, 174.6, 143.6, 137.2, 132.9, 123.1, 123.0, 108.5, 104.1, 87.0, 68.1, 62.8, 61.8, 43.9, 29.3, 28.8, 27.2, 24.3, 21.8. (potassium carboxylate salt of the acid, methanol as an internal standard 49.50 ppm). **–ESI-HRMS** m/z: calc'd for $[M–H]^-$ $C_{20}H_{19}N_2O_7^-$ = 399.11977, found $C_{20}H_{19}N_2O_7^-$ = 399.1200. **FTIR (Neat)** 3360, 2903, 2531, 1737, 1688, 1644, 1617, 1479, 1414, 1391, 1370, 1289, 1269, 1188, 1172, 1131, 1044, 1018, 994, 887, 844, 802, 746, 724, 710, 692, 674, 659, 645 cm^{-1}.

*Preparation of Cyclic Carbonate **3.100***

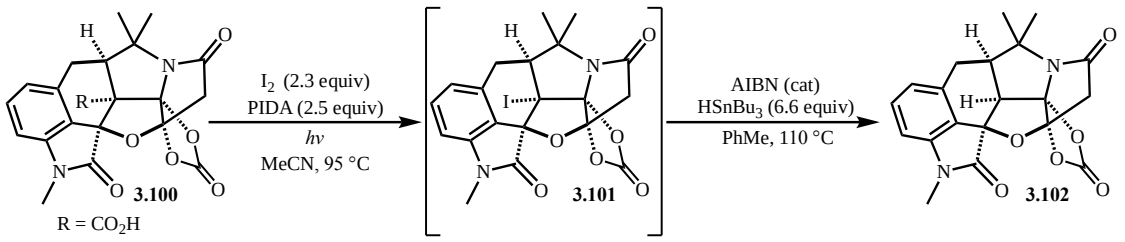


R = CO_2H

This reaction was run on the same scale twice and the two reactions combined for purification. To a dry vial was added hexacyclic acid **3.99** (5 mg, 0.0125 mmol). The acid was suspended in dry DCM (1 mL) and then triphosgene (6.6 mg, 0.022 mmol) was added, followed Et_3N (7 μL, 0.05 mmol). An additional 7 μL of Et_3N (0.05 mmol) was added

over 10 minutes. After 2.5 hours DMAP (0.6 mg, 0.0049 mmol) was added and the reaction allowed to stir for an additional 4 hour and 5 minutes and the solvent was then evaporated. The residue from the combined reactions was dissolved in DCM containing trace TFA and loaded directly onto a reverse phase TLC plate for preparative TLC. The plate was eluted with 40:60 MeCN: H2O solvent system which contained 0.25% formic acid. this gave 6.2 mg (58% Yield) of cyclic carbonate **3.100** (white - light yellow amorphous solid). **^{1}H NMR** (600 MHz, Acetonitrile-d_3) δ 7.39 (t, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 7.7 Hz, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 3.20 (d, *J* = 18.5 Hz, 1H), 3.12 (dd, *J* = 18.4, 0.5 Hz, 1H), 3.08 (s, 3H), 2.94 (dd, *J* = 14.3, 5.5 Hz, 1H), 2.72 (dd, *J* = 12.1, 5.5 Hz, 1H), 2.44 – 2.35 (m, 1H), 1.65 (s, 3H), 1.61 (s, 3H). **^{13}C NMR** (101 MHz, Acetonitrile-d_3) δ 174.6, 174.5, 169.6, 151.8, 145.2, 136.8, 133.4, 122.6, 122.2, 113.6, 112.2, 108.1, 89.7, 71.5, 65.2, 63.5, 44.6, 29.9, 28.3, 26.9, 21.9. **–ESI-HRMS** m/z: calc'd for $[M–H]^-$ $C_{21}H_{17}N_2O_8^-$ = 425.09904, found $C_{21}H_{17}N_2O_8^-$ = 425.09892. **FTIR (Neat)** 3435, 2925, 1825, 1725, 1644, 1615, 1477, 1398, 1369, 1296, 1264, 1187, 1137, 1107, 1092, 1064, 1008, 992, 969, 947, 885, 781, 755, 723, 679, 650, 604 cm^{-1}.

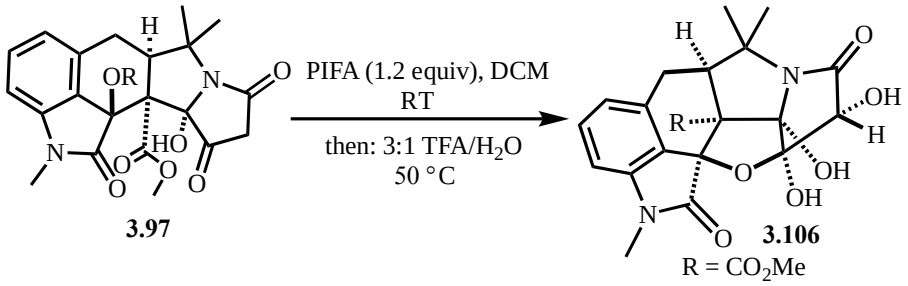
*Preparation of Heptacycle **3.102***



Cyclic carbonate **3.100** (3.3 mg, 0.00774 mmol), PIDA (3 mg, 0.0093 mmol) and iodine (2.3 mg, 0.0091 mmol) were dissolved in of MeCN (0.32 mL). The reaction mixture was allowed to stir for five minutes then heated to 95 °C while being irradiated by two tungsten lamps. after 2 hours the reaction was allowed to cool to room temperature and PIDA (3 mg, 0.0093 mmol) and iodine (2.3 mg, 0.0091 mmol) were added and the reaction stirred for five minutes and then heated to 95 °C while being irradiated with two tungsten lamps for an additional 9 h and 50 minutes. the solvent was then evaporated and toluene added and evaporated once then 0.2 mL of toluene was added, followed by tributyl tin hydride (12 μL, 0.045 mmol) and catalytic AIBN. This reaction was heated to reflux for 15 minutes then cooled to room temperature and allowed to stir for an additional one hour and 25 minutes the solvent was evaporated and the residue purified by preparative TLC using an eluent system consisting of 40:60 ethyl acetate: hexanes. This gave 1.5 mg (51% Yield) of compound **3.102** as a clear film. R_f = 0.2 (40% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, Acetonitrile-d_3) δ 7.36 (t, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 3.59 (d, *J* = 8.3 Hz, 1H), 3.23 (d, *J* = 18.5 Hz, 1H), 3.13 (d, *J* = 18.1 Hz, 1H), 3.12 (s, 3H), 2.82 (dd, *J* = 14.1, 5.1 Hz, 1H), 2.48 – 2.40 (m, 1H), 2.33 – 2.23 (m, 1H), 1.67 (s, 3H), 1.45 (s, 3H). **^{13}C NMR** (101 MHz, Acetonitrile-d_3) δ 175.1, 174.9, 152.4, 144.9, 138.3, 133.5, 122.5, 122.3, 115.3, 112.8, 108.1, 87.3, 72.7, 56.6, 52.4, 44.8, 29.5,

27.4, 26.9, 20.6. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{20}H_{18}N_2O_6Na^+$ = 405.10626, found $C_{20}H_{18}N_2O_6Na^+$ = 405.10608. **FTIR (Neat)** 2928, 1825, 1723, 1635, 1613, 1476, 1396, 1368, 1329, 1295, 1280, 1251, 1228, 1179, 1150, 1131, 1080, 1062, 1021, 993, 978, 963, 949, 908, 886, 843, 815, 797, 781, 759, 734, 707, 671, 643, 618 cm^{-1}.

*Preparation of Hexacyclic Alcohol **3.106***

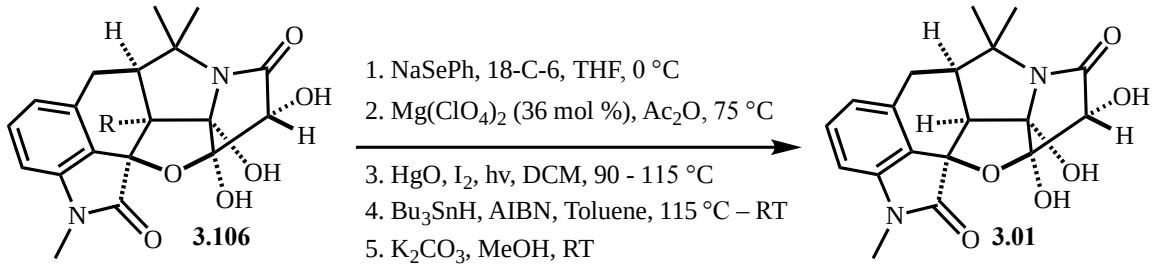


3.97 **3.106**

R = CO_2Me

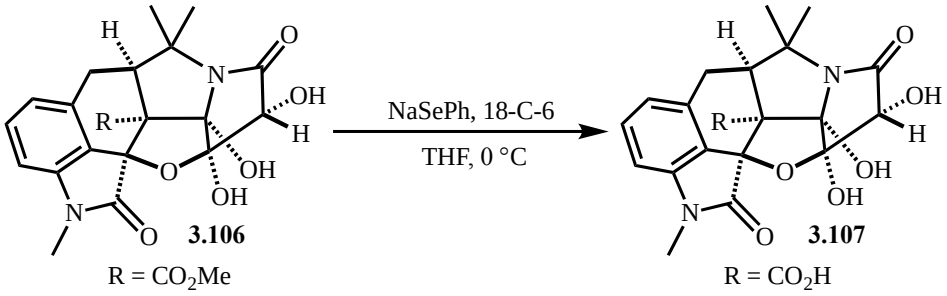
Tetramic acid **3.97** (44 mg, 0.09 mmol, 1 equiv) was added to a flame dried vial and the vial evacuated and back filled with nitrogen three times. The tetramic was then dissolved in DCM (0.85 mL) and PIFA added (47 mg, 1.1 mmol, 1.2 equiv). A bleed needle was placed through the septum and the vial was purged with nitrogen. The reaction was then allowed to stir for one hour and twenty minutes at room temperature. A pump freeze thawed 3:1 trifluoroacetic acid: H_2O solution was then added and the solution immediately placed into a 55 ^oC oil bath. After seventeen hours, the vial was removed from the oil bath and solvent evaporated. The residue was purified by MPLC using a 4-gram column and a gradient beginning at 0% ethyl acetate in hexanes and progressing to 85% ethyl acetate in hexanes. This gave 10.3 mg (26 % Yield) of the hexacyclic alcohol **3.106** as a viscous oil. R_f = 0.28 (85% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.36 (t, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 7.7 Hz, 1H), 6.74 (d, *J* = 7.9 Hz, 1H), 6.67 (s, 1H), 6.21 (s, 1H), 4.05 (s, 1H), 3.53 (s, 3H), 3.22 (s, 3H), 2.83 (d, *J* = 8.4 Hz, 1H), 2.72 – 2.58 (m, 2H), 1.78

(s, 3H), 1.61 (s, 3H).**^{13}C NMR** (151 MHz, Chloroform-*d*) δ 177.2, 172.4, 171.2, 143.2, 136.6, 132.4, 122.2, 121.7, 107.2, 106.1, 104.1, 85.6, 75.2, 67.1, 63.6, 62.2, 53.3, 30.1, 28.7, 26.9, 22.4. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{21}H_{22}N_2O_8Na^+$ = 453.12739, found $C_{21}H_{22}N_2O_8Na^+$ = 453.12704. **FTIR (Neat)** 3339, 2955, 2928, 2854, 1693, 1642, 1617, 1498, 1478, 1459, 1437, 1395, 1371, 1297, 1266, 1240, 1198, 1155, 1092, 1016, 994, 955, 891, 833, 784, 735, 705, 643 cm^{-1}*Notes: Stringent oxygen free conditions are needed for this reaction sequence as the intermediates are highly prone to decomposition in the presence of oxygen. After two hours of heating the vial was removed from the oil bath, purged with argon, sealed and then placed again in the warm oil bath, this is due to the tendency of trifluoroacetic acid to dissolve the septum and expose the reaction to air. An analytically pure sample was obtained by preparative TLC. Two sequential preparative TLCs were run, the first utilized 75:25 ethyl acetate: hexanes as the eluent and the second 70:30 ethyl acetate: hexanes. Crystals for X-ray analysis were grown by vapor diffusion, hexanes into DCM (with trace methanol) solution of the compound.



No purifications were performed other than work-ups or trituration until the final step. Crude proton NMR spectra are provided for each intermediate.

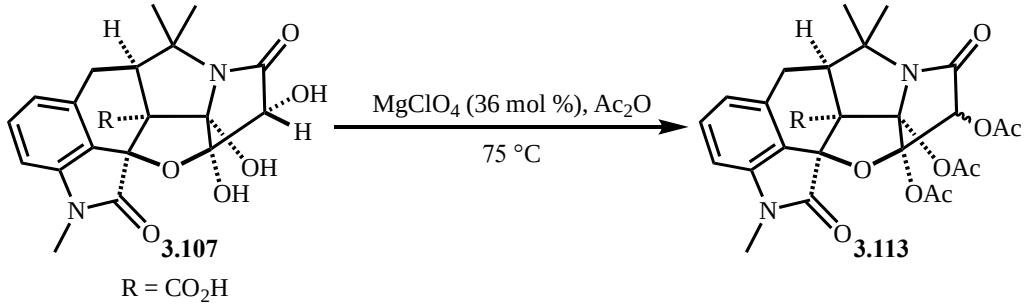
*Preparation of Hexacyclic Acid **3.107***



To a vial was added degreased NaH (6.3 mg, 0.26 mmol, 7.4 equiv), THF (0.43 mL), and benzeneselenol (28 µL, 0.26 mmol, 7.4 equiv). After the bubbling had subsided 18-Crown-6 (1.8 mg, 0.0068 mmol, 0.19 equiv) was added. The solution was stirred for ten minutes and then cooled in an ice bath. To the sodium phenyl selenide solution was added hexacyclic alcohol **3.106** (15.2 mg, 0.0353 mmol, 1 equiv) as a solution in THF (0.3 mL). After 25 minutes the reaction was quenched with 0.1 mL trifluoroacetic acid and the solvent then evaporated under a stream of N_2. The residue was dissolved in chloroform and hexanes and extracted several times with 15% Sat. $NaHCO_3$. The aqueous layer was then washed several times with chloroform, and once with DCM and once more with ethyl ether. To the aqueous layer was added trifluoroacetic acid till acidic and the aqueous layer was washed with diethyl ether (the carboxylic acid is insoluble in diethyl ether, this washing is to further remove impurities). The aqueous layer was then extracted several times with 3:1 $CHCl_3$: 2-propanol. The $CHCl_3$/2-propanol layers were combined and dried over sodium sulfate. The solvent was removed by rotary evaporation. The crude carboxylic acid **3.107** was carried on to the next step without further purification. R_f = 0.19 (100% EtOAc), UV; **^{1}H NMR** (300 MHz, Methanol-d_4) δ 7.37 (t, J = 7.8 Hz, 1H), 7.00 (d, J = 7.7 Hz, 1H), 6.87 (d, J = 7.8 Hz, 1H), 3.88 (s, 1H), 3.19 (s, 3H), 2.90 (dd, J = 13.5, 5.6 Hz, 1H), 2.71 (dd, J

= 11.7, 5.6 Hz, 1H), 2.55 – 2.41 (m, 1H), 1.73 (s, 3H), 1.63 (s, 3H). **-ESI-HRMS** m/z: calc'd for $[M - H]^-$ $C_{20}H_{19}N_2O_8^-$ = 415.11469, found $C_{20}H_{19}N_2O_8^-$ = 415.11490. *Notes: The compound often contains residual 18-C-6 as an impurity. Partial removal of the remaining 18-Crown-6 can be achieved by trituration with 10:1 DCM: methanol followed by diethyl ether. Crude proton NMR spectra is provided for this intermediate. 15% Sat. $NaHCO_3$ means diluting 15 mL saturated sodium bicarbonate with deionized water to 100 mL of total solution volume.

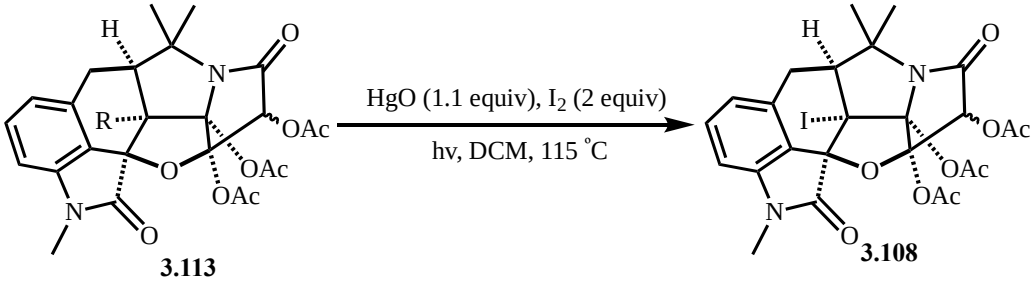
*Preparation of Hexacyclic Triacetate **3.113***



To the vial containing carboxylic acid **3.107** isolated from the previous step was added 0.8 mL acetic anhydride and $Mg(ClO_4)_2$ (2 mg, 0.009 mmol, 0.26 equiv). The vial was purged with argon, sealed and placed into a pre-heated 75 ^oC oil bath for four hours and ten minutes. Then 10 mol % additional of $Mg(ClO_4)_2$ (0.8 mg, 0.0036 mmol, 0.1 equiv) was added and the reaction vial purged with argon, sealed and heating at 75 ^oC was continued. After an additional nine hours and fifteen minutes the reaction was cooled and 0.15 mL of deionized water was added the solution placed into the oil bath and the solvent evaporated under a stream of nitrogen. The product was transferred to a vial for the subsequent step by dissolving it in DCM. Evaporation of the transfer solvent gave 7.3 mg of triacetate **3.113** as a green/brown oil which was carried through to the next step without

further purification. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.32 (t, *J* = 7.8 Hz, 1H), 6.88 (d, *J* = 7.7 Hz, 1H), 6.66 (d, *J* = 7.8 Hz, 1H), 5.91 (s, 1H), 3.13 (s, 3H), 2.93 – 2.76 (m, 2H), 2.55 (at, *J* = 14.3 Hz, 1H), 2.17 (s, 3H), 2.10 (s, 3H), 1.95 (s, 3H), 1.72 (s, 3H), 1.65 (s, 3H). **ESI-HRMS** m/z: calc'd for $[M - H]^-$ $C_{26}H_{25}N_2O_{11}^-$ = 541.14638, found $C_{26}H_{25}N_2O_{11}^-$ = 541.14642. *Notes: The stereocenter bearing the secondary acetate can epimerize during this reaction or in the subsequent steps, but in the final deprotection it reverts to the stereochemistry found in the natural product. Crude proton NMR spectra is provided for this intermediate. The equivalents of reagents for this step are based on the hexacyclic ester **3.106** starting material and not the crude mass of **3.107** obtained in the demethylation step.

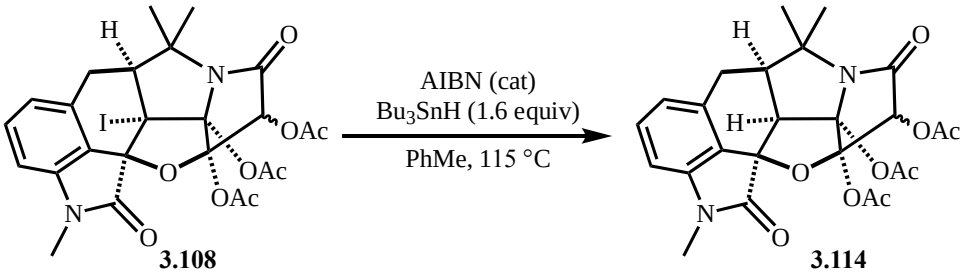
*Preparation of Hexacyclic Iodide **3.108***



To the vial containing triacetate **3.113** (7.3 mg, 0.014 mmol, 1 equiv) was added HgO (3.2 mg, 0.015 mmol, 1.1 equiv) and iodine (6.8 mg, 0.027 mmol, 2 equiv). Then dry DCM (1.2 mL) was added and the vial purged with argon and sealed. The solution was allowed to stir at RT for five minutes and then placed in a pre-heated 90 °C oil bath and irradiated with a 300-watt tungsten lamp for one hour. The temperature of the oil bath rose to 115 °C over the course of the reaction. The reaction was then allowed to cool, the solvent evaporated and the residue held under high vacuum. The product was dissolved in toluene

and transferred to another vial. Evaporation of the transfer solvent gave 8.2 mg of iodide **3.108** that was used for the next step without further purification. **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.36 (t, *J* = 7.8 Hz, 1H), 6.90 (d, *J* = 7.7 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 5.93 (s, 1H), 3.29 – 3.17 (m, 1H), 3.17 (s, 3H), 2.70 – 2.49 (m, 2H), 2.29 (s, 3H), 2.18 (s, 3H), 2.11 (s, 3H), 1.79 (s, 3H), 1.64 (s, 3H). **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{25}H_{25}N_2O_9INa^+$ = 647.05024, found $C_{25}H_{25}N_2O_9INa^+$ = 647.04956. *Notes: heating past 90 °C was due to the tungsten lamp. Crude proton NMR spectra is provided for this intermediate.

*Preparation of Reduced Hexacycle **3.114***

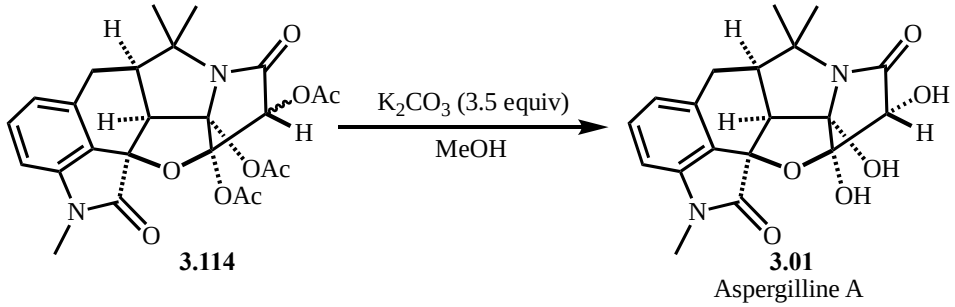


3.108 **3.114**

To the vial containing iodide **3.108** (8.2 mg, 0.013 mmol, 1 equiv) was added toluene (0.95 mL), tributyltin hydride (5.8 µL, 0.022 mmol, 1.6 equiv) and AIBN (cat). The vial was purged with argon, sealed and then placed in a pre-heated 115 °C oil bath for twenty minutes. The reaction was then allowed to cool and stirred for an additional 90 minutes at RT. The solvent was removed under stream of nitrogen and the reaction mixture partitioned between methanol and hexanes. The methanol layer was washed a total of four times with hexanes. The methanol layer was evaporated and the residue triturated with hexanes. This gave 5 mg of crude acetate **3.114** combined with a small amount of organotin impurities. The crude mixture was carried forward without further purification **^{1}H NMR**

(600 MHz, Chloroform-*d*) δ 7.28 (t, *J* = 7.8 Hz, 1H), 6.86 (d, *J* = 7.7 Hz, 1H), 6.62 (d, *J* = 7.8 Hz, 1H), 5.94 (s, 1H), 3.43 (d, *J* = 7.8 Hz, 1H), 3.12 (s, 3H), 2.76 – 2.69 (m, 1H), 2.48 – 2.37 (m, 2H), 2.19 (s, 3H), 2.14 (s, 3H), 2.10 (s, 3H), 1.71 (s, 3H), 1.47 (s, 3H). **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{25}H_{26}N_2O_9Na^+$ = 521.15360, found $C_{25}H_{26}N_2O_9Na^+$ = 521.15320. *Notes: Crude proton NMR spectra is provided for this intermediate.

*Preparation of Aspergilline A **3.01***

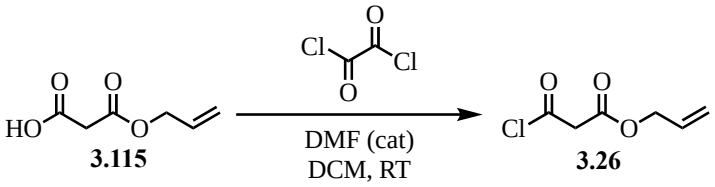


3.114 **3.01** Aspergilline A

To the vial containing acetate **3.114** (5 mg, 0.01 mmol, 1 equiv) was added methanol (0.8 mL) and potassium carbonate (4.9 mg, 0.035 mmol, 3.5 equiv). The solution was allowed to stir for two hours and then quenched with a slight excess of formic acid. The solvent was removed and the residue purified by reverse phase prep TLC using 28:62:0.5 MeCN: H_2O: Formic acid this gave 0.9 mg of aspergilline A **3.01** as a white solid. (7% yield over five steps). **^{1}H NMR** (400 MHz, Pyridine-d_5) δ 7.33 (t, *J* = 7.7 Hz, 1H), 7.00 (d, *J* = 7.7 Hz, 1H), 6.69 (d, *J* = 7.8 Hz, 1H), 4.70 (s, 1H), 3.25 (d, *J* = 8.6 Hz, 1H), 2.97 (s, 3H), 2.68 (d, *J* = 8.8 Hz, 2H), 2.36 (q, *J* = 8.8 Hz, 1H), 1.91 (s, 3H), 1.71 (s, 3H). **^{13}C NMR** (101 MHz, Pyridine-d_5) δ 178.4, 174.5, 143.2, 138.2, 131.7, 122.9, 122.0, 107.2, 107.2, 106.1, 82.9, 76.7, 67.8, 56.4, 54.8, 30.5, 28.0, 26.2, 21.8. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{19}H_{20}N_2O_6Na^+$ = 395.12191, found $C_{19}H_{20}N_2O_6Na^+$ = 395.12173.

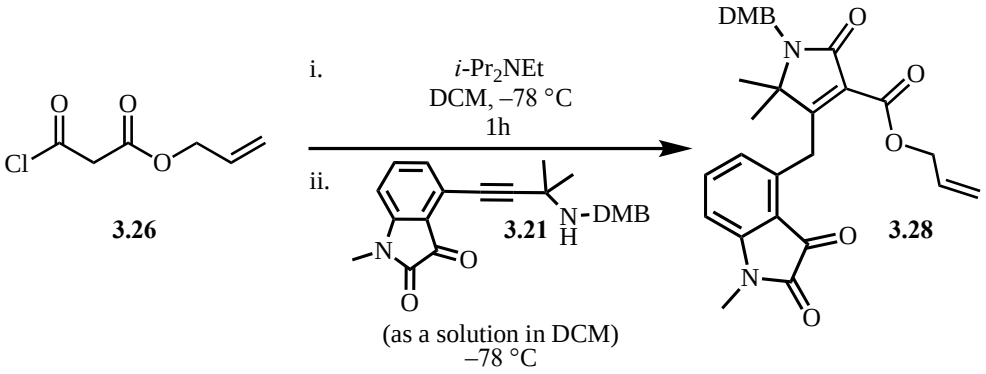
FTIR (Neat) 3340, 2928, 1695, 1638, 1615, 1476, 1370, 1294, 1257, 1195, 1157, 1123, 1103, 1066, 1037, 994, 957, 785, 767, 740, 693, 674 cm^{-1}.

*Preparation of Allyl Malonyl Chloride **3.26***



The starting acid (**3.115**, 6.5 g, 45 mmol, 1.0 equiv) was dissolved in dry DCM (49 mL) and five drops of DMF were added.[2] Following this oxalyl chloride (4.2 mL, 49 mmol, 1.08 equiv) was added dropwise. The reaction was then allowed to stir for 1 hour and 30 minutes. The solvent was then removed by rotary evaporation. The crude acid chloride **3.26** was used without further purification. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 5.92 (ddt, *J* = 17.1, 10.4, 5.9 Hz, 1H), 5.37 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.30 (dd, *J* = 10.5, 1.2 Hz, 1H), 4.70 – 4.68 (m, 2H), 3.89 (s, 2H).*Note: a crude proton NMR spectrum is provided

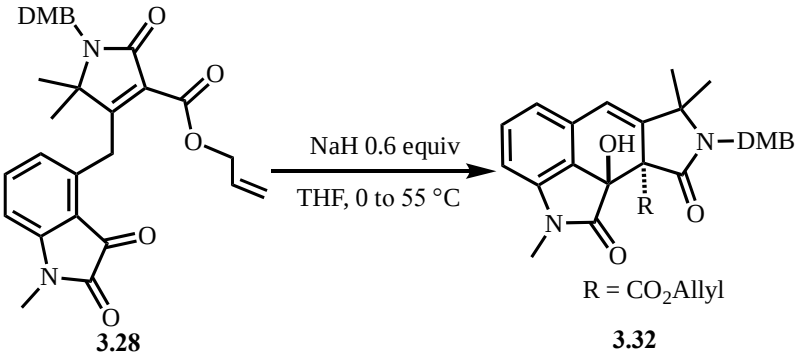
*Preparation of Allyl Pyrrolinone **3.28***



To a flame dried round bottomed flask was added Hünig's base (5 mL, 28.7 mmol 7.55 equiv) and dry DCM (48 mL), the solution was then cooled to –78 °C in a dry ice/acetone bath. To the Hünig's base solution was then dropwise added allyl malonyl chloride **3.26** (2.2 g, 13.5 mmol, 3.55 equiv and the solution stirred for 1 hour. The substrate **3.21** (1.5 g, 3.8 mmol, 1 equiv), which had been placed in a flame dried flask and dissolved in dry DCM (17 mL) was then taken up into a syringe and added slowly over fifteen minutes to the flask containing the Hünig's base/acyl chloride solution. After addition the reaction mixture was allowed to stir for an additional 1 hour at –78 °C and subsequently was quenched with 24 mL of saturated $NaHCO_3$ aqueous solution. The dry ice acetone/bath was removed and the flask was allowed to warm slightly. The mixture was then transferred to a separatory funnel which contained a half saturated brine solution and extracted several times with DCM. The organic layer was dried over sodium sulfate and solvent removed by rotary evaporation. The residue was purified by MPLC. A gradient from 0% ethyl acetate in hexanes to 56% ethyl acetate in hexanes was used; this yielded 892 mg (45.0% Yield) of pyrrolinone **3.28** as an orange foam. R_f = 0.64 (100% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.44 (t, J = 7.9 Hz, 1H), 7.32 (d, J = 8.3 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 7.8 Hz, 1H), 6.48 – 6.35 (m, 2H), 5.92 (ddt, J = 16.3, 10.9, 5.7

Hz, 1H), 5.40 (dd, J = 17.3, 1.6 Hz, 1H), 5.23 (dd, J = 10.6, 1.4 Hz, 1H), 4.73 – 4.70 (m, 2H), 4.58 (s, 2H), 4.46 (s, 2H), 3.81 (s, 3H), 3.77 (s, 3H), 3.23 (s, 3H), 1.11 (s, 6H).**^{13}C NMR** (151 MHz, Chloroform-*d*) δ 184.1, 170.3, 165.7, 162.9, 160.2, 157.9, 157.6, 151.9, 139.6, 138.4, 131.7, 131.0, 126.2, 124.5, 119.0, 119.0, 115.1, 108.3, 104.7, 98.2, 65.9, 65.9, 55.5, 55.5, 35.8, 27.0, 26.4, 23.6. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{29}H_{30}N_2O_7Na^+$ = 541.19507, found $C_{29}H_{30}N_2O_7Na^+$ = 541.19501. **FTIR (Neat)** 2972, 2937, 2838, 1737, 1688, 1605, 1508, 1464, 1438, 1397, 1359, 1324, 1293, 1265,1208, 1157,1128,1106,1055, 1035,1012, 935, 896, 834 cm^{-1}.

*Preparation of Allyl Tetracycle **3.32***

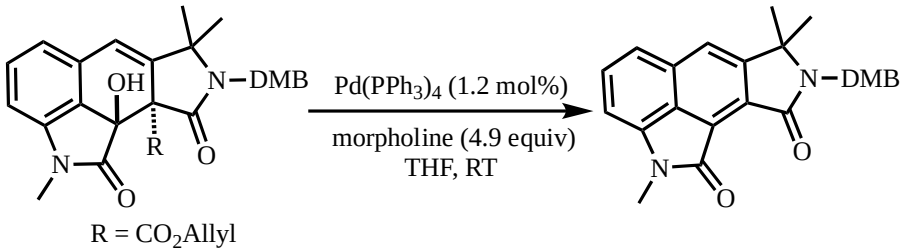


3.28 **3.32**

To a flame-dried vial was added pyrrolinone starting material **3.28** (100 mg, 0.193 mmol, 1.0 equiv) and dry THF (0.65 mL). The solution was then cooled in an ice bath and 60% dispersion of sodium hydride in mineral oil was added (4.5 mg, 0.11 mmol, 0.58 equiv). The solution was stirred in the ice bath for an additional fifteen minutes and then allowed to warm to room temperature. An additional 0.65 mL THF was added and the solution warmed to 55 °C in an oil bath. As the solution warms the solution's colour darkens and progresses to a green color and finally to a deep blue color. After fifteen minutes of heating at 55 °C the solution was quenched with 1 mL of 0.5 M NH_4Cl and the

reaction mixture extracted several times with DCM. The combined organic layers were dried over sodium sulfate and the solvent removed by rotary evaporation. The residue was purified by flash chromatography using a gradient which began at 50% ethyl acetate in hexanes and progressed to 100% ethyl acetate (the 50% ethyl acetate solution was utilized to elute the remaining starting material from the column and the following 100% ethyl acetate was used to elute the product) This gave 25 mg (25% Yield) of the desired tetracycle **3.32** (white solid) along with 72.4 mg (72.4%) of recovered pyrrolinone **3.28**, which could be resubjected to the reaction conditions. R_f = 0.4 (100% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, Acetonitrile-d_3) δ 7.31 – 7.21 (m, 2H), 6.81 (d, *J* = 7.7 Hz, 1H), 6.75 (d, *J* = 7.8 Hz, 1H), 6.71 (s, 1H), 6.53 (d, *J* = 2.4 Hz, 1H), 6.44 (dd, *J* = 8.5, 2.4 Hz, 1H), 5.65 (ddt, *J* = 16.4, 10.9, 5.6 Hz, 1H), 5.14 – 5.04 (m, 2H), 4.55 – 4.35 (m, 4H), 3.86 (s, 3H), 3.76 (s, 3H), 3.12 (s, 3H), 1.41 (s, 3H), 1.41 (s, 3H) (very closely overlapping singlets) .**^{13}C NMR** (151 MHz, Chloroform-*d*) δ 175.5, 166.3, 166.2, 160.2, 157.5, 145.1, 144.8, 131.6, 131.3, 130.9, 130.5, 119.4, 119.2, 118.8, 118.8, 108.2, 104.6, 98.3, 71.2, 66.9, 64.1, 62.7, 55.5, 55.5, 36.5, 28.1, 26.7, 26.5. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{29}H_{30}N_2O_7Na^+$ = 541.19507, found $C_{29}H_{30}N_2O_7Na^+$ = 541.19464. **FTIR (Neat)** 3430, 2970, 2936, 1733, 1693, 1646, 1616, 1593, 1508, 1474, 1437, 1407, 1369, 1298, 1264, 1209, 1156, 1127, 1085, 1036, 987, 917, 833, 782, 746, 730, 646 cm^{-1}.

*Preparation of Aromatized Compound **3.33***

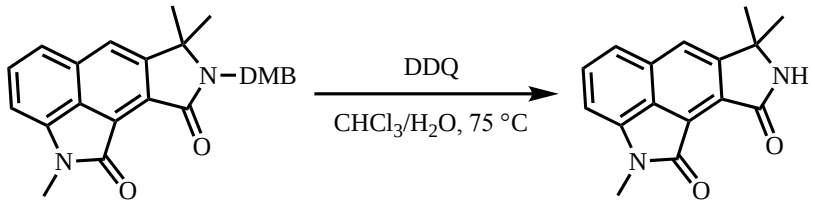


3.32 **3.33**

To a flame-dried round bottomed flask was added tetracycle **3.32** (38.9 mg, 0.075 mmol, 1.0 equiv), dry THF (1.7 mL) and morpholine (32 µL, 0.37 mmol, 4.9 equiv). Following this was added $Pd(PPh_3)_4$ (1 mg, 0.00087 mmol, 0.012 equiv). The solution quickly becomes deep yellow in color. The reaction mixture was allowed to stir for 2 hours and fifteen minutes. Half saturated brine and DCM were then added and the aqueous layer extracted with DCM several times, until all the yellow compound had been extracted into the organic layers. The organic layers were combined and dried over sodium sulfate and the solvent removed by rotary evaporation. The residue was purified by MPLC using a 2.5 g column with a flow rate of 25 mL/min. A gradient which began at 0% ethyl acetate in hexanes and progressed to 90% ethyl acetate in hexanes was used for purification. This gave 26.0 mg (83% Yield) of the title compound **3.33** as a yellow solid. R_f = 0.19 (100% EtOAc/hexanes), UV; **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.93 (s, 1H), 7.54 – 7.50 (m, 2H), 7.48 (d, *J* = 8.5 Hz, 1H), 6.90 – 6.85 (m, 1H), 6.45 – 6.43 (m, 1H), 6.40 (dd, *J* = 8.5, 2.4 Hz, 1H), 4.82 (s, 2H), 3.88 (s, 3H), 3.77 (s, 3H), 3.47 (s, 3H), 1.49 (s, 6H). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 165.5, 164.9, 160.2, 157.6, 152.4, 141.7, 131.2, 130.7, 130.2, 129.2, 125.9, 123.7, 122.5, 120.1, 119.2, 104.6, 104.5, 98.3, 63.8, 55.6, 55.5, 35.8, 26.9, 26.6. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{25}H_{24}N_2O_4Na^+$ = 439.16338, found

$C_{25}H_{24}N_2O_4Na^+$ = 439.16312. **FTIR (Neat)** 2971, 2936, 2836, 1708, 1636, 1615, 1589, 1506, 1463, 1388, 1293, 1265, 1208, 1180, 1157, 1128, 1044, 998, 968, 909, 834, 766, 729, 669 cm^{-1}.

*Preparation of Cyclopiamide A **3.02***

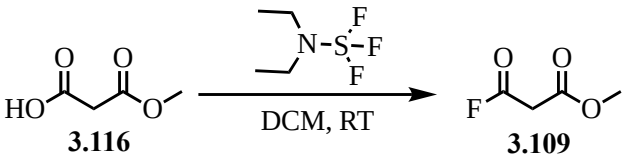


3.33 **3.02** Cyclopiamide A

To a round bottomed flask was added starting material **3.33** (146.6 mg, 0.0352 mmol, 1.0 equiv), $CHCl_3$(3.4 mL), H_2O (0.05 mL), and DDQ (2,3-Dichloro-5,6-dicyano-p-benzoquinone, 119.7 mg, 0.0527 mmol, 1.51 equiv). The flask was purged with nitrogen and sealed. The flask was then placed in a preheated 75 ^oC oil bath for 55 minutes, the flask was then removed from the heat, cooled for ten minutes and an additional 119.7 mg (0.0527 mmol, 1.51 equiv) of DDQ were added. The flask was once again purged with nitrogen, sealed and replaced into the 75 ^oC oil bath for an additional 50 minutes. The flask was then removed from the oil bath, allowed to cool and then DCM was added. The reaction solution was poured into a separatory funnel and washed three times with aqueous half saturated $NaHCO_3$. To the aqueous layer was then added brine, and the aqueous layer was extracted several times with DCM. All the organic layers were combined and dried over sodium sulfate, the solvent was then removed by rotary evaporation. The residue was then purified by MPLC using a 24-gram column with a flow rate of 35 mL/min. A gradient beginning at 0% ethyl acetate in hexanes and progressing to 100% ethyl acetate in hexanes was used to purify the material. This gave 87.5 mg (93% Yield) of cyclopiamide A (**3.02**) as a yellow

powder. R_f = 0.3 (10% MeOH/DCM), UV; **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.96 (s, 1H), 7.58 – 7.52 (m, 2H), 6.89 (dd, *J* = 4.9, 2.7 Hz, 1H), 6.32 (s, 1H br), 3.46 (s, 3H), 1.66 (s, 6H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 166.3, 165.4, 153.3, 141.7, 131.0, 130.6, 128.9, 125.8, 124.3, 122.8, 120.2, 104.7, 59.7, 28.9, 26.6. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{16}H_{14}N_2O_2Na^+$ = 289.09530, found $C_{16}H_{14}N_2O_2Na^+$ = 289.09531. **FTIR (Neat)** 3229, 2971, 2932, 1723, 1637, 1499, 1421, 1393, 1381, 1309, 1209, 1188, 1046, 1018, 986, 912, 761, 730, 689 cm^{-1}.

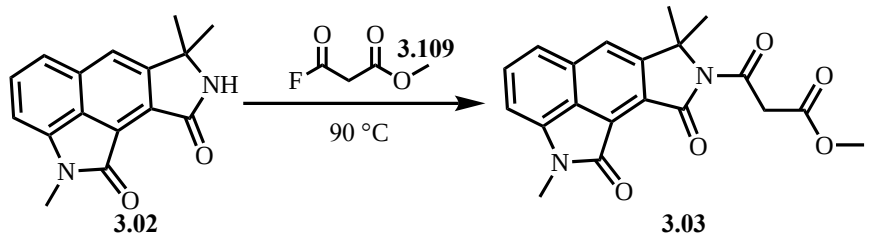
*Preparation of Methyl Malonyl Fluoride **3.109***



3.116 **3.109**

The starting acid (**3.116**, 3.8 g, 32 mmol, 1.0 equiv) was dissolved in dry DCM (171 mL) and DAST (DiethylAminoSulfur Trifluoride, 5.11 mL, 38.5 mmol, 1.2 equiv) was added dropwise over five minutes.[3] The solution was allowed to stir for 2 hours then the DCM solution was poured into a separatory funnel and washed with 100 mL half saturated brine. The aqueous layer was extracted several times with DCM and the combined organic layers dried over Na_2SO_4. The solvent was removed by rotary evaporation. This gave 3.5 g of crude acyl fluoride **3.109** which was used without further purification. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.81 (s, 3H), 3.59 (d, *J* = 3.8 Hz, 2H). *Note: a crude proton NMR spectrum is provided.

*Preparation of Speradine E **3.03***



Cyclopiamide A — Speradine E

To a flame-dried vial was added cyclopiamide A **(3.02)** (9.1 mg, 0.034 mmol, 1.0 equiv) and methyl malonyl fluoride **3.107** (206.7 mg, 0.979 mmol, 28.8 equiv, the compound was used crude after preparation, Q NMR showed that the solution used was 56.9% acyl fluoride by weight.) The reaction vial was purged with argon, sealed and placed in a 90 °C oil bath for six hours and fifteen minutes. The vial was then allowed to cool and an additional 105.0 mg (0.498 mmol, 14.6 equiv) of the acyl fluoride was added. The vial was once again purged with argon, sealed and placed in a 90 °C oil bath. The reaction mixture was heated in the oil bath for an additional thirteen hours and eight minutes. The vial was then removed from the oil bath and allowed to cool. DCM was added and the reaction solution transferred to a larger 20 mL vial. Saturated $NaHCO_3$ was then added and the solution stirred vigorously to quench the remaining acyl fluoride. The reaction mixture was then extracted several times with DCM. Solid NaCl was then added to the aqueous layer and the aqueous layer was again extracted once with DCM. The combined organic layers were dried over sodium sulfate and the solvent removed by rotary evaporation. The residue was then purified by prep TLC using 1:1 ethyl acetate: hexanes as the eluent. The plate was eluted twice with this solvent system. The purified material was then triturated twice with diethyl ether to give 6.7 mg (54% Yield) of speradine E (**3.03)** as an orange powder. R_f = 0.45 (90% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.03

(s, 1H), 7.63 – 7.53 (m, 2H), 6.90 (d, *J* = 5.9 Hz, 1H), 4.21 (s, 2H), 3.76 (s, 3H), 3.46 (s, 3H), 1.91 (s, 6H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 168.2, 167.2, 165.0, 164.9, 152.8, 141.8, 132.5, 131.7, 126.6, 125.8, 125.5, 123.3, 120.3, 105.1, 66.3, 52.5, 45.7, 27.0, 26.7. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{20}H_{18}N_2O_5Na^+$ = 389.11134, found $C_{20}H_{18}N_2O_5Na^+$ = 389.11093. **FTIR (Neat)** 2951, 1737, 1698, 1636, 1500, 1436, 1391, 1373, 1323,1292, 1197, 1178, 1140, 1047, 1017, 886, 767, 730, 672 cm^{-1}. Note that the neat acyl fluoride (**3.109**) utilized in this reaction is carried crude from its synthesis. The impurities present in the acyl fluoride were not identified.

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CHAPTER FOUR

Synthetic Studies Toward (±)-Isopalhinine A

4.1 Isolation and Background

4.1.1 Isolation and Related Natural Products

Isopalhinine A **4.01** was isolated in 2013 by Zhao and coworkers from the nodding club moss *Palhinhaea cernua* (Figure 4.01). This club moss is notable for its use in Chinese herbal medicine as a treatment for rheumatism, scald and contusions.[1] In the isolation, 60 kg of dried and powdered *Palhinhaea cernua* was extracted three times with methanol and the combined extracts partitioned between 1% HCl and ethyl acetate. The aqueous layer was adjusted to pH 9 with sodium carbonate and then extracted with chloroform. The crude alkaloidal extract was then purified by MPLC using MCI gel and then further purified several times by silica gel chromatography eventually giving 3.0 mg of isopalhinine A **4.01**.

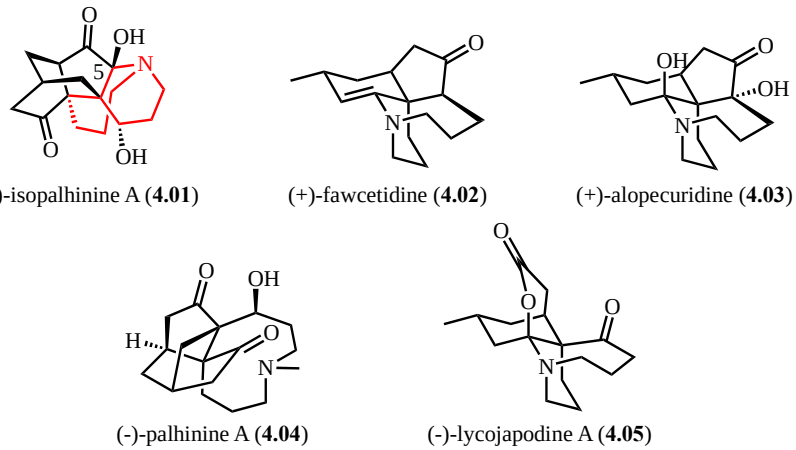


Figure 4.01 Fawcettimine-type alkaloids – adapted from Lei

Isopalhinine **4.01** belongs to a large and structurally diverse class of natural products, the lycopodium alkaloids. To date, more than 300 different lycopodium alkaloids have been isolated![2] More specifically, isopalhinine A belongs to the fawcettimine sub-class of lycopodium alkaloids; it is unique among the fawcettimines in that it bears a 1-azabicyclo [4.3.1] decane moiety constructed through a N – C5 bond (red highlight, Figure 4.01).[1] Although many members of these natural product families possess bioactivity, isopalhinine A itself has yet to be shown to possess any bioactivity.

4.1.2 Background – Previous Work

Despite its lack of known bioactivity, we were drawn to isopalhinine A due to its synthetically challenging and complex architecture. Isopalhinine A boasts a 5/6/6/6/7 fused ring system which bears a cycloheptane hemiaminal and four contiguous stereocenters, two of which are adjacent quaternary centers. Isopalhinine A also features an isotwistane moiety the cyclopentanone of which is highly substituted (Figure 4.02).

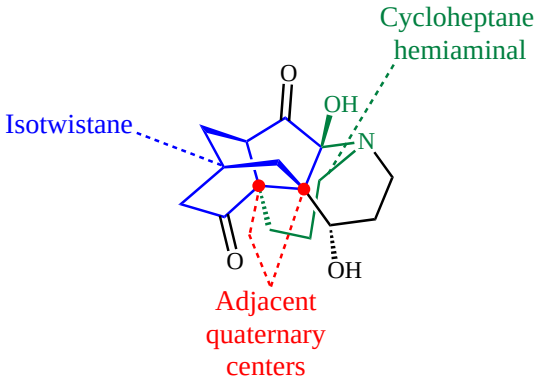
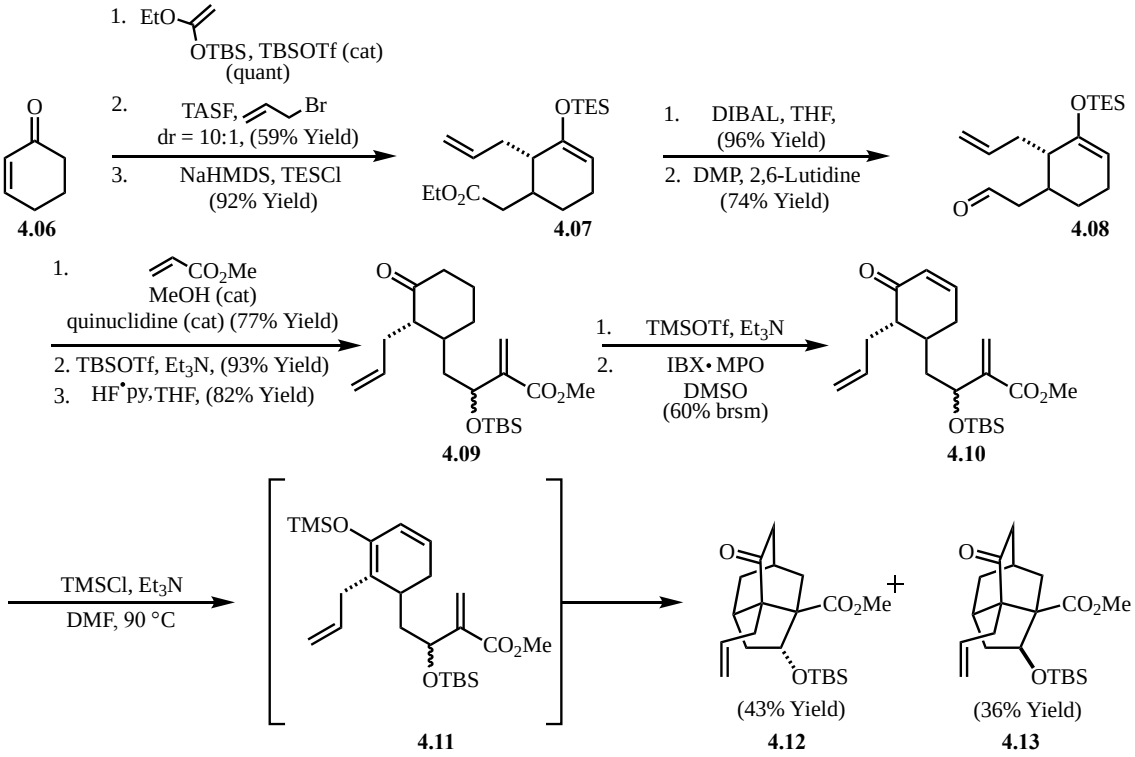


Figure 4.02 Structural features of isopalhinine A

Though no total synthesis of this natural product has been reported, the Rychnovsky group at Irvine has detailed a synthetic study toward isopalhinine A (Scheme

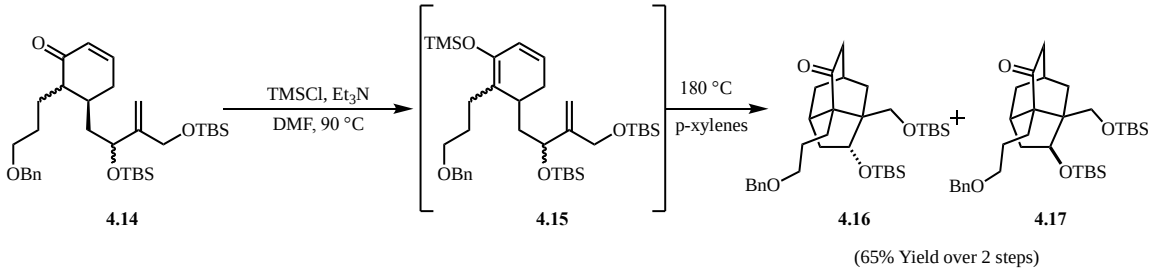
4.01).[3] In their work, the Rychnovsky group sought to first construct the isotwistane moiety of the natural product through an intramolecular Diels-Alder reaction. Subsequently,



Scheme 4.01 Intramolecular Diels Alder approach to isotwistane – Rychnovsky

they planned to utilize this scaffolding to direct the completion of the natural product. Beginning with cyclohexenone **4.06**, they performed a Mukaiyama Michael reaction with the silyl ketene acetal of ethyl acetate. Allylation with allyl bromide was then followed by TES enol ether formation to give enol ether **4.07**. Elaboration to aldehyde **4.08** was then effected by DIBAL reduction of the ester to the alcohol and re-oxidation to the aldehyde. Morita-Baylis-Hillman reaction with methyl acrylate, trapping of the secondary alcohol with TBS-triflate and enol ether cleavage furnished cyclohexanone **4.09**. Oxidation to the enone was then followed by selective TMS enol ether formation and spontaneous intramolecular Diels-Alder reaction providing a nearly 1:1 mixture the isotwistanes **4.12**

and **4.13**, with concurrent construction of one of the quaternary centers. Despite having made good progress in constructing two of the more challenging features present in the natural product, work on isopalhinine A was discontinued due to the disclosure by Fan and coworkers of a similar strategy towards the structurally related palhinine A **4.04** (Scheme 4.02).[4]

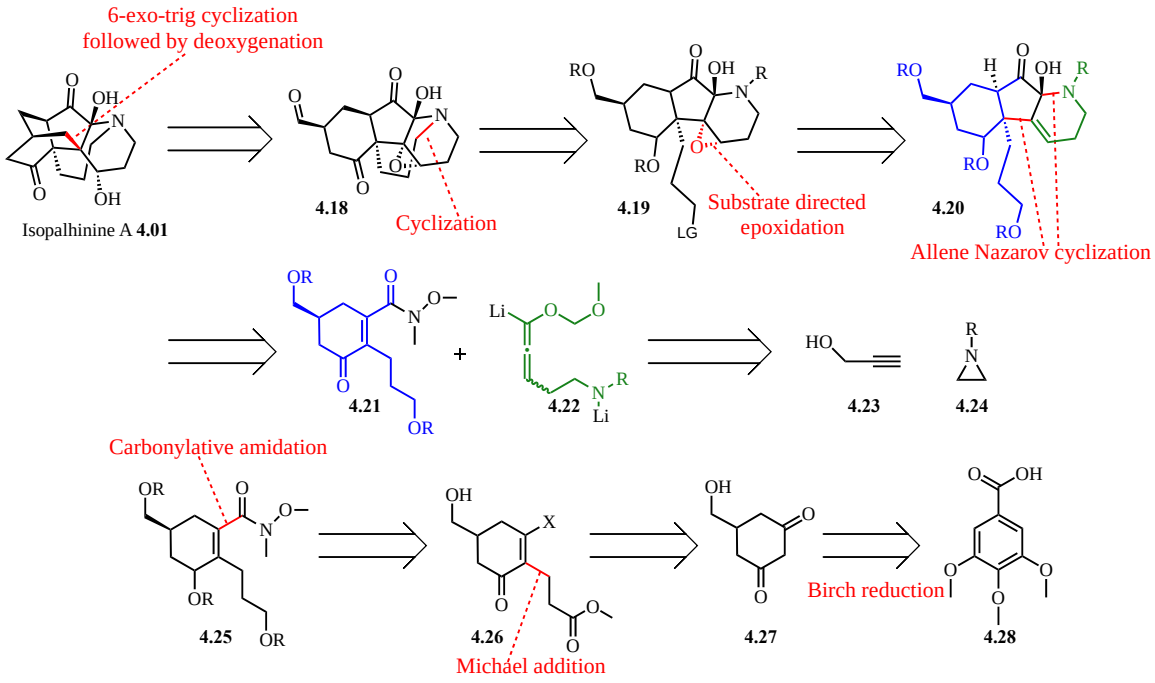


Scheme 4.02 Fan's synthesis of the isotwistane core of palhinine A

4.2 Synthetic Studies Toward Isopalhinine A

Our synthetic strategy toward isopalhinine A differs from those of Rychnovsky and Fan; as illustrated in Scheme 4.03 we envisioned late-stage construction of the isotwistane through an intramolecular 6-*exo*-trig radical cyclization and deoxygenation sequence from epoxy aldehyde **4.18**. The medium-sized ring of **4.18** was envisioned to arise via reductive amination or intramolecular S_N2- type reaction of hemiaminal **4.19** (Scheme 4.03).[5] The α-face epoxide in **4.19** would be installed through a directed epoxidation of trisubstituted alkene **4.20**. The central cyclopentanone, trisubstituted alkene, hemiaminal and quaternary center present in **4.20** were seen as arising in a single transformation involving an allene Nazarov cyclization/hemiaminal formation cascade reaction that would occur upon addition of lithioallene **4.22** into Weinreb amide **4.21**. The proposed allene would be prepared in a few synthetic steps from propargyl alcohol **4.23** and a protected aziridine

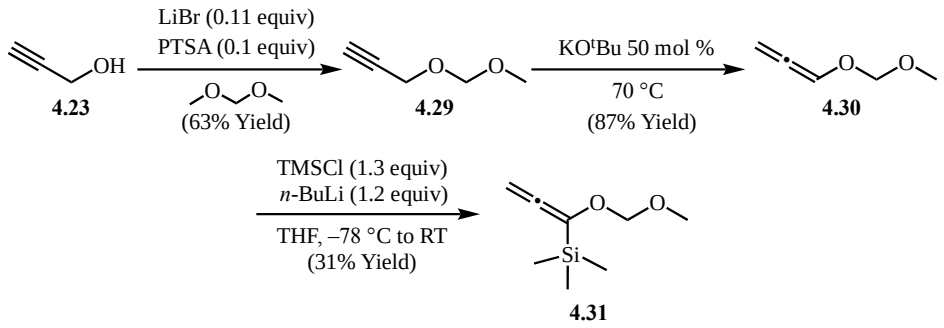
4.24. As for the Weinreb amide component, it was expected that **4.21** would derive from carbonylative amination of vinyl halide or triflate **4.26**; which in turn would be arise from 1,3-diketone **4.27** via Michael addition to methyl acrylate. Finally, diketone **4.27** is known and has been previously prepared from trimethoxybenzoic acid through a Birch reduction and acidic hydrolysis of the incipient methyl enol ethers.



Scheme 4.03 Isopalhinine retrosynthesis

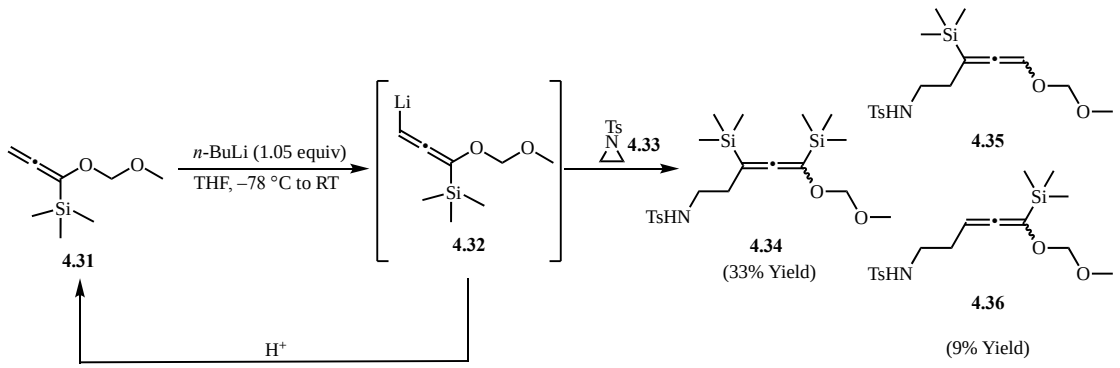
4.2.1 Accessing the Allene Component

We first wished to access the allene component of the key Nazarov cyclization. Following precedent from Arens, we converted commercially available propargyl alcohol **4.23** to its MOM acetal and then isomerized the alkyne to an allene (**4.30**) through the action of 50 mol % of potassium tert-butoxide.[6] Subjecting **4.30** to α-Lithiation and quenching with trimethyl silyl chloride gave the TMS protected allene **4.31** in poor yield (Scheme 4.04).[7] We then sought to append the nitrogen containing chain to the γ-position



Scheme 4.04 TMS protected allene synthesis

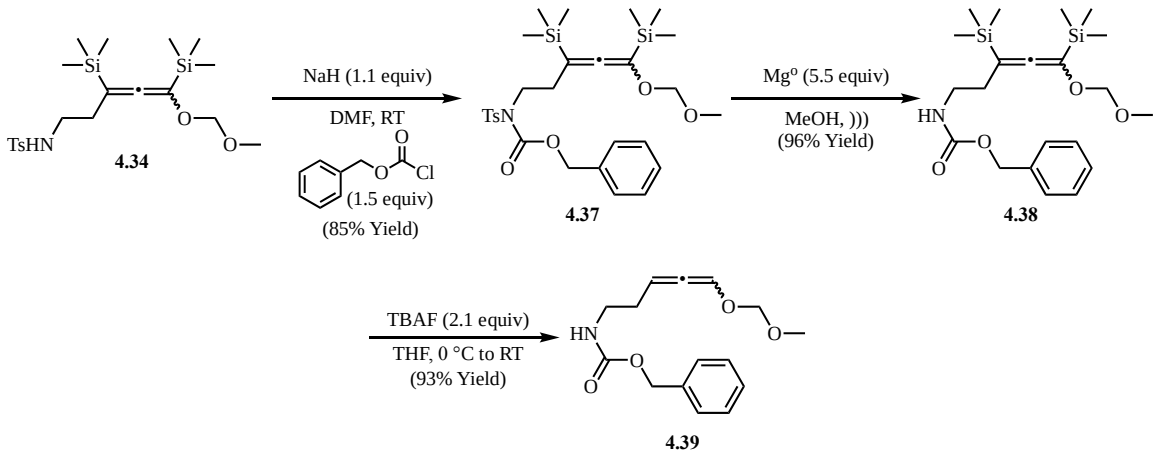
of the allene. As illustrated in Scheme 4.05, γ-lithiation of 4.31 to **4.32** followed by addition to a THF solution of tosyl aziridine (**4.33**) was found to deliver a ternary mixture of allenes (**4.34**–**4.36)** Intriguingly, lithiation of **4.31** followed by quenching with a proton source



Scheme 4.05 Appending of nitrogen containing chain to allene

gave only returned starting material, suggesting that the observed scrambling of the TMS groups was occurring after addition to the aziridine and was perhaps promoted by the insipient amide anion generated upon aziridine opening! Furthermore, on scaling up of this reaction only di-TMS protected allene **4.34**, was observed to any significant extent in the reaction. Despite the low yield of di-TMS allene **4.34** we were eager to explore the key Nazarov cyclization. Thus, **4.34** was Cbz protected and the tosyl group reductively cleaved

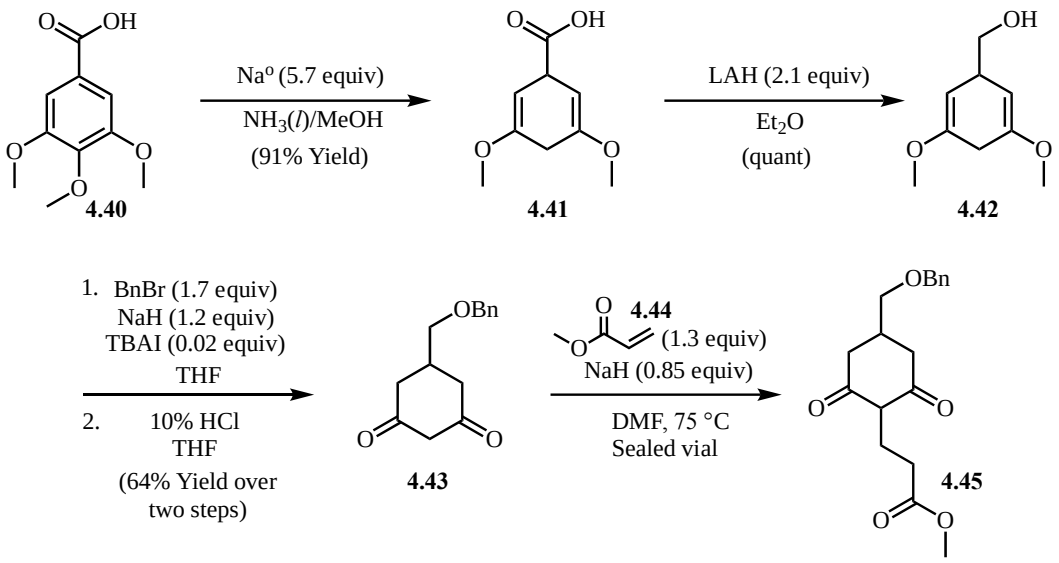
to give **4.38** in excellent yield (Scheme 4.06).[8] The de-tosylated allene was carried forward crude whereupon exposure to TBAF revealed allene reaction partner **4.39** (Scheme 4.06).



Scheme 4.06 Synthesis of Cbz protected allene **4.39**

4.2.2 Accessing the Weinreb Amide

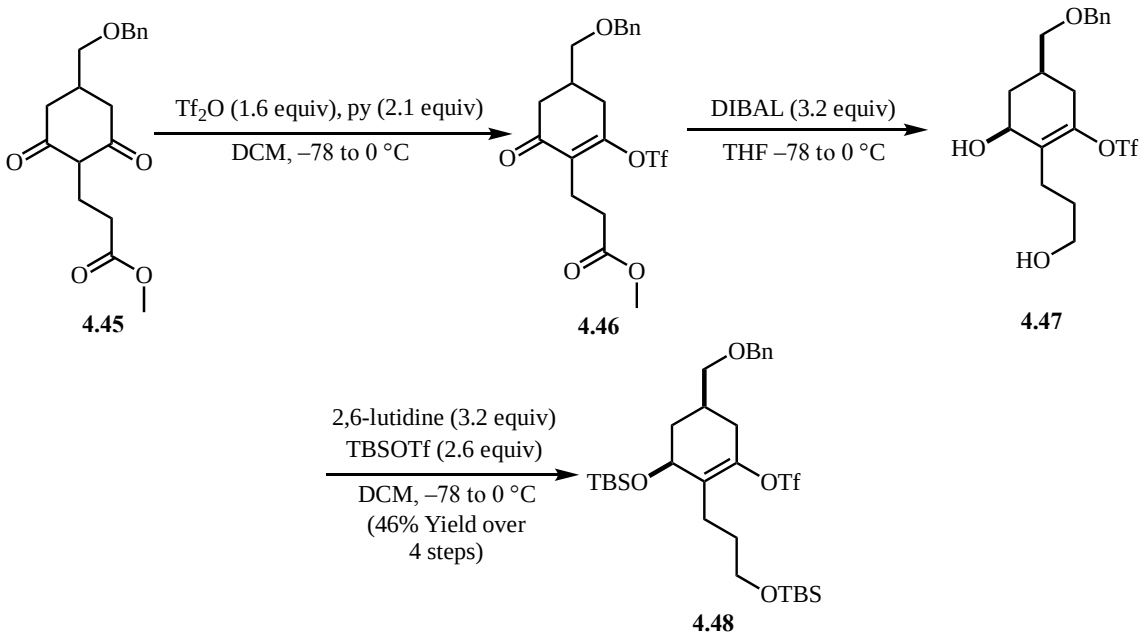
With the allene component in hand we began exploring the synthesis of the Weinreb amide. According to literature precedent, commercially available trimethoxybenzoic acid was exposed to Birch reduction conditions providing bis-enol ether **4.41** which was carried on crude (Scheme 4.07).[9] Reduction of carboxylic acid **4.41** was followed by benzylation and acid-mediated hydrolysis, smoothly furnishing known 1,3-di-ketone **4.43** on small scale.[10] On scaling up, acid-mediated hydrolysis proceeded sluggishly, but could be achieved in reasonable yield by prolonging the reaction time. Deprotonation of **4.43**



Scheme 4.07 Synthesis of 1,3-diketone **4.45**

with sodium hydride followed by heating with methyl acrylate in DMF in a sealed tube effected a Michael addition to give **4.45,** which was also carried forward crude. Subsequently, **4.45** was first converted to the corresponding enol triflate and then subjected to DIBAL reduction of both the ester and remaining ketone moieties. Protection of the incipient alcohols as their TBS ethers furnished **4.48**, the first purified compound in the four-step sequence, in 46% yield overall (Scheme 4.08). With **4.48** in hand, the carbonylative amination was attempted employing literature derived conditions (entry one table 4.1) which, unfortunately, were found to only returned starting material.[11] A solvent screen revealed that THF and MeCN gave partial conversion at 60 °C; toluene gave good conversion but the isolated product was tentatively assigned to be the compound in which N–O bond cleavage had occurred after carbonylative amination. DMF appeared to be the optimum solvent for this reaction, giving full conversion at 105 °C within 2 hours. Analysis of this reaction (Entry 5, Table 4.01) showed that desired product **4.50** along with carboxylic acid **4.49** and an unknown decomposition product were obtained. Lowering the

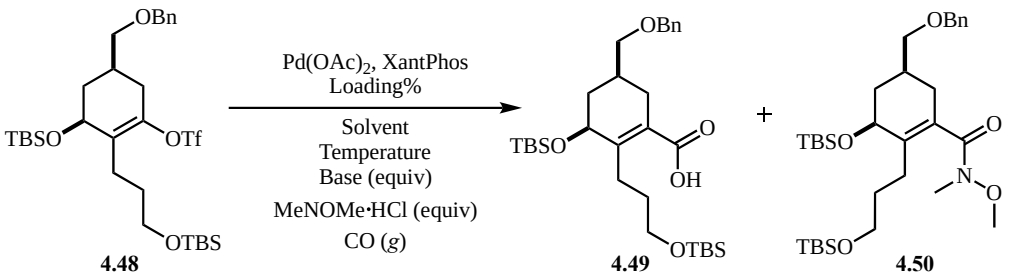
reaction temperature to 75 °C provided slow conversion to the desired product and a significant amount of carboxylic acid **4.49**. Temperatures above 90 °C caused formation



Scheme 4.08 Accessing vinyl triflate **4.48**

of the unknown decomposition product initially observed in entry 5. Thus, the temperature for future reactions was adjusted to 85 °C. Azeotropically drying all components of the reaction and the inclusion of molecular sieves surprisingly, did not reduce the formation of carboxylic acid **4.49**. Changing the base to Hünig's base and increasing the equivalents of the MeNHOMe•HCl salt did finally circumvent formation of the carboxylic acid. Attempting to lower the catalyst and ligand loading to 10 mol % gave lower yields (Entry 9, Table 4.1). With these factors in mind the optimum reaction conditions were chosen to be 20 mol % of $Pd(OAc)_2$, 20 mol % Xantphos, in DMF with 9 equivalents of Hünig's base and 7 equivalents of MeNHOMe•HCl at 85 °C, which provided **4.50** in 92% yield.

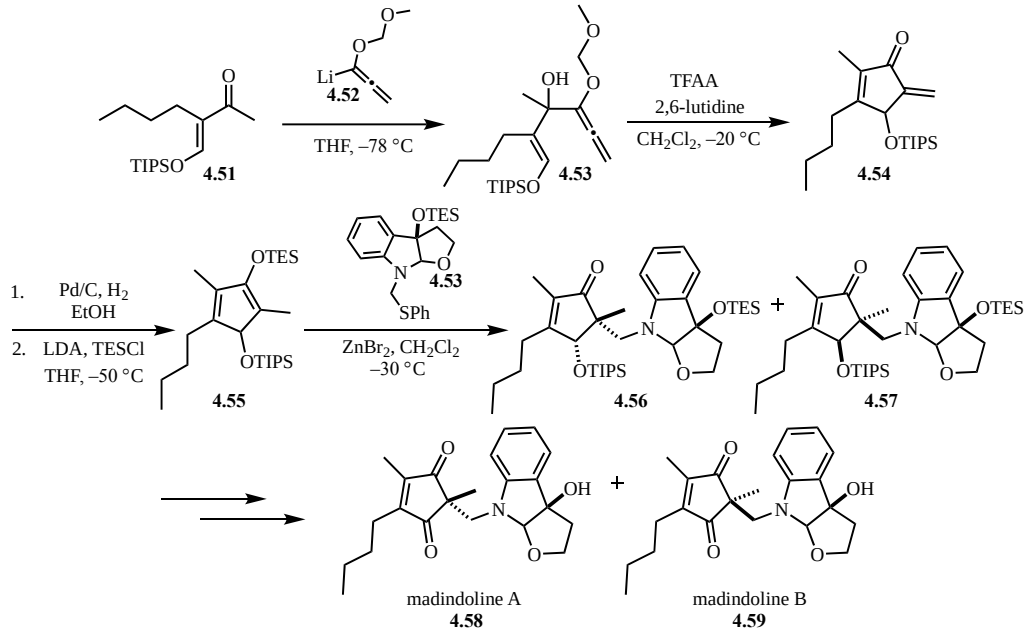
Table 4.1 Optimization of carbonylative amination



Entry	Solvent	Temperature	Loading %	Base (equiv)	MeNOMe HCl	Result
1	THF	22 °C	8	Na_2CO_3 (3)	1 (equiv)	No Reaction
2	THF	55 °C	20	Na_2CO_3 (3)	1.5 (equiv)	Partial conversion to **4.50**
3	MeCN	55 °C	20	Na_2CO_3 (3)	1.5 (equiv)	Partial conversion to **4.50**
4	Toluene	105 °C	20	Na_2CO_3 (3)	1.5 (equiv)	N-O bond cleaved product
5	DMF	105 °C	20	Na_2CO_3 (3)	1.5 (equiv)	Complete conversion with decomposition
6	DMF	75 °C	20	Na_2CO_3 (3)	2 (equiv)	Mostly **4.49** formed
7	DMF	75 – 90 °C	20	Na_2CO_3 (3)	2 (equiv)	5% **4.49** 27% **4.50**
8	DMF	85 °C	20	Hünig's Base (9)	7 (equiv)	92% **4.50**
9	DMF	85 °C	10	Hünig's Base (9)	7 (equiv)	80% **4.50**

4.2.3 Allene Nazarov Cyclization

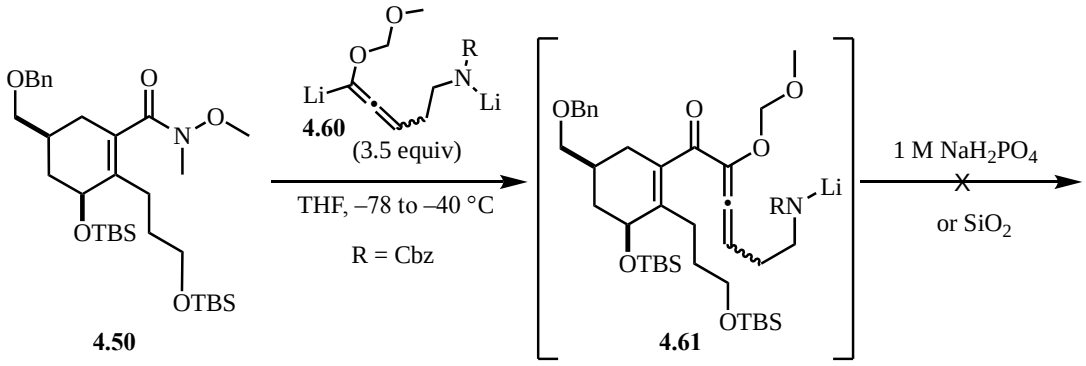
To date, several total synthesis and methodologies utilizing a key allene Nazarov cyclization step have been accomplished (Scheme 4.09). The most notable of these accomplishments were put forth by the Tius group, both in the realm of total synthesis as



Scheme 4.09 Allene Nazarov reaction in the total synthesis of the madindolines – Tius

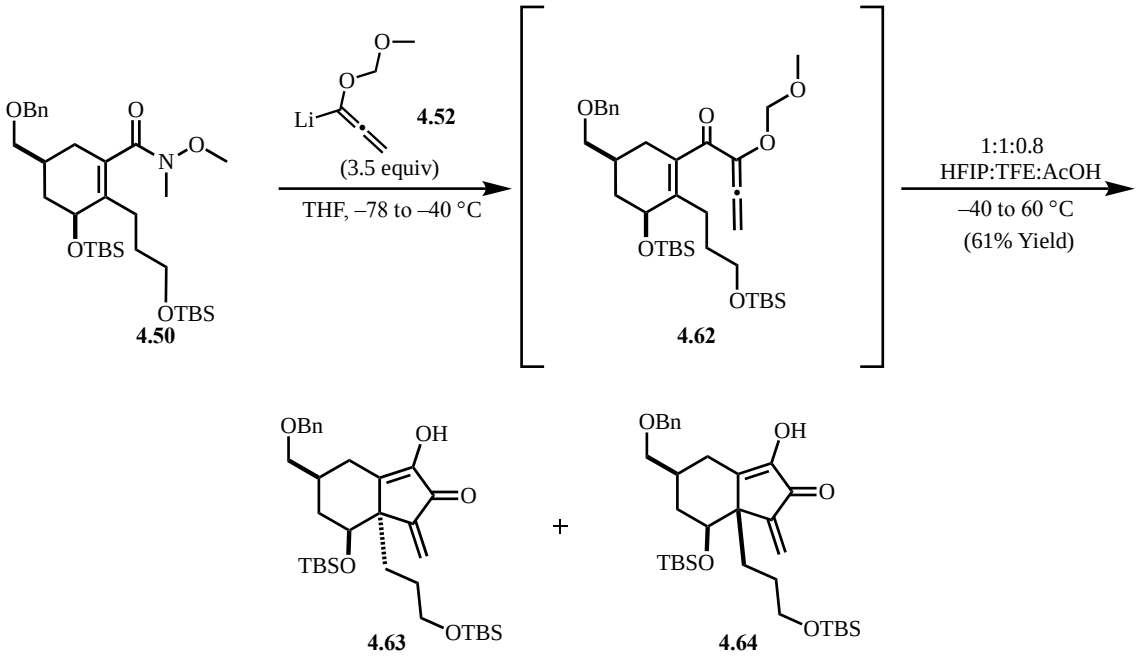
well as method development.[12] Scheme 4.09 details an example of such a total synthesis by Tius. In this work enone, **4.51** is exposed to lithioallene **4.52** and the resultant alcohol exposed to trifluoroacetic anhydride. The derived doubly allylic trifluoroacetate proved labile, ionizing and inducing a Nazarov cyclization to provide cyclopentenone **4.54**. Exo-methylene reduction followed by TES enol ether formation gave cyclopentadiene **4.55**. Reaction of **4.55** with the iminium generated from **4.53** gave diastereomers **4.56** and **4.57** which were elaborated in two steps to madinodoline A (**4.58**) and madindoline B (**4.59**)

With the stage set for our system the key allene Nazarov cyclization was now explored. Reaction optimization revealed that 3.5 equivalents of the lithioallene **4.60** were needed to ensure complete conversion of the Weinreb amide **4.50** to divinyl ketone



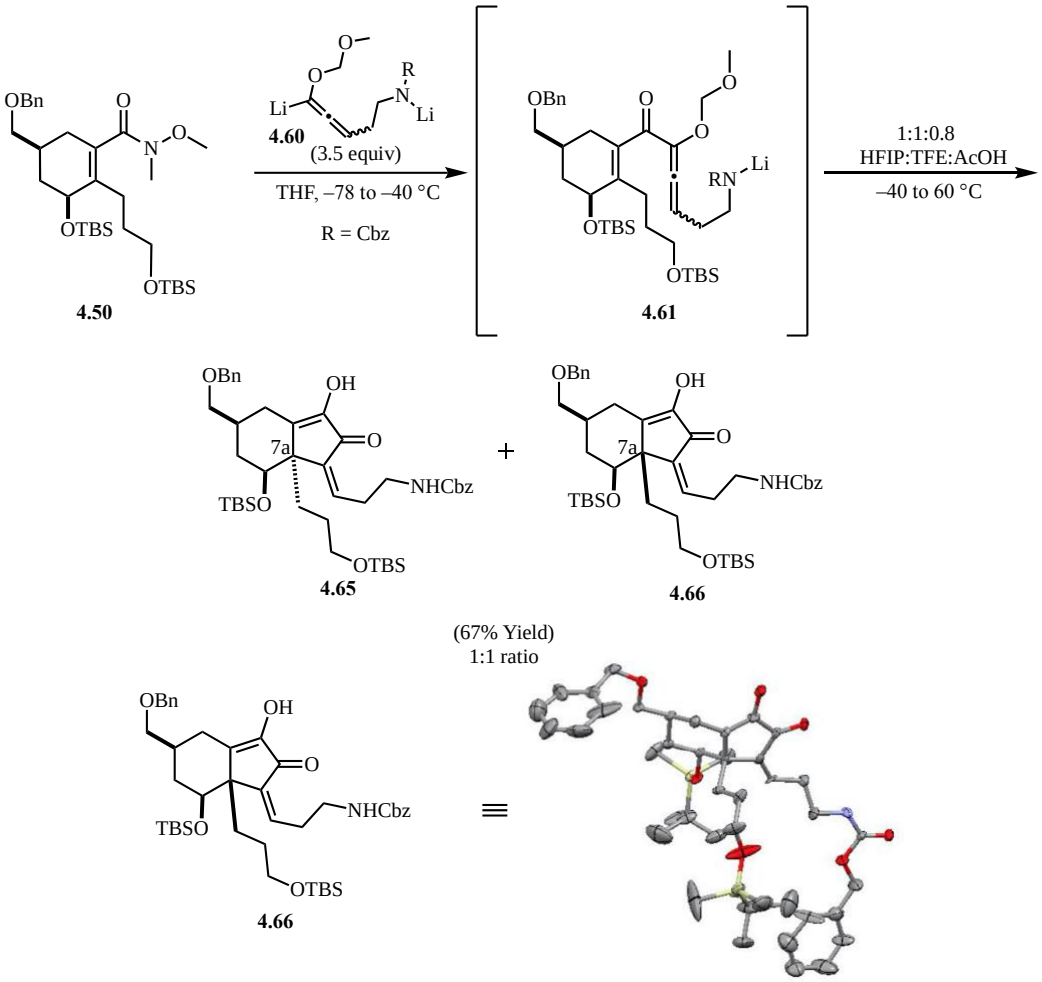
Scheme 4.10 Attempted allene Nazarov under mild conditions

intermediate **4.61** (Scheme 4.10). NMR analysis of crude **4.61** was not conclusive on the formation of the divinyl ketone, although high resolution mass spec analysis of the crude reaction mixture did show the desired mass to be present. Precedent suggested to us that mild reaction conditions such as 1 M sodium phosphate (aq) or aging on silica gel would induce the Nazarov cyclization of divinyl ketone **4.61**.[13] The reasoning behind the mildness of these conditions as opposed to standard, harsher Nazarov cyclization conditions is the lack of steric encumbrance about the allenyl carbon. Disappointingly, 1 M sodium phosphate failed to induce the desired transformation; while aging on silica gel gave a plethora of unidentified products, and none of the desired electrocyclization products. Due to the complexity of both substrates **4.50** and **4.60,** as well as the small supply of **4.60**, we opted to explore the viability of this Nazarov reaction using allene **4.30**, which had served as precursor to the more elaborate variant **4.60** (Scheme 4.11).



Scheme 4.11 Model Nazarov cyclization

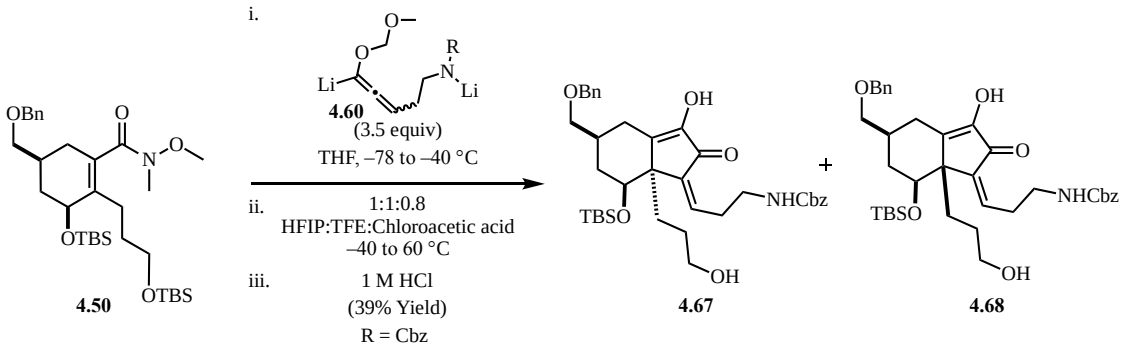
After some experimentation we were once again inspired by precedent from Tius which showed that exposure of divinyl ketones to *in-situ* generated HCl (from acetyl chloride) in trifluoroethanol and hexafluoroisopropanol could induce electrocyclization. In our hands *in-situ* generated HCl gave a low yield of the Nazarov cyclization product along with significant amounts of unidentifiable products.[14] Hypothesizing that the acid used was too strong, we utilized AcOH in instead. When divinyl ketone **4.62** was subjected to a 1:1:0.8 ratio of a TFE, HFIP and AcOH at 60 °C we observed formation of substantial quantities of Nazarov products **4.63** and **4.64** as a 1:1 mixture of diastereomers. Extending similar conditions to the actual system, we were delighted to find that **4.65** and **4.66** were produced in reasonable yield, albeit in a nearly 1:1 mixture of diastereomers about the quaternary center at C7a (Scheme 4.12). Compound **4.66** produced X-ray quality crystals on slow crystallization from acetonitrile allowing us to confirm the structure and relative stereochemistry (scheme 4.12)!



Scheme 4.12 Allene Nazarov cyclization on full system

Disappointingly, cyclization did not proceed fully to give the 6/5/6 system by formation of the hemiaminal. Likely, this was due to the nitrogen atom being part of a carbamate. Focusing our efforts on increasing reaction yield we explored a few acids of varying strength for this cyclization. Exposing **4.50** to the reaction conditions while replacing the acetic acid with pivalic acid gave **4.65** and **4.66** in good yield but generated an unknown by product derived from the allene which co-eluted with the product. In the case of acetic acid, yield of up to 67% was obtained with only trace quantities of the unknown by-product. Increasing the acidity by utilizing chloroacetic acid resulted in a

reduction in reaction time to two hours versus nine to twelve hours with acetic acid. Additionally, the chloroacetic acid also partially cleaved the primary TBS ether. To avoid a mixture of protected and de-protected products we simply exposed the reaction mixture to 1 M HCl solution to give **4.67** and **4.68** in 39% combined yield over the two steps (Scheme 4.13).

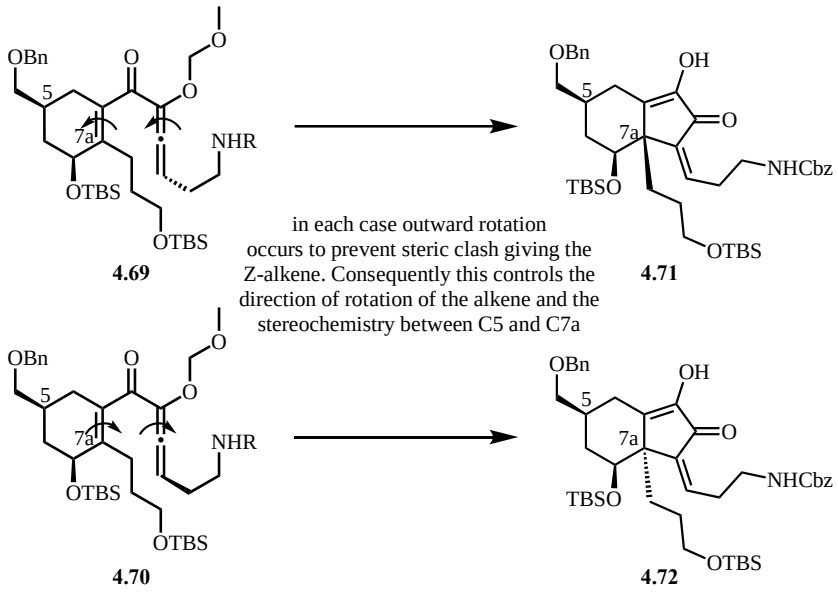


Scheme 4.13 Allene Nazarov with chloroacetic acid

As mentioned earlier, allene Nazarov cyclizations are precedented to occur under mild conditions due to the relative lack of steric encumbrance about the allenyl carbon. We believe that in our system the tetra-substituted alkene component of the divinyl ketone hinders the requisite co-planarity of the alkene and allene in **4.61** (Scheme 4.12) hence the need for elevated temperatures. Furthermore, the chosen conditions appear to take advantage of the hydrophobic effect, in essence, forcing a higher population of the co-planer conformer.

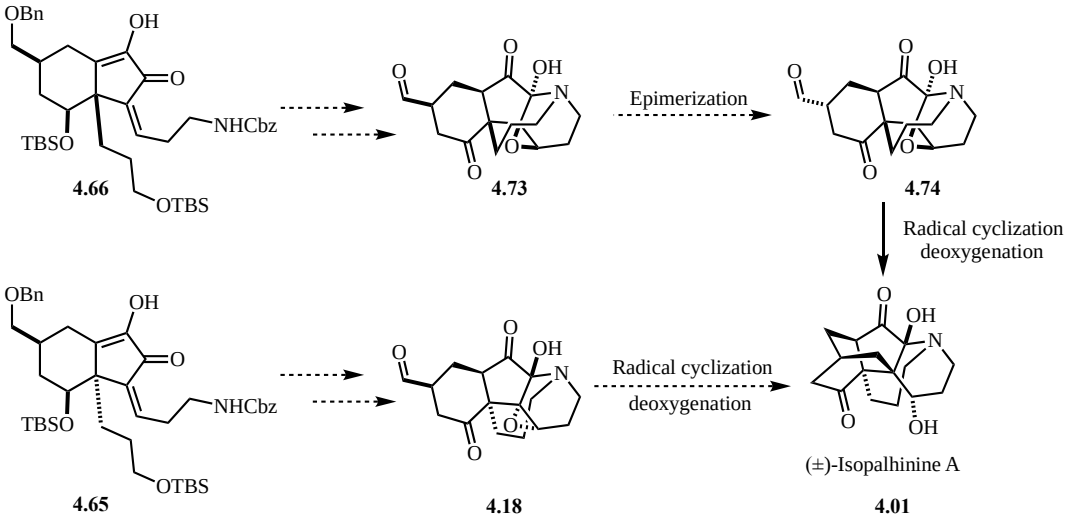
Although with **4.50** the entire cascade sequence leading to the desired 6/5/6 ring system was not observed the results provided important insight with regard to stereochemical outcomes. In rationalizing the latter it is perhaps best to first discuss the origin of the observed sole formation of the (Z)-geometrical isomer. Studies on such

systems have indicated that the substitution on the terminal carbon of the allene often has a controlling effect upon the torquoselectivity of the reaction.[15] The larger substituent on the terminal carbon of the allene generally causes rotation to proceed in the direction which would prevent its clash with other portions of the molecule during the Nazarov cyclization. In our case, since the nitrogen-containing chain preferentially rotates outwardly and away from the cyclohexene portion of the molecule, this phenomenon results in products possessing only Z-alkenes (Scheme 4.14). As for the diastereotopic face selectivity (or lack thereof) that one might expect to govern the stereochemical relationship between the quaternary carbon (C7a, numbered as in **4.66**) and the carbon bearing the benzyl ether containing chain (C5), a few factors need to be considered. First, the aforementioned torquoselectivity, which controlled outward rotation of the chain on the allene, also directs the direction of rotation of the alkene's orbitals (Nazarov cyclizations proceed by conrotation) and thus impacts not only the olefin geometry but also the resultant relative



Scheme 4.14 Stereochemical rational

stereochemistry. Secondly, it is important to note that both the allene and Weinreb Amide component in the reactions are racemic. Thus, the coupling of these compounds results in two diastereomers of the divinyl ketone (**4.69**, **4.70**) in a 1:1 ratio (Scheme 4.14). This then leads to the two diastereomeric cyclization products (**4.71**, **4.72**). To obtain solely the desired diastereomer, a single enantiomer of the Weinreb amide and the matched enantiomer of the allene would need to react. Fortunately, both diastereomers can serve as viable synthetic intermediates since the requisite keto aldehydes derived from **4.65** and **4.66** (**4.18** and **4.73**, respectively) would converge to the same diastereomeric series by simple epimerization of the aldehyde in **4.73** (Scheme 4.15).

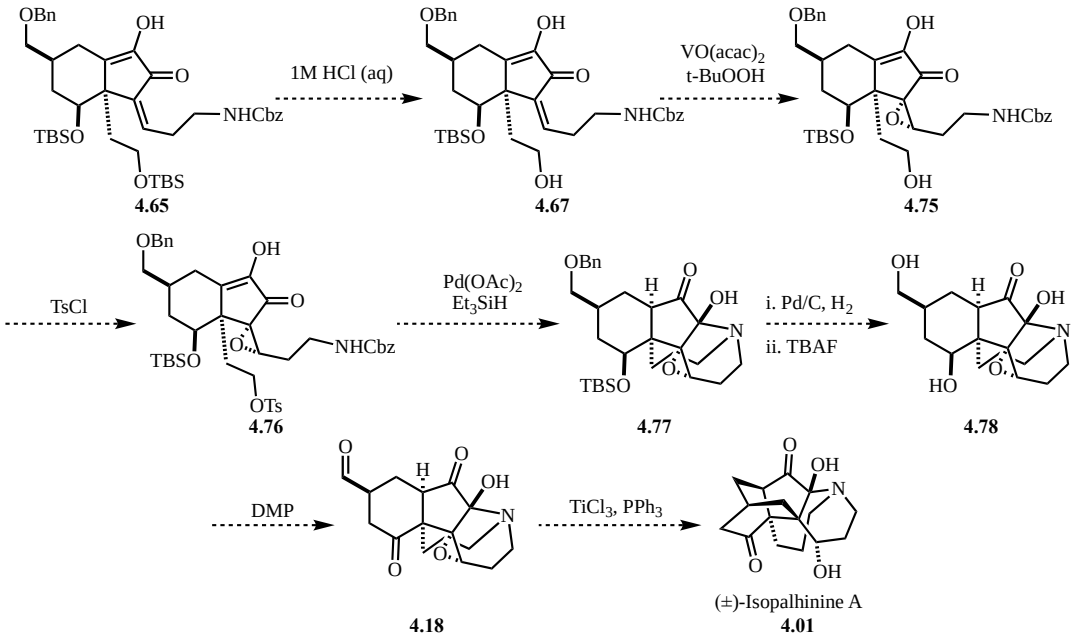


Scheme 4.15 Convergence of **4.65** and **4.66** to (±)-Isopalhinine A

4.2.4 Future Work

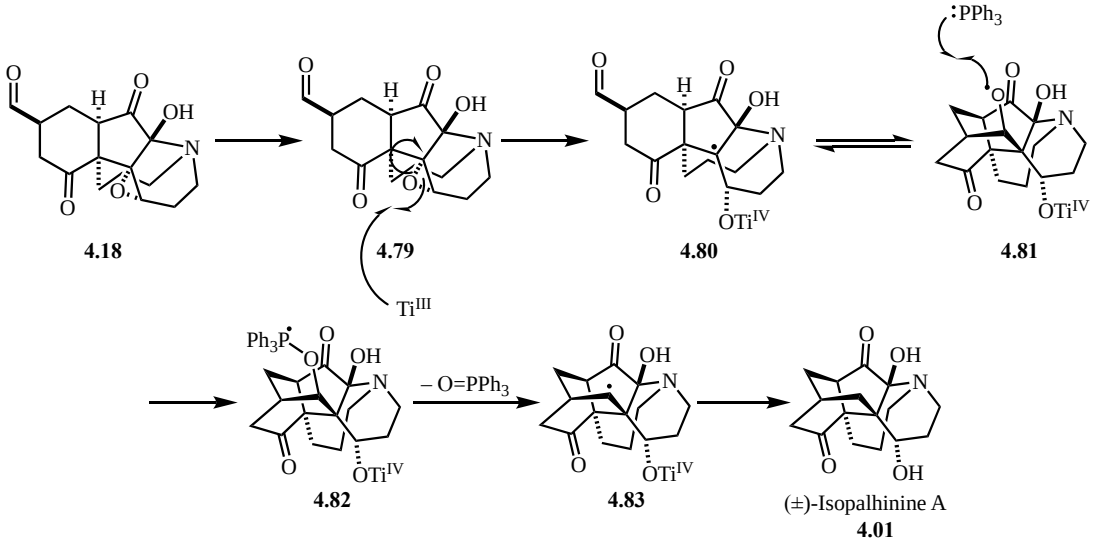
Having established a means of accessing the core [5,6]-ring system with all the carbons in the natural product installed, there are only a few transformations remaining to complete the total synthesis. To this end, we envision the quaternary center generated in the Nazarov cyclization as directing the stereochemical outcomes in the remainder of the

synthesis (Scheme 4.16). Thus, a selective revealing of the primary alcohol would allow for a tris-homoallylic alcohol directed epoxidation of the trisubstituted alkene to furnish the α-face epoxide **4.75**.[16] Tosylate installation followed by selective deprotection of the Cbz group will construct the medium sized nitrogen-containing ring, as well as the hemiaminal moiety (**4.77**).[17] A one-pot deprotection would provide diol **4.78**. Cyclization precursor **4.18** will then be accessed by oxidation of the diol with Dess Martin periodinane. Finally, a titanium (III)-mediated radical epoxide opening, 6-*exo*-trig cyclization and subsequent deoxygenation would provide isopalhinine A (Scheme 4.17). In regards to the order of events just described, closing of the medium-sized ring prior to the final step appears from computer modeling (MM2) to be critical; the closure of the medium-sized ring forces the left side cyclohexanone into a boat like conformation placing the aldehyde containing chain of **4.18** directly above the tertiary carbon of the epoxide.

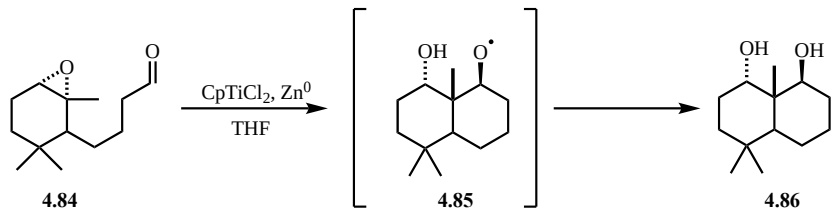


Scheme 4.16 Endgame strategy

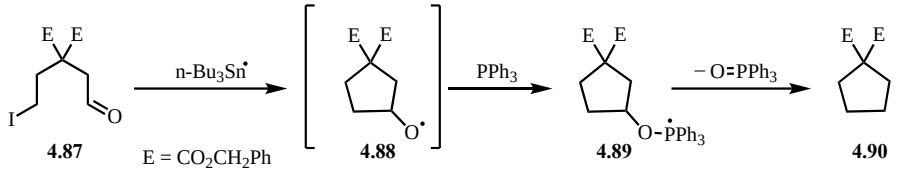
Arguably the most interesting portion of the endgame strategy is the final radical cyclization/deoxygenation sequence of **4.18** to give the natural product. As shown in Scheme 4.17 titanium mediated homolytic cleavage of the epoxide would generate tertiary radical **4.80** as well install the requisite α-face alcohol. Radical **4.80** exists in some small equilibrium with alkoxy radial **4.81**. The alkoxy radical, in the presence of triphenyl phosphine reacts to generate phosphorus radical **4.82**. Loss of triphenyl phosphine then gives secondary radical **4.83**, which may abstract a hydrogen atom from the solvent to generate the natural product. Although alkoxy radicals are known to be high energy species, a process as just described is not unprecedented (Scheme 4.18). As shown by Fernández-Mateos and Kim, reactions proceeding through alkoxy radicals generated by reaction of a tertiary radical and an aldehyde are viable and in the presence of triphenyl phosphine may result in deoxygenation.[18]



Scheme 4.17 Proposed isotwistane synthesis



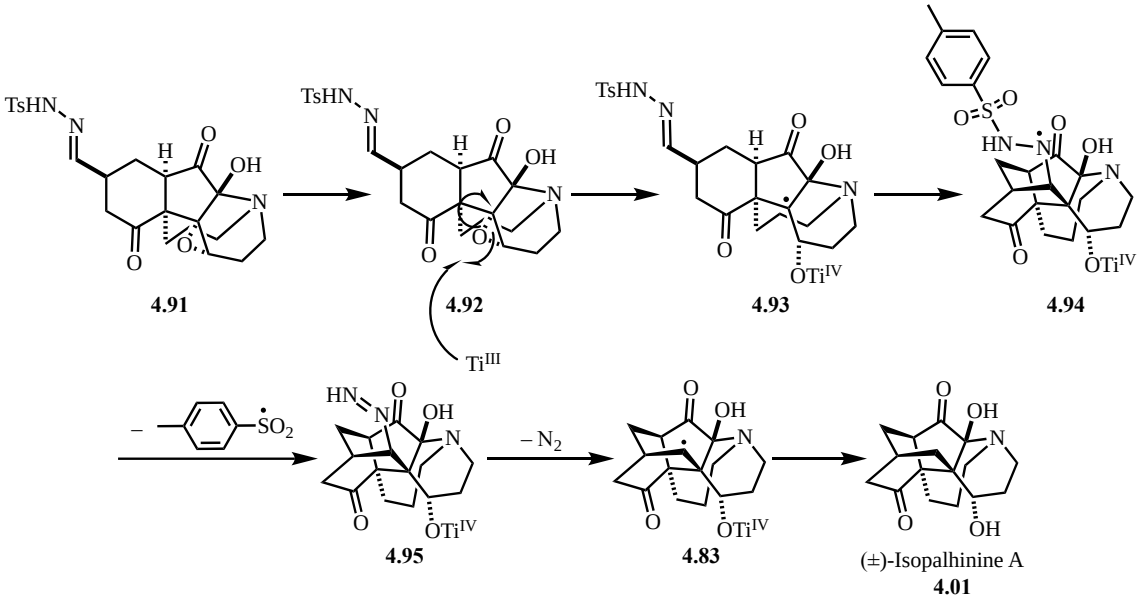
Radical epoxy aldehyde cyclization – Fernández-Mateos



Alkoxy radical deoxygenation with triphenyl phosphine – Kim

Scheme 4.18 Precedent for radical cyclization deoxygenation sequence

Failing this, precedent does exist for the performing of a similar reaction sequence from a tosyl hydrazone such as **4.91**. This reaction would obviate the need to proceed through a high energy alkoxy radical and will be driven by the loss of dinitrogen (Scheme 4.19).[19]



Scheme 4.19 More favorable isotwistane synthesis driven by loss of dinitrogen

Another facet of these reactions is that the construction of an isotwistanes [2.2.2] bicycle in this manner is unprecedented. Previously, isotwistanes had been accessed through two predominant methods; intramolecular Diels-Alder reactions, as shown by Fan and Rychnovsky, and through enolate or enamine chemistry.[20]

4.2.5 Conclusion

In conclusion, versatile intermediates **4.65** and **4.66** have been accessed through the application of an allene Nazarov cyclization in eight linear steps from known materials through a convergent sequence. With all the carbons of the natural product in place, as well as a key quaternary center established, only a few steps remain to be explored prior to completion of the total synthesis. The most interesting step of which is the unprecedented forging of the [2.2.2] bicycle of an isotwistane through a radical ring closure and subsequent deoxygenation sequence.

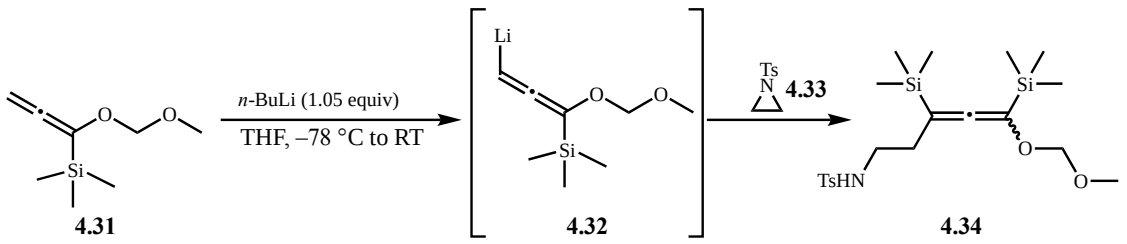
4.3 Experimental

4.3.1 General

Unless otherwise stated, all reactions were performed in flame dried glassware under a nitrogen atmosphere, using reagents as received from the manufacturers. The reactions were monitored and analytical samples purified by normal phase thin-layer chromatography (TLC) using Millipore glass-backed 60 Å plates (indicator F-254, 250 μM) or by using Sigma Aldrich glass-backed 60 Å reverse phase C-18 fully end-capped plates (fluorescent indicator, 250 μM). Tetrahydrofuran, dichloromethane, acetonitrile, dimethylformaide and toluene were dried using a solvent purification system manufactured by SG Water U.S.A., LLC. Manual flash chromatography was performed using the

indicated solvent systems with Silicycle SiliaFlash® P60 (230–400 mesh) silica gel as the stationary phase. Flash Chromatography on a Teledyne RF+UV-Vis Ms Comp MPLC was performed using the indicated solvent systems, and Teledyne RediSep® Rf normal phase disposable columns of the indicated size and at the indicated flow rate. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III 300, a Bruker AscendTM 400 autosampler or a Bruker AscendTM 600 autosampler. Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual solvent resonance and coupling constants (J) are reported in hertz (Hz). NMR peak pattern abbreviations are as follows: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, at = apparent triplet, q = quartet, ABq = AB quartet, m = multiplet. NMR spectra were calibrated relative to their respective residual NMR solvent peaks, $CDCl_3$ = 7.26 ppm (^{1}H NMR)/ 77.16 ppm (^{13}C NMR), DMSO = 2.50 ppm (^{1}H NMR)/ 39.52 ppm (^{13}C NMR), MeOD = 3.31 ppm (^{1}H NMR) MeCN = 1.94 ppm (^{1}H NMR)/118.26 ppm (^{13}C NMR) CD_2Cl_2 5.32 ppm (^{1}H NMR)/ 53.84 ppm (^{13}C NMR) $(CD_3)_2CO$ 2.05 ppm (^{1}H NMR)/ 29.84 ppm (^{13}C NMR of methyl carbon). IR spectra were recorded on Bruker Platinum-ATR IR spectrometer using a diamond window, all stretches are reported in cm^{-1}. High Resolution mass spectra (HRMS) were obtained in the Baylor University Mass Spectrometry Center on a Thermo Scientific LTQ Orbitrap Discovery spectrometer using +ESI or –ESI and reported for the molecular ion ($[M+H]^+$ & $[M+Na]^+$ or $[M-H]^-$ respectively). Single crystal X-ray diffraction data were collected on a BrukerApex II-CCD detector using Mo-Kα radiation (λ = 0.71073 Å). Crystals were selected under oil, mounted on micromounts then immediately placed in a cold stream of N_2. Structures were solved and refined using SHELXTL.[29]

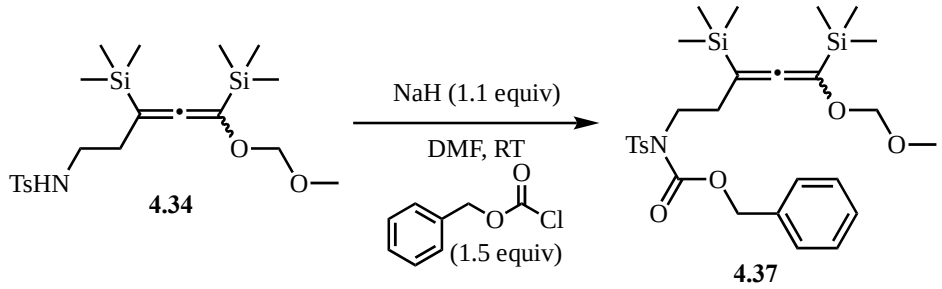
*Preparation of Di-TMS Allene **4.34***



To a dried round bottomed flask was added TMS protected allene **4.31** (4.1 g, 24 mmol) and dry THF (41mL). The solution was cooled to –78 °C in a dry ice acetone bath and 2.5 M BuLi was added slowly (9.0 mL, 22.5 mmol). After 1 hour, tosyl aziridine (4.69 g, 23.7 mmol) dissolved in dry THF (41 mL) was slowly added to the lithioallene solution over 20 minutes. After allowing the reaction mixture to stir at –78 °C for 15 minutes, the solution was warmed to RT and let stir for 1 hour. Concurrently, another solution of the lithioallene was prepared in the same way as the first. After the solution which contained the tosyl aziridine and lithioallene had stirred at RT for 1 hour it was quickly added to the freshly prepared solution of lithioallene at –78 °C. The combined reaction solutions were quickly warmed to RT and allowed to stir for three minutes then quenched with half saturated brine and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and the solvent removed under reduced pressure. The residue was purified by MPLC over 40 minutes using a gradient which began at 0% ethyl acetate in hexanes and progressed to 20 % ethyl acetate in hexanes. All column solvents contained 1% triethyl amine. This gave 3.07 g (29.3% Yield) of Di-TMS allene **4.34** as a thick oil which solidified to an off white solid in the –20 °C freezer. *Note, on smaller scale (less than 2 g) this reaction also yields an inseparable mixture of the two possible mono protected TMS allenes in useful quantities, these may be carried through the same sequence as the

Bis-TMS protected allene to arrive at the same final allene product. **Data for 4.34:** R_f = 0.4 (20% EtOAc/hexanes), UV; **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.73 (d, *J* = 7.9 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 6.31 (dd, *J* = 8.5, 4.3 Hz, 1H), 4.91 (d, *J* = 6.3 Hz, 1H), 4.73 (d, *J* = 6.3 Hz, 1H), 3.47 (s, 3H), 3.26 – 3.18 (m, 1H), 3.14 – 3.05 (m, 1H), 2.40 (s, 3H), 2.15 – 2.01 (m, 2H), 0.10 – 0.03 (m, 9H), 0.00 – -0.05 (m, 9H).**^{13}C NMR** (151 MHz, Chloroform-*d*) δ 198.1, 142.9, 138.7, 129.7, 126.9, 125.6, 108.2, 94.3, 55.8, 41.5, 30.9, 21.6, -1.7, -2.0. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{20}H_{35}NO_4SSi_2Na^+$ = 464.17230, found $C_{20}H_{35}NO_4SSi_2Na^+$ = 464.17181. **FTIR (Neat)** 3235, 2955, 2896, 1901, 1599, 1437, 1332, 1247, 1210, 1160, 1095, 1051, 967, 912, 840, 816, 752, 694, 663. **Data for 4.35 and 4.36 (Mono silylated allenes): ^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.77 – 7.69 (m, 3.6H), 7.29 – 7.26 (m, 3H), 6.55 (t, *J* = 2.6 Hz, 0.7H), 6.15 (t, *J* = 6.1 Hz, 1H), 5.91 (dd, *J* = 8.0, 4.7 Hz, .7H), 5.40 (dd, *J* = 6.5, 5.1 Hz, 1H), 5.01 (d, *J* = 6.3 Hz, 1H), 4.84 (d, *J* = 6.5 Hz, 0.8H), 4.75 (d, *J* = 6.4 Hz, 1H), 4.72 (d, *J* = 6.5 Hz, 0.8H), 3.48 (s, 1.6H), 3.47 (s, 3H), 3.26 – 3.18 (m, 1H), 3.16 – 3.11 (m, 1H), 3.11 – 3.06 (m, 2H), 2.41 (s, 5H), 2.24 – 2.13 (m, 2.5H), 2.13 – 2.06 (m, 1.5H), 0.09 (s, 9H), 0.01 (s, 4.7H). Major isomer TMS peak set to 9 protons, ratio of major to minor is 1: 0.52. **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 197.2, 196.1, 143.0, 143.0, 138.4, 138.2, 129.7, 129.7, 128.9, 127.0, 127.0, 118.5, 115.4, 99.0, 94.4, 94.1, 56.3, 55.9, 41.4, 41.1, 31.3, 30.5, 21.6, 21.6, -1.9, -2.2. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{17}H_{27}NO_4SSiNa^+$ = 392.13278, found $C_{17}H_{27}NO_4SSiNa^+$ = 392.13260. **FTIR (Neat)** 3252, 2956, 2897, 1599, 1495, 1434, 1379, 1330, 1306, 1290, 1249, 1217, 1160, 1095, 1040, 963, 842, 916, 756, 694, 663, 631.

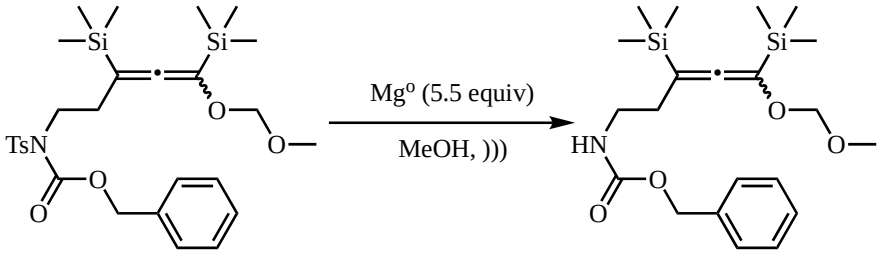
*Preparation of Cbz Protected Allene **4.37***



Bis-TMS allene **4.34** (10 g, 23 mmol) was added to a dried round bottomed flask and dissolved in dry DMF (200 mL). The solution was placed under high vacuum to remove any trace solvent, water, or amine impurities and then the flask back filled with N_2. The reaction flask was cooled in an ice water bath and subsequently NaH as a 60% dispersion in oil (1.13 g, 28.3 mmol) was added. The ice bath was removed and the solution allowed to warm up to room temperature (22 °C) for 15 minutes. Benzyl chloroformate (4.9 mL, 34 mmol) was added and the reaction allowed to stir for five hours at which point an additional 0.5 mL of benzyl chloroformate (3.5 mmol) was added. After an additional hour the reaction was quenched with basic half saturated brine (contained a small amount of sodium bicarbonate solution) and extracted with ethyl acetate several times and once with diethyl ether. The combined organic layers were dried over sodium sulfate and the solvent removed under reduced pressure. The residue was then purified by MPLC using a gradient which began at 0% ethyl acetate in hexanes and progressed to 20% ethyl acetate in hexanes. This gave 10.77g (83% Yield) of the Cbz-protected allene **4.37** as a thick light yellow oil. R_f = 0.45 (20% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.34 – 7.29 (m, 3H), 7.23 – 7.18 (m, 4H), 5.09 (s, 2H), 4.75 (s, 2H), 4.02 – 3.82 (m, 2H), 3.34 (s, 3H), 2.55 – 2.41 (m, 3H), 2.41 (s, 2H) (the overlapping peaks integrate to 5H in the drawn spectrum), 0.13 (s, 9H), 0.10 (s, 9H).**^{13}C NMR** (101

MHz, Chloroform-*d*) δ 200.4, 152.3, 144.5, 136.8, 134.7, 129.4, 128.7, 128.7, 128.5, 128.4, 124.7, 106.8, 94.8, 69.0, 55.4, 47.0, 31.0, 21.7, -1.6, -1.9. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{28}H_{41}NO_6SSi_2Na^+$ 598.20908, found $C_{28}H_{41}NO_6SSi_2Na^+$ = 598.20876. **FTIR (neat)** 2956, 2897, 1902, 11731, 1597, 1496, 1454, 1386, 1359, 1323, 1270, 1248, 1207, 1186, 1168, 1138, 1088, 1051, 962, 841, 814, 753, 735, 697, 662, 630.

*Preparation of Allene **4.38***

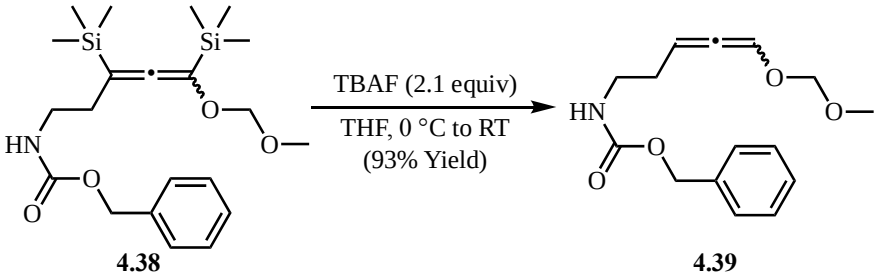


4.37 **4.38**

Cbz-protected allene **4.37** (1.1g, 1.9 mmol) was placed in a round bottomed flask and dissolved in dry methanol (19 mL), powdered magnesium (257 mg, 10.5 mmol) was then added. To the flask was attached an argon balloon and the flask purged with argon. The flask was then placed in a sonicator and sonicated for 30 minutes at room temperature. To the reaction was then added ethyl acetate, hexanes, DCM, and water and the mixture shaken in order to precipitate the magnesium salts. The solution was then filtered and the filtrate washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure giving 783 mg (97% Yield) of the desired allene **4.38** which was carried forward without further purification. R_f = 0.45 (20% EtOAc/hexanes), UV; **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.39 – 7.27 (m, 5H), 6.14 (s, 1H), 5.14 (d, *J* = 12.3 Hz, 1H), 5.06 (d, *J* = 12.4 Hz, 1H), 4.89 (d, *J* = 6.2 Hz, 1H), 4.71 (d, *J* = 6.2 Hz, 1H), 3.57 – 3.46 (m, 1H), 3.31 (s, 3H), 3.26 – 3.16 (m, 1H), 2.31 – 2.17 (m, 2H), 0.11 (s, 9H), 0.08 (s, 9H). **^{13}C**

NMR (151 MHz, Chloroform-*d*) δ 198.6, 156.8, 137.2, 128.5, 128.0, 128.0, 125.1, 108.7, 94.3, 66.4, 55.3, 39.5, 31.4, -1.6, -1.9. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{21}H_{35}NO_4Si_2Na^+ = 444.20023$, found $C_{21}H_{35}NO_4Si_2Na^+ = 444.20007$. **FTIR (Neat)** 3335, 2955, 2897, 1900, 1722, 1529, 1455, 1403, 1365, 1320, 1246, 1152, 1099, 1051, 966, 917, 838, 751, 696, 629.

*Preparation of Allene **4.39***

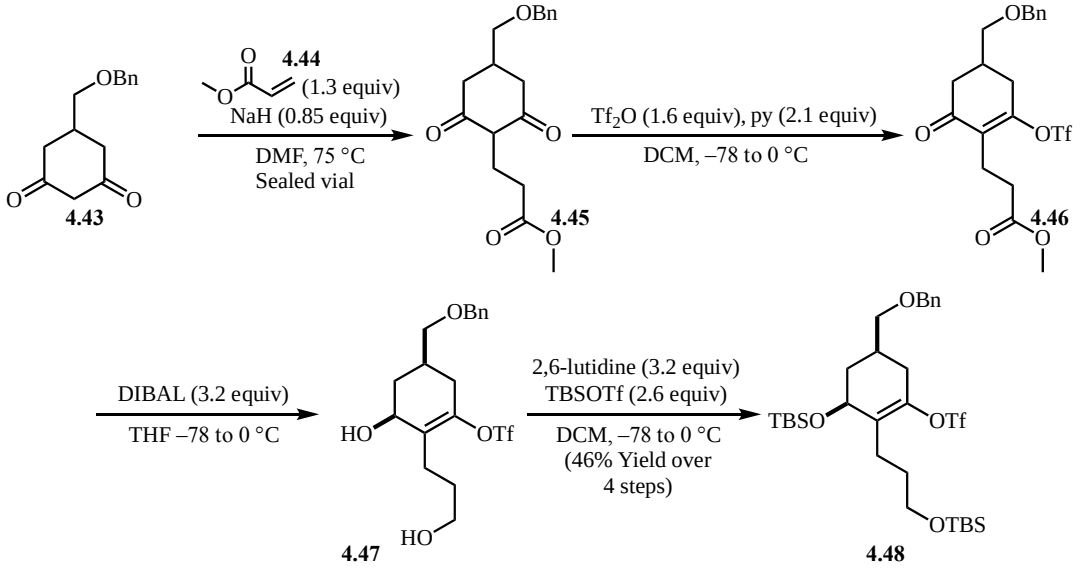


4.38 **4.39**

Two reactions were run in parallel, one at 3.2 g scale and the other at 3.6 g scale, the reactions were combined for purification. The written procedure describes the 3.6 g scale reaction. Allene **4.38** (3.6 g, 8.5 mmol) was dissolved in dry THF (85 mL) then cooled in an ice bath. To this solution was added 1 M TBAF in THF solution (15.1 mL, 15.1 mmol). After 20 minutes the ice bath was removed and the reaction allowed to stir until TLC indicated reaction completion (1 – 2 hours). The reactions were then combined, diluted with ethyl acetate and quenched with a 1:1:2 Brine: NH_4Cl (sat.):H_2O solution. The quench was used to wash the organic layer and the aqueous layer was then back extracted with minimal ethyl acetate. The organic layer was dried over sodium sulfate and the solvent evaporated. This gave 4.0 g (89% Yield) of the deprotected allene **4.39** as a clear light brown oil. *Note, if excess tetrabutylammonium salts remain in the product after the first work up another work up may be performed to remove them. R_f = 0.22 (20%

EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.39 – 7.27 (m, 5H), 6.62 (dt, *J* = 5.4, 2.5 Hz, 1H), 5.81 (apparent q, *J* = 5.8 Hz, 1H), 5.65 (br s, 1H), 5.10 (apparent q, *J* = 12.3 Hz, 2H), 4.90 (d, *J* = 6.4 Hz, 1H), 4.73 (d, *J* = 6.4 Hz, 1H), 3.49 – 3.24 (m, 5H), 2.40 – 2.20 (m, 2H). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 194.07, 156.70, 136.94, 128.59, 128.11, 119.30, 104.28, 94.36, 66.61, 56.12, 39.09, 31.32. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{15}H_{19}NO_4Na^+$ = 300.12118, found $C_{15}H_{19}NO_4Na^+$ = 300.12085. **FTIR (Neat)** 3336, 3033, 2951, 2828, 1959, 1719, 1707, 1530, 1454, 1431, 1397, 1365, 1334, 1297, 1244, 1217, 1154, 1094, 1039, 921, 847, 776, 751, 738, 698, 676, 642, 606.

*Preparation of Vinyl Triflate **4.48***



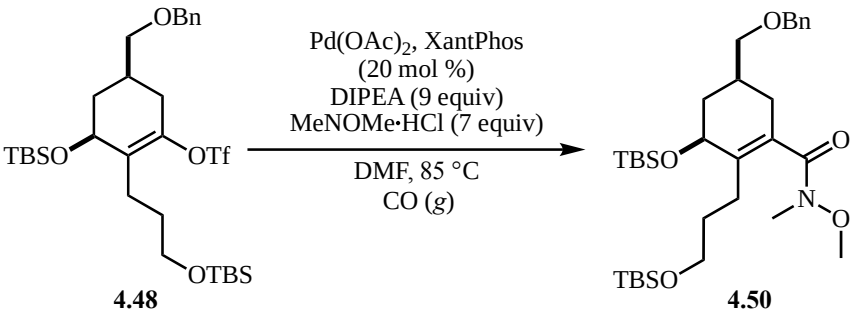
Diketone **4.43** (542 mg, 2.33 mmol) was placed in a dry sealed tube and dissolved in dry DMF (7 mL) then sodium hydride as a 60% dispersion in oil (77 mg, 1.9 mmol) was added. After 25 minutes, methyl acrylate (271 μL, 3.01 mmol) was added, the reaction vessel purged with argon, placed in a 75 °C oil bath and the reaction vigorously stirred. After 4 hours and 20 minutes the reaction was removed from the heating bath and allowed

to cool. Once cooled the reaction solution was poured into 3:1:3 Brine: NH_4Cl (sat.):H_2O and extracted twice with ethyl acetate. The combined organic layers were washed again with 3:1:3 Brine:NH_4Cl (sat.):H_2O and twice with brine. The organic layer was dried over sodium sulfate and the solvent removed under reduced pressure. This gave 527 mg of crude ester **4.45** which was carried forward without further purification. (**vinyl triflate 4.46**): The crude ester **4.44** from the previous step was dissolved in dry DCM (7.2 mL) and cooled to –78 °C in a dry ice acetone bath. Dry pyridine (0.27 ml, 3.4 mmol) was then added followed by the dropwise addition of Tf_2O (0.43 mL, 2.6 mmol). After 30 minutes the solution was allowed to warm to 0 °C (ice water bath) for 20 minutes and then quenched with 1 M HCl (5 mL). The reaction mixture was extracted twice with ethyl acetate and the combined organic layer washed with sodium bicarbonate which had been saturated with sodium chloride. The organic layer was then dried over sodium sulfate and the solvent removed under reduced pressure. This gave 733 mg of vinyl triflate **4.46** which was used without further purification for the next step. (**diol 4.47**): The crude vinyl triflate **4.46** from the previous step was dissolved in dry THF (16 mL) and cooled to –78 °C in a dry ice acetone bath. Then 1 M DIBAL in hexanes (5.2 mL, 5.2 mmol) was added dropwise. twenty minutes later the reaction was warmed to 0 °C (ice water bath) and allowed to stir for an additional 30 minutes. Moistened sodium sulfate was then added to quench the remaining DIBAL. The crude reaction mixture was then eluted through a silica plug using 400 mL of 7% methanol in DCM to remove residual aluminum salts. The solvent was then removed under reduced pressure to give 565 mg of crude diol **4.47** as a single diastereomer which was carried through without further purification. (**vinyl triflate 4.48**): Crude diol **4.47** from the previous step was dissolved in dry DCM (6 mL) and 2,6 lutidine (496 μL, 4.26 mmol)

was added. The solution was cooled to –78 °C in a dry ice acetone bath and TBS-OTf (796 μL, 3.47 mmol) was added dropwise. After 40 minutes the dry ice acetone bath was removed and the reaction was allowed to stir for an additional 40 minutes. The reaction was then quenched with methanol then NH_4Cl (sat.). The reaction mixture was then extracted several times with DCM and purified on a 12 gram MPLC column using a gradient which began at 0% ethyl acetate in hexanes and progressed to and was held at 20% ethyl acetate in hexanes. This gave 700 mg (46% Yield over four steps, an average of ~82.5% yield for each step) of vinyl triflate **4.48** as a colourless oil. *Notes, Crude NMR spectra for each intermediate are provided. **Data for 4.45:** R_f = 0.13 (30% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.43 – 7.18 (m, 5H), 4.47 (s, 2H), 3.55 (s, 3H), 3.36 (d, *J* = 5.8 Hz, 2H), 2.44 – 2.32 (m, 4H), 2.30 – 2.15 (m, 5H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 173.10, 138.48, 128.23, 127.36, 127.29, 112.43, 72.69, 71.96, 51.10, 35.58 (br s), 33.03, 32.58, 17.66. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+ = C_{18}H_{22}O_5Na^+$ 341.13649, found = 341.13605. **FTIR (Neat)** 3086, 2924, 2855, 1733, 1577, 1496, 1436, 1384, 1269, 1240, 1168, 1097, 1066, 1027, 987, 931, 866, 830, 737, 698. **Data for 4.46:** R_f = 0.5 (30% EtOAc/hexanes), UV; **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.38 – 7.34 (m, 2H), 7.32 – 7.29 (m, 3H), 4.55 – 4.47 (m, 2H), 3.66 (s, 3H), 3.46 (dd, *J* = 9.4, 4.9 Hz, 1H), 3.42 (dd, *J* = 9.4, 6.1 Hz, 1H), 2.81 – 2.76 (m, 2H), 2.67 – 2.63 (m, 2H), 2.58 (dd, *J* = 16.2, 4.1 Hz, 1H), 2.53 – 2.46 (m, 1H), 2.43 – 2.36 (m, 3H). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 196.7, 172.6, 161.9, 137.9, 130.0, 128.6, 128.0, 127.8, 118.4 (q, *J* = 320.0 Hz), 73.4, 72.0, 51.9, 40.1, 33.8, 32.2, 32.0, 19.6. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+ C_{19}H_{21}F_3O_7SNa^+$ = 473.08578, found $C_{19}H_{21}F_3O_7SNa^+$ = 473.08539. **FTIR (Neat)**: 2953, 2858, 1738, 1688, 1664, 1604, 1496, 1419, 1366, 1244, 1216, 1173, 1138, 1115, 1031, 922, 808, 750, 700,

609. **Data for 4.47:** R_f = 0.25 (50% EtOAc/hexanes), UV; **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.38 – 7.28 (m, 5H), 4.52 (s, 2H), 4.36 (s, 1H), 3.69 – 3.60 (m, 2H), 3.45 (d, *J* = 5.5 Hz, 2H), 2.45 (dd, *J* = 16.1, 6.6 Hz, 2H), 2.41 – 2.35 (m, 1H), 2.30 – 2.21 (m, 1H), 2.22 – 2.10 (m, 2H), 1.81 – 1.70 (m, 2H), 1.54 – 1.43 (m, 1H). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 144.8, 137.9, 132.9, 128.6, 128.0, 127.9, 118.4 (q, *J* = 319.5 Hz), 73.7, 73.5, 67.9, 62.4, 34.8, 32.6, 31.2, 30.2, 23.2. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{18}H_{23}F_3O_6SNa^+$ = 447.10651 found $C_{18}H_{23}F_3O_6SNa^+$ = 447.10611. **FTIR (Neat)** 3344, 2924, 2857, 1454, 1408, 1363, 1244, 1205, 1138, 1092, 1058, 1027, 962, 921, 851, 817, 738, 698, 607. **Data for 4.48:** R_f = 0.64 (20% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.38 – 7.28 (m, 5H), 4.51 (s, 2H), 4.44 – 4.35 (m, 1H), 3.60 (t, *J* = 6.6 Hz, 2H), 3.39 (d, *J* = 6.3 Hz, 2H), 2.44 – 2.22 (m, 4H), 2.16 – 1.98 (m, 2H), 1.75 – 1.55 (m, 2H), 0.89 (s, 18H) (two very close singlets integrating to 9H each), 0.10 (s, 6H) (two very close singlets integrating to 3H each), 0.04 (s, 6H). **^{13}C NMR** (151 MHz, Chloroform-d) δ 144.1, 138.4, 133.8, 128.6, 127.8, 127.7, 118.5 (q, J = 319.5 Hz), 73.6, 73.2, 68.6, 63.3, 35.6, 33.0, 31.3, 31.0, 26.1, 26.0, 23.1, 18.5, 18.1, -3.7, -4.7, -5.2, -5.2. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{30}H_{51}F_3O_6SSi_2Na^+$ = 675.27947 found $C_{30}H_{51}F_3O_6SSi_2Na^+$ = 675.27881. **FTIR (Neat)** 2953, 2930, 2857, 1472, 1412, 1361, 1246, 1207, 1141, 1097, 1006, 976, 921, 880, 834, 812, 774, 736, 697, 667, 628, 606.

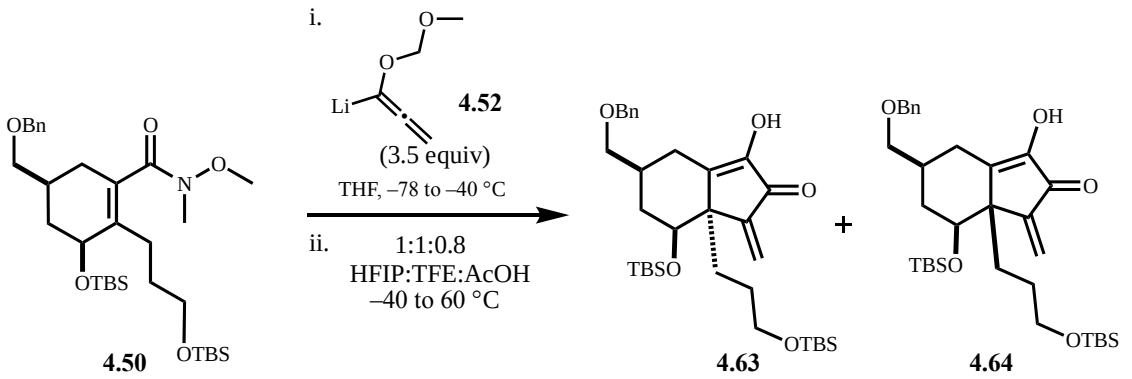
*Preparation of Weinreb Amide **4.50***



To a dry vial was added vinyl triflate **4.48** (85 mg, 0.13 mmol), palladium acetate (5.8 mg, 0.026 mmol). Xantphos (15 mg, 0.026 mmol), Hünig's base (200 μL, 1.15 mmol) and Weinreb amine hydrochloride salt (89 mg, 0.91 mmol). The vial was evacuated and backfilled with CO (*g*). DMF (1.3 mL) was then added and the solution spared with CO (*g*). The reaction vial was warmed to 85 °C for 1 hour and 20 minutes and then allowed to cool. The reaction solution was diluted with diethyl ether and passed through a plug of silica, eluting with diethyl ether and ethyl acetate. The filtrate was then washed twice with half saturated brine and the aqueous washes back extracted with a diethyl ether/hexane mixture. The combined organic layers were dried over sodium sulfate and the solvent removed under reduced pressure. The residue was then purified by silica gel chromatography using 1:1 diethyl ether: hexane as the eluent. This gave 71 mg (92% Yield) of the Weinreb amide **4.50** as a clear oil. *Notes, elution of the crude reaction mixture quickly through a silica plug is critical as the crude reaction mixture begins to decompose after removal of the CO atmosphere/ exposure to oxygen. The ethyl ether hexane mixture used for back extraction is to prevent extraction of the DMF from the aqueous layer while still extracting the product, usually a 1:1 ethyl ether: hexane mixture is used). The yield of this reaction varies significantly on scale up. Usually larger scale reactions yield ~ 70%. R_f

= 0.3 (20% EtOAc/hexanes), UV; **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.36 – 7.30 (m, 4H), 7.29 – 7.26 (m, 1H), 4.50 (s, 2H), 4.32 (br s, 1H), 3.76 (br s, 1H) (this is part of a methyl group present on the oxygen of the Weinreb amide it is distributed over a large area), 3.57 (t, *J* = 6.6 Hz, 4H) (this overlaps with the rest of the oxygens methyl group signal, this signal sharpens at 50 °C, a spectrum for this is provided), 3.43 – 3.31 (m, 2H), 3.20 (s, 3H), 2.36 – 2.25 (m, 1H), 2.23 (br d, *J* = 15.7 Hz, 1H), 2.05 (br s, 3H), 2.00 – 1.90 (m, 1H), 1.72 – 1.64 (m, 1H), 1.64 – 1.54 (m, 1H), 1.38 (apparent q, *J* = 11.1 Hz, 1H), 0.88 (s, 18H), (two very close singlets integrating to 9H each), 0.09 (s, 6H), 0.02 (s, 6H) (This is data for a mixture of rotamers at room temperature). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 172.5, 138.6, 138.0, 129.7, 128.5, 127.7, 74.5, 73.1, 68.1, 63.7, 61.6, 36.3, 33.0, 32.3, 31.6, 30.3, 27.2, 26.1, 26.0, 18.5, 18.1, -3.5, -4.7, -5.2. (This is data for a mixture of rotamers at room temperature, several of the carbons are broad and take a large number of scans to become visible). **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{32}H_{57}NO_5Si_2Na^+$ = 614.36730, found $C_{32}H_{57}NO_5Si_2Na$ = 614.36658. **FTIR (Neat)** 2953, 2928, 2887, 2856, 1715, 1650, 1471, 1462, 1407, 1361, 1253, 1205, 1177, 1091, 1005, 974, 939, 835, 774, 736, 698, 665.

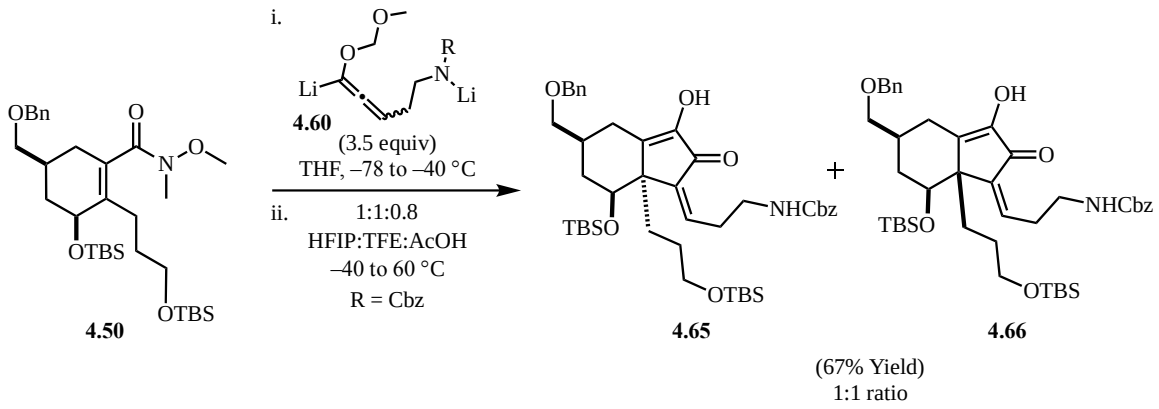
*Preparation of Bicycle **4.63** and **4.64** (model)*



To allene **4.30** (19 mg, 0.19 mmol) dissolved in dry THF (0.5 mL) and cooled to –78 °C was added 2.5 M BuLi in hexanes (76 μL, 0.19 mmol) and the reaction allowed to proceed for 1 hour. To this solution was added a solution of Weinreb amide **4.50** (32 mg, 0.054 mmol) in dry THF (0.9 mL). After 30 minutes the reaction was warmed to –40 °C in an acetonitrile dry ice bath and allowed to stir at this temperature for 1 hour. To the reaction solution was added a solution of 0.6:0.6:0.5 HFIP:TFE:AcOH (v/v/v) and the reaction allowed to stir for 10 minutes at –40 °C. The reaction solution was then warmed to 60 °C in an oil bath for six hours. The solution was allowed to cool and the solvent was evaporated. The residue was purified by preparative TLC using 20% ethyl acetate in hexanes. This gave two diastereomers who's relative stereochemistry was not determined directly but tentatively by analogy to the actual system. Diastereomer 1 (**4.63**): 10.4 mg isolated (32.6% Yield) as a clear oil. Diastereomer 2 (**4.64**): 9.1 mg isolated (28.5% Yield) as a clear oil which solidifies at –20 °C. This is a total 61% Yield. **Data for diastereomer 1** (**4.63**): R_f = 0.47 (20% EtOAc/hexanes), UV; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.38 – 7.28 (m, 4H), 7.30 – 7.23 (m, 1H), 6.04 (s, 1H), 5.81 (br s, 1H), 5.18 (s, 1H), 4.48 (ABq, $\Delta\delta_{AB}$ = 0.06, 2H), 3.95 (s, 1H), 3.61 – 3.44 (m, 3H), 3.35 (dd, *J* = 9.3, 3.9 Hz, 1H), 3.15

(d, *J* = 13.6 Hz, 1H), 2.39 – 2.26 (m, 1H), 2.21 – 2.10 (m, 2H), 2.06 – 1.92 (m, 1H), 1.69 – 1.55 (m, 2H), 1.21 – 1.11 (m, 2H), 0.88 (s, 9H), 0.70 (s, 9H), 0.01 (s, 6H), -0.07 (s, 3H), -0.11 (s, 3H).**^{13}C NMR** (151 MHz, Chloroform-*d*) δ 190.0, 151.3, 145.2, 140.1, 138.7, 128.4, 128.0, 127.6, 114.2, 74.7, 74.7, 73.5, 62.9, 50.9, 34.8, 31.7, 29.0, 27.1, 26.1, 26.0, 23.4, 18.4, 17.8, -3.5, -5.2, -5.2, -5.8. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{33}H_{54}O_5Si_2Na^+$ = 609.34075, found $C_{33}H_{54}O_5Si_2Na^+$ = 609.34027. **FTIR (Neat)** 3304, 2951, 2928, 2894, 2856, 1687, 1631, 1471, 1461, 1400, 1341, 1362, 1341, 1252, 1195, 1095, 1055, 1005, 958, 937, 904, 832, 773, 735, 697, 663. **Data for diastereomer 2** (**4.64**): R_f = 0.42 (20% EtOAc/hexanes), UV; **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.37 – 7.31 (m, 4H), 7.31 – 7.27 (m, 1H), 6.10 (d, *J* = 1.3 Hz, 1H), 5.63 (d, *J* = 1.4 Hz, 1H), 4.53 (s, 2H), 3.53 (t, 2H), 3.45 (dd, *J* = 11.3, 4.3 Hz, 1H), 3.41 (dd, *J* = 5.7, 1.5 Hz, 2H), 2.90 (dd, *J* = 13.1, 2.4 Hz, 1H), 2.05 – 1.93 (m, 1H), 1.87 – 1.78 (m, 3H), 1.78 – 1.70 (m, 1H), 1.60 (apparent q, *J* = 13.1 Hz, 1H), 1.14 – 1.06 (m, 2H), 0.91 (s, 9H), 0.87 (s, 9H), 0.04 (s, 3H), 0.01 (s, 6H), -0.04 (s, 3H).**^{13}C NMR** (151 MHz, Chloroform-*d*) δ 189.8, 148.9, 146.1, 144.5, 138.5, 128.5, 127.7, 127.6, 117.8, 77.1, 74.5, 73.2, 63.3, 50.0, 37.3, 34.6, 26.6, 26.1, 26.1, 25.0, 23.9, 18.4, 18.2, -3.6, -4.2, -5.1, -5.2. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{33}H_{54}O_5Si_2Na^+$ = 609.34075 found $C_{33}H_{54}O_5Si_2Na^+$ = 609.34015. **FTIR (Neat)** 3301, 2953, 2929, 2886, 2856, 1686, 1627, 1472, 1462, 1362, 1255, 1103, 1006, 940, 908, 836, 775, 736, 697.

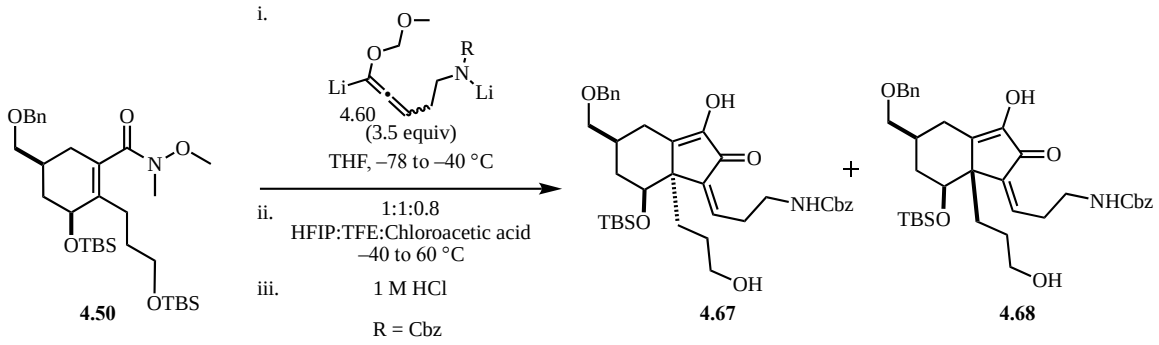
*Preparation of Bicycle **4.65** and **4.66***



To allene **4.39** (40 mg, 0.14 mmol) dissolved in dry THF (0.65 mL) and cooled to –78 °C was added 2.5 M BuLi in hexanes (118 μL, 0.295 mmol) and the reaction allowed to proceed for 1 hour. To this solution was added a dry ice acetone bath cooled solution of Weinreb amide **4.50** (25 mg, 0.042 mmol) in dry THF (0.4 mL). After 25 minutes the reaction was warmed to –40 °C in an acetonitrile dry ice bath and allowed to stir at this temperature for 1 hour. The reaction solution was then transferred by cannula to a 0.6:0.6:0.5 HFIP:TFE:AcOH (v/v/v) solution which was also at –40 °C and stirred for 10 minutes. The reaction solution was then warmed to 60 °C in an oil bath for nine hours. The reaction was allowed to cool, diluted with ethyl acetate and washed several times with a saturated sodium bicarbonate solution. The organic layer was dried over sodium sulfate and the solvent evaporated under reduced pressure. The residue was purified by MPLC using a gradient which began at 0% ethyl acetate in hexanes progressed to 20% ethyl acetate in hexanes. This gave 10.7 mg of diastereomer **4.65** (clear oil) and 10.8 mg of diastereomer **4.66** (clear oil which crystalizes on standing concentrated in acetonitrile, total 67% Yield). **Data for 4.65:** R_f = 0.25 (20% EtOAc/hexanes), UV; **^{1}H NMR** (600 MHz, Acetone-d_6) δ 7.39 – 7.28 (m, 10H), 6.37 (s, 1H), 5.89 (dd, *J* = 9.1, 5.6 Hz, 1H), 5.08 (d, *J*

= 12.6 Hz, 1H), 5.02 (d, *J* = 12.6 Hz, 1H), 4.50 (apparent q, 2H), 3.99 (s, 1H), 3.61 – 3.37 (m, 6H), 3.34 – 3.23 (m, 2H), 3.09 (d, *J* = 13.4 Hz, 1H), 2.56 – 2.51 (m, 1H), 2.28 – 2.16 (m, 3H), 1.68 (d, *J* = 14.5 Hz, 1H), 1.59 (td, *J* = 12.6, 4.7 Hz, 1H), 1.26 – 1.17 (m, 1H), 1.16 – 1.07 (m, 1H), 0.89 (s, 9H), 0.71 (s, 9H), 0.03 (s, 3H), 0.03 (s, 3H) (two closely overlapping singlets integrating to a total of 6H), -0.03 (s, 3H), -0.06 (s, 3H).**^{13}C NMR** (151 MHz, Chloroform-*d*) δ 191.2, 156.5, 151.3, 138.8, 138.2, 137.3, 136.7, 132.4, 128.6, 128.5, 128.2, 128.2, 127.9, 127.6, 74.8, 74.8, 73.5, 66.7, 62.8, 50.8, 40.7, 34.6, 31.7, 29.0, 28.1, 26.9, 26.1, 25.9, 23.3, 18.4, 17.7, -3.4, -5.1, -5.2, -5.7. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{43}H_{65}NO_7Si_2Na^+$ = 786.41973, found $C_{43}H_{65}NO_7Si_2Na^+$ = 786.41840. **FTIR (Neat)** 3327, 2949, 2928, 2881 ,2856, 1688, 1629, 1531, 1498, 1470, 1455, 1401, 1364, 1332, 1252, 1215, 1144, 1128, 1093, 1054, 1030, 1006, 938, 910, 856, 835, 773, 736, 698, 674. **Data for 4.66:** R_f = 0.21 (20% EtOAc/hexanes), UV; **^{1}H NMR** (600 MHz, Acetone-d_6) δ 7.81 (s, 1H), 7.39 – 7.26 (m, 10H), 6.36 – 6.27 (m, 2H), 5.05 (ABq, $\Delta\delta_{AB}$ = 0.03, 2H), 4.54 (s, 2H), 3.62 – 3.52 (m, 3H), 3.46 (d, *J* = 5.7 Hz, 2H), 3.39 – 3.31 (m, 1H), 3.32 – 3.27 (m, 2H), 2.88 (ddd, *J* = 12.8, 4.1, 1.7 Hz, 1H), 2.76 – 2.68 (m, 1H), 2.02 – 1.96 (m, 1H), 1.95 – 1.80 (m, 3H), 1.78 – 1.72 (m, 1H), 1.63 (apparent q, *J* = 12.1 Hz, 1H), 1.19 – 1.02 (m, 2H), 0.95 (s, 9H), 0.88 (s, 9H), 0.09 (s, 3H), 0.04 – 0.01 (m, 9H). **^{13}C NMR** (151 MHz, Acetone-d_6) δ 191.0, 157.0, 150.9, 141.2, 140.0, 139.9, 138.5, 136.6, 129.2, 129.1, 128.6, 128.5, 128.2, 128.2, 78.4, 75.3, 73.4, 66.4, 63.8, 50.0, 41.4, 38.2, 35.6, 28.7, 27.2, 26.5, 26.4, 25.3, 24.7, 18.8, 18.6, -3.6, -4.1, -5.1, -5.1. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{43}H_{65}NO_7Si_2Na^+$ = 786.41973, found $C_{43}H_{65}NO_7Si_2Na^+$ = 786.41895. **FTIR (Neat)** 3303, 2952, 2928, 2885, 2855, 1725, 1698, 1628, 1518, 1498, 1471, 1462, 1400, 1360, 1302, 1252, 1101, 1068, 1028, 1006, 982, 939, 911, 879, 836, 813, 775, 735, 697, 669, 614.

*Preparation of Bicycle **4.67** and **4.68***



To allene **4.39** (40 mg, 0.14 mmol) dissolved in dry THF (0.65 mL) and cooled to –78 °C was added 2.5 M BuLi in hexanes (118 μL, 0.295 mmol) and the reaction allowed to proceed for 1 hour. To this solution was added a dry ice acetone bath cooled solution of Weinreb amide **4.50** (25 mg, 0.042 mmol) in dry THF (0.4 mL). After 30 minutes the reaction was warmed to –40 °C in an acetonitrile dry ice bath and allowed to stir at this temperature for 1 hour. The reaction solution was then transferred by cannula to a solution of HFIP:TFE:chloroacetic acid (0.6 mL:0.6 mL:825 mg) which was also at –40 °C and stirred for 10 minutes. The reaction solution was then warmed to 60 °C in an oil bath for 1 hour and 50 minutes. The reaction was allowed to cool and 1 M HCl (1.5 mL) was added. After 30 minutes the reaction solution was diluted with ethyl acetate and washed several times with a saturated sodium bicarbonate solution and brine. The organic layer was dried over sodium sulfate and the solvent evaporated under reduced pressure. The residue was purified by MPLC using a gradient which began at 0% ethyl acetate in hexanes progressed to 100% ethyl acetate. This gave 13.9 mg of **4.67** and **4.68** as a mixture of diastereomers which was purified again by prep TLC using 1:1 ethyl acetate: hexanes to give and 4.2 mg of diastereomer **4.67** and 6.4 mg of diastereomer **4.68** (clear oils, 39% Yield total). *Notes:

chloroacetic acid used in this reaction refers to mono-chloroacetic acid. **Data for 4.67:** R_f = 0.21 (50% EtOAc/hexanes), UV; **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.38 – 7.27 (m, 10H), 5.83 (dd, *J* = 10.4, 5.7 Hz, 1H), 5.05 (ABq, $\Delta\delta_{AB}$ = 0.05, 2H), 4.47 (ABq, $\Delta\delta_{AB}$ = 0.05, 2H), 3.87 (s, 1H), δ 3.76 – 3.65 (m, 1H), 3.58 – 3.53 (m, 1H), 3.47 (t, *J* = 9.8 Hz, 2H), 3.38 – 3.31 (m, 3H), 3.15 (dd, *J* = Hz, 1H), 2.32 – 2.19 (m, 2H), 2.16 – 2.06 (m, 2H), 1.83 (td, *J* = 12.7, 5.3 Hz, 1H), 1.75 (t, *J* = 12.2 Hz, 1H), 1.62 (d, *J* = 15.2 Hz, 2H), 1.10 – 1.00 (m, 1H), 1.00 – 0.90 (m, 1H), 0.69 (s, 9H), -0.07 (s, 3H), -0.14 (s, 3H). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 191.4, 157.0, 151.4, 138.7, 138.2, 137.2, 136.5, 132.8, 128.7, 128.5, 128.2, 128.0, 127.9, 127.6, 74.8, 74.6, 73.5, 66.7, 62.4, 50.9, 40.8, 34.6, 31.8, 28.7, 28.0, 26.9, 25.9, 23.4, 17.7, -3.5, -5.7. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{37}H_{51}NO_7SiNa^+$ = 672.33325, found $C_{37}H_{51}NO_7SiNa^+$ = 672.33228. **FTIR (Neat)** 3327**,** 2949, 2928, 2881, 2856, 1688, 1629, 1531, 1498, 1470, 1455, 1401, 1364, 1332, 1252, 1215, 1144, 1128, 1093, 1054, 1030, 1006, 938, 910, 856, 835, 773, 736, 698. **Data for 4.68:** R_f = 0.39 (50% EtOAc/hexanes), UV; **^{1}H NMR** (600 MHz, Methylene Chloride-d_2) δ 7.38 – 7.26 (m, 10H), 6.32 (dd, *J* = 10.0, 6.2 Hz, 1H), 5.89 (br d, *J* = 7.6 Hz, 1H), 5.22 (s, 1H), 5.03 (ABq, $\Delta\delta_{AB}$ = 0.03, 2H), 4.51 (s, 2H), 3.54 – 3.46 (m, 2H), 3.47 – 3.30 (m, 7H), 2.84 (dd, 1H), 2.52 – 2.43 (m, 1H), 2.07 – 1.96 (m, 1H), 1.83 – 1.66 (m, 4H), 1.58 (q, *J* = 13.1 Hz, 1H), 1.12 – 0.96 (m, 2H), 0.92 (s, 9H), 0.05 (s, 3H), -0.03 (s, 3H). **^{13}C NMR** (151 MHz, Methylene Chloride-d_2) δ 189.3, 155.2, 147.6, 139.7, 137.5, 137.4, 135.9, 135.5, 127.1, 127.0, 126.6, 126.4, 126.1, 76.0, 73.1, 71.6, 65.0, 61.3, 48.3, 39.3, 36.1, 33.3, 26.5, 25.1, 24.4, 23.5, 22.1, 16.6, -5.5, -6.0. **+ESI-HRMS** m/z: calc'd for $[M+Na]^+$ $C_{37}H_{51}NO_7SiNa^+$ = 672.33325, found $C_{37}H_{51}NO_7SiNa^+$ = 672.33270. **FTIR (Neat)** 3308, 3065, 3032, 2929,

2855, 1692, 1627, 1525, 1498, 1455, 1399, 1361, 1251, 1100, 1067, 1028, 1006, 938, 909, 879, 836, 775, 736, 697, 670, 611.

4.4 References

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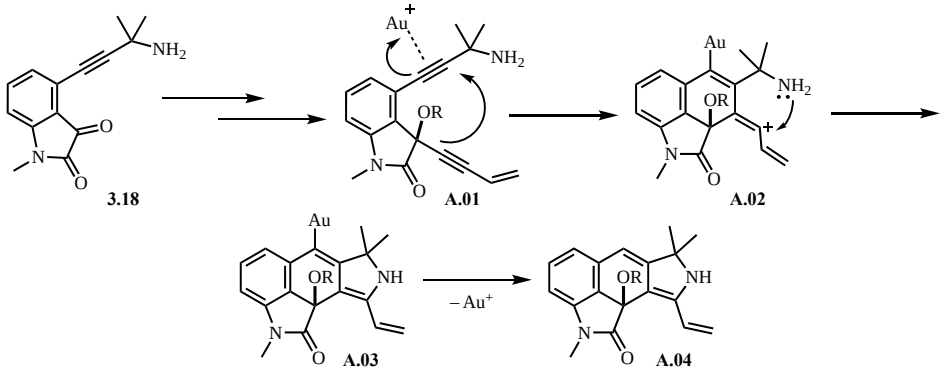
APPENDICES

APPENDIX A

An Enediyne Route Towards Aspergilline A

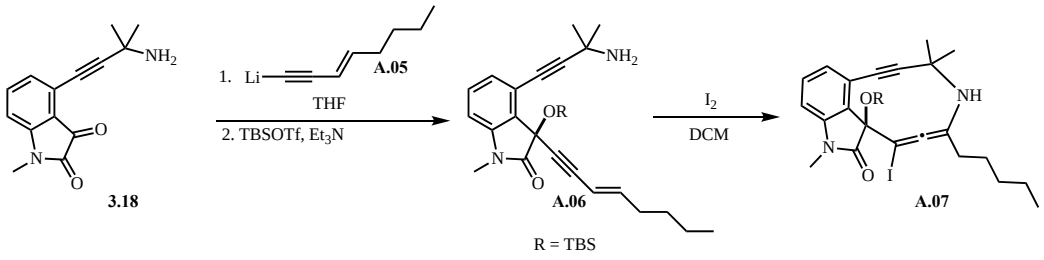
A.1 Accessing a Macrocyclic Allene

In an initial attempt to synthesis a tetracylic intermediate **A.04** towards the total synthesis of aspergilline A we had envisioned a gold catalyzed or iodine mediated cyclization of an enyne or a diyne (Scheme A.01).[1] In this work we accessed compound **3.18** through a Sonogashira cross coupling and advanced it to **A.06** by 1,2 - addition of



Scheme A.01 Gold mediated tetracycle formation

lithium acetylide **A.05**. Having accessed **A.06** we exposed the compound to iodine in DCM and were surprised to find that the desired cyclization product was not obtained. Instead macrocyclic allene **A.07** was produced in 24% Yield. Mechanistically, this may have occurred through initial activation of an alkyne by iodine and subsequent addition of the amine nitrogen into the alkene to generate iodoallene A.07 (Scheme A.02).



Scheme A.02 Iodoallene synthesis

Exposure of allene **A.07** to HCl in diethyl ether provided the crystalline hydrochloride salt **A.08** which allowed for structural confirmation by X-Ray analysis (Figure A.1).

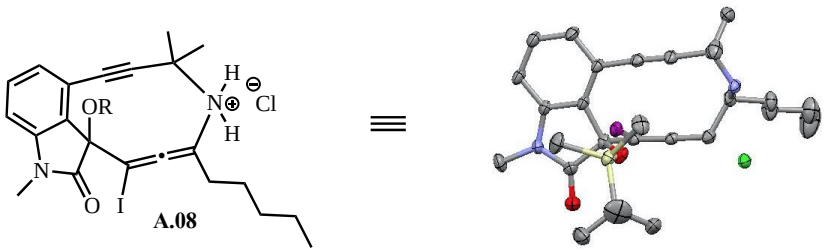
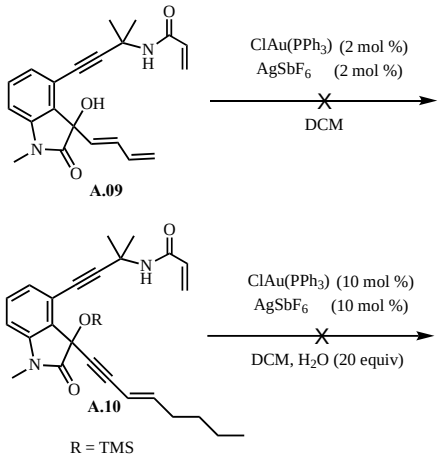


Figure A.1 X-ray structure of Allene **A.08**

Suffice it to say that various structurally similar substrates were explored (Scheme A.03) under various cyclization conditions but none produced the desired tetracylic products.



Scheme A.03 Representative examples of attempts to generate a tetracyclic substrate

A.1 Conclusion

In retrospect, the lack of co-planarity of the pi systems in these substrates precluded the possibility of cyclization. Rather than produce planer substrates, which would lack needed oxidation at C3 of what would be an oxindole, we opted to redesign the route.

A.2 Reference

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APPENDIX B

Spectral Data for Chapter Two

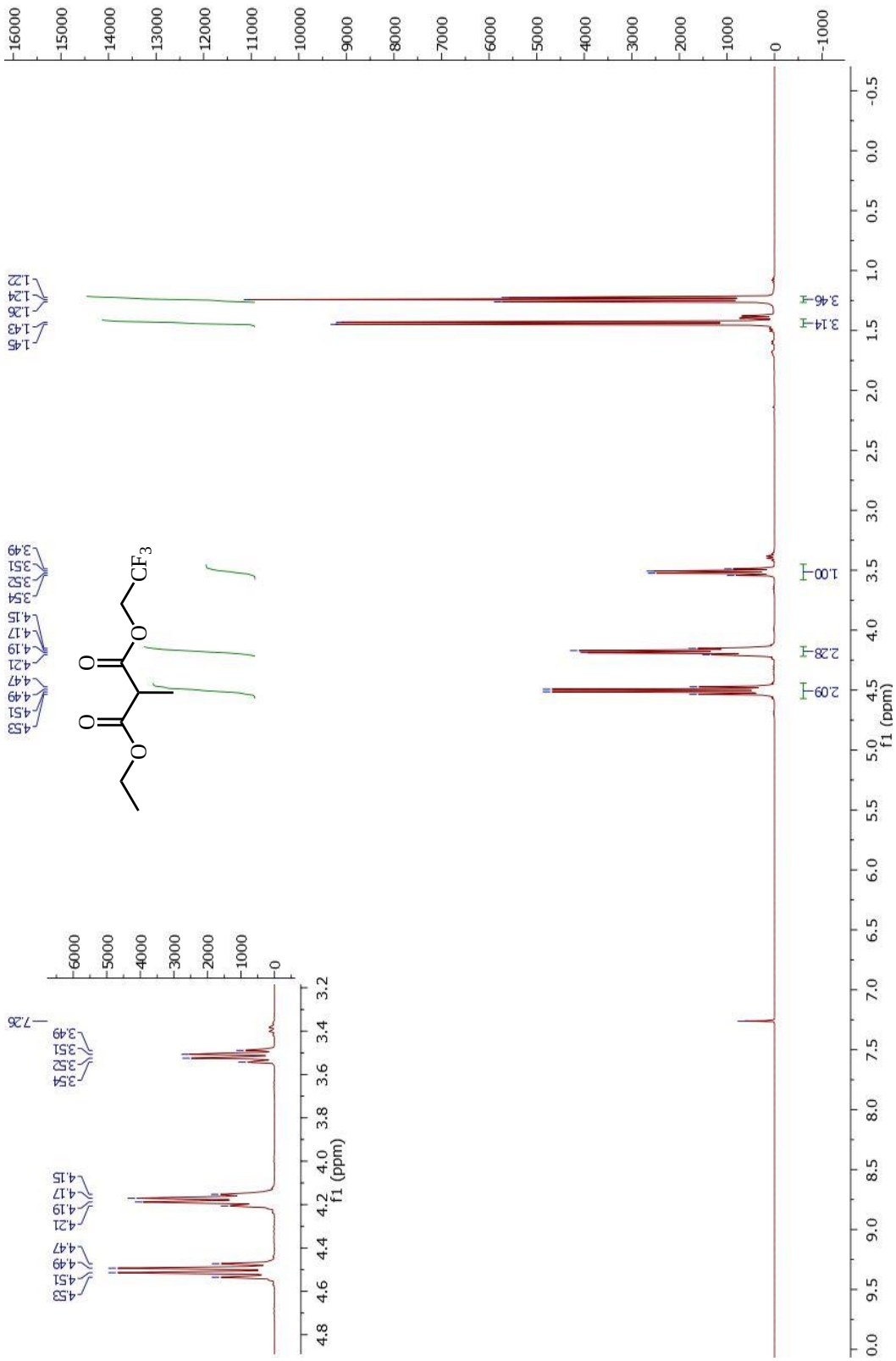

Figure B.01. **^{1}H NMR** (400 MHz, $CDCl_3$) of malonate **2.34**

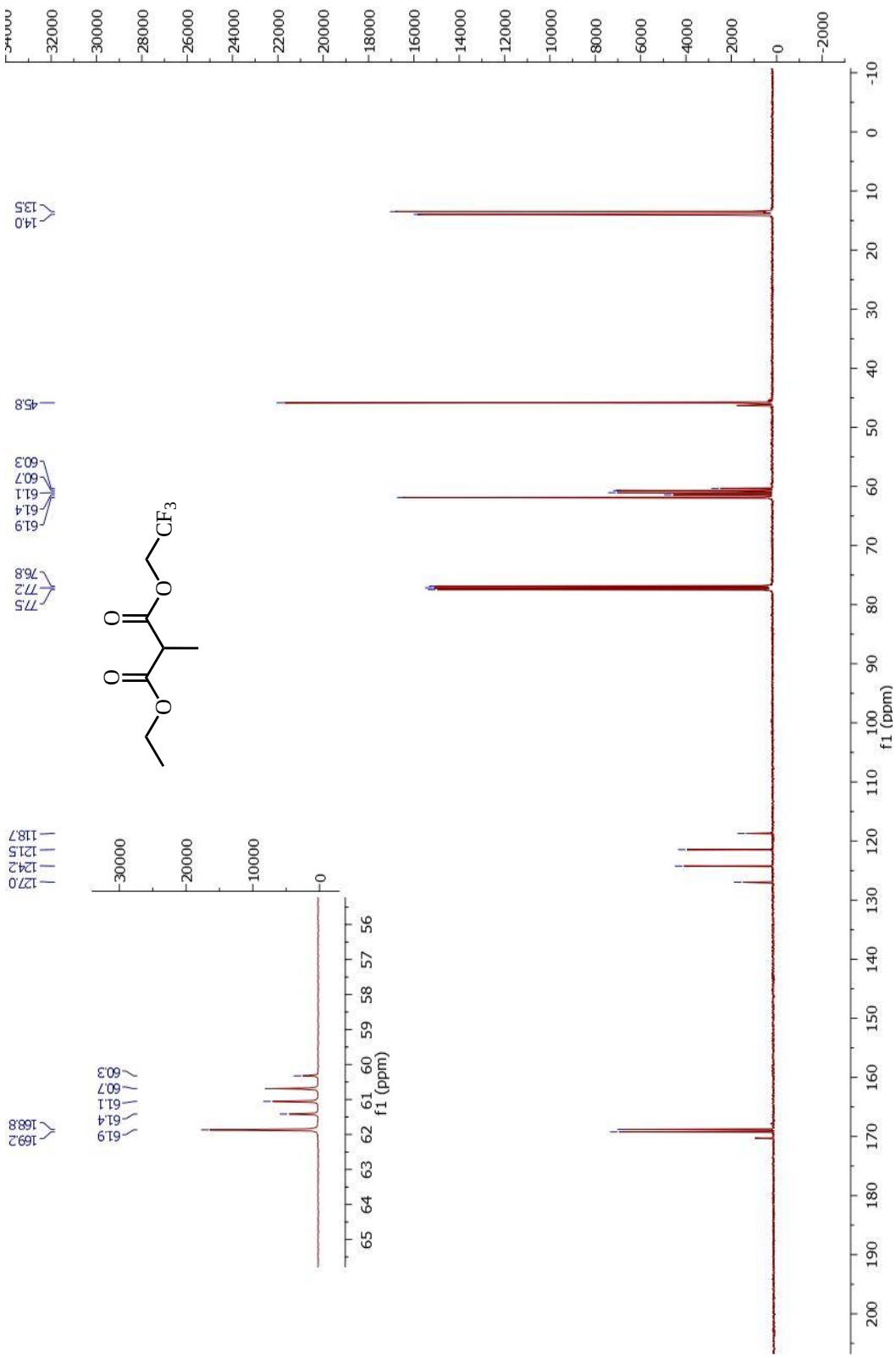

Figure B.02. **^{13}C NMR** (101 MHz, $CDCl_3$) of malonate **2.34**

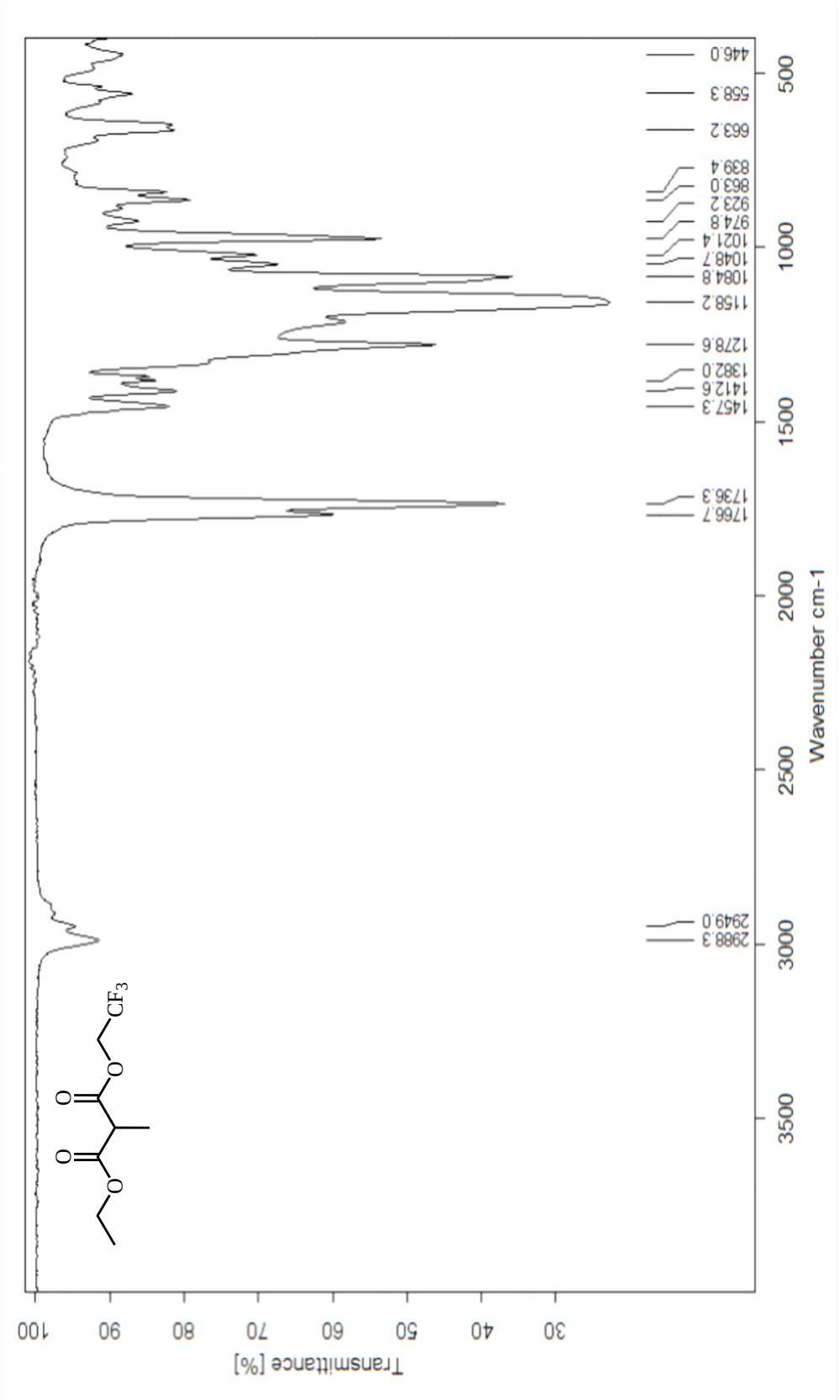

Figure B.03. FTIR Spectrum (neat) of malonate **2.34**

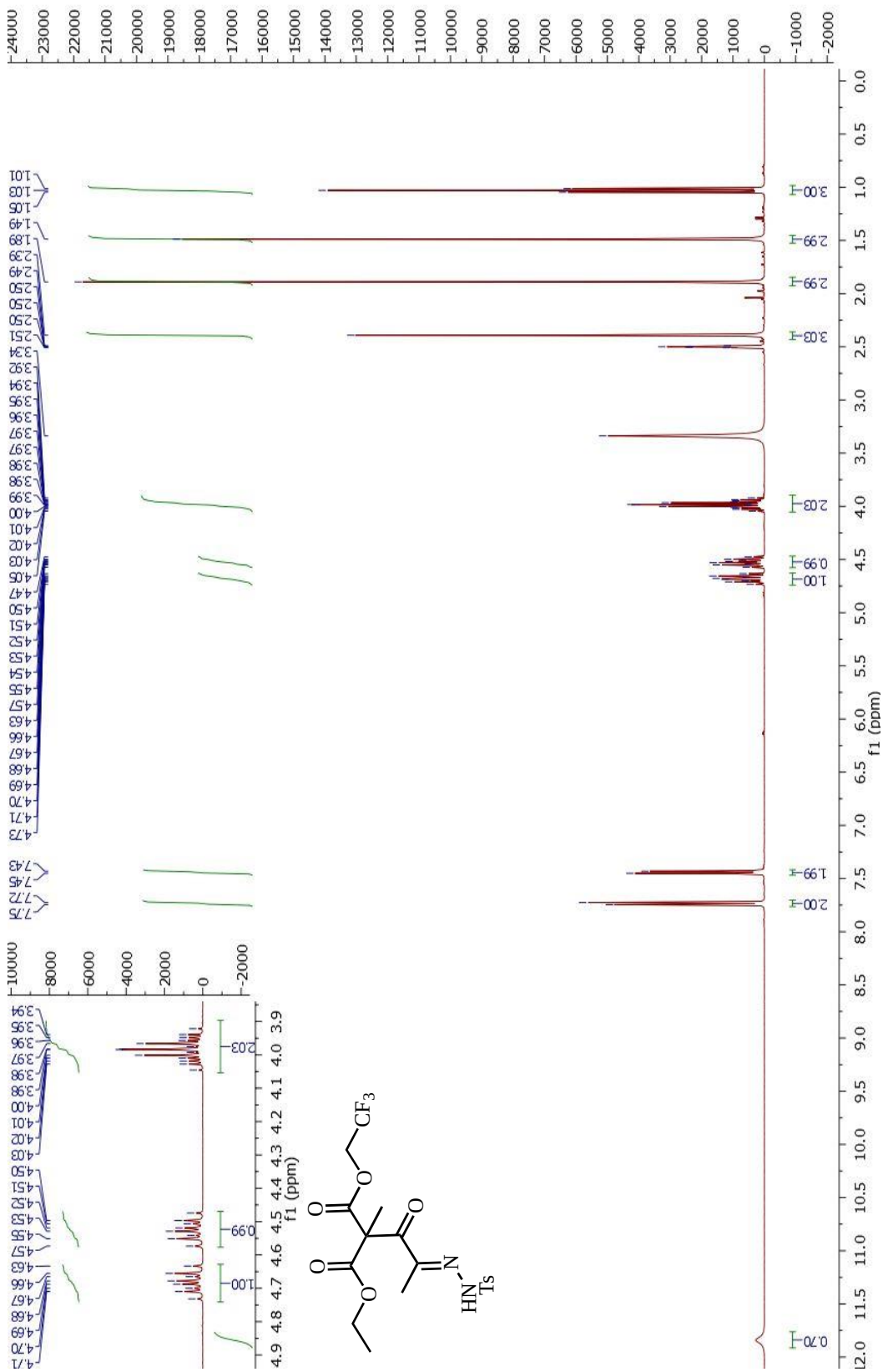

Figure B.04. **^{1}H NMR** (400 MHz, DMSO-d6) of tosyl hydrazone **2.35**

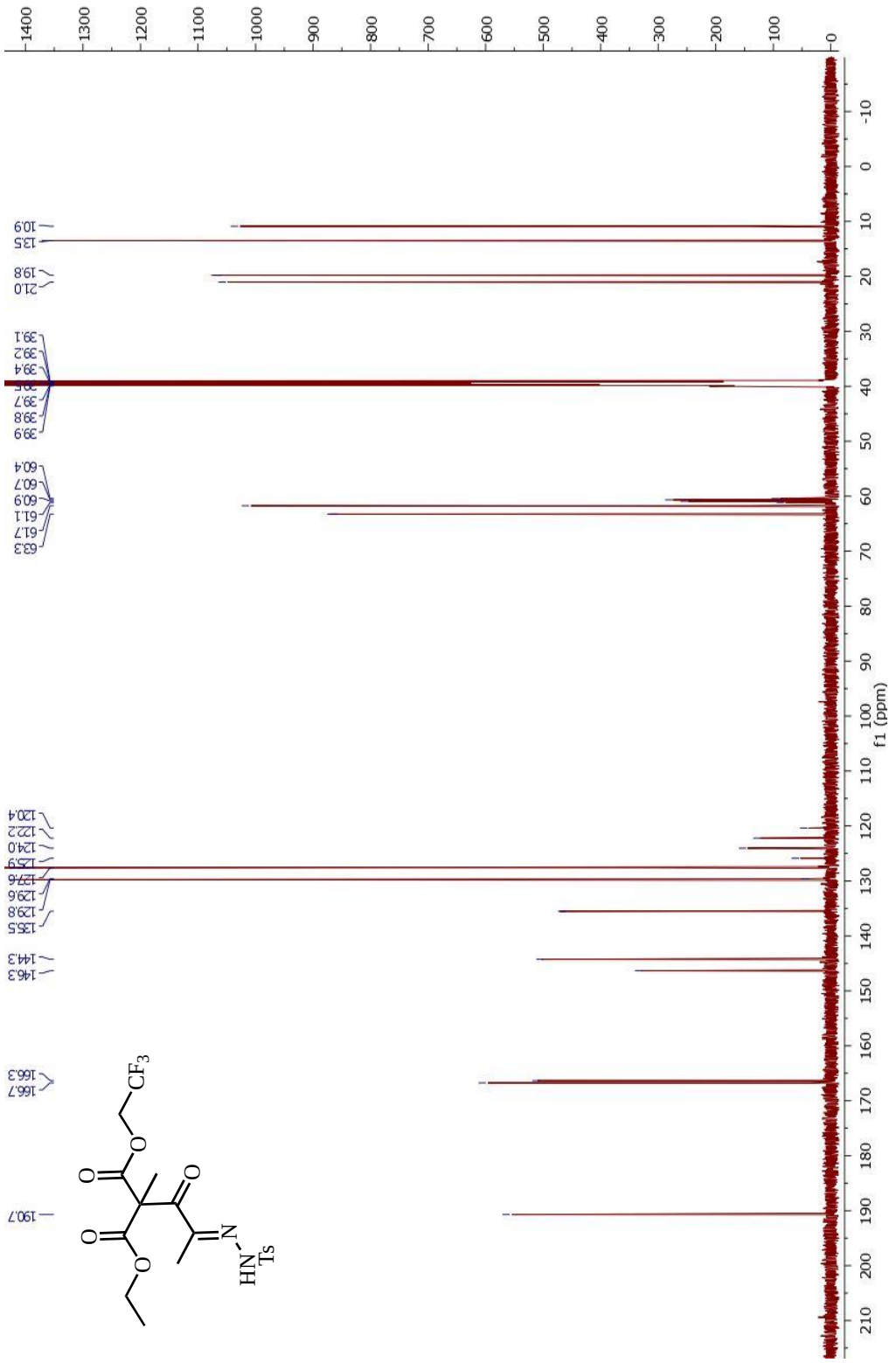

Figure B.05. **^{13}C NMR** (151 MHz, DMSO-d6) of tosyl hydrazone **2.35**

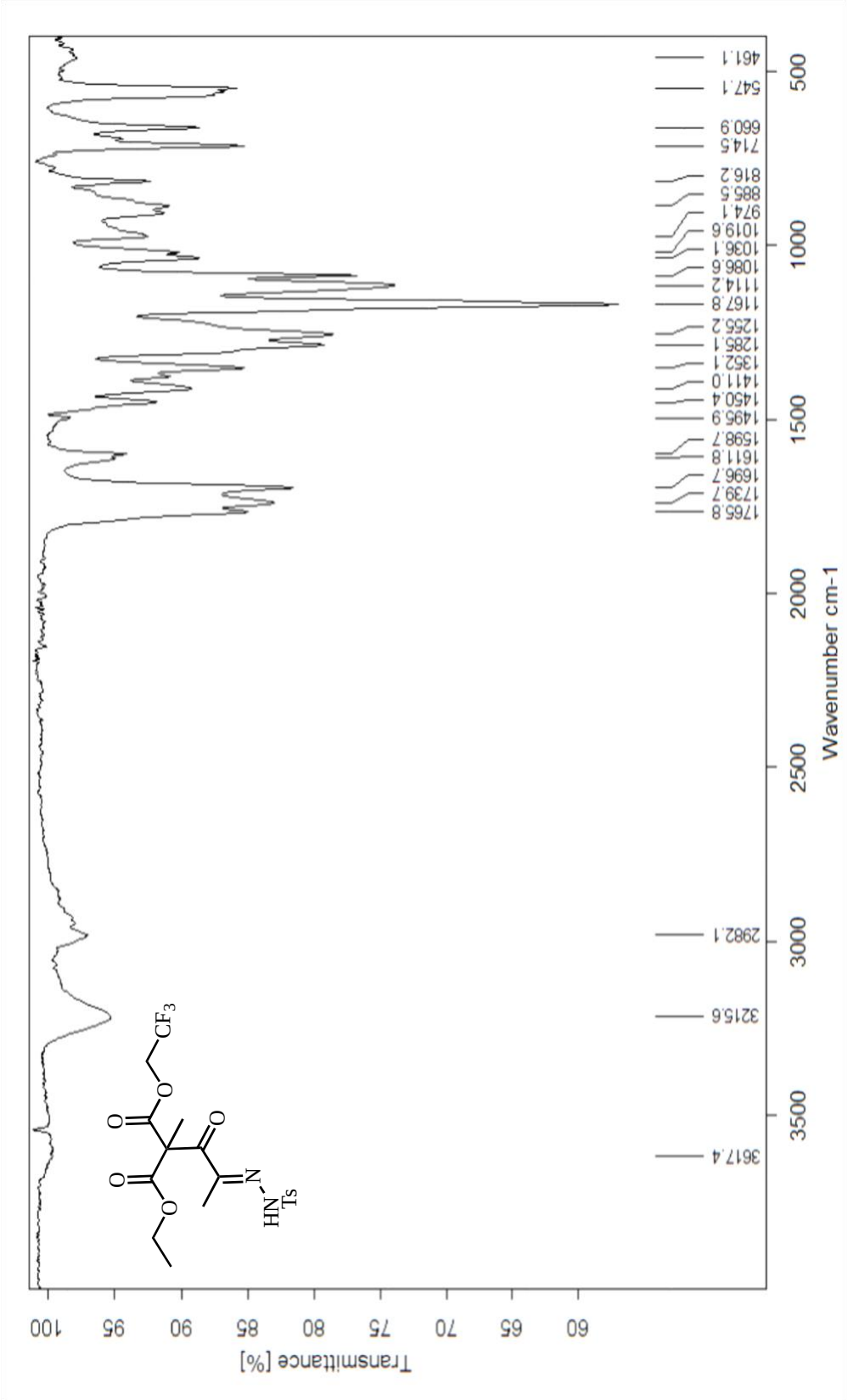

Figure B.06. FTIR Spectrum (neat) of tosyl hydrazone **2.35**

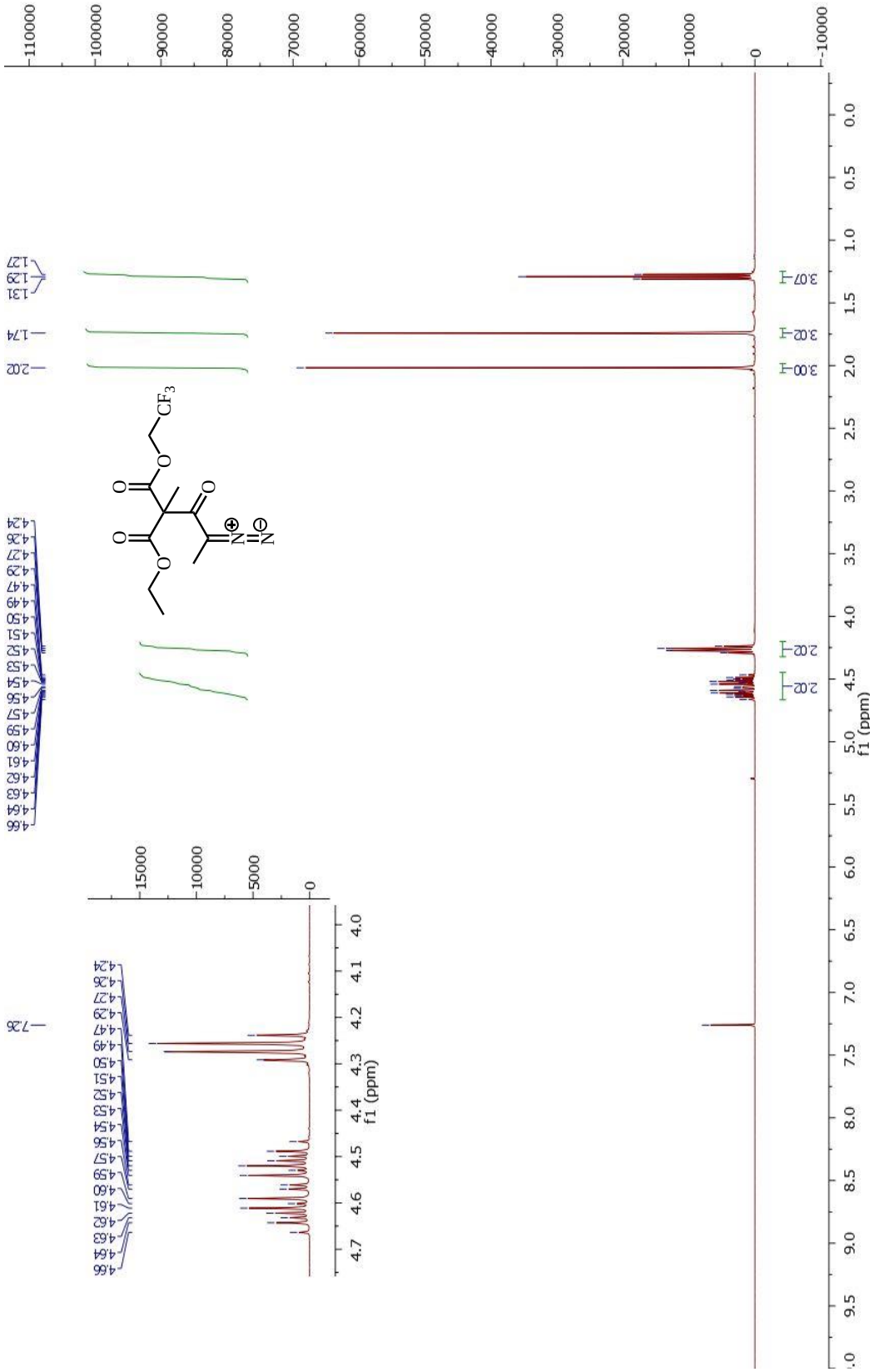

Figure B.07. **^{1}H NMR** (400 MHz, $CDCl_3$) of diazomalonate **2.08**

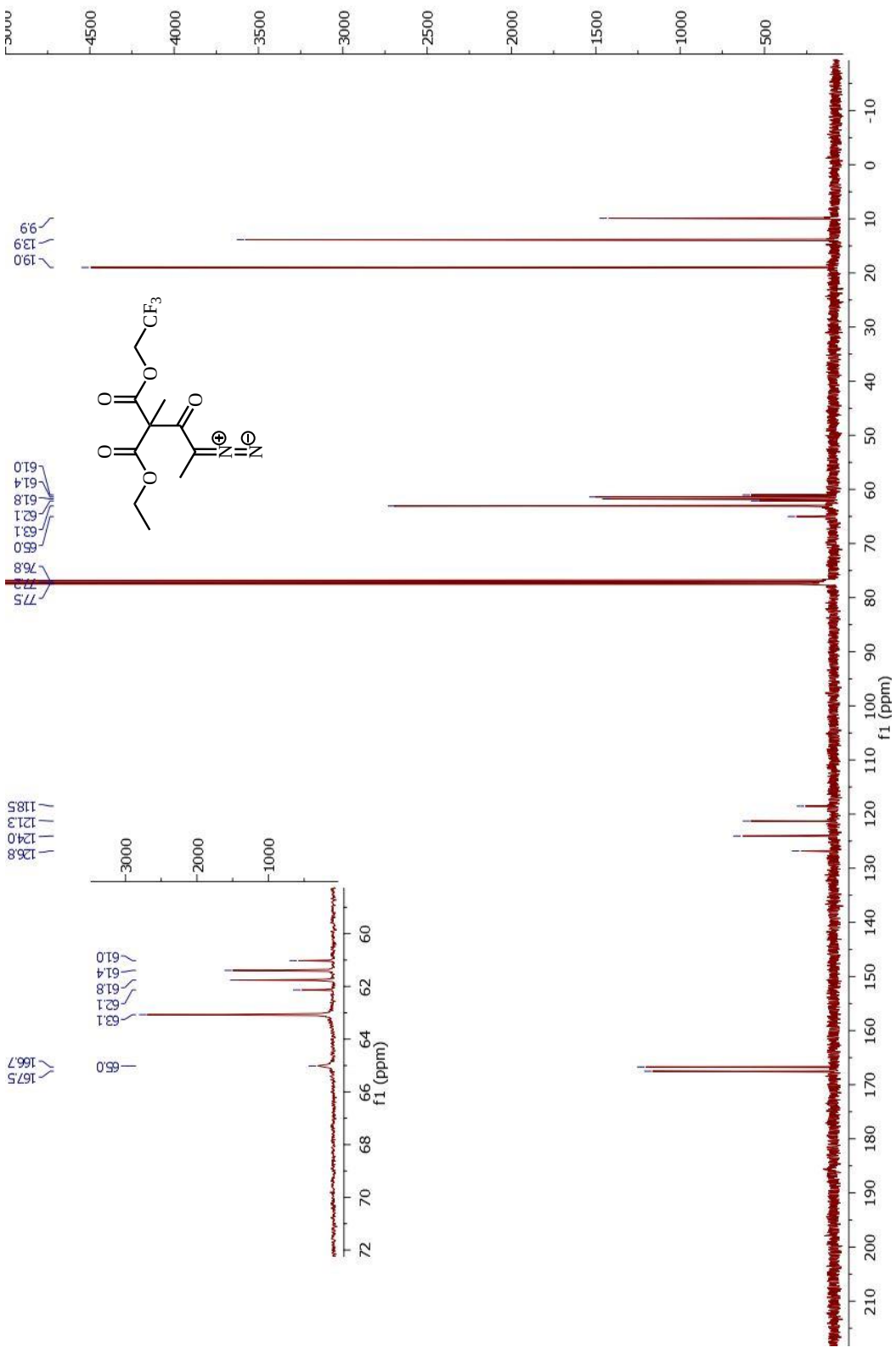

Figure B.08. **^{13}C NMR** (101 MHz, $CDCl_3$) of diazomalonate **2.08**

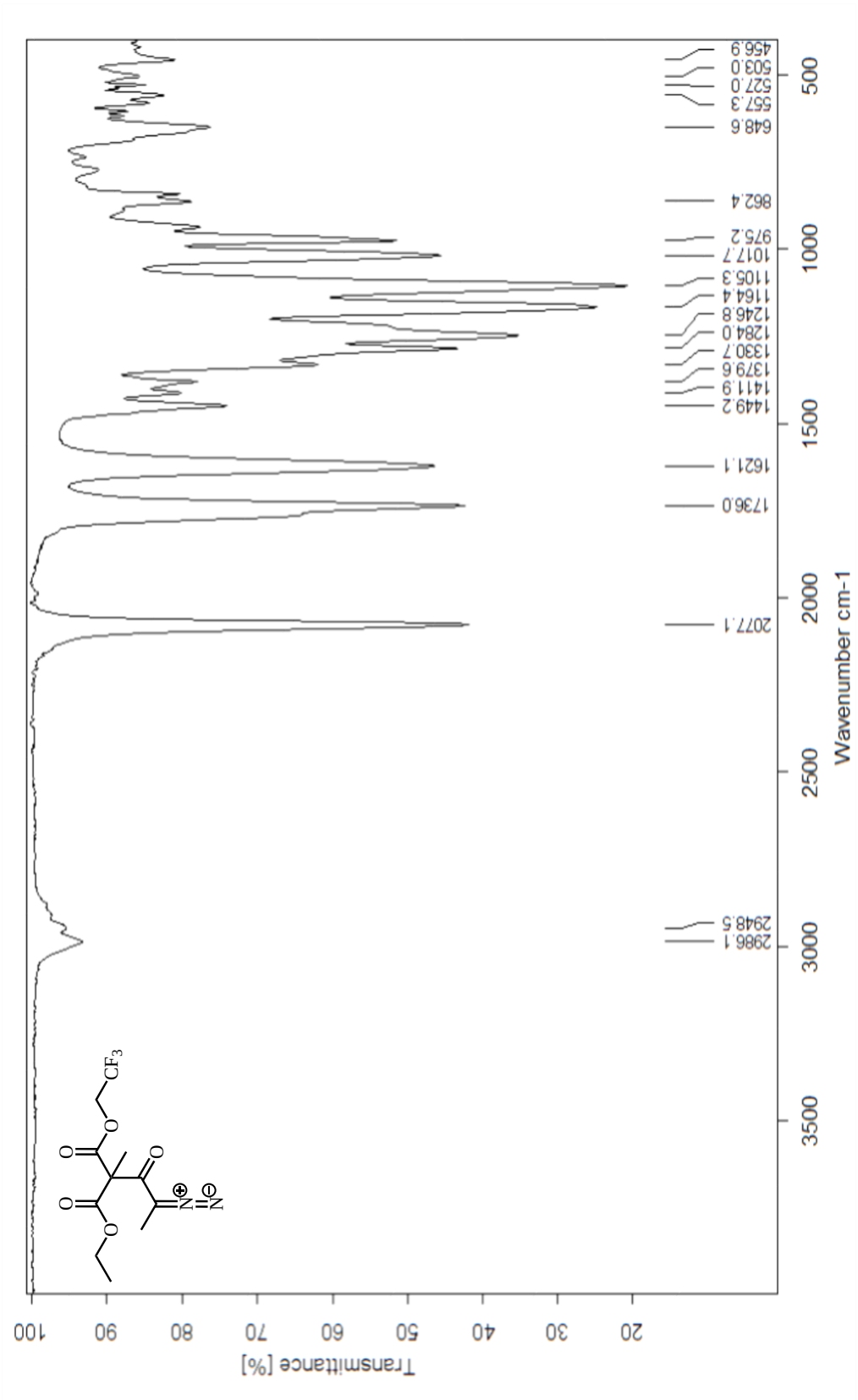

Figure B.09. FTIR Spectrum (neat) of diazomalonate **2.08**

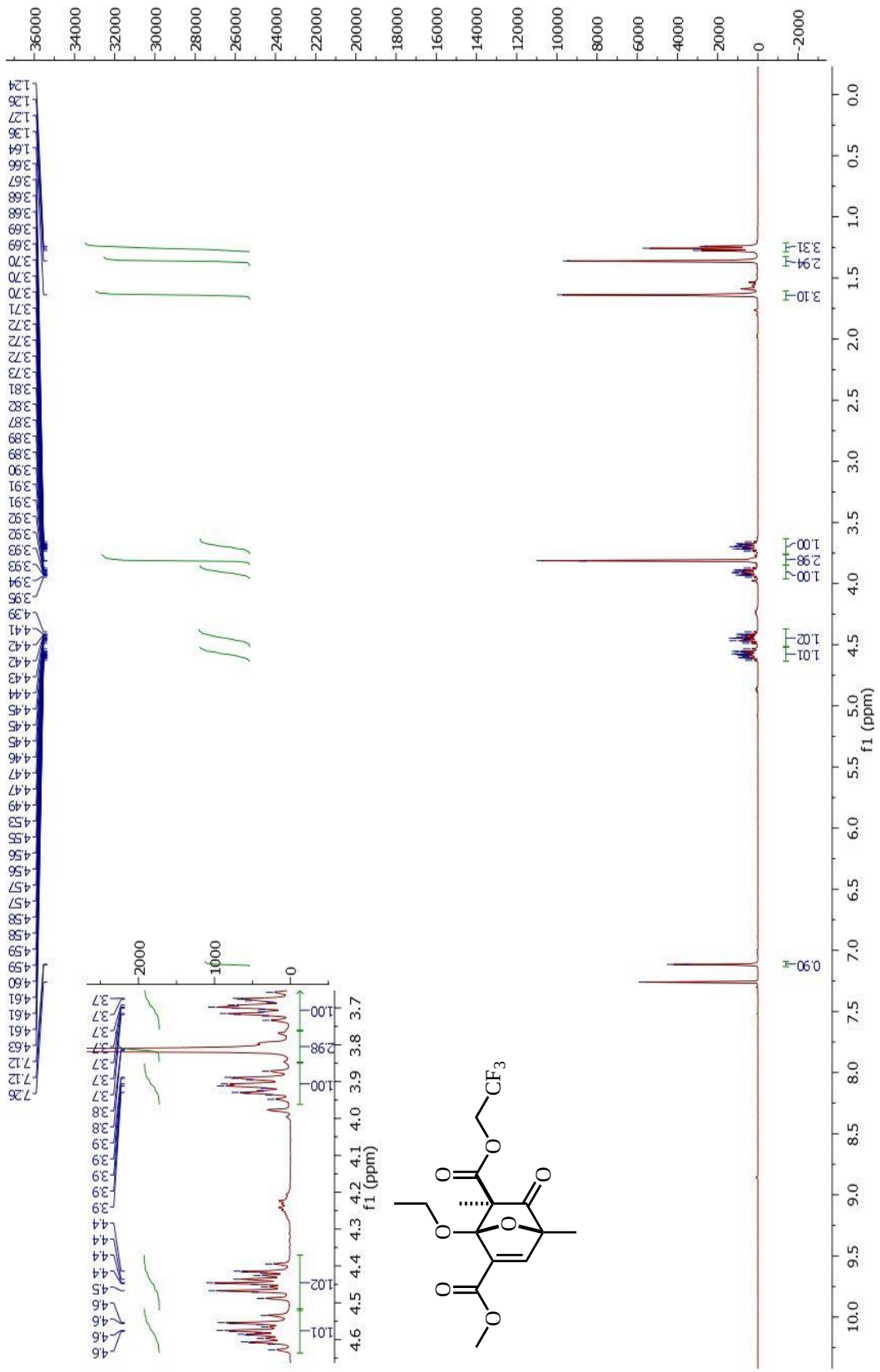

Figure B.10. **^{1}H NMR** (400 MHz, $CDCl_3$) of oxabicycle **2.14**

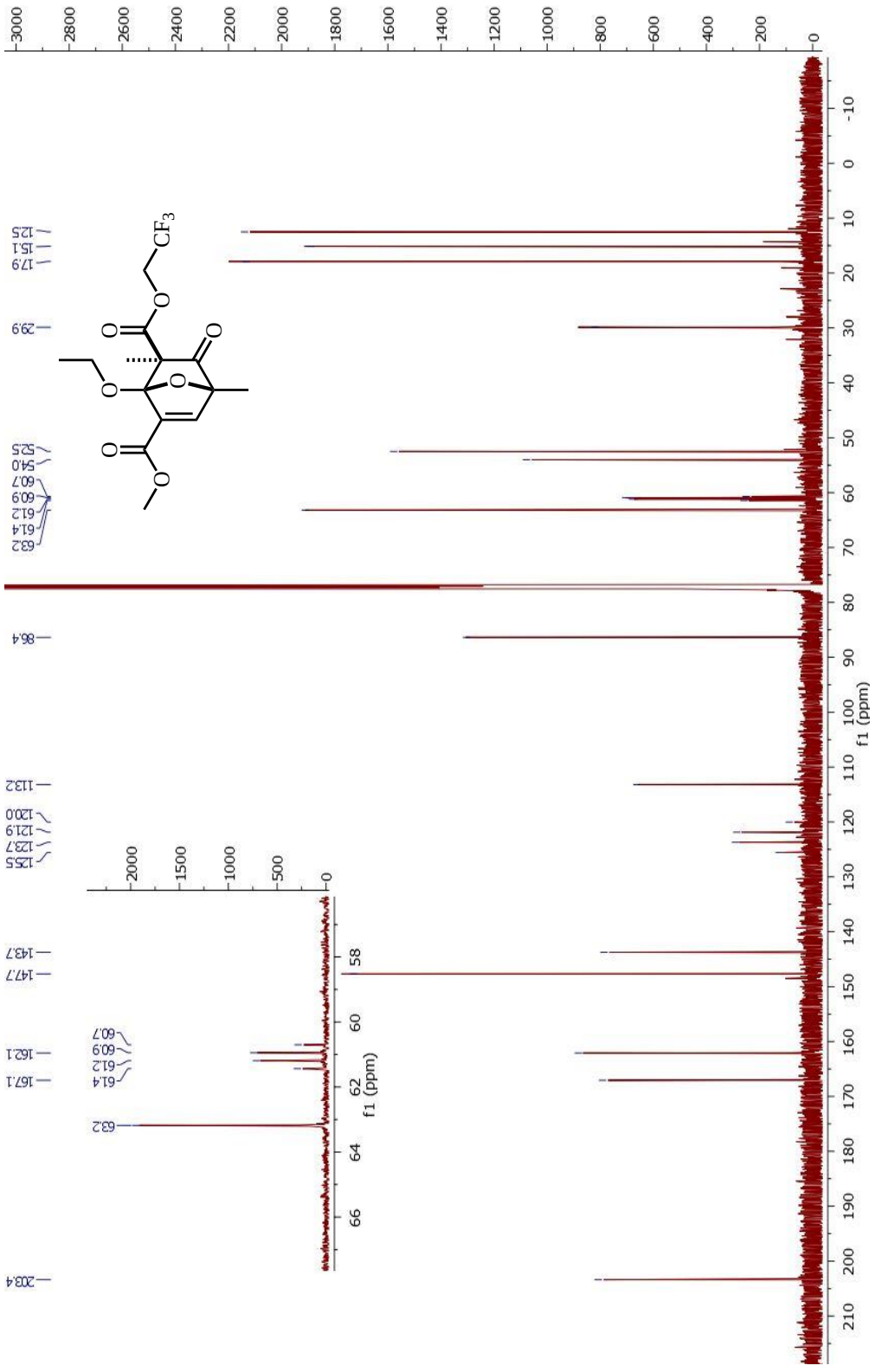

Figure B.11. **^{13}C NMR** (151 MHz, $CDCl_3$) of oxabicycle **2.14**

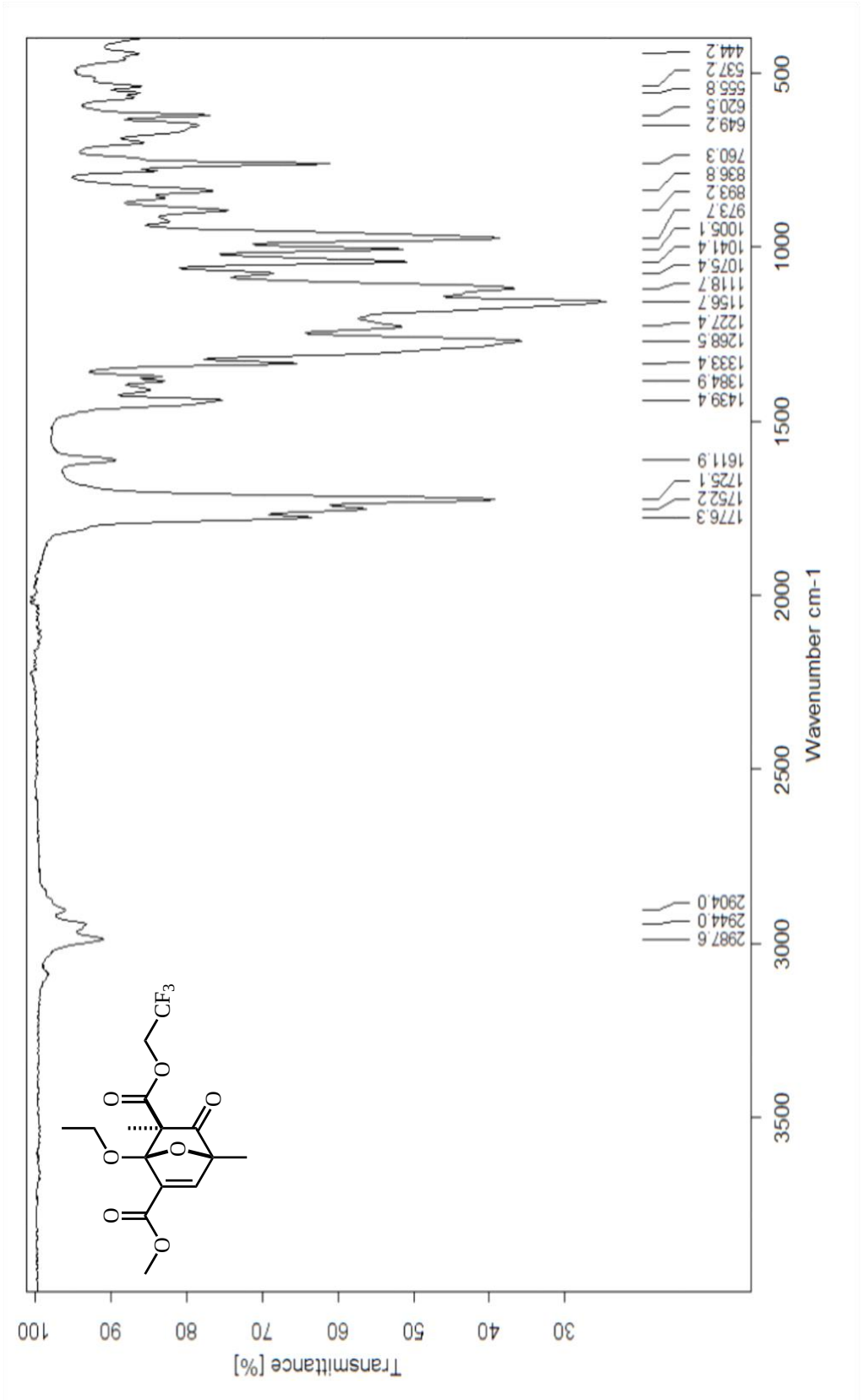

Figure B.12. FTIR Spectrum (neat) of oxabicycle **2.14**

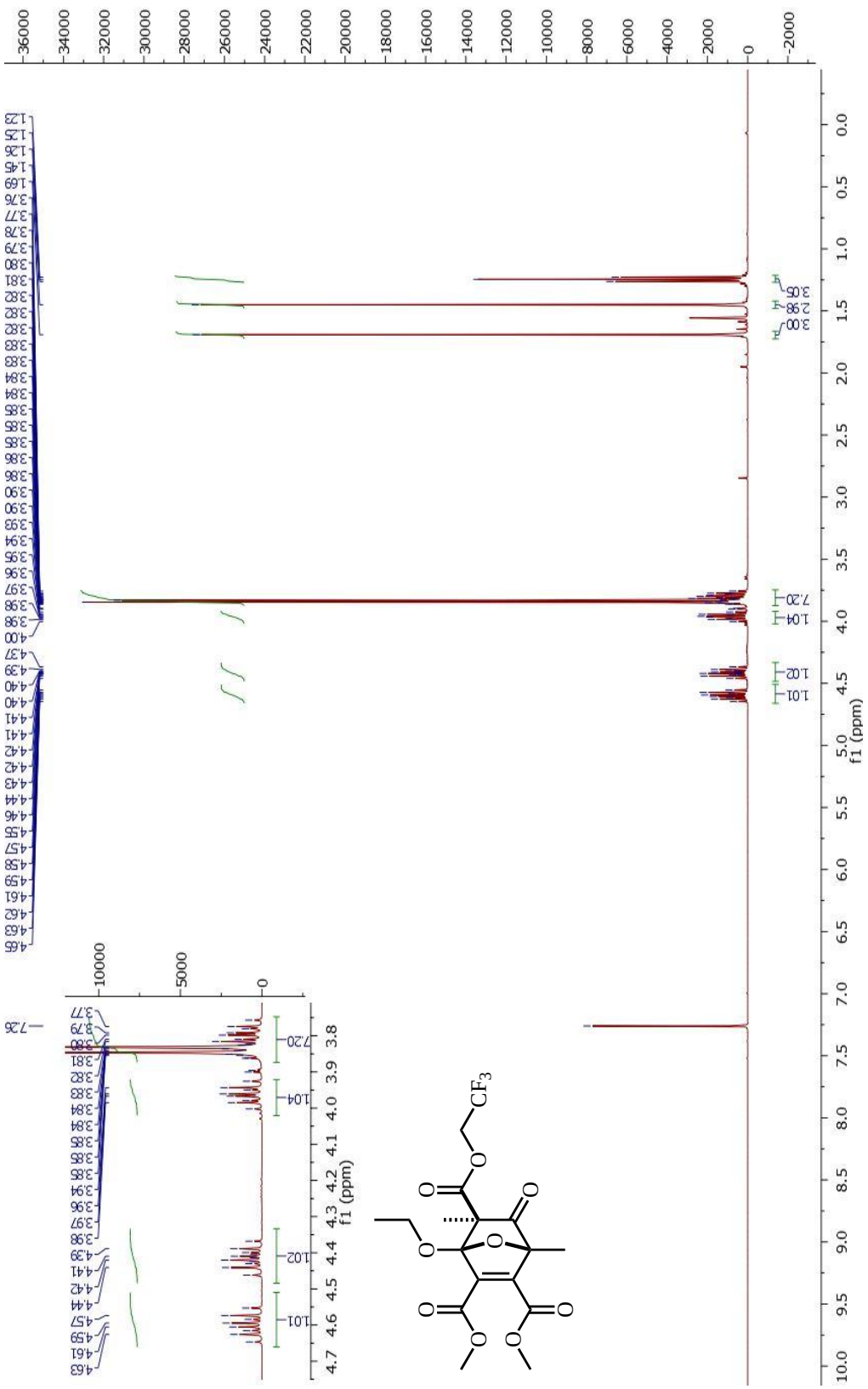

Figure B.13. **^{1}H NMR** (600 MHz, $CDCl_3$) of oxabicycle **2.17**

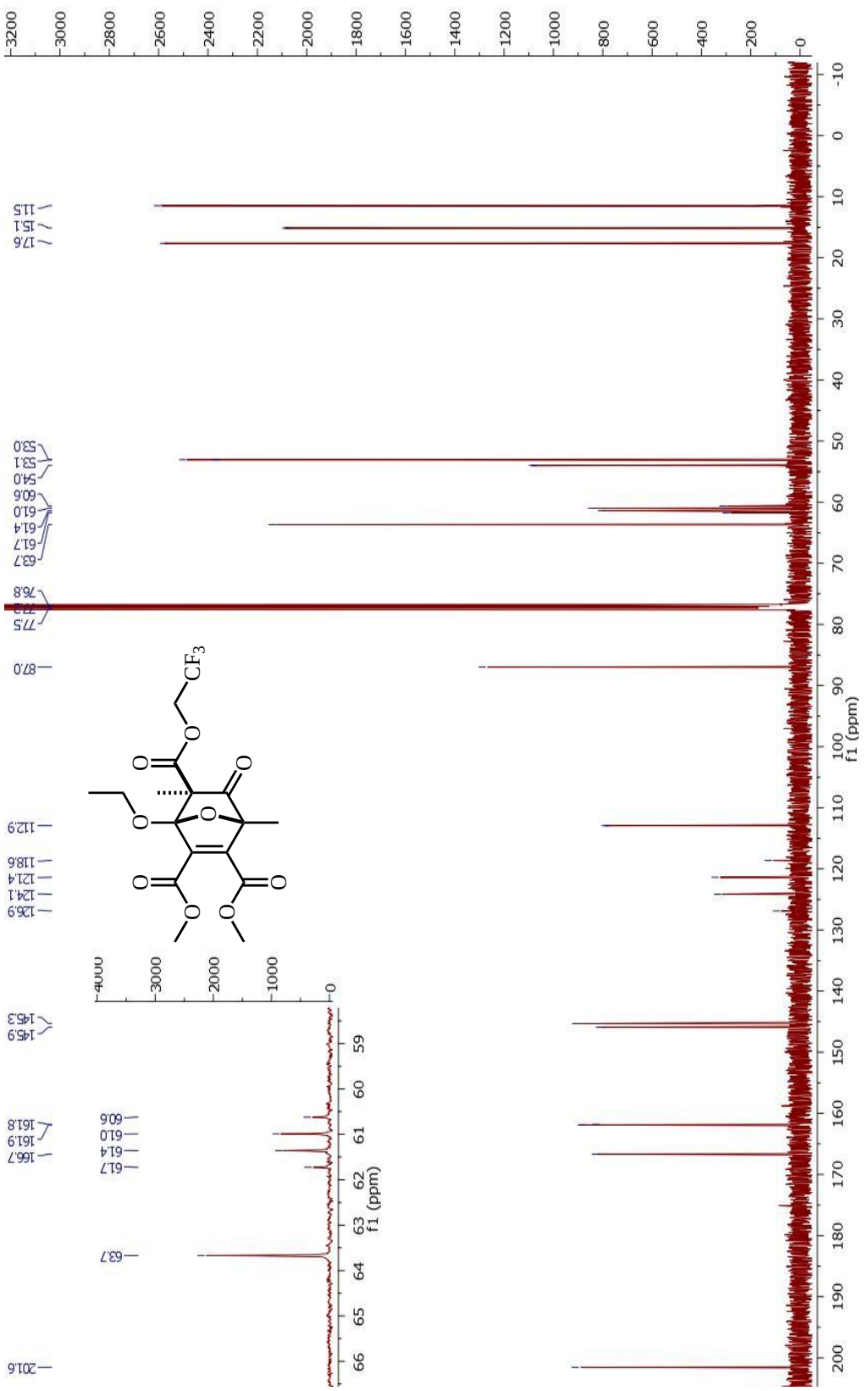

Figure B.14. **^{13}C NMR** (101 MHz, $CDCl_3$) of oxabicycle **2.17**

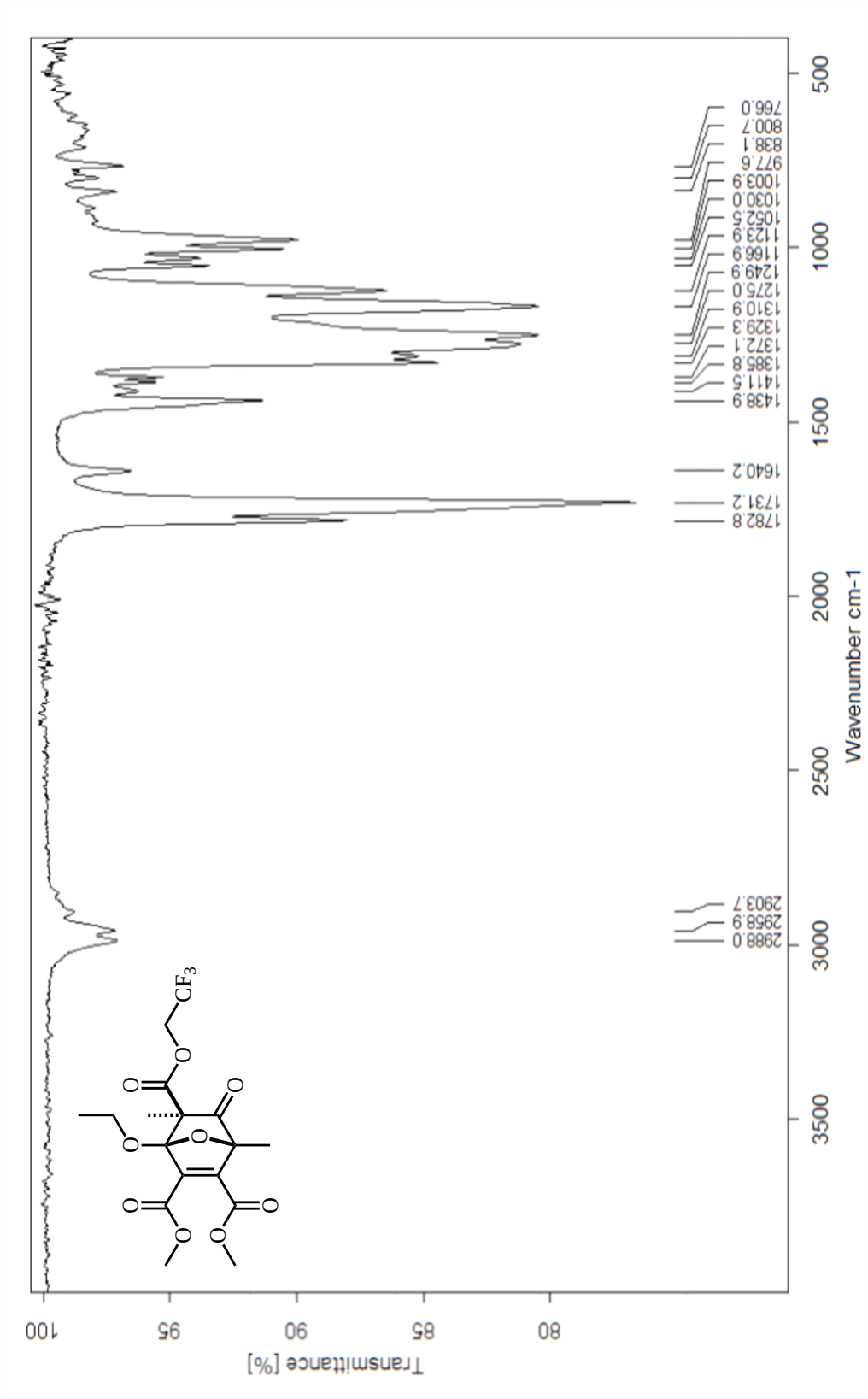

Figure B.15. FTIR Spectrum (neat) of oxabicycle **2.17**

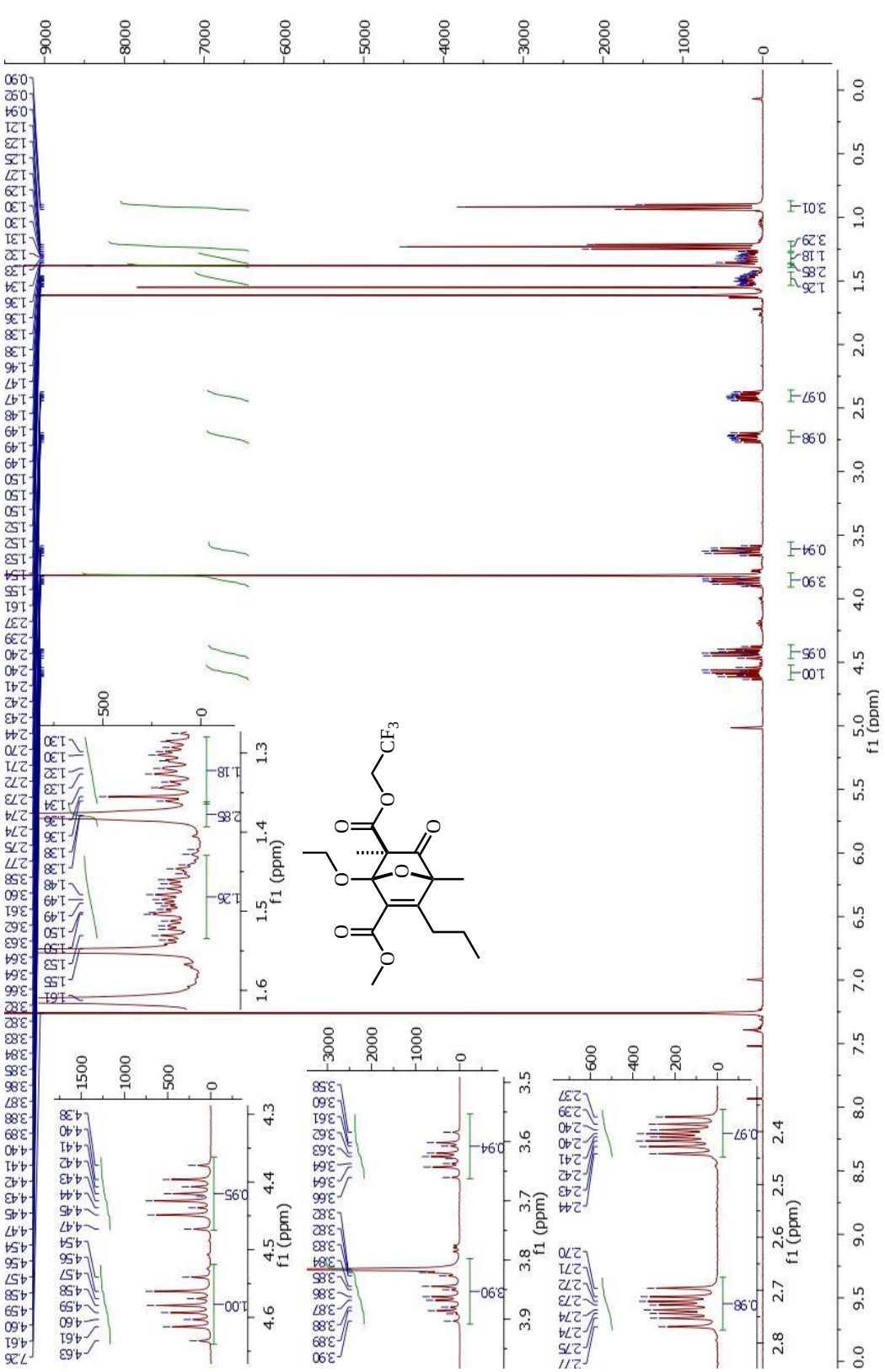

Figure B.16. **^{1}H NMR** (400 MHz, $CDCl_3$) of oxabicycle **2.18**

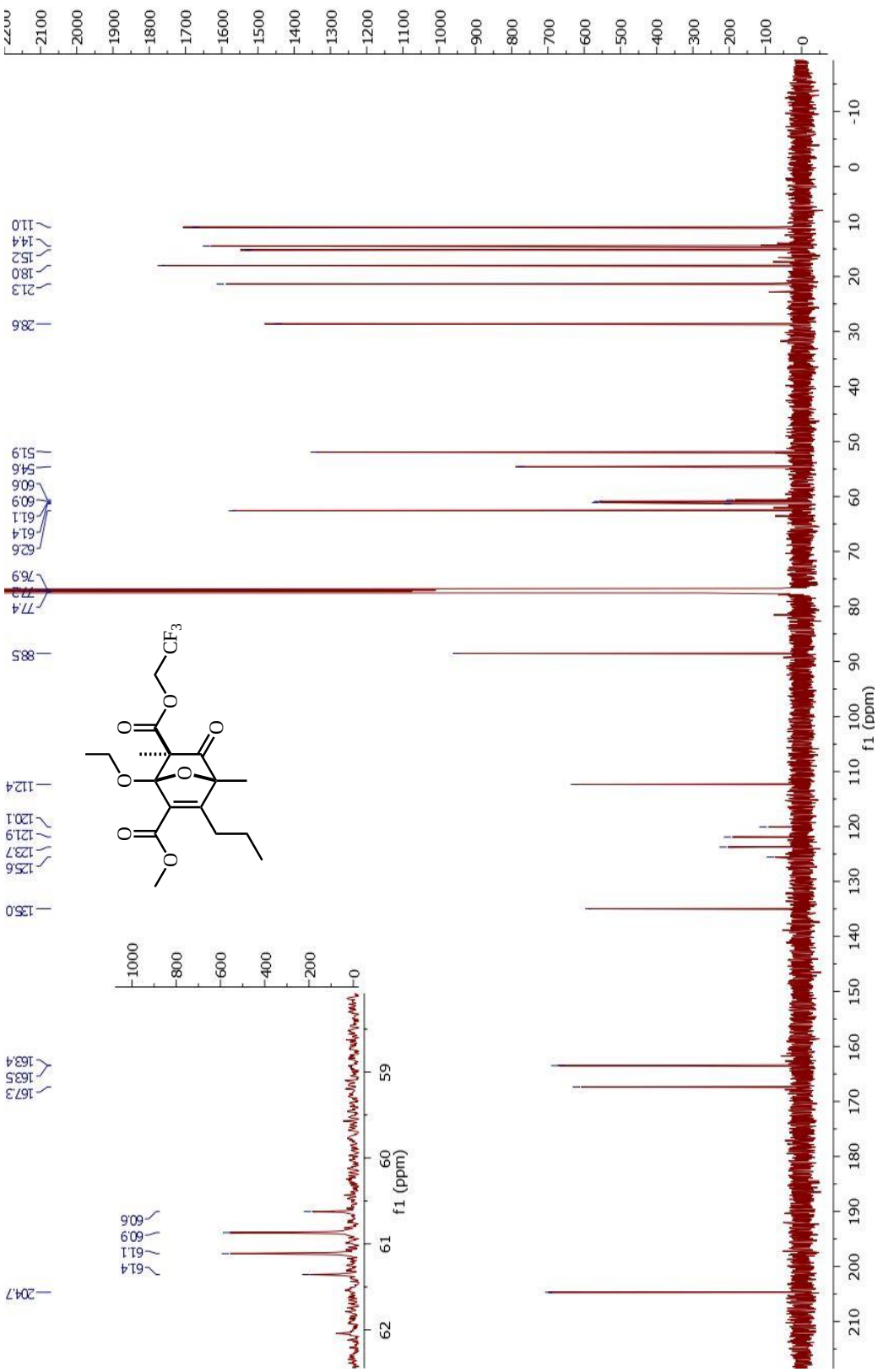

Figure B.17. **^{13}C NMR** (151 MHz, $CDCl_3$) of oxabicycle **2.18**

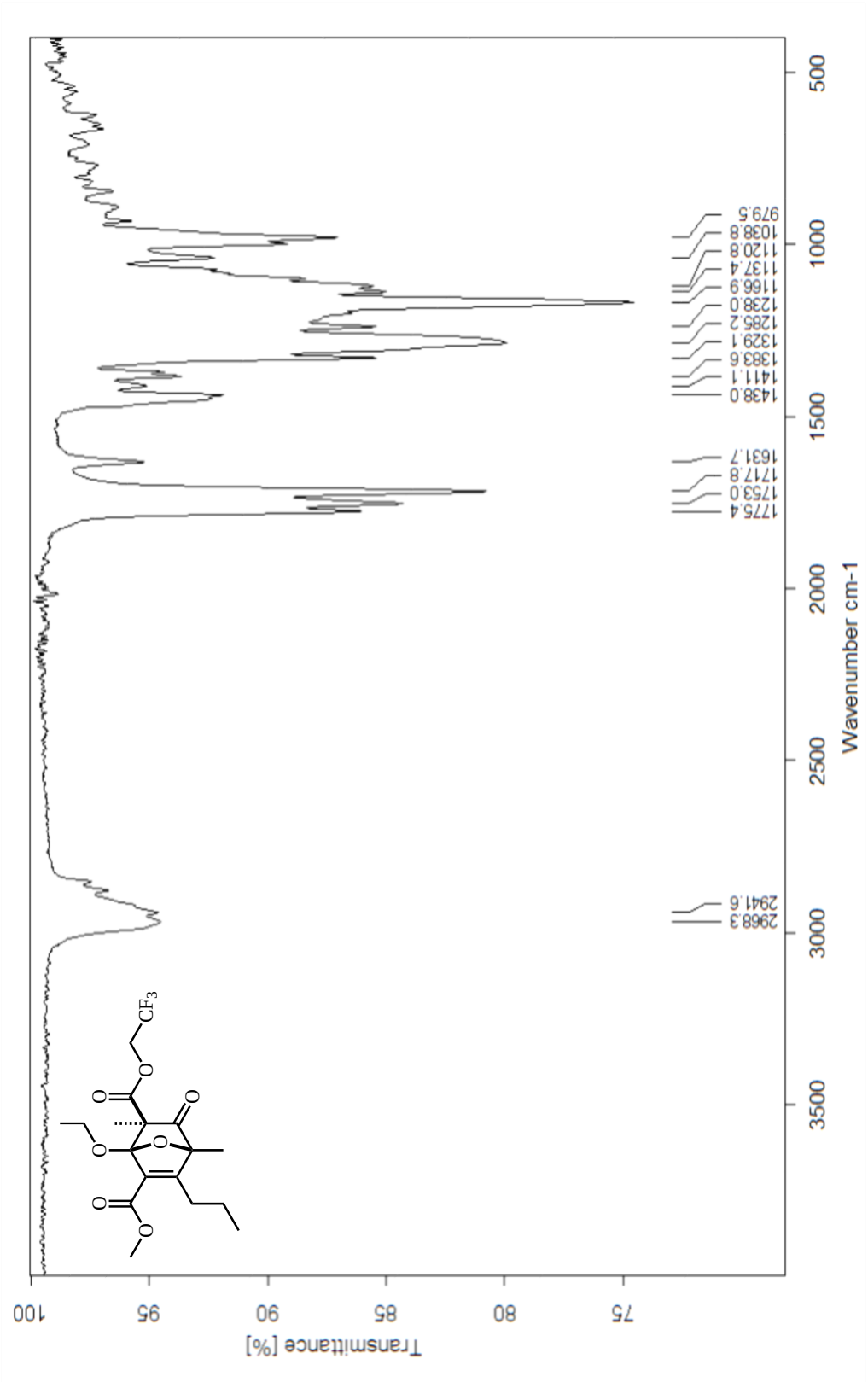

Figure B.18. FTIR Spectrum (neat) of oxabicycle **2.18**

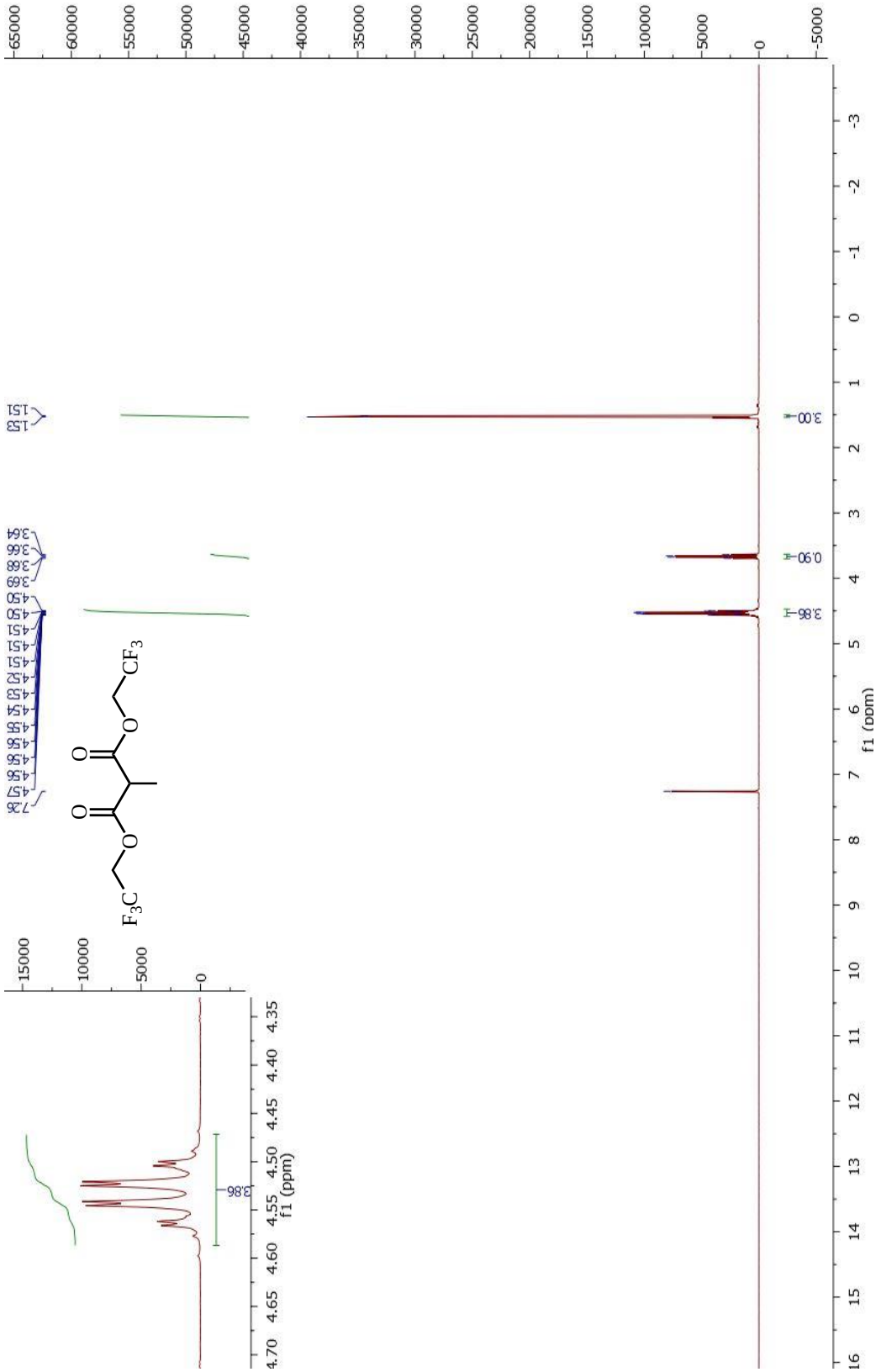

Figure B.19. **^{1}H NMR** (400 MHz, $CDCl_3$) of malonate **2.38**

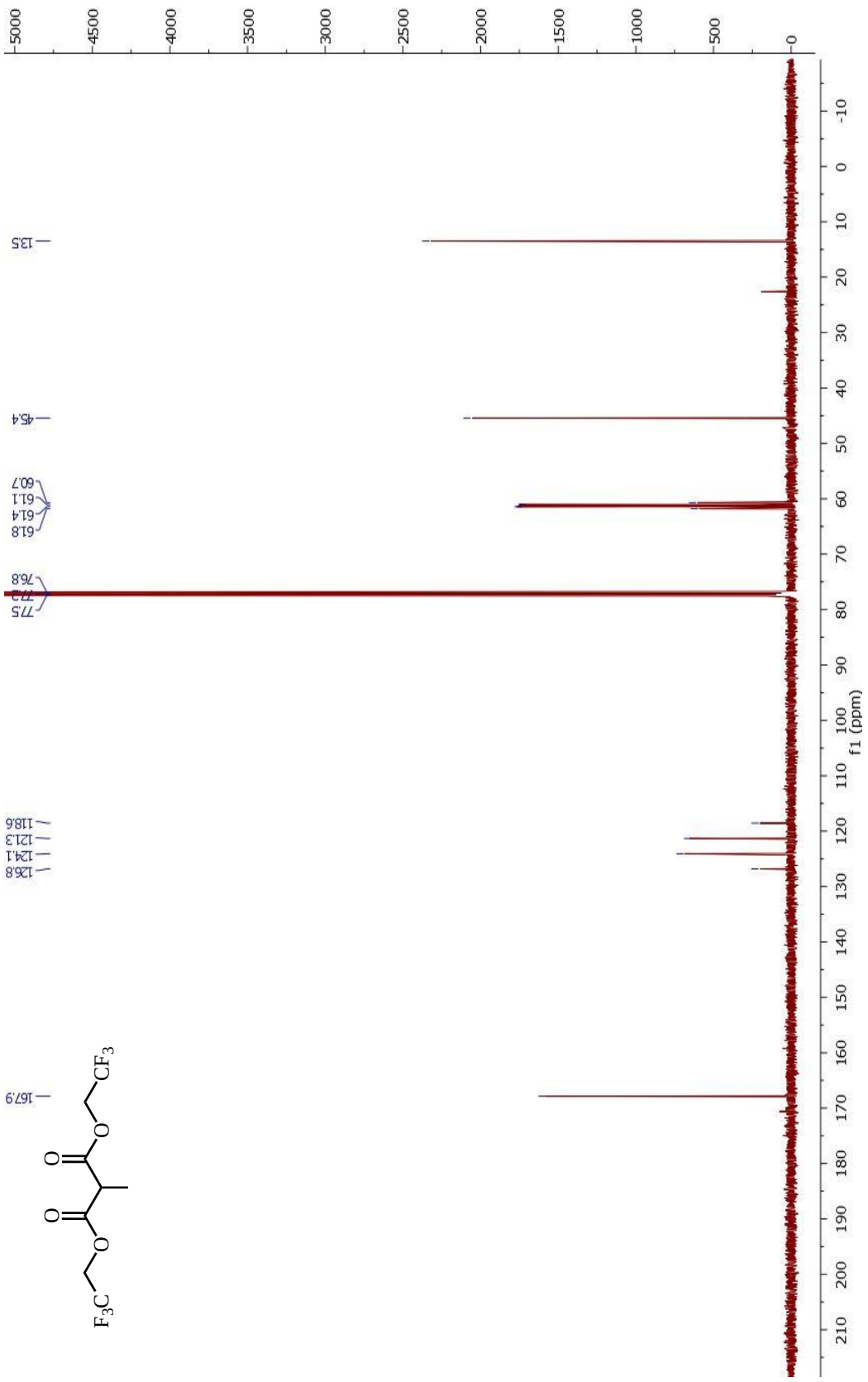

Figure B.20. **^{13}C NMR** (151 MHz, $CDCl_3$) of malonate **2.38**

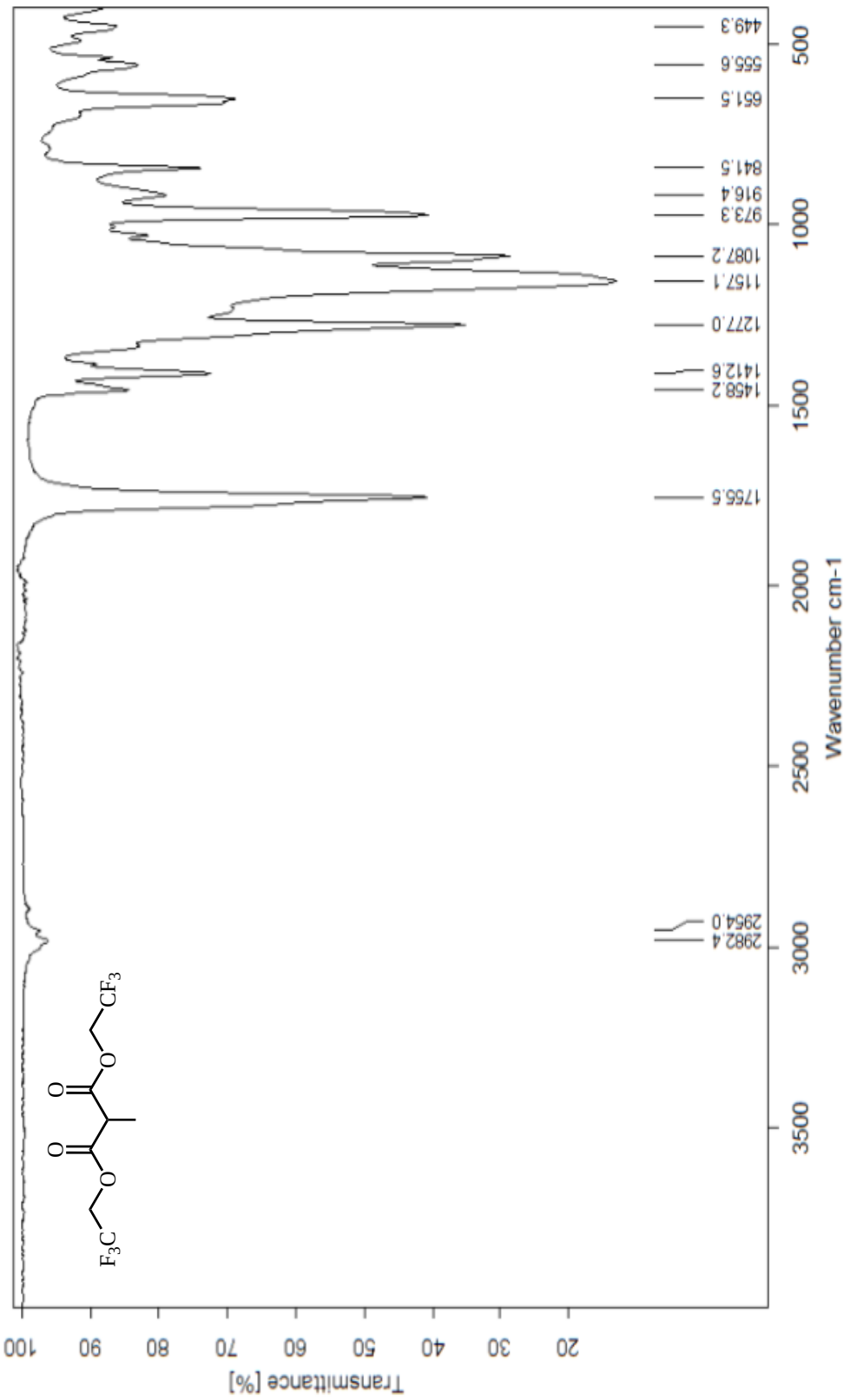

Figure B.21. FTIR Spectrum (neat) of malonate **2.38**

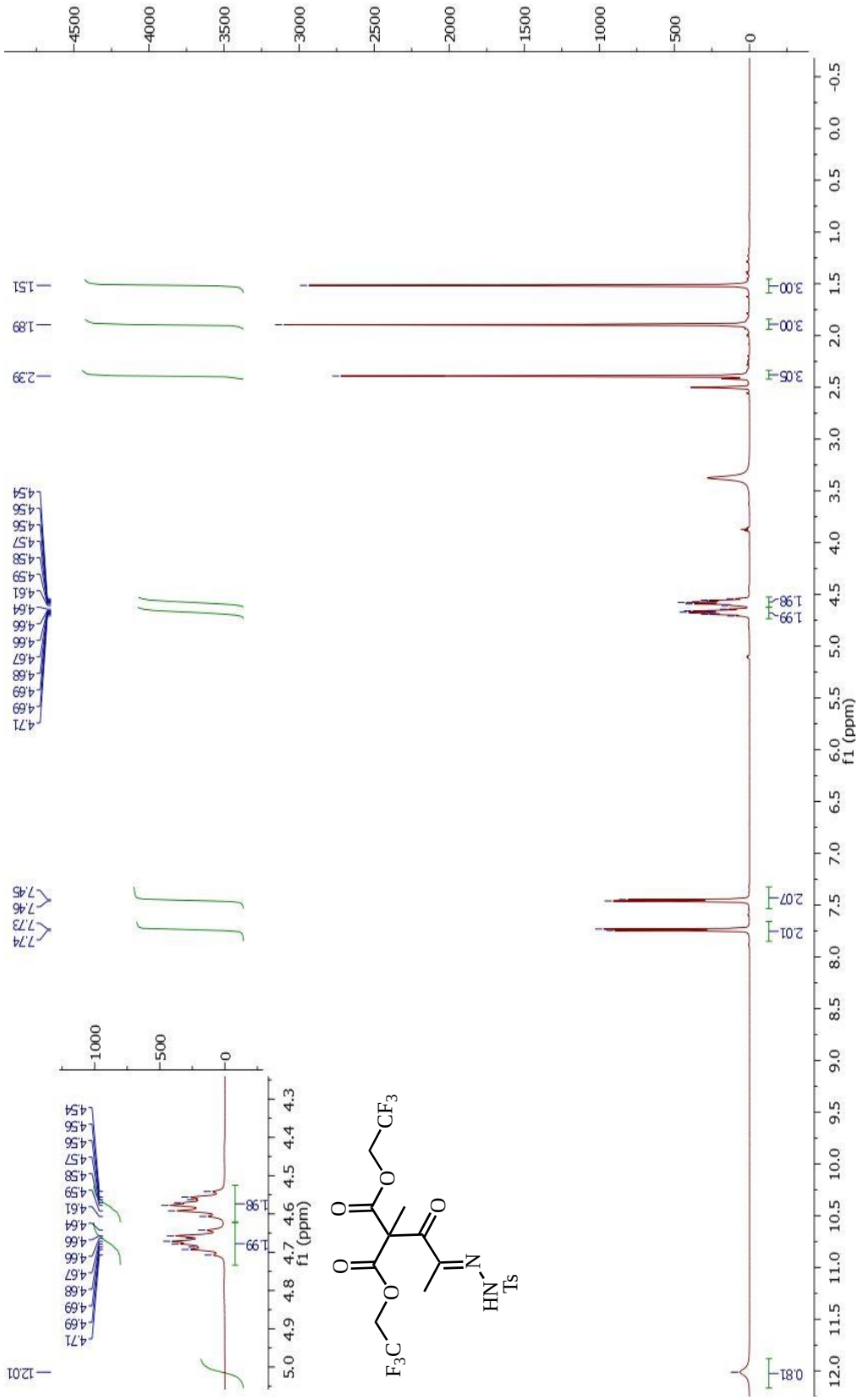

Figure B.22. **^{1}H NMR** (600 MHz, DMSO-*d6*) of tosyl hydrazone **2.39**

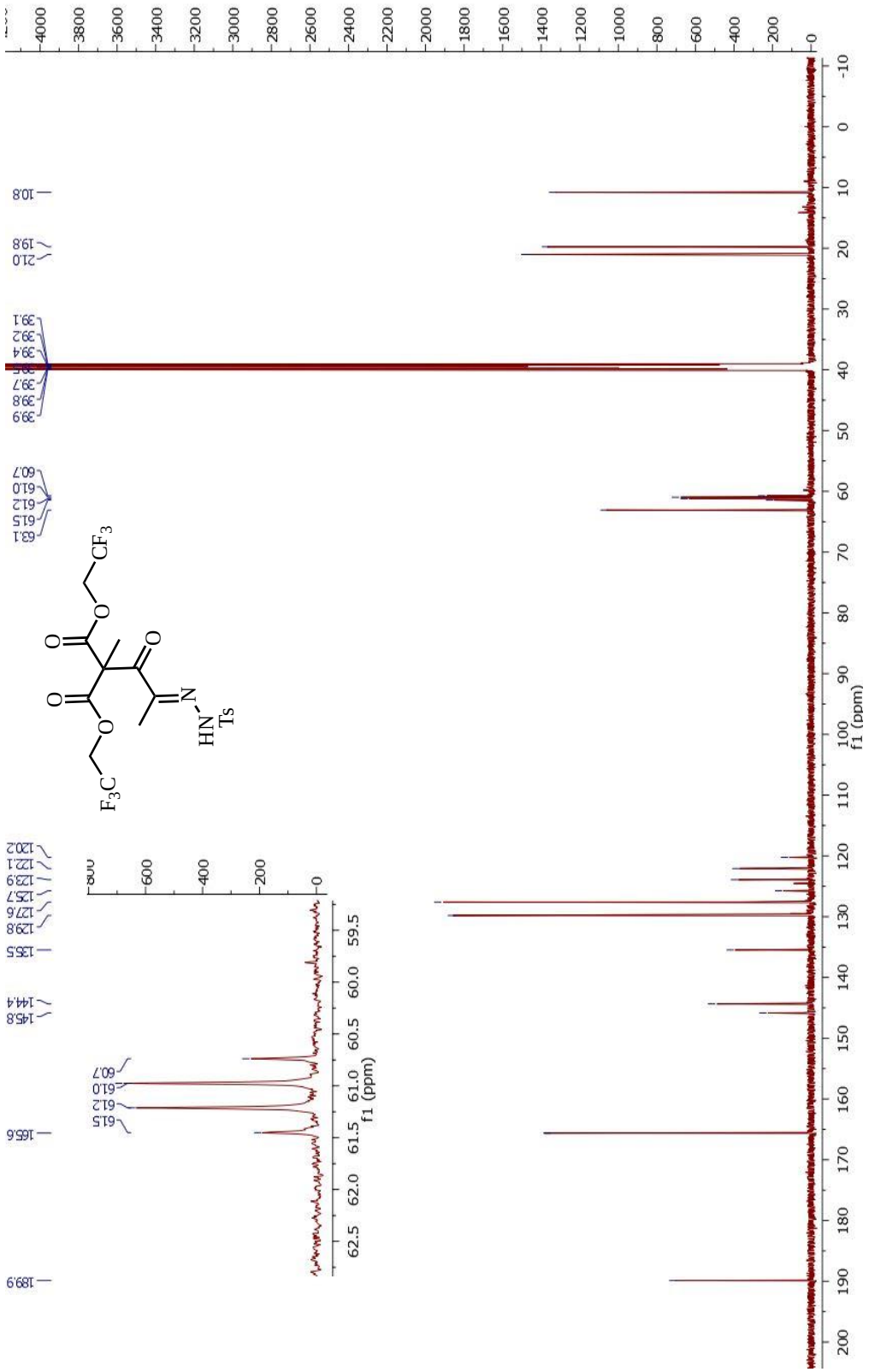

Figure B.23. **^{13}C NMR** (101 MHz, DMSO-*d6*) of tosyl hydrazone **2.39**

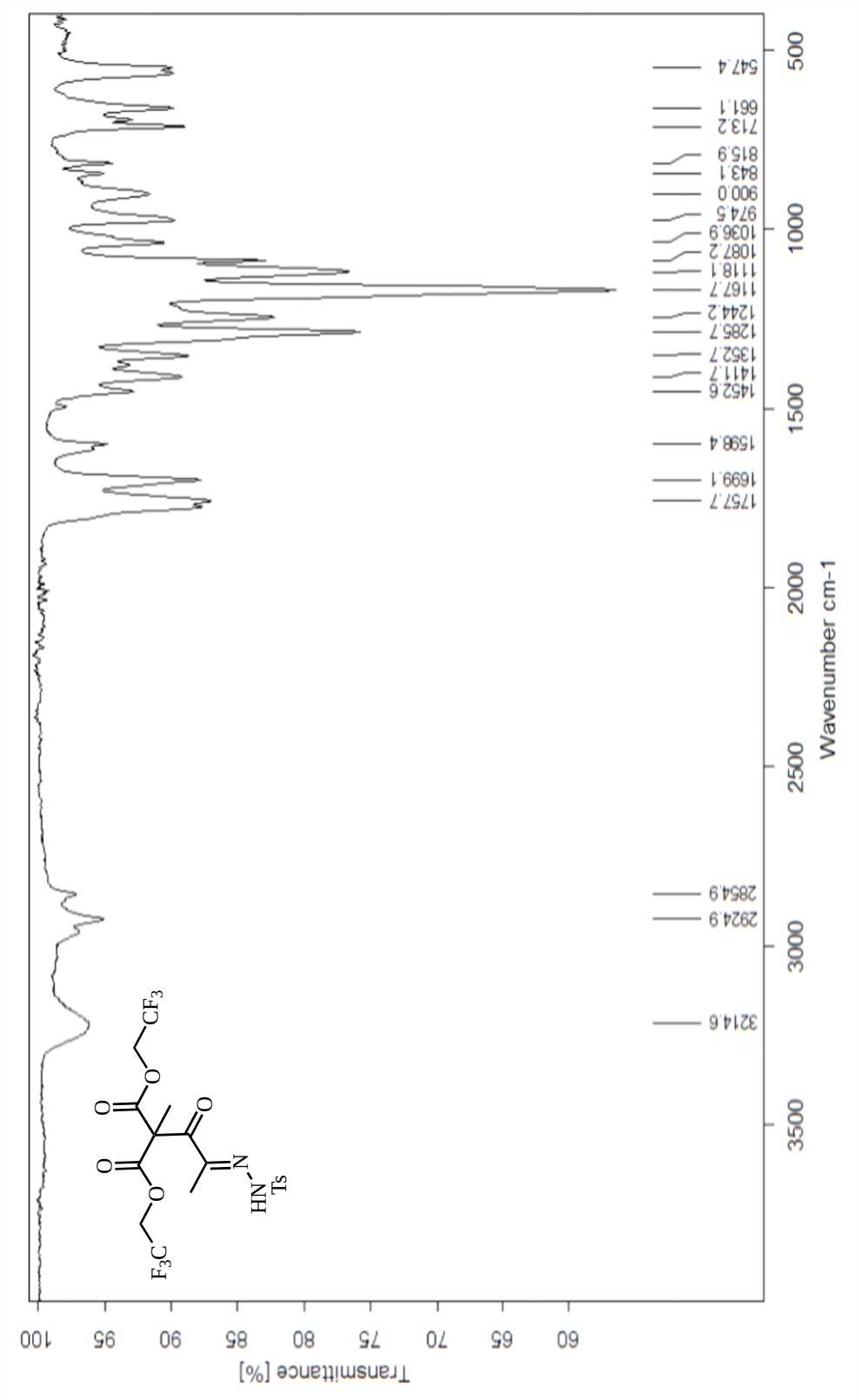

Figure B.24. FTIR Spectrum (neat) of tosyl hydrazone **2.39**

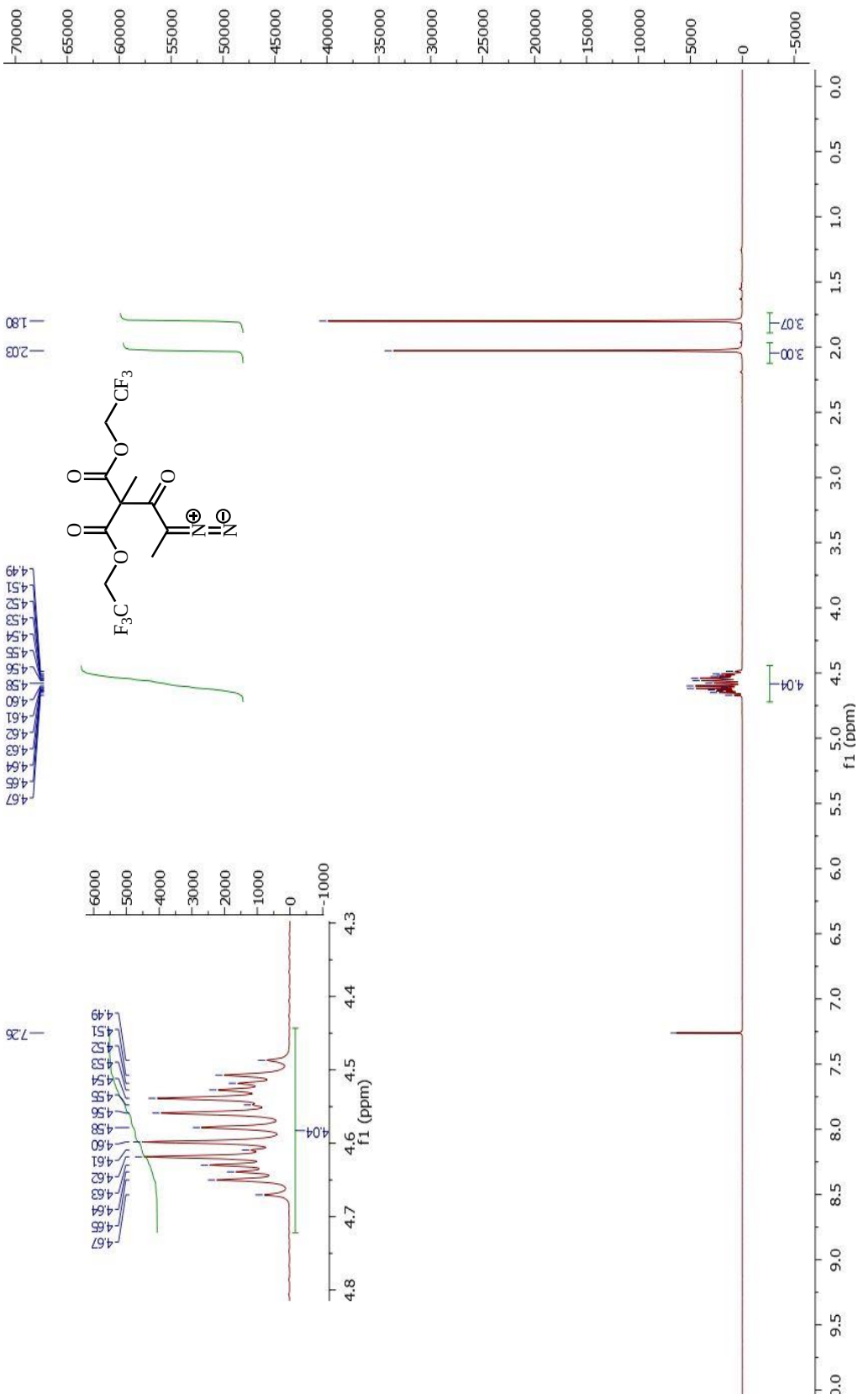

Figure B.25. **^{1}H NMR** (400 MHz, $CDCl_3$) of diazomalonate **2.11**

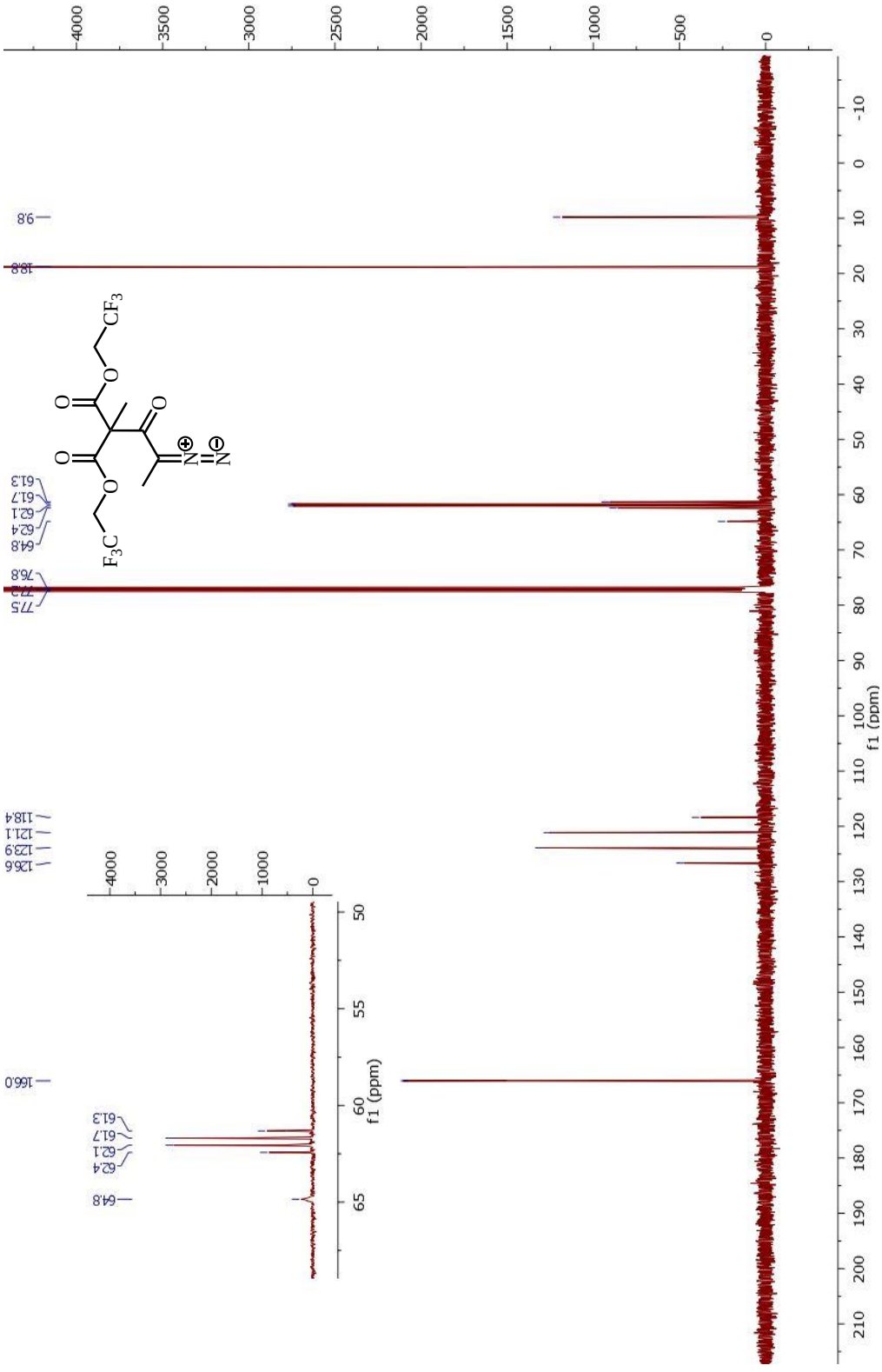

Figure B.26. **^{13}C NMR** (101 MHz, $CDCl_3$) of diazomalonate **2.11**

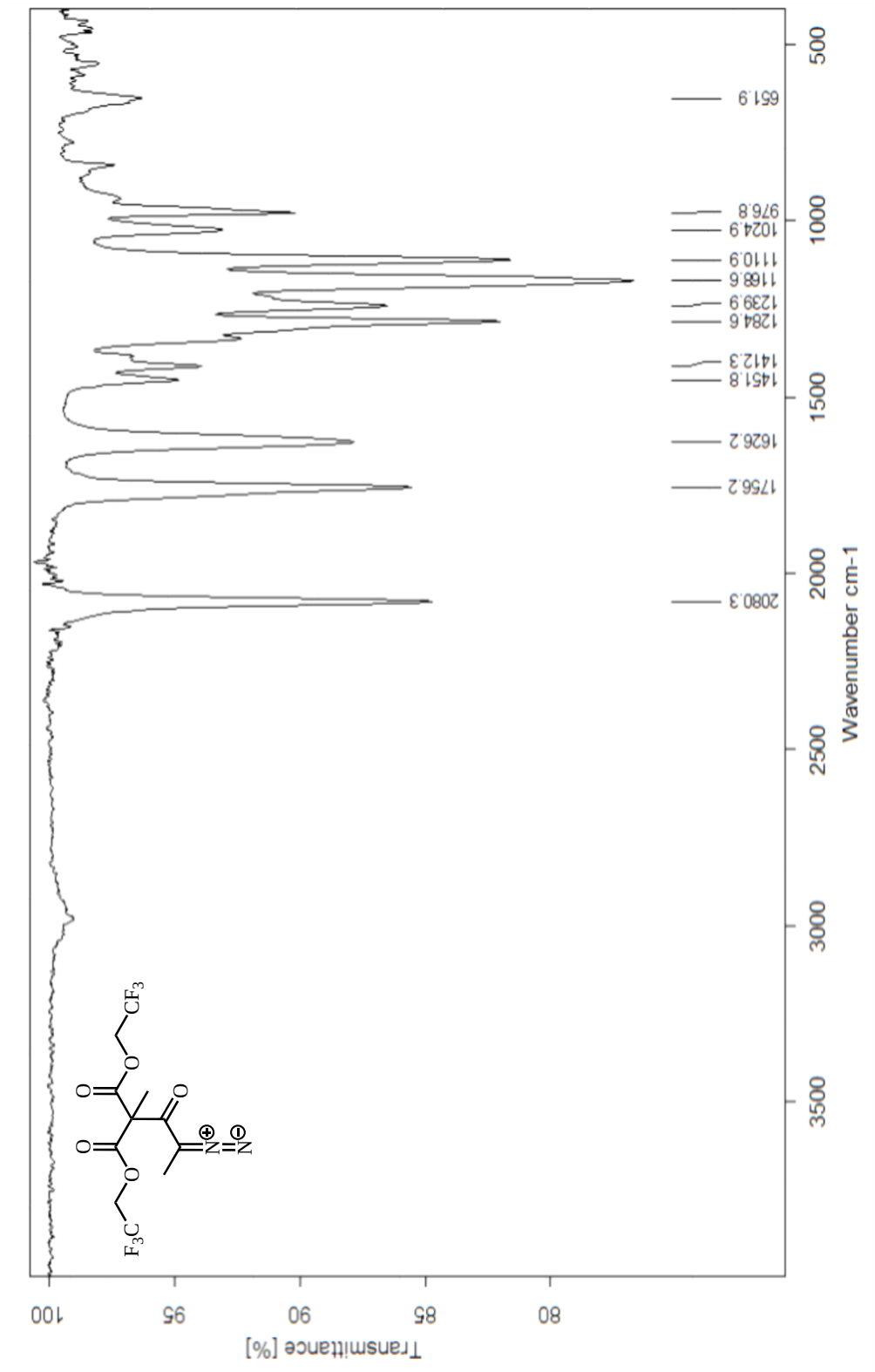

Figure B.27. FTIR Spectrum (neat) of diazomalonate **2.11**

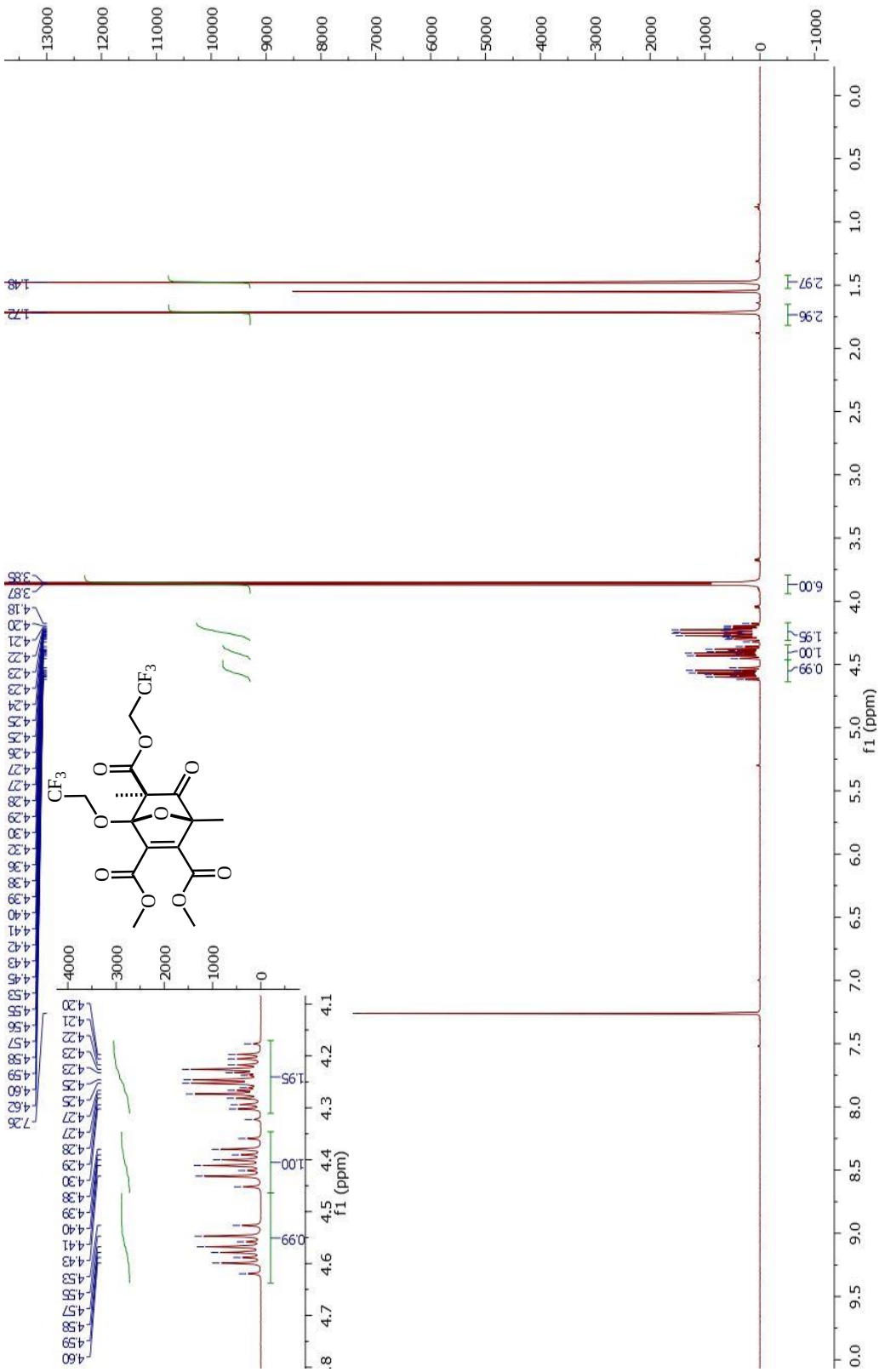

Figure B.28. **^{1}H NMR** (400 MHz, $CDCl_3$) of oxabicycle **2.21**

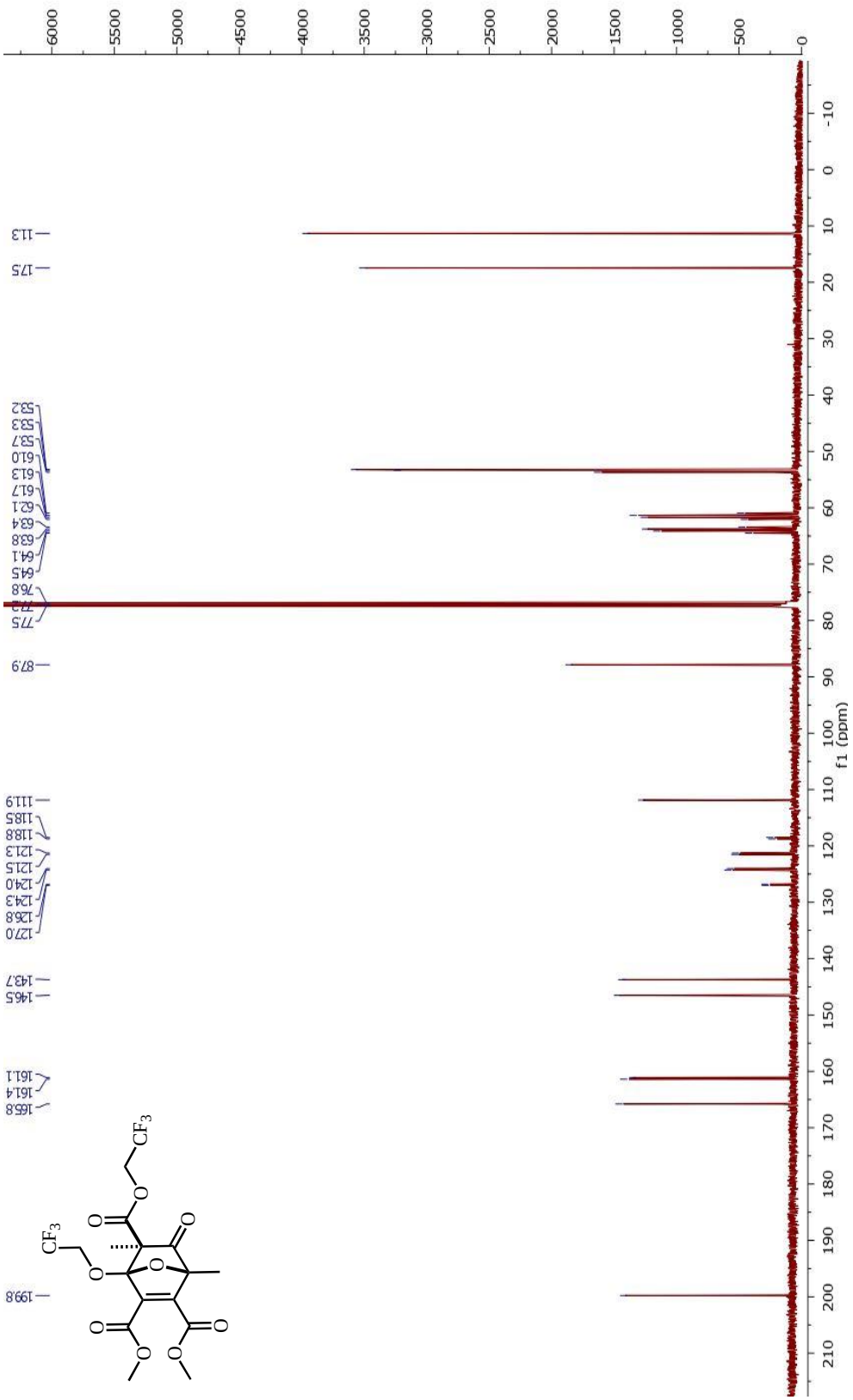

Figure B.29. **^{13}C NMR** (101 MHz, $CDCl_3$) of oxabicycle **2.21**

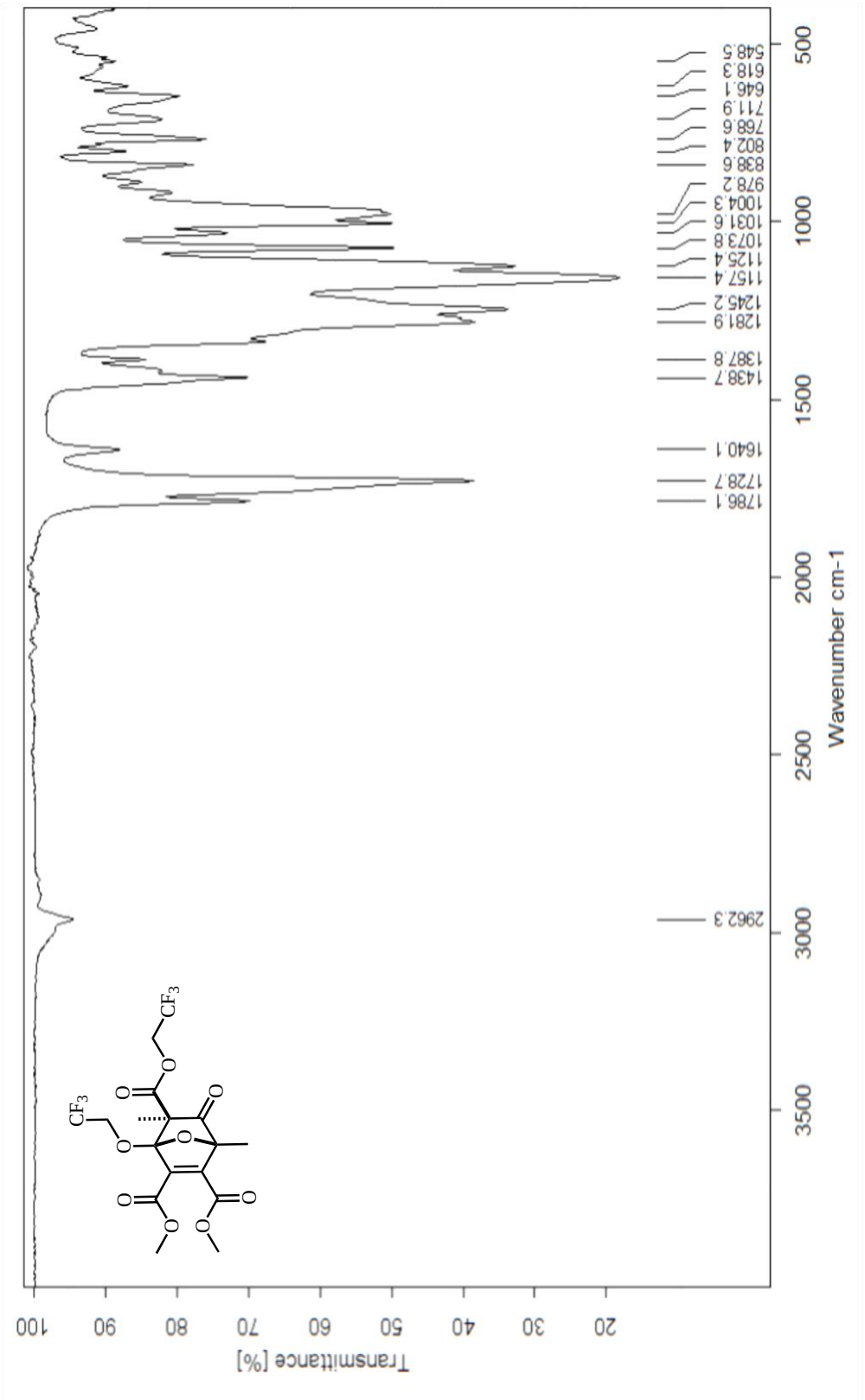

Figure B.30. FTIR Spectrum of oxabicycle **2.21**

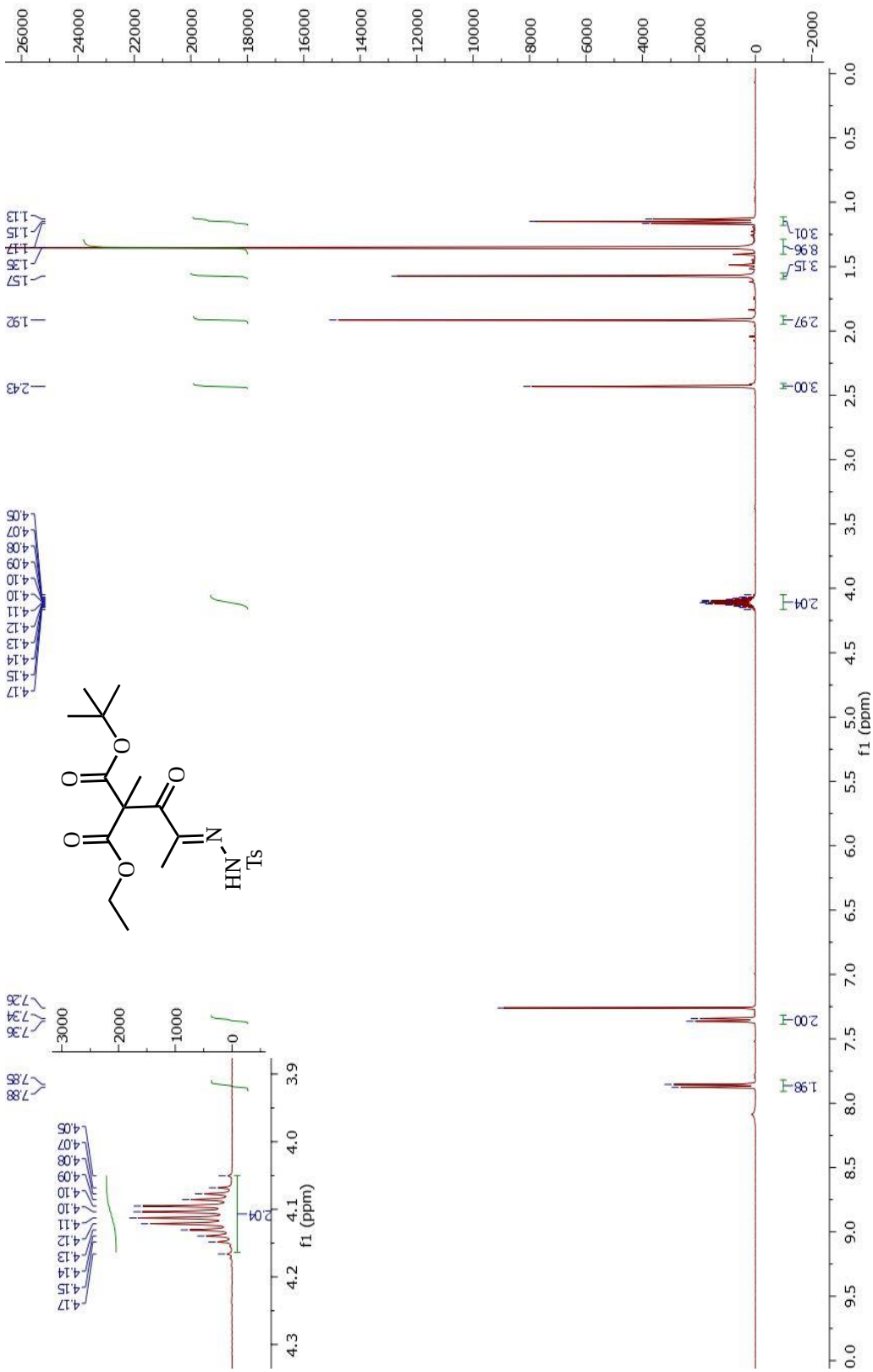

Figure B.31. **^{1}H NMR** (400 MHz, $CDCl_3$) of tosyl hydrazone **2.41**

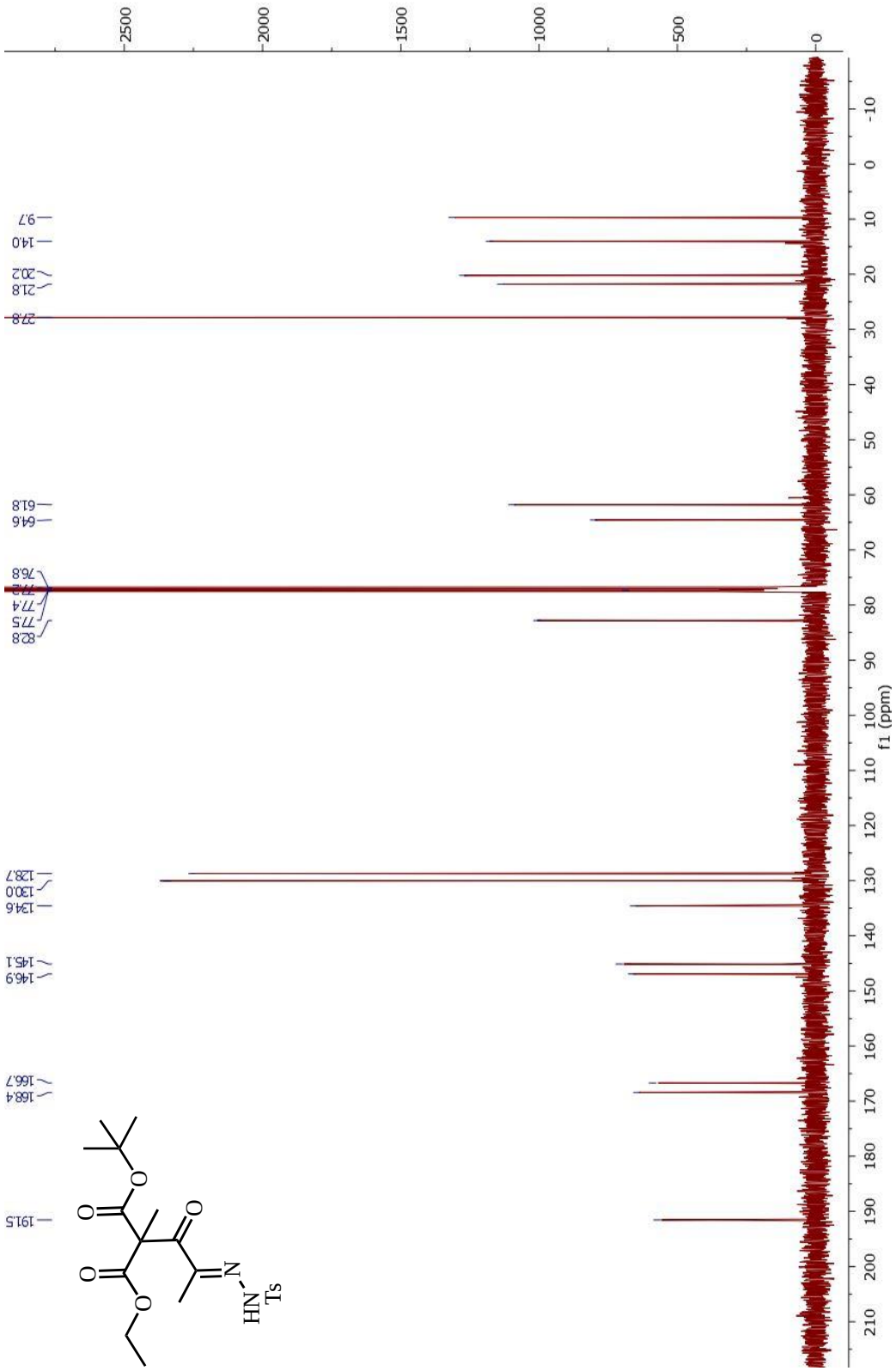

Figure B.32. **^{13}C NMR** (101 MHz, $CDCl_3$) of tosyl hydrazone **2.41**

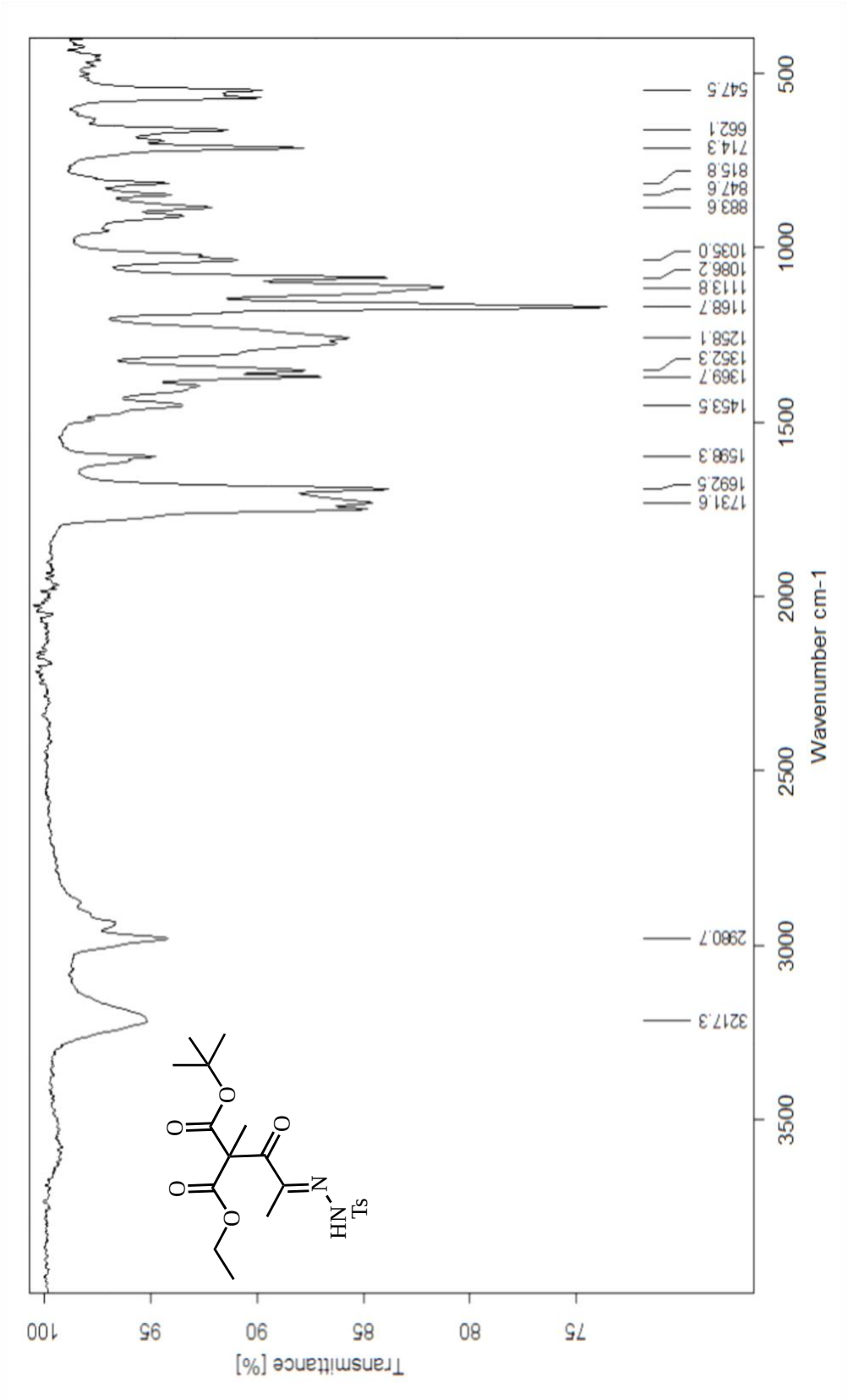

Figure B.33. FTIR Spectrum (neat) of tosyl hydrazone **2.41**

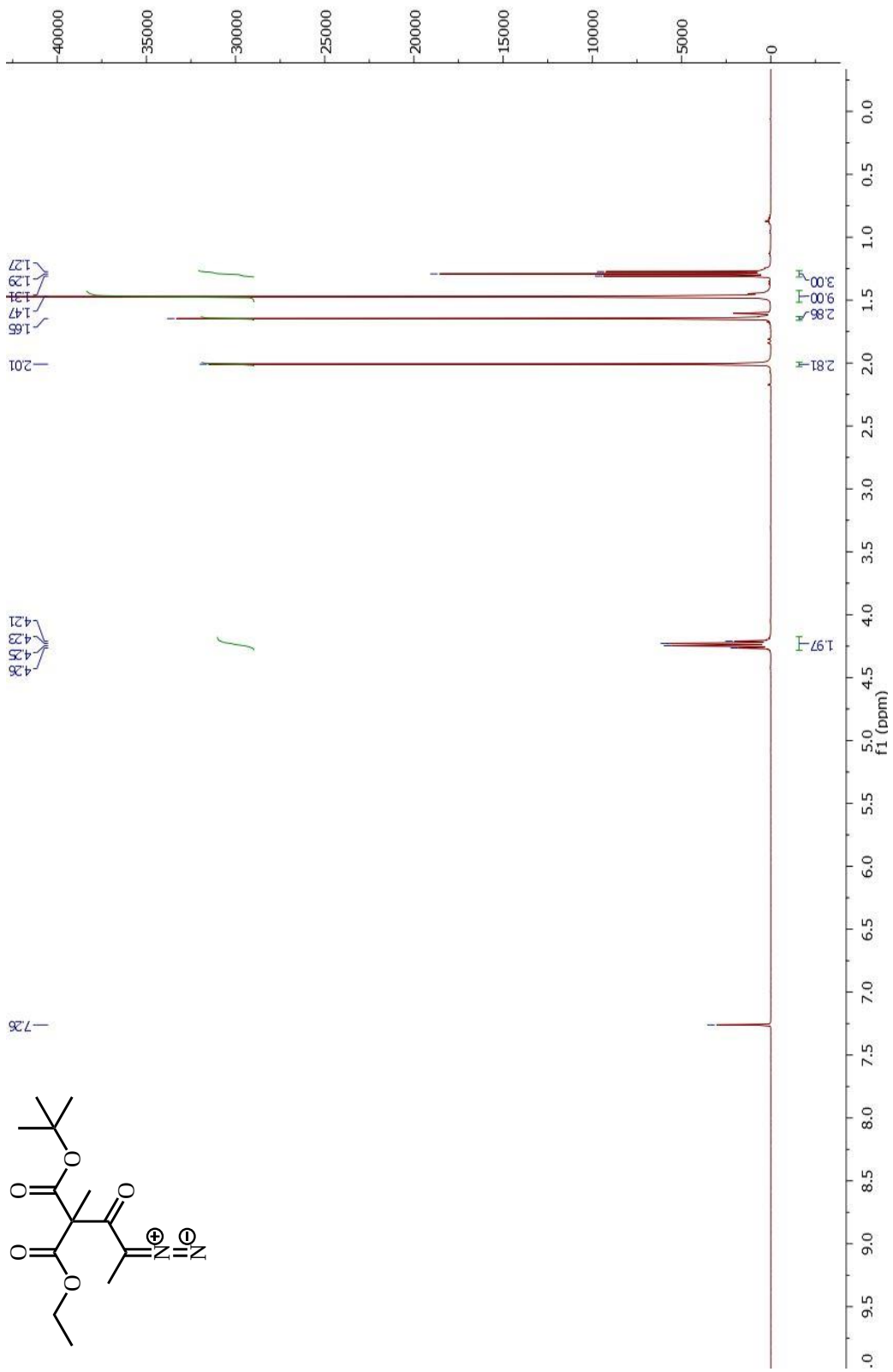

Figure B.34. **^{1}H NMR** (400 MHz, $CDCl_3$) of diazomalonate **2.09**

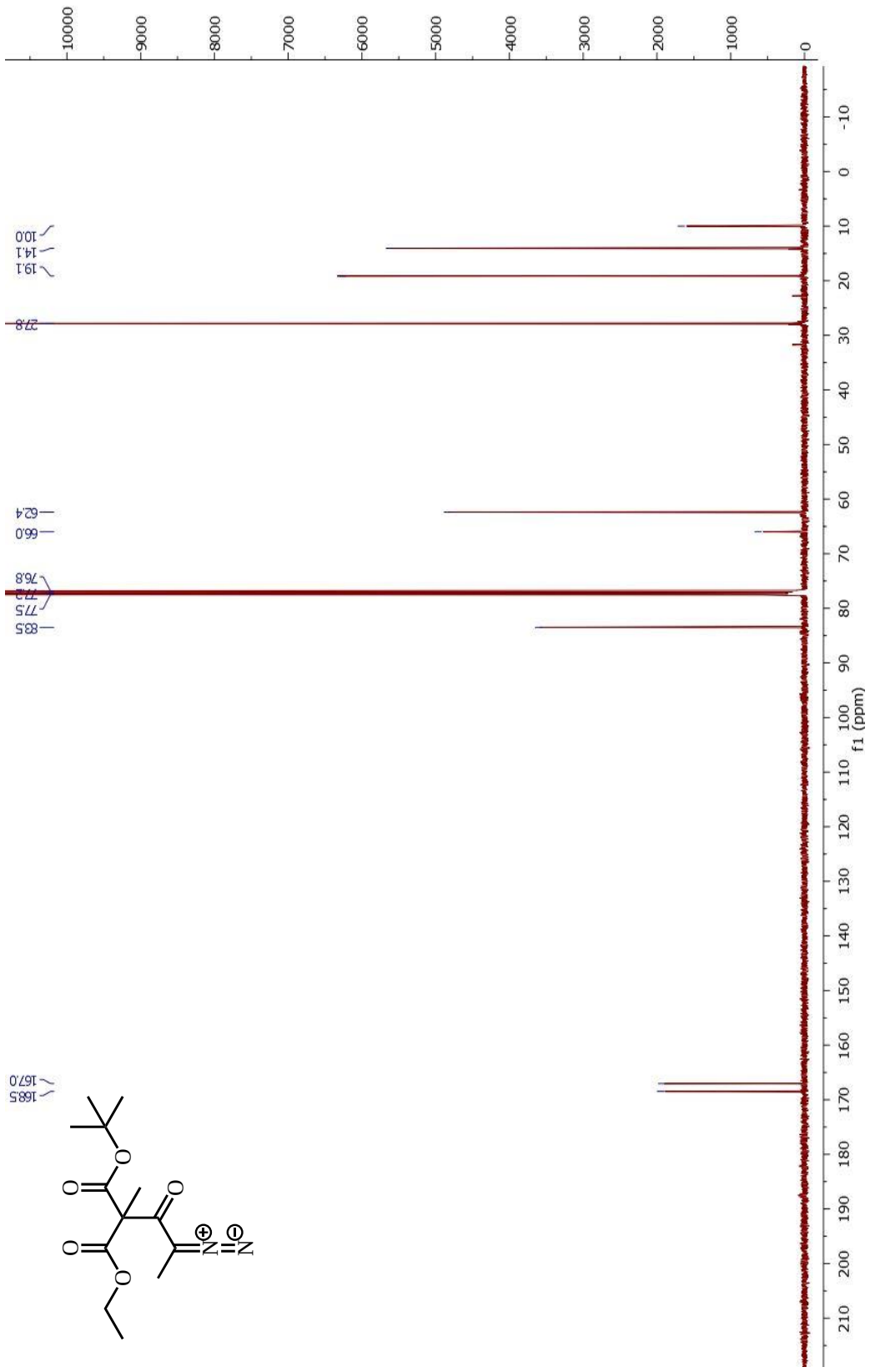

Figure B.35. **^{13}C NMR** (101 MHz, $CDCl_3$) of diazomalonate **2.09**

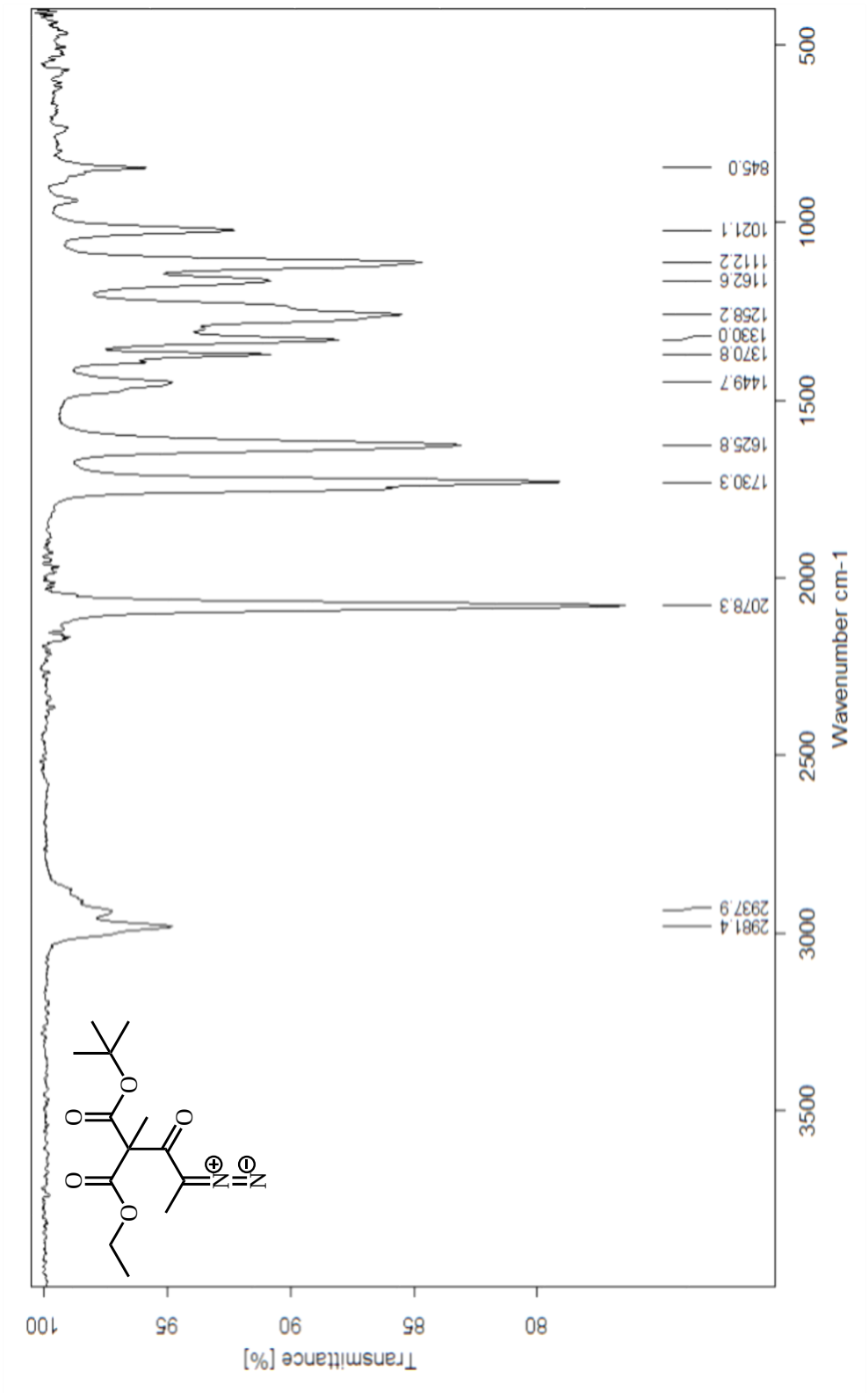

Figure B.36. FTIR Spectrum (neat) of diazomalonate **2.09**

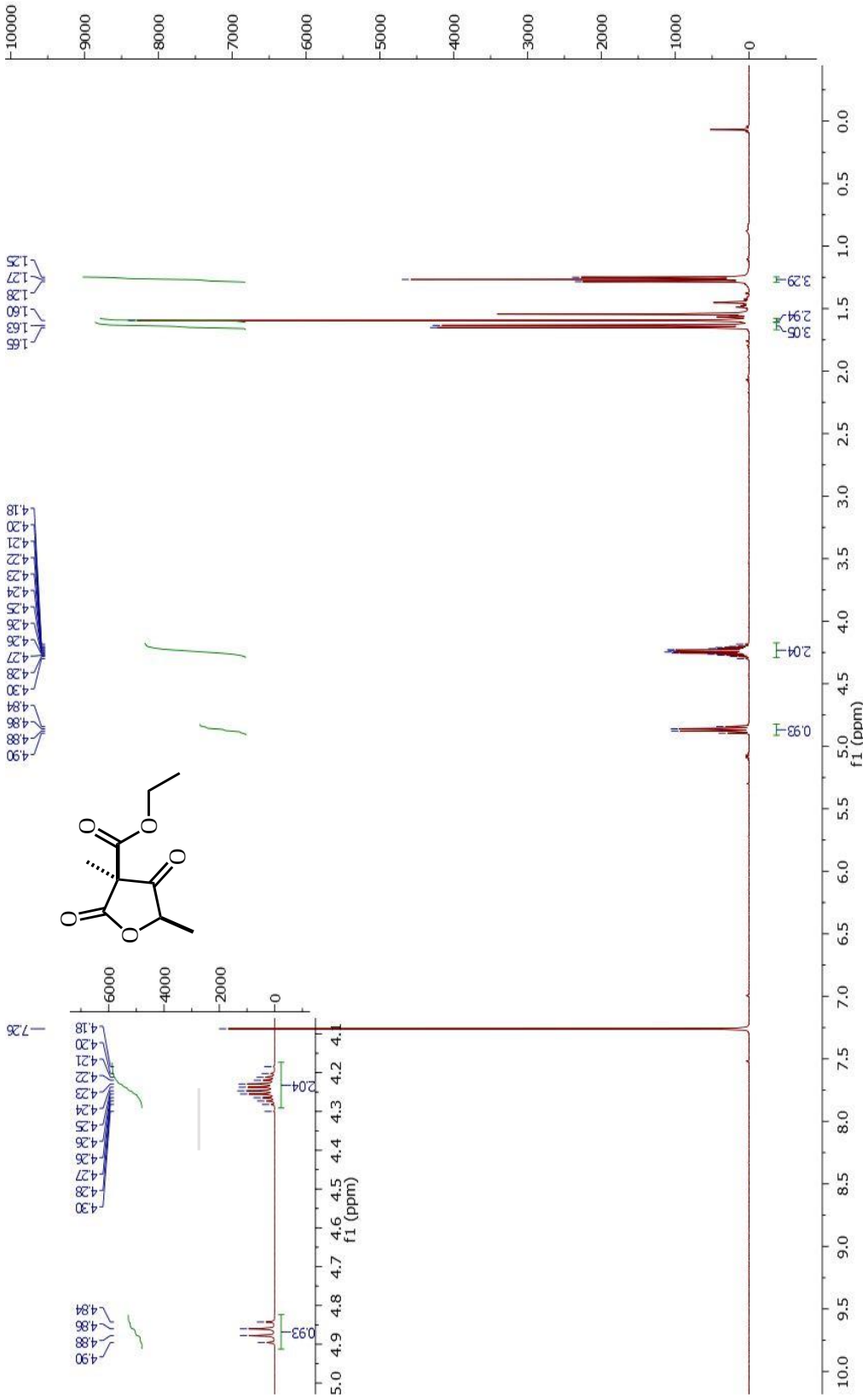

Figure B.37. **^{1}H NMR** (600 MHz, $CDCl_3$) of tetronic acid **2.22**

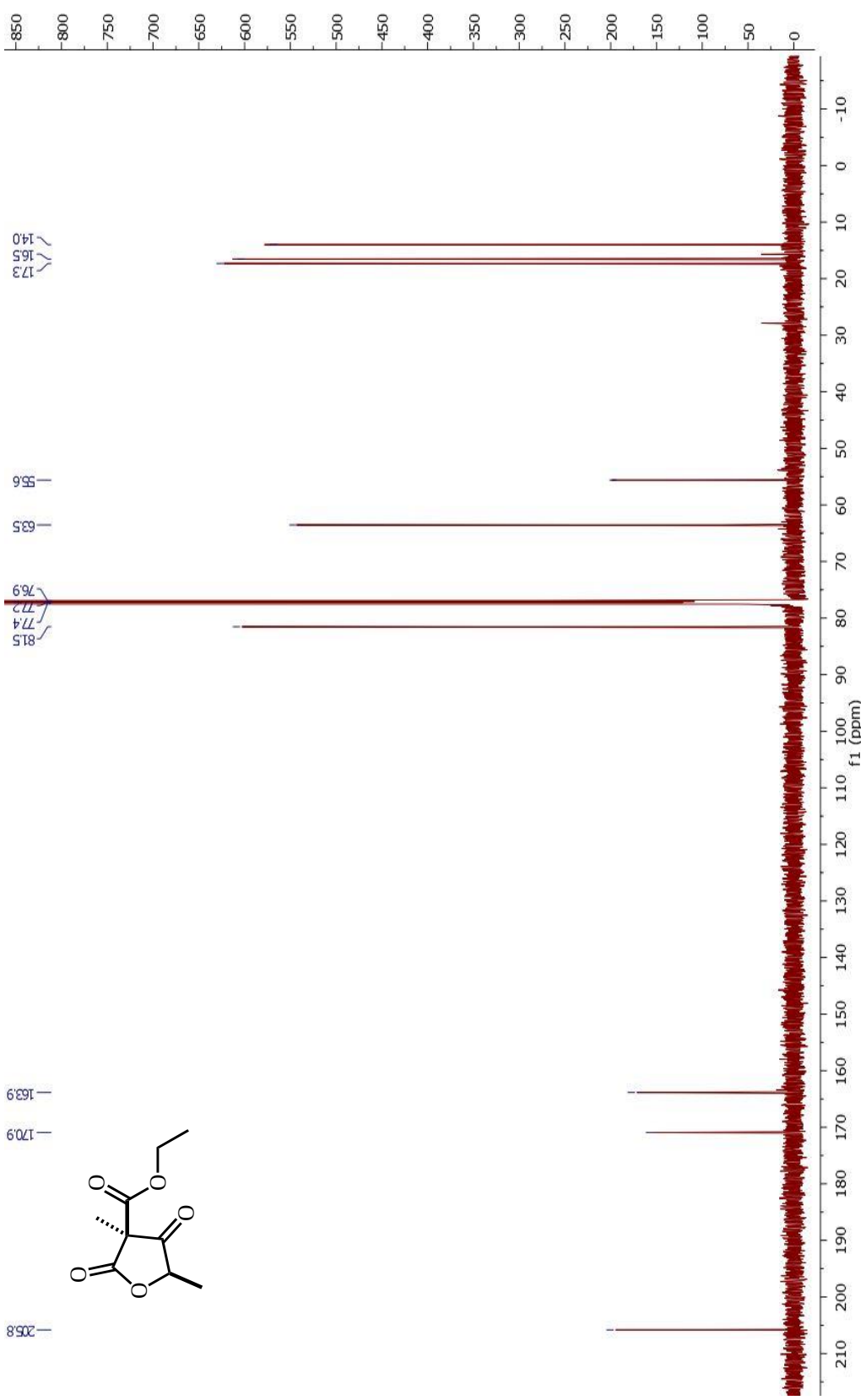

Figure B.38. **^{13}C NMR** (151 MHz, $CDCl_3$) of tetronic acid **2.22**

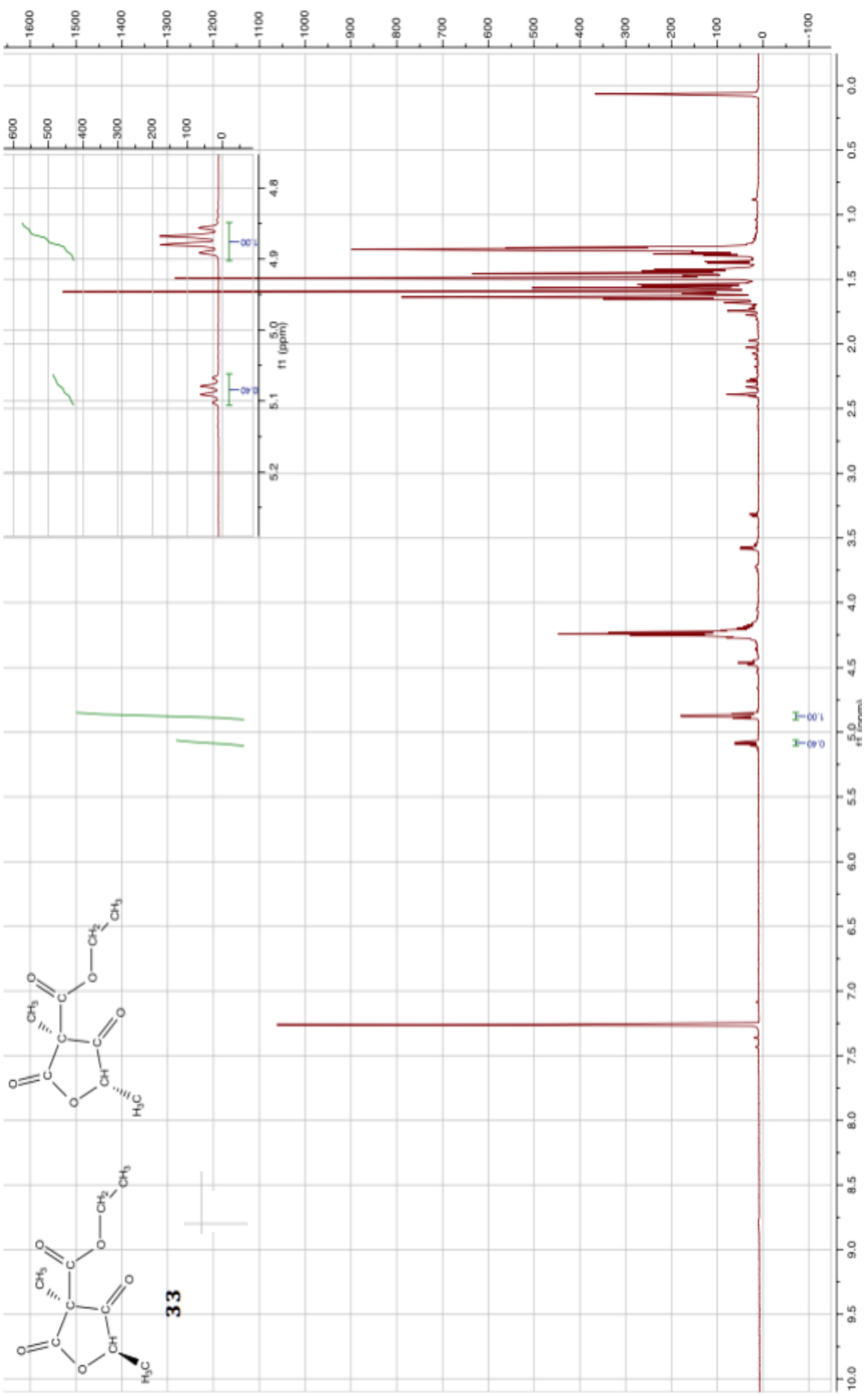

Figure B.39. **^{1}H NMR** (600 MHz, $CDCl_3$) of crude tetronic acids **2.22** & **2.23**

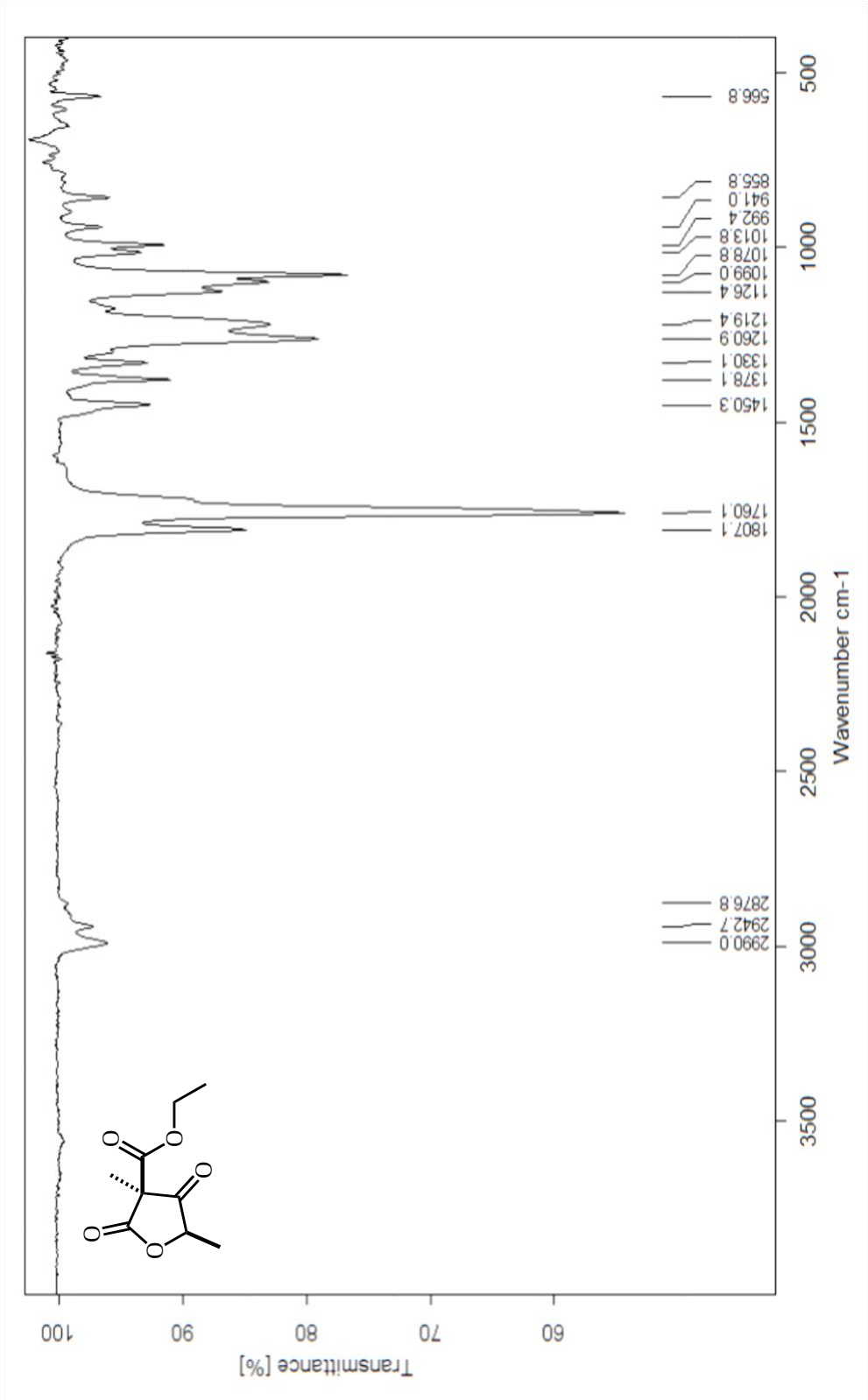

Figure B.40. FTIR Spectrum (neat) of tetronic acid **2.22**

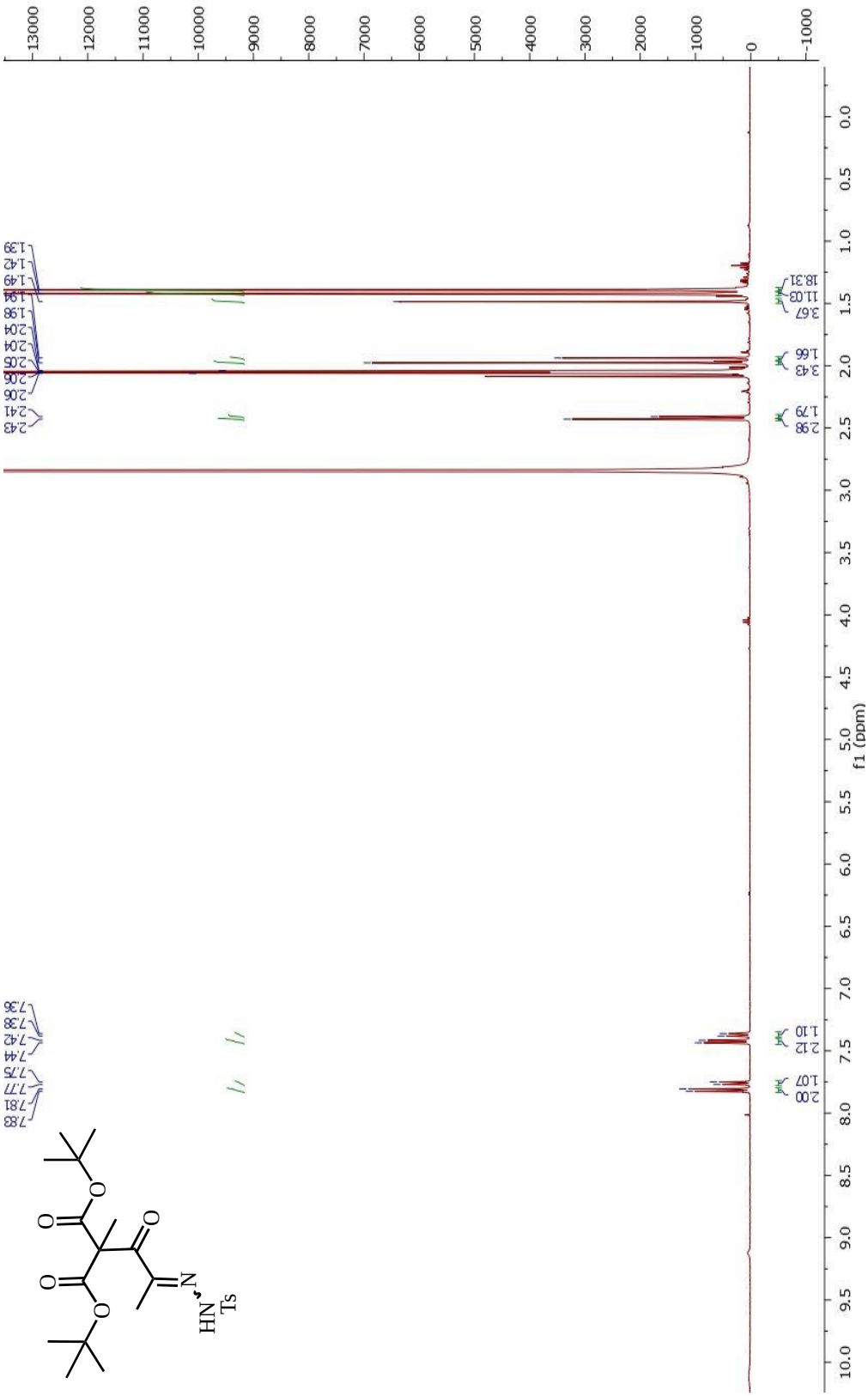

Figure B.41. **^{1}H NMR** (400 MHz, $CO(CD_3)_2$) of tosyl hydrazone **2.43**

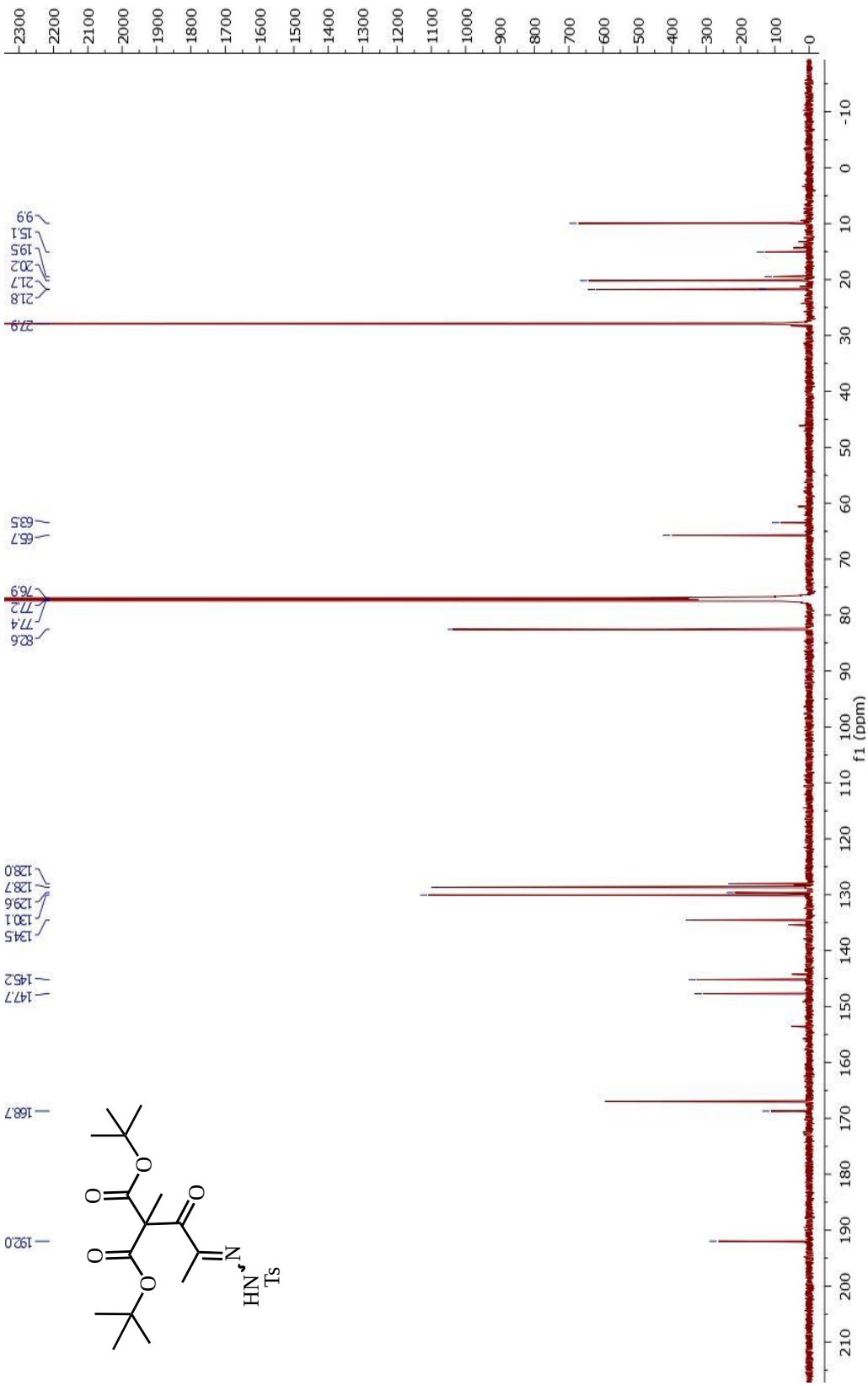

Figure B.42. **^{13}C NMR** (151 MHz, $CDCl_3$) of tosyl hydrazone **2.43**

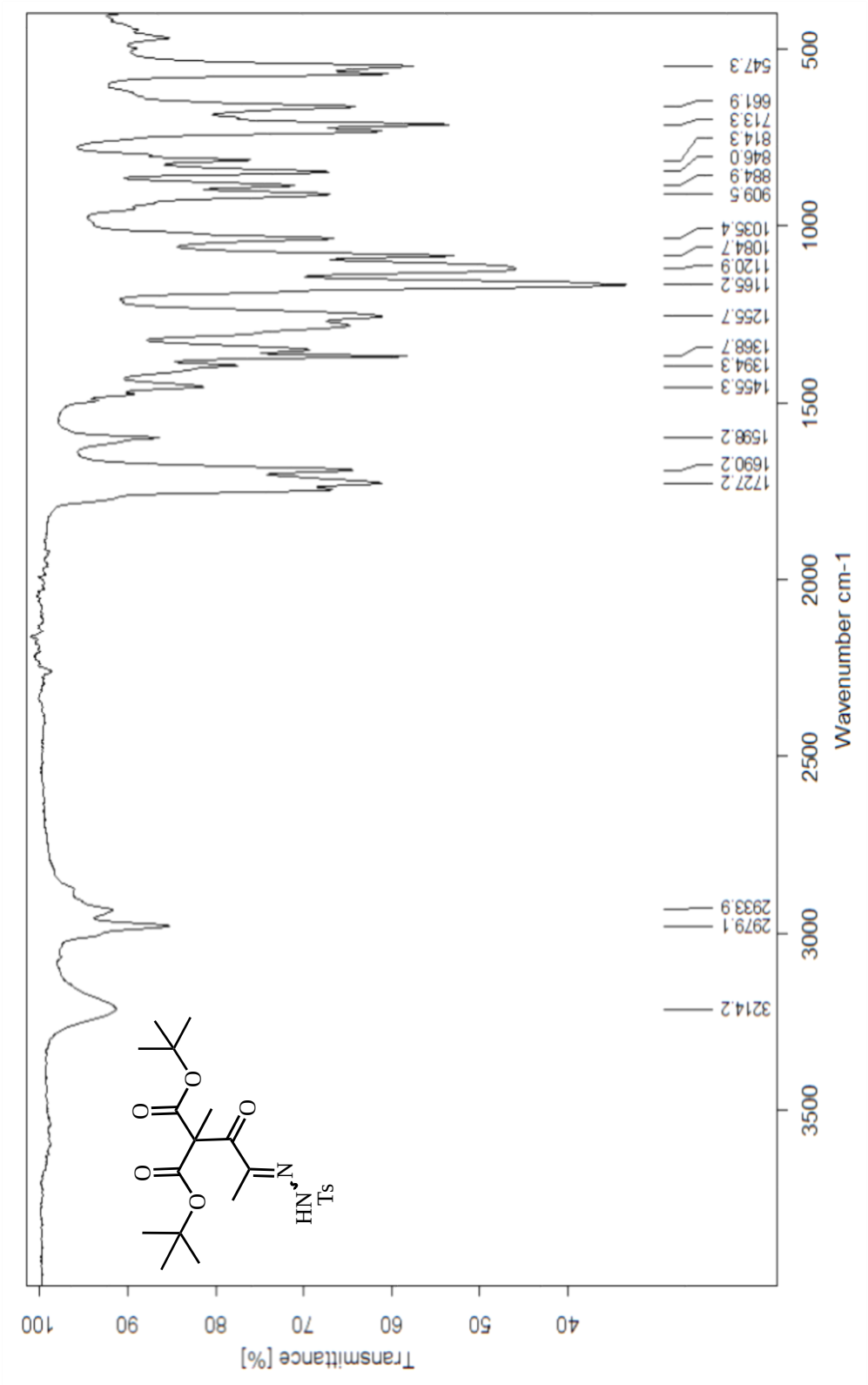

Figure B.43. FTIR Spectrum (neat) of tosyl hydrazone **2.43**

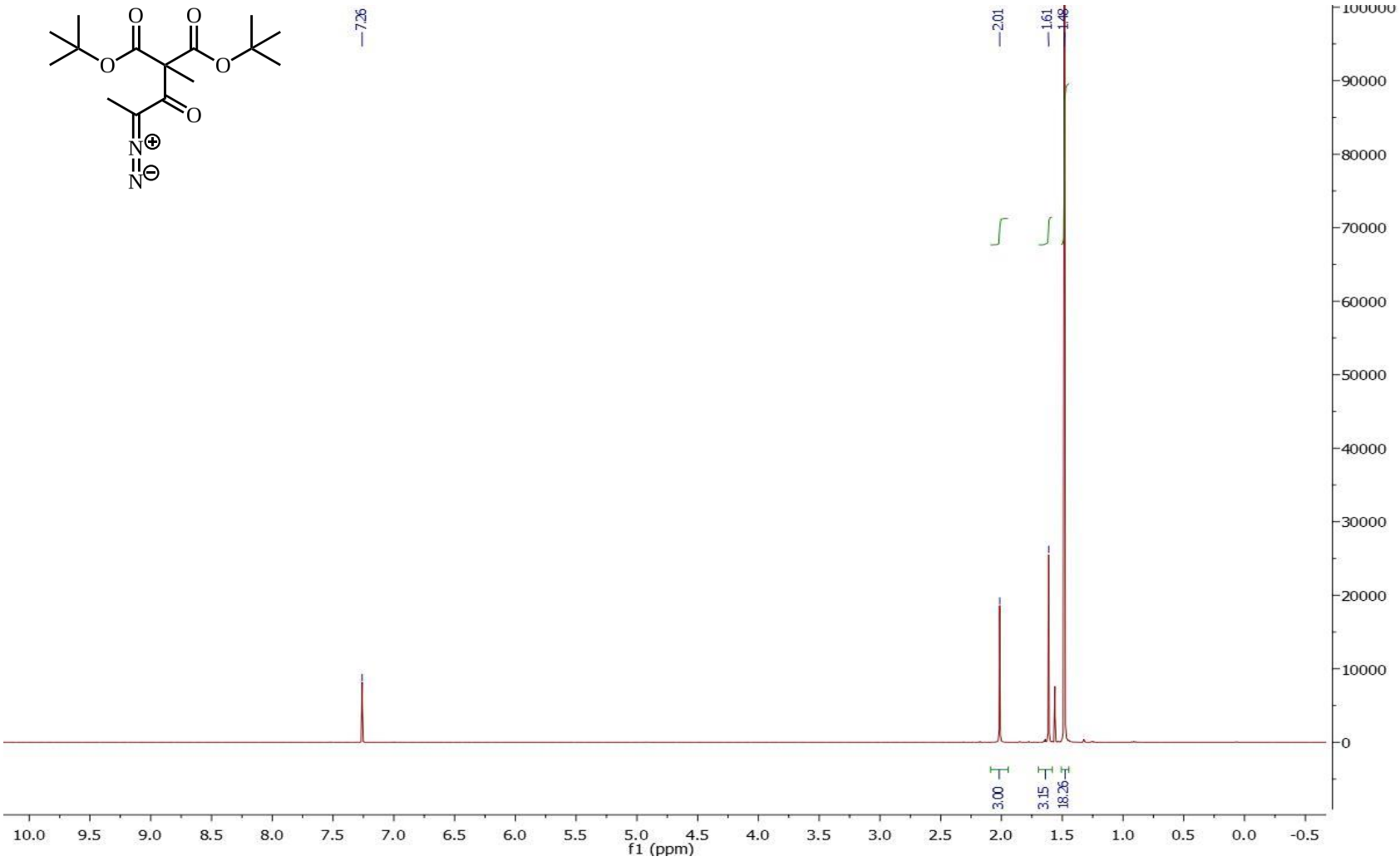

Figure B.44. **^{1}H NMR** (400 MHz, $CDCl_3$) of diazomalonate **2.12**

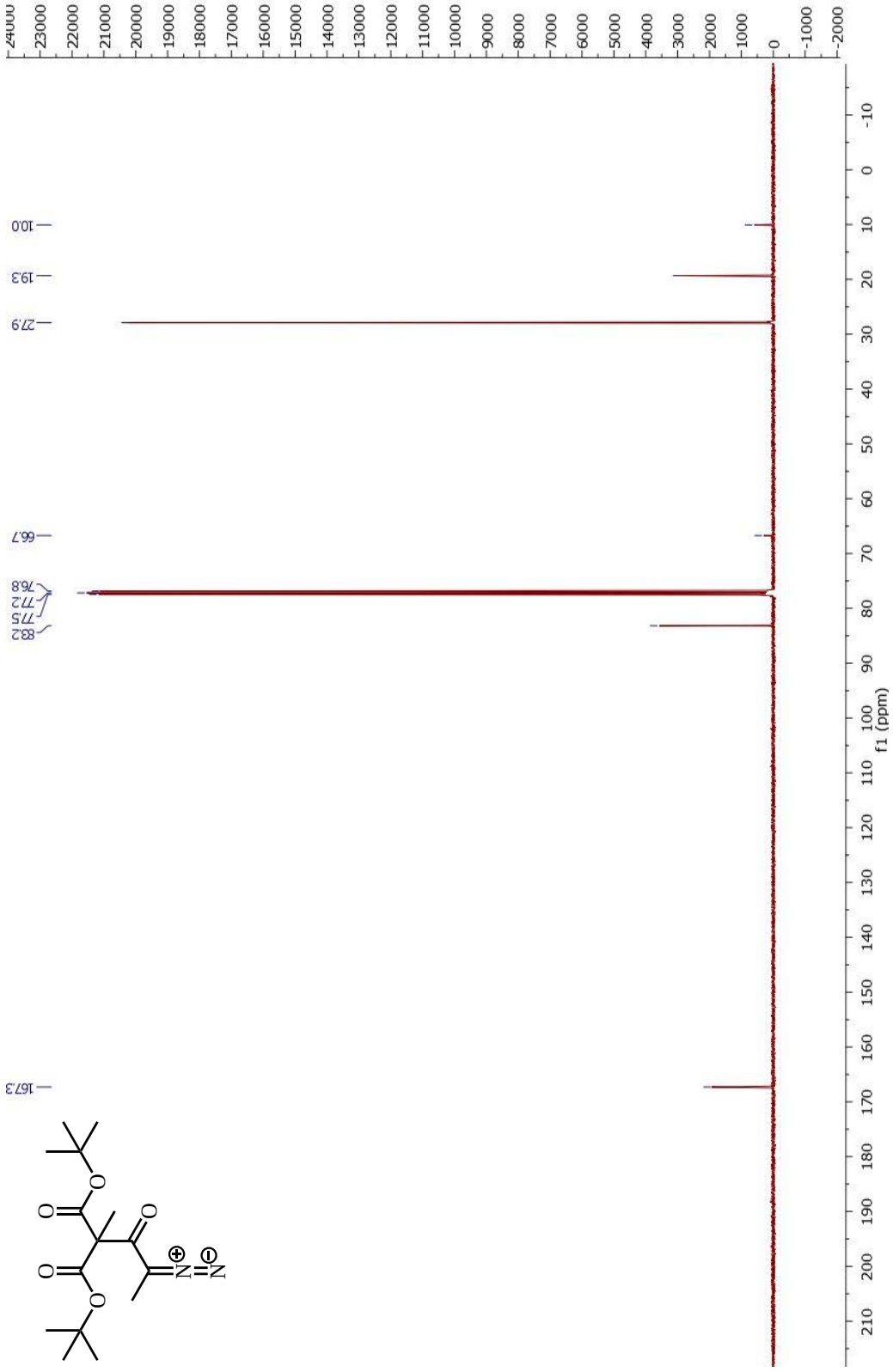

Figure B.45. **^{13}C NMR** (101 MHz, $CDCl_3$) of diazomalonate **2.12**

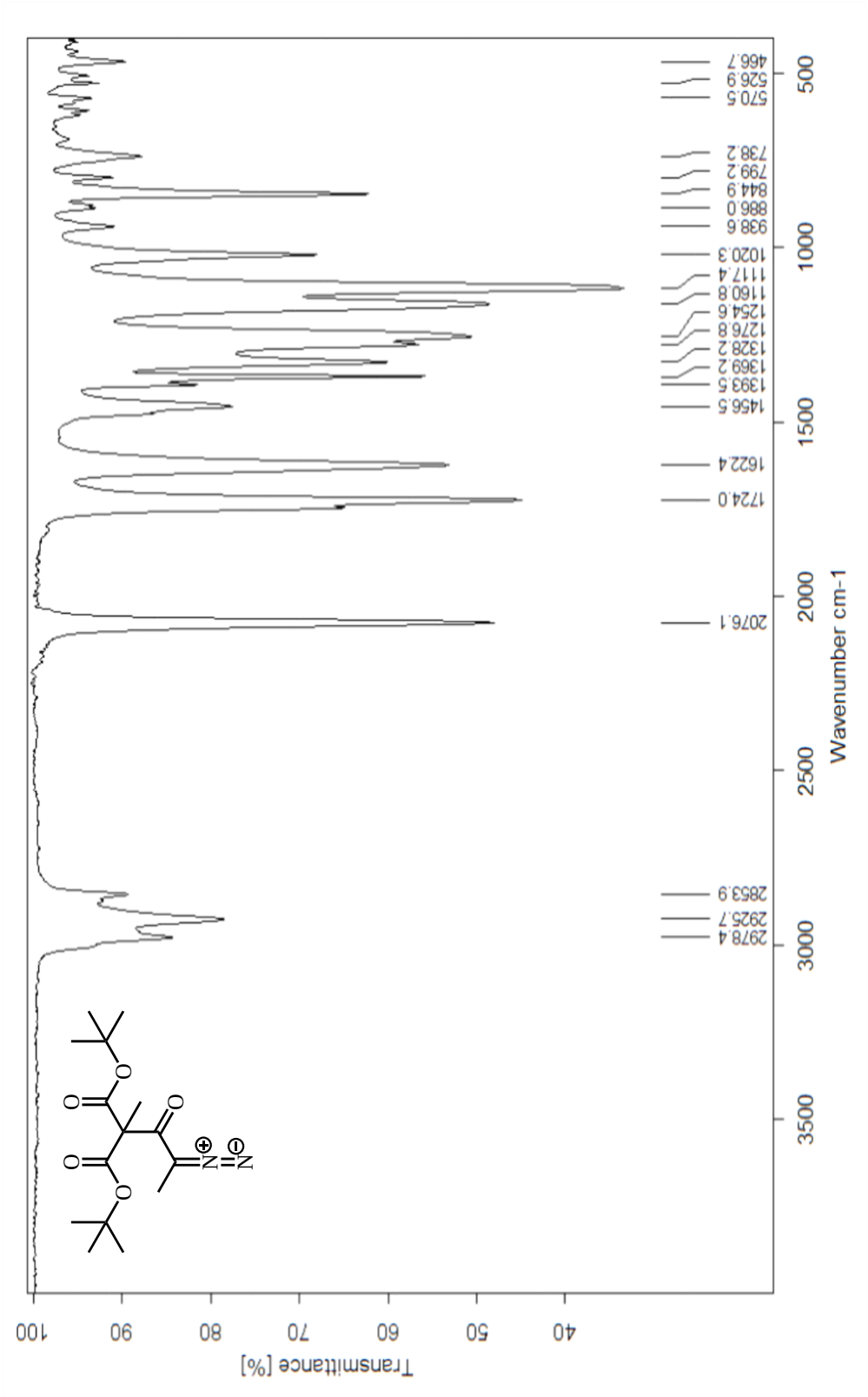

Figure B.46. FTIR Spectrum (neat) of diazomalonate **2.12**

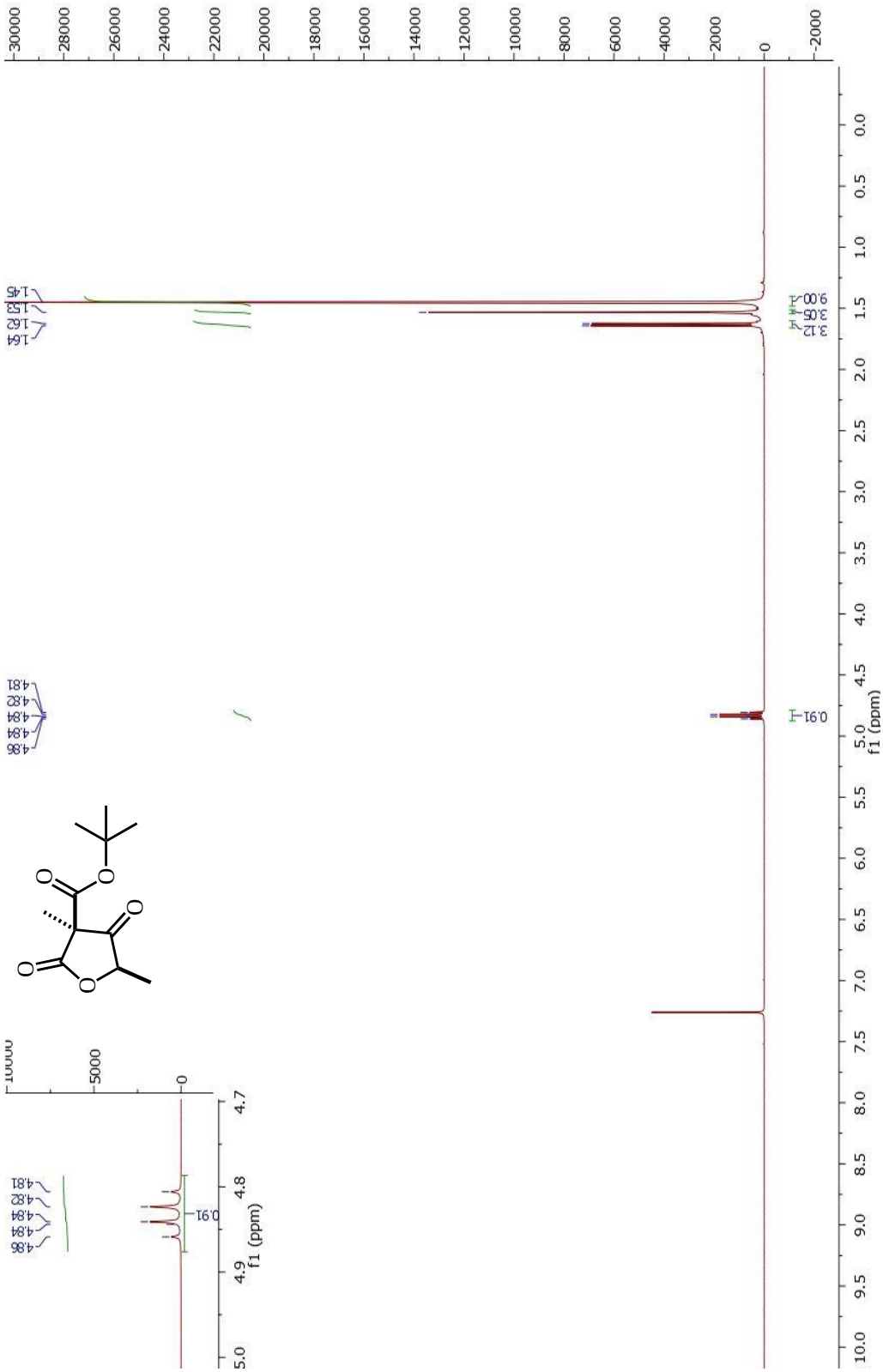

Figure B.47. **^{1}H NMR** (400 MHz, $CDCl_3$) of tetronic acid **2.24**

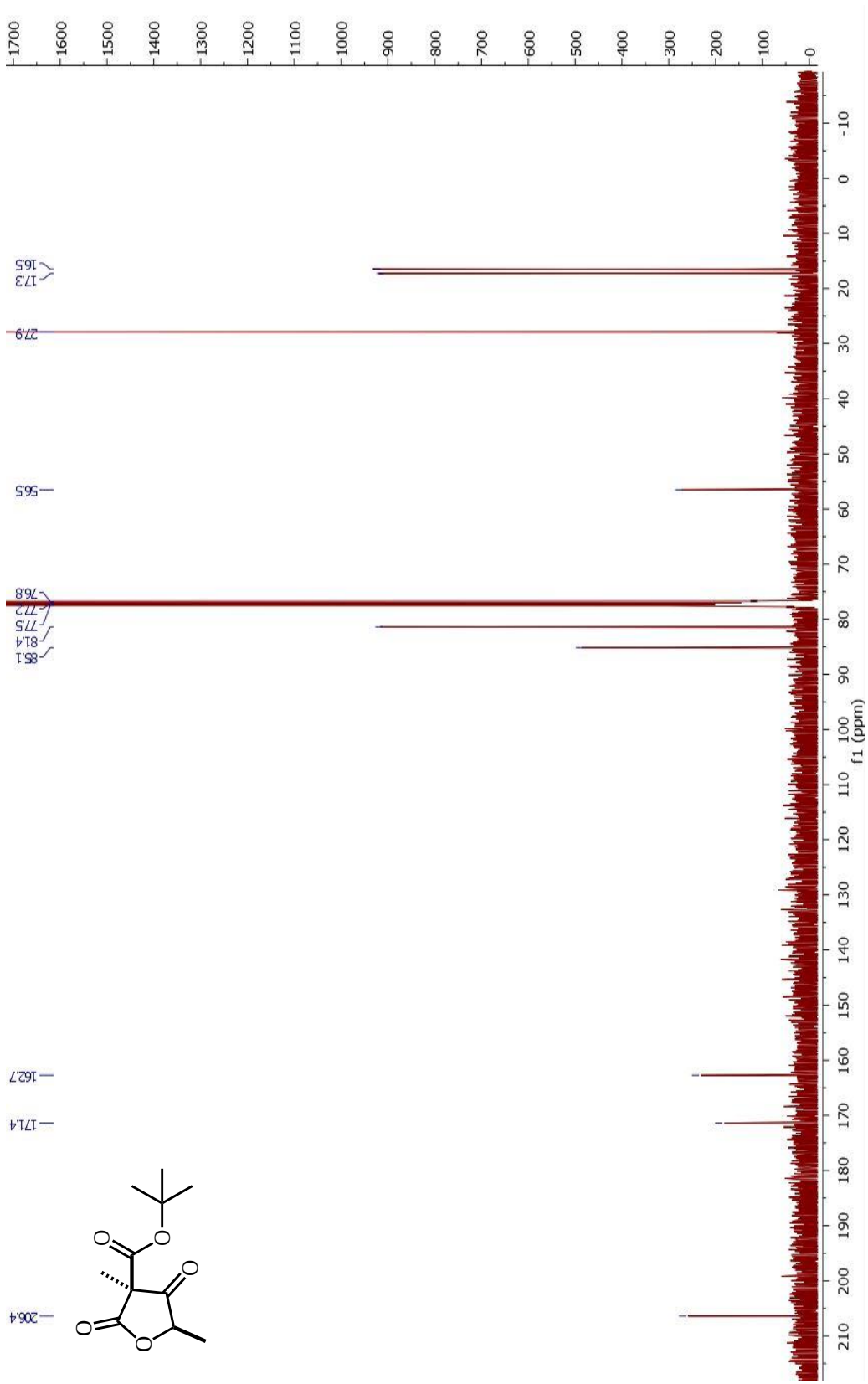

Figure B.48. **^{13}C NMR** (101 MHz, $CDCl_3$) of tetronic acid **2.24**

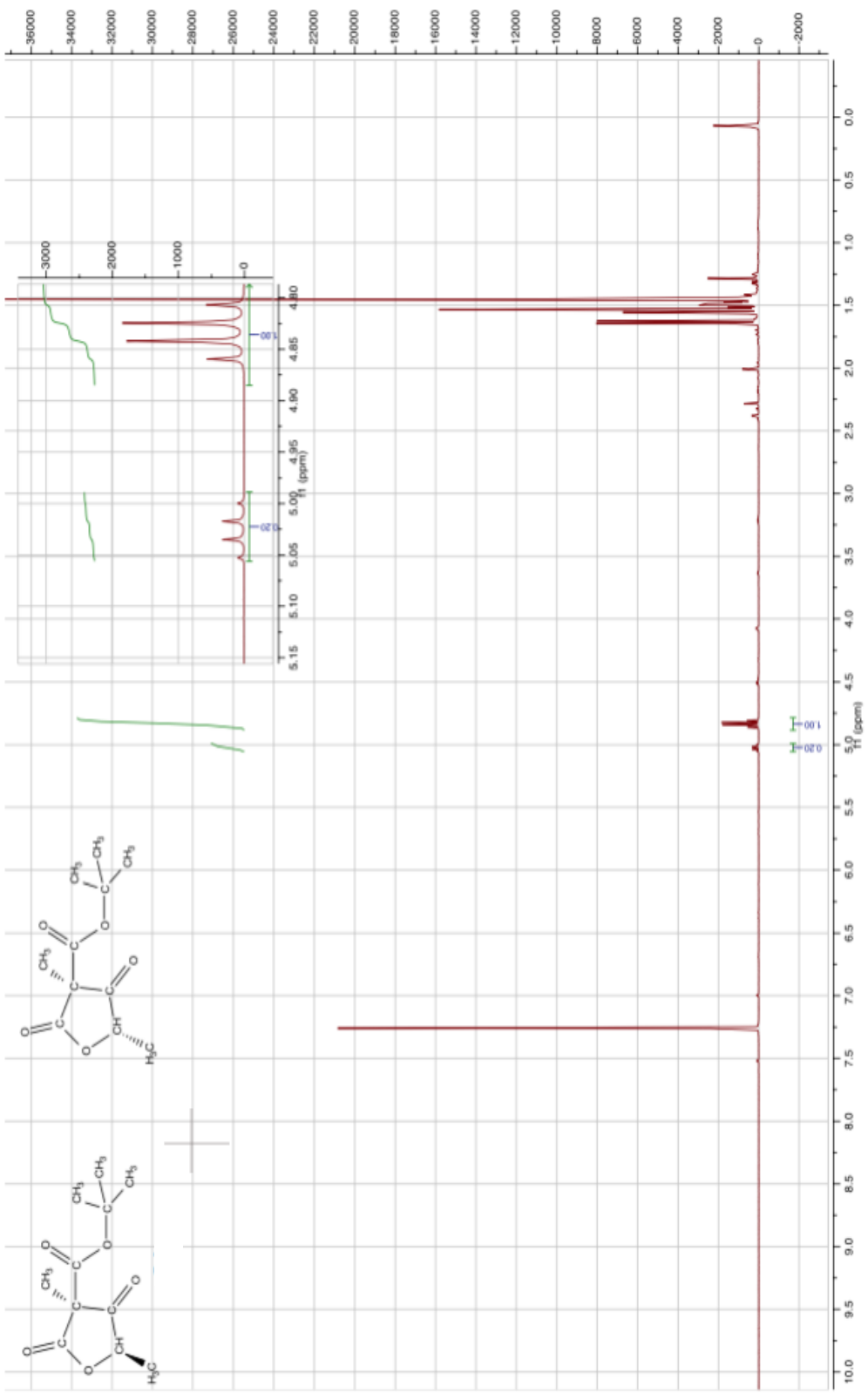

Figure B.49. **^{1}H NMR** (400 MHz, $CDCl_3$) of crude tetronic acids **2.24** & **2.25**

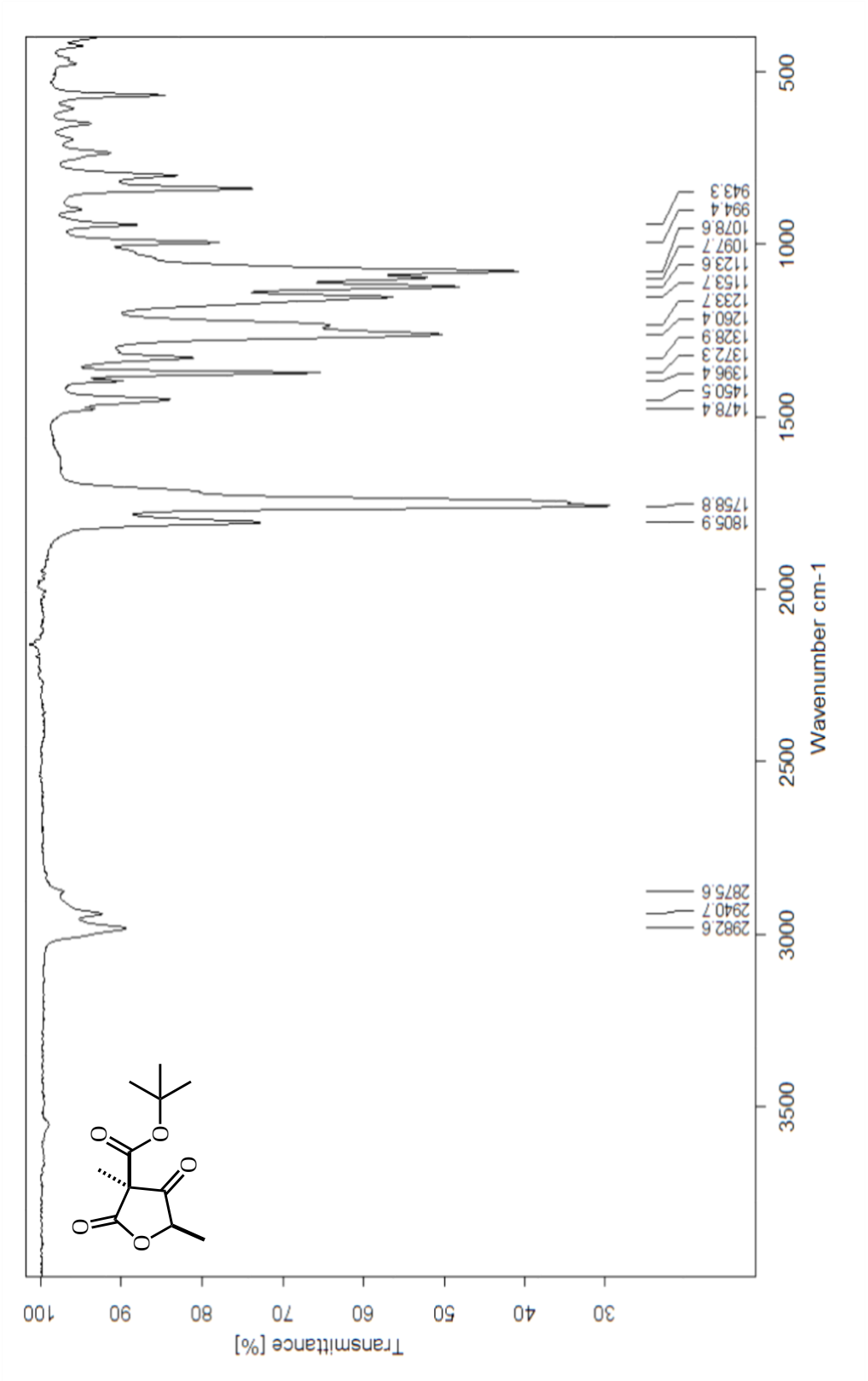

Figure B.50. FTIR Spectrum (neat) of tetronic acid **2.24**

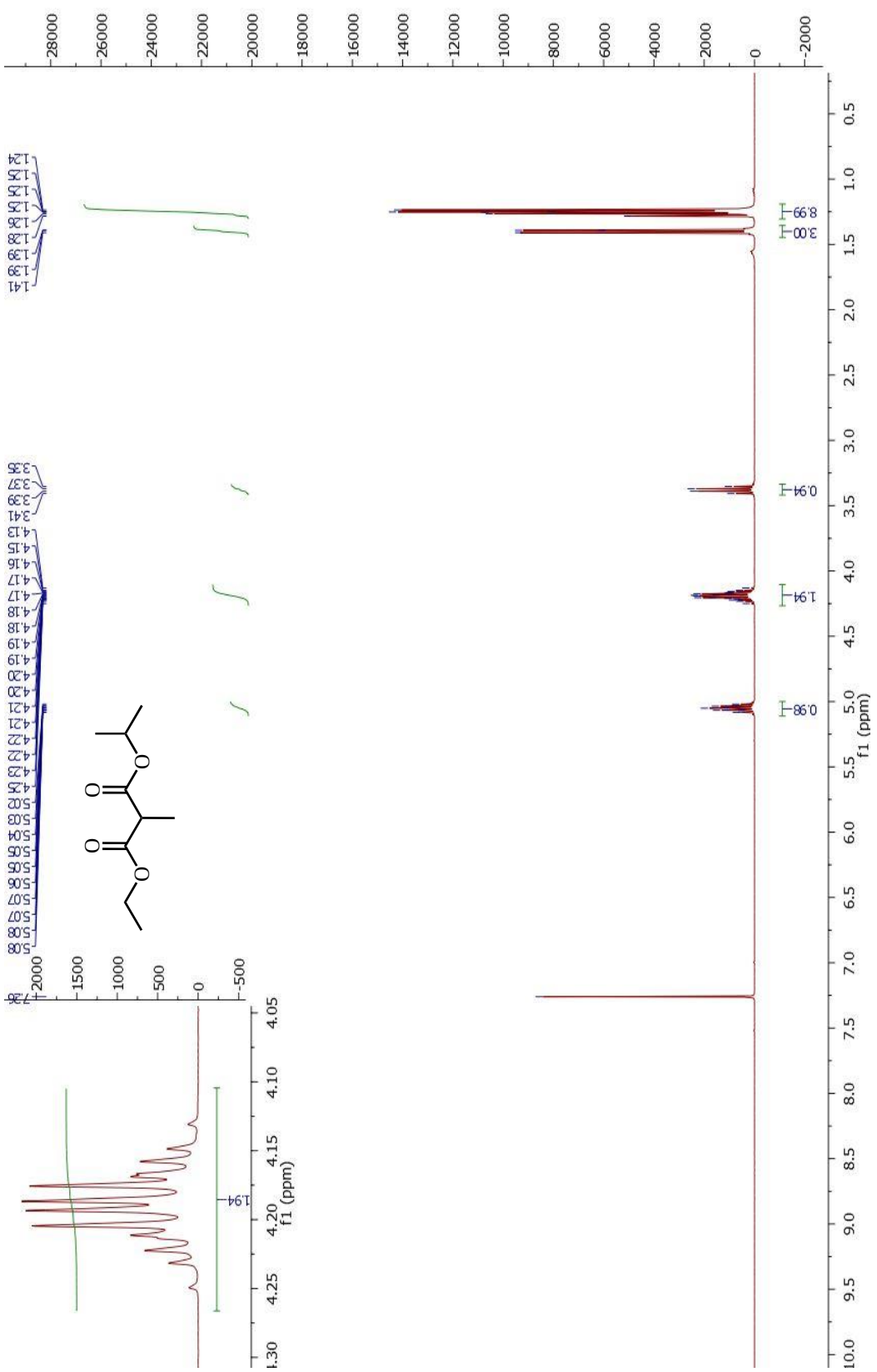

Figure B.51. **^{1}H NMR** (400 MHz, $CDCl_3$) of malonate **2.44**

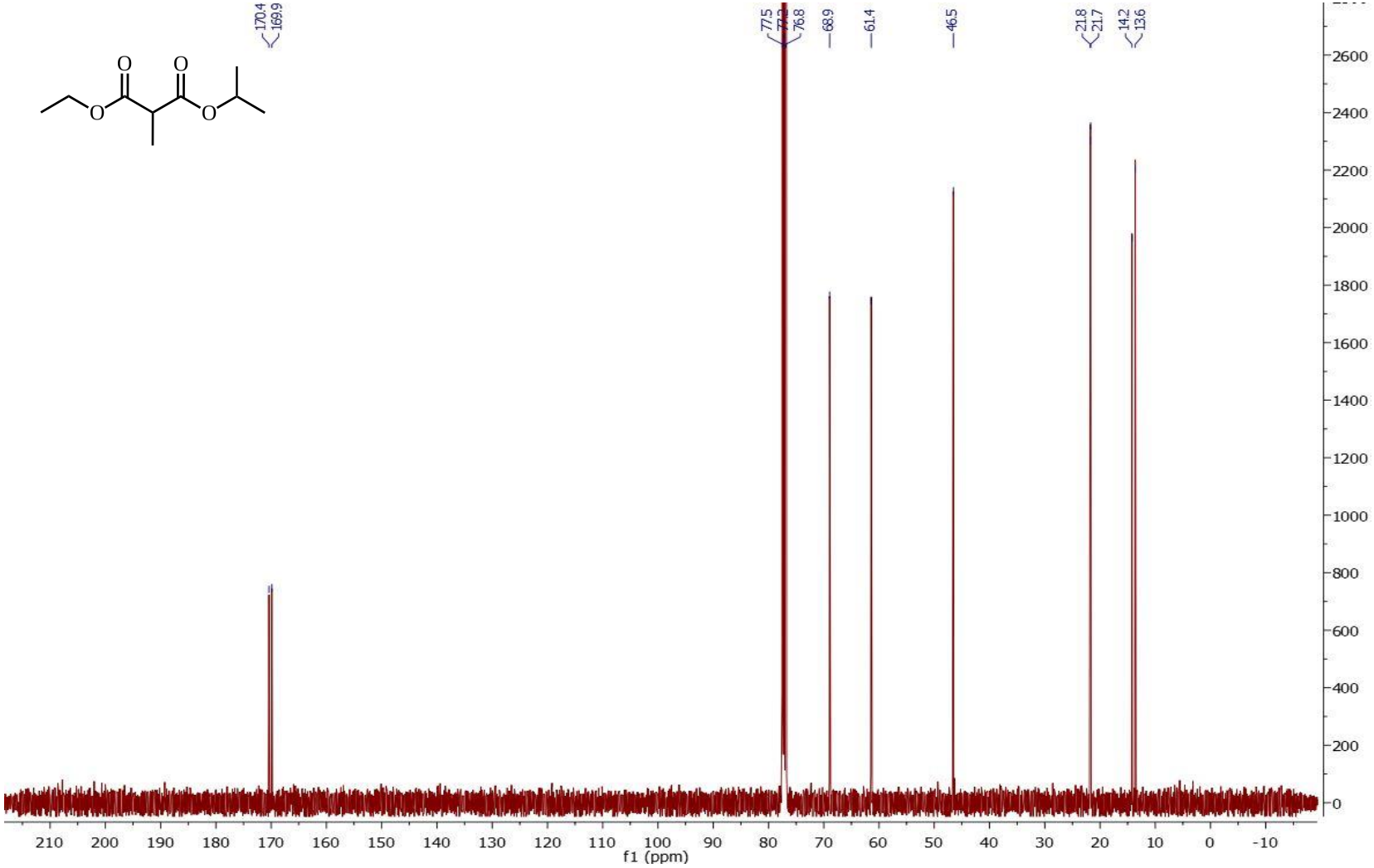

Figure B.52. **^{13}C NMR** (101 MHz, $CDCl_3$) of malonate **2.44**

2.24

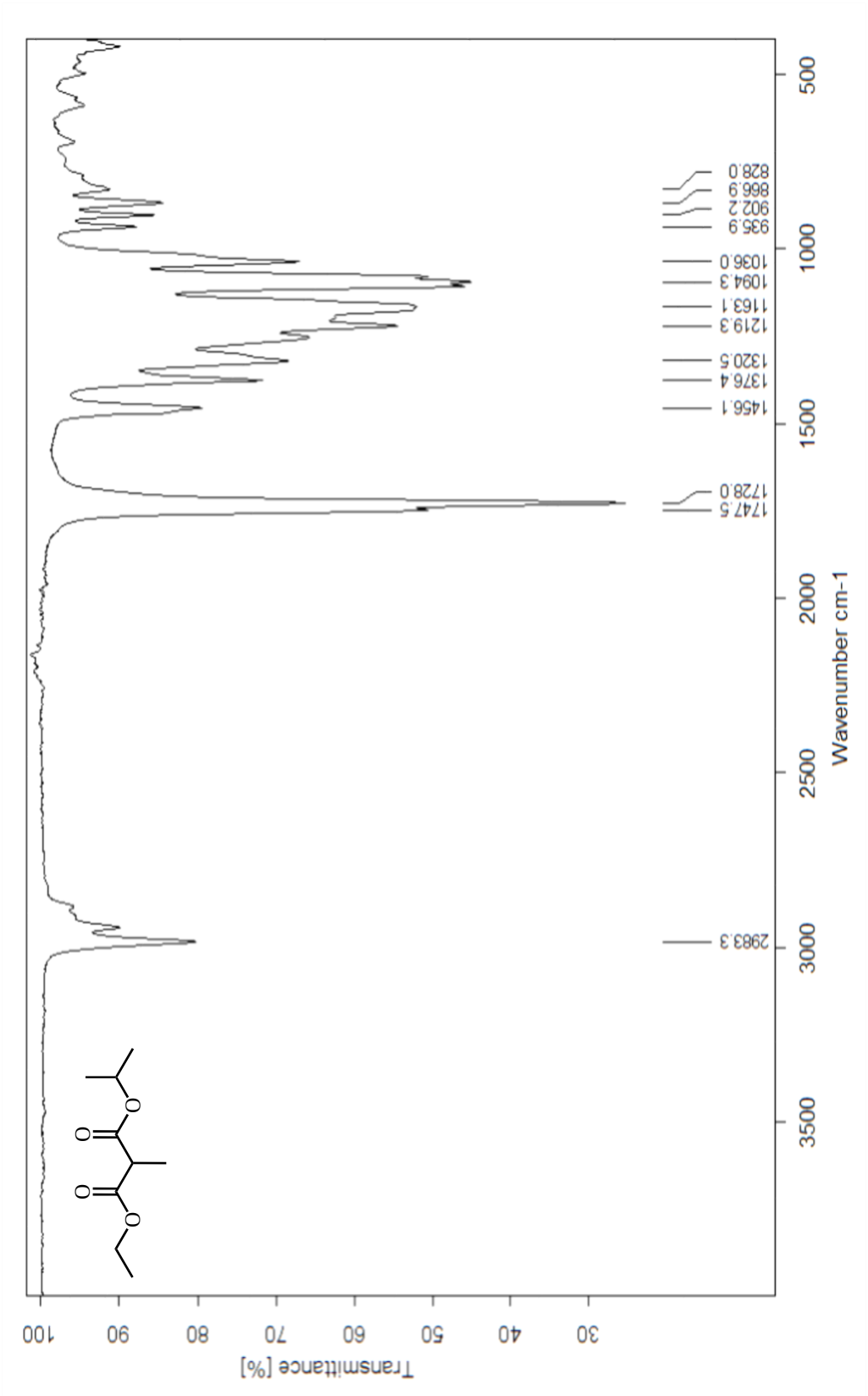

Figure B.53. FTIR Spectrum (neat) of malonate **2.44**

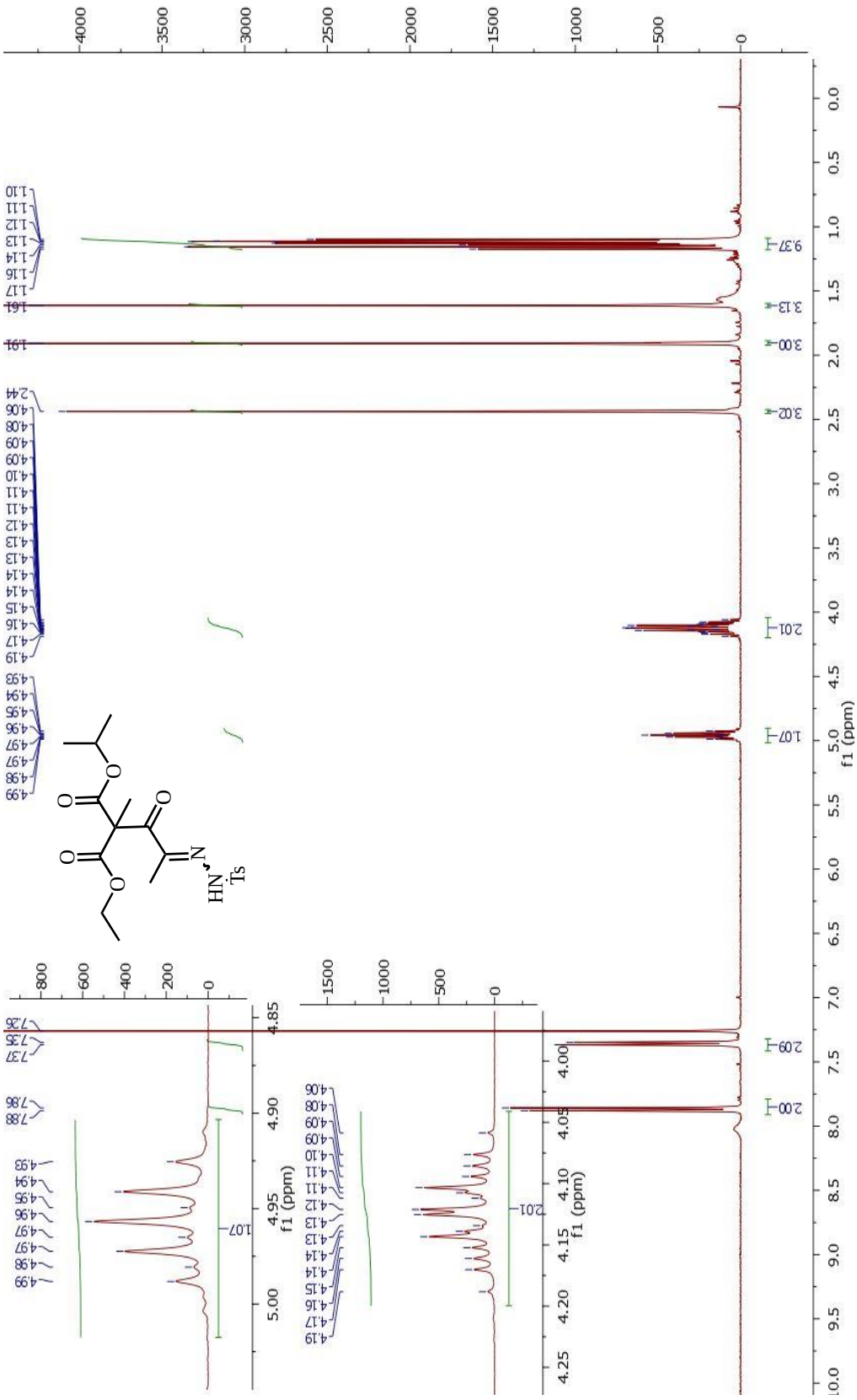

Figure B.54. **^{1}H NMR** (400 MHz, $CDCl_3$) of tosyl hydrazone **2.45**

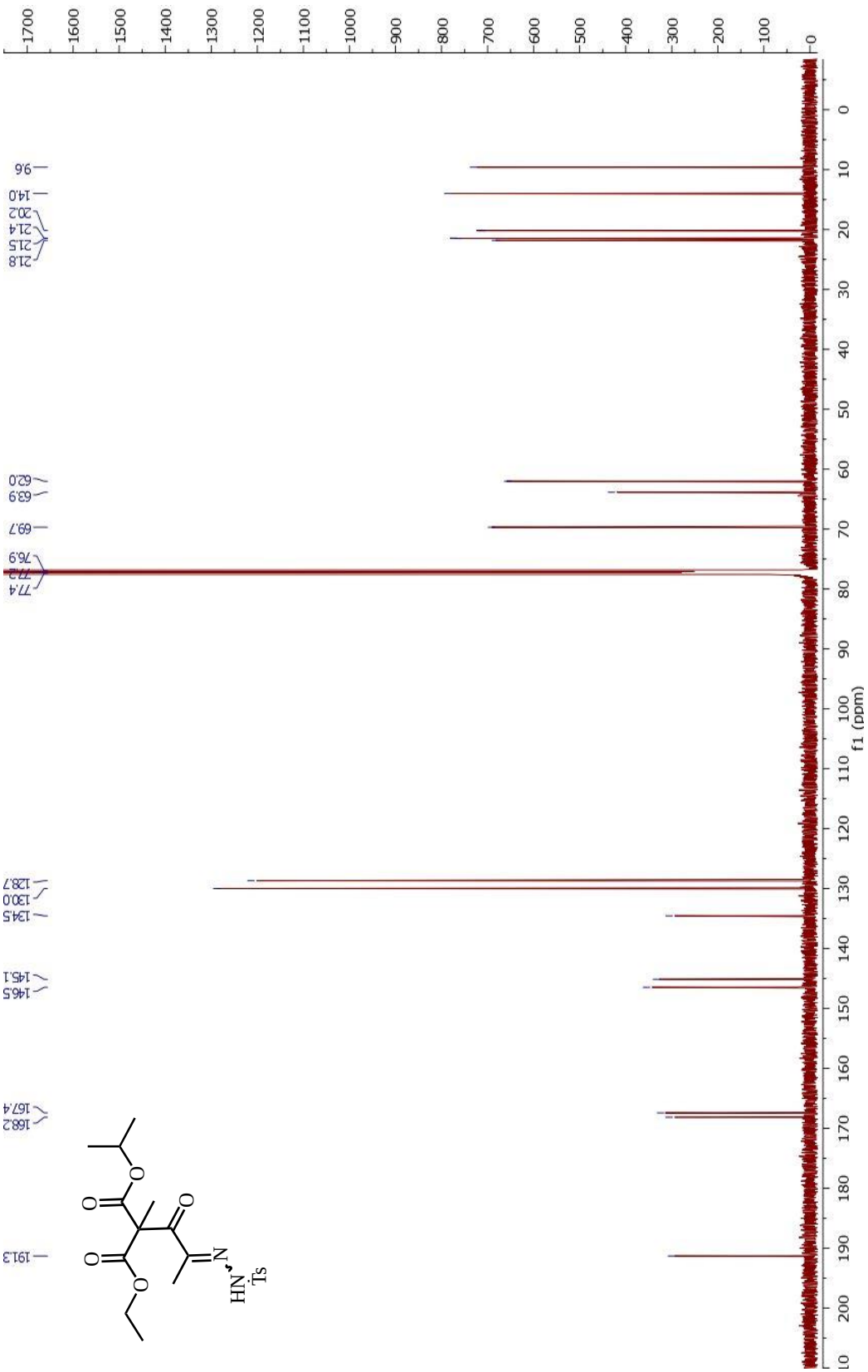

Figure B.55. **^{13}C NMR** (151 MHz, $CDCl_3$) of tosyl hydrazone **2.45**

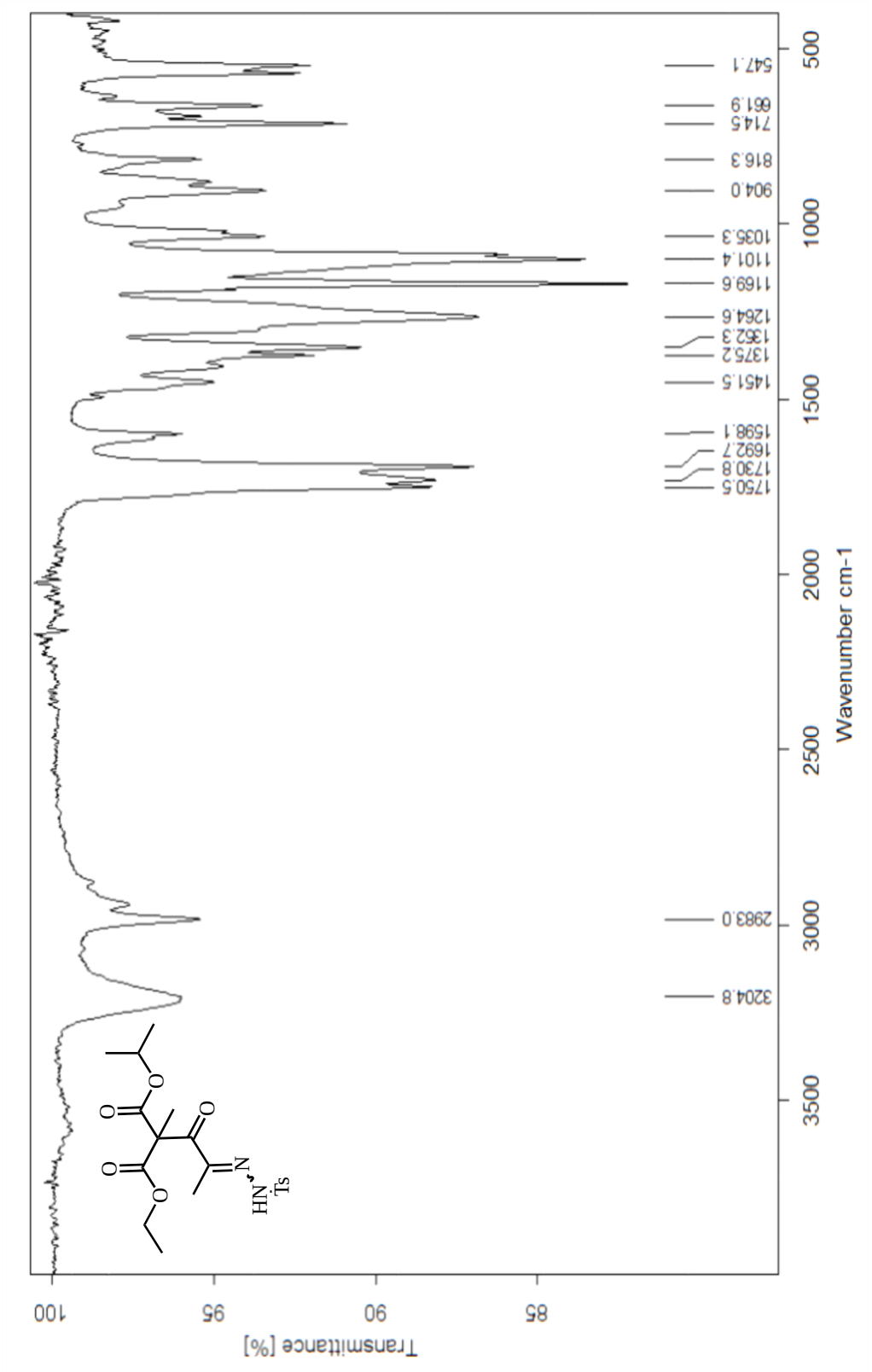

Figure B.56. FTIR Spectrum (neat) of tosyl hydrazone **2.45**

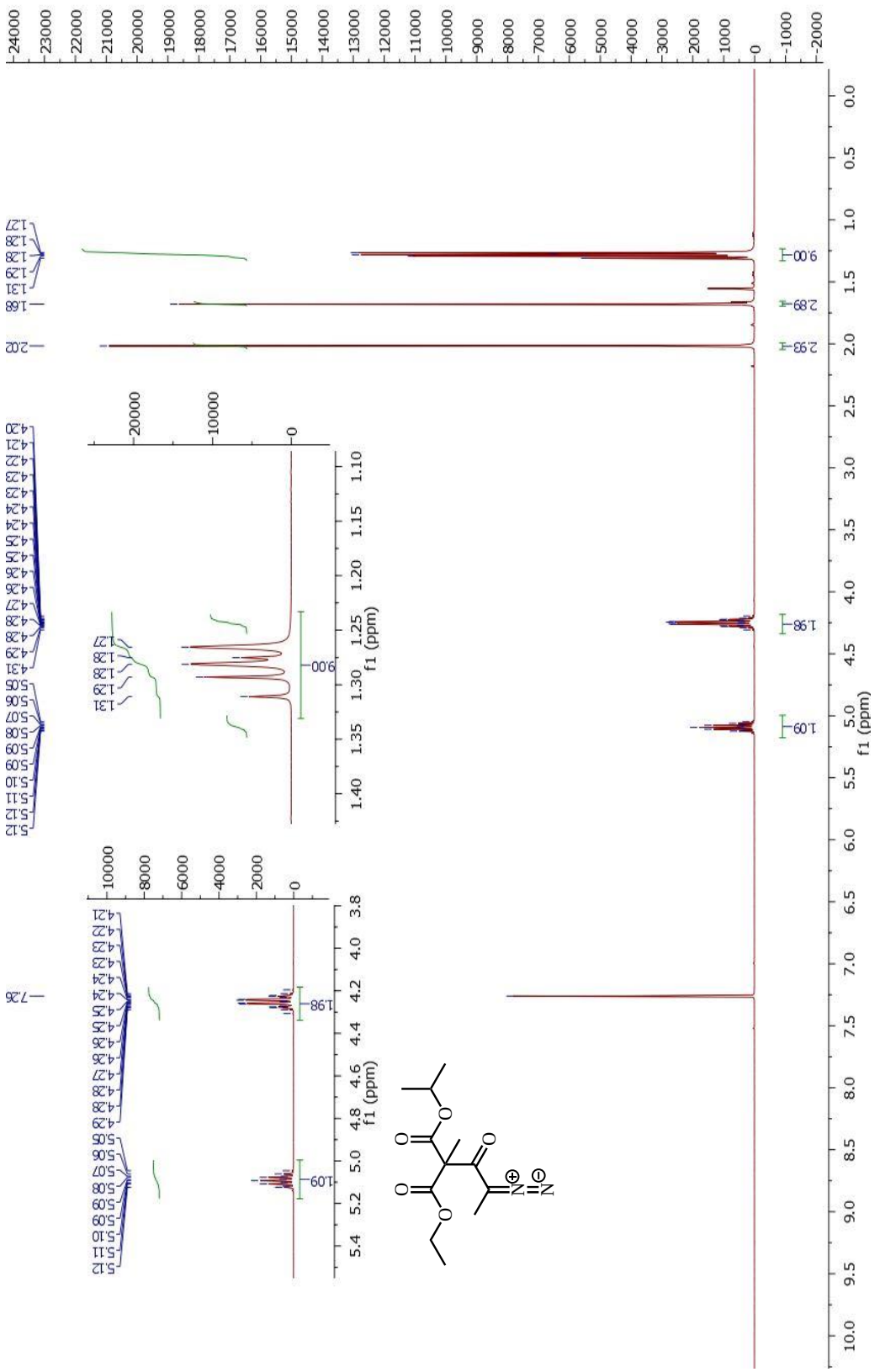

Figure B.57. **^{1}H NMR** (400 MHz, $CDCl_3$) of diazomalonate **2.10**

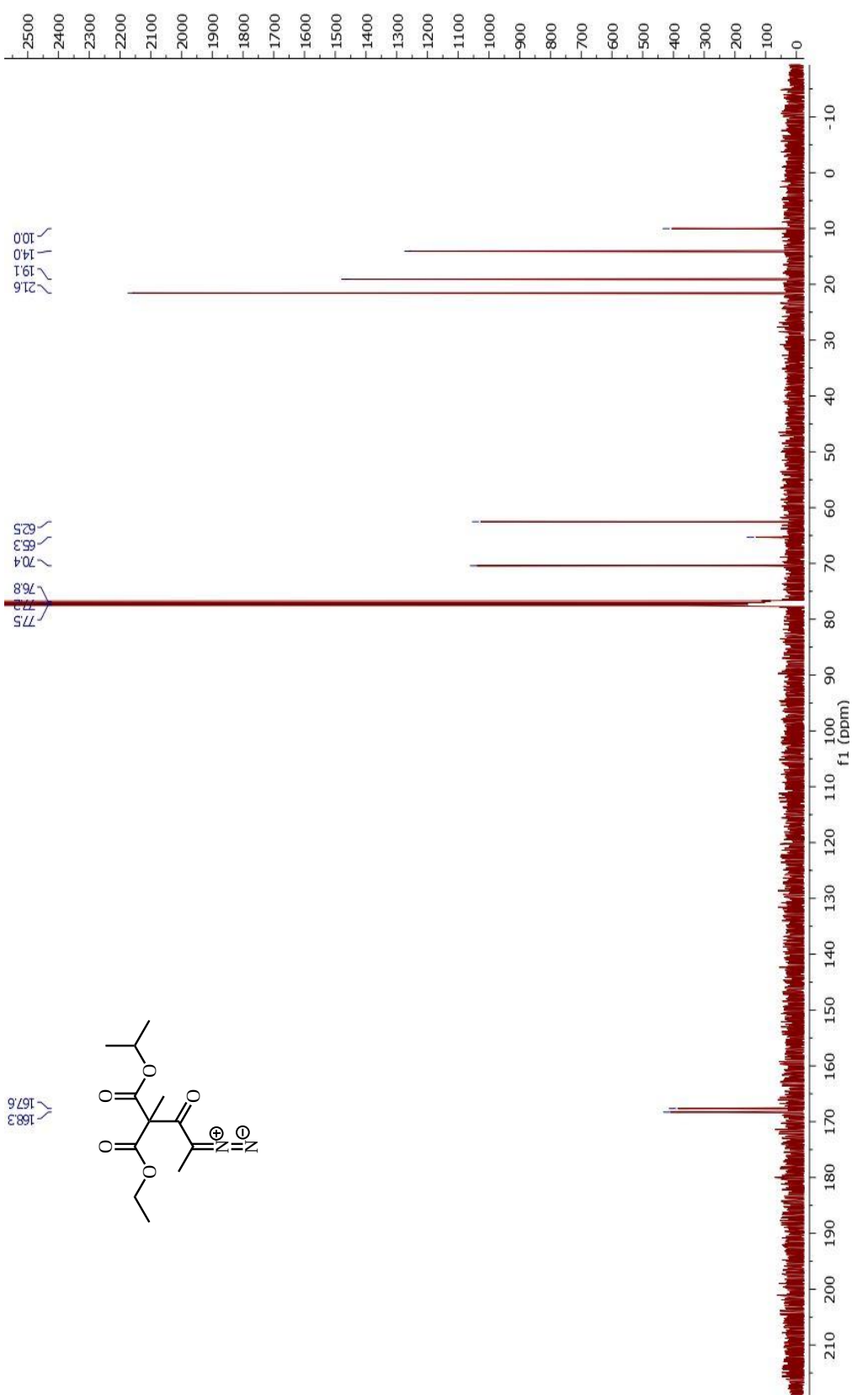

Figure B.58. **^{13}C NMR** (101 MHz, $CDCl_3$) of diazomalonate **2.10**

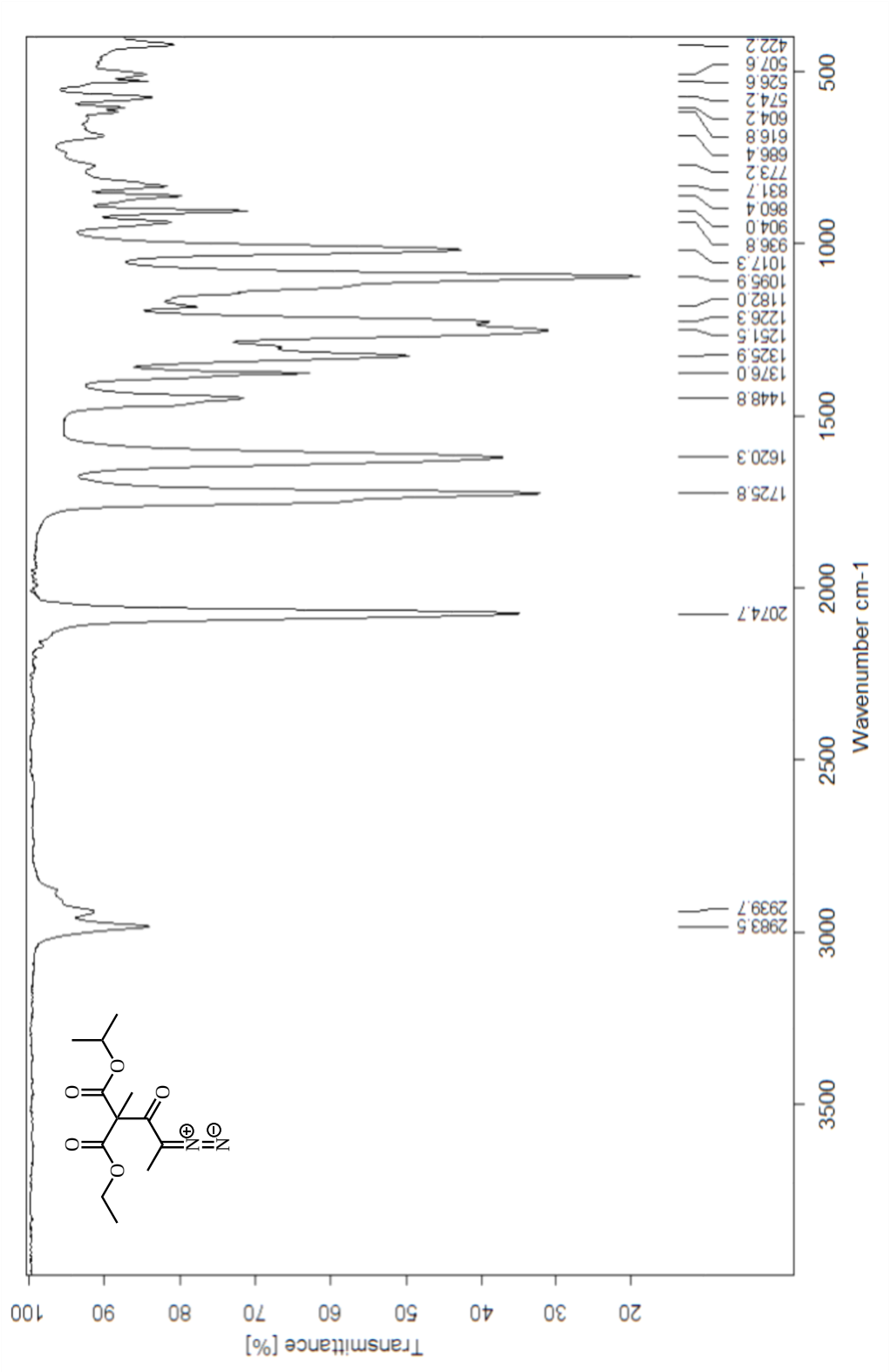

Figure B.59. FTIR Spectrum (neat) of diazomalonate **2.10**

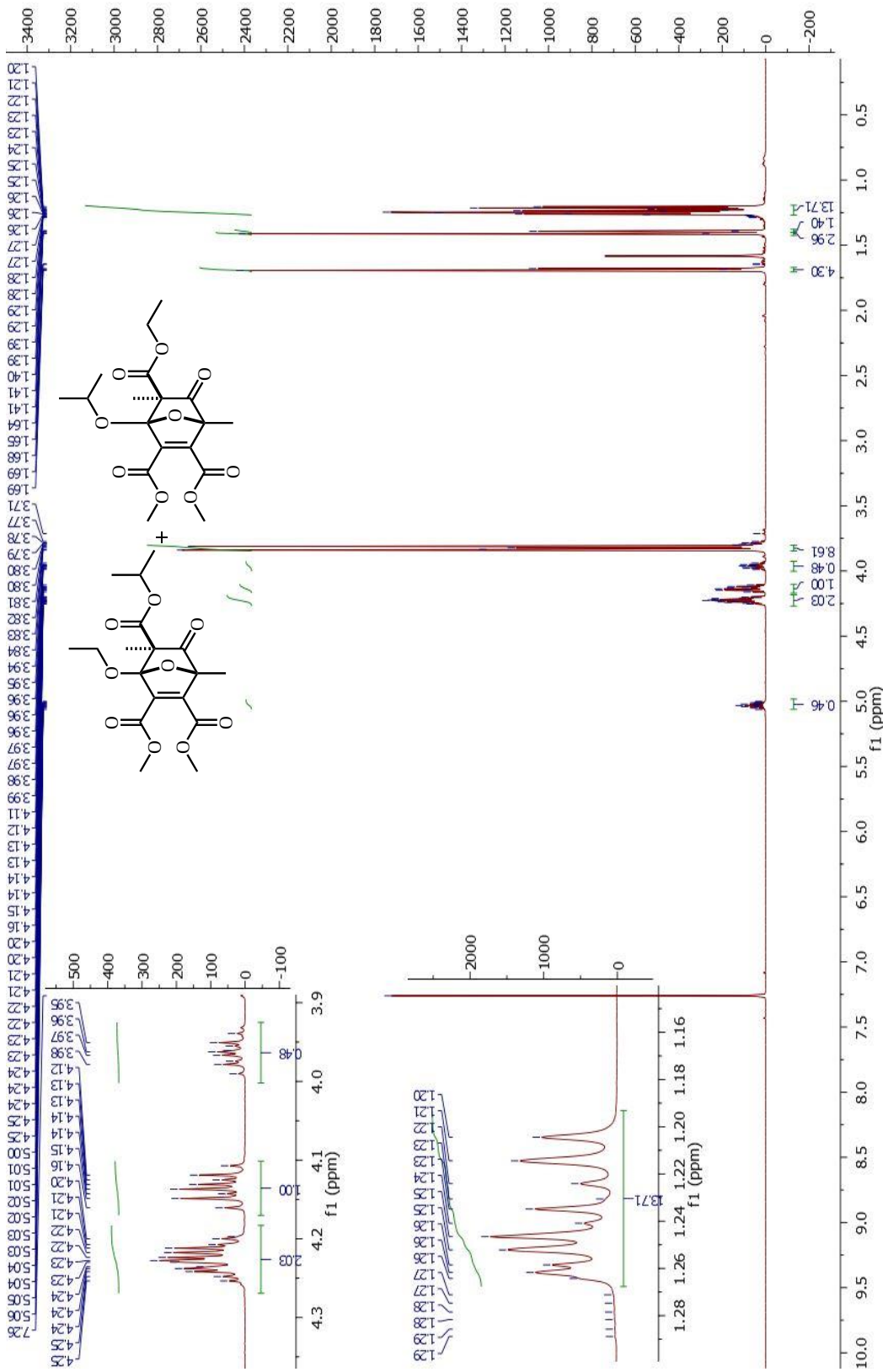

Figure B.60. **^{1}H NMR** (600 MHz, $CDCl_3$) of oxabicycles **2.31** & **2.32**

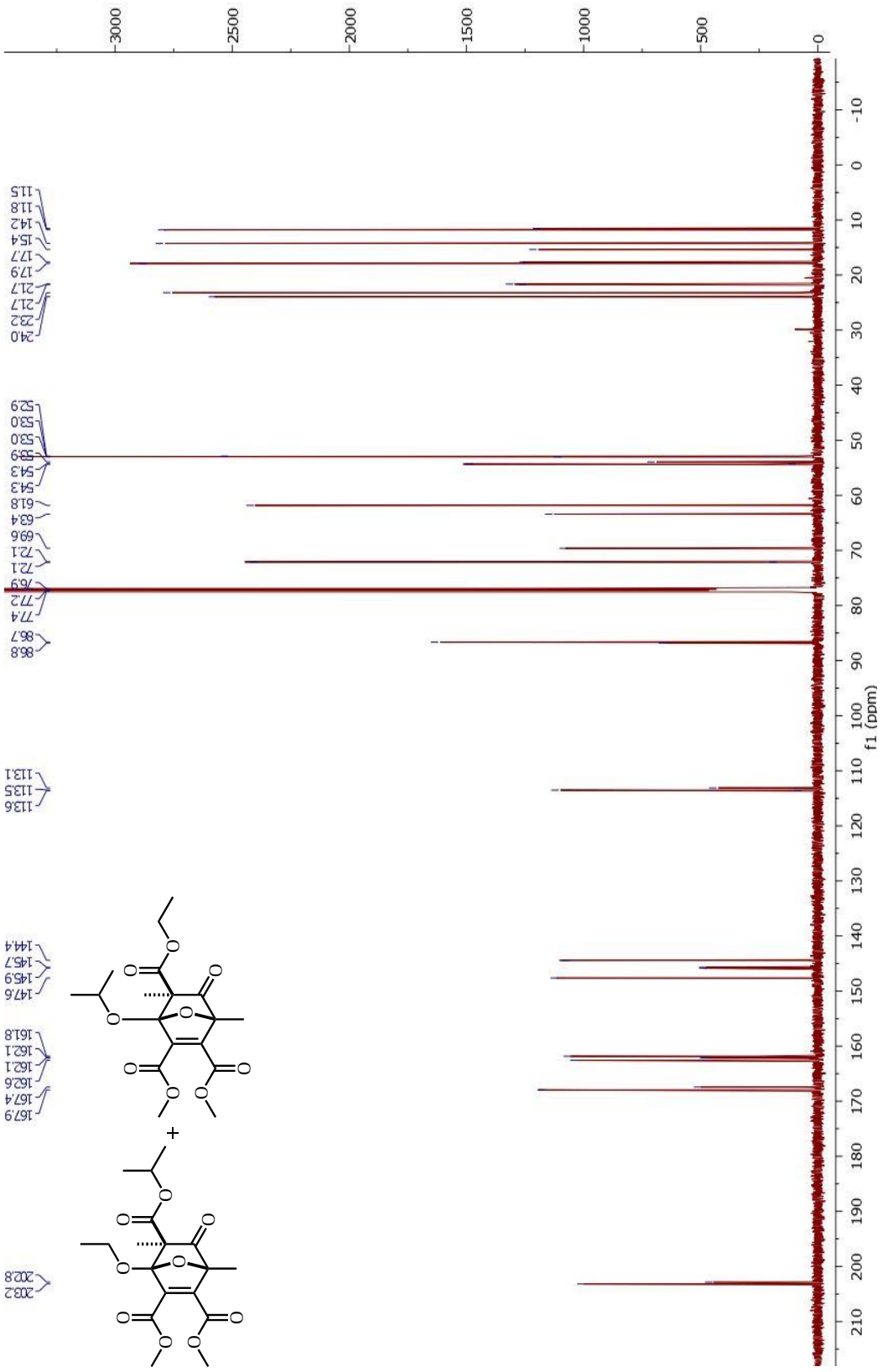

Figure B.61. **^{13}C NMR** (151 MHz, $CDCl_3$) of oxabicycles **2.31** & **2.32**

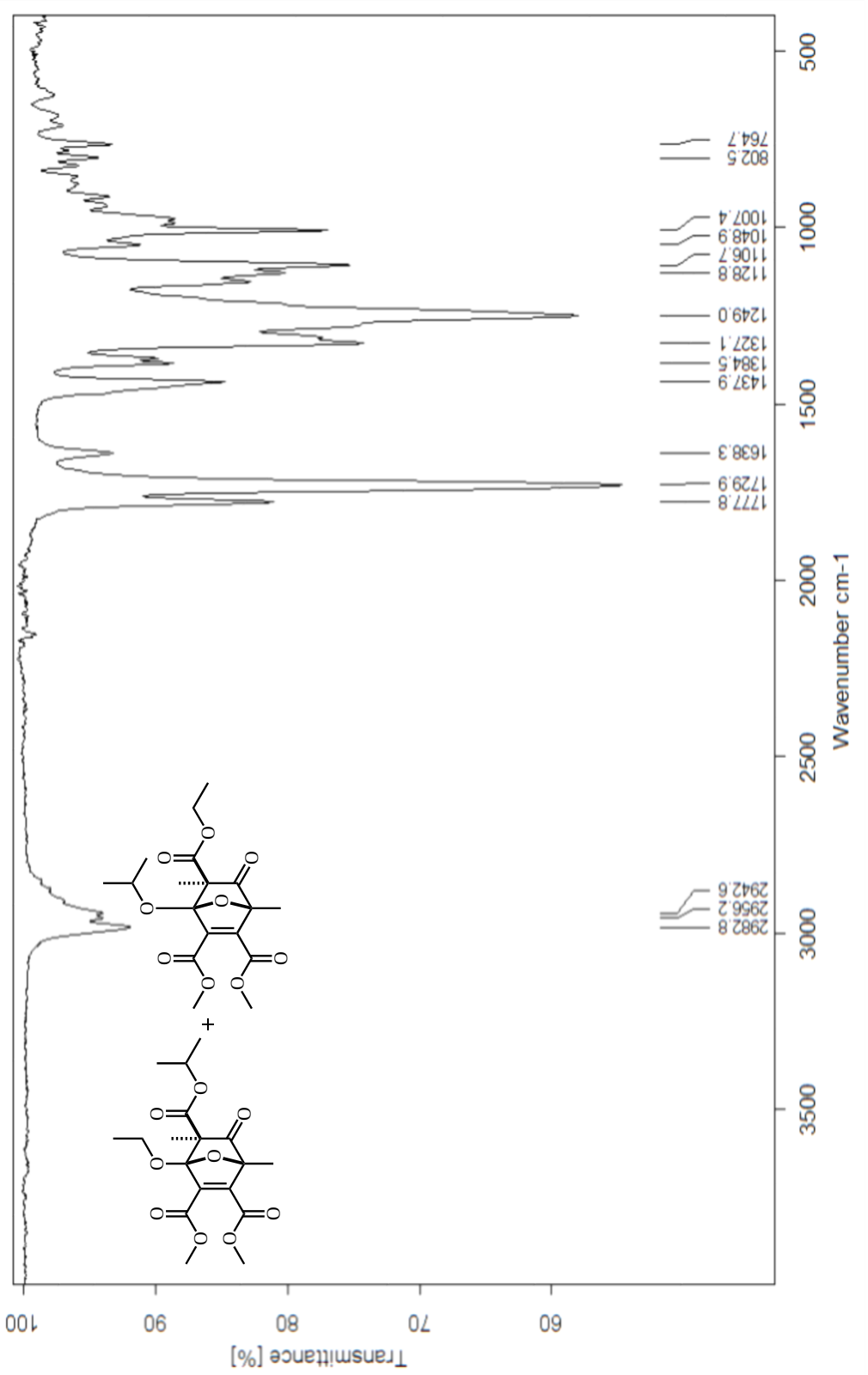

Figure B.62. FTIR Spectrum (neat) of oxabicycles **2.31** & **2.32**

APPENDIX C

Spectral Data for Chapter Three

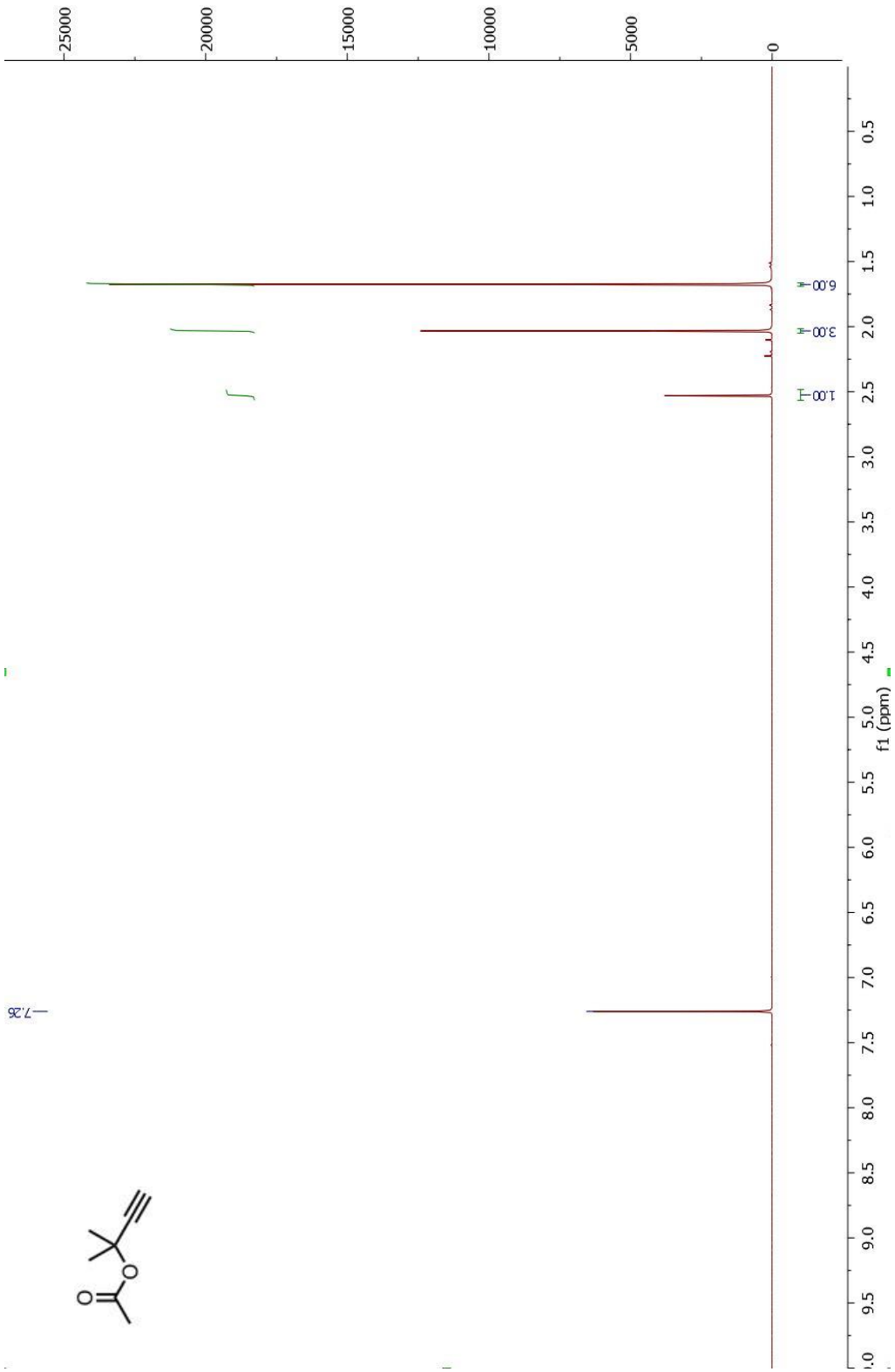

Figure C.01. **^{1}H NMR** (400 MHz, $CDCl_3$) of propargyl acetate **3.111**

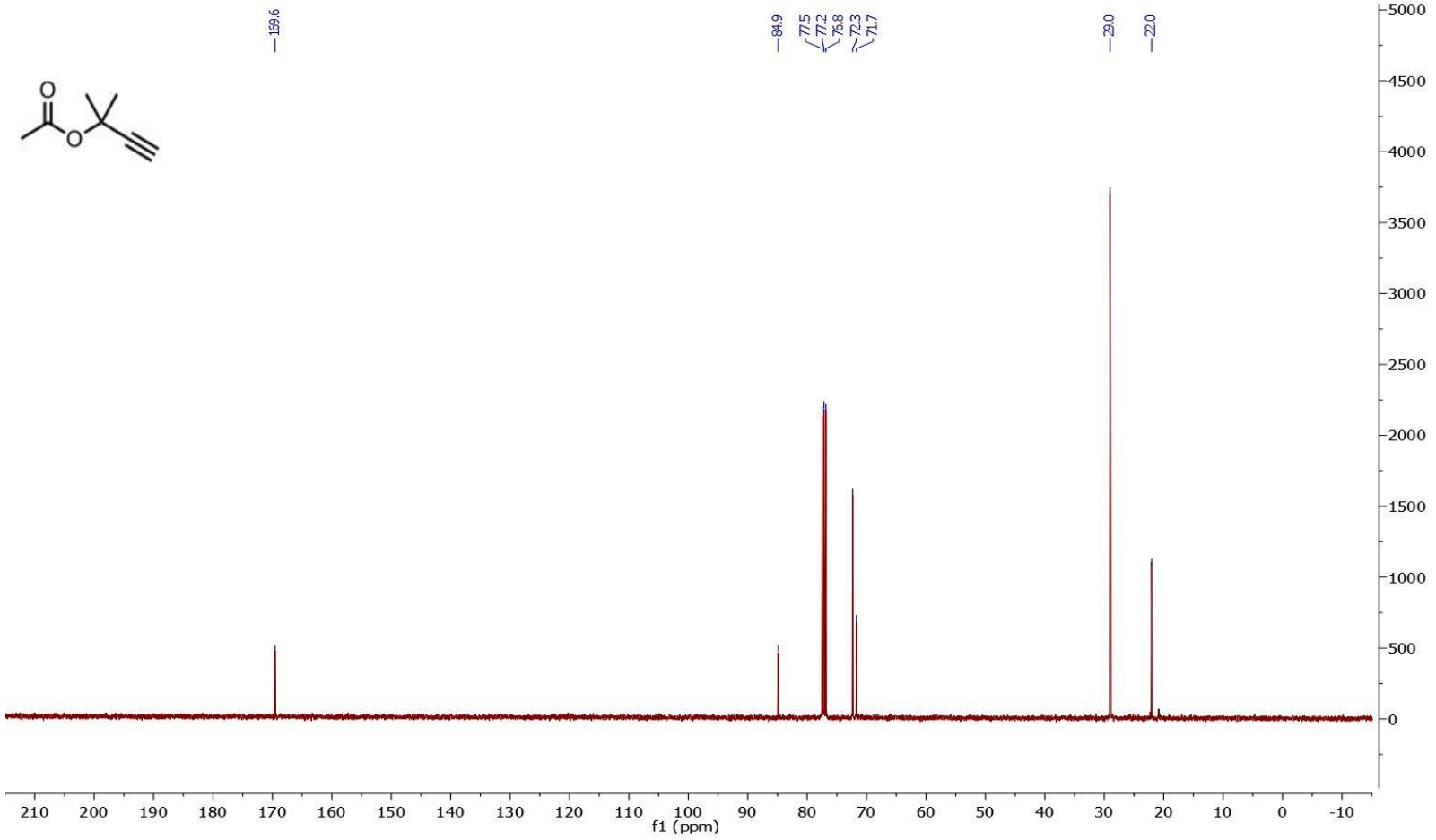

Figure C.02. **^{13}C NMR** (101 MHz, $CDCl_3$) of propargyl acetate **3.111**

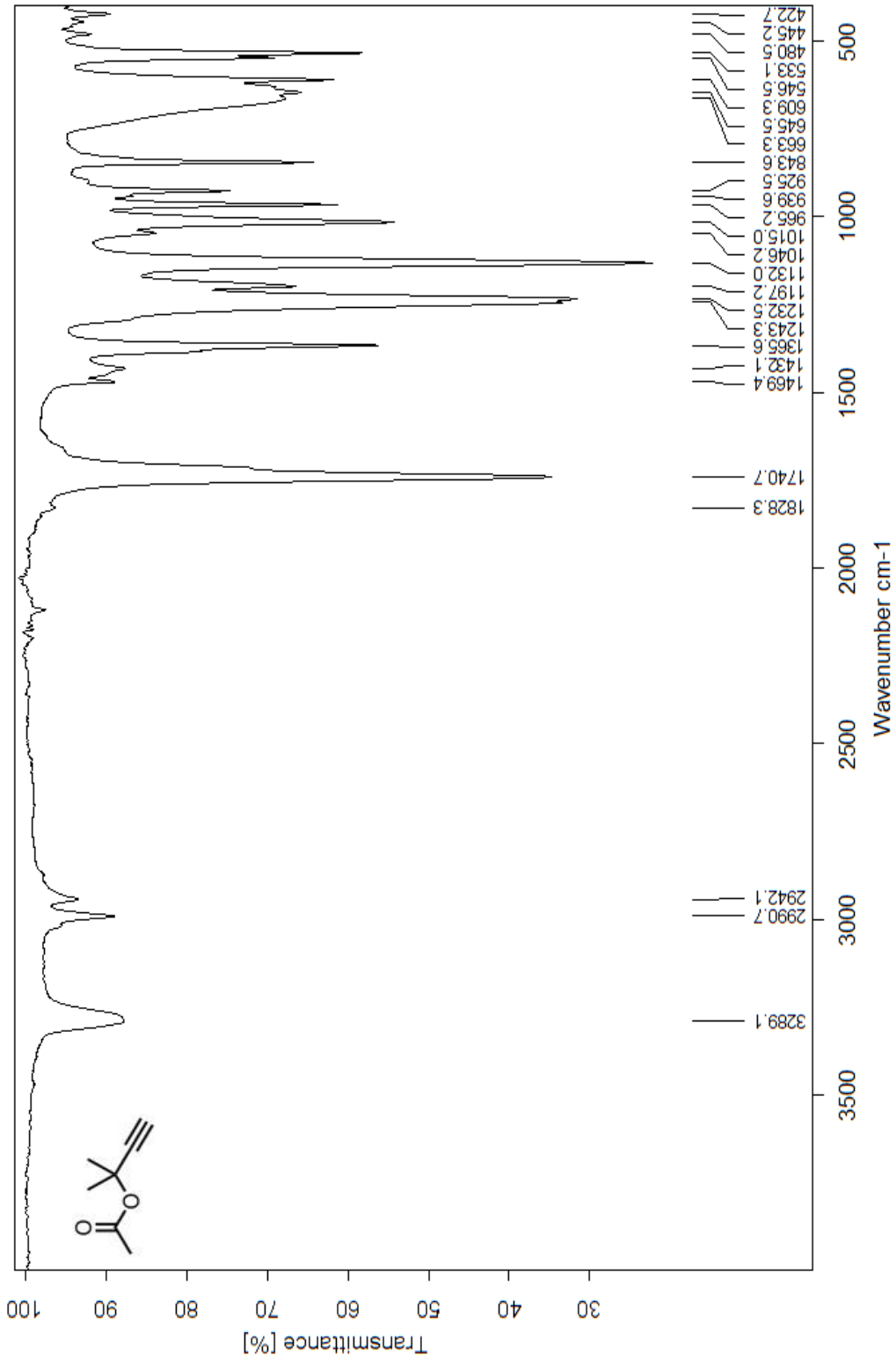

Figure C.03. FTIR Spectrum (neat) of propargyl acetate **3.111**

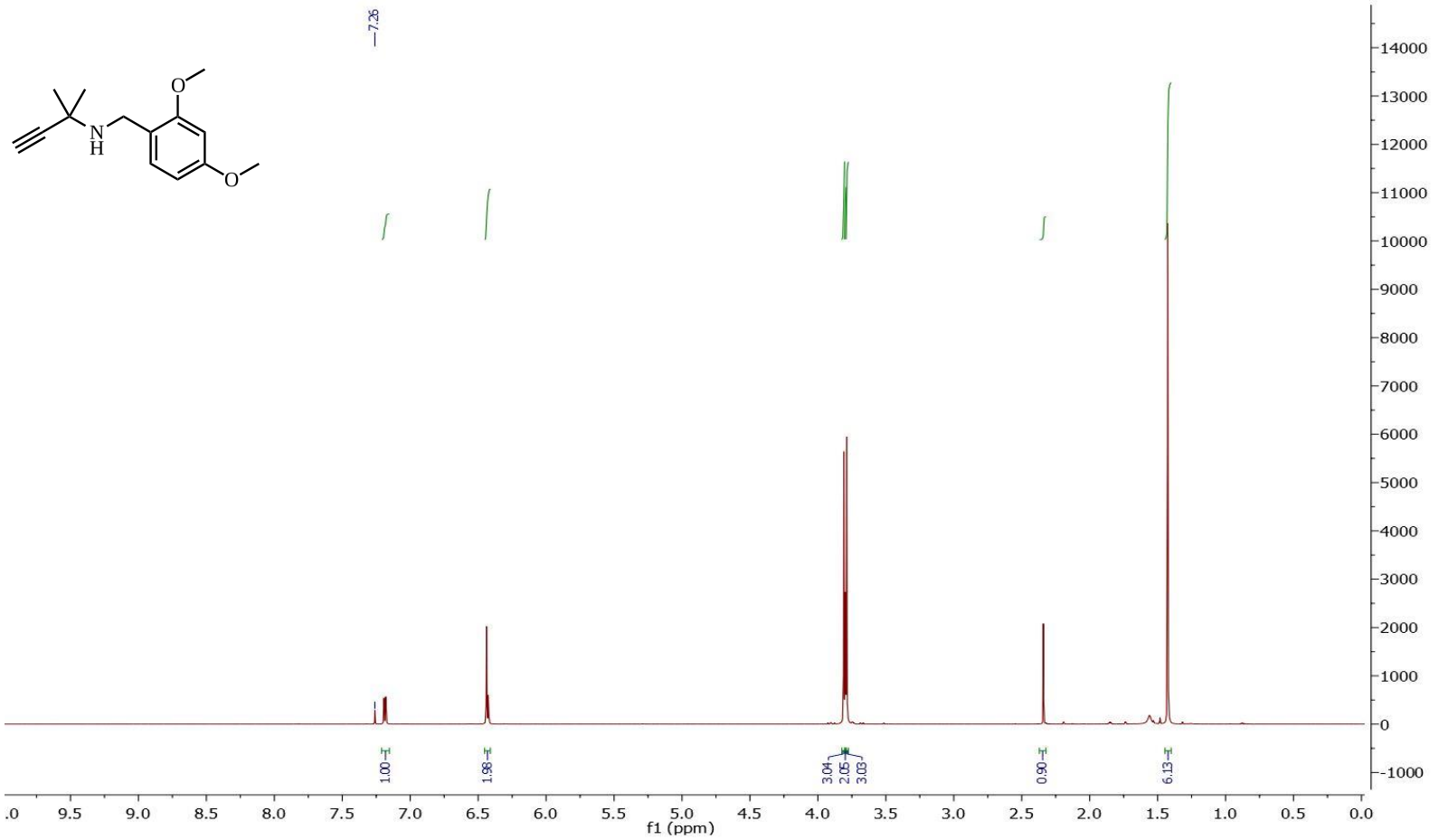

Figure C.04. **^{1}H NMR** (600 MHz, $CDCl_3$) of propargyl amine **3.20**

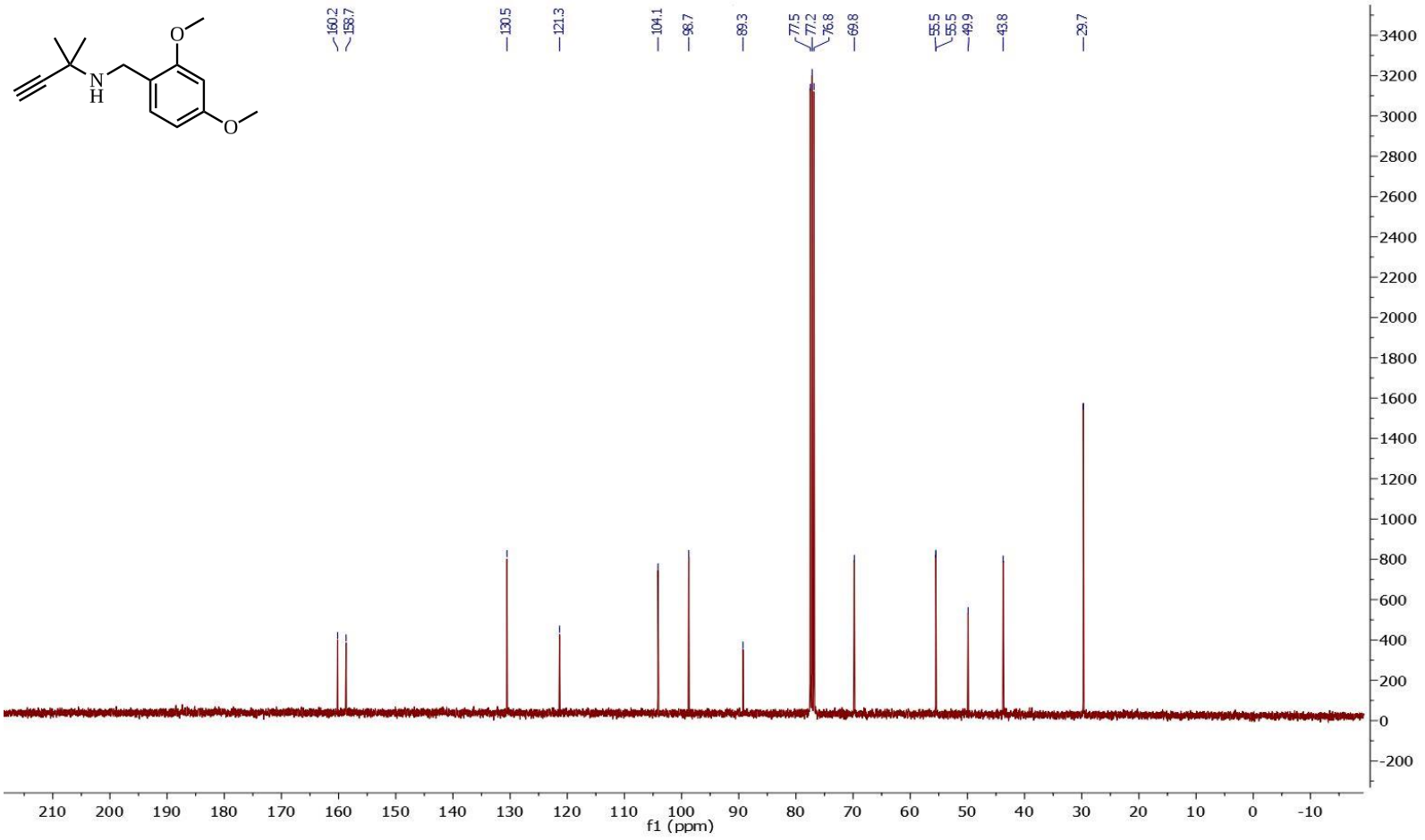

Figure C.05. **^{13}C NMR** (101 MHz, $CDCl_3$) of propargyl amine **3.20**

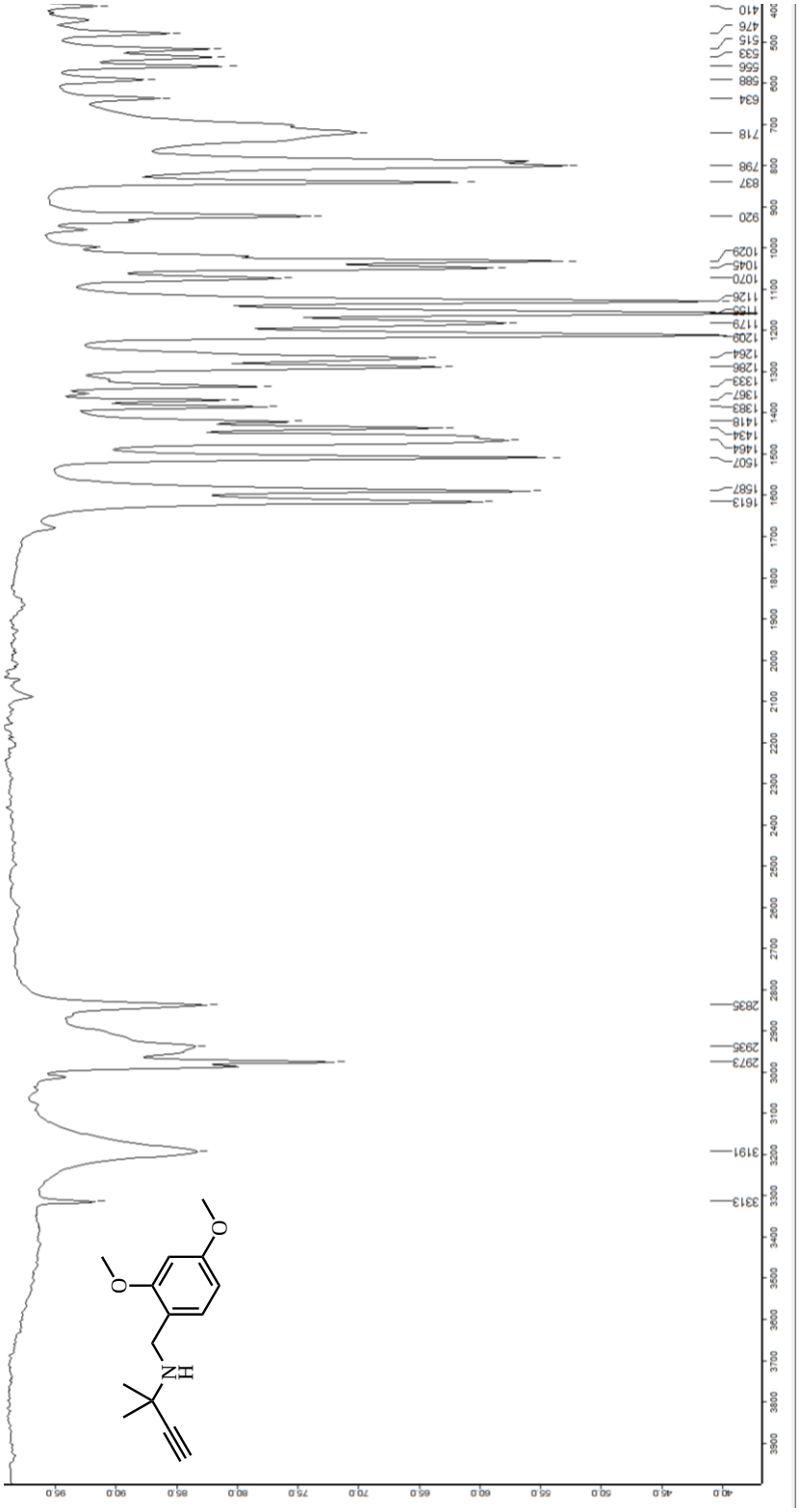

Figure C.06. FTIR Spectrum (neat) of propargyl amine **3.20**

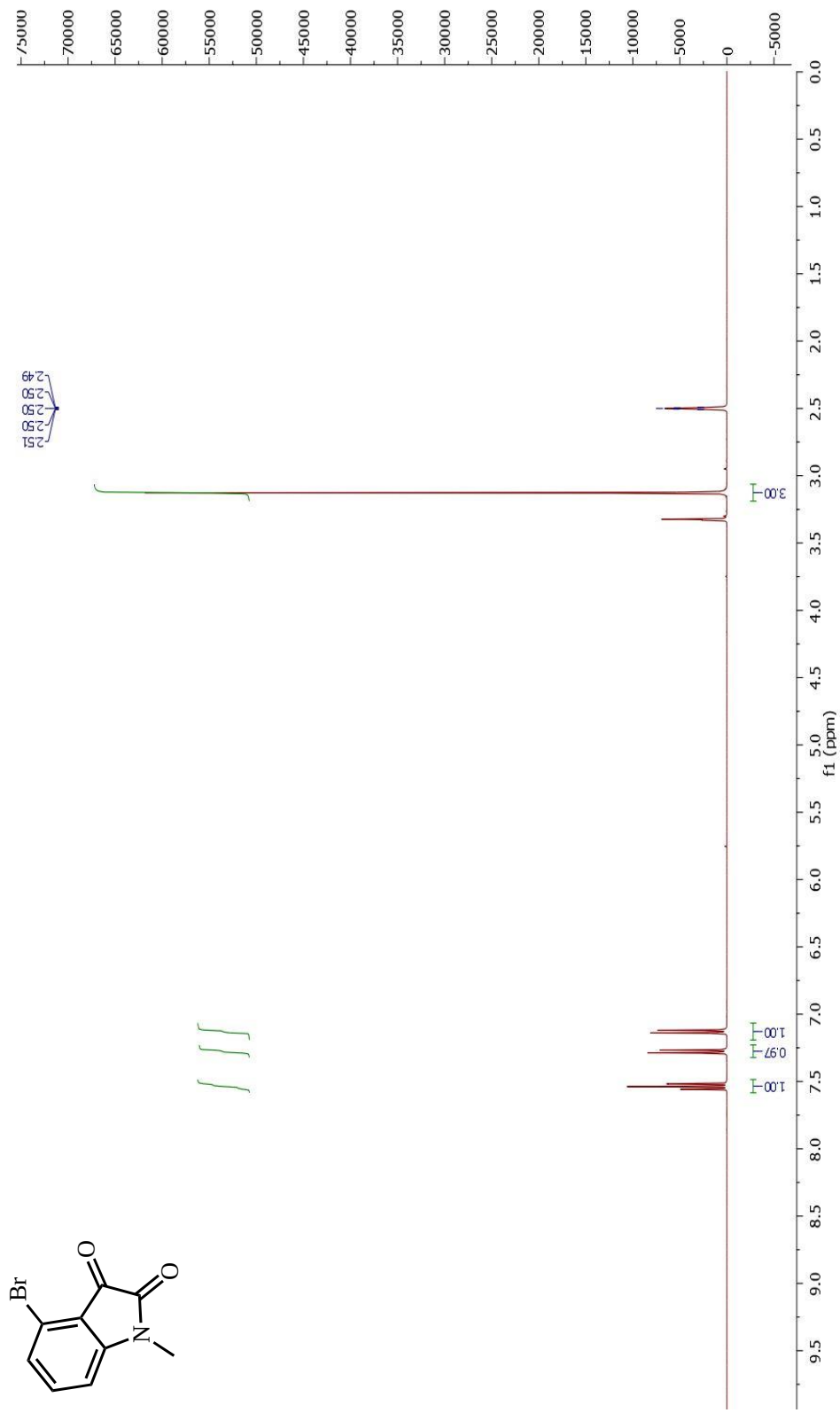

Figure C.07. **^{1}H NMR** (400 MHz, DMSO-*d6*) of isatin **3.11**

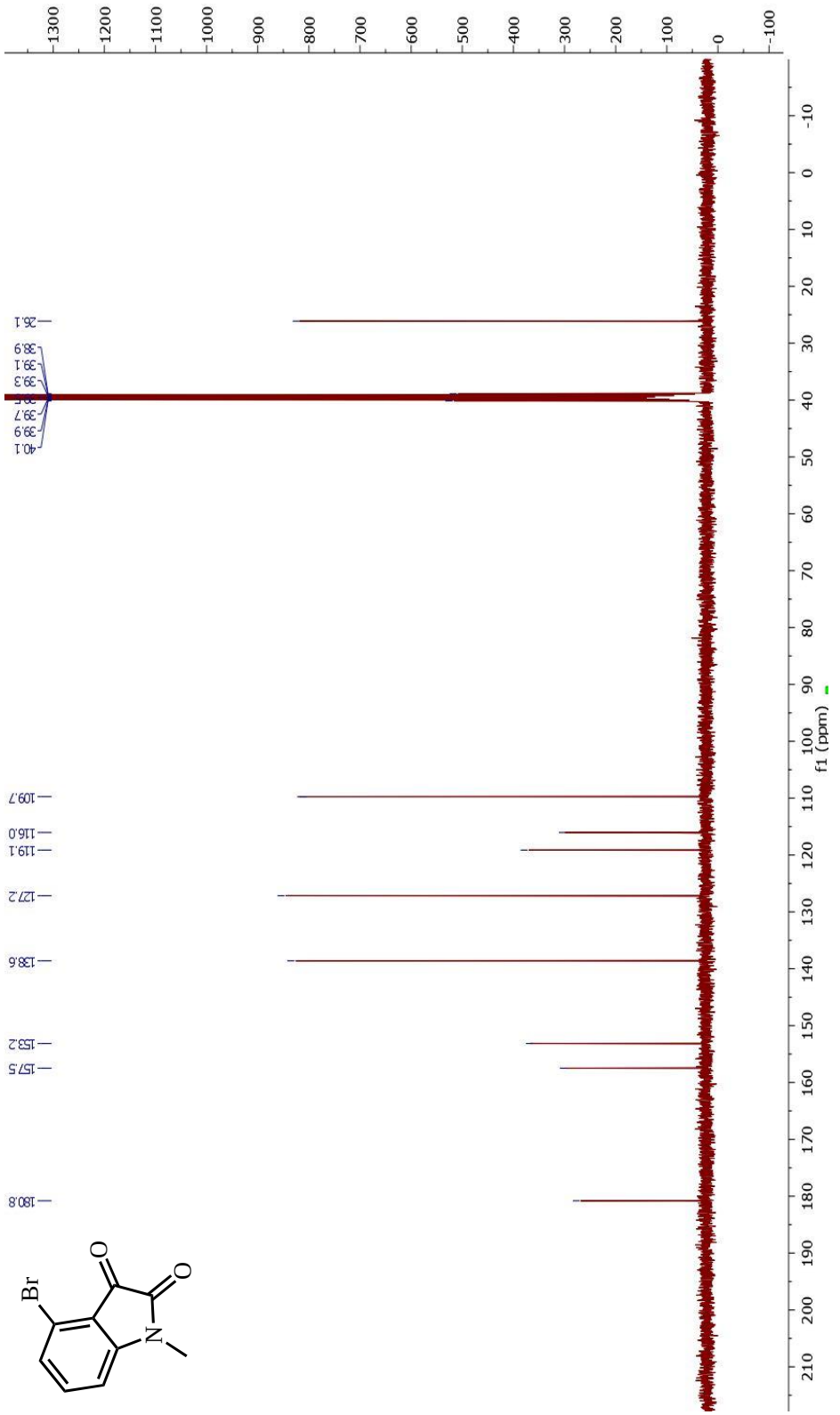

Figure C.08. **^{13}C NMR** (101 MHz, DMSO-*d6*) of isatin **3.11**

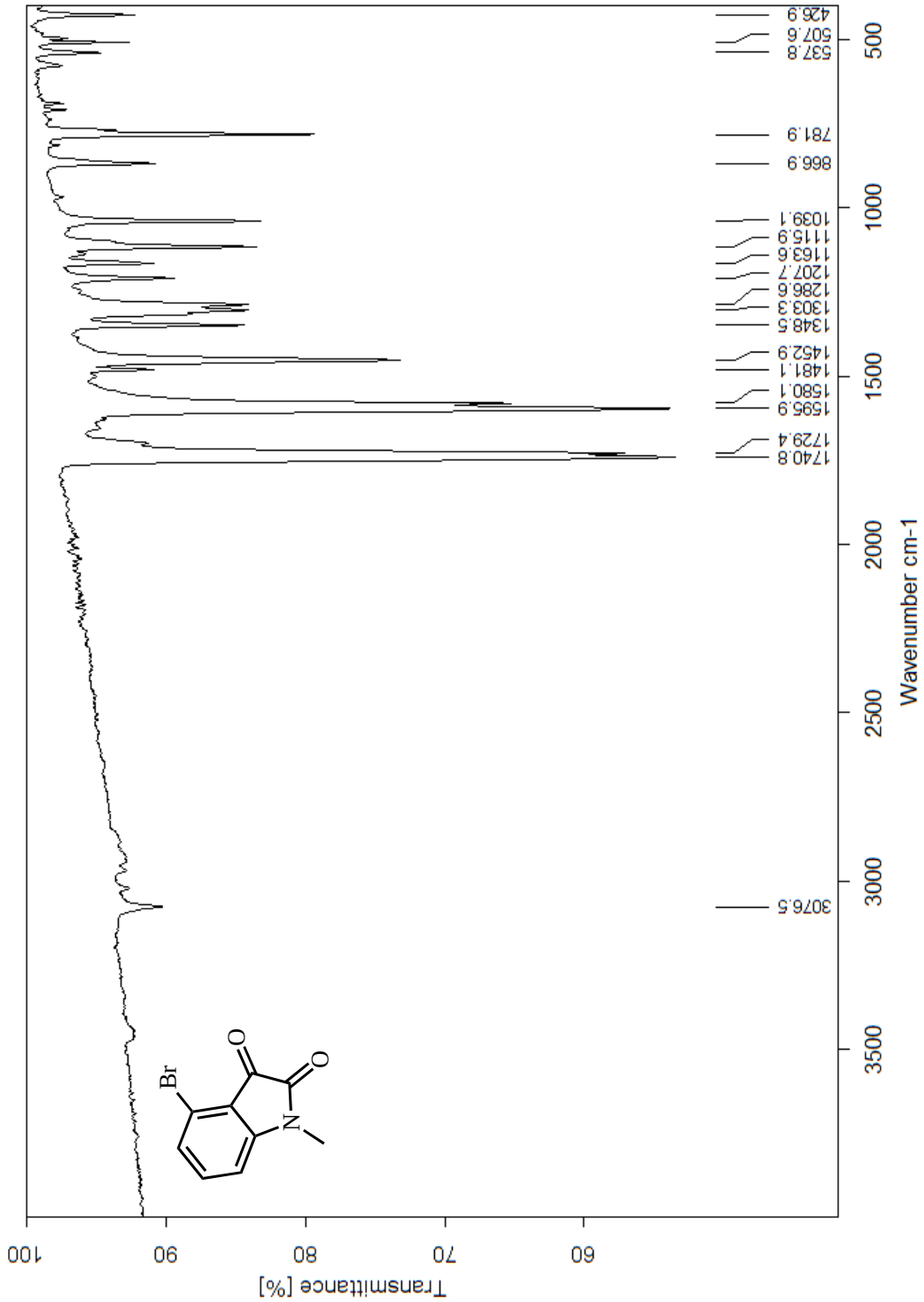

Figure C.09. FTIR Spectrum (neat) of isatin **3.11**

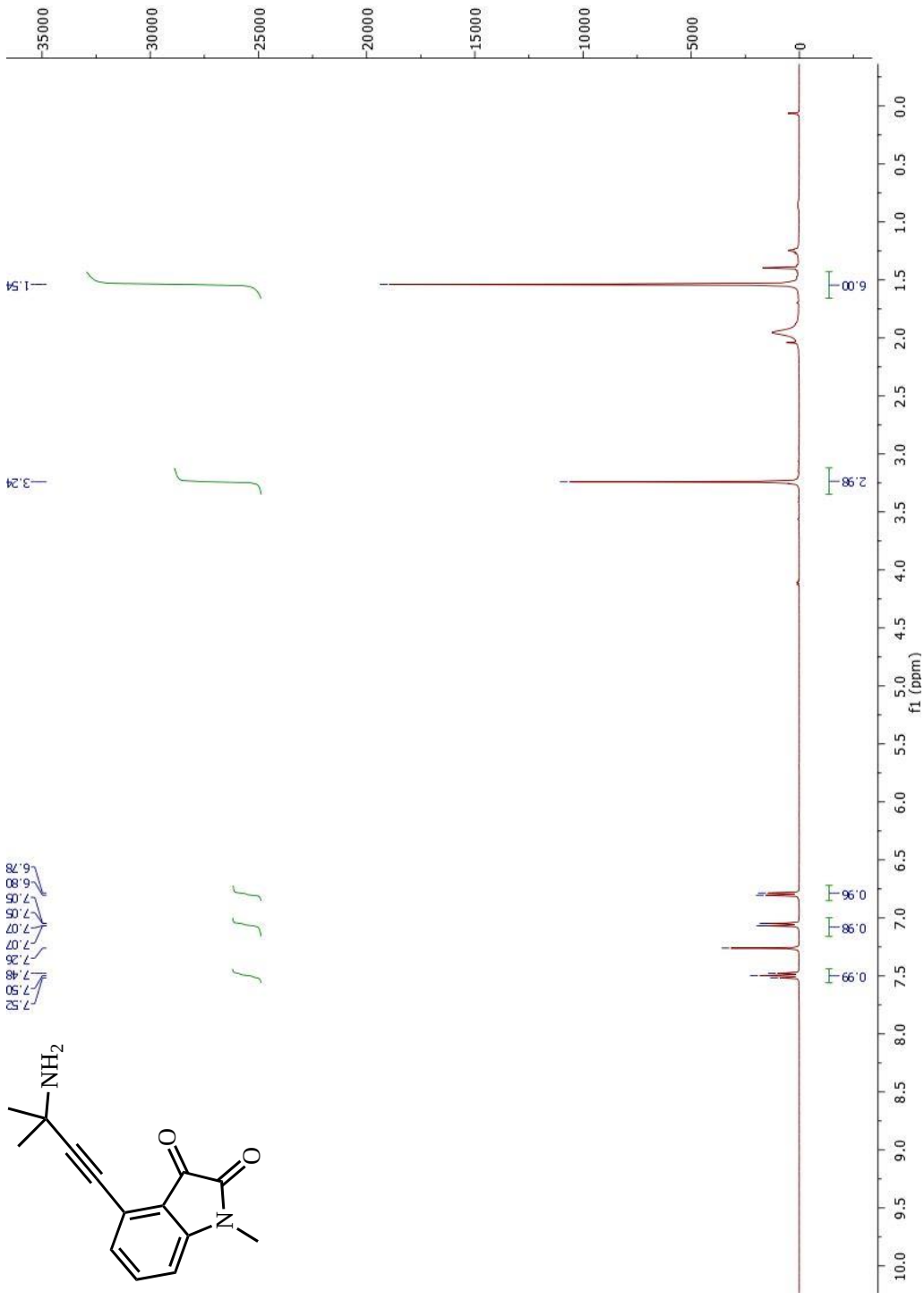

Figure C.10. **^{1}H NMR** (400 MHz, $CDCl_3$) of propargyl amine **3.18**

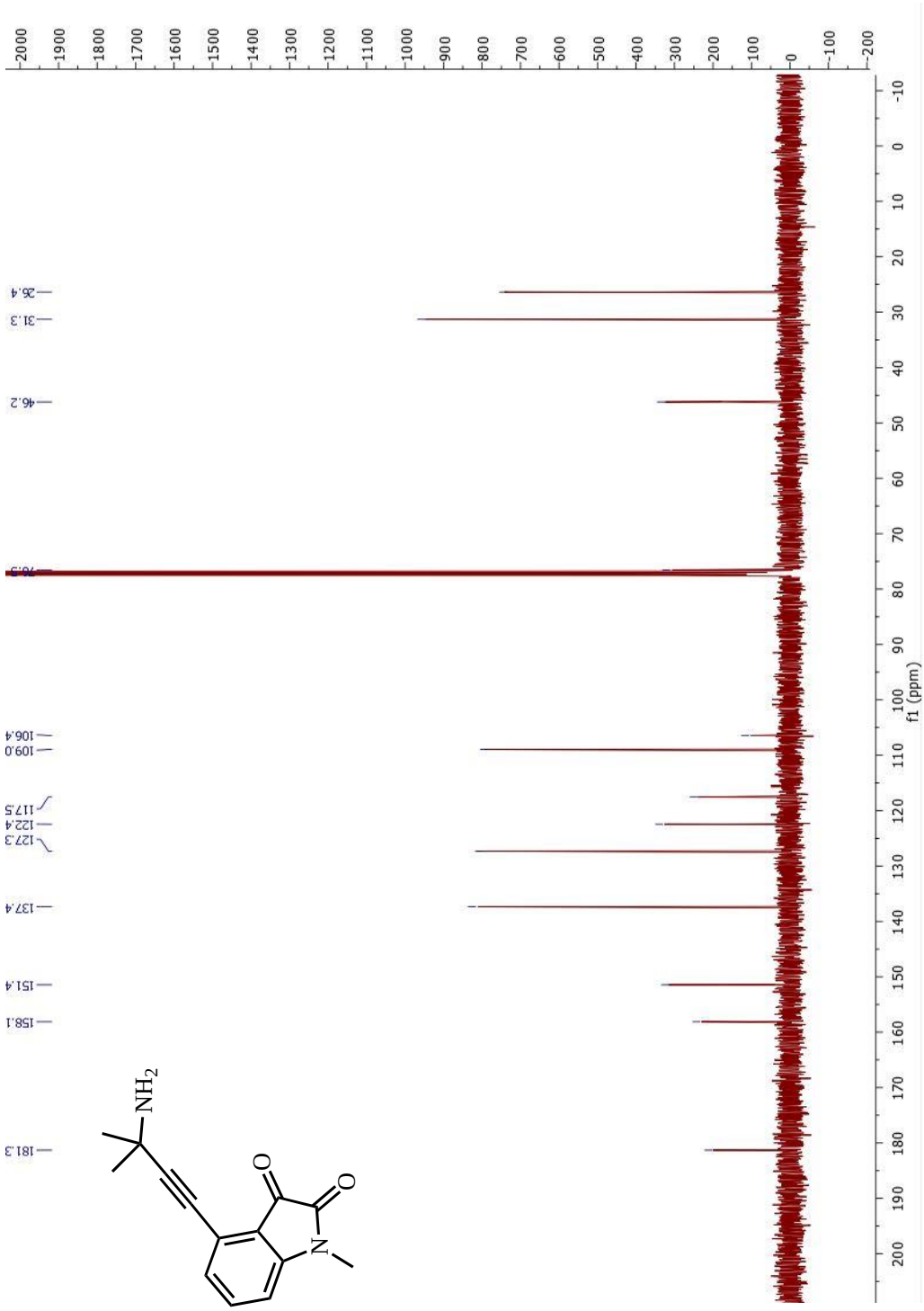

Figure C.11. **^{13}C NMR** (101 MHz, $CDCl_3$) of propargyl amine **3.18**

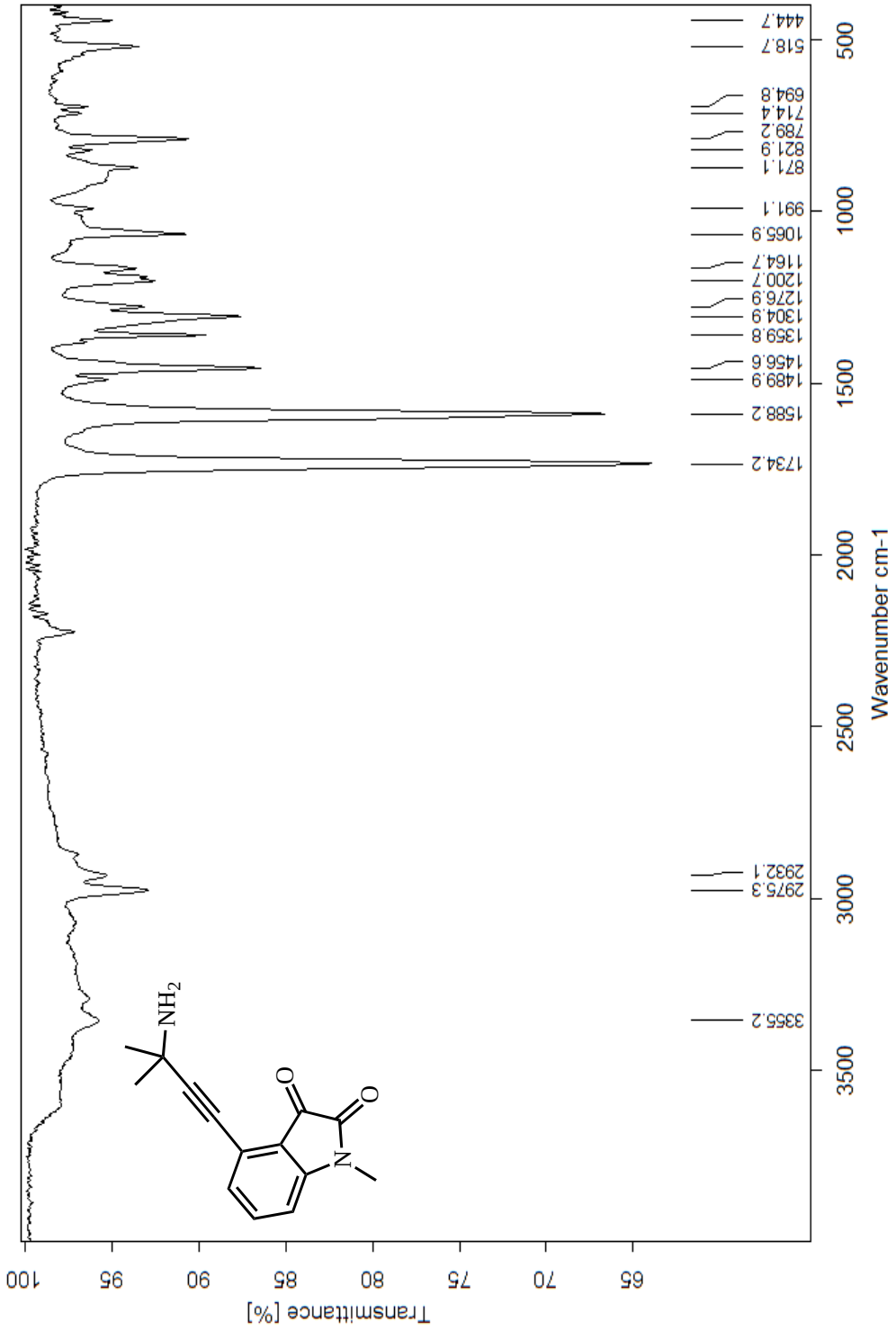

Figure C.12. FTIR Spectrum (neat) of propargyl amine **3.18**

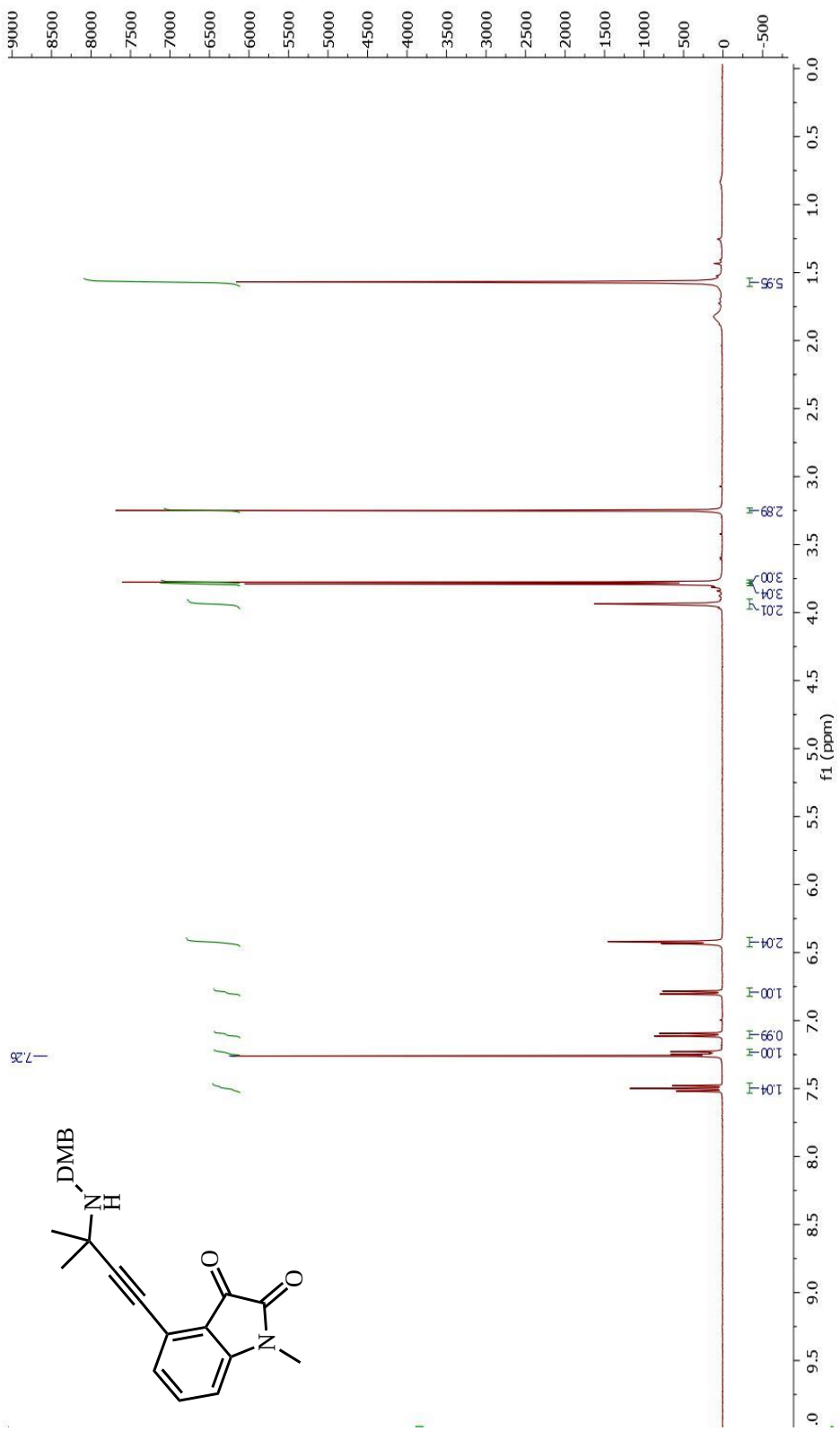

Figure C.13. **^{1}H NMR** (400 MHz, $CDCl_3$) of propargyl amine **3.21**

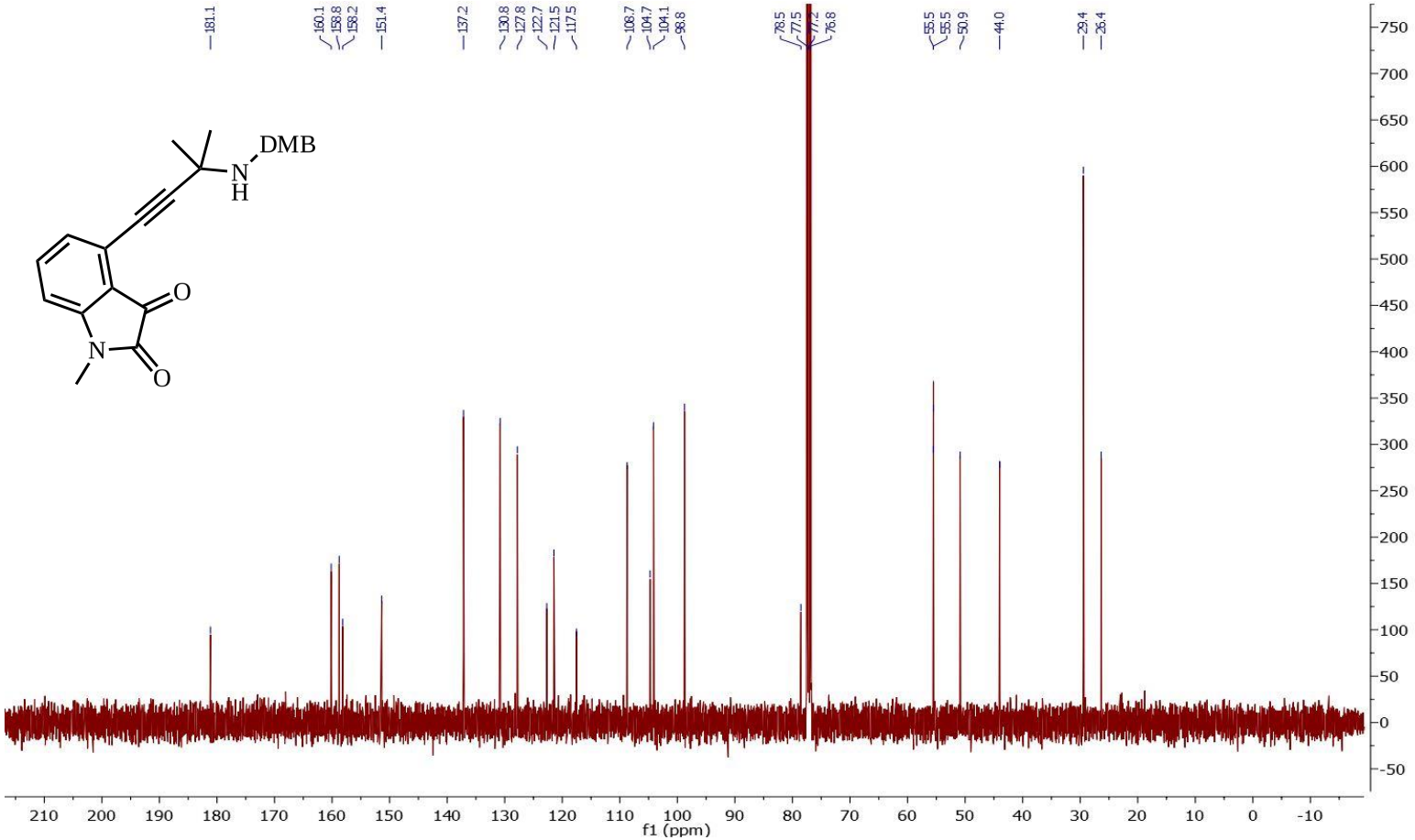

Figure C.14. **^{13}C NMR** (101 MHz, $CDCl_3$) of propargyl amine **3.21**

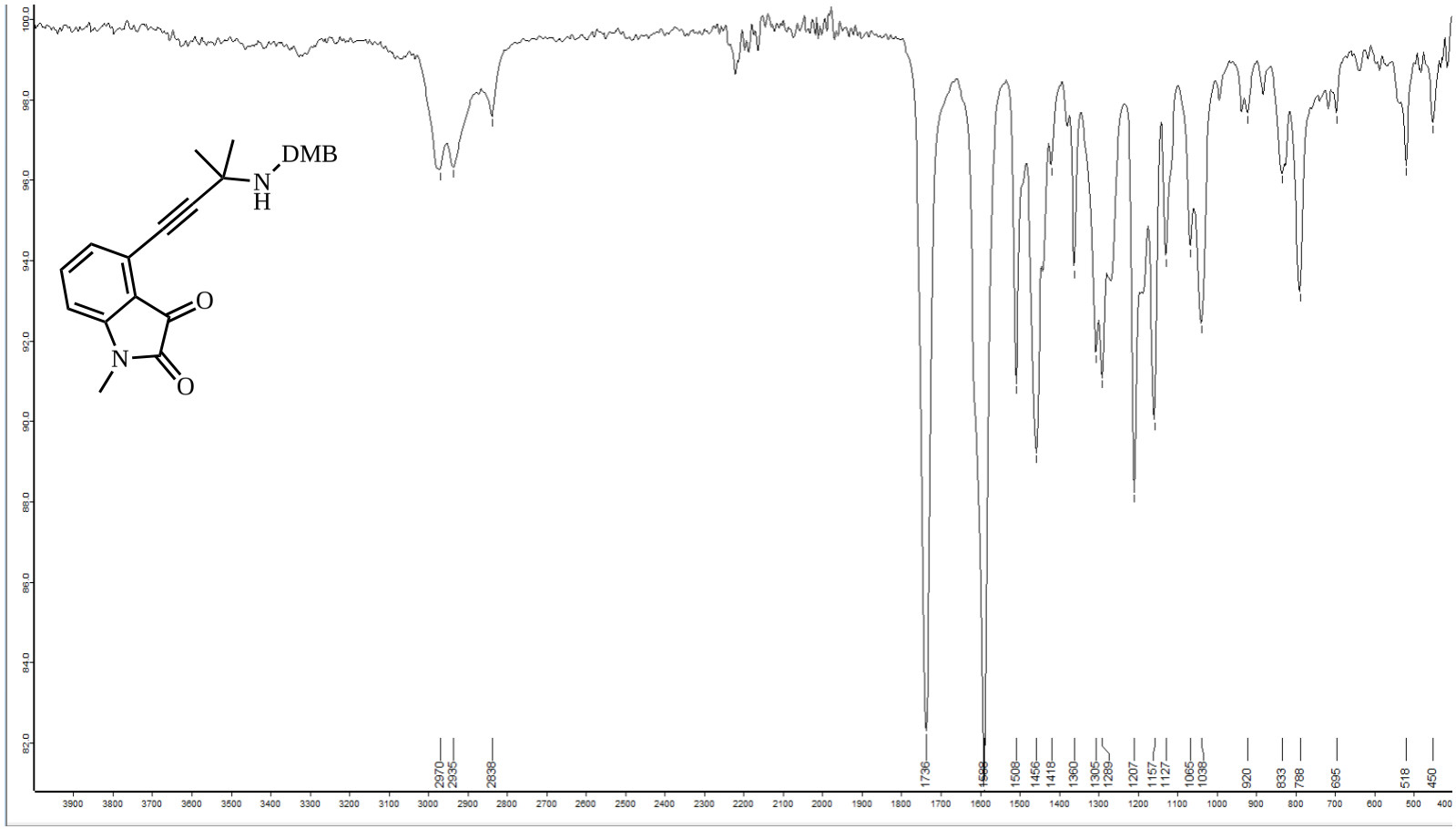

Figure C.15. FTIR Spectrum (neat) of propargyl amine **3.21**

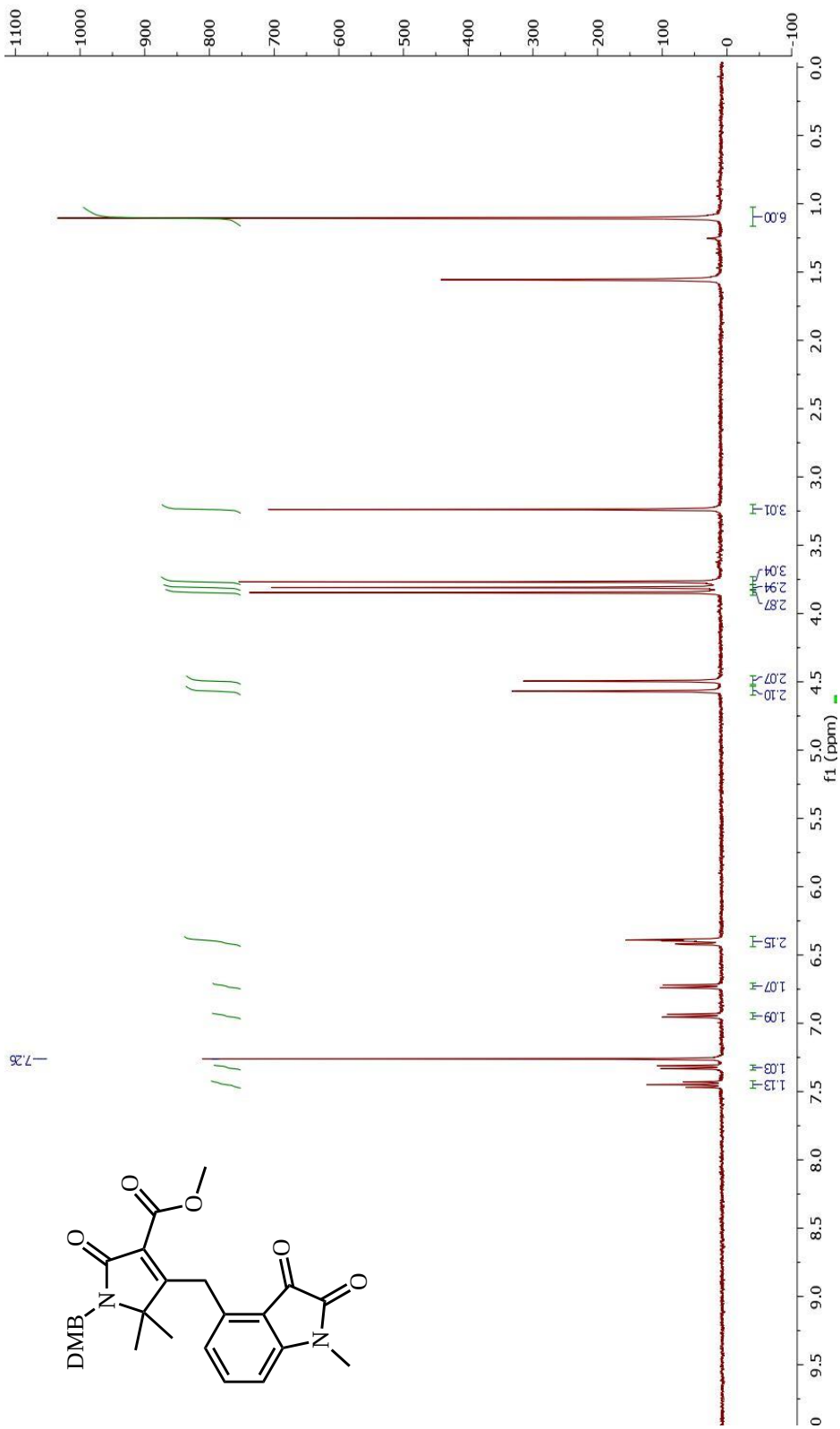

Figure C.16. **^{1}H NMR** (400 MHz, $CDCl_3$) of pyrrolinone **3.31**

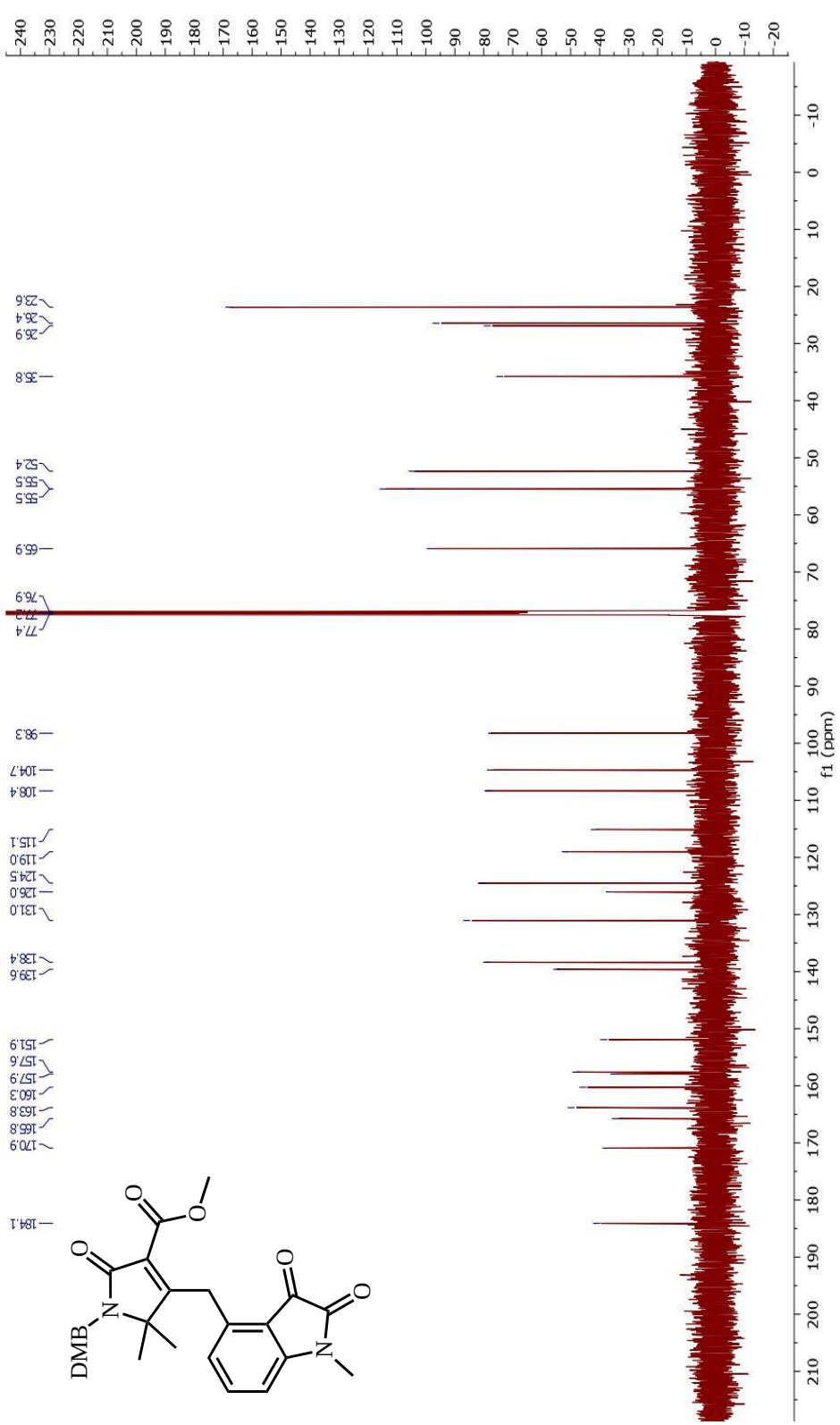

Figure C.17. **^{13}C NMR** (151 MHz, $CDCl_3$) of pyrrolinone **3.31**

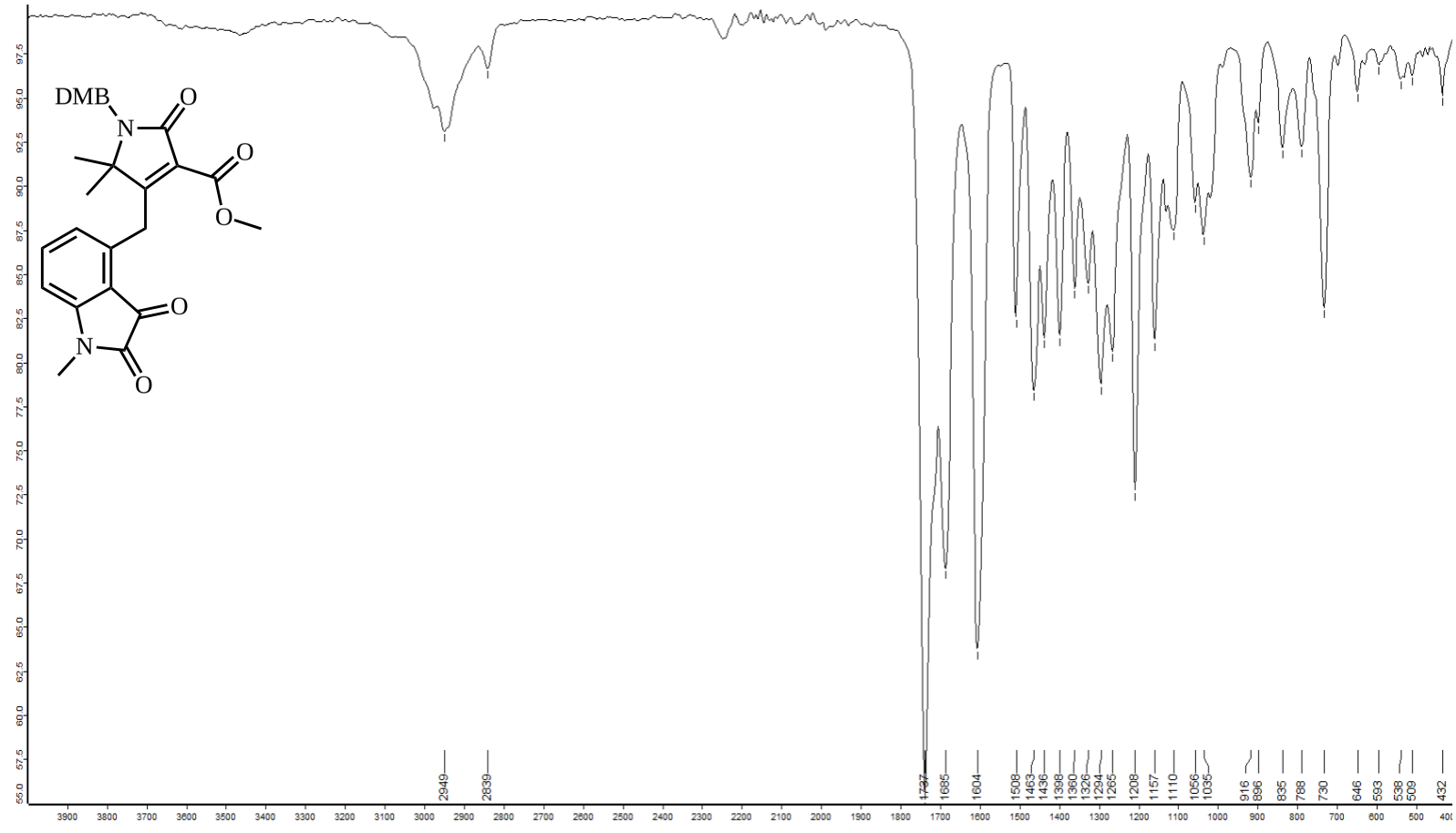

Figure C.18. FTIR Spectrum (neat) of pyrrolinone **3.31**

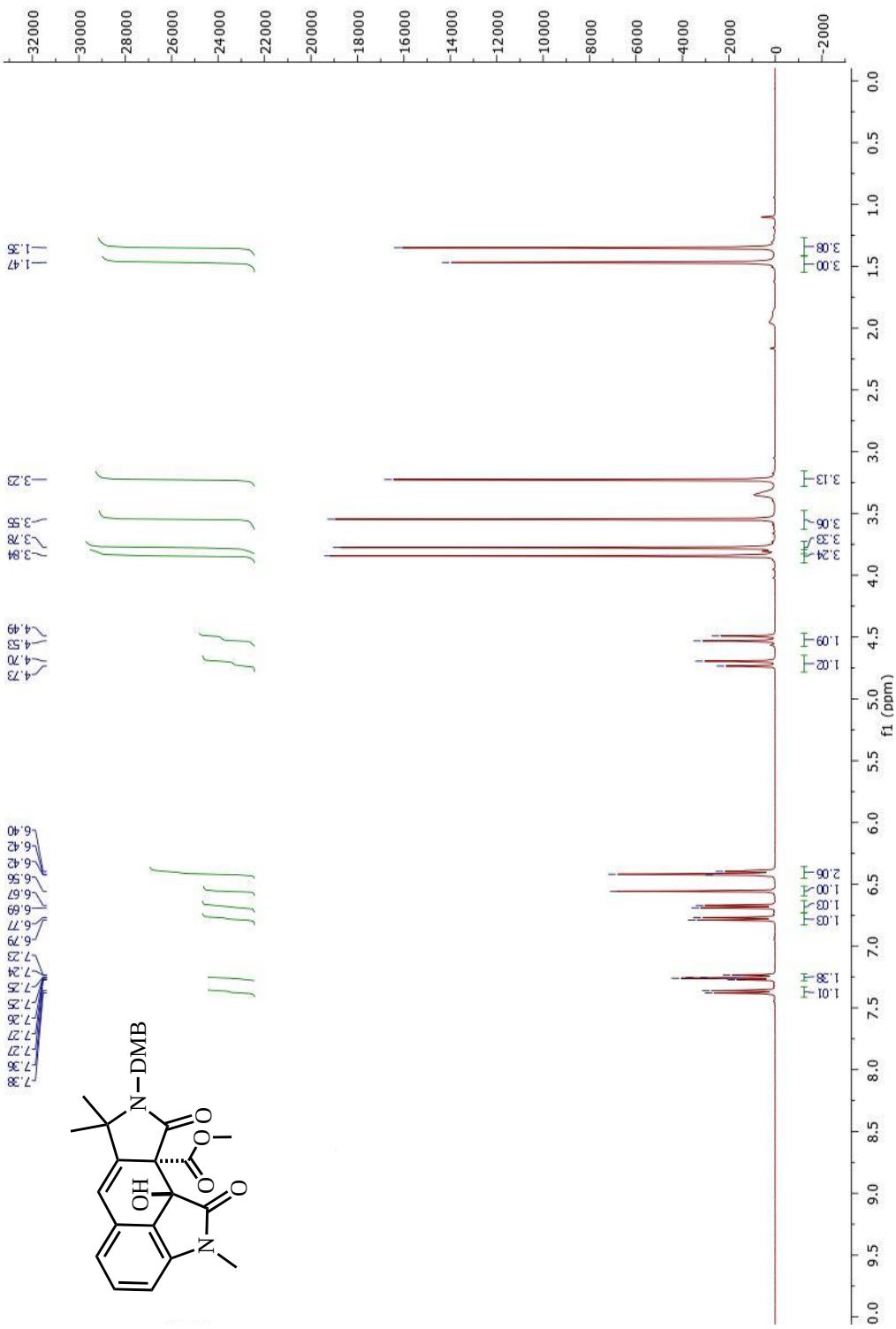

Figure C.19. **^{1}H NMR** (400 MHz, $CDCl_3$) of tetracycle **3.34**

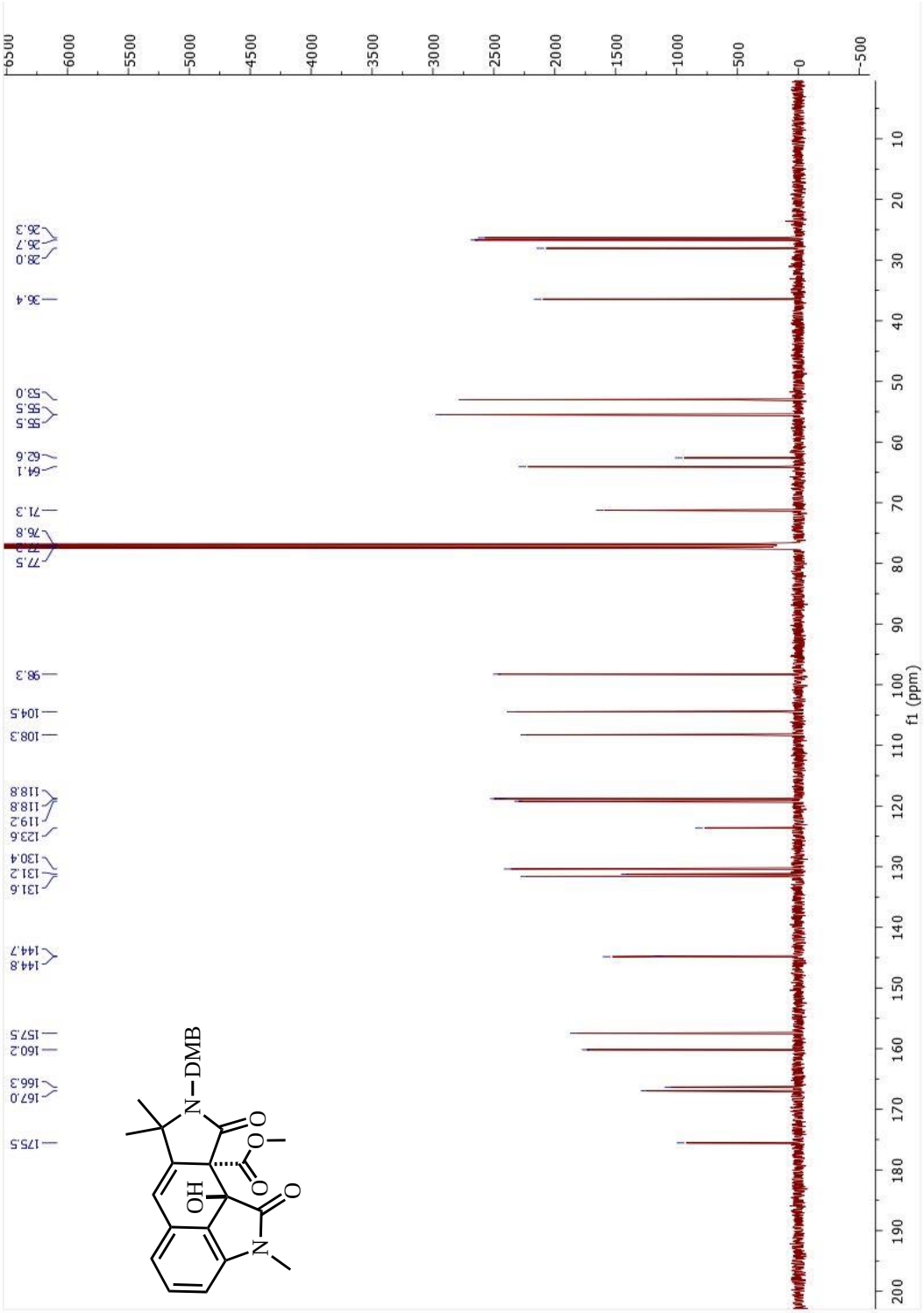

Figure C.20. **^{13}C NMR** (101 MHz, $CDCl_3$) of tetracycle **3.34**

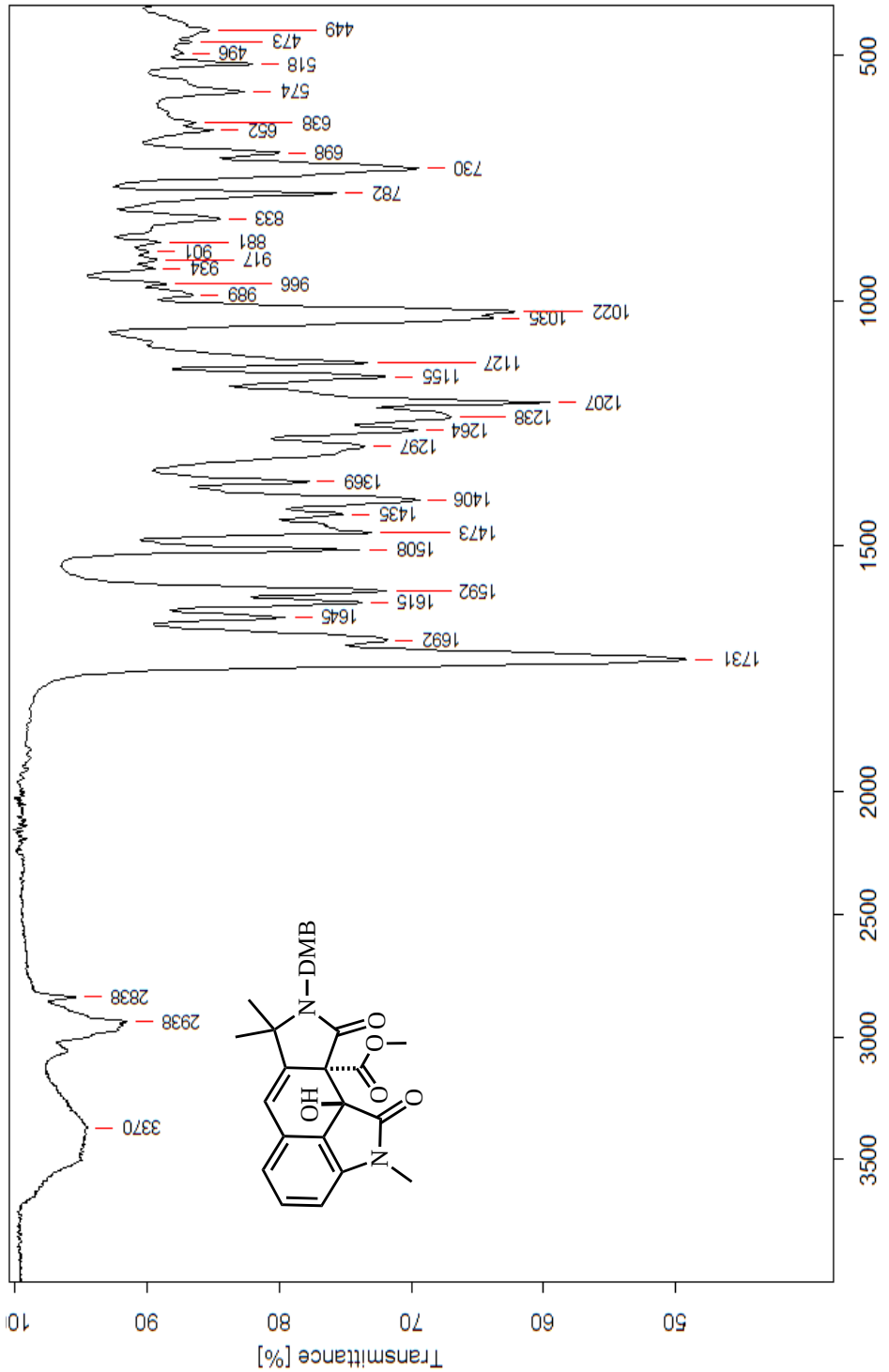

Figure C.21. FTIR Spectrum (neat) of tetracycle **3.34**

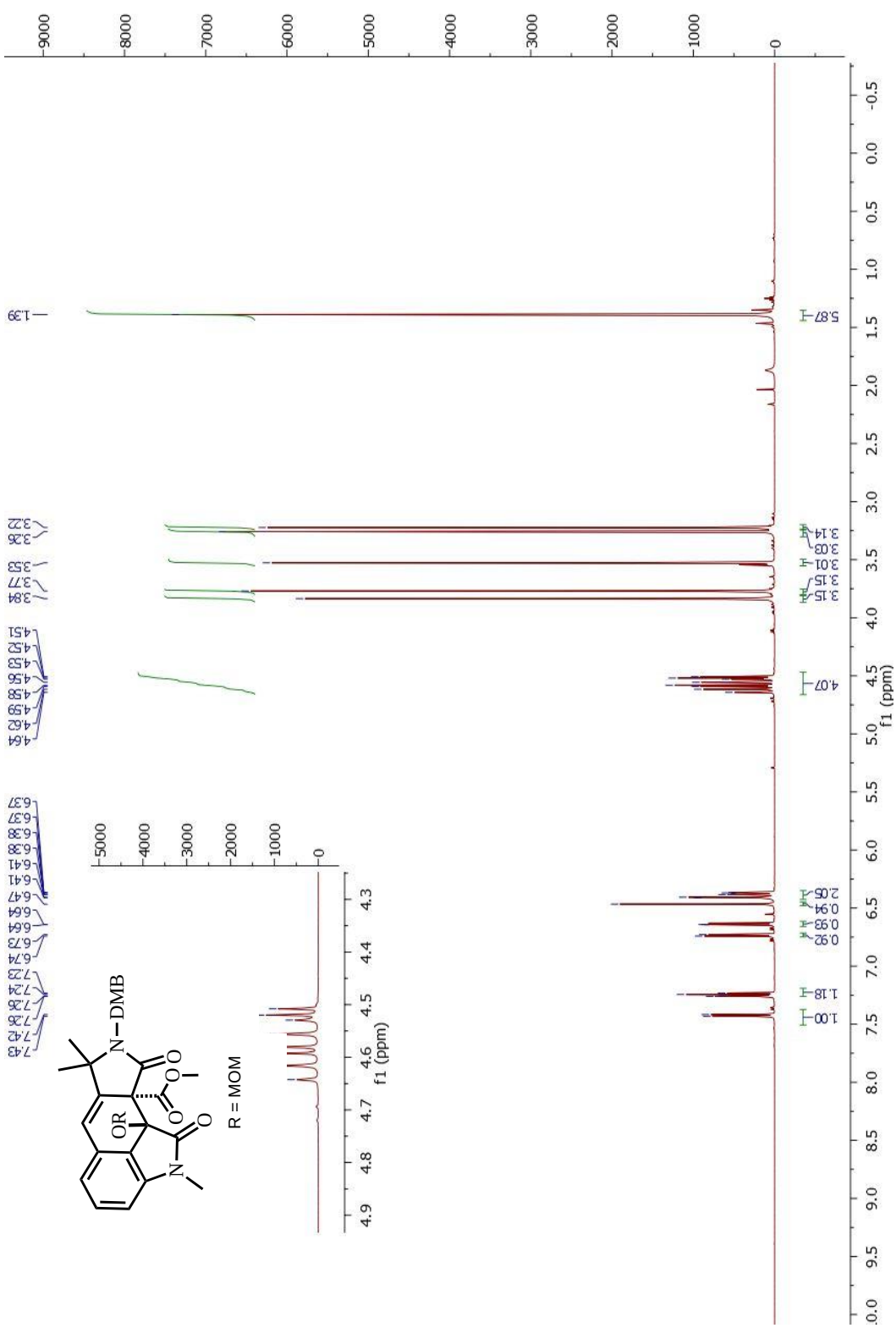

Figure C.22. **^{1}H NMR** (400 MHz, $CDCl_3$) of MOM tetracycle **3.35**

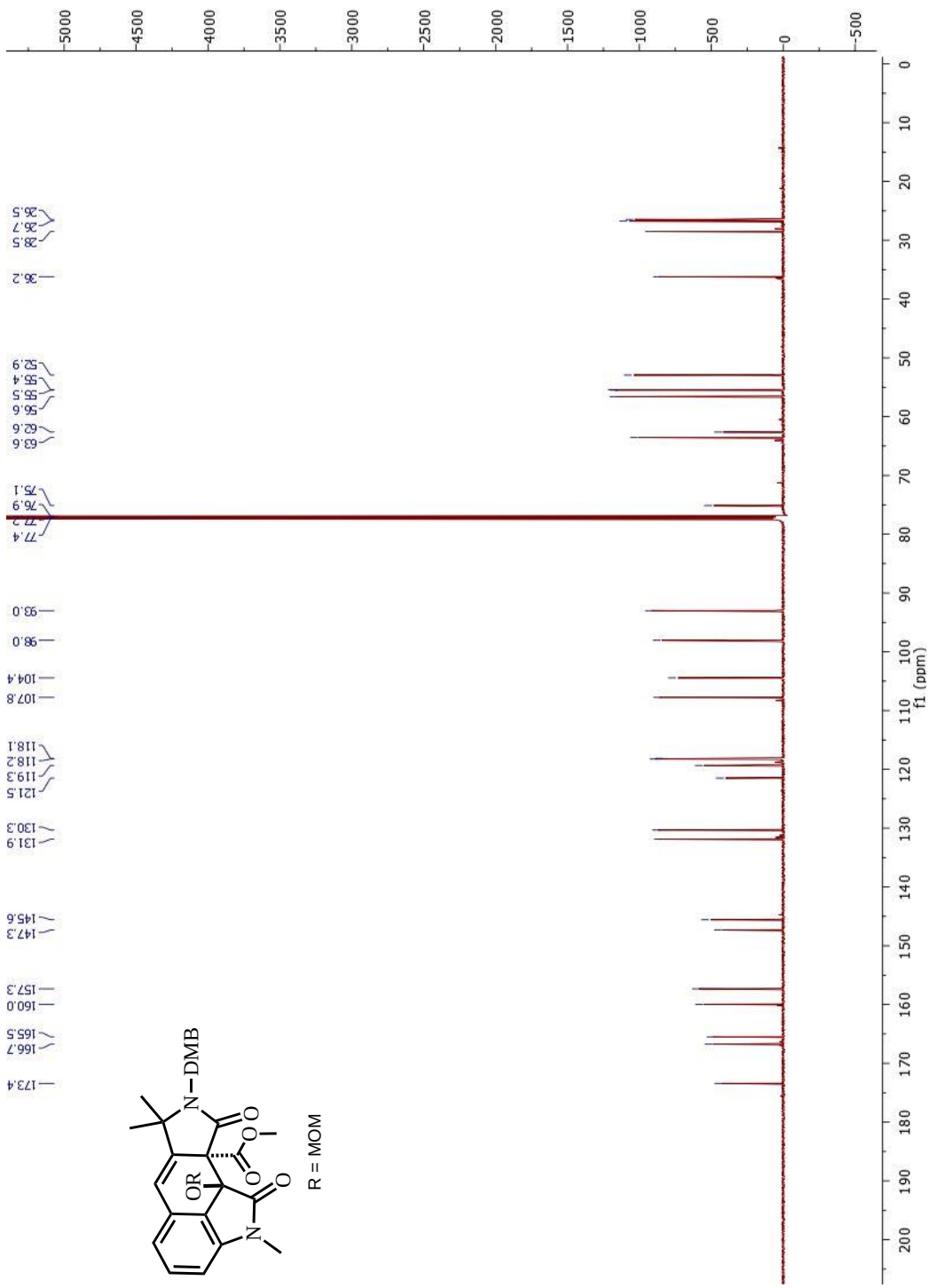

Figure C.23. **^{13}C NMR** (151 MHz, $CDCl_3$) of MOM tetracycle **3.35**

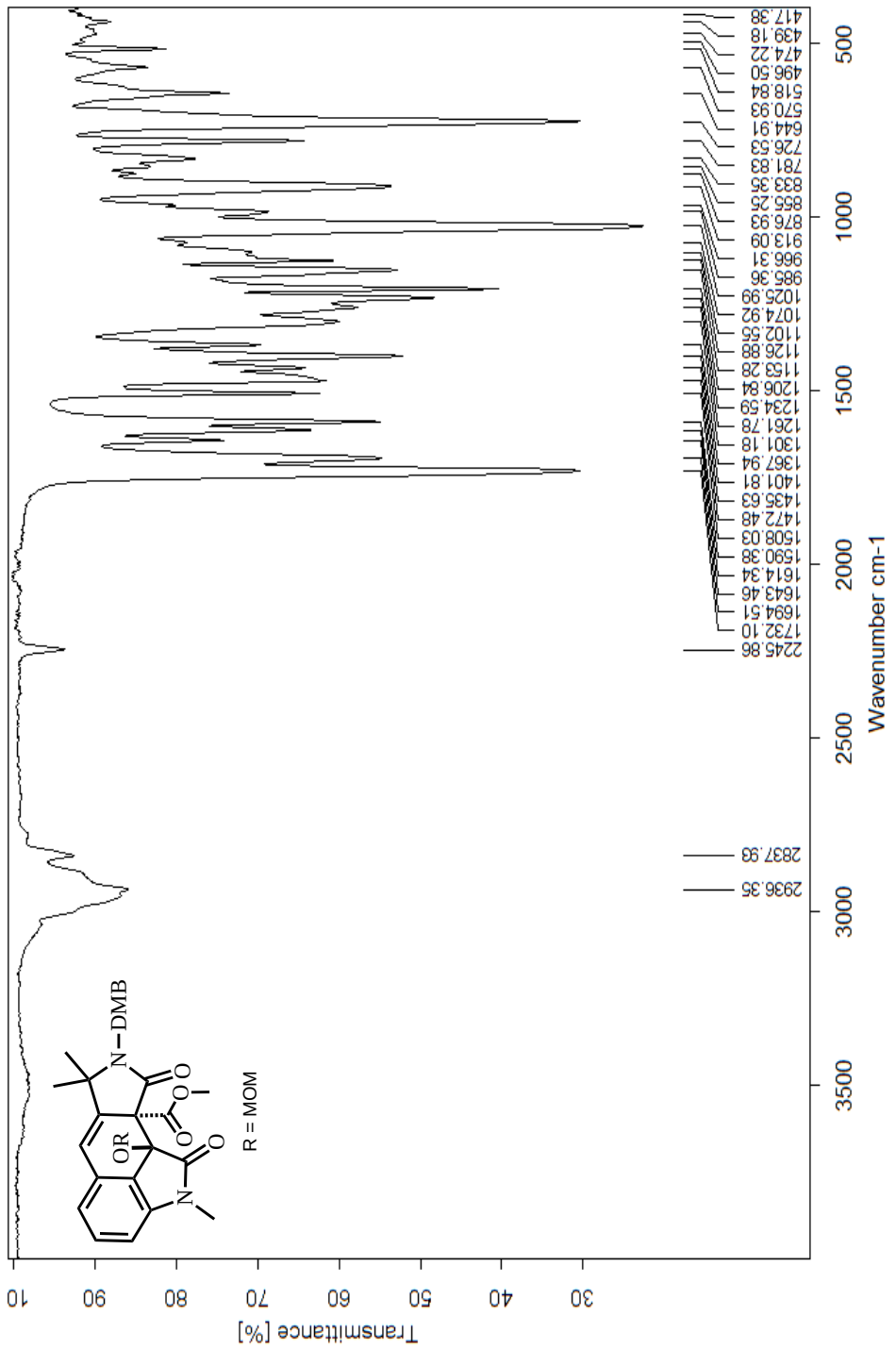

Figure C.24. FTIR Spectrum (neat) of MOM tetracycle **3.35**

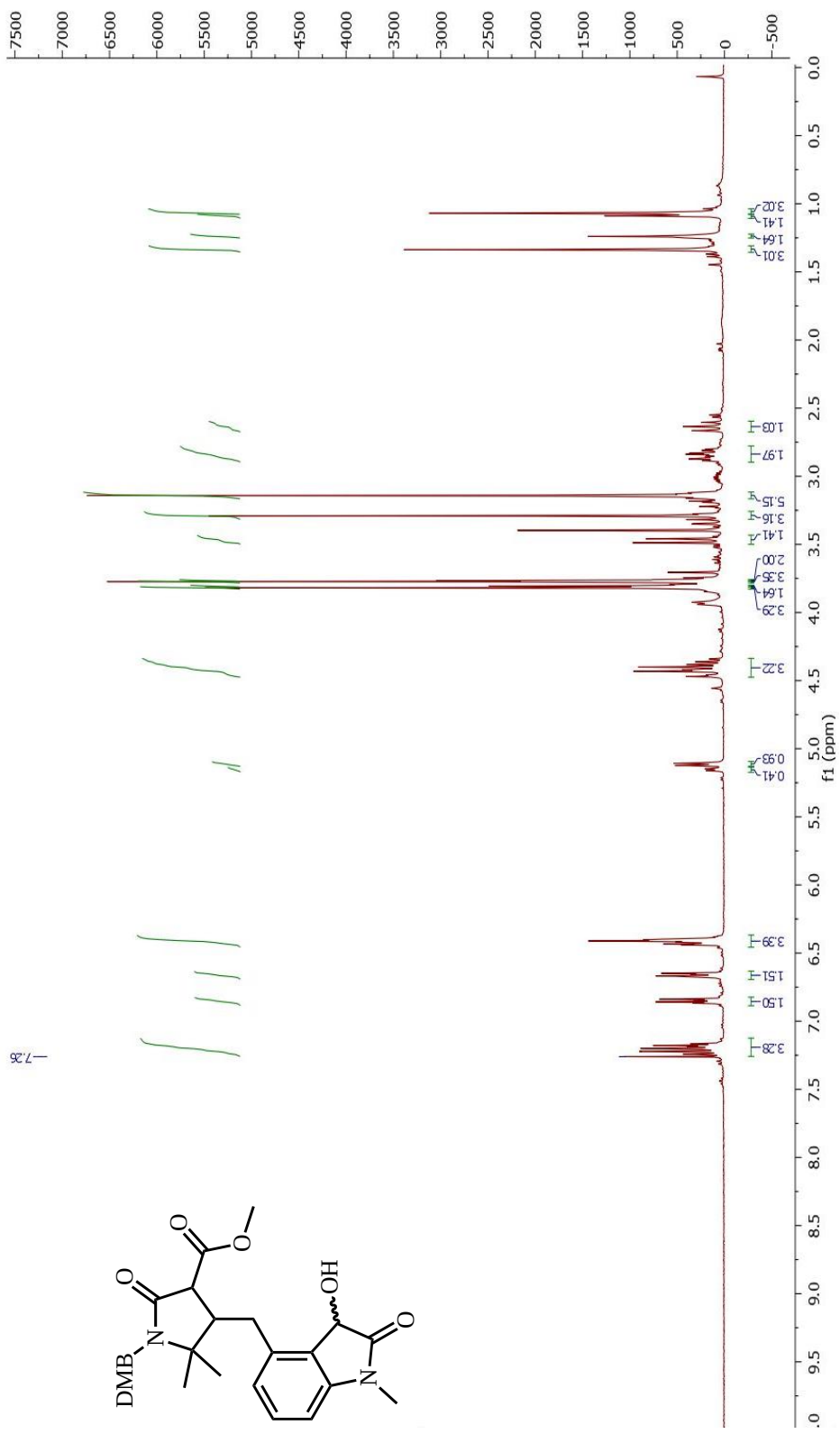

Figure C.25. **^{1}H NMR** (400 MHz, $CDCl_3$) of pyrrolidone **3.45**

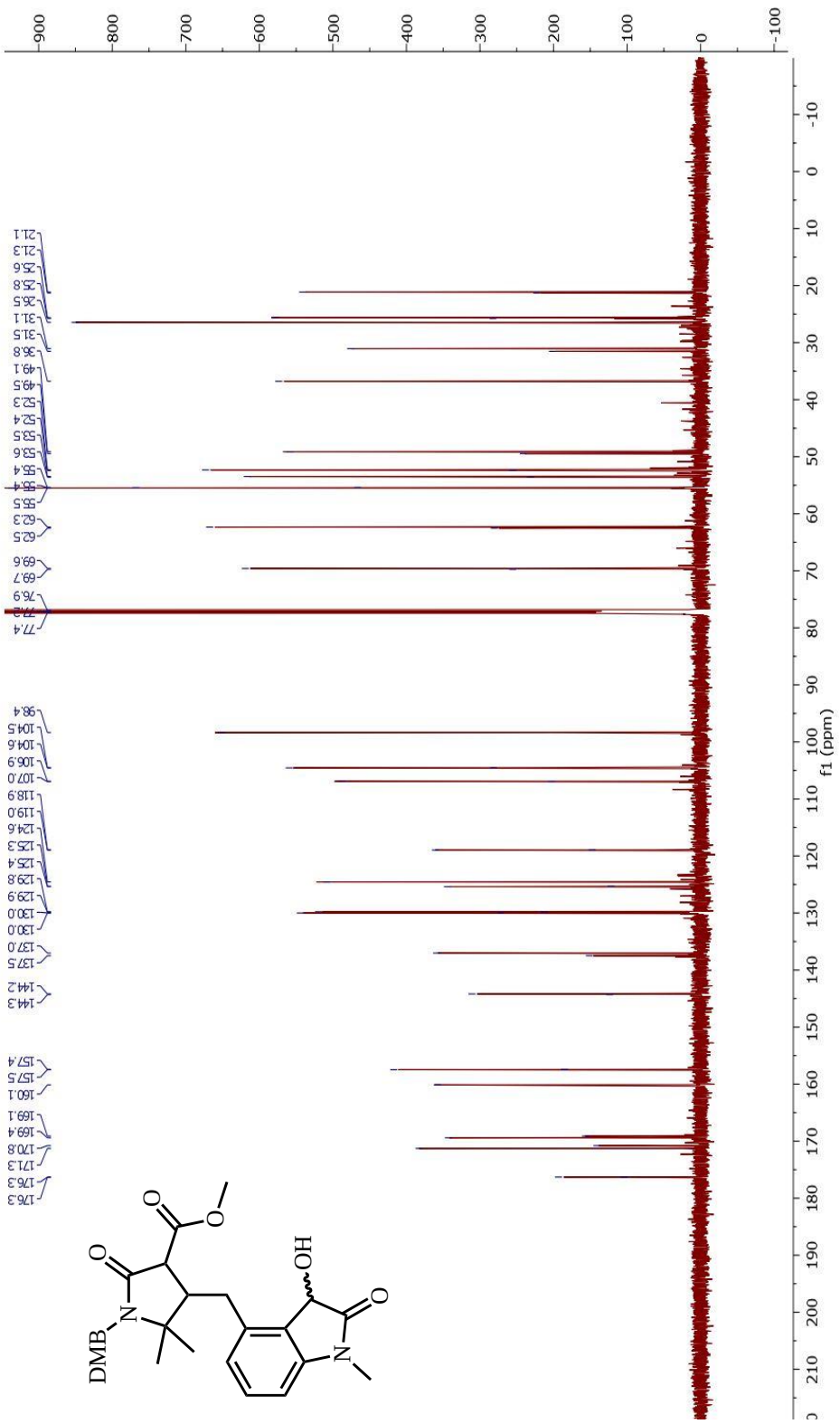

Figure C.26. **^{13}C NMR** (101 MHz, $CDCl_3$) of pyrrolidone **3.45**

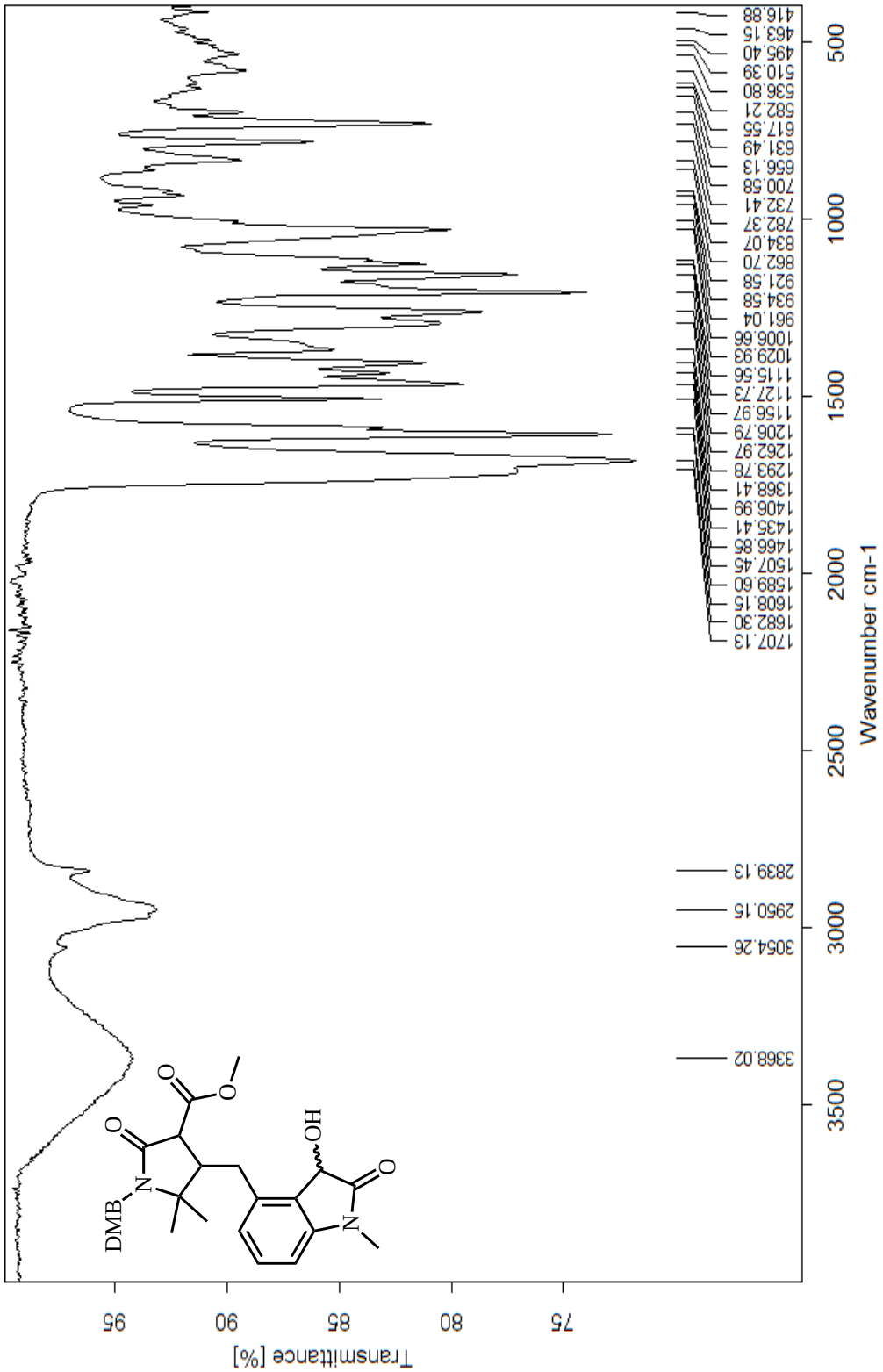

Figure C.27. FTIR Spectrum (neat) of pyrrolidone **3.45**

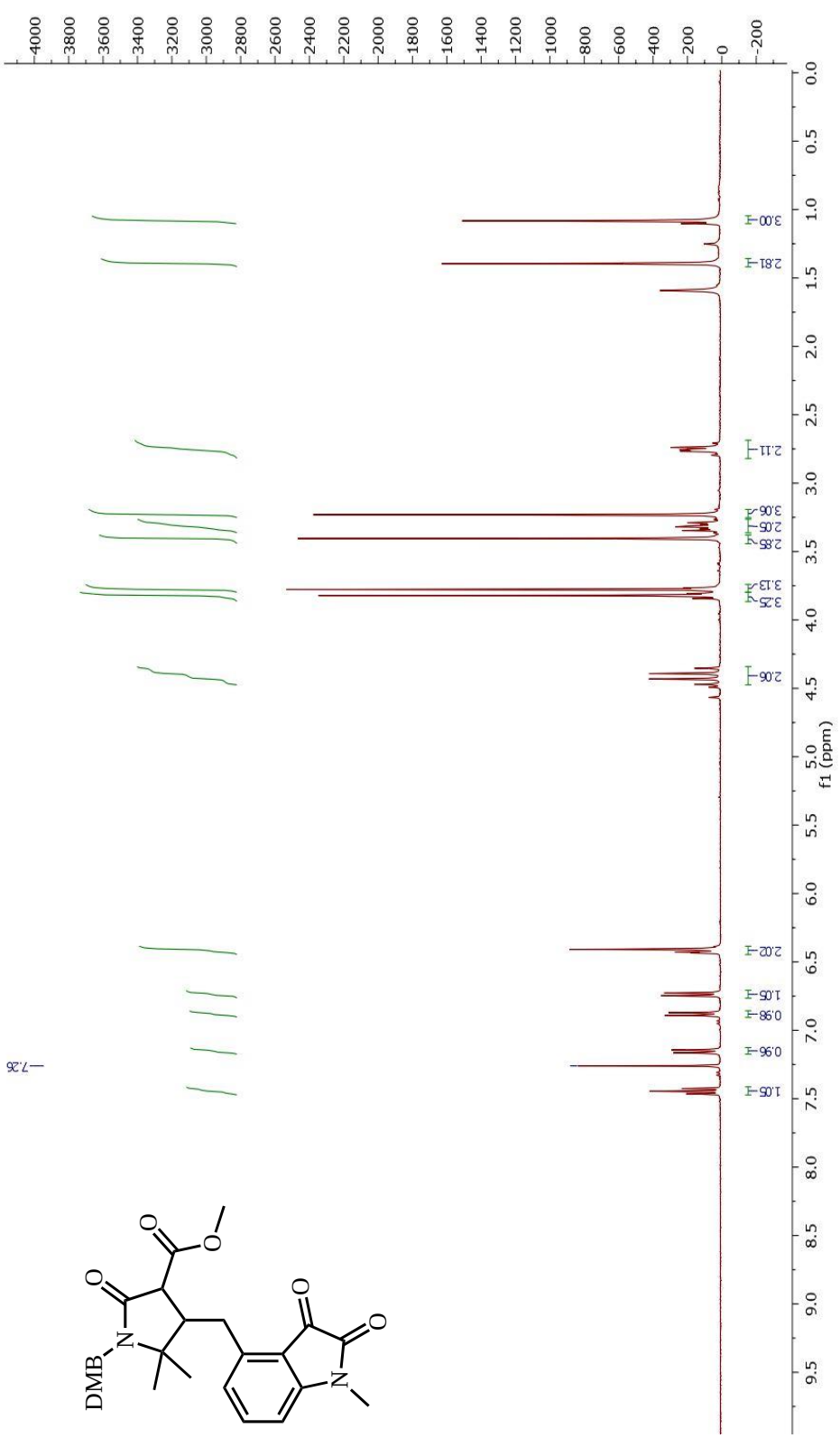

Figure C.28. **^{1}H NMR** (400 MHz, $CDCl_3$) of pyrrolidone **3.46**

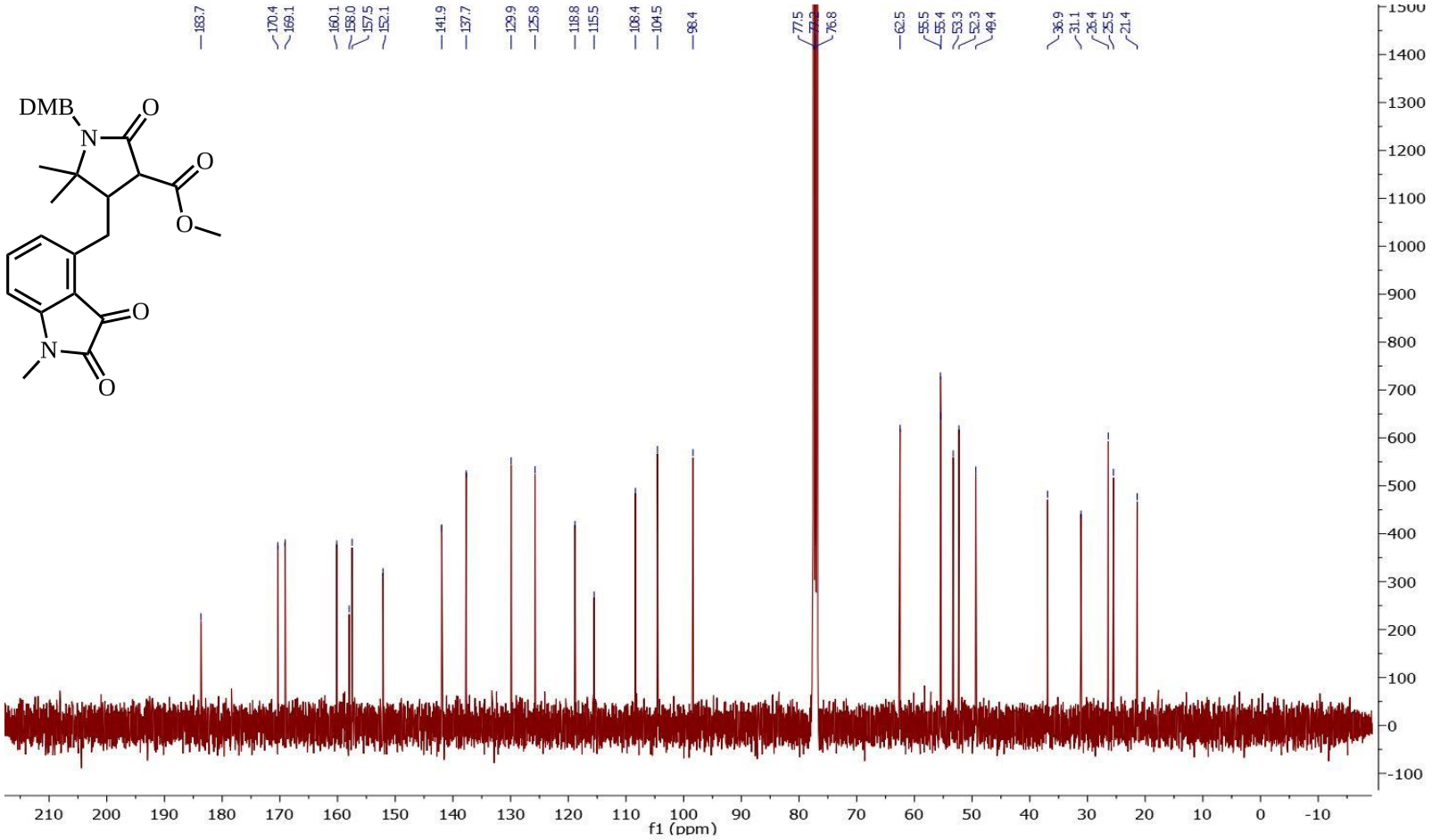

Figure C.29. **^{13}C NMR** (101 MHz, $CDCl_3$) of pyrrolidone **3.46**

3.46

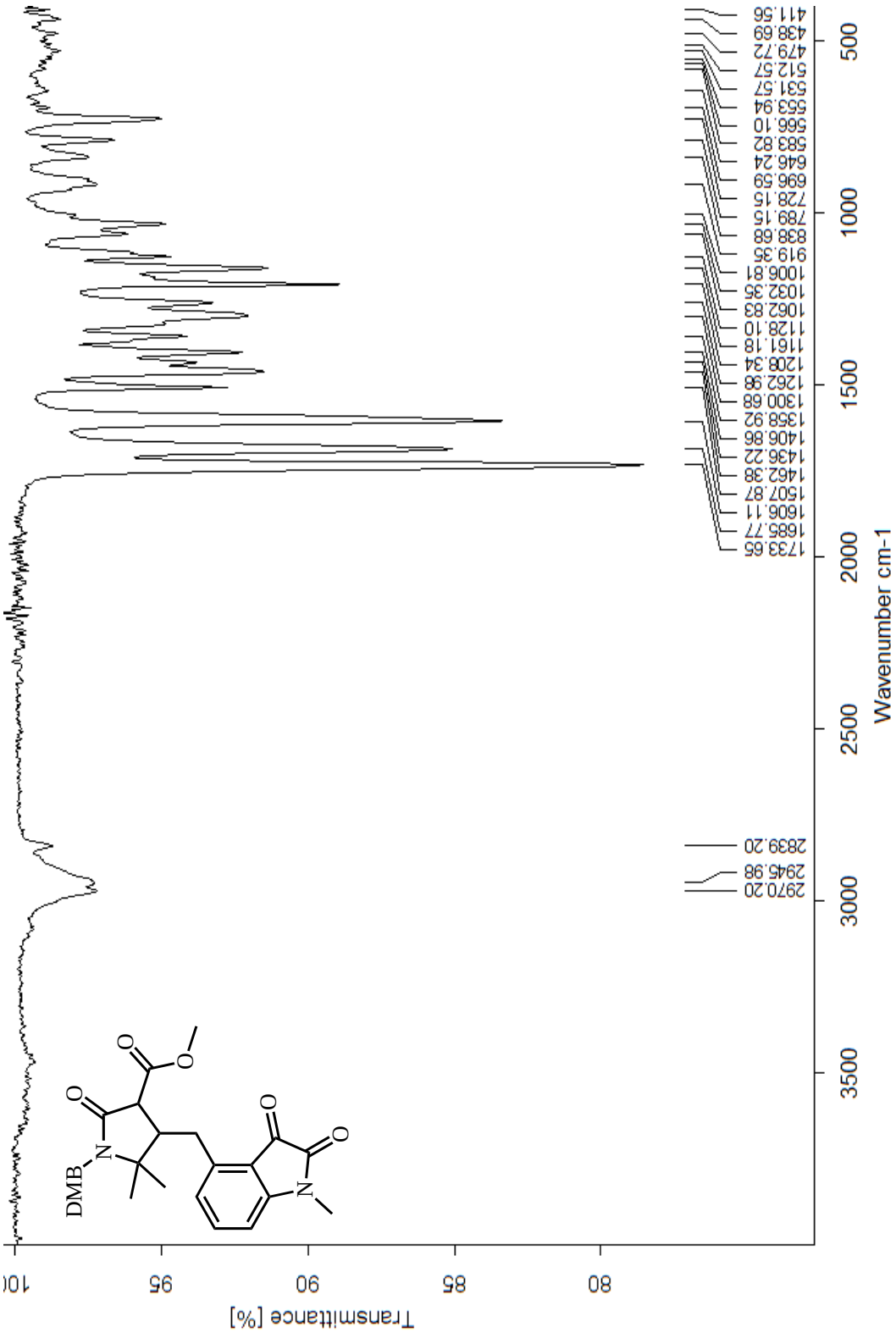

Figure C.30. FTIR Spectrum (neat) of pyrrolidone **3.46**

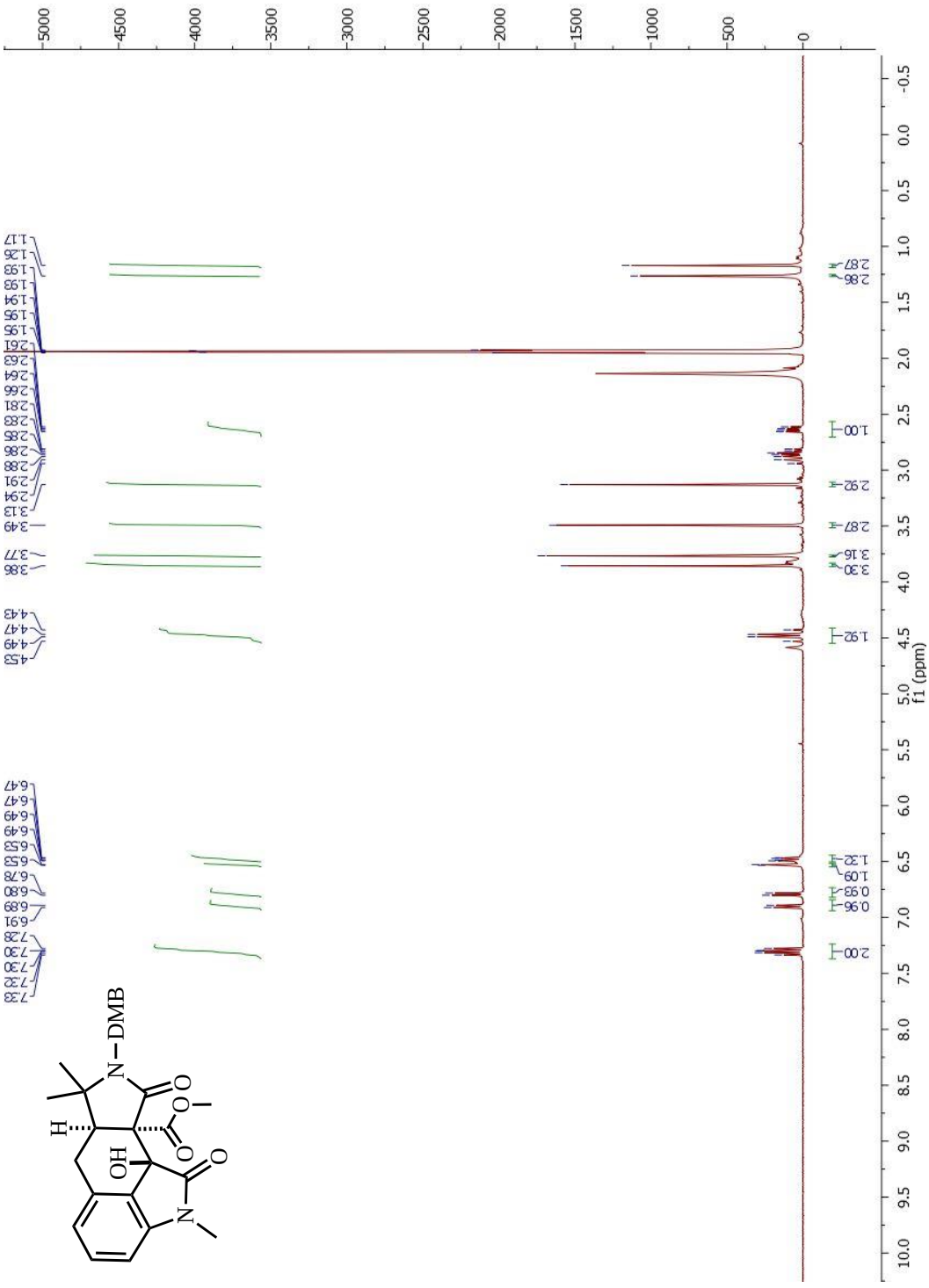

Figure C.31. **^{1}H NMR** (400 MHz, MeCN-*d3*) of tetracycle **3.47**

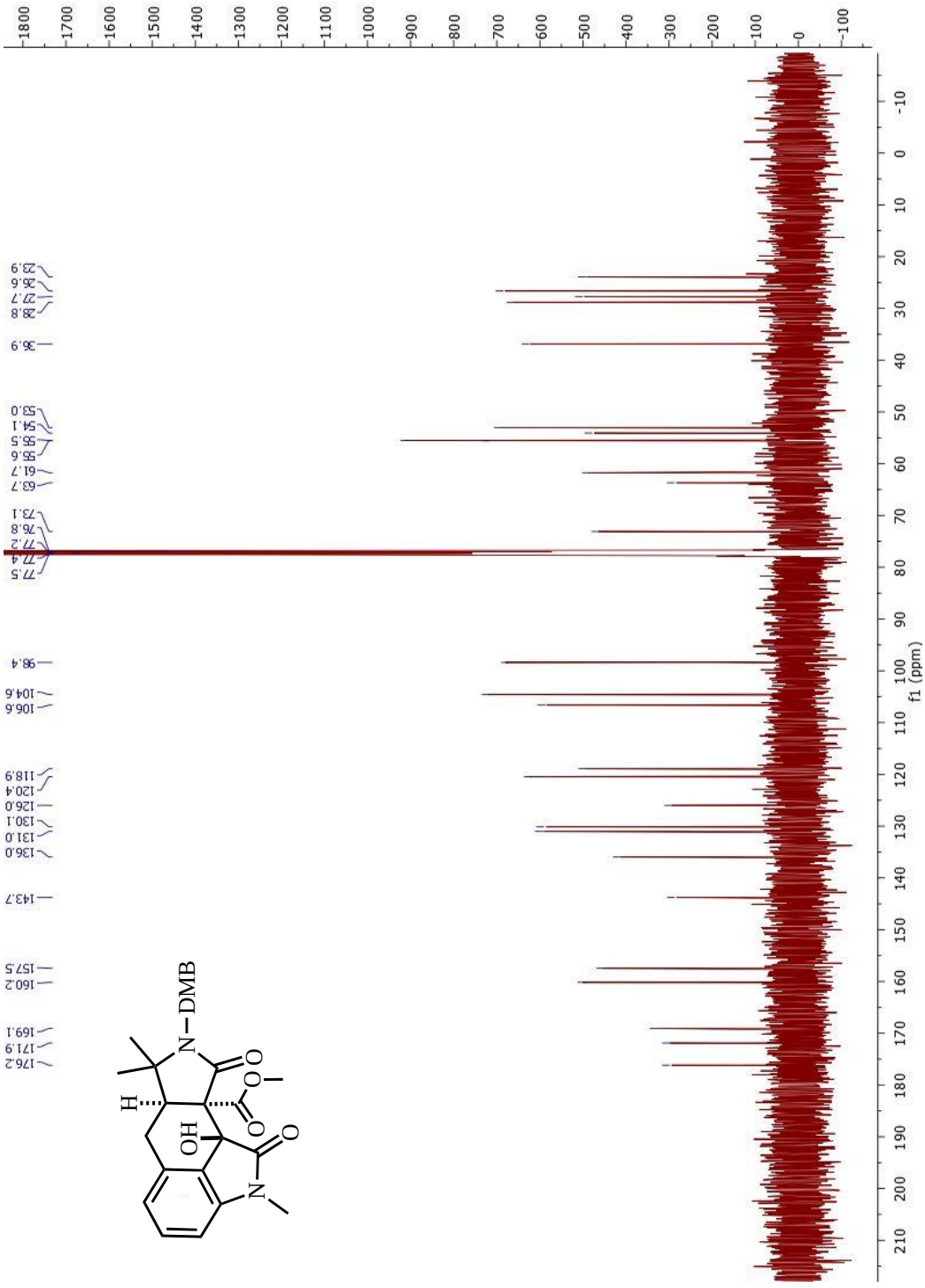

Figure C.32. **^{13}C NMR** (101 MHz, $CDCl_3$) of tetracycle **3.47**

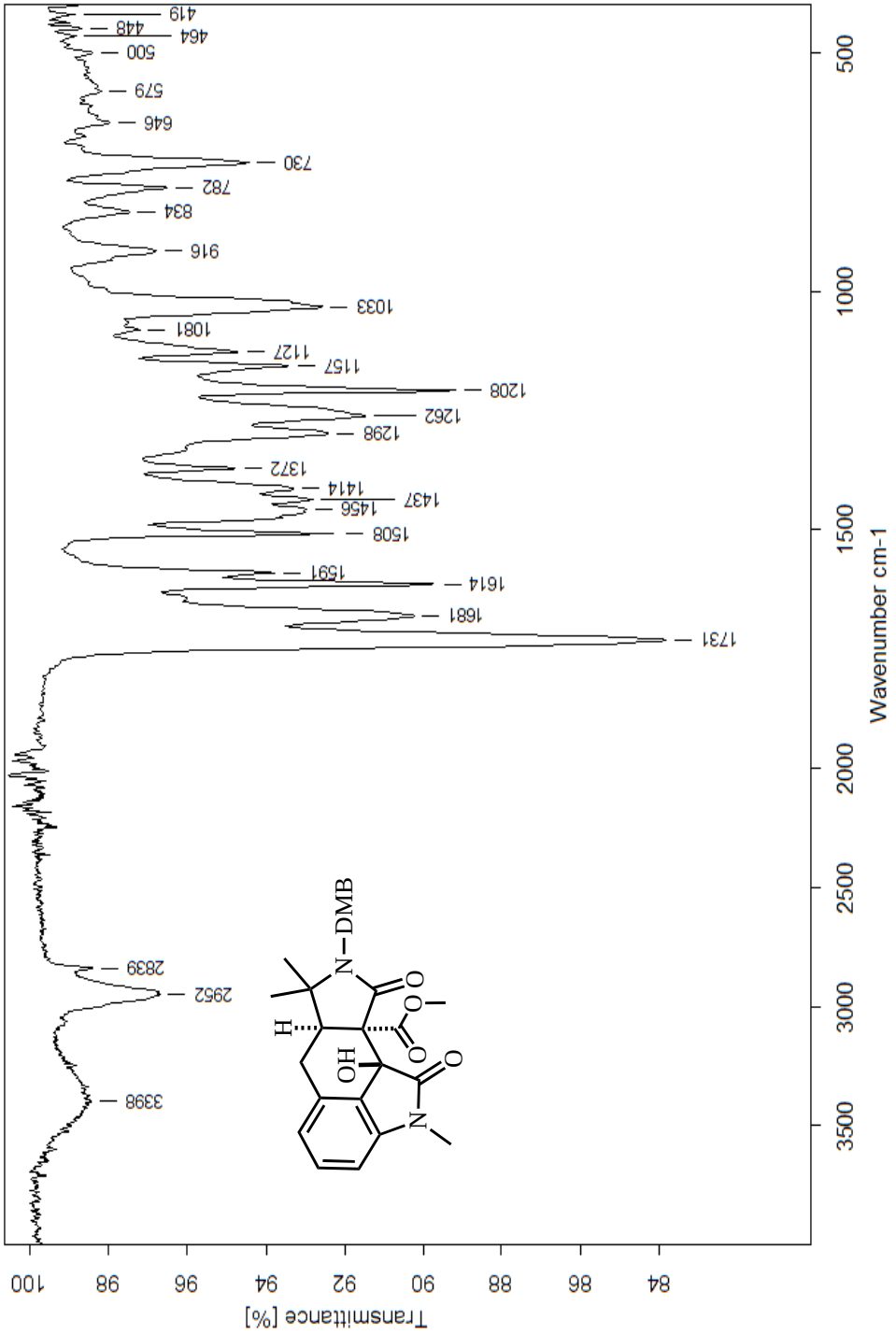

Figure C.33. FTIR Spectrum (neat) of tetracycle **3.47**

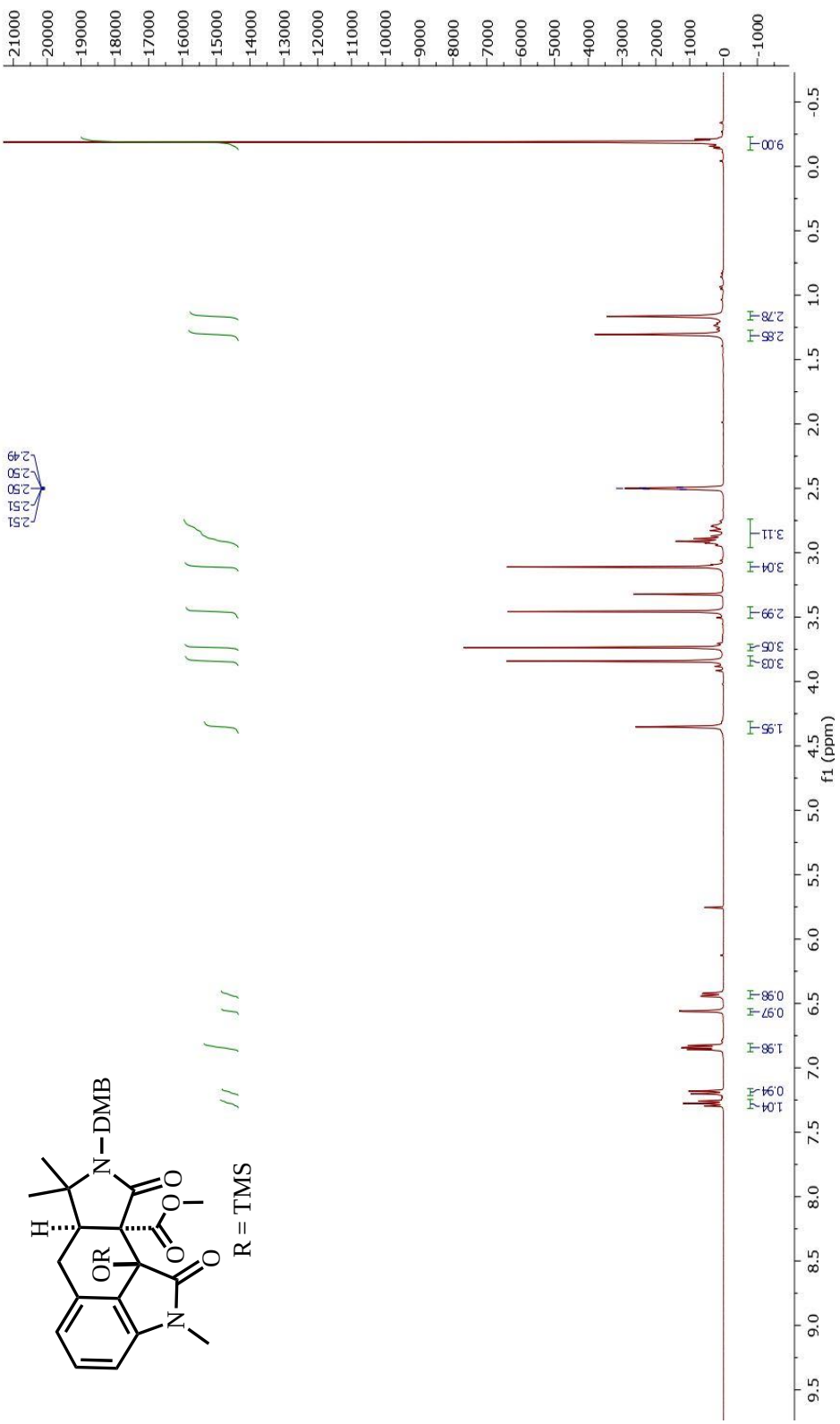

Figure C.34. **^{1}H NMR** (400 MHz, MeCN-*d3*) of tetracycle **3.49**

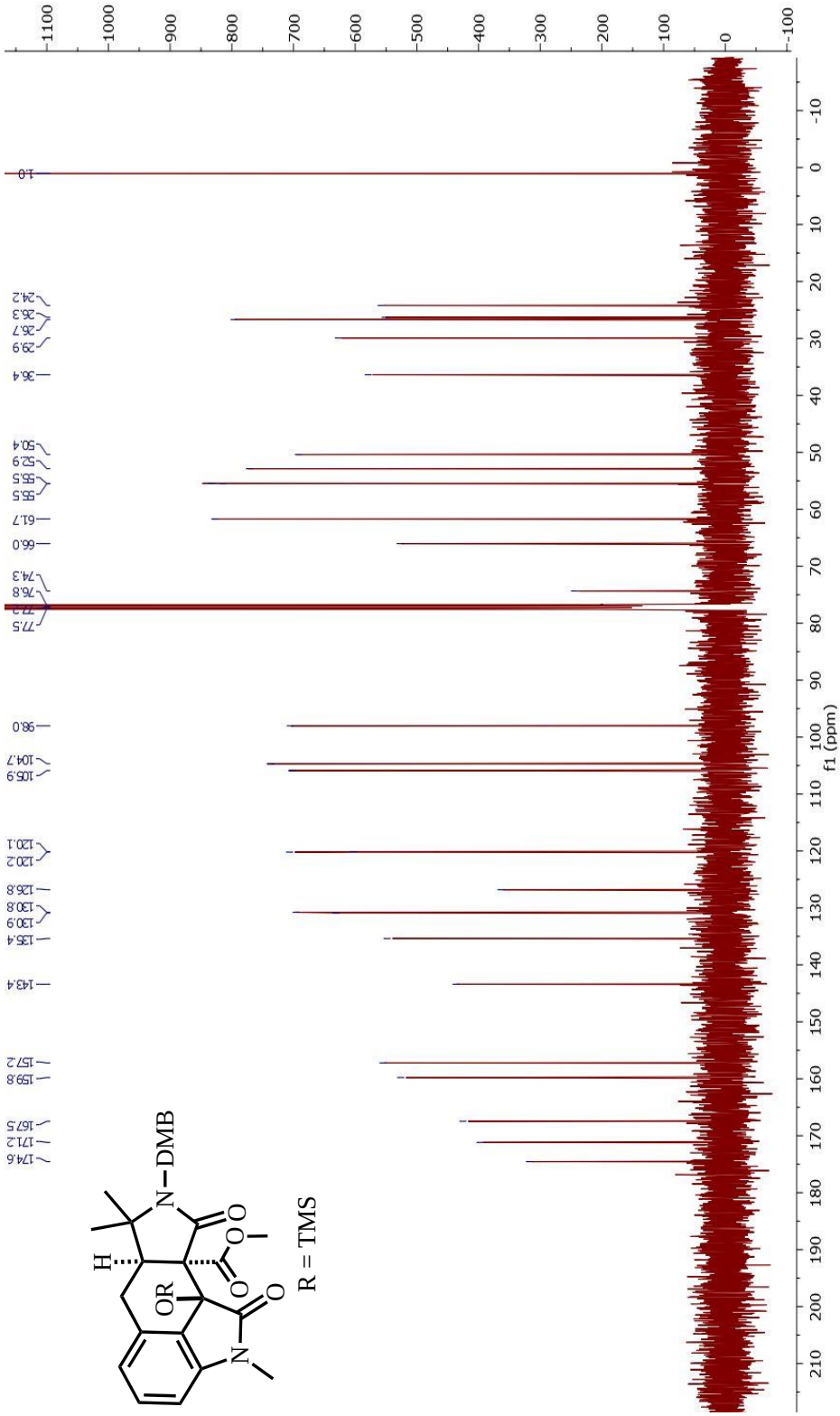

Figure C.35. **^{13}C NMR** (101 MHz, $CDCl_3$) of tetracycle **3.49**

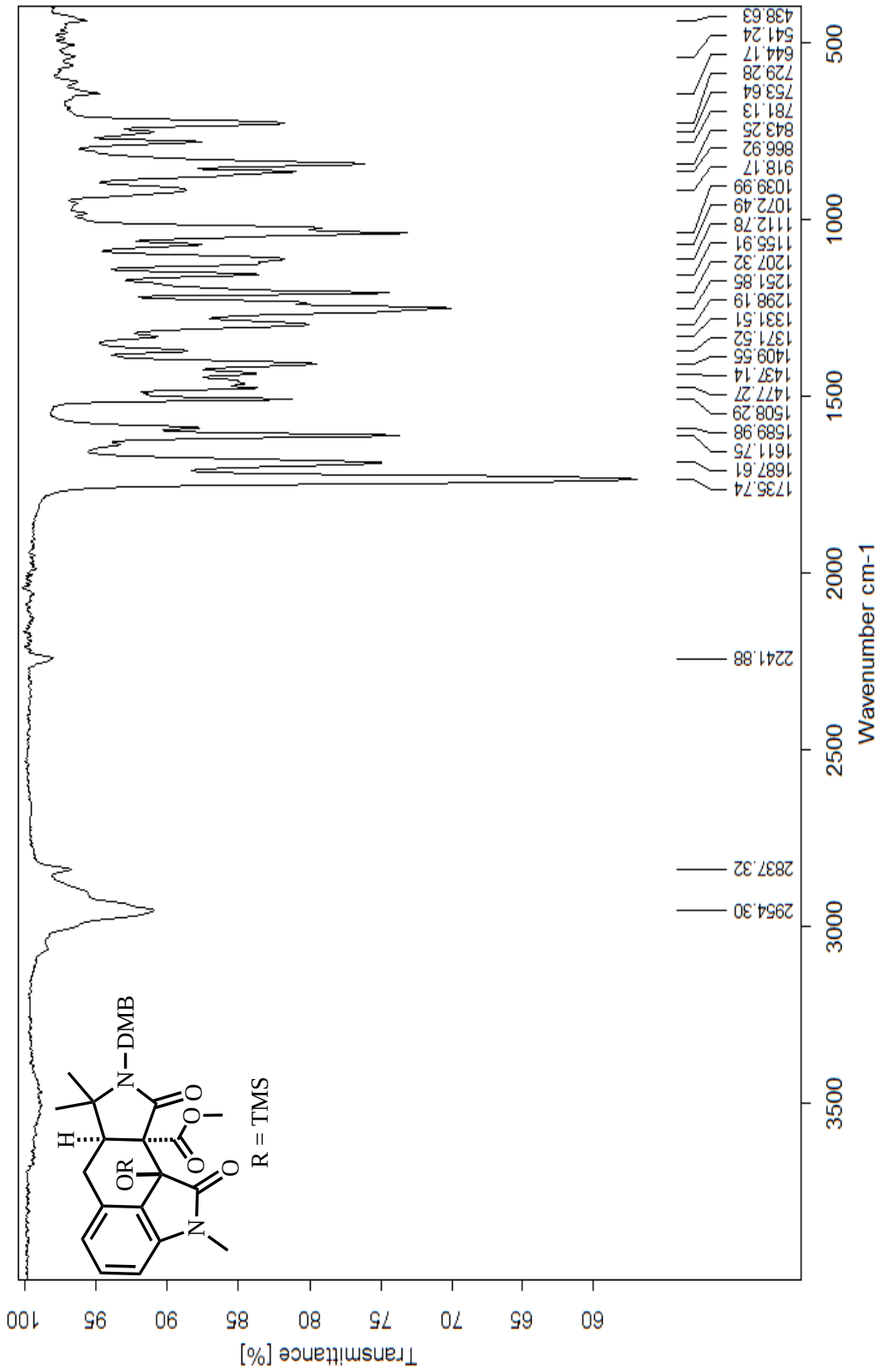

Figure C.36. FTIR Spectrum (neat) of tetracycle **3.49**

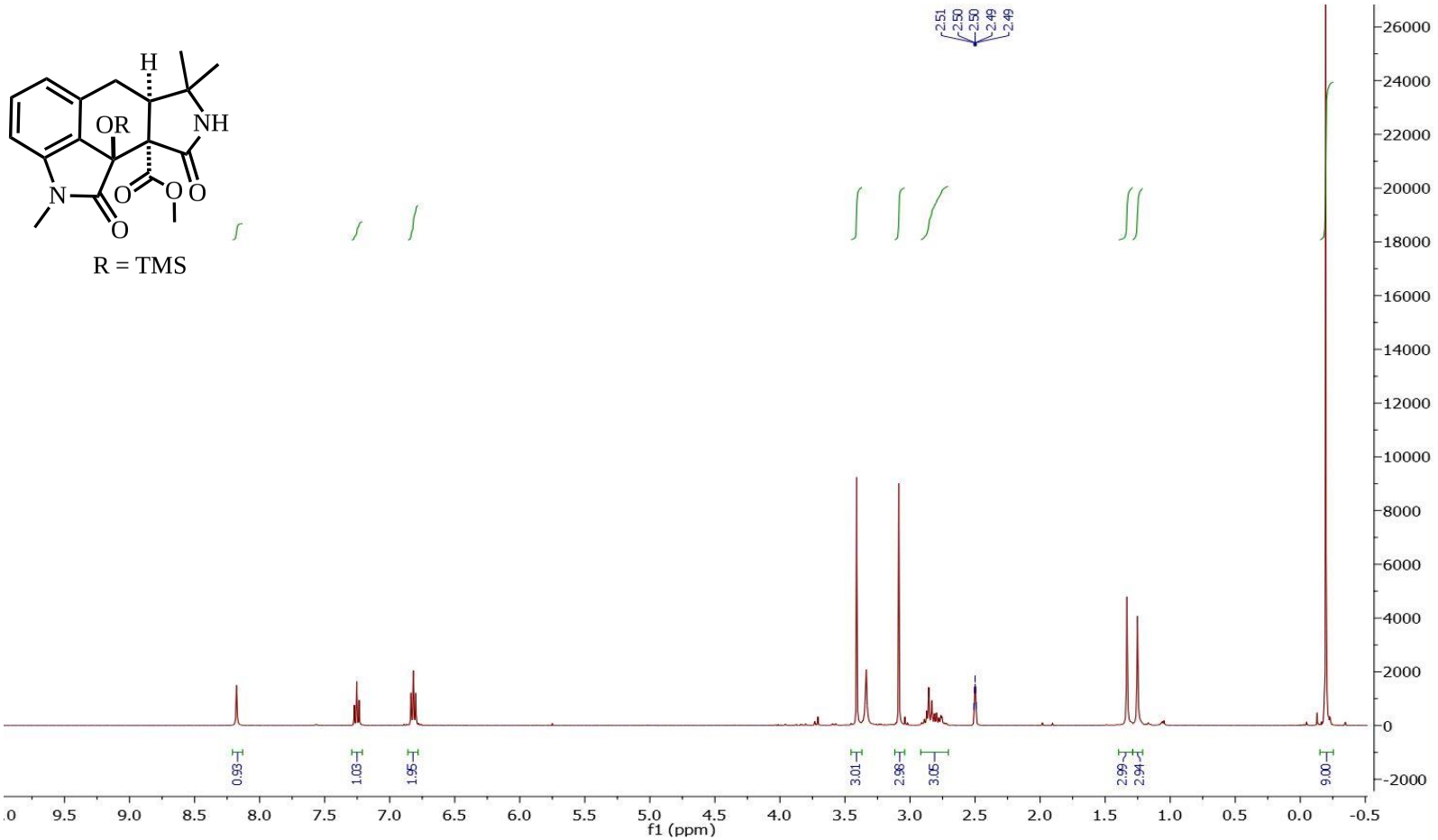

Figure C.37. **^{1}H NMR** (400 MHz, DMSO-*d6*) of amide **3.54**

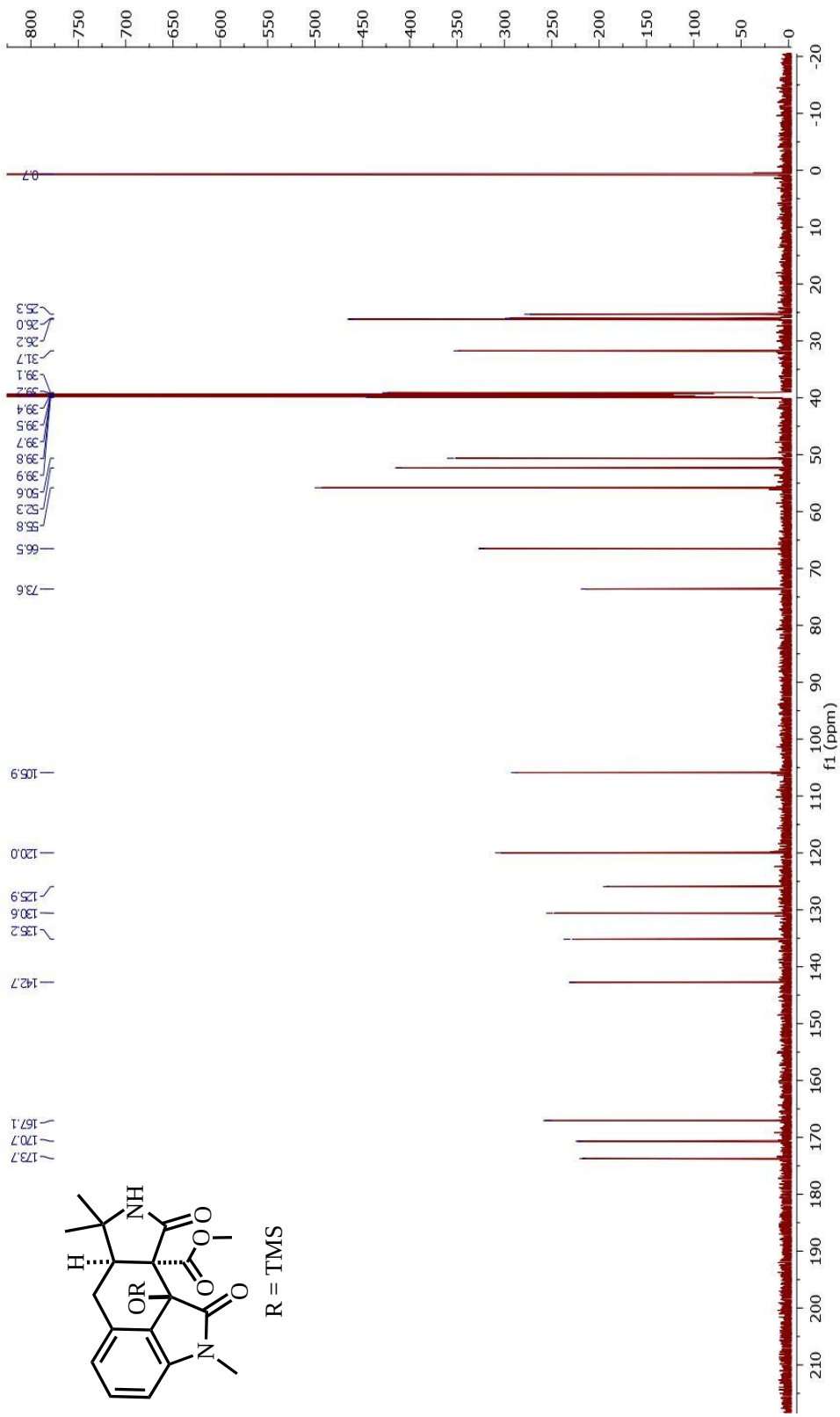

Figure C.38. **^{13}C NMR** (151 MHz, DMSO-*d6*) of amide **3.54**

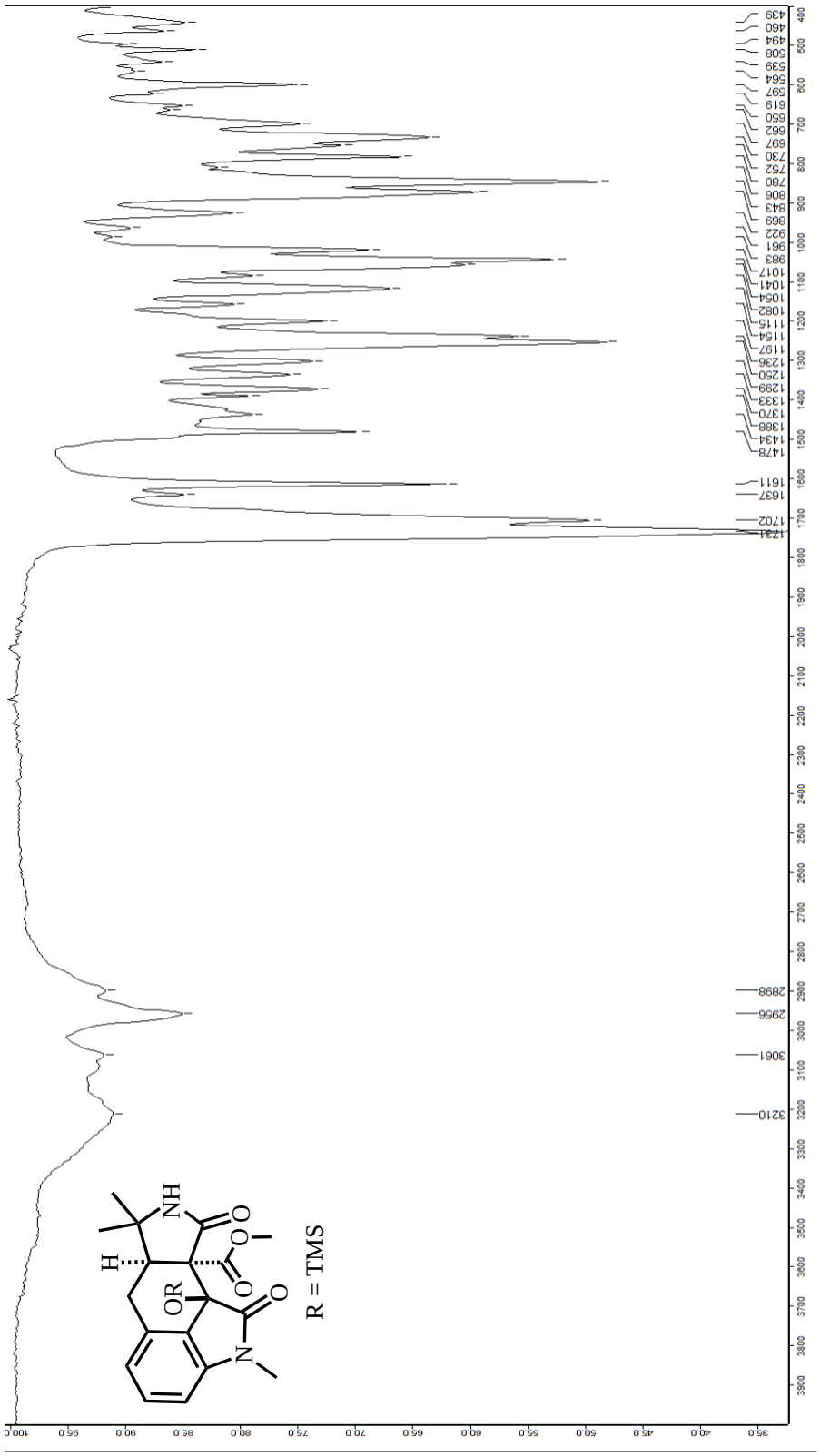

Figure C.39. FTIR Spectrum (neat) of amide **3.54**

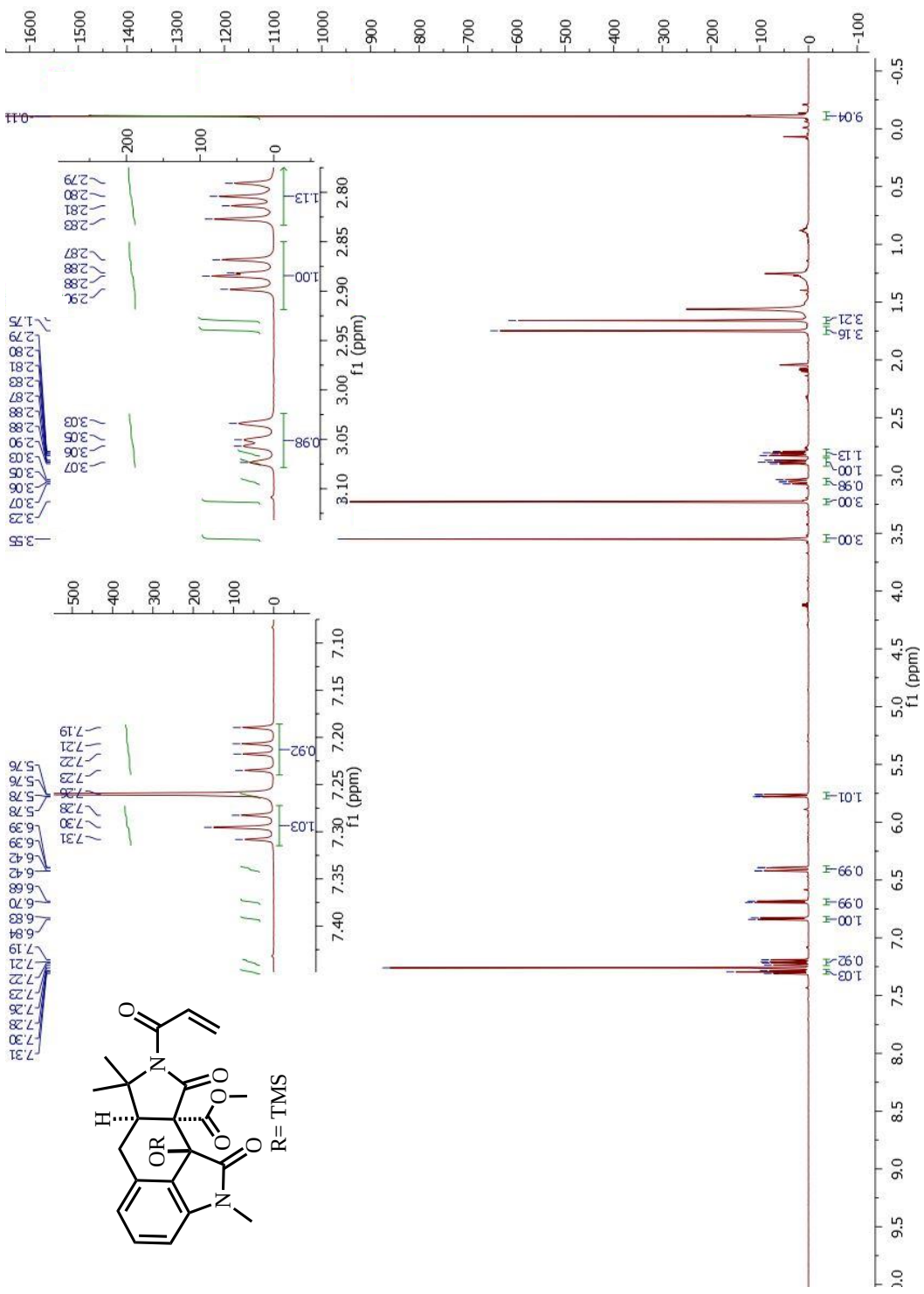

Figure C.40. **^{1}H NMR** (400 MHz, $CDCl_3$) of imide **3.55**

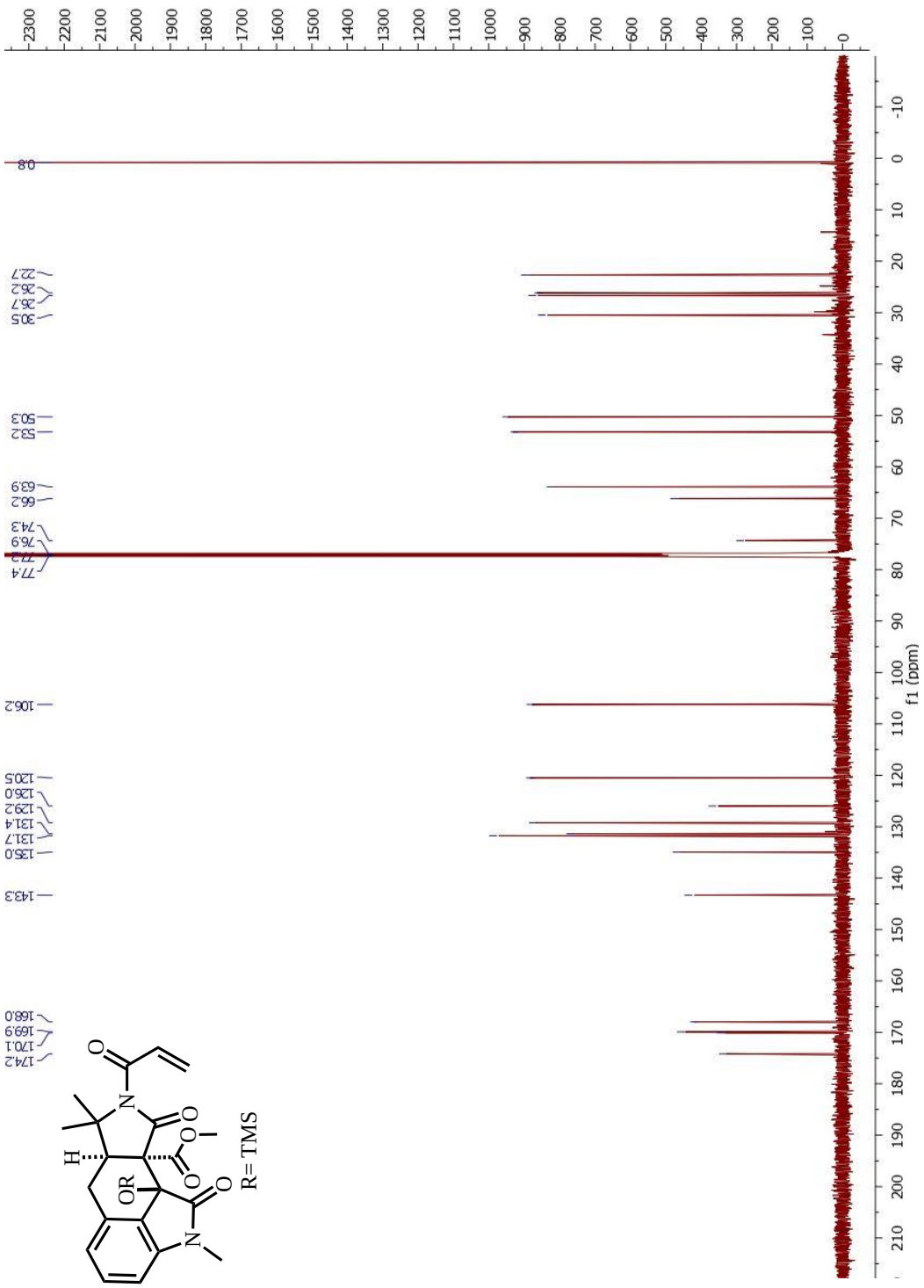

Figure C.41. **^{13}C NMR** (151 MHz, $CDCl_3$) of imide **3.55**

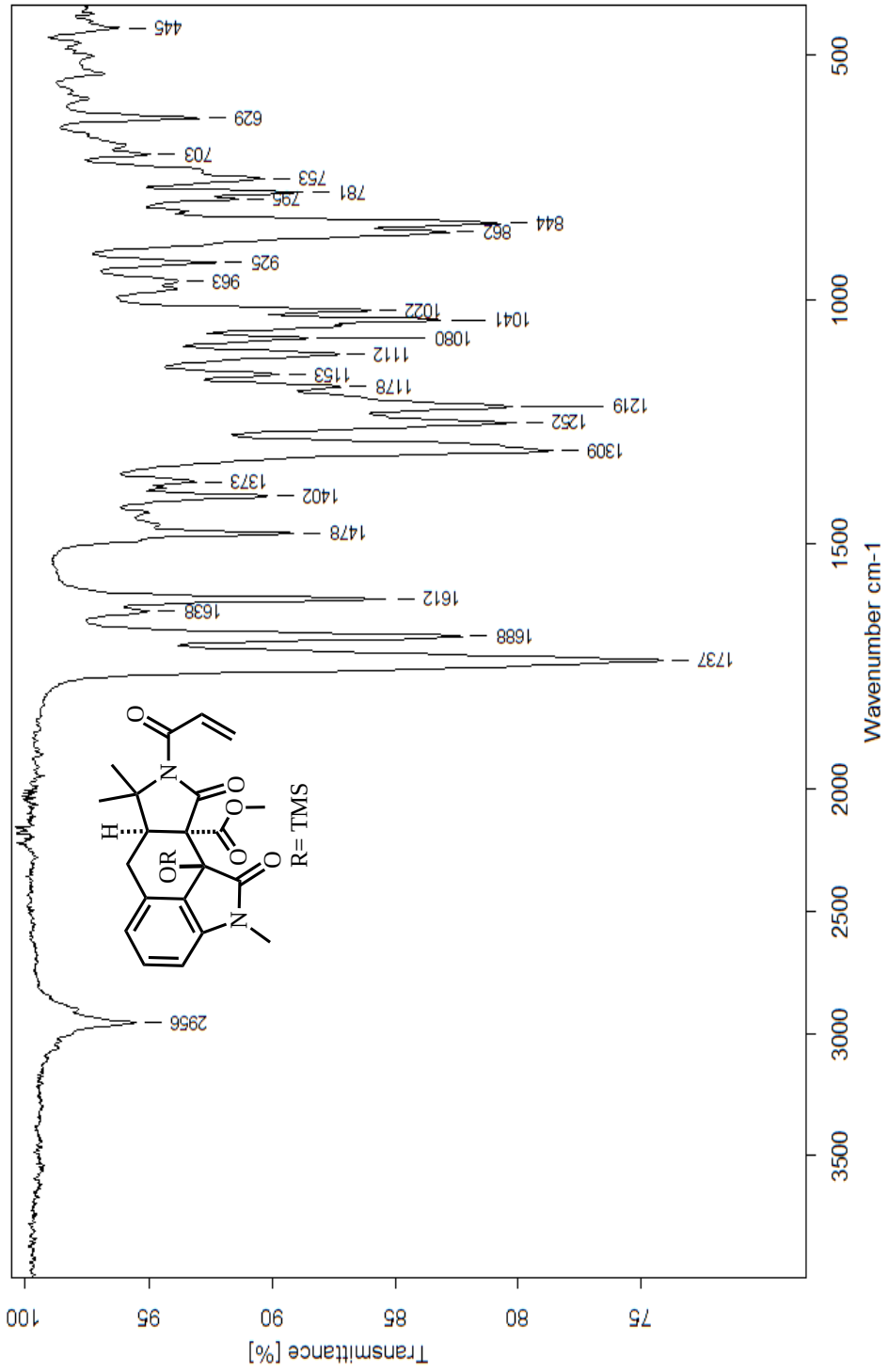

Figure C.42. FTIR Spectrum (neat) of imide **3.55**

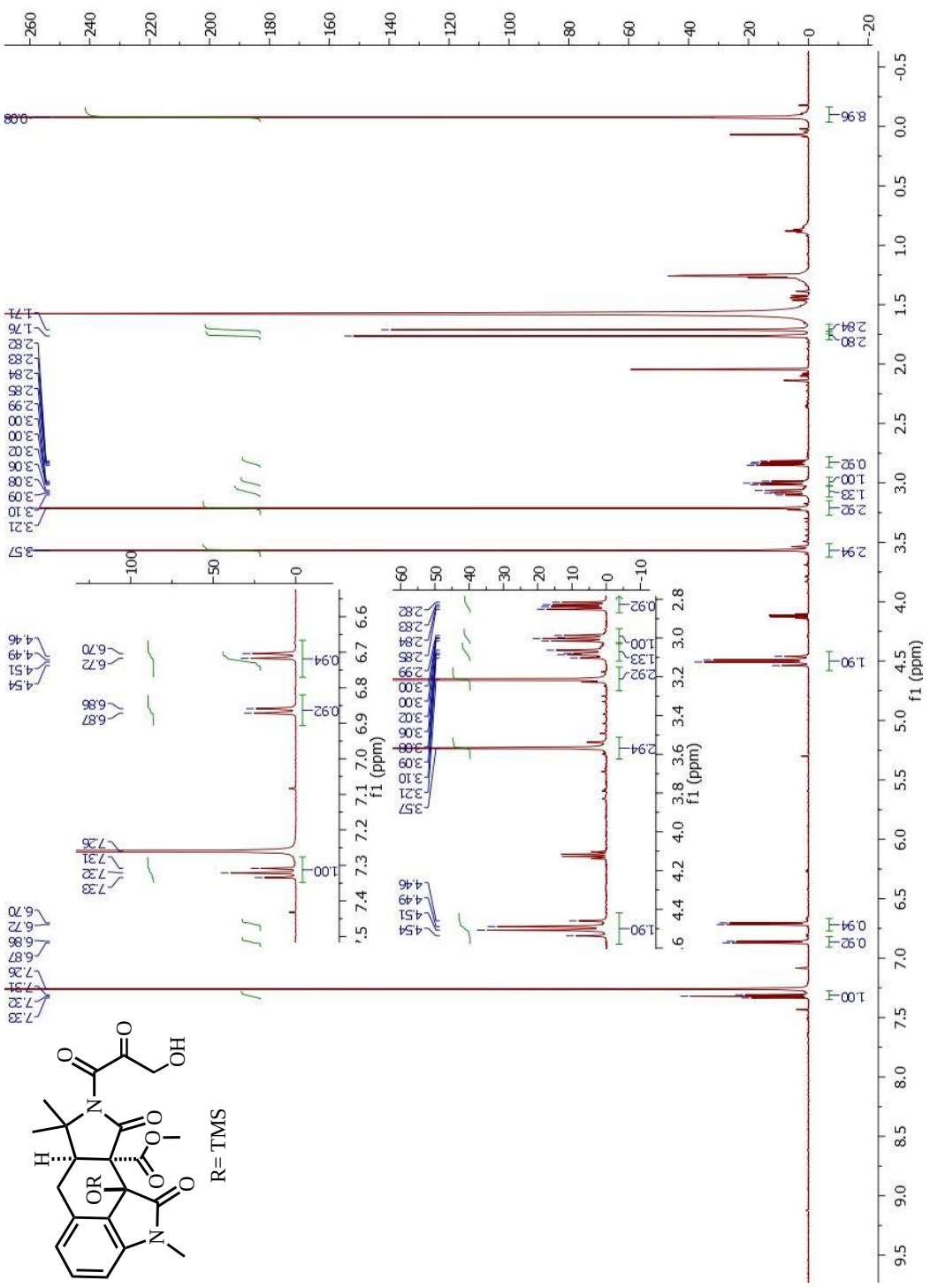

Figure C.43. **^{1}H NMR** (600 MHz, $CDCl_3$) of acyloin **3.58**

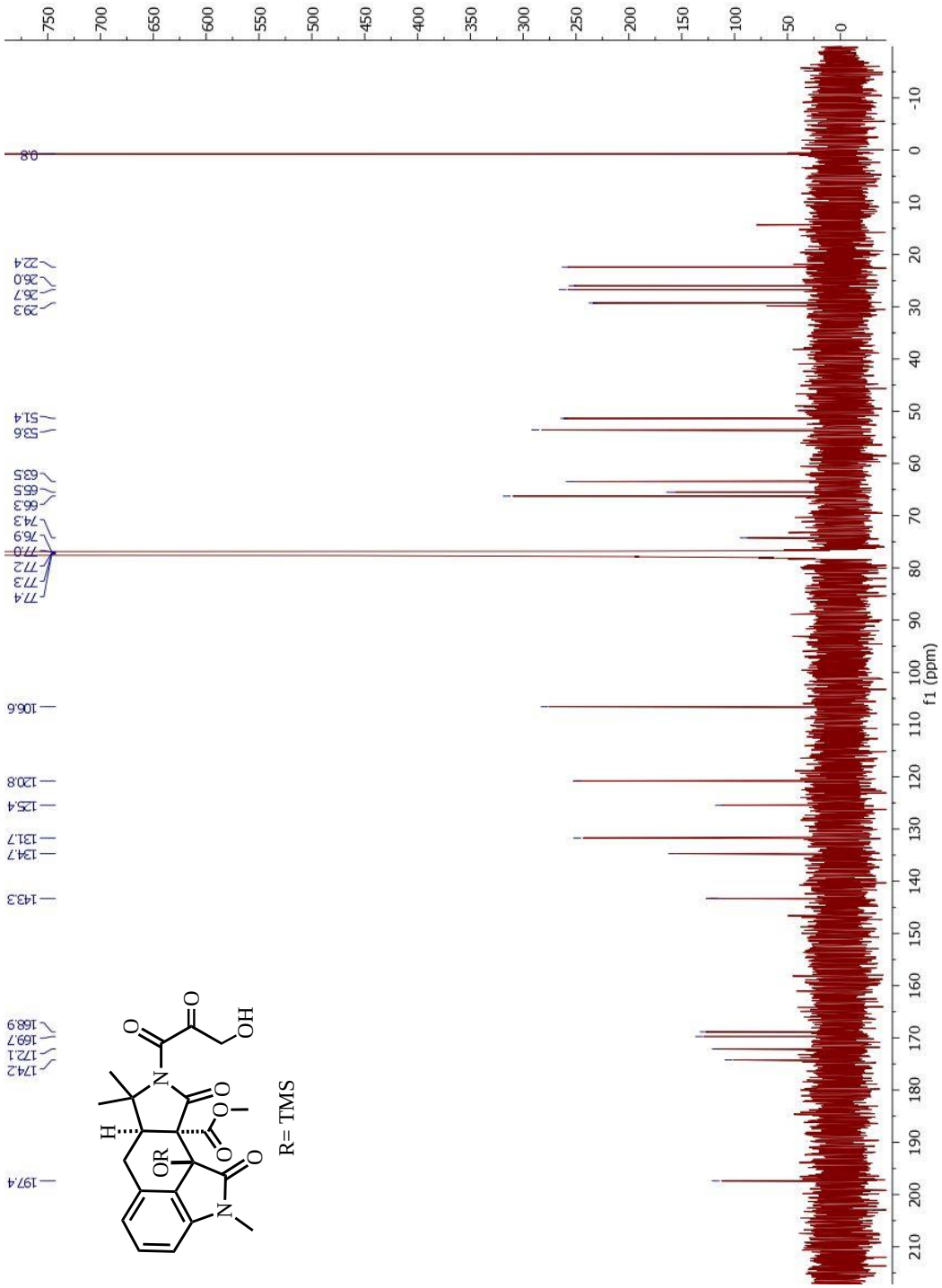

Figure C.44. **^{13}C NMR** (151 MHz, $CDCl_3$) of acyloin **3.58**

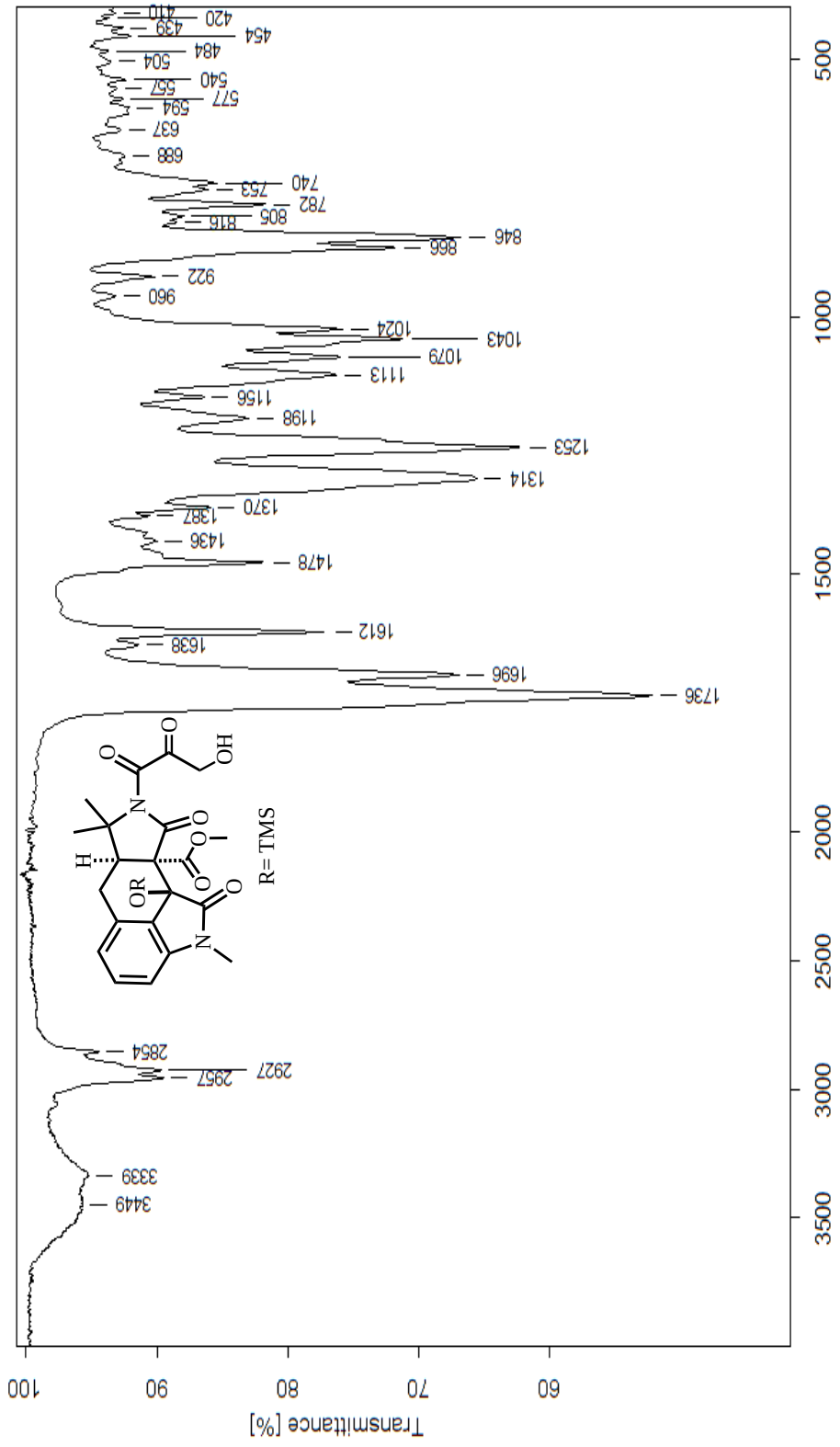

Figure C.45. FTIR Spectrum (neat) of acyloin **3.58**

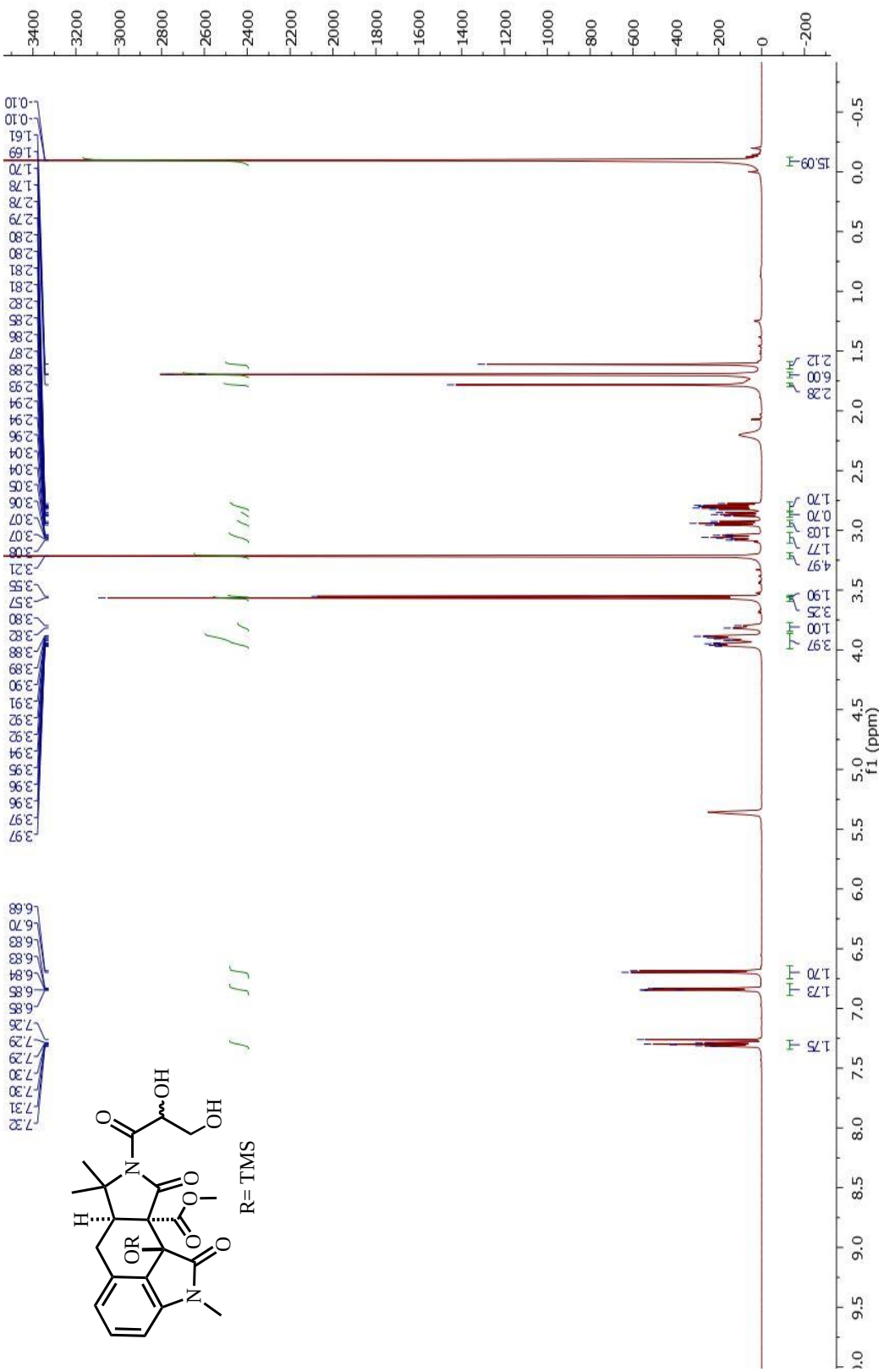

Figure C.46. **^{1}H NMR** (600 MHz, $CDCl_3$) of diols **3.56**

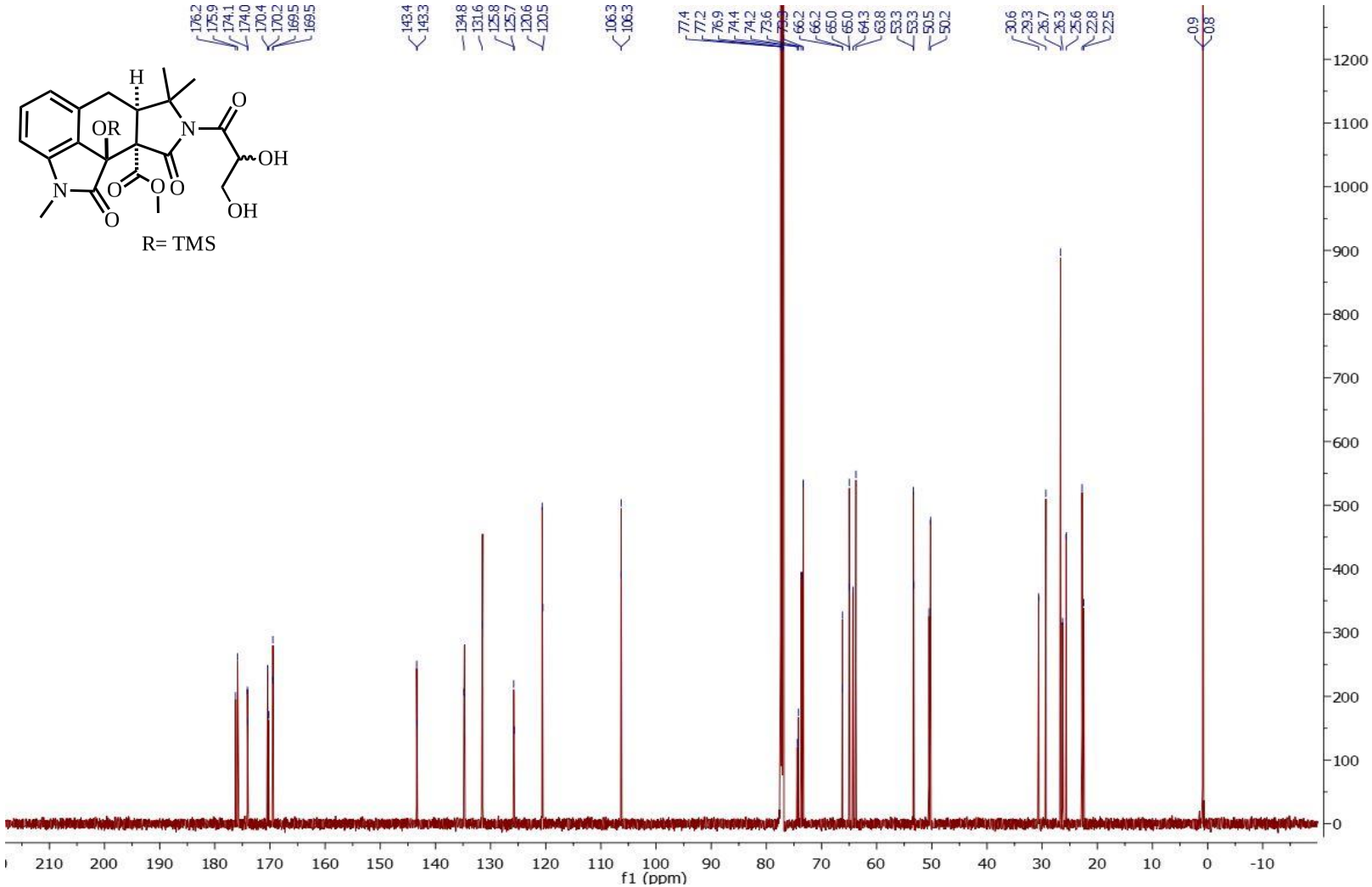

Figure C.47. **^{13}C NMR** (151 MHz, $CDCl_3$) of diols **3.56**

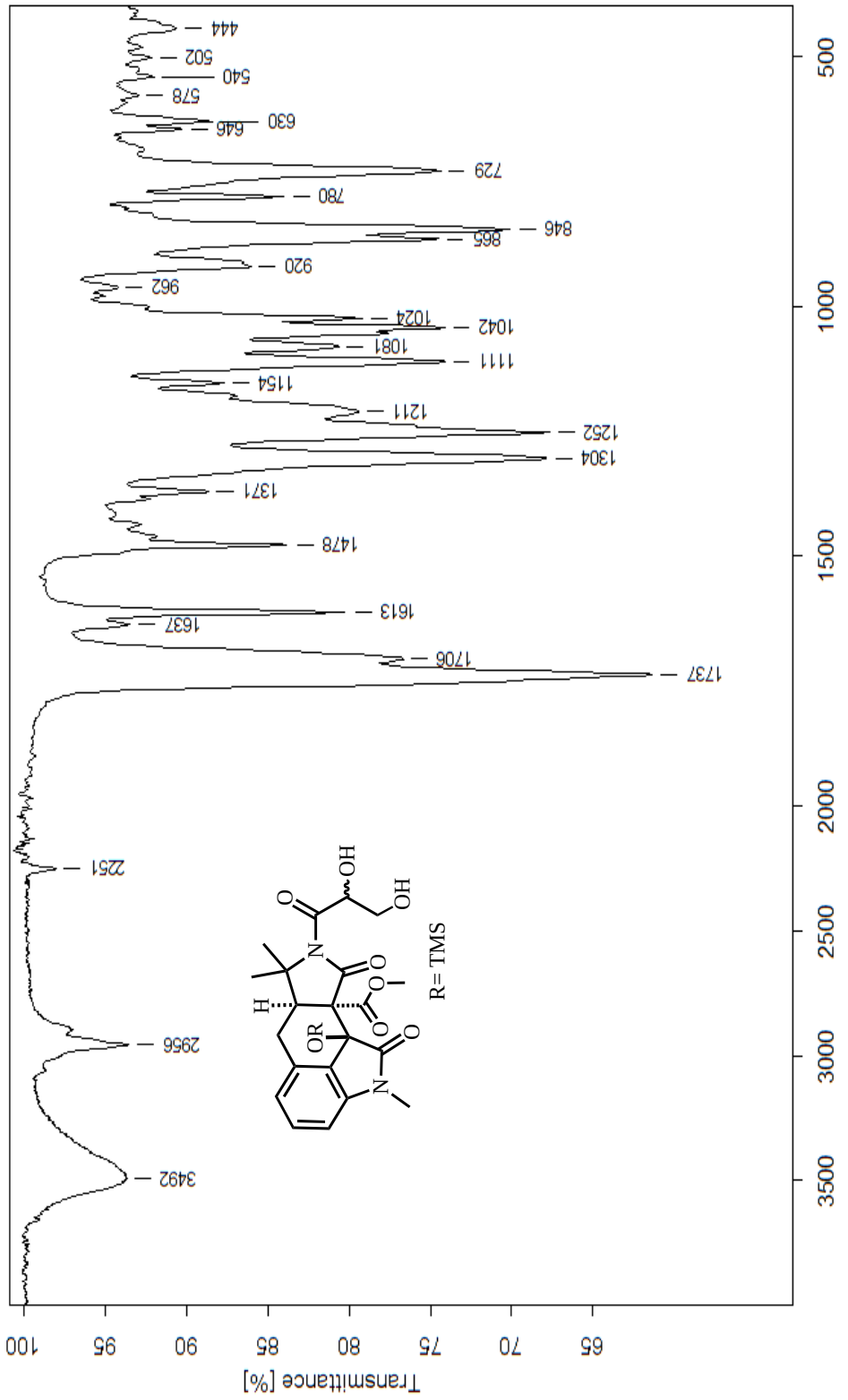

Figure C.48. FTIR Spectrum (neat) of diols **3.56**

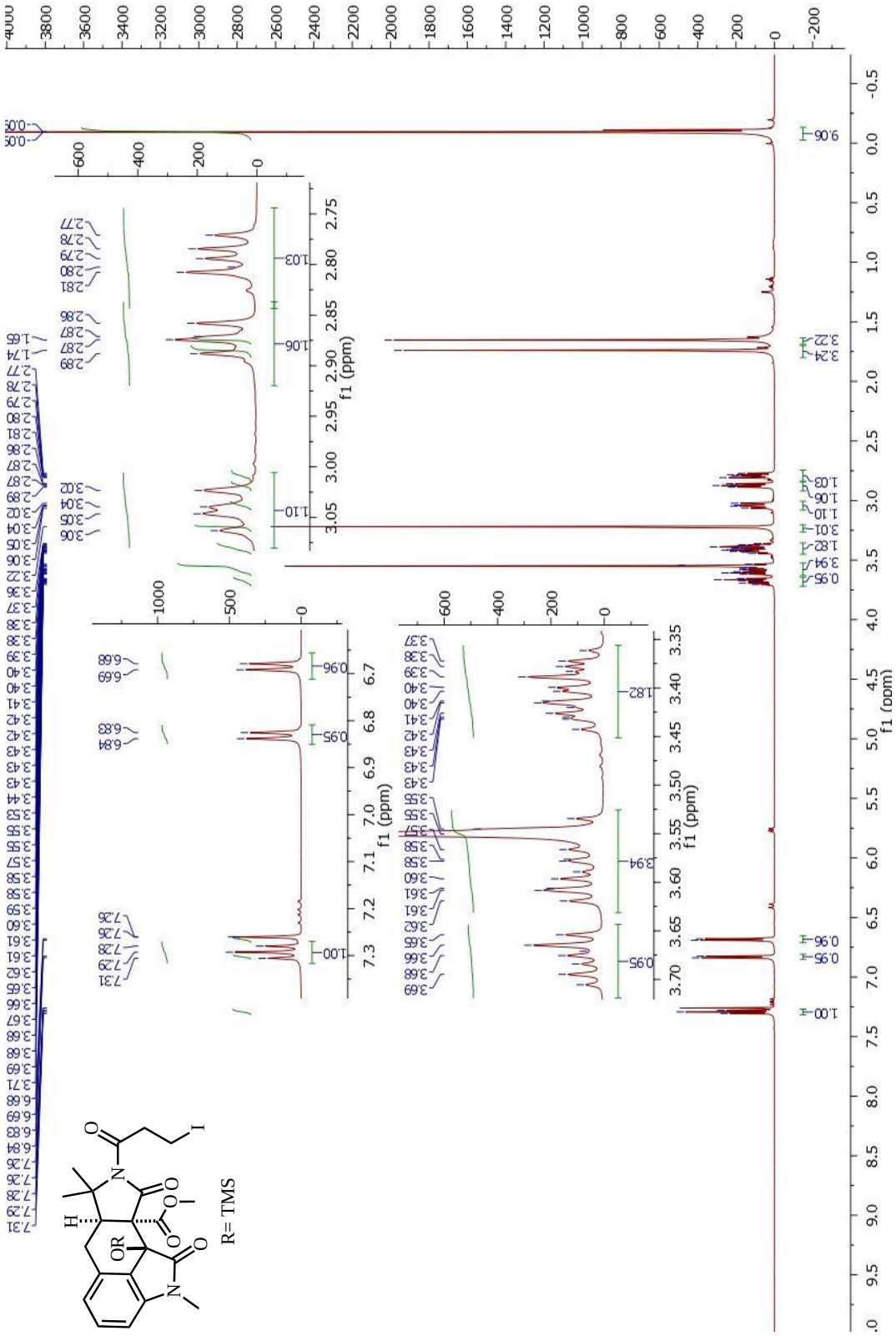

Figure C.49. **^{1}H NMR** (600 MHz, $CDCl_3$) of iodide **3.68**

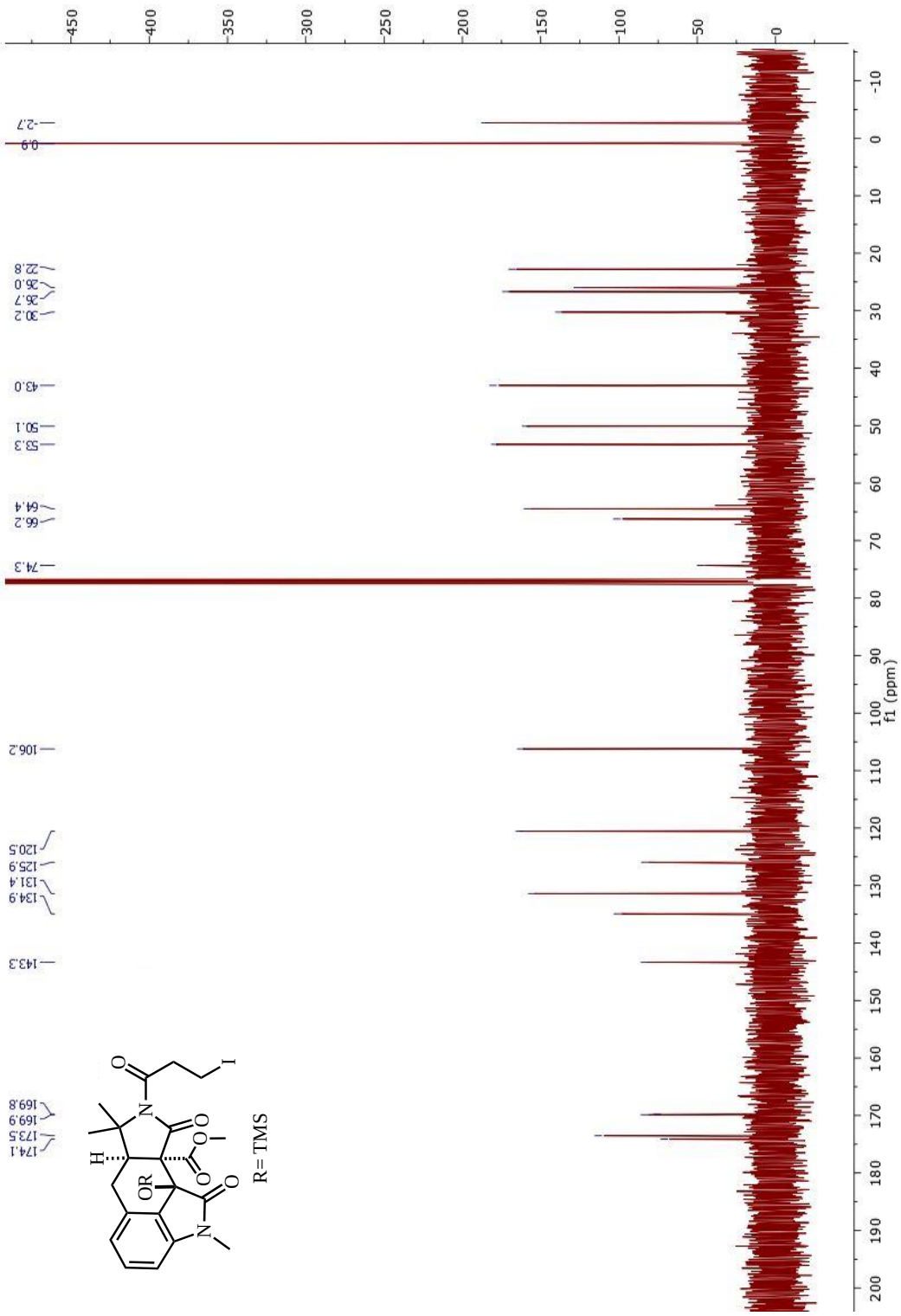

Figure C.50. **^{13}C NMR** (101 MHz, $CDCl_3$) of iodide **3.68**

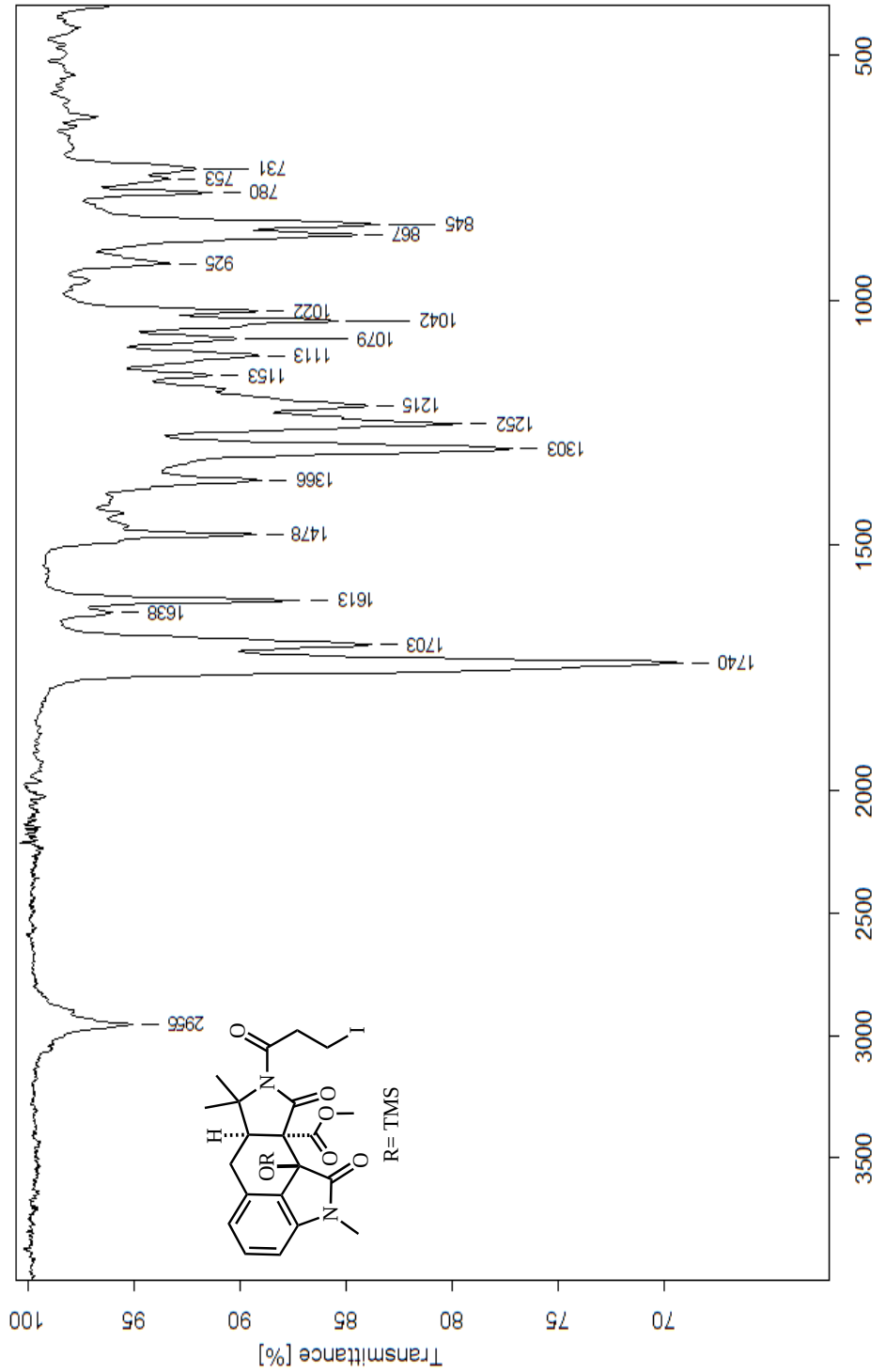

Figure C.51. FTIR Spectrum (neat) of iodide **3.68**

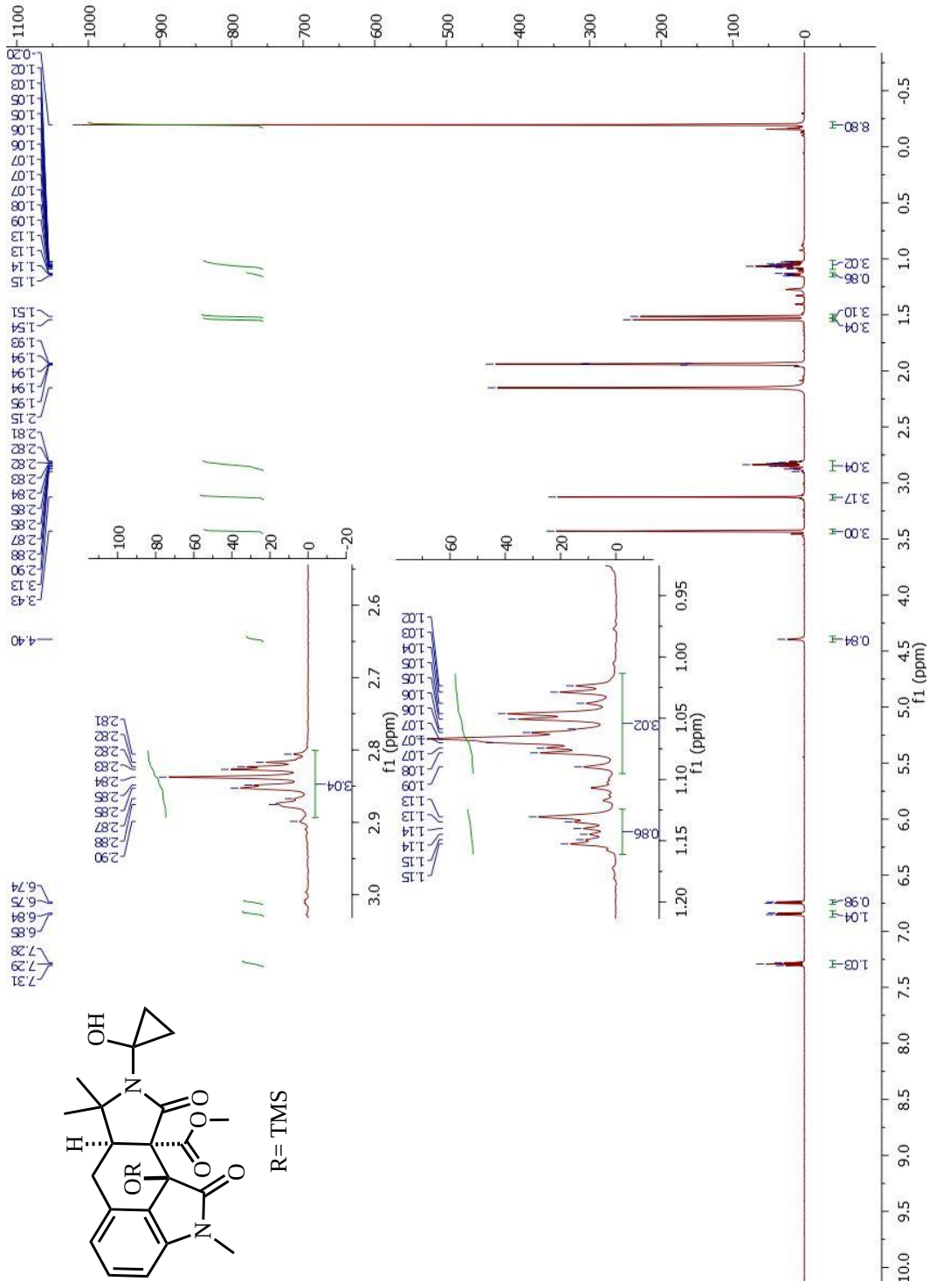

Figure C.52. **^{1}H NMR** (600 MHz, $CDCl_3$) of hemiaminal **3.70**

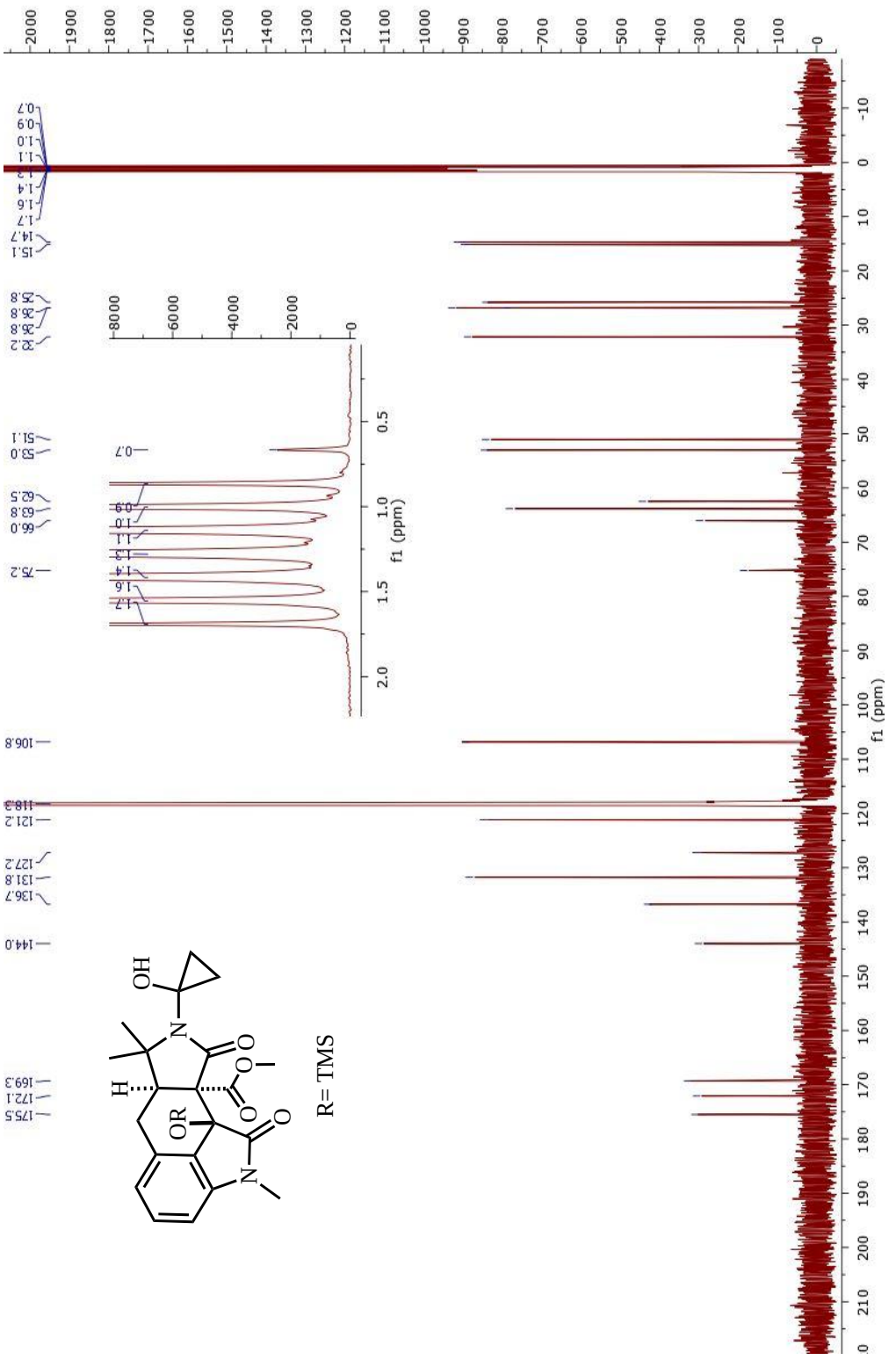

Figure C.53. **^{13}C NMR** (151 MHz, $CDCl_3$) of hemiaminal **3.70**

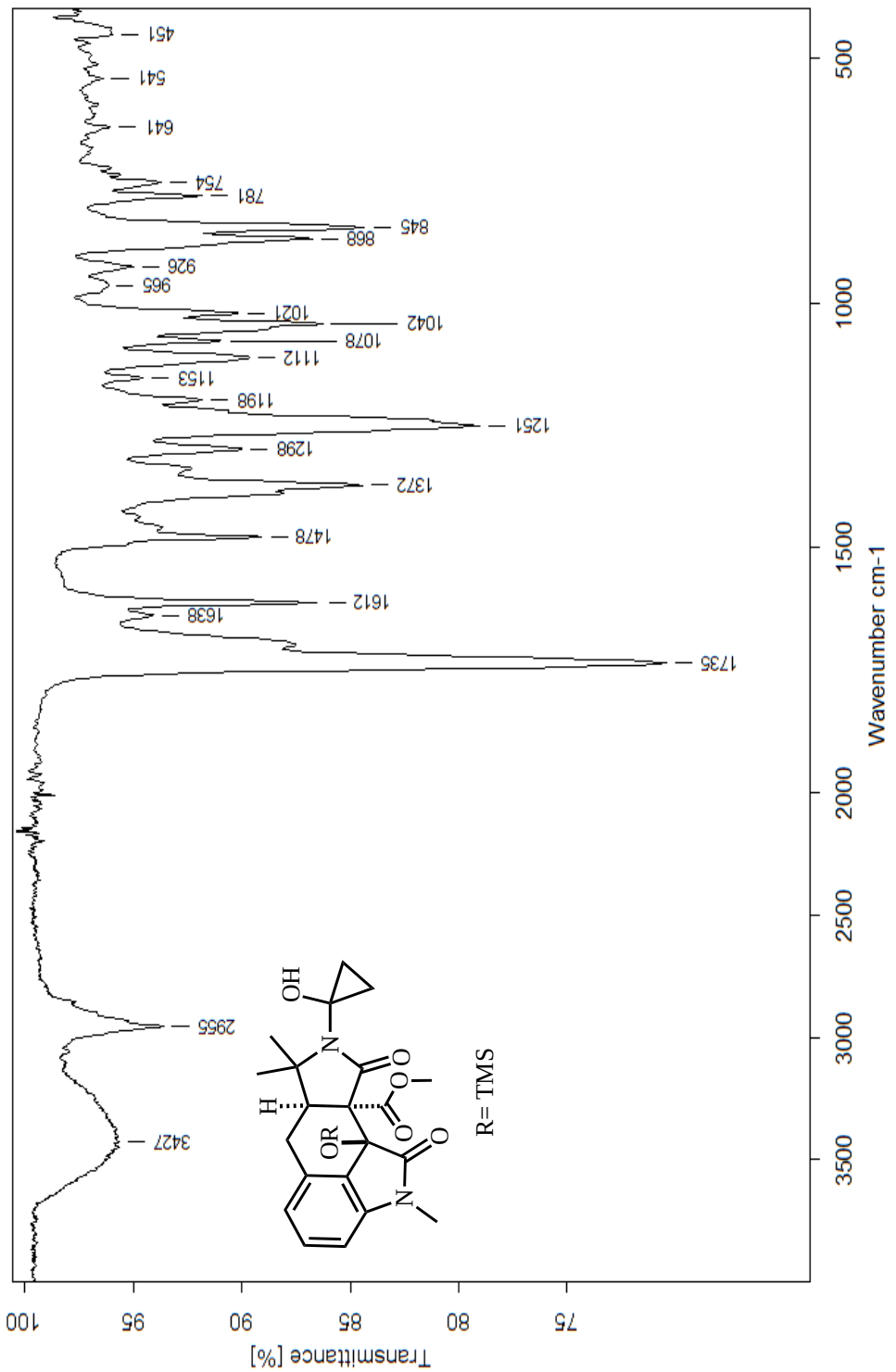

Figure C.54. FTIR Spectrum (neat) of hemiaminal **3.70**

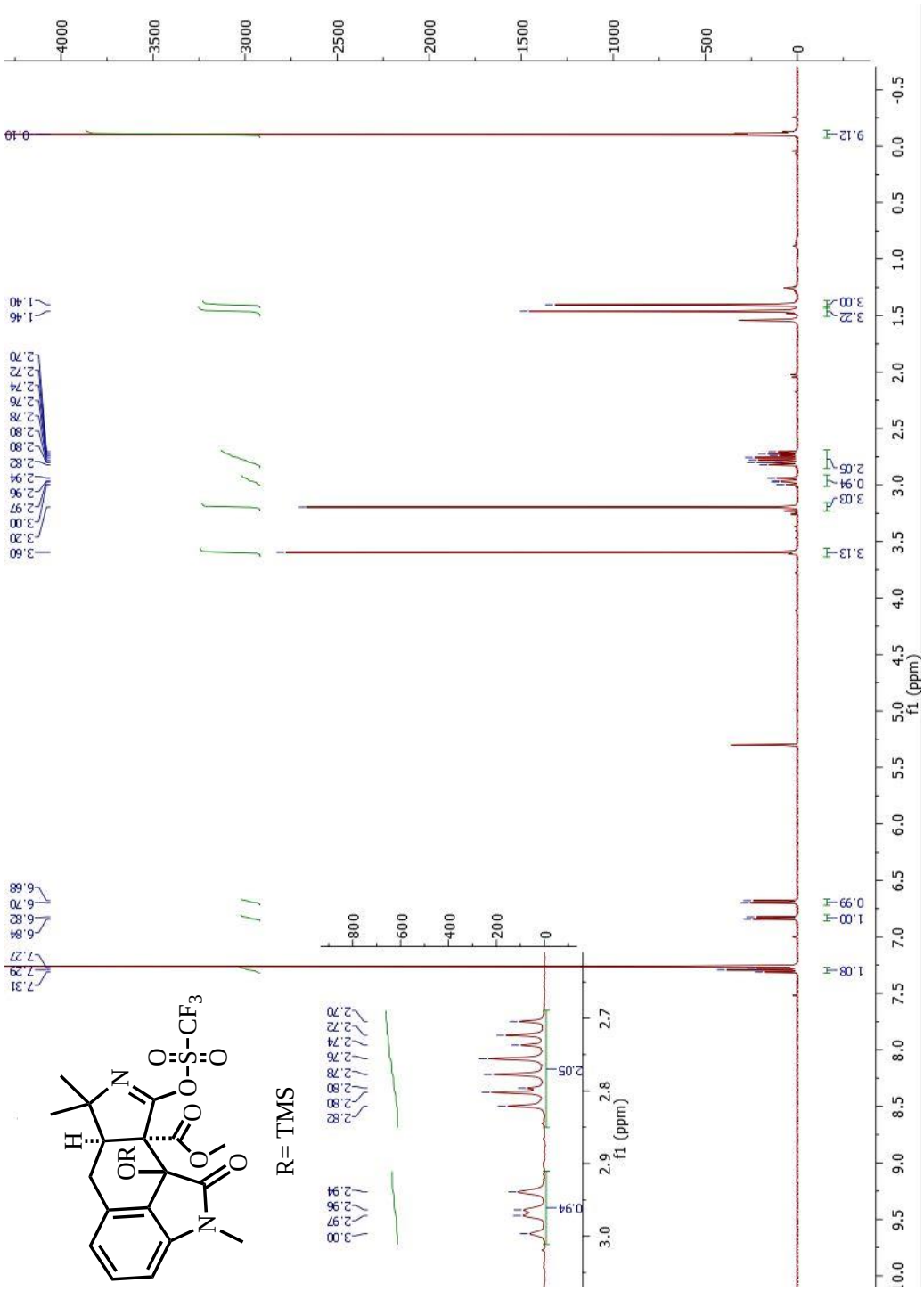

Figure C.55. **^{1}H NMR** (400 MHz, $CDCl_3$) of imidoyl triflate **3.73**

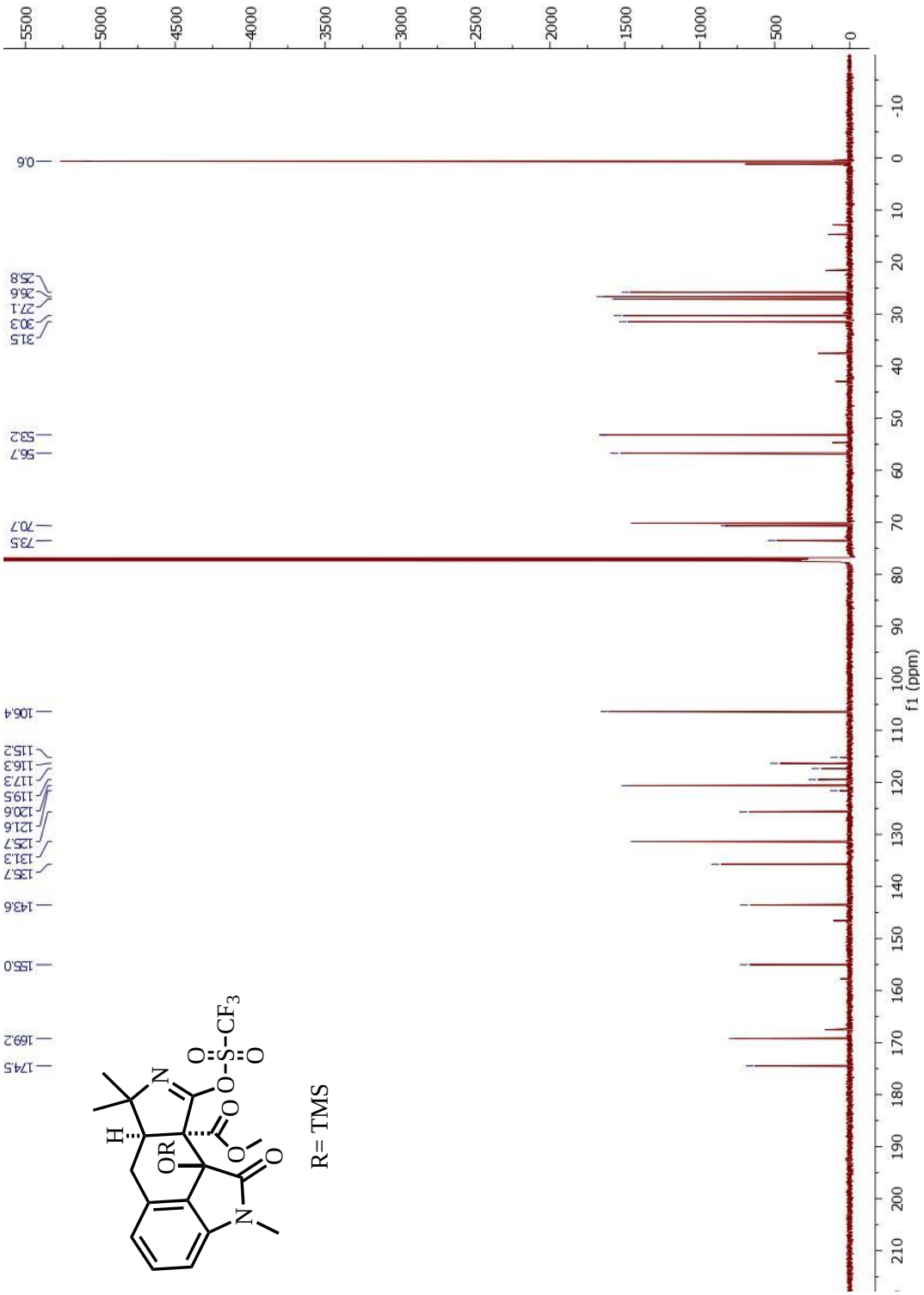

Figure C.56. **^{13}C NMR** (151 MHz, $CDCl_3$) of imidoyl triflate **3.73**

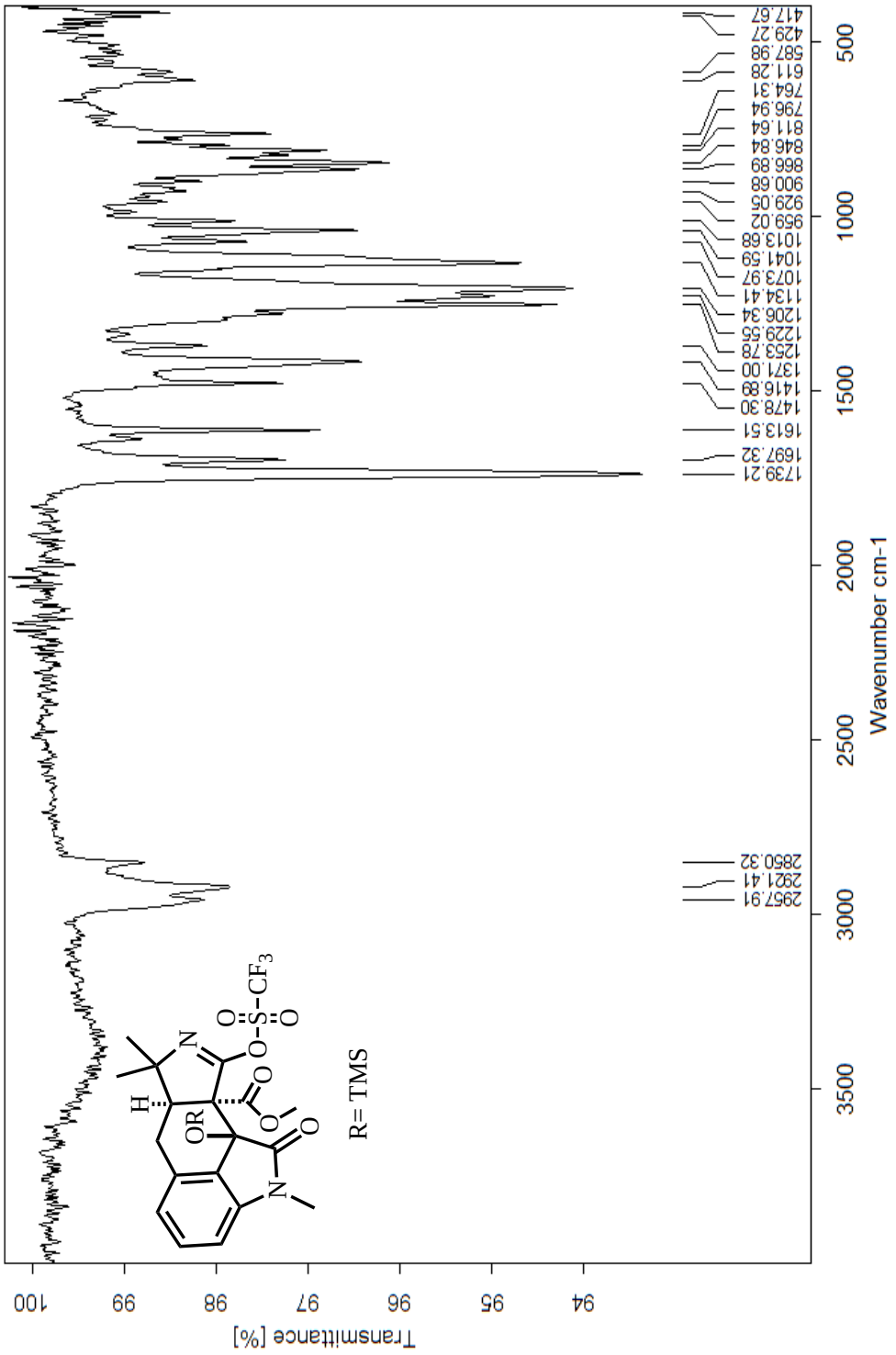

Figure C.57. FTIR Spectrum (neat) of imidoyl triflate **3.73**

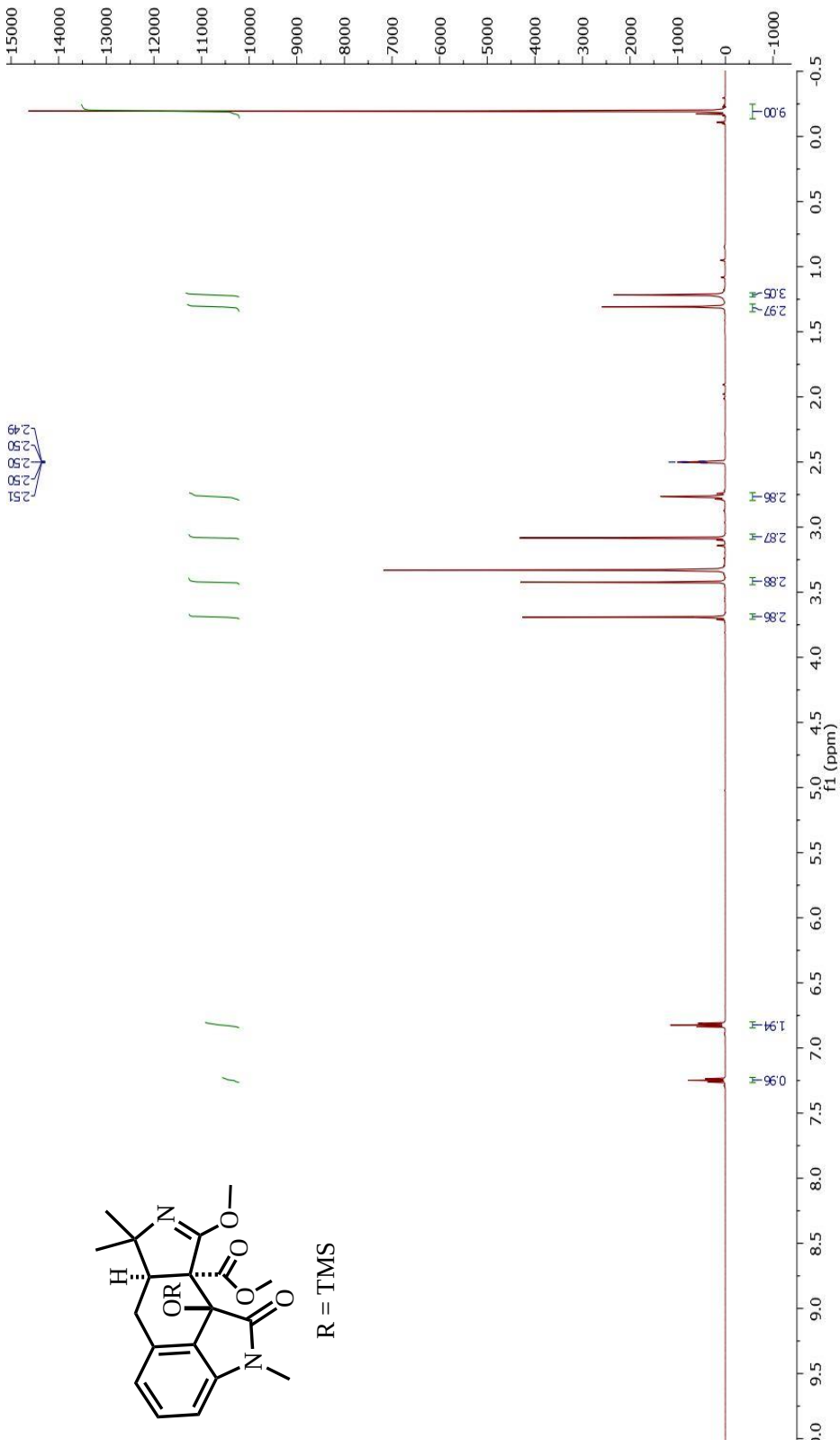

Figure C.58. **^{1}H NMR** (600 MHz, DMSO-*d6*) of imidate **3.85**

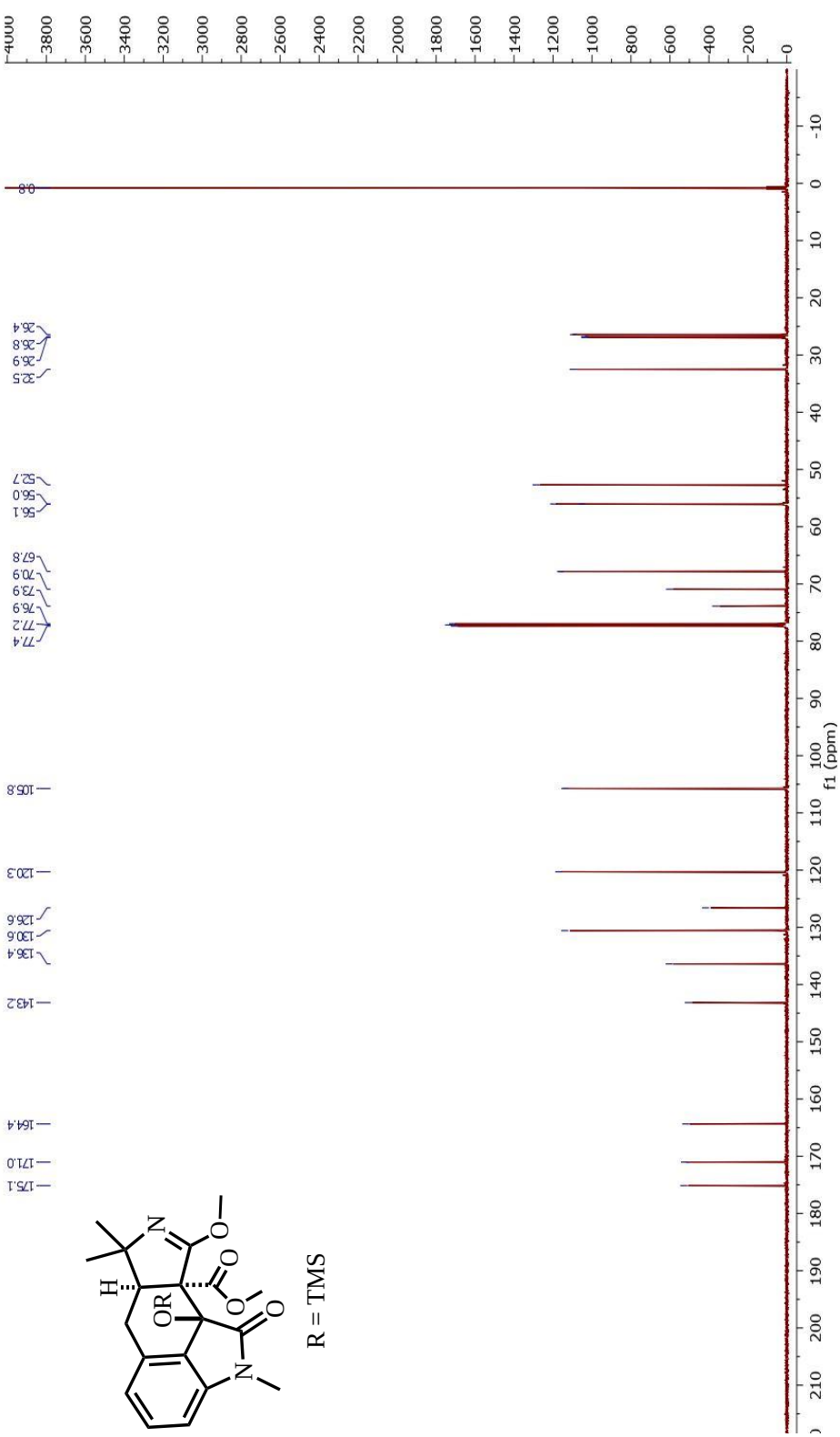

Figure C.59. **^{13}C NMR** (151 MHz, $CDCl_3$) of imidate **3.85**

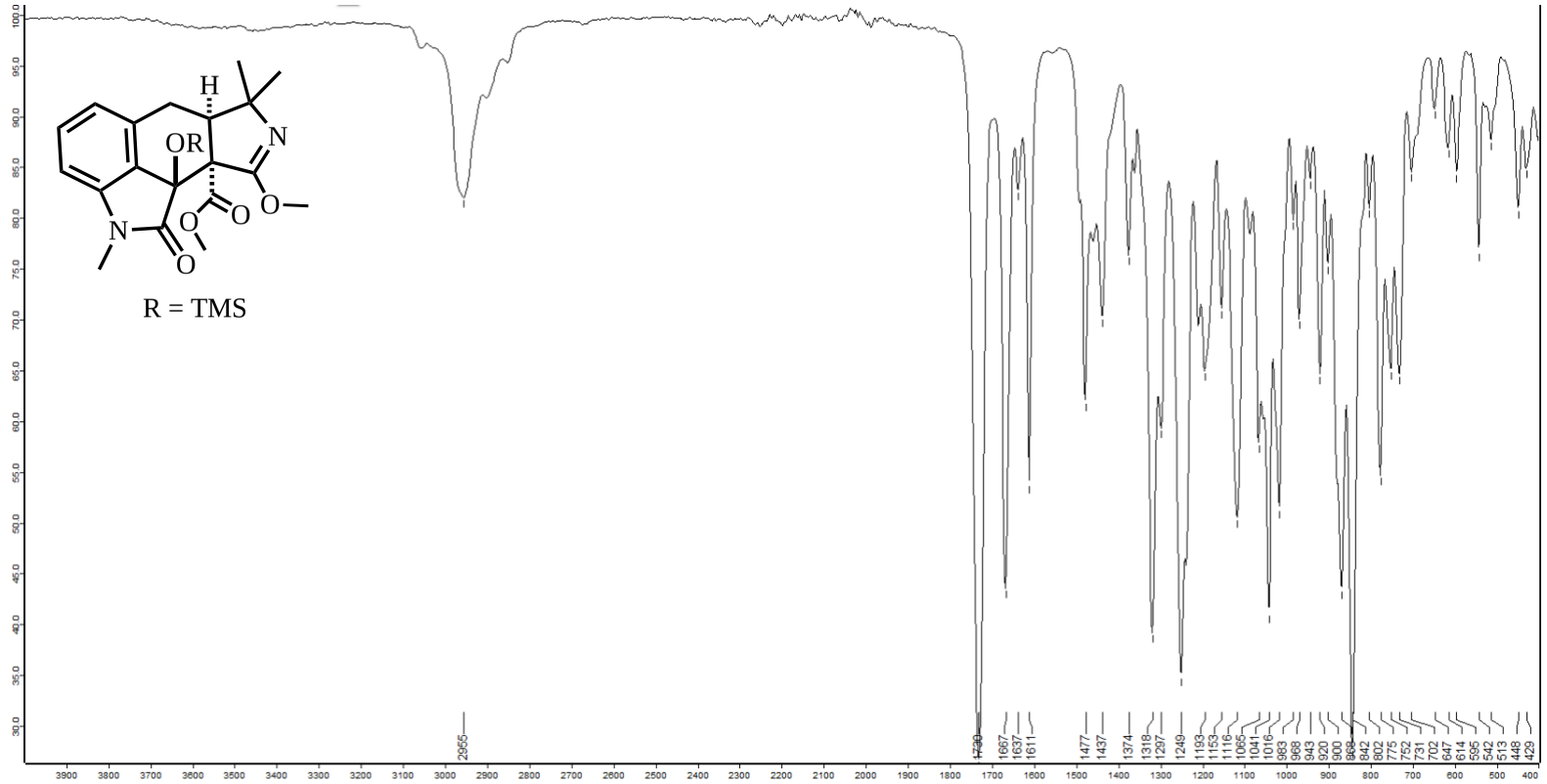

Figure C.60. FTIR Spectrum (neat) of imidate **3.85**

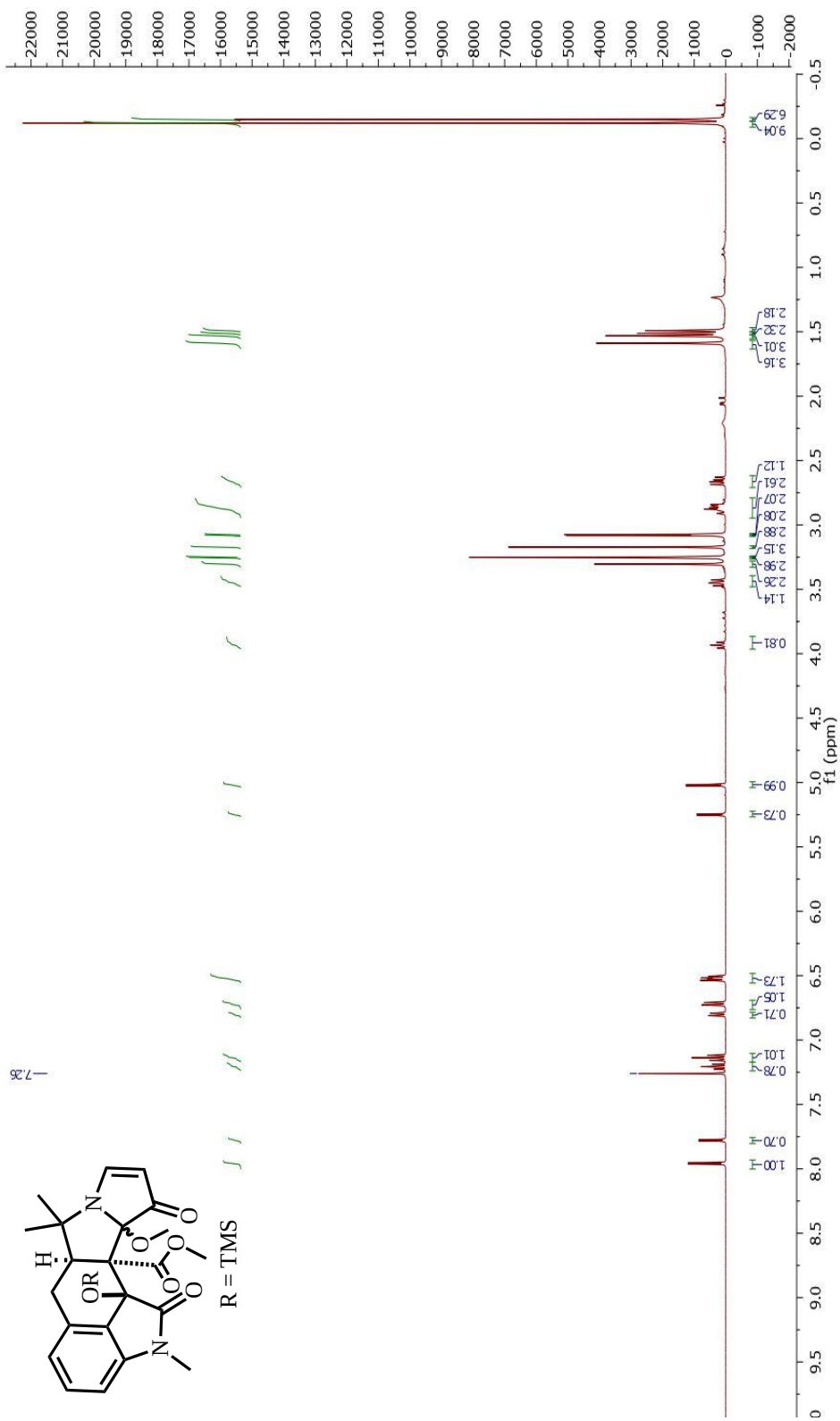

Figure C.61. **^{1}H NMR** (400 MHz, $CDCl_3$) of vinylogous amides **3.86** & **3.87**

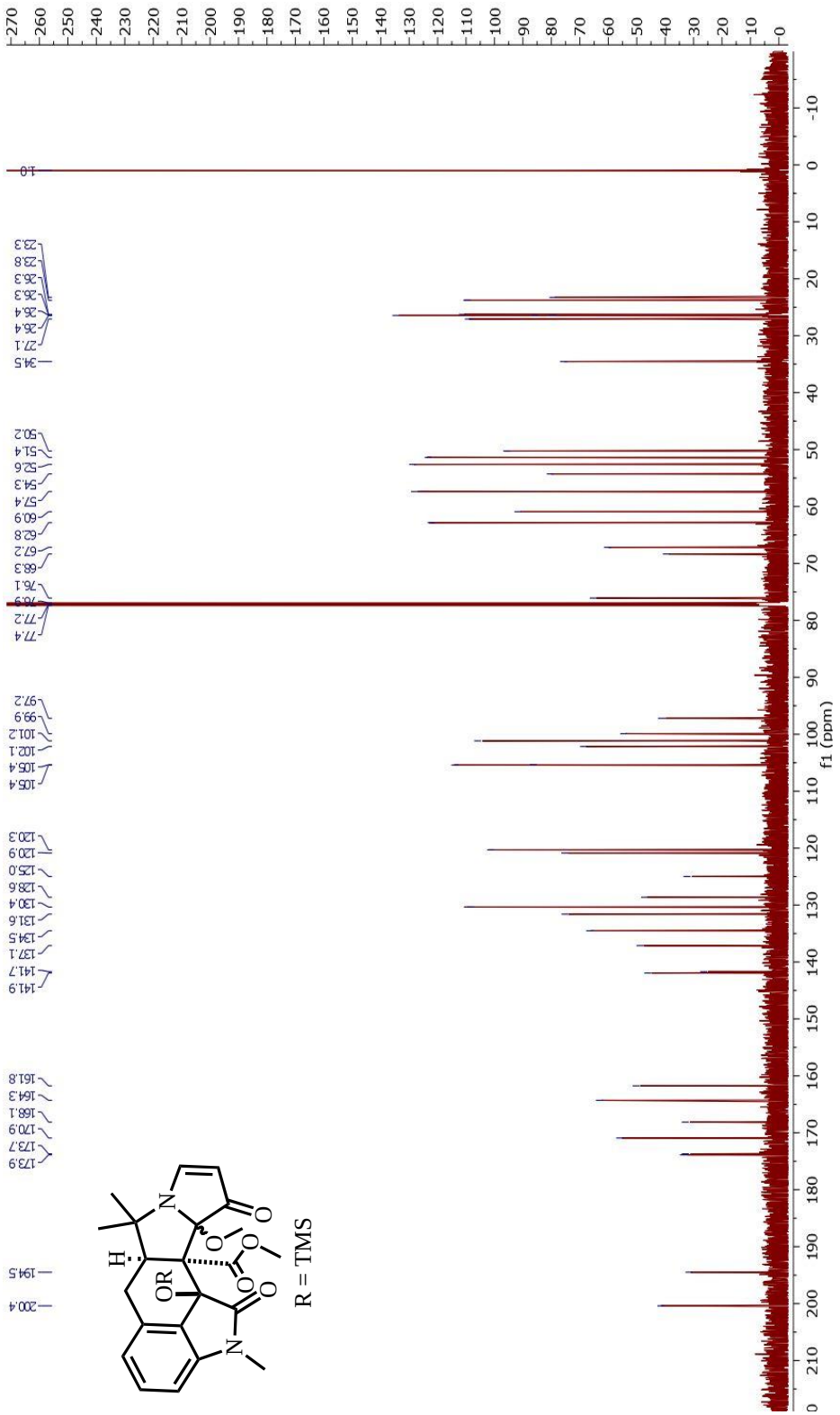

Figure C.62. **^{13}C NMR** (151 MHz, $CDCl_3$) of vinylogous amides **3.86** & **3.87**

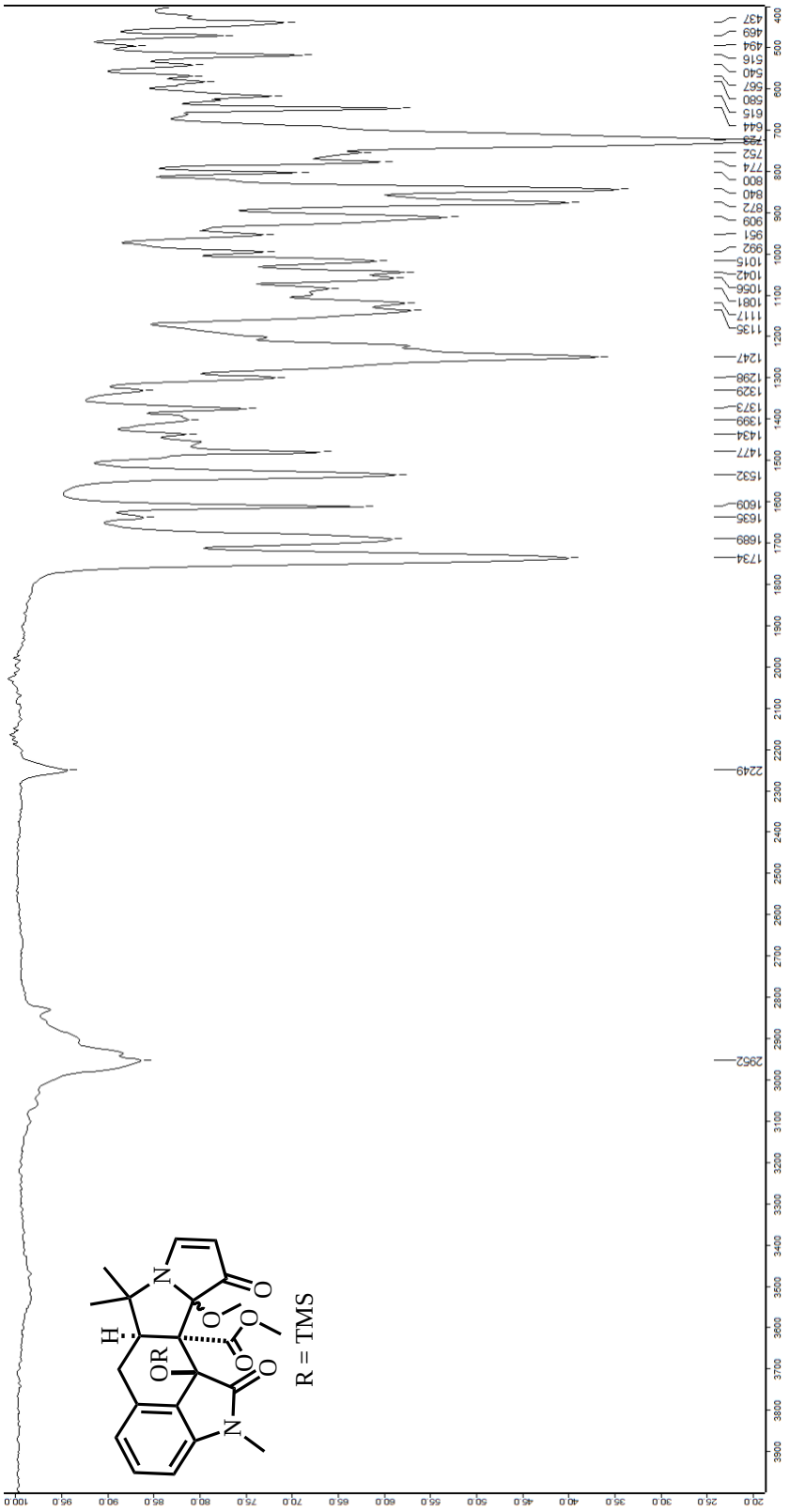

Figure C.63. FTIR Spectrum (neat) of vinylogous amides **3.86** & **3.87**

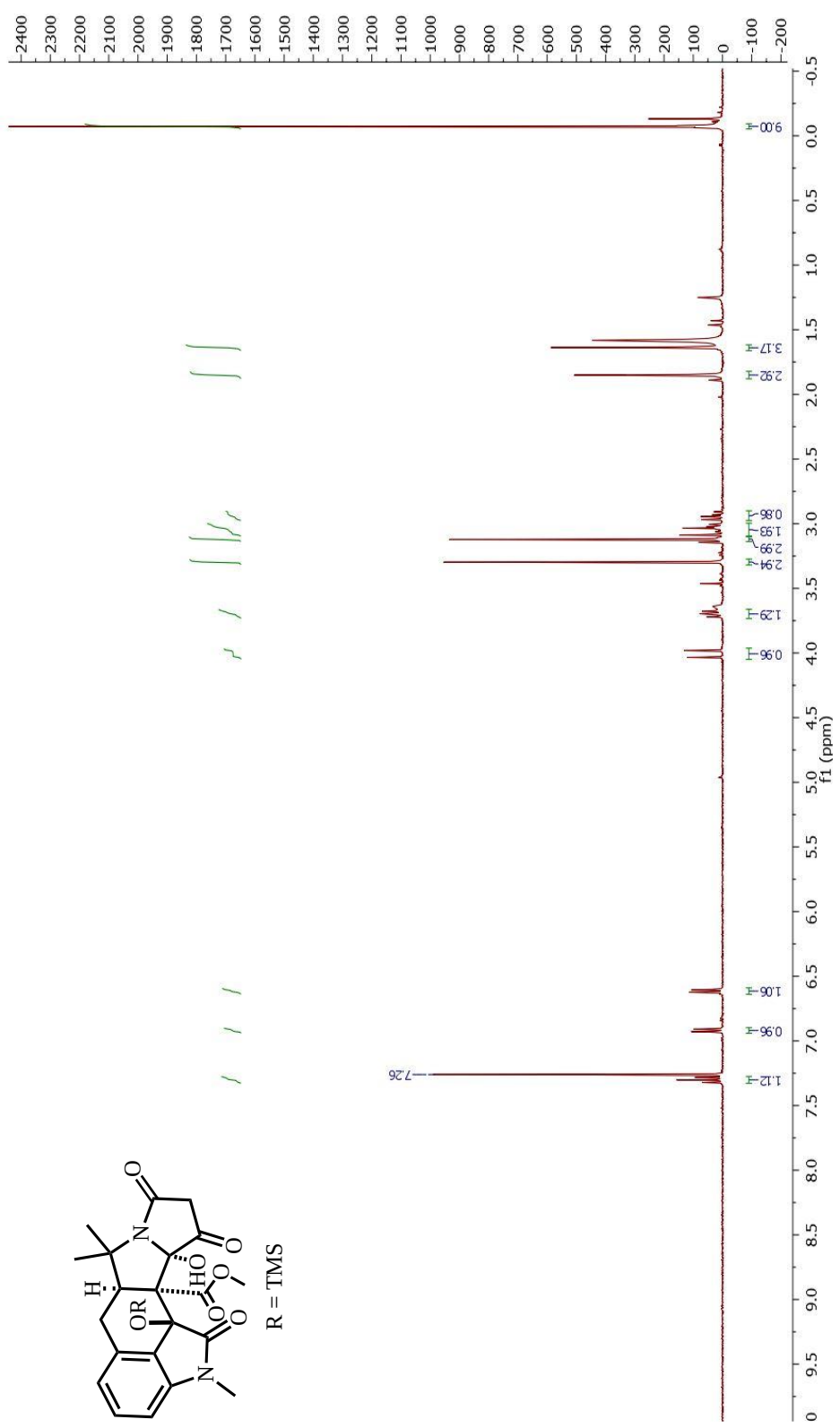

Figure C.64. **^{1}H NMR** (400 MHz, $CDCl_3$) of tetramic acid **3.97**

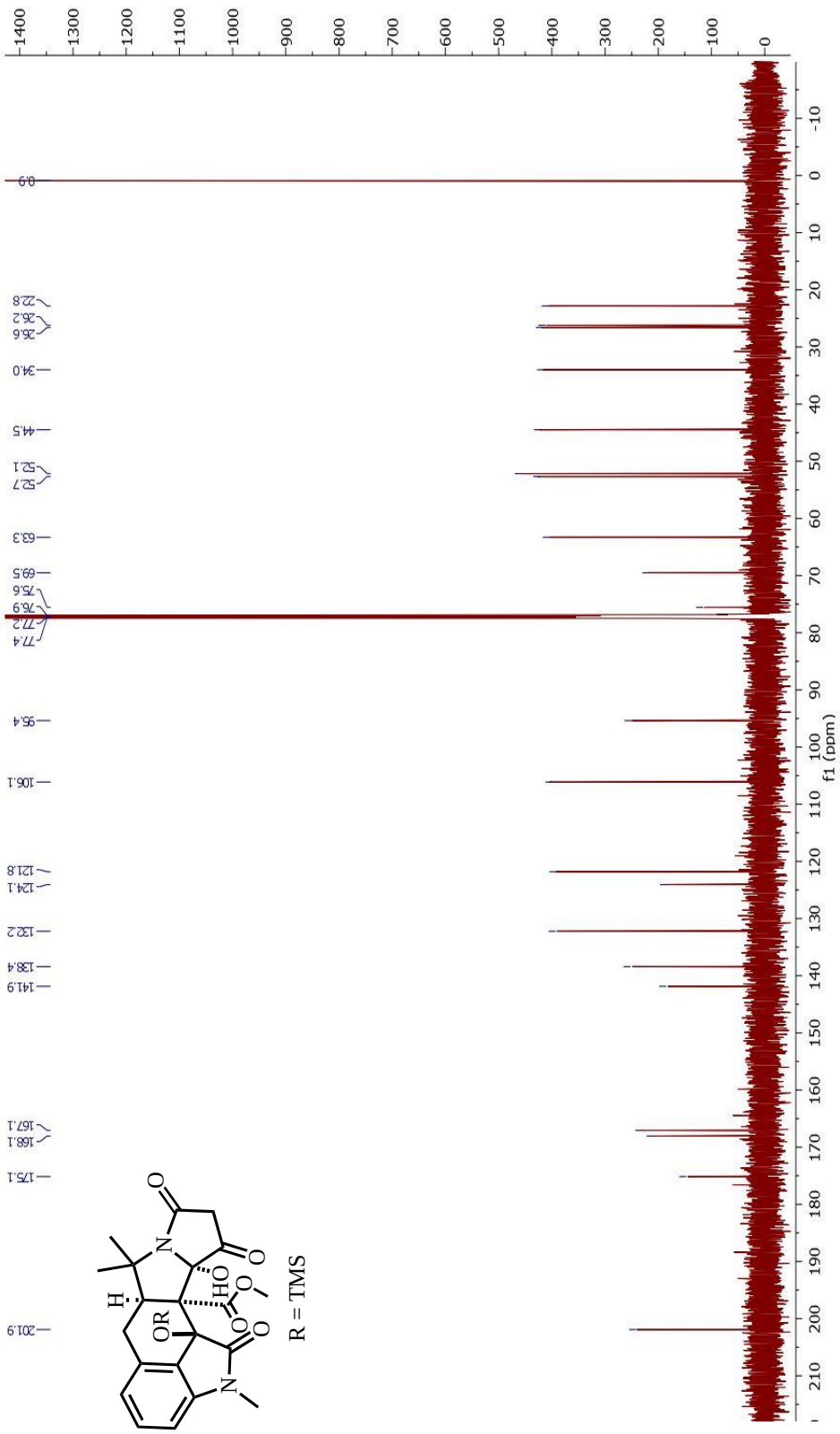

Figure C.65. **^{13}C NMR** (151 MHz, $CDCl_3$) of tetramic acid **3.97**

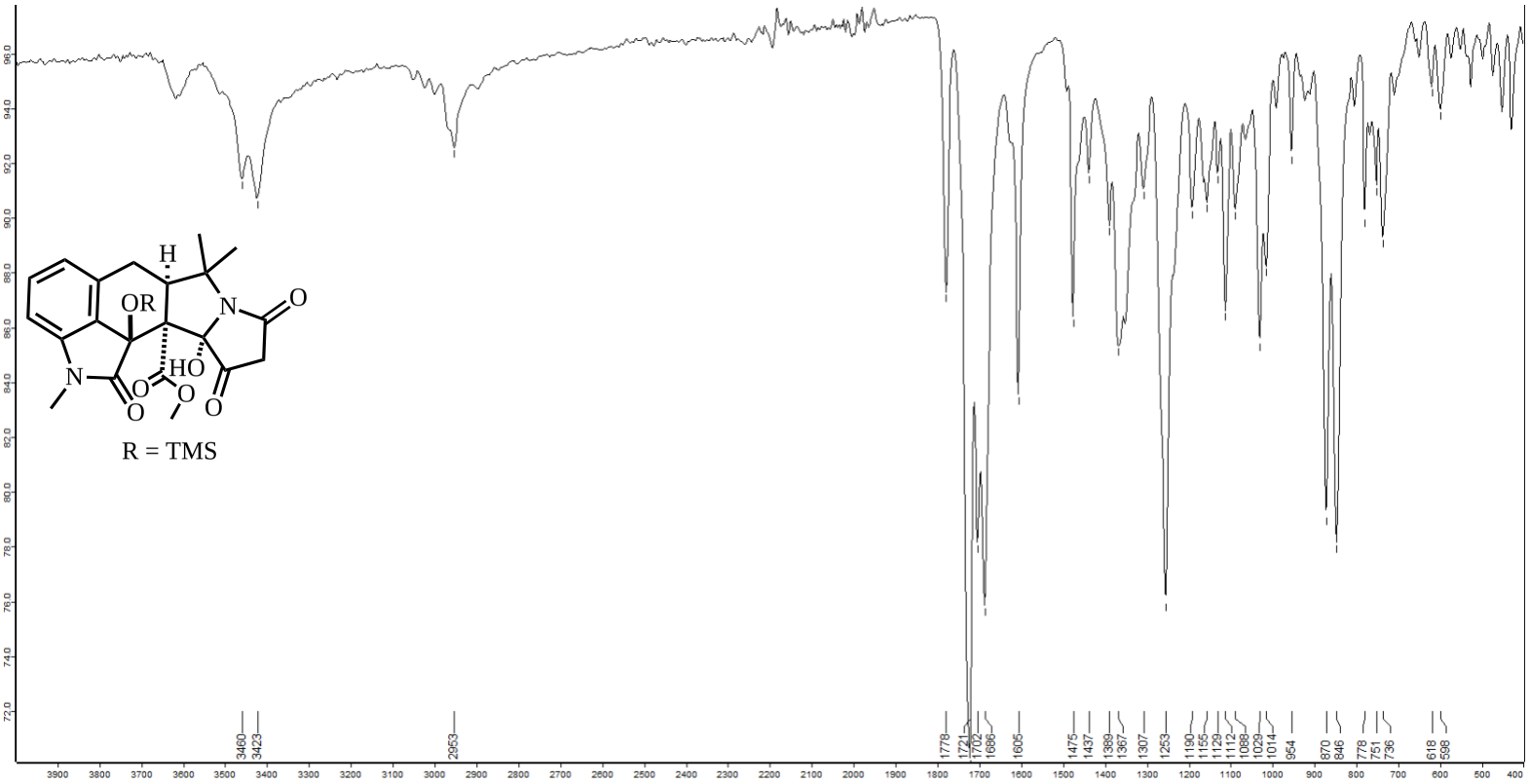

Figure C.66. FTIR Spectrum (neat) of tetramic acid **3.97**

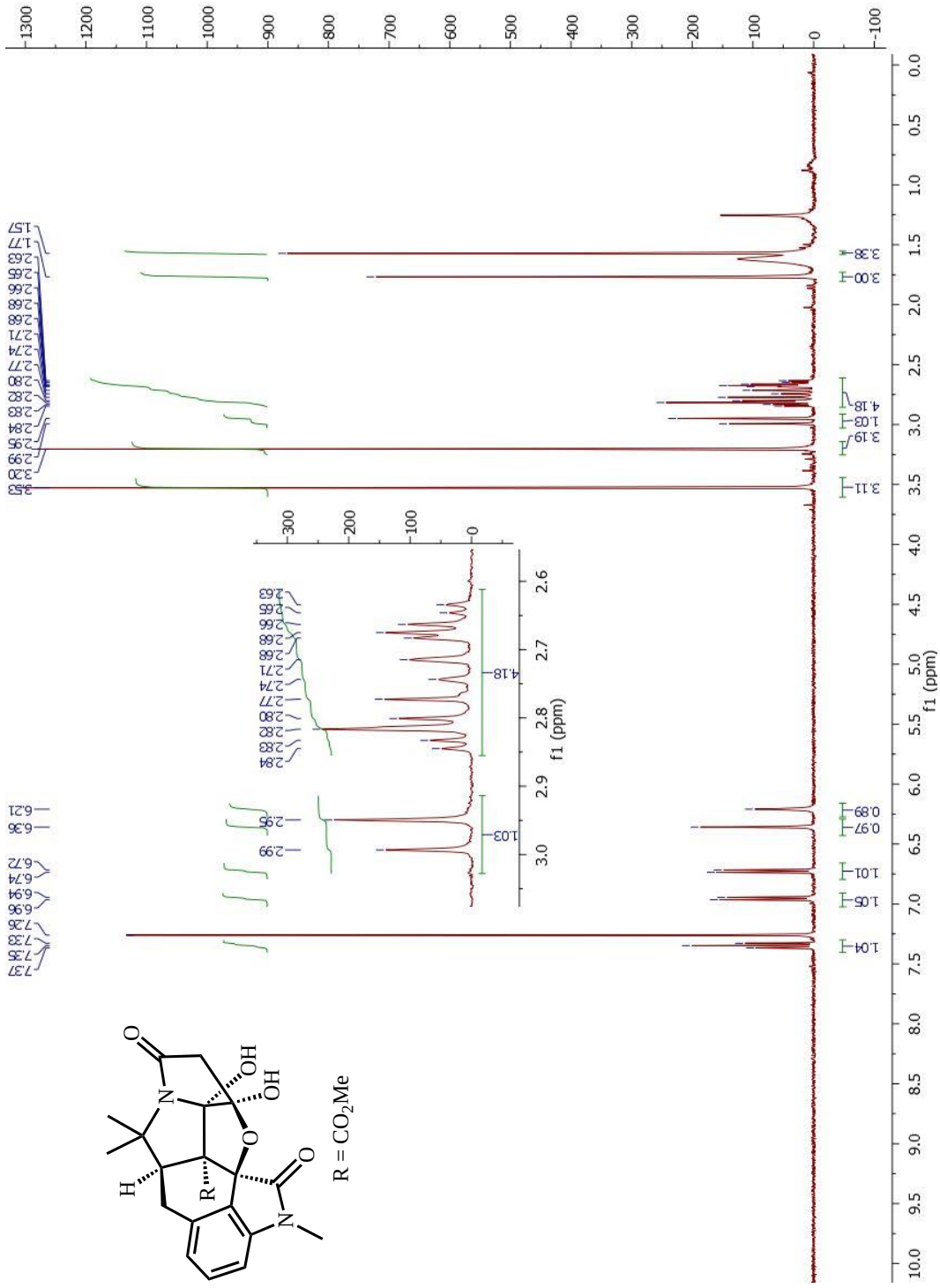

Figure C.67. **^{1}H NMR** (400 MHz, $CDCl_3$) of hexacyclic methyl ester **3.98**

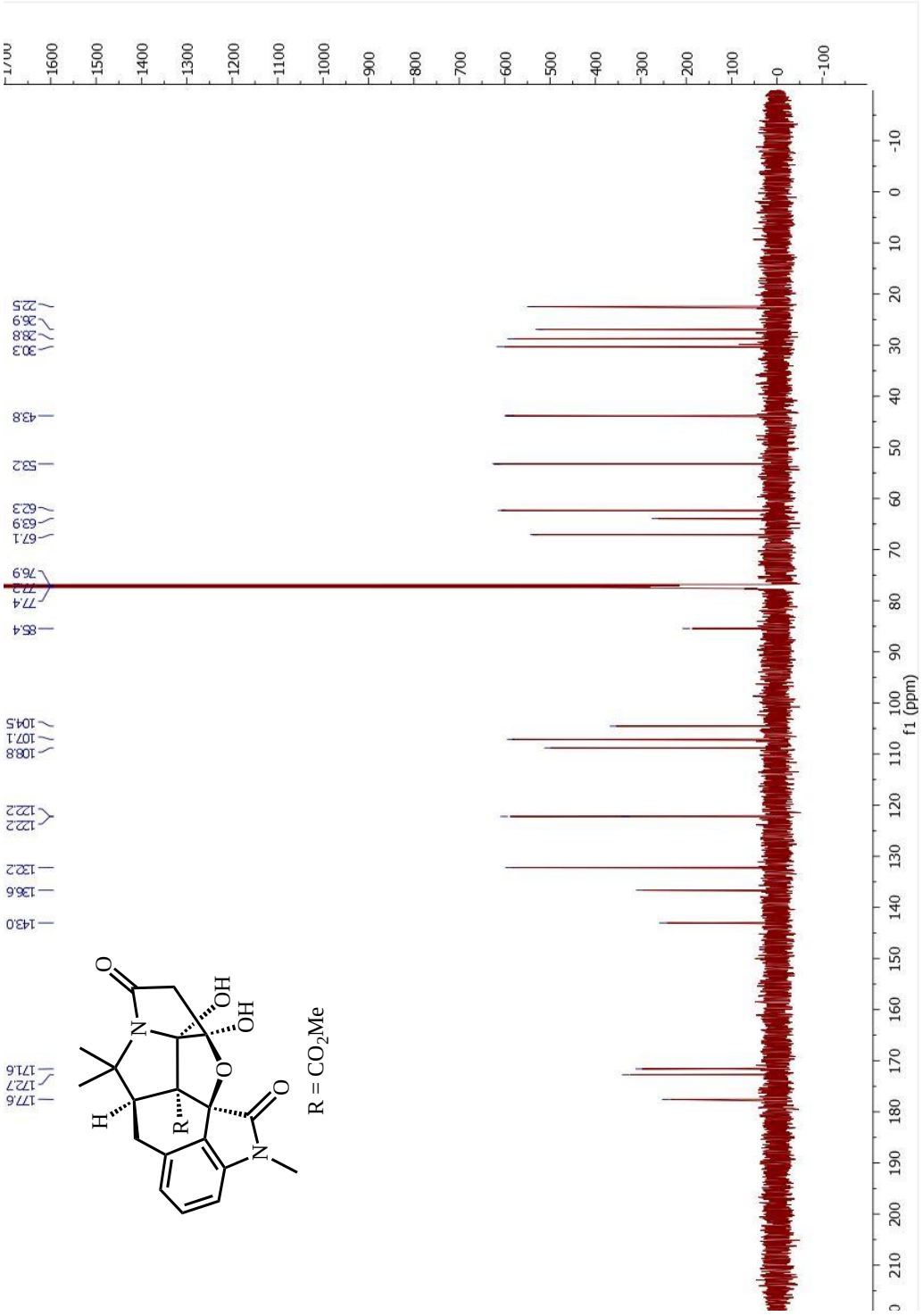

Figure C.68. **^{13}C NMR** (151 MHz, $CDCl_3$) of hexacyclic methyl ester **3.98**

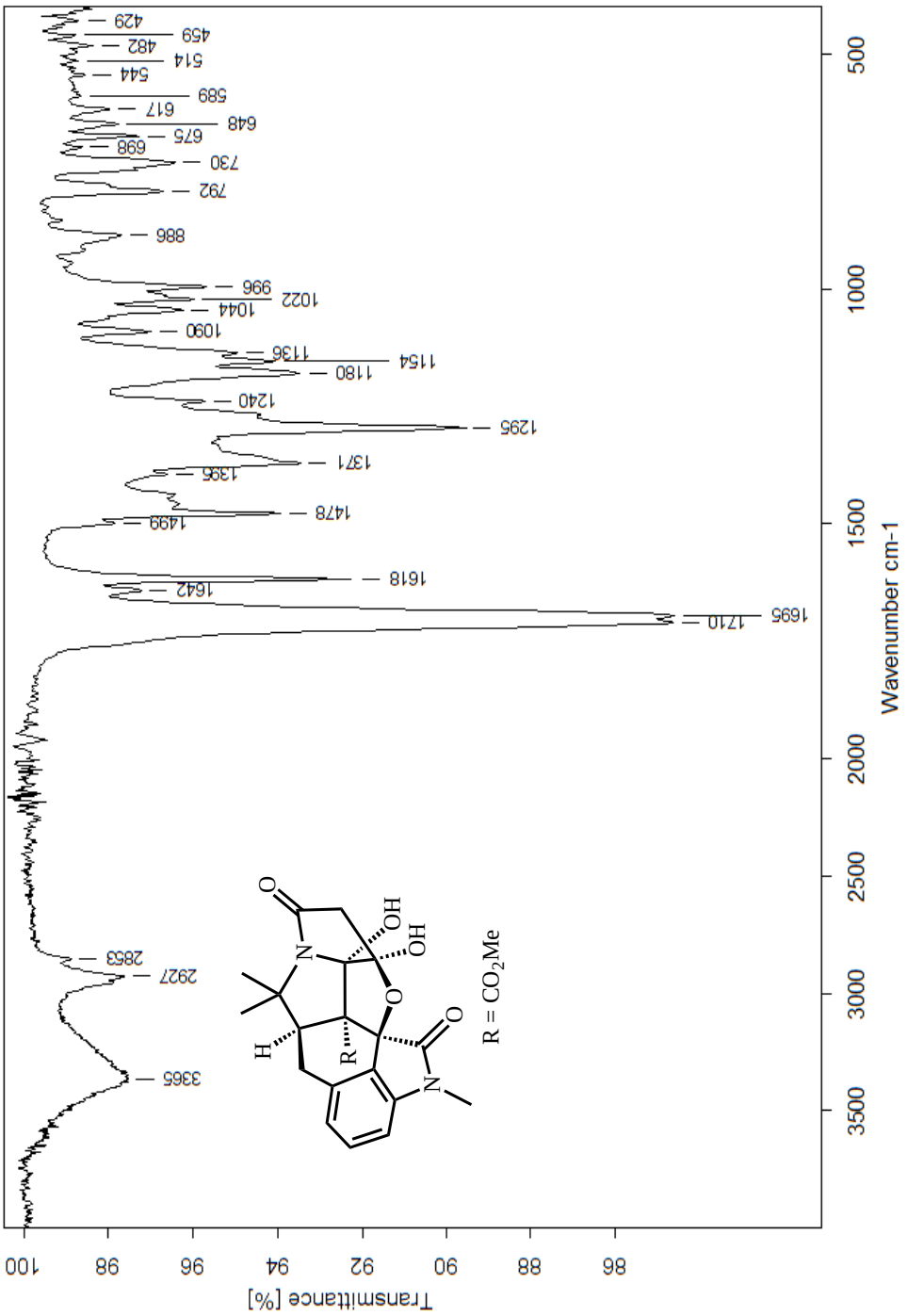

Figure C.69. FTIR Spectrum (neat) of hexacyclic methyl ester **3.98**

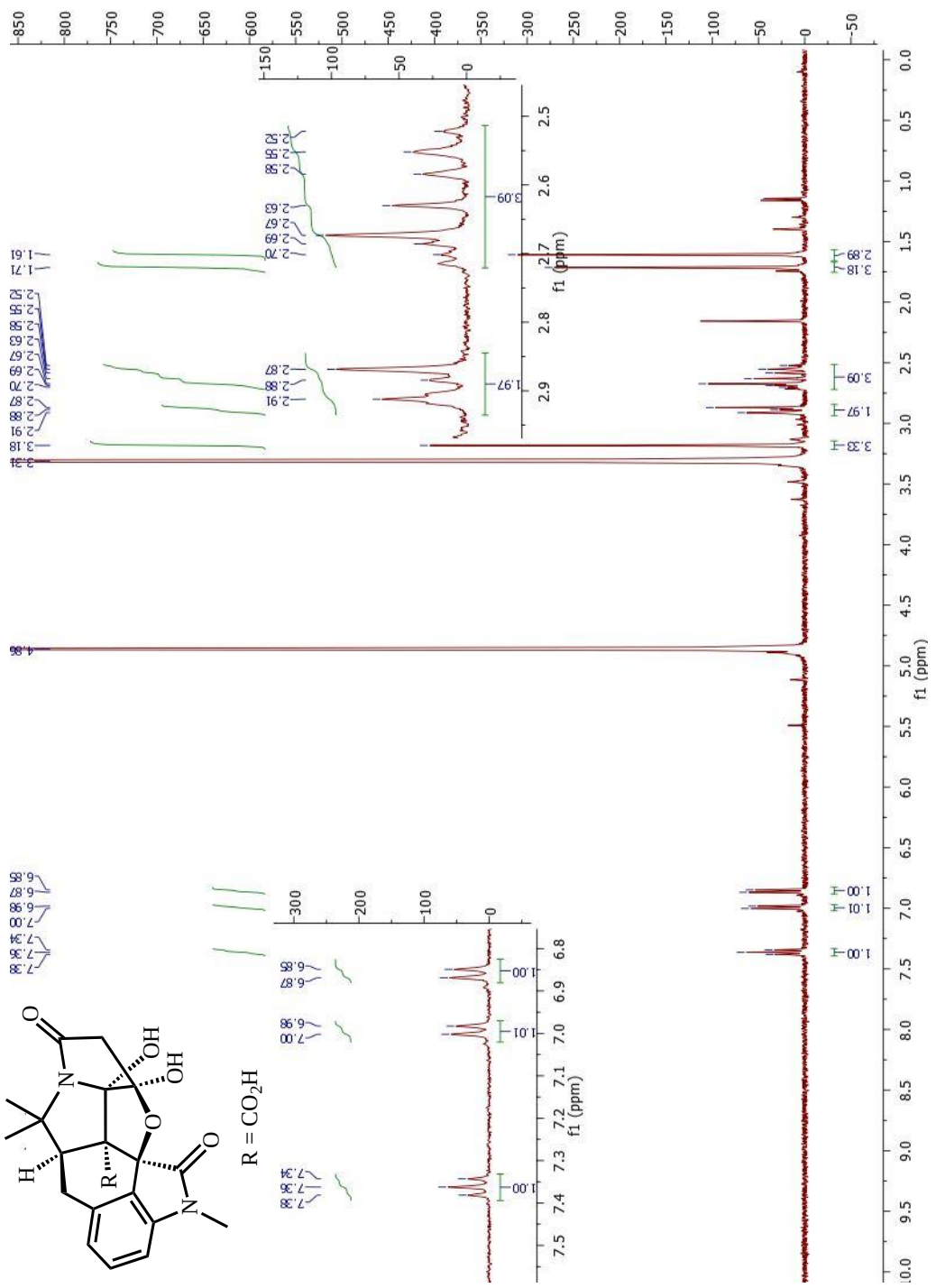

Figure C.70. **^{1}H NMR** (400 MHz, CD_3OD) of hexacyclic acid **3.99**

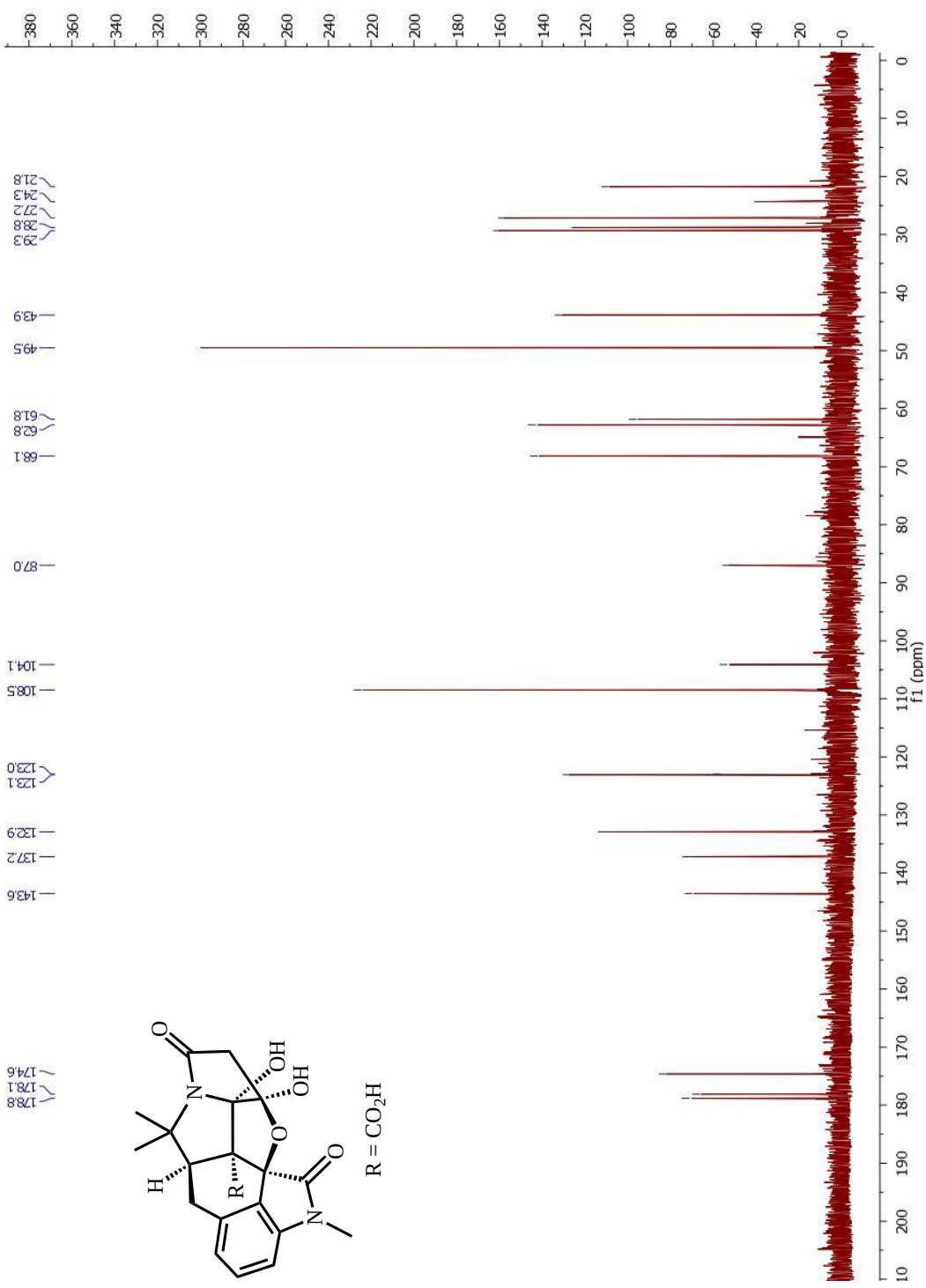

Figure C.71. **^{13}C NMR** (151 MHz, D_2O) of hexacyclic acid (potassium salt) **3.99**

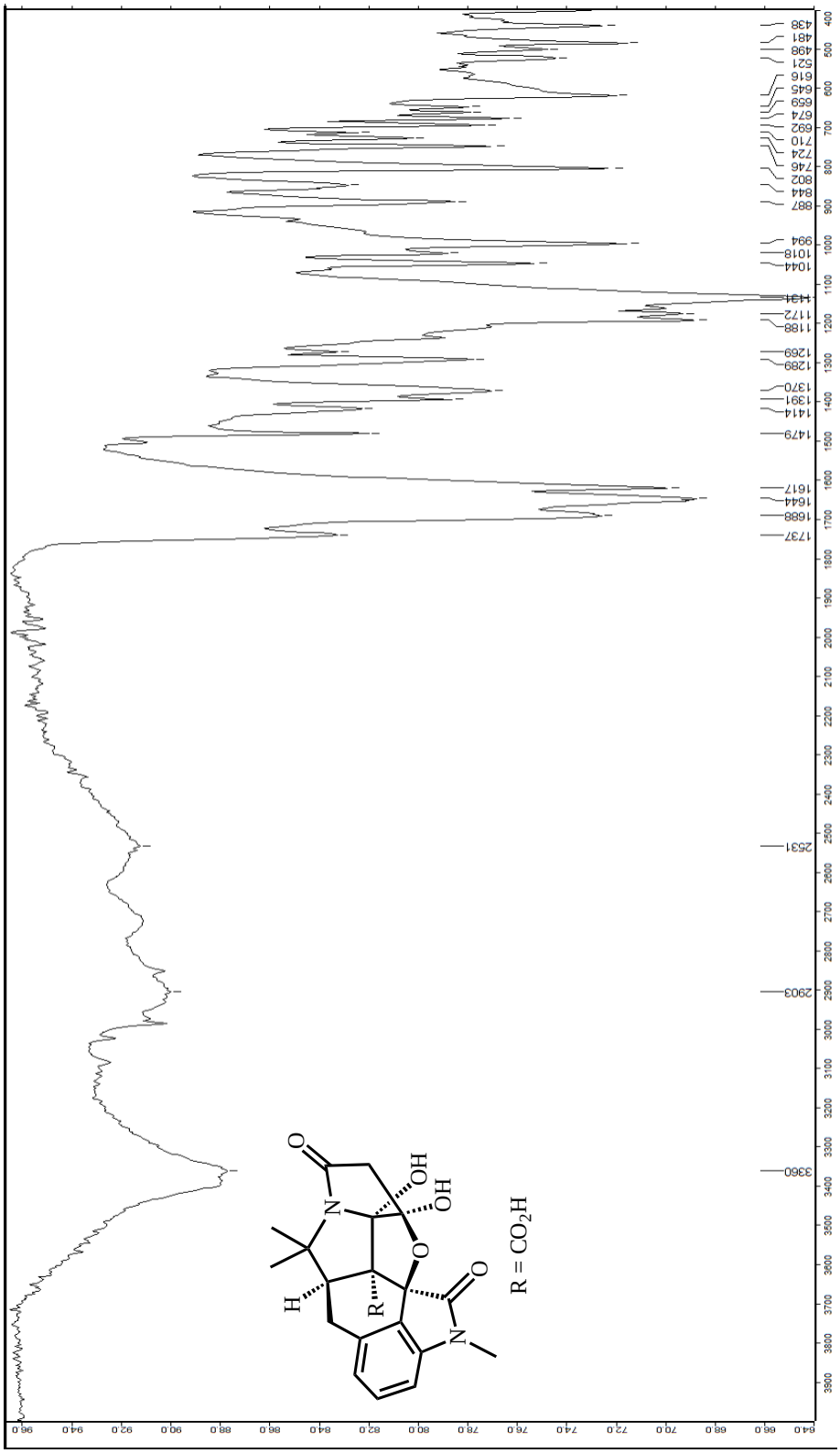

Figure C.72. FTIR Spectrum (neat) hexacyclic acid **3.99**

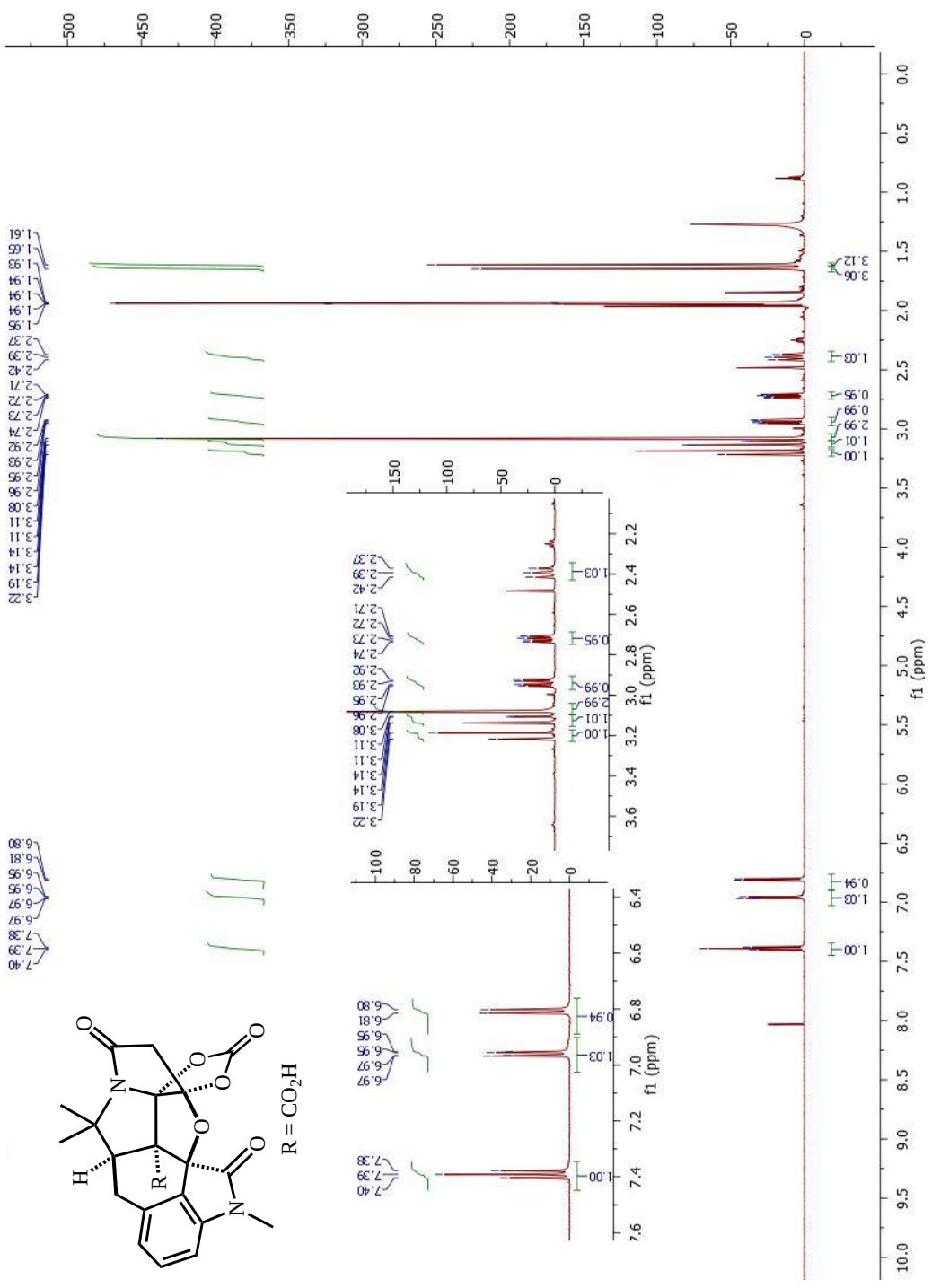

Figure C.73. **^{1}H NMR** (600 MHz, CD_3CN) of carbonate **3.100**

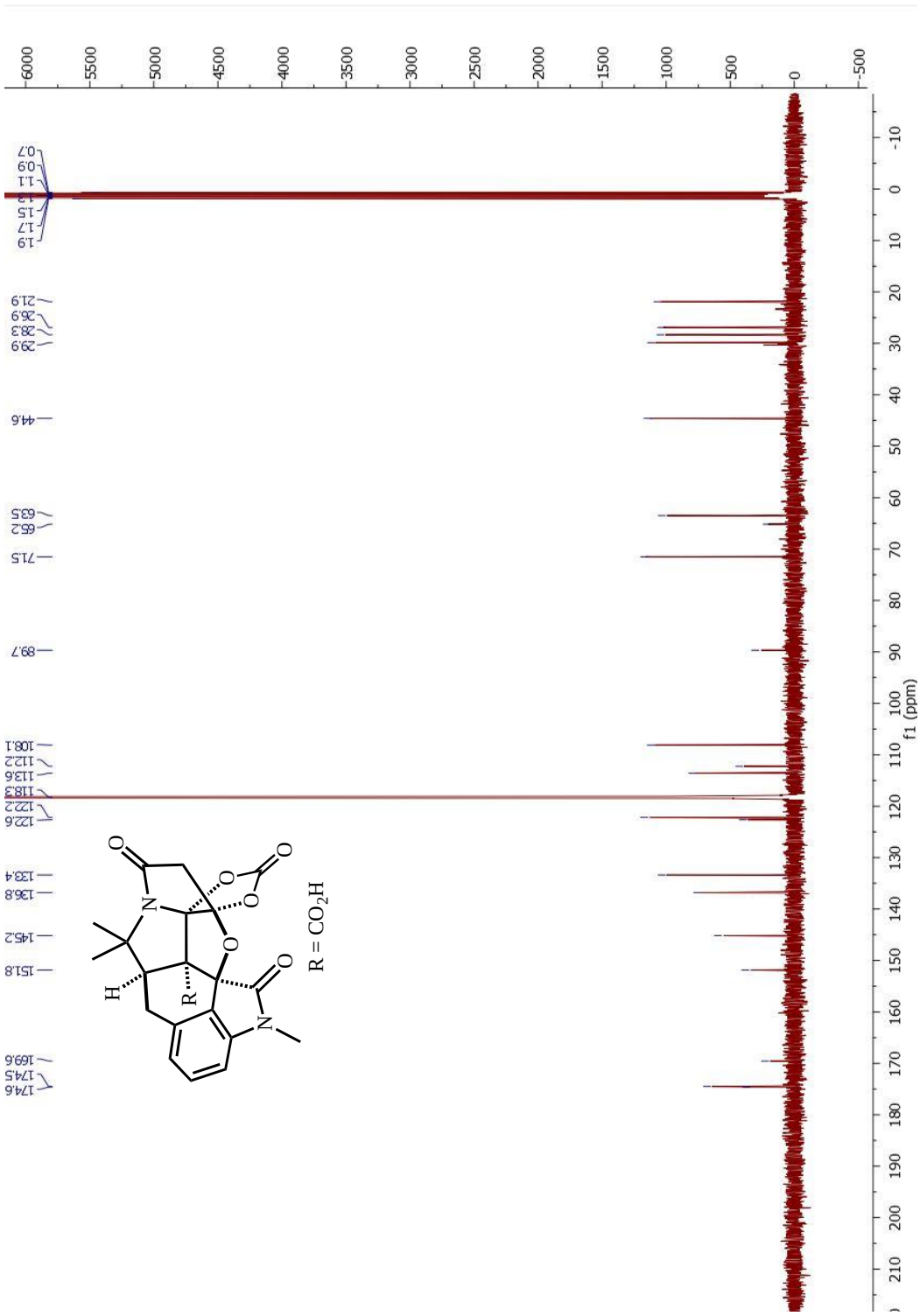

Figure C.74. **^{13}C NMR** (101 MHz, CD_3CN) of carbonate **3.100**

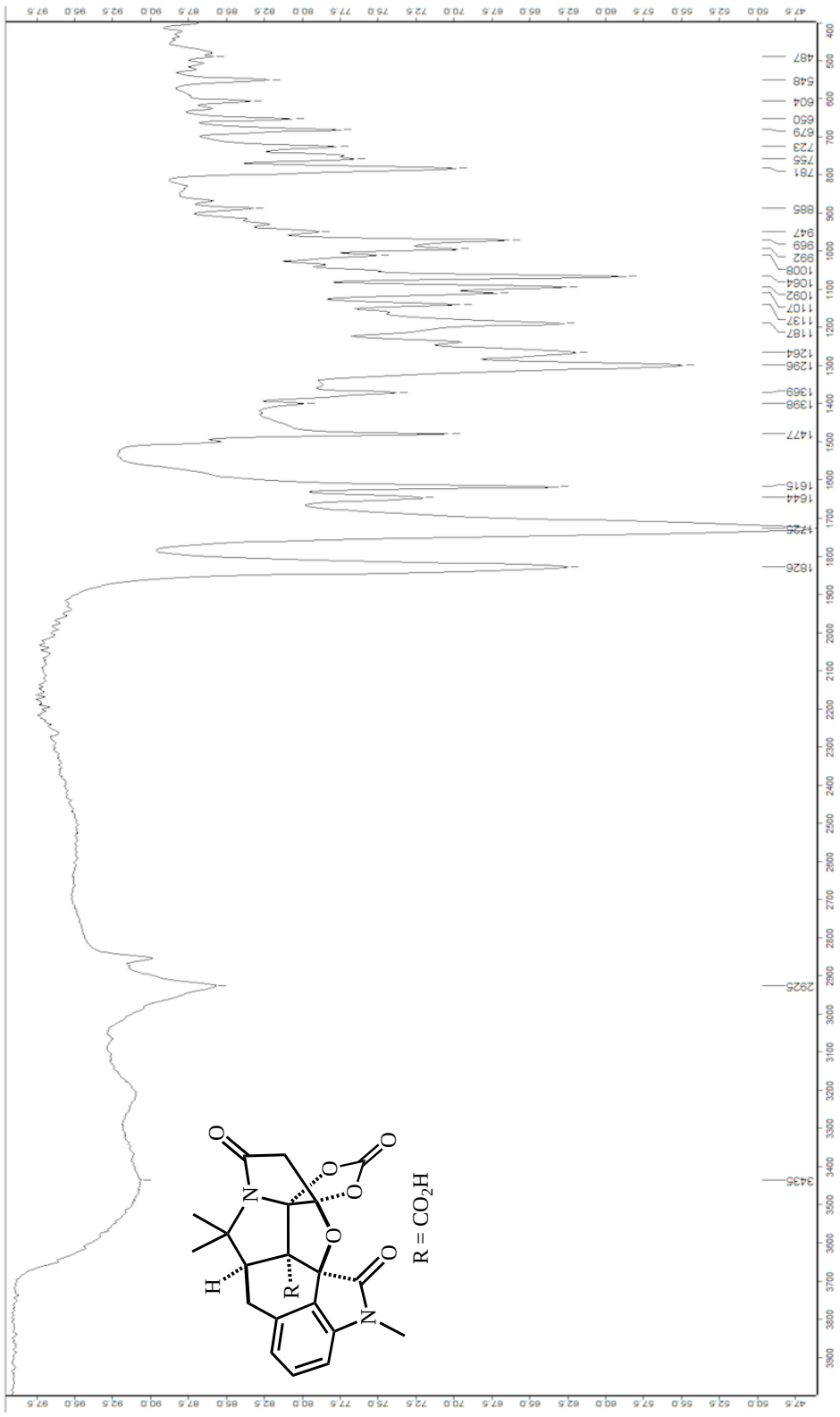

Figure C.75. FTIR Spectrum (neat) of carbonate **3.100**

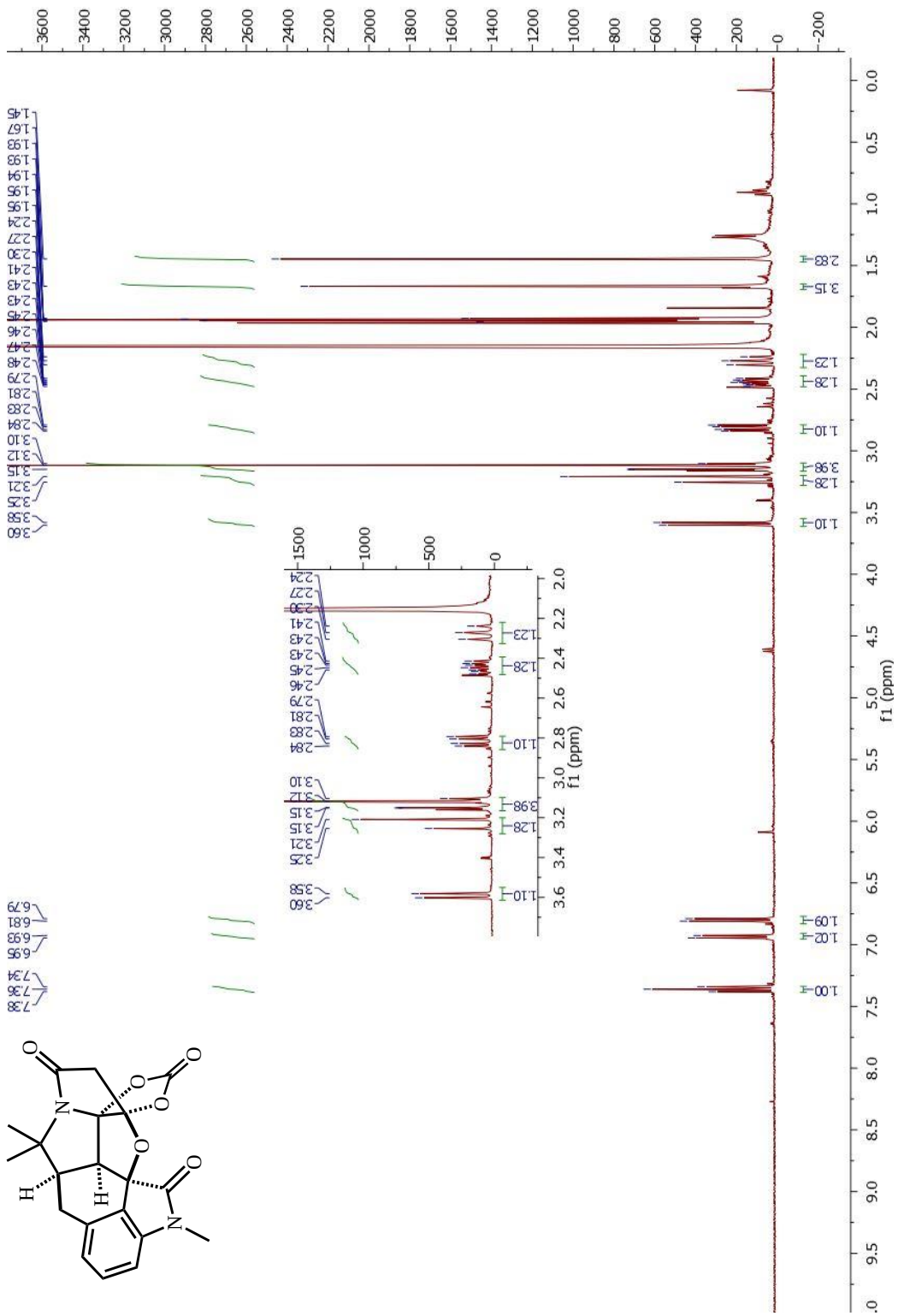

Figure C.76. **^{1}H NMR** (400 MHz, CD_3CN) of carbonate **3.102**

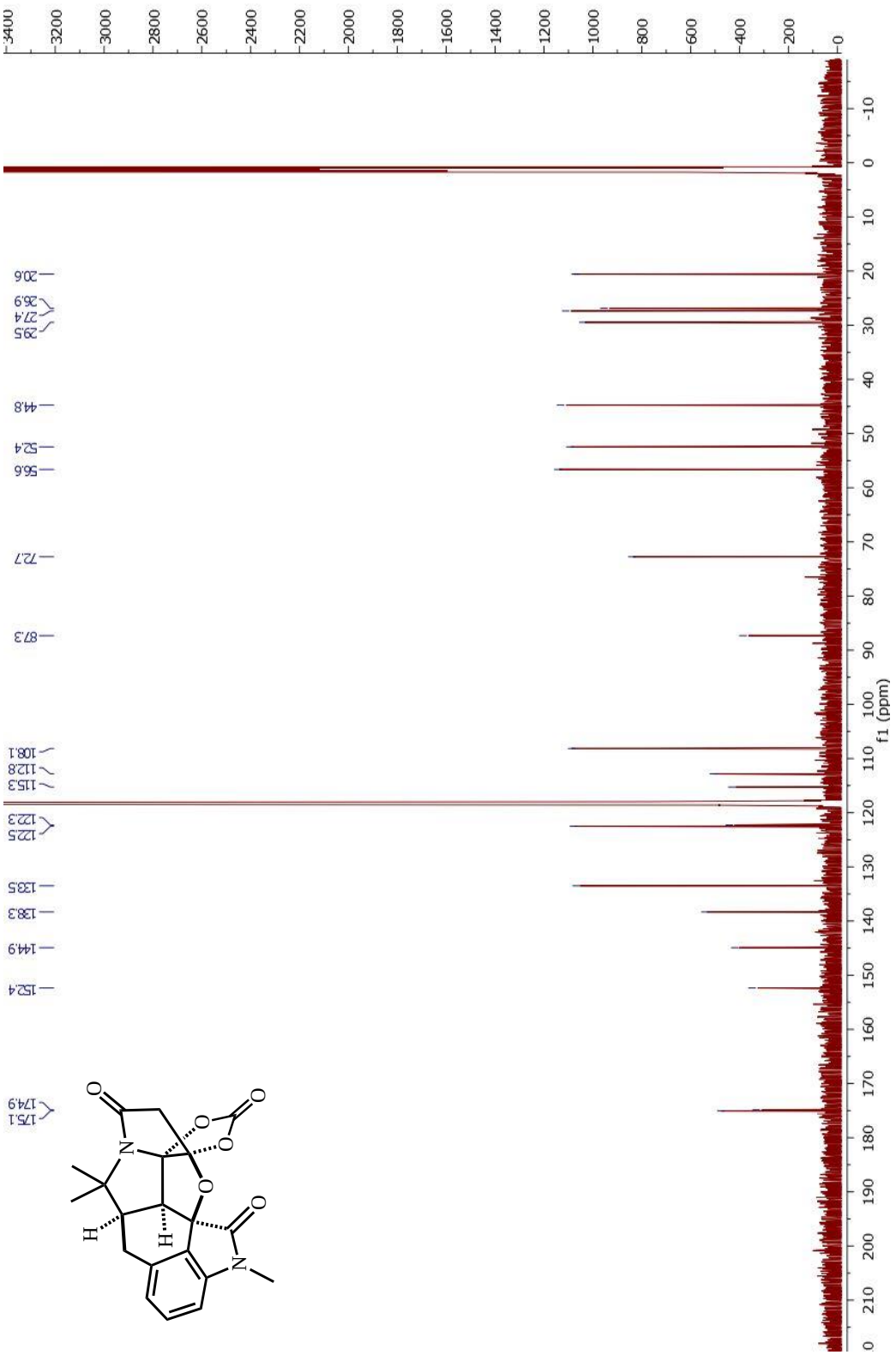

Figure C.77. **^{13}C NMR** (101 MHz, CD_3CN) of carbonate **3.102**

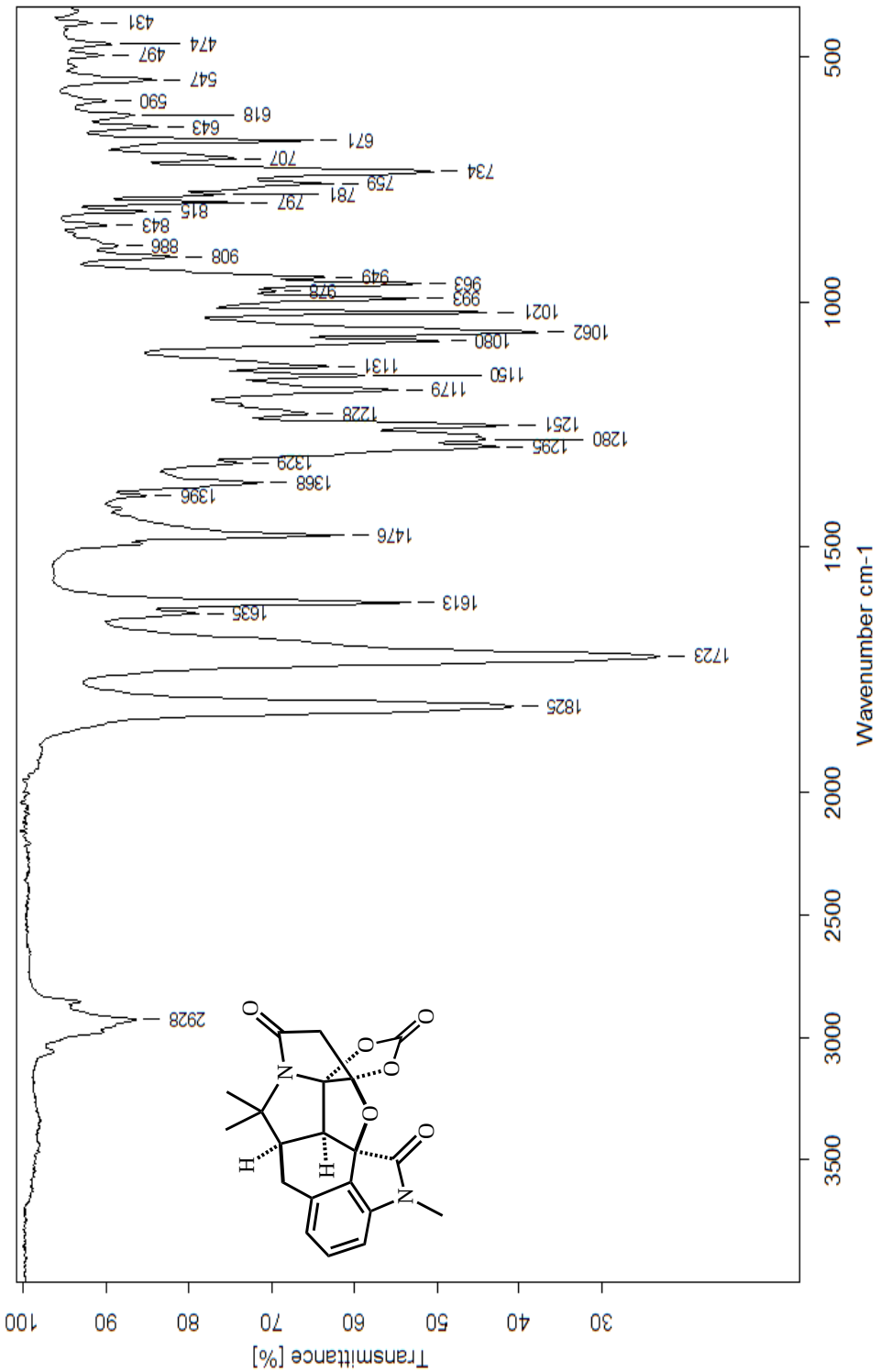

Figure C.78. FTIR Spectrum (neat) of carbonate **3.102**

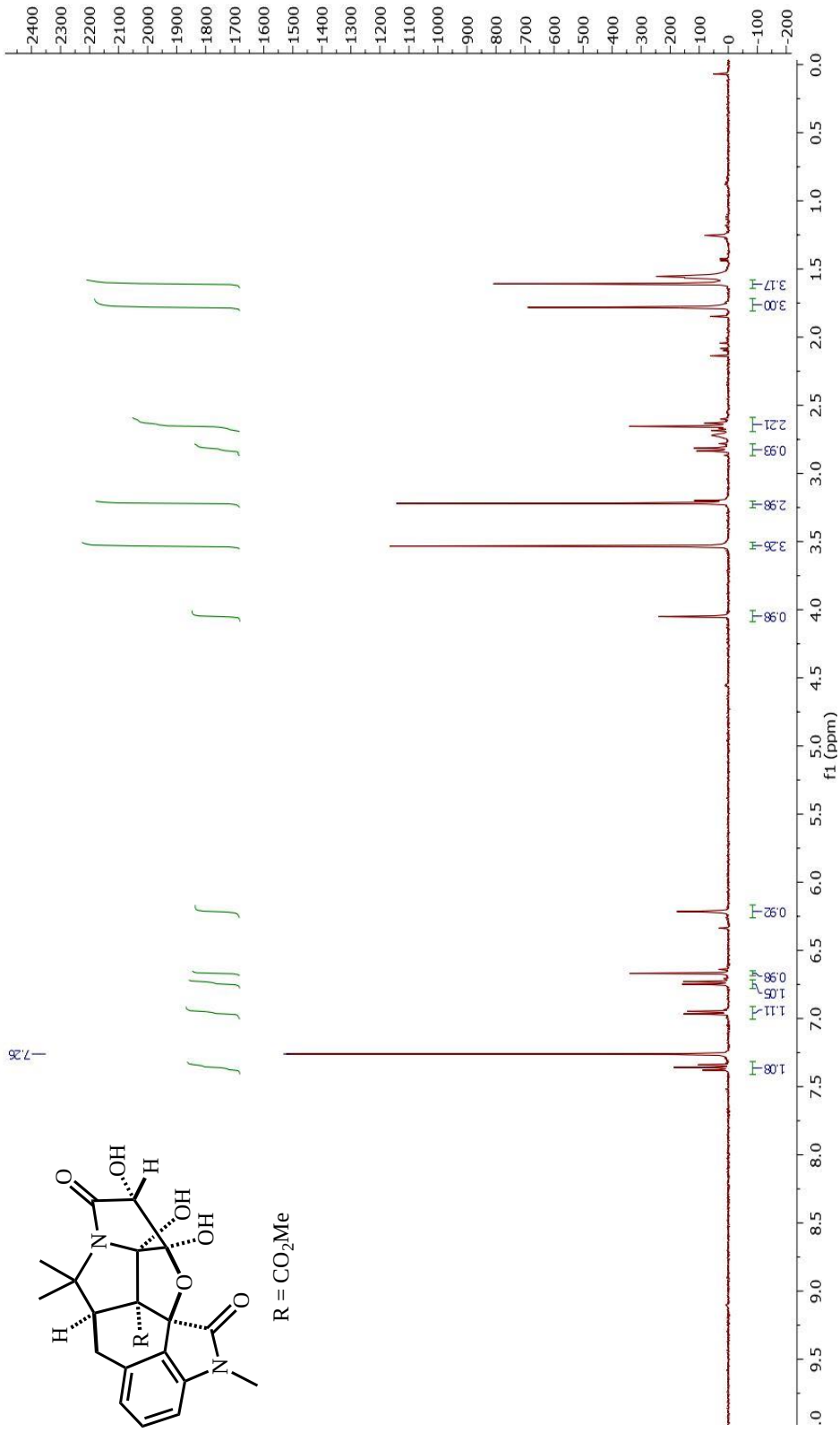

Figure C.79. **^{1}H NMR** (400 MHz, $CDCl_3$) of hexacyclic methyl ester **3.106**

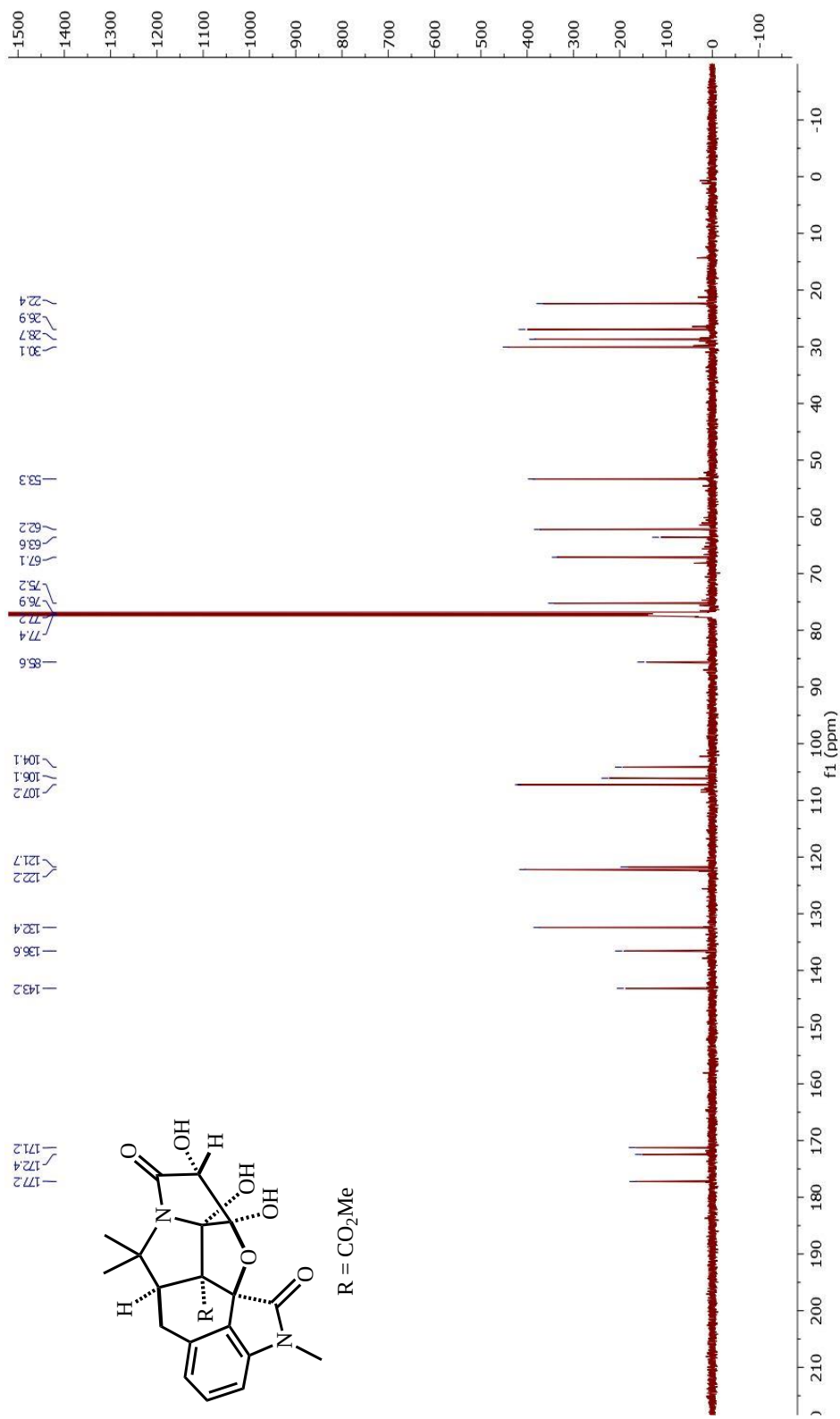

Figure C.80. **^{13}C NMR** (151 MHz, $CDCl_3$) of hexacyclic methyl ester **3.106**

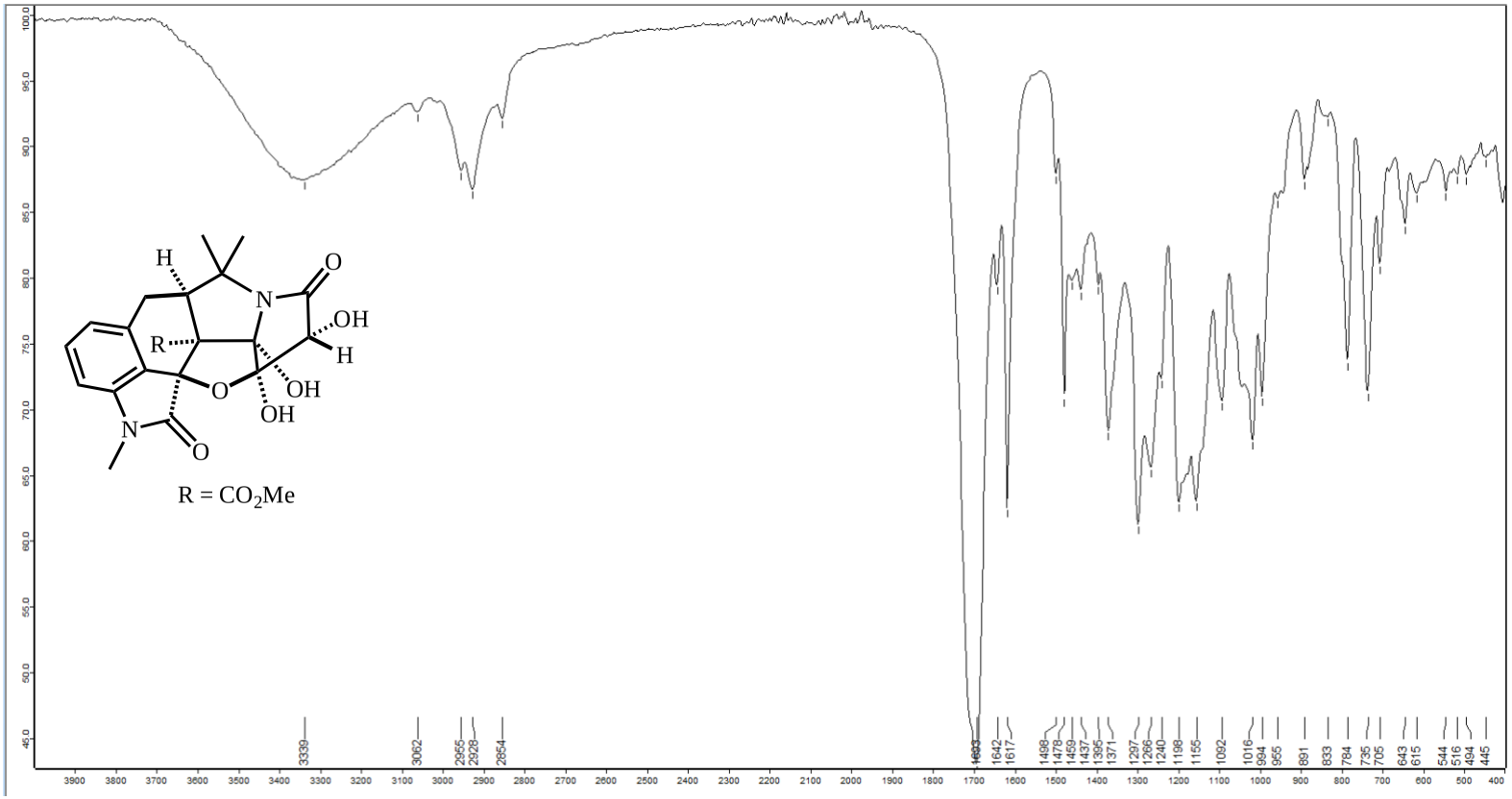

Figure C.81. FTIR Spectrum (neat) of hexacyclic methyl ester **3.106**

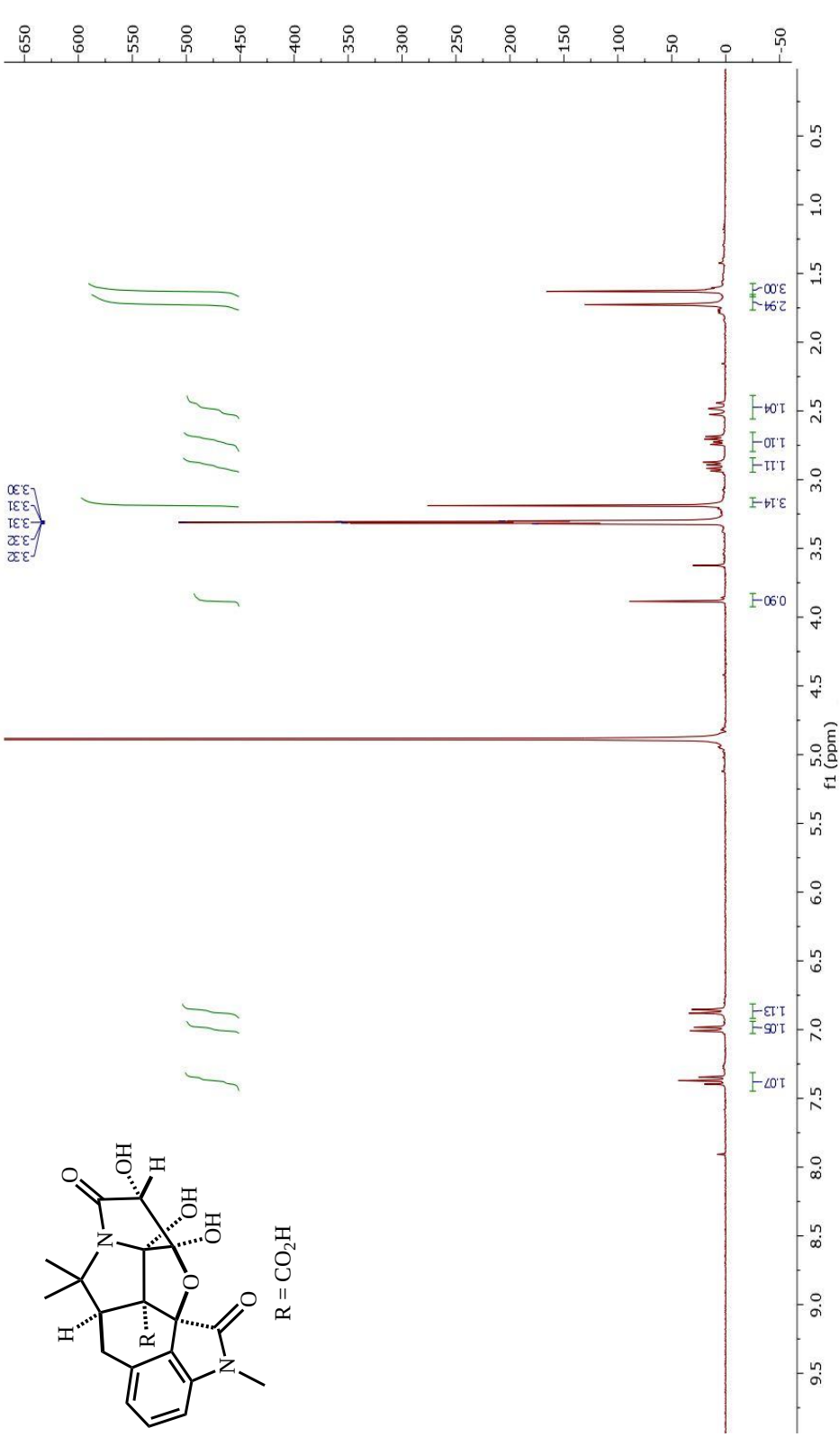

Figure C.82. **^{1}H NMR** (300 MHz, CD_3OD) of crude hexacyclic acid **3.107**

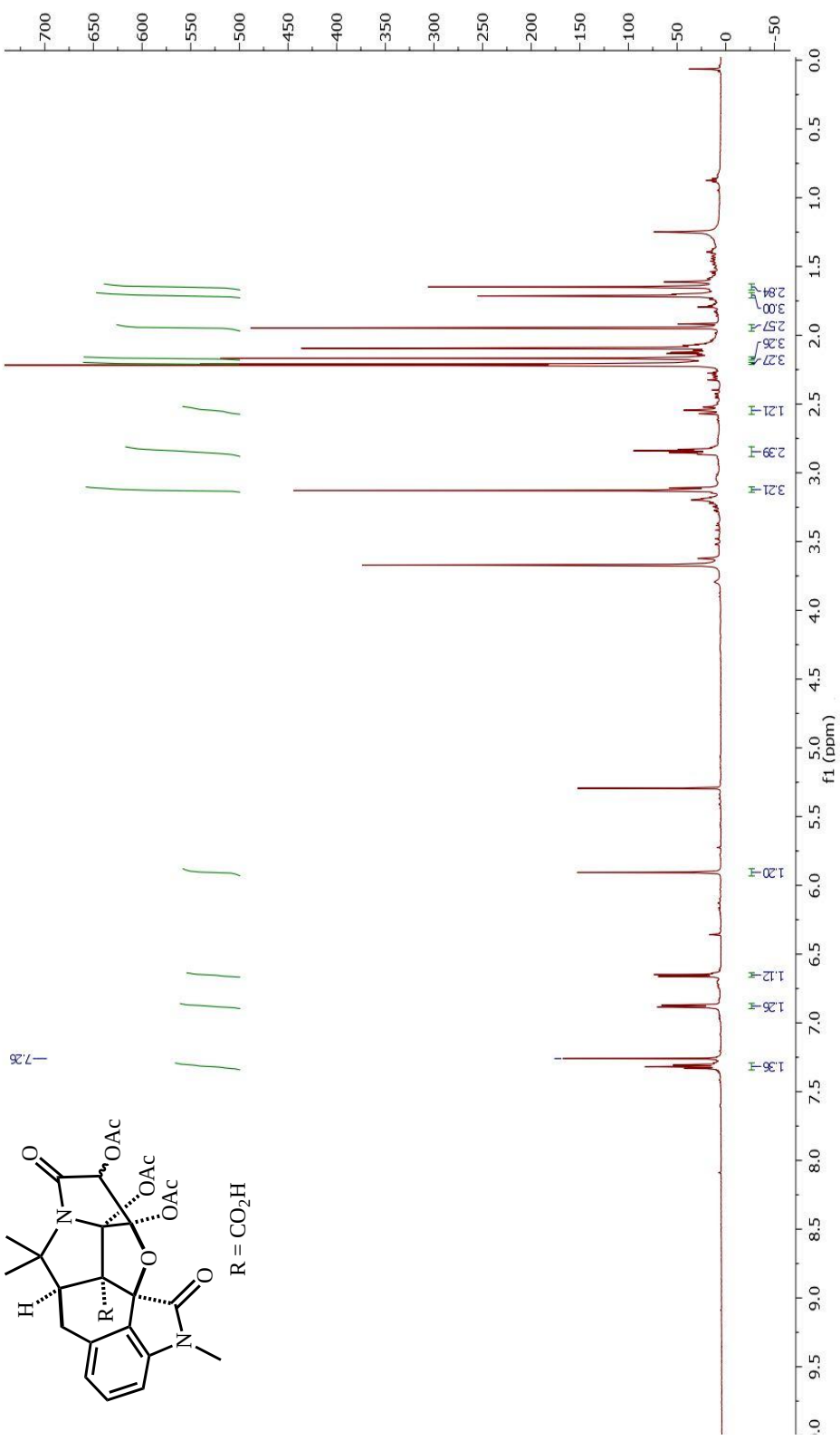

Figure C.83. **^{1}H NMR** (400 MHz, $CDCl_3$) of crude acetate **3.113**

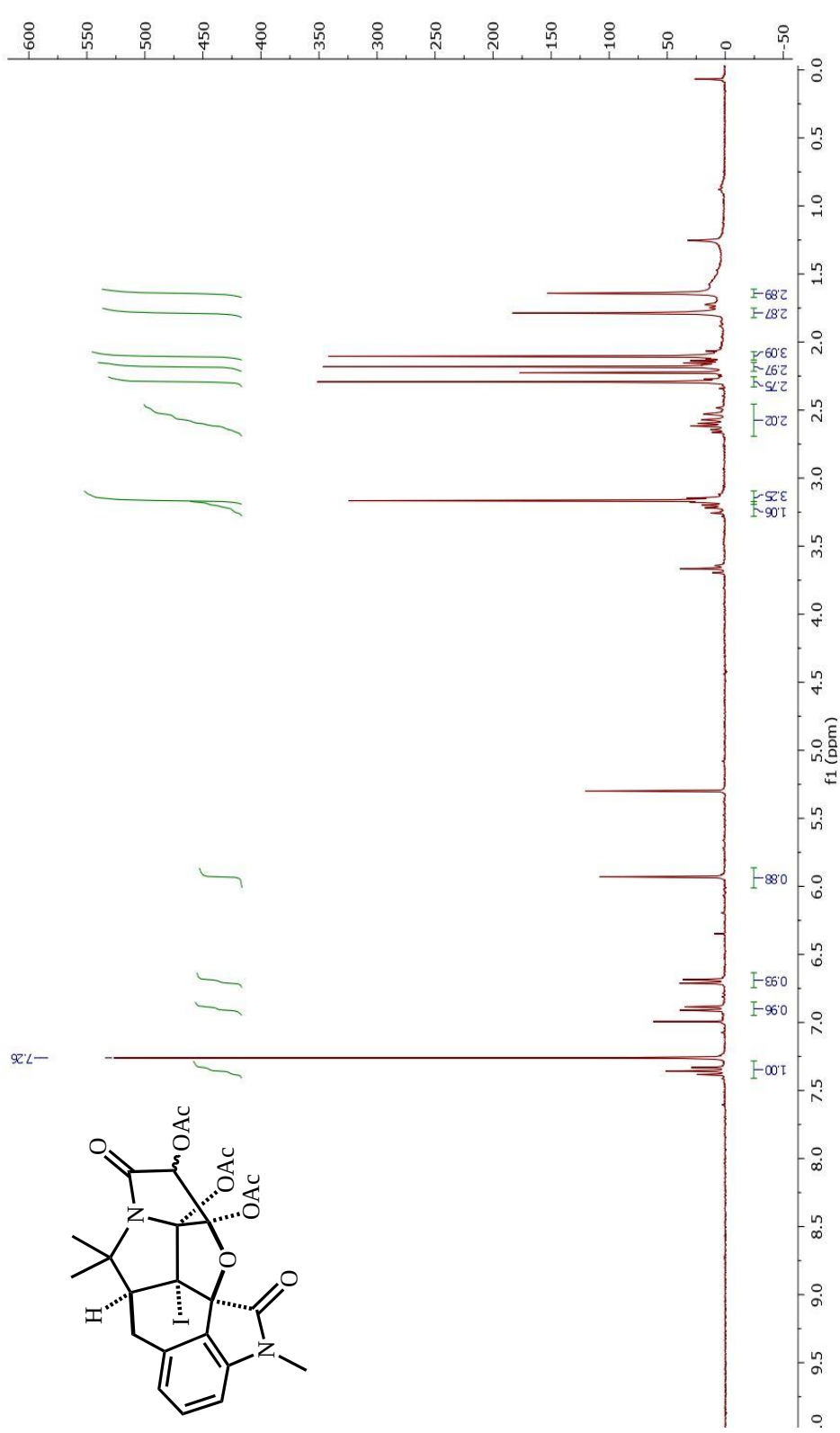

Figure C.84. **^{1}H NMR** (300 MHz, $CDCl_3$) of crude iodide **3.108**

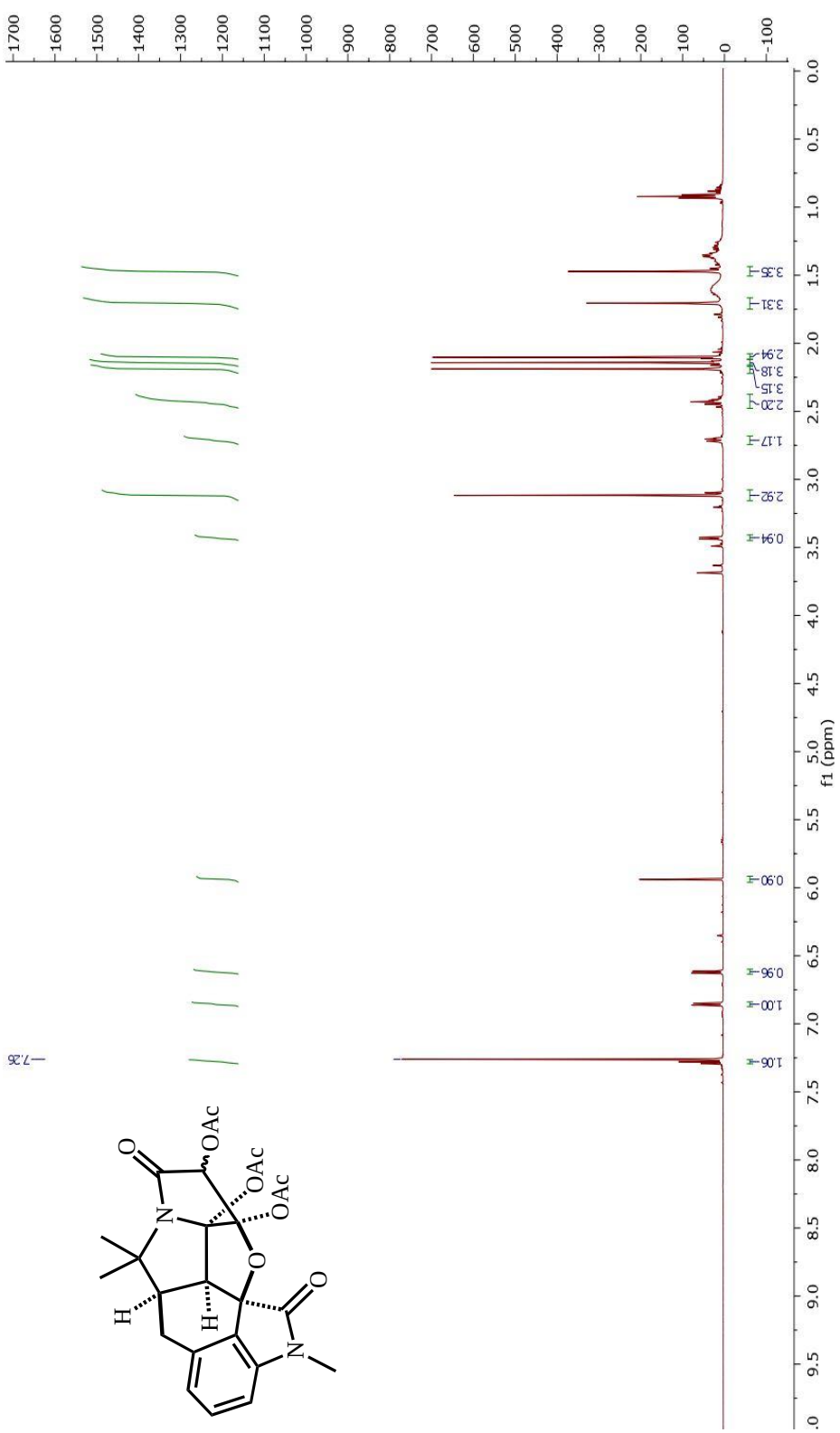

Figure C.85. **^{1}H NMR** (600 MHz, $CDCl_3$) of crude acetate **3.114**

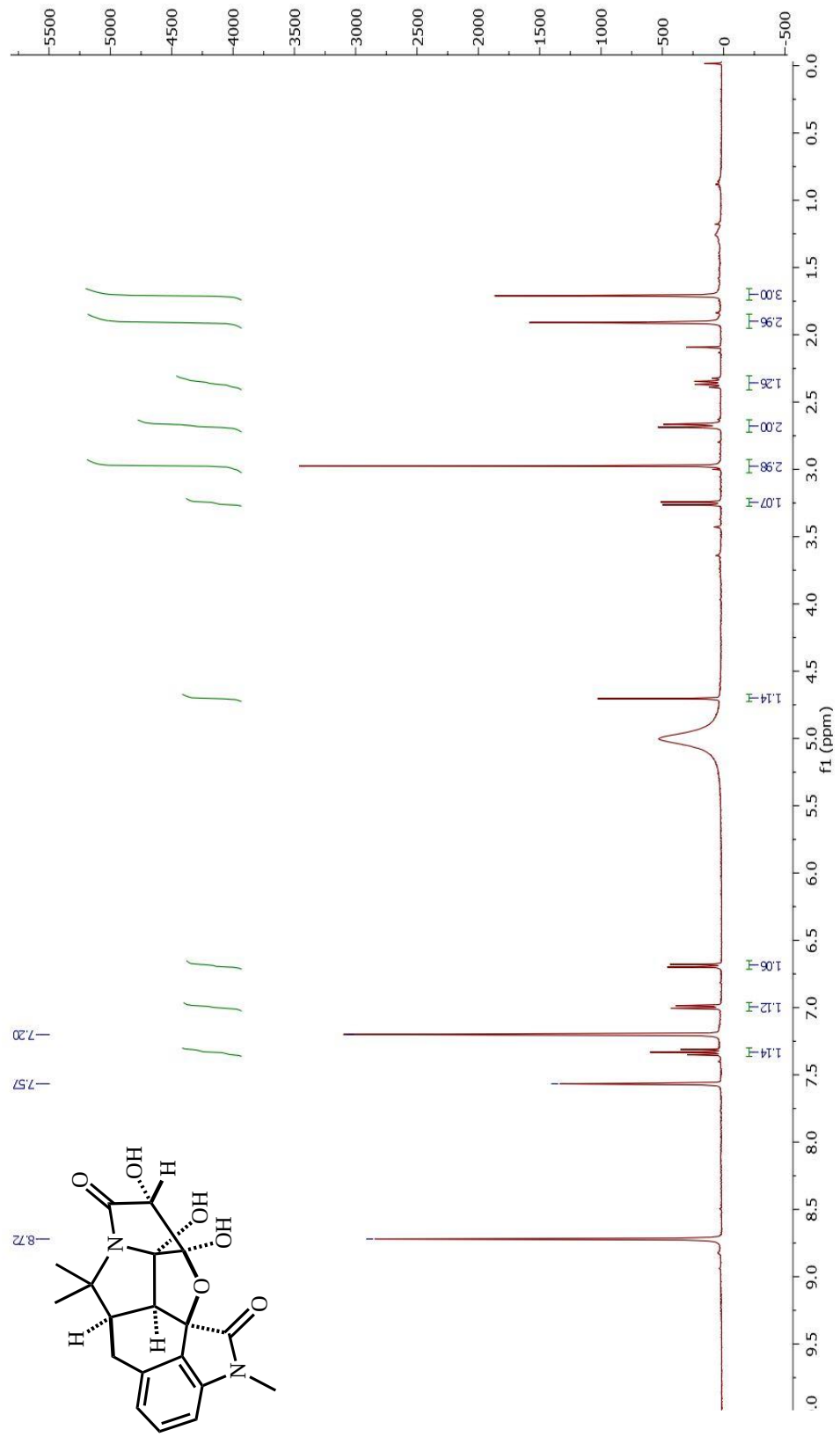

Figure C.86. **^{1}H NMR** (400 MHz, C_5D_5N) of aspergilline *A* **3.01**

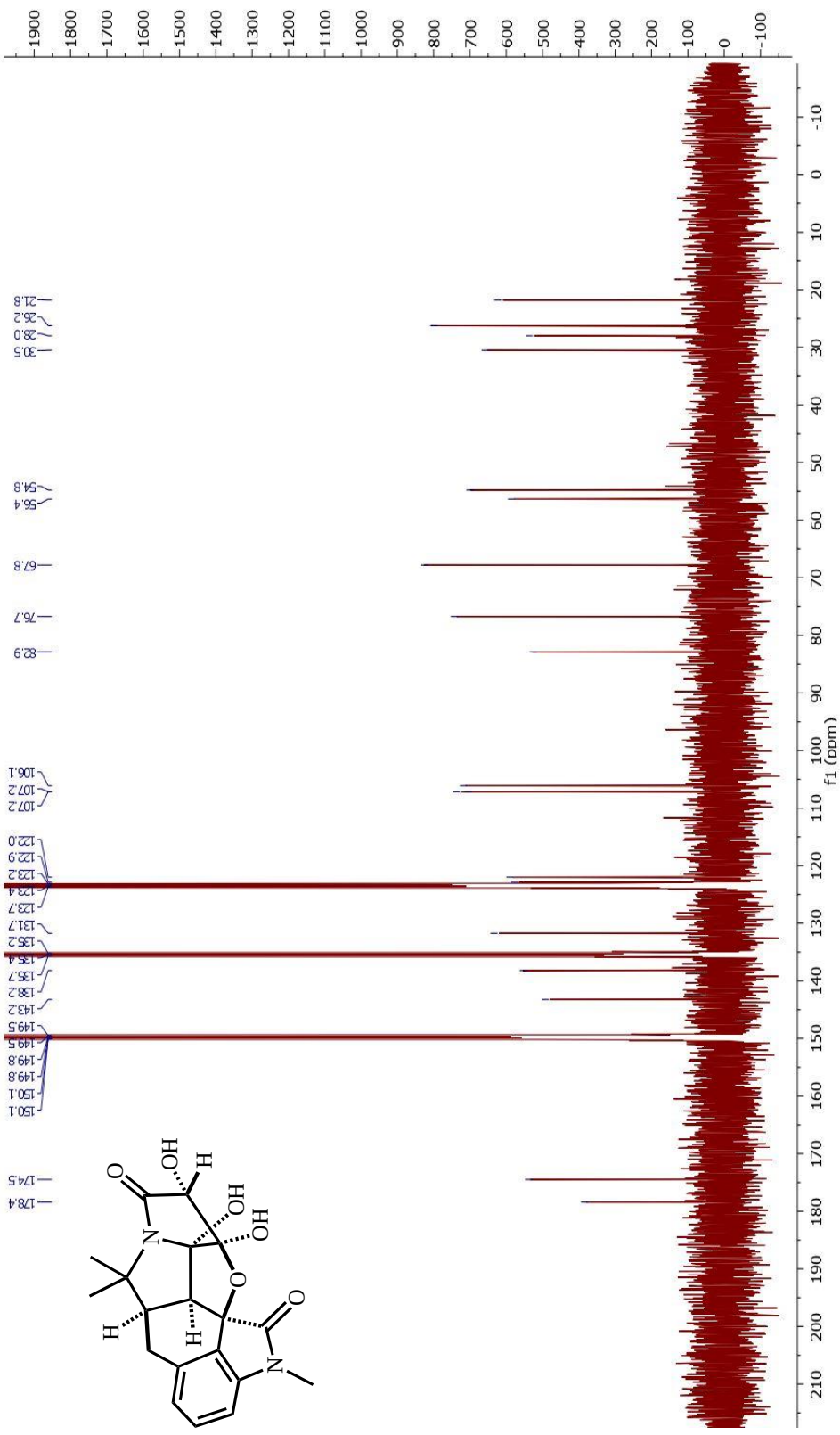

Figure C.87. **^{13}C NMR** (101 MHz, C_5D_5N) of aspergilline *A* **3.01**

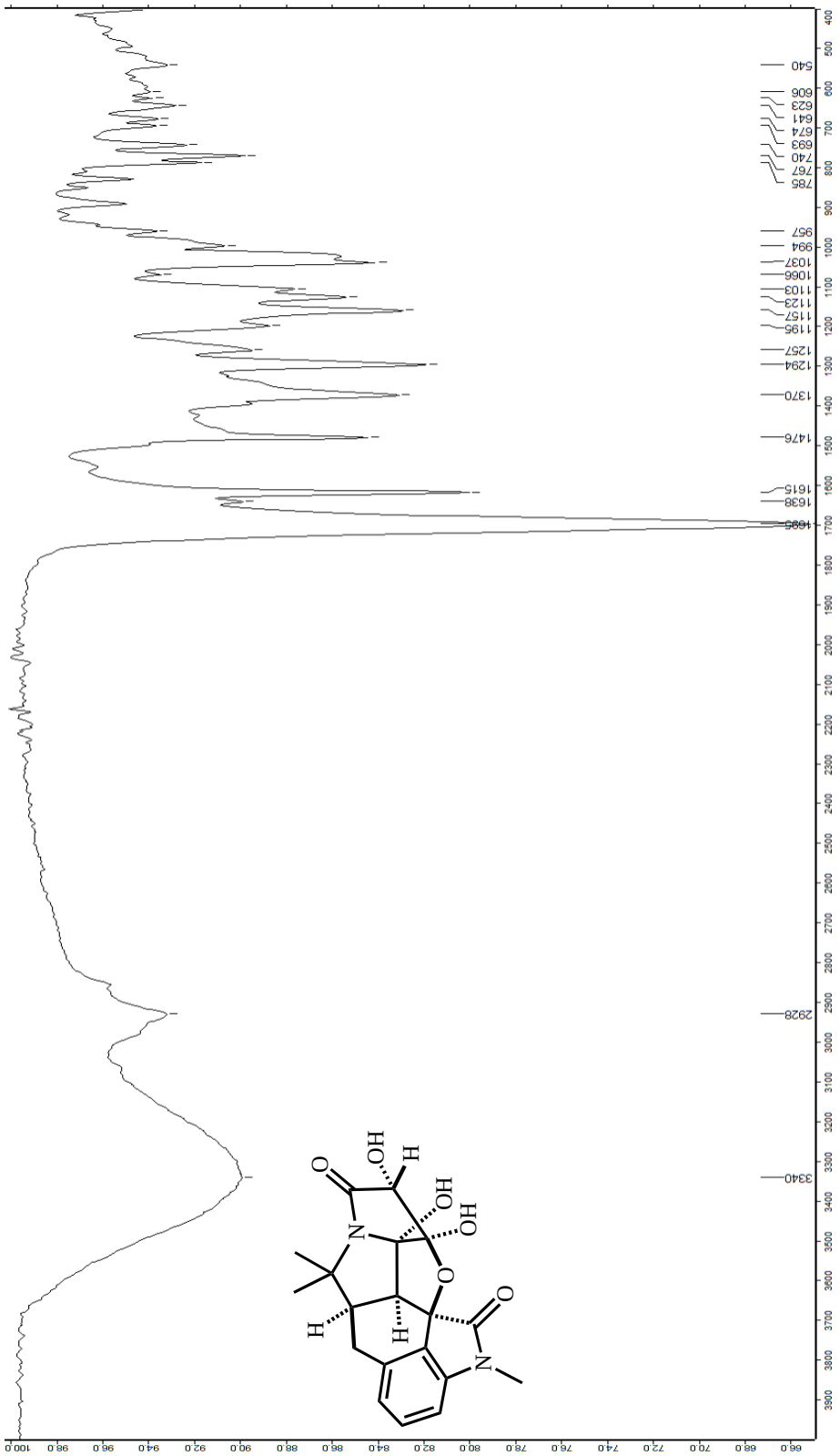

Figure C.88. FTIR Spectrum (neat) of aspergilline A **3.01**

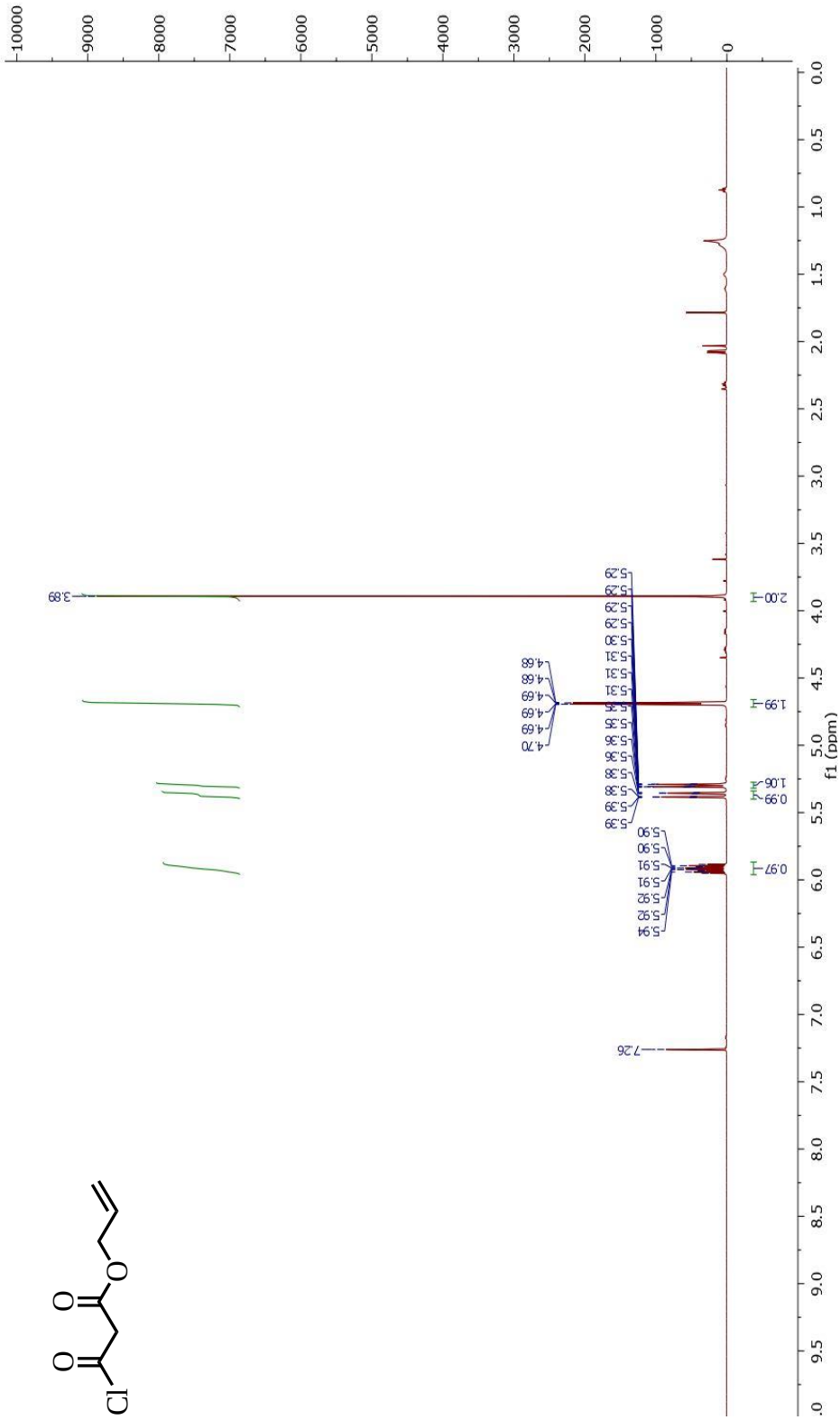

Figure C.89. **^{1}H NMR** (400 MHz, $CDCl_3$) of crude malonyl chloride **3.26**

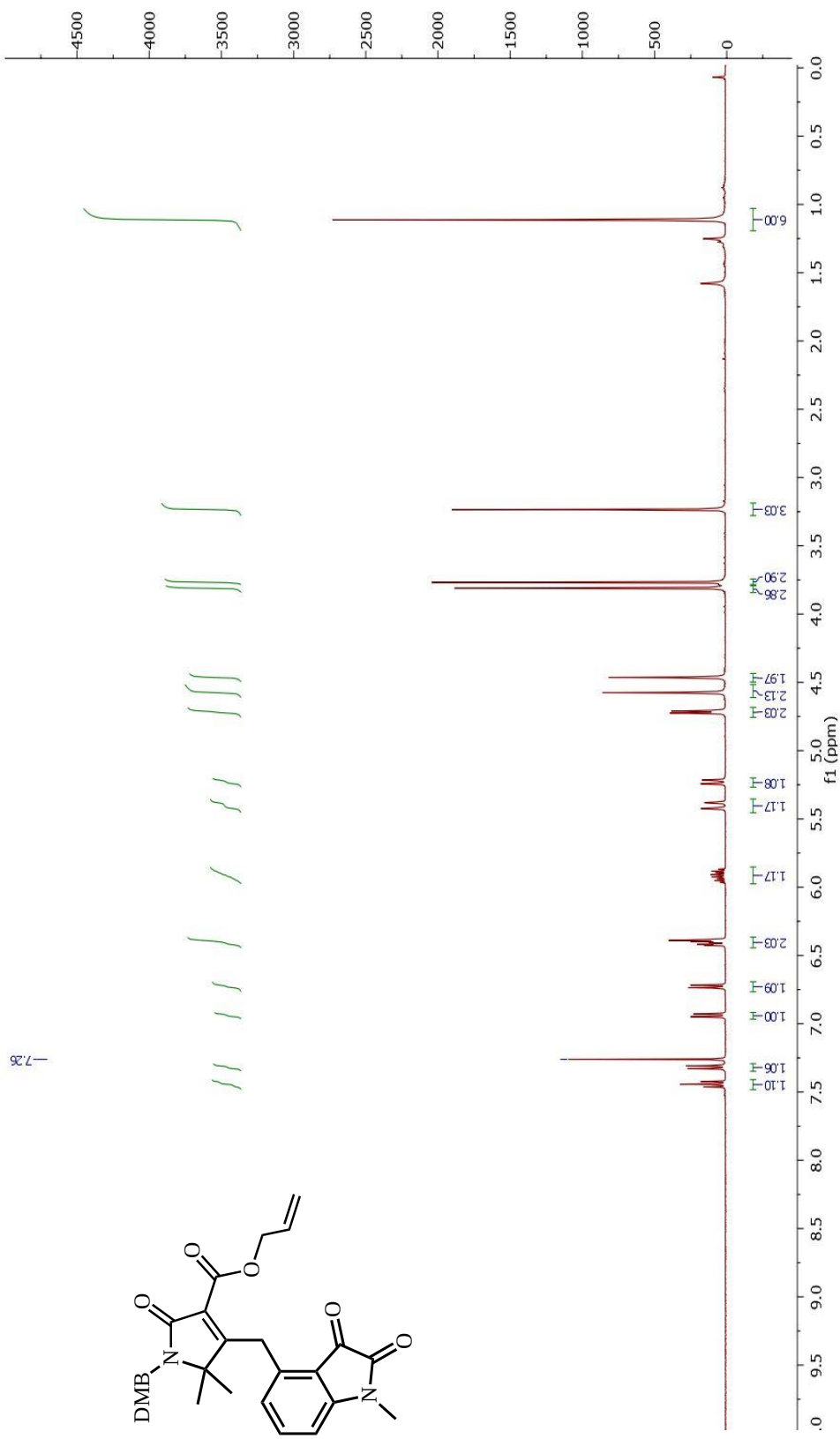

Figure C.90. **^{1}H NMR** (400 MHz, $CDCl_3$) of pyrrolinone **3.28**

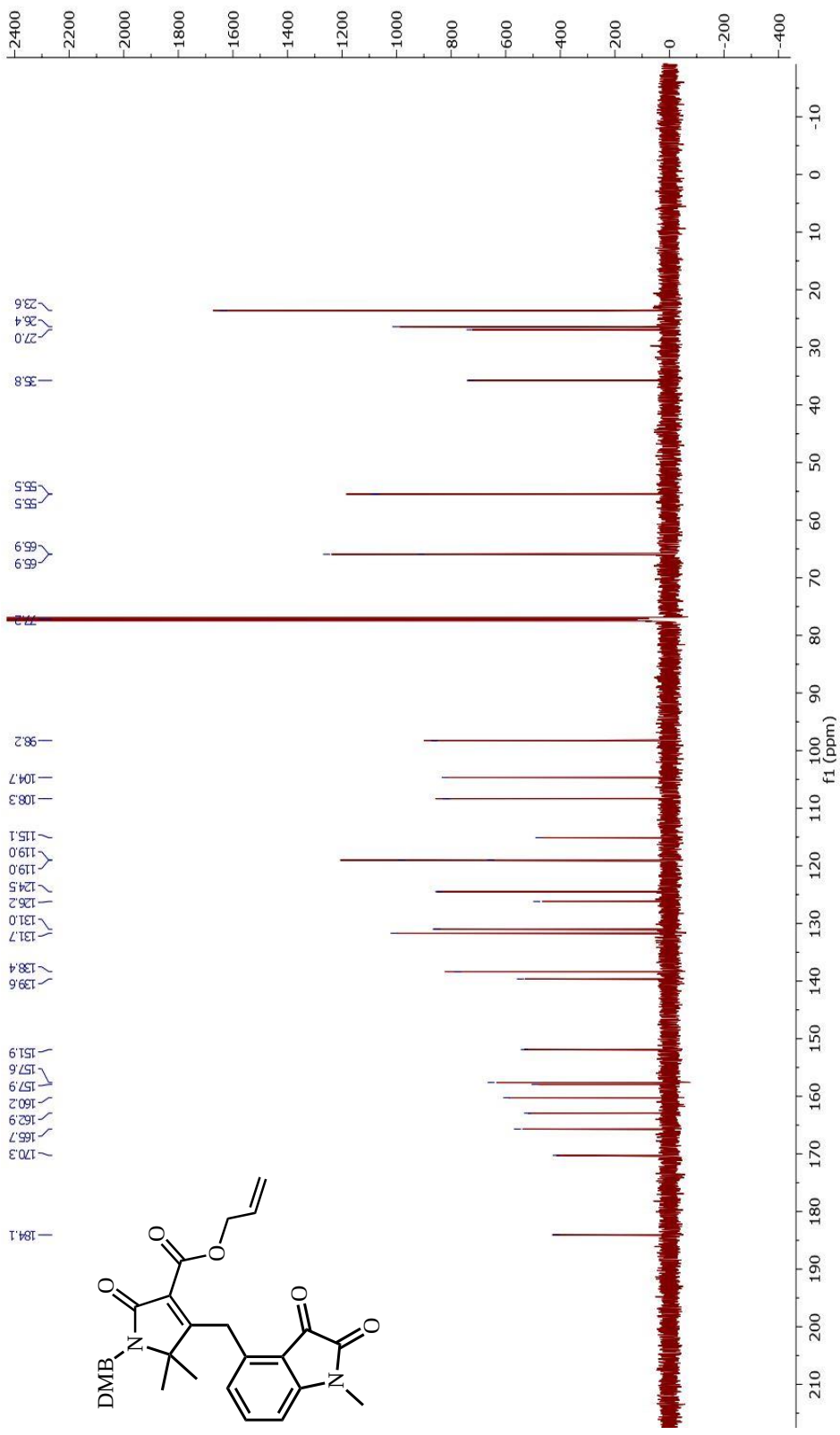

Figure C.91. **^{13}C NMR** (151 MHz, $CDCl_3$) of pyrrolinone **3.28**

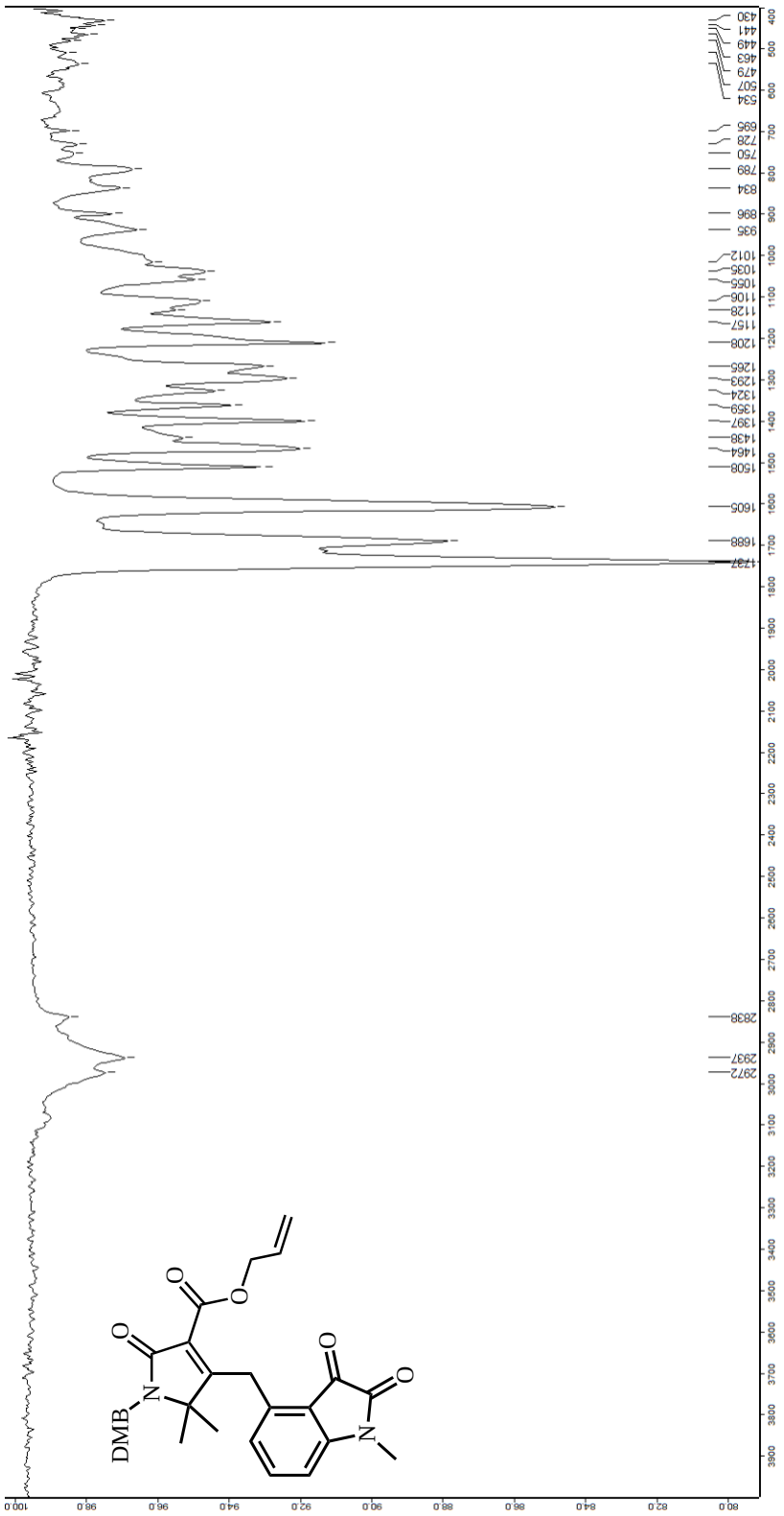

Figure C.92. FTIR Spectrum (neat) of pyrrolinone **3.28**

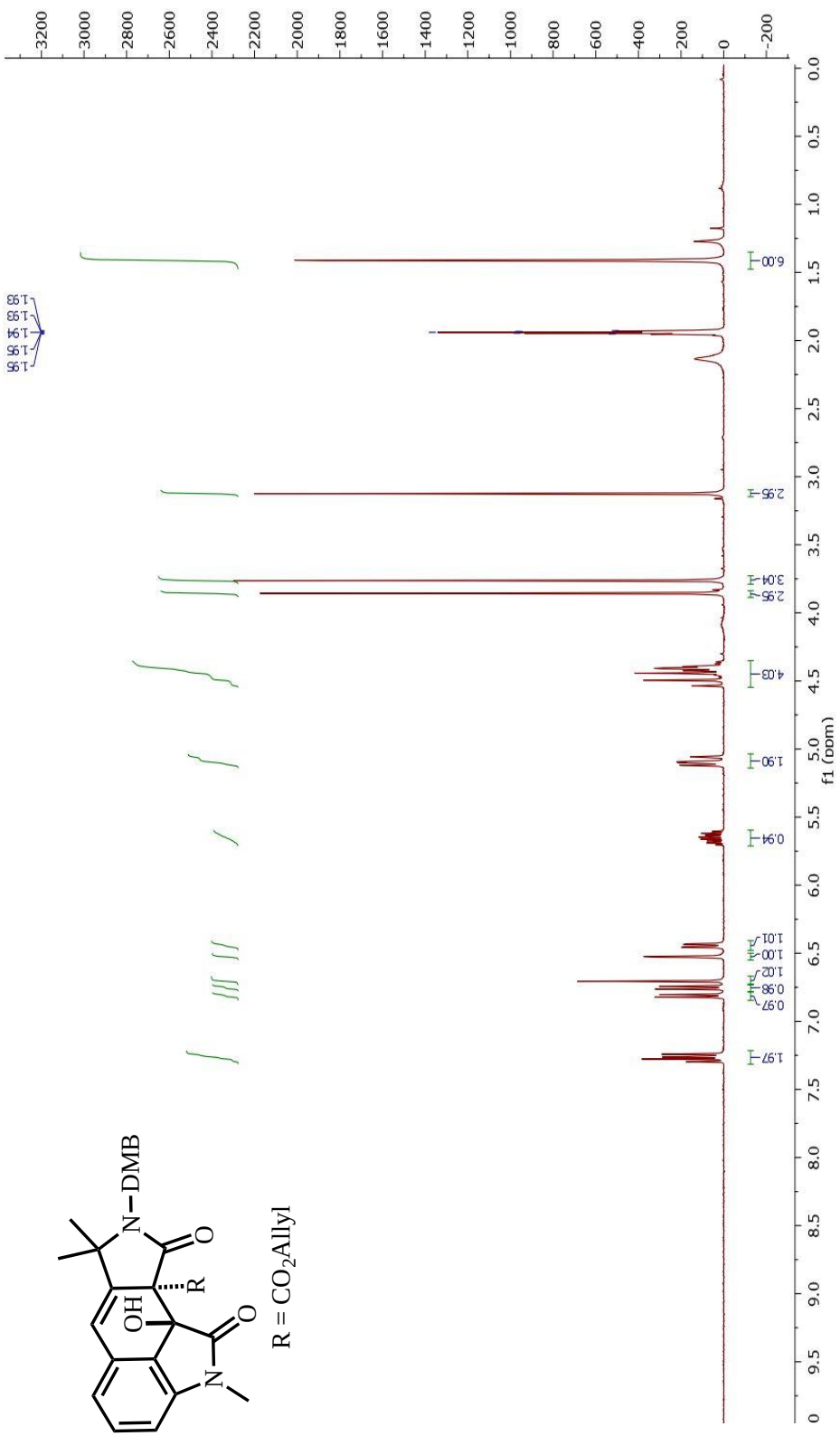

Figure C.93. **^{1}H NMR** (400 MHz, CD_3CN) of tetracycle **3.32**

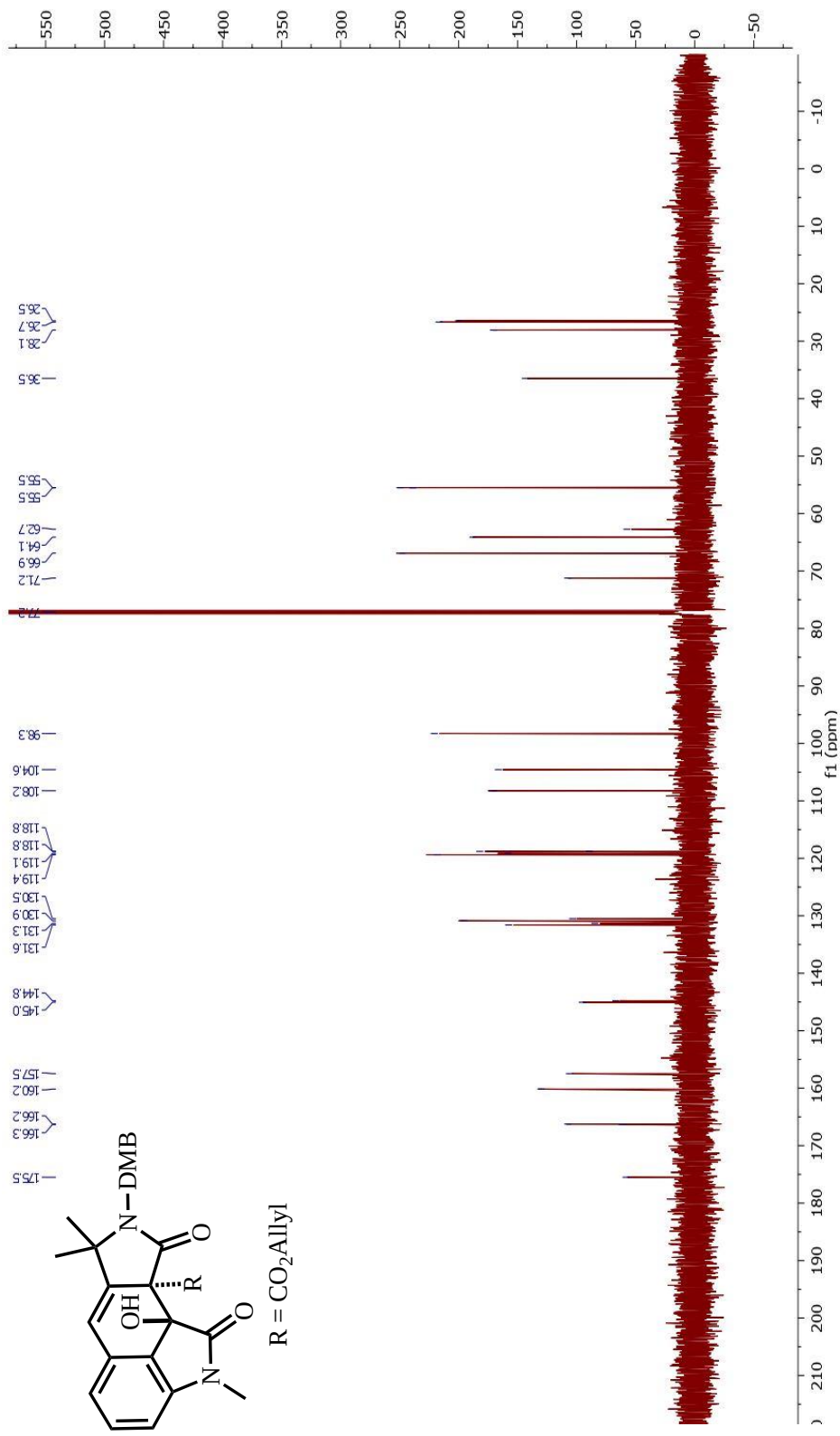

Figure C.94. **^{13}C NMR** (151 MHz, $CDCl_3$) of tetracycle **3.32**

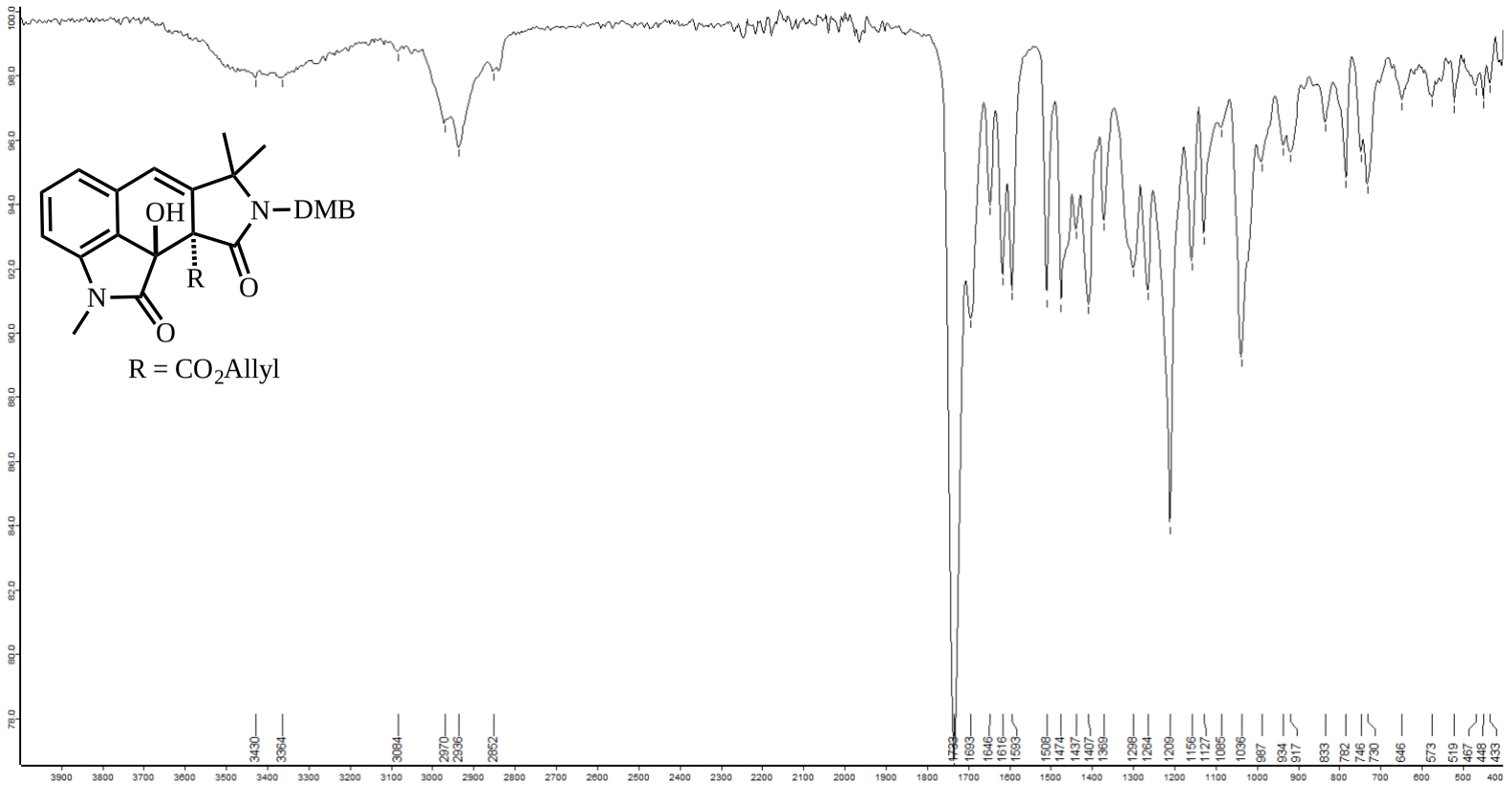

Figure C.95. FTIR Spectrum (neat) of tetracycle **3.32**

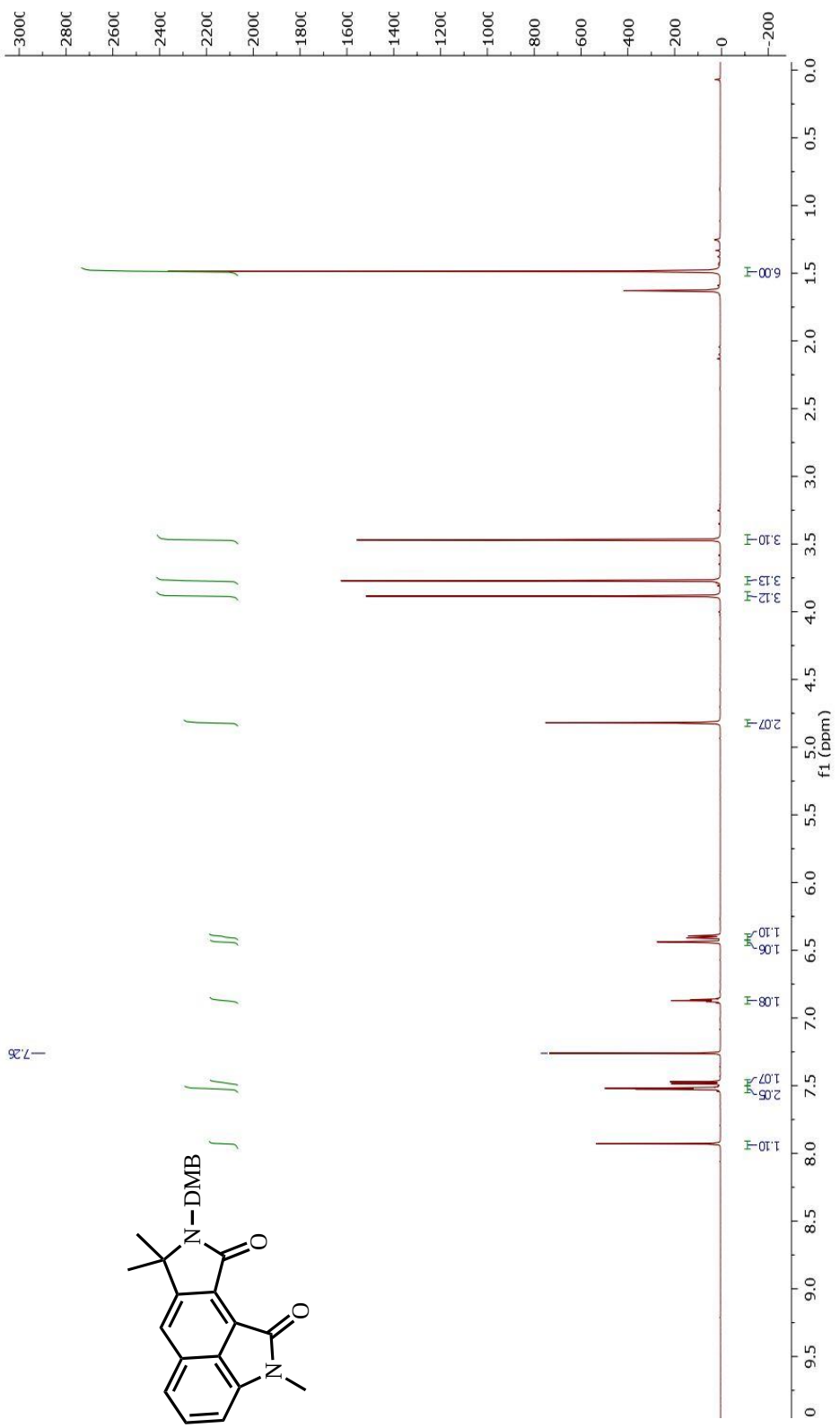

Figure C.96. **^{1}H NMR** (600 MHz, $CDCl_3$) of amide **3.33**

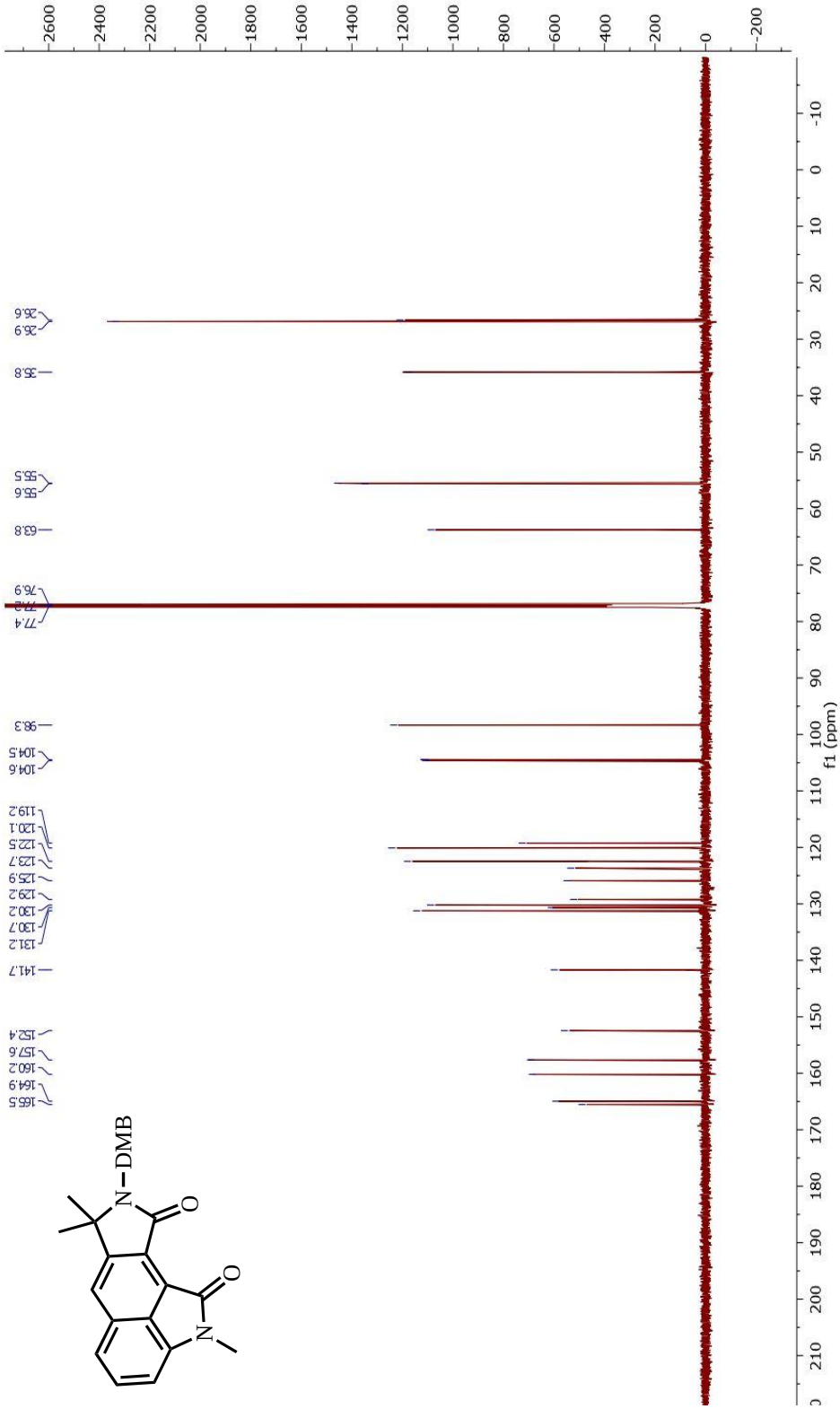

Figure C.97. **^{13}C NMR** (151 MHz, $CDCl_3$) of amide **3.33**

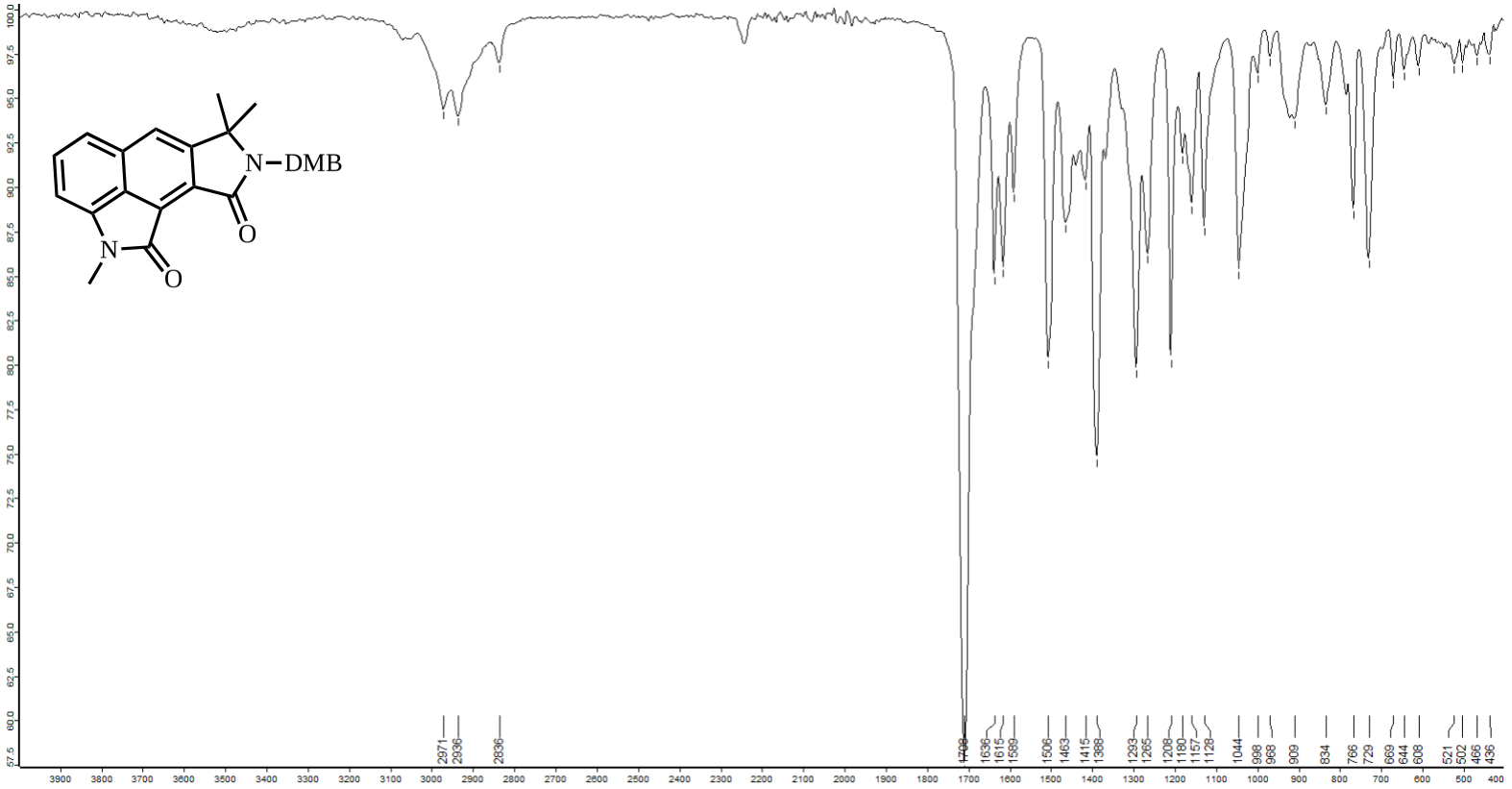

Figure C.98. FTIR Spectrum (neat) of amide **3.33**

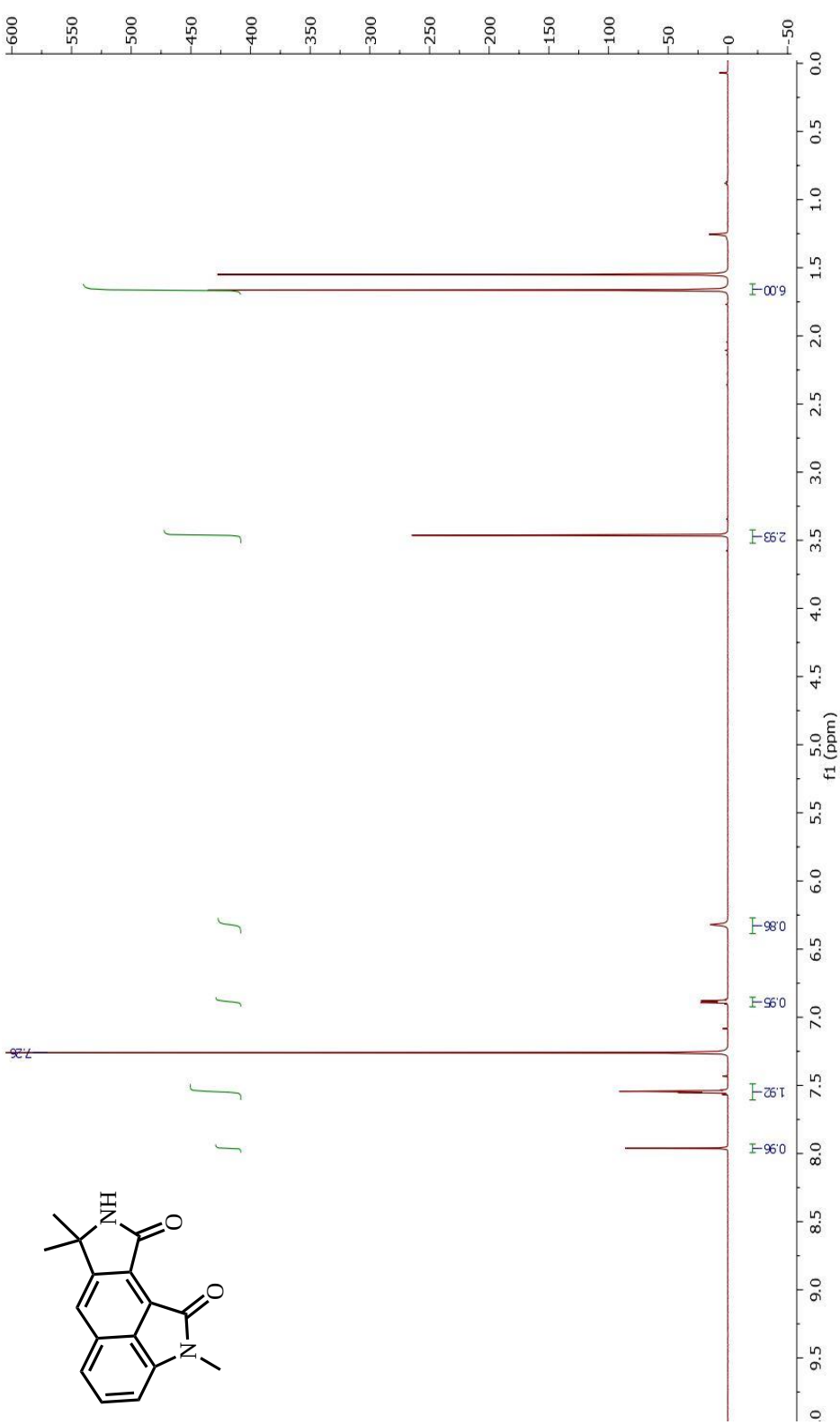

Figure C.99. **^{1}H NMR** (600 MHz, $CDCl_3$) of cyclopiamide *A* **3.02**

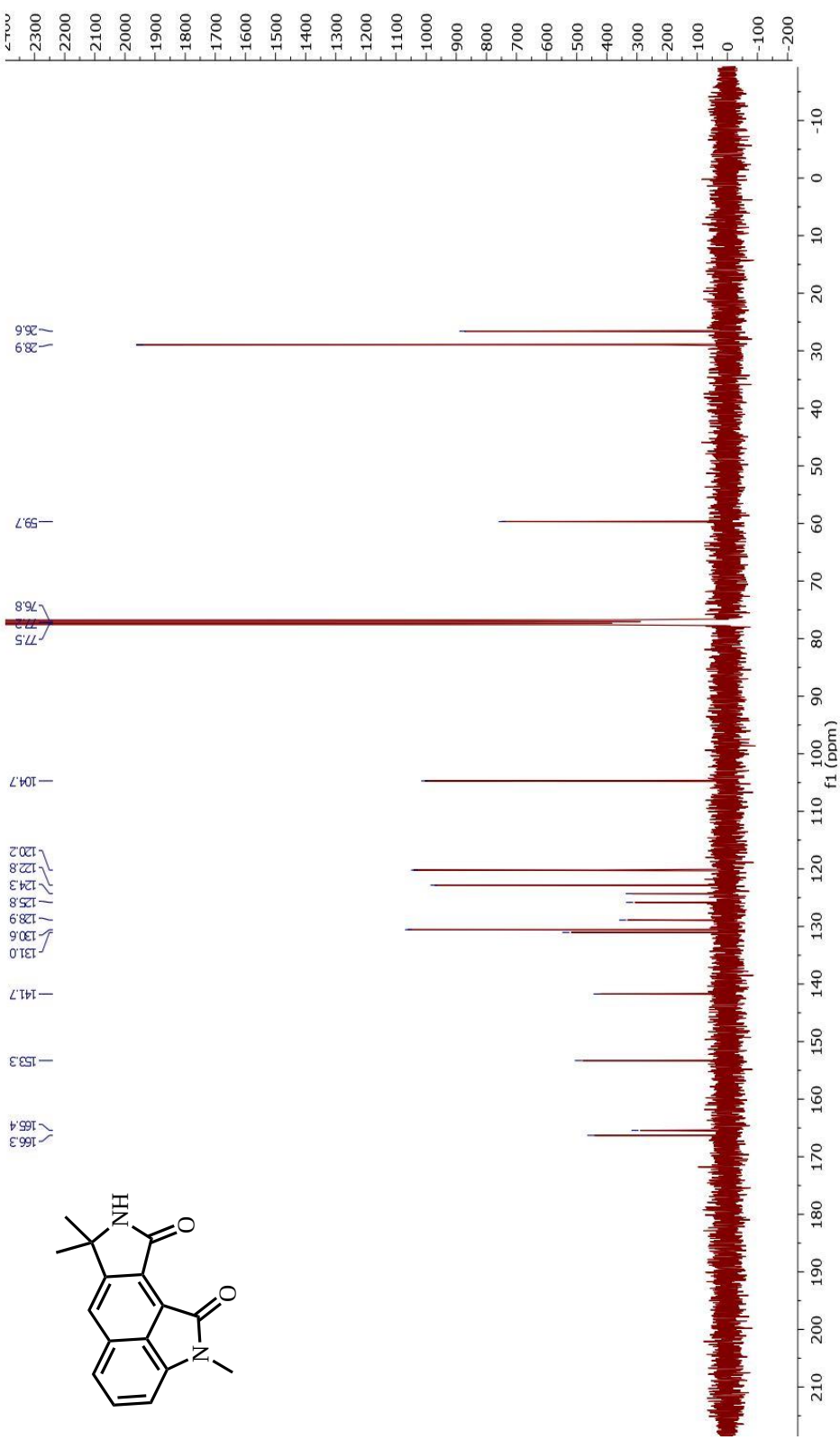

Figure C.100. **^{13}C NMR** (101 MHz, $CDCl_3$) of cyclopiamide *A* **3.02**

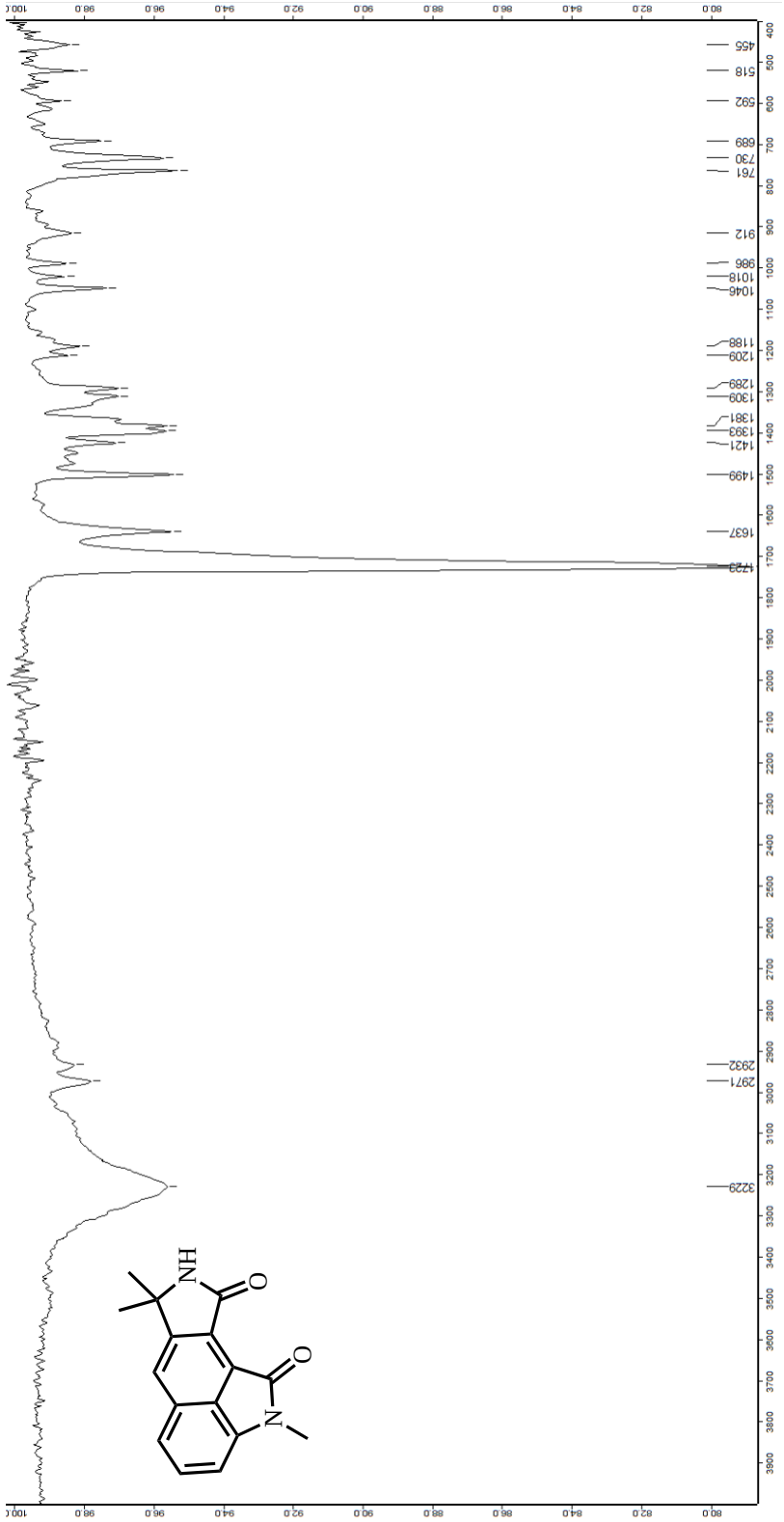

Figure C.101. FTIR Spectrum (neat) of cyclopiamide A **3.02**

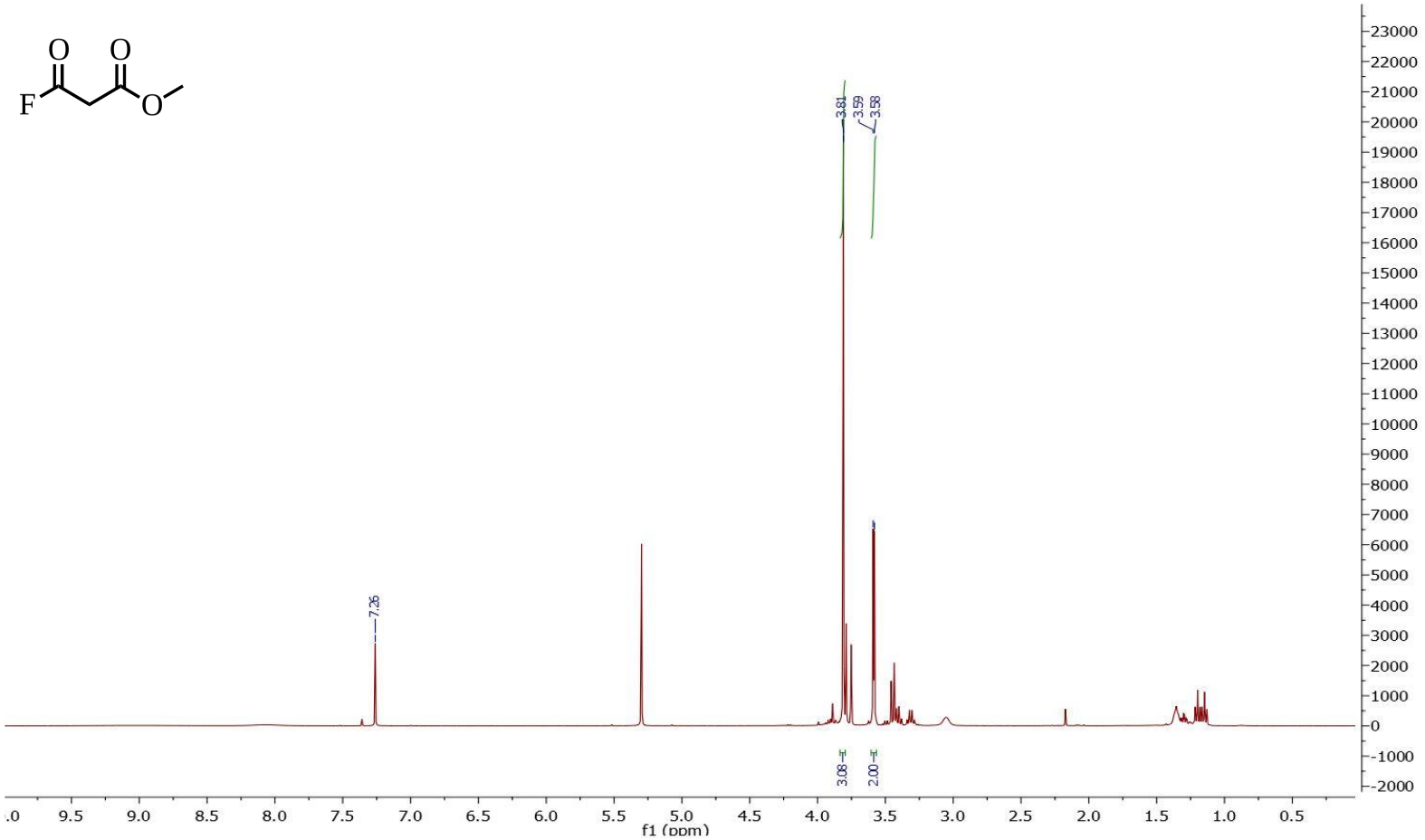

Figure C.102. **^{1}H NMR** (400 MHz, $CDCl_3$) of crude malonyl fluoride **3.109**

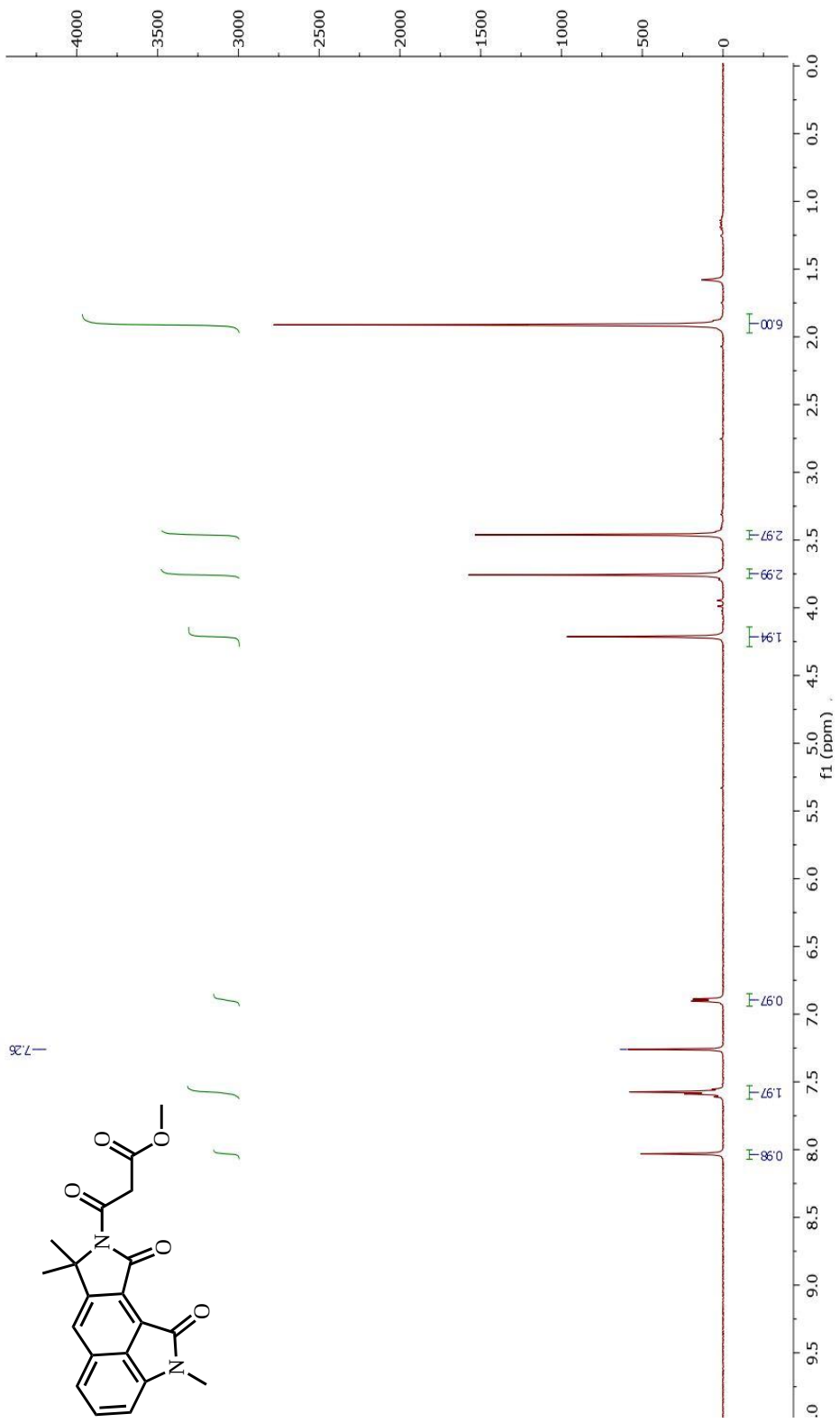

Figure C.103. **^{1}H NMR** (400 MHz, $CDCl_3$) of speradine E **3.03**

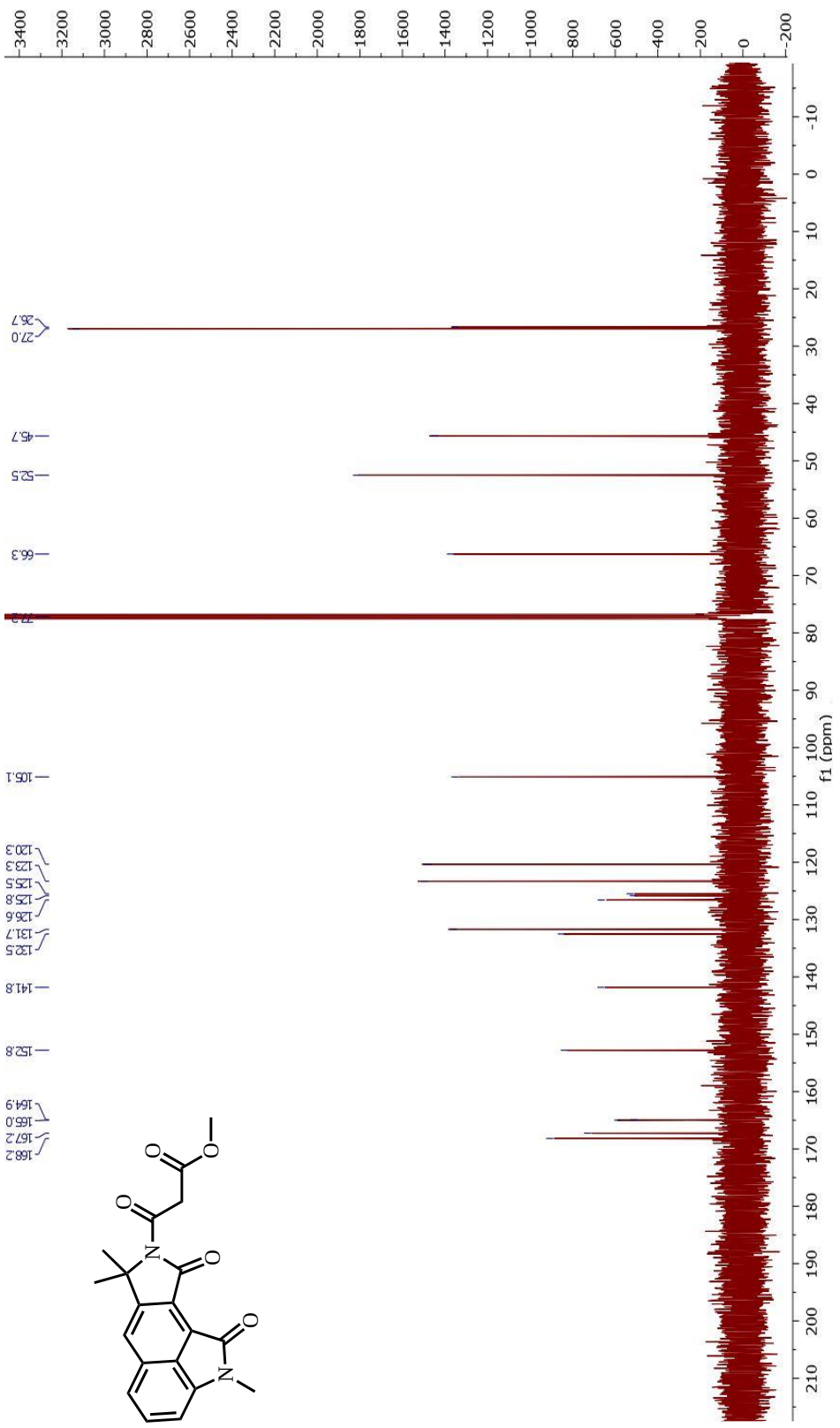

Figure C.104. **^{13}C NMR** (101 MHz, $CDCl_3$) of speradine E **3.03**

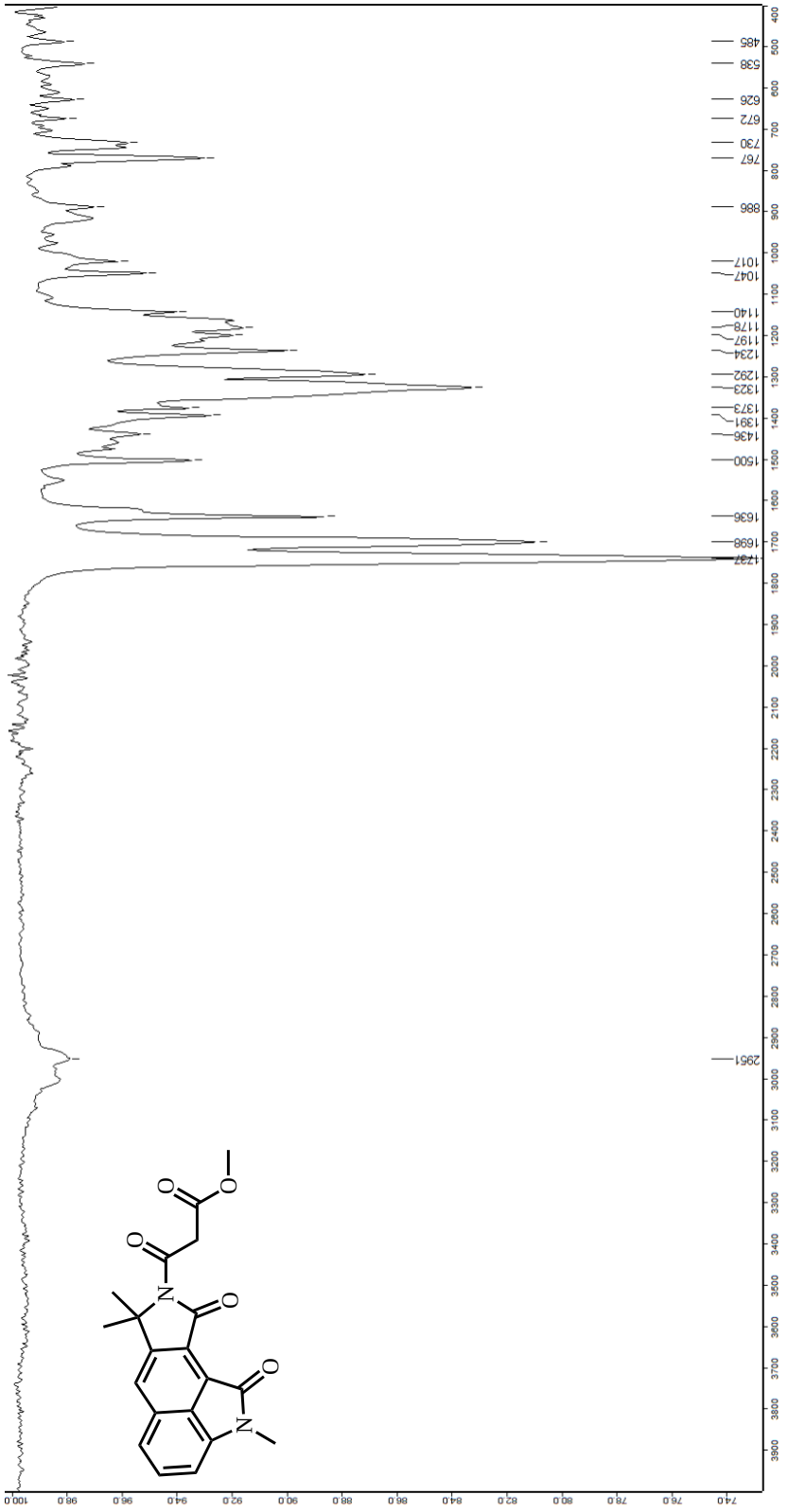

Figure C.105. FTIR Spectrum (neat) of speradine E **3.03**

APPENDIX D

Spectral Data for Chapter Four

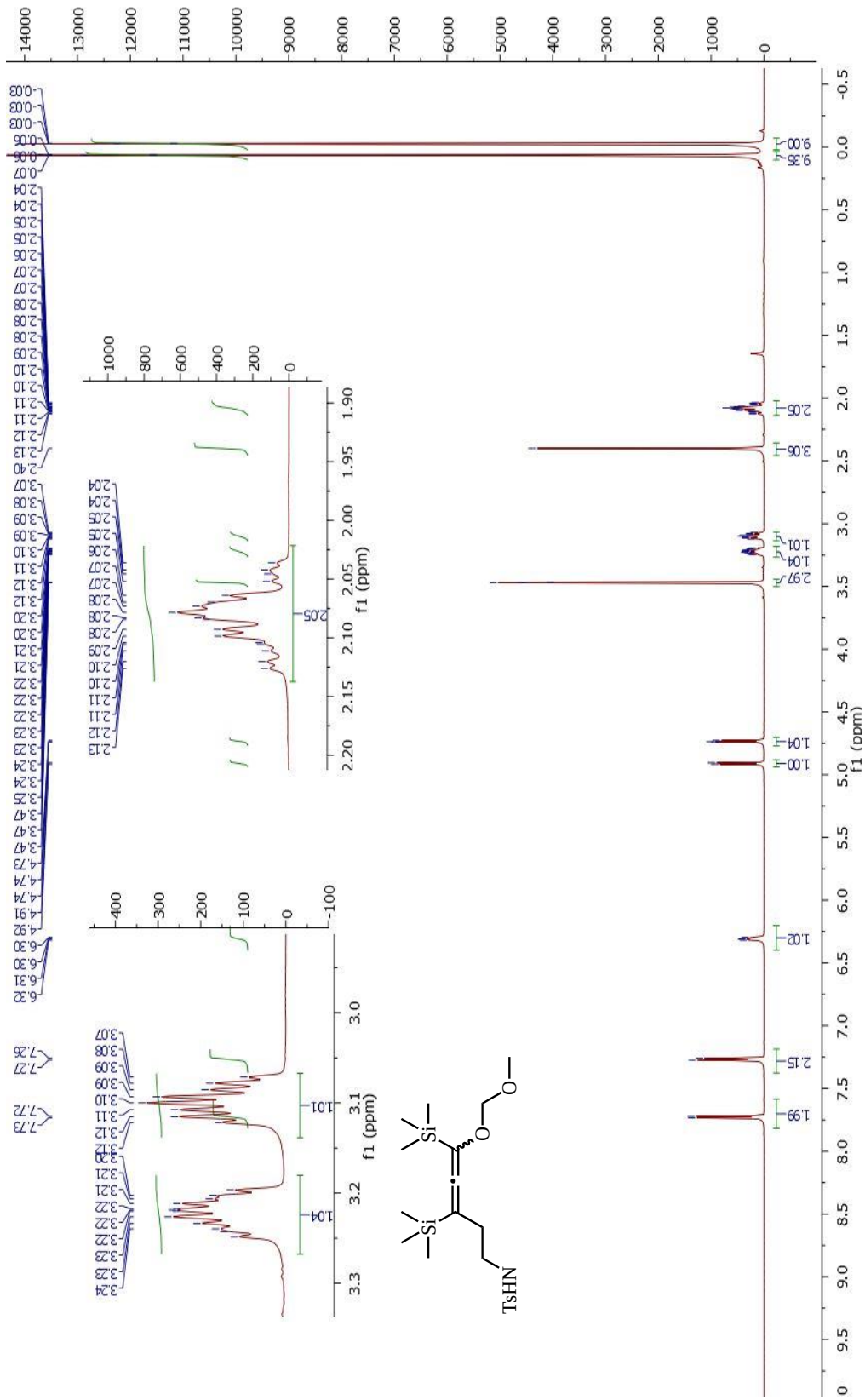

Figure D.01. **^{1}H NMR** (600 MHz, $CDCl_3$) of allene **4.34**

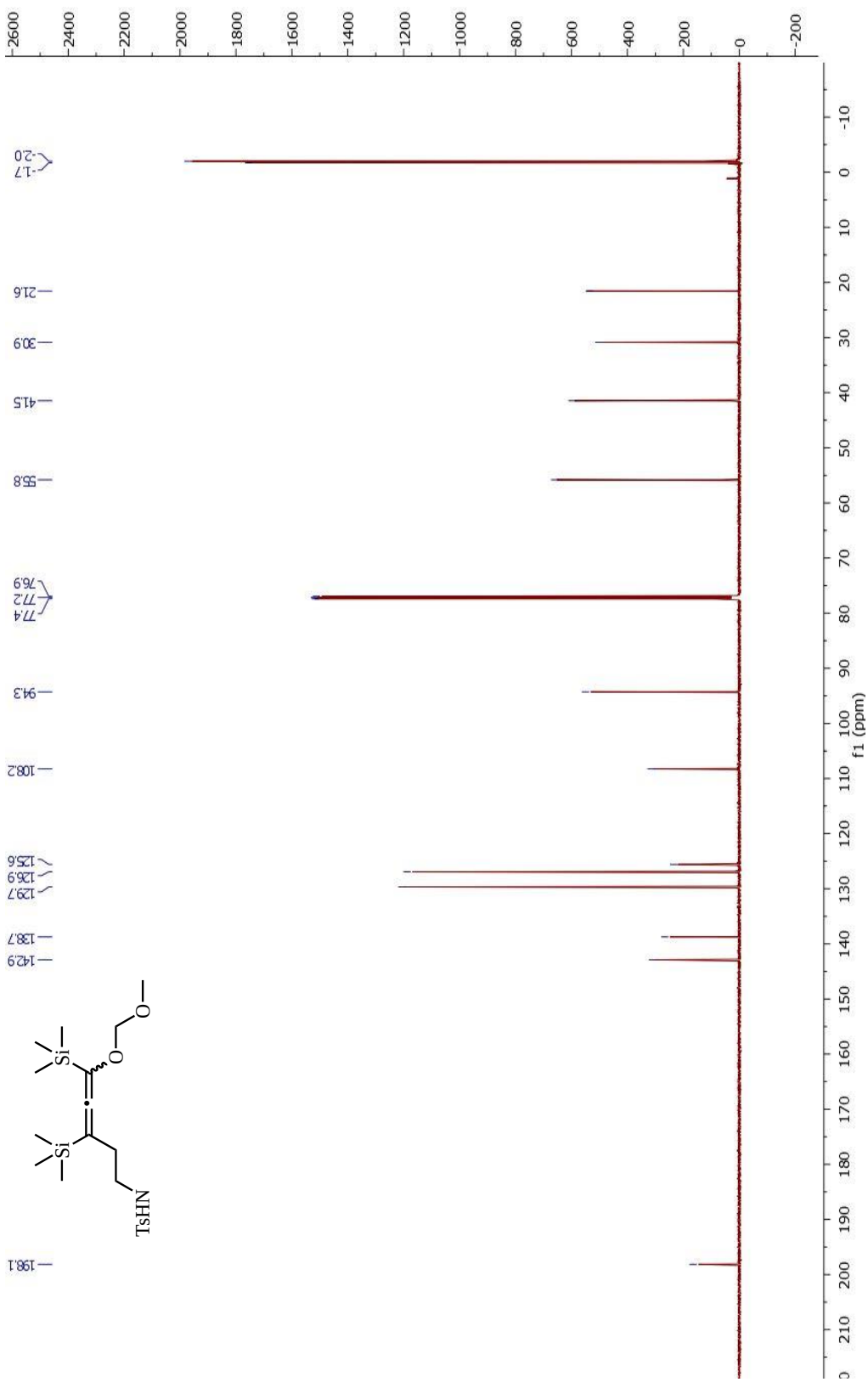

Figure D.02. **^{13}C NMR** (151 MHz, $CDCl_3$) of allene **4.34**

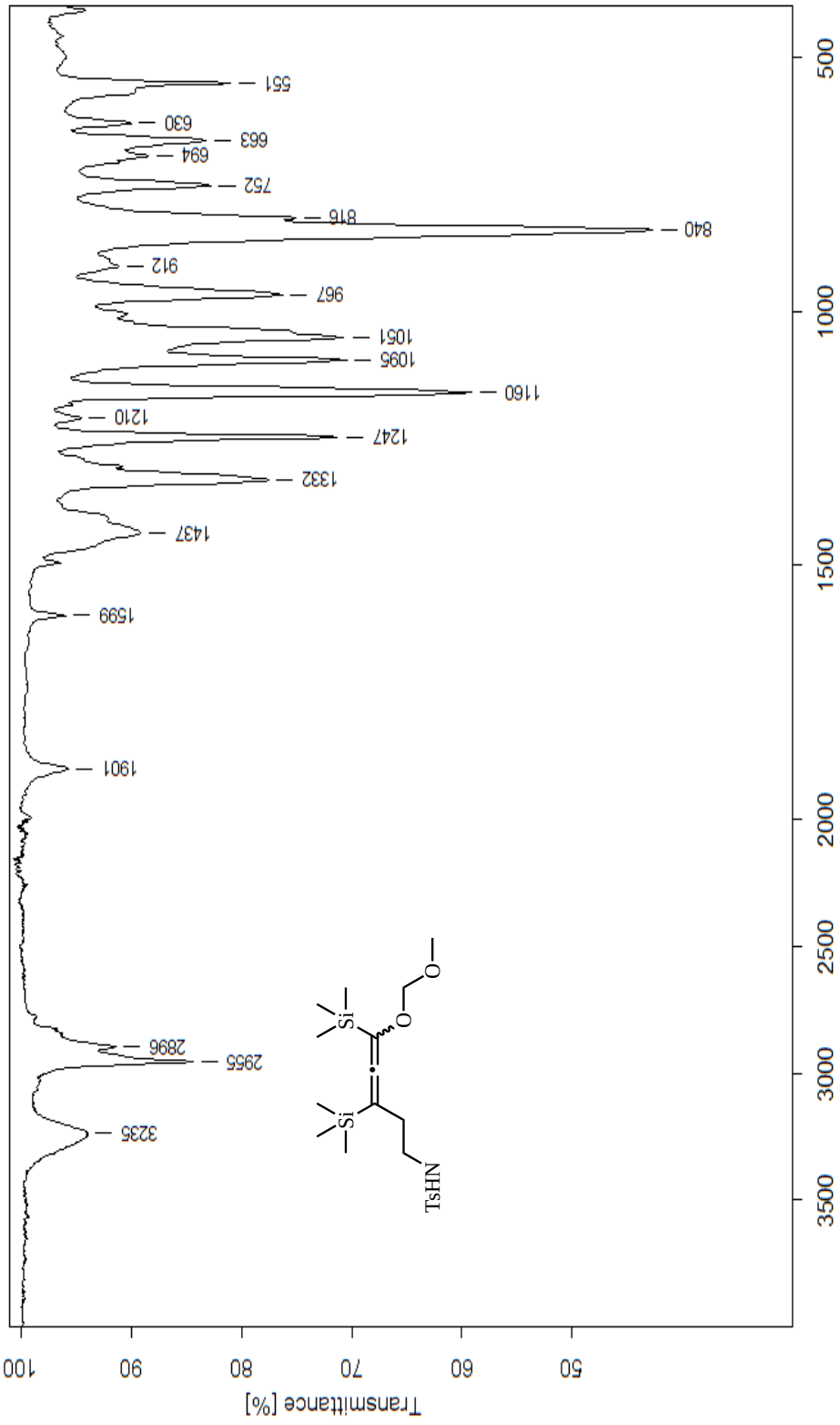

Figure D.03. FTIR Spectrum (neat) of allene **4.34**

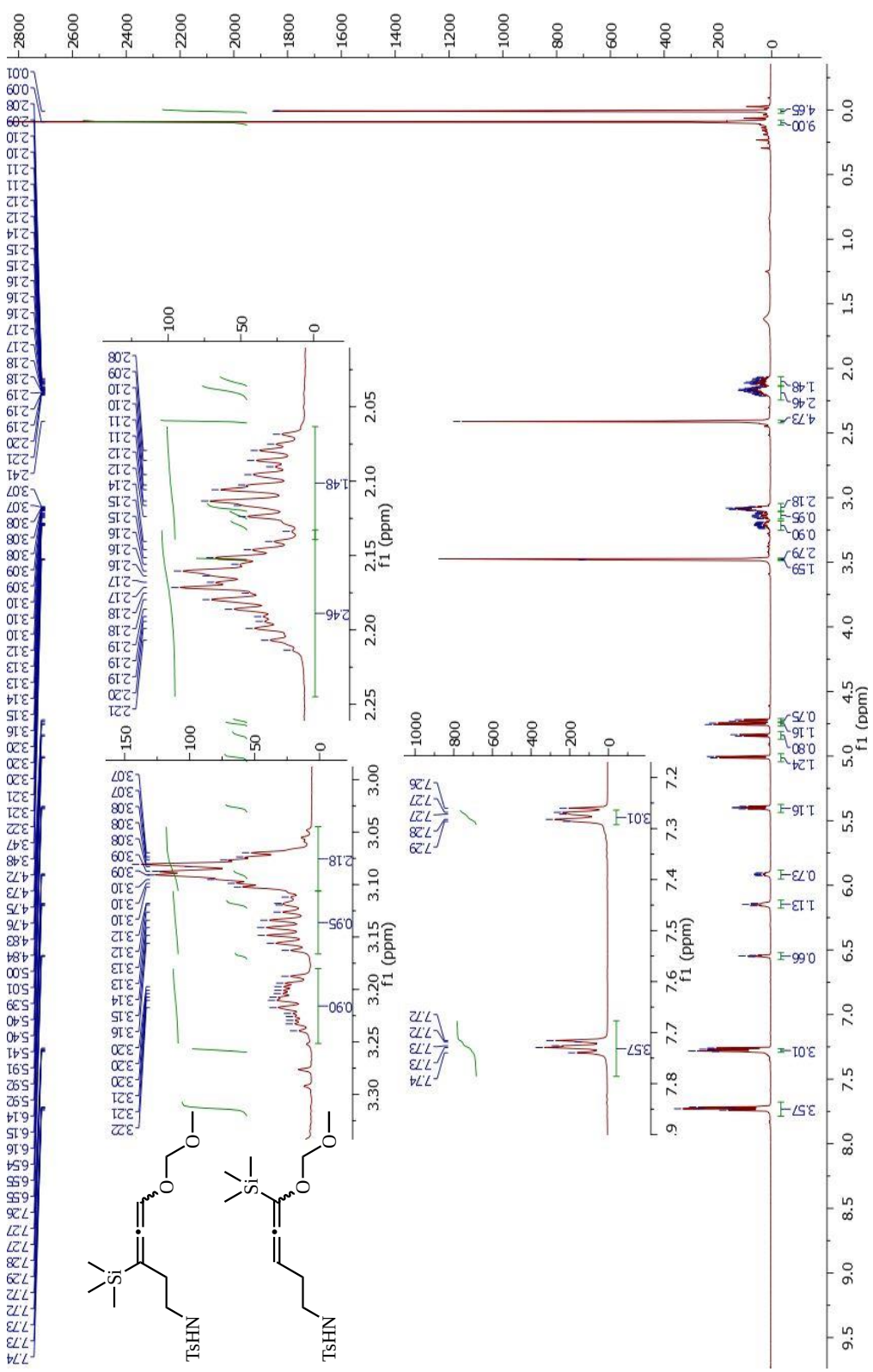

Figure D.04. **^{1}H NMR** (600 MHz, $CDCl_3$) of allenes **4.35** & **4.36**

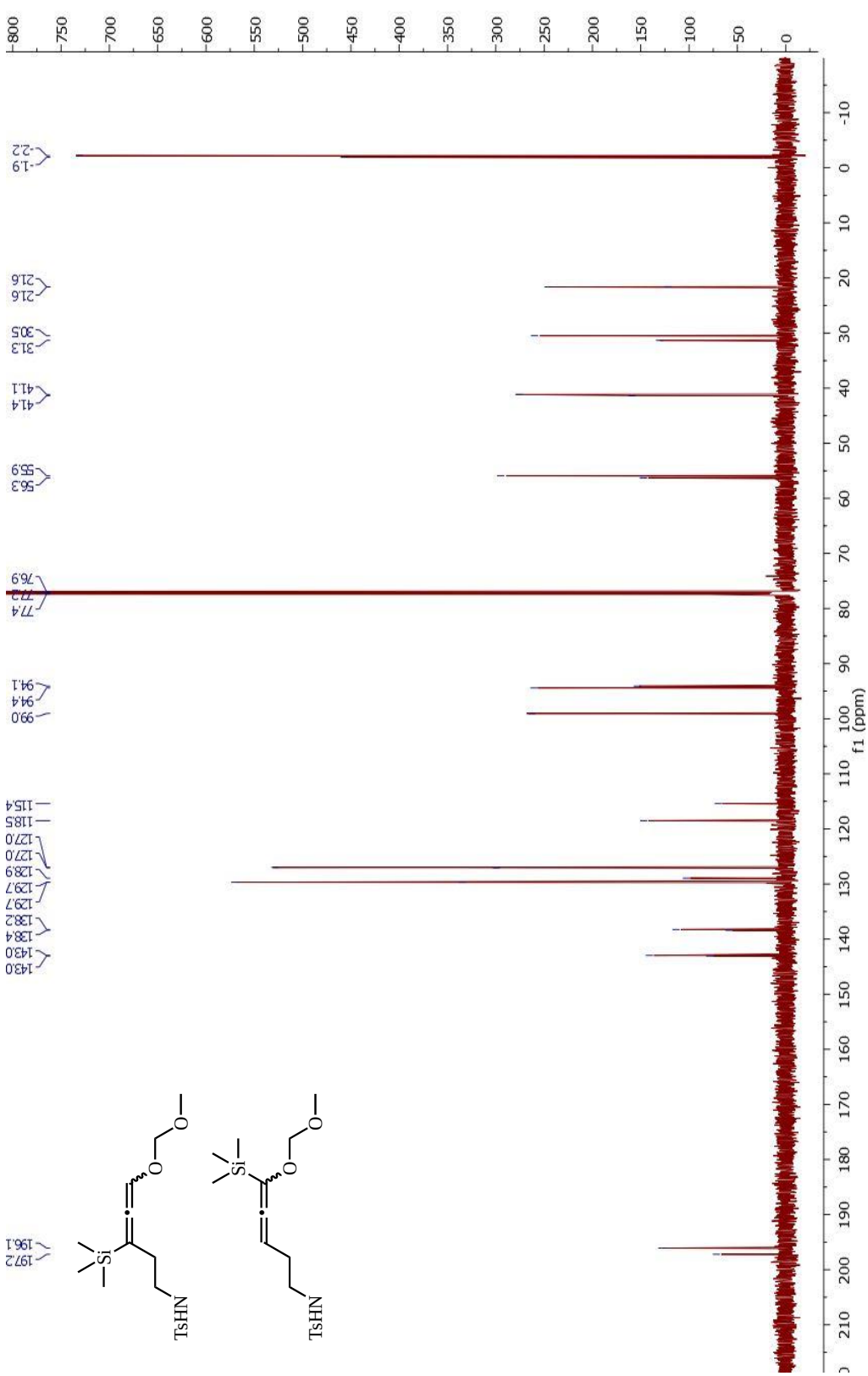

Figure D.05. **^{13}C NMR** (151 MHz, $CDCl_3$) of allenes **4.35** & **4.36**

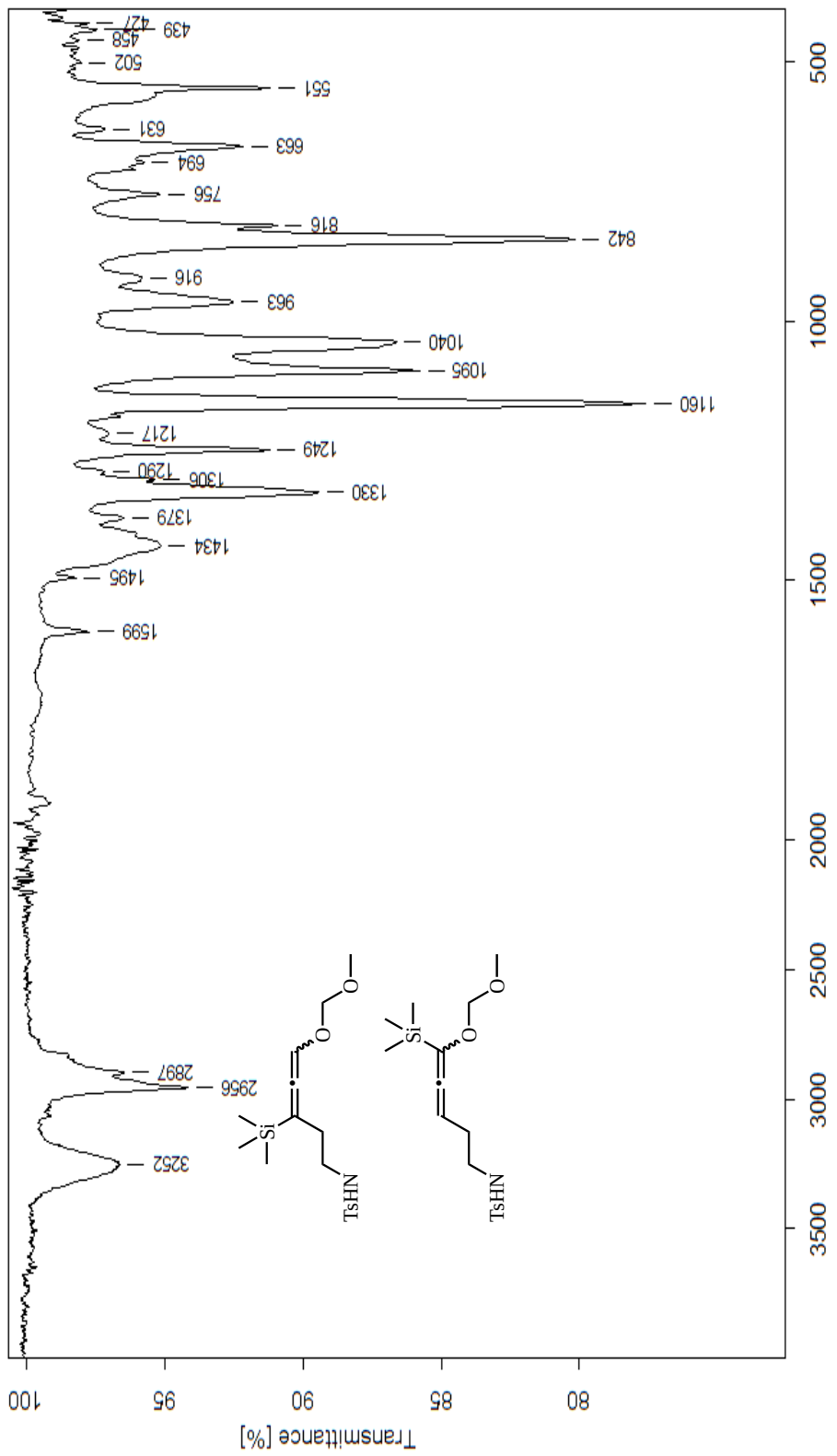

Figure D.06. FTIR Spectrum (neat) of allenes **4.35** & **4.36**

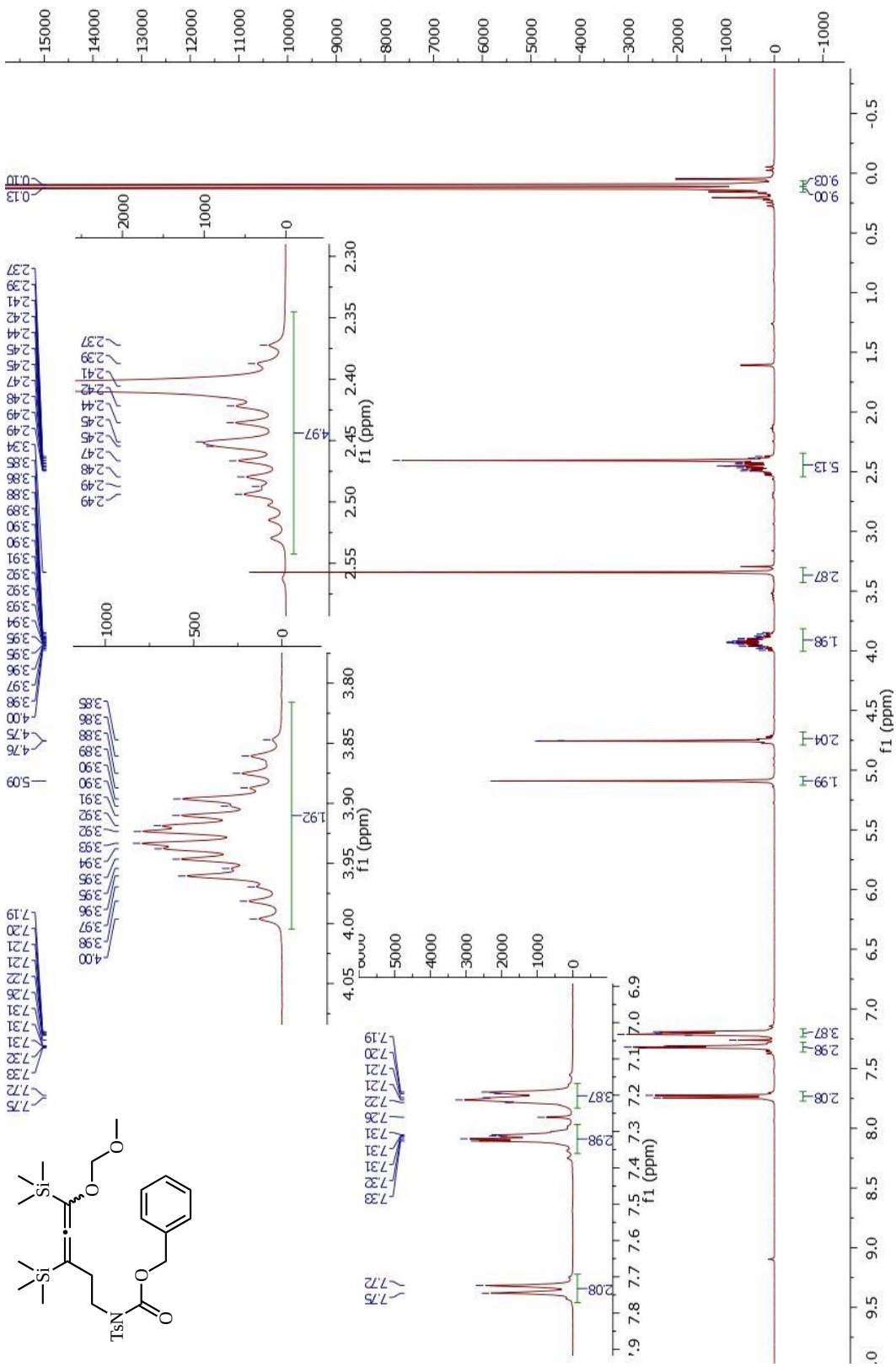

Figure D.07. **^{1}H NMR** (400 MHz, $CDCl_3$) of allene **4.37**

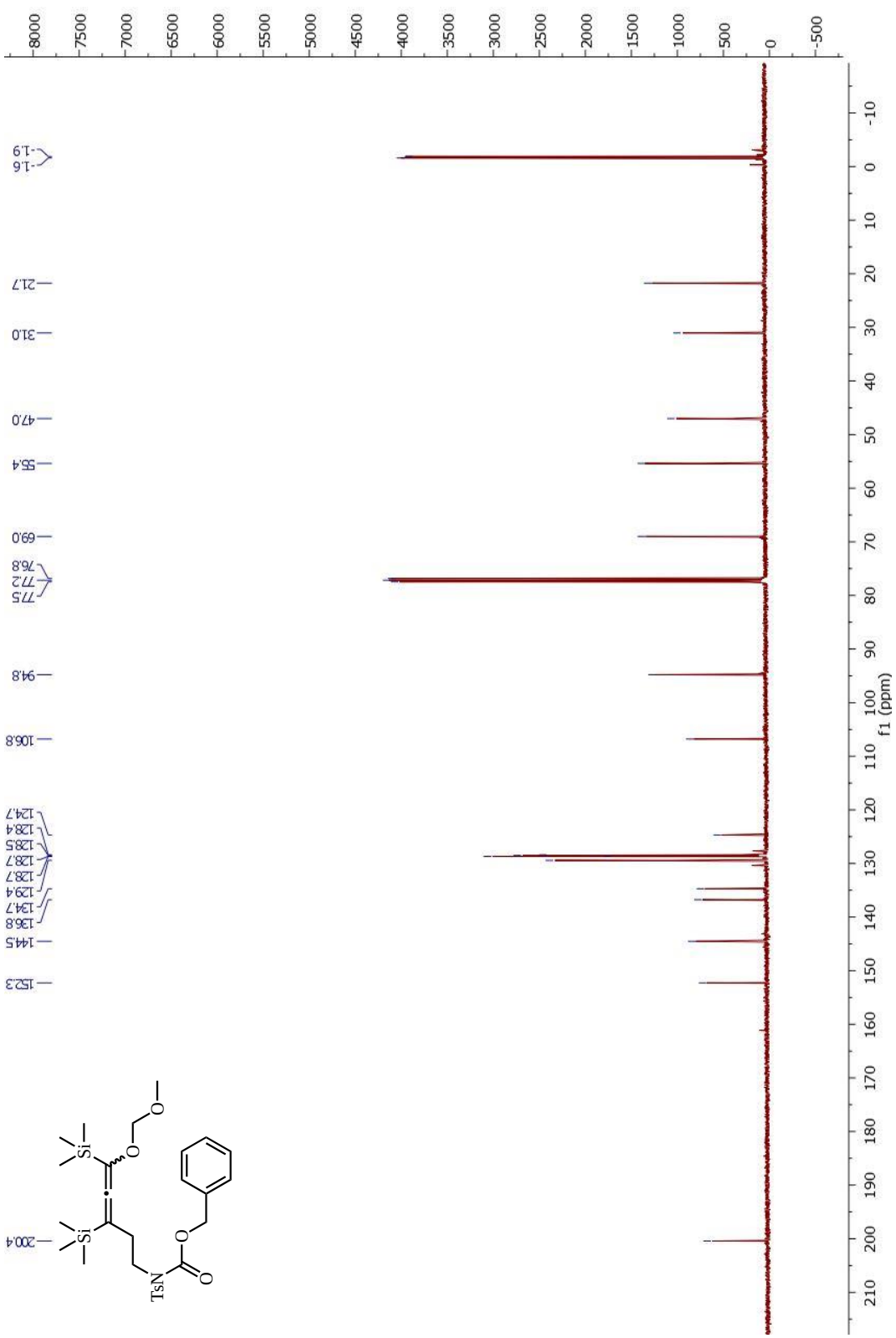

Figure D.08. **^{13}C NMR** (101 MHz, $CDCl_3$) of allene **4.37**

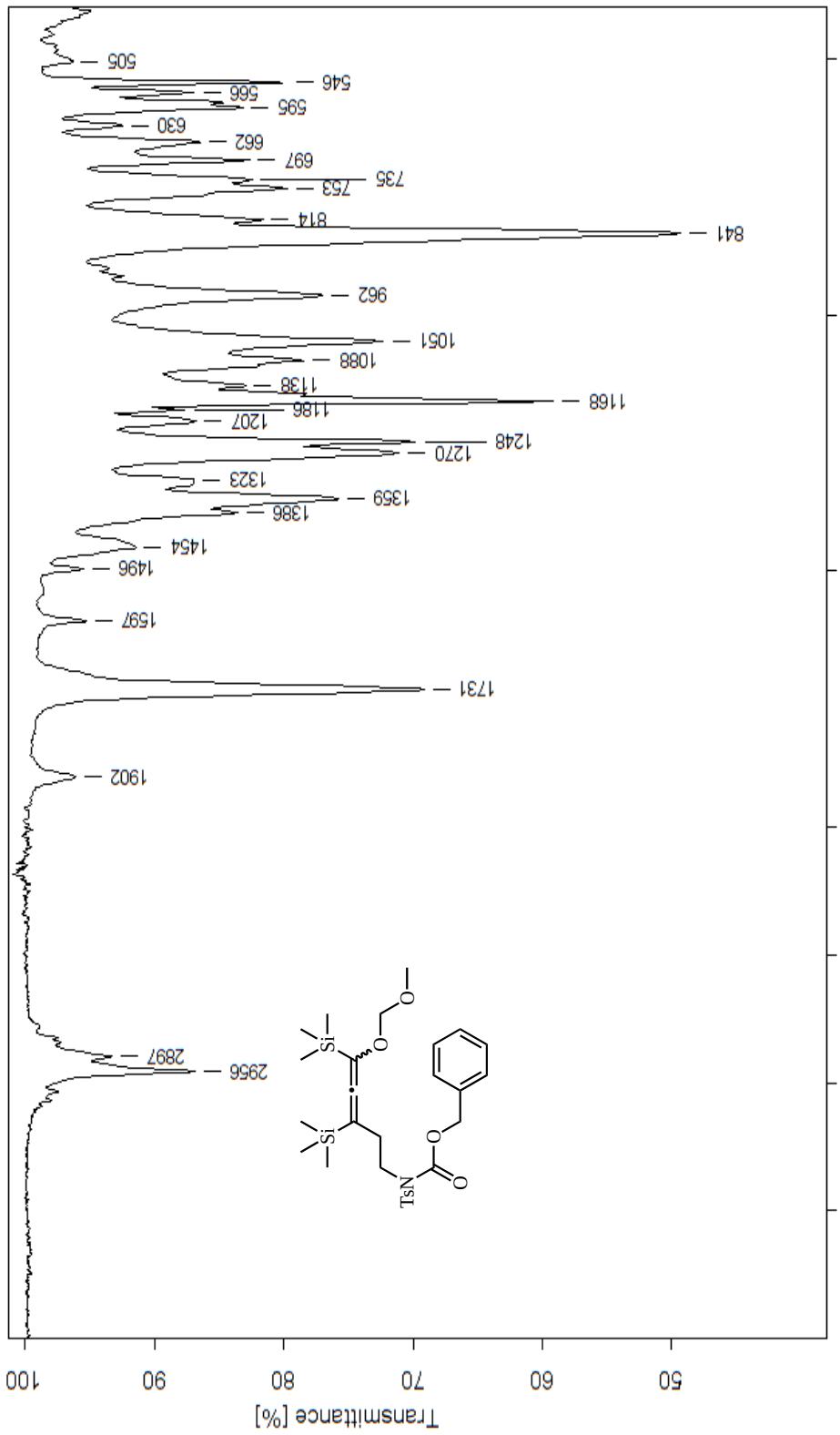

Figure D.09. FTIR Spectrum (neat) of allene **4.37**

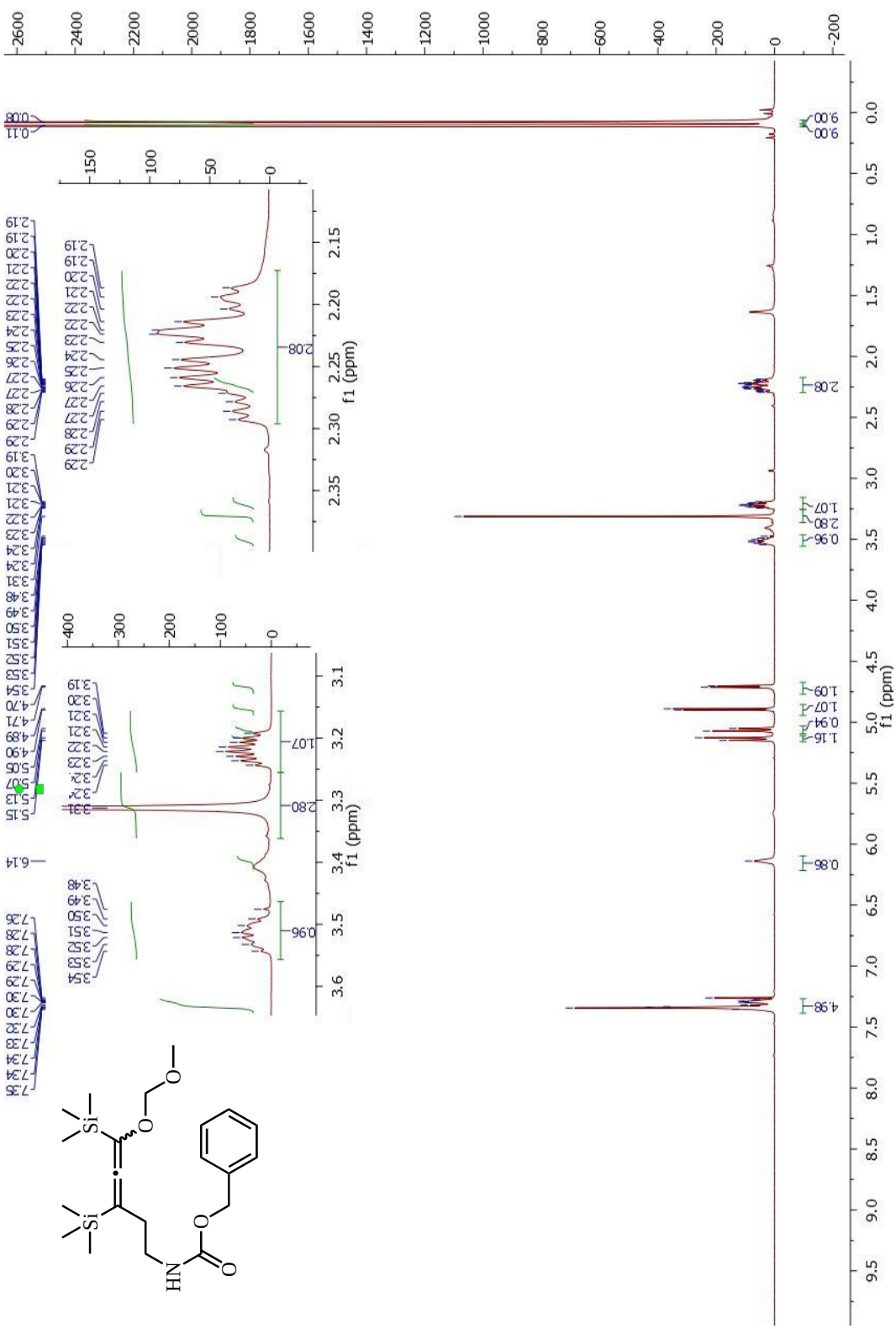

Figure D.10. **^{1}H NMR** (600 MHz, $CDCl_3$) of allene **4.38**

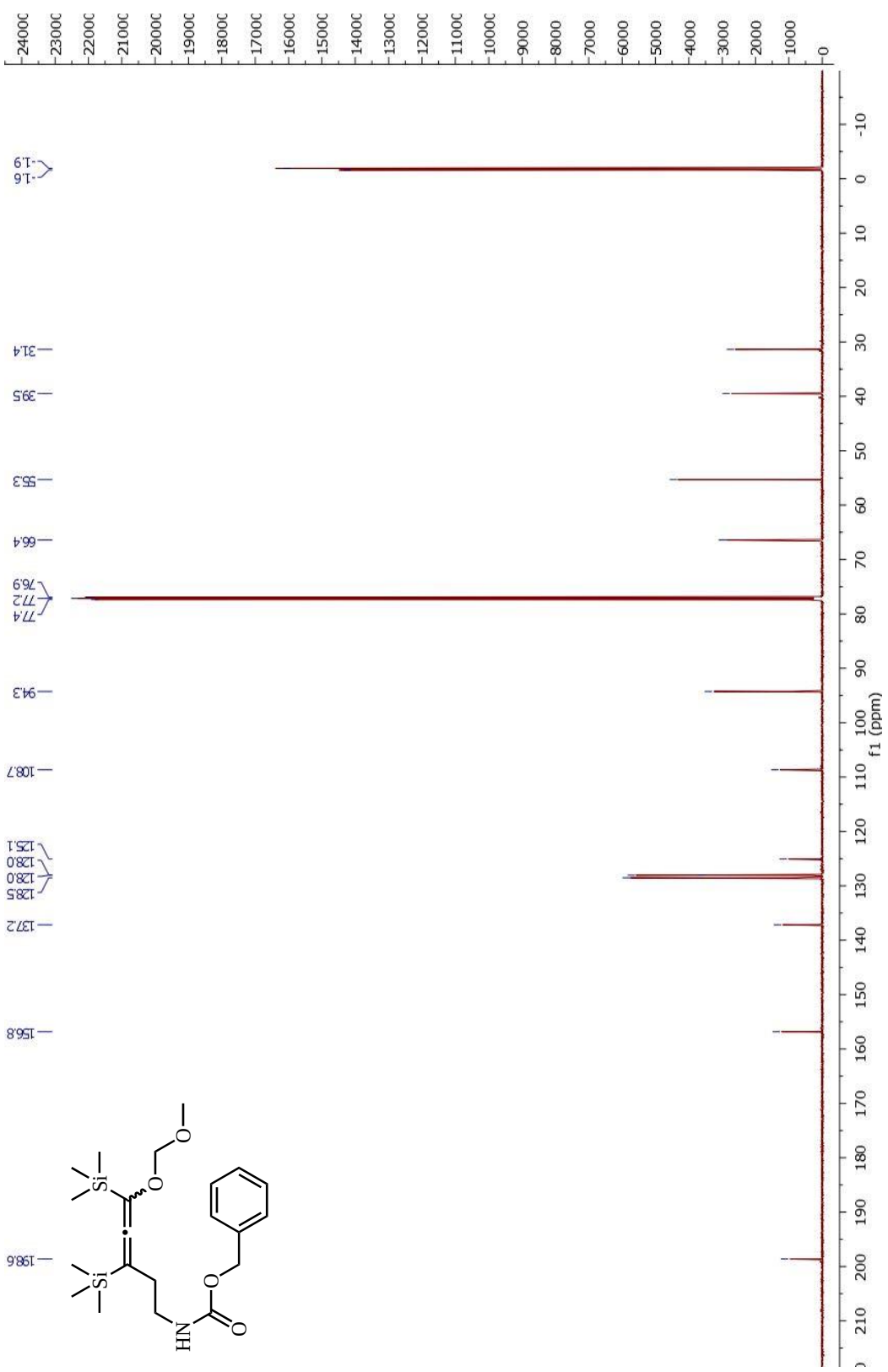

Figure D.11. **^{13}C NMR** (151 MHz, $CDCl_3$) of allene **4.38**

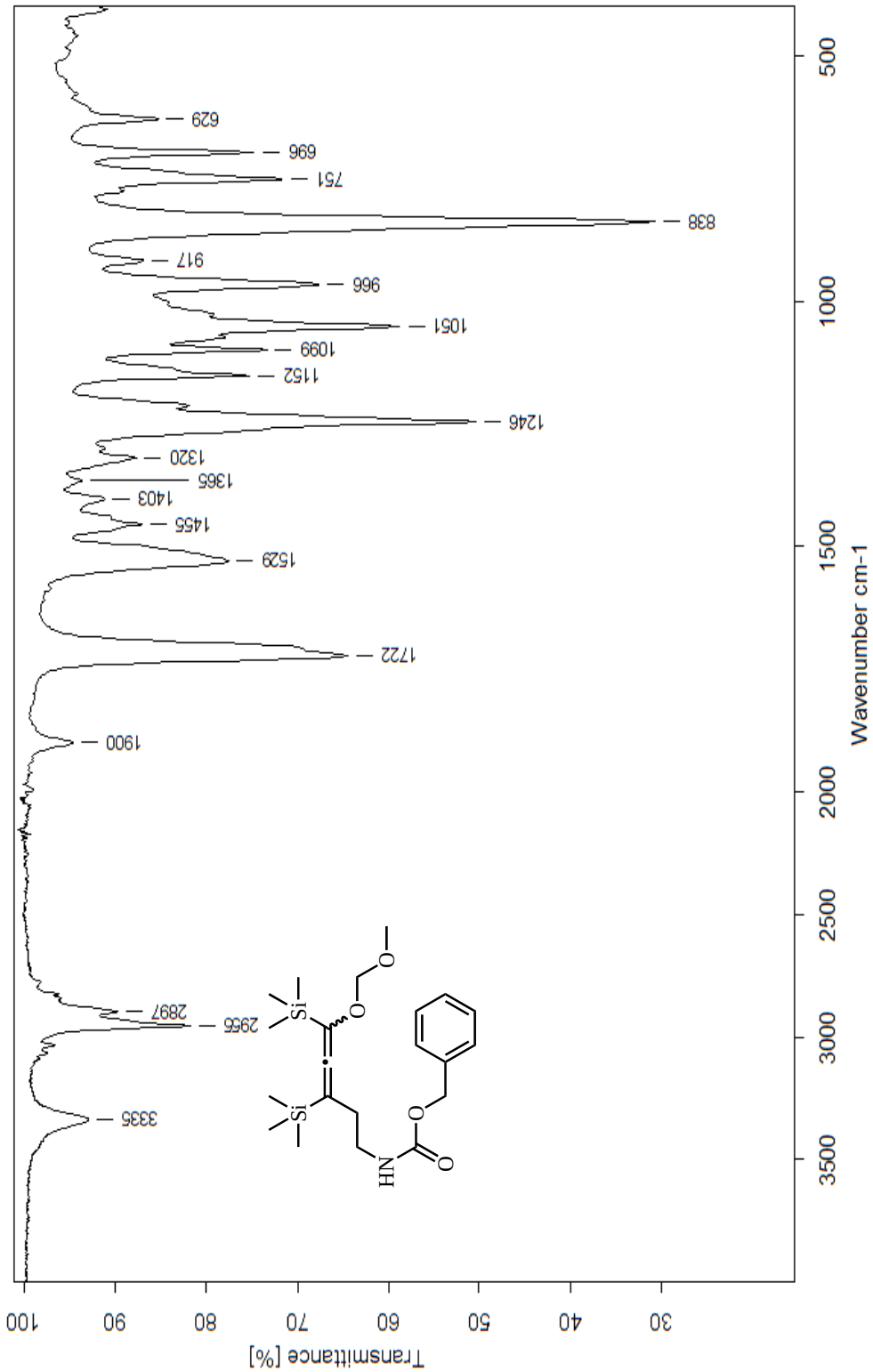

Figure D.12. FTIR Spectrum (neat) of allene **4.38**

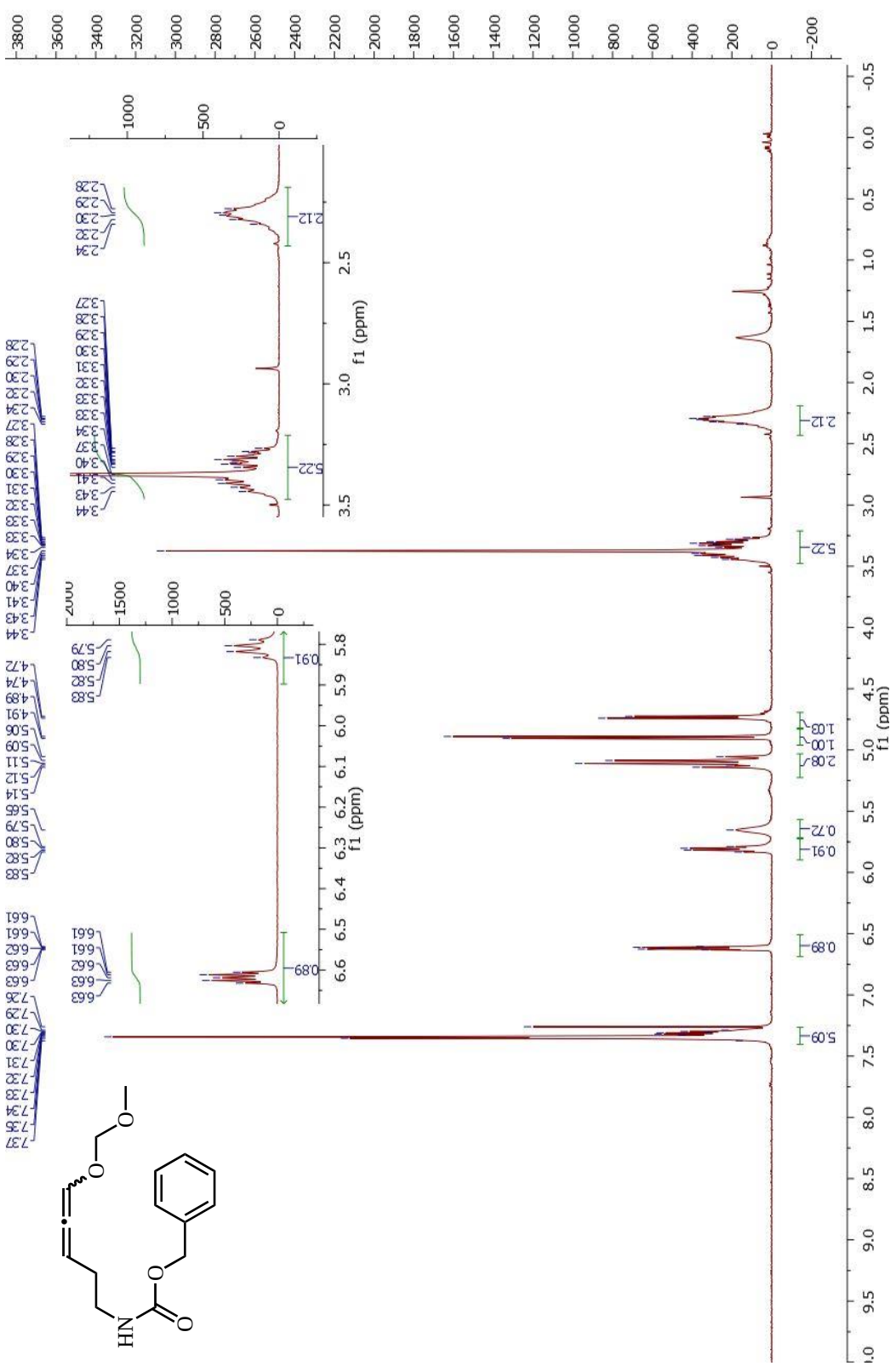

Figure D.13. **^{1}H NMR** (400 MHz, $CDCl_3$) of allene **4.39**

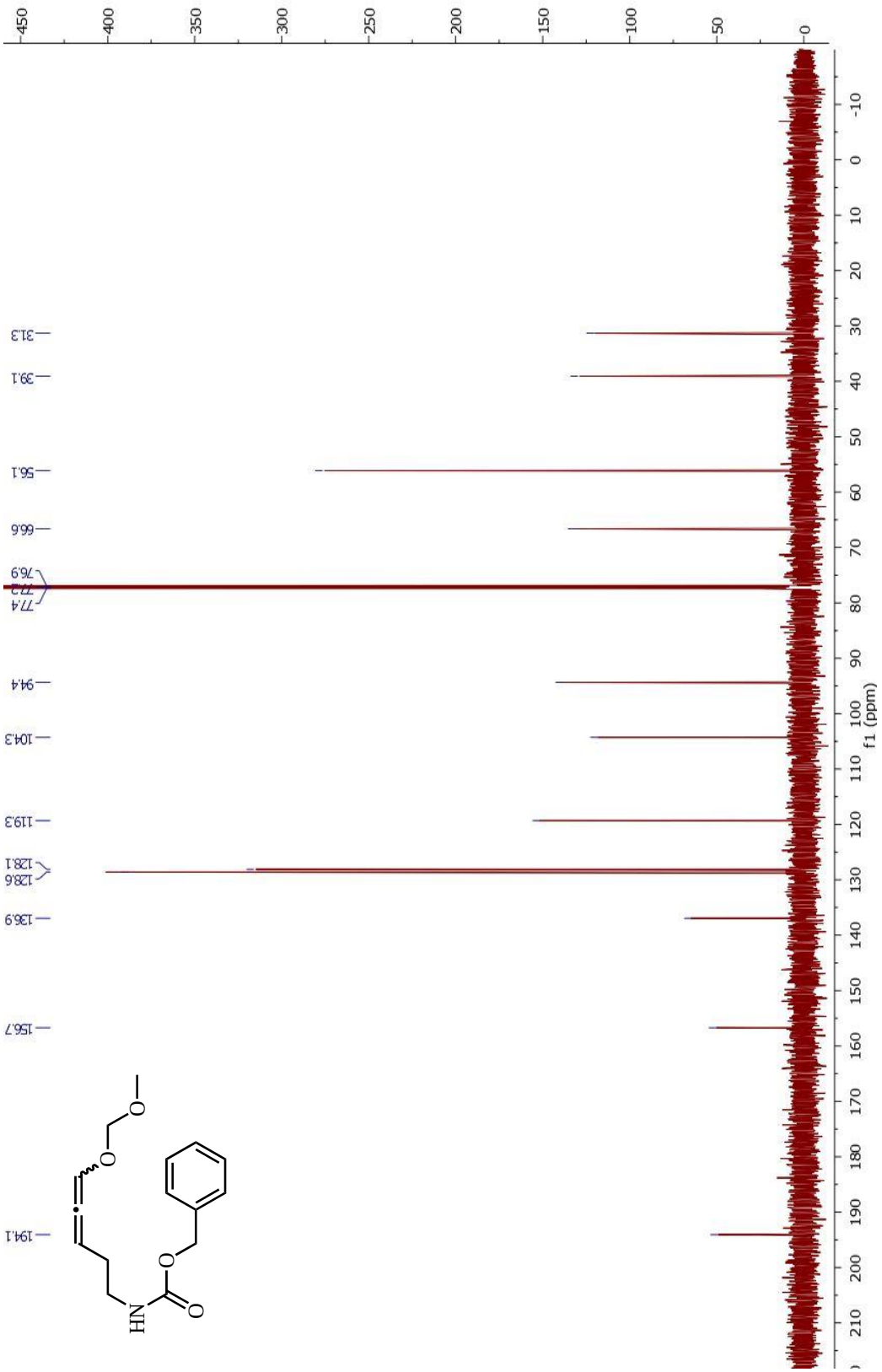

Figure D.14. **^{13}C NMR** (151 MHz, $CDCl_3$) of allene **4.39**

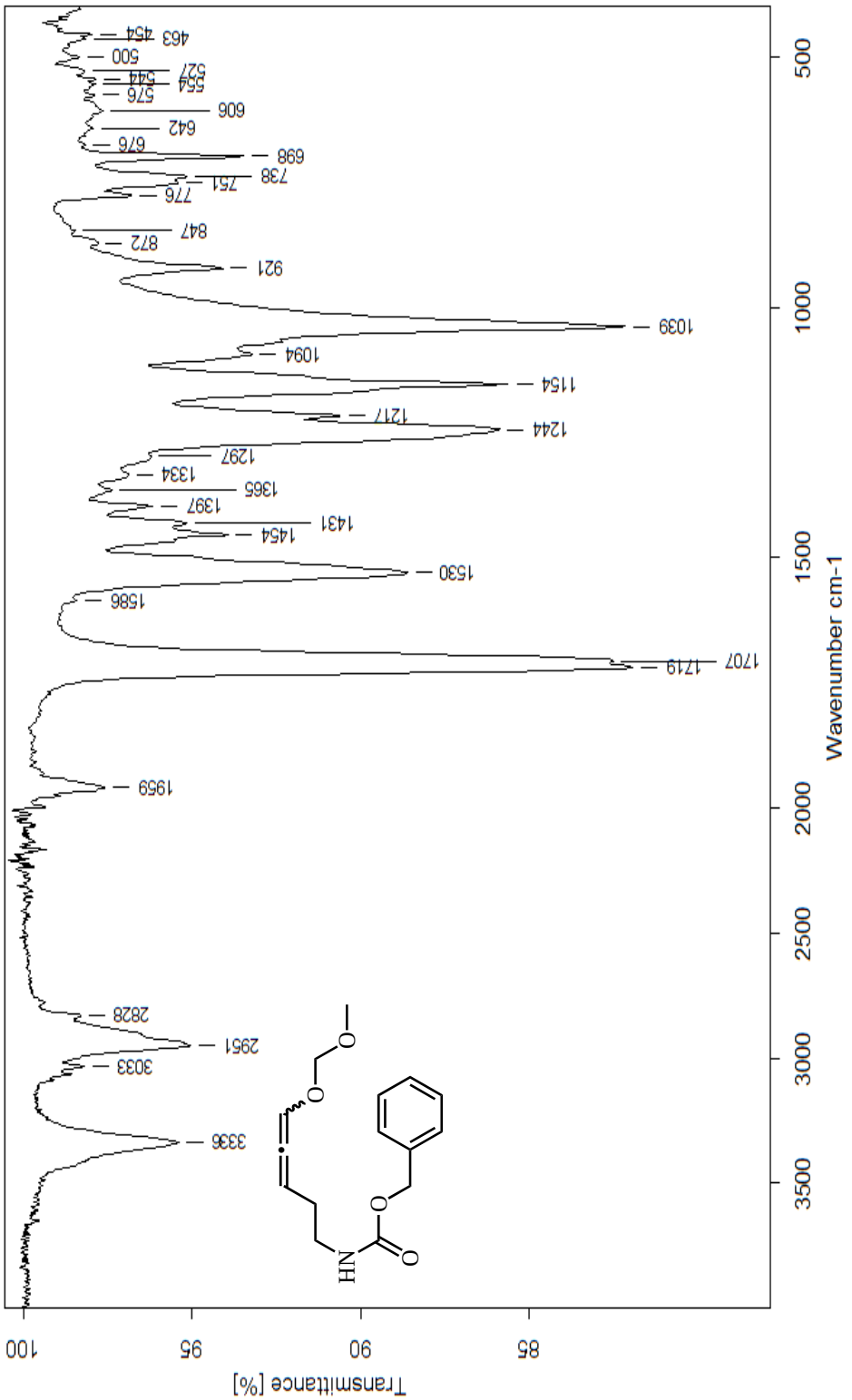

Figure D.15. FTIR Spectrum (neat) of allene **4.39**

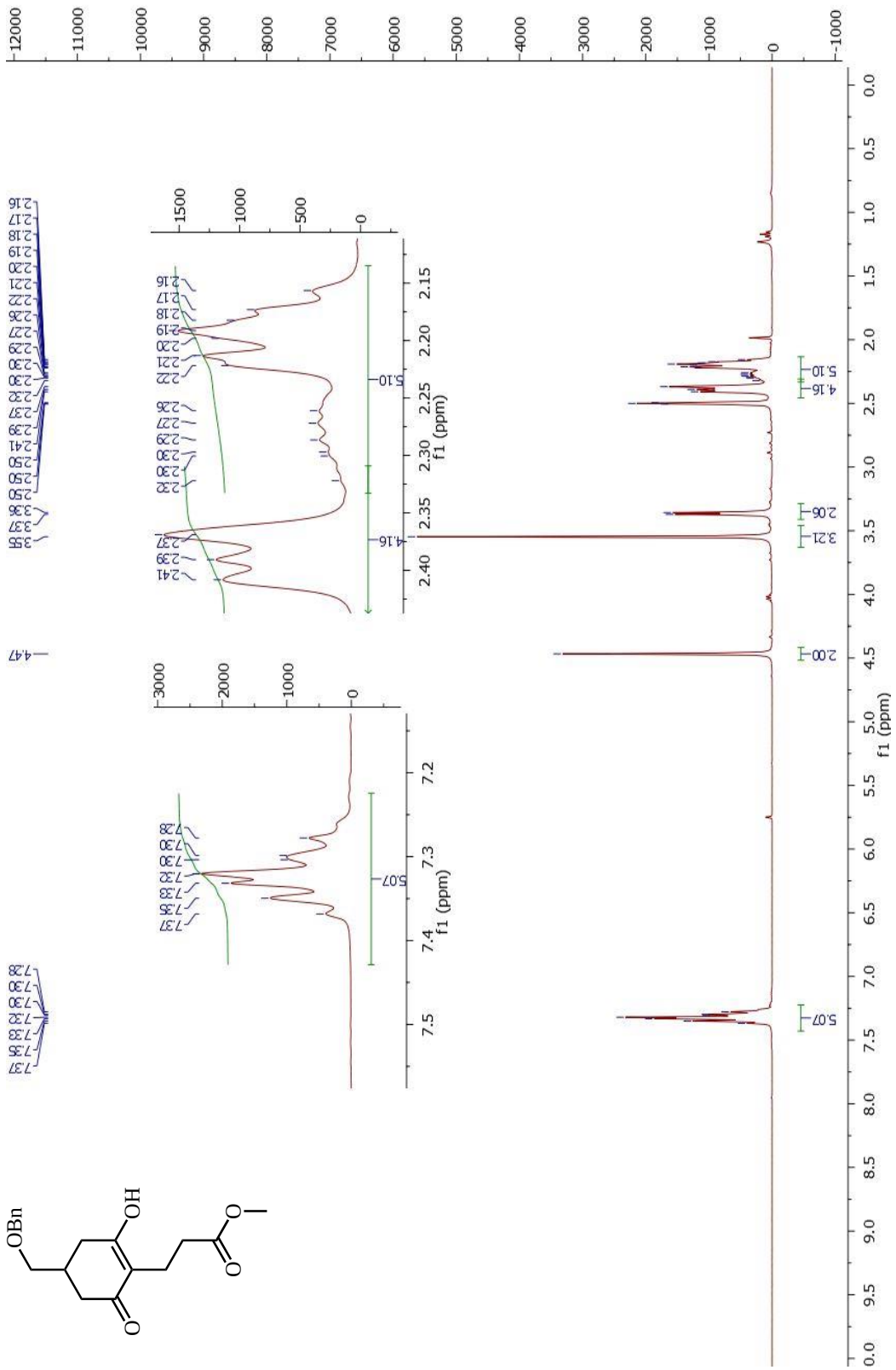

Figure D.16. **^{1}H NMR** (400 MHz, DMSO-*d6*) of ester **4.45**

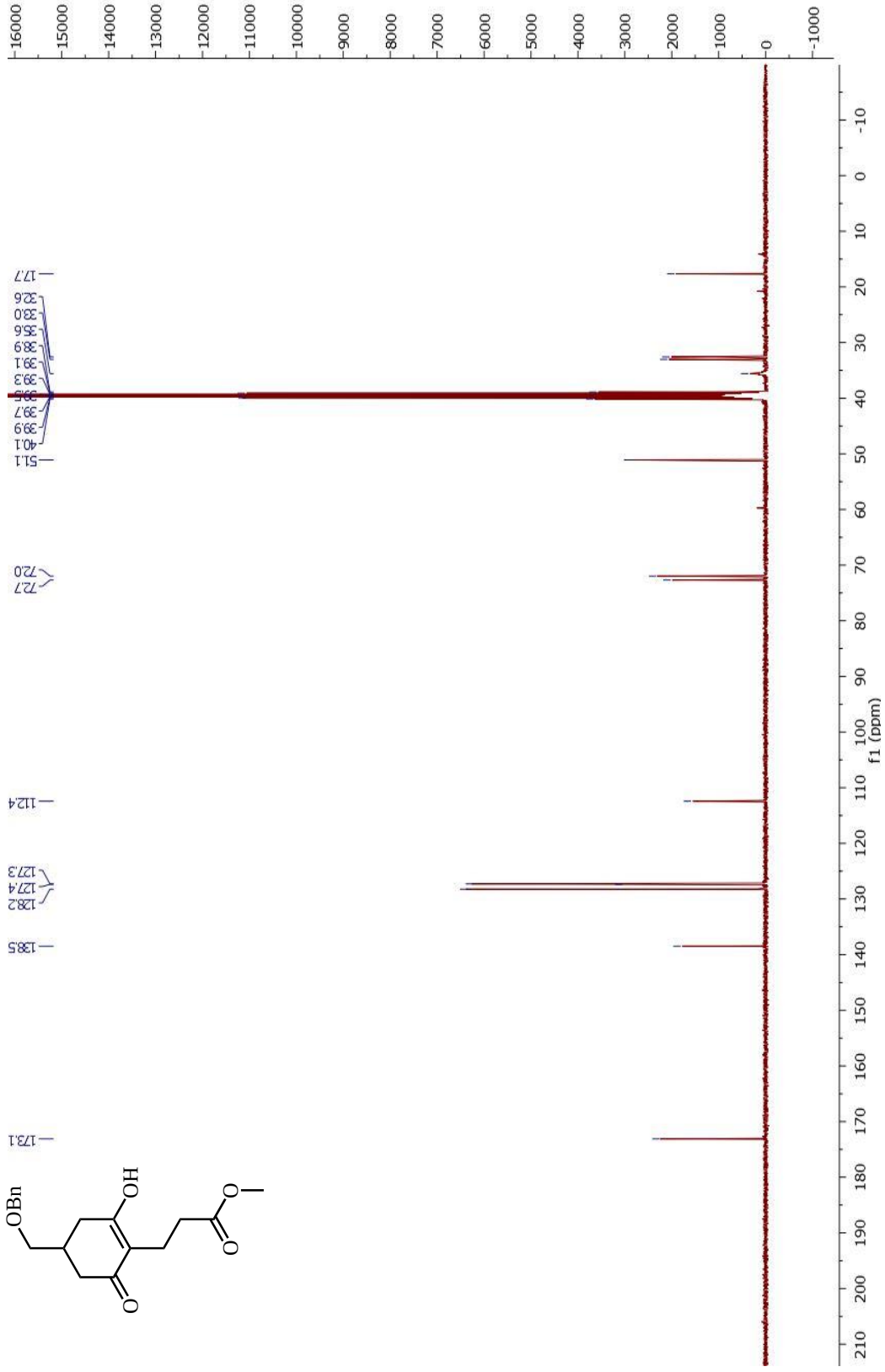

Figure D.17. ^{13}C **NMR** (101 MHz, DMSO-*d6*) of ester **4.45**

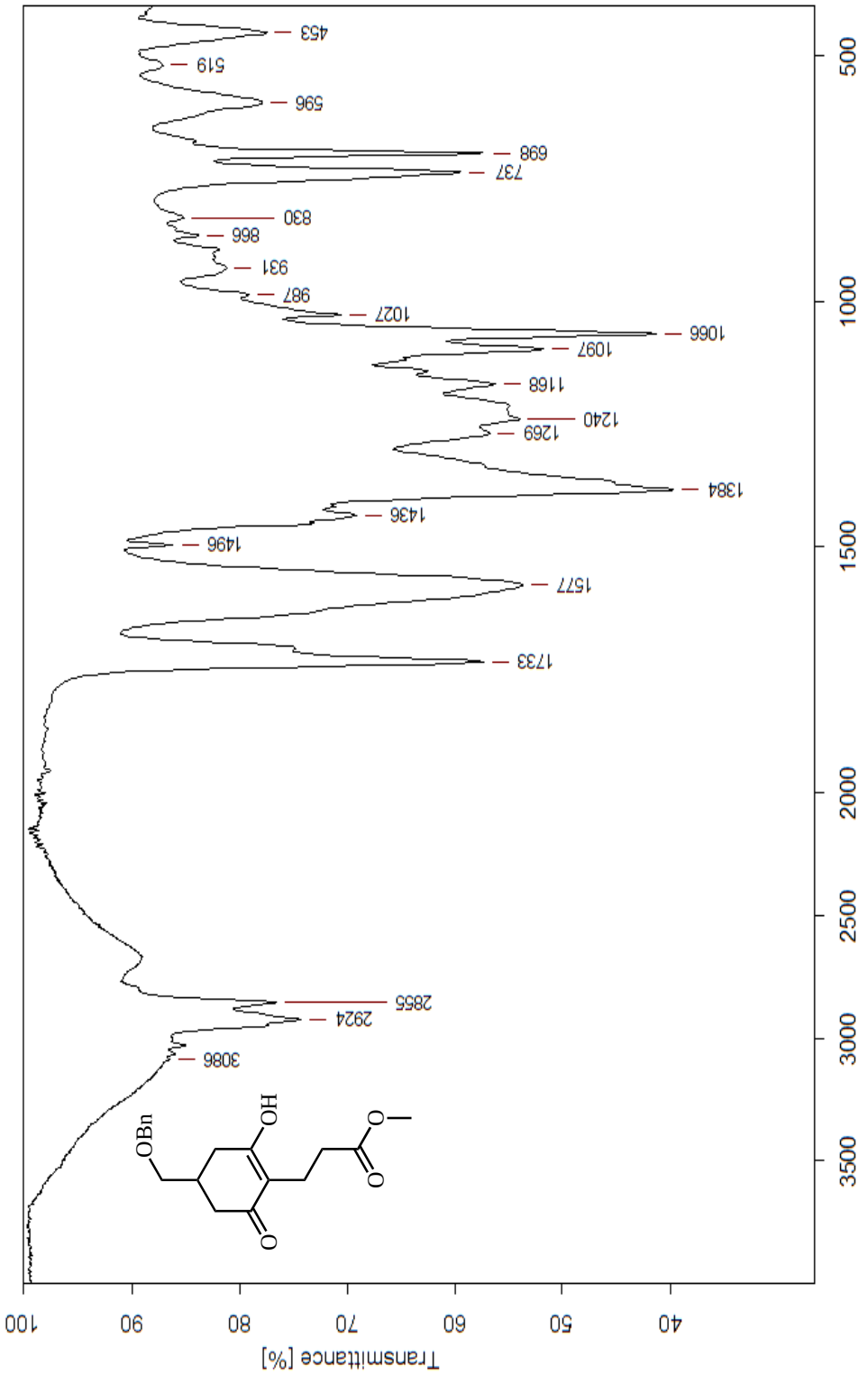

Figure D.18. FTIR Spectrum of ester **4.45**

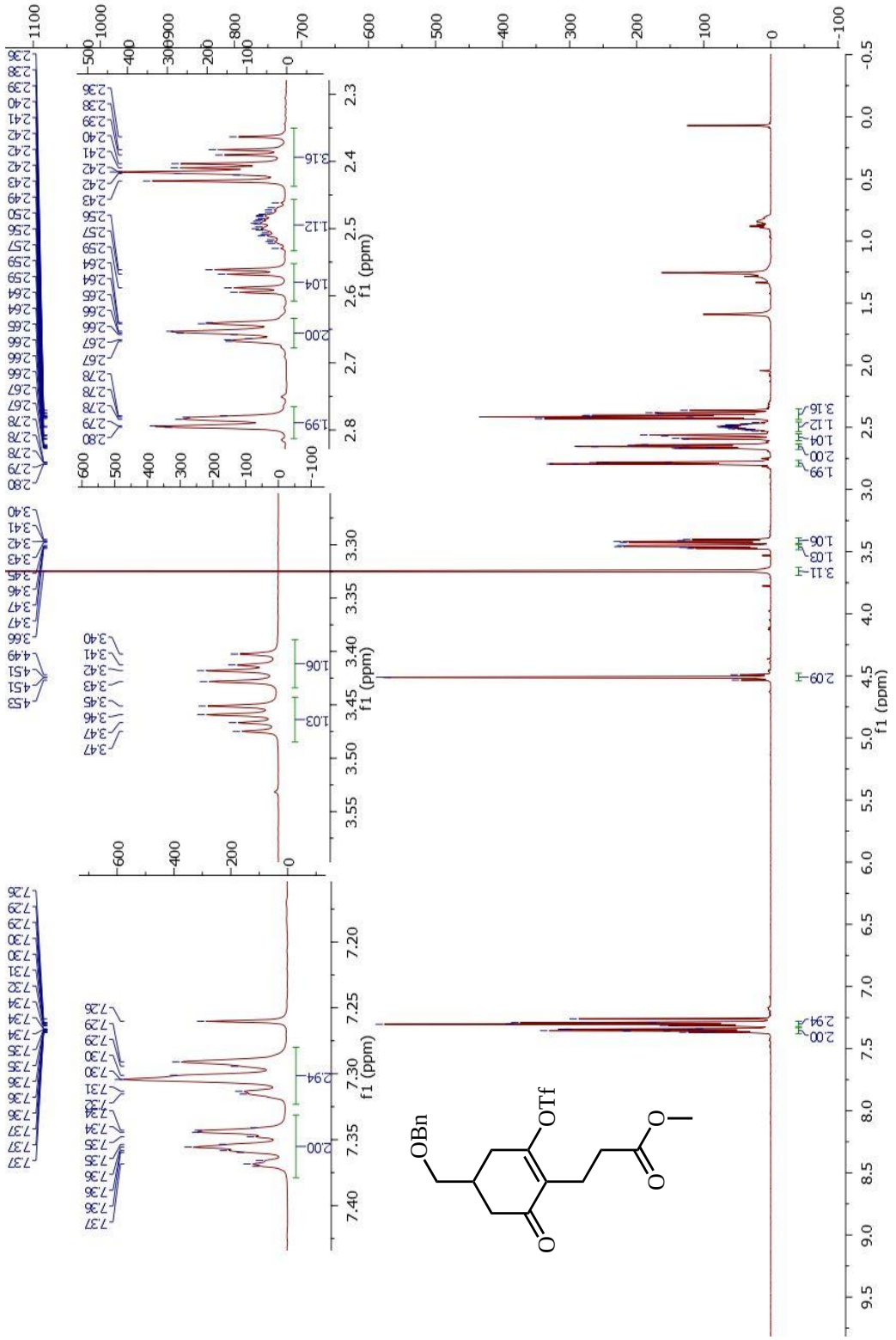

Figure D.19. **^{1}H NMR** (600 MHz, $CDCl_3$) of crude triflate **4.46**

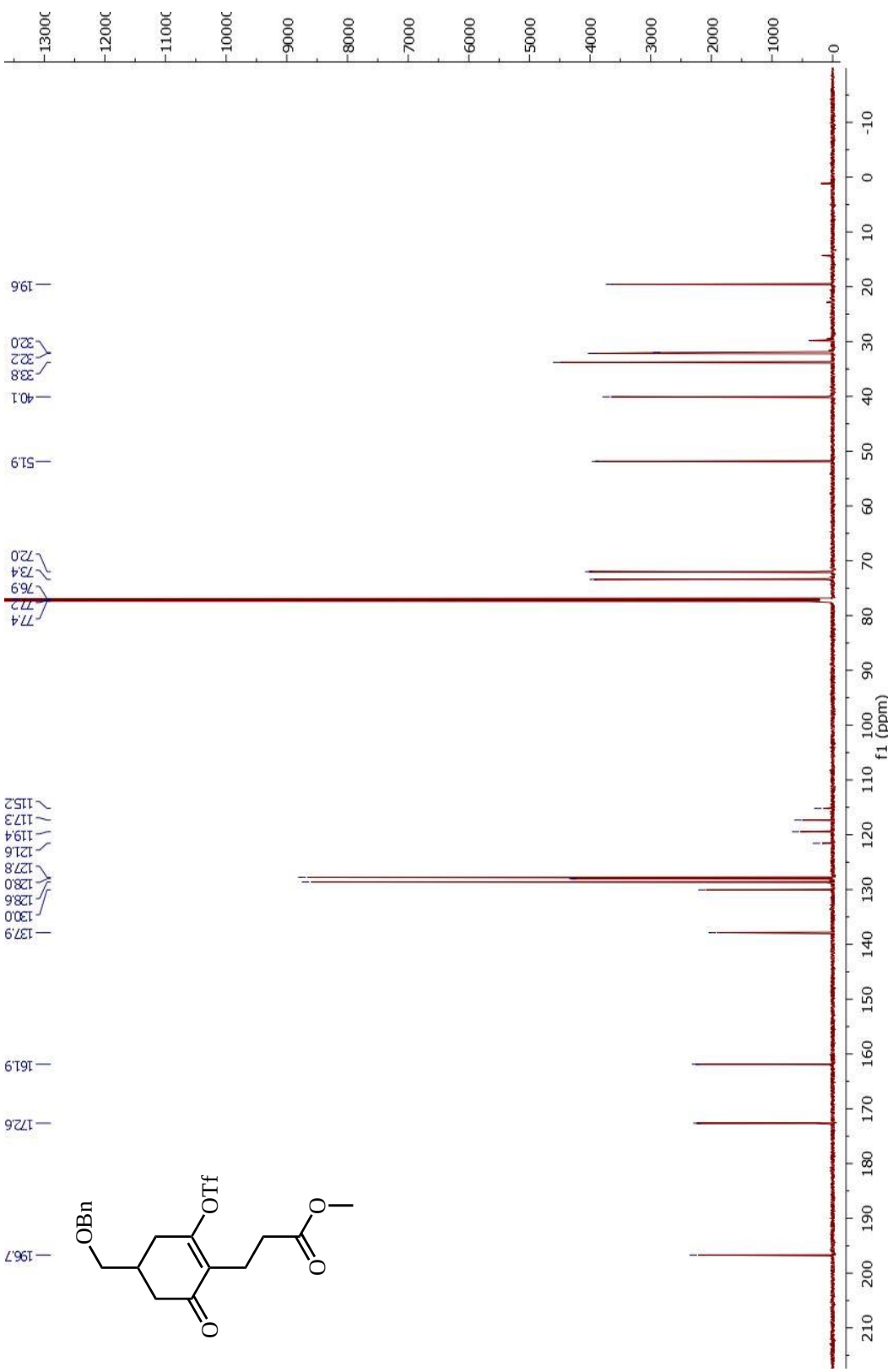

Figure D.20. **^{13}C NMR** (151MHz, $CDCl_3$) of crude triflate **4.46**

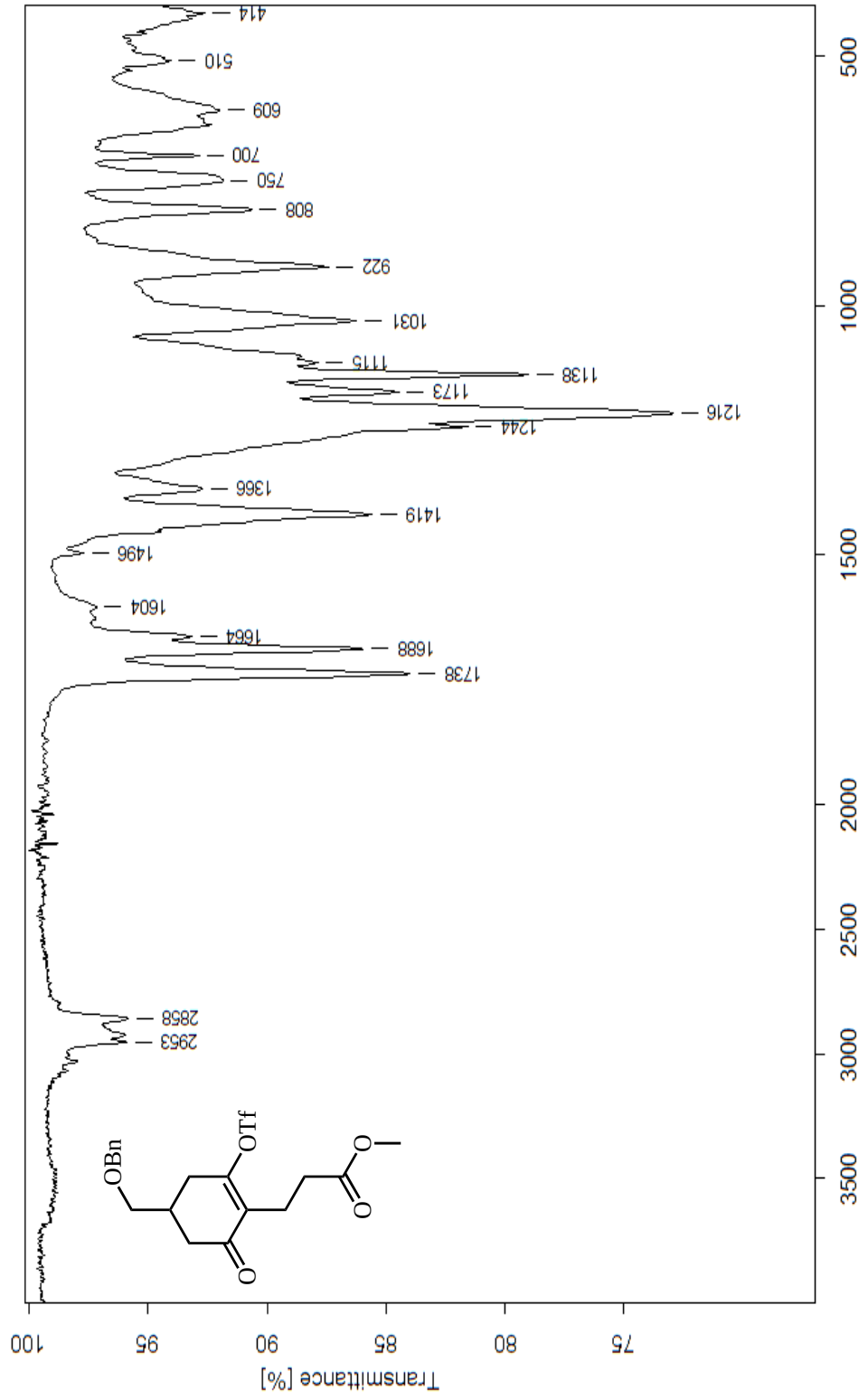

Figure D.21. FTIR Spectrum (neat) of crude triflate **4.46**

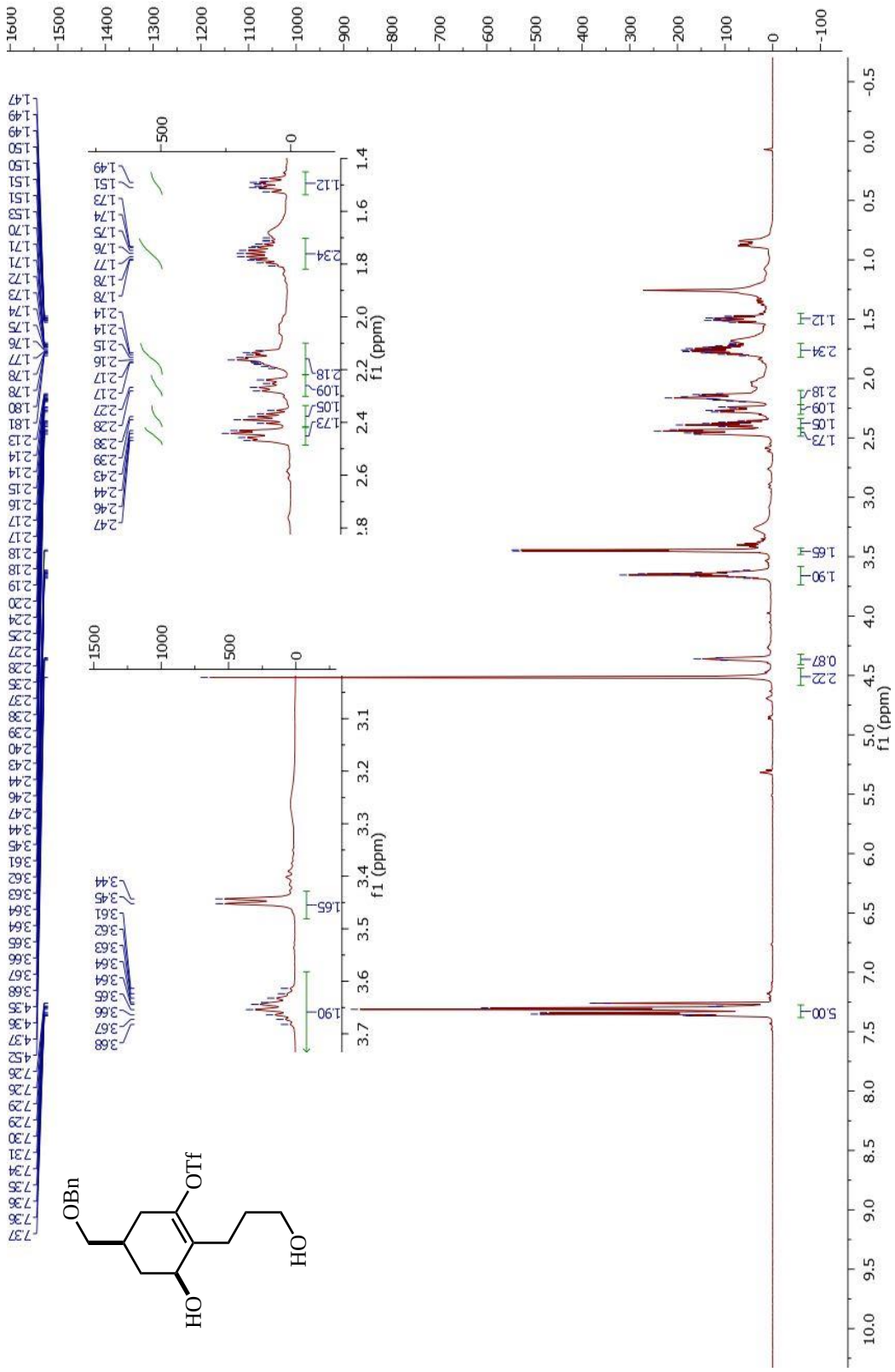

Figure D.22. **^{1}H NMR** (600 MHz, $CDCl_3$) of crude diol **4.47**

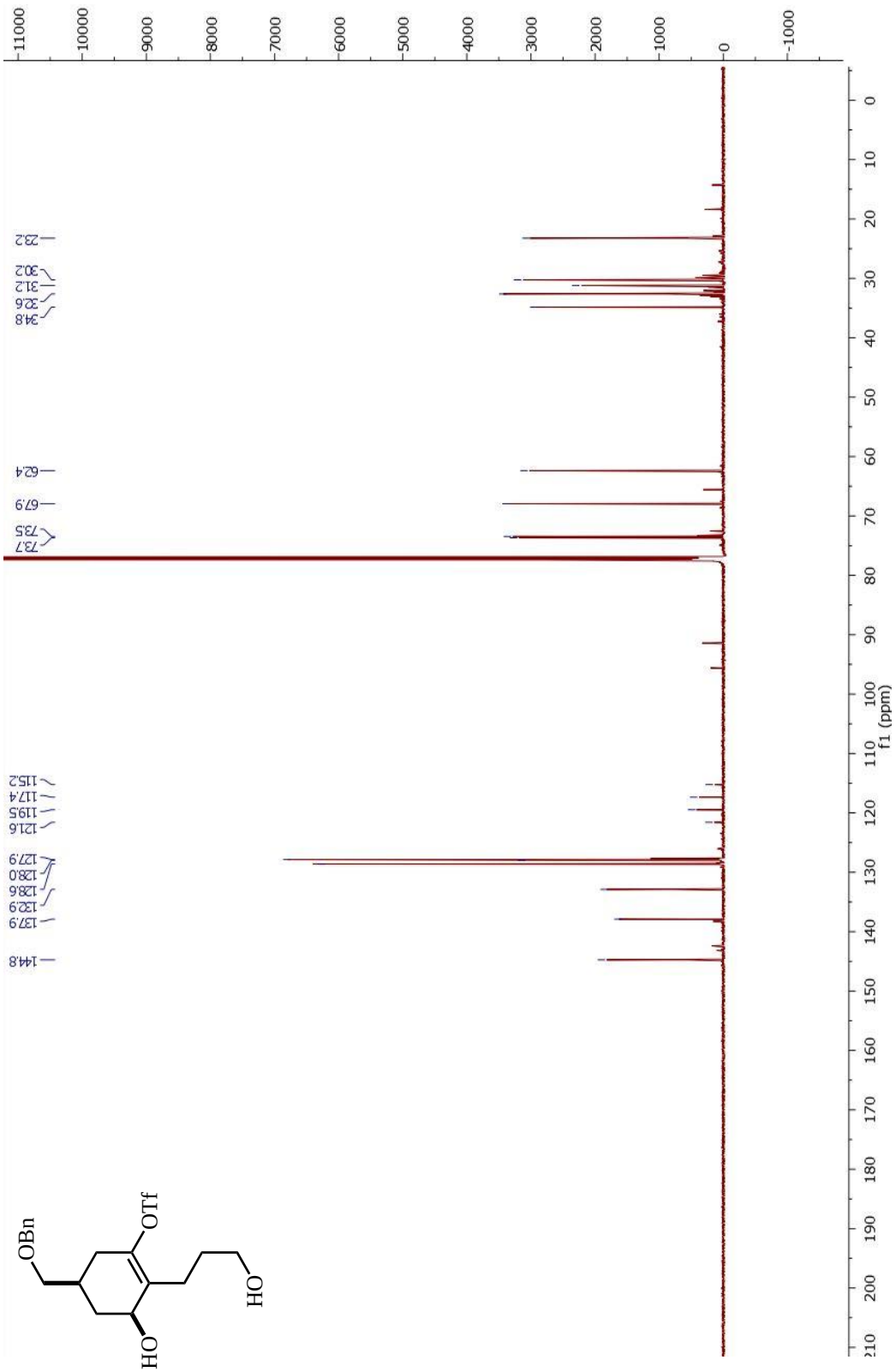

Figure D.23. **^{13}C NMR** (151 MHz, $CDCl_3$) of crude diol **4.47**

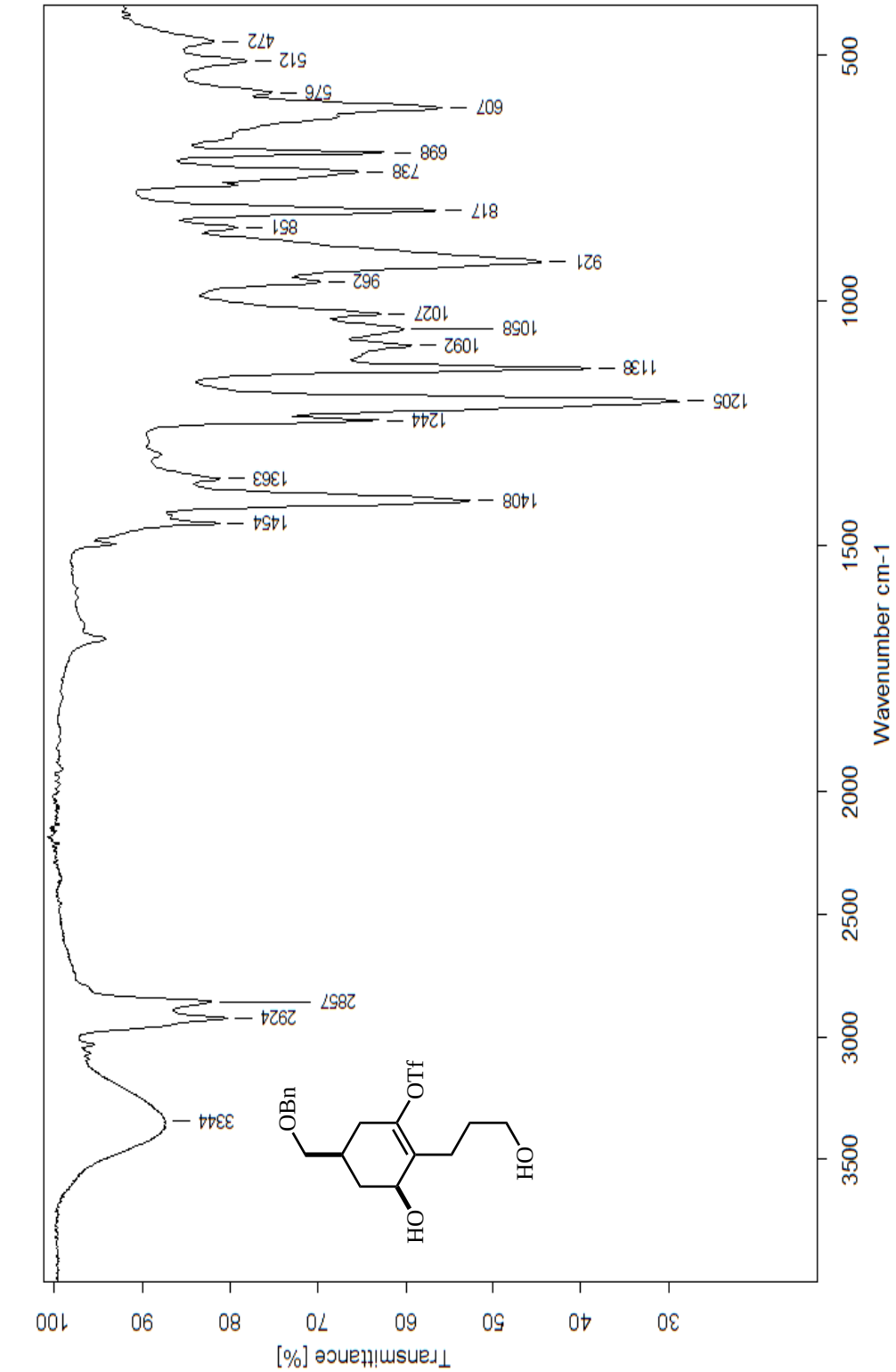

Figure D.24. FTIR Spectrum (neat) of crude diol **4.47**

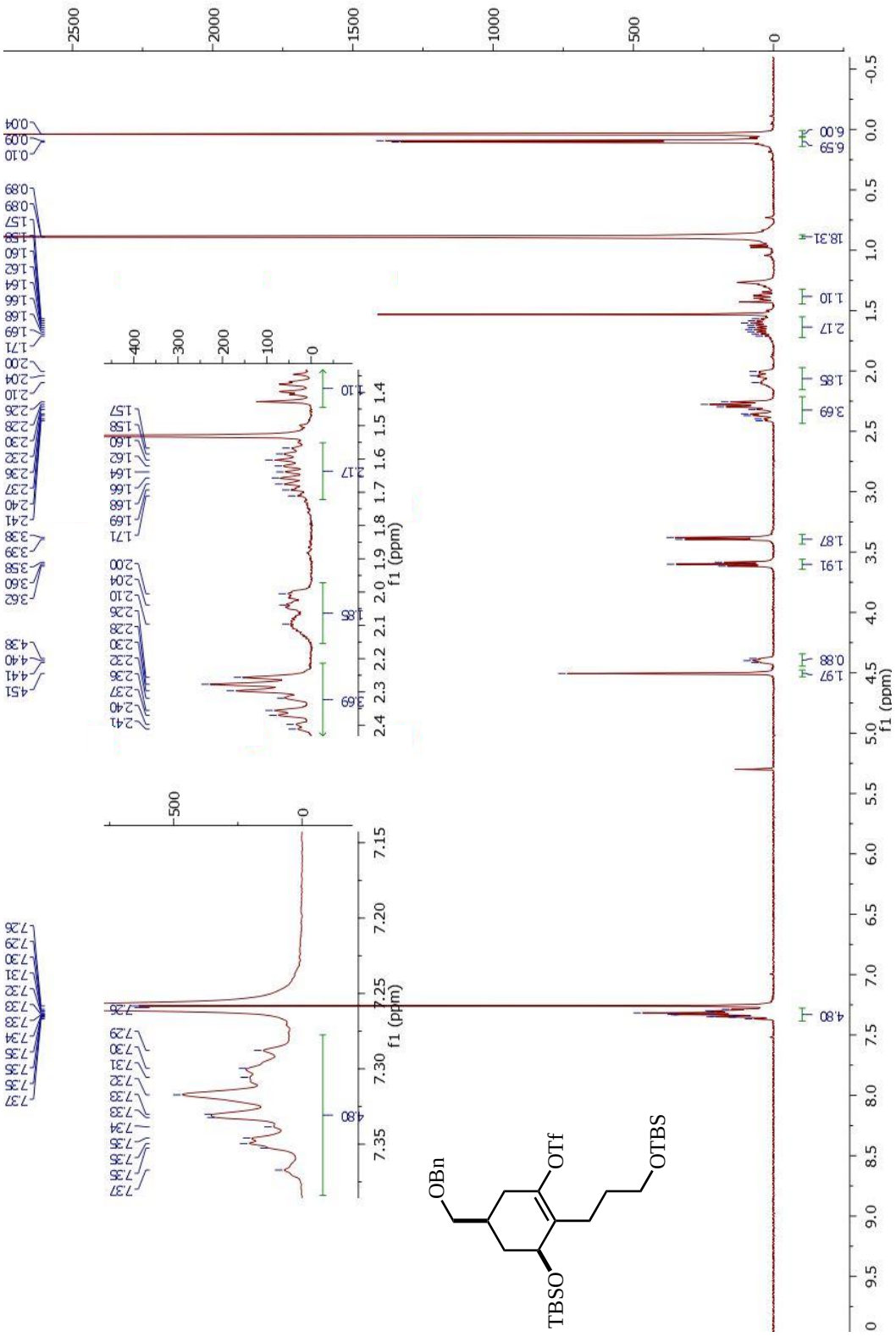

Figure D.25. **^{1}H NMR** (400 MHz, $CDCl_3$) of vinyl triflate **4.48**

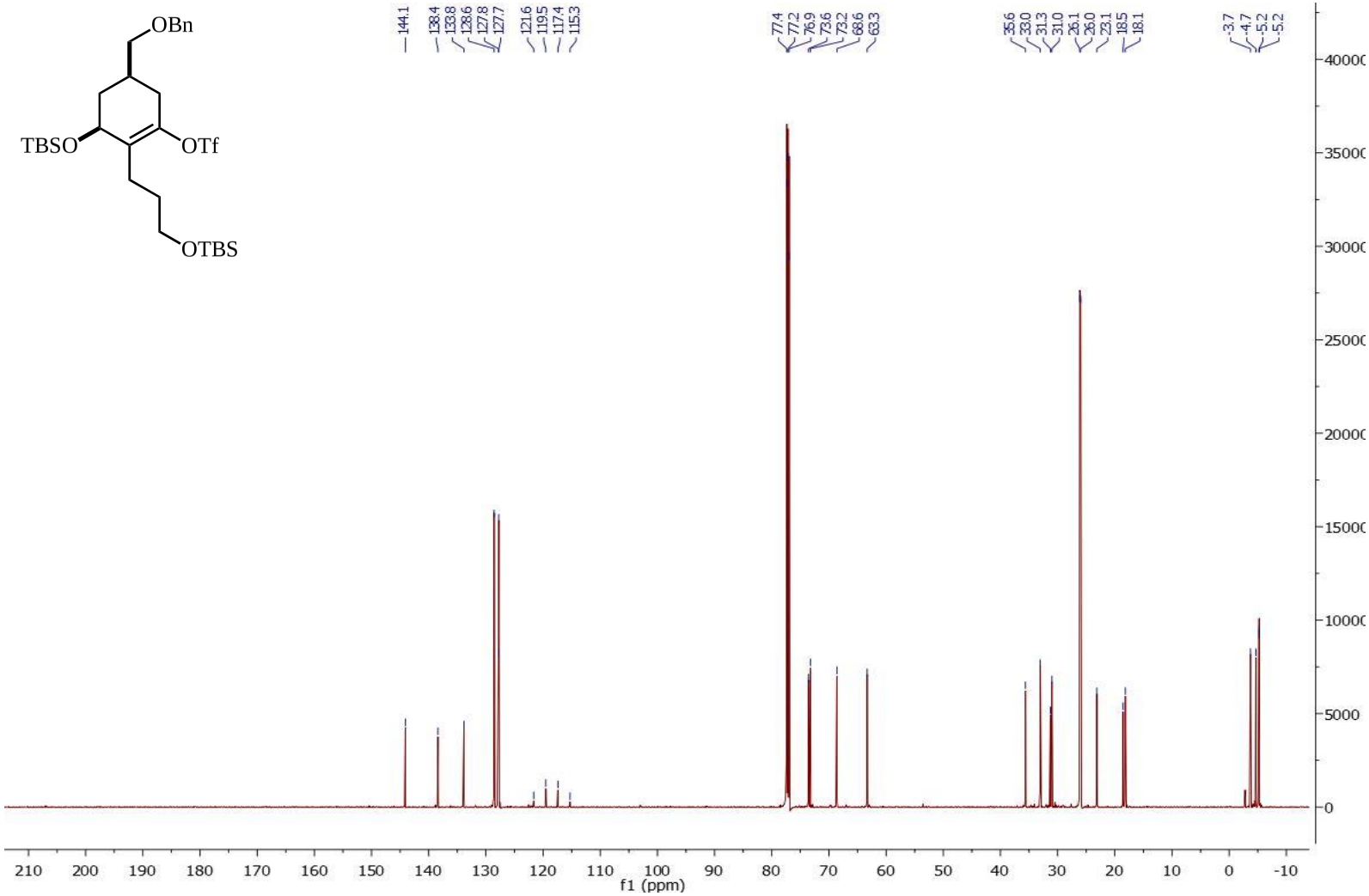

Figure D.26. **^{13}C NMR** (151 MHz, $CDCl_3$) of vinyl triflate **4.48**

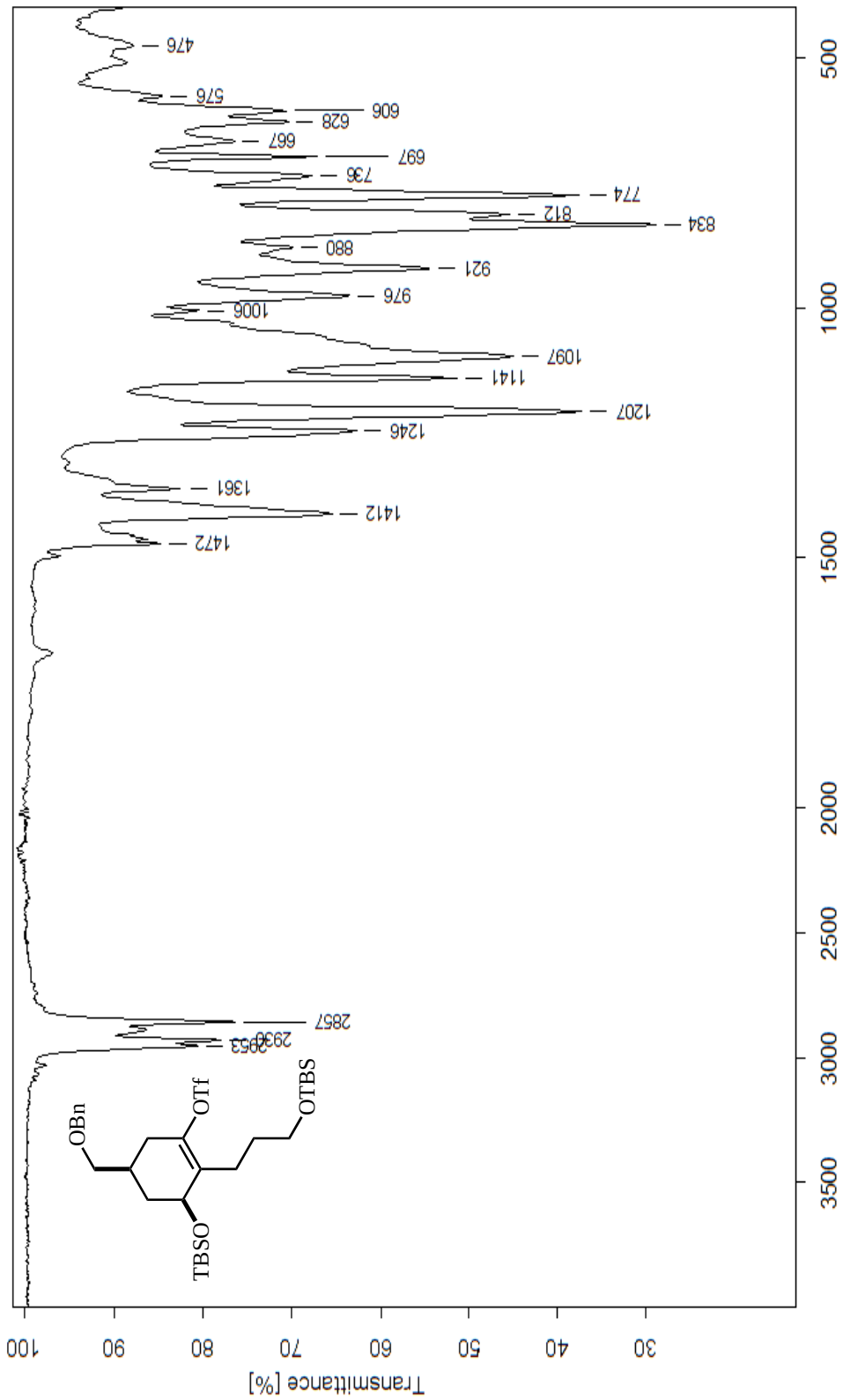

Figure D.27. FTIR Spectrum (neat) of vinyl triflate **4.48**

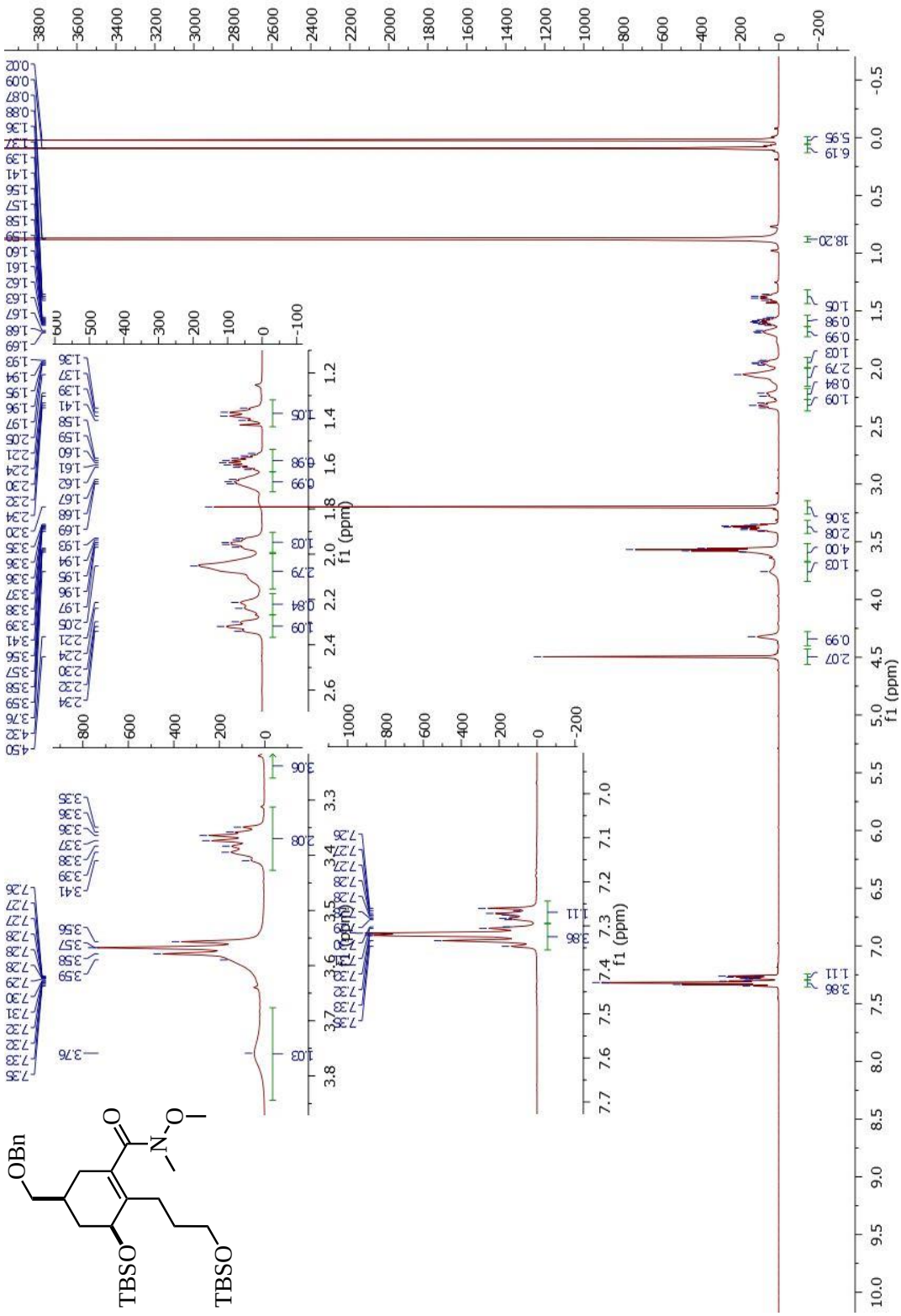

Figure D.28. **^{1}H NMR** (600 MHz, $CDCl_3$) of Weinreb amide **4.50**

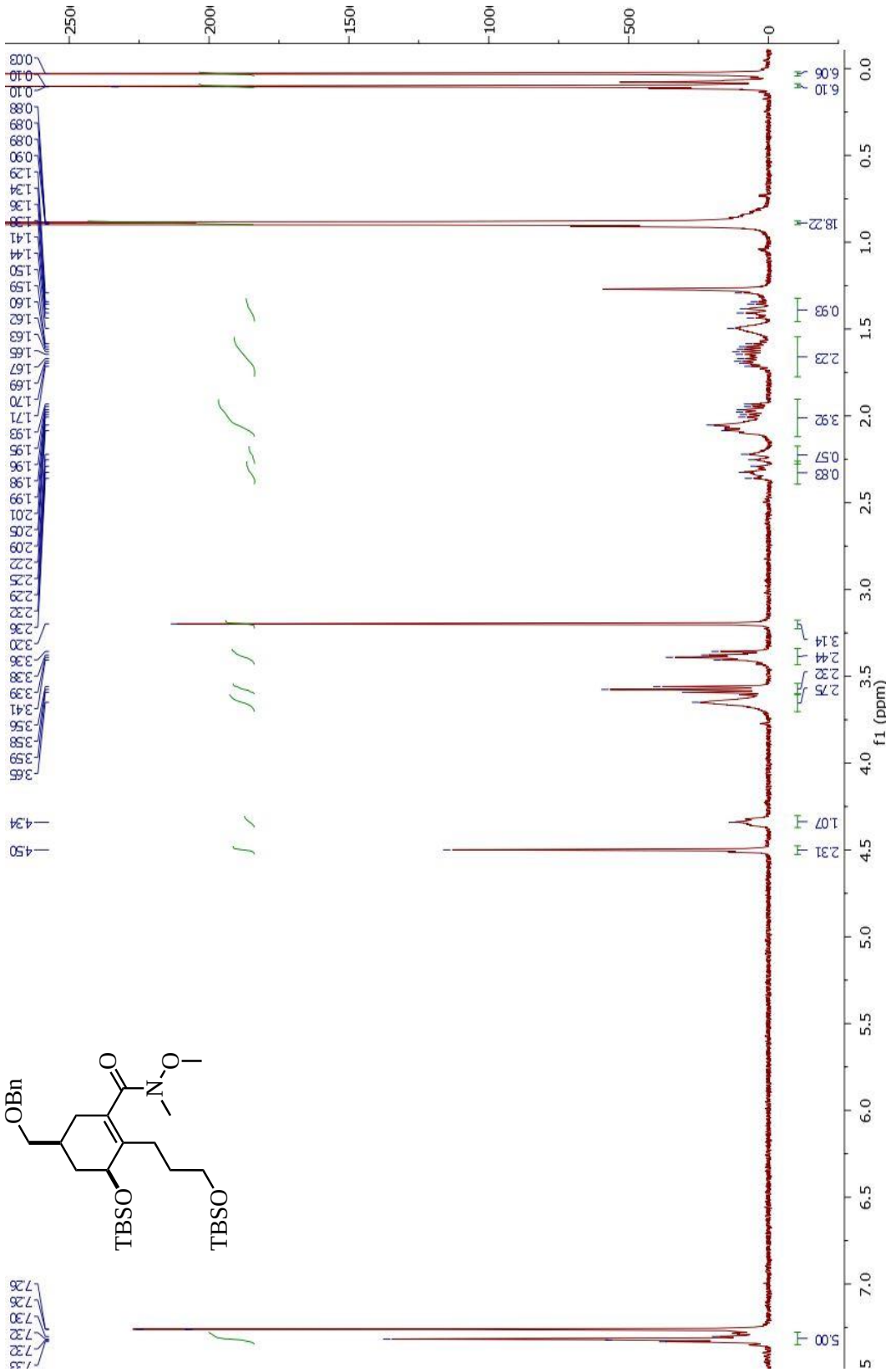

Figure D.29. **^{1}H NMR** (400 MHz, $CDCl_3$) of Weinreb amide **4.50** at 50 °C

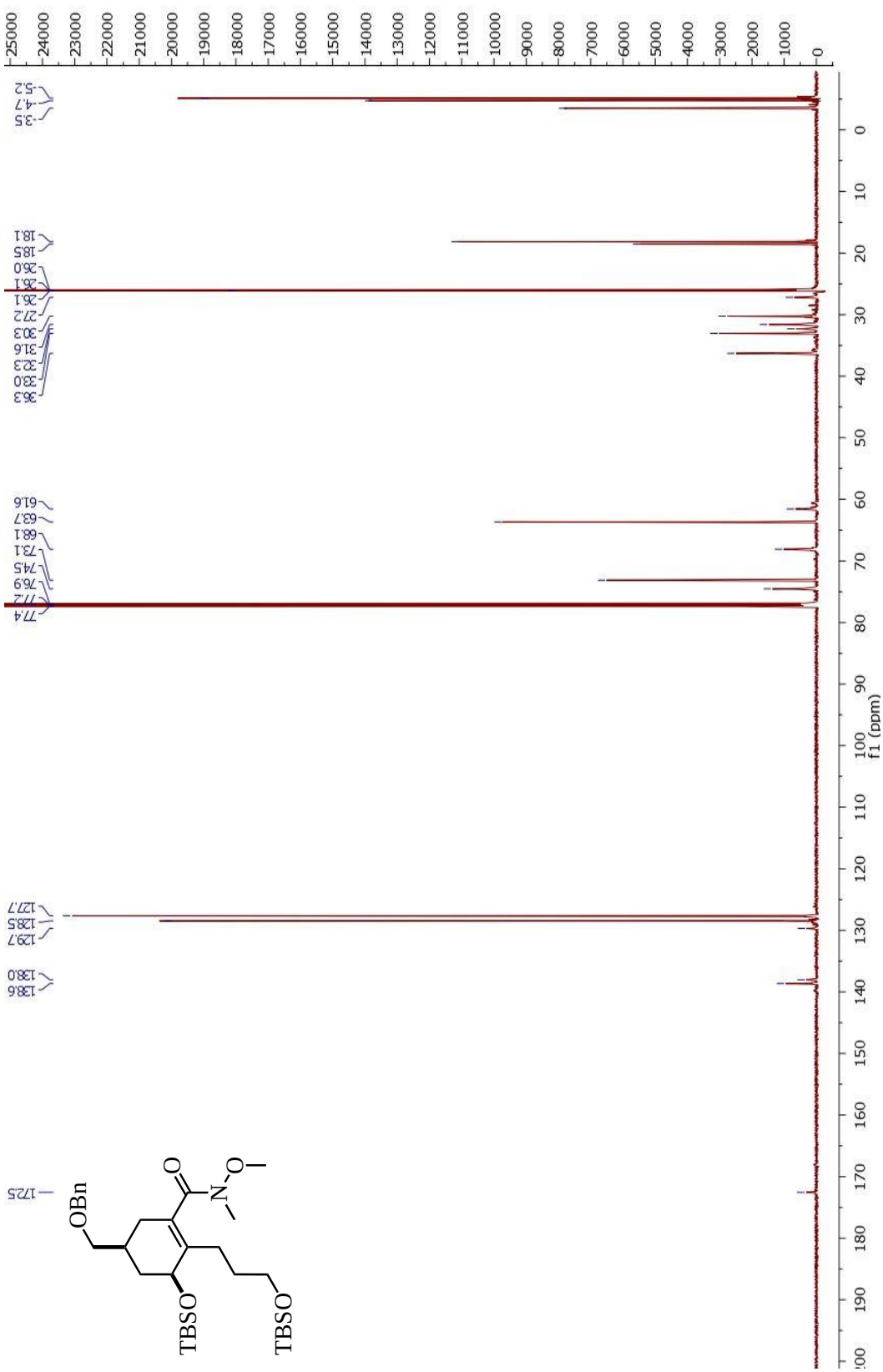

Figure D.30. **^{13}C NMR** (151 MHz, $CDCl_3$) of Weinreb amide **4.50**

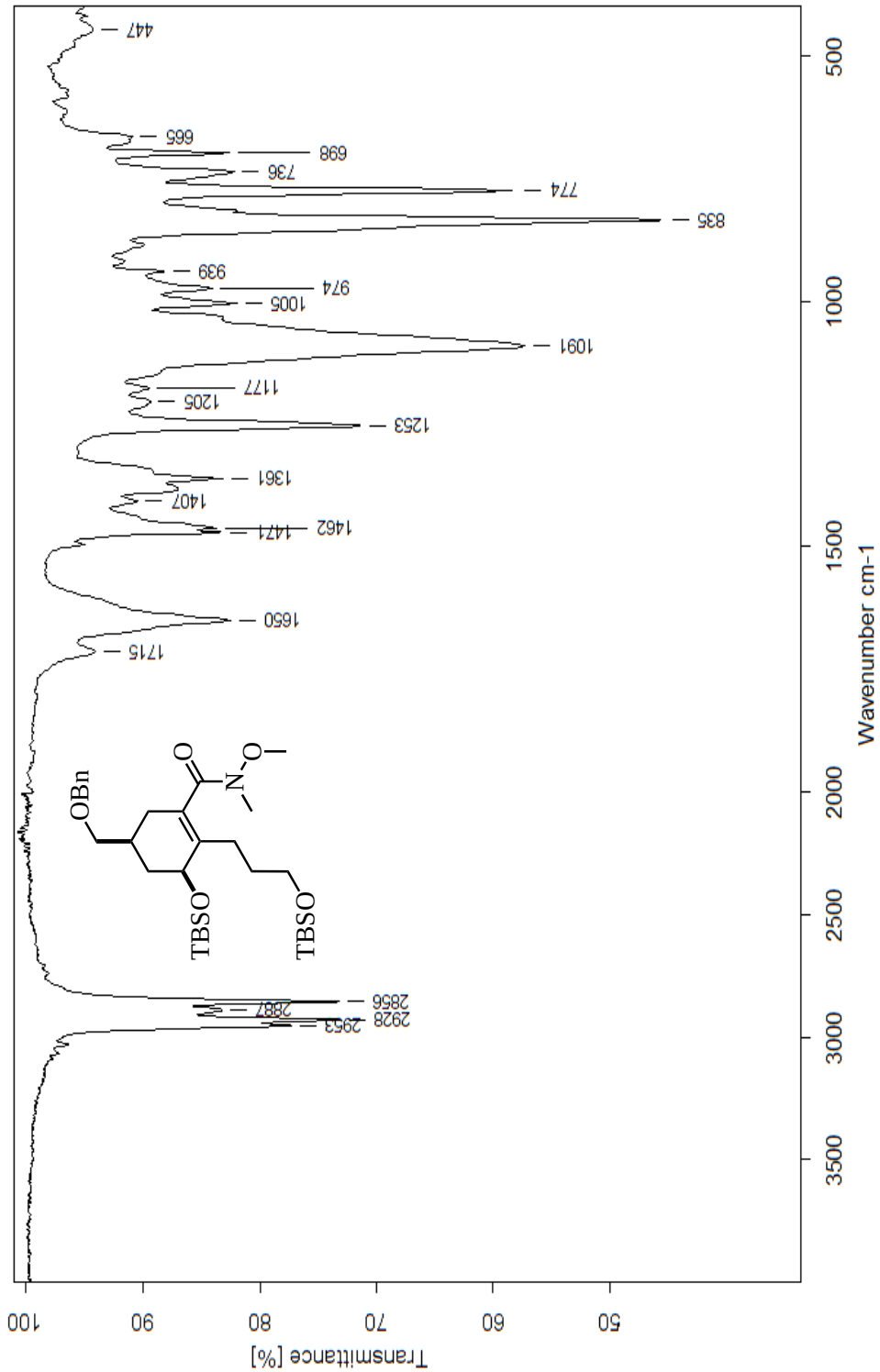

Figure D.31. FTIR Spectrum (neat) of Weinreb amide **4.50**

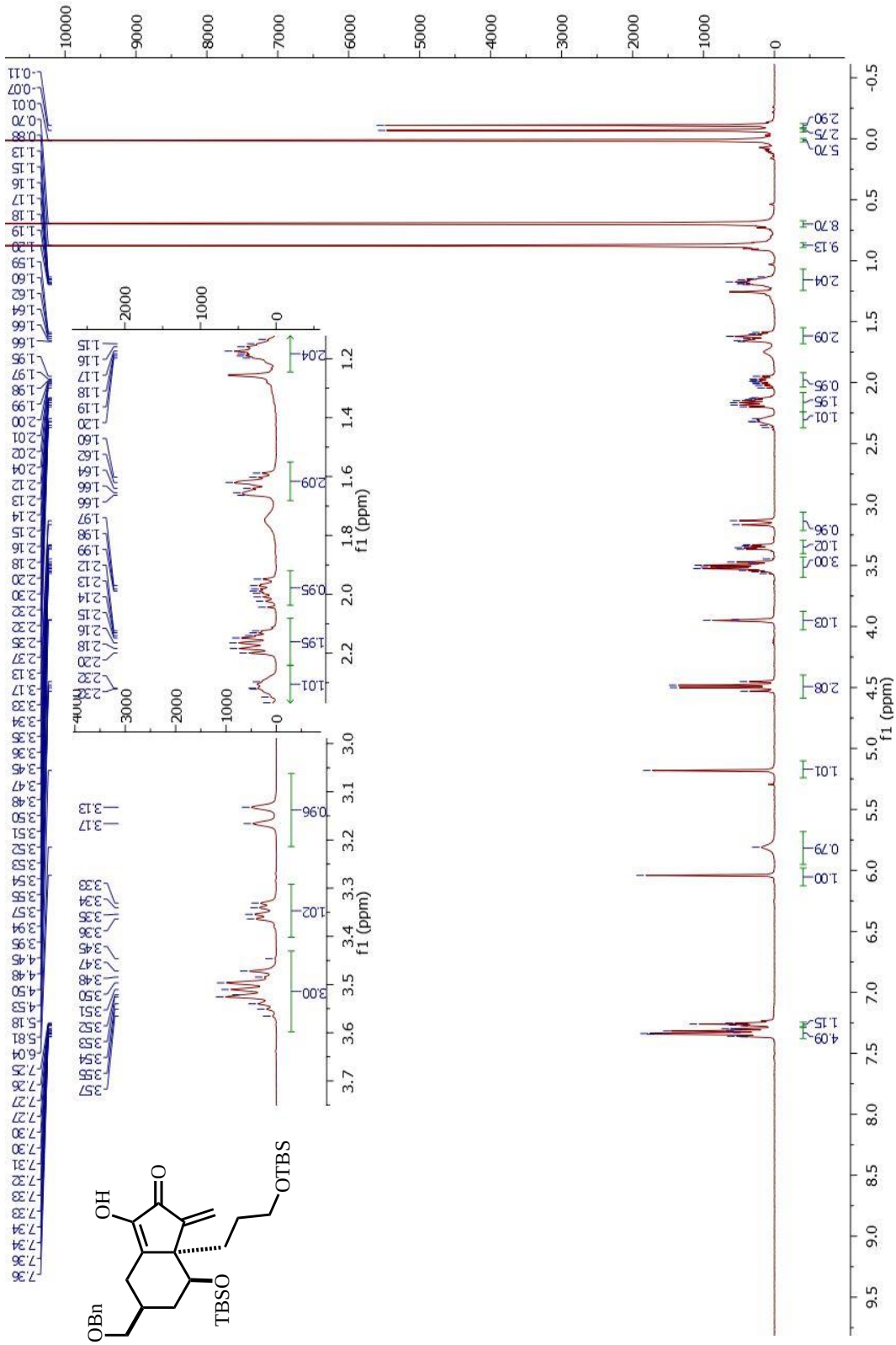

Figure D.32. **^{1}H NMR** (400 MHz, $CDCl_3$) of bicycle **4.63**

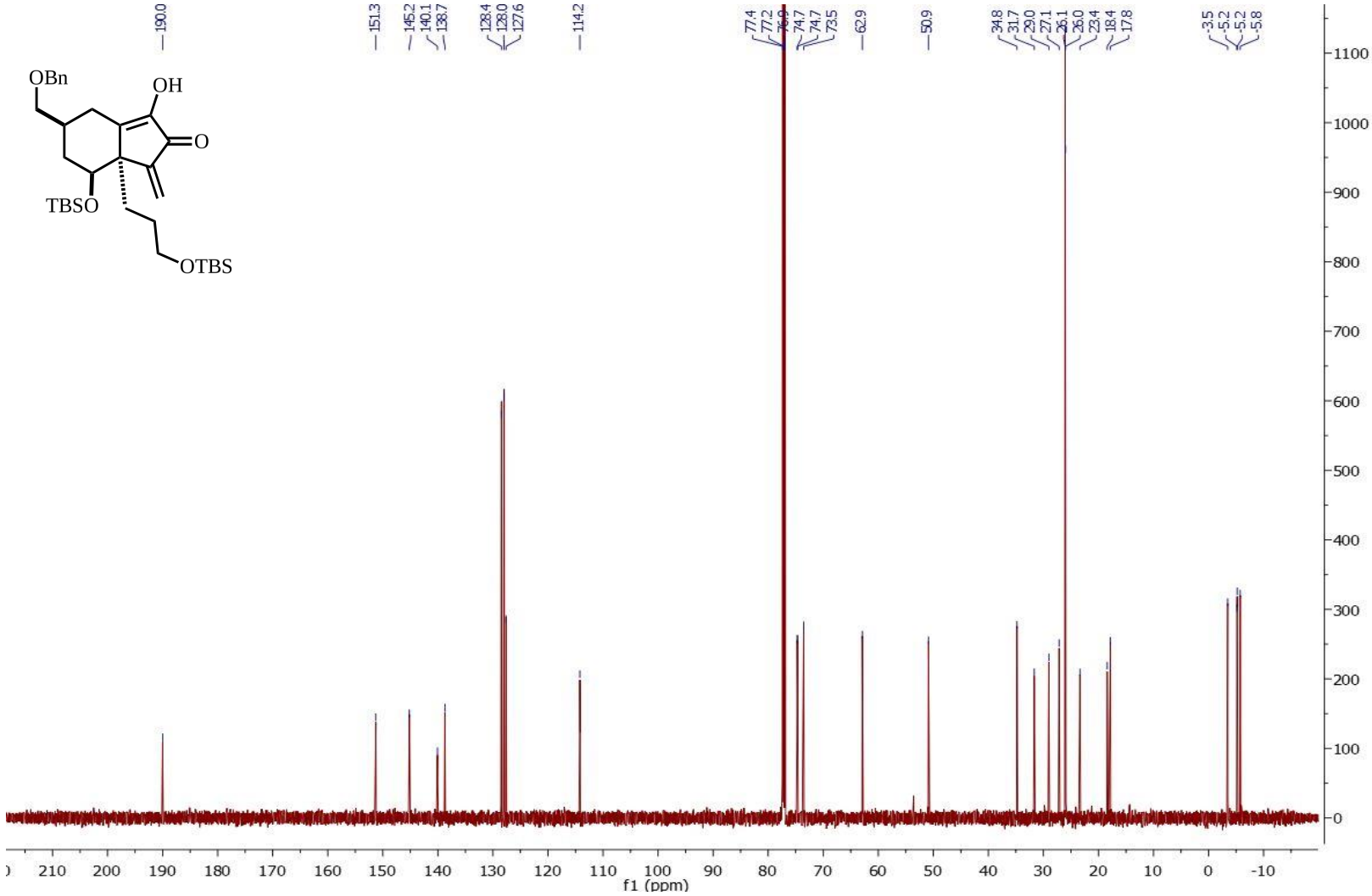

Figure D.33. **^{13}C NMR** (151 MHz, $CDCl_3$) of bicycle **4.63**

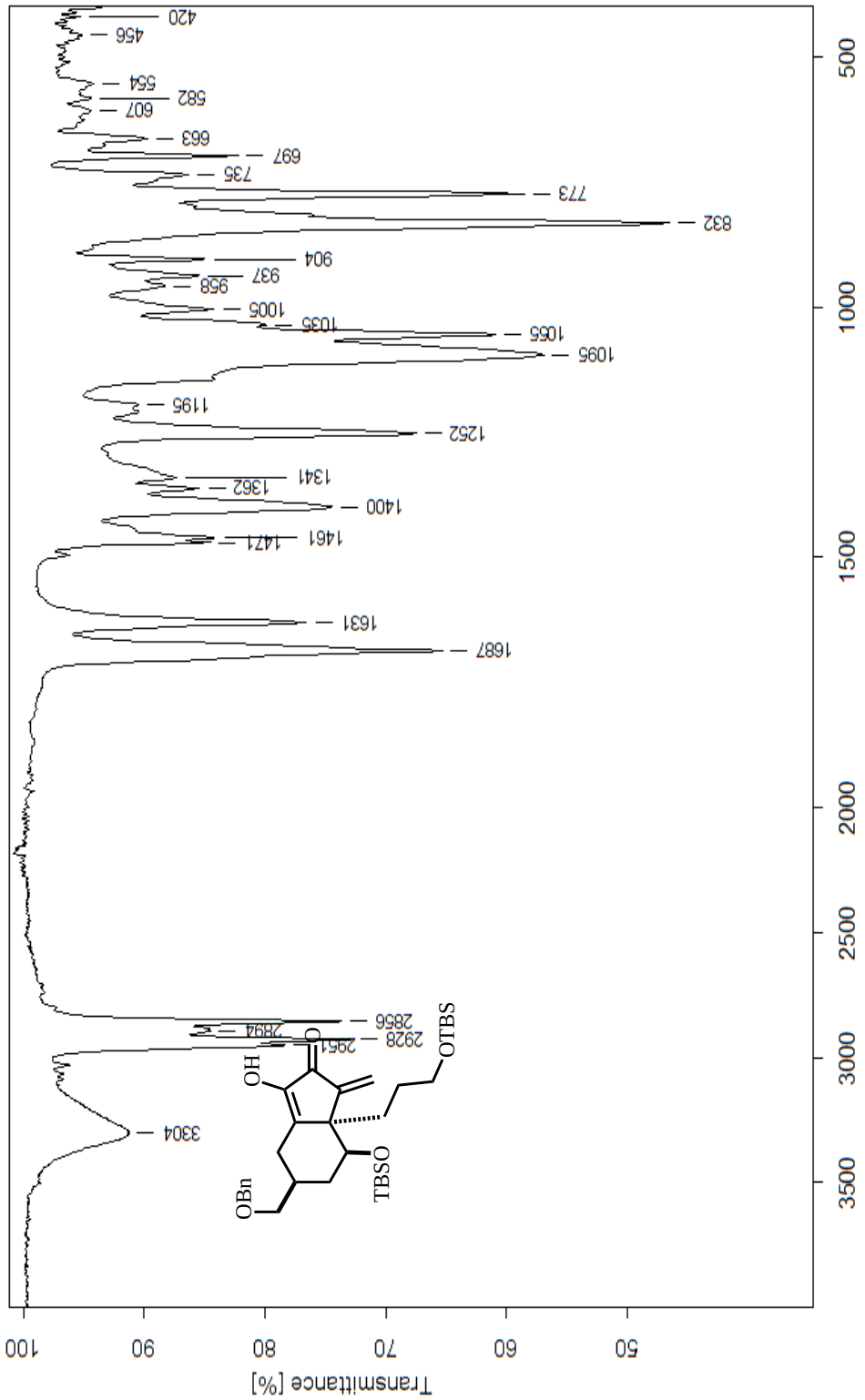

Figure D.34. FTIR Spectrum (neat) of bicycle **4.63**

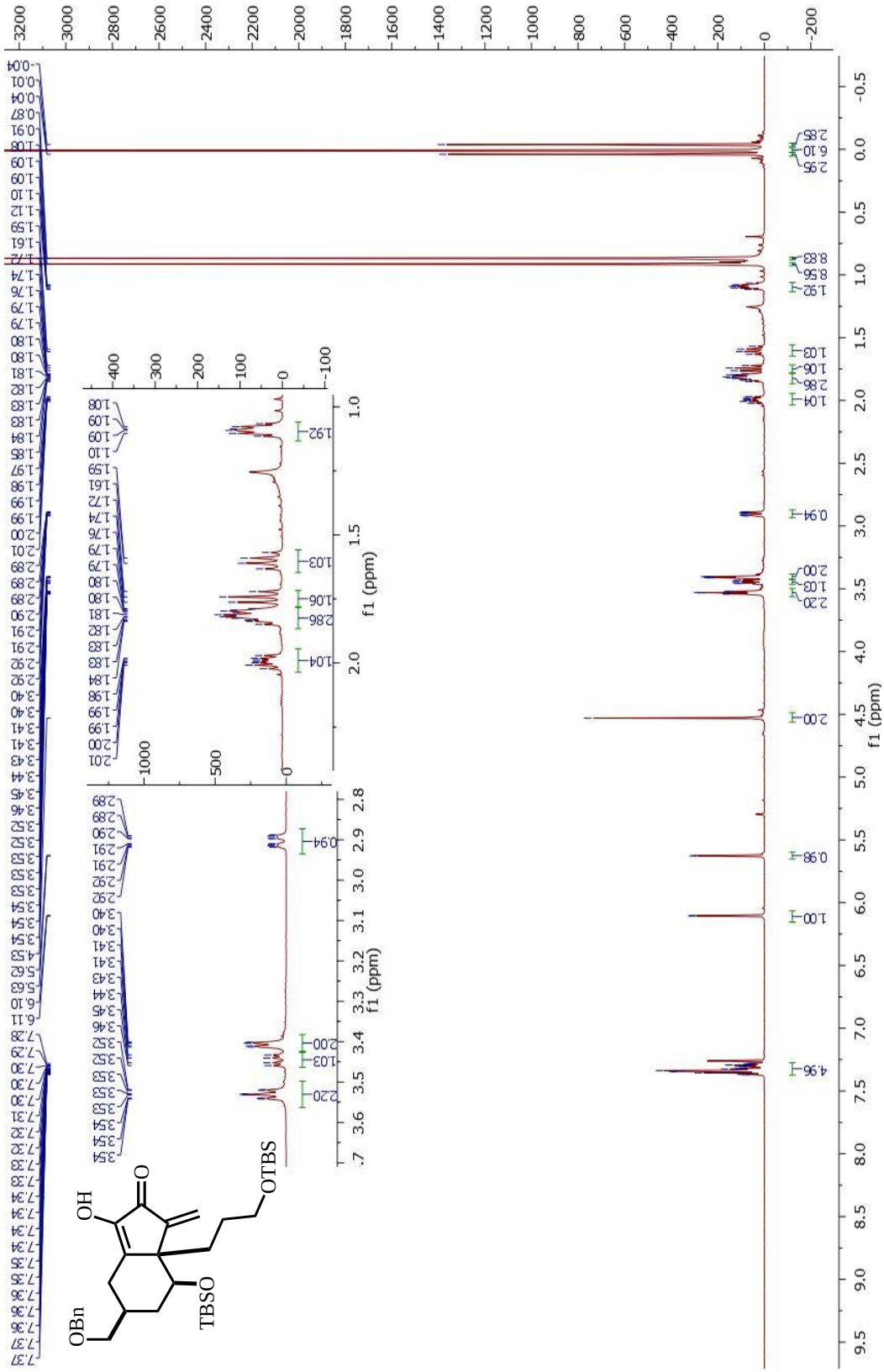

Figure D.35. **^{1}H NMR** (600 MHz, $CDCl_3$) of bicycle **4.64**

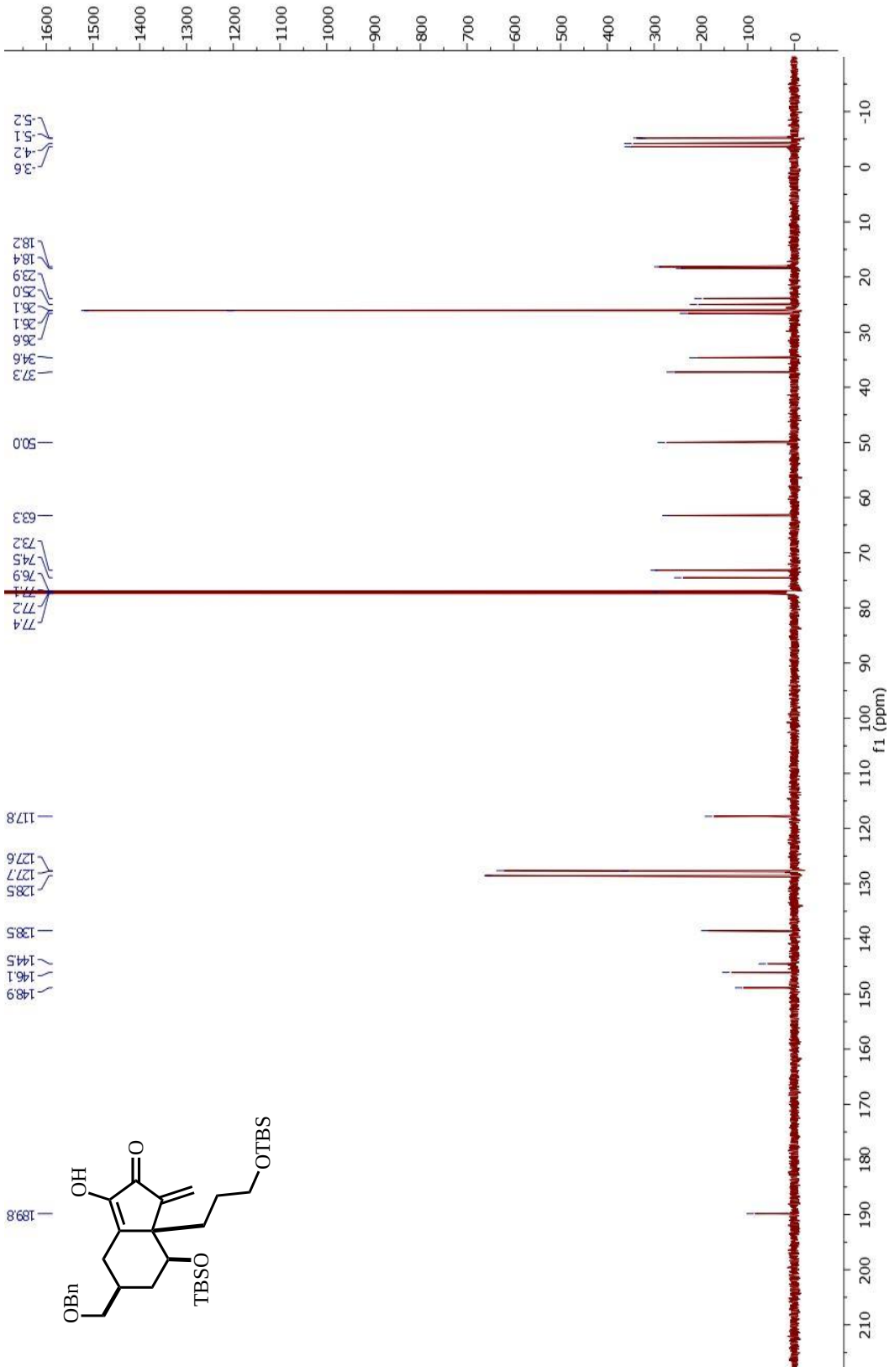

Figure D.36. **^{13}C NMR** (151 MHz, $CDCl_3$) of bicycle **4.64**

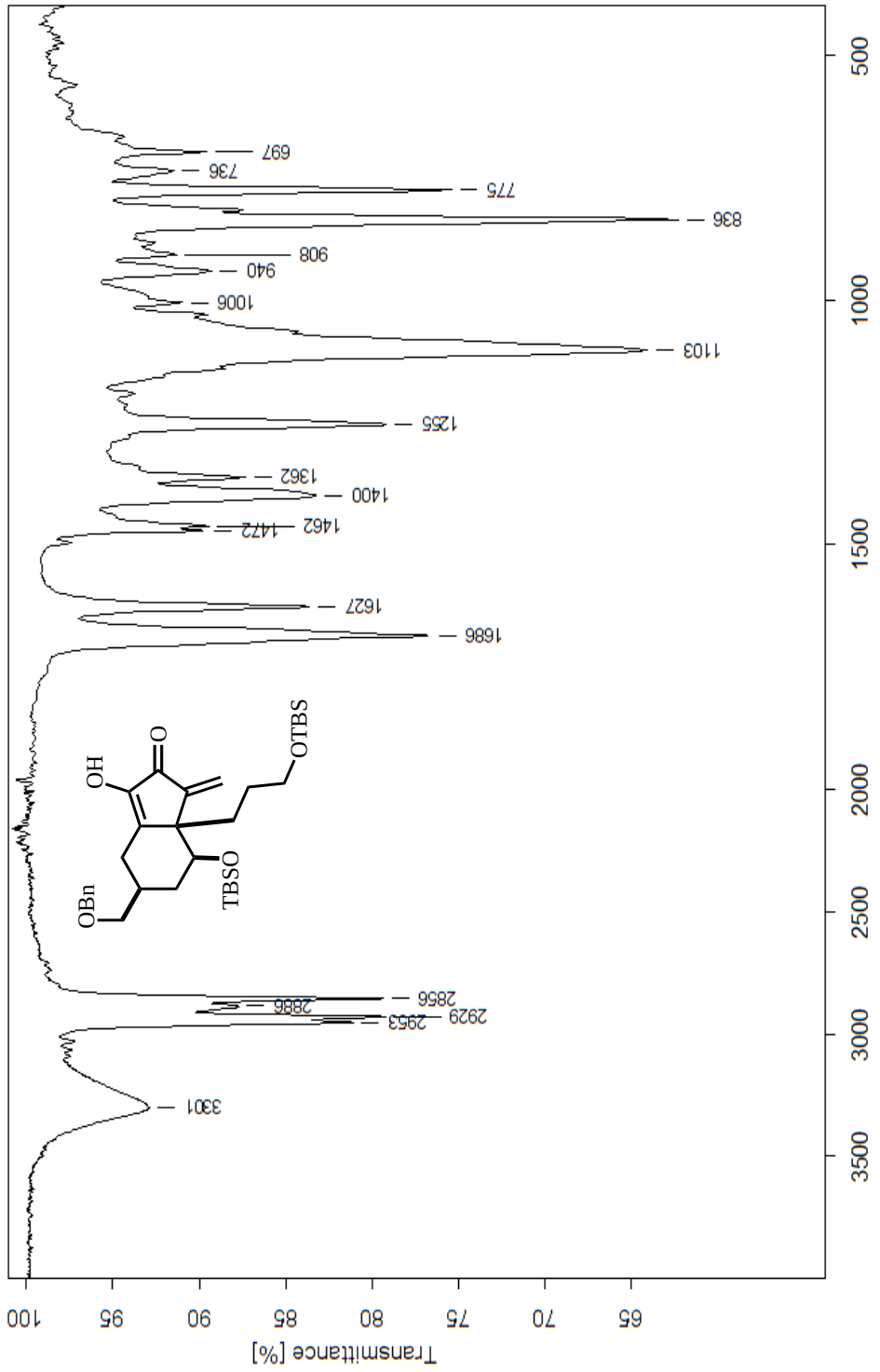

Figure D.37. FTIR Spectrum (neat) of bicycle **4.64**

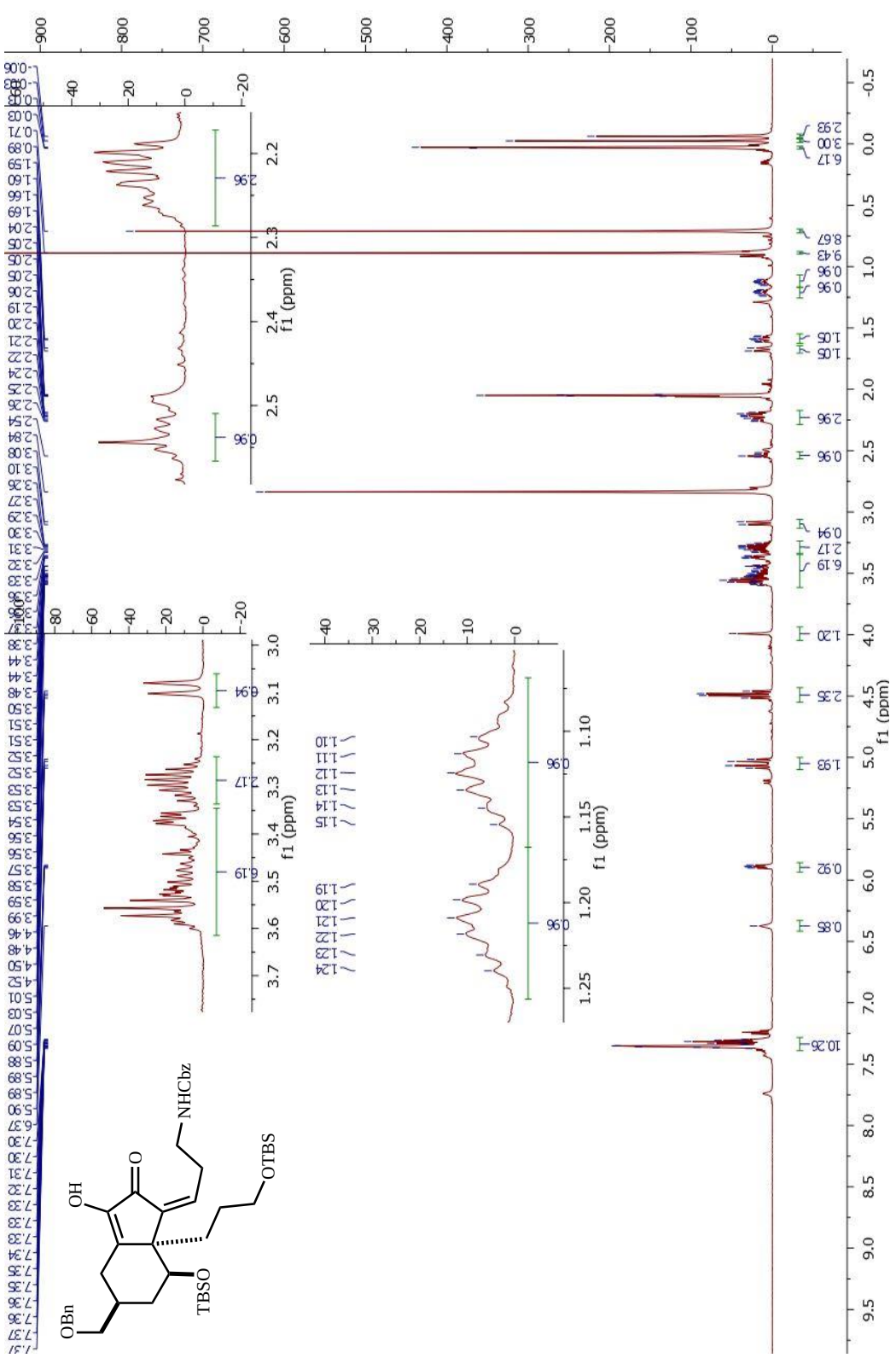

Figure D.38. **^{1}H NMR** (600 MHz, $CO(CD_3)_2$) of bicycle **4.65**

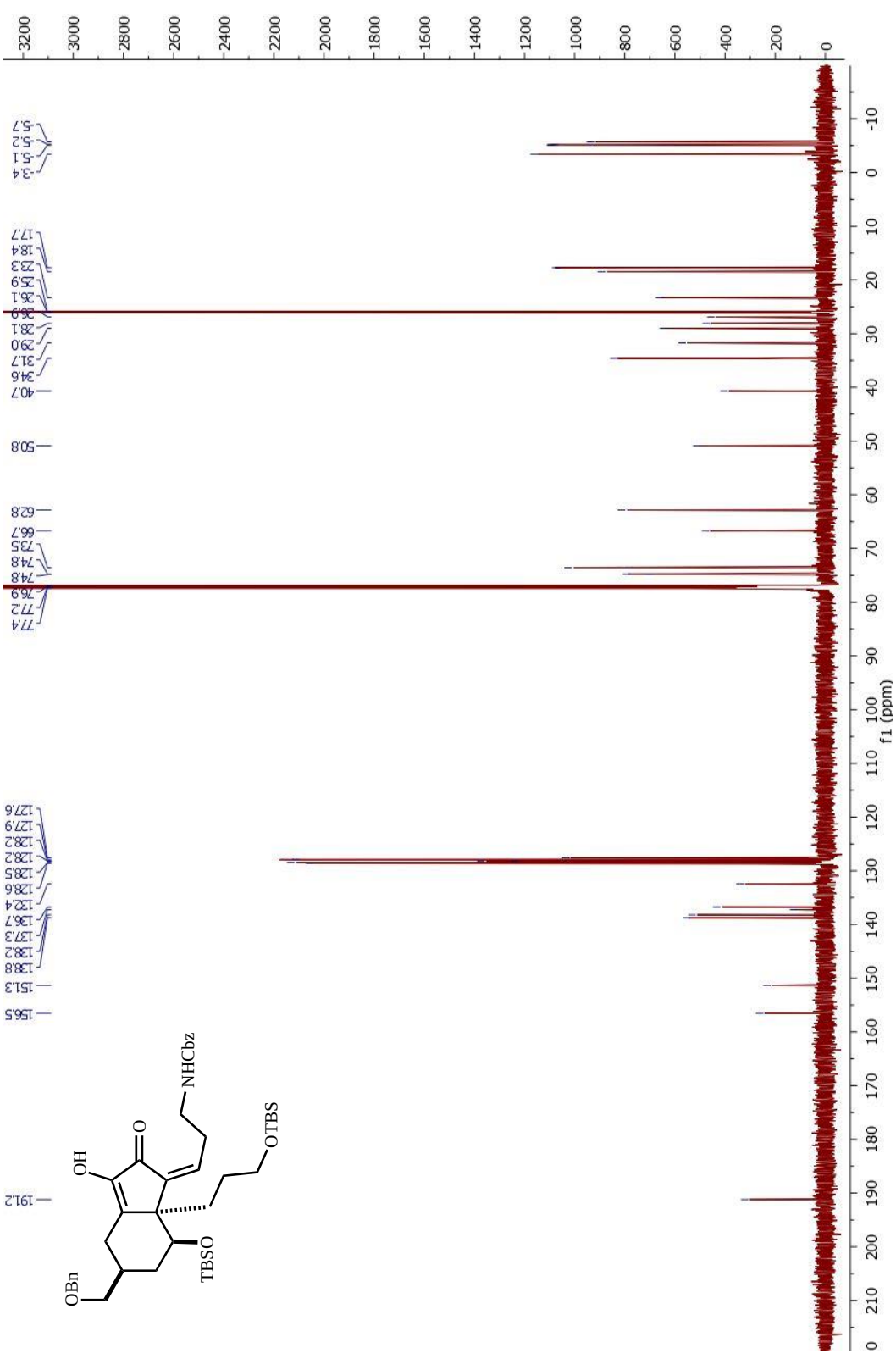

Figure D.39. **^{13}C NMR** (151 MHz, $CDCl_3$) of bicycle **4.65**

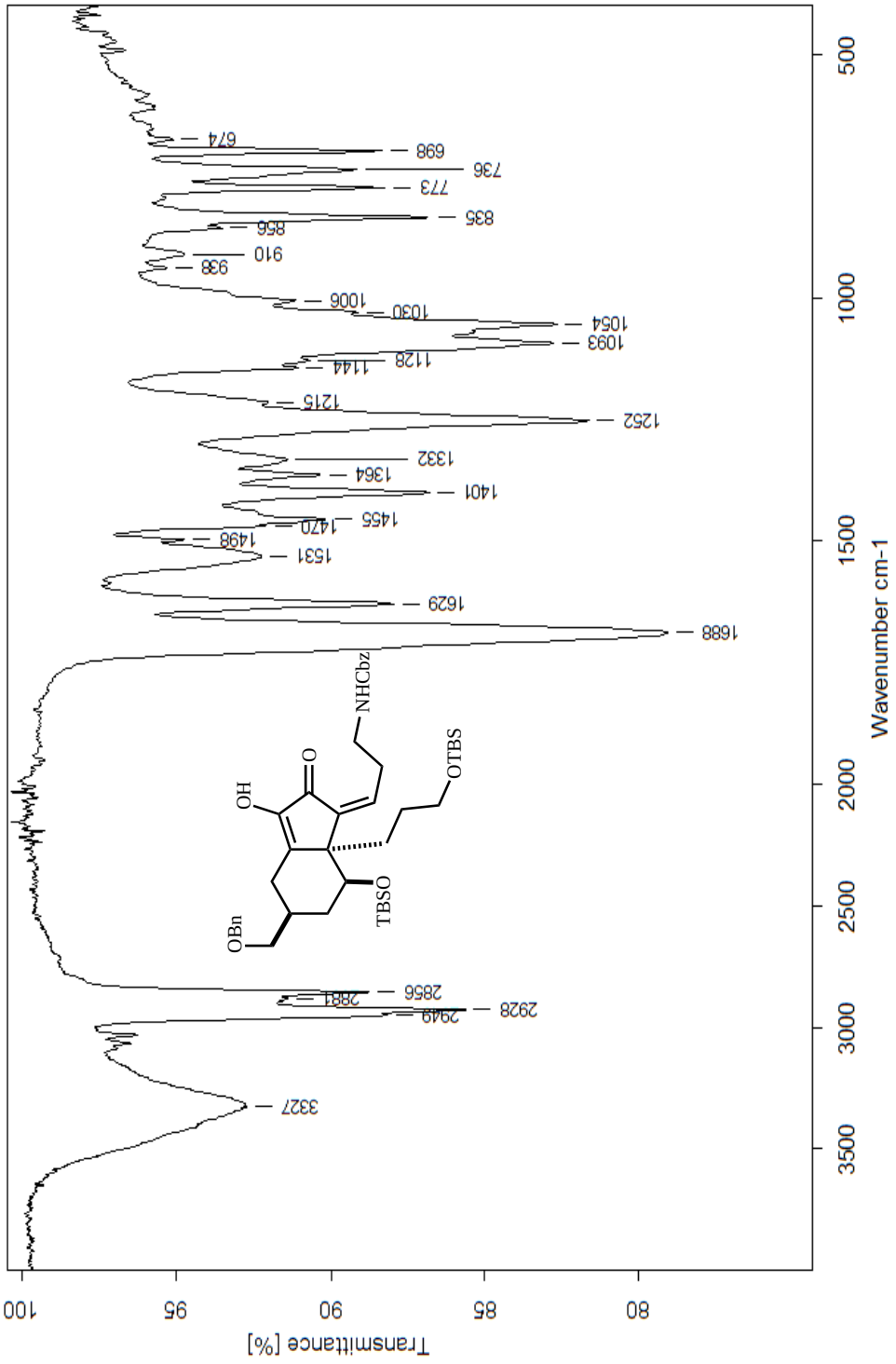

Figure D.40. FTIR Spectrum (neat) of bicycle **4.65**

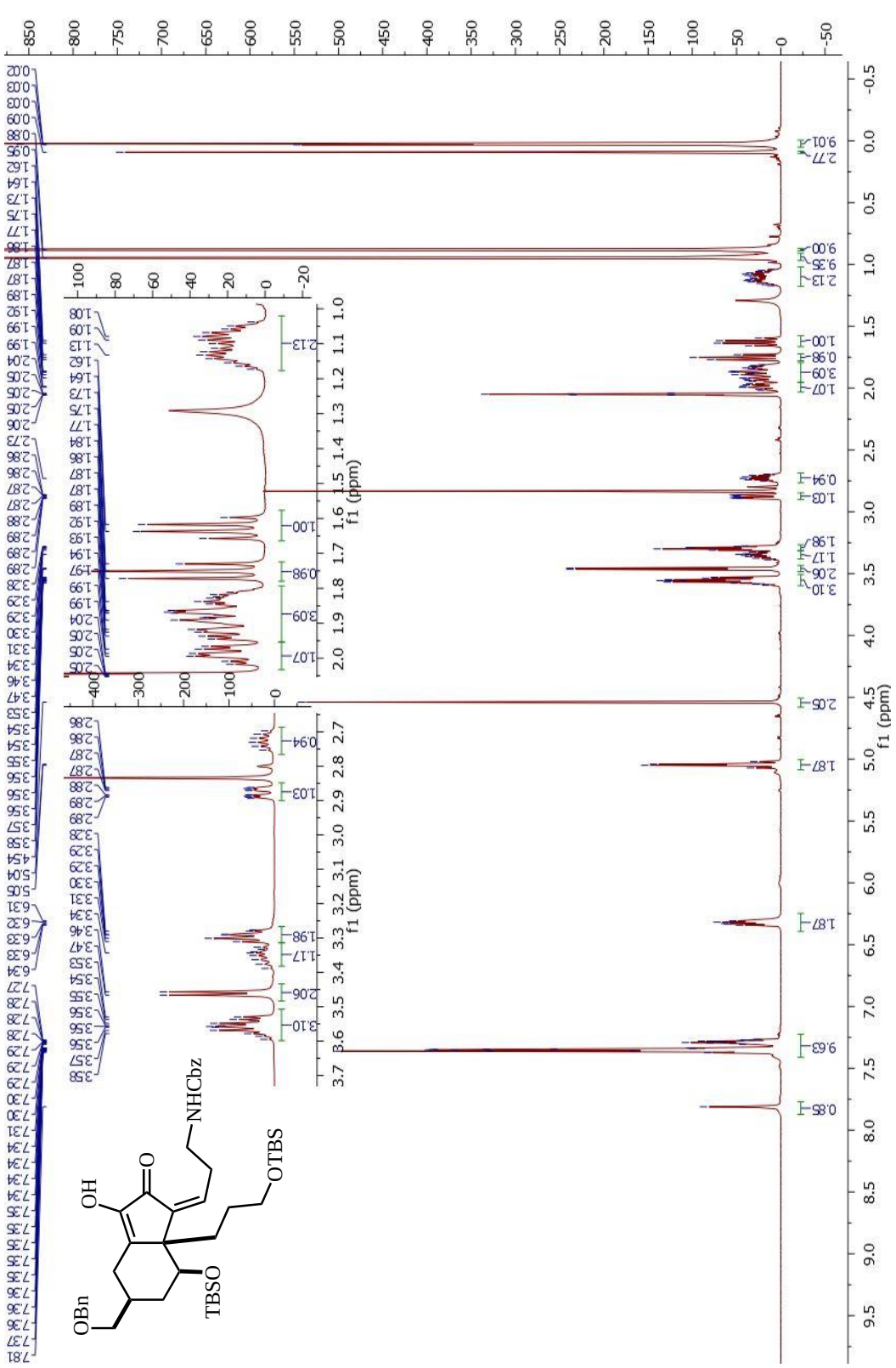

Figure D.41. **^{1}H NMR** (600 MHz, $CO(CD_3)_2$) of bicycle **4.66**

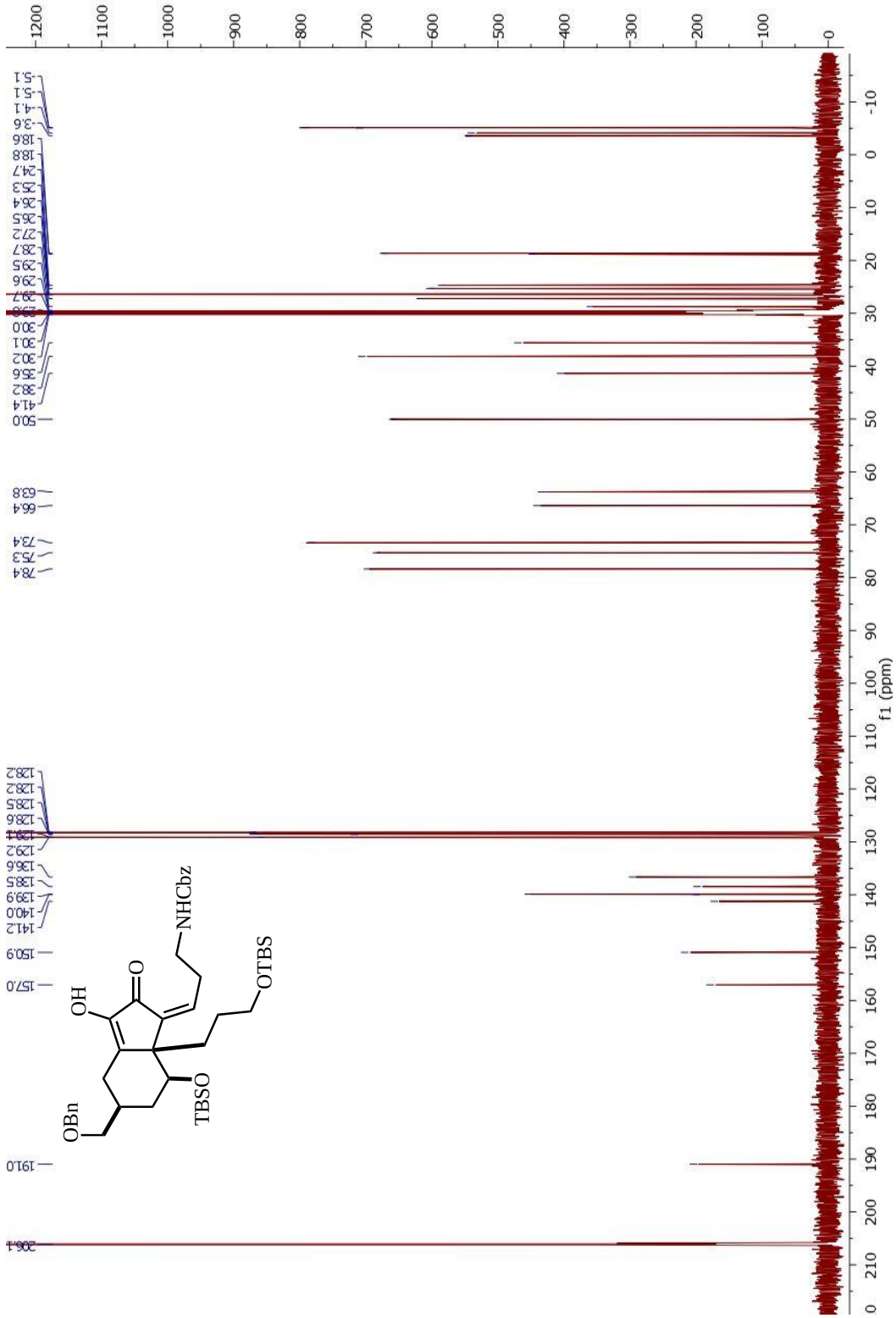

Figure D.42. **^{13}C NMR** (151 MHz, $CO(CD_3)_2$) of bicycle **4.66**

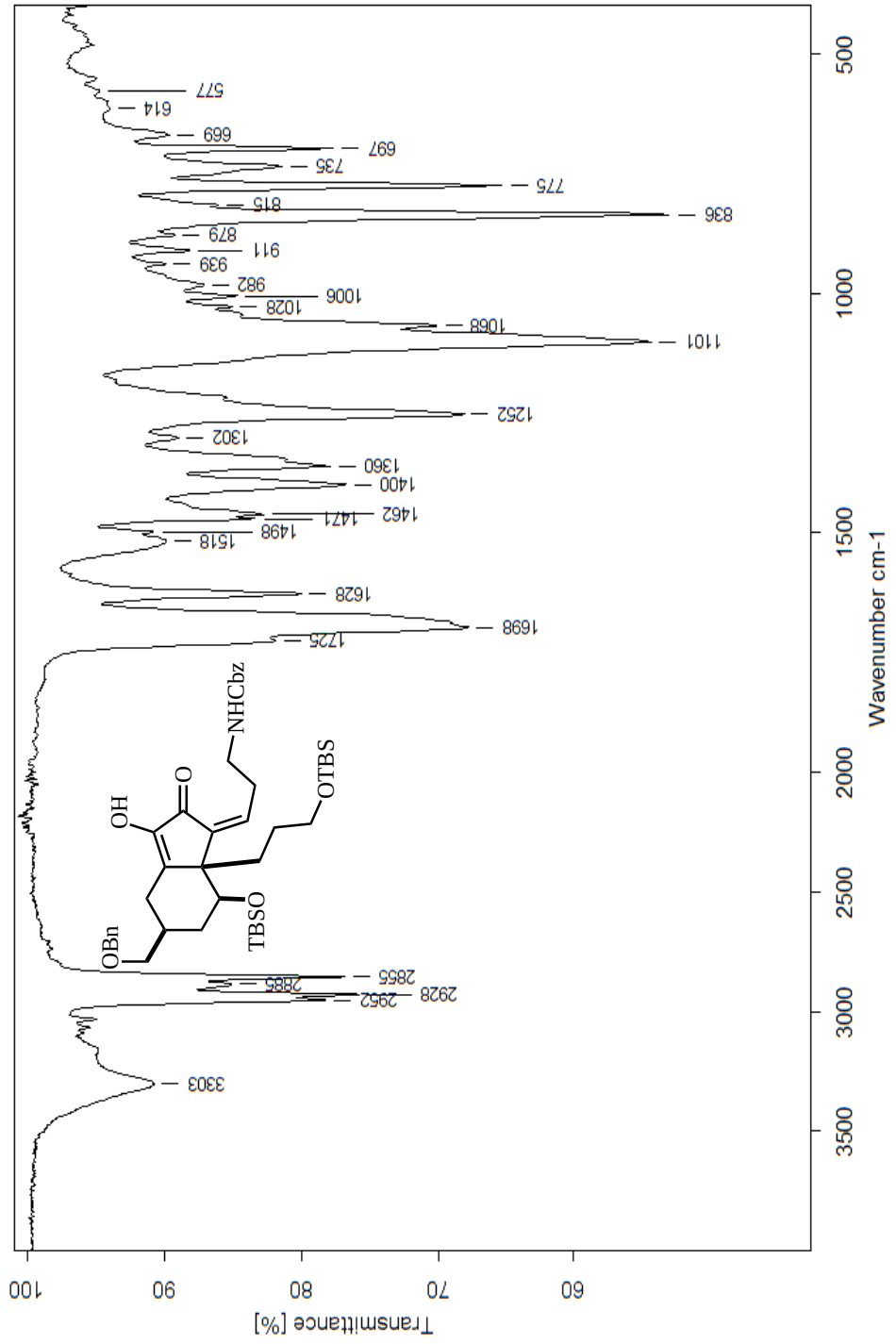

Figure D.43. FTIR Spectrum (neat) of bicycle **4.66**

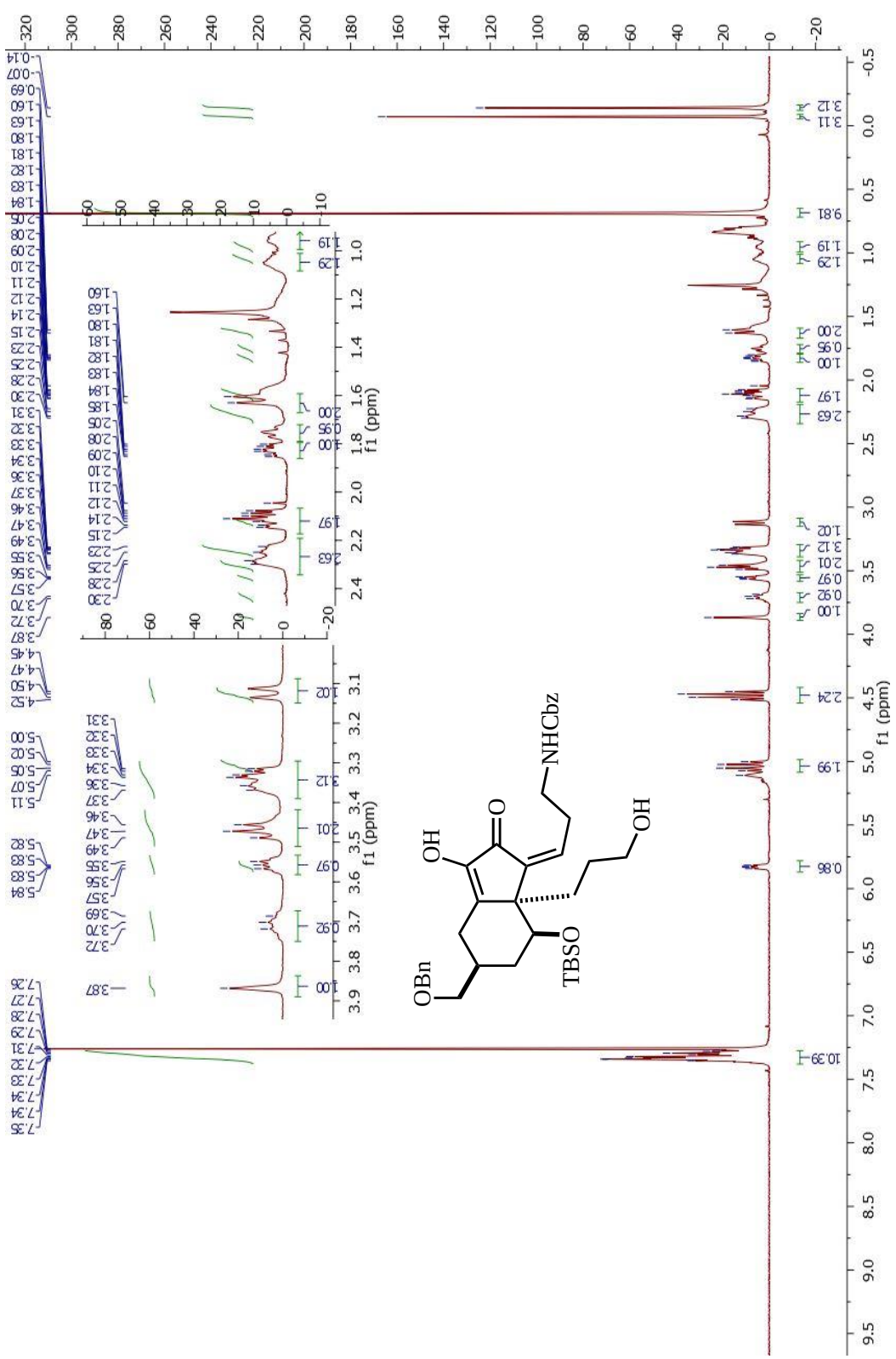

Figure D.44. **^{1}H NMR** (600 MHz, $CDCl_3$) of bicycle **4.67**

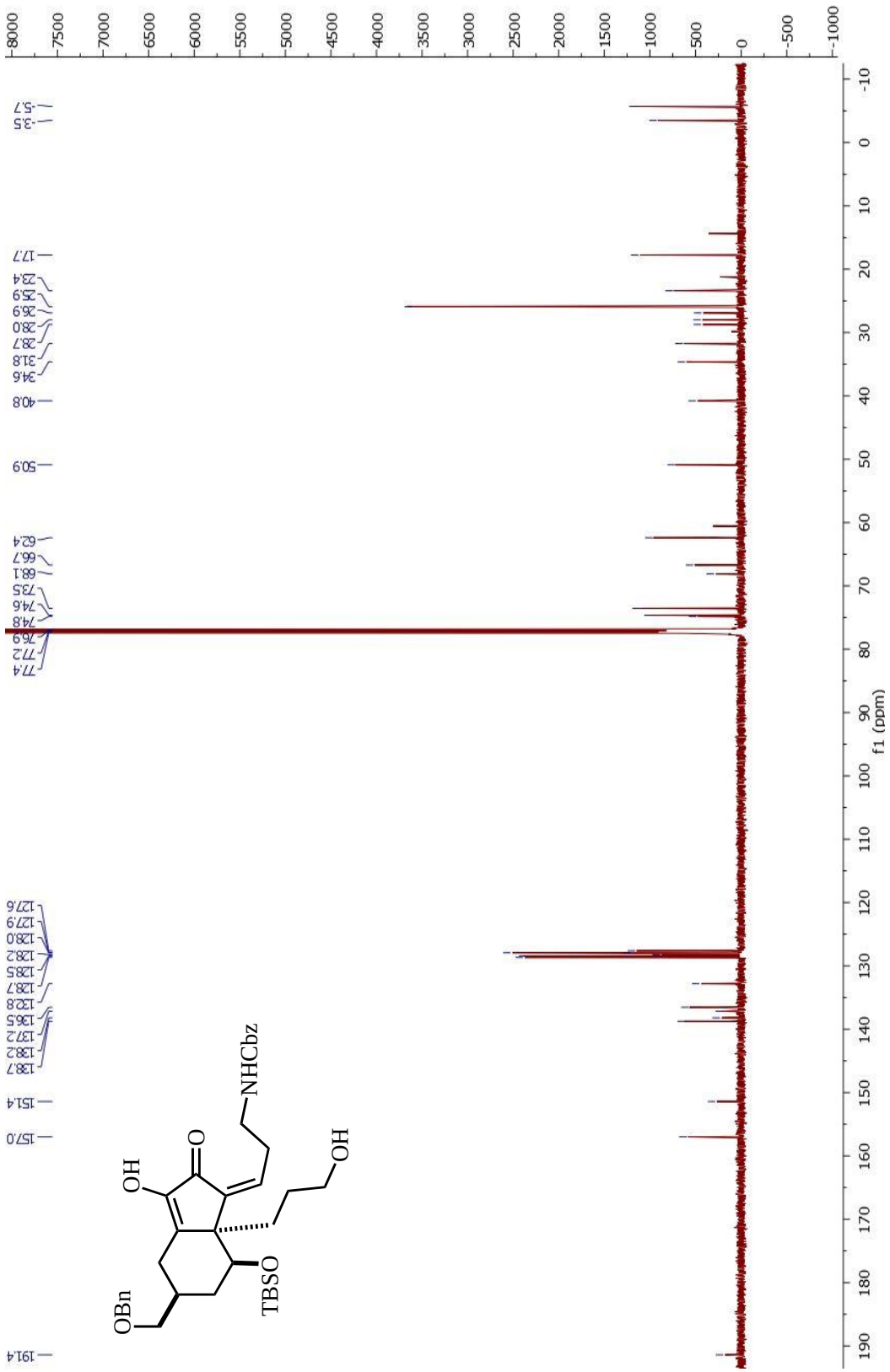

Figure D.45. **^{13}C NMR** (151 MHz, $CDCl_3$) of bicycle **4.67**

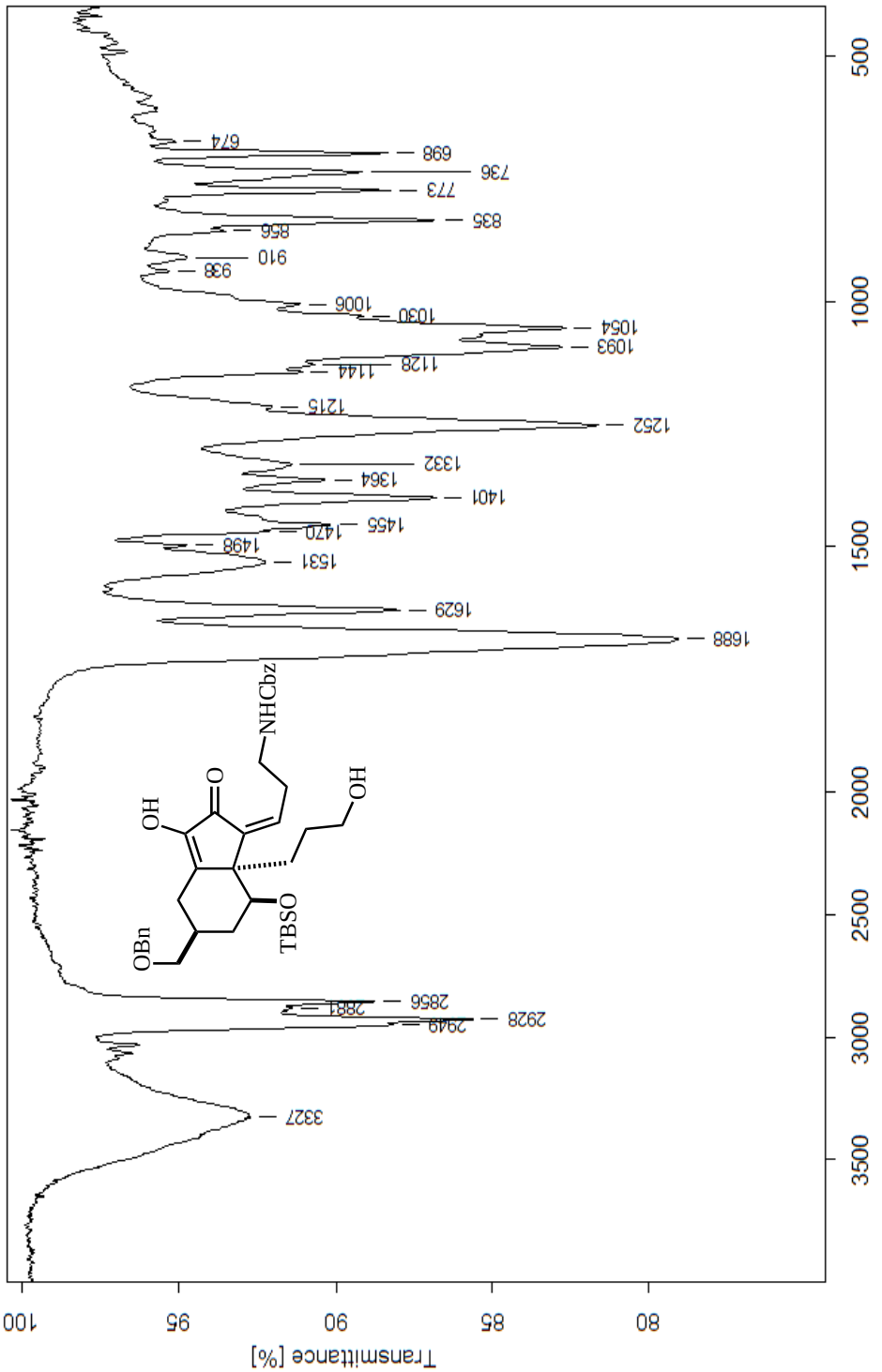

Figure D.46. FTIR Spectrum (neat) of bicycle **4.67**

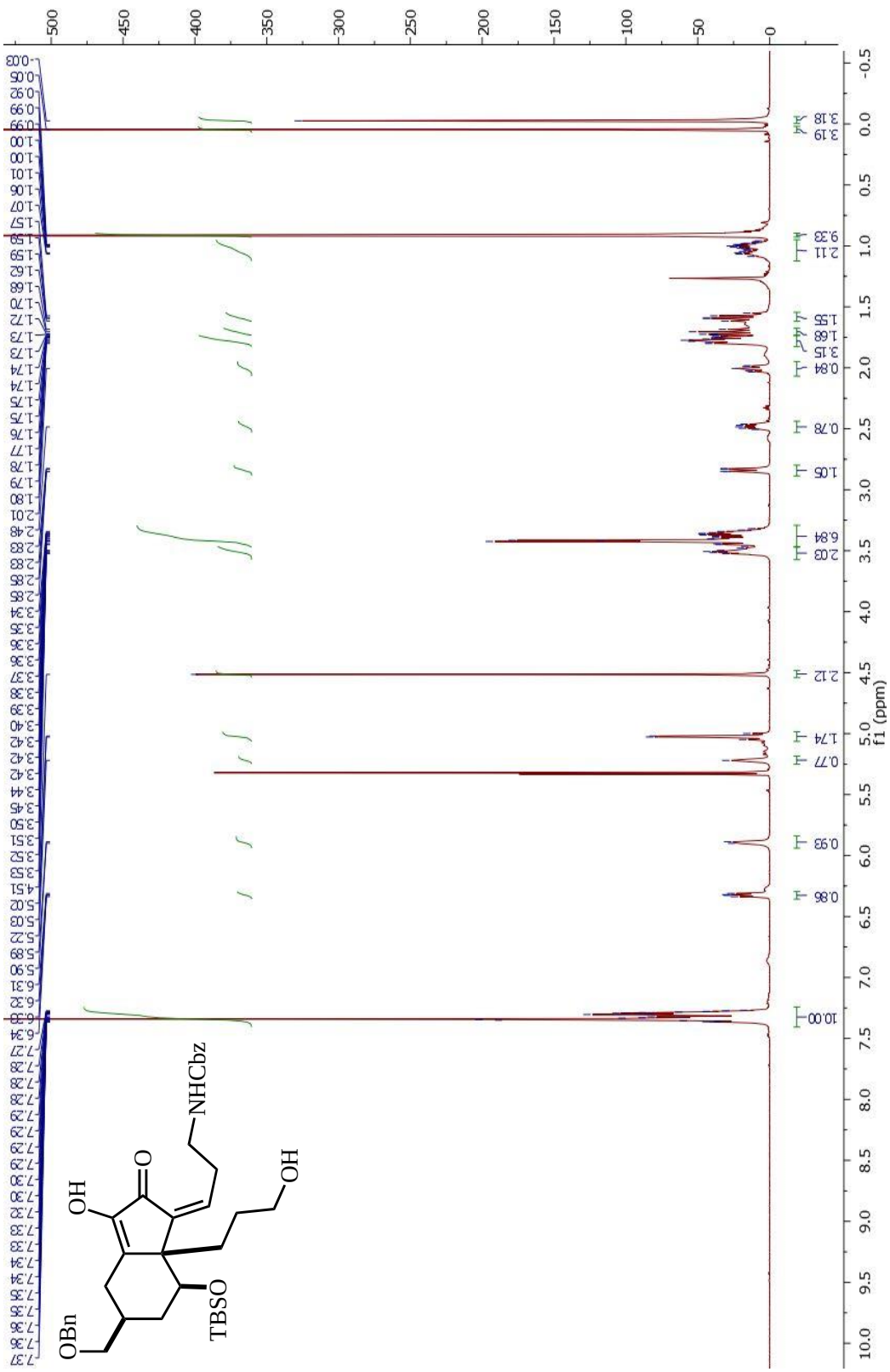

Figure D.47. **^{1}H NMR** (600 MHz, CD_2Cl_2) of bicycle **4.68**

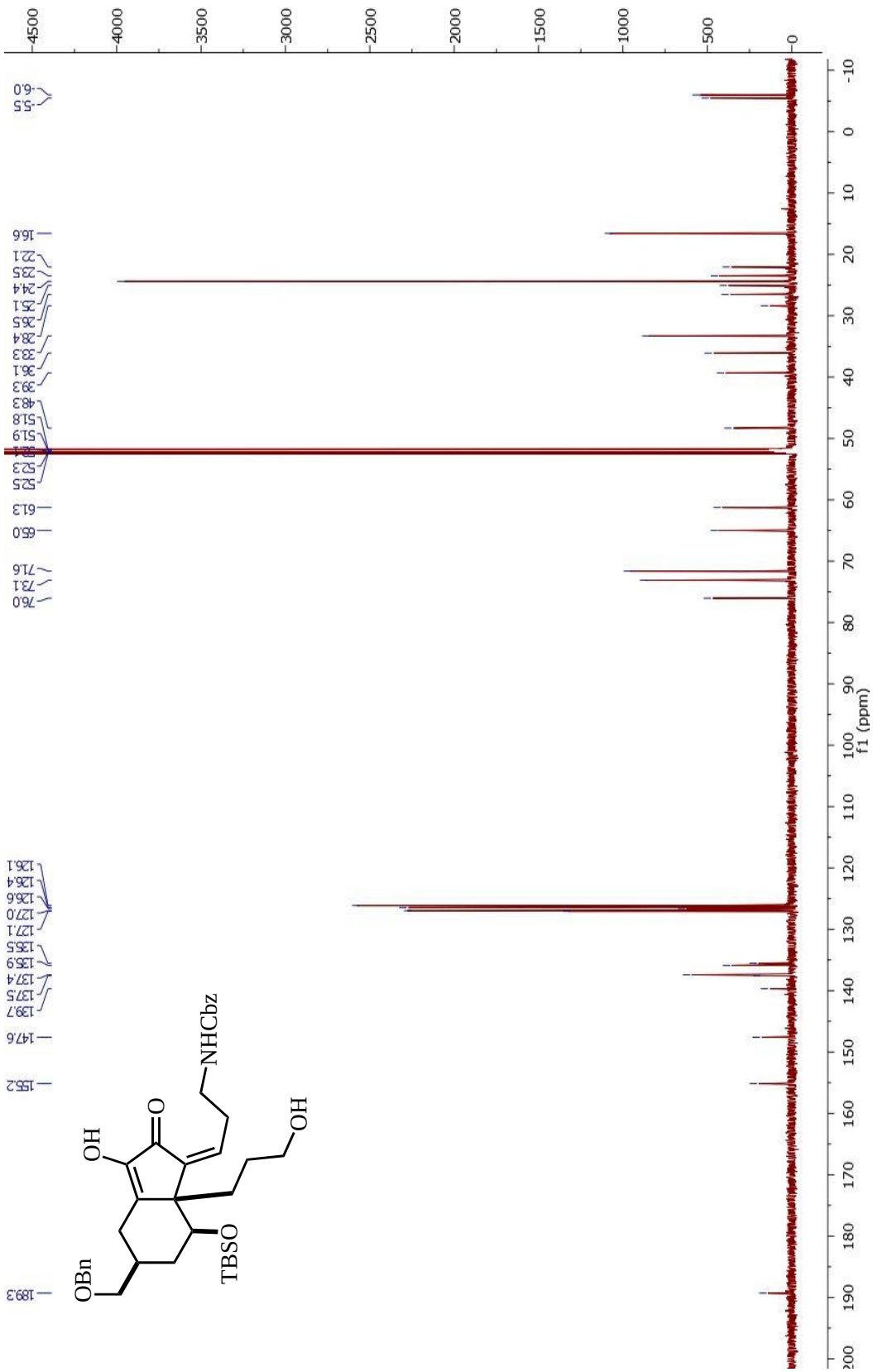

Figure D.48. **^{13}C NMR** (151 MHz, CD_2Cl_2) of bicycle **4.68**

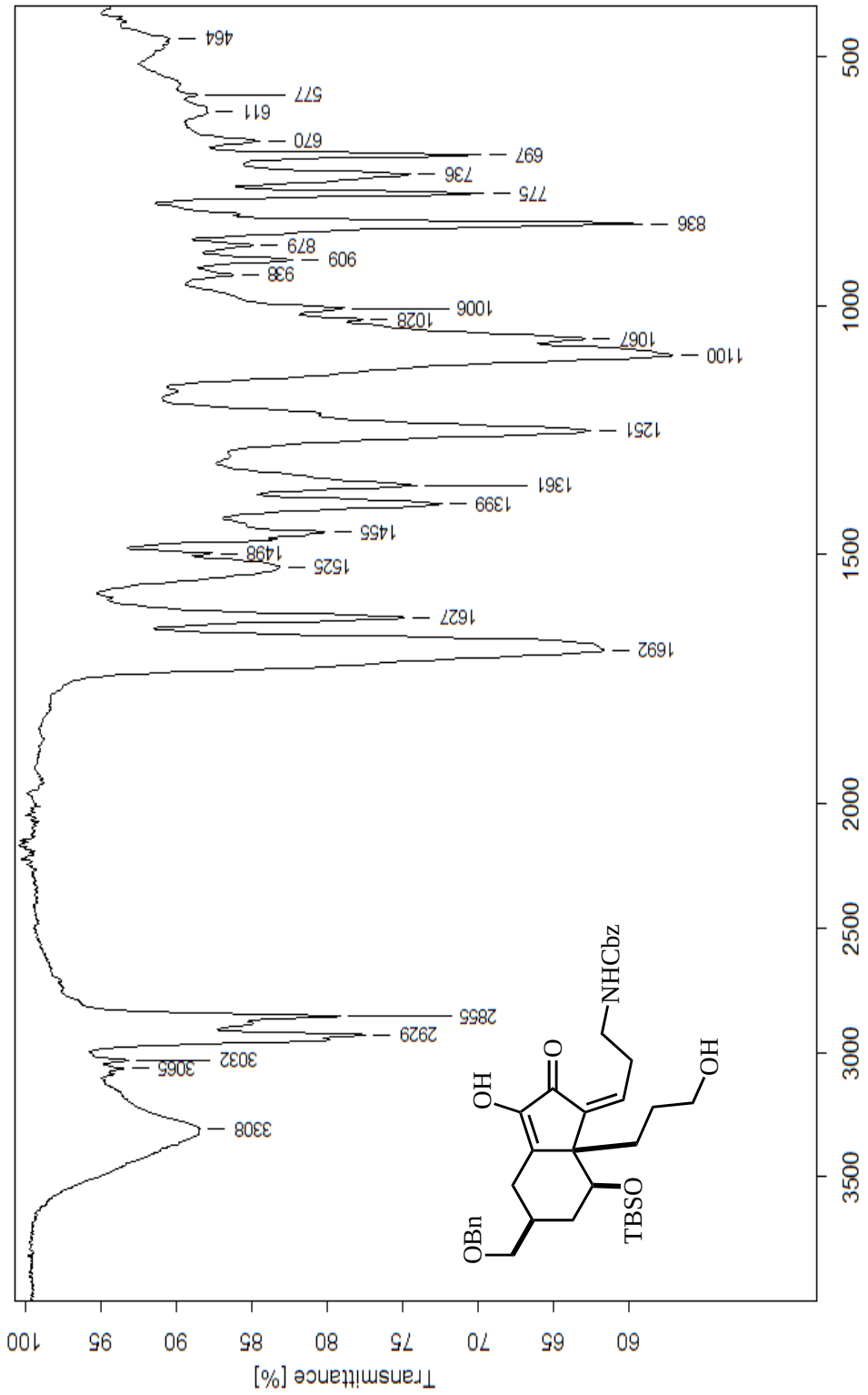

Figure D.49. FTIR Spectrum (neat) of bicycle **4.68**

APPENDIX E

X-ray Crystallography Data

*E.1. Crystal Structure Analysis of Oxabicyclic Compound **2.17***

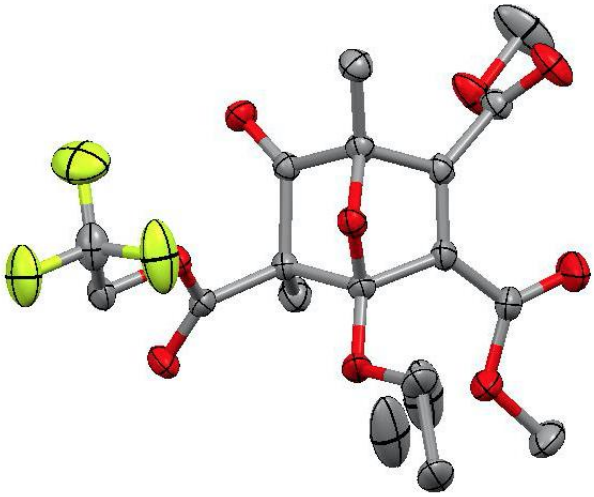

Figure E.01. ORTEP drawing of oxabicyclic compound **2.17**

Table E.01 Crystal data and structure refinement for oxabicyclic compound **2.17**

Identification code	JLW16_0m	
Empirical formula	$C_{17}H_{16}F_3O_9$	
Formula weight	421.30	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 13.9325(8) Å	α= 90°.
	b = 8.4366(5) Å	β= 92.536(2)°.
	c = 16.9502(9) Å	γ= 90°.
Volume	1990.4(2) $Å^3$	
Z	4	
Density (calculated)	1.406 Mg/m^3	
Absorption coefficient	0.131 mm^{-1}	
F(000)	868	
Crystal size	0.529 x 0.416 x 0.412 mm^3	
Theta range for data collection	2.406 to 27.164°.	
Index ranges	-17<=h<=17, -10<=k<=10, -21<=l<=21	
Reflections collected	50096	
Independent reflections	4409 [R(int) = 0.0426]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4409 / 0 / 259	
Goodness-of-fit on F^2	2.050	
Final R indices [I>2sigma(I)]	R1 = 0.0681, wR2 = 0.2411	
R indices (all data)	R1 = 0.0814, wR2 = 0.2531	
Extinction coefficient	n/a	
Largest diff. peak and hole	1.232 and -0.852 $e.Å^{-3}$	

Table E.02. ($x10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 x\ 10^3$) for JLW16_0m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
O(4)	6342(2)	7736(5)	8462(2)	18(1)
C(10)	5787(3)	8586(6)	9026(3)	25(1)
C(11)	4842(4)	9037(6)	8591(3)	84(1)
O(14)	6248(4)	7390(7)	8339(3)	20(1)
C(100)	5570(6)	8177(10)	8849(4)	31(2)
C(111)	5589(10)	9898(16)	8794(7)	100(5)
F(1)	9524(1)	12002(2)	7538(1)	55(1)
F(2)	10077(1)	10196(2)	8328(1)	65(1)
F(3)	8710(2)	11281(2)	8521(1)	70(1)
O(1)	7752(2)	2256(2)	9946(1)	46(1)
O(2)	8515(1)	8284(2)	7953(1)	26(1)
O(3)	7724(1)	7171(2)	6912(1)	32(1)
O(5)	7594(1)	7434(2)	9330(1)	23(1)
O(6)	9270(1)	4950(2)	8659(1)	28(1)
O(7)	7488(2)	3639(2)	11035(1)	40(1)
O(19)	5192(1)	4653(3)	8608(1)	38(1)
C(1)	7961(3)	847(4)	10430(2)	68(1)
C(2)	7537(2)	3549(3)	10338(1)	22(1)
C(3)	7388(2)	4903(3)	9781(1)	22(1)
C(4)	6635(2)	5232(3)	9300(1)	24(1)
C(5)	6956(2)	6616(3)	8777(1)	23(1)
C(6)	7679(2)	5895(3)	8186(1)	21(1)
C(7)	7962(2)	7168(3)	7604(1)	22(1)
C(8)	8787(2)	9549(3)	7447(1)	29(1)
C(9)	9275(2)	10747(3)	7966(2)	38(1)
C(12)	8162(2)	6107(2)	9596(1)	20(1)
C(13)	8513(2)	5544(2)	8787(1)	20(1)
C(14)	5744(2)	4279(3)	9238(1)	27(1)
C(15)	4289(2)	3805(4)	8501(2)	43(1)
C(16)	8920(2)	6539(3)	10219(1)	29(1)
C(17)	7342(2)	4426(3)	7734(1)	29(1)
O(9)	5547(1)	3304(2)	9716(1)	45(1)

Table E.03. Bond lengths [Å] for oxabicycle **2.17**

Atom-Atom	Bond lengths [Å]	Atom-Atom	Bond lengths [Å]
O(4)-C(5)	1.367(4)	C(3)-C(4)	1.329(3)
O(4)-C(10)	1.447(5)	C(3)-C(12)	1.524(3)
C(10)-C(11)	1.529(7)	C(4)-C(14)	1.480(3)
O(14)-C(5)	1.374(5)	C(4)-C(5)	1.543(3)
O(14)-C(100)	1.467(8)	C(5)-C(6)	1.574(3)
C(100)-C(111)	1.455(16)	C(6)-C(7)	1.521(3)
F(1)-C(9)	1.339(3)	C(6)-C(17)	1.520(3)
F(2)-C(9)	1.335(3)	C(6)-C(13)	1.541(3)
F(3)-C(9)	1.332(3)	C(8)-C(9)	1.485(4)
O(1)-C(2)	1.319(3)	C(8)-H(15)	0.9900
O(1)-C(1)	1.466(3)	C(8)-H(16)	0.9900
O(2)-C(7)	1.337(3)	C(12)-C(16)	1.505(3)
O(2)-C(8)	1.430(3)	C(12)-C(13)	1.551(3)
O(3)-C(7)	1.207(3)	C(14)-O(9)	1.195(3)
O(5)-C(12)	1.432(2)	C(15)-H(7)	0.9800
O(5)-C(5)	1.439(3)	C(15)-H(8)	0.9800
O(6)-C(13)	1.196(3)	C(15)-H(6)	0.9800
O(7)-C(2)	1.188(3)	C(16)-H(11)	0.9800
O(19)-C(14)	1.327(3)	C(16)-H(10)	0.9800
O(19)-C(15)	1.452(3)	C(16)-H(9)	0.9800
C(1)-H(3)	0.9800	C(17)-H(12)	0.9800
C(1)-H(4)	0.9800	C(17)-H(13)	0.9800
C(1)-H(1)	0.9800	C(17)-H(14)	0.9800
C(2)-C(3)	1.491(3)		

Table E.04. Bond angles [°] for oxabicycle **2.17**

Atom-Atom-Atom	Bond angles [°]	Atom-Atom-Atom	Bond angles [°]
C(5)-O(4)-C(10)	115.3(3)	O(2)-C(8)-H(16)	110.5
O(4)-C(10)-C(11)	106.2(4)	C(9)-C(8)-H(16)	110.5
C(5)-O(14)-C(100)	111.2(4)	H(15)-C(8)-H(16)	108.7
C(111)-C(100)-O(14)	113.6(7)	F(3)-C(9)-F(1)	106.9(2)
C(2)-O(1)-C(1)	115.6(2)	F(3)-C(9)-F(2)	107.6(2)
C(7)-O(2)-C(8)	115.08(17)	F(1)-C(9)-F(2)	107.0(2)
C(12)-O(5)-C(5)	98.45(15)	F(3)-C(9)-C(8)	112.3(2)
C(14)-O(19)-C(15)	116.8(2)	F(1)-C(9)-C(8)	109.9(2)
O(1)-C(1)-H(3)	109.5	F(2)-C(9)-C(8)	112.7(2)
O(1)-C(1)-H(4)	109.5	O(5)-C(12)-C(16)	113.11(18)
H(3)-C(1)-H(4)	109.5	O(5)-C(12)-C(3)	101.50(17)
O(1)-C(1)-H(1)	109.4	C(16)-C(12)-C(3)	119.85(18)
H(3)-C(1)-H(1)	109.5	O(5)-C(12)-C(13)	98.79(15)
H(4)-C(1)-H(1)	109.5	C(16)-C(12)-C(13)	117.10(18)
O(7)-C(2)-O(1)	125.3(2)	C(3)-C(12)-C(13)	103.42(17)
O(7)-C(2)-C(3)	124.6(2)	O(6)-C(13)-C(6)	127.29(19)
O(1)-C(2)-C(3)	110.04(18)	O(6)-C(13)-C(12)	127.2(2)
C(4)-C(3)-C(2)	129.3(2)	C(6)-C(13)-C(12)	105.51(17)
C(4)-C(3)-C(12)	106.30(19)	O(9)-C(14)-O(19)	124.6(2)
C(2)-C(3)-C(12)	124.11(19)	O(9)-C(14)-C(4)	122.9(2)
C(3)-C(4)-C(14)	124.5(2)	O(19)-C(14)-C(4)	112.44(18)
C(3)-C(4)-C(5)	105.66(19)	O(19)-C(15)-H(7)	109.5
C(14)-C(4)-C(5)	129.37(19)	O(19)-C(15)-H(8)	109.5
O(4)-C(5)-O(5)	106.3(2)	H(7)-C(15)-H(8)	109.5
O(14)-C(5)-O(5)	122.1(3)	O(19)-C(15)-H(6)	109.5
O(4)-C(5)-C(6)	115.1(2)	H(7)-C(15)-H(6)	109.5
O(14)-C(5)-C(6)	107.7(3)	H(8)-C(15)-H(6)	109.5
O(5)-C(5)-C(6)	101.89(16)	C(12)-C(16)-H(11)	109.5
O(4)-C(5)-C(4)	123.7(2)	C(12)-C(16)-H(10)	109.5
O(14)-C(5)-C(4)	116.8(3)	H(11)-C(16)-H(10)	109.5
O(5)-C(5)-C(4)	100.09(16)	C(12)-C(16)-H(9)	109.5
C(6)-C(5)-C(4)	106.43(17)	H(11)-C(16)-H(9)	109.5
C(7)-C(6)-C(17)	109.44(17)	H(10)-C(16)-H(9)	109.5
C(7)-C(6)-C(13)	110.74(17)	C(6)-C(17)-H(12)	109.5
C(17)-C(6)-C(13)	112.57(18)	C(6)-C(17)-H(13)	109.5
C(7)-C(6)-C(5)	109.36(18)	H(12)-C(17)-H(13)	109.5
C(17)-C(6)-C(5)	116.33(18)	C(6)-C(17)-H(14)	109.5
C(13)-C(6)-C(5)	97.93(16)	H(12)-C(17)-H(14)	109.5
O(3)-C(7)-O(2)	123.8(2)	H(13)-C(17)-H(14)	109.5
O(3)-C(7)-C(6)	124.3(2)		
O(2)-C(7)-C(6)	111.87(17)		
O(2)-C(8)-C(9)	106.24(19)		
O(2)-C(8)-H(15)	110.5		
C(9)-C(8)-H(15)	110.5		

E.2. Crystal Structure Analysis of Tetronic acid ***2.25***

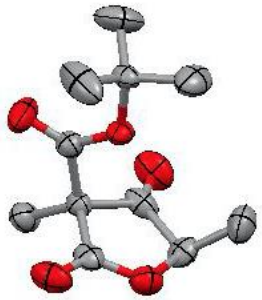

Figure E.02. ORTEP drawing of tetronic acid **2.25**

Table E.05 Crystal data and structure refinement for tetronic acid **2.25**

Identification code	JLW14_0m	
Empirical formula	$C_{11}H_{17}O_5$	
Formula weight	229.24	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 6.4697(6) Å	α= 90°.
	b = 11.6627(11) Å	β= 93.278(3)°.
	c = 16.0124(14) Å	γ= 90°.
Volume	1206.23(19) $Å^3$	
Z	4	
Density (calculated)	1.262 Mg/m^3	
Absorption coefficient	0.099 mm^{-1}	
F(000)	492	
Crystal size	0.130 x 0.080 x 0.050 mm^3	
Theta range for data collection	2.162 to 27.169°.	
Index ranges	-8<=h<=8, -14<=k<=14, -20<=l<=20	
Reflections collected	36886	
Independent reflections	2675 [R(int) = 0.0923]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2675 / 0 / 150	
Goodness-of-fit on F^2	1.077	
Final R indices [I>2sigma(I)]	R1 = 0.0781, wR2 = 0.1815	
R indices (all data)	R1 = 0.1459, wR2 = 0.2165	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.722 and -0.242 $e.Å^{-3}$	

Table E.06. ($x10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 x\ 10^3$) for JLW14. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)	
O(1)	1112(3)	6781(2)	8516(1)	36(1)	
O(2)	-1734(5)	7533(3)	7854(2)	71(1)	
O(3)	-1772(4)	6317(2)	10139(2)	63(1)	
O(4)	2105(4)	8418(2)	10156(2)	50(1)	
O(5)	1292(4)	9620(2)	9130(2)	62(1)	
C(1)	2957(6)	6462(4)	10545(3)	62(1)	
C(2)	1325(5)	7408(3)	10534(2)	45(1)	
C(3)	-631(5)	7087(3)	10016(2)	44(1)	
C(4)	-929(5)	7961(3)	9308(2)	32(1)	
C(5)	-607(5)	7397(3)	8463(2)	37(1)	
C(6)	1833(5)	6110(3)	7796(2)	35(1)	
C(7)	3713(6)	5487(4)	8180(3)	67(1)	
C(8)	2419(9)	6924(4)	7133(3)	85(2)	
C(9)	-2986(5)	8586(3)	9313(2)	49(1)	
C(10)	903(5)	8764(3)	9501(2)41(1)		C(11)
	235(7)	5240(4)	7530(3)	75(1)	

Table E.07. Bond lengths [Å] for tetronic acid **2.25**

Atom-Atom	Bond lengths [Å]	Atom-Atom	Bond lengths [Å]
O(1)-C(5)	1.322(4)	C(4)-C(5)	1.529(4)
O(1)-C(6)	1.491(4)	C(6)-C(8)	1.489(5)
O(2)-C(5)	1.194(4)	C(6)-C(11)	1.493(5)
O(3)-C(3)	1.186(4)	C(6)-C(7)	1.516(5)
O(4)-C(10)	1.332(4)	C(7)-H(14)	0.9800
O(4)-C(2)	1.429(4)	C(7)-H(15)	0.9800
O(5)-C(10)	1.197(4)	C(7)-H(2)	0.9800
C(1)-C(2)	1.527(5)	C(8)-H(3)	0.9800
C(1)-H(9)	0.9800	C(8)-H(16)	0.9800
C(1)-H(8)	0.9800	C(8)-H(17)	0.9800
C(1)-H(1)	0.9800	C(9)-H(6)	0.9800
C(2)-C(3)	1.519(5)	C(9)-H(4)	0.9800
C(2)-H(10)	1.0000	C(9)-H(5)	0.9800
C(3)-C(4)	1.529(5)	C(11)-H(13)	0.9800
C(4)-C(9)	1.517(5)	C(11)-H(11)	0.9800
C(4)-C(10)	1.528(5)	C(11)-H(12)	0.9800

Table E.08. Bond angles [°] for tetronic acid **2.25**

Atom-Atom-Atom	Bond angles [°]	Atom-Atom-Atom	Bond angles [°]
C(5)-O(1)-C(6)	122.3(2)	O(1)-C(6)-C(7)	102.5(2)
C(10)-O(4)-C(2)	112.2(3)	C(11)-C(6)-C(7)	108.5(3)
C(2)-C(1)-H(9)	109.5	C(6)-C(7)-H(14)	109.5
C(2)-C(1)-H(8)	109.4	C(6)-C(7)-H(15)	109.5
H(9)-C(1)-H(8)	109.5	H(14)-C(7)-H(15)	109.5
C(2)-C(1)-H(1)	109.5	C(6)-C(7)-H(2)	109.5
H(9)-C(1)-H(1)	109.5	H(14)-C(7)-H(2)	109.5
H(8)-C(1)-H(1)	109.5	H(15)-C(7)-H(2)	109.5
O(4)-C(2)-C(3)	106.0(3)	C(6)-C(8)-H(3)	109.4
O(4)-C(2)-C(1)	109.9(3)	C(6)-C(8)-H(16)	109.4
C(3)-C(2)-C(1)	112.5(3)	H(3)-C(8)-H(16)	109.5
O(4)-C(2)-H(10)	109.5	C(6)-C(8)-H(17)	109.5
C(3)-C(2)-H(10)	109.5	H(3)-C(8)-H(17)	109.5
C(1)-C(2)-H(10)	109.5	H(16)-C(8)-H(17)	109.5
O(3)-C(3)-C(2)	127.1(4)	C(4)-C(9)-H(6)	109.5
O(3)-C(3)-C(4)	125.1(4)	C(4)-C(9)-H(4)	109.5
C(2)-C(3)-C(4)	107.8(3)	H(6)-C(9)-H(4)	109.5
C(9)-C(4)-C(3)	112.9(3)	C(4)-C(9)-H(5)	109.5
C(9)-C(4)-C(10)	112.0(3)	H(6)-C(9)-H(5)	109.5
C(3)-C(4)-C(10)	101.2(3)	H(4)-C(9)-H(5)	109.5
C(9)-C(4)-C(5)	112.0(3)	O(5)-C(10)-O(4)	121.0(3)
C(3)-C(4)-C(5)	110.6(3)	O(5)-C(10)-C(4)	126.4(3)
C(10)-C(4)-C(5)	107.4(2)	O(4)-C(10)-C(4)	112.6(3)
O(2)-C(5)-O(1)	126.6(3)	C(6)-C(11)-H(13)	109.5
O(2)-C(5)-C(4)	123.9(3)	C(6)-C(11)-H(11)	109.5
O(1)-C(5)-C(4)	109.5(3)	H(13)-C(11)-H(11)	109.5
C(8)-C(6)-O(1)	108.7(3)	C(6)-C(11)-H(12)	109.4
C(8)-C(6)-C(11)	115.5(4)	H(13)-C(11)-H(12)	109.5
O(1)-C(6)-C(11)	109.6(3)	H(11)-C(11)-H(12)	109.5
C(8)-C(6)-C(7)	111.3(4)		

*E.3. Crystal Structure Analysis of Tetracycle **3.47***

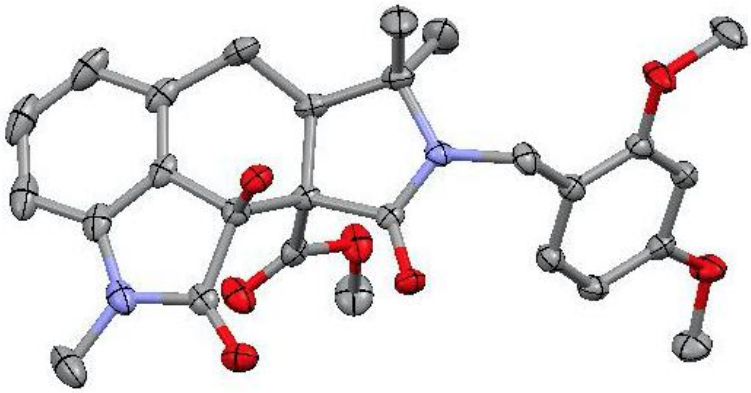

Figure E.03. ORTEP drawing of tetracycle **3.47**

Table E.09 Crystal data and structure refinement for tetracycle **3.47**

Identification code	jlw42_0m	
Empirical formula	$C_{27}H_{30}N_2O_7$	
Formula weight	494.53	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 11.1070(9) Å	α= 95.683(2)°.
	b = 11.6528(10) Å	β= 109.541(2)°.
	c = 11.9191(10) Å	γ= 117.298(2)°.
Volume	1231.82(18) $Å^3$	
Z	2	
Density (calculated)	1.333 Mg/m^3	
Absorption coefficient	0.097 mm^{-1}	
F(000)	524	
Crystal size	0.233 x 0.117 x 0.074 mm^3	
Theta range for data collection	2.347 to 29.600°.	
Index ranges	-15<=h<=15, -16<=k<=16, -16<=l<=16	
Reflections collected	37675	
Independent reflections	6891 [R(int) = 0.1145]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.703 and 0.693	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6891 / 0 / 334	
Goodness-of-fit on F^2	1.067	
Final R indices [I>2sigma(I)]	R1 = 0.0661, wR2 = 0.1146	
R indices (all data)	R1 = 0.1496, wR2 = 0.1432	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.299 and -0.257 $e.Å^{-3}$	

Table E.10. ($x10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 x\ 10^3$) for jlw42_0m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
O(1)	9416(2)	9798(1)	8434(1)	24(1)
O(2)	7558(2)	8454(2)	10080(1)	24(1)
O(3)	9120(2)	7226(2)	9232(1)	31(1)
O(4)	6408(2)	6207(2)	6535(1)	34(1)
O(5)	6476(2)	7897(2)	5764(1)	32(1)
O(6)	8877(2)	12246(2)	3273(1)	32(1)
O(7)	8327(2)	13699(2)	6839(2)	35(1)
N(1)	7700(2)	10456(2)	7938(2)	21(1)
N(2)	6856(2)	5436(2)	8959(2)	32(1)
C(1)	8141(2)	9574(2)	8147(2)	19(1)
C(2)	6775(2)	8176(2)	7852(2)	20(1)
C(3)	5449(2)	8443(2)	7568(2)	24(1)
C(4)	6175(2)	10004(2)	7818(2)	27(1)
C(5)	5339(3)	10324(3)	6723(3)	44(1)
C(6)	6315(3)	10741(3)	9040(2)	42(1)
C(7)	6938(2)	7498(2)	8899(2)	21(1)
C(8)	7810(3)	6742(2)	9019(2)	25(1)
C(9)	5398(3)	5168(2)	8649(2)	31(1)
C(10)	5408(2)	6352(2)	8613(2)	25(1)
C(11)	4136(2)	6413(2)	8223(2)	30(1)
C(12)	2776(3)	5204(3)	7890(2)	42(1)
C(13)	2773(3)	4023(3)	7973(2)	49(1)
C(14)	4062(3)	3965(2)	8341(2)	42(1)
C(15)	4406(2)	7795(2)	8208(2)	31(1)
C(16)	6529(2)	7289(2)	6659(2)	22(1)
C(17)	6303(3)	7172(2)	4599(2)	38(1)
C(18)	7291(4)	4441(3)	9097(3)	47(1)
C(19)	8719(2)	11811(2)	7934(2)	26(1)
C(20)	8701(2)	11873(2)	6664(2)	23(1)
C(21)	8925(2)	11006(2)	5993(2)	25(1)
C(22)	8990(2)	11077(2)	4858(2)	25(1)
C(23)	8839(2)	12062(2)	4379(2)	24(1)
C(24)	8611(2)	12956(2)	5024(2)	24(1)
C(25)	8540(2)	12855(2)	6152(2)	24(1)
C(26)	9254(3)	11452(3)	2624(2)	37(1) C(27)
	8156(3)	14710(3)	6350(3)	44(1)

Table E.11. Bond lengths [Å] for tetracycle **3.47**

Atom-Atom	Bond lengths [Å]	Atom-Atom	Bond lengths [Å]
O(1)-C(1)	1.229(2)	C(9)-C(14)	1.388(3)
O(2)-C(7)	1.426(2)	C(10)-C(11)	1.370(3)
O(2)-H(2)	0.89(3)	C(11)-C(12)	1.400(3)
O(3)-C(8)	1.214(3)	C(11)-C(15)	1.500(3)
O(4)-C(16)	1.194(2)	C(12)-C(13)	1.388(4)
O(5)-C(16)	1.337(3)	C(12)-H(12)	0.9500
O(5)-C(17)	1.456(2)	C(13)-C(14)	1.385(4)
O(6)-C(23)	1.367(3)	C(13)-H(13)	0.9500
O(6)-C(26)	1.434(3)	C(14)-H(14)	0.9500
O(7)-C(25)	1.370(2)	C(15)-H(15A)	0.9900
O(7)-C(27)	1.426(3)	C(15)-H(15B)	0.9900
N(1)-C(1)	1.338(3)	C(17)-H(17A)	0.9800
N(1)-C(19)	1.463(3)	C(17)-H(17B)	0.9800
N(1)-C(4)	1.473(3)	C(17)-H(17C)	0.9800
N(2)-C(8)	1.375(3)	C(18)-H(18A)	0.9800
N(2)-C(9)	1.403(3)	C(18)-H(18B)	0.9800
N(2)-C(18)	1.450(3)	C(18)-H(18C)	0.9800
C(1)-C(2)	1.530(3)	C(19)-C(20)	1.516(3)
C(2)-C(16)	1.534(3)	C(19)-H(19A)	0.9900
C(2)-C(7)	1.546(3)	C(19)-H(19B)	0.9900
C(2)-C(3)	1.578(3)	C(20)-C(21)	1.389(3)
C(3)-C(15)	1.547(3)	C(20)-C(25)	1.402(3)
C(3)-C(4)	1.561(3)	C(21)-C(22)	1.387(3)
C(3)-H(3)	1.0000	C(21)-H(21)	0.9500
C(4)-C(5)	1.519(3)	C(22)-C(23)	1.383(3)
C(4)-C(6)	1.537(3)	C(22)-H(22)	0.9500
C(5)-H(5A)	0.9800	C(23)-C(24)	1.398(3)
C(5)-H(5B)	0.9800	C(24)-C(25)	1.386(3)
C(5)-H(5C)	0.9800	C(24)-H(24)	0.9500
C(6)-H(6A)	0.9800	C(26)-H(26A)	0.9800
C(6)-H(6B)	0.9800	C(26)-H(26B)	0.9800
C(6)-H(6C)	0.9800	C(26)-H(26C)	0.9800
C(7)-C(10)	1.493(3)	C(27)-H(27A)	0.9800
C(7)-C(8)	1.565(3)	C(27)-H(27B)	0.9800
C(9)-C(10)	1.380(3)	C(27)-H(27C)	0.9800

Table E.12. Bond angles [°] for tetracycle **3.47**

Atom-Atom-Atom	Bond angles [°]	Atom-Atom-Atom	Bond angles [°]
C(7)-O(2)-H(2)	110.2(16)	C(14)-C(13)-H(13)	118.5
C(16)-O(5)-C(17)	115.77(17)	C(12)-C(13)-H(13)	118.5
C(23)-O(6)-C(26)	117.59(17)	C(13)-C(14)-C(9)	116.7(3)
C(25)-O(7)-C(27)	117.62(17)	C(13)-C(14)-H(14)	121.6
C(1)-N(1)-C(19)	121.52(17)	C(9)-C(14)-H(14)	121.6
C(1)-N(1)-C(4)	115.26(17)	C(11)-C(15)-C(3)	110.80(18)
C(19)-N(1)-C(4)	123.03(17)	C(11)-C(15)-H(15A)	109.5
C(8)-N(2)-C(9)	111.49(19)	C(3)-C(15)-H(15A)	109.5
C(8)-N(2)-C(18)	123.5(2)	C(11)-C(15)-H(15B)	109.5
C(9)-N(2)-C(18)	124.8(2)	C(3)-C(15)-H(15B)	109.5
O(1)-C(1)-N(1)	126.32(19)	H(15A)-C(15)-H(15B)	108.1
O(1)-C(1)-C(2)	123.96(18)	O(4)-C(16)-O(5)	123.98(19)
N(1)-C(1)-C(2)	109.49(17)	O(4)-C(16)-C(2)	125.28(19)
C(1)-C(2)-C(16)	106.24(16)	O(5)-C(16)-C(2)	110.74(17)
C(1)-C(2)-C(7)	114.66(16)	O(5)-C(17)-H(17A)	109.5
C(16)-C(2)-C(7)	109.83(17)	O(5)-C(17)-H(17B)	109.5
C(1)-C(2)-C(3)	103.77(16)	H(17A)-C(17)-H(17B)	109.5
C(16)-C(2)-C(3)	109.79(16)	O(5)-C(17)-H(17C)	109.5
C(7)-C(2)-C(3)	112.21(16)	H(17A)-C(17)-H(17C)	109.5
C(15)-C(3)-C(4)	115.56(17)	H(17B)-C(17)-H(17C)	109.5
C(15)-C(3)-C(2)	115.88(18)	N(2)-C(18)-H(18A)	109.5
C(4)-C(3)-C(2)	106.03(16)	N(2)-C(18)-H(18B)	109.5
C(15)-C(3)-H(3)	106.2	H(18A)-C(18)-H(18B)	109.5
C(4)-C(3)-H(3)	106.2	N(2)-C(18)-H(18C)	109.5
C(2)-C(3)-H(3)	106.2	H(18A)-C(18)-H(18C)	109.5
N(1)-C(4)-C(5)	110.47(18)	H(18B)-C(18)-H(18C)	109.5
N(1)-C(4)-C(6)	108.04(18)	N(1)-C(19)-C(20)	113.55(16)
C(5)-C(4)-C(6)	110.3(2)	N(1)-C(19)-H(19A)	108.9
N(1)-C(4)-C(3)	102.84(15)	C(20)-C(19)-H(19A)	108.9
C(5)-C(4)-C(3)	110.94(19)	N(1)-C(19)-H(19B)	108.9
C(6)-C(4)-C(3)	114.02(19)	C(20)-C(19)-H(19B)	108.9
C(4)-C(5)-H(5A)	109.5	H(19A)-C(19)-H(19B)	107.7
C(4)-C(5)-H(5B)	109.5	C(21)-C(20)-C(25)	117.30(19)
H(5A)-C(5)-H(5B)	109.5	C(21)-C(20)-C(19)	121.15(19)
C(4)-C(5)-H(5C)	109.5	C(25)-C(20)-C(19)	121.46(18)
H(5A)-C(5)-H(5C)	109.5	C(22)-C(21)-C(20)	122.8(2)
H(5B)-C(5)-H(5C)	109.5	C(22)-C(21)-H(21)	118.6
C(4)-C(6)-H(6A)	109.5	C(20)-C(21)-H(21)	118.6
C(4)-C(6)-H(6B)	109.5	C(23)-C(22)-C(21)	118.65(19)
H(6A)-C(6)-H(6B)	109.5	C(23)-C(22)-H(22)	120.7
C(4)-C(6)-H(6C)	109.5	C(21)-C(22)-H(22)	120.7
H(6A)-C(6)-H(6C)	109.5	O(6)-C(23)-C(22)	124.85(18)
H(6B)-C(6)-H(6C)	109.5	O(6)-C(23)-C(24)	114.77(19)
O(2)-C(7)-C(10)	110.47(16)	C(22)-C(23)-C(24)	120.37(19)
O(2)-C(7)-C(2)	110.12(16)	C(25)-C(24)-C(23)	119.7(2)
C(10)-C(7)-C(2)	107.32(16)	C(25)-C(24)-H(24)	120.1
O(2)-C(7)-C(8)	108.60(16)	C(23)-C(24)-H(24)	120.1
C(10)-C(7)-C(8)	100.57(17)	O(7)-C(25)-C(24)	123.0(2)
C(2)-C(7)-C(8)	119.23(16)	O(7)-C(25)-C(20)	115.88(18)
O(3)-C(8)-N(2)	125.2(2)	C(24)-C(25)-C(20)	121.12(18)
O(3)-C(8)-C(7)	127.2(2)	O(6)-C(26)-H(26A)	109.5
N(2)-C(8)-C(7)	107.39(18)	O(6)-C(26)-H(26B)	109.5

C(10)-C(9)-C(14)	120.2(2)	H(26A)-C(26)-H(26B)	109.5
C(10)-C(9)-N(2)	108.70(19)	O(6)-C(26)-H(26C)	109.5
C(14)-C(9)-N(2)	131.0(2)	H(26A)-C(26)-H(26C)	109.5
C(11)-C(10)-C(9)	123.5(2)	H(26B)-C(26)-H(26C)	109.5
C(11)-C(10)-C(7)	124.9(2)	O(7)-C(27)-H(27A)	109.5
C(9)-C(10)-C(7)	111.28(19)	O(7)-C(27)-H(27B)	109.5
C(10)-C(11)-C(12)	117.0(2)	H(27A)-C(27)-H(27B)	109.5
C(10)-C(11)-C(15)	114.31(19)	O(7)-C(27)-H(27C)	109.5
C(12)-C(11)-C(15)	128.7(2)	H(27A)-C(27)-H(27C)	109.5
C(13)-C(12)-C(11)	119.5(2)	H(27B)-C(27)-H(27C)	109.5
C(13)-C(12)-H(12)	120.3		
C(11)-C(12)-H(12)	120.3		
C(14)-C(13)-C(12)	123.1(2)		

Table E.13. [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2)...O(1)#1	0.89(3)	1.91(3)	2.758(2)	158(2)

Symmetry transformations used to generate equivalent atoms:

#1 -x+2,-y+2,-z+2

*E.4. Crystal Structure Analysis of Cyclopropyl Hemiaminal **3.70***

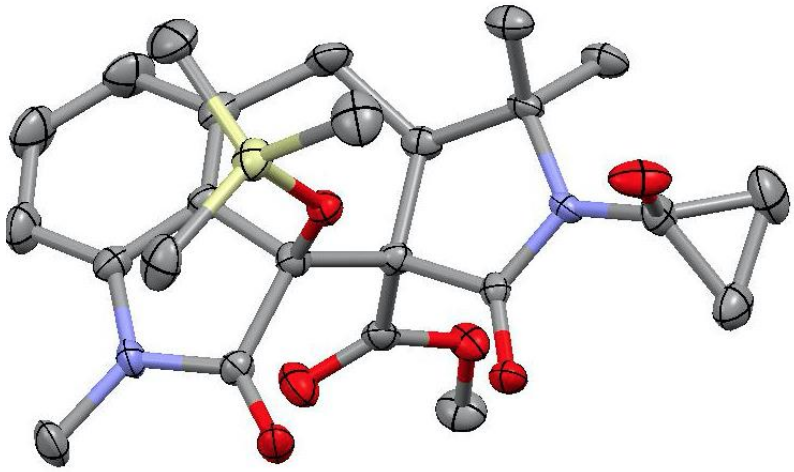

Figure E.04. ORTEP drawing of cyclopropyl hemiaminal **3.70**

Table E.14 Crystal data and structure refinement cyclopropyl hemiaminal **3.70**

Identification code	JLW55	
Empirical formula	$C_{24}H_{32}N_2O_6Si$	
Formula weight	472.60	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 15.6077(9) Å	α= 90°.
	b = 9.8812(6) Å	β= 101.265(2)°.
	c = 16.1346(10) Å	γ= 90°.
Volume	2440.4(3) $Å^3$	
Z	4	
Density (calculated)	1.286 Mg/m^3	
Absorption coefficient	0.138 mm^{-1}	
F(000)	1008	
Crystal size	0.141 x 0.055 x 0.029 mm^3	
Theta range for data collection	2.430 to 25.712°.	
Index ranges	-16<=h<=19, -11<=k<=12, -19<=l<=16	
Reflections collected	9329	
Independent reflections	4491 [R(int) = 0.1055]	
Completeness to theta = 25.242°	97.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.829 and 0.816	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4491 / 0 / 308	
Goodness-of-fit on F^2	1.009	
Final R indices [I>2sigma(I)]	R1 = 0.0718, wR2 = 0.1292	
R indices (all data)	R1 = 0.1535, wR2 = 0.1574	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.330 and -0.341 $e.Å^{-3}$	

Table E.15. ($x10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 x\ 10^3$) for JLW55. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
Si(1)	8226(1)	6192(1)	175(1)	28(1)
O(1)	8805(2)	10634(2)	-511(2)	24(1)
O(2)	6438(2)	10510(3)	-1594(2)	33(1)
O(3)	6912(2)	12206(2)	-701(2)	25(1)
O(4)	8073(2)	8473(2)	-1803(2)	27(1)
O(5)	9904(2)	10007(3)	1485(2)	36(1)
O(6)	8018(1)	7833(2)	13(1)	22(1)
N(1)	8511(2)	10829(3)	824(2)	18(1)
N(2)	6734(2)	7467(3)	-1859(2)	22(1)
C(1)	7375(2)	10002(3)	-250(2)	19(1)
C(2)	7345(2)	8521(3)	-563(2)	20(1)
C(3)	6443(2)	8000(4)	-573(2)	22(1)
C(4)	5961(2)	8242(4)	30(3)	28(1)
C(5)	6421(2)	8986(4)	809(2)	30(1)
C(6)	7023(2)	10137(4)	591(2)	22(1)
C(7)	7831(2)	10456(4)	1307(2)	20(1)
C(8)	8320(2)	10514(3)	-10(2)	17(1)
C(9)	7449(2)	8211(3)	-1487(2)	20(1)
C(10)	6113(2)	7383(4)	-1344(2)	23(1)
C(11)	5276(2)	6873(4)	-1504(3)	34(1)
C(12)	4794(3)	7045(4)	-875(3)	42(1)
C(13)	5103(2)	7741(4)	-126(3)	37(1)
C(14)	6857(2)	10914(4)	-926(2)	21(1)
C(15)	6402(2)	13150(4)	-1297(3)	33(1)
C(16)	7604(3)	11646(4)	1829(2)	30(1)
C(17)	8158(2)	9295(4)	1909(2)	29(1)
C(18)	6605(3)	6958(4)	-2722(2)	33(1)
C(19)	9399(2)	11145(4)	1200(2)	24(1)
C(20)	9823(3)	12289(4)	844(3)	34(1)
C(21)	9598(3)	12422(4)	1704(3)	43(1)
C(22)	7353(3)	5361(4)	628(3)	43(1)
C(23)	8340(3)	5308(4)	-812(3)	37(1) C(24)
	9269(3)	6196(4)	959(3)	44(1)

Table E.16. Bond lengths [Å] for cyclopropyl hemiaminal **3.70**

Atom-Atom	Bond lengths [Å]	Atom-Atom	Bond lengths [Å]
Si(1)-O(6)	1.665(2)	C(10)-C(11)	1.376(5)
Si(1)-C(23)	1.855(4)	C(11)-C(12)	1.387(6)
Si(1)-C(24)	1.856(4)	C(11)-H(11)	0.9500
Si(1)-C(22)	1.858(4)	C(12)-C(13)	1.393(6)
O(1)-C(8)	1.217(4)	C(12)-H(12)	0.9500
O(2)-C(14)	1.214(4)	C(13)-H(13)	0.9500
O(3)-C(14)	1.325(4)	C(15)-H(15A)	0.9800
O(3)-C(15)	1.459(4)	C(15)-H(15B)	0.9800
O(4)-C(9)	1.213(4)	C(15)-H(15C)	0.9800
O(5)-C(19)	1.399(4)	C(16)-H(16A)	0.9800
O(5)-H(5)	0.82(5)	C(16)-H(16B)	0.9800
O(6)-C(2)	1.431(4)	C(16)-H(16C)	0.9800
N(1)-C(8)	1.356(4)	C(17)-H(17A)	0.9800
N(1)-C(19)	1.435(4)	C(17)-H(17B)	0.9800
N(1)-C(7)	1.481(5)	C(17)-H(17C)	0.9800
N(2)-C(9)	1.373(4)	C(18)-H(18A)	0.9800
N(2)-C(10)	1.398(5)	C(18)-H(18B)	0.9800
N(2)-C(18)	1.457(5)	C(18)-H(18C)	0.9800
C(1)-C(14)	1.520(5)	C(19)-C(20)	1.482(5)
C(1)-C(8)	1.536(5)	C(19)-C(21)	1.501(5)
C(1)-C(2)	1.546(5)	C(20)-C(21)	1.504(6)
C(1)-C(6)	1.565(5)	C(20)-H(20A)	0.9900
C(2)-C(3)	1.495(5)	C(20)-H(20B)	0.9900
C(2)-C(9)	1.560(5)	C(21)-H(21A)	0.9900
C(3)-C(4)	1.362(5)	C(21)-H(21B)	0.9900
C(3)-C(10)	1.391(5)	C(22)-H(22A)	0.9800
C(4)-C(13)	1.403(5)	C(22)-H(22B)	0.9800
C(4)-C(5)	1.511(5)	C(22)-H(22C)	0.9800
C(5)-C(6)	1.559(5)	C(23)-H(23A)	0.9800
C(5)-H(5A)	0.9900	C(23)-H(23B)	0.9800
C(5)-H(5B)	0.9900	C(23)-H(23C)	0.9800
C(6)-C(7)	1.567(5)	C(24)-H(24A)	0.9800
C(6)-H(6)	1.0000	C(24)-H(24B)	0.9800
C(7)-C(17)	1.525(5)	C(24)-H(24C)	0.9800
C(7)-C(16)	1.528(5)		

Table E.17. Bond angles [°] for cyclopropyl hemiaminal **3.70**

Atom-Atom-Atom	Bond angles [°]	Atom-Atom-Atom	Bond angles [°]
O(6)-Si(1)-C(23)	111.85(16)	C(12)-C(13)-H(13)	120.4
O(6)-Si(1)-C(24)	102.86(16)	C(4)-C(13)-H(13)	120.4
C(23)-Si(1)-C(24)	111.6(2)	O(2)-C(14)-O(3)	123.7(3)
O(6)-Si(1)-C(22)	110.94(17)	O(2)-C(14)-C(1)	124.1(3)
C(23)-Si(1)-C(22)	109.3(2)	O(3)-C(14)-C(1)	112.2(3)
C(24)-Si(1)-C(22)	110.3(2)	O(3)-C(15)-H(15A)	109.5
C(14)-O(3)-C(15)	115.9(3)	O(3)-C(15)-H(15B)	109.5
C(19)-O(5)-H(5)	106(3)	H(15A)-C(15)-H(15B)	109.5
C(2)-O(6)-Si(1)	131.3(2)	O(3)-C(15)-H(15C)	109.5
C(8)-N(1)-C(19)	118.5(3)	H(15A)-C(15)-H(15C)	109.5
C(8)-N(1)-C(7)	115.1(3)	H(15B)-C(15)-H(15C)	109.5
C(19)-N(1)-C(7)	124.3(3)	C(7)-C(16)-H(16A)	109.5
C(9)-N(2)-C(10)	111.7(3)	C(7)-C(16)-H(16B)	109.5
C(9)-N(2)-C(18)	123.5(3)	H(16A)-C(16)-H(16B)	109.5
C(10)-N(2)-C(18)	124.5(3)	C(7)-C(16)-H(16C)	109.5
C(14)-C(1)-C(8)	109.5(3)	H(16A)-C(16)-H(16C)	109.5
C(14)-C(1)-C(2)	110.4(3)	H(16B)-C(16)-H(16C)	109.5
C(8)-C(1)-C(2)	111.1(3)	C(7)-C(17)-H(17A)	109.5
C(14)-C(1)-C(6)	110.2(3)	C(7)-C(17)-H(17B)	109.5
C(8)-C(1)-C(6)	103.6(3)	H(17A)-C(17)-H(17B)	109.5
C(2)-C(1)-C(6)	111.8(3)	C(7)-C(17)-H(17C)	109.5
O(6)-C(2)-C(3)	114.4(3)	H(17A)-C(17)-H(17C)	109.5
O(6)-C(2)-C(1)	105.4(3)	H(17B)-C(17)-H(17C)	109.5
C(3)-C(2)-C(1)	107.3(3)	N(2)-C(18)-H(18A)	109.5
O(6)-C(2)-C(9)	109.1(3)	N(2)-C(18)-H(18B)	109.5
C(3)-C(2)-C(9)	101.3(3)	H(18A)-C(18)-H(18B)	109.5
C(1)-C(2)-C(9)	119.7(3)	N(2)-C(18)-H(18C)	109.5
C(4)-C(3)-C(10)	123.8(3)	H(18A)-C(18)-H(18C)	109.5
C(4)-C(3)-C(2)	125.6(3)	H(18B)-C(18)-H(18C)	109.5
C(10)-C(3)-C(2)	110.1(3)	O(5)-C(19)-N(1)	113.6(3)
C(3)-C(4)-C(13)	116.8(4)	O(5)-C(19)-C(20)	118.4(3)
C(3)-C(4)-C(5)	116.2(3)	N(1)-C(19)-C(20)	118.0(3)
C(13)-C(4)-C(5)	127.0(4)	O(5)-C(19)-C(21)	117.0(3)
C(4)-C(5)-C(6)	112.1(3)	N(1)-C(19)-C(21)	119.5(3)
C(4)-C(5)-H(5A)	109.2	C(20)-C(19)-C(21)	60.5(3)
C(6)-C(5)-H(5A)	109.2	C(19)-C(20)-C(21)	60.3(3)
C(4)-C(5)-H(5B)	109.2	C(19)-C(20)-H(20A)	117.7
C(6)-C(5)-H(5B)	109.2	C(21)-C(20)-H(20A)	117.7
H(5A)-C(5)-H(5B)	107.9	C(19)-C(20)-H(20B)	117.7
C(5)-C(6)-C(1)	117.5(3)	C(21)-C(20)-H(20B)	117.7
C(5)-C(6)-C(7)	114.4(3)	H(20A)-C(20)-H(20B)	114.9
C(1)-C(6)-C(7)	106.8(3)	C(19)-C(21)-C(20)	59.1(3)
C(5)-C(6)-H(6)	105.7	C(19)-C(21)-H(21A)	117.9
C(1)-C(6)-H(6)	105.7	C(20)-C(21)-H(21A)	117.9
C(7)-C(6)-H(6)	105.7	C(19)-C(21)-H(21B)	117.9
N(1)-C(7)-C(17)	109.8(3)	C(20)-C(21)-H(21B)	117.9
N(1)-C(7)-C(16)	111.5(3)	H(21A)-C(21)-H(21B)	115.0
C(17)-C(7)-C(16)	108.2(3)	Si(1)-C(22)-H(22A)	109.5
N(1)-C(7)-C(6)	102.5(3)	Si(1)-C(22)-H(22B)	109.5
C(17)-C(7)-C(6)	116.1(3)	H(22A)-C(22)-H(22B)	109.5
C(16)-C(7)-C(6)	108.7(3)	Si(1)-C(22)-H(22C)	109.5
O(1)-C(8)-N(1)	126.3(3)	H(22A)-C(22)-H(22C)	109.5

O(1)-C(8)-C(1)	123.9(3)	H(22B)-C(22)-H(22C)	109.5
N(1)-C(8)-C(1)	109.8(3)	Si(1)-C(23)-H(23A)	109.5
O(4)-C(9)-N(2)	125.5(3)	Si(1)-C(23)-H(23B)	109.5
O(4)-C(9)-C(2)	127.0(3)	H(23A)-C(23)-H(23B)	109.5
N(2)-C(9)-C(2)	107.2(3)	Si(1)-C(23)-H(23C)	109.5
C(11)-C(10)-C(3)	120.1(4)	H(23A)-C(23)-H(23C)	109.5
C(11)-C(10)-N(2)	130.7(4)	H(23B)-C(23)-H(23C)	109.5
C(3)-C(10)-N(2)	109.1(3)	Si(1)-C(24)-H(24A)	109.5
C(10)-C(11)-C(12)	116.6(4)	Si(1)-C(24)-H(24B)	109.5
C(10)-C(11)-H(11)	121.7	H(24A)-C(24)-H(24B)	109.5
C(12)-C(11)-H(11)	121.7	Si(1)-C(24)-H(24C)	109.5
C(11)-C(12)-C(13)	123.3(4)	H(24A)-C(24)-H(24C)	109.5
C(11)-C(12)-H(12)	118.3	H(24B)-C(24)-H(24C)	109.5
C(13)-C(12)-H(12)	118.3		
C(12)-C(13)-C(4)	119.1(4)		

Table E.18. [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(5)-H(5)...O(1)#1	0.82(5)	2.05(5)	2.858(4)	168(4)
C(15)-H(15A)...O(4)#2	0.98	2.37	3.340(5)	168.2
C(17)-H(17A)...O(6)	0.98	2.57	3.352(5)	136.7
C(17)-H(17C)...O(5)	0.98	2.50	3.021(5)	113.0
C(20)-H(20B)...O(4)#1	0.99	2.62	3.429(5)	138.7

*E.5. Crystal Structure Analysis of Imidoyl Triflate **3.73***

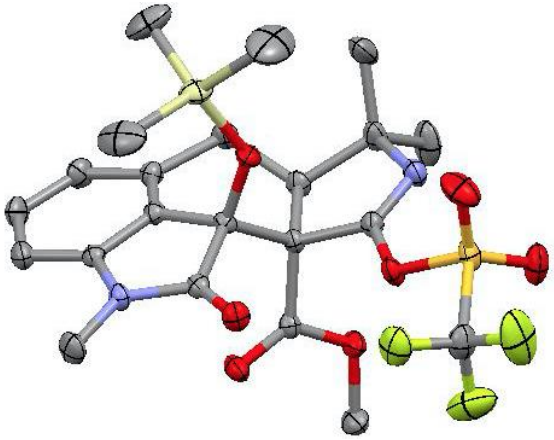

Figure E.05. ORTEP drawing of imidoyl triflate **3.73**

Table E.19 Crystal data and structure refinement imidoyl triflate **3.73**

Identification code	jlw56	
Empirical formula	$C_{22}H_{27}F_3N_2O_7SSi$	
Formula weight	548.60	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 10.6980(4) Å	α= 90°.
	b = 15.2272(6) Å	β= 105.5150(14)°.
	c = 16.6580(7) Å	γ= 90°.
Volume	2614.72(18) $Å^3$	
Z	4	
Density (calculated)	1.394 Mg/m^3	
Absorption coefficient	0.235 mm^{-1}	
F(000)	1144	
Crystal size	0.196 x 0.124 x 0.081 mm^3	
Theta range for data collection	2.386 to 28.324°.	
Index ranges	-14<=h<=14, -20<=k<=20, -22<=l<=22	
Reflections collected	62465	
Independent reflections	6506 [R(int) = 0.0520]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.946 and 0.921	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6506 / 0 / 332	
Goodness-of-fit on F^2	1.027	
Final R indices [I>2sigma(I)]	R1 = 0.0396, wR2 = 0.0910	
R indices (all data)	R1 = 0.0587, wR2 = 0.0990	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.399 and -0.355 $e.Å^{-3}$	

Table E.20. ($x10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 x\ 10^3$) for jlw56. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
S(1)	741(1)	9177(1)	2241(1)	23(1)
Si(2)	3614(1)	6224(1)	2050(1)	27(1)
F(1)	1842(1)	10691(1)	2660(1)	56(1)
F(2)	2818(1)	9632(1)	3414(1)	41(1)
F(3)	1005(1)	10095(1)	3561(1)	65(1)
O(1)	4691(1)	8690(1)	2550(1)	24(1)
O(2)	4451(1)	9469(1)	729(1)	25(1)
O(3)	2378(1)	9839(1)	136(1)	25(1)
O(4)	3133(1)	7195(1)	1605(1)	21(1)
O(5)	1836(1)	9052(1)	1777(1)	23(1)
O(6)	577(1)	8400(1)	2666(1)	41(1)
O(7)	-331(1)	9647(1)	1755(1)	37(1)
N(1)	494(1)	8268(1)	679(1)	24(1)
N(2)	6054(1)	8035(1)	1865(1)	19(1)
C(1)	2742(1)	8417(1)	699(1)	16(1)
C(2)	1588(1)	8557(1)	1040(1)	19(1)
C(3)	595(2)	7795(1)	-84(1)	26(1)
C(4)	2027(1)	7946(1)	-146(1)	20(1)
C(5)	2698(2)	7127(1)	-398(1)	24(1)
C(6)	4148(2)	7147(1)	-64(1)	20(1)
C(7)	4612(1)	7467(1)	728(1)	17(1)
C(8)	3806(1)	7829(1)	1254(1)	16(1)
C(9)	4864(1)	8271(1)	1972(1)	17(1)
C(10)	5920(1)	7581(1)	1113(1)	18(1)
C(11)	6846(2)	7291(1)	730(1)	24(1)
C(12)	6381(2)	6917(1)	-62(1)	28(1)
C(13)	5068(2)	6856(1)	-468(1)	26(1)
C(14)	3316(1)	9295(1)	530(1)	18(1)
C(15)	2800(2)	10682(1)	-106(1)	27(1)
C(16)	-362(2)	8214(2)	-833(1)	43(1)
C(17)	228(2)	6840(1)	19(2)	41(1)
C(18)	7277(2)	8272(1)	2439(1)	30(1)
C(19)	1687(2)	9950(1)	3016(1)	32(1)
C(20)	3587(2)	5381(1)	1248(1)	49(1)
C(21)	5250(2)	6276(2)	2779(1)	55(1) C(22)
	2388(3)	6011(2)	2624(2)	71(1)

Table E.21. Bond lengths [Å] for imidoyl triflate **3.73**

Atom-Atom	Bond lengths [Å]	Atom-Atom	Bond lengths [Å]
S(1)-O(7)	1.4093(13)	N(2)-C(10)	1.4027(19)
S(1)-O(6)	1.4136(14)	N(2)-C(18)	1.4449(19)
S(1)-O(5)	1.5779(11)	C(1)-C(2)	1.506(2)
S(1)-C(19)	1.8371(18)	C(1)-C(14)	1.529(2)
Si(2)-O(4)	1.6725(11)	C(1)-C(8)	1.545(2)
Si(2)-C(21)	1.846(2)	C(1)-C(4)	1.583(2)
Si(2)-C(20)	1.847(2)	C(3)-C(16)	1.526(2)
Si(2)-C(22)	1.847(2)	C(3)-C(17)	1.528(3)
F(1)-C(19)	1.305(2)	C(3)-C(4)	1.580(2)
F(2)-C(19)	1.307(2)	C(4)-C(5)	1.551(2)
F(3)-C(19)	1.327(2)	C(5)-C(6)	1.501(2)
O(1)-C(9)	1.2105(18)	C(6)-C(7)	1.370(2)
O(2)-C(14)	1.1996(18)	C(6)-C(13)	1.404(2)
O(3)-C(14)	1.3304(18)	C(7)-C(10)	1.385(2)
O(3)-C(15)	1.4533(19)	C(7)-C(8)	1.491(2)
O(4)-C(8)	1.4197(17)	C(8)-C(9)	1.561(2)
O(5)-C(2)	1.4042(18)	C(10)-C(11)	1.386(2)
N(1)-C(2)	1.245(2)	C(11)-C(12)	1.401(2)
N(1)-C(3)	1.490(2)	C(12)-C(13)	1.389(2)
N(2)-C(9)	1.3798(19)		

Table E.22. Bond angles [°] for imidoyl triflate **3.73**

Atom-Atom-Atom	Bond angles [°]	Atom-Atom-Atom	Bond angles [°]
O(7)-S(1)-O(6)	121.44(9)	C(5)-C(4)-C(1)	117.13(12)
O(7)-S(1)-O(5)	112.09(7)	C(3)-C(4)-C(1)	104.70(12)
O(6)-S(1)-O(5)	110.63(8)	C(6)-C(5)-C(4)	113.01(13)
O(7)-S(1)-C(19)	106.81(8)	C(7)-C(6)-C(13)	116.96(14)
O(6)-S(1)-C(19)	107.68(8)	C(7)-C(6)-C(5)	115.86(13)
O(5)-S(1)-C(19)	94.56(7)	C(13)-C(6)-C(5)	127.16(14)
O(4)-Si(2)-C(21)	112.31(8)	C(6)-C(7)-C(10)	123.55(13)
O(4)-Si(2)-C(20)	110.45(8)	C(6)-C(7)-C(8)	125.48(13)
C(21)-Si(2)-C(20)	109.55(12)	C(10)-C(7)-C(8)	110.64(13)
O(4)-Si(2)-C(22)	101.99(10)	O(4)-C(8)-C(7)	115.25(12)
C(21)-Si(2)-C(22)	110.28(13)	O(4)-C(8)-C(1)	105.48(11)
C(20)-Si(2)-C(22)	112.12(13)	C(7)-C(8)-C(1)	108.17(11)
C(14)-O(3)-C(15)	115.97(12)	O(4)-C(8)-C(9)	108.80(11)
C(8)-O(4)-Si(2)	130.82(9)	C(7)-C(8)-C(9)	101.21(11)
C(2)-O(5)-S(1)	120.07(9)	C(1)-C(8)-C(9)	118.37(12)
C(2)-N(1)-C(3)	108.03(13)	O(1)-C(9)-N(2)	125.64(13)
C(9)-N(2)-C(10)	111.47(12)	O(1)-C(9)-C(8)	127.08(13)
C(9)-N(2)-C(18)	123.58(13)	N(2)-C(9)-C(8)	107.09(12)
C(10)-N(2)-C(18)	124.87(13)	C(7)-C(10)-C(11)	120.24(14)
C(2)-C(1)-C(14)	110.83(12)	C(7)-C(10)-N(2)	108.96(12)
C(2)-C(1)-C(8)	113.76(12)	C(11)-C(10)-N(2)	130.75(14)
C(14)-C(1)-C(8)	110.44(11)	C(10)-C(11)-C(12)	116.49(14)
C(2)-C(1)-C(4)	98.63(11)	C(13)-C(12)-C(11)	122.96(15)
C(14)-C(1)-C(4)	110.77(12)	C(12)-C(13)-C(6)	119.51(15)
C(8)-C(1)-C(4)	111.92(12)	O(2)-C(14)-O(3)	124.97(14)
N(1)-C(2)-O(5)	123.10(14)	O(2)-C(14)-C(1)	124.64(13)
N(1)-C(2)-C(1)	121.84(14)	O(3)-C(14)-C(1)	110.39(12)
O(5)-C(2)-C(1)	115.05(12)	F(1)-C(19)-F(2)	109.76(16)
N(1)-C(3)-C(16)	108.05(14)	F(1)-C(19)-F(3)	109.07(16)
N(1)-C(3)-C(17)	106.58(15)	F(2)-C(19)-F(3)	108.51(15)
C(16)-C(3)-C(17)	110.67(16)	F(1)-C(19)-S(1)	110.40(12)
N(1)-C(3)-C(4)	106.18(12)	F(2)-C(19)-S(1)	112.32(13)
C(16)-C(3)-C(4)	109.62(15)	F(3)-C(19)-S(1)	106.66(13)
C(17)-C(3)-C(4)	115.37(14)		
C(5)-C(4)-C(3)	115.31(13)		

*E.6. Crystal Structure Analysis of Vinylogous Amide **3.86***

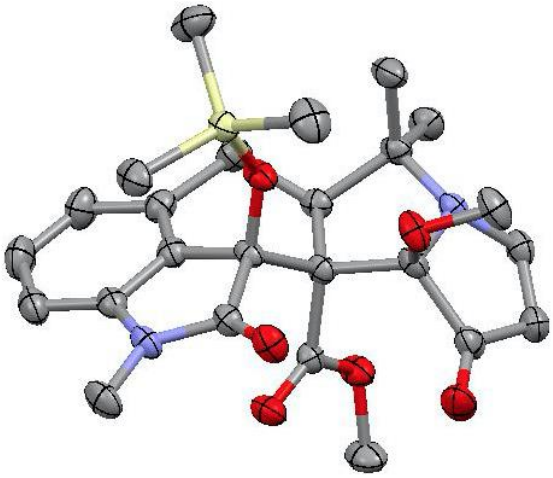

Figure E.06. ORTEP drawing of vinylogous amide **3.86**

Table E.23 Crystal data and structure refinement vinylogous amide **3.86**

Identification code	jlw60	
Empirical formula	$C_{25}H_{32}N_2O_6Si$	
Formula weight	484.61	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.2475(3) Å	α= 90.3290(10)°.
	b = 15.4739(5) Å	β= 96.8740(10)°.
	c = 15.5849(5) Å	γ= 91.8260(10)°.
Volume	2452.15(13) $Å^3$	
Z	4	
Density (calculated)	1.313 Mg/m^3	
Absorption coefficient	0.139 mm^{-1}	
F(000)	1032	
Crystal size	0.197 x 0.121 x 0.108 mm^3	
Theta range for data collection	2.261 to 26.427°.	
Index ranges	-12<=h<=12, -19<=k<=19, -19<=l<=19	
Reflections collected	38788	
Independent reflections	10074 [R(int) = 0.0364]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.933 and 0.922	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10074 / 0 / 629	
Goodness-of-fit on F^2	1.041	
Final R indices [I>2sigma(I)]	R1 = 0.0465, wR2 = 0.1127	
R indices (all data)	R1 = 0.0645, wR2 = 0.1219	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.433 and -0.299 $e.Å^{-3}$	

Table E.24. ($x10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 x\ 10^3$) for jlw60. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
Si(1)	10639(1)	6526(1)	3921(1)	26(1)
Si(2)	8194(1)	8320(1)	8709(1)	22(1)
O(1)	6189(1)	5876(1)	726(1)	31(1)
O(2)	7017(2)	7189(1)	1127(1)	32(1)
O(3)	9599(1)	6197(1)	3090(1)	30(1)
O(4)	7908(2)	7790(1)	3082(1)	34(1)
O(5)	4854(2)	6535(1)	2408(1)	42(1)
O(6)	7161(2)	5826(1)	3429(1)	32(1)
O(7)	3495(1)	8550(1)	6858(1)	25(1)
O(8)	3799(1)	9077(1)	5566(1)	31(1)
O(9)	6591(1)	7223(1)	6809(1)	22(1)
O(10)	7382(1)	8660(1)	7797(1)	20(1)
O(11)	5092(1)	7653(1)	8391(1)	23(1)
O(12)	3877(1)	6893(1)	6011(1)	33(1)
N(1)	9360(2)	8056(1)	2094(1)	29(1)
N(2)	6718(2)	4652(1)	2426(1)	26(1)
N(3)	6801(2)	7915(1)	5453(1)	20(1)
N(4)	4589(2)	9065(1)	8582(1)	22(1)
C(1)	4567(2)	5002(1)	2117(1)	33(1)
C(2)	5257(2)	5808(1)	2339(1)	31(1)
C(3)	6747(2)	5585(1)	2566(1)	26(1)
C(4)	7778(2)	5945(1)	1966(1)	23(1)
C(5)	8902(2)	6579(1)	2356(1)	23(1)
C(6)	9802(2)	6702(1)	1683(1)	26(1)
C(7)	10085(2)	7573(1)	1563(1)	28(1)
C(8)	10972(2)	7820(2)	1003(1)	37(1)
C(9)	11523(2)	7161(2)	571(2)	42(1)
C(10)	5199(2)	6273(2)	135(2)	42(1)
C(11)	6984(2)	6422(1)	1227(1)	24(1)
C(12)	9730(3)	6449(2)	4876(2)	47(1)
C(13)	11295(2)	7651(1)	3842(2)	38(1)
C(14)	11987(2)	5761(2)	3969(2)	49(1)
C(15)	8588(2)	7530(1)	2556(1)	26(1)
C(16)	9388(2)	8990(1)	2165(2)	38(1)
C(17)	11214(2)	6285(2)	677(2)	38(1)
C(18)	10317(2)	6049(1)	1250(1)	30(1)
C(19)	9878(2)	5152(1)	1493(1)	32(1)
C(20)	8394(2)	5098(1)	1611(1)	25(1)
C(21)	7957(2)	4332(1)	2169(1)	27(1)
C(22)	5461(2)	4373(1)	2146(1)	30(1)
C(23)	6432(3)	5399(1)	4037(1)	38(1)
C(24)	8875(2)	4151(1)	2987(2)	37(1)
C(25)	7730(2)	3504(1)	1638(2)	34(1)
C(26)	4916(2)	11370(1)	7904(1)	32(1)
C(27)	5758(2)	11241(1)	7284(1)	29(1)
C(28)	6194(2)	10413(1)	7133(1)	22(1)
C(29)	7074(2)	10135(1)	6481(1)	23(1)
C(30)	6530(2)	9296(1)	6010(1)	18(1)
C(31)	5708(2)	8646(1)	6532(1)	17(1)
C(32)	5976(2)	7732(1)	6147(1)	18(1)

C(33)	4749(2)	7226(1)	5643(1)	24(1)
C(34)	4965(2)	7223(1)	4756(1)	29(1)
C(35)	2098(2)	8578(2)	6613(2)	37(1)
C(36)	4241(2)	8803(1)	6256(1)	20(1)
C(37)	7010(2)	6415(1)	6511(1)	28(1)
C(38)	7539(2)	8754(1)	5592(1)	21(1)
C(39)	5761(2)	9757(1)	7633(1)	18(1)
C(40)	6041(2)	8823(1)	7531(1)	17(1)
C(41)	9898(2)	8737(2)	8655(2)	41(1)
C(42)	8217(2)	7123(1)	8772(2)	38(1)
C(43)	7574(2)	8784(2)	9677(1)	37(1)
C(44)	5162(2)	8405(1)	8187(1)	19(1)
C(45)	3734(2)	8931(1)	9246(1)	33(1)
C(46)	4899(2)	9878(1)	8236(1)	22(1)
C(47)	4460(2)	10692(1)	8391(1)	28(1)
C(48)	7847(2)	9151(1)	4743(1)	30(1)
C(49)	8825(2)	8591(1)	6158(1)	28(1)
C(50)	6111(2)	7658(1)	4680(1)	25(1)

Table E.25. Bond lengths [Å] for vinylogous amide **3.86**

Atom-Atom	Bond lengths [Å]	Atom-Atom	Bond lengths [Å]
Si(1)-O(3)	1.6436(14)	C(18)-C(19)	1.509(3)
Si(1)-C(14)	1.843(2)	C(19)-C(20)	1.553(3)
Si(1)-C(12)	1.850(2)	C(19)-H(17)	0.9900
Si(1)-C(13)	1.855(2)	C(19)-H(18)	0.9900
Si(2)-O(10)	1.6567(13)	C(20)-C(21)	1.560(3)
Si(2)-C(41)	1.854(2)	C(20)-H(19)	1.0000
Si(2)-C(43)	1.855(2)	C(21)-C(25)	1.518(3)
Si(2)-C(42)	1.856(2)	C(21)-C(24)	1.525(3)
O(1)-C(11)	1.335(2)	C(22)-H(23)	0.9500
O(1)-C(10)	1.441(3)	C(23)-H(21)	0.9800
O(2)-C(11)	1.198(2)	C(23)-H(20)	0.9800
O(3)-C(5)	1.417(2)	C(23)-H(22)	0.9800
O(4)-C(15)	1.213(2)	C(24)-H(24)	0.9800
O(5)-C(2)	1.219(3)	C(24)-H(25)	0.9800
O(6)-C(3)	1.406(2)	C(24)-H(26)	0.9800
O(6)-C(23)	1.427(2)	C(25)-H(29)	0.9800
O(7)-C(36)	1.332(2)	C(25)-H(27)	0.9800
O(7)-C(35)	1.438(2)	C(25)-H(28)	0.9800
O(8)-C(36)	1.202(2)	C(26)-C(27)	1.388(3)
O(9)-C(32)	1.403(2)	C(26)-C(47)	1.401(3)
O(9)-C(37)	1.427(2)	C(26)-H(33)	0.9500
O(10)-C(40)	1.419(2)	C(27)-C(28)	1.398(3)
O(11)-C(44)	1.210(2)	C(27)-H(51)	0.9500
O(12)-C(33)	1.221(2)	C(28)-C(39)	1.377(3)
N(1)-C(15)	1.380(3)	C(28)-C(29)	1.505(3)
N(1)-C(7)	1.404(3)	C(29)-C(30)	1.543(3)
N(1)-C(16)	1.449(3)	C(29)-H(54)	0.9900
N(2)-C(22)	1.366(3)	C(29)-H(53)	0.9900
N(2)-C(3)	1.457(2)	C(30)-C(38)	1.552(3)
N(2)-C(21)	1.476(3)	C(30)-C(31)	1.581(2)
N(3)-C(50)	1.372(2)	C(30)-H(55)	1.0000
N(3)-C(32)	1.474(2)	C(31)-C(36)	1.540(3)
N(3)-C(38)	1.483(2)	C(31)-C(40)	1.574(2)
N(4)-C(44)	1.373(2)	C(31)-C(32)	1.577(2)
N(4)-C(46)	1.413(2)	C(32)-C(33)	1.582(3)
N(4)-C(45)	1.446(2)	C(33)-C(34)	1.426(3)
C(1)-C(22)	1.355(3)	C(34)-C(50)	1.353(3)
C(1)-C(2)	1.433(3)	C(34)-H(34)	0.9500
C(1)-H(1)	0.9500	C(35)-H(63)	0.9800
C(2)-C(3)	1.575(3)	C(35)-H(35)	0.9800
C(3)-C(4)	1.583(3)	C(35)-H(64)	0.9800
C(4)-C(11)	1.536(3)	C(37)-H(38)	0.9800
C(4)-C(5)	1.553(3)	C(37)-H(37)	0.9800
C(4)-C(20)	1.596(3)	C(37)-H(36)	0.9800
C(5)-C(6)	1.487(3)	C(38)-C(49)	1.525(3)
C(5)-C(15)	1.555(3)	C(38)-C(48)	1.525(3)
C(6)-C(18)	1.366(3)	C(39)-C(46)	1.381(3)
C(6)-C(7)	1.387(3)	C(39)-C(40)	1.494(2)
C(7)-C(8)	1.381(3)	C(40)-C(44)	1.571(2)
C(8)-C(9)	1.389(3)	C(41)-H(39)	0.9800
C(8)-H(30)	0.9500	C(41)-H(41)	0.9800
C(9)-C(17)	1.398(3)	C(41)-H(40)	0.9800

C(9)-H(2)	0.9500	C(42)-H(43)	0.9800
C(10)-H(32)	0.9800	C(42)-H(44)	0.9800
C(10)-H(3)	0.9800	C(42)-H(42)	0.9800
C(10)-H(31)	0.9800	C(43)-H(46)	0.9800
C(12)-H(6)	0.9800	C(43)-H(45)	0.9800
C(12)-H(5)	0.9800	C(43)-H(47)	0.9800
C(12)-H(4)	0.9800	C(45)-H(49)	0.9800
C(13)-H(9)	0.9800	C(45)-H(48)	0.9800
C(13)-H(7)	0.9800	C(45)-H(50)	0.9800
C(13)-H(8)	0.9800	C(46)-C(47)	1.379(3)
C(14)-H(10)	0.9800	C(47)-H(52)	0.9500
C(14)-H(12)	0.9800	C(48)-H(56)	0.9800
C(14)-H(11)	0.9800	C(48)-H(57)	0.9800
C(16)-H(13)	0.9800	C(48)-H(58)	0.9800
C(16)-H(14)	0.9800	C(49)-H(59)	0.9800
C(16)-H(15)	0.9800	C(49)-H(60)	0.9800
C(17)-C(18)	1.399(3)	C(49)-H(61)	0.9800
C(17)-H(16)	0.9500	C(50)-H(62)	0.9500

Table E.26. Bond angles [°] for vinylogous amide **3.86**

Atom-Atom-Atom	Bond angles [°]	Atom-Atom-Atom	Bond angles [°]
O(3)-Si(1)-C(14)	104.65(10)	O(6)-C(23)-H(22)	109.5
O(3)-Si(1)-C(12)	106.17(10)	H(21)-C(23)-H(22)	109.5
C(14)-Si(1)-C(12)	112.29(13)	H(20)-C(23)-H(22)	109.5
O(3)-Si(1)-C(13)	114.65(9)	C(21)-C(24)-H(24)	109.5
C(14)-Si(1)-C(13)	110.14(12)	C(21)-C(24)-H(25)	109.5
C(12)-Si(1)-C(13)	108.91(12)	H(24)-C(24)-H(25)	109.5
O(10)-Si(2)-C(41)	103.39(9)	C(21)-C(24)-H(26)	109.5
O(10)-Si(2)-C(43)	112.27(9)	H(24)-C(24)-H(26)	109.5
C(41)-Si(2)-C(43)	109.16(12)	H(25)-C(24)-H(26)	109.5
O(10)-Si(2)-C(42)	112.65(9)	C(21)-C(25)-H(29)	109.5
C(41)-Si(2)-C(42)	108.35(12)	C(21)-C(25)-H(27)	109.5
C(43)-Si(2)-C(42)	110.66(11)	H(29)-C(25)-H(27)	109.5
C(11)-O(1)-C(10)	115.52(16)	C(21)-C(25)-H(28)	109.5
C(5)-O(3)-Si(1)	136.69(12)	H(29)-C(25)-H(28)	109.5
C(3)-O(6)-C(23)	113.60(16)	H(27)-C(25)-H(28)	109.5
C(36)-O(7)-C(35)	115.60(15)	C(27)-C(26)-C(47)	122.28(19)
C(32)-O(9)-C(37)	113.53(14)	C(27)-C(26)-H(33)	118.9
C(40)-O(10)-Si(2)	133.73(11)	C(47)-C(26)-H(33)	118.9
C(15)-N(1)-C(7)	111.77(16)	C(26)-C(27)-C(28)	120.22(18)
C(15)-N(1)-C(16)	122.68(18)	C(26)-C(27)-H(51)	119.9
C(7)-N(1)-C(16)	125.55(17)	C(28)-C(27)-H(51)	119.9
C(22)-N(2)-C(3)	109.32(17)	C(39)-C(28)-C(27)	116.68(18)
C(22)-N(2)-C(21)	128.23(17)	C(39)-C(28)-C(29)	114.93(16)
C(3)-N(2)-C(21)	113.31(15)	C(27)-C(28)-C(29)	128.38(17)
C(50)-N(3)-C(32)	108.46(15)	C(28)-C(29)-C(30)	111.01(15)
C(50)-N(3)-C(38)	123.96(15)	C(28)-C(29)-H(54)	109.4
C(32)-N(3)-C(38)	111.87(14)	C(30)-C(29)-H(54)	109.4
C(44)-N(4)-C(46)	111.73(15)	C(28)-C(29)-H(53)	109.4
C(44)-N(4)-C(45)	123.48(16)	C(30)-C(29)-H(53)	109.4
C(46)-N(4)-C(45)	124.75(16)	H(54)-C(29)-H(53)	108.0
C(22)-C(1)-C(2)	108.2(2)	C(29)-C(30)-C(38)	116.25(15)
C(22)-C(1)-H(1)	125.9	C(29)-C(30)-C(31)	117.04(15)

C(2)-C(1)-H(1)	125.9	C(38)-C(30)-C(31)	106.90(14)
O(5)-C(2)-C(1)	130.9(2)	C(29)-C(30)-H(55)	105.1
O(5)-C(2)-C(3)	122.96(19)	C(38)-C(30)-H(55)	105.1
C(1)-C(2)-C(3)	106.03(17)	C(31)-C(30)-H(55)	105.1
O(6)-C(3)-N(2)	112.93(15)	C(36)-C(31)-C(40)	109.47(14)
O(6)-C(3)-C(2)	108.94(16)	C(36)-C(31)-C(32)	105.90(14)
N(2)-C(3)-C(2)	102.31(16)	C(40)-C(31)-C(32)	119.59(14)
O(6)-C(3)-C(4)	109.60(16)	C(36)-C(31)-C(30)	107.48(14)
N(2)-C(3)-C(4)	104.19(15)	C(40)-C(31)-C(30)	110.00(14)
C(2)-C(3)-C(4)	118.70(16)	C(32)-C(31)-C(30)	103.70(14)
C(11)-C(4)-C(5)	106.89(15)	O(9)-C(32)-N(3)	113.37(14)
C(11)-C(4)-C(3)	106.25(15)	O(9)-C(32)-C(31)	109.03(14)
C(5)-C(4)-C(3)	119.14(16)	N(3)-C(32)-C(31)	105.08(13)
C(11)-C(4)-C(20)	110.68(15)	O(9)-C(32)-C(33)	110.73(14)
C(5)-C(4)-C(20)	109.52(16)	N(3)-C(32)-C(33)	102.10(14)
C(3)-C(4)-C(20)	104.26(15)	C(31)-C(32)-C(33)	116.38(14)
O(3)-C(5)-C(6)	108.91(16)	O(12)-C(33)-C(34)	131.37(19)
O(3)-C(5)-C(4)	109.20(15)	O(12)-C(33)-C(32)	122.49(17)
C(6)-C(5)-C(4)	106.57(15)	C(34)-C(33)-C(32)	106.05(16)
O(3)-C(5)-C(15)	110.62(15)	C(50)-C(34)-C(33)	108.71(18)
C(6)-C(5)-C(15)	101.20(15)	C(50)-C(34)-H(34)	125.6
C(4)-C(5)-C(15)	119.60(16)	C(33)-C(34)-H(34)	125.6
C(18)-C(6)-C(7)	123.93(19)	O(7)-C(35)-H(63)	109.5
C(18)-C(6)-C(5)	124.89(18)	O(7)-C(35)-H(35)	109.5
C(7)-C(6)-C(5)	111.17(18)	H(63)-C(35)-H(35)	109.5
C(8)-C(7)-C(6)	120.0(2)	O(7)-C(35)-H(64)	109.5
C(8)-C(7)-N(1)	131.76(19)	H(63)-C(35)-H(64)	109.5
C(6)-C(7)-N(1)	108.26(17)	H(35)-C(35)-H(64)	109.5
C(7)-C(8)-C(9)	116.7(2)	O(8)-C(36)-O(7)	123.19(17)
C(7)-C(8)-H(30)	121.7	O(8)-C(36)-C(31)	124.75(17)
C(9)-C(8)-H(30)	121.7	O(7)-C(36)-C(31)	111.95(15)
C(8)-C(9)-C(17)	123.3(2)	O(9)-C(37)-H(38)	109.5
C(8)-C(9)-H(2)	118.4	O(9)-C(37)-H(37)	109.5
C(17)-C(9)-H(2)	118.4	H(38)-C(37)-H(37)	109.5
O(1)-C(10)-H(32)	109.5	O(9)-C(37)-H(36)	109.5
O(1)-C(10)-H(3)	109.5	H(38)-C(37)-H(36)	109.5
H(32)-C(10)-H(3)	109.5	H(37)-C(37)-H(36)	109.5
O(1)-C(10)-H(31)	109.5	N(3)-C(38)-C(49)	107.80(15)
H(32)-C(10)-H(31)	109.5	N(3)-C(38)-C(48)	111.86(15)
H(3)-C(10)-H(31)	109.5	C(49)-C(38)-C(48)	109.09(16)
O(2)-C(11)-O(1)	123.54(18)	N(3)-C(38)-C(30)	100.82(14)
O(2)-C(11)-C(4)	125.07(18)	C(49)-C(38)-C(30)	116.04(16)
O(1)-C(11)-C(4)	111.31(16)	C(48)-C(38)-C(30)	111.00(15)
Si(1)-C(12)-H(6)	109.5	C(28)-C(39)-C(46)	123.35(17)
Si(1)-C(12)-H(5)	109.5	C(28)-C(39)-C(40)	124.84(17)
H(6)-C(12)-H(5)	109.5	C(46)-C(39)-C(40)	111.51(16)
Si(1)-C(12)-H(4)	109.5	O(10)-C(40)-C(39)	111.40(14)
H(6)-C(12)-H(4)	109.5	O(10)-C(40)-C(44)	109.65(13)
H(5)-C(12)-H(4)	109.5	C(39)-C(40)-C(44)	100.69(14)
Si(1)-C(13)-H(9)	109.5	O(10)-C(40)-C(31)	110.04(14)
Si(1)-C(13)-H(7)	109.5	C(39)-C(40)-C(31)	103.93(14)
H(9)-C(13)-H(7)	109.5	C(44)-C(40)-C(31)	120.47(14)
Si(1)-C(13)-H(8)	109.5	Si(2)-C(41)-H(39)	109.5
H(9)-C(13)-H(8)	109.5	Si(2)-C(41)-H(41)	109.5
H(7)-C(13)-H(8)	109.5	H(39)-C(41)-H(41)	109.5
Si(1)-C(14)-H(10)	109.5	Si(2)-C(41)-H(40)	109.5

Si(1)-C(14)-H(12)	109.5	H(39)-C(41)-H(40)	109.5
H(10)-C(14)-H(12)	109.5	H(41)-C(41)-H(40)	109.5
Si(1)-C(14)-H(11)	109.5	Si(2)-C(42)-H(43)	109.5
H(10)-C(14)-H(11)	109.5	Si(2)-C(42)-H(44)	109.5
H(12)-C(14)-H(11)	109.5	H(43)-C(42)-H(44)	109.5
O(4)-C(15)-N(1)	124.39(18)	Si(2)-C(42)-H(42)	109.5
O(4)-C(15)-C(5)	127.92(17)	H(43)-C(42)-H(42)	109.5
N(1)-C(15)-C(5)	107.28(17)	H(44)-C(42)-H(42)	109.5
N(1)-C(16)-H(13)	109.5	Si(2)-C(43)-H(46)	109.5
N(1)-C(16)-H(14)	109.5	Si(2)-C(43)-H(45)	109.5
H(13)-C(16)-H(14)	109.5	H(46)-C(43)-H(45)	109.5
N(1)-C(16)-H(15)	109.5	Si(2)-C(43)-H(47)	109.5
H(13)-C(16)-H(15)	109.5	H(46)-C(43)-H(47)	109.5
H(14)-C(16)-H(15)	109.5	H(45)-C(43)-H(47)	109.5
C(9)-C(17)-C(18)	119.0(2)	O(11)-C(44)-N(4)	124.48(17)
C(9)-C(17)-H(16)	120.5	O(11)-C(44)-C(40)	127.59(16)
C(18)-C(17)-H(16)	120.5	N(4)-C(44)-C(40)	107.50(15)
C(6)-C(18)-C(17)	117.0(2)	N(4)-C(45)-H(49)	109.5
C(6)-C(18)-C(19)	114.53(18)	N(4)-C(45)-H(48)	109.5
C(17)-C(18)-C(19)	128.4(2)	H(49)-C(45)-H(48)	109.5
C(18)-C(19)-C(20)	112.07(17)	N(4)-C(45)-H(50)	109.5
C(18)-C(19)-H(17)	109.2	H(49)-C(45)-H(50)	109.5
C(20)-C(19)-H(17)	109.2	H(48)-C(45)-H(50)	109.5
C(18)-C(19)-H(18)	109.2	C(47)-C(46)-C(39)	120.50(18)
C(20)-C(19)-H(18)	109.2	C(47)-C(46)-N(4)	131.03(18)
H(17)-C(19)-H(18)	107.9	C(39)-C(46)-N(4)	108.43(16)
C(19)-C(20)-C(21)	115.69(17)	C(46)-C(47)-C(26)	116.91(19)
C(19)-C(20)-C(4)	117.03(16)	C(46)-C(47)-H(52)	121.5
C(21)-C(20)-C(4)	106.38(15)	C(26)-C(47)-H(52)	121.5
C(19)-C(20)-H(19)	105.6	C(38)-C(48)-H(56)	109.5
C(21)-C(20)-H(19)	105.6	C(38)-C(48)-H(57)	109.5
C(4)-C(20)-H(19)	105.6	H(56)-C(48)-H(57)	109.5
N(2)-C(21)-C(25)	111.72(17)	C(38)-C(48)-H(58)	109.5
N(2)-C(21)-C(24)	108.19(17)	H(56)-C(48)-H(58)	109.5
C(25)-C(21)-C(24)	108.72(17)	H(57)-C(48)-H(58)	109.5
N(2)-C(21)-C(20)	101.07(15)	C(38)-C(49)-H(59)	109.5
C(25)-C(21)-C(20)	111.26(17)	C(38)-C(49)-H(60)	109.5
C(24)-C(21)-C(20)	115.70(17)	H(59)-C(49)-H(60)	109.5
C(1)-C(22)-N(2)	114.01(19)	C(38)-C(49)-H(61)	109.5
C(1)-C(22)-H(23)	123.0	H(59)-C(49)-H(61)	109.5
N(2)-C(22)-H(23)	123.0	H(60)-C(49)-H(61)	109.5
O(6)-C(23)-H(21)	109.5	C(34)-C(50)-N(3)	114.21(17)
O(6)-C(23)-H(20)	109.5	C(34)-C(50)-H(62)	122.9
H(21)-C(23)-H(20)	109.5	N(3)-C(50)-H(62)	122.9

*E.7. Crystal Structure Analysis of Tetramic acid **3.97***

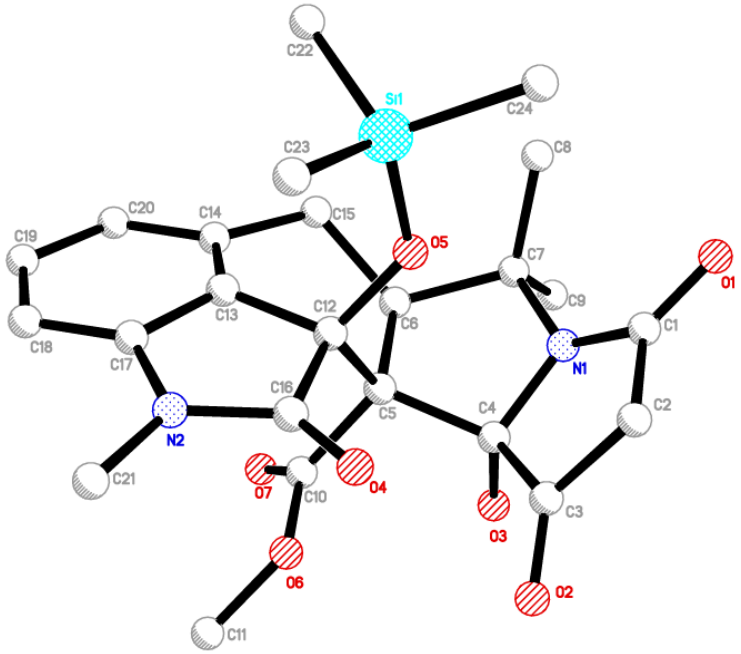

Figure E.07. ORTEP drawing of tetramic acid **3.97**

Table E.27 Crystal data and structure refinement tetramic acid **3.97**

Identification code	jlw61	
Empirical formula	$C_{24}H_{30}N_2O_8Si$	
Formula weight	502.59	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 10.9474(6) Å	α= 90°.
	b = 10.1261(6) Å	β= 90.925(2)°.
	c = 11.0142(5) Å	γ = 90°.
Volume	1220.81(11) $Å^3$	
Z	2	
Density (calculated)	1.367 Mg/m^3	
Absorption coefficient	0.148 mm^{-1}	
F(000)	532	
Crystal size	0.077 x 0.076 x 0.019 mm^3	
Theta range for data collection	2.645 to 26.024°.	
Index ranges	-13<=h<=13, -10<=k<=12, -13<=l<=12	
Reflections collected	12704	
Independent reflections	4476 [R(int) = 0.0534]	
Completeness to theta = 25.242°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.951 and 0.943	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4476 / 1 / 326	
Goodness-of-fit on F^2	1.034	
Final R indices [I>2sigma(I)]	R1 = 0.0467, wR2 = 0.1013	
R indices (all data)	R1 = 0.0622, wR2 = 0.1079	
Absolute structure parameter	-0.01(9)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.361 and -0.496 e.$Å^{-3}$	

Table E.28. ($x10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 x\ 10^3$) for jlw61. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
Si(1)	5735(1)	7477(1)	8550(1)	22(1)
O(1)	6732(3)	9699(3)	5077(3)	38(1)
O(2)	10512(2)	8703(3)	6872(2)	25(1)
O(3)	9876(3)	6847(3)	5075(2)	20(1)
O(4)	9082(2)	7801(3)	9105(2)	22(1)
O(5)	6923(2)	7220(3)	7629(2)	17(1)
O(6)	10404(2)	5645(3)	7559(2)	21(1)
O(7)	9731(3)	4081(3)	6284(3)	28(1)
N(1)	7894(3)	7807(3)	5249(3)	16(1)
N(2)	8724(3)	5654(4)	9692(3)	20(1)
C(1)	7588(4)	9080(4)	5516(4)	23(1)
C(2)	8495(4)	9608(4)	6452(4)	25(1)
C(3)	9470(4)	8570(4)	6532(3)	20(1)
C(4)	8983(3)	7330(4)	5875(3)	16(1)
C(5)	8536(3)	6093(4)	6554(3)	16(1)
C(6)	7604(3)	5489(4)	5587(3)	18(1)
C(7)	7128(3)	6687(4)	4779(4)	22(1)
C(8)	5760(3)	6987(5)	4882(4)	26(1)
C(9)	7424(4)	6419(5)	3455(4)	28(1)
C(10)	9609(3)	5137(4)	6761(4)	18(1)
C(11)	11420(4)	4804(5)	7899(4)	32(1)
C(12)	7881(3)	6281(4)	7792(3)	16(1)
C(13)	7522(3)	4904(4)	8123(4)	19(1)
C(14)	6994(3)	4011(4)	7336(4)	20(1)
C(15)	6613(4)	4562(4)	6114(4)	24(1)
C(16)	8673(3)	6707(4)	8909(3)	18(1)
C(17)	8076(3)	4552(4)	9220(4)	20(1)
C(18)	8015(4)	3263(4)	9629(4)	25(1)
C(19)	7408(4)	2360(5)	8871(4)	29(1)
C(20)	6917(4)	2704(5)	7737(4)	28(1)
C(21)	9398(4)	5656(5)	10834(4)	29(1)
C(22)	4585(4)	6137(5)	8389(5)	44(1)
C(23)	6223(4)	7574(6)	10173(4)	39(1)
C(24)	5101(5)	9079(5)	8031(5)	40(1)
O(8)	7213(4)	12319(7)	3941(5)	97(2)

Table E.29. Bond lengths [Å] for tetramic acid **3.97**

Atom-Atom	Bond lengths [Å]	Atom-Atom	Bond lengths [Å]
Si(1)-O(5)	1.682(3)	C(8)-H(8B)	0.9800
Si(1)-C(24)	1.852(5)	C(8)-H(8C)	0.9800
Si(1)-C(22)	1.857(5)	C(9)-H(9A)	0.9800
Si(1)-C(23)	1.860(4)	C(9)-H(9B)	0.9800
O(1)-C(1)	1.221(5)	C(9)-H(9C)	0.9800
O(2)-C(3)	1.203(5)	C(11)-H(11A)	0.9800
O(3)-C(4)	1.414(4)	C(11)-H(11B)	0.9800
O(3)-H(3)	0.74(6)	C(11)-H(11C)	0.9800
O(4)-C(16)	1.213(5)	C(12)-C(13)	1.496(6)
O(5)-C(12)	1.424(5)	C(12)-C(16)	1.555(5)
O(6)-C(10)	1.331(5)	C(13)-C(14)	1.374(6)
O(6)-C(11)	1.446(5)	C(13)-C(17)	1.389(6)
O(7)-C(10)	1.200(5)	C(14)-C(20)	1.398(6)
N(1)-C(1)	1.365(5)	C(14)-C(15)	1.510(6)
N(1)-C(4)	1.450(5)	C(15)-H(15A)	0.9900
N(1)-C(7)	1.498(5)	C(15)-H(15B)	0.9900
N(2)-C(16)	1.372(5)	C(17)-C(18)	1.382(6)
N(2)-C(17)	1.417(5)	C(18)-C(19)	1.399(6)
N(2)-C(21)	1.447(5)	C(18)-H(18A)	0.9500
C(1)-C(2)	1.517(6)	C(19)-C(20)	1.396(6)
C(2)-C(3)	1.500(6)	C(19)-H(19A)	0.9500
C(2)-H(2A)	0.9900	C(20)-H(20A)	0.9500
C(2)-H(2B)	0.9900	C(21)-H(21A)	0.9800
C(3)-C(4)	1.540(6)	C(21)-H(21B)	0.9800
C(4)-C(5)	1.543(6)	C(21)-H(21C)	0.9800
C(5)-C(10)	1.536(5)	C(22)-H(22A)	0.9800
C(5)-C(12)	1.562(5)	C(22)-H(22B)	0.9800
C(5)-C(6)	1.586(5)	C(22)-H(22C)	0.9800
C(6)-C(15)	1.554(6)	C(23)-H(23A)	0.9800
C(6)-C(7)	1.588(6)	C(23)-H(23B)	0.9800
C(6)-H(6A)	1.0000	C(23)-H(23C)	0.9800
C(7)-C(9)	1.523(5)	C(24)-H(24A)	0.9800
C(7)-C(8)	1.533(5)	C(24)-H(24B)	0.9800
C(8)-H(8A)	0.9800	C(24)-H(24C)	0.9800

Table E.30. Bond angles [°] for tetramic acid **3.97**

Atom-Atom-Atom	Bond angles [°]	Atom-Atom-Atom	Bond angles [°]
O(5)-Si(1)-C(24)	103.84(19)	O(6)-C(10)-C(5)	110.1(3)
O(5)-Si(1)-C(22)	111.0(2)	O(6)-C(11)-H(11A)	109.5
C(24)-Si(1)-C(22)	111.1(3)	O(6)-C(11)-H(11B)	109.5
O(5)-Si(1)-C(23)	112.03(16)	H(11A)-C(11)-H(11B)	109.5
C(24)-Si(1)-C(23)	110.5(3)	O(6)-C(11)-H(11C)	109.5
C(22)-Si(1)-C(23)	108.3(3)	H(11A)-C(11)-H(11C)	109.5
C(4)-O(3)-H(3)	101(4)	H(11B)-C(11)-H(11C)	109.5
C(12)-O(5)-Si(1)	127.0(2)	O(5)-C(12)-C(13)	117.2(3)
C(10)-O(6)-C(11)	115.8(3)	O(5)-C(12)-C(16)	108.4(3)
C(1)-N(1)-C(4)	114.5(3)	C(13)-C(12)-C(16)	102.2(3)
C(1)-N(1)-C(7)	130.7(3)	O(5)-C(12)-C(5)	108.6(3)
C(4)-N(1)-C(7)	111.3(3)	C(13)-C(12)-C(5)	103.0(3)
C(16)-N(2)-C(17)	111.5(3)	C(16)-C(12)-C(5)	117.8(3)
C(16)-N(2)-C(21)	124.1(4)	C(14)-C(13)-C(17)	123.6(4)
C(17)-N(2)-C(21)	124.4(3)	C(14)-C(13)-C(12)	124.7(4)
O(1)-C(1)-N(1)	126.1(4)	C(17)-C(13)-C(12)	109.8(3)
O(1)-C(1)-C(2)	125.3(4)	C(13)-C(14)-C(20)	116.8(4)
N(1)-C(1)-C(2)	108.6(4)	C(13)-C(14)-C(15)	115.3(4)
C(3)-C(2)-C(1)	104.5(4)	C(20)-C(14)-C(15)	127.9(4)
C(3)-C(2)-H(2A)	110.8	C(14)-C(15)-C(6)	111.8(3)
C(1)-C(2)-H(2A)	110.8	C(14)-C(15)-H(15A)	109.3
C(3)-C(2)-H(2B)	110.8	C(6)-C(15)-H(15A)	109.3
C(1)-C(2)-H(2B)	110.8	C(14)-C(15)-H(15B)	109.3
H(2A)-C(2)-H(2B)	108.9	C(6)-C(15)-H(15B)	109.3
O(2)-C(3)-C(2)	127.6(4)	H(15A)-C(15)-H(15B)	107.9
O(2)-C(3)-C(4)	123.9(4)	O(4)-C(16)-N(2)	125.9(4)
C(2)-C(3)-C(4)	107.6(3)	O(4)-C(16)-C(12)	126.4(4)
O(3)-C(4)-N(1)	113.0(3)	N(2)-C(16)-C(12)	107.4(3)
O(3)-C(4)-C(3)	109.7(3)	C(18)-C(17)-C(13)	120.2(4)
N(1)-C(4)-C(3)	103.2(3)	C(18)-C(17)-N(2)	130.6(4)
O(3)-C(4)-C(5)	104.4(3)	C(13)-C(17)-N(2)	109.0(3)
N(1)-C(4)-C(5)	103.7(3)	C(17)-C(18)-C(19)	116.6(4)
C(3)-C(4)-C(5)	123.0(3)	C(17)-C(18)-H(18A)	121.7
C(10)-C(5)-C(4)	109.6(3)	C(19)-C(18)-H(18A)	121.7
C(10)-C(5)-C(12)	108.0(3)	C(20)-C(19)-C(18)	122.8(4)
C(4)-C(5)-C(12)	118.5(3)	C(20)-C(19)-H(19A)	118.6
C(10)-C(5)-C(6)	109.8(3)	C(18)-C(19)-H(19A)	118.6
C(4)-C(5)-C(6)	101.1(3)	C(19)-C(20)-C(14)	119.6(4)
C(12)-C(5)-C(6)	109.5(3)	C(19)-C(20)-H(20A)	120.2
C(15)-C(6)-C(5)	115.3(3)	C(14)-C(20)-H(20A)	120.2
C(15)-C(6)-C(7)	116.5(3)	N(2)-C(21)-H(21A)	109.5
C(5)-C(6)-C(7)	106.5(3)	N(2)-C(21)-H(21B)	109.5
C(15)-C(6)-H(6A)	105.9	H(21A)-C(21)-H(21B)	109.5
C(5)-C(6)-H(6A)	105.9	N(2)-C(21)-H(21C)	109.5
C(7)-C(6)-H(6A)	105.9	H(21A)-C(21)-H(21C)	109.5
N(1)-C(7)-C(9)	109.8(3)	H(21B)-C(21)-H(21C)	109.5
N(1)-C(7)-C(8)	111.5(3)	Si(1)-C(22)-H(22A)	109.5
C(9)-C(7)-C(8)	109.2(3)	Si(1)-C(22)-H(22B)	109.5
N(1)-C(7)-C(6)	102.0(3)	H(22A)-C(22)-H(22B)	109.5
C(9)-C(7)-C(6)	109.1(3)	Si(1)-C(22)-H(22C)	109.5
C(8)-C(7)-C(6)	115.0(3)	H(22A)-C(22)-H(22C)	109.5
C(7)-C(8)-H(8A)	109.5	H(22B)-C(22)-H(22C)	109.5

C(7)-C(8)-H(8B)	109.5	Si(1)-C(23)-H(23A)	109.5
H(8A)-C(8)-H(8B)	109.5	Si(1)-C(23)-H(23B)	109.5
C(7)-C(8)-H(8C)	109.5	H(23A)-C(23)-H(23B)	109.5
H(8A)-C(8)-H(8C)	109.5	Si(1)-C(23)-H(23C)	109.5
H(8B)-C(8)-H(8C)	109.5	H(23A)-C(23)-H(23C)	109.5
C(7)-C(9)-H(9A)	109.5	H(23B)-C(23)-H(23C)	109.5
C(7)-C(9)-H(9B)	109.5	Si(1)-C(24)-H(24A)	109.5
H(9A)-C(9)-H(9B)	109.5	Si(1)-C(24)-H(24B)	109.5
C(7)-C(9)-H(9C)	109.5	H(24A)-C(24)-H(24B)	109.5
H(9A)-C(9)-H(9C)	109.5	Si(1)-C(24)-H(24C)	109.5
H(9B)-C(9)-H(9C)	109.5	H(24A)-C(24)-H(24C)	109.5
O(7)-C(10)-O(6)	123.9(4)	H(24B)-C(24)-H(24C)	109.5
O(7)-C(10)-C(5)	126.0(4)		

Table E.31. [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(3)-H(3)...O(7)#1	0.74(6)	2.02(6)	2.750(4)	174(5)

Symmetry transformations used to generate equivalent atoms:

#1 -x+2,y+1/2,-z+1

*E.8. Crystal Structure Analysis of Hexacyclic Ester **3.98***

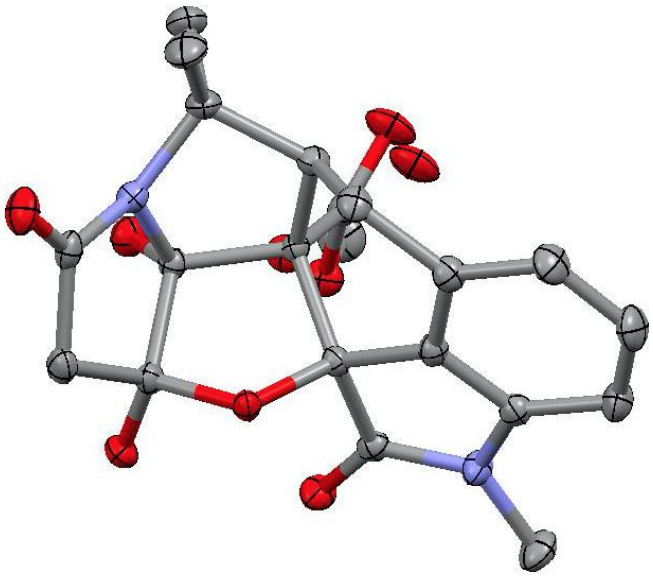

Figure E.08. ORTEP drawing of hexacyclic ester **3.98**

Table E.32 Crystal data and structure refinement hexacyclic ester **3.98**

Identification code	JLW66_2	
Empirical formula	$C_{21}H_{22}N_2O_7$	
Formula weight	414.40	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 12.4620(6) Å	α= 90°.
	b = 8.1989(4) Å	β= 93.8768(17)°.
	c = 18.0499(9) Å	γ = 90°.
Volume	1840.02(16) $Å^3$	
Z	4	
Density (calculated)	1.496 Mg/m^3	
Absorption coefficient	0.113 mm^{-1}	
F(000)	872	
Crystal size	0.200 x 0.172 x 0.051 mm^3	
Theta range for data collection	2.702 to 26.440°.	
Index ranges	-15<=h<=15, -10<=k<=10, -22<=l<=22	
Reflections collected	46758	
Independent reflections	3789 [R(int) = 0.0426]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.967 and 0.951	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3789 / 0 / 291	
Goodness-of-fit on F^2	1.022	
Final R indices [I>2sigma(I)]	R1 = 0.0374, wR2 = 0.0958	
R indices (all data)	R1 = 0.0445, wR2 = 0.1008	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.361 and -0.327 $e.Å^{-3}$	

Table E.33. ($x10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 x\ 10^3$) for JLW66. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
O(1)	7839(1)	-50(1)	1305(1)	16(1)
O(2)	7853(1)	-223(1)	2(1)	21(1)
O(3)	9632(1)	1377(1)	534(1)	21(1)
O(4)	6579(1)	2612(1)	-38(1)	25(1)
O(5)	4570(1)	-809(1)	1112(1)	27(1)
N(1)	5666(1)	1398(1)	931(1)	17(1)
N(2)	10147(1)	1982(2)	1745(1)	19(1)
C(1)	7853(1)	1960(2)	2837(1)	19(1)
C(2)	8267(1)	2390(2)	3549(1)	26(1)
C(3)	9367(1)	2638(2)	3680(1)	28(1)
C(4)	10088(1)	2508(2)	3124(1)	24(1)
C(5)	9656(1)	2071(2)	2427(1)	18(1)
C(6)	8570(1)	1750(2)	2302(1)	16(1)
C(7)	6694(1)	1848(2)	2558(1)	20(1)
C(8)	6510(1)	2970(2)	1872(1)	18(1)
C(9)	7334(1)	2737(2)	1252(1)	15(1)
C(11)	8276(1)	1537(2)	1496(1)	15(1)
C(12)	9415(1)	1665(2)	1172(1)	17(1)
C(13)	11306(1)	2024(2)	1684(1)	27(1)
C(14)	6699(1)	1755(2)	628(1)	15(1)
C(15)	7235(1)	45(2)	597(1)	16(1)
C(16)	6310(1)	-1154(2)	594(1)	21(1)
C(17)	5408(1)	-214(2)	913(1)	19(1)
C(18)	5383(1)	2700(2)	1457(1)	20(1)
C(19)	5003(1)	4224(2)	1024(1)	26(1)
C(20)	4509(1)	2184(2)	1962(1)	28(1)
C(10)	7729(1)	4397(2)	996(1)	17(1)
O(6)	7470(2)	5684(2)	1261(1)	31(1)
O(7)	8375(2)	4264(2)	446(1)	21(1)
C(21)	8575(1)	5746(2)	46(1)	31(1)
C(10A)	7729(1)	4397(2)	996(1)	17(1)
O(6A)	7872(19)	5440(20)	1352(10)	31(1)
O(7A)	7975(17)	4272(17)	275(10)	21(1)
C(21A)	8575(1)	5746(2)	46(1)	31(1)

Table E.34. Bond lengths [Å] for hexacyclic ester **3.98**

Atom-Atom	Bond lengths [Å]	Atom-Atom	Bond lengths [Å]
O(1)-C(15)	1.4410(15)	C(8)-C(9)	1.5809(18)
O(1)-C(11)	1.4431(16)	C(8)-H(8)	1.0000
O(2)-C(15)	1.3795(16)	C(9)-C(10)	1.5297(19)
O(2)-H(2A)	0.90(2)	C(9)-C(14)	1.5570(18)
O(3)-C(12)	1.2232(17)	C(9)-C(11)	1.5712(18)
O(4)-C(14)	1.3908(16)	C(11)-C(12)	1.5748(18)
O(4)-H(4A)	1.12(3)	C(13)-H(13A)	0.9800
O(5)-C(17)	1.2283(18)	C(13)-H(13B)	0.9800
N(1)-C(17)	1.3594(19)	C(13)-H(13C)	0.9800
N(1)-C(14)	1.4621(17)	C(14)-C(15)	1.5561(18)
N(1)-C(18)	1.4875(18)	C(15)-C(16)	1.5148(19)
N(2)-C(12)	1.3579(18)	C(16)-C(17)	1.509(2)
N(2)-C(5)	1.4123(18)	C(16)-H(16A)	0.9900
N(2)-C(13)	1.4563(18)	C(16)-H(16B)	0.9900
C(1)-C(6)	1.3712(19)	C(18)-C(20)	1.527(2)
C(1)-C(2)	1.396(2)	C(18)-C(19)	1.533(2)
C(1)-C(7)	1.4999(19)	C(19)-H(19A)	0.9800
C(2)-C(3)	1.391(2)	C(19)-H(19B)	0.9800
C(2)-H(2)	0.9500	C(19)-H(19C)	0.9800
C(3)-C(4)	1.397(2)	C(20)-H(20A)	0.9800
C(3)-H(3)	0.9500	C(20)-H(20B)	0.9800
C(4)-C(5)	1.381(2)	C(20)-H(20C)	0.9800
C(4)-H(4)	0.9500	C(10)-O(6)	1.212(2)
C(5)-C(6)	1.3831(19)	C(10)-O(7)	1.3234(19)
C(6)-C(11)	1.4850(18)	O(7)-C(21)	1.444(2)
C(7)-C(8)	1.5474(19)	C(21)-H(21A)	0.9800
C(7)-H(7A)	0.9900	C(21)-H(21B)	0.9800
C(7)-H(7B)	0.9900	C(21)-H(21C)	0.9800
C(8)-C(18)	1.5613(19)		

Table E.35. Bond angles [°] for hexacyclic ester **3.98**

Atom-Atom-Atom	Bond angles [°]	Atom-Atom-Atom	Bond angles [°]
C(15)-O(1)-C(11)	109.27(10)	N(2)-C(13)-H(13B)	109.5
C(15)-O(2)-H(2A)	107.5(14)	H(13A)-C(13)-H(13B)	109.5
C(14)-O(4)-H(4A)	109.6(14)	N(2)-C(13)-H(13C)	109.5
C(17)-N(1)-C(14)	113.49(11)	H(13A)-C(13)-H(13C)	109.5
C(17)-N(1)-C(18)	130.30(12)	H(13B)-C(13)-H(13C)	109.5
C(14)-N(1)-C(18)	110.33(11)	O(4)-C(14)-N(1)	112.22(11)
C(12)-N(2)-C(5)	111.47(11)	O(4)-C(14)-C(15)	116.45(11)
C(12)-N(2)-C(13)	124.41(12)	N(1)-C(14)-C(15)	102.94(10)
C(5)-N(2)-C(13)	123.72(12)	O(4)-C(14)-C(9)	112.57(11)
C(6)-C(1)-C(2)	117.55(13)	N(1)-C(14)-C(9)	104.52(10)
C(6)-C(1)-C(7)	114.41(12)	C(15)-C(14)-C(9)	107.06(10)
C(2)-C(1)-C(7)	127.77(13)	O(2)-C(15)-O(1)	113.34(11)
C(3)-C(2)-C(1)	119.54(14)	O(2)-C(15)-C(16)	110.99(11)
C(3)-C(2)-H(2)	120.2	O(1)-C(15)-C(16)	108.68(11)
C(1)-C(2)-H(2)	120.2	O(2)-C(15)-C(14)	115.80(11)
C(2)-C(3)-C(4)	122.72(13)	O(1)-C(15)-C(14)	102.47(10)
C(2)-C(3)-H(3)	118.6	C(16)-C(15)-C(14)	104.84(11)
C(4)-C(3)-H(3)	118.6	C(17)-C(16)-C(15)	104.68(11)
C(5)-C(4)-C(3)	116.42(13)	C(17)-C(16)-H(16A)	110.8
C(5)-C(4)-H(4)	121.8	C(15)-C(16)-H(16A)	110.8
C(3)-C(4)-H(4)	121.8	C(17)-C(16)-H(16B)	110.8
C(4)-C(5)-C(6)	121.00(13)	C(15)-C(16)-H(16B)	110.8
C(4)-C(5)-N(2)	129.93(13)	H(16A)-C(16)-H(16B)	108.9
C(6)-C(5)-N(2)	108.92(12)	O(5)-C(17)-N(1)	125.69(14)
C(1)-C(6)-C(5)	122.57(13)	O(5)-C(17)-C(16)	125.35(13)
C(1)-C(6)-C(11)	125.16(12)	N(1)-C(17)-C(16)	108.95(12)
C(5)-C(6)-C(11)	110.88(12)	N(1)-C(18)-C(20)	113.07(12)
C(1)-C(7)-C(8)	108.68(11)	N(1)-C(18)-C(19)	109.71(12)
C(1)-C(7)-H(7A)	110.0	C(20)-C(18)-C(19)	108.81(12)
C(8)-C(7)-H(7A)	110.0	N(1)-C(18)-C(8)	99.45(10)
C(1)-C(7)-H(7B)	110.0	C(20)-C(18)-C(8)	114.08(12)
C(8)-C(7)-H(7B)	110.0	C(19)-C(18)-C(8)	111.46(12)
H(7A)-C(7)-H(7B)	108.3	C(18)-C(19)-H(19A)	109.5
C(7)-C(8)-C(18)	112.28(11)	C(18)-C(19)-H(19B)	109.5
C(7)-C(8)-C(9)	115.17(11)	H(19A)-C(19)-H(19B)	109.5
C(18)-C(8)-C(9)	104.49(11)	C(18)-C(19)-H(19C)	109.5
C(7)-C(8)-H(8)	108.2	H(19A)-C(19)-H(19C)	109.5
C(18)-C(8)-H(8)	108.2	H(19B)-C(19)-H(19C)	109.5
C(9)-C(8)-H(8)	108.2	C(18)-C(20)-H(20A)	109.5
C(10)-C(9)-C(14)	113.51(11)	C(18)-C(20)-H(20B)	109.5
C(10)-C(9)-C(11)	113.10(11)	H(20A)-C(20)-H(20B)	109.5
C(14)-C(9)-C(11)	102.31(10)	C(18)-C(20)-H(20C)	109.5
C(10)-C(9)-C(8)	110.13(11)	H(20A)-C(20)-H(20C)	109.5
C(14)-C(9)-C(8)	104.57(10)	H(20B)-C(20)-H(20C)	109.5
C(11)-C(9)-C(8)	112.73(10)	O(6)-C(10)-O(7)	124.03(14)
O(1)-C(11)-C(6)	113.86(11)	O(6)-C(10)-C(9)	123.74(14)
O(1)-C(11)-C(9)	103.56(10)	O(7)-C(10)-C(9)	112.23(12)
C(6)-C(11)-C(9)	109.32(11)	C(10)-O(7)-C(21)	116.09(14)
O(1)-C(11)-C(12)	107.83(10)	O(7)-C(21)-H(21A)	109.5
C(6)-C(11)-C(12)	100.81(10)	O(7)-C(21)-H(21B)	109.5
C(9)-C(11)-C(12)	121.90(11)	H(21A)-C(21)-H(21B)	109.5
O(3)-C(12)-N(2)	125.01(12)	O(7)-C(21)-H(21C)	109.5
O(3)-C(12)-C(11)	126.86(12)	H(21A)-C(21)-H(21C)	109.5
N(2)-C(12)-C(11)	107.77(11)	H(21B)-C(21)-H(21C)	109.5
N(2)-C(13)-H(13A)	109.5		

Table E.36. [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2A)...O(3)	0.90(2)	1.82(2)	2.6972(15)	163(2)
O(4)-H(4A)...O(5)#1	1.12(3)	1.64(3)	2.7605(15)	177(2)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y,-z

*E.9. Crystal Structure Analysis of Hexacyclic Ester **3.106***

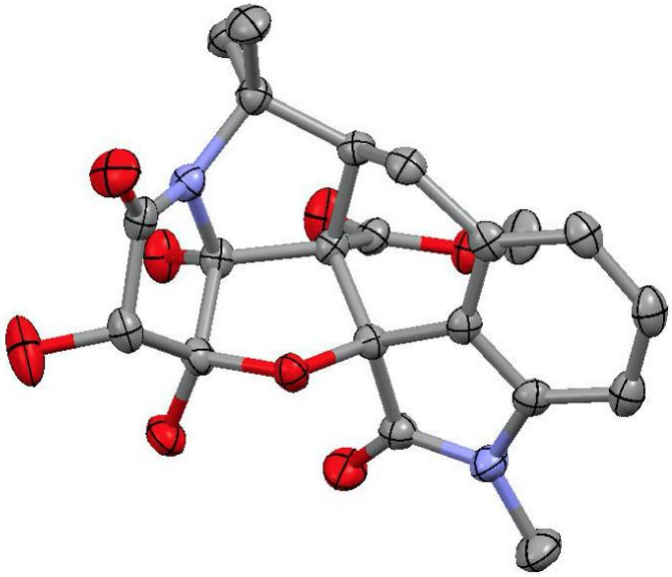

Figure E.09. ORTEP drawing of hexacyclic ester **3.106**

Table E.37 Crystal data and structure refinement hexacyclic ester **3.106**

Identification code	jlw70	
Empirical formula	$C_{21}H_{22}N_2O_8$	
Formula weight	430.40	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 10.4970(13) Å	α= 90°.
	b = 14.738(2) Å	β= 97.466(4)°.
	c = 25.566(4) Å	γ = 90°.
Volume	3921.7(9) $Å^3$	
Z	8	
Density (calculated)	1.458 Mg/m^3	
Absorption coefficient	0.113 mm^{-1}	
F(000)	1808	
Crystal size	0.207 x 0.109 x 0.049 mm^3	
Theta range for data collection	2.396 to 25.743°.	
Index ranges	-12<=h<=12, -17<=k<=18, -31<=l<=31	
Reflections collected	114236	
Independent reflections	7476 [R(int) = 0.0687]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.944 and 0.927	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7476 / 5 / 594	
Goodness-of-fit on F^2	1.021	
Final R indices [I>2sigma(I)]	R1 = 0.0607, wR2 = 0.1587	
R indices (all data)	R1 = 0.0823, wR2 = 0.1753	
Extinction coefficient	n/a	
Largest diff. peak and hole	1.025 and -0.454 e.$Å^{-3}$	

Table E.24. ($x10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 x\ 10^3$) for jlw70. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
O(1)	6677(2)	2670(2)	2637(1)	44(1)
O(2)	9184(3)	3514(2)	3146(1)	58(1)
O(3)	11178(2)	2459(2)	2923(1)	34(1)
O(4)	10007(2)	1190(1)	3465(1)	36(1)
O(5)	9935(2)	1922(1)	2152(1)	26(1)
O(6)	12511(2)	1062(2)	2523(1)	38(1)
O(7)	10620(2)	-484(1)	3238(1)	39(1)
O(8)	10624(2)	-832(1)	2386(1)	31(1)
N(1)	8083(2)	1488(2)	2897(1)	25(1)
N(2)	11978(2)	618(2)	1656(1)	30(1)
C(1)	7753(3)	2360(2)	2742(1)	29(1)
C(2)	8982(3)	2902(2)	2721(1)	30(1)
C(3)	9990(2)	2170(2)	2697(1)	26(1)
C(4)	9451(2)	1310(2)	2943(1)	24(1)
C(5)	9576(2)	511(2)	2554(1)	22(1)
C(6)	8142(2)	207(2)	2360(1)	24(1)
C(7)	7355(3)	636(2)	2774(1)	27(1)
C(8)	7433(3)	50(2)	3272(1)	35(1)
C(9)	5931(3)	785(2)	2570(1)	37(1)
C(10)	10237(2)	970(2)	2113(1)	23(1)
C(11)	11719(3)	880(2)	2140(1)	28(1)
C(12)	10833(3)	400(2)	1323(1)	27(1)
C(13)	10661(3)	-11(2)	836(1)	33(1)
C(14)	9398(3)	-236(2)	639(1)	35(1)
C(15)	8368(3)	-97(2)	918(1)	32(1)
C(16)	8570(3)	325(2)	1410(1)	25(1)
C(17)	9797(2)	597(2)	1584(1)	23(1)
C(18)	7617(2)	499(2)	1789(1)	27(1)
C(19)	13268(3)	513(3)	1511(1)	44(1)
C(20)	10338(2)	-313(2)	2774(1)	25(1)
C(21)	11283(3)	-1681(2)	2532(1)	41(1)
O(9)	4817(2)	8902(1)	-646(1)	37(1)
O(10)	5328(2)	9267(2)	537(1)	41(1)
O(11)	3646(2)	8356(2)	1051(1)	37(1)
O(12)	4840(2)	6947(2)	573(1)	51(1)
O(13)	2113(2)	8394(1)	293(1)	25(1)
O(14)	1577(2)	7344(2)	1249(1)	47(1)
N(3)	4222(2)	7617(2)	-218(1)	26(1)
N(4)	-358(3)	7442(2)	716(1)	46(1)
C(22)	4450(2)	8515(2)	-265(1)	28(1)
C(23)	4174(2)	9000(2)	240(1)	28(1)
C(24)	3429(3)	8284(2)	507(1)	27(1)
C(25)	3794(3)	7370(2)	280(1)	28(1)
C(26)	2501(3)	6854(2)	112(1)	30(1)
C(27)	2420(3)	6760(2)	-511(1)	28(1)
C(28)	3829(3)	6911(2)	-624(1)	29(1)
C(29)	3967(3)	7224(2)	-1183(1)	33(1)
C(30)	4654(3)	6060(2)	-501(1)	38(1)
C(31)	1479(3)	7525(2)	276(1)	27(1)
C(32)	935(3)	7404(2)	813(1)	36(1)

C(33)	-793(3)	7496(2)	168(1)	41(1)
C(34)	-2002(3)	7473(3)	-108(2)	57(1)
C(35)	-2089(3)	7461(3)	-656(2)	56(1)
C(36)	-1023(3)	7439(2)	-924(1)	44(1)
C(37)	210(3)	7470(2)	-635(1)	31(1)
C(38)	274(3)	7532(2)	-100(1)	31(1)
C(39)	1484(3)	7427(2)	-836(1)	29(1)
C(40)	-1210(4)	7439(3)	1126(2)	65(1)
C(41)	2392(3)	5937(2)	371(1)	38(1)
O(15)	3270(3)	5519(2)	616(1)	44(1)
O(16)	1196(3)	5725(2)	384(2)	60(1)
C(42)	940(6)	4902(4)	672(3)	80(2)
C(41A)	2392(3)	5937(2)	371(1)	38(1)
O(15A)	1958(9)	5242(6)	29(4)	44(1)
O(16A)	2110(10)	5856(7)	815(4)	60(1)
C(42A)	1740(20)	5063(12)	1098(9)	80(2)

Table E.38. Bond lengths [Å] for hexacyclic ester **3.106**

Atom-Atom	Bond lengths [Å]	Atom-Atom	Bond lengths [Å]
O(1)-C(1)	1.216(3)	O(10)-C(23)	1.399(3)
O(2)-C(2)	1.408(3)	O(10)-H(10A)	0.8400
O(2)-H(2A)	0.88(5)	O(11)-C(24)	1.385(3)
O(3)-C(3)	1.372(3)	O(11)-H(11A)	0.83(4)
O(3)-H(3A)	0.86(4)	O(12)-C(25)	1.394(3)
O(4)-C(4)	1.397(3)	O(12)-H(12A)	0.98(6)
O(4)-H(4A)	0.8400	O(13)-C(24)	1.427(3)
O(5)-C(3)	1.435(3)	O(13)-C(31)	1.441(3)
O(5)-C(10)	1.445(3)	O(14)-C(32)	1.228(4)
O(6)-C(11)	1.228(3)	N(3)-C(22)	1.353(4)
O(7)-C(20)	1.210(3)	N(3)-C(25)	1.451(3)
O(8)-C(20)	1.319(3)	N(3)-C(28)	1.489(3)
O(8)-C(21)	1.455(3)	N(4)-C(32)	1.350(4)
N(1)-C(1)	1.376(3)	N(4)-C(33)	1.418(4)
N(1)-C(4)	1.450(3)	N(4)-C(40)	1.463(4)
N(1)-C(7)	1.482(3)	C(22)-C(23)	1.537(4)
N(2)-C(11)	1.357(4)	C(23)-C(24)	1.525(4)
N(2)-C(12)	1.416(4)	C(23)-H(23A)	1.0000
N(2)-C(19)	1.458(4)	C(24)-C(25)	1.536(4)
C(1)-C(2)	1.523(4)	C(25)-C(26)	1.566(4)
C(2)-C(3)	1.518(4)	C(26)-C(41)	1.516(4)
C(2)-H(2B)	1.0000	C(26)-C(31)	1.557(4)
C(3)-C(4)	1.553(4)	C(26)-C(27)	1.590(4)
C(4)-C(5)	1.558(3)	C(27)-C(39)	1.552(4)
C(5)-C(20)	1.522(3)	C(27)-C(28)	1.559(4)
C(5)-C(10)	1.553(3)	C(27)-H(27A)	1.0000
C(5)-C(6)	1.587(3)	C(28)-C(29)	1.526(4)
C(6)-C(18)	1.552(3)	C(28)-C(30)	1.534(4)
C(6)-C(7)	1.561(4)	C(29)-H(29A)	0.9800
C(6)-H(6A)	1.0000	C(29)-H(29B)	0.9800
C(7)-C(8)	1.532(4)	C(29)-H(29C)	0.9800
C(7)-C(9)	1.534(4)	C(30)-H(30A)	0.9800
C(8)-H(8A)	0.9800	C(30)-H(30B)	0.9800
C(8)-H(8B)	0.9800	C(30)-H(30C)	0.9800
C(8)-H(8C)	0.9800	C(31)-C(38)	1.486(4)
C(9)-H(9A)	0.9800	C(31)-C(32)	1.566(4)
C(9)-H(9B)	0.9800	C(33)-C(34)	1.369(5)
C(9)-H(9C)	0.9800	C(33)-C(38)	1.388(4)
C(10)-C(17)	1.477(3)	C(34)-C(35)	1.393(6)
C(10)-C(11)	1.553(4)	C(34)-H(34A)	0.9500
C(12)-C(13)	1.375(4)	C(35)-C(36)	1.386(5)
C(12)-C(17)	1.380(4)	C(35)-H(35A)	0.9500
C(13)-C(14)	1.395(4)	C(36)-C(37)	1.404(4)
C(13)-H(13A)	0.9500	C(36)-H(36A)	0.9500
C(14)-C(15)	1.386(4)	C(37)-C(38)	1.363(4)
C(14)-H(14A)	0.9500	C(37)-C(39)	1.495(4)
C(15)-C(16)	1.395(4)	C(39)-H(39A)	0.9900
C(15)-H(15A)	0.9500	C(39)-H(39B)	0.9900
C(16)-C(17)	1.366(4)	C(40)-H(40A)	0.9800
C(16)-C(18)	1.503(4)	C(40)-H(40B)	0.9800
C(18)-H(18A)	0.9900	C(40)-H(40C)	0.9800
C(18)-H(18B)	0.9900	C(41)-O(15)	1.213(4)

C(19)-H(19A)	0.9800	C(41)-O(16)	1.298(4)
C(19)-H(19B)	0.9800	O(16)-C(42)	1.461(5)
C(19)-H(19C)	0.9800	C(42)-H(42A)	0.9800
C(21)-H(21A)	0.9800	C(42)-H(42B)	0.9800
C(21)-H(21B)	0.9800	C(42)-H(42C)	0.9800
C(21)-H(21C)	0.9800	O(16A)-C(42A)	1.453(14)
O(9)-C(22)	1.233(3)	C(42A)-H(42D)	0.9800
		C(42A)-H(42E)	0.9800
		C(42A)-H(42F)	0.9800

Table E.39. Bond angles [°] for hexacyclic ester **3.106**

Atom-Atom-Atom	Bond angles [°]	Atom-Atom-Atom	Bond angles [°]
C(2)-O(2)-H(2A)	109(3)	C(33)-N(4)-C(40)	124.1(3)
C(3)-O(3)-H(3A)	104(2)	O(9)-C(22)-N(3)	126.8(3)
C(4)-O(4)-H(4A)	109.5	O(9)-C(22)-C(23)	124.2(3)
C(3)-O(5)-C(10)	109.42(19)	N(3)-C(22)-C(23)	109.0(2)
C(20)-O(8)-C(21)	116.8(2)	O(10)-C(23)-C(24)	114.2(2)
C(1)-N(1)-C(4)	113.7(2)	O(10)-C(23)-C(22)	110.0(2)
C(1)-N(1)-C(7)	128.8(2)	C(24)-C(23)-C(22)	102.6(2)
C(4)-N(1)-C(7)	110.0(2)	O(10)-C(23)-H(23A)	109.9
C(11)-N(2)-C(12)	111.0(2)	C(24)-C(23)-H(23A)	109.9
C(11)-N(2)-C(19)	124.4(2)	C(22)-C(23)-H(23A)	109.9
C(12)-N(2)-C(19)	124.5(2)	O(11)-C(24)-O(13)	113.6(2)
O(1)-C(1)-N(1)	127.3(3)	O(11)-C(24)-C(23)	111.6(2)
O(1)-C(1)-C(2)	124.2(3)	O(13)-C(24)-C(23)	106.2(2)
N(1)-C(1)-C(2)	108.5(2)	O(11)-C(24)-C(25)	115.5(2)
O(2)-C(2)-C(3)	116.8(2)	O(13)-C(24)-C(25)	103.4(2)
O(2)-C(2)-C(1)	110.6(2)	C(23)-C(24)-C(25)	105.7(2)
C(3)-C(2)-C(1)	103.1(2)	O(12)-C(25)-N(3)	105.8(2)
O(2)-C(2)-H(2B)	108.7	O(12)-C(25)-C(24)	114.0(2)
C(3)-C(2)-H(2B)	108.7	N(3)-C(25)-C(24)	103.4(2)
C(1)-C(2)-H(2B)	108.7	O(12)-C(25)-C(26)	121.7(2)
O(3)-C(3)-O(5)	114.1(2)	N(3)-C(25)-C(26)	103.7(2)
O(3)-C(3)-C(2)	111.3(2)	C(24)-C(25)-C(26)	106.3(2)
O(5)-C(3)-C(2)	106.3(2)	C(41)-C(26)-C(31)	110.8(2)
O(3)-C(3)-C(4)	116.2(2)	C(41)-C(26)-C(25)	115.1(2)
O(5)-C(3)-C(4)	102.38(19)	C(31)-C(26)-C(25)	102.7(2)
C(2)-C(3)-C(4)	105.7(2)	C(41)-C(26)-C(27)	111.3(2)
O(4)-C(4)-N(1)	112.7(2)	C(31)-C(26)-C(27)	112.1(2)
O(4)-C(4)-C(3)	111.2(2)	C(25)-C(26)-C(27)	104.4(2)
N(1)-C(4)-C(3)	103.3(2)	C(39)-C(27)-C(28)	111.1(2)
O(4)-C(4)-C(5)	117.0(2)	C(39)-C(27)-C(26)	115.4(2)
N(1)-C(4)-C(5)	104.5(2)	C(28)-C(27)-C(26)	104.1(2)
C(3)-C(4)-C(5)	107.0(2)	C(39)-C(27)-H(27A)	108.7
C(20)-C(5)-C(10)	110.7(2)	C(28)-C(27)-H(27A)	108.7
C(20)-C(5)-C(4)	116.8(2)	C(26)-C(27)-H(27A)	108.7
C(10)-C(5)-C(4)	102.5(2)	N(3)-C(28)-C(29)	112.8(2)
C(20)-C(5)-C(6)	108.8(2)	N(3)-C(28)-C(30)	109.3(2)
C(10)-C(5)-C(6)	113.07(19)	C(29)-C(28)-C(30)	108.7(2)
C(4)-C(5)-C(6)	104.97(19)	N(3)-C(28)-C(27)	99.0(2)
C(18)-C(6)-C(7)	111.8(2)	C(29)-C(28)-C(27)	115.1(2)
C(18)-C(6)-C(5)	114.9(2)	C(30)-C(28)-C(27)	111.7(2)
C(7)-C(6)-C(5)	103.7(2)	C(28)-C(29)-H(29A)	109.5

C(18)-C(6)-H(6A)	108.7	C(28)-C(29)-H(29B)	109.5
C(7)-C(6)-H(6A)	108.7	H(29A)-C(29)-H(29B)	109.5
C(5)-C(6)-H(6A)	108.7	C(28)-C(29)-H(29C)	109.5
N(1)-C(7)-C(8)	109.4(2)	H(29A)-C(29)-H(29C)	109.5
N(1)-C(7)-C(9)	113.8(2)	H(29B)-C(29)-H(29C)	109.5
C(8)-C(7)-C(9)	108.0(2)	C(28)-C(30)-H(30A)	109.5
N(1)-C(7)-C(6)	100.6(2)	C(28)-C(30)-H(30B)	109.5
C(8)-C(7)-C(6)	111.0(2)	H(30A)-C(30)-H(30B)	109.5
C(9)-C(7)-C(6)	113.9(2)	C(28)-C(30)-H(30C)	109.5
C(7)-C(8)-H(8A)	109.5	H(30A)-C(30)-H(30C)	109.5
C(7)-C(8)-H(8B)	109.5	H(30B)-C(30)-H(30C)	109.5
H(8A)-C(8)-H(8B)	109.5	O(13)-C(31)-C(38)	111.4(2)
C(7)-C(8)-H(8C)	109.5	O(13)-C(31)-C(26)	104.0(2)
H(8A)-C(8)-H(8C)	109.5	C(38)-C(31)-C(26)	112.9(2)
H(8B)-C(8)-H(8C)	109.5	O(13)-C(31)-C(32)	107.0(2)
C(7)-C(9)-H(9A)	109.5	C(38)-C(31)-C(32)	101.1(2)
C(7)-C(9)-H(9B)	109.5	C(26)-C(31)-C(32)	120.4(2)
H(9A)-C(9)-H(9B)	109.5	O(14)-C(32)-N(4)	126.2(3)
C(7)-C(9)-H(9C)	109.5	O(14)-C(32)-C(31)	125.9(3)
H(9A)-C(9)-H(9C)	109.5	N(4)-C(32)-C(31)	107.8(3)
H(9B)-C(9)-H(9C)	109.5	C(34)-C(33)-C(38)	120.1(3)
O(5)-C(10)-C(17)	112.3(2)	C(34)-C(33)-N(4)	131.6(3)
O(5)-C(10)-C(5)	104.51(19)	C(38)-C(33)-N(4)	108.2(3)
C(17)-C(10)-C(5)	112.7(2)	C(33)-C(34)-C(35)	116.9(3)
O(5)-C(10)-C(11)	107.9(2)	C(33)-C(34)-H(34A)	121.5
C(17)-C(10)-C(11)	101.6(2)	C(35)-C(34)-H(34A)	121.5
C(5)-C(10)-C(11)	118.0(2)	C(36)-C(35)-C(34)	123.1(3)
O(6)-C(11)-N(2)	126.4(3)	C(36)-C(35)-H(35A)	118.5
O(6)-C(11)-C(10)	126.0(2)	C(34)-C(35)-H(35A)	118.5
N(2)-C(11)-C(10)	107.6(2)	C(35)-C(36)-C(37)	119.2(3)
C(13)-C(12)-C(17)	120.8(3)	C(35)-C(36)-H(36A)	120.4
C(13)-C(12)-N(2)	130.3(3)	C(37)-C(36)-H(36A)	120.4
C(17)-C(12)-N(2)	108.7(2)	C(38)-C(37)-C(36)	116.8(3)
C(12)-C(13)-C(14)	116.0(3)	C(38)-C(37)-C(39)	114.7(2)
C(12)-C(13)-H(13A)	122.0	C(36)-C(37)-C(39)	128.5(3)
C(14)-C(13)-H(13A)	122.0	C(37)-C(38)-C(33)	123.7(3)
C(15)-C(14)-C(13)	123.2(3)	C(37)-C(38)-C(31)	125.1(3)
C(15)-C(14)-H(14A)	118.4	C(33)-C(38)-C(31)	110.7(3)
C(13)-C(14)-H(14A)	118.4	C(37)-C(39)-C(27)	112.1(2)
C(14)-C(15)-C(16)	119.5(3)	C(37)-C(39)-H(39A)	109.2
C(14)-C(15)-H(15A)	120.2	C(27)-C(39)-H(39A)	109.2
C(16)-C(15)-H(15A)	120.2	C(37)-C(39)-H(39B)	109.2
C(17)-C(16)-C(15)	116.8(3)	C(27)-C(39)-H(39B)	109.2
C(17)-C(16)-C(18)	114.7(2)	H(39A)-C(39)-H(39B)	107.9
C(15)-C(16)-C(18)	128.5(2)	N(4)-C(40)-H(40A)	109.5
C(16)-C(17)-C(12)	123.3(2)	N(4)-C(40)-H(40B)	109.5
C(16)-C(17)-C(10)	125.2(2)	H(40A)-C(40)-H(40B)	109.5
C(12)-C(17)-C(10)	110.4(2)	N(4)-C(40)-H(40C)	109.5
C(16)-C(18)-C(6)	111.9(2)	H(40A)-C(40)-H(40C)	109.5
C(16)-C(18)-H(18A)	109.2	H(40B)-C(40)-H(40C)	109.5
C(6)-C(18)-H(18A)	109.2	O(15)-C(41)-O(16)	122.4(3)
C(16)-C(18)-H(18B)	109.2	O(15)-C(41)-C(26)	125.7(3)
C(6)-C(18)-H(18B)	109.2	O(16)-C(41)-C(26)	110.7(3)
H(18A)-C(18)-H(18B)	107.9	C(41)-O(16)-C(42)	117.1(3)
N(2)-C(19)-H(19A)	109.5	O(16)-C(42)-H(42A)	109.5
N(2)-C(19)-H(19B)	109.5	O(16)-C(42)-H(42B)	109.5

H(19A)-C(19)-H(19B)	109.5	H(42A)-C(42)-H(42B)	109.5
N(2)-C(19)-H(19C)	109.5	O(16)-C(42)-H(42C)	109.5
H(19A)-C(19)-H(19C)	109.5	H(42A)-C(42)-H(42C)	109.5
H(19B)-C(19)-H(19C)	109.5	H(42B)-C(42)-H(42C)	109.5
O(7)-C(20)-O(8)	124.5(2)	O(16A)-C(42A)-H(42D)	109.5
O(7)-C(20)-C(5)	125.4(2)	O(16A)-C(42A)-H(42E)	109.5
O(8)-C(20)-C(5)	110.1(2)	H(42D)-C(42A)-H(42E)	109.5
O(8)-C(21)-H(21A)	109.5	O(16A)-C(42A)-H(42F)	109.5
O(8)-C(21)-H(21B)	109.5	H(42D)-C(42A)-H(42F)	109.5
H(21A)-C(21)-H(21B)	109.5	H(42E)-C(42A)-H(42F)	109.5
O(8)-C(21)-H(21C)	109.5		
H(21A)-C(21)-H(21C)	109.5		
H(21B)-C(21)-H(21C)	109.5		
C(23)-O(10)-H(10A)	109.5		
C(24)-O(11)-H(11A)	103(2)		
C(25)-O(12)-H(12A)	93(3)		
C(24)-O(13)-C(31)	109.37(19)		
C(22)-N(3)-C(25)	113.7(2)		
C(22)-N(3)-C(28)	131.2(2)		
C(25)-N(3)-C(28)	110.2(2)		
C(32)-N(4)-C(33)	111.8(3)		
C(32)-N(4)-C(40)	124.1(3)		

Table E.40. [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2A)...O(11)#1	0.88(5)	2.06(5)	2.871(3)	152(4)
O(3)-H(3A)...O(6)	0.86(4)	1.95(4)	2.761(3)	156(3)
O(10)-H(10A)...O(9)#2	0.84	1.88	2.720(3)	175.2
O(11)-H(11A)...O(14)	0.83(4)	1.94(4)	2.736(3)	162(3)
O(12)-H(12A)...O(4)#3	0.98(6)	2.03(6)	2.686(3)	122(4)

Symmetry transformations used to generate equivalent atoms:

#1 -x+3/2,y-1/2,-z+1/2 #2 -x+1,-y+2,-z #3 -x+3/2,y+1/2,-z+1/2

*E.10. Crystal Structure of Bicycle **4.66***

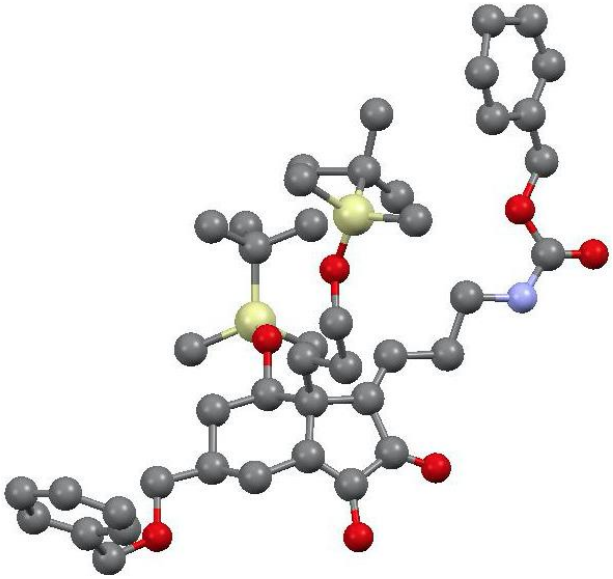

Figure E.10. Ball and stick model of **4.66**

X-ray data for this compound was poor, resolving only up to ~ 1 Å. The data though, was sufficient to allow for elucidation of the connectivity and relative stereochemistry.

*E.11. Crystal Structure of Allene **A.08***

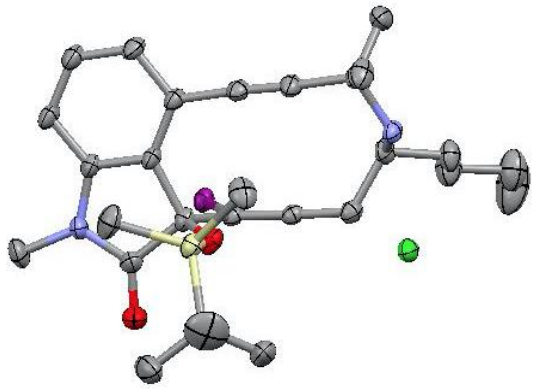

Figure E.11. ORTEP drawing of Allene **A.08**

APPENDIX F

Biological Screening Data

*F.01. Screening Data for Hexacyclic Ester **3.98***

Developmental Therapeutics Program
One Dose Mean Graph

NSC: D-802508 / 1	Conc: 1.00E-5 Molar	Test Date: Dec 04, 2017
Experiment ID: 1712OS07		Report Date: Aug 13, 2018

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	97.00
HL-60(TB)	129.36
K-562	165.59
RPMI-8226	97.13
Non-Small Cell Lung Cancer	
A549/ATCC	97.19
EKVX	104.16
HOP-62	90.68
HOP-92	117.67
NCI-H226	113.17
NCI-H23	106.70
NCI-H322M	98.35
NCI-H460	107.62
NCI-H522	85.79
Colon Cancer	
HCC-2998	92.86
HCT-116	97.63
HCT-15	105.69
HT29	105.14
KM12	107.87
SW-620	102.96
CNS Cancer	
SF-268	107.91
SF-295	104.19
SF-539	103.73
SNB-19	95.47
SNB-75	79.54
U251	98.70
Melanoma	
MALME-3M	96.32
M14	103.59
MDA-MB-435	103.12
SK-MEL-2	88.49
SK-MEL-28	74.86
SK-MEL-5	114.00
UACC-257	100.10
UACC-62	95.71
Ovarian Cancer	
IGROV1	120.26
OVCAR-3	118.06
OVCAR-4	103.15
OVCAR-5	103.85
OVCAR-8	97.17
NCI/ADR-RES	101.25
SK-OV-3	101.34
Renal Cancer	
786-0	100.44
A498	111.70
ACHN	92.10
CAKI-1	101.84
RXF 393	117.64
SN12C	104.11
TK-10	103.94
UO-31	88.83
Prostate Cancer	
PC-3	101.80
DU-145	104.70
Breast Cancer	
MCF7	104.29
MDA-MB-231/ATCC	121.09
HS 578T	103.67
BT-549	95.21
MDA-MB-468	111.86
Mean	103.57
Delta	28.71
Range	90.73

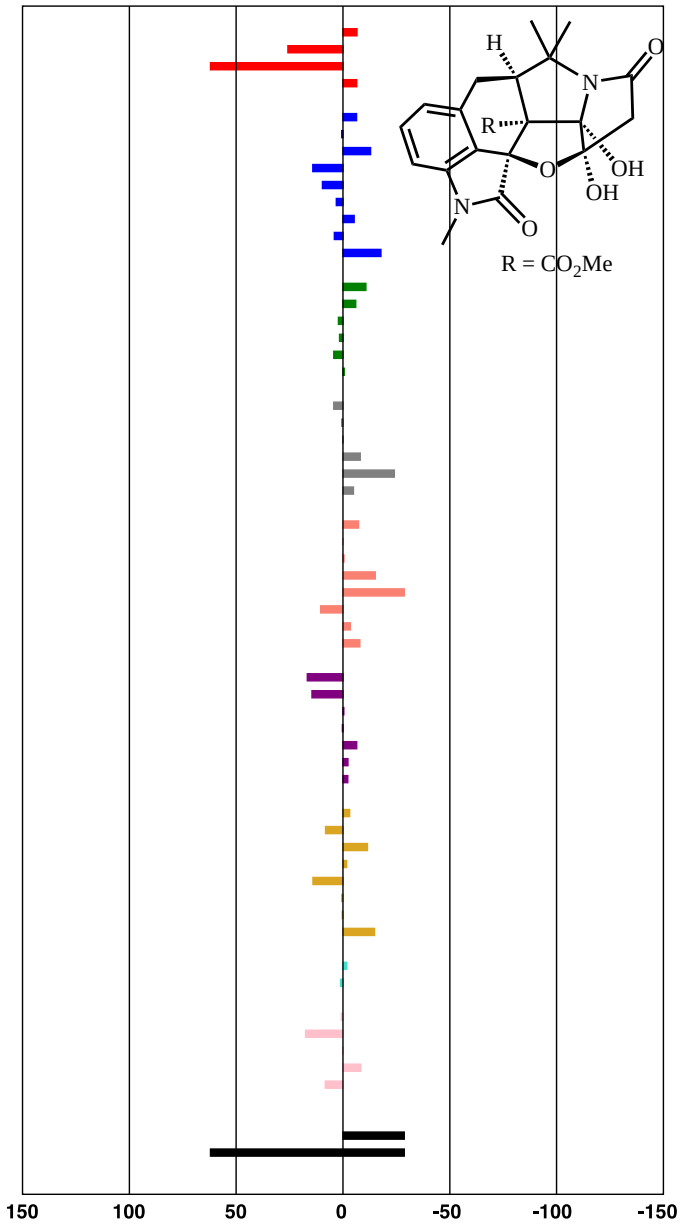

Figure F.01. Biological screening results for hexacyclic ester **3.97**

*F.02. Screening Data for Hexacyclic Acid **3.99***

Developmental Therapeutics Program
One Dose Mean Graph

NSC: D-802509 / 1	Conc: 1.00E-5 Molar	Test Date: Dec 04, 2017
Experiment ID: 1712OS07		Report Date: Aug 13, 2018

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	96.33
HL-60(TB)	98.32
K-562	98.06
RPMI-8226	93.44
Non-Small Cell Lung Cancer	
A549/ATCC	94.94
EKVX	103.72
HOP-62	94.70
HOP-92	100.43
NCI-H226	105.79
NCI-H23	102.88
NCI-H322M	99.07
NCI-H460	107.50
NCI-H522	87.05
Colon Cancer	
HCC-2998	98.88
HCT-116	97.82
HCT-15	103.26
HT29	91.96
KM12	103.42
SW-620	109.34
CNS Cancer	
SF-268	99.75
SF-295	103.30
SF-539	100.80
SNB-19	103.90
SNB-75	86.08
U251	104.64
Melanoma	
MALME-3M	125.29
M14	100.76
MDA-MB-435	101.77
SK-MEL-2	105.31
SK-MEL-28	115.57
SK-MEL-5	107.29
UACC-257	97.46
UACC-62	104.93
Ovarian Cancer	
IGROV1	111.35
OVCAR-3	109.89
OVCAR-4	110.22
OVCAR-5	91.84
OVCAR-8	97.56
NCI/ADR-RES	102.04
SK-OV-3	105.22
Renal Cancer	
786-0	100.22
A498	103.26
ACHN	101.68
CAKI-1	96.88
RXF 393	127.99
SN12C	101.42
TK-10	95.45
UO-31	89.61
Prostate Cancer	
PC-3	102.89
DU-145	94.94
Breast Cancer	
MCF7	99.05
MDA-MB-231/ATCC	117.17
HS 578T	105.73
BT-549	104.90
MDA-MB-468	110.52
Mean	102.25
Delta	16.17
Range	41.91

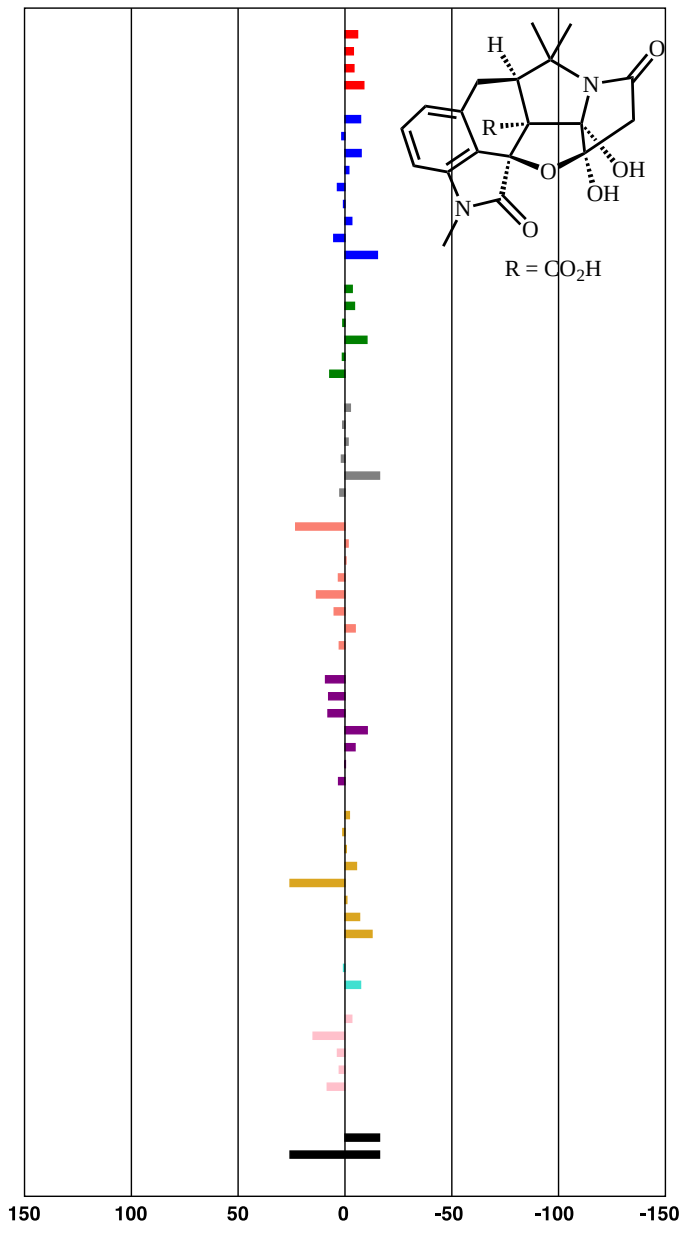

Figure F.02. Biological screening results for hexacyclic acid **3.98**

F.03. Screening Data for Cyclopiamide A ***3.02***

Developmental Therapeutics Program
One Dose Mean Graph

NSC: D-802510 / 1 | **Conc:** 1.00E-5 Molar | **Test Date:** Jan 08, 2018
Experiment ID: 1801OS23 | **Report Date:** Aug 13, 2018

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	95.14
HL-60(TB)	91.82
K-562	103.49
MOLT-4	97.53
RPMI-8226	97.35
Non-Small Cell Lung Cancer	
A549/ATCC	86.58
EKVX	107.61
HOP-62	91.84
HOP-92	82.74
NCI-H226	86.97
NCI-H23	101.56
NCI-H322M	99.30
NCI-H460	101.61
NCI-H522	77.58
Colon Cancer	
COLO 205	106.34
HCC-2998	99.42
HCT-116	89.98
HCT-15	100.73
HT29	88.36
KM12	110.15
SW-620	92.75
CNS Cancer	
SF-268	96.29
SF-295	107.16
SF-539	99.08
SNB-19	101.79
SNB-75	96.67
U251	96.90
Melanoma	
LOX IMVI	103.13
MALME-3M	126.66
M14	94.40
MDA-MB-435	111.43
SK-MEL-2	89.12
SK-MEL-28	102.79
SK-MEL-5	101.79
UACC-257	96.29
UACC-62	93.48
Ovarian Cancer	
IGROV1	101.01
OVCAR-3	112.89
OVCAR-4	106.04
OVCAR-5	82.43
OVCAR-8	95.54
NCI/ADR-RES	96.99
SK-OV-3	91.90
Renal Cancer	
786-0	91.74
A498	92.78
ACHN	105.65
CAKI-1	90.21
RXF 393	108.05
SN12C	99.47
TK-10	83.49
UO-31	82.84
Prostate Cancer	
PC-3	92.91
DU-145	110.48
Breast Cancer	
MCF7	92.35
MDA-MB-231/ATCC	104.93
HS 578T	101.50
BT-549	94.39
T-47D	79.47
MDA-MB-468	102.73
Mean	97.38
Delta	19.80
Range	49.08

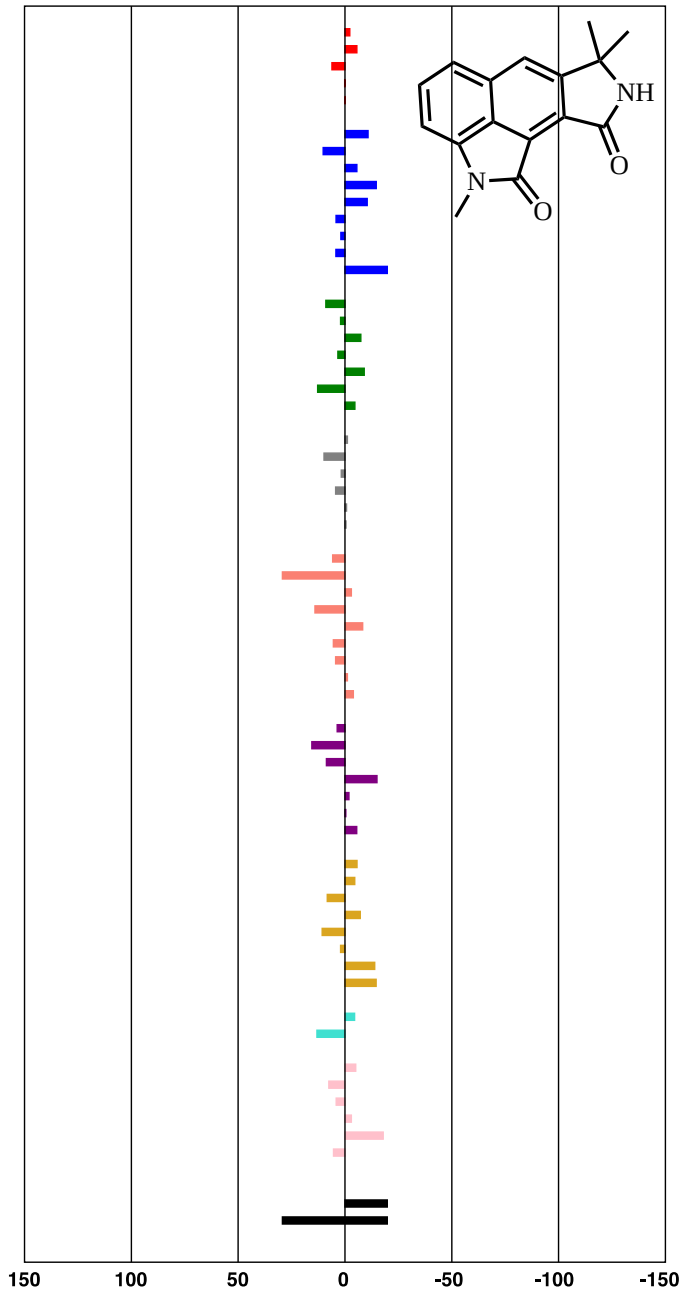

Figure F.03. Biological screening results for cyclopiamide A **3.02**

APPENDIX G

Compound Notebook Cross Reference

COMPOUND NOTEBOOK CROSS REFERENCE

2.34..... MCN_1_249
2.35.....MCN_1_253 & MCN_2_028
2.08..... MCN_2_029
2.14..... MCN_2_034
2.17..... MCN_2_009
2.18..... MCN_2_031
2.38..... MCN_1_268
2.39..... MCN_2_016
2.11..... MCN_2_017
2.21..... MCN_2_018
2.41..... MCN_2_020
2.09..... MCN_2_021
2.22..... MCN_2_032
2.43..... MCN_2_022
2.12..... MCN_2_023
2.24..... MCN_2_030
2.44..... MCN_2_036
2.45..... MCN_2_037
2.10..... MCN_2_038
2.31& 2.32..... MCN_2_039

3.111..... MCN_2_105
3.20..... MCN_4_040
3.11..... MCN_4_043
3.18..... MCN_2_048
3.21..... MCN_4_053
3.31..... MCN_4_055
3.34..... MCN_2_136
3.35..... MCN_2_143
3.45..... MCN_4_057
3.46..... MCN_4_058
3.47..... MCN_3_014
3.49..... MCN_4_059
3.54..... MCN_4_060
3.55..... MCN_3_057
3.58..... MCN_3_059
3.56..... MCN_3_065
3.68..... MCN_3_081
3.70..... MCN_3_089
3.73..... MCN_4_004

3.85..... MCN_4_025
3.86 & 3.87.....MCN_4_023 & MCN_5_062
3.97..... MCN_5_073
3.98..... MCN_4_026
3.99..... MCN_4_034
3.100..... MCN_4_052
3.102..... MCN_4_056
3.107..... MCN_5_075
3.113..... MCN_5_096
3.108..... MCN_5_097
3.114..... MCN_5_098
3.01..... MCN_5_099
3.26..... MCN_2_119
3.28..... MCN_5_118
3.32..... MCN_5_119
3.33..... MCN_5_120
3.02..... MCN_5_123
3.109..... MCN_5_131
3.03..... MCN_5_133

4.34..... MCN_6_029
4.35 & 3.87..... MCN_5_261
4.37..... MCN_6_035
4.38..... MCN_6_036
4.39..... MCN_6_038
4.45..... MCN_6_010
4.46..... MCN_6_013
4.47..... MCN_6_020
4.48..... MCN_6_029
4.50..... MCN_5_255
4.63 & 4.64..... MCN_5_283
4.65 & 4.66..... MCN_6_047
4.67..... MCN_6_050
4.68..... MCN_6_049

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ABOUT THE AUTHOR

Mina Cyril Nakhla was born in Adelaide, Australia, on May 26th 1990 to Jacqueline Girgis and Fady Nakhla. After spending 2.5 years in Australia, Mina moved to Montreal in the province of Quebec in Canada and in 1994 moved to Toronto, Ontario. Mina attended Mississauga Christian Academy from kindergarten to the 4th grade (ages 5 – 9). At the age of eight he obtained his first chemistry set and began to be infinitely enamoured with science. Despite the chemistry sets coming with detailed instructions, Mina did completely ignore essentially all instructions provided and decided to set up experiments of his own design. This attitude, which has been a staple of the author's personality throughout his life, has always led to many interesting discoveries … and even more trouble. In late 1999, Fady decided to relocate his family to Austin,Texas. Mina initially attended Wells Branch elementary school in Pflugerville, Texas (4th grade) but quickly relocated to Hilltop Christian Academy until the end of the 9th grade (skipping the 8th grade). Mina then attended Vista Ridge high school (2004–2007). All through this time his interest in science did not diminish; due to this he attended St. Edward's university and majored in biochemistry, with a pre-med track (2007–2011). Quickly after beginning to study organic chemistry in his sophomore year, he realized that he did not wish to attend medical school but would rather continue studying organic chemistry. His first formal introduction to chemistry research was begun in his sophomore year under the direction of Eammon Healy. Dr. Healy's research focused on *in-silico* design and modeling of inhibitors and their binding modes into protein's active sites. Specifically, Mina designed inhibitors for the mycobacterium tuberculosis bacterium's enol acyl protein reductase. Though Dr. Healy's

students did not generally synthesize the inhibitors, Mina convinced him to allow for the synthesis of some of the more potent ones. Despite all of the research and studies, Mina found his desire to explore and experiment unsatisfied and as such constructed a home laboratory, fully equipped with all the needed glassware, fume hoods, vacuum pumps and even a double manifold. In this lab, much discovery and mischief ensued, ultimately solidifying Mina's desire to attend graduate school. At the beginning of his senior year of undergrad Mina begun applying to graduate programs and was in the winter accepted to The Ohio State University. After graduating with a bachelor's degree in May of 2011, Mina began graduate research at The Ohio State University in the summer prior to his first year. His research during the summer of 2011 was performed under the direction of Craig Forsyth and focused on the synthesis of a ribose based inhibitor. In the middle of his first year of graduate school he joined the Badjić group. The Badjić group focuses on the design of molecular baskets for the encapsulation of various guests, particularly organophosphate nerve agent surrogates. While working under the direction of Jovica Badjić, Mina, with a bit of guidance from Dr. Bao-Yu Wang, designed and synthesized a molecular claw cavitand which was functionalized on its interior surface. At the end of his second year, due to poor judgement and a large portion of misdirected passion towards chemistry Mina left Ohio State University and soon began work at a Samsung processor fabrication facility in Austin, Texas. After a year away from academia Mina entered Baylor University, being drawn in by the elegant work of John L. Wood. With reinvigorated passion Mina begun research in the Wood group. Over the next four years he was able to complete a methodology involving chemoselective carbonyl ylide formation and the total synthesis of (±)-aspergilline A, cyclopiamide A and speradine E. Finally, he also began synthetic

studies toward Isopalhinine A. In Mina's fourth year he passed the final project onto then first year student Collin Mondrick in preparation of his upcoming move to Harvard for post-doctoral research under Yoshito Kishi. The post-doctoral position under professor Kishi was not a planned moved, instead it was a twist in life initiated by the surprising call of professor Kishi to professor John Wood in search of a post doc. With a post-doctoral position lined up the author defended at the end of September 2018 looking forward to the move to Boston and Harvard in the following November.