UNIVERSITY OF CALIFORNIA, SAN DIEGO

Synthetic Studies Applied to Polyketide Natural Products

A dissertation submitted in partial satisfaction of the
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in

Chemistry

by

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2008

The dissertation of Alexander Mandel is approved, and it is acceptable in quality and form for publication on microfilm:

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Chair

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2008

DEDICATION

To Mom and Dad.

EPIGRAPH

To waste, to destroy, our natural resources, to skin and exhaust the land instead of using it so as to increase its usefulness, will result in undermining in the days of our children the very prosperity which we ought by right to hand down to them.

—Theodore Roosevelt

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LIST OF ABBREVIATIONS

Å	angstrom
AA	amino acid
Ac	acetyl
AcOH	acetic acid
ACP	acyl carrier protein
amu	atomic mass units
AT	acyl transferase
b	broad NMR peak
Bn	benzyl
BnBr	benzyl bromide
BOM	benzyloxymethyl
Bu	butyl
$C_{\#}$	carbon #
c	concentration in 10mg / mL
calcd.	calculated
CoA	coenzyme A
COSY	correlation spectroscopy
cm^{-1}	wave number (IR)
CP	carrier protein
CSA	camphorsulfonic acid
d	doublet (NMR)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone

d.e.	diastereomeric excess
DH	dehydratase
DIBALH	diisobutylaluminum hydride
DIPEA	diisopropylethylamine – Hünig's base
dm	decimeters
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane – glyme
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
EDC	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride
e.e.	enantiomeric excess
eq.	equivalents
ER	enoyl reductase
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
FAB	fast atom bombardment
FAS	fatty acid synthase
Fmoc	9-fluorenylmethoxycarbonyl
g	grams
Glu	glutamic acid
H	hydrogens (NMR integration)
h	hours
HCl	hydrochloric acid
HMG-CoA	β-hydroxy-β-methylglutaryl-CoA

HOAc	Acetic Acid
HOBt	hydroxybenzotriazole
HRMS	high-resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons olefination
Hz	hertz
IR	infared spectroscopy
J	coupling constants
KR	β-ketoreductase
KS	ketosynthase
L	liters
m	multiple signals (NMR)
M	molar
M	molecular ion (in the context of $[M]^+$)
$\frac{m}{z}$	mass per charge ratio of detected ion
Me	methyl
MeOH	methanol
mg	milligrams
MHz	megahertz
μg	micrograms
μL	microliters
μmol	micromoles
mL	milliliters
mM	millimolar
mmol	millimoles
mol	moles
MS	mass spectrometry

NADP	nicotinamide-adenine dinucleotide phosphate (oxidized)
NADPH	nicotinamide-adenine dinucleotide phosphate (reduced)
NHS	*N*-hydroxysuccinimide
nM	nanomolar
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
NOESY	nuclear overhauser effect spectroscopy
NRPS	non-ribosomal peptide synthase
p	pentet
PAGE	polyacrylamide gel electrophoresis
PAP	3'-phosphoadenoside-5'-phosphate
Ph	phenyl
PKS	polyketide synthase
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
$P_{\#}$	protecting group #
ppm	parts per million
PPTase	4'-phopsphopantetheinyl transferase
PT	(1*H*)-phenyltetrazole
q	quartet (NMR)
RCM	ring-closing metathesis
R_f	retention factor (TLC)
rt	room temperature (usually 25°C)
s	singlet (NMR)
SAR	structure activity relationship
t	triplet

TBDPS	*tert*-butyldiphenylsilyl
TBDPSCl	*tert*-butyldiphenylsilyl chloride
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butyldimethylsilyl chloride
TBSOTf	tert-butyldimethylsilyl trifluoromethanesulfonate
^{t}Bu	*tert*-butyl
TE	thioesterase
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
Tr	trityl – triphenylmethyl
TrCl	trityl chloride – triphenylmethyl chloride
UV	ultraviolet light
$[\alpha]_{\text{D}}^{25}$	standard rotation at 25℃
℃	degrees celsius
δ	chemical shift in ppm (NMR)

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PUBLICATIONS

Mandel, A. L.; La Clair, J. J.; Burkart, M. D. "The modular synthesis of pantetheine and phosphopantetheine" *Org. Lett.* **2004**, *6*, 4801–4803.

Mandel, A. L.; Jones, B. D.; La Clair J. J.; Burkart. M. D. "A synthetic entry to pladienolide B and FD-895" *Bio. Org. Med. Chem. Lett.* **2007**, *17*, 5159–5164.

Mandel, A. L.; Jones, B. D.; La Clair J. J.; Burkart. M. D. "Synthesis and biological evaluation of minimized derivatives of FD-895" *in preparation*.

ABSTRACT OF THE DISSERTATION

Synthetic Studies Applied to Polyketide Natural Products

by

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Polyketide natural products are valuable components of the modern pharmacopea. These secondary metabolites have a diverse range of structures and activities. Studies of their biosynthesis and activity will help to provide access to better medicinal compounds. To this end, directly probing these mechanisms with derivatives of natural products is an important goal. Synthetic organic chemistry allows production of a greater variety of compounds than can be accessed by manipulation of isolated natural products. In some cases, these bioactive molecules are only obtainable in small quantities or at great expense.

Herein, a modular synthesis of the Coenzyme A (**10**) precursors pantethine (**35**) and phosphopantetheine (**14**) is described. CoA is a cofactor that interacts with an estimated 4% of all enzymes known in nature, and it is central to the biosynthesis of polyketide antibiotics. Using D-pantolactone (**50**) to provide the key units, **53** and

63, pantetheine, phosphopantetheine, and derivatives were assembled through peptide couplings.

Next, synthetic methods were applied toward the total synthesis of two related macrolide antibiotics, pladienolide B (**70b**) and FD-895 (**71**), in an attempt to elucidate their stereochemistries and to get a supply of each molecule for studies into the mode of action and biosynthesis of each compound. The general breakdown of each molecule relies on a Stille coupling to connect the sidechain (**133**) to the 12-membered macrocyclic core (**111**), and an esterification / ring-closing metathesis sequence to furnish the ring from compounds **115** and **114**. The sidechain of pladienolide B was completed and involved in model studies to demonstrate the overall retrosynthetic background. The core structure was proposed to arise from the chiral pool, but the strategy to combine the two units with the neccessary stereochemistry met with failure under many different conditions. Due to complications in obtaining an authentic sample of pladienolide B (**70b**), and subsequent outside publication of a total synthesis incorporating many aspects of the work contained herein, FD-895 (**71**) was chosen as an alternative target. The same retrosynthetic breakdown was applied to FD-895.

Chapter 1

Introduction

1.1 A justification for the study of natural products

Natural products, also known as secondary metabolites, are small molecules that are produced by many organisms with the aid of proteins and primary metabolites such as acetates, malonates, terpenes, amino-acids, sugars, and others. Many of these natural products, especially those isolated from microorganisms, are medicinally useful. These natural products carry out a variety of functions for the producer organisms such as engaging in chemical warfare with other invading species, poisoning predators or herbivores, disabling host organisms in a parasitic infection, signaling cells to change states in a organism, quorum sensing, and attracting organisms for reproduction or seed distribution just to name a few. For many products that are discovered, the intended natural function is not known.

According to the American Cancer Society, 45% of men and 38% of women will face a cancer diagnosis in their lifetimes.[1] 1.3 million people are diagnosed with cancer and more than half a million die from it every year. Certainly, with its increasing prevalence in our society, the burden of cancer demands more and better treatments

to combat this rising threat. Polyketide natural products like those shown in Figure 1.1 have promising pharmaceutical activities against cancer. Polyketides are a specific class of secondary metabolites that are produced by polyketide synthases (PKS) which iteratively construct the molecular framework from consecutive condensations of acyl units. PKS systems consist of reactive domains that modify a growing molecular structure in a fashion similar to an assembly line. Much remains to be learned about these systems before their full potential can be realized.

The Burkart lab is attempting to build tools that will allow these biosynthetic systems to be probed through proteomic means. One goal of our work is a tag that will generally label one or more domains in a PKS system that exists in low concentration, and allow the unknown synthase to be isolated and sequenced. A protein sequence would then lead to the genome. It is also important to probe the interactions between domains, and the selectivities / reactivities of the enzymes. Toward this end, chapter 2 of this thesis covers the modular synthesis of pantetheine and phosphopantetheine. The synthesis allows derivitization at any part of the 4'-phosphopantetheine backbone which is loaded onto carrier proteins from coenzyme A.

Chapters 3 and 4 discuss the efforts toward a total synthesis of pladienolide B and FD-895, two very powerful cytotoxic polyketides found in *Streptomyces*. Pladienolide B itself was a lead compound in the production of a chemotherapeutic agent that is in phase III clinical trials in Japan. A total synthesis of each molecule, especially pladienolide B, would help us to investigate the modes of action of these compounds, but also would give us access to intermediates that would also allow us to investigate the pharmacological properties of the two macrolides. Derivatives of the molecules themselves could also be used to assist in investigations into their biosynthesis. The stereochemistry of pladienolide B and FD-895 was unknown at the time this project started, thus making the synthesis much more difficult, but as one will read in chapters

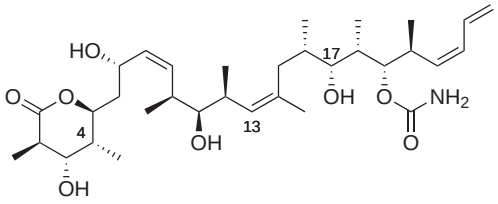
3 and 4, the synthesis was designed to assist in the elucidation of the stereochemistry.

1.2 Important macrolide natural products

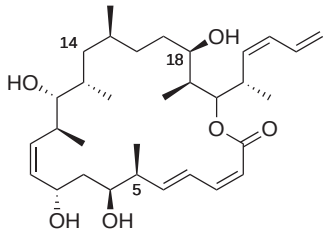
Polyketide natural products are an important class of highly functionalized natural products that have diverse biological activities. Many of these polyketides are macrolides, natural products containing large rings.[2] Several recently discovered polyketides that have promising clinical applications are shown in Figure 1.1. These compounds also have complex structures with many stereocenters making them challenging synthetic targets. In several cases, synthesis has allowed activity to be probed and pharmacological properties to be enhanced. In the first case presented below, total synthesis turned out to be the only method to obtain enough of the compound for clinical testing and use.

Discodermolide (**1**) is a polyketide isolated from the marine sponge *Discodermia dissoluta*, a native of the Bahamas that contains a 6-membred lactone.[3] Discodermolide was the subject of great excitement because of its potential to be used as a cancer treatment.[4–6] Discodermolide has turned out to be a very potent inhibitor of tumor cells that are resistant to taxol and epothilone. Other members of the class have been discovered but none of them are available in large enough quantities from *Discodermia* to allow them to be tested in the clinic. Synthetic methods to produce discodermolide were of the utmost importance for future studies. Several syntheses have been presented,[7–17] but Novartis created a large-scale synthesis that was able to produce kilogram quantities of the compound for clinical testing.[18–22]

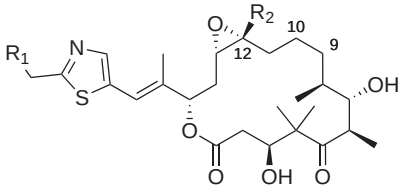
A similar polyketide is dictyostatin (**2**) which was isolated from a marine sponge of the genus *Spongia*, and which contains a large 22-membered ring with demonstrated activity against leukemia cells.[23] A scan of the substitution pattern reveals that is has



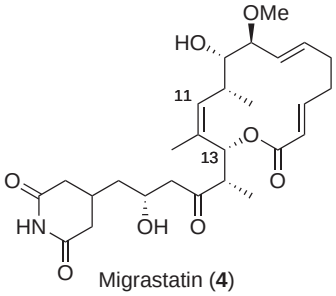
Discodermolide (**1**)



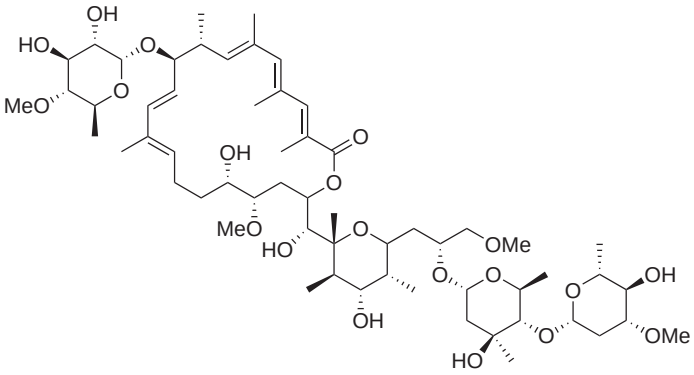
Dictyostatin (**2**)



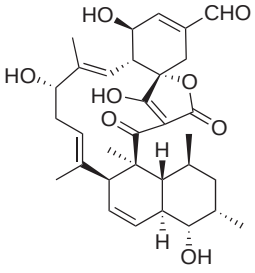
$R_1 = R_2 = H$: Epothilone A (**3a**)
$R_1 = H$, $R_2 = Me$: Epothilone B (**3b**)
$R_1 = H$, $R_2 = H$, 12,13-deoxy: Epothilone C (**3c**)
$R_1 = H$, $R_2 = Me$, 12,13-deoxy: Epothilone D (**3d**)



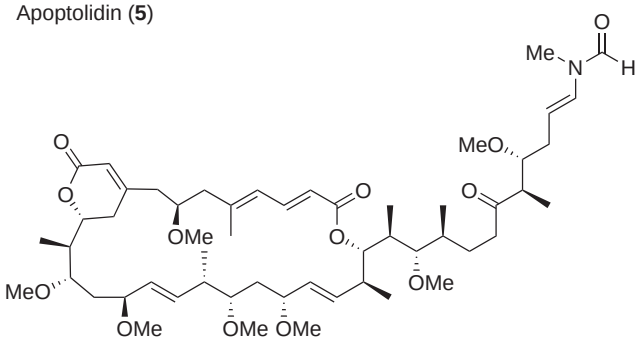
Migrastatin (**4**)



Apoptolidin (**5**)



Tetronolide (**6**)



Reidispongiolide (**7**)

Figure 1.1: Some polyketides with promising medicinal activities

several of the same structural motifs as **1**. In fact, the $C_5 - C_{14}$ portion of dictyostatin is exactly the same as the $C_4 - C_{13}$ unit of discodermolide. Toward the diene terminus, $C_{18} - C_{25}$ are exactly that same as discodermolide's $C_{17} - C_{24}$ with the exception of the amide which was probably added in a post-synthase modification. Several synthetic efforts have lead to analogue synthesis and investigations of activity.[24–29] Because of their similarities, a hybrid molecule combining **1** and **2** was prepared, and it was found to have an order of magnitude lower activity against tumor cell growth relative to discodermolide itself.[30]

Epothilones A (**3a**) and B (**3b**) isolated from *Sorangium cellulosum*, a myxobacterium, exhibit a wide range of cytotoxic activity against eukaryotes. The epothilones (**3a** – **d**) have been the subject of many synthetic efforts.[31–37] Several analogues have been prepared in attempts to improve pharmalogical properties.[38–46] For example, it had been found that the epoxide resulted in a large amount of non-specifc activity.[36] Chou *et al.* synthesized **3d** and found it has activity similar to taxol.[43] To increase potency, an *E* unsaturation was introduced between C_9 and C_{10}, but the non-specific activity returned. The R_2 methyl was replaced with a CF_3 in order to prevent unwanted oxidation back to the epoxide while in the body, and it was found that this modification increased the therapeutic index substantially.

Migrastatin (**4**) is a 14-membered macrolide isolated from *Streptomyces platensis* with a unique glutarimide unit.[47,48] It also exists in a 12-membered ring variety known as iso-migrastatin, where the lactone rearranges in a 3,3-sigmatropic rearrangement to place the lactone at C_{11}, and the double bond shifts to outside the ring.[49,50] Because of it's inbhibitory effects on tumor cell migration, it has been of great interest to the synthetic community,[49,51–53] and also those interested in its biosynthesis.[50,54,55]

Apoptolidin (**5**) has attracted great interest from the synthetic community because it has several challenging features,[56–59] but also is a candidate for patient treat-

ment because it selectively induces apoptosis in cancerous cells.[60] Isolated from *Nocardiopsis*, apoptolidin features a large 20-membered ring, a tetrahydropyran, two sets of conjugated olefins, and several glycosides.[61,62] It was found to be among the top 0.1% most selective of the 37,000 compounds that had been subjected to the NCI-60 cancer screen *circa* 2003.[63]

Tetronolide (**6**) is the aglycone of tetrocarcin, one member of the unique class of polyketide antibiotics called the spirotetronates.[64–67] Most active spirotetronates also contain the *trans*-decene bicyclic structure and several glycosides. The tetracarcins have activity against Gram-positive bacteria, but more importantly they are active against several lines of cancer cells, although not solid tumors.[68] It appears that tetrocarcin A is a candidate for preclinical trials.[69–72] Because of its complexity, tetronolide (**6**) presents an excellent proving ground for synthetic methods.[73,74]

The last compound presented is the large macrolide reidispongiolide A (**7**), isolated from the sponge *Reidispongia coerulea*; it exhibits nanomolar *in vitro* activity against human tumor cell lines.[75] This compound is an excellent example for the work to be presented in chapter 3 because it embodies the strategem which we applied to pladienolide B. Compound **7** contains 16-stereocenters, and initially none were assigned. Several synthetic efforts were undertaken to create panels of diastereomers that represent ozonolysis fragments of **7** and compare them to the natural fragments.[76–79] In such a way, reidiospongiolide A was synthesized and its stereochemistry was confirmed.[80]

1.3 Polyketide synthases

The macrolides as well as other polyketide natural products are constructed in a modular fashion from polyketide synthases.[2] Polyketide synthase (PKS) systems consist of multiple enzymatic domains that each perform a specific function. These

domains are connected together as large proteins in type I PKS systems. These synthases are similar to fatty acid synthases (FAS), and their domains perform the same functions, except that they can vary the final oxidation states of each ketide fragment in the molecule they produce.[81] In type II PKS's, the domains are all free floating but they interact to perform the same chemistry as type I systems.

Shown in Figure 1.2 is the domain organization of the pikromycin polyketide synthase.[82–84] The PKS segment of the biosynthesis is encoded in four open reading frames, PikI – PikIV, which code for the four proteins that complete the ketide protion of the synthesis. The start module, and each subsequent "module", is designed to add and tailor one ketide unit to provide narbonolide **8**. Shown on each module is the end product of the condensation and tailoring up to that carrier protein (ACP). The starter unit loads propionate into the 4'-phosphopantetheinyl arm of the *holo* carrier protein. Next, on module 1, a propionate is condensed onto the starter unit, and the β-ketone is reduced to the alcohol. The following iteration on module 2 includes condensation with an acetate, reduction of the β-ketone and elimination. Module 3 adds another propionate but the resulting ketone is not reduced at all. The next step in module 4 adds a propionate, and it is fully reduced to the alkane at the α and β position. Module 5 is like module 1 as it adds a propionate and reduced the ketone, but it gives the opposite stereochemistry. The stereochemistry of these reactions is controlled by the reducing enzymes. Module 6 add the final propionate without reduction of the ketone and the thioesterase (TE) cyclized and ejects narbonolide (**8**). From this point, two post-synthase modifications are made: the oxidation of C_{12}; and, glycosolation to give pikromycin (**9**)[85]

To better understand the functions of these domains, Figure 1.3 shows where the ketides originate and the chemistry involved in the condensation reactions. Part **A** on Figure 1.3 shows the acyl carrier protein (ACP) as it holds each "starter" unit

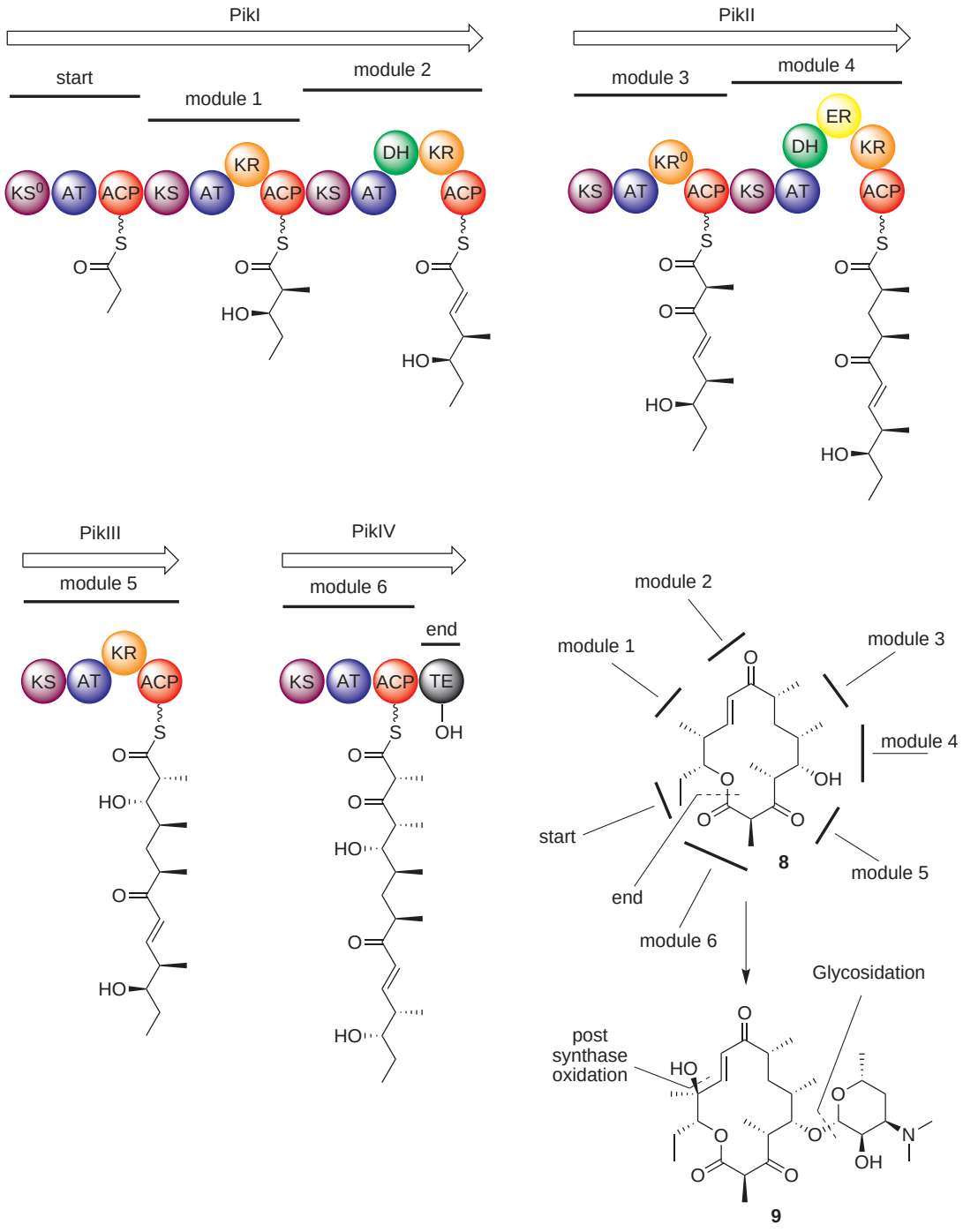


Figure 1.2: Domain organization of the pikromycin (**9**) PKS system. The four ORF's PikI – PikIV represent four multi-modular enzymes that assemble the polyketide and eject it as the 14-membered lactone. The growing ketide chain is shown after condensation and tailoring by the enzymes on the respective modules. ACP = acyl carrier protein, AT = acyl transferase, KS = ketosynthase, KR = β-ketoreductase, DH = dehydratase, ER = enoyl reductase, TE = thioesterase.

that will become the carbons in pikromycin (**9**). The ACP unit is central to polyketide biosynthesis. The ACP holds the growing chain as it is tailored until it is condensed with the next ketide unit. The ACP contains a 4'-phosphopantetheinyl arm that originates from Coenzyme A from the action of a phosphopantetheinyl transferase.[81] All ketide units that are introduced by modules 1 – 6 come from malonates. Modules 1 and 3 – 6 use methylmalonate, and module 2 uses malonate. Only the first unit originates from plain propionate, but this unit probably results from a decarboxylation of methyl malonate by a special ketosynthase (KS^0) at the beginning of the synthase.

Part **B** shows the role of the acyltransferase. The acyltransferases of each module move the propionyl, malonyl, and methylmalonyl units from free CoA to the *holo* ACP's.[86] The AT is responsible for discriminating which unit is loaded onto each ACP. Once the ACP is loaded, the growing chain, starting from the left is transferred to the ketosynthase (KS) domain, which places it in the correct position to condense with the next ketide (Part **C**, Figure 1.3).[87] On the next module, elimination of CO_2 furnishes the propionate anion which attacks the thioester on the KS and the growing chain ends up on the next ACP. The unit is then ready for the tailoring enzymes to reduce the β-keto group if neccessary. There is one domain in the pikromycin synthase that appears to be a ketoreductase (KR^0 in module 3) by homology of the gene sequence, but has an unknown function.

There are three basic types of tailoring that can occur in a polyketide after the condensation as outlined in Figure 1.4, parts **A** – **C**.[87,88] If the ketone is reduced to the alcohol, it requires the NADPH-dependent β-ketoreductase (KR) (Part **A**). If the double bond is desired, then first the KR acts on the alcohol, and then the dehydratase (DH) will eliminate the alcohol (Part **B**).[89] If the product is to be fully reduced, then the KR and DH convert the substrate to the double bond and then the enoyl reductase, another NADPH dependent enzyme, completes the reduction (Part **C**).[90]

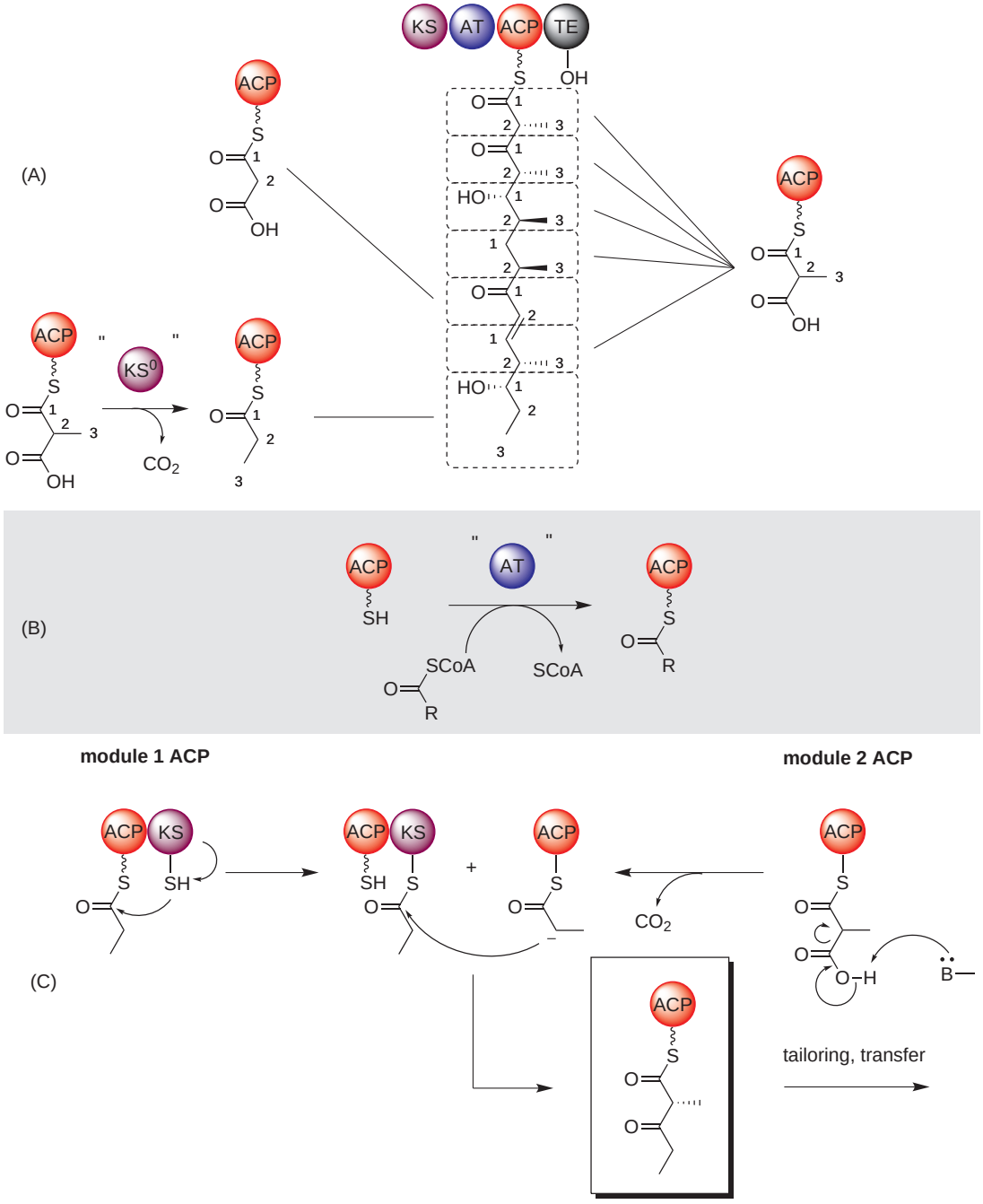


Figure 1.3: The origins and chemistry in the condensation of ketides. (**A**) Schematic showing the origins of each ketide unit from primary metabolites in the pikromycin synthase. (**B**) The acyltrasferase domain takes a CoA thioester and transfers it to the ACP. (**C**) The growing chain of ketides is transferred to the ketosynthase where another unit on the next ACP will condense with it. The quotation marks represent that the enzyme is not a seperate unit, but is "acting" seperately to carry out the reaction.

These enzymes can only act in this order, thus, the KR must always be first, the DH second, and if required, the ER third.

The final domain in macrolide biosynthesis is almost always the thioesterase (TE).[91,92] In most fatty acids, the TE ejects a long chain fatty acid. For secondary metabolites, it is the scaffold which allows the product to cyclize while it is rolled off the molecular assembly line. The thioesterase domain is remarkable in that is also differentiates possible lactonization sites within the module, probably due to the way this module folds the straight chain in the enzyme pocket.[93] Pikromycin has two alcohols that could form a lactone to displace the product and the the 14-membered ring predominates over the possible 6-membered one. The thioesterase has a conserved structure motif known as the "catalytic triad". As shown in Figure 1.4, Part **D**, the catalytic triad consists of a proximal Asp, His, and Ser. The aspartic acid and histidine enhance the nucleophilicity of the serine so that is attacks the thioester. Once the polyketide is on the serine, the molecule is lactonized and ejected from the system. Studying the mechanisms of the thioesterase is very important because it is the lynchpin of polyketide synthesis, and learning how to inhibit a TE selectively can provide another target for inhibiting bacterial growth and toxicity.

1.4 Concluding thoughts on natural product synthases

The modular nature of polyketides and their synthases make them an excellent proving ground for proteomic technologies that can be applied generally to elucidate, inhibit, and discover natural product synthases. Most of the current work that uncovers the catalytic domains and enzymes relies on homology searches based on genetic library methods, as well as looking at the natural product and matching the proposed domain order. The former approach requires one to invest a large amount of time on an

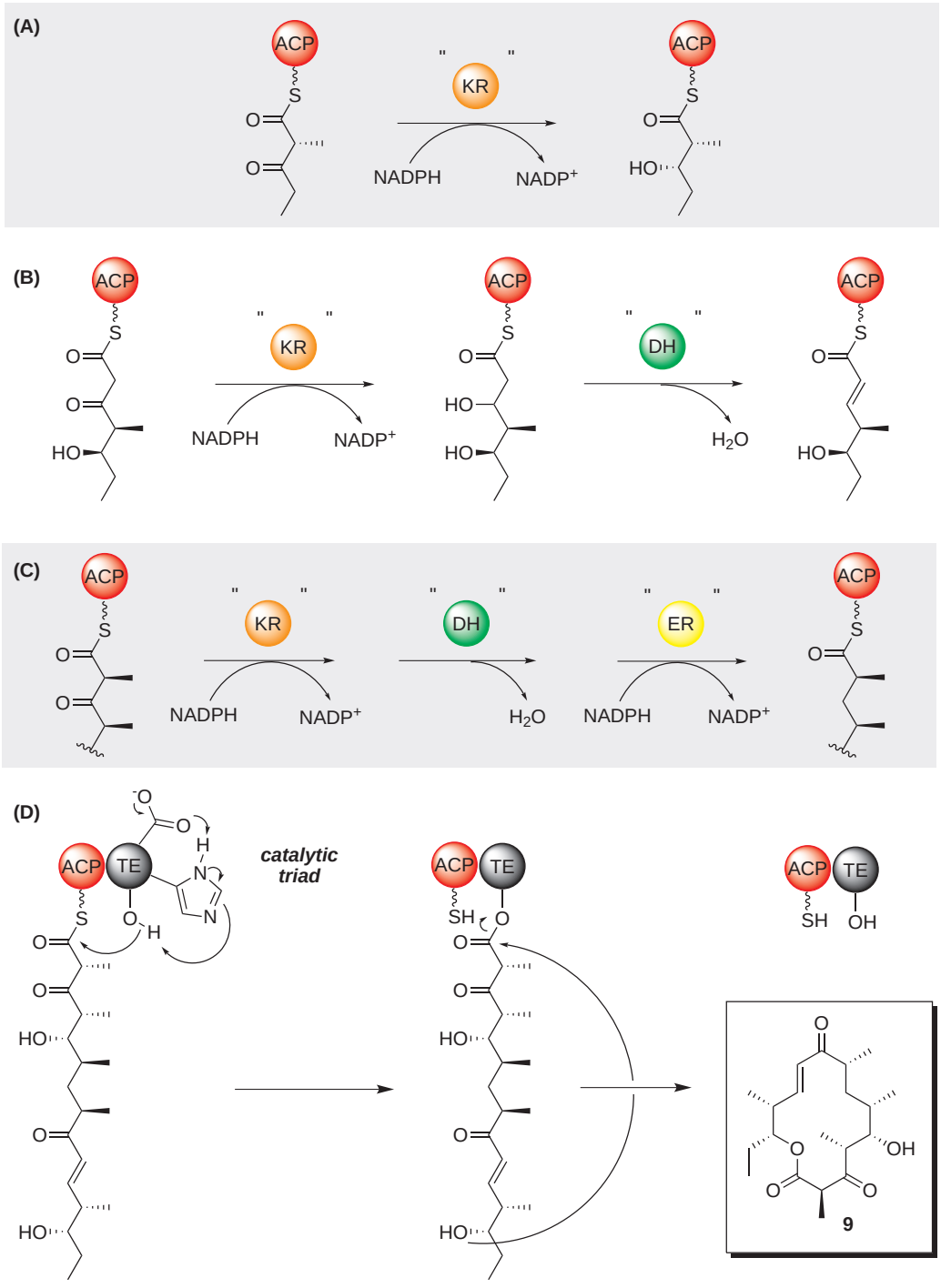


Figure 1.4: Tailoring enzymes and the thioesterase. (**A**) the β-ketoreductase (KR) catalyzes the reduction of a β-ketone to alcohol. (**B**) The dehydratase (DH) will additionally eliminate the alcohol to form an olefin. (**C**) The action of the KR, DH, and enoyl reductase (ER) will reduce the ketone to a CH_2. (**D**) The thioesterase (TE) domain uses the catalytic triad to transfer the polyketide to active site serine where it then cyclizes the releases the 14-membered pikromycin precursor (**8**)

organism, and can be tedious to implement for systems that are difficult or impossible to culture like sponges. The latter approach requires one to have already discovered and eludicated a natural product genetic pathway from an organism, and still for the most part requires the genome sequence. The structure may be a guide for primer design to try to amplify the synthase, but is no guarantee that the genes will be found.

The field has many challenges that spherical domain cartoons can not represent. There is some homology in primary structure between domains, but there is no one size fits all domain. Systems are being discovered all the time that do not match canonical motifs. The modules are also not interchangable like lego blocks. Individual domains have evolved to accept specific substrates, so mix-and-match strategies rarely work. The mode by which the enzymes recognize each other to carry out condensations between two separate enzymes is a topic that requires much more investigation. Also, cloning of the systems in *E. coli* or other lab strains requries a lot of time and many of these substances will kill the clone unless the resistance gene can be expressed as well.

Organic synthesis will be an important practice to expand the methods available to probe polyketide synthases. Organic synthesis also continues to be an important practice in the discovery and tuning of pharmacogenic natural products. Studies into these systems are in their infancy, and there is a lot of room for new chemical tools to assit in their discovery, elucidation, manipulation and production.

Chapter 2

The Modular Syntheses of Pantetheine and Phosphopantetheine

2.1 Introduction

Coenzyme A (**10**) (Figure 2.1) is one of the most important cofactors in nature. CoA mediates the activation and transfer of acyl groups in fatty acid biosynthesis, secondary metabolite biosynthesis, primary metabolic pathways, and regulatory processes. CoA plays an important role in cellular development, aging, toxicity, and cancer.[94–98] CoA is used in an estimated 4% of all known enzymes. Coenzyme A is central to the biosynthesis of small molecules and fatty acids. Thus, cleverly designed CoA derivatives can lead to important proteomic tools for understanding secondary metabolism.

From a chemical standpoint, CoA (**10**) can be dissected into four modules as outlined in Figure 2.1. The first module, cystamine (**M1**), presents a terminal thiol that serves as the linkage point for acyl groups. The cystamine moiety is connected via an amide linkage to β-alanine (**M2**) that is further joined through an amide bond to

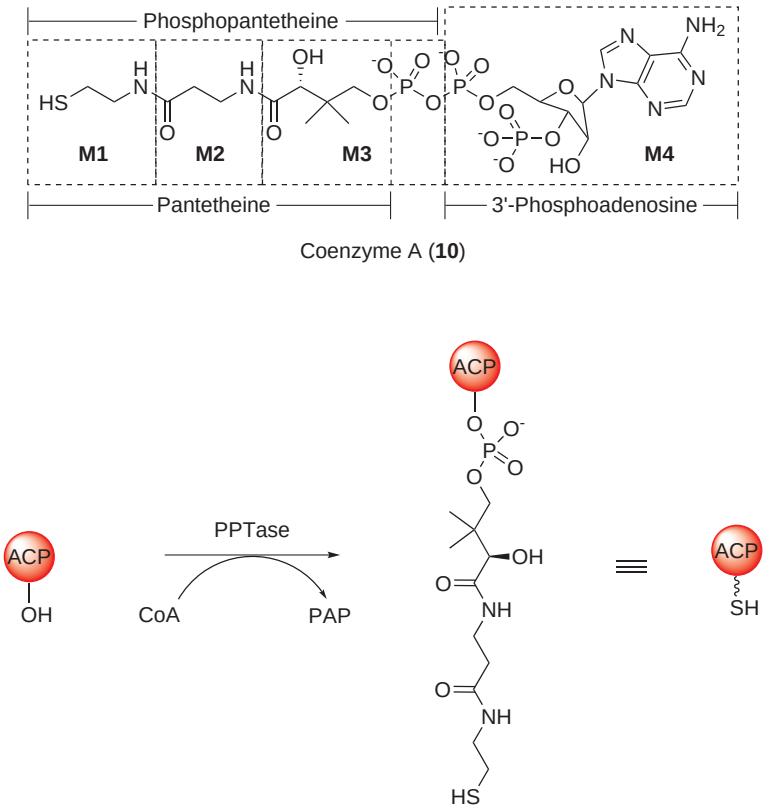


Figure 2.1: Coenzyme A (**10**) and its role in adding the 4'-phosphopantetheinyl arm to the acyl carrier protein. The phosphopantetheinyl transferase (PPTase) adds 4'-phosphopantetheine to an ACP's active site serine to convert it from an *apo*-ACP to a *holo* ACP. 3'-phosphoadenosylphosphate (PAP) is released.

pantoic acid (**M3**). Most of the chemistry occurs at the thiol group, whereas the rest of the molecule serves as a recognition element for binding proteins.[97] These three units make up pantetheine. **M2** and **M3** together make up pantothenic acid, also known as vitamin B_5. In CoA, pantetheine (**M1** – **M3**) is joined to a 3'-phosphoadenosine (**M4**) through a 5'-pyrophosphate bridge. Carrier proteins, the subject of many projects in the Burkart lab, are unique in that **10** must cleaved and **M1** through **M3** become covalently linked through a phosphodiester to a free serine to make the protein active. This is the case for type I and II PKS, FAS, and NRPS systems whereas in all other cases it is not necessary for the pantetheine moiety of CoA to be covalently bonded

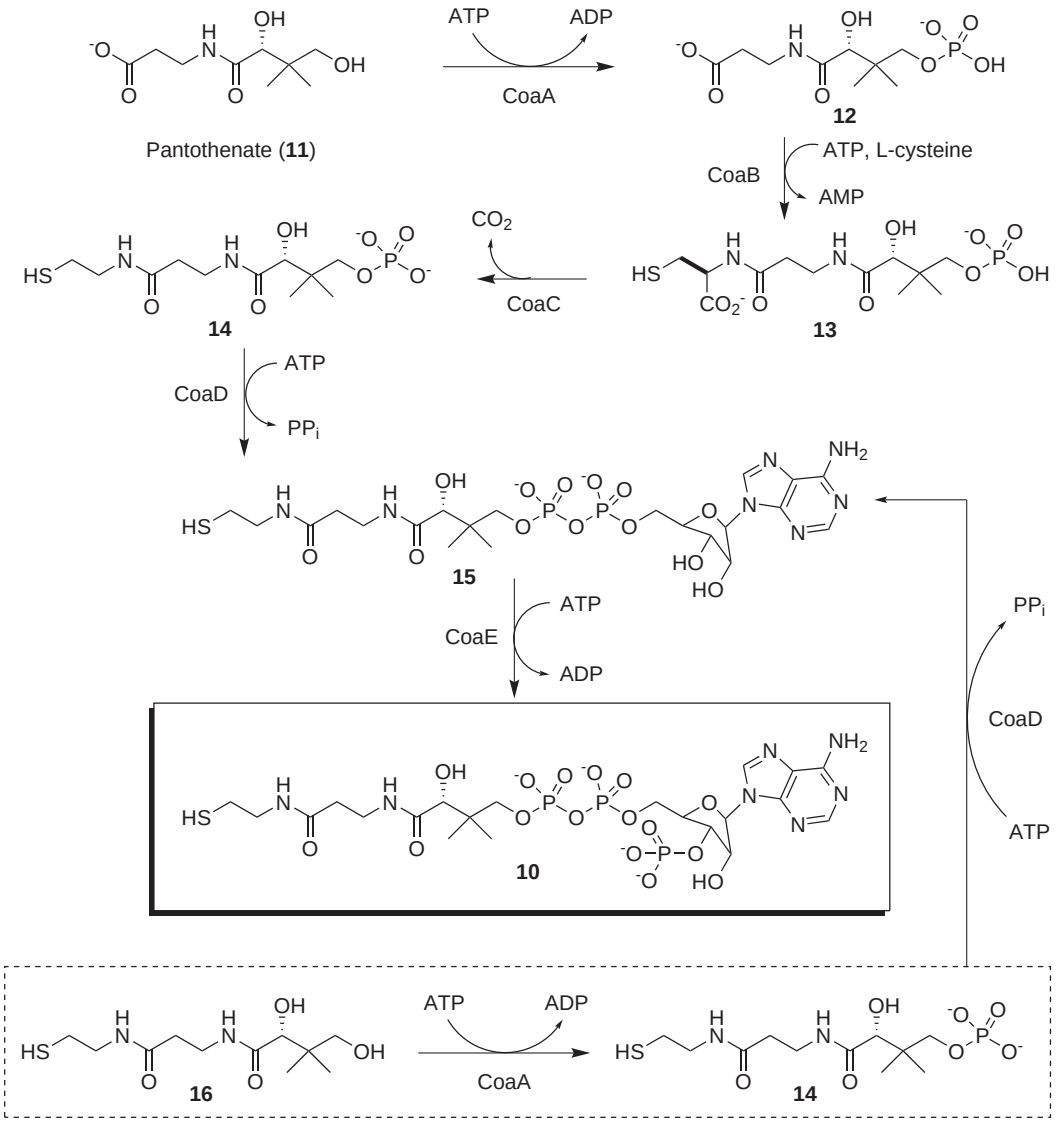
to an enzyme to assist in acyl transfer.[95]

2.2 The CoA biosynthetic pathway

Coenzyme A (**10**), being ubiquitous in nature, is synthesized by a similar set of enzymes in every organism. Humans and mammals need to start with CoA as pantothenic acid (**11**) and pass it through the series of steps outlined in Scheme 2.1. This process was first elucidated by Brown *et al.* in *Proteus morganni*[99] and then later in mammals.[100] Prokaryotes also share this pathway, but many are also able to biosynthesize **11** from aspartate and α-ketovalerate through a separate series of steps. For mammals, pantothenic acid is readily avaialble in almost every food source, so there is no need for a seperate pathway to vitamin B_5.[101]

Beginning from pantotheinic acid (**11**), the enzyme CoaA phosphorylates the 4'-hydroxyl of the pantoic acid moiety to give 4'-phosphopantothenic acid (**12**) (Figure 2.1). Next, cysteine is added by CoaB to yield 4'-phosphopantethenoylcysteine (**13**). CoaC decarboxylates **13** to yield phosphopantetheine (**14**). At this point we can see how derivatives of **14** can be incorporated into the CoA biosynthetic pathway to yield derivatives of CoA. CoaD adds adenoside mono-phosphate to give the next to last compound in the cycle: dephospho-CoA (**15**). Finally, the adenoside is phosphorylated at the 3' position by CoaE to yield CoA (**10**).

Recently, it has been shown that pantetheine (**16**), and derivatives of pantetheine can be converted to phosphopantetheine (**14**) by CoaA[102–104] (bottom of Scheme 2.1) This finding is particularly important for the synthetic community because it allows preparation of CoA derivatives by enzymatic reactions of the simpler, pantetheine derivatives with CoaA, D, and E successively.



Scheme 2.1: The CoA biosynthetic pathway

2.3 CoA derivatives and their uses

In light of the ability of some more promiscous PPTases to load coenzyme A derivatives onto many different carrier proteins, these derivatives have become extremely important as labels, reporters, or inhibitors of secondary metabolic systems. It is most compelling that derivatives or analogues of CoA could be used as inhibitors

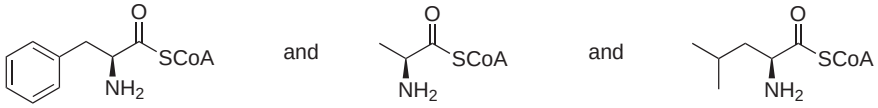
of toxin synthesis, or as inhibitors of prokaryote fatty acid synthesis. Studying these systems can open up new targets for a pharmaceutical world that is running out of effective antibiotics. A brief sampling of CoA derivatives and their functions is represented in Figure 2.2. This section is meant to serve as an introduction to some of the derivatives in use. A more thorough treatment of this subject is available in the review by Mishra and Drueckhammer.[97]

CoA derivatives traditionally vary at the thioester, as presented by work done in the Walsh lab by Belshaw *et al.* on the tyrocidine synthase.[105] CoA was esterified with selected amino acids to form **17**, **18**, and **19** and they were directly loaded onto peptidyl carrier proteins (PCP's) that would bypass the adenylation domain, the enzymatic domain which discriminates amino acids to load onto the PCP's. It was found that the condensation domain had low selectivity in discriminating the donor residue when it was the wrong peptide, and higher selectivity when discriminating the amino acid on the acceptor residue.

Both Freund *et al.* and Powell *et al.* used 3-alkyonyl CoA derivatives **20a**, **b**, and **c** to inactivate acyl CoA dehydrogenase from pig liver.[106,107] These inhibitors are mechanism based, in that in the enzyme pocket, the base that normally peforms α-deprotonation will rearrange the alkyne into a 2',3'-alleneyl CoA, to which an active site nucleophile will add. The Glu-401 residue was identified through radiolabelling and Edman degradation to be the site that is modified by the **20** series.

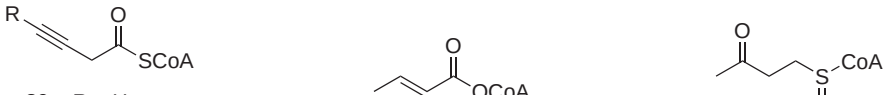
In some studies, the thiol itself is altered. Dai *et al.* used crotonyl-oxyCoA (**21**) to probe the mechanism of enoyl-CoA hydratase, the enzyme that catalyzes the 3-hydroxylation of α,β unsaturanted fatty acids.[103] It was found that once the crotonyl group was hydroxylated the ester of oxo-CoA was more stable than the respective thioester of CoA. This synthesis was unique in that what is prepared is the crotylated oxo-pantetheine, and then treated it with CoA biosynthetic enzymes CoaA, CoaD, and

Belshaw:



17 **18** **19**

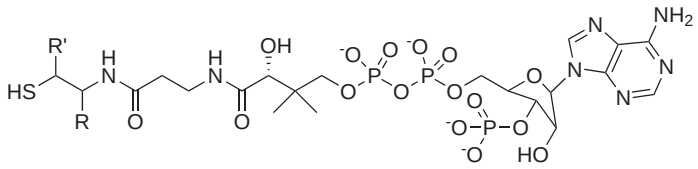
Freund *et al.* & Powell *et al.*: **Dai *et al.*:** **Charlier *et al.*:**



20a, R = H
20b, R = CH_3
20c, R = nC_4H_9

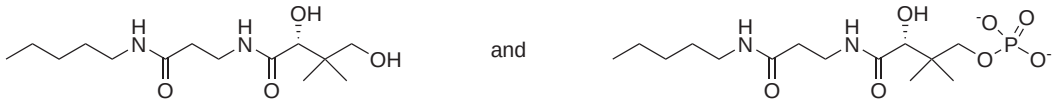
21 **22**

Shimizu:



23a, R = CH_3, R' = H; **23b**, R = H, R' = CH_3; **23c**, R = CO_2^-, R' = H

Strauss & Begley:



24 **25**

Figure 2.2: A sampling of CoA derivatives

CoaE to produce **21** which was used in the studies.

Charlier *et al.* prepared a derivative of CoA that had a sulfoxide instead of a thioester (**22**).[108] This sulfoxide is an inhibitor of HMG-CoA lyase, HMG-CoA synthase, and β-keto thiolase. The postulated mechanism involves β-elimination of the sulfoxide when the α proton to the ketone is removed by base, and the sulfenic acid forms a thioester with an active site thiol. Activity was restored upon reducing the thiol with DTT.

While CoA has been the subject of numerous studies, derivatives that vary in the pantetheine backbone are rare. One example is by Shimizu, who utilized similar phosphorylation conditions as Moffatt[109] (see next section for more details) to produce derivatives (**23a**, **b**, and **c**) that varied the cystamine position.[110] Strauss and Begley recently found that complete removal of the cystamine from pantetheine and phosphopantetheine (**24** and **25**) formed products that could interlope into the CoA biosynthetic pathway, and they resulted in formation of their respective CoA analogues ten times faster than the natural substrates.[102] This competetion effectively results in a large amount of inactive CoA derivatives that down-regulate further production of CoA. the compounds therefore inhibit bacterial growth.

Currently, in an effort to develop proteomic methods to label carrier proteins, the Burkart laboratory has published several new methods using pantetheine derivatives (Figure 2.3). Many modifications at **M1** have been used to introduce reporter molecules that allow the visualization and isolation of carrier proteins from *in vitro* and *in vivo* experiments. La Clair *et al.* showed that maleamide modified Coenzyme A (**10**) can be loaded onto carrier proteins with Sfp as the PPTase. These results defined the possibility of using CoA derivatives to extract CP's from systems where the biosynthetic machinery has not yet been characterized.[111] This method was expanded through the use of a competition assay among three differentially labeled CoA derivatives (**26**, **27**, **28**) that would have different rates of addition to a carrier protein.[112] The results could then be measured colorimetrically to give a fingerprint response for different CP's.

Important breakthroughs occurred when Dai *et al.* and Nazi *et al.* were able to synthesize CoA and oxy-CoA derivatives through enzymatic methods,[103,104] thus confirming that the CoA biosynthetic pathway could start from pantetheine (**16**) instead of pantothenic acid (**11**) (Scheme 2.1). This discovery lead to the one pot synthesis

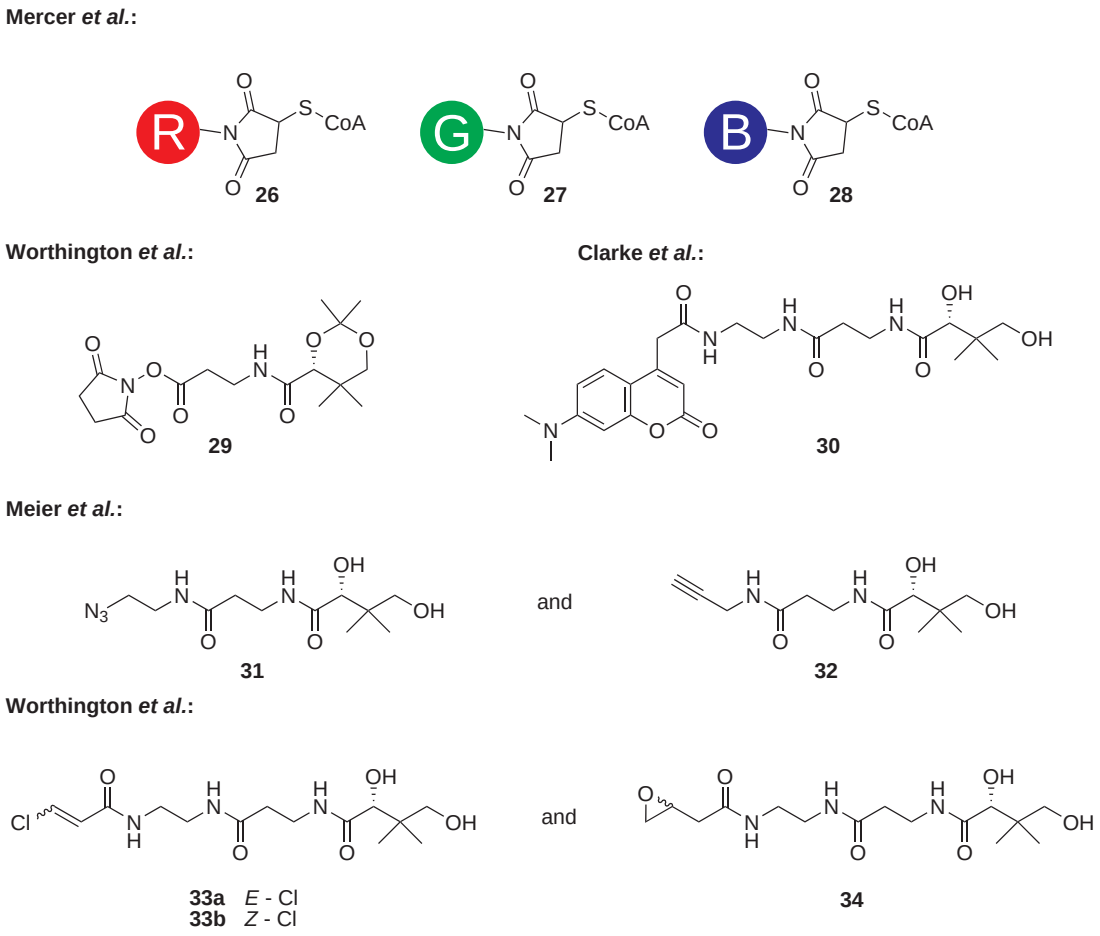


Figure 2.3: CoA derivatives in use in the Burkart group

by Worthington *et al.* which allows pantetheine drivatives to be directly converted to CoA derivatives.[113] In a single flask, the NHS-protected pantetheine **29** was combined with an amine in THF that displaces the *N*-hydroxysuccinimide, and then HCl was added to deprotect the acetonide. Following evaporation and neutralization of the acid, CoaA, CoaD, CoaE, a carrier protein (ACP) and Sfp could be added and labeled by the derivative *in situ*.

Carrying forward with derivative work, Clarke *et al.* showed that labeled pantetheine derivatives such as **30** can cross the cellular membrane and coerce the CoA enzymatic pathway *in vivo* to convert them to CoA derivatives.[114] Once the pan-

tetheine derivatives are converted into labeled CoA derivatives, they are loaded onto *apo*-carrier proteins which will produce fluorescent bands when subjected to PAGE.

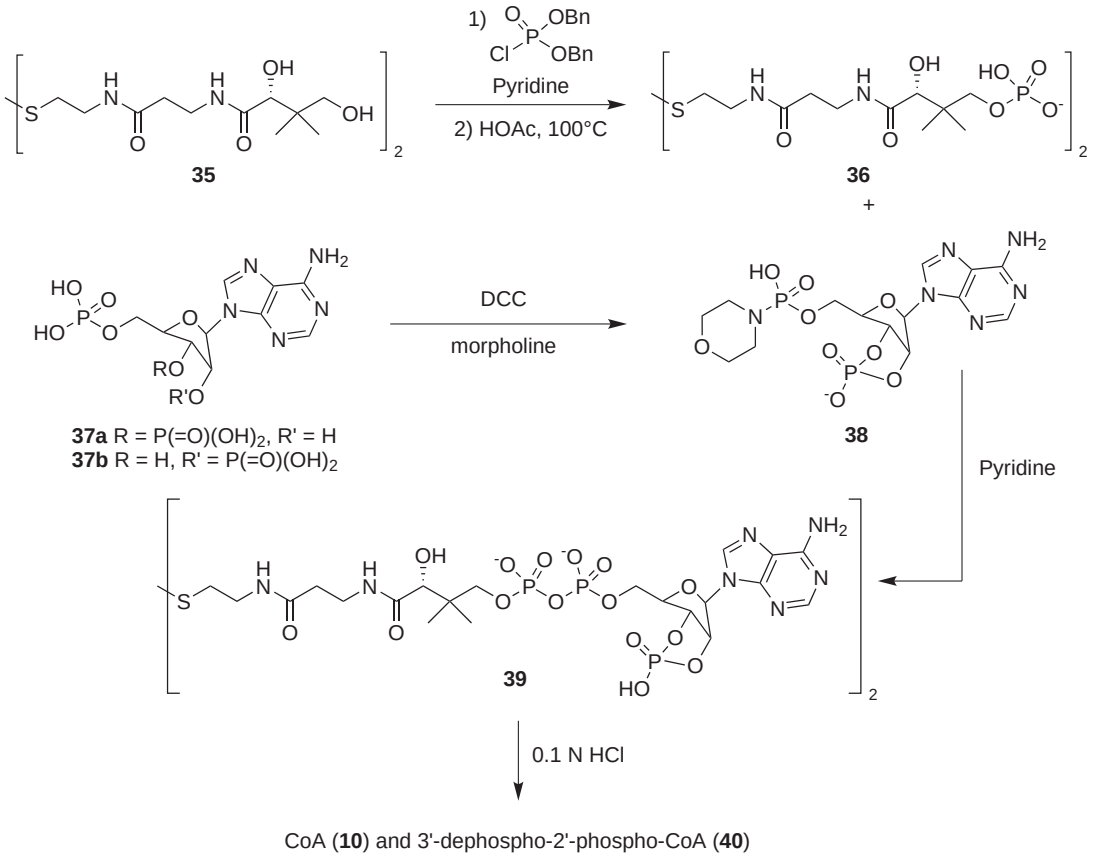
Meier *et al.* improved on this technique by designing azido and alkynyl pantetheines such as **31** or **32** that also enter into the CoA biosynthetic pathway and are loaded onto CP's.[115] Alkynes and azides will react with the other to form a triazole under copper catalysis. Since these functional groups are not found in nature, they are bioorthogonal, and reporters that react under the "click" conditions will only label proteins that are loaded with the unnatural phosphopantetheine. These modified carrier proteins allow several different reporters to be clicked onto carrier proteins after cell lysis. The method opens up a wider selection of reporters with which to label CP's, and it makes affinity labeling and pull-down assays more robust.

Finally, derivatives in this fashion can be used as inhibitors or cross-linking agents as Worthington *et al.* demonstrated.[116] Once **33a**, **33b**, or epoxide **34** are loaded onto *E. coli* ACP, the free sulfurs of the cysteines on ketosynthases KASI and KASII attack the epoxide or chloroacrylates and the proteins become crosslinked. The reactive ACP, loaded with **33a**, **33b**, or **34** will also crosslink to some type II PKS ketosynthase domains.

2.4 Previous syntheses of coenzyme A

2.4.1 The Moffatt and Khorana synthesis of CoA

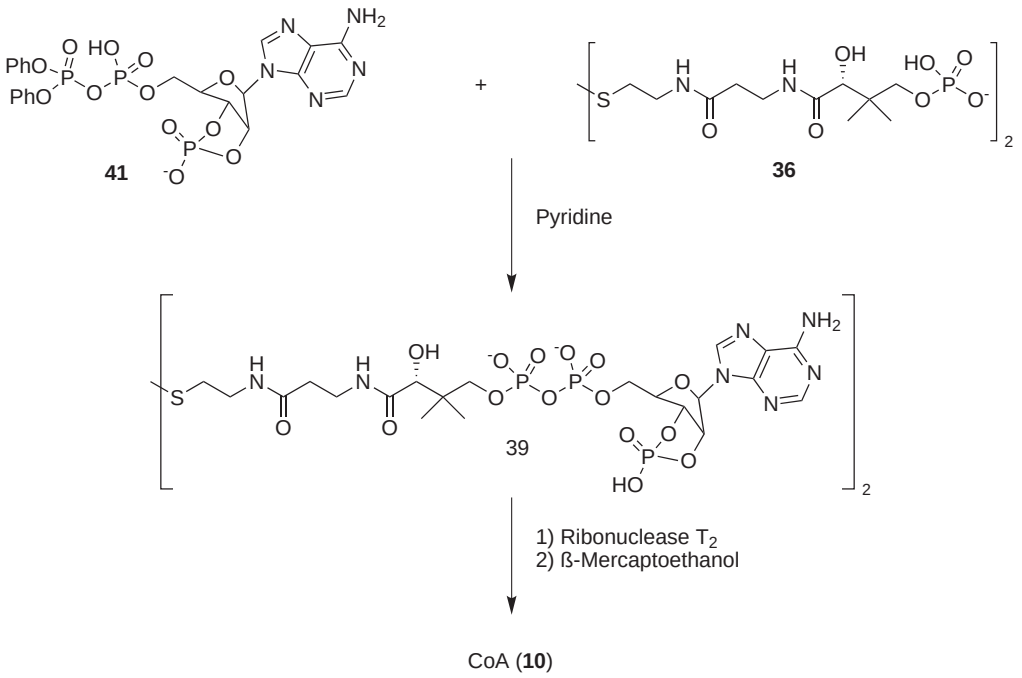
The first total synthesis of **10** was completed in 1961 by Moffatt and Khorana (Scheme 2.2).[109] Their synthesis was based on earlier progress by Baddiley and Thain in the 1950's.[117] Badilley and Thain were able to produce pantetheine through the basic aminolysis of pantolactone with β-alanine (Not shown). This procedure unfortunately leads to racemization of D-Pantolactone. Keeping these results in mind, later when



Scheme 2.2: The Moffatt and Khorana synthesis of Coenzyme A

the modular syntheses are presented, this is the main reason D-pantolactone was not used directly as **M3**. It turns out that recent syntheses have circumvented this problem by using a milder base.[115,118] Moffatt and Khorana explored this methodology to synthesize 4'-phosphopantetheine **14** as an advanced intermediate, but they also got a racemic product, and though they used it for their studies, they also completed synthesis of the enantiopure (*S*)-CoA (**10**)

Beginning with pantethine (**35**), available from biological sources, phosphorylation with dibenzylphosphorochloridate produced the disulfide of 4'-phosphopantetheine (**36**). In parallel, 2,5-diphosphoadenosine (**37a**) and 3,5-diphosphoadenosine (**37b**) were prepared using standard methods, and activated with DCC to form the 2',3'-



Scheme 2.3: The Michelson synthesis of Coenzyme A

cyclic-phosphate 5'-phosphoromorpholidate **38**. Combining the two phosphates in pyridine yielded the disulfide of CoA with a 2',3'-cyclic phosphate (**39**). Finally, hydrolysis of the phosphate followed by reduction with β-mercaptoethanol produced an essentially 1:1 mixture of CoA (**10**) and 3'-dephospho-2'-phosphoadenosyl-CoA (**40**).

2.4.2 The Michelson synthesis of CoA

Three years later, Michelson produced a more selective synthesis that also used a higher yielding phosphate coupling (Scheme 2.3).[119] Michelson used the pyrophosphate **41**, derived from adenosine 2',3'-cyclic phosphate as a more active coupling regent. Combining the same disulfide of phosphopantetheine (**36**) and **41** gave disulfide **39**. Finally, treatment with T_2 ribonuclease and then β-mercaptoethanol produced only the correct 3'-phosphoadenolsyl moeity and yielded CoA in 63% after the coupling.

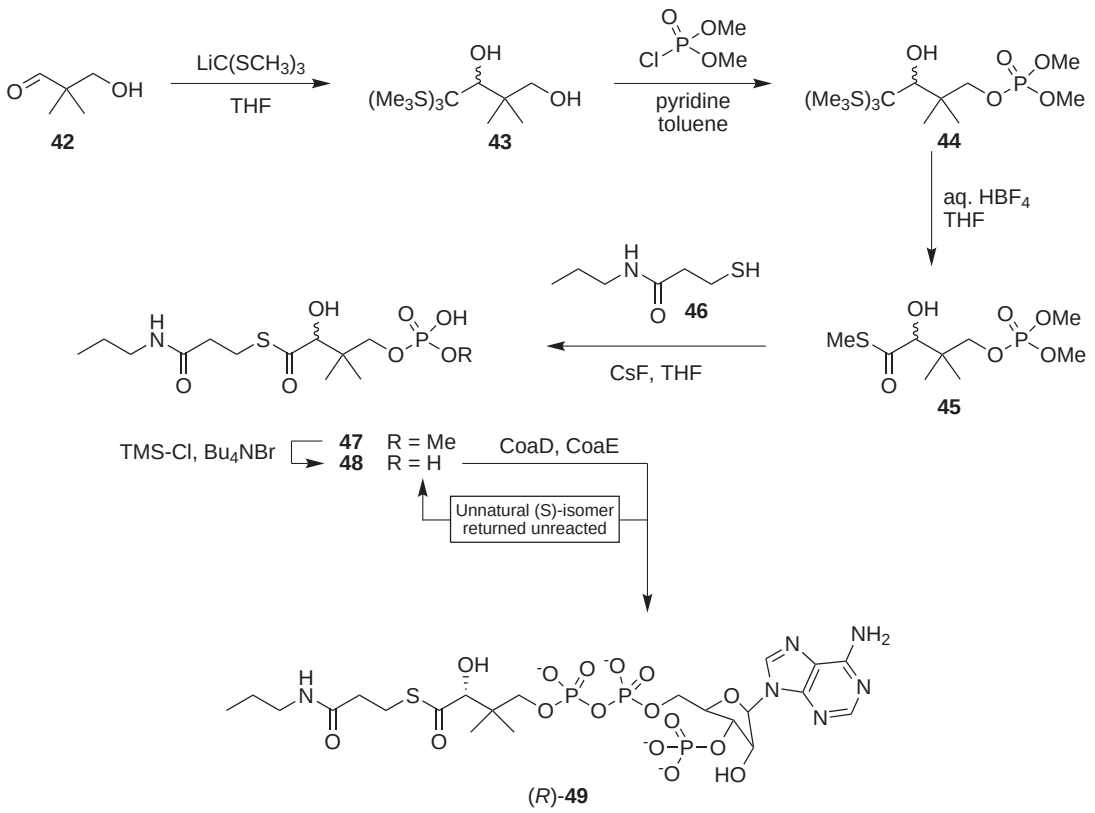
2.4.3 Drueckhammer's synthesis of a CoA derivative synthon

In pursuit of derivatives, the synthetic work pervious to 1992 did not prove that useful in modifying the pantetheine backbone (**M1** – **M3**). In 1992, Drueckhammer came up with a thioester that could be used as a quick derivative synthon.[120] This work was expanded in 1999 to make a more versatilie synthon which would allow an almost complete coenzyme A to be substituted past the β-alanine (Scheme 2.4).[121] These synthons use the CoA biosynthetic enzymes to install the adenosine and 3'-phosphate onto a phosphopantetheine derivative; a significant advance over the complicated chemical methods. This CoA derivative is then activated so that another amine can displace the thioester to yield a useful CoA variant.

The synthesis began with an organometallic addition of lithium tris(methylthio)methane to aldehyde **42**, to give orthothioester **43**. Treatment with dimethylphosphochloridate phosohorylated the primary hydroxyl as **44**. Acid converted the phosphorylated ortho thioester **44** to the methyl thioester **45**. Next, **45** was trans-esterifed with thiol **46** to mimic the natural coenzyme A backbone as **47**. This step leads to hydrolysis of one of the methyl groups on the phosphate. Finally, the phosphate was completely deprotected with TMS bromide to give **48**.

With phosphopantetheine derivative **48** in hand, the next step was to treat it with the biosynthetic enzymes phosphopantetheine adenylyltransferase (CoaD) and dephospho-CoA kinase (CoaE). It is important to note that the first step in this synthesis was not stereoselective. As it turned out, CoaD did not convert any of the (*S*)-**48**, and only the proper (*R*)-**49** was isolated.

Compound **49** was subjected to aminolysis with a variety of amine substrates, and they provided analogues under extended reaction times of 4 – 7 days. The main drawbacks of this synthesis are the many steps required for manipulation of the pantoic acid piece, the extended reaction time, and racemic nature of the synthesis.



Scheme 2.4: Bibart and Dreuckhammer's synthesis of a CoA derivative synthon. A thioester that mimics phosphopantetheine is treated with the biosynthetic enzymes CoaD and CoaE to produce a synthon that can be easily substituted to produce CoA analogues.

In the next section, a synthesis is presented that addresses these problems, and it leads to derivatives of pantetheine (**16**) and phosphopantetheine (**14**) that can be converted to CoA via chemical, enzymatic, or *in vivo* means.[122] This synthesis is also suitable for solid phase synthesis, or complex derivatives with labor intensive compounds that substitute **M1** and/or **M2**.

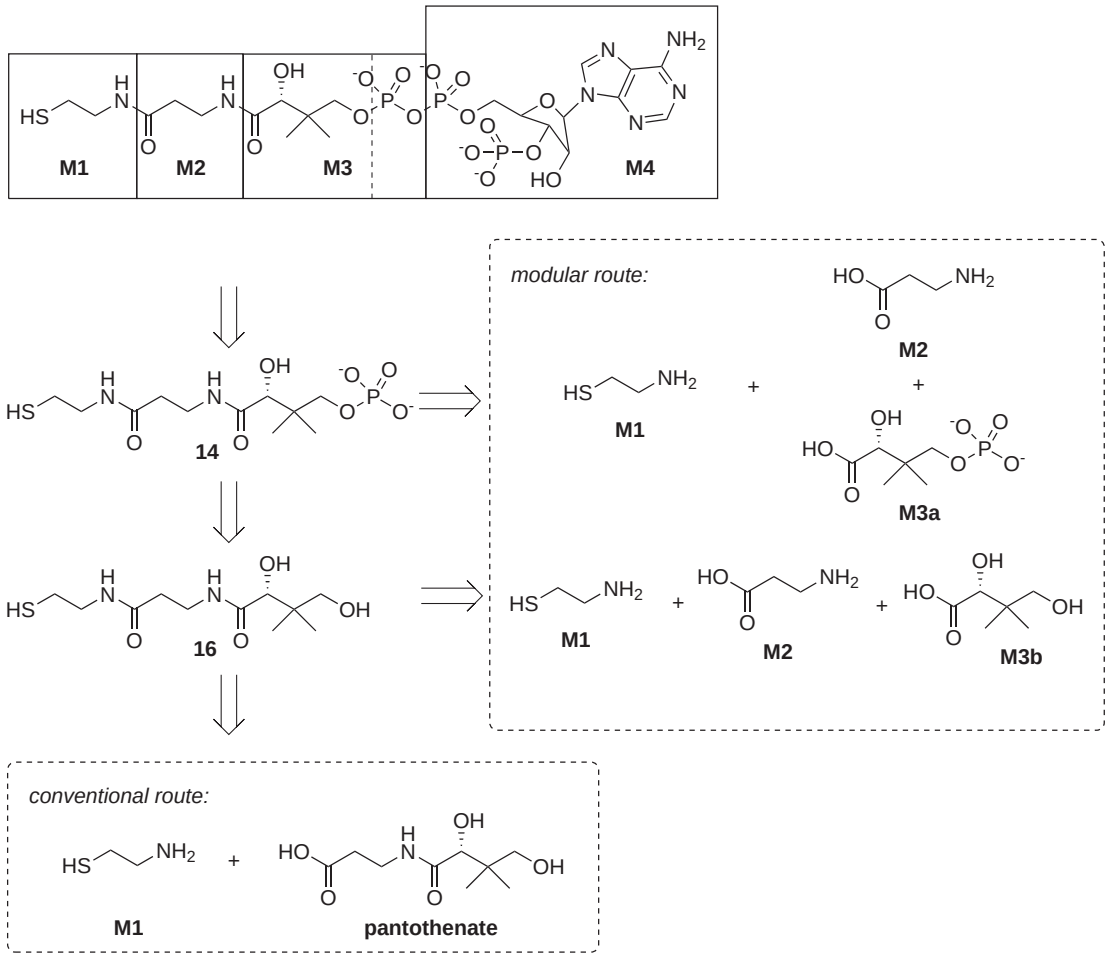
2.5 A synthetic view of coenzyme A

Two of the total syntheses presented above (Schemes 2.2 and 2.3) attempted to make use of pantolactone (**50**), the highly stable product of pantethenic acid hydrolysis, as a convienent synthon. Several problems however, including low yields, racemization at the α-carbon of pantolactone, and unusual side reactions, have limited the viability of schemes beginning with pantolactone. As a result, derivatives varying at the β-alanine moiety have generally been avoided,[97] and the β-alanine (**M2**) and pantoic acid (**M3**) modules are installed as a pair in pantothenate. Here we describe a modular route that permits individual substitution for each module (Scheme 2.5).

Furthermore, taking into account recent advances in understanding the biosynthesis of CoA, both pantetheine (**16**) and phosphopantetheine (**14**) can be used as precursors to CoA, and this limits the need to use chemical means to extend both products to the actual derivatives of **10**. Instead, the laboratory chose to synthesize derivatives that could act as intermediates knowing that Moffat and Khorana's, Michelson's, or White's methods could be applied to furnish the active CoA derivatives that the lab requires for probing biosynthetic machinery.

2.6 The modular synthesis of pantetheine

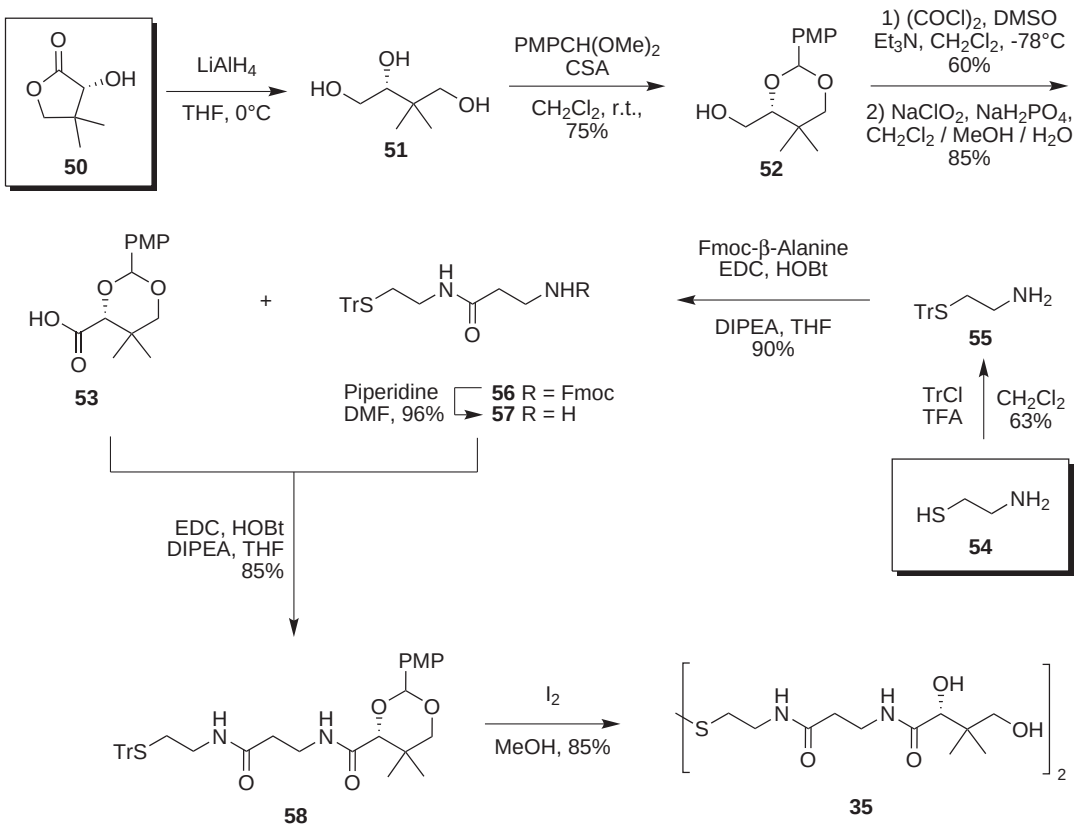
While pantolactone (**50**) can be coupled directly onto β-alanine to afford the necessary pantotheinic acid analogue, such strategies depend solely on the nucleophilicity of the β-alaninylamine (**M2**). Several disadvantages such as adverse effects from protecting groups and low-yielding reactions discourage variations that must be installed in this early stage of the synthesis. In addition, pantolactone is extremely stable to hydrolysis and contains a sensitive α-hydroxyl group that enhances the potential for α-carbon racemization under acidic or basic conditions.[123]



Scheme 2.5: Modular and conventional retrosyntheses of coenzyme A (**10**)

Accordingly, a scheme for opening pantolactone was developed (Scheme 2.6).[124] D-Pantolactone (**50**) was reduced with lithium aluminum hydride to afford triol **51** in high yield. Subsequent conversion to *p*-anisealdehyde acetal **52** selectively protected the 1,3-diol, permitting a Swern oxidation followed by a mild Krauss oxidation to furnish protected pantoic acid **53**.

In parallel, cystamine (**54**) was *S*-protected with trityl chloride under acidic condtions, and then neutralized with sodium hydroxide to amine **55** (Scheme 2.6). Subsequent coupling with Fmoc-β-alanine provided amide **56** through standard carbodiimide conditions. The protected **M1** – **M2** block **56** was deprotected to **57**

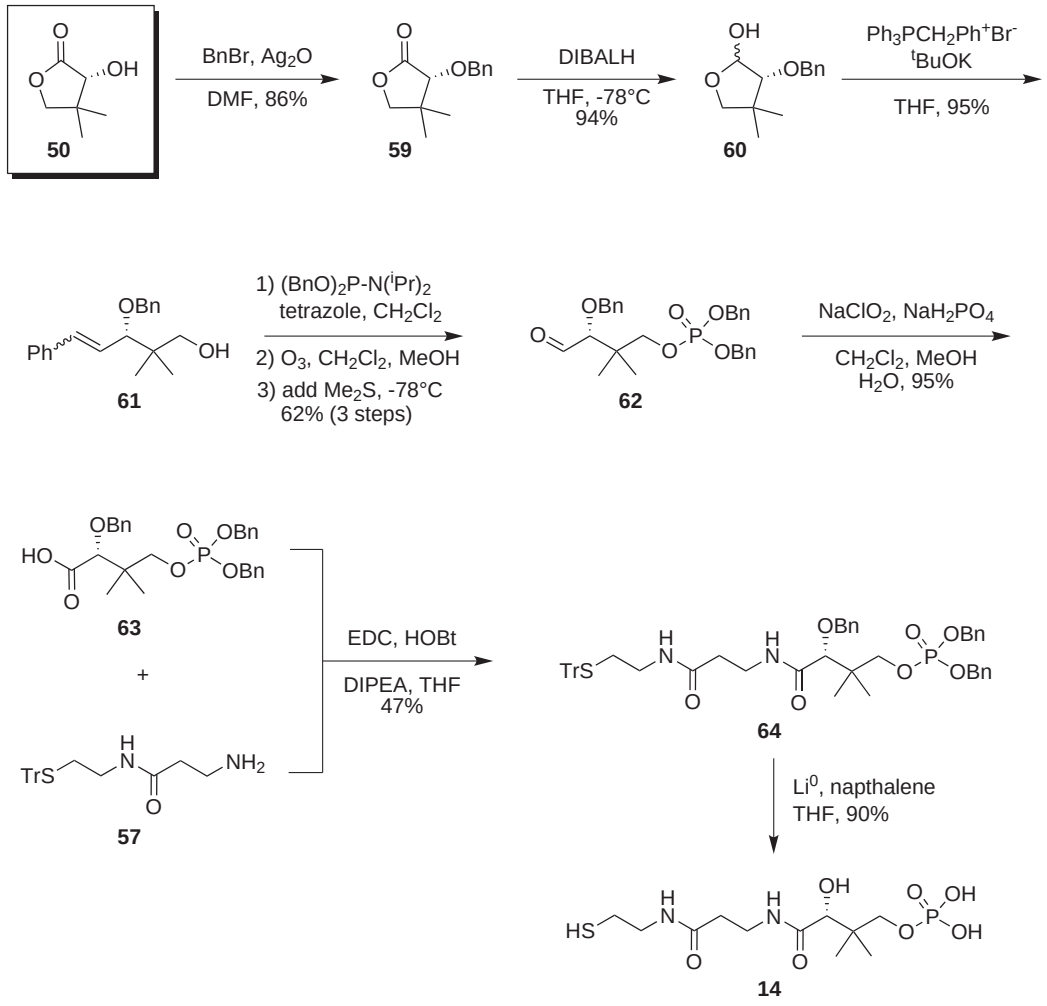


Scheme 2.6: The modular synthesis of pantethine

with piperidine and immediately coupled with **53** to provide protected pantetheine **58**. Global deprotection was achieved with iodine in methanol to afford pantethine (**35**), the disulfide of pantetheine, in 41% overall yield from cystamine or 28% from D-pantolactone (**50**).

2.7 The modular synthesis of phosphopantetheine

While both chemical and chemoenzymatic methods exist to convert pantetheine (**16**) to CoA, established procedures require 4'-phosphopantetheine (**14**).[102,104,109,119] Some alterations in the pantetheine backbone such as reversing the pantoic acid stereocenter from *R* to *S* will hinder the biosynthetic pathway to CoA.[121] Therefore, for



Scheme 2.7: The modular synthesis of phosphopantetheine

access to a wider range of CoA derivatives, it would be useful to build CoA chemically. Chemical phosphorylation of pantetheine (**16**) has been reported to give **14**, albiet in poor yield. Accordingly, we developed a route to directly couple a 4'-phosphorylated pantoic acid to amide **57** (Scheme 2.7) which would facilitate a more robust access to phosphopantetheine and derivatives thereof.

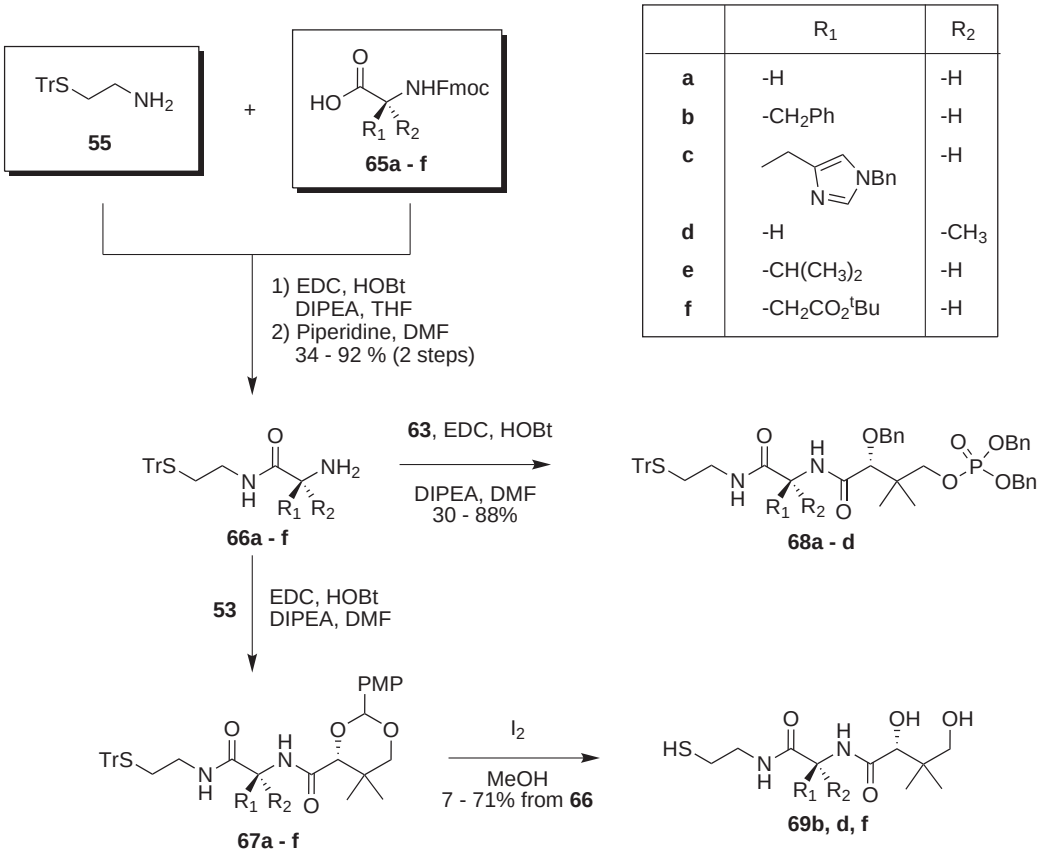
To begin, the α-hydroxyl of D-pantolactone (**50**) was protected by benzylation under mildly basic conditions. Careful control of pH was neccessary to prevent epimerization. Benzyl pantolactone (**59**) was subsequently reduced to lactol **60** with

DIBALH. Several conditions were attempted to open the lactol, but it was found that masking the aldehyde as an olefin **61** under Wittig conditions[125,126] provided a facile and high yielding means to open the ring. A sample of **61** was esterified with (*R*)-2-phenylbutyric acid and it was verified that the product remained enantiomerically pure.[127] From this point, the phosphate was added by incubation with dibenzyl-*N*,*N*-diisopropylphosphoramidite followed by immediate ozonolysis to provide aldehyde **62** in 62% yield from **61**. Variations on this scheme can also be used to isolate the dibenzyl phosphite of **61**. Partial ozonolysis or oxidation with oxygen can also be used to generate the dibenzyl phosphate of olefin **61**. The phosphate oxidizes easily in the presence of ozone, whereas olefin cleavage takes several minutes of exposure in a gram scale reaction.

As in Scheme 2.6, a mild chlorite oxidation of **62** completed the synthesis of **63**. After isolation, **63** was coupled to **57** using standard peptide coupling conditions to provide protected phosphopantethein **64**. The final deprotection to phosphopantetheine (**14**) was achieved through reduction with lithium napthalenide.[128] The ^{1}H NMR spectrum of **14** matched the published spectra[129] with the exception of a downfield shift in the methylene group adjacent to the thiol (δ = 2.83 ppm found vs. δ = 2.64 reported by Sarma). This was attributed to a different state of sulfur oxidation, as we suspect that Sarma examined the disulfide of **14**.

2.8 The modular synthesis of pantethine and phosphopantetheine derivatives

Both **53** and **63** were used to generate a set of pantethine and phosphopantetheine analogues bearing an internal amino acid residue in place of β-alanine (Scheme 2.8). Using methods established in Scheme 2.6, (*S*)-trityl cystamine was coupled to



	R_1	R_2
a	-H	-H
b	$-CH_2Ph$	-H
c		-H
d	-H	$-CH_3$
e	$-CH(CH_3)_2$	-H
f	$-CH_2CO_2{}^tBu$	-H

Scheme 2.8: The modular synthesis of pantethine and phosphopantetheine derivatives

Fmoc-protected amino acids **65a – f** to provide **66a – f** in yields ranging from 30 to 88%. Low yields in couplings of **65e** and **65f** were due to extended reaction times. Alternate coupling reagents could be screened to increase the yield of these reactions. Amides **66** provided access to analogues of pantethine and phosphopantetheine through conversion to **67a – f** or **68a – d**. Once coupled, there are a variety of potential conditions to deprotect **67a – f**.[130–132] As shown in Scheme 2.8, the deprotection of **67b**, **d**, and **f** with iodine in methanol offered **69b d**, and **f** in unoptimized yields of 7, 71, and 11%, respectively from **65b**, **d**, and **f**. Comparable schemes are also available for the modification of **68a – d**.[128,133]

2.9 Concluding thoughts

Schemes 2.6 – 2.8 provide access to the three component modular synthesis of pantethine, 4'-phosphopantetheine, and analogues therein. With this approach, modifications may be introduced at any of the three peptoid modules **M1**, **M2**, and **M3** of the pantetheine structure. We are currently following various avenues of parallel chemical and chemoenzymatic synthesis to investigate novel analogues of CoA in primary and secondary metabolic pathways.

2.10 Acknowledgements

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2.11 Experimental data

Reactions were performed under Ar atmosphere at room temperature (rt) in oven dried glassware expect where indicated or when water is used as a solvent. Column chromatography was performed with EM Silica Gel 60, and thin layer chromatography was performed on EMD Silica Gel 60 F_{254} pre-coated plates. Visualization of TLC was with a ceric ammonium molybdate solution preceeded by UV if necessary. NMR spectroscopy was performed on Varian Mercury 300 MHz, 400 MHz, or Unity 500 MHz instruments at ambient temperature. ^{1}H and ^{13}C NMR spectra are reported in parts per million relative to TMS and standardized to chloroform (^{1}H δ = 7.26 ppm,

^{13}C δ = 77.16 ppm) with multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiple peaks, br = broad), coupling constants, and integration. All ^{13}C NMR spectra are reported with complete proton decoupling. ^{31}P NMR spectra are reported in ppm relative to H_3PO_4 (δ = 0 ppm). Mass spectra were taken on a ThermoFinnigan LCQdeca mass spectrometer and high resolution spectra were taken on ThermoFinnigan MAT900XL high resolution mass spectrometer with electron impact or fast atom bombardment as ionization methods.

2.11.1 New compounds from Scheme 2.6

Protected pantoic triol (52) – See literature preparation by Miyaoka.[126]

Protected pantoic acid (53) – Swern oxidation was carried out on **52** (2.56 g, 18.44 mmol) as per Miyaoka[126] procedure for the preparation of (2*R*, 4*R*)-2-(4-Methoxy-phenyl)-5,5-dimethyl-1,3-dioxane-4-carbaldehyde and the resultant oil was purified by silica gel chromatography (6:1 to 2:1 hexanes / EtOAc) to yield the product as a clear oil that crystallized under high vacuum (2.07 g, 81%). The product was recrystallized in hexane / Pentane (1:1, 30 mL), to afford long white needles (1.51 g, 60% overall)

The product aldehyde of the preceding reaction (199 mg, 0.796 mmol) was dissolved in acetone / CH_2Cl_2 (3:1, 12 mL). A fresh solution of $NaH_2PO_4 \cdot H_2O$ (1.10 g, 7.96 mmol) and $NaClO_2$ (360 mg, 3.98 mmol) was prepared in 3 mL of water, and it was added dropwise to the stirring solution of the aldehyde. After 8 minutes, the volatile solvents were evaporated *in vacuo*, leaving flakes of white solid in the aqueous remnants. Solid $NaHSO_3$ was added to remove the bleach, and the solid was filtered out to give **53** (180 mg, 85%). The product was prue by NMR, but it could be recrystallized in THF/hexanes (1:4) to give clear prisms (123 mg, 85% (recrystallization yield)).

The product should be stored cold, as it will spontaneously deprotect and reform pantolactone, and the scent of anisealdehyde will become marked in the residue. ^{1}H-NMR: δ ($CDCl_3$, 300 MHz) 7.41 (d, J = 9.0 Hz, 2H), 6.90 (d, J = 11.6 Hz, 2H), 5.51 (s, 1H), 4.22 (s, 1H), 3.80 (s, 3H), 3.76 (d, J = 11.7 Hz, 1H), 3.66 (d, J = 11.6 Hz, 1H), 1.19 (s, 3H), 1.09 (s, 3H). ^{13}C-NMR: δ ($CDCl_3$, 100 MHz) 169.5, 160.2, 129.3, 127.5, 113.8, 101.6, 82.9, 78.2, 55.3, 33.1, 21.6, 19.3.

S-Trityl cystamine (55) – To cystamine · HCl (**54**) (1.50 g, 14.4 mmol) and trifluoroacetic acid (3.28 g, 2.22 mL, 28.7 mol) dissolved in CH_2Cl_2 with a drying tube, trityl chloride (4.20 g, 15.1 mmol) was added. The solution immediately turned a dark yellow color. After 30 minutes the reaction was quenched with 1 M NaOH (30 mL) turning the solution back to clear. The organic layer was diluted with CH_2Cl_2 (75 mL), and additional 1 M NaOH (20 mL) was added, and the aqueous layer was separated. The organic layer was then washed with brine (20 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give a yellow oil. The oil was purified by flash chromatography (1:4 to 1:1 MeOH / EtOAc) to give **55** (3.14 g, 63%) as a clear oil which solidified when left under vacuum overnight. ^{1}H-NMR: δ (400MHz, $CDCl_3$) 7.41 (m, 6H), 7.27 (m, 6H), 7.20 (m, 3H), 2.57 (t, J = 8 Hz, 2H), 2.33 (t, J = 8 Hz, 2H).

S-Trityl cystamine Fmoc-β-alanine (56) – **55** (50 mg, 0.14 mmol), Fmoc-β-alanine (65 mg, 0.21 mmol), EDC (67 mg, 0.35 mmol), and HOBt (56 mg, 0.42 mmol) were combined and dissolved in dry THF (10 mL). DIPEA (110 mg, 0.84 mmol) was added, and the reaction was allowed to stir for 4.5 hours. The reaction was quenched with 25% $NH_4Cl_{(aq)}$ and diluted with diethyl ether (20 mL). The organic layer was washed with water (5 mL), brine (5 mL), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The resultant oil was purified by column chromatography (1:1, hexanes / EtOAc) to yield **56** (81 mg, 90%) as a sticky white solid. ^{1}H-NMR: δ (300MHz, $CDCl_3$) 7.73

(d, J = 7.5 Hz, 2H), 7.55 (d, *J* = 7.5 Hz, 2H), 7.45 – 7.15 (m, 19H), 5.46 (b, 2H), 4.33 (d, *J* = 7.2 Hz, 2H), 4.17 (t, *J* = 6.6 Hz, 1H), 3.42 (m, 2H), 3.06 (q, *J* = 6.3 Hz, 2H), 2.41 (t, *J* = 6.0 Hz, 2H), 2.30 (t, 2H). ^{13}C-NMR: δ (100 MHz, $CDCl_3$) 170.9, 156.3, 144.3, 143.7, 141.1, 129.3 – 126.7 (multiple signals), 125.0, 119.8, 66.7, 47.3, 38.2, 35.9, 31.9. ESI-MS: found $\frac{m}{z}$ = 635.12 amu. $[M+Na]^+$ calcd. $C_{39}H_{36}O_3N_2SNa^+$: 635.23 amu.

Protected pantetheine (58) – **56** (58 mg, 0.090 mmol) was dissolved in DMF (3 mL), and piperidine was added (0.75 mL). The DMF and piperidine were evaporated under reduced pressure, and to the dry residue (crude **57**) EDC (36 mg, 0.19 mmol), HOBt (31 mg, 0.23 mmol), and **53** (20 mg, 0.075 mmol) were added. The flask was evacuated and filled with argon. The contents were dissolved in THF and DIPEA (59 mg, 0.080 mL, 0.46 mmol) was added. The reaction was allowed to stir overnight and it was quenched with 25% $NH_4Cl_{(aq)}$ and diluted with diethyl ether (15 mL). The organic layer was separated and washed with water (5 mL), brine (10 mL), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The product was purified by silica get chromatography (1:1 to 1:5 hexanes / EtOAc) to give **58** (41 mg, 85%) as a clear film. It should be noted that in this form the product will slowly deprotect in chloroform to give S-trityl pantetheine. ^{1}H-NMR: δ ($CDCl_3$, 400 MHz) 7.40 – 7.37 (m, 6H), 7.28 – 7.26 (m, 6H), 7.21 – 7.18 (m, 5H), 6.97 (t, J $\sim$ 8 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.76 (t, J $\sim$ 8 Hz 1H), 5.39 (s, 1H), 4.02 (s, 1H), 3.79 (s, 3H), 3.67 (d, *J* = 12 Hz, 1H), 3.60 (d, *J* = 12 Hz, 1H), 3.48 (d, *J* = 6 Hz, 1H), 3.45 (d, *J* = 6 Hz, 1H), 3.02 (8-plet, *J* = 6.4 Hz, 1H), 2.98 (8-plet, *J* = 6.0 Hz, 1H), 2.385 (t, *J* = 6.8 Hz, 1H), 2.378 (t, *J* = 6.4 Hz, 1H), 2.31 (t, *J* = 6.0 Hz, 2H), 1.05 (s, 3H), 1.04 (s, 3H). ^{13}C-NMR: δ ($CDCl_3$, 100 MHz) 170.6, 169.5, 144.6, 130.1, 129.5 – 126.6 (multiple signals), 113.7, 101.2, 83.8, 78.4, 66.8, 55.3, 38.2, 35.9, 34.8, 33.0, 31.7, 21.8, 19.1.

1 H-COSY couplings 6.97 – 3.46, 5.76 – 3.00, 3.46 – 2.31, 3.00 – 2.38.

Pantethine (35) – **58** (13 mg, 0.020 mmol) was dissolved in methanol (2 mL), and a 0.1 M solution of iodine in methanol (2 mL) was added. After 20 minutes, zinc metal was added to remove the iodine. The solution was filtered through celite and evaporated *in vacuo*. The remaining residue was purified twice by silica gel chromatography (1:1 MeOH / EtOAc) to remove iodine salts from the product **35** (5 mg, ~85%). ^{1}H-NMR: δ (D_2O, 400 MHz) 4.00 (s, 1H), 3.51 – 3.54 (m, 5H), 3.40 (d, J = 11.2 Hz, 1H), 2.87 (t, J = 6.0 Hz, 2H), 2.53 (t, J = 6.4 Hz, 2H), 0.94 (s, 3H), 0.90 (s, 3H). ESI-MS: found $\frac{m}{z}$ = 577.22, calcd. $C_{22}H_{42}O_8N_4S_2Na^+$: 577.23

2.11.2 New compounds from Scheme 2.7

Benzyl pantolactone (59) – Silver oxide (3.54 g, 15.3 mmol) and benzyl bromide (1.4 g, 8.4 mmol) were added to a solution of D-Pantolactone (**50** (1.0 g, 7.7 mmol) in dry DMF (25 mL) at 0°C under nitrogen. The mixture was stirred at 0°C for 2 h, then warmed to r.t. and stirred for an additional 20 h. The solution as diluted with CH_2Cl_2 (100 mL) and filtered. The filtrate was concentrated *in vacuo*, diluted with EtOAc, and washed with 0.5 N HCl, water, and brine. The solvent was removed *in vacuo* and then excess benzyl alcohol was removed by co-evaporation with water under reduced pressure to give a crystalline solid. The product was recrystallized from hexanes to give **59** (1.46 g, 86%) ^{1}H-NMR: δ (300 MHz, $CDCl_3$) 7.30 – 7.36 (m, 5H), 5.02 (d, J = 12.0 Hz, 1H), 4.73 (d, J = 12.3 Hz, 1H), 3.97 (d, J = 9.0 Hz, 1H), 3.85 (d, J = 8.7 Hz, 1H), 3.71 (s, 1H), 1.12 (s, 3H), 1.08 (s, 3H). ^{13}C-NMR: δ (100MHz, $CDCl_3$) 175.4, 137.2, 128.4, 127.98, 127.97, 80.4, 76.4, 40.3, 23.2, 19.3. Note: this product has been synthesized previously using benzyl chloride by a different

method which required base; however, the optical purity was reduced even with the mild base Cs_2CO_3. Optical purity is preserved in this procedure and was confirmed by derivitization with a chiral ester.

Benzyl pantolactol (60) – To a stirred solution of **59** (3.00 g, 13.6 mmol) in CH_2Cl_2 (50 mL) at –78°C, DIBALH (1 M in hexanes, 16.3 mL, 16.3 mmol) was added over 30 minutes. After 2 hours, the reaction was quenched slowly at first with 60mL of a 1:1 diethyl ether / 1 M H_2SO_4 mixture. The reaction was then diluted with EtOAc (100 mL) and the organic layer was washed with 100 mL 1 M H_2SO_4, 10 mL of $NaHCO_{3(sat)}$, 10 mL of water, and twice with 20 mL of brine. The organic phase was then dried with Na_2SO_4, and concentrated *in vacuo*. The crude oil was purified by flash chromatography (2:1 hexanes / EtOAc to pure EtOAc) to yield **60** (2.85 g, 94%) as a clear oil that solidified to white clumps after it was removed from the freezer and disturbed. The product turned out to be an inseparable mixture of anomers in an approximate 2:3 ratio. ^{1}H-NMR: δ ($CDCl_3$, 400 MHz) 7.34 – 7.32 (m, 5H), 5.46 (m, $\frac{3}{5}$H), 5.36 (d, J = 2.8 Hz, $\frac{2}{5}$H), 4.70 (d, J = 12.0 Hz, $\frac{2}{5}$H), 4.66 (d, J = 11.6 Hz, $\frac{3}{5}$H), 4.61 (d, J = 11.2 Hz, $\frac{3}{5}$H), 4.57 (d, J = 12.0 Hz, $\frac{2}{5}$H), 3.98 (b, $\frac{3}{5}$H), 3.81 (d, J = 8.4 Hz, $\frac{2}{5}$H), 3.71 (d, J = 8.0 Hz, $\frac{3}{5}$H), 3.63 (d, J = 8.4 Hz, $\frac{2}{5}$H), 3.52 (d, J = 2.8 Hz, $\frac{2}{5}$H), 3.46 (d, J = 4.0 Hz, $\frac{3}{5}$H), 3.41 (d, J = 8.4 Hz, $\frac{3}{5}$H), 1.12 (s, $\frac{9}{5}$H), 1.12 (s, $\frac{6}{5}$H), 1.11 (s, $\frac{6}{5}$H), 1.07 (s, $\frac{9}{5}$H). ^{13}C-NMR: δ ($CDCl_3$, 100 MHz) 127.5 – 128.7, 103.1, 97.8, 91.8, 85.6, 76.7, 79.1, 74.7, 72.7, 42.5, 26.1, 24.4, 20.8, 20.1. ESI-MS: found $\frac{m}{z}$ = 245.07, $[M + Na]^+$ calcd. $C_{13}H_{18}O_3Na^+$ = 245.12 amu.

Styrene 61 – To a stirred solution of benzyl triphenylphosphonium bromide (1.21 g, 2.78 mmol) in THF (15 mL) at –78°C, potassium ^{t}butoxide (1 M in THF, 2.69 mL, 2.69 mmol) was added. The solution immediately turned orange, and was allowed to stir as it turned to crimson-orange. After 30 minutes, a solution of **60** (206 mg, 0.928

mmol) in THF was cannulated into the stirring ylide, and the reaction was allowed to warm to room temperature. After two hours, the reaction was driven to completion by heating to reflux for 40 minutes. The reaction was quenched with $NH_4Cl_{(sat)}$ (3 mL), diluted with diethyl ether (50 mL) and the organic layer was washed with water (10 mL) and brine (10 mL) whereupon it was dried with Na_2SO_4 and concentrated *in vacuo* until a yellow oil remained. The compound (**61**) was purified by flash chromatography (8:1 to 4:1 hexanes / EtOAc) and concentrated to a clear yellowish oil (260 mg, 95%). The product was a mixture of regioisomers that was about 3:2 *E/Z*. ^{1}H-NMR: δ (300 MHz, $CDCl_3$) 7.45 – 7.20 (m, $10H^{E\&Z}$), 7.10 – 7.08 (m, 2HE&Z), 6.83 (d, J = 12.0 Hz, $1H^Z$), 6.54 (d, J=15.9 Hz, $1H^E$), 6.19 (dd, J = 16.2, 8.4 Hz, $1H^E$), 5.71 (dd, J = 12.0, 10.8 Hz, $1H^Z$), 4.64 (d, J = 11.7 Hz, $1H^E$), 4.55 (d, J = 11.7 Hz, $1H^Z$), 4.34 (d, J = 11.7 Hz, $1H^E$), 4.28 (d, J = 11.1 Hz, $1H^Z$), 4.11 (d, J = 11.7 Hz, $1H^Z$), 3.80 (d, J = 8.4 Hz, $1H^E$), 3.58 (d, J = 10.9 Hz, $1H^E$), 3.54 (d, J = 10.9 Hz, $1H^Z$), 3.40 (d, J = 11.1 Hz, $1H^E$), 3.33 (d, J = 11.1 Hz, $1H^E$), 0.91 – 0.94 (m, 6H). ^{13}C-NMR: δ (100 MHz, $CDCl_3$) 137.91, 137.85, 136.6, 134.5, 126.3 – 128.8 (many signals), 87.67, 87.63, 71.4, 70.5, 70.0, 39.35, 39.31, 22.84, 22.79, 20.1, 19.9. ESI-MS: found $\frac{m}{z}$ = 319.08, $[M+Na]^+$ calcd. $C_{20}H_{24}O_2Na^+$: 319.18 amu.

Aldehyde 62 – To a stirred suspension of tetrazole (27 mg, 0.38 mmol) in CH_2Cl_2 (5 mL) at room temperature, N,N-diisopropyl-O,O'-dibenzyl phosphoramidite (131 mg, 0.127 mL, 0.38 mmol) was added. After 15 minutes, **61** dissolved in CH_2Cl_2 (2 mL) was cannulated into the stirring solution. After 2.5 hours, the solution was diluted with CH_2Cl_2, washed with water (5 mL), brine (5 mL), and dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residual oil was redissolved in a solution of CH_2Cl_2/MeOH (9:1, 5 mL), cooled to –78°C, and ozone was bubbled through the solution for 3 minutes. Dimethyl sulfide (1 mL) was added, and white vapor evolved

in the flask. The flask was then removed from the –78°C bath, and the solvent was evaporated *in vacuo*. Purification followed by flash chromatography (2:1 to 1:2 hexanes / EtOAc) to yield aldehyde **62** (113 mg, 62%) as a clear viscous oil. ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 9.66 (d, J = 2.8 Hz, 1H), 7.34 – 7.23 (m, 15H), 5.04 – 4.99 (m, 4H), 4.55 (d, J = 11.2 Hz, 1H), 4.40 (d, J = 11.6 Hz, 1H), 3.87 (dd, J = 9.6, 4.4 Hz, 1H), 3.80 (dd, J = 9.6, 4.4 Hz, 1H), 3.46 (d, J = 2.8 Hz, 1H), 0.95 (s, 3H), 0.94 (s, 3H). ^{13}C-NMR: δ (100 MHz, $CDCl_3$) 203.6, 137.0, 135.6 (d, J = 6.8 Hz), 127.7 – 128.5 (multiple signals), 86.4, 73.1, 72.1 (d, J = 6.1 Hz), 69.3 (d, J = 5.3 Hz), 39.8 (d, J = 8.3 Hz), 21.5, 19.8. ^{31}P NMR δ (121.4 MHz, $CDCl_3$) –1.15 ppm.

Protected phosphopantoic acid (63) – Aldehyde **62** (74 mg, 0.15 mmol) was dissolved in MeOH / CH_2Cl_2 / H_2O (6:3:2, 5 mL). NaH_2PO_4 (83 mg, 0.60 mmol) was added followed by 80% $NaClO_2$ (34 mg, 0.30 mmol). The solution turned green after 10 minutes. After 3.5 hours, the reaction was complete by TLC (1:2 hexanes / EtOAc). The reaction was quenched with 1 M HCl (1 mL) and the volatile solvents were evaporated *in vacuo*. The remaining material was extracted with CH_2Cl_2 (3x, 30 mL), and the organic extractions were combined washed with brine (10 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to yield **63** as a clear oil (75 mg, 99%). The product was used and characterized without further purification. It should be noted that the NMR is pH sensitive, and reported spectra were taken immediately after extraction. Further manipulation can cause some peaks to shift relative positions. ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 7.33 – 7.24 (m, 15H), 5.00 – 4.97 (m, 4H), 4.58 (d, J = 11.2 Hz, 1H), 4.35 (d, J = 10.8 Hz, 1H), 3.93 (dd, J = 9.6, 4.8 Hz, 1H), 3.80 (dd, J = 10.0, 4.8 Hz, 1H), 3.80 (s, 1H), 0.99 (s, 3H), 0.95 (s, 3H). ^{13}C-NMR: δ (100 MHz, $CDCl_3$) 173.0, 136.9, 135.7, 128.9 – 128.0 (multiple signals), 81.6, 72.6 (d, J = 6.1 Hz), 69.6 – 69.3 (m), 73.2, 38.9 (d, J = 8.4 Hz), 21.3, 20.0.

Protected phosphopantetheine (64) – **56** was deprotected by treatment with 20% piperidine in DMF (5 mL). Once the deprotection was apparent by TLC (1:2 hexanes / EtOAc), the mixture was concentrated and evaporated under vacuum until there was no remaining piperidine or DMF. The crude film of **57** was taken to the next step without further treatment.

EDC (19 mg, 0.098 mmol), and HOBt (15 mg, 0.098 mmol) were dissolved in THF (3 mL), and in separate flasks **63** (49 mg, 0.098 mmol) and **56** (78 mg, 0.187 mmol), were dissolved in THF (2 mL each). The solution of **56** was cannulated into the flask with EDC and HOBt, followed by cannulation of the solution containing **63**. DIPEA (100 μL) was then added and all of the solids within the flask dissolved. The reaction was allowed to stir for 23 hours before quenching with water. The solution was diluted with diethyl ether to 50 mL, the aqueous layer was removed, and the organic was washed with 1 M HCl (5 mL), $NaHCO_{3(sat)}$ (10 mL), and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resultant film was azeotroped twice with 25mL MeOH and purified by silica gel chromatography (1:1 hexanes / EtOAc to pure EtOAc). **64** (41 mg, 47%) was obtained as a clear film. ^{1}H-NMR: δ (300 MHz, $CDCl_3$) 7.40 – 7.15 (m, 30H), 7.00 (t, J = 6.6 Hz, 1H), 5.71 (t, J $\sim$ 6 Hz, 1H), 4.99 (t, J = 7.8 Hz, 4H), 4.39 (d, J = 10.8 Hz, 1H), 4.27 (d, J = 10.8 Hz, 1H), 3.93 (dd, J = 9.6, 4.5 Hz, 1H), 3.72 (dd, J = 9.6, 4.5 Hz, 1H), 3.62 (s, 1H), 3.46 (q, J $\sim$ 6 Hz, 2H), 3.00 (q, J $\sim$ 6 Hz, 2H), 2.35 (t, J = 6.6 Hz, 2H), 2.27 (t, J = 6.9 Hz, 2H), 0.93 (s, 3H), 0.83 (s, 3H). 1H-COSY couplings 7.00 – 3.46, 5.71 – 3.00, 4.39 – 4.27, 3.93 – 3.72, 3.46 – 2.27, 3.00 – 2.35. ^{13}C-NMR: δ (100 MHz, $CDCl_3$) 170.6, 170.4, 144.4, 136.7, 129.4 – 126.6 (multiple signals), 83.3, 73.6, 73.0 (m), 69.2 (m), 38.9 (d, J = 9.1 Hz), 38.3, 35.6, 35.0, 31.8, 21.2, 20.1. ^{31}P NMR δ (121 MHz, $CDCl_3$) –1.45 ppm.

Phosphopantetheine (14) – Napthalene (271 mg, 2.10 mmol) in THF (2 mL), was added to lithium metal (15 mg, 2.2 mmol) that had been rinsed with dry hexanes. After 30 minutes, a dark green color evolved which turned so dark it appeared black 1 hour after addition of naphthalene. After 1.25 hours, the solution was cooled to –20°C in an isopropanol / dry ice bath, and **64** (25 mg, 0.028 mmol) in THF (3 mL) was added by cannula. The solution turned from black to light red immediately. After 2 more hours water (2.5 mL) was added to the solution which removed all color. More water was added (5 mL), and the solution was washed with CH_2Cl_2 (4x, 20 mL) and 1x with diethyl ether (15 mL). Extra solvent was evaporated, and then the aqueous layer was lyopolized. After lyopolization, a yellow solid remained, and this solid was passed through a small column of acid form AG-50W-X8 ion exchange resin, and the eluant was immediately passed through a column of Na^+ loaded AG-50W-X8 ion exchange resin. The eluant was lyopolized to give **14** (10 mg, 90 +/- 5%) as a white sticky solid. ^{1}H-NMR: δ (400 MHz, D_2O) 4.12 (s, 1H), 3.75 (dd, J = 10.8, 6.8 Hz, 1H), 3.52 (m, 4H), 3.40 (dd, J = 10.0, 5.2 Hz, 1H), 2.86 (t, J = 10.8 Hz, 2H), 2.53 (t, J = 10.4 Hz, 2H), 1.00 (s, 3H), 0.84 (s, 3H). ^{31}P NMR δ (D_2O, 121 MHz) 4.50 ppm. Note that the spectra of Phosphopantetheine are pH sensitive.

2.11.3 New compounds from Scheme 2.8

General procedure for preparation of Tr-cystamine-amino acid combinations (**66a** – **f**) – **55** (100 mg, 0.287 mmol, 1.0 eq), EDC (138 mg, 0.718 mmol 2.5 eq), HOBt (132 mg, 0.861 mmol, 3.0 eq), and one Fmoc protected amino acid of **65a** –**f** (0.431 mmol, 1.5 eq) were combined and dissolved in THF (5 mL). DIPEA (186 mg, 250 uL, 1.44 mmol, 5.0 eq) was added, and the solutions were allowed to stir for 4 hr. The reactions were quenched with 25% $NH_4Cl_{(aq)}$ (2 mL), diluted with diethyl ether (25

mL), washed with water (5 mL) and brine (5 mL), dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography with conditions specific for each amino acid.

S-Trityl cystamine-Fmoc glycine (66a) – The residue was purified by silica gel chromatography (2:1 hexanes / EtOAc to EtOAc) to yield **66a** (147 mg, 84%) as a flaky solid. ^{1}H-NMR: δ (400MHz, $CDCl_3$) 7.75 (d, J = 7.2 Hz, 2H), 7.67 (d, J = 7.6 Hz, 2H), 7.41 – 7.19 (m, 19H), 5.92 (b, 1H), 5.38 (b, 1H), 4.41 (d, J = 7.6 Hz, 2H), 4.20 (t, J = 7.6 Hz, 1H), 3.77 (d, J = 5.2 Hz, 2H), 3.10 (q, J = 9.0 Hz, 2H), 2.42 (t, J = 8.0 Hz, 2H). ^{13}C-NMR: δ (100MHz, $CDCl_3$) 168.6, 162.6, 144.6, 143.7, 141.3, 129.5 – 126.8 (multiple signals), 125.0, 120.0, 67.2, 66.9, 47.1, 44.4, 38.2, 36.5, 31.7, 31.5. ESI-MS: found $\frac{m}{z}$ = 621.07, $[M+Na]^+$ calcd. $C_{38}H_{34}O_3N_2SNa^+$: 621.22 amu.

S-Trityl cystamine-Fmoc phenylalanine (66b) – The residue was purified by silica gel chromatography (2:1 to 1:1 hexanes / EtOAc) to yield **66b** (174 mg, 87%) as a clear film. ^{1}H-NMR: δ (400MHz, $CDCl_3$) 7.76 (d, J = 8.0 Hz, 2H), 7.53 (t, J = 6.8 Hz, 2H), 7.41 – 7.15 (m, 24H), 5.58 (b, 1H), 5.35 (b, 1H), 4.41 (t, J = 7.2 Hz, 1H), 4.32 (b, 1H), 4.28 (m, 1H), 4.17 (t, J = 6.8 Hz, 1H), 3.08 (b, 1H), 2.94 (m, 3H), 2.27 (m, 2H). ^{13}C-NMR: δ (100MHz, $CDCl_3$) 170.3, 155.8, 144.5, 141.3, 129 – 126 (multiple peaks) 125.0, 120.0, 66.9, 56.2, 47.1, 38.8, 38.3, 31.4, 21.0, 14.1. ESI-MS: found $\frac{m}{z}$ = 711.16, $[M+Na]^+$ calcd. $C_{45}H_{40}O_3N_2SNa^+$: 711.27 amu.

S-trityl cystamine-fmoc (N-benzyl histidine) (66c) – The residue was purified by silica gel chromatography (1:1 hexanes / EtOAc to 1:4 Methanol / EtOAc) to yield **66c** (190 mg, 86%) as a clear glass. ^{1}H-NMR: δ (400MHz, $CDCl_3$) 7.75 (d, J = 7.8 Hz, 2H), 7.59 (d, J = 7.0 Hz, 2H), 7.39 – 7.18 (m, ∼20H), 7.10 (s, 1H) 7.09 (s, 1H), 6.70 (b, 1H), 4.93 (s, 2H), 4.42 (q, J = 4.4 Hz, 1H), 4.34 (m, 2H), 4.21 (t, J = 7.3 Hz, 1H), 3.05 – 2.95 (m, 4H), 2.31 (t, J = 6.2 Hz, 2H). ^{13}C-NMR: δ (100MHz,

$CDCl_3$) 170.9, 144.7, 136.8, 129.6 - 126.8 (multiple signals), 117.1, 83.2, 73.7, 69.4, 53.0, 51.0, 38.6, 32.1, 30.6, 21.7, 20.0. ESI-MS: found $\frac{m}{z}$ = 769.10, $[M+Na]^+$ calcd. $C_{49}H_{44}O_3N_4SNa^+$: 769.32 amu.

S-Trityl cystamine-Fmoc ᴅ-alanine (66d) – The residue was purified by silica gel chromatography (2:1 to 1:1 hexanes / EtOAc) to yield **66d** (157 mg, 88%) as a clear film. ^{1}H-NMR: δ (400MHz, $CDCl_3$) 7.76 (d, J = 7.6 Hz, 2H), 7.55 (d, J = 6.8 Hz, 2H), 7.41 – 7.17 (m, 19H), 6.17 (b, 1H), 5.45 (d, J $\sim$ 6.0 Hz, 1H), 4.37 (d, J $\sim$ 5.0 Hz, 2H), 4.19 (t, J $\sim$ 5.0 Hz, 1H), 3.07 (q, J = 6.4 Hz, 2H), 2.40 (b, 2H), 1.34 (d, J $\sim$ 6.4 Hz, 3H). ^{13}C-NMR: δ (100MHz, $CDCl_3$) 172.1, 155.9, 144.6, 143.8, 143.7, 141.3, 129.5 – 126.8 (multiple signals), 125.1, 120.0, 670, 66.8, 50.5, 47.1, 38.3, 31.8, 18.8. ESI-MS: found $\frac{m}{z}$ = 635.10, $[M+Na]^+$ calcd. $C_{39}H_{36}O_3N_2SNa^+$: 635.23 amu.

S-Trityl cystamine-Fmoc (^{t}butyl aspartate) (66e) – The residue was purified by silica gel chromatography (2:1 to 1:1 hexanes / EtOAc) to yield **66e** (64 mg, 30%) as a clear film. ^{1}H-NMR: δ (400MHz, $CDCl_3$) 7.76 (t, J = 8.0 Hz, 2H), 7.70 (d, J = 7.6 Hz, 2H), 7.57 (t, J = 6.8 Hz, 2H), 7.40 – 7.17 (m, 17H), 6.56 (b, 1H), 5.01 (b, 1H), 4.41 (m, 2H), 4.20 (t, J = 6.8 Hz, 2H), 3.06 (m, 2H), 2.86 (dd, 1H), 2.57 (dd, J = 16.8, 6.8 Hz, 1H), 2.40 (t, J = 6.8 Hz, 2H), 1.43 (s, 9H). ^{13}C-NMR: δ (100MHz, $CDCl_3$) 171.1, 170.1, 155.9, 144.5, 143.7, 141.2, 140.1, 137.9, 129.4 – 126.7 (multiple signals), 124.9, 120.9, 120.0, 119.7, 107.8, 81.8, 77.2, 67.1, 66.7, 50.9, 47.1, 38.3, 37.4, 31.6, 28.0. ESI-MS: found $\frac{m}{z}$ = 735.11, $[M+Na]^+$ calcd. $C_{44}H_{44}O_5N_2SNa^+$: 735.29 amu.

S-Trityl cystamine-Fmoc valine (66f) – The residue was purified by silica gel chromatography (2:1 to 1:1 hexanes / EtOAc) to yield **66f** (68 mg, 35%) as a clear film. ^{1}H-NMR: δ (300MHz, $CDCl_3$) 7.76 (d, J = 7.5 Hz, 2H), 7.57 (d, J = 7.2 Hz, 2H), 7.41 – 7.17 (m, 19H), 5.84 (b, 1H), 5.34 (d, J = 7.8 Hz, 1H), 4.38 (p, J = 7.8 Hz, 2H), 4.20 (t, J = 6.9 Hz, 1H), 3.87 (t, J = 7.5 Hz, 1H), 3.06 (m, 2H), 2.07 (m, 1H),

0.92 (d, J = 7.2 Hz, 3H), 0.90 (d, J = 7.5 Hz, 3H). 13^{13}C-NMR: δ (100MHz, $CDCl_3$) 170.6, 156.1, 144.3, 143.6, 141.1, 129 – 126 (multiple signals), 124.9, 119.8, 66.9, 60.3, 47.2, 38.2, 31.9, 31.2, 19.3, 18.0. ESI-MS: found $\frac{m}{z}$ = 663.15, $[M+Na]^+$ calcd. $C_{41}H_{40}O_3N_2SNa^+$: 663.27 amu.

General procedure for preparation of Amino Acid Substituted, Protected Pantetheines (**67a** – **f**) – Tr-Cystamine-AA **66a** – **f** (1.0 eq) was dissolved in DMF (2 mL), and piperidine (1 mL) was added. After 30 minutes, the DMF and piperidine were evaporated *in vacuo* at 50°C. To the residue, **53** (1.5 eq), EDC (2.5 eq), HOBt (3.0 eq), and dry DMF (4 mL) were added. Immediately, DIPEA was added (6.0 eq). The reaction was stirred for 5 hr, and then quenched with 25% $NH_4Cl_{(aq)}$ solution, diluted in EtOAc (20 mL), washed with water (5 mL), brine (5 mL), dried over Na_2SO_4, and evaporated *in vacuo*. Each product was purified by silica gel chromatography according to its individual properties.

Protected glycine pantetheine (67a) – The product was purified by prep TLC (1:1 hexanes / EtOAc) to afford **67a** (13 mg, 52%) from **66a** (25 mg, 0.040 mmol) as a clear film. ^{1}H-NMR: δ (400MHz, $CDCl_3$) 7.43 – 7.21 (m, 17H), 7.07 (t, J = 5.1 Hz, 1H), 6.91 (J = 8.6 Hz, 2H), 6.11 (b, 1H), 5.43 (s, 1H), 4.11 (s, 1H), 3.82 (s, 3H), 3.71 (d, J = 11.4 Hz, 1H), 3.64 (d, J = 11.4 Hz, 1H), 3.05 (q, J = 6.0 Hz, 2H), 2.40 (t, J = 6.4, 2H), 1.13 (s, 3H), 1.09 (s, 3H). ^{13}C-NMR: δ (100MHz, $CDCl_3$) 170.0, 168.5, 144.7, 130 – 126 (multiple signals), 113.9, 101.6, 83.9, 78.5, 55.4, 42.8, 38.2, 33.3, 31.8, 21.9, 19.3. ESI-MS: found $\frac{m}{z}$ = 647.13, $[M+Na]^+$ calcd. $C_{37}H_{40}O_5N_2SNa^+$: 647.26 amu.

Protected phenylalanine pantetheine (67b) – The product was purified by prep TLC (1:1 hexanes / EtOAc) to afford **67b** (16 mg, 59%) from **66b** (29 mg, 0.040 mmol) as a clear film. ^{1}H-NMR: δ (400MHz, $CDCl_3$) 7.45 – 6.91 (m, ∼25H), 5.85 (t, J =

5.6 Hz, 1H), 5.41 (s, 1H), 4.50 (q, J = 7.4 Hz, 1H), 4.02 (s, 1H), 3.84 (s, 3H), 3.71 – 3.60 (m, 3H), 3.55 (q, J = 5.7 Hz, 1H), 3.02 – 2.87 (m, 4H), 2.274 (t, J = 6.5 Hz, 1H), 2.268 (t, J = 6.8 Hz, 1H), 1.61 (m, 1H), 1.55 (m, 1H), 1.021 (s, 3H), 1.017 (s, 3H). ^{13}C-NMR: δ (100MHz, $CDCl_3$) 170.2, 169.5, 160.3, 144.7, 136.5, 130.1 – 126.8 (multiple signals), 113.8, 102.2, 101.4, 84.0, 83.8, 79.8, 78.5, 66.9, 55.4, 53.8, 47.3, 43.5, 38.4, 37.7, 33.5, 31.5, 26.7, 25.8, 24.7, 21.8, 19.4 ESI-MS: found $\frac{m}{z}$ = 737.14, $[M+Na]^+$ calcd. $C_{44}H_{46}O_5N_2SNa^+$: 737.30 amu.

Protected N-benzyl histidine pantetheine (67c) – The product was purified by prep TLC (1:4 Methanol / EtOAc) to afford **67c** (7 mg, 37%) from **66c** (19 mg, 0.024 mmol) as a clear film. ^{1}H-NMR: δ (400MHz, $CDCl_3$) 8.29 (d, J = 6.8 Hz, 1H), 7.53 (d, J = 8.5 Hz, 2H), 7.36 – 7.28 (m, ∼11H), 7.07 (m, 2H), 6.99 (b, 1H), 6.88 (d, J = 8.7 Hz, 2H), 6.65 (s, 1H), 5.48 (s, 1H), 4.89 (s, 2H), 4.62 (q, 1H), 4.09 (s, 1H), 3.79 (s, 3H), 3.67 (s, 2H), 3.08 (dd, J = 14.8, 4.1 Hz, 1H), 2.96 (q, J = 6.3 Hz, 2H), 2.83 (dd, J = 14.7, 6.4 Hz, 1H), 2.29 (t, J = 6.6 Hz, 2H), 1.07 (s, 6H). ^{13}C-NMR: δ (100MHz, $CDCl_3$). 170.9, 169.6, 144.7, 138.6, 136.7, 136.1, 130 – 126 (multiple signals), 117.4, 113.7, 101.5, 84.0, 79.0, 77.8, 67.0, 55.7, 52.8, 51.0, 38.6, 33.7, 32.1, 30.0, 22.3, 19.8 ESI-MS: found $\frac{m}{z}$ = 795.35, $[M+H]^+$ calcd. $C_{48}H_{51}O_5N_4S^+$: 795.35 amu.

Protected D-alanine pantetheine (67d) – The product was purified by prep TLC (1:1 hexanes / EtOAc) to afford **67d** (24 mg, 92%) from **66d** (26 mg, 0.041 mmol) as a clear film. ^{1}H-NMR: δ (400MHz, $CDCl_3$) 7.42 – 7.21 (m, 17H), 6.96 (d, J = 7.9 Hz, 1H), 6.92 (d, J = 8.7 Hz, 2H), 6.24 (t, J = 5.6 Hz, 1H), 5.36 (s, 1H), 4.41 (p, J = 7.4 Hz, 1H), 4.04 (s, 1H), 3.83 (s, 3H), 3.70 (d, J = 11.4 Hz, 1H), 3.60 (d, J = 11.4 Hz, 1H), 3.04 (q, J = 6.4 Hz, 2H), 2.38 (t, J = 7.1 Hz, 2H), 1.33 (d, J = 7.0 Hz, 2H), 1.12 (s,. 3H), 1.09 (s, 3H). ^{13}C-NMR: δ (100MHz, $CDCl_3$) 171.1, 169.5, 160.5, 144.9,

130.3 – 127.0, 114.0, 101.6, 83.9, 78.6, 77.5, 66.9, 55.6, 48.3, 38.3, 33.4, 32.0, 22.1, 19.3, 18.0. ESI-MS: found $\frac{m}{z}$ = 661.14, $[M+Na]^+$ calcd. $C_{38}H_{42}O_5N_2SNa^+$: 661.27 amu.

Protected ^{t}butyl aspartic acid pantetheine (67e) – The product was purified by prep TLC (1:1 hexanes / EtOAc) to afford **67e** (12 mg, 60%) from **66e** (20 mg, 0.027 mmol) as a clear film. ^{1}H-NMR: δ (400MHz, $CDCl_3$) 7.63 (d, J = 8.4 Hz, 1H), 7.40 – 7.38 (m, 6H), 7.27 – 7.25 (m, 6H), 7.20 (t, J = 6.1 Hz, 3H), 6.88 (d, J = 8.8 Hz, 2H), 6.55 (t, J = 5.8 Hz, 1H), 5.46 (s, 1H), 4.67 (m, 1H), 4.11 (s, 1H), 3.80 (s, 3H), 3.69 (d, J = 11.2 Hz, 1H), 3.65 (d, J – 11.2 Hz, 1H), 3.09 (sextet, J = 7.2 Hz, 1H), 2.95 (sextet, J = 6.9 Hz, 1H),. 2.85 (dd, J = 17.0, 4.4 Hz, 1H), 2.52 (dd, J = 17.1, 6.4 Hz, 1H), 2.35 (t, J = 6.7 Hz, 2H), 1.33 (s, 9H), 1.07 (s, 3H), 1.06 (s, 3H). ^{13}C-NMR: δ 170.9, 170.1, 169.8, 160.4, 144.8, 130.2 – 126.9 (multiple peaks), 113.9, 101.6, 83.9, 87.0, 78.7, 55.5, 48.8, 38.6, 36.6, 33.5, 31.9, 28.1, 22.0, 19.7. ESI-MS: found $\frac{m}{z}$ = 761.16, $[M+Na]^+$ calcd. $C_{43}H_{50}O_7N_2SNa^+$: 761.32 amu.

Protected valine pantetheine (67f) – The product was purified by prep TLC (2:1 hexanes / EtOAc) to afford **67f** (17 mg, 81%) from **66f** (21 mg, 0.031 mmol) as a clear film. ^{1}H-NMR: δ (400MHz, $CDCl_3$) 7.42 – 7.26 (m, 17H), 6.90 (d, J = 6.6 Hz, 2H), 5.99 (t, J = 5.7 Hz, 1H), 5.47 (s, 1H), 4.12 (s, 1H), 4.08 (dd, J = 8.8, 4.1 Hz, 1H), 3.82 (s, 3H), 3.70 (d, J = 11.4 Hz, 1H), 3.65 (d, J = 11.5 Hz, 1H), 3.18 – 2.98 (m, 2H), 2.50 – 2.30 (m, 2H), 2.14 (sextet, J = 6.8, 1H), 1.05 (s, 6H), 0.89 (d, J = 6.8, 2H), 0.84 (d, J = 6.8, 2H). ^{13}C-NMR: δ (100MHz, $CDCl_3$) 170.3, 169.3, 144.5, 130 – 126 (multiple peaks), 113.7, 101.3, 83.9, 78.5, 58.1, 55.4, 38.2, 33.5, 32.0, 30.3, 27.0, 19.7, 19.5, 18.2. ESI-MS: found $\frac{m}{z}$ = 689.21, $[M+Na]^+$ calcd. $C_{40}H_{46}O_5N_2SNa^+$: 689.30 amu.

General procedure for preparation of amino acid substituted pantethines (**69a** – **f**) – To

a stirred solution of **67a – f** in MeOH (2 mL), a solution of Iodine in MeOH (0.03M) was dropped in until the solution remained dark brown ($\sim$ 1mL). After ten minutes, no starting material was detected by TLC (1:2 hexanes / EtOAc), and solid $NaHSO_3$ was added. The methanol solution was then diluted to 10 mL and washed 3x with hexanes (10 mL). The solution was passed through a bed of H^+ form AG50W-X8 ion exchange resin and OH^- form Dowex AG 1-X8 resin to remove salts, and the eluant was evaporated *in vacuo*.

Phenylalanine pantethine (69b) – Workup yielded **69b** (1 mg, 14%) as a clear film. ^{1}H-NMR: δ (400MHz, $CDCl_3$) 7.30 – 7.20 (m, 5H), 4.63 (dd, J = 8.4, 6.4 Hz, 1H), 3.80 (s, 1H), 3.48 – 3.40 (m, 4H), 3.11 (dd, J = 13.6, 6.4 Hz, 1H), 2.99 (dd, J = 14.0, 7.6 Hz, 1H), 0.90 (s, 3H), 0.84 (s, 3H). ^{13}C-NMR: δ (100MHz, $CDCl_3$) 130.3, 130.2, 129.4, 127.7, 77.1, 69.4, 55.4, 40.7, 39.6, 39.2, 38.2, 22.2, 21.2. ESI-MS: found $\frac{m}{z}$ = 729.31, $[M+Na]^+$ calcd. $C_{34}H_{50}O_8N_4S_2Na^+$: 729.23 amu (disulfide)

D-alanine pantethine (69d) – Workup yielded **69d** (7 mg, 95%) as a clear film. ^{1}H-NMR: δ (400MHz, $CDCl_3$) 4.41 ppm (q, J = 7.2 Hz, 1H), 3.92 (s, 1H), 3.50 (dt, J = 6.8, 2.4 Hz, 2H), 3.48 (d, J = 11.2 Hz, 1H), 3.38 (d, J = 11.2 Hz, 1H), 2.82 (t, J = 7.2 Hz, 1H), 1.36 (d, J = 6.8 Hz, 3H), 0.94 (s, 3H), 0.93 (s, 3H). ^{31}P NMR δ (162MHz, $CDCl_3$) 175.2, 77.1, 70.1, 40.5, 39.6, 38.4, 21.3, 21.0, 19.0. ESI-MS: found $\frac{m}{z}$ = 577.22, $[M+Na]^+$ calcd. $C_{22}H_{42}O_8N_4S_2Na^+$: 577.23 amu (disulfide).

Aspartic acid ^{t}butyl ester pantethine (69e) – Workup yielded **69e** (3.5 mg, 60%) as a clear film. ^{1}H-NMR: δ (400MHz, $CDCl_3$) 4.78 (t, J = 5.8 Hz, 1H), 3.88 (s, 1H), 3.64 (d, J = 11.2 Hz, 1H), 3.55 (t, J = 7.2 Hz, 2H), 3.37 (d, 1H), 2.90 – 2.70 (m, 4H), 1.52 (s, 9H), 1.09 (s, 3H), 0.99 (s, 3H).

General procedure for preparation of amino acid substituted, protected phosphopan-

tetheines (**68a** – **d**) – Tr-cystamine-AA **66a** – **f** (1.0 eq) was dissolved in DMF (2 mL), and piperidine (1 mL) was added. After 30 minutes, the DMF and piperidine were evaporated *in vacuo* at 50°C. To the residue, **63** (1.0 eq), EDC (2.0 eq), HOBt (2.5 eq), and dry DMF (4 mL) were added. Immediately, DIPEA was added (5.0 eq). The reaction was stirred for 5 hr, and then quenched with 25% $NH_4Cl_{(aq)}$ solution, diluted in EtOAc (20 mL), washed with water (5 mL), brine (5 mL), dried over Na_2SO_4, and evaporated *in vacuo*. Each product was purified by silical gel chromatography according to its individual properties.

Protected glycine phosphopantetheine (68a) – **66a** (20 mg, 0.032 mmol) yielded **68a** (21 mg, 75%) after purification by silica gel chromatography (2:1 hexanes / EtOAc to EtOAc). ^{1}H-NMR: δ (400MHz, $CDCl_3$) 7.40 – 7.19 (m, ∼30H), 7.09 (t, J = 5.6 Hz, 1H), 5.90 (t, J = 5.7 Hz, 1H), 5.03 – 4.99 (m, 4H), 4.50 (d, J = 10.9 Hz, 1H), 4.36 (d, J = 11.0 Hz, 1H), 3.98 (dd, J = 9.5, 4.1 Hz, 1H), 3.78 – 3.75 (m, 2H), 3.72 (s, 1H), 3.06 (q, J = 6.3 Hz, 2H), 2.40 (t, J = 6.4 Hz, 2H), 0.98 (s, 3H), 0.88 (s, 3H). ^{13}C-NMR: δ (100MHz, $CDCl_3$) 171.2, 168.2, 144.4, 136.8, 129.4 – 126.8 (multiple signals), 83.2, 74.0, 73.1 (d, J = 6.1 Hz), 69.3 (d, J = 5.3 Hz), 67.0, 42.7, 39.2 (d, J = 8.3 Hz), 38.4, 31.9, 21.5, 20.0. ^{31}P NMR δ (162MHz, $CDCl_3$) –1.047 ppm. ESI-MS: found $\frac{m}{z}$ = 879.22, $[M+Na]^+$ calcd. $C_{50}H_{53}O_7N_2PSNa^+$: 879.32 amu.

Protected phenylalanine phosphopantetheine (68b) – **66b** (26 mg, 0.036 mmol) yielded **68b** (11 mg, 31%) after purification by silica gel chromatography (2:1 hexanes / EtOAc to EtOAc). ^{1}H-NMR: δ (400MHz, $CDCl_3$) 7.38 – 7.08 (m, ∼35H), 6.96 (d, J = 8.0 Hz, 1H), 5.88 (t, J = 5.8 Hz, 1H), 4.99 (t, J = 8.1 Hz, 1H), 4.56 (q, J = 7.0 Hz, 1H), 4.10 (d, J = 11.4 Hz, 1H), 4.07 (d, J = 11.3 Hz, 1H), 3.95 (dd, J = 11.3, 4.4 Hz, 1H), 3.68 (dd, J = 9.5, 4.6 Hz, 1H), 3.61 (s, 1H), 3.12 – 2.82 (m, 4H), 2.28 (t, J = 6.5 Hz, 2H), 0.91 (s, 3H), 0.79 (s, 3H). ^{13}C-NMR: δ 170.7, 170.2, 144.5,

136.8, 136.4, 129.5 – 126.7, 82.8, 73.4, 73.2, 69.5, 66.9, 53.7, 39.3, 38.5, 37.8, 31.6, 21.5, 19.9. ^{31}P NMR δ (162MHz, $CDCl_3$) –0.999 ppm. ESI-MS: found $\frac{m}{z}$ = 969.23, $[M+Na]^+$ calcd. $C_{57}H_{59}O_7N_2PSNa^+$: 969.37 amu.

Protected N-benzyl histidine phosphopantetheine (68c) – **66c** (27 mg, 0.034 mmol) yielded **68c** (9 mg, 26%) after purification by silica gel chromatography (2:1 hexanes / EtOAc to EtOAc). ^{1}H-NMR: δ (400MHz, $CDCl_3$) 7.92 (d, J = 7.3 Hz, 1H), 7.37 – 7.05 (m, ∼35H), 6.64 (s, 1H), 5.02 – 4.97 (m, 4H), 4.87 (d, J = 14.6 Hz, 1H), 4.83 (d, J = 15.0 Hz, 1H), 4.62 (q, J = 5.7 Hz, 1H), 4.45 (d, J = 11.1 Hz, 1H), 4.27 (d, J = 11.2 Hz, 1H), 3.99 (dd, J = 9.3, 4.3 Hz, 1H), 3.73 (dd, J = 9.3, 4.5 Hz, 1H), 3.71 (s, 1H), 3.10 – 2.90 (m, 3H), 2.85 (dd, J = 14.9, 6.6 Hz, 1H), 2.30 (sextet, J = 7.5 Hz, 2H). ^{13}C-NMR: δ 170.9, 144.7, 137.4, 136.8, 129.7 – 126.8 (multiple signals), 117.1, 83.2, 73.7, 69.4, 53.0, 51.1, 38.6, 32.1, 30.6, 21.7, 20.1. ^{31}P NMR δ (162MHz, $CDCl_3$) –1.034 ppm. ESI-MS: found $\frac{m}{z}$ = 1049.23, $[M+Na]^+$ calcd. $C_{61}H_{63}O_7N_4PSNa^+$: 1049.41 amu.

Protected D-alanine phosphopantetheine (68d) – **66d** (20 mg, 0.031 mmol) yielded **68d** (8 mg, 29%) after purification by silica gel chromatography (2:1 hexanes / EtOAc to EtOAc). ^{1}H-NMR: δ (400MHz, $CDCl_3$) 7.42 – 7.17 (m, ∼30H), 7.06 (d, J = 7.7 Hz, 1H), 5.98 (t, J = 5.6 Hz, 1H), 5.05 – 5.00 (m, 4H), 4.47 (d, J = 10.7 Hz, 1H), 4.35 (8plet, J = 7.3 Hz, 1H), 4.28 (d, J = 10.7 Hz, 1H), 3.98 (dd, J = 9.4, 4.3 Hz, 1H), 3.77 (dd, J = 9.4, 4.5 Hz, 1H), 3.68 (s, 1H), 3.17 – 3.01 (m, 2H), 2.41 (t, J = 6.4 Hz, 2H), 1.29 (d, J = 7.0 Hz, 3H), 0.99 (s, 3H), 0.88 (s, 3H). ^{13}C-NMR: δ 171.4, 144.5, 136.7, 129.5 – 126.7 (multiple signals), 82.9, 74.0, 73.1, 69.4, 48.3, 39.2, 38.4, 32.0, 21.5, 19.9, 18.5. ^{31}P NMR δ (162MHz, $CDCl_3$) –0.984 ppm. ESI-MS: found $\frac{m}{z}$ = 893.22, $[M+Na]^+$ calcd. $C_{51}H_{55}O_7N_2PSNa^+$: 893.34 amu.

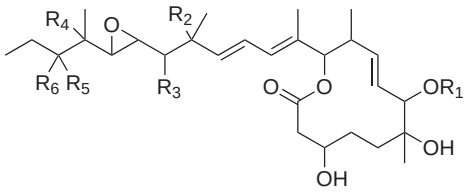
Chapter 3

The sidechain synthesis and model studies toward the synthesis of pladienolide B

3.1 An introduction to the pladienolides

The pladienolides (**70a** – **g**) are 12-membered ring macrolides isolated from a strain of *Streptomyces platensis* found in Japanese soil.[134–136] The pladienolides exhibit nanomolar cytotoxic activities and anti-tumor properties. They have similar structures to FD-895 (**71**), a macrolide isolated from *Streptomyces hygroscopicus* that also has high cytotoxicity (Figure 3.1).[137] The stereochemistries of the pladienolides (**70a** – **g**) and FD-895 (**71**) were not disclosed upon publication.

The basic strategy that was decided upon was to attempt to culture the organism and obtain an authentic sample, and simultaneously begin synthetic efforts. With cleverly chosen synthons, intermediates in the synthesis will match degradation products of **70b**, and a panel of such diasteromers can be compared to the actual degradants to de-



		R_1	R_2	R_3	R_4	R_5	R_6
pladienolide A	**70a**	H	H	H	H	OH	H
pladienolide B	**70b**	Ac	H	H	H	OH	H
pladienolide C	**70c**	Ac	H	H	H	=O	
pladienolide D	**70d**	Ac	OH	H	H	OH	H
pladienolide E	**70e**	Ac	H	H	OH	OH	H
pladienolide F	**70f**	H	OH	H	H	OH	H
pladienolide G	**70g**	H	H	H	OH	OH	H
FD-895	**71**	Ac	H	OH	H	OCH_3	H

Figure 3.1: The pladienolides (**70a** – **g**) and FD-895 (**71**)

termine which relative stereochemistry is correct. Further derivitization with Mosher's acid can confirm the absolute stereochemistry of the product. Strategies like these have been used in the elucidation of stereochemistry of reidispongiolide A (**7**)[76–79] and in the ongoing studies on the daunting 62-membered macrolide zooxanthellatoxins.[138]

The strategy to tackle pladienolide B (**70b**) stereochemistry is outlined in Figure 3.2. The producer organism, *Streptomyces platensis* Mer-11107 was deposited in a Japanese patented strain bank. The goal was to obtain the strain, ferment and isolate a small supply of **70b**, and reductively ozonize it to give the 5 stereocenter fragment **72**. The diol is known to cyclize under acidic conditions to **73**, which has very distinct ^{1}H NMR spectra between its diastereomers. Synthetically, diastereomers of **74** could be prepared and cyclized to form the matching **73** that would be compared with the panel to decide a match. Presumably, ozonolysis and reduction with $NaBH_4$ would also provide fragments C_1 – C_8 and C_9 – C_{12} which could be matched with smaller panels of diastereomers.

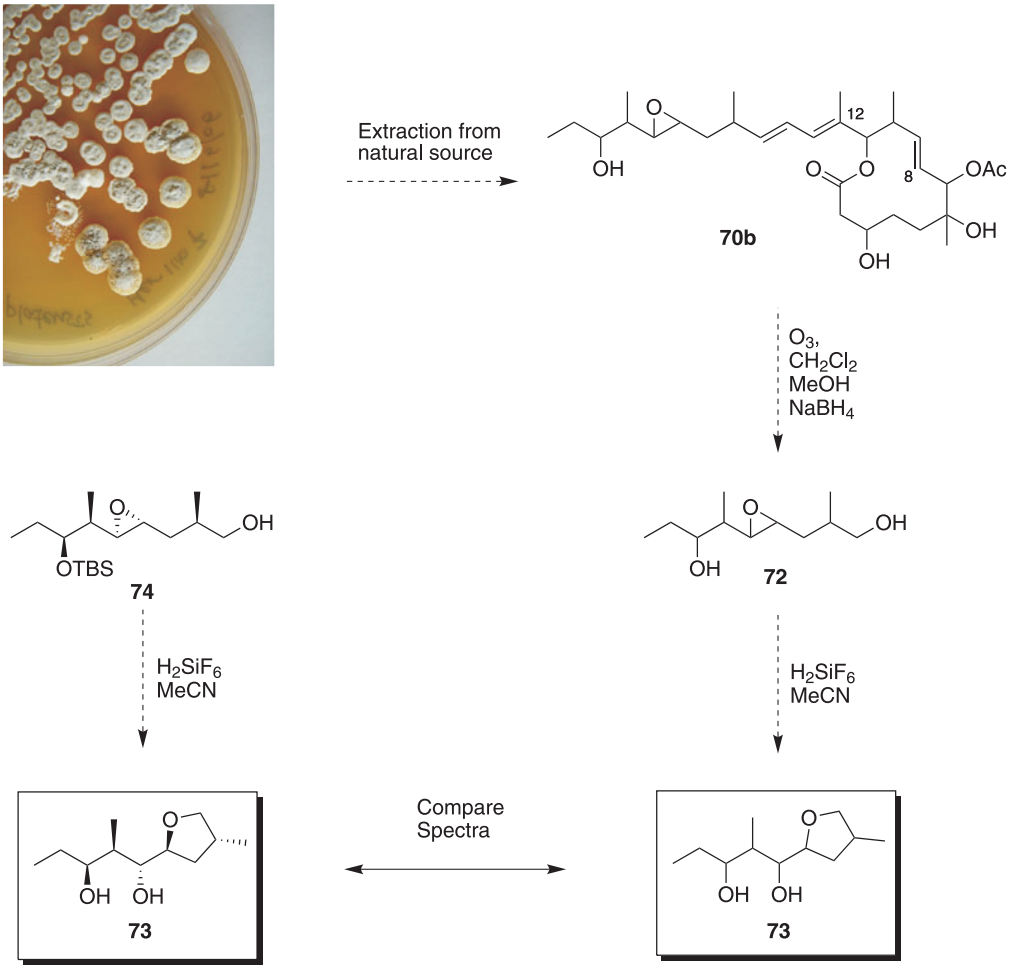


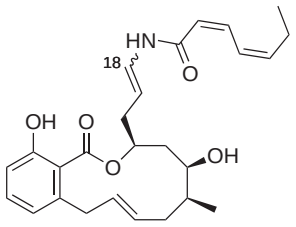
Figure 3.2: Degradation and comparison strategy for elucidating the pladienolide B (**70b**) sidechain stereochemistry

3.2 Synthetic methods applied to 12-membered macrolides

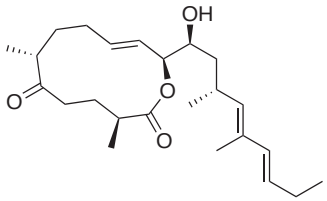
Polyketides with 12-membered lactones, termed *undecenolides*, have a wide range of functions. Several *undecenolides* are shown in Figure 3.3 on page 55. Salicylihalamides A (**75a**) and B (**75b**) have recently become of interest because they can reversibly inhibit the V-ATPase proton pumps in mammalian cells, leading to apoptosis.[139] Amphidinolide W (**76**) was found in *Amphidinium* sp. and it had cytoxic activity against murine lymphoma L1210 cells.[140] Amphidinolide W was the first *undecenolide* to be found in the prodigious library of metabolites discovered from *Amphidinium*. Methymycin (**77**), isolated from *Streptomyces*, displays antibiotic properties against gram positive bacteria. Methymycin and related compounds such as neomethymycin and deoxymethymycin require a sugar moiety in order to be active.[141–144] Interest in these natural products stems from their high substitution and similarities to Erythromycin. Molecular modeling shows that methymycin is a rigid structure due to the steric crowding.[145]

Spinosyn A (**78**), isolated from the soil microbe *Saccharopolyspora spinosa* by Eli Lilly, contains both sugar modificiation, and a fused 5,6,5-*cis-anti-trans* tricyclic ring system.[146] **78** is sold commercially as an insecticide, and there have been several syntheses and conformational analyses in an attempt to discern the effect of the fused ring system.[147–149] It turned out that conformational effects afford spinosyn A (**78**) unusual stability and low reactivity to many hydrolytic and reductive conditions.

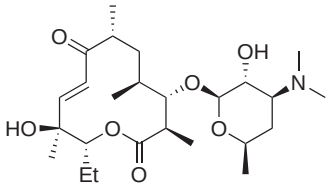
Brefeldin A (**79**) has been the subject of numerous studies because it has a wide range of biological effects including antiviral, antimitotic, and antibiotic activities.[150–152] Synthesis has played a role in enhancing its anticancer effects.[153] Patulolide A (**80**) also has a wide range of biological activities including antifungal, antibacterial,



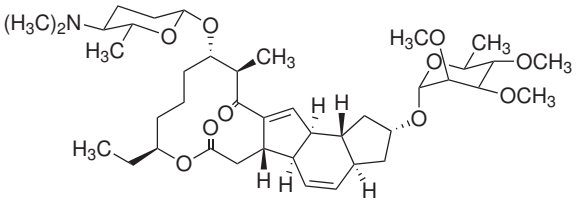
18-*E:* Salicylihalamide A (**75a**)
18-*Z:* Salicylihalamide B (**75b**)
Cytotoxic



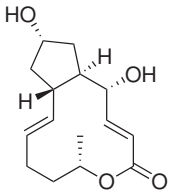
Amphidinolide W (**76**)
Cytotoxic



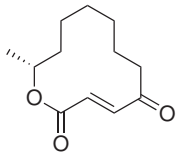
Methymycin (**77**)
Antibiotic



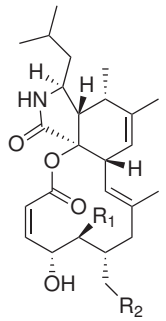
Spinosyn A [(-) - A83543A] (**78**)
Insecticide



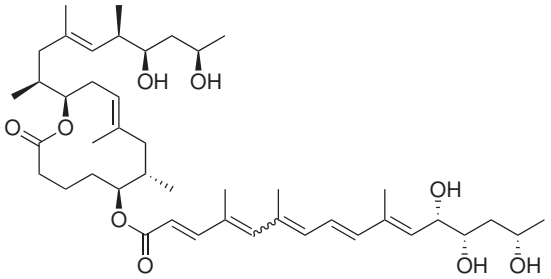
(+) Brefeldin A (**79**)
Cytostatic, antimitotic
antibiotic, and antiviral



(+)-Patulolide A (**80**)
Antifungal, antibacterial,
and antiinflammatory



R_1 = OH, R_2 = H: Phomacin A (**81a**)
R_1 = H, R_2 = OH: Phomacin B (**81b**)
Antitumor



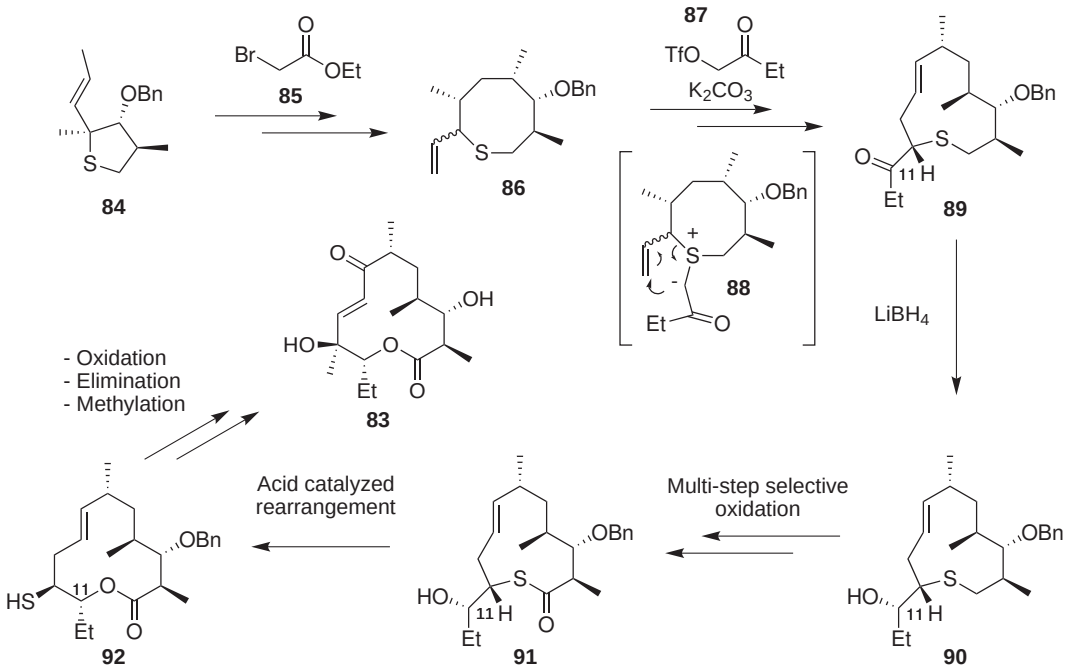
5'-*Z*: Mycolactone A (**82a**)
5'-*E:* Mycolactone B (**82a**)
Necrosis, unknown mechanism

Figure 3.3: A sampling of undecenolides

and antiinflammatory properties.[154] The patulolides are relatively simple macrolides, and that has lent them to a number of syntheses.[155–158] The phomacins (**81a** and **b**) are potent anti-proliferative agents and cytotoxic to colonic adenocarcinoma cells.[159] As of today there are no reported syntheses of these compounds.

The last molecules to be discussed are the mycolactones (**82a** and **b**). Produced by the pathogen *Mycobacterium ulcerans*, **82** has been implicated in the progression of the Buruli ulcer.[160] The Buruli ulcer is characterized by the formation of large, painless, necrotic lesions, and can not be resolved with any known antibiotics. Treatment requires surgical removal of the infected tissue. The disease primarily affects the developing world. **82a** and **b** are similar to pladienolide B (**70b**) in that the stereochemistry was unknown when synthesis was begun, and semi-synthesis was essential to elucidate their stereochemistries. While the full structure and stereochemistry of mycolactone is now elucidated,[161–163] its mode of action, and its role in the infection is still poorly understood. Interestingly, it is the first polyketide to be isolated from a human pathogen.[164] **82** has been of interest to our laboratory, and is the subject of an ongoing synthetic study.[165]

All *undecenolides* have an unsaturation somewhere in the ring, which lends well to their synthesis using an olefin forming reaction. With the development of several robust olefin metathesis catalysts, syntheses of *undecenolides* and macrolides in general have taken off. These products, because they are of polyketide origins, also serve as excellent test beds for asymmetric aldol chemistry. It is easy to see that the *undecenolides* lend themselves to a common set of reactions that stitch up their general structure, so the creativity is in how efficiently the unique parts can be prepared, and finding an efficient synthesis for forming the gross structure. In the following subsections, a few examples of syntheses of *undecenolides* similar to pladienolide B (**70b**) are reviewed to give the reader a picture of the methods that are



Scheme 3.1: Vedejs' synthesis of methynolide (**83**)

used in these synthetic routes.

3.2.1 Methynolide

Methynolide (**83**), the aglycone of methymycin (**77**) has been synthesized a number of times.[145,166,167] Vedejs' synthesis deserves special attention because it does not require any asymmetric aldol reactions.[168,169] Instead stereochemistry is inducted from the starting materials by passing through several cyclic thioether intermediates. (Scheme 3.1). In the synthesis, sulfur enforced relative stereocontrol and it assisted in three diastereoselective ring expansions. This contrasts most other syntheses that require a macrolactonization. What is important, is that the conformations of the medium size rings were predictable, therefore the outcomes of the stereochemical induction were predictable.

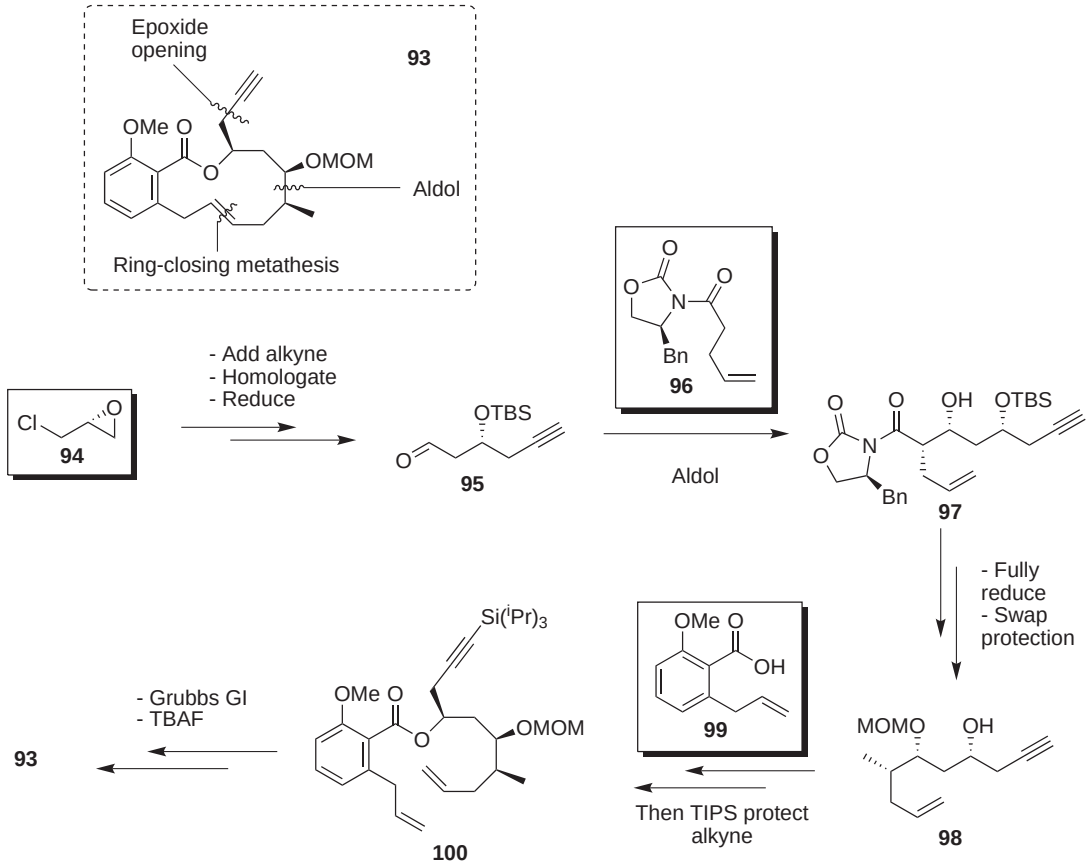
In summary, thioether **84** originated from conventional chemistry in a highly

stereoselective manner. Next, **84** was *S*-alkylated with bromoethyl glycolate (**85**) to create a sulfonium salt that underwent an ylide rearrangement to form the 8-membered ring **86**. Following additional manipulations, another ylide rearrangement with **87** through the intermediate **88** gave the 11-membered ring sulfide **89** in high yield as the correct diastereomer. The ketone was then reduced with Felkin-Ahn chelation control to afford one diastereomer at C_{11} as the single diastereomer **90**. A sequence of alcohol protection, sulfur oxidation, sulfoxide anion phosphenylation, and a Horner-Bestmann oxidation converted **90** into the thiolactone **91**. Deprotection and treatment with acid resulted in intramolecular acyl transfer to furnish lactone **92**. Finally, a series of oxidations and methylation of a ketone formed at C_{10} resulted in d,l-methynolide (**83**). The only drawbacks of the synthesis were the linear route, and racemic starting material.

3.2.2 Salicylihalamide

In an effort to gain access to sidechain derivatives of salicylihalamide (**75**) for SAR studies, Herb *et al.* synthesized the core with an alkyne (**93**) instead of the normal eneamide sidechain (Scheme 3.2).[170] The synthesis shows off several staple methods of macrolide synthesis including asymmetric aldols and ring-closing metathesis.

Herb's synthesis began with (*R*)-epichlorohydrin (**94**), which is opened by attack to TMS-acetylene followed by protection of the alcohol and homologation of the chloride to an aldehyde through cyanide addition and reduction to **95**. Next, an asymmetric aldol with **96** gave compound **97**. Protecting groups were swapped and the auxiliary was completey reduced by treatment with $LiBH_4$ followed by tosylation and reduction with $LiEt_3BH$ to give alcohol **98**. Next, The free alcohol was esterified with **99** using an inverting Mitsunobu displacement and the alkyne was protected with a bulky triisopropylsilane to give **100**. Finally, treatment with the first generation Grubbs



Scheme 3.2: The synthesis of the salicylihalamide core (**93**)

olefin metathesis catalyst and removal of the alkyne protecting group gave **93** with a 30:1 *E* to *Z* ratio. It turned out that the second generation Grubbs catalyst did not provide a very good *E* to *Z* ratio (2.2:1) and the alkyne would scramble the metathesis if left unprotected. This core product could be derivitized via a Sonogashira coupling or by converting the alkyne into an iodide.

3.2.3 Amphidinolide W

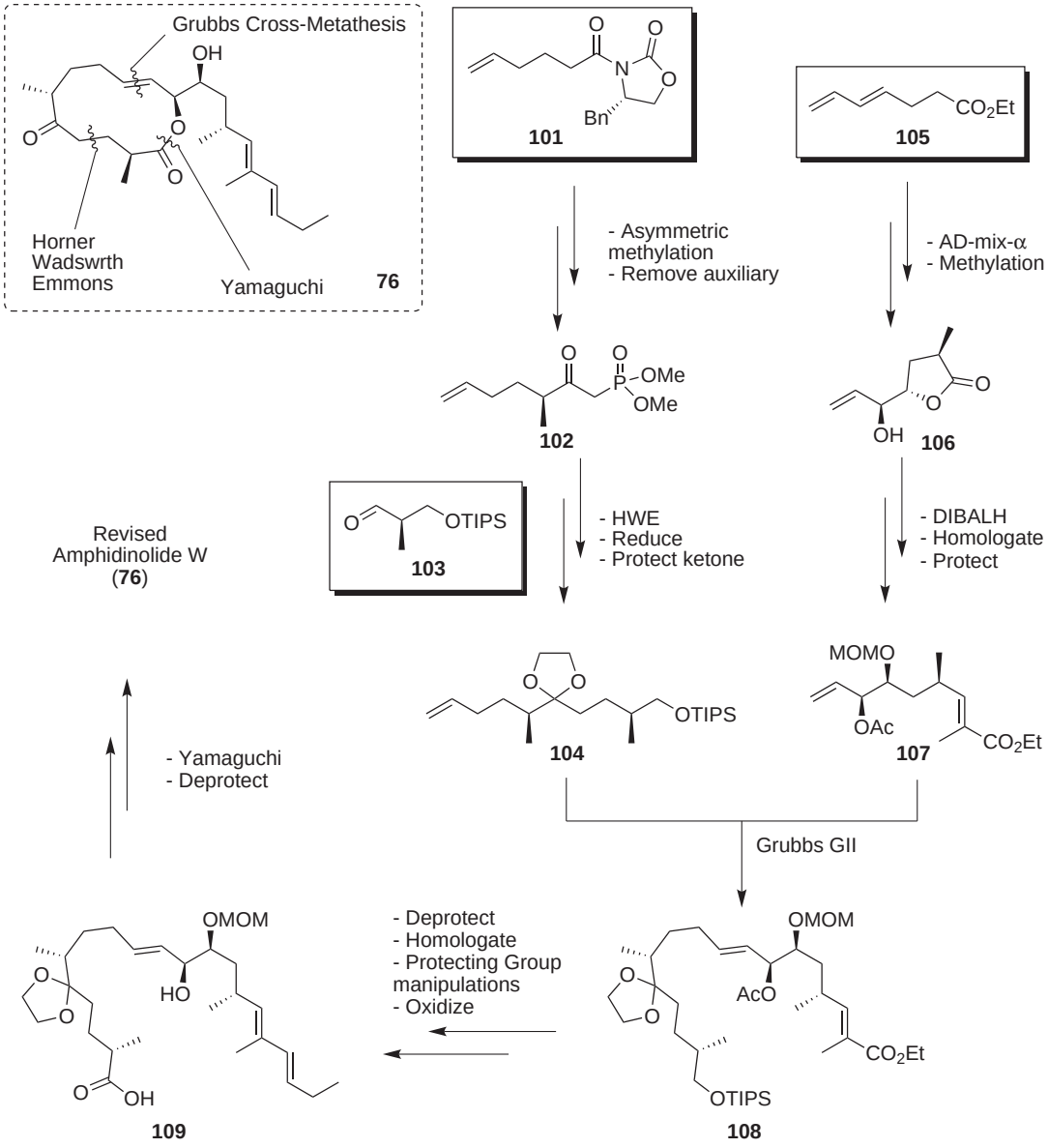
Amphidinolide W (**76**), one member of the prodigious family of amphidinolides,[140] became one of the many natural products to have its stereochemistry revised through total synthesis (Scheme 3.3).[171] The retrosynthetic breakdown involved a Yam-

aguchi macrolactonization, a Grubbs cross-metathesis and Horner-Wadsworth-Emmons olefination to connect the stereogenic units. In the course of the project, Ghosh and Gong found that the completed molecule did not match the published NMR spectra, and they realized that the published spectra was the C_6 epimer of **76**. The synthesis was repeated with the correction to yield amphidinolide W (**76**) matching all of the literature spectra.

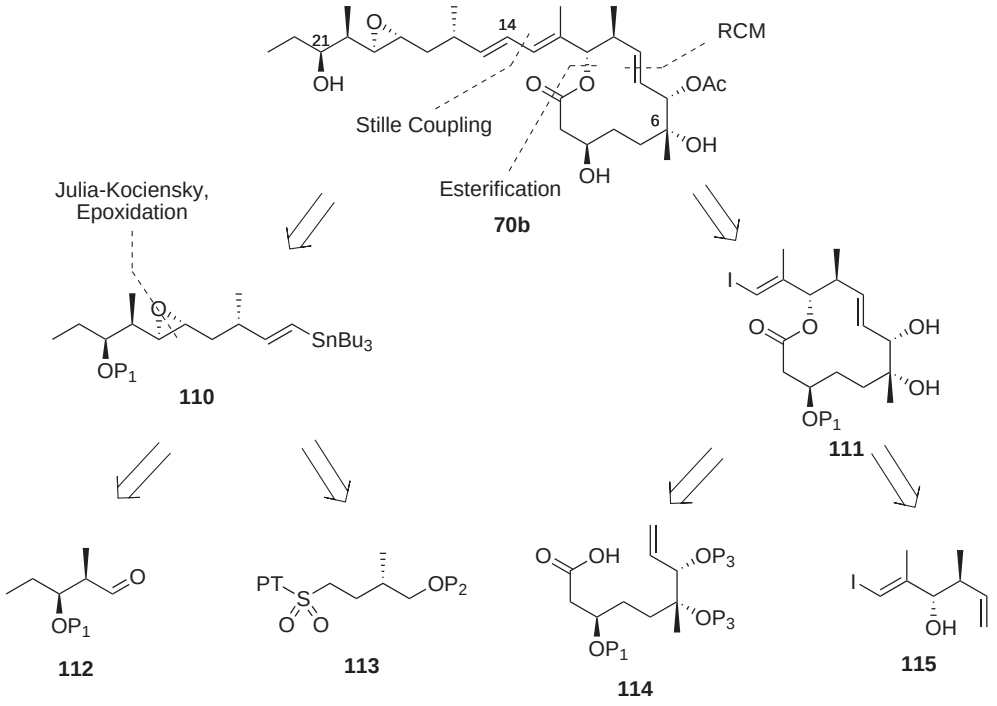
Ghosh began with the known oxazolidinone **101** to perform an asymmetric methylation at the α position, then removed the auxiliary and replaced it with diethylmethylphosphonate to form **102**. Next, an HWE olefination with **103** followed by reduction of the olefin and protection of the ketone furnished cross-metathesis partner **104**. On the other side, the known diene **105** is dihydoxylated with sharpless conditions to spontaneously form a cyclic lactone that can be methylated with stereocontrol to **106**. The lactone was then reduced and homologated and protected to yield **107**. In a suprisingly high yielding step, **104** and **107** were joined to form **108** by cross-metathesis with Grubbs second generation catalyst in 85% yield and an 11:1 *E* to *Z* ratio. The trisubstituted olefin next to the ester was left untouched by this reaction. Protecting group manipulations and homologation, then oxidation of the primary alcohol yielded **109**. Finally, Yamaguchi macrolactonization followed by deprotection gave the revised amphidinolide W (**76**).

3.3 The retrosynthetic approach to pladienolide B

Taking a look at the structure of pladienolide B (**70b**) (Scheme 3.4), there is a clear disconnection point at the diene between carbons C_{13} and C_{14}. A Negishi coupling, Suzuki coupling, or Stille coupling could make this bond do the job. Because of side reactivity that will be discussed later in this chapter, the conditions required to



Scheme 3.3: Ghosh and Gong's amphidinolide W (**76**) synthesis



Scheme 3.4: Retrosynthetic breakdown of pladienolide B (**70b**)

form the Negishi or Suzuki coupling partners would probably destroy the epoxide, and would also be incompatible with the lactone functionality. Thus, a Stille coupling was chosen as the means to bridge the two halves of the molecule. This led to stannane **110** which had the C_{21}-OH protected with a group that could be removed in the final step (P_1). The other coupling partner would be vinyl iodide **111** and this strategy was modeled after several macrolide syntheses.

It follows logically that stannane **110** can originate from epoxidation[172] of an (*E*) olefin, that was derived from a julia coupling of aldehyde **112** and sulfone **113**.[173] **112** can be prepared from one of a plethora of available asymmetric aldol reactions. **113** can originate from mitsunobu displacement of a commercially available diol.

Meanwhile, Lactone **111** is envisioned to originate from an esterification of **114** with **115** followed by ring-closing metathesis.[165,174,175] **115** has been dubbed the "keystone" as this piece is available from propargyl alcohol in three steps, and combines

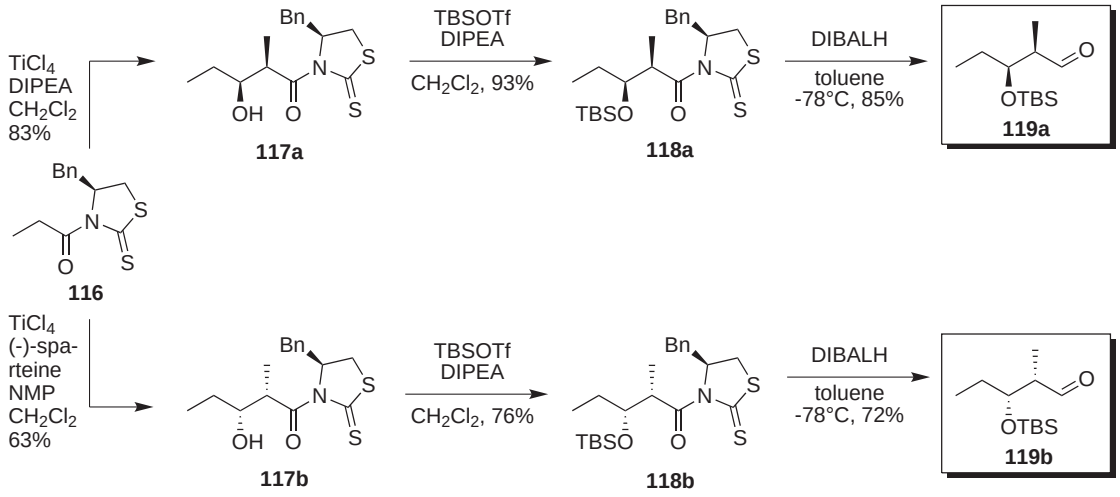
all three reactive moieties that stitch **70b** together. No protection or deprotection on the keystone is neccessary because the reactivities chosen for the three main coupling reactions are orthogonal.

3.4 Divergent synthesis as an approach to elucidating the stereochemistry of pladienolide B

During the initial work on pladienolide B, the stereochemistry was not disclosed. Work was begun with the goal of working out the necessary chemistry simultaneously with elucidation of the stereochemistry. Given recent advances in NMR techniques and the use of libraries[160,163,176–178] to elucidate the three-dimensional configuration of natural products, we felt that this study would prodvide an ideal platform to use chemical synthesis in concert with more traditional methods to determine the stereochemistry of **70b**.[179–182] As mentioned above, the published data guided our initial guesses,[183–190] and keeping in mind the *trans* epoxide, and *syn* stereochemistry at C_{20} and C_{21} synthetic efforts toward an arbitrary diastereomer of the pladienolide B sidechain were initiated.

3.4.1 Synthesis of the Julia coupling partners

The trek to Pladienolide B was begun with the synthesis of two enantiomeric aldehydes to represent retron **112** from the retrosynthesis. For the requisite aldol condensation, the Crimmins thiazolidinethione **116** was chosen for its ease of preparation and the reagent control that can afford both the Evans or non-evans type *syn* aldol product from the same starting material.[191,192] This versatile reagent also gives the aldol products a distinct yellow color which can be seen and isolated during flash

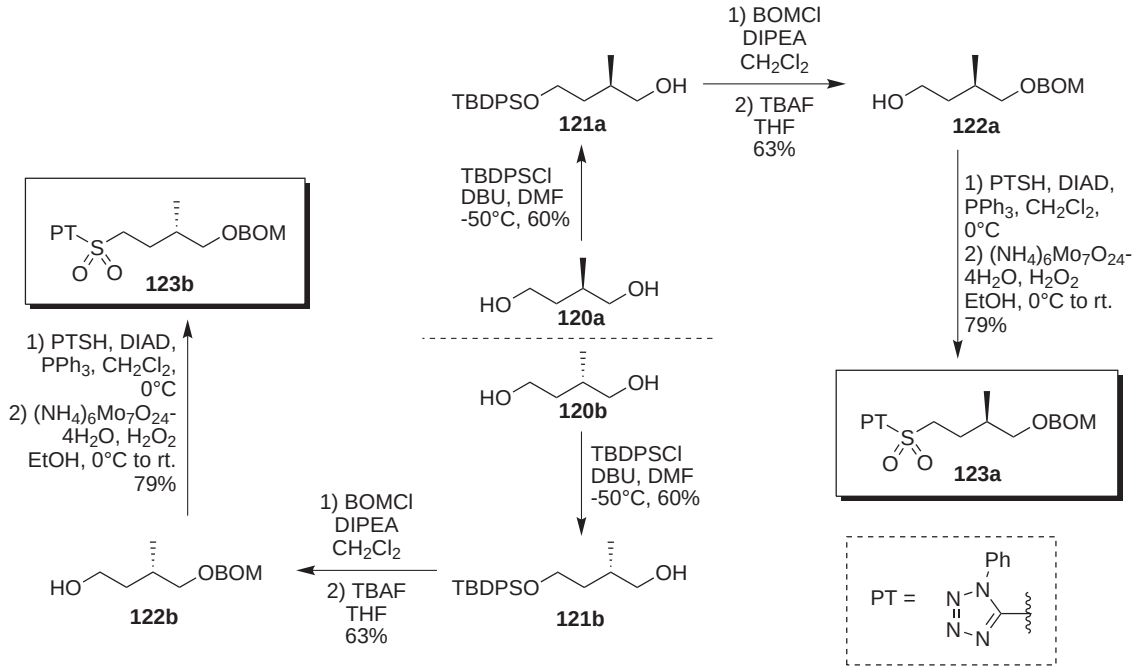


Scheme 3.5: Divergent route to aldehydes **119a** and **b**

chromatography.

Starting with propionate **116**, treatment with $TiCl_4$ and Hünig's base yielded the non-Evans aldol product **117a** (Scheme 3.5). In contrast, treatment of **116** with $TiCl_4$, (-)-spartiene, and the *N*-methyl pyrrolidinone–a ligand for titanium–gave the Evans like aldol product **117b**. The two products were then protected as TBS ethers **118a** and **b**.[193] Finally, the thiazolidinethione auxiliary was reduced off efficiently with diisobutylaluminum hydride to afford aldehydes **119a** and **b**.[194]

Concurrently, the sulfones representing **113** were prepared from (*R*) and (*S*)-2-methyl-1,4-diol (**120a** and **b** respectively). The diol was protected via conditions that protect the less hindered alcohol selectively with the bulky TBDPS silyl ether to afford **121a** and **b**. Next, in two steps the remaining free alcohol was protected with a benzyloxymethyl group, and the silyl ether was cleaved with TBAF to release the less hindered alcohol in **122a** and **b**.[195,196] Finally, in two steps, a Mitsunobu displacement with (*1H*)-phenyltetrazole thiol followed by a mild ammonium molybdate catalyzed oxidation yielded sulfones **123a** and **b**.[197] In some reactions, there was a small amount of contamination with a sulfone in which the SO_2PT and OBOM were reversed. Be-

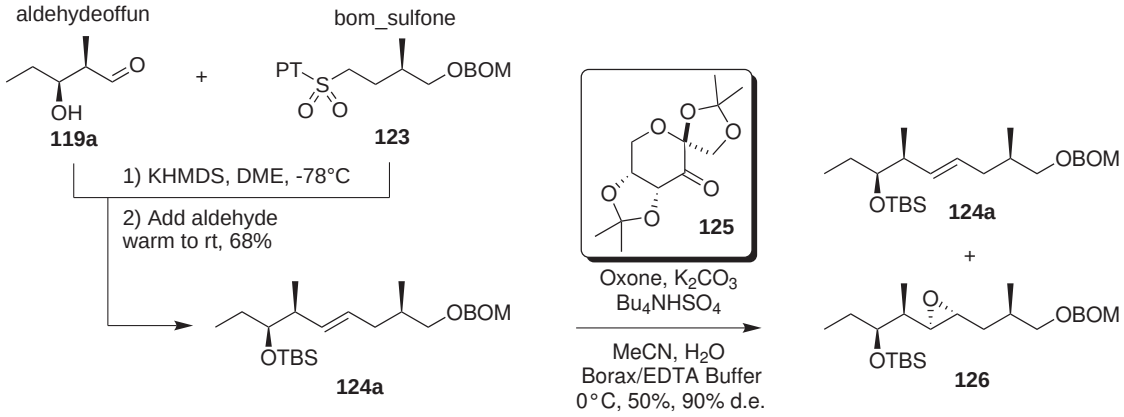


Scheme 3.6: Divergent route to sulfones **123a** and **b**

cause **123a** and **b** would solidify upon standing, it was found that recrystallization in a combination of hexanes / ethyl acetate could remove those impurities.

3.4.2 Preparation of a panel of sidechain diastereomers and degradation products

Requests to provide a sample of the natural product for analysis were denied, however an application for a sample of the producer organism from the Japanese patented strain databank was honored. It was anticipated that under the published conditions, a small sample of pladienolide B (**70b**) would be obtained. The synthesis of the sidechain could then lead to degradation products that could be compared to the synthetic intermediates. First, the chemistry was worked out with a single diastereomer as shown in Schemes 3.7 and 3.8. Later, a panel consisting of 4 postulated



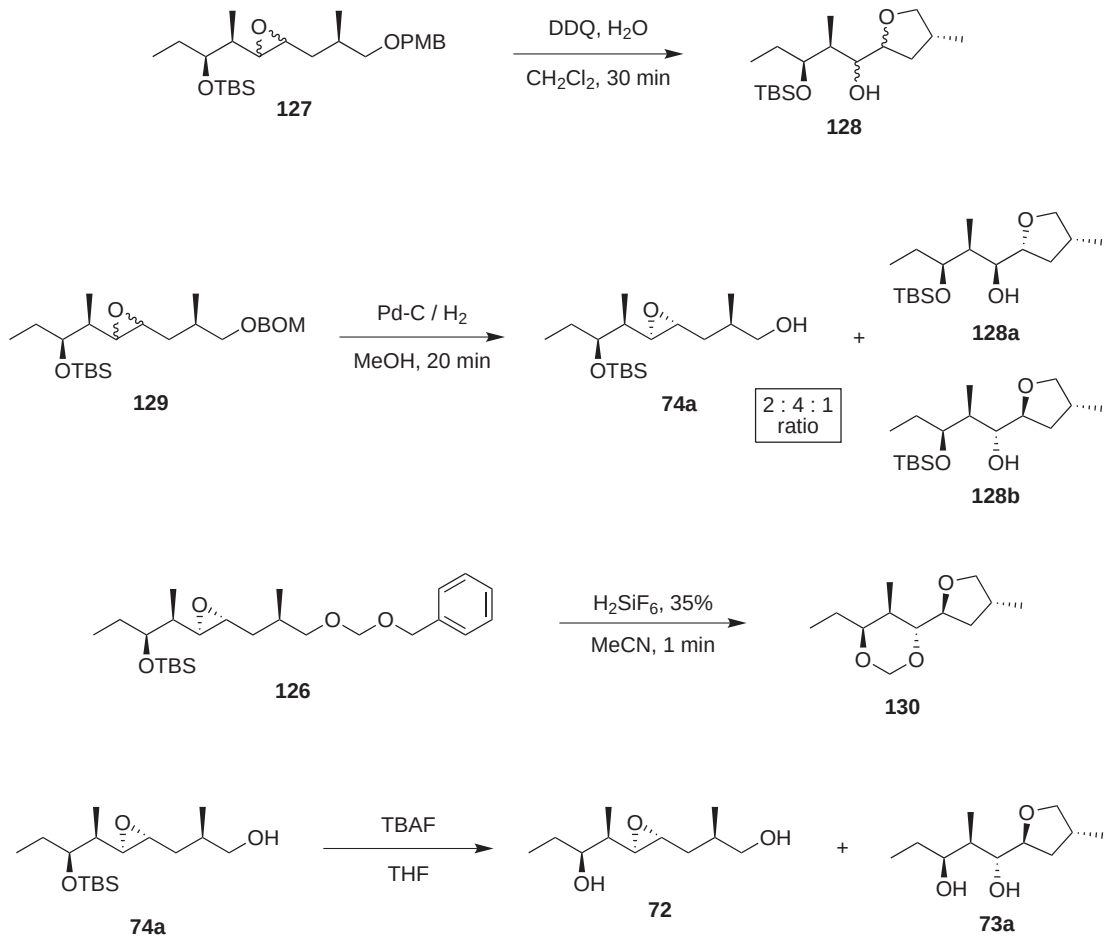
Scheme 3.7: Testing the Julia and Shi chemistry on an arbitrary diastereomer

diastereomers was synthesized in anticipation that **70b** could be isolated and degraded (Scheme 3.9).

To begin, sulfone **123** was dissolved in glyme and treated with KHMDS in toluene in a dry ice bath to form the sulfone anion. Then aldehyde **119a** was added and the solution was immediately allowed to warm to room temperature (Scheme 3.7. Workup yielded **124a** in 68% yield with respect to the aldehyde. It was found that if the reaction was stirred at –78°C the sulfone would degrade and aldehyde **119** would be returned unreacted.

For the asymmetric epoxidation, the Shi epoxidation was one of the only methods that could yield good d.e. Ketone **125** was prepared according to the literature from D-fructose.[172] Using oxone as the stoichiometric oxidant, along with a basic buffer solution, the epoxide **126** was formed in moderate yield and good d.e. Starting material was also returned, and it could be re-reacted later, but adding more ketone **125** or oxone would not increase the yield.

In these preliminary studies, many problems were encountered during the deprotection of **126** (Scheme 3.8). When using the *p*-methoxybenzyl ether **127**, deprotection was swift with DDQ, but only the diastereomers of **128** were found. It should



Scheme 3.8: Unwanted 5-*exo*-tet cyclizations that made deprotection difficult

be noted, that these two products could be seperated by column chromatography and differentiated by NOE. Switching to the BOM protecting group with the mixture of epoxides **129**, deprotection with hydrogenation afforded a 2:4:1 mixture of **74a**, **128a** and **128b** in an interesting sort of resolution.

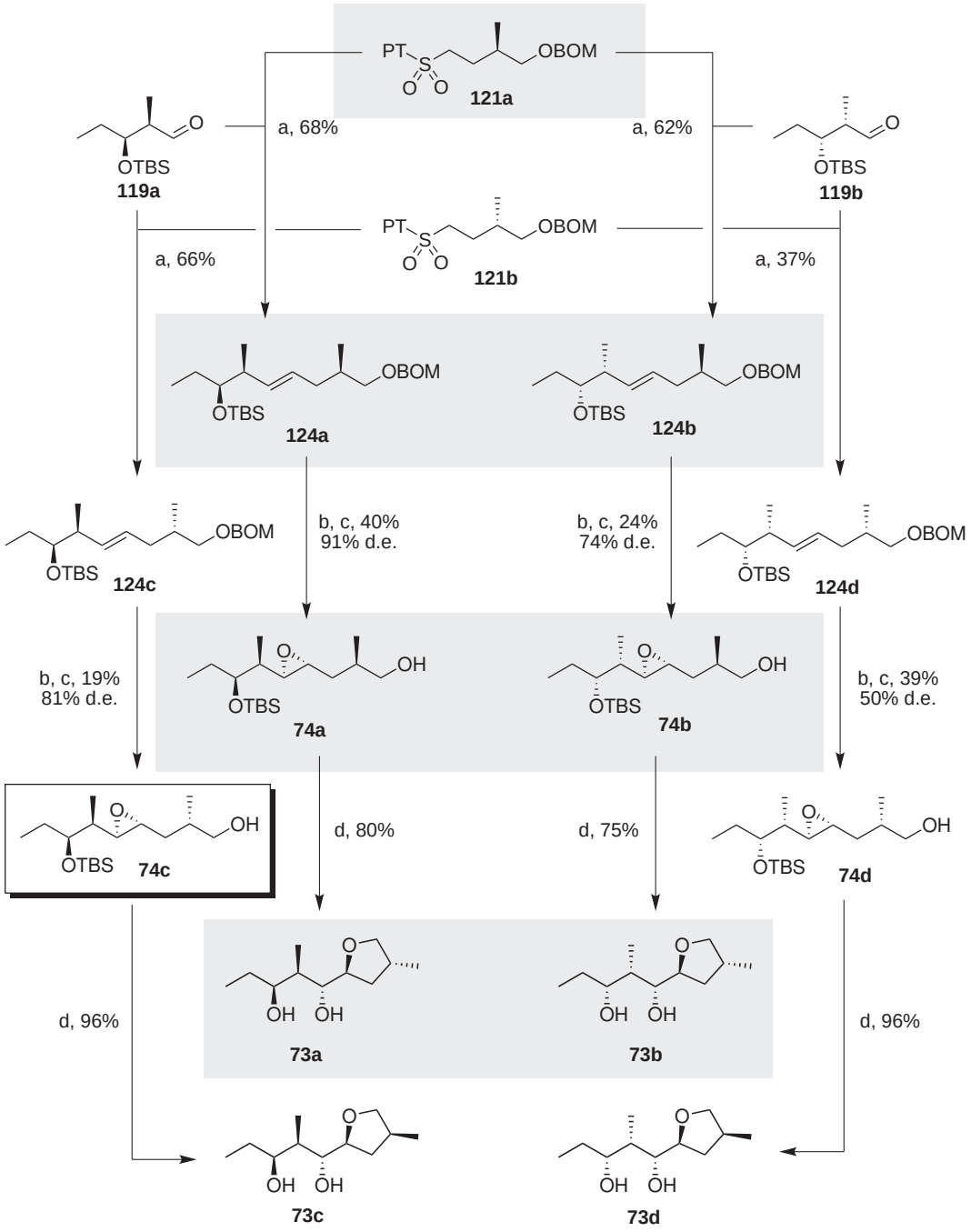
In an attempt to remove the TBS group as well, the powerful fluorosilicic acid was used. It was anticipated that the acid could also deprotect the BOM group of **126** but the product cyclized into the unusual formyl acetal **130**. Without the BOM group, the cycle would form with the 1,3-diol as we will see in the next paragraphs. Unfortunately, even mild conditions such as TBAF could not remove the TBS group

from **74a** without cyclizing most of the desired product (**72**) to **73a**.

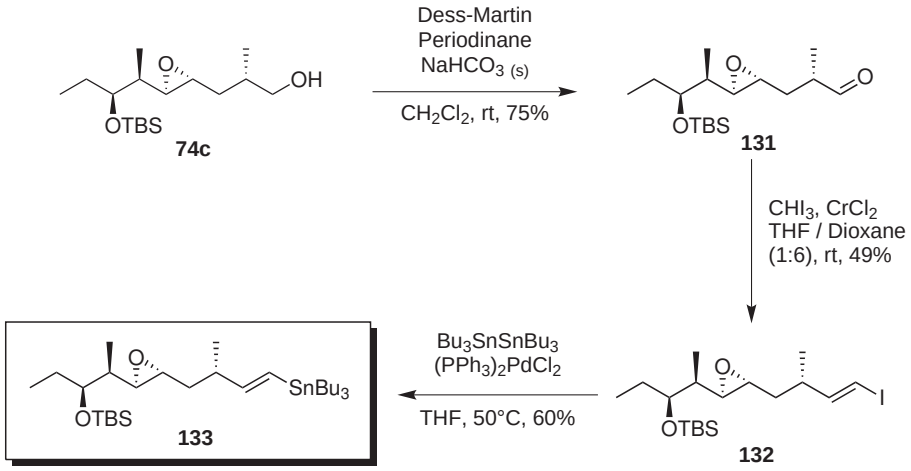
In light of the complications presented by the 5-*exo*-tet cyclization[198] it was decided that the tetrahydrofuran **73** would be a likely product of reductive ozonolysis of pladienolide B and acid catalyzed cyclization. Therefore, a panel of diastereomers (Scheme 3.9) was prepared using chemistry from the synthesis of the sidechain.

Using the methods outlined in Scheme 3.7, olefins **124a** – **d** were prepared in 68 – 37% yield. Next, it was decided that the BOM group should be deprotected at this stage to avoid the problems discussed in Scheme 3.8. Lithium napthelenide turned out to be the best conditions for this reaction, and the olefins were deprotected in good yields.[128] Subsequently, the free alcohols were subjected to the Shi conditions with no significant changes in yield or d.e. It is interesting to note the varying diastereomeric excesses which depended on the pendant stereochemistry on each of the olefins. When the epoxide was installed on the same side as the other groups, as with **74d**, only a 50% d.e. was recorded. On the other hand, when it was installed on the opposite side as the other groups, as with **74a** the d.e. was as high as 91% Later, when the stereochemistry of pladienolide B (**70b**) was disclosed it turned out that **74c** was the correct diastereomer, and it was acquired in 81% d.e.

The resultant alcohols were the appropriate synthons for carrying on with the next steps, but first a sample of each (**74a** – **d**) was deprotected and cyclized with fluorosilicic acid[199] to afford tetrahydrofurans **73a** – **d** in good yields. The relative stereochemistry inducted by the Shi epoxidation could be verified thorough NOE studies of these products.[200–202] It was important to check because in certain cases the reaction has favored the wrong diastereomer.[203] These products displayed very distinct ^{1}H and ^{13}C NMR signatures, and it was anticipated that it would be easy to match one of them with the degradation products of pladienolide B to obtain the relative stereochemistry of the sidechain. A Mosher's ester and optical rotation measurements



Scheme 3.9: Panel of diastereomers synthesized to compare to pladienolide B (**70b**) degradation products. Conditions: (a) KHMDS, DME, –78°C, then add aldehyde and warm to rt; (b) Li wire, napthalene, THF; (c) **125**, oxone, K_2CO_3, Bu_4NHSO_4, CH_3CN, H_2O, borax-EDTA buffer, 0°C, H_2SiF_6, CH_3CN, rt.



Scheme 3.10: Synthesis of the correct stereoisomer of stannane **133**

would have then confirmed the absolute stereochemistry of the sidechain.

3.4.3 Complete synthesis of the pladienolide B Stille coupling partner

With the stereochemistry no longer a mystery, the pladienolide B (**70b**) sidechain stannane **110** could be completed. Using alcohol **74c** from the panel of diastereomers, oxidation with the Dess-Martin Periodinane gave aldehyde **131** in 75% yield. Solid $NaHCO_3$ was neccessary to prevent the 5-*exo*-tet cyclization in this reaction. Next, the aldehyde was homologated with the conditions of Takai to yield vinyl iodide **132**.[204] The 1:6 mixture of THF / dioxanes was described by Evans and coworkers, and it gave only the *E* stereoisomer.[205] The yield of this reaction was low, but **132** was the only product found after workup. Historically, the Takai reaction gives 50 – 60% yields in total syntheses, but it could not be determined why so much mass was lost. There is a method to convert aldehydes directly to *E* stannanes, but it failed to produce any product.[206] The final step, a palladium catalyzed trans-stannylation took place in moderate yield, but fortunately the product could be purified by column chromatography

to yield the pure stannane **133**.[207,208]

3.5 Model studies of the esterification, ring-closing, and Stille coupling strategy

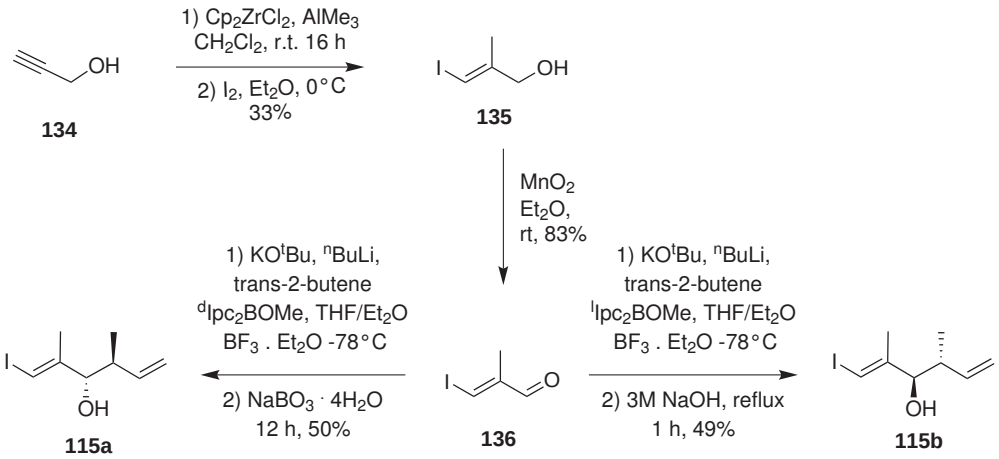
3.5.1 Divergent synthesis of two keystone diastereomers

Before the pladienolide B (**70b**) stereochemistry was disclosed, the central fragment (**115**) that became known as the "keystone" was produced in order to test the final coupling strategies. Two diastereomers were synthesized, although by the end, it was known which one represented the actual stereochemistry.

The keystone was prepared from propargyl alcohol (**134**) in three steps, based on a similar preparation in the White lab.[207] Several attempts to use a carboalumination with secondary propargylic alcohols, and protected propargyl alcohol were met with failure. It seems that any additional steric bulk around the alkyne would prevent this reaction from taking place despite literature precedent.[209] Methodology developed by Lipshutz may have provided a solution to this problem,[210] but the new synthetic strategy proved to be more environmental and economical.

Simply beginning with unprotected propargyl alcohol (**134**), a low yielding Negishi carboalumination afforded alcohol **135** (Scheme 3.11).[211] The yield was also similar to that reported in the literature, but was of little concern because **134** is an inexpensive starting material, and this branch of the synthesis has the smallest number of linear steps.

Next, the non-volatile iodide **135** was oxidized with mild manganese(IV) oxide to give the very u.v. active aldehyde **136**. This material was also non-volatile, and was purifyable through a short flash column. Moving forward, in another divergent



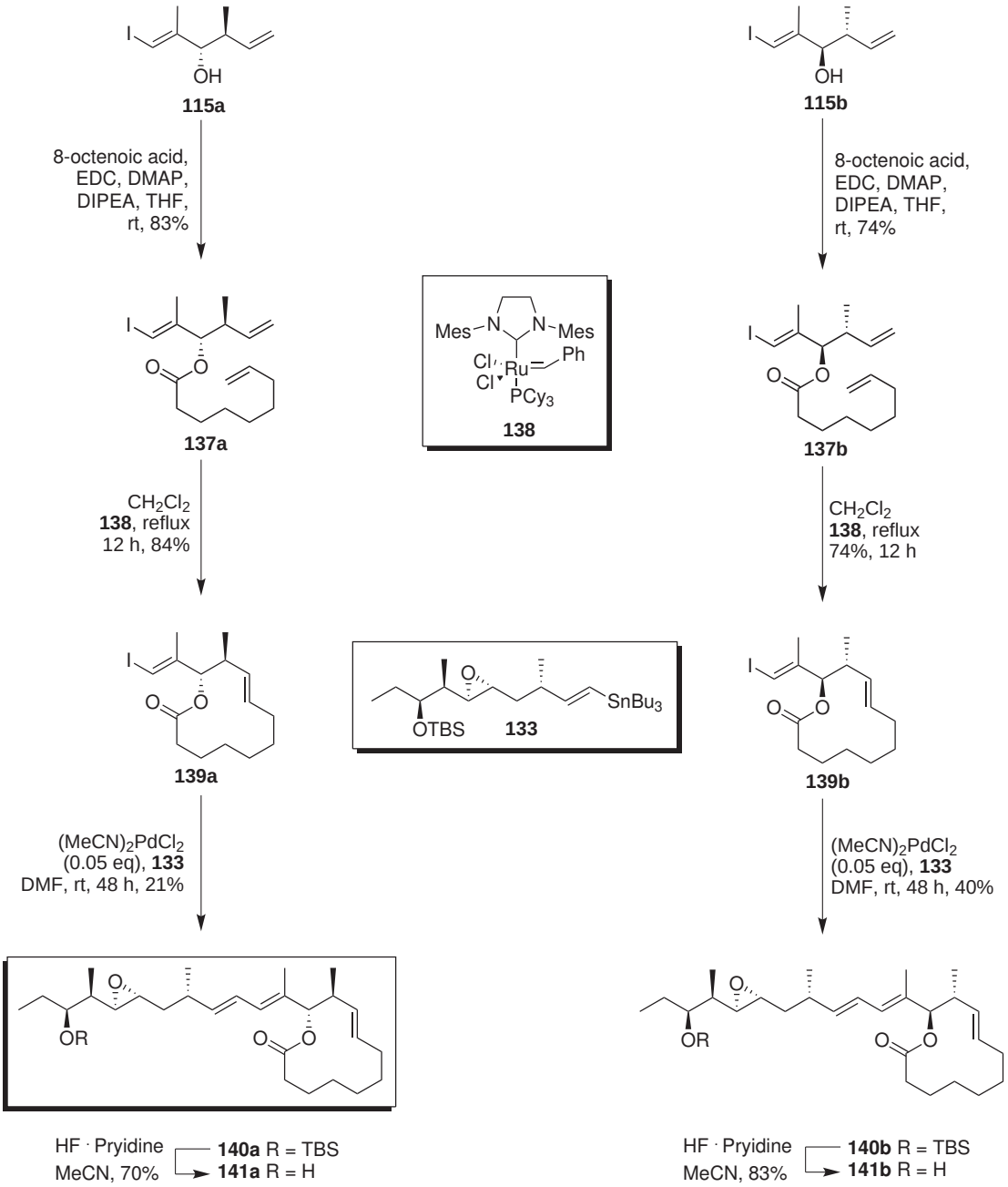
Scheme 3.11: Synthesis of two keystone diastereomers **115a** and **b**

step, the aldehyde was crotylated using Brown conditions to give alcohols **115a** and **b** in very similar yields.[212,213] The crotylboration gave mostly the desired *anti* product, but it also resulted in some undesired *syn*-**115** which could be removed with flash chromatography.

3.5.2 Modeling the Esterification, ring-closing, and Stille coupling strategy

With the successful synthesis of the keystone fragments **115a** and **b** the stage was set to model the chemistry that could bring together pladienolide B (Scheme 3.12). Esterification onto 8-octenoic acid with EDC and DMAP smoothly afforded esters **137a** and **b**. These esters participated in a facile and efficient ring-closing upon treatment with Grubbs' second generation catalyst (**138**) to produce only the *E* isomer of lactones **139a** and **b**.[175] No *Z* isomer was found before or after purification.

All that remained was to test to see if the Stille coupling would work with the stannane that was outlined in Scheme 3.10. The coupling was attempted with both lactones **139a** and **b** to produce **140a** and **b**. The reactions were sluggish, and both



Scheme 3.12: Modeling the chemistry neccessary to complete pladienolide B (**70b**)

were allowed to stir for two days before workup. However like the Shi epoxidation, both seemed to stall. Starting materials **139a** and **b** were recovered completely, but the stannane **133** was usually used up or degraded. A byproduct of **133** was found that no longer had the tin. The problem is probably due to slow palladium insertion into the hindered trisubstituted vinyl iodide, which gives the palladium time to insert into the tin, and then β-eliminate before substitution with the vinyl iodide. This reaction might be optimized by addition of silver salts and triphenylarsine ligands.

With a small amount of each surrogate lactone **140a** and **b**, the deprotection was achieved with HF · pyridine. TBAF was too weak to produce results, but H_2SiF_6 was too strong and yielded nothing recognizable. Like in the story of Goldilocks, HF · pyridine in acetonitrile turned out to be just right, and gave the fully deprotected pladienolide B surrogates **141a** and **b**. The ^{1}H NMR spectrum of the correct model compound **141a** was not very close to the published NMR data, meaning any attempt to deduce the stereochemistry of the sidechain by comparing a library of diasteromers would have been tenuous at best.

3.6 Concluding thoughts

Unfortunately, no member of the panel of diastereomers **74a** – **d** by itself was comparable to the published data, so the library approach from this standpoint would not have been effective. If the TBS group could have been deprotected reliably, it may have been possible to compare the resulting products. Without a natural sample, and a complete NMR spectrum, all conjectures about the stereochemisty would remain supposition. Since no photographs of the spectra for pladienolide B (**70b**) were provided either, it would be difficult to compare multiplets and complicated splitting patterns that were recorded as (m) in the spectral data. The lab tried to ferment **70b**

itself using the provided literature conditions.[136] After several attempts using different media, solvents, resins, and purification methods, we concluded that for some reason the strain of *Streptomyces platensis* we had would not produce the compound. Perhaps more importantly, the total synthesis had been achieved, and the methods used in this synthesis bore a striking resemblance to our own. These issues lead us to the final chapter in this saga, where we try to apply what we have learned in chapter 3 to FD-895 (**71**)

3.7 Acknowledgements

I would like to thank Elsevier for allowing me to reprint work as published in their journal. Material in this section was published as Mandel, A. L.; Jones, B. D.; La Clair J. J.; Burkart. M. D. "A synthetic entry to pladienolide B and FD-895" *Bio. Org. Med. Chem. Lett.*, **2007**, *17*, 5159–5164. I would like to acknowledge Dr. Jim La Clair and Brian Jones as co-authors of the paper that this work is based on. Brian was assisted in the scaleup of the keystone units (**115a** and **b**) Also, assisting with the culture and extraction work were Brian and Dr. Min-Jin Kang. If not for Min, I would not know the first thing about *Streptomyces* and how to properly go from spores to liquid culture.

3.8 Experimental data

Reactions were performed under Ar atmosphere at room temperature (rt) in oven dried glassware expect where indicated or when water is used as a solvent. THF, toluene, ether, DMF and dichloromethane for dry reactions were degassed and distilled through an alumina-packed solvent system. 1,2-dimethoxyethane was distilled

over sodium metal and benzophenone. DIPEA was purified by distillation over ninhydrin and then distillation over potassium hydroxide. Pyridine was distilled over potassium hydroxide. Triethylamine was distilled over sodium metal. Propionaldehyde was freshly distilled over anhydrous $CaCl_2$ before use. Other reagents were obtained from commercial suppliers and used directly from the bottle unless specifically noted. Column chromatography was performed with EM Silica Gel 60, and thin layer chromatography was performed on EMD Silica Gel 60 F_{254} pre-coated plates. Visualization of TLC was with a ceric ammonium molybdate solution preceeded by UV if necessary.

NMR spectroscopy was performed on Varian Mercury 300 MHz, 400 MHz, or Unity 500 MHz instruments at ambient temperature. Select NOESY and HMQC experiments were run on a Bruker DMX500. ^{1}H and ^{13}C NMR spectra are reported in parts per million relative to TMS and standardized to chloroform (^{1}H δ = 7.26 ppm, ^{13}C δ = 77.16 ppm) with multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiple peaks, br = broad), coupling constants, and integration. All ^{13}C spectra are reported with complete proton decoupling. ^{31}P NMR spectra are reported in ppm relative to H_3PO_4 (δ = 0 ppm). IR spectra were taken on a Nicolet magna-IR 550 series II Spectrometer and peaks are reported in wavenumber (cm^{-1}). Mass spectra were taken on a ThermoFinnigan LCQdeca mass spectrometer and high resolution spectra were taken on ThermoFinnigan MAT900XL high resolution mass spectrometer with electron impact or fast atom bombardment as ionization methods. All masses are expessed in amu. Optical rotations were taken with a Perkin-Elmer 241 Polarimeter with a 1 dm path length.

3.8.1 New compounds from Scheme 3.5

Aldol product 117a – To a solution of **116** (1.00 g, 3.77 mmol), stirring in 30 mL DCM at 0°C is added titanium tetrachloride (432 μL, 3.95 mmol), creating a red-brown mixture. After 5 minutes, DIPEA (721 μL, 4.15 mmol) is added, turning the reaction mixture black. After 15 minutes, the reaction mixture is cooled to -78°C and propionaldehyde (311 μL, 4.15 mmol) was added. The reaction was allowed to stir for 2.5 h, and then it was warmed to 0°C and checked by TLC. The desired product (**117a**) is the higher spot (R_f = 0.35, 2:1 hexanes / EtOAc), where a trace of **117b** is seen as the lower spot (R_f = 0.30, 2:1 hexanes / EtOAc). The reaction was quenched by the addition of 10 mL 25% NH_4Cl and extracted with 3 x 30 mL portions of DCM. The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and evaporated *in vacuo* to yield an oil. This product was purified by flash chromatography (6:1 to 2:1 hexanes / EtOAc) to yield **117a** (770 mg, 63%) as a bright yellow oil. ^{1}H-NMR: δ (500 MHz, $CDCl_3$) 7.33 (m, 2H), 7.27 (m , 3H), 5.37 (ddd, J = 4.5, 7.0, 10.5 Hz, 1H), 4.73 (dq, J = 2.0, 7.0 Hz, 1H), 3.97 (m, 1H), 3.37 (dd, J = 7.5, 12 Hz, 1H), 3.24 (dd, J = 4.0, 13 Hz, 1H), 3.04 (dd, J = 11, 13.5 Hz, 1H), 2.88 (d, J = 11.5 Hz, 1H), 2.74 (d, J = 3.0 Hz, 1H), 1.59 (m, 1H), 1.46 (m, 1H), 1.18 (d, J = 7.0 Hz, 3H), 0.98 (t, J = 8.0 Hz, 3H). ^{13}C-NMR: δ (100 MHz, $CDCl_3$) 201.4, 178.5, 136.4, 129.5, 129.0, 127.3, 72.7, 69.1, 42.5, 37.2, 32.1, 26.9. 10.8, 10.7. IR νmax: 3444, 3027, 2964, 2937, 2876, 1689, 1455, 1342, 1258, 1191, 1164, 1137, 1041, 1029, 960. ESI-MS: calcd. $C_{16}H_{21}NO_2S_2$ $[M]^+$: 323.10, found $[M+H]^+$: $\frac{m}{z}$ = 323.85.

Aldol product 117b – To a stirred solution of **116** (200 mg, 0.754 mmol) in 5 mL DCM at 0°C was added titanium tetrachloride (87 μL, 0.792 mmol) turning the solution the characteristic red-brown color. After 10 minutes (-)-sparteine (191 μL,

0.830 mmol) was added, turning the solution black. After 15 minutes the reaction was cooled to -78°C and *N*-methylpyrrolidinone (80 uL, 0.830 mmol) was added. After 5 minutes propionaldehyde (110 μL, 1.51 mmol) was added. The reaction was warmed to 0°C after 2.5 h and analyzed by TLC to show that there was mostly the lower spot (R_f = 0.30, 2:1 hexanes / EtOAc) as product, and the slightest trace of byproduct **117a**. The reaction was quenched by the addition of 25% NH_4Cl (5 mL), followed by extraction with 3 x 15 mL DCM. The combined organics were washed with brine (5 mL), dried over Na_2SO_4, and evaporated *in vacuo*. The resultant yellow oil was purified by flash chromatography (6:1 to 2:1 hexanes / EtOAc) to give **117b** (189 mg, 83%) as a bright yellow oil. ^{1}H-NMR: δ (500 MHz, $CDCl_3$) 7.35 (m, 2H), 7.30 (m , 3H), 5.36 (ddd, *J* = 4.0, 7.0, 10.5 Hz, 1H), 4.52 (dq, *J* = 3.0, 7.0 Hz, 1H), 3.86 (m, 1H), 3.41 (dd, *J* = 7.0, 11.5 Hz, 1H), 3.24 (dd, *J* = 4.0, 13.5 Hz, 1H), 3.06 (dd, *J* = 10.5, 13.5 Hz, 1H), 2.91 (d, *J* = 11.5 Hz, 1H), 2.64 (d, *J* = 3.0 Hz, 1H), 1.57 (m, 1H), 1.45 (m, 1H), 1.25 (d, *J* = 7.0 Hz, 3H), 0.97 (t, *J* = 7.5 Hz, 3H). ^{13}C-NMR: δ (100 MHz, $CDCl_3$) 201.6, 178.7, 136.6, 129.7, 129.2, 127.5, 73.9, 69.1, 43.1, 37.0, 32.3, 27.5, 10.6, 10.5. IR νmax: 3441, 2960, 2925, 2873, 1684, 1449, 1344, 1265, 1160, 741, 732. ESI-MS: calcd. $C_{16}H_{21}NO_2S_2$ $[M]^+$: 323.10, found $[M+H]^+$: $\frac{m}{z}$ = 323.85, $[M+Na]^+$: $\frac{m}{z}$ = 345.93.

TBS protected aldol 118a – To a stirred solution of **117a** (770 mg, 2.38 mmol) in 20 mL DCM at 0°C, DIPEA (1.03 mL, 5.95 mmol) was added, followed by ^{t}butyldimethylsilyl triflate (712 μL, 3.10 mmol). The reaction was allowed to warm to room temperature after addition of reagents. After 45 minutes, 10 mL of water was added. After 30 minutes, the organic and aqueous layers were separated and the organic layer was washed with 5 mL saturated $NaHCO_3$, 5 mL brine, dried over Na_2SO_4, and evaporated *in vacuo*. The remaining semi-solid yellow oil was purified

by flash chromatography (9:1 to 6:1 hexanes / EtOAc) to yield **118a** (970mg, 93%) as a bright yellow oil. ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 7.40 – 7.30 (m, 2H), 7.30 – 7.20 (m, 3H), 5.35 (dddd, J = 0.8, 2.8, 6.0, 10 Hz, 1H), 4.75 (p, J = 6.8 Hz, 1H), 4.14 (dt, J = 5.2, 6.4 Hz, 1H), 3.33 (dd, J = 7.2, 11.2 Hz, 1H), 3.21 (dd, J = 3.6, 12.8 Hz, 1H), 3.03 (dd, J = 10.8, 12.8 Hz, 1H), 2.85 (dd, J = 0.8, 11.6 Hz, 1H), 1.58 (m, 2H), 1.20 (d, J = 6.8 Hz, 3H), 0.91 (s, 9H), 0.88 (dd, J = 7.6, 9.2 Hz, 3H), 0.08 (s, 3H), 0.07 (s, 3H). ^{13}C-NMR: δ (100 MHz, $CDCl_3$) 201.0, 176.9, 136.7, 129.5, 129.1, 127.4, 73.9, 69.3, 43.4, 37.5, 32.0, 28.7, 26.4, 18.6, 14.8, 9.7, -3.6, -3.9. IR νmax: 2958, 2930, 2881, 2856, 1693, 1361, 1341, 1292, 1253, 1161, 1107, 1027, 836, 775, 702. ESI-MS: calcd. $C_{22}H_{35}NO_2S_2Si$ $[M]^+$: 437.19, found $[M+H]^+$: $\frac{m}{z}$ = 437.83. R_f = 0.5 (6:1 hexanes / EtOAc).

TBS protected aldol 118b – To a stirred solution of **117b** (195 mg, 0.603 mmol) in 10 mL DCM at 0°C, DIPEA (274 μL, 1.58 mmol) is added followed by ^{t}butyldimethylsilyl triflate (181 μL, 0.789 mmol). The reaction was allowed to warm to rt and after 45 minutes was worked up according to the procedure for **118a**. The residual oil was purified by flash chromatography (9:1 to 6:1 hexanes / EtOAc) to yield **118b** (200 mg, 76%). ^{1}H-NMR: δ (500 MHz, $CDCl_3$) 7.44 – 7.13 (m, 5H), 5.18 (ddd, J = 3.7, 6.8, 10.6 Hz, 1H), 4.58 (dq, J = 5.4, 6.7 Hz, 1H), 3.97 (q, J = 5.6 Hz, 1H), 3.32 (ddd, J = 0.8, 6.9, 11.4 Hz, 1H), 3.28 (dd, J = 2.7, 12.9, 2.7 Hz, 1H), 3.04 (dd, J = 13.1, 10.8 Hz, 1H), 2.88 (d, J = 11.5 Hz, 1H), 1.62 – 1.46 (m, 2H), 1.21 (d, J = 6.7 Hz, 3H), 0.90-0.85 (m, 12H), 0.04 (s, 3H), 0.02 (s, 3H) ^{13}C-NMR: δ (100 MHz, $CDCl_3$) 201.1, 177.1, 137.0, 129.7, 129.2, 127.4, 75.2, 69.8, 44.0, 36.8, 32.2, 28.3, 26.1, 18.3, 12.3, 9.7, –3.8, –4.4. IR νmax: 2960, 2855, 1693, 1449, 1335, 1256, 1160, 1134, 1029, 837, 776, 697. ESI-MS: calcd. $C_{22}H_{35}NO_2S_2Si$ $[M]^+$: 437.19, found $[M+H]^+$: $\frac{m}{z}$ = 437.79, $[M+Na]^+$: $\frac{m}{z}$ = 459.95. R_f = 0.5 (6:1 hexanes / EtOAc).

Aldehyde 119a – 118a (302 mg, 0.692 mmol) was dissolved in 7 mL toluene and cooled to -78°C. Diisobutylaluminumhydride (1.04 mL, 1.04 mmol, 1M in toluene) was dispensed with an air-tight syringe and 500 μL of the solution was added and the reaction was allowed to stir for 1.5 h. At this time, another 250 μL of the solution was injected into the flask. After 15 minutes another 100 μL was added, and after another 15 minutes 100 μL was added and the yellow color of the solution faded almost completely. The reaction was quenched with 10 mL of 10% $KHSO_4$, diluted with 60 mL ether, separated and the organic was washed 3 more times with 10 mL of the 10% $KHSO_4$. The organic layer was then washed twice with 10 mL of 1 M sodum hydroxide and the washings were set aside to later recover the chiral auxiliary. Finally the organic layer was washed once with 10 mL brine, dried over Na_2SO_4, and evaporated *in vacuo*. The remaining oil was purified by flash chromatography (10:1 hexanes / EtOAc) to yield **119a** (134 mg, 85%). ^{1}H-NMR: δ (500 MHz, $CDCl_3$) 9.77 (d, J = 1.2 Hz, 1H), 4.04 (dt, J = 3.6, 6.8Hz), 2.47 (ddq, J = 1.2, 3.6, 6.8 Hz, 1H). 1.54 (m, 2H), 1.06 (d, J = 6.8 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H), 0.86 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H). ^{13}C-NMR: δ (75 MHz, $CDCl_3$) 205.8, 73.6, 51.0, 27.6, 26.0, 18.3, 10.4, 7.8, –4.0, –4.7. IR νmax: 2956, 2630, 2851, 1724, 1468, 1252, 1101, 1023, 833, 775. ESI-MS: calcd. $C_{12}H_{26}O_2Si$ $[M]^+$: 230.17, found $[M+H+MeOH]^+$: $\frac{m}{z}$ = 246.84, $[M+Na+MeOH]^+$ $\frac{m}{z}$ = 284.97. R_f = 0.45 (8:1 hexanes / EtOAc).

Aldehyde 119b – The compound was prepared through an identical procedure to the preparation of **119a**. **118b** (195 mg, 0.446 mmol) yielded **119b** (73 mg, 72%) with proton and carbon spectra that were identical to **119a**.

3.8.2 New compounds from Scheme 3.6

(*R*)-4-(benzyloxymethoxy)-3-methylbutan-1-ol (122a) – (*R*)-2-methyl-1,4-butanediol (**120**a) (2.5 g, 24.0 mmol) was treated with ^{t}butyldiphenylsilylchloride (6.9 g, 25.2 mmol) and DBU (5.4 g, 36.0 mmol) in 95 mL of anhydrous DMF. After 8 h, the reaction was terminated by the addition of 100 mL of saturated $NaHCO_3$. The product was extracted with 4 x 100 mL DCM and the organic phases were collected and washed with water and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The product was purifed by flash chromatography (hexanes to 2:1 hexanes / EtOAc) to afford **121a** (4.44 g, 54%) as a clear oil. In order to optimize product purity, it was found to be critical to purify **121a** at this stage. Spectral characteristics matched those in the literature.[195]

A sample of **121a** (4.0 g, 11.7 mmol) was dissolved in 200 mL DCM containing DIPEA (17.7 mL, 35.0 mmol). After cooling in an ice bath, BOMCl (3.66 g, 23.4 mmol) was added dropwise over 2 h in 50 mL of dry DCM. Upon completion of the addition, the reaction was warmed to rt and terminated by the addition of 100 mL of saturated $NaHCO_3$. The product was extracted 4 x 80 mL DCM and the organic phases were collected and washed with water and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The crude product was treated with $TBAF \cdot 3\,H_2O$ (9.2g, 29.1 mmol) in 100 mL wet THF at rt for 6 h, at which point saturated NH_4Cl (50 mL) was added and the product was isolated by extraction 6 x 50 mL DCM. The organic phases were collected and washed with water and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The product was purified by flash chromatography (hexanes to 1:1 hexanes / EtOAc) to afford **122a** (1.95 g, 74%). ^{1}H-NMR: δ (500 MHz, $CDCl_3$) 7.35 (m, 4H), 7.32 (m, 1H), 4.77 (s, 2H), 4.61 (s, 2H), 3.73 (ddd, J = 6.0, 6.5, 11.0 Hz, 1H), 3.66 (ddd, J = 6.0, 6.5, 10.5 Hz, 1H), 3.48 (dd, J = 5.5, 9.5 Hz, 1H), 3.44 (dd, J = 6.5, 9.5 Hz, 1H), 1.98 (b, 1H), 1.92 (m, 1H), 1.67 (m, 1H), 1.52 (m, 1H), 0.96 (d, J =

6.5 Hz, 3H). ^{13}C-NMR: δ (100 MHz, $CDCl_3$) 138.0, 128.6, 128.0, 127.9, 94.9, 73.7, 69.6, 61.2, 37.6, 31.1, 17.6. IR νmax: 3412, 2922, 2875, 1448, 1366, 1108, 1047. ESI-MS: calcd. $C_{13}H_{20}O_3$ $[M]^+$: 224.15, found $[M+H]^+$: $\frac{m}{z}$ = 224.78

Sulfone 123a – To an oven dried flask were added **122a** (470 mg, 2.10 mmol), 1-phenyl-1H-tetrazole thiol (748 mg, 4.20 mmol), and triphenylphosphine (825 mg, 3.15 mmol). The flask was purged with Argon, and 25 mL THF was added to dissolve the contents. The mixture was cooled to 0°C and Diisopropyldiazodicarboxylate (732 μL, 3.78 mmol) was added via syringe. The reaction was allowed to run overnight with the ice bath melting to slowly warm the reaction to room temperature. After 18 h, the reaction was poured onto a saturated bicarbonate solution, and extracted with 3 x 50 mL portions of ether. The combined organics were washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The remaining crude sulfide was purified by flash chromatography (4:1 to 2:1 hexanes / EtOAc) and isolated as a clear, slightly foggy oil (660 mg, 82%). ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 7.60 – 7.50 (m, 5H), 7.34 (m, 4H), 7.30 (m, 1H), 4.75 (s, 2H), 4.59 (s, 2H), 3.53 – 3.38 (m, 4H), 2.04 – 1.90 (m, 2H), 1.75 – 1.65 (m, 1H), 1.01 (d, J = 6.8 Hz, 3H). ^{13}C-NMR: δ (100 MHz, $CDCl_3$) 138.1, 130.3, 130.0, 128.7, 128.1, 127.9, 124.1, 95.1, 73.0, 69.7, 33.4, 33.1, 31.5, 17.0. R_f = 0.50 (2:1 hexanes / EtOAc).

The pure sulfide (650 mg, 1.69 mmol), was dissolved in 20 mL of absolute ethanol, cooled to 0°C and a solution of ammonium molybdate tetrahydrate (418 mg, 0.338 mmol) in 30% H_2O_2 (862 mg, 25.4 mmol) was added dropwise. The reaction was stirred for 16 h, allowing the ice bath to melt to room temperature after an h. The reaction mixture was poured onto 10 mL brine and extracted 3 x 50 mL portions of ether. The combined organics were washed again with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The crusty oily residue was purified by flash chromatography

(4:1 to 2:1 hexanes / EtOAc) to yield **123a** (640 mg, 91%) as a clear oil that solidified upon standing. ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 7.70 (m, 2H), 7.60 (m, 3H), 7.34 (m, 4H), 7.29 (m, 1H), 4.74 (s, 2H), 4.60 (s, 2H), 3.83 (d, J = 8.0 Hz, 1H), 3.81 (d, J = 8.0 Hz), 3.52 (dd, J = 5.2 Hz, 9.6 Hz, 1H), 3.41 (dd, J = 6.8 Hz, 9.6 Hz), 2.12 – 2.05 (m, 1H), 1.95 (m, 1H), 1.92 – 1.84 (m, 1H), 1.00 (d, J = 6.8 Hz, 3H). ^{13}C-NMR: δ (100 MHz, $CDCl_3$) 153.6, 131.7, 130.0, 128.7, 128.1, 128.0, 125.3, 95.1, 72.7, 69.8, 54.6, 32.8, 26.4, 17.0. IR νmax: 3065, 3020, 2943, 2882, 1728, 1510, 1457, 1352, 1160, 1108, 1047, 763, 742, 695, 689. ESI-MS: calcd. $C_{20}H_{24}N_4O_4S$ $[M]^+$: 416.15, found: $[M+H]^+$: $\frac{m}{z}$ = 416.76, R_f = 0.45 (2:1 hexanes / EtOAc).

3.8.3 New compounds from Scheme 3.9

Olefin 124a – Sulfone **123a** (310 mg, 0.745 mmol), toluene azeotroped and dried over high vacuum, was dissolved in 5 mL 1,2-dimethoxyethane and cooled to -−78°C. A 0.75M KHMDS solution in toluene (0.754 mL, 0.565 mmol) was added, yielding a yellow solution. After 20 minutes, a solution of aldehyde **119a** in 1 mL 1,2-dimethoxyethane was added by cannula, causing the yellow color to fade. The solution was allowed to warm to room temperature and stirred for an h. The reaction was quenched with 5 mL 25% NH_4Cl and the mixture was extracted twice with 25 mL ether. The combined organics were washed once with brine and dried over Na_2SO_4, and evaporated *in vacuo*. The residual oil was purified by flash chromatography (20:1 hexanes / EtOAc) to yield **124a** (135 mg, 68%) as a clear oil. ^{1}H-NMR: δ (500 MHz, $CDCl_3$) 7.35 (m, 4H), 7.29 (m, 1H), 5.43 – 3.33 (m, 2H), 4.75 (s, 2H), 4.60 (s, 2H), 3.43 (dd, J = 6.0, 9.5 Hz, 1H), 3.38 (dd, J = 5.5, 10.5 Hz, 1H), 3.35 (dd, J = 7.0, 9.5 Hz, 1H), 2.20 (m, 1H), 2.10 (dt, J = 6.0, 13.5 Hz, 1H), 1.85 (ddd, J = 6.5, 7.5, 13.5 Hz, 1H), 1.76 (m, 1H), 1.44 – 1.35 (m, 2H), 0.94 (d, J = 6.5 Hz, 3H), 0.93 (d,

J = 6.0 Hz, 3H), 0.90 (s, 9H), 0.85 (t, *J* = 7.5, 3H), 0.03 (s, 6H). ^{13}C-NMR: δ (125 MHz, $CDCl_3$) 138.2, 135.4, 128.7, 128.1, 127.9, 127.5, 95.0, 77.5, 73.3, 69.5, 41.7, 37.1, 34.1, 26.8, 26.2, 18.5, 17.1, 16.3, 9.5, 1.3, –4.0, –4.2. IR νmax: 2958, 2929, 2881, 2857, 1462, 1378, 1255, 1104, 1051, 1028, 971, 862, 835. HR-MS: calcd. $C_{25}H_{44}O_3Si$ $[M]^+$: 420.3054, found $[M]^+$: $\frac{m}{z}$ = 420.3072. $[\alpha]_D^{25}$ = –18.8° (c = 1.15, $CHCl_3$). R_f = 0.40 (10:1 hexanes / EtOAc).

Olefin 124b – **124b** was prepared following the procedure and proportions for the preparation of **124a** using **123a** (199 mg, 0.478 mmol), **119b** (73 mg, 0.319 mmol), and 0.75M KHMDS in toluene (0.53 mL, 0.40 mmol). Silica gel purification of the crude product yielded **124b** (83 mg, 62%) as a clear oil. ^{1}H-NMR: δ (500 MHz, $CDCl_3$) 7.35 (m, 4H), 7.29 (m, 1H), 5.43 – 5.33 (m, 2H), 4.75 (s, 2H), 4.60 (s, 2H), 3.46 (dd, *J* = 6.0, 9.5 Hz, 1H), 3.41 (dd, *J* = 5.5, 11.0 Hz, 1H), 3.38 (dd, *J* = 7.0, 9.5 Hz, 1H), 2.25 (m, 1H), 2.15 (dt, *J* = 6.0, 13.0 Hz, 1H), 1.85 (ddd, *J* = 6.0, 6.5, 13.5 Hz, 1H), 1.79 (m, 1H), 1.47 - 1.39 (m, 2H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.85 (t, *J* = 7.5, 3H), 0.03 (s, 6H). ^{13}C-NMR: δ (125 MHz, $CDCl_3$) 138.2, 135.4, 128.7, 128.1, 127.9, 127.6, 95.0, 77.5, 73.3, 69.5, 41.7, 37.1, 34.1, 26.9, 26.2, 18.4, 17.1, 16.3, 9.5, 1.3, -4.0, -4.2. IR νmax: 2958, 2929, 2881, 2857, 1458, 1378, 1252, 1104, 1054, 1028, 831, 765. HR-MS: calcd. $C_{25}H_{43}O_3Si$ $[M\text{-}H]+$: 419.2976, found $[M\text{-}H]^+$: $\frac{m}{z}$ = 419.2972. $[\alpha]_D^{25}$ = +13.4° (c = 0.8, $CHCl_3$). R_f = 0.40 (10:1 hexanes / EtOAc).

Olefin 124c – **124c** was prepared following the procedure and proportions for the preparation of **124a** using **123b** (151.8 mg, 0.365 mmol), **119a** (70 mg, 0.304 mmol), and 0.75M KHMDS in toluene (0.49 mL, 0.365 mmol). Silica gel purification of the crude product yielded **124c** (47.5 mg, 37%) as a clear oil. 1H-NMR was an exact match to **124b** as expected for the enantiomer. $[\alpha]_D^{25}$ = –12.8° (c = 1.3, $CHCl_3$).

Olefin 124d – **124d** was prepared following the procedure and proportions for the preparation of **124a** using **123b** (260 mg, 0.625 mmol), **119b** (120 mg, 0.521 mmol), and 0.75M KHMDS in toluene (0.833 mL, 0.625 mmol). Silica gel purification of the crude product yielded **124d** (145 mg, 66%) as yellow oil, contaminiated with a trace of **118b**. ^{1}H-NMR was an exact match to **124a** as expected for the enantiomer. $[\alpha]_D^{25}$ = +27.2° (c = 1.0, $CHCl_3$).

Epoxy-alcohol 74a – **124a** (29.2 mg, 0.070 mmol) and naphthalene (106 mg, 0.83 mmol) were dissolved in 5 mL THF in a glass vial with a glass coated stirbar. Lithium wire (4.4 mg, 0.63 mmol) was freshly cut and rinsed with hexanes and added to the reaction vessel, which was promptly re-sealed. The solution darkened over an hour, and as soon as the solution appeared to be opaque green (about 1.5 h) it was quenched by the addition of about 1 mL MeOH. The cloudy solution was filtered through a small column of silica-gel, and was washed with 20 mL EtOAc and the filtrate was concentrated *in vacuo*. The crude extract was purified by flash chromatography (20:1 to 6:1 hexanes / EtOAc) to give the intermediate olefin-alcohol (15.7 mg, 71%) as a clear oil. ^{1}H-NMR: δ (500 MHz, $CDCl_3$) 5.45 – 5.36 (m, 2H), 3.53 – 3.50 (m, 1H), 3.40 – 3.45 (m, 2H), 2.26 (m, 1H), 2.10 – 2.05 (m, 1H), 1.94 – 1.88 (m, 1H), 1.70 (m, 1H), 1.48 – 1.35 (m, 3H), 0.94 (d, J = 7.0 Hz, 3H), 0.91 (d, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.85 (t, J = 7.5 Hz, 3H), 0.03 (s, 6H). ^{13}C-NMR: δ (125 MHz, $CDCl_3$) 135.3, 127.8, 77.6, 68.3, 41.7, 37.2, 36.3, 26.8, 26.2, 18.5, 16.8, 16.3, 9.7, –4.1, –4.2. IR νmax: 3346, 2959, 2930, 2858, 1462, 1377, 1255, 1102, 1017, 971, 862, 835, 773, 666. HR-MS: calcd. $C_{17}H_{35}O_2Si$ $[M]^+$ calcd: 300.2479, found: $[M]^+$: $\frac{m}{z}$ = 300.2477. R_f = 0.30 (2:1 hexanes / EtOAc).

A solution of the olefin-alcohol (14.7 mg, 0.047 mmol), ketone **125** (29 mg, 0.023 mmol), and Bu_4NHSO_4 (2 mg, 0.006 mmol) in 1 mL acetonitrile and 0.75 mL 0.05M

$Na_2B_4O_7$ was prepared with stirring and cooled to 0°C. 3 separate solutions were prepared with **125** (29 mg, 0.023 mmol) in 18 drops MeCN, potassium carbonate (65 mg, 0.47 mmol) in 18 drops water, and Oxone (58 mg, 0.094 mmol) in 18 drops of 4mM Na_2(EDTA). A drop of each solution was added every 5 minutes until they were exhausted about 1.5 h later, and the reaction was allowed to stir at 0°C for another 30 minutes. 25% potassium carbonate was added to the solution, and the mixture was extracted 3 times with 15 mL ether. The combined organic extracts were washed with brine, and dried over Na_2SO_4, and evaporated *in vacuo* to yield a somewhat wet film. The film was purified by flash chromatography (6:1 to 2:1 hexanes / EtOAc) to yield a mixture of **74a** and **125** (12.2 mg, 72% pure [w/w], 56 % [actual yield], 91% d.e.) Spectral data excluding contaminants: ^{1}H-NMR: δ (500 MHz, $CDCl_3$) 3.73 (dt, J = 3.0, 6.5 Hz, 1H), 3.60 (dd, J = 5.0, 10.5 Hz, 1H), 3.48 (dd, J = 5.5, 11 Hz, 1H), 2.77 (ddd, J = 2.5, 4.0, 8.0 Hz, 1H), 2.69 (dd, J = 2.5, 8.0 Hz, 1H), 1.88 (m, 1H), 1.64 (ddd, J = 4.0, 7.0, 14.0 Hz), 1.56 – 1.46 (m, 1H), 1.44 – 1.35 (m, 2H), 0.99 (d, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.89 (d, J ~7.5 Hz, 3H), 0.82 (t, J = 7.5 Hz, 3H), 0.07 (s, 6H). ^{13}C-NMR: δ (125 MHz, $CDCl_3$) 74.4, 68.3, 61.9, 57.7, 40.0, 37.2, 34.5, 27.7, 26.2, 18.4, 17.7, 10.1, 9.9, –3.9, –4.4. IR νmax: 3441, 2960, 2935, 2881, 2858, 1460, 1375, 1258, 1069, 1018, 835. HR-MS: calcd. $C_{17}H_{35}O_3Si$ $[M-H]^+$ calcd : 315.2350, found $[M-H]^+$: $\frac{m}{z}$ = 315.2356. R_f = 0.35 (2:1 hexanes / EtOAc).

Epoxy-alcohol 74b – The precursor olefin-alcohol was prepared using the same procedure and proportions as in the preparation of **74a** using **124b** (30.0 mg, 0.071 mmol), naphthalene (110 mg, 0.856 mmol), and lithium wire (4.4 mg, 0.642 mmol). Flash chromatography yielded the olefin alcohol (17.3 mg, 81%) as a clear oil. ^{1}H-NMR: δ (500 MHz, $CDCl_3$) 5.45 – 5.35 (m, 2H), 3.54 – 3.49 (m, 1H), 3.40 – 3.47 (m, 2H), 2.26 (m, 1H), 2.10 (dt, J = 6.5, 13.5 Hz, 1H), 1.92 – 1.86 (m, 1H), 1.70 (m, 1H), 1.49

– 1.36 (m, 2H), 1.31 (t, J = 5.5 Hz, 1H), 0.94 (d, J = 7.0 Hz, 3H), 0.91 (d, J = 6.5 Hz, 3H), 0.89 (s, 9H), 0.85 (t, J = 7.5 Hz, 3H), 0.03 (s, 6H). ^{13}C-NMR: δ (125 MHz, $CDCl_3$) 135.4, 127.7, 77.6, 68.4, 41.7, 37.1, 36.3, 26.8, 26.2, 18.5, 16.7, 16.3, 9.6, –4.0, –4.2. IR νmax: 3332, 2952, 2927, 2853, 1458, 1367, 1244, 1252, 1095, 1013, 848, 765. HR-MS: calcd. $C_{17}H_{35}O_2Si$ $[M-H]^+$ calcd : 299.2401, found $[M-H]^+$: $\frac{m}{z}$ = 299.2403. R_f = 0.30 (2:1 hexanes / EtOAc).

74b was prepared using the same method and proportions as **74a** using **124b** (15.1 mg, 0.050 mmol) to yield a mixture of **125** and **74b** (9.3 mg, 52% pure [w/w], 30% yield, 74% d.e.). Starting olefin-alcohol (8.0 mg, 53%) was also recovered pure. ^{1}H-NMR: δ (500 MHz, $CDCl_3$) 3.63 – 3.55 (m, 2H), 3.52 – 3.46 (m, 1H), 2.84 (dt, J = 2.5, 8.5 Hz, 1H), 2.71 (dd, J = 2.5, 7.5 Hz, 1H), 1.93 – 1.85 (m, 2H), 1.71 (ddd, J = 3.0, 6.5, 14.5 Hz, 1H), 1.58 – 1.38 (m, 3H), 1.31 (ddd, J = 7.5, 8.0, 16.0 Hz, 1H), 1.00, (d, J = 7.0 Hz, 3H), 0.97 (d, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.86 (t, J = 7.0 Hz, 3H), 0.05 (s, 3H), 0.03 (s, 3H). ^{13}C-NMR: δ (125 MHz, $CDCl_3$) 76.0, 68.2, 62.3, 57.7, 41.0, 37.0, 34.6, 26.9, 26.2, 17.7, 12.0, 10.5, –4.0, –4.2. IR νmax: 3455, 2952, 2925, 2861, 1458, 1367, 1252, 1087, 1000, 872, 839. HR-MS: calcd. $C_{17}H_{35}O_3Si$ $[M-H]^+$ calcd : 315.2350, found $[M-H]^+$: $\frac{m}{z}$ = 315.2356. R_f = 0.35 (2:1 hexanes / EtOAc).

Epoxy-alcohol 74c – The intermediate olefin-alcohol was prepared using the same procedure and proportions as in the preparation of **74a** using **124c** (37.1 mg, 0.088 mmol), naphthalene (136 mg, 1.06 mmol), and lithium wire (5.5 mg, 0.794 mmol). Following flash chromatography, the olefin-alcohol (14.3 mg, 54%) was isolated as a clear oil. ^{1}H-NMR was identical to its enantiomer.

74c was prepared using the same method and proportions as **74a** using the olefin-alcohol above (14.3 mg, 0.048 mmol) to yield a mixture of **125** and **74c** (8.6 mg, 63% pure [w/w], 36% yield, 80% d.e.). Starting olefin-alcohol was not pure after recovery.

^{1}H-NMR: δ (500 MHz, $CDCl_3$) 3.73 (dt, J = 7.0, 3.5 Hz, 1H), 3.53 (t, J = 5.0 Hz, 2H), 2.79 (ddd, J = 7.0, 4.0, 2.5 Hz, 1H), 2.66 (dd, J = 7.0, 2.0 Hz, 1H), 1.90 (6-plet, J = 6.5 Hz, 1H), 1.82 – 1.73 (m, 2H), 1.56 – 1.34 (m, 3H), 1.01 (d, J = 6.5 Hz, 3H), 0.90 – 0.88 (m, 12H), 0.82 (t, J = 7.5 Hz, 3H), 0.07 (s, 6H). ^{13}C-NMR: δ (125 MHz, $CDCl_3$) 74.3, 67.9, 61.0, 56.8, 40.0, 36.0, 34.1, 27.6, 26.1, 18.3, 16.8, 10.0, 9.9, -4.0, -4.5. IR νmax: 3450, 2958, 2917, 2849, 1462, 1454, 1379, 1256, 1101, 1045, 1018, 834, 774. HR-MS: calcd. C17H35O3Si $[M+H]^+$ calcd : 317.2506, found $[M+H]^+$: $\frac{m}{z}$ = 317.2503. R_f = 0.35 (2:1 hexanes / EtOAc).

Epoxy-alcohol 74d – The intermediate olefin-alcohol was prepared using the same procedure and proportions as in the preparation of **74a** using **124d** (37.1 mg, 0.088 mmol), naphthalene (136 mg, 1.06 mmol), and lithium wire (5.5 mg, 0.794 mmol). Following flash chromatography, the olefin-alcohol (14.3 mg, 54%) was isolated as a clear oil. 1H-NMR was identical to its enantiomer.

74d was prepared using the same method and proportions as **74a** using **124d** (50.9 mg, 0.048 mmol) to yield a mixture of **125** and 18d (32.2 mg, 77% pure [w/w], 47% yield, 50% d.e.). Starting olefin-alcohol (32.6 mg, 56% pure [w/w], 35% recovery) was recovered. ^{1}H-NMR: δ (500 MHz, $CDCl_3$) 3.56 (dt, J = 6.0, 4.0 Hz, 1H), 3.54 - 3.51 (m, 2H), 2.86 (dt, J = 8.0, 3.0 Hz, 1H), 2.67 (dd, J = 7.5, 2.5 Hz, 1H), 1.91 (m, 1H), 1.84 (ddd, J = 14.5, 5.5, 3.5 Hz, 1H), 1.65 (b, 1H), 1.55 – 1.41 (m, 3H), 1.32 (ddd, J = 14.5, 8.0, 6.5 Hz, 1H), 1.01 (d, J = 7.0 Hz, 3H), 0.97 (d, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.85 (t, J = 7.5 Hz, 3H), 0.05 (s, 3H), 0.03 (s, 3H). ^{13}C-NMR: δ (125 MHz, $CDCl_3$) 76.0, 67.8, 61.3, 56.9, 41.0, 35.9, 34.1, 26.7, 26.1, 18.2, 16.8, 12.0, 10.3, –4.1, –4.3. IR νmax: 3450, 2957, 2928, 2857, 1462, 1377, 1253, 1226, 1096, 1016, 834, 773. HR-MS: calcd. $C_{17}H_{35}O_3Si$ $[M+H]^+$ calcd : 317.2506, found $[M+H]^+$: $\frac{m}{z}$ = 317.2509. R_f = 0.35 (2:1 hexanes / EtOAc).

Tetrahydrofuran 73a – To a stirred solution of **74a** (6.3 mg, 72% pure, 0.014 mmol) in 1 mL acetonitrile in a polypropylene vial with a Teflon stirbar, was added fluorosilicic acid (35% aq, $\sim$5 μL, $\sim$ 0.02 mmol). After one minute, TLC confirmed the reaction to be complete. The reaction was quenched with triethylamine, and passed through a pipette sized silica gel column, eluting with 10 mL EtOAc. The eluant was evaporated *in vacuo* and the material was purified through flash chromatography through a pipette column (2:1 to 1:1 hexanes / EtOAc) to yield **73a** (2.3 mg, 80%, 91% d.e.). ^{1}H-NMR: δ (500 MHz, $CDCl_3$) 4.06 (dt, *J* = 7.5, 5.0 Hz, 1H), 4.00 (dd, *J* = 8.5, 5.0 Hz, 1H), 3.77 (m, 1H), 3.72 (dd, *J* = 7.5, 5.0 Hz, 1H), 3.31 (dd, *J* = 7.5, 7.0, 1H), 2.62 (b, 2H), 2.31 (m, 1H), 2.10 (ddd, *J* = 15.0, 8.0, 7.0 Hz, 1H), 1.79 (pd, *J* = 7.0, 2.5 Hz, 1H), 1.58 – 1.39 (m, 3H), 1.05 (d, *J* = 6.5 Hz, 3H), 0.99 (t, *J* = 7.5 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H) ^{13}C-NMR: δ (125 MHz, $CDCl_3$) 79.8, 76.2, 75.7, 75.2, 39.3, 34.1, 33.9, 26.3, 18.1, 11.2, 11.0. IR νmax: 3380, 2960, 2925, 2873, 1457, 1379, 1082, 1047, 968. HR-MS: calcd. $C_{11}H_{22}O_3$ $[M]^+$ calcd : 202.1563, found $[M]^+$: $\frac{m}{z}$ = 202.1569. R_f = 0.10 (2:1 hexanes / EtOAc). $[\alpha]_D^{25}$ = –18.2° (c = 0.23, $CHCl_3$).

Tetrahydrofuran 73b – **73b** was prepared using the same proportions and procedure as in the preparation of **73a** using **74b** (4.0 mg, 0.013 mmol) to yield **73b** (2.5 mg, 96%, 75% d.e.). ^{1}H-NMR: δ (500 MHz, $CDCl_3$) 3.95 – 3.93 (m, 2H), 3.76 (m, 1H), 3.67 (dd, *J* = 8.0, 2.0 Hz, 1H), 3.28 (t, *J* = 7.5 Hz, 1H), 2.97 (b, 1H), 2.32 (m, 1H), 2.12 (b, 1H), 2.06 (ddd, *J* = 13.0, 8.0, 6.0 Hz, 1H), 1.88 (qt, *J* = 7.0, 2.0 Hz, 1H), (dt, *J* = 12.5, 7.0 Hz, 1H), 1.59 – 1.46 (m, 2H), 1.05 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 7.5 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 3H). ^{13}C-NMR: δ (125 MHz, $CDCl_3$) 79.2, 79.1, 79.0, 75.3, 37.5, 36.6, 33.5, 28.4, 17.8, 10.6, 5.0. IR 3400, 2970, 2934, 2882, 1460, 1390, 1100, 1040, 975. HR-MS: calcd. $C_{11}H_{22}O_3$ $[M]^+$ calcd : 202.1563, found $[M]^+$: $\frac{m}{z}$ = 202.1561. R_f = 0.10 (2:1 hexanes / EtOAc). $[\alpha]_D^{25}$ = –10.8° (c = 0.25, $CHCl_3$).

Tetrahydrofuran 73c – 73c was prepared using the same proportions and procedure as in the preparation of **73a** using 10c (6.0 mg, 0.019 mmol) to yield **73c** (3.6 mg, 95%, 80% d.e.). ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 4.00 (ddd, *J* = 10.4, 6.0, 4.8 Hz, 1H), 3.95 (t, *J* = 7.6 Hz, 1H), 3.80 – 3.71 (m, 2H), 3.35 (t, *J* = 8.4 Hz, 1H), 2.72 (d, *J* = 6.4 Hz, 1H), 2.63 (d, *J* = 3.2 Hz, 1H), 2.44 – 2.35 (m, 1H), 2.04 (dt, *J* = 12.0, 6.0 Hz, 1H), 1.77 (pd, *J* = 7.2, 2.4 Hz, 1H), 1.60 – 1.38 (m, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.99 (t, *J* = 7.2 Hz, 3H), 0.88 (d, *J* = 7.2 Hz, 3H) ^{13}C-NMR: δ (100 MHz, $CDCl_3$) 81.2, 75.7, 75.4, 75.3, 39.6, 34.6, 34.5, 26.6, 17.4, 11.2, 11.0. IR νmax: 3373, 2968, 2935, 2878, 1458, 1376, 1095, 1046, 971. HR-MS: calcd. $C_{11}H_{22}O_3$ $[M]^+$ calcd : 202.1563, found $[M]^+$ 202.1566. R_f = 0.30 (1:1 hexanes / EtOAc). $[\alpha]_D^{25}$ = +31.4° (c = 0.35, $CHCl_3$).

Tetrahydrofuran 73d – 73d was prepared using the same proportions and procedure as in the preparation of **73d** using **74d** (16.0 mg, 0.051 mmol) to yield **73d** (7.7 mg, 75%, 50% d.e.). ^{1}H-NMR: δ (500 MHz, $CDCl_3$) 3.92 – 3.85 (m, 2H), 3.78 – 3.73 (m, 2H), 3.31 (t, *J* = 8.0 Hz, 1H), 2.99 (d, *J* = 1.5 Hz, 1H), 2.35 (m, 1H), 2.60 (d, *J* = 4.0Hz, 1H), 2.22 (dt, *J* = 12.5, 6.5 Hz, 1H), 1.85 (qt, *J* = 7.0, 2.0 Hz, 1H), 1.60 – 1.36 (m, 3H), 1.06 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.93 (t, *J* = 7.0 Hz, 3H). ^{13}C-NMR: δ (75 MHz, $CDCl_3$) 80.4, 79.9, 78.9, 75.1, 38.1, 37.9, 34.7, 28.3, 17.6, 10.7, 5.1. IR νmax: 3386, 2963, 2931, 2875, 1458, 1376, 1087, 1042, 971, 955. HR-MS: calcd. $C_{11}H_{22}O_3$ $[M]^+$ calcd : 202.1563, found $[M]^+$ 202.1562. R_f = 0.30 (1:1 hexanes / EtOAc). $[\alpha]_D^{25}$ = –23.0° (c = 0.7, $CHCl_3$).

3.8.4 New compounds from Scheme 3.10

Epoxy aldehyde 131 – To a solution of **74c** (30.7 mg, 0.097 mmol) in 2 mL DCM was added solid $NaHCO_3$ (12.2 mg, 0.145 mmol) and then solid Dess-Martin periodinane (57.3 mg, 0.145 mmol). The reaction was stirred for 30 minutes and then concentrated *in vacuo*, and the residue was purified by silica gel chromatography (20:1 to 10:1 hexanes / EtOAc) to yield **131** (22.9 mg, 75%) as a clear film. ^{1}H-NMR: δ (500 MHz, $CDCl_3$) 9.67 (s, 1H), 3.71 (dt, J = 3.3, 6.6 Hz, 1H), 2.77 (ddd, J = 2.2, 4.5, 6.7 Hz, 1H), 2.67 (dd, J = 2.2, 7.9 Hz, 1H), 2.57 (sextet, J = 7.0 Hz, 1H), 2.05 (ddd, J = 4.5, 7.4, 14.7 Hz, 1H), 1.49 (m, 3H), 1.33 (dq, J = 3.3, 7.4 Hz, 1H), 1.20 (d, J = 7.4 Hz, 3H), 0.89 (s, 9H), 0.87 (d, J = 7.4 Hz, 3H), 0.81 (t, J = 7.6 Hz, 3H), 0.06 (s, 6H). ^{13}C-NMR: δ (75 MHz, $CDCl_3$) 203.9, 74.2, 61.1 56.4, 44.3, 39.8, 33.4, 27.6, 26.0, 18.3, 14.0, 10.0, 9.8, –4.0, –4.6. IR νmax: 2959, 2931, 2857, 2881, 1729, 1473, 1463, 1379, 1254, 1141, 107, 1017, 867, 834, 775. HR-MS: calcd. $C_{17}H_{34}O_3Si$ $[M]^+$ calcd : 314.2272, found $[M]^+$: $\frac{m}{z}$ = 314.2272. $[\alpha]_D^{25}$ = +14.6° (c = 2.29, $CHCl_3$) R_f = 0.35 (6:1 hexanes / EtOAc).

Vinyl iodide 132 – **131** (19.2 mg, 0.061 mmol) and iodoform (48.1 mg, 0.122 mmol) were dissolved in 3 mL dioxanes and cannulated into a suspension of anhydrous chromium(II) chloride (45.0 mg, 0.366 mmol) in 0.5 mL THF at room temperature. After 3 h TLC (10:1 hexanes / EtOAc) revealed no remaining starting material and the reaction was diluted with 10 mL ether, poured into 2 mL water, and separated The aqueous layer was extracted twice more with 10 mL ether. The combined organic extracts were washed with 5mL brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by preparative TLC (10:1 hexanes / EtOAc) to yield 21 (10.7 mg, 40%) as a clear film. ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 6.43 (dd, J = 8.5, 14.3 Hz, 1H), 6.08 (d, J = 14.4 Hz, 1H), 3.72 (m, 1H), 2.66 (ddd, J = 2.2, 4.8, 7.1, 1H), 2.62

(dd, J = 2.2, 8.0 Hz, 1H), 2.44 (septet, J = 7.2 Hz, 1H), 1.59 – 1.43 (m, 4H), 1.30 (dp, J = 3.2, 7.3 Hz, 1H), 1.07 (d, J = 6.8 Hz, 3H), 0.90 – 0.86 (m, 12H), 0.81 (t, J = 7.6 Hz, 3H), 0.06 (s, 6H). ^{13}C-NMR: δ (100 MHz, $CDCl_3$) 151.0, 74.8, 74.2, 61.4, 56.8, 40.0, 39.2, 39.0, 27.7, 26.1, 20.4, 18.3, 10.0, –4.0, –4.5. IR νmax:. 2958, 2928, 2856, 1462, 1378, 1253, 1076, 1017, 946, 867. 834, 774, 666. HR-MS: calcd. $C_{18}H_{35}O_2ISi$ calcd: $[M]^+$ 438.1446, found: $[M]^+$: $\frac{m}{z}$ = 438.1447. R_f = 0.55 (6:1 hexanes / EtOAc). $[\alpha]_D^{25}$ = +27.1° (c = 1.86, $CHCl_3$).

Vinyl stannane 133 – Vinyl iodide **132** (17.2 mg, 0.039 mmol) was dissolved in 1 mL THF, and hexabutylditin (39.7 μL, 0.078 mmol) was added followed by bistriphenylphosphinepalladium(II) chloride ($Pd(PPh_3)_2Cl_2$) (0.3 mg in 0.6 mL DMF, 0.39 μmol) and the reaction is heated to 50°C and stirred for 12 h. At the completion of the reaction TLC (1:1 hexanes / $CHCl_3$) showed no remaining starting material (**132**). The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography (Hexanes to 2:1 hexanes:$CHCl_3$ with a few drops Et_3N) to yield **133** as a clear film (14.3 mg, 65%). ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 5.93 (d, J = 18.7 Hz, 1H), 5.84 (dd, J = 6.3, 18.8 Hz, 1H), 3.73 (dt, J = 3.6, 6.6 Hz, 1H), 2.70 (ddd, J = 2.3, 4.8, 7.0, Hz 1H), 2.62 (dd, J = 2.3, 8.1 Hz, 1H), 2.40 (septet, J = 7.0 Hz, 1H), 1.60 – 1.40 (m, 10H), 1.40 – 1.20 (m, 7H), 1.06 (d, 6.9 Hz, 3H), 0.90 – 0.78 (m, 30H), 0.07 (s, 3H), 0.06 (s, 3H). ^{13}C-NMR: δ (100 MHz, $CDCl_3$) 153.7, 126.1, 74.3, 61.3, 57.5, 40.2, 39.7, 39.6, 29.4, 27.8, 27.5, 26.2, 21.0, 14.0, 10.1, 9.7, –3.8, –4.3. IR νmax: 2958, 2928, 2856, 1464, 1377, 1253, 1073, 1017, 867, 834, 774. HR-MS: calcd. $C_{30}H_{62}O_2SiSn$ $[M]^+$ calcd : 602.3536, found $[M]^+$: $\frac{m}{z}$ = 602.3540. $[\alpha]_D^{25}$ = +11.4° (c = 0.65, $CHCl_3$) R_f = 0.65 (1:1 hexanes:$CHCl_3$).

3.8.5 New compounds from Scheme 3.11

(3*S*, 4*S*)-1-Iodo-2,4-dimethyl-penta-1,5-diene-3-ol (115a) – Potassium ^{t}butoxide (88.2 mg, 0.786 mmol) was heated overnight to 110°C in order to remove all traces of moisture. The dry ^{t}butoxide was then dissolved in THF (1 mL), cooled to −78°C and *trans*-2-butene (500 μL, excess) was cannulated into the solution. ^{n}butyllithium (534 μL, 0.786 mmol, 1.47 M in hexanes) was added via syringe, and the reaction was warmed to –45°C for ten minutes, then the yellow-orange solution was recooled to −78°C. Next, a solution of (-)-*B*-methoxy-isocampheylborane (derived from (+)-pinene) (298 mg, 0.943 mmol) in 1 mL ether, was cannulated into the crotyl solution. After stirring for 30 minutes, borontrifluoride etherate (129 μL, 1.046 mmol) was added followed by a solution of aldehyde **136** (79.2 mg, 0.404 mmol) in 1 mL ether. The reaction was stirred for 3 h, and then an aqueous solution of sodium perborate was added and the reaction was allowed to warm to room temperature and was stirred overnight. 10 mL of ether was added and the layers were separated, and the aqueous was reextracted twice with 10 mL ether. The combined organic extracts were washed with brine, dried over Na_2SO_4, and solvent removed *in vacuo*. The product was purified by flash chromatography (10:1 hexanes / EtOAc) to yield **115a** contaminated by a small amount of pinanol (100 mg, 48% pure [w/w], 50% yield) as a clear oil. Excess pinanol could be removed by flash chromatography in (1:1 hexanes / $CHCl_3$) to provide an analytical sample, but further purification was not necessary to continue to the next step. ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 6.26 (s, 1H), 5.72 (ddd, J = 8.0, 9.7. 17.9 Hz, 1H), 5.18 (d, J = 16.1 Hz, 1H), 5.17 (d, J = 11.7 Hz,1H), 3.87 (dd, J = 2.9, 8.1 Hz, 1H), 2.36 (m, 2H), 1.82 (s, 3H), 0.92 (d, J = 6.7 Hz, 3H). ^{13}C-NMR: δ (100 MHz, $CDCl_3$) 148.1, 140.0, 117.4, 80.2, 79.9, 42.4, 19.4, 16.6. IR νmax: 3320, 2959, 2928, 2917, 2871, 1453, 1376, 1269, 1009, 916, 783. HR-MS: calcd. $C_8H_{13}IO$

$[M]^+$ calcd : 252.0006, found $[M]^+$: $\frac{m}{z}$ = 252.0006, $[M\text{-}H]^+$ calcd : 250.9934, found $[M\text{-}H]^+$: $\frac{m}{z}$ = 250.9927. $[\alpha]_D^{25}$ = –10.0° (c = 0.10, $CHCl_3$) R_f = 0.45 (6:1 hexanes / EtOAc).

(3*R*, 4*R*)-1-Iodo-2,4-dimethyl-penta-1,5-diene-3-ol (115b) – Alcohol **115b** was prepared according to the procedure for the preparation of **115a** using aldehyde **136** (154 mg, 0.786 mmol) and (+)-*B*-methoxy-isocampheylborane (derived from (-)-pinene) and quenching with the standard hydrogen peroxide and sodium hydroxide reflux (1 h) to yield **115b** (92.1 mg, 49%). The compound shared identical ^{1}H-NMR and ^{13}C-NMR spectra to its enantiomer **115a**.

3.8.6 New compounds from Scheme 3.12

(3*S*, 4*S*) Vinyl iodide ester (137a) – Vinyl iodide alcohol **115a** (33.0 mg, 0.131 mmol) was combined with 8-nonenoic acid (30.7 mg, 0.196 mmol), EDC (50.0 mg, 0.262 mmol), and a single crystal of DMAP (¡ 3 mg, ¡ 0.026 mmol) in a dry scintillation vial that had been purged with Ar. The mixture was dissolved in THF (3 mL), and DIPEA (68.4 μL, 0.393 mmol) was added, and the vial was capped and allowed to stir overnight. TLC (4:1 hexanes / EtOAc) revealed the reaction to be complete after 12 h, and the reaction mixture was poured onto 1 mL 25% NH_4Cl solution. The mixture was extracted once with 5 mL ether, and twice with 7.5 mL EtOAc, and the combined organic extracts were washed with brine, and dried over Na_2SO_4. The solvent was removed *in vacuo* to yield a crude oil that was purified by flash chromatography (25:1 hexanes / EtOAc) to yield **136** (42.2 mg, 83%) as a clear oil. ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 6.31 (s, 1H), 5.80 (ddt, *J* = 6.5, 10.0, 17.0 Hz, 1H), 5.66 (ddd, *J* = 8.3, 9.3, 17.0, 1H), 5.15 (d, *J* = 8.3 Hz, 1H), 5.08 – 4.91 (m, 4H), 2.49 (octet, *J* = 7.0 Hz, 1H),

2.28 (t, *J* = 7.5 Hz, 2H), 2.04 (q, *J* = 7.2 Hz, 2H), 1.80 (s, 3H), 1.59 (m, 2H), 1.37 (m, 2H), 1.30 (m, 4H), 0.92 (d, *J* = 7.0 Hz, 3H). ^{13}C-NMR: δ (100 MHz, $CDCl_3$) 172.8, 144.7, 139.4, 114.4, 81.6, 80.2, 40.4, 34.5, 33.8, 29.1, 28.8, 25.0, 20.3, 16.6. IR νmax: 3077, 2927, 2856, 1738, 1641, 1618, 1457, 1376, 1277, 1229, 1162, 1015, 993, 911, 784, 685. HR-MS: calcd. $C_{17}H_{27}IO_2$ $[M]^+$ calcd : 390.1050, found $[M]^+$: $\frac{m}{z}$ = 390.1046. R_f = 0.70 (4:1 hexanes / EtOAc). R_f = 0.40 (1:1 hexanes / $CHCl_3$).

(3*R*, 4*R*) Vinyl iodide ester (137b) – 137b was prepared according to the procedure for the preparation of **137a** using **115b** (30.0 mg, 0.119 mmol) to yield **137b** (35.8 mg, 77%). ^{1}H-NMR and ^{13}C-NMR spectra matched the enantiomer. $[\alpha]_D^{25}$ = +18.7° (c = 1.87, $CHCl_3$).

(3*S*, 4*S*) Vinyl iodide lactone (139a) – Ester **137a** (42.2 mg, 0.108 mmol) was dissolved in DCM (15 mL) under Ar at rt. Grubbs' second generation catalyst (4.6 mg, 5.4 μmol) was added as a solid, and the reaction was heated to reflux. After 14 h, TLC (1:1 hexanes / $CHCl_3$) indicated a spot to spot transformation, and the reaction was allowed to cool and solvent was removed *in vacuo*. The residue was purified by flash chromatography (1:1 hexanes / $CHCl_3$) to yield lactone **139a** (32.8 mg, 84%) as a clear oil. ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 6.42 (s, 1H), 5.34 (ddd, *J* = 3.4, 11.4, 14.9 Hz, 1H), 5.17 (d, *J* = 10.8 Hz, 1H), 5.08 (ddd, *J* = 2.3, 9.7, 15.0 Hz, 1H), 2.50 – 1.10 (m, 12H), 1.83 (s, 3H), 0.85 (d, *J* = 6.8 Hz, 3H). ^{13}C-NMR: δ (100 MHz, $CDCl_3$) 172.8, 144.6, 132.8, 132.2, 83.2, 80.1, 41.0, 3.8, 30.1, 25.0, 24.5, 24.4, 23.0, 19.3, 17.0. IR νmax: 2968, 2933, 2855, 1734, 1448, 1376, 1357, 1229, 1217, 1149, 1113, 1073, 1016, 975. HR-MS: calcd. $C_{15}H_{23}IO_2$ $[M]^+$ calcd : 362.0737, found $[M]^+$: $\frac{m}{z}$ = 362.0734. $[\alpha]_D^{25}$ = -35.0° (c = 0.58, $CHCl_3$) R_f = 0.35 (6:1 hexanes:$CHCl_3$).

(3*R*, 4*R*) Vinyl iodide lactone (139b) – Lactone **139b** was prepared according to the procedure for the preparation of **139a** using **137b** (34.5 mg, 0.088 mmol) to yield

139b (23.8 mg, 74%). ^{1}H-NMR and ^{13}C-NMR spectra matched the enantiomer. $[\alpha]_D^{25}$ = +41.6° (c = 1.78, $CHCl_3$).

TBS-Protected model lactone 140a – 139a (10.3 mg, 0.0285 mmol) and **133** (14.3 mg, 0.0238 mmol) were dissolved in a 3 mL vial in dry DMF (0.75 mL). To this solution was added bis(acetonitrile)palladium(II) dichloride ($Pd(MeCN)_2Cl_2$) (0.185 mg, 0.0007 mmol) in 0.185 mL DMF. The solution was stirred for 41 h in the dark and then diluted with 5 mL ether and washed with saturated $NaHCO_3$. The aqueous washing was re-extracted with 5 mL ether, and the combined organics were washed with water and brine, then dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude film was purified by flash chromatograpy (1:1 hexanes / $CHCl_3$ then switched to 20:1 to 10:1 hexanes / EtOAc) to yield **140a** (2.8 mg, 21%) of fairly pure material. Some starting stannane (**133**) and lactone (**139a**) were recovered. ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 6.25 (dd, J = 10.5, 14.8 Hz, 1H), 6.07 (d, J = 10.5 Hz, 1H), 5.60 (dd, J = 8.5, 14.9 Hz, 1H), 5.31 (ddd, J = 3.1, 11.0, 14.7 Hz, 1H), 5.12 (ddd, J = 1.6, 9.6, 14.9 Hz, 1H), 5.02 (d, J = 10.8 Hz, 1H), 3.71 (dt, J = 3.3, 6.3, 1H), 2.67 (dt, J = 2.0, 5.8, 1H), 2.60 (dd, J = 2.1, 8.2 Hz, 1H). 2.45 (m, 2H), 2.37 (ddd, J = 3.9, 12.0, 13.8, 1H), 2.19 (m, 2H), 1.97 (m, 1H), 1.83 (m, 1H), 1.74 (s, 3H), 1.65 – 1.00 (m, 13H), 1.07 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.83 (m, 9H), 0.07 (s, 3H), 0.06 (s, 3H). ^{1}H-^{13}C HSQC correlations δ 6.25, 124.8, 6.07, 130.5, 5.60, 140.6, 5.31, 131.5, 5.12, 133.6, 5.02, 82.3, 3.71, 74.1, 2.67, 57.3, 2.60, 61.3, 2.45, 40.7, 2.45, 35.3, 2.37, 32.8, 2.19, 32.7, 2.19, 29.7, 1.97, 29.8, 1.74, 11.8, 1.48, 24.5, 1.47, 39.8, 1.45, 27.4, 1.25, 40.1, 1.22, 29.6, 1.01, 21.0, 0.89, 25.9, 0.83, 16.8, 0.83, 9.9. HR-MS: calcd. $C_{33}H_{58}O_4Si$ $[M]^+$ calcd : 546.4099, found $[M]^+$: $\frac{m}{z}$ = 546.4106. R_f = 0.55 (10:1 hexanes / EtOAc).

TBS-Protected model lactone 140b – 139b (3.0 mg, 0.008 mmol) and **133** (6.8 mg,

0.011 mmol) were dissolved in a 3mL vial in dry DMF (0.20 mL). To this solution was added bis(acetonitrile)palladium(II) dichloride ($Pd(MeCN)_2Cl_2$) (0.1 mg, 0.0004 mmol) in 0.05 mL DMF. The solution was stirred for 48 h in the dark and then diluted with 5 mL ether and washed with saturated $NaHCO_3$. The aqueous washing was re-extracted twice with 5 mL ether, and the combined organics were washed with water and brine, then dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude film was purified by flash chromatograpy (20:1 to 10:1 hexanes / EtOAc) to yield **140b** (1.8 mg, 40%) of fairly pure material. Some starting lactone (**139b**) was recovered. ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 6.25 (dd, J = 11.0, 15.1 Hz, 1H), 6.07 (d, J = 11.0 Hz, 1H), 5.61 (dd, J = 8.3, 15.0 Hz, 1H), 5.31 (ddd, J = 3.3, 11.1, 14.9 Hz, 1H), 5.12 (ddd, J = 2.0, 9.7, 14.9 Hz, 1H), 3.72 (m, 1H), 2.69 (ddd, J = 2.3, 4.7, 7.0 Hz, 1H), 2.61 (dd, J = 2.3, 8.1 Hz, 1H), 2.50 – 2.31 (m, 3H), 2.20 (m, 2H), 1.97 (m, 1H), 1.73 (s, 3H), 1.60 – 1.30 (m, 9H), 1.28 (m, 1H), 1.08 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 7.1 Hz, 3H), 0.85 (d, J = 6.6 Hz, 3H), 0.81 (t, J = 7.3 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H). HR-MS: calcd. $C_{33}H_{58}O_4Si$ $[M]^+$ calcd : 546.4099, found $[M]^+$: $\frac{m}{z}$ = 546.4107. R_f = 0.55 (10:1 hexanes / EtOAc).

Model lactone 141a – **140a** (2.7 mg, 0.005 mmol) was dissolved in 2 mL acetonitrile in a plastic vial, and 50 μL HF · Pyridine was added by plastic syringe. The reaction was stirred for 72 h, and then 5 drops of Et_3N were added to quench. The mixture was filtered through a plug of silica gel in a pipette tip and washed with 5 mL 1:1 hexanes / EtOAc. The eluant was evaporated *in vacuo* and purified by preparative TLC on a 5" x 5" plate with 2:1 hexanes / EtOAc to yield **141a** (1.4 mg, 67%) as a clear film. ^{1}H-NMR: δ (500 MHz, $CDCl_3$) 6.33 (dd, J = 10.9, 14.9 Hz, 1H), 6.15 (d, J = 10.8 Hz, 1H), 5.68 (dd, J = 8.4, 15.0 Hz, 1H), 5.39 (ddd, J = 3.3, 11.4, 14.8 Hz, 1H), 5.19 (ddd, J = 1.5, 9.7, 14.9 Hz, 1H), 5.10 (d, J =10.8 Hz, 1H), 3.66 (m, 1H), 2.85 (dt, J

= 2.3, 5.8, 1H), 2.75 (dd, *J* = 2.3, 7.4, 1H), 2.54 (m, 2H), 2.44 (ddd, *J* = 4.0, 11.8, 14.0), 2.27 (m, 2H), 2.20 – 1.80 (m, 3H), 1.82 (s, 3H), 1.70 – 1.10 (m, 11H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.03 (m, 6H), 0.91 (d, *J* = 6.6 Hz, 3H). HR-MS: calcd. $C_{27}H_{44}O_4$ $[M]^+$ calcd : 432.3234, found $[M]^+$: $\frac{m}{z}$ = 432.3239. R_f = 0.10 (4:1 hexanes / EtOAc).

Model lactone 141b – **141b** was prepared using the same procedure as in the preparation of **141a** with **140b** (0.7 mg, 0.001 mmol) to yield **141b** (0.5 mg, 80%). ^{1}H-NMR: δ (500 MHz, $CDCl_3$) 6.25 (dd, *J* = 10.9, 15.1 Hz, 1H), 6.07 (d, *J* = 10.9 Hz, 1H), 5.59 (dd, *J* = 8.3, 15.4 Hz, 1H), 5.32 (ddd, *J* = 3.0, 11.1, 14.8 Hz, 1H) 5.11 (dd, *J* = 9.5, 15.1 Hz, 1H), 5.02 (d, *J* = 10.5 Hz, 1H), 3.58 (m, 1H), 2.78 (dt, *J* = 2.6, 5.8 Hz, 1H), 2.68 (dd, *J* = 2.5, 7.6, 1H), 2.48 – 2.15 (m, 5H), 2.02 (m, 1H), 2.00 – 1.10 (m, 12H), 1.74 (s, 3H), 1.08 (d, *J* = 6.3 Hz, 3H), 0.96 (d, *J* = 7.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.85 (t, *J* = 6.9 Hz, 3H). R_f = 0.10 (4:1 hexanes / EtOAc).

Chapter 4

Toward the synthesis of FD-895

4.1 Introduction to FD-895

During the time before the stereochemistry of pladienolide B (**70b**) was disclosed, synthetic efforts toward an arbitrary diastereomer gave us hope that once we figured out the stereochemistry, our methods could be quickly applied to produce the correct diastereomer. At the completion of work on the sidechain (**133**) and "keystone" (**115**) our efforts turned to the synthesis of the last three stereocenters on the core structure. Unfortunately, the publication of a synthesis of pladienolide B with many similarities to our own threw a monkey wrench into our plans, and eventually led to the choice of FD-895 (**71**) as the new target for the synthetic effort.

4.1.1 Reasons for switching the target to FD-895

Many roadblocks were encountered while searching for good ways to prepare the final acid piece (compound **114**, Scheme 3.4, page 62). Without knowing the stereochemistry, it did not make sense nor would it have been feasible to develop a targeted strategy that would be creative and efficient. Approaches from the chiral pool

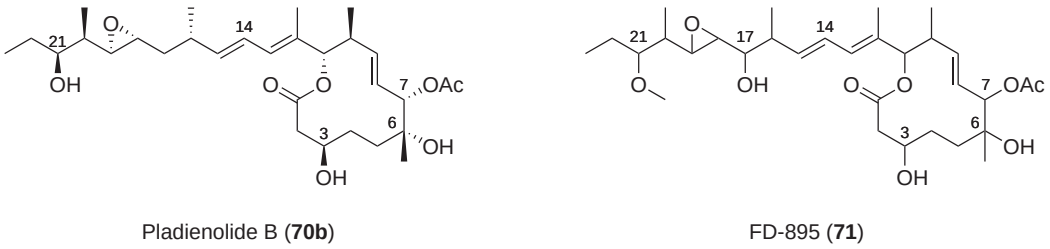


Figure 4.1: Pladienolide B (**70b**), shown with recently disclosed stereochemistry, and FD-895 (**71**)

were promising, but we got to the point where the only thing holding up the project was the unknown stereochemistry.

Thankfully, we were able to obtain a small sample of FD-895 **71**. Isolated from *Streptomyces hygroscopicus*, this cytotoxic cousin of the pladienolides is highly active, showing an IC_{50} of 2.0 ng / mL against HL-60 cells and a IC_{50} of 4.0 ng / mL against HeLa cells. FD-895 retains all of its activity against adriamycin resistant cells, suggesting that it has a different mode of action. Pladienolide B and FD-895 are very similar (Figure 4.1) and were expected to have similar stereochemistries. Having a molecule to analyze that was so similar to pladienolide B gave hope to the synthetic efforts, but not long after obtaining the compound, disaster struck.

4.1.2 Recently published work regarding the pladienolides

Work on pladienolide B (**70b**) was proceeding smoothly until several papers were published by researchers at the Eisai corporation. The stereochemistry of Pladienolide B had never been disclosed, but it didn't stop synthetic efforts. The first paper to come out regarding pladienolide B this year was its total synthesis.[214] This synthesis used nerol as the starting material and required and a Sharpless asymmetric dihydroxylation[215] to furnish the C_6, C_7 diol. The diastereomeric excess of this reaction was only 76%, however, the benzylidine acetal protected form could be recrystallized

to a single diastereomer. The resulting compound was incorporated into the macrolide ring using a ring-closing metathesis in a similar fashion to my model studies. The sidechain was fashioned from the same synthons as the synthesis in chapter 3, and it was coupled to the core structure using a Julia-Kociensky olefination rather than a Stille coupling.

After the synthesis was published, Eisai published the stereochemistry of pladienolide B.[216] The elucidation process involved a Mosher's ester analysis for the stereochemistry of the alcohols at C_3 and C_{21}, NOESY correlations to assign the relative stereochemistry of the macrolide, and a 7-step degradation protocol which went through the tetrahydrofuran discussed in the last chapter (**73c**). Another NOESY analysis of the bromobenzylidine of **73c** provided the relative stereochemistry of the sidechain.

Finally, another paper was published that investigated the mode of action of the pladienolides.[217] Using fluorescence, affinity, and radioisotopically labelled derivatives of **70b**, followed by immunoblotting and *in vivo* assays, Kotake *et al.* were able to determine that pladienolide D (**70d**) hits splicing factor SF3b. The work was not unexpected, as Eisai is pushing a derivative of pladienolide D through clinical trials as a cancer drug; but at the completion of our synthesis, it was hoped that the lab could use labeled derivatives to carry out our own mode of action studies on **70b**.[218]

4.2 The retrosynthetic approach to FD-895

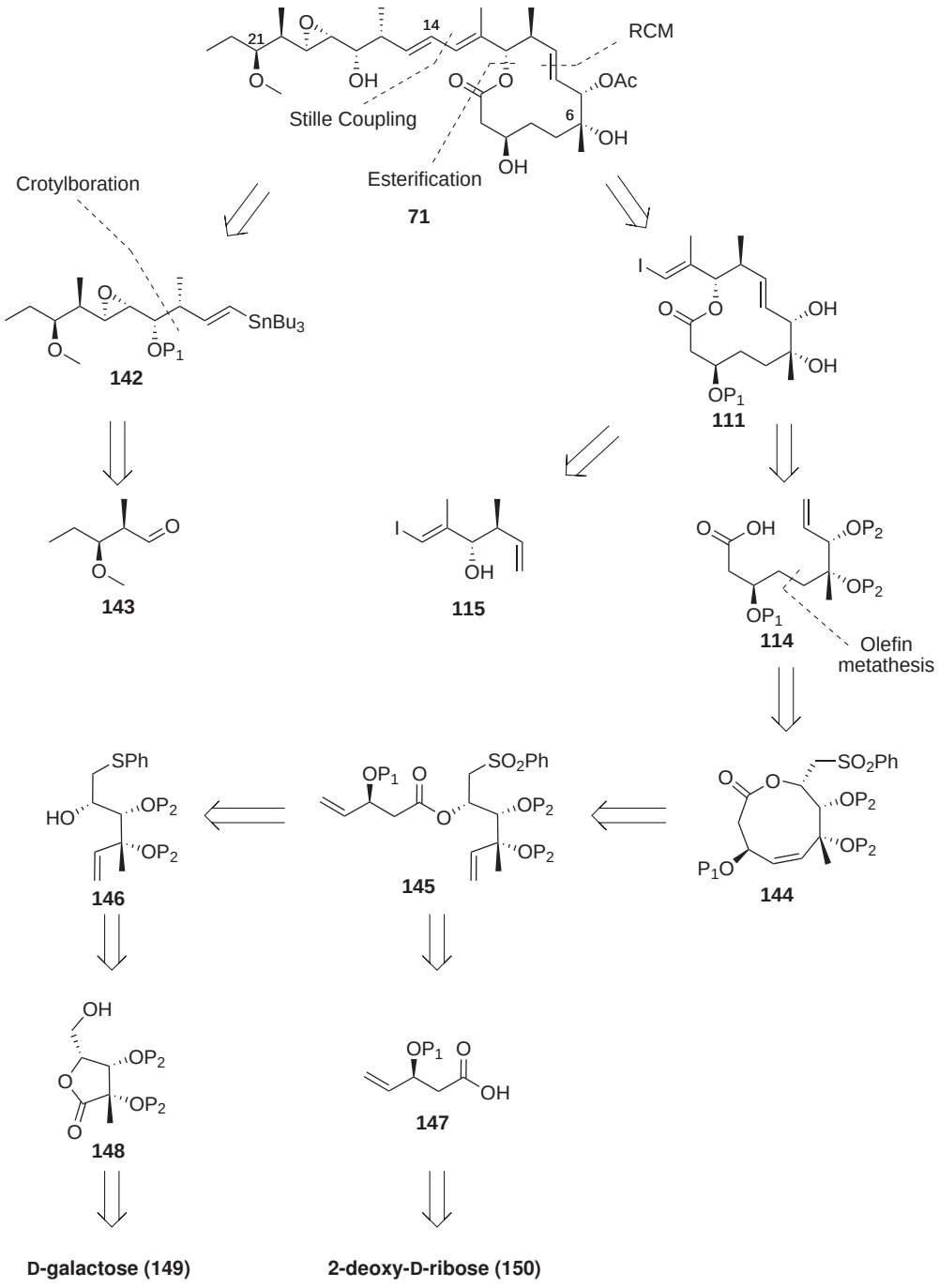
The release of the total synthesis of pladienolide B (**70b**) set back the lab's synthetic efforts because the methods used in the synthesis of the sidechain and core structure were very similar to our own. Besides the esterification and ring-closing metathesis strategy, Eisai also prepared the sidechain using a Julia-Kociensky of alde-

hyde **119a** and sulfone **123b** and the only differences were different protecting groups (Scheme 3.9, page 69). Eisai also used the Shi epoxidation and a dissolving metal reduction to furnish a compound similar to **74c**.[214] Nowhere in the paper was a reference to this author's talk at the ACS eight months prior, where the results in Chapter 3 were presented.

With the target already synthesized and the stereochemistry known, FD-895 (**71**) changed from a glimmer of hope to a lifeboat. The objective was shifted to synthesis of FD-895 and confirmation that the stereochemistry was similar to FD-895. Considering the biosynthetic origins and activity of the two compounds, it is reasonable to assume that they have the same stereochemistry. Performing a NOESY analysis confirmed that the C_6 and C_7 stereochemistry and the C_{10} and C_{11} stereochemistries are *syn* and *anti* respectively, just as in **70b**. The sidechain stereochemistry should have been the same, but the extra hydroxyl at C_{17} is hypothesized to be *S* based on the same comparisons as in chapter 3. Mosher's ester analysis failed in this case because the (*S*,*S*) bis-ester of FD-895 formed readily, but the (*R*,*R*) bis-ester failed to form under a variety of conditions.

The retrosynthetic breakdown of FD-895 (**71**) shown in Scheme 4.1 mirrors the retrosynthesis of pladienolide B. The diene can be formed from a Stille coupling of stannane **142** and iodide **111**. Sidechain **142** can originate from homologation, epoxidation, and crotylboration of aldehyde **143**, which itself is available from a number of asymmetric aldols. On the other side, like with paldienolide B, lactone **111** comes from the indispensable keystone (**115**) and the same acid (**114**) that was not dealt with in chapter 3.

By this time, the necessary stereochemistry on **114** was disclosed, so a targeted approach would suffice to complete the structure. Originally, methods were being developed that would get to **114** through a sharpless epoxidation on geraniol. This



Scheme 4.1: Retrosynthetic breakdown of FD-895 (**71**)

methodology happened to be almost exactly the same as Kanada's synthesis, which used Sharpless on the *Z* isomer of geraniol, nerol. A scan of the literature showed that there were not many published ways to create the stereodiad at C_6 and C_7 while also including the necessary functionalization to complete the core structure. Two common methods for incorporating the tertiary and secondary alcohol in that fashion were both Sharpless chemistries. Otherwise, only a few routes were available using glycosidic transformations.

Neither our preliminary results nor Kanada's gave very good selectivities for the asymmetric reactions; the synthesis of pladienolide B was helped by several re-crystallizations. Therefore, an approach from the chiral pool seemed prudent. Thus, the retrosynthesis continues through the 9-membered ring **144**, which can be reduced and opened to afford acid **114** by mercury amalgam elimination. In turn, that ring is envisioned to originate from another ring-closing metathesis of ester **145**. Medium sized ring-closings can be an iffy proposition, especially with a sulfur unit, but we were encouraged by recent progress in this area as long as the sulfide is oxidized to the sulfone prior to treatment with Ruthenium.[219] Ester **145** could then come from the union of two compounds, olefin **146** and acid **147**. Olefin **146** can come from the known lactone **148**.[220,221] Therefore, the two sides of ester **145** originate from the chiral pool materials D-galactose (**149**) and 2-deoxy-D-ribose (**150**).[222]

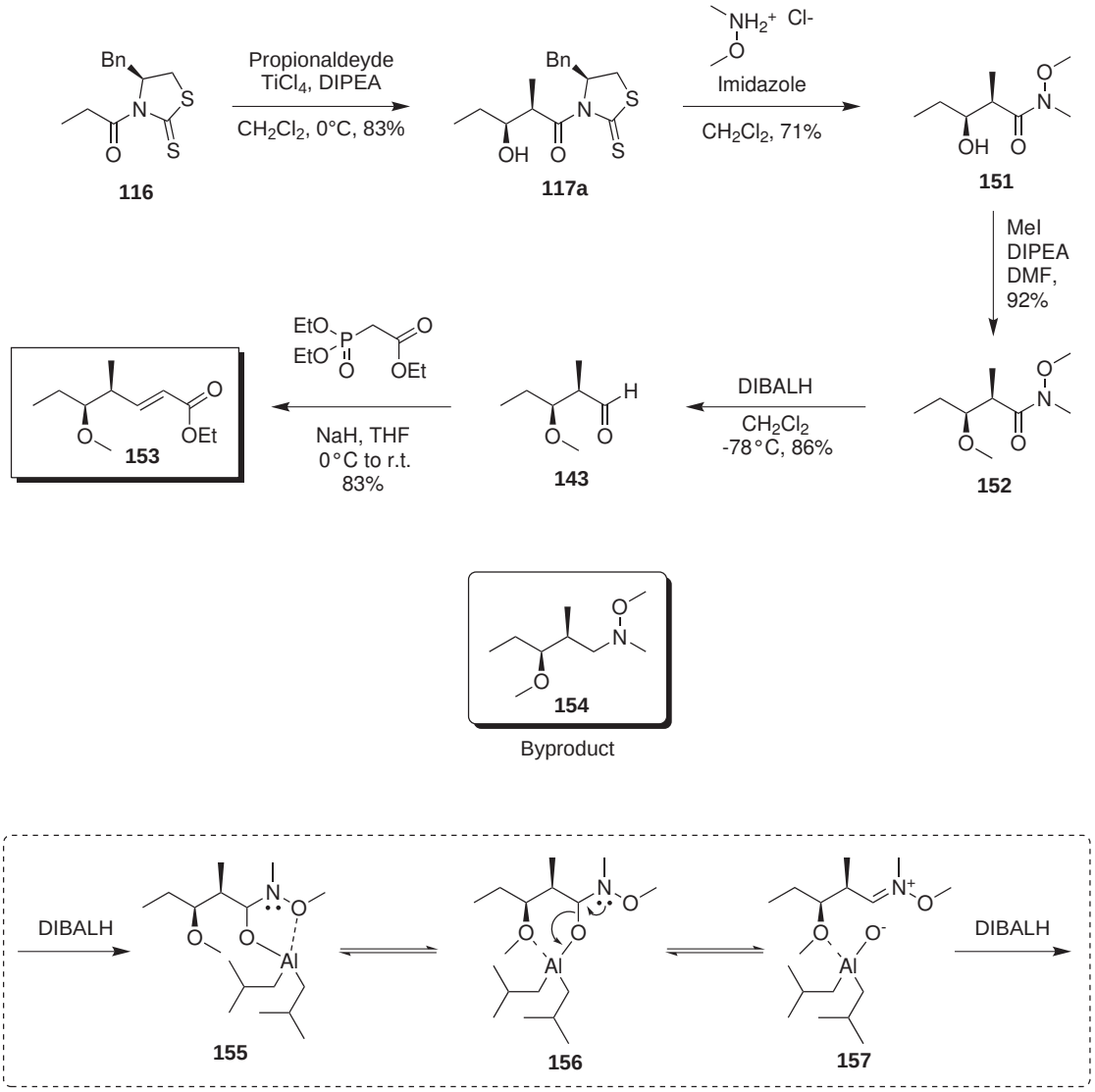
It deserves mention that there are many known methods to join two molecules to form an olefin. Unfortunately, most require one side to be an aldehyde, and then other side to be a nucleophile. No matter which component is which, in this case one side would have a β-hydroxyl that would eliminate and render a Wittig, Julia, Aldol, or Horner-Wadsworth-Emmons olefination useless. Therefore, olefin metathesis was envisioned as the best possible way to make the C_4, C_5 bond.

4.3 Toward the synthesis of the FD-895 sidechain

Synthesis of the sidechain began with the same Crimmins aldol chemistry as used in the chapter 3 (Scheme 4.2).[191,223] The Crimmins auxiliary **116** was treated with $TiCl_4$ and Hünig's base, then propionaldehyde was added at 0°C to afford alcohol **117a**. Next, the auxiliary was displaced with Weinreb's amine and Imidazole to give amide **151**. This displacement was very easy to monitor because the deep yellow color of acylated thiazolidinethione (**117a**) fades away with the displacement. The auxiliary could be recovered after flash chromatography. The methylation had to be performed after removal of the thiazolidinethione because it can act as a nucleophile.[224] This is a major drawback to the widespread use of the Crimmins auxiliary.

Next, amide **151** was *O*-methylated in good yield to give compound **152** which was subsequently reduced to aldehyde **143** in good yield.[225] The aldehyde was then be homologated by Horner-Wadsworth-Emmons olefination with triethylphosphonoacetate to give ester **153** with complete *E* selectivity.[226] As a side note, using ethyl dimethylphosphonoacetate gave a 2:1 mixture of *E* to *Z* product.

Curiously, several attempts to reduce amide **152** resulted in formation of byproduct **154**. Normally, one can safely use an excess of DIBALH to reduce the Weinreb's amine and complex **155** holds the tetrahedral intermediate so that there is insufficient electron density for either substituent of the hemiaminal to eliminate until quenching. In this case however, we postulate that the aluminum at elevated temperatures can coordinate to the C_3 methoxy in **156**, releasing the hydroxylamine so that it can knock off aluminum oxide and form imine **157**. The resulting imine can be attacked by another equivalent of DIBALH, resulting in **154**. This side reaction was prevented by maintaining the reaction below –78°C and a timely quench with Rochelle's salt in water.

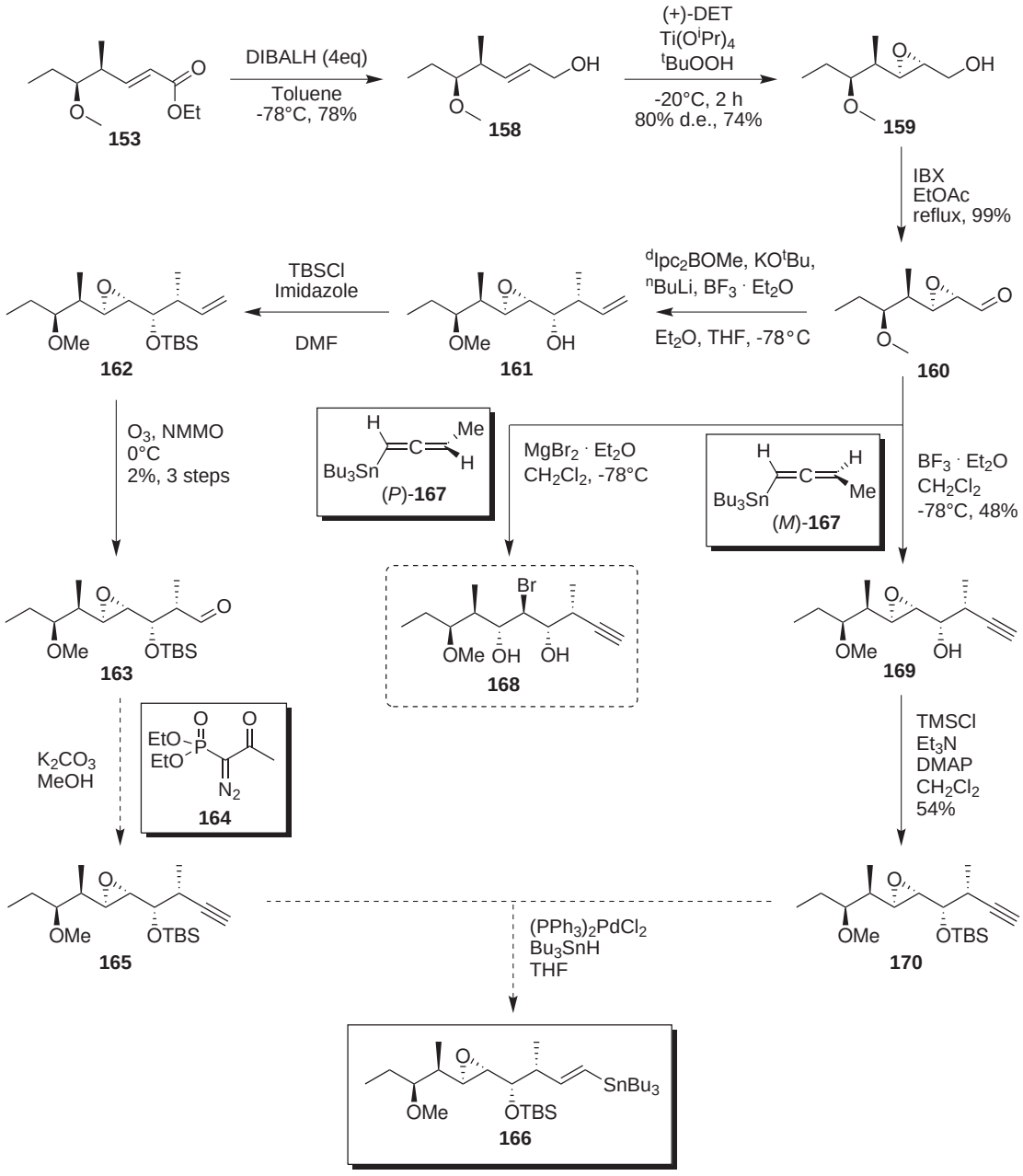


Scheme 4.2: Synthesis of the FD-895 sidechain to ester **153**

Compound **153** set the stage for the challenging asymmetric chemistry to install the $C_{16} - C_{20}$ stereotetrad (Scheme 4.3). First, reduction of the ethyl ester provideed alcohol **158** in good yield and purity.[224] Next, the Sharpless asymmetric epoxidation with (+)-diethyl tartrate gave epoxide **159** in good yield, and acceptable diastereomeric excess.[227] In several repetitions an 80% d.e. was consistently returned in this reaction. If the proportions of tartrate and $Ti(O^iPr)_4$ were not correct (2:1), then the reaction was sluggish, or the d.e. returned was worse. It is interesting to note, that treatment of **158** with *m*-CPBA alone, gave a 33% d.e. for the correct diastereomer.

A mild IBX oxidation set the stage for the final two stereocenters by giving aldehyde **160** in quantitative yield.[228] Other oxidation conditions such as Dess-Martin[229] and Parikh-Döering[230] provided yields below 60%, although no byproducts could be found. Aldehyde **160** was crotylborated using the conditions of Brown to give **161** in a horrible yield of 2.2%.[212] Yields for this reaction were consistently bad, and it is known that the transition state mismatches this stereochemistry.[231] Other problems arose in the purification, where the byproduct, pinanol, co-elutes with **161**. It was better to continue with the excess contaminants, and **161** was protected with TBSCl to afford **162**. Even at this stage, TBS protected pinanol stuck around, so the material was carried forward with ozonolysis to **163** under the recently published conditions of Dussault.[232]

At that point, there was insufficient material to continue to the end of the synthesis and the scheme was retooled. Originally, aldehyde **163** was going to be homologated with the Bestmann reagent (**164**),[233] and then a hydrostannylation[234] would give the *E* stannane **166**. The end-game differed a bit from the pladienolide B sidechain (Scheme 3.10) because of several disappointing results when attempting the Takai iodination on a model substrate that was similar to **163** but lacked the epoxide. The alkyne thus seemed to be an easier intermediate than the bulky Iodide.



Scheme 4.3: Completing the FD-895 sidechain coupling partner **166**

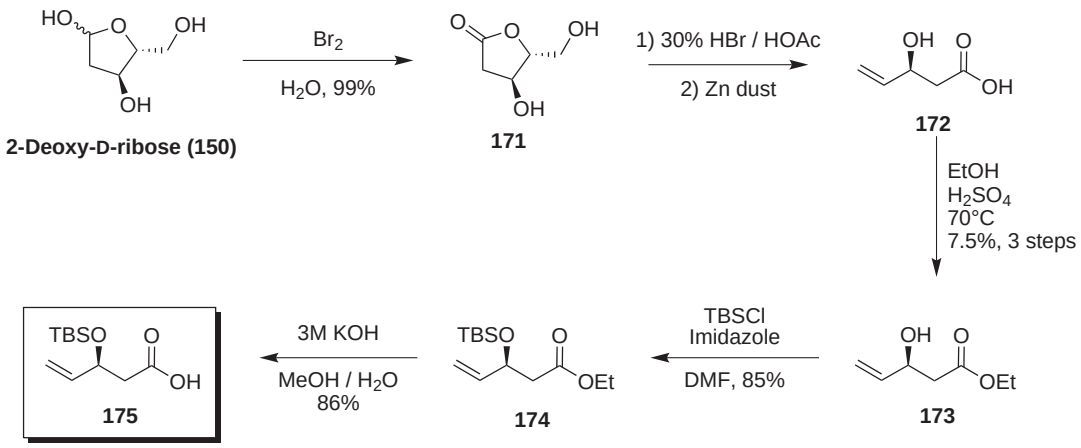
Fortunately, Marshall *et al.* developed a new allenylstannane that can add to α-substituted aldehydes with great selectivity.[235] This reagent has the advantage that is can proceed with Felkin control, or it can be directed to the anti-Felkin *syn* stereoisomer with chelate control. Allenylstannane (*P*)-**167** was prepared in two steps according to the literature from (*R*)-3-butyn-2-ol. Treatment of **160** with (*P*)-**167** under chelate conditions gave **168** due to lewis acid catalyzed epoxide opening by bromide ion. Unfortunately, this product could not be reclosed to the epoxide selectively, and extensive spectral analysis revealed that the bromine was between the two free alcohols.

Using a non-nucleophilic lewis acid like $BF_3 \cdot Et_2O$ in the non-chelate reaction with (*M*)-**167** was a better strategy and yielded alkyne **169** in O.K. yield. At 48% this yield was twenty times higher than the crotylboration route. Plus, only two steps remained to complete the sidechain coupling partner. First, the sidechain was protected as compound **170**–The bulkier tert-butyl dimethyl silyl ether would not form on the free alcohol of alkyne **169**. Then, the plan if time permitted was to furnish stannane **166** by hydrostannylation.[234]

4.4 Synthetic efforts toward the pladienolide B and FD-895 core structure

4.4.1 Obtaining the core stereochemistry from the chiral pool

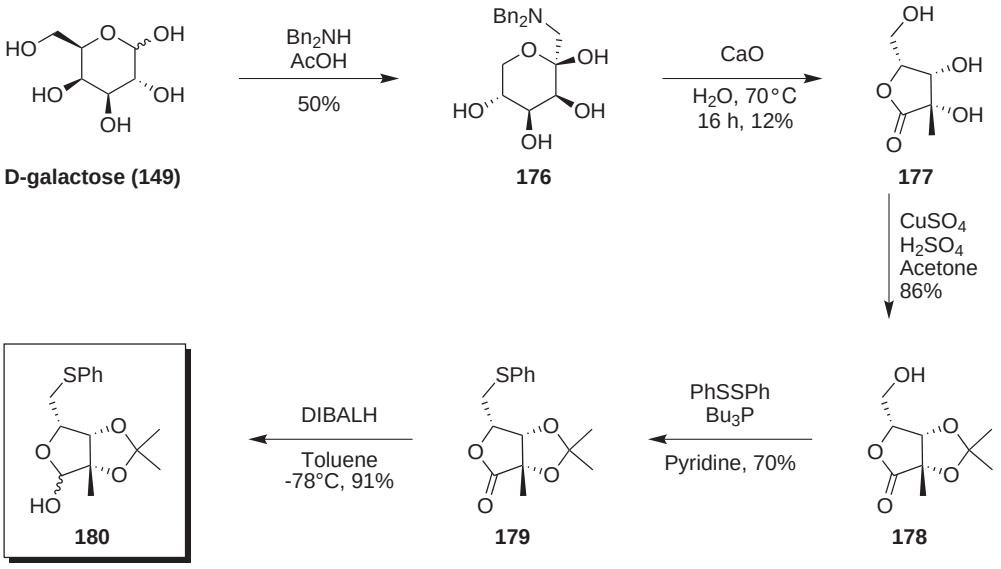
The core structure for both pladienolide B (**70b**) and FD-895 (**71**) appears to be the same. Therefore, though the lab aims to synthesize FD-895, these methods would be relevant to the synthesis of derivatives of pladienolide as well. Because asymmetric reactions applied to our synthesis, and to the synthesis of Eisai[214] were inefficient, the chiral pool was tapped as the source of the stereochemistry for retron **114** (Scheme



Scheme 4.4: Synthesis of the C_3 stereochemistry contained in **175**

4.1 on page 103).

Using the outlined ring-closing metathesis scheme, the stereochemistry at C_3 can originate from 2-deoxy-D-ribose (Scheme 4.4).[222] A simple bromine oxidation yielded quantitaive conversion of **150** into D-ribonolactone (**171**). Compound **171** was treated with hydrobromic acid in acetic acid, proceeded by removal of the acid and stirring with zinc dust to give acid **172** in a very messy mixture. Acid **172** was difficult to purify alone, so it was treated with ethanol and sulfuric acid in the classic Fischer esterification to yield ester **173** which could be purified by column. The yield for this sequence was much lower than declared in the paper, and after several attempts, it was found that the reason was that lactone **171** was not being brominated at C_5 efficiently, and thus the zinc could not eliminate a halogen to open the structure. Ester **173** was carried forward by protection with TBSCl to give ester **174** and then basic hydrolysis with potassium hydroxide afforded acid **175**. Using methanol instead of THF as a co-solvent decreased the reaction time significantly, presumably due to the methoxide knocking out the less reactive ethyl ester first, then its subsequent hydrolysis. The use of excess base in this case was not a problem as β-elimination was only observed if the workup was too acidic.



Scheme 4.5: Preparation of lactol **180** from D-galactose (**149**).

The other ring-closing partner, **146** was accessed from D-galactose (**149**) (Scheme 4.5). First, an Amadori rearrangement furnished dibenzyl tagatoseamine (**176**).[236] The recrystallized product was then treated with calcium oxide in water to produce what can only be described as a mess.[220,221] The desired lactone (**177**) was obtained in 12% yield after filtration of a gloppy suspension, then acidic ion exchange and then at least one flash purification; on par with the literature. In some cases, triol **177** was contaminated with its C_2 diastereomer, but further purification was unneccessary because the next step, protection with acetone, produced the correct 2,3-acetonide (**178**) while the undesired stereoisomer gave the 3,5-acetonide, and the products were easily seperated by a column. Treatment of triol **177** with camphorsulfonic acid in 2,2-dimethoxypropane however, causes the desired stereoisomer to also form the 3,5-acetal. This accidental byproduct can be converted directly to **178** by subjecting it to the H_2SO_4, $CuSO_4$, and acetone conditions. Next, the free alcohol of compound **178** was displaced by diphenyldisulfide with the conditions of Nakagawa to give sulfide **179**.[237,238] Lastly, lactone **179** was reduced with diisobutylaluminum hydride to give

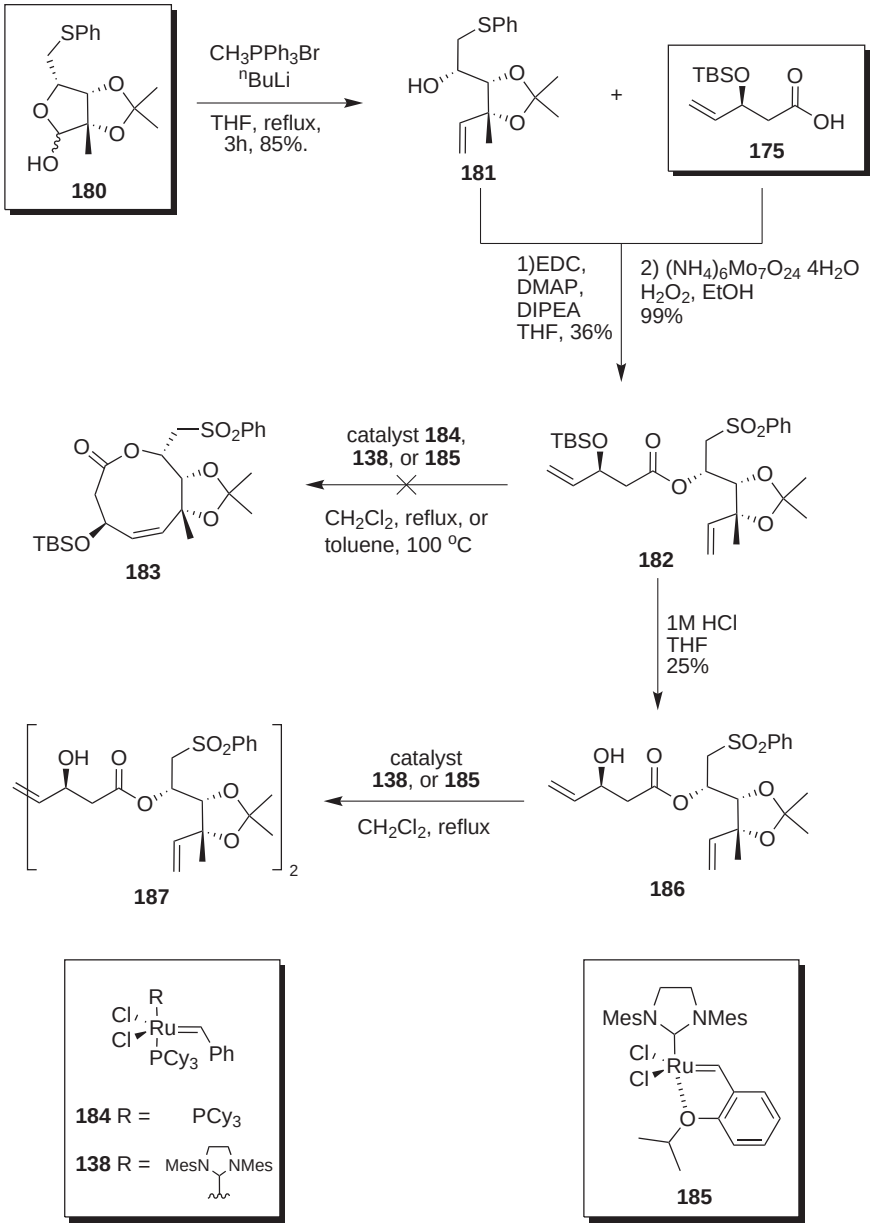
lactol **180**. This lactol was consistently contaminated with another interconvertable isomer which was never conclusively assigned, but carrying this mixture forward indicated that both "isomers" were based on the same aldehyde, and it is likely that the contaminant was a hydrate. Column purification could not seperate the mixture, but it could change the relative proportions of the products as seen by ^{1}H NMR.

4.4.2 The critical ring-closing reaction to join the stereocenters

Coming from the chiral pool, enantiopurity was not an issue. All that remained once the key reactions had established the stereochemistry was to connect the two pieces and reduce the olefin and the retron **114** would be complete. The proposed ring-closing turned out to be more difficult than imagined.

Moving to Scheme 4.6, lactol **180** was opened and homologated by a Wittig reaction to furnish olefin **181**.[33,239] Acid **175** was esterified in poor yield using EDC, and the sulfide was oxidized to give **182** using the mild ammonium molybdate / hydrogen peroxide conditions. Using oxone for this transition in methanol resulted in deprotection of the TBS group along with sulfide oxidation.[240]

Compound **182** was poised to close to the nine-membered lactone **183**. Unfortunately, no conditions were able to push this transformation forward. Neither Grubbs 1st (**184**) nor 2nd generation (**138**) catalysts,[175] nor the Hoveyda-Grubbs 2nd generation olefin metathesis catalyst[241] (**185**) had any effect under the normal DCM reflux, or even heating in toluene with sparging and catalyst recharge.[242] The starting material stubbornly remained. Ester **182** could be deprotected with 1M HCl to give **186**, and this product dimerized into **187** with catalysts **138** and **185**. Catalyst **184** returned starting material. That deprotection was originally meant to remove the acetonide, but this TBS group proved to be particularly sensitive to acidic conditions while the acetonide was so resistant, even 50% TFA in water would not remove it.

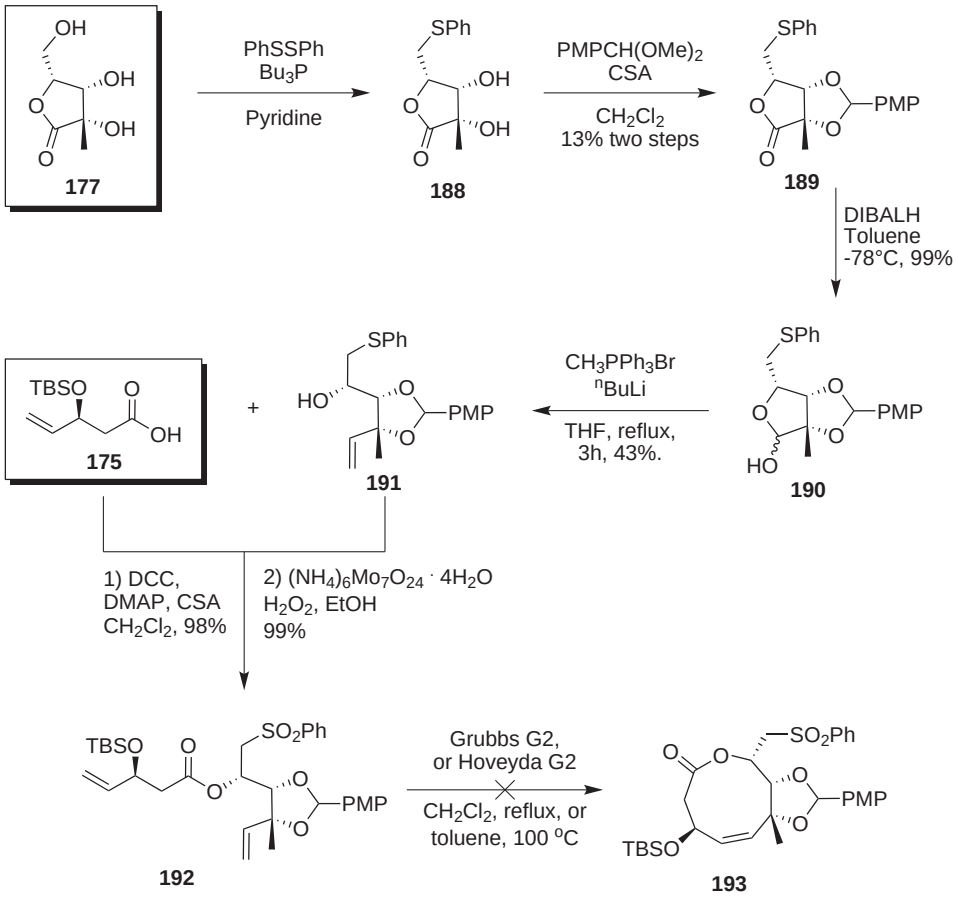


Scheme 4.6: Attempted ring-closing metatheses to join fragments **175** and **180**.

In light of the dimerization reaction to form **187**, it was supposed that steric bulk around both olefins was causing the reaction to fail. Deprotection rendered the olefin near the TBS group too reactive, and it would dimerize rather than reach around to grab the other olefin next to the tertiary alcohol and acetonide. It was hoped that deprotection of the acetonide only would make this olefin more accessible and flexible, and that it would be able to reach the other olefin that has the secondary alcohol. Unfortunately, all conditions to remove the acetonide failed, and a new synthesis was concocted to replace the acetonide with a more labile *p*-methoxybenzylidine acetal (Scheme 4.7). Even if the ring-closing were to have worked, and we had made it through the Stille coupling, it is unlikely that this acetal would be able to be removed without destroying FD-895.

The route was launched from triol **177** by reaction with the Nakagawa conditions to afford sulfide **188**.[237] The reaction is advertised to yield only displacement at primary alcohols when in the presence of other secondary and teritary alcohols, however in this case, a complex mixture of products was found, and after partial purification sulfide **188** was obtained in a disappointing yield. The material was still quite messy, and the mixture was taken on to the next step without further treatment. PMP protection went well, and gave lactone **189** in good yield as a single stereoisomer of the PMP acetal. The crystalline material was then reduced with DIBALH to give lactol **190** and the crude mixture contained a similar unidentifiable isomer as with lactol **180**. The essentially clean crude material was carried forward by opening with the Wittig conditions to give olefin **191**. The Keck modified Steiglich esterification conditions were applied to esterify acid **175** and olefin **191**, and oxidation to sulfone **192** proceeded in excellent yield.[243]

At this point, it was found that the traditional oxidative conditions to remove the PMP acetal were ineffective with this structure. DDQ failed to react at all, and ceric



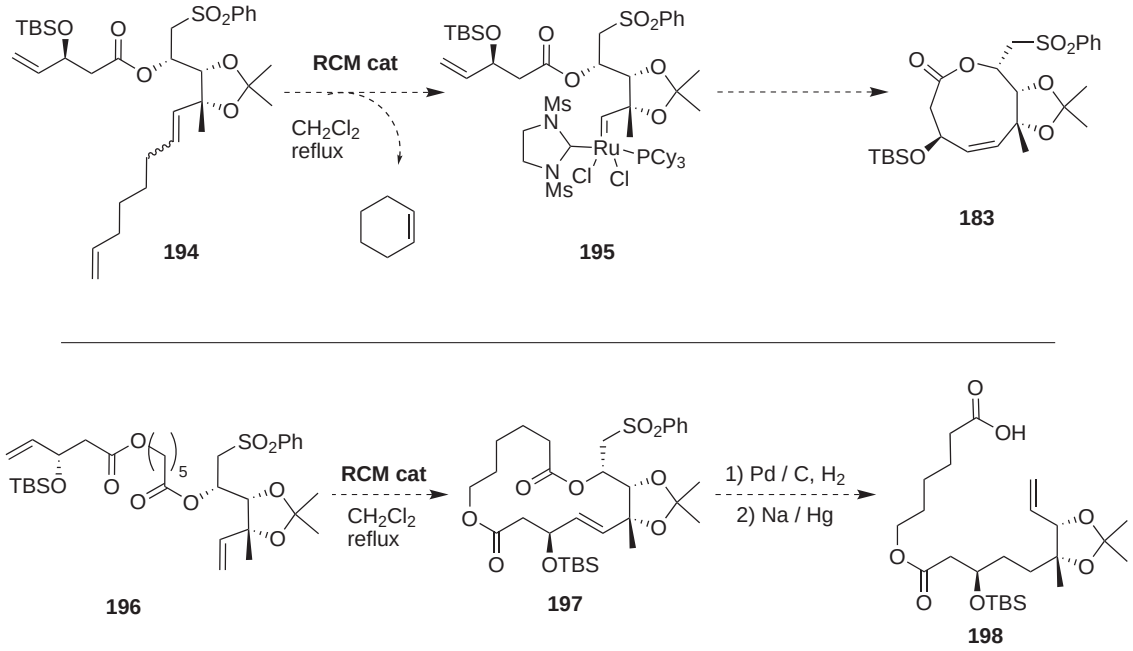
Scheme 4.7: Preparation and attempted ring closing of a PMP protected version of retron **145**.

ammonium nitrate resulted in unrecognizable decomposition. Reductive conditions were out because of both the sulfone and the olefins, and acids would deprotect the TBS as described in Scheme 4.6. Ring-closings of the protected materials were attempted with the hope that the PMP would change the sterics and allow access to cycle **193**, but with catalysts **138** and **185** there was no reaction in both DCM reflux, and hot toluene.

4.4.3 Alternatives to lower the barriers to ring-closing

At this point, there was no time left to start with different protecting groups, but a few last ditch efforts were made to hammer away at this tough ring-closing. Scheme 4.8 shows two methods that could overcome steric bulk or infavorable thermodynamics. The first route is an example of relay RCM.[244,245] A compound is created where a terminal olefin is tied to the end of the more hindered olfein (**194**). When treated with a RCM catalyst, the most accessible, tethered olefin reacts first, and the catalyst is positioned to reach the most hindered olefin in a more kinetically and thermodynamically favorable manner. When it reacts with the next olefin, the ruthenium then ends up on the most hindered olefin, and cyclohexane is released in a very favorable manner to give **195**. Now, the catalyst is poised to react with the less hindered olefin, and if successful, would cyclize to compound **183**.

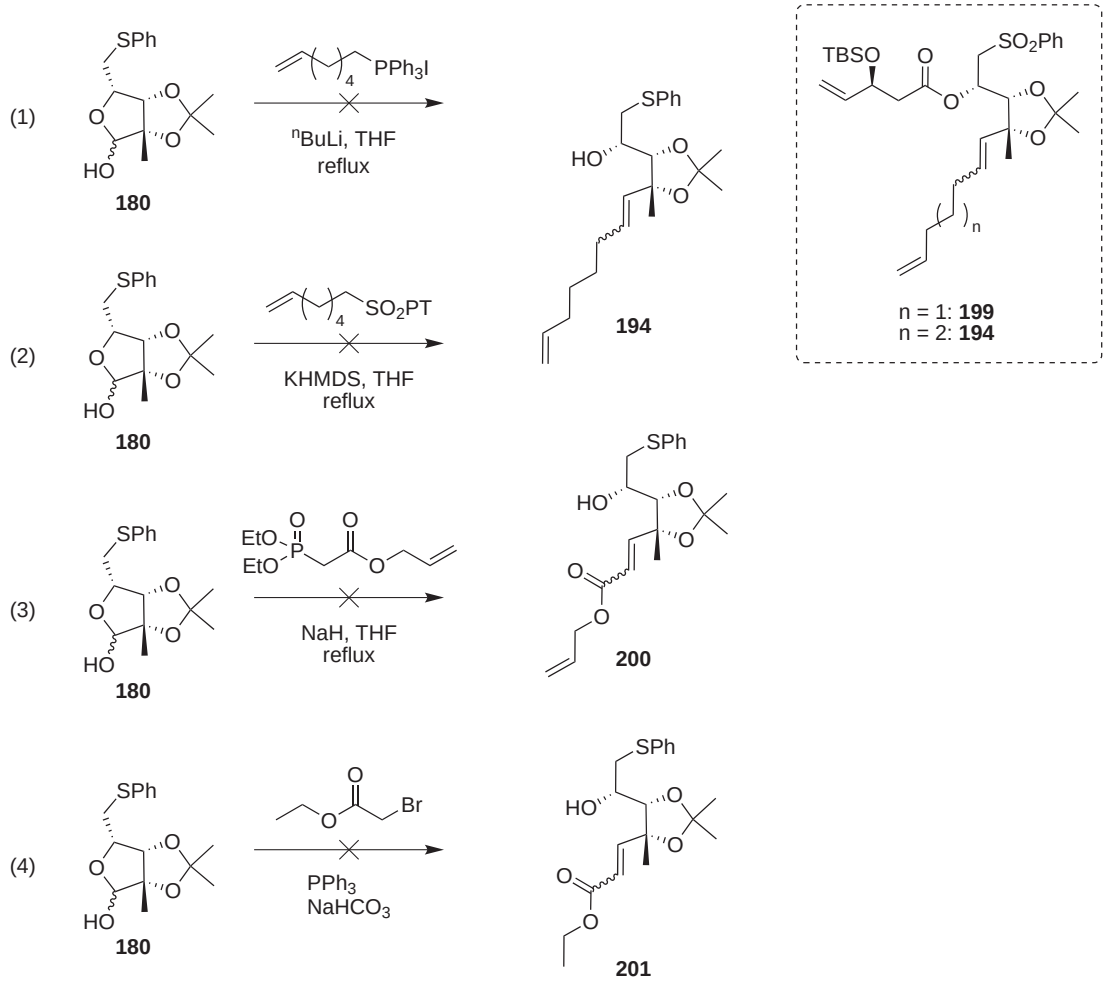
The second route is a way to get around the a thermodynamic barrier. Medium sized rings (7, 8, or 9 atoms) are the highest in energy, and they may simply not be accessible in this case by **192**. Because the 9-membered intermediate will be cleaved, it doesn't matter what the ring is as long as the spacer is removed. The extended ester **196** could be prepared and subjected to RCM to form the 16-membered lactone **197**. This ring could be reduced cleaved using the envisioned mercury amalgam method to give ester **198** which could be hydrolyzed. Trying both of these methods would give



Scheme 4.8: Alternative methods to probe the ring-closing metathesis strategy

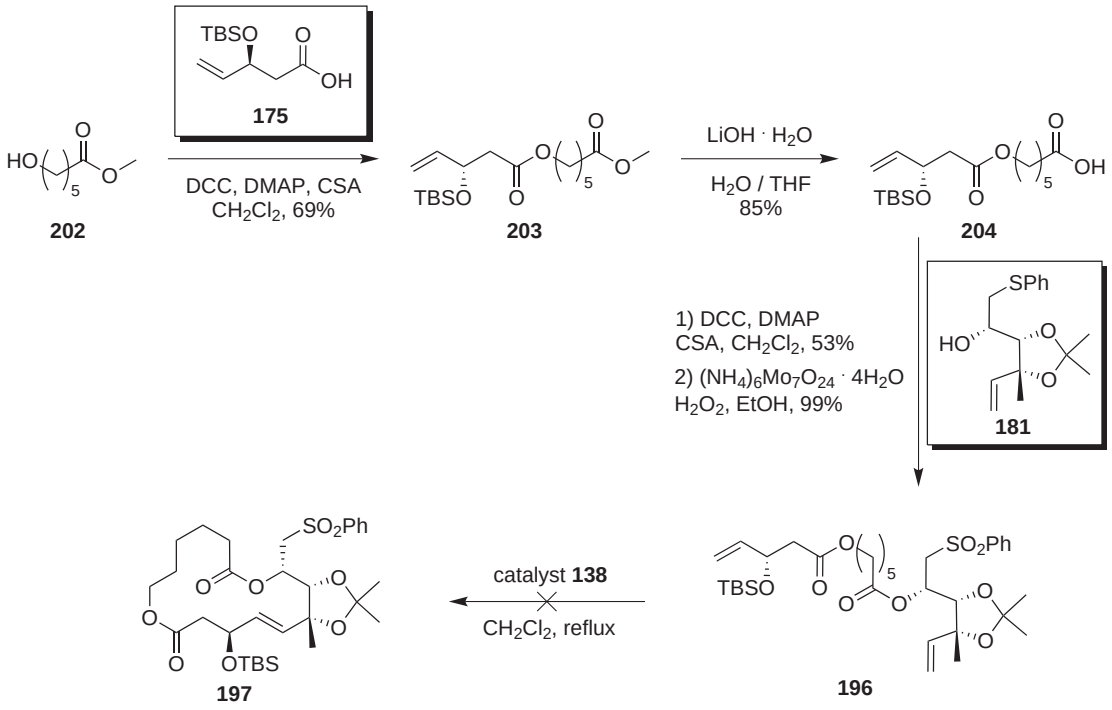
insight into the causes for this reaction's failure.

Toward the relay RCM scheme, it seemed apparent that the neccessary intermediates **194** or **199** would be available from simply changing the ylide in the lactol opening reaction. The results in Scheme 4.9 said otherwise. Treating lactol **180** with heptenyltriphenylphosphonium iodide which was deprotonated with ^{n}BuLi in refluxing THF resulted in no reaction (entry 1). Treatment of **180** with Julia-Kociensky conditions caused an uncharacterized, open byproduct to form that still contained the phenyltetrazole sulfone, and may have been an intermediate that was trapped by the lactol hydroxyl (entry 2). This may be why there are almost no examples of the Julia-Kociensky reaction on lactols.[246] Because of time constraints, the intermediate was not characterized. Entry 3 shows an attempt to prepare a relay substrate (**200**) that would eject butyrolactone upon metathesis. Treatment of **180** with allyl diethylphosphonoacetate returned only starting material. HWE tests on pantolactol (compound



Scheme 4.9: Attempts to access the relay substrates **199** and **194** which would eject cyclopentene and cyclohexene respectively

60, Scheme 2.7 on page 30) had at least given moderate yields of the equivalent olefin, and it was hoped that these conditions would be less sterically demanding than entry 1. Finally, in entry 4 an aqueous Wittig was attempted that uses a much weaker base but none of the product **201** was found.[247] Some of these reactions were also attempted on the PMP protected lactol **190** (not shown) but to no avail. Other methods to access the aldehyde and add the relay olefin were deemed too cumbersome to carry out, and the relay scheme was abandoned.



Scheme 4.10: Attempt to form the olefinic bond with a larger ring.

The expanded ring structure remained to be tested, and it was accessed by a few extra reactions on the regular acid piece **175** (Scheme 4.10). First, methyl caproate (**202**) was esterified using the Keck modified Steiglich conditions to afford **203**.[243] The methyl ester was deprotected with Lithium Hydroxide to prepare acid **204**. This reaction ususally went to 90% completion before it was terminated, or else some of the other ester bond would be cleaved. The crude mixture was then esterified again with DCC / DMAP / CSA to give the expanded RCM substrate **196**. The ester was subjected to Grubbs 2nd generation catalyst (**138**) but no reaction took place and starting material was returned. This told us that thermodynamics of ring size was not the primary problem with this scheme, and some solution to the steric problems of accessing the olefins would have to be found before this method could successfully lead to retron **114**.

4.5 Concluding remarks

In conclusion, the strategy outlined to approach the core structure (**114**) was unsucessful. There are still alternative schemes that can use the stereochemistry derived from D-galactose, but they are not as elegant as the metathesis that was attempted. The synthesis of the FD-895 stille coupling partner was one step from completion at the publication of the thesis, but it is expected to have been completed before the conclusion of this writer's tenure in the lab. In the future, these syntheses will be used to prepare derivatives of FD-895 that can be used in investigations of the compound's mode of action and biosynthesis.

4.6 Acknowledgements

Work in this section regarding the synthesis of the FD-895 (**71**) sidechain up to compound **161** was published in the paper Mandel, A. L.; Jones, B. D.; La Clair J. J.; Burkart. M. D. "A synthetic entry to pladienolide B and FD-895" *Bio. Org. Med. Chem. Lett.*, **2007**, *17*, 5159–5164. I would like to thank Dr. James La Clair for helpful advice and direction on this project and for helping us get a sample of **71**, and Brian Jones for help scaling up and working out the chemistry displayed in Schemes 4.2 and 4.3. Brian prepared compounds **168** and **169** and they are included in the experimental data for thoroughness.

4.7 Experimental data

Reactions were performed under Ar atmosphere at room temperature (rt) in oven dried glassware expect where indicated or when water is used as a solvent. THF, toluene, ether, DMF and dichloromethane for dry reactions were degassed and dis-

tilled through an alumina-packed solvent system. 1,2-dimethoxyethane was distilled over sodium metal and benzophenone. DIPEA was purified by distillation over ninhydrin and then distillation over potassium hydroxide. Pyridine was distilled over potassium hydroxide. Triethylamine was distilled over sodium metal. Propionaldehyde was freshly distilled over anhydrous $CaCl_2$ before use. Other reagents were obtained from commercial suppliers and used directly from the bottle unless specifically noted. Column chromatography was performed with EM Silica Gel 60, and thin layer chromatography was performed on EMD Silica Gel 60 F_{254} pre-coated plates. Visualization of TLC was with a ceric ammonium molybdate solution preceeded by UV if necessary.

NMR spectroscopy was performed on Varian Mercury 300 MHz, 400 MHz, or Unity 500 MHz instruments at ambient temperature. Select NOESY and HMQC experiments were run on a Bruker DMX500. ^{1}H and ^{13}C NMR spectra are reported in parts per million relative to TMS and standardized to chloroform (^{1}H δ = 7.26 ppm, ^{13}C δ = 77.16 ppm) with multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiple peaks, br = broad), coupling constants, and integration. All ^{13}C spectra are reported with complete proton decoupling. ^{31}P NMR spectra are reported in ppm relative to H_3PO_4 (δ = 0 ppm). IR spectra were taken on a Nicolet magna-IR 550 series II Spectrometer and peaks are reported in wavenumber (cm^{-1}). Mass spectra were taken on a ThermoFinnigan LCQdeca mass spectrometer and high resolution spectra were taken on ThermoFinnigan MAT900XL high resolution mass spectrometer with electron impact or fast atom bombardment as ionization methods. All masses are expessed in amu. Optical rotations were taken with a Perkin-Elmer 241 Polarimeter with a 1 dm path length.

4.7.1 New compounds from Scheme 4.2

Weinreb amide 151 – Starting with the known thiazolidinethione aldol adduct **117a** (4.28 g, 13.2 mmol) in 200 mL dichloromethane; solid imidazole (2.70 g, 39.7 mmol) then solid N,O-dimethylhydroxylamine hydrochloride (2.58 g, 26.5 mmol) were added and the reaction was stirred until the bright yellow color had faded significantly. After 6 h TLC (2:1 hexanes / EtOAc) showed no remaining starting material. 20 mL 1M HCl was added and the layers were agitated and then separated. The aqueous layer was extracted twice with 50 mL DCM and the combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residual oil was purified by flash chromatography (2:1 to 1:3 hexanes / EtOAc) to yield **151** (1.69 g, 73%) as a clear oil. Spectral characteristics matched data for this compound as prepared through a different method.*find and place this reference* R_f = 0.35 (1:2 hexanes / EtOAc).

Methyl ether 152 – Amide **151** (1.37 g, 7.82 mmol) was dissolved in 50 mL THF, and 15 mL DMF in a schlenk flask with iodomethane (14.96 g, 6.56 mL, 78.2 mmol) and cooled in a water / ice bath; solid sodium hydride (760 mg, 19.5 mmol, 60% w/w dispersion in mineral oil) was added in small portions being aware of the evolving hydrogen gas. After 2 h, the reaction was quenched by the addition of $\sim$10 mL pH 7.0 phosphate buffer which caused more gas to be evolved. The mixture was partitioned between 35 mL DCM and 70 mL brine and extracted. The layers were separated and the aqueous layer was extracted three times with 50 mL DCM and the combined organic extracts were washed with brine and evaporated *in vacuo*. The residue was purified by flash chromatography (4:1 to 1:1 hexanes / EtOAc) to yield **152** (1.36 g, 92%) as a clear oil. ^{1}H-NMR: δ (500 MHz, $CDCl_3$) 3.68 (s, 3H), 3.40 (s, 3H), 3.30 (dt J = 3.8, 7.8 Hz, 1H), 3.18 (s, 3H), 3.03 (b, 1H), 1.58 (d6, J = 4.0, 7.5 Hz, 1H),

1.42 (7-plet, J = 7.4 Hz, 1H), 1.20 (d, J = 7.0 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H). ^{13}C-NMR: δ (100 MHz, $CDCl_3$) 176.4, 83.8, 61.5, 58.5, 39.5, 32.2, 25.1, 14.3, 9.5. IR νmax: 3581, 3502, 2969, 2934, 2882, 2820, 1658, 1457, 1379. HR-MS: calcd. $C_9H_{19}O_3N$ $[M]^+$ calcd : 189.1359, found $[M]^+$: $\frac{m}{z}$ = 189.1362. $[\alpha]_D^{25}$ = –13.0° (c = 1.0, $CHCl_3$). R_f = 0.25 (2:1 hexanes / EtOAc).

Aldehyde 143 – Methyl ether **152** (970 mg, 5.13 mmol) was dissolved in 75 mL dichloromethane and cooled to -78°C and diisobutylaluminum hydride (10.3 mL, 10.3 mmol, 1M in toluene) was added slowly. After 2 h, the reaction was quenched by the addition of 5 mL acetone, and the reaction was allowed to warm up and 10% $KHSO_4$ (20 mL) was added and the layers were shaken and separated. The aqueous layer was extracted three more time with 50 mL ether, an the combined organic extracts were washed twice with 20 mL 10% $KHSO_4$, then brine, and then dried over Na_2SO_4. The organic layer was evaporated *in vacuo* until a bit of toluene solution remained and the residue was purified by flash chromatography (Hexanes to 6:1 hexanes / EtOAc) to yield **143** (573 mg, 86%) as a clear light oil. ^{1}H-NMR: δ (500 MHz, $CDCl_3$) 9.76 (s, 1H), 3.52 (dt, J = 3.8, 6.5 Hz, 1H), 3.35 (s, 3H), 2.53 (dq, J = 3.9, 7.0 Hz, 1H), 1.65 (m, 1H), 1.50 (m, 1H), 1.10 (d, J = 7.1 Hz, 3H), 0.94 (t, J = 7.5 Hz, 3H). ^{13}C-NMR: δ (100 MHz, $CDCl_3$) 204.9, 82.2, 57.9, 49.2, 24.2, 10.3, 8.0. IR νmax: 3422, 2964, 2930, 2879, 1724, 1463, 1454, 1379, 1112. HR-MS: calcd. $C_7H_{13}O_2$ $[M-H]^+$ calcd : 129.0910, found $[M-H]^+$: $\frac{m}{z}$ = 129.0908. $[\alpha]_D^{25}$ = –19.3° (c = 1.0, $CHCl_2$) R_f = 0.45 (2:1 hexanes / EtOAc).

Olefin ester 153 – Triethylphosphonoacetate (1.58 mL, 1.79 g, 7.97 mmol) was added dropwise to a suspension of sodium hydride (297 mg, 7.44 mmol, 60% w/w dispersion in mineral oil) in 30 mL THF in a water / ice bath and hydrogen gas bubbled out of solution. After the addition was complete, the reaction was stirred for 30 minutes as

the solution clarified. Next, aldehyde **143** (346 mg, 2.66 mmol) was added in 5 mL THF via cannula. After 3 h, the reaction was quenched with 25% NH_4Cl, and the mixture was extracted three times with 50 mL ether. The combined organic extracts were washed with brine and dried over Na_2SO_4, evaporated *in vacuo*. The crude residue was purified by flash chromatography (40:1 to 20:1 hexanes / EtOAc) to yield the intermediate unsaturated ethyl ester (440 mg, 83%) as a clear oil. ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 6.95 (dd, J = 7.6, 15.8 Hz, 1H), 5.82 (d, J = 15.7 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.37 (s, 3H), 3.00 (dt, J = 5.1, 10.0 Hz, 1H), 2.57 (m, 1H), 1.51 (m, 1H), 1.42 (m, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.07 (d, J = 6.8 Hz, 3H), 0.91 (t, J = 7.3 Hz, 3H). ^{13}C-NMR: δ (100 MHz, $CDCl_3$) 166.9, 151.4, 121.2, 85.7, 60.4, 58.0, 39.4, 24.0, 14.9, 14.4, 10.0. IR νmax: 2978, 2934, 2882, 2820, 1719, 1650, 1466. HR-MS: calcd. $C_{11}H_{20}O_3$ $[M]^+$ calcd : 200.1407, found $[M]^+$: $\frac{m}{z}$ = 200.1405. $[\alpha]_D^{25}$ = –45.4° (c = 1.0, CH_2Cl_2) R_f = 0.35 (10:1 hexanes / EtOAc).

4.7.2 New compounds from Scheme 4.3

Olefin alcohol 158 – Unsaturated ester **153** (720 mg, 3.60 mmol) was dissolved in 100 mL dichloromethane, cooled to -78°C, and diisobutylaluminum hydride (14.4 mL, 14.4 mmol, 1M in toluene) was added in one portion via syringe. After one hour, TLC (6:1 hexanes / EtOAc) showed the reaction was complete. Saturated RochelleÕs salt solution was added to quench the reaction and it was allowed to warm to room temperature. After 2.5 h, 50 mL DCM was added, the layers were separated and the aqueous layer was extracted twice more with 50 mL DCM. The combined organic layers were washed with water, then brine, dried over Na_2SO_4, and evaporated *in vacuo*. The crude oil was purified by flash chromatography (6:1 to 5:3 hexanes / EtOAc) to yield **159** (504 mg, 89%) as a clear oil. ^{1}H-NMR: δ (400 MHz, $CDCl_3$)

5.66 (m, 2H), 4.11 (m, 2H), 3.36 (s, 3H), 2.92 (ddd, J = 5.7, 7.5, 10.0 Hz, 1H), 2.44 (m, 1H), 1.51 (m, 1H), 1.41 (m, 1H), 1.01 (d, J = 7.0 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H). ^{13}C-NMR: δ (100 MHz, $CDCl_3$) 135.3, 129.0, 86.4, 64.0, 57.8, 39.0, 23.6, 16.0, 10.0. IR νmax: 3388, 2968, 2932, 2876, 2826, 1460, 1375. HR-MS: calcd. $C_9H_{17}O_2$ [M-H]$^+$ calcd : 157.1223, found [M-H]$^+$: $\frac{m}{z}$ = 157.1226. $[\alpha]_D^{25}$ = –34.5° (c = 0.20, $CHCl_3$). R_f = 0.40 (6:1 hexanes / EtOAc).

Epoxy alcohol 159 – (-)-diethyl tartrate (85 mg, 70 μL, 0.411 mmol) was added into 15 mL of DCM over activated crushed 4Å molecular sieves ($\sim$ 200 mg) at –20°C. Next, titanium(IV) isopropoxide (100 mg, 104 μL, 0.353 mmol) was added to the solution. Finally, a solution of t-butylhydroperoxide in decane (0.71 mL, 3.92 mmol, 5.5 M) was added slowly to the stirring mixture and the temperature was held at –20°C. After 30 minutes, a solution of allylic alcohol **158** (310 mg, 1.96 mmol) in 10 mL DCM over activated crushed 4 Å molecular sieves ($\sim$ 200 mg) was added slowly via cannula to the catalyst mixture and the reaction was allowed to warm to -10°C and the temperature was maintained for 2 h. TLC (2:1 hexanes / EtOAc) indicated the reaction was complete, and the reaction mixture was poured onto a solution of ferrous sulfate (3.3 g) and tartaric acid (1.0 g) in 10 mL water cooled to 0°C. After stirring the resultant biphasic mixture for 10 minutes, the layers were separated, and the aqueous remnants were extracted three times with 15 mL ether. The combined organics were returned to an erlenmeyer and a 30% w/v mixture of sodium hydroxide in saturated brine (20 mL) that had been precooled to 0°C was added and stirred for an hour at 0°C. The mixture was separated and the aqueous layer was separated and extracted three times with 25 mL ether. The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by flash chromatography (2:1 to 1:2 hexanes / EtOAc) to yield **159** (280 mg, 82%, 82% d.e.) as a clear oil.

^{1}H-NMR: δ (400 MHz, $CDCl_3$) 3.93 (ddd, *J* = 2.2, 5.7, 12.4 Hz, 1H), 3.63 (ddd, *J* = 4.3, 7.2, 12.8 Hz, 1H), 3.41 (s, 3H), 3.19 (dt, *J* = 4.1, 6.5 Hz, 1H), 2.96 (m, 2H), 1.78 (b, 1H), 1.63 (m, 1H), 1.54 (m, 1H), 1.51 (m, 1H), 0.91 (m, 6H). ^{13}C-NMR: δ (100 MHz, $CDCl_3$) 83.9, 62.1, 58.3, 58.0, 57.9, 38.5, 23.9, 10.4, 10.2. IR νmax: 3422, 2972, 2930, 2879, 1468, 1103. HR-MS: calcd. $C_9H_{18}O_3$ $[M]^+$ calcd : 174.1250, found $[M]^+$: $\frac{m}{z}$ = 174.1249. $[\alpha]_D^{25}$ = +4.0° (c = 0.075, $CHCl_3$). R_f = 0.10 (2:1 hexanes / EtOAc).

Epoxy aldehyde 160 – Epoxy alcohol **159** (277 mg, 1.6 mmol) was dissolved in 10 mL of EtOAc. To the solution was added IBX (1.78 g, 6.4 mmol), and the suspension was heated to reflux for 3 h. TLC (2:1 hexanes / EtOAc) indicated the presence of starting material, and another portion of IBX (300 mg, 1.0 mmol) was added. After an additional hour, the suspension was cooled to room temperature and filtered through a plug of silica gel eluting with EtOAc. The solvent was evaporated *in vacuo* to leave **160** (272 mg, 99%) as a clear oil. ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 9.03 (d, *J* = 6.4 Hz, 1H), 3.43 (s, 3H), 3.28 (dd, *J* = 2.0, 7.5 Hz, 1H), 3.23 (dt, *J* = 3.7, 6.6 Hz, 1H), 3.17 (dd, *J* = 2.0, 6.3 Hz, 1H), 1.65 (m, 2H), 1.49 (m, 1H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C-NMR: δ (100 MHz, $CDCl_3$) 198.6, 83.7, 59.0, 58.7, 58.3, 38.3, 23.8, 10.2, 10.0. IR νmax: 2972, 2930, 2879, 2828, 1732, 1468, 1103. HR-MS: calcd. $C_9H_{17}O_3$ $[M+H]^+$ calcd : 173.1172, found $[M+H]^+$: $\frac{m}{z}$ = 173.1174. $[\alpha]_D^{25}$ = –69.5° (c = 1.0, $CHCl_3$). R_f = 0.55 (2:1 hexanes / EtOAc).

Sidechain Olefin 161 – Potassium ^{t}butoxide (127 mg, 1.13 mmol) was heated overnight to 80°C in order to remove all traces of moisture. The dry tert-butoxide was cooled to -78°C. To the dry tert-butoxide was added 0.7 mL of a solution of cis-2-butene (3 mL) in THF (7.6 mL) to deliver an excess of the condensed gas. Next, n-butyllithium (420 μL, 1.10 mmol, 2.7 M in hexanes) was added via syringe, and the reaction

was warmed to -45°C for ten minutes, then the yellow-orange solution was recooled to -78°C. Next, a solution of (-)-B-methoxy-isocampheylborane (derived from (+)-pinene) (393 mg, 1.24 mmol) in 1 mL THF was cannulated into the crotyl solution and the color faded immediately. After stirring for 30 minutes, boranetrifluoride etherate (190 μL, 1.50 mmol) was added followed by a solution of Aldehyde **160** (266 mg, 1.5 mmol) in 1 mL THF. The reaction was stirred for 8 h, and then an aqueous solution of sodium perborate was added and the reaction was allowed to warm to room temperature and was stirred overnight. 10 mL of ether was added and the layers were separated, and the aqueous was reextracted twice with 10 mL ether. The combined organic extract were washed with brine, dried over Na_2SO_4, and solvent removed *in vacuo*. The product was purified by flash chromatography (10:1 to 1:1 hexanes / ether) to yield **161** contaminated by a trace of pinanol (5.7 mg, 2.2%) as a clear oil. ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 5.81 (ddd, J = 8.0, 10.4, 17.2 Hz, 1H), 5.14 (d, J = 17.3 Hz, 1H), 5.10 (d, J = 10.4 Hz, 1H), 3.41 (s, 3H), 3.35 (m, 1H), 3.18 (dt, J = 4.0, 6.5, Hz, 1H), 2.92 (dd, J = 2.3, 8.0 Hz, 1H), 2.85 (dd, J = 2.3, 4.8 Hz, 1H), 2.44 (q, J = 7.0 Hz, 1H), 1.92 (bd, $J \sim$ 6.0 Hz, 1H), 1.65 (m, 1H), 1.46 (m, 1H), 1.14 (d, J = 6.9 Hz, 3H), 0.92 (d, J = 6.9 Hz, 3H), 0.90 (t, J = 7.3 Hz, 3H). ^{13}C-NMR: δ (100 MHz, $CDCl_3$) 139.8, 116.2, 83.8, 74.1, 59.7, 59.1, 58.3, 43.0, 39.0, 23.9, 15.9, 10.4, 10.2. HR-MS: calcd. $C_{13}H_{23}O_3$ [M-H]$^+$ calcd : 227.1642, found [M]$^+$: $\frac{m}{z}$ = 227.1638. $[\alpha]_D^{25}$ = +10.0° (c = 0.10, $CHCl_3$). R_f = 0.35 (1:1 hexanes / ether).

Aldehyde 163 – A mixture of compound **161** (49.0 mg, 0.215 mmol) was dissolved in DMF (4 mL) and added to the solution were imidazole (43.8 mg, 0.644 mmol), ^{t}butyldimethylsilyl chloride (64.7 mg, 0.429 mmol), and a single crystal of DMAP and it was allowed to stir. After 16 h, the reaction was quenched by the addition of 5 mL NH_4Cl (25%). The mixture was extracted three times with 5 mL ether, organic

washed with brine, and dried over Na_2SO_4. The solvent was removed *in vacuo*, and the crude residue was purified by flash chromatography (20:1 to 10:1 hexanes / EtOAc) to yield a mixture of compound **162** and TBS protected pinanol which was too much of a mess to characterize but was taken to the next step without further purification.

The mixture (37.6 mg) was dissolved in 5 mL DCM and *N*-methylmorpholine *N*-oxide (38.6 mg, 0.329 mmol) it was cooled to 0°C and ozone was bubbled through the stirring solution for one minute. Next, air was bubbled through the solution for a minute, and then solvent was removed *in vacuo*. The crude residue was purified by flash chromatography (10:1 to 4:1 hexanes / EtOAc) to yield aldehyde **163** (1.5 mg, 2.0 %) as a clear oil. ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 9.74 (d, *J* = 0.9 Hz, 1H), 3.79 (dd, *J* = 3.9, 6.6 Hz, 1H), 3.41 (s, 3H), 3.21 (td, *J* = 3.6, 6.6 Hz, 1H), 2.84 (ddd, *J* = 2.3, 7.1, 8.9 Hz, 1H), 2.52 (qdd, *J* = 0.8, 3.9, 7.0 Hz, 1H), 1.66 (m, 1H), 1.44 (m, 2H), 1.20 (d, *J* = 7.1 Hz, 3H), 0.89 (m, 15H), 0.15 (s, 3H), 0.06 (s, 3H) ^{13}C-NMR: δ IR νmax: 2960, 2925, 2864, 1650, 1457, 1379, 1248, 1020, 907, 837, 776. HR-MS: calcd. $C_{18}H_{36}O_4Si$ $[M]^+$ calcd : 344.2377, found $[M]^+$: $\frac{m}{z}$ = 344.2384. $[\alpha]_D^{25}$ = +37.3° (c = 0.15, $CHCl_3$). R_f = 0.25 (10:1 hexanes / EtOAc).

Bromohydrin 168 – *This compound graciously provided by Brian D. Jones*. ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 4.87 (d, *J* = 8.2 Hz, 1H), 4.12 (m, 3H), 3.99 (dt, *J* = 3.2, 9.2 Hz, 1H), 3.52 (ddd, *J* = 2.3, 4.7, 9.6 Hz, 1H), 3.38 (s, 3H), 3.20 (m, 1H), 2.41 (qt, *J* = 2.8, 7.2 Hz, 1H), 2.16 (d, *J* = 2.5 Hz, 1H), 1.80 (m, 1H), 1.42 (m, 1H), 1.28 (d, *J* = 6.9 Hz, 3H), 1.06 (d, *J* = 7.3 Hz, 3H), 0.88 (t, *J* = 7.5 Hz, 3H) ^{13}C-NMR: δ (101 MHz, $CDCl_3$) 86.99, 83.13, 79.78, 78.55, 69.88, 56.27, 55.37, 34.79, 31.66, 31.12, 21.98, 15.34, 10.97, 9.87. IR νmax: 3441, 2969, 2934, 2873, 1650, 1457, 1431, 1380, 1235, 1082, 933, 636. HR-MS: calcd. $C_{13}H_{24}O_3Br$ $[M+H]^+$ calcd : 307.0903, found $[M+H]^+$: $\frac{m}{z}$ = 307.0902. $[\alpha]_D^{25}$ = +21.7° (c = 0.75, $CHCl_3$). R_f = (2:1 hexanes /

EtOAc).

Sidechain alkyne alcohol 169 – *This compound graciously provided by Brian D. Jones*. ^{1}H-NMR: δ 300 MHz, CDCl3) 3.72 (m, 1H), 3.41 (s, 3H), 3.19 (td, *J* = 4.2, 6.4 Hz, 1H), 3.12 (m, 1H), 3.05 (dd, *J* = 2.4, 8.1 Hz, 1H), 2.61 (pd, *J* = 2.5, 7.0 Hz, 1H), 2.16 (d, *J* = 2.5 Hz, 1H), 2.11 (d, *J* = 2.7 Hz, 1H), 1.67 (m, 1H), 1.50 (m, 2H), 1.32 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H) ^{13}C-NMR: δ (101 MHz, $CDCl_3$) 85.0, 84.9, 84.6, 83.9, 71.7, 71.1, 71.1, 59.1, 58.5, 58.2, 57.7, 56.9, 38.8, 38.1, 30.6, 23.9, 23.6, 23.0, 22.8, 17.0, 14.3, 10.6, 10.3, 10.1. HR-MS: calcd. $C_{13}H_{22}O_3$ $[M+H]^+$ calcd : , found $[M+H]^+$: $\frac{m}{z}$ = . $[\alpha]_D^{25}$ = –33.3° (c = 1.40, $CHCl_3$). R_f = 0.48 (2:1 hexanes / EtOAc).

***O*-TMS sidechain alkyne 170** – Alkyne **169** (14.0 mg, 0.082 mmol) was dissolved in DCM (2 mL) and were added to the solution, trimethylsilyl chloride (17.9 mg, 0.164 mmol), triethylamine (24.9 mg, 0.247), and a crystal of DMAP. The reaction was allowed to stir for 24 h, where TLC (2:1 hexanes / EtOAc) showed a spot to spot reaction. The reaction was quenched by the addition of 5 mL pH 7.0 phosphate buffer, and the mixture was extracted three times with 5 mL DCM. The organics were dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The residue was purified by flash chromatography (20:1 hexanes / EtOAc) to yield alkyne **170** (10.7 mg, 54%) as a clear oil. ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 3.64 (dd, *J* = 3.7, 6.6 Hz, 1H), 3.42 (s, 3H), 3.19 (td, *J* = 4.1, 6.5 Hz, 1H), 3.03 (dd, *J* = 2.2, 3.7 Hz, 1H), 2.91 (dd, *J* = 2.2, 8.3 Hz, 1H), 2.54 (pd, *J* = 2.4, 6.9 Hz, 1H), 2.13 (d, *J* = 2.4 Hz, 1H), 1.65 (m, 1H), 1.48 (m, 1H), 1.40 (m, 1H), 1.24 (d, *J* = 7.0 Hz, 3H), 0.96 (dd, *J* = 6.0, 9.4 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H), 0.12 (s, 6H). ^{13}C-NMR: δ (101 MHz, $CDCl_3$) 86.1, 83.9, 77.5, 77.2, 76.8, 73.6, 70.6, 59.3, 58.4, 57.2, 39.1, 31.2, 24.1, 16.9, 10.7, 10.2, 0.5. HR-MS: calcd. $C_{16}H_{31}O_3Si$ $[M+H]^+$ calcd : 299.2037, found $[M+H]^+$: $\frac{m}{z}$ = 299.2039.

$[\alpha]_D^{25}$ = –3.6° (c = 0.95, $CHCl_3$). R_f = 0.70 (2:1 hexanes / EtOAc).

4.7.3 New compounds from Scheme 4.4

O-TBS protected ethyl ester 174 – Ester **173** (200 mg, 1.39 mmol) was dissolved in DMF (5 mL) and to this solution were added imidazole (189 mg, 2.778 mmol), ^{t}butyldimethylsilyl chloride (251 mg, 1.67 mmol), and a crystal of DMAP and it was stirred for 26 h. TLC (2:1 hexanes / EtOAc) indicated the reaction was near completion after 4 hours, however it was allowed to stir overnight. The reaction was quenched by the addition of pH 7.0 phosphate buffer, and the mixture was extracted three times with 15 mL ether. The combined organics were washed with 25% NH_4Cl and brine. The solvent was dried over Na_2SO_4 and evaporated *in vacuo*. The residual oil was purified by flash chromatography (20:1 hexanes / EtOAc) to yield ester **174** (303 mg, 85%) as a light clear oil. ^{1}H-NMR: δ (500 MHz, $CDCl_3$) 5.84 (ddd, *J* = 6.2, 10.4, 16.9 Hz, 1H), 5.22 (d, *J* = 17.1 Hz, 1H), 5.07 (d, *J* = 10.3 Hz, 1H), 4.58 (dd, *J* = 6.3, 13.1 Hz, 1H), 4.12 (tdd, *J* = 3.7, 7.1, 10.9 Hz, 2H), 2.52 (dd, *J* = 8.1, 14.5 Hz, 1H), 2.43 (dd, *J* = 5.2, 14.5 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H). ^{13}C-NMR: δ (101 MHz, $CDCl_3$) 171.3, 140.4, 114.8, 71.0, 60.5, 43.9, 25.9, 25.8, 18.2, 14.4, -2.8, -4.2, -5.0. IR νmax: 3448, 2957, 2930, 2858, 1741, 1473, 1362, 1254, 1180, 1129, 1084, 837, 778. HR-MS: calcd. $C_7H_{12}O_3$ $[M]^+$ calcd : 144.0781 , found $[M]^+$: $\frac{m}{z}$ = 144.0781. $[\alpha]_D^{25}$ = –5.7° (c = 1.76 , $CHCl_3$). R_f = 0.65 (6:1 hexanes / EtOAc).

O-TBS protected olefin acid 175 – Ester **174** was dissolved in MeOH (3 mL) and H_2O and 100 μL 3 M KOH was added and the solution was stirred for 16 h. The reaction was poured onto 10 mL H_2O, extracted three times with 15 mL ether and the

organic extracts were set aside. The aqueous layers were acidified gently to pH 4 with 1 M HCl and a cloudy precipitate formed. The mixture was extracted three times with 10 mL DCM and dried over Na_2SO_4, and evaporated *in vacuo* to yield acid **175** (22.3 mg, 84%) as a clear oil. No further purification was required. ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 5.85 (ddd, J = 6.1, 10.4, 16.7 Hz, 1H), 5.27 (d, J = 17.1 Hz, 1H), 5.14 (d, J = 10.4 Hz, 1H), 4.58 (q, J = 6.0 Hz, 1H), 2.57 (d, J = 5.9 Hz, 2H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H). ^{13}C-NMR: δ (75 MHz, $CDCl_3$) 178.8, 141.2, 114.1, 71.5, 46.4, 26.1, 18.4, -4.4, -4.6.

4.7.4 New compounds from Scheme 4.5

Sulfide lactone 179 – Lactone **178** (156 mg, 0.773 mmol) and diphenyl disulfide (506 mg, 2.32 mmol) were dissolved in 0.35 mL dry pyridine. Tributylphosphine (469 mg, 579 μL, 2.32 mmol) was added to form a thick yellow solution. After 8 h, volatiles were evaporated *in vacuo* and then crude oil was purified by flash chromatography (20:1 to 4:1 hexanes / EtOAc) to yield sulfide **179** (160 mg, 70%) as a clear viscous oil. ^{1}H-NMR: δ (500 MHz, $CDCl_3$) 7.43 (d, J = 8.0 Hz, 2H), 7.33 (t, J = 7.6 Hz, 2H), 7.25 (t, J = 7.4 Hz, 1H), 4.44 (d, J = 3.2 Hz, 1H), 4.41 (ddd, J = 3.2, 5.6, 8.8 Hz, 1H), 3.38 (dd, J = 5.7, 13.9 Hz, 1H), 3.33 (dd, J = 8.6, 13.9 Hz, 1H), 1.52 (s, 3H), 1.44 (s, 3H), 1.38 (s, 3H). ^{13}C-NMR: δ (101 MHz, $CDCl_3$) 176.1, 134.6, 131.1, 130.2, 129.5, 129.4, 127.2, 113.3, 83.2, 80.6, 76.7, 32.0, 27.0, 26.8, 18.2. IR νmax: 2989, 2925, 1789, 1440, 1377, 1218, 1175, 1102, 1011, 987, 743, 691. HR-MS: calcd. $C_{15}H_{18}O_4Si$ $[M]^+$ calcd : 294.0920, found $[M]^+$: $\frac{m}{z}$ = 294.0921. $[\alpha]_D^{25}$ = –20.4° (c = 1.24, $CHCl_3$). R_f = 0.5 (2:1 hexanes / EtOAc).

Sulfide lactol 180 – Sulfide **179** (77.2 mg, 0.263 mmol) was dissolved in 2.5 mL

toluene and cooled to –78°C. DIBALH (1 M solution in hexanes, 289 μL, 0.289 mmol) was added slowly and the solution was stirred for an hour. After an hour, TLC (2:1 hexanes / EtOAc) indicated the reaction was complete, and saturated Rochelle's salt (4 mL) was added and the solution was allowed to warm to rt. After another 3 hours, the mixture was extracted three times with 15 mL DCM, organics washed with brine, dried over Na_2SO_4 and evaporated *in vacuo* to yield a clear oil that was essentially pure lactol **180** (70.7 mg, 91%). ^{1}H-NMR: δ (500 MHz, $CDCl_3$) 7.39 (d, J = 7.3 Hz, 2H), 7.29 (t, J = 7.8 Hz, 2H), 7.19 (t, J = 7.3 Hz, 1H), 5.23 (d, J = 2.7 Hz, 1H), 4.34 (d, J = 3.1 Hz, 1H), 4.29 (td, J = 3.1, 6.9 Hz, 1H), 3.23 (m, 2H), 2.41 (d, J = 2.7 Hz, 1H), 1.48 (s, 3H), 1.46 (s, 3H), 1.42 (s, 3H). IR νmax: 3483, 2986, 2934, 1789, 1580, 1439, 1379, 1207, 1118, 1064, 1024, 990, 740, 691, 668. HR-MS: calcd. $C_{15}H_{20}O_4Si$ $[M]^+$ calcd : 296.1077, found $[M]^+$: $\frac{m}{z}$ = 296.1075. $[\alpha]_D^{25}$ = –23.6° (c = 0.60, $CHCl_3$). R_f = 0.41 (2:1 hexanes / EtOAc).

4.7.5 New compounds from Scheme 4.6

Olefin alcohol 181 – Methyltriphenylphosphonium bromide (255.7 mg, 0.716 mmol) was dried overnight under vacuum at 120°C in a two necked flask equipped with a reflux condenser, then cooled to rt and suspended in 10 mL THF and cooled further to –78°C. ^{n}butyllithium (2.47 M in hexanes, 0.280μL, 0.692 mmol was added to the suspension, and it took on a bright yellow color. The solution was allowed to warm to rt and stirred until all solids dissolved into a dark yellow solution. Next, lactol **180** (54.9 mg, 185 mmol) in 3 mL THF was added by cannula, and the reaction was heated to reflux. After two hours, TLC (2:1 hexanes / EtOAc) indicated the reaction had gone to completion and the color hard turned from yellow to brown. The reaction was cooled to rt, then quenched by the addition of 25% NH_4Cl (5 mL) and extracted

three times with 25 mL ether. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was relatively pure, but excess phosphine oxide was removed by flash chromatography (6:1 to 2:1 hexanes / EtOAc) to yield olefin **181** (46.1 mg, 85%) as a clear oil. ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 7.40 (d, J = 7.2 Hz, 2H), 7.29 (t, J = 7.5 Hz, 2H), 7.21 (t, J = 7.3 Hz, 1H), 5.83 (dd, J = 10.7, 17.2 Hz, 1H), 5.27 (dd, J = 1.3, 17.2 Hz, 1H), 5.08 (dd, J = 1.3, 10.7 Hz, 1H), 3.98 (d, J = 4.7 Hz, 1H), 3.72 (dt, J = 5.0, 10.7 Hz, 1H), 3.08 (dd, J = 5.8, 13.6 Hz, 1H), 3.01 (dd, J = 7.0, 13.6 Hz, 1H), 2.69 (d, J = 5.0 Hz, 1H), 1.50 (s, 3H), 1.39 (s, 3H), 1.38 (s, 3H). ^{13}C-NMR: δ (101 MHz, $CDCl_3$) 139.3, 135.2, 130.4, 129.2, 126.9, 114.7, 108.5, 84.5, 81.6, 68.0, 38.1, 28.2, 27.0, 25.1. IR νmax: 3478, 2985, 2933, 1584, 1481, 1439, 1404, 1380, 1254, 1214, 1191, 1091, 1045, 928, 870, 740, 691. HR-MS: calcd. $C_{16}H_{23}O_3Si$ $[M]^+$ calcd : 294.1984, found $[M]^+$: $\frac{m}{z}$ = 294.1986. $[\alpha]_D^{25}$ = +40.4° (c = 2.62, $CHCl_3$). R_f = 0.50 (2:1 hexanes / EtOAc).

Ester sulfone 182 – Olefin **181** (13.3 mg, 0.045 mmol) and acid **175** (12.5 mg, 0.054 mmol) were combined in a dry scintillation vial that had been purged with Ar, and 3 mL of dry THF was added. Next, solid EDC (17.3 mg, 0.090 mmol), and DMAP (single crystal), and DIPEA (17.5 mg, 0.136 mmol) were added and the reaction was allowed to stir under Ar overnight. After 20 h, the reaction was worked up by adding 4 mL 25% NH_4Cl and extracting three times with 15 mL ether. The combined organics were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The product was purified by flash chromatography (20:1 to 4:1 hexanes / EtOAc) to yield the intermediate sulfide ester (8.0 mg, 36%) and starting olefin alcohol (6.5 mg, 49%). No acid **175** was recovered. ^{1}H-NMR: δ (400 MHz, CDCl3) 7.40 (d, J = 7.1 Hz, 2H), 7.29 (t, J = 7.5 Hz, 2H), 7.20 (t, J = 7.3 Hz, 1H), 5.85 (ddd, J = 6.1, 10.4, 16.4 Hz, 1H), 5.77 (dd, J = 10.8, 17.3 Hz, 1H), 5.22 (d, J = 17.1 Hz, 1H), 5.20 (d, J = 17.3

Hz, 1H), 5.04 (m, 3H), 4.55 (dd, *J* = 6.5, 12.7 Hz, 1H), 4.19 (d, *J* = 5.0 Hz, 1H), 3.16 (dd, *J* = 6.4, 14.0 Hz, 1H), 3.06 (dd, *J* = 6.3, 14.0 Hz, 1H), 2.49 (dd, *J* = 6.6, 15.4 Hz, 1H), 2.36 (dd, *J* = 6.5, 15.4 Hz, 1H), 1.48 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H). R_f = 0.7 (6:1 hexanes / EtOAc).

The purified sulfide form the last step (8.0 mg, 0.016 mg) was dissolved in 1 mL of EtOH and cooled to 0°C and a freshly prepared solution of $(NH_4)_6Mo_7O_{24} \cdot 4\,H_2O$ (3.9 mg, 0.003 mmol) in 30% hydrogen peroxide (26.8 mg, 0.237 mmol) was added and allowed to warm to rt overnight. After 12 h, the reaction was poured onto brine, extracted three times with 10 mL ether, combined organics were washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to yield essentially pure sulfone **182** (8.5 mg, 99%). ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 7.90 (d, *J* = 7.4 Hz, 2H), 7.67 (t, *J* = 7.3 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 2H), 5.82 (ddd, *J* = 6.0, 10.3, 16.7 Hz, 1H), 5.72 (dd, *J* = 10.7, 17.2 Hz, 1H), 5.44 (dd, *J* = 6.6, 10.7 Hz, 1H), 5.22 (d, *J* = 17.2 Hz, 1H), 5.07 (d, *J* = 10.4 Hz, 1H), 4.98 (d, *J* = 11.0 Hz, 1H), 4.53 (dd, *J* = 5.7, 12.4 Hz, 1H), 4.09 (d, *J* = 5.9 Hz, 1H), 3.47 (dd, *J* = 4.0, 14.9 Hz, 1H), 3.41 (dd, *J* = 7.4, 14.9 Hz, 1H), 2.41 (dd, *J* = 7.2, 16.0 Hz, 1H), 2.26 (dd, *J* = 5.7, 15.9 Hz, 1H), 1.44 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H), 0.86 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). HR-MS: calcd. $C_{27}H_{41}O_7SSi$ $[M\text{-}H]^+$ calcd : 537.2337, found $[M\text{-}H]^+$: $\frac{m}{z}$ = 537.2338. R_f = 0.60 (2:1 hexanes / EtOAc).

Deprotected ester 186 – Sulfone **182** (3.0 mg, 0.006 mmol) was dissolved in 1 mL THF and 1 mL 1 M HCl was added and the reaction was stirred. After 2 h, TLC (2:1 hexanes / EtOAc) showed a spot to spot reaction and H_2O was added and the reaction was extracted three times with 3 mL EtOAc, and the combined organics were dried over Na_2SO_4 and evaporated *in vacuo* to yield, essentially pure **186** (0.7 mg, 25%). ^{1}H-NMR: δ (500 MHz, $CDCl_3$) 7.92 (d, *J* = 8.0 Hz, 2H), 7.70 (t, *J* = 7.4 Hz, 1H),

7.60 (t, J = 7.8 Hz, 2H), 5.86 (ddd, J = 5.3, 10.5, 17.2 Hz, 1H), 5.67 (dd, J = 10.7, 17.2 Hz, 1H), 5.50 (m, 1H), 5.33 (d, J = 17.2 Hz, 1H), 5.20 (d, J = 17.3 Hz, 1H), 5.16 (d, J = 10.5 Hz, 1H), 4.96 (d, J = 10.7 Hz, 1H), 4.56 (m, 1H), 4.01 (d, J = 6.5 Hz, 1H), 3.48 (dd, J = 8.8, 14.9 Hz, 1H), 3.36 (dd, J = 2.8, 14.9 Hz, 1H), 3.17 (d, J = 3.8 Hz, 1H), 2.44 (dd, J = 3.4, 15.6 Hz, 1H), 2.38 (dd, J = 9.0, 15.6 Hz, 1H), 1.44 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H). R_f = 0.20 (2:1 hexanes / EtOAc).

4.7.6 New compounds from Scheme 4.7

PMP protected sulfide 189 – Compound **177** (1.27 g, 7.83 mmol) and diphenyl disulfide (5.13 g, 23.5 mmol) were dissolved in 3.0 mL pyridine and tributylphosphine (4.75 g, 5.87 mL, 23.5 mmol) was added and then yellow suspension was stirred vigorously. TLC (1:2 hexanes / EtOAc) was a mess and after 22 h the volatiles were evaporated *in vacuo*. The complex mixture was purified by flash chromatography (6:1 to 1:2 hexanes / EtOAc) to yield a mixture of **188** and other sulfides and tributyl phosphine (1.98 g).

The mixture of sulfide **188** and other compounds was dissolved in 75 mL DCM, and *p*-methoxybenzaldehyde dimethyl acetal (3.04 g, 2.84 mL, 16.7 mmol) and camphor-sulfonic acid (193 mg, 0.834 mmol) were added with stirring. After 20 h, the reaction was quenched by the addition of 1 mL triethylamine, and volatiles were removed *in vacuo*. The crude mixture was purified by flash chromatography (10:1 to 2:1 hexanes / EtOAc) to yield acetal **189** (380 mg, 13%) as a crystalline solid. ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 7.42 (d, J = 7.2 Hz, 2H), 7.34 (m, 4H), 7.25 (dd, J = 5.7, 8.9 Hz, 1H), 6.90 (d, J = 8.7 Hz, 2H), 4.62 (d, J = 3.4 Hz, 1H), 4.50 (ddd, J = 3.5, 5.6, 9.0 Hz, 1H), 3.80 (s, 3H), 3.41 (dd, J = 5.6, 13.9 Hz, 1H), 3.35 (dd, J = 8.9, 13.9 Hz,

1H), 1.60 (s, 3H). ^{13}C-NMR: δ (101 MHz, $CDCl_3$) 174.8, 161.1, 134.4, 130.1, 129.4, 128.5, 127.6, 127.2, 114.0, 106.4, 83.3, 82.2, 76.1, 55.4, 31.9, 17.5. IR νmax: 3056, 2934, 2829, 1789, 1615, 1527, 1440, 1396, 1309, 1248, 1117, 1012, 828, 732, 688. HR-MS: calcd. $C_{20}H_{20})_5Si$ $[M]^+$ calcd : 372.1026, found $[M]^+$: $\frac{m}{z}$ = 372.1027. $[\alpha]_D^{25}$ = –48.7° (c = 4.79, $CHCl_3$). R_f = 0.35 (2:1 hexanes / EtOAc).

PMP protected sulfide lactol 190 – Lactone **189** (330 mg, 0.886 mmol) was dissolved in toluene (20 mL) and cooled to –78°C and DIBALH ((1 M in hexanes, 0.975 mL, 0.975 mmol) was added dropwise over 3 minutes. TLC (2:1 hexanes / EtOAc) was inconclusive because product and starting material have the same R_f. After one hour, the reaction was quenched by adding a saturated solution of Rochelle's salt, and allowed to warm to rt. After stirring the solution for 5 h, it was extracted three times with 25 mL EtOAc, the combined organics were washed with H_2O and brine, dried over Na_2SO_4, and evaporated *in vacuo* to yield lactol **190** (330 mg, 99%) as a clear oil that required no further purification. ^{1}H-NMR: δ (500 MHz, $CDCl_3$) 7.47 (m, 2H), 7.39 (d, J = 8.3 Hz, 2H), 7.30 (m, 2H), 7.20 (m, 1H), 6.91 (d, J = 8.7 Hz, 1H), 5.89 (s, 1H), 5.39 (d, J = 2.5 Hz, 1H), 4.41 (m, 1H), 4.37 (d, J = 3.5 Hz, 1H), 3.82 (s, 3H), 3.28 (d, J = 6.9 Hz, 2H), 2.45 (d, J = 2.5 Hz, 1H), 1.52 (s, 3H). ^{13}C-NMR: δ (101 MHz, $CDCl_3$) 161.1, 160.9, 135.9, 135.7, 129.4, 129.2, 129.2, 129.1, 128.7, 128.7, 128.5, 128.0, 126.4, 126.4, 114.1, 113.9, 105.1, 104.7, 101.7, 100.9, 92.1, 86.4, 86.1, 85.5, 78.4, 73.6, 55.5, 55.4, 32.1, 31.3, 19.4, 17.4. IR νmax: 3432, 2930, 2916, 2849, 1614, 1584, 1518, 1481, 1458, 1395, 1304, 1250, 1171, 1077, 1025, 831, 739, 691. HR-MS: calcd. $C_{20}H_{22}O_5S$ $[M]^+$ calcd : 374.1182, found $[M]^+$: $\frac{m}{z}$ = 374.1181. R_f = 0.35 (2:1 hexanes / EtOAc).

PMP protected olefin alcohol 191 – Methyltriphenylphosphonium bromide (308 mg, 0.862 mmol) was heated under vacuum in a two necked flask fitted with a reflux

condenser for 3 h, then suspended in 5 mL THF and cooled to –78°C. To the stirring solution, ^{n}butyllithium (2.47 M in hexanes, 0.337 mL, 0.833 mmol) was added turning the solution yellow. The stirring solution was allowed to warm to rt and after 2 hours, the phosphonium salt did not completely dissolve or turn as dark yellow as in the reaction to furnish **181**. To the turbid solution, lactol **190** (108 mg, 0.287 mmol) in 3 mL THF was added via cannula and the solution was heated to reflux. After 4 hours, it appeared by TLC (2:1 hexanes / EtOAc) that the reaction had stalled and the reaction was allowed to cool to rt. The reaction was quenched with 25% NH_4Cl, extracted three times with 15 mL ether, the combined organics washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The crude mixture was purified by flash chromatography (6:1 to 2:1 hexanes / EtOAc) to afford olefin **191** (45.6 mg, 43%) and starting lactol **190** (35 mg, 33%) ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 7.48 (d, J = 8.7 Hz, 2H), 7.39 (d, J = 7.1 Hz, 2H), 7.29 (t, J = 7.5 Hz, 2H), 7.21 (t, J = 7.3 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 6.03 (dd, J = 10.8, 17.4 Hz, 1H), 5.94 (s, 1H), 5.35 (dd, J = 1.2, 17.4 Hz, 1H), 5.20 (dd, J = 1.2, 10.8 Hz, 1H), 4.03 (d, J = 3.8 Hz, 1H), 3.82 (s, 3H), 3.77 (ddd, J = 3.8, 6.4, 12.3 Hz, 1H), 3.08 (d, J = 6.8 Hz, 2H), 2.57 (d, J = 5.8 Hz, 1H), 1.49 (s, 3H). ^{13}C-NMR: δ (101 MHz, $CDCl_3$) 160.8, 138.9, 135.5, 130.1, 129.1, 129.0, 128.5, 126.7, 115.7, 114.0, 102.0, 85.7, 81.8, 68.7, 55.4, 37.9, 23.8. R_f = 0.50 (2:1 hexanes / EtOAc).

PMP protected ester 192 – Olefin **191** (45.6 mg, 0.122 mmol) and acid **175** (41.9 mg, 0.182 mmol) were combined and dissolved in 10 mL DCM. To this solution, dicyclohexylcarbodiimide (63.1 mg, 0.306 mmol), dimethylaminopyridine (3.0 mg, 0.024 mmol), and camphorsulfonic acid (2.8 mg, 0.012 mmol) were added. Solids began crashing out of solution after 10 minutes. After 18 h, TLC (6:1 hexanes / EtOAc) showed no olefin **191** remaining. 10 mL ether was added, and then reaction

was filtered, then evaporated *in vacuo* and taken up in ether again and filtered again and evaporated again *in vacuo*. The residue was purified by flash chromatography (20:1 to 6:1 hexanes / EtOAc) to yield the intermediate ester-sulfide (70.4 mg, 98%) ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 7.49 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.30 (t, J = 7.6 Hz, 2H), 7.20 (t, J = 7.3 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 5.90 (s, 1H), 5.84 (m, 2H), 5.27 (dd, J = 1.3, 17.4 Hz, 1H), 5.21 (dt, J = 1.4, 17.1 Hz, 1H), 5.08 (dd, J = 1.2, 10.9 Hz, 1H), 5.04 (m, 2H), 4.53 (q, J = 6.5 Hz, 1H), 4.27 (d, J = 3.6 Hz, 1H), 3.82 (s, 3H), 3.16 (d, J = 6.7 Hz, 1H), 2.49 (dd, J = 6.6, 15.3 Hz, 1H), 2.37 (dd, J = 6.7, 15.3 Hz, 1H), 1.46 (s, 3H), 0.86 (s, 9H), 0.04 (s, 6H). ^{13}C-NMR: δ 170.2, 160.7, 140.3, 138.4, 135.4, 129.5, 129.5, 129.2, 128.7, 126.5, 115.1, 114.9, 113.8, 102.1, 83.4, 81.7, 70.5, 70.4, 55.4, 43.5, 34.1, 25.9, 24.4, 18.3, –4.3, –4.7. IR νmax: 2960. 2934, 2855, 1737, 1518, 1239, 1169, 1073, 1039, 994, 933, 828, 770, 690. HR-MS: calcd. $C_{32}H_{44}O_5SSi$ $[M]^+$ calcd : 584.2622, found $[M]^+$: $\frac{m}{z}$ = 584.2627. $[\alpha]_D^{25}$ = +36.1° (c = 1.86, $CHCl_3$). R_f = 0.33 (6:1 hexanes / EtOAc).

The intermediate sulfide (49.1 mg, 0.084 mmol) from the last step was dissolved in 10 mL EtOH and cooled to 0°C. A solution of $(NH_4)_6Mo_7O_{24} \cdot 4\,H_2O$ in hydrogen peroxide (143 mg, 1.26 mmol) was added to the reaction, and it was allowed to warm to rt overnight. After 16 h, the reaction was poured onto 10 mL brine, extracted three times with ether, combined organics washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to afford sulfone **192** (52.8 mg, 99%). ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 7.85 (d, J = 7.2 Hz, 2H), 7.65 (t, J = 7.4 Hz, 1H), 7.55 (t, J = 7.7 Hz, 2H), 7.41 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 5.90 (s, 1H), 5.81 (m, 2H), 5.38 (m, 1H), 5.34 (dd, J = 1.3, 17.3 Hz, 1H), 5.18 (dt, J = 1.4, 17.1 Hz, 1H), 5.10 (dd, J = 1.2, 10.9 Hz, 1H), 5.03 (d, J = 10.4 Hz, 1H), 4.49 (dd, J = 5.9, 13.0 Hz, 1H), 4.16 (d, J = 4.4 Hz, 1H), 3.82 (s, 3H), 3.51 (dd, J = 5.0, 14.7 Hz, 1H), 3.41 (dd,

J = 6.7, 14.7 Hz, 1H), 2.42 (dd, J = 7.1, 15.7 Hz, 1H), 2.30 (dd, J = 5.9, 15.8 Hz, 1H), 1.46 (s, 3H), 0.83 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H). ^{13}C-NMR: δ (101 MHz, $CDCl_3$) 169.6, 160.6, 140.2, 139.2, 137.9, 134.1, 129.4, 129.0, 128.4, 128.3, 115.6, 114.9, 113.8, 101.9, 83.5, 82.0, 70.1, 66.3, 56.0, 55.4, 43.2, 25.9, 25.0, 18.2, –4.3, –4.8. IR νmax: 2954, 2929, 2856, 1749, 1615, 1518, 1447, 1308, 1251, 1147, 1087, 1005, 930, 832, 778, 689. HR-MS: calcd. $C_{32}H_{44}O_8SSi$ $[M+H]^+$ calcd : 616.2521, found $[M]^+$: $\frac{m}{z}$ = 616.2533. $[\alpha]_D^{25}$ = +5.8° (c = 0.89, $CHCl_3$). R_f = 0.50 (2:1 hexanes / EtOAc).

4.7.7 New compounds from Scheme 4.10

Methyl extended ester 203 – acid **175** (5.8 mg, 0.025 mmol) and methyl caproate (**202**) (18.4 mg, 0.126 mmol) were combined and dissolved in 2 mL DCM. Dicyclohexylcarbodiimide (13.0 mg, 0.063 mmol), DMAP (3.1 mg, 0.025 mmol), and CSA (5.6 mg, 0.024 mmol) were added, and the reaction was allowed to stir overnight. After 16 h, 5 drops of MeOH and one drop HOAc were added to quench the reaction. After 5 minutes, the reaction was evaporated *in vacuo* and the residue was taken up in ether, filtered, and evaporated *in vacuo* again. The remnants were purified by flash chromatography (20:1 to 10:1 hexanes / EtOAc) to yield ester **203** (6.2 mg, 69%) as a clear film. ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 5.83 (ddd, J = 6.3, 10.5, 17.2 Hz, 1H), 5.22 (dt, J = 1.4, 17.2 Hz, 1H), 5.07 (dt, J = 1.4, 10.4 Hz, 1H), 4.57 (dd, J = 6.4, 13.1 Hz, 1H), 4.05 (m, 2H), 3.67 (s, 3H), 2.52 (dd, J = 8.0, 14.5 Hz, 1H), 2.43 (dd, J = 5.3, 14.5 Hz, 1H), 2.32 (t, J = 7.5 Hz, 2H), 1.64 (m, 4H), 1.38 (m, 2H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C-NMR: δ (75 MHz, $CDCl_3$) 174.1, 171.3, 140.4, 114.8, 71.0, 64.4, 51.7, 43.8, 34.0, 28.4, 25.9, 25.7, 24.7, 18.2, –4.3, –5.0. R_f = 0.60 (6:1 hexanes / EtOAc).

Extended ester acid 204 – Ester **203** (6.2 mg, 0.037 mmol) was dissolved in 1.5 mL THF and 0.4 mL H_2O and lithium hydroxide (1 M in H_2O, 87μL, 0.086 mmol) was added. After 16 h, the reaction was gently acidified with 1 M HCl (5 drops), extracted three times with 5 mL DCM, and dried over Na_2SO_4 and evaporated *in vacuo* to yield acid **204** (5.1 mg, 85%) contaminated with ¡ 10% starting ester **203**. ^{1}H-NMR: δ (500 MHz, $CDCl_3$) 5.84 (ddd, *J* = 6.2, 10.3, 16.9 Hz, 1H), 5.22 (d, *J* = 17.1 Hz, 1H), 5.07 (d, *J* = 10.3 Hz, 1H), 4.57 (dd, *J* = 6.3, 13.1 Hz, 1H), 4.06 (m, 3H), 2.52 (dd, *J* = 8.0, 14.5 Hz, 1H), 2.43 (dd, *J* = 5.2, 14.5 Hz, 1H), 2.37 (t, *J* = 7.4 Hz, 2H), 1.66 (m, 4H), 1.40 (m, 2H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).

Extended ester sulfone 196 – Acid **204** (6.1 mg, 0.017 mmol) and **181** (4.8 mg, 0.016 mmol) were combined in 1 mL DCM and DCC (8.8 mg, 0.043 mmol), DMAP (single crystal), and CSA (single crystal) were added and the reaction was stirred overnight. After 18 h, the volatiles were evaporated *in vacuo*, taken up in ether, filtered, and evaporated again. The compound was purified by preparatory TLC (6:1 hexanes / EtOAc) to yield the intermediate ester-sulfide (4.2 mg, 39%). ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 7.41 (d, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 5.83 (m, 1H), 5.77 (m, 1H), 5.22 (d, *J* = 17.1 Hz, 1H), 5.19 (dd, *J* = 1.2, 17.3 Hz, 1H), 4.57 (dd, *J* = 6.4, 13.0 Hz, 1H), 4.18 (d, *J* = 4.7 Hz, 1H), 4.05 (m, 1H), 3.16 (dd, *J* = 6.3, 14.0 Hz, 1H), 3.08 (dd, *J* = 6.6, 14.0 Hz, 1H), 2.52 (dd, *J* = 8.0, 14.5 Hz, 1H), 2.43 (dd, *J* = 5.3, 14.5 Hz, 1H), 2.23 (t, *J* = 7.5 Hz, 2H), 1.63 (m, 4H), 1.55 (s, 3H), 1.49 (s, 3H), 1.37 (m, 5H), 0.87 (s, 6H), 0.04 (s, 3H), 0.04 (s, 3H). R_f = 0.6 (6:1 hexanes / EtOAc).

The intermediate sulfide (4.2 mg, 0.007 mmol) was dissolved in 1 mL EtOH, cooled to 0°C, and a solution of $(NH_4)_6Mo_7O_{24} \cdot 4\,H_2O$ in hydrogen peroxide (11.5 mg, 0.101 mmol) was added and the reaction was allowed to warm to rt overnight. After 16

h, the reaction was poured onto 5 mL brine, extracted three times with 5 mL ether, combined organics were dried over Na_2SO_4 and evaporated *in vacuo* to yield pure ester **196** (4.4 mg, 99%). ^{1}H-NMR: δ (400 MHz, $CDCl_3$) 7.91 (d, J = 7.1 Hz, 2H), 7.68 (t, J = 7.4 Hz, 1H), 7.59 (t, J = 7.6 Hz, 2H), 5.83 (ddd, J = 6.3, 10.5, 17.3 Hz, 1H), 5.81 (dd, J = 6.4, 10.6 Hz, 1H), 5.69 (dd, J = 10.7, 17.3 Hz, 1H), 5.45 (ddd, J = 4.4, 6.0, 7.2 Hz, 1H), 5.22 (dt, J = 1.4, 17.1 Hz, 2H), 5.20 (dd, J = 1.2, 17.3 Hz, 1H), 5.07 (m, 1H), 4.95 (dd, J = 1.2, 10.7 Hz, 1H), 4.57 (ddt, J = 1.0, 6.2, 8.7 Hz, 1H), 4.05 (m, 3H), 3.43 (m, 2H), 2.52 (dd, J = 8.0, 14.5 Hz, 1H), 2.43 (dd, J = 5.3, 14.5 Hz, 1H), 2.15 (t, J = 7.3 Hz, 2H), 1.61 (m, 4H), 1.44 (s, 3H), 1.36 (s, 8H), 0.86 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H). ^{13}C-NMR: δ (101 MHz, $CDCl_3$) 172.1, 171.3, 140.4, 138.5, 134.1, 129.5, 128.5, 115.1, 114.8, 108.9, 82.8, 81.7, 71.0, 65.4, 64.4, 56.3, 43.8, 33.9, 28.4, 28.1, 26.9, 26.1, 25.9, 25.5, 24.2, 18.2, –4.2, –5.0. IR νmax: 2934, 2864, 1737, 1466, 1370, 1317, 1239, 1151, 1090, 837, 776. HR-MS: calcd. $C_{33}H_{52}O_9SSi$ $[M+H]^+$ calcd : 652.3096, found $[M]^+$: $\frac{m}{z}$ = 652.3107. $[\alpha]_D^{25}$ = +22.0° (c = 0.25, $CHCl_3$). R_f = 0.44 (2:1 hexanes / EtOAc).

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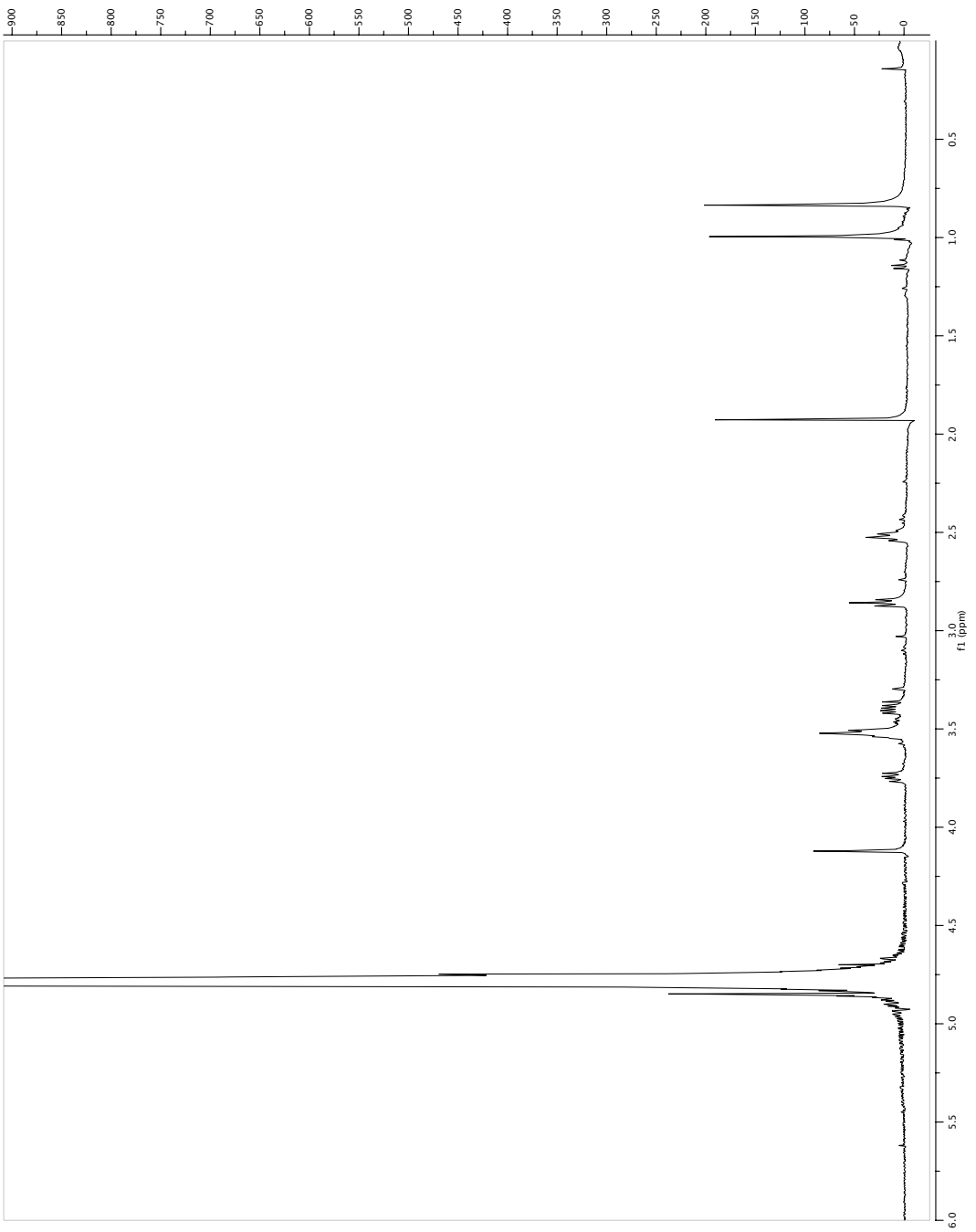
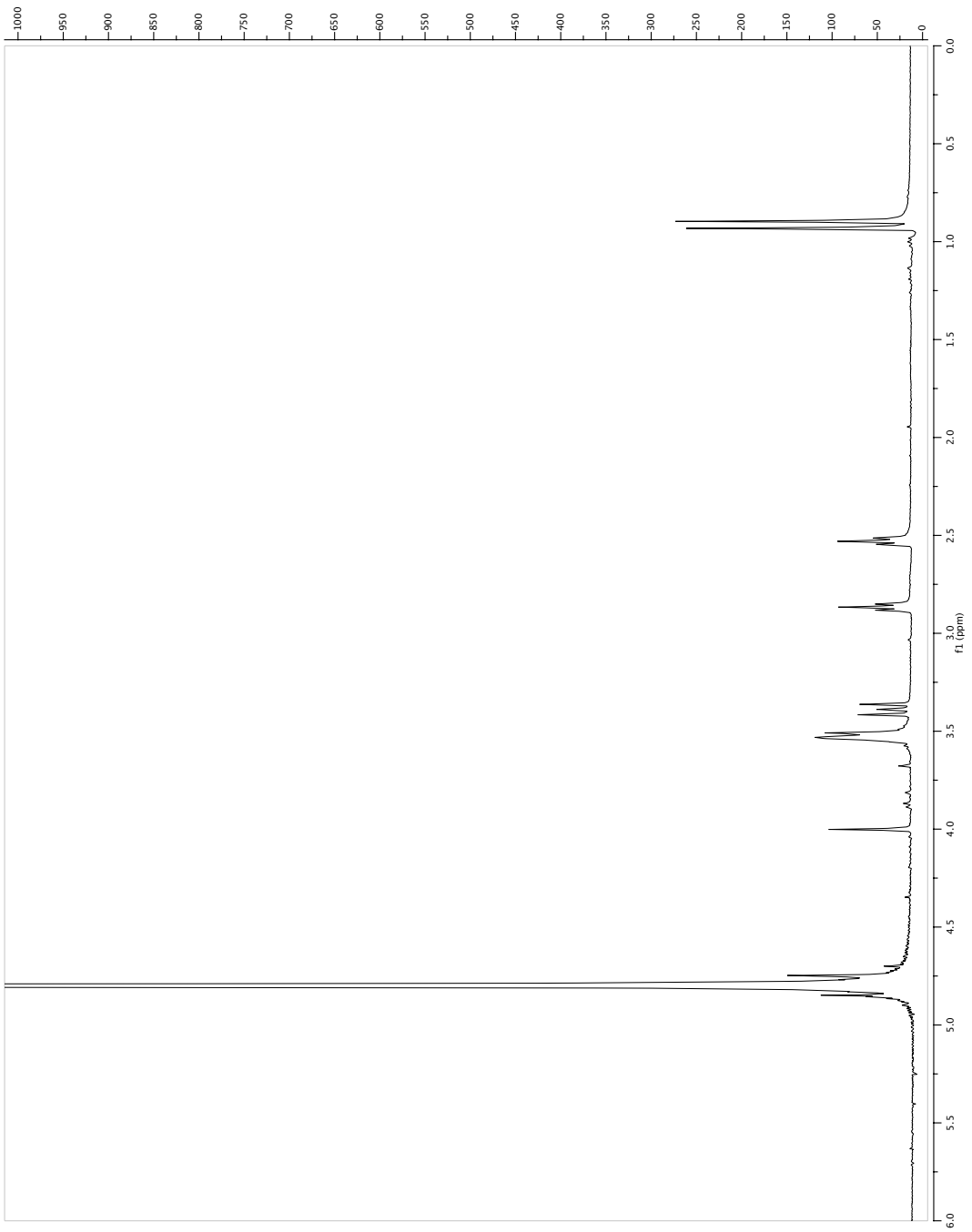
Appendix A

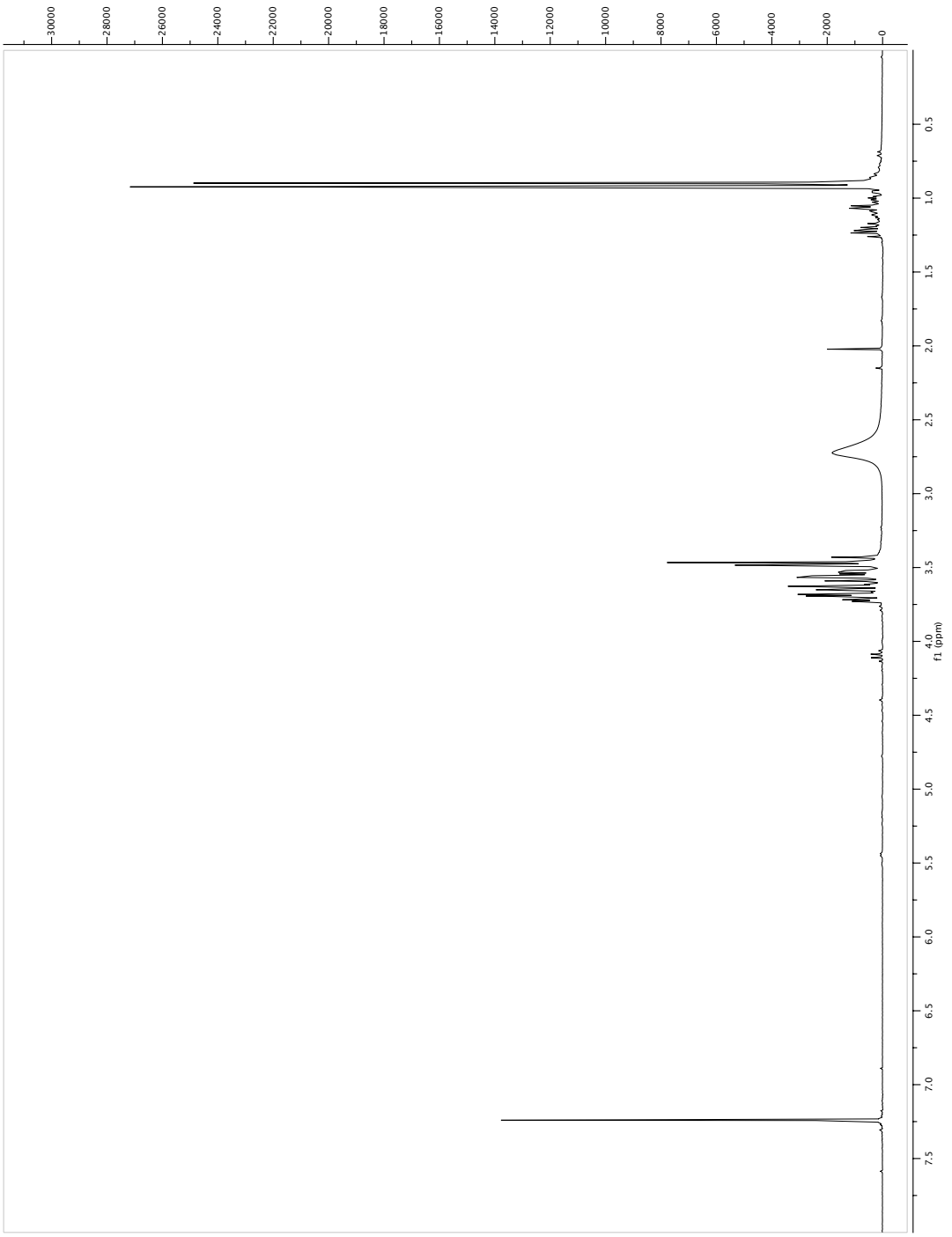
^{1}H and ^{13}C NMR spectra for new compounds



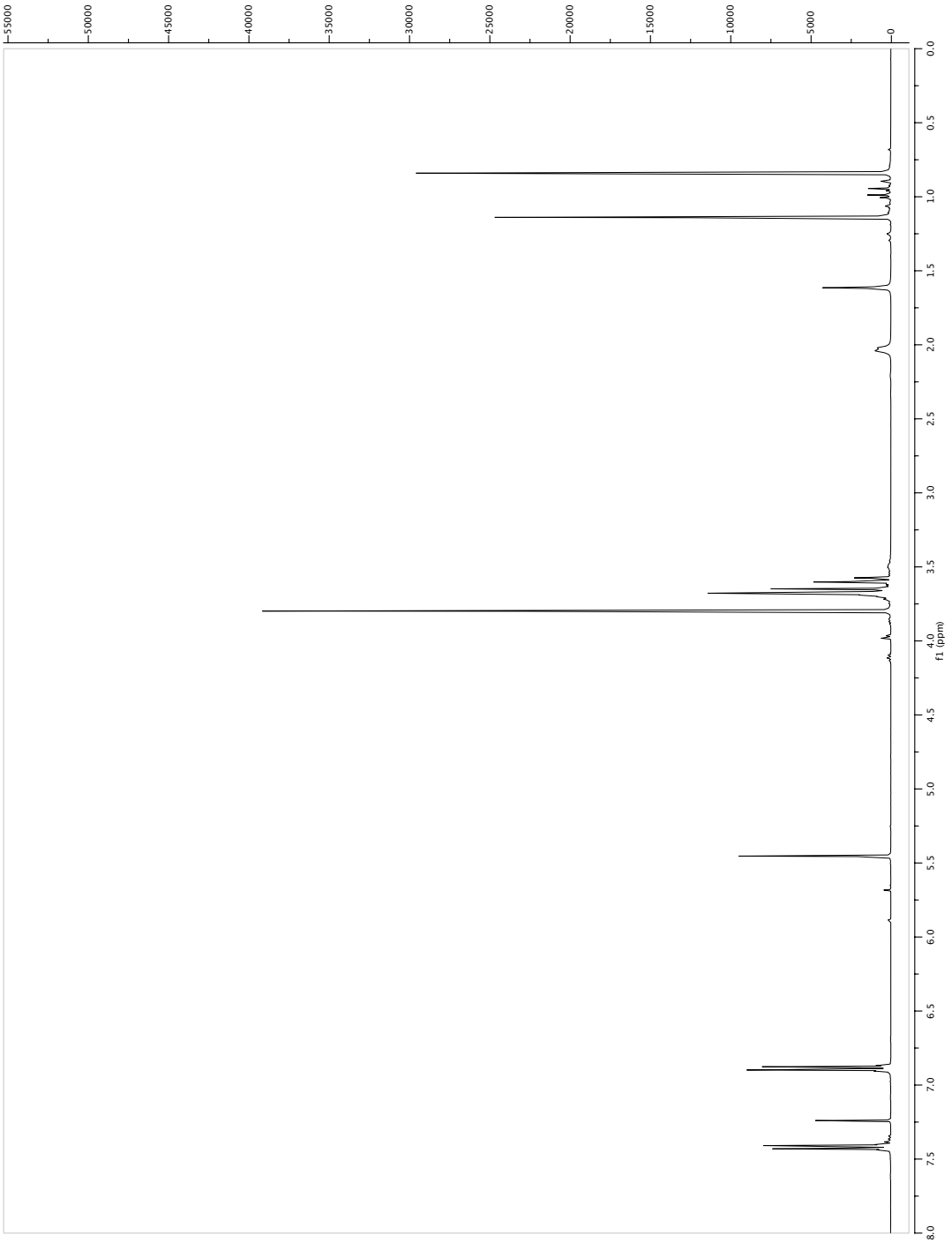
Spectrum A.1: ^{1}H spectrum of compound **14**.



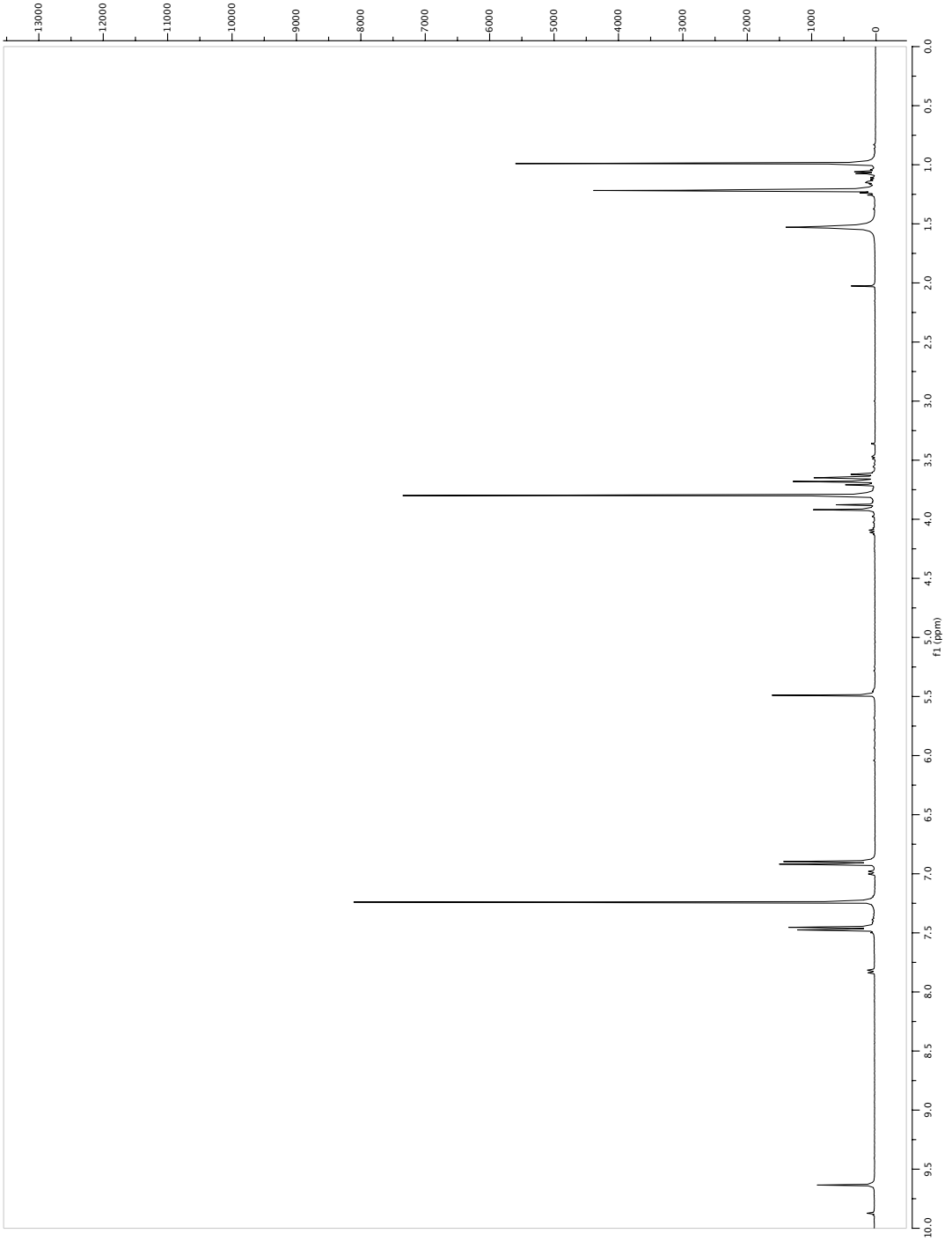
Spectrum A.2: ^{1}H spectrum of compound **35**.



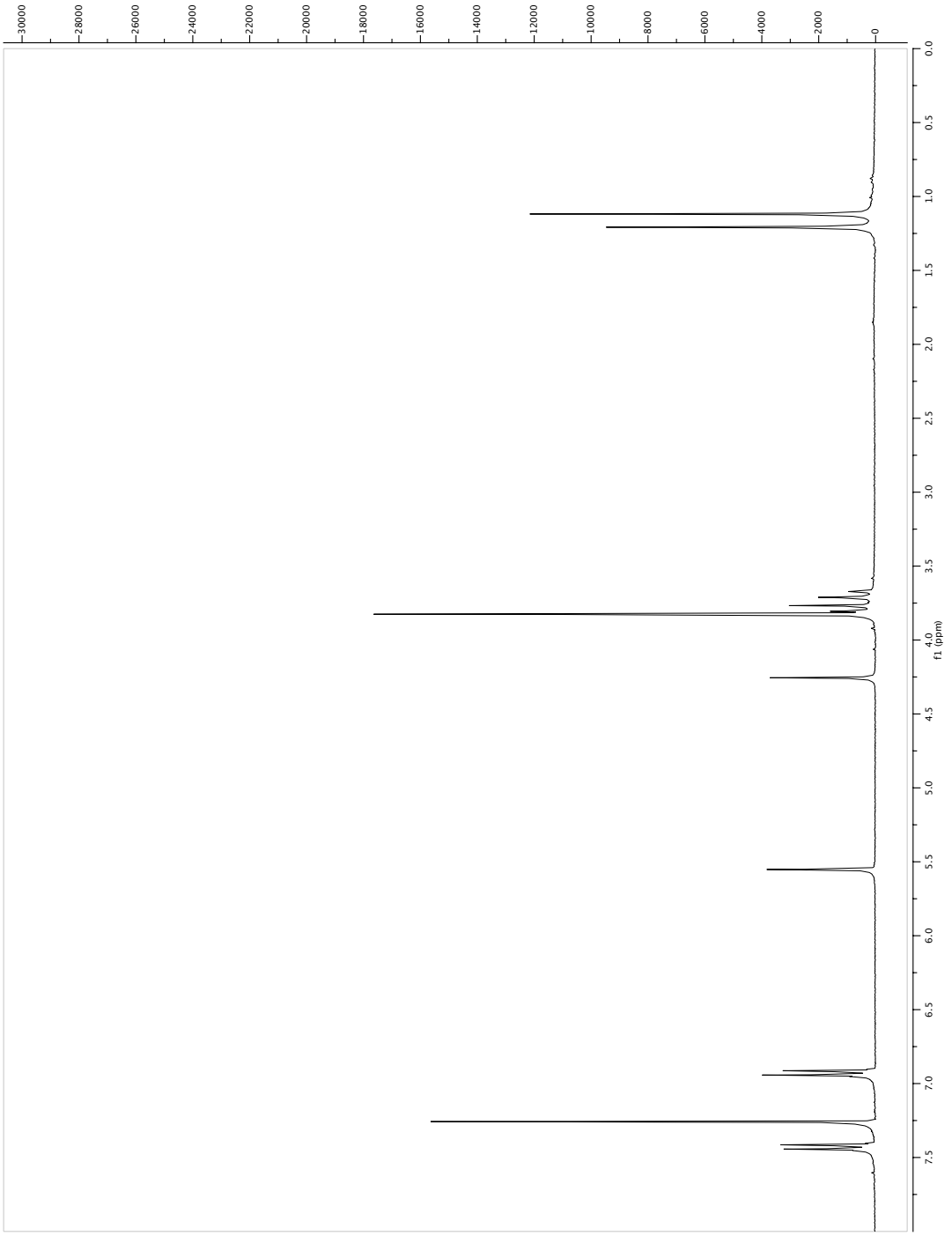
Spectrum A.3: ^{1}H spectrum of compound **51**.



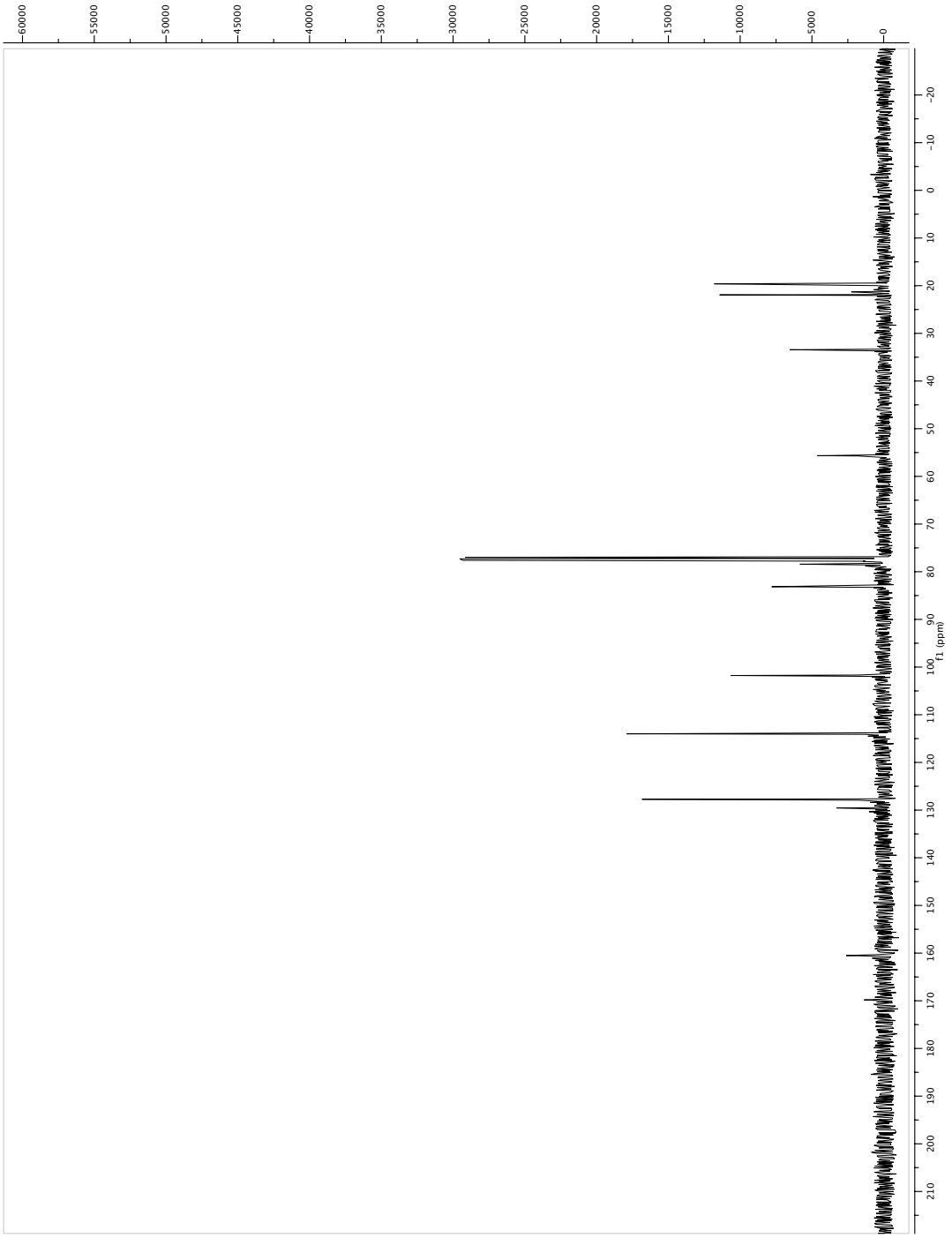
Spectrum A.4: ^{1}H spectrum of compound **52**.



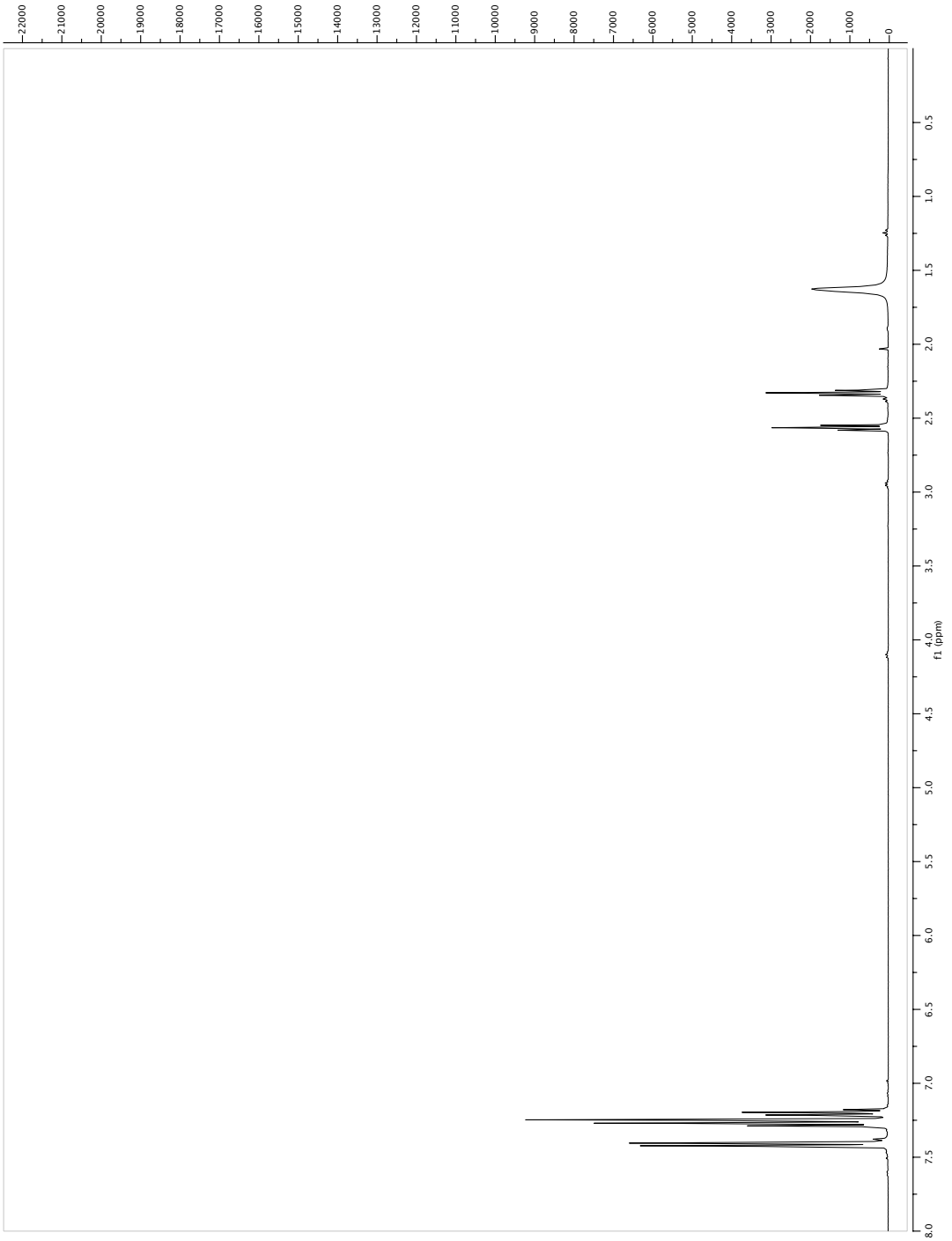
Spectrum A.5: ^{1}H spectrum of the intermediate aldehyde before oxidation to compound **53**



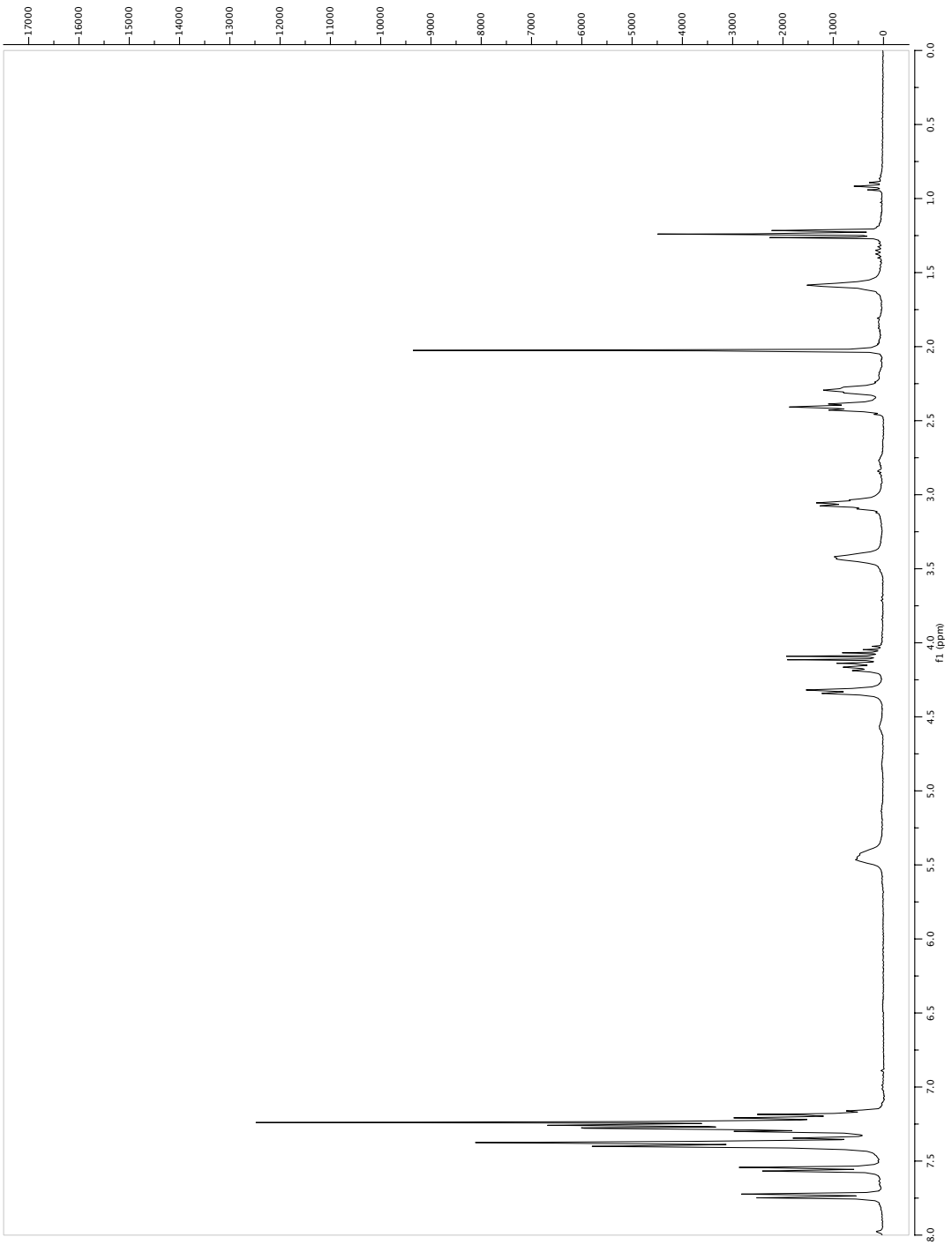
Spectrum A.6: ^{1}H spectrum of compound **53**.



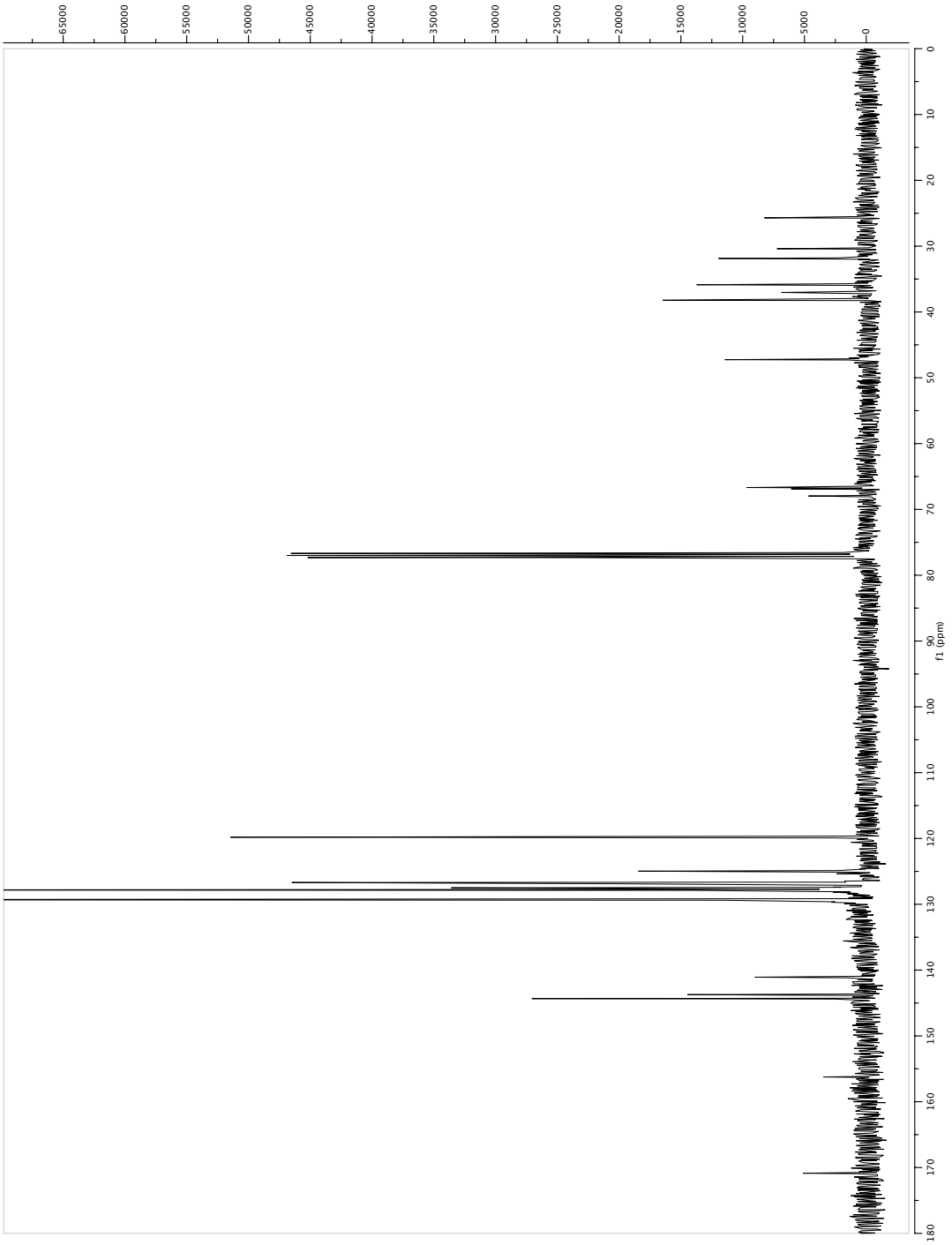
Spectrum A.7: ^{13}C spectrum of compound **53**.



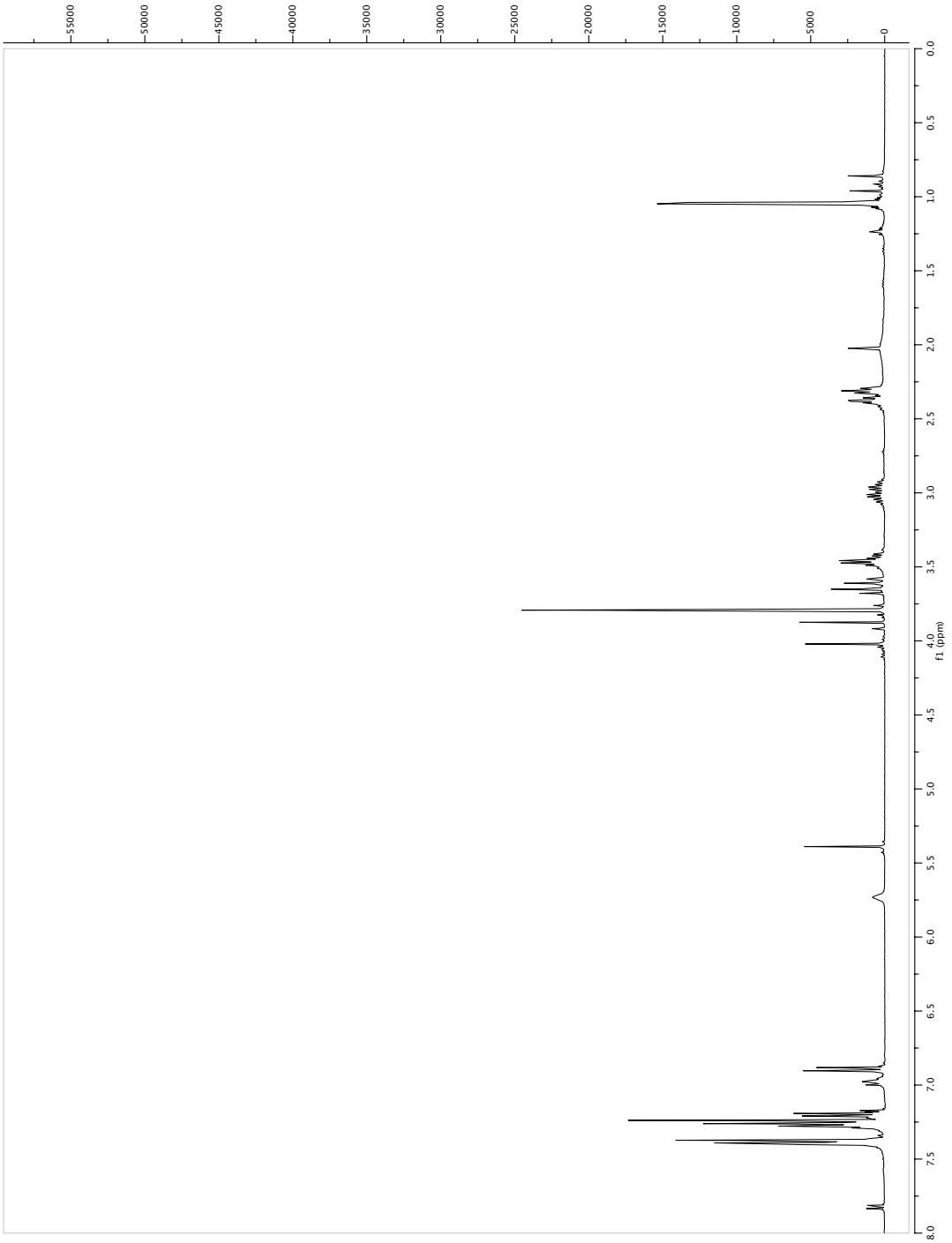
Spectrum A.8: ^{1}H spectrum of compound **55**.



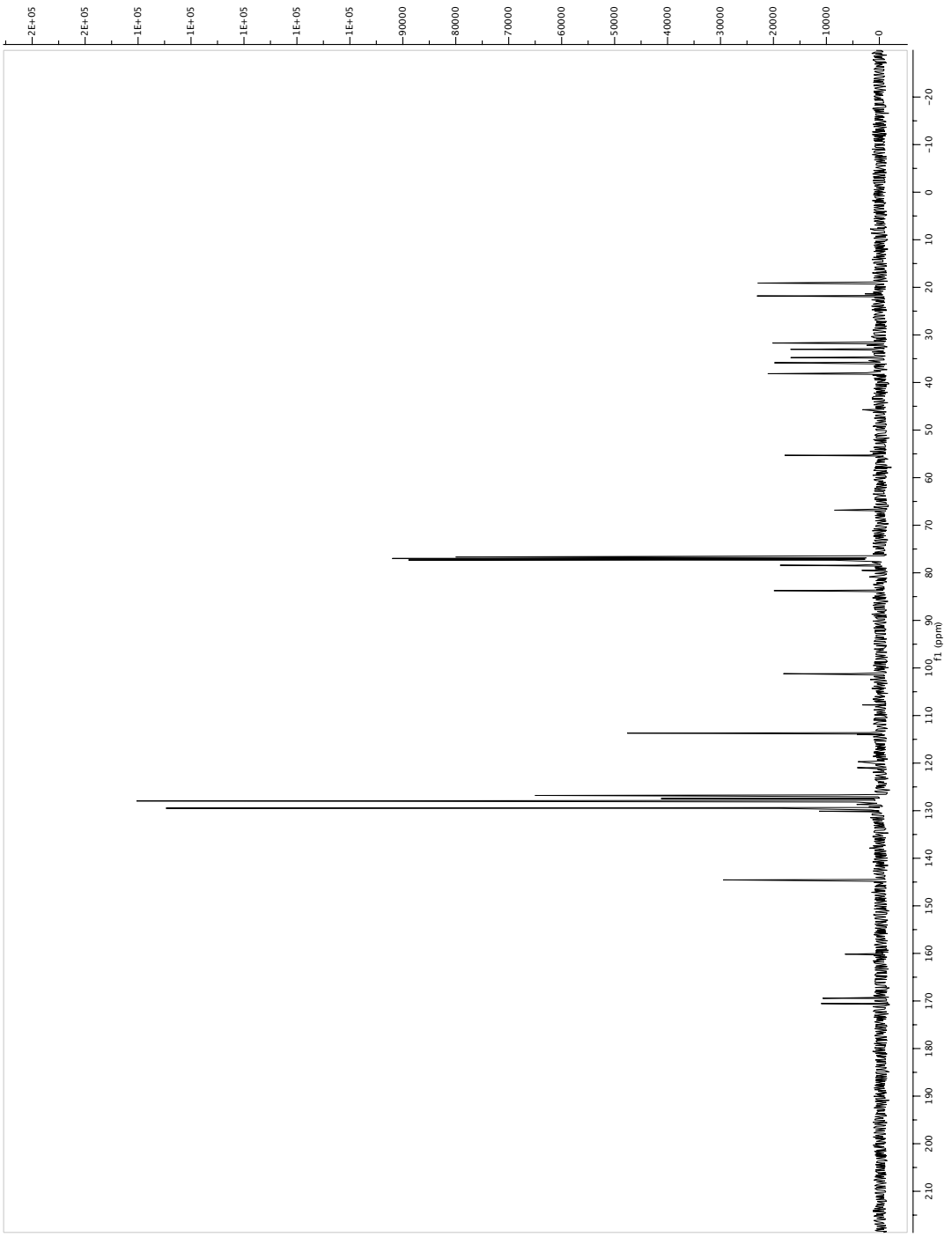
Spectrum A.9: ^{1}H spectrum of compound **56**.



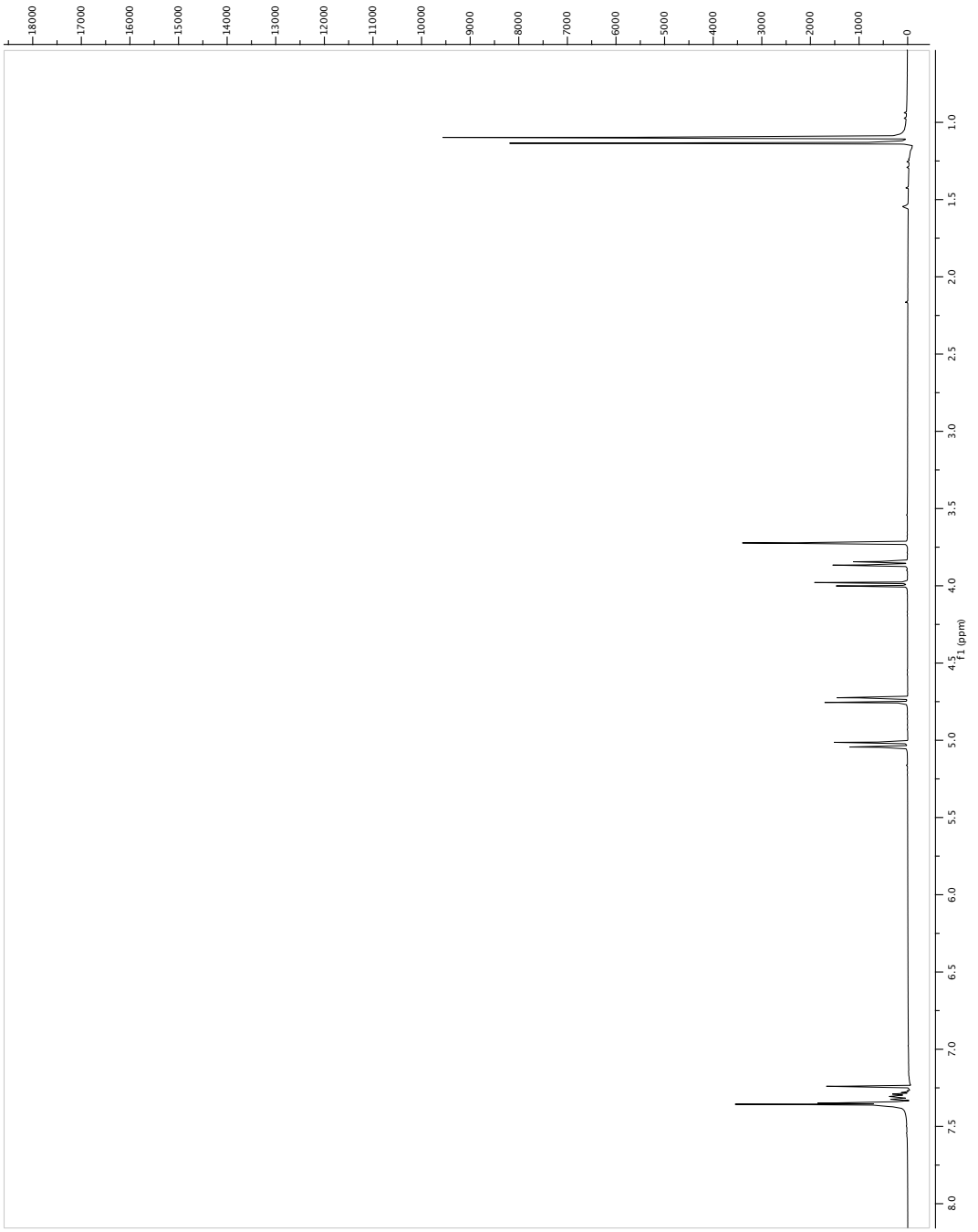
Spectrum A.10: ^{13}C spectrum of compound **56**.



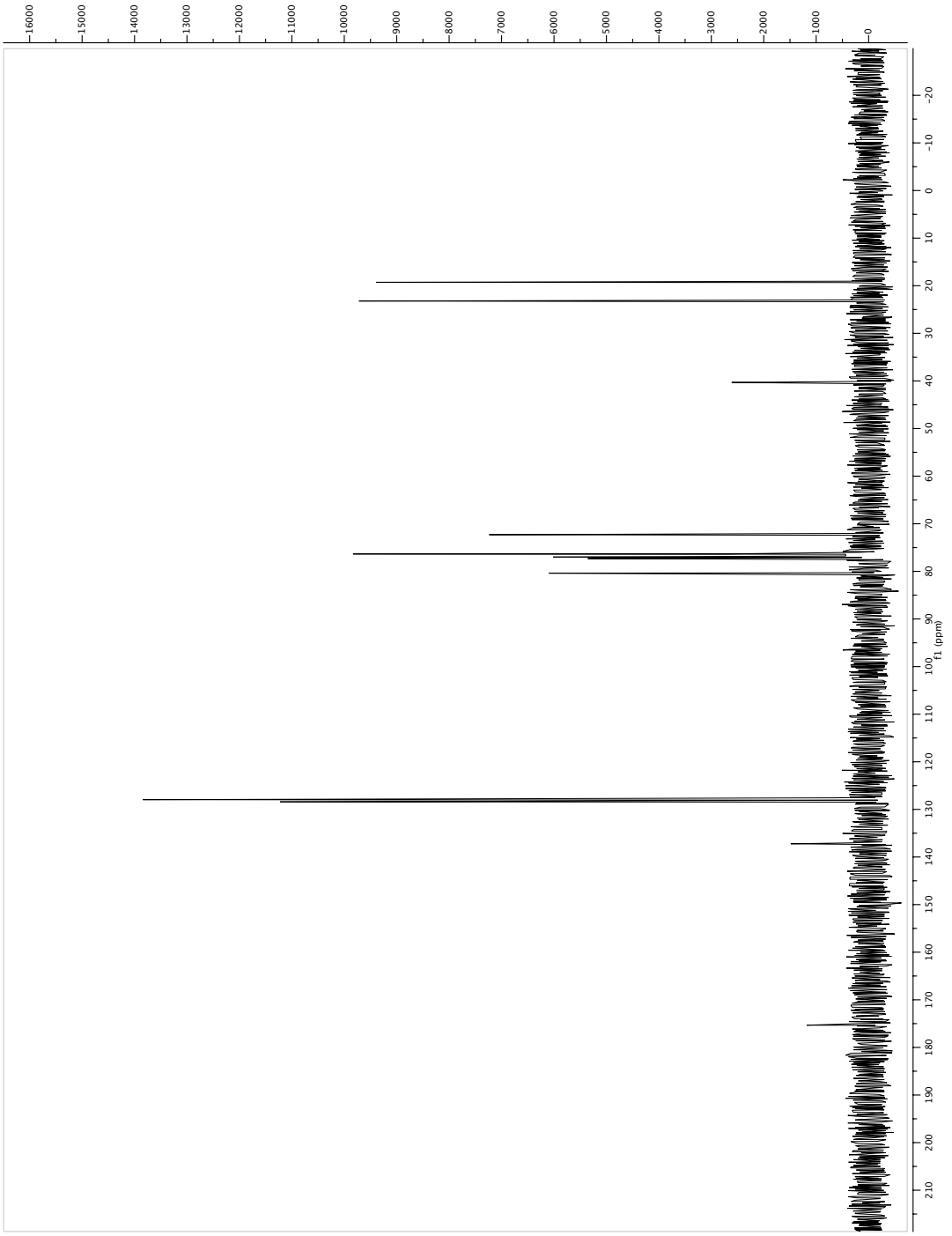
Spectrum A.11: ^{1}H spectrum of compound **58**.



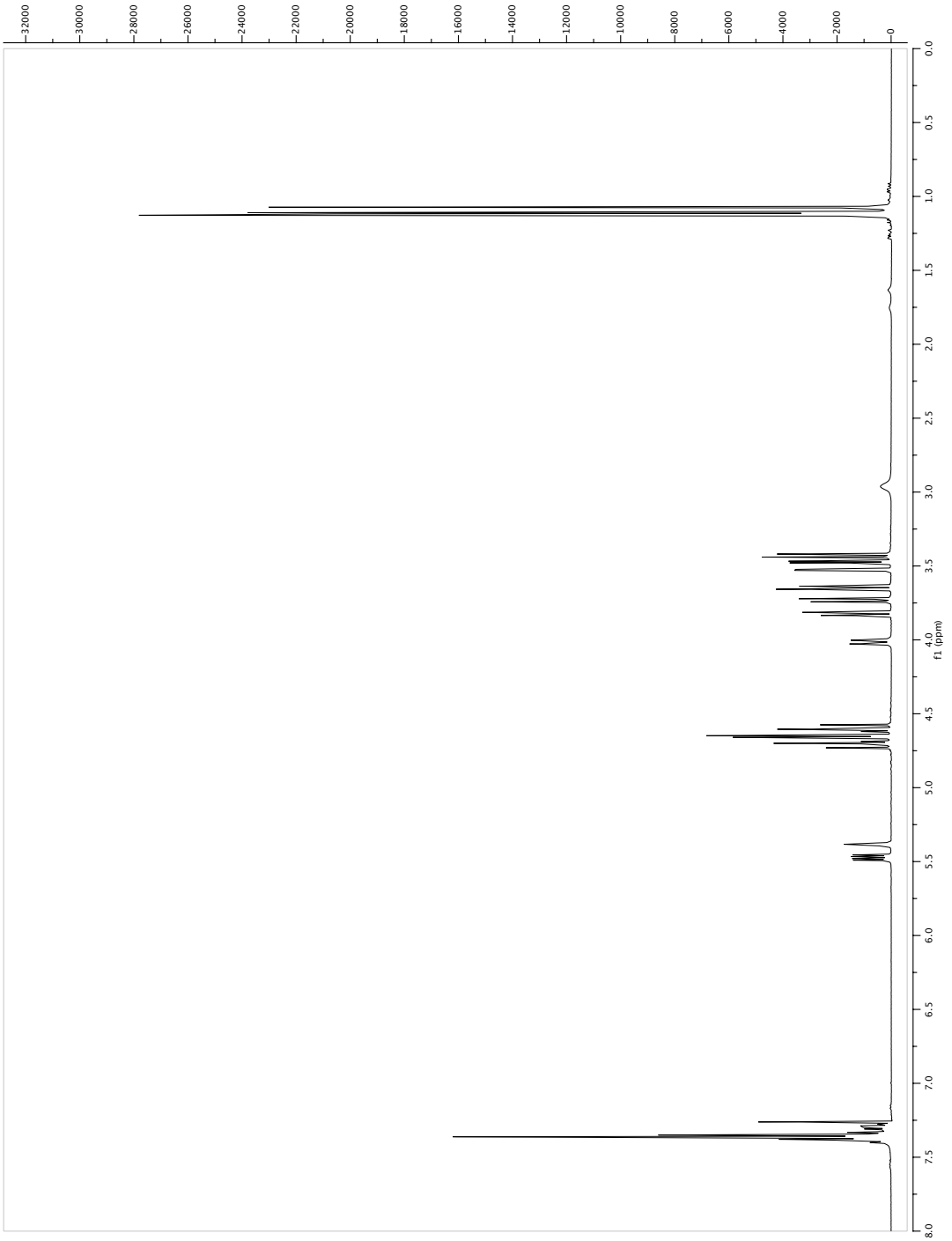
Spectrum A.12: ^{13}C spectrum of compound **58**.



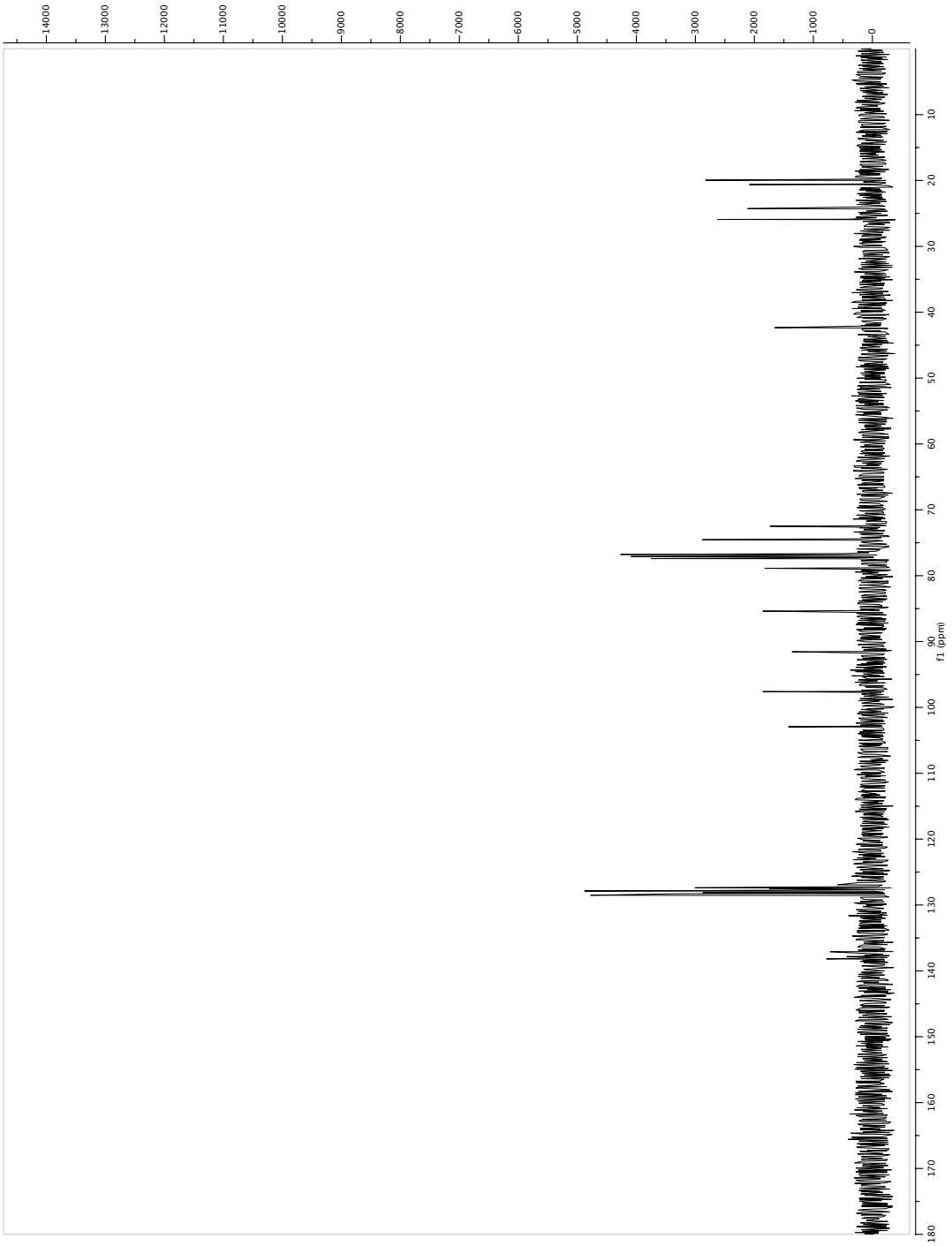
Spectrum A.13: ^{1}H spectrum of compound **59**.



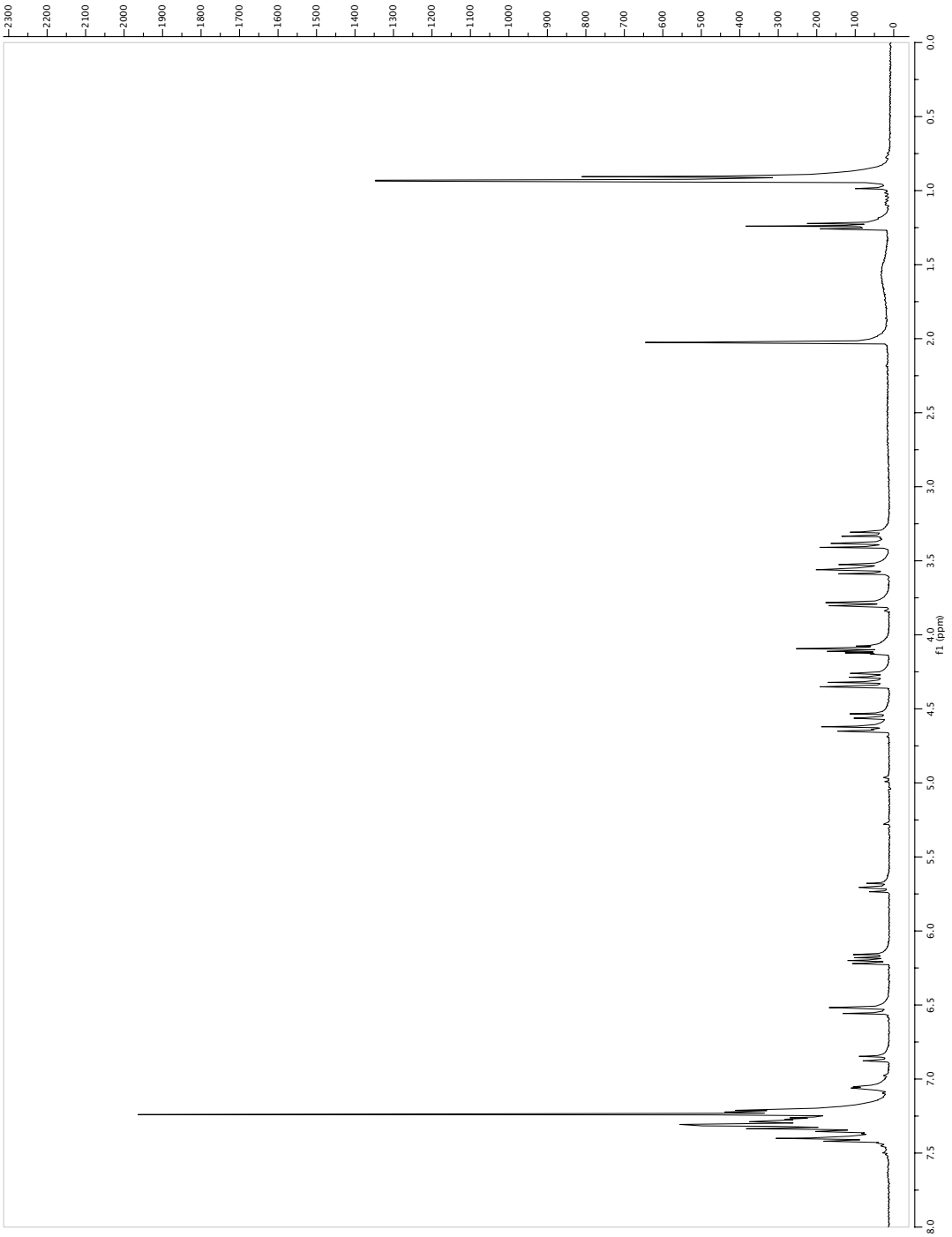
Spectrum A.14: ^{13}C spectrum of compound **59**.



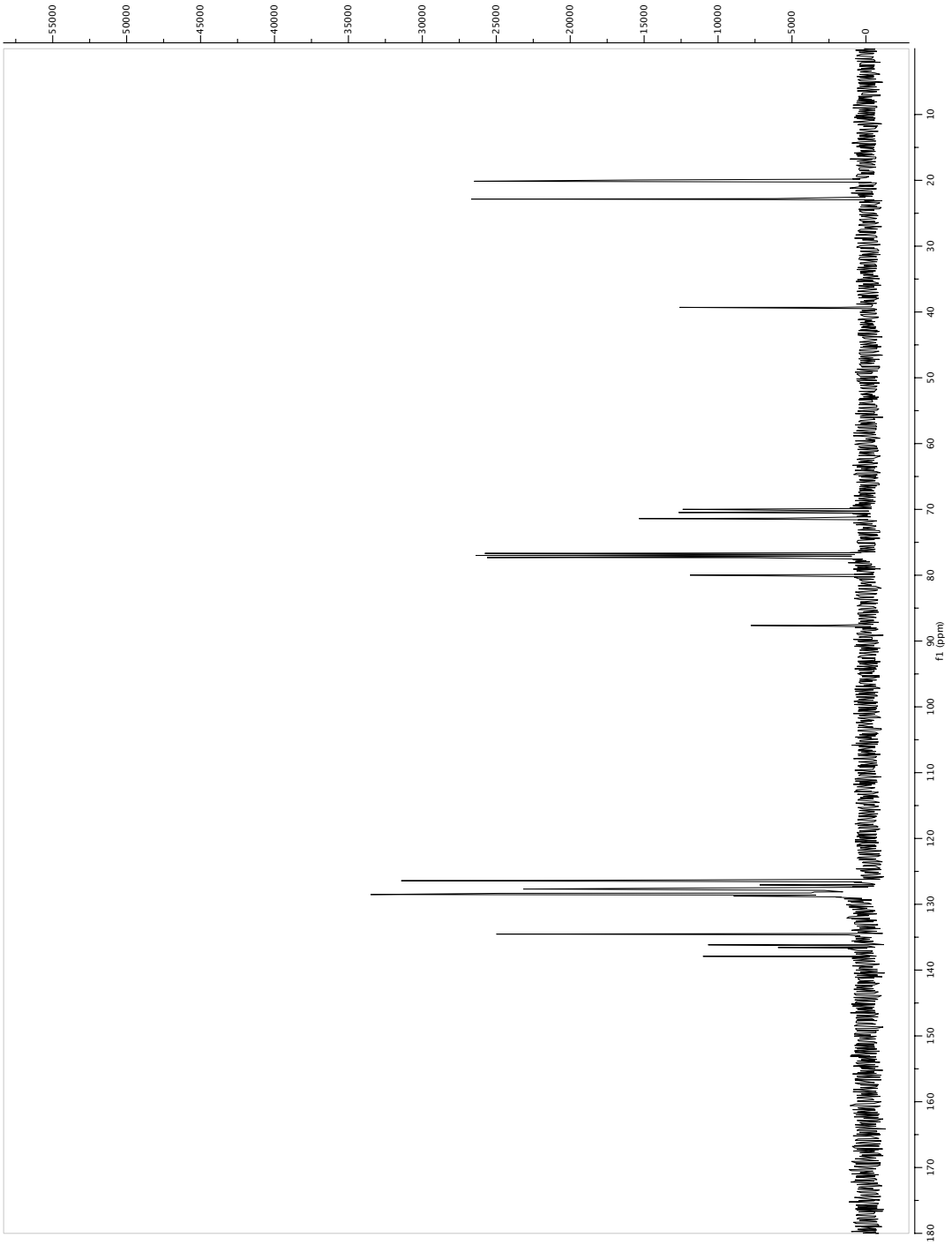
Spectrum A.15: ^{1}H spectrum of compound **60**.



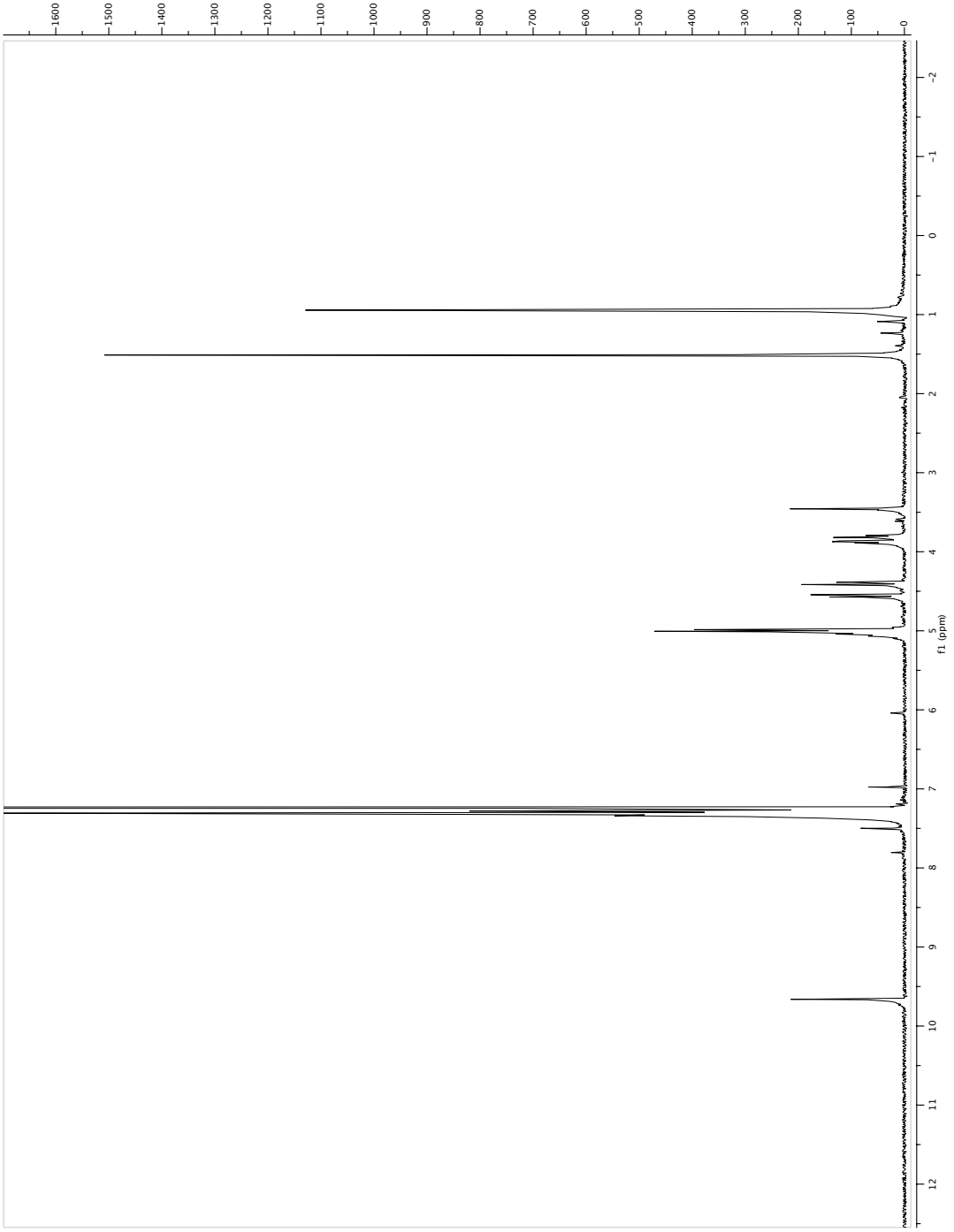
Spectrum A.16: ^{13}C spectrum of compound **60**.



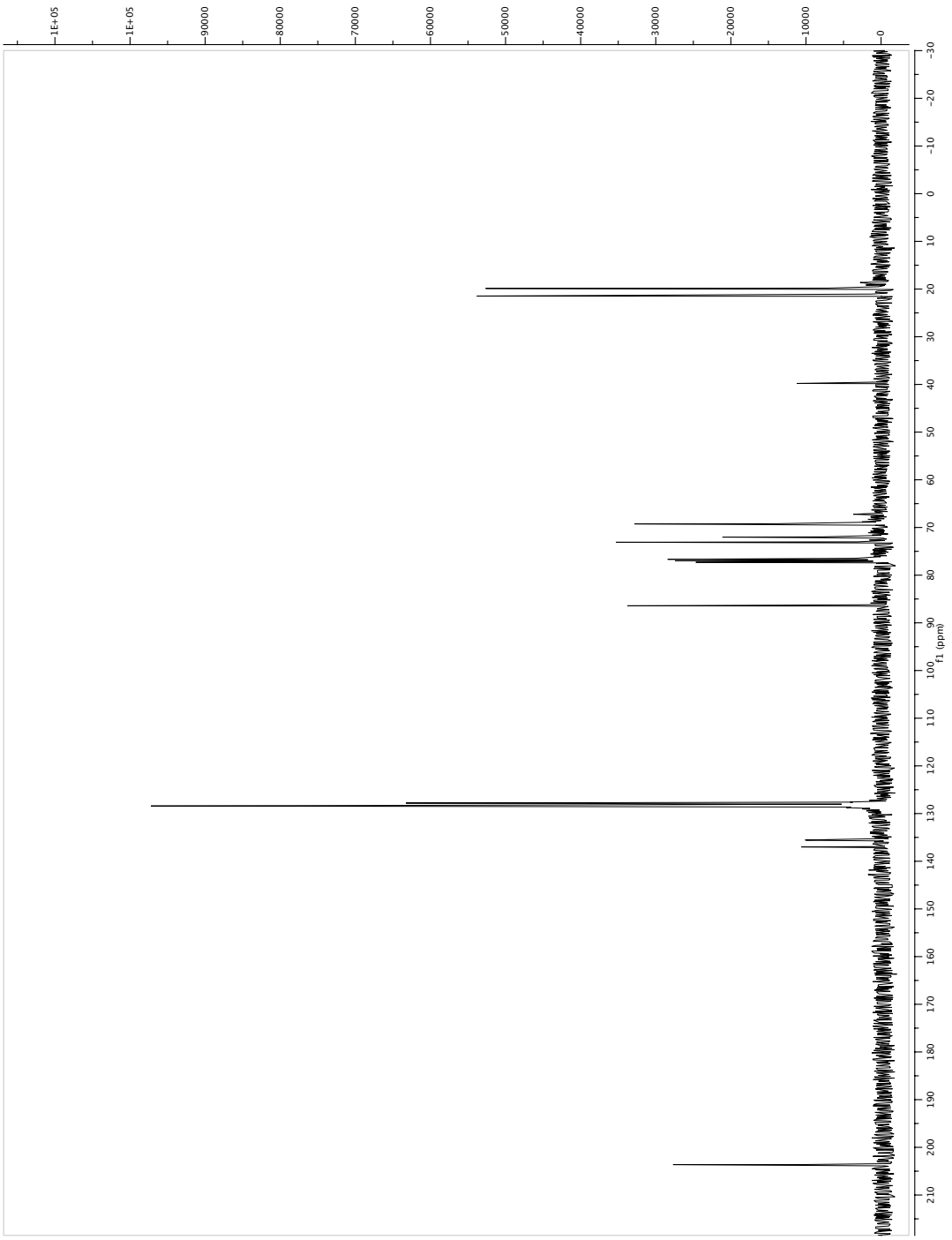
Spectrum A.17: ^{1}H spectrum of compound **61**.



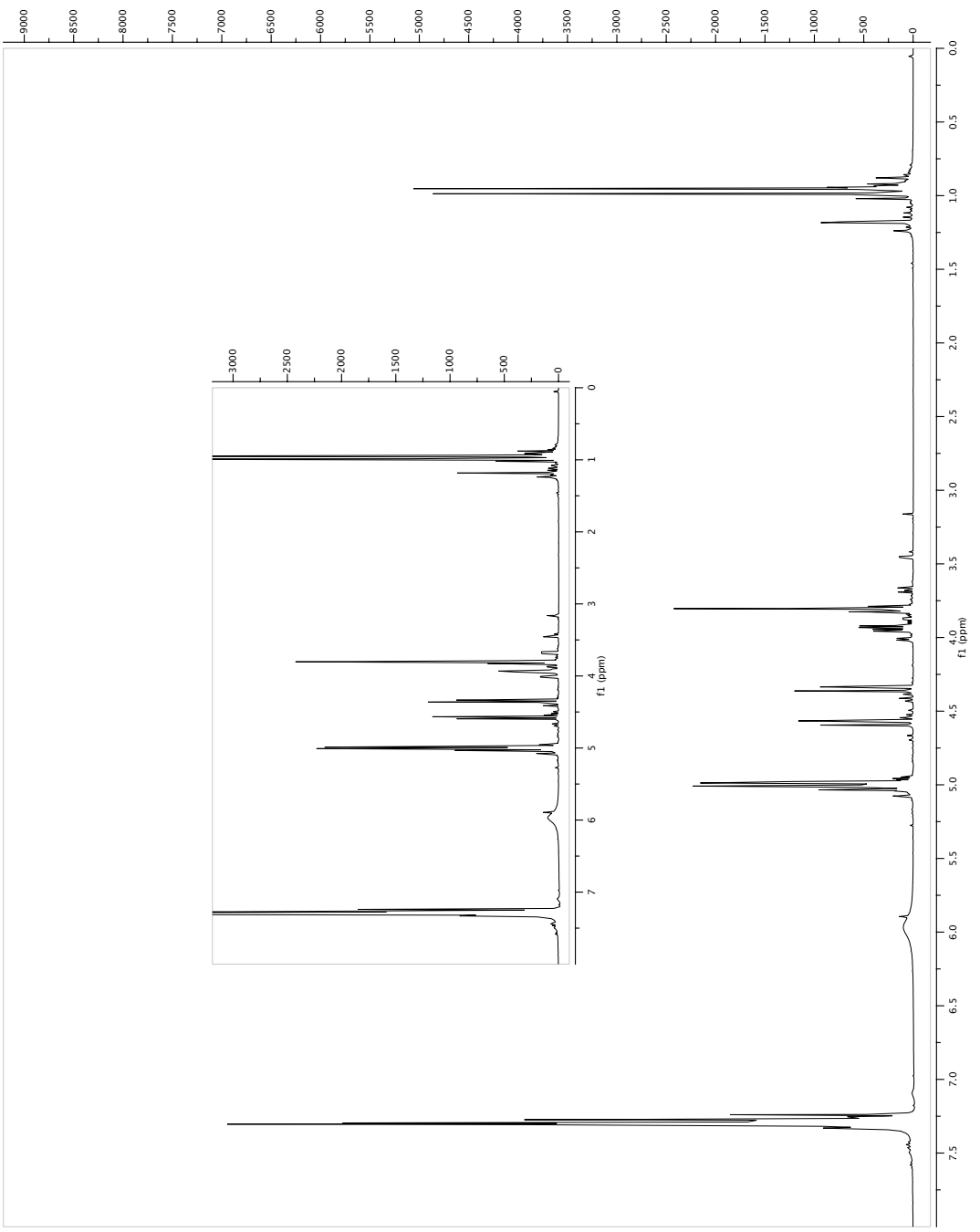
Spectrum A.18: ^{13}C spectrum of compound **61**.



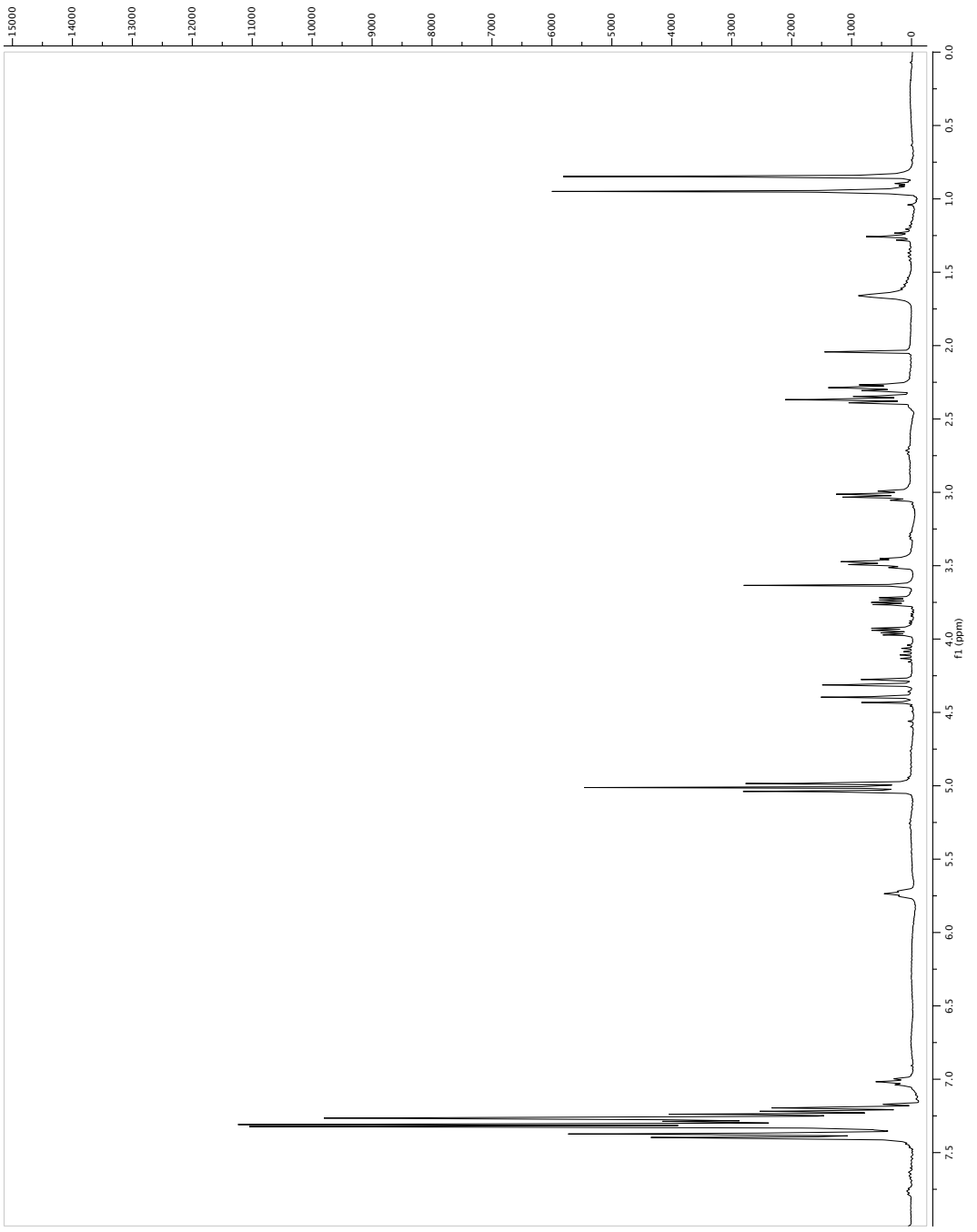
Spectrum A.19: ^{1}H spectrum of compound **62**.



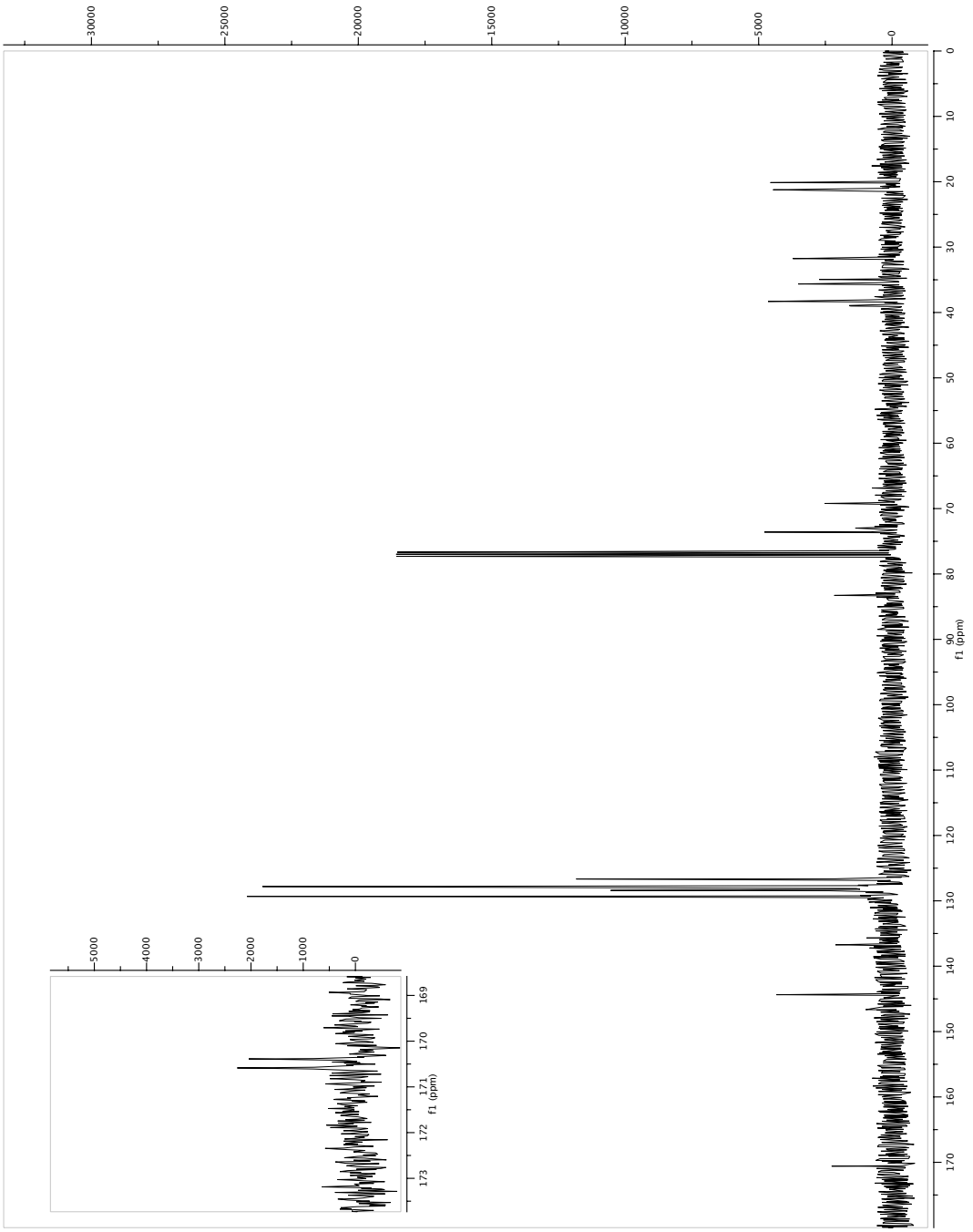
Spectrum A.20: ^{13}C spectrum of compound **62**.



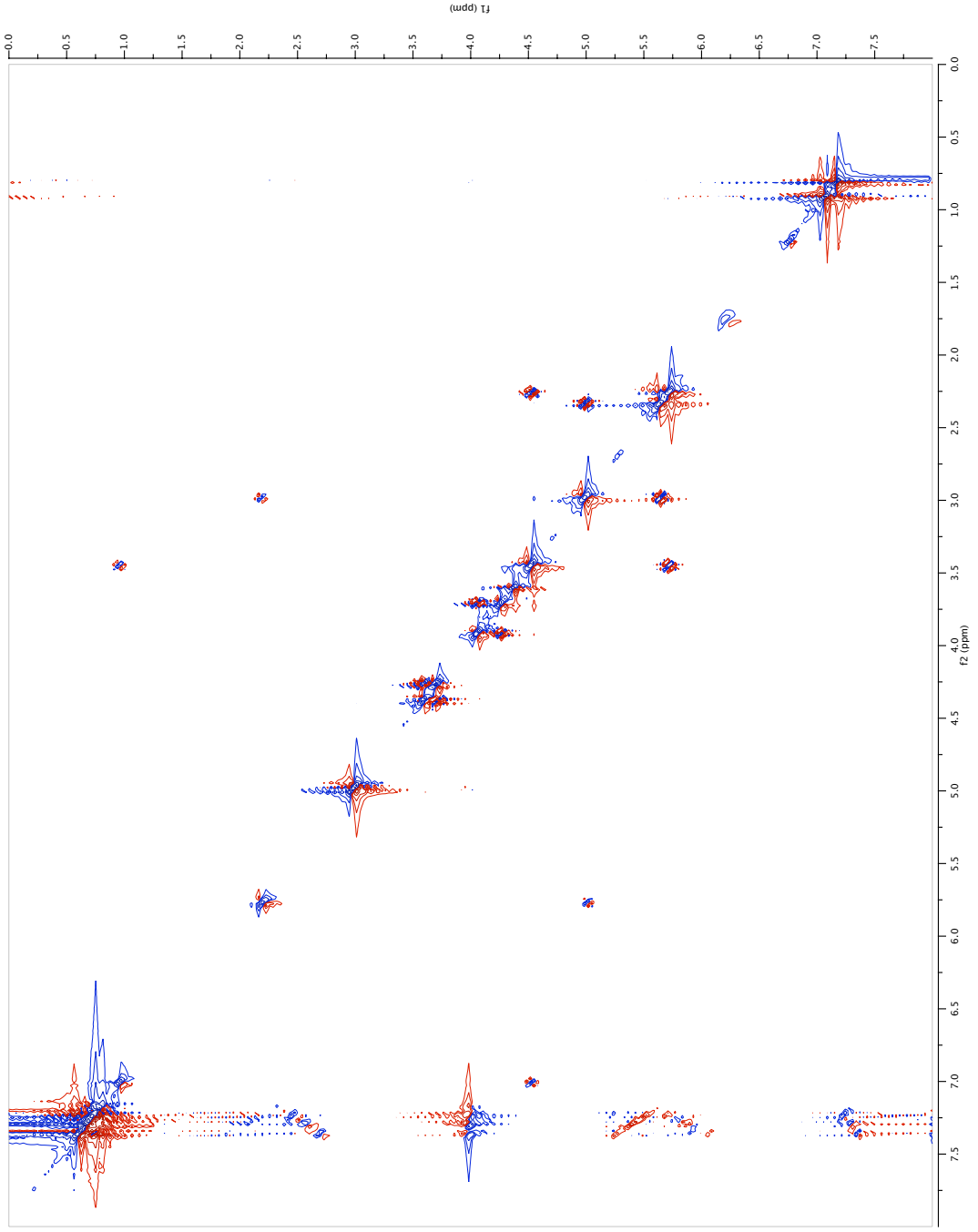
Spectrum A.21: ^{1}H spectrum of compound **63**.



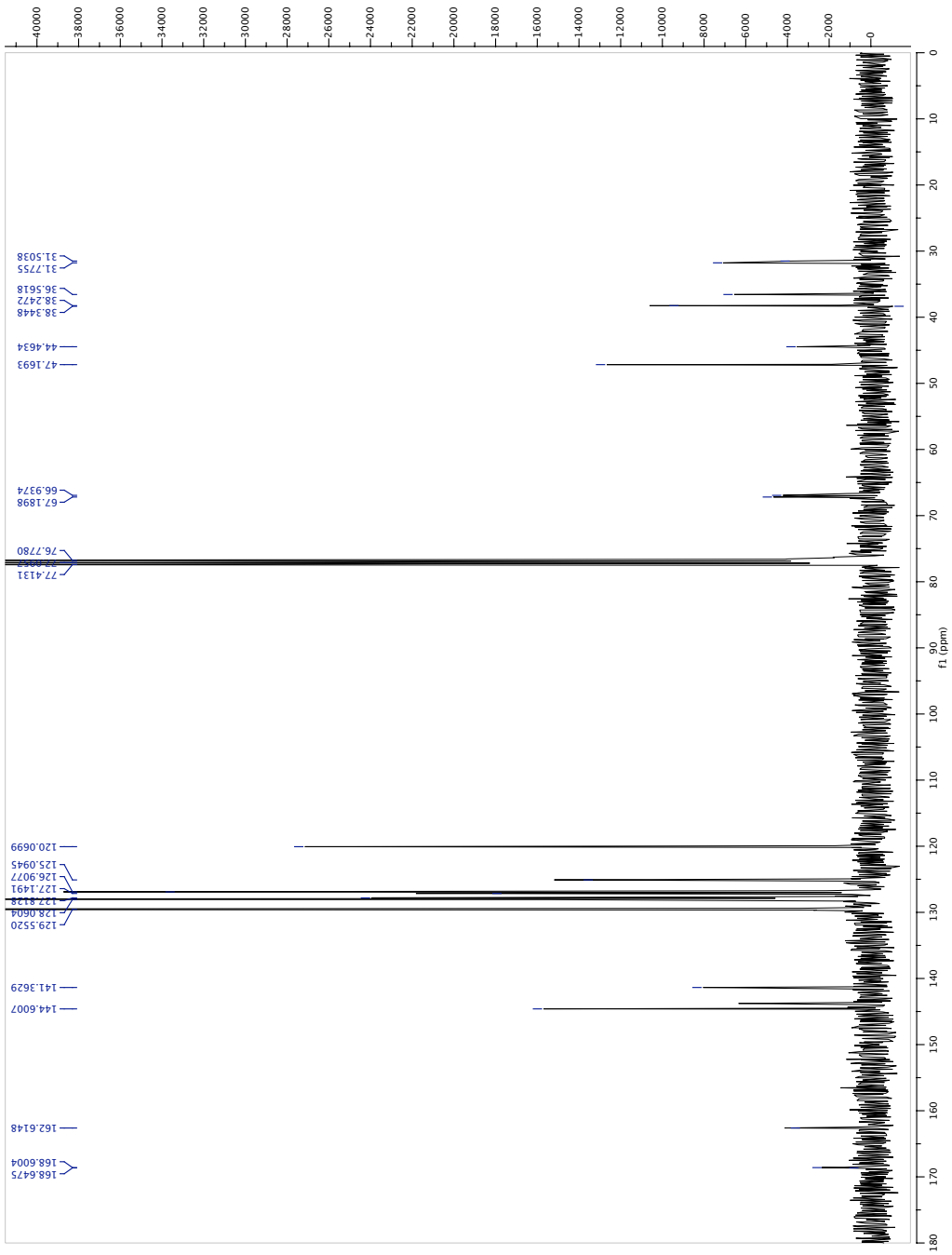
Spectrum A.22: ^{1}H spectrum of compound **64**.



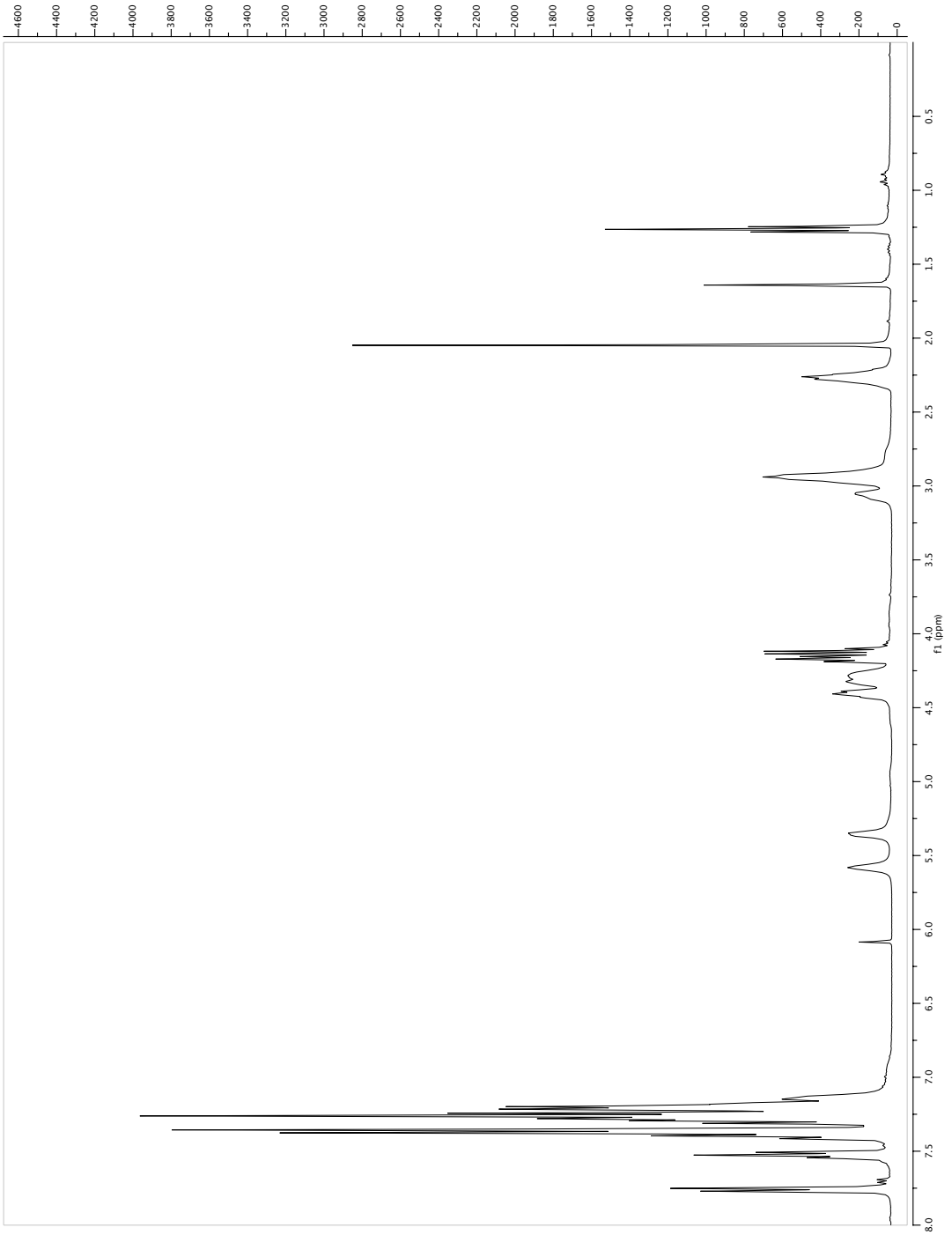
Spectrum A.23: ^{13}C spectrum of compound **64**.



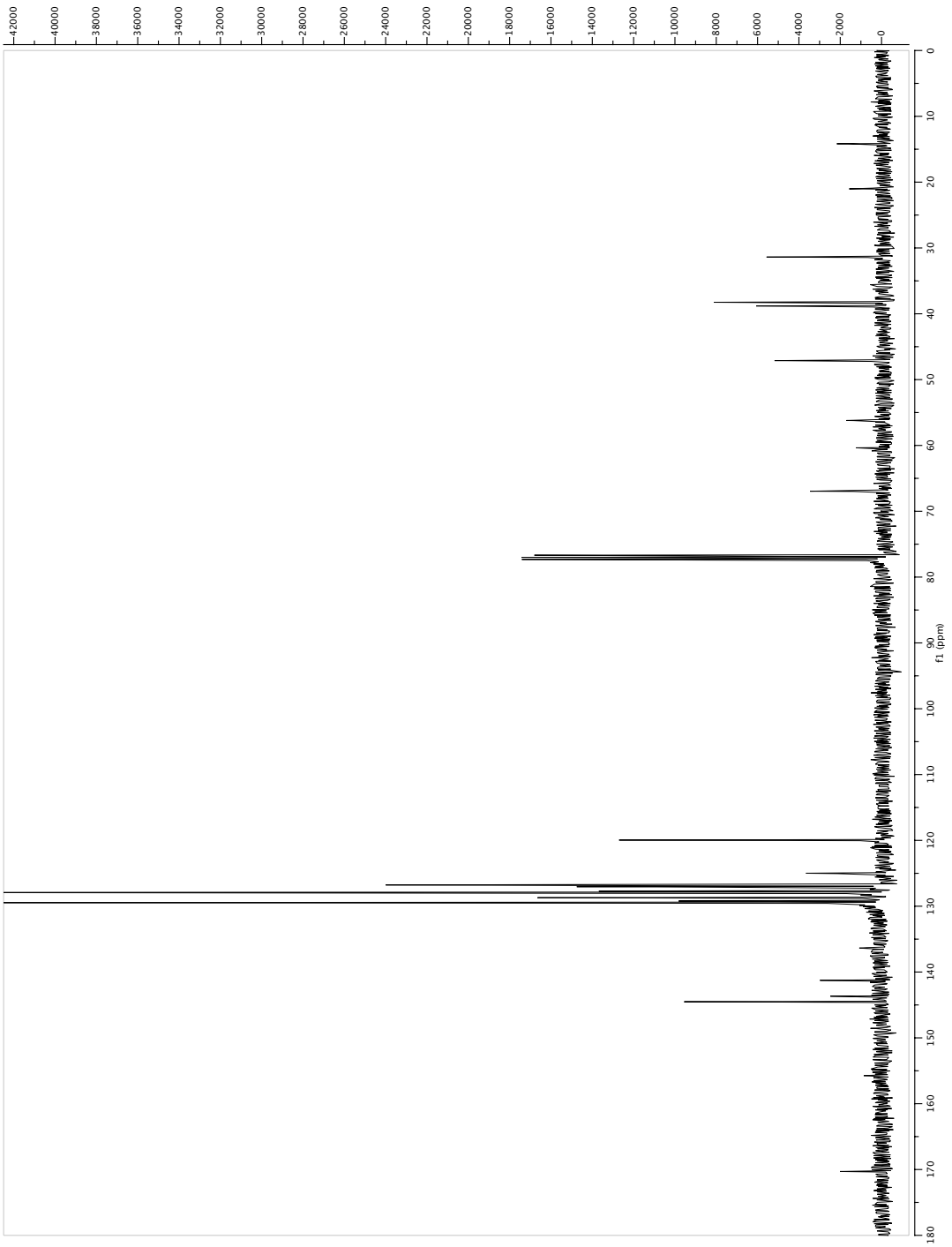
Spectrum A.24: ^{1}H gCOSY spectrum of **64**



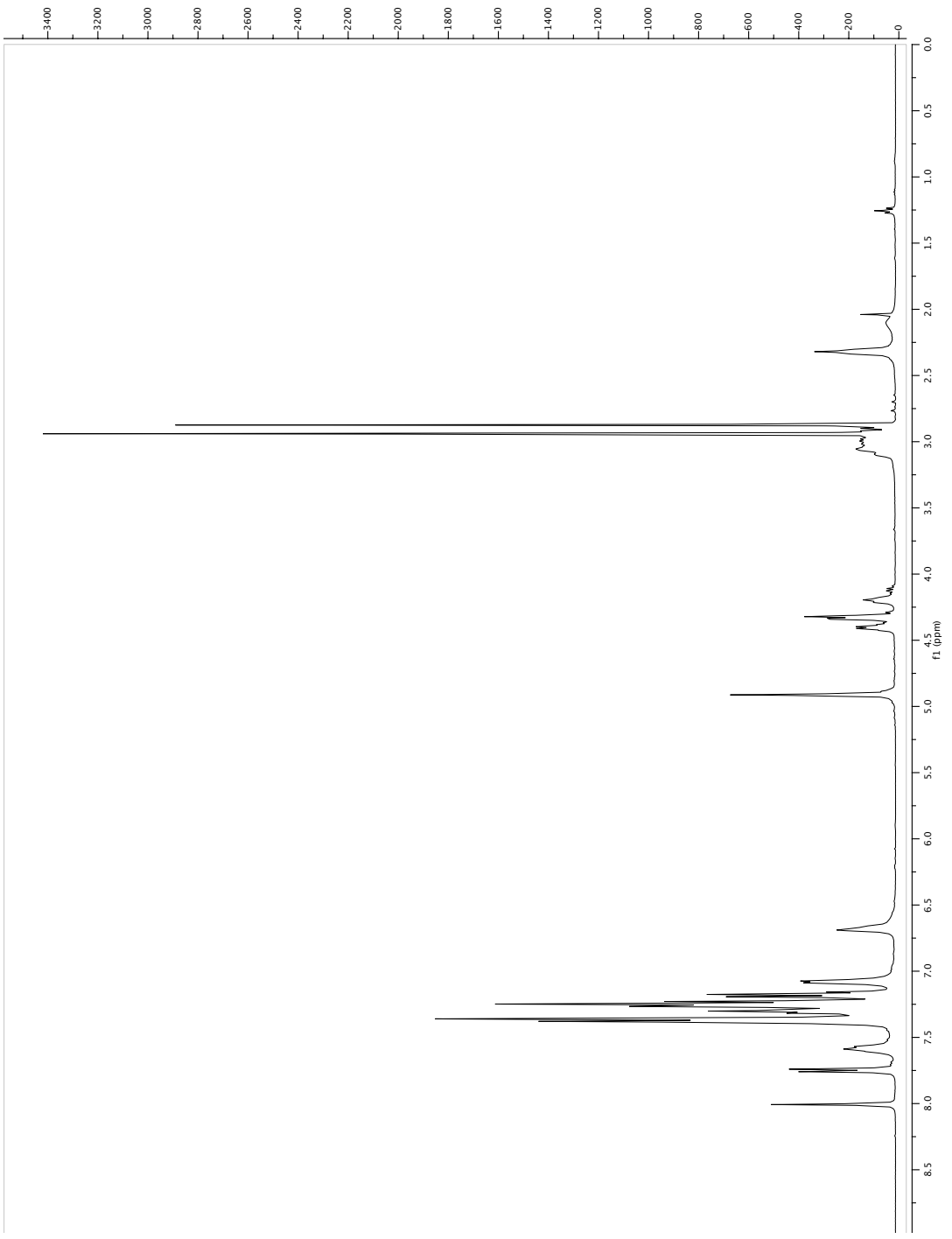
Spectrum A.25: ^{13}C spectrum of compound **66a**.



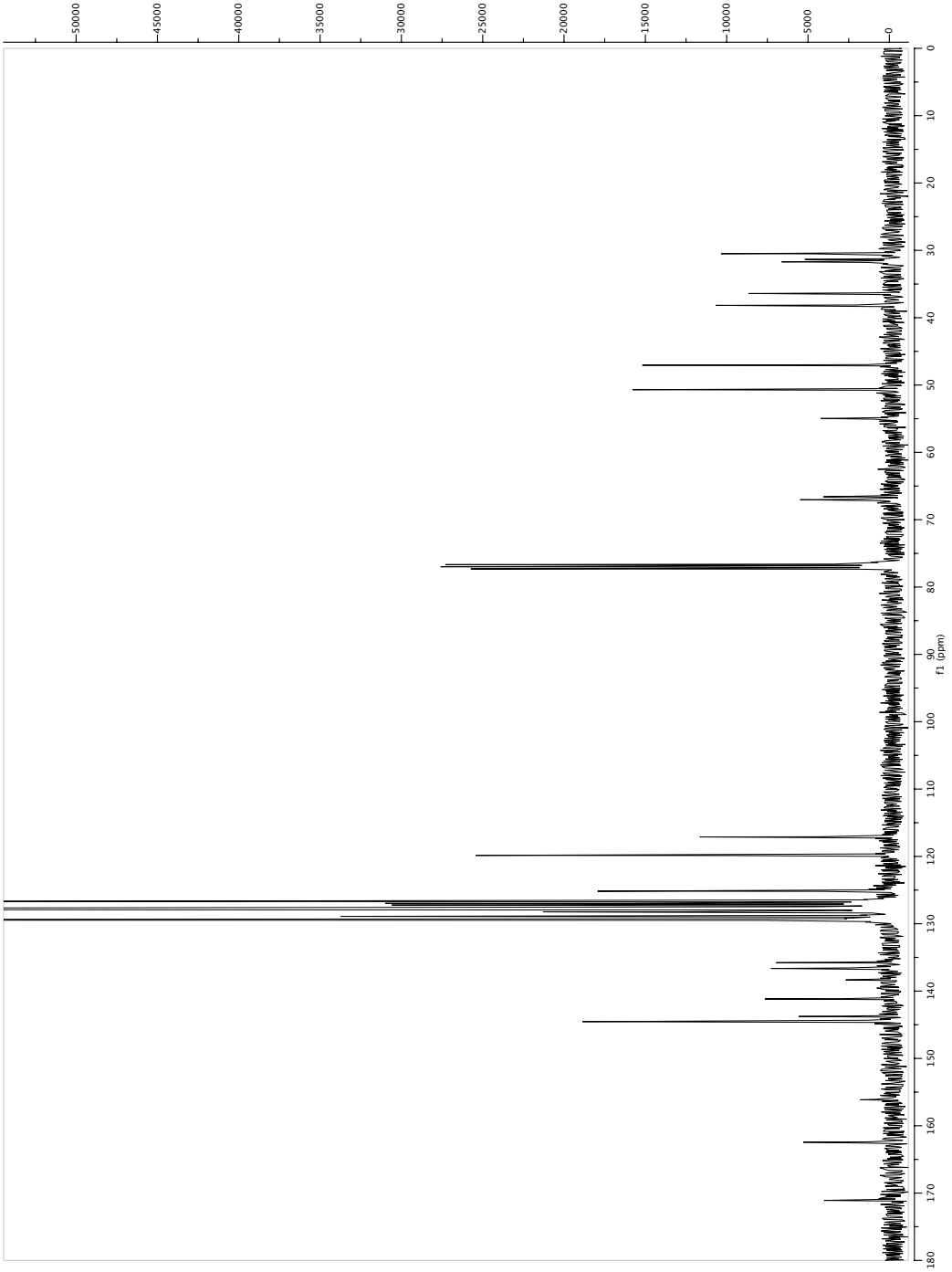
Spectrum A.26: ^{1}H spectrum of compound **66b**.



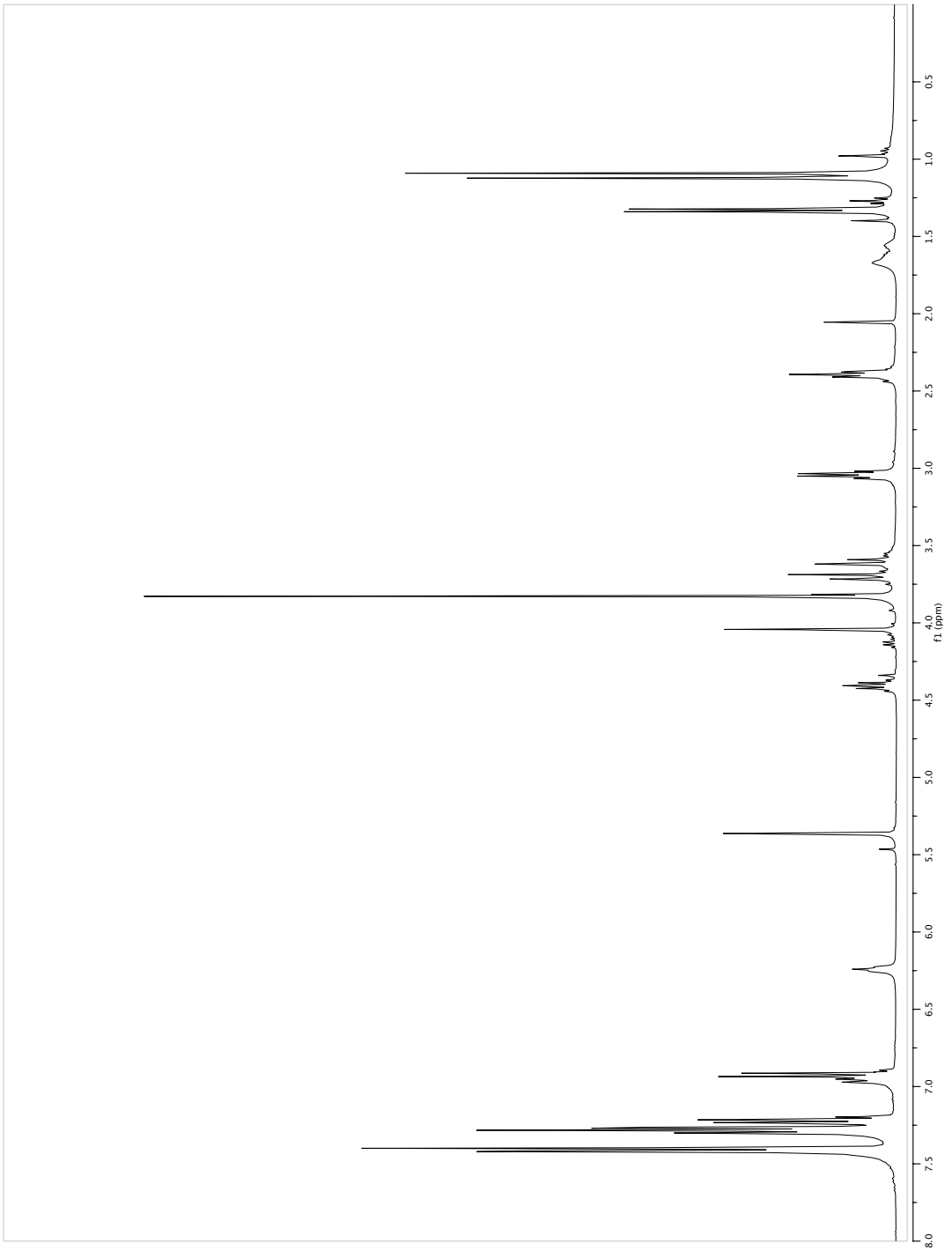
Spectrum A.27: ^{13}C spectrum of compound **66b**.



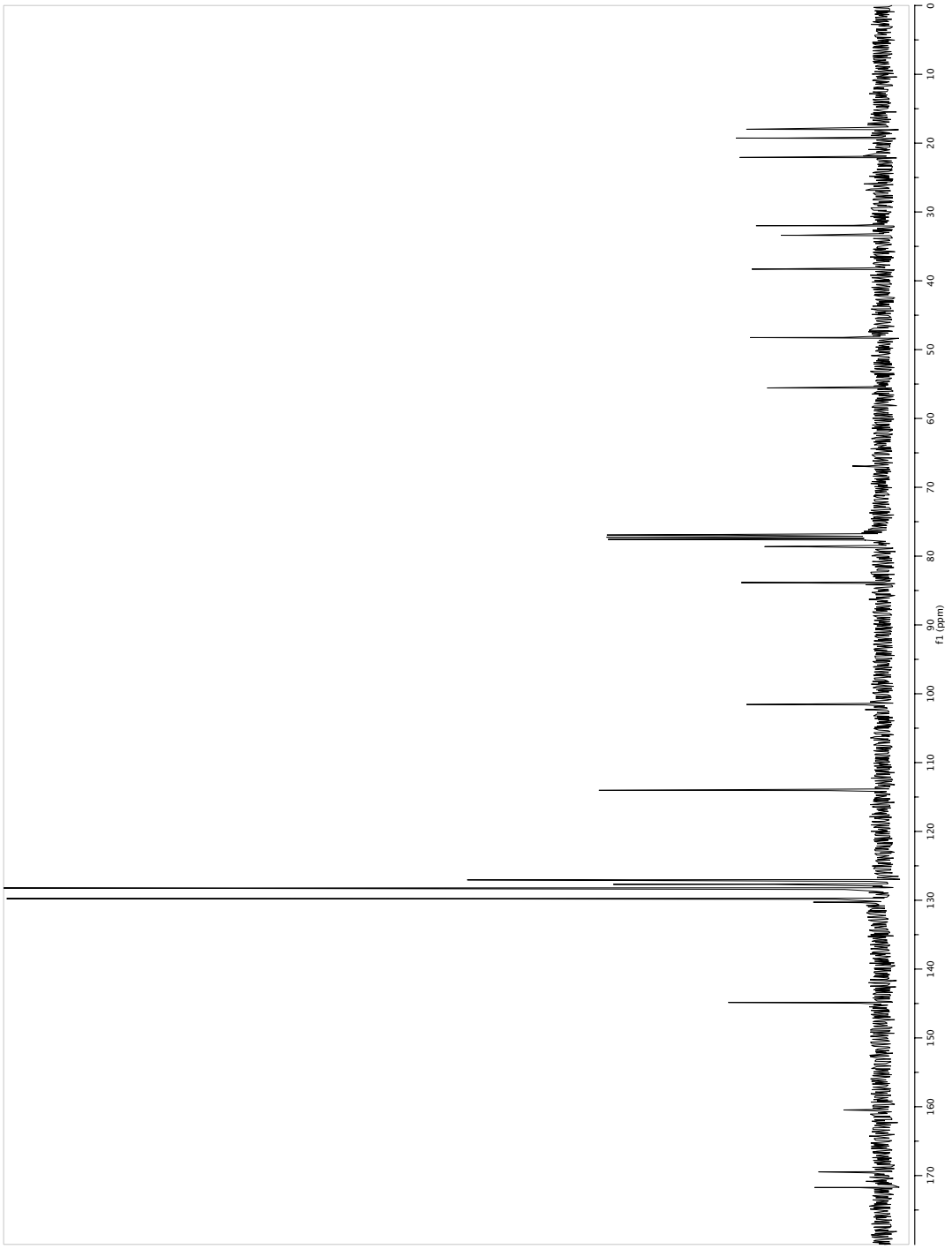
Spectrum A.28: ^{1}H spectrum of compound **66c**.



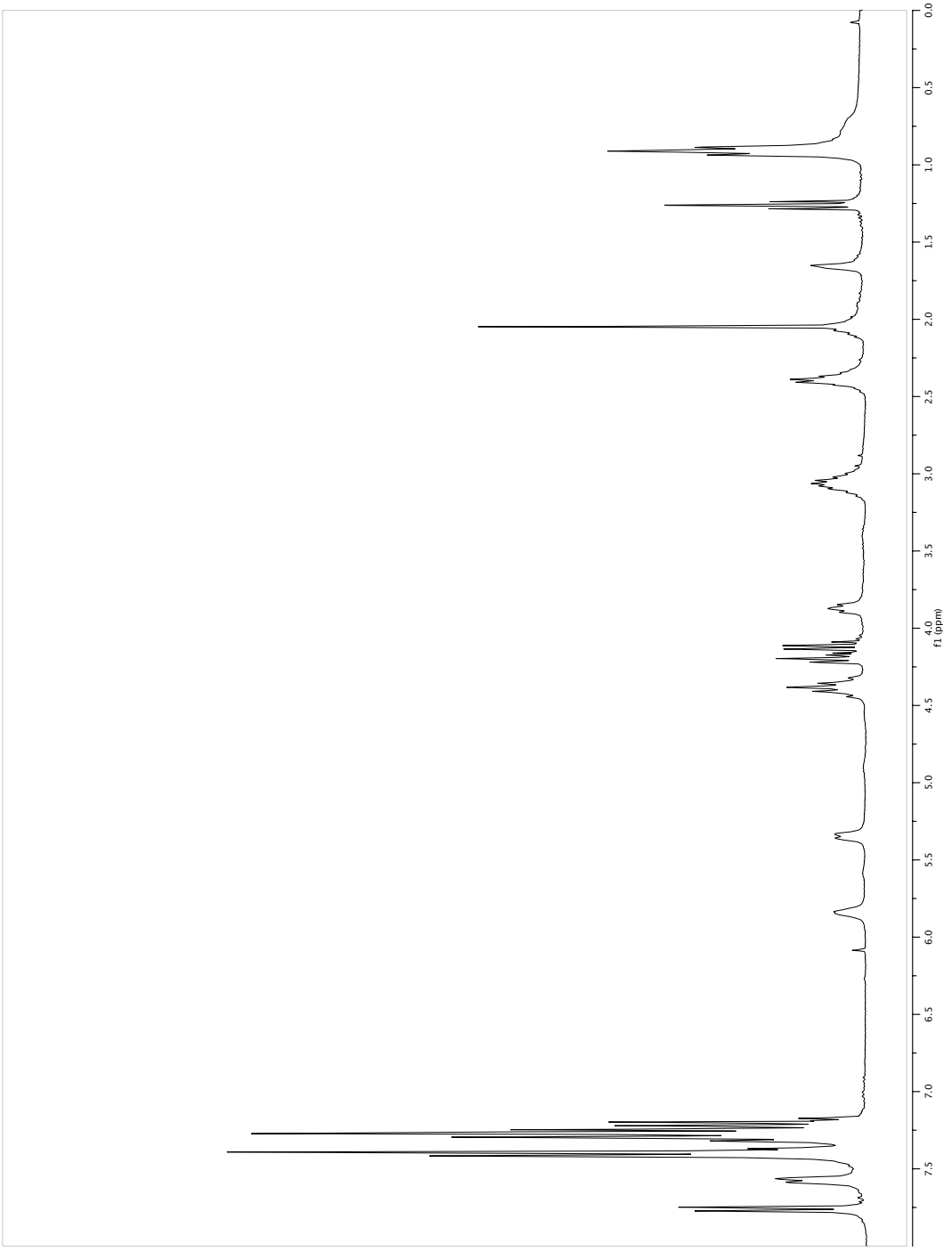
Spectrum A.29: ^{13}C spectrum of compound **66c**.



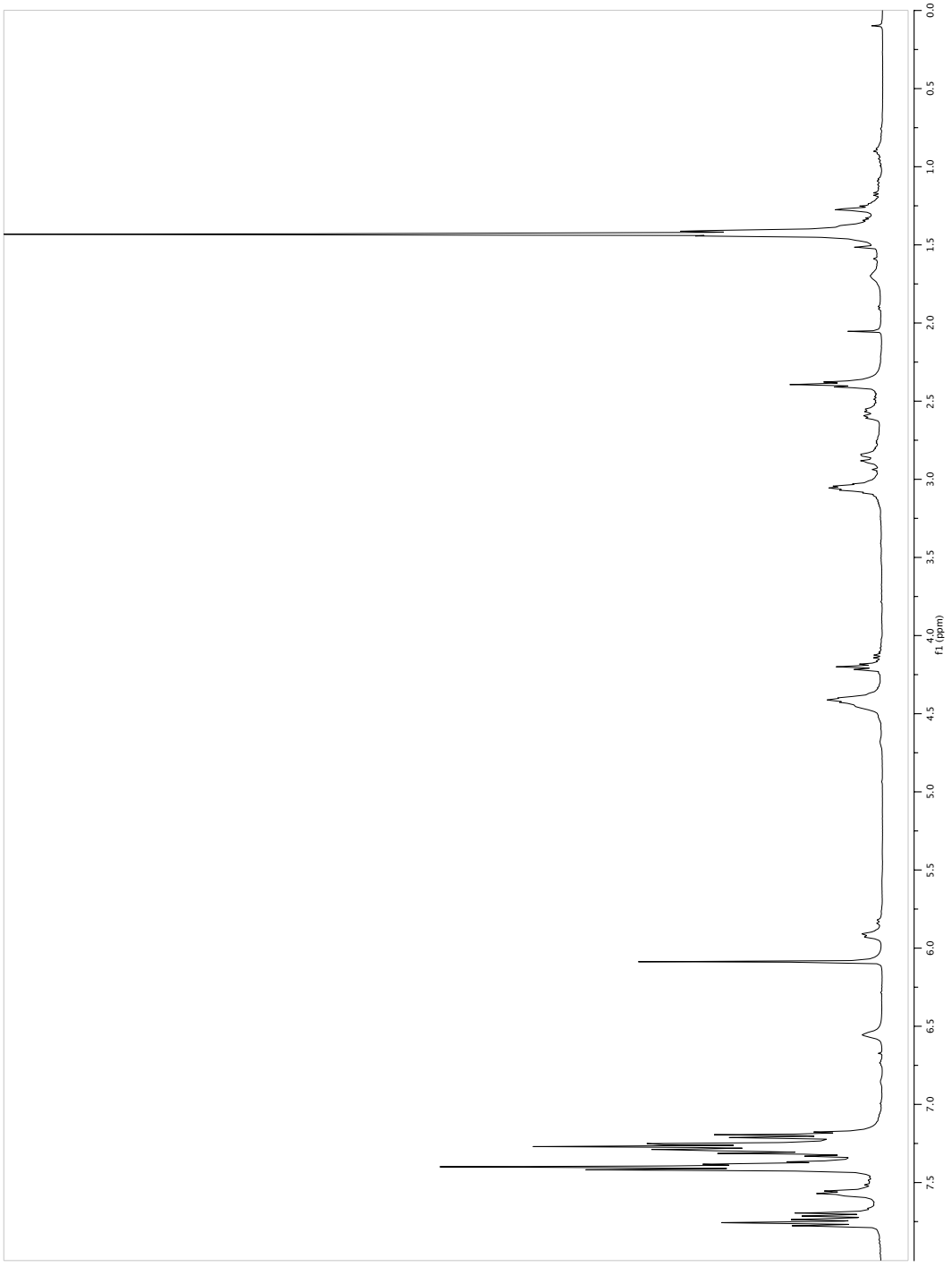
Spectrum A.30: ^{1}H spectrum of compound **66d**.



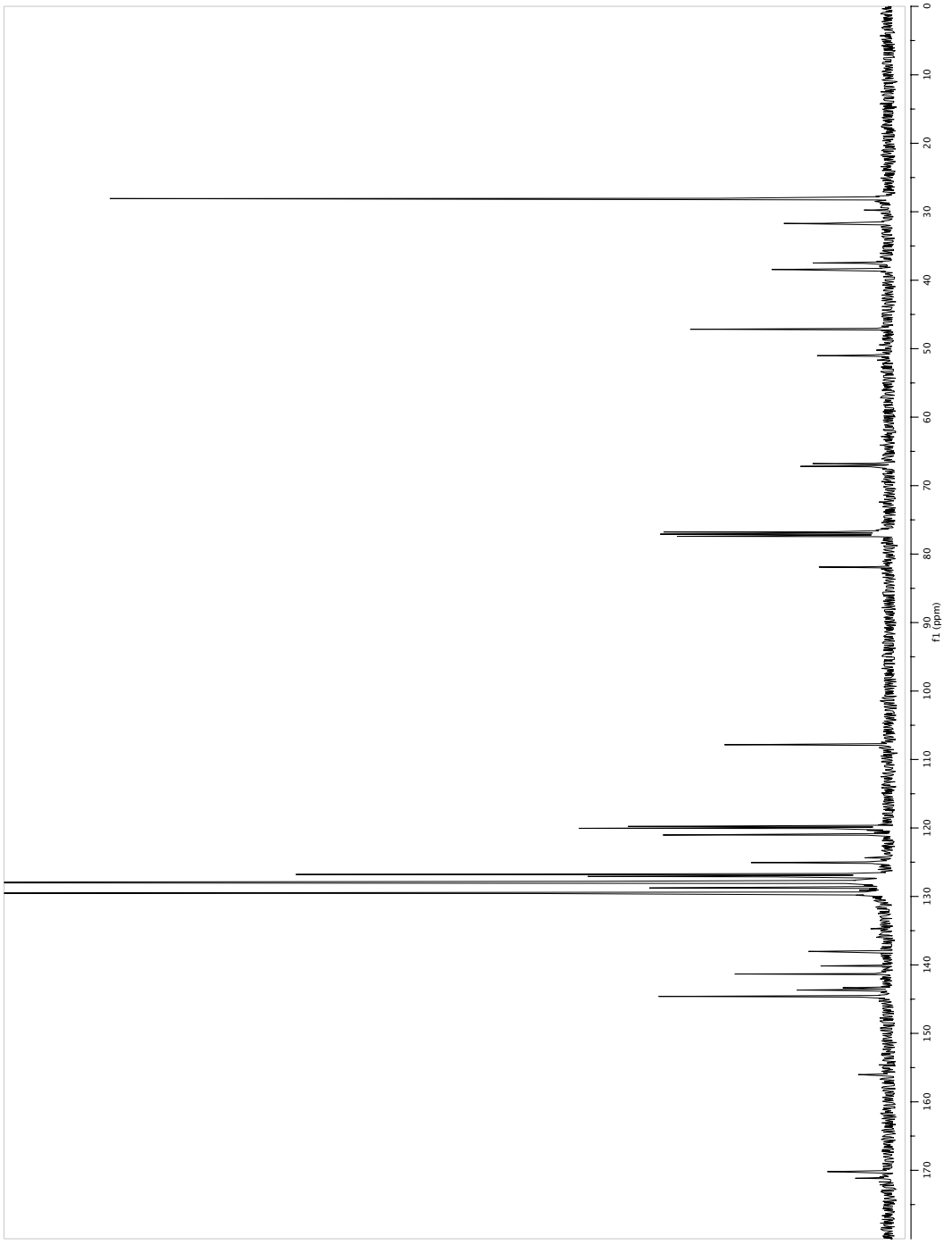
Spectrum A.31: ^{13}C spectrum of compound **66d**.



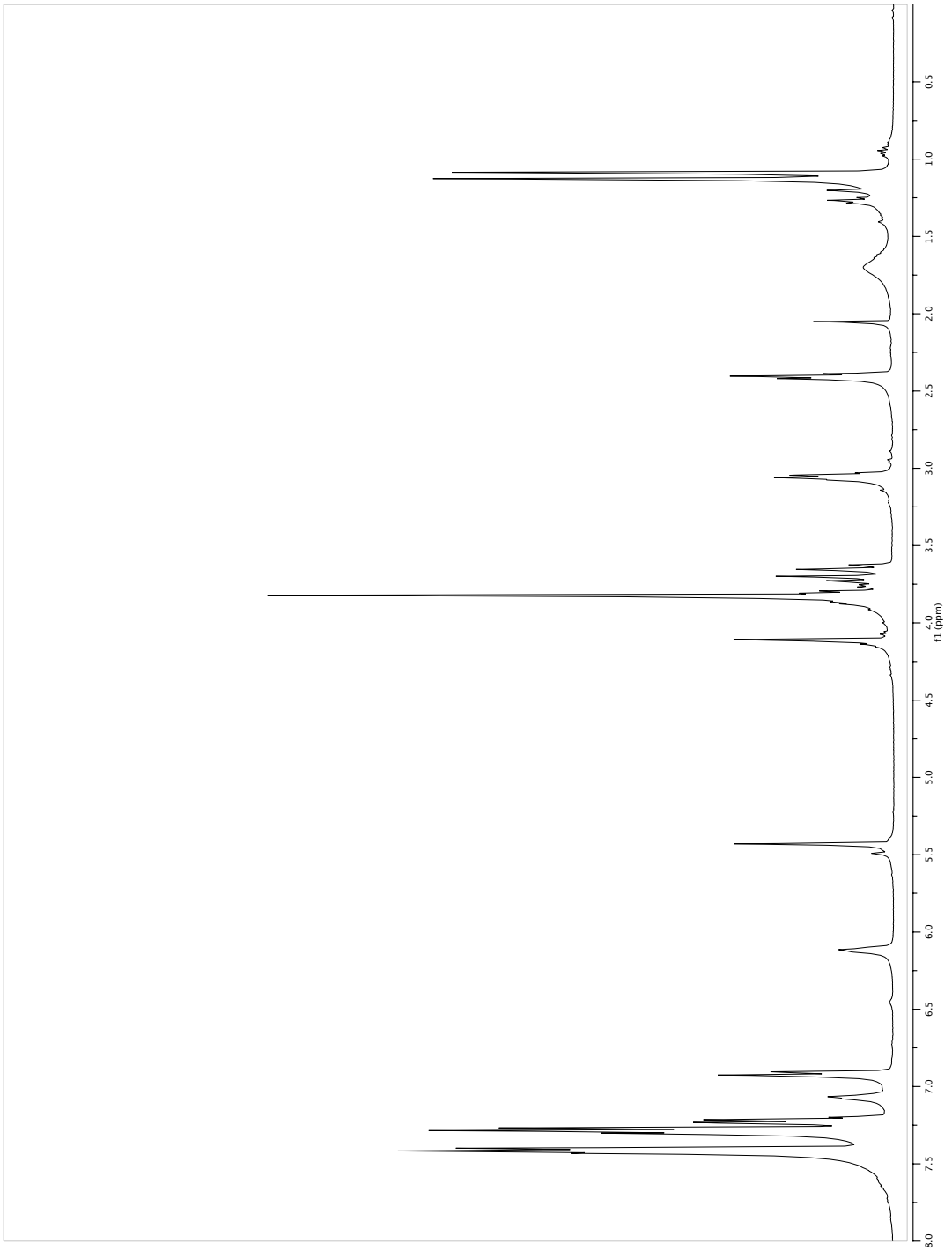
Spectrum A.32: ^{1}H spectrum of compound **66e**.



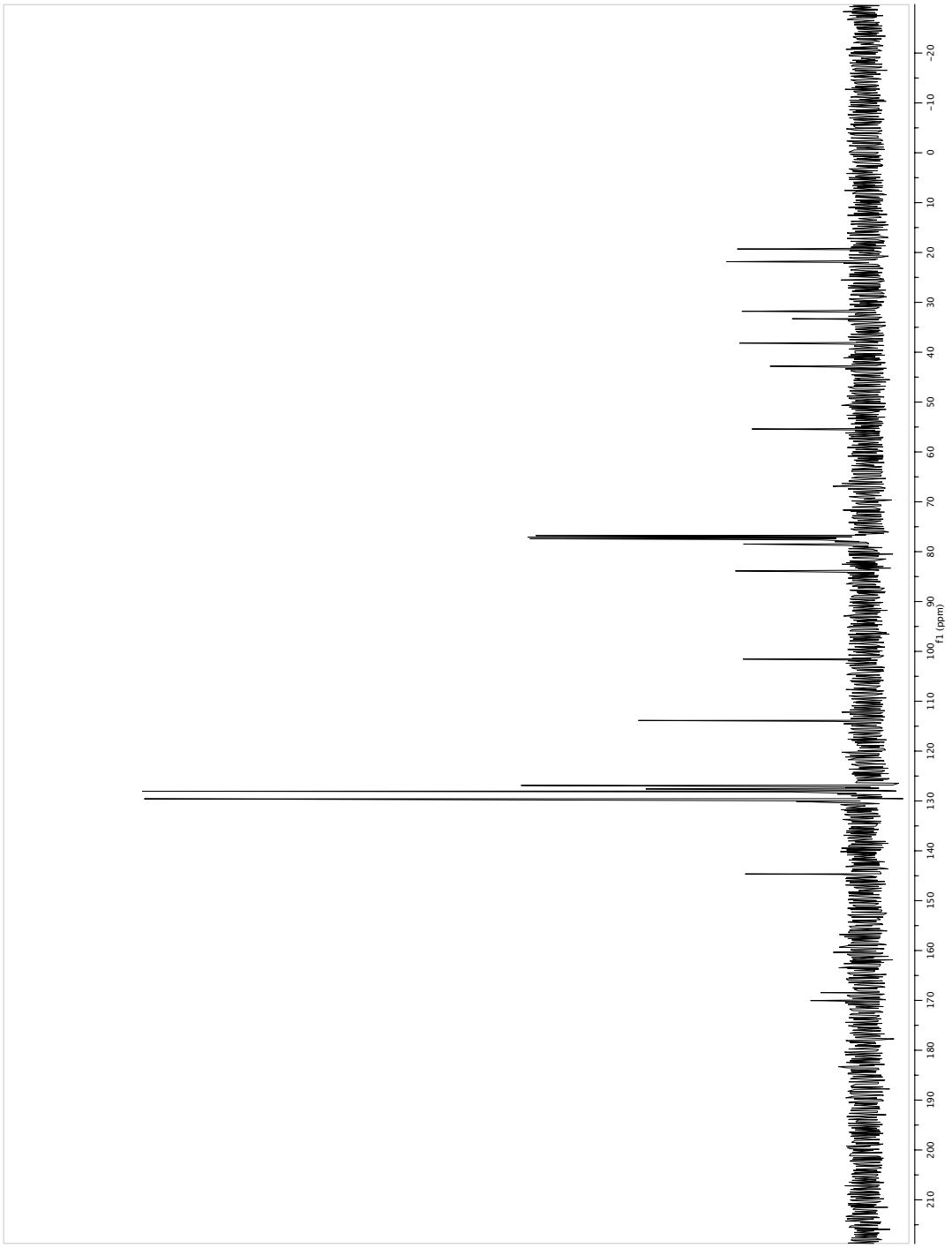
Spectrum A.33: ^{1}H spectrum of compound **66f**.



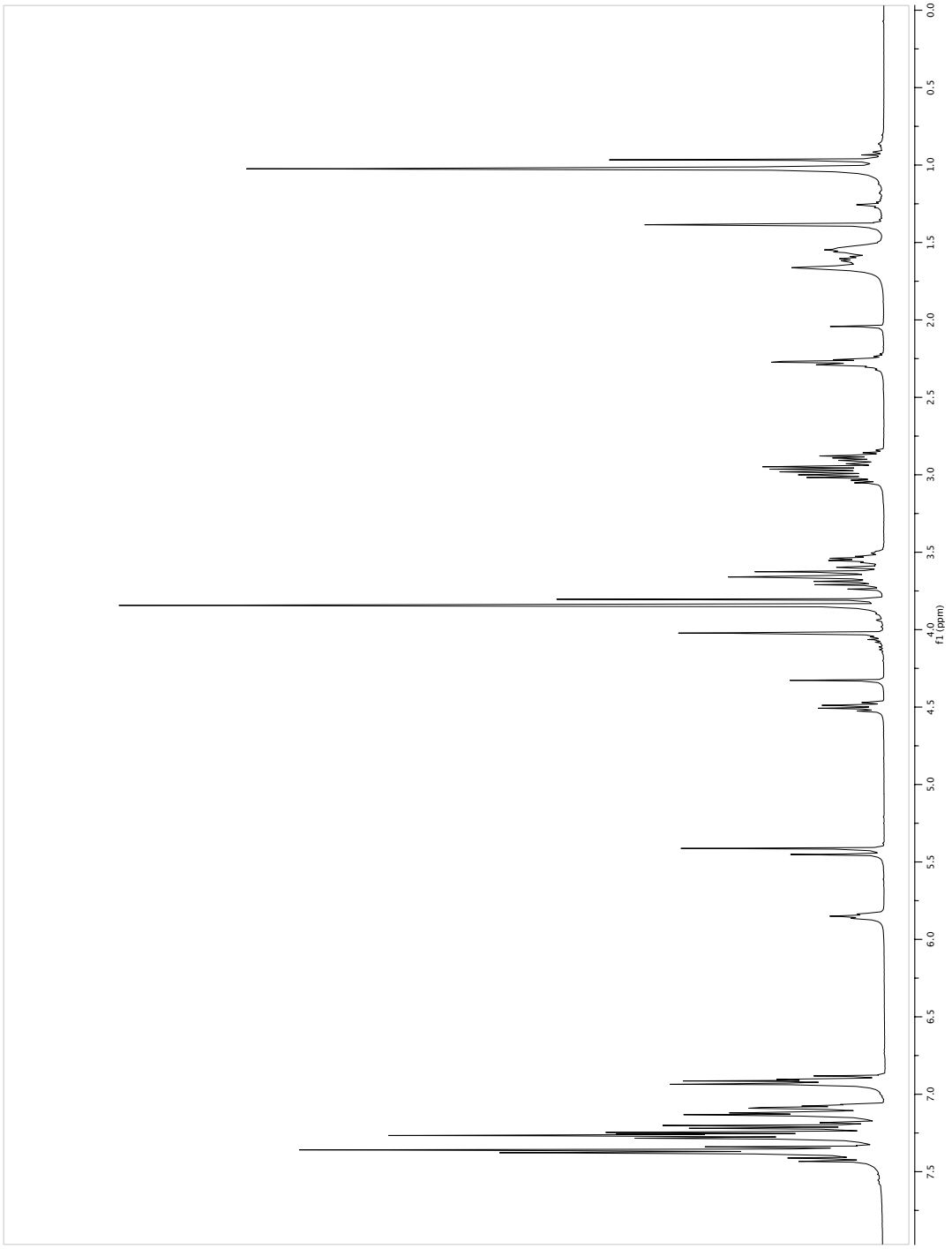
Spectrum A.34: ^{13}C spectrum of compound **66f**.



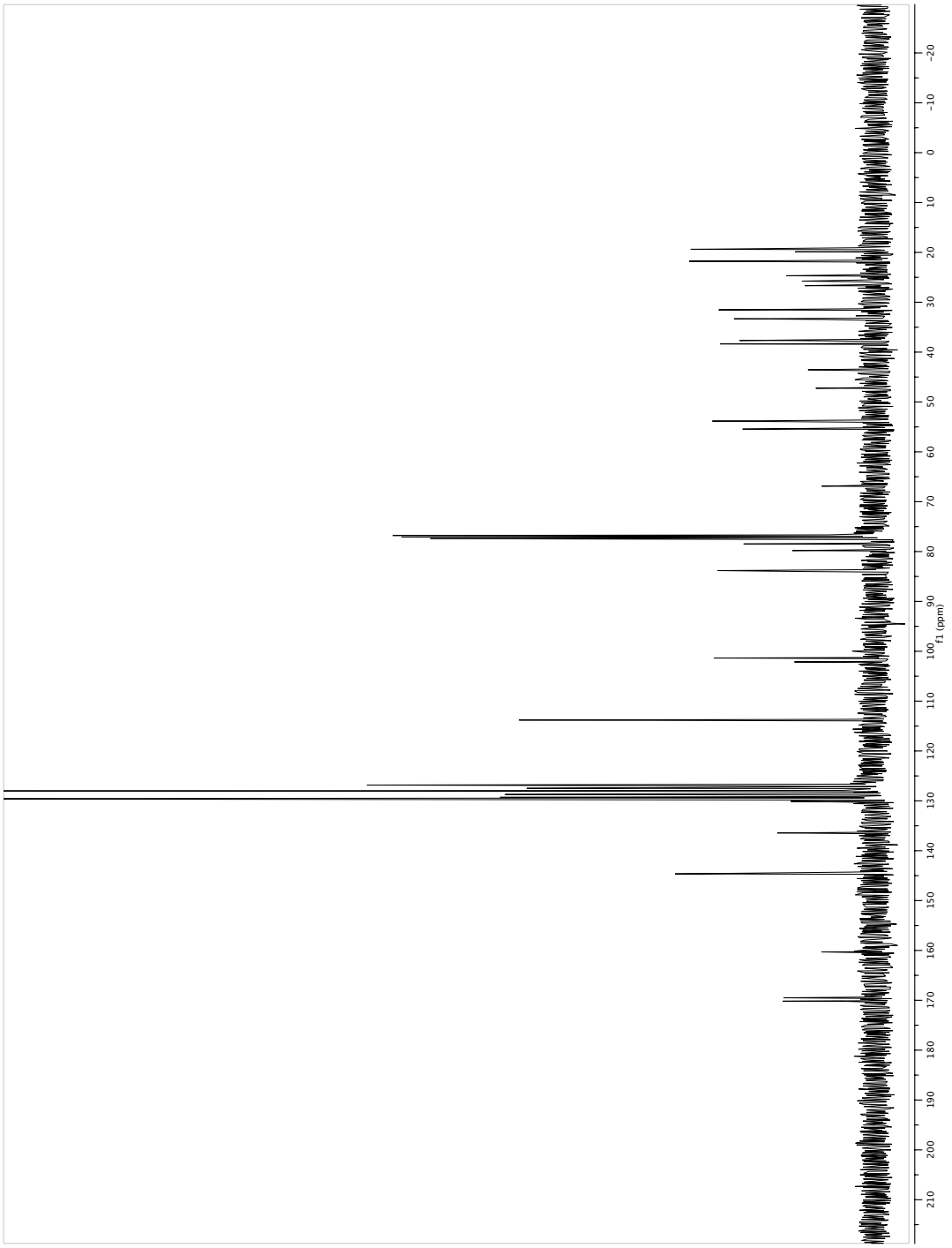
Spectrum A.35: ^{1}H spectrum of compound **67a**.



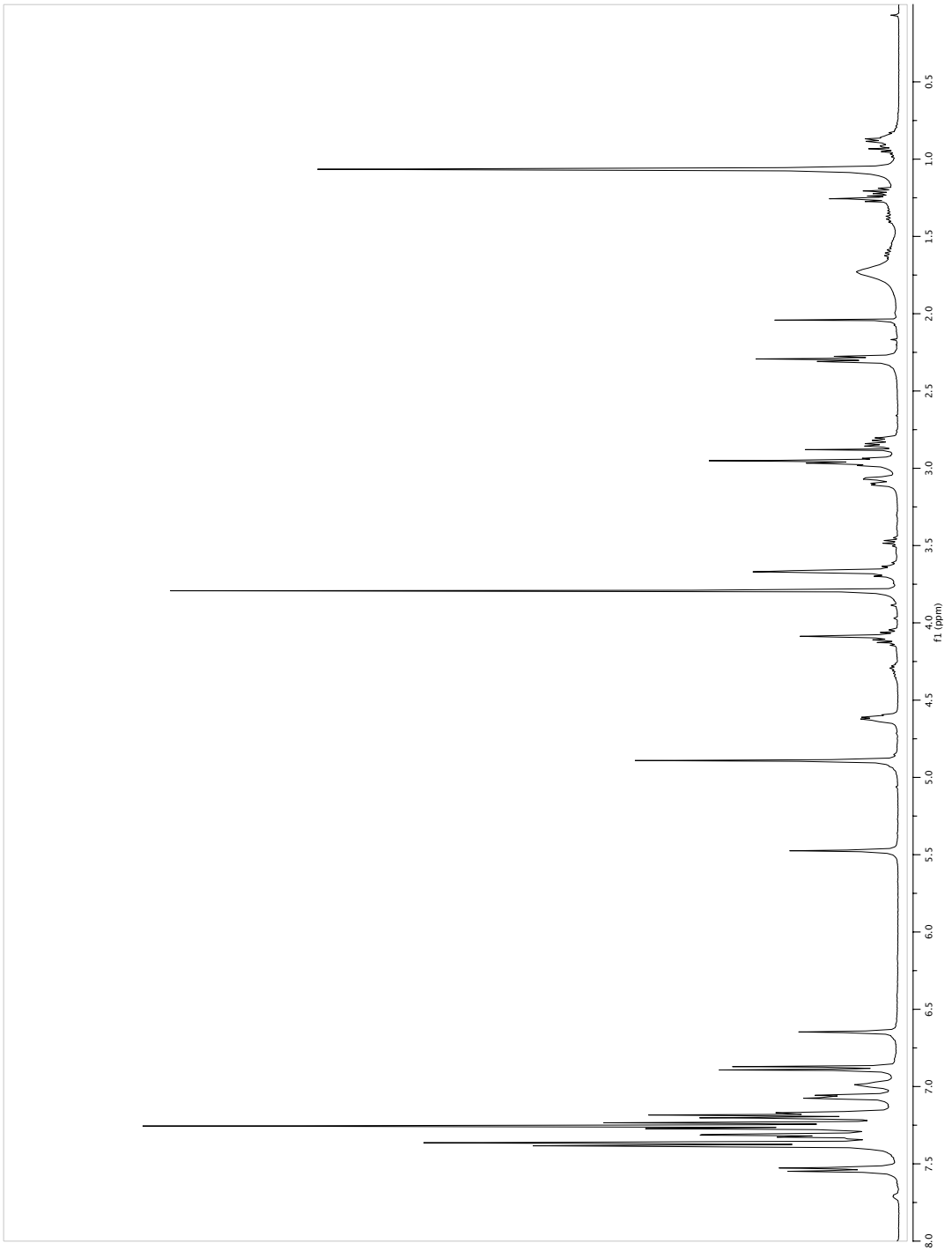
Spectrum A.36: ^{13}C spectrum of compound **67a**.



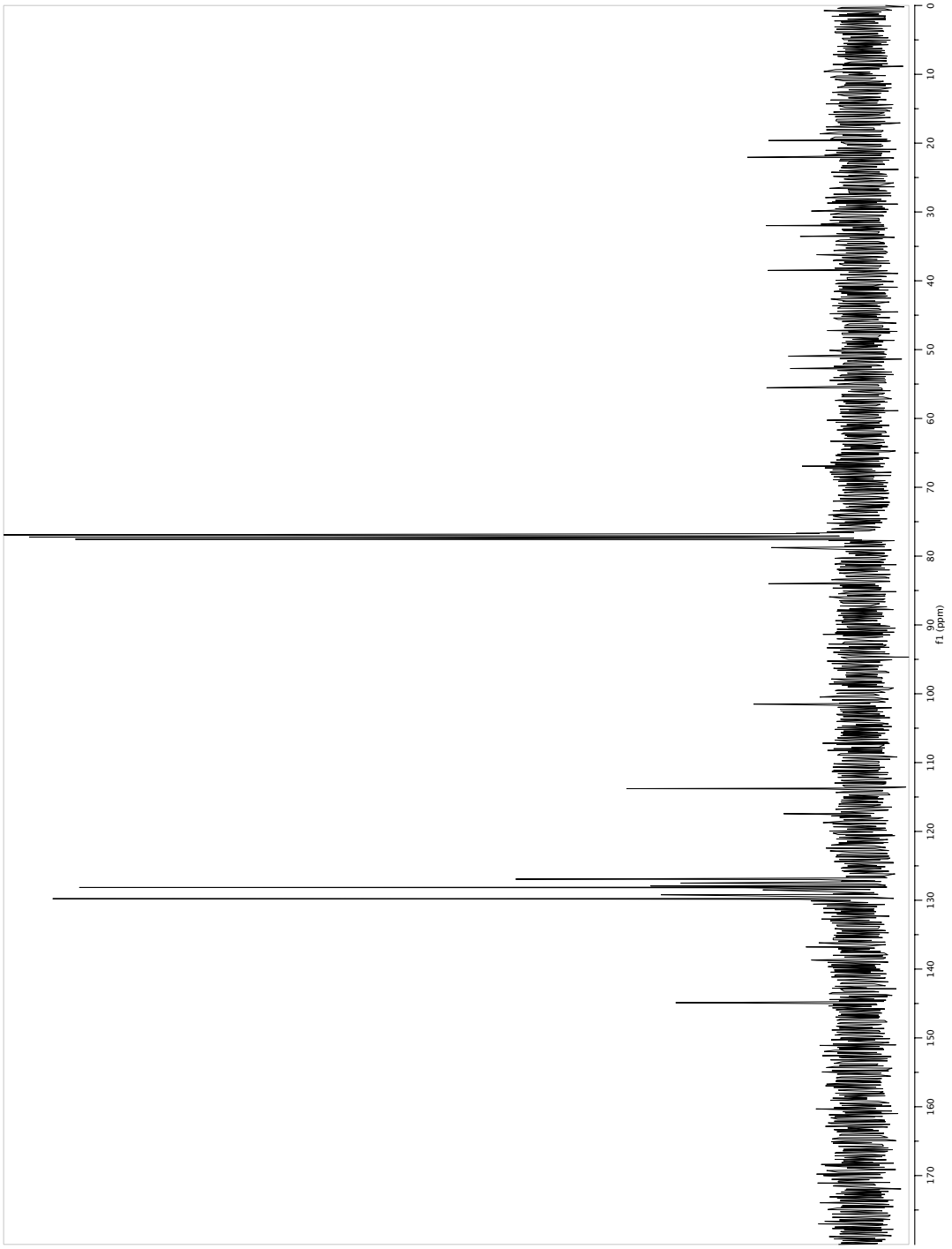
Spectrum A.37: ^{1}H spectrum of compound **67b**.



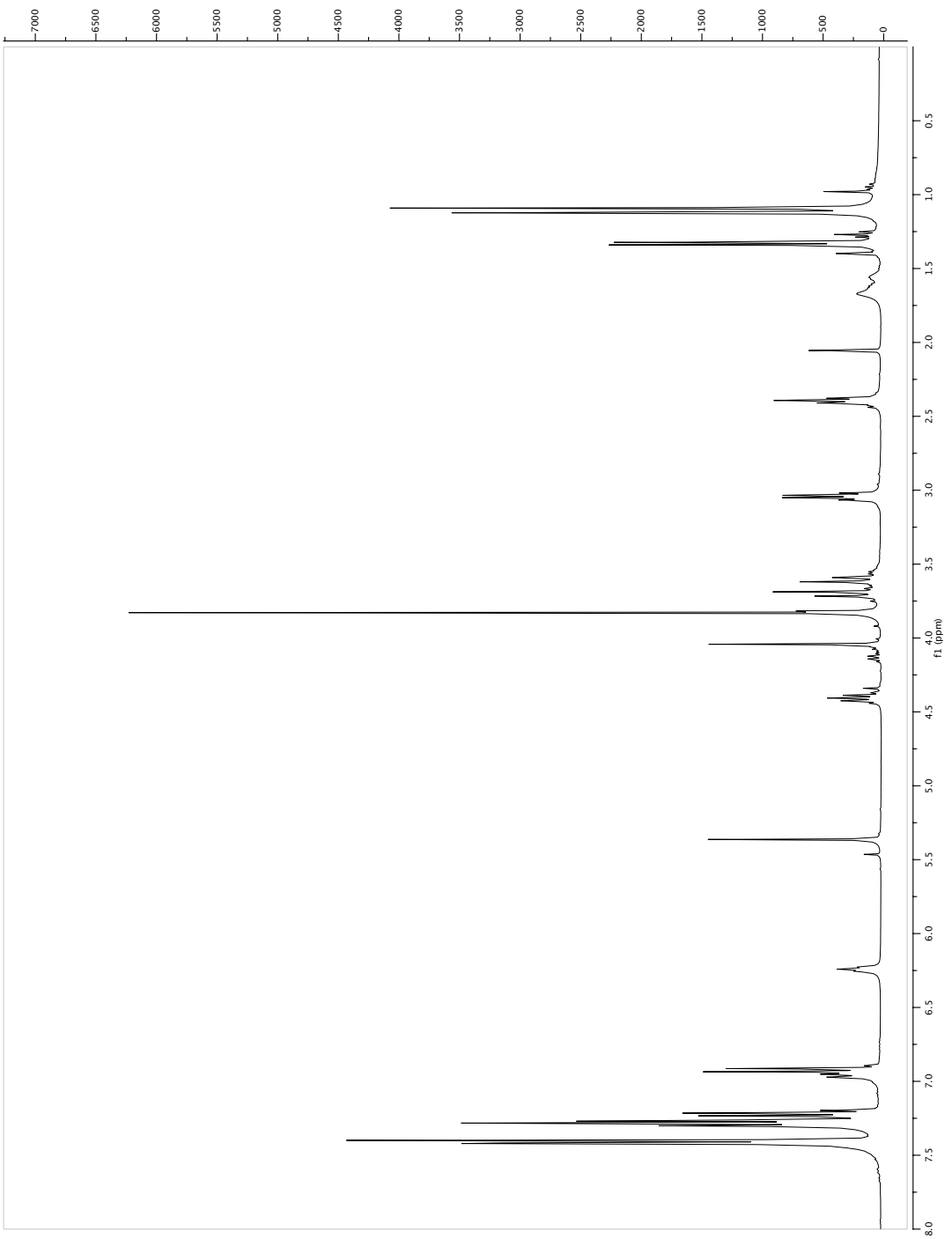
Spectrum A.38: ^{13}C spectrum of compound **67b**.



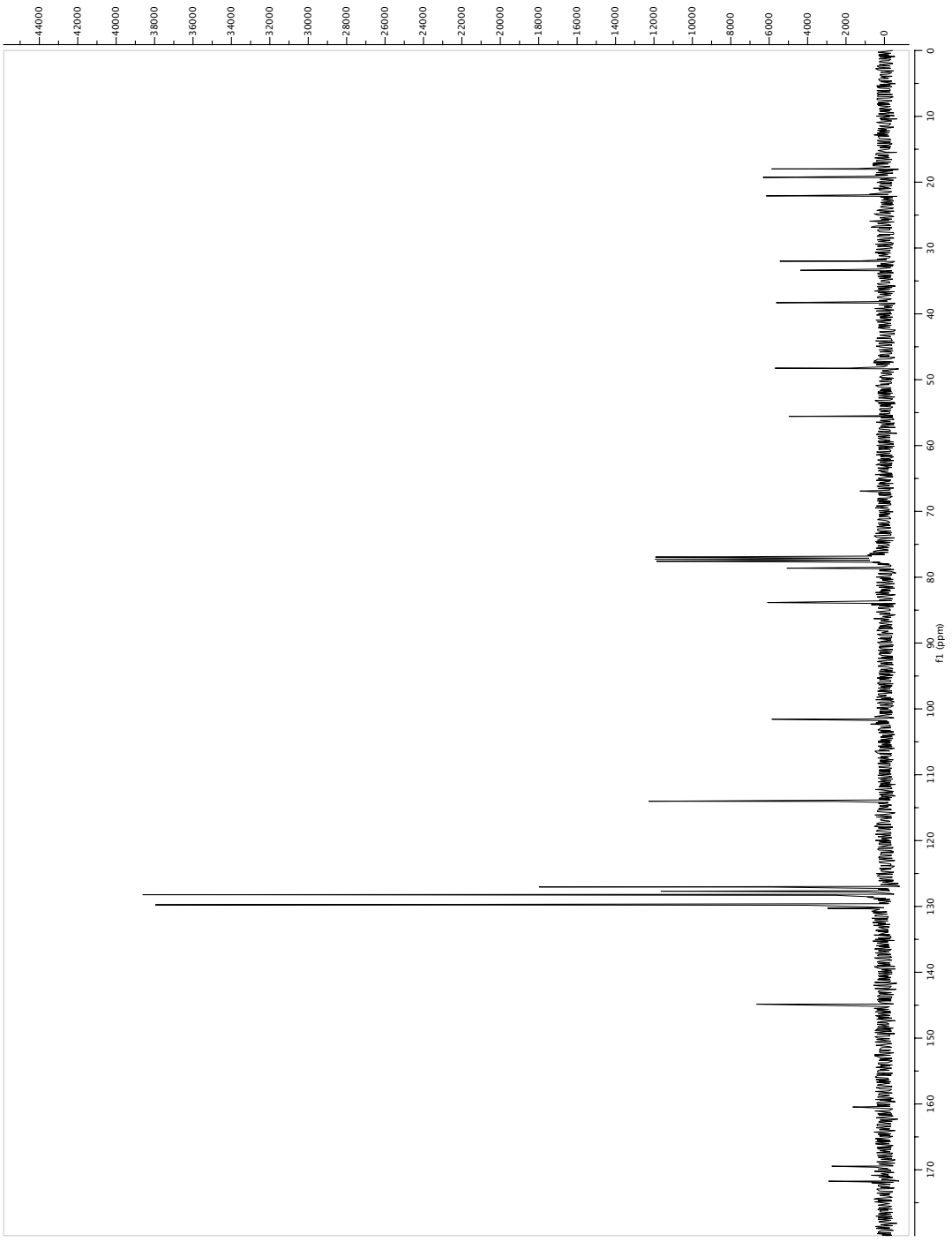
Spectrum A.39: ^{1}H spectrum of compound **67c**.



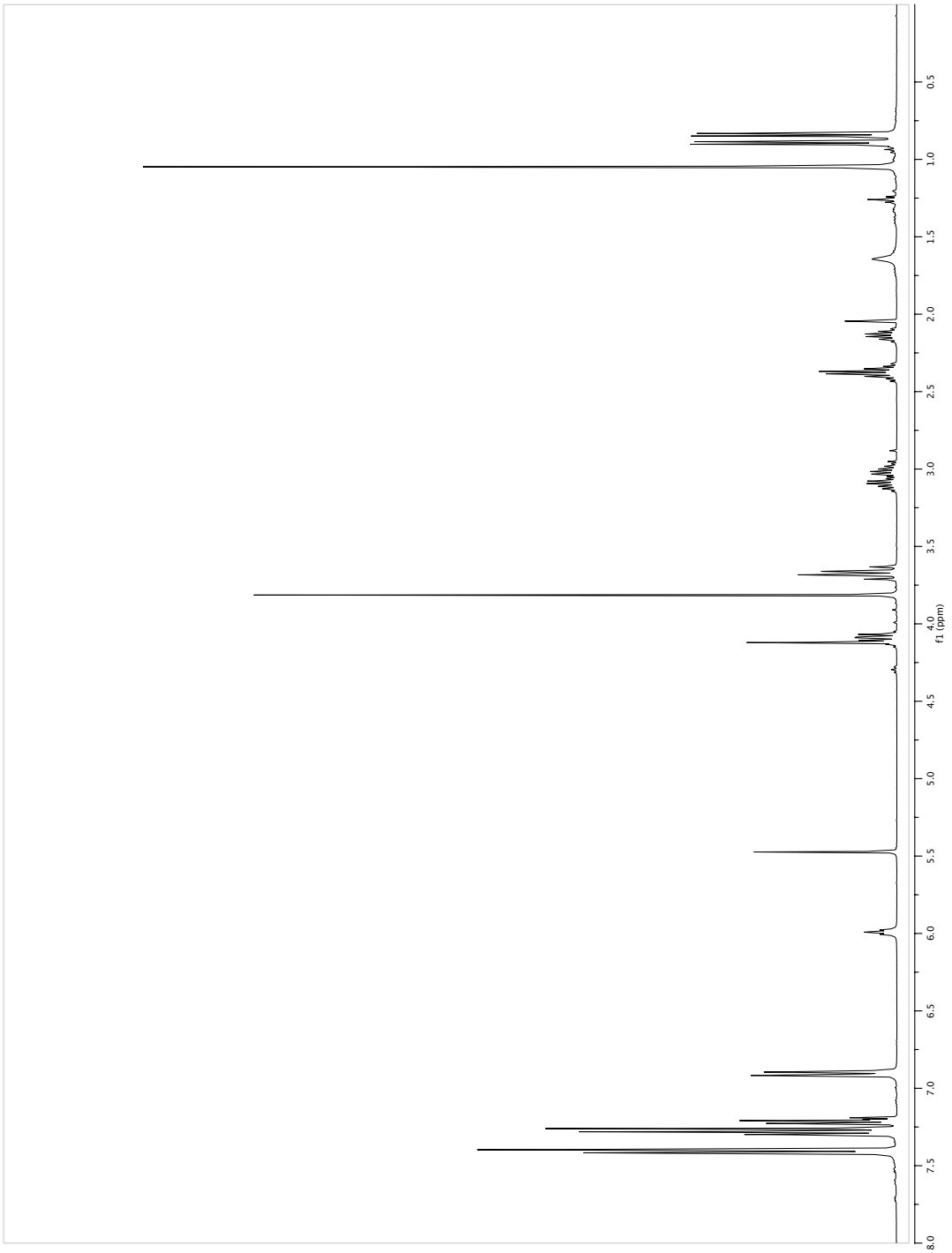
Spectrum A.40: ^{13}C spectrum of compound **67c**.



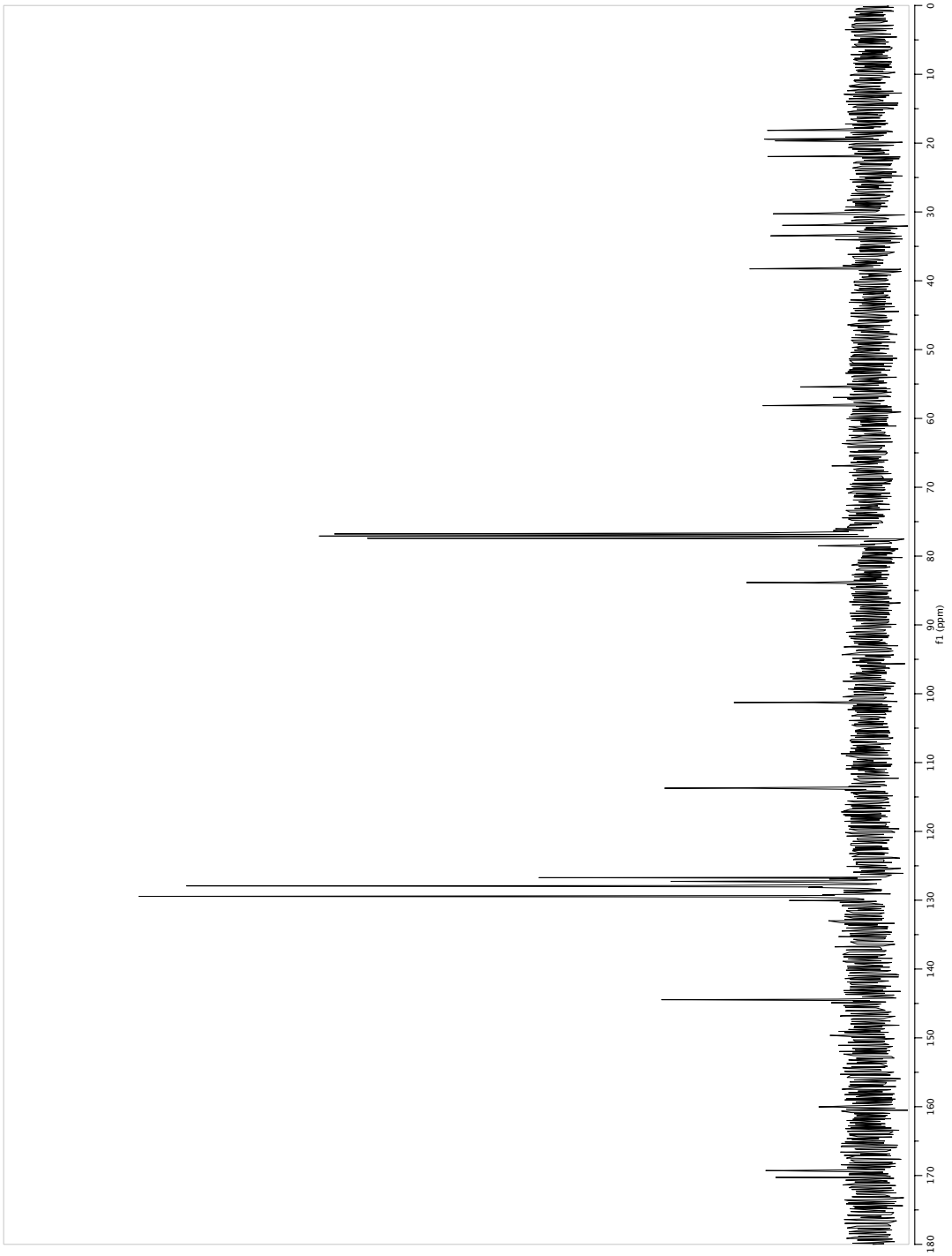
Spectrum A.41: ^{1}H spectrum of compound **67d**.



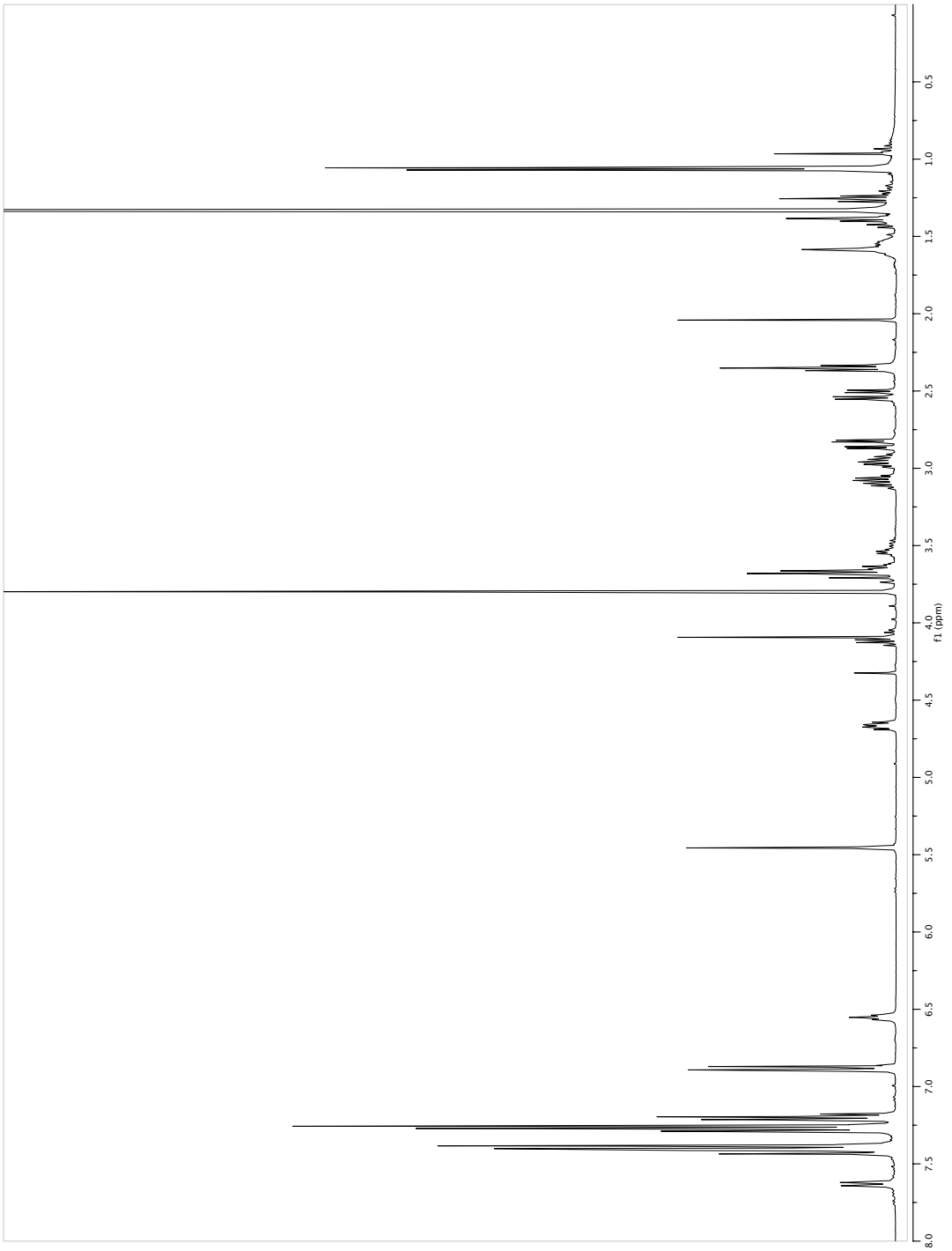
Spectrum A.42: ^{13}C spectrum of compound **67d**.



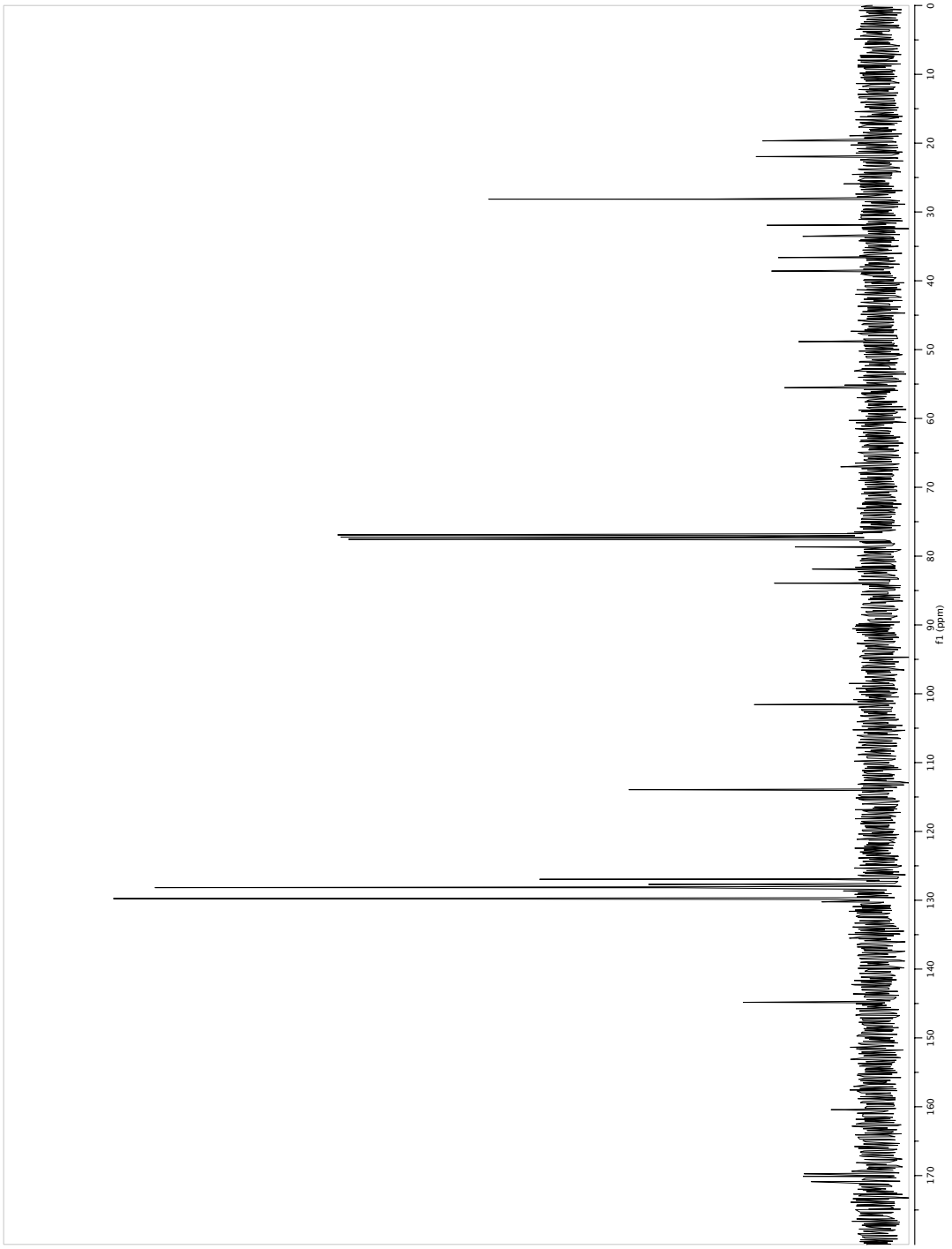
Spectrum A.43: ^{1}H spectrum of compound **67e**.



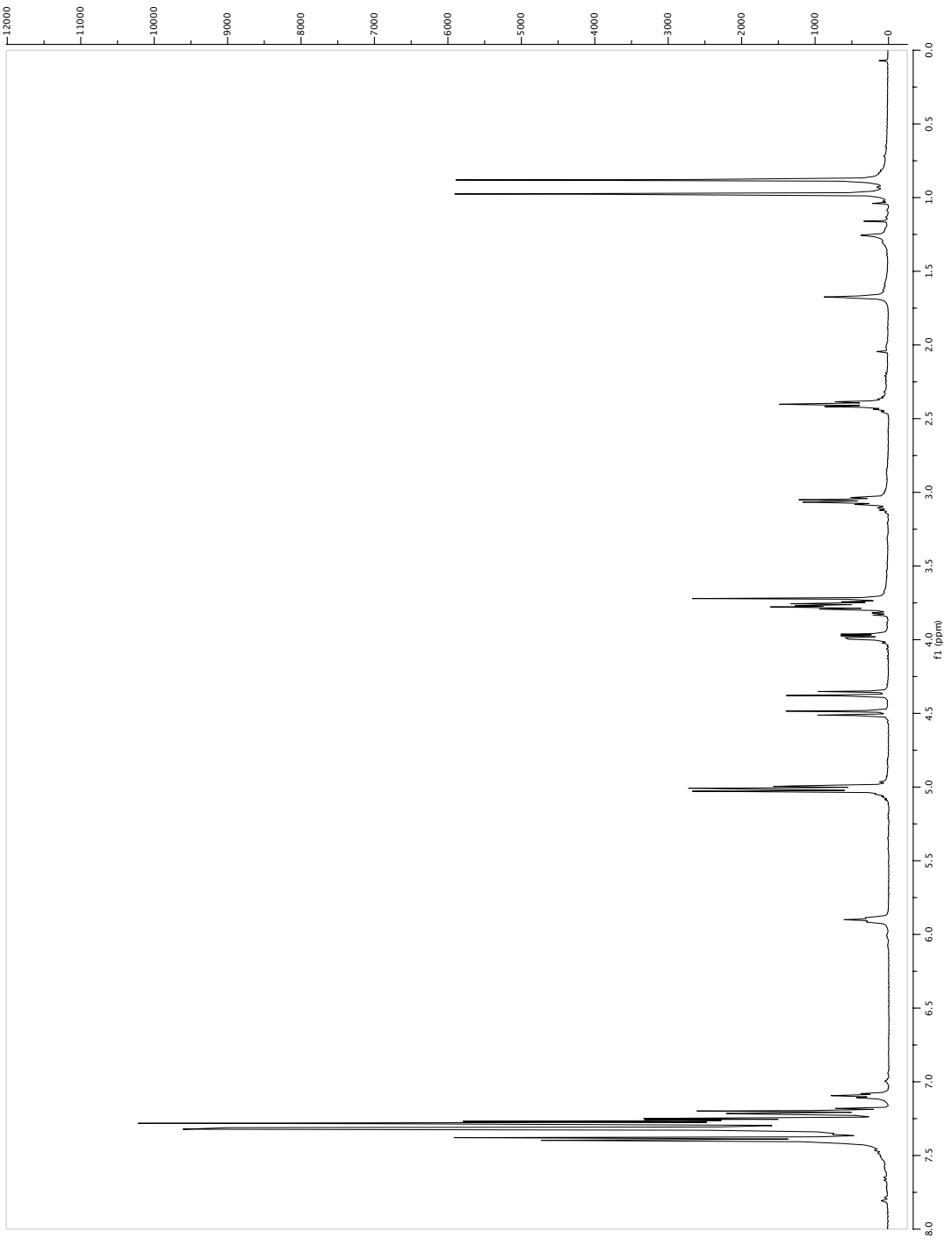
Spectrum A.44: ^{13}C spectrum of compound **67e**.



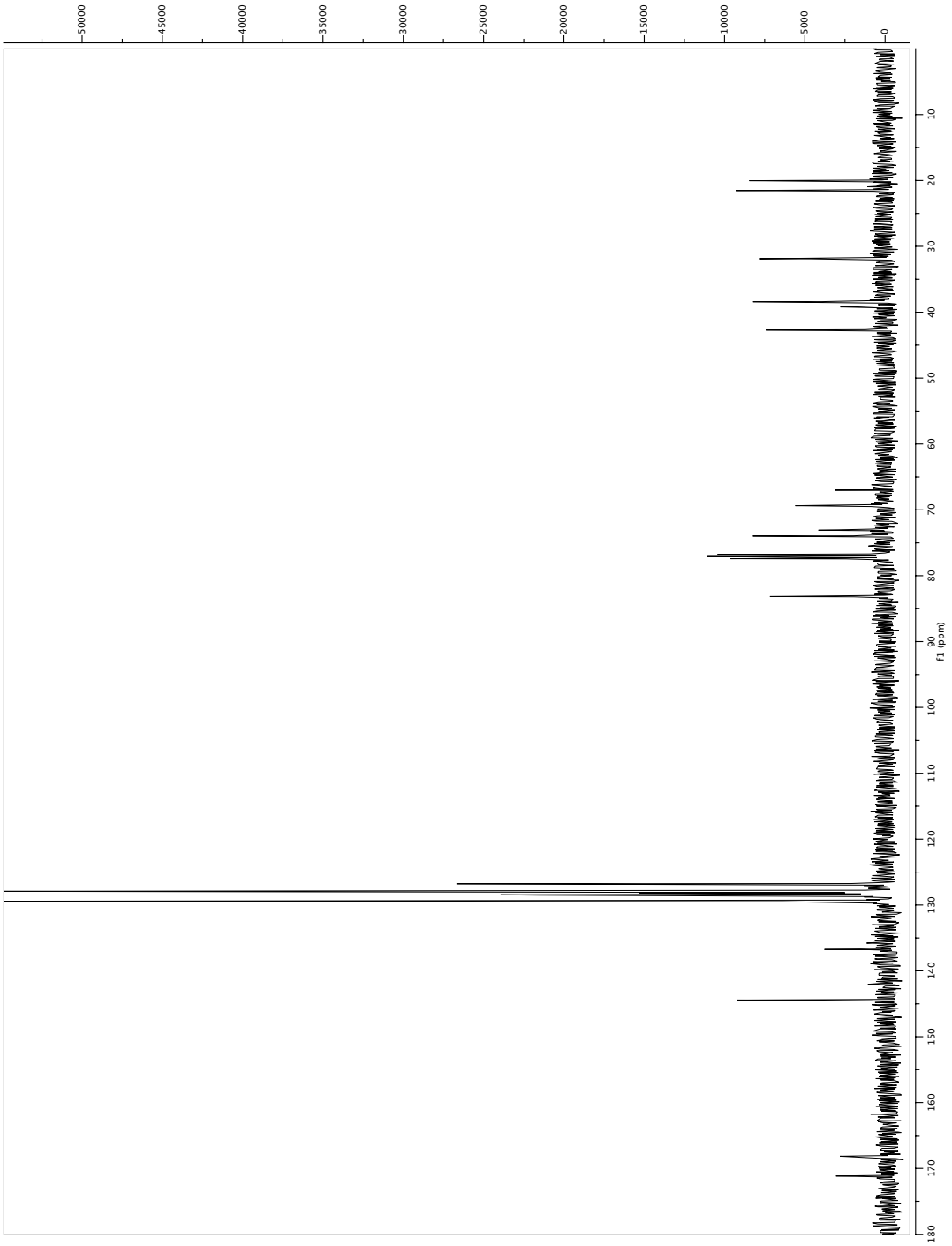
Spectrum A.45: ^{1}H spectrum of compound **67f**.



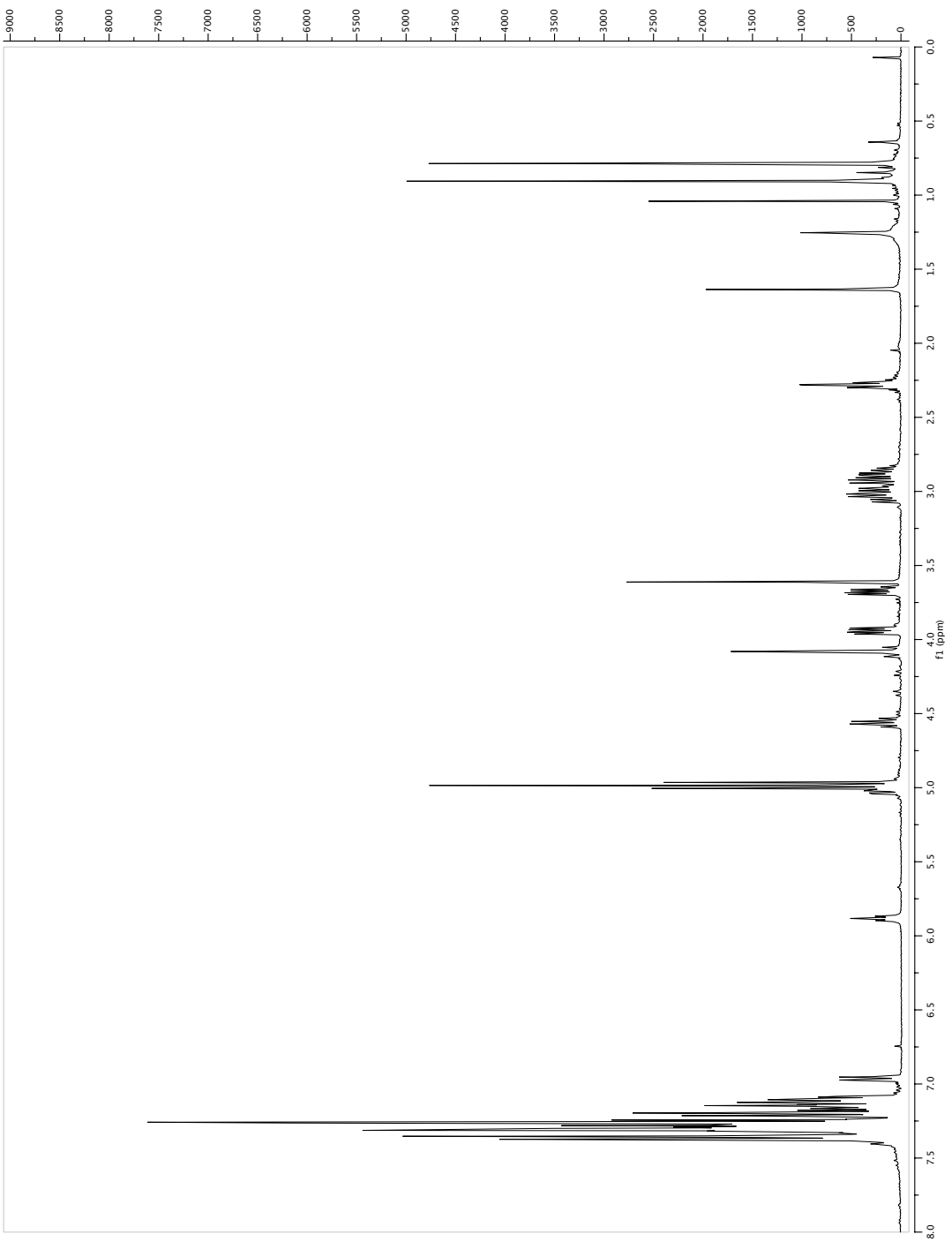
Spectrum A.46: ^{13}C spectrum of compound **67f**.



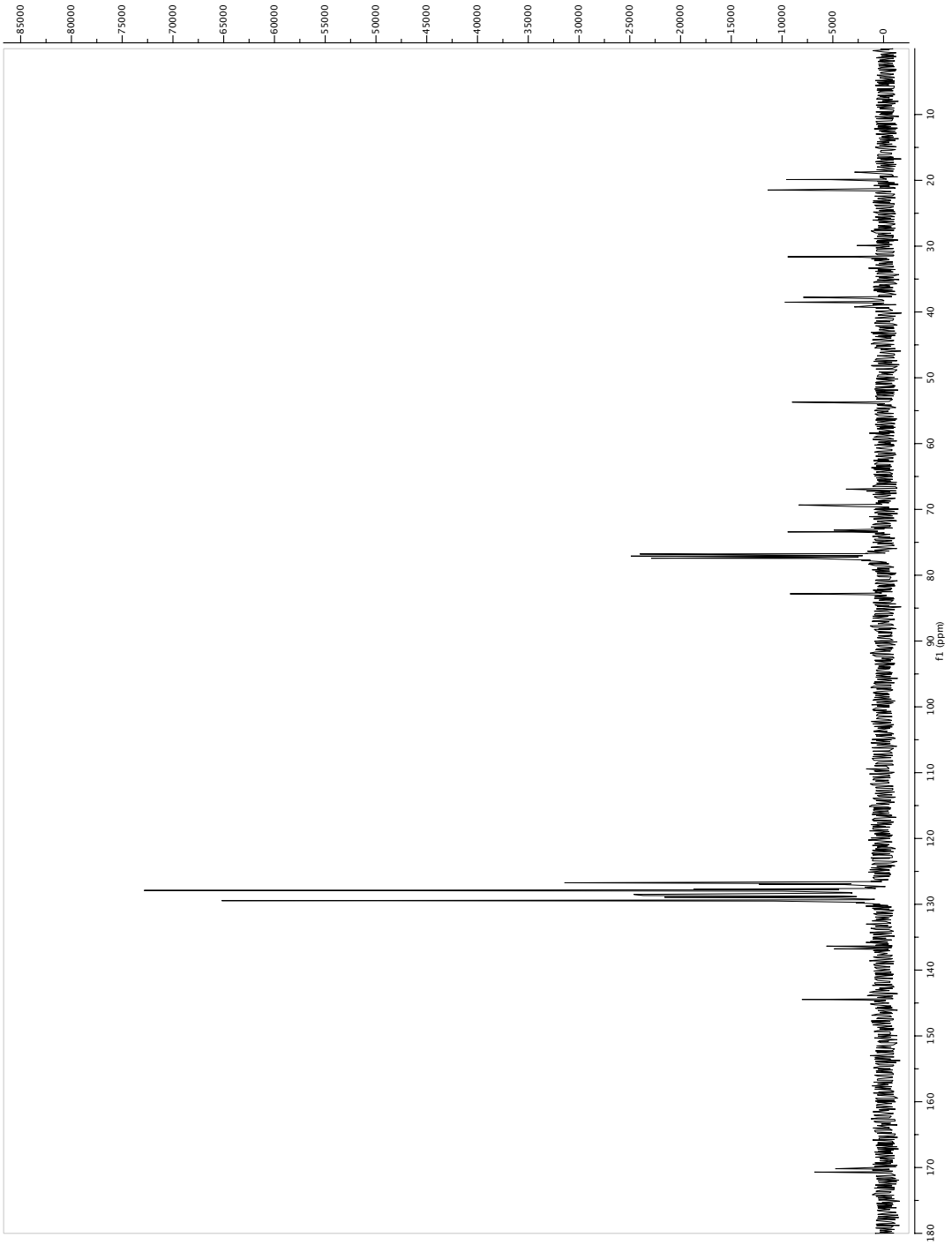
Spectrum A.47: ^{1}H spectrum of compound **68a**.



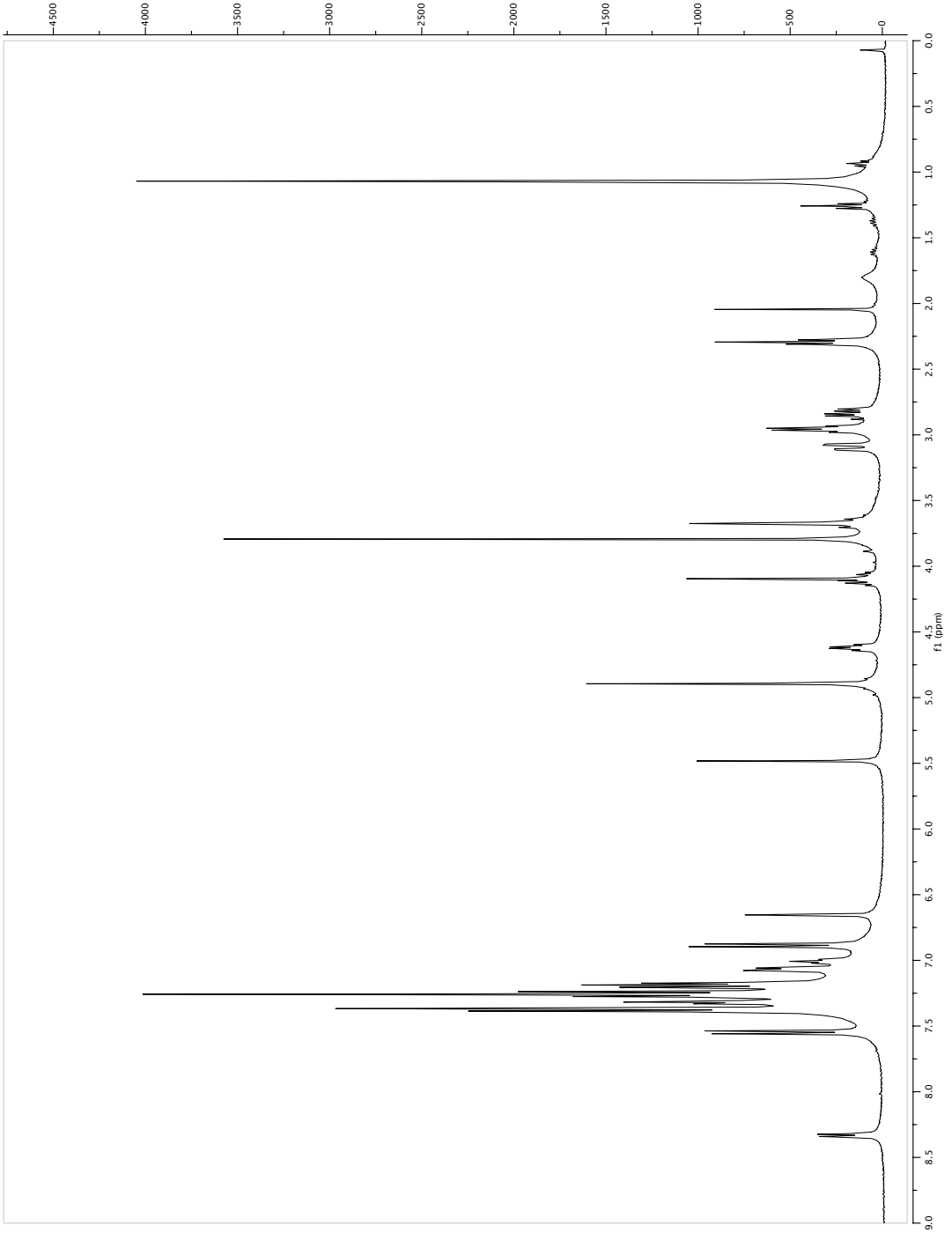
Spectrum A.48: ^{13}C spectrum of compound **68a**.



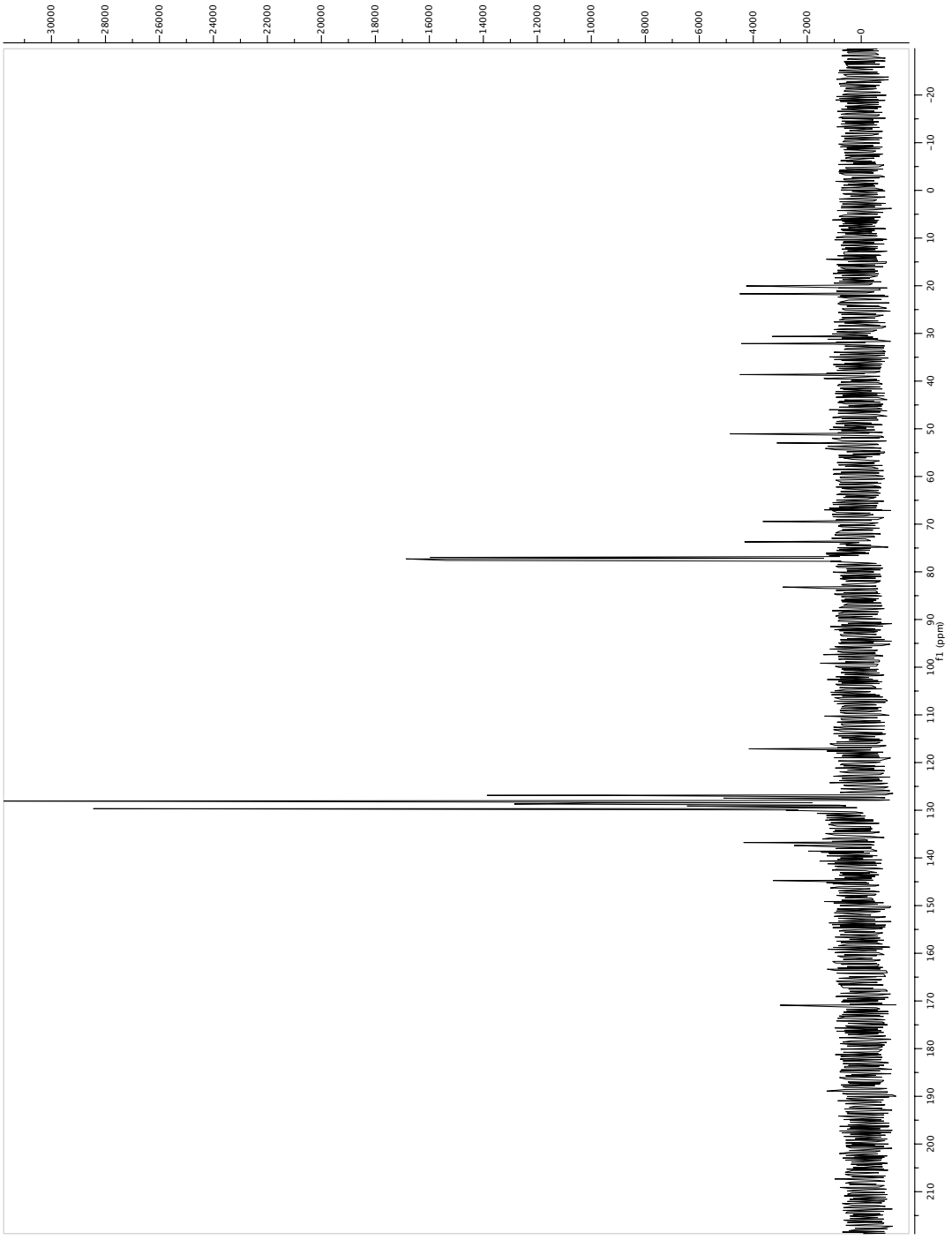
Spectrum A.49: ^{1}H spectrum of compound **68b**.



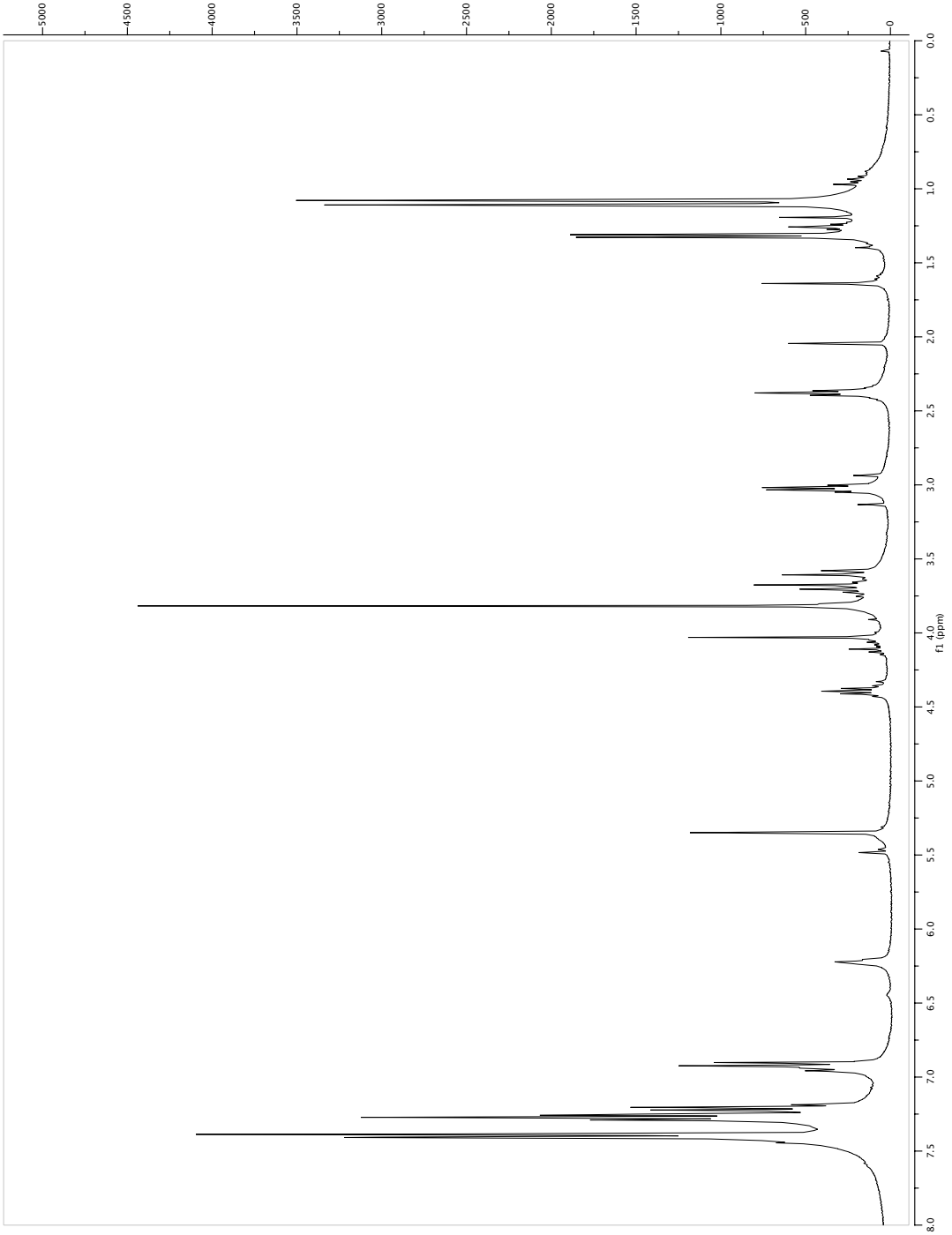
Spectrum A.50: ^{13}C spectrum of compound **68b**.



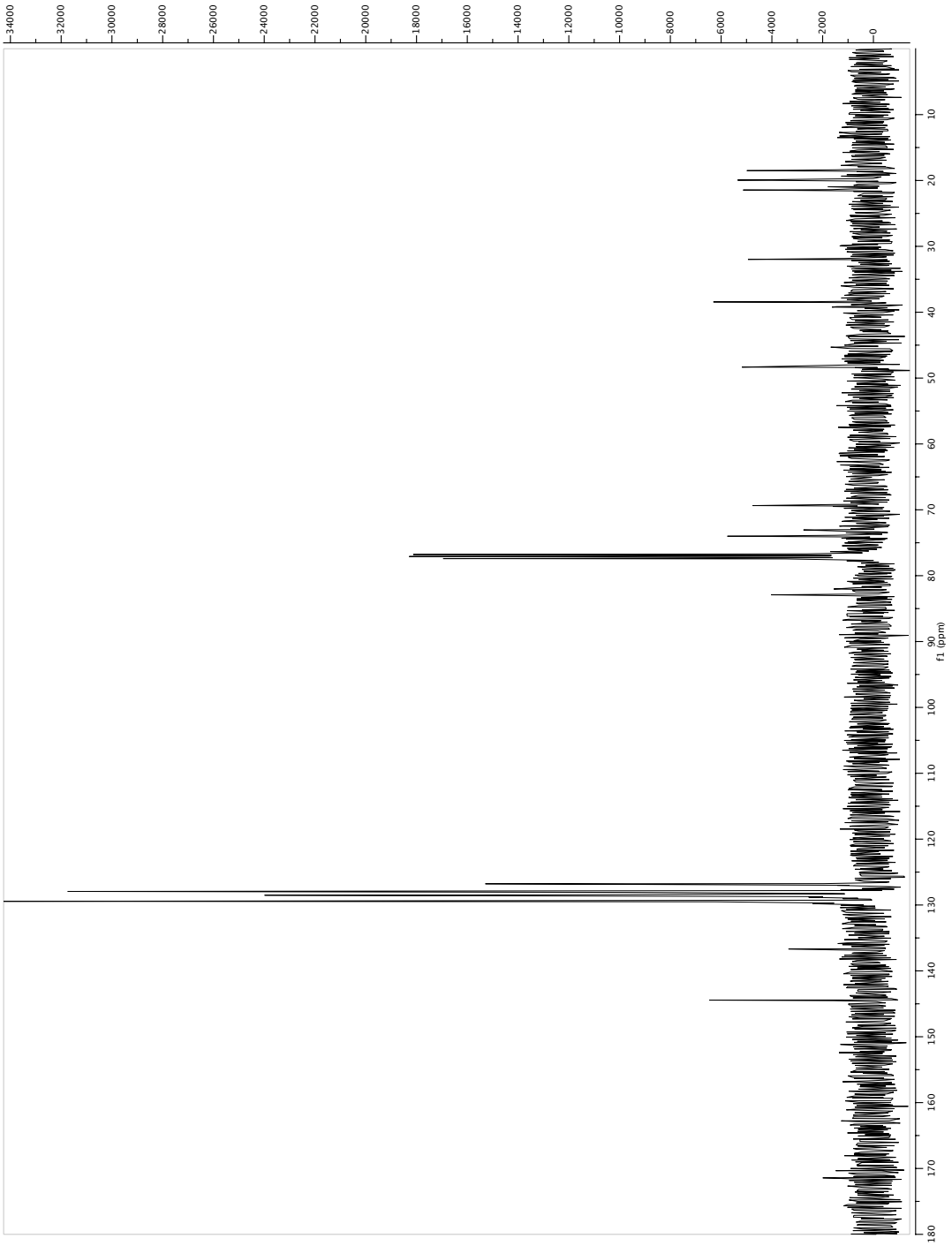
Spectrum A.51: ^{1}H spectrum of compound **68c**.



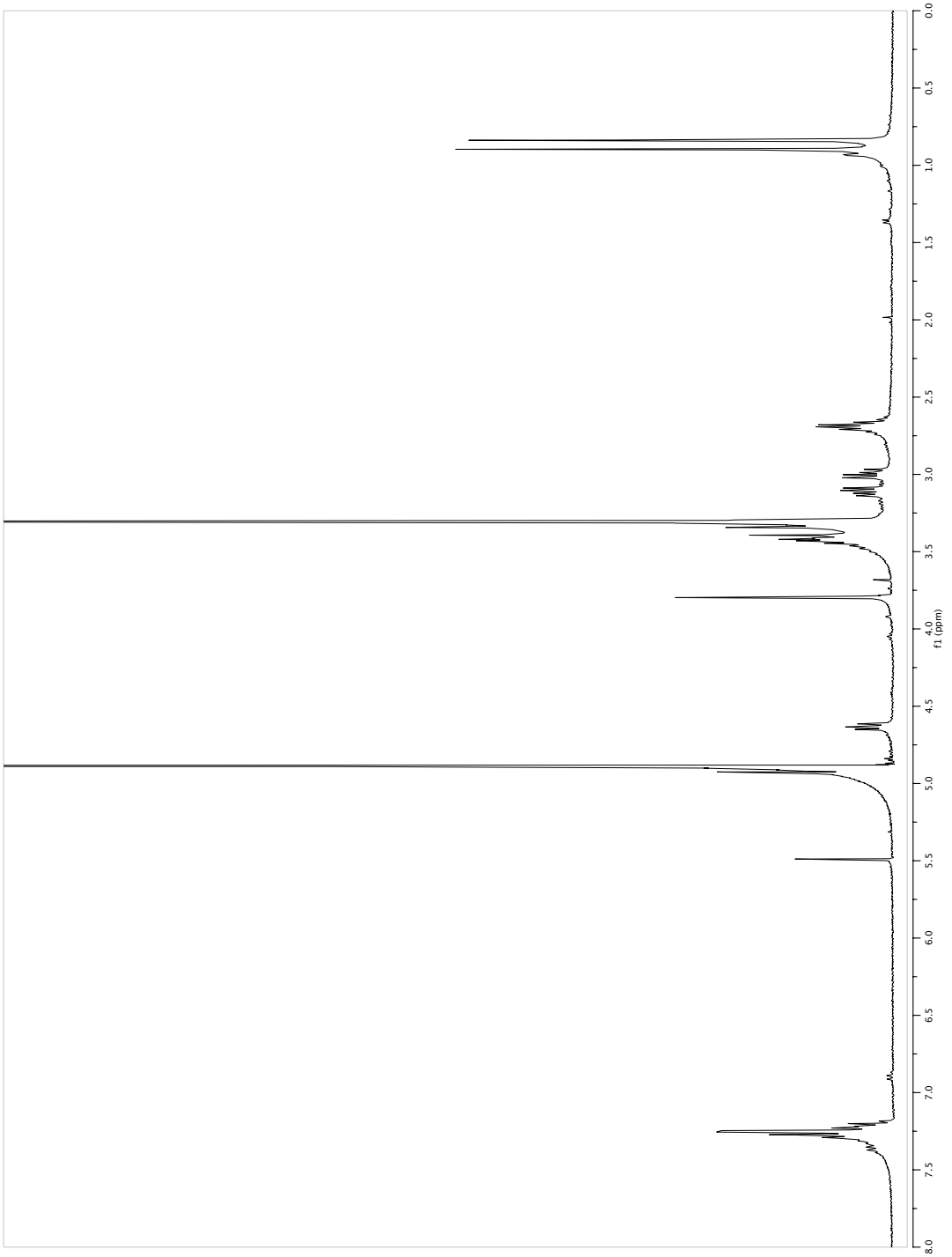
Spectrum A.52: ^{13}C spectrum of compound **68c**.



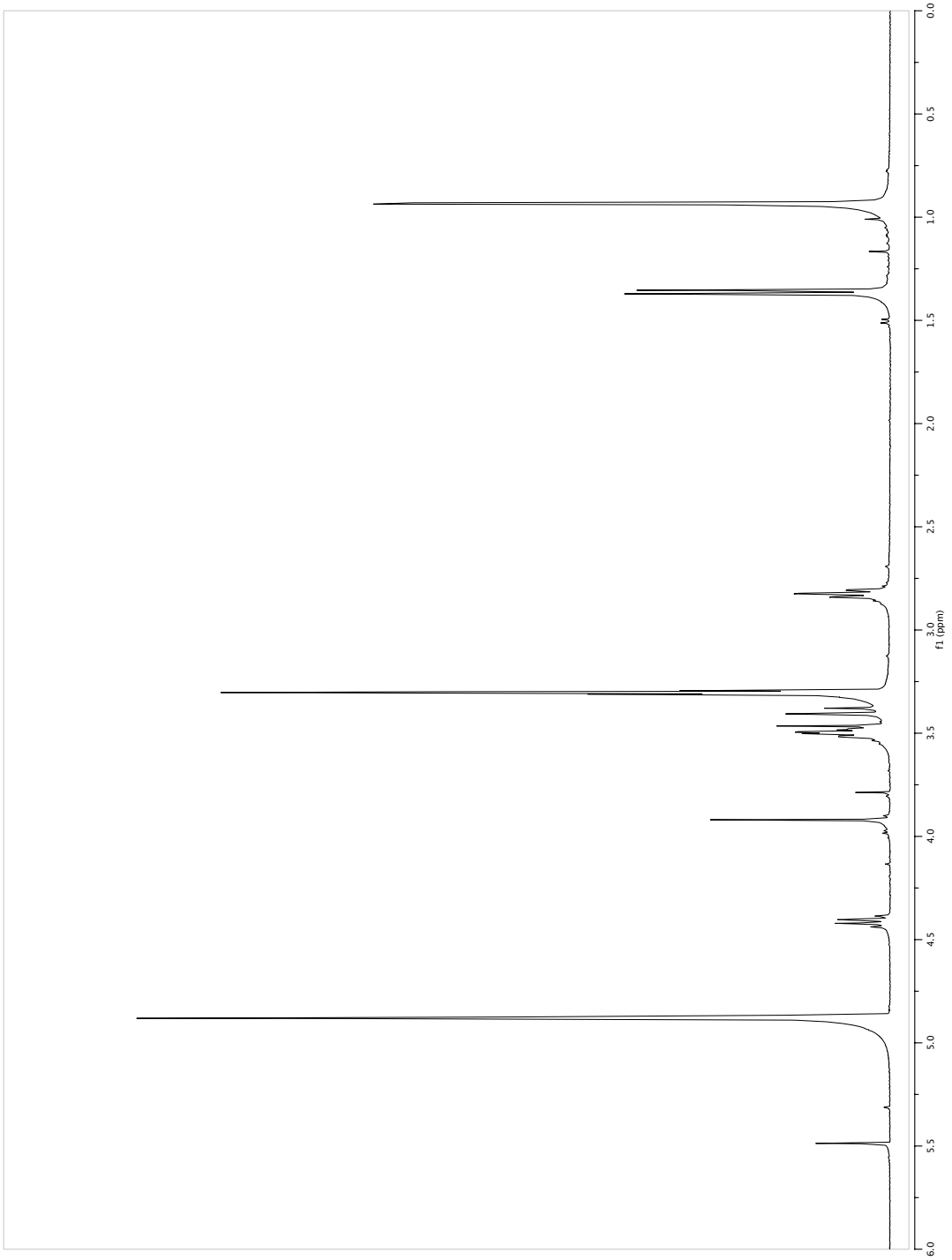
Spectrum A.53: ^{1}H spectrum of compound **68d**.



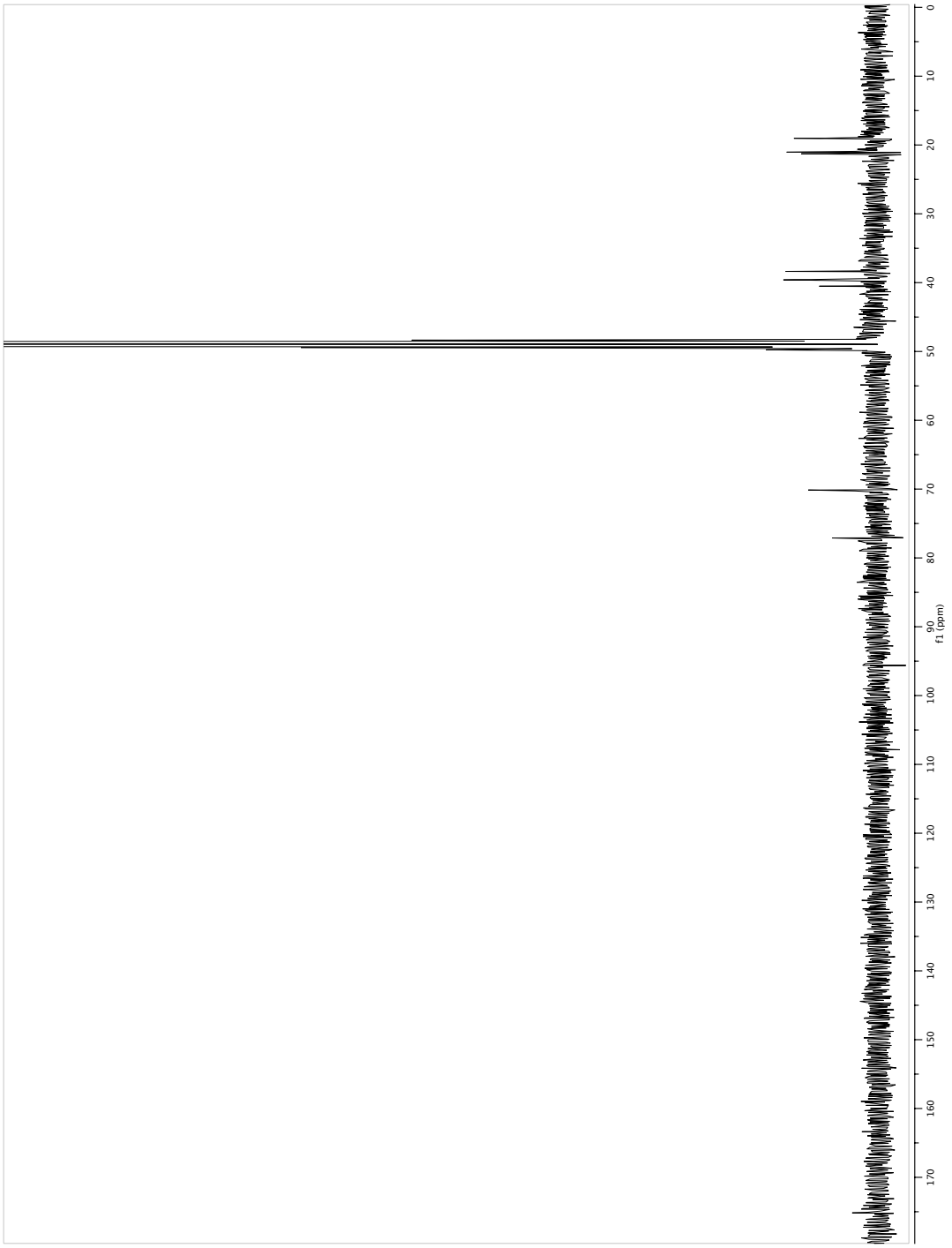
Spectrum A.54: ^{13}C spectrum of compound **68d**.



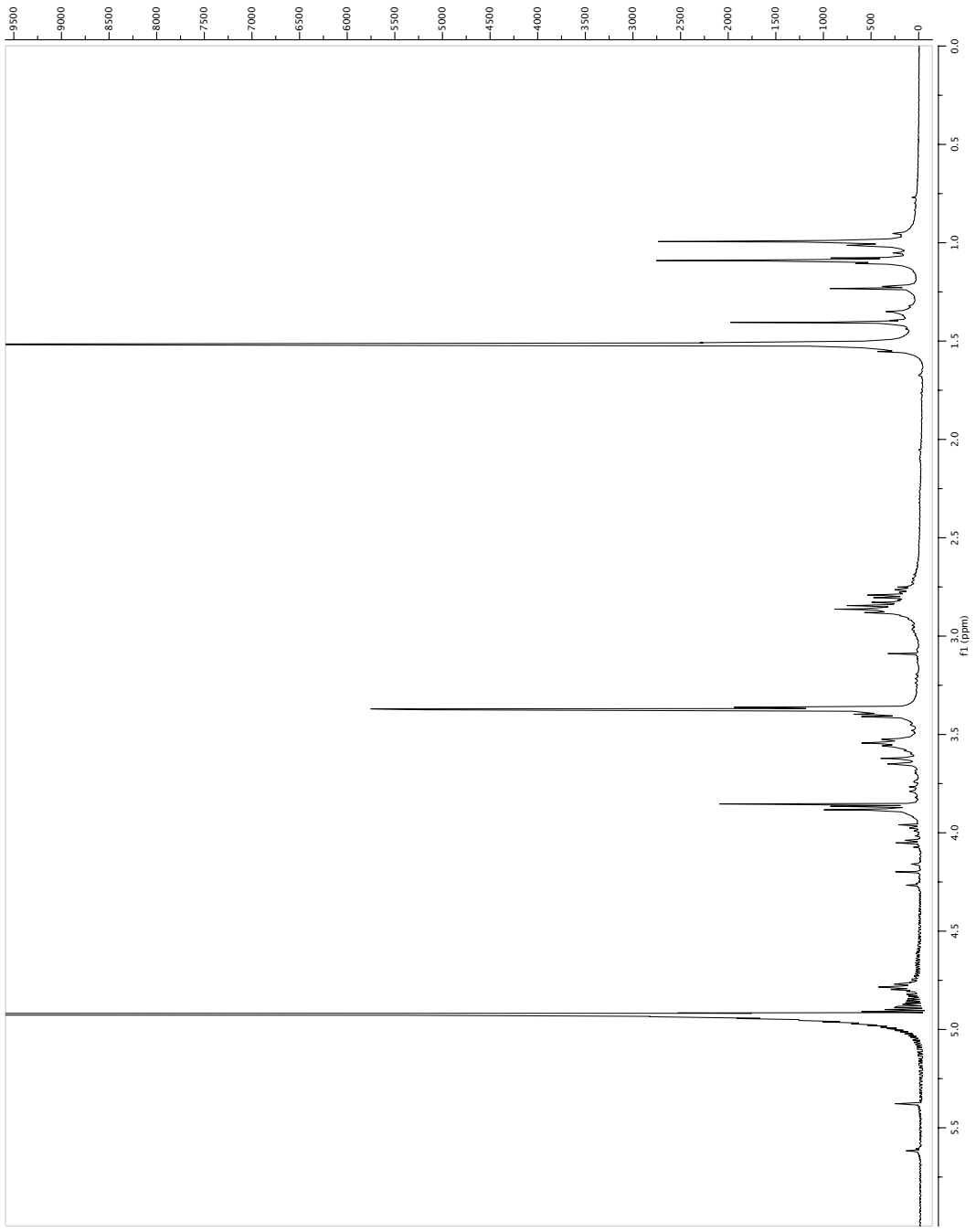
Spectrum A.55: ^{1}H spectrum of compound **69b**.



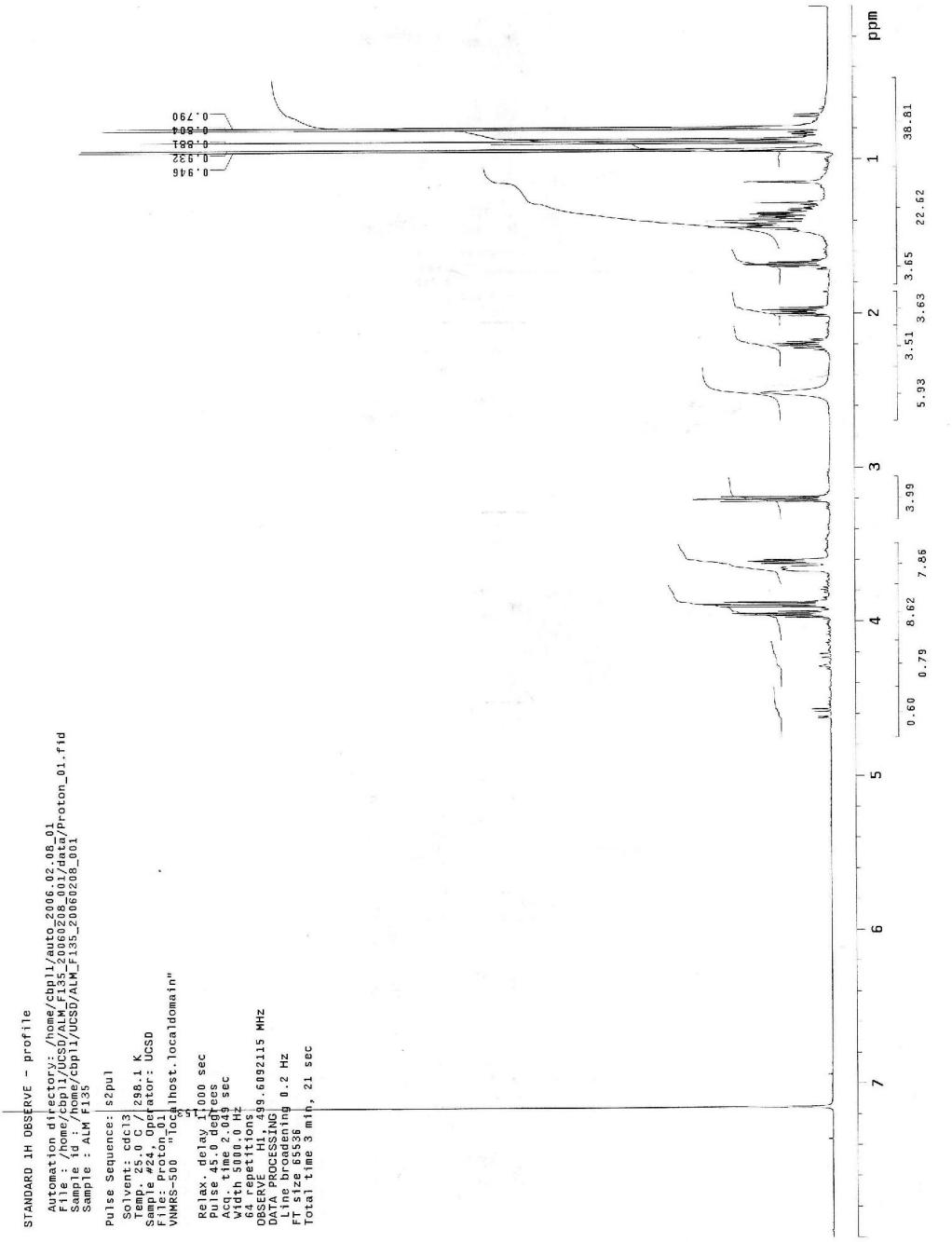
Spectrum A.56: ^{1}H spectrum of compound **69d**.



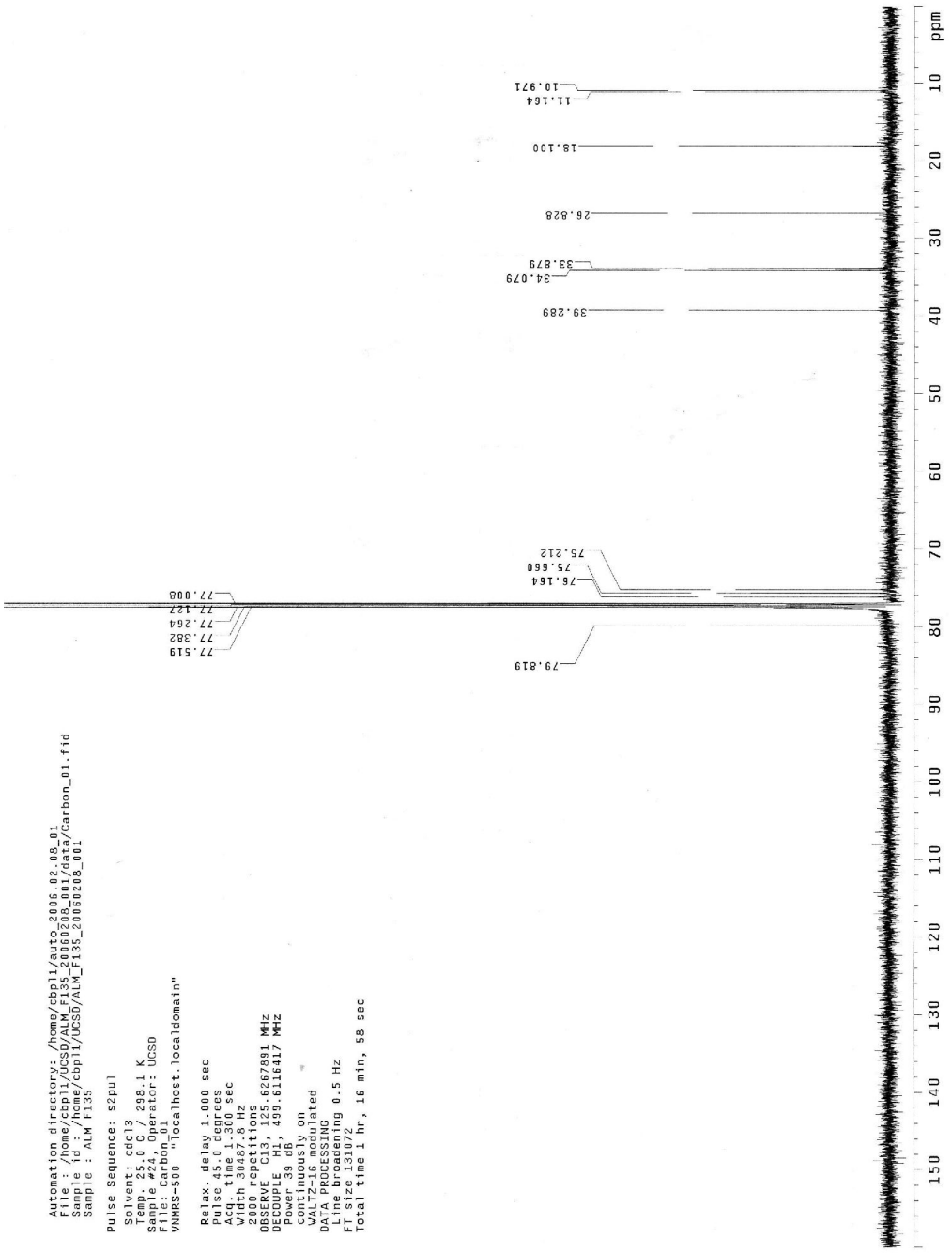
Spectrum A.57: ^{13}C spectrum of compound **69d**.



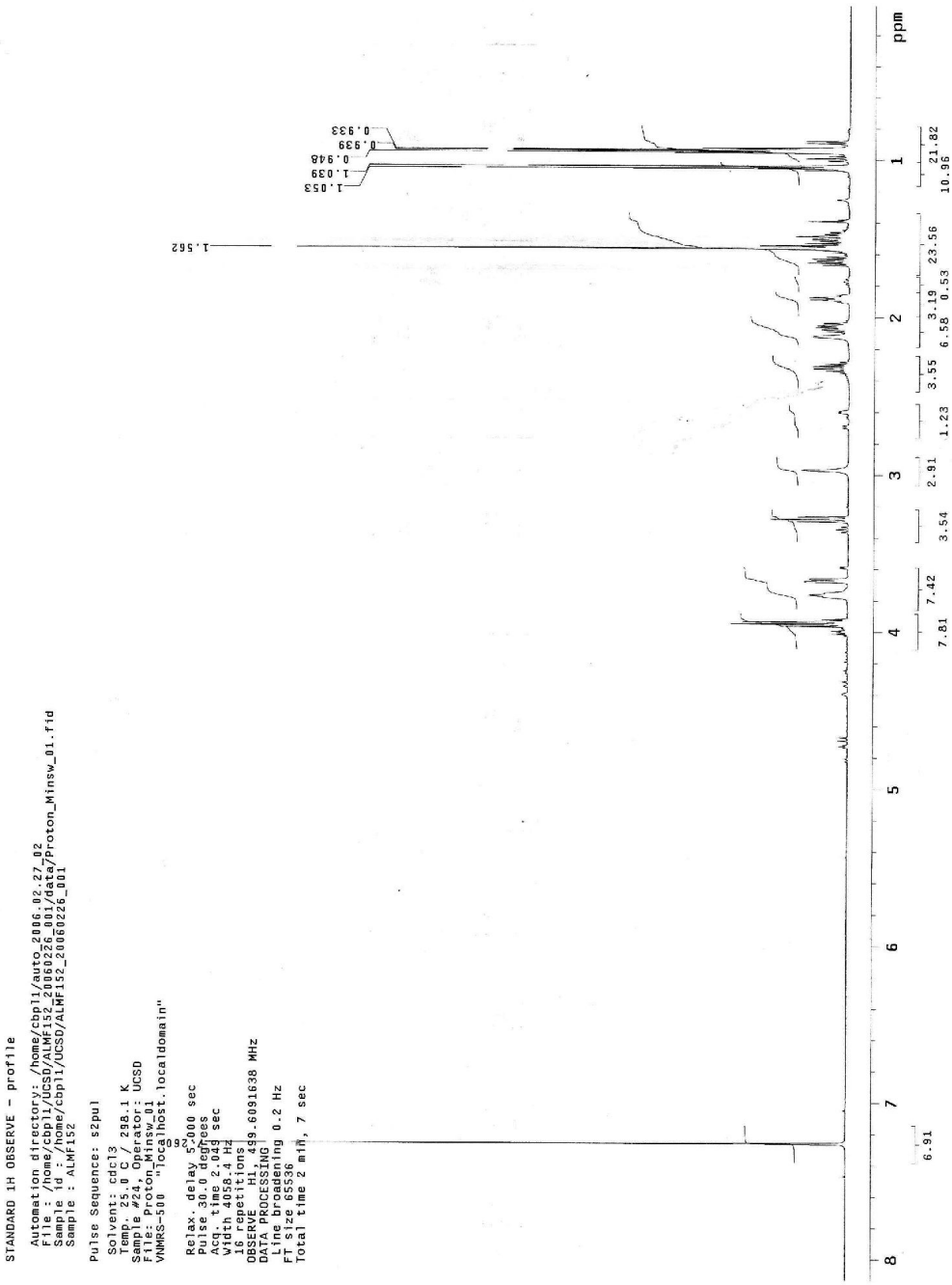
Spectrum A.58: ^{1}H spectrum of compound **69f**.



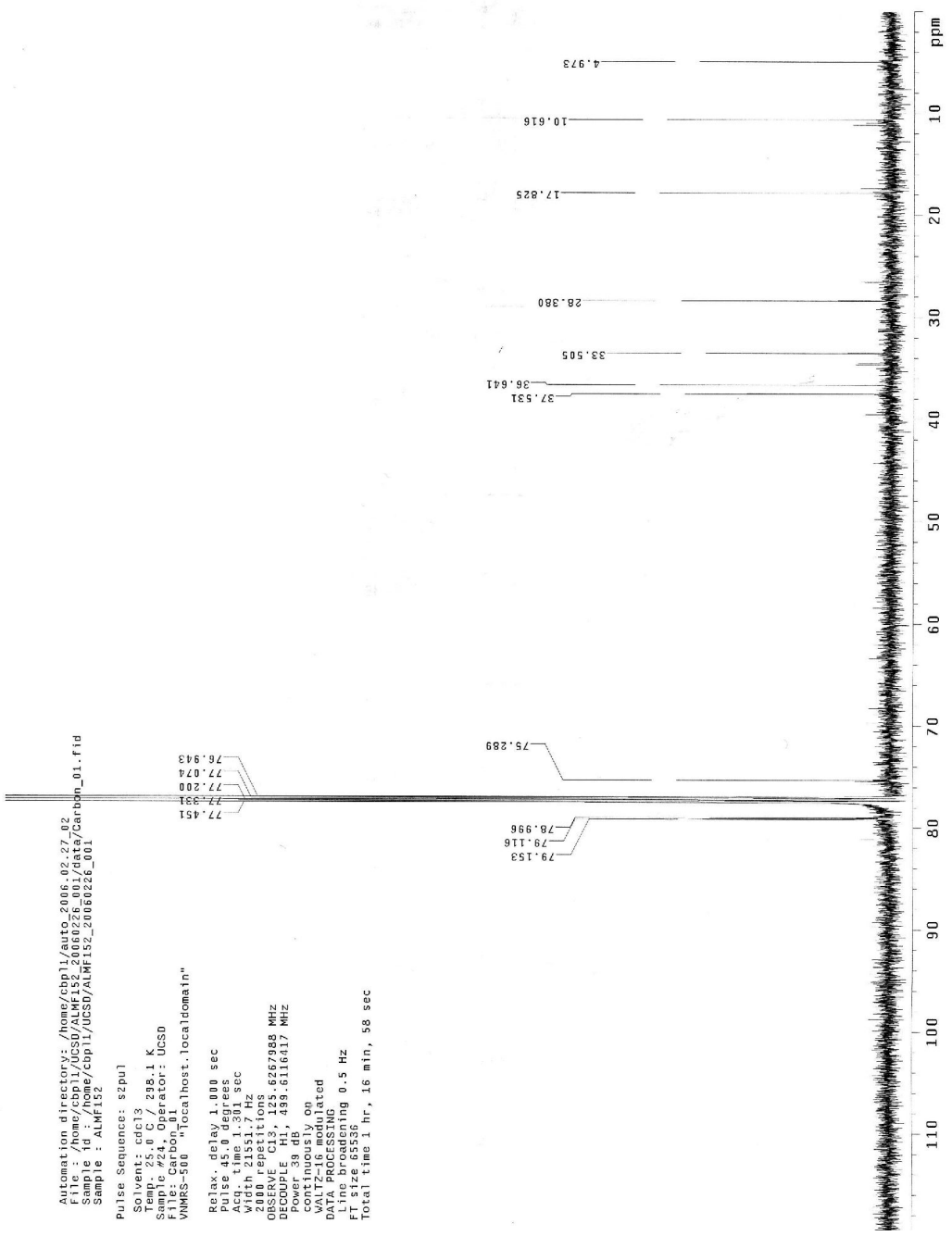
Spectrum A.59: ^{1}H spectrum of compound **73a**.



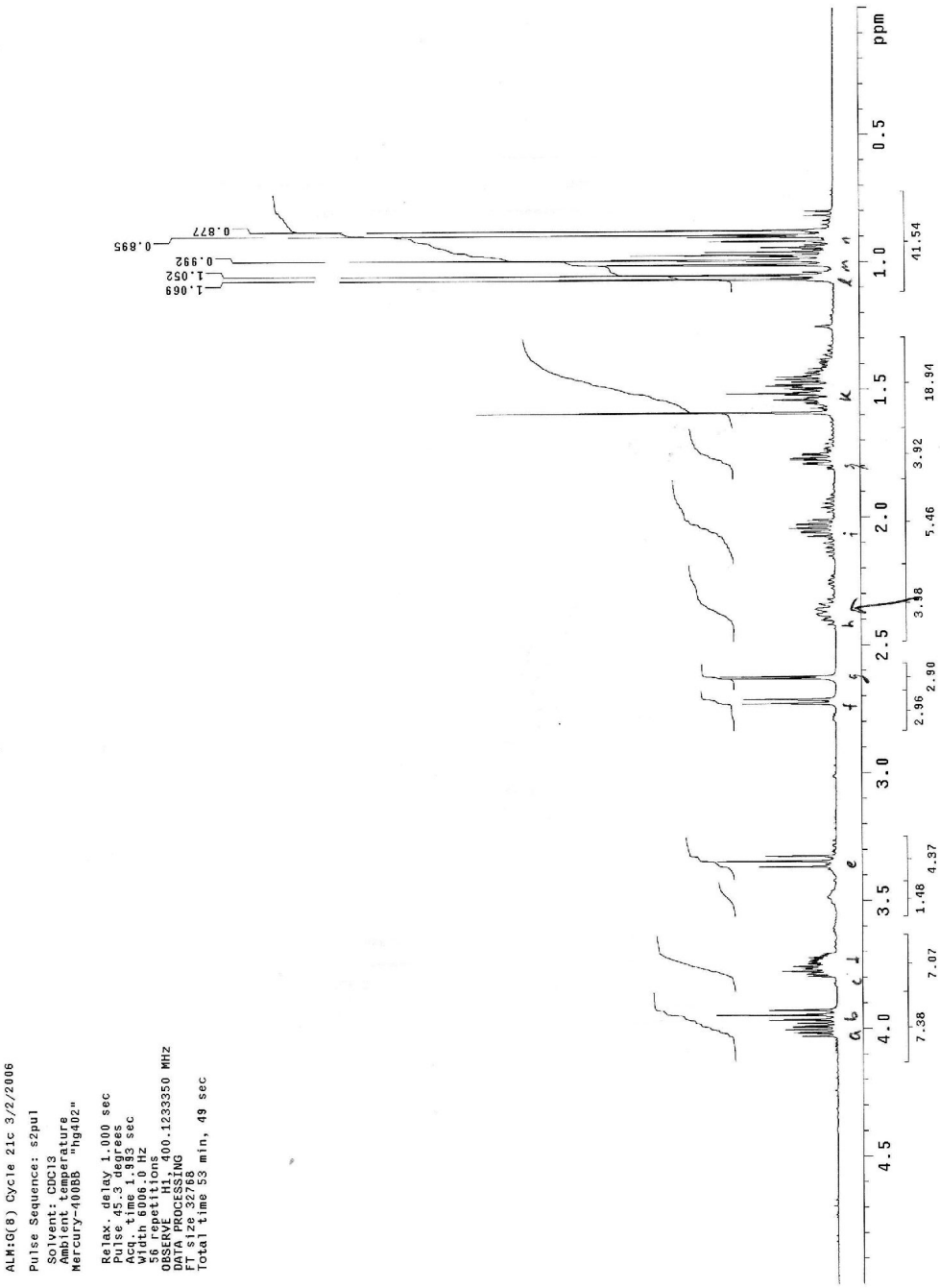
Spectrum A.60: ^{13}C spectrum of compound **73a**.



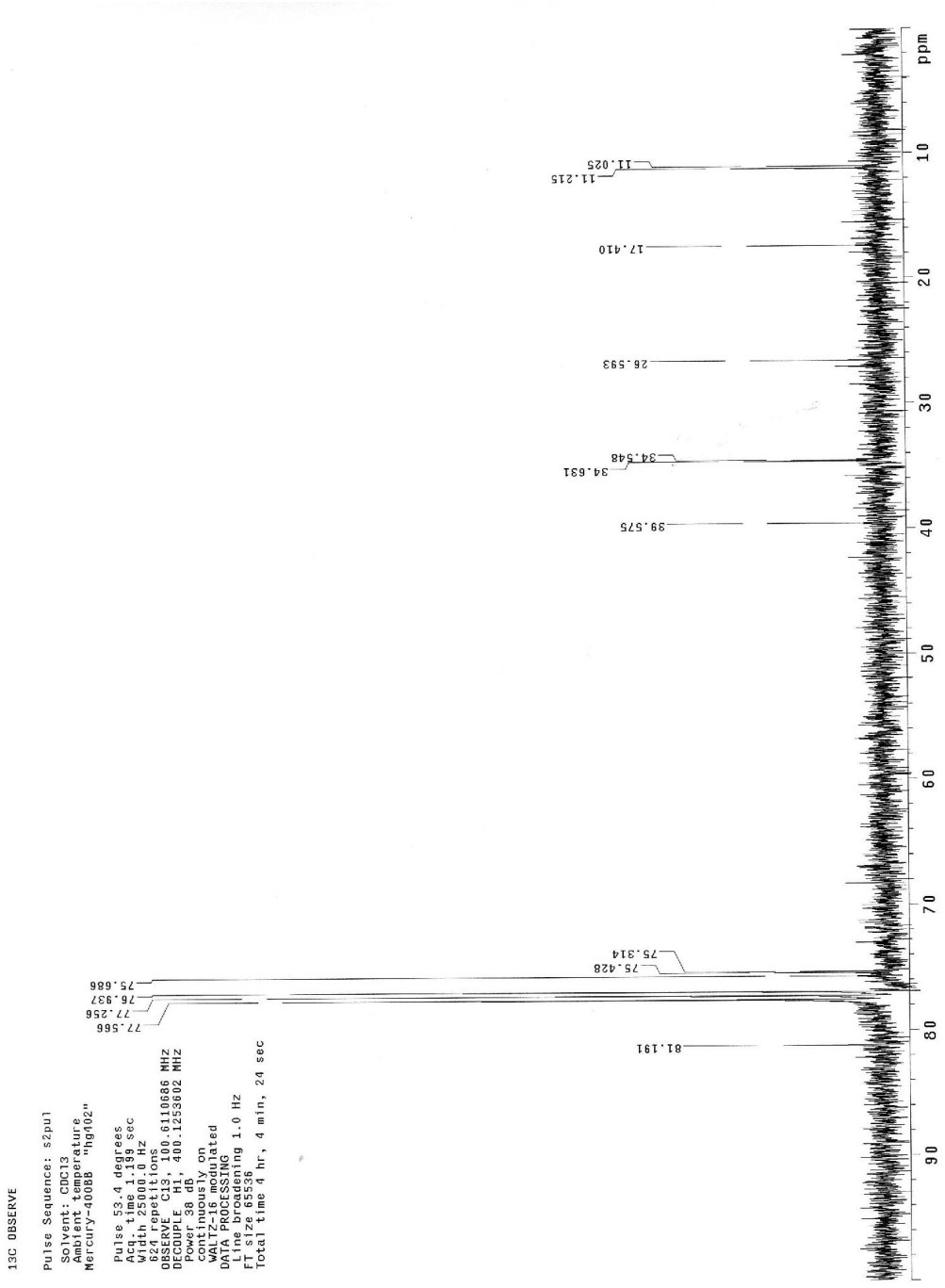
Spectrum A.61: ^{1}H spectrum of compound **73b**.



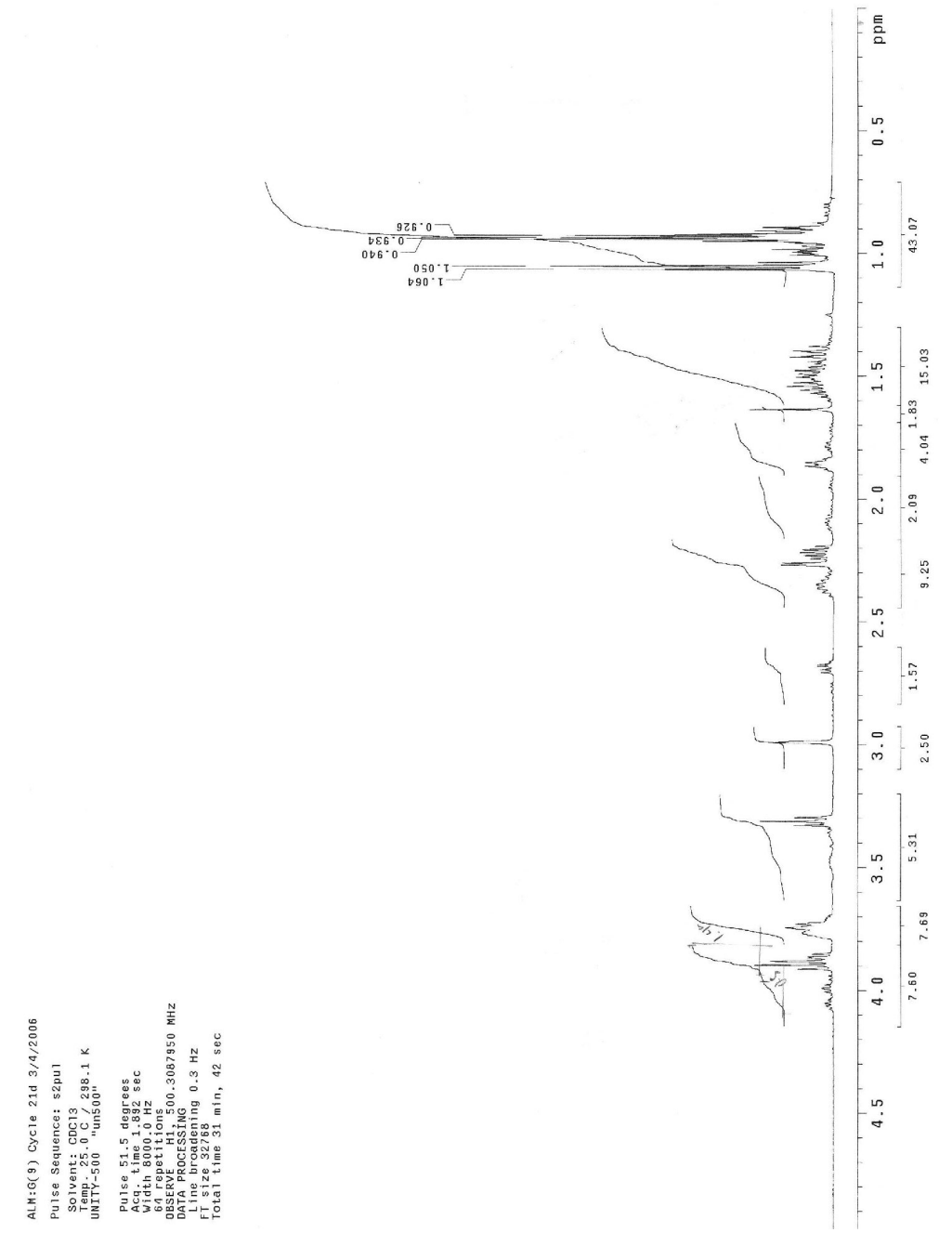
Spectrum A.62: ^{13}C spectrum of compound **73b**.



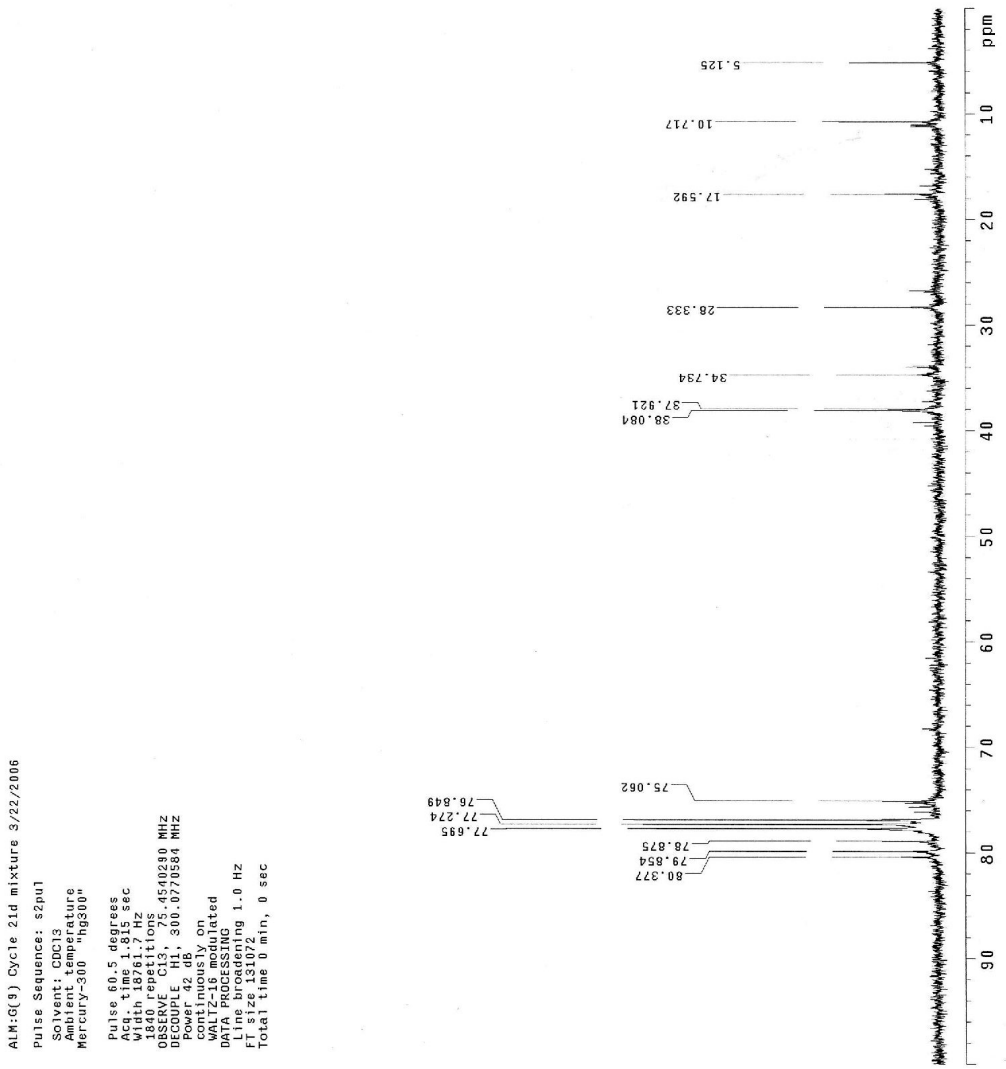
Spectrum A.63: ^{1}H spectrum of compound **73c**.



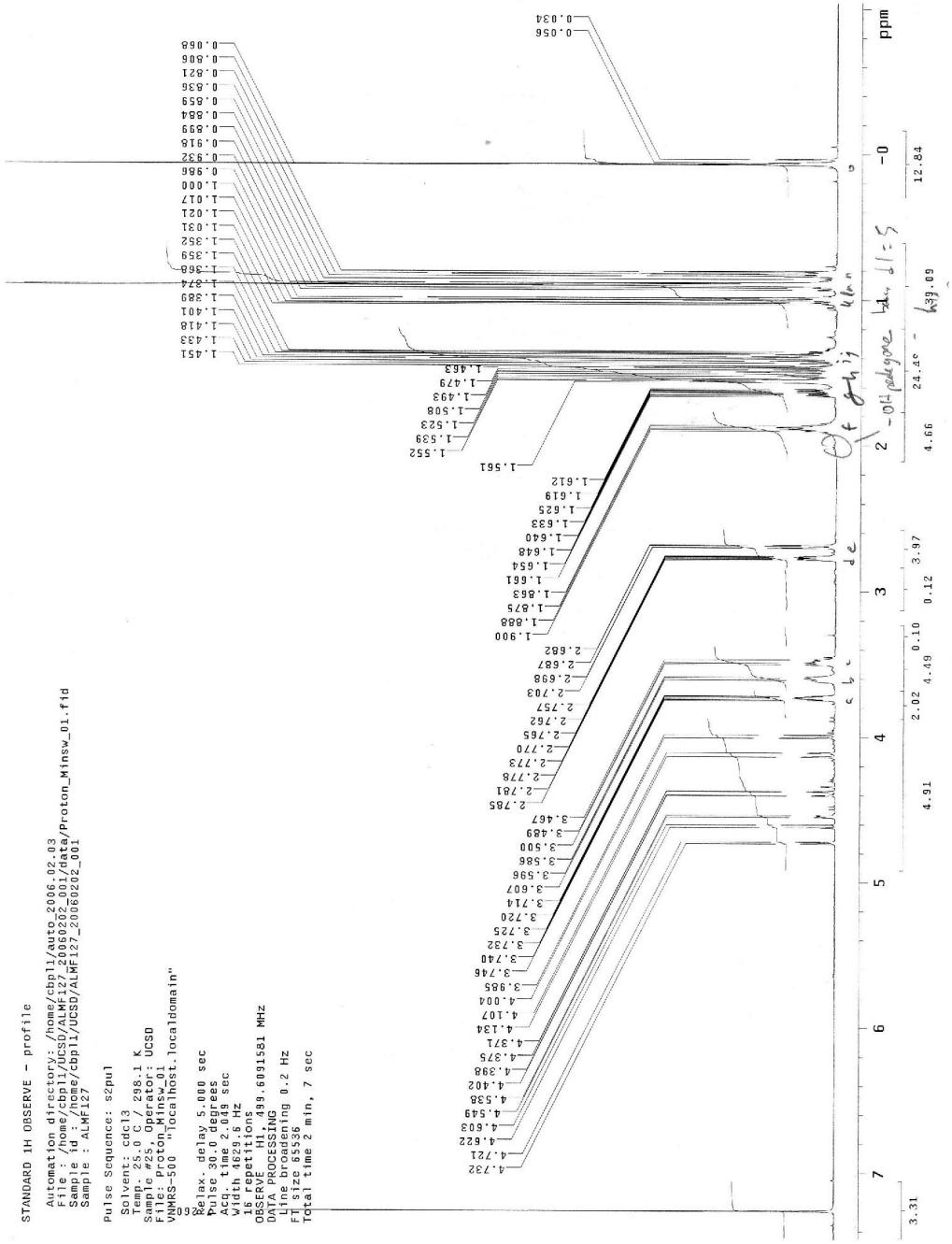
Spectrum A.64: ^{13}C spectrum of compound **73c**.



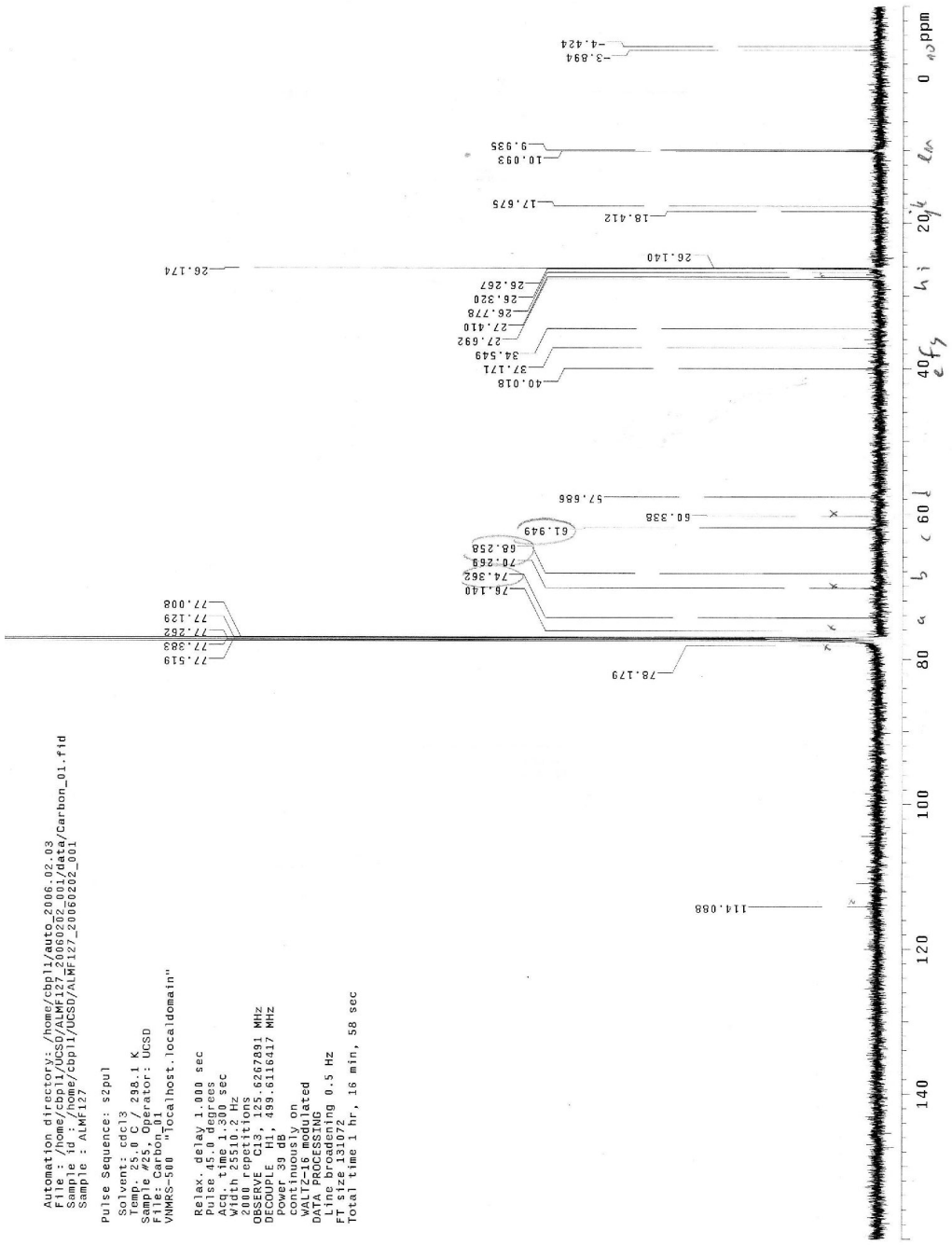
Spectrum A.65: ^{1}H spectrum of compound **73d**.



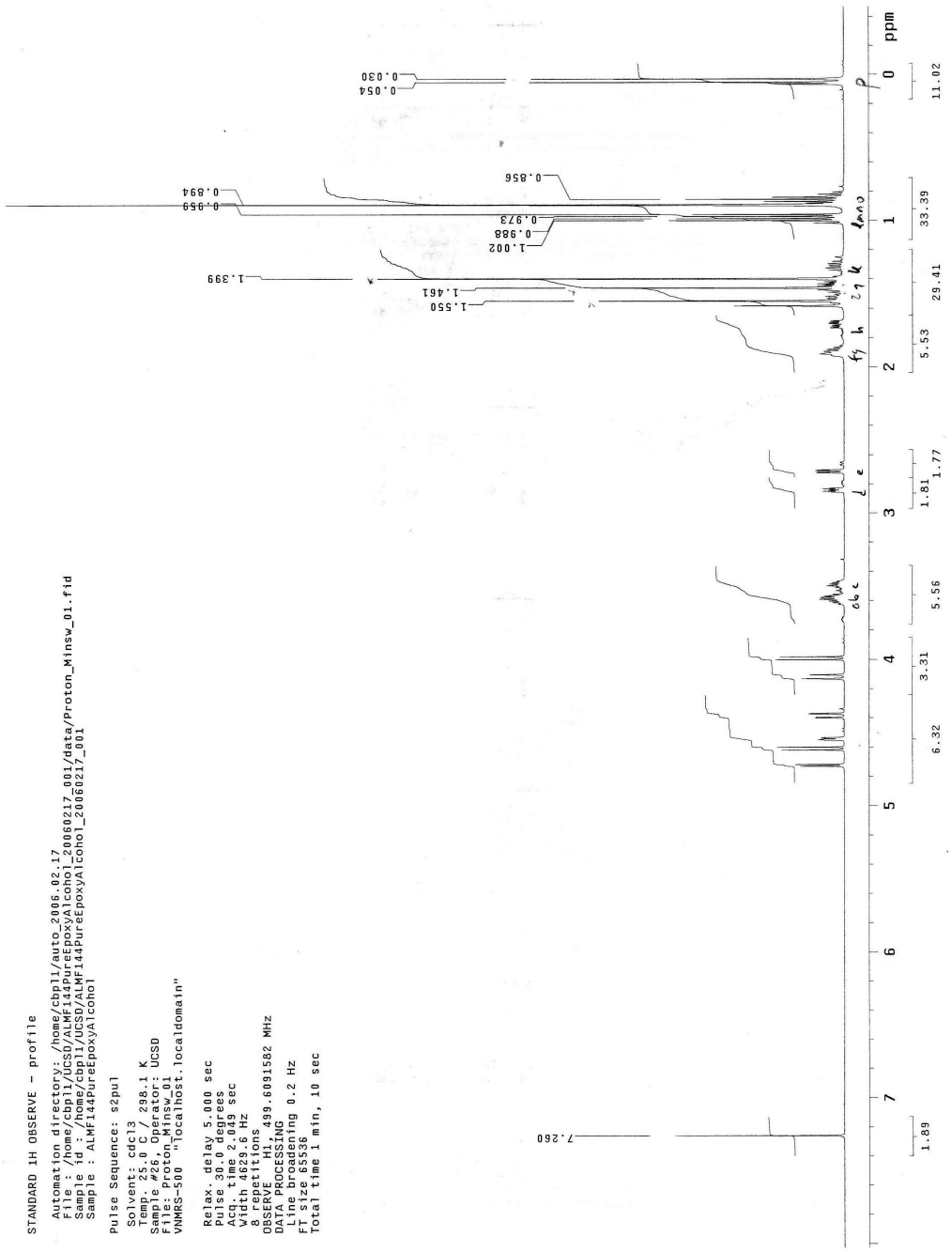
Spectrum A.66: ^{13}C spectrum of compound **73d**.



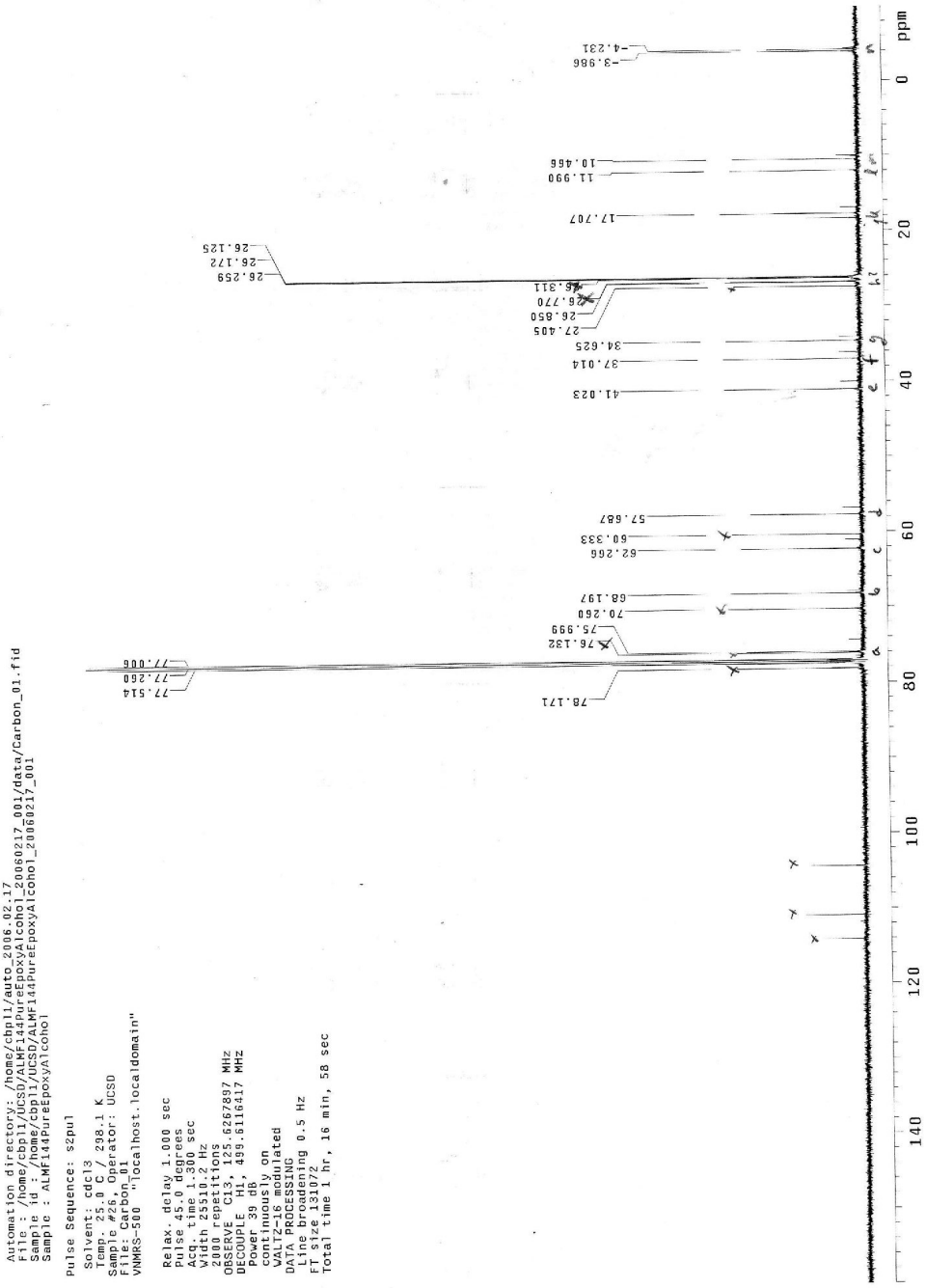
Spectrum A.67: ^{1}H spectrum of compound **74a**.



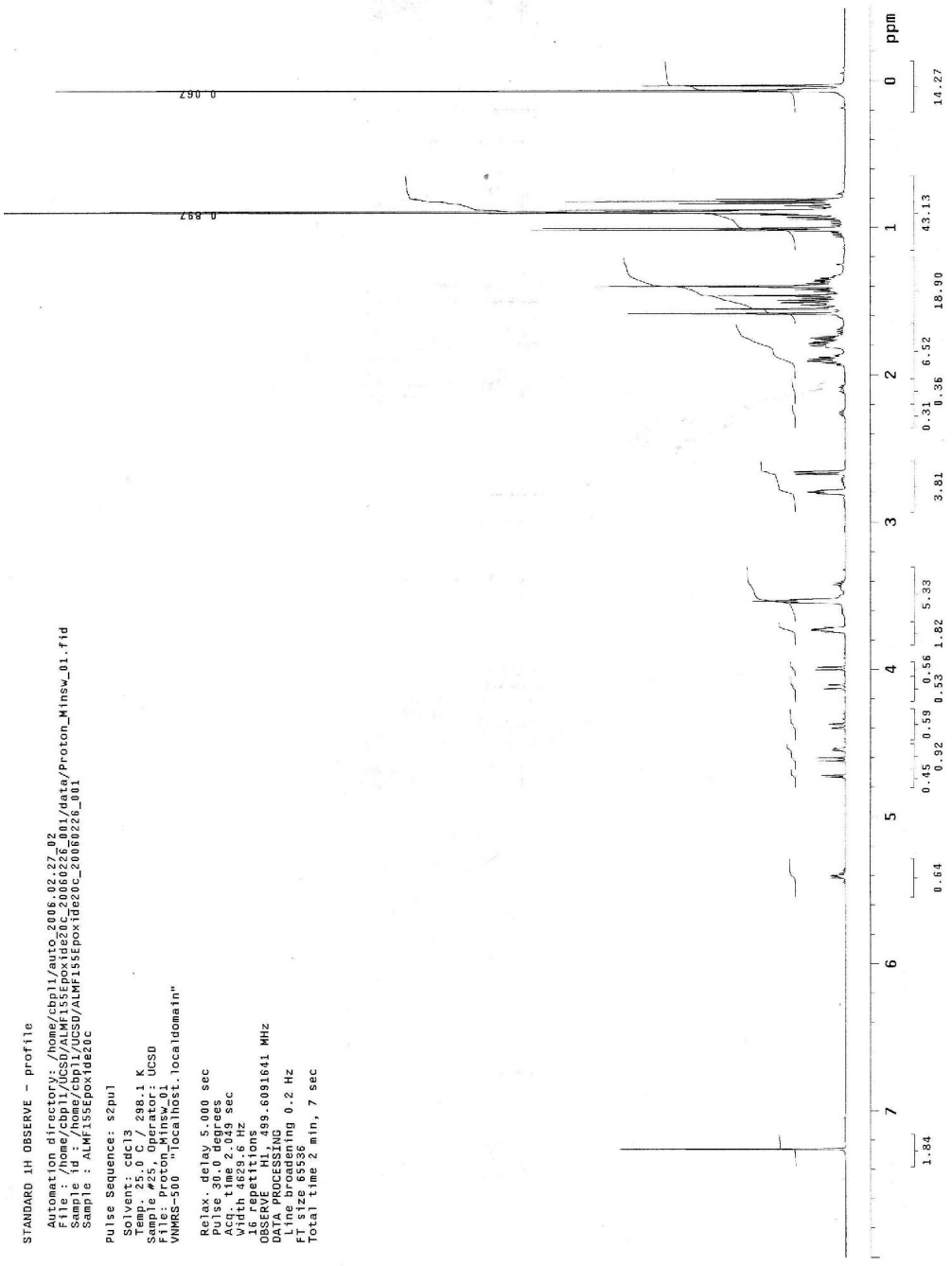
Spectrum A.68: ^{13}C spectrum of compound **74a**.



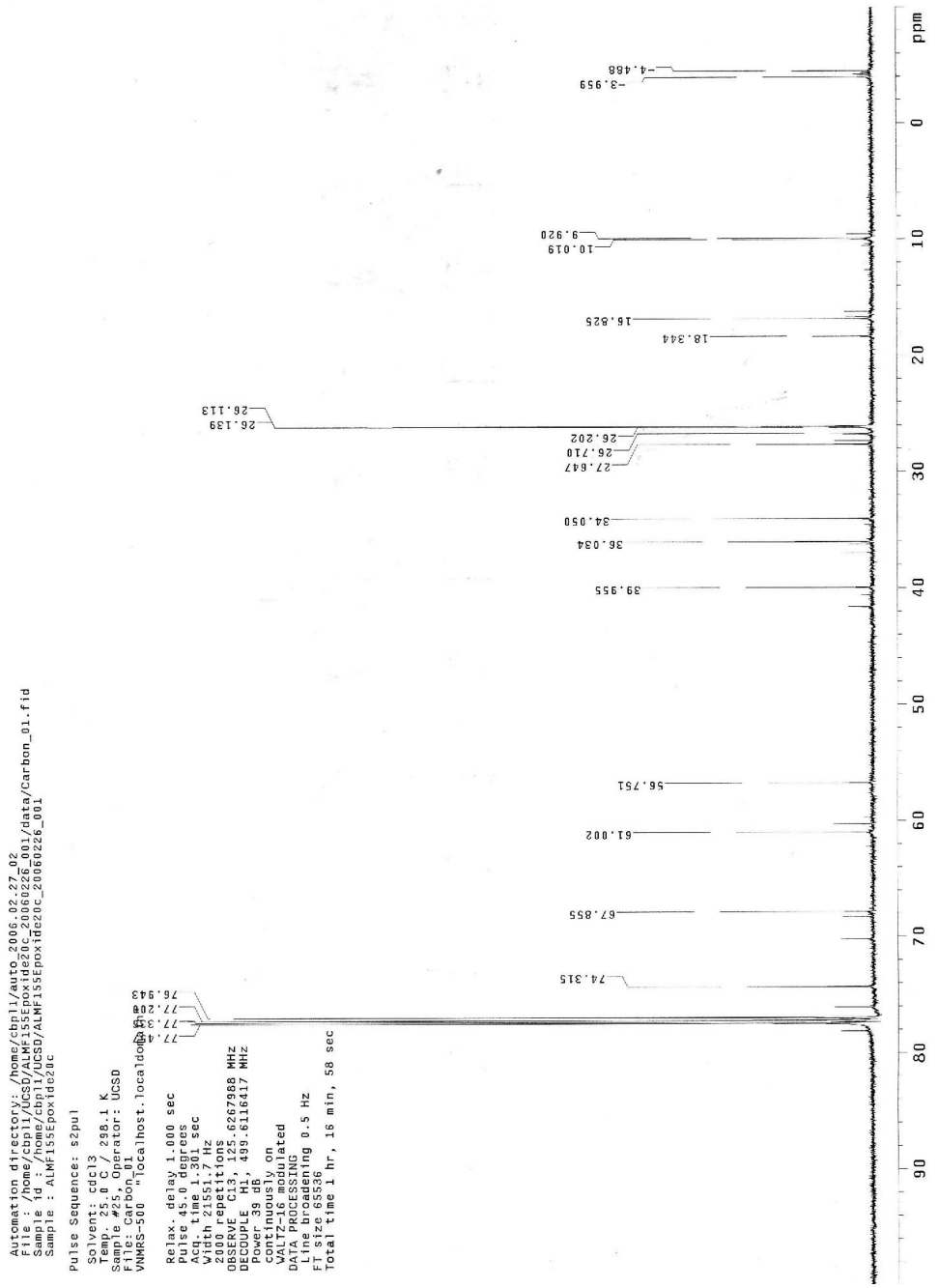
Spectrum A.69: ^{1}H spectrum of compound **74b**.



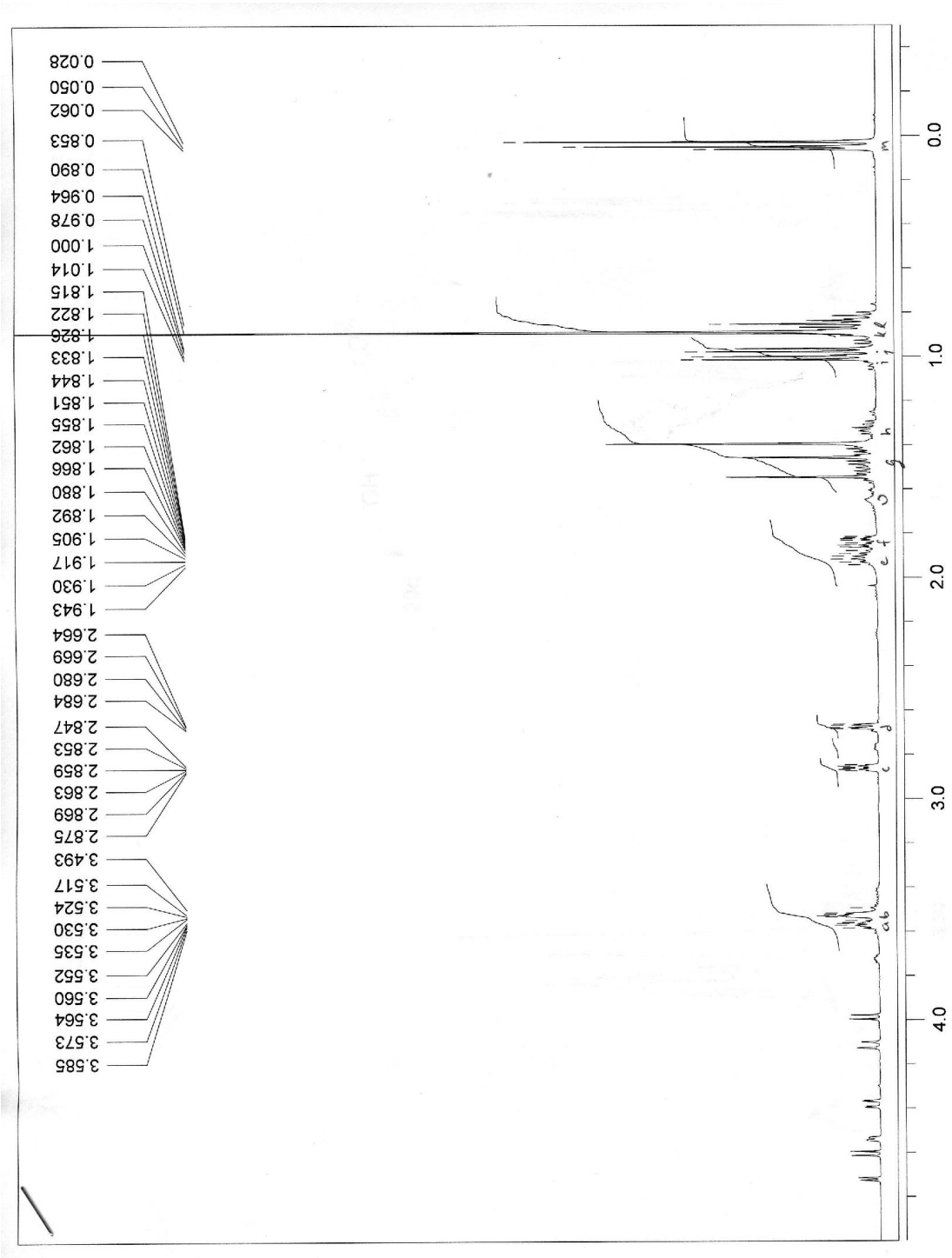
Spectrum A.70: ^{13}C spectrum of compound **74b**.



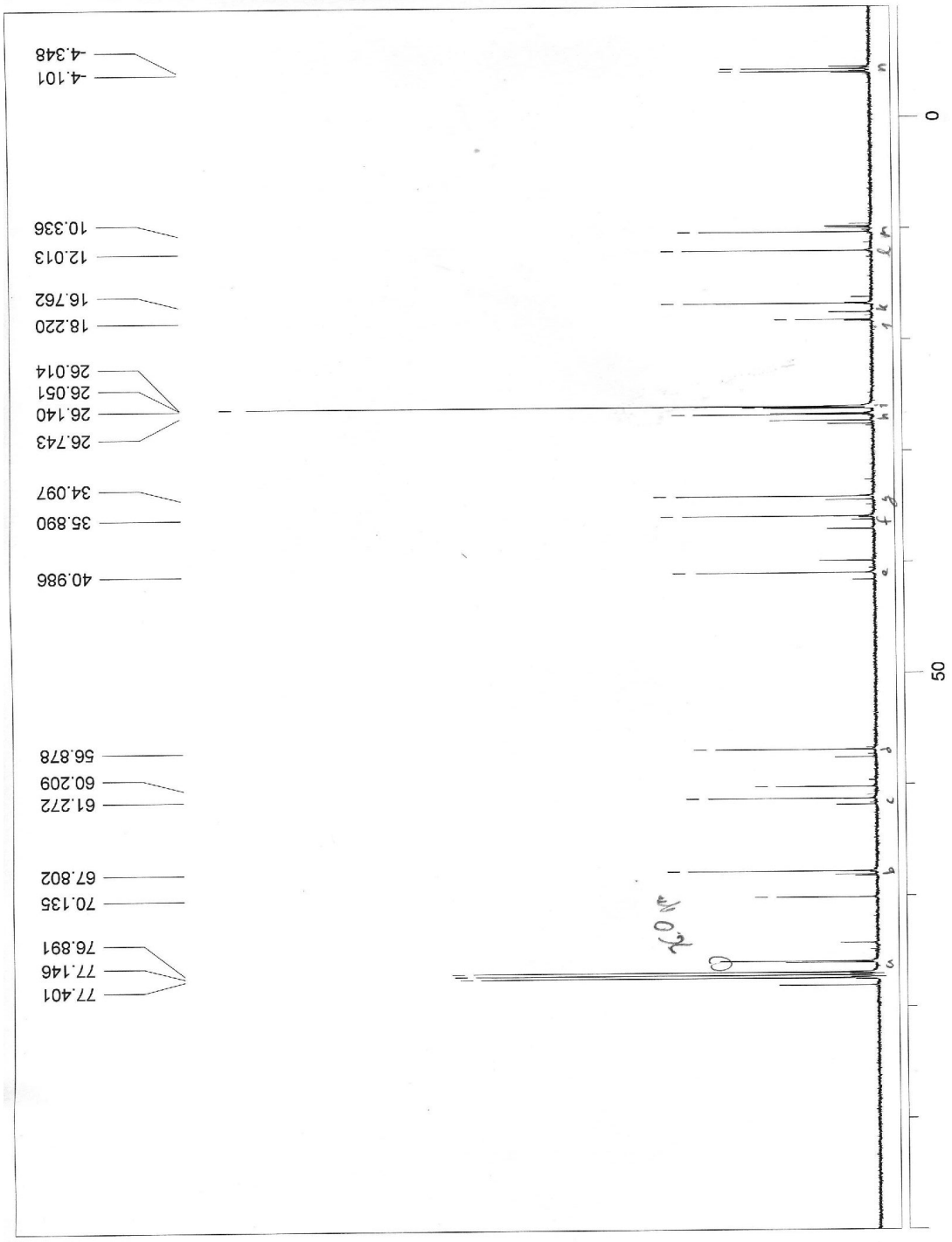
Spectrum A.71: ^{1}H spectrum of compound **74c**.



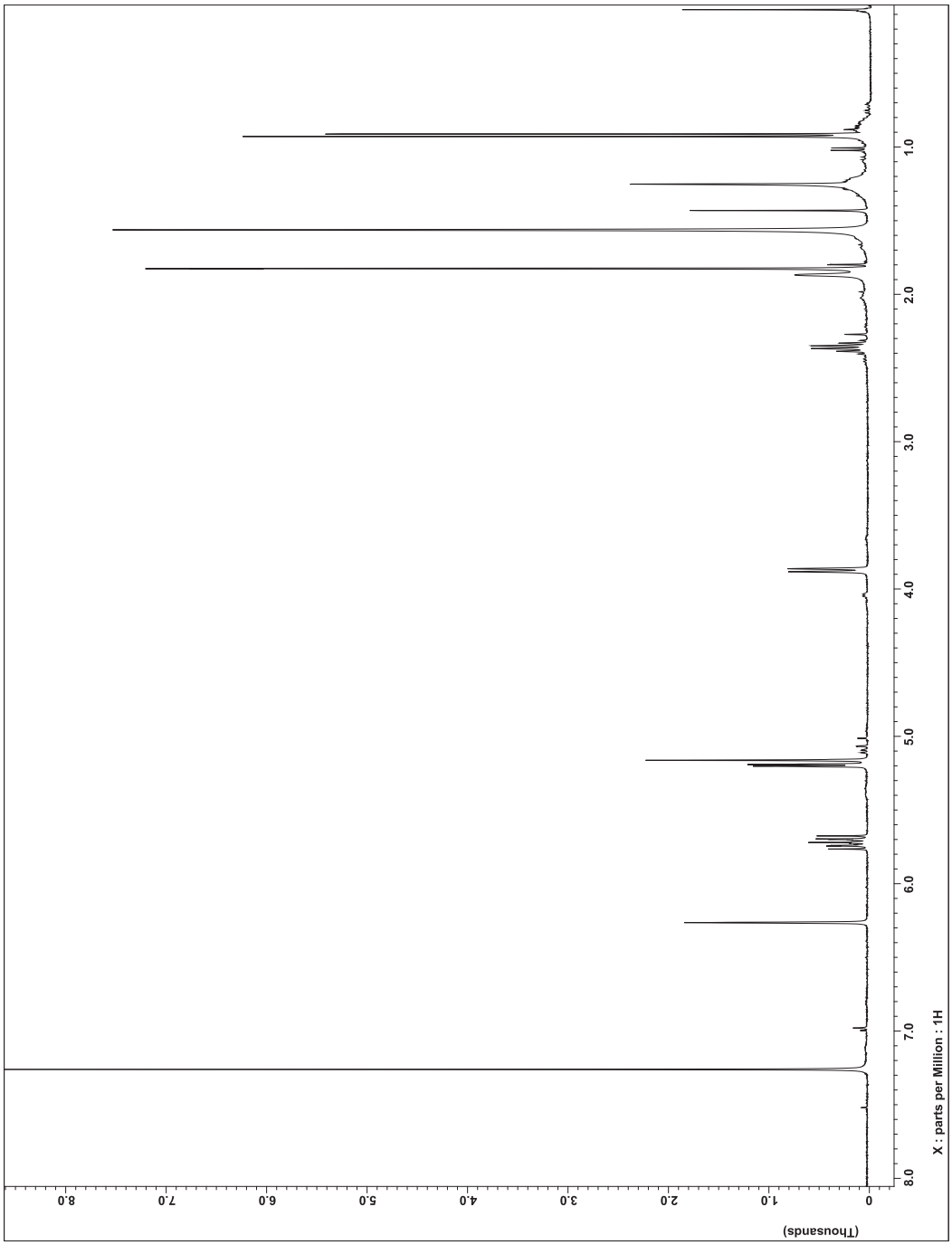
Spectrum A.72: ^{13}C spectrum of compound **74c**.



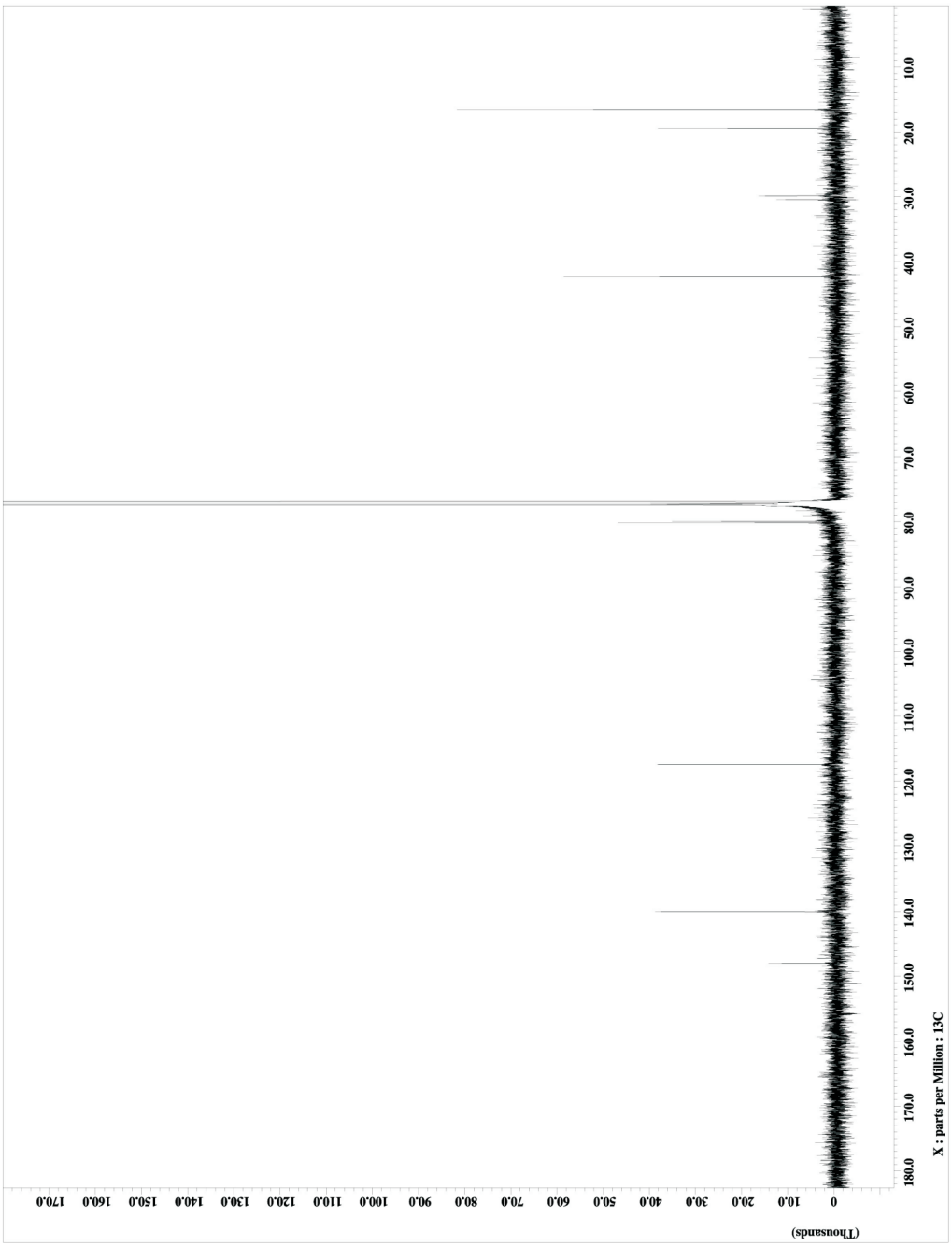
Spectrum A.73: ^{1}H spectrum of compound **74d**.



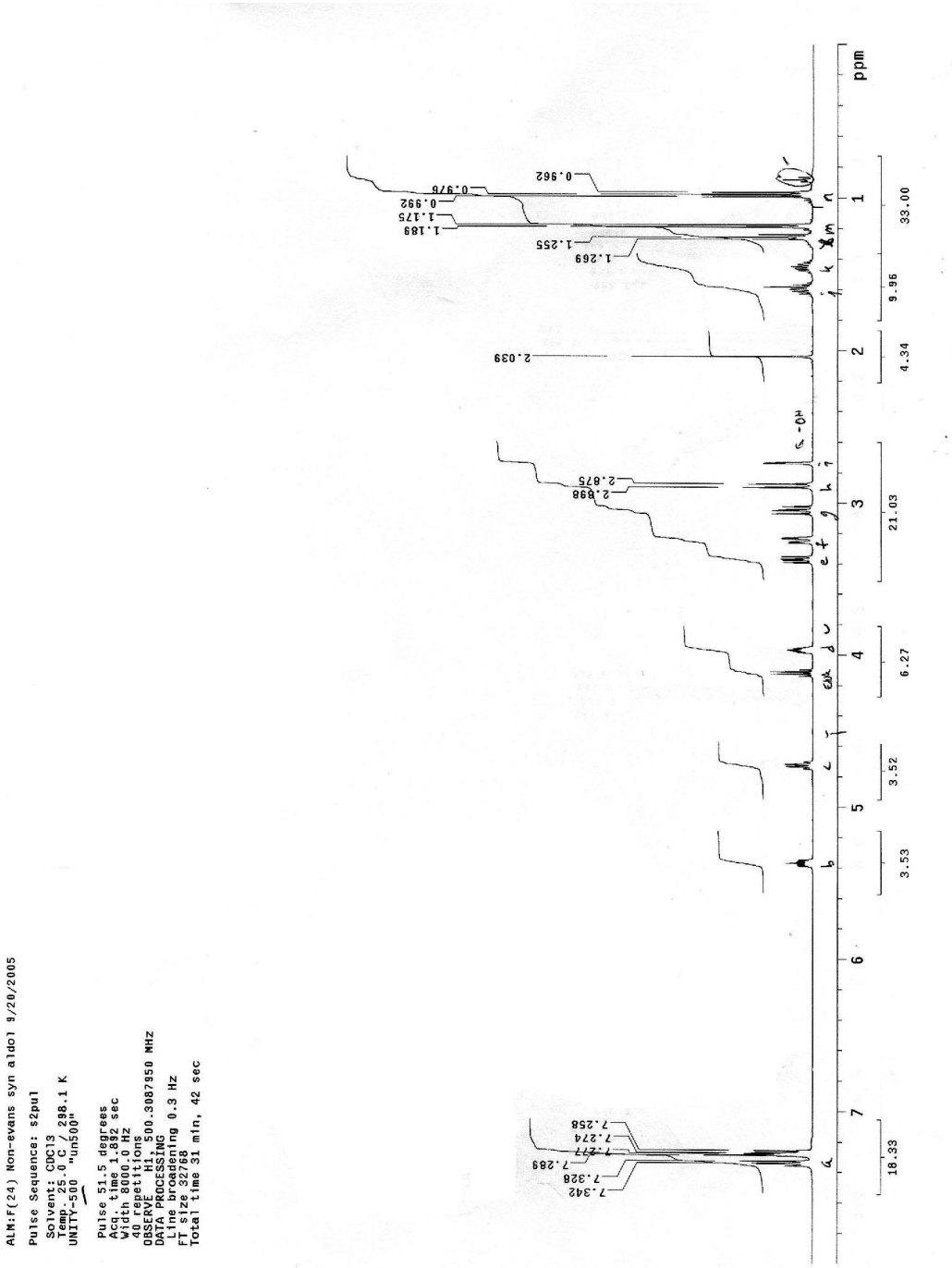
Spectrum A.74: ^{13}C spectrum of compound **74d**.



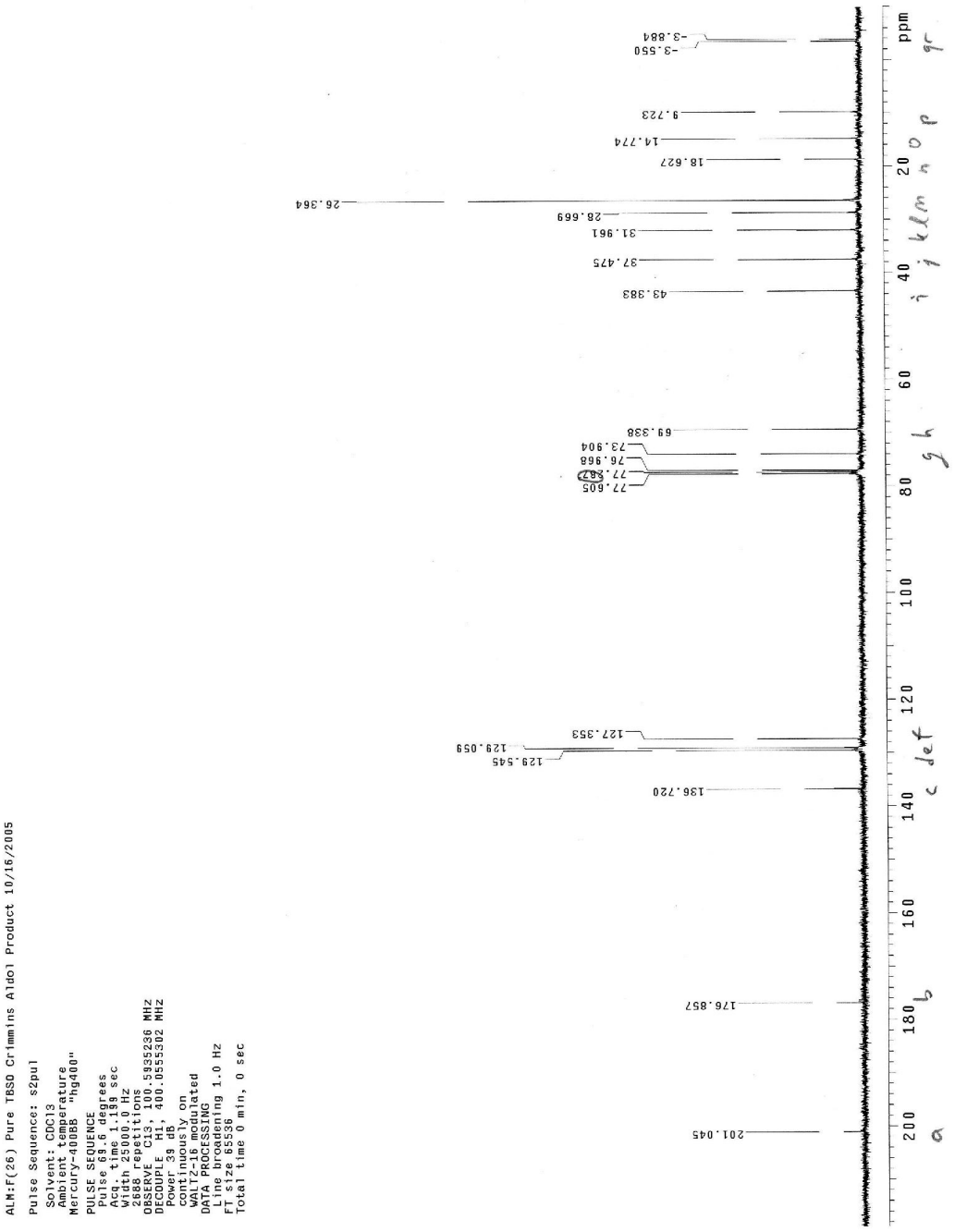
Spectrum A.75: ^{1}H spectrum of compound **115a**.



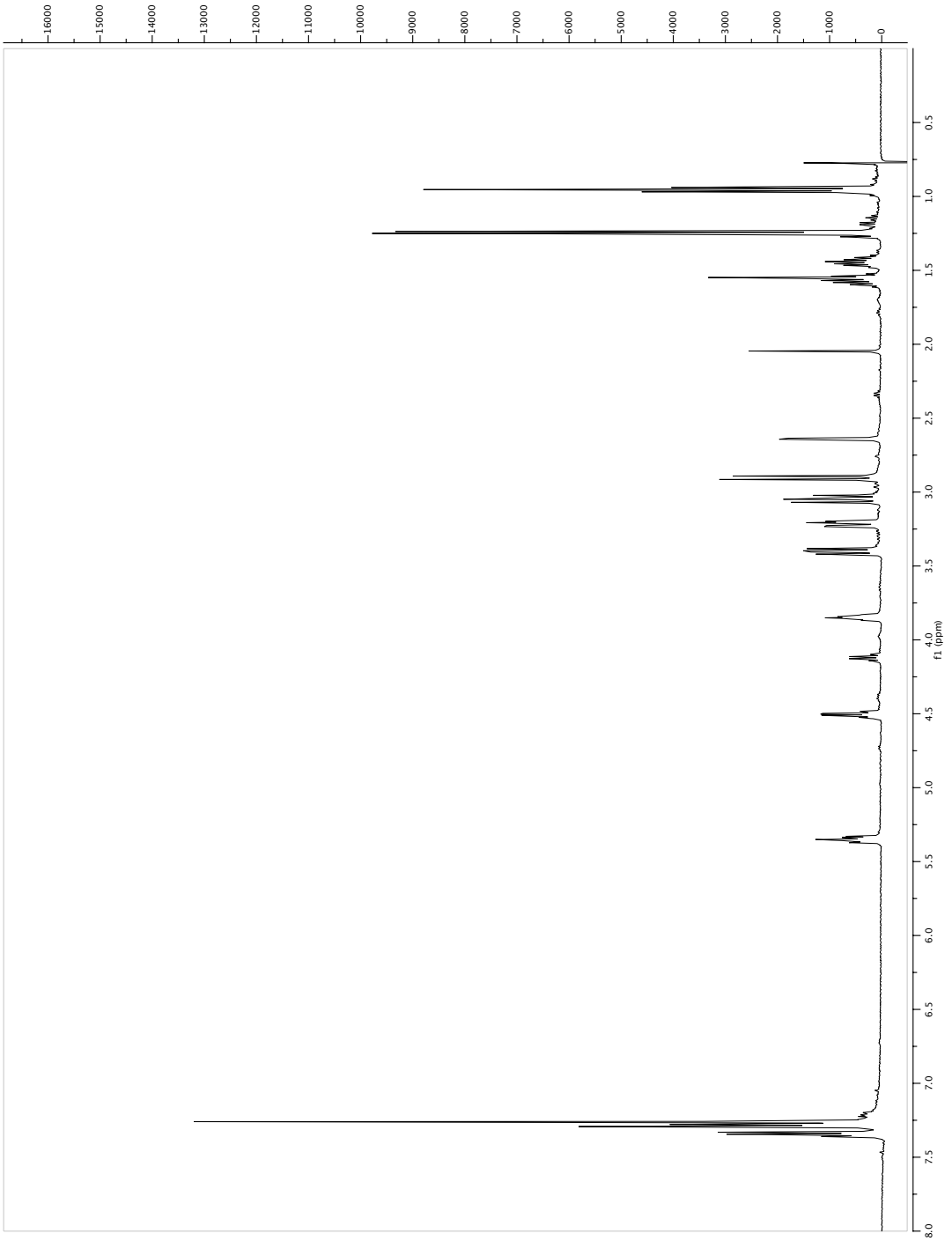
Spectrum A.76: ^{13}C spectrum of compound **115a**.



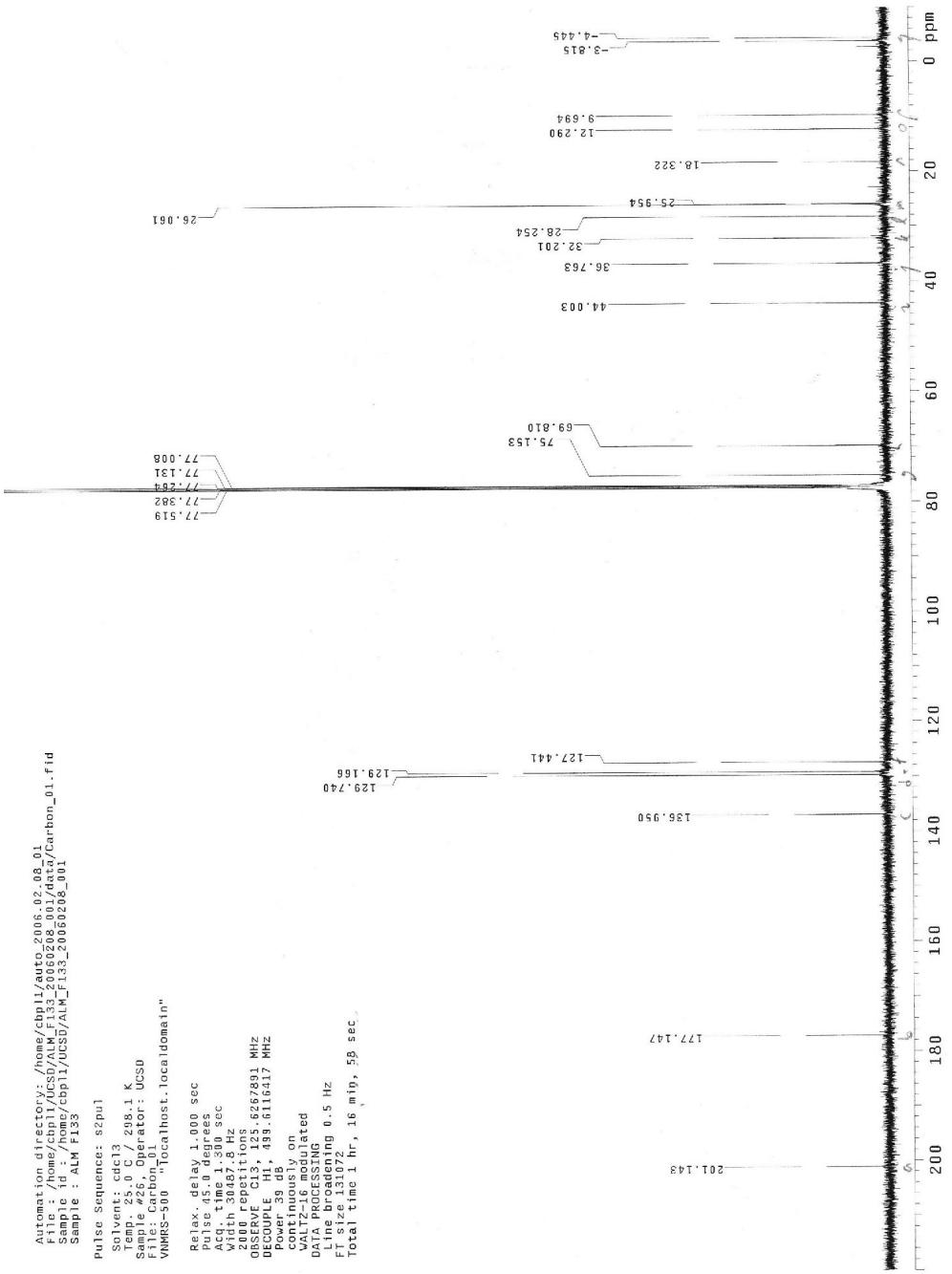
Spectrum A.77: ^{1}H spectrum of compound **117a**.



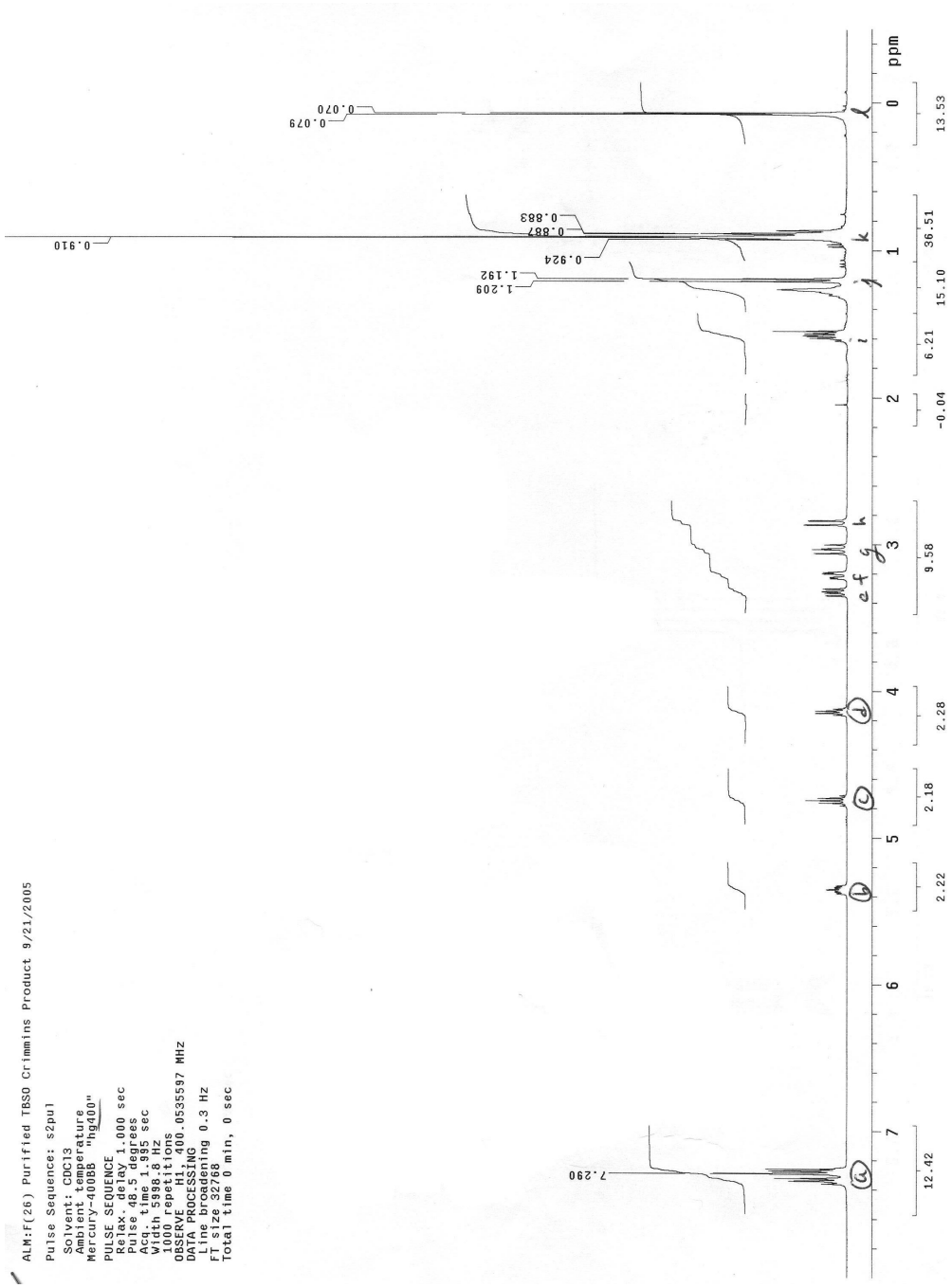
Spectrum A.78: ^{13}C spectrum of compound **117a**.



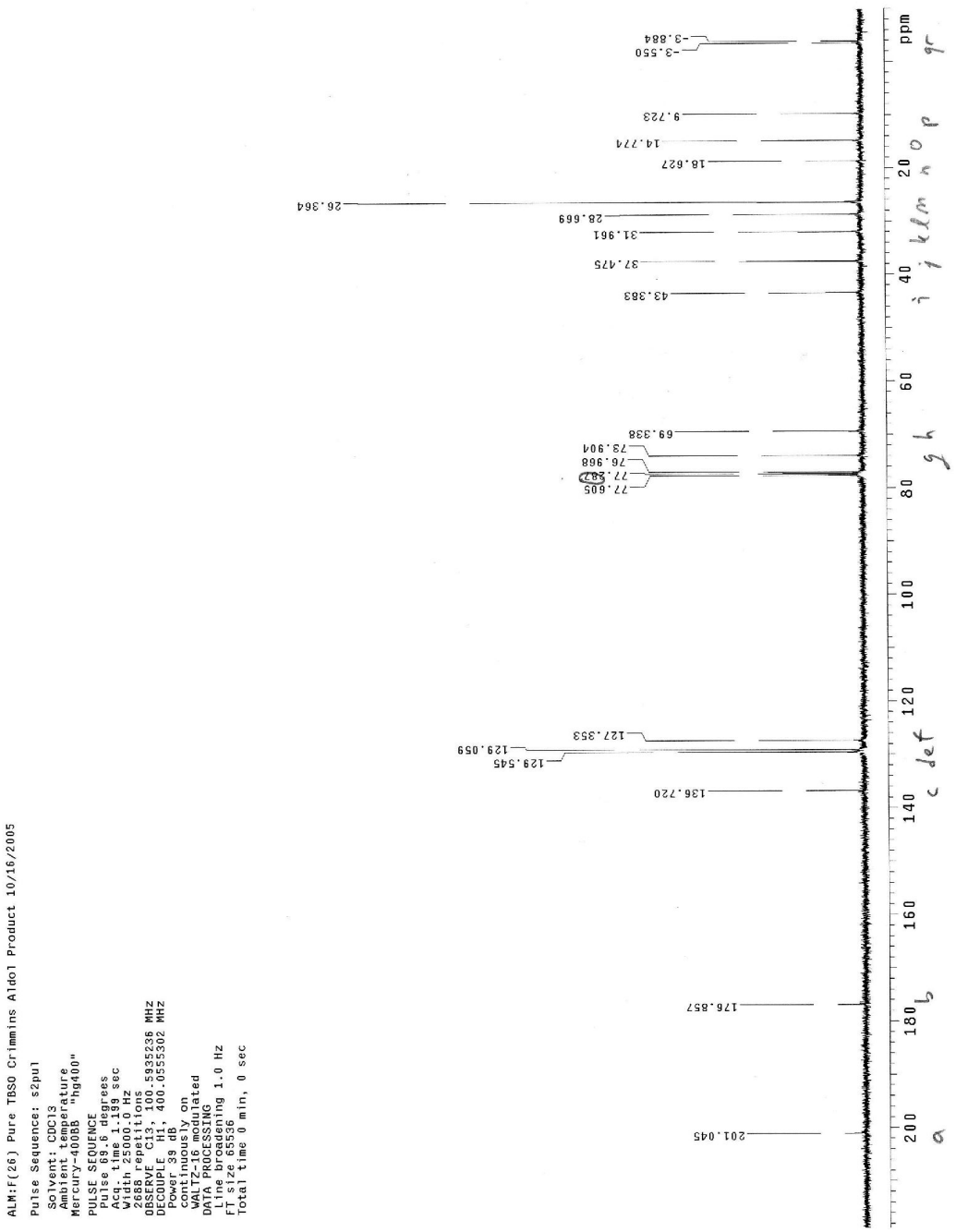
Spectrum A.79: ^{1}H spectrum of compound **117b**.



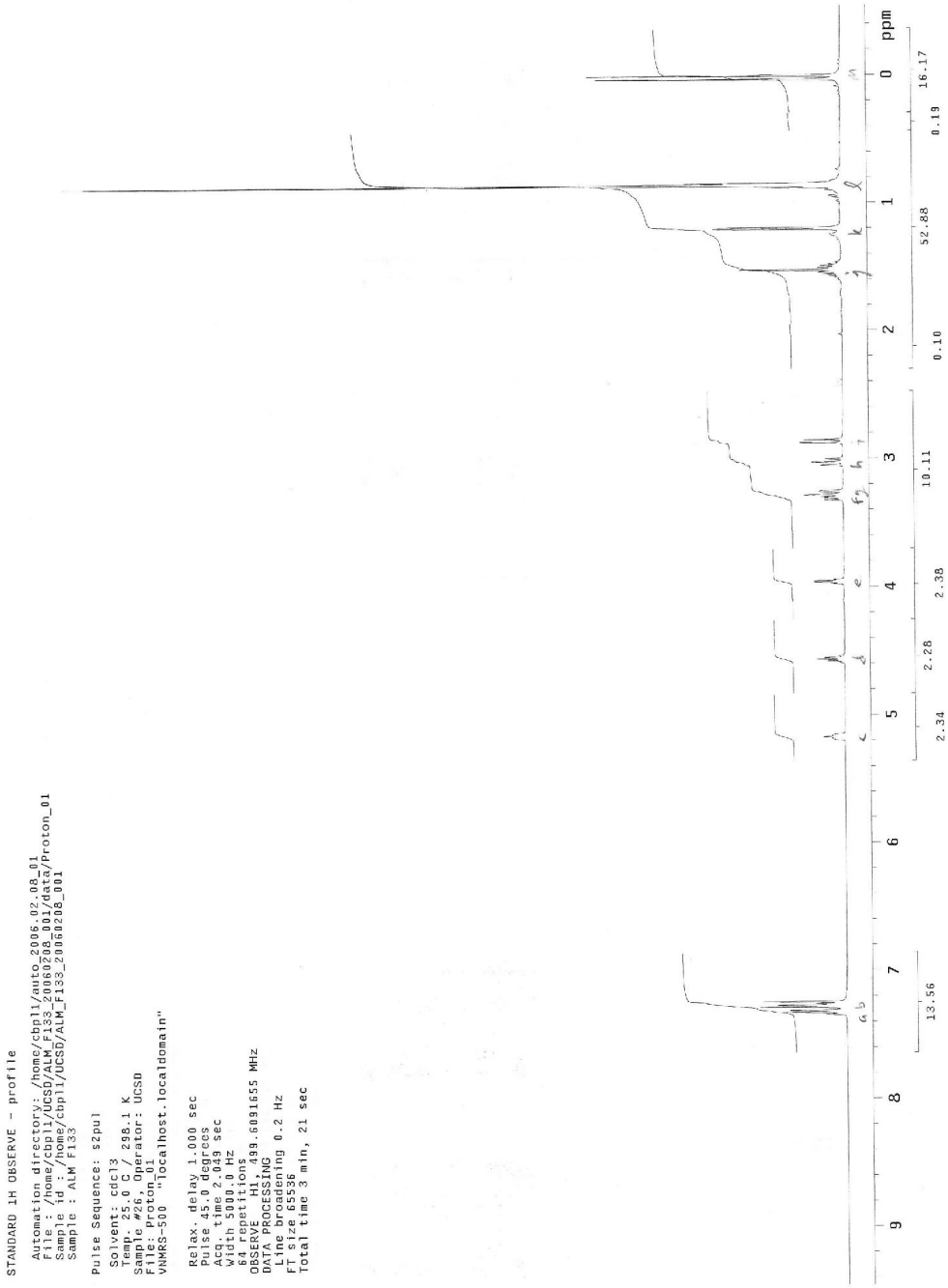
Spectrum A.80: ^{13}C spectrum of compound **117b**.



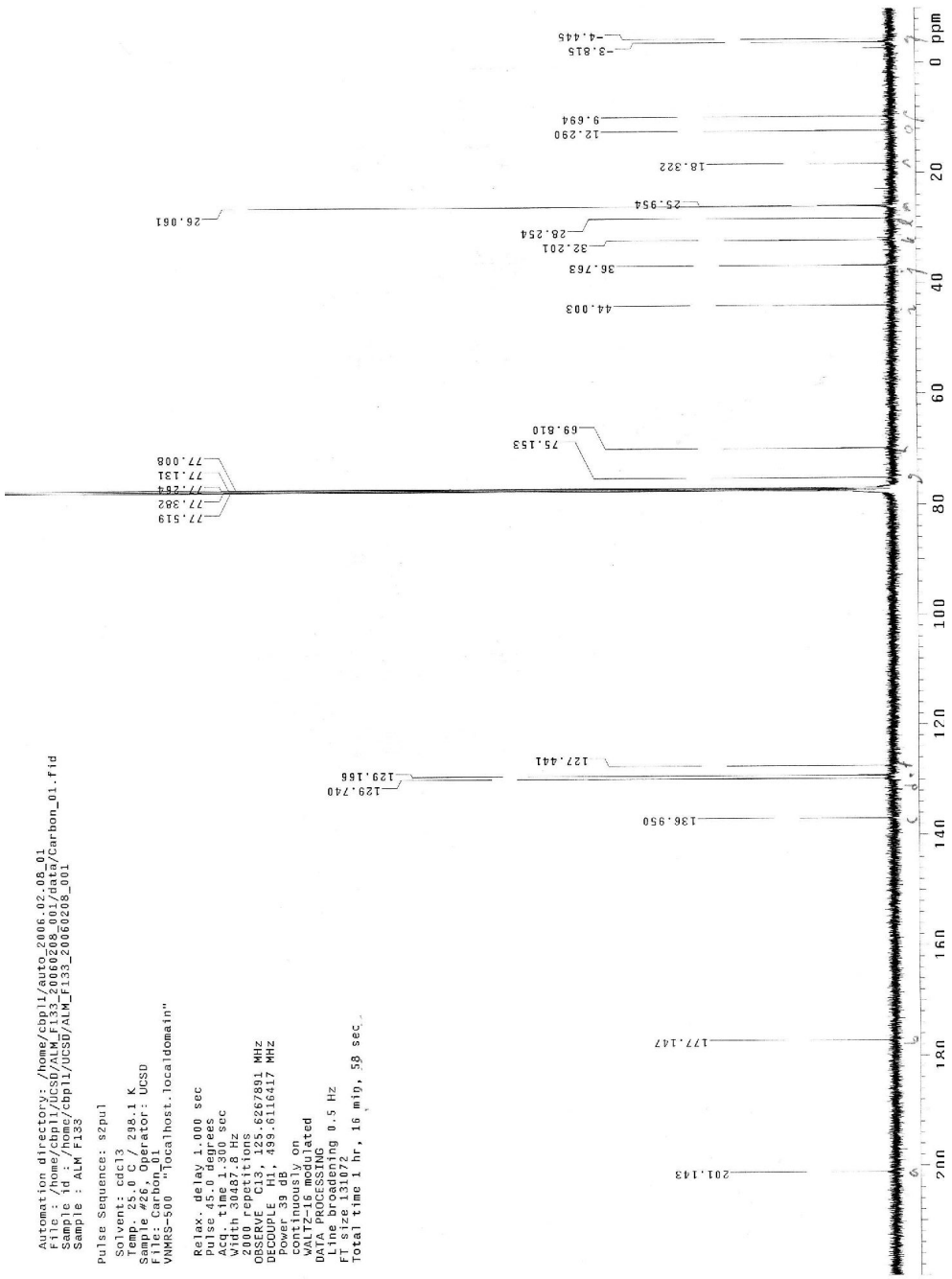
Spectrum A.81: ^{1}H spectrum of compound **118a**.



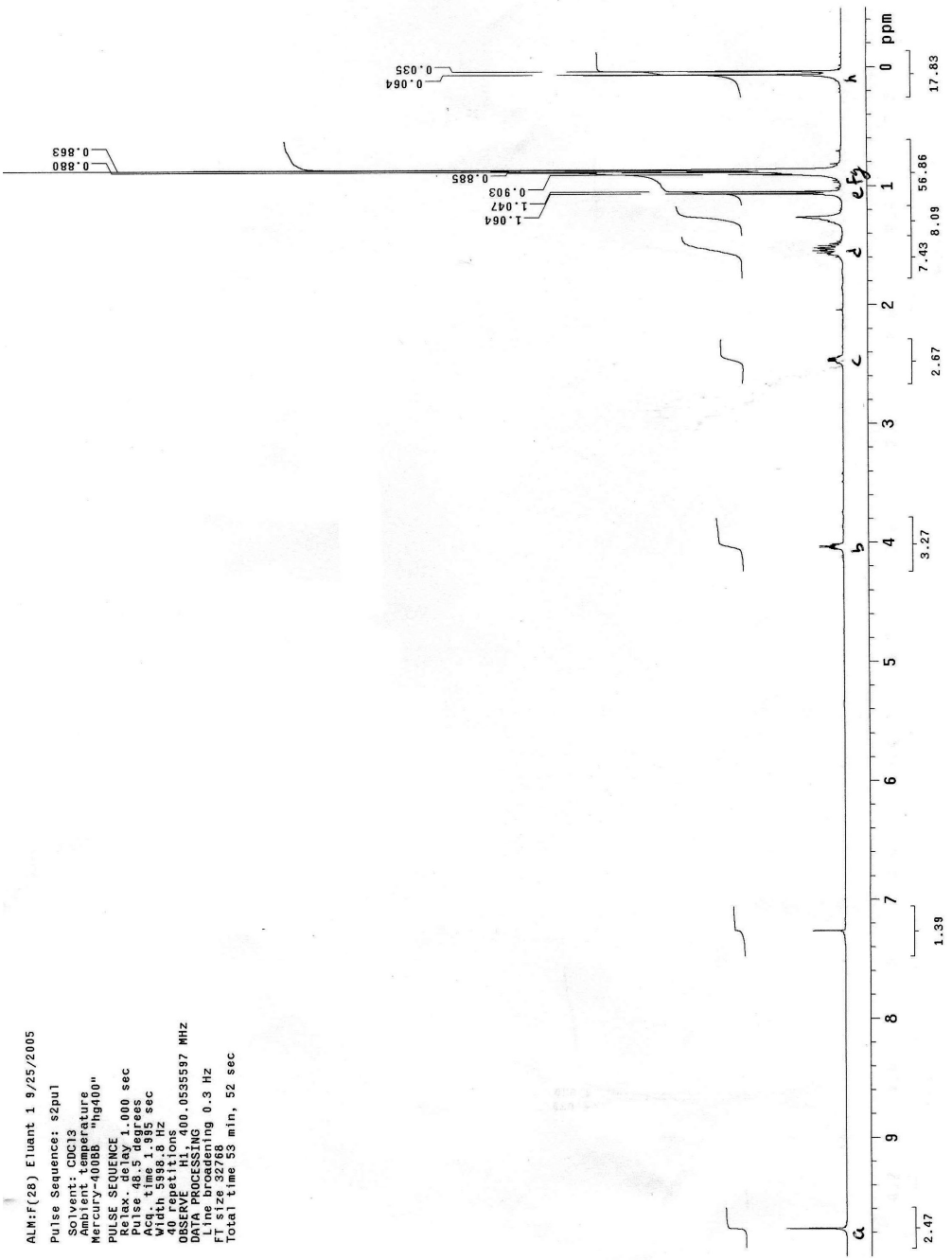
Spectrum A.82: ^{13}C spectrum of compound **118a**.



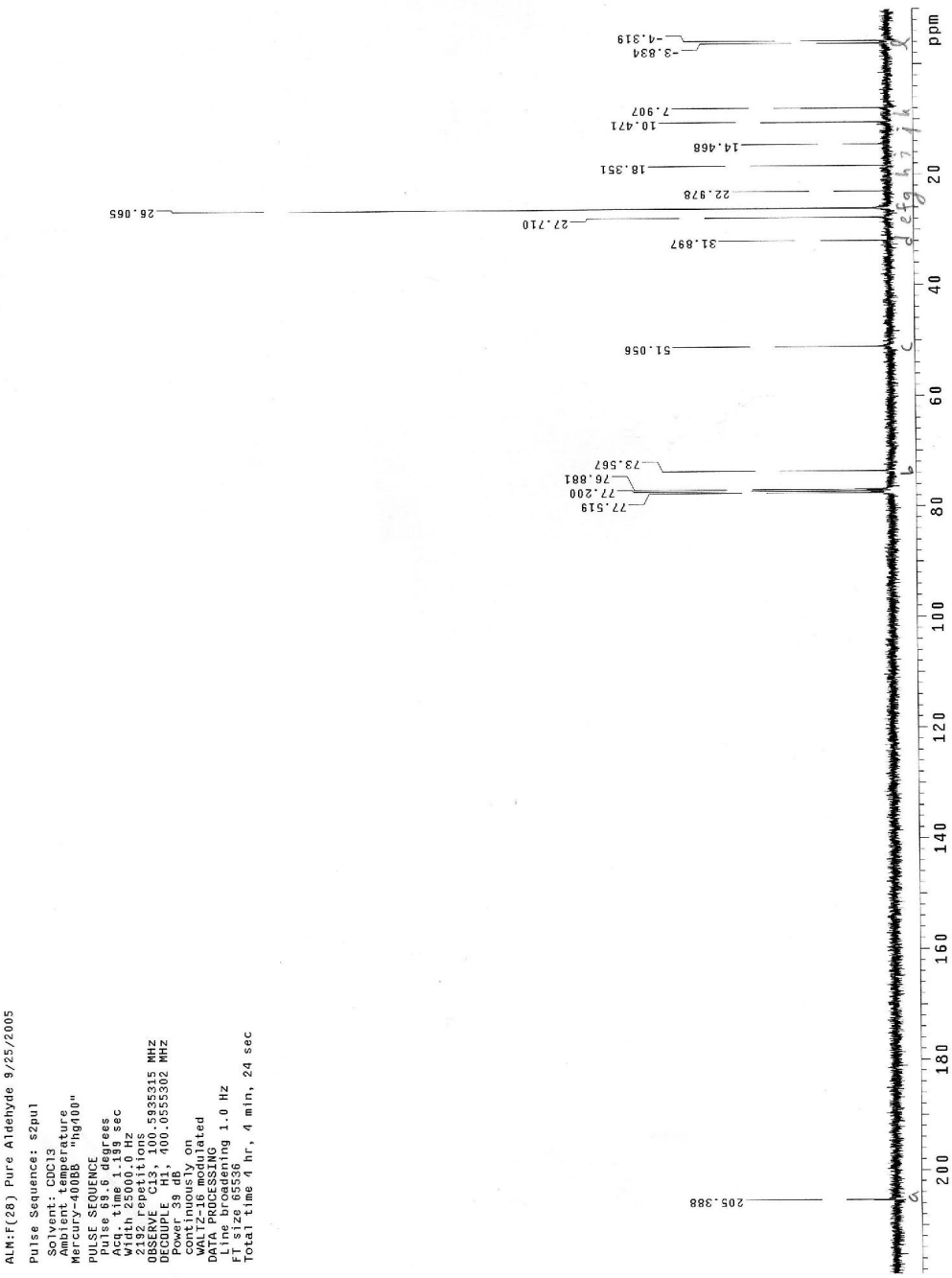
Spectrum A.83: ^{1}H spectrum of compound **118b**.



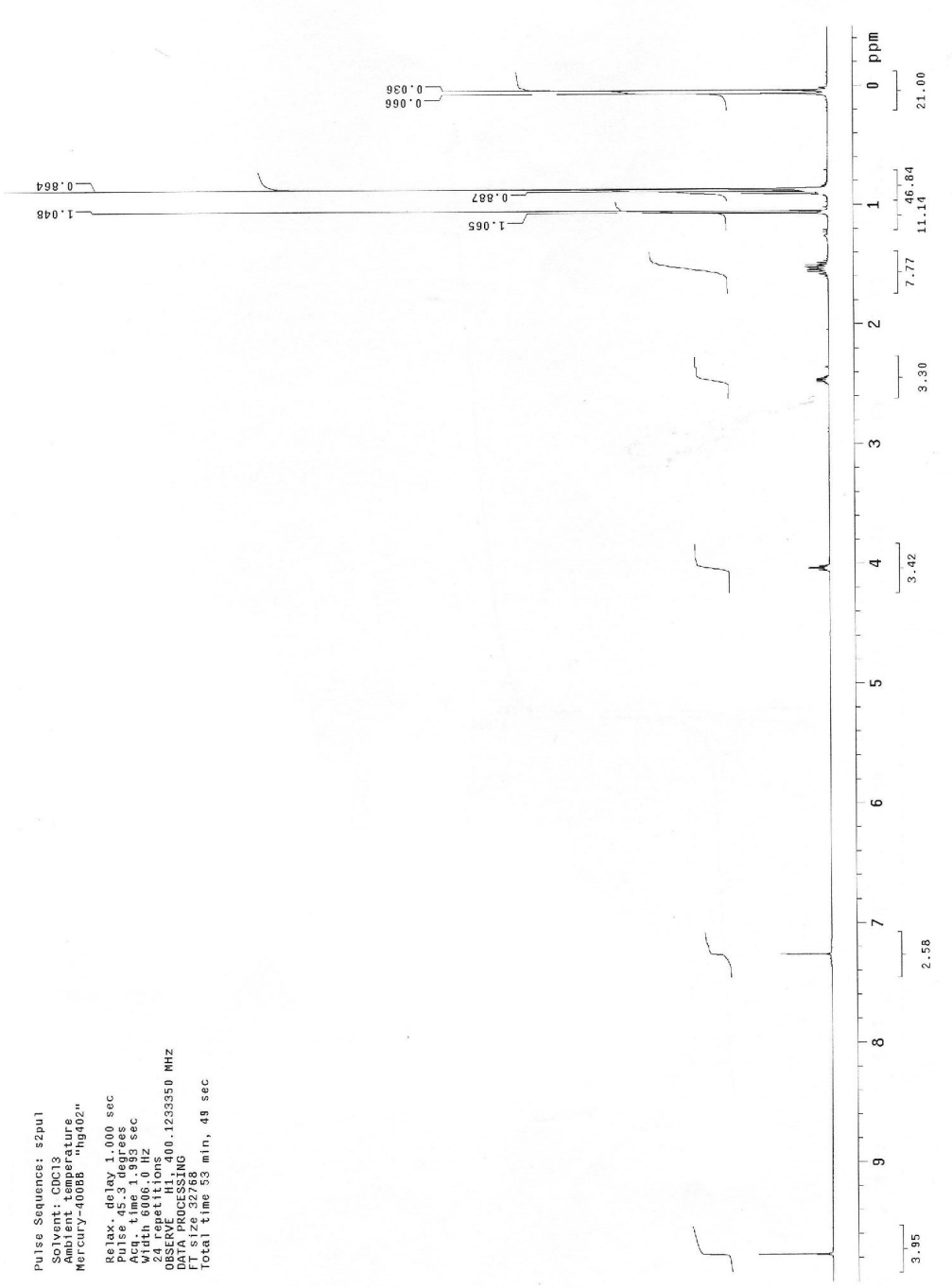
Spectrum A.84: ^{13}C spectrum of compound **118b**.



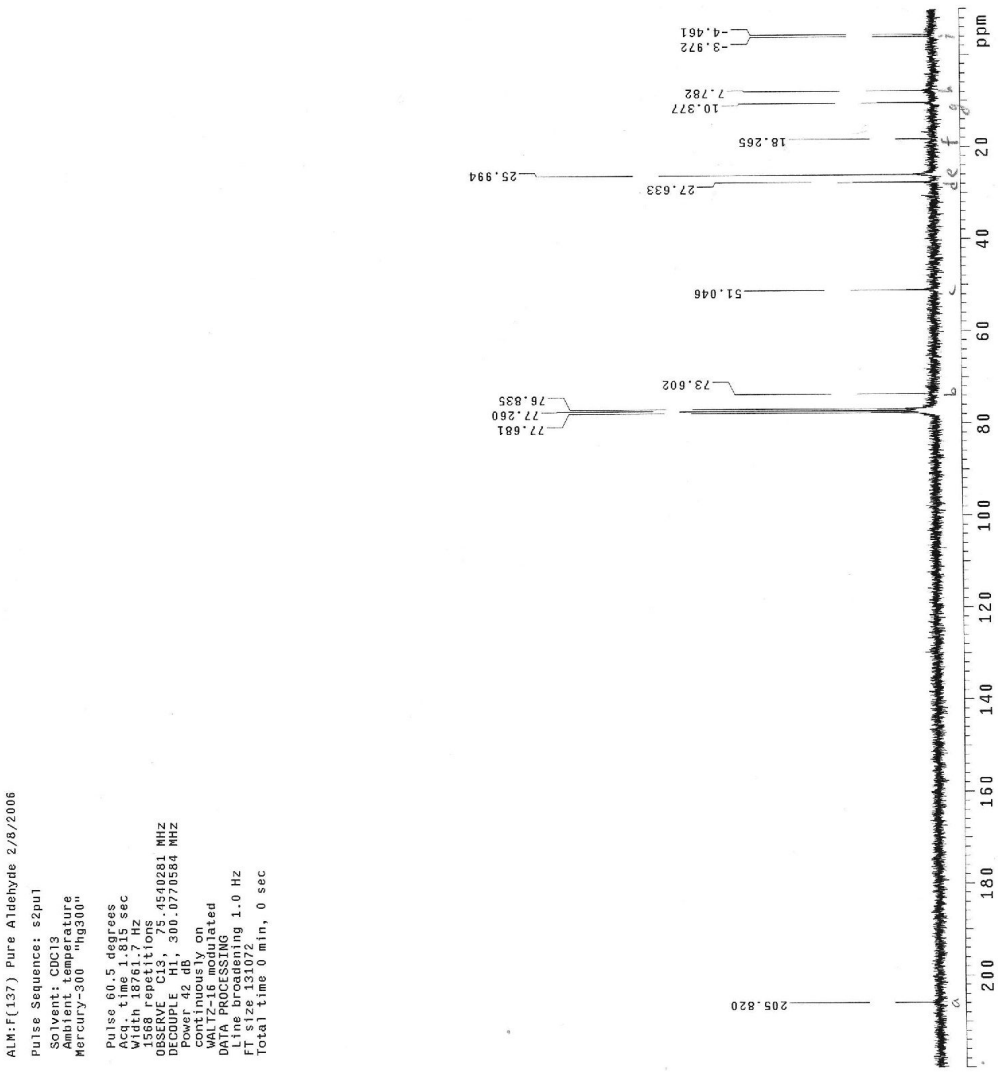
Spectrum A.85: ^{1}H spectrum of compound **119a**.



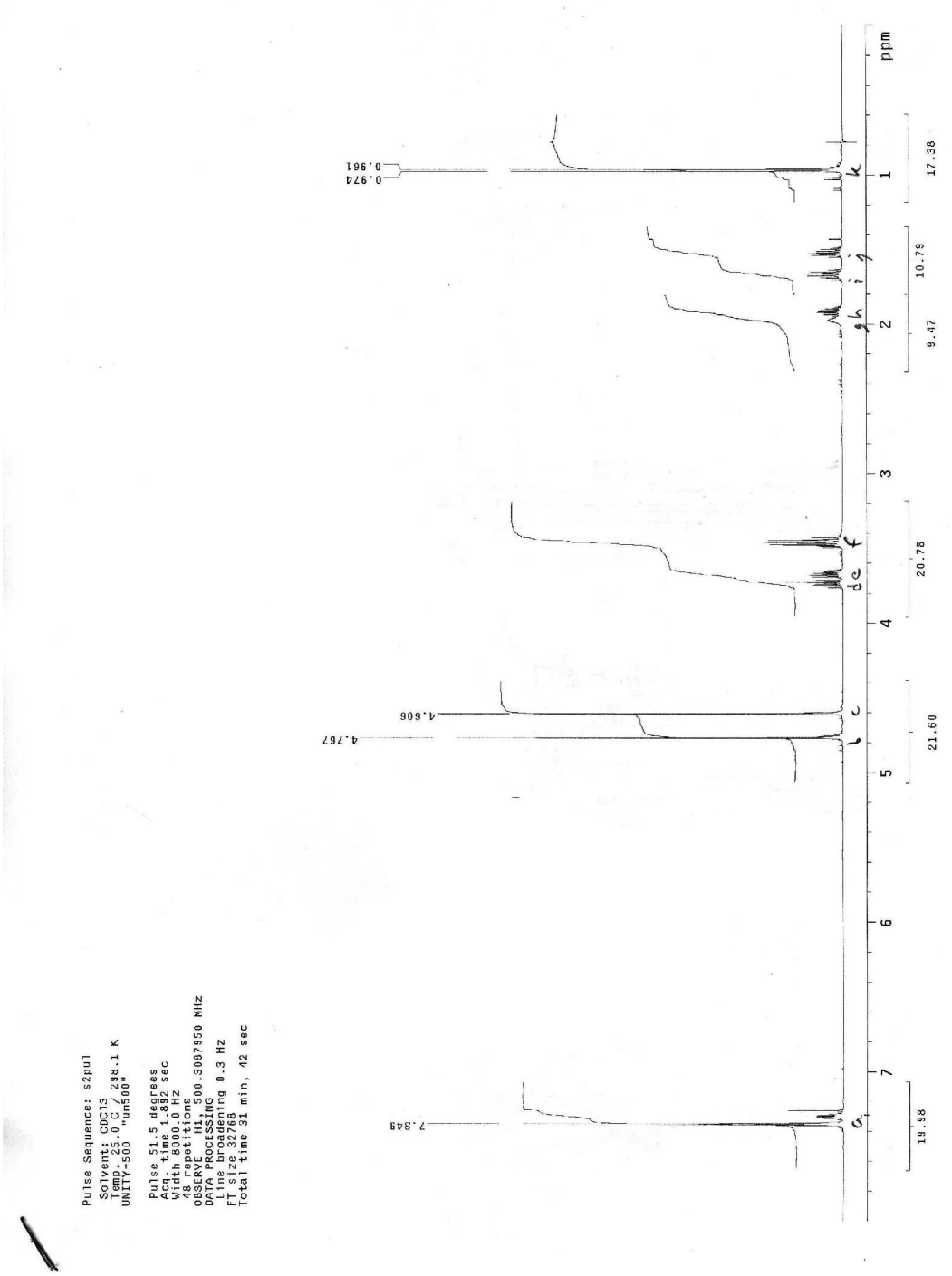
Spectrum A.86: ^{13}C spectrum of compound **119a**.



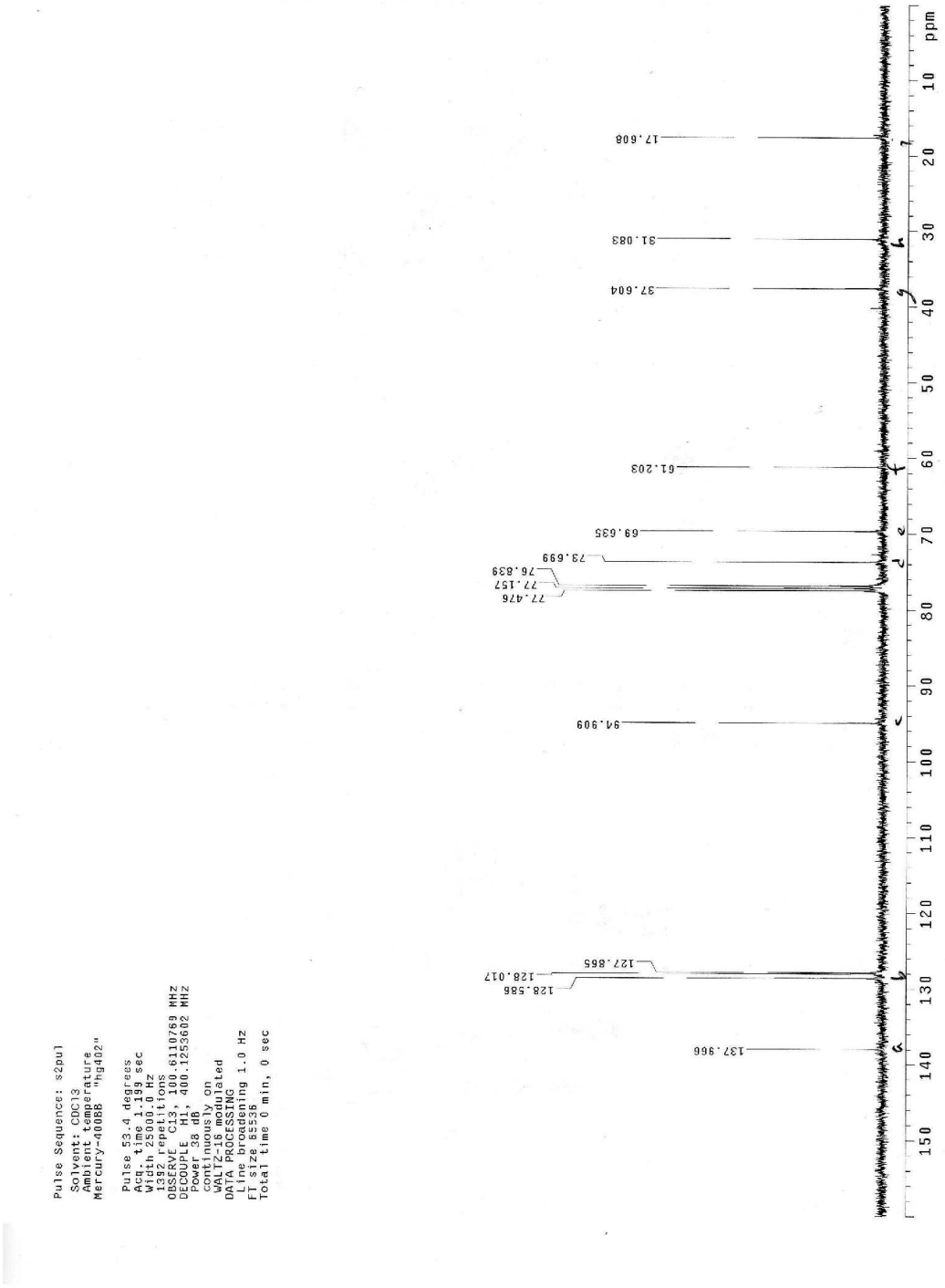
Spectrum A.87: ^{1}H spectrum of compound **119b**.



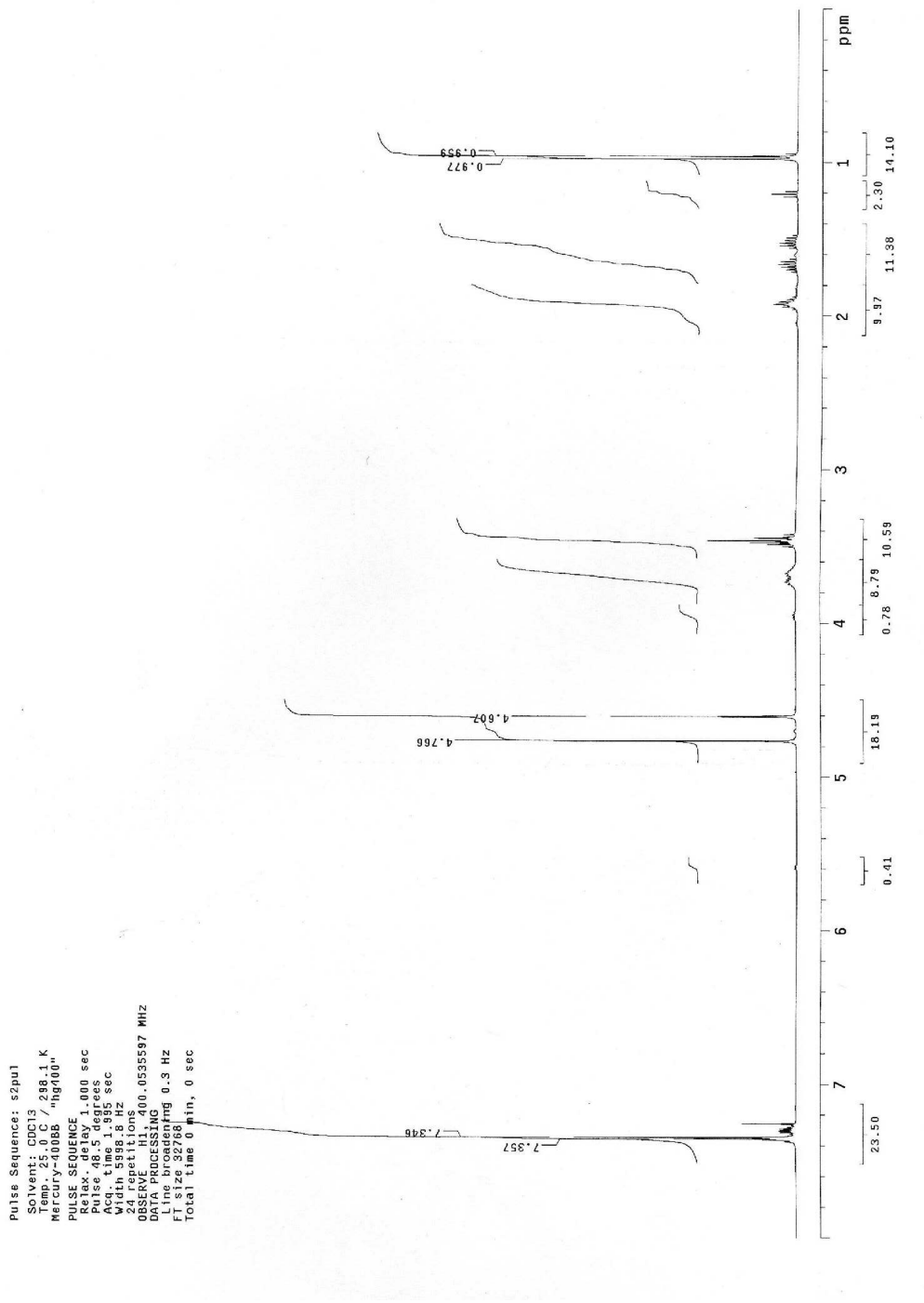
Spectrum A.88: ^{13}C spectrum of compound **119b**.



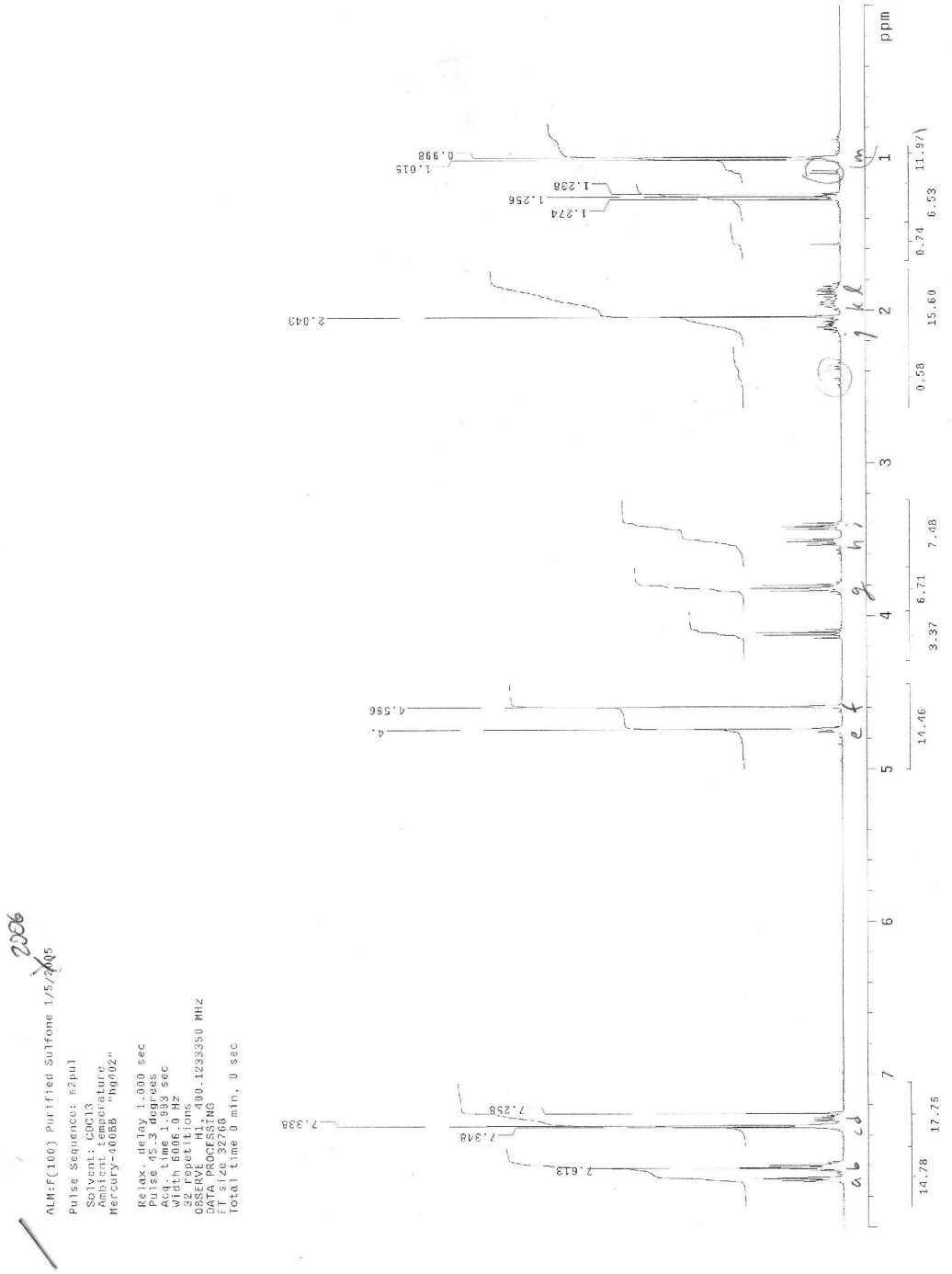
Spectrum A.89: ^{1}H spectrum of compound **122a**.



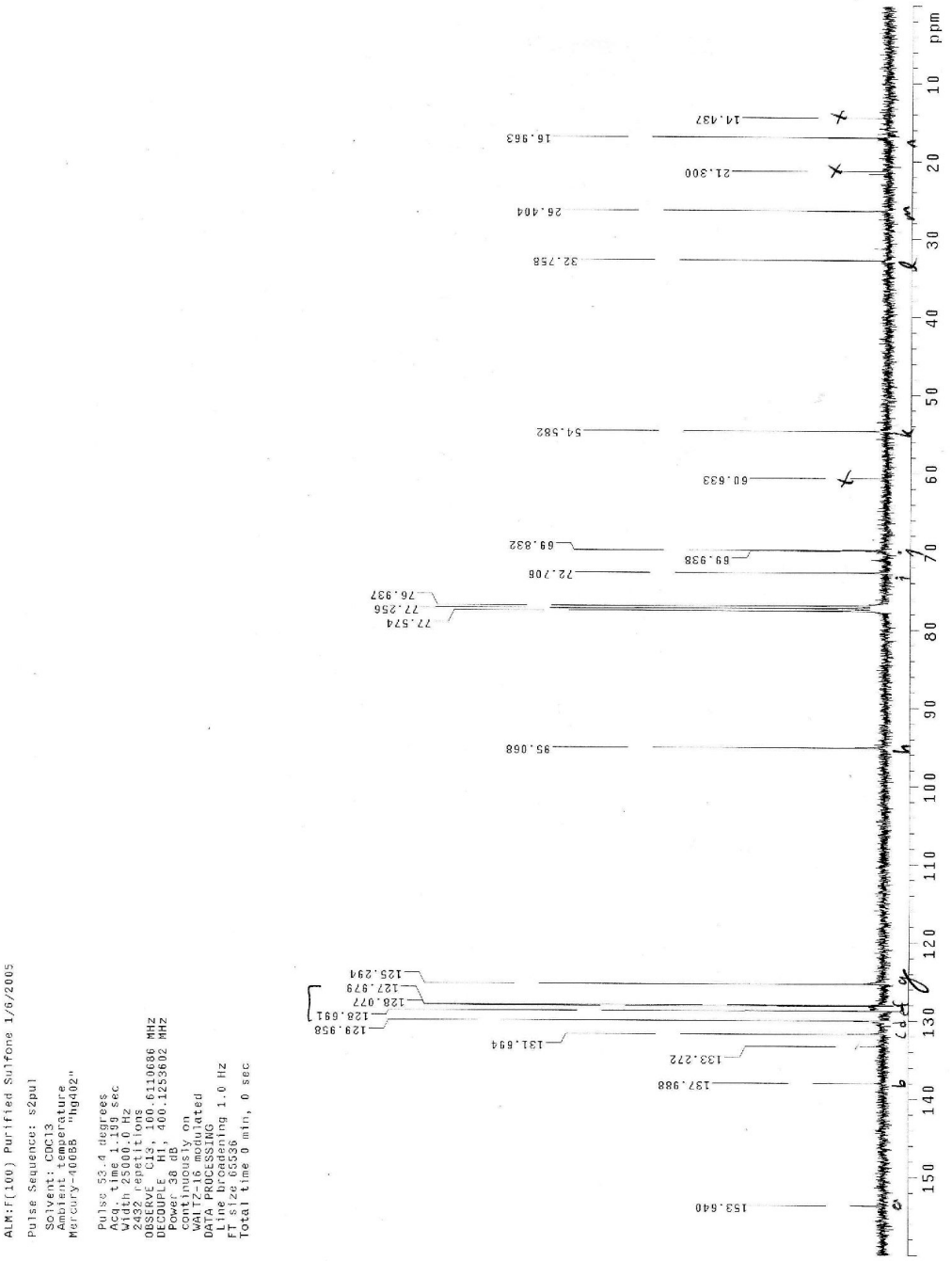
Spectrum A.90: ^{13}C spectrum of compound **122a**.



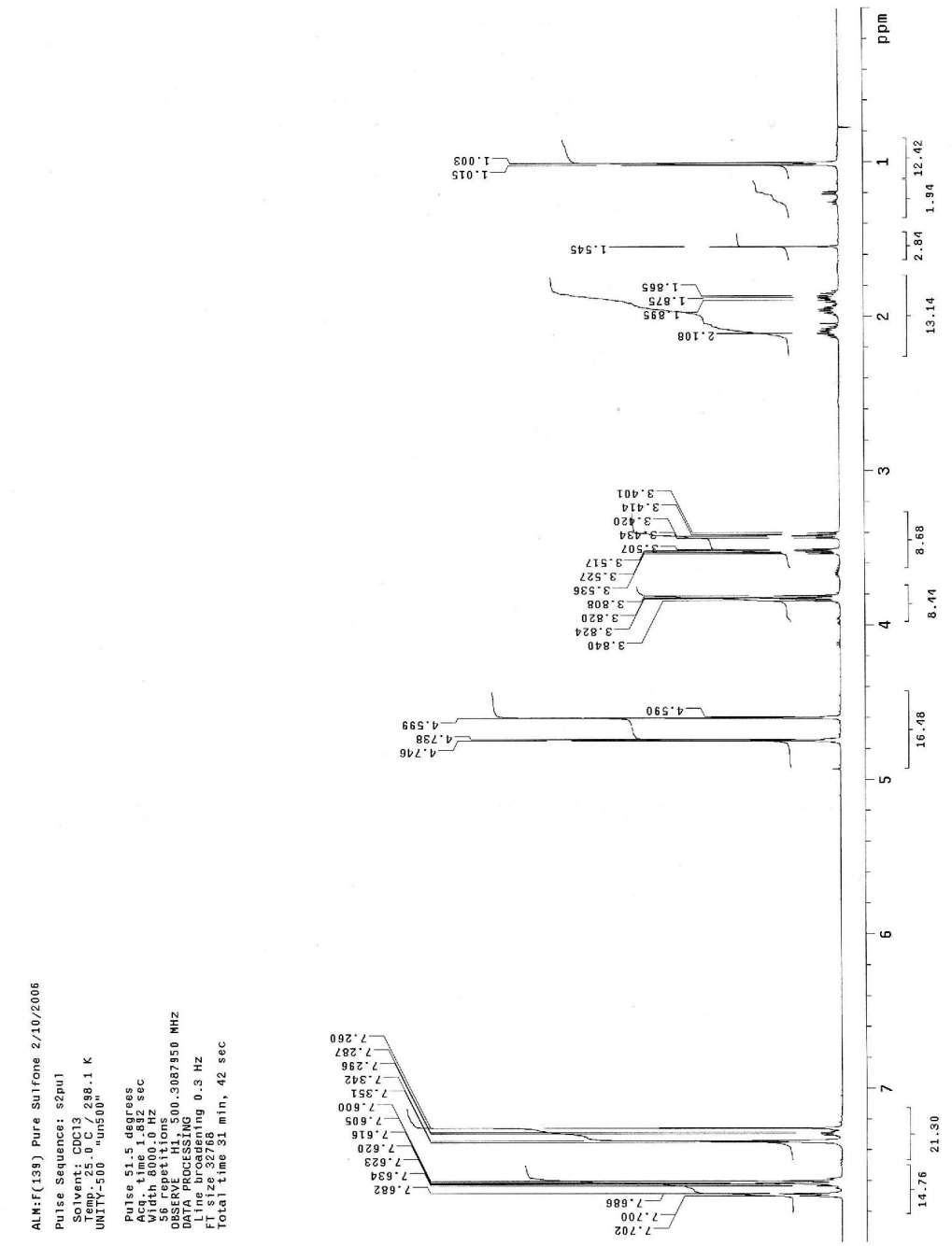
Spectrum A.91: ^{1}H spectrum of compound **122b**.



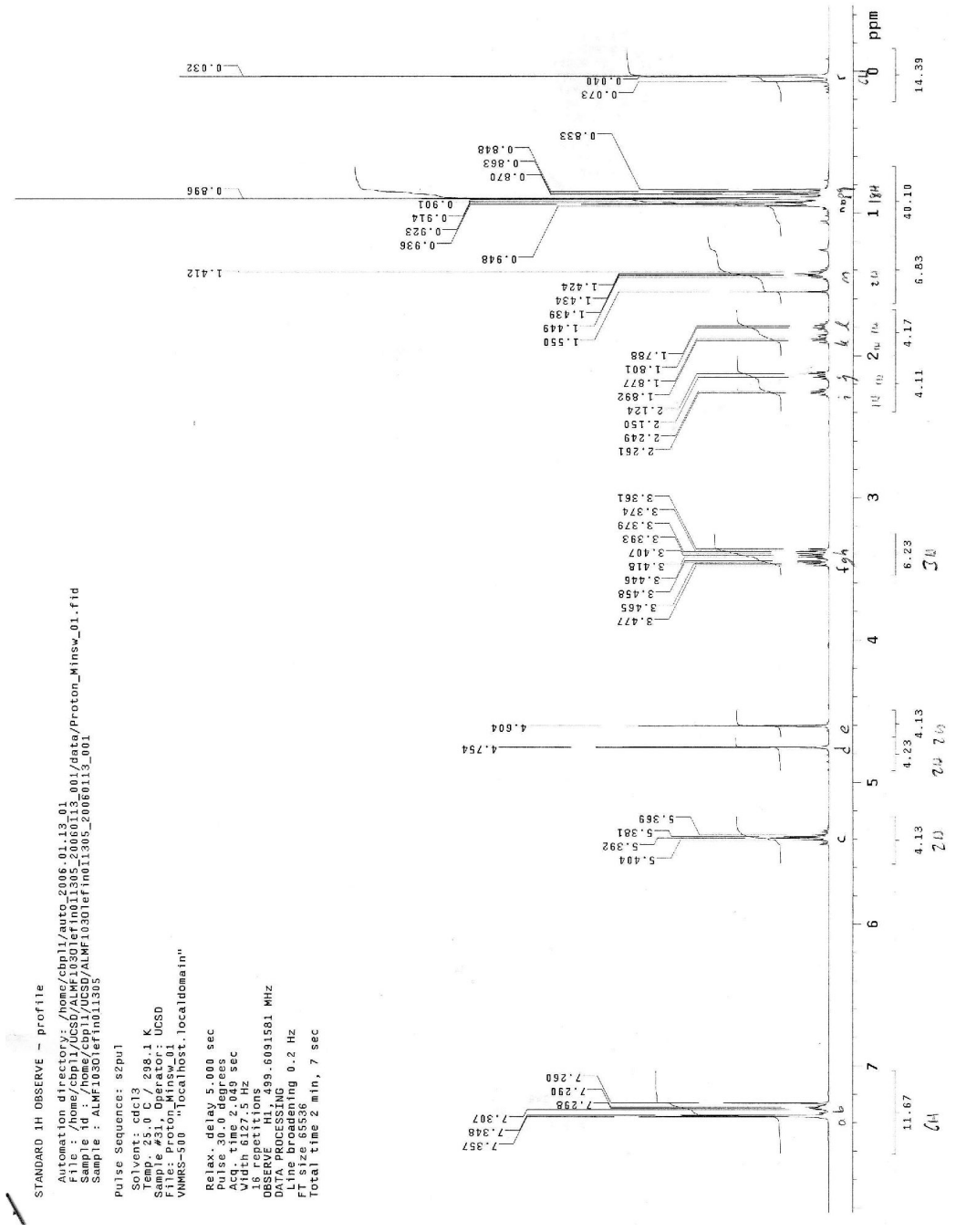
Spectrum A.92: ^{1}H spectrum of compound **123a**.



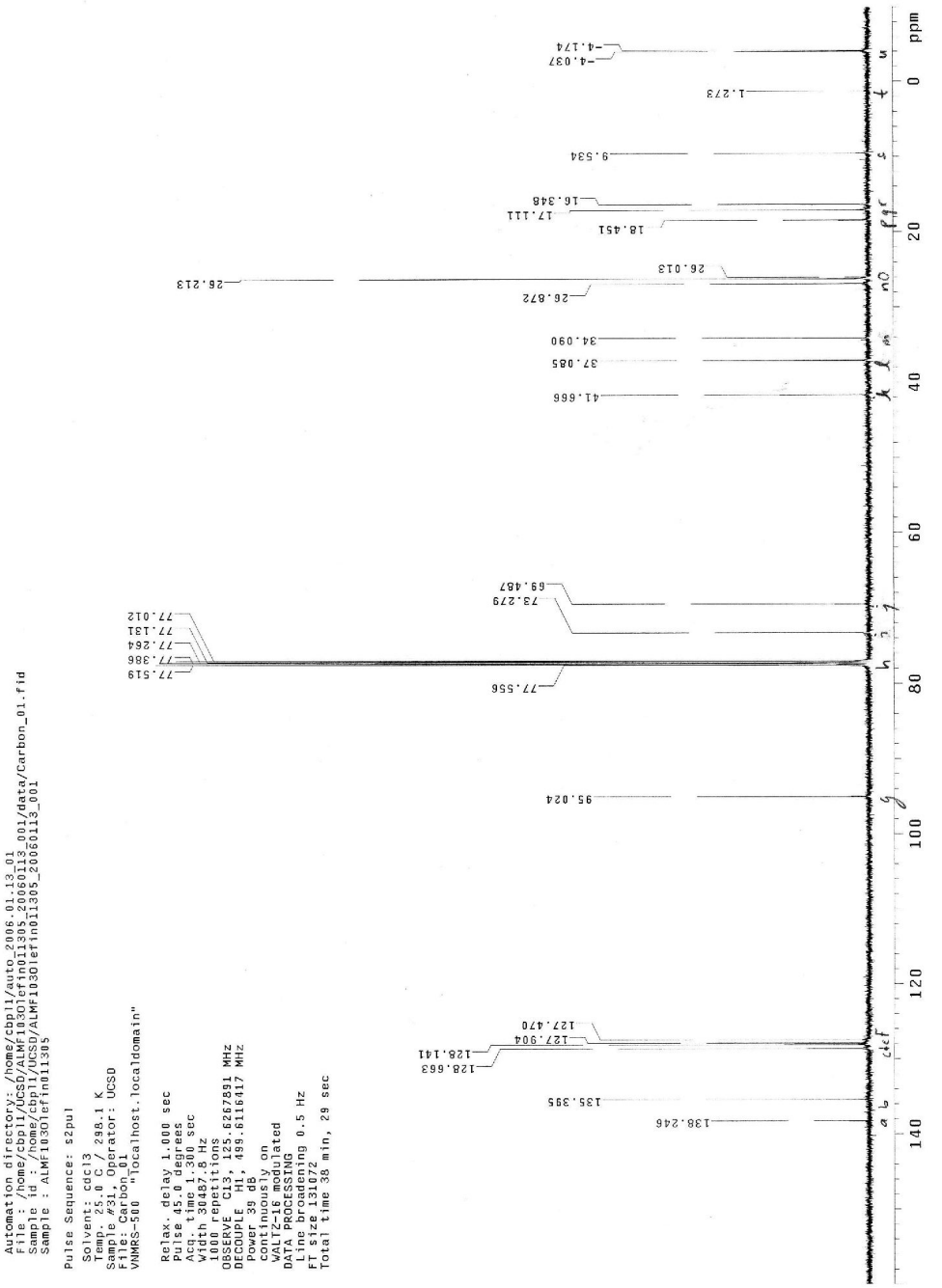
Spectrum A.93: ^{13}C spectrum of compound **123a**.



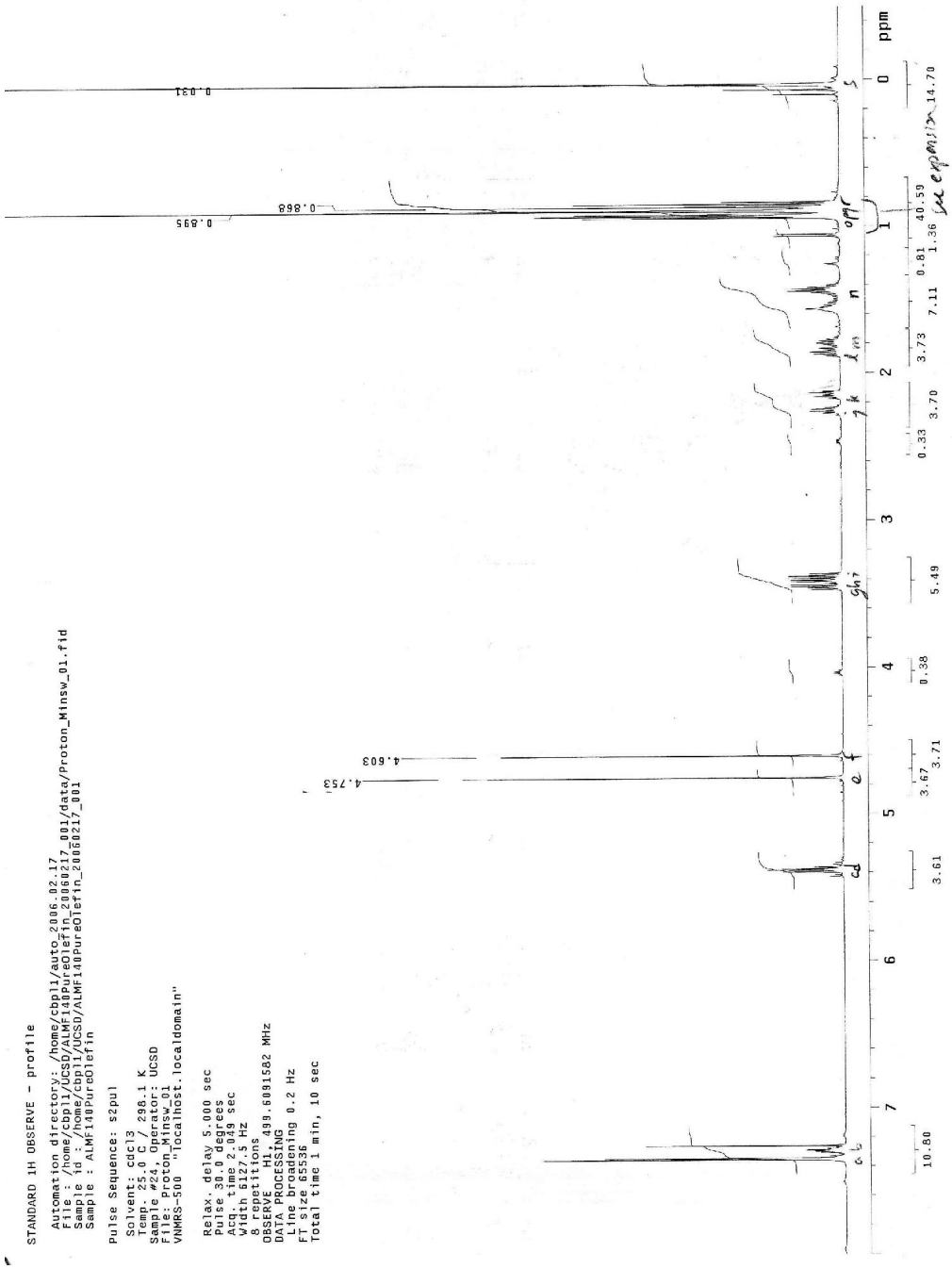
Spectrum A.94: ^{1}H spectrum of compound **123b**.



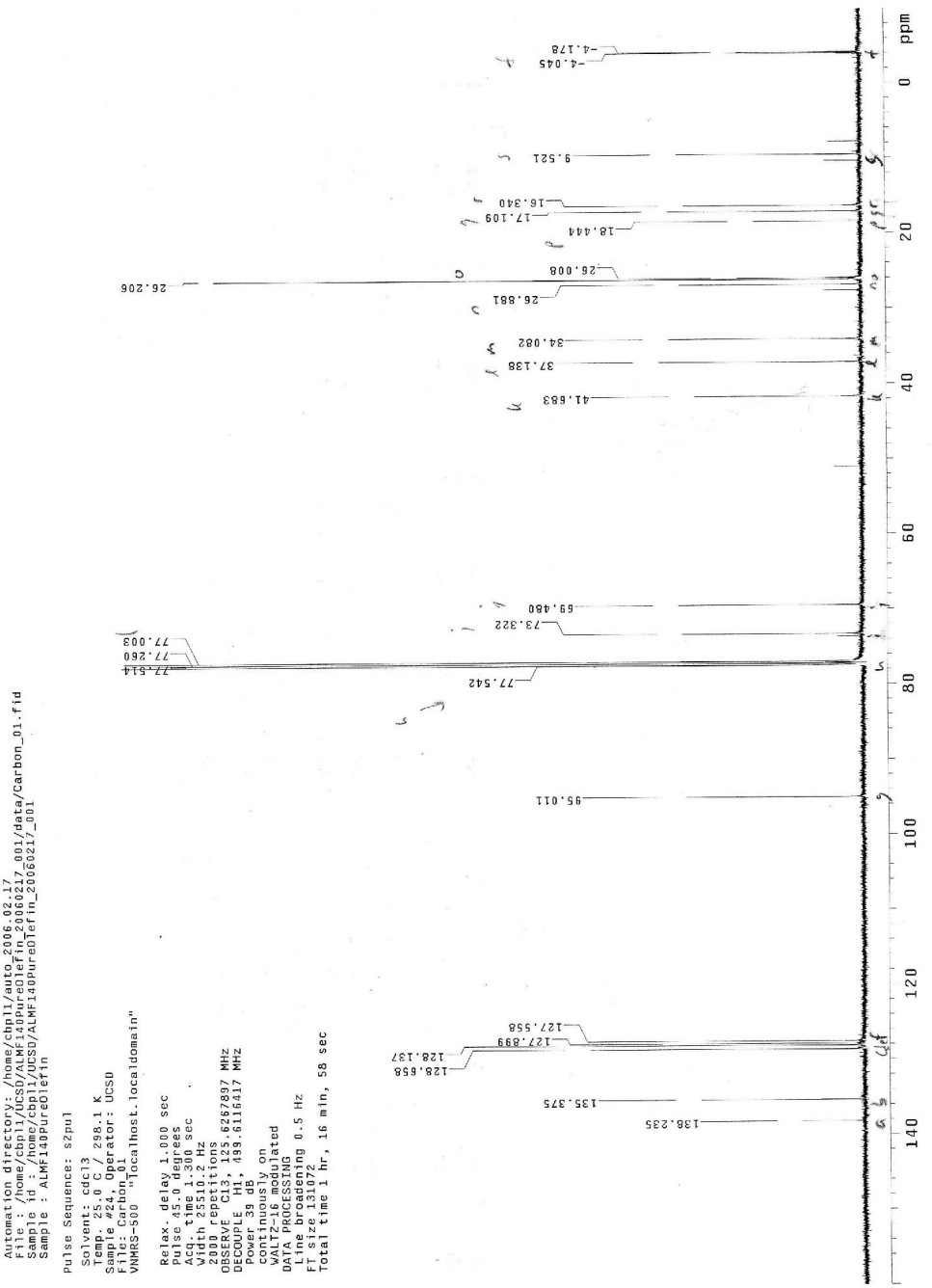
Spectrum A.95: ^{1}H spectrum of compound **124a**.



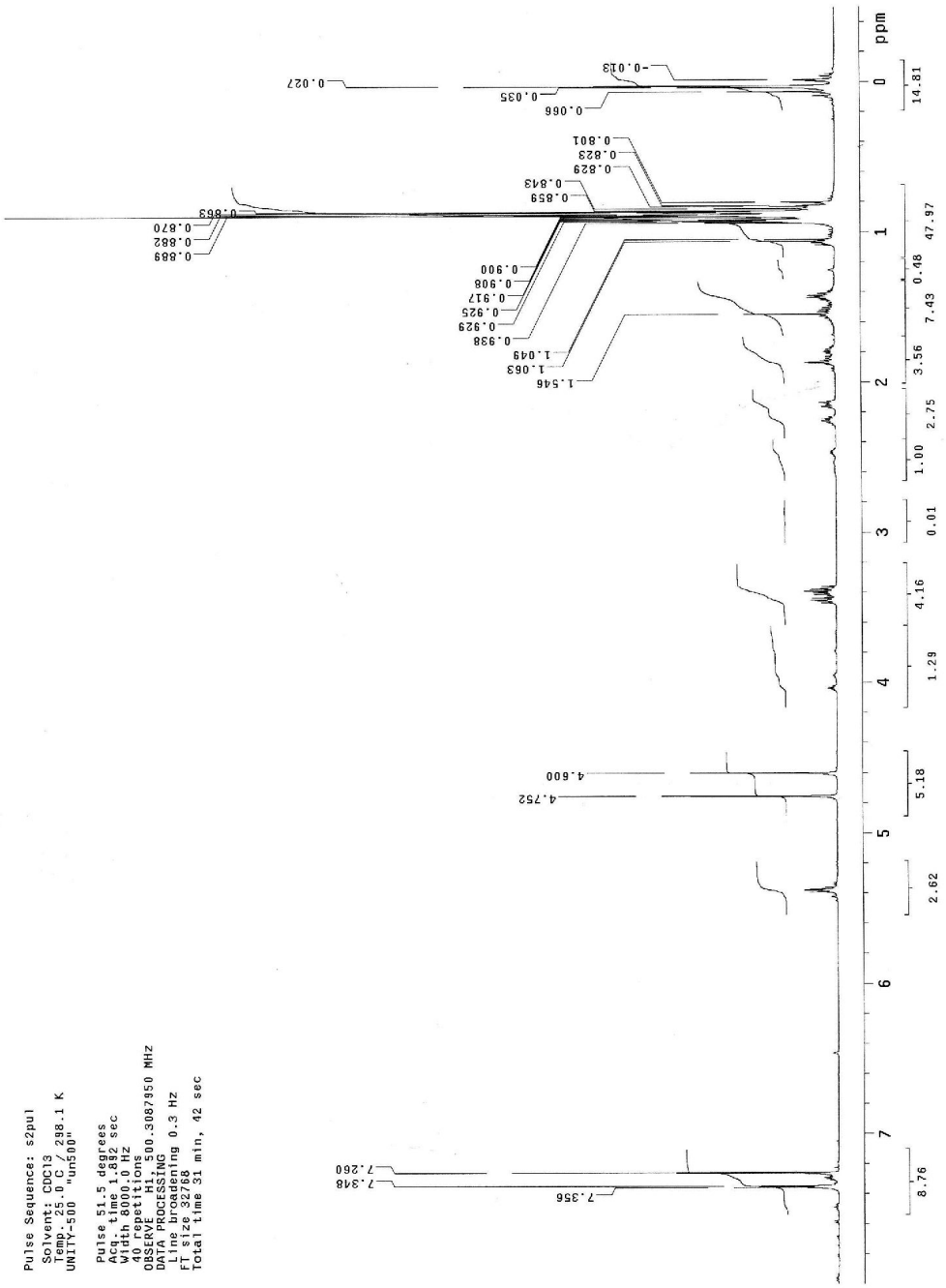
Spectrum A.96: ^{13}C spectrum of compound **124a**.



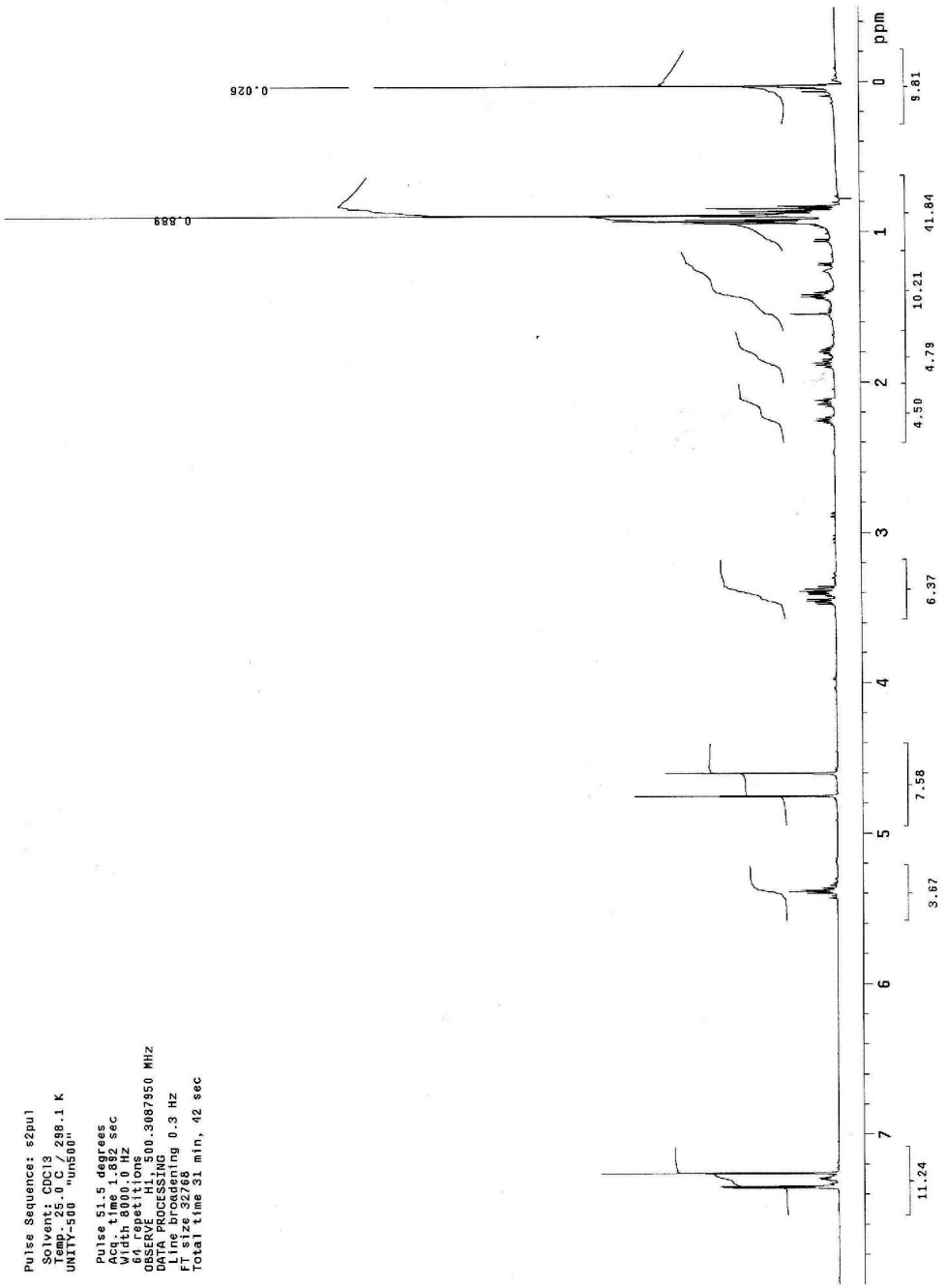
Spectrum A.97: ^{1}H spectrum of compound **124b**.



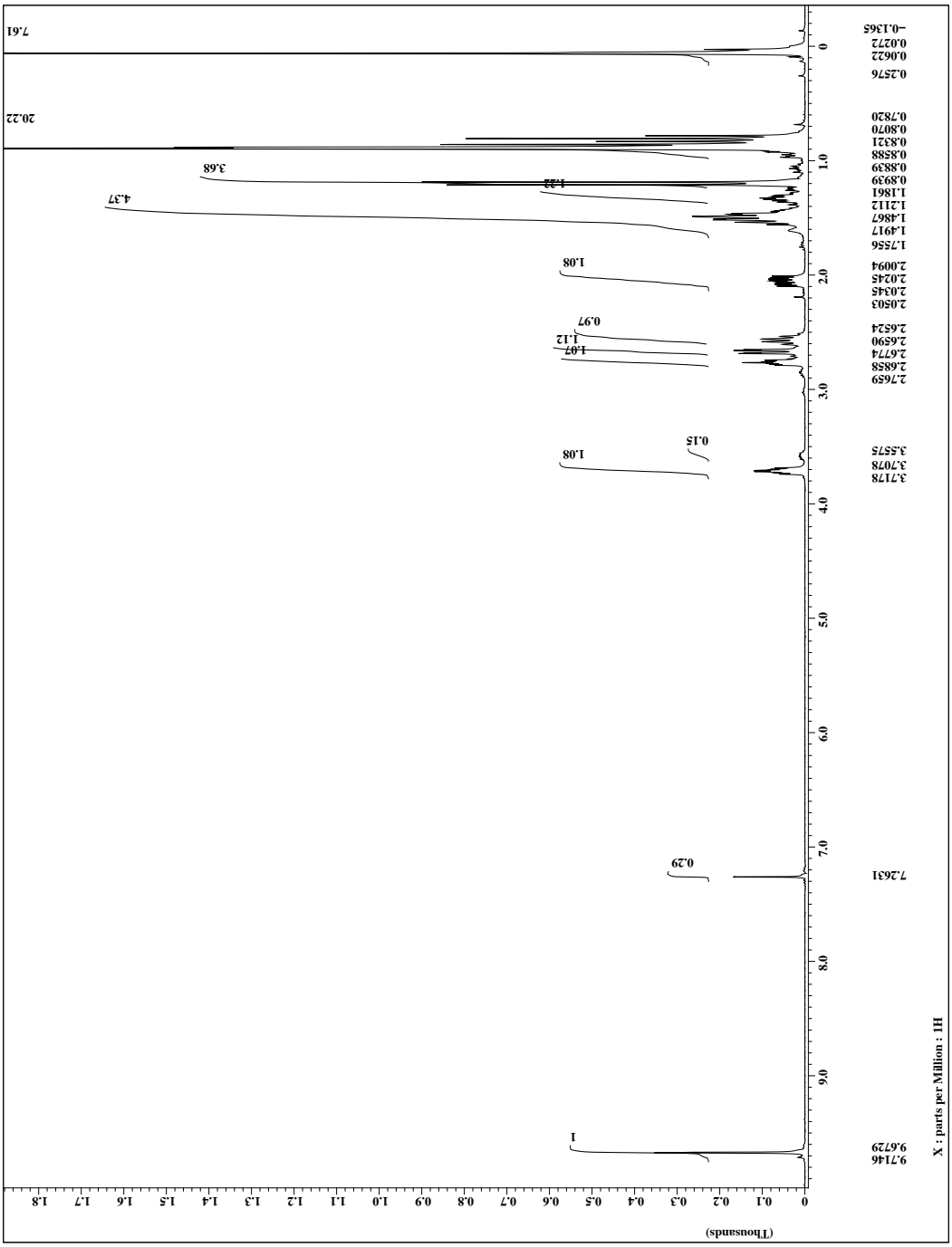
Spectrum A.98: ^{13}C spectrum of compound **124b**.



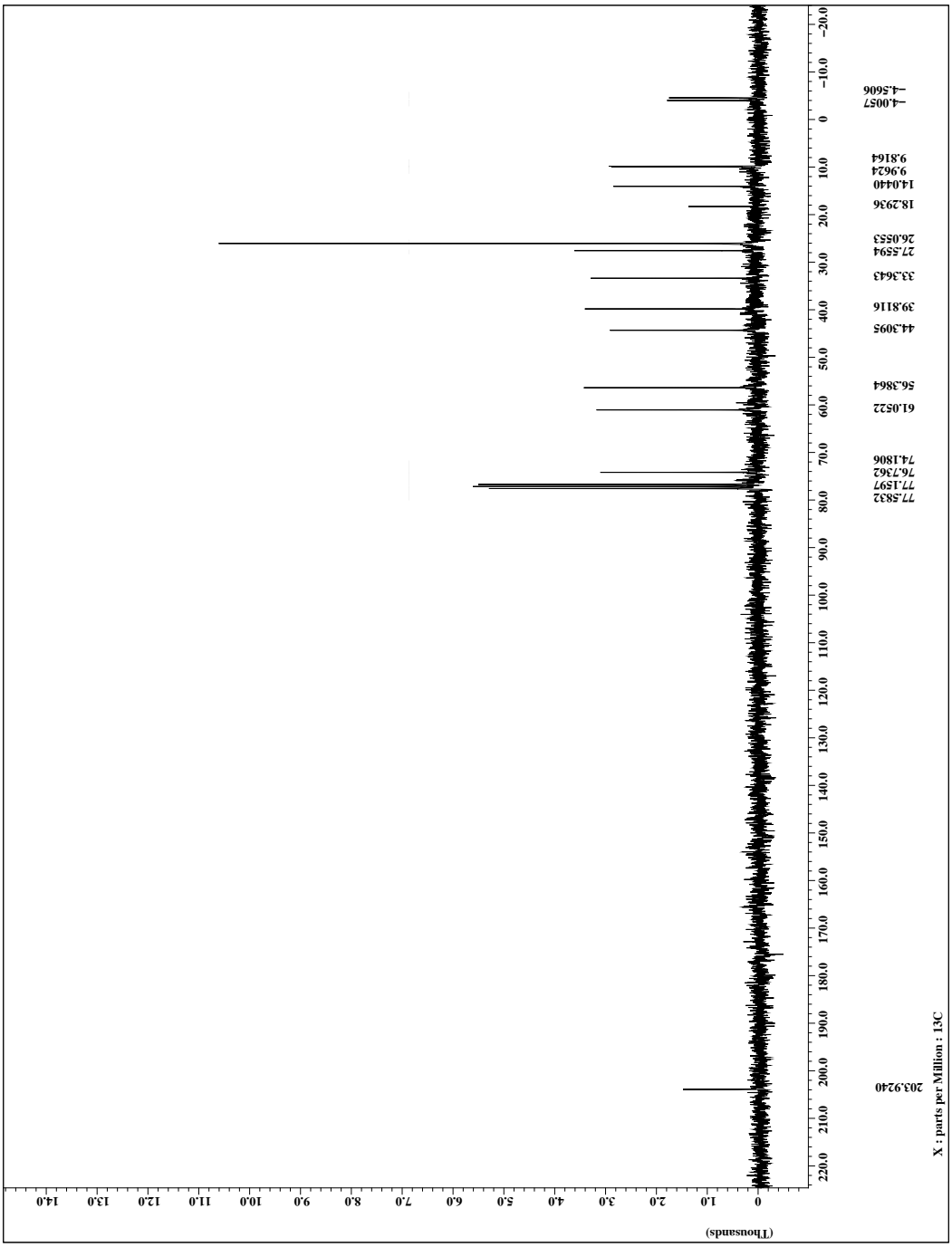
Spectrum A.99: ^{1}H spectrum of compound **124c**.



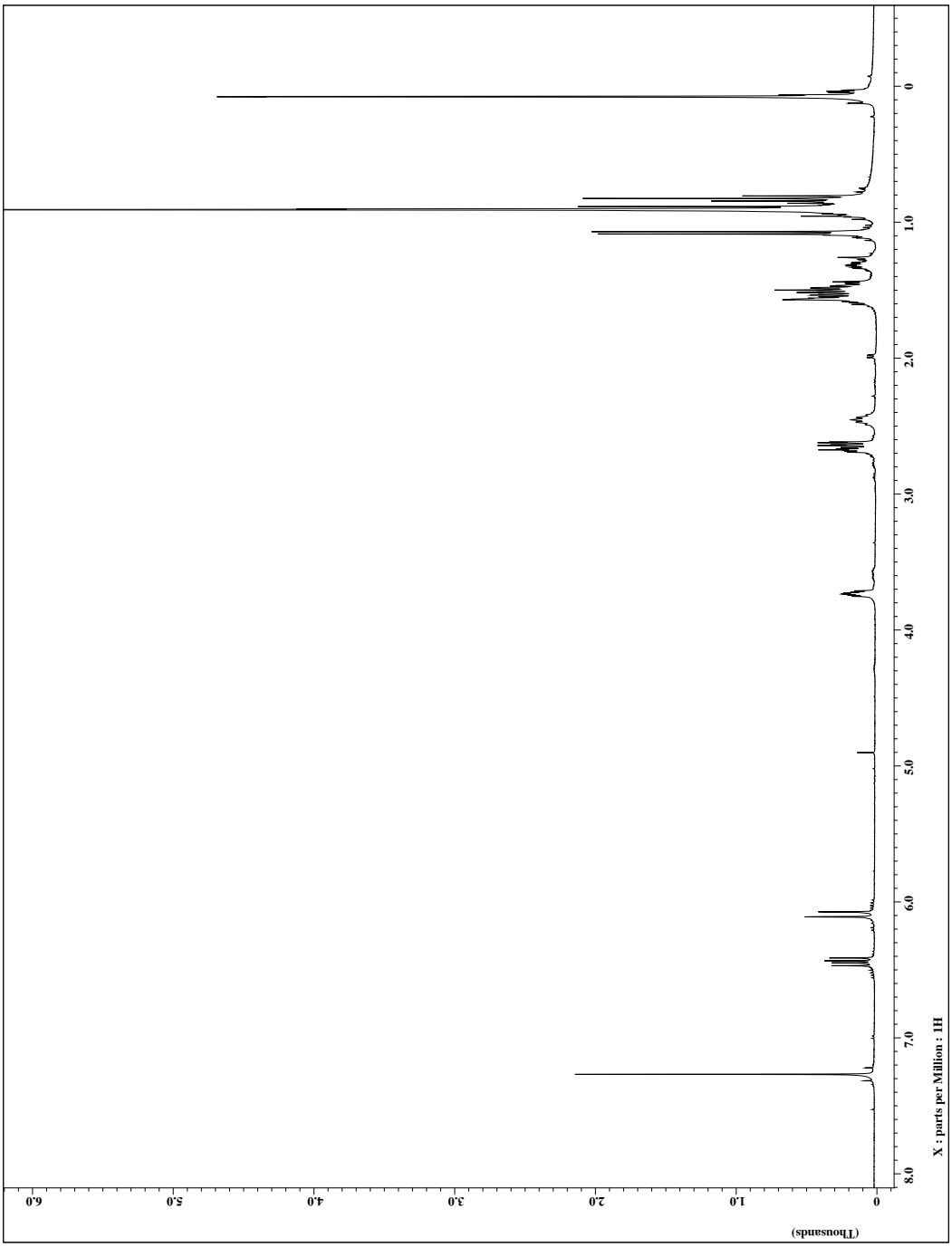
Spectrum A.100: ^{1}H spectrum of compound **124d**.



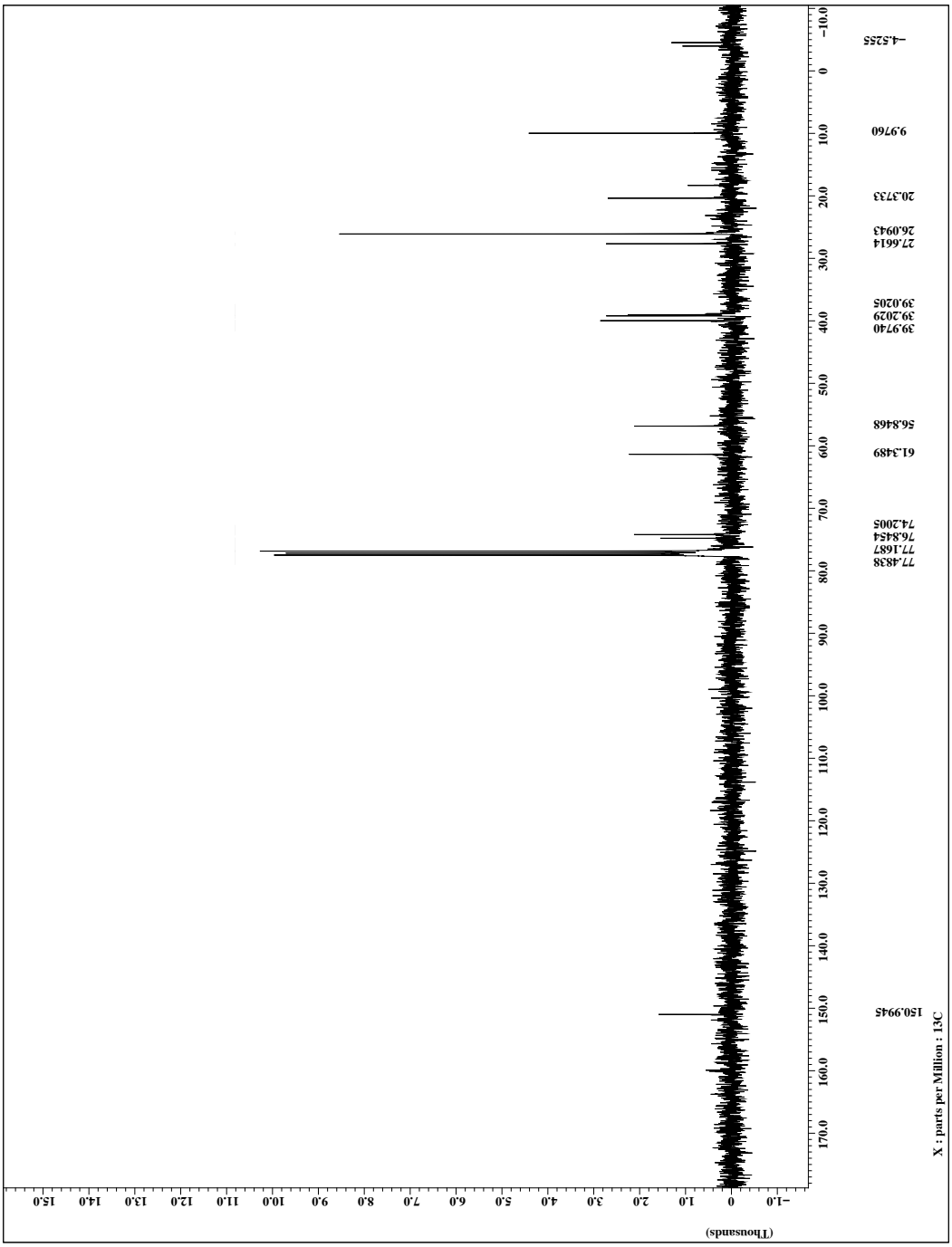
Spectrum A.101: ^{1}H spectrum of compound **131**.



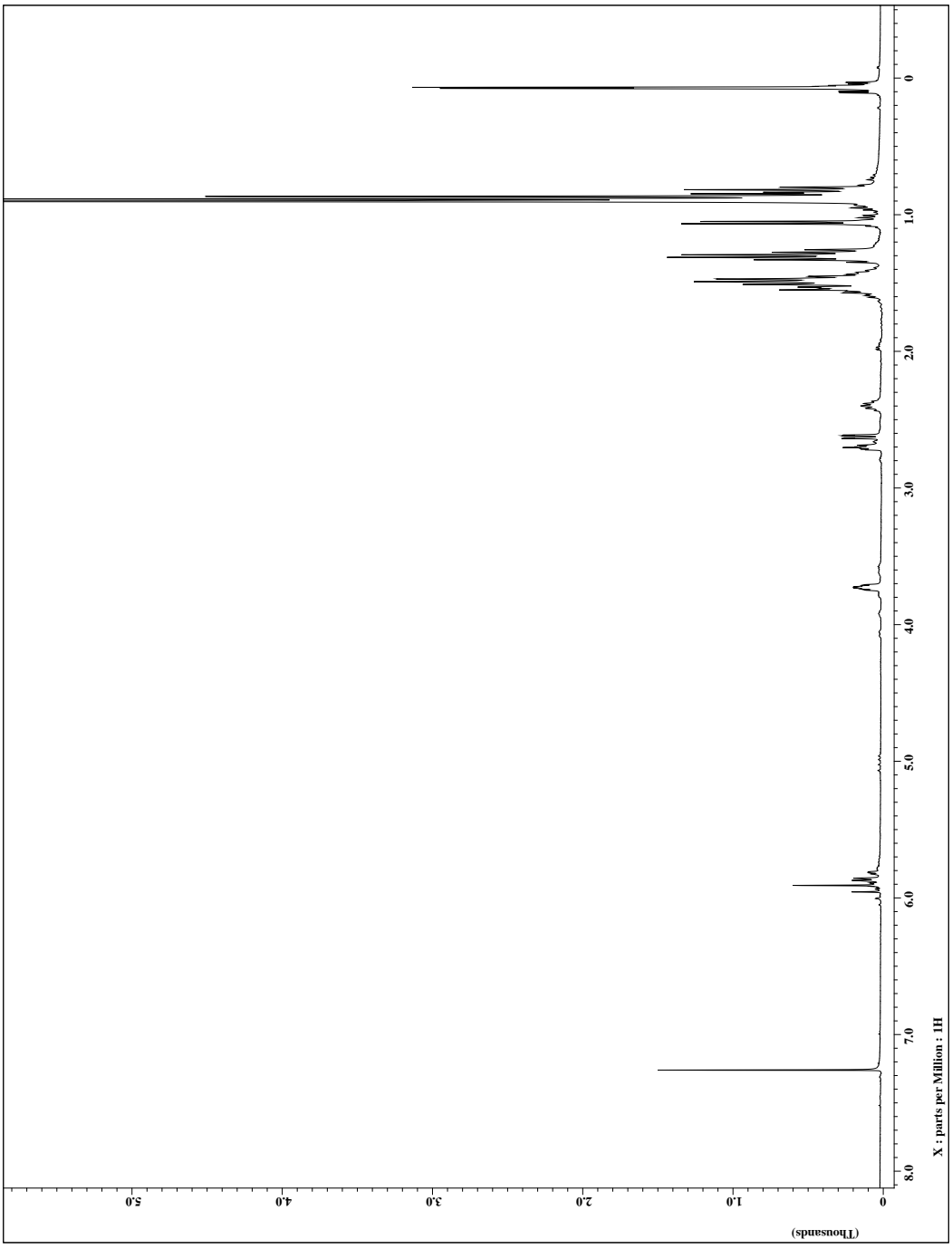
Spectrum A.102: ^{13}C spectrum of compound **131**.



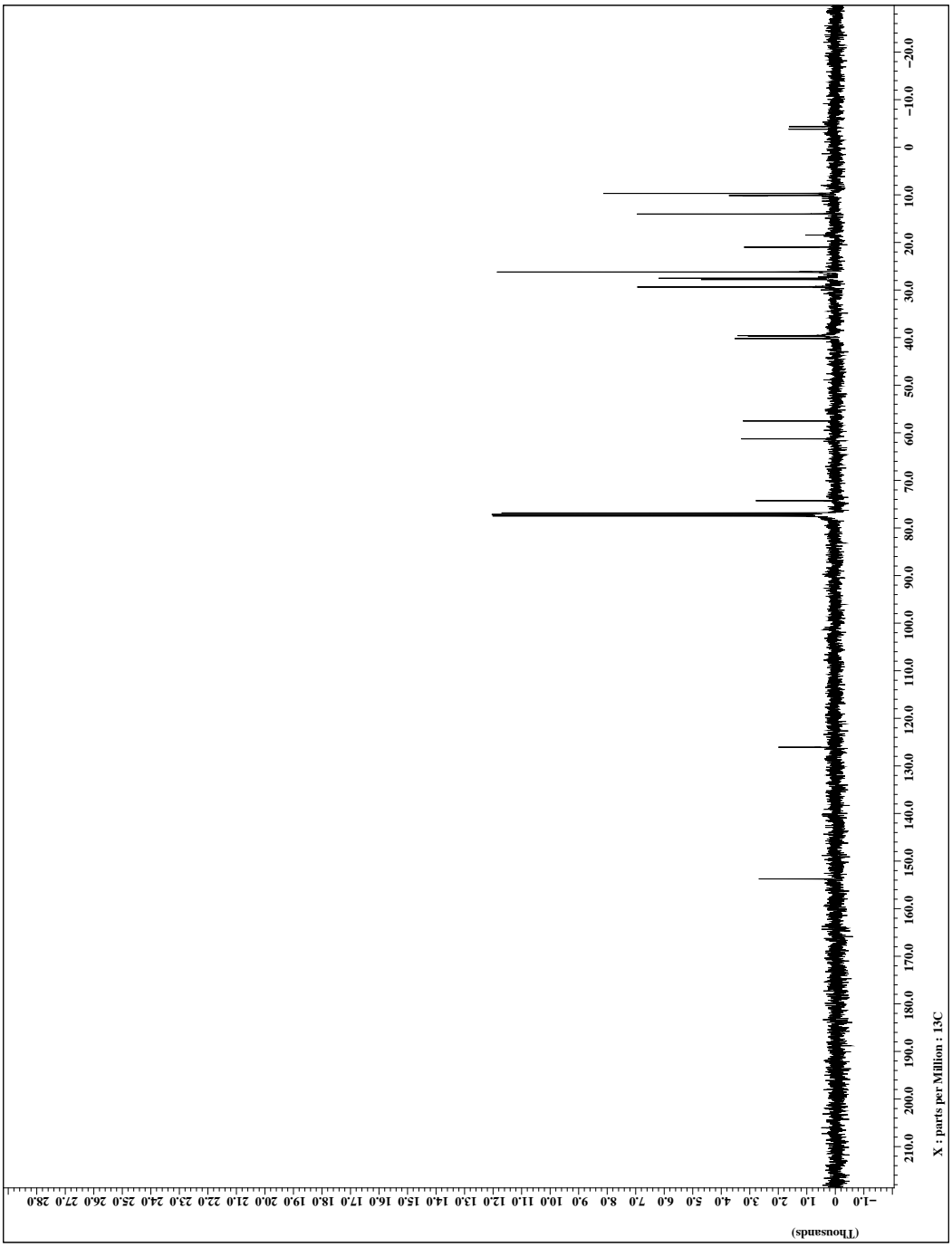
Spectrum A.103: ^{1}H spectrum of compound **132**.



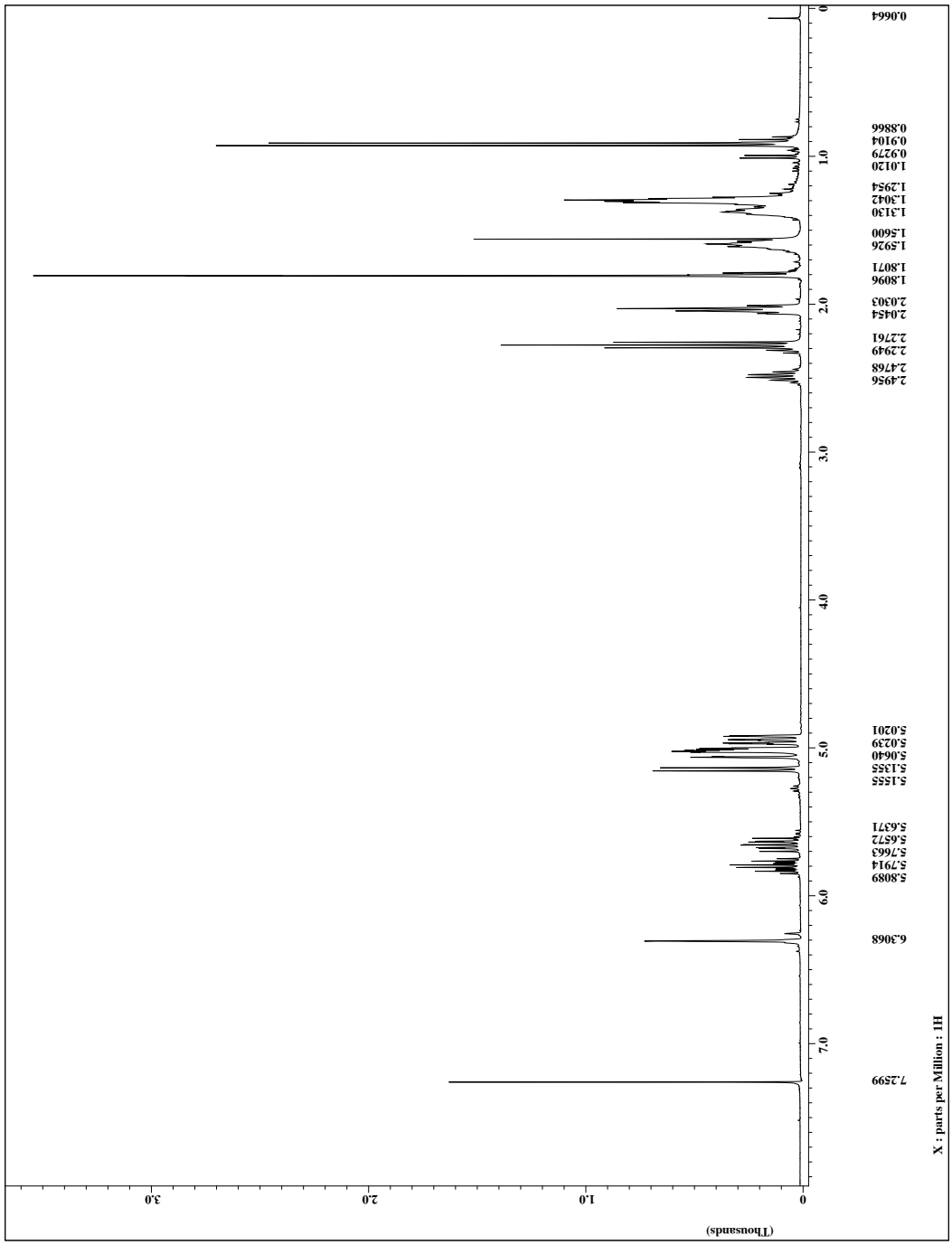
Spectrum A.104: ^{13}C spectrum of compound **132**.



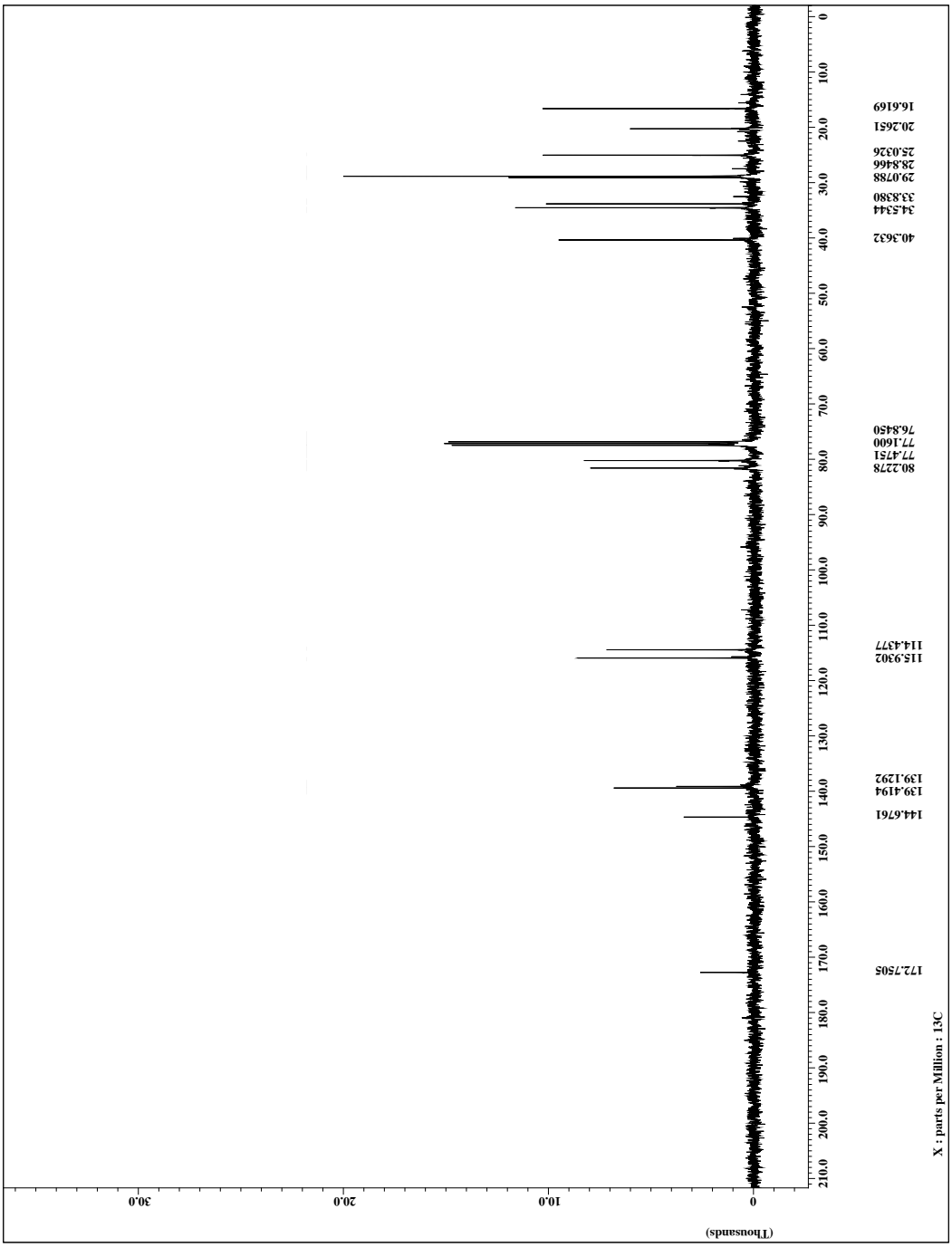
Spectrum A.105: ^{1}H spectrum of compound **133**.



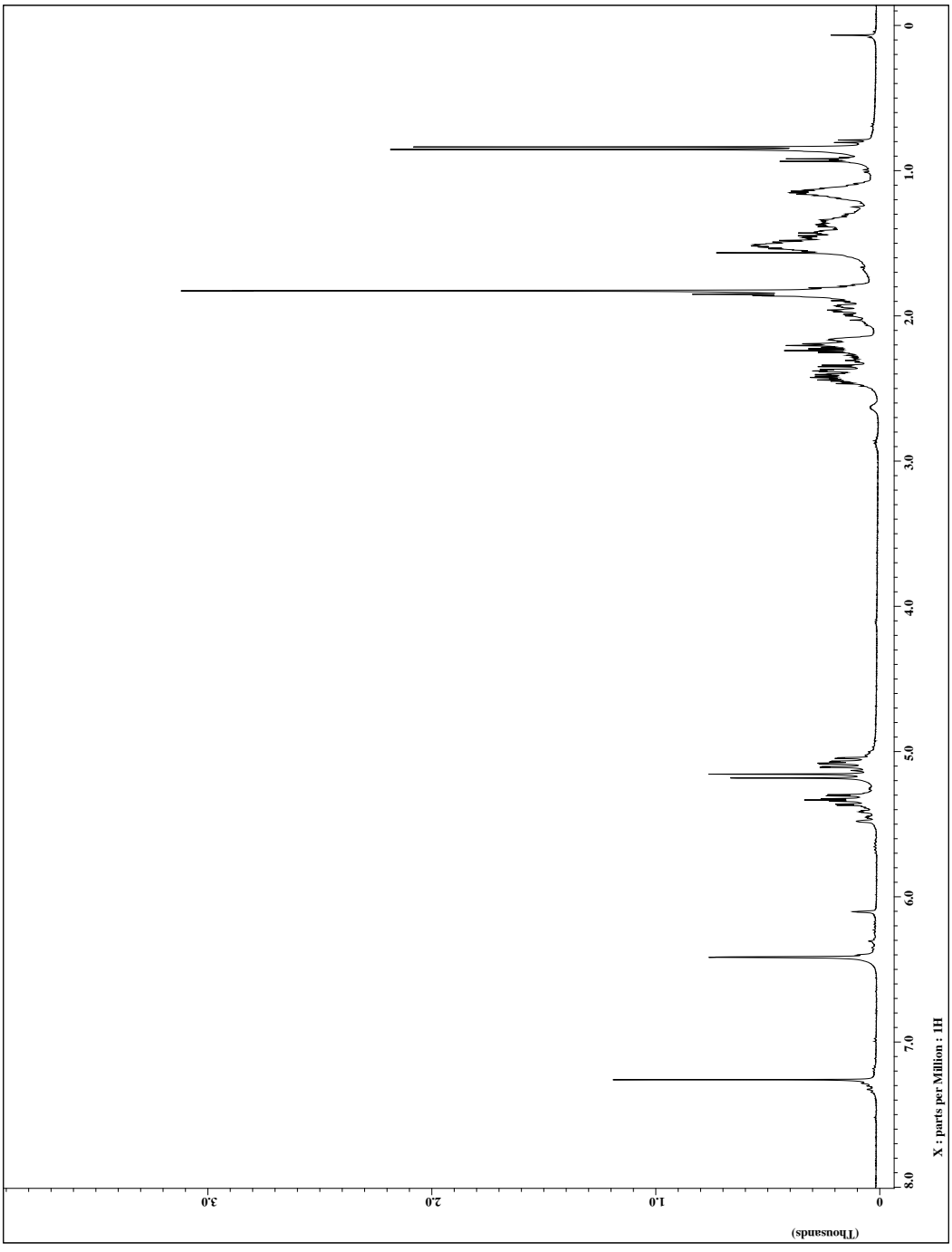
Spectrum A.106: ^{13}C spectrum of compound **133**.



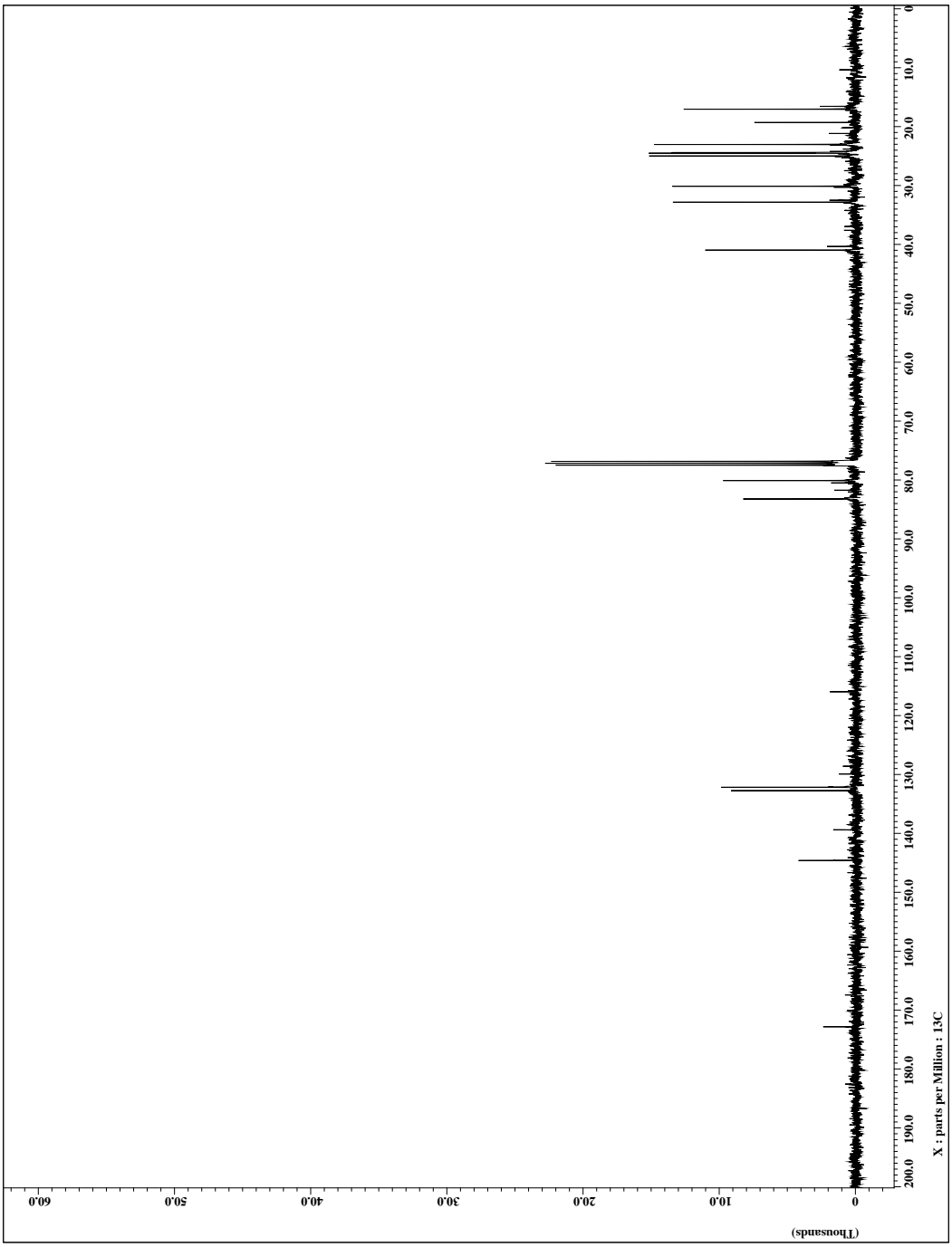
Spectrum A.107: ^{1}H spectrum of compound **137a**.



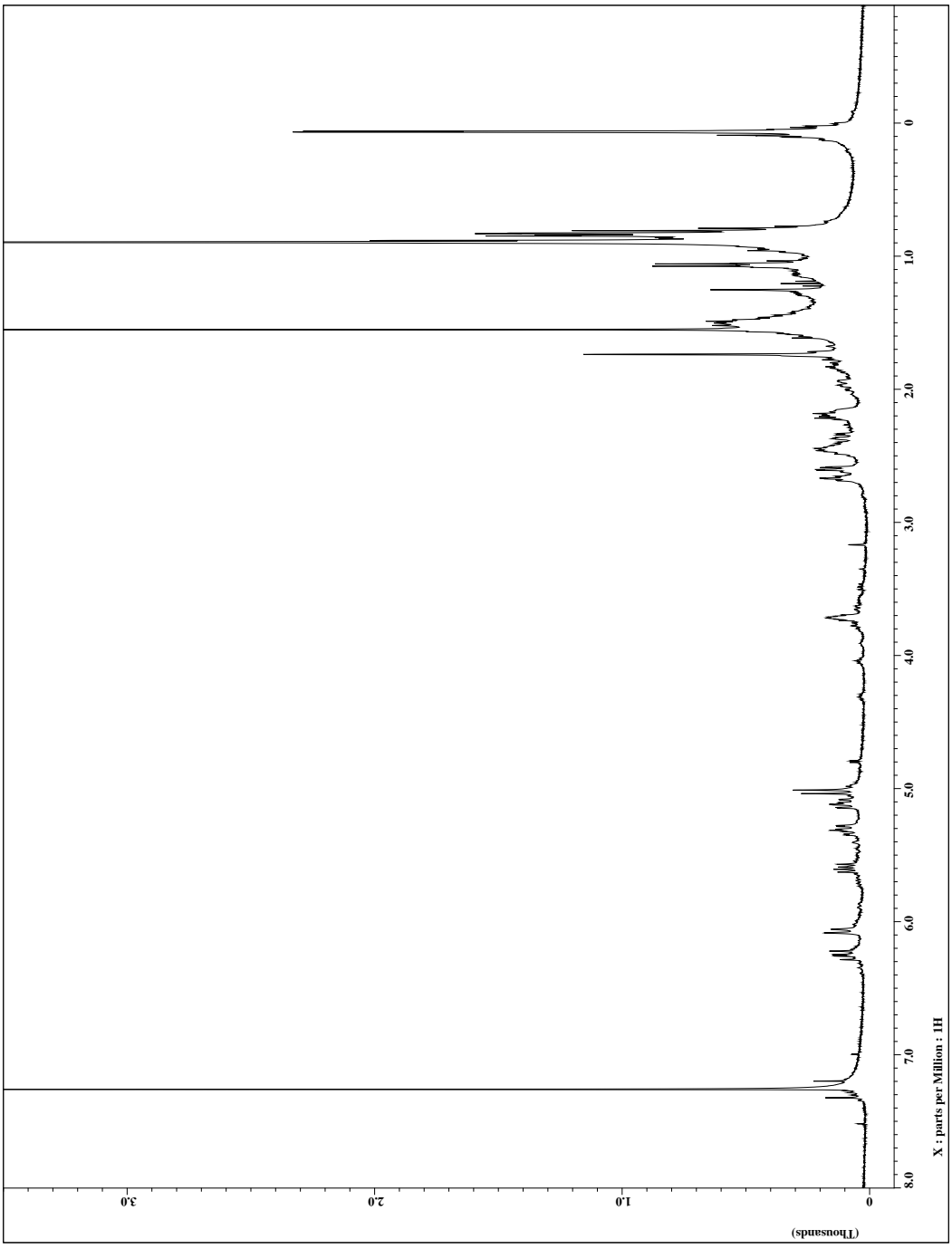
Spectrum A.108: ^{13}C spectrum of compound **137a**.



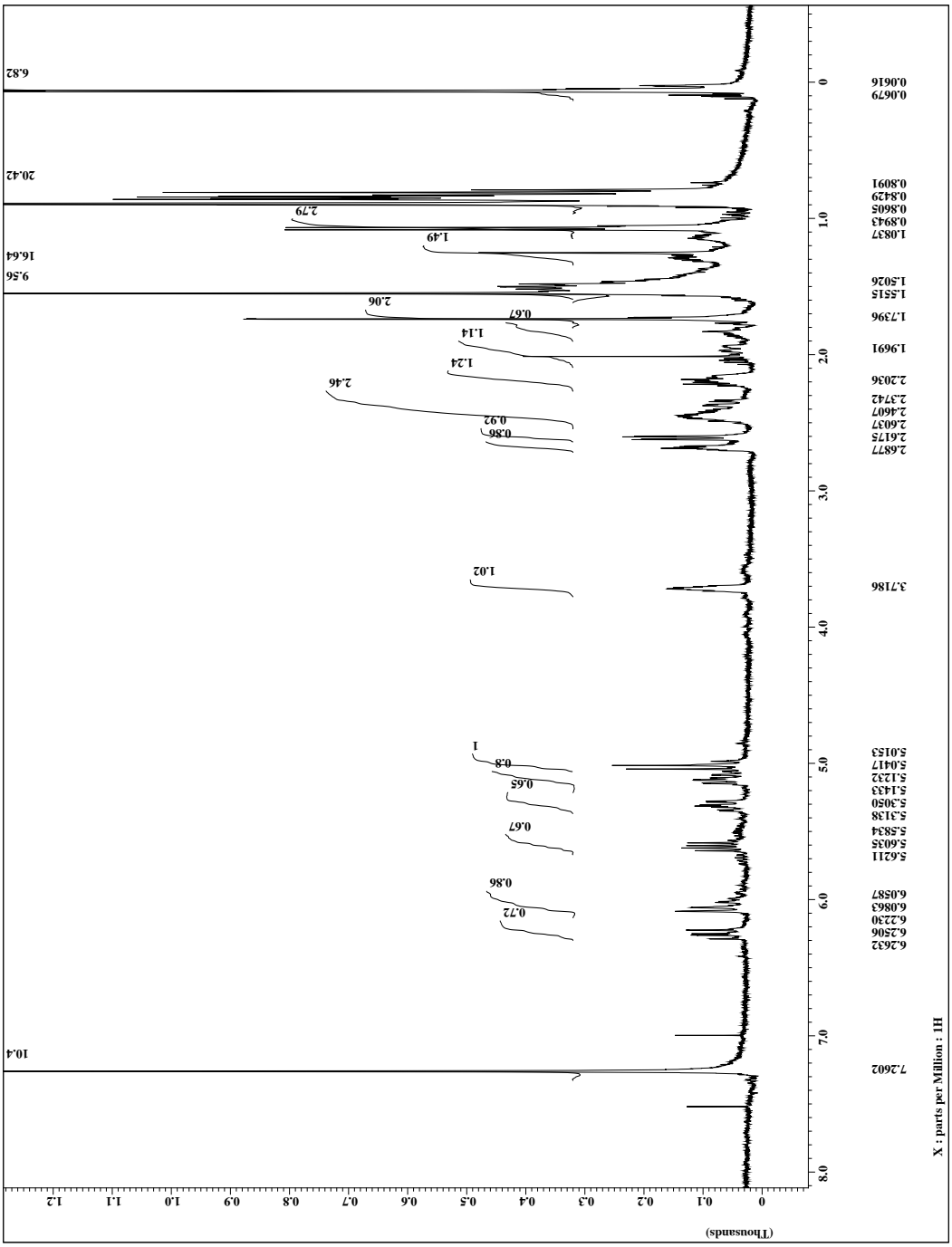
Spectrum A.109: ^{1}H spectrum of compound **139a**.



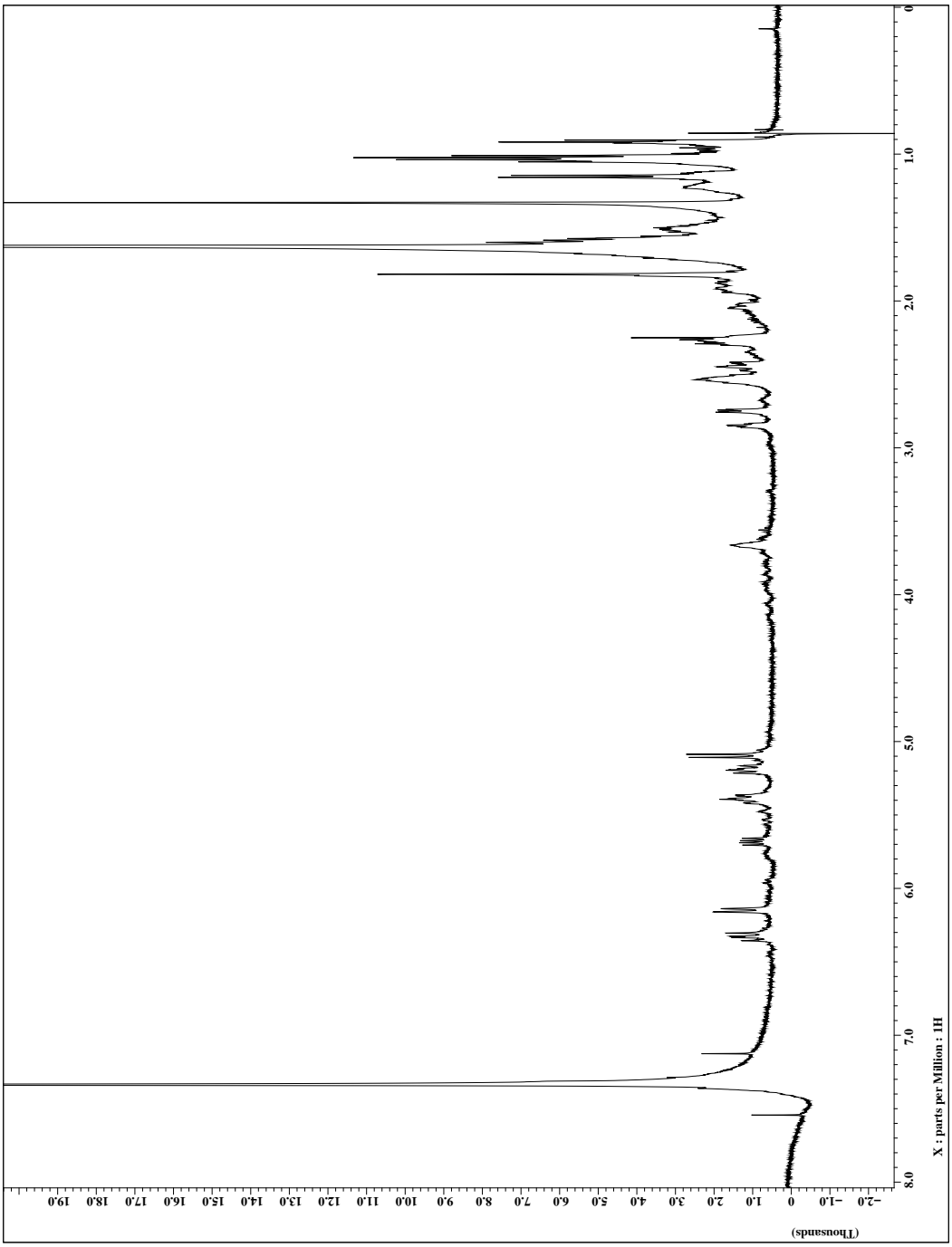
Spectrum A.110: ^{13}C spectrum of compound **139a**.



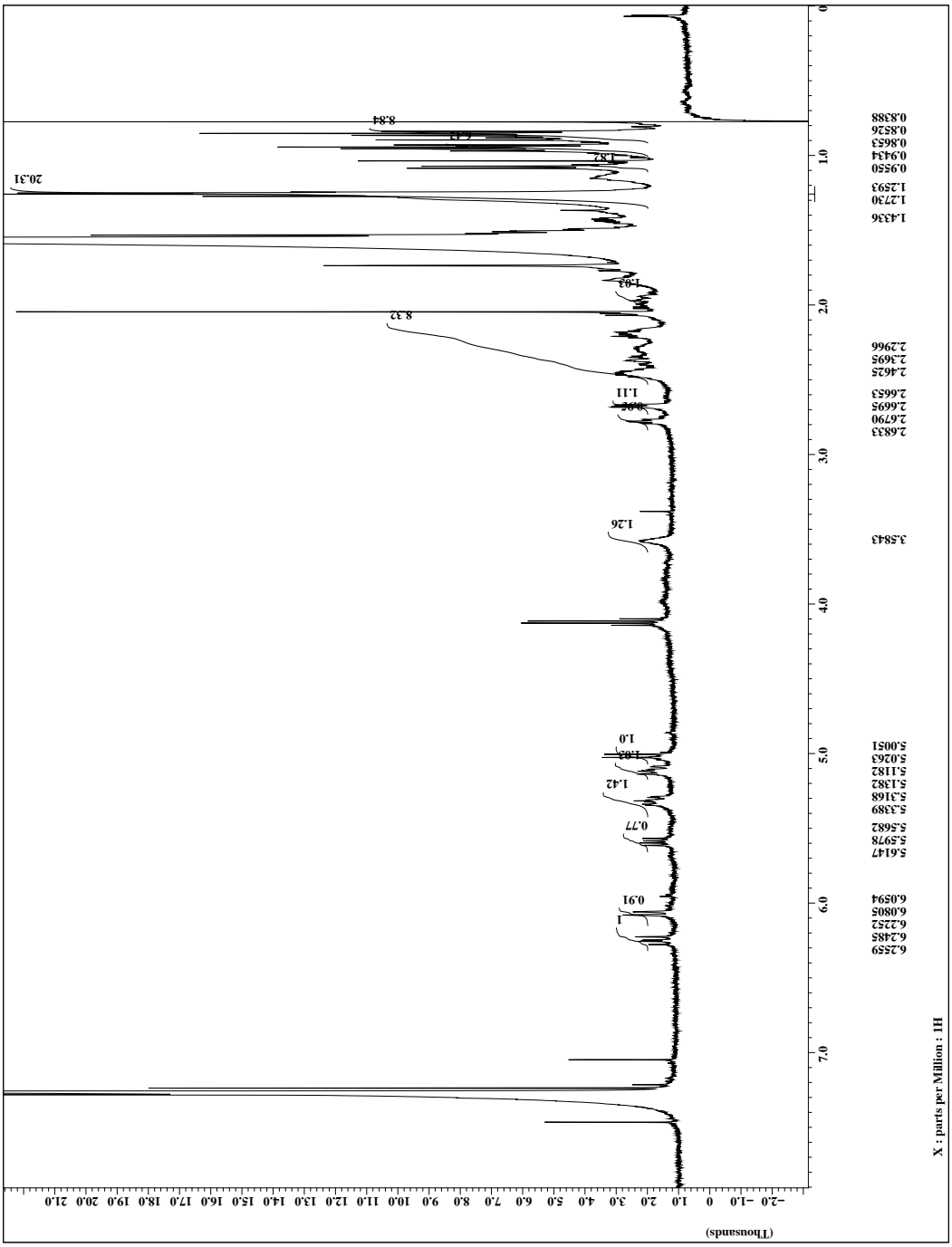
Spectrum A.111: ^{1}H spectrum of compound **140a**.



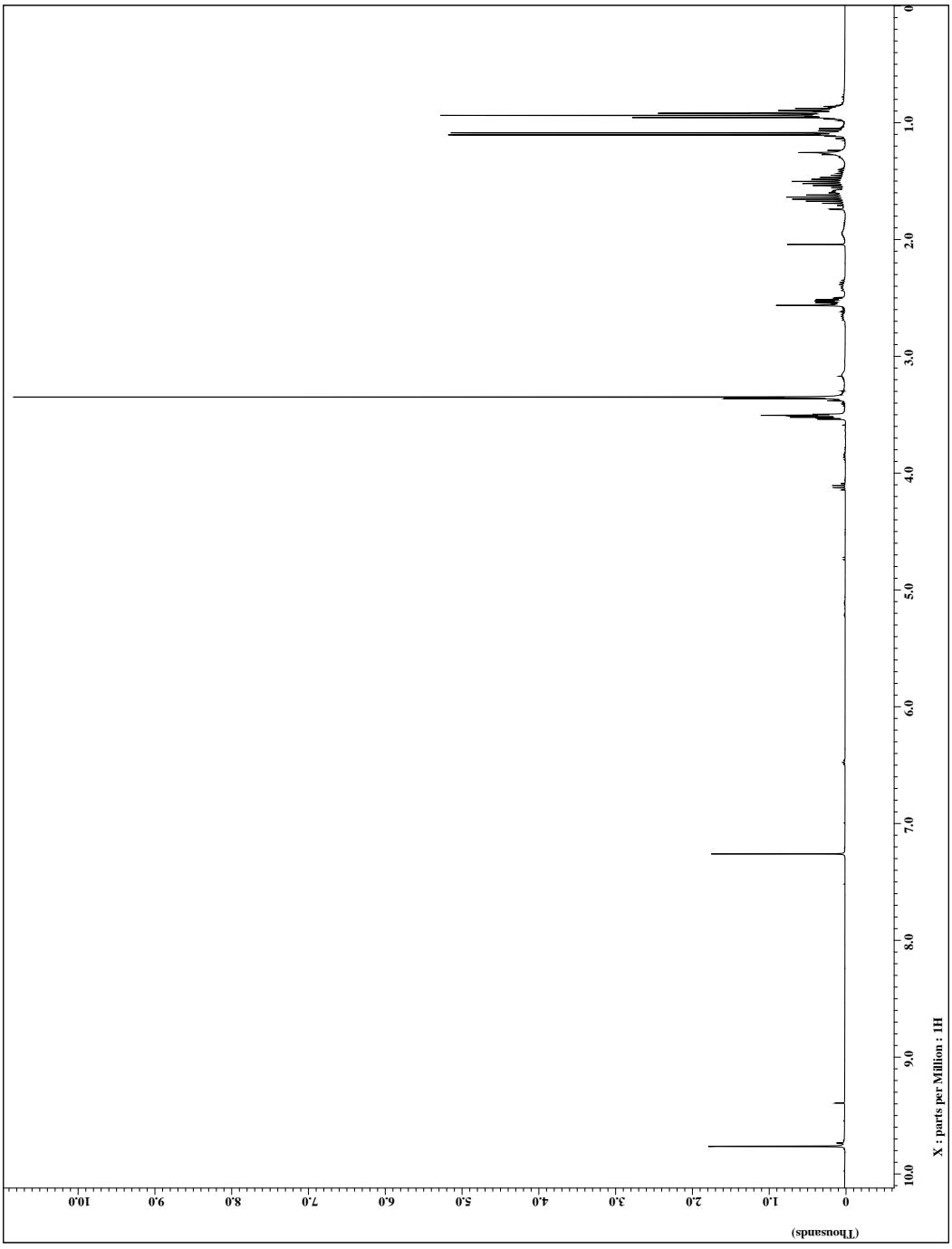
Spectrum A.112: ^{1}H spectrum of compound **140b**.



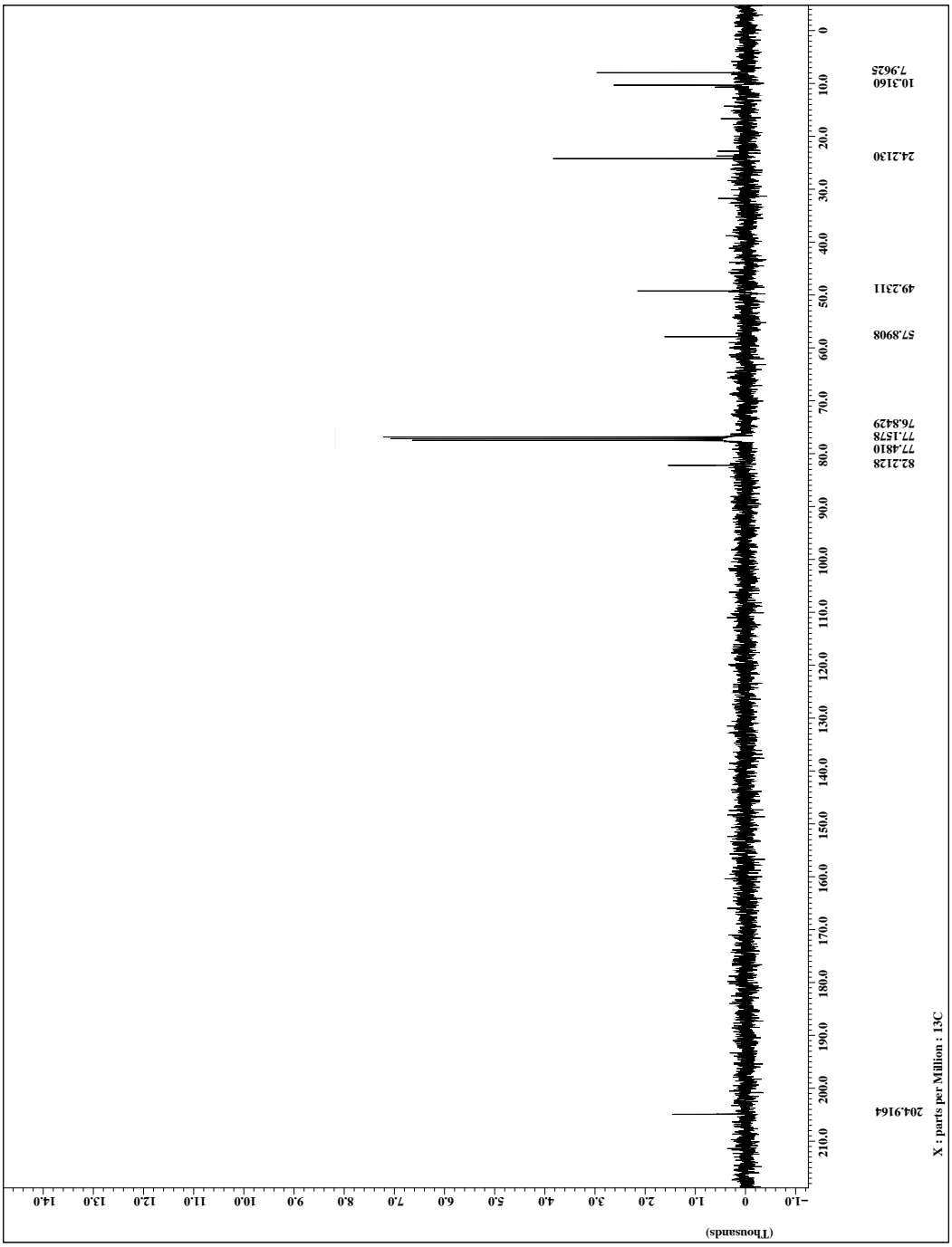
Spectrum A.113: ^{1}H spectrum of compound **141a**.



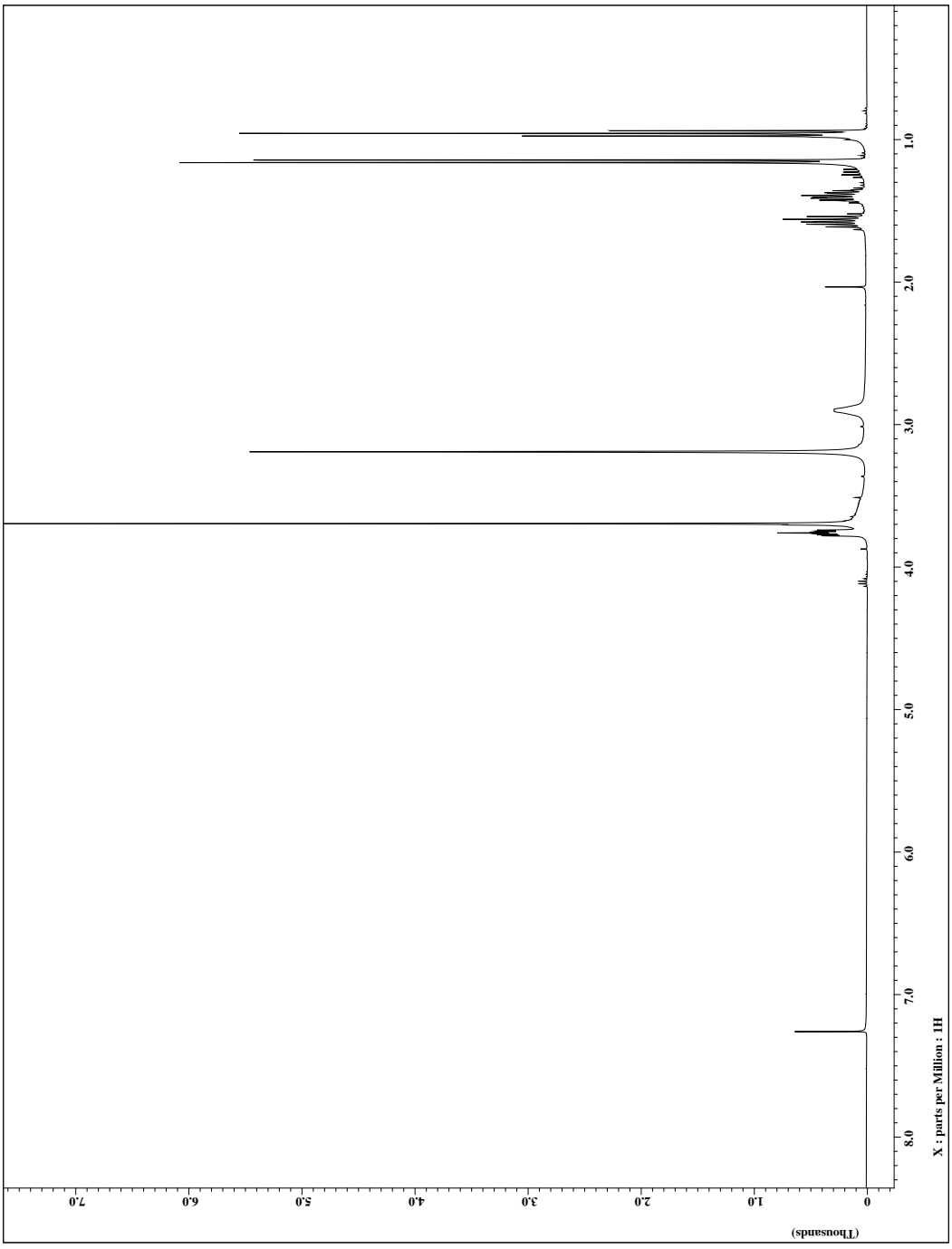
Spectrum A.114: ^{1}H spectrum of compound **141b**.



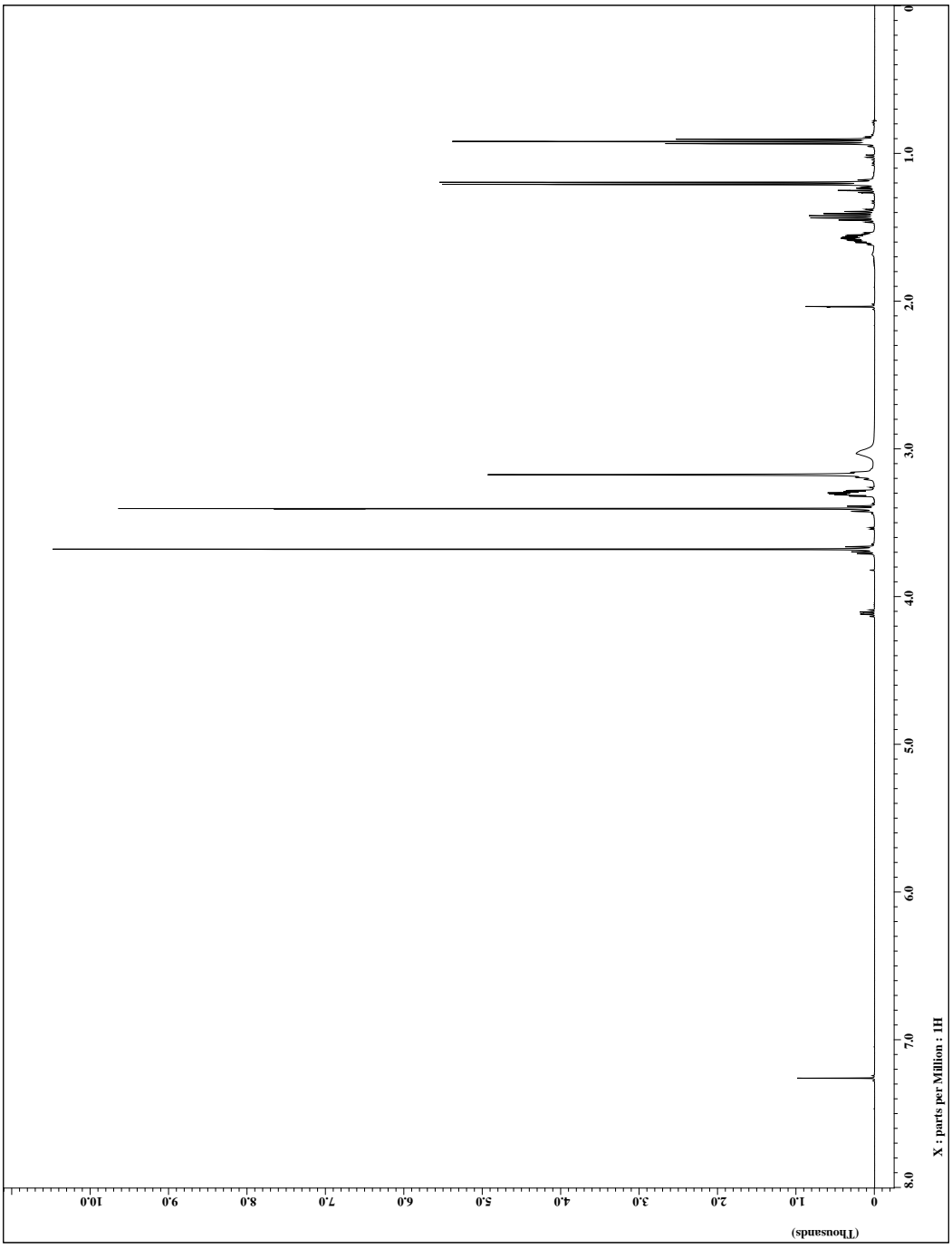
Spectrum A.115: ^{1}H spectrum of compound **143**.



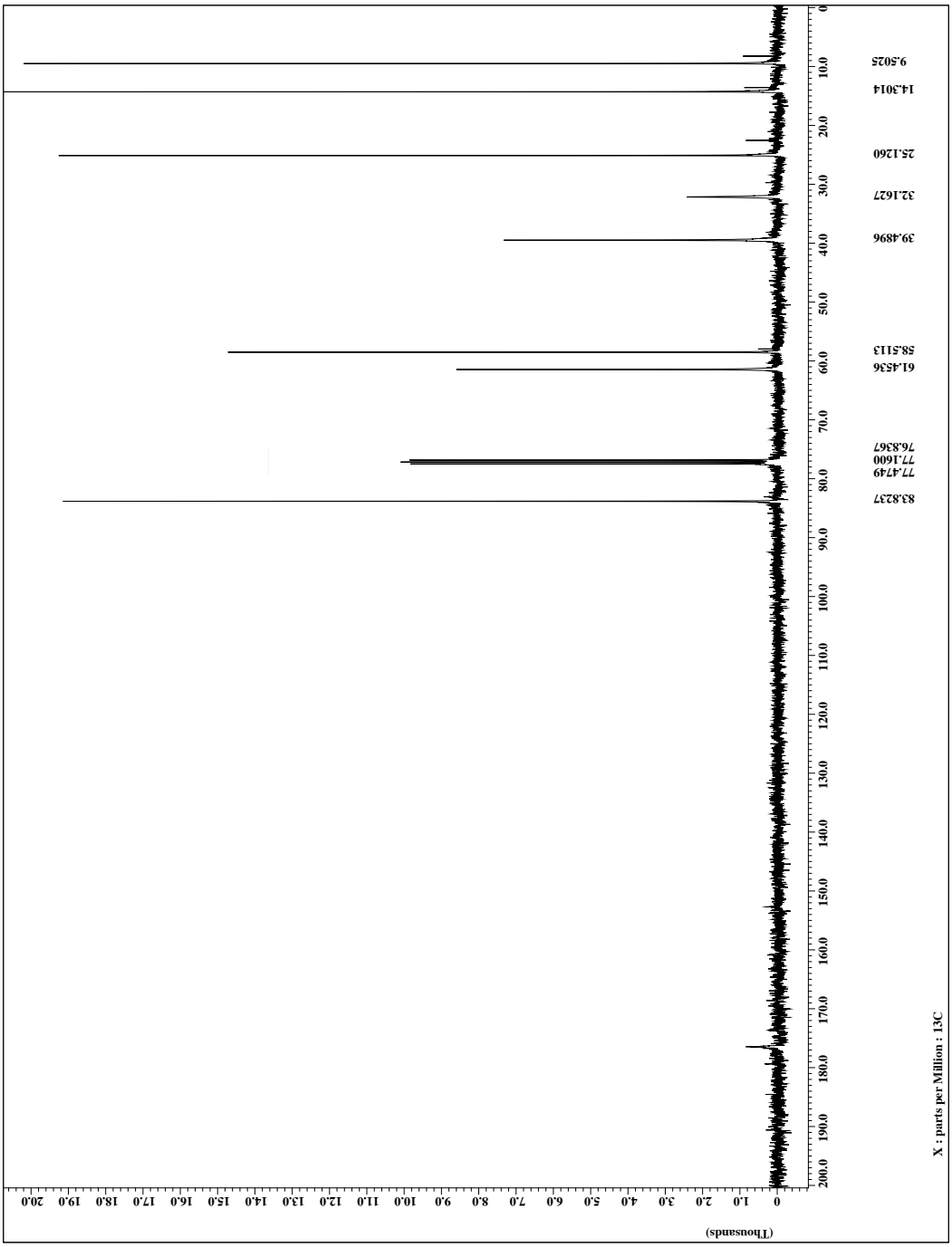
Spectrum A.116: ^{13}C spectrum of compound **143**.



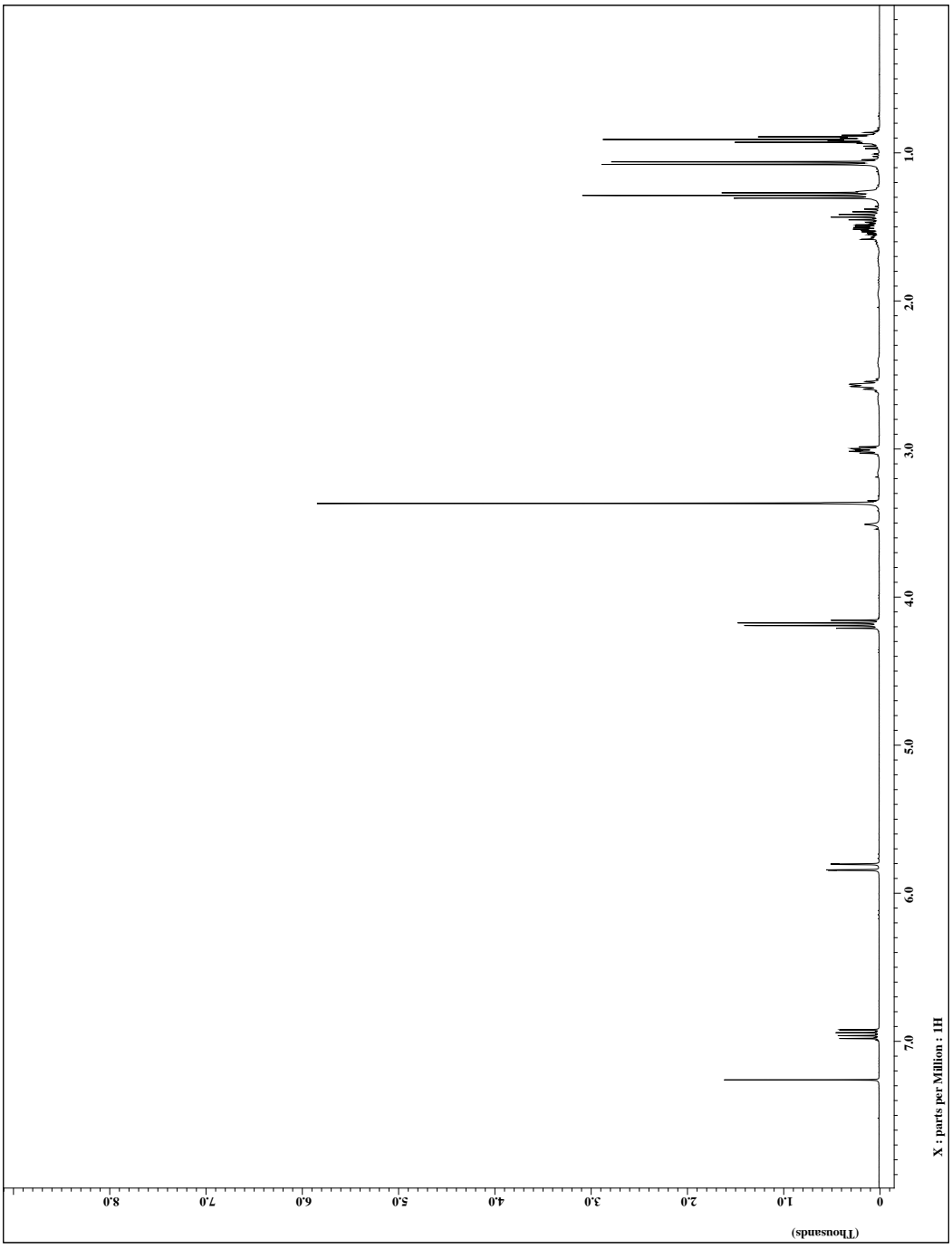
Spectrum A.117: ^{1}H spectrum of compound **151**.



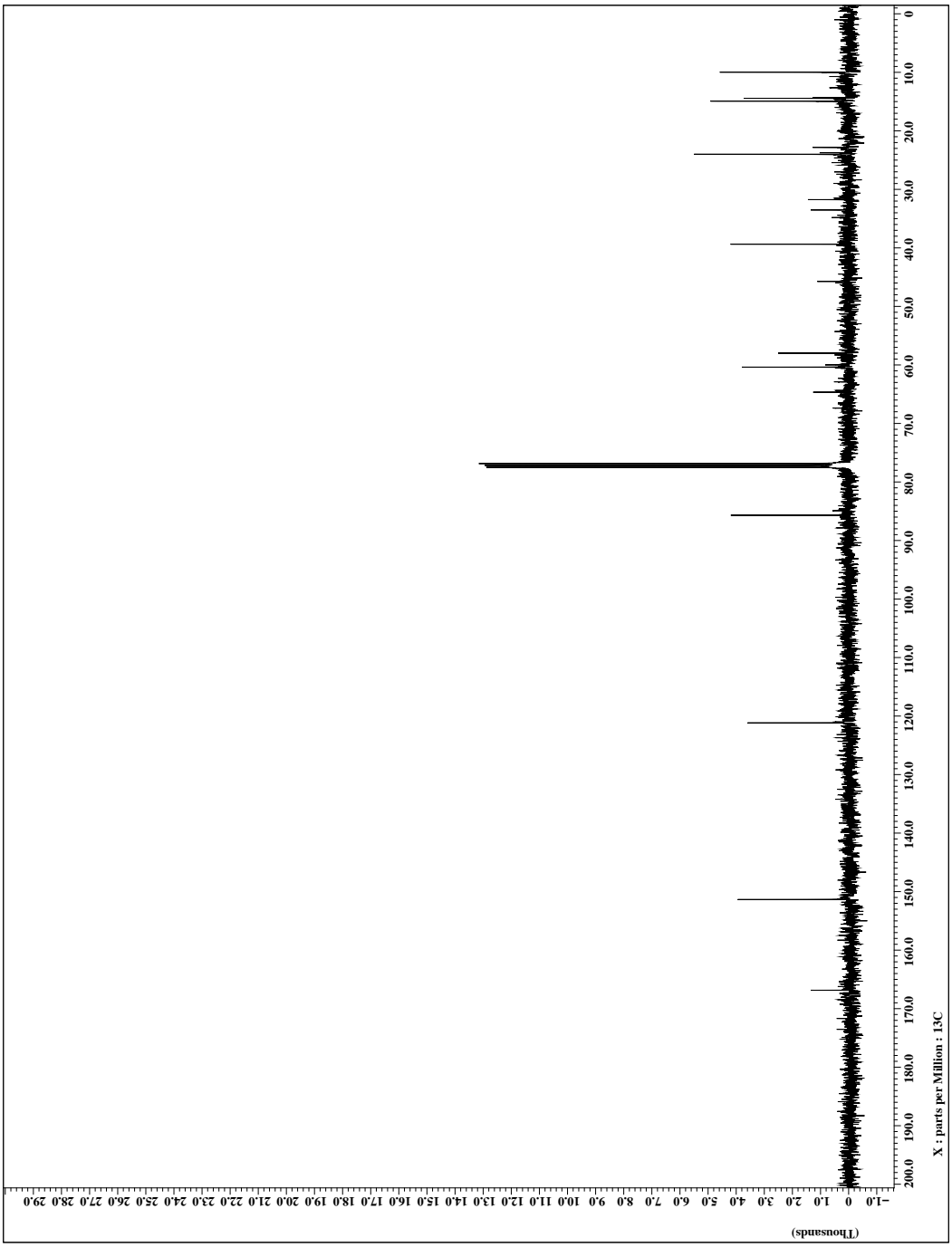
Spectrum A.118: ^{1}H spectrum of compound **152**.



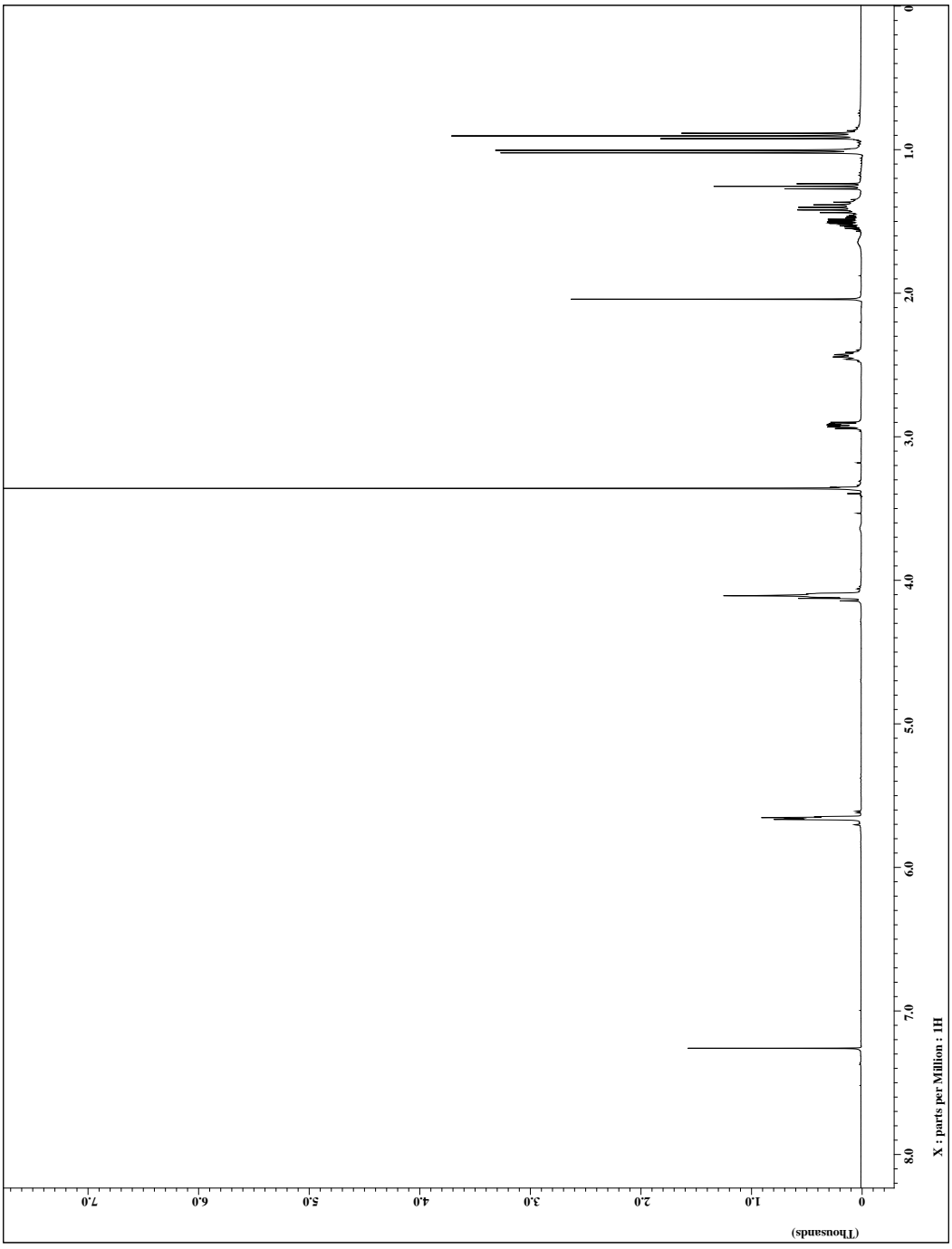
Spectrum A.119: ^{13}C spectrum of compound **152**.



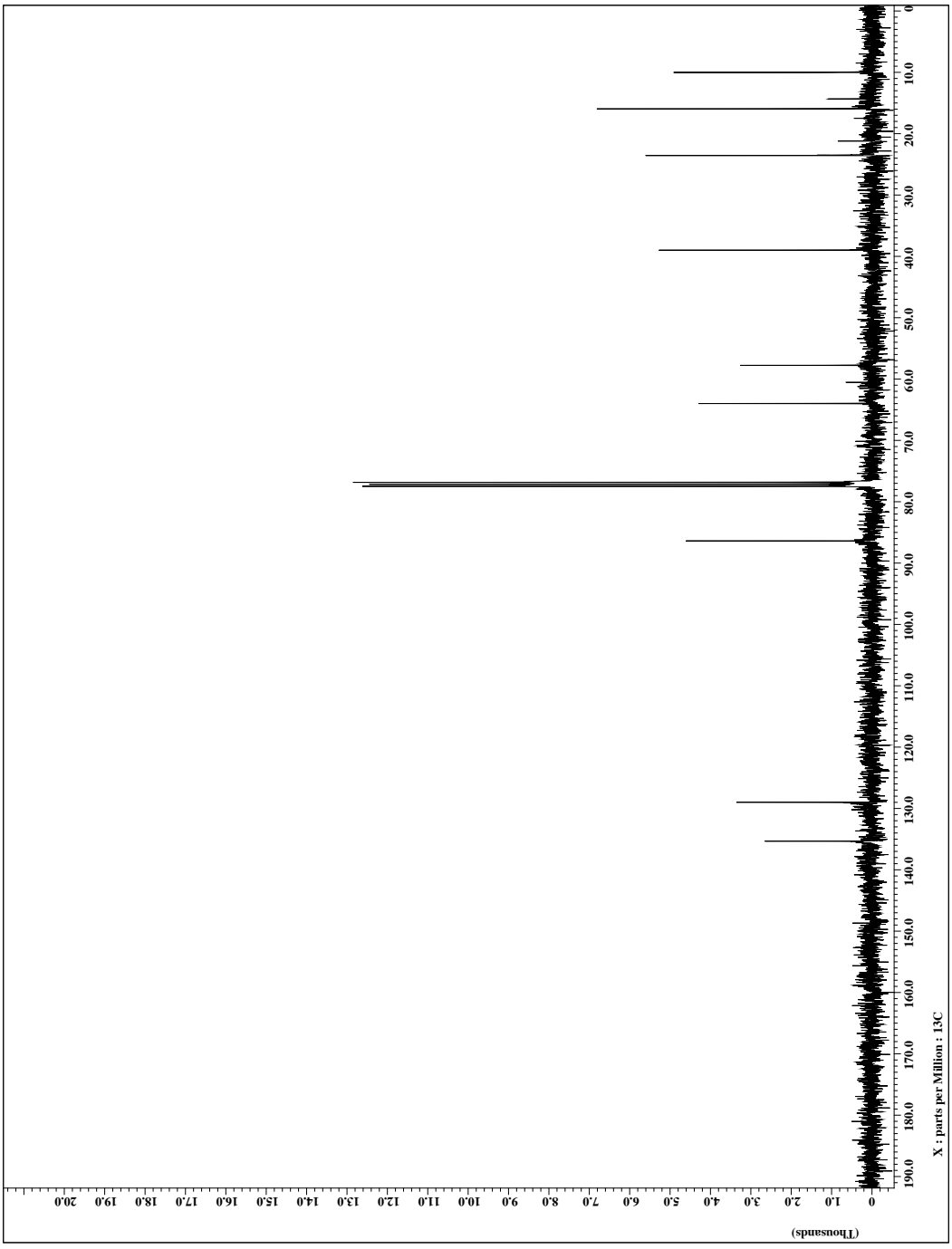
Spectrum A.120: ^{1}H spectrum of compound **153**.



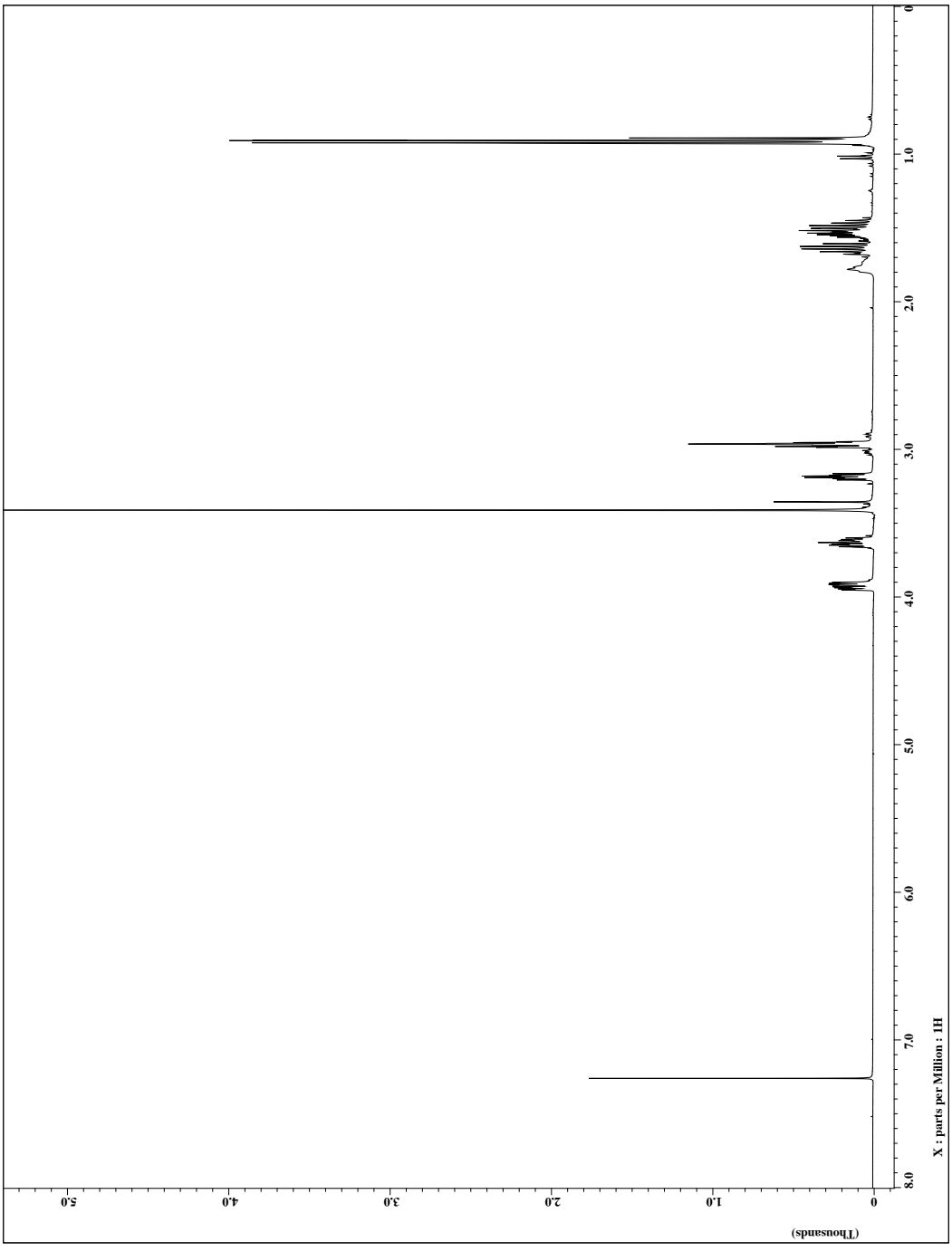
Spectrum A.121: ^{13}C spectrum of compound **153**.



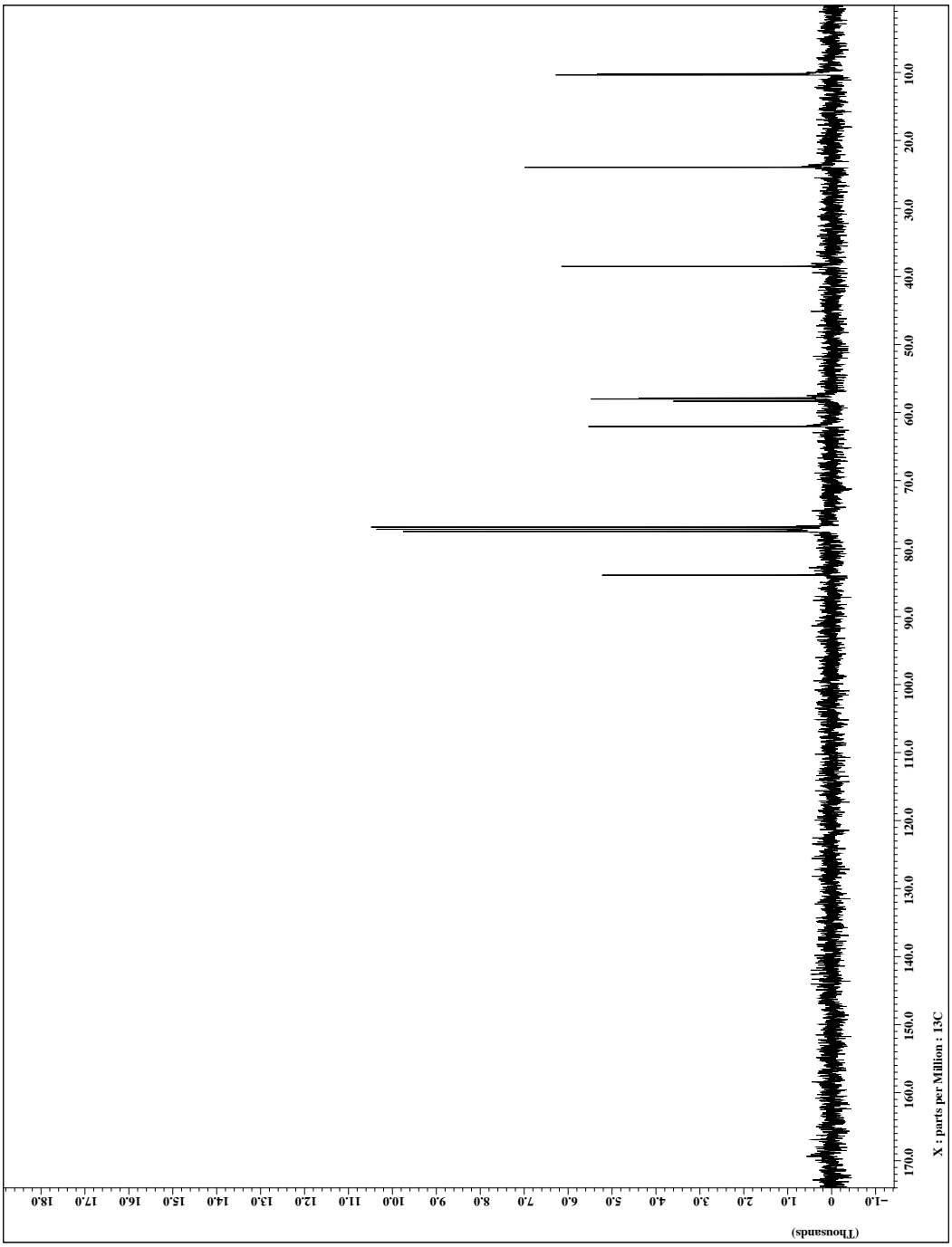
Spectrum A.122: ^{1}H spectrum of compound **158**.



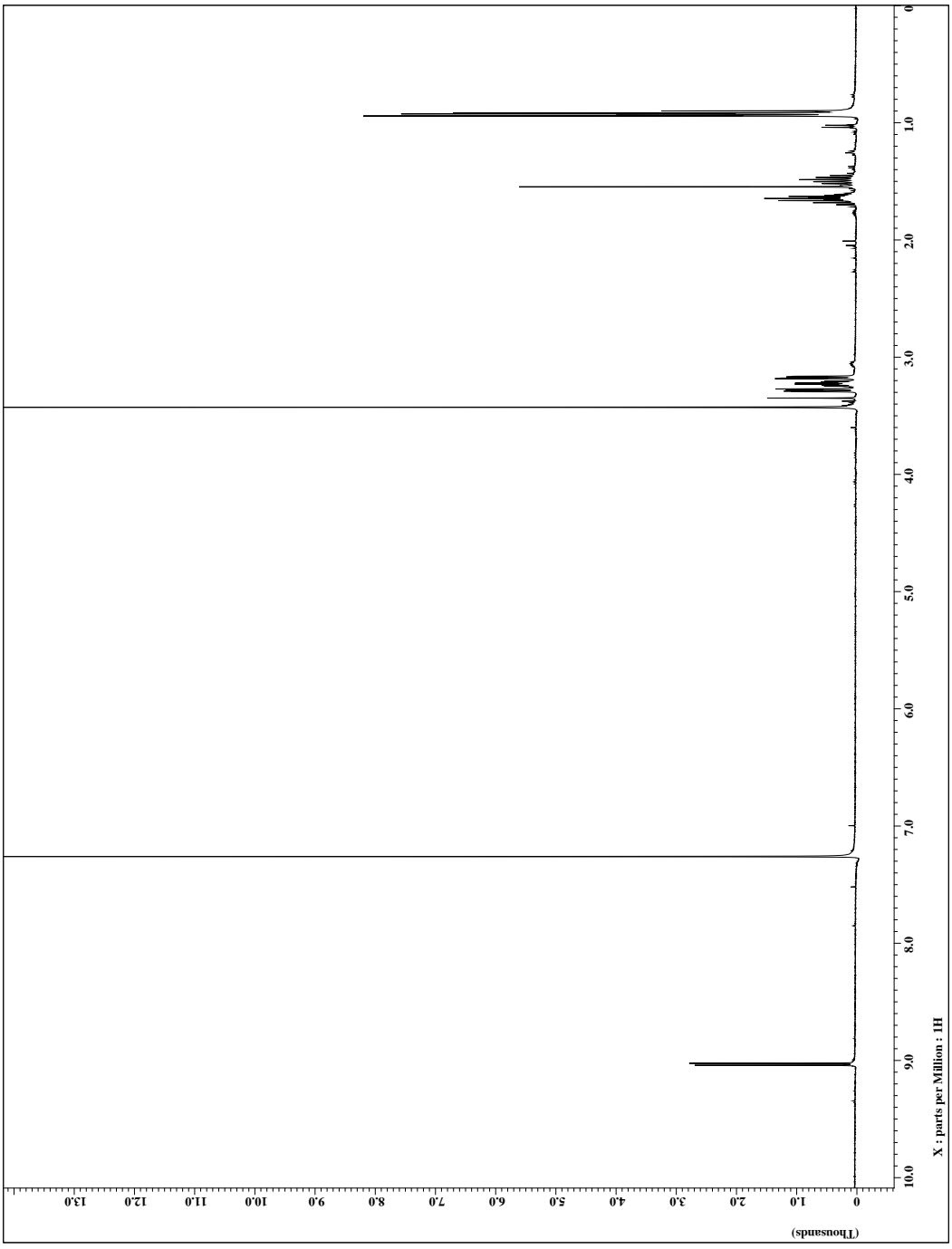
Spectrum A.123: ^{13}C spectrum of compound **158**.



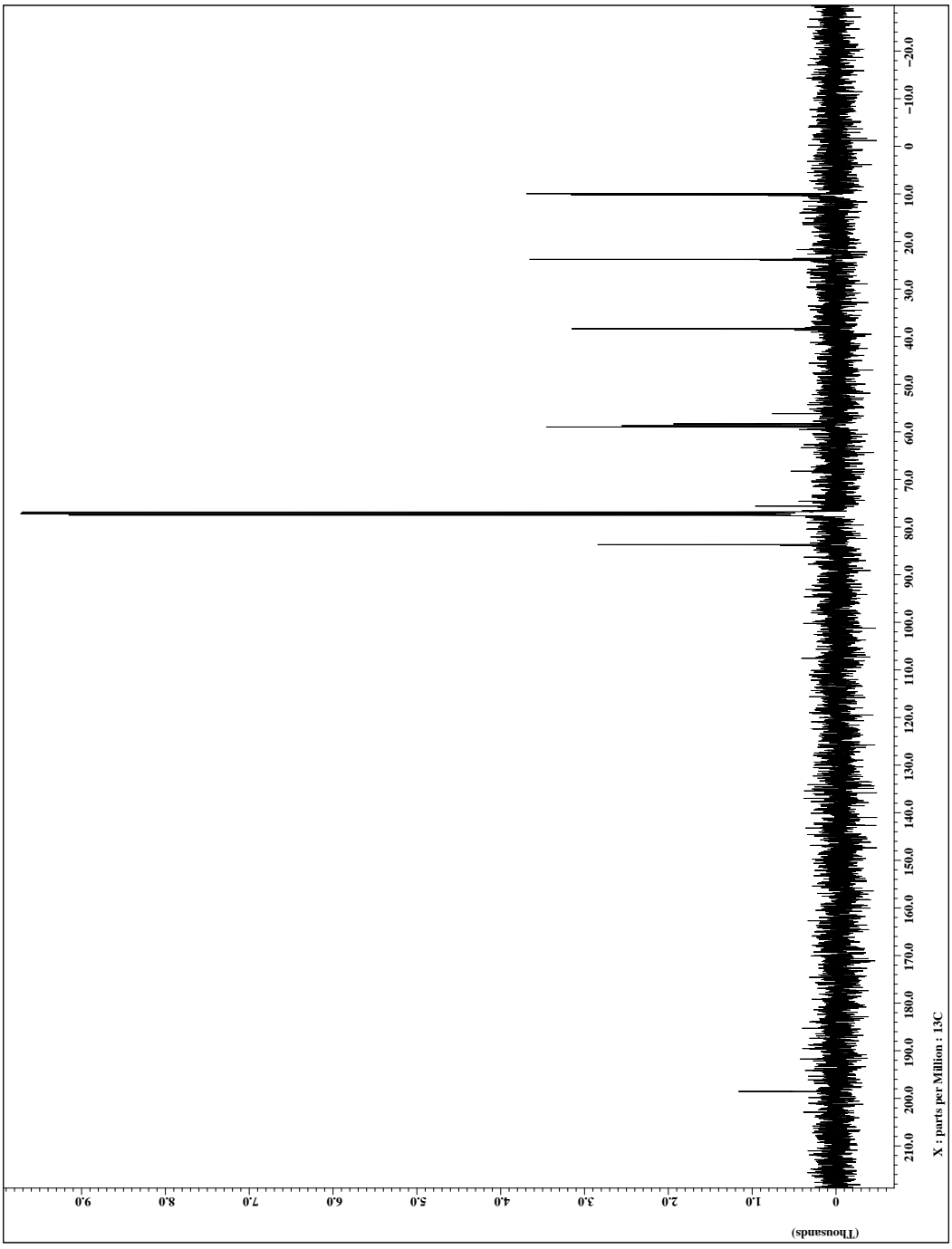
Spectrum A.124: ^{1}H spectrum of compound **159**.



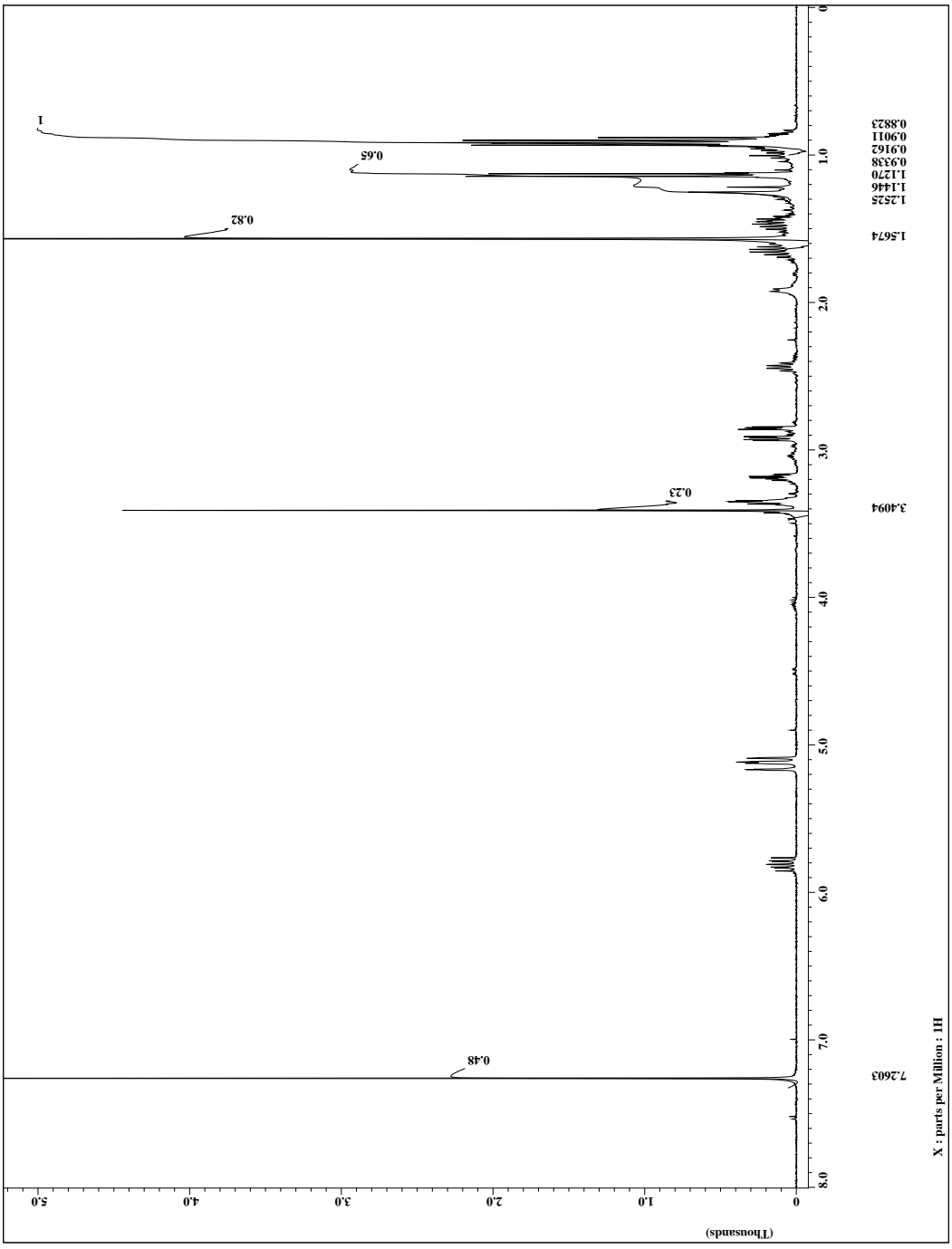
Spectrum A.125: ^{13}C spectrum of compound **159**.



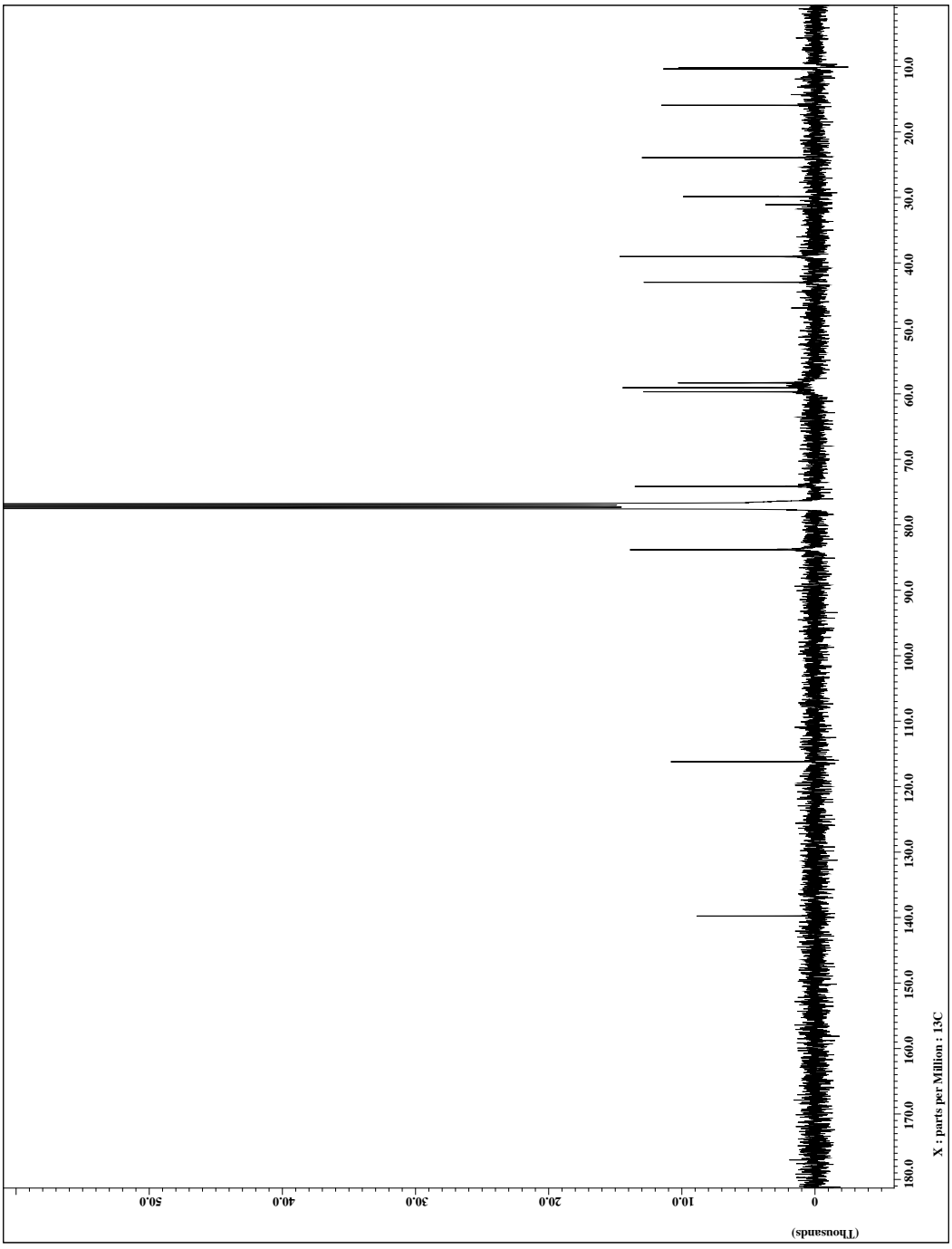
Spectrum A.126: ^{1}H spectrum of compound **160**.



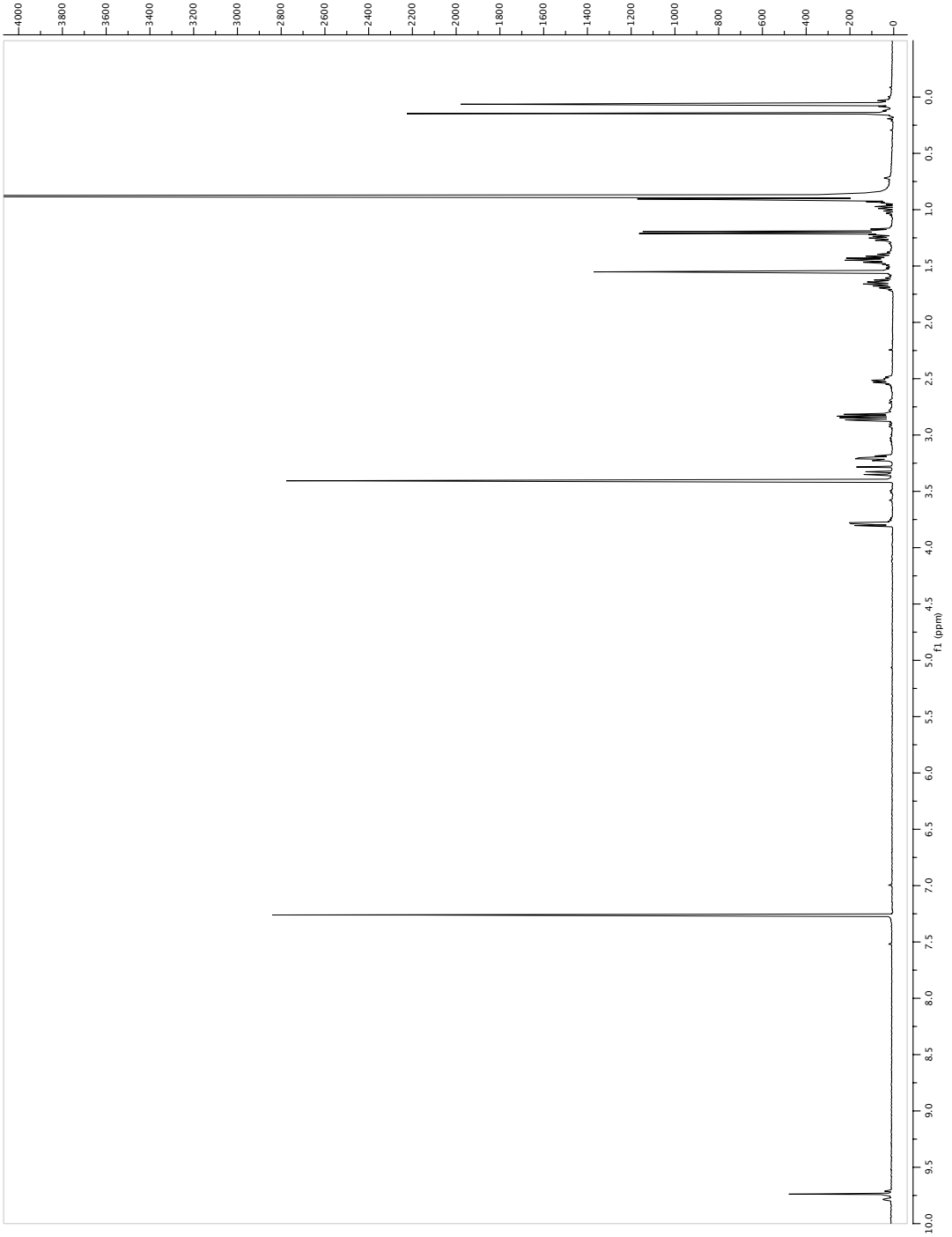
Spectrum A.127: ^{13}C spectrum of compound **160**.



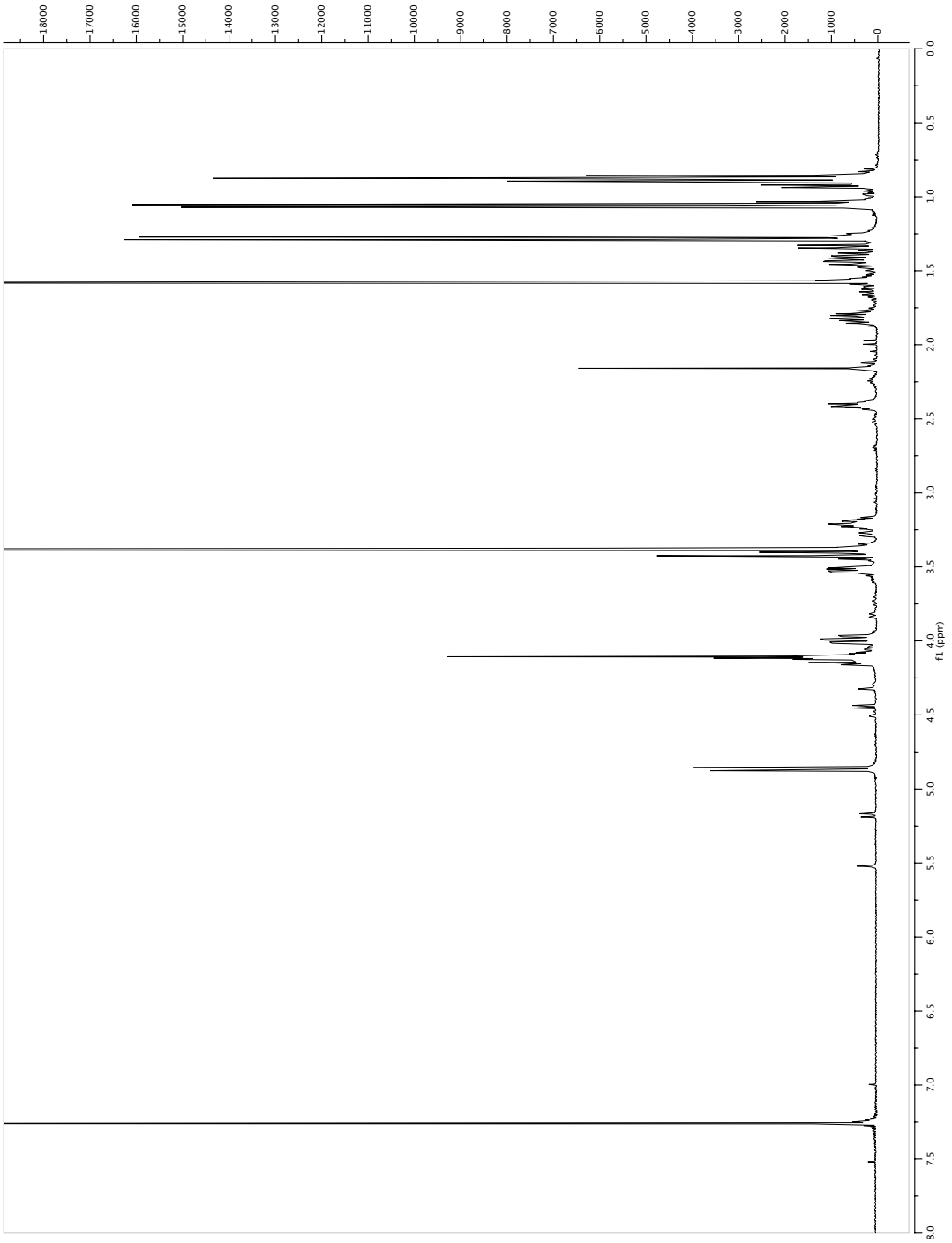
Spectrum A.128: ^{1}H spectrum of compound **161**.



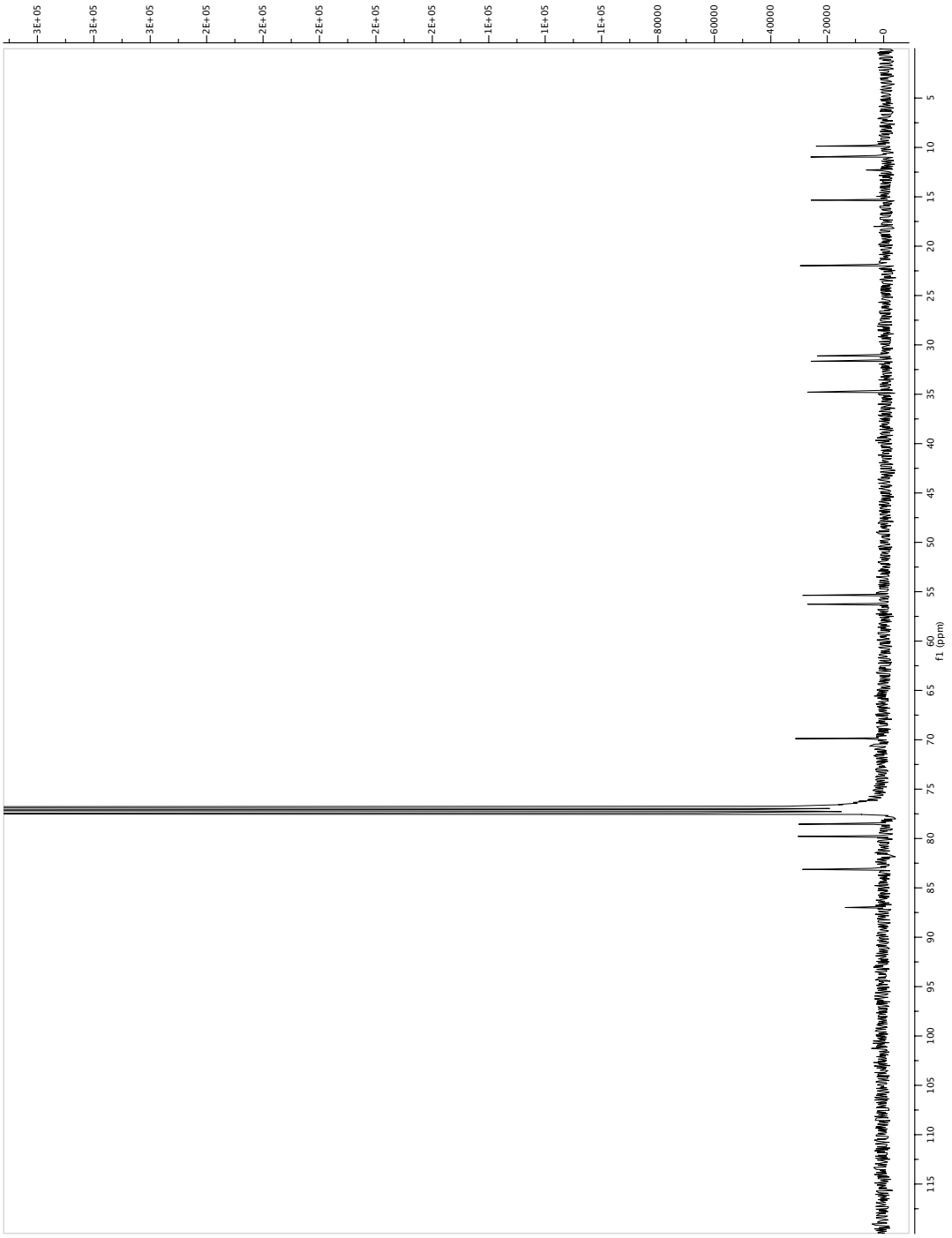
Spectrum A.129: ^{13}C spectrum of compound **161**.



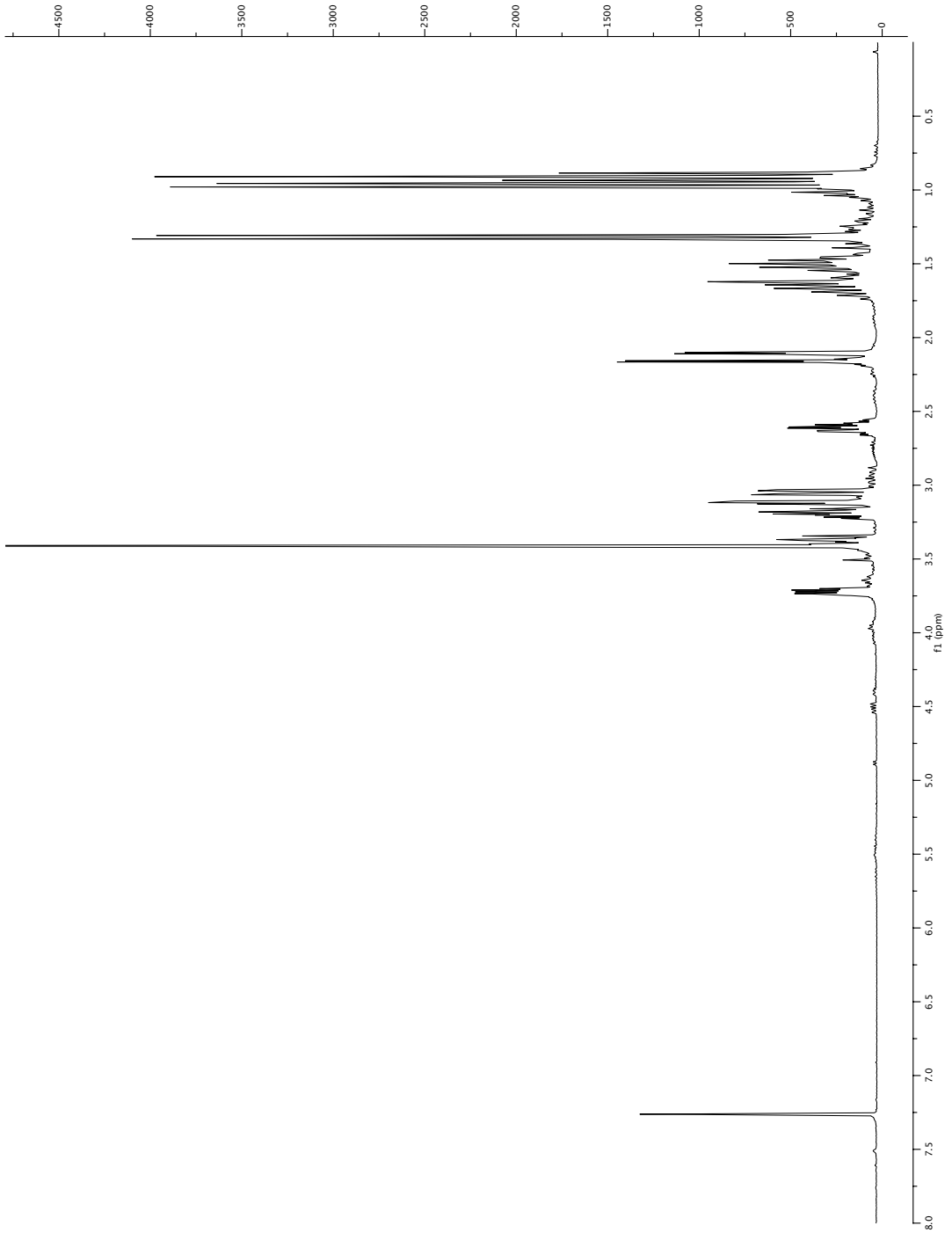
Spectrum A.130: ^{1}H spectrum of compound **163**.



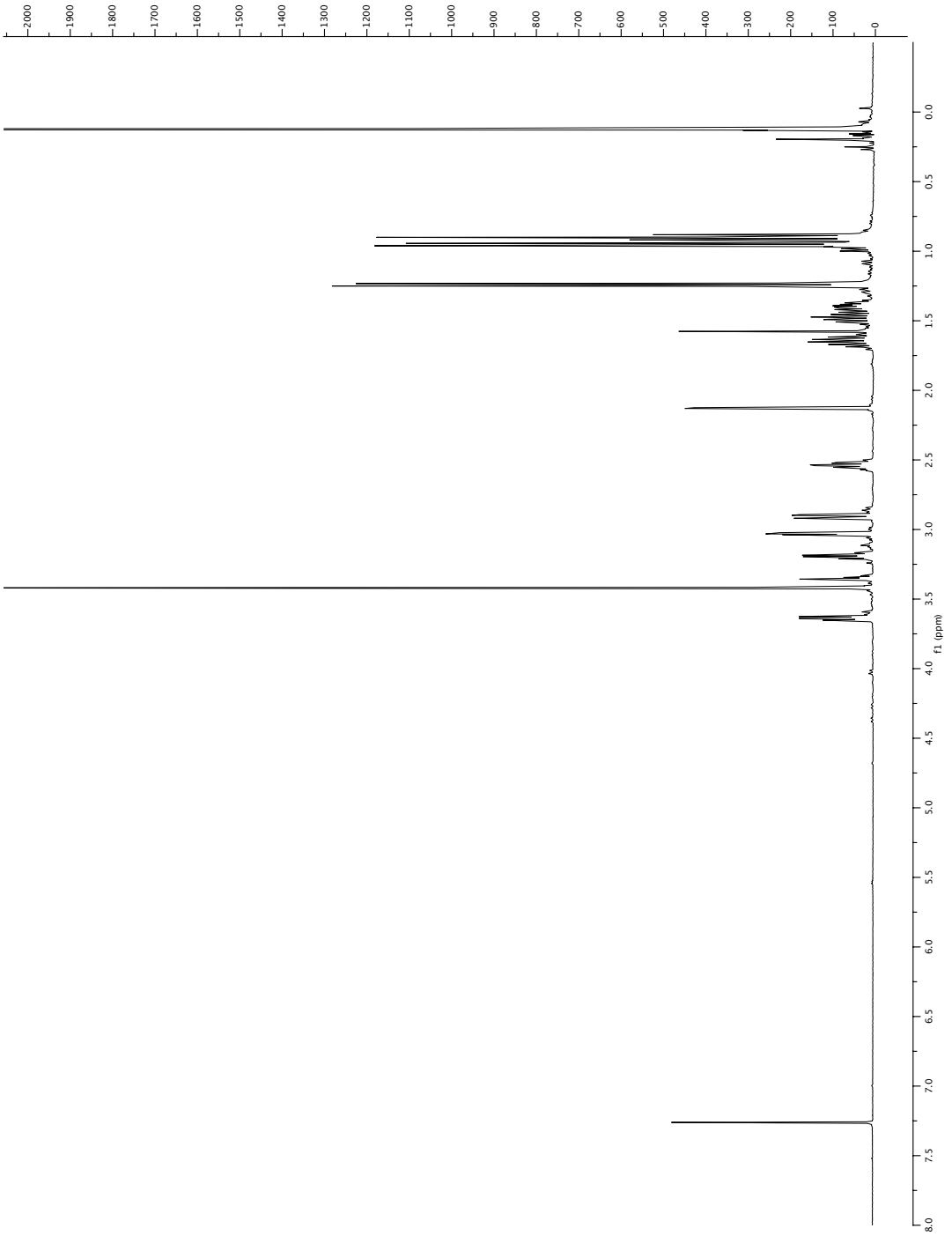
Spectrum A.131: ^{1}H spectrum of compound **168**.



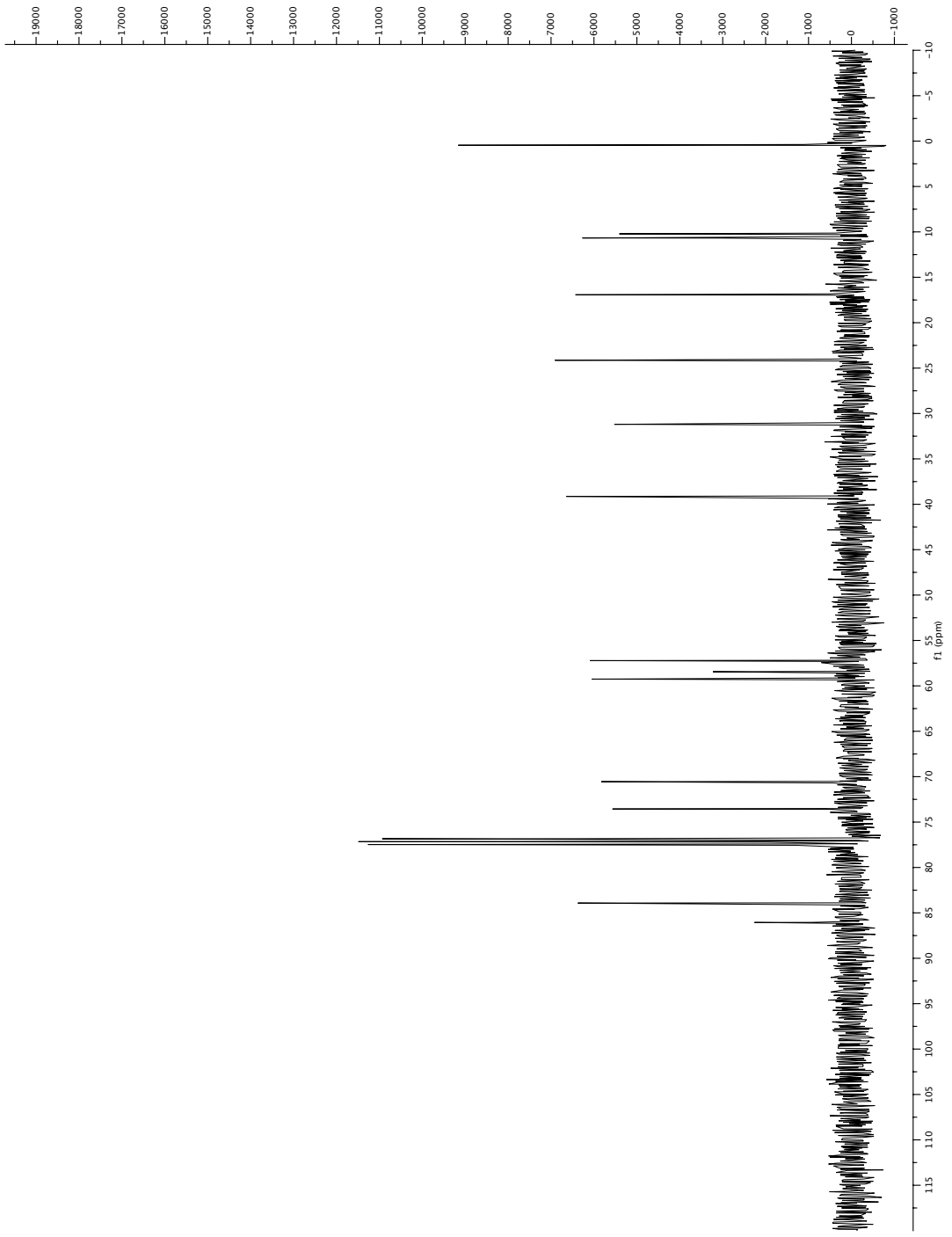
Spectrum A.132: ^{13}C spectrum of compound **168**.



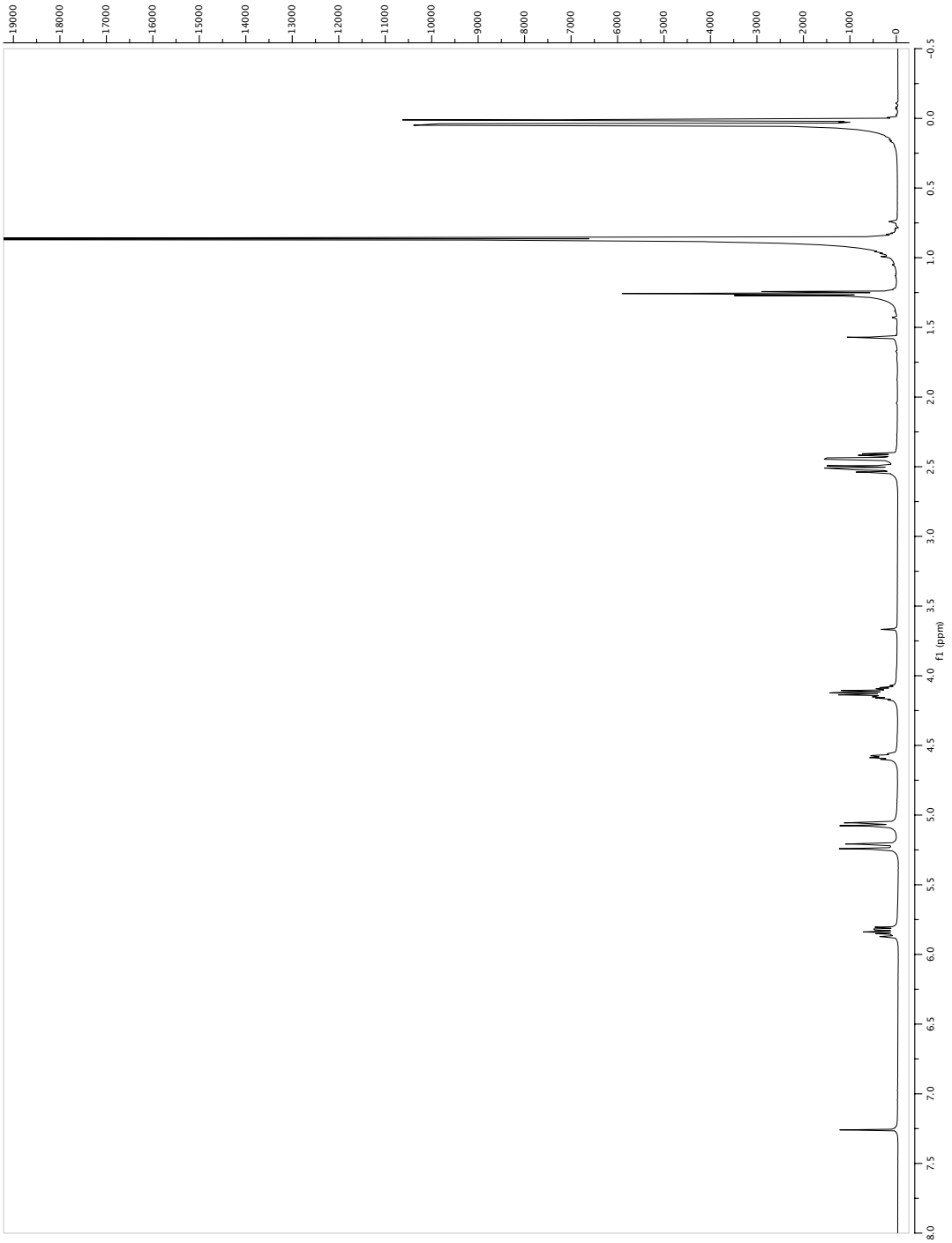
Spectrum A.133: ^{1}H spectrum of compound **169**.



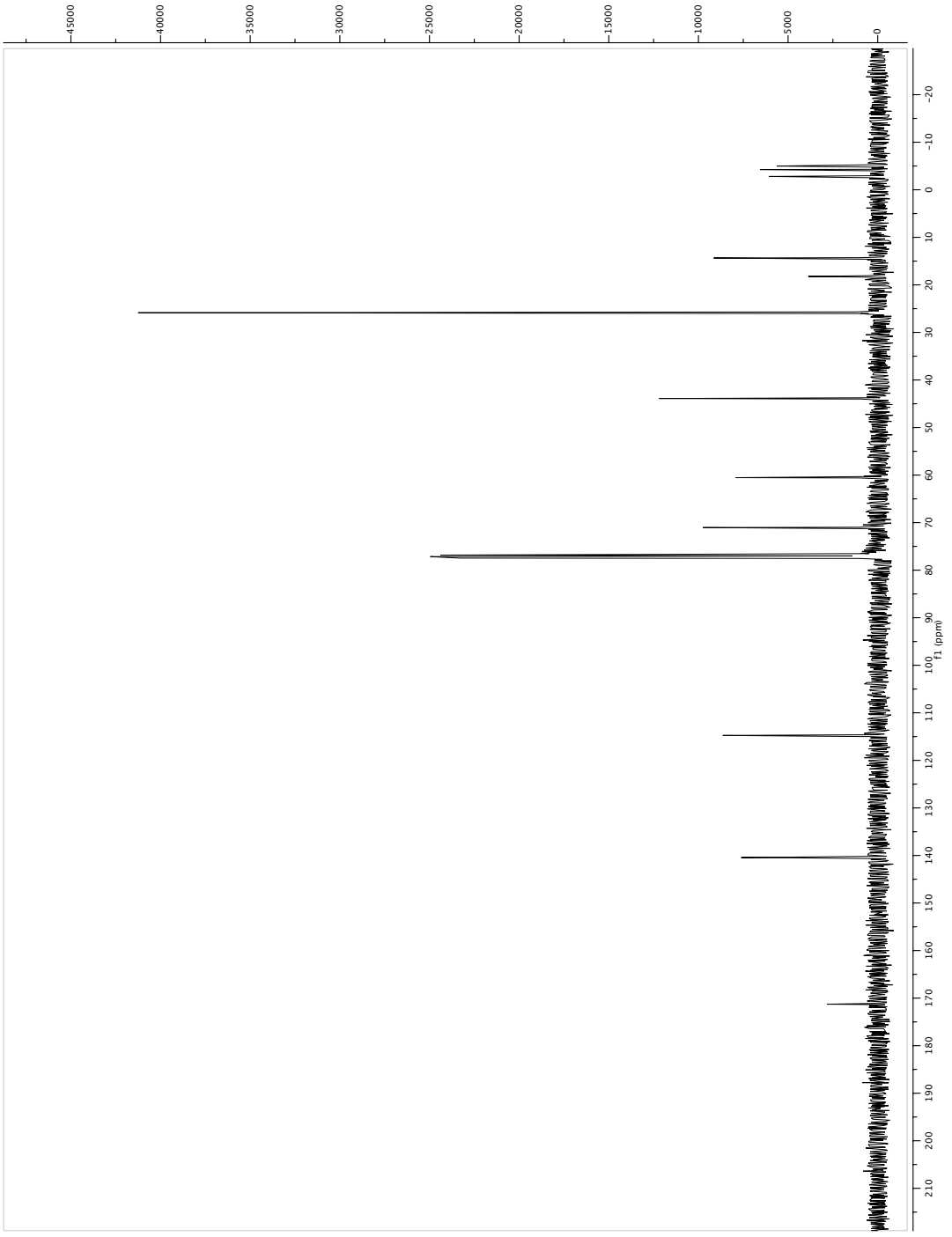
Spectrum A.134: ^{1}H spectrum of compound **170**.



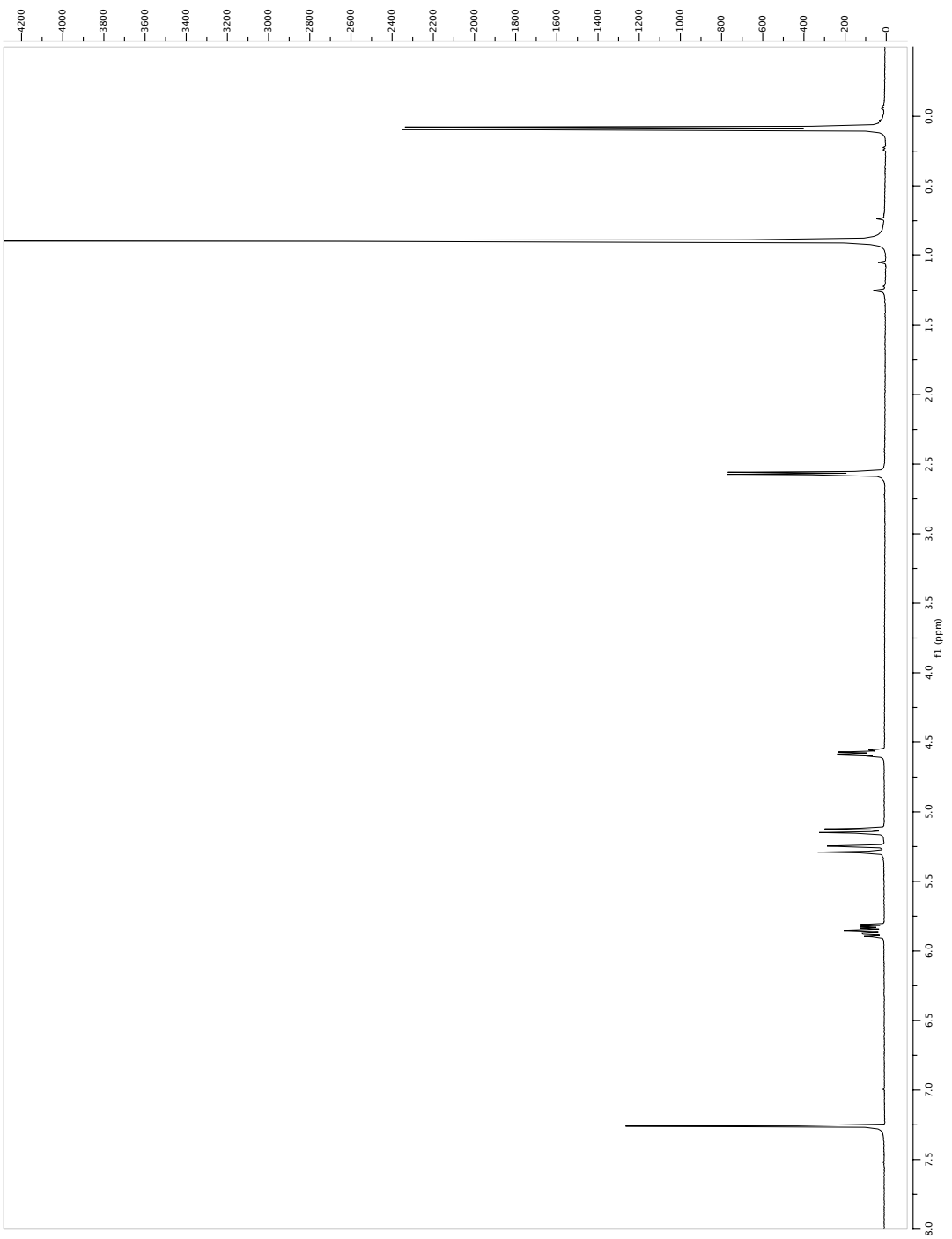
Spectrum A.135: ^{13}C spectrum of compound **170**.



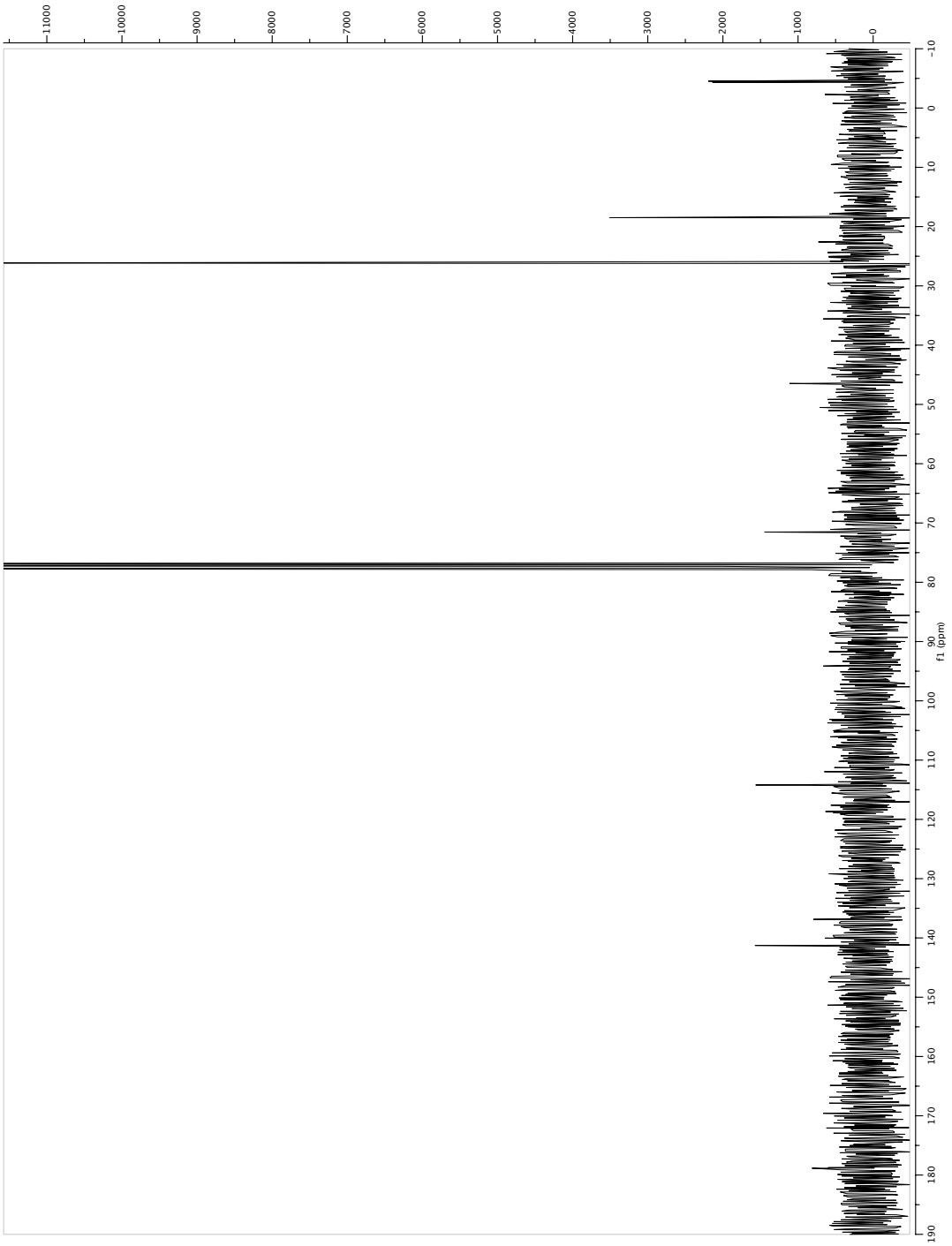
Spectrum A.136: ^{1}H spectrum of compound **174**.



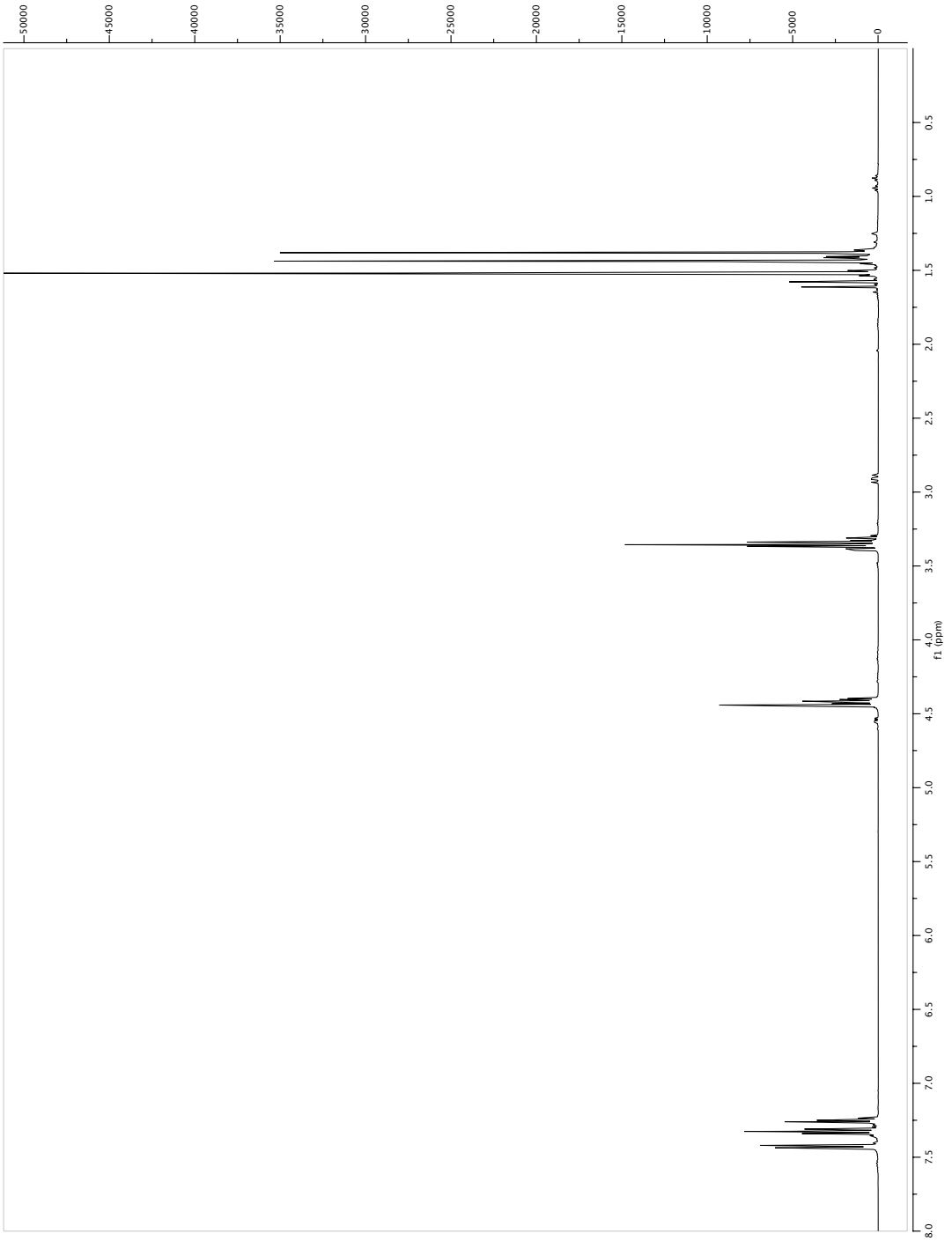
Spectrum A.137: ^{13}C spectrum of compound **174**.



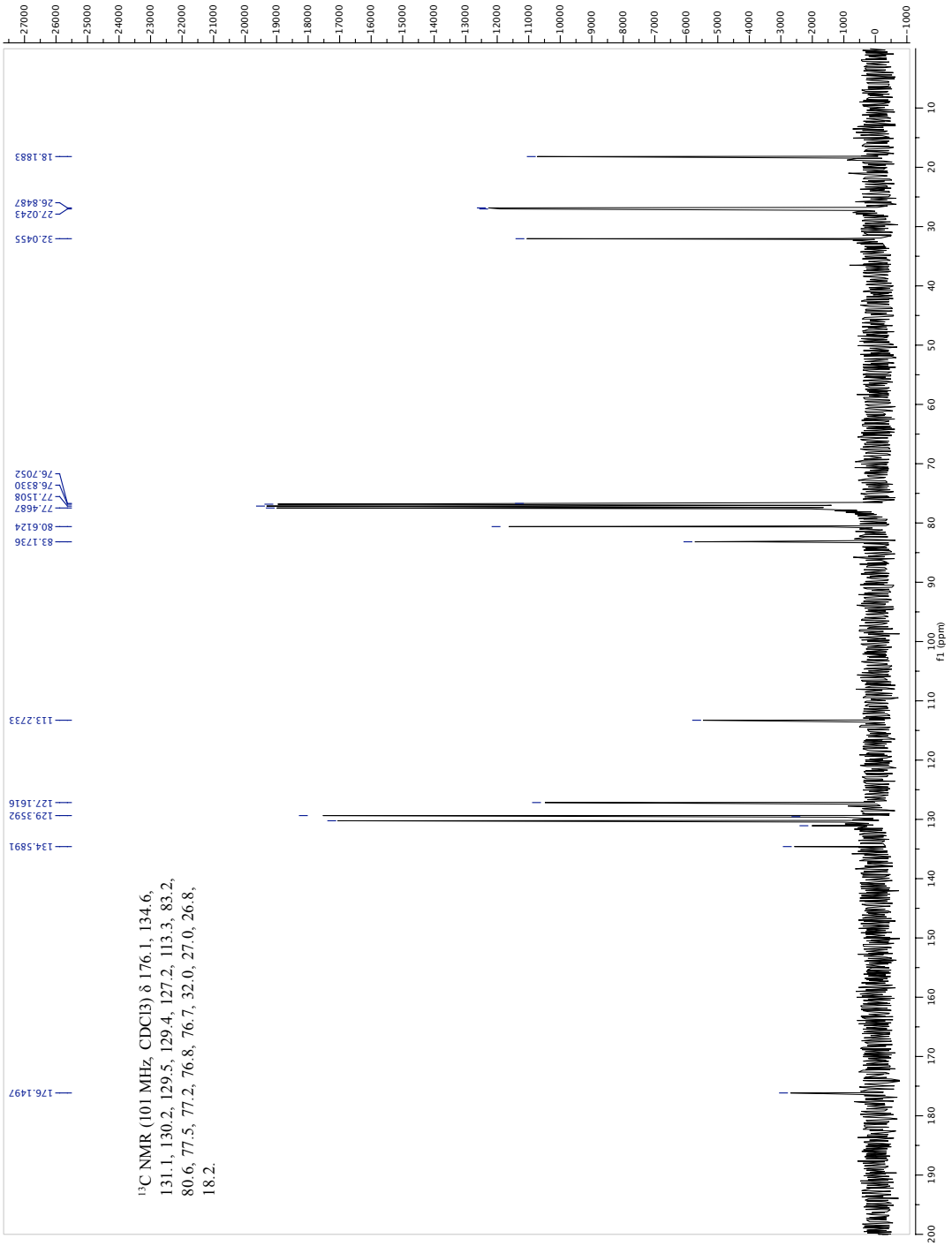
Spectrum A.138: ^{1}H spectrum of compound **175**.



Spectrum A.139: ^{13}C spectrum of compound **175**.

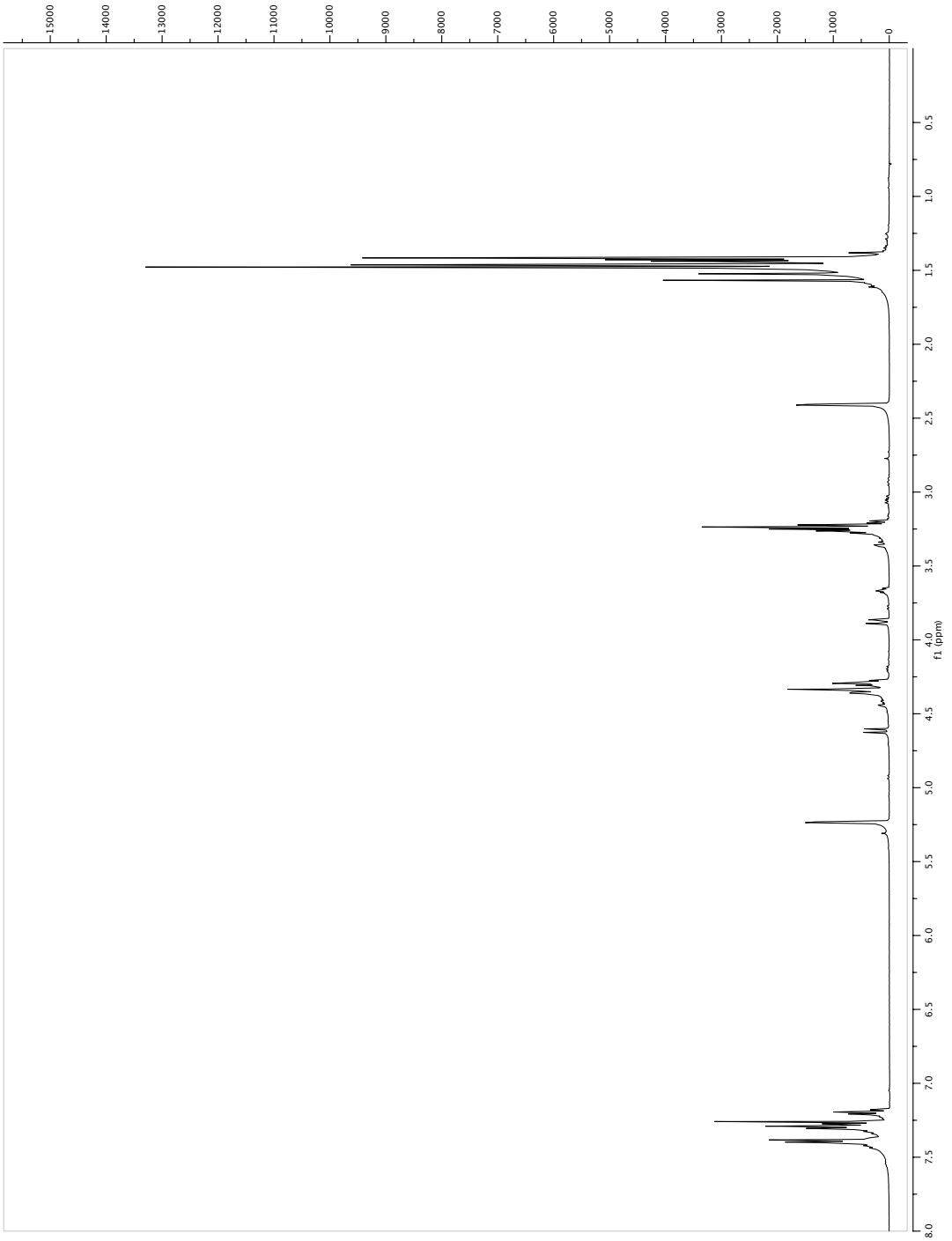


Spectrum A.140: ^{1}H spectrum of compound **179**.

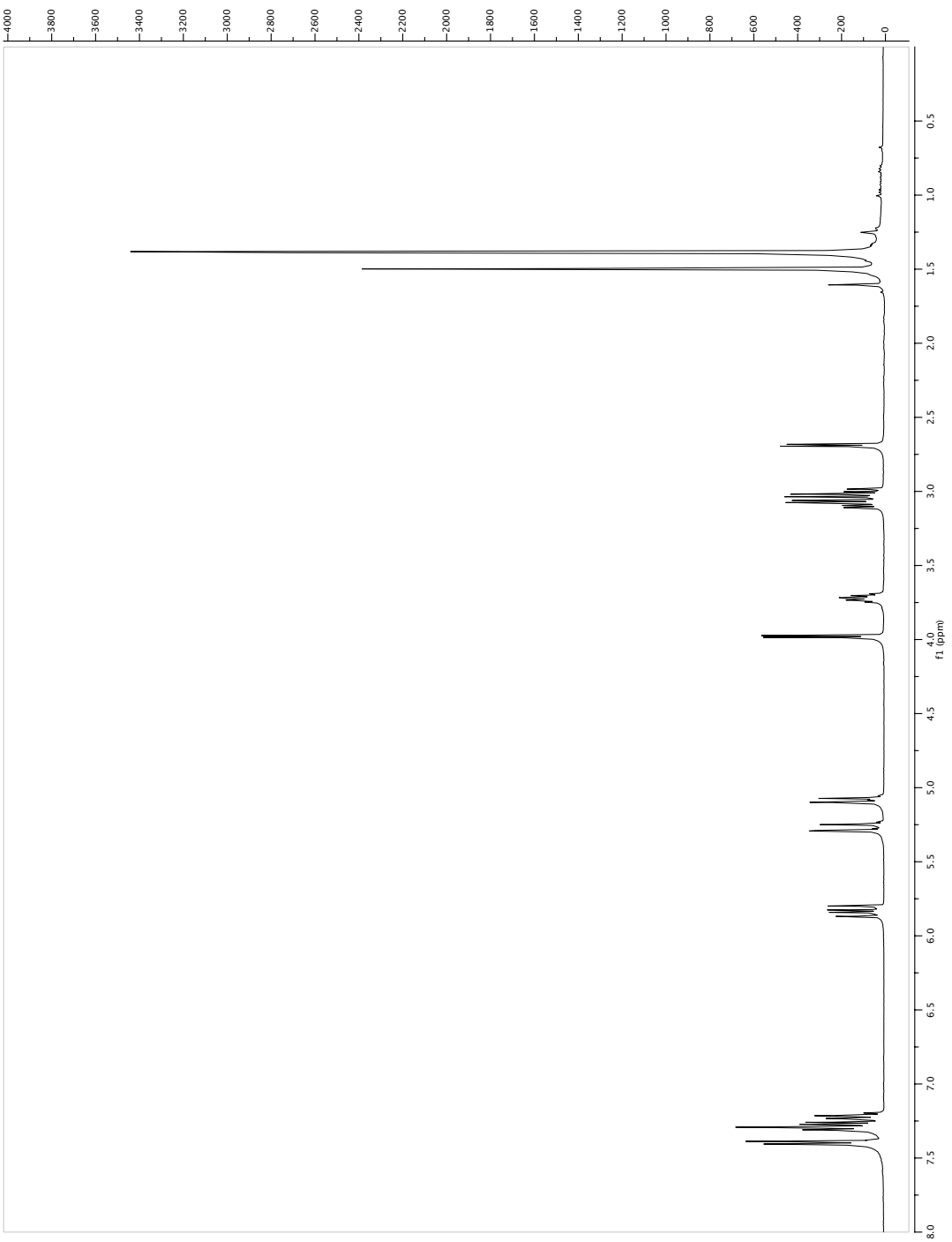


^{13}C NMR (101 MHz, CDCl3) δ 176.1, 134.6, 131.1, 130.2, 129.5, 129.4, 127.2, 113.3, 83.2, 80.6, 77.5, 77.2, 76.8, 76.7, 32.0, 27.0, 26.8, 18.2.

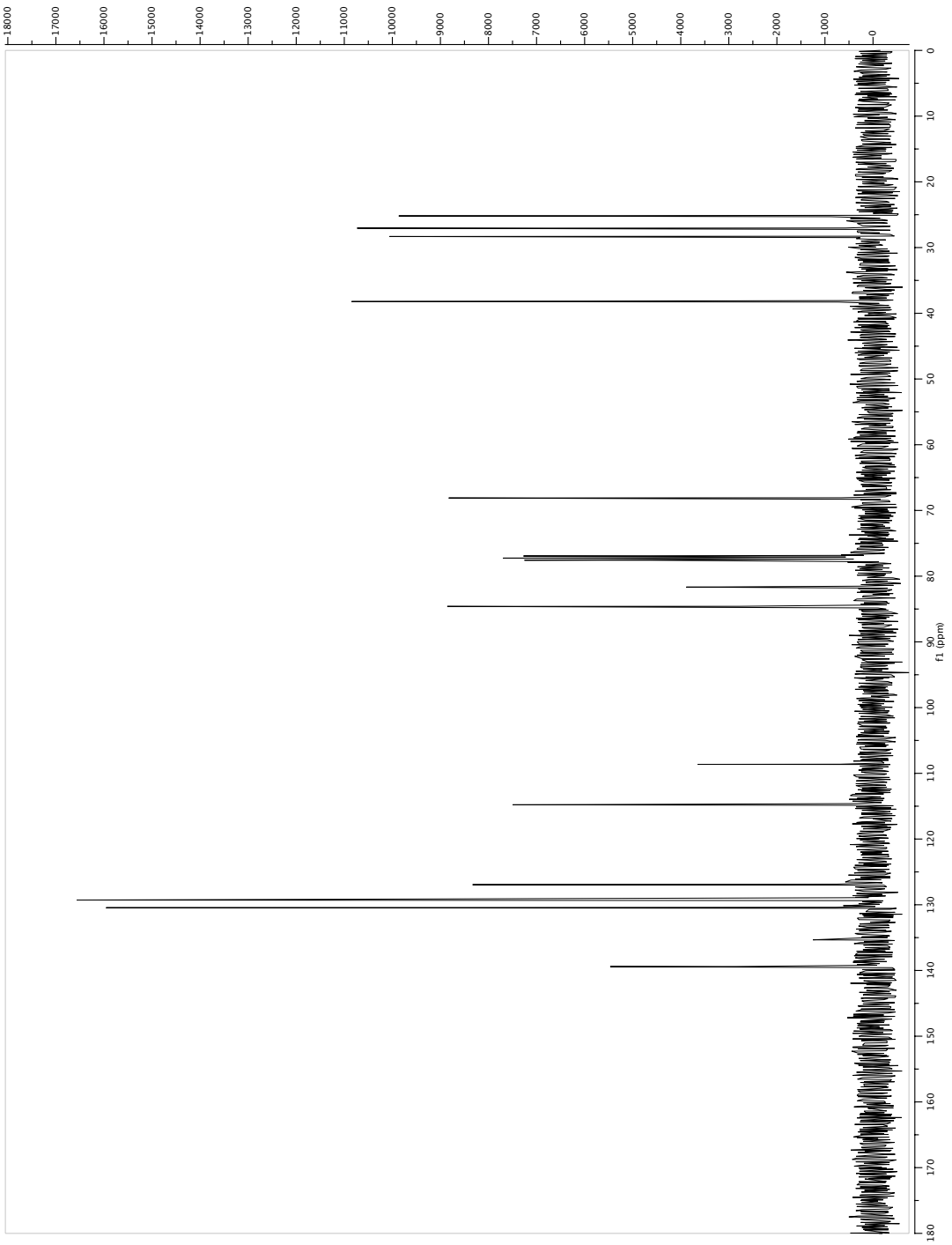
Spectrum A.141: ^{13}C spectrum of compound **179**.



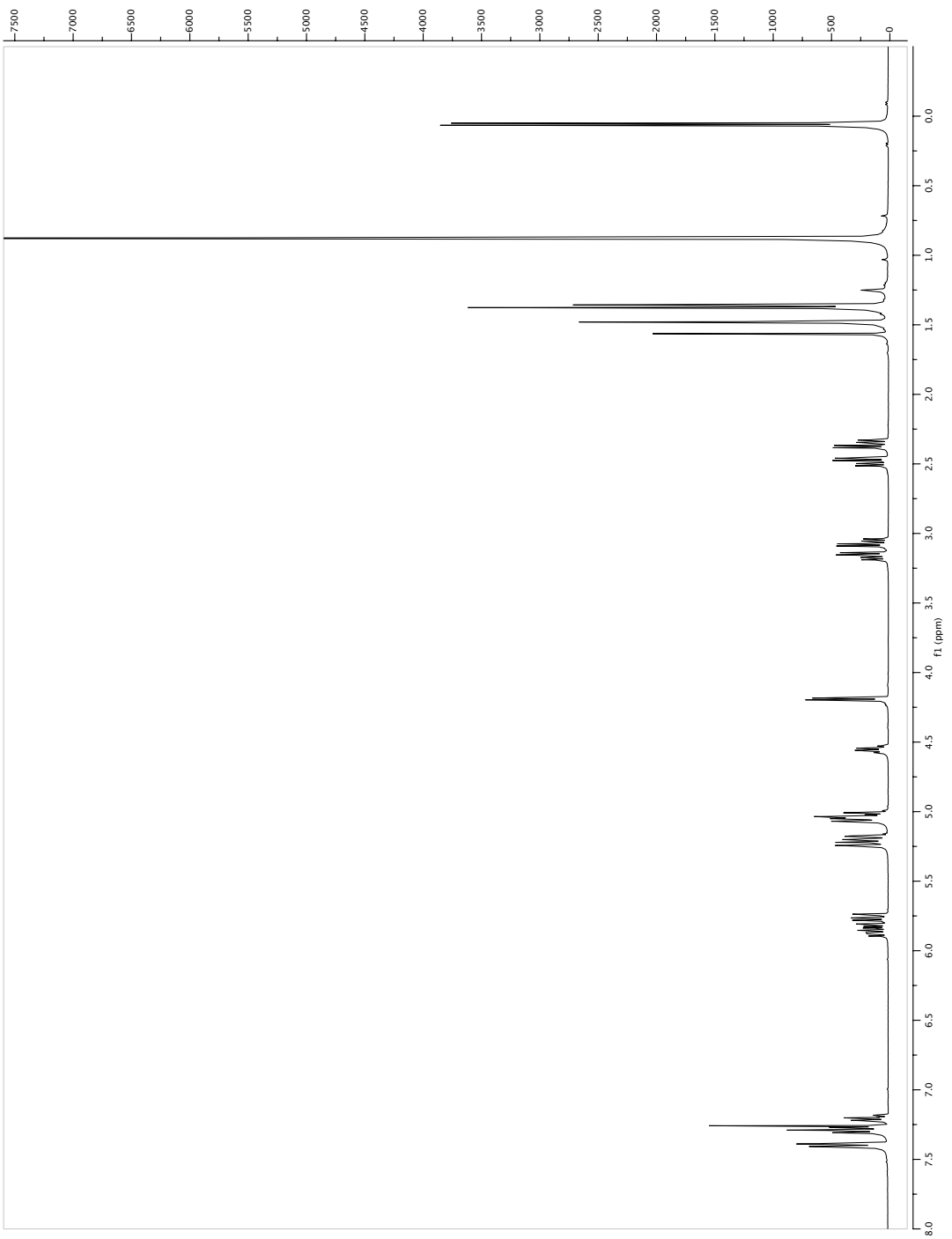
Spectrum A.142: ^{1}H spectrum of compound **180**.



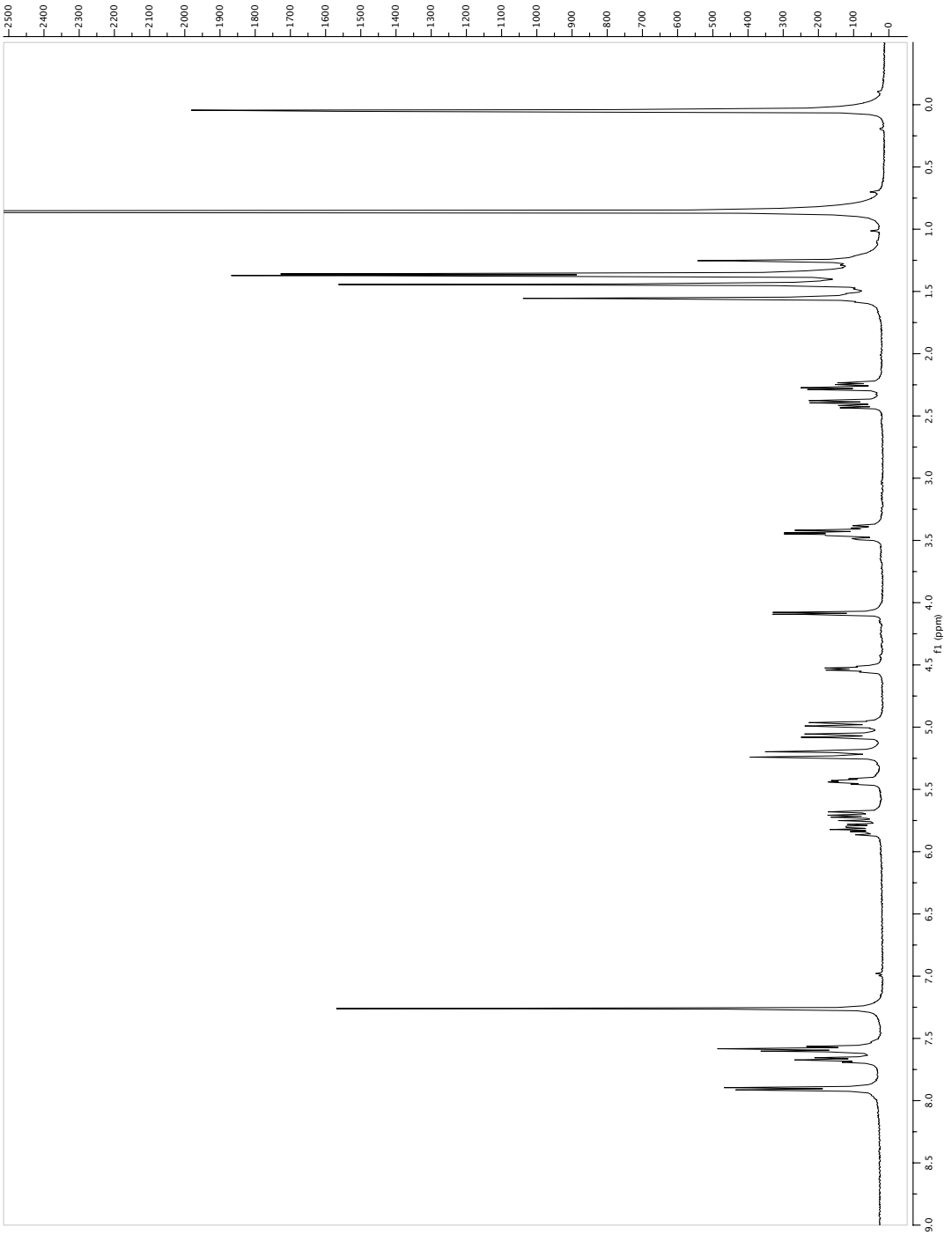
Spectrum A.143: ^{1}H spectrum of compound **181**.



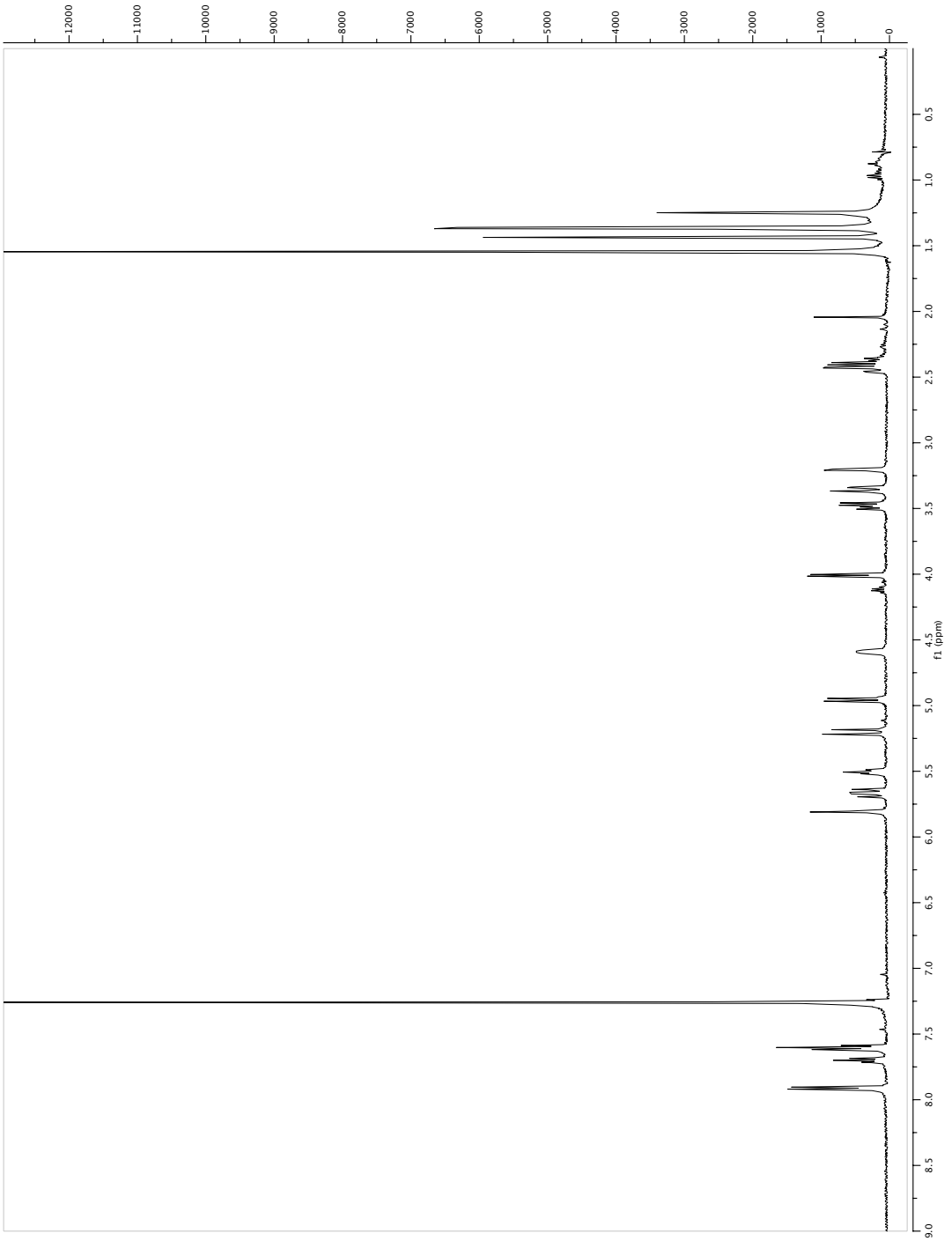
Spectrum A.144: ^{13}C spectrum of compound **181**.



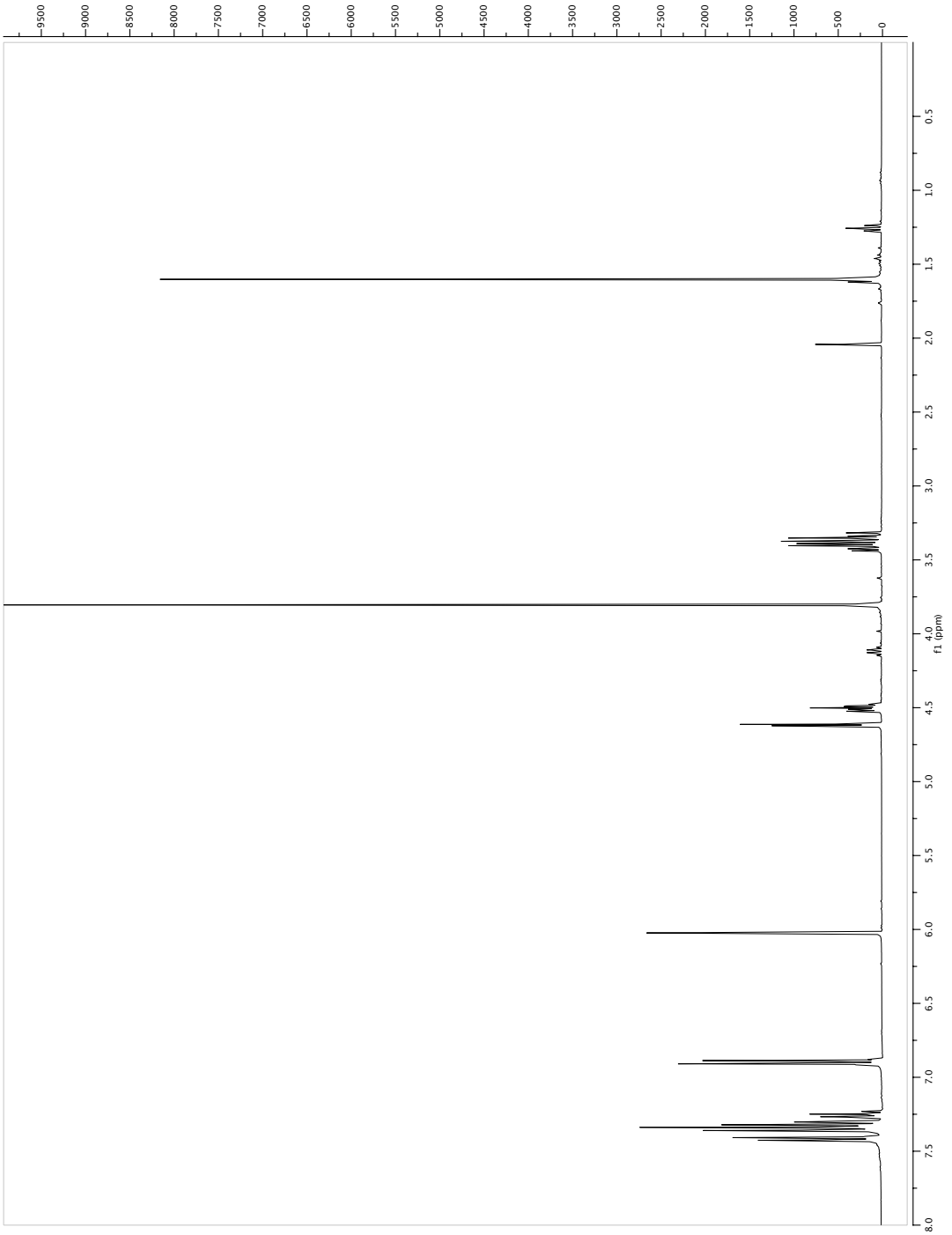
Spectrum A.145: ^{1}H spectrum of intermediate sulfide before oxidation to compound **182**



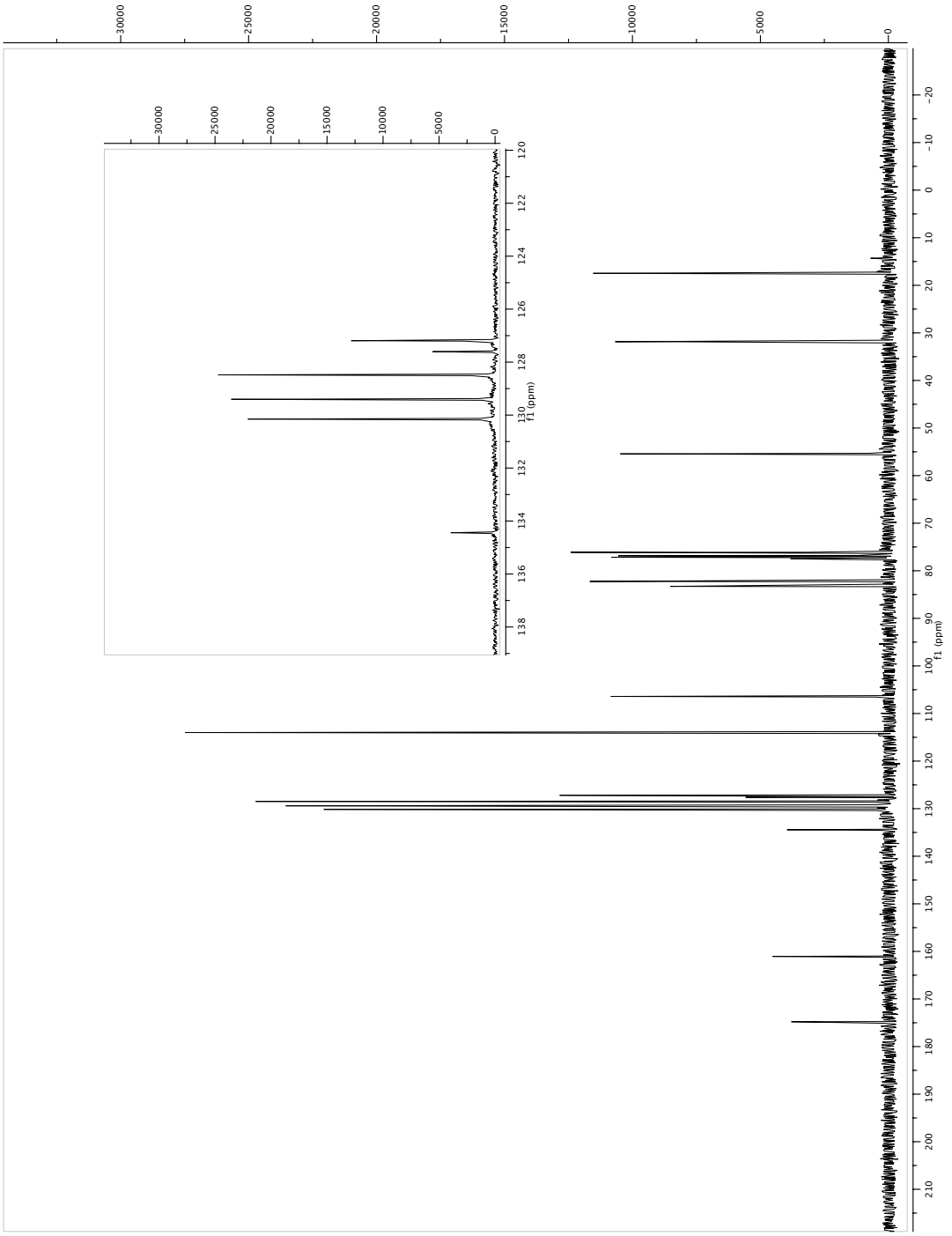
Spectrum A.146: ^{1}H spectrum of compound **182**.



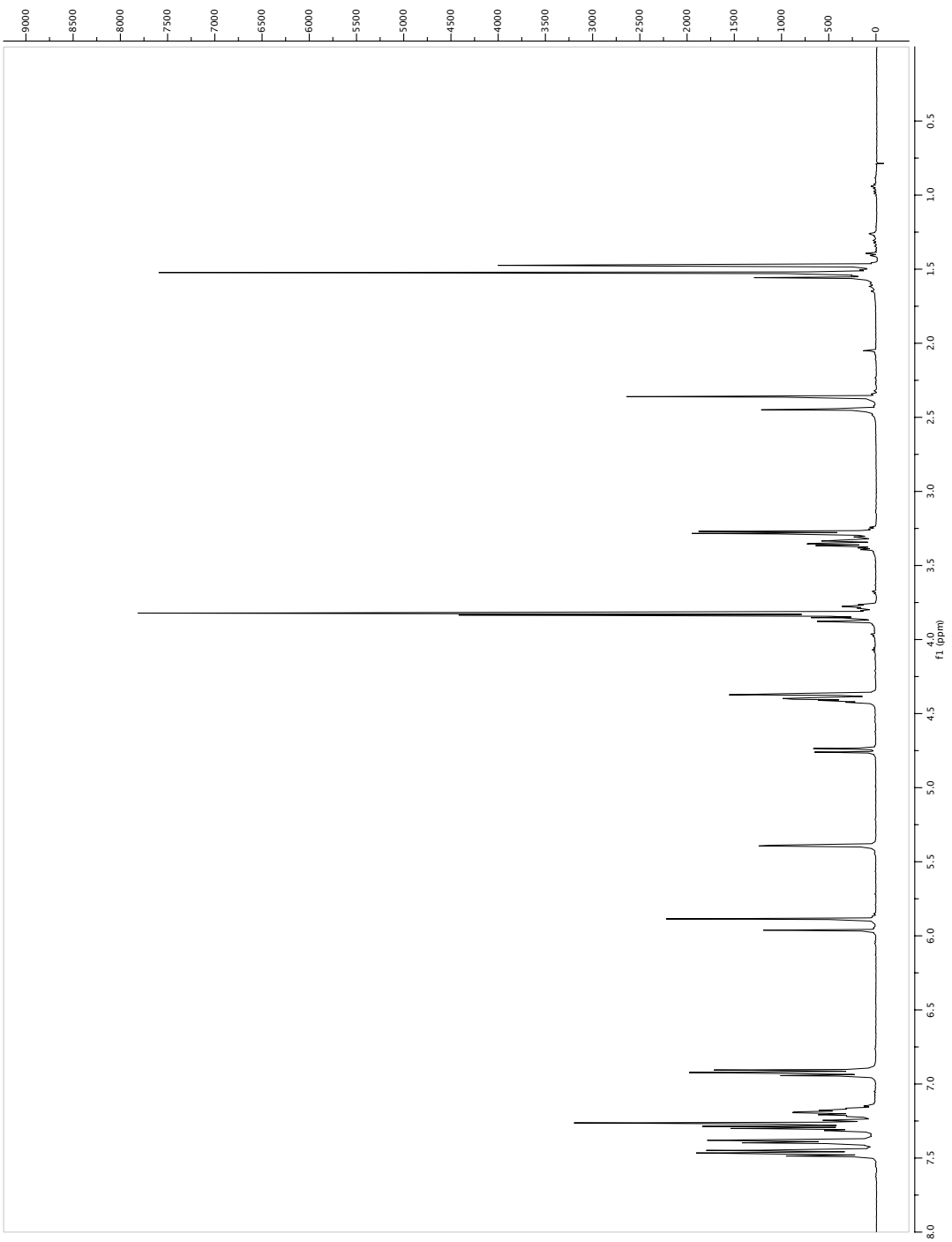
Spectrum A.147: ^{1}H spectrum of compound **187**.



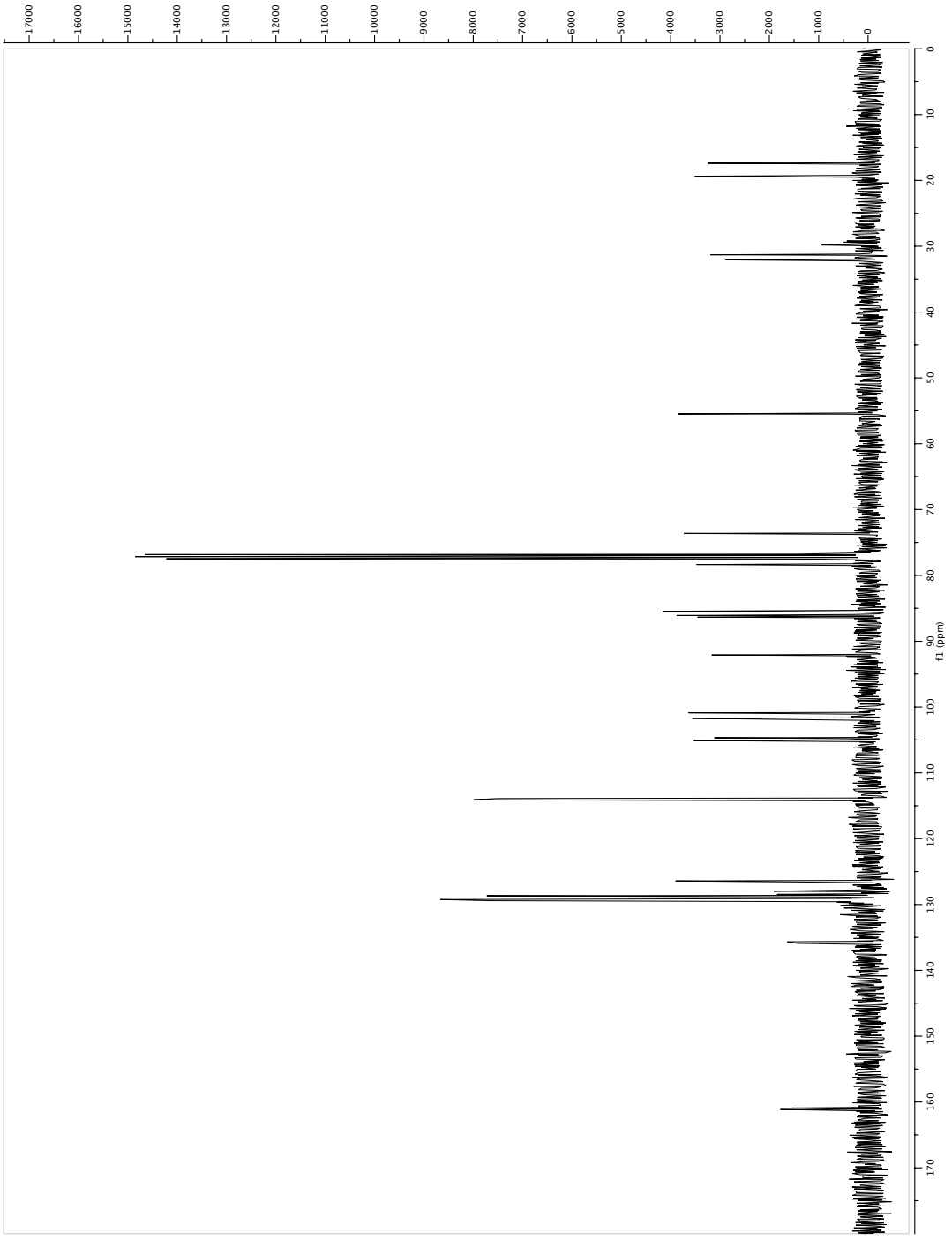
Spectrum A.148: ^{1}H spectrum of compound **189**.



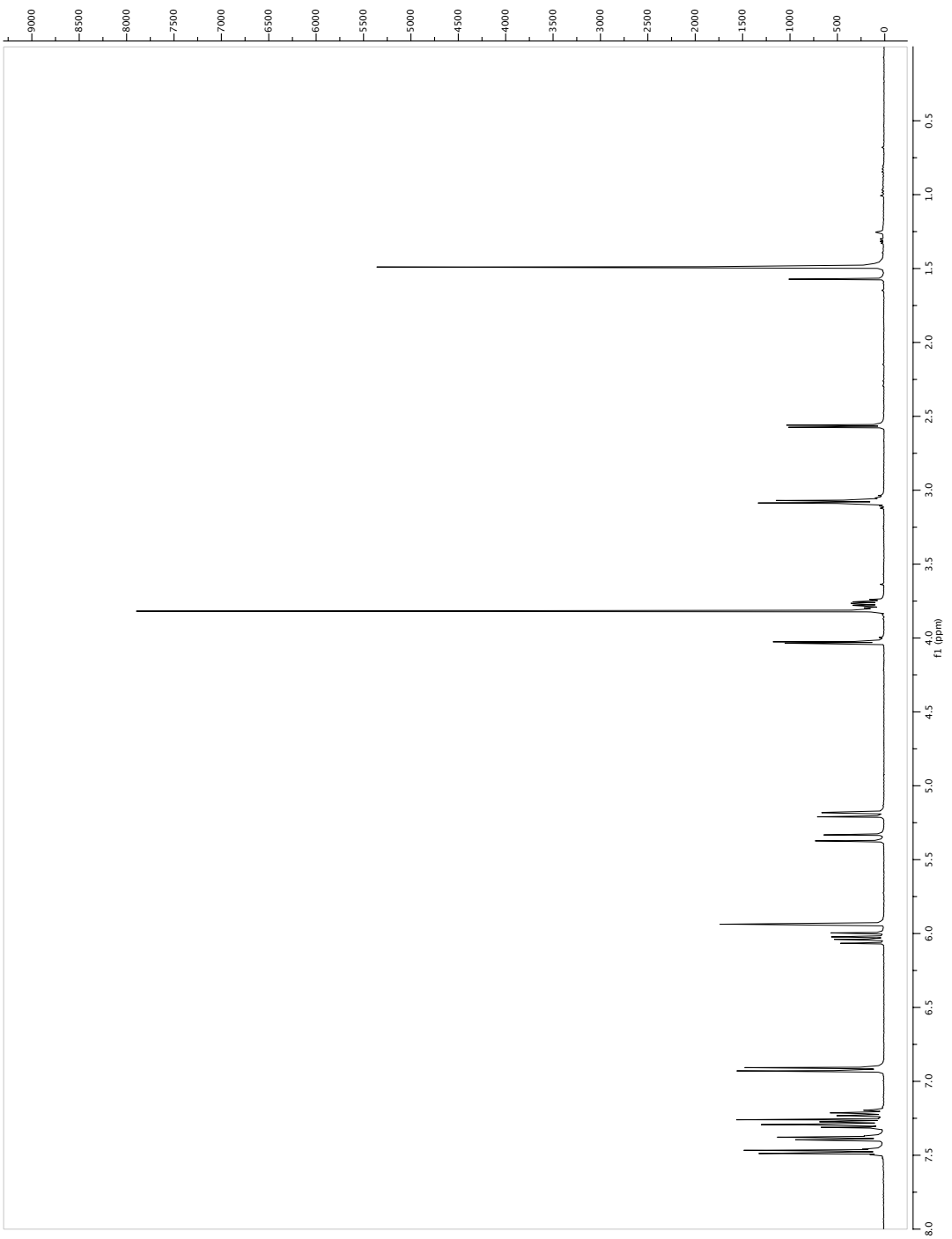
Spectrum A.149: ^{13}C spectrum of compound **189**.



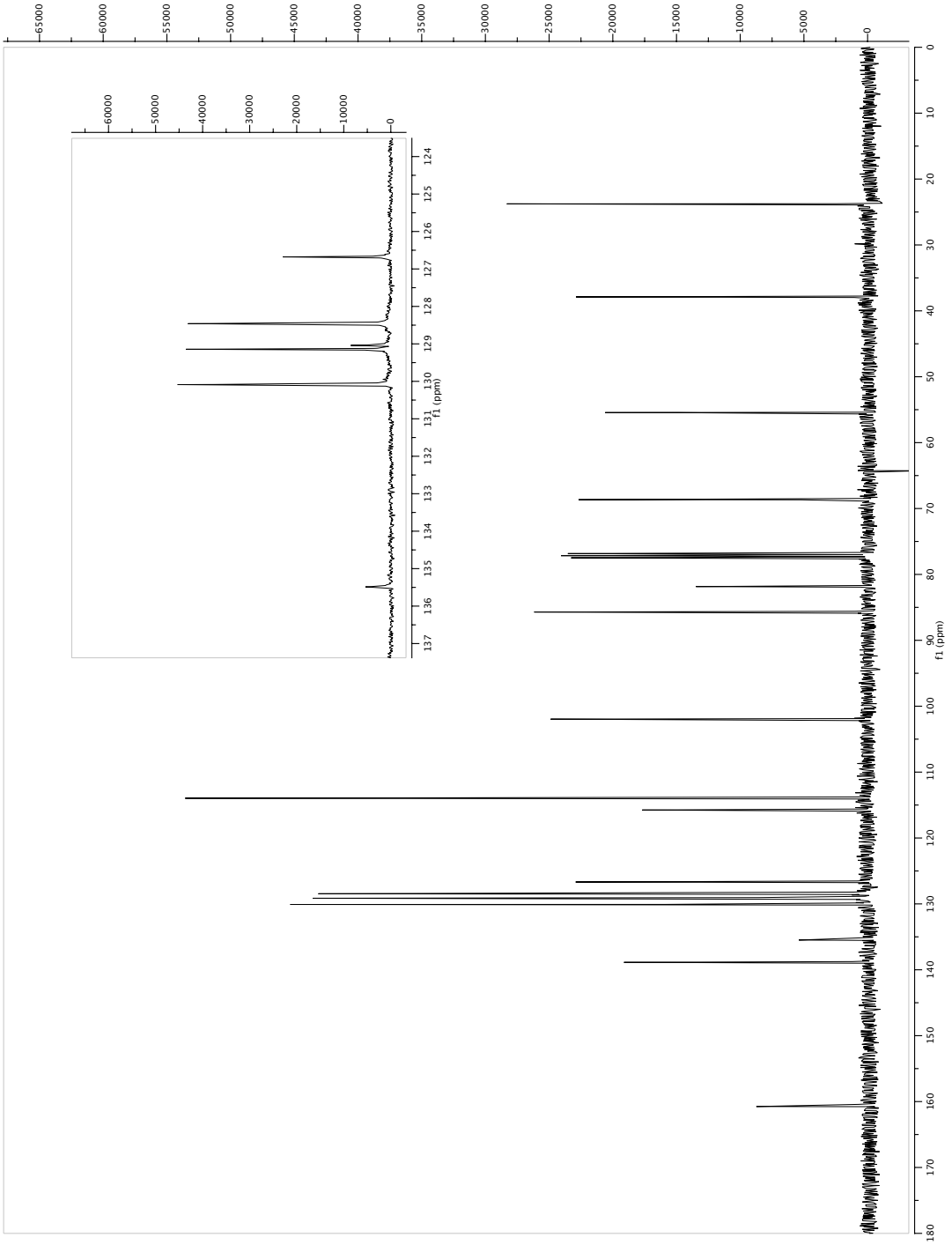
Spectrum A.150: ^{1}H spectrum of compound **190**.



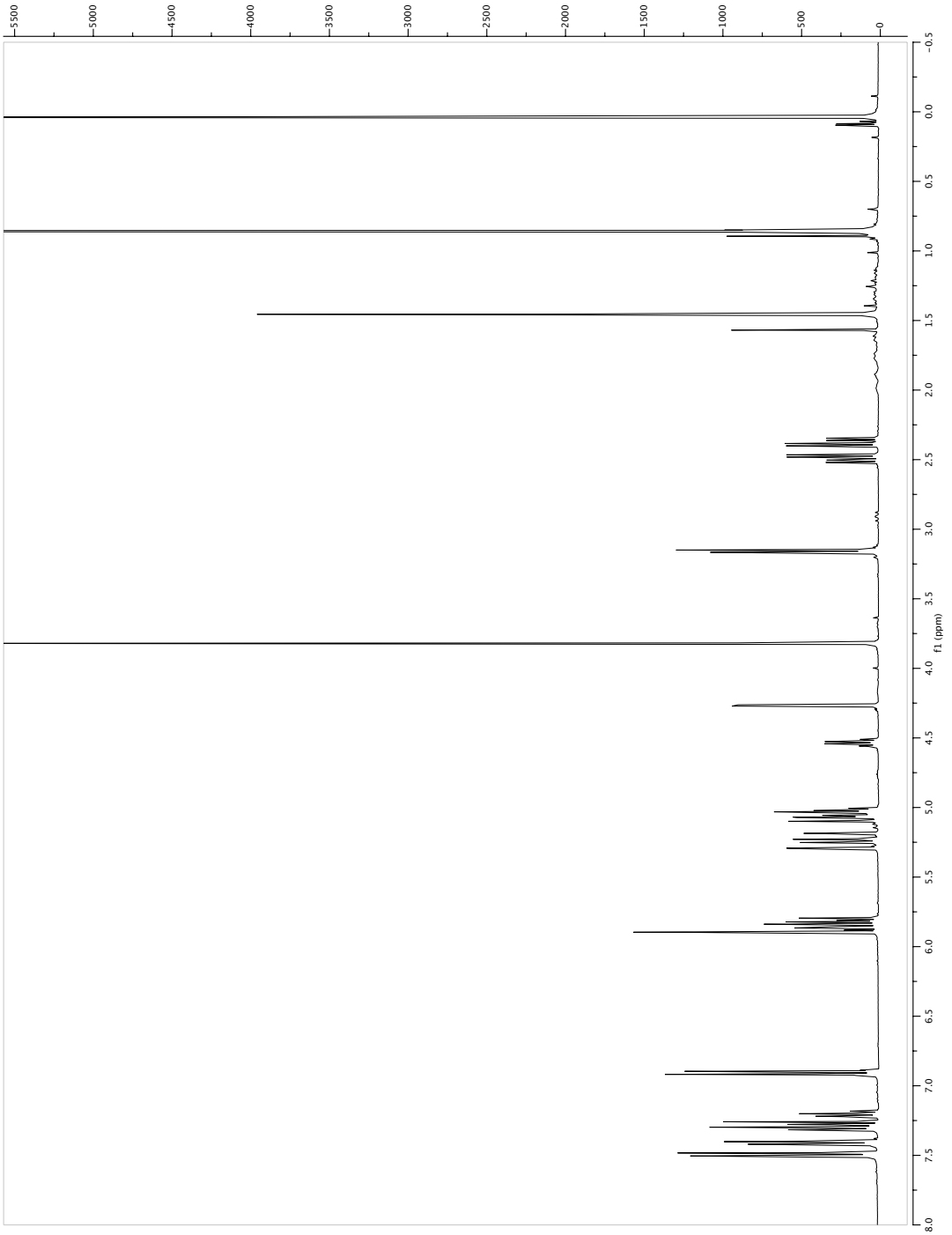
Spectrum A.151: ^{13}C spectrum of compound **190**.



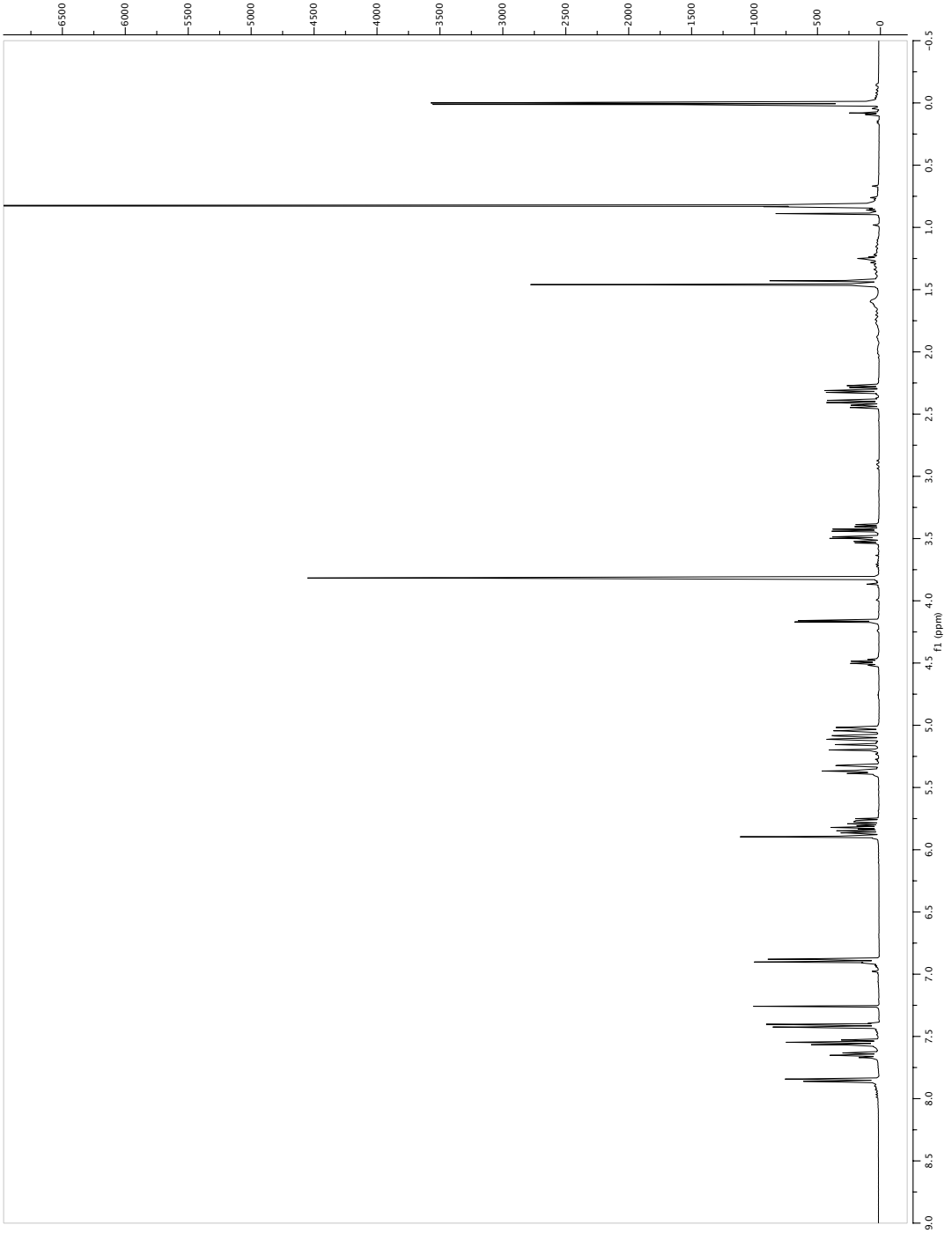
Spectrum A.152: ^{1}H spectrum of compound **191**.



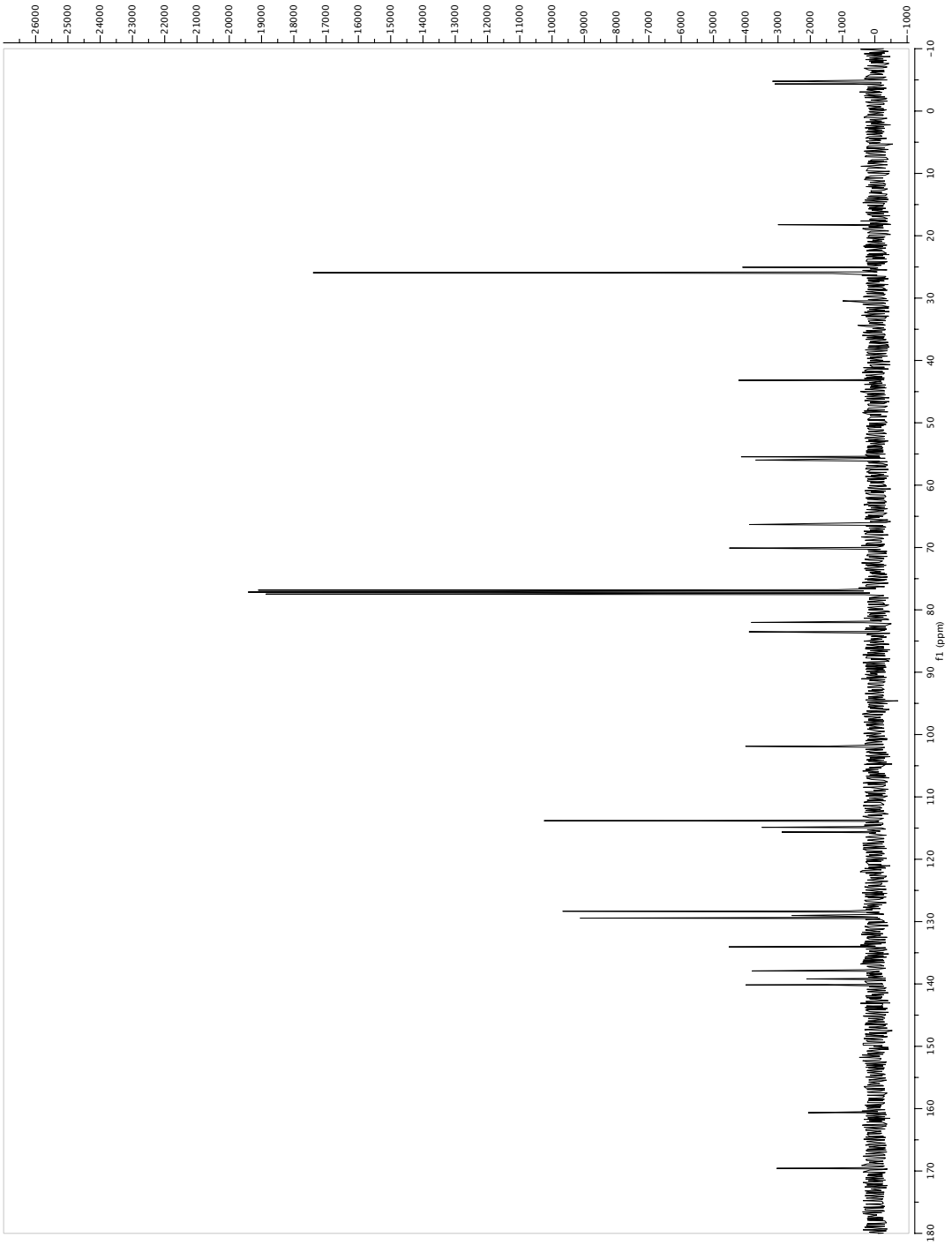
Spectrum A.153: ^{13}C spectrum of compound **191**.



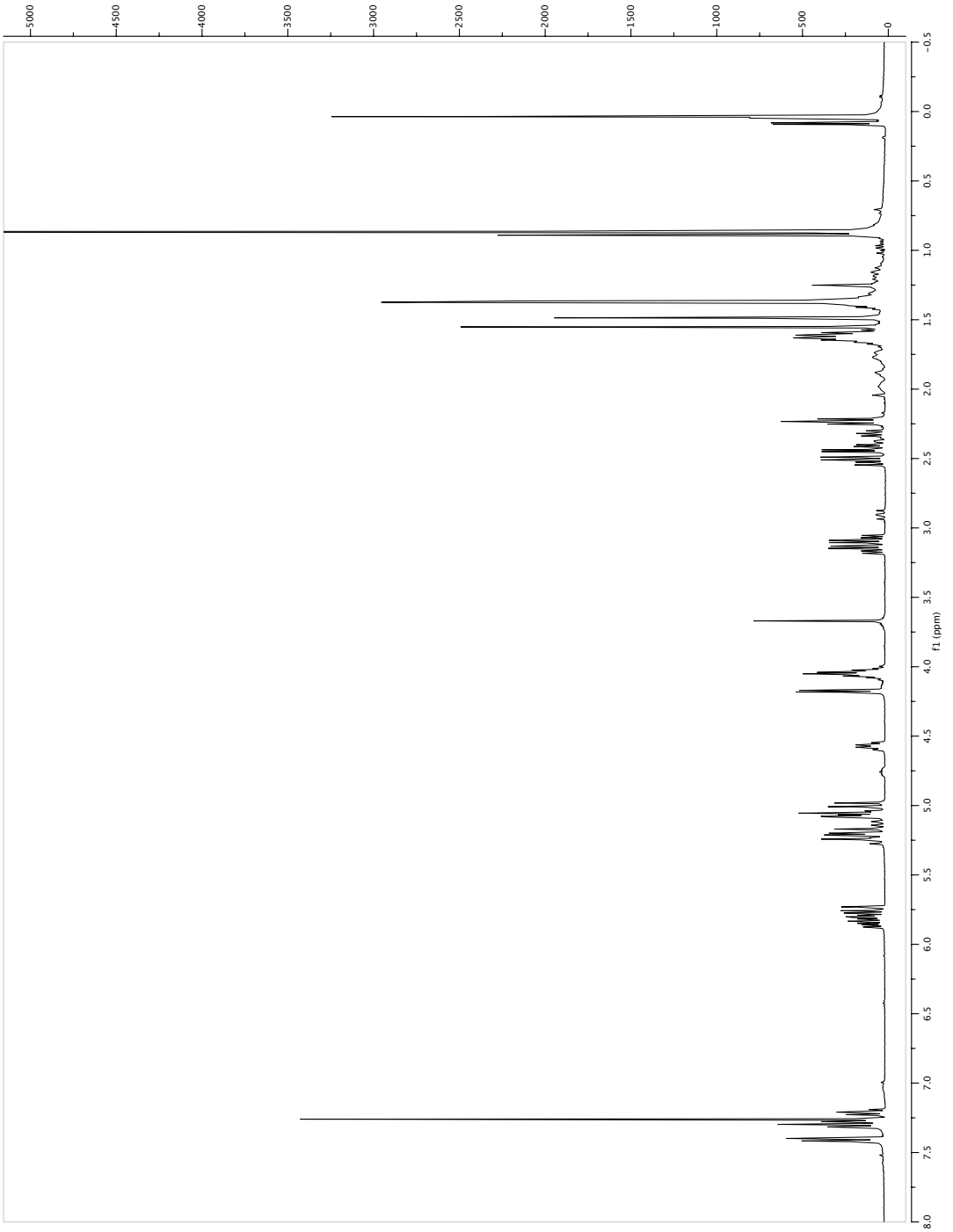
Spectrum A.154: ^{1}H spectrum of intermediate sulfide before oxidation to compound **192**



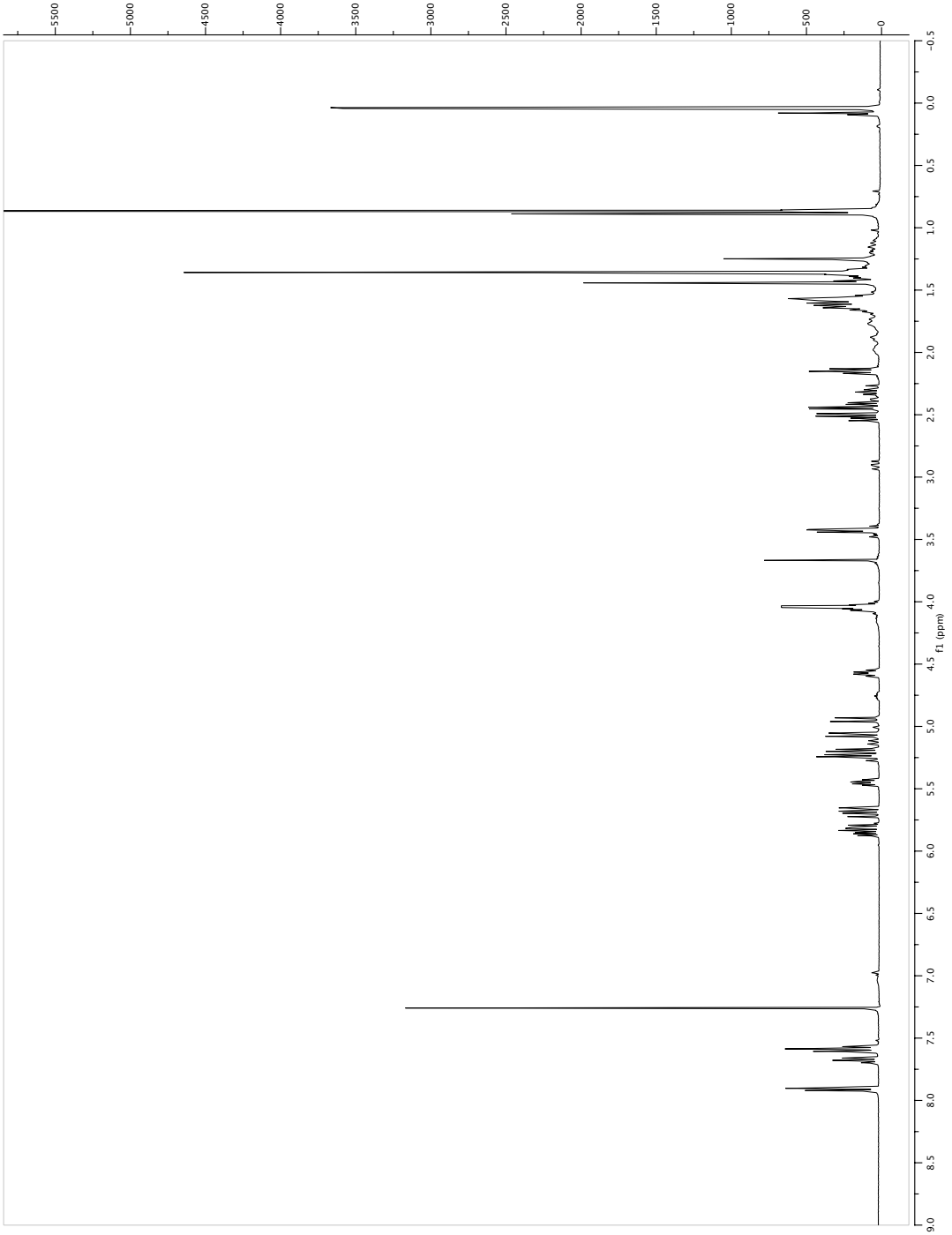
Spectrum A.155: ^{1}H spectrum of compound **192**.



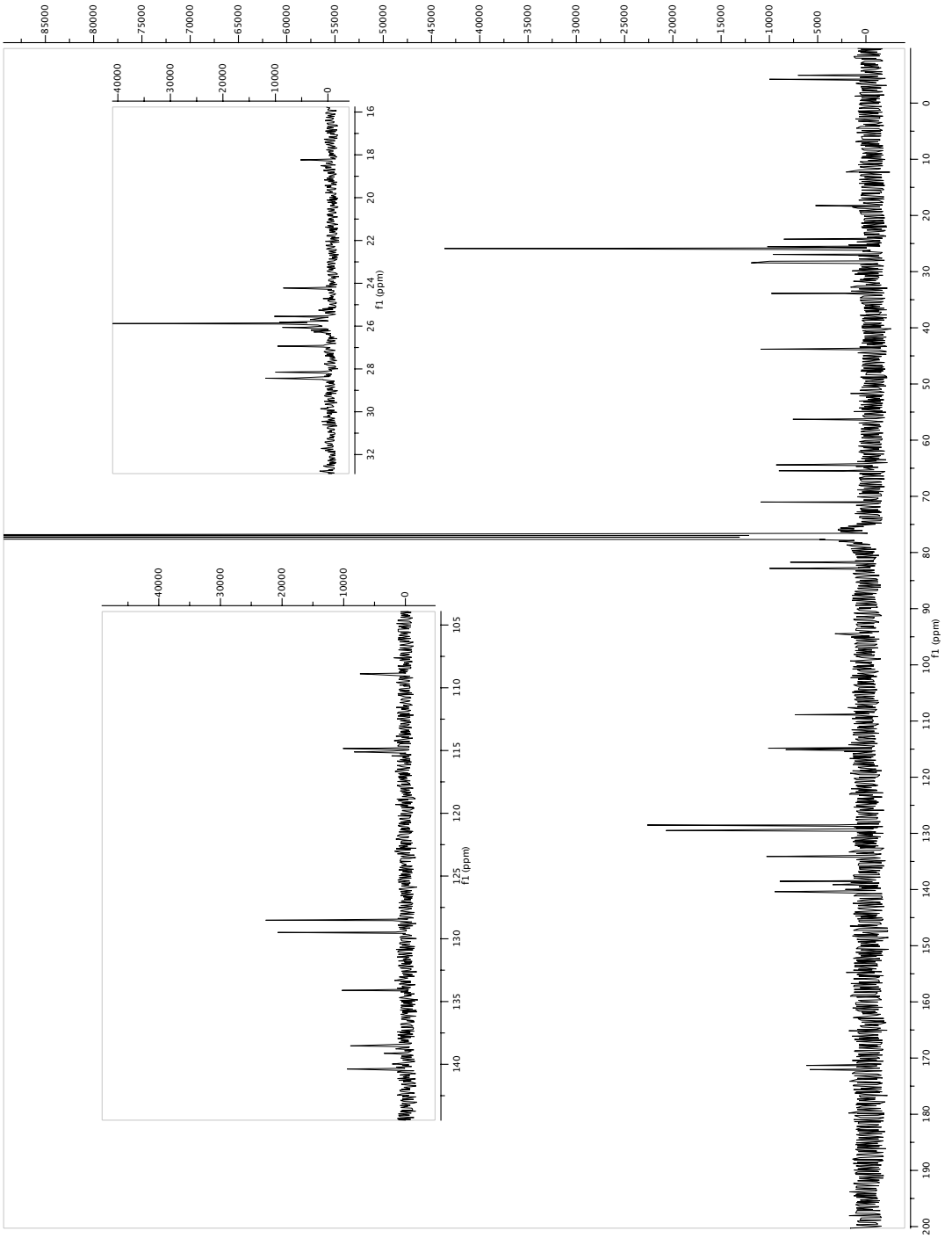
Spectrum A.156: ^{13}C spectrum of compound **192**.



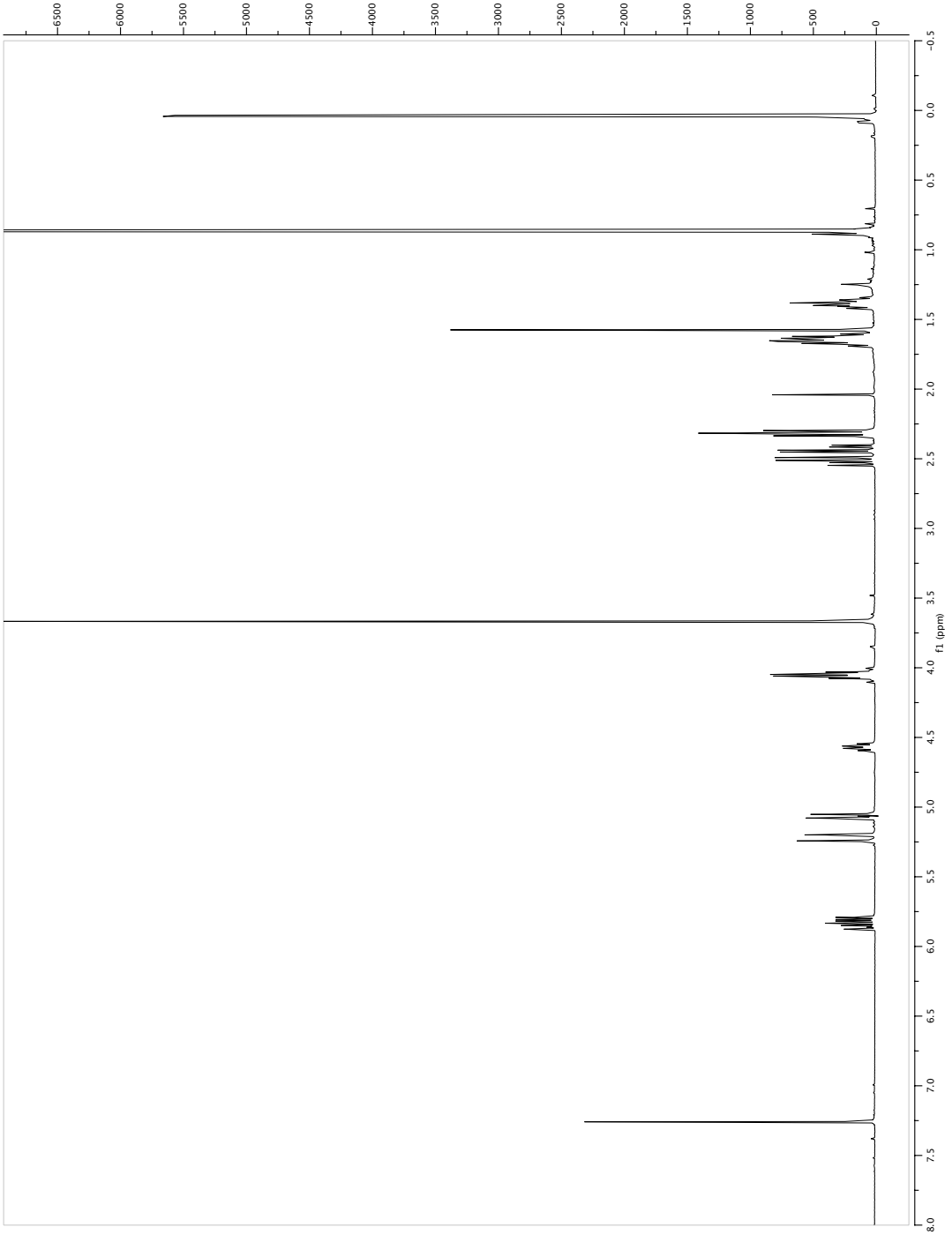
Spectrum A.157: ^{1}H spectrum of intermediate sulfide before oxidation to compound **196**



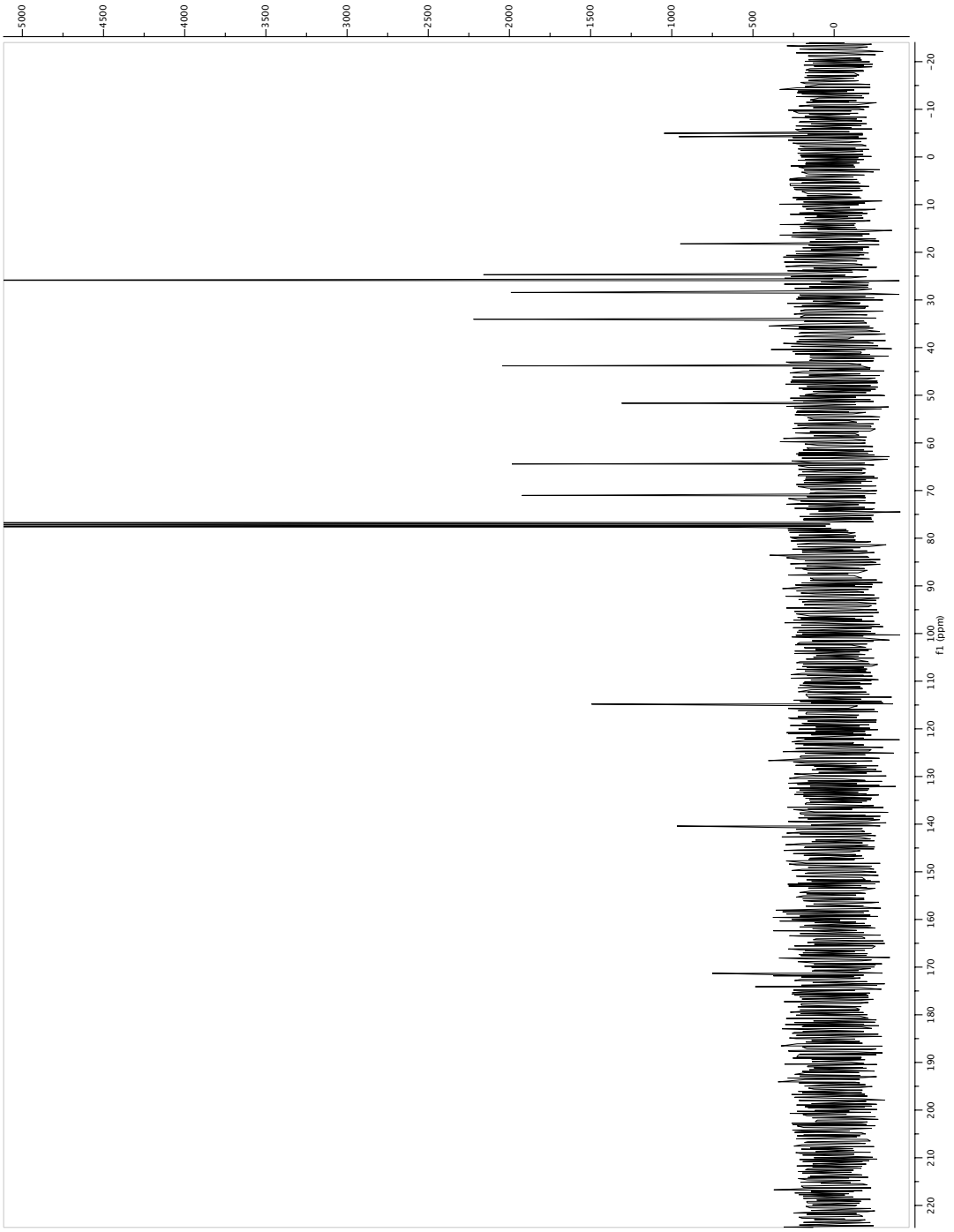
Spectrum A.158: ^{1}H spectrum of compound **196**.



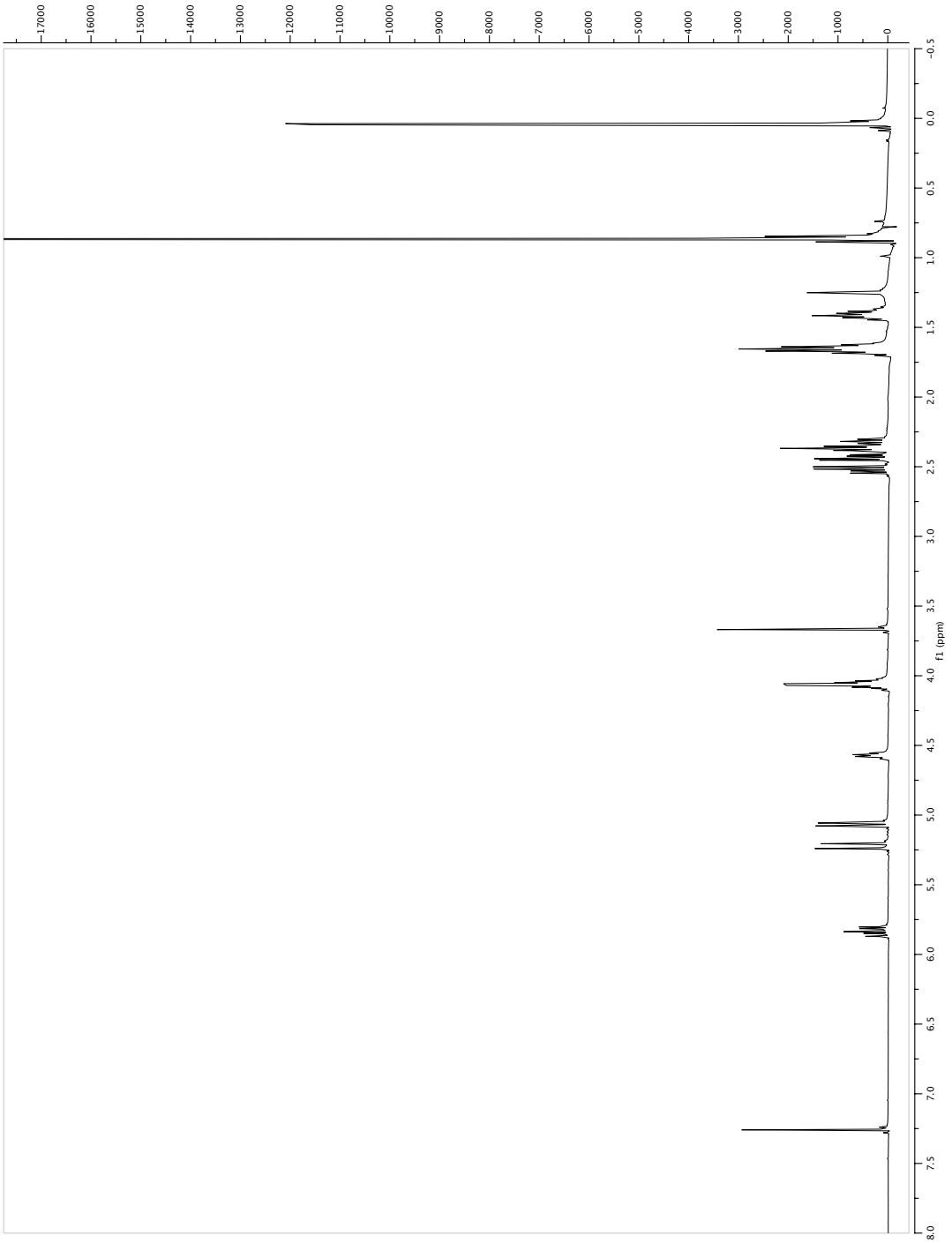
Spectrum A.159: ^{13}C spectrum of compound **196**.



Spectrum A.160: ^{1}H spectrum of compound **203**.



Spectrum A.161: ^{13}C spectrum of compound **203**.



Spectrum A.162: ^{1}H spectrum of compound **204**.