SYNTHESIS OF THE KEY FRAGMENTS OF MICROCOCCIN P1 AND THIOCILLIN I

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Synthesis of the Key Fragments of Micrococcin P1 and Thiocillin I

Thesis Directed by Assistant Professor Maciej Walczak

ABSTRACT

Thiopeptide antibiotics are members of the ribosomally synthesized and post-translationally modified peptide class of natural products. They contain a unique trisubstituted six-membered nitrogen ring decorated with azol(in)e heterocycles, dehydroamino acids, and a macrocyclic structure. Thiopeptides act by inhibiting the bacterial ribosome and have demonstrated potent activities against a wide range of Gram-positive pathogens.

This work describes the synthesis of the two key fragments used in our total syntheses of micrococcin P1 and thiocillin I. The “bottom” fragments were assembled through modification and coupling of amino acids as well as the use of a molybdenum catalyzed cyclodehydration of cysteine residue to form the unique thiazole which differs from micrococcin P1 and thiocillin I. The “top” fragment was constructed using a C-H activation as the first step, a molybdenum catalyzed cyclodehydration to install the second thiazole, and a Stille/Hantzsch strategy to install the final thiazole heterocycle. The studies that lead to the efficient syntheses of these two fragments is reported.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

Ac	Acetyl, acetate
Alloc	Alloxycarbonyl
Anh	anhydrous
Aq.	Aqueous
Bn	Benzyl
Boc	*tert*-butoxycarbonyl
br	Broad
b.r.s.m	Based on recovered starting material
BTEAC	Benzyltriethylammonium chloride
Bu	butyl
ºC	Degrees Celsius
Calcd	calculated
Cbz	Carboxybenzyl
CSA	Camphorsulfonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DME	1,2-dimethoxyethane
DMF	Dimethylformamide
DPPA	Diphenylphosphoryl azide
EDCI	1-Ethyl-3-(3dimethylaminopropyl)carbodiimide
Equiv.	Equivalent
ESI	Electrospray ionization
Et	Ethyl
Fmoc	Fluorenylmethyloxycarbonyl
h	hour
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate, N-[(Dimethylamino)-1H-1,2,3-triazolo-[4,5-

	b]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate *N*-oxide
HOBt	Hydroxybenzotriazole
HRMS	High Resolution Mass Spectrometry
*i*Pr	Isopropyl
IR	Infrared
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	Methyl
MeCN	Acetonitrile
Ms	Methanesulfonyl
MsCl	Methanesulfonyl chloride
NBS	*N*-bromosuccinimide
NMR	Nuclear Magnetic Resonance
p	*para*
pH	Hydrogen ion concentration in aqueous solution
PIDA	(diacetoxyiodo)benzene
PPTS	Pyridinium *p*-toluenesulfonate
PTSA	*p*-toluenesulfonic acid
pyr	Pyridine
q	Quartet
rt	Room temperature
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TBSOTf	*tert*-Butyldimethylsilyl trifluoromethanesulfonate
t-Bu	*tert*-butyl
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy, free radical, 2,2,6,6-Tetramethylpiperidine 1-oxyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography

Trt	Trityl

CHAPTER ONE

Thiopeptides: A Class of Biologically Active Peptide Natural Products

1.1 The Problem of Antibiotic Resistance

The early antibiotic era began at the turn of the 20th century, following in the footsteps of the chemical dye industry that exploded decades prior. The German biochemist Paul Ehrlich had been fascinated with dyes because they had a strong affinity for tissues. He hypothesized that the treatment of infectious disease could operate similarly, and molecules could be created that had heightened affinities for specific organisms, allowing them to selectively bind and kill pathogens. Ehrlich screened hundreds of compounds which resulted in the in the discovery of Salvarsan in 1909, the first widely used antibiotic for the treatment of syphilis. A few decades later in 1932, the discovery of Prontosil, which contained a sulfanilamide functional group, led to the widespread use of the sulfonamide class of antibiotics. However, it wasn't until the discovery of penicillin in 1928 by Alexander Fleming that the golden age of antibiotics truly began. Unlike previous antibiotics that were fully synthetic, penicillin was isolated from a natural source and produced by fermentation, which enabled its large-scale preparation and application in the 1940's. Thus, the primary method for finding new antibiotic agents shifted away from strictly chemical synthesis towards natural products isolation.[1-2]

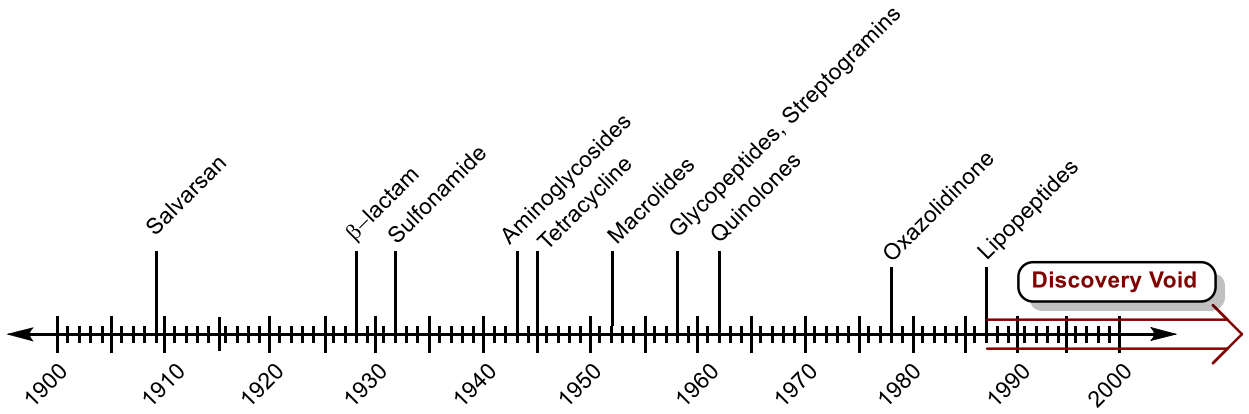


Figure 1.1 Timeline of discovery for selected antibiotic classes from 1900 to 2000.[3]

The decades following the 1940's were a bountiful time that witnessed the discovery of virtually all classes of antibiotics in use today. For example, β-lactams, aminoglycosides, cephalosporins, glycopeptides, streptogramins, tetracyclines, macrolides, and quinolones are some of the major classes that were discovered during this time.[3] Since the 1980's, however, the rate of new antibiotic discovery has significantly diminished. Furthermore, antibiotic resistance was observed for the majority of the antibiotics discovered even a few years after their introduction into the clinic. As of 2013, over 2 million cases of drug-resistant pathogenic diseases were identified and has resulted in over 23,000 deaths. It has become evident that the inappropriate use of current antibiotic treatments has accelerated the rate at which resistance develops.[4]

Our collective ability to combat the rise of antibiotic resistance hinges on the (1) economic feasibility of new drug discovery and (2) the rapid rate at which pathogens develop resistance to new treatments. The pharmaceutical industry, once a leading force in the discovery of antibiotics, abandoned their search for antibiotics leaving the majority of drug discovery to research laboratories.[5] Despite the efforts sustained towards discovering new chemical entities, the rediscovery rate of natural products remains high because classical antibiotic screening methods

are ineffective.[3, 6] This pressure forced researchers to develop new strategies for discovering natural products. These efforts culminated in the discovery and methods for mining biosynthetic gene clusters (BGCs), cryptic and often silent genes, that contain the information necessary for producing novel natural products. [2, 6-10] Thiopeptides are an increasingly important class of natural products, found in BGCs of several organisms, and display potent biological activities. This promising class of natural products have the potential to overcome the problem of antibiotic resistance.

1.2 The Biosynthesis and Structure of Thiopeptides

For a long time, the biosynthetic origin of thiopeptides was unknown, however, the discovery of biosynthetic gene clusters belonging to thiopeptides settled the debate as to the origin of these natural products.[11] It was found that thiopeptides belong to a class of natural products termed ribosomally synthesized and post translationally modified peptides (RiPPs). This family of natural products typically contains dehydroamino acids and azol(in)e heterocycles. Thiopeptides, lanthipeptides, cyanobactins, bottrimycins and linear azol(in)e peptides are all classes of RiPPs.[12]

Thiopeptides are distinguished from the other RiPP classes by their central six membered nitrogen heterocycle encased in a larger macrocyclic structure. Thiopeptides are classified as A-E, depending on the oxidation states of the heterocyclic core (**Figure 1.2**). The A-type core contains a fully-saturated piperidine ring, the B-type contains an unsaturated dehydropiperidine ring (e.g. thiostrepton), the C-type contains a fused piperidine-imidazoline ring, the D-type contains a pyridine ring (e.g. micrococcin/thiocillin I, LFF571), and the E-type contains a 5-hydroxypyridine ring (e.g. nosiheptide). Thiopeptides also contain other structural features common to the RiPPs

such as the presence of thiazol(in)e and oxazol(in)e heterocycles, dehydroalanine and dehydrobutyrine fragments, and a quinaldic or indolic acid residue.

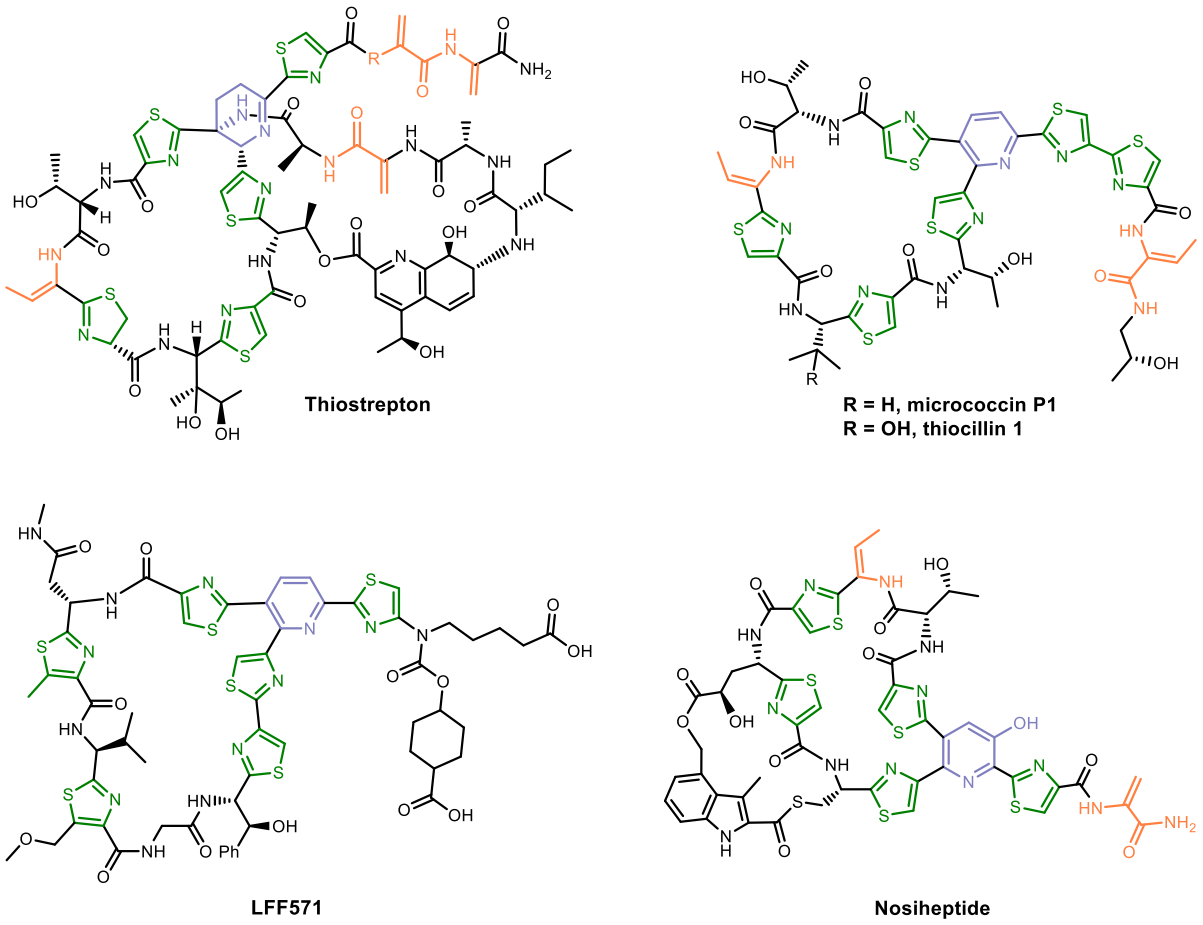


Figure 1.2 Selected thiopeptide structures.

The structure of thiopeptides is intimately related to their specific BGCs.[13-14] The BGCs for thiostrepton, thiocillin, nosiheptide, nocathiacin, siomycin and many others have been found and characterized.[15-17] A minimum of six enzymes carry out the necessary biosynthetic transformations to fully form the natural product from the structural peptide. This structural peptide is rich in serine, threonine, and cysteine residues which are transformed into the various azole heterocycles and dehydroamino acid residues. The first modification is performed by

cyclodehydratases which cyclize cysteine and threonine or serine residues to form thiazoline and oxazoline heterocycles respectively. The dehydratases then oxidize the azoline into an azole heterocycle. In the second step, serine and threonine hydroxyl groups are eliminated to form the dehydroalanine and dehydrobutyrine residues.[18] Lastly the combination of two dehydroalanine residues are enzymatically combined via a [4+2] aza-cycloaddition reaction.[19] Further modifications like methylations, oxidations, cyclizations, or incorporation of quinaldic/indolic acid residues are performed by tailoring enzymes after macrocyclization has occurred.[14]

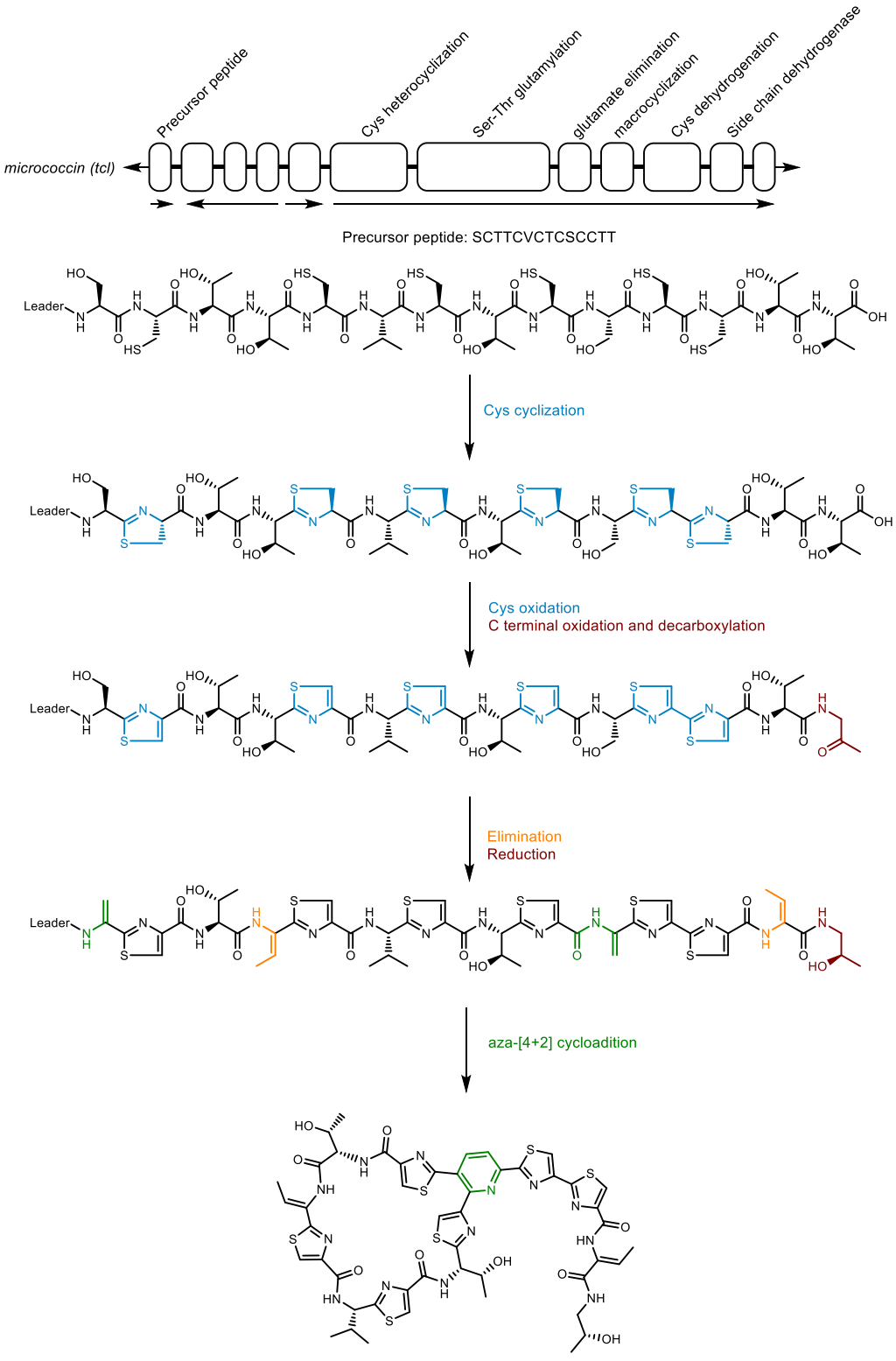


Figure 1.3 Proposed biosynthetic pathway for micrococcin.

1.3 The Biological Activities of Thiopeptides

Thiopeptides display numerous biological activities. The most important is their antibacterial activity against drug resistant pathogens. They inhibit the ribosome of Gram-positive bacteria and, depending on the size and macrocycle type, the mechanism of inhibition can vary.[11] Thiostrepton, nosiheptide, and micrococcin block the binding of elongation factor G (EF-G) to the L11 ribosomal protein/23S RNA complex which prevents translocation of tRNA and growth of the peptide chain.[20-22] Thiomuracins and GE2270A exhibit a separate mode of action by binding to EF-Tu, which shuttles the aminoacylated tRNA to the ribosome. Binding to EF-Tu prevents its association with the ribosome and halts protein synthesis.[23-25]

Many of the thiopeptides such as nocathiacin,[26-31] thiostrepton,[21-22, 32] amythiamicin,[33] GE2270A,[34] and nosiheptide[35] strongly inhibit the drug resistant pathogens *Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus pneumonia*, *Bacillus subtilis*, and *Klebsiella pneumoniae* in the nM to low μM range. Moreover, thiazomycin and nocathiacin demonstrated activity against drug resistant clinical strains of *Mycobacterium tuberculosis*.[36] Recently, the Fischbach group discovered lactocillin, a D-series thiopeptide, and initial screening demonstrated intriguing activities against various oral and vaginal pathogens. Lactocillin's recent discovery and low bioavailability has prevented further studies.[37]

Despite their strong biological profiles, there are few thiopeptides actively utilized in a therapeutic capacity. A representative example is thiostrepton, which finds applications as an animal antibiotic due to its (1) low toxicity toward mammalian cells and (2) target-specificity for the bacterial ribosome.[22] Unfortunately, its poor solubility and susceptibility toward pathogen-resistance precludes its use in humans. Another promising therapeutic candidate was LFF571, a

semisynthetic thiopeptide based on GE2270A that reached Phase II clinical trials under Novartis. It displayed a good solubility profile, didn't cause resistance, and had good activities against pathogens;[38-46] unfortunately, Novartis discontinued pursuit of this target due to the high cost of development.

1.4 Total Synthesis of Thiopeptides

The first thiopeptide to be reported in the literature was micrococcin in 1948.[47] In the following years the same substance was identified from multiple sources around the globe.[48-50] While the structure remained elusive for several decades, researches determined in the 1970s that micrococcin was a 7:1 mixture of two compounds designated micrococcin P1 and micrococcin P2. They determined the chemical constitution of micrococcin via acid hydrolysis experiments,[51] although the exact structure of micrococcin P1 remained uncertain until its total synthesis in 2009 by Ciufolini.[52-53] Prior to this critical insight, Shin and coworkers began work on synthesizing micrococcin in the 1990s and reported its total synthesis in 1998.[54-56] Unfortunately, the authors mistakenly claimed they synthesized micrococcin P and micrococcin P1, (as if they were the same entity) when they had, in fact, failed to produce the correct molecule.

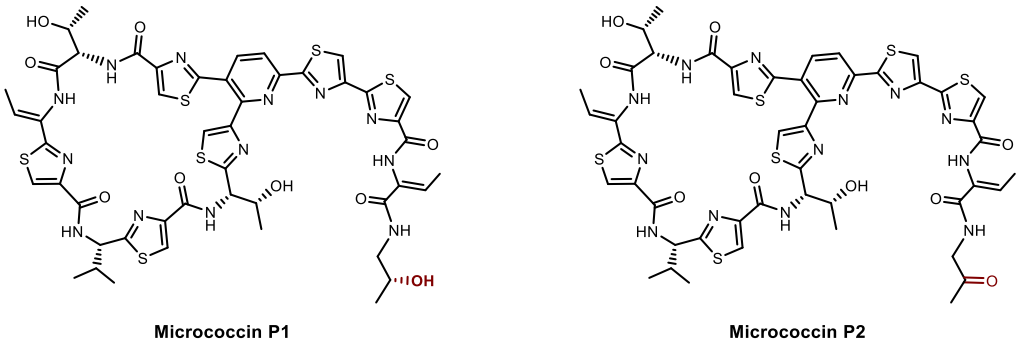


Figure 1.4 Structures of micrococcin P1 and P2

Moody's group successfully synthesized two thiopeptides: and their work marks the first complete total synthesis of a thiopeptide, promothiocin A, which they finished in 1998.[57-59] Moody then set out to work on the synthesis of amythiamicin D which was completed in 2004.[60-61] Nicolaou began the synthesis of thiostrepton in 2000, which culminated in a series of papers published in JACS in 2005.[62-65] The years 2007 to 2011 witnessed a peak in productivity for the total synthesis of thiopeptides with GE2270A (Bach, 2007),[66] Siomycin A (Nakata, 2008),[67-68] amythiamicin A, B, C (Nicolaou, 2008),[69] GE2270 A, T, C1 (Nicolaou, 2008),[70] micrococcin P1 (Ciufolini, 2009),[52] Amythiamicin C, D (Bach, 2010),[71] and thiocillin I (Ciufolini, 2011)[72] – all being synthesized in quick succession. Over the next five years only two total syntheses were published, namely, baringolin (Alvarez, 2013)[73] and Nosiheptide (Arndt, 2016).[74]

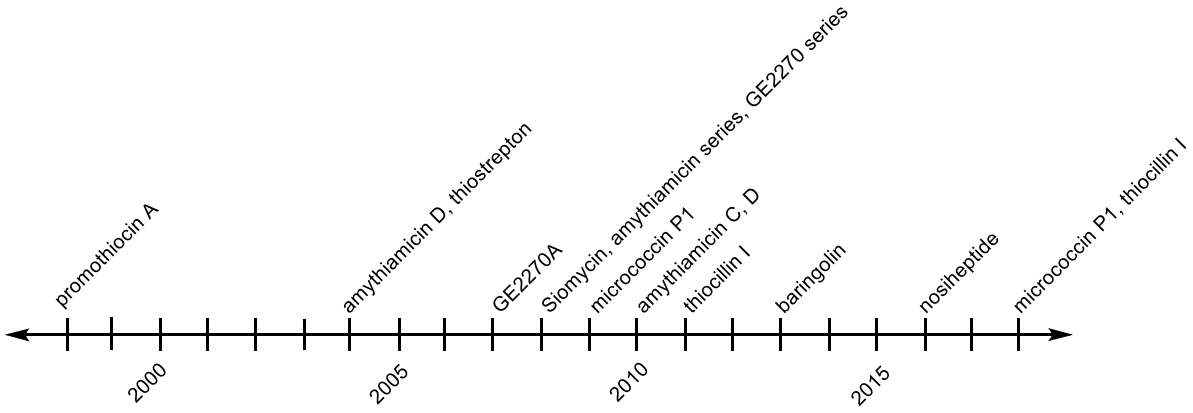
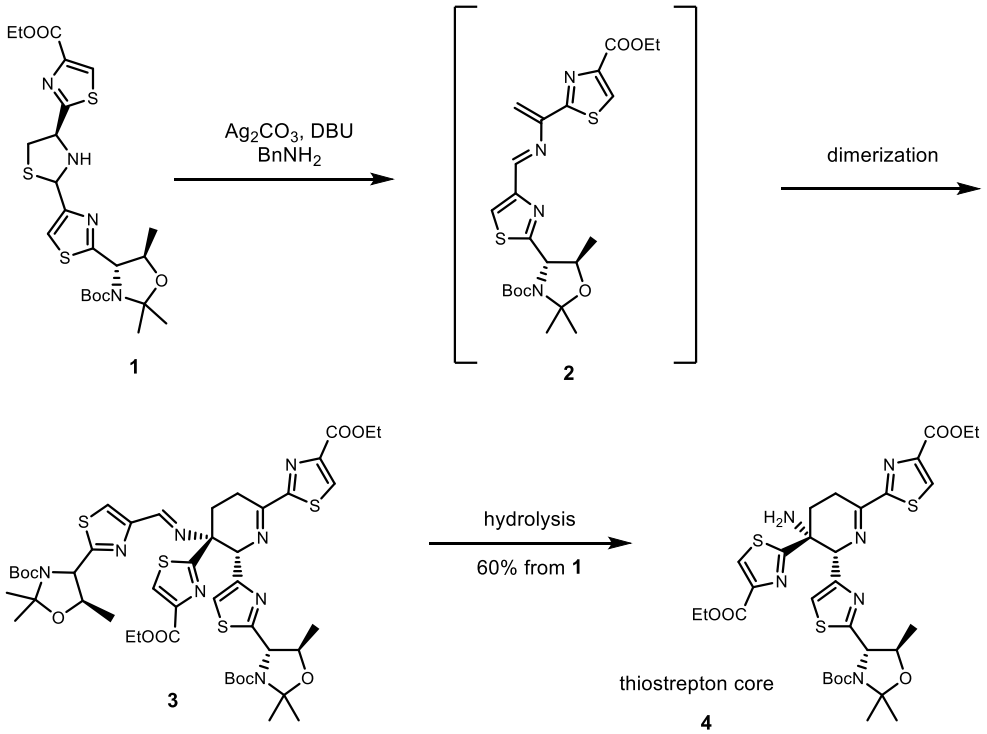


Figure 1.5 Publication Timeline for the total synthesis of thiopeptide antibiotics.

Two approaches have been utilized to construct the central six-membered heterocycle: (1) construction of the nitrogen core *de novo* and (2) modification of a pyridine ring. For example, Ciufolini and Nicolaou synthesized the pyridine ring through a Hantzsch-type pyridine synthesis

and aza-Diels Alder respectively. Bach took the latter approach and modified a pyridine ring through sequential cross coupling reactions.

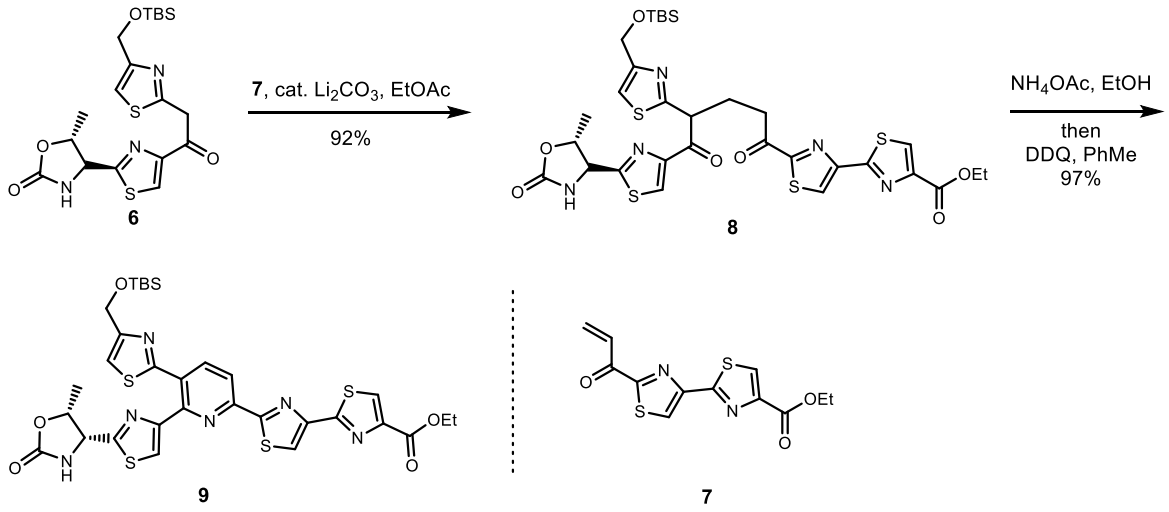
Extensive studies to synthesize the piperidine ring in thiostrepton was undertaken by Nicolaou et. al. (**Scheme 1.1**). He found that thiazolidine **1** could be transformed into an aza-diene **2** using Ag_2CO_3 and DBU, and then dimerized to form intermediate **3**, which hydrolyzes in the presence of benzylamine and water to give thiostrepton core **4**. In Nicolaou's syntheses of the amythiamicin series and the GE2270 series, he demonstrated that the aminodehydropiperidine ring can be converted into the pyridine core in the presence of DBU.[65, 75]



Scheme 1.1 Nicolaou's synthesis of the thiostrepton core.

Ciufolini has done important work in the synthesis and characterization of micrococcin P1. It's structure and configuration were a mystery until his landmark total synthesis in 2009. He

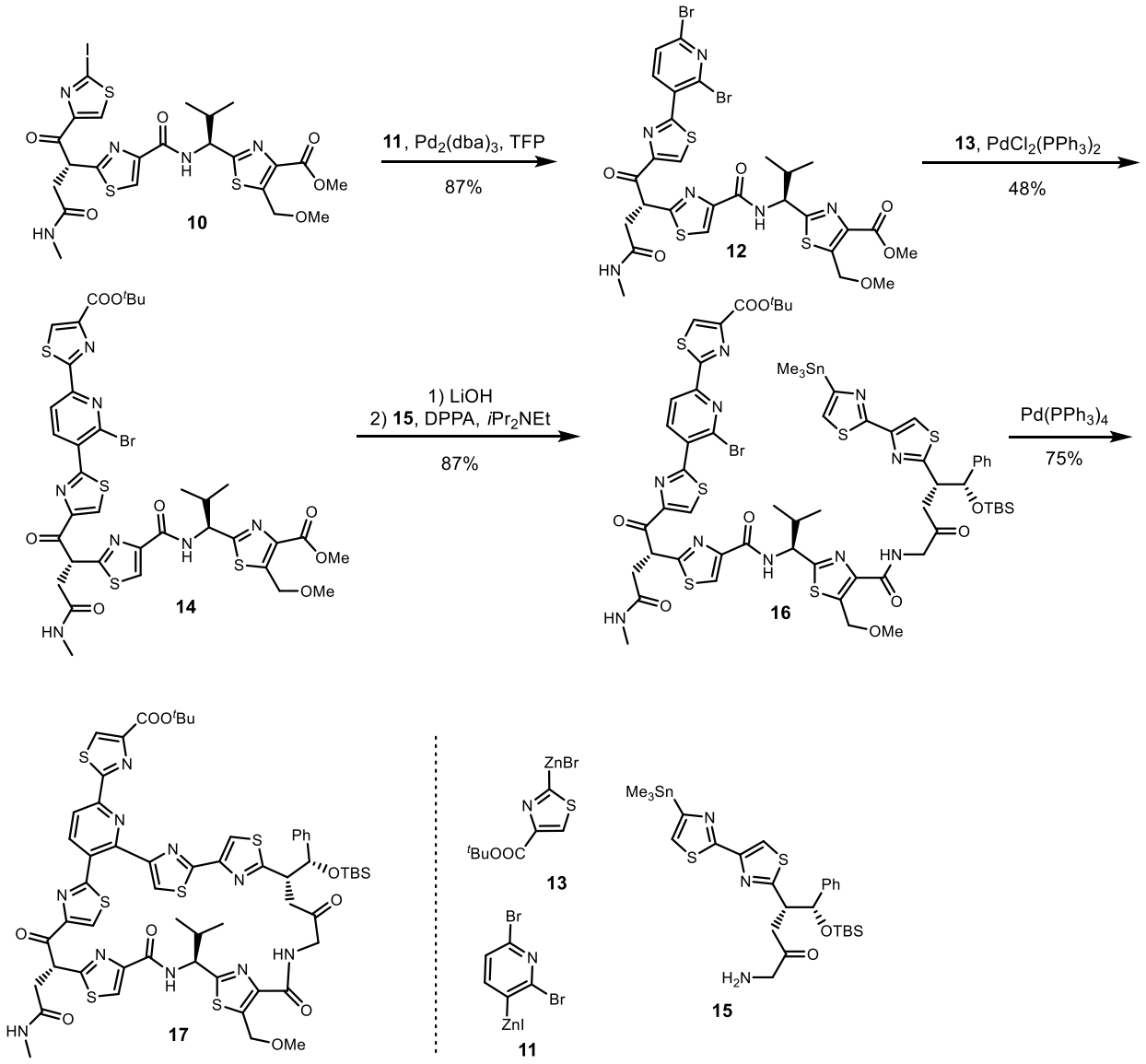
approached the synthesis of the pyridine core by combining two fragments **6** and **7** together and aromatizing into the core. After synthesizing **6** and **7**, he experimented extensively for conditions that would allow for the Michael addition of enolizable **6** and α, β- unsaturated ketone **7**. Eventually he found that a catalytic system using $LiCO_3$ in ethyl acetate cleanly afforded the product without decomposition, polymerization or side reactions. Thus **8** was obtained in a 92% yield. Cyclization with NH_4OAc, and aromatization with DDQ formed the core **9** in 97%. Building off of this work he completed the synthesis of thiocillin I using a modified procedure to complete the core.[52, 72, 76]



Scheme 1.2 Ciufolini's synthesis of micrococcin P1 core.

Bach's contribution to thiopeptide synthesis is applying the use of cross coupling reactions to the synthesis of thiopeptides. In the synthesis of GE2270A, Bach and coworkers used advanced peptide intermediate **10** and performed a Negishi coupling to trisubstituted bromopyridine **11** to form the coupled product **12** in 87%. This intermediate was subjected to another Negishi coupling but with zinc iodide reagent **13** which coupled at the *C*-6 position to form **14**. After a peptide

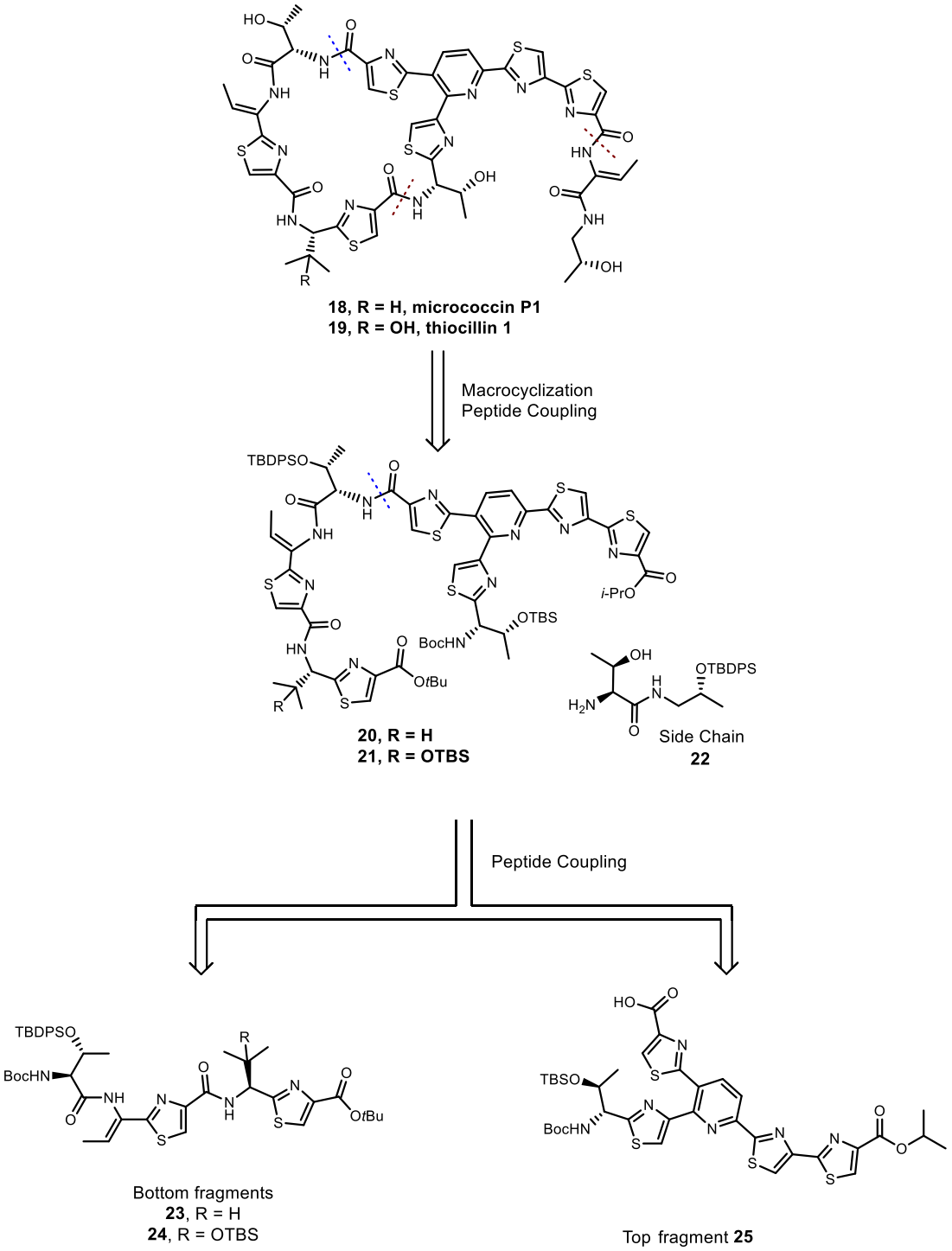
coupling to advanced intermediate stannane **15**, **16** was cross-coupled intramolecularly to yield macrocycle **17** in 75%.[66, 77]



Scheme 1.3 Bach's synthesis of GE2270A core.

1.5 General Retrosynthetic Strategy

Micrococcin and thiocillin can be assembled from three distinct pieces: the top fragment **25**, the bottom fragments **23/24** and a side chain **22**. Each of these retrosynthetic disconnections is made at an amide bond. Macrocyclization can occur in two places, those represented on **Scheme 1.4** as red and blue disconnections on **18/19**. Previous work by Ciufolini established that macrocyclization at the blue disconnection does not result in an efficient cyclization while those at the red disconnection react much more readily. Thus the order of joining the top and bottom fragments would be peptide coupling at the blue disconnection first and macrocyclization at the red disconnection second. In addition to this, the use of protecting groups is important and orthogonal deprotection strategies are required. In our studies, acidic and basic labile protecting groups were used. We imagined that the alcohols of the threonine residues be protected with silyl protecting groups and the C- and N- termini would be protected with acid sensitive protecting groups (Boc and -O*t*Bu). In this way, a global deprotection of the natural product could be achieved directly pre-macrocyclization. Side chain **22** would be attached after the first peptide coupling between the top and bottom fragments, as the isopropyl ester is labile under basic conditions.



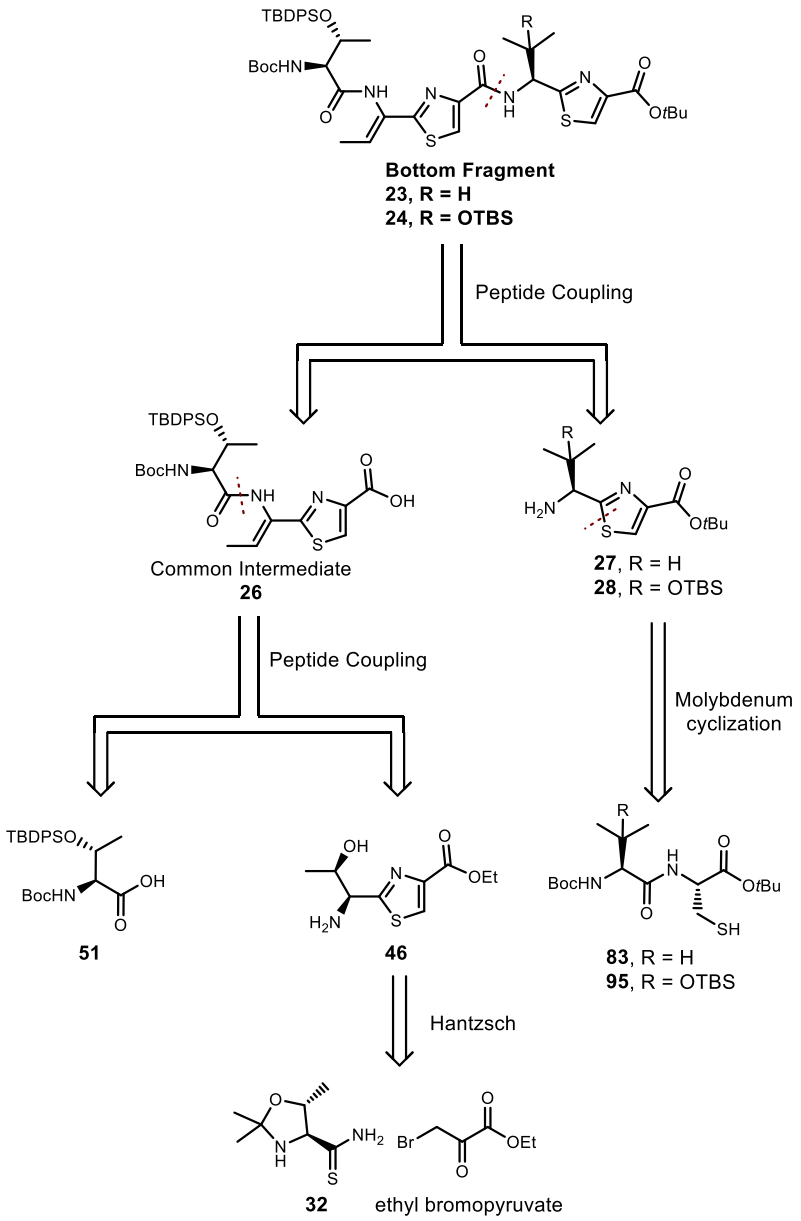
Scheme 1.4 General retrosynthetic analysis of micrococcin P1 and thiocillin I.

CHAPTER TWO

Synthesis of the Bottom Fragments 23 and 24

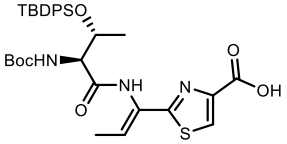
2.1 Retrosynthetic Analysis of 23 and 24

Micrococcin P1 and thiocillin I differ by one hydroxyl group on the valine residue, the latter thiopeptide containing the hydroxyl group. The first disconnection is made between the thiazole and the (hydroxy) valine fragment to reveal the common bottom fragment intermediate **26** and the unique fragment **27**/**28**. Bond disconnections made at amide junctions are a logical choice due to the ease and versatility of their construction. The common intermediate **26** can be cut at the amide bond between the dehydrobutyrine thiazole and the threonine to give **51** and **46.** The thiazole ring of **46** can be separated into thioamide **32** and ethyl bromopyruvate for combination in a Hantzsch thiazole synthesis. The unique fragment **27**/**28** can be constructed from dipeptide **83**/**95** in a molybdenum cyclization/oxidation sequence.



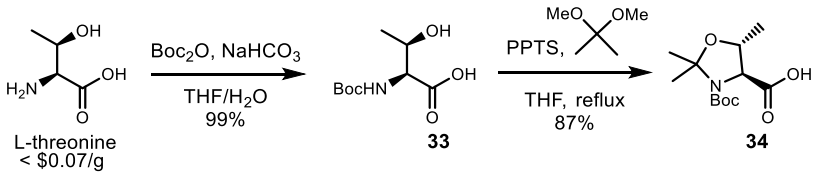
Scheme 2.1 Retrosynthetic analysis of the bottom fragments **23** & **24**.

2.2 Synthesis of Common Intermediate 26



Common Intermediate 26

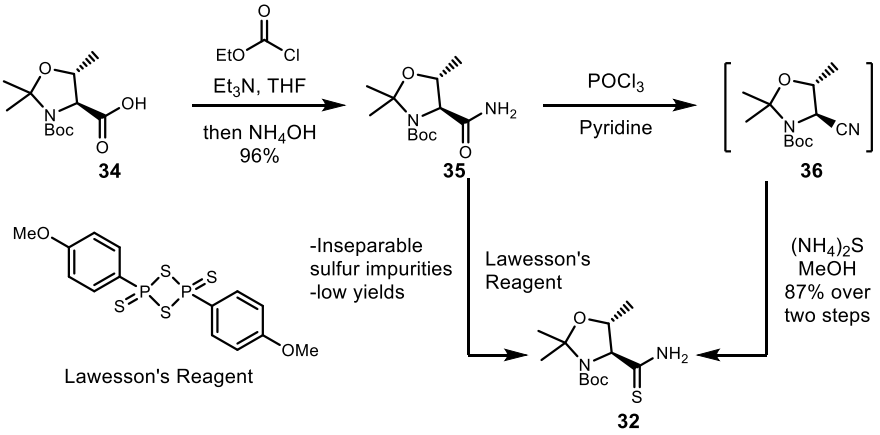
As previously mentioned, thiopeptides are proteinogenic molecules so L-amino acids were used as a cheap source of chiral starting material. The synthesis of the bottom fragment commenced with the Boc protection of L-threonine using Boc_2O, $NaHCO_3$, in THF/water to form Boc-threonine **33**. Longer times (>24 hours) were required for near quantitative yield. We installed an acetonide protecting group which is hydrolyzed under acidic conditions. To achieve this, **33** was refluxed with catalytic amounts of PPTS and an excess of dimethoxypropane in THF to form the protected threonine **34** in 87%. Suboptimal yields resulted if other acid catalysts (i.e. CSA, pTSA) were used.



Scheme 2.2 Synthesis of acetonide and Boc protected threonine **34.**

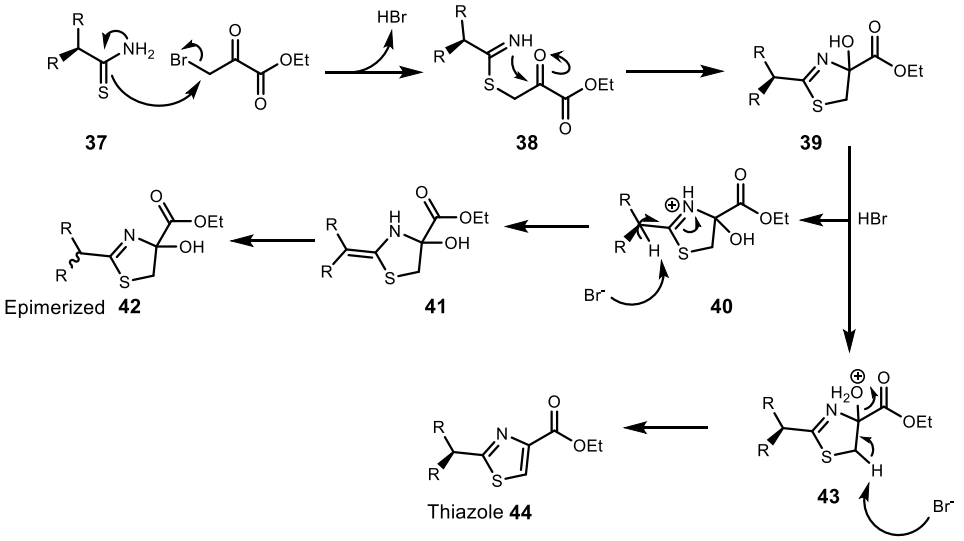
Several conditions exist in the literature to form amides from carboxylic acids, though the principle is the same – a peptide coupling reagent activates the carboxylic acid and subsequent attack of the amine creates the amide bond. Acid **34** reacted with ethyl chloroformate followed by aminolysis with aqueous ammonia to produce **35** in a 96% yield. Lawesson's reagent is a common reagent used for the conversion of carbonyl groups into thiones and the procedures are generally simple. However, our initial attempts to convert **35** into a thioamide were met with limited success. We initially speculated that the reagent decomposed and lost its reactivity. However, upon repeating the reaction with newly ordered reagent, the yields were still low and the reaction produced unpleasant, inseparable sulfur impurities. This strategy was abandoned in favor of the two-step process of dehydration into a nitrile followed by conversion into the thioamide.

Specifically, **35** was dehydrated with $POCl_3$ in pyridine to form a nitrile intermediate **36**; the crude material was immediately reacted with ammonium sulfide in methanol to afford **32** in 87% yield after purification.



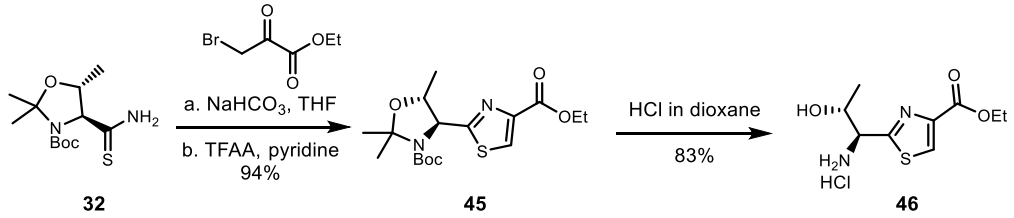
Scheme 2.3 Synthesis of thioamide **32**.

The first thiazole ring was constructed through a modified Hantzsch thiazole synthesis. Under typical Hantzsch conditions, a thioamide and an α-bromoketone are reacted to form the thiazole. Unfortunately, thiazolines (an intermediate in the reaction) with chiral carbons attached to the *C*-2 position epimerize due to the formation of hydrobromic acid *in situ* (**Scheme 2.4**).



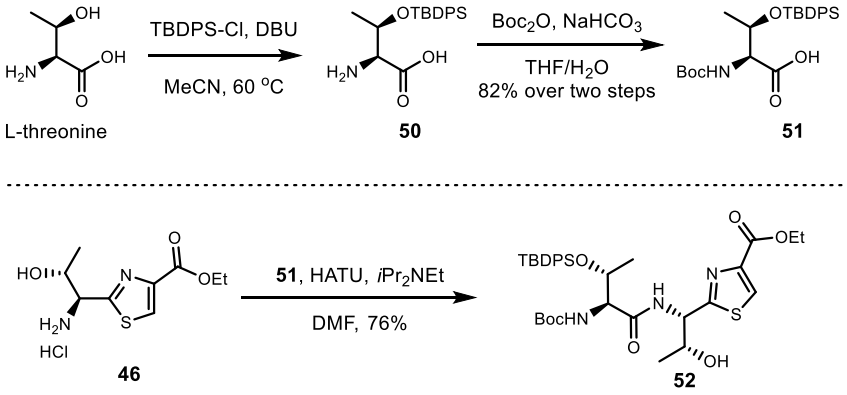
Scheme 2.4 Mechanism of Hantzsch thiazole synthesis and the mechanism of epimerization.

Bagley compiled and tested several modifications of the Hantzsch reaction in the synthesis of thiopeptide thiazole fragments. Under these conditions, a thioamide and an α-bromoketone are reacted in the presence of a solid carbonate salt (i.e. sodium or potassium) in an ethereal solvent (i.e. THF, DME) to form a hydroxythiazoline intermediate. The hydrobromic acid produced *in situ* is quenched by the bicarbonate which prevents the acid from epimerizing the sensitive thiazoline. The solution is then filtered and the intermediate is dehydrated into the thiazole with trifluoroacetic anhydride and a pyridine base. Thiazole **45** was constructed in a 94% yield under these conditions. The acid protecting groups on thiazole **45** were cleanly removed using 4N HCl in 1,4-dioxane to from **46** in 83%.



Scheme 2.5 Synthesis of thiazole **46**.

L-threonine was converted into **50** by using TBDPS-Cl and DBU in hot acetonitrile. The thick white suspension was filtered and dried and a Boc protecting group was installed to afford threonine fragment **51** in 82% over two steps. Interestingly, if the protection order was reversed (i.e. Boc protection then TBDPS protection) the reaction did not undergo smooth conversion. The reason for this is still unclear.

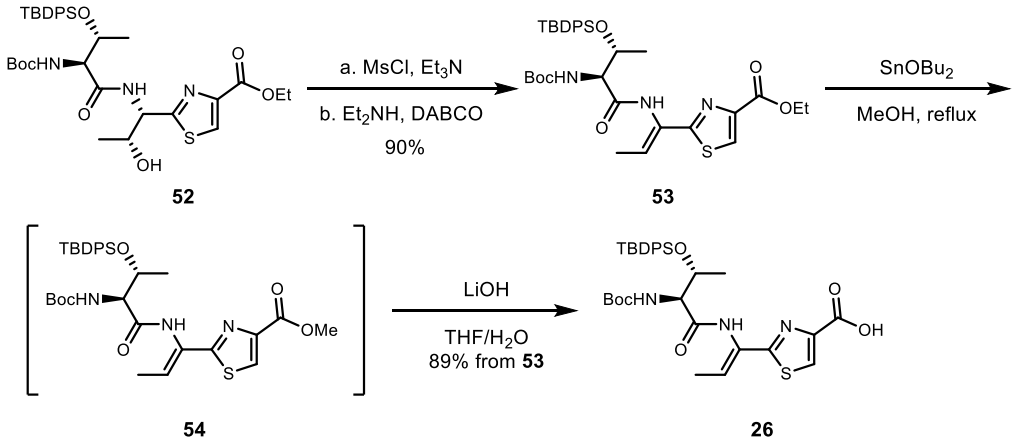


Scheme 2.6 Peptide coupling between thiazole **46** and acid **51** to form alcohol **52**.

Initial attempts to couple acid **51** and thiazole **46** were met with limited success. When isobutyl chloroformate was used as the coupling reagent, yields were low and inconsistent. There was greater consistency when EDC was used although yields remained low. When the coupling reagent was switched to HATU the coupling between acid **51** and thiazole **46** gave alcohol **52** in 76%. The elimination of the alcohol was attempted using triethylamine and MsCl. Despite complete conversion on TLC, the olefin was not formed under these condition, the reaction stopped after the mesylation of the alcohol. Several other reported literature conditions were attempted in order to eliminate the alcohol (MsCl, DBU; MsCl, DBU, Et_3N; Martin's sulfurane; EDCI, CuCl, HOBt; $DPPMO_2$, Tf_2O) yet none of these conditions succeeded in forming the product. To our delight a two-step system successfully converted the alcohol into the olefin.

Reaction of the alcohol with MsCl and triethylamine followed by subjecting the intermediate to DABCO and Et_2NH produced desired olefin **53** in 90% yield. A workup was necessary after mesylation to remove any remaining MsCl from the mixture before addition of DABCO/Et_2NH otherwise Et_2NH would react with MsCl to form an inseparable sulfonamide.

Initial attempts to hydrolyze the ethyl ester **53** using LiOH resulted in low yields. The reaction progressed slowly and after several hours a competing side reaction occurred. We suspect that nucleophilic hydroxide cleaves the TBDPS group. In order to remedy this, the ethyl ester was transesterified to methyl ester **54** using dibutyltin oxide. After filtration, the substrate was subjected to LiOH in THF/H_2O which resulted in the clean cleavage of the ester to the carboxylic acid **26** in an 89% yield over two steps, completing the synthesis of common fragment **26** in multigram quantities.

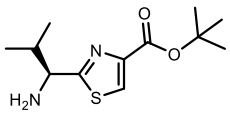


52 **53** **54** **26**

Scheme 2.7 Synthesis of common intermediate **26** from alcohol **52**.

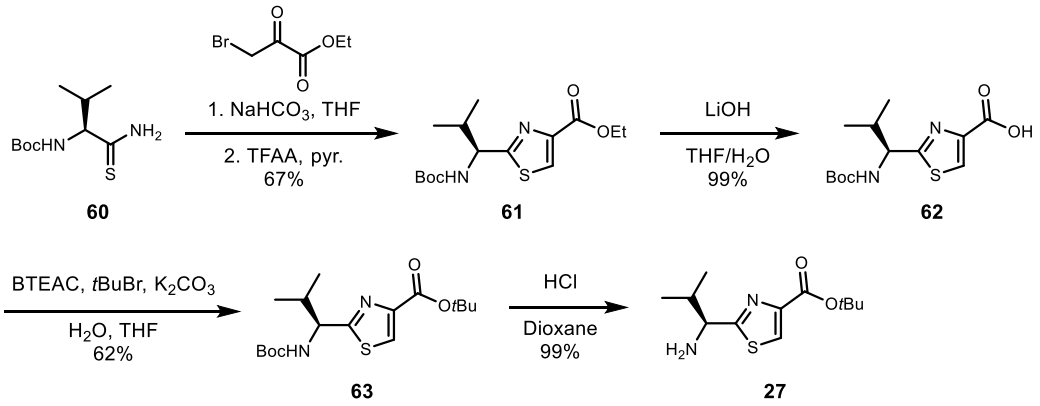
2.3 The use of MoO_2L_2 catalyst to synthesize fragments 27 and 28

2.3.1 Synthesis of micrococcin fragment 27



Micrococcin Fragment 27

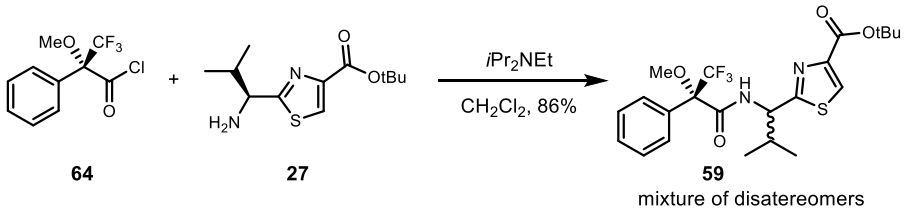
Our first strategy to synthesize valine-thiazole fragment **27** implemented the Hantzsch thiazole reaction between thioamide **60** and ethyl bromopyruvate. We had previous experience executing this reaction to form thiazole rings during our synthesis of common intermediate **26**. This route started by taking Boc-valine and converting it to the thioamide using procedures previously described. The ethyl ester was hydrolyzed to form **62** and esterified into *tert*-butyl ester **63**. The Boc group was removed using HCl in 1,4-dioxane to afford **27** in quantitative yield. Epimerization is possible under Hantzsch conditions and Bagley's study confirmed that unless lower temperatures (-20 to -40 ºC) and other bases (2,6-lutidine in place of pyridine) are used, epimerization of the valine substrate occurs to a significant degree. In fact, we observed racemization of substrate **27** under Hantzsch conditions.



Scheme 2.8 Hantzsch thiazole synthesis to access **27**.

We implemented Mosher's acid test to measure the level of racemization by converting **27** to **59** and analyzing via ^{19}F NMR and ^{1}H NMR. These data confirmed that the compound had

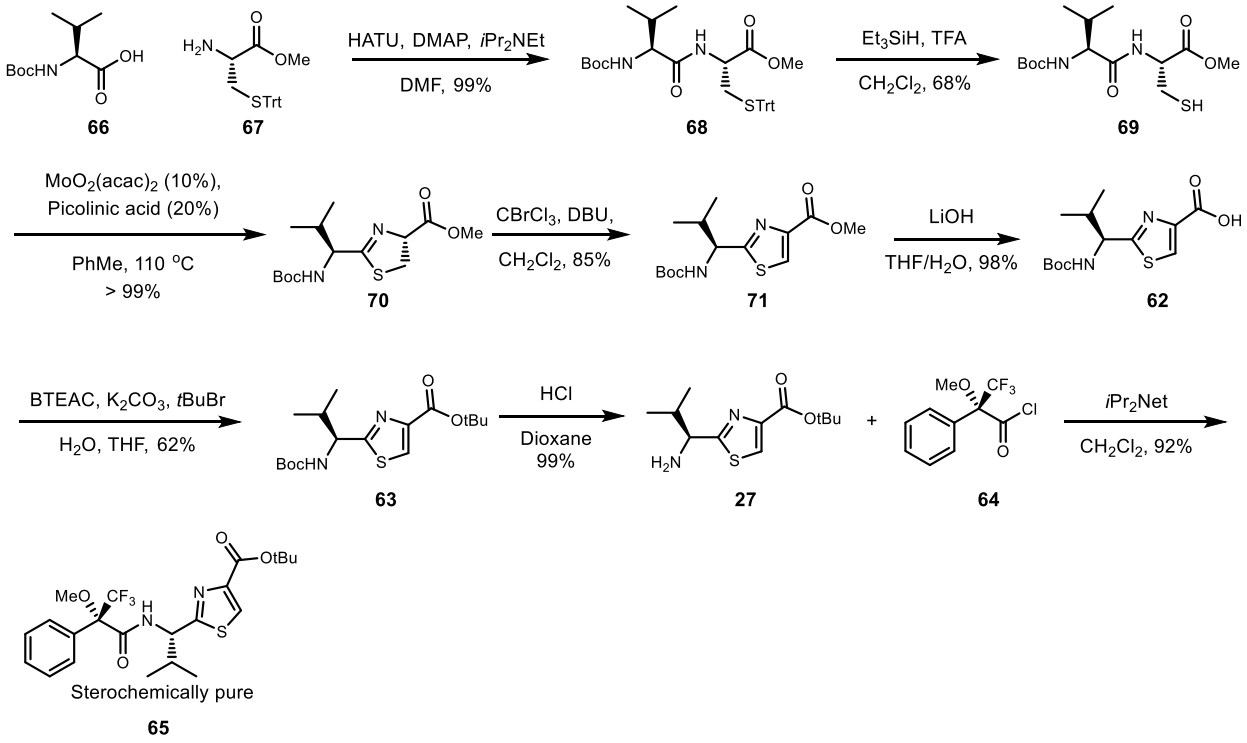
indeed racemized under Hantzsch conditions (~ 60%) so we altered our strategy to address this problem.



Scheme 2.9 Mosher's acid test for diastereomeric purity of **59.**

Biosynthetically, thiazole and oxazole heterocycles are installed into thiopeptides through cyclodehydration reactions. We sought the literature for a more viable way to synthesize thiazoles using a cyclodehydration which avoids racemization. There are many reagents which effect this transformation (DAST, Deoxo-Fluor®, Selectfluor®, PPh_3/I_2 etc.) but each of these reagents are used in stoichiometric quantities and often result in low yields. Ishihara published an article that describes the cyclization of cysteine, threonine or serine dipeptides into thiazoline or oxazoline heterocycles using $MoO_2(acac)_2$ as the catalyst.[78-79] We implemented this methodology to form thiazole **27** in hopes of solving the epimerization problem. The use of $MoO_2(acac)_2$ formed the thiazoline **70** in low yields (**Table 2.1**, entry 1) and gave inconsistent results due to precipitation of the catalyst from solution. Nonetheless, thiazoline **70** was converted into a thiazole **71**, hydrolyzed into **62**, esterified, and finally the Boc protecting group was cleaved to give **27**. **27**

reacted with Mosher's acid to reveal a single diastereomer based on ^{19}F NMR and ^{1}H NMR analysis.

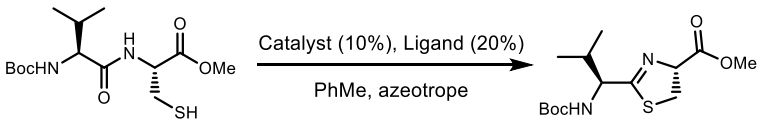


66 **67** **68** **69** **70** **71** **62** **63** **27** **64** **65**

Scheme 2.10 Stereoselective access to **65** via molybdenum cyclization and Mosher's acid test.

Due to the inconsistent and low yields of the molybdenum cyclization, we sought to optimize the reaction condition. We found picolinic to be a suitable ligand during the molybdenum cyclization. Picolinic acid acted to stabilize the molybdenum, preventing it from decomposition, increased the solubility, and increased the activity of the catalyst.

Several different picolinic acid ligands were tested to understand how the nature of the ligand affects the conversion from a dipeptide into a thiazoline. **69** was used as the substrate to optimize the reaction conditions. The results are summarized in **Table 2.1**.



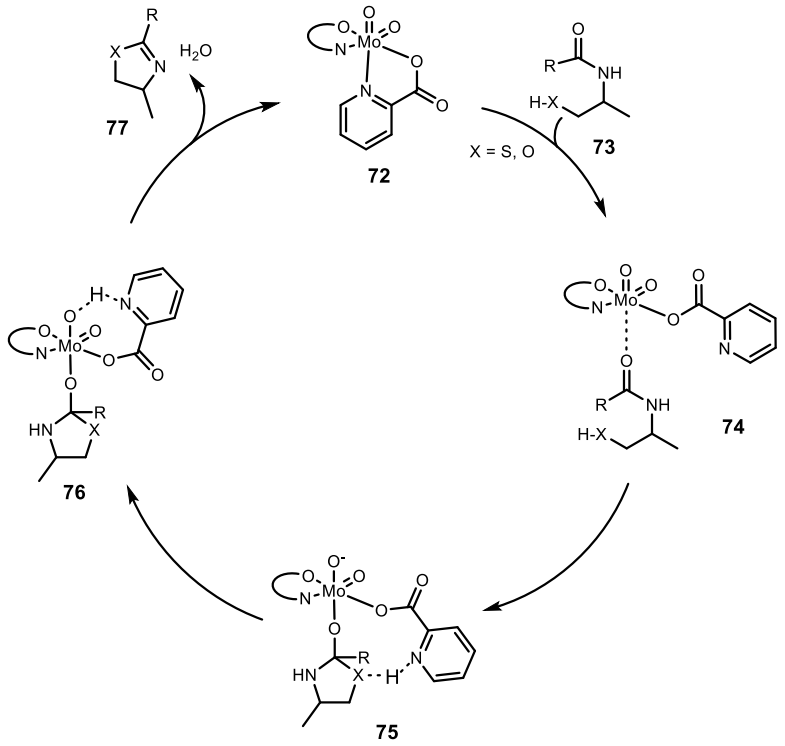
69 **70**

Entry	Catalyst	Ligand	Time	Yield
1	$MoO_2(acac)_2$	none	16	18%
2	$MoO_2(acac)_2$	picolinic acid	16	85%
3	$MoO_2(acac)_2$	6-methylpicolinic acid	16	97%
4	$MoO_2(acac)_2$	6-methylpicolinic acid	2	87%
5	$MoO_2(acac)_2$	6-ethylpicolinic acid	16	98%
6	$MoO_2(acac)_2$	6-methoxypicolinic acid	16	26%
7	$MoO_2(acac)_2$	2,6-pyridinedicarboxylic acid	16	19%
8	$MoO_2(acac)_2$	4-methylpicolinic acid	16	8%
9	$MoO_2(acac)_2$	4-hydroxypicolinic acid	16	9%
10	$MoO_2(acac)_2$	4-nitropicolinic acid	16	68%
11	$MoO_2(acac)_2$	quinaldic acid	16	62%
12	$MoO_2(acac)_2$	L-proline	16	<1%
13	none	6-methylpicolinic acid	16	<1%
14	*p*TSA	none	16	<1%

Table 2.1 Optimization table for dehydrative cyclization of **69** using molybdenum catalysts.

We hypothesized that utilizing a ligand which modifies the solubility of the complex, Lewis acidity, and coordination to the amide would result in a more effective cyclization. Indeed, picolinic acid was found to be a suitable ligand. *P*-toluenesulfonic acid was used as an acid catalyst control that demonstrated the necessity of molybdenum to catalyze the cyclization. Attempts to modify the groups on picolinic acid were met with mixed results. It is presumed that electron donating groups (entries 6, 8, and 9) increase the basicity of the ligand so it more strongly coordinates to molybdenum which prevents the substrate from associating. Electron withdrawing

groups (entries 7 and 10) also negatively impacted the reaction relative to unsubstituted picolinic acid. Quinaldic acid, entry 11, gave a moderate result – a 62% yield for the cyclization. The only substituents that improved the reaction were 6-alkyl substituted picolinic acids (entries 11 and 12). We presume that the sterics of the alkyl groups outweigh its electron donating capabilities and give rise to a more sterically congested complex. Thus, the ligands more easily dissociate and allow for coordination to the amide of the substrate. 6-methyl picolinic acid was chosen as the optimized ligand due to its price and superior activity to picolinic acid and the other ligands.

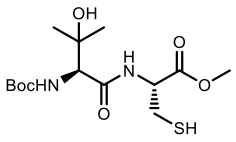


Scheme 2.11 Mechanistic proposal of molybdenum cyclization with picolinic acid ligand.

Mechanistically, we postulate that the first step in the reaction is dissociation of the pyridine nitrogen of picolinic acid from the metal center which allows for association of the amide group (**73)** to the molybdenum. The molybdenum acts as a Lewis acid increasing the electrophilicity of the carbonyl carbon allowing for nucleophilic attack of the alcohol or thiol (**75**).

The proximal pyridine nitrogen acts as a proton shuttle and transfers the proton to the oxygen on molybdenum (**76**). The nitrogen can collapse and release the molybdenum species as a leaving group forming a thiazoline and water molecule while reforming the catalyst. With this mechanistic hypothesis, adding an alkyl group to the 6 position can increases the rate of dissociation of the ligand during the first step allowing for the substrate to bind.

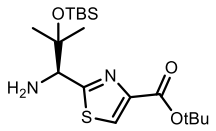
It is also noteworthy that the cyclization of **69** in **Scheme 2.12** which utilizes **1a** as the ligand achieves nearly quantitative yield for gram scale cyclizations. We found that if 5% catalyst is added after a few hours, the reaction proceeds in higher yields. After optimizing the catalytic system, we modified the route which resulted in a concise synthesis of **27**.



Scheme 2.12 Optimized route to access valine thiazole **27**.

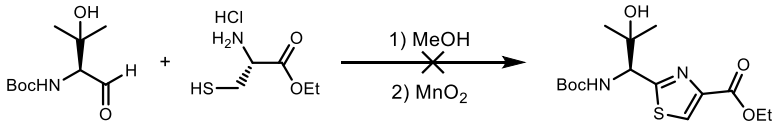
tert-Butyl cystine **81** was reacted with two equivalents of Boc-valine **66** using HATU to form **82** in 60% yield. The disulfide **82** was then cleaved using tributyl phosphine and water to form thiol **83** in 94%. Dipeptide **83** was efficiently cyclized using $MoO_2(acac)_2$ (10%) and 6-methylpicolinic acid (20%) as the catalytic system to afford **84** in 92%. Thiazoline **84** was isolated and oxidized with $CBrCl_3$ and DBU and finally the Boc group was removed with HCl in 1,4-dioxane to liberate **27** in 96%.

2.3.2 Synthesis of thiocillin fragment 28



thiocillin fragment 28

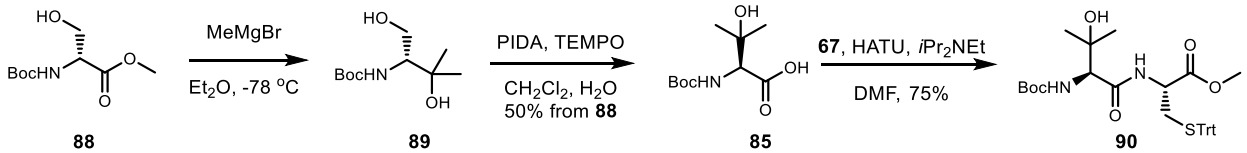
Thiocillin I differs from micrococcin P1 by a single hydroxyl group. Micrococcin contains a valine and thiocillin contains a hydroxyvaline. In order to synthesize fragment **28**, we initially repeated the work of Ciufolini by reacting aldehyde **146** with cysteine **86** but were unable to reproduce his results to form **87**.



146 **86** **87**

Scheme 2.13 Attempted synthesis of hydroxyvaline thiazole **87**.

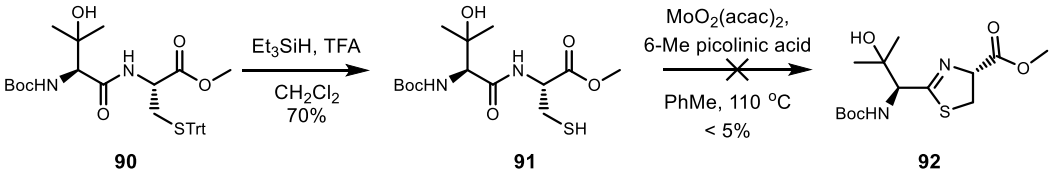
Thus, we applied our molybdenum cyclization methodology to the synthesis of the thiocillin fragment. Our initial attempt to synthesize the hydroxyvaline fragment **28** began with the addition of methylmagnesium bromide to protected D-serine **88** to give diol **89** as an intermediate. Diol **89** was oxidized into a carboxylic acid **85** using PIDA and catalytic TEMPO in 50% over two steps. Boc-hydroxyvaline **85** was then coupled to methyl *S*-trityl-L-cysteinate **67** using HATU to form the dipeptide **90** in 75%.



88 **89** **85** **90**

Scheme 2.14 Synthesis of hydroxyvaline dipeptide **90**.

The trityl group was removed from **90** using Et_3SiH and TFA and the thiol **91** was subjected to molybdenum cyclization. Unfortunately, despite the attempt to cyclize **91** the reaction did not proceed in greater than 5% or without the formation of side products. We suspected that the unprotected hydroxy group sequesters and inactivates the molybdenum catalyst despite the presence of the picolinic acid.



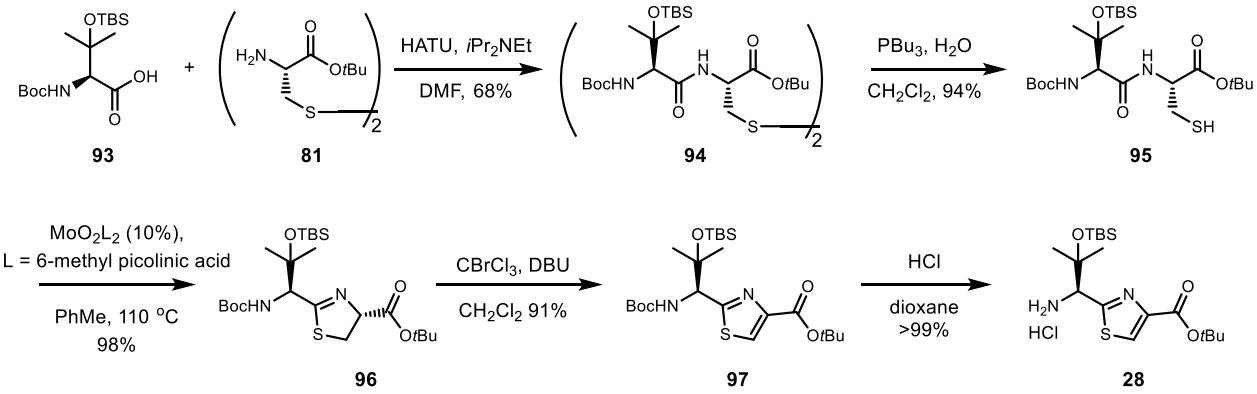
90 **91** **92**

Scheme 2.15 Failed molybdenum cyclization of free hydroxy valine **91**.

To solve this problem, we reluctantly decided to install a TBS group. Our hesitancy arose because TBS is an acid labile protecting group and HCl is used multiple times throughout the rest of the synthesis so we anticipated TBS removal or elimination. Nonetheless we decided to proceed with the synthesis. TBSOTf is a commonly used reagent to protect tertiary alcohols due to its high reactivity and when **85** or **90** was subjected to these conditions, the Boc protecting group was completely removed. In addition to this, the nitrogen reacted with the excess TBSOTf. Therefore, we sought another route to obtain **95.**

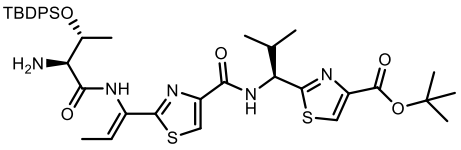
Another student in our laboratory, Wyatt Powell, synthesized *N*-Boc-*O*-TBS-hydroxyvaline **93**. *tert*-Butyl cysteine **81** was reacted with two equivalents of **93** using HATU and to afford **94** in 68% yield. The resulting disulfide was cleaved using tributyl phosphine and water to generate the thiol **95**. Interestingly, during the first few attempts to cyclize **95**, the reaction did not proceed because residual amounts of tributyl phosphine from the previous reaction inhibited the reaction from occurring. After this problem was fixed the cyclization still did not proceed

effectively. Eventually it was found that forming the catalytic molybdenum complex *in situ* (normal protocol for previous substrates) did not work well for this substrate. Thus the catalyst MoO_2L_2 (L = 6-methylpicolinic acid) was used. Addition of the preformed complex effectively cyclized **95** in gram quantities in nearly quantitative yield under the optimized conditions without the need to add extra catalyst to from thiazoline **96**. The thiazoline was then oxidized with $CBrCl_3$ and DBU to afford **97** in 91% yield and finally HCl in dioxane removed the Boc protecting group to liberate amine hydrochloride **28**.



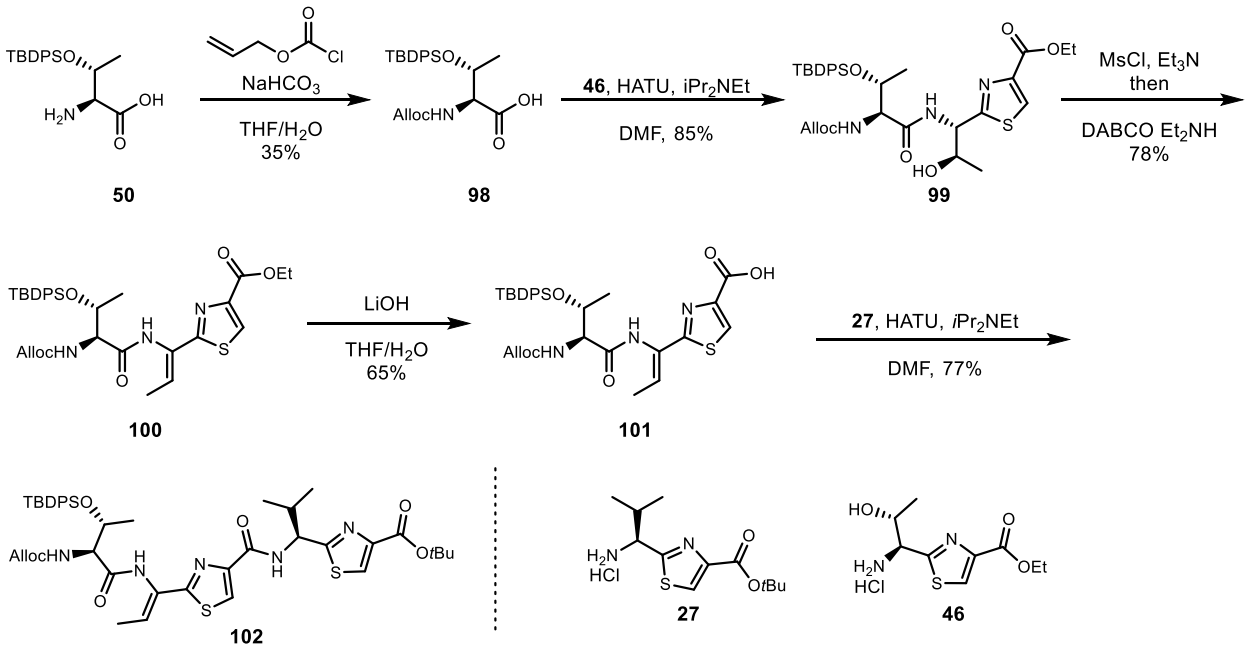
Scheme 2.16 Successful synthesis of thiocillin fragment **28**.

2.4 Synthesis of the Bottom Fragment of Micrococcin P1 (23)



Our first synthetic strategy to synthesize micrococcin bottom fragment was to utilize an Alloc protecting group for orthogonal access to the free amine **23**. **98** was made in a similar manner as protected threonine **51** – installation of the TBDPS protecting group followed by Alloc

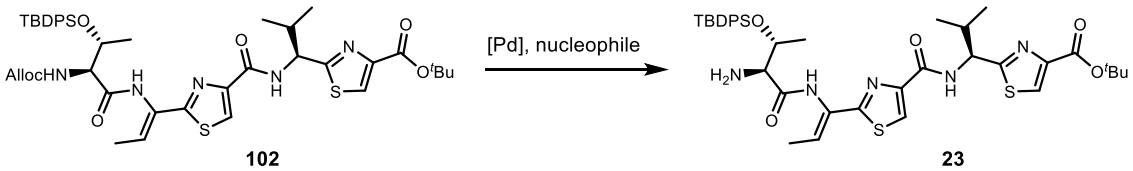
protection of nitrogen. **98** was coupled with thiazole **46** in 85% yield. Mesylation and elimination with DABCO and Et_2NH afforded olefin **100** in 78% yield. The ethyl ester was cleaved and coupled to the micrococcin fragment **27** to give the fully protected bottom fragment for micrococcin **102**.



Scheme 2.17 Synthesis of Alloc protected micrococcin bottom fragment **102**.

We originally used an Alloc protecting to avoid the potential problems of deprotection with HCl as the *tert*-butyl ester and silyl protecting groups are sensitive under acidic conditions. Unfortunately, the deprotection of Alloc group to release the free amine was ineffective despite several conditions tested (see **Table 2.2**). Yields were low (40-60%) and multiple unknown side products formed during the reaction. We screened several different Pd catalysts and nucleophilic sources but were unable to cleanly isolate **23** in synthetically useful yields. We suspected the olefin participated in the reaction leading to other side products. In fact, Nicolaou published similar

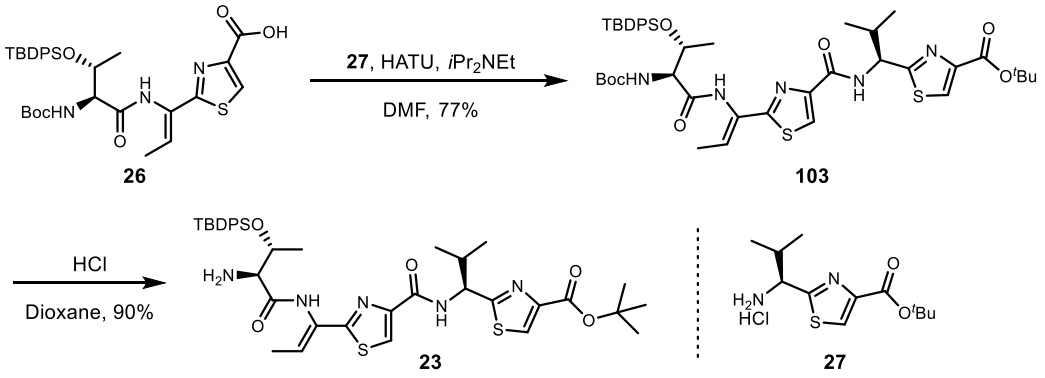
results during his synthesis of thiostrepton when an Alloc deprotection was performed in the presence of an olefin.[65]



Entry	Pd	Nucleophile	Result
1	$Pd(PPh_3)_4$	Et_2NH	Product + many side products
2	$Pd(PPh_3)_4$	$PhSiH_3$	Product + many side products
3	$Pd(dba)_3$ & PPh_3	Et_3SiH	Product + many side products
4	$Pd(dba)_3$ & PPh_3	Et_2NH	Product + many side products
5	Pd/C	$PhSiH_3$	Clean but progress stopped at 50%
6	Pd/C	Et_3SiH	Clean but progress stopped at 50%
7	$Pd(OH)_2$	Et_3SiH	Progress stopped and then decomposed

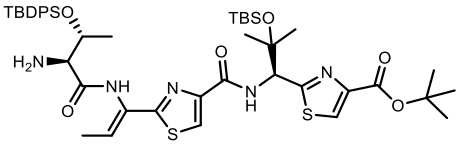
Table 2.2 Attempted Alloc deprotection conditions.

The Alloc protecting group strategy was abandoned in favor of utilizing a Boc protecting group. Thus the final scheme used was the reaction between acid **26** and amine **27** to form fully protected **103** in 77%. The Boc protecting group was selectively removed using HCl in dioxane in 90% yield to reveal the micrococcin bottom fragment **23**.



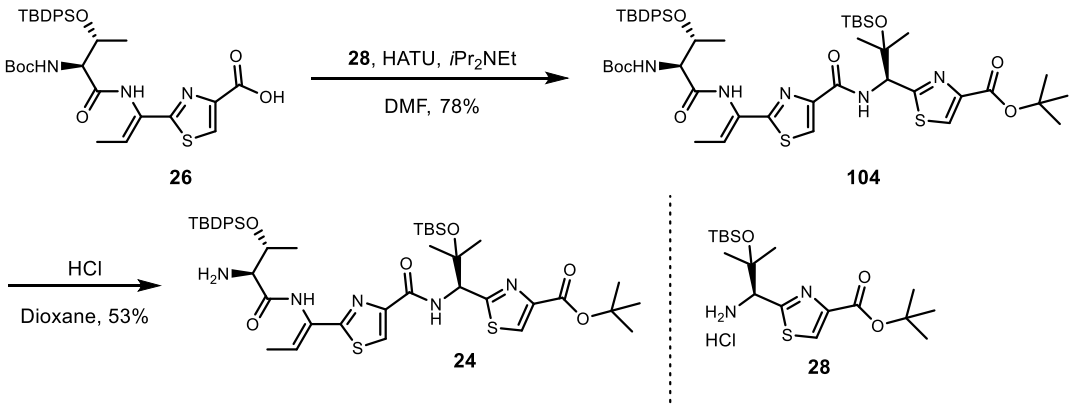
Scheme 2.18 Successful synthesis of micrococcin P1 bottom fragment **23.**

2.5 Synthesis of the Bottom Fragment of Thiocillin I (24)



Thiocillin Bottom Fragment 24

Route optimization of micrococcin bottom fragment **23** allowed for analogous application to access to thiocillin bottom fragment **24**. Following the same sequence of reactions, **26** and **28** were coupled to give **104** in 78% yield. The deprotection of **104** using HCl in dioxane gave **24** in 53%. Under these reaction conditions, several side products formed which made the purification of **24** very difficult. In addition to this, despite being stored in a -20 ºC freezer, the compound progressively decomposed. At this point, we are unsure why it decomposes or what it decomposes into. Nonetheless, the material was used and we proceeded with the rest of the synthesis.



Scheme 2.19 Synthesis of thiocillin I bottom fragment **24**.

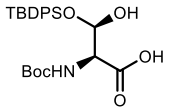
2.6 Experimental Section

2.6.1 Materials and Methods

All chemicals were purchased as reagent grade and used without further purification, unless otherwise noted. All reaction mixtures were carried out under anh. N_2 in oven-dried glassware. TLC analyses were performed on Merck TLC plates and visualizations were performed with UV light and/or Hanessian stain. A 10% w/v aqueous solution of citric acid was used during work-ups unless indicated otherwise. Column chromatography was performed on silica gel (230-400 mesh). Melting points were recorded in open capillaries and uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 300/ Varian 400/ Varian 500 MHz instruments are reported as follows: chemical shift (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. The residual solvent reference peaks were used from published literature.[1] 2D NMR experiments were performed using standard parameters (*200 and More NMR Experiments,* S. Berger, S. Braun, Wiley-VCH, **2004**). IR measurements were

performed on Agilent Cary 630 ATR instrument and optical rotations were measured on JASCO P-1030.

2.6.2 Preparative Procedures

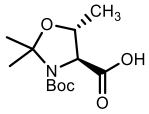


51

(2S,3R)-2-((*tert*-Butoxycarbonyl)amino)-3-((*tert*-butyldiphenylsilyl)oxy)-3-hydroxypropanoic acid. To a suspension of L-threonine (10.0 g, 83.9 mmol, 1.00 equiv.) in acetonitrile (150 mL) was added DBU (23.0 mL, 101 mmol, 1.2 equiv.) and TBDPS-Cl (23.0 mL, 88.0 mmol, 1.05 equiv.). The reaction mixture was heated to 60 °C for 24 h. The resulting suspension was cooled, filtered and the solid was washed with acetonitrile. The resulting white solid, **50**, (25.0 g) was dried *in vacuo*.

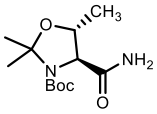
50 (25.0 g, 69.9 mmol, 1.00 equiv.) was then suspended in THF (160 mL) and water (80 mL) and cooled to 0 °C. $NaHCO_3$ (29.0 g, 350 mmol, 5.00 equiv.) was added and it stirred for 10 min before Boc_2O (16.8g, 76.9 mmol, 1.10 equiv.) was added. The reaction mixture was allowed to warm to rt and stirred for 24 h. After this time the solvent was evaporated and the pH was adjusted to 3 using 1N HCl. The aqueous layer was extracted with EtOAc (3 x 200 mL) and the combined organic layers were washed with brine (200 mL), dried (Na_2SO_4), and concentrated to afford **51** (31.7 g, 82% over two steps) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.83 (s, 2H), 7.68 (ddd, *J* = 12.5, 8.1, 1.5 Hz, 5H), 7.52 – 7.34 (m, 8H), 6.07 (d, *J* = 9.1 Hz, 0H), 5.38 (d, *J* = 9.6 Hz, 1H), 4.48 (qd, *J* = 6.3, 2.2 Hz, 1H), 4.38 (d, *J* = 6.7 Hz, 0H), 4.31 (dd, *J* = 9.6, 2.3 Hz, 1H), 4.12

(d, *J* = 9.1 Hz, 0H), 1.53 (s, 9H), 1.47 (s, 2H), 1.09 (d, *J* = 6.2 Hz, 3H), 1.05 (s, 10H) Characterization data matched the literature report.[80]



34

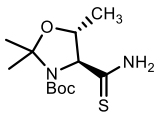
(4S,5R)-3-(*tert*-Butoxycarbonyl)-2,2,5-trimethyloxazolidine-4-carboxylic acid. Boc-threonine (12.0 g, 55.0 mmol, 1.00 equiv.) was dissolved in THF (250 mL) followed by the addition of 2,2-dimethoxypropane (67.0 mL, 550 mmol, 10.0 equiv.) and PPTS (2.75 g, 10.9 mmol, 0.200 equiv.). The solution was heated to 90 °C and refluxed for 16 h under N_2. The reaction mixture was concentrated and diluted with water (100 mL). The aqueous layer was extracted with EtOAc (3 x 100mL) and the organic layers were washed with brine (100 mL), dried (Na_2SO_4), and concentrated to afford **34** (12.4 g, 87%) as a clear viscous oil which crystallized to form white crystals: ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.77 – 11.51 (s, 1H), 4.22 (tq, *J* = 12.1, 6.3 Hz, 1H), 3.99-3.91 (m, 1H), 1.64 (s, 2H), 1.56 (t, *J* = 12.1 Hz, 4H), 1.47 (s, 3H), 1.44 – 1.38 (m, 9H). Characterization data matched the literature report.[81]



35

(4S,5R)-*tert*-Butyl 4-carbamoyl-2,2,5-trimethyloxazolidine-3-carboxylate. 34 (12.4 g, 48.0 mmol, 1.00 equiv.) was dissolved in THF (200 mL) and cooled to 0 °C. Et_3N (20.0 mL, 143 mmol,

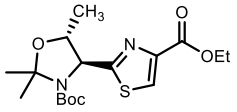
3.00 equiv.) and ethyl chloroformate (11.4 mL, 120 mmol, 2.50 equiv.) were added and the resulting thick white suspension was stirred for 1.5 h. 28% aq. NH_4OH (15 mL) was added and the solution was allowed to warm to rt and stirred for 16 h. The solution was concentrated and diluted with sat. $NaHCO_3$ (100 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL) and the organic layers were washed with brine (100 mL), dried (Na_2SO_4), and concentrated. The resulting orange-tinted oil crystallized to afford **35** (11.8 g, 96%) a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.18 (s, 2H), 4.20 (s, 1H), 3.77 (d, *J* = 7.8 Hz, 1H), 1.58 (d, *J* = 10.5 Hz, 6H), 1.43 (s, 9H), 1.38 (d, *J* = 6.1 Hz, 3H). Characterization data matched the literature report.[81]



32

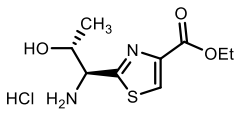
(4S,5R)-*tert*-Butyl 4-Carbamothioyl-2,2,5-trimethyloxazolidine-3-carboxylate. 35 (5.70 g, 22.0 mmol, 1.00 equiv.) was dissolved in pyridine (40 mL) and cooled to 0 °C under N_2. $POCl_3$ (5.23 mL, 57.2 mmol, 2.60 equiv.) was added dropwise and the reaction mixture stirred for 45 min. After this time, the reaction mixture was poured over ice, diluted with H_2O and extracted with Et_2O (3 x 100 mL). The organic layer was washed with a 20% w/v aq. $NaHSO_3$ solution (2 x 100 mL), water (50 mL), and brine (100 mL). The solution was dried (Na_2SO_4), and concentrated. The resulting oil was dissolved in MeOH (40 mL) and 40% aq. $(NH_4)_2S$ solution (7.5 mL, 44 mmol, 2 equiv.) was added. After 16 h the reaction mixture was concentrated, diluted with water (100 mL) and extracted with EtOAc (3 x 100 mL). The organic layers were washed with brine (100 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on SiO_2 using 17% EtOAc/hexanes to afford **32** (5.27 g, 87%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.86 (s, 1H), 7.58 (s, 1H), 4.26 (d, *J* = 7.7 Hz, 1H), 4.21 – 4.04 (m, 1H), 1.61 (s, 6H), 1.44 (d, 12H). Characterization data matched the literature report.[81]



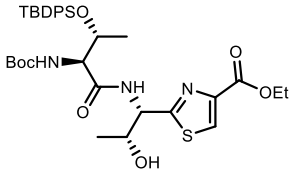
45

(4S,5R)-*tert*-Butyl 4-[4-(ethoxycarbonyl)thazol-2-yl]-2,2,5-trimethyloxazolidine-3-carboxylate. 32 (5.27 g, 19.3 mmol, 1.00 equiv.) was dissolved in anh. THF (100 mL) under N_2 and cooled to 0 °C. $NaHCO_3$ (16.2 g, 192 mmol, 10.0 equiv.) was added followed by dropwise addition of ethyl bromopyruvate (80%, 6.10 g, 25.0 mmol, 1.30 equiv.). The mixture was allowed to warm to rt and stirred for 16 h. The suspension was filtered over Celite and cooled to 0 °C followed by the addition of pyridine (15.5 mL, 192 mmol, 10.0 equiv.) and dropwise addition of trifluoroacetic anhydride (11.7 mL, 83.0 mmol, 4.30 equiv.). TLC analysis indicated complete consumption of starting material after 20 min. Et_3N (5.40 mL, 39.0 mmol, 2.00 equiv.) was added and the reaction mixture was allowed to warm to rt. The solution was concentrated and diluted with sat. NH_4Cl (100 mL). The aqueous layer was extracted with $CHCl_3$ (3 x 100 mL) and the organic layer was washed with sat. $NaHCO_3$ (75 mL), brine (100 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on SiO_2 using 17% EtOAc/hexanes to afford **45** (6.67 g, 94%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 4.79 (d, *J* = 7.7 Hz, 1H), 4.47 – 4.38 (m, 3H), 4.25 – 4.08 (m, 1H), 1.69 (d, *J* = 5.8 Hz, 6H), 1.46 – 1.36 (m, 12H), 1.22 – 1.14 (m, 6H). Characterization data matched the literature report.[81]



46

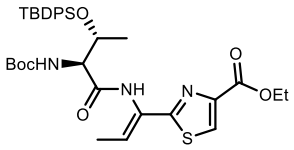
Ethyl 2-((1S,2R)-1-amino-2-hydroxypropyl)thiazole-4-carboxylate hydrochloride. **45** (6.67 g, 18.0 mmol, 1.00 equiv.) was dissolved in 1,4-dioxane (20 mL) and 4N HCl in 1,4-dioxane (40 mL). TLC analysis indicated complete consumption of starting material after 7 h. The solution was concentrated and the remaining solvent was azeotropically removed with toluene (3x). The yellow foam was purified by column chromatography on SiO_2 using 33% EtOAc/hexanes then flushed with 10% MeOH/CH_2Cl_2 to afford **46** (3.97 g, 83%) as a white foam: α_D^{25} = -7.0 (c = 1.0, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3198, 2978, 2932, 2090, 1713, 1586, 1480, 1371, 1338, 1218, 1095, 1017, 877, 759, 574, 519 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.48 (s, 4H), 7.33 – 7.07 (m, 1H), 5.02 (s, 1H), 4.54 (d, *J* = 8.0 Hz, 1H), 4.31 (q, *J* = 7.0 Hz, 2H), 2.34 (s, 1H), 1.33 (t, *J* = 7.0 Hz, 3H), 1.28 – 1.21 (m, 3H). ^{13}C NMR (75 MHz, CDCl3) δ 165.0, 161.5, 146.4, 130.0, 128.7 (d, J = 81.4 Hz), 68.4, 62.0, 58.6, 19.9, 14.4.



52

Ethyl 2-((1S,2R)-1-((2S,3R)-2-((*tert*-butoxycarbonyl)amino)-3-((*tert*-butyldiphenylsilyl)oxy) butanamido)-2-hydroxypropyl)thiazole-4-carboxylate. 46 (2.27 g, 9.84 mmol, 1.00 equiv.) and **51** (5.40 g, 11.8 mmol, 1.20 equiv.) were dissolved in DMF (50 mL) and cooled to 0 °C under N_2. *i*-Pr_2NEt (2.40 mL, 13.7 mmol, 1.40 equiv.) and HATU (5.24 g, 13.8 mmol, 1.40 equiv.) were added and the reaction mixture was allowed to warm to rt and stirred for 1 h. The reaction mixture

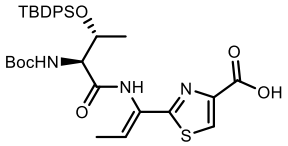
was transferred to a separatory funnel and aq. citric acid (250 mL) was added. The aqueous layer was extracted with EtOAc (3 x 100 mL) and the organic layers were washed with sat. $NaHCO_3$ (100 mL), brine (100 mL), dried (Na_2SO_4), and concentrated. The compound was purified by column chromatography on SiO_2 using 33% EtOAc/hexanes to afford **52** (4.08g, 70%) as a white solid: $[\alpha]_D^{25} = -46.4$ (c = 1.0, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3379, 2976, 2942, 2867, 2360, 1717, 1713, 1485, 1367, 1215, 1168, 1106, 1022, 954, 873, 758, 704, 614, 507, 423 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.73 – 7.56 (m, 5H), 7.38 (ddt, *J* = 23.4, 15.3, 7.2 Hz, 7H), 5.40 (d, *J* = 7.6 Hz, 1H), 5.23 (dd, *J* = 8.7, 1.6 Hz, 1H), 4.67 (q, *J* = 6.5 Hz, 1H), 4.46 – 4.28 (m, 4H), 1.43 (s, 8H), 1.38 (t, *J* = 7.1 Hz, 2H), 1.30 (d, *J* = 6.4 Hz, 3H), 1.03 (s, 9H), 0.84 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 161.0, 146.6, 136.0, 135.7, 133.7, 132.4, 130.0, 129.8, 127.8 (2), 127.6, 80.1, 69.8, 68.0, 61.4, 59.4, 55.0, 30.9, 28.3, 27.0, 19.5, 19.2, 18.6, 14.3; FT-HRMS (ESI) *m/z* calcd for $C_{34}H_{47}N_3O_7SSiNa^+$ $[M + Na]^+$: 692.2796, found 692.2790.



53

Ethyl 2-((Z)-1-((2S,3R)-2-((*tert*-butoxycarbonyl)amino)-3-((*tert*-butyldiphenylsilyl) oxy) butanamido) prop-1-en-1-yl)thiazole-4-carboxylate. 52 (725 mg, 1.08 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C under N_2. MsCl (0.17 mL, 2.16 mmol, 2.00 equiv.) and Et_3N (0.60 mL, 4.32 mmol, 4.00 equiv.) were added and the reaction mixture stirred for 1 h. The reaction mixture was diluted with CH_2Cl_2 and 1N HCl. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the resulting organic layer was washed with sat. $NaHCO_3$ (50 mL), brine

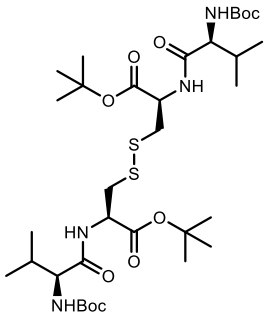
(50 mL), dried (Na_2SO_4), and concentrated. The mesylated compound was then dissolved in CH_2Cl_2 (10 mL), cooled to 0 °C under N_2 and DABCO (1.21 g, 10.8 mmol, 10.0 equiv.) was added. After 20 min Et_2NH (0.56 mL, 5.40 mmol, 5.00 equiv.) was added and the solution was allowed to warm to rt and stirred for 16 h. The reaction mixture was transferred to a separatory funnel and aq. citric acid (50 mL) was added. The aqueous layer was extracted with EtOAc (3 x 40 mL) and the organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Column chromatography on SiO_2 using 17% EtOAc/hexanes was used to purify the material to afford **53** (644 mg, 91%) as a white foam: $[\alpha]_D^{25} = -1.2$ (c = 1.0, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3306, 2976, 2942, 2865, 2360, 1689, 1473, 1365, 1322, 1210, 1164, 1094, 1020, 821, 749, 702, 611, 506 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.05 (s, 1H), 7.74 – 7.63 (m, 4H), 7.47 – 7.32 (m, 6H), 6.69 (q, *J* = 7.1 Hz, 1H), 5.50 (d, *J* = 7.2 Hz, 1H), 4.53 – 4.43 (m, 2H), 4.37 (qd, *J* = 7.1, 2.7 Hz, 2H), 1.86 (s, 1H), 1.83 (d, *J* = 7.2 Hz, 3H), 1.45 (s, 8H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 6.3 Hz, 3H), 1.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 167.2, 161.3, 155.7, 147.6, 135.9, 135.8, 133.6, 132.4, 130.1, 129.9, 128.0, 127.9, 127.8 (2), 127.7, 126.7, 80.1, 69.9, 61.3, 59.6, 28.3, 27.0, 19.2, 18.7, 14.3 (2); FT-HRMS (ESI) *m/z* calcd for $C_{34}H_{45}N_3O_7SSiNa^+$ $[M + Na]^+$: 674.2691, found 674.2695.



26

2-((Z)-1-((2S,3R)-2-((*tert*-Butoxycarbonyl)amino)-3-((*tert*-butyldiphenylsilyl)oxy)butanamido)prop-1-en-1-yl)thiazole-4-carboxylic acid. To a MeOH

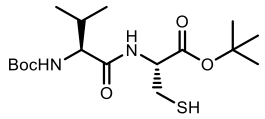
(20 mL) solution of **53** (1.42 g, 2.17 mmol, 1.00 equiv.), $SnOBu_2$ (542 mg, 2.17 mmol, 1.00 equiv.) was added and the reaction mixture was heated to 80 °C for 4 h.[82] After this time, the reaction mixture was cooled, concentrated, and filtered over Celite. The crude oil was then dissolved in THF (26 mL) and water (13 mL) and cooled to 0 °C under N_2. LiOH•H_2O (186 mg, 4.45 mmol, 2.05 equiv.) was added and the reaction mixture stirred for 3 h. The pH of the solution was adjusted to 3 using aq. citric acid and the aqueous layer was extracted with EtOAc (3 x 30 mL). The organic layers were washed with brine (40 mL), dried (Na_2SO_4), and concentrated. The crude material was purified by column chromatography on SiO_2 using 33% to 50% EtOAc/hexanes to 10% CH_2Cl_2/MeOH to afford **26** (1.21 g, 89%) as a white foam.



82

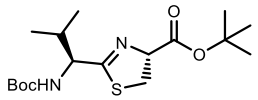
***tert*-Butyl (6S,9R,14R)-9-(*tert*-butoxycarbonyl)-14-((S)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-6-isopropyl-2,2-dimethyl-4,7-dioxo-3-oxa-11,12-dithia-5,8-diazapentadecan-15-oate.** Boc-valine (4.03g, 18.54 mmol, 2.10 equiv.) and **81** (3.13g, 8.89 mmol, 1.00 equiv.) were dissolved in anh. DMF (150 mL) and cooled to 0 °C under N_2. The reaction mixture was treated with HATU (8.47g, 22.3 mmol, 2.50 equiv.) and *i*-Pr_2NEt (3.87 mL, 22.3 mmol, 2.50 equiv.) and allowed to warm to rt. After 16 h, the reaction mixture was poured into water (1.0 L) resulting in the formation of a precipitate. The precipitate was collected by

filtration, and washed with water then dissolved into EtOAc, washed with aq. citric acid, sat. $NaHCO_3$, and brine. The organic layers were dried (Na_2SO_4), and concentrated to afford **82** (4.01 g, 60%) as a white foam: $[\alpha]_D^{25} =$ + 2.8 (c = 1.00, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3302, 2975, 2932, 1736, 1657, 1525, 1367, 1248, 1155 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 – 7.20 (m, 2H), 5.46 (d, *J* = 9.1 Hz, 2H), 4.76 (dt, *J* = 7.5, 5.5 Hz, 2H), 4.12 (t, *J* = 8.1 Hz, 2H), 3.10 (q, *J* = 10.9, 8.3 Hz, 4H), 2.11 (q, *J* = 6.6 Hz, 2H), 1.44 (d, *J* = 9.4 Hz, 36H), 0.97 (dd, *J* = 13.7, 6.9 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 169.2, 156.3, 82.9, 79.8, 59.9, 53.0, 40.6, 31.1, 28.5, 28.1, 19.5, 18.2; FT-HRMS (ESI) *m/z* calcd for $C_{34}H_{62}N_4O_{10}S_2Na^+$ $[M + Na]^+$: 773.3800, found 773.3781.



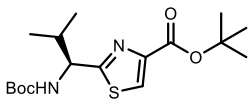
83

***tert*-Butyl (*tert*-butoxycarbonyl)-L-valyl-L-cysteinate**. **82** (108 mg, 0.144 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (1.5 ml). Water (42 μL, 2.30 mmol, 16 equiv.) and PBu_3 (0.142 mL, 0.575 mmol, 4.00 equiv.) were added and the reaction mixture stirred for 3 h. The reaction mixture was concentrated and purified by column chromatography on SiO_2 using 10% EtOAc/hexanes to 17% EtOAc/hexanes to afford **83** (101 mg, 94%) as a white solid: $[\alpha]_D^{25} =$ + 6.6 (c = 1.0, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3310, 2975, 1726, 1653, 1522, 1367, 1247, 1157, 1018, 847, 772 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.74 (d, *J* = 7.1 Hz, 1H), 5.05 (d, *J* = 8.7 Hz, 1H), 4.72 (dt, *J* = 7.5, 4.0 Hz, 1H), 4.05 – 3.90 (m, 1H), 3.16 – 2.85 (m, 2H), 2.15 (h, *J* = 6.7, 6.1 Hz, 1H), 1.71 (s, 1H), 1.48 (s, 8H), 1.44 (s, 9H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 168.7, 155.8, 83.0, 80.1, 60.1, 53.9, 30.7, 28.3, 28.0, 26.9, 19.3, 17.8; FT-HRMS (ESI) *m/z* calcd for $C_{17}H_{32}N_2O_5SNa^+$ $[M + Na]^+$: 399.1924, found 399.1925.



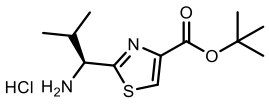
84

***tert*-Butyl 2-((S)-1-((*tert*-butoxycarbonyl)amino)-2-methylpropyl)-4,5-dihydrothiazole-4-carboxylate. 83** (143 mg, 0.380 mmol, 1.00 equiv.), $MoO_2(acac)_2$ (12.4 mg, 0.0380 mmol, 0.100 equiv.) and 6-methylpicolinic acid (10.4 mg, 0.0760 mmol, 0.200 equiv.) were suspended in degassed toluene (38 mL; sparged with N_2 for 1 h) under N_2. A Dean stark apparatus was assembled and the reaction mixture was refluxed at 130 °C under azeotropic conditions for 2.5 h. The mixture was concentrated, diluted with sat. $NaHCO_3$ (40 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The organic layers were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. The compound was purified by column chromatography on SiO_2 using 13% EtOAc/hexanes to afford **84** (136 mg, 92%) as a clear oil: $[\alpha]_D^{25} = +39.2$ (c = 1.0, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3439, 3010, 2976, 2360, 1709, 1618, 1495, 1368, 1214, 1153, 1038, 872, 748, 667, 490 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.27 (dd, *J* = 61.0, 9.1 Hz, 1H), 5.07 (td, *J* = 8.1, 7.6, 4.7 Hz, 1H), 4.49 (t, *J* = 6.5 Hz, 1H), 3.61 – 3.43 (m, 2H), 2.36 – 2.06 (m, 1H), 1.49 (s, 9H), 1.45 (d, *J* = 1.7 Hz, 9H), 1.01 (dd, *J* = 6.8, 1.6 Hz, 3H), 0.93 (dd, *J* = 6.9, 4.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5 (2), 155.5, 82.4, 82.3, 79.8, 79.6, 78.4, 78.0, 58.3, 57.8, 36.0, 35.4, 32.5, 32.3, 28.3, 28.1, 28.0, 27.9, 19.3, 17.1, 16.8; FT-HRMS (ESI) *m/z* calcd for $C_{17}H_{31}N_2O_4S^+$ $[M+H]^+$: 359.1999, found 359.1995.



63

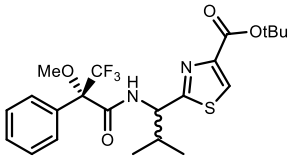
***tert*-Butyl (S)-2-(1-((*tert*-butoxycarbonyl)amino)-2-methylpropyl)thiazole-4-carboxylate**. **84** (61.3 mg, 0.170 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C under N_2. DBU (51 μL, 0.34 mmol, 2.0 equiv.) was added and after 10 min, $CBrCl_3$ (19 μL, 0.19 mmol, 1.1 equiv.). The reaction mixture stirred for 1 h after which TLC analysis showed complete consumption of the starting material. The reaction mixture was poured into a separatory funnel and diluted with CH_2Cl_2 (20 mL) and aq. citric acid (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL) and the organic layer was washed with sat. $NaHCO_3$ (20 mL), brine (20 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on SiO_2 using 13% EtOAc/hexanes to afford **63** (58.9 mg, 97%) as a white solid: $[\alpha]_D^{25} = -32.7$ (c = 1.0, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3343, 2971, 2345, 2114, 1702, 1495, 1366, 1228, 1157, 1094, 1010, 960, 873, 752, 624, 503 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (t, *J* = 1.3 Hz, 1H), 5.32 (d, *J* = 9.3 Hz, 1H), 4.93 – 4.76 (m, 1H), 2.47 – 2.39 (m, 1H), 1.59 (t, *J* = 1.7 Hz, 9H), 1.44 (s, 9H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 155.6, 148.8, 126.0, 82.0, 80.1, 77.4, 58.1, 33.5, 28.5, 28.3, 28.1, 19.6, 17.5; FT-HRMS (ESI) *m/z* calcd for $C_{17}H_{28}N_2O_4SNa^+$ $[M + Na]^+$: 379.1662, found 379.1659.



27

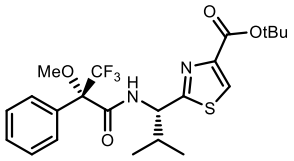
***tert*-Butyl (S)-2-(1-amino-2-methylpropyl)thiazole-4-carboxylate hydrochloride**. To a cooled solution of 4N HCl in 1,4-dioxane (8.00 mL) was added **63** (130.8 mg, 0.366 mmol, 1.00 equiv.). After 5 min the reaction mixture was warmed to rt. After stirring for 40 min, TLC analysis

indicated complete consumption of starting material. The reaction mixture was concentrated to afford **27** (107 mg, >99%) as a white solid which was used without further purification.



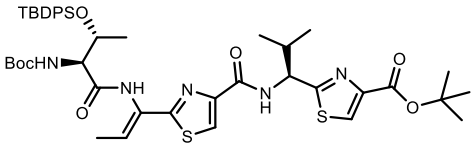
59

***tert*-Butyl 2-(2-methyl-1-((S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamido) propyl) thiazole-4-carboxylate**. Racemic **27** (10.7 mg, 0.042 mmol, 1.00 equiv.) and iPr_2NEt (9 μL, 0.05 mmol, 1.20 equiv.) were dissolved in CH_2Cl_2 (0.4 mL) and cooled to 0 ºC. (R)-(−)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride (8.6 μL, 0.046 mmol, 1.1 equiv.) was added and the mixture stirred for 10 min. The solution was transferred into a separatory funnel and diluted with citric acid and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3x) and the combined organic layers were washed with sat. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on SiO_2 using 17% % EtOAc/hexanes to afford **59** (20 mg, 86%) as an off white oil: $[\alpha]_D^{25} =$ + 6.4 (c = 1.00, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3416, 3353, 2968, 1703, 1503, 1253, 1161, 1103, 985, 770, 714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 – 7.89 (m, 1H), 5.20 (ddd, *J* = 9.3, 7.1, 6.4 Hz, 1H), 3.50 (q, *J* = 1.7 Hz, 2H), 3.40 (q, *J* = 1.4 Hz, 1H), 2.49 (dq, *J* = 22.4, 6.7 Hz, 1H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 170.0, 166.4, 160.2, 148.6, 132.8, 131.9, 129.5, 129.5, 128.6, 128.5, 128.0, 127.4, 127.4, 126.3, 126.1, 82.0, 81.9, 56.6, 56.3, 55.4, 55.0, 33.4, 33.1, 29.7, 28.3, 28.2, 19.6, 19.4, 17.8, 17.6; FT-HRMS (ESI) m/z calcd for $C_{22}H_{27}F_3N_2O_4SNa^+$ $[M+Na]^+$: 495.1536, found 495.1591.



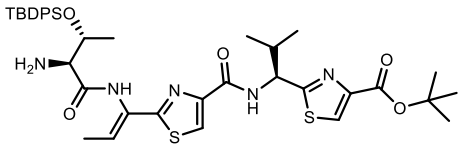
65

***tert*-Butyl 2-((S)-2-methyl-1-((S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamido) propyl) thiazole-4-carboxylate**. **27** (9.6 mg, 0.037 mmol, 1.00 equiv.) and iPr_2NEt (8 μL, 0.045 mmol, 1.20 equiv.) were dissolved in CH_2Cl_2 (0.4 mL) and cooled to 0 ºC. (R)-(−)-α-Methoxy-α-(trifluoromethyl) phenylacetyl chloride (7.7 μL, 0.041 mmol, 1.1 equiv.) was added and the mixture stirred for 10 min. The solution was transferred into a separatory funnel and diluted with citric acid and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3x) and the combined organic layers were washed with sat. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on SiO_2 using 17% EtOAc/hexanes to afford **65** (25 mg, 92%) as an off white oil: $[\alpha]_D^{25} = -42.0$ (c = 1.00, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3414, 2970, 2360, 1702, 1505, 1330, 1253, 1160, 1104, 986, 763, 633 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.70 – 7.53 (m, 2H), 7.46 – 7.30 (m, 3H), 5.22 (dd, *J* = 9.2, 6.2 Hz, 1H), 3.50 (q, *J* = 1.7 Hz, 3H), 2.89 – 2.15 (m, 1H), 1.60 (s, 9H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 166.5, 160.4, 148.7, 132.9, 129.7, 128.6, 127.6, 127.5, 126.4, 125.7, 82.2, 56.5, 55.6, 55.5, 33.6, 28.3, 19.7, 17.8; FT-HRMS (ESI) m/z calcd for $C_{22}H_{27}F_3N_2O_4SNa^+$ $[M+Na]^+$: 495.1536, found 495.1599.



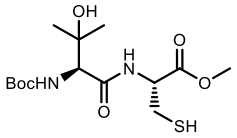
103

***tert*-Butyl 2-((1S)-1-(2-((Z)-1-(2-((*tert*-butoxycarbonyl)amino)-3-((*tert*-butyldiphenylsilyl) oxy) butanamido)prop-1-en-1-yl)thiazole-4-carboxamido)-2-methylpropyl)thiazole-4-carboxylate. 26** (549 mg, 0.880 mmol, 1.00 equiv.) and **27** (258 mg, 0.880 mmol, 1.00 equiv.) were dissolved in DMF (10 mL) and cooled to 0 °C under N_2. *i*-Pr_2NEt (0.320 mL, 1.85 mmol, 2.10 equiv.) was added and after 10 min of stirring HATU (402 mg, 1.06 mmol, 1.20 equiv.) was added in one portion. After 2 h the TLC analysis showed completion of the reaction. The reaction mixture was transferred to a separatory funnel and diluted with aq. citric acid (75 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the organic layers were washed with sat. $NaHCO_3$ (50 mL), brine (50 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on SiO_2 using 33% EtOAc/hexanes to afford **103** (550 mg, 72%) as a white foam: $[\alpha]_D^{25} =$ + 30.6 (c = 1.0, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3298, 2969, 2869, 2867, 1685, 1522, 1477, 1357, 1230, 1158, 1105, 955, 749, 702, 610, 505 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.02 (s, 1H), 7.95 (d, *J* = 9.2 Hz, 1H), 7.92 (s, 1H), 7.78 – 7.63 (m, 4H), 7.43 (td, *J* = 7.0, 6.3, 1.3 Hz, 2H), 7.40 – 7.33 (m, 4H), 6.74 (q, *J* = 7.1 Hz, 1H), 5.48 (d, *J* = 7.0 Hz, 1H), 5.32 (dd, *J* = 9.3, 6.5 Hz, 1H), 4.52 (t, *J* = 5.3 Hz, 1H), 4.45 (s, 1H), 2.60 (h, *J* = 6.8 Hz, 1H), 1.86 (d, *J* = 7.2 Hz, 3H), 1.80 (s, 2H), 1.58 (s, 9H), 1.43 (s, 9H), 1.13 (d, *J* = 6.3 Hz, 3H), 1.04 (s, 9H), 0.98 (dd, *J* = 8.2, 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 168.9, 167.0, 160.8, 160.3, 149.8, 148.8, 135.9, 135.7, 133.5, 132.3, 130.1, 130.0, 127.9, 127.8, 127.7, 126.0, 123.3, 81.8, 80.2, 69.6, 59.6, 56.5, 33.0, 29.7, 28.3, 28.2, 27.0, 19.6, 19.3, 18.9, 18.0, 14.2; FT-HRMS (ESI) *m/z* calcd for $C_{44}H_{59}N_5O_7S_2SiNa^+$ $[M + Na]^+$: 884.3517, found 884.3497.



23

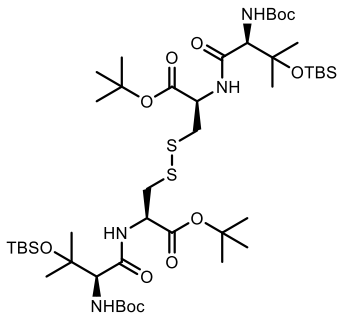
***tert*-Butyl 2-((1S)-1-(2-((Z)-1-(2-amino-3-((*tert*-butyldiphenylsilyl)oxy)butanamido)prop-1-en-1-yl)thiazole-4-carboxamido)-2-methylpropyl)thiazole-4-carboxylate.** Chilled 4N HCl in 1,4-dioxane (1.3 mL) was added at 0 °C to **103** (55.1 mg, 0.0640 mmol, 1.00 equiv.). The reaction mixture was stirred for 5 min at 0 °C before warming to rt for 30 min. After this time TLC analysis indicated complete consumption of starting material. Solid $NaHCO_3$ was added slowly to quench the HCl. Water (50 mL) was slowly added to the reaction mixture and the aqueous layer was extracted with EtOAc (3 x 20 mL). The organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The compound was purified by column chromatography on SiO_2 using 17% to 20% to 25% to 33% EtOAc/CH_2Cl_2 to afford **23** (43 mg, 90%) as a white foam: $[\alpha]_D^{25} =$ + 11.8 (c = 1.0, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3386, 2959, 2929, 2864, 2506, 2068, 1653, 1536, 1473, 1426, 1368, 1232, 1157, 1109, 974, 820, 742, 703, 610, 506 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 8.21 (s, 1H), 8.14 (d, *J* = 1.4 Hz, 1H), 7.82 – 7.63 (m, 6H), 7.54 – 7.25 (m, 6H), 6.73 (q, *J* = 7.2 Hz, 1H), 5.26 (d, *J* = 7.6 Hz, 1H), 4.51 (dq, *J* = 6.5, 3.3 Hz, 1H), 3.69 (d, *J* = 3.2 Hz, 1H), 2.48 (h, *J* = 6.7 Hz, 1H), 1.82 (dd, *J* = 7.1, 1.5 Hz, 3H), 1.62 (d, *J* = 1.5 Hz, 9H), 1.21 (d, *J* = 6.4 Hz, 3H), 1.10 – 1.02 (m, 12H), 0.98 (d, *J* = 6.9 Hz, 3H).^{13}C NMR (75 MHz, CD_3OD) δ 173.0, 162.9, 161.8, 150.3, 149.1, 137.1 (2), 135.0, 134.1, 131.2, 131.1, 129.5, 128.8 (2), 128.5, 125.0, 83.4, 71.7, 61.4, 58.2, 34.5, 28.4, 27.5, 21.3, 20.1, 19.9, 18.9, 14.6; FT-HRMS (ESI) *m/z* calcd for $C_{39}H_{51}N_5O_5S_2Si$ [M + Na]$^+$ 784.2993, found 784.3016.



91

Methyl ((S)-2-((*tert*-butoxycarbonyl)amino)-3-hydroxy-3-methylbutanoyl)-L-cysteinate. (S)-2-((*tert*-butoxycarbonyl)amino)-3-hydroxy-3-methylbutanoic acid (1.11 g, 4.74 mmol, 1.00 equiv.) and methyl *S*-trityl-L-cysteinate (1.79 g, 4.74 mmol, 1.00 equiv.) were dissolved in DMF (50 mL) and cooled to 0 ºC under N_2. *i*Pr_2NEt (0.93 mL, 5.21 mmol, 1.10 equiv.) and HATU (2.16 g, 5.69 mmol, 1.20 equiv.) were added and the reaction mixture was allowed to warm to rt. After 3 h the mixture was poured into a separatory funnel and aq. citric acid was added. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were washed with sat. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography using 50% EtOAc/hexanes to afford **90** (2.09 g, 74%) as an orange foam.

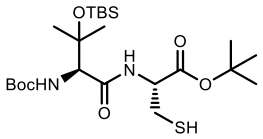
(1.24 g, 2.09 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (18 mL) and cooled to 0 °C. TFA (2 mL) and Et_3SiH (0.67 mL, 4.18 mmol, 2.00 equiv.) were added and it stirred for 1 h. The reaction mixture was quenched with solid $NaHCO_3$ and then diluted with H_2O. The aqueous later was extracted with CH_2Cl_2 (3x) and then washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on SiO_2 using 50% EtOAc/hexanes which afforded **91** (500 mg, 69%) as a white solid: $[\alpha]_D^{25} = -6.5$ (c = 1.00; $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3316, 2978, 2360, 1657, 1517, 1458, 1367, 1310, 1215, 1166, 1051, 956, 862, 615 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.1 Hz, 1H), 5.51 (d, *J* = 8.7 Hz, 1H), 4.87 (dt, *J* = 8.3, 4.4 Hz, 1H), 3.98 (d, *J* = 8.7 Hz, 1H), 3.79 (s, 3H), 3.73 (d, *J* = 3.9 Hz, 1H), 1.44 (s, 10H), 1.33 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 170.4, 156.3, 80.5, 72.0, 60.6, 53.8, 53.1, 28.5, 27.6, 26.5, 25.4; FT-HRMS (ESI) m/z calcd for $C_{14}H_{26}N_2O_6SNa^+$ $[M+Na]^+$: 373.1404, found 373.1432.



94

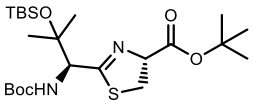
***tert*-Butyl (6S,9R,14R)-9-(*tert*-butoxycarbonyl)-6-((*tert*-butoxycarbonyl)amino)-14-((S)-2-((*tert*-butoxycarbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)-3-methylbutanamido)-2,2,3,3,5,5-hexamethyl-7-oxo-4-oxa-11,12-dithia-8-aza-3-silapentadecan-15-oate.** A solution of **93** (1.77 g, 5.11 mmol, 2.2 equiv.) and **81** (840 mg, 2.38 mmol, 1.00 equiv.), in anh. DMF (51 mL, 0.1 M) was cooled to 0 °C under N_2. The reaction mixture was treated with HATU (2.33 g, 6.13 mmol, 2.5 equiv.) and *i*-Pr_2NEt (1.04 mL, 5.96 mmol, 2.5 equiv.) and was allowed to warm to rt. After 18 h, the reaction mixture was poured into water (500 mL) and brine (30 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with aq. citric acid (50 mL), sat. $NaHCO_3$ (50 mL), brine (50 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on SiO_2 using a gradient of 5-30% EtOAc/hexanes which afforded **94** (1.64 g, 68%) as a white foam: $[\alpha]_D^{25} = +1.9$ (c = 1.00, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3343, 2979, 2931, 2857, 1737, 1681, 1506, 1391, 1368, 1307, 1253, 1157, 1052, 837, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (s, 2H), 5.51 (s, 2H), 4.70 (td, *J* = 6.9, 5.0 Hz, 2H), 4.11 (dd, *J* = 7.5, 3.6 Hz, 2H), 3.17 (dd, *J* = 13.8, 5.0 Hz, 2H), 2.99 (dd, *J* = 13.8, 6.7 Hz, 2H), 1.44 (d, *J* = 10.0 Hz, 36H), 1.38 (s, 6H), 1.29 (s, 6H), 0.89 (s, 18H), 0.13 (d, *J* = 6.6 Hz, 12H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 170.4, 169.2, 82.7, 79.7, 75.8, 53.1, 40.5, 28.6, 28.5, 28.1, 27.4, 26.9, 26.1 (2), 18.3, -1.9, -2.0; FT-HRMS (ESI) *m/z* calcd for $C_{46}H_{90}N_4O_{12}S_2Si_2Na^+$ $[M + Na]^+$: 1033.5427, found 1033.5422.



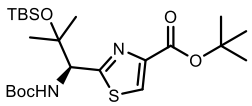
95

***tert*-Butyl ((S)-2-((*tert*-butoxycarbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)-3-methylbutanoyl) cysteinate. 94** (523 mg, 0.517 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (20 mL) and water (0.186 mL, 10.3 mmol, 20 equiv.). PBu_3 (1.30 mL, 5.17 mmol, 10.0 equiv.) was added and the reaction mixture stirred for 3 h at rt. The reaction mixture was concentrated and purified by column chromatography using 6% EtOAc/hexanes to remove the tributylphosphine oxide and 10% EtOAc/hexanes to elute the product to afford **95** (492 mg, 94%) a clear oil: $[\alpha]_D^{25} =$ + 8.2 (c = 1.0, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3331, 2941, 2359, 1663, 1500, 1366, 1311, 1250, 1152, 1047, 835, 754, 679, 529, 461 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.01 (s, 1H), 5.39 (s, 1H), 4.67 (dt, *J* = 6.9, 4.4 Hz, 1H), 4.02 (d, *J* = 7.6 Hz, 1H), 2.96 (dddd, *J* = 54.7, 13.9, 8.7, 4.4 Hz, 2H), 1.47 (s, 9H), 1.43 (s, 9H), 1.35 (s, 3H), 1.30 (s, 3H), 0.89 (s, 9H), 0.14 (d, *J* = 11.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 168.6, 82.8, 80.0, 75.6, 63.6, 54.5, 28.3, 28.2, 28.0, 27.4, 26.7, 26.0, 18.1, -1.9, -2.1; FT-HRMS (ESI) *m/z* calcd for $C_{23}H_{46}N_2O_6SSiNa^+$ $[M + Na]^+$: 529.2738, found 529.3563.



96

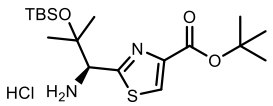
***tert*-Butyl 2-((S)-2,2,3,3,5,5,10,10-octamethyl-8-oxo-4,9-dioxa-7-aza-3-silaundecan-6-yl)-4,5-dihydrothiazole-4-carboxylate.** In a 3-neck RBF, **95** (1.07 g, 2.11 mmol, 1.00 equiv.), $MoO_2(acac)_2$ (68.8 mg, 0.211 mmol, 0.100 equiv.), and 6-methylpicolinic acid (57.9 mg, 0.422 mmol, 0.200 equiv.) were dissolved in degassed toluene (200 mL; sparged with N_2 for 1 h). A Dean stark apparatus was assembled and the reaction mixture was refluxed under azeotropic conditions at 130 °C for 4.5 h. The mixture was concentrated and diluted with CH_2Cl_2 (50 mL) and washed with sat. $NaHCO_3$ (50 mL). The aqueous layer was extracted with CH_2Cl_2 (50 mL) before the organic layer was washed with brine (50 mL), dried (Na_2SO_4), and concentrated. The compound was purified by column chromatography on SiO_2 using 9% to 10% to 11% EtOAc/hexanes to afford **96** (1.01 g, 98%) as a clear oil: $[\alpha]_D^{25} =$ + 35.4 (c = 0.5, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3437, 2943, 1711, 1608, 1491, 1215, 1153, 1026, 836, 749, 527, 477 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.58 – 5.05 (m, 1H), 5.05 – 4.77 (m, 1H), 4.42 (dd, *J* = 94.9, 9.0 Hz, 1H), 3.57 – 3.24 (m, 2H), 1.51 (s, 9H), 1.45 (s, 9H), 1.39 – 1.23 (m, 6H), 0.92 (s, 9H), 0.13 (d, *J* = 2.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 155.3, 79.6, 75.9, 62.1, 35.8, 28.3, 28.0, 27.3, 26.7, 26.0, 18.2, -2.1; FT-HRMS (ESI) *m/z* calcd for $C_{23}H_{44}N_2O_5SSiNa^+$ $[M + Na]^+$: 511.2632, found 511.2628.



97

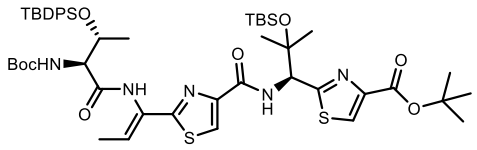
***tert*-Butyl (S)-2-(2,2,3,3,5,5,10,10-octamethyl-8-oxo-4,9-dioxa-7-aza-3-silaundecan-6-yl)thiazole-4-carboxylate. 96** (0.964 g, 1.97 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C under N_2. DBU (0.883 mL, 5.92 mmol, 3.00 equiv.) was added and after 10

min, $CBrCl_3$ (0.291 mL, 0.291 mmol, 1.50 equiv.). The reaction mixture stirred for 1 h after which TLC analysis showed complete consumption of starting material. The reaction mixture was poured into a separatory funnel and aq. citric acid (50 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the organic layer was washed with sat. $NaHCO_3$ (50 mL), brine (50 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on SiO_2 using 9% EtOAc/ 9% CH_2Cl_2/hexanes to afford **97** (876 mg, 91%) as a white foam: $[\alpha]_D^{25} =$ – 8.5 (c = 1.0, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3341, 2943, 2867, 1712, 1479, 1227, 1155, 1095, 1025, 899, 835, 750, 690, 521 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (s, 1H), 5.68 (s, 1H), 4.92 (d, *J* = 8.5 Hz, 1H), 1.61 (s, 9H), 1.44 (s, 9H), 1.37 – 1.26 (m, 6H), 0.91 (s, 9H), 0.11 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 126.6, 81.7, 28.3, 28.2, 27.5, 26.0, 18.2, -2.2 (2); FT-HRMS (ESI) *m/z* calcd for $C_{23}H_{43}N_2O_5SSi^+$ $[M+H]^+$: 487.2656, found 487.2657.



28

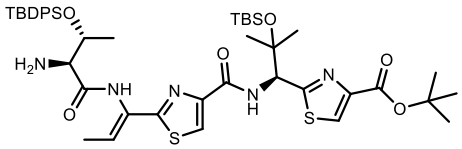
***tert*-Butyl (S)-2-(1-amino-2-((*tert*-butyldimethylsilyl)oxy)-2-methylpropyl)thiazole-4-carboxylate hydrochloride.** To **97** (766 mg, 1.57 mmol, 1.00 equiv.) at 0 °C, chilled HCl in 1,4-dioxane (31 mL) was added. The reaction mixture was cooled to 0 ºC and. After 5 min the reaction mixture was warmed to rt. After stirring for 40 min, TLC analysis indicated complete consumption of starting material. The reaction mixture was concentrated and **28** (682 mg, 100%) was collected as a white foam and was used without further purification.



104

***tert*-Butyl 2-((S)-1-(2-((Z)-1-((2S,3R)-2-((*tert*-butoxycarbonyl)amino)-3-((*tert*-butyldiphenylsilyl) oxy)butanamido)prop-1-en-1-yl)thiazole-4-carboxamido)-2-((*tert*-butyldimethylsilyl)oxy)-2-methylpropyl)thiazole-4-carboxylate. 26** (980 mg, 1.57 mmol, 1.00 equiv.) and **28** (664 mg, 1.57 mmol, 1.00 equiv.) were dissolved in DMF (16 mL) and cooled to 0 °C. *i*-Pr_2NEt (0.574 mL, 3.30 mmol, 2.10 equiv.) was added and after 10 min of stirring, followed by PyBOP (980 mg, 1.88 mmol, 1.20 equiv.) in one portion. After 2 h TLC analysis showed completion of the reaction. The reaction mixture was transferred to a separatory funnel and diluted with aq. citric acid (100 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the organic layer was washed with sat. $NaHCO_3$ (75 mL), brine (75 mL), dried (Na_2SO_4), and concentrated. The residue was purified twice by column chromatography on SiO_2 using 33% EtOAc/hexanes and the second time using 6% to 17% EtOAc/CH_2Cl_2 to afford **104** (1.21 g, 78%) a white foam: $[\alpha]_D^{25} =$ + 72.2 (c = 0.5, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3399, 3309, 2931, 2865, 1708, 1528, 1475, 1367, 1253, 1163, 1108, 1023, 837, 755, 704, 612, 507 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 9.0 Hz, 1H), 8.19 (s, 1H), 8.00 (d, *J* = 1.1 Hz, 1H), 7.96 (s, 1H), 7.70 (dd, *J* = 19.3, 7.3 Hz, 4H), 7.53 – 7.32 (m, 6H), 6.94 (q, *J* = 7.2 Hz, 1H), 5.44 (dd, *J* = 18.7, 7.9 Hz, 2H), 4.52 (td, *J* = 6.4, 3.9 Hz, 1H), 4.44 (s, 1H), 1.85 (d, *J* = 7.2 Hz, 3H), 1.59 (d, *J* = 1.1 Hz, 9H), 1.43 (d, *J* = 12.5 Hz, 12H), 1.33 (s, 3H), 1.11 (d, *J* = 6.3 Hz, 3H), 1.06 (s, 9H), 1.02 – 0.96 (m, 9H), 0.18 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 169.0, 160.6, 160.5, 150.3, 147.7, 135.9, 135.7, 132.3, 130.2, 130.0, 127.9, 127.8, 127.4, 127.2, 126.7, 123.2, 81.7, 75.6, 69.6, 60.8, 30.9,

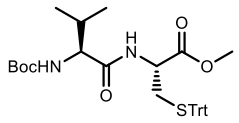
28.3, 28.2, 28.1, 27.4, 27.1, 26.1, 19.3, 18.9, 18.3, 13.9, -2.1, -2.3; FT-HRMS (ESI) *m/z* calcd for $C_{50}H_{73}N_5O_8S_2Si_2Na^+$ $[M + Na]^+$: 1014.4331 found 1014.4323.



24

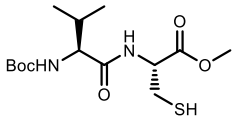
***tert*-Butyl 2-((S)-1-(2-((Z)-1-((2S,3R)-2-amino-3-((*tert*-butyldiphenylsilyl)oxy)butanamido)prop-1-en-1-yl)thiazole-4-carboxamido)-2-((*tert*-butyldimethylsilyl)oxy)-2-methylpropyl)thiazole-4-carboxylate.** Chilled HCl in 1,4-dioxane (18 mL) was added to **104** (928 mg, 0.935 mmol, 1.0 equiv.) at 0 °C. After 5 min, the reaction mixture was warmed to rt and after 45 min solid $NaHCO_3$ was added slowly to quench the excess HCl. Water (50 mL) was slowly added and the resulting solution was extracted with EtOAc (3 x 50 mL). The organic layers were washed with brine (50 mL), dried (Na_2SO_4), and concentrated. The material was purified by column chromatography on SiO_2 using CH_2Cl_2/EtOAc with a gradient 17% to 20% to 25% to 33% to afford **24** (440 mg, 53%) as a white foam: $[\alpha]_D^{25} = +52.2$ (c = 1.0, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3396, 2930, 2863, 2360, 1675, 1529, 1472, 1367, 1227, 1157, 1108, 1022, 955, 903, 824, 751, 703, 622, 506 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.67 (s, 1H), 8.45 (d, *J* = 9.1 Hz, 1H), 7.98 (s, 1H), 7.94 (s, 1H), 7.79 – 7.59 (m, 4H), 7.54 – 7.30 (m, 7H), 6.76 (q, *J* = 7.1 Hz, 1H), 5.46 (d, *J* = 9.1 Hz, 1H), 4.73 (dd, *J* = 6.4, 2.7 Hz, 1H), 3.65 (s, 1H), 1.85 (d, *J* = 7.2 Hz, 3H), 1.59 (s, 9H), 1.41 (d, *J* = 11.0 Hz, 6H), 1.17 (d, *J* = 6.3 Hz, 3H), 1.06 (s, 9H), 1.00 (s, 9H), 0.17 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 167.3, 160.7, 160.6, 149.7, 147.4, 135.9, 135.8, 134.1, 132.8, 129.9, 129.8, 128.1, 127.8, 127.6, 126.9, 125.9, 123.1, 81.8,

75.8, 69.8, 60.6, 28.2, 27.6, 27.4, 27.1, 26.1, 20.7, 19.4, 18.3, 14.3, -2.1, -2.2; FT-HRMS (ESI) *m/z* calcd for $C_{45}H_{66}N_5O_6S_2Si_2^+$ $[M+H]^+$: 892.3988, found 892.3986.



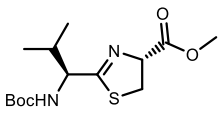
68

Methyl N-((*tert*-butoxycarbonyl)-L-valyl)-S-trityl-L-cysteinate. Boc-valine (6.0 g, 27.0 mmol, 1 equiv.) and methyl *S*-trityl-L-cysteinate (10.5 g, 27.0 mmol, 1.00 equiv.) were dissolved in CH_2Cl_2 and cooled to 0 °C. HATU (12.6 g, 33.1 mmol, 1.20 equiv.) and DMAP (703 mg, 5.52 mmol, 0.20 equiv.) were added. *i*-Pr_2NEt (10.5 mL, 60.8 mmol, 2.20 equiv.) was added and the reaction was allowed to warm to rt. After 5 h the reaction was complete and was concentrated. The reaction mixture was diluted with ethyl acetate and citric acid was added. The aqueous layer was extracted with EtOAc (3x) and then the organic layer was washed with sat. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography on SiO_2 using 17% EtOAc/hexanes to 20% EtOAc/hexanes which afforded **68** (14.8 g, 93%) as a clear oil: $[\alpha]_D^{25} = +5.9$ (c = 1.0, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3318, 3058, 2964, 2926, 2359, 2250, 2112, 1663, 1492, 1442, 1366, 1208, 1167, 1034, 909, 871, 733, 700, 619, 527 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 6H), 7.33 – 7.27 (m, 6H), 7.25 – 7.20 (m, 3H), 6.19 (d, *J* = 7.6 Hz, 1H), 5.05 (d, *J* = 8.7 Hz, 1H), 4.54 (ddd, *J* = 7.6, 5.8, 4.6 Hz, 1H), 3.94 (dd, *J* = 8.7, 5.4 Hz, 1H), 3.70 (s, 3H), 2.75 – 2.50 (m, 2H), 2.10 (q, *J* = 6.6 Hz, 1H), 1.45 (s, 9H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 170.7, 144.4, 129.6, 128.2, 128.1, 127.1, 77.6, 77.4, 77.2, 76.7, 67.2, 52.8, 51.3, 33.7, 31.4, 31.1, 28.5, 19.3, 17.6; FT-HRMS (ESI+) *m/z* calcd for $C_{33}H_{40}N_2O_5SNa^+$ $[M + Na]^+$: 599.2550, found 599.2554.



69

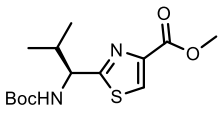
Methyl (*tert*-butoxycarbonyl)-L-valyl-L-cysteinate. **68** (6.15 g, 10.7 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (95 mL) and cooled to 0 °C. TFA (11 mL) and Et_3SiH (3.41 mL, 21.3 mmol, 2.00 equiv.) were added and it stirred for 15 min. The reaction mixture was quenched with solid $NaHCO_3$ and then diluted with H_2O. The aqueous later was extracted with CH_2Cl_2 (3x) and then washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on SiO_2 using 20% EtOAc/hexanes which afforded **69** (2.42 g, 68%) as a white solid: $[\alpha]_D^{25} =$ + 17.8 (c = 1.0, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3312, 3063, 2963, 2565, 2359, 2125, 1745, 1645, 1521, 1454, 1366, 1298, 1247, 1161, 1043, 879, 784, 736, 620 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (d, *J* = 7.6 Hz, 1H), 5.18 (d, *J* = 8.7 Hz, 1H), 4.85 (dt, *J* = 8.0, 4.3 Hz, 1H), 4.03 – 3.90 (m, 1H), 3.75 (s, 3H), 2.97 (dt, *J* = 8.5, 4.0 Hz, 2H), 2.11 (q, *J* = 6.8 Hz, 1H), 1.55 – 1.47 (m, 1H), 1.41 (s, 9H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 170.4, 155.9, 80.1, 77.6, 77.4, 77.2, 76.7, 53.8, 52.8, 30.8, 28.4, 26.7, 19.3, 18.0; FT-HRMS (ESI+) *m/z* calcd for $C_{14}H_{26}N_2O_5SNa^+$ $[M + Na]^+$: 357.1455, found 357.1445.



70

Methyl (R)-2-((S)-1-((*tert*-butoxycarbonyl)amino)-2-methylpropyl)-4,5-dihydrothiazole-4-carboxylate. In two separate 500 mL RBF equipped with stir bar and Dean stark apparatus, **69** (1.34 g, 4.02 mmol, 1.00 equiv.), $MoO_2(acac)_2$ (262 mg, 0.802, 0.2 equiv.), and picolinic acid (200

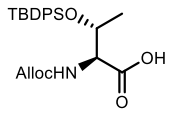
mg, 0.802 mmol, 0.40 equiv.) were dissolved in 400 mL (200 mL each) of dry, degassed toluene. The reaction was heated to 130 °C for 13 hours. An additional 0.20 equiv. of $MoO_2(acac)_2$ was added and stirred for 3 hours. The reaction mixtures were combined and concentrated. The crude solid was dissolved in CH_2Cl_2 and quenched with sat. $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2 (3x). The organic layer was washed with brine, and dried (Na_2SO_4), and concentrated. The crude material was purified by column chromatography on SiO_2 using 17% EtOAc/hexanes to 20% EtOAc/hexanes to 33% EtOAc/hexanes to afford **70** (1.27 g, >99%) a yellow tinted oil: $[\alpha]_D^{25} =$ + 44.6 (c = 1.0, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3375, 2965, 2357, 2120, 1704, 1617, 1494, 1457, 1365, 1233, 1162, 1008, 931, 873, 775, 543 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.21 (d, *J* = 9.3 Hz, 1H), 5.12 (ddd, *J* = 9.6, 7.9, 1.6 Hz, 1H), 4.51 – 4.44 (m, 1H), 3.77 (s, 4H), 3.63 – 3.44 (m, 3H), 2.16 (ddt, *J* = 11.4, 9.3, 5.7 Hz, 1H), 1.42 (s, 12H), 0.97 (d, *J* = 6.8 Hz, 4H), 0.87 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.2, 171.2, 155.6, 79.8, 77.7, 77.4, 58.0, 52.8, 35.7, 32.5, 28.4, 19.5, 16.6. FT-HRMS (ESI+) *m/z* calcd for $C_{14}H_{24}N_2O_4SNa^+$ $[M + Na]^+$: 339.1349, found 339.1345.



71

Methyl (S)-2-(1-((tert-butoxycarbonyl)amino)-2-methylpropyl)thiazole-4-carboxylate. **70** (1.27 g, 4.00 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 and cooled to 0 ºC under N_2. DBU (1.79 mL, 12.00 mmol, 3.00 equiv.) and $CBrCl_3$ (0.59 mL, 6.0 mmol, 1.5 equiv.) was added. The reaction stirred for 15 min and poured into a separatory funnel. Citric acid was added and the aqueous layer was extracted with CH_2Cl_2 (5x). The combined organic layers were washed with

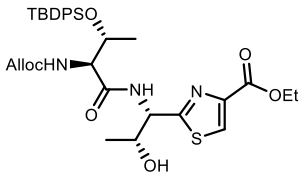
sat. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on SiO_2 using 20% EtOAc/hexanes which afforded **71** (1.06 g, 84%) as a white solid: IR (ATR) $\tilde{\nu}$ = 3347, 3120, 2964, 2354, 2109, 1701, 1499, 1366, 1343, 1211, 1162, 1093, 989, 916, 871, 754, 625 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 5.28 (d, *J* = 8.3 Hz, 1H), 4.89 (dd, *J* = 9.1, 5.5 Hz, 1H), 3.93 (s, 3H), 2.44 (dd, *J* = 13.8, 7.2 Hz, 1H), 1.74 (s, 1H), 1.44 (s, 8H), 0.97 (d, *J* = 6.8 Hz, 4H), 0.89 (d, *J* = 6.9 Hz, 3H); FT-HRMS (ESI+) *m/z* calc for $C_{14}H_{22}N_2O_4SNa^+$ $[M+Na]^+$: 337.1192, found 337.1194.



98

***N*-((allyloxy)carbonyl)-O-(*tert*-butyldiphenylsilyl)-L-threonine**: Threonine (7.40 g, 62.0 mmol, 1.00 equiv.) was suspended in MeCN (60 mL) and cooled to 0 °C under N_2. DBU (13.0 mL, 87.0 mmol, 1.40 equiv.) and TBDPS-Cl (19.4 mL, 74.6 mmol, 1.20 equiv.) were added and the reaction mixture warmed to rt and stirred for 36 h. The resulting white precipitate was filtered and rinsed with cool MeCN and dried *in vacuo*. The solid was suspended in a 2:1 THF/H_2O (40 mL), and cooled to 0 ºC under a nitrogen atmosphere. Allyl chloroformate (7.91 mL, 74.4 mmol, 1.20 equiv.) was added and the reaction mixture was stirred at rt for 16 h. The reaction was concentrated, diluted with water, and the pH was adjusted to 3 using aq. 1 N HCl. The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on SiO_2 using 7 to 10 to 20% EtOAc/hexanes to afford **98** (6.50 g, 24%) as a green tinted viscous oil: $[\alpha]_D^{25} = -4.2$ (c = 0.75, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3444, 3071, 2932, 2091, 1722, 1508, 1427, 1310, 1211, 1104, 975,

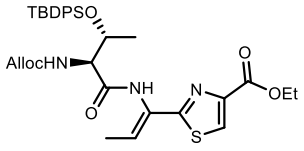
936, 822, 703, 612, 506 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (ddd, *J* = 8.1, 4.5, 1.6 Hz, 5H), 7.52 – 7.33 (m, 8H), 5.97 (ddt, *J* = 16.3, 10.6, 5.6 Hz, 1H), 5.55 (d, *J* = 9.1 Hz, 1H), 5.36 (dd, *J* = 17.0, 1.7 Hz, 1H), 5.29 – 5.22 (m, 1H), 4.63 (dt, *J* = 5.8, 1.5 Hz, 2H), 4.51 – 4.42 (m, 1H), 4.33 (dd, *J* = 9.1, 2.4 Hz, 1H), 1.06 (d, *J* = 6.3 Hz, 3H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 156.6, 136.0, 136.0, 133.6, 132.7, 132.4, 130.3, 130.0, 127.9, 127.8, 118.2, 70.1, 66.3, 59.6, 27.0, 20.2, 19.4; FT-HRMS (ESI) calcd for $C_{24}H_{31}NO_5SiNa^+$ $[M + Na]^+$: 464.1864, found 464.1869.



99

Ethyl 2-((1S,2S)-1-((2S,3R)-2-(((allyloxy)carbonyl)amino)-3-((*tert*-butyldiphenylsilyl) oxy) butanamido)-2-hydroxypropyl)thiazole-4-carboxylate: **98** (6.30 g, 14.2 mmol, 1.00 equiv.) was dissolved in DMF (110 mL) and cooled to 0 ºC under N_2. *i*-Pr_2NEt (7.64 mL, 44.0 mmol, 3 equiv.) and HATU (7.23 g, 19.0 mmol, 1.30 equiv.) were added and the solution stirred for 15 min before a solution of **46** (3.90 g, 14.6 mmol, 1.02 equiv.) in DMF (15 mL) was added dropwise to the mixture. The solution was allowed to warm to rt stirred for 16 h. The reaction mixture was poured into a separatory funnel 1N HCl (100 mL) was added. The aqueous layer was extracted with EtOAc (3 x 75 mL) and the combined organic layers were washed with sat. $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on SiO_2 using 33% EtOAc/hexanes to afford **99** (7.70 g, 81%) as a white solid: $[\alpha]_D^{25} = -58.7$ (c = 1.0, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3347, 3051, 2932, 2101, 1717, 1674, 1487, 1440, 1372, 1322, 1200, 1099, 993, 965,

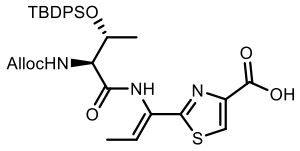
873, 821, 737, 702, 611, 596 cm^{-1}; ^{1}H NMR (400 MHz, CDCl3) δ 8.13 (s, 1H), 5.89 (tt, *J* = 10.7, 5.2 Hz, 1H), 5.73 (d, *J* = 6.9 Hz, 1H), 5.34 – 5.17 (m, 3H), 4.70 – 4.63 (m, 1H), 4.55 (d, *J* = 5.1 Hz, 2H), 4.40 (q, *J* = 7.1 Hz, 5H), 3.20 (s, 2H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.29 (d, *J* = 6.5 Hz, 3H), 0.83 (d, *J* = 6.2 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4 (2), 161.1, 156.1, 146.7, 135.9 (2), 132.5 (2), 130.1 (2), 129.3, 118.0, 70.8, 60.5 (2), 55.1, 27.1, 19.6, 18.8 (2), 14.5; HRMS (m/z) calc. for $C_{33}H_{43}N_3O_7SSiNa^+$ $[M+Na]^+$: 676.2483 found 676.2488.



100

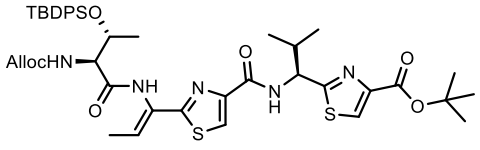
Ethyl 2-((Z)-1-((2S,3R)-2-(((allyloxy)carbonyl)amino)-3-((*tert*-butyldiphenylsilyl) oxy) butanamido)prop-1-en-1-yl)thiazole-4-carboxylate: **99** (7.70 g, 12.0 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (120 mL) and cooled to 0 ºC under N_2. Et_3N (6.70 mL, 48.0 mmol, 4.00 equiv.) and MsCl (1.90 mL, 24.0 mmol, 2.00 equiv.) were added and stirred. After 1 h the solution was poured into a separatory funnel and washed with 1N aq. HCl. The aq. layer was extracted with CH_2Cl_2 (3 x 50 mL) and the organic layer was washed with sat. $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated. The resulting foamy oil and DABCO (13.5 g, 120 mmol, 10.0 equiv.) were dissolved in CH_2Cl_2 and cooled to 0 ºC under N_2. After 20 min diethylamine (6.20 mL, 60.2 mmol, 5.00 equiv.) was added and the solution warmed to rt and stirred for 16 hours. The reaction mixture was washed with 1N aq. HCl and the aq. layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with sat. $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on SiO_2 using 50% EtOAc/hexanes to afford

100 (6.16 g, 81%) as a white solid: $[\alpha]_D^{25} =$ + 5.1 (c = 1.0, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3322, 3049, 2932, 2106, 1718, 1492, 1442, 1380, 1322, 1235, 1109, 995, 822, 742, 704, 611, 507 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.05 (s, 1H), 7.77 – 7.63 (m, 4H), 7.50 – 7.30 (m, 7H), 6.67 (q, *J* = 7.1 Hz, 1H), 6.02 – 5.76 (m, 2H), 5.45 – 5.25 (m, 1H), 5.20 (d, *J* = 10.5 Hz, 1H), 4.67 – 4.44 (m, 5H), 4.37 (qd, *J* = 7.1, 1.4 Hz, 2H), 2.89 (s, 0.48H), 1.83 (d, *J* = 7.1 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.15 (d, *J* = 6.2 Hz, 3H), 1.05 (s, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7 (2), 161.4, 156.2, 147.6, 135.9 (2), 132.6, 130.2 (2), 127.9 (2), 126.8, 118.0, 68.0 (2), 61.5, 59.7, 27.1, 19.4, 18.3, 14.5 (2); FT-HRMS (ESI+) *m/z* calc for $C_{33}H_{41}N_3O_6SSiNa^+$ $[M+Na]^+$: 658.2378, found 658.2372.



101

Ethyl 2-((Z)-1-((2S,3R)-2-(((allyloxy)carbonyl)amino)-3-((*tert*-butyldiphenylsilyl) oxy) butanamido)prop-1-en-1-yl)thiazole-4-carboxylic acid. 100 (997 mg, 1.57 mmol, 1.00 equiv.) was dissolved in a 2:1 THF/H_2O (1.5 mL) and cooled to 0 ºC under N_2. LiOH-H_2O (140 mg, 3.30 mmol, 2.10 equiv.) was added in one portion and the reaction mixture stirred for 10 h. The reaction mixture was concentrated and citric acid was added until the pH reached 3. The aqueous layer was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The resulting solid was purified by column chromatography on SiO_2 using 33% EtOAc/hexanes then CH_2Cl_2 then 2% MeOH/CH_2Cl_2 to 5% MeOH/CH_2Cl_2 to 10% MeOH/CH_2Cl_2 to afford **101** (758 mg, 80%) as a white solid.



102

***tert*-Butyl 2-((S)-1-(2-((Z)-1-((2S,3R)-2-(((allyloxy)carbonyl)amino)-3-((tert-butyldiphenylsilyl)oxy)butanamido)prop-1-en-1-yl)thiazole-4-carboxamido)-2-methylpropyl)thiazole-4-carboxylate**. **101** (73.2 mg, 0.12 mmol, 1.0 equiv.) and **27** (30.9 mg, 0.12 mmol, 1.00 equiv.) were dissolved in DMF and cooled to 0 ºC. *i*-Pr_2NEt (25 ul, 0.14 mmol, 1.2 equiv.) and HATU (55 mg, 0.14 mmol, 1.2 equiv.) were added. After 2 h the reaction mixture was transferred into a separatory funnel and diluted with EtOAc and citric acid. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were washed with sat. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on SiO_2 using 33% EtOAc/hexanes to afford **102** (98 mg, 97%) as a white foam: $[\alpha]_D^{25} =$ + 27.3 (c = 1.0, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3299, 2927, 2360, 2089, 1705, 1532, 1478, 1328, 1228, 1158, 1106, 968, 821, 610, 506 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.02 (s, 1H), 7.95 – 7.89 (m, 2H), 7.71 (d, *J* = 7.3 Hz, 2H), 7.69 – 7.63 (m, 2H), 7.50 – 7.30 (m, 7H), 6.71 (q, *J* = 7.1 Hz, 1H), 5.86 (s, 2H), 5.31 (dd, *J* = 9.3, 6.6 Hz, 1H), 5.27 – 5.14 (m, 2H), 4.66 – 4.43 (m, 4H), 2.58 (h, *J* = 7.1 Hz, 1H), 1.85 (d, *J* = 7.2 Hz, 3H), 1.81 (s, 1H), 1.58 (s, 8H), 1.17 (d, *J* = 6.3 Hz, 3H), 1.06 (s, 9H), 0.97 (dd, *J* = 6.7, 4.4 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$ δ 171.2, 166.9, 160.9, 160.4, 149.9, 148.9, 136.0, 135.8, 132.6, 132.3, 130.4, 130.2, 128.0, 127.9, 126.2, 123.5, 118.1, 82.0, 69.7, 66.2, 59.7, 56.6, 33.2, 31.1, 28.3, 27.2, 19.8, 19.4, 18.7, 18.2, 14.4; FT-HRMS (ESI+) *m/z* calc for $C_{43}H_{55}N_5O_7S_2SiNa^+$ $[M+Na]^+$: 868.3204, found 868.3198.

2.6.3 NMR Spectra

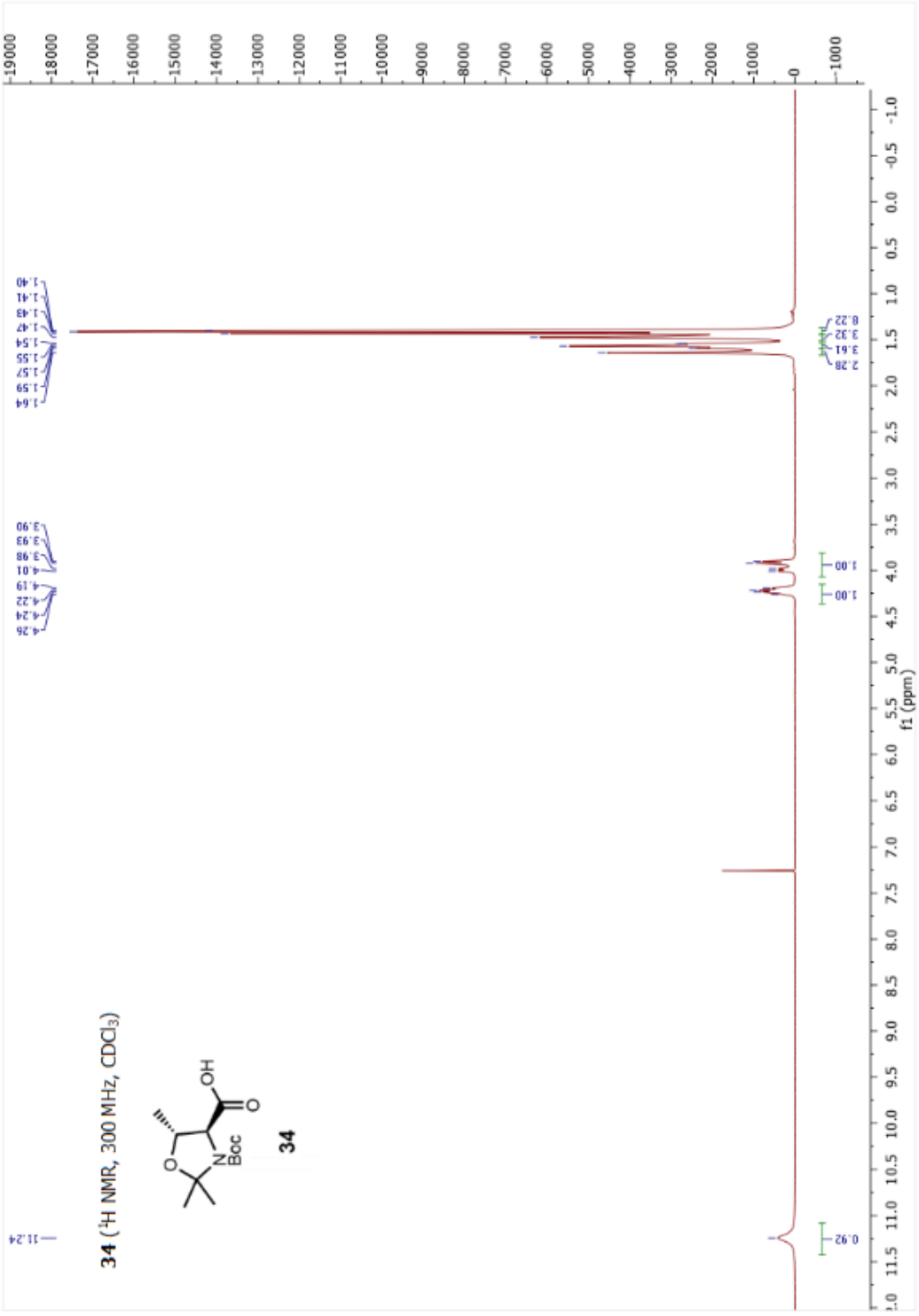


Figure 2.1 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **34**.

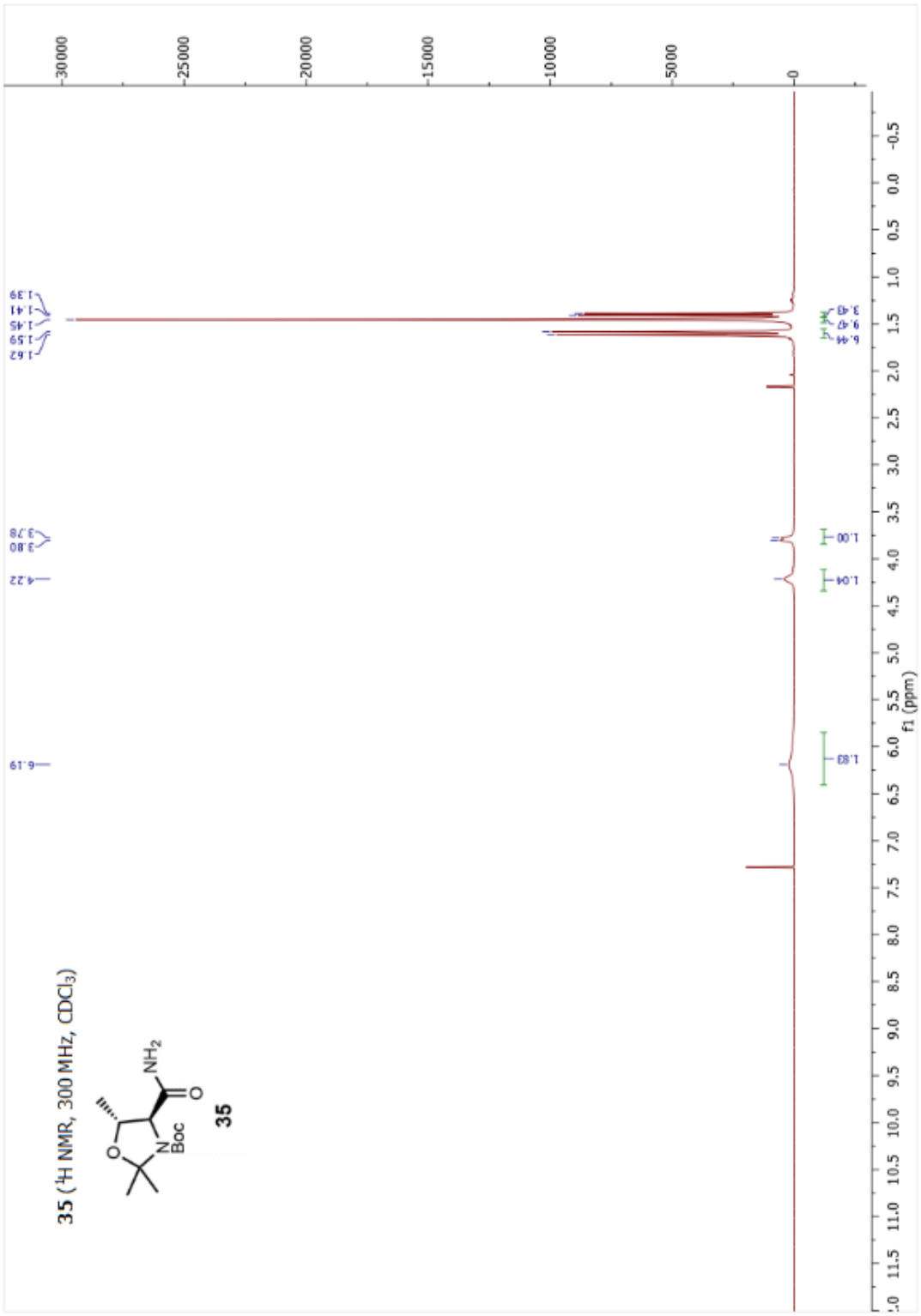


Figure 2.2 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **35**.

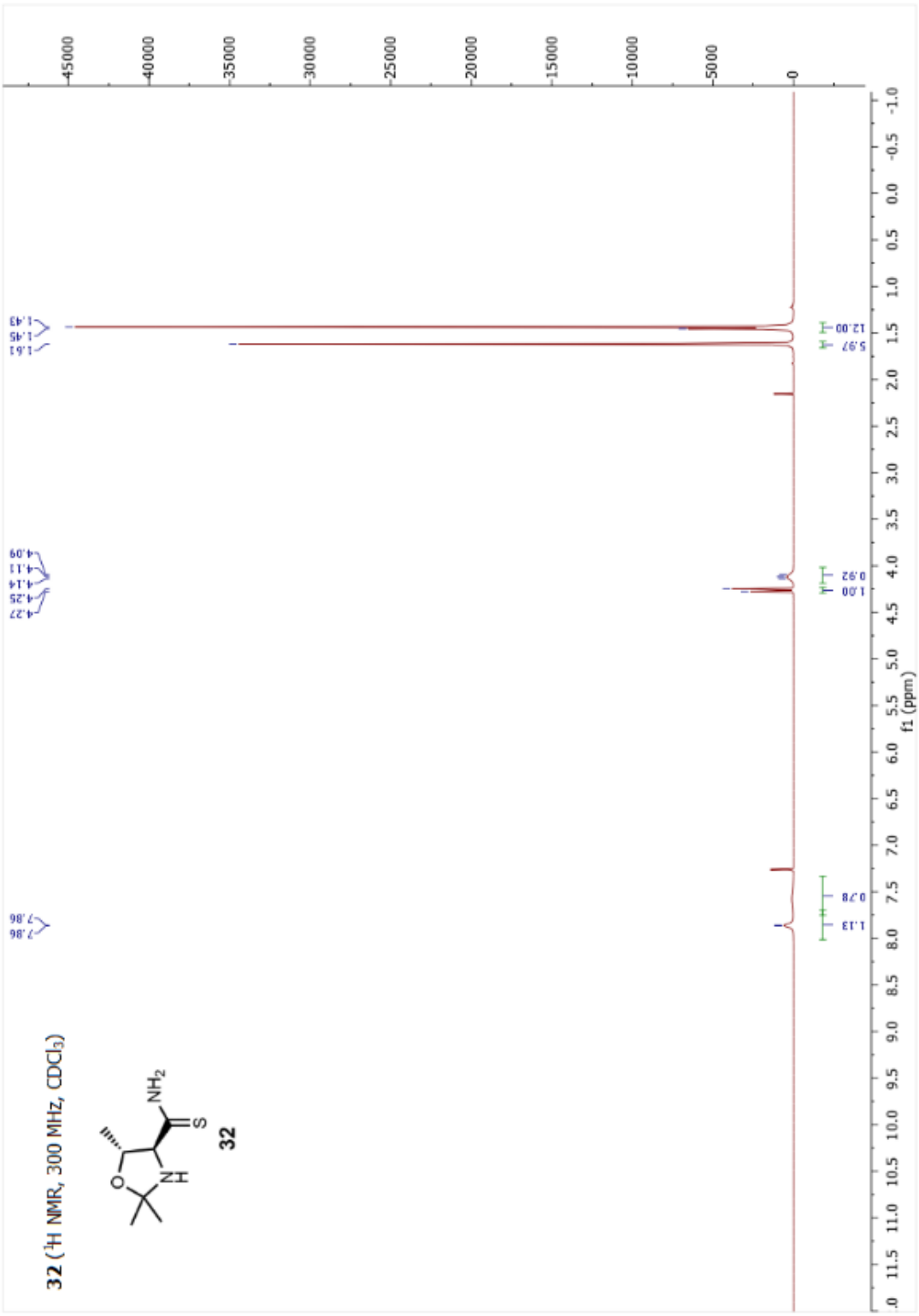


Figure 2.3 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **32**.

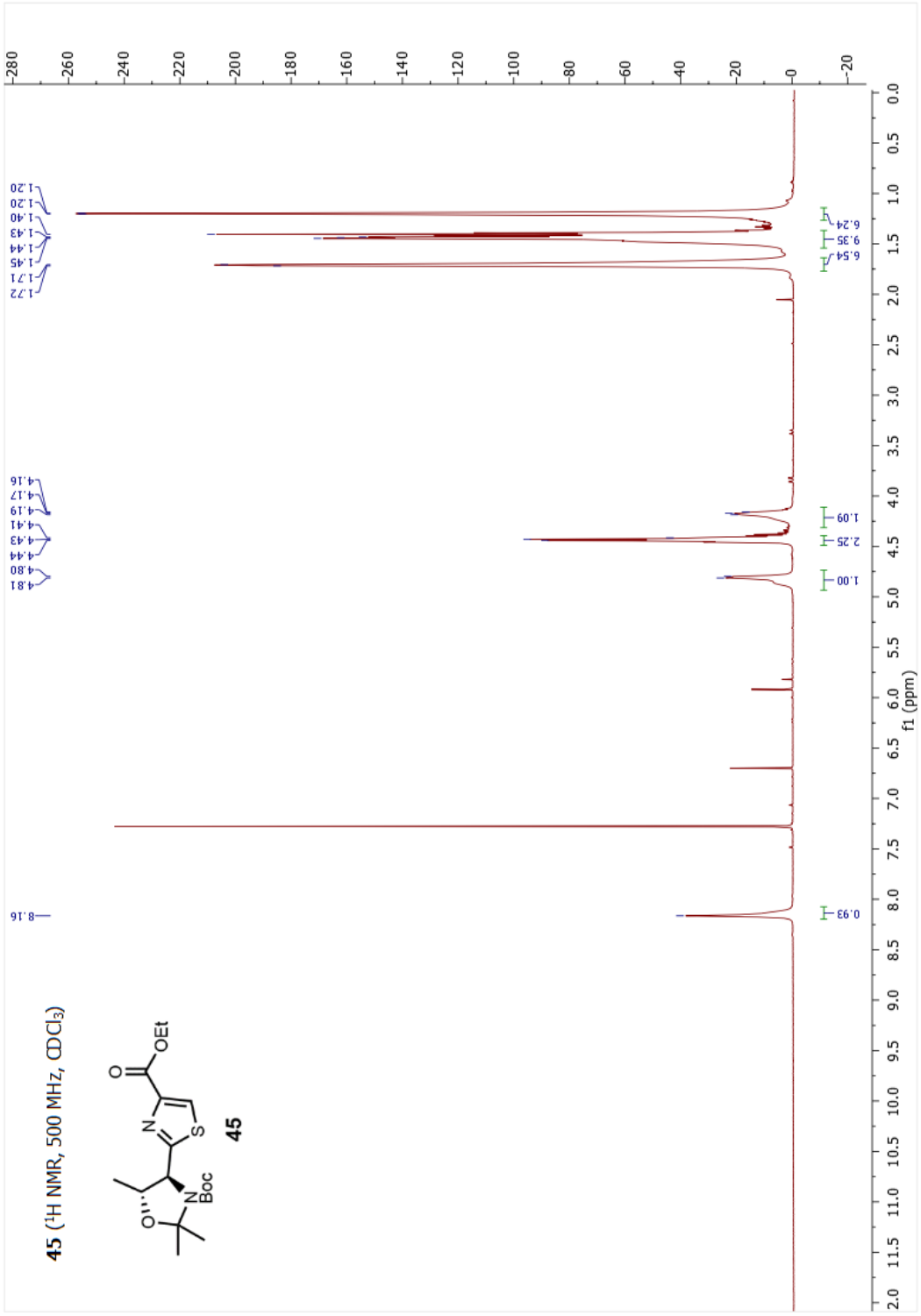


Figure 2.4 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **45**.

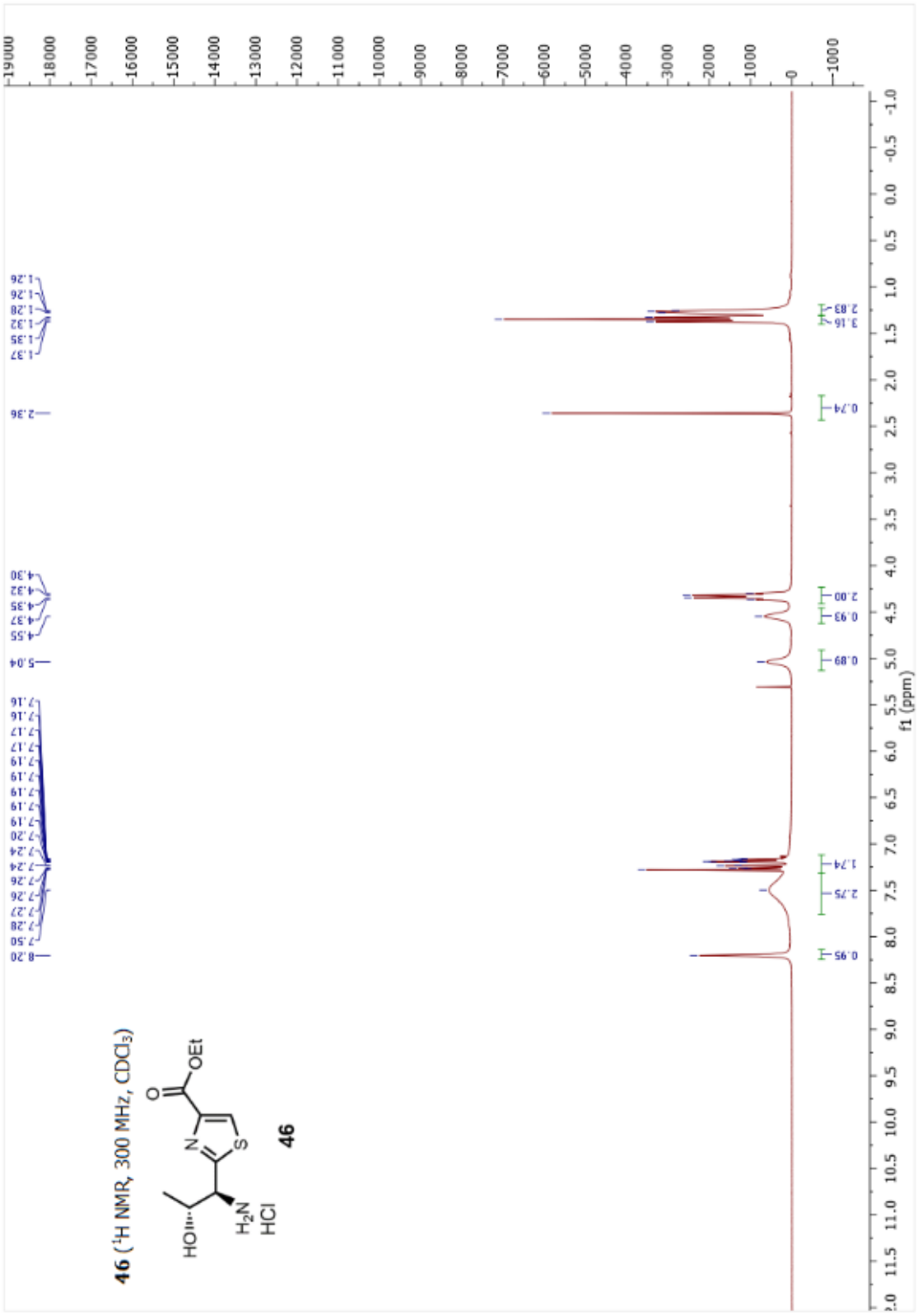


Figure 2.5 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **46**.

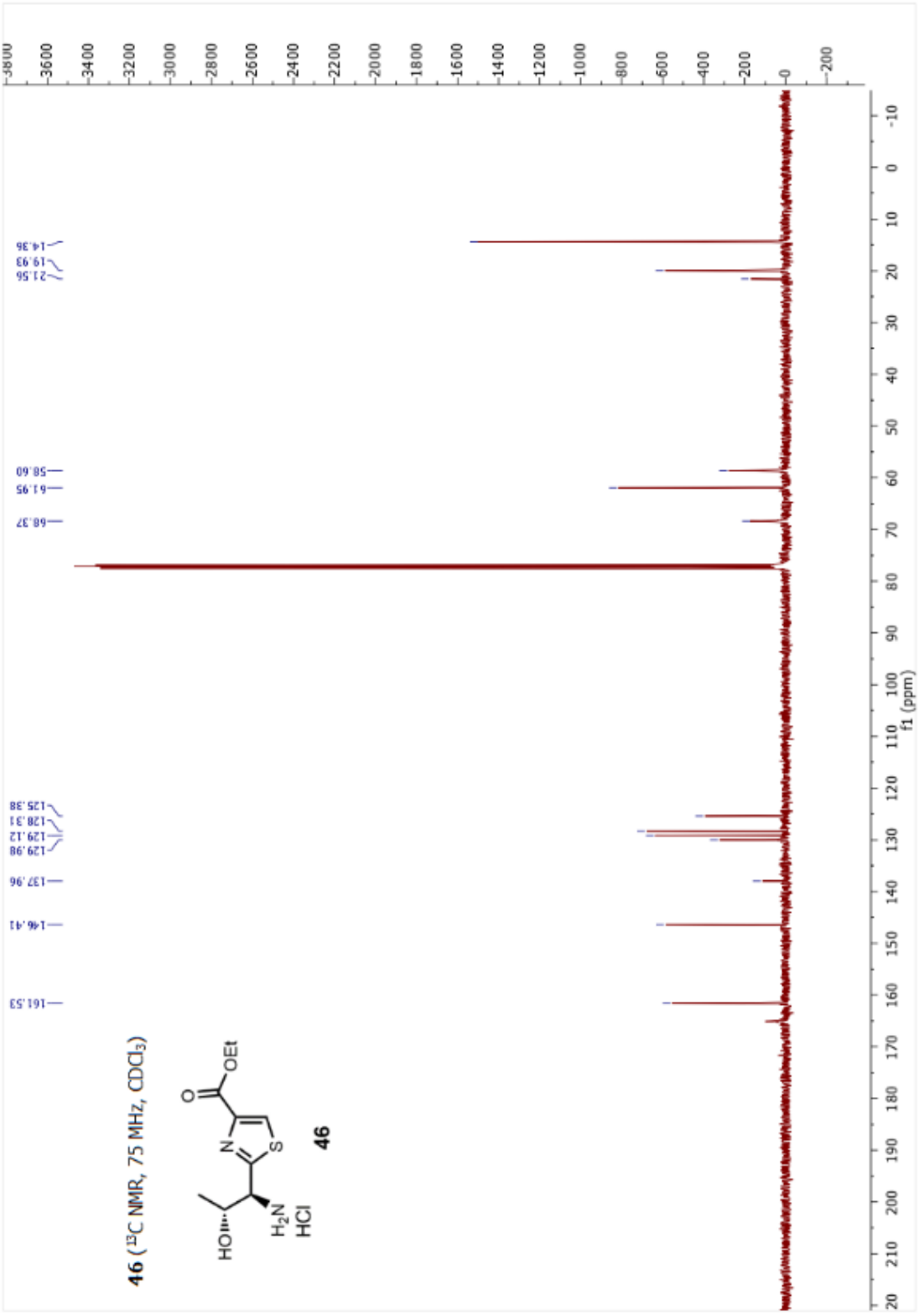


Figure 2.6 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **46**.

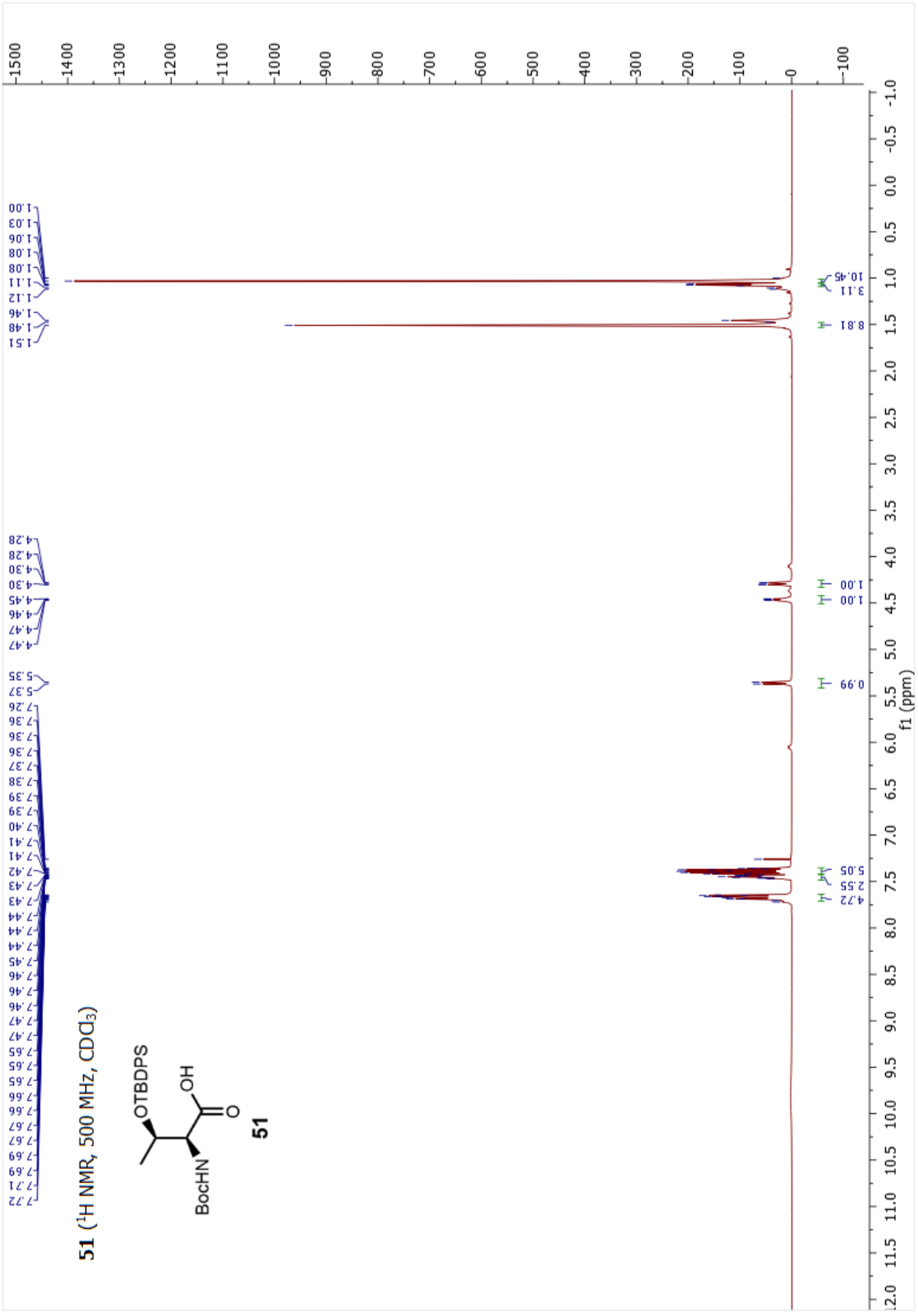


Figure 2.7 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **51**.

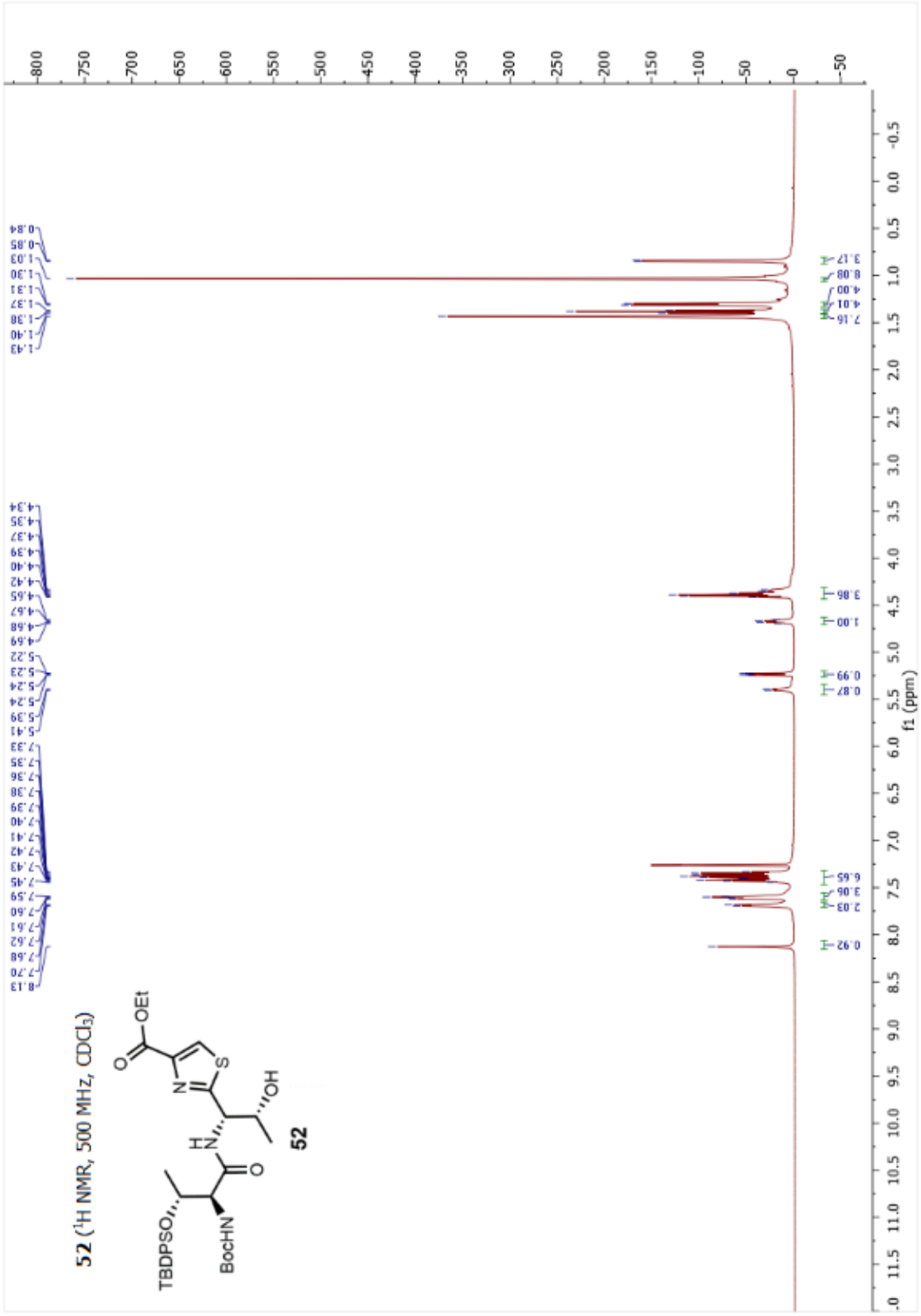


Figure 2.8 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **52**.

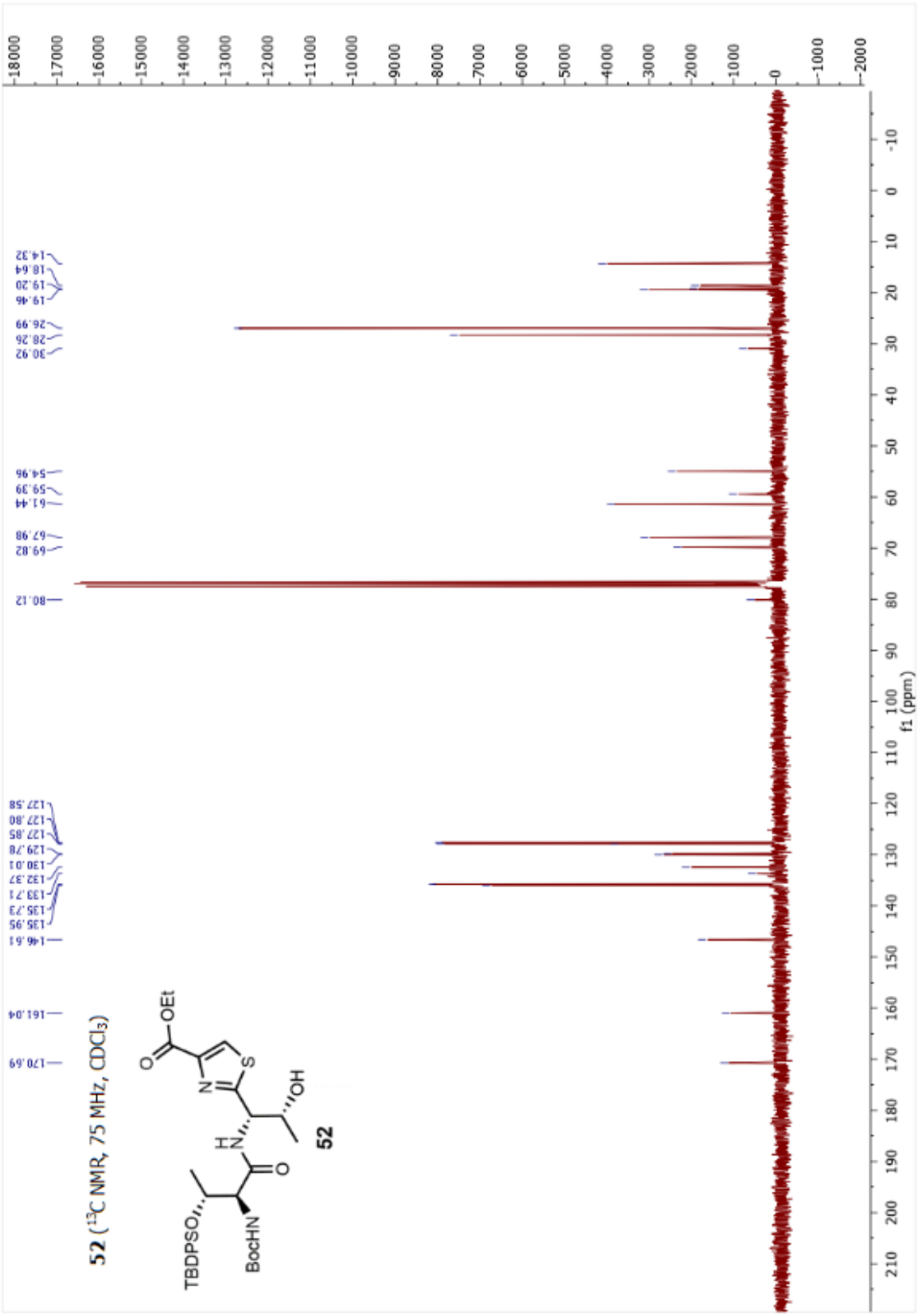


Figure 2.9 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **52**.

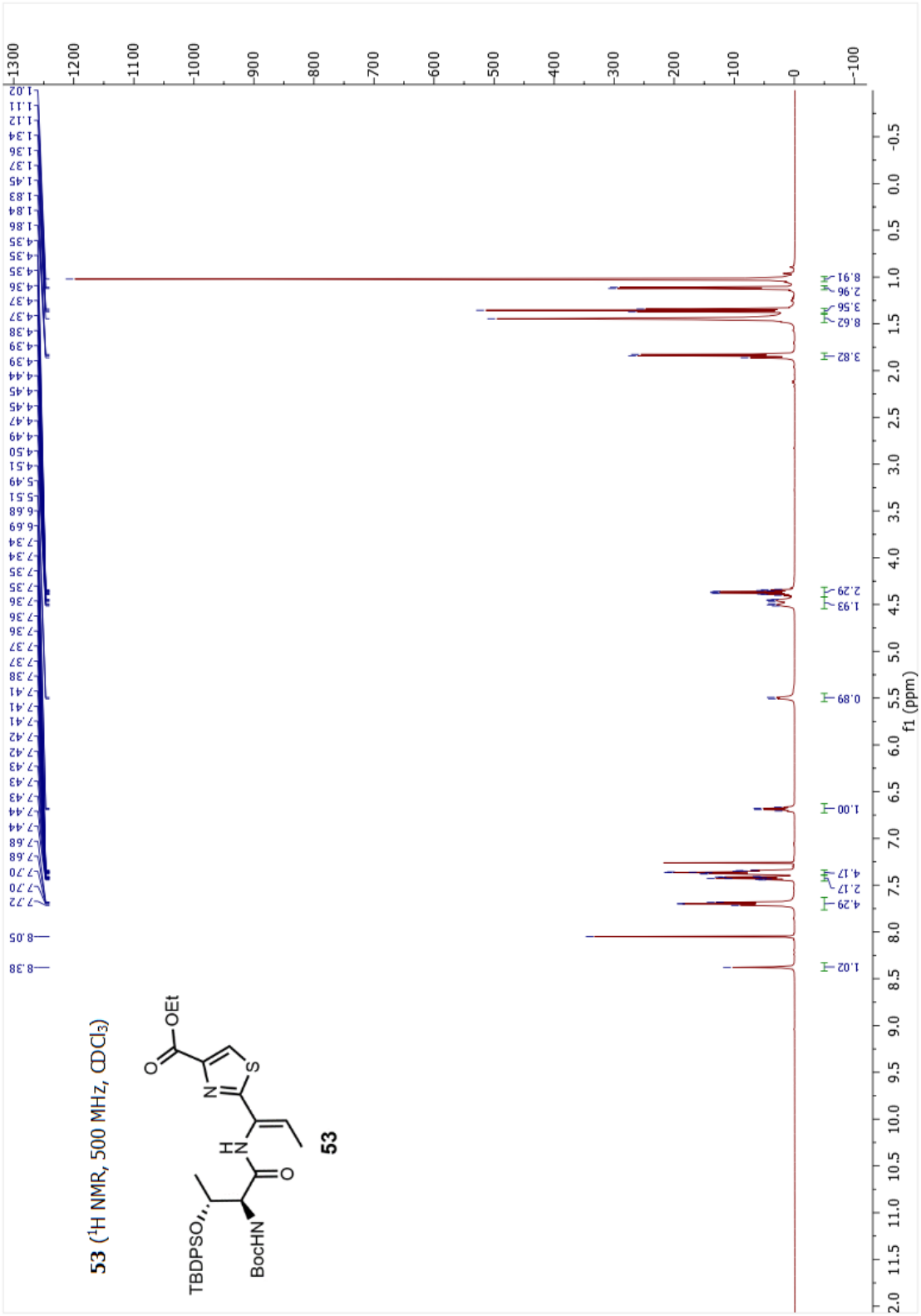


Figure 2.10 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **53**.

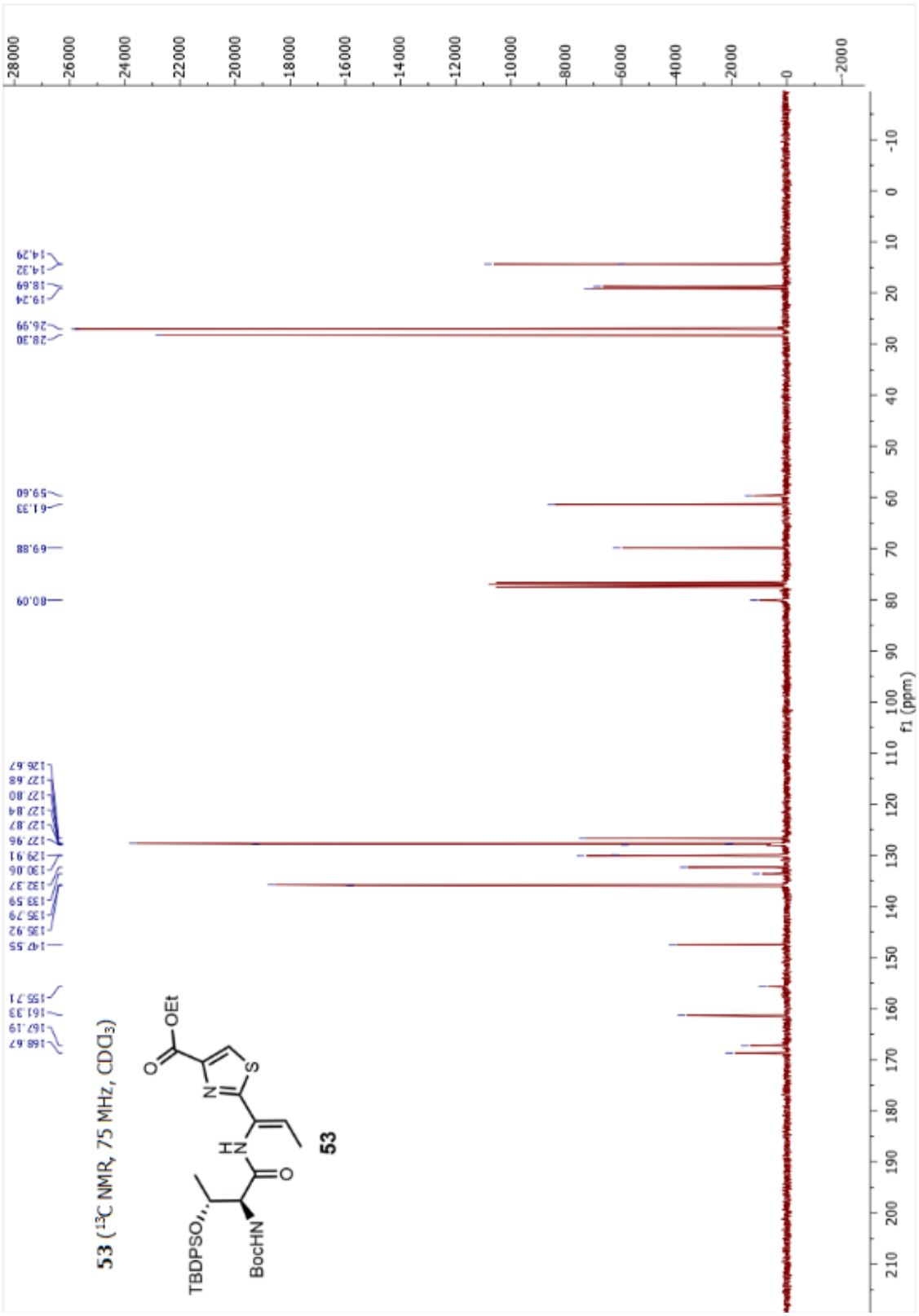


Figure 2.11 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **53**.

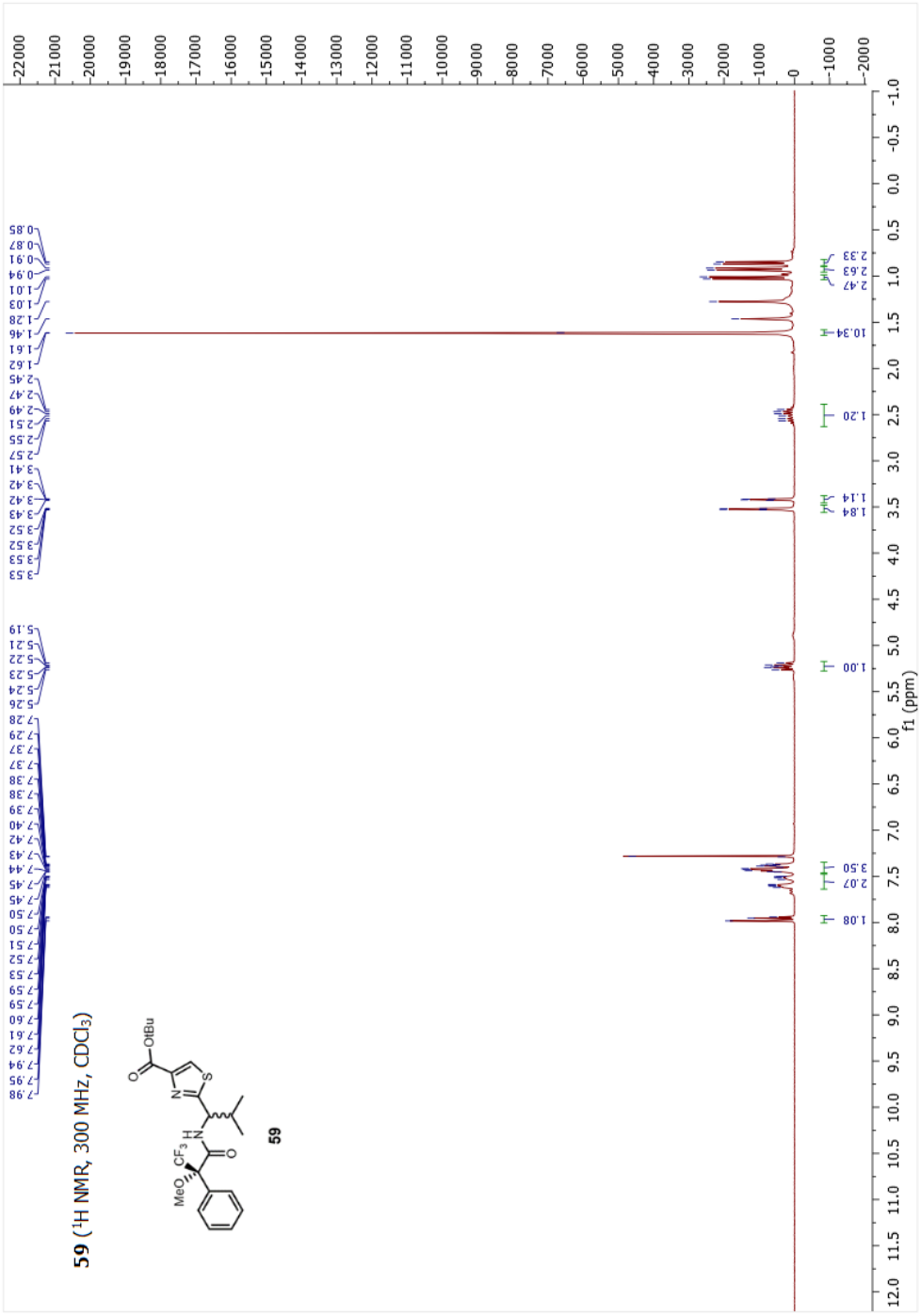


Figure 2.12 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **59**.

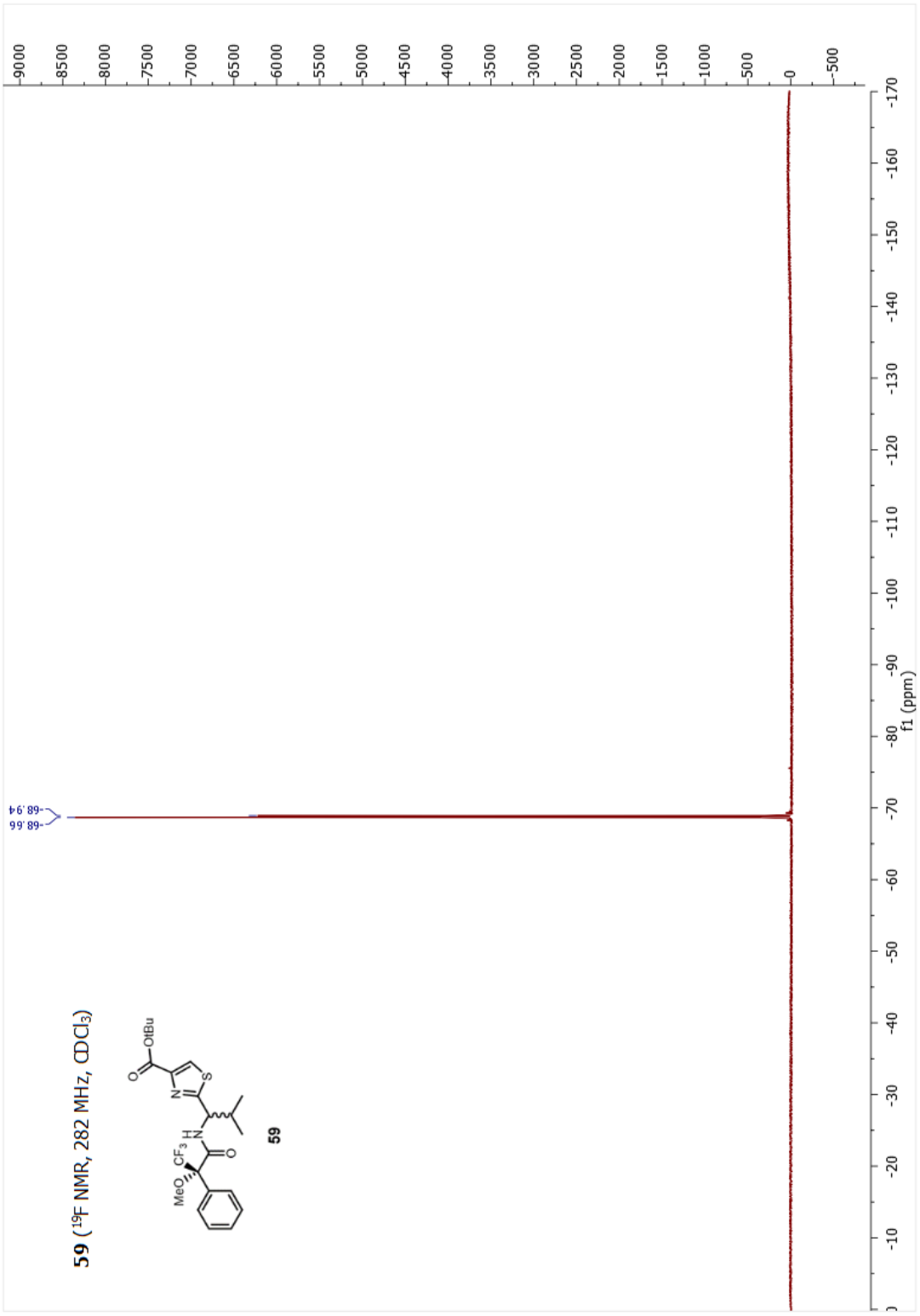


Figure 2.13 ^{19}F NMR (282 MHz, $CDCl_3$) of compound **59**.

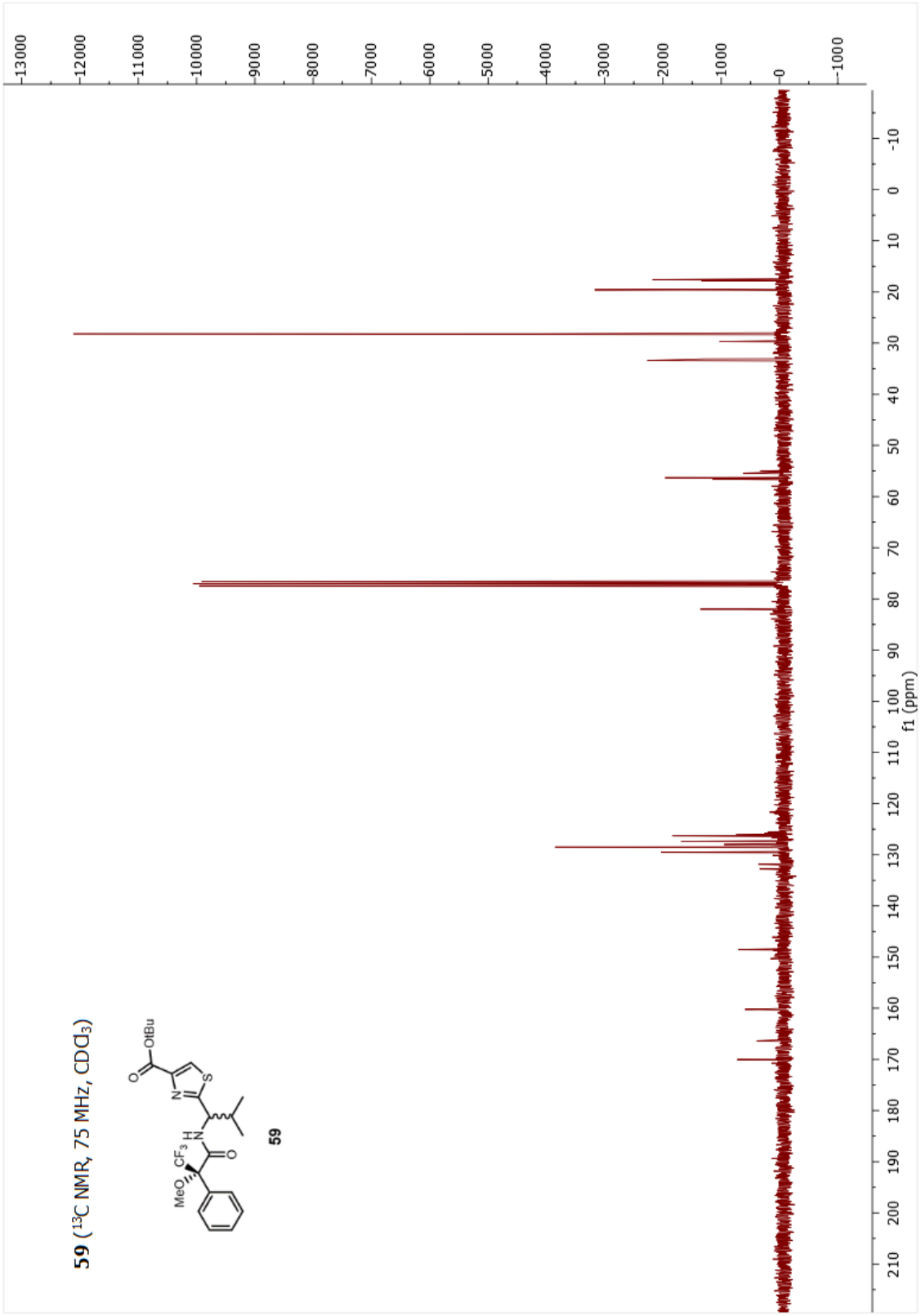


Figure 2.14 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **59**.

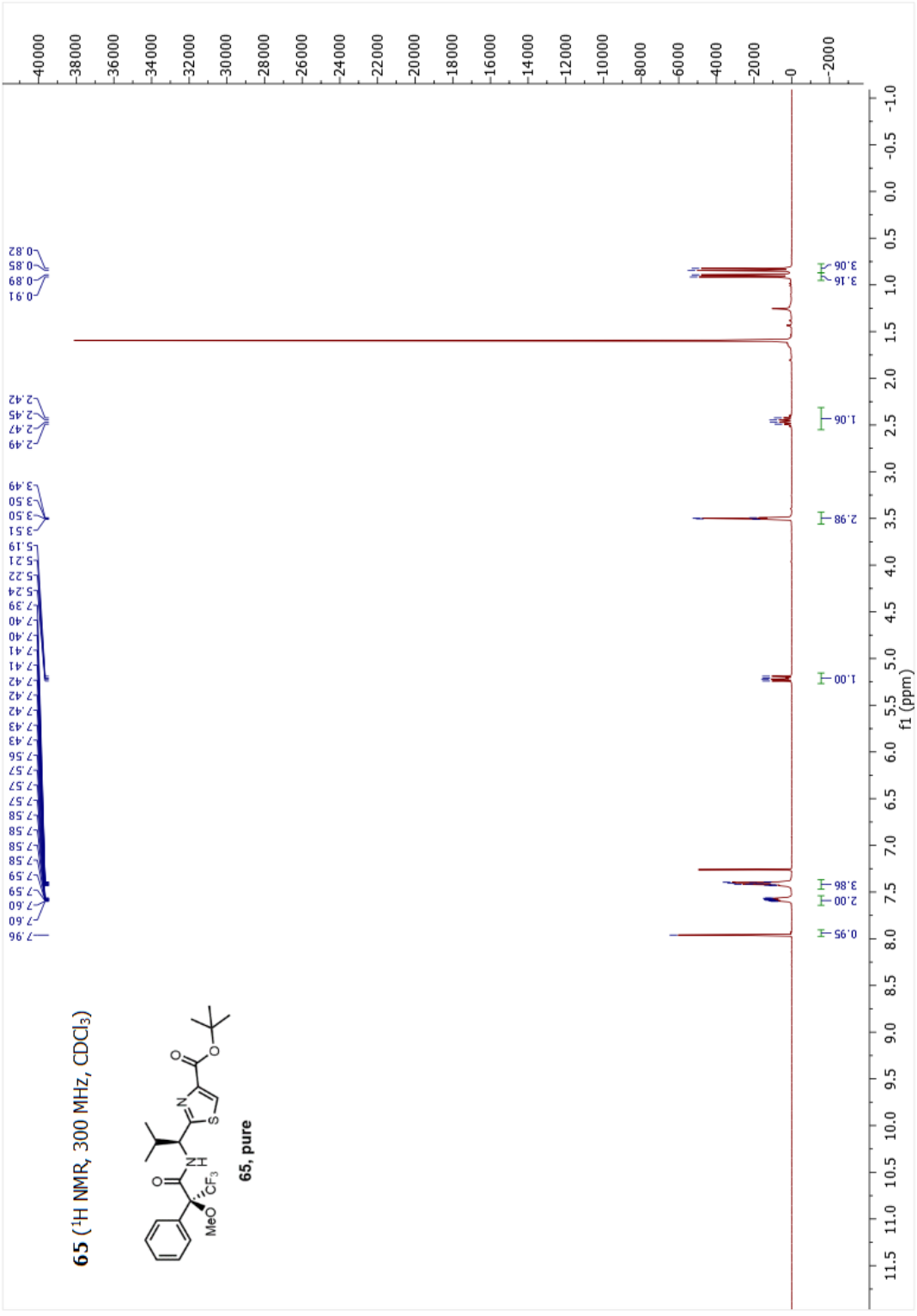


Figure 2.15 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **65**.

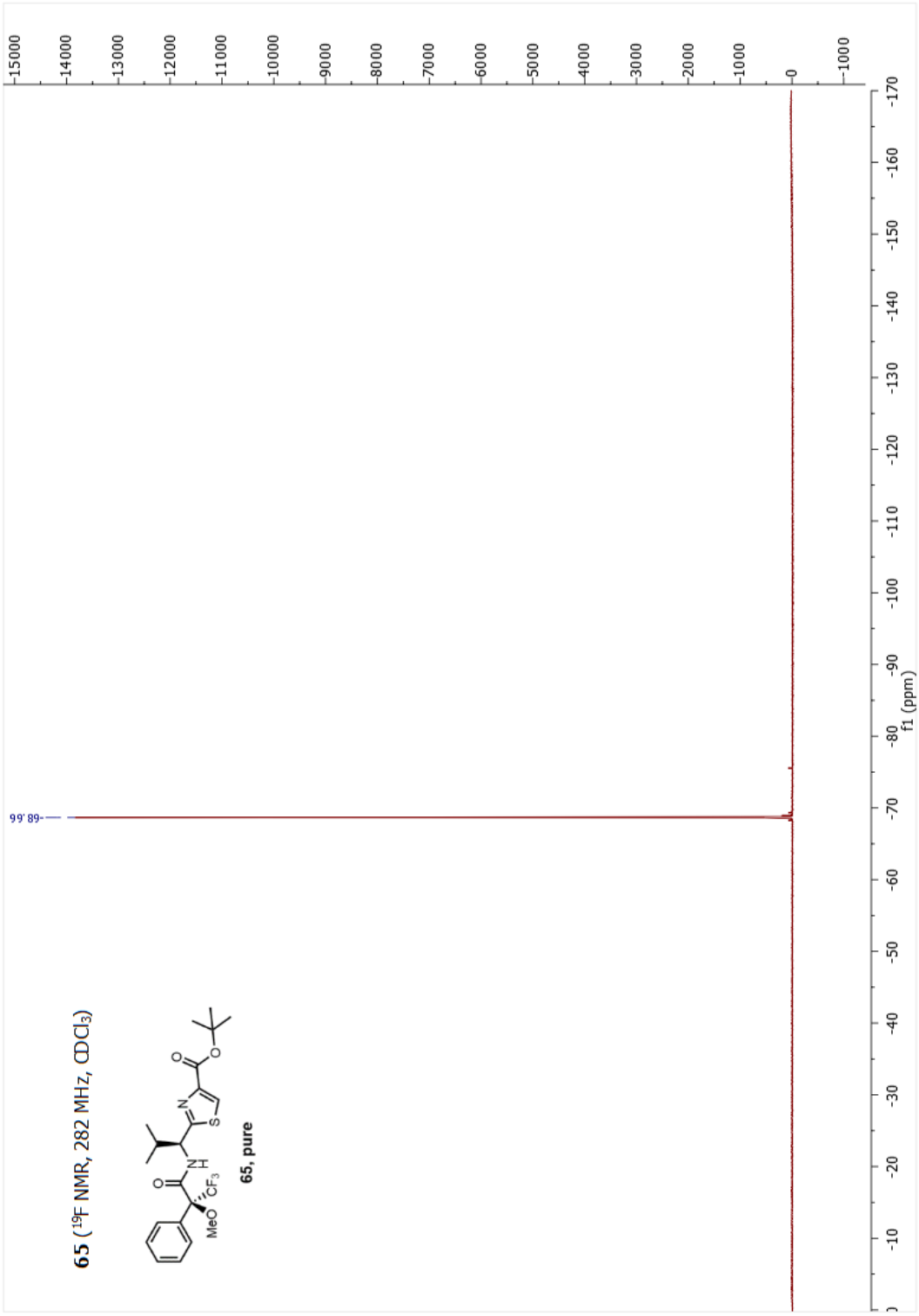


Figure 2.16 ^{19}F NMR (282 MHz, $CDCl_3$) of compound **65**.

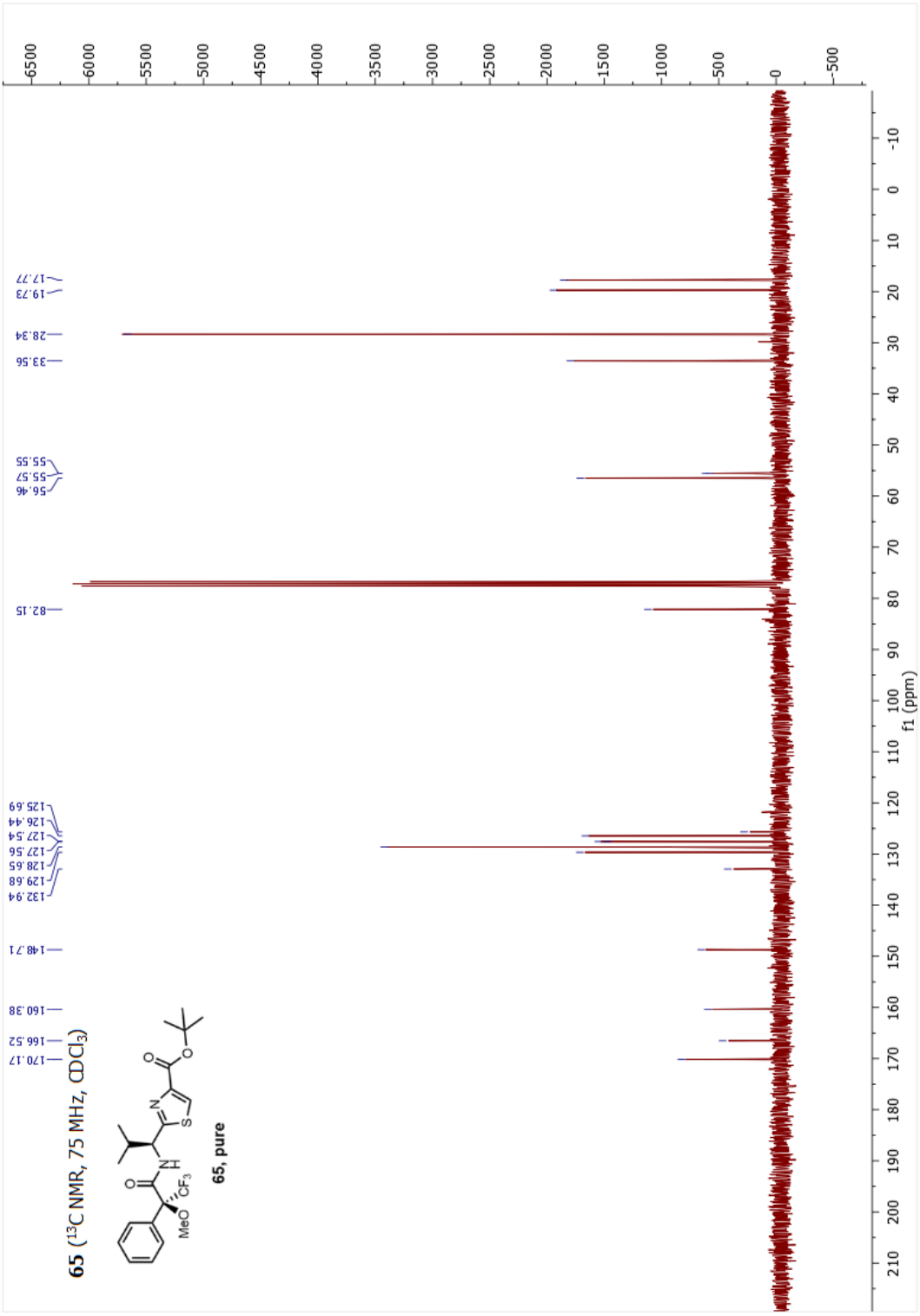


Figure 2.17 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **65**.

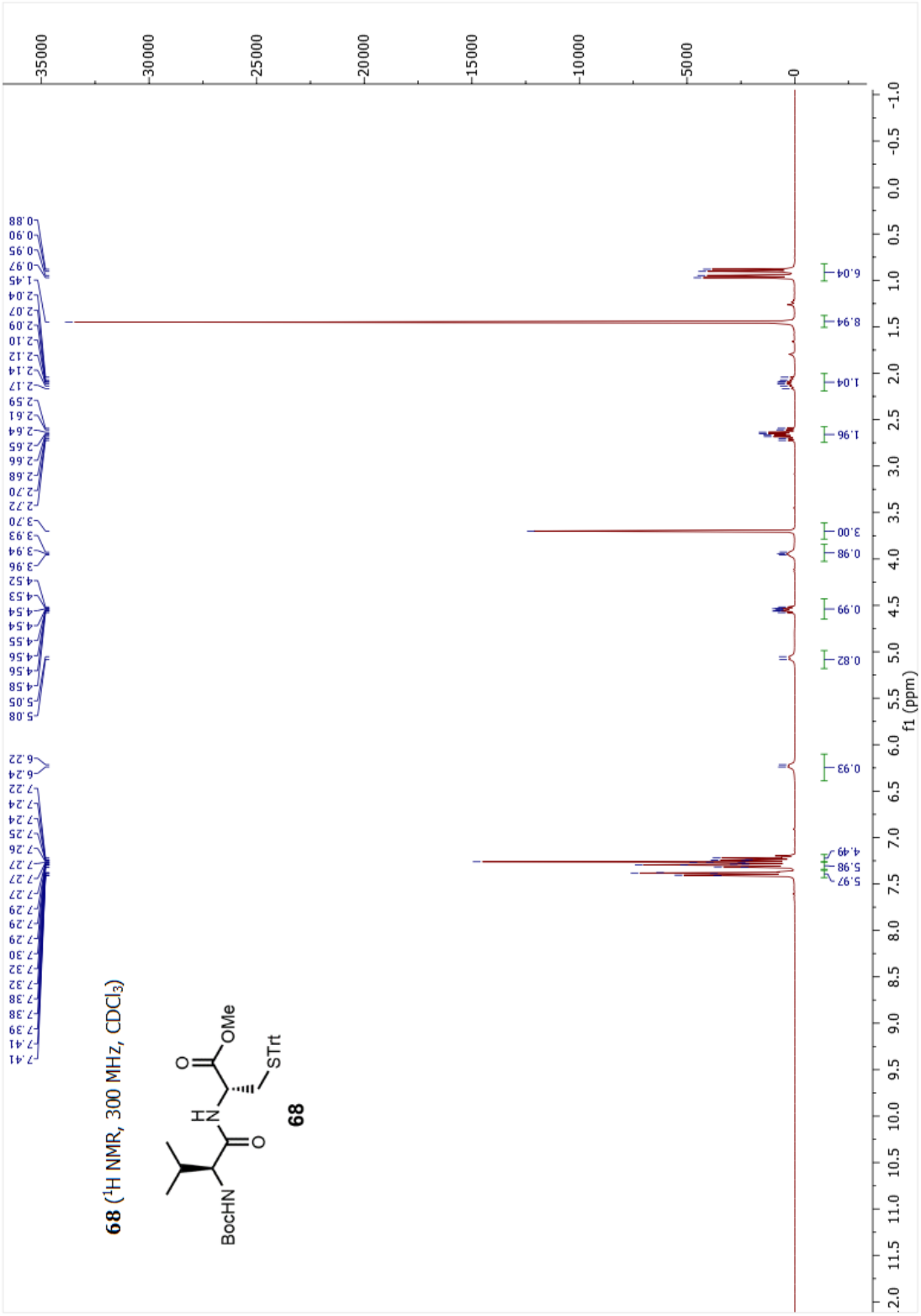


Figure 2.18 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **68**.

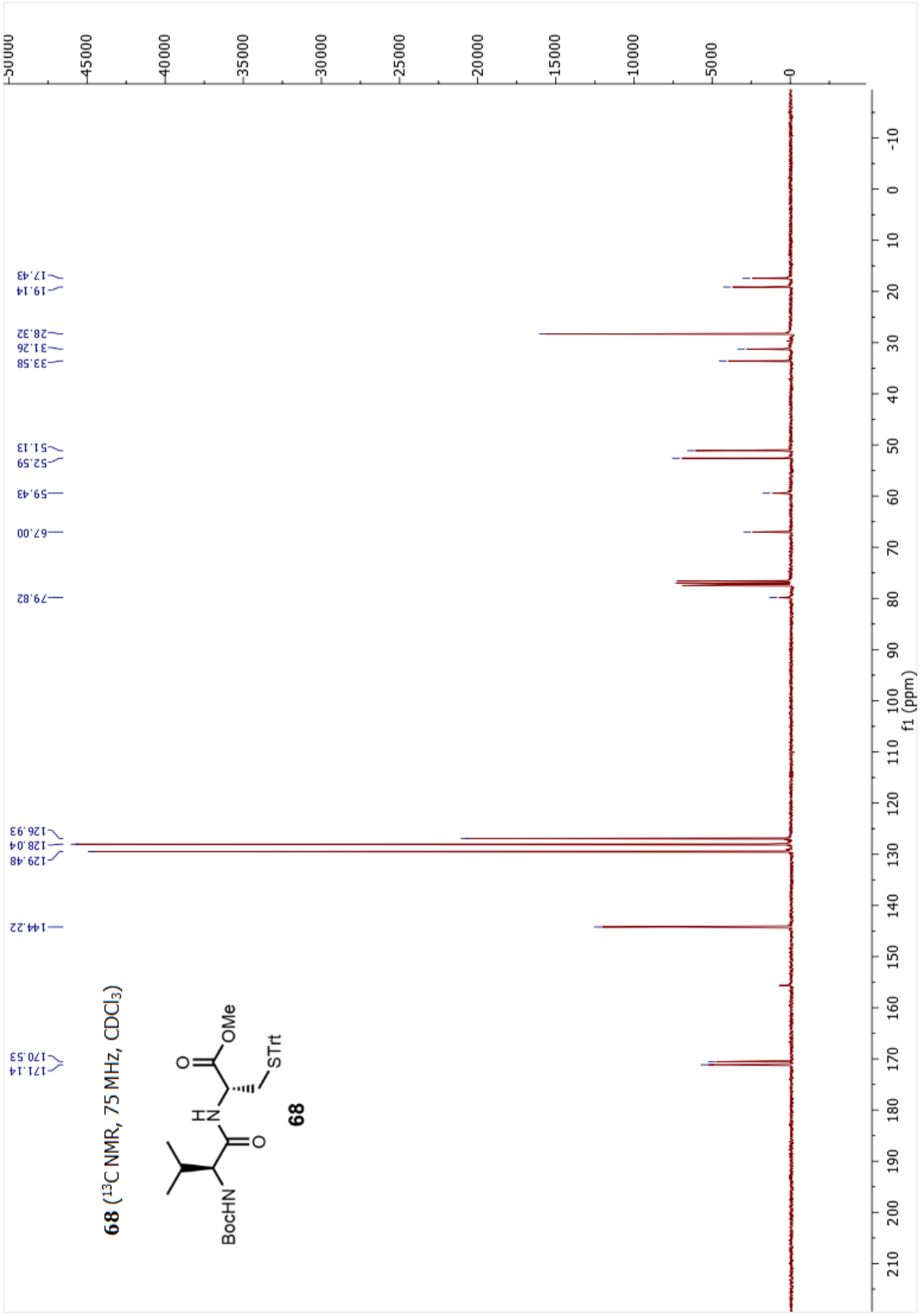


Figure 2.19 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **68**.

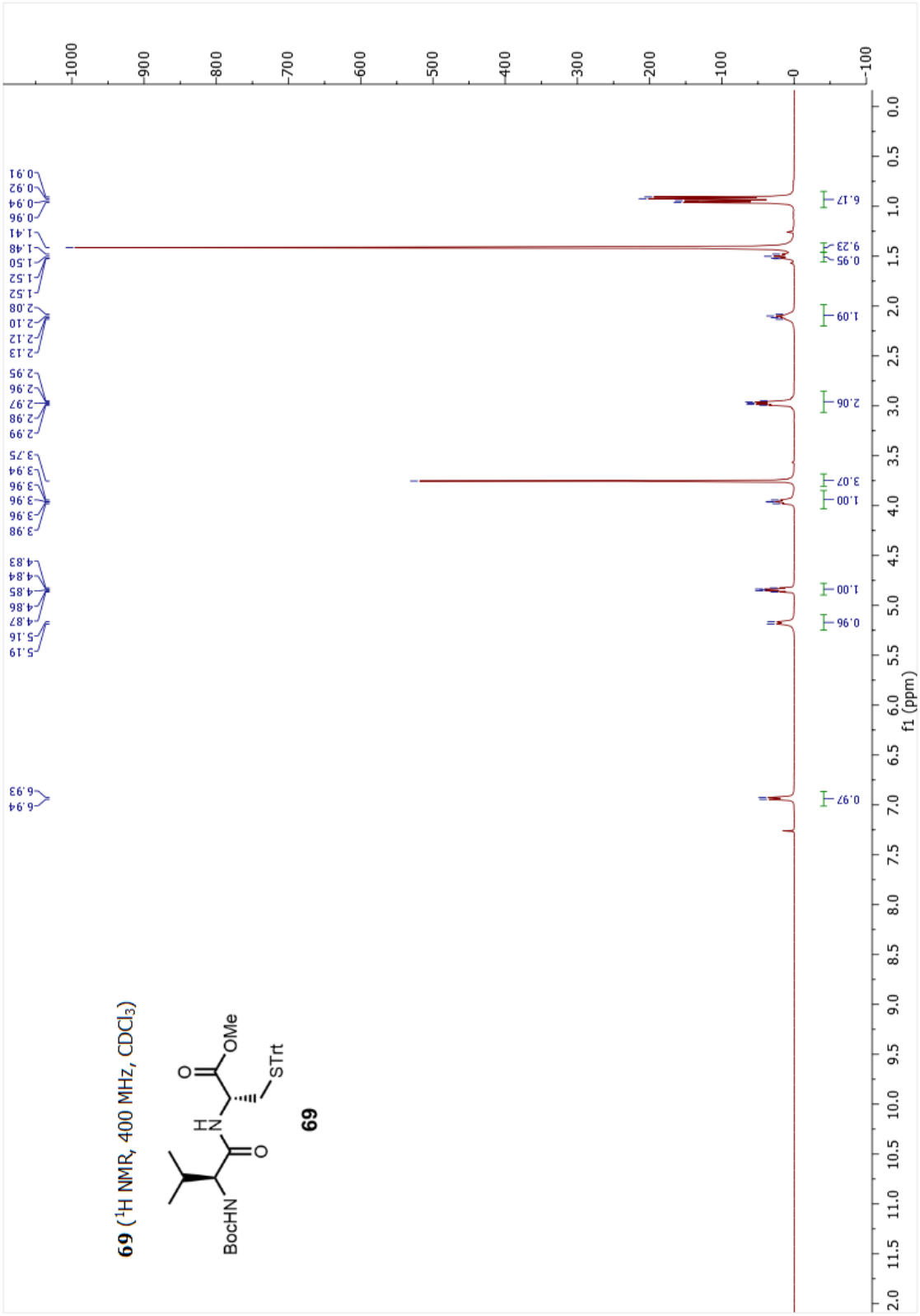


Figure 2.20 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **69**.

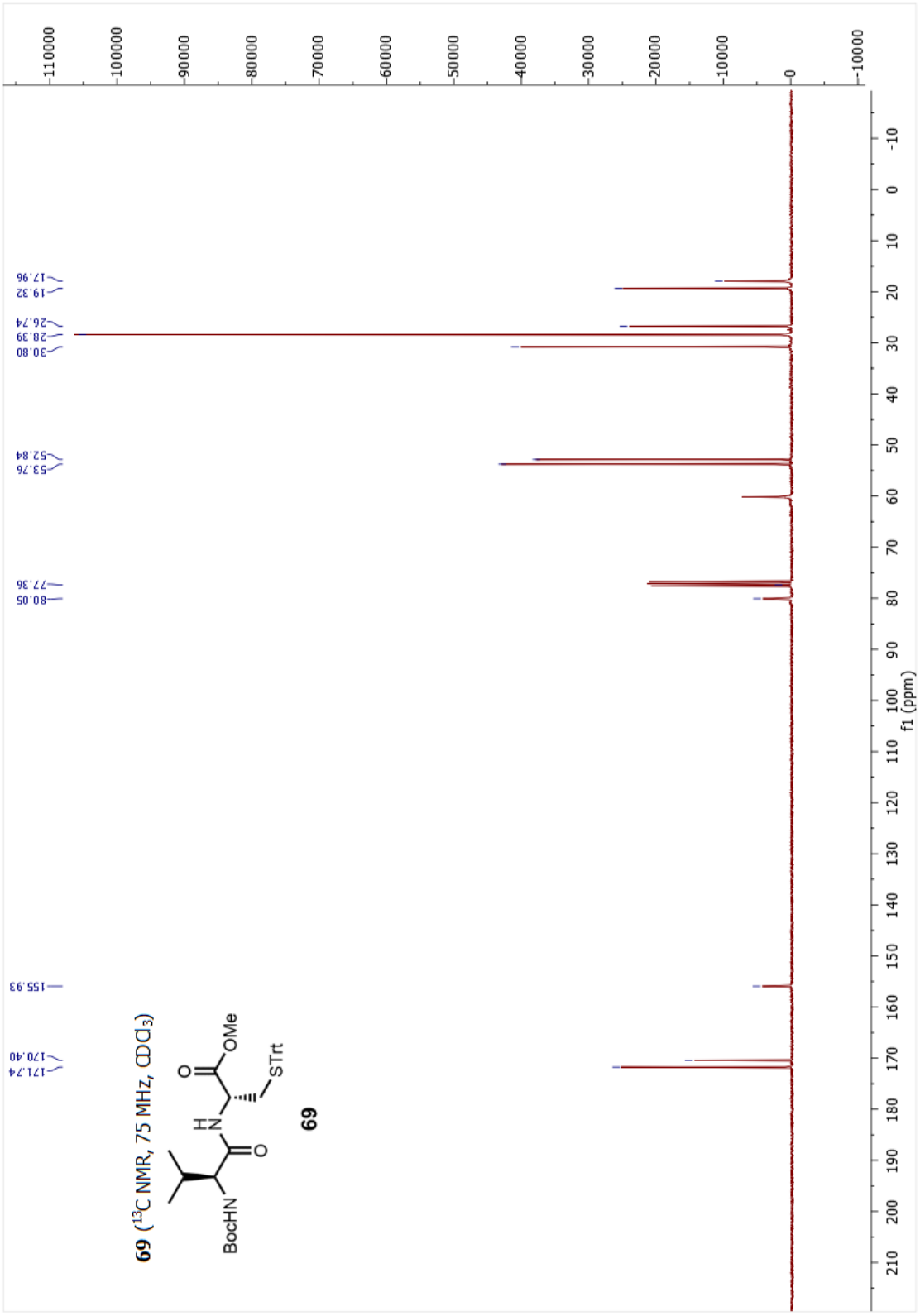


Figure 2.21 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **69**.

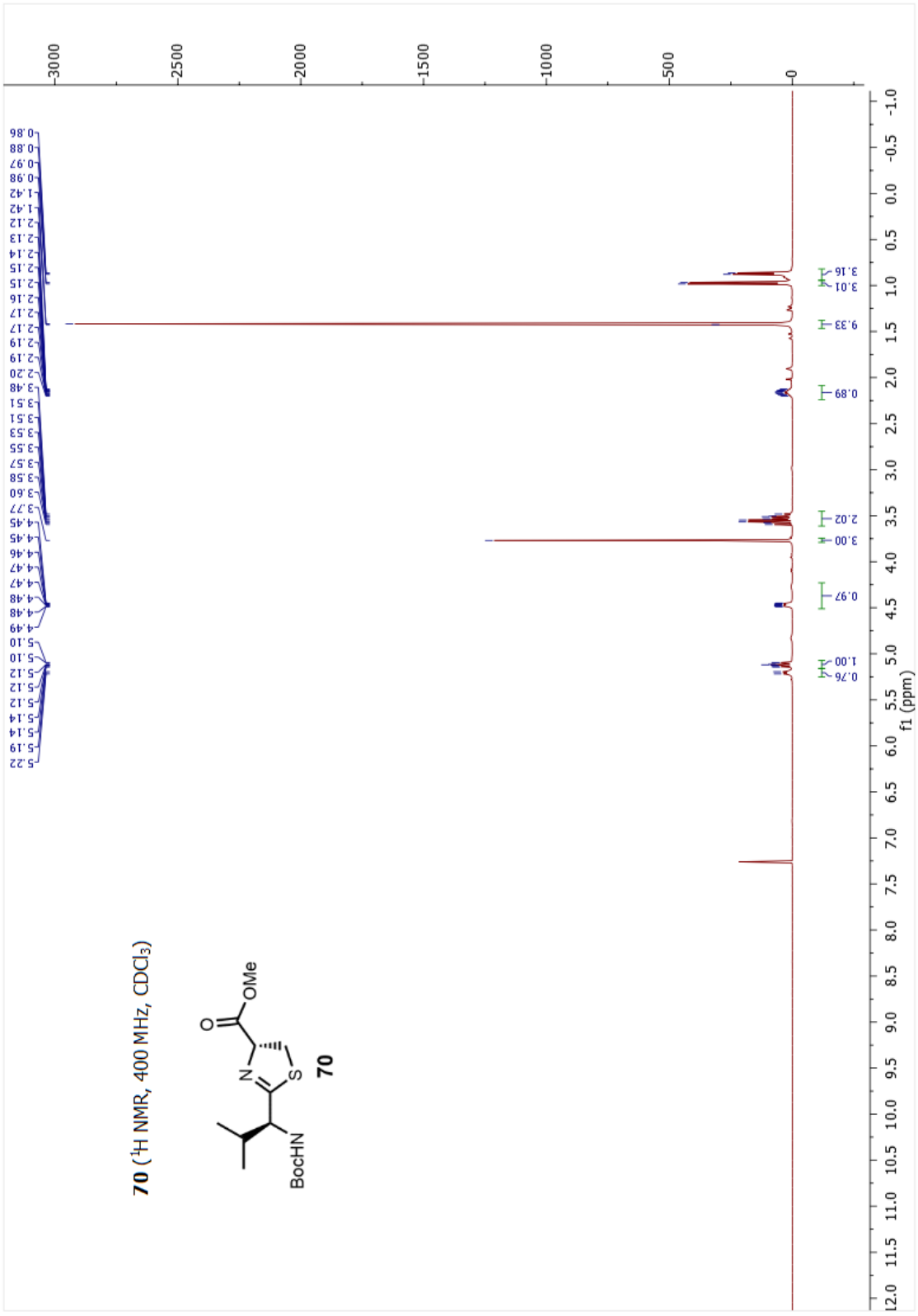


Figure 2.22 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **70**.

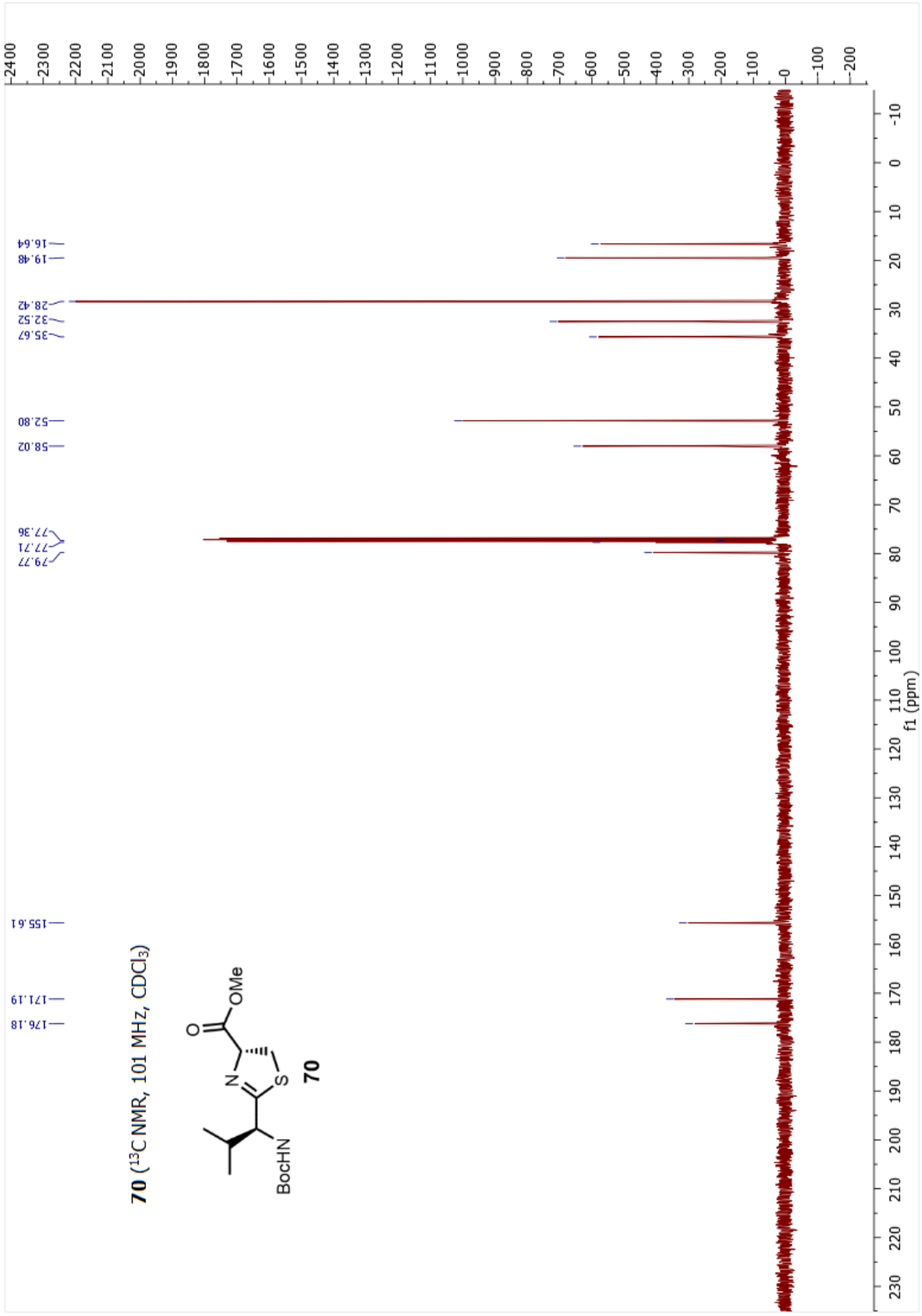


Figure 2.23 ^{13}C NMR (101 MHz, $CDCl_3$) of compound **70**.

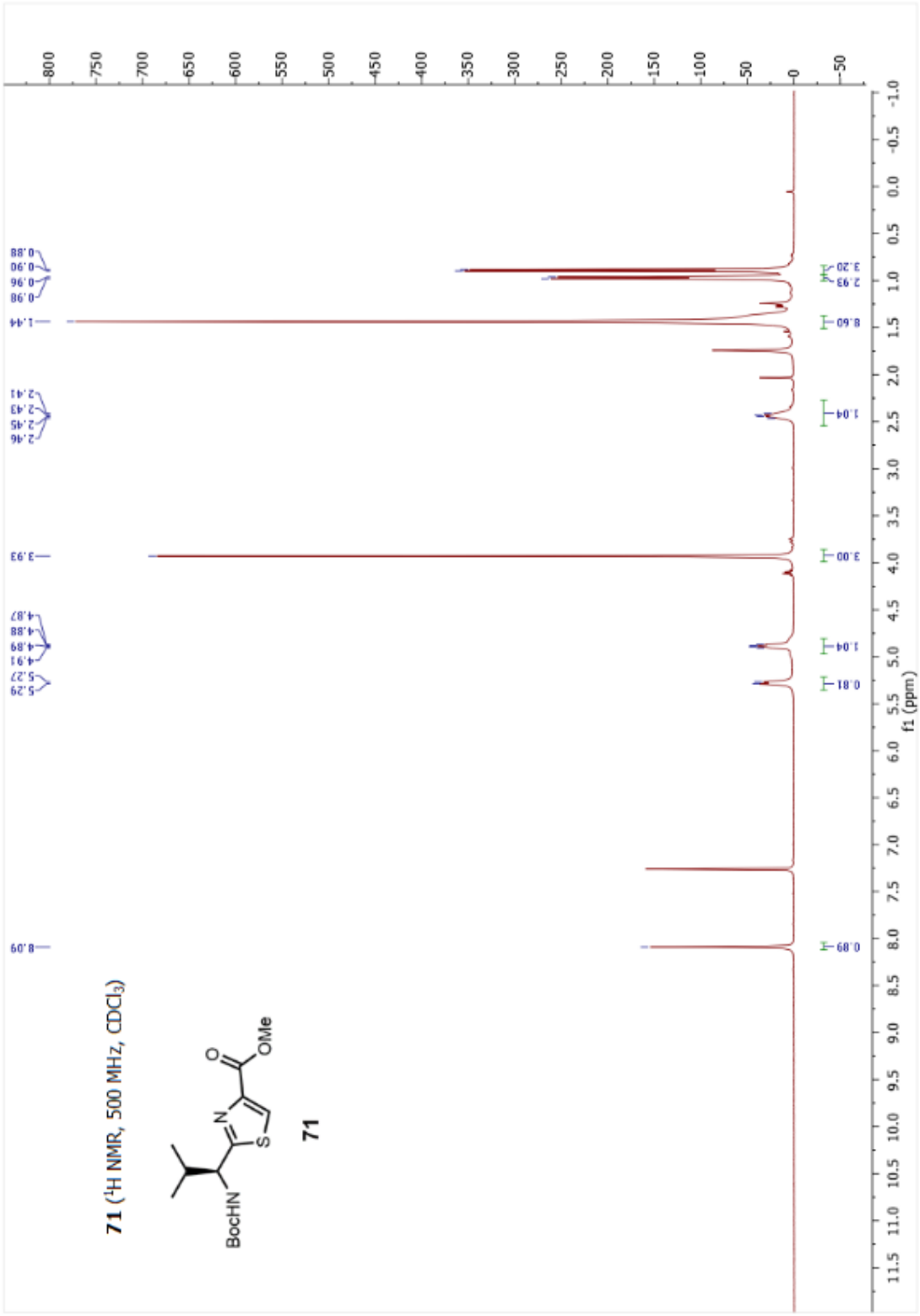


Figure 2.24 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **71**.

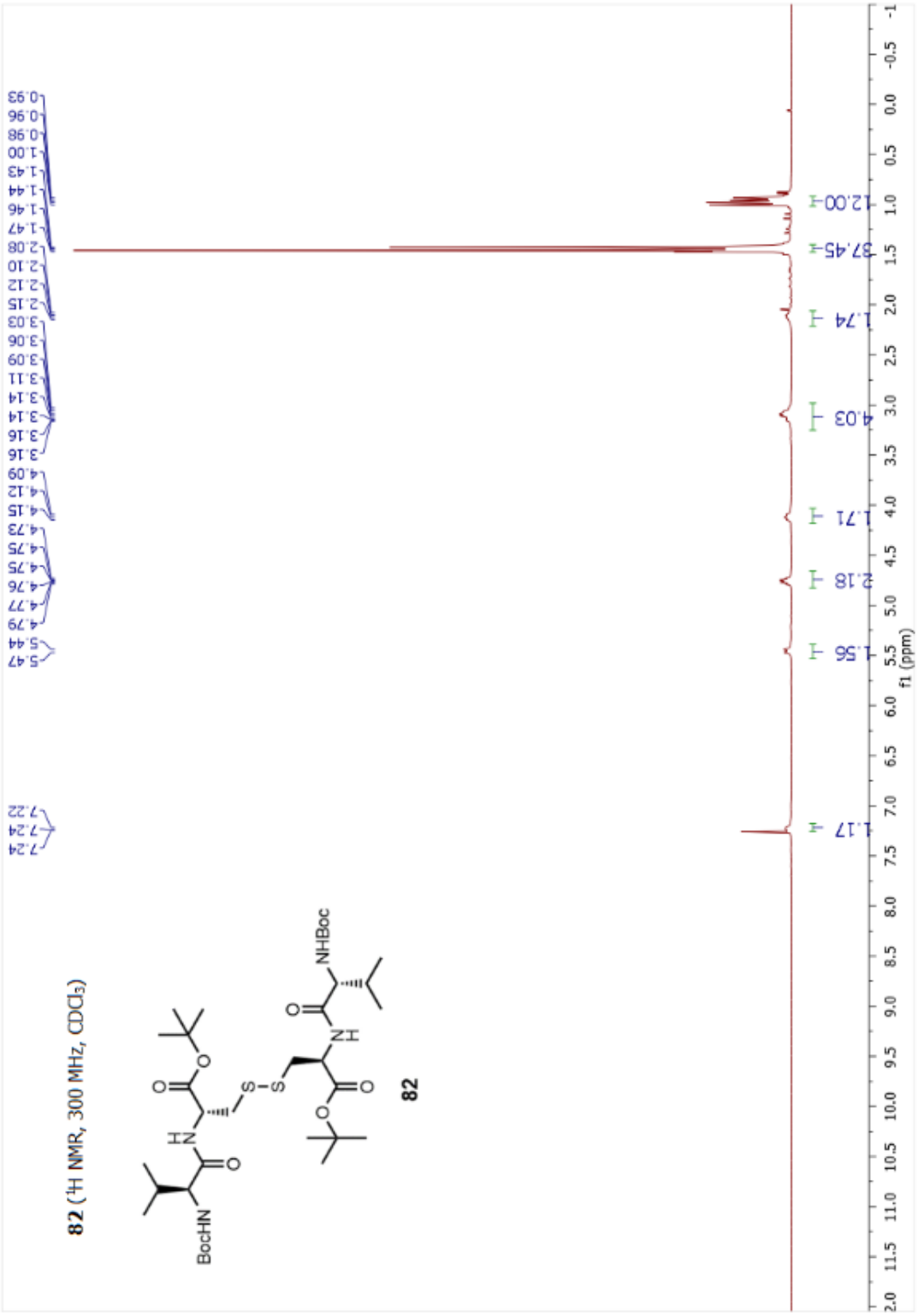


Figure 2.25 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **82**.

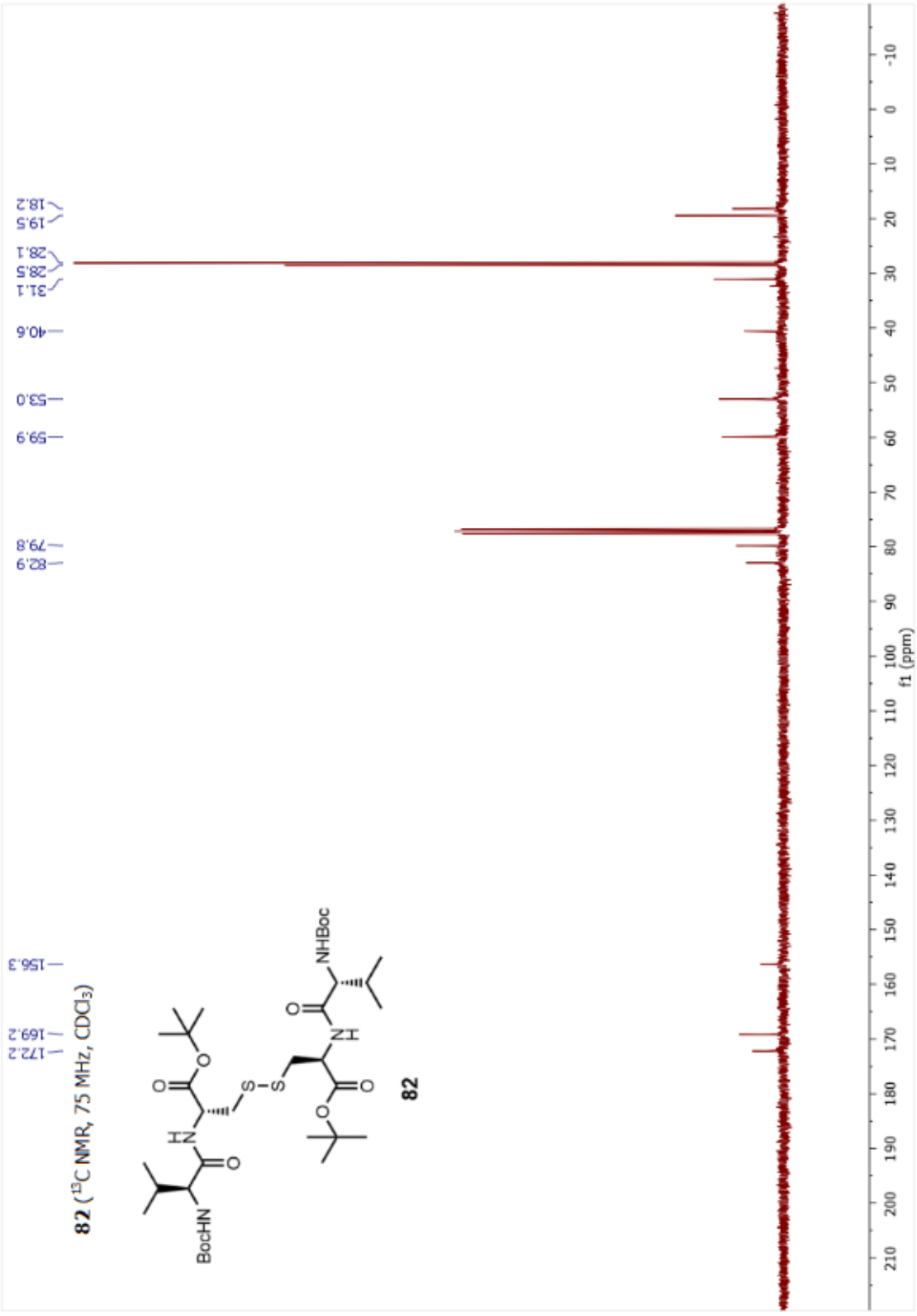


Figure 2.26 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **82**.

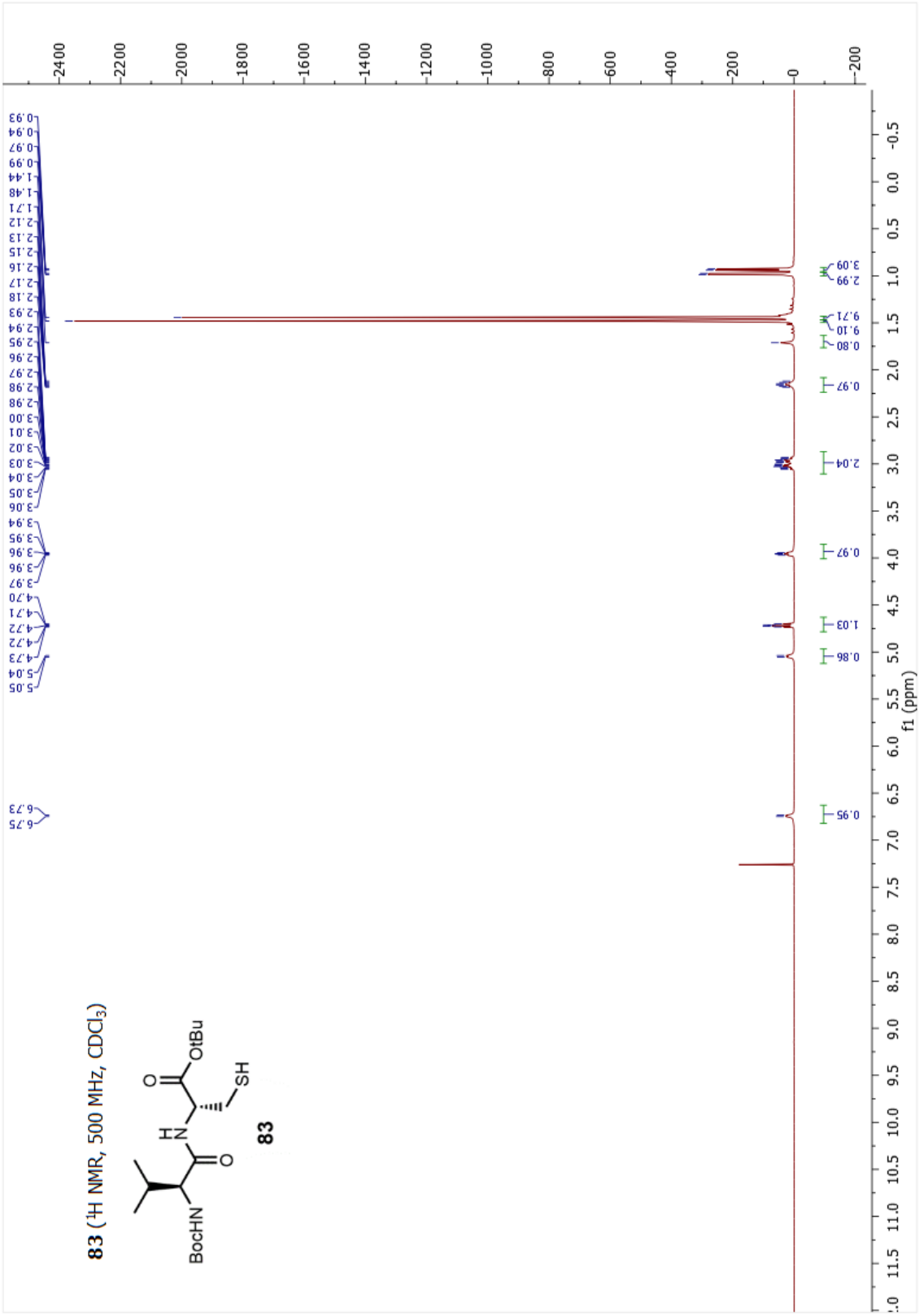


Figure 2.27 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **83**.

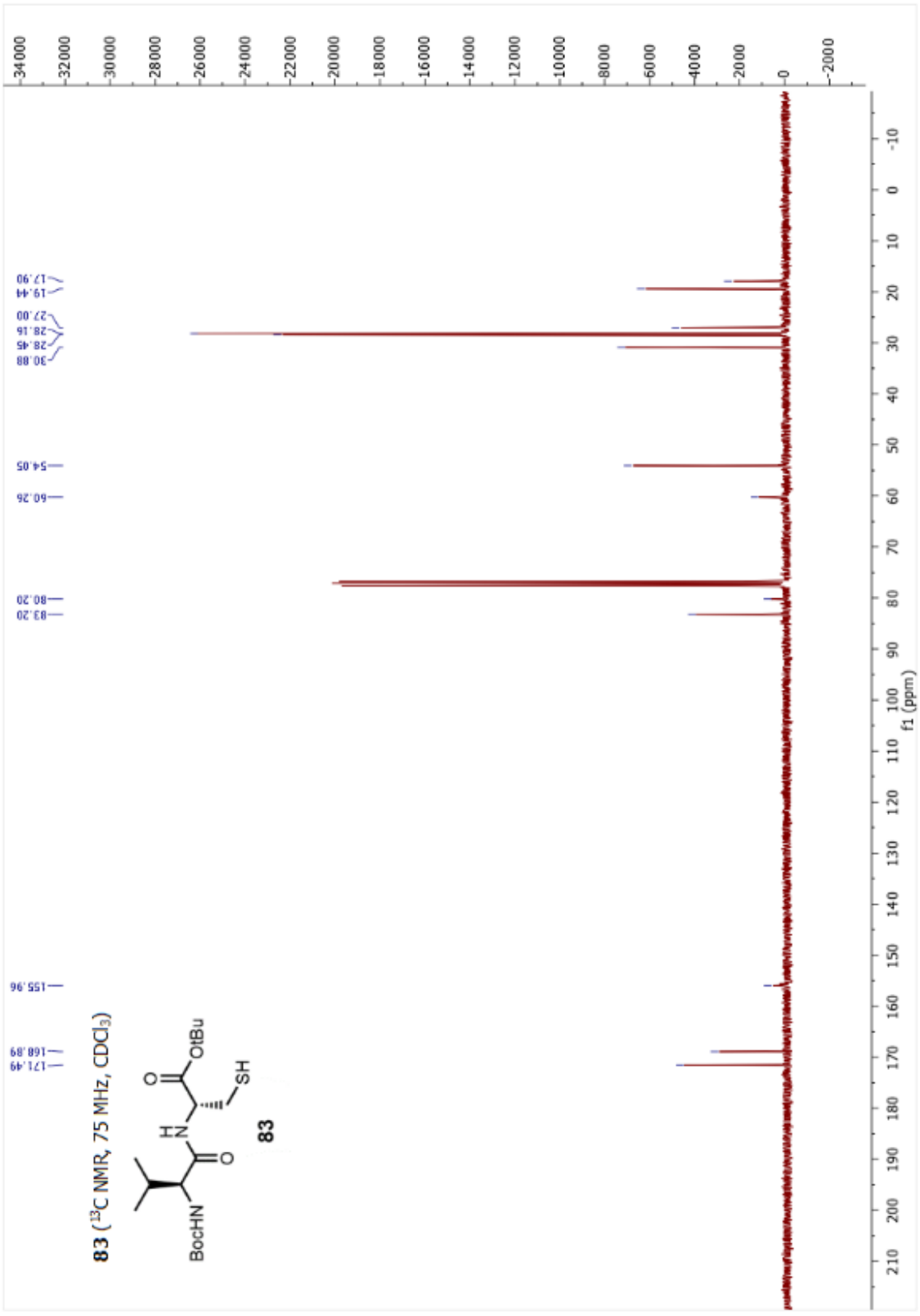


Figure 2.28 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **83**.

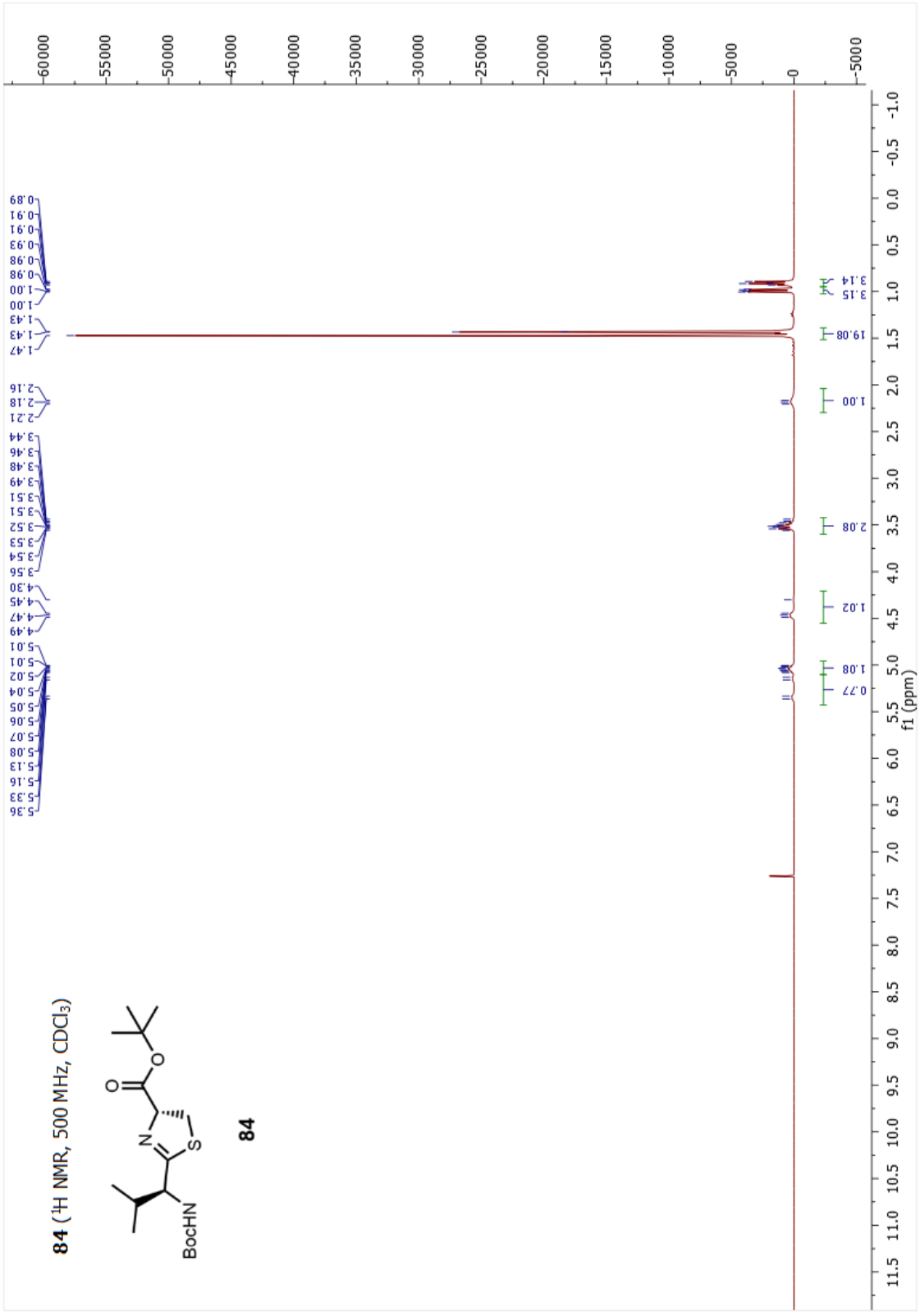


Figure 2.29 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **84**.

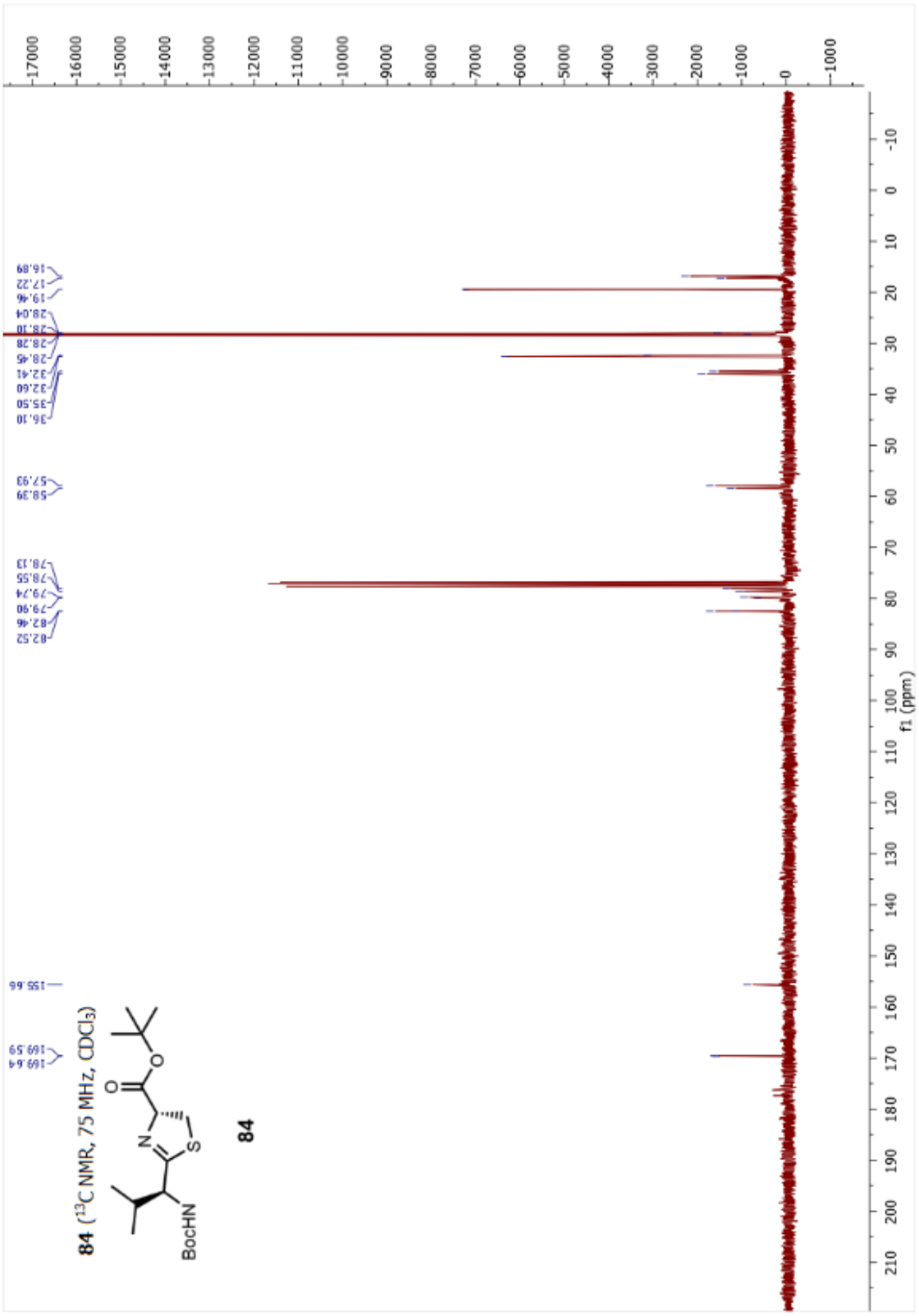


Figure 2.30 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **84**.

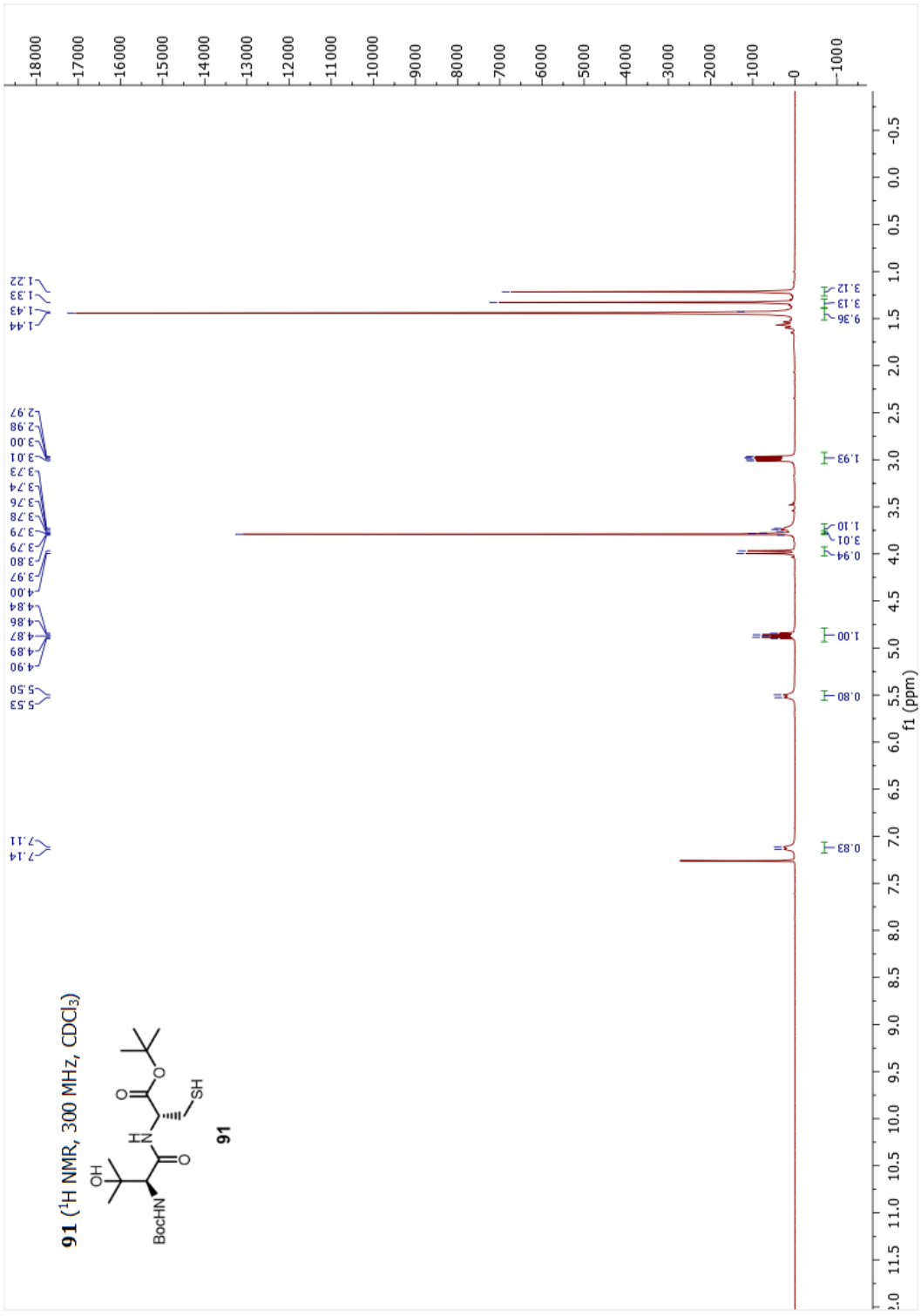


Figure 2.31 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **91**.

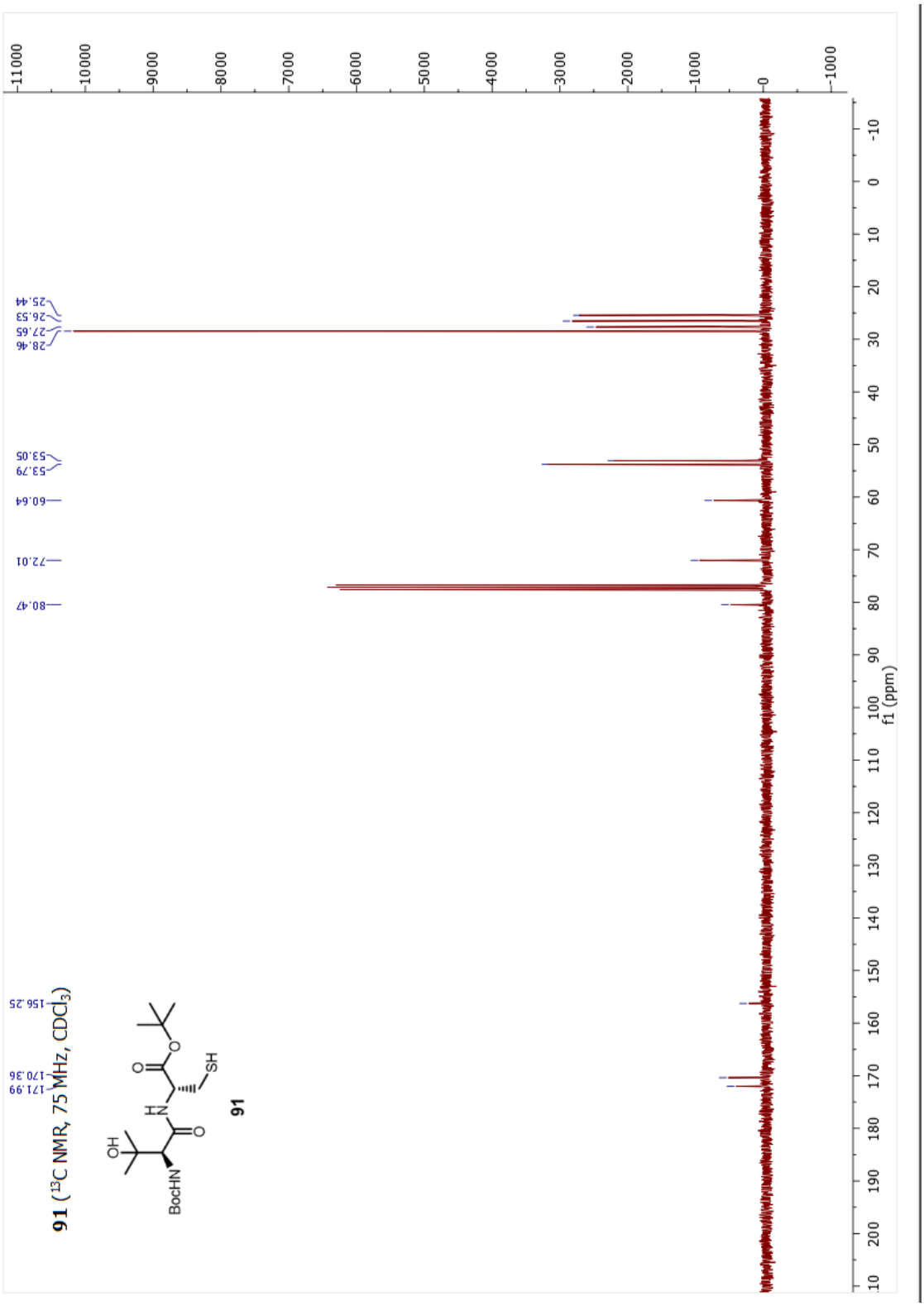


Figure 2.32 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **91**.

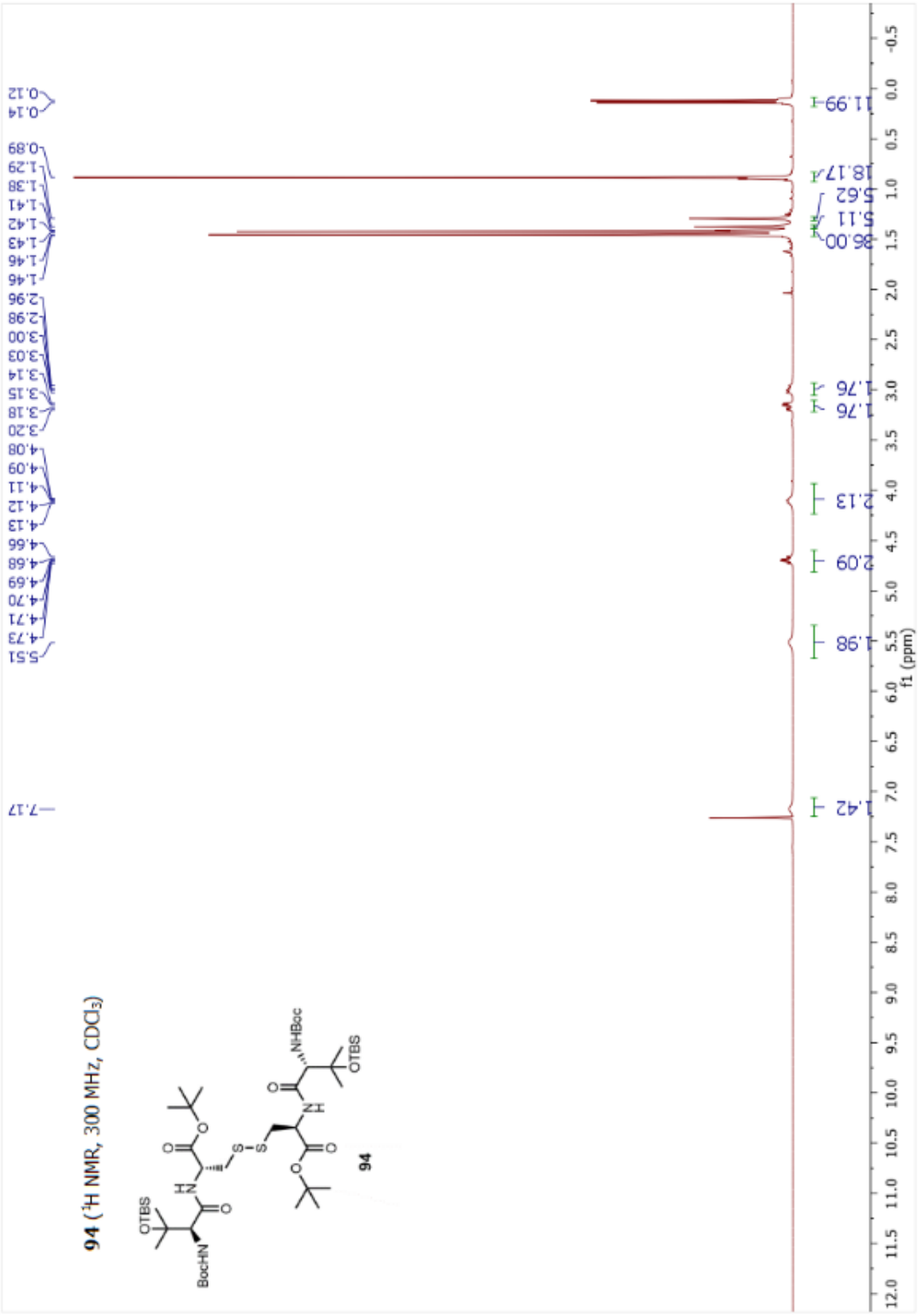


Figure 2.33 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **94**.

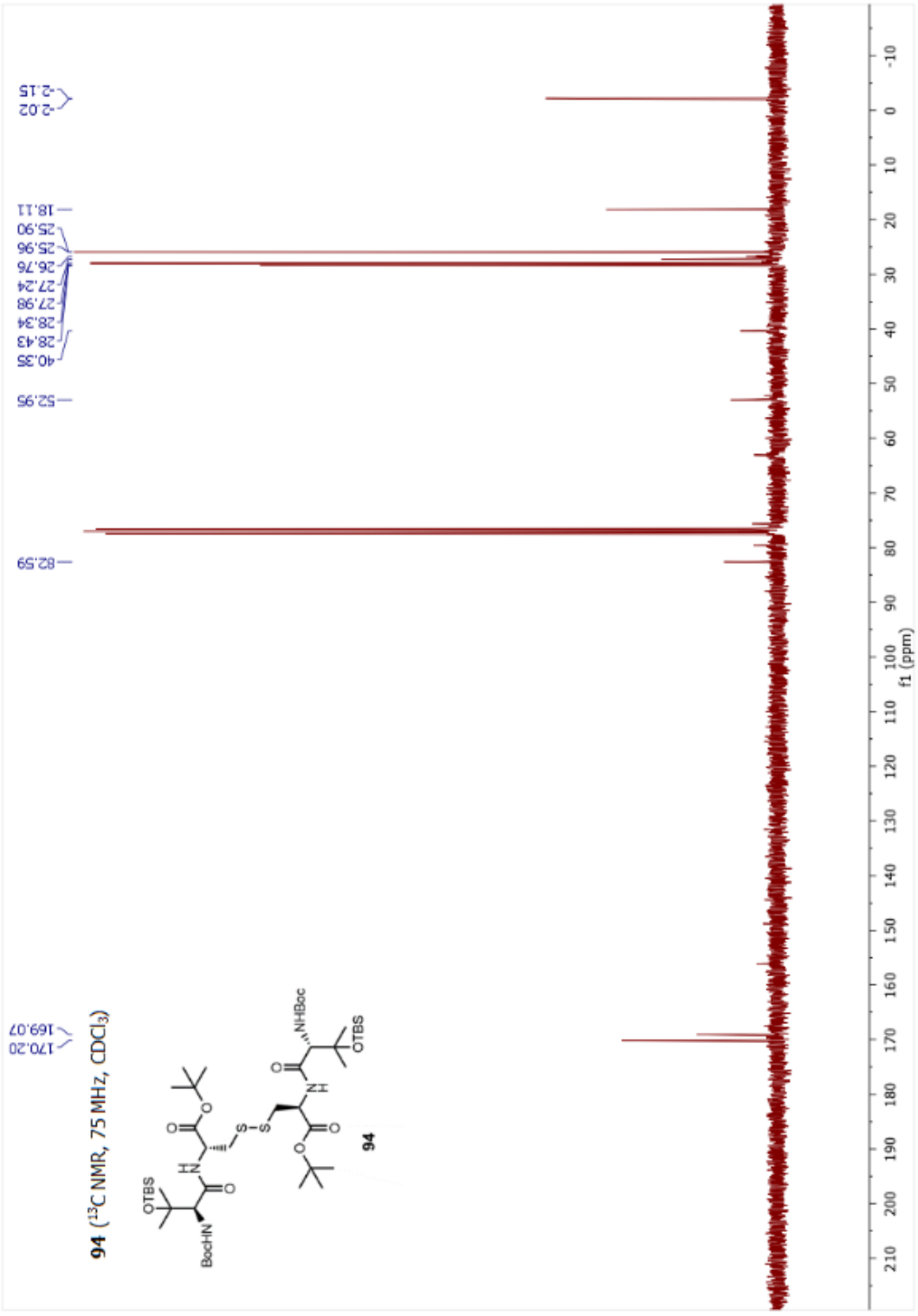


Figure 2.34 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **94**.

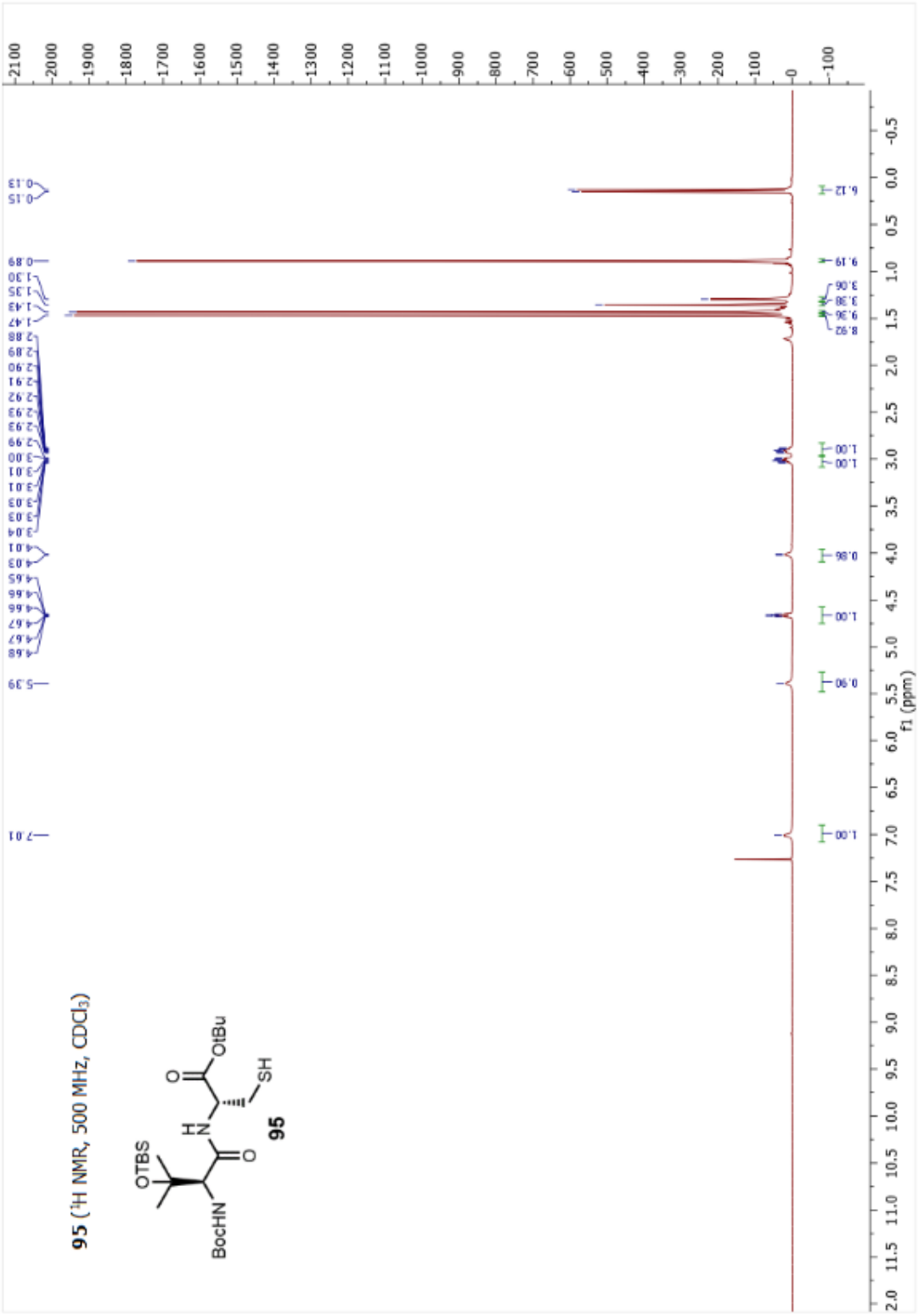


Figure 2.35 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **95**.

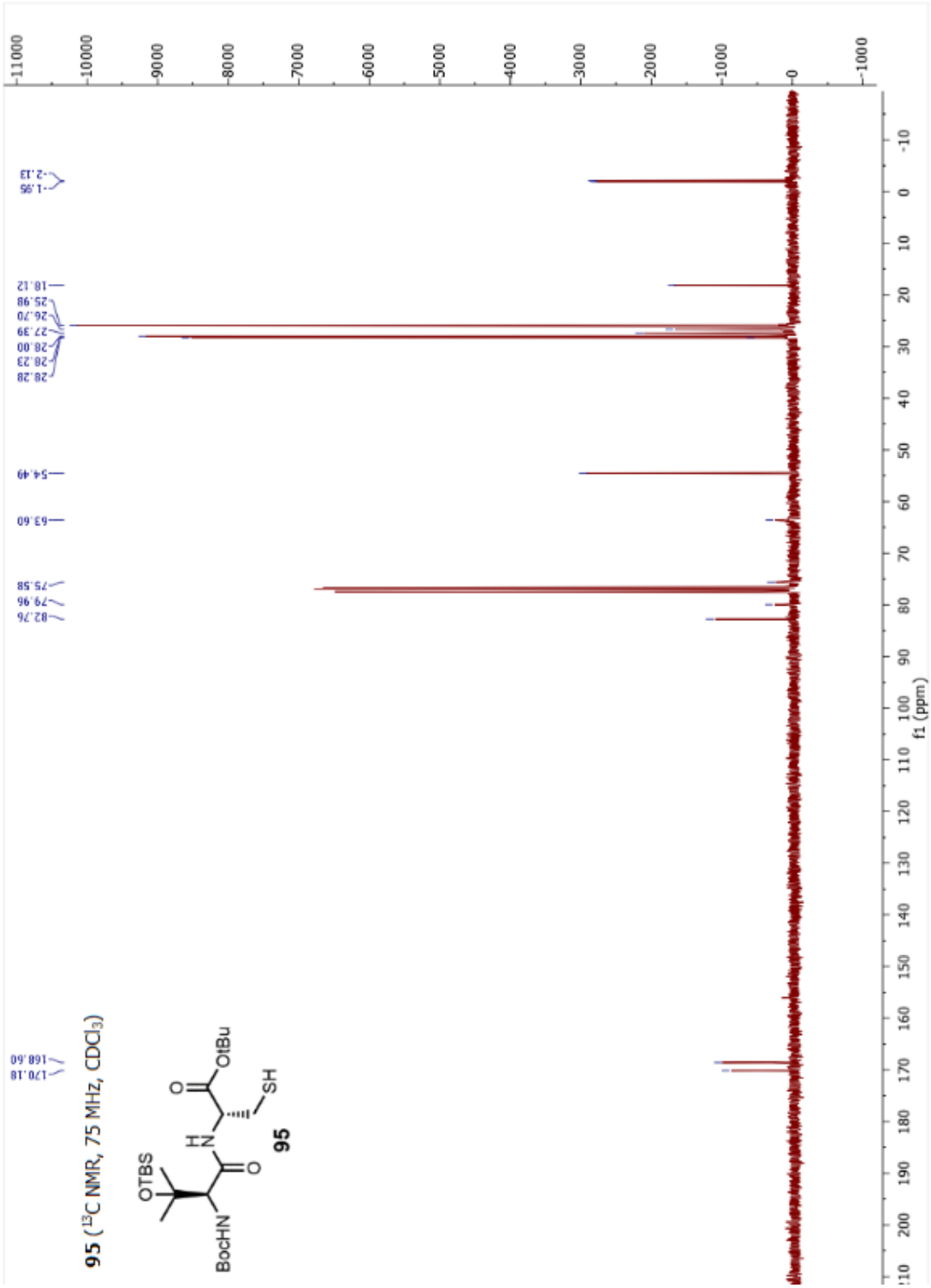


Figure 2.36 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **95**.

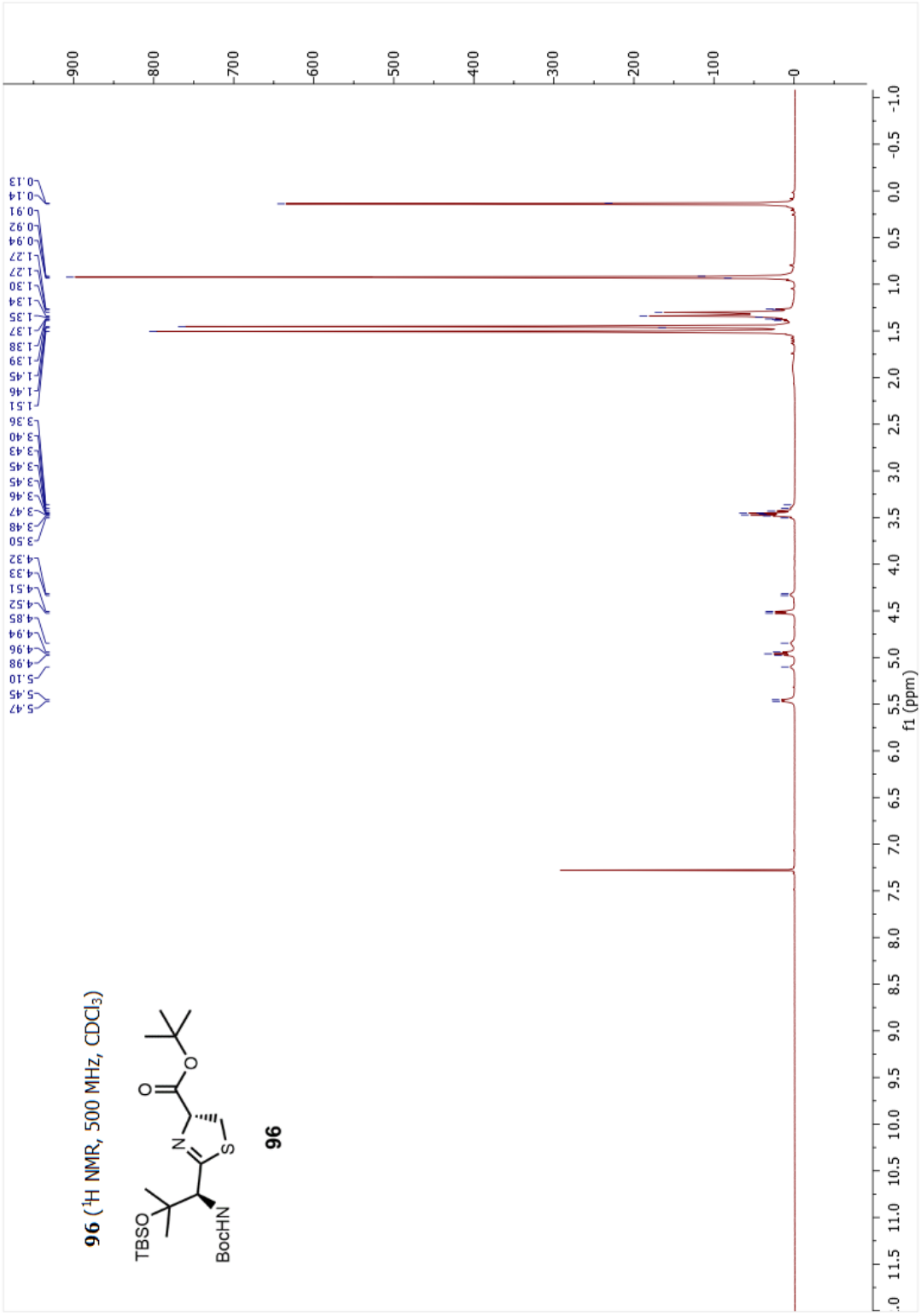


Figure 2.37 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **96**.

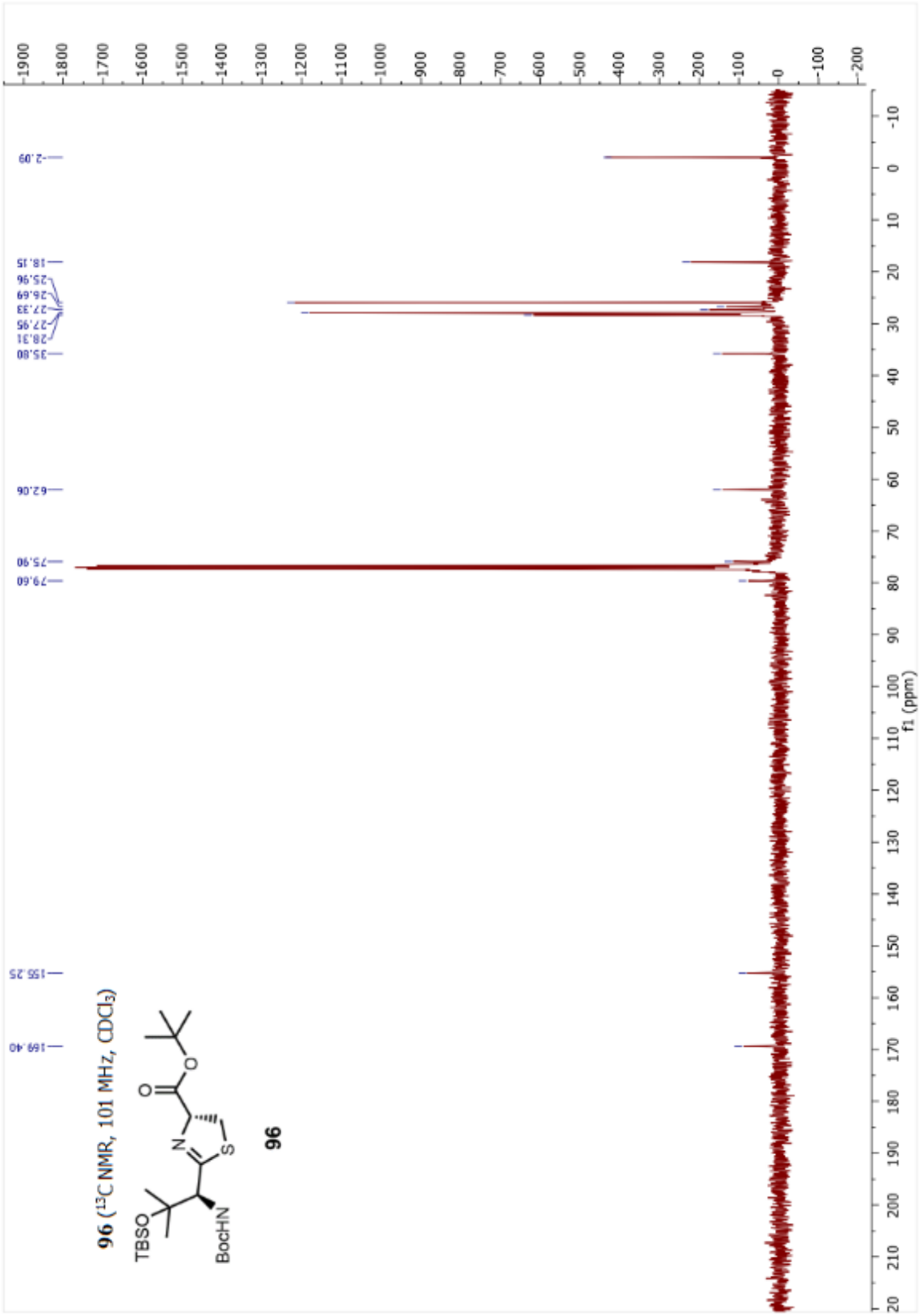


Figure 2.38 ^{13}C NMR (101 MHz, $CDCl_3$) of compound **96**.

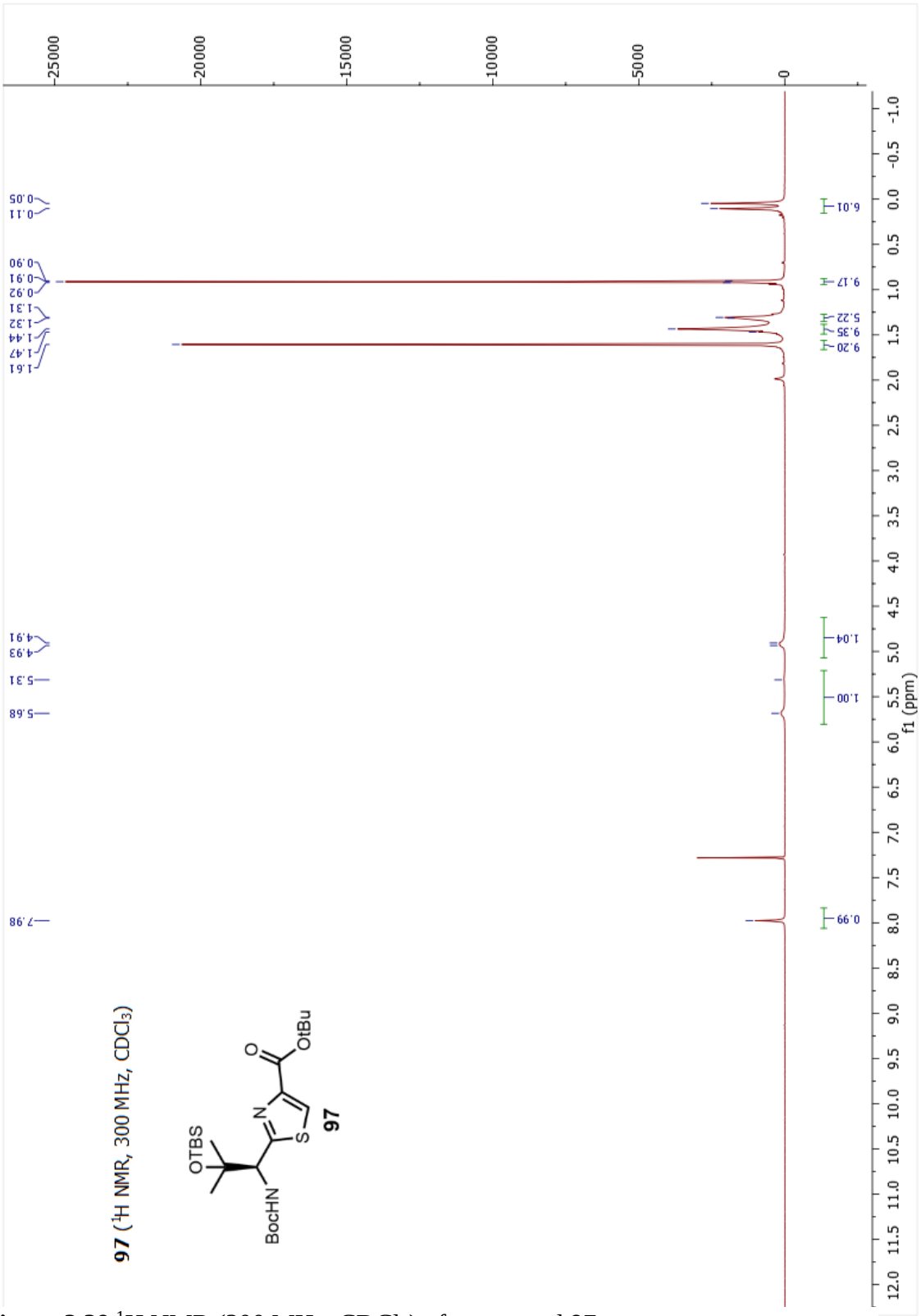


Figure 2.39 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **97**.

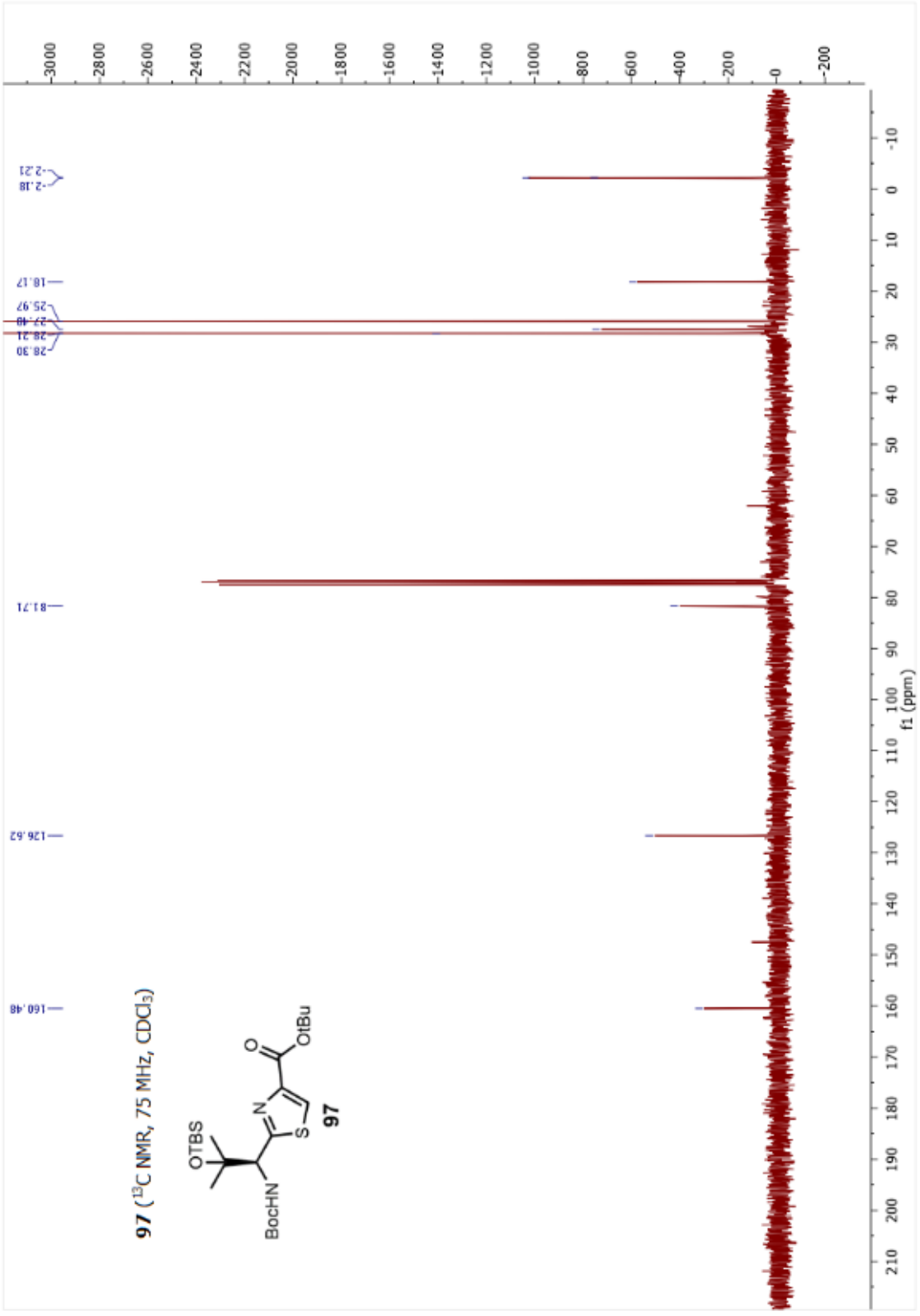


Figure 2.40 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **97**.

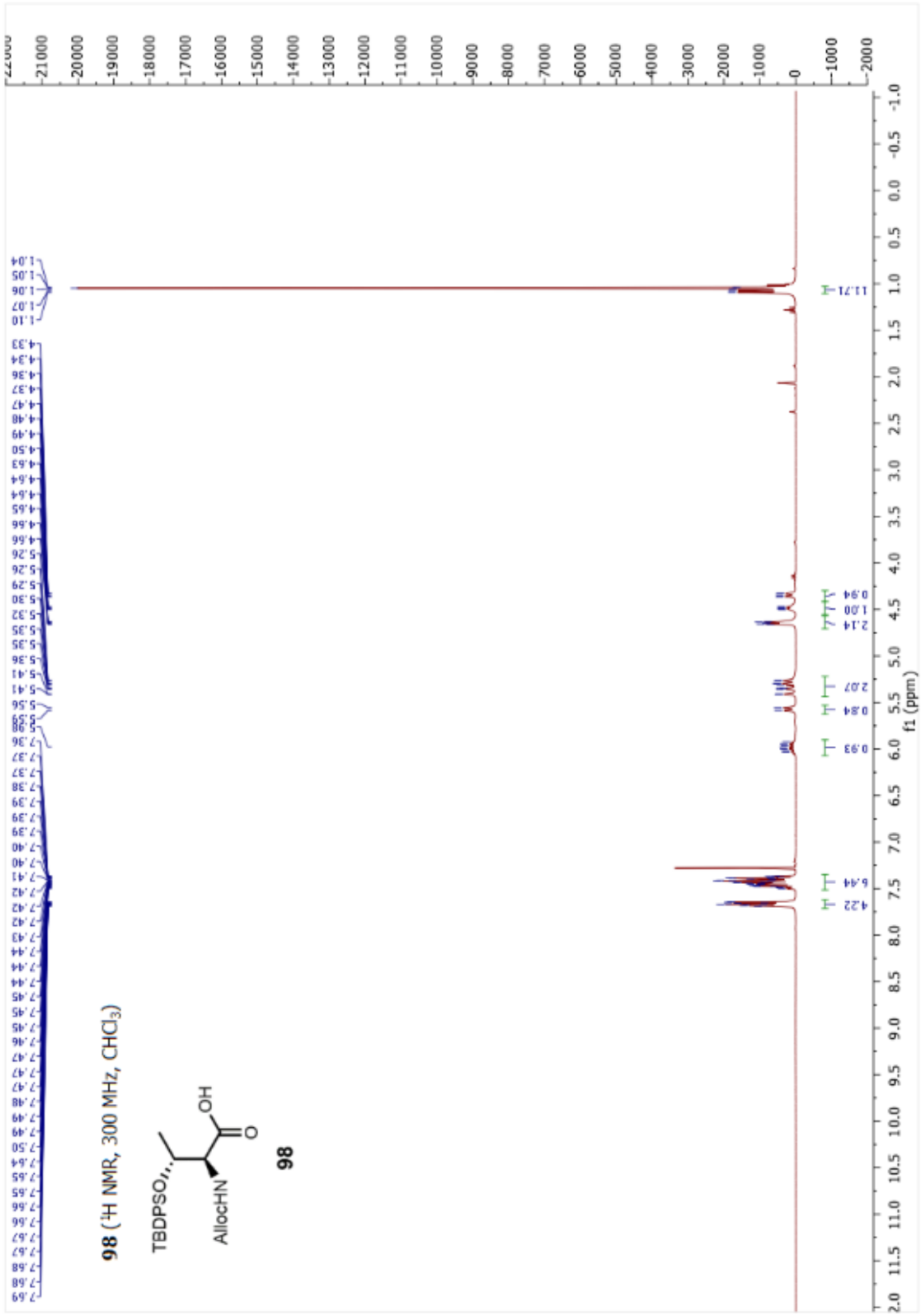


Figure 2.41 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **98**.

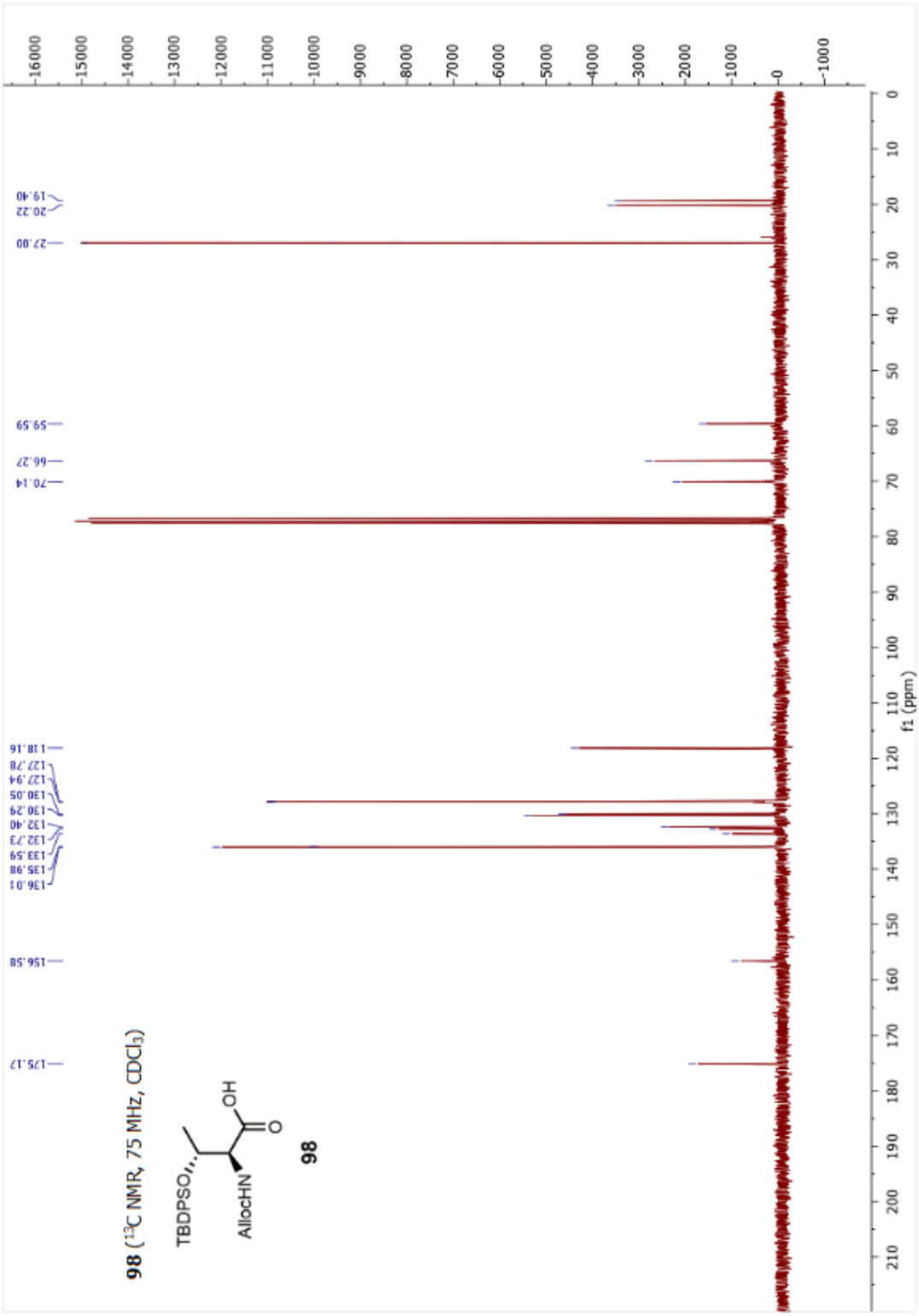


Figure 2.42 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **98**.

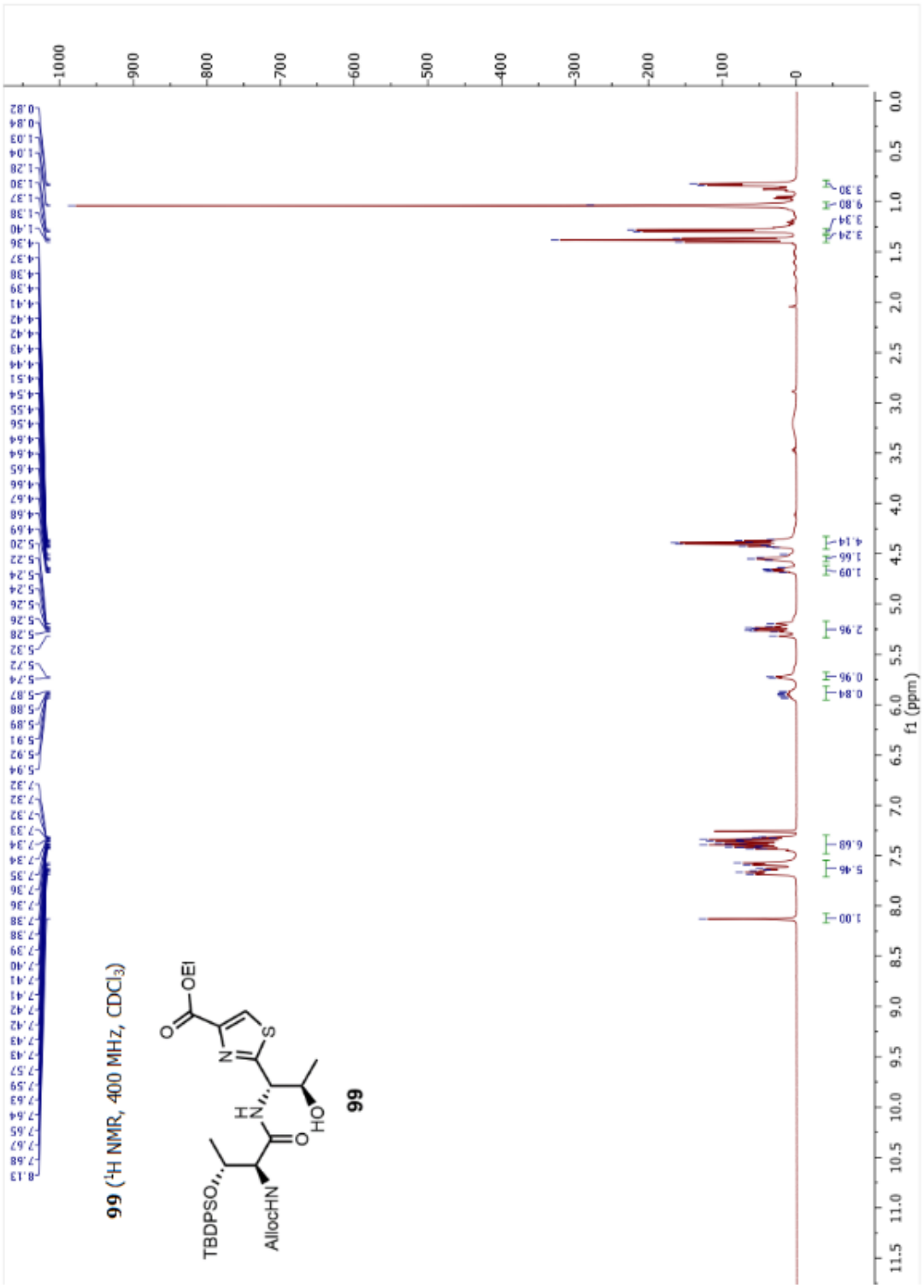


Figure 2.43 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **99**.

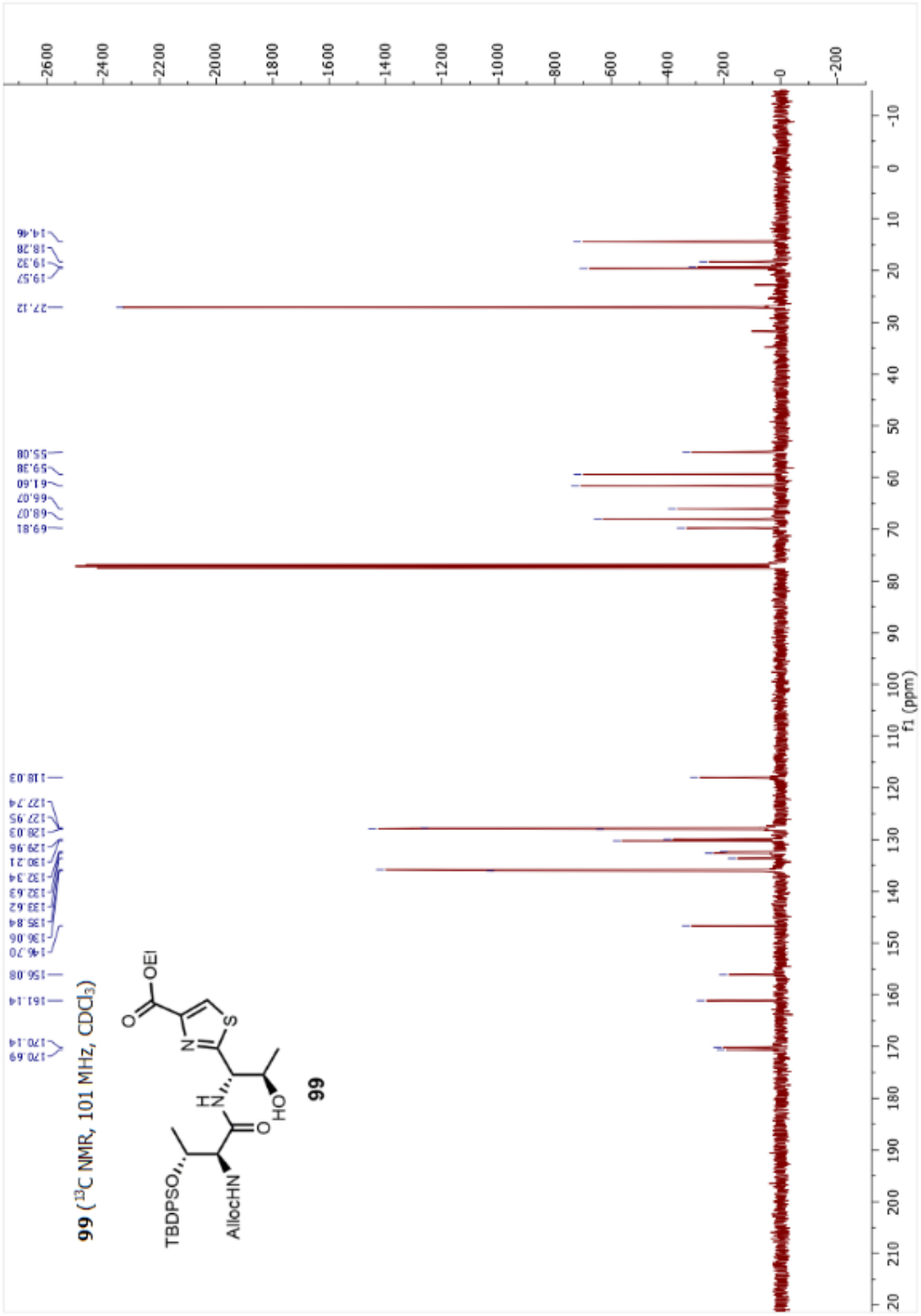


Figure 2.44 ^{13}C NMR (101 MHz, $CDCl_3$) of compound **99**.

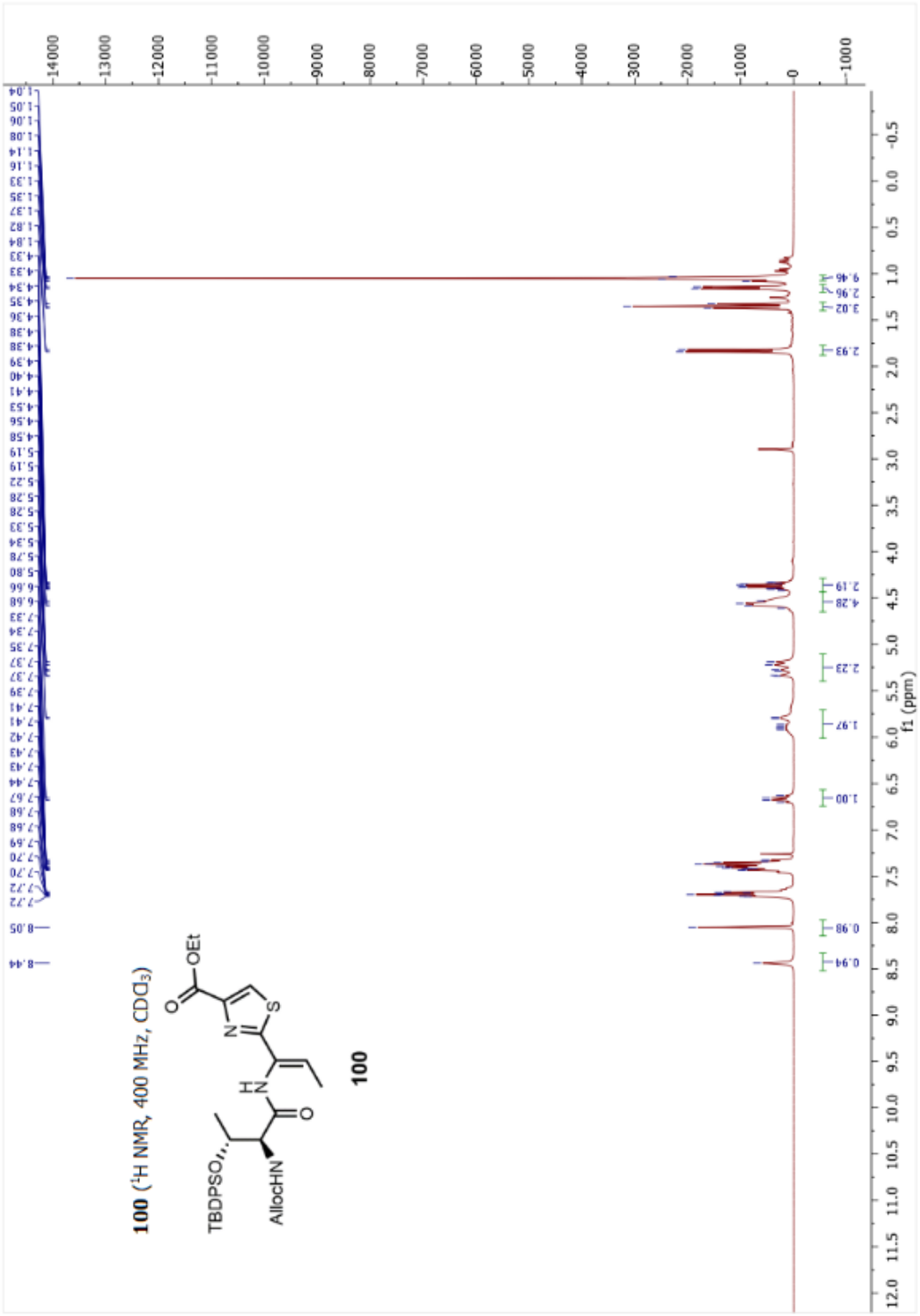


Figure 2.45 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **100**.

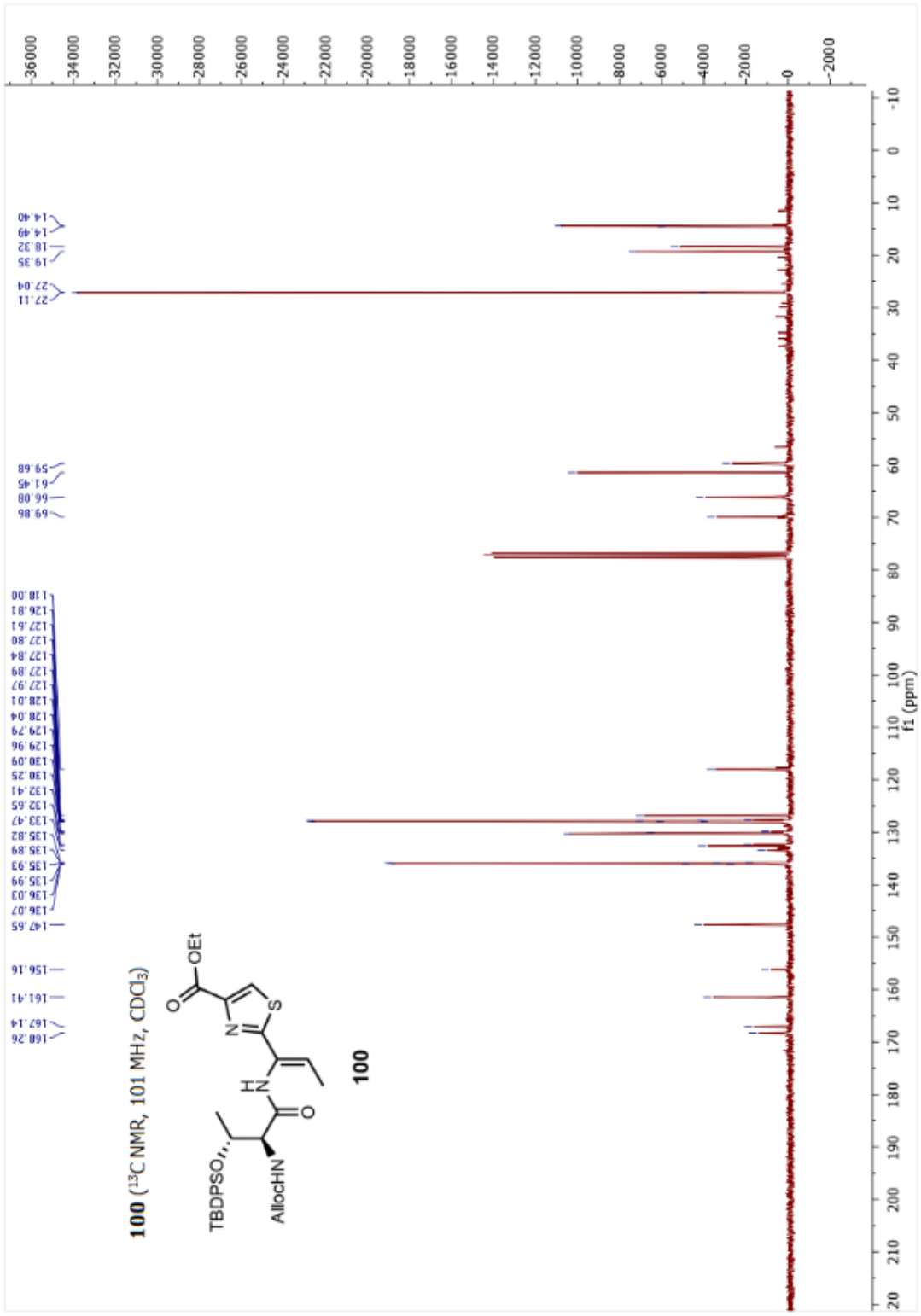


Figure 2.46 ^{13}C NMR (101 MHz, $CDCl_3$) of compound **100.**

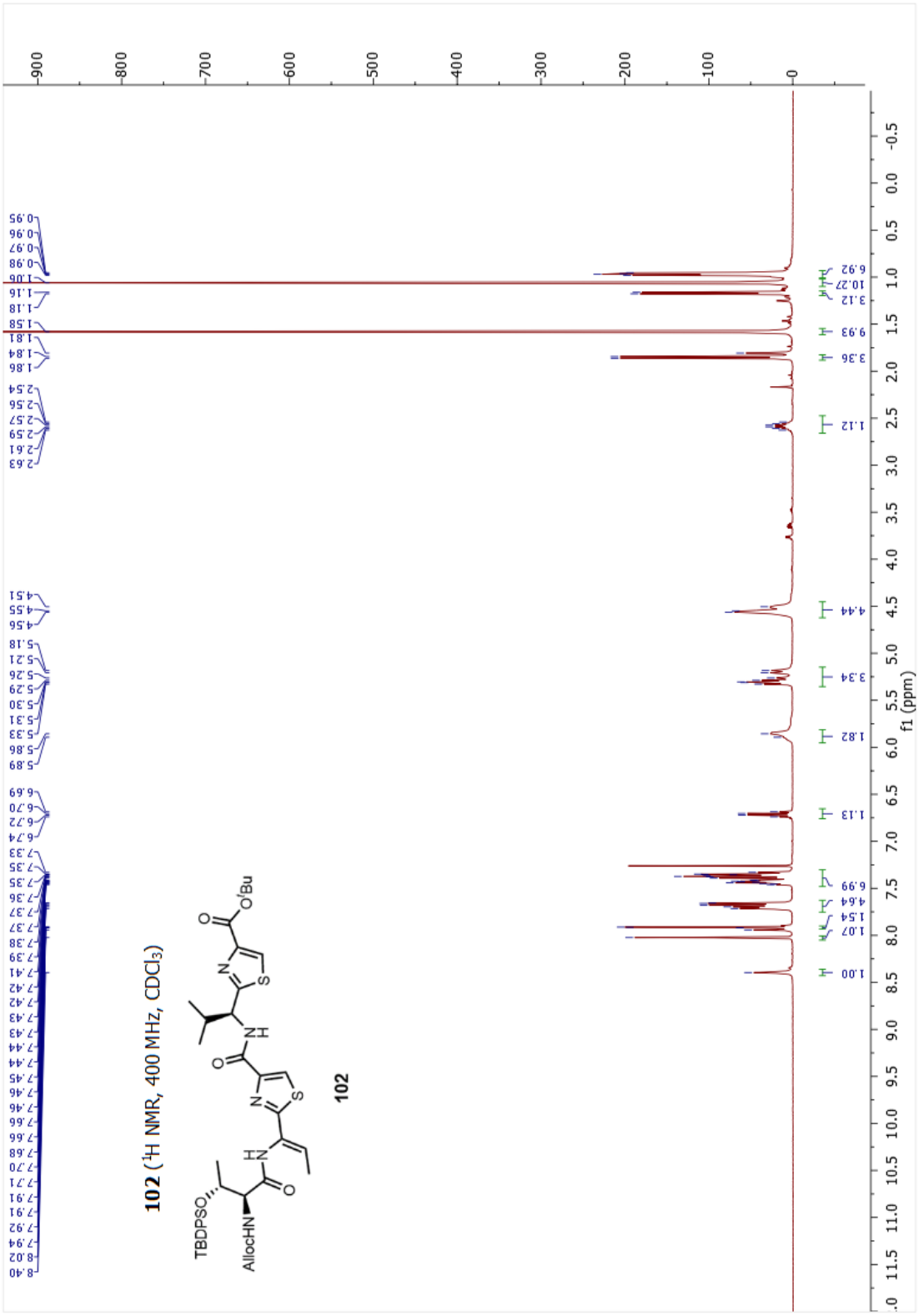


Figure 2.47 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **102**.

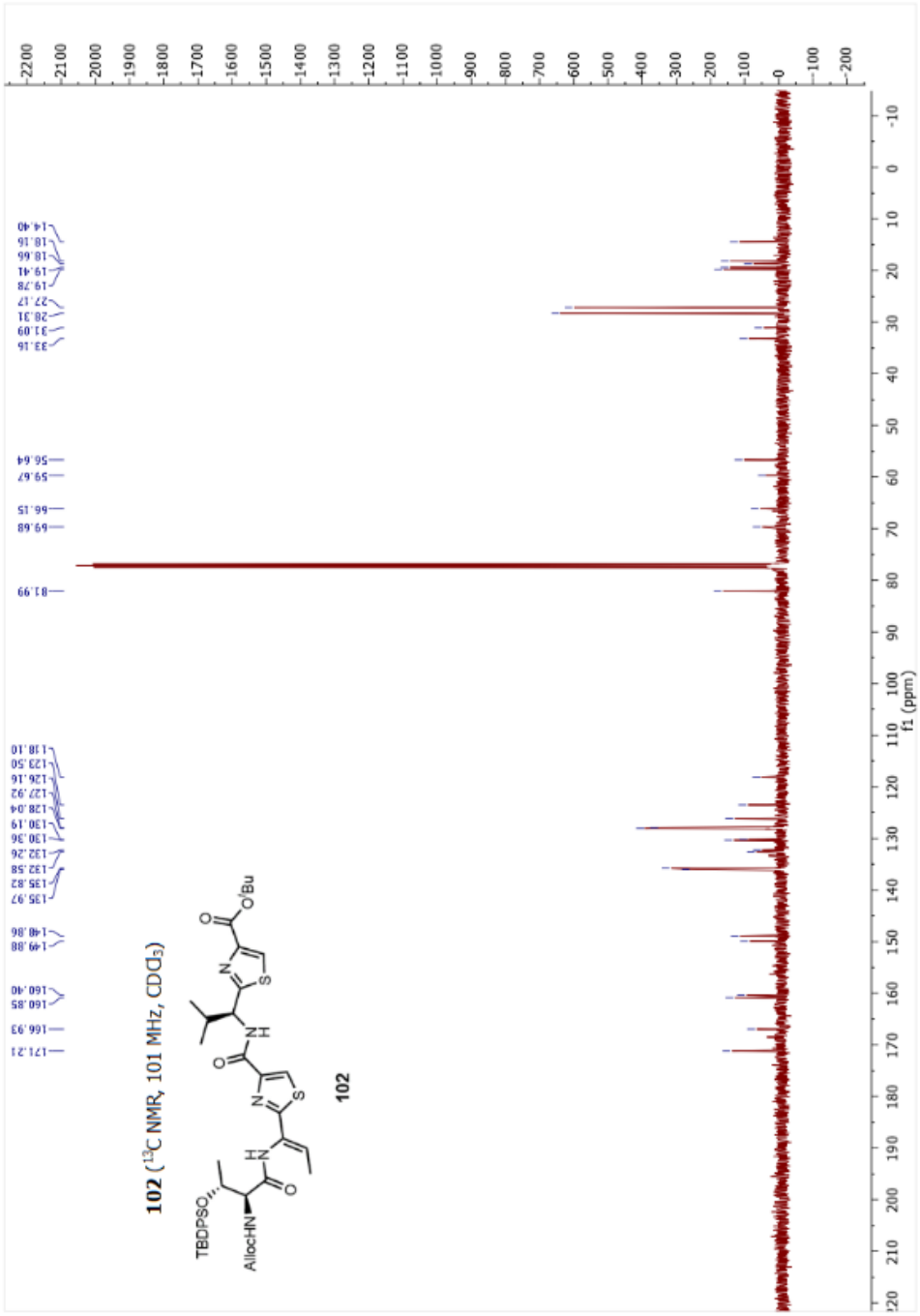


Figure 2.48 ^{13}C NMR (101 MHz, $CDCl_3$) of compound **102**.

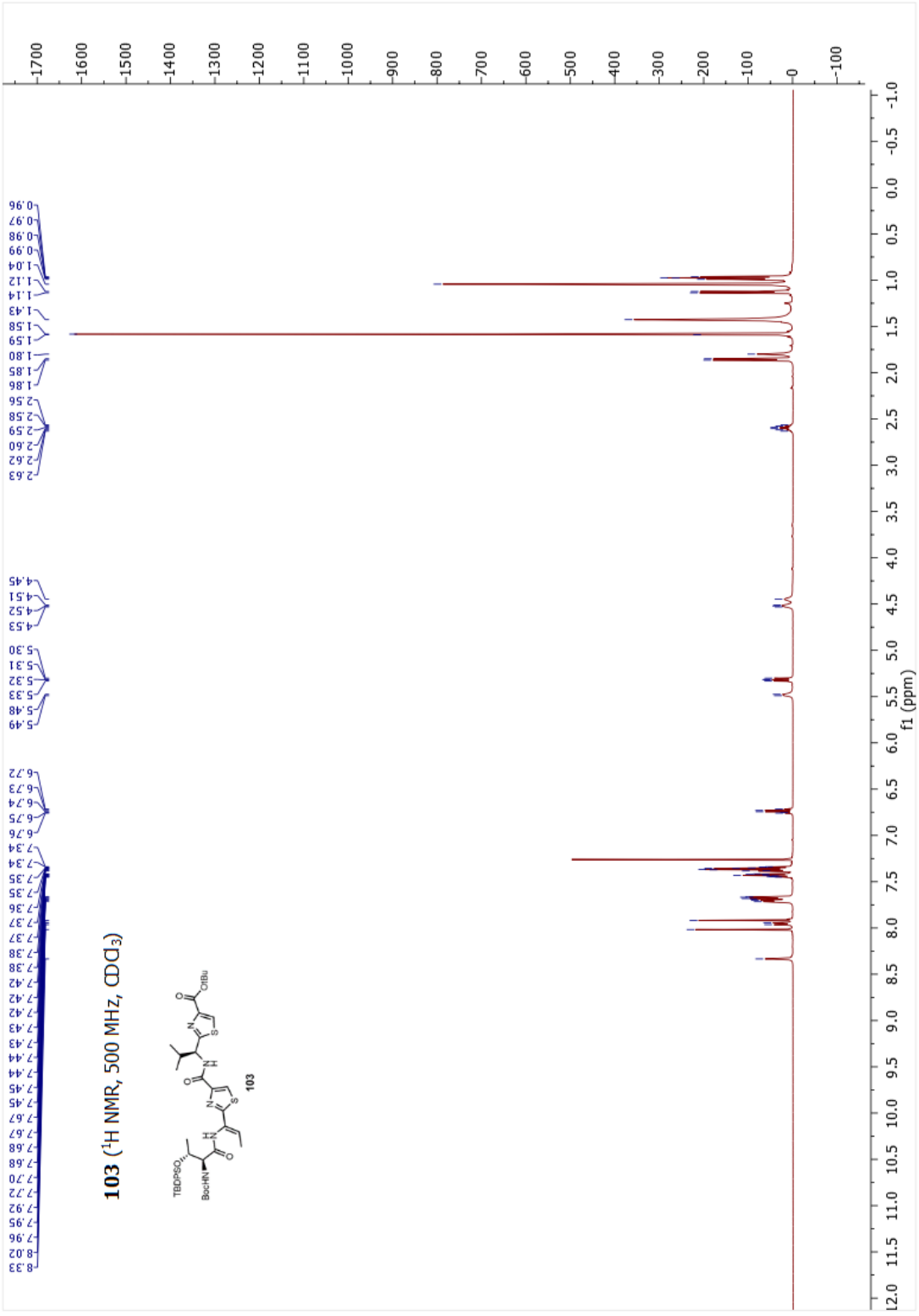


Figure 2.49 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **103**.

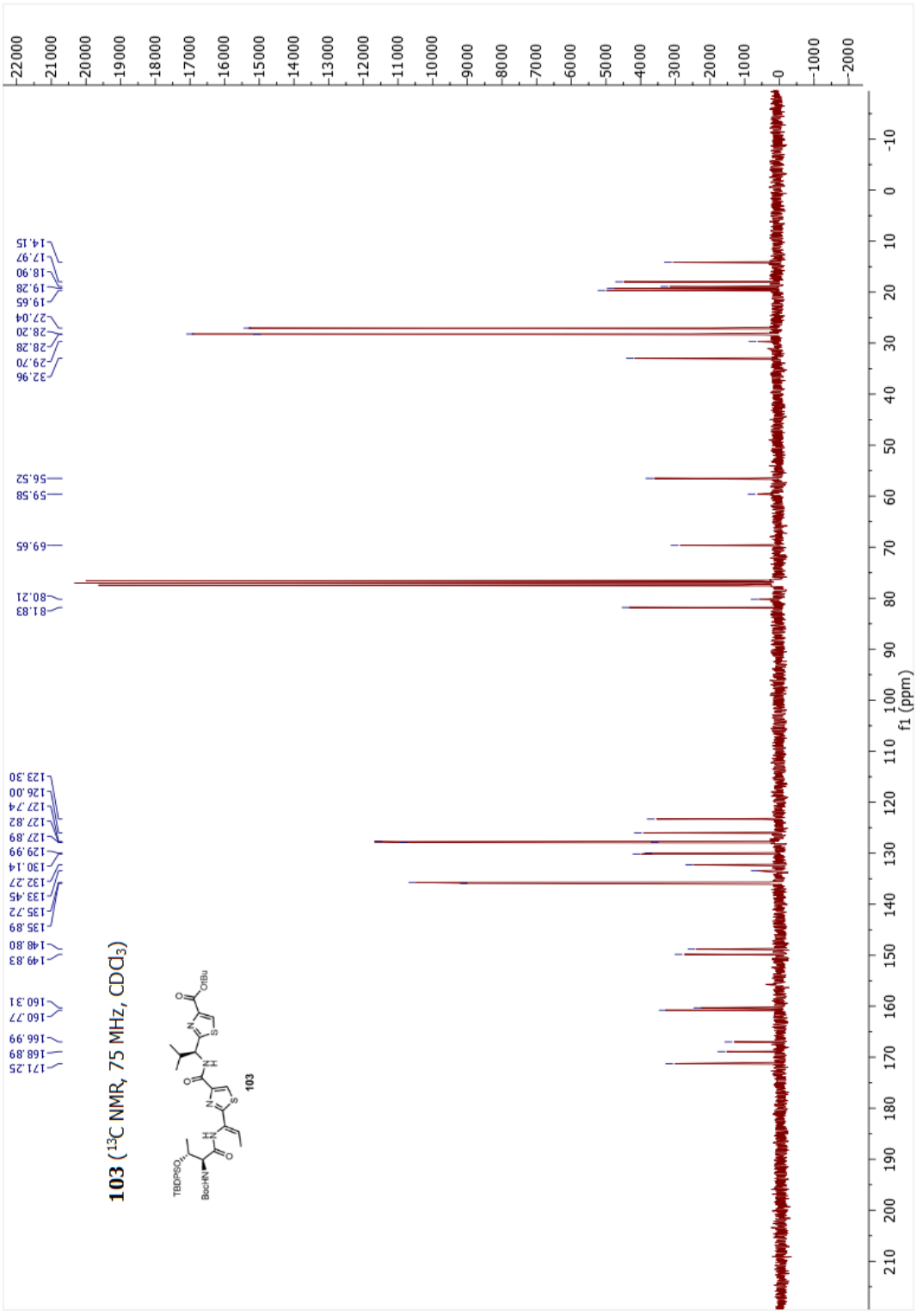


Figure 2.50 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **103**.

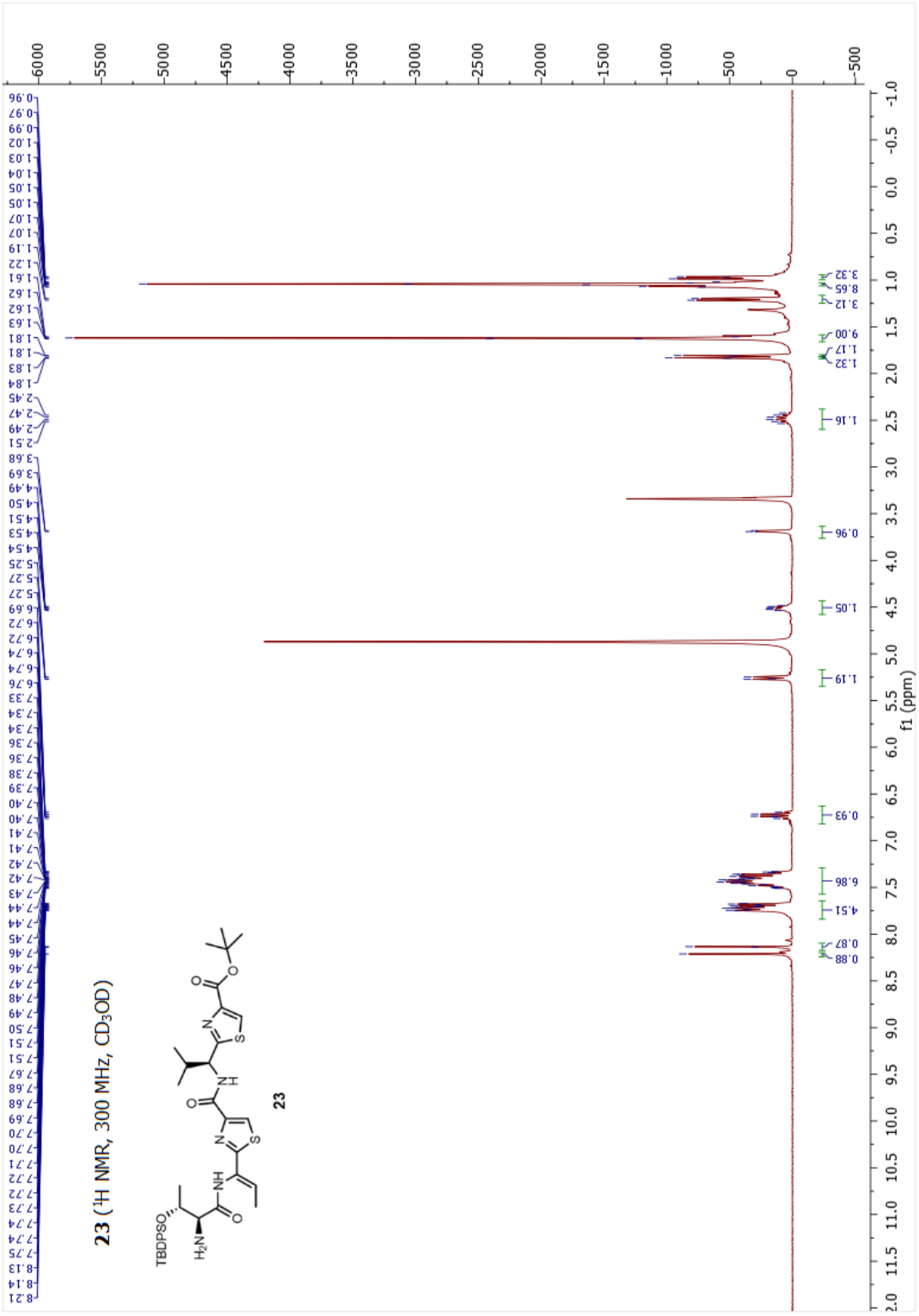


Figure 2.51 ^{1}H NMR (300 MHz, CD_3OD) of compound **23**.

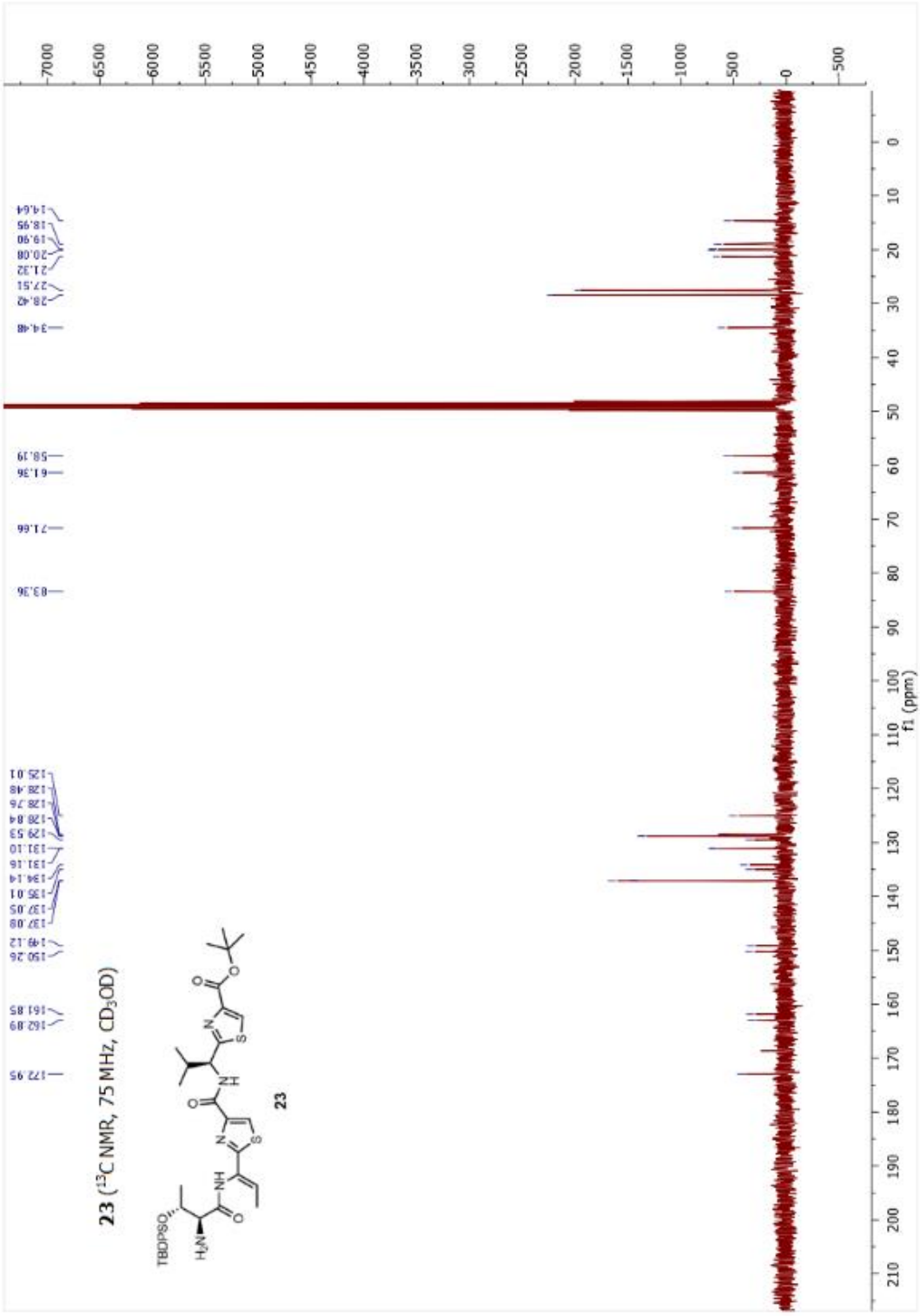


Figure 2.52 ^{13}C NMR (75 MHz, CD_3OD) of compound **23**.

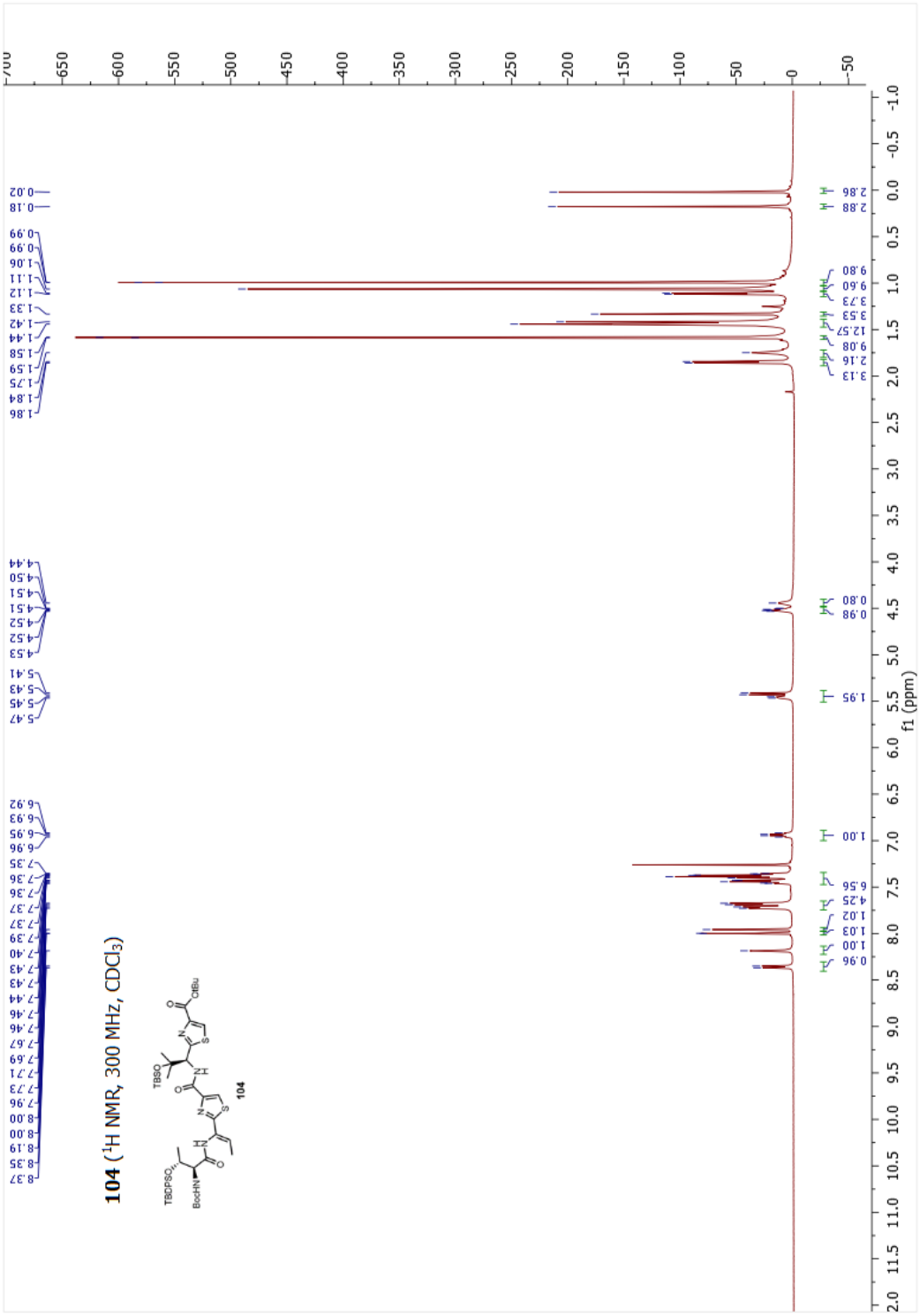


Figure 2.53 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **104**.

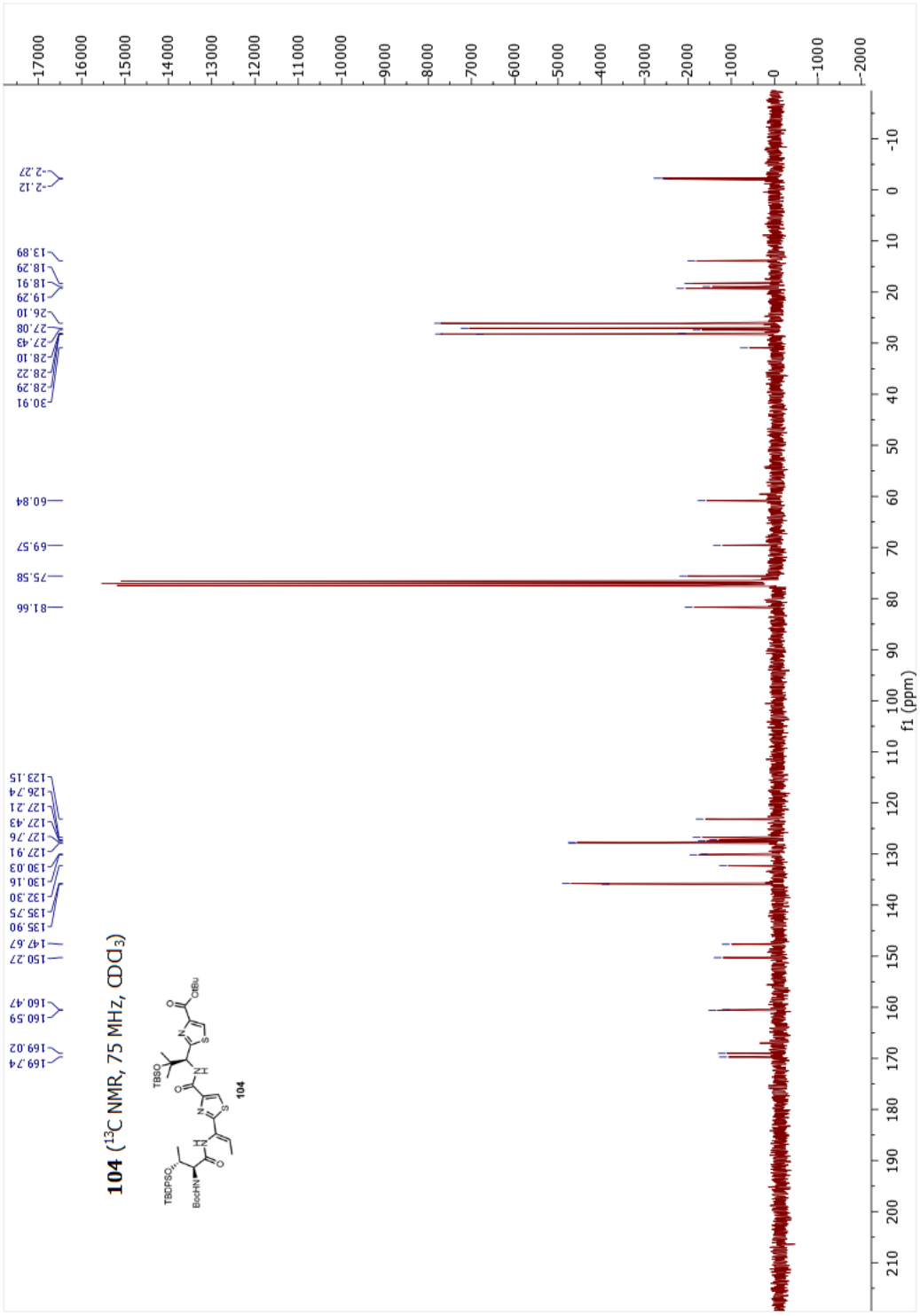


Figure 2.54 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **104**.

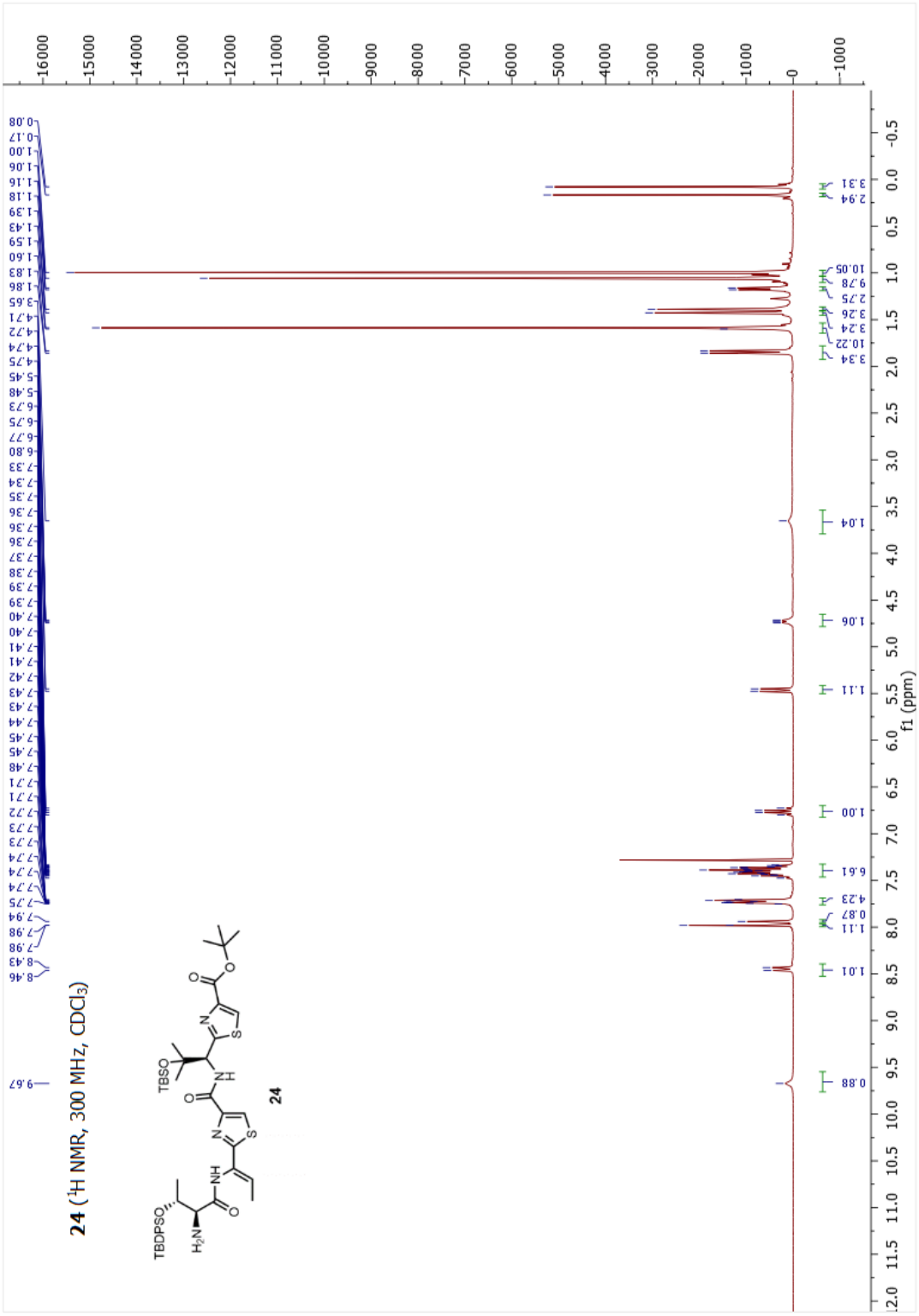


Figure 2.55 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **24**.

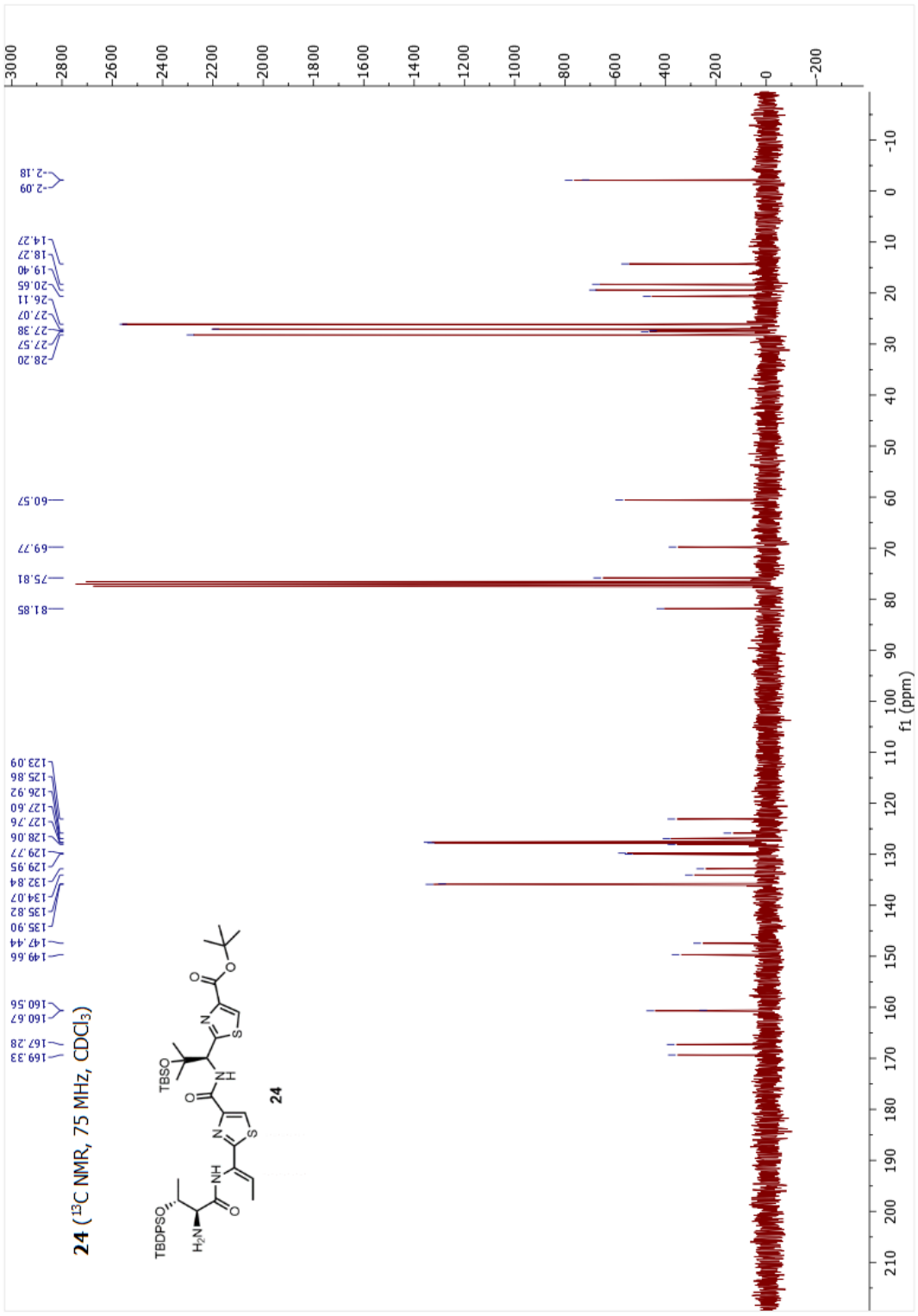


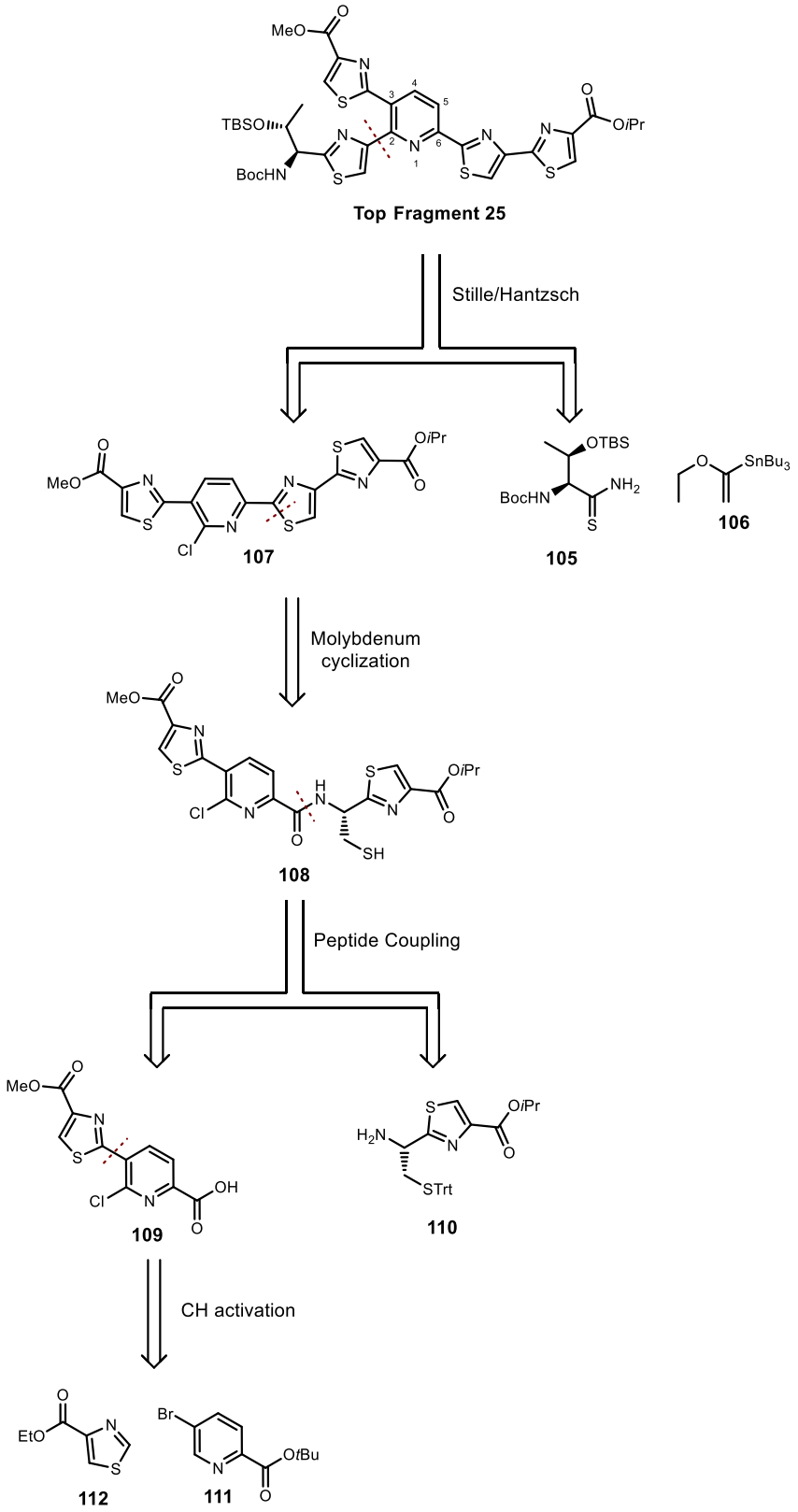
Figure 2.56 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **24**.

CHAPTER THREE

Synthesis of the Top Fragment 25

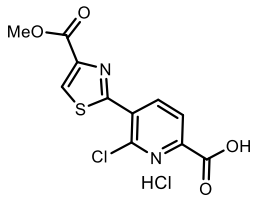
3.1 Retrosynthetic Analysis of 25

The top fragment of micrococcin P1 and thiocillin I contains a trisubstituted pyridine ring. The thiazoles occupy the 2,3, and 6 positions of pyridine and contain different functionalities: thiazole at *C*-2 contains a protected threonine moiety, *C*-3 contains a thiazole methyl ester, and *C*-6 contains a bisthiazole moiety. The first disconnection can be made at the *C*-2 thiazole and constructed in a Stille coupling/Hantzsch sequence. Vinyl stannane **106** would be cross coupled to chloropyridine **107** and brominated into an α-bromoketone. From there it would be combined with thioamide **105** in a Hantzsch reaction. The *C*-6 thiazole in **107** could be constructed by applying the molybdenum cyclization methodology developed earlier to reveal thiol **108**. A disconnection can be made at the amide bond revealing chloropyridine **109** and amine **110**. The final thiazole ring **112** would be installed directly using a C-H activation to bromopyridine **111**.



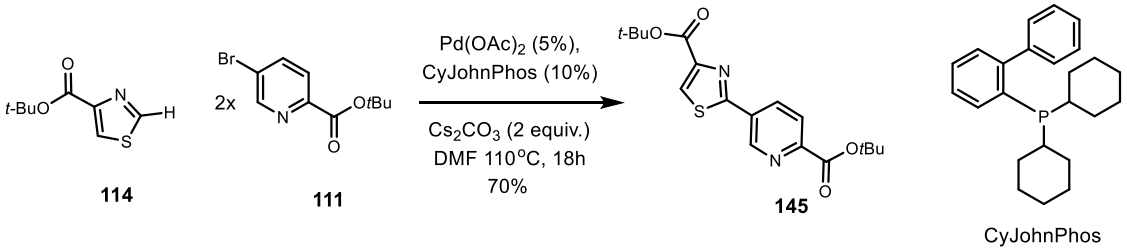
Scheme 3.1 Retrosynthetic analysis of top fragment **25**.

3.2 Synthesis of intermediate 109



109

In contemplating synthetic routes to access **109**, Dr. Akasapu found a literature report utilizing a C-H activation between thiazole-4-carboxylate **114** and bromopyridine **111**.[83] Under the reported reaction conditions, one equivalent of **114** was reacted with two equivalents of **111** using $Pd(OAc)_2$ (5%) as the catalyst, CyJohnPhos (10%) as the ligand, and Cs_2CO_3 as the base. The reaction was heated to 110 ºC in DMF for 18 hours and afforded **145** in a 70% yield.

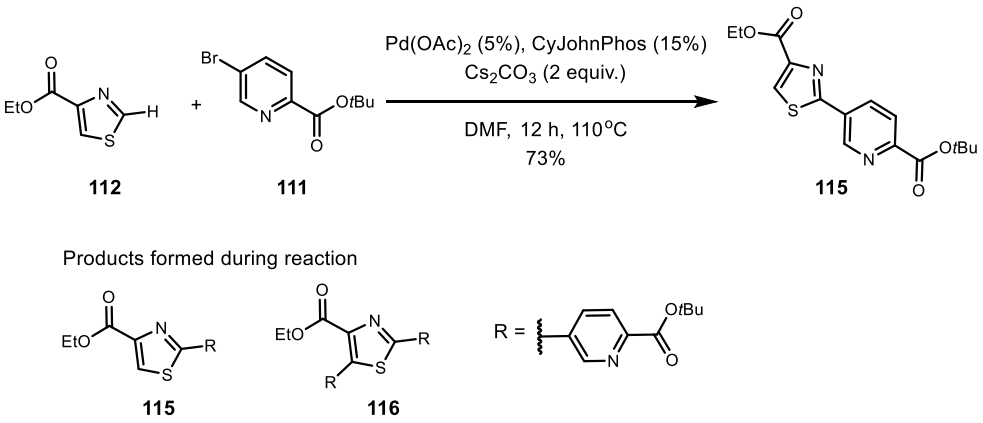


114 **111** **145**

Scheme 3.2 Literature protocol of C-H activation.

We adapted this methodology in our synthesis to install the first thiazole. Under optimized conditions **111** and **112** were reacted together in decagram quantities with Pd (5%) and ligand (15%) in DMF at 110 ºC for 12 hours which afforded **115** in 73% yield after purification. When we subjected the reaction to longer reaction times several side products formed. Subjecting the reaction to longer times resulted in an extra C-H activation occurring within the same molecule (**116**). If a methyl ester was used in place of an ethyl ester on **112** the amount of **115** isolated

dropped significantly and **116** formed to a much larger degree. This analysis is congruent with the published results.

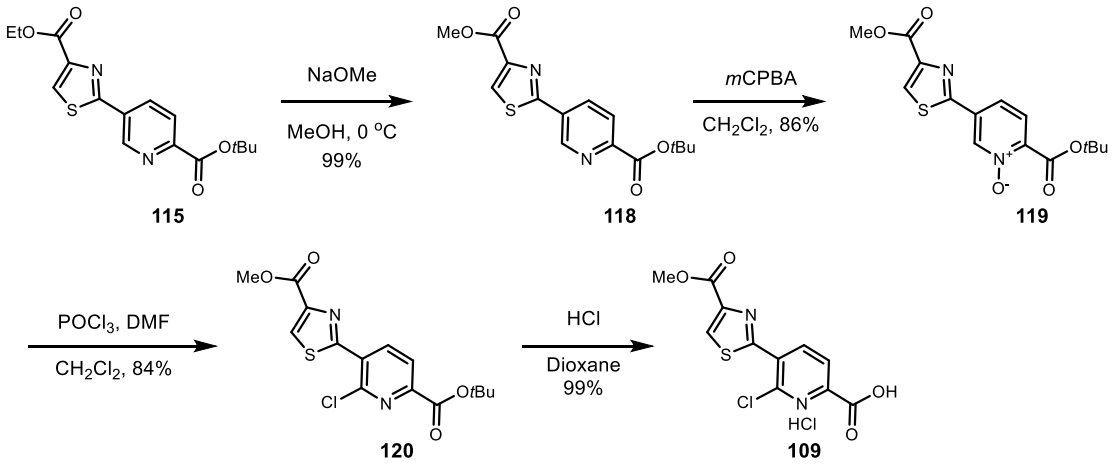


Scheme 3.3 C-H activation to form **115**.

Despite the inconvenience of the thiazole methyl ester not reacting well during the C-H activation, transesterification to the methyl ester **118** using NaOMe proceeded efficiently. NaOMe was freshly prepared by dissolving sodium metal in anhydrous methanol before use in the reaction. It was found that if an excess (>1.1 equiv.) of NaOMe was used during the reaction, the **115** would be converted into a bismethyl ester, a useless product.

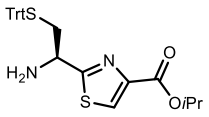
Chlorination of pyridines can be accomplished in a two-step process: conversion of pyridine into a pyridine-*N*-oxide followed by a reaction with $POCl_3$ and DMF. For the first step, *m*CPBA was used as the oxidant to convert **118** into an *N*-oxide. Under the reaction conditions an orange side product formed but the desired product could easily be precipitated from ethyl acetate as a white solid yielding **119** in 86%. The *N*-oxide was converted to the chlorinated pyridine using $POCl_3$, DMF, in CH_2Cl_2. Despite our reported success of this reaction on a small scale (~50 mg, 97%), the chloropyridine **120** was never isolated in larger than 70% from **118** during scale-up

reactions on multigram quantities. The intermediate **120** was converted into the acid hydrochloride **109** using HCl in 1,4-dioxane.



Scheme 3.4 Synthesis of intermediate **109**.

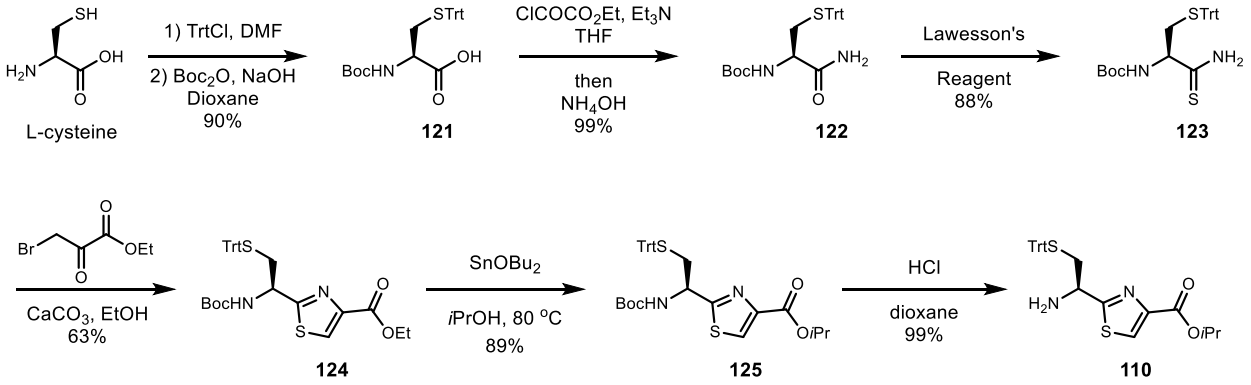
3.3 Synthesis of fragment 110



Fragment 110

With intermediate **109** in hand, we set out to synthesize fragment **110**. The synthesis of **110** began with the trityl protection of sulfur and the Boc protection of nitrogen on L-cysteine to form **121**. In a similar manner as before, the carboxylic acid was converted to amide **122** using ethyl chloroformate and ammonium hydroxide in near quantitative yield. The amide was then converted to the thioamide **123** using Lawesson's reagent in 88% yield. Since this substrate was produced on >50 g scale, Lawesson's reagent was a better choice of reagent due to the ease of workup and purification. A Hantzsch thiazole synthesis was performed on thioamide **123** using ethyl bromopyruvate and $CaCO_3$ to give thiazole **124**. Side reactions and decomposition of the

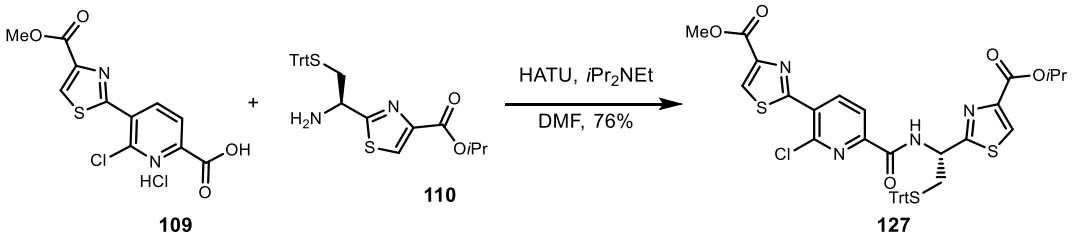
starting material capped the yield at 63%. To convert the ethyl ester **124** into isopropyl ester **125** a few approaches were attempted. Our first strategy involved the hydrolysis of ethyl ester on **124** to the carboxylic acid using lithium hydroxide followed by activation of the acid with DIC and displacement with isopropyl alcohol. While this method succeeded, yields were modest (~ 60%). A second strategy involved reacting thioamide **123** with isopropyl bromopyruvate to directly form **125**. This method yielded **125** in 78% on a small scale, though applications on a large scale were not feasible due to the cost of isopropyl bromopyruvate. Our third and most successful method involved the transesterification of the ethyl ester **124** to isopropyl ester **125**. A literature search revealed $SnOBu_2$ as an effective transesterification reagent. The original paper utilized this reagent in catalytic amounts although in our hands the rate of reaction was too slow so stoichiometric amounts of reagent were required to complete the reaction. The ethyl ester was converted into isopropyl ester **125** in nearly 90% yield. The Boc protecting group was removed using 4N HCl in 1,4-dioxane to produce fragment **110**.



Scheme 3.5 Synthesis of cysteine thiazole fragment **110**.

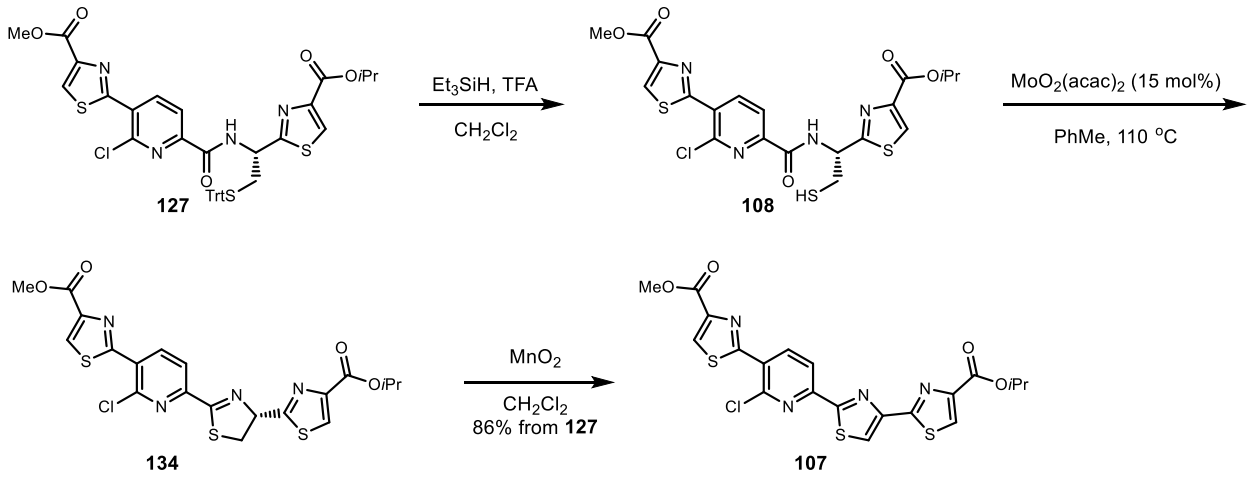
3.4 Completion of Top Fragment

Acid **109** and amine **110** were coupled together to form **127** in a 76% yield. The trityl group was cleanly removed using triethylsilane in a 10% TFA/CH_2Cl_2 solution to form thiol **108**.



Scheme 3.6 Peptide coupling between **109** and **110** to form **127.**

Before we understood the intricacies of the molybdenum cyclization, cyclization yields of **108** were low and high catalyst loadings (40%) were required to push the reaction to 70%. The reaction mixture often turned dark purple, green, or brown. It was thought that the catalyst decomposed to various insoluble, dark-colored molybdenum solids such as MoO_2. After extensive experimentation, it was found that several conditions needed to be met for the molybdenum cyclization to proceed effectively. Dry and degassed toluene was required to prevent decomposition of the catalyst and formation of the disulfide. In addition to this, efficient azeotropic removal of water was required. If water was not removed from the solution the reaction did not progress. Consistent results were achieved if these conditions were met and the reaction mixture no longer had dark brown color after completion of the reaction but a light brown/peach color when the cyclization proceeded effectively. We found that reaction progress ceases after a few hours likely due to decomposition of the catalyst so and an extra 5% of $MoO_2(acac)_2$ was needed to complete conversion to thiazoline **134**. Yields were reproducibly raised (c.a. >80%) after optimization.

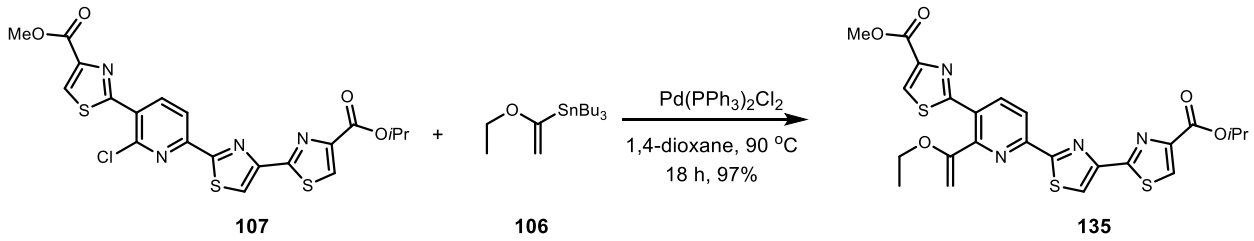


Scheme 3.7 Synthesis of chloropyridine **107** using molybdenum catalyzed cyclization.

Another particular feature of this reaction is that in addition to formation of thiazoline **134** thiazole **107** (~5%) also formed. Interestingly, the use of any sort of picolinic acid ligand retarded the reaction and significantly increased the amount of **107** formed in the reaction. We suspected that **134** produced in the reaction acts as a ligand itself and modifies the conditions of the reaction. After optimization, multigram quantities of thiol was reliably converted to thiazoline **134**. In addition to this trityl deprotection, cyclization and oxidation could be done sequentially without the need for purification.

The thiazoline was converted into thiazole **107** using MnO_2 in 86% from **127**. The product was insoluble in virtually all common organic solvents which posed a problem for large scale synthesis. Typical oxidation conditions of thiazolines occur by using the reagents $CBrCl_3$ and DBU. These conditions worked well in the conversion of **134** to **107** on a small scale when an excess of solvent dissolved the product but posed greater problems on multigram quantities. Freshly prepared, highly active MnO_2 was used to quantitatively convert thiazoline **134** to thiazole **107**. Instead of a workup or column, only a filtration was necessary to remove all MnO_2. Wyatt

Powell converted the chloropyridine **107** to vinyl stannane **135** in 97% yield through a Stille cross coupling using $Pd(PPh_3)_2Cl_2$ (10 %).

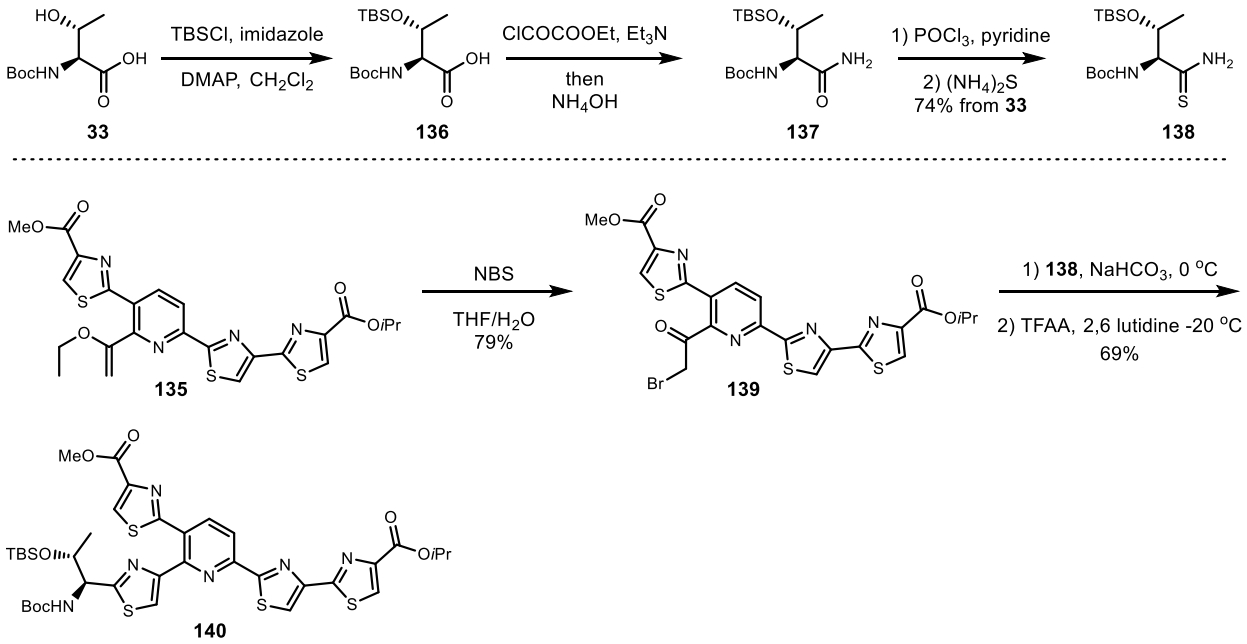


107 **106** **135**

Scheme 3.8 Stille coupling to access vinyl ether **135**.

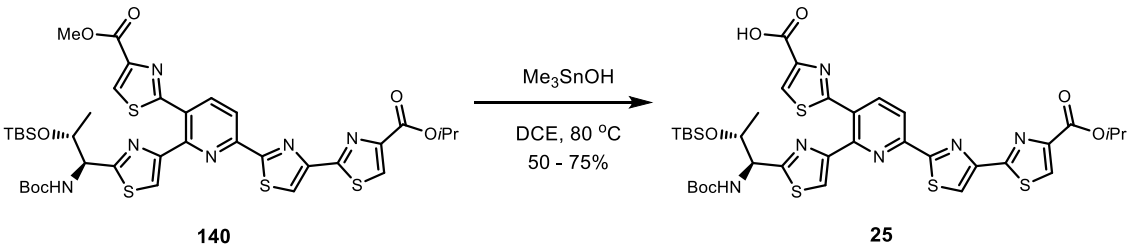
The vinyl ether **135** was converted into an α-bromoketone **139** using NBS. Initial trials for this reaction were low yielding due to the low solubility of the product. It was found that an increasingly polar gradient was required to be passed through the silica during purification to remove all of the compound. Yields were as high as 79% for this reaction.

Thioamide **138** was synthesized from threonine beginning with Boc and TBS protections of nitrogen and oxygen respectively. The acid was converted to the thioamide using previously discussed conditions. The fully protected top fragment **140** was completed by reacting the α-bromoketone **139** with the thioamide **138** in a Hantzsch thiazole synthesis. Following the same modified procedures as before (TFAA, pyridine) resulted in low yields or decomposition of the product. Initial optimization studies focused on controlling the temperature during the second step of the reaction and using 2,6-lutidine as the pyridine base instead of pyridine itself. Yields were improved to nearly 70%.



Scheme 3.9 Hantzsch thiazole synthesis to reach top fragment **140**.

Dr. Akasapu further optimized the Hantzsch reaction to increase the yield and prevent decomposition. In order to control the reactivity, thioamide was slowly added to the bromoketone **139** and $KHCO_3$ at -20 ºC and allowed to warm to room temperature until **139** was fully consumed. The resulting solution was filtered and cooled to -20 ºC again and 2,6-lutidine and TFAA (4.0 equiv.) were added dropwise. The reaction mixture was stirred until complete conversion of starting material was observed. The top fragment methyl ester **140** was cleaved with trimethyl tin hydroxide which produced **25** in 50-70%. Unfortunately, two side products were observed depending on the reaction time. We suspected the side products to be hydrolysis of the isopropyl ester and double hydrolysis of both esters based on R_f values. Separation of the two compounds was difficult, although if the next step (peptide coupling with bottom fragment) was done without pristine **25**, several side products formed that were impossible to separate on HPLC.



140 **25**

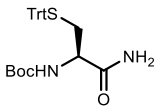
Scheme 3.10 Hydrolysis of methyl ester to form top fragment acid **25**.

3.5 Experimental Section

3.5.1 Materials and Methods

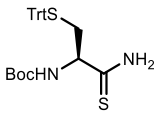
All chemicals were purchased as reagent grade and used without further purification, unless otherwise noted. All reaction mixtures were carried out under anh. N_2 in oven-dried glassware. TLC analyses were performed on Merck TLC plates and visualizations were performed with UV light and/or Hanessian stain. A 10% w/v aqueous solution of citric acid was used during work-ups unless indicated otherwise. Column chromatography was performed on silica gel (230-400 mesh). Melting points were recorded in open capillaries and uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 300/ Varian 400/ Varian 500 MHz instruments are reported as follows: chemical shift (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. The residual solvent reference peaks were used from published literature.[1] 2D NMR experiments were performed using standard parameters (*200 and More NMR Experiments,* S. Berger, S. Braun, Wiley-VCH, **2004**). IR measurements were performed on Agilent Cary 630 ATR instrument and optical rotations were measured on JASCO P-1030.

3.5.2 Preparative Procedures



122

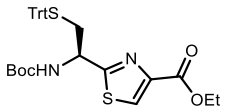
***tert*-Butyl (R)-(1-amino-1-oxo-3-(tritylthio)propan-2-yl)carbamate.** A solution of Boc-*S*-Trt-Cys (127 g, 275 mmol, 1.00 equiv.) Was dissolved in THF (1 L) and cooled to 0 ºC. Et_3N (76.0 mL, 550 mmol, 2.0 equiv.) and ethyl chloroformate (39.2 mL, 412 mmol, 1.5 equiv.) were added. After 30 min 28% NH_4OH (43 mL) was added and was allowed to warm to rt. After 16 h the reaction mixture was concentrated and partitioned between citric acid and CH_2Cl_2 in a separatory funnel. The aqueous layer was washed with CH_2Cl_2 and the combined organic layers were washed with sat. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated. The residue was stirred with a minimal amount of EtOAc precipitated **122** (91.8 g, 72%) as a pink-tinted solid: mp = 177.9 – 178.9 °C; $[\alpha]_D^{25} = +1.4$ (c = 1.00, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3324, 3056, 2978, 2920, 1681, 1595, 1491, 1445, 1392, 1367, 1249, 1165, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 6H), 7.34 – 7.17 (m, 9H), 5.95 (d, *J* = 59.6 Hz, 2H), 4.92 (d, *J* = 7.6 Hz, 1H), 3.91 (s, 1H), 2.69 (dd, *J* = 12.9, 7.1 Hz, 1H), 2.55 (dd, *J* = 12.9, 5.3 Hz, 1H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 144.5, 129.7, 128.2, 127.0 , 77.4, 67.3, 33.8, 28.4, 27.9; FT-HRMS (ESI) *m/z* calcd for $C_{27}H_{30}N_2O_3SNa^+$ $[M + Na]^+$: 485.1869, found 485.1875.



123

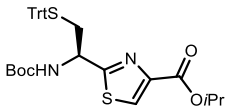
***tert*-Butyl (S)-(1-amino-1-thioxo-3-(tritylthio)propan-2-yl)carbamate.** A solution of **122** (31.7 g, 68.5 mmol, 1.00 equiv.) in anh. THF (750 mL, 0.09 M) was cooled to 0 °C under N_2. Lawesson's reagent (14.4 g, 35.6 mmol, 0.52 equiv.) was added and the reaction mixture was allowed to warm up to rt. After 20 h the reaction mixture was concentrated and taken up in sat. $NaHCO_3$ and EtOAc. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were dried

(Na_2SO_4) and concentrated. The residue was dissolved in a minimal amount of hot EtOAc and refluxed. A solution of 10% EtOAc/hexanes (150 mL) was slowly dripped into the refluxing solution over 6 h, and allowed to come to rt while stirring overnight. The white crystals were filtered and washed with hexanes to afford **123** (22.8 g, 70%) as a fine white crystalline powder: mp = 154.3 – 155.4 °C; $[\alpha]_D^{25} = +2.7$ (c = 1.00, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3301, 3188, 2976, 1696, 1491, 1444, 1392, 1367, 1249, 1164, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.43 (m, 6H), 7.35 – 7.24 (m, 9H), 5.02 (dd, *J* = 7.8, 1.2 Hz, 1H), 4.15 – 4.04 (m, 1H), 2.84 (dd, *J* = 13.0, 7.3 Hz, 1H), 2.67 (dd, *J* = 13.0, 5.5 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.2, 144.5, 129.7, 128.2, 127.0, 77.4, 67.6, 36.6, 28.4, 28.0; FT-HRMS (ESI) *m/z* calcd for $C_{27}H_{30}N_2O_2S_2Na^+$ $[M + Na]^+$: 501.1646, found 501.1644.



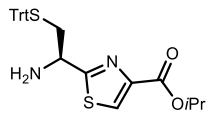
124

ethyl (S)-2-(1-((*tert*-butoxycarbonyl)amino)-2-(tritylthio)ethyl)thiazole-4-carboxylate. 123 (29.5 g, 61.6 mmol, 1.00 equiv.) and $CaCO_3$ (12.3 g, 123 mmol, 2.00 equiv.) were dissolved in anh. EtOH (1.2 L) and cooled to 0 °C under N_2. 90% Ethyl bromopyruvate (20 g, 92.4 mmol, 1.50 equiv.) was added. After 24 h the reaction mixture was concentrated and filtered. The residue was purified by column chromatography on SiO_2 using 20% to 33% to 50% EtOAc/hexanes to afford **124** as a yellow solid which was triturated with Et2O which afforded **124** (22.5 g, 64%) as a white solid.



125

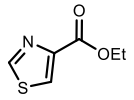
***iso*-Propyl (*S*)-2-(1-((*tert*-butoxycarbonyl)amino)-2-(tritylthio)ethyl)thiazole-4-carboxylate.** In a pressure tube **124** (15.4 g, 26.8 mmol, 1.00 equiv.) and $SnOBu_2$ (6.67 g, 26.8 mmol, 1.00 equiv.) was dissolved in 300 mL *i*PrOH and heated to 85 ºC. After 24 h the reaction mixture was cooled, filtered over Celite. The residue was purified by column chromatography using 10% to 33% EtOAc/hexanes to afford **125** (14.1 g, 89%) as a white solid: $[\alpha]_D^{25} = -1.4$ (c = 1.00, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3400, 3057, 2978, 2925, 2360, 2120, 1893, 1708, 1486, 1366, 1318, 1242, 1163, 1092, 1034, 909, 852, 735, 700, 505 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.42 – 7.36 (m, 6H), 7.32 – 7.19 (m, 10H), 5.28 (p, *J* = 6.3 Hz, 1H), 5.11 (s, 1H), 4.91 (s, 1H), 2.96 (d, *J* = 7.7 Hz, 1H), 2.77 (dd, *J* = 12.5, 5.1 Hz, 1H), 1.42 (s, 9H), 1.38 (dd, *J* = 6.2, 0.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7, 147.8, 144.3, 129.5, 128.1, 126.9, 68.9, 67.4, 36.8, 28.3, 21.9; FT-HRMS (ESI) *m/z* calcd for $C_{33}H_{36}N_2O_4S_2Na^+$ $[M + Na]^+$: 611.2009, found 611.2014.



110

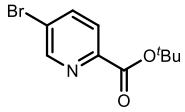
***iso*-Propyl (S)-1-amino-2-(tritylthio)ethyl)thiazole-4-carboxylate.** A solution of **125** (3.20 g, 5.44 mmol, 1.00 equiv.) in anh. 1,4-dioxane (27.0 mL, 0.20 M) was cooled to 0 °C and treated with 4N HCl in 1,4-dioxane (26.0 mL, 104 mmol). After 1.5 h, TLC analysis indicated complete consumption of the starting material. The reaction mixture was neutralized with sat. $NaHCO_3$, concentrated on rotary evaporator, and extracted with EtOAc (3x). The combined organic extracts

were washed with brine, dried (Na_2SO_4), and concentrated to give **110** (2.40 g, 90%) as a yellow oil. The residue was used without further purification.



112

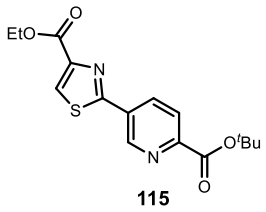
Ethyl thiazole-4-carboxylate. A solution of thiazole-4-carboxylic acid (10.2 g, 79.0 mmol, 1.00 equiv.) in anh. ethanol (475 mL, 0.166 M) was treated with *p*TSA (1.50 g, 8.00 mmol, 0.100 equiv.) and refluxed for 21 h under N_2. After cooling to rt, the volatiles were removed, and the residue was taken up in CH_2Cl_2 (150 mL) and sat. $NaHCO_3$ (100 mL). The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (2 x 150 mL). The organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The crude solid was purified by column chromatography on SiO_2 using 40% EtOAc/hexanes to afford **112** (9.70 g, 78%): as a yellow solid ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (d, *J* = 2.1 Hz, 1H), 8.25 (d, *J* = 2.1 Hz, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H). Characterization data matched the literature report.[84]



111

***tert*-Butyl 5-bromopicolinate.** Boc_2O (41.6 g, 190.7 mmol, 1.20 equiv.) was added to a solution of 5-bromo-2-pyrdine carboxylic acid (32.1 g, 158.9 mmol, 1.00 equiv.) and 4-DMAP (1.94 g, 15.9 mmol, 0.100 equiv.), in anh. toluene (650 mL, 0.244 M) at 0 °C under N_2. The reaction mixture was equipped with a condenser and heated to 50 °C. After 20 h, the reaction mixture was

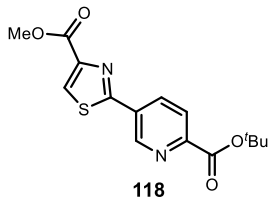
cooled to rt, transferred into a separatory funnel, and washed with water. The aqueous layer was extracted with EtOAc (2x) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The solidified mass was purified by column chromatography on SiO_2 using 3% EtOAc/hexanes to give **111** (36.9 g, 90%) as an amorphous white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (dd, *J* = 1.3 Hz, 1H), 7.93 (d, *J* = 0.5 Hz, 1H), 7.93 (s, 1H), 1.63 (s, 9H). Characterization data matched the literature report.[83]



115

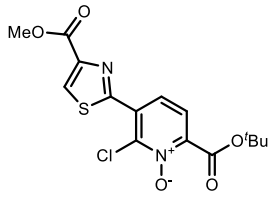
Ethyl 2-(6-(*tert*-butoxycarbonyl)pyridin-3-yl)thiazole-4-carboxylate. 112 (1.98 g, 12.6 mmol, 1.00 equiv.) and **111** (5.84 g, 22.6 mmol, 1.80 equiv.) were weighed in a 250 mL oven dried pressure tube, sealed under N_2, and transferred into a glove box. $Pd(OAc)_2$ (154 mg, 0.629 mmol, 0.050 equiv.), Cy-JohnPhos (661 mg, 1.89 mmol, 0.150 equiv.), and Cs_2CO_3 (8.87 g, 25.1 mmol, 2.00 equiv.) were added to the reaction flask and suspended in anh. and degassed DMF (46.5 mL, freeze-pump-thaw method). The reaction flask was sealed and removed from the glove box. The reaction mixture was stirred vigorously to ensure an even suspension and heated at 110 °C for 12 h. After cooling to rt, the suspension was filtered through a pad of Celite, washed with EtOAc, and concentrated. The mixture was purified by column chromatography on SiO_2 using 3% EtOAc/hexanes to recover 1.44 g of **27**. 11%-17% EtOAc/hexanes was used to give non-polar impurities, and 18% EtOAc/hexanes afforded **115** (3.07 g, 73%) as an amorphous white solid: IR (ATR) $\tilde{\nu}$ = 3130, 2978, 1722, 1565, 1479, 1368, 1308, 1285, 1232, 1184, 1152, 1124, 991, 852,

770 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.25 (dd, *J* = 2.3, 0.8 Hz, 1H), 8.48 (dd, *J* = 8.2, 2.3 Hz, 1H), 8.27 (s, 1H), 8.13 (dd, *J* = 8.2, 0.8 Hz, 1H), 4.46 (q, *J* = 7.1 Hz, 2H), 1.66 (s, 9H), 1.44 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 163.6, 161.1, 150.8, 149.0, 147.9, 134.9, 131.1, 128.3, 124.9, 82.9, 61.9, 28.2, 14.4; FT-HRMS (ESI) *m/z* calcd for $C_{16}H_{18}N_2O_4SNa^+$ [M + Na]$^+$: 357.0879, found 357.0885.



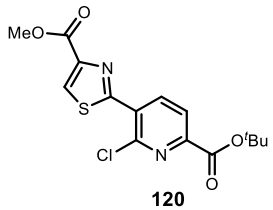
118

Methyl 2-(6-(*tert*-butoxycarbonyl)pyridin-3-yl)thiazole-4-carboxylate. A solution of NaOMe (3.00 M) was prepared by stirring 2.53g of Na in 27.3 mL of anh. MeOH. This solution (22.1 mL, 1.15 equiv.) was slowly added to solution of **115** (19.3 g, 57.5 mmol, 1.00 equiv.) in anh. MeOH (900 mL, 0.064 M) at 0 °C under N_2. The solution stirred for 30 min and quenched with sat. NH_4Cl (2 mL) at 0 °C before concentrating. $NaHCO_3$ was added and the aqueous layer was extracted with EtOAc (3x). The organic extracts were combined, washed with brine, dried (Na_2SO_4), and concentrated. The resulting solid was purified by column chroma2wtography on SiO_2 using 17% EtOAc/hexanes to give **118** (18.3 g, 99%) as an amorphous white solid: IR (ATR) $\tilde{\nu}$ = 3445, 3105, 2922, 2919, 2858, 2360, 2109, 1842, 1727, 1563, 1454, 1368, 1316, 1239, 1137, 1000, 848, 761, 700, 642, 522 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (dd, *J* = 2.3, 0.8 Hz, 1H), 8.47 (dd, *J* = 8.2, 2.3 Hz, 1H), 8.29 (s, 1H), 8.13 (dd, *J* = 8.2, 0.8 Hz, 1H), 4.00 (s, 3H), 1.66 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 163.6, 161.6, 150.9, 148.6, 147.9, 135.0, 131.0, 128.6, 125.0, 82.9, 52.8, 28.2; FT-HRMS (ESI) *m/z* calcd for $C_{15}H_{16}N_2O_4SNa^+$ [M + Na]$^+$: 343.0723, found 343.0728.



119

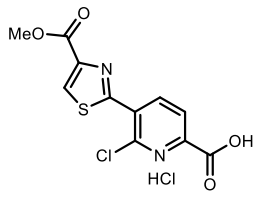
6-(tert-butoxycarbonyl)-2-chloro-3-(4-(methoxycarbonyl)thiazol-2-yl)pyridine 1-oxide. A solution of **118** (4.65 mg, 14.5 mmol, 1.00 equiv.) in CH_2Cl_2 (140 mL, 0.1 M) was treated with 75% *m*CPBA (10.0 g, 43.5 mmol, 3.00 equiv.). After 26 h, *m*CPBa (1.9 g, 1.00 equiv.) was added and after 3 h TLC analysis indicated completion of the reaction. The reaction mixture was quenched with 10% (w/v) aq. $Na_2S_2O_3$, extracted with CH_2Cl_2 (3 x 20 mL), washed with 5 % (w/v) Na_2CO_3, brine, dried (Na_2SO_4), and concentrated. EtOAc was added to precipitate **119** (4.21 g, 86%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, *J* = 1.7 Hz, 1H), 8.31 (d, *J* = 2.3 Hz, 1H), 7.86 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.58 (d, *J* = 8.3 Hz, 1H), 3.99 (d, *J* = 2.1 Hz, 3H), 1.64 (d, *J* = 2.1 Hz, 10H).



120

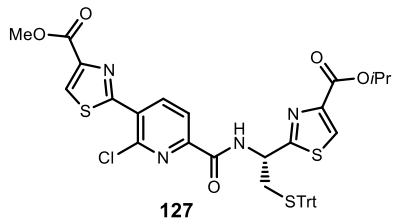
Methyl 2-(6-(*tert*-butoxycarbonyl)-2-chloropyridin-3-yl)thiazole-4-carboxylate (X). 119 (11.3 g, 33.5 mmol, 1.00 equiv.) was dissolved in anh. CH_2Cl_2 (670 mL) and anh. DMF (15.6 mL, 201 mmol, 6.0 equiv.) and cooled to 0 °C under N_2 followed by treatment with $POCl_3$ (6.13 mL, 33.5 mmol, 2.0 equiv.). After 6 h, the reaction mixture was quenched with sat. $NaHCO_3$, (3 mL) and

stirred at 0 °C for 1 h. The biphasic mixture was extracted with CH_2Cl_2 (3 x 20 mL), washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on SiO_2 with 1% EtOAc in CH_2Cl_2 to afford **120** (9.94 g, 84%) as an amorphous yellow solid: IR (ATR) $\tilde{\nu}$ = 3583, 3421, 3106, 2917, 2849, 1718, 1351, 1317, 1251, 1213, 1144, 1082 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.87 (d, *J* = 8.1 Hz, 1H), 8.39 (s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 3.99 (s, 3H), 1.64 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 161.7, 161.6, 149.9, 148.1, 147.3, 140.6, 130.6, 130.0, 123.6, 83.4, 52.8, 28.2; FT-HRMS (ESI) *m/z* calcd for $C_{15}H_{15}ClN_2O_4SNa^+$ [M + Na]$^+$: 377.0339, found 377.0340.



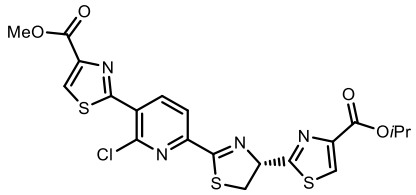
109

6-Chloro-5-(4-(methoxycarbonyl)thiazol-2-yl)picolinic acid hydrochloride. A solution of **120** (5.90 g, 16.6 mmol, 1.00 equiv.) in anh. 1,4-dioxane (165 mL, 0.100 M) at 0 °C was equipped with a gas bubbler venting into the fume hood and purged with a constant stream of anh. hydrogen chloride gas, at such a rate to ensure the HCl becomes dissolved. Once the reaction mixture was saturated with HCl (after 45 min), the gas was leaving the bubbler. The HCl stream was stopped, the bubbler was removed, and the sealed reaction mixture slowly came to rt. After 8 h, TLC analysis indicated complete consumption of **120**, and the flask was concentrated. Residual hydrogen chloride was removed by co-evaporating with toluene several times to afford **109** (5.50 g, 99%) as a white solid.



127

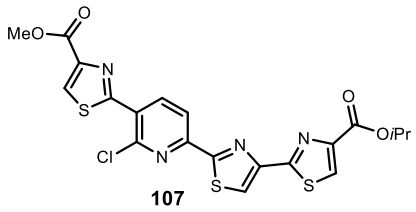
***iso*-Propyl (S)-2-(1-(6-chloro-5-(4-(methoxycarbonyl)thiazol-2-yl)picolinamido)-2-(tritylthio)ethyl) thiazole-4-carboxylate. 110** (11.6 g, 23.7 mmol, 1.00 equiv.) and **109** (7.96 g, 23.7 mmol, 1.00 equiv.) were dissolved in DMF (95 mL) and cooled to 0 °C. *i*-Pr_2NEt (10.3 mL, 59.4 mmol, 2.50 equiv.) and HATU (13.5 g, 35.6 mmol, 1.50 equiv.) were added, the reaction mixture was warmed to rt and stirred for 2 h. Aq. citric acid (400 mL) was added to the reaction mixture and the aqueous layer was extracted with EtOAc (3 x 200 mL). The organic layer was washed with sat. $NaHCO_3$ (200 mL), brine (200 mL), dried (Na_2SO_4), and concentrated. The compound was purified by column chromatography on SiO_2 using 17% to 25% to 33% to 50% EtOAc/hexanes to afford **127** (13.1 g, 72%) as a white solid: $[\alpha]_D^{25} = +1.1$ (c = 1.00, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3436, 2096, 1641, 1508, 1348, 1245, 1215, 1103, 746 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.91 (d, *J* = 8.0 Hz, 1H), 8.40 (s, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 8.01 (s, 1H), 7.46 – 7.39 (m, 5H), 7.34 – 7.13 (m, 10H), 5.32 – 5.16 (m, 2H), 4.00 (s, 3H), 3.14 (dd, *J* = 12.8, 7.3 Hz, 1H), 2.96 (dd, *J* = 12.9, 5.9 Hz, 1H), 1.37 (dd, *J* = 6.3, 1.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 162.0, 161.7, 161.5, 160.8, 149.7, 147.9, 147.4, 146.9, 144.4, 141.3, 130.7, 130.0, 129.7, 128.2, 127.4, 127.1, 121.8, 69.2, 67.7, 52.8, 50.69, 36.51, 22.0; FT-HRMS (ESI) *m/z* calcd for $C_{39}H_{33}ClN_4O_5S_3Na^+$ $[M + Na]^+$: 791.1194, found 791.1199.



134

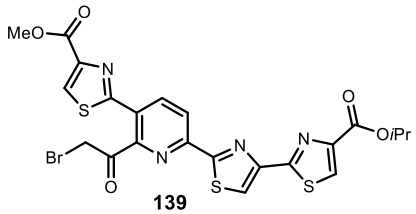
***iso*-Propyl (S)-2'-(6-chloro-5-(4-(methoxycarbonyl)thiazol-2-yl)pyridin-2-yl)-4',5'-dihydro-[2,4'-bithiazole]-4-carboxylate. 127** (8.90 g, 10.3 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (90 mL) and cooled to 0 °C under N_2. TFA (10.0 mL) and Et_3SiH (3.37 mL, 6.00 mmol, 2.00 equiv.) were added dropwise and the reaction mixture stirred for 1 h after which TLC analysis showed complete consumption of the starting material. The reaction mixture was quenched with solid $NaHCO_3$ (30.0 g). The reaction mixture was diluted with water and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The organic layer was washed with brine (100 mL), dried (Na_2SO_4), and concentrated equally into four 3-neck 500 mL RBF and dried *in vacuo*. $MoO_2(acac)_2$ (84.0 mg, 0.257 mmol, 0.100 equiv.) was added to the 3-neck round bottom flask and a Dean stark apparatus was attached. The apparatus and flask was evacuated and purged three times with N_2. The reaction mixture was suspended in 265 mL of anh. and degassed toluene and heated to 130 °C to achieve azeotropic removal of water. After 13 h TLC analysis indicated complete consumption of starting material. The reaction mixtures were then recombined, concentrated, and suspended in CH_2Cl_2. Sat. $NaHCO_3$ (150 mL) was added to the solution, the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL) and the organic layers were washed once with brine (150 mL), dried (Na_2SO_4), and concentrated. The crude material was purified by column chromatography on SiO_2 using 11% EtOAc/CH_2Cl_2 to afford **107** as an amorphous yellow solid (367 mg, 4%) and **134** (6.73 g, 82%) as a white solid: $[\alpha]_D^{25} = -6.3$ (c = 0.2, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3421, 3082, 2924, 2688, 2320, 2111, 1710, 1598, 1540, 1471, 1349, 1208, 1095, 993, 907, 853,

734, 465 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, *J* = 8.1 Hz, 1H), 8.24 (d, *J* = 8.1 Hz, 1H), 6.17 (dd, *J* = 9.4, 8.3 Hz, 1H), 5.29 (h, *J* = 6.3 Hz, 1H), 3.74 (dd, *J* = 11.5, 8.3 Hz, 1H), 1.39 (dd, *J* = 6.3, 1.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 171.8, 161.7, 161.6, 161.0, 151.1, 148.0, 147.5, 147.3, 140.5, 130.1, 130.0, 127.5, 120.8, 78.6, 69.3, 52.8, 38.5, 22.1, 22.0; FT-HRMS (ESI) *m/z* calcd for $C_{20}H_{17}ClN_4O_4S_3Na$ $[M + Na]^+$: 530.9993, found 530.9998.



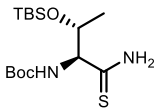
107

***iso*-Propyl 2'-(6-chloro-5-(4-(methoxycarbonyl)thiazol-2-yl)pyridin-2-yl)-[2,4'-bithiazole]-4-carboxylate. 134** (6.73 g, 13.3 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (130 mL) and freshly prepared MnO_2[85-86] (11.5 g, 133 mmol, 10 equiv.) was added at rt. The reaction mixture stirred for 24 h and the reaction mixture was filtered over Celite and rinsed with CH_2Cl_2 and EtOAc. The crude mixture was purified by column chromatography on SiO_2 (50% EtOAc/CH_2Cl_2) to **107** (6.72 g, >99%) as an amorphous pale yellow solid: IR (ATR) $\tilde{\nu}$ = 3418, 3111, 2922, 2852, 2330, 1708, 1581, 1462, 1352, 1243, 1105, 1016, 910, 835, 768, 495 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, *J* = 8.1 Hz, 1H), 8.39 (d, *J* = 0.5 Hz, 1H), 8.34 (s, 1H), 8.30 (d, *J* = 8.2 Hz, 1H), 8.19 (d, *J* = 0.5 Hz, 1H), 5.30 (h, *J* = 6.3 Hz, 1H), 4.01 (s, 3H), 1.42 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 162.9, 161.9, 161.8, 161.0, 151.2, 150.3, 148.6, 147.8, 147.1, 140.9, 129.7, 128.9, 127.9, 121.3, 118.9, 69.4, 52.8, 22.1; FT-HRMS (ESI) *m/z* calcd for $C_{20}H_{15}ClN_4O_4S_3Na^+$ $[M + Na]^+$: 528.9842, found 528.9843.



139

***iso*-Propyl 2'-(6-(2-bromoacetyl)-5-(4-(methoxycarbonyl)thiazol-2-yl)pyridin-2-yl)-[2,4'-bithiazole]-4-carboxylate. 135** (752 mg, 1.38 mmol, 1.00 equiv.) was dissolved in 4:1 THF/H_2O. NBS (355 mg, 2.00 mmol, 1.45 equiv.) was added and the reaction stirred for 1 h. After this time, sat. $NaHCO_3$ was added and the aqueous layer was extracted with EtOAc (3x). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The material was purified by chromatography on SiO_2 using 20% EtOAc/20% CH_2Cl_2/60% Hexanes to 25% EtOAc/ 25% CH_2Cl_2/ 60% hexanes to 33% EtOAc/33% CH_2Cl_2/33 hexanes to afford **139** (647 mg, 79%) as a yellow solid.



138

***tert*-Butyl ((2S,3R)-1-amino-3-((*tert*-butyldimethylsilyl)oxy)-1-thioxobutan-2-yl)carbamate.** N-Boc-threonine (8.50 g, 36.4 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C. Imidazole (7.43 g, 109.2 mmol, 3.00 equiv.) and TBS-Cl (11.0 g, 72.8 mmol, 2.0 equiv.) were added and the reaction mixture was allowed to warm to rt, stirred for 24 h, and was concentrated. The pH of the solution was adjusted to 3 using aq. citric acid and the mixture was extracted with EtOAc (3 x 100 mL). The organic layers were washed with brine (100 mL), dried (Na_2SO_4), and concentrated. The material was purified by column chromatography on SiO2 using

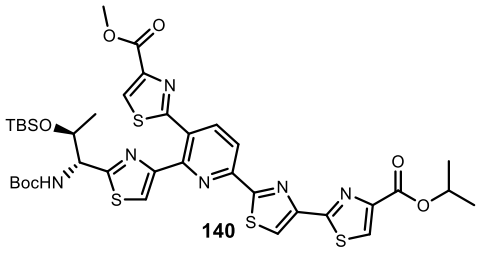
17% EtOAc/hexanes to remove excess TBS reagent and 33% EtOAc/hexanes to elute the carboxylic acid as a clear oil.

The carboxylic acid (5.10 g, 15.6 mmol, 1.0 equiv.) was dissolved in THF (60 mL) and cooled to 0 °C. Et_3N (6.52 mL, 46.8 mmol, 3.00 equiv.) was added followed by dropwise addition of ethyl chloroformate (3.72 mL, 39.0 mmol, 2.50 equiv.). After stirring for 1.5 h, 28% NH_4OH (15 mL) was added and the solution was allowed to warm to rt overnight. The reaction mixture was then concentrated and diluted with EtOAc (100 mL) and sat. $NaHCO_3$ solution (100 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL) and the organic layers were washed with brine (100 mL), dried (Na_2SO_4), and concentrated to give the amide as a clear oil.

This crude amide was dissolved in pyridine (40 mL) and cooled to 0 °C. $POCl_3$ (3.71 mL, 40.56 mmol, 2.60 equiv.) was added dropwise to the reaction mixture stirred for 1.5 h before pouring over ice. The mixture was then diluted with water (100 mL) and extracted with Et_2O (4 x 100 mL). The organic layers were combined and washed sequentially with 20% aq. $NaHSO_4$ (2 x 100mL), water (100 mL), brine (100 mL), dried (Na_2SO_4), and concentrated.

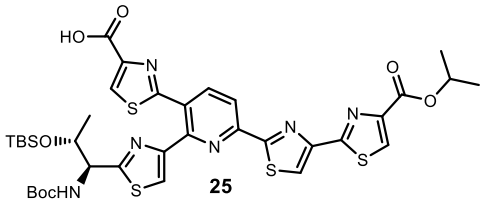
This mixture was then dissolved in MeOH (40 mL) and aq. $(NH_4)_2S$ (40% wt., 5.30 mL, 31.2 mmol, 2.00 equiv.) was added. The reaction mixture was stirred for 16 h, concentrated, partitioned between water (50 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the organic layers were washed with brine (50 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on SiO_2 using 14% EtOAc/hexanes to **138** (4.07 g, 74%) as a clear oil: $[\alpha]_D^{25} =$ + 40.4 (c = 1.0, $CDCl_3$); IR (ATR) $\tilde{\nu}$ = 3344, 3188, 2930, 2729, 2359, 2092, 1775, 1699, 1616, 1486, 1367, 1252, 1158, 1062, 911, 834, 777, 733, 560 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.54 (s, 1H), 5.67 (s, 1H), 4.56 (s, 1H), 4.37 – 4.17

(m, 2H), 1.46 (d, *J* = 1.5 Hz, 9H), 1.19 – 1.13 (m, 3H), 0.88 (s, 12H), 0.11 (d, *J* = 9.4 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 70.7, 28.4, 25.9, 18.0, -4.6, -4.8; FT-HRMS (ESI) *m/z* calcd for $C_{15}H_{32}N_2O_3SSiNa^+$ $[M + Na]^+$: 371.1801, found 371.1794.



***iso*-Propyl 2'-(6-(2-((5S,6R)-2,2,3,3,5,10,10-heptamethyl-8-oxo-4,9-dioxa-7-aza-3-silaundecan-6-yl)thiazol-4-yl)-5-(4-(methoxycarbonyl)thiazol-2-yl)pyridin-2-yl)-[2,4'-bithiazole]-4-carboxylate. 139** (104 mg, 0.176 mmol, 1.00 equiv.) and $NaHCO_3$ (148 mg, 1.76 mmol, 10.0 equiv.) were dissolved in anh. 1,2-dimethoxyethane (2.0 mL) under N_2. The resulting suspension was cooled to 0 °C for 15 min followed by addition of a solution of **138** (122 mg, 0.351 mmol, 2.00 equiv.) in 1,2-dimethoxyethane (0.5 mL). The reaction mixture was allowed to warm to rt and stirred for 16 h. The reddish- brown suspension was filtered through Celite and rinsed several times with 1,2-dimethoxyethane. The solution was concentrated used in next step without further purification. 1,2-dimethoxyethane (20 mL) was added to the reddish oil and cooled to -20 °C under N_2. After 15 min, 2,6-lutidine (41 μL, 0.35 mmol, 2.0 equiv.) and TFAA (27 μL, 0.19 mmol, 1.1 equiv.) were added. The reaction mixture was stirred for 5 min at -20 °C, diluted with $CHCl_3$, and then washed successively with aq. citric acid, sat. $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated. The crude material was purified by column chromatography on SiO_2 using 33% EtOAc/hexanes to afford **140** (103 mg, 77% b.r.s.m.) as a yellow solid: $[\alpha]_D^{25} = -19.0$ (c = 1.0, $CHCl_3$); IR (ATR) $\tilde{\nu}$ = 3418, 3117, 2927, 2360, 1717, 1581, 1487, 1366, 1308, 1210, 1168, 1093,

1002, 910, 835, 777, 751, 683, 460 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 – 8.23 (m, 4H), 8.19 (s, 1H), 7.88 (s, 1H), 5.43 (d, *J* = 8.2 Hz, 1H), 5.31 (hept, *J* = 6.3 Hz, 1H), 4.79 (dd, *J* = 8.3, 2.6 Hz, 1H), 4.29 (dd, *J* = 6.3, 2.7 Hz, 1H), 3.96 (s, 3H), 1.49 (s, 9H), 1.41 (d, *J* = 6.3 Hz, 7H), 1.06 (d, *J* = 6.2 Hz, 3H), 0.81 (s, 9H), -0.01 (s, 3H), -0.17 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 168.7, 166.1, 163.2, 161.9, 161.1, 155.6, 152.6, 151.1, 151.0, 150.0, 148.5, 146.7, 140.3, 129.6, 128.8, 127.7, 121.5, 120.7, 118.4, 80.2, 77.4, 70.0, 69.3, 58.6, 52.7, 29.8, 28.5, 25.9, 22.1, 19.9, 18.0, -4.6, -5.1; FT-HRMS (ESI) *m/z* calcd for $C_{37}H_{46}N_6O_7S_4SiNa^+$ $[M + Na]^+$: 865.1972, found 865.1984.



25

2-(2-(2-((5R,6S)-2,2,3,3,5,10,10-Heptamethyl-8-oxo-4,9-dioxa-7-aza-3-silaundecan-6-yl)thiazol-4-yl)-6-(4-(isopropoxycarbonyl)-[2,4'-bithiazol]-2'-yl)pyridin-3-yl)thiazole-4-carboxylic acid (X). Me_3SnOH (57 mg, 0.32 mmol, 2.0 equiv.) was added to a solution of **140** (134 mg, 0.16 mmol, 1.0 equiv.) in 1,2-dichloroethane (1.6 mL) in a sealed tube and heated to 80 °C under N_2 for 20 h.[87] The reaction mixture was quenched with aq. citric acid and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The crude material was purified by column chromatography on SiO_2 using. 50% EtOAc/hexanes to remove unreacted starting material followed by elution using a gradient of 5% MeOH/CH_2Cl_2 to afford the product **25** (63.8 mg, 53%, b.r.s.m.) as a yellow solid

3.5.3 NMR Spectra

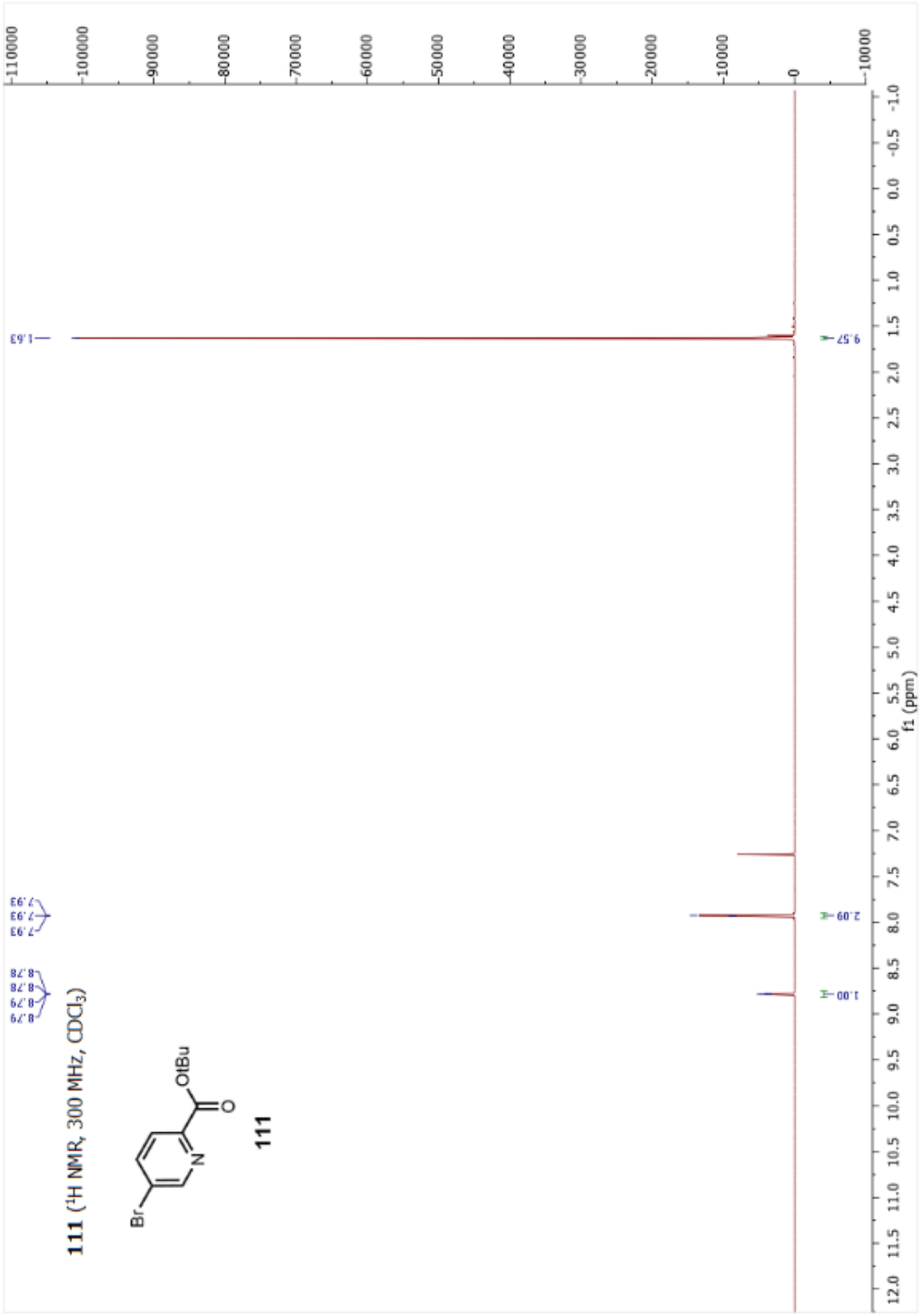


Figure 3.1 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **111**.

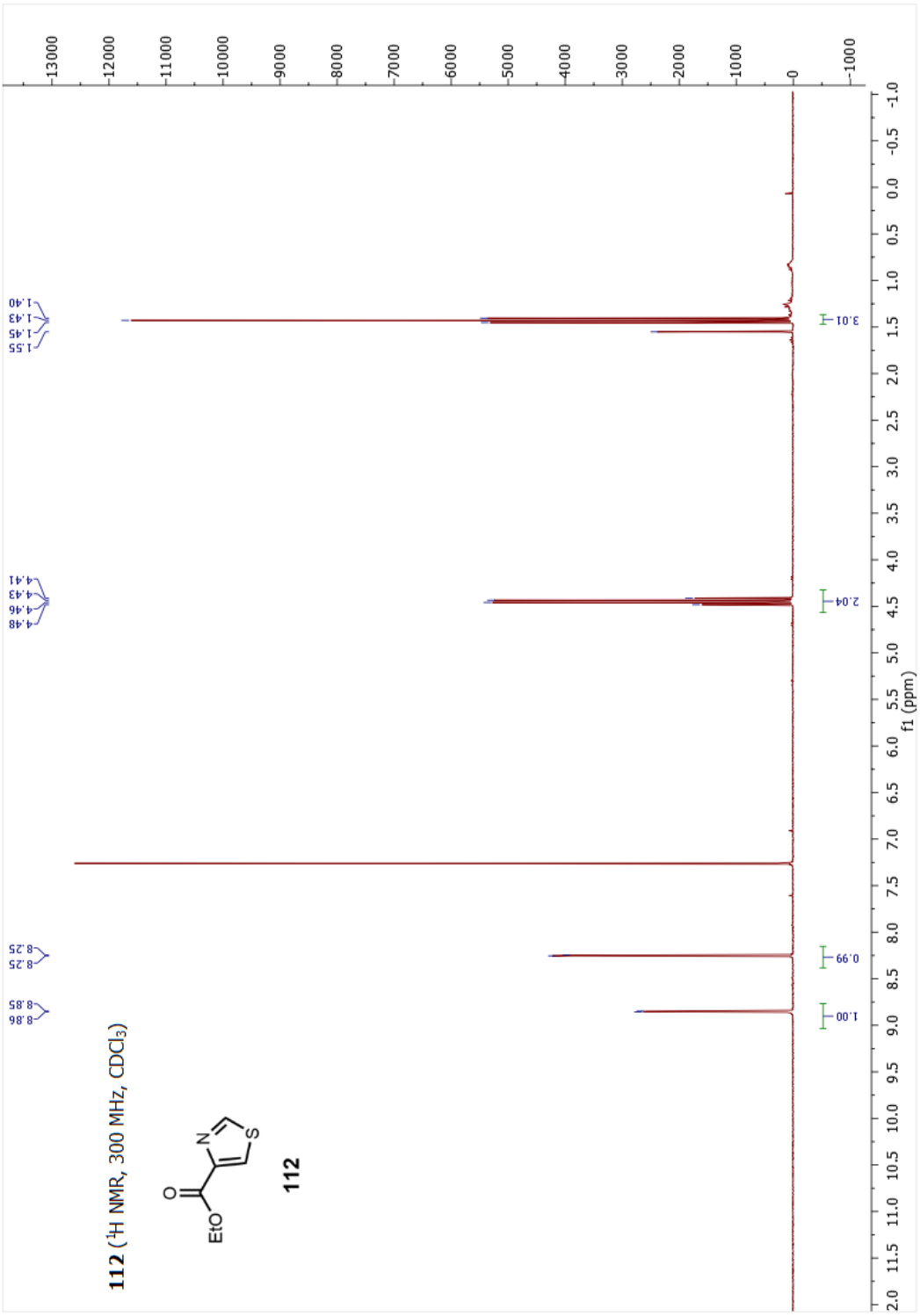


Figure 3.2 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **112**.

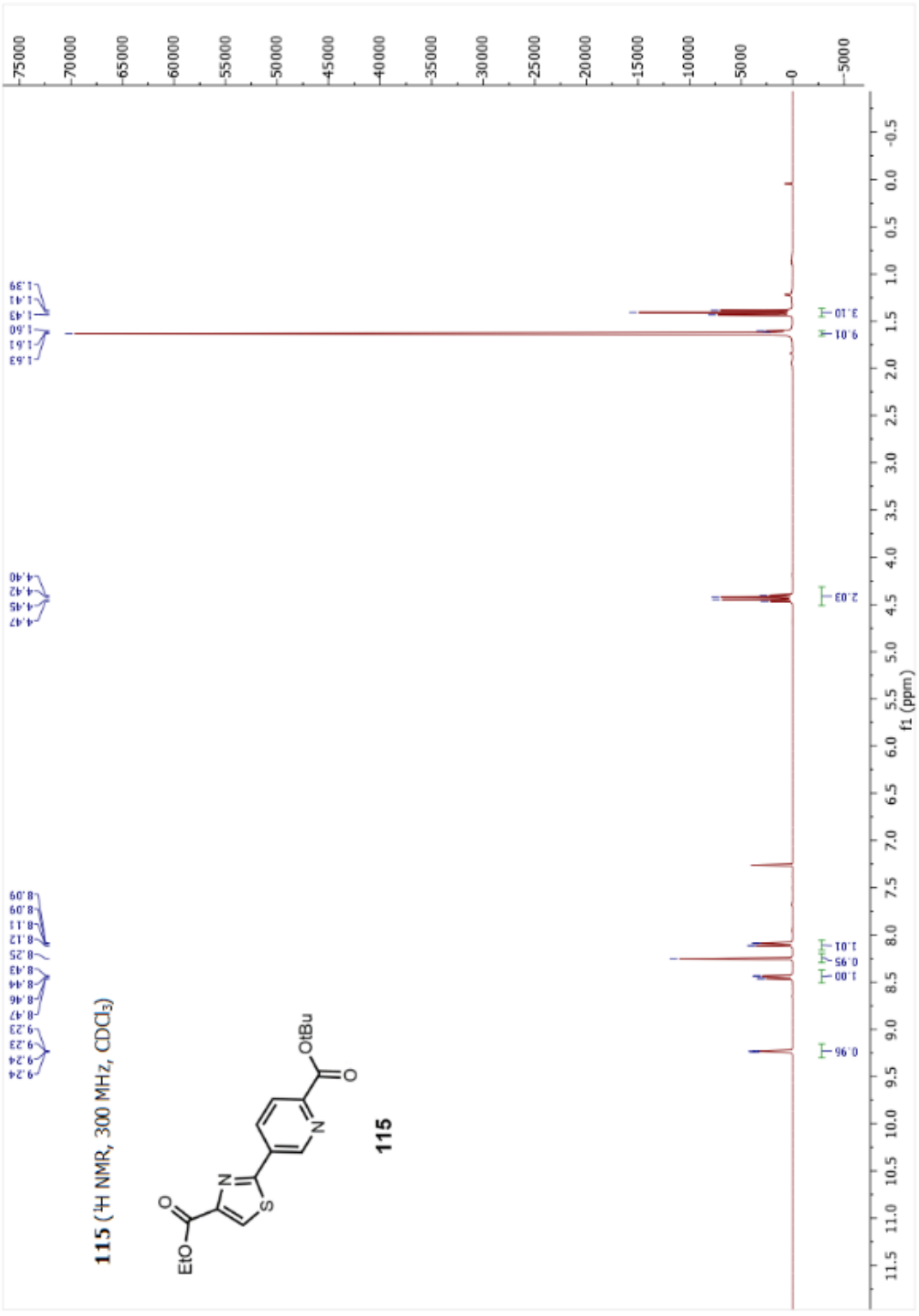


Figure 3.3 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **115**.

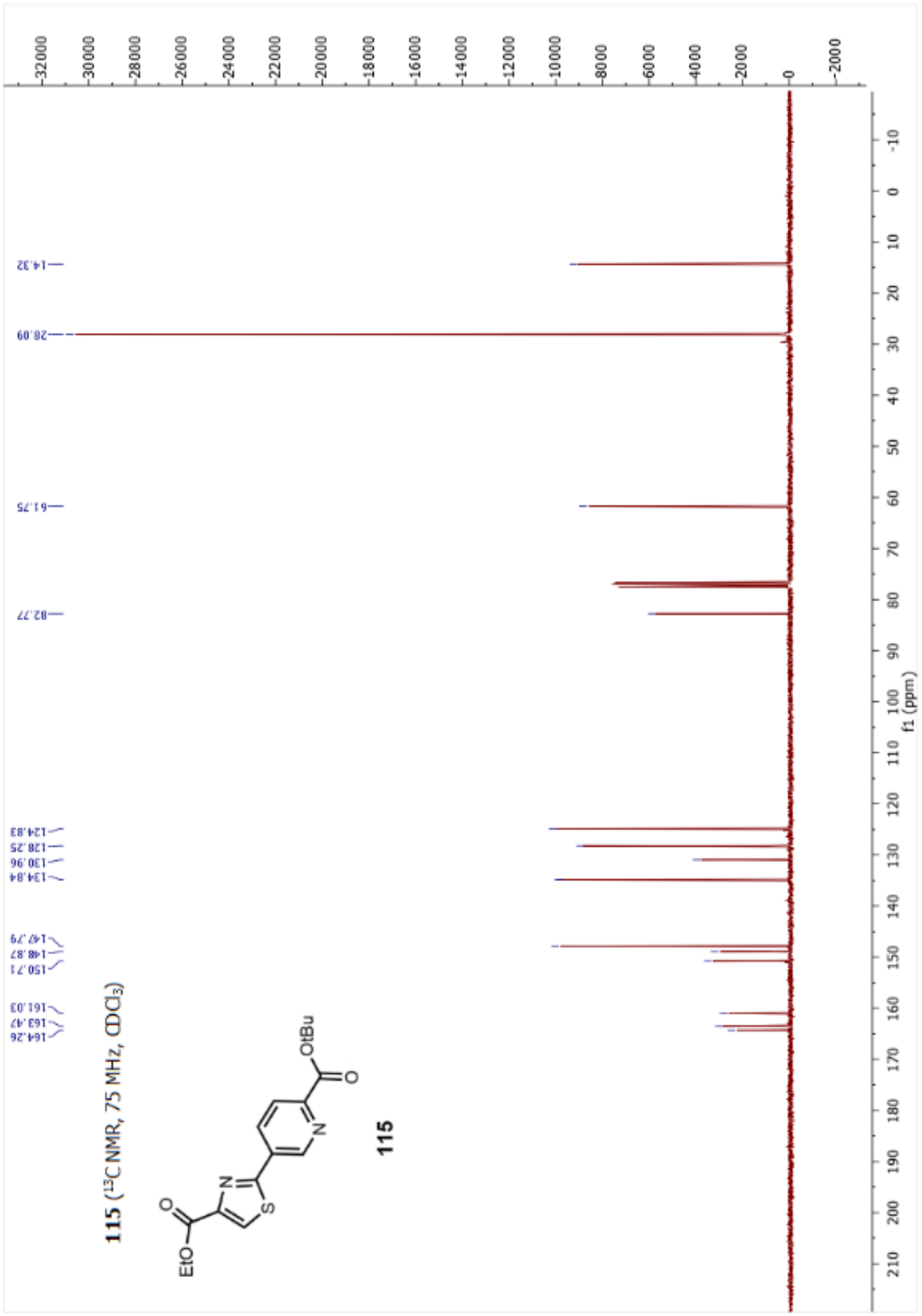


Figure 3.4 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **115**.

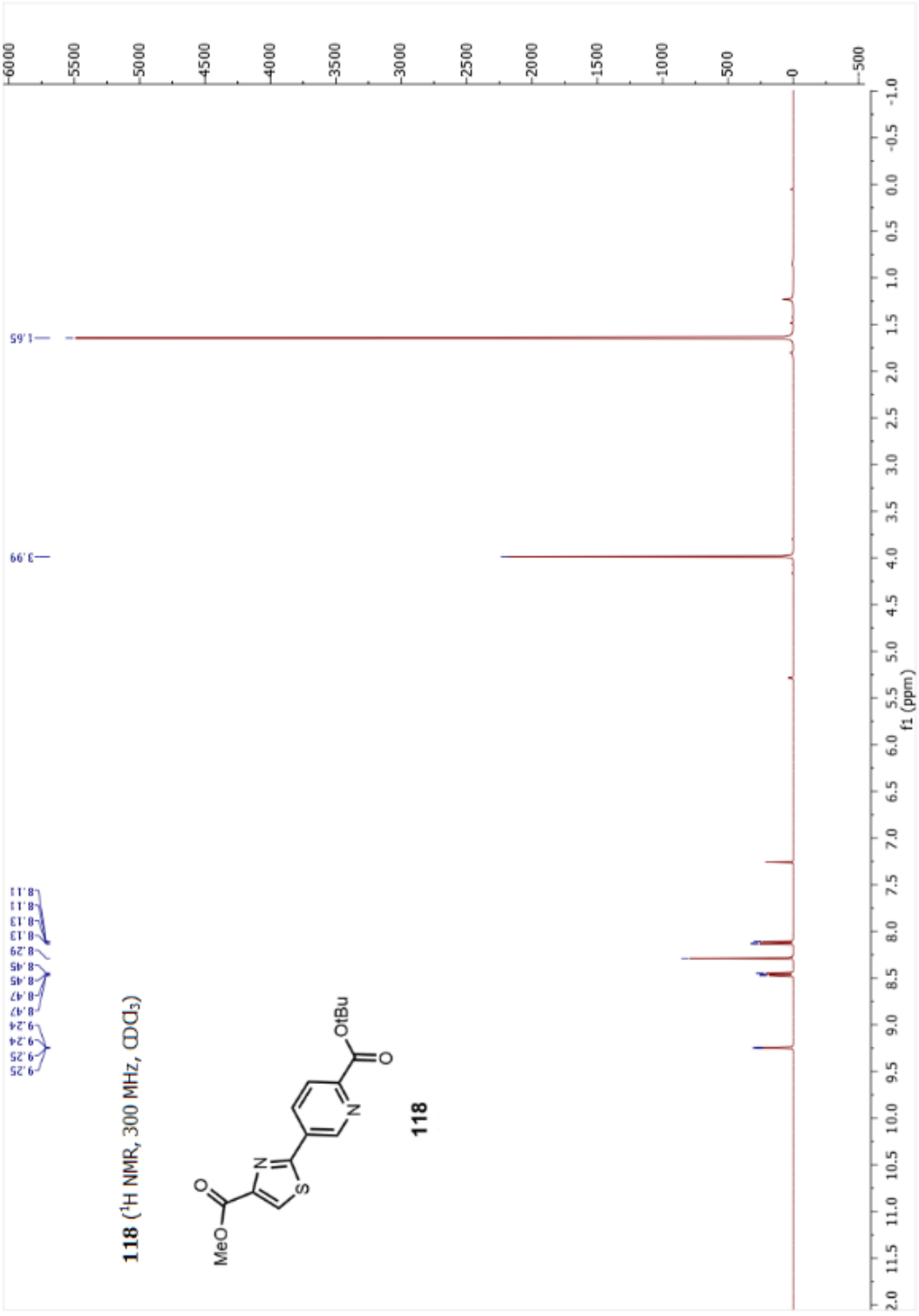


Figure 3.5 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **118**.

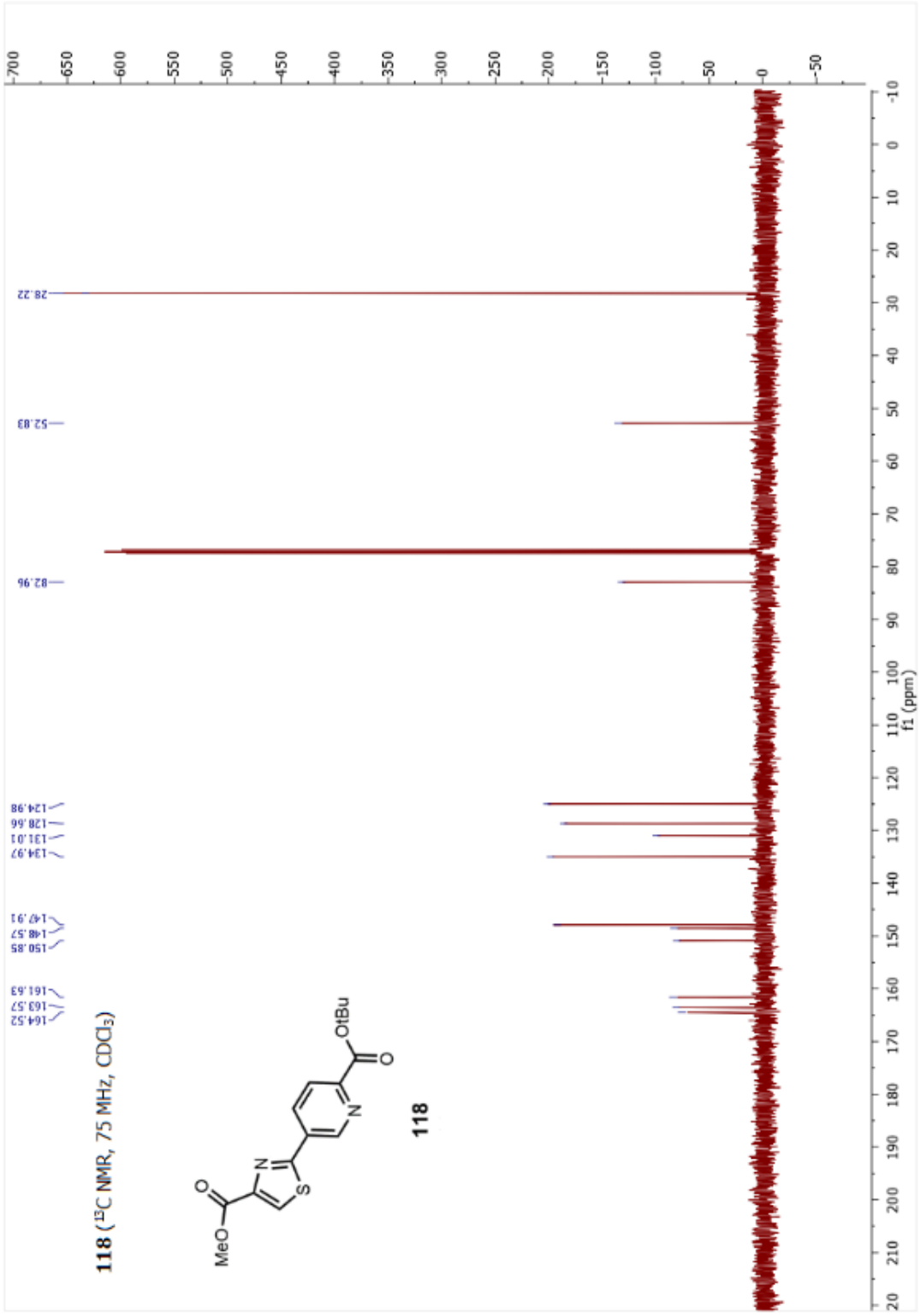


Figure 3.6 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **118**.

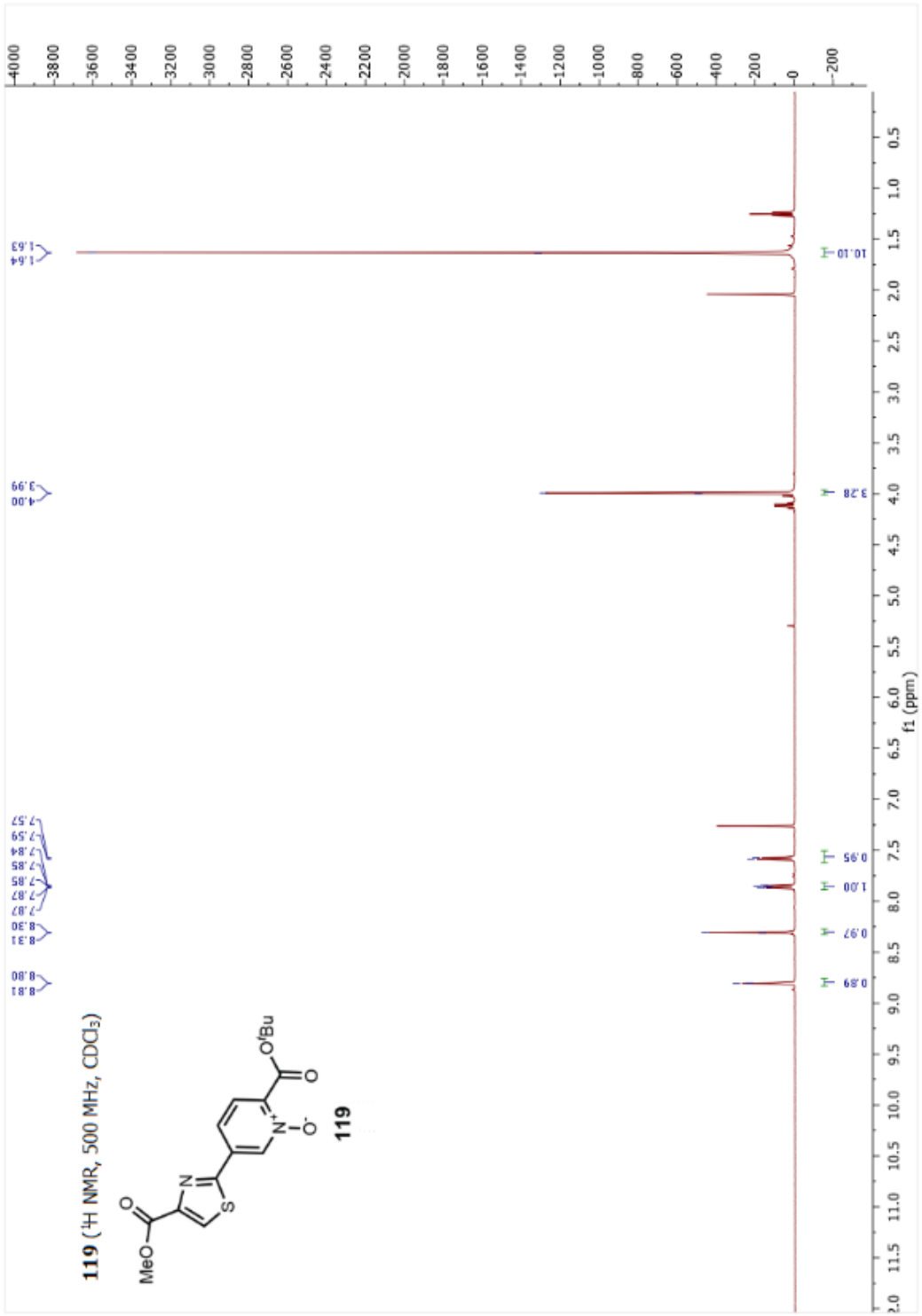


Figure 3.7 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **119**.

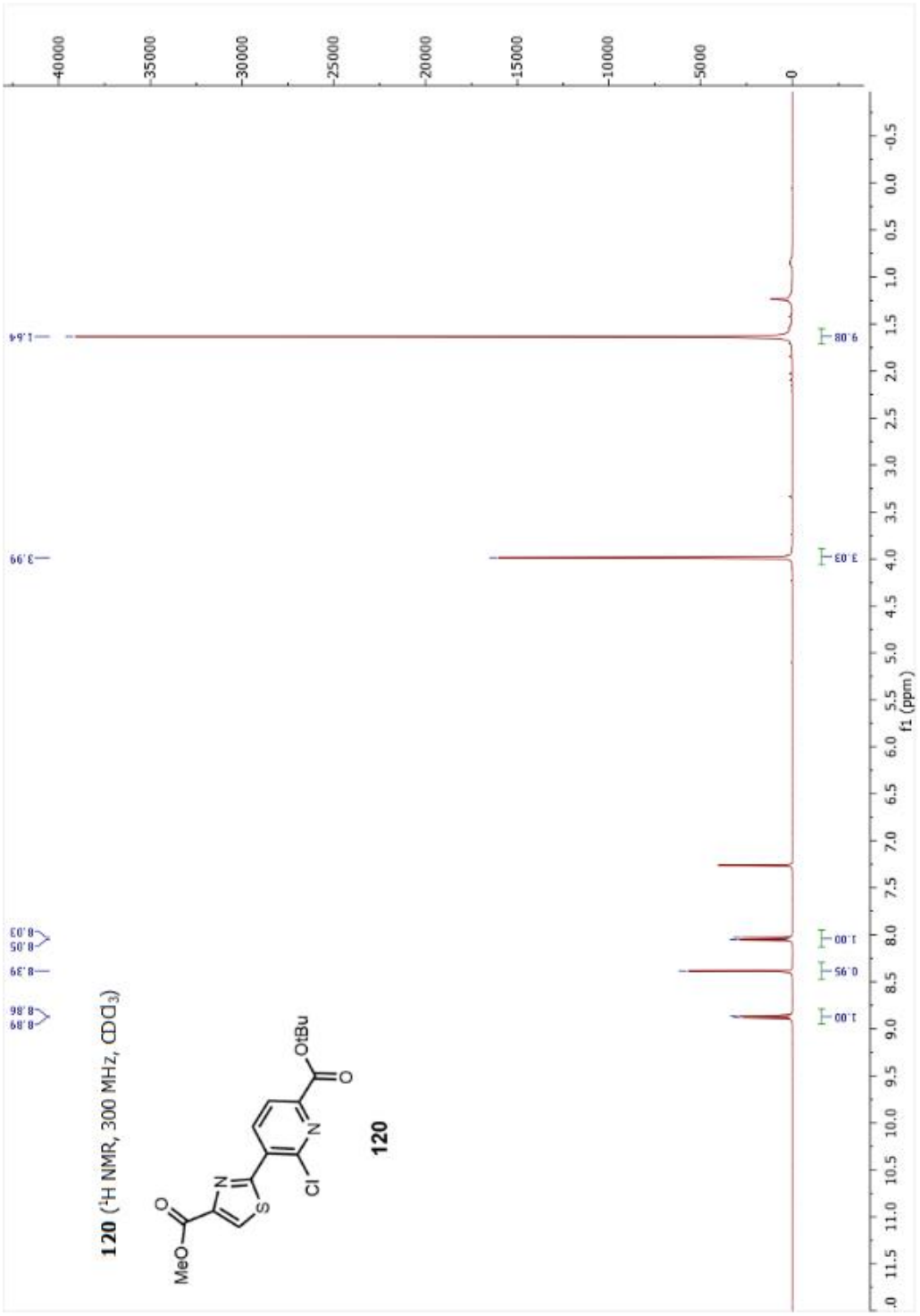


Figure 3.8 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **120**.

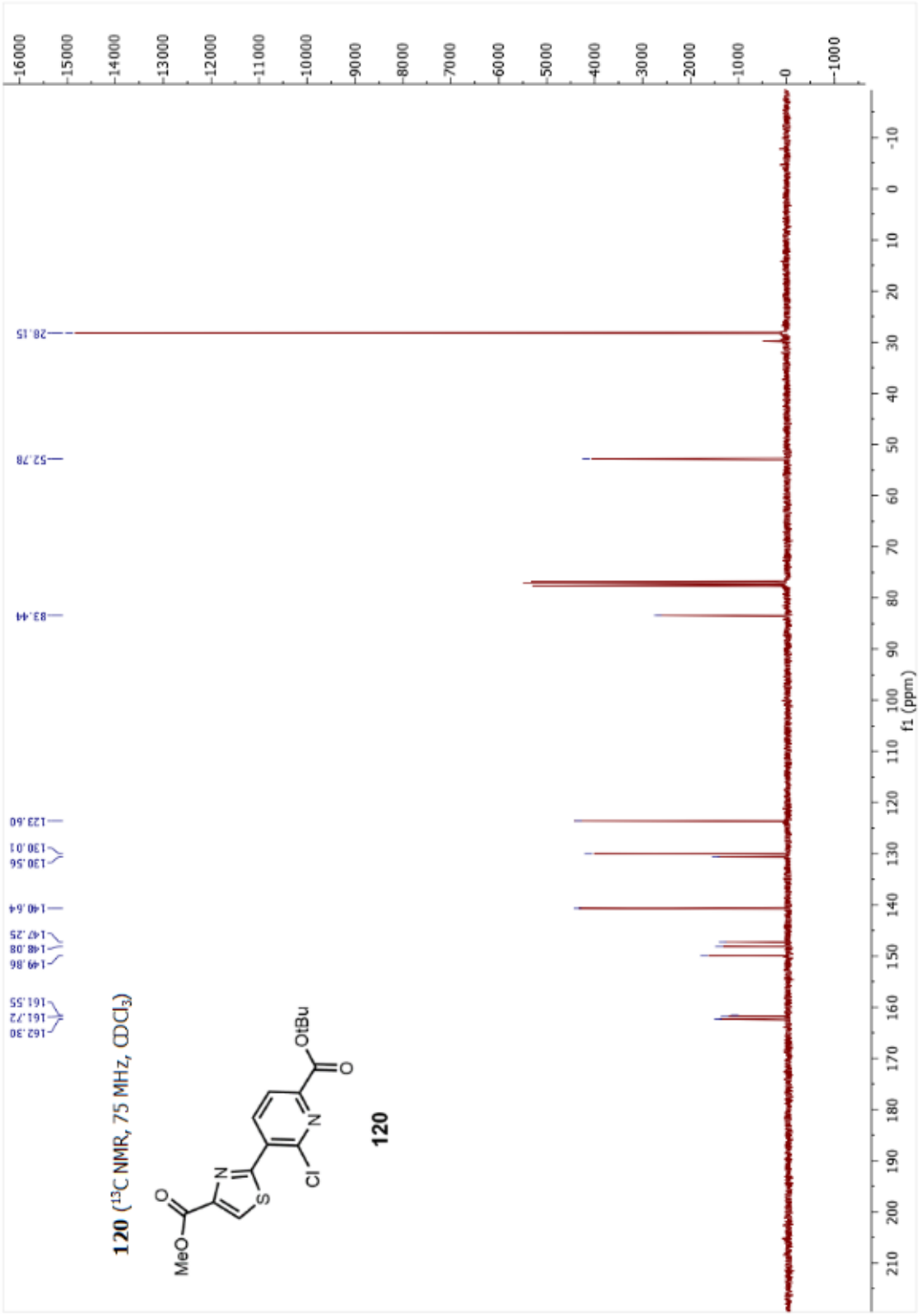


Figure 3.9 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **120**.

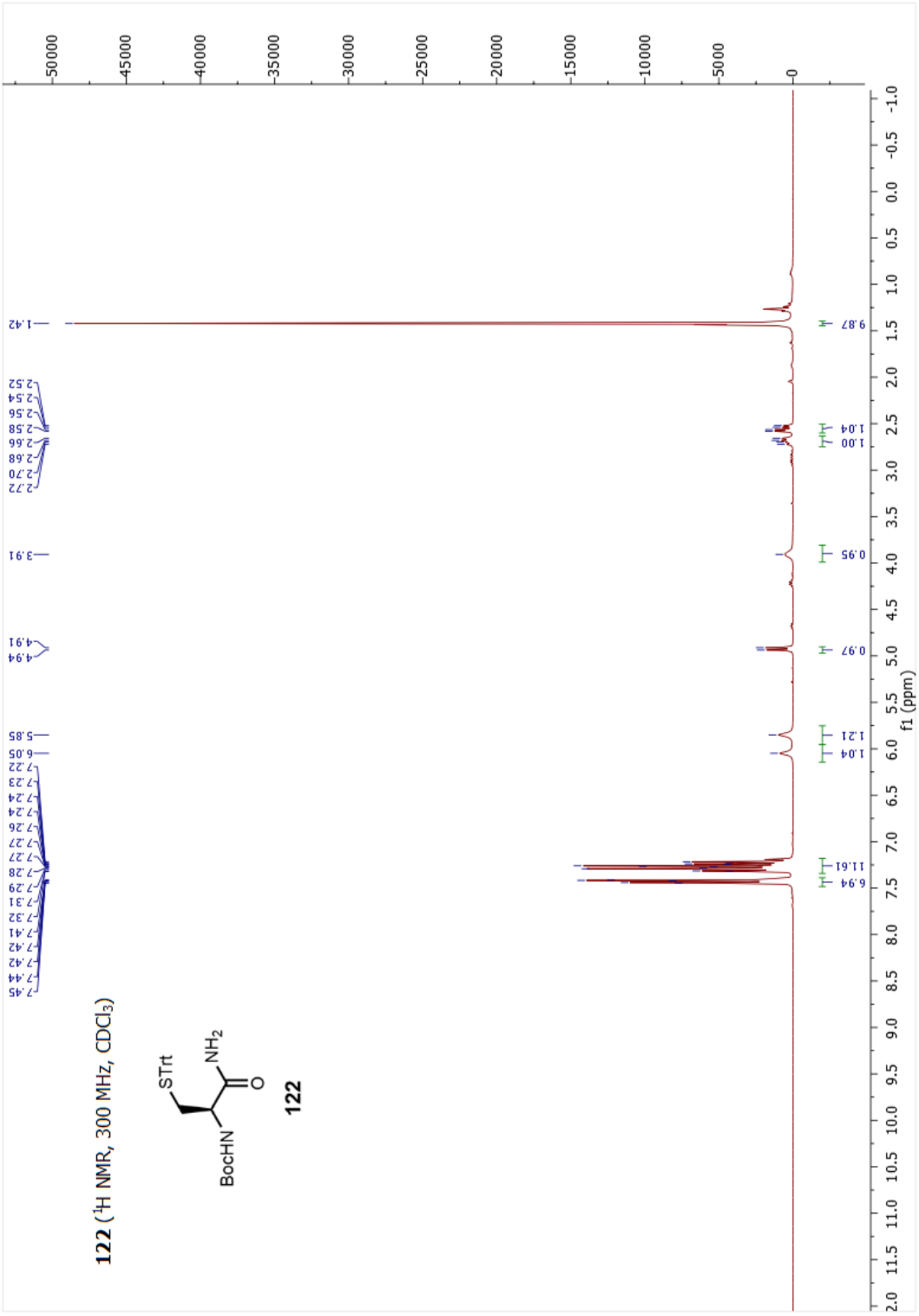


Figure 3.10 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **122**.

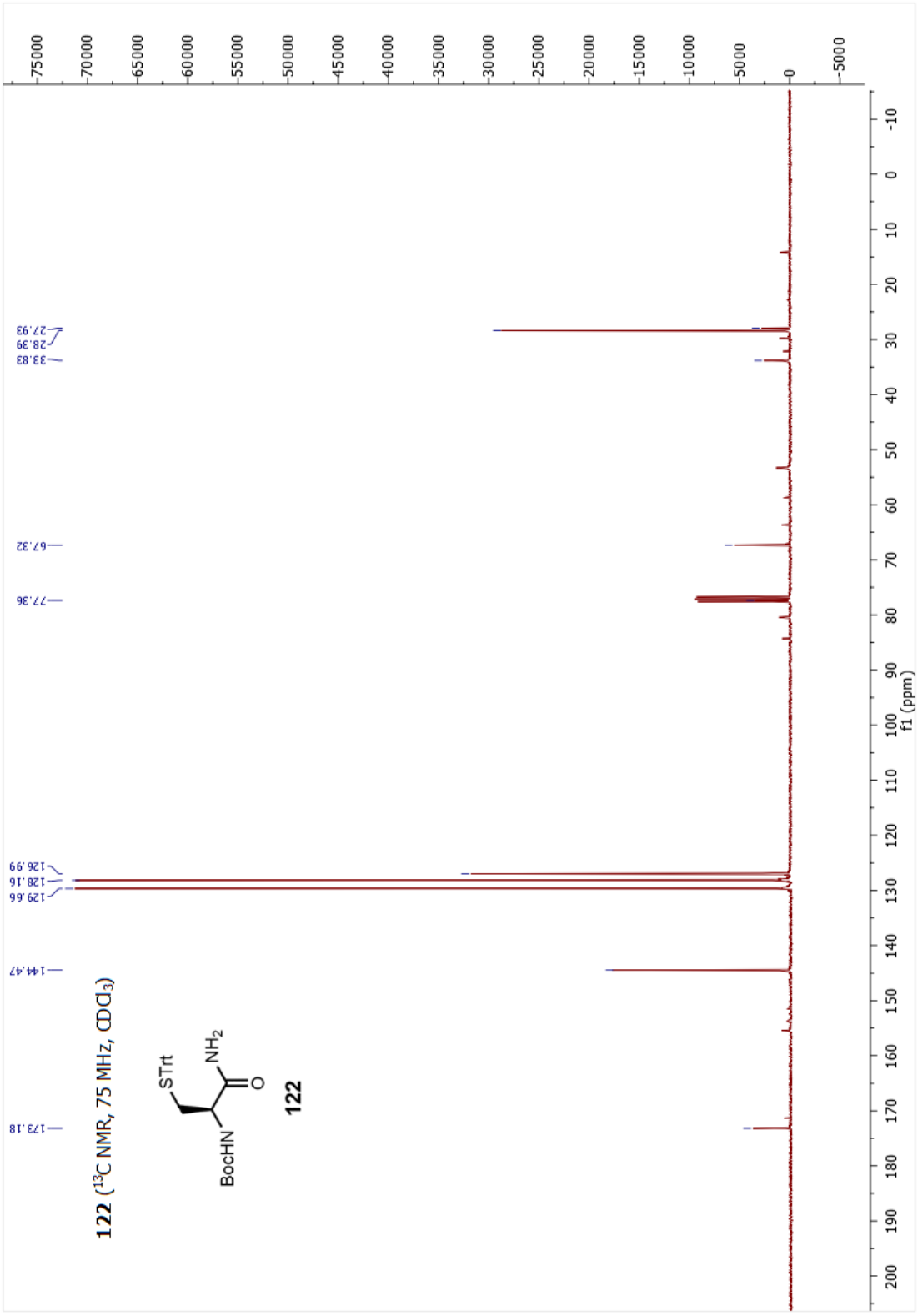


Figure 3.11 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **122**.

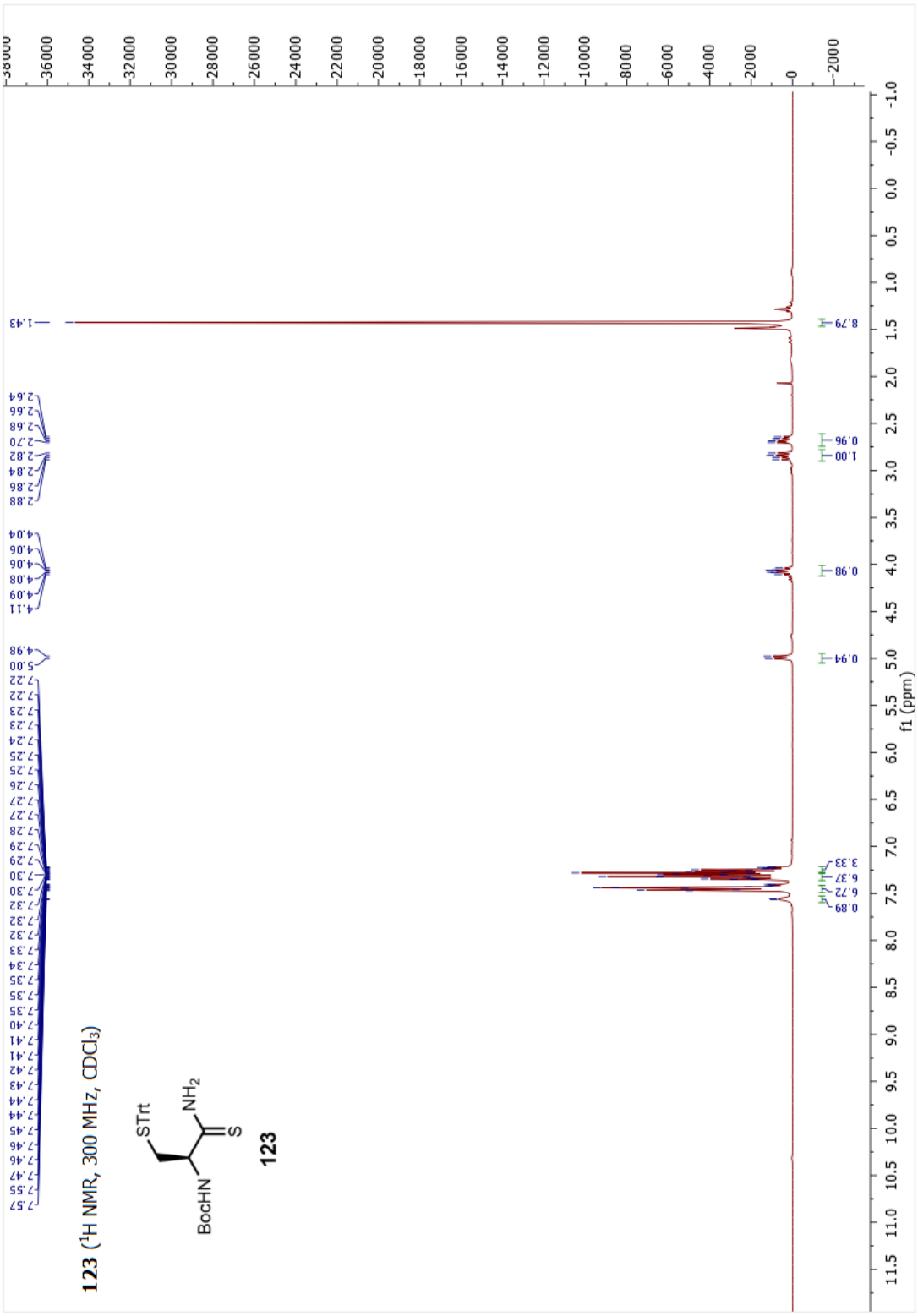


Figure 3.12 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **123**.

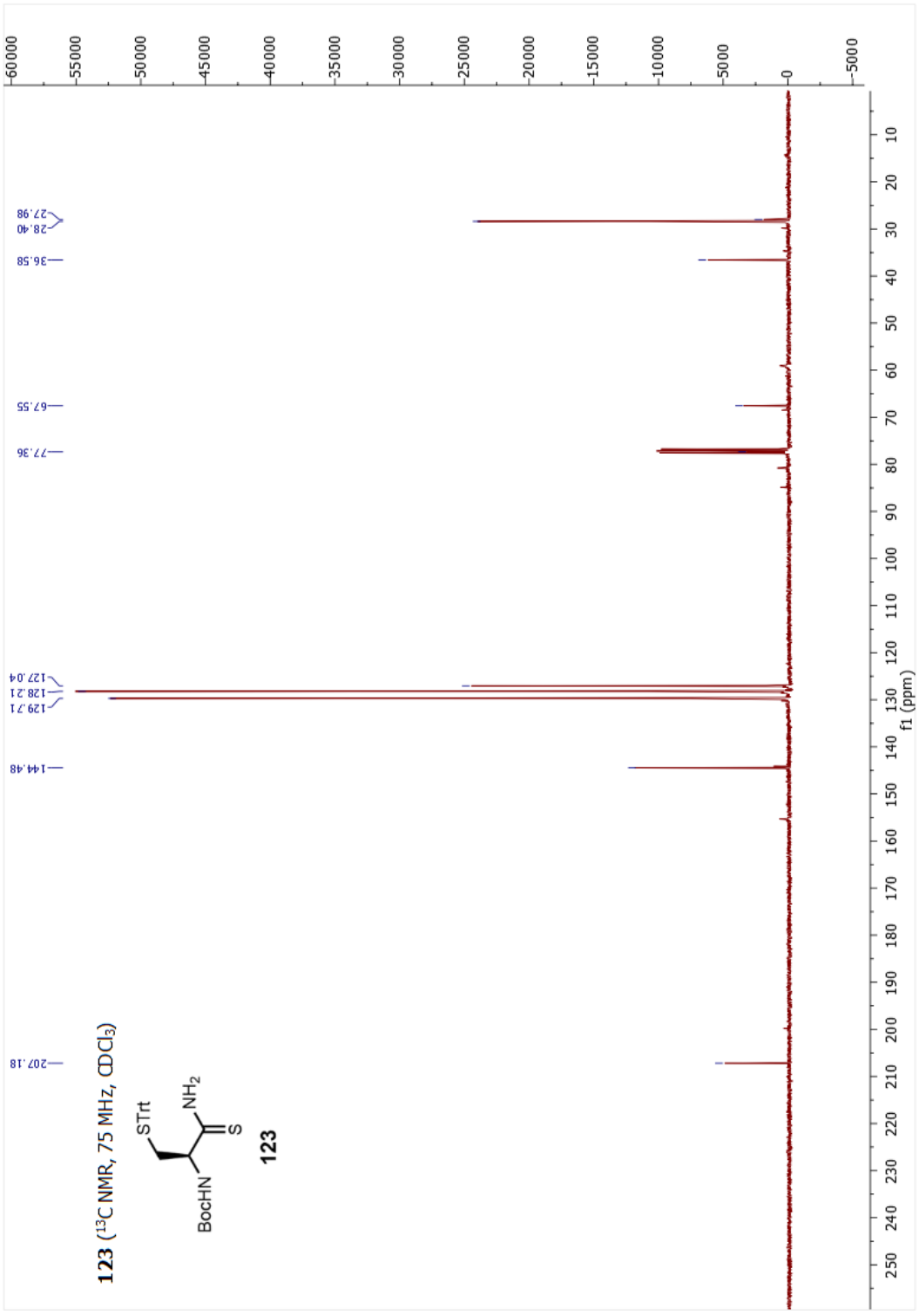


Figure 3.13 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **123**.

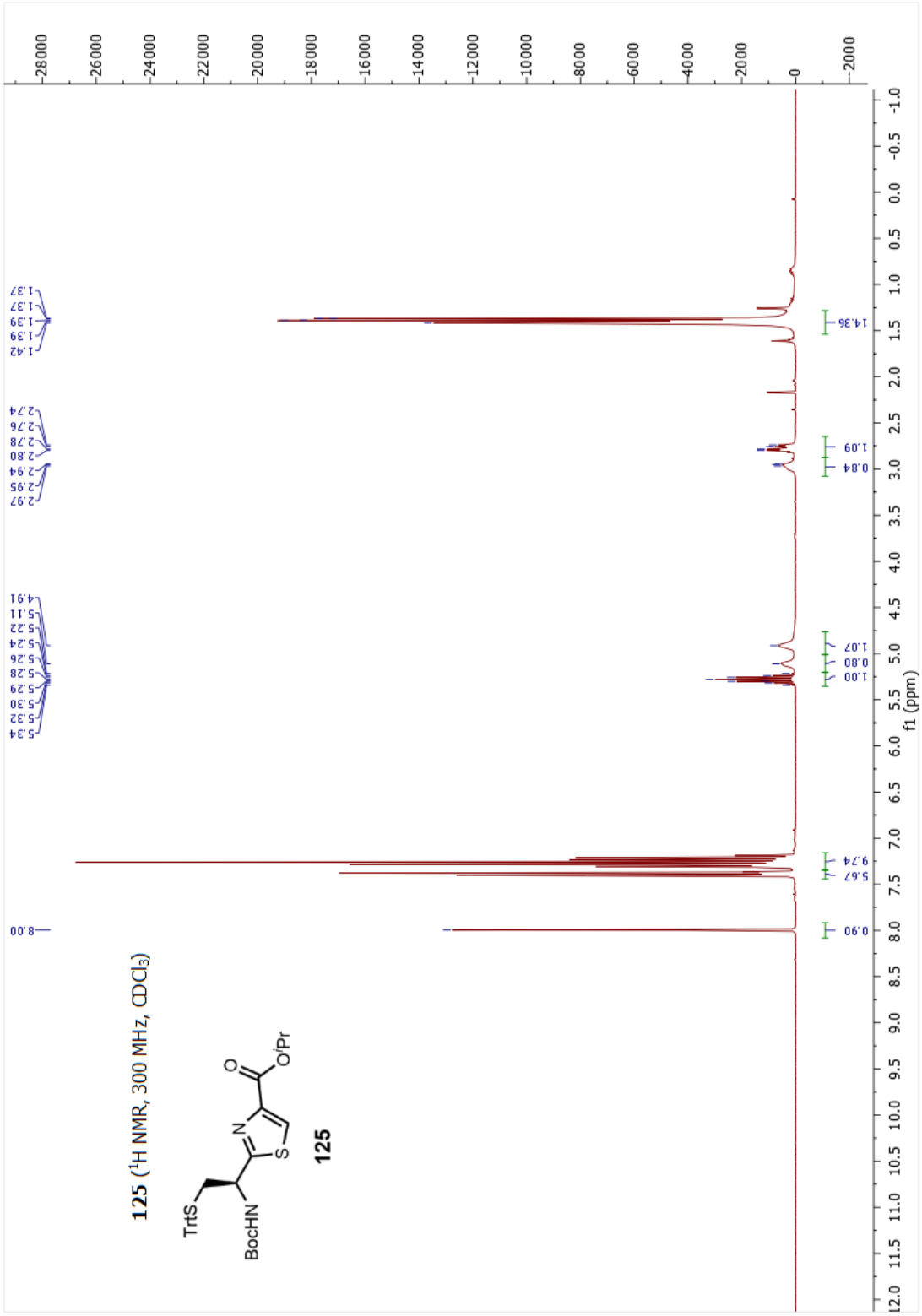


Figure 3.14 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **125**.

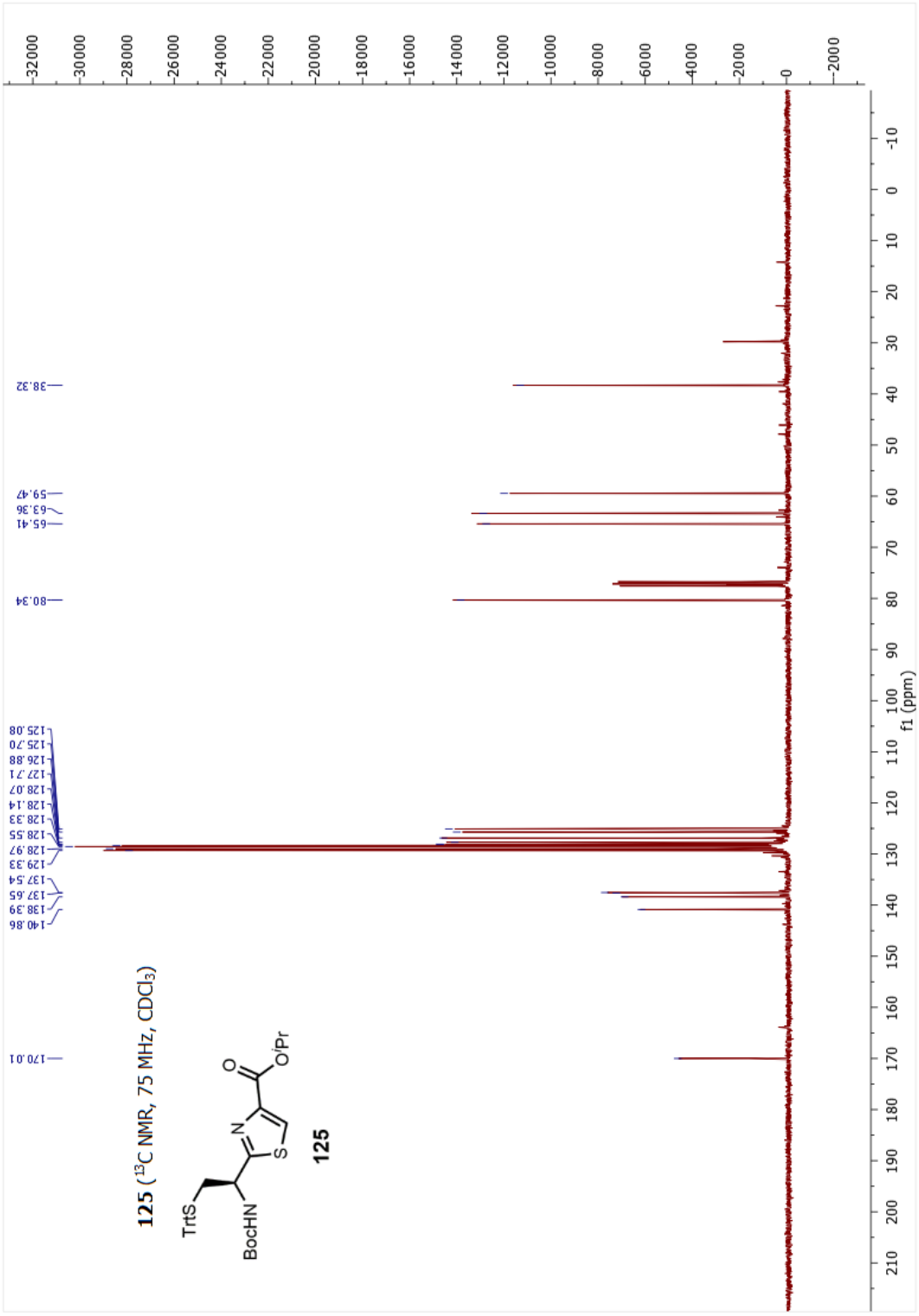


Figure 3.15 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **125**.

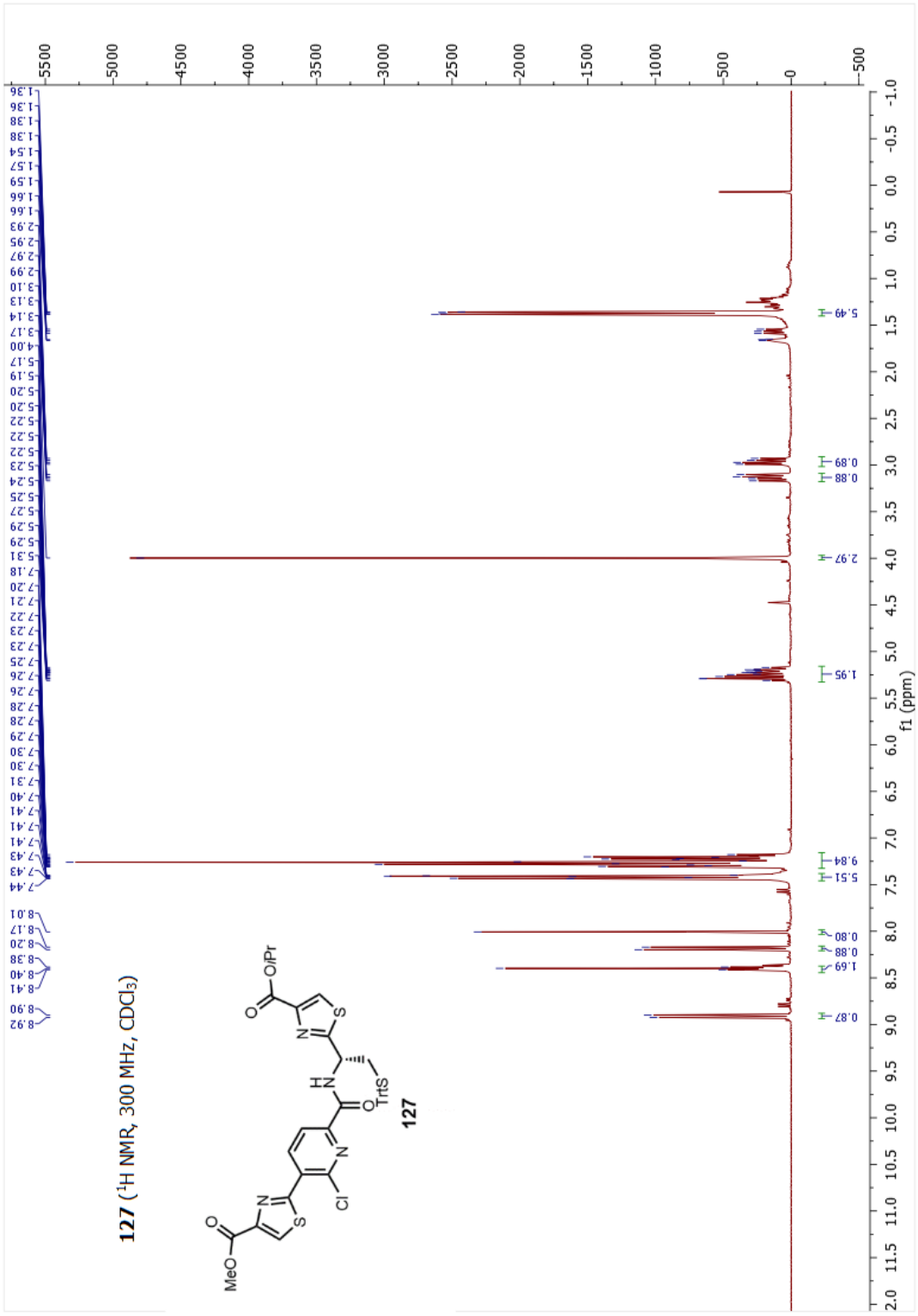


Figure 3.16 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **127**.

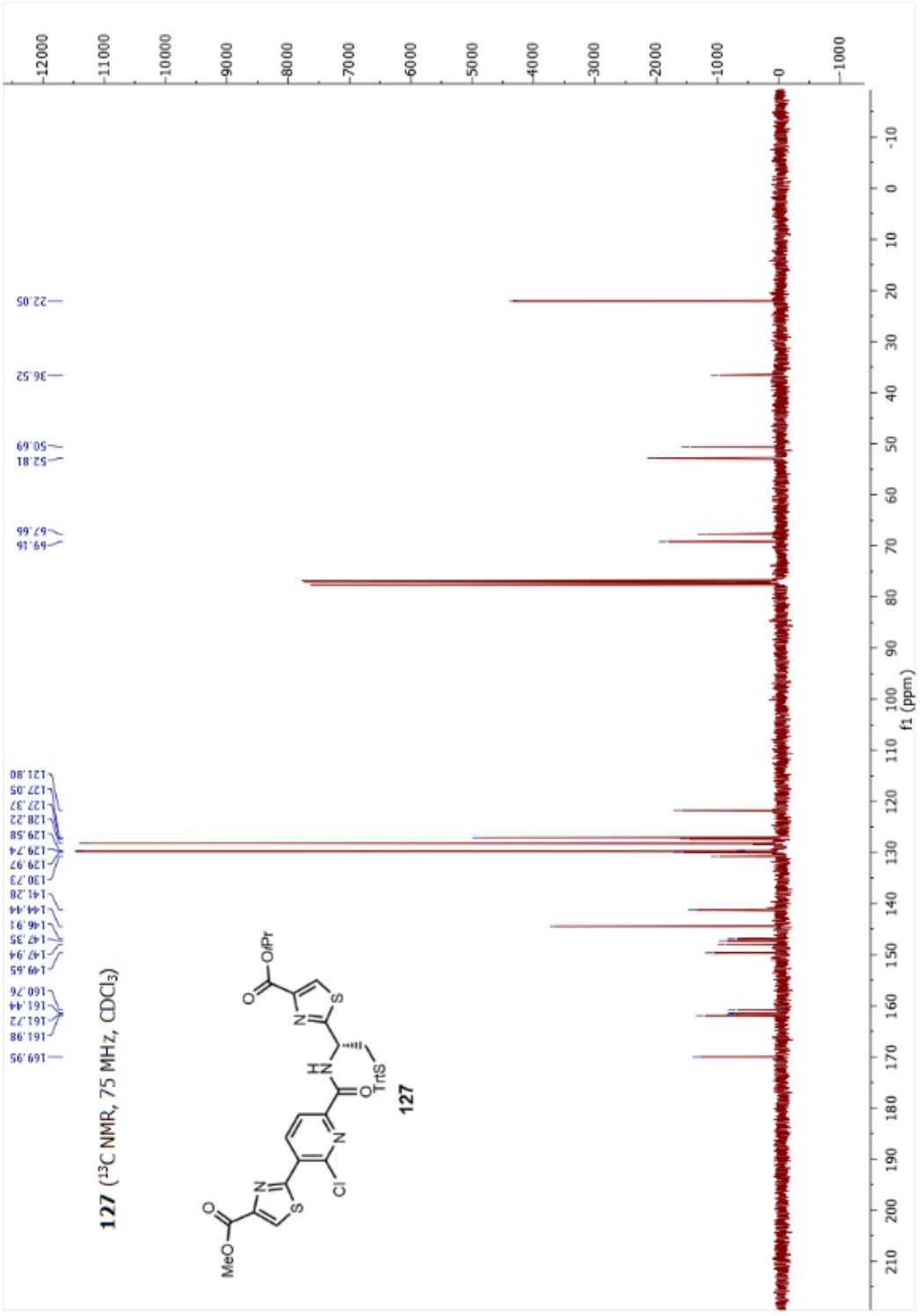


Figure 3.17 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **127**.

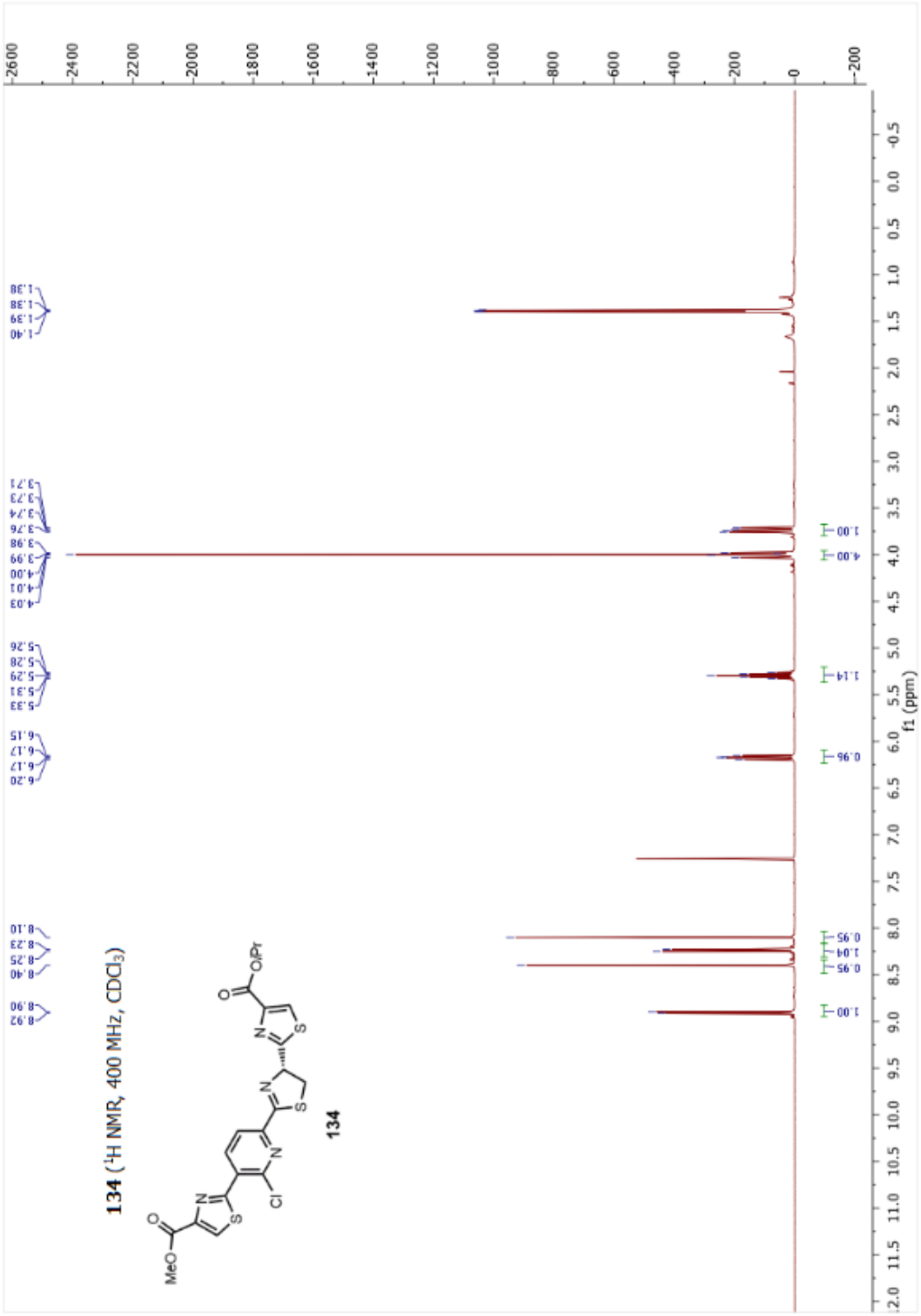


Figure 3.18 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **134**.

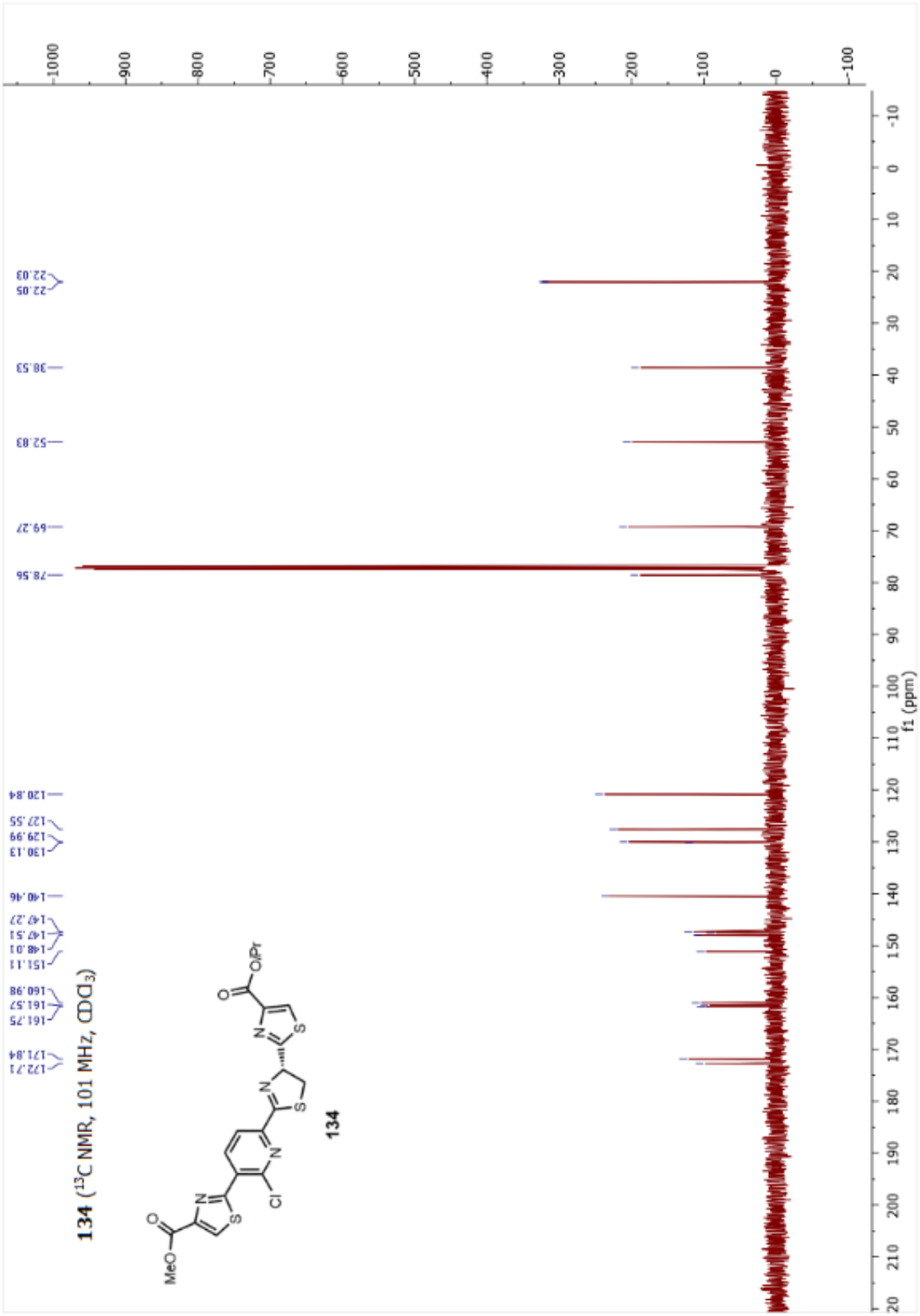


Figure 3.19 ^{13}C NMR (101 MHz, $CDCl_3$) of compound **134**.

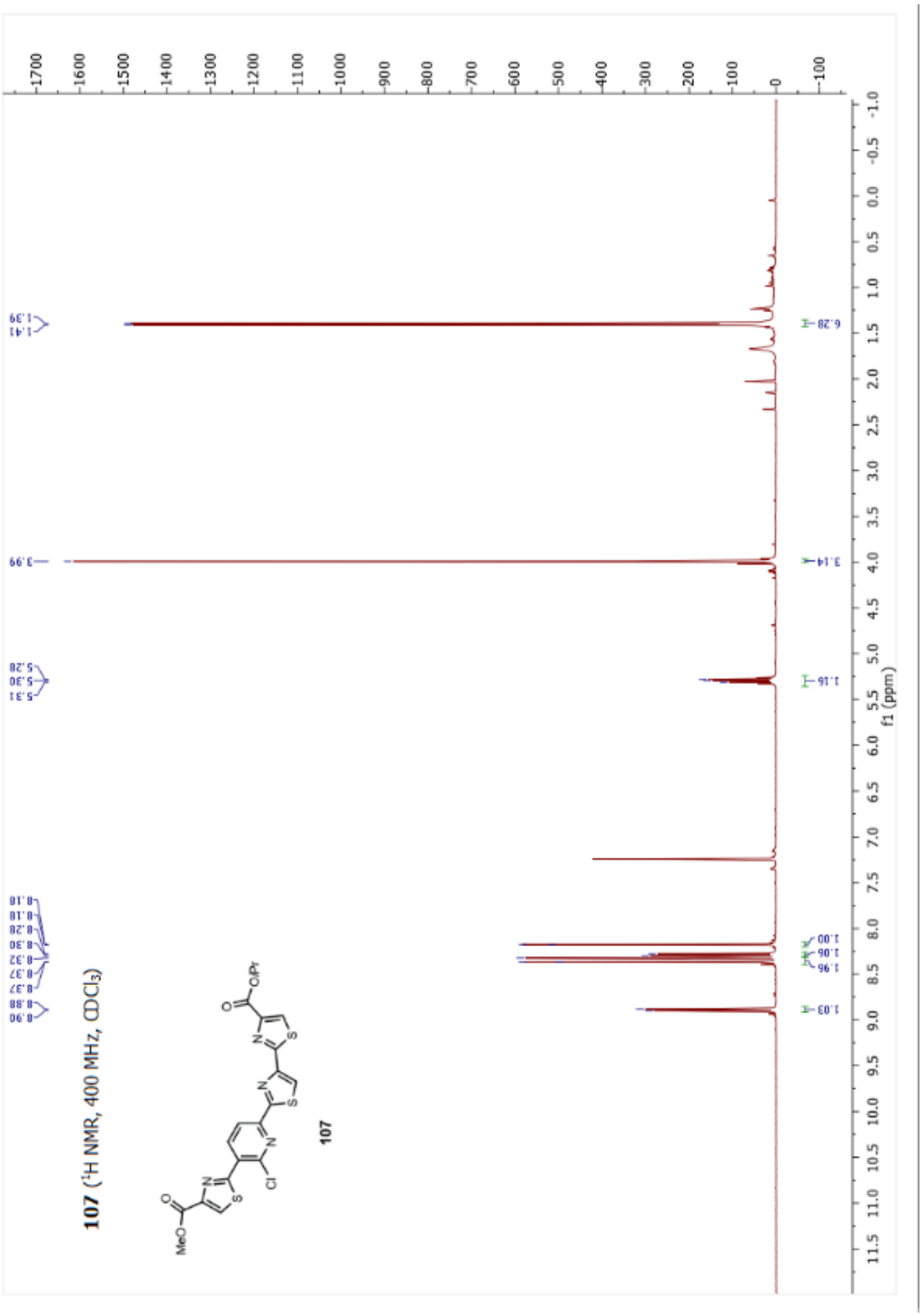


Figure 3.20 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **107**.

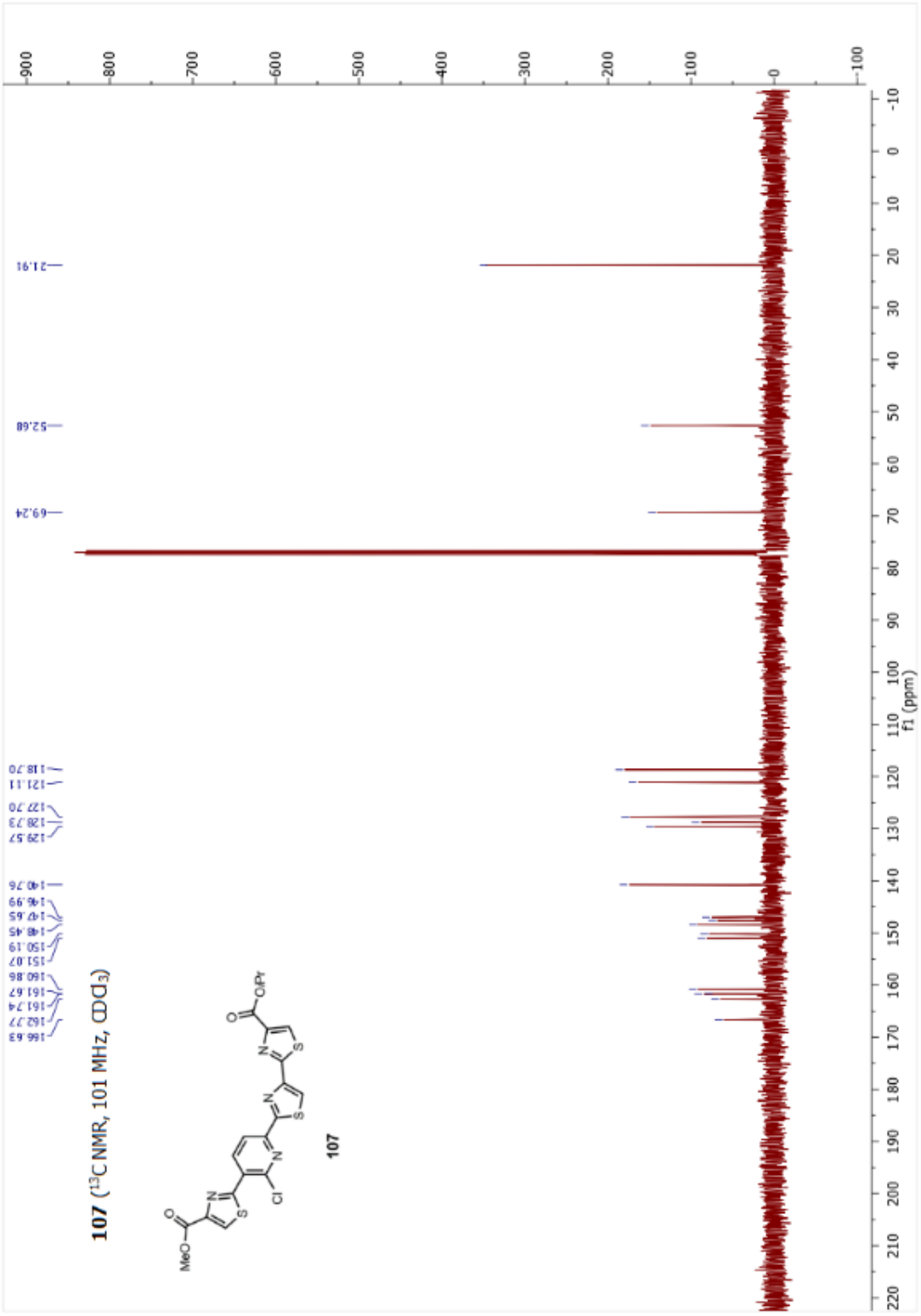


Figure 3.21 ^{13}C NMR (101 MHz, $CDCl_3$) of compound **107**.

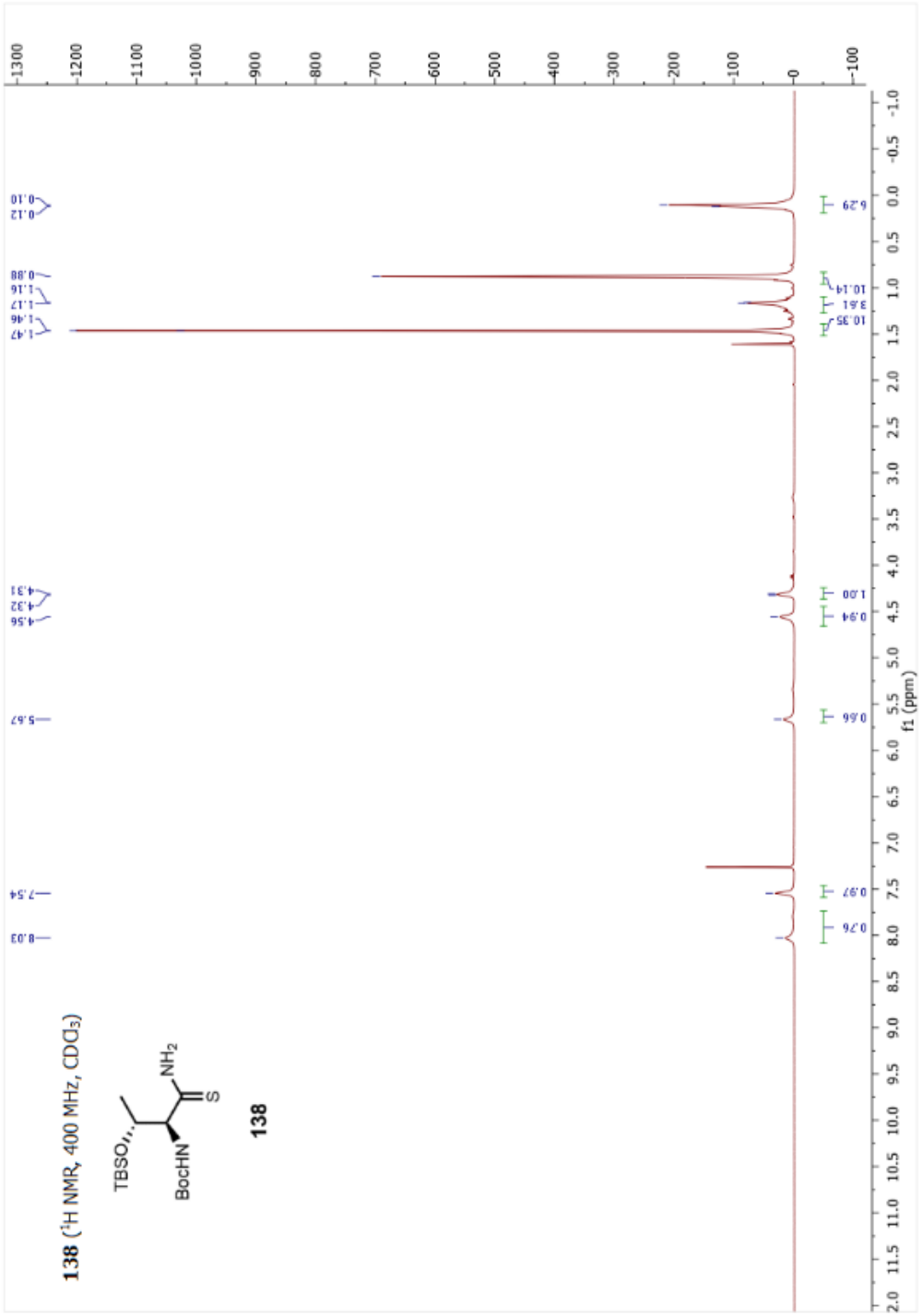


Figure 3.22 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **138**.

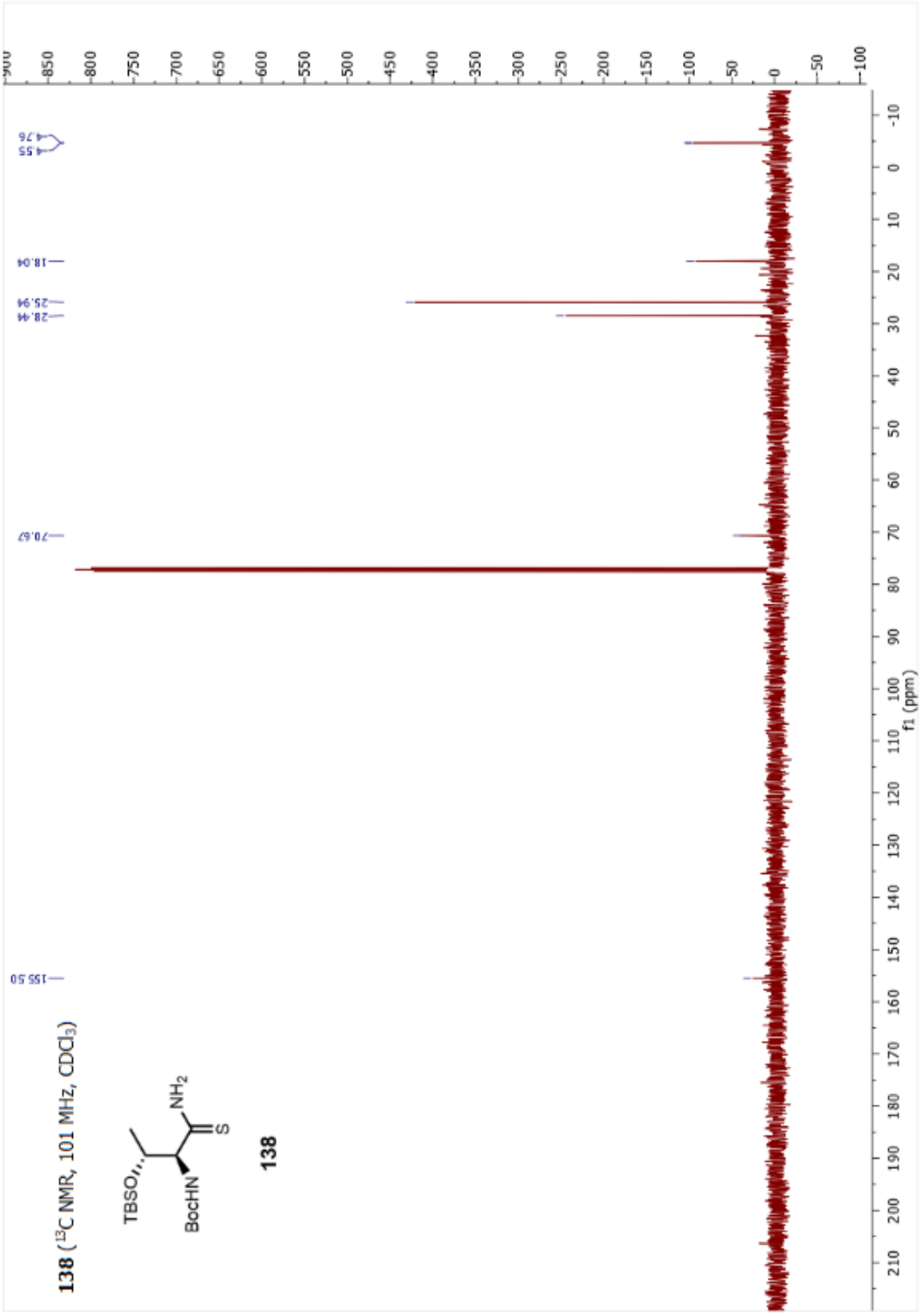


Figure 3.23 ^{13}C NMR (101 MHz, $CDCl_3$) of compound **138**.

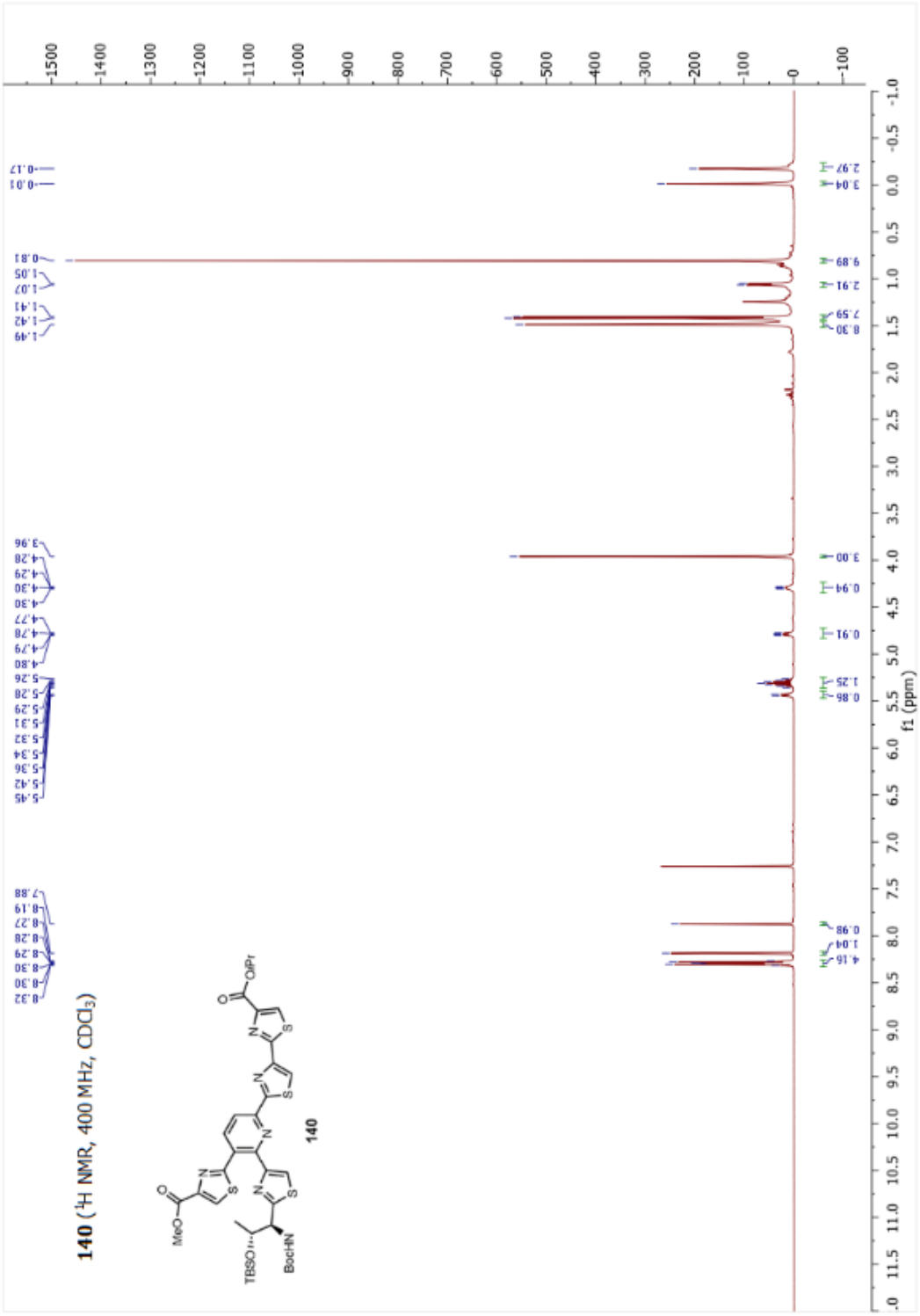


Figure 3.24 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **140**.

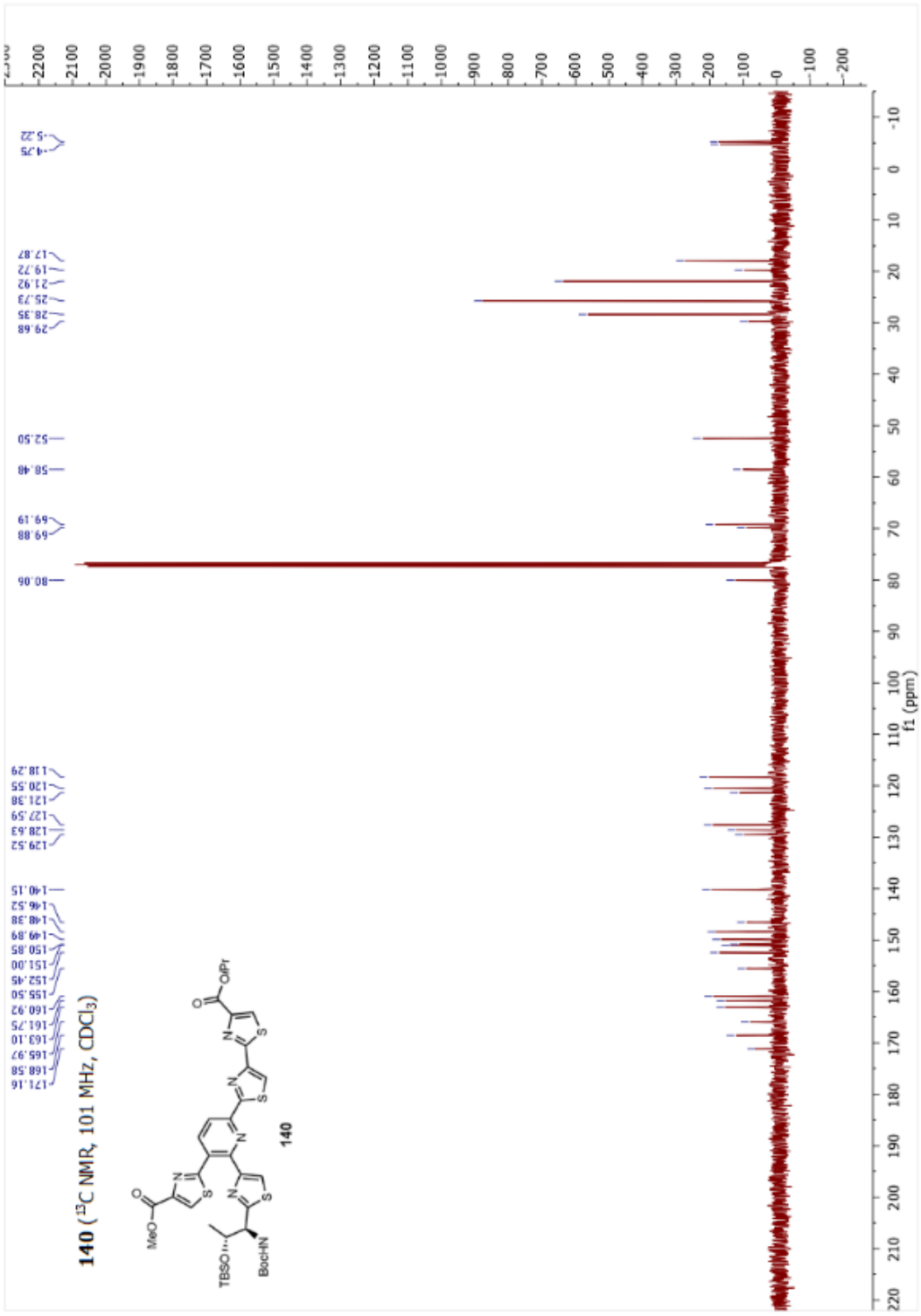
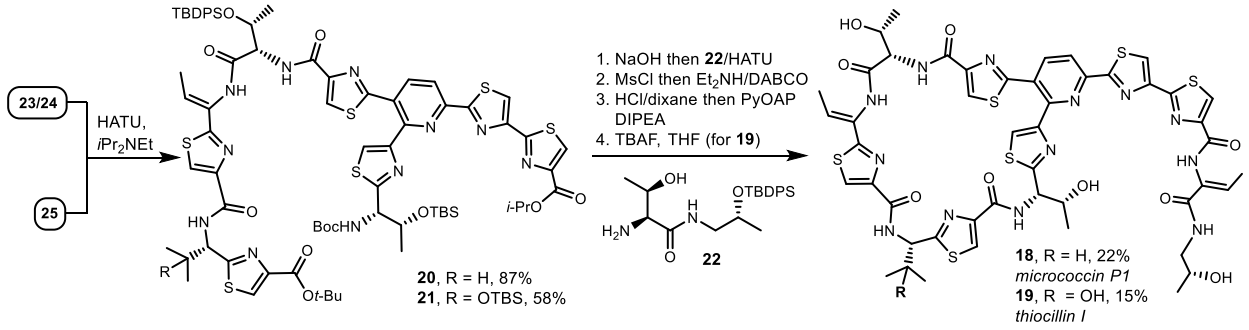


Figure 3.25 ^{13}C NMR (101 MHz, $CDCl_3$) of compound **140**.

CHAPTER FOUR

4.1 Concluding Remarks

Dr. Akasapu completed the syntheses of both thiocillin I and micrococcin P1. Briefly, he coupled the bottom fragment **23**/**24** to the top fragment **25** to give **20/21**. The isopropyl ester was hydrolyzed and coupled to side chain **22**. Global deprotection was achieved using HCl in 1,4-dioxane, and the product was macrocyclized to give the final product in the case of micrococcin. For the case of thiocillin, the HCl did not fully deprotect the tertiary alcohol so an additional step using TBAF was required. After HPLC purification, micrococcin P1 and thiocillin I were obtained.



Scheme 4.1 Completion of the syntheses for micrococcin P1 and thiocillin I.

Lactocillin presents a more challenging endeavor as it has other unique structural features. Lactocillin contains a delicate thiazoline residue which is prone to epimerize under both acidic and basic conditions. The presence of an indolyl thioester fragment presents another interesting synthetic problem. Our preliminary work towards lactocillin confirms the problems associated with both thioester formation and thiazoline epimerization. During the macrocyclization the thiazoline epimerizes under standard peptide coupling conditions gave a diastereomeric mixture

of products. The cysteine adjacent to the thiazoline ring also has a trityl protecting group. Under normal deprotection conditions (TFA and Et_3SiH) a mixture of compounds was obtained.

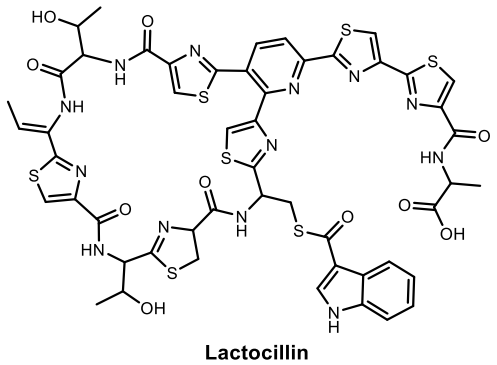


Figure 4.1 Structure of lactocillin.

In summary, the key fragments of thiocillin and micrococcin were synthesized allowing for the total syntheses of two thiopeptide natural products. In addition to this, a catalytic dehydrative cyclization methodology was utilized and optimized to form key thiazole heterocycles within each of the molecules allowing for modular access to each. We hope the methods developed herein will allow for the efficient synthesis of lactocillin.

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