UNIVERSITY OF CALIFORNIA, SAN DIEGO

Synthetic Studies Toward Complex Schisandraceae and Zoanthamine Natural Products

A Dissertation submitted in partial satisfaction of the requirements for the degree

Doctor of Philosophy

in

Chemistry

by

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2008

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University of California, San Diego

2008

DEDICATION

To my family and Beth; thank you for the unconditional love, support, and encouragement.

EPIGRAPH

The end of the road is a true beginning.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
Boc	*tert*-butoxycarbonyl
Bu	butyl
t-Bu	*tert*-butyl
Bn	benzyl
°C	degrees celsius
calcd	calculated
$CDCl_3$	deuterated chloroform
$CHCl_3$	chloroform
CD_2Cl_2	deuterated methylene chloride
C_6D_6	deuterated benzene
CCDC	Cambridge Crystallographic Data Center
CI	chemical ionization
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCM	dichloromethane
DIBAL-H	diisobutylaluminum hydride
DIEA	diisopropylethylamine
DMA	*N*,*N*-dimethylacetamide

DMAP	*N*,*N*-4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DMSO-*d6*	deuterated dimethylsulfoxide
Et	ethyl
EtOAc	ethyl acetate
FAB	fast atom bombardment
FT-IR	Fourier transform-infrared
h	hours
HCl	hydrogen chloride
hν	irradiation with light
HMPA	hexamethylphosphoramide
KHMDS	potassium bis(trimethylsilyl)amide
HRMS	high-resolution mass spectrometry
IBX	o-iodoxybenzoic acid
IC_{50}	mean inhibitory concentration
IR	infrared
LHMDS	lithium bis(trimethylsilyl)amide
m-CPBA	m-chloroperoxybenzoic acid
Me	methyl

MeI	methyl iodide
MEM	methoxy ethoxy methyl
MeOH	methanol
MOM	methoxymethyl
MHz	megahertz
mL	milliliter
μL	microliter
Mmol	millimole
NBS	N-bromosuccinimide
NaHMDS	sodium bis(trimethylsilyl)amide
NIS	N-iodosuccinimide
NMO	4-methylmorpholine N-oxide
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
ORTEP	Oak Ridge thermal ellipsoid plot
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
PG	protecting group
Piv	pivaloyl
Ph	phenyl
PMA	phosphomolybdic acid
PPh_3	triphenylphosphine
ppm	part per million

PPTS	pyridinium p-toluenesulfonate
R_f	retention factor
SAR	structure – activity relationship
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TES	triethylsilyl
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
TFE	trifluoroethanol
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl
UV	ultraviolet

LIST OF FIGURES

LIST OF SCHEMES

LIST OF TABLES

LIST OF SPECTRA

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ABSTRACT OF THE DISSERTATION

Synthetic Studies Toward Complex Schisandraceae and Zoanthamine Natural Products

by

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Doctor of Philosophy in Chemistry

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Professor Emmanuel Theodorakis, Chair

Natural products, or secondary metabolites of plants and animals, have proven invaluable to humanity. We have used them for myriad reasons throughout history, including non-essential purposes such as dyes for textiles and paints. Less trivial uses, such as those related to food and health better demonstrate the importance of natural products. We have made use of toxic natural products to bolster hunting efficiency (e.g. poison tipped darts), and insect pheromones and natural products with antifeedant properties have assisted agricultural growth. Therapeutic natural products have long been used as dietary supplements and medicines. The ubiquitous nature of

natural products and their derivatives in current health care validates continued laboratory work in all areas of natural product research.

We (The Theodorakis Lab) have viewed natural product synthesis as a tool for expanding our understanding of organic chemistry. Of particular interest, are natural products which contain rare or novel architectural features. The synthetic study of these natural products therefore inspires creative solutions to complicated synthetic challenges, and often necessitates the development of new methodologies. Unique structural characteristics of two natural product families, Schisandraceae dilactones and zoanthamine alkaloids , caught our interest for the stated reasons.

Research herein describes work directed towards synthesis of the unprecedented micrandilactone A ABC ring system and a distinctive approach to the zoanthamine alkaloids. Chapter I narrates research related to the micrandilactone A ABC ring motif which culminated in an interesting multi-step one pot acid mediated reaction for AC ring formation. Chapter II reports attempts at poly-cyclization cascade reactions directed toward zoanthamine alkaloid synthesis.

Chapter I

Studies Toward Schisandraceae Natural Products

Section 1.1 Introduction to Schisandraceae and Related Natural Products

The plant family Schisandraceae belongs to the order Austrobaileyales and contains the genera *Schisandra* and *Kadsura*. This family is composed of flowering plants, typically vines and shrubs indigenous to many regions of the world. Fruits and extracts from the plant family Schisandraceae have been used since antiquity (*Schisandra chinensis* was referenced in 2697 BC)[1] in Chinese culture for their astringent, anti-hepatotoxic, anti-asthmatic, antitussive, anti-fatigue, antioxidant, anti-cancer, sedative, immunostimulant, and liver protecting properties.[2] Dried berries of the plants belonging to the genus *Schisandra*, often referred to as Wu-Wei-Zi or Schisandra, are currently marketed as dietary supplements with healing properties. Schisandra is now commonly found in U.S. health stores and is even prominently displayed as an ingredient in the 2008 spring beer, Springboard Ale brewed by New Belgium Brewing.

The long history of natural product use as medicinal remedies and/or treatments of human disease has been the impetus for the study of their pharmacological properties. The quest for new natural products that possess biological activity has been facilitated by technological advancements and has prompted researchers to examine

other components of *Schisandra* plants, less abundant in molecules of interest, in addition to the traditionally studied fruits. In recent years new compounds have been discovered from stem, branch, root, and leaf extracts. Investigations into the chemical components of Schisandraceae plants, specifically of the *Schisandra* and *Kadsura* genera, have led to the identification of a large volume of natural products. Many of these natural products exhibit interesting biological properties. For example, nigranoic acid (*S. sphaerandra*)[3], lancilactone C (*K. lancilimba* How)[4], rubriflordilactones A and B (*S. rubriflora*)[5], and micrandilactone C (*S. micrantha*)[6] have all demonstrated anti-HIV activity.

Although limited biological activity has been displayed by many of the Schisandraceae compounds, our interests lie in the unprecedented structural arrangements. A number of architecturally unique and complex naturally products have been isolated from this family in recent years. Of particular interest is the dilactone group, which includes: micrandilactones[6,7], lancifodilactones[8], henridilactones[9], sphenadilactones[10], schindilactones[11], wuweizidilactones[12], and propindilactone A[13] (Fig 1.0). This group of natural products is characterized by a heavily modified and highly oxygenated cycloartane core. With the exception of lancifodilactone F, all natural products of this group thus reported contain a unique fused cycloheptyl-hydrofuran-butyrolactone motif. To date, this unique moiety has only been reported in the Schisandraceae class of natural products. The structure of micrandilactone A, the first reported member of the dilactone family, was initially disclosed in 2003.[7]

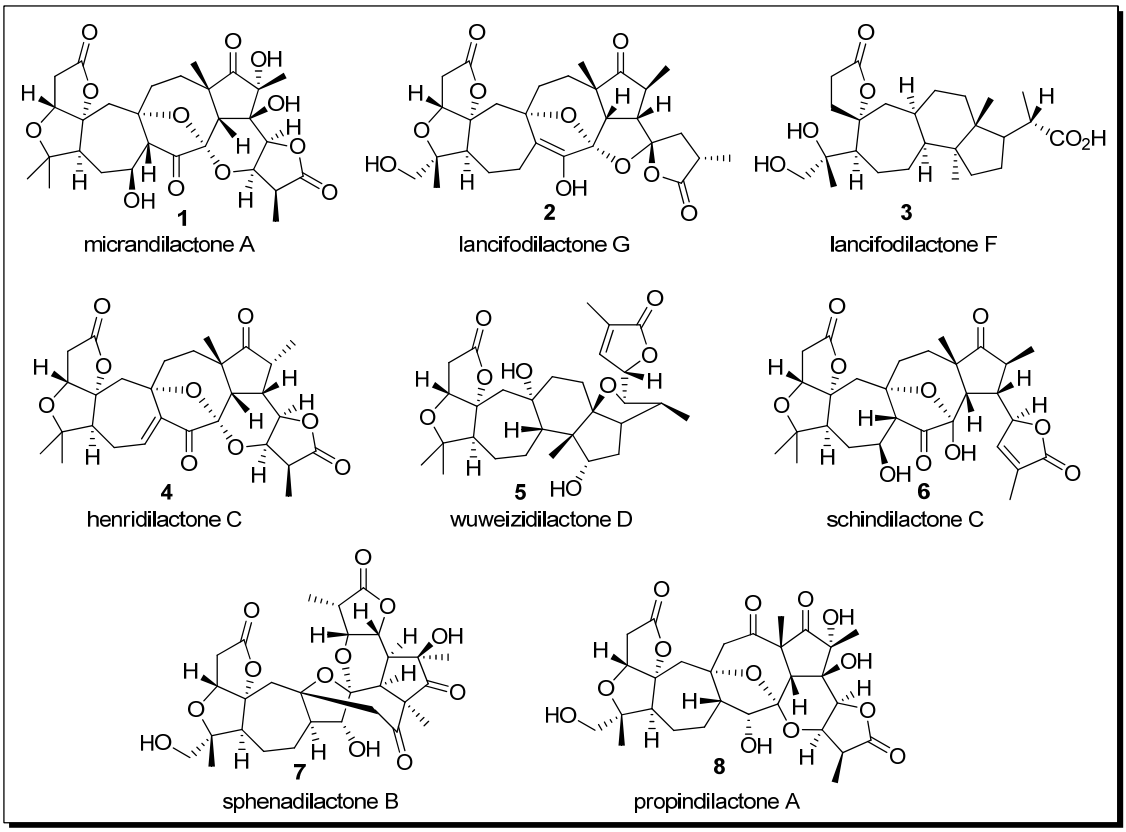


Figure 1.0 Representative Schisandraceae dilactone natural products.

Interestingly, several of the compounds in Figure 1.0 are not species specific. For example, micrandilactone A (**1**) has been isolated from *S. micrantha*,[7] *S. propinque* var. propinqua,[13] *S. lancifolia*,[8] and *S. rubriflora*.[14] It is conceivable that these compounds share a similar biosynthetic pathway, although they are produced by unique plant species.

A series of less densely functionalized compounds, some thought to be important biogenetic precursors to the dilactone group, have also been isolated from the same plant specimens as many of the dilactones (Fig. 1.1). The cycloartane core is more

obvious in this group of compounds. Accordingly, the cyclopropane ring is conserved in each structure. Other structural similarities are also observed within this group of compounds. The tetracyclic steroidal core is conserved in schizandronic acid[15] (**11**) and kadsulactone[16] (**12**). kadsudilactone[16] (**13**) contains an oxidized A ring (steroid assignment) while schisanlactone B[17] (**13b**) contains an unsaturated and oxidized A ring. Micranoic acid B[18] (**9**) and nigranoic acid[3] (**10**) have abbreviated cores in which the A ring has presumably been oxidatively opened.

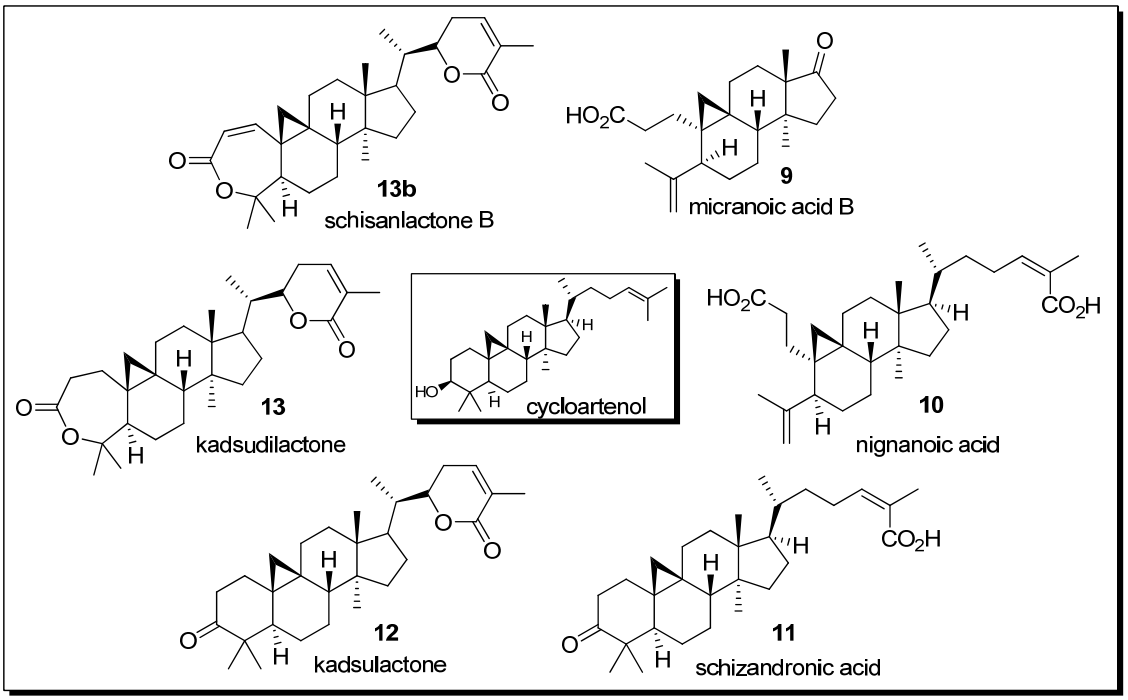


Figure 1.1 Selected Schisandraceae cycloartane natural products.

Some members of this group of compounds are found in different species and genera. For instance, schizandronic acid (**11**) has been found in at least four *Schisandra* species (*S. nigra* Max,[15] *S. micrantha*,[18] and *S. henryi* var. yunnanensis[9]) and within a

species that shares the same family but has been classified outside the genus, *Illicium verum* Hook f.[19] Moreover, they share structural similarities with natural products isolated from *Buxus papillosa*.

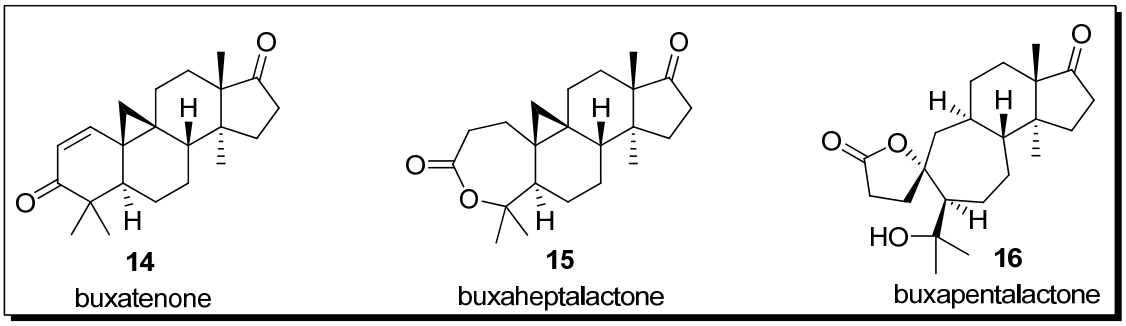


Figure 1.2 Natural products of *Buxus papillosa*.

Buxatenone (**14**), buxaheptalactone (**15**), and buxapentalactone (**16**) have been isolated from root extracts of *Buxus papillosa* (Fig. 1.2). Buxatenone[20] had previously been reported when Clardy and coworkers disclosed the structures of buxaheptalactone (**15**) and buxapentalactone (**16**) in 1992.[21] In the isolation paper, Clardy's group recognized a potential biogenetic relationship between the 3 *Buxus* natural products. It was postulated that a combination of olefin reduction and ketone oxidation of buxatenone (**14**) would give rise to buxaheptalactone (**15**). Ring opening of the cyclopropane ring and rearrangement of the heptalactone (**15**) could lead directly to buxapentalactone (**16**). Notably, buxatenone (**14**) bares a strong resemblance to micranoic acid B (**9**).

The combination of novel structural scaffolds and putative pharmacological profiles contained within the Schisandraceae natural products makes them attractive

targets for synthetic chemists. Indeed, several synthetic efforts have been published for these complex natural products.

Section 1.2 Synthetic Studies Toward Schisandraceae Natural Products

Section 1.2.1 Reported Synthetic Studies

The size (octacyclic skeleton) and many stereochemical complexity (13 stereocenters) of micrandilactone A (**1**) make it an imposing synthetic target. Other structural highlights include: the high level of oxygenation, 3 hydroxy groups, 2 butyrolactones, 2 ketones, a hydrofuran, and a fused 7,5,6 ketal forming the DEG ring system. Any successful synthetic attempt of this molecule would necessitate great effort or incredible foresight.

The published synthetic work will be briefly reviewed. It should be noted that the structure of micrandilactone A (**1**) was originally incorrectly reported as its enantiomer and the correct structure was published in 2006.[22] Prior to the correction, the published studies depict the structure with the enantiomeric stereochemistry. However, the studies presented herein were performed with racemic materials. Original micrandilactone A (**1**) numbering, which was unchanged by the structural revision, will be used throughout this manuscript (Fig. 1.3).

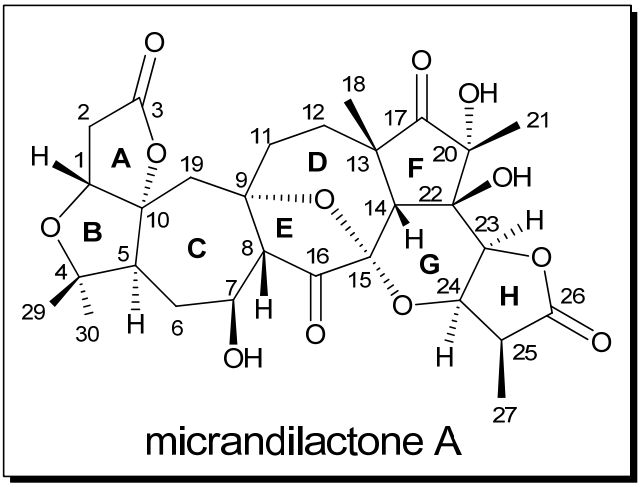
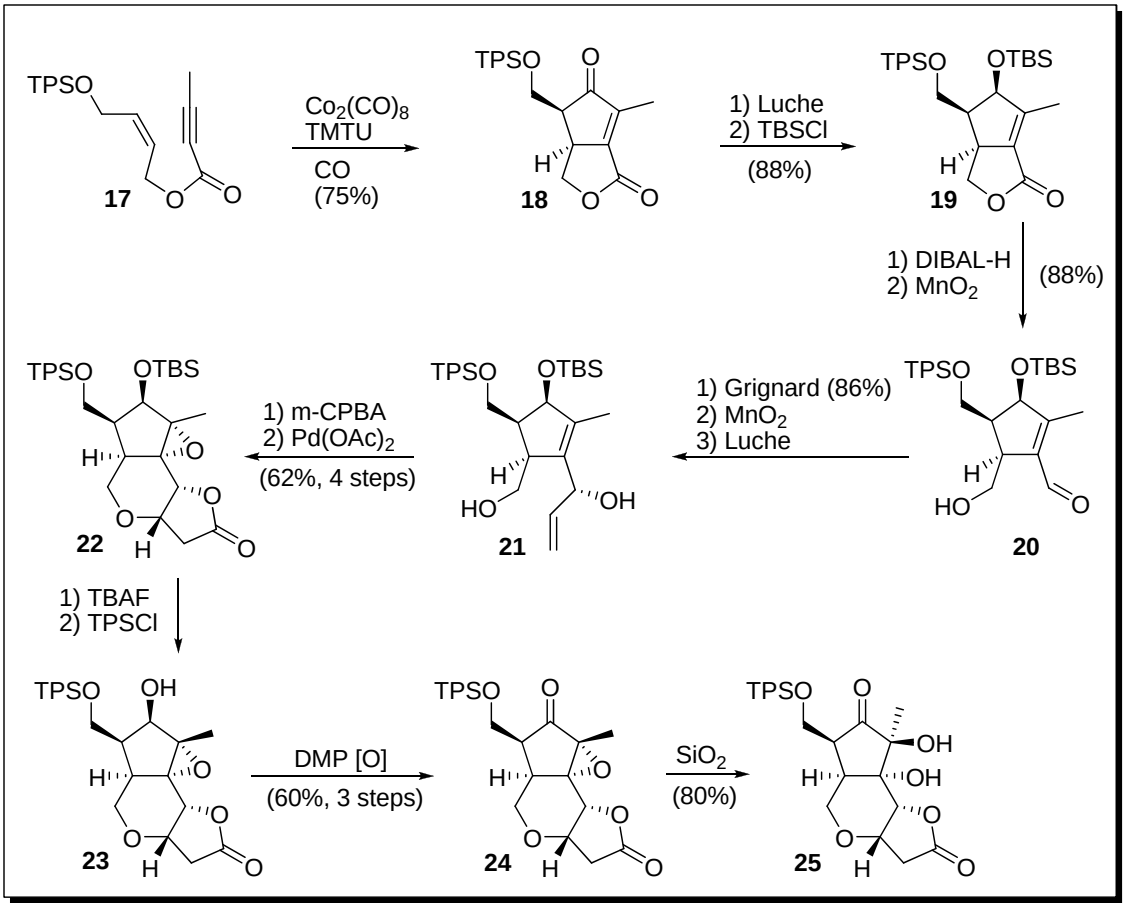


Figure 1.3 Micrandilactone A numbering scheme.

Zhen Yang and coworkers have published approaches directed at the western, central, and eastern fragments of micrandilactone A. Yang's approach to the eastern fragment focused on a Pauson-Khand reaction and palladium mediated carbonylation as the key steps in forming the FGH ring fragment (Scheme 1.0).[23] Diels-Alder, a Horner-Wadsworth-Emmons cascade, and ring-closing metathesis reactions were integral to the formation of the reported western fragment, rings ABC.[24] A [3+3] sigmatropic rearrangement has been used to develop a 7,8 fused ring system potentially applicable to the fused CD ring system.[25]

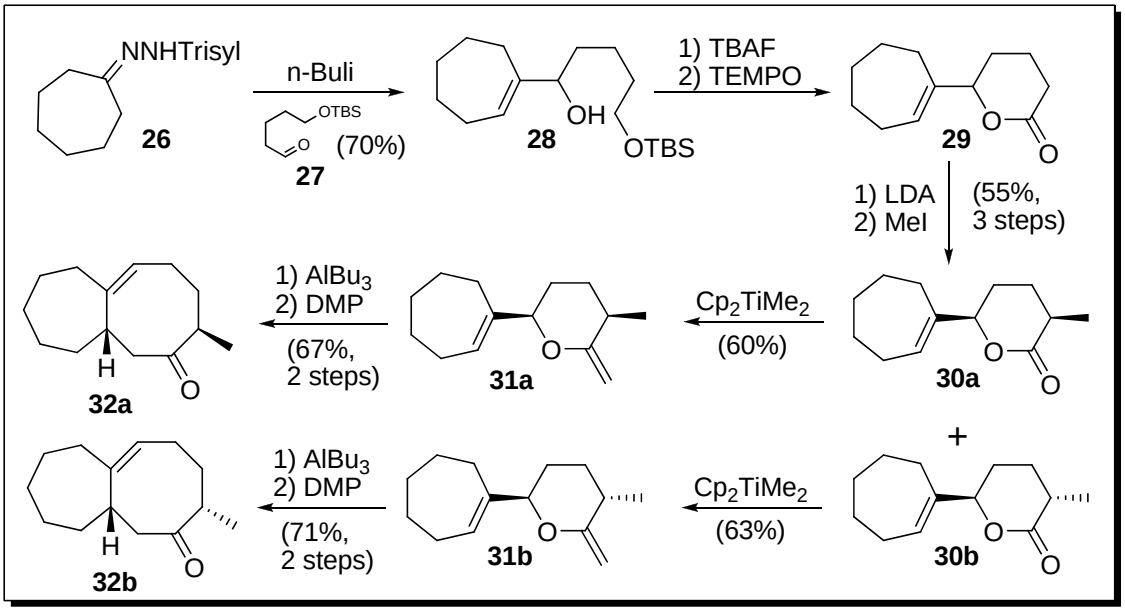


Scheme 1.0 Yang's approach to the FGH ring system of micrandilactone A.

The FGH ring study began with a two step sequence from butene-diol, which provided enyne **17**. When reacted under Pauson-Khand conditions, **17** gave the bicyclic system (**18**). The ketone was stereoselectively reduced under Luche conditions and the resultant allylic alcohol protected as the TBS ether. The lactone functionality was reduced to the corresponding diol and the resultant allylic alcohol oxidized to aldehyde **20** in excellent yields. Addition of vinyl magnesium bromide to **20** resulted in a mixture of allylic alcohols. After collection of the desired alcohol, **21**, the undesired diastereomer was converted to **21** by oxidation and Luche reduction. Carbonylative

annulations of diol **21** were achieved only in low yields. It was speculated that an intermediate allylic arrangement, involving the terminal olefin hindered the carbonylative annulation. This side reaction was mitigated by converting the olefin to an epoxide. The epoxide gave an excellent yield (95%) of the desired tricycle **22** when treated under carbonylation conditions. Protecting group manipulation and oxidation provided **24**, which upon treatment with silica decomposed to **25** in good yield. With the exception of 3 stereocenters, **25** represents the fully functionalized FGH ring system. This work stands as an impressive entry into the Micrandilactone A (**1**) synthetic effort.

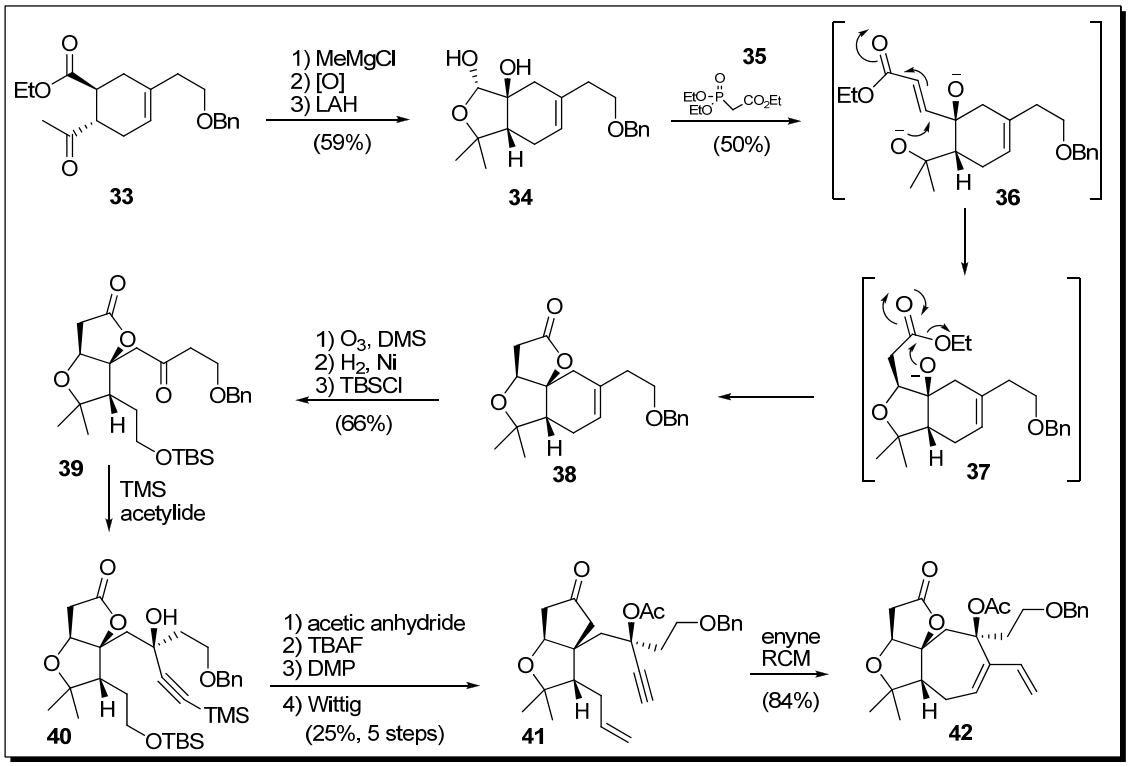
Yang has also addressed formation of the unique 7,8 (CD) ring system of micrandilactone A (**1**) via a model system (Scheme 1.1).[25] The addition-elimination of **26** and **27** provided allylic alcohol **28**, which was then deprotected and oxidized to give lactone **29**. It is worth noting that the oxidation reaction involves selective oxidation of a primary alcohol over a secondary and subsequent oxidation of the resultant lactol in one pot with catalytic TEMPO. Lactone **29** was alkylated without selectivity, providing a 1:1 mixture of methylated lactones, **30a**, and **30b**. The lactones were homologated with the Petasis reagent and treated with Lewis acid at low temperature to instigate the [3+3] sigmatropic rearrangement. Subsequent oxidation provided **32a** and **32b**.



Scheme 1.1 Yang's approach to the CD ring system of micrandilactone A.

Although Yang's model system is simple, the good stereocontrol of the Claisen is an important observation that may allow its strategic use in future synthetic efforts. Also, it appears that C14 substitution may not significantly affect the Claisen stereoselectivity. This will potentially allow a fully, or mostly, functionalized eastern fragment to be formed prior to formation of the central CE ring system. Taken together, this work has given the researchers important insight into synthetic strategies.

Of particular interest to us is the reported work toward the western fragment. Yang has utilized a very interesting Horner-Wadsworth-Emmons cascade reaction to form the butyrolactone A ring and an enyne RCM reaction to fuse ring C to the B ring (Scheme 1.2).[24]

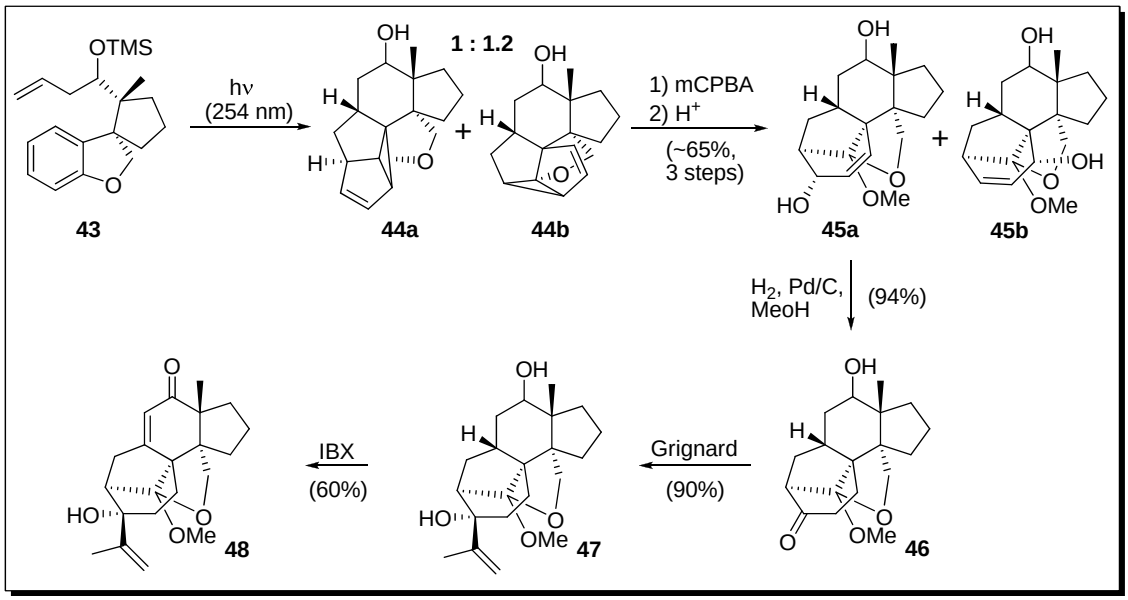


Scheme 1.2 Yang's approach to the ABC ring system of micrandilactone A.

A regioselective Diels-Alder reaction provided cyclohexene **33**, which was treated with a methyl Grignard reagent at low temperature to install the second C4 methyl. The resultant tertiary alcohol cyclized to form the butyrolactone B ring, and oxygen was installed at C10. Stereoselective reduction gave lactol **34**. Treatment of **34** with phosphonate **35** and excess base provided **38**. The mechanism is speculated to involve a Michael addition to the α,β unsaturated ester (**36-37**) followed by lactonization (**37-38**) involving the C10 alkoxy anion. A yield of 50% for this reaction is impressive as it involves multiple anionic manipulations and provides the fully functionalized A ring with the correct stereochemistry.

Reductive ozonolysis and selective reduction of the resultant aldehyde followed by TBS protection provided ketone **39** in 66% yield over 3 steps. Treatment of **39** with lithium TMS acetylide gave propargyl alcohol **40** with good selectivity (72% yield). The free alcohol was protected as the acetate and the primary alcohol revealed by TBAF treatment. Oxidation and single-carbon Wittig homologation provided the enyne RCM substrate **41**. The enyne RCM reaction worked extremely well, yielding 84% of **42**. This fragment contains the fully functionalized AB ring system, with a nearly fully functionalized C ring. C9 has the necessary oxygen and alkyl substituents, while the C7 hydroxy group could potentially be inserted across the C8-C7 olefin through hydroboration.

More recently, Qiaoling Wang and Chuo Chen have published an approach to the lancifodilactone F (**3**) and buxapentalactone (**16**) cores (Scheme 1.3).[26] Their approach is focused on an interesting arene-olefin *meta*-photocycloaddition used to build the 7 and 6 membered rings simultaneously. A 7-step sequence provided a mixture of separable alcohols which were protected to provide the photocycloaddition substrate(s). Studies on the individual diastereomers suggested it was unnecessary to separate them. The individual hydroxyl centers did not affect the cycloaddition and were subsequently destroyed by oxidation, converging to enantiomers.



Scheme 1.3 Chen's approach to the lancifodilactone F and buxapentalactone cores.

Photocycloaddition of **43** gave the exo isomers **44a** and **44b** exclusively as a 1:1.2 mixture in yields over 90%. Epoxidation using mCPBA and acid treatment opened the cyclopropane ring, revealing the 7 membered ring, and allylic isomerization occurred when **45a** was treated with Pd/C under a hydrogen atmosphere. Treatment of ketone **46** with isopropenyl Grignard and IBX oxidation provided **48**. While **48** contains the desired 7,6,5 core, it is not clear how the researchers plan to cleave and functionalize the two 5-membered rings surrounding the methylketal.

In summary, the Chen group has outlined an approach to the 7,6,5 ring system present in lancifodilactone F (**3**) and and buxapentalactone (**16**). While the use of an arene-olefin photocycloaddition allows the rapid development of multiple rings and stereochemical complexity, additional research will be necessary if this approach is applied to the total synthesis of the specified natural products.

The Yang group has developed three unique approaches to the western, central, and eastern fragments of micrandilactone A (**1**). They have synthesized highly functionalized western and eastern fragments in the course of this investigation and each approach appears to be amenable to their plan for total synthesis (Fig. 1.8).

Section 1.2.2 Retrosynthesis of Western Fragment and Abbreviated Biosynthetic Proposal

Our interest was focused on the western fragment of the Schisandraceae natural products. With the exception of lancifodilactone F (**3**), the micrandilactone A (**1**) tricyclic moiety is ubiquitous within the dilactone group of natural products, making it an ideal scaffold for initial studies. A general approach to building the lancifodilactone F (**3**) western fragment and the tricyclic micrandilactone A (**1**) moiety was desirable (Fig. 1.4).

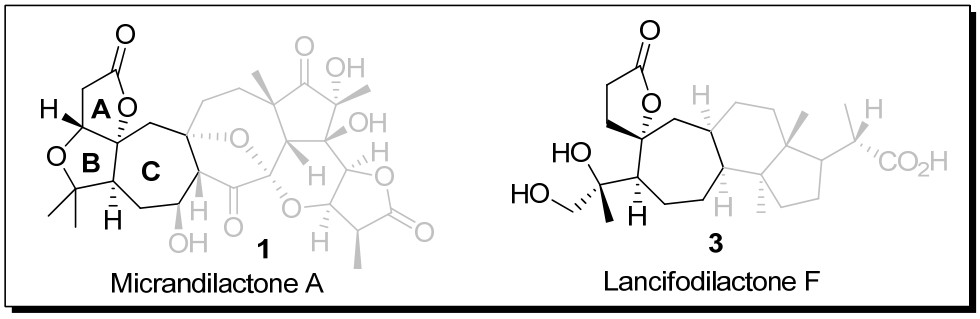
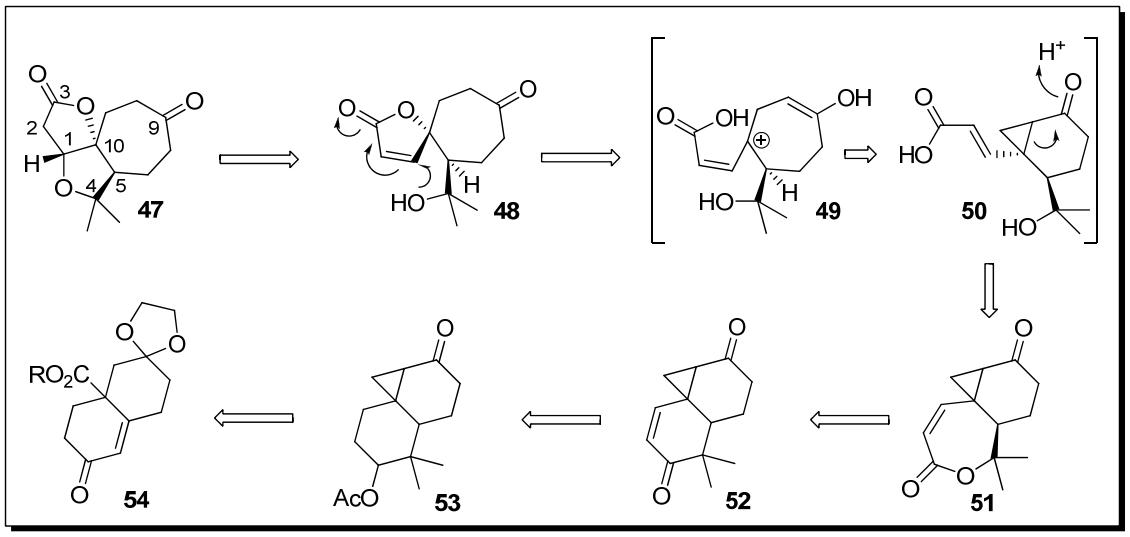


Figure 1.4 Fragments targeted for synthesis.

With the idea that the compounds of interest may arise from a cycloartane steroidal intermediate, we recognized the diversity of isolated compounds containing differing ring A (steroid ring assignment) oxidation (Figures 1.0 and 1.1). For example,

kadsulactone (**12**), kadsudilactone (**13**), and schisanlactone B (**13b**) differ structurally only in the A ring. The A ring of kadsulactone (**12**) is a standard cyclohexanone cycloartane motif, the A ring of kadsudilactone (**12**) is a heptalactone, while the A ring of schisanlactone B (**13b**) is an unsaturated heptalactone. The cycloartane cyclopropyl ring remains intact for each and imagining a ring expansion arising from cyclopropyl cleavage is academic. Lancifodilactone F (**3**) and buxapentanone (**14**) contain a rearranged A,C (micrandilactone A numbering) ring system in the form of spirolactones connected to substituted heptane rings. The spirolactone (A ring) of lancifodilactone F (**3**) and buxapentalactone (**16**) was recognized as a potential intermediate in a path of increasing oxidation, culminating in formation of the B ring of the dilactones.

Guided by the observations discussed, we decided on a route which incorporated the structural clues from natural A (steroid) ring modifications (Scheme 1.4). Our plan was centered on a cascade reaction involving cyclopropyl cleavage/ring expansion, spirolactone formation, and B ring cyclization. A model system simple in nature yet a scaffold applicable to the complex Schisandraceae natural products was the main criteria for our decision.



Scheme 1.4 Retrosynthetic plan and potential biosynthesis of the ABC ring system.

We felt ketone **48** to be a sufficient model for ABC ring formation (**47**). It also contains a handle, C9 ketone, for potential functionalization. To that end, we felt the penultimate cyclization event may be a Michael addition from the C4 hydroxy group to the C1 olefin. Synthetic studies by Yang and coworkers have supported this Michael addition proposal as a 1,4 addition is likely taking place on the conversion of **34** to **38** (Scheme 1.2).[24] The stereoselectivity would likely be substrate controlled and is expected to provide the desired Schisandraceae stereocenter through attack from the most accessible face. We expected the spirolactone **48** to arise from a carbocation intermediate such as **49**. The planar nature of carbocations often limits stereocontrol in synthetic reactions, and with a minimally-substituted model we expected little stereoselectivity. There are alternative mechanisms based on this carbocation intermediate that may provide **48**. For instance, the cyclopropyl ring may cleave prior to lactone opening. However, under acidic conditions all mechanisms considered

involve a cyclopropyl ring expansion through a tertiary cation. It is conceivable that a carbocation such as **48**, could arise from a bicyclic lactone such as **51**.

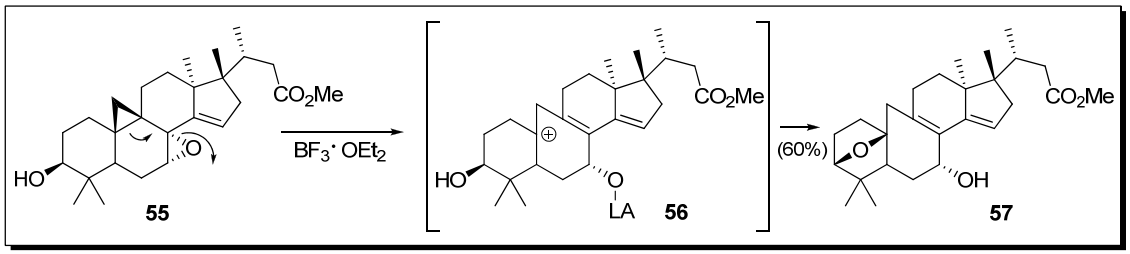
The lactone **51** could presumably be a direct product of Baeyer-Villiger oxidation on a bicyclic system such as **52**. Simple manipulations were expected to provide **52** from the reported acetate **53**, which has been synthesized from Robinson annulation adduct **54**.[27] We began the study with this potentially biomimetic proposal as a guide.

Section 1.2.3 Literature Background of Key Rearrangement

Cyclopropylcarbinol ring expansions, or related variations, have been used in natural product synthesis as a means of ring expansion. Although the reaction is typically performed under acidic conditions, several reports indicate good stereoselectivity. Of particular interest to us were the reactions used by Corey in the synthesis of Glycinoeclepin[28] and by Matsumoto in the conversion of Humulene to Dactylol[29]. The epoxide functionality conjugated to the cyclopropane ring provides a bond activated for cleavage through a push-pull concept, and rearrangement occurs without loss of the oxygen. This mechanism resembles our proposed route where a conjugated keto-cyclopropyl system expands to form an enol expected to tautomerize to the ketone.

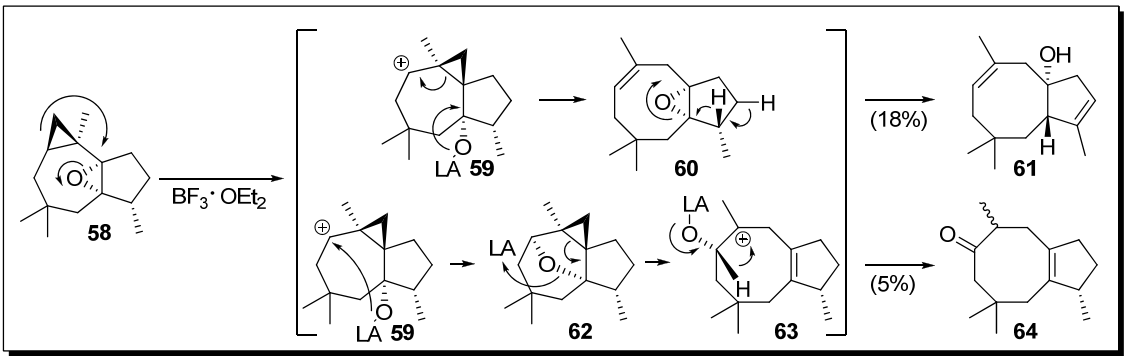
An additional feature of the Glycinoeclepin synthesis is the fact that Corey and Hong used a cycloartane scaffold (Scheme 1.5). The rearrangement of cyclopropyl epoxide **55** was achieved by treatment with boron trifluoride. The Lewis acid presumably forms cation **56**, which is trapped by the C4 hydroxy to form the ether

bridge of **57**. Features of note are the fact that a cycloartane skeleton applicable to our proposal was used, the cyclopropane was activated by a "non-cleavable" withdrawing group, the internal nucleophile apparently controlled the stereoselectivity, and the carbocation was trapped by an internal nucleophile to form an additional small ring.



Scheme 1.5 Cyclopropyl ring expansion in Corey's glycinoeclepin synthesis.

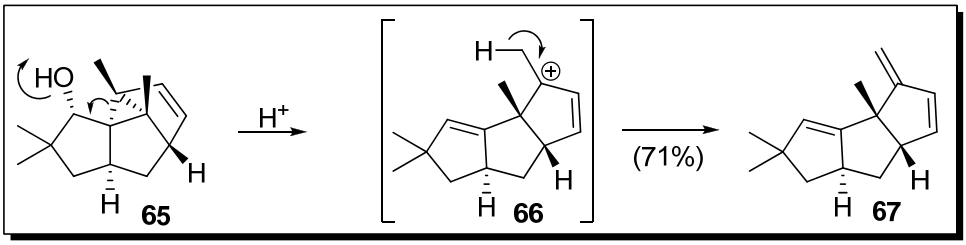
Matsumoto and coworkers took advantage of a similar reaction in their Dactylol synthesis (Scheme 1.6). Epoxide-activated cyclopropane (**58**) was converted to tertiary alcohol **61** and ketone **64** was obtained upon low temperature treatment with boron trifluoride. It is presumed that the cyclopropane opening was preceded by epoxide activation and a cyclopropyl shift leading to the cation **59**. Additional events, proposed in Figure 1.11, would potentially lead to the reported products. No additional reaction products were reported, leaving us to speculate the low yields may result from alternative initial cyclopropane ring expansion pathways. While not directly related to our studies, this work demonstrates a cyclopropylcarbinol like ring-expansion utilizing a non-cleavable withdrawing group and demonstrates the unpredictable nature of cations.



Scheme 1.6 Cyclopropyl ring expansion in Matsumoto's dactylol synthesis.

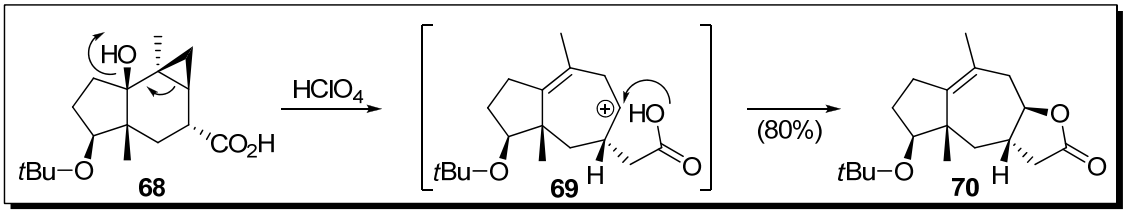
Examples of true cyclopropylcarbinol ring modifications in total synthesis have been provided by Wender through the total synthesis of Hirsutene[30] and in the total synthesis of Confertin[31] by Marshall. In contrast to the epoxide activated cyclopropanes, the cyclopropylcarbinol system uses a hydroxyl group to activate the cyclopropane ring. In this strategy the hydroxyl group is lost through elimination under acidic conditions, resulting in an unsaturated ring system.

Wender and Howbert built the highly strained cyclopropyl compound **65** through an arene-olefin cycloaddition (Scheme 1.7). When treated with Bronsted acid camphorsulfonic acid, **65** rearranged to form the Hirsutene skeleton (**66)** in good yield. This appears to be an E1 mechanism as the departing hydroxyl group and the fragile cyclopropane bond are not periplanar.



Scheme 1.7 Cyclopropylcarbinol ring expansion in Wender's hirsutene synthesis.

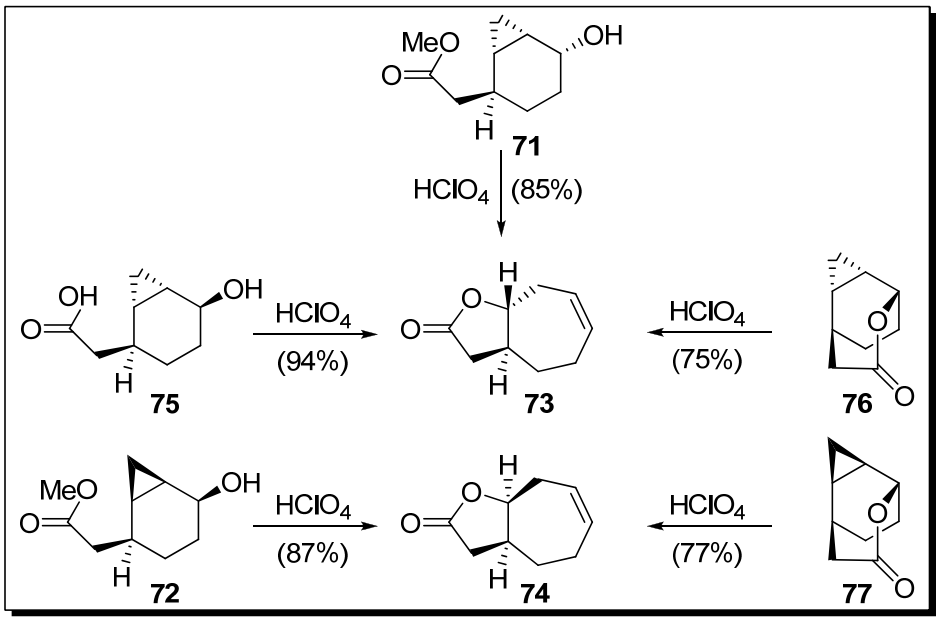
Marshall and Ellison have also taken advantage of the relative fragility associated with a hydroxyl activated cyclopropane (Scheme 1.8). Synthetic work towards Confertin yielded cyclopropane **68**. Treatment of **68** with perchloric acid initiated a cascade of events. Ring expansion and elimination likely occurred to provide carbocation **69**, prior to cyclization by the internal nucleophile. Trans fused lactone **70** was produced in 80% yield with no diastereomers reported. The manuscript contained no speculation as to the source stereoselectivity, however earlier studies by Marshall's group may have predicted the outcome of this reaction.



Scheme 1.8 Cyclopropylcarbinol ring expansion in Marshall's confertin synthesis.

Marshall and Ellsion reported results of a series of relevant cyclopropylcarbinol studies prior to the Confertin synthesis (Scheme 1.9).[32] Work with methyl esters **71** and **72** gave impressive yields of single isomers **73** and **74**. Worthy of note, is the

observation that carboxylic acid **75** gave a high yield of **73**. The fact that **71** and **75**, epimeric at the hydroxyl carbon, gave the same reaction product suggested alcohol stereochemistry was not critical and supports an E1 mechanism. Marshall also found that the butyrolactones **73** and **74** could be formed from lactones **76** and **77**. The study showed cyclopropane stereochemistry to be the most important predictor for the reaction outcome. Marshall commented that the acid or ester side chain might have played an anchimeric role. However, an explanation for the surprising stereoselectivity was not provided.



Scheme 1.9 Cyclopropylcarbinol ring expansion studies by Marshall and Ellison.

Section 1.2.4 Synthesis of Isomeric Fragment

Without a clear understanding of expected stereoselectivity from the key ring expansion step, we required a route amenable to controlling cyclopropane

stereochemistry. We sought to test the reaction on compounds resembling **78** and **79**, which are diastereomeric at the decalin ring junction (Fig. 1.15). We felt the reported compound **80**[27] (Fig. 1.5) matched our synthetic design and intermediates within its synthesis could allow for stereochemical diversity at the ring junction.

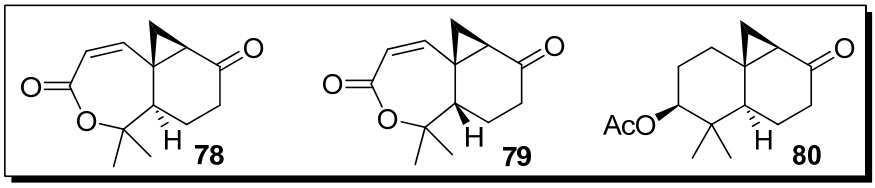
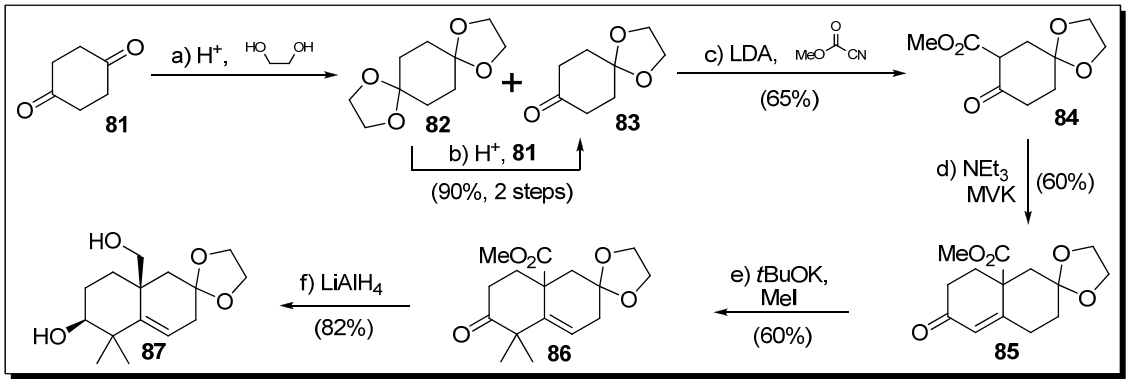


Figure 1.5 Targeted synthetic intermediates.

We targeted diol **87** as an intermediate capable of synthetic divergence (Scheme 1.10). Our route began with protection of 1,4 cyclcohexanedione as the mono dioxolane. Slow addition of ethylene glycol to an acidic solution of the dione **81** provided monodioxolane **83** in acceptable yields, but separation from the di-dioxolane (**82**) proved difficult. Accordingly, a literature procedure was followed for the preparation of dioxolane **82**.[33] Di-dioxolane was prepared by refluxing ethylene glycol with 1,4-cyclohexanedione (**81**) in benzene with pTSOH under dehydrating conditions (Dean-Stark trap). The di-dioxolane (**82**) was refluxed in an acidic (pTSOH) toluene solution with 1.5 eq. 1,4-cyclohexanedione, which allowed equilibration to dioxolane **83** in excellent yield. The mono ketal (**83**) was easily separated from the excess **81** through chromatography.

Acylation methodology developed by Mander and Sethi allowed for acylation of dioxolane **83** by enolization with LDA and treatment with methyl cyanoformate.[34]

Robinson annelations of **84** with methyl vinyl ketone worked best when performed under conditions developed for the analogous ethyl ester by Tsuda and coworkers.[27] In addition, conditions use by Kabuto and coworkers[35] (MeOH, NaOMe) also produced the reported enone (**85**). Treatment of keto-ester **84** with triethylamine and methyl vinyl ketone in methanol for several days followed by refluxing with a solution of pyrrolidine and acetic acid in benzene (Dean-Stark dehydrating conditions) provided Robinson adduct **85** in 65% yield. Uncyclized intermediates were often isolated from this reaction after chromatography and could generally be converted to the cyclized product by retreatment.

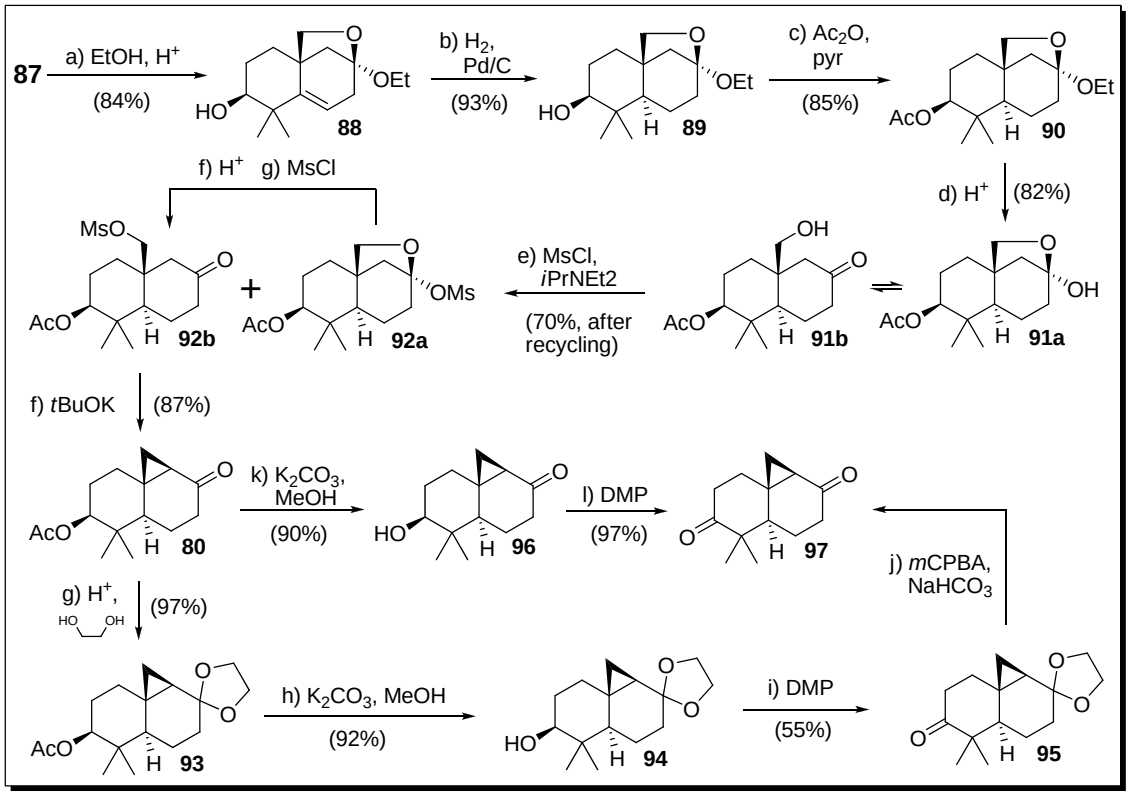


Scheme 1.10 Synthetic route to diol **87**.

Dimethylation of **85** was achieved through the extended enolate by treatment with excess methyl iodide over extended time periods. Di-methylated keto-ester **86** was reduced to diol **87** with lithium aluminum hydride. The bulky reducing agent approached the cyclohexanol axially, from the face opposite the methyl ester, to provide the equatorial alcohol in 82% yield. Analyses of the crude mixture suggested a

significant amount of the epimeric alcohol was produced. However, an amount of sufficient purity for characterization was not obtained.

With diol **87** in hand, cyclopropyl diketone **97** became the immediate goal (Scheme 1.11). Diol **87** was stirred in ethanol with pTSOH to provide ethyl ketal **88**. This ketal was reduced under standard hydrogenation conditions with 10% Pd/C. Reduction occurred from the less hindered α-face to provide **89** in excellent yield. Acetylation preceded pTSOH treatment to form the hemiketal **91**.



Scheme 1.11 Synthetic route to cyclopropyl ketone **97**.

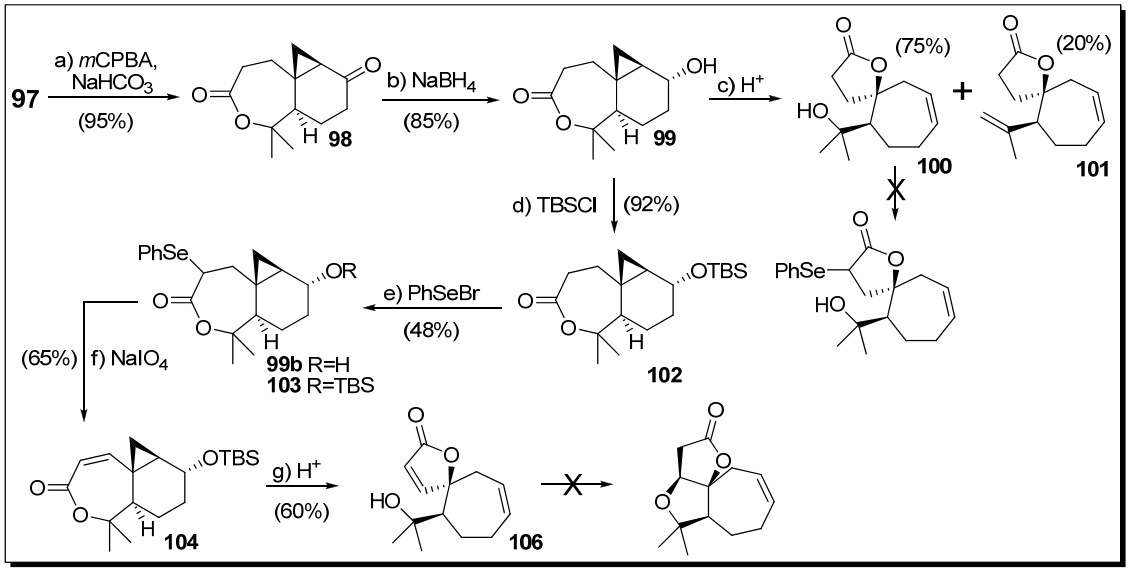
Treatment of hemiketal **91** with mesyl chloride and base gave a mixture of primary mesylate **92b** and mesylketal **92a** (4:5, 90% overall yield). Fortunately, hemiketal **91** could be recovered by treatment of mesylketal **92a** with acid and retreated to provide primary mesylate **92b**. Sequential treatments in this manner allowed for production of **92b** in 70% overall yield.

Treatment of **92b** with base allowed cyclopropane formation under mild conditions. Purification of cyclopropyl acetate **80** gave crystals of sufficient quality for single crystal X-ray analysis. In this manner, the structure of **80** was unambiguously confirmed.

We had some concern over future the selectivity the planned Baeyer-Villiger reaction and decided to mask the ketone again as a dioxolane. This was achieved under standard conditions with pTSOH and ethylene glycol. Subsequent deprotection of the acetate and oxidation by Dess-Martin periodinane provided ketone **95**. This compound decomposed under Baeyer-Villiger conditions to the diketone **97**. Fortunately we learned that diketone **87** underwent very efficient and selective Baeyer-Villiger oxidation and the protection step was unnecessary. With this knowledge, keto acetate **96** was deprotected and oxidized to diketone **97** in excellent yield.

As mentioned, the oxidation of **97** to heptalactone **98** worked with excellent selectivity, oxidizing the most highly substituted position (Scheme 1.12). We decided to attempt the rearrangement with **98**, prior to installing lactone unsaturation. Unfortunately, treatment of ketone **98** with boron trifluoride and Bronsted acids resulted

in complex mixtures of uncharacterized products. We switched focus and decided to perform the reaction with a true cyclopropylcarbinol.

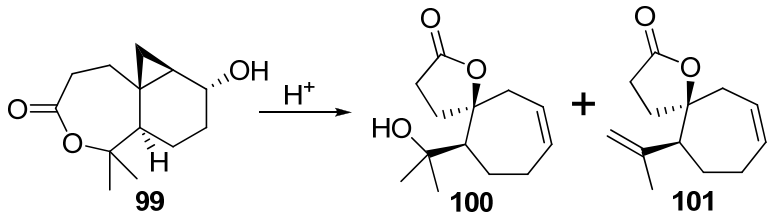


Scheme 1.12 Synthetic route to rearrangement substrates **99** and **104**.

To this end, selective hydride reduction of **98** by sodium borohydride in THF gave an excellent yield of alcohol **99**. Reduction attempts in protic solvents (methanol and ethanol) gave complex product mixtures, presumably due to lactone decomposition. The alcohol stereochemistry **99** has been tentatively assigned based on comparison of ^{1}H NMR data of related structures.[36] Alcohol **99** underwent selective rearrangement to spirolactone **100** when treated with a variety of acids (Table 1.0). Spirolactone **100** was characterized by single crystal x-ray analysis in conjunction with standard NMR and mass spectroscopy techniques. Olefinic spirolactone **101** was also produced in the reaction, typically the ratio of **101** to **100** increased with longer reaction times. This suggests the cyclopropyl bond cleavage was more facile than C4 elimination of water to

form **101**. The best yields of **100** were achieved by treatment with aqueous perchloric acid in acetonitrile coupled with frequent reaction monitioring.

Table 1.0 Survey of acid effect on the rearrangement of **99**.



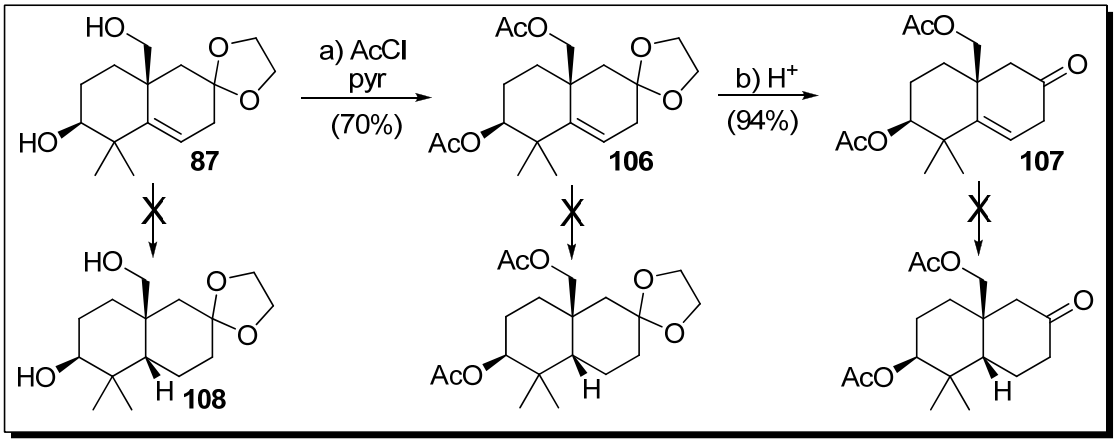
Solvent	Acid	yield 100	yield 101
acetonitrile	$HClO_4/H_2O$	75%	20%
acetone		65%	15%
dioxane		60%	7%
DMSO		20%	trace
acetone (0.5 h)	H_2SO_4	20%	50%
acetone (1.5h)		trace	65%
acetone	HCl	30%	35%
acetone	HF	40%	7%
acetone	HNO_3	50%	7%
dichloromethane	TFA	trace	trace
dichloromethane	$BF3{\cdot}OEt_2$	trace	20%

Although spriolactone **100** contains the incorrect C5 and C10 (Micrandilactone numbering) stereochemistry, confirmation of the rearrangement reaction prompted us to explore the penultimate Michael addition. Attempts to install unsaturation to the spirolactone through a selenation-elimination process failed due to limited material. We felt tackling this issue at an earlier stage to be prudent, and perhaps allow for the Michael reaction to occur concomitantly with the cyclopropyl expansion reaction. Selenation of **99** was poor-yielding, and the corresponding selenide (**99b)** was isolated

in only 15%. After protection of the alcohol (**99**) as the TBS ether, treatment with phenylselenium bromide followed by oxidative elimination provided unsaturated lactone **104**. Treatment of **104** with aqueous perchloric acid cleaved the silyl ether and gave spirolactone **105** as the only isolated product. Spirolactone **105** was reduced via hydrogenation and compared to the hydrogenation product of **100** for structural assignment in conjunction with standard NMR and mass spectroscopy techniques. Attempts to cyclize spirolactone **105** via a base catalyzed Michael addition failed and limited material prevented further study. Attention was turned to developing the desired Schisandraceae stereochemistry.

Section 1.2.5 Synthesis of Stereochemically Correct Fragment

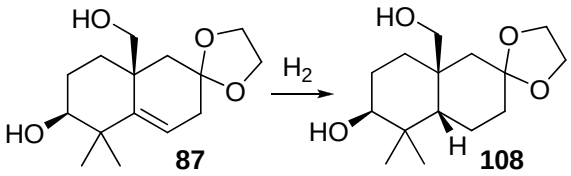
Given the stereoselectivity observed in the rearrangements of **99** and **104**, we decided to invert the C5 stereochemistry. Attempts to form the desired ring junction through standard Pd/C catalyzed hydrogenatation failed. Hydrogenation of diol **108** resulted in inseparable mixtures, as did diacetate **106**, and diacetate **107**.



Scheme 1.13 Initial attempts at forming cis ring junction through hydrogenation.

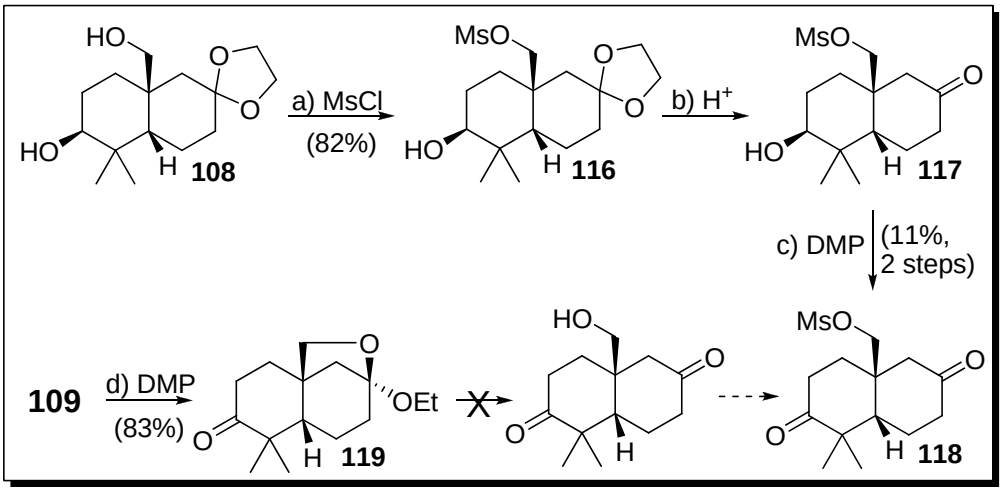
We decided to use the hydroxy functionalities as directing groups and attempted a number of hydrogenations with this in mind (Table 1.1). As previously mentioned, hydrogenation reactions using Pd/C failed to produce acceptable results. We hoped that deprotonation of diol **87** would enhance and directing ability. Notwithstanding, Pd/C hydrogenations reactions with added potassium hydride or triethylamine failed to improve the reaction. Likewise, the use of platinum oxide as a catalyst failed. Based on literature reports of alkoxy directed hydrogenations, we turned to Wilkinson's catalyst.[37] Unfortunately these attempts failed as well. The more expensive Crabtree's catalyst became of interest, as many reports of substrate directed reductions of congested olefins exist in the literature.[38] We were edified to find it worked well, giving the desired cis decalin **108** in good yield.

Table 1.1 Hydrogenation attempts at forming cis decalin **108**.



catalyst	isolated yield 108
$(Ph_3P)_3RhCl$	0
KH + $(Ph_3P)_3RhCl$	0
Pd/C	0
Pd/C, NEt_3	0
Pd/C, KH	0
PtO_2	0
$[Ir(Cod)Py(PCy_3)]PF_6$	77%

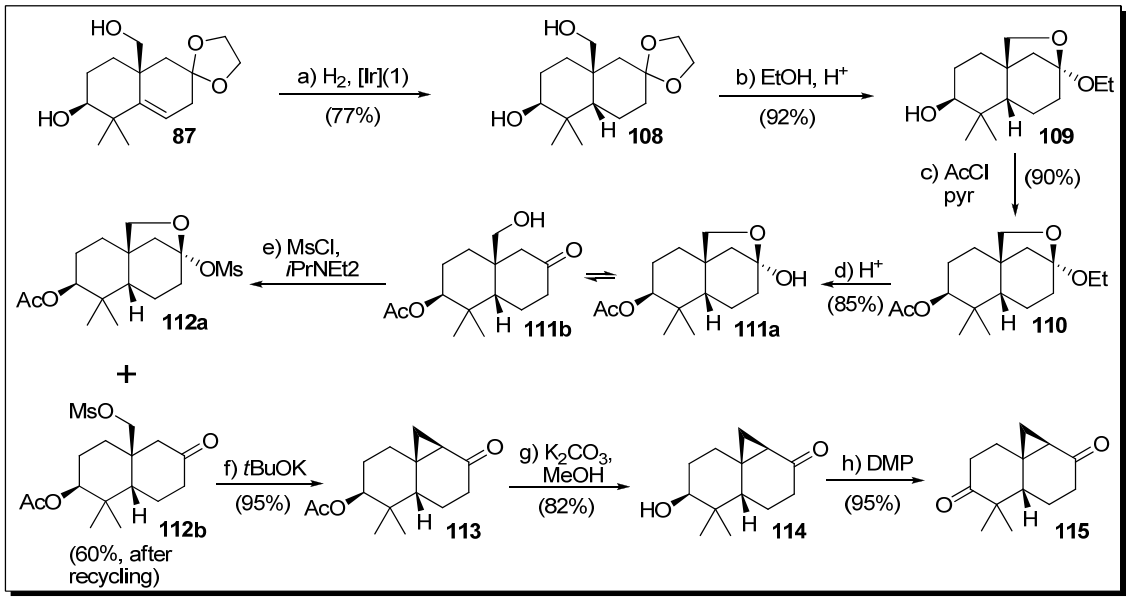
With the solution to forming the cis decalin system in hand, we hoped to shorten the existing route (trans decalin) and avoid the issue of hemiketal mesylation as well as the associated recycling reactions (Scheme 1.14). With diketone mesylate **118** as a goal, diol **108** was converted to the primary mesylate **116** under mild conditions in surprising yield, 82%. Acidic deprotection of **116** proved problematic and oxidation of **117** provided only 11% yield (2 steps) of the desired diketone **118**. Cyclization trials of **118** failed primarily as a result of limited material.



Scheme 1.14 Synthetic route optimization attempts.

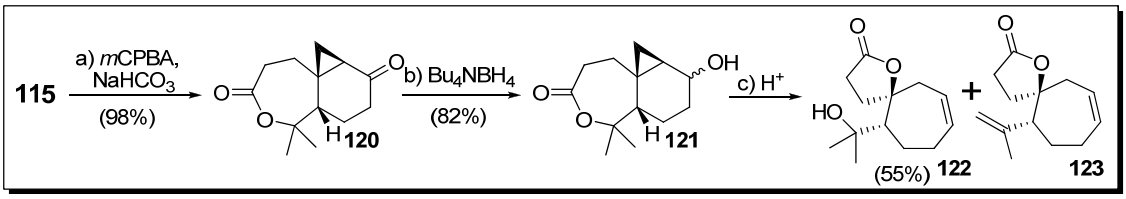
An alternative approach with the same target was attempted beginning from alcohol **109**. Dess-Martin oxidation worked well and provided ethyl ketal **119** in 83% yield. However, attempts to unmask the ketone resulted in complex mixtures. It is suspected that ketalization at the C4 ketone may have interfered.

These failures convinced us to work with proven chemistry. Accordingly, diol **108** was treated with acid in ethanol to unmask the ketone and form ethyl ketal **109** (Scheme 1.15). Acetylation and acidic deprotection provided the hemiketal/ketone mixture (**111**). The hemiketal (**111a**) provided crystals suitable for single crystal X-ray analysis, which confirmed the cis ring junction. As with the trans decalin system, the mesylation of **111** required recycling of the hemimesylate.



Scheme 1.15 Synthesis of diketone **115**.

Cyclopropane formation and deprotection of cyclopropyl acetate **113** followed by oxidation gave the cis decalin Baeyer-Villiger substrate (**115**) in good yield as expected. Oxidation of **115** proceeded in excellent yield to form **120** (Scheme 1.16). Attempts to reduce **120** with sodium borohydride failed in several solvents. However tetrabutyl ammonium borohydride was found to be a suitable reducing agent, although approximately a 1:1 mixture of diastereomers was isolated. When treated with perchloric acid, the mixture of alcohols (**121**) cyclized to form **122** as expected. Butyrolactone **122** and small amounts of dehydration product **123** were the only products isolated.



Scheme 1.16 Cyclopropyl carbinol rearrangement of cis decalin **121**.

No attempts to introduce unsaturation and to form the fused cycloheptyl-tetrahydrofuran-butyrolactone motif composing the Schisandraceae ABC ring system were made on the cis material (**120-122**). The lengthy route was not ideal for producing the necessary amount of material needed for further studies. Moreover, attention to peripheral synthetic projects was needed.

Section 1.2.6 Stereoselectivity Discussion and Conclusion

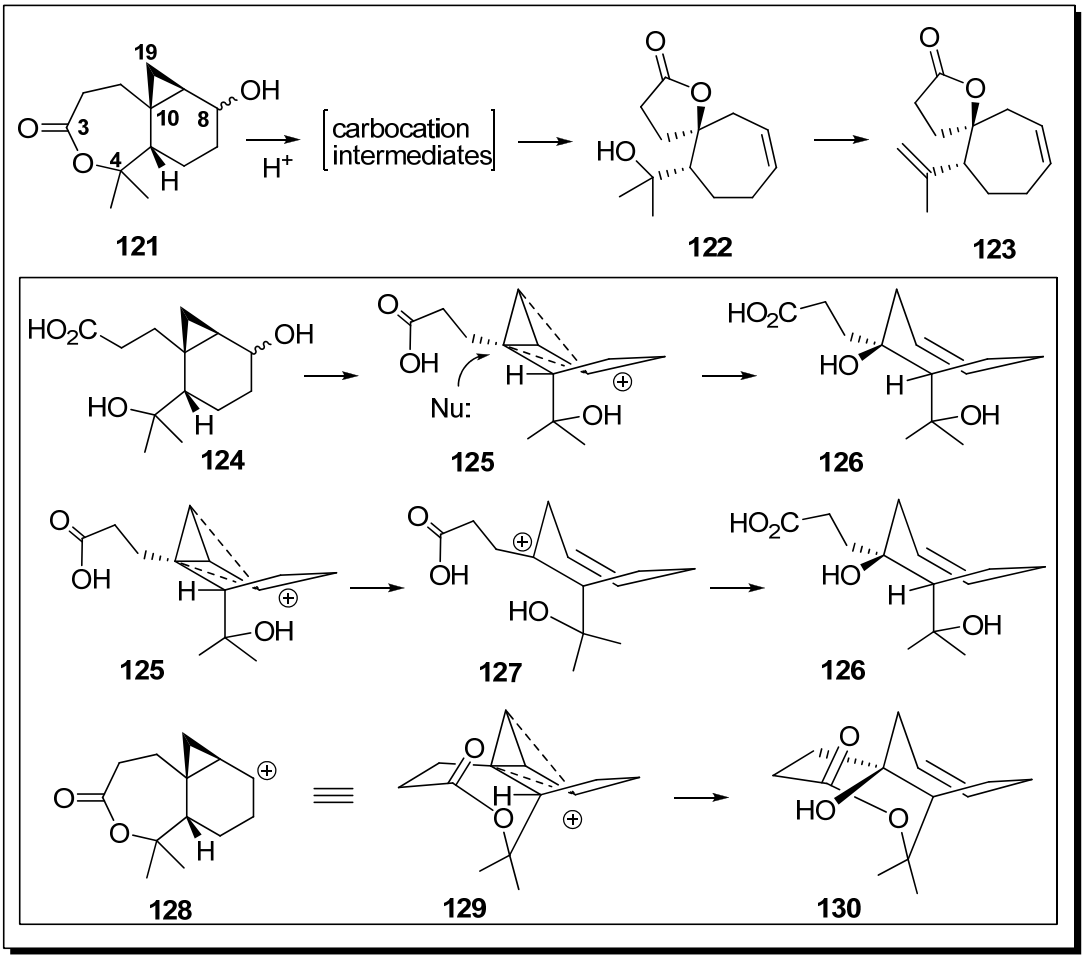
The cyclopropyl carbinol reactions explored involve water elimination (C8), cyclopropyl ring expansion (C9-C10), lactone hydrolysis (C3-C4), and spirolactonization (C10) in a single step, but not necessarily in that order. An additional dehydration occurs through elimination of water from C4 after spirolactonization. The fact that C4 water elimination likely occurs subsequent to spirolactonization is evidenced by the conversion of spirolactone **100** to the dehydration product (**101**) with increased reaction times.

These reactions are of also of significance due to the observed stereoselectivity, which is in agreement with previous reports. Although the source of stereoselectivity in many carbocation-mediated reactions is not apparent when obvious substrate control is

absent, intimate ion pairs,[39] non-classical ions,[40] and neighboring group or anchimeric effect[31, 32, 41] have been proposed.

Figure 1.17 depicts possible transition states leading to stereoselectivity in the acid mediated rearrangement of **121**. Intermediate **124** can arise from initial lactone hydrolysis. Subsequent water elimination will potentially create a C8 carbonium. A non-classical carbocation may resemble intermediate **125** where the positive charge is shared between C8, C10, and C19. The non-classical ion model allows the weakened cyclopropane ring to retain some conformational identity. Additional stabilization may come from interaction of the C4 hydroxy with the C8 cation. It is worth noting that this mode of anchimeric assistance may be more significant in compounds forming fused butyrolactones, as opposed to spirobutyrolactones, as a transient hydrofuran ring can form at this stage. The conformational identity of **125** can equate to substrate controlled addition of water to form intermediate **126** or the internal carboxyl functionality could act as the nucleophile to form **122** directly.

Alternatively, cation **125** could convert to C10 cation **127**. Association of C4 hydroxy with cation **127** from the bottom face would force an incoming nucleophile (water or the internal carboxyl group) to approach from the top face. Lactonization of **126** would lead to **122**.



Scheme 1.17 Potential mechanisms for rearrangement of cyclopropane **121** to **122**.

It is also plausible that elimination of water from C8 could occur prior to lactone hydrolysis, leading to an intermediate resembling **129**. Quenching of a non classical ion such as **129** by water could potentially be directed by the intact lactone functionality, providing intermediate **130**. Lactonization of **130** would lead to **122**.

In all reactions the end result is installation of an oxygen through an apparent backside attack of the weaked cyclopropane bond (C10-C9). The fact that several modifications occur in one pot with stereocontrol is a highlight of cyclopropylcarbinol

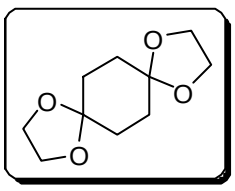
rearrangement reactions and makes these reactions synthetically useful. However the true nature of this stereoselectivity remains unexplained. We have taken advantage of the positive aspects of this reaction to build a minimized A,C ring system of lancifodilactone (**3**).

Appendix Experimental Information

Section A.1 General Techniques

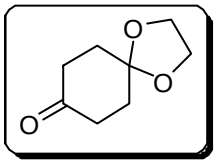
All reagents were obtained (Aldrich, Acros) at the highest commercial quality and used without further purification except where noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 45 °C at approximately 20 mmHg. All non-aqueous reactions were carried out under anhydrous conditions, *i.e.* using flame-dried glassware, under an argon atmosphere and in dry, freshly distilled solvents, unless otherwise noted. Yields refer to chromatographically and spectroscopically (^{1}H NMR, ^{13}C NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) and visualized under UV light and/or developed by dipping in solutions of cerric ammonium molybdate (CAM) or p-anisaldehyde and applying heat. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. NMR spectra were recorded on Varian Mercury 300, 400, Varian Unity 500, and/or Jeol eca 500 MHz instruments and calibrated using the residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. IR spectra were recorded on a Nicolet 320 Avatar FT-IR spectrometer and values are reported in cm^{-1} units. High resolution mass spectra (HRMS) were recorded on a ThermoFinnigan MAT900XL under fast atom bombardment (FAB) conditions with 3-nitrobenzyl alcohol matrix and polyethylene glycol reference. X-ray data were recorded on a Bruker SMART APEX 3kW Sealed Tube X-ray diffraction system.

Section A.2 Experimental Procedures and Data

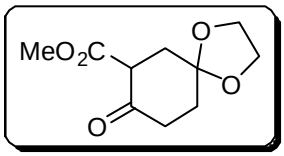


Compound 82: 1,4-cyclohexanedione (12.3 g, 109.8 mmol) was dissolved in benzene (60 mL) at room temperature. Ethylene glycol (17.7 g, 285.5 mmol) was added to the reaction vessel followed by *p*-toluenesulfonic acid (1.9 g, 9.9 mmol). The solution was refluxed 3 hours under a Dean-Stark trap. After

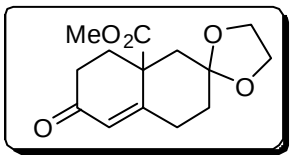
cooling to room temperature, triethylamine was added and the reaction concentrated with a rotary evaporator. The resultant oil was filtered through silica. Concentration and crystallization from ether/hexane (4:1) provided **82** as a crystalline solid (20.9 g, 95%). TLC (ethyl acetate/hexanes 3:2): $R_f = 0.6$.



Compound 83: Diketal **82** (20 g, 100 mmol), 1,4-cyclohexanedione (16.8g, 150 mmol), and *p*-toluenesulfonic acid (400 mg, 2.1 mmol) were dissolved in toluene and refluxed 1.25 hours under a Dean-Stark trap. After cooling to room temperature, triethylamine was added and the reaction concentrated. The resultant oil was filtered through silica. Concentration and crystallization from ether/hexane (4:1) provided **83** as a crystalline solid (14.4 g, 93%). TLC (ethyl acetate/hexanes 3:2): $R_f = 0.5$.

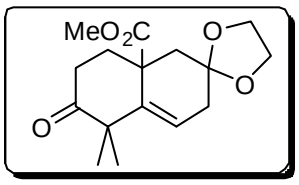


Compound 84: Diisopropylamine (26 mL, 184.3 mmol) was added to n-BuLi (187.5 mmol as 2.5 M hexane solution) in THF (100 mL) at -70°C. After stirring 1 hour, ketal **83** (24.8 g, 159.0 mmol) was added dropwise to the LDA solution at -60°C. Upon complete addition, the solution was warmed to 0°C and stirred 30 minutes. The solution was cooled to -60°C and HMPA (28 mL, 151.9 mmol) added. After stirring 10 minutes, methyl cyanoformate (15.0 mL, 189.2 mmol) was added dropwise. The reaction was stirred 30 minutes at -60°C before adding aqueous NH_4Cl (saturated). The ester was extracted with ether and dried over $MgSO_4$ prior to purification by column chromatography. Ester **84** (22.1 g, 65%) was obtained as an oil. TLC (ethyl acetate/hexanes 2:3): $R_f = 0.5$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.8 (t, J = 6.8 Hz, 2H), 2.46 (b, 2H), 2.5 (t, J = 6.8 Hz, 2H), 3.74 (s, 3H), 3.99 (m, 4H), 12.14 (b, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 170.9, 107.5, 95.1, 79.1, 64.6, 51.5, 32.7, 30.4, 28.0; HRMS: *m/z* calcd. for $C_{10}H_{15}O_5$: 215.0841, found: 215.0837 $[M+H]^+$.

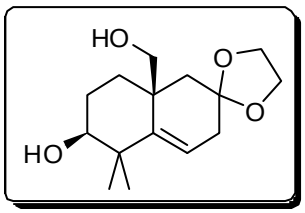


Compound 85: Ester **84** (7.5 g, 35.0 mmol) was dissolved in methanol (80 mL) at room temperature. Triethylamine (1.7 mL, 12.2 mmol) and methyl vinyl ketone (5.1 mL, 62.8 mmol) were added. After stirring at room temperature 40 hours, the reaction was concentrated and the residue dissolved in benzene. The benzene solution was washed with 2% HCL, then water before drying over $MgSO_4$. Pyrrolidine (1.4 mL) was added followed by acetic acid (1.0 mL. The solution was refluxed under a Dean-Stark trap. When TLC showed no further conversion, the reaction was cooled and partitioned between ether and water. The ether extracts were dried over $MgSO_4$ and concentrated. Column chromatography provided **86** (6.0 g, 65%) as an oil. TLC (ethyl acetate/hexanes 2:3): $R_f = 0.5$; ^{1}H NMR (400

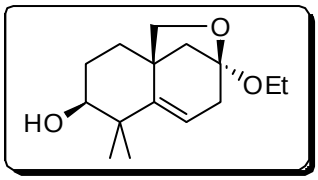
MHz, $CDCl_3$): δ 1.5 (d, J = 13.6 Hz, 1H), 1.71-1.96 (m, 3H), 2.19 (m, 1H), 2.29-2.37 (m, 2H), 2.47 (m, 1H), 2.60 (dd, J = 3.2, 13.6 Hz, 1H), 2.89 (m, 1H), 3.72 (s, 3H), 3.83-4.04 (m, 4H), 5.96 (d, J = 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 173.2, 160.2, 127.2, 107.0, 64.7, 64.3, 52.6, 48.4, 43.9, 35.7, 34.8, 34.4, 31.6; HRMS: *m/z* calcd. for $C_{14}H_{19}O_5$: 267.1227, found: 267.1232 $[M+H]^+$.



Compound 86: *t*BuOK (3.0 g, 26.73 mmol) was added to **85** (3.4 g, 12.8 mmol) in *t*BuOH (25 mL). The solution was stirred 15 minutes at room temperature. MeI (4.5 mL, 72.1 mmol) was added and the solution heated to reflux. Additional MeI (2.0 mL, 32.1 mmol) was added after 1 hour. The reaction was monitored and cooled to room temperature when the product composed >95% of the reaction mixture by GC-MS. The reaction was partitioned between ethyl acetate and water. The ethyl acetate layers were dried over $MgSO_4$ and concentrated. Column chromatography yielded **86** (2.25 g,60%) as an oil which crystallized upon storage at -20°C. TLC (ethyl acetate/hexanes 2:3): R_f = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (s, 3H), 1.32 (s, 3H), 1.51 (d, J = 13.2 Hz, 1H), 1.79-2.54 (m, 7H), 3.53 (s, 3H), 3.73-3.96 (m, 4H), 5.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.3, 175.5, 142.8, 121.0, 106.3, 64.29, 64.25, 51.7, 47.9, 41.3, 36.3, 34.3, 33.5, 31.8, 31.2, 25.3; ESI-MS: *m/z* calcd. for $C_{16}H_{22}O_5$: 294.1, found: 294.3 $[M+H]^+$.

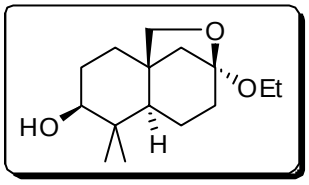


Compound 87: To a stirred solution of **86** (4.7 g, 15.99) in THF (200 mL), was added lithium aluminum hydride (25 mmol, as 1.0 M THF solution) dropwise at 0°C. The reaction was allowed to warm to room temperature overnight. After cooling to 0°C, water was added, the solution partitioned with ethyl acetate, washed with brine, and dried over $MgSO_4$ before concentration. Column chromatography provided a single isomer, **87** (3.5 g, 82%) as a white solid. TLC (ethyl acetate/hexanes 4:1): R_f = 0.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 3H), 1.14 (s, 3H), 1.50 (d, J = 13.6 Hz, 1H), 1.60-1.75 (m, 3H), 1.82 (dd, J = 1.6, 13.6 Hz, 1H), 2.12 (b, 1H), 2.31 (m, 1H), 3.38 (dd, J = 3.4, 18.6 Hz, 1H), 3.21 (dd, J = 4.2, 11.0 Hz, 1H), 3.45 (d, J = 10.0 Hz, 1H), 3.70 (m, 2H), 3.83-4.04 (m, 4H), 5.61 (t, J = 3.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 120.4, 107.2, 77.0, 68.0, 64.5, 63.7, 46.2, 41.6, 41.3, 36.8, 34.2, 27.0, 26.6, 21.0; HRMS: *m/z* calcd. for $C_{15}H_{25}O_4$: 269.1675, found: 269.1752 $[M+H]^+$.

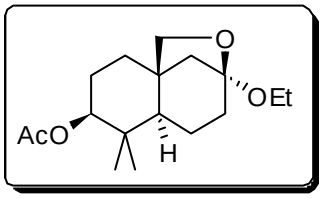


Compound 88: To a stirred solution of diol **87** (6.0 g, 22.3 mmol) in ethanol (120 mL), was added *p*-toluenesulfonic

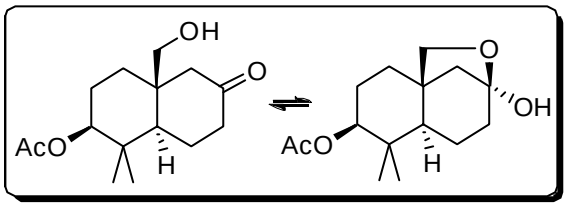
acid (52 mg, 0.3 mmol). The solution was heated at 90°C for 20 minutes. After cooling to room temperature, triethylamine was added and the solution was concentrated under reduced pressure. Column chromatography and concentration provided ethyl acetal **88** (4.8 g, 84%) as a white solid. TLC (ethyl acetate/hexanes 3:2): R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (s, 3H), 1.17 (m, 6H), 1.53 (d, J = 10.8 Hz, 1H), 1.63-1.73 (m, 3H), 1.95 (m, 2H), 2.33 (dd, J = 3.8, 17.4 Hz, 1H), 2.44 (m, 1H), 3.35 (dd, J = 3.4, 11.0 Hz, 1H), 3.55-3.70 (m, 3H), 4.09 (dd, J = 1.4, 6.6 Hz, 1H), 5.59 (dd, J = 2.4, 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9, 119.8, 107.1, 82.5, 76.2, 57.3, 45.1, 44.5, 40.1, 40.2, 29.9, 28.0, 25.6, 24.0, 15.6; HRMS: *m/z* calcd. for $C_{15}H_{25}O_3$: 253.1725, found: 253.1800 $[M+H]^+$.



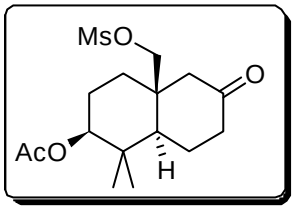
Compound 89: Olefin **88** (4.2 g, 16.6 mmol) was dissolved in ethanol (60 mL) and 10% Pd/C (200 mg) added. An atmosphere of hydrogen was developed (balloon) and the solution stirred overnight. The solution was filtered through celite and concentrated. Column chromatography provided **89** (3.9 g, 93%) as an oil. TLC (ethyl acetate/hexanes 3:2): R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (s, 3H), 1.00 (s, 3H), 1.16 (t, J = 7.0 Hz, 3H), 1.17-1.25 (m, 2H), 1.27-1.39 (m, 1H), 1.55-1.80 (m, 6H), 1.91 (m, 1H), 1.98 (dd, J = 3.0, 11.0 Hz, 1H), 3.23 (dd, J = 3.4, 11.4 Hz, 1H), 3.47-3.68 (m, 2H), 4.20 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 107.5, 78.5, 75.1, 57.4, 49.7, 47.2, 44.5, 39.1, 35.9, 33.5, 28.6, 27.4, 21.1, 15.8, 14.4; HRMS: *m/z* calcd. for $C_{15}H_{27}O_3$: 255.1955, found: 255.1959 $[M+H]^+$.



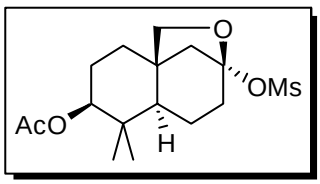
Compound 90: To a stirred solution of alcohol **89** (3.25 g, 12.8 mmol) in dichloromethane (60 mL), was added pyridine (2.0 mL) followed by acetic anhydride (1.4 mL, 14.8 mmol) at room temperature. After the reaction had stirred 20 hours, additional pyridine (5 mL) and acetic anhydride (1.0 mL, 10.6 mmol) was added. The reaction was stirred an additional 10 hours before partitioning the crude material between ether and water. The ether extracts were combined and dried over $MgSO_4$ prior to concentration. Column chromatography and concentration provided **90** (3.2 g, 85%) as a white solid. TLC (ethyl acetate/hexanes 3:2): R_f = 0.6; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82 (s, 3H), 0.88 (s, 3H), 1.06-1.35 (m, 6H), 1.47-1.74 (m, 6H), 1.79-2.00 (m, 5H), 4.15 (d, J = 7.8 Hz, 1H), 4.42 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 107.2, 79.9, 74.5, 57.1, 49.5, 46.8, 44.1, 37.8, 35.7, 32.9, 27.0, 25.0, 21.1, 20.7, 15.6, 15.3; HRMS: *m/z* calcd. for $C_{17}H_{29}O_4$: 297.2060, found: 297.2062 $[M+H]^+$.



Compound 91: Acetate **90** (1.7 g, 5.7 mmol) was dissolved in wet acetone (30 mL) and *p*-toluenesulfonic acid (200 mg, 1.1 mmol) added at room temperature. The solution was heated at 60°C 30 minutes. After cooling to room temperature, triethylamine was added and the solution concentrated at room temperature under reduced pressure. Partitioning between ethyl acetate and aqueous sodium bicarbonate (saturated) followed by drying of the combined organic layers over $MgSO_4$ provided an orange oil after concentration. Filtration through silica provided a mixture of primary alcohol **91b** and hemiketal **91a** (combined yield: 1.3 g, 82%). The isomeric compounds could be separated by silica chromatography and stored for short periods of time at low temperature, but were generally used in subsequent reactions as the mixture. TLC (ethyl acetate/hexanes 2:3): R_f = 0.1-0.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (m, 11H), 1.11-1.95 (m, 20H), 2.01-2.08 (m, 5H), 2.08-2.53 (m, 3H), 3.31-4.65 (m, 5H); HRMS: *m/z* calcd. for $C_{15}H_{25}O_4$: 269.1747, found: 269.1751 $[M+H]^+$.

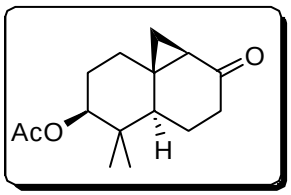


Compound 92b: The mixture of alcohol **91b** and hemiketal **91a** (combined: 650 mg, 2.4 mmol) was dissolved in dichloromethane (15 mL) and treated with diisopropylethylamine (0.5 mL, 2.9 mmol) at room temperature. After cooling the solution to 0°C, mesyl chloride (0.23 mL, 2.9 mmol) was added via cannula over 1 hour. After stirring 3 hours at 0°C, additional diisopropylethylamine (1.0 mL, 5.8 mmol) was added in one portion followed by additional mesyl chloride (0.1 mL, 1.3 mmol) added portion wise over 30 minutes. The reaction was allowed to slowly warm to room temperature. After 5 hours from the original addition of mesyl chloride, water was added to the reaction and the crude material partitioned with ether prior to drying over $MgSO_4$. Column chromatography provided primary mesylate **92b** (336 mg , 40%) and ketal-mesylate **92a** (420 mg, 50%). Ketal-mesylate **92a** could be easily converted to **92b** by stirring in wet acetone with catalytic HCl. TLC (ethyl acetate/hexanes 3:2): R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (s, 3H), 0.99 (s, 3H), 1.33 (m, 1H), 1.61 (m, 1H), 1.70-1.80 (m, 2H), 1.90 (m, 1H), 2.01-2.11 (m, 6H), 2.35 (m, 1H), 2.50 (m, 2H), 3.00 (s, 3H), 3.99 (d, J = 10.4 Hz, 1H), 4.42 (dd, J = 1.2, 10.4 Hz, 1H), 4.61 (dd, J = 4.4, 11.6, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.0, 170.5, 79.5, 68.8, 52.2, 51.5, 41.5, 40.9, 37.8, 37.3, 33.1, 28.2, 23.4, 21.9, 21.3, 17.1; HRMS: *m/z* calcd. for $C_{16}H_{27}O_6S_1$: 347.1523, found: 347.1511 $[M+H]^+$.

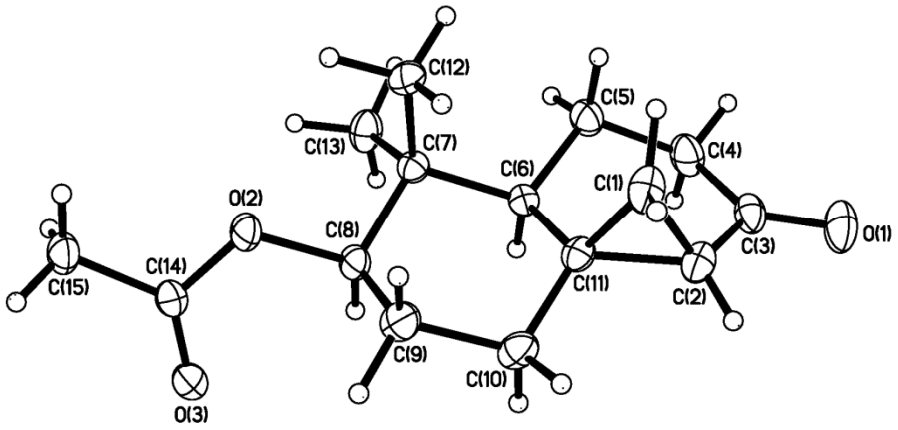


Compound 92a: TLC (ethyl acetate/hexanes 3:2): R_f = 0.6; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (s, 3H), 0.91 (s, 3H),

1.30 (m, 2H), 1.56-1.87 (m, 7H), 1.98 (s, 3H), 2.12 (m, 1H), 2.46 (m, 1H), 3.05 (s, 3H), 3.70 (m, 1H), 4.28 (m, 1H), 4.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 114.3, 79.5, 76.4, 49.6, 48.7, 44.3, 41.1, 37.7, 36.4, 31.8, 26.8, 24.8, 21.0, 20.7, 15.2; HRMS: *m/z* calcd. for $C_{16}H_{27}O_6S_1$: 347.1523, found: 347.1513 $[M+H]^+$.



Compound 80: Mesylate **92b** (171 mg, 0.494 mmol) was dissolved in benzene (15 mL) at room temperature and *t*BuOK (65 mg, 0.580 mmol) added in one portion. After stirring 1.5 hours, the reaction was quenched with aqueous NH_4Cl. Repeated ethyl acetate extractions were performed and the combined organic layers were dried over $MgSO_4$ and concentrated. Column chromatography (ethyl acetate/hexanes 2:3) and concentration provided **80** as a crystalline solid (108 mg, 87%). TLC (ethyl acetate/hexanes 2:3): R_f = 0.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (s, 3H), 0.94 (s, 3H), 0.96–1.04 (m, 2H), 1.35-1.49 (m, 2H), 1.59-1.82 (m, 5H), 1.96-2.07 (m, 2H), 2.04 (s, 3H), 2.36 (dd, J = 5.4, 19.2 Hz, 1H), 4.61 (dd, J = 4.4, 11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.9, 170.4, 79.4, 43.2, 38.7, 36.6, 34.0, 31.2, 26.4, 26.3, 25.1, 21.3, 17.6, 17.1, 14.6; HRMS: *m/z* calcd. for $C_{15}H_{23}O_3$: 251.1642, found: 251.1647 $[M+H]^+$; Crystal data has been deposit with CCDC (CCDC-643516) and can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif:



Crystal data and structure refinement for theod16.

Identification code	theod16	
Empirical formula	C15 H22 O3	
Formula weight	250.33	
Temperature	208(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 8.7451(8) Å	a= 90°.
	b = 15.8027(14) Å	b= 90°.
	c = 19.5008(18) Å	g = 90°.
Volume	2694.9(4) $Å^3$	
Z	8	
Density (calculated)	1.234 Mg/m^3	
Absorption coefficient	0.084 mm^{-1}	
F(000)	1088	
Crystal size	0.35 x 0.25 x 0.20 mm^3	
Theta range for data collection	2.09 to 28.20°.	
Index ranges	-11<=h<=11, -19<=k<=20, -25<=l<=25	
Reflections collected	19970	
Independent reflections	3211 [R(int) = 0.0340]	

Completeness to theta = 28.20°	96.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000 and 0.782
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3211 / 0 / 251
Goodness-of-fit on F^2	1.093
Final R indices [I>2sigma(I)]	R1 = 0.0514, wR2 = 0.1442
R indices (all data)	R1 = 0.0658, wR2 = 0.1532
Largest diff. peak and hole	0.309 and -0.174 e.$Å^{-3}$

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for theod16. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	4000(2)	-472(1)	6218(1)	71(1)
O(2)	11512(1)	2186(1)	6412(1)	47(1)
O(3)	11682(1)	2760(1)	7459(1)	60(1)
C(1)	8966(2)	419(1)	7048(1)	48(1)
C(2)	10446(2)	893(1)	6884(1)	51(1)
C(3)	10085(2)	1758(1)	6591(1)	40(1)
C(4)	9089(2)	1744(1)	5950(1)	35(1)
C(5)	7584(2)	1283(1)	6149(1)	33(1)
C(6)	6401(2)	1258(1)	5575(1)	49(1)
C(7)	4929(2)	833(1)	5806(1)	57(1)
C(8)	5096(2)	-4(1)	6158(1)	47(1)
C(9)	6590(2)	-221(1)	6455(1)	45(1)
C(10)	7902(2)	410(1)	6442(1)	37(1)
C(11)	7955(2)	-332(1)	5972(1)	51(1)
C(12)	9925(2)	1312(1)	5354(1)	47(1)
C(13)	8724(2)	2660(1)	5751(1)	52(1)
C(14)	12158(2)	2683(1)	6887(1)	43(1)
C(15)	13535(2)	3119(1)	6611(1)	51(1)

Bond lengths [Å] and angles [°] for theod16.

O(1)-C(8)	1.2158(19)	C(5)-C(10)	1.5192(18)
O(2)-C(14)	1.3395(18)	C(5)-C(6)	1.524(2)
O(2)-C(3)	1.4609(17)	C(5)-H(5)	0.968(15)
O(3)-C(14)	1.1984(19)	C(6)-C(7)	1.520(2)
C(1)-C(10)	1.504(2)	C(6)-H(6A)	1.034(17)
C(1)-C(2)	1.528(2)	C(6)-H(6B)	0.99(2)
C(1)-H(1A)	1.003(19)	C(7)-C(8)	1.498(3)
C(1)-H(1B)	1.00(2)	C(7)-H(7A)	1.00(2)
C(2)-C(3)	1.515(2)	C(7)-H(7B)	0.99(2)
C(2)-H(2A)	1.02(2)	C(8)-C(9)	1.470(2)
C(2)-H(2B)	0.90(2)	C(9)-C(10)	1.520(2)
C(3)-C(4)	1.525(2)	C(9)-C(11)	1.531(2)
C(3)-H(3)	1.001(16)	C(9)-H(9)	0.90(2)
C(4)-C(13)	1.5311(19)	C(10)-C(11)	1.489(2)
C(4)-C(12)	1.533(2)	C(11)-H(11A)	0.965(19)
C(4)-C(5)	1.5534(19)	C(11)-H(11B)	1.020(18)

C(12)-H(12A)	0.98(2)	C(8)-C(7)-H(7A)	110.2(14)
C(12)-H(12B)	1.01(2)	C(6)-C(7)-H(7A)	112.7(14)
C(12)-H(12C)	1.056(19)	C(8)-C(7)-H(7B)	105.1(12)
C(13)-H(13A)	1.03(2)	C(6)-C(7)-H(7B)	107.3(12)
C(13)-H(13B)	0.98(2)	H(7A)-C(7)-H(7B)	104.1(19)
C(13)-H(13C)	0.97(2)	O(1)-C(8)-C(9)	121.41(16)
C(14)-C(15)	1.487(2)	O(1)-C(8)-C(7)	120.27(16)
C(15)-H(15A)	0.98(3)	C(9)-C(8)-C(7)	118.24(13)
C(15)-H(15B)	0.89(3)	C(8)-C(9)-C(10)	120.75(13)
C(15)-H(15C)	0.88(3)	C(8)-C(9)-C(11)	118.45(15)
C(14)-O(2)-C(3)	117.80(11)	C(10)-C(9)-C(11)	58.42(9)
C(10)-C(1)-C(2)	111.35(13)	C(8)-C(9)-H(9)	113.9(13)
C(10)-C(1)-H(1A)	108.0(11)	C(10)-C(9)-H(9)	119.1(13)
C(2)-C(1)-H(1A)	109.5(11)	C(11)-C(9)-H(9)	114.8(13)
C(10)-C(1)-H(1B)	106.6(13)	C(11)-C(10)-C(1)	118.21(14)
C(2)-C(1)-H(1B)	113.6(13)	C(11)-C(10)-C(5)	119.26(13)
H(1A)-C(1)-H(1B)	107.5(17)	C(1)-C(10)-C(5)	113.56(12)
C(3)-C(2)-C(1)	110.18(13)	C(11)-C(10)-C(9)	61.17(10)
C(3)-C(2)-H(2A)	111.6(11)	C(1)-C(10)-C(9)	117.39(13)
C(1)-C(2)-H(2A)	107.6(11)	C(5)-C(10)-C(9)	117.64(12)
C(3)-C(2)-H(2B)	108.7(12)	C(10)-C(11)-C(9)	60.40(9)
C(1)-C(2)-H(2B)	108.3(12)	C(10)-C(11)-H(11A)	120.3(11)
H(2A)-C(2)-H(2B)	110.5(16)	C(9)-C(11)-H(11A)	115.6(11)
O(2)-C(3)-C(2)	109.26(12)	C(10)-C(11)-H(11B)	118.2(10)
O(2)-C(3)-C(4)	107.38(11)	C(9)-C(11)-H(11B)	113.4(11)
C(2)-C(3)-C(4)	114.48(13)	H(11A)-C(11)-H(11B)	116.3(15)
O(2)-C(3)-H(3)	108.4(9)	C(4)-C(12)-H(12A)	110.9(12)
C(2)-C(3)-H(3)	108.6(9)	C(4)-C(12)-H(12B)	109.0(10)
C(4)-C(3)-H(3)	108.5(9)	H(12A)-C(12)-H(12B)	108.7(15)
C(3)-C(4)-C(13)	108.25(12)	C(4)-C(12)-H(12C)	108.9(10)
C(3)-C(4)-C(12)	110.82(12)	H(12A)-C(12)-H(12C)	109.5(15)
C(13)-C(4)-C(12)	109.18(13)	H(12B)-C(12)-H(12C)	109.9(14)
C(3)-C(4)-C(5)	106.63(10)	C(4)-C(13)-H(13A)	110.3(12)
C(13)-C(4)-C(5)	109.29(12)	C(4)-C(13)-H(13B)	112.6(11)
C(12)-C(4)-C(5)	112.56(11)	H(13A)-C(13)-H(13B)	108.3(16)
C(10)-C(5)-C(6)	112.17(12)	C(4)-C(13)-H(13C)	109.5(12)
C(10)-C(5)-C(4)	111.43(11)	H(13A)-C(13)-H(13C)	110.7(17)
C(6)-C(5)-C(4)	113.81(11)	H(13B)-C(13)-H(13C)	105.4(16)
C(10)-C(5)-H(5)	106.8(9)	O(3)-C(14)-O(2)	123.85(14)
C(6)-C(5)-H(5)	106.1(9)	O(3)-C(14)-C(15)	124.81(15)
C(4)-C(5)-H(5)	105.9(9)	O(2)-C(14)-C(15)	111.34(14)
C(7)-C(6)-C(5)	111.64(14)	C(14)-C(15)-H(15A)	110.1(18)
C(7)-C(6)-H(6A)	107.4(9)	C(14)-C(15)-H(15B)	106.9(19)
C(5)-C(6)-H(6A)	111.1(9)	H(15A)-C(15)-H(15B)	108(2)
C(7)-C(6)-H(6B)	109.1(12)	C(14)-C(15)-H(15C)	110.1(17)
C(5)-C(6)-H(6B)	107.6(11)	H(15A)-C(15)-H(15C)	108(2)
H(6A)-C(6)-H(6B)	109.9(14)	H(15B)-C(15)-H(15C)	114(2)
C(8)-C(7)-C(6)	116.36(15)		

Symmetry transformations used to generate equivalent atoms:

Anisotropic displacement parameters ($Å^2 x\ 10^3$) for theod16. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	48(1)	68(1)	97(1)	-13(1)	15(1)	-22(1)
O(2)	30(1)	63(1)	47(1)	-9(1)	7(1)	-10(1)
O(3)	52(1)	85(1)	43(1)	-7(1)	0(1)	-20(1)
C(1)	38(1)	58(1)	48(1)	16(1)	1(1)	4(1)
C(2)	34(1)	67(1)	52(1)	13(1)	-2(1)	3(1)
C(3)	28(1)	52(1)	41(1)	-6(1)	6(1)	-5(1)
C(4)	35(1)	34(1)	36(1)	0(1)	2(1)	1(1)
C(5)	31(1)	33(1)	36(1)	-4(1)	1(1)	2(1)
C(6)	45(1)	53(1)	50(1)	5(1)	-12(1)	-7(1)
C(7)	42(1)	62(1)	68(1)	-2(1)	-13(1)	-7(1)
C(8)	40(1)	48(1)	55(1)	-18(1)	11(1)	-10(1)
C(9)	45(1)	36(1)	54(1)	-1(1)	12(1)	-3(1)
C(10)	32(1)	39(1)	40(1)	-1(1)	8(1)	1(1)
C(11)	46(1)	36(1)	70(1)	-9(1)	17(1)	-1(1)
C(12)	50(1)	54(1)	38(1)	-5(1)	13(1)	-8(1)
C(13)	48(1)	38(1)	71(1)	8(1)	-3(1)	-4(1)
C(14)	32(1)	51(1)	45(1)	0(1)	-4(1)	-3(1)
C(15)	34(1)	58(1)	60(1)	7(1)	-5(1)	-7(1)

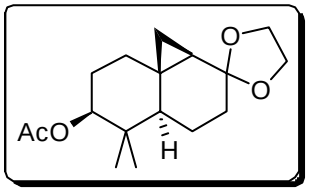
Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for theod16.

	x	y	z	U(eq)
H(1A)	8430(20)	707(11)	7438(10)	55(5)
H(1B)	9130(30)	-185(15)	7183(11)	79(6)
H(2A)	11060(20)	936(12)	7328(10)	61(5)
H(2B)	10970(20)	594(12)	6567(10)	53(5)
H(3)	9553(18)	2100(10)	6951(8)	40(4)
H(5)	7134(18)	1615(10)	6514(7)	35(4)
H(6A)	6805(19)	926(11)	5156(9)	48(4)
H(6B)	6180(20)	1848(13)	5443(9)	62(5)
H(7A)	4150(30)	792(16)	5430(12)	87(7)
H(7B)	4450(30)	1208(13)	6149(11)	69(6)
H(9)	6540(20)	-600(13)	6798(11)	65(6)
H(11A)	8620(20)	-805(12)	6071(9)	53(5)
H(11B)	7690(20)	-240(11)	5468(10)	57(5)
H(12A)	9280(20)	1299(12)	4941(11)	63(5)
H(12B)	10890(20)	1639(12)	5247(9)	58(5)
H(12C)	10200(20)	687(13)	5500(10)	59(5)
H(13A)	8170(30)	2677(13)	5286(12)	72(6)
H(13B)	9640(20)	3012(12)	5719(9)	57(5)
H(13C)	8100(20)	2918(13)	6106(11)	66(6)
H(15A)	13900(40)	2830(19)	6199(15)	115(10)
H(15B)	13240(30)	3640(18)	6491(14)	105(9)
H(15C)	14280(30)	3111(17)	6918(14)	101(8)

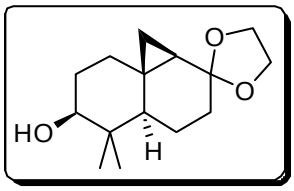
Torsion angles [°] for theod16.

C(10)-C(1)-C(2)-C(3)	51.8(2)	C(14)-O(2)-C(3)-C(2)	-91.97(16)

C(14)-O(2)-C(3)-C(4)	143.33(13)	C(2)-C(1)-C(10)-C(9)	164.29(14)
C(1)-C(2)-C(3)-O(2)	-177.69(13)	C(6)-C(5)-C(10)-C(11)	38.15(18)
C(1)-C(2)-C(3)-C(4)	-57.24(19)	C(4)-C(5)-C(10)-C(11)	-90.78(15)
O(2)-C(3)-C(4)-C(13)	-62.90(15)	C(6)-C(5)-C(10)-C(1)	-175.19(13)
C(2)-C(3)-C(4)-C(13)	175.62(13)	C(4)-C(5)-C(10)-C(1)	55.89(15)
O(2)-C(3)-C(4)-C(12)	56.80(14)	C(6)-C(5)-C(10)-C(9)	-32.55(17)
C(2)-C(3)-C(4)-C(12)	-64.68(16)	C(4)-C(5)-C(10)-C(9)	-161.48(12)
O(2)-C(3)-C(4)-C(5)	179.61(10)	C(8)-C(9)-C(10)-C(11)	-106.56(17)
C(2)-C(3)-C(4)-C(5)	58.13(15)	C(8)-C(9)-C(10)-C(1)	144.63(15)
C(3)-C(4)-C(5)-C(10)	-55.55(14)	C(11)-C(9)-C(10)-C(1)	-108.81(16)
C(13)-C(4)-C(5)-C(10)	-172.34(13)	C(8)-C(9)-C(10)-C(5)	3.4(2)
C(12)-C(4)-C(5)-C(10)	66.17(15)	C(11)-C(9)-C(10)-C(5)	109.98(15)
C(3)-C(4)-C(5)-C(6)	176.40(12)	C(1)-C(10)-C(11)-C(9)	107.49(15)
C(13)-C(4)-C(5)-C(6)	59.60(16)	C(5)-C(10)-C(11)-C(9)	-107.37(15)
C(12)-C(4)-C(5)-C(6)	-61.88(16)	C(8)-C(9)-C(11)-C(10)	110.46(15)
C(10)-C(5)-C(6)-C(7)	54.71(18)	C(3)-O(2)-C(14)-O(3)	4.4(2)
C(4)-C(5)-C(6)-C(7)	-177.62(13)	C(3)-O(2)-C(14)-C(15)	-175.93(13)
C(5)-C(6)-C(7)-C(8)	-49.2(2)		
C(6)-C(7)-C(8)-O(1)	-163.25(17)		
C(6)-C(7)-C(8)-C(9)	19.8(2)		
O(1)-C(8)-C(9)-C(10)	-173.42(15)		
C(7)-C(8)-C(9)-C(10)	3.5(2)		
O(1)-C(8)-C(9)-C(11)	118.34(17)		
C(7)-C(8)-C(9)-C(11)	-64.73(19)		
C(2)-C(1)-C(10)-C(11)	94.07(17)		
C(2)-C(1)-C(10)-C(5)	-52.97(18)		

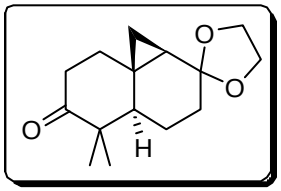


Compound 93: **80** (50 mg, 0.23 mmol), ethylene glycol (0.014 mL, 0.25 mmol), and *p*-toluenesulfonic acid (trace, 1 crystall) were dissolved in benzene (10 mL) and refluxed 5 hours under a Dean-Stark trap. After cooling to room temperature, triethylamine was added and the reaction concentrated. Column chromatography of the resultant oil provided **93** (30 mg, 60%) as an oil. TLC (ethyl acetate/hexanes 3:2): R_f = 0.7; CRUDE ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.4-0.5 (dd, 1H), 0.7-2.1 (m, 28H), 3.8-4.0 (m, 4H), 4.6 (dd, 1H); ESI-MS: *m/z* calcd. for $C_{17}H_{27}O_4$: 294.2, found: 294.4 $[M+H]^+$.

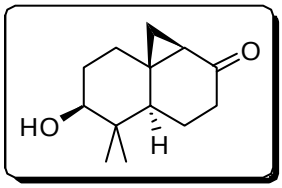


Compound 94: **93** (32 mg, 0.11 mmol) was stirred in methanol (1 mL) with potassium carbonate (17.1 mg, 0.12 mmol) overnight at room temperature. Dilution with water, ether extraction, drying of the combined ether layers, and concentration gave an oil which was purified by column chromatography. After concentration, **94** (26 mg , 92%) was obtained as an oil. TLC (ethyl acetate/hexanes 3:2): R_f = 06; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.42 (dd, J = 5.2,

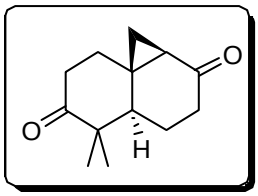
9.6 Hz, 1H), 0.78 (dt, 1.6, 5.2 Hz, 1H), 0.82 (s, 3H), 0.85 (m, 1H), 0.90 (s, 3H), 1.02 (dd, J = 3.2, 12.4 Hz, 1H), 1.37-1.9 (m, 10H), 3.33 (dd, J = 4.4, 11.6 Hz, 1H), 3.85-4.02 (m, 4H); ESI-MS: *m/z* calcd. for $C_{15}H_{25}O_3$: 253.2, found: 253.2 $[M+H]^+$.



Compound 95: To a stirred solution of **94** (28 mg, 0.11 mmol) in dichloromethane (3 mL), was added Dess-Martin periodinane (55 mg, 0.13 mmol) at room temperature. Prior to drying over $Mgso_4$ the reaction was partitioned between water and ether after stirring 5 hours. Concentration and silica chromatography provided **95** (15 mg , 55%). TLC (ethyl acetate/hexanes 4:2): R_f= 0.6; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.67 (dd, J = 5.4, 9.8 Hz, 1H), 0.96 (d, J = 9.6 Hz, 1H), 1.01 (m, 1H), 1.08 (s, 3H), 1.11 (s, 3H), 1.14-1.22 (m, 1H), 1.47-1.86 (m, 2H), 2.13 (m, 1H), 2.30 (m, 1H), 2.75 (m, 1H), 3.88-4.06 (m, 4H); APCI-MS: *m/z* calcd. for $C_{15}H_{23}O_3$: 251.2, found: 251.0 $[M+H]^+$.

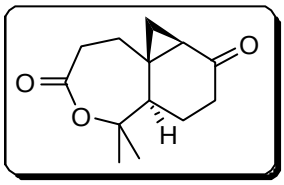


Compound 96: Acetate **80** (260 mg, 1.039 mmol) was dissolved in methanol (8 mL) at room temperature and K_2CO_3 (150 mg, 1.090 mmol) added in one portion. After stirring 12 hours, the reaction was quenched with aqueous NH_4Cl. Repeated ethyl acetate extractions were performed and the combined organic layers were dried over $MgSO_4$ and concentrated. Column chromatography (ethyl acetate/hexanes 3:2) provided the free alcohol **96** as an amorphous solid (194 mg, 90%). TLC (ethyl acetate/hexanes 3:2): R_f= 0.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (s, 3H), 0.96-1.05 (m, 2H), 1.06 (s, 3H), 1.36-1.48 (m, 3H), 1.59-1.82 (m, 6H), 1.93-2.09 (m, 2H), 2.38 (ddd, J = 1.6, 5.6, 19.2 Hz, 1H), 3.39 (dd, J = 4.0, 11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.7, 78.0, 43.1, 39.8, 36.6, 34.4, 31.3, 29.7, 26.7, 25.1, 17.6, 17.2, 13.3; HRMS: *m/z* calcd. for $C_{13}H_{21}O_2$: 209.1536, found: 209.1539 $[M+H]^+$.

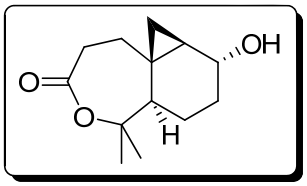


Compound 97: Alcohol **96** (180 mg, 0.865 mmol) was dissolved in dichloromethane (10 mL) and Dess-Martin Periodinane (473 mg, 1.116 mmol) added at room temperature. After stirring 1.5 hours the reaction was diluted with 25 mL diethyl ether, and a $Na_2S_2O_3$ solution (500mg $Na_2S_2O_3$ in 20 mL aqueous saturated $NaHCO_3$) was added. After stirring 20 minutes, this solution was diluted with 50 mL diethyl ether. After vigorous stirring, the ether layer was collected and washed with water (2 x 5 mL). The ether layer was dried over $MgSO_4$ and concentrated. Column chromatography (ethyl acetate/hexanes 1:1) provided diketone **97** as a white solid (173 mg, 97%). TLC (ethyl acetate/hexanes 4:1): R_f= 0.5; ^{1}H NMR

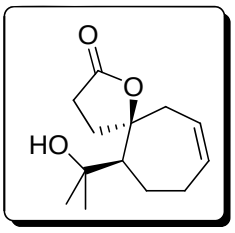
(400 MHz, $CDCl_3$): δ 1.13 (s, 3H), 1.17 (s, 3H), 1.18-1.24 (m, 1H), 1.32 (ddd, J = 2.0, 6.4, 13.2 Hz, 1H), 1.52-1.75 (m, 4H), 1.99 (dd, J = 4.0, 12.8 Hz, 1H), 2.03-2.14 (m, 1H), 2.19-2.28 (m, 1H), 2.35 (ddd, J = 2.2, 4.4, 13.6 Hz, 1H), 2.43 (ddd, J = 2.0, 5.6, 19.2 1H), 2.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.0, 207.3, 49.1, 44.2, 36.8, 36.1, 35.4, 31.2, 26.0, 21.9, 20.5, 18.0, 16.4; HRMS: *m/z* calcd. for $C_{13}H_{19}O_2$: 207.1380, found: 207.1372 $[M+H]^+$.



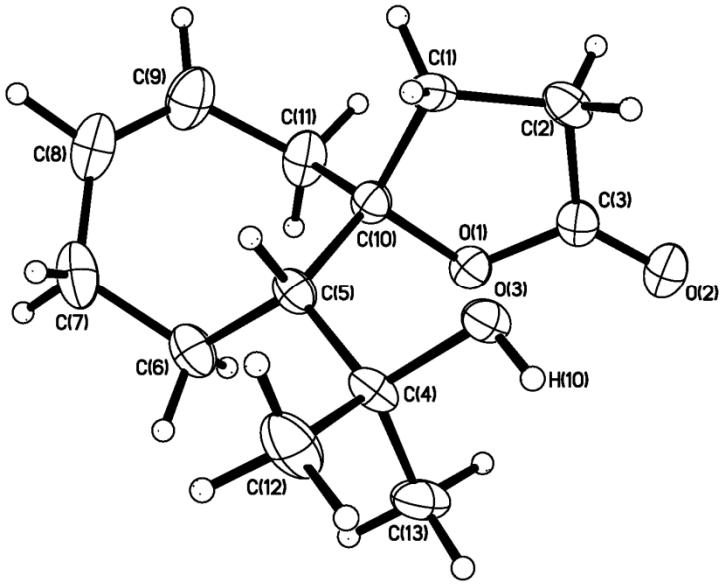
Compound 98: A dichloromethane (20 mL) solution of **97** (152 mg, 0.738 mmol) was cooled to 0°C. *m*CPBA (190 mg, 1.103 mmol) was added in one portion, followed rapidly by solid $NaHCO_3$ (123 mg, 1.461 mmol). Stirring was continued for 6 hours at 0°C, after which, 5 mL saturated aqueous $NaHCO_3$ was added and the reaction allowed to warm to room temperature with stirring. The aqueous layer was discarded and the organic layer collected, diluted with 50 mL ethyl acetate, and washed with saturated aqueous $NaHCO_3$ (2 x 10 mL). The aqueous layers were combined and washed with ethyl acetate (3 x 30 mL). All organic layers were combined, dried over $MgSO_4$, and concentrated. Column chromatography (acetone/ethyl acetate 1:9) provided the keto-lactone **98** (163 mg, 95%). TLC (ethyl acetate/hexanes 4:1): R_f = 0.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98-1.06 (m, 1H), 1.17 (dd, J = 5.4, 10.2 Hz, 1H), 1.23-1.36 (m, 1H), 1.47 (s, 3H), 1.47-1.55 (m, 2H), 1.55 (s, 3H), 1.81-1.90 (m, 1H), 2.08-2.19 (m, 1H), 2.25-2.44 (m, 3H), 2.72-2.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.3, 173.9, 85.6, 46.0, 36.4, 35.1, 34.4, 33.4, 31.2, 27.9, 21.9, 21.5, 15.8; HRMS: *m/z* calcd. for $C_{13}H_{19}O_3$: 223.1329, found: 223.1333 $[M+H]^+$.



Compound 99: Ketolactone **98** (19 mg, 0.086 mmol) was dissolved in THF (1 mL), cooled to 0°C, and $NaBH_4$ (1.5 mg, 0.039 mmol) was added in one portion. The reaction temperature was maintained at 0°C and monitored by ^{1}HNMR (starting material and product co-spot under the chosen TLC conditions). After 5 hours, a small amount of silica gel was added and the solvent evaporated at room temperature under reduced pressure. Column chromatography (ethyl acetate 100%) provided hydroxylactone **99** (16 mg, 85%). TLC (ethyl acetate/hexanes 4:1): R_f = 0.2; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.42-0.47 (m, 1H), 0.60-0.96 (m, 4H), 1.09-1.27 (m, 1H), 1.39 (s, 3H), 1.46 (s, 3H), 1.59-1.63 (m, 1H), 1.89-1.99 (m, 1H), 2.06-2.25 (m, 3H), 2.61-2.73 (m, 2H), 3.76 (dd, J = 6.3, 10.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8, 86.8, 68.7, 48.2, 36.2, 35.4, 33.0, 31.0, 27.6, 24.1, 22.5, 21.5, 14.2; IR (film): ν_{max} 1709; HRMS: *m/z* calcd. for $C_{13}H_{21}O_3$: 225.1485, found: 225.1488 $[M+H]^+$.



Compound 100: To a stirred acetonitrile (0.15 mL) solution of compound **99** (3.5 mg, 0.015 mmol), was added a 7% $HClO_4$ (0.2 mL, 0.014 mmol) aqueous solution at room temperature. After stirring 1.5 hours, the solution was diluted with diethyl ether and H_2O. Solid sodium carbonate was added in portions at 0°C, with stirring, until the solution tested neutral by pH paper. The ether layer was collected and repeated ether extractions performed until no product remained in the aqueous layer by TLC. The combined organic layers were dried over $MgSO_4$ and concentrated. Column chromatography (ethyl acetate/hexanes, 1:2) was performed to yield **100** as an amorphous solid (2.5 mg, 75%). TLC (ethyl acetate/hexanes, 3:2): $R_f = 0.45$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (s, 3H), 1.36 (s, 3H), 1.64–1.71 (m, 1H), 1.80–1.87 (bs, 1H), 1.88–2.15 (m, 4H), 2.49–2.33 (m, 1H), 2.36–2.44 (m, 1H), 2.48–2.63 (m, 3H), 3.07–3.12 (m, 1H), 5.43–5.50 (m, 1H), 5.59–5.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 131.8, 122.7, 92.2, 74.7, 56.1, 37.0, 35.2, 32.1, 30.8, 28.1, 26.7, 25.5; IR (film): ν_{max} 1755; HRMS: *m/z* calcd. for $C_{13}H_{20}O_3$: 225.1492, found: 225.1488 $[M+H]^+$; Crystal data has been deposited with CCDC (CCDC-643492) and can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif:



Crystal data and structure refinement for theod17.

Identification code	theod17	
Empirical formula	C13 H20 O3	
Formula weight	224.29	
Temperature	208(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 26.153(3) Å	□= 90°.
	b = 8.1060(10) Å	□= 118.628(2)°.
	c = 13.3801(16) Å	□ = 90°.
Volume	2489.8(5) Å^3	
Z	4	
Density (calculated)	1.197 Mg/m^3	
Absorption coefficient	0.083 mm^{-1}	
F(000)	976	
Crystal size	0.40 x 0.21 x 0.03 mm^3	
Theta range for data collection	1.77 to 28.20°.	
Index ranges	-34<=h<=32, -9<=k<=10, -17<=l<=17	
Reflections collected	9204	
Independent reflections	2896 [R(int) = 0.0286]	
Completeness to theta = 28.20°	94.3 %	
Absorption correction	Muti-scan	
Max. and min. transmission	1.000 and 0.692	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2896 / 0 / 225	
Goodness-of-fit on F^2	0.959	
Final R indices [I>2sigma(I)]	R1 = 0.0663, wR2 = 0.1856	
R indices (all data)	R1 = 0.0918, wR2 = 0.2063	
Largest diff. peak and hole	0.253 and -0.147 e.Å^{-3}	

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for theod17. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	2113(1)	1601(2)	1800(1)	44(1)
O(2)	2945(1)	1086(2)	1820(1)	60(1)
O(3)	1610(1)	2157(2)	-571(1)	44(1)
C(1)	1512(1)	-586(3)	625(2)	53(1)
C(2)	2132(1)	-808(3)	883(2)	55(1)
C(3)	2450(1)	691(3)	1522(2)	45(1)
C(4)	1330(1)	3330(3)	-197(2)	46(1)
C(5)	1100(1)	2351(3)	496(2)	43(1)
C(6)	866(1)	3472(4)	1102(2)	60(1)
C(7)	323(1)	2786(5)	1102(3)	76(1)
C(8)	348(1)	1034(5)	1491(3)	77(1)
C(9)	807(1)	77(5)	1984(2)	78(1)
C(10)	1514(1)	992(3)	1280(2)	42(1)
C(11)	1421(1)	574(4)	2297(2)	63(1)
C(12)	821(2)	4060(5)	-1253(3)	76(1)

C(13)	1771(2)	4691(3)	473(3)	63(1)

Bond lengths [Å] and angles [°] for theod17.

O(1)-C(3)	1.331(3)	C(1)-C(2)-H(2B)	114.8(18)
O(1)-C(10)	1.462(3)	H(2A)-C(2)-H(2B)	108(3)
O(2)-C(3)	1.202(3)	O(2)-C(3)-O(1)	120.8(2)
O(3)-C(4)	1.427(3)	O(2)-C(3)-C(2)	128.6(2)
O(3)-H(1O)	0.82(3)	O(1)-C(3)-C(2)	110.5(2)
C(1)-C(2)	1.499(4)	O(3)-C(4)-C(12)	107.5(2)
C(1)-C(10)	1.549(3)	O(3)-C(4)-C(13)	108.4(2)
C(1)-H(1A)	0.97(3)	C(12)-C(4)-C(13)	109.9(2)
C(1)-H(1B)	1.05(3)	O(3)-C(4)-C(5)	106.27(17)
C(2)-C(3)	1.489(4)	C(12)-C(4)-C(5)	109.7(2)
C(2)-H(2A)	1.04(3)	C(13)-C(4)-C(5)	114.69(19)
C(2)-H(2B)	0.92(3)	C(6)-C(5)-C(4)	112.6(2)
C(4)-C(12)	1.523(3)	C(6)-C(5)-C(10)	113.01(18)
C(4)-C(13)	1.536(4)	C(4)-C(5)-C(10)	115.14(18)
C(4)-C(5)	1.545(3)	C(6)-C(5)-H(5)	105.4(13)
C(5)-C(6)	1.529(3)	C(4)-C(5)-H(5)	104.1(13)
C(5)-C(10)	1.548(3)	C(10)-C(5)-H(5)	105.4(14)
C(5)-H(5)	0.99(2)	C(7)-C(6)-C(5)	113.2(2)
C(6)-C(7)	1.523(4)	C(7)-C(6)-H(6A)	111.6(16)
C(6)-H(6A)	1.03(3)	C(5)-C(6)-H(6A)	109.0(16)
C(6)-H(6B)	0.99(3)	C(7)-C(6)-H(6B)	103.4(18)
C(7)-C(8)	1.503(5)	C(5)-C(6)-H(6B)	112.6(18)
C(7)-H(7A)	0.95(3)	H(6A)-C(6)-H(6B)	107(2)
C(7)-H(7A)	1.03(4)	C(8)-C(7)-C(6)	117.4(3)
C(8)-C(9)	1.312(5)	C(8)-C(7)-H(7A)	104.4(19)
C(8)-H(8)	1.03(3)	C(6)-C(7)-H(7A)	107.4(18)
C(9)-C(11)	1.508(4)	C(8)-C(7)-H(7A)	107(2)
C(9)-H(9)	0.98(3)	C(6)-C(7)-H(7A)	110(2)
C(10)-C(11)	1.530(3)	H(7A)-C(7)-H(7A)	111(3)
C(11)-H(11A)	1.04(3)	C(9)-C(8)-C(7)	127.5(3)
C(11)-H(11B)	0.98(3)	C(9)-C(8)-H(8)	117.9(18)
C(12)-H(12A)	0.99(4)	C(7)-C(8)-H(8)	114.4(18)
C(12)-H(12B)	1.01(5)	C(8)-C(9)-C(11)	125.4(3)
C(12)-H(12C)	1.02(4)	C(8)-C(9)-H(9)	116.6(17)
C(13)-H(13A)	1.10(4)	C(11)-C(9)-H(9)	118.0(17)
C(13)-H(13B)	0.99(3)	O(1)-C(10)-C(11)	104.03(17)
C(13)-H(13C)	0.95(4)	O(1)-C(10)-C(5)	108.94(17)
C(3)-O(1)-C(10)	112.46(17)	C(11)-C(10)-C(5)	113.8(2)
C(4)-O(3)-H(1O)	104.6(19)	O(1)-C(10)-C(1)	105.11(17)
C(2)-C(1)-C(10)	104.99(19)	C(11)-C(10)-C(1)	111.1(2)
C(2)-C(1)-H(1A)	111.7(16)	C(5)-C(10)-C(1)	113.07(17)
C(10)-C(1)-H(1A)	108.3(17)	C(9)-C(11)-C(10)	114.5(2)
C(2)-C(1)-H(1B)	112.7(15)	C(9)-C(11)-H(11A)	109.3(16)
C(10)-C(1)-H(1B)	111.1(14)	C(10)-C(11)-H(11A)	107.5(16)
H(1A)-C(1)-H(1B)	108(2)	C(9)-C(11)-H(11B)	111.3(17)
C(3)-C(2)-C(1)	106.2(2)	C(10)-C(11)-H(11B)	104.8(18)
C(3)-C(2)-H(2A)	105.8(17)	H(11A)-C(11)-H(11B)	109(2)
C(1)-C(2)-H(2A)	114.0(17)	C(4)-C(12)-H(12A)	110(2)
C(3)-C(2)-H(2B)	107.5(19)	C(4)-C(12)-H(12B)	118(2)

H(12A)-C(12)-H(12B)	106(3)	C(4)-C(13)-H(13B)	108.7(15)
C(4)-C(12)-H(12C)	109(2)	H(13A)-C(13)-H(13B)	111(2)
H(12A)-C(12)-H(12C)	114(3)	C(4)-C(13)-H(13C)	107(2)
H(12B)-C(12)-H(12C)	100(3)	H(13A)-C(13)-H(13C)	112(3)
C(4)-C(13)-H(13A)	110.8(18)	H(13B)-C(13)-H(13C)	107(3)

Symmetry transformations used to generate equivalent atoms:

Anisotropic displacement parameters ($Å^2 x\ 10^3$) for theod17. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	39(1)	49(1)	38(1)	1(1)	13(1)	0(1)
O(2)	45(1)	82(1)	50(1)	17(1)	22(1)	5(1)
O(3)	57(1)	37(1)	43(1)	1(1)	28(1)	4(1)
C(1)	57(1)	33(1)	67(2)	3(1)	28(1)	-1(1)
C(2)	61(2)	43(1)	58(1)	10(1)	26(1)	16(1)
C(3)	43(1)	53(1)	38(1)	15(1)	18(1)	10(1)
C(4)	58(1)	36(1)	42(1)	3(1)	23(1)	14(1)
C(5)	43(1)	45(1)	36(1)	-2(1)	13(1)	8(1)
C(6)	62(2)	61(2)	57(1)	-7(1)	29(1)	14(1)
C(7)	53(2)	107(3)	71(2)	-13(2)	31(2)	16(2)
C(8)	48(2)	122(3)	62(2)	4(2)	28(1)	-2(2)
C(9)	63(2)	110(3)	65(2)	27(2)	35(1)	0(2)
C(10)	38(1)	45(1)	40(1)	6(1)	16(1)	3(1)
C(11)	51(1)	88(2)	49(1)	20(1)	25(1)	8(1)
C(12)	85(2)	79(2)	59(2)	28(2)	32(2)	40(2)
C(13)	95(2)	35(1)	70(2)	-4(1)	48(2)	-2(1)

Hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for theod17.

	x	y	z	U(eq)
H(1A)	1379(12)	-1500(40)	910(20)	67(8)
H(1B)	1225(11)	-460(30)	-250(20)	57(7)
H(1O)	1732(11)	2710(30)	-930(20)	55(8)
H(2A)	2187(13)	-850(40)	170(30)	78(9)
H(2B)	2317(13)	-1710(40)	1330(30)	74(9)
H(5)	755(10)	1760(30)	-90(20)	45(6)
H(6A)	1194(12)	3700(30)	1920(30)	65(8)
H(6B)	735(13)	4550(40)	730(30)	76(9)
H(7A)	20(13)	2790(40)	340(30)	71(9)
H(7A)	214(16)	3500(50)	1610(40)	107(12)
H(8)	-52(15)	530(40)	1290(30)	82(9)
H(9)	744(12)	-1030(40)	2200(30)	74(9)
H(11A)	1703(13)	-380(40)	2740(30)	66(8)
H(11B)	1539(13)	1570(40)	2770(30)	68(9)
H(12A)	965(16)	4680(50)	-1710(30)	100(11)
H(12B)	551(19)	4840(60)	-1140(30)	125(14)
H(12C)	534(16)	3150(40)	-1700(30)	90(11)

H(13A)	2171(15)	4160(40)	1170(30)	94(11)
H(13B)	1854(11)	5340(30)	-60(20)	56(7)
H(13C)	1585(16)	5420(50)	760(30)	102(12)

Torsion angles [°] for theod17.

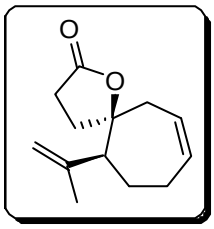
C(10)-C(1)-C(2)-C(3)	-7.0(2)	C(3)-O(1)-C(10)-C(5)	-118.88(18)
C(10)-O(1)-C(3)-O(2)	175.22(18)	C(3)-O(1)-C(10)-C(1)	2.6(2)
C(10)-O(1)-C(3)-C(2)	-7.3(2)	C(6)-C(5)-C(10)-O(1)	-92.0(2)
C(1)-C(2)-C(3)-O(2)	-173.7(2)	C(4)-C(5)-C(10)-O(1)	39.3(2)
C(1)-C(2)-C(3)-O(1)	9.1(3)	C(6)-C(5)-C(10)-C(11)	23.5(3)
O(3)-C(4)-C(5)-C(6)	171.68(18)	C(4)-C(5)-C(10)-C(11)	154.8(2)
C(12)-C(4)-C(5)-C(6)	-72.4(3)	C(6)-C(5)-C(10)-C(1)	151.5(2)
C(13)-C(4)-C(5)-C(6)	51.9(3)	C(4)-C(5)-C(10)-C(1)	-77.2(2)
O(3)-C(4)-C(5)-C(10)	40.2(2)	C(2)-C(1)-C(10)-O(1)	3.1(2)
C(12)-C(4)-C(5)-C(10)	156.1(2)	C(2)-C(1)-C(10)-C(11)	-108.8(2)
C(13)-C(4)-C(5)-C(10)	-79.6(2)	C(2)-C(1)-C(10)-C(5)	121.8(2)
C(4)-C(5)-C(6)-C(7)	141.8(2)	C(8)-C(9)-C(11)-C(10)	-64.4(5)
C(10)-C(5)-C(6)-C(7)	-85.6(3)	O(1)-C(10)-C(11)-C(9)	173.9(3)
C(5)-C(6)-C(7)-C(8)	50.5(4)	C(5)-C(10)-C(11)-C(9)	55.5(4)
C(6)-C(7)-C(8)-C(9)	10.3(5)	C(1)-C(10)-C(11)-C(9)	-73.4(3)
C(7)-C(8)-C(9)-C(11)	1.9(5)		
C(3)-O(1)-C(10)-C(11)	119.5(2)		

Symmetry transformations used to generate equivalent atoms:

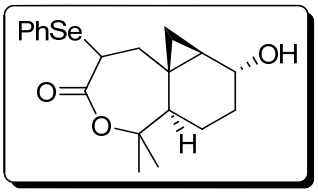
Hydrogen bonds for theod17 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(3)-H(1O)...O(2)#1	0.82(3)	2.01(3)	2.836(2)	176(3)

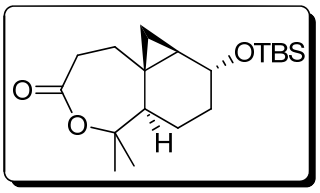
Symmetry transformations used to generate equivalent atoms:
#1 -x+1/2,-y+1/2,-z



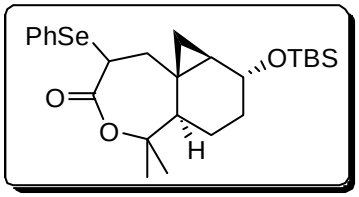
Compound 101: Olefin **101** was isolated as a side product of the reaction which produced **100**. In the synthesis of **100**, extended reaction times produced olefin **101** (up to 80% TLC yield). Alternatively, treatment of **100** with acid produced **101**. TLC (ethyl acetate/hexanes 2:3): R_f=0.7; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56–1.64 (m, 2H), 1.74 (s, 3H), 1.89–2.03 (m, 2H), 2.10–2.20 (m, 1H), 2.28–2.70 (m, 7H), 4.78 (s, 1H), 4.85 (s, 1H), 5.53–5.60 (m, 1H), 5.84–5.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6, 146.7, 133.4, 124.3, 114.2, 88.0, 57.1, 38.5, 32.8, 28.7, 286, 27.6, 21.8; HRMS: *m/z* calcd. for $C_{13}H_{18}O_2$: 207.1487, found: 207.1490 $[M+H]^+$.



Compound 99b: Alcohol **99** (8 mg, 0.036 mmol) was dissolved in THF (1 mL) and cooled to -78°C before adding LiHMDS (0.125 mL of 1.0 M THF solution, 0.125 mmol). After stirring 30 minutes, PhSeBr (0.23 mL as a 0.39 mmol/mL THF solution, 0.089 mmol) was added in one portion. The reaction was stirred 30 minutes before water addition followed by aqueous NH_4Cl (saturated). The reaction was extracted with ethyl acetate and dried over $MgSO_4$ before concentration. Silica filtration provided **99b** (2 mg, 15%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.06 (m, 1H), 0.30 (m, 1H), 0.54 (dd, J = 2.2, 10.2 Hz, 1H), 0.62 (m, 1H), 0.88 (m, 1H), 0.99 (m, 1H), 1.12 (m, 1H), 1.43 (s, 3H), 1.49 (s, 3H), 1.52 (m, 1H), 1.91 (m, 1H), 2.15 (dd, J = 4.2, 12.6 Hz, 1H), 2.43 (m, 1H), 3.67 (m, 1H), 4.29 (m, 1H), 7.30 (m, 3H), 7.56 (d, J = 7.6 Hz, 2H); ESI-MS: *m/z* calcd. for $C_{19}H_{25}O_3Se$: 381.1, found: 381.2 $[M+H]^+$.

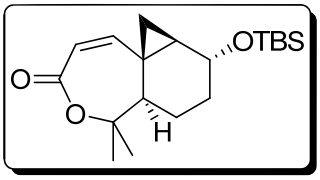


Compound 102: **99** (65 mg, 0.29 mmol) was dissolved in dimethylformamide (2 mL) at room temperature. Imidazole (60 mg, 0.89 mmol) and DMAP (6 mg, 0.5 mmol) were added in single portions before TBSCl (88 mg, 0.58 mmol) addition. The reaction was stirred 1.5 hours before adding water and partitioning with ether. The residue was dried over $MgSO_4$ and concentrated prior to purification. Column chromatography provided **102** (90 mg, 92%). TLC (ethyl acetate/hexanes 3:2): R_f = 0.7; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.40 (m, 1H), 0.57-0.69 (m, 2H), 0.77 (m, 1H), 0.86-0.92 (m, 10H), 1.20 (m, 1H), 1.39 (s, 3H), 1.45 (s, 3H), 1.60 (m, 1H), 1.77 (m, 1H), 2.09-2.23 (m, 2H), 2.62-2.76 (m, 2H), 3.66 (dd, J = 6.2, 10.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8, 86.8, 70.1, 48.1, 36.3, 35.4, 33.4, 31.0, 28.2, 26.0, 24.3, 22.5, 21.8, 18.4, 14.3, -4.5, -4.6; FAB-MS: *m/z* calcd. for $C_{19}H_{35}O_3Si_1$: 339.2, found: 339.3 $[M+H]^+$.

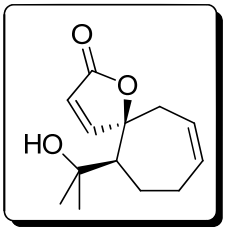


Compound 103: **102** (67 mg, 0.198 mmol) was dissolved in THF (4 mL) and cooled to -78°C before adding LiHMDS (2.5 mL, 2.5 mmol). After stirring 35 minutes, PhSeBr (455 mg, 1.9 mmol) was added in one portion as the solid. After 20 minutes, the reaction was quenched with water followed by NH_4Cl. Partitioning with ethyl acetate, drying over $MgSO_4$, and concentration gave a brown oil. Column chromatography provided **103** (57 mg, 55%). TLC (ethyl acetate/hexanes 1:4): R_f = 0.4; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.02 (s, 6H), 0.07 (m, 1H), 0.26 (m, 1H), 0.49-0.65 (m, 2H), 0.86 (s, 9H), 1.00 (m, 1H), 1.16 (m, 1H), 1.42 (s, 3H), 1.48 (s, 3H), 1.56 (m, 1H), 1.74 (m, 1H), 2.12 (dd, J = 1.35, 12.6 Hz, 1H), 2.44 (m, 1H), 3.57 (dd, J = 6.3,

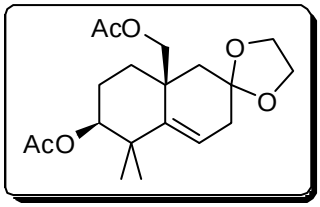
10.2 Hz, 1H), 4.28 (dd, J = 2.4, 12.6 Hz, 1H); FAB-MS: *m/z* calcd. for $C_{25}H_{39}O_3Se_1Si_1$: 495.2, found: 495.3 $[M+H]^+$.



Compound 104: Selenide **103** (19 mg, 0.038 mmol) was dissolved in a THF/H_2O solution (1:1) and cooled to 0°C. $NaIO_4$ (16 mg, 0.74 mmol) was added portion wise and reaction monitored by TLC. Upon disappearance of **103**, the reaction was partitioned between ether and water. After drying over $MgSO_4$ and concentration, the residue was purified by column chromatography. Lactone **104** (8 mg, 65%) was obtained. TLC (100% ethyl acetate): R_f = 0.8; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.76 (m, 1H), 0.89 (s, 9H), 0.92-1.00 (m, 2H), 1.26-1.35 (m, 2H), 1.36 (s, 3H), 1.38 (s, 3H), 1.72 (m, 1H), 1.82 (m, 1H), 2.53 (dd, J = 4.8, 12.8, 1H), 3.93 (m, 1H), 5.55 (d, J = 12.0 Hz, 1H), 5.87 (d, J = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 153.8, 119.0, 84.3, 68.1, 44.4, 32.0, 30.5, 29.0, 28.2, 25.9, 22.3, 20.7, 18.2, 16.7, -4.5, -4.6; HRMS: *m/z* calcd. for $C_{19}H_{33}O_3Si_1$: 337.2193, found: 337.2197 $[M+H]^+$.

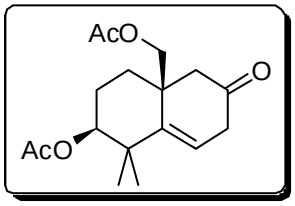


Compound 105: To a stirred acetone (0.08 mL) solution of lactone **104** (1.5 mg, 0.004 mmol), a 7% $HClO_4$ (0.12 mL) aqueous solution was added at room temperature. After stirring 3 hours, the solution was diluted with ethyl acetate and H_2O. Solid sodium carbonate was added in portions at 0°C, with stirring, until the solution tested neutral by pH paper. The ethyl acetate layer was collected and repeated ether extractions performed until no product remained in the aqueous layer by TLC. The combined organic layers were dried over $MgSO_4$ and concentrated. Column chromatography provided **105** (0.6 mg , 60%). TLC (ethyl acetate/hexanes 2:3): R_f = 0.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34–1.38 (m, 1H), 1.43 (s, 3H), 1.45 (s, 3H), 1.48–1.63 (m, 2H), 2.22–2.36, (m, 2H), 5.33–5.62 (m, 2H), 5.88-5.91 (d, J = 16 Hz, 1H), 6.02–6.06 (ddd, J = 4, 6.8, 12 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 153.0, 126.2, 123.3, 119.1, 83.9, 77.2 ($CHCl_3$ overlap), 40.8, 28.9, 25.8, 22.9, 21.3, 19.8; IR (film): ν_{max} 1737. HRMS: *m/z* calcd. for $C_{13}H_{18}O_3$: 223.1336, found: 223.1338 $[M+H]^+$.

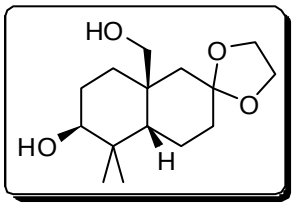


Compound 106: Diol **87** (332 mg, 1.24 mmol) was dissolved in dichloromethane (20 mL) and pyridine (5 mL). DMAP (20 mg, 0.16 mmol) was added at room temperature followed by acetyl chloride (0.38 mL, 5.3 mmol). Additional acetyl chloride (0.1 mL, 1.4 mmol) was added after stirring 3 hours. The solution was stirred an additional

12 hours before water was added and the mixture partitioned between water and ether. All ether layers were combined and dried over $MgSO_4$. Column chromatography provided **106** (330 mg, 76%). TLC (ethyl acetate/hexanes 3:2): R_f = 0.6; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (s, 3H), 1.02 (s, 3H), 1.12-1.21 (m, 2H), 1.59-1.78 (m, 3H), 1.98 (s, 3H), 1.99 (s, 3H), 2.12 (dd, J = 1.2, 13.2 Hz, 1H), 2.23 (m, 1H), 2.39 (dd, J = 3.6, 18.8 Hz, 1H), 3.80-3.90 (m, 4H), 4.08 (d, J = 12.0 Hz, 1H), 4.42-4.31 (m, 2H), 5.64 (t, J = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 170.2, 143.0, 122.3, 106.7, 78.7, 64.53, 64.45, 63.4, 40.3, 40.2, 40.1, 36.8, 32.6, 27.2, 23.9, 23.2, 21.2, 20.9; HRMS: *m/z* calcd. for $C_{19}H_{28}O_6$: 352.1880, found: 352.1883 $[M+H]^+$.

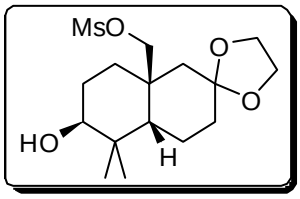


Compound 107: Ketal **106** (330 mg, 0.94 mmol) was dissolved in wet acetone (10 mL) and *p*-toluenesulfonic acid (30 mg, 0.16 mmol). was added. The solution was stirred at room temperature 6 hours. Triethylamine was added prior to adding water and partitioning the mixture with ether. The combined ether layers were dried over $MgSO_4$ and concentrated. Column chromatography provided **107** (265 mg, 92%). TLC (ethyl acetate/hexanes 3:2): R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04 (s, 3H), 1.11 (s, 3H), 1.41-1.77 (m, 4H), 1.91 (s, 3H), 2.01 (s, 3H), 2.21 (d, J = 14.4 Hz, 1H), 2.34 (d, J = 14.4 Hz, 1H), 2.76 (dd, J = 3.2, 22.8 Hz, 1H), 2.90 (dd, J = 4.4, 22.8 Hz, 1H), 3.91 (d, J = 11.2 Hz, 1H), 4.09 (d, J = 11.2 Hz, 1H), 4.57 (dd, J = 3.6, 11.0 Hz, 1H), 5.89 (t, J = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.9, 170.4, 170.2, 144.2, 122.3, 77.9, 68.7, 52.8, 41.6, 40.0, 39.6, 32.8, 26.5, 24.2, 23.4, 21.0, 20.4; HRMS: *m/z* calcd. for $C_{17}H_{25}O_5$: 309.1624, found: 309.1627 $[M+H]^+$.

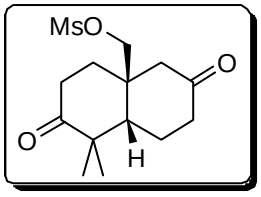


Compound 108: Diol **87** (2.0 g, 7.45 mmol) was dissolved in dichloromethane (100 mL) under argon and a hydrogen atmosphere was created. A dichloromethane (10 mL) solution of $[Ir(Cod)Py(PCy_3)]PF_6$ (123 mg, 0.15 mmol) was prepared. Portions (0.5 mL) of the catalyst solution were added every 5-10 minutes at room temperature until complete addition. Upon each catalyst addition, the reaction solution turned orange and slowly became yellow with stirring. After stirring 3 hours from point of initial catalyst addition, solid catalyst was added in 30 mg portions (127 mg, 0.15 mmol total) with hydrogen flushing of the reaction flask over 20 minutes. Stirring was continued 2 hours after complete catalyst addition, at which point the solution was concentrated at room temperature under reduced pressure. Column chromatography provided **108** (1.55 g, 77%). TLC (100% ethyl acetate): R_f = 0.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 3H), 0.99, (s, 3H), 1.14 (m, 1H), 1.55-1.93 (m, 11H), 1.97 (d, J = 11.2 Hz, 1H), 3.03 (b, 1H), 3.44 (b, 1H), 3.57 (dd, J = 7.8, 17.4 Hz, 2H), 3.67 (m, 2H), 3.77 (m, 1H); ^{13}C NMR (100 MHz,

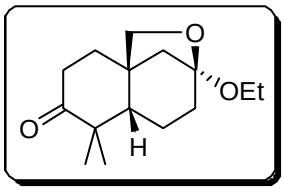
$CDCl_3$): δ 109.6, 80.1, 75.6, 63.7, 62.2, 45.3, 42.4, 39.3, 38.6, 28.1, 27.8, 27.1, 23.5, 20.3; HRMS: *m/z* calcd. for $C_{15}H_{27}O_4$: 271.1831, found: 271.1836 $[M+H]^+$.



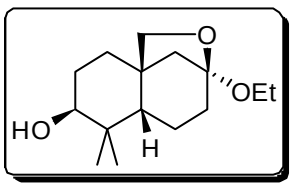
Compound 116: Diol **87** (204 mg, 0.76 mmol) was dissolved in dichloromethane (15 mL) and triethylamine (0.16 mL, 1.2 mmol). The solution was cooled to 0°C and mesyl chloride (0.85 mL, 1.1 mmol) was added dropwise over 20 minutes. The solution was stirred 5 minutes after complete mesyl chloride addition, at which point, water (5 mL) was added. The mixture was partitioned between water and ethyl acetate. The combined organics were dried over $MgSO_4$ and concentrated. Column chromatography provided **116** (215 mg, 82%). TLC (methanol/ether 1:9): R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (s, 3H), 1.00 (s, 3H), 1.55-1.98 (m, 11H), 3.04 (s, 3H), 3.45 (b, 1H), 3.53 (d, J = 7.6 Hz, 1H) 3.60 (d, J = 7.6 Hz, 1H), 3.75 (m, 1H), 3.90 (m, 1H), 4.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 109.6, 80.2, 75.6, 69.8, 59.7, 45.3, 42.4, 39.2, 38.6, 37.8, 35.5, 28.1, 27.8, 27.1, 23.5, 20.3.



Compound 118: To a stirred acetone (20 mL) solution of **117** (215 mg, 0.62 mmol) was added water (3 mL) followed by *p*-toluenesulfonic acid (40 mg, 0.21 mmol). The reaction was heated at 50°C 3 hours. Basic work up and chromatography provided **118** (20 mg, 11%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (s, 3H), 1.20 (s, 3H), 1.83-2.44 (m, 10H), 2.71 (m, 1H), 3.14 (s, 3H), 3.83 (dd, J = 3.4, 8.8 Hz, 1H), 3.99 (d, J = 8.8 Hz, 1H).

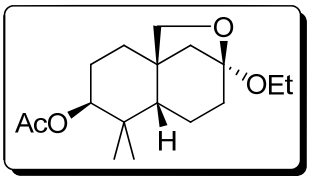


Compound 119: Alcohol **109** (37 mg, 0.145 mmol) was dissolved in dichloromethane (3 mL). Dess-Martin periodinane (81 mg, 0.17 mmol) was added and the solution stirred 4 hours. The reaction mixture was partitioned between water and ether, dried over $MgSO_4$, and purified. Column chromatography provided **119** (30 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (s, 3H), 1.19 (s, 3H), 1.22 (t, J = 7.0 Hz, 3H), 1.63-2.09 (m, 8H), 2.17 (d, J = 10.8 Hz, 1H), 2.36 (m, 1H), 2.69 (m, 1H), 3.59-3.77 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.0, 109.3, 79.0, 57.3, 49.2, 48.8, 45.2, 38.5, 36.4, 35.3, 33.5, 25.3, 22.9, 21.4, 15.7.

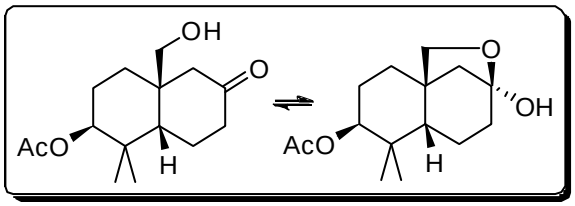


Compound 109: To a stirred solution of diol **108** (890 mg, 3.29 mmol) in ethanol (20 mL), was added *p*-toluenesulfonic

acid (67 mg, 0.35 mmol). The solution was heated at 40°C 15 minutes. After cooling to room temperature, triethylamine was added and the solution was concentrated under reduced pressure. Column chromatography and concentration provided ethyl ketal **109** (821 mg, 98%). TLC (100% ethyl acetate): R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (s, 3H), 0.96 (s, 3H), 1.16 (t, J = 6.8 Hz, 3H), 1.54 (m, 1H), 1.62 (m, 1H), 1.64-1.90 (m, 9H), 1.92 (d, J = 10.8 Hz, 1H), 3.41 (b, 1H), 3.49-3.69 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 109.4, 80.1, 75.6, 57.0, 45.0, 42.4, 39.2, 38.4, 35.3, 28.0, 27.7, 27.0, 23.4, 20.1, 15.6; HRMS: *m/z* calcd. for $C_{15}H_{27}O_3$: 255.1882, found: 255.1880 $[M+H]^+$.



Compound 110: To a stirred dichloromethane (40 mL) solution of **109** (1.35 g, 5.31 mmol), was added pyridine (20 mL) and DMAP (43 mg, 0.35 mmol). Acetyl chloride (630 mg, 8.0 mmol) was added at room temperature. The mixture was stirred 2 hours before adding water followed by NH_4Cl. The mixture was partitioned with ethyl acetate and dried over $MgSO_4$. Column chromatography provided **110** (1.4 g, 90%). TLC (ethyl acetate/hexanes 3:2): R_f = 0.7; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (s, 3H), 1.04 (s, 3H), 1.19 (t, J = 7.0 Hz, 3H), 1.53-1.97 (m, 11H), 2.03 (s, 3H), 3.53-3.72 (m, 4H), 4.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 109.3, 80.1, 77.7, 57.2, 45.1, 43.6, 39.2, 37.8, 35.4, 28.6, 27.8, 24.7, 23.2, 21.3, 20.2, 15.8; HRMS: *m/z* calcd. for $C_{17}H_{29}O_4$: 297.1988, found: 297.1991 $[M+H]^+$.



Compound 111: Ketal **110** (671 mg, 2.26 mmol) was dissolved in wet acetone (30 mL) and *p*-toluenesulfonic acid (60 mg, 0.31 mmol) was added at room temperature. The solution was stirred 1.5 hours at 45°C. After cooling to room temperature, triethylamine was added and the solution was concentrated under reduced pressure at room temperature. Column chromatography and concentration provided a mixture of hemiketal **111a** and ketone **111b** (516 mg, 85%). Upon standing, the mixture crystallized (**111a**) and was submitted for single crystal x-ray analysis. TLC (ethyl acetate/hexanes 3:2): R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (b, 3H), 1.06, (b, 3H), 1.09-1.24 (m, 2H), 1.58-1.99 (m, 8H), 2.03 (b, 3H), 2.24 (m, 1H), 3.54 (b, 2H), 4.67 (b, 1H); HRMS: *m/z* calcd. for $C_{15}H_{25}O_4$: 269.1675, found: 269.1679 $[M+H]^+$; Crystal Data for **111a** has been deposited with CCDC (CCDC-643492) and can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif:

Crystal data and structure refinement for theod20a.

Identification code	theod20a	
Empirical formula	C15 H24 O4	
Formula weight	268.34	
Temperature	213(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pccn	
Unit cell dimensions	a = 21.483(4) Å	a= 90°
	b = 11.0294(19) Å	b= 90°
	c = 11.916(2) Å	g = 90°
Volume	2823.4(9) $Å^3$	
Z	8	
Density (calculated)	1.263 g/cm^3	
Absorption coefficient	0.090 mm^{-1}	
F(000)	1168	
Crystal size	0.30 x 0.30 x 0.20 mm^3	
Theta range for data collection	2.08 to 24.00°	
Index ranges	-24<=h<=24, -12<=k<=12, -13<=l<=13	
Reflections collected	11723	
Independent reflections	2216 [R(int) = 0.0246]	
Completeness to theta = 24.00°	99.8 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2216 / 0 / 172	
Goodness-of-fit on F^2	1.047	
Final R indices [I>2sigma(I)]	R1 = 0.0518, wR2 = 0.1387	
R indices (all data)	R1 = 0.0569, wR2 = 0.1425	
Largest diff. peak and hole	0.394 and -0.318 e $Å^{-3}$	

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)for theod20a. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	4204(1)	-2702(1)	10108(1)	30(1)
O(2)	3268(1)	-3755(2)	9993(1)	33(1)
O(3)	3996(1)	2325(1)	8821(1)	31(1)
O(4)	3430(1)	4031(2)	8919(2)	36(1)
C(1)	3579(1)	-2728(2)	9611(2)	26(1)
C(2)	3645(1)	-2682(2)	8339(2)	27(1)
C(3)	4084(1)	-1634(2)	7989(2)	28(1)
C(4)	3981(1)	-432(2)	8630(2)	26(1)
C(5)	3820(1)	-676(2)	9891(2)	26(1)
C(6)	3281(1)	-1582(2)	10034(2)	27(1)
C(7)	4345(1)	-1461(2)	10398(2)	31(1)
C(8)	3715(1)	506(2)	10530(2)	30(1)
C(9)	3222(1)	1282(2)	9953(2)	32(1)
C(10)	3415(1)	1597(2)	8756(2)	30(1)

C(11)	3551(1)	492(2)	8004(2)	28(1)
C(13)	2911(1)	-26(2)	7630(2)	32(1)
C(14)	3933(1)	3525(2)	8881(2)	28(1)
C(15)	4549(1)	4170(2)	8865(2)	35(1)
C(112)	3891(1)	923(2)	6935(2)	36(1)

Bond lengths [Å] and angles [°] for theod20a.

O(1)-C(7)	1.445(3)	C(6)-C(1)-C(2)	110.22(18)
O(1)-C(1)	1.468(3)	C(1)-C(2)-C(3)	110.50(18)
O(2)-C(1)	1.391(3)	C(4)-C(3)-C(2)	114.81(18)
O(3)-C(14)	1.333(3)	C(3)-C(4)-C(5)	111.03(18)
O(3)-C(10)	1.485(3)	C(3)-C(4)-C(11)	114.03(18)
O(4)-C(14)	1.216(3)	C(5)-C(4)-C(11)	115.98(18)
C(1)-C(6)	1.503(3)	C(8)-C(5)-C(6)	112.88(18)
C(1)-C(2)	1.523(3)	C(8)-C(5)-C(7)	112.98(18)
C(2)-C(3)	1.549(3)	C(6)-C(5)-C(7)	98.16(18)
C(3)-C(4)	1.546(3)	C(8)-C(5)-C(4)	111.41(19)
C(4)-C(5)	1.565(3)	C(6)-C(5)-C(4)	112.67(18)
C(4)-C(11)	1.566(3)	C(7)-C(5)-C(4)	108.00(18)
C(5)-C(8)	1.527(3)	C(1)-C(6)-C(5)	100.95(17)
C(5)-C(6)	1.538(3)	O(1)-C(7)-C(5)	106.45(18)
C(5)-C(7)	1.546(3)	C(5)-C(8)-C(9)	110.89(18)
C(8)-C(9)	1.526(3)	C(8)-C(9)-C(10)	111.06(19)
C(9)-C(10)	1.526(3)	O(3)-C(10)-C(9)	107.63(18)
C(10)-C(11)	1.540(3)	O(3)-C(10)-C(11)	107.43(18)
C(11)-C(112)	1.543(3)	C(9)-C(10)-C(11)	114.6(2)
C(11)-C(13)	1.554(3)	C(10)-C(11)-C(112)	109.05(19)
C(14)-C(15)	1.504(3)	C(10)-C(11)-C(13)	106.89(18)
C(7)-O(1)-C(1)	107.89(16)	C(112)-C(11)-C(13)	107.15(19)
C(14)-O(3)-C(10)	117.06(17)	C(10)-C(11)-C(4)	110.47(18)
O(2)-C(1)-O(1)	108.87(17)	C(112)-C(11)-C(4)	108.33(19)
O(2)-C(1)-C(6)	111.79(18)	C(13)-C(11)-C(4)	114.79(19)
O(1)-C(1)-C(6)	103.74(18)	O(4)-C(14)-O(3)	123.2(2)
O(2)-C(1)-C(2)	113.40(19)	O(4)-C(14)-C(15)	124.5(2)
O(1)-C(1)-C(2)	108.30(18)	O(3)-C(14)-C(15)	112.30(19)

Symmetry transformations used to generate equivalent atoms:

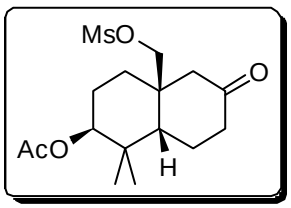
Anisotropic displacement parameters ($Å^2 x\ 10^3$) for theod20a. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	30(1)	31(1)	31(1)	4(1)	-3(1)	3(1)
O(2)	36(1)	28(1)	33(1)	3(1)	6(1)	-1(1)
O(3)	29(1)	23(1)	41(1)	-1(1)	-5(1)	3(1)
O(4)	31(1)	29(1)	49(1)	-2(1)	-2(1)	5(1)
C(1)	23(1)	28(1)	26(1)	4(1)	1(1)	-1(1)
C(2)	32(1)	23(1)	26(1)	-3(1)	0(1)	2(1)
C(3)	30(1)	28(1)	25(1)	1(1)	2(1)	4(1)

C(4)	24(1)	27(1)	26(1)	1(1)	1(1)	0(1)
C(5)	26(1)	30(1)	23(1)	-1(1)	-2(1)	2(1)
C(6)	27(1)	32(1)	23(1)	1(1)	3(1)	1(1)
C(7)	32(1)	34(1)	26(1)	1(1)	-3(1)	0(1)
C(8)	31(1)	32(1)	26(1)	-5(1)	1(1)	-2(1)
C(9)	29(1)	29(1)	37(1)	-10(1)	1(1)	1(1)
C(10)	25(1)	27(1)	38(1)	-2(1)	-5(1)	2(1)
C(11)	31(1)	27(1)	28(1)	-2(1)	-4(1)	3(1)
C(13)	34(1)	31(1)	32(1)	-2(1)	-9(1)	6(1)
C(14)	32(1)	26(1)	25(1)	1(1)	-2(1)	6(1)
C(15)	32(1)	30(1)	44(1)	-4(1)	-3(1)	3(1)
C(112)	45(2)	31(1)	31(1)	3(1)	-4(1)	2(1)

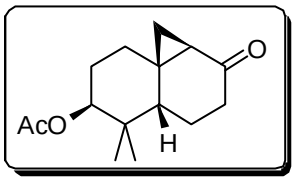
Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for theod20a.

	x	y	z	U(eq)
H(2A)	3359	-4342	9589	49
H(2B)	3235	-2563	7996	32
H(2C)	3814	-3454	8067	32
H(3A)	4516	-1895	8104	33
H(3B)	4029	-1481	7185	33
H(4A)	4396	-40	8647	31
H(6A)	3156	-1657	10822	33
H(6B)	2920	-1354	9580	33
H(7A)	4750	-1223	10087	37
H(7B)	4359	-1363	11215	37
H(8A)	4107	958	10571	36
H(8B)	3581	323	11298	36
H(9A)	3159	2031	10382	38
H(9B)	2826	841	9938	38
H(10A)	3085	2092	8404	36
H(13A)	2678	597	7239	48
H(13B)	2679	-290	8285	48
H(13C)	2977	-711	7132	48
H(15A)	4480	5039	8856	53
H(15B)	4780	3934	8200	53
H(15C)	4785	3952	9529	53
H(11A)	3629	1491	6531	54
H(11B)	3980	231	6460	54
H(11C)	4277	1318	7142	54

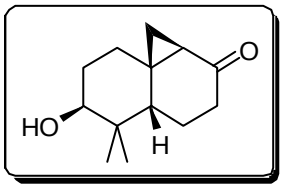


Compound 112: A mixture of alcohols; **111b** and hemiketal **111a** (combined: 138 mg, 0.51 mmol) was dissolved in dichloromethane (6 mL) and treated with diisopropylethylamine (0.12 mL, 0.69 mmol) at room temperature. After cooling the solution to 0°C, mesyl chloride (0.05 mL, 0.64 mmol) was added via syringe in a rapid

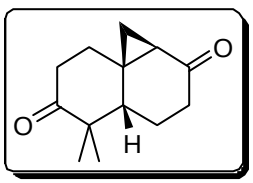
dropwise fashion. After stirring 30 minutes at 0°C the solution was purified by placing directly onto a silica column. Column chromatography provided primary mesylate **112b** (336 mg , 40%) and ketal-mesylate **112a** (53.5 mg, 30%). Ketal-mesylate **112a** could be easily converted to **112b** by stirring in wet acetone with catalytic HCl. TLC (ethyl acetate/hexanes 3:2): $R_f = 0.3$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (s, 3H), 1.17 (s, 3H), 1.37 (m, 1H), 1.71-1.89 (m, 4H), 2.07 (m, 3H), 2.17 (d, J = 15.6 Hz, 1H), 2.30-2.49 (m, 2H), 2.61 (d, J = 15.6 Hz, 1H), 3.01 (s, 3H), 3.97 (d, J = 10.0 Hz, 1H), 4.03 (d, J = 10.0 Hz, 1H), 4.75 (m, 1H); 13C NMR (100 MHz, CDCl3): δ 210.7, 170.3, 77.3, 75.9, 46.4, 41.5, 39.4, 38.9, 37.5, 37.3, 27.9, 27.1, 25.4, 22.4, 22.3, 21.1.



Compound 113: Mesylate **112b** (59 mg, 0.170 mmol) was dissolved in benzene (4 mL) at room temperature and *t*BuOK (22 mg, 0.196 mmol) added in one portion. After stirring 4 hours, the reaction was quenched with aqueous NH_4Cl. Repeated ethyl acetate extractions were performed and the combined organic layers were dried over $MgSO_4$ and concentrated. Column chromatography (ethyl acetate/hexanes 1:1) provided cyclopropyl acetate **113** as a white solid (40 mg, 95%). TLC (ethyl acetate/hexanes 3:2): $R_f = 0.4$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.72-0.85 (m, 2H), 0.89 (s, 3H), 0.96 (s, 3H), 1.42-1.47 (m, 1H), 1.65-1.94 (m, 7H), 2.07 (s, 3H), 2.14-2.31 (m, 2H), 4.67-4.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.0, 170.3, 78.7, 38.0, 35.8, 35.3, 32.9, 30.9, 29.9, 26.2, 24.6, 22.5, 21.1, 18.2, 16.2; HRMS: *m/z* calcd. for $C_{15}H_{23}O_3$: 251.1642, found: 251.1647 $[M+H]^+$.

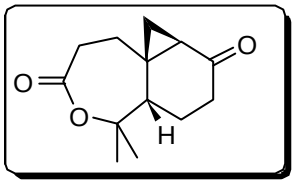


Compound 114: Cyclopropyl acetate **113** (146 mg, 0.583 mmol) was dissolved in methanol (9 mL) at room temperature and K_2CO_3 (97 mg, 0.702 mmol) added in one portion. After stirring 24 hours, the reaction was quenched with aqueous NH_4Cl. Repeated ethyl acetate extractions were performed and the combined organic layers were dried over $MgSO_4$ and concentrated. Column chromatography (ethyl acetate/hexanes 1:1) provided the free alcohol **114** (100 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.67-0.73 (m, 1H), 0.77-0.83 (m, 2H), 0.83 (s, 3H), 1.05 (s, 3H), 1.40-1.44 (m, 1H), 1.57-1.64 (m, 1H), 1.74-1.97 (m, 4H), 2.14-2.19 (m, 2H), 2.29-2.43 (m, 2H), 3.45-3.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.4, 76.9, 38.8, 35.6, 34.9, 33.2, 30.4, 30.3, 27.3, 26.7, 23.0, 18.5, 16.5; HRMS: *m/z* calcd. for $C_{13}H_{21}O_2$: 209.1436, found: 209.1439 $[M+H]^+$.

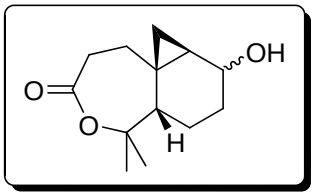


Compound 115: Alcohol **114** (51 mg, 0.245 mmol) was dissolved in dichloromethane (8 mL) and Dess-Martin Periodinane (151 mg, 0.319) was added at room temperature in

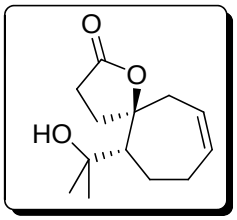
one portion. After stirring 30 minutes, saturated aqueous $NaHCO_3$ was added, followed by saturated aqueous $Na_2S_2O_3$. The diketone was extracted from the aqueous layer with diethyl ether, dried over $MgSO_4$, and concentrated. Column chromatography (ethyl acetate/hexanes 3:7) provided **115** (48 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04 (dd, J = 4.0, 9.6 Hz, 1H), 1.07 (s, 3H), 1.15 (s, 3H), 1.40 (ddd, J = 2.8, 3.2, 14 Hz, 1H), 1.47 (m, 1H), 1.86-2.35 (m, 8H), 2.71-2.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 213.8, 208.8, 49.4, 42.4, 36.8, 35.4, 34.6, 33.4, 29.9, 23.4, 22.7, 20.7, 17.5; HRMS: *m/z* calcd. for $C_{13}H_{19}O_2$: 207.1380, found: 207.1372 $[M+H]^+$.



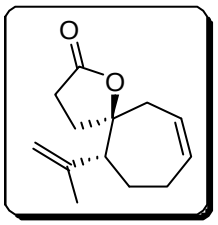
Compound 120: A dichloromethane (10 mL) solution of **115** (47 mg, 0.228 mmol) was cooled to 0°C. mCPBA (59 mg, 0.343 mmol) was added in one portion, followed rapidly by solid $NaHCO_3$ (40 mg, 0.952 mmol). Stirring was continued for 8 hours, with warming to room temperature, after which, saturated aqueous $NaHCO_3$ was added with stirring. The aqueous layer was discarded and the organic layer collected, diluted with ethyl acetate, and washed with saturated aqueous $NaHCO_3$. The aqueous layers were combined and washed with ethyl acetate. The organic layers were combined, dried over $MgSO_4$, and concentrated. Column chromatography provided the ketolactone **120** (50 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (dd, J = 5.8, 9.4 Hz, 1H), 1.08 (ddd, J = 2.4, 5.6, 15.2 Hz, 1H), 1.48 (s, 3H), 1.49 (s, 3H), 1.62-1.66 (m, 1H), 1.80-2.35 (m, 6H), 2.46-2.50 (m, 1H), 2.66 (ddd, J = 2.2, 6.0, 16.4 Hz, 1H), 2.79 (ddd, J = 2.4, 13.2, 18.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.5, 174.2, 85.1, 43.3, 34.8, 34.7, 33.9, 32.2, 31.8, 31.2, 24.4, 21.1, 18.4; HRMS: *m/z* calcd. for $C_{13}H_{19}O_3$: 223.1329, found: 223.1333 $[M+H]^+$.



Compound 121: Ketolactone **120** (52 mg, 0.234 mmol) was dissolved in dichloromethane (3 mL), cooled to 0°C, and Bu_4NBH_4 (299 mg, 1.162 mmol) added in one portion. The reaction was allowed to warm to room temperature and aliquots collected for ^{1}HNMR (starting material and product are difficult to differentiate under the chosen TLC conditions). After 8 hours, a small amount of silica gel was added and the solvent evaporated at room temperature under reduced pressure. Column chromatography provided **121** (43 mg, 82%). TLC (100% ethyl acetate): R_f = 0.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.36-0.40 (m, 1H), 0.53-0.67 (m, 3H), 0.77-0.81 (m, 1H), 0.97-1.11 (m, 2H), 1.25-1.41 (m, 4H), 1.43 (s, 3H), 1.49 (s, 3H), 1.61 (s, 3H), 1.65 (s, 3H), 1.66-1.84 (m, 6H), 1.91-2.00 (m, 1H), 2.11-2.21 (m, 1H), 2.64-2.75 (m, 2H), 2.79-2.92 (m, 2H), 3.66-3.72 (m, 1H), 4.29-4.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 174.5, 85.0, 83.7, 68.6, 64.5, 46.9, 45.9, 34.9, 34.7, 31.4, 30.5 30.4, 30.2, 29.6, 28.8, 28.7, 28.7, 27.7, 27.1, 26.3, 21.0, 20.5, 20.2, 20.2, 16.2; HRMS: *m/z* calcd. for $C_{13}H_{21}O_3$: 225.1485, found: 225.1488 $[M+H]^+$.

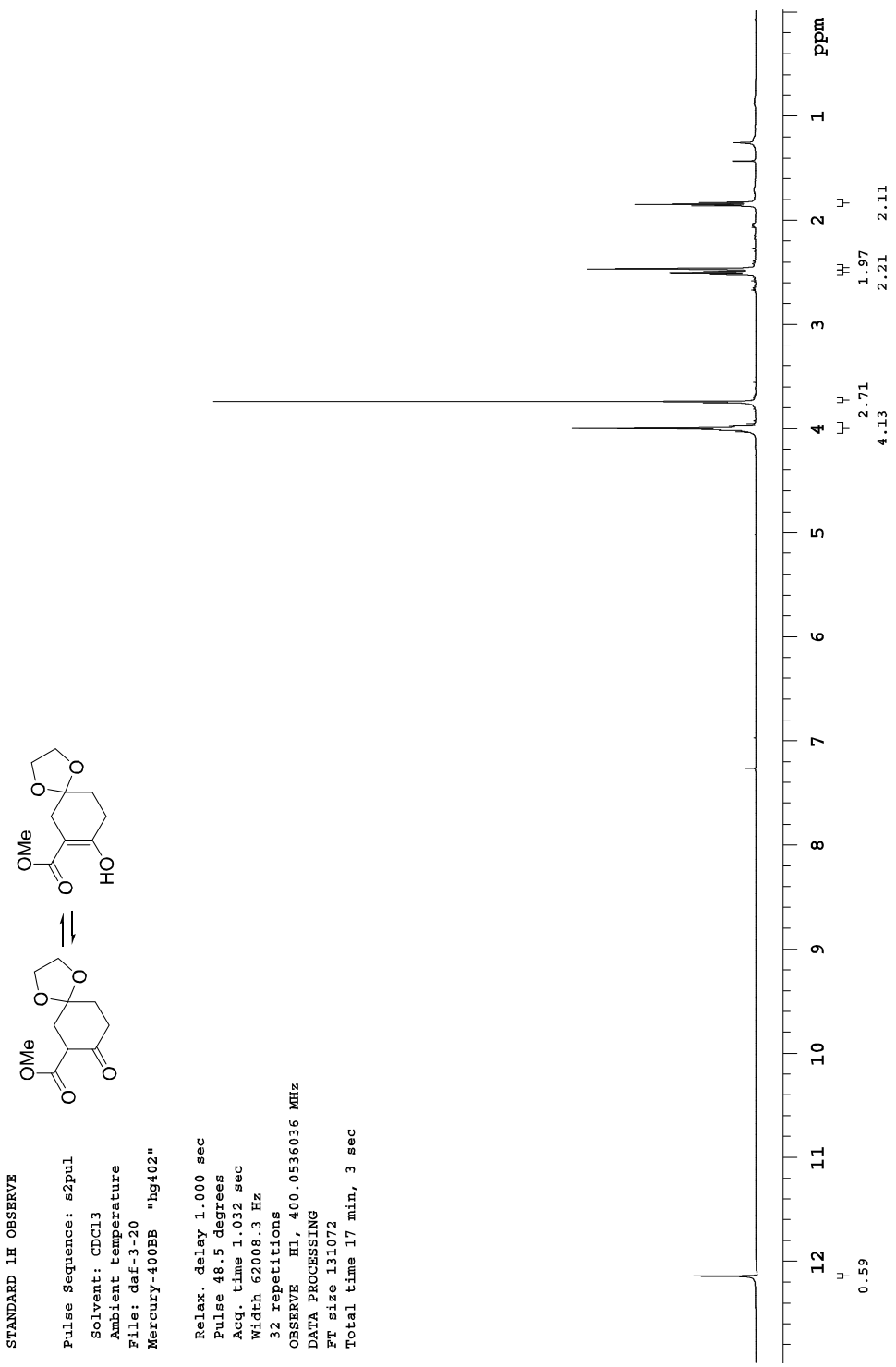


Compound 122: To a stirred acetone (5 mL) solution of compound **121** (5 mg, 0.022 mmol), a 7% $HClO_4$ (0.3 mL) aqueous solution was added at room temperature. After stirring 1.5 hours, the solution was diluted with diethyl ether and H_2O. Solid sodium carbonate was added in portions, with stirring, until the solution tested neutral by pH paper. The ether layer was collected and repeated ether extractions performed until no product remained in the aqueous layer by TLC. The combined organic layers were dried over $MgSO_4$ and concentrated. Column chromatography (ethyl acetate/hexanes, 1:2) was performed to yield **122** as an amorphous solid (2.8 mg, 55%). TLC (ethyl acetate/hexanes 3:2): R_f= 0.4; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (s, 3H), 1.29 (s, 3H), 1.81-1.89 (m, 1H), 2.09–2.12 (m, 2H), 2.18–2.22 (m, 1H), 2.32–2.45 (m, 3H), 2.48–2.56 (m, 1H), 2.60–2.64 (m, 3H), 5.52–5.61 (m, 1H), 5.82–5.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.4, 133.2, 124.2, 91.6, 77.2 ($CHCl_3$ overlap), 56.9, 41.9, 31.4, 28.9, 28.5, 28.1, 27.0, 24.4; IR (film): ν_{max} 1759. HRMS: *m/z* calcd. for $C_{13}H_{20}O_3$: 225.1492, found: 225.1488 $[M+H]^+$.

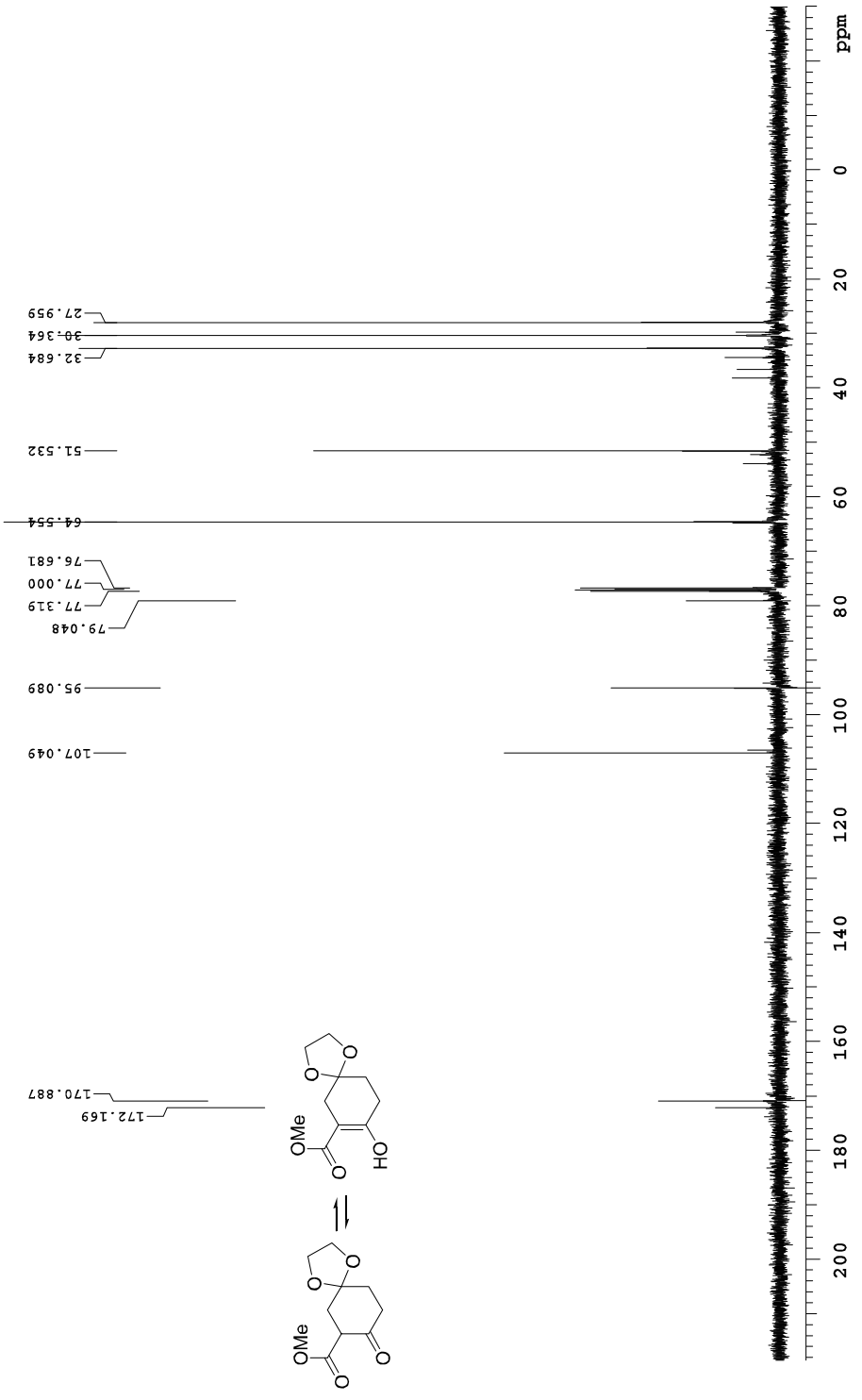


Compound 123: Olefin **123** was isolated as a side product of the reaction which produced **122**. In the synthesis of **122**, extended reaction times produced olefin **123**. TLC (100% ethyl acetate): R_f = 0.8; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.75 (m, 2H), 1.84 (s, 3H), 2.12 (m, 1H), 2.21-2.65 (m, 8H), 4.78 (b, 1H), 4.99 (b, 1H), 5.63 (m, 1H), 6.02 (m, 1H); CRUDE ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 135.3, 124.8, 114.0, 77.2, 65.9, 56.9, 40.5, 31.6, 29.7, 29.2, 29.0, 27.6, 25.8, 25.71, 22.6, 15.3.

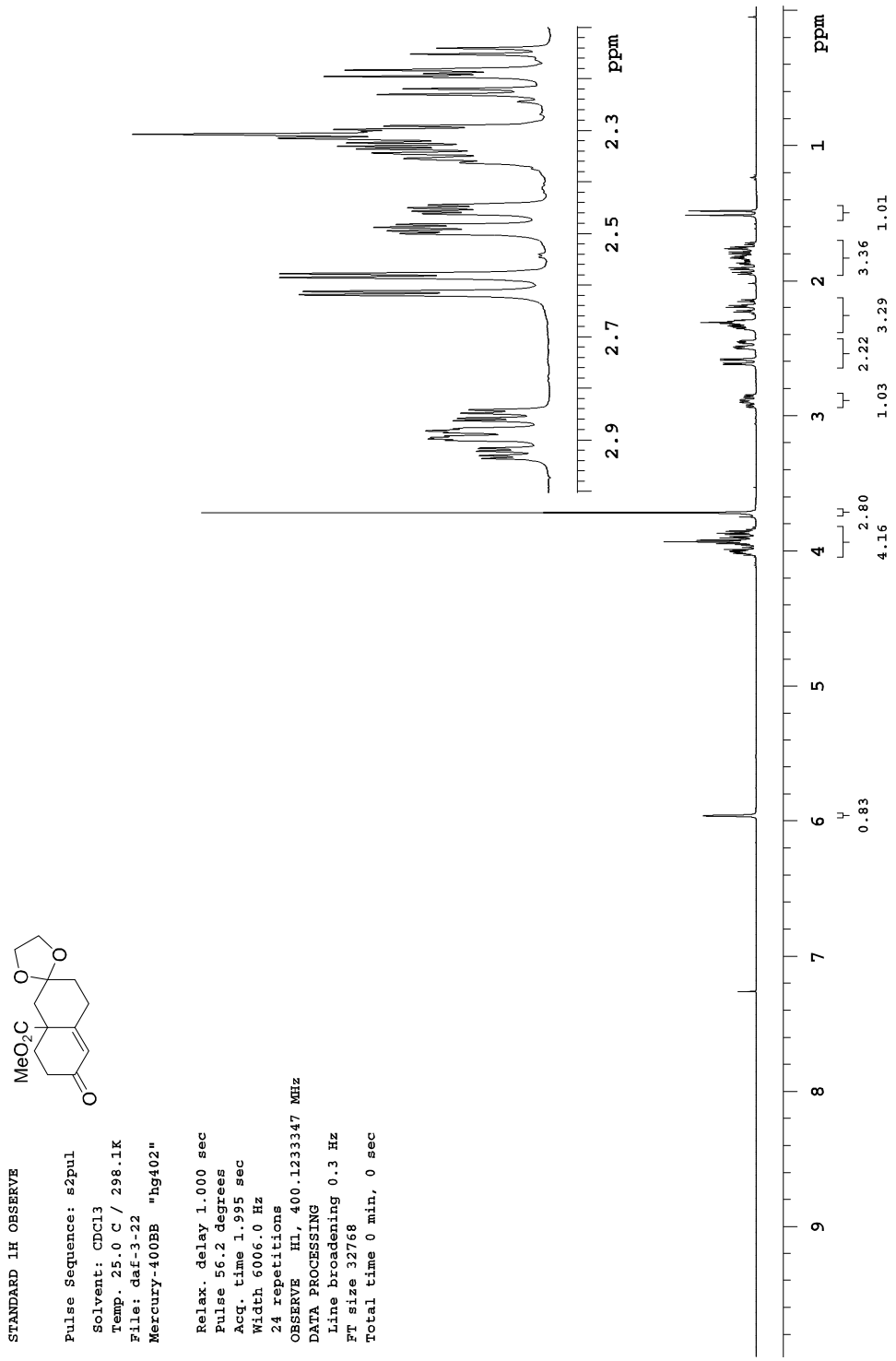
Section A.3 Selected NMR Spectra



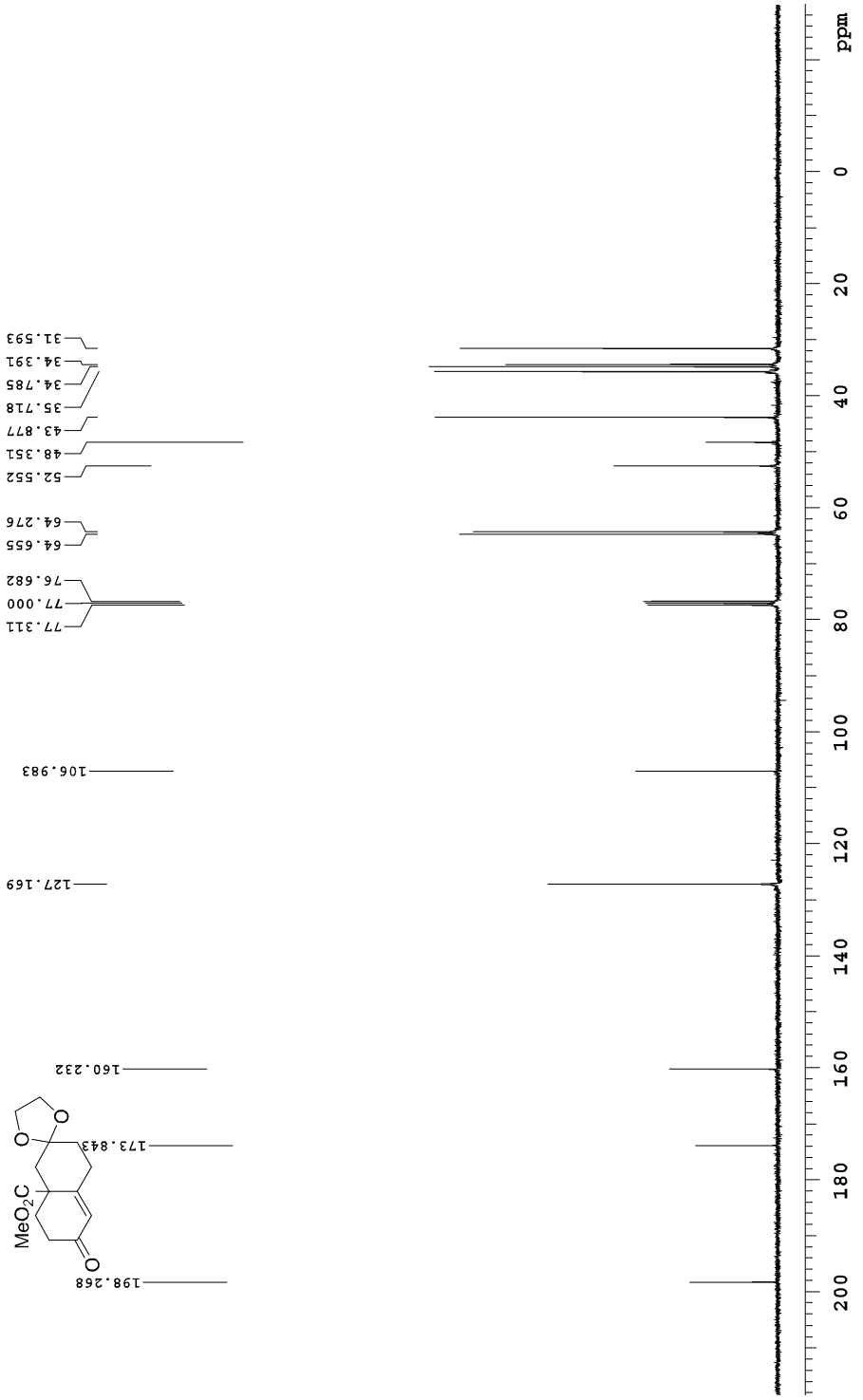
Spectrum 1.0 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **84**



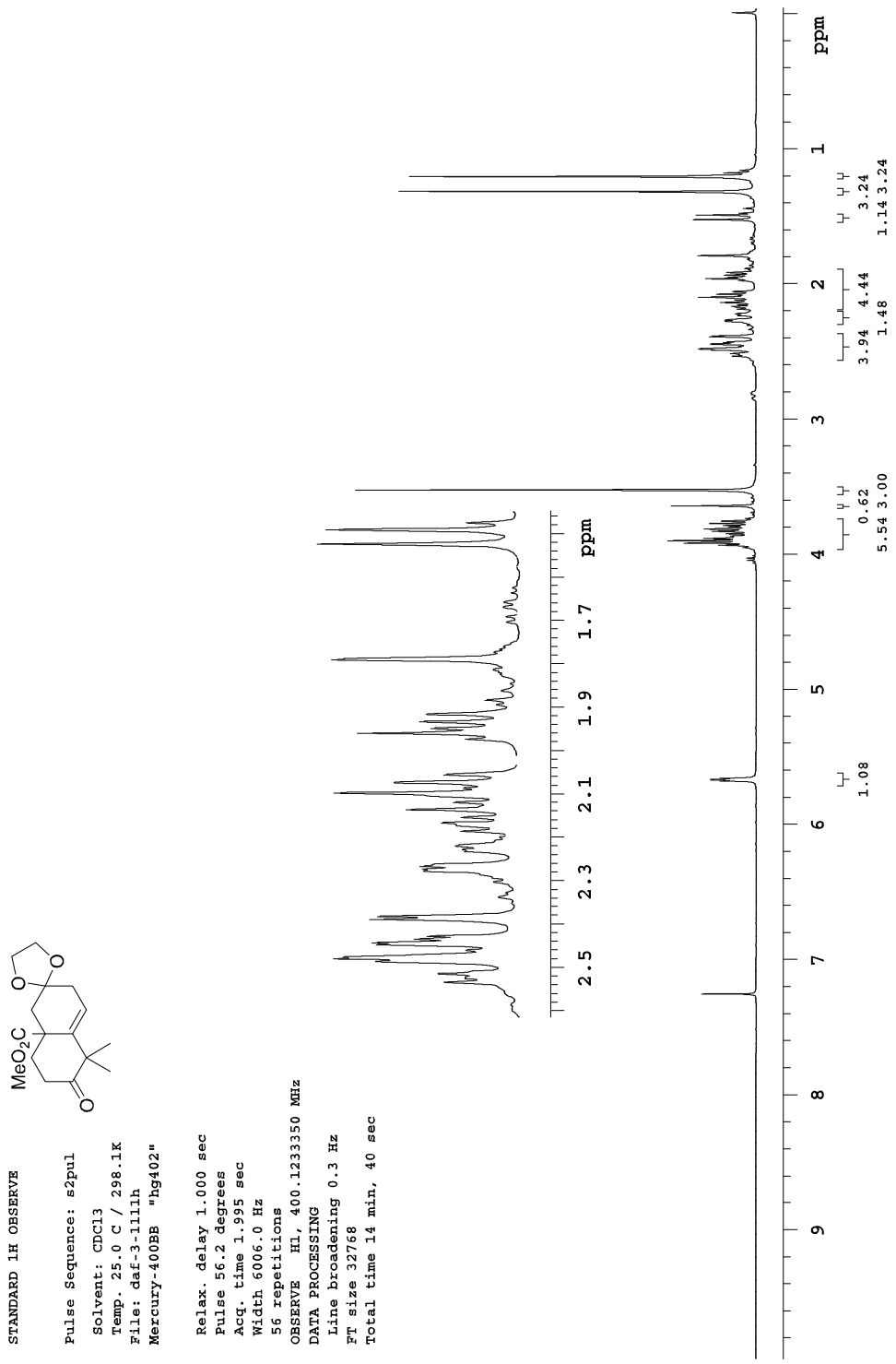
Spectrum 1.1 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **84**



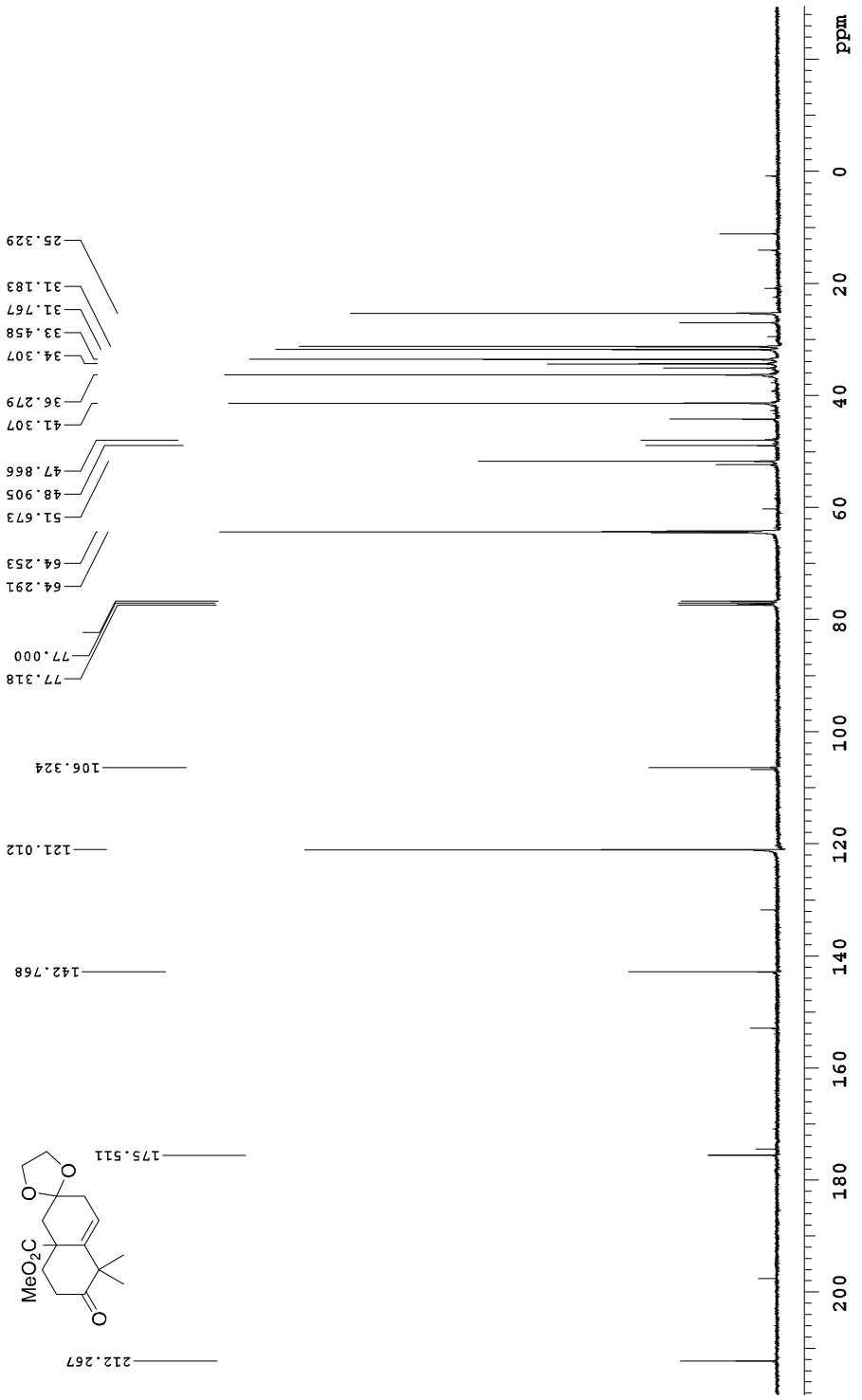
Spectrum 1.2 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **85**



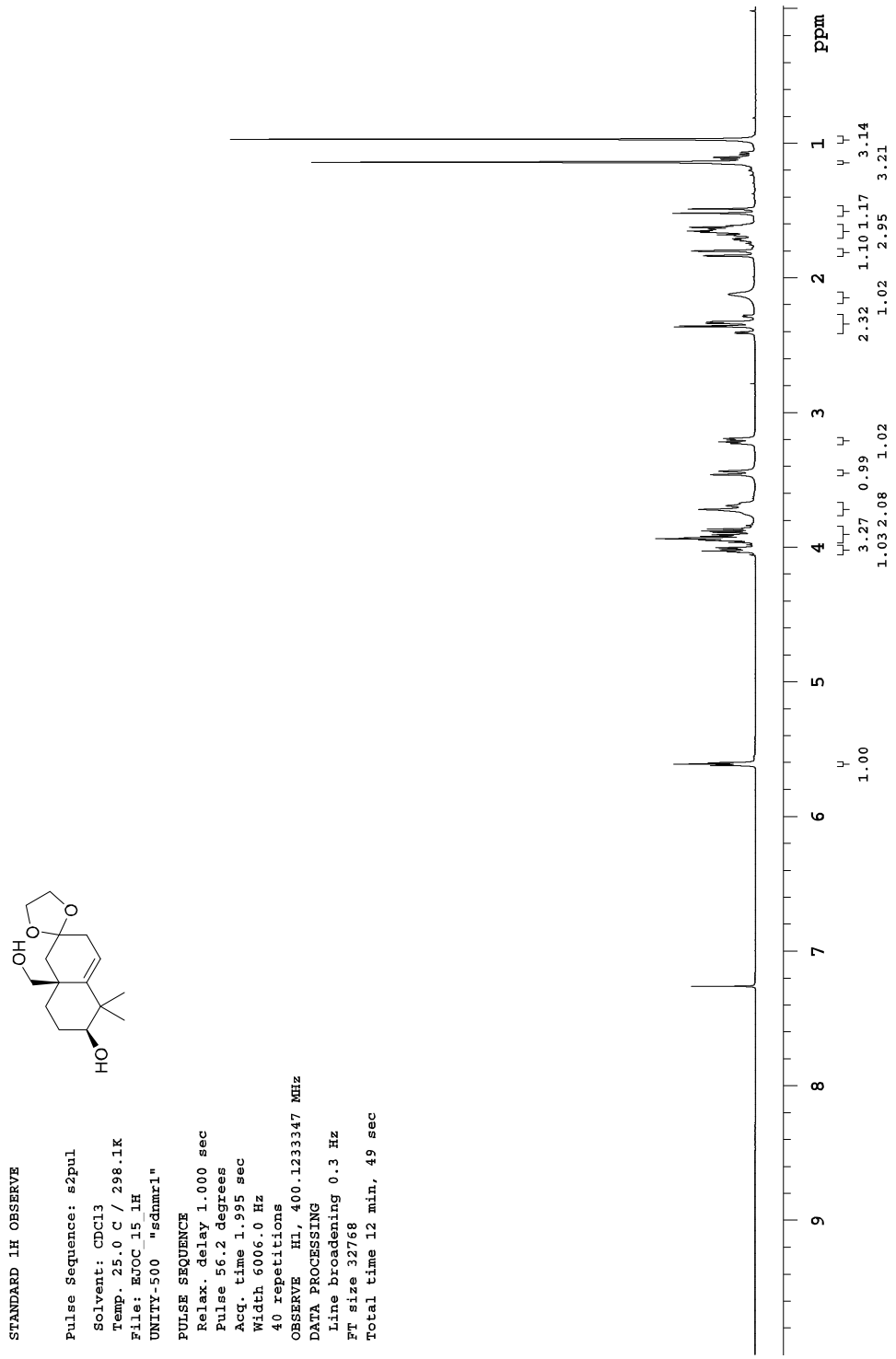
Spectrum 1.3 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **85**



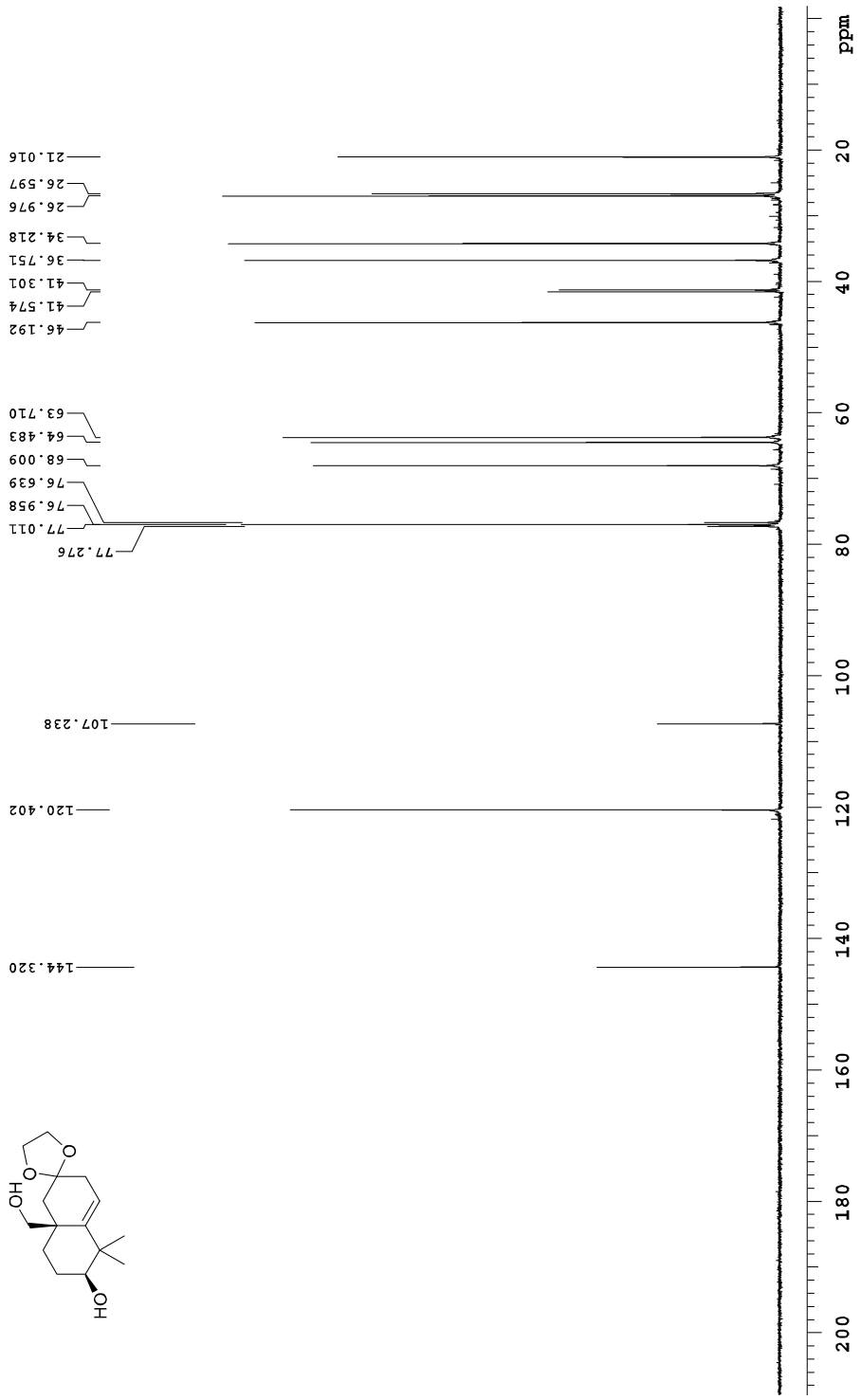
Spectrum 1.4 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **86**



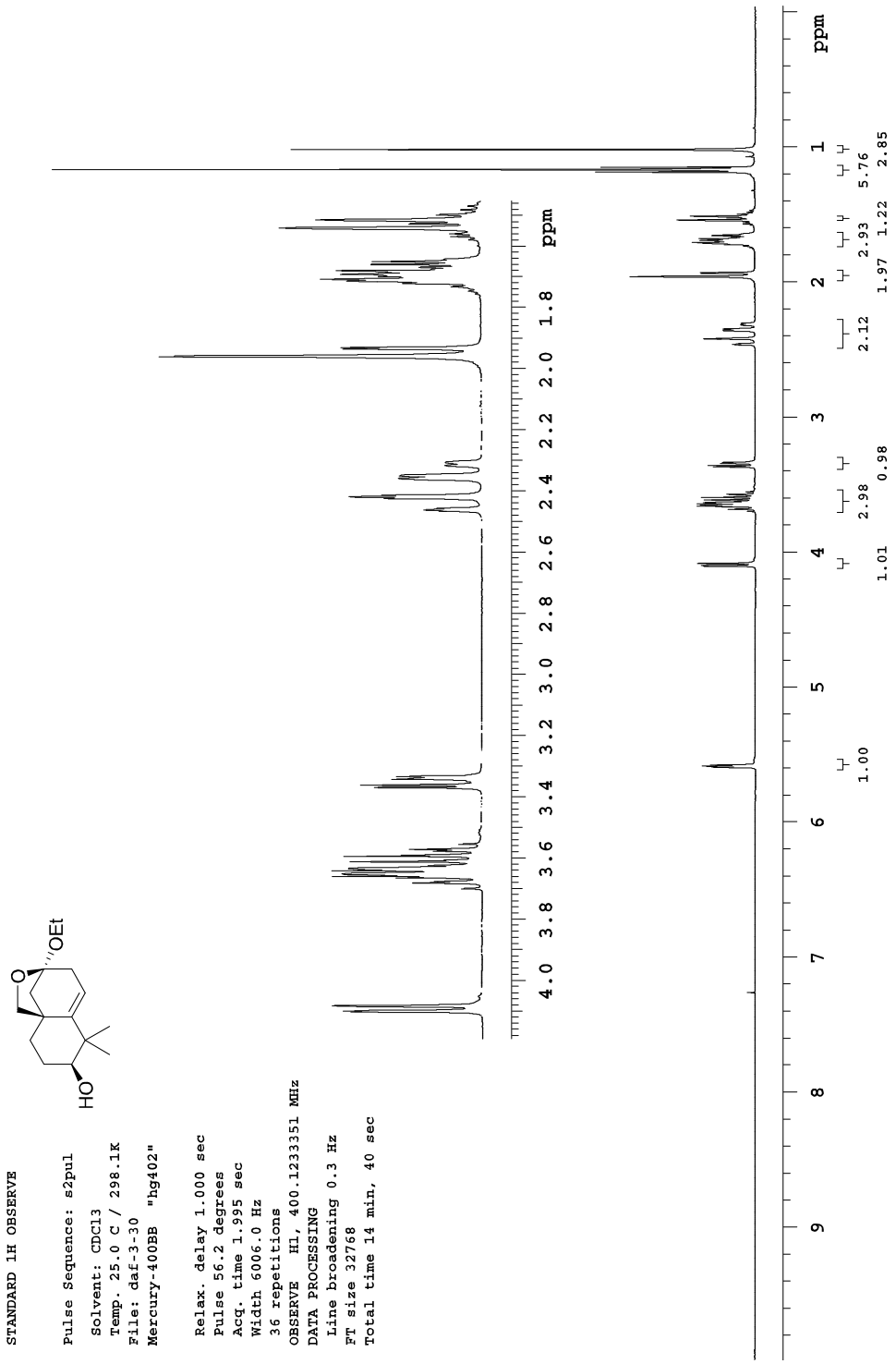
Spectrum 1.5 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **86**



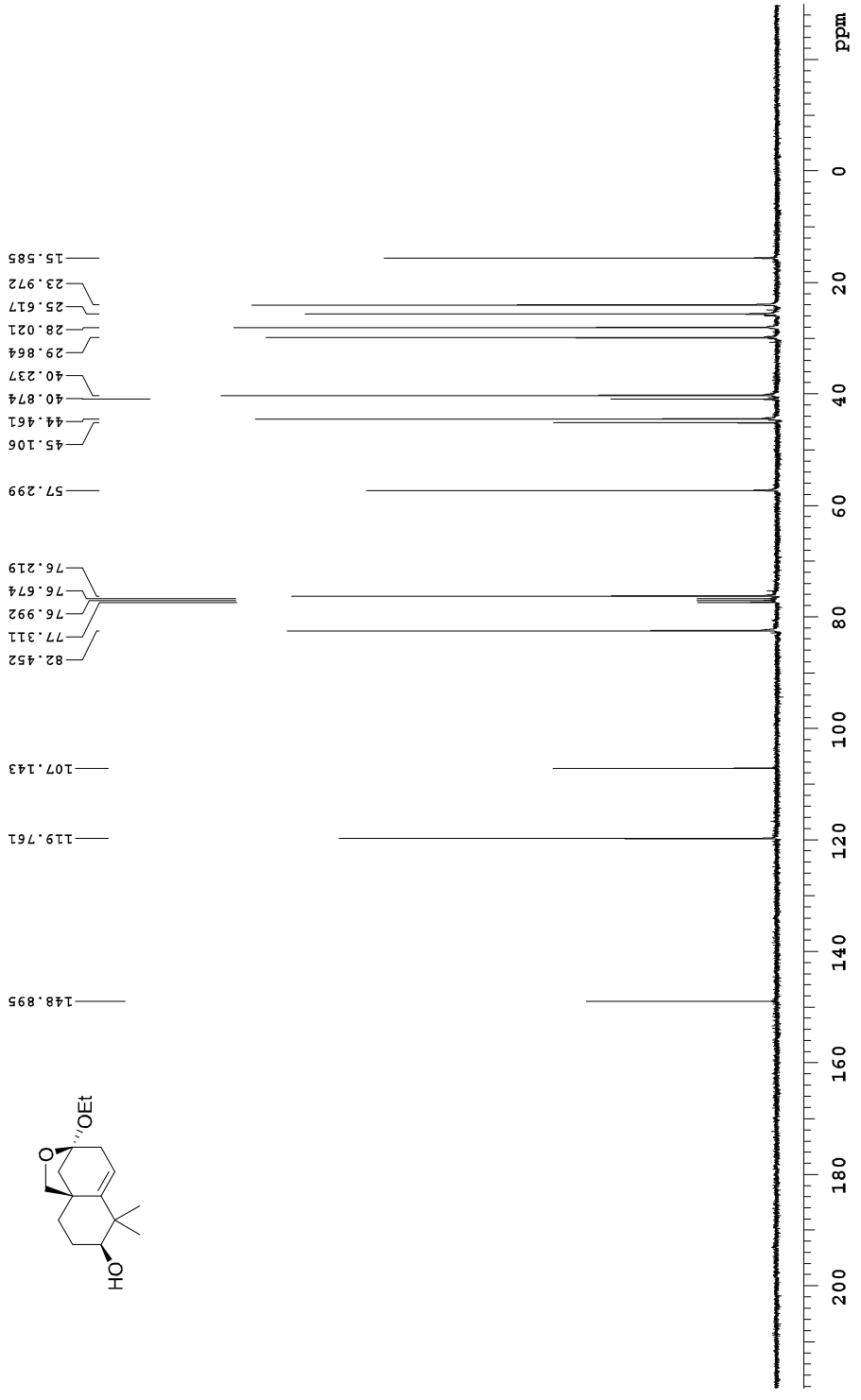
Spectrum 1.6 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **87**



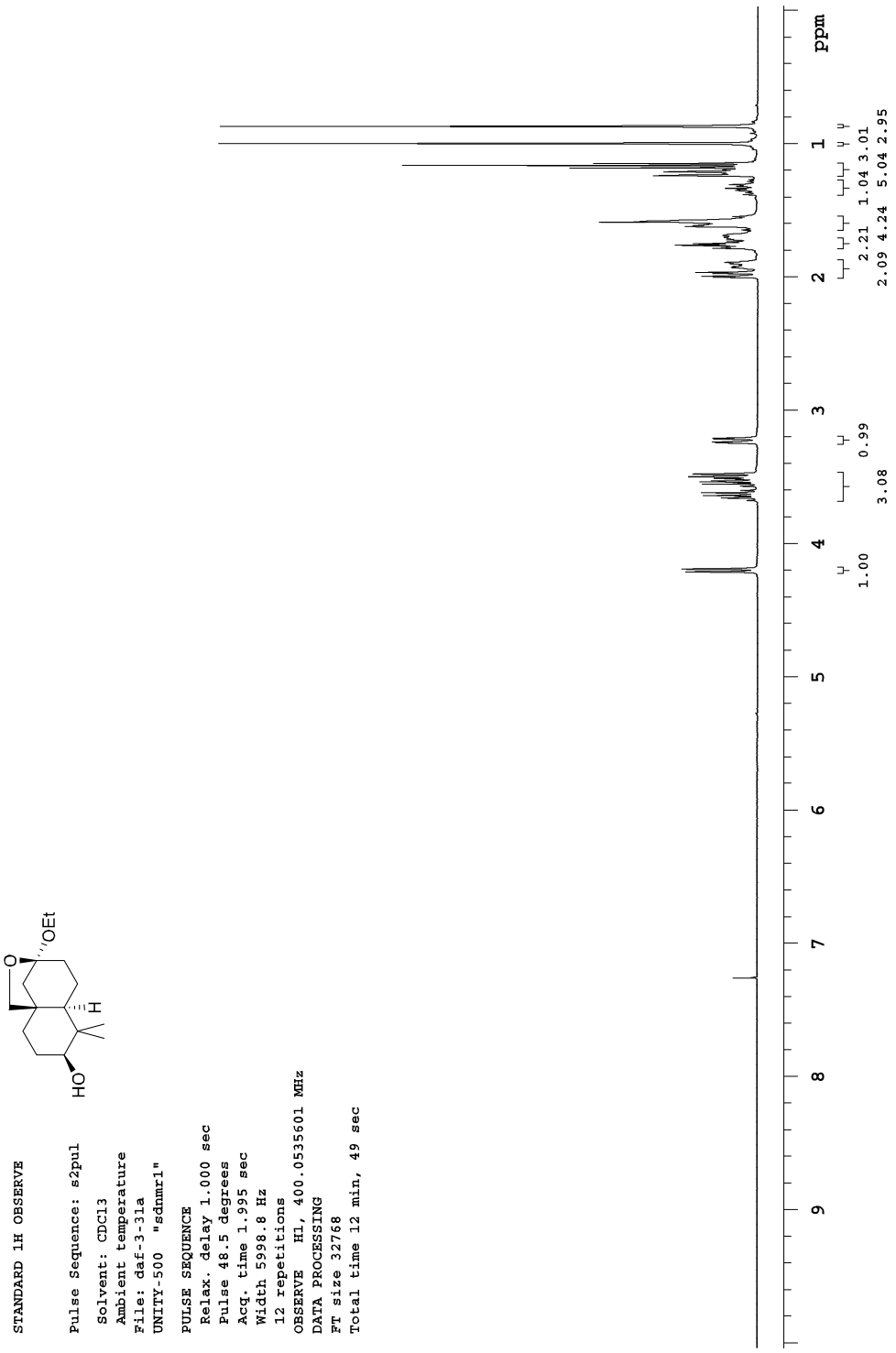
Spectrum 1.7 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **87**



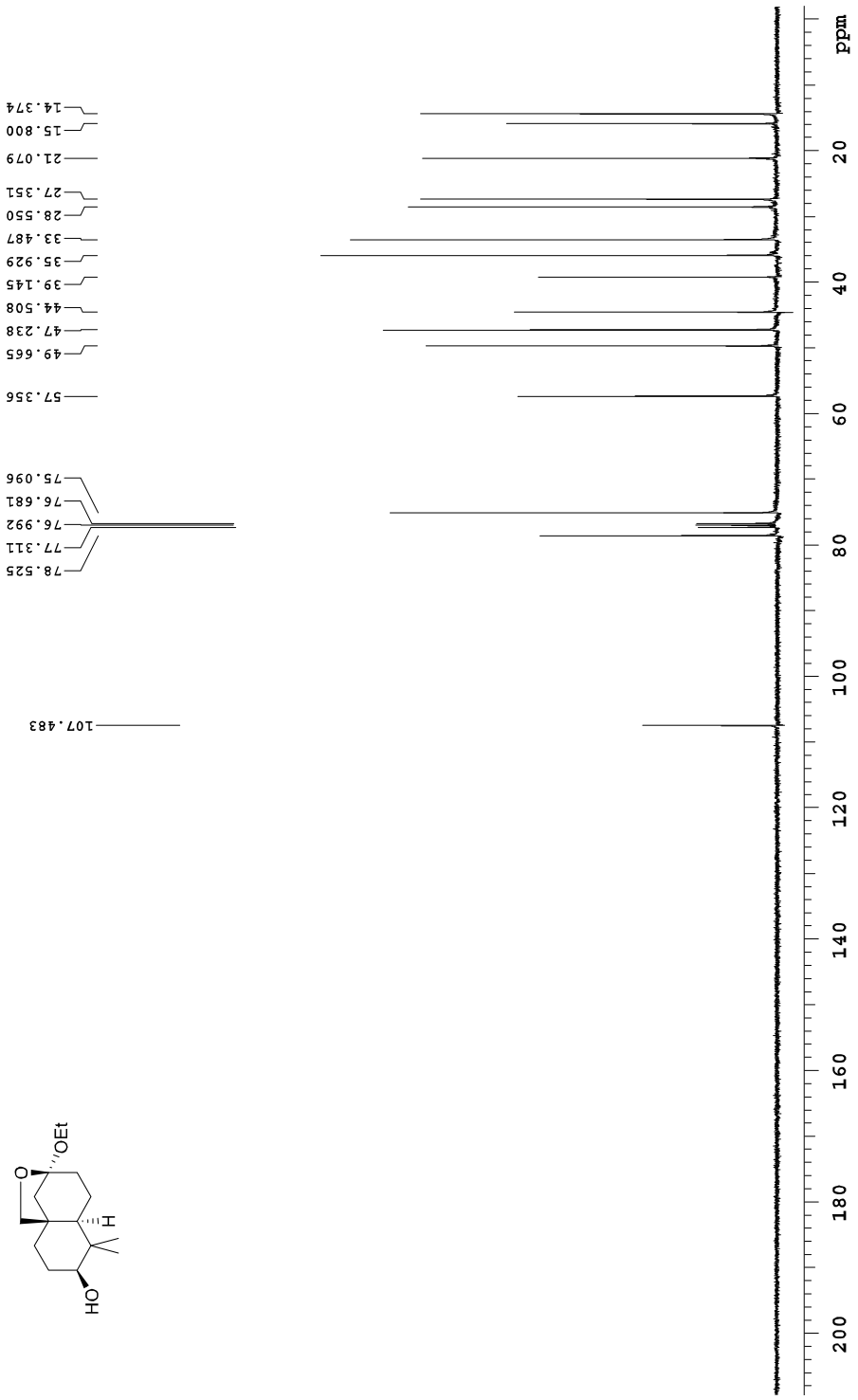
Spectrum 1.8 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **88**



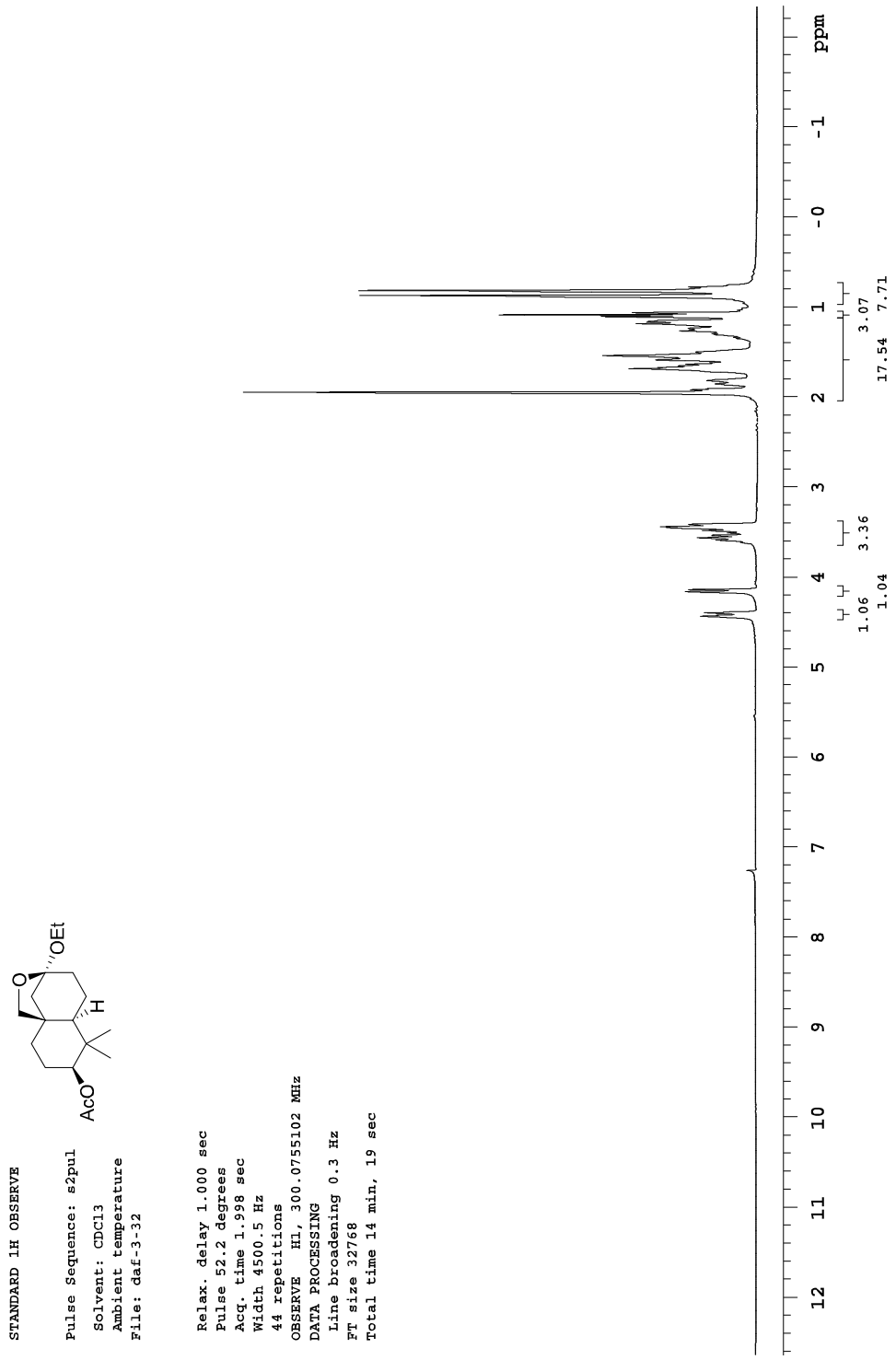
Spectrum 1.9 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **88**



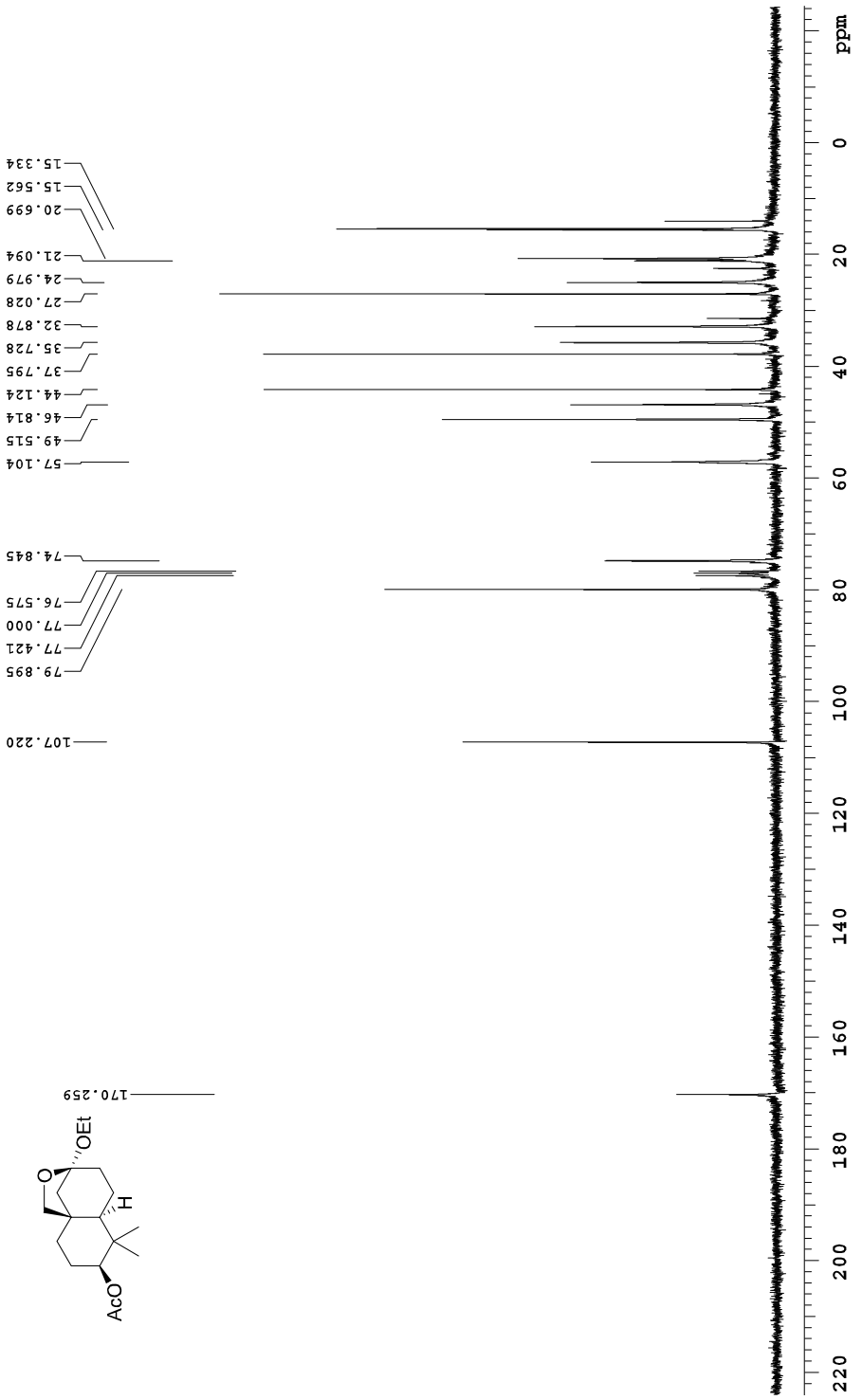
Spectrum 1.10 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **89**



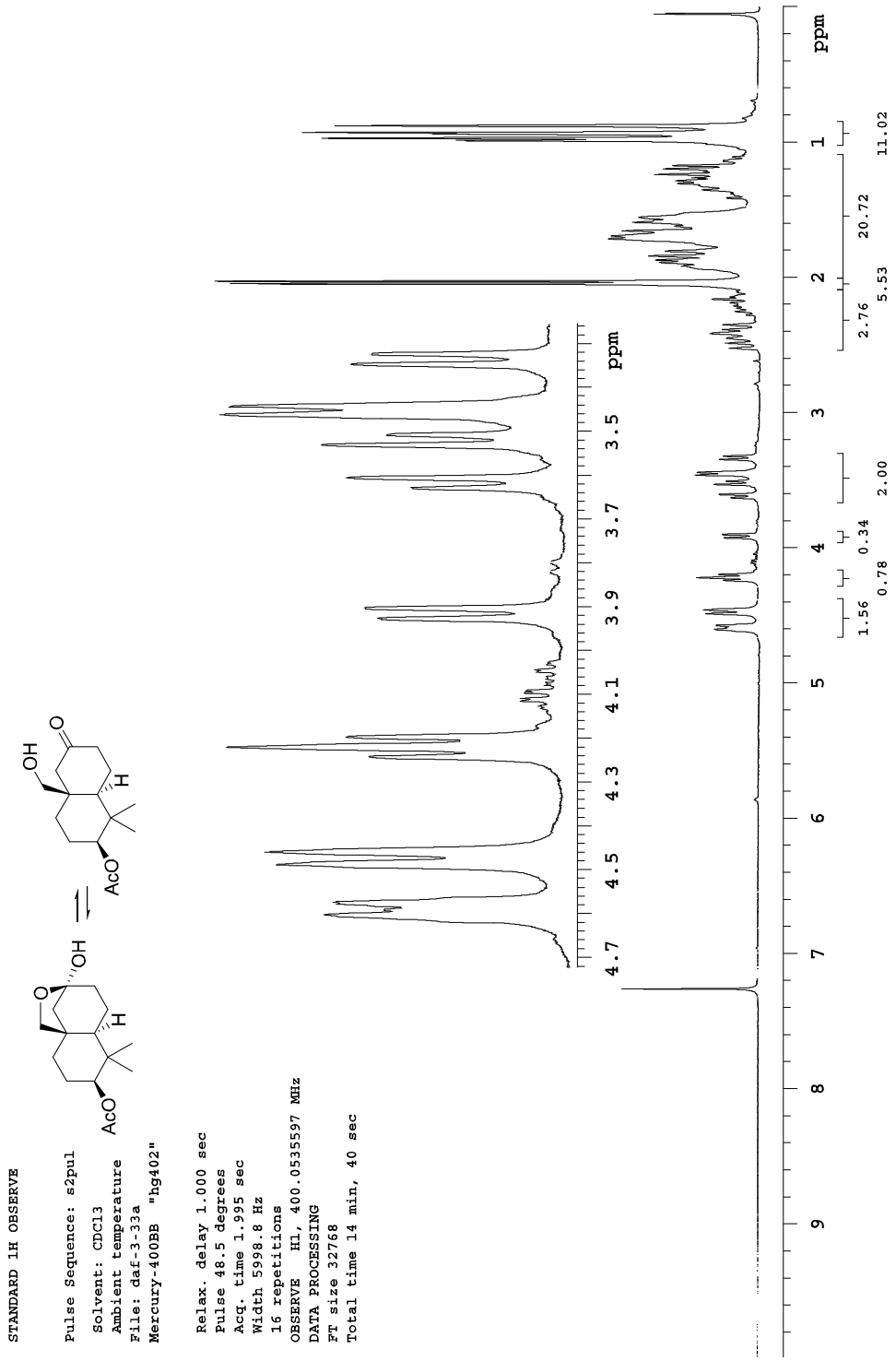
Spectrum 1.11 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **89**



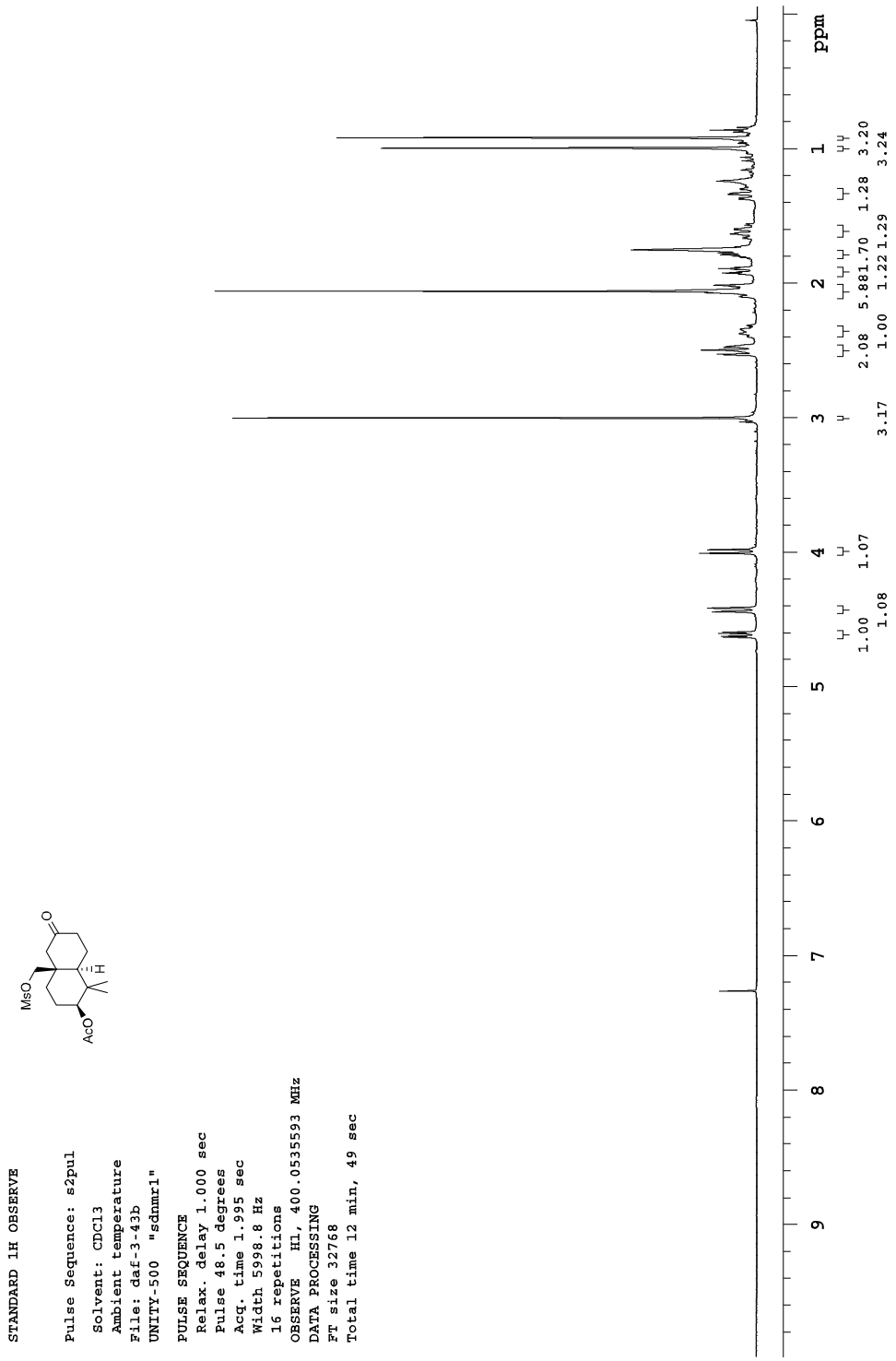
Spectrum 1.12 ^{1}H NMR ($CDCl_3$, 300 MHz) of compound **90**



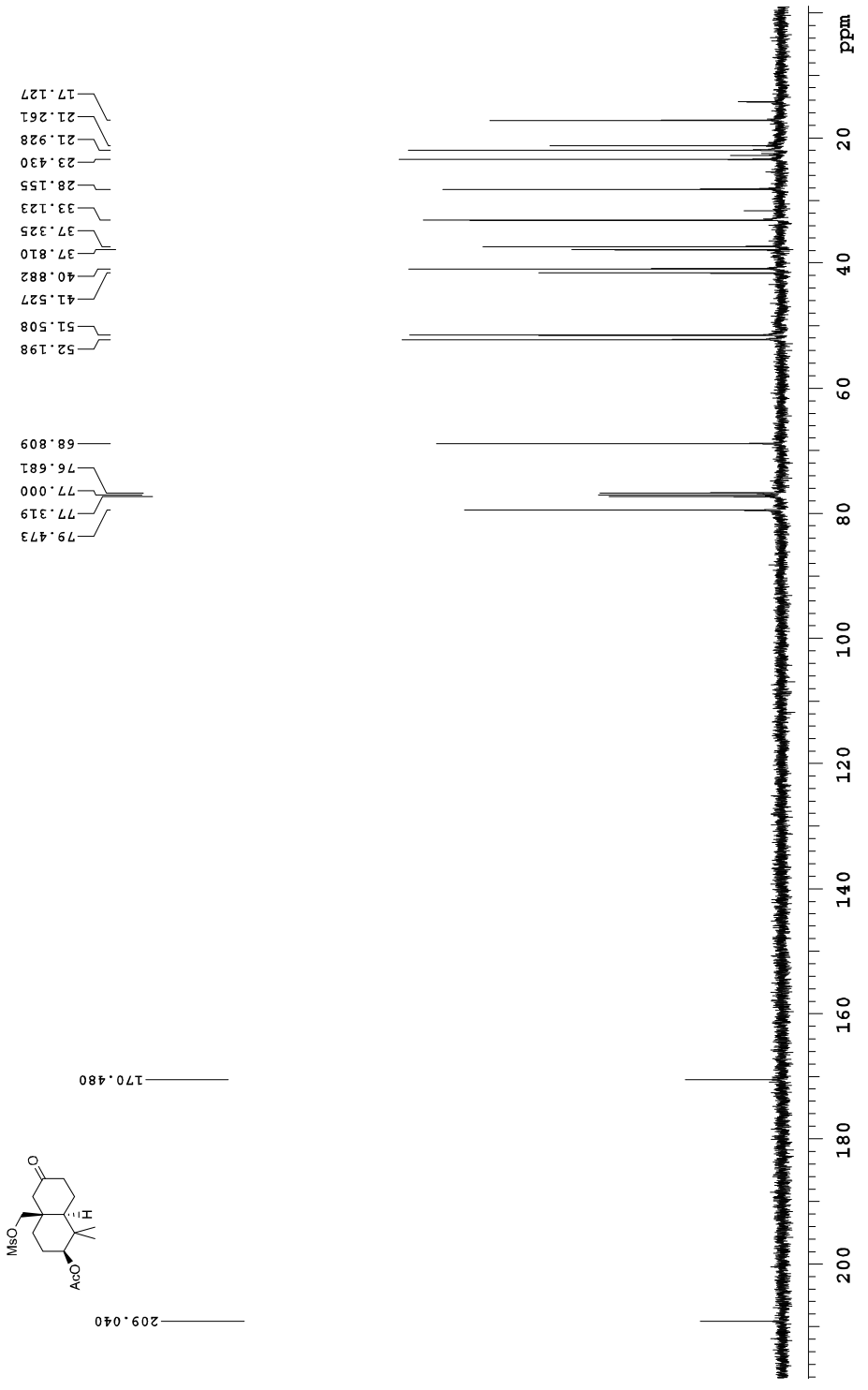
Spectrum 1.13 ^{13}C NMR ($CDCl_3$, 75 MHz) of compound **90**



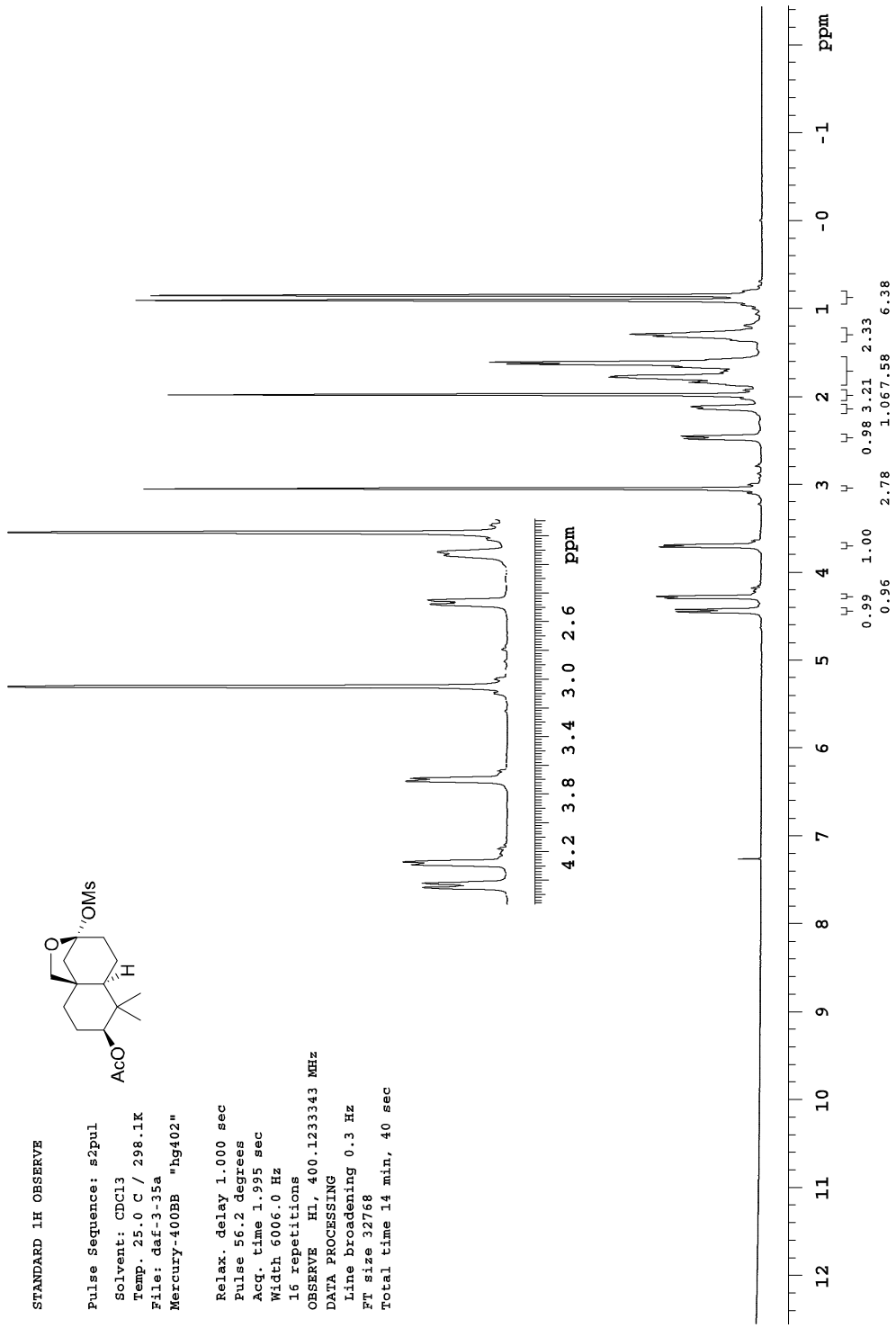
Spectrum 1.14 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **91**



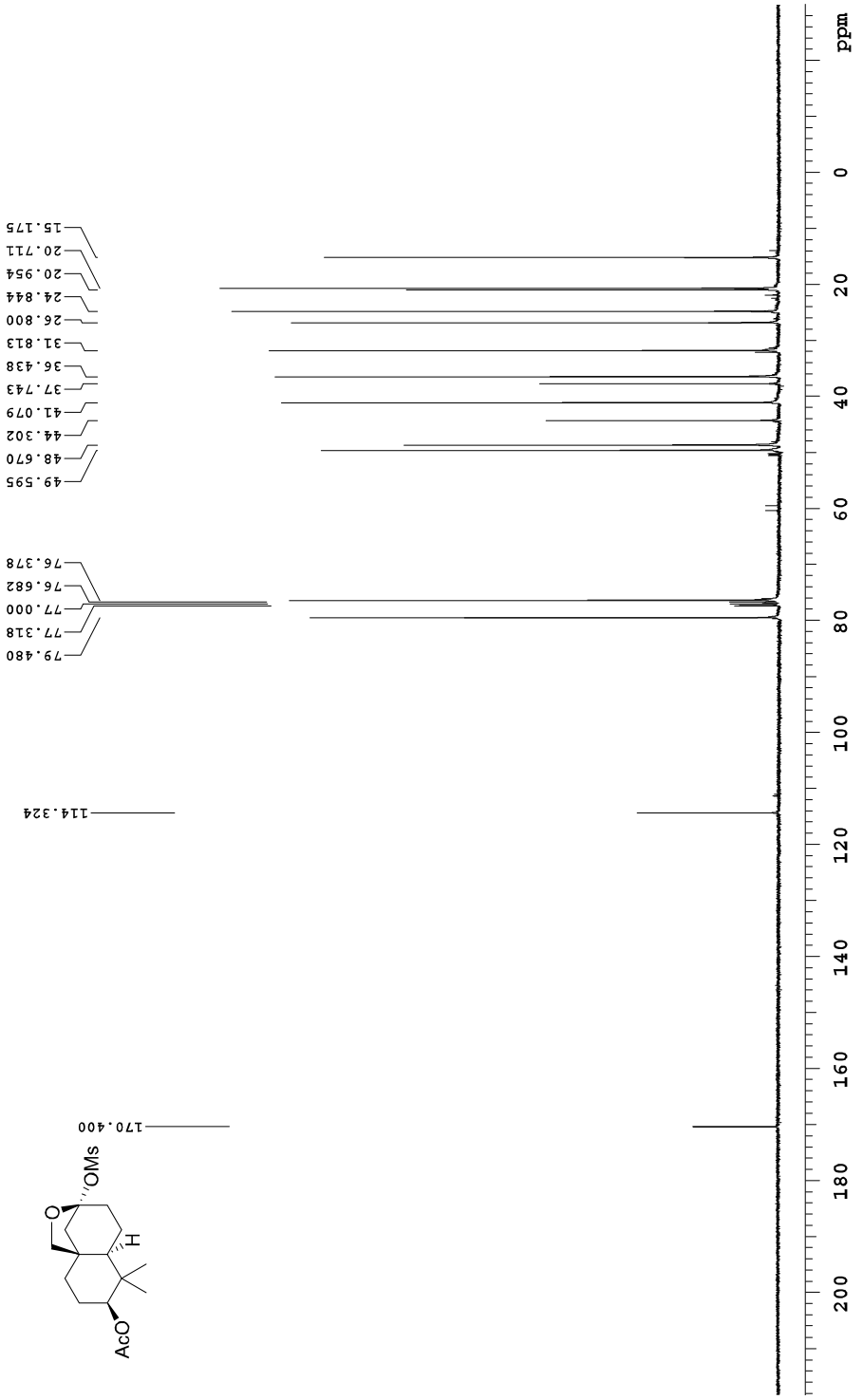
Spectrum 1.15 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **92b**



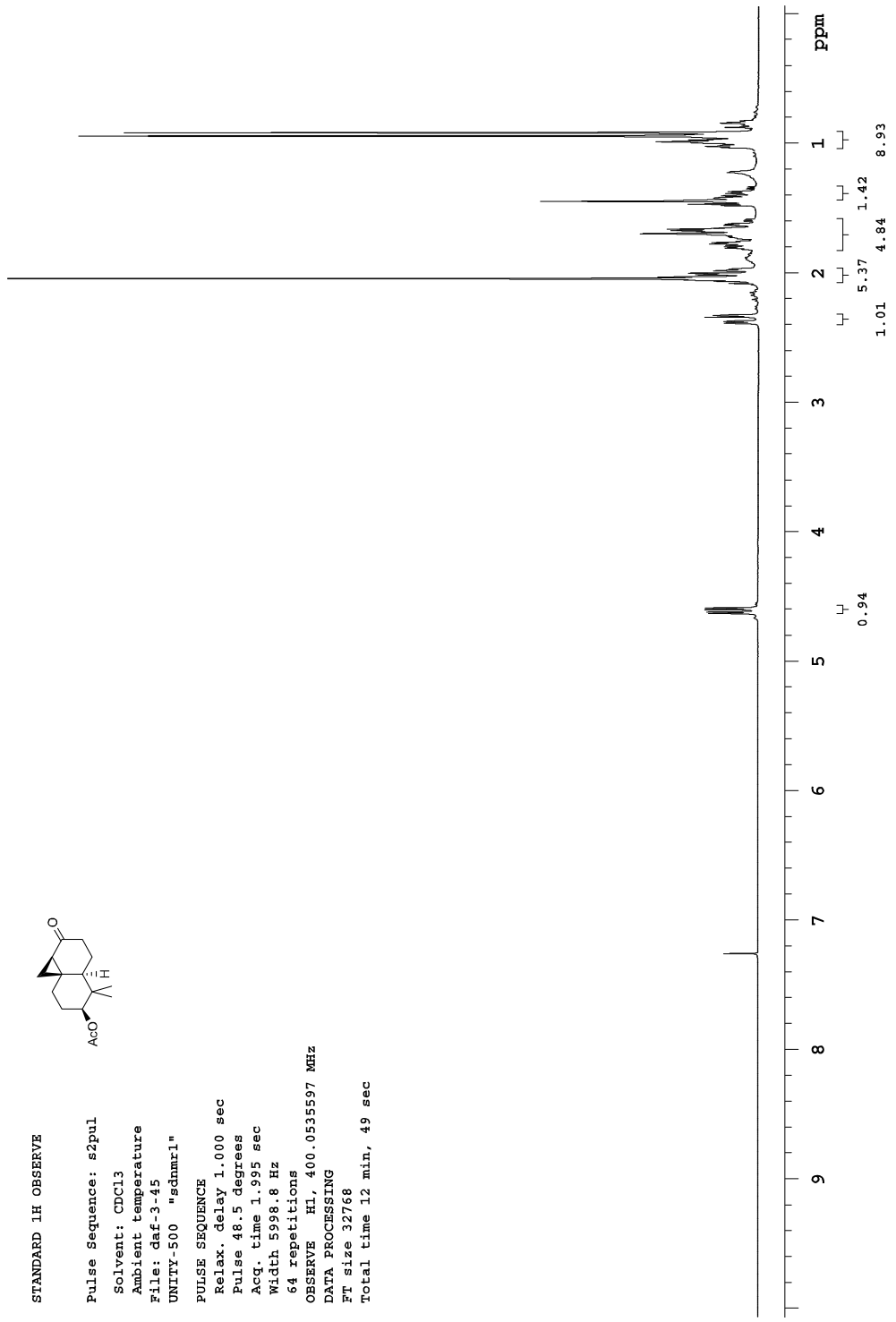
Spectrum 1.16 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **92b**



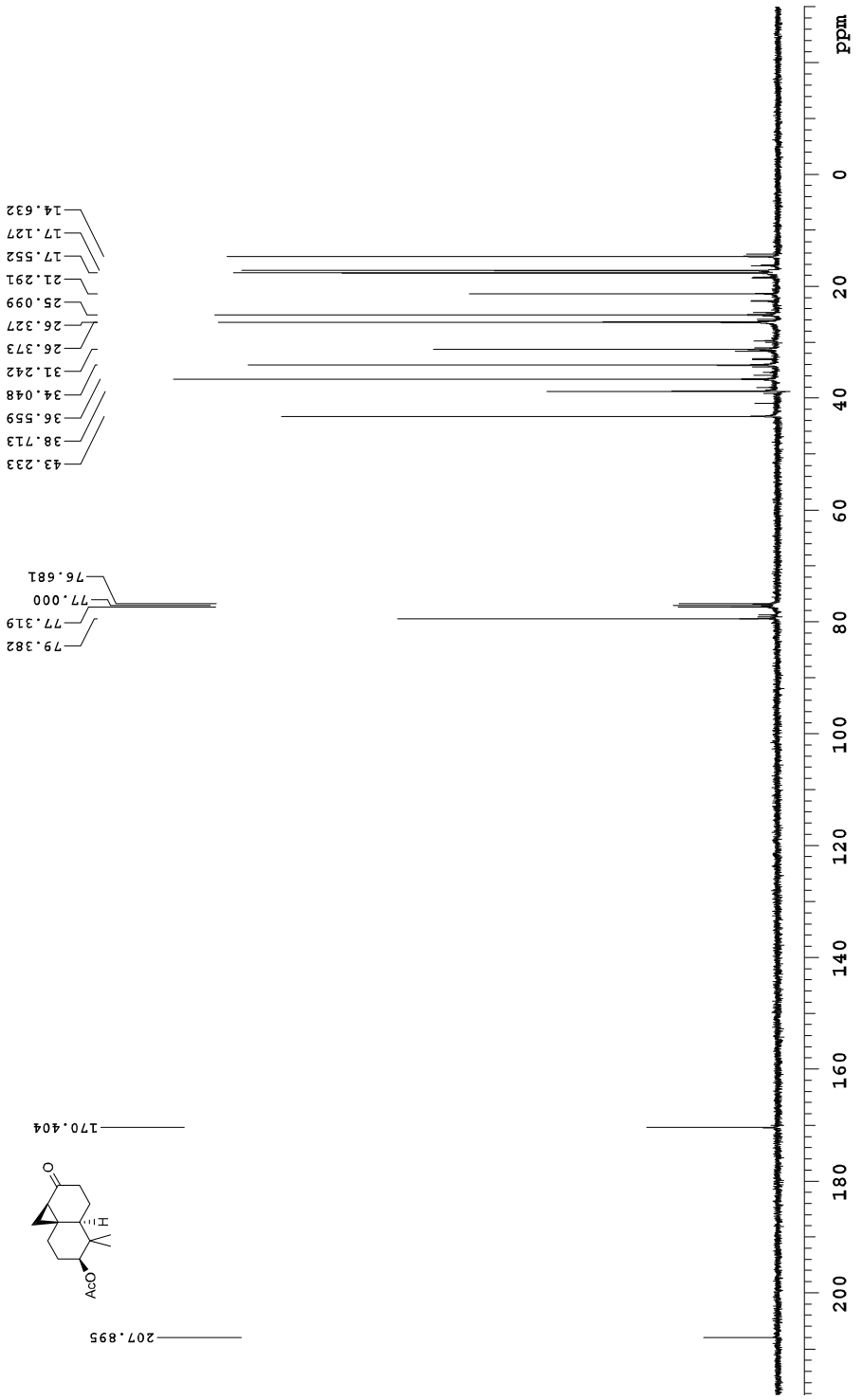
Spectrum 1.17 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **92a**



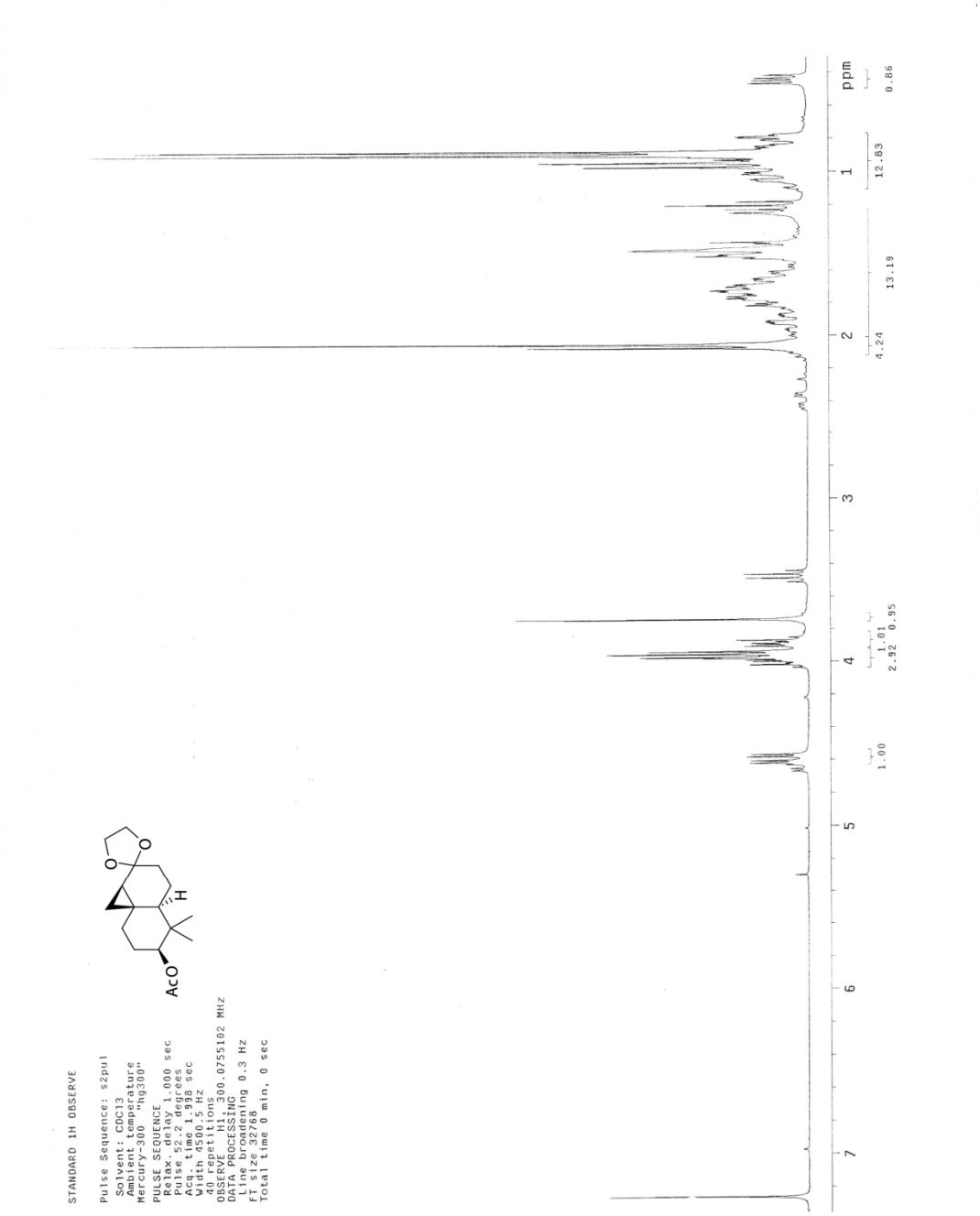
Spectrum 1.18 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **92a**



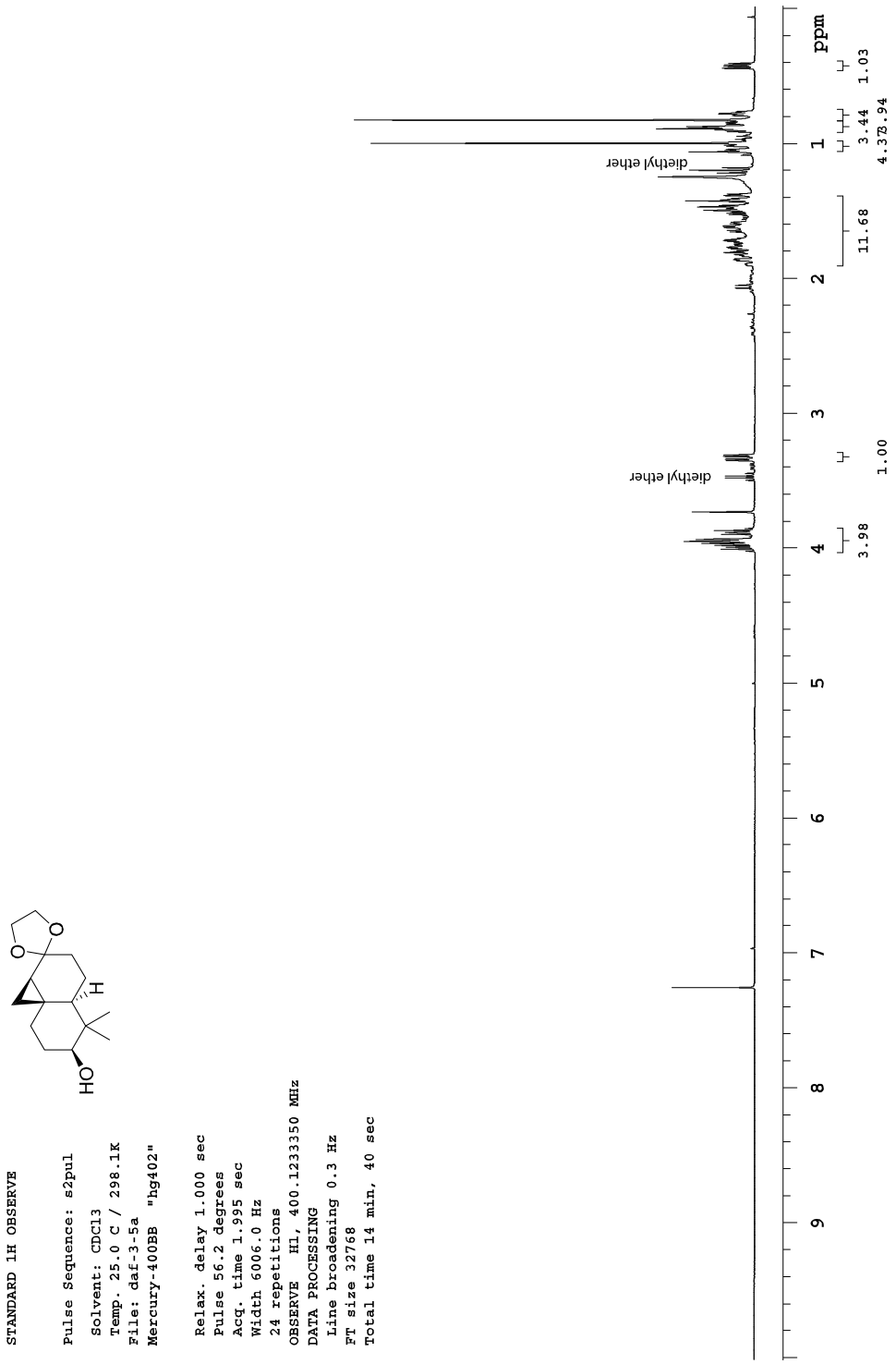
Spectrum 1.19 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **80**



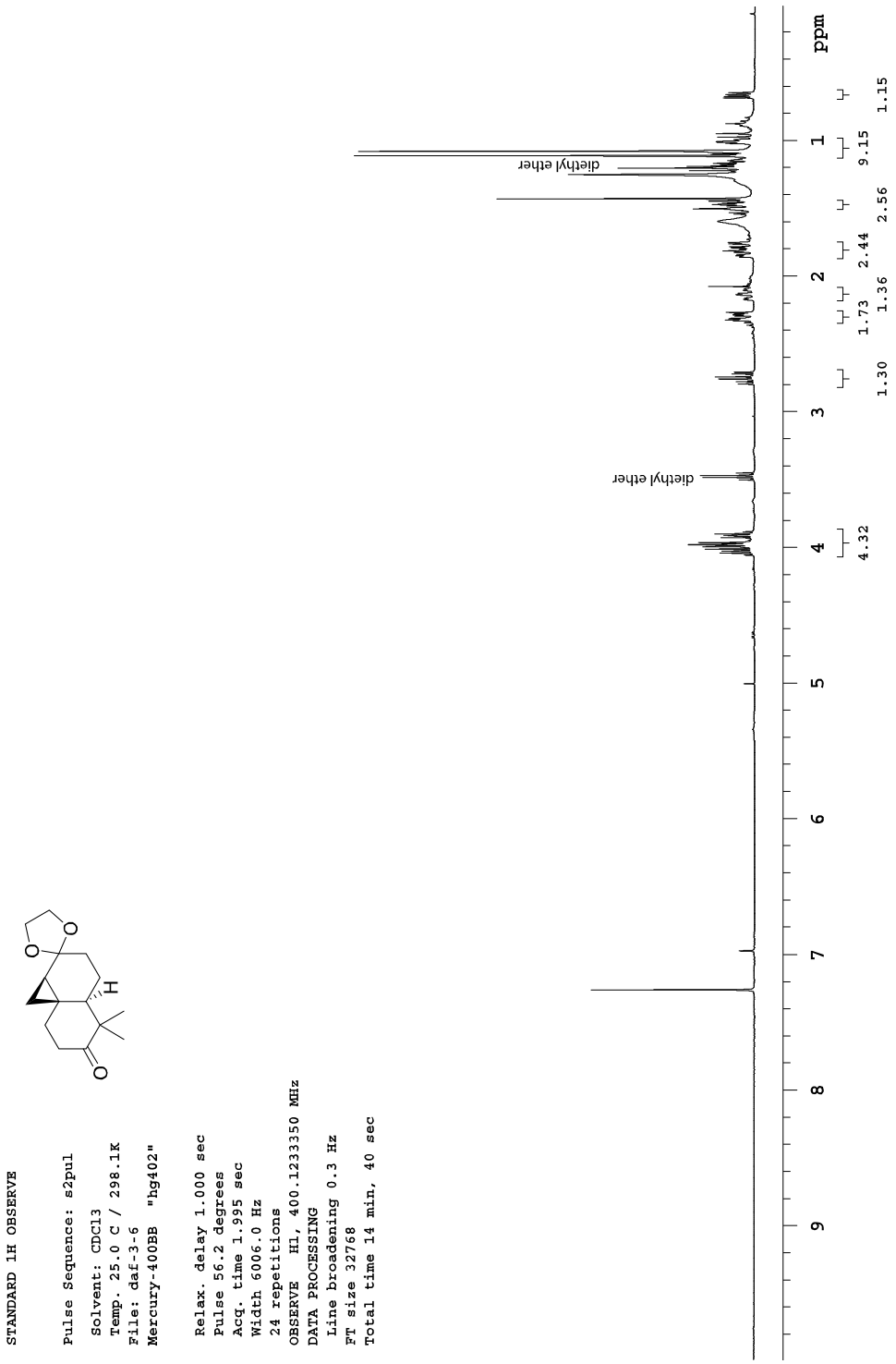
Spectrum 1.20 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **80**



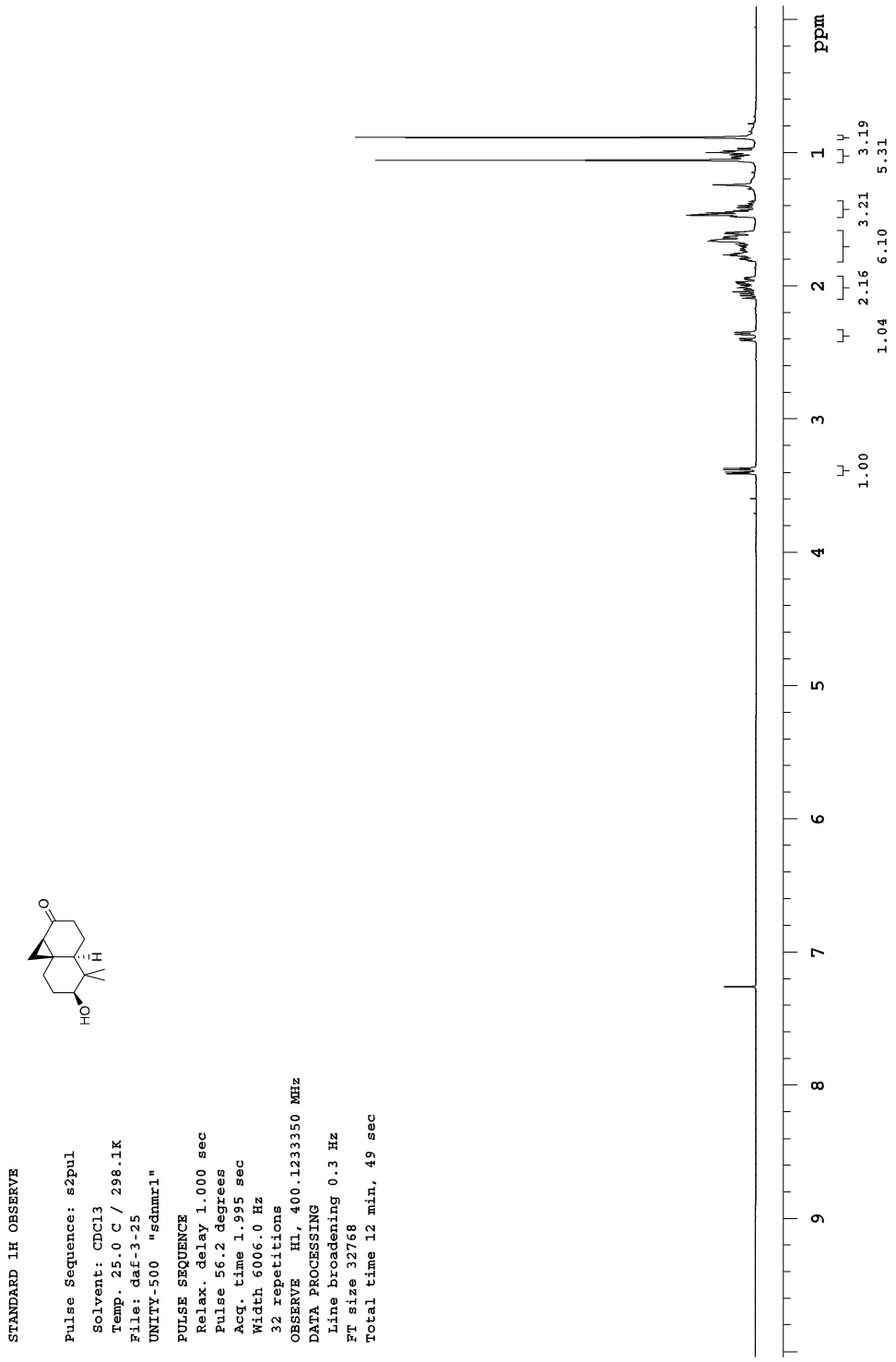
Spectrum 1.21 ^{1}H NMR ($CDCl_3$, 300 MHz) of compound **93**



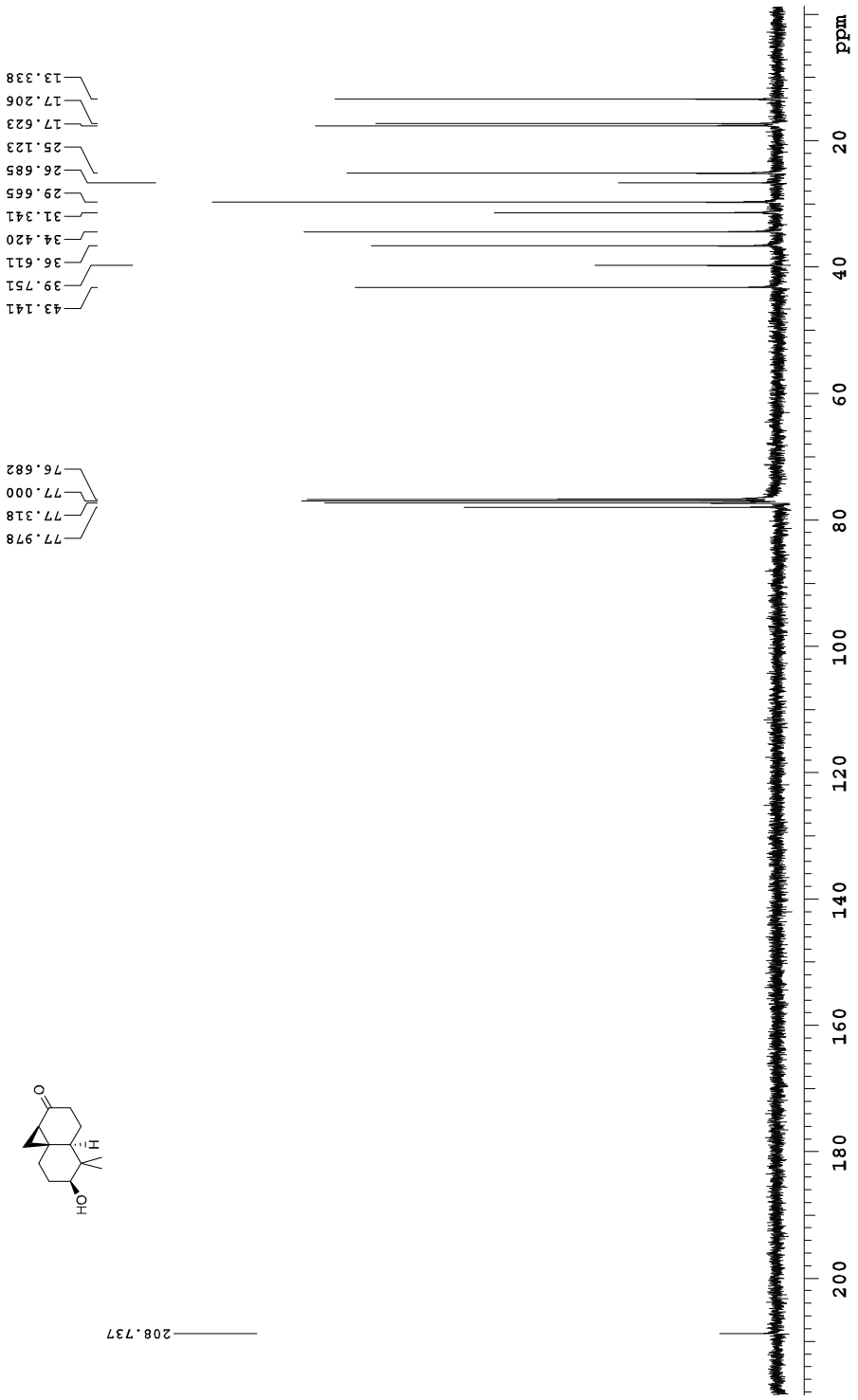
Spectrum 1.22 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **94**



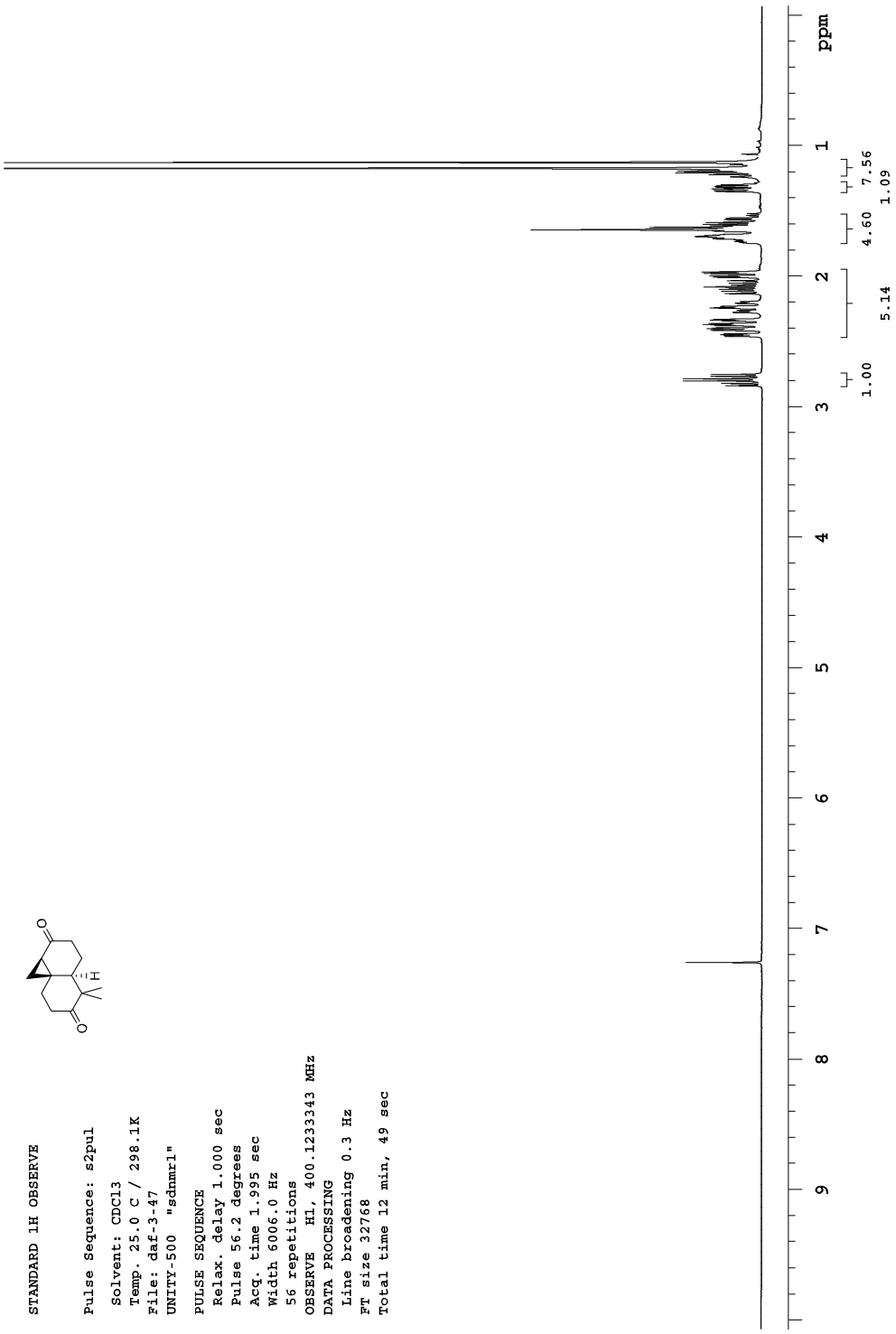
Spectrum 1.23 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **95**



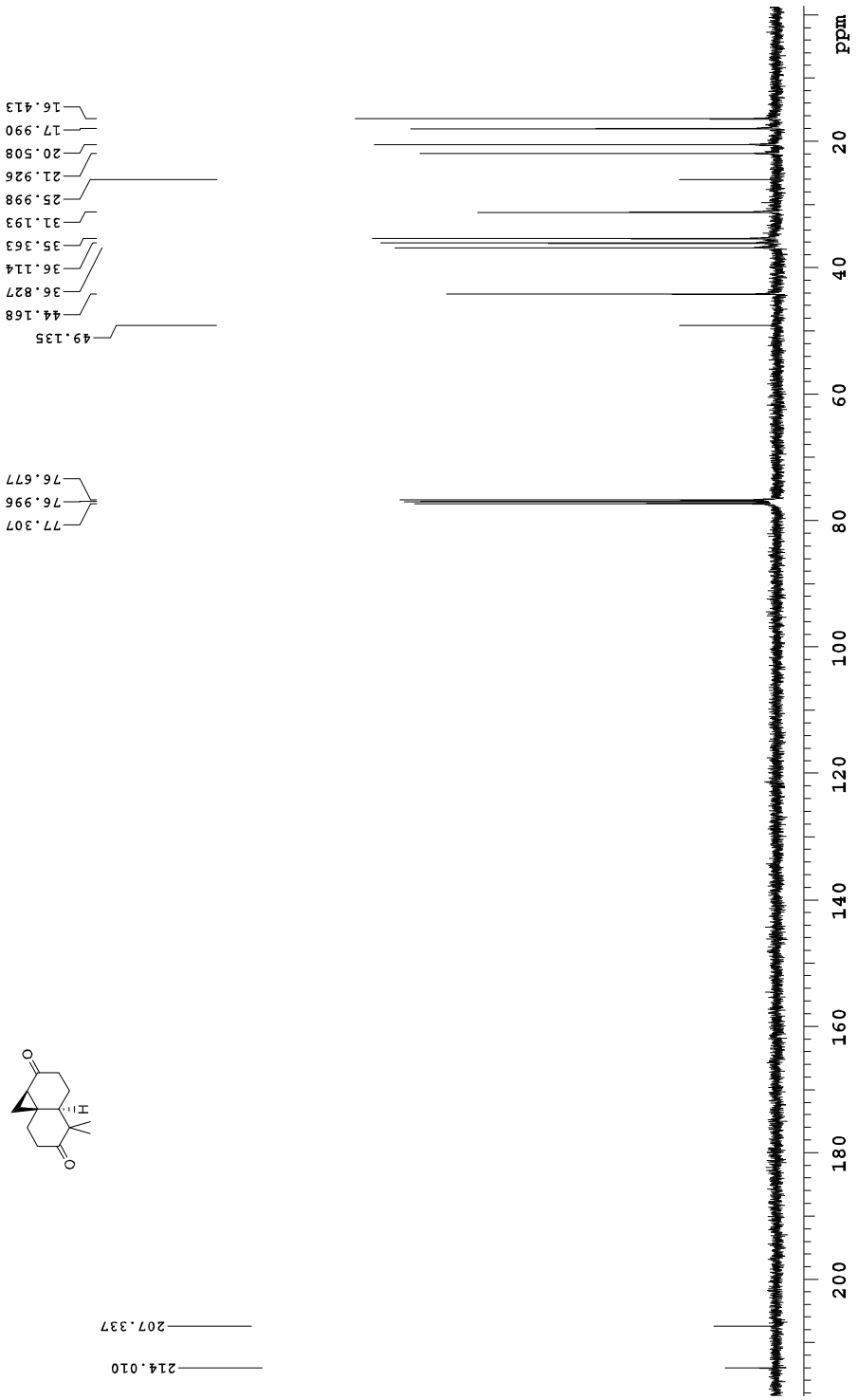
Spectrum 1.24 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **96**



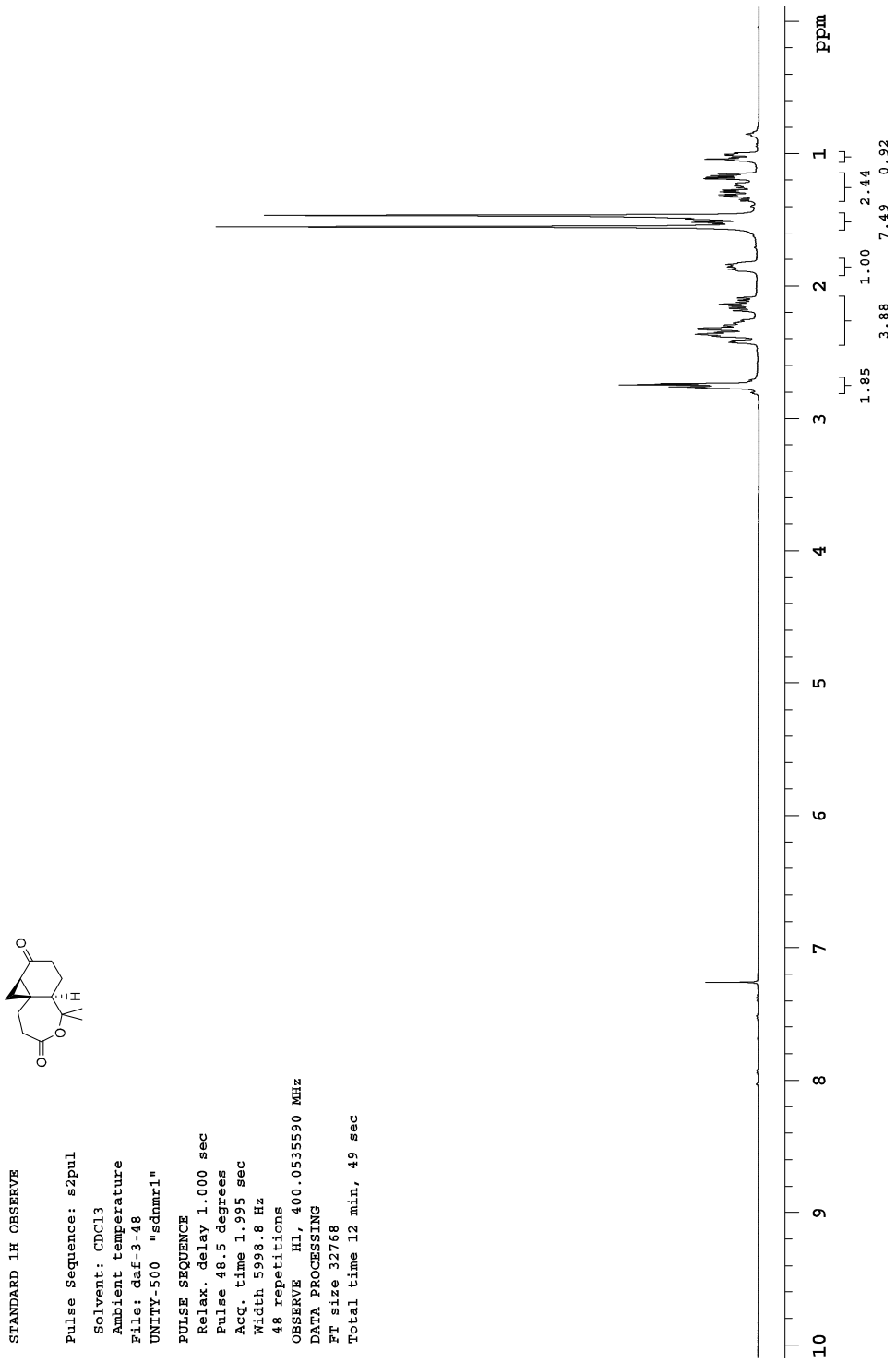
Spectrum 1.25 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **96**



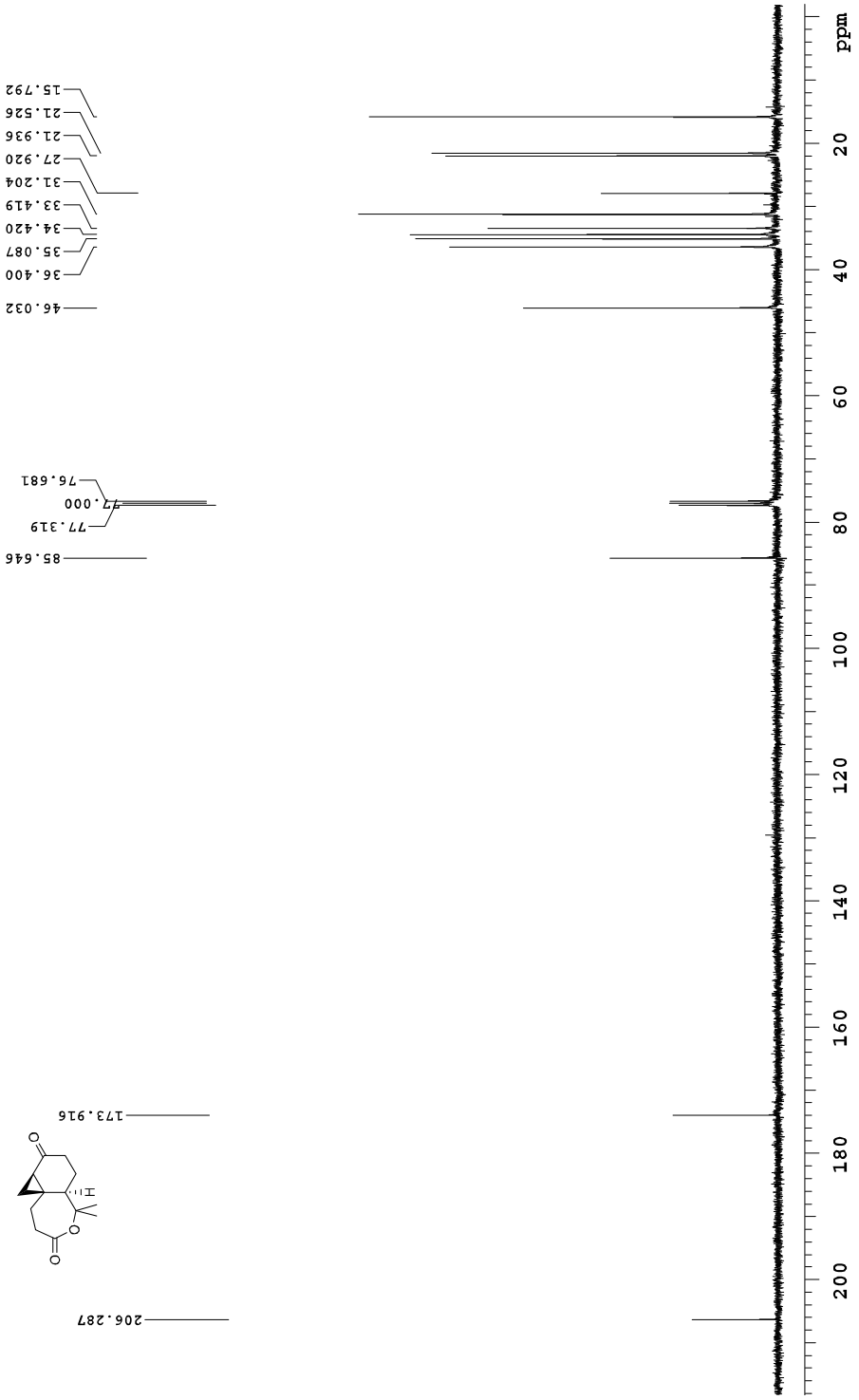
Spectrum 1.26 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **97**



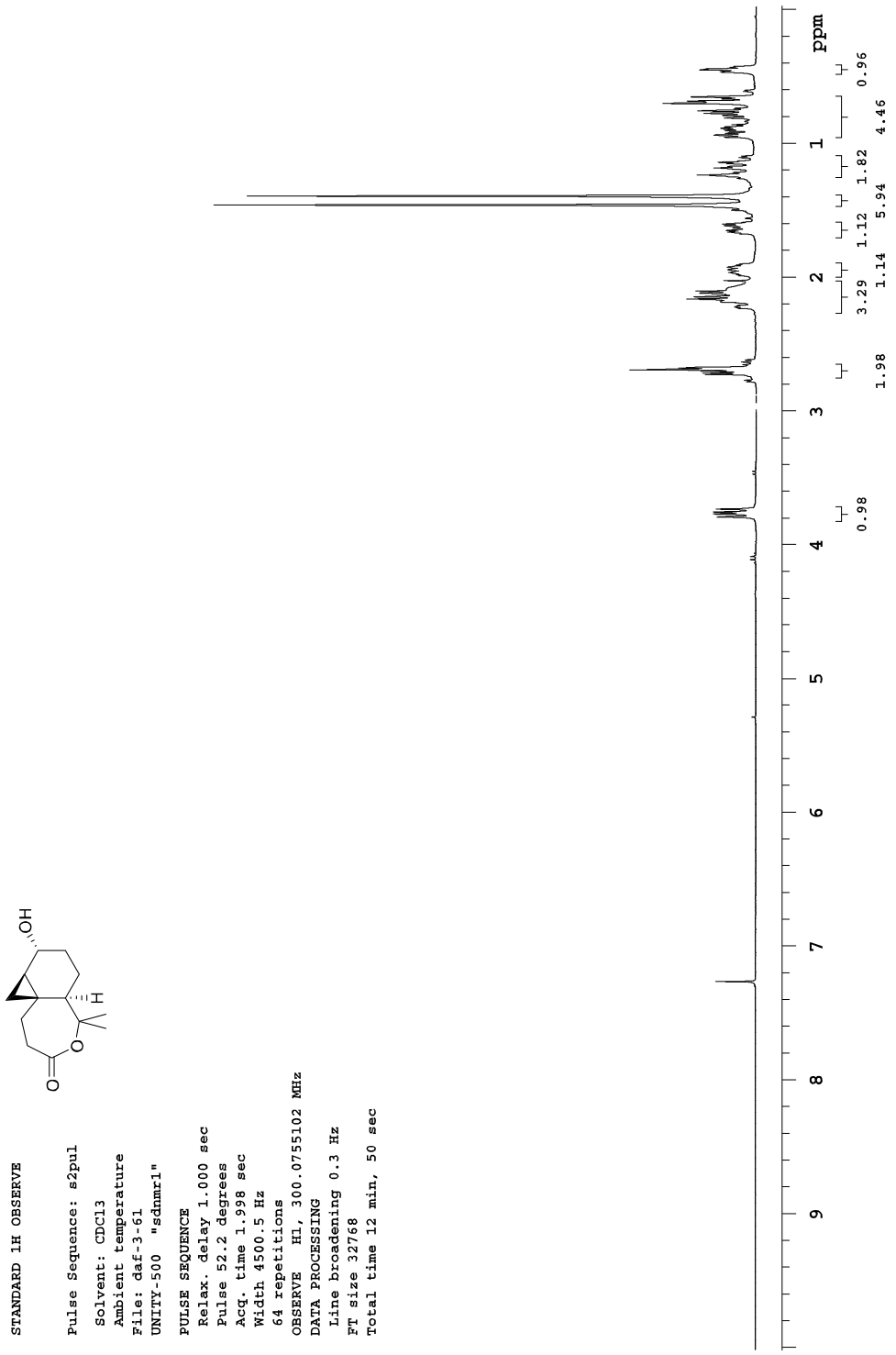
Spectrum 1.27 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **97**



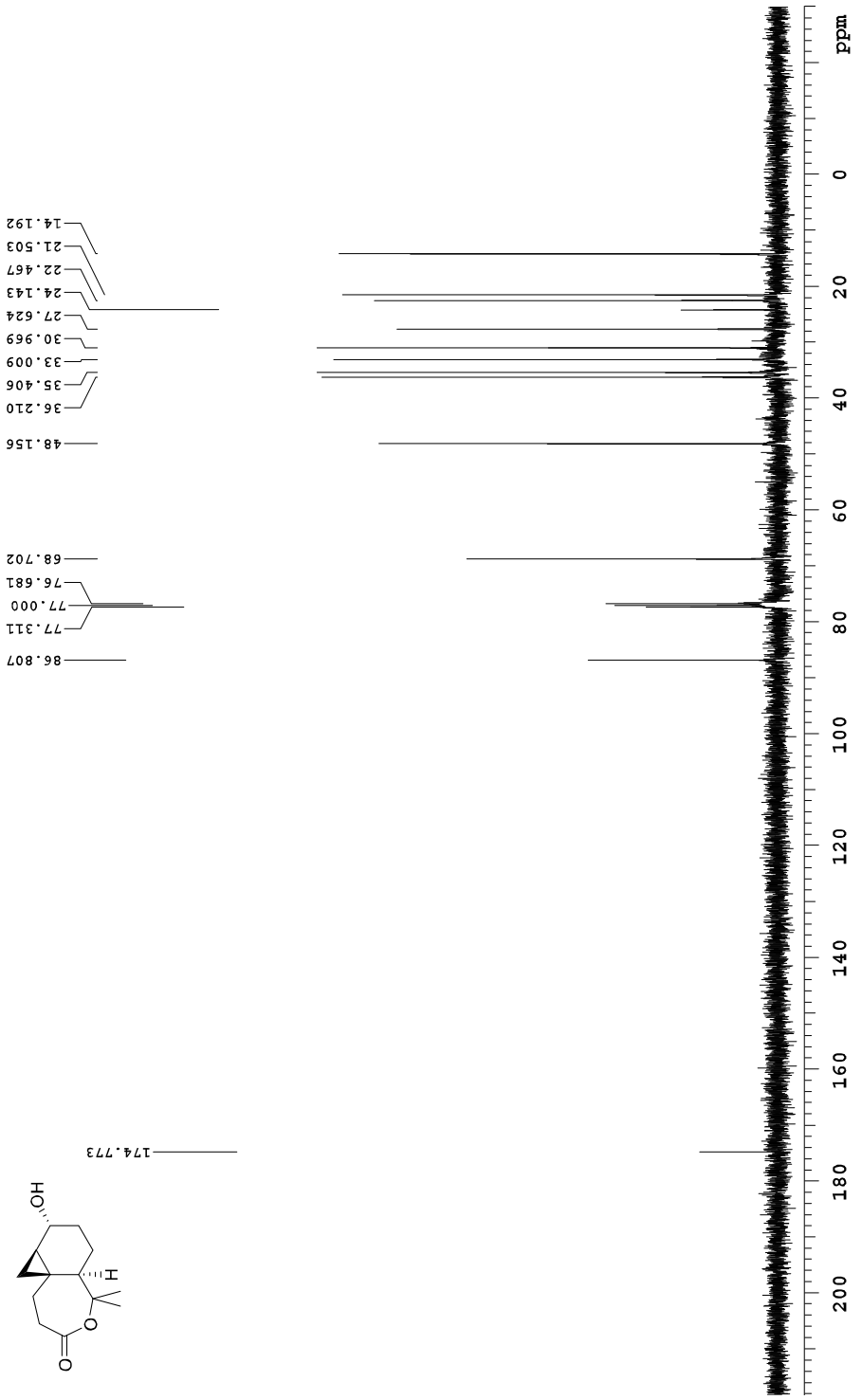
Spectrum 1.28 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **98**



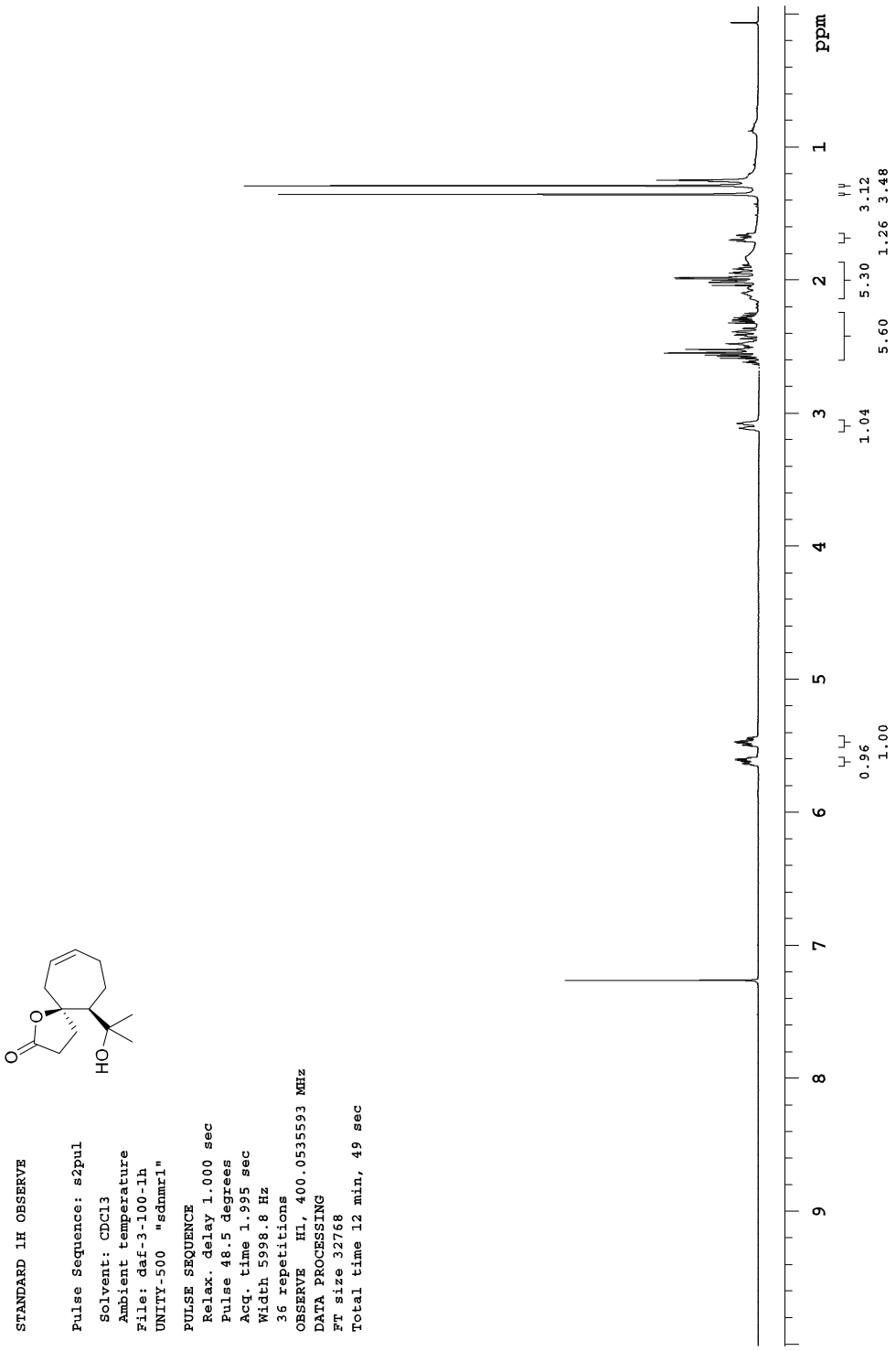
Spectrum 1.29 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **98**



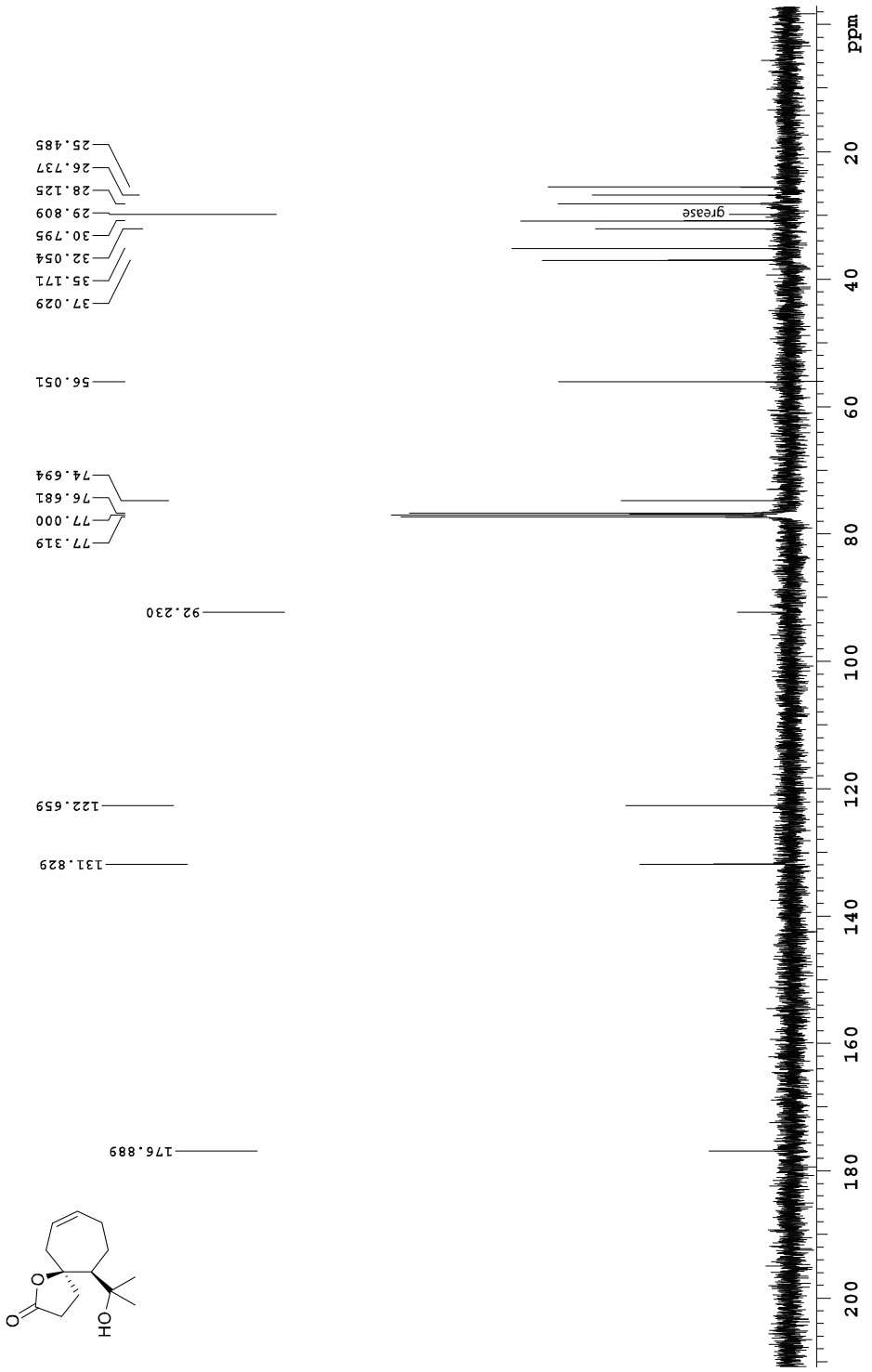
Spectrum 1.30 ^{1}H NMR ($CDCl_3$, 300 MHz) of compound **99**



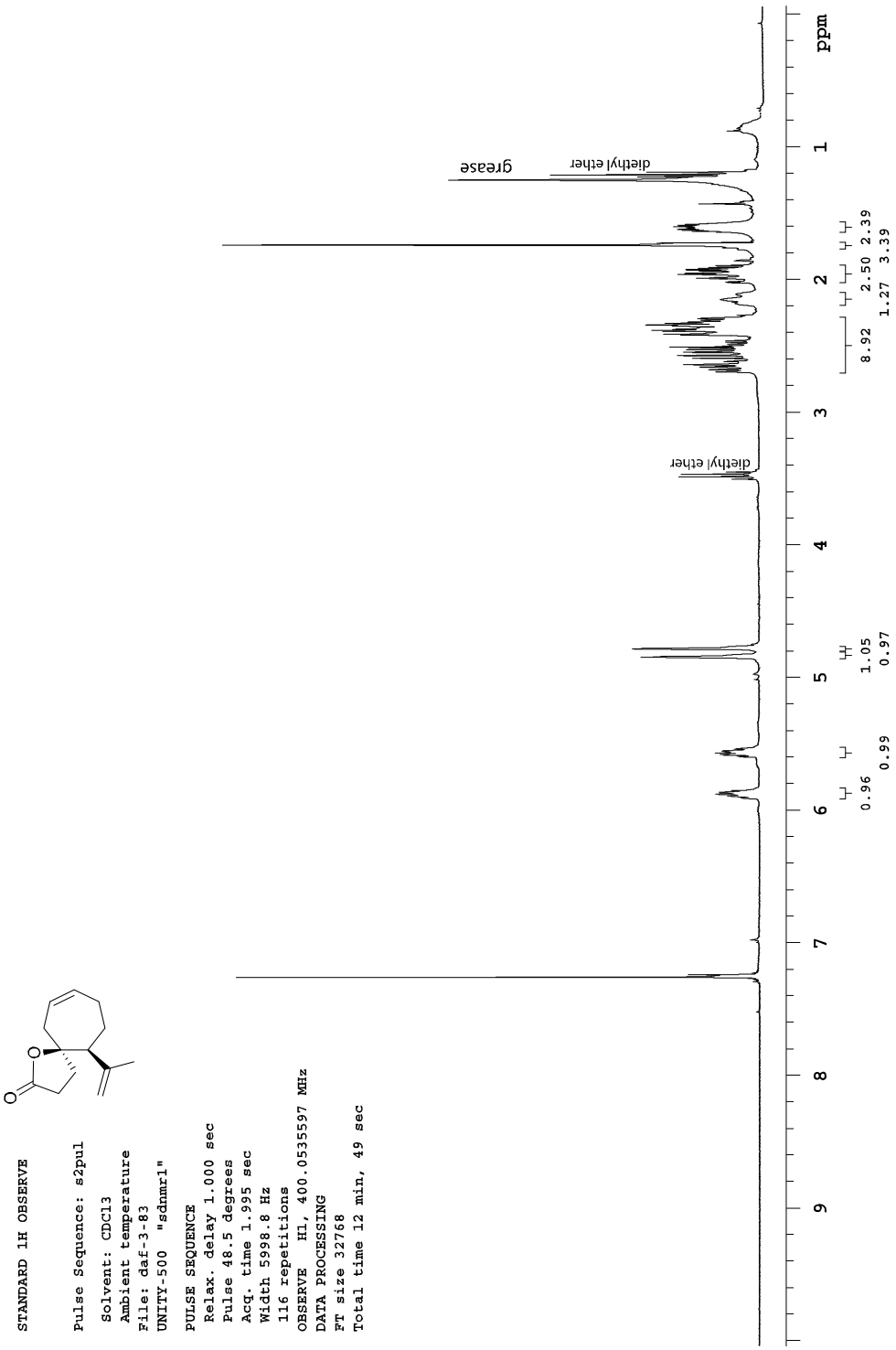
Spectrum 1.31 ^{13}C NMR ($CDCl_3$, 75 MHz) of compound **99**



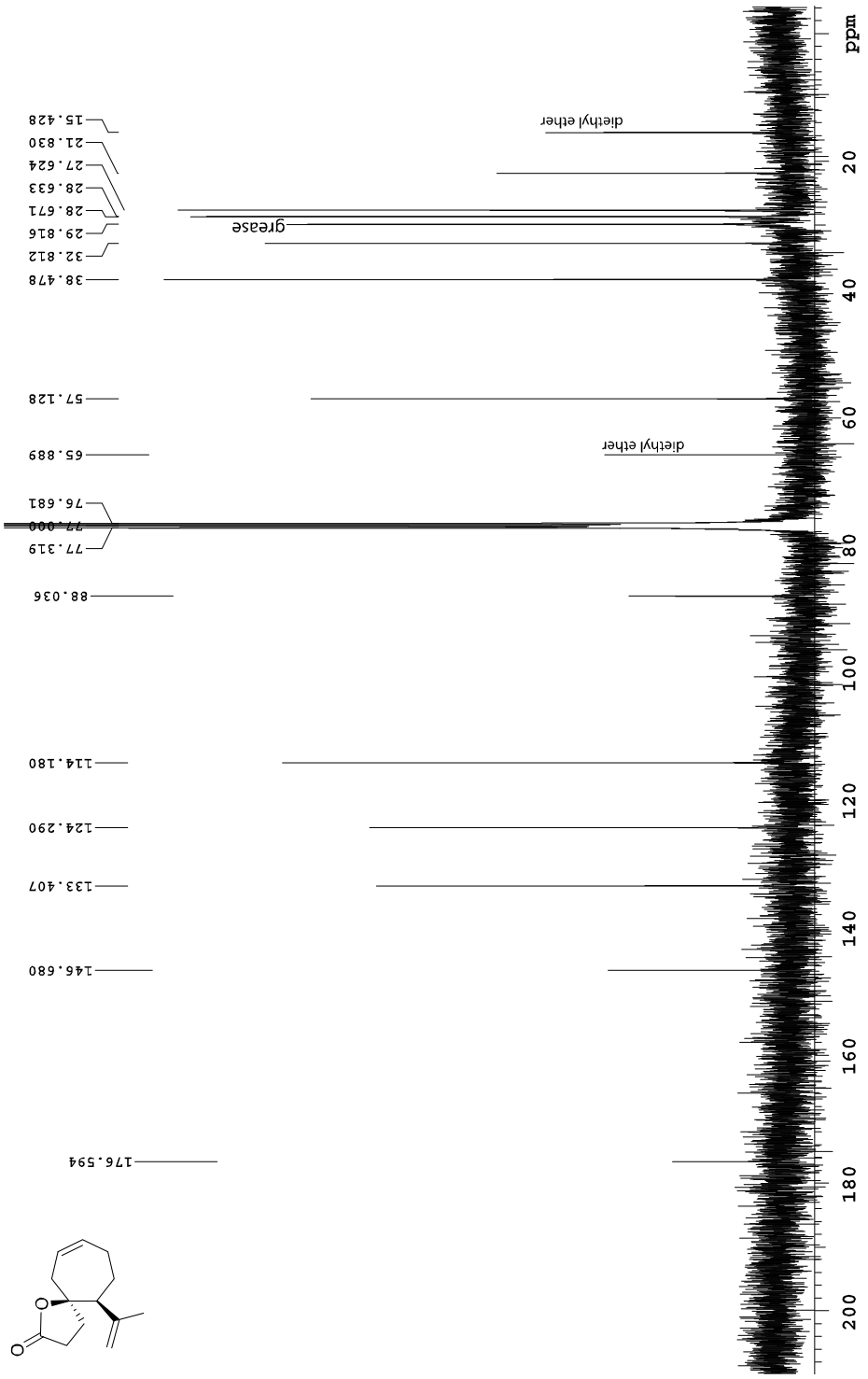
Spectrum 1.32 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **100**



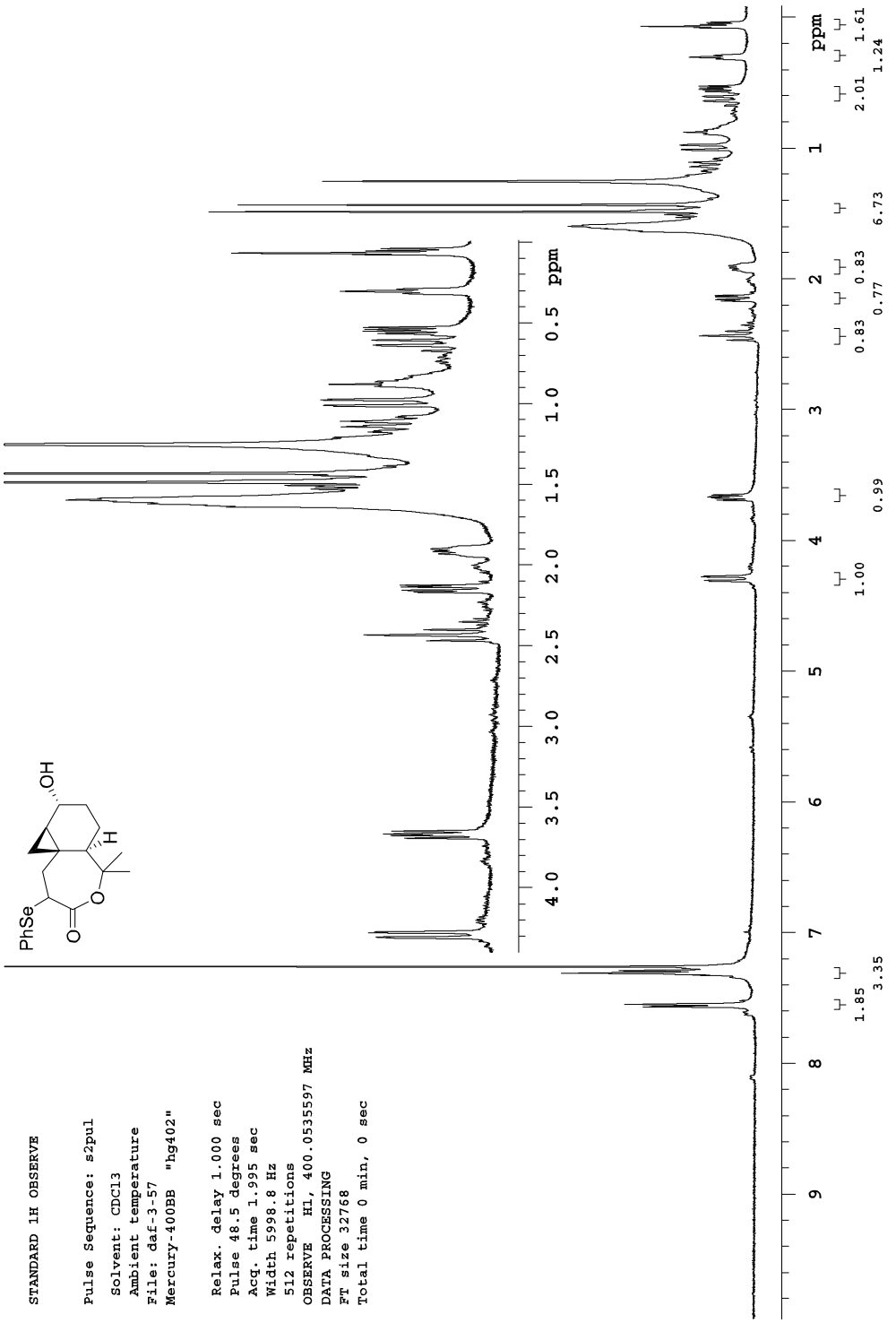
Spectrum 1.33 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **100**



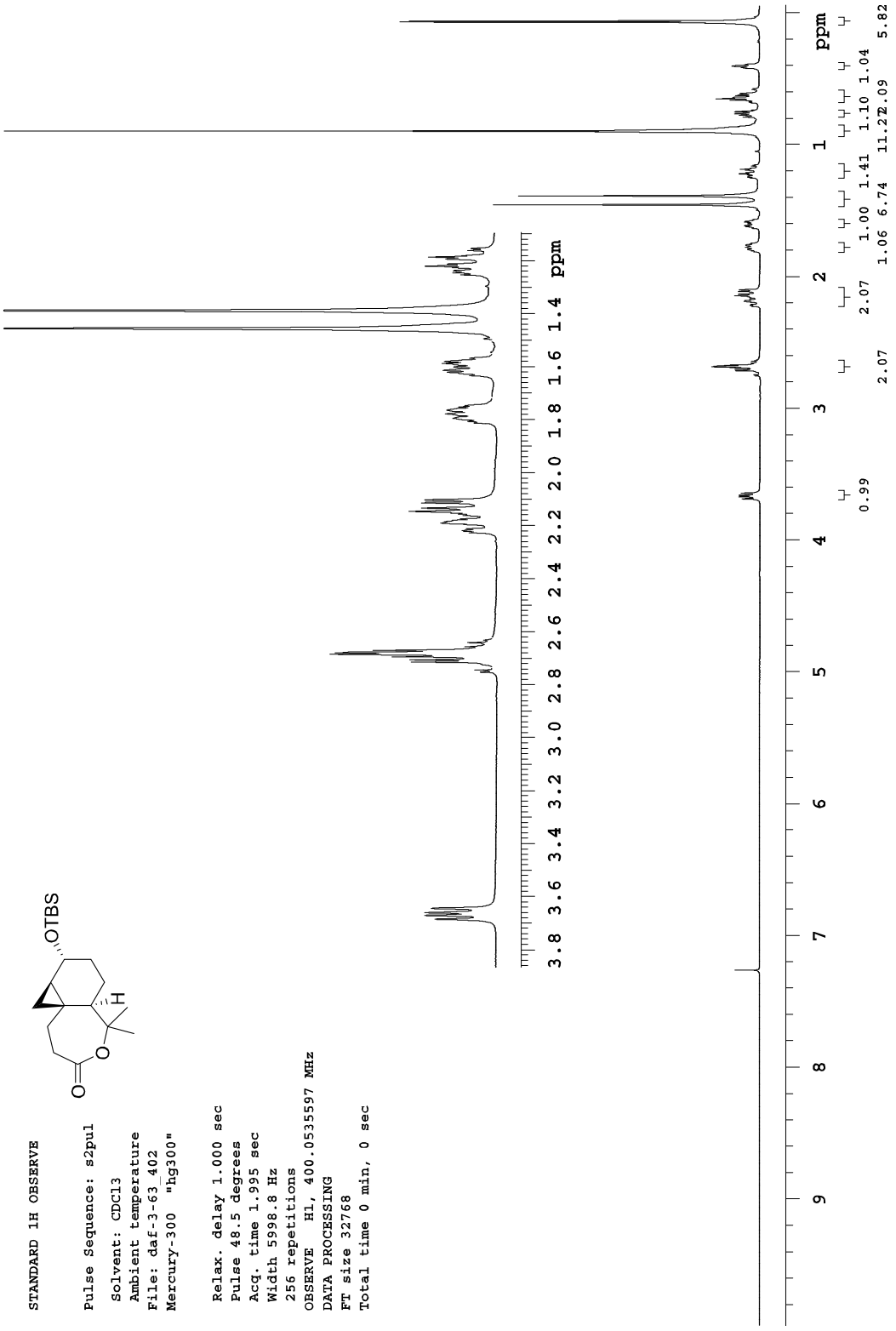
Spectrum 1.34 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **101**



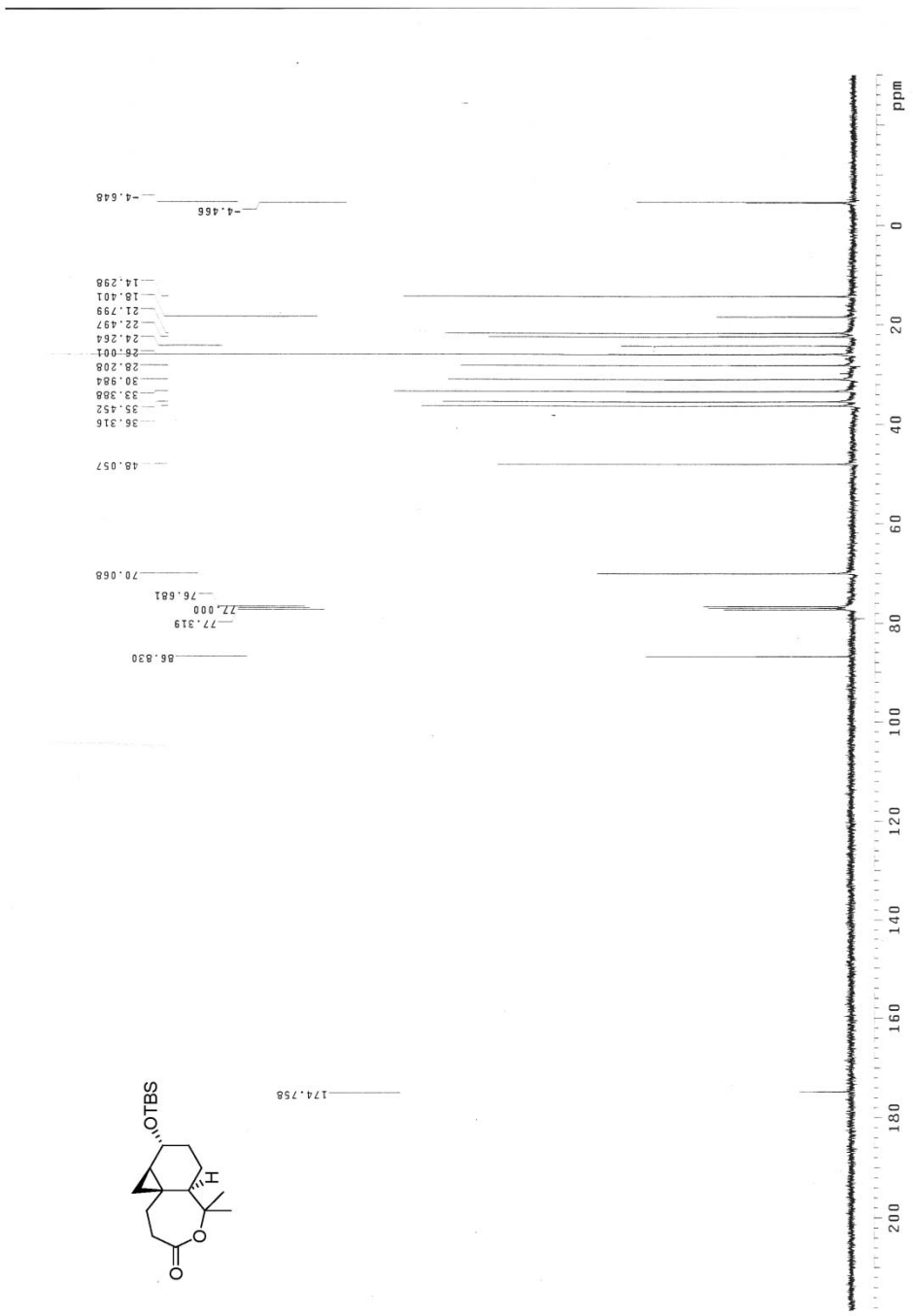
Spectrum 1.35 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **101**



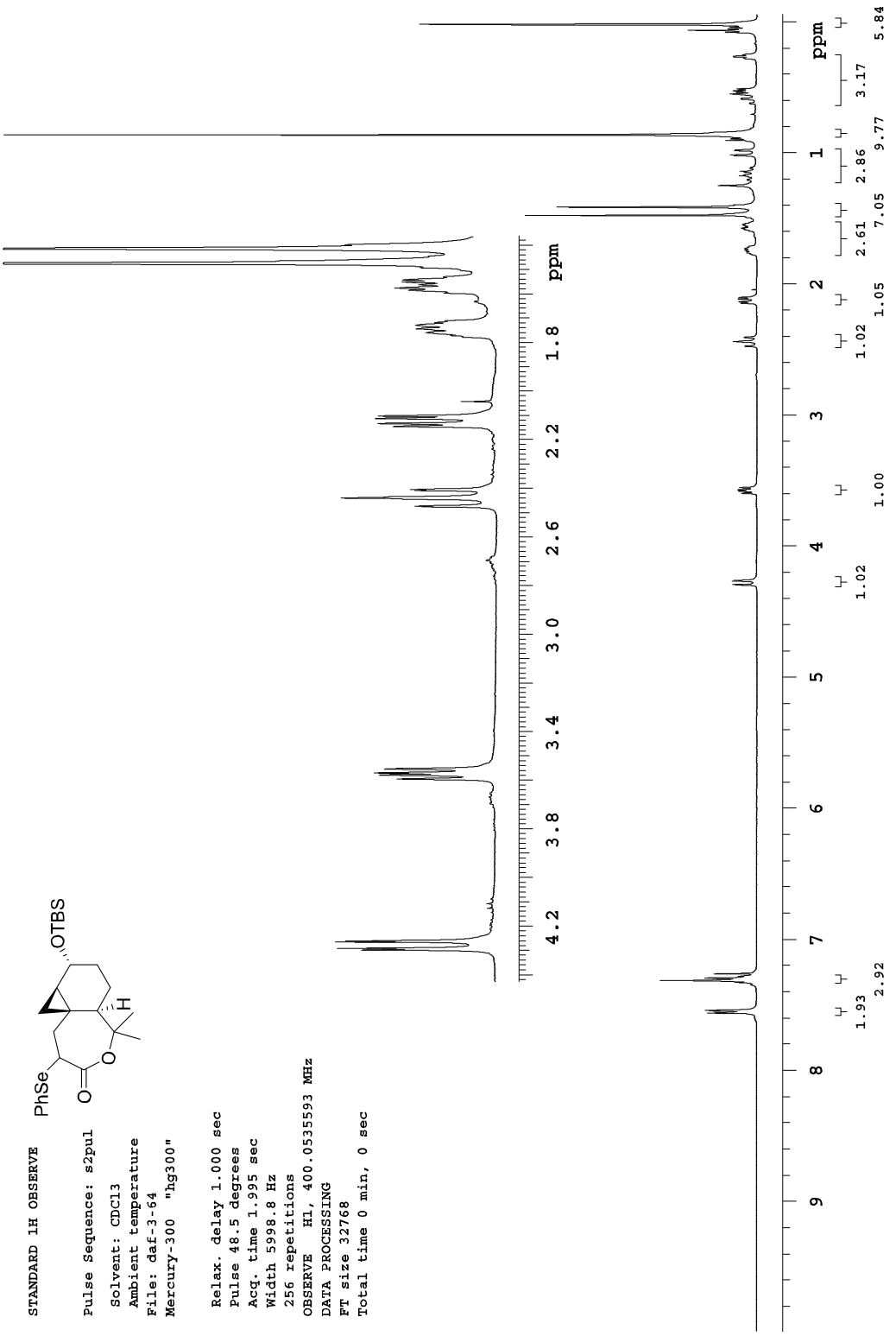
Spectrum 1.36 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **99b**



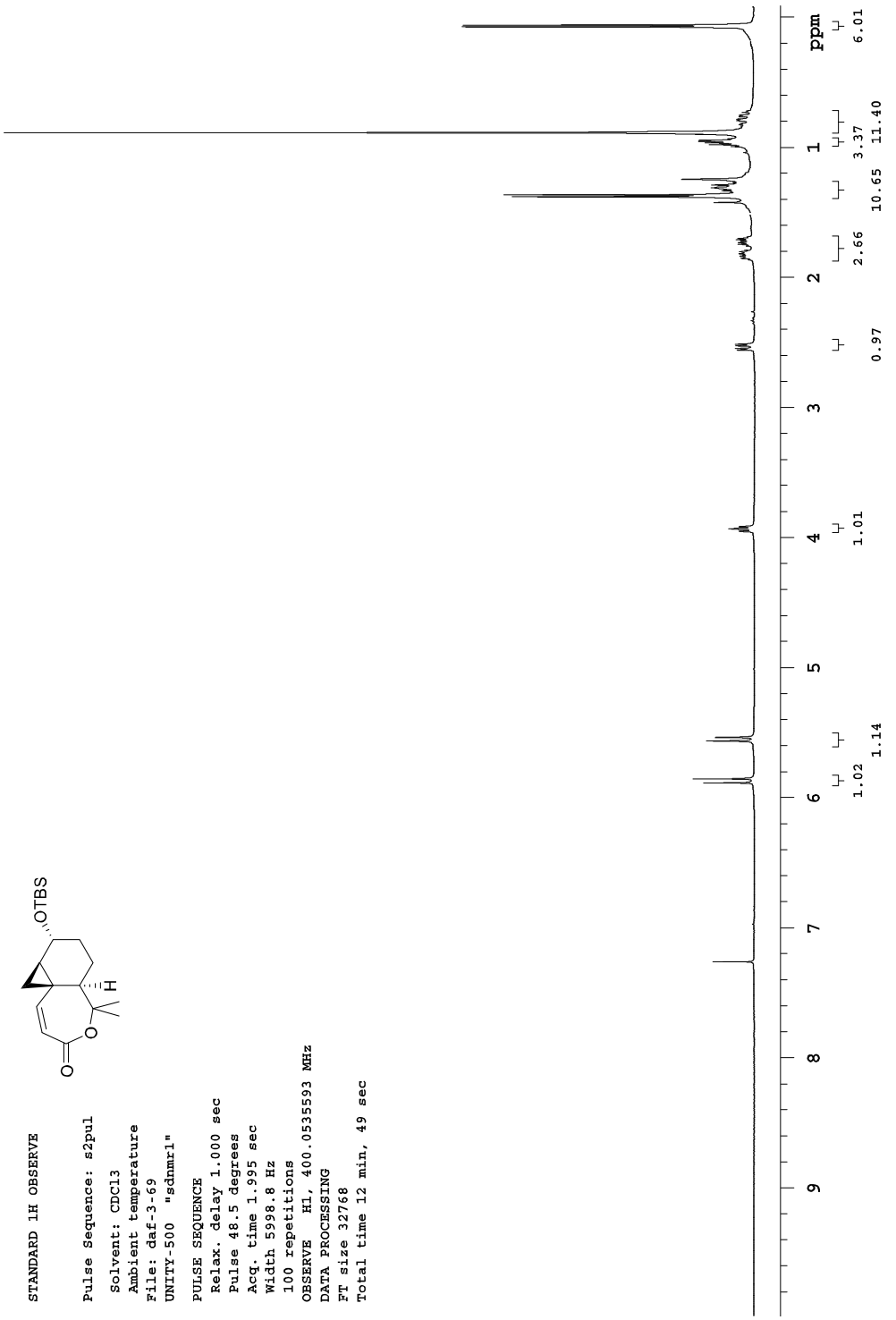
Spectrum 1.37 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **102**



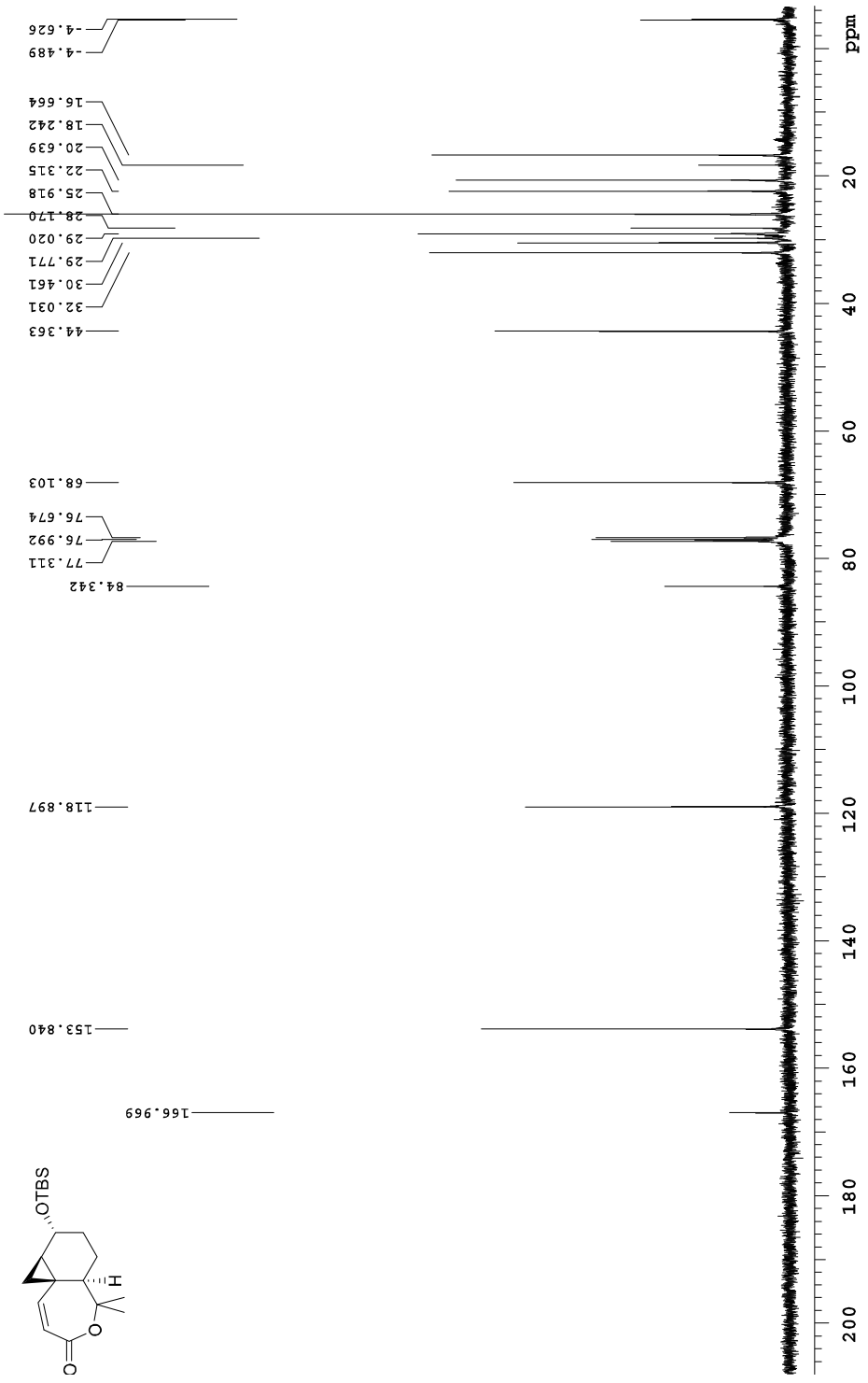
Spectrum 1.38 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **102**



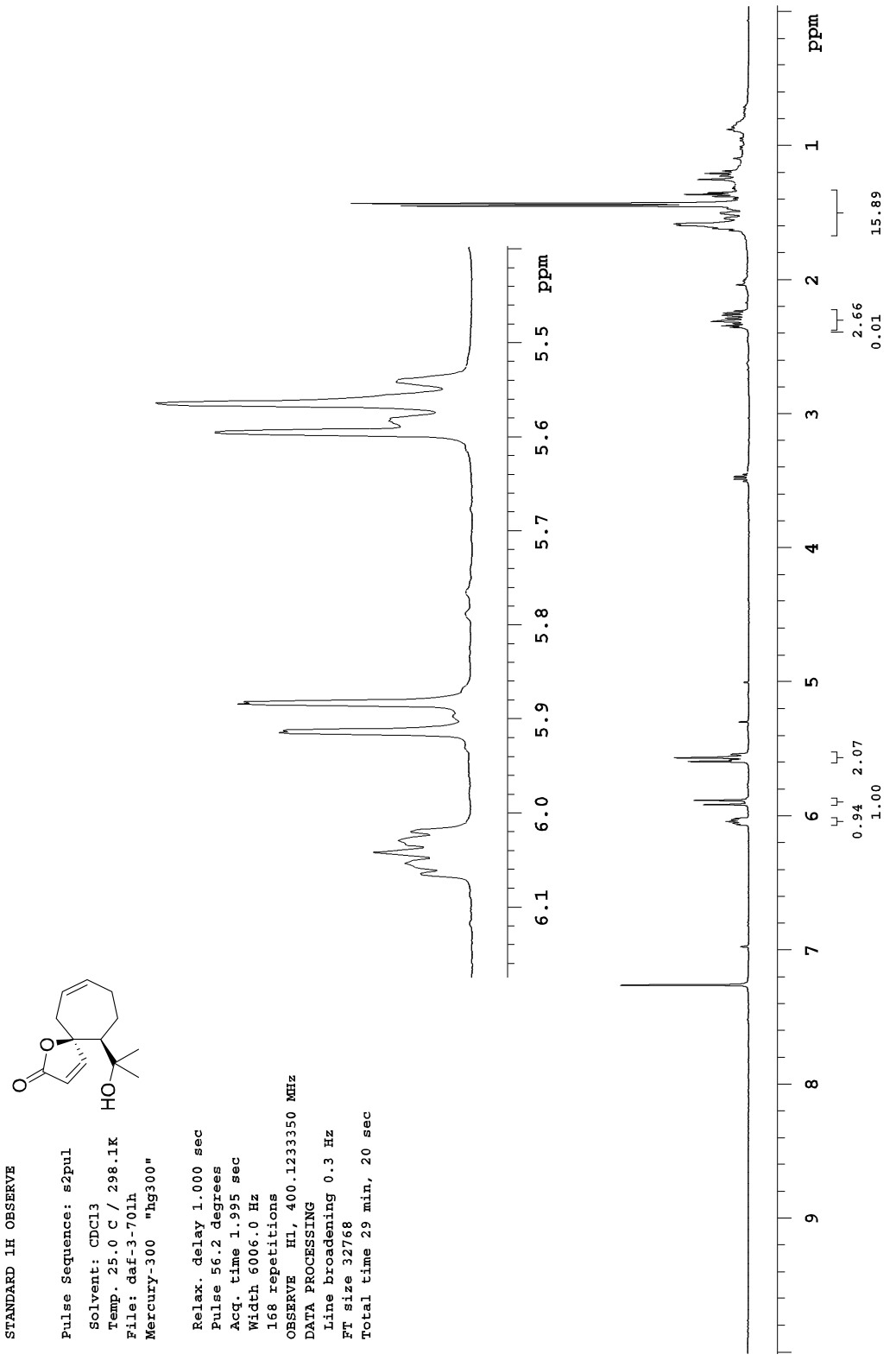
Spectrum 1.39 ^{1}H NMR ($CDCl_3$, 300 MHz) of compound **103**



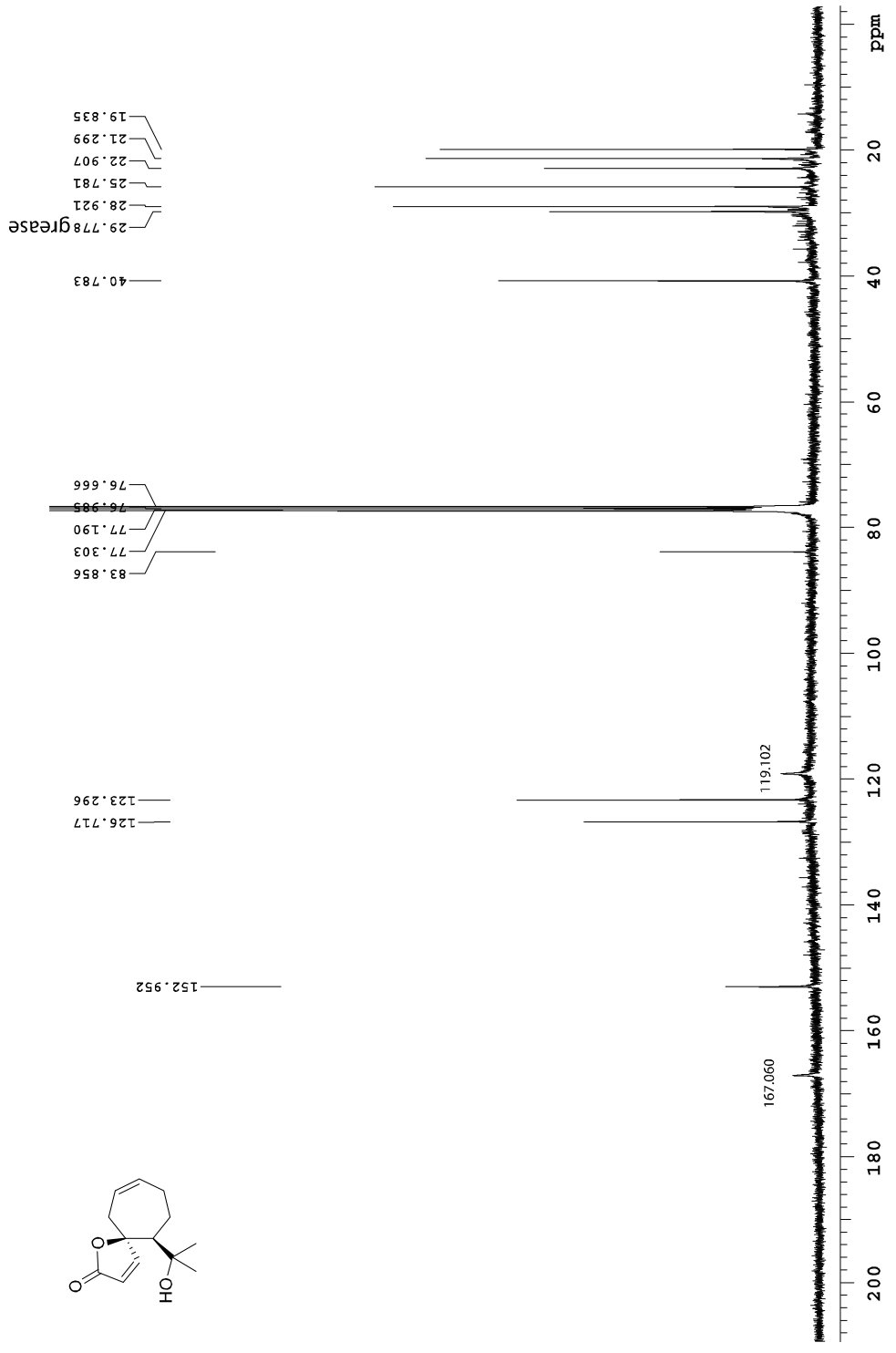
Spectrum 1.40 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **104**



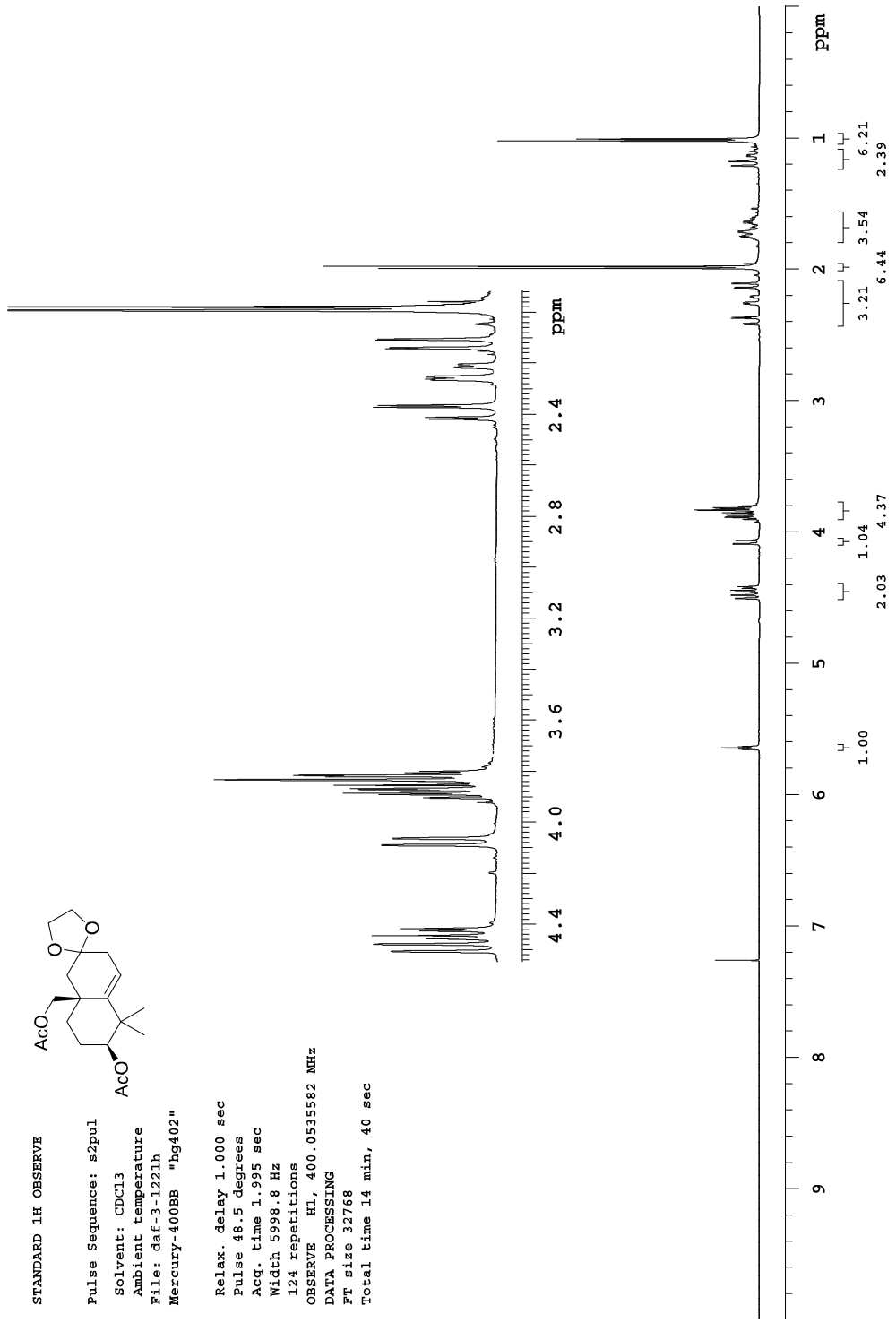
Spectrum 1.41 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **104**



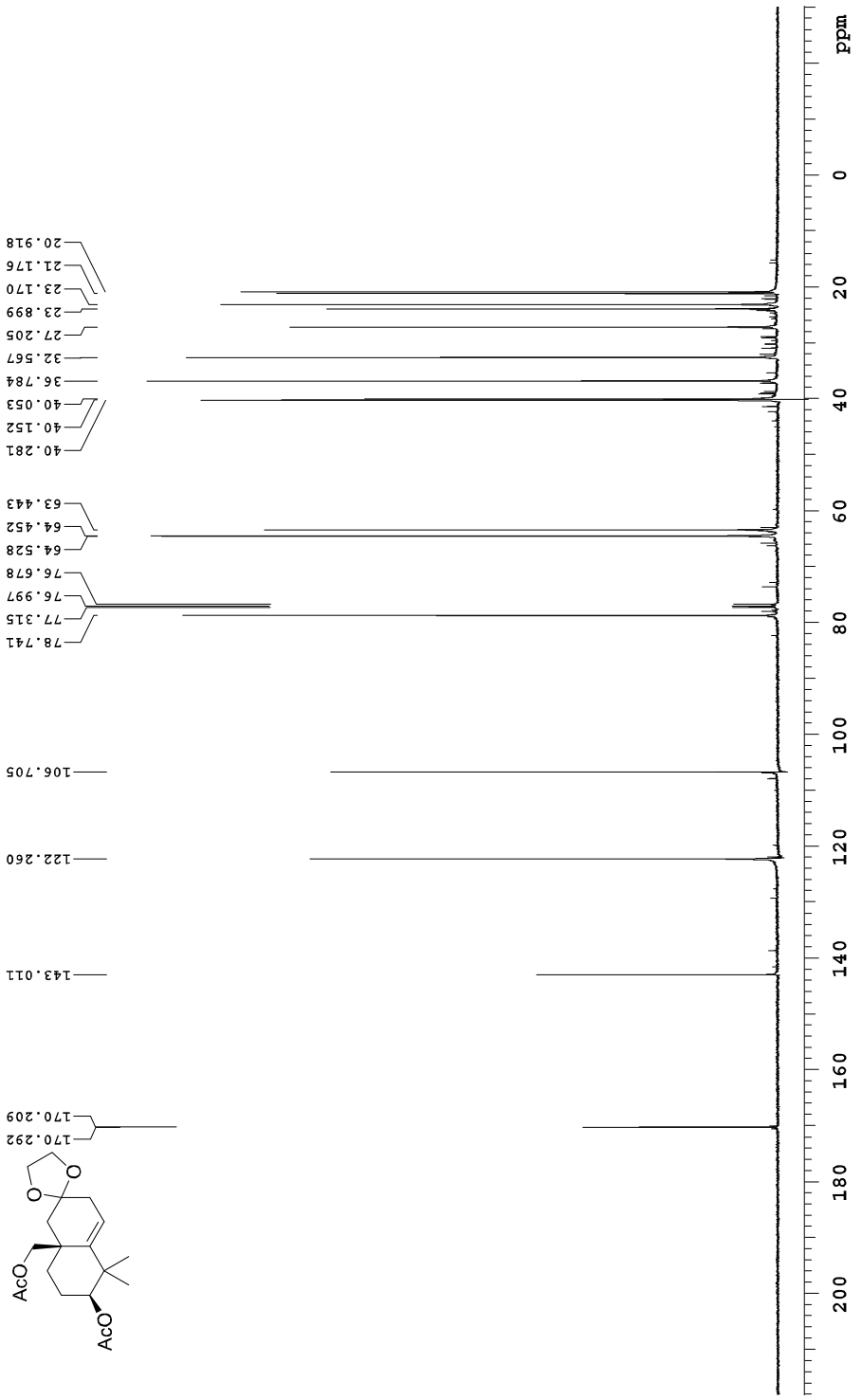
Spectrum 1.42 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **105**



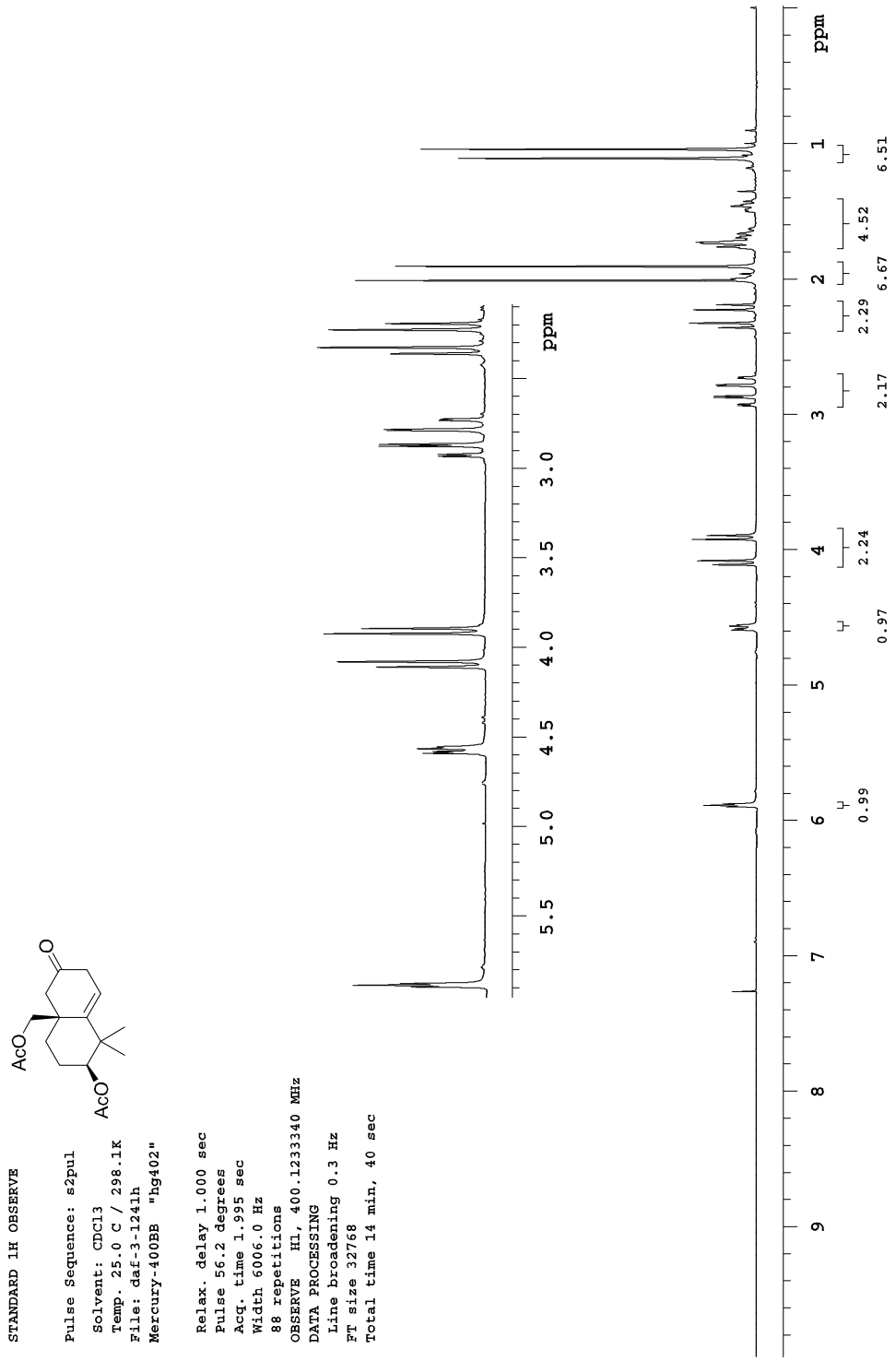
Spectrum 1.43 ^{13}C NMR ($CDCl_3$, 100MHz) of compound **105**



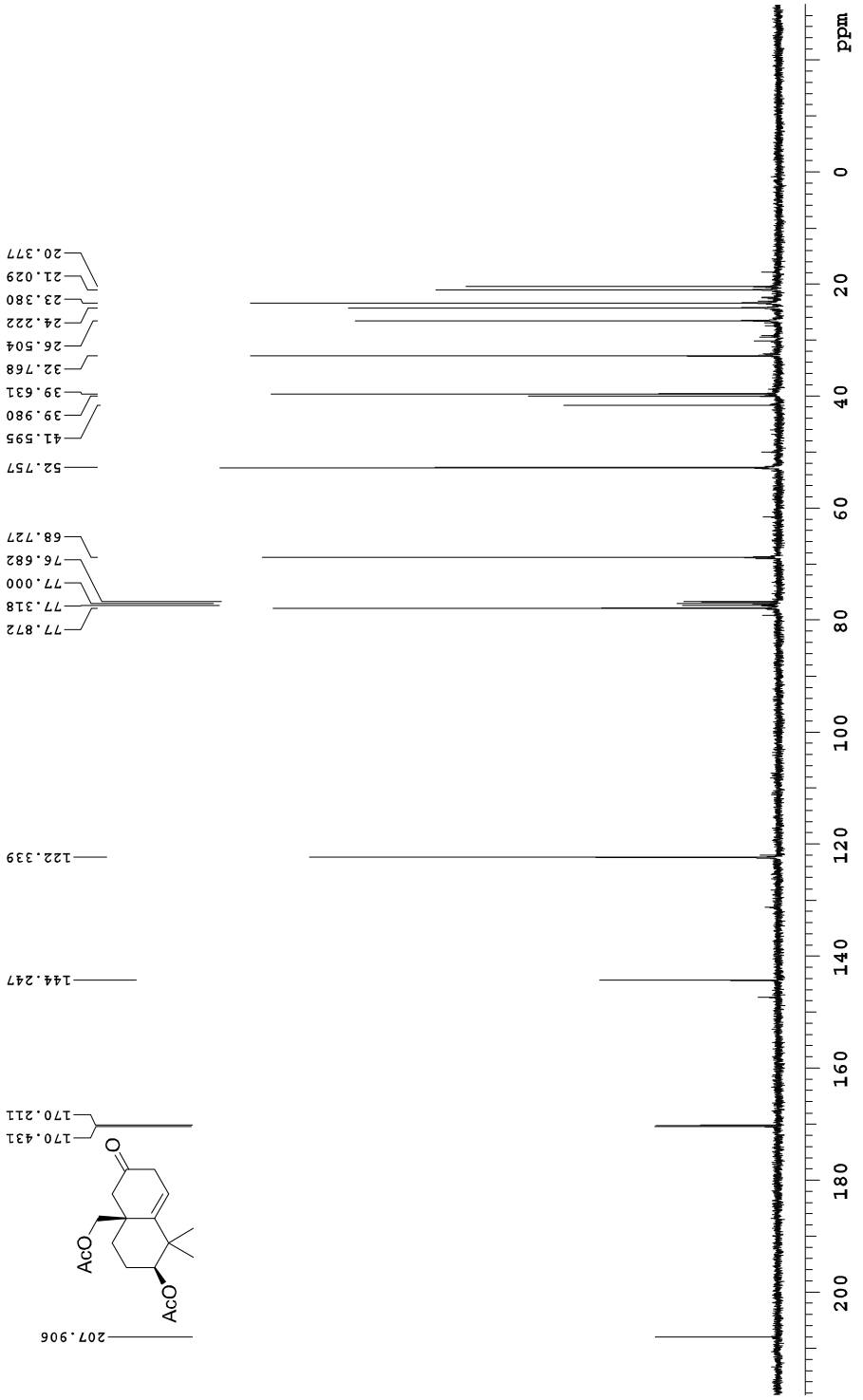
Spectrum 1.44 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **106**



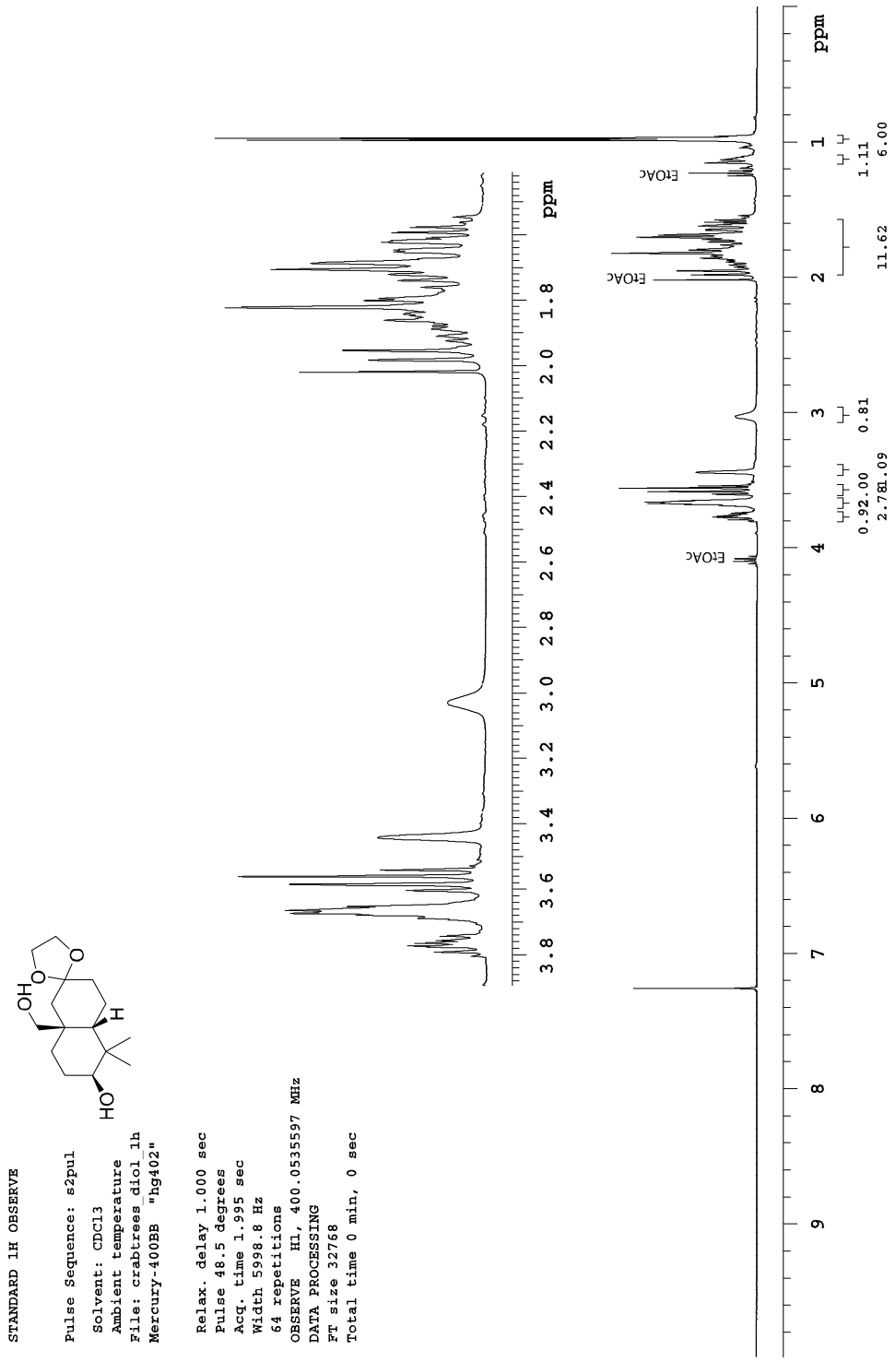
Spectrum 1.45 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **106**



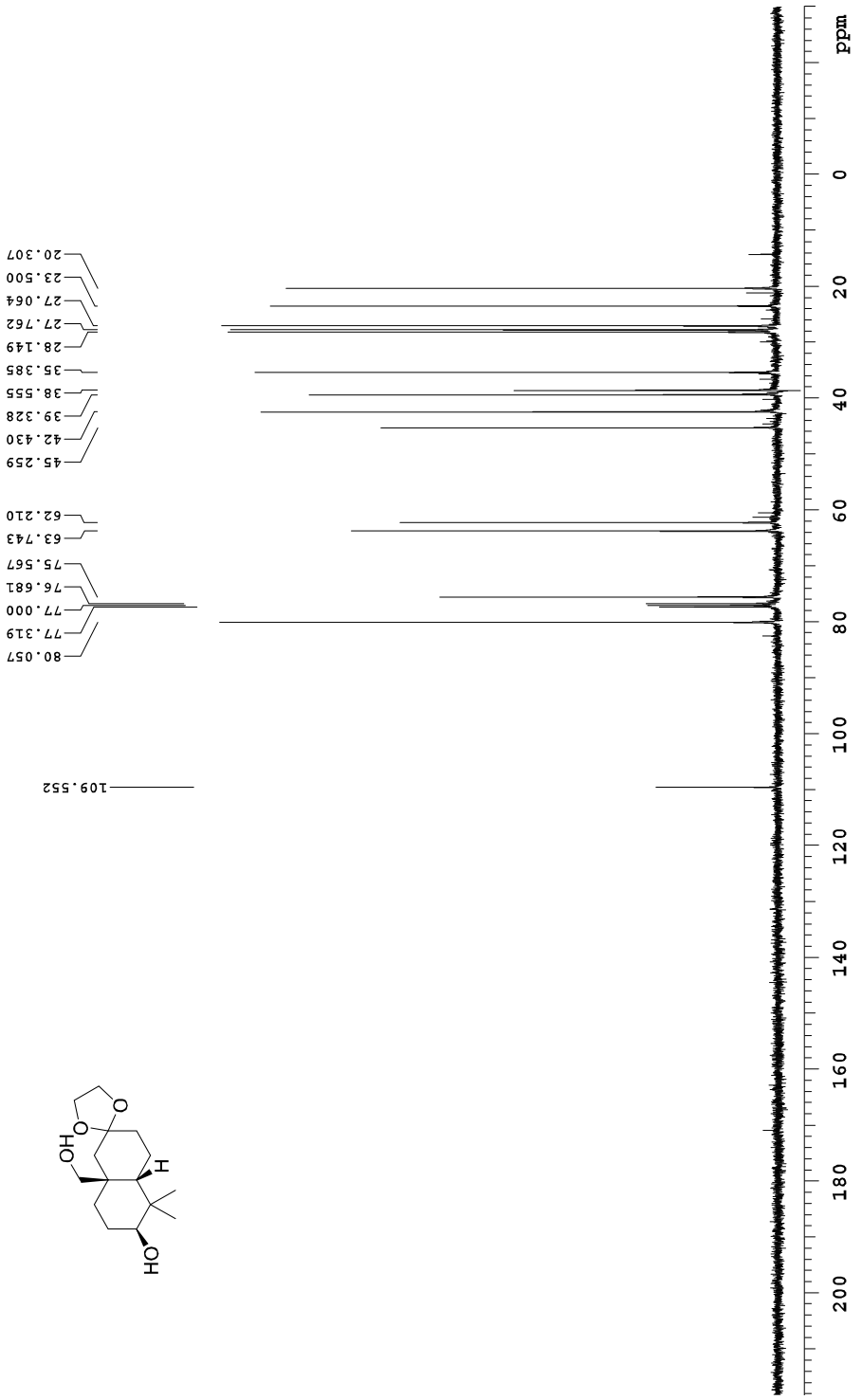
Spectrum 1.46 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **107**



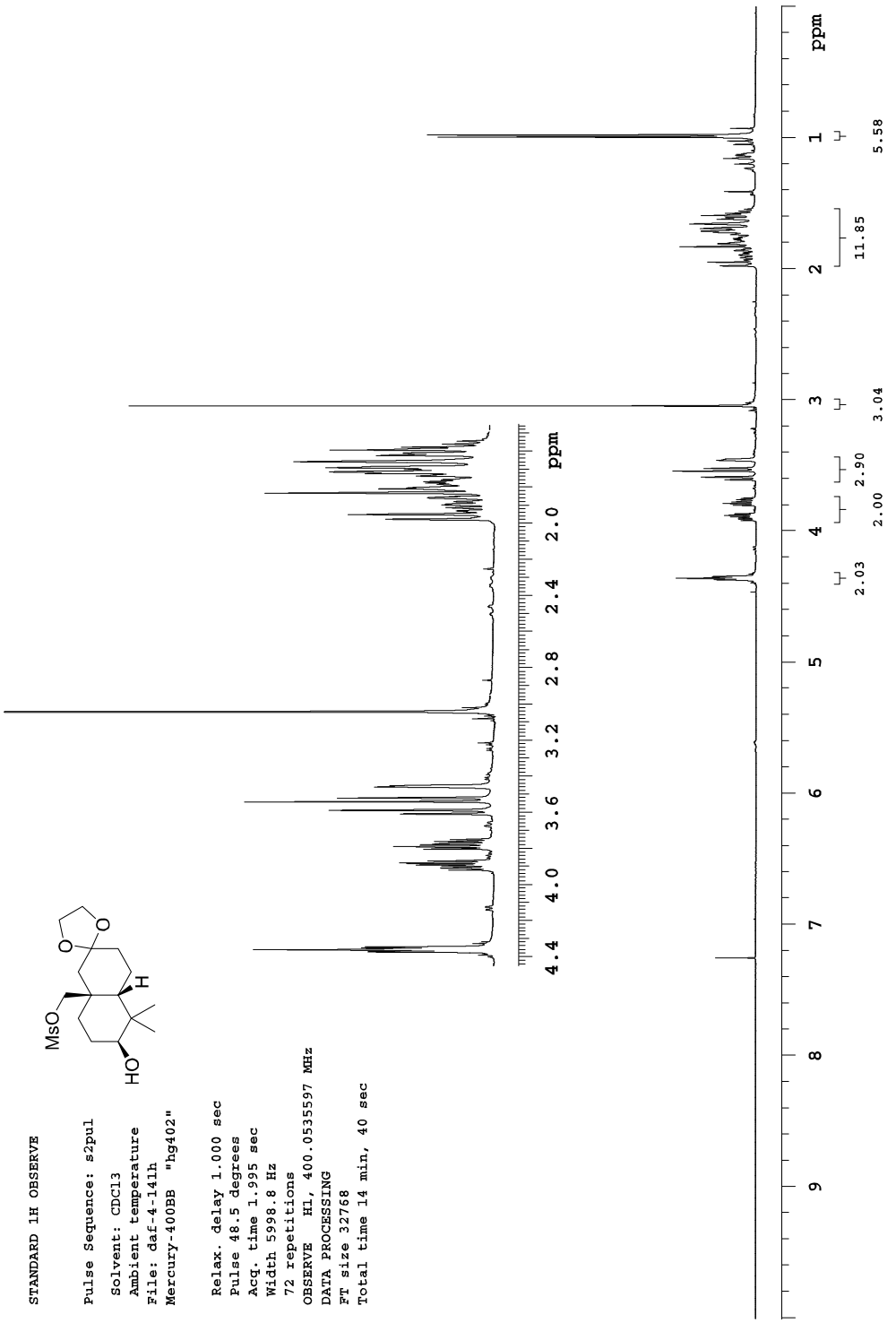
Spectrum 1.47 ^{13}C NMR ($CDCl_3$, 100MHz) of compound **107**



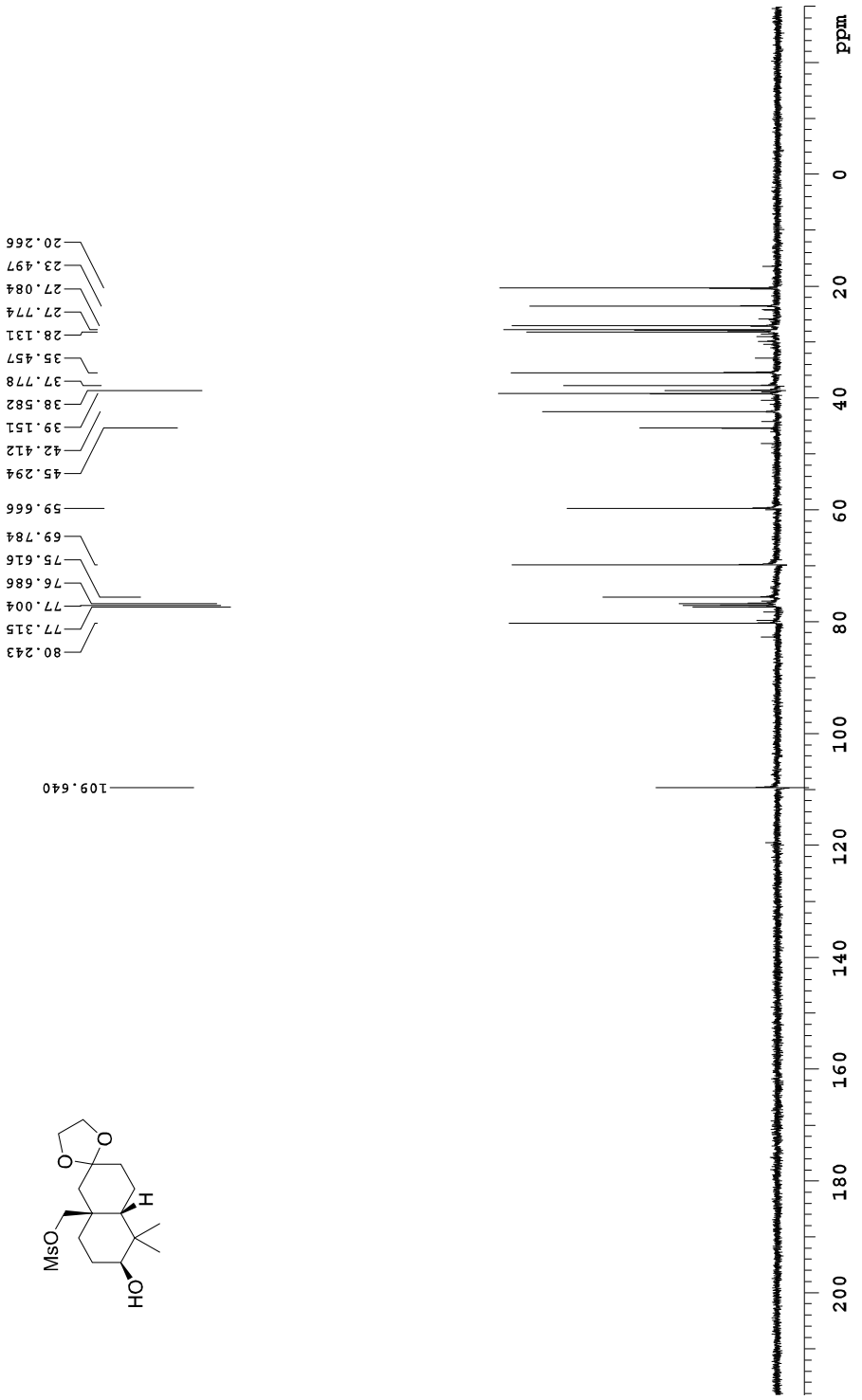
Spectrum 1.48 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **108**



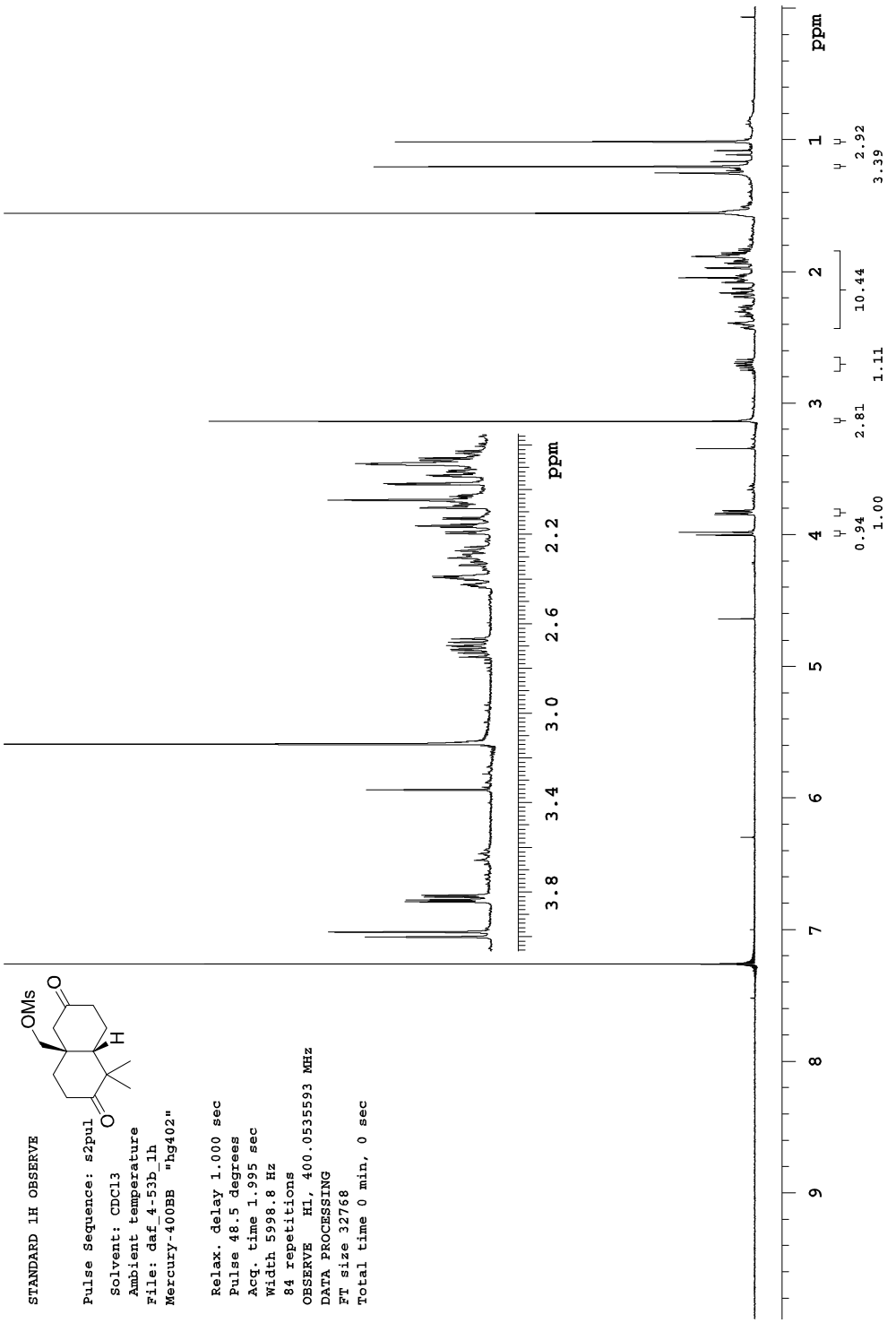
Spectrum 1.49 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **108**



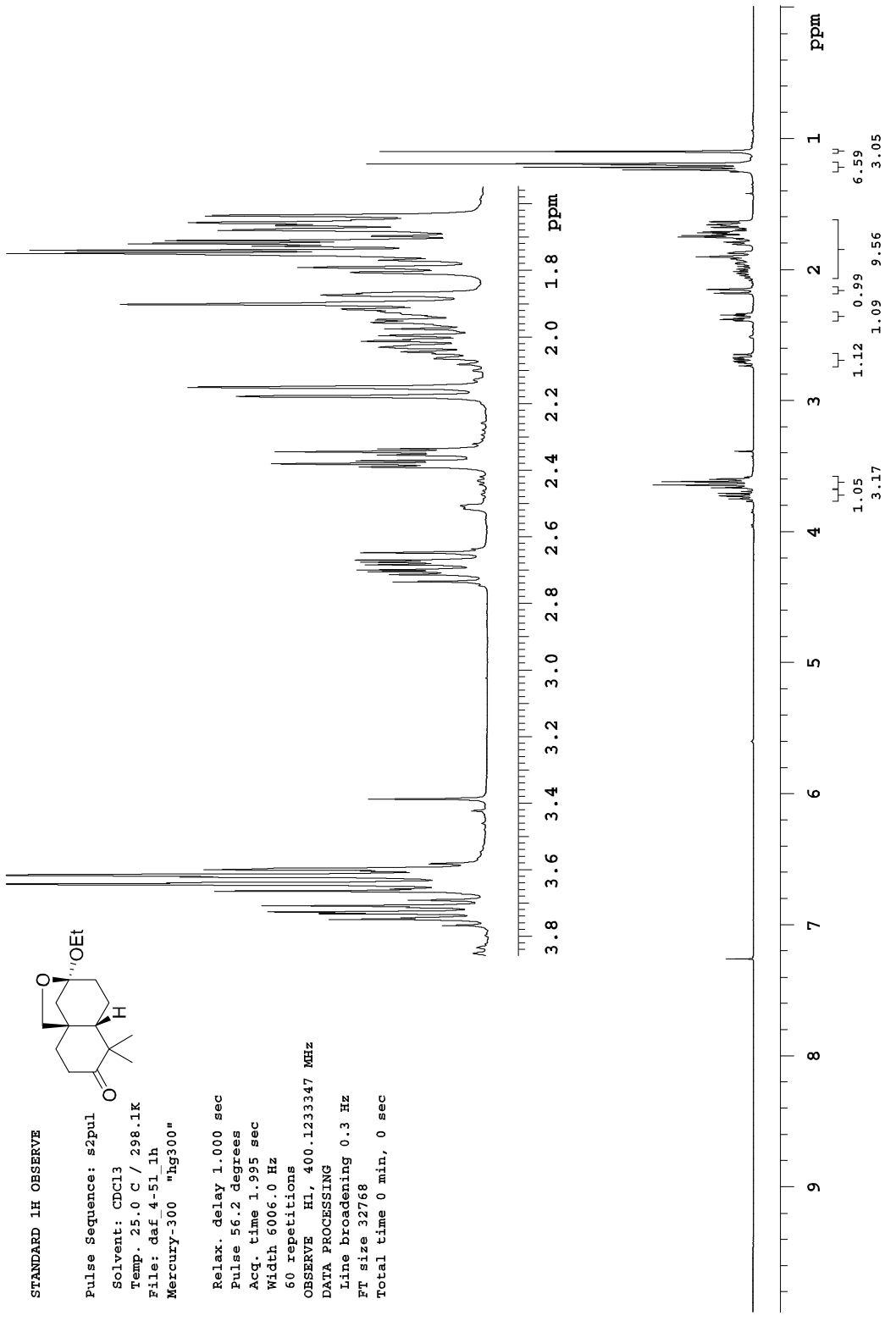
Spectrum 1.50 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **116**



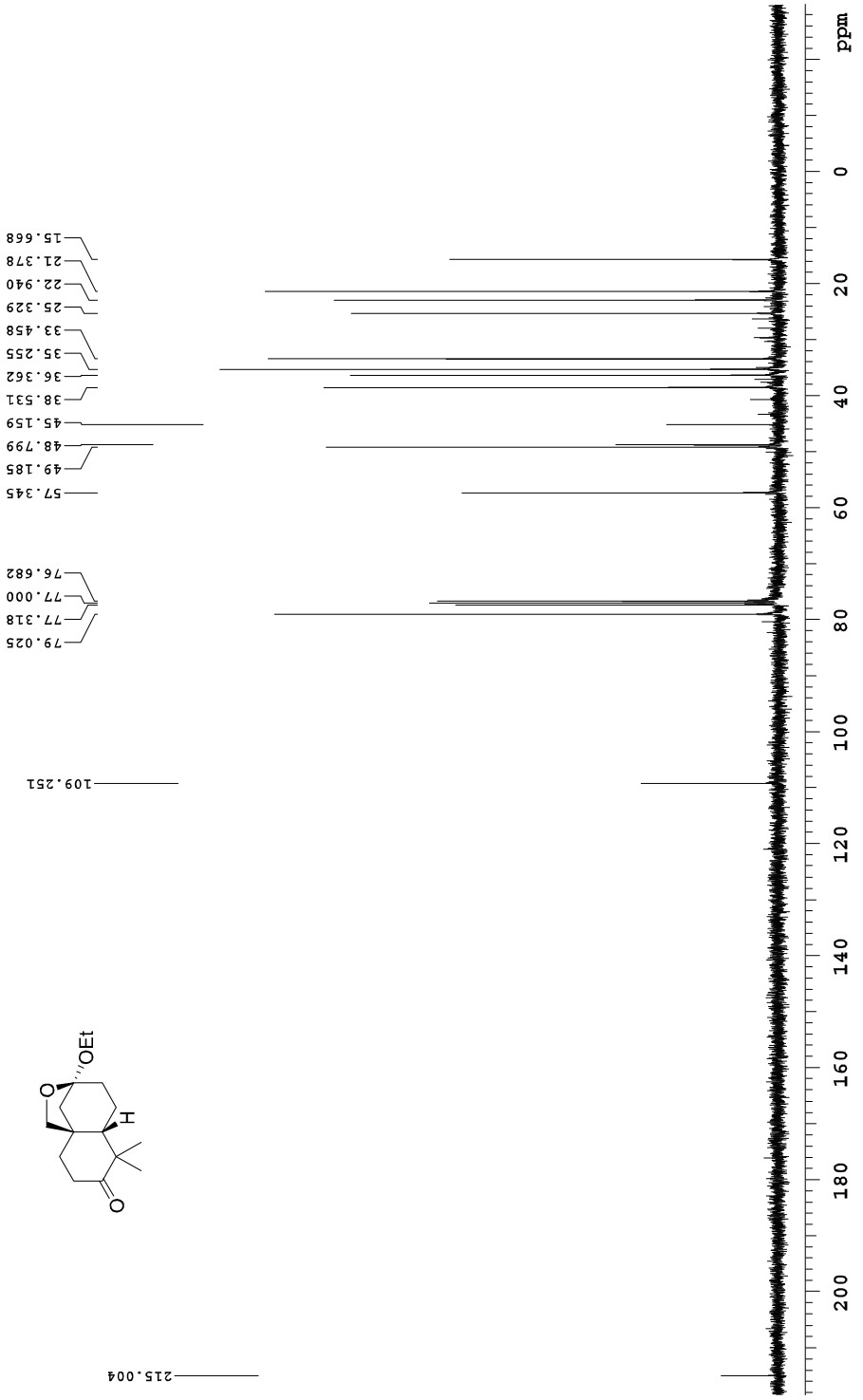
Spectrum 1.51 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **116**



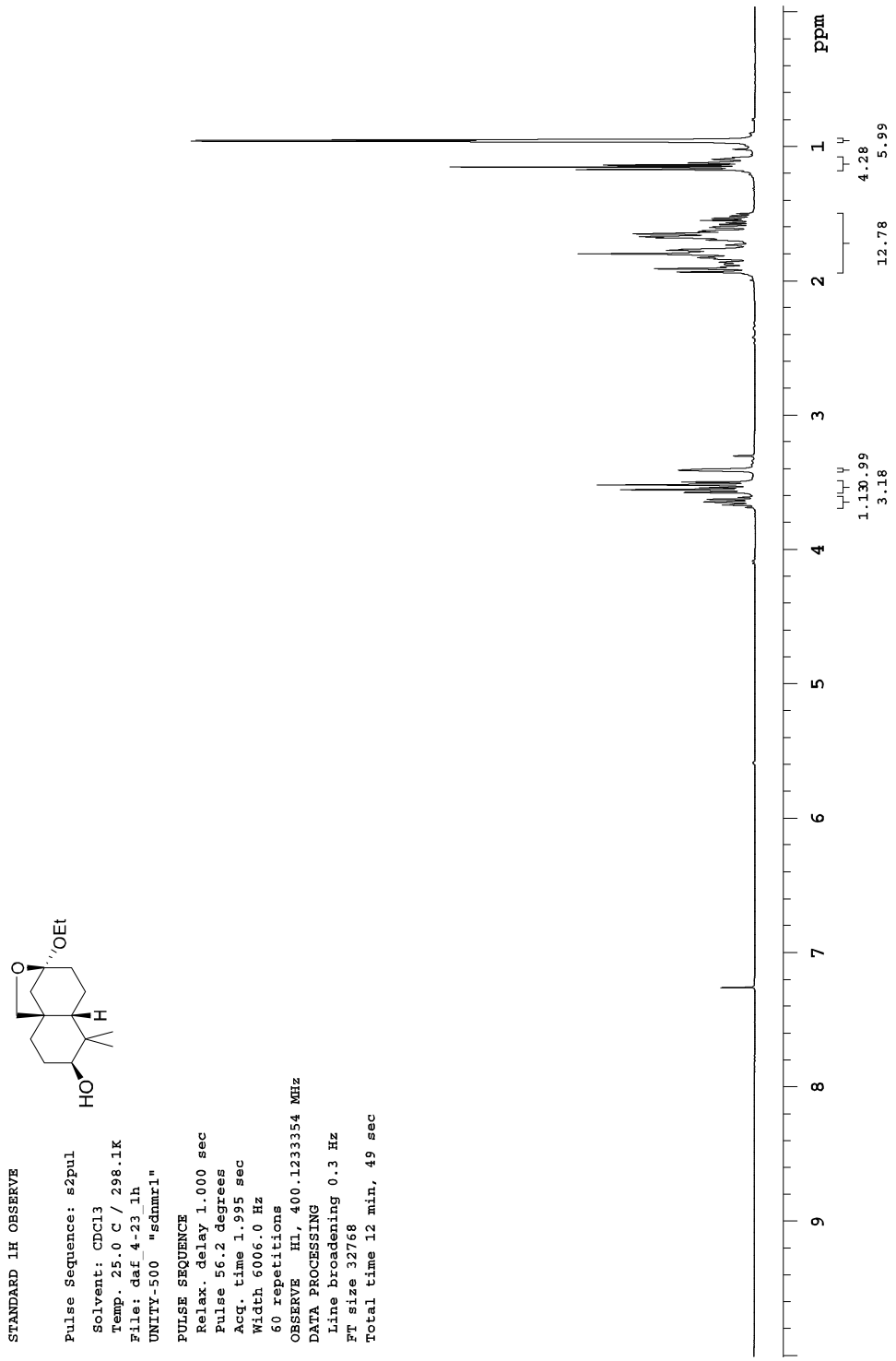
Spectrum 1.52 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **118**



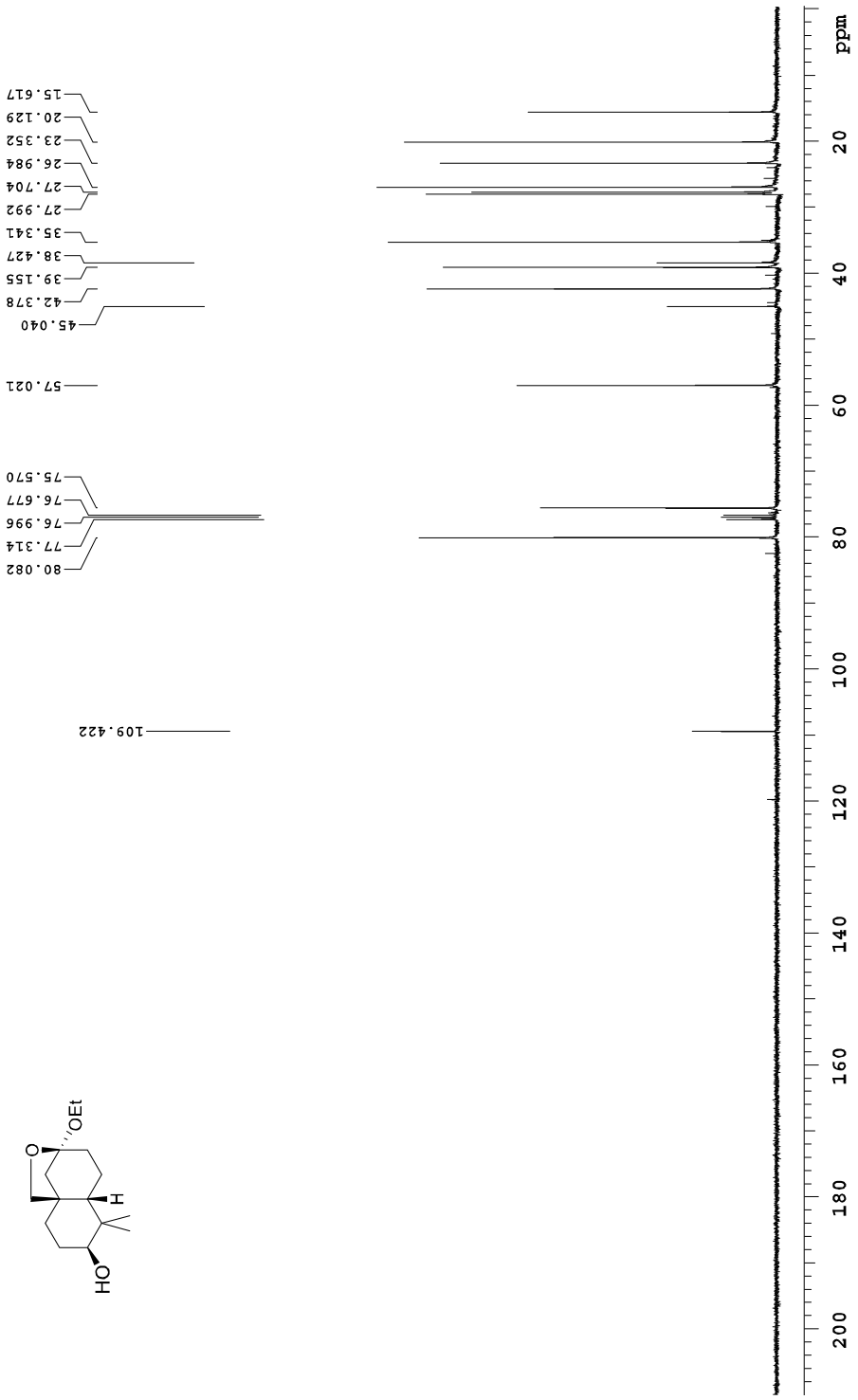
Spectrum 1.53 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **119**



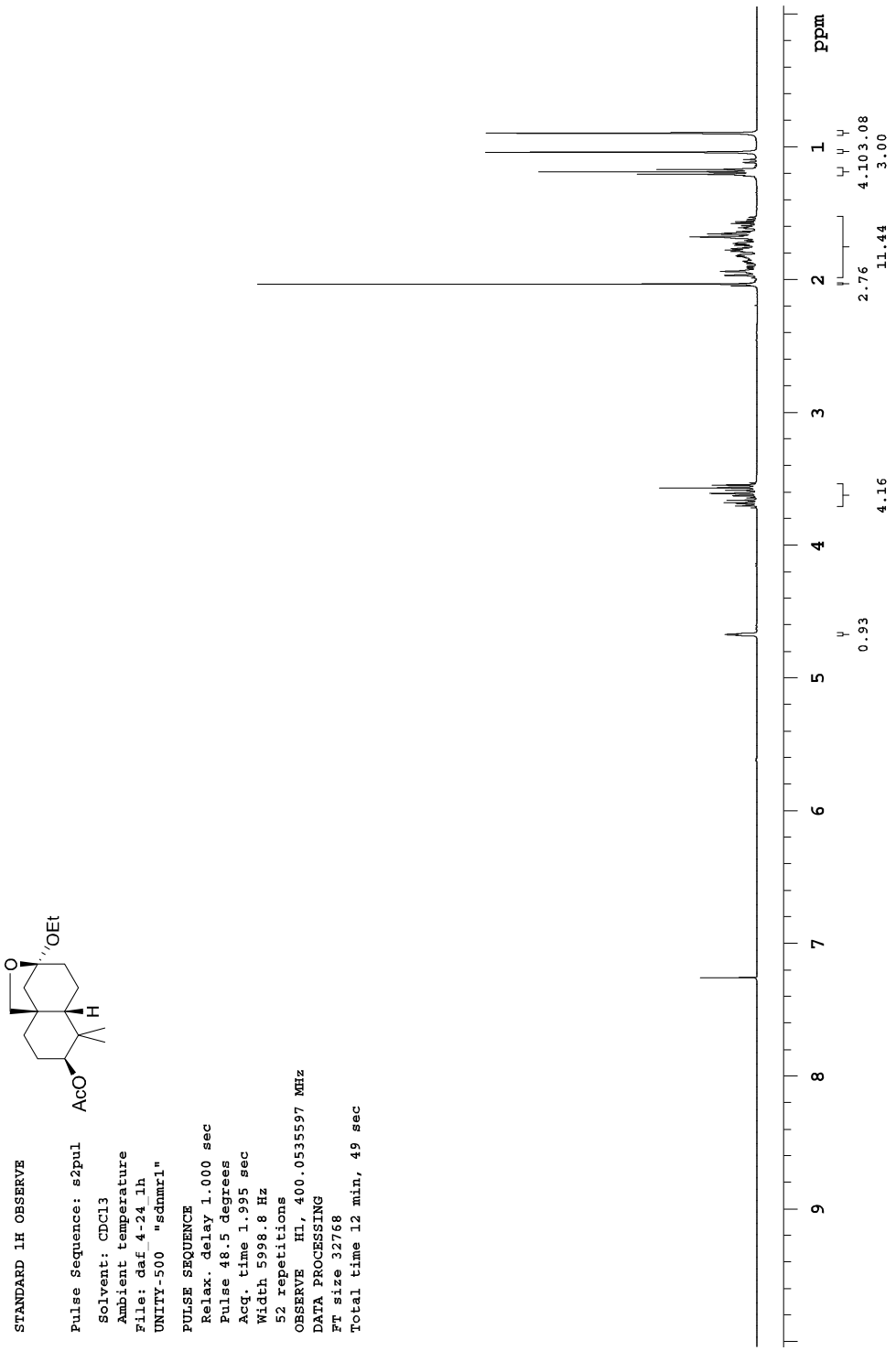
Spectrum 1.54 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **119**



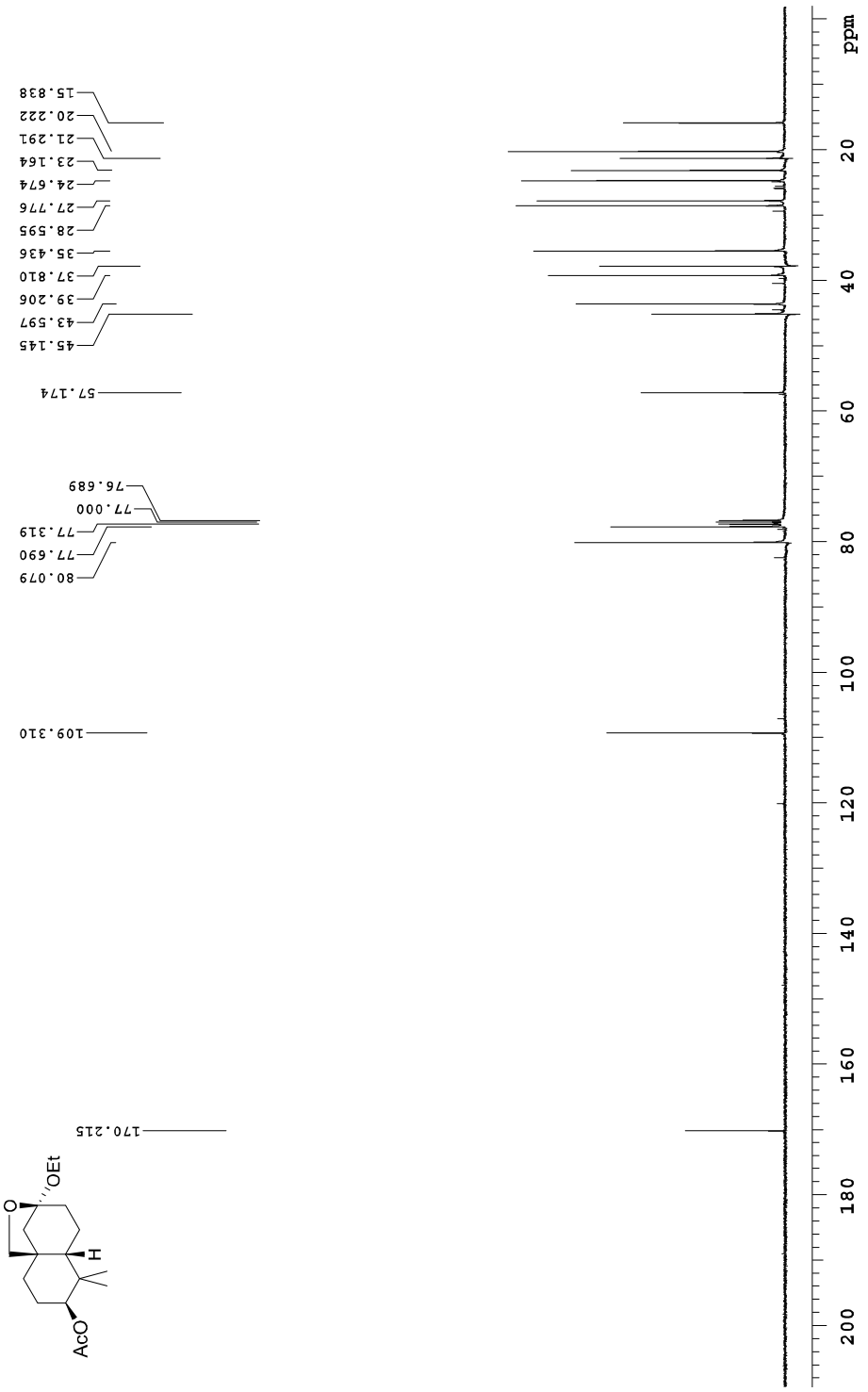
Spectrum 1.55 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **109**



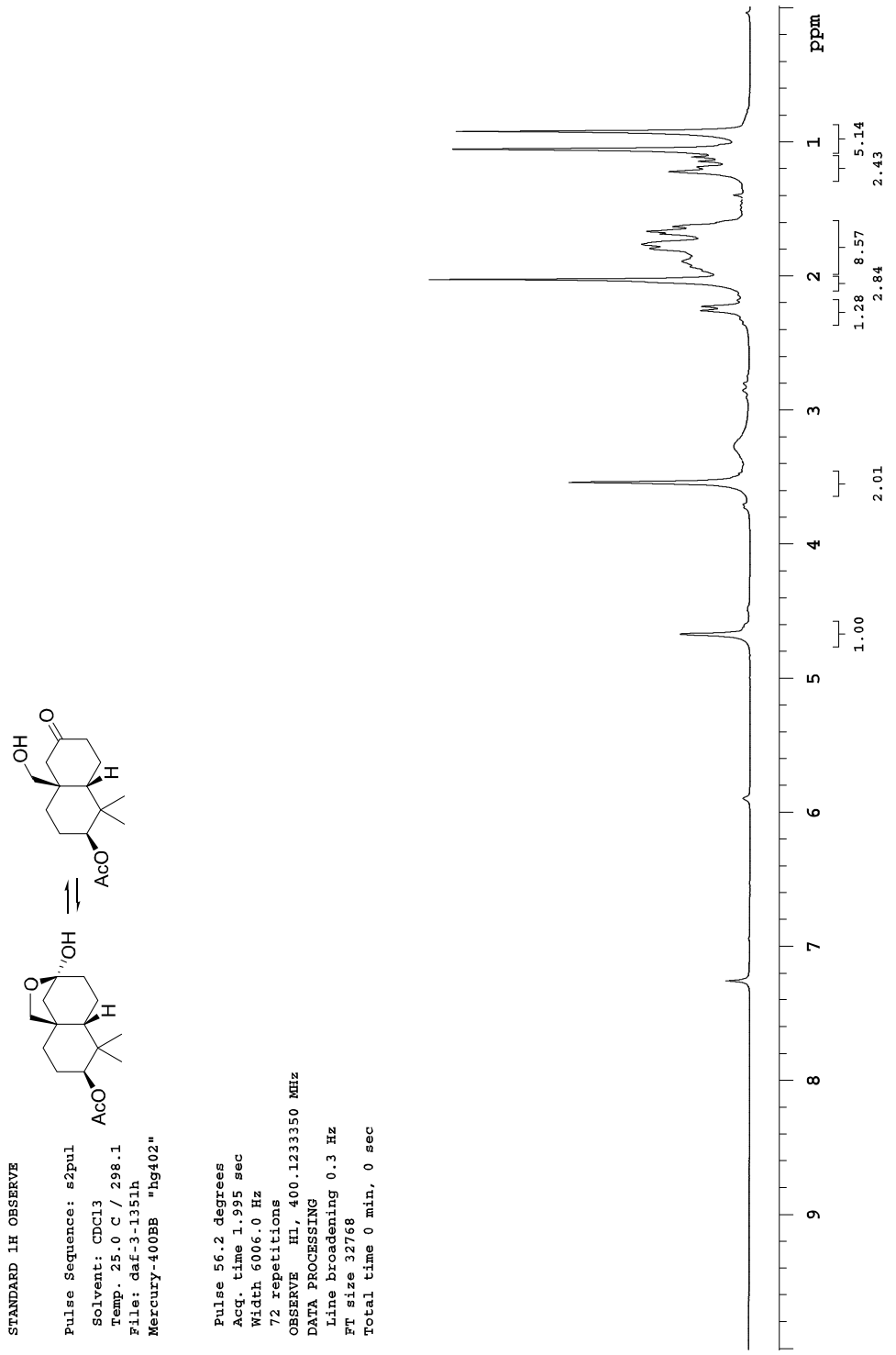
Spectrum 1.56 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **109**



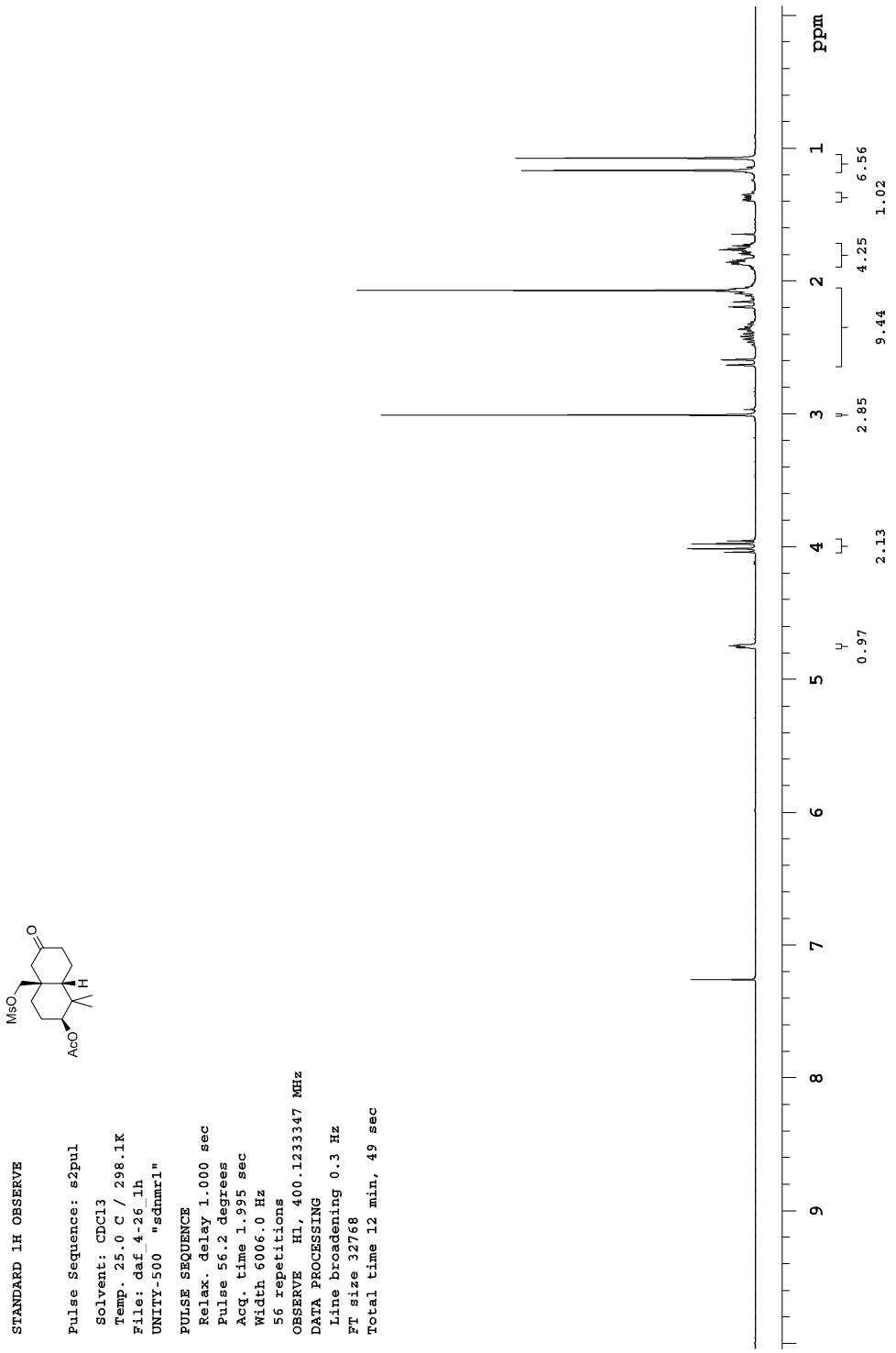
Spectrum 1.57 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **110**



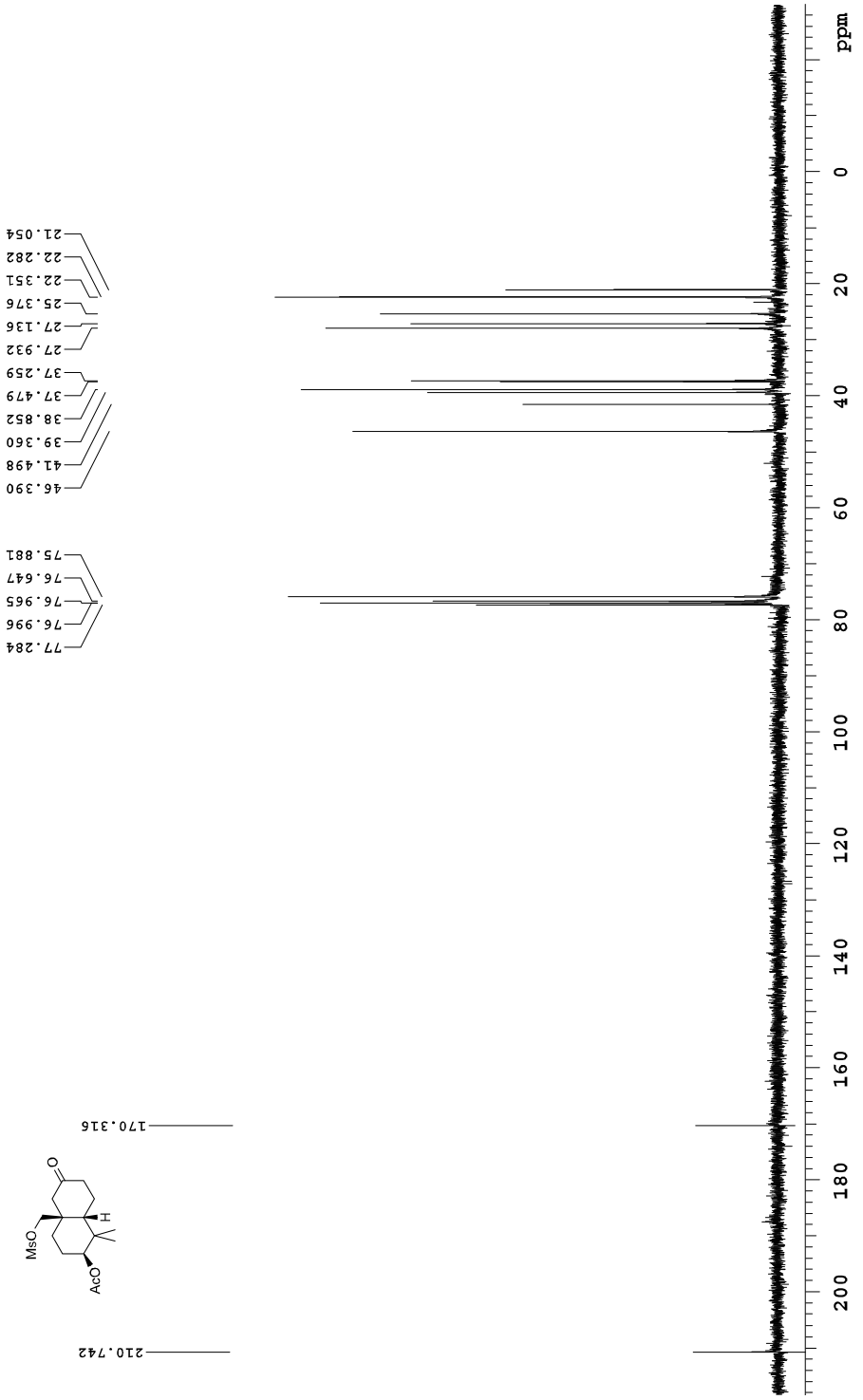
Spectrum 1.58 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **110**



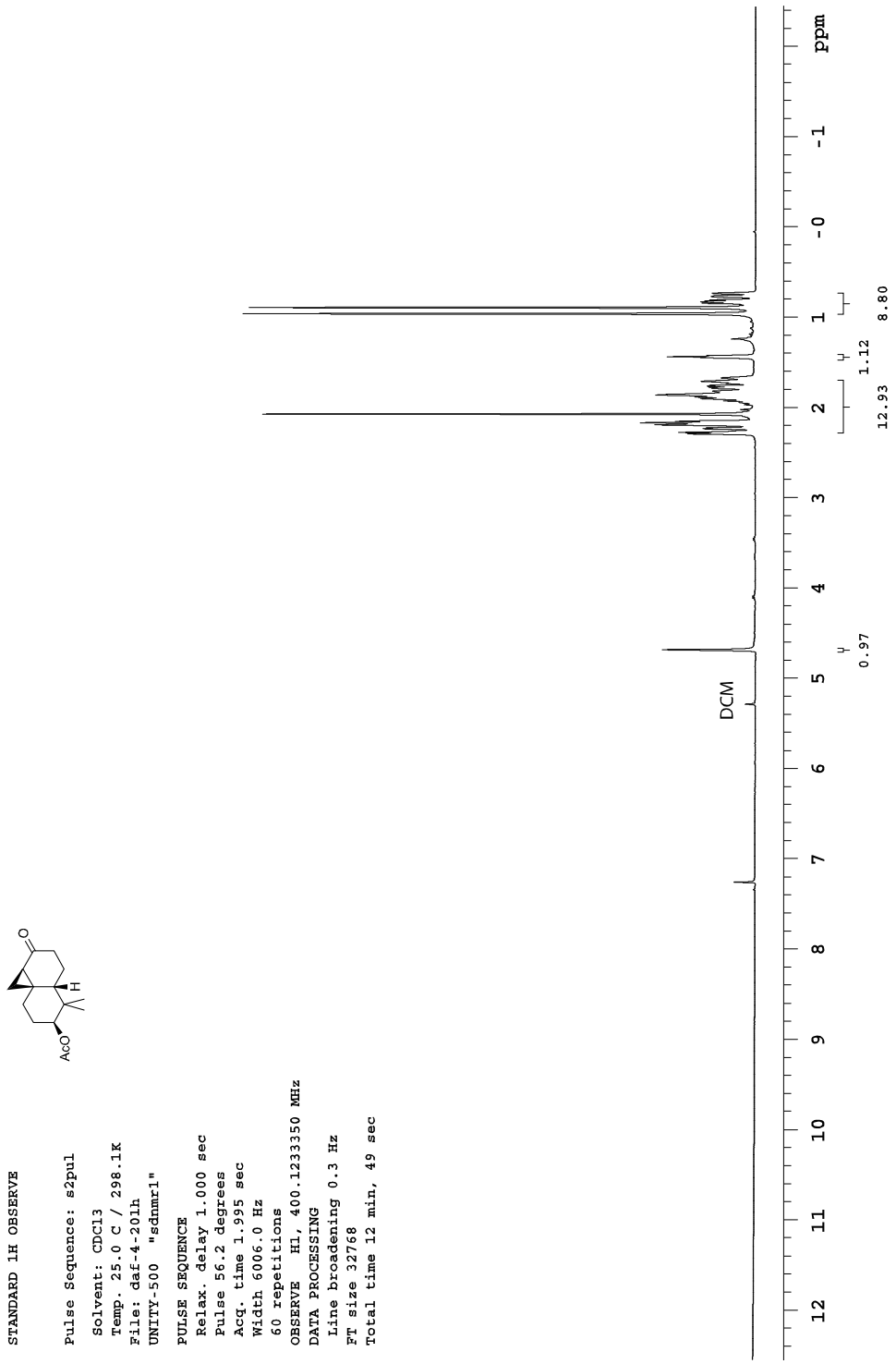
Spectrum 1.59 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **111**



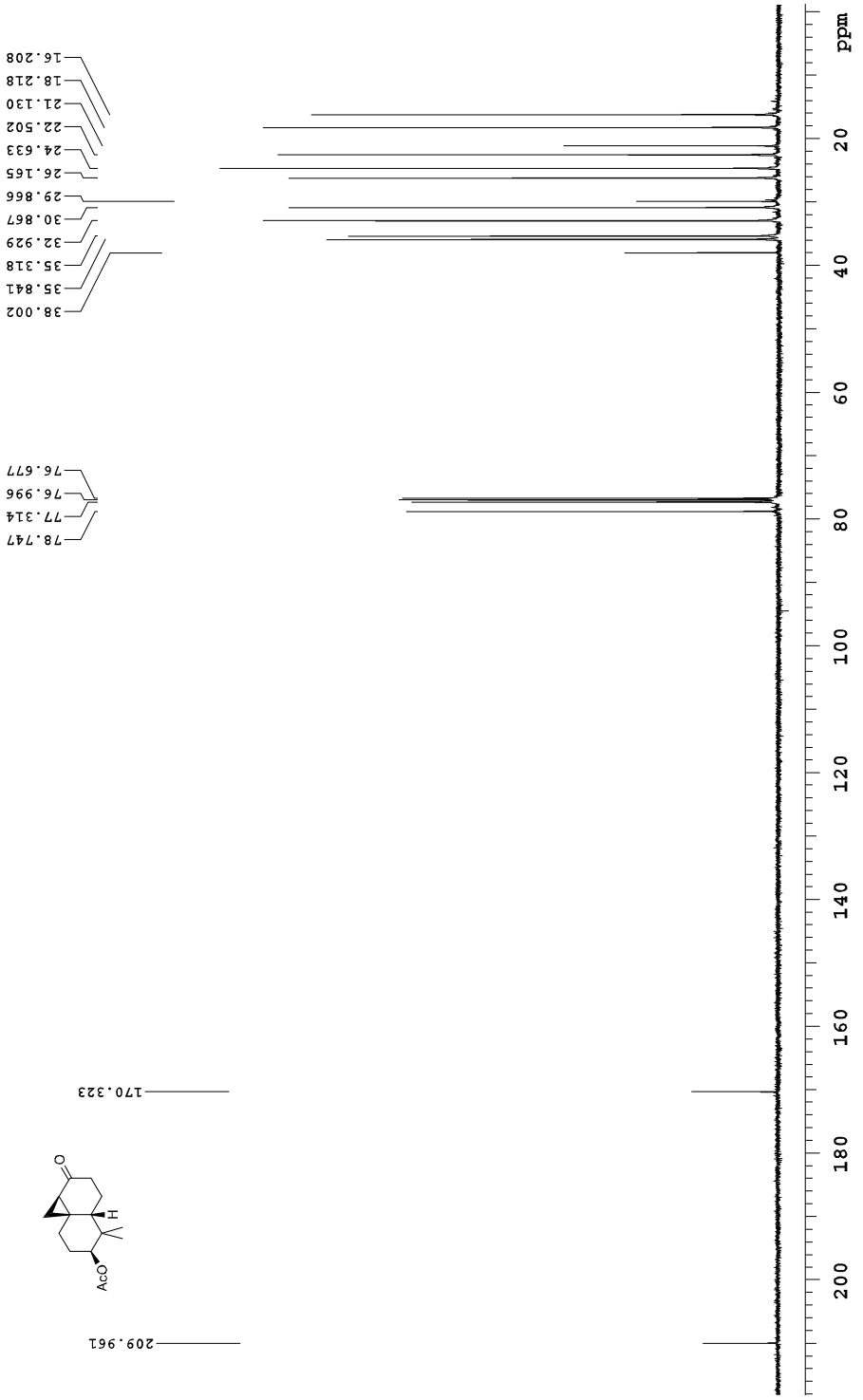
Spectrum 1.60 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **112b**



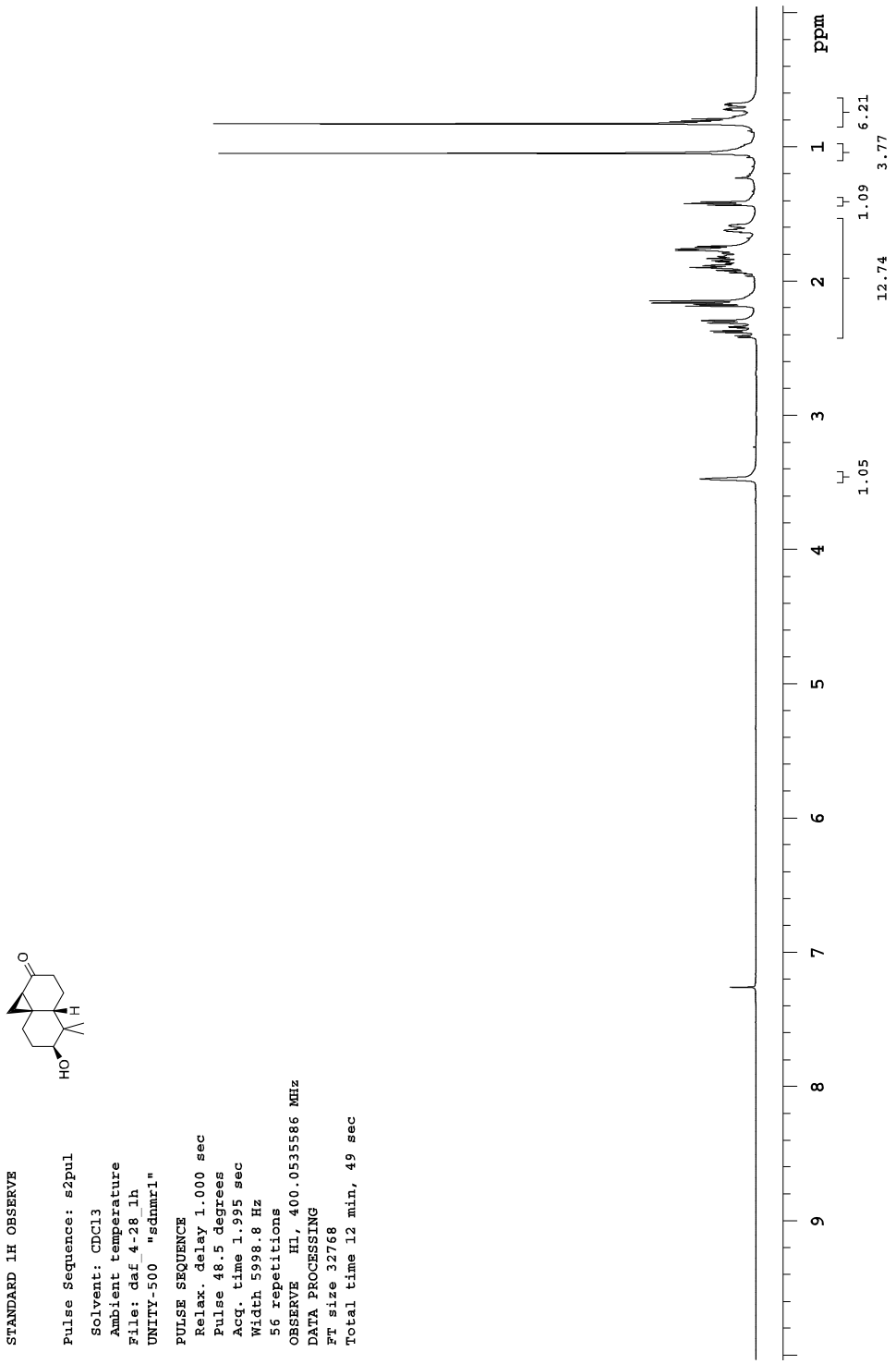
Spectrum 1.61 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **112b**



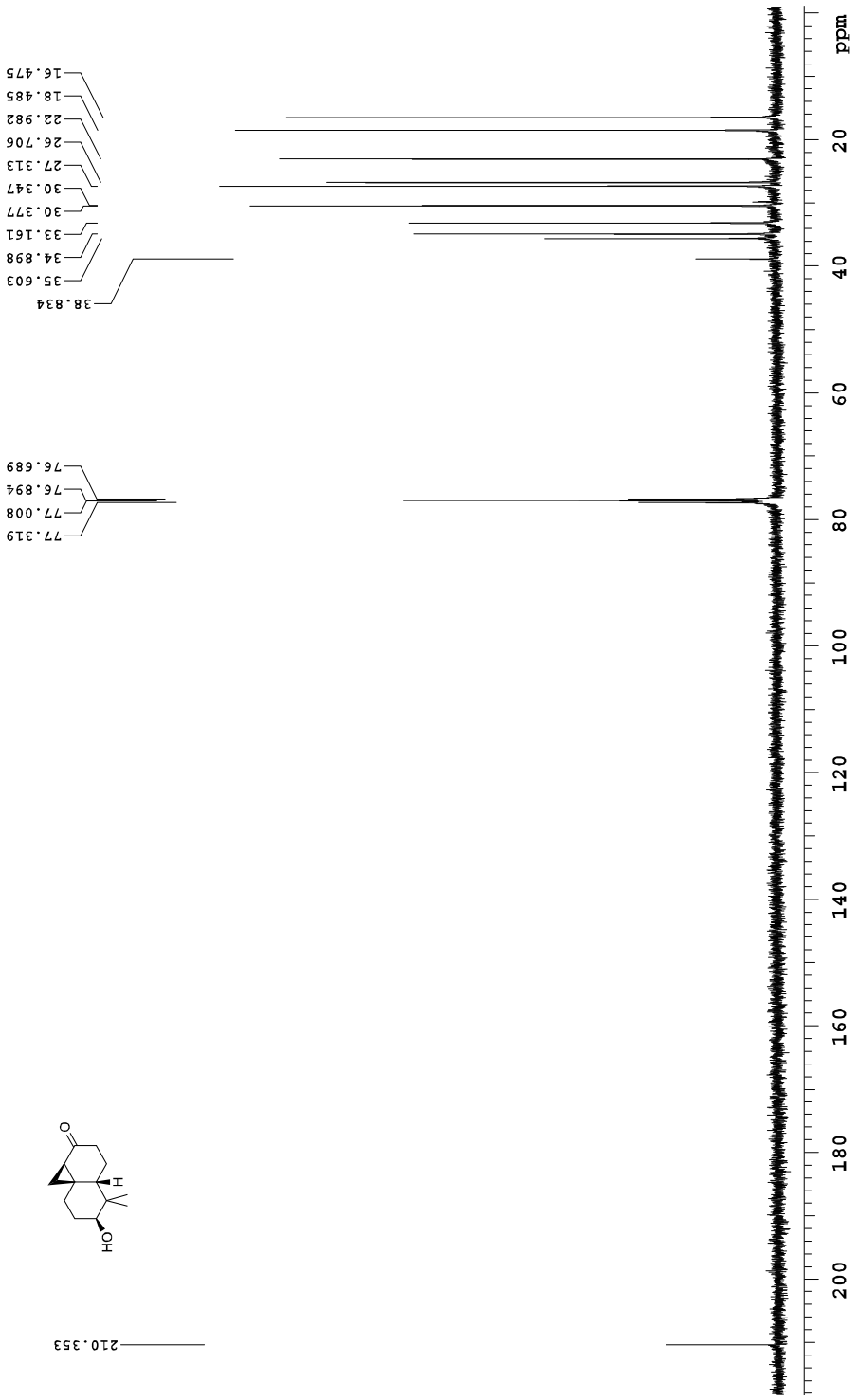
Spectrum 1.62 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **113**



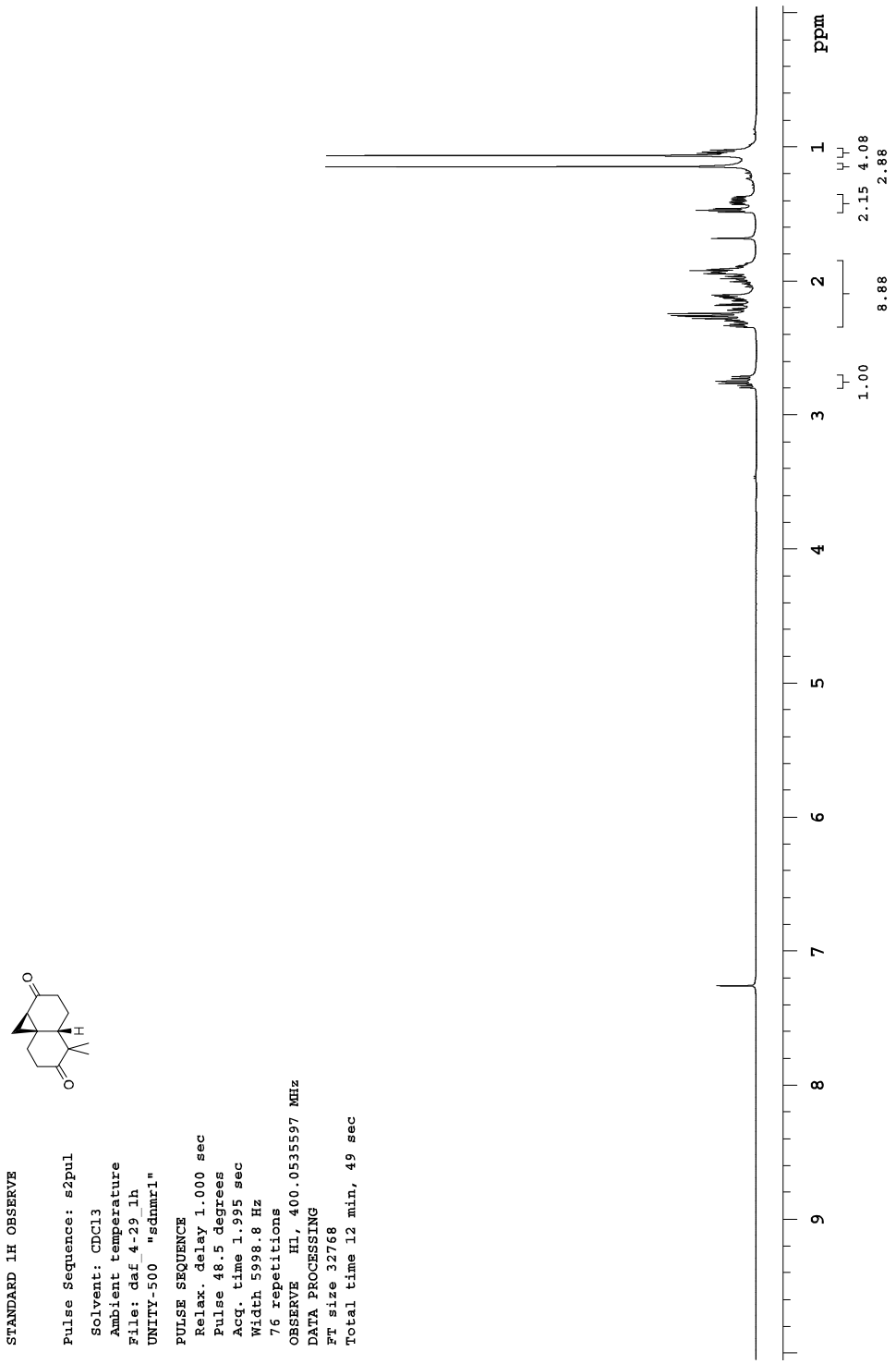
Spectrum 1.63 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **113**



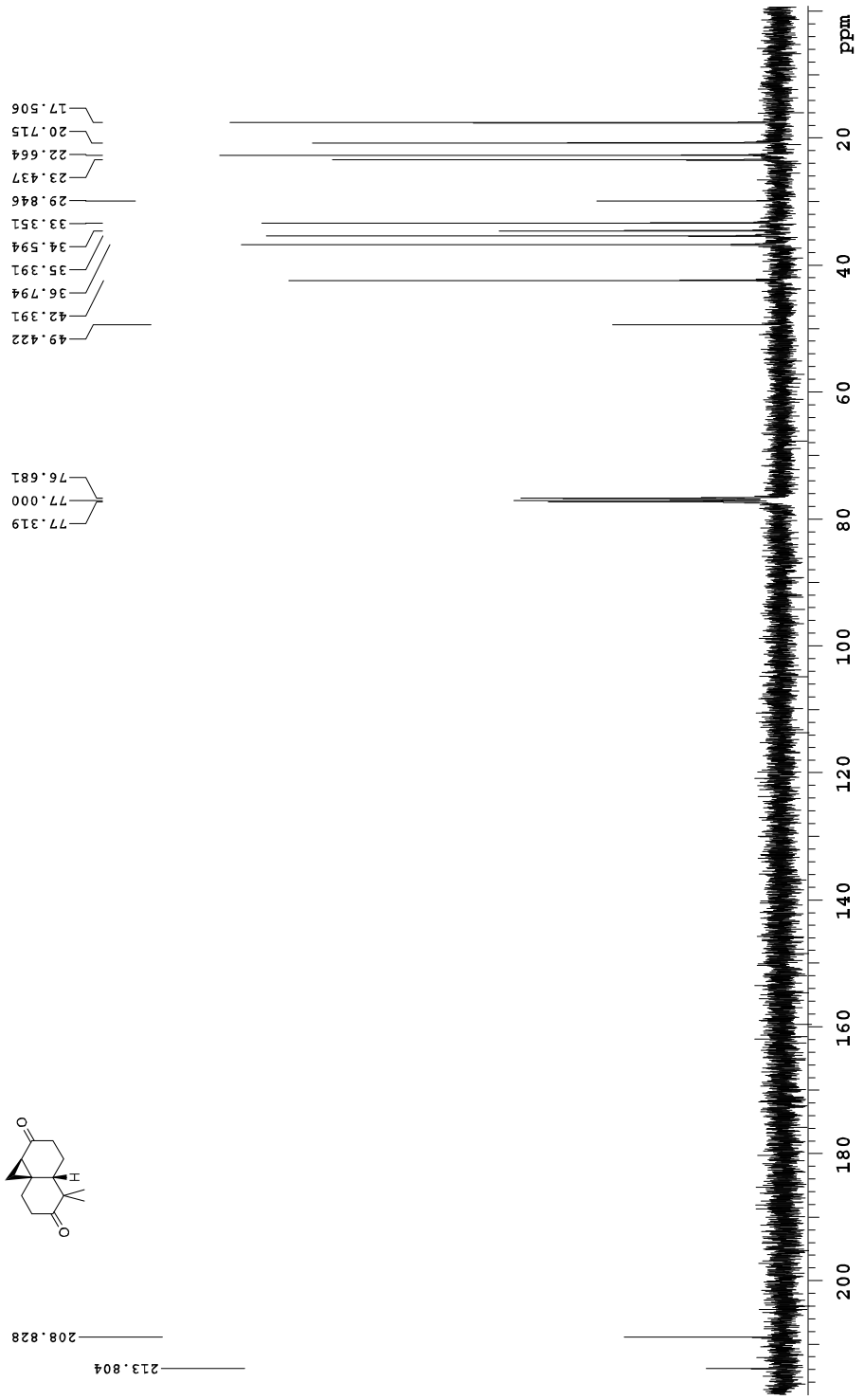
Spectrum 1.64 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **114**



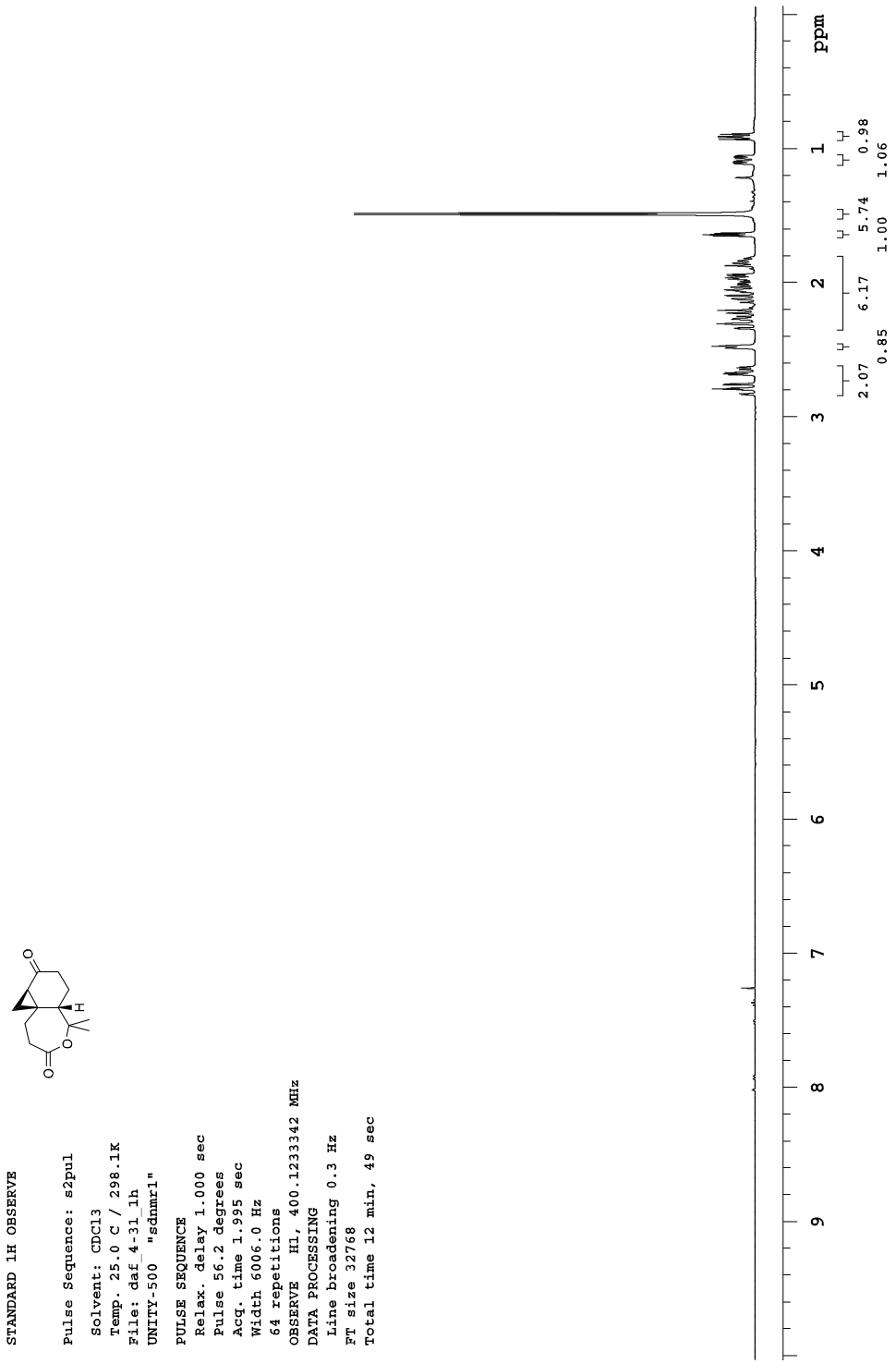
Spectrum 1.65 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **114**



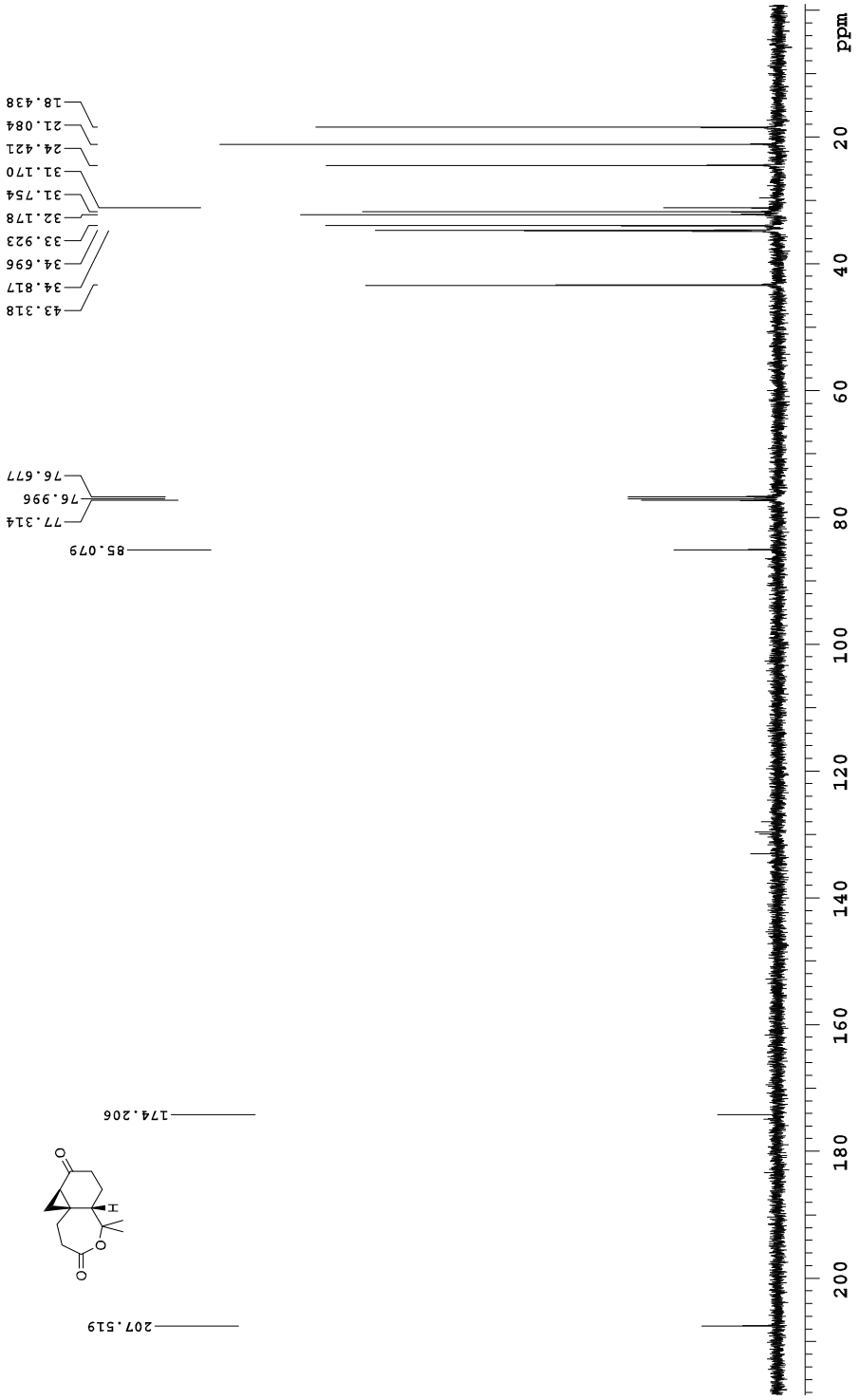
Spectrum 1.66 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **115**



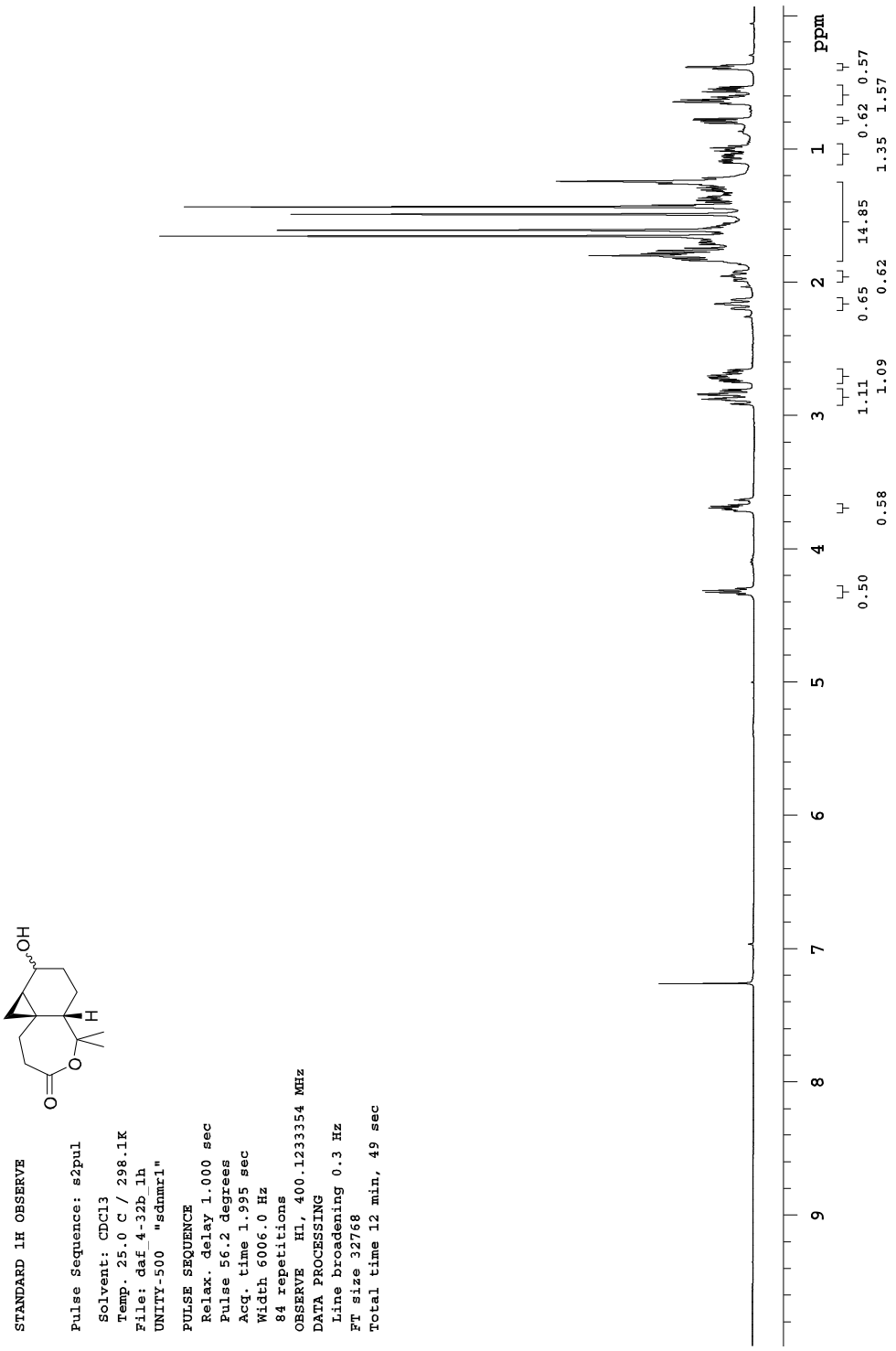
Spectrum 1.67 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **115**



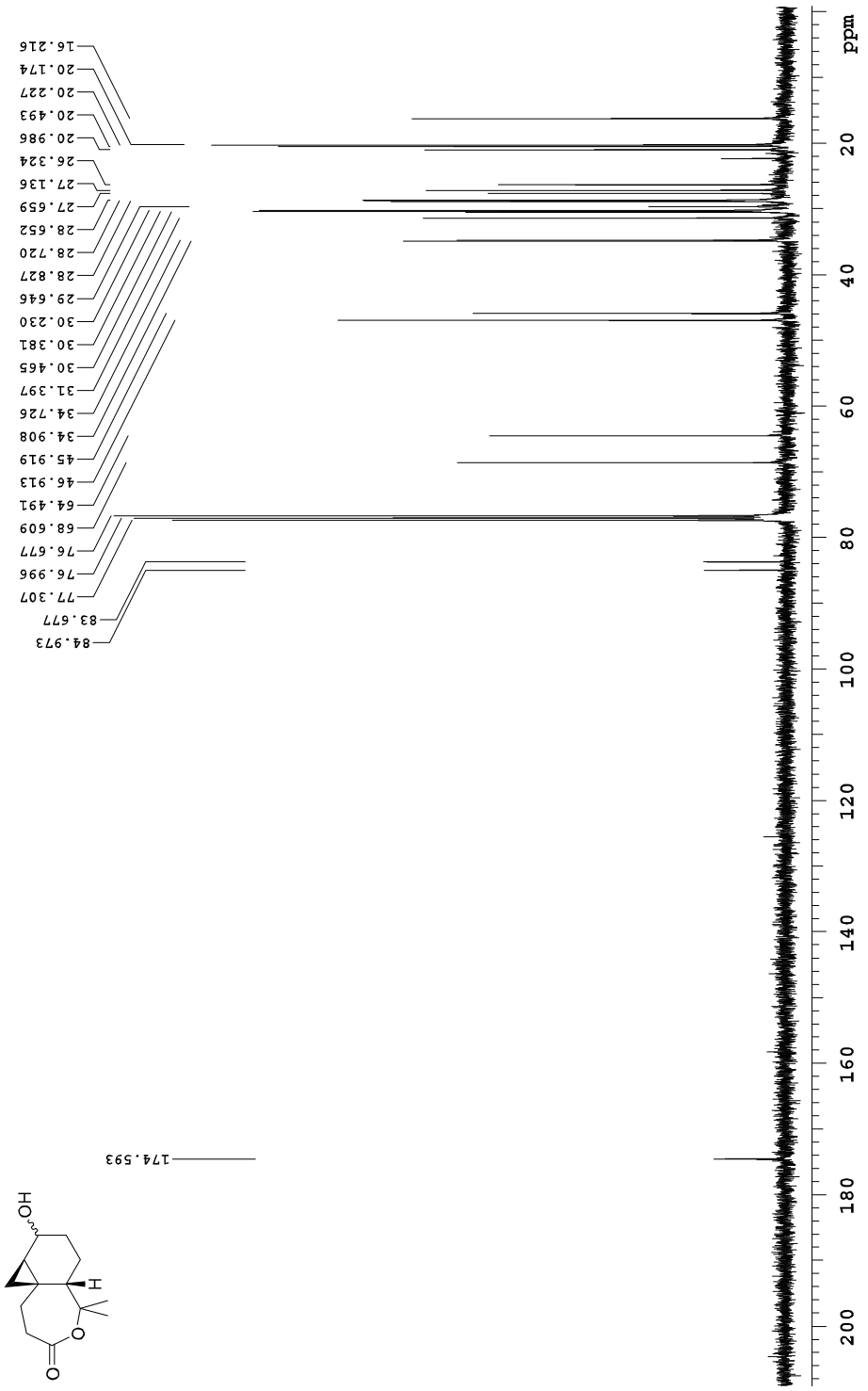
Spectrum 1.68 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **120**



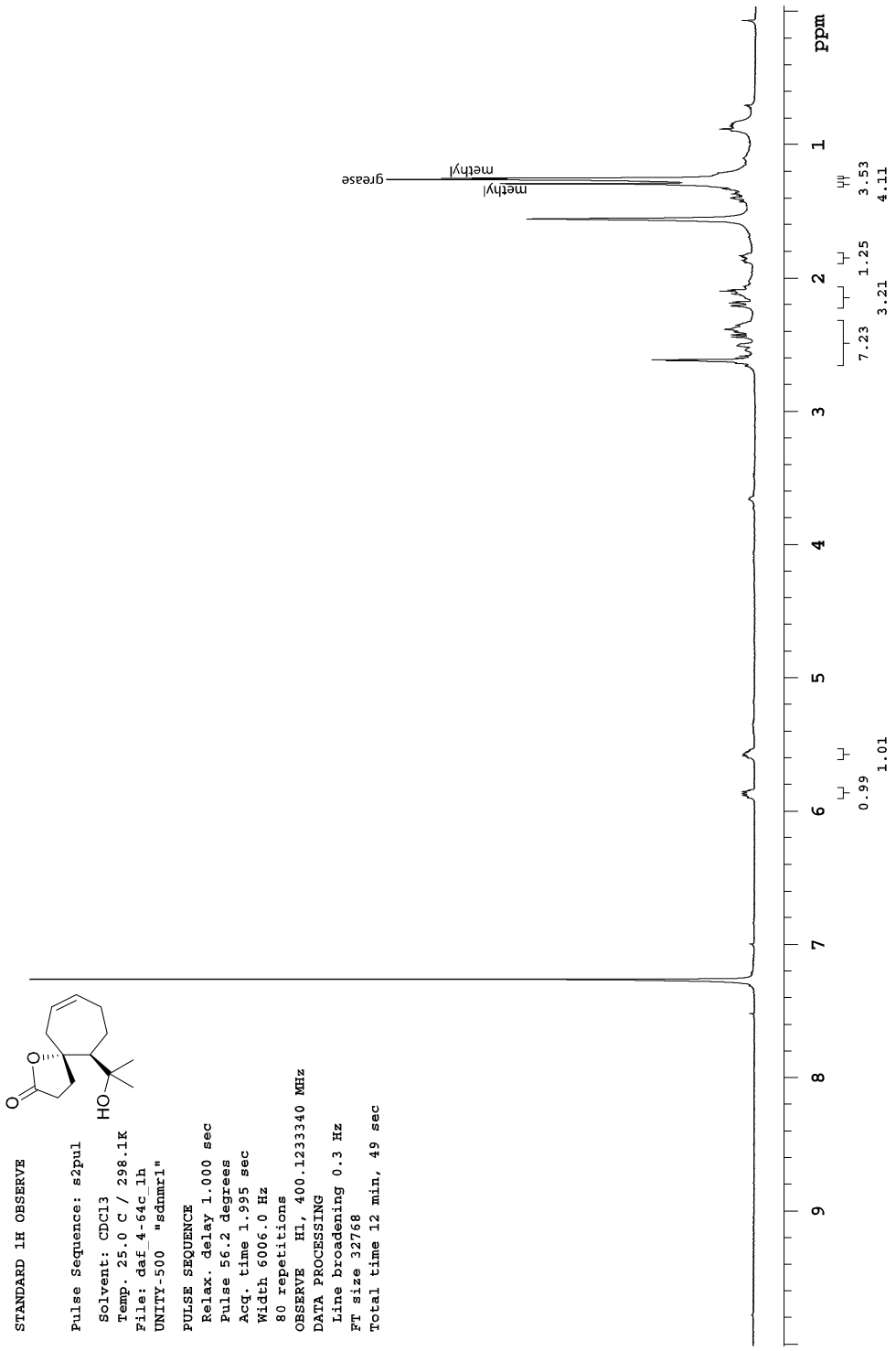
Spectrum 1.69 ^{13}C NMR ($CDCl_3$, 100MHz) of compound **120**



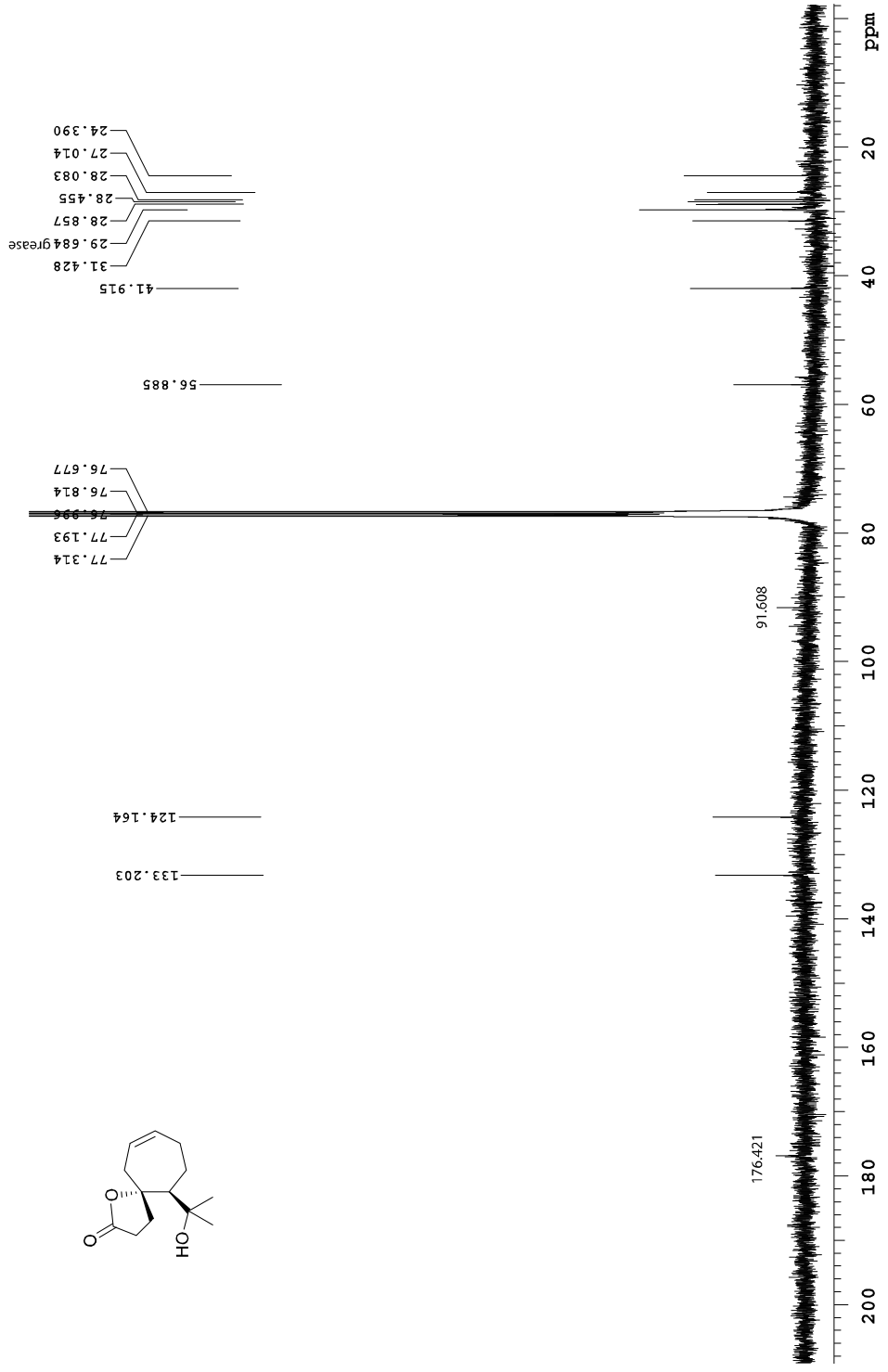
Spectrum 1.70 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **121**



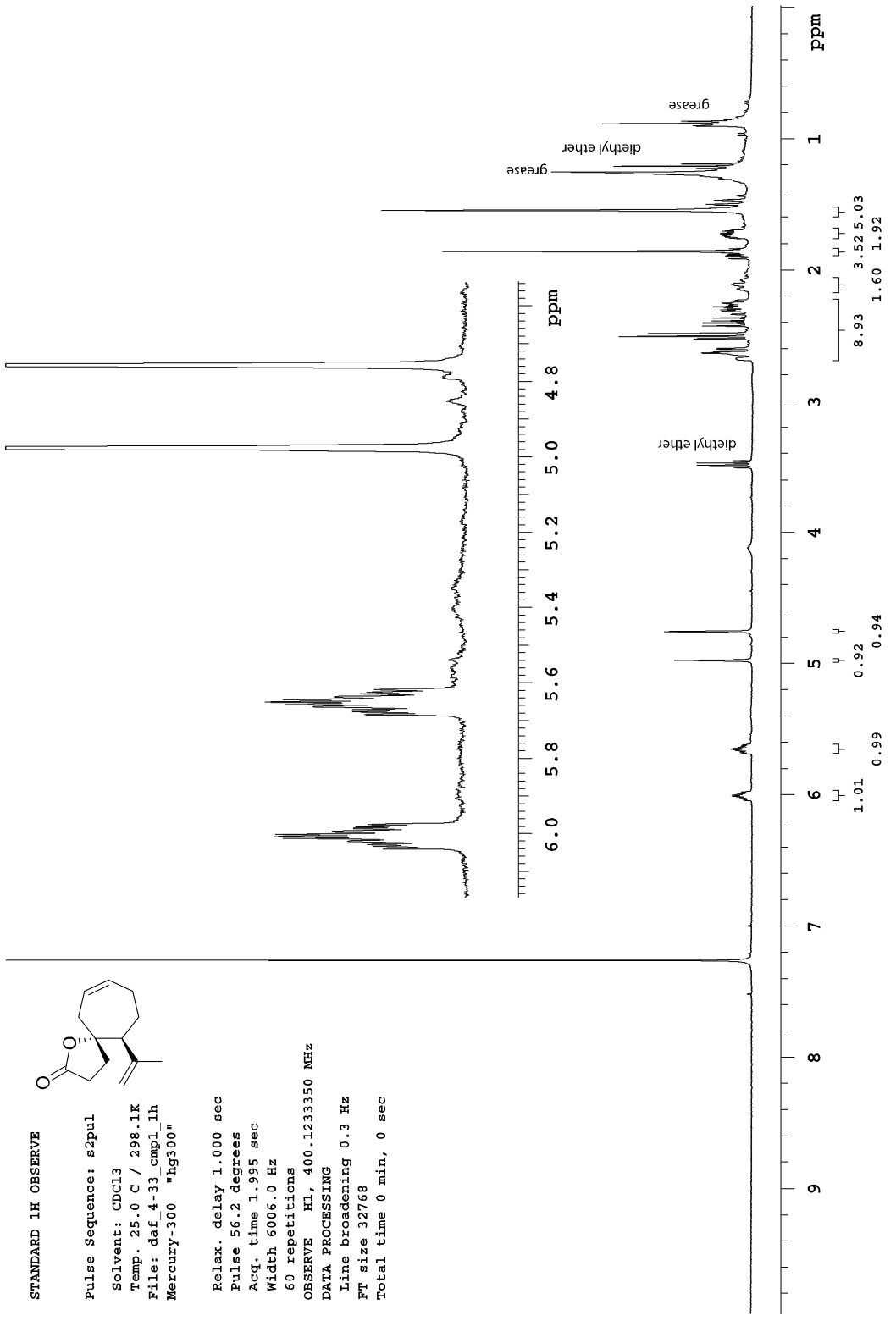
Spectrum 1.71 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **121**



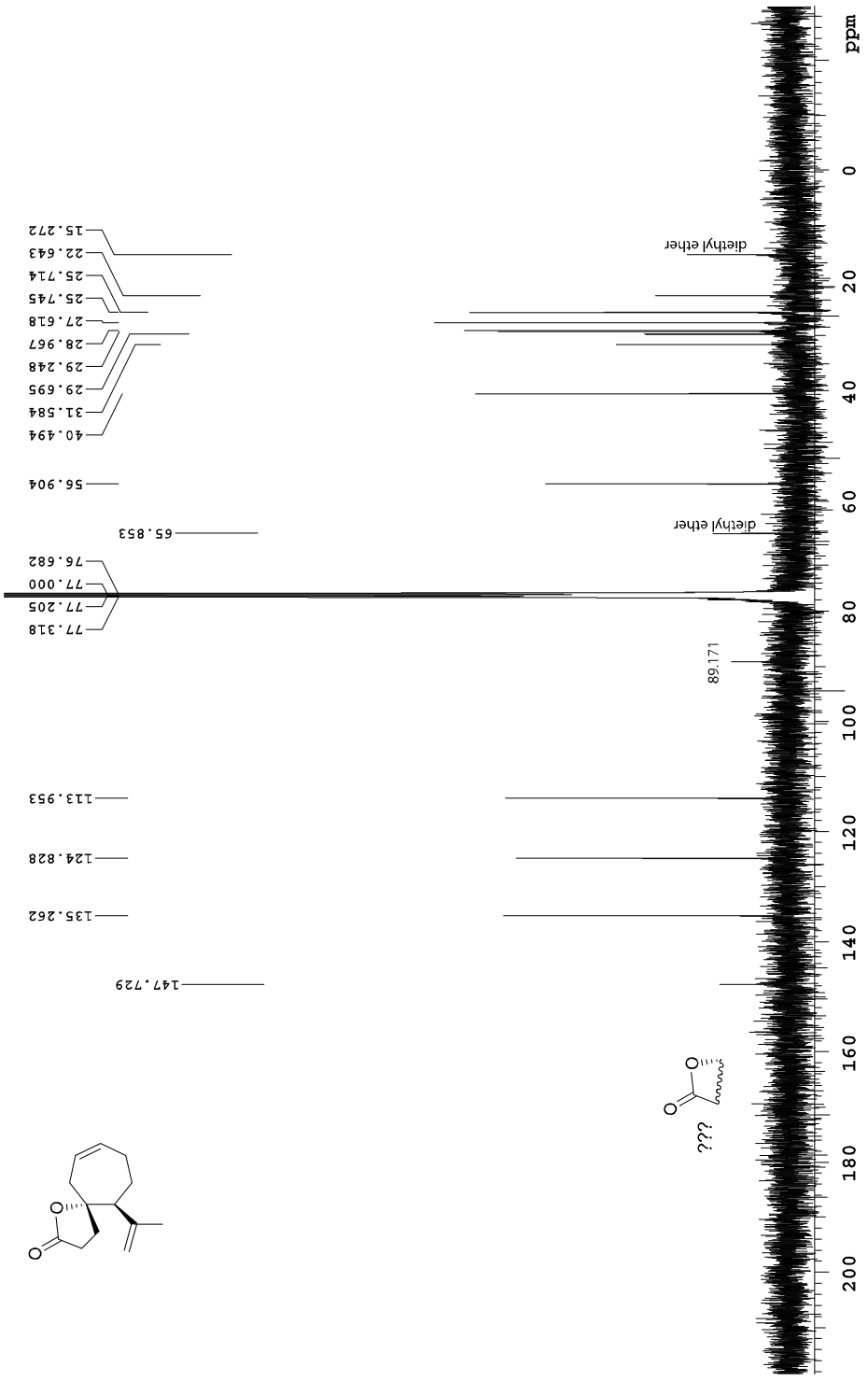
Spectrum 1.72 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **122**



Spectrum 1.73 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **122**



Spectrum 1.74 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **123**



Spectrum 1.75 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **123**

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Chapter II

Studies Toward Zoanthamine Natural Products

Section 2.1 Introduction to Zoanthamine Fauna and Natural Products

Zoanthamine (**150**) was isolated from an unidentified zoanthid collected off the Visakhapatnam coast of India and reported by Faulkner and collaborators in 1984.[1] Zoanthids are coral-like polyps existing as colonial mats or solitary animals in temperate and tropical regions of the Indian, Pacific, and Atlantic oceans. The ability of some zoanthids to eject an irritating stream of water was noted in the zoanthamine (**150**) isolation paper. This stream causes tearing, redness, and pain if it comes in contact with the victim's eyes. The powerful defense mechanism is assumed to be composed of toxins from within the zoanthid's body. However, it is not clear whether the zoanthids actually produce the toxins. It has been postulated that many or some of the secondary metabolites isolated from zoanthids are actually produced by symbiotic dinoflagellates and incorporated by the zoanthid. Support for this theory is building and zooxanthellamine (**164**), a structure remarkably similar to zoanthamine (**150**), has recently been isolated from cultured dinoflagellates.[2]

Continued reports of new zoanthamine alkaloids have grown this family to at least 19 members (Figure 2.0). Shortly after the initial report of zoanthamine (**150**), Faulkner and collaborators disclosed the structures of zoanthenamine (**166**) and zoanthamide

(**165**).[3] Both of these alkaloids were isolated from the same zoanthid specimen as zoanthamine (**150**). The ABCEFG core of zoanthamine (**150**) is conserved in zoanthenamine (**166**) while only the ABCE ring system is conserved in zoanthamide (**165**). Each of these structures contains a spirocyclic butyrolactone D ring in place of zoanthamine's valerolactone and an enamine functionality at C10 in place of the aminal-ester functionality. Additionally, zoanthenamine (**166**) displays an additional ring in the form of a hemiketal centered at C20 and zoanthamide (**165**) has a modified FG ring system.

In 1989, Clardy and co-workers reported the isolation of zoanthaminone (**152**) from an unidentified zoanthid found in the Arabian Sea.[4] The structure of zoanthaminone bears a strong resemblance to zoanthamine (**150**), differing only in the oxidation state of C11. In addition, zoanthaminone's (**152**) C11 carbon is a ketone functionality instead of the typical methylene unit.

Two alkaloids, 28-deoxyzoanthamine (**167**) and 22-*epi*-28-deoxyzoanthamine (**168**), isolated from a zoanthid collected from the Bay of Bengal were reported in 1989 by Rao and coworkers.[5] Each of these alkaloids contains the spirocyclic butyrolactone connected at C22, however the stereochemistry at the core point of attachment has been transposed in 22-*epi*-28-deoxyzoanthamine (**168**), relative to zoanthenamine (**166**) and zoanthamine (**150**).

In 1995, Daisuke Uemura and coworkers reported five new zoanthamine alkaloids from an unidentified zoanthid collected off the Ayamaru coast of the Amani islands.[6]

Norzoanthamine (**151**) differs from zoanthamine (**150**) only in the lack of methyl substitution at C19. Oxyzoanthamine (**158**) also closely resembles zoanthamine (**150**), with the only structural difference being an oxidized C26 in the form of a methyl group. Norzoanthaminone (**153**) is identical to zoanthaminone with the exception of the C19 methyl group. Cyclozoanthamine (**162**) contains a modified A ring with C28-C16 connection forming an additional ring. Epinorzoanthamine (**160**) resembles norzoanthamine (**151**) with a modified A ring where the C17 enone has been reduced to an alcohol and the C15-C16 olefin has shifted to C15-C27.

Epioxyzoanthamine (**159**) was reported in 1998 by Norte and coworkers from a zoanthid collected off the north coast of Tenerife.[7] Epioxyzoanthamine (**159**) is epimeric at C19 to the previously reported oxyzoanthamine (**158**). Norte and coworkers also reported five additional alkaloids isolated from a zoanthid collected off the coast of Tenerife in 1999.[8] The alkaloids, 11-Hydroxyzoanthamine (**156**) and 11-hydroxynorzoanthamine (**157**) both strongly resemble the parent compounds, respectively. The only modification being hydroxyl functionalities attached at C11. 3-Hydroxyzoanthamine (**154**) differs from zoanthamine (**150**) only through the addition of a hydroxyl functionality at C3, while 30-hydroxyzoanthamine differs only at C30.

Recently, a zoanthamine alkaloid has been isolated from a non-zoanthid genus. Fattorusso and coworkers isolated lobozoanthamine (**161**) from a soft coral of the genus *Lobophytum* collected along the island of Siladen (Indonesia).[9] The structural similarity between lobozoanthamine (**161**) and zooxanthellamine (**164**) is very interesting. The two compounds differ only in the oxidation state of C27, zooxanthellamine (**164**)

possesses a methyl group while lobozanthamine (**161**) has a terminal olefin. The fact that zooxanthellamine (**164**) was isolated from dinoflagellates while lobozoanthamine (**161**) was isolated from a non-zoanthid genus known to live symbiotically with dinoflagellates further suggests that zoanthamine alkaloids may arise from symbiotic relationships and/or dietary intake of dinoflagellates.

It should be noted that to the best of our knowledge, the absolute configuration has been reported only for norzoanthamine (**151**)[10] and lobozoanthamine (**161**). Both assignments have been made through derivitization by conversion to Mosher's esters. All other zoanthamine alkaloids have been assigned stereochemistry based on the complete characterization of norzoanthamine (**151**).

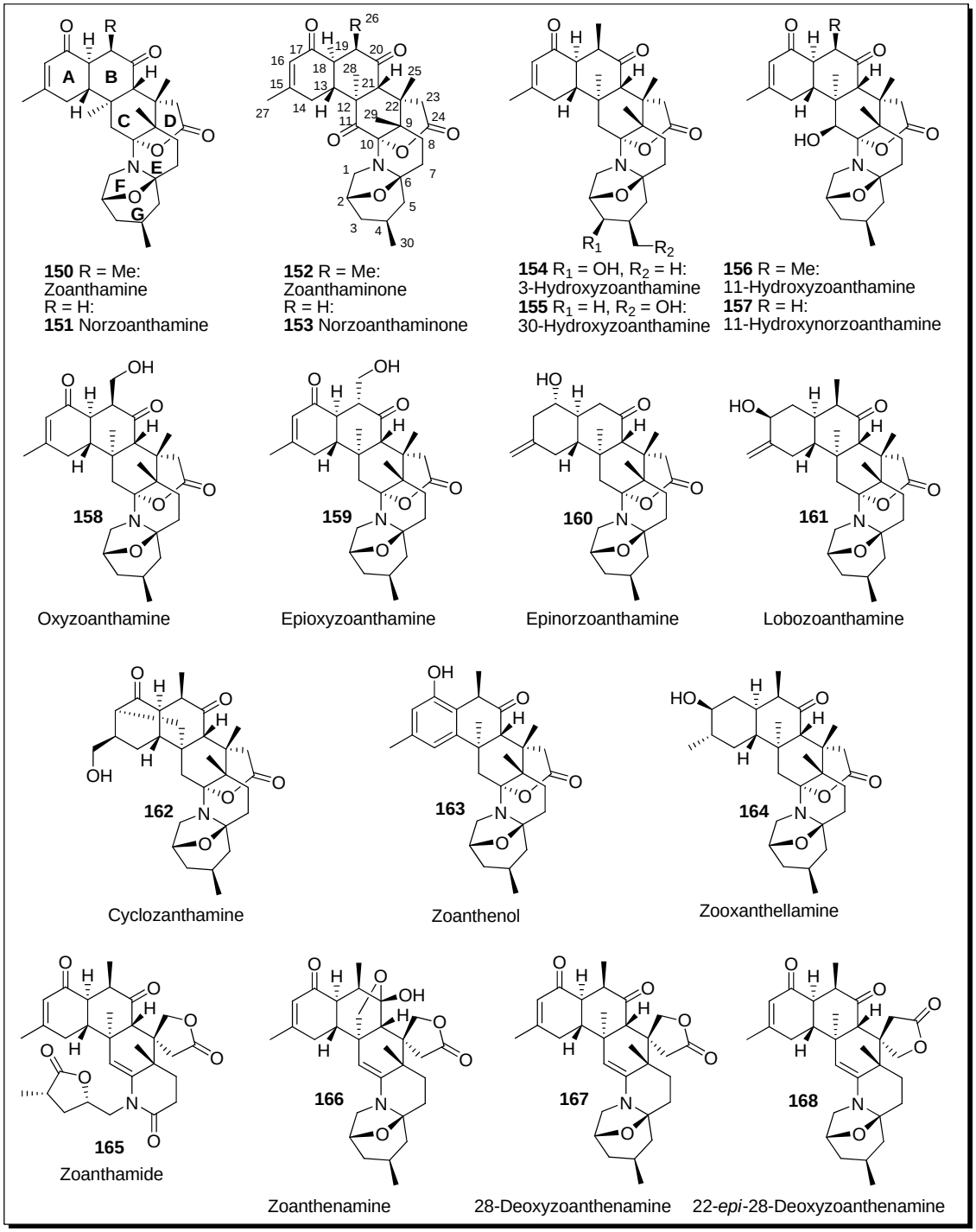


Figure 2.0 Representative zoanthamine natural products

In addition to their beautiful architecture, the inherent biological activity of these alkaloids has attracted considerable attention. The most exciting may be norzoanthamine (**151**), which has exhibited unique anti-osteoporotic properties. Accordingly, it has been proposed that norzoanthamine (**151**) acts as a bone growth stimulator and bone resorption suppressor.[11] The ability to reduce bone resorption, has been documented in ovariectomized mice (a post-menopausal model) in which treatment leads to the suppression of femoral weight and strength loss.[12] The mode of action is thought to involve suppression of Interlukin-6 (IL-6), which acts as a stimulator for osteoclast formation, thereby enhancing bone resorption. Norzoanthamine (**151**) and its hydrochloride salt have been shown to inhibit secretion of IL-6 from preosteoblastic cells at concentrations of 13 and 4.6 μg/mL.[10,13] Structure activity relationship studies have found that A and D rings are important for suppression of IL-6 secretion, as modification to these rings resulted in deleterious effects.[12a,13] Another additional SAR study performed by Hirama and coworkers suggested that southern hemisphere aminal function may be most important for IL-6 suppression.[14] These researchers found that an ABC ring analog of zoanthenol (**163**) (IC_{50}: > 100 μM) and a CDEFG ring analog (IC_{50}: > 100 μM) were both less efficacious than norzoanthamine (**151**). However, when the CDEFG ring analog HCL salt was tested, results showed activity closer to that of the norzoanthamine HCl salt (IC_{50}: 70 μM vs. 13 μM).

The zoanthamine group of alkaloids has demonstrated a myriad of biological activities. Zoanthenamine (**150**), zoanthamide (**165**), and 28-deoxyzoanthamine (**167**)

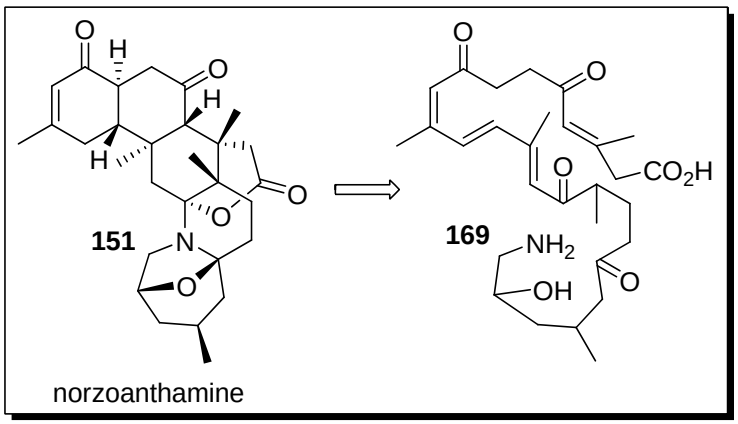
have all been shown to posses anti-inflammatory[15] and analgesic properties.[16] Cytotoxicity against P388 murine leukemia cells has also been demonstrated for norzoanthamine (**151**), norzoanthaminone (**153**), oxyzoanthamine (**158**), cyclozoanthamine (**162**), and epinorzoanthamine (**160**) with IC_{50} values ranging from 1.0 to 24 μg/mL.[6]

11-Hydroxyzoanthamine (**156**), zoanthenol (**163**), oxyzoanthamine (**158**) and zoanthaminone (**152**) have all been shown to effect human platelet aggregation.[17] Platelet aggregation has been implicated in thrombosis related ailments ranging from atherosclerosis to strokes and heart attacks resulting from arterial thrombosis. While zoanthenol (**163**) and 11-hydroxyzoanthamine (**156**) inhibited platelet aggregation, oxyzoanthamine (**158**) and zoanthaminone (**152**) exhibited irreversible platelet aggregation. This finding is indicative of how subtle structural changes (11-hydroxyzoanthamine (**156**) and zoanthaminone (**152**) differ in the C11 oxidation state) can effect biological activity. Accordingly, oxidation of the C11 hydroxyl group of 11-hydroxyzoanthamine (**156**) to the corresponding ketone, zoanthaminone (**152**), converted the structure from a platelet aggregation inhibitor to an aggregation agent.

The interesting pharmacological properties exhibited by many zoanthamine alkaloids, has stimulated research in this area and is expected to continue. The complexity of the zoanthamine alkaloids and limitations of modern total synthetic methods may prompt particular focus on SAR studies.

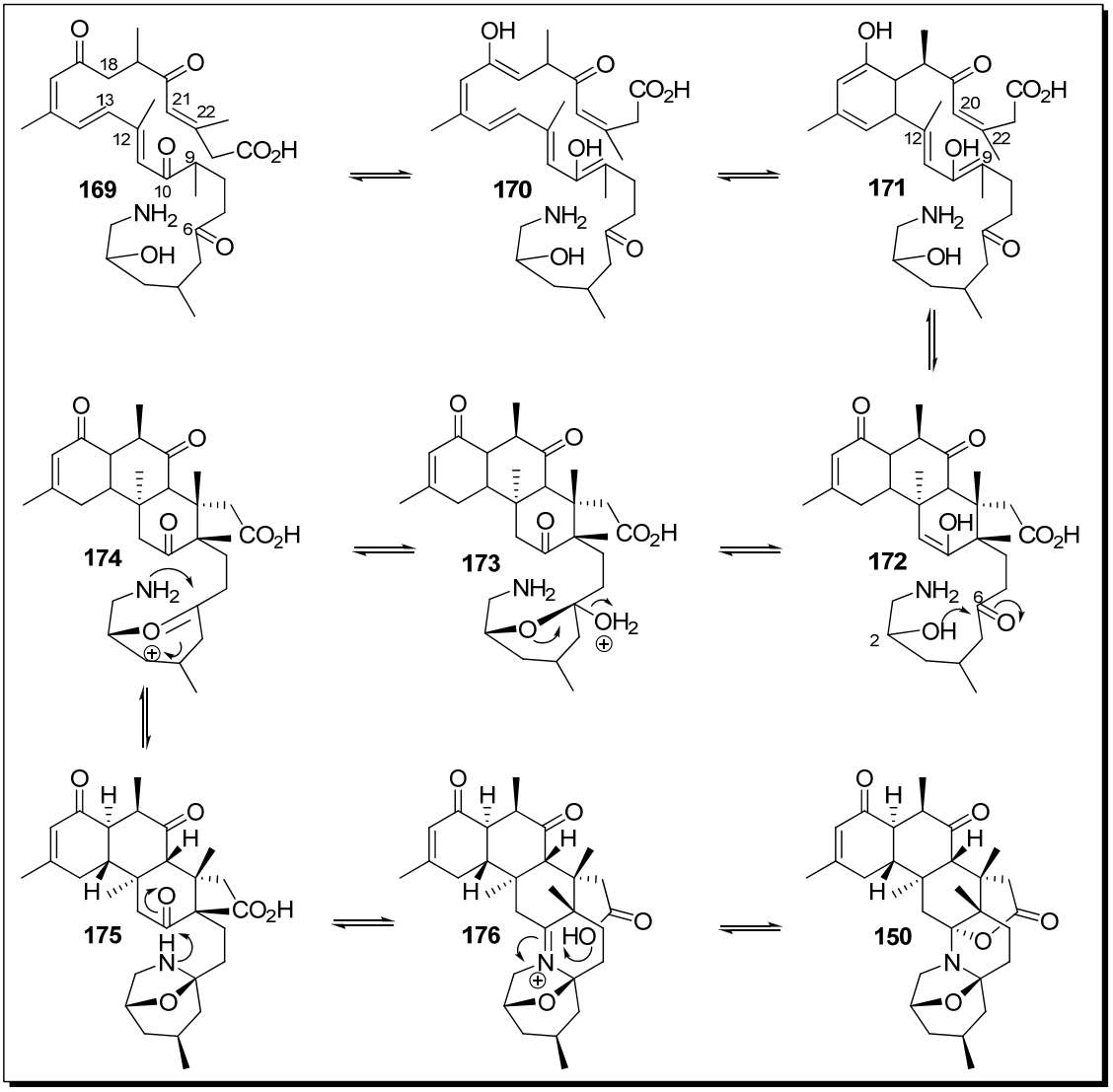
Section 2.2 Uemura's Proposed Biosynthesis

While there is no consensus on the biogenetic source of the zoanthamine alkaloids, they have been proposed to be terpene in origin based on the 30 carbon composition for the zoanthamine (**150**) skeleton. However, application of the isoprene rule fails to provide the apparent connectivity, as a linear triterpene poly-cyclization substrate would require non head-to-tail isoprene linkages or a series of unobvious methyl shifts. Uemura and coworkers first proposed a polyketide biogenetic pathway for norzoanthamine (**151**) in 1997.[10] Scheme 2.1 shows the original proposal by Uemura.



Scheme 2.0 Umuera's norzoanthamine (**151**) biosynthetic proposal.

Unfortunately, no explanation for this proposal has been provided. However, at least one detailed interpretation involving this linear zoanthamine precursor has been published. Stoltz and coworkers recently published an excellent review paper discussing the biology and chemistry of zoanthamine alkaloids, and Stoltz's interpretation of the original Umuera biosynthetic proposal is outlined in Scheme 2.1.[18]

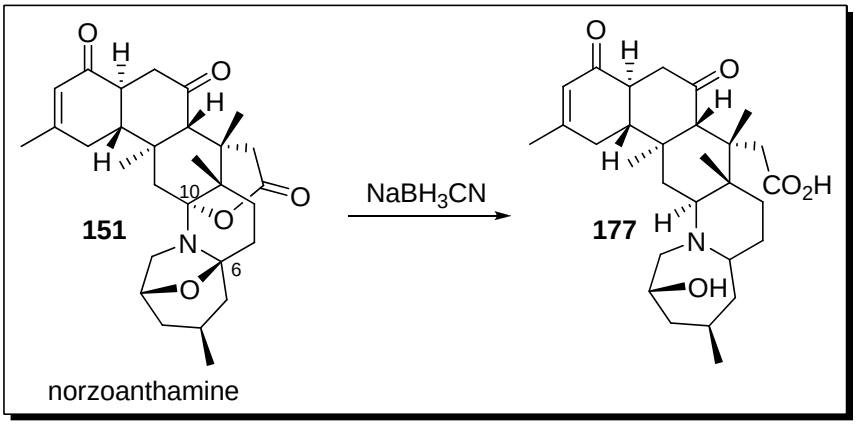


Scheme 2.1 Stoltz's interpretation of Umuera's zoanthamine (**150**) biogenetic proposal.

The first step of this proposal would require tautomerization of the C18 ketone to the corresponding enol, and possibly of the C10 ketone as depicted by intermediate **170**. A conrotatory electrocyclization could set the correct AB ring junction stereochemistry, followed by tautomerization to the A ring enone. A [4+2] cycloaddition between the depicted C9-C12 diene system and the C22-C20 enone dienophile is suspected of

closing rings B and C. Subsequently, C10 tautomerization could subsequently return the C10 ketone functionality. C2 hydroxyl attack at ketone C6 and subsequent loss of water through oxonium formation would provide intermediate **174**. F ring closure would occur through amine attack of oxonium **174**. Condensation of the amine at the C10 ketone could close ring E and would presumably provide an iminium (**176**) under acidic conditions which could be trapped by the caboxylate group to form ring D as the final step.

Stoltz noted that the last several steps might be particularly prone to retro reactivity, allowing the system to equilibrate to the thermodynamically favored product. Work performed by Uemura might support the final steps of this proposal.[13] When norzoanthamine (**151**) was treated with sodium cyanoborohydride, compound **177** was produced (Scheme 2.2). This was suggestive of an immediate C10 iminium formation and opening of the lactone ring followed by iminium reduction. Subsequent iminium formation at C6 followed by reduction might explain the product. This reaction could potentially mimic the DEFG ring forming events in reverse and might lend support to the proposed biosynthesis. More importantly, synthetic studies have indicated the stereochemistry of the southern hemisphere to be favored and will be discussed shortly.



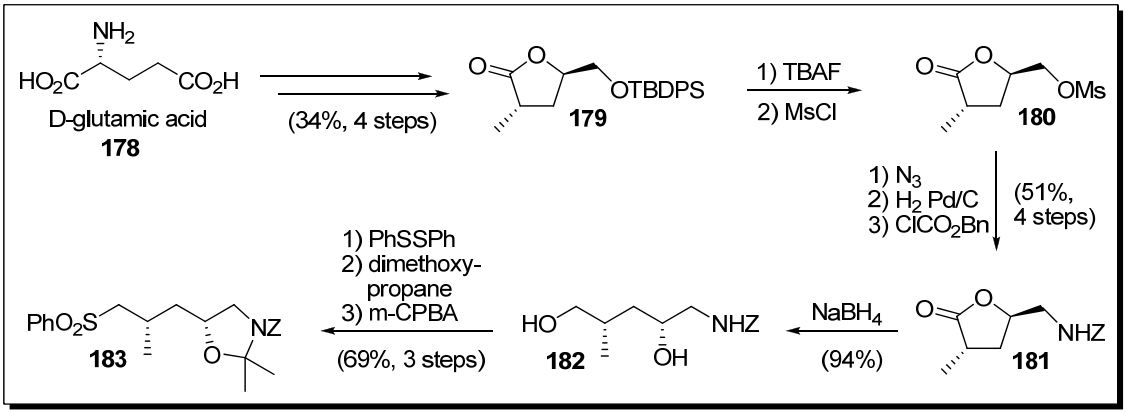
Scheme 2.2 Norzoanthamine (**151**) degradation with $NaBH_3CN$.

Section 2.3 Reported Synthetic Efforts

The structural complexity and potential for medicinal use has created significant interest from the synthetic community. At least 24 papers directly related to zoanthamine alkaloid synthesis have been published since 1994 by 8 different research groups. The strategy and key reactions of each group will be discussed.

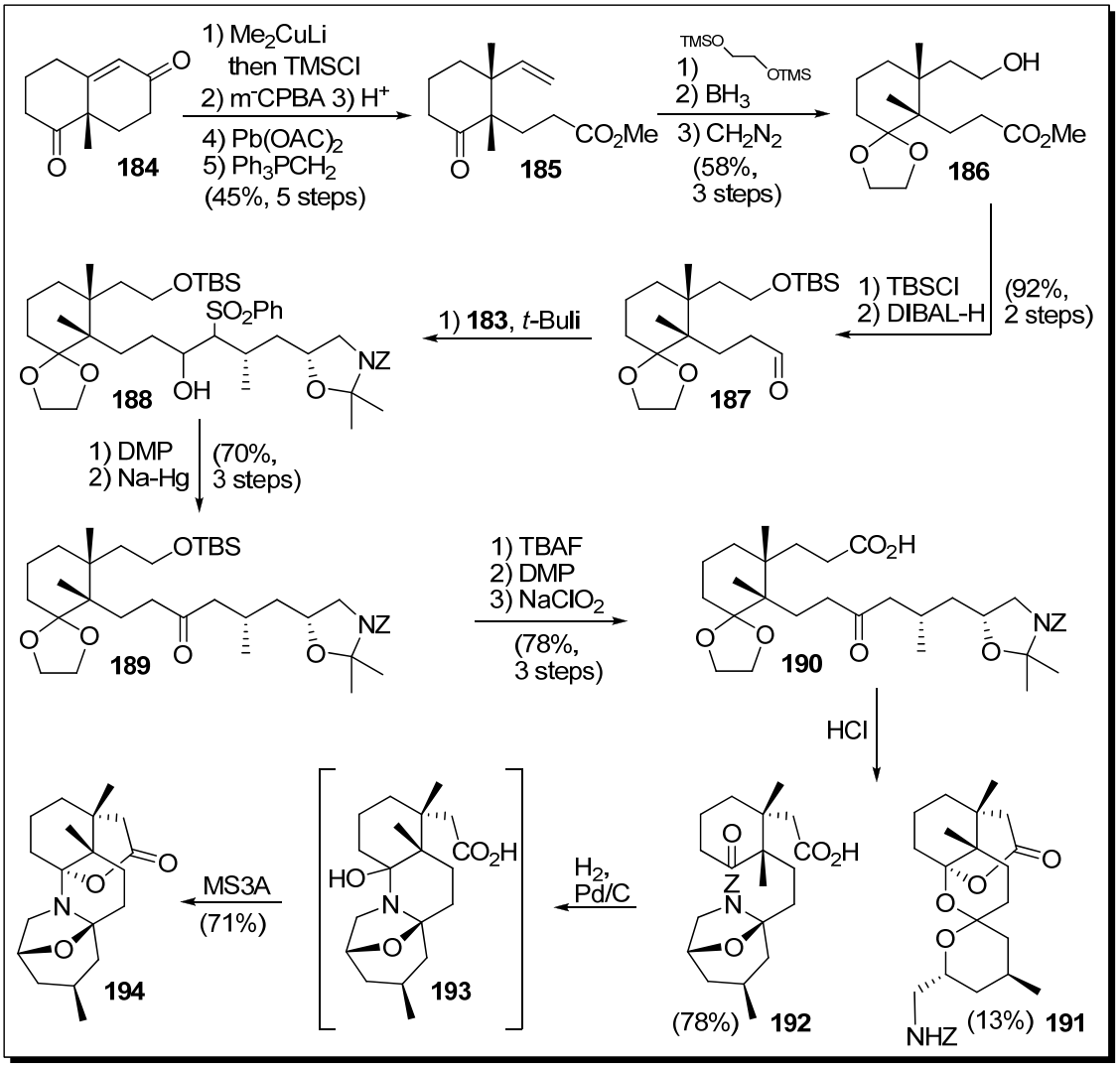
Kobayashi and coworkers published their seminal work on the southern hemisphere (rings C-G) in 1998.[19] The chiral C1-C5 sulfone fragment (**183**) was synthesized from glutamic acid (Scheme 2.3). Manipulation of D-glutamic acid (**178**) provided butyrolactone (**179**) as previously reported by Hanessian and coworkers.[20] Butyrolactone (**179**) was converted to the aminobutyrolactone (**181**) through a series of modifications at the hydroxyl carbon. Deprotection and mesylation provided mesylate **180**, which was treated with sodium azide to displace the mesyl group. The azide was reduced to the amine by hydrogenation and protected as the benzyl carbamate (**181**). Butyrolactone **181** was opened to the diol (**182**) by treatment with sodium borohydride.

Sulfone **183** was formed by conversion of the primary alcohol (**182**) to the phenyl thiol prior to protection of the amino-alcohol moiety as the N,O-ketal, which was then oxidized to the sulfone. A series of 13 steps provided the desired C1-C5 fragment with the necessary chirality in good yield.



Scheme 2.3 Kobayashi's synthesis of sulfone **183**.

The CDE fragment synthesis began from the reported chiral Wieland-Miescher ketone (WMK) (**184**) (Scheme 2.4).[21] It should be noted that the C9 methyl group was installed in the first step of C ring formation. A diastereoselective cuprate addition to the WMK (**184**) followed by trapping of the enolate as the vinyl TMS ether and epoxidation provided the substrate for oxidative cleavage which underwent aldehyde-selective single carbon Wittig homologation to give olefin **185**. The ketone was protected as the dioxolane and hydroboration performed on the olefin. Treatment with diazomethane was noted but not discussed, this action was presumably necessitated by hydrolysis of the methyl ester during the previous modifications.



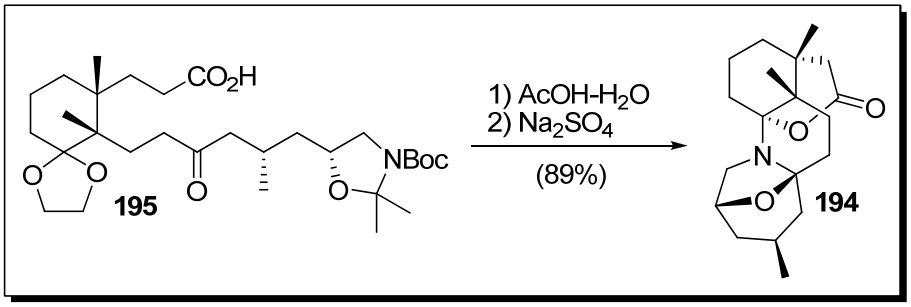
Scheme 2.4 Kobayashi's southern fragment synthesis.

Protection of the alcohol and reduction of the methyl ester provided the coupling substrate, aldehyde **187**. Coupling of aldehyde **187** and sulfone **183** was achieved by conversion of sulfone **183** to the corresponding lithiate with *t*-butyl lithium followed by reaction with aldehyde **187** to provide a diastereomeric mixture of sulfones (**188**). Oxidation and desulfurization with Na-Hg provided ketone **189** in excellent yield.

Deprotection of the silyl ether and sequential oxidation (Dess-Martin periodinane then sodium chlorite) provided the cyclization substrate (**190**).

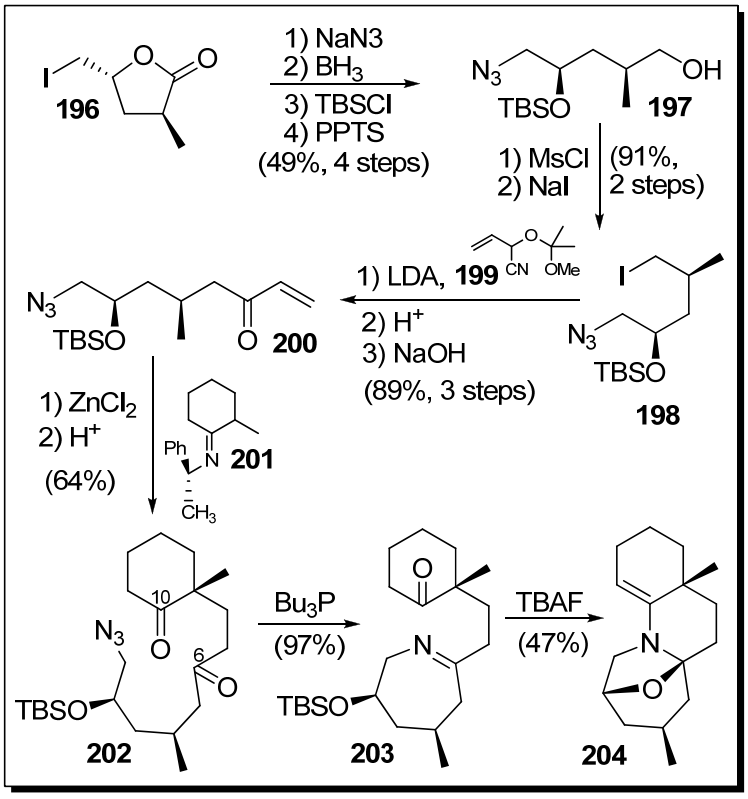
Cleavage of the benzyl carbamate (**190**) by hydrogenation failed at this stage, but treatment with acid initiated formation of aminal ring system (**192**) in surprising yield, while ketal **191** was isolated as a minor side product. Hydrogenation of aminal **192** was successful at this stage, however standard work up conditions resulted in decomposition of the product(s). Notwithstanding, aminal **194** was isolated when molecular sieves were added as a dehydrating agent. This compound represents the CDEFG ring system, with rings D-G fully functionalized.

By replacing the benzyl carbamate with a Boc carbamate, Kobayashi was able to perform the deprotection and cyclization in a single step. Heating under acidic conditions provided aminal **194** in excellent yield (Scheme 2.5). This important contribution offers a highly efficient method for construction of the southern fragment as 4 rings and two new stereocenters weree formed in a single step under simple reaction conditions.



Scheme 2.5 Kobayashi's optimized cyclization step.

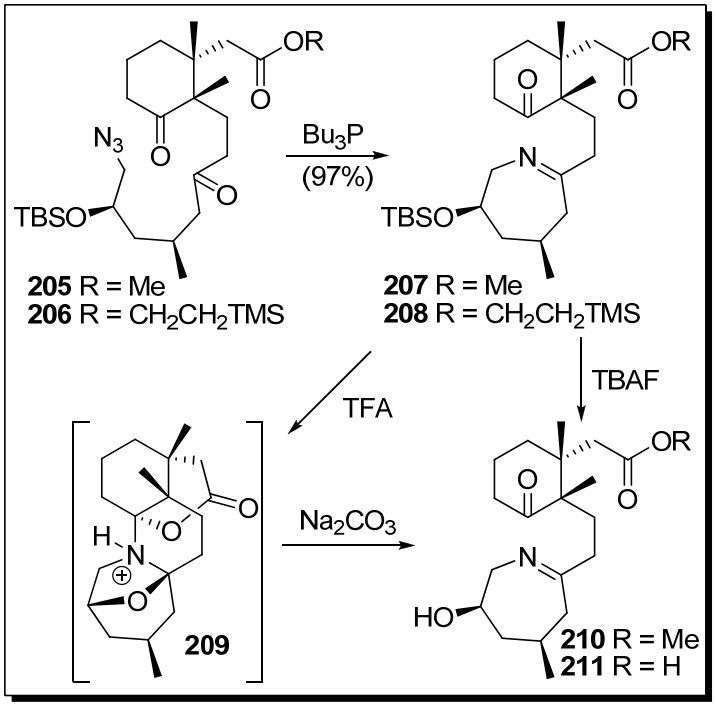
The Williams group has published work directed at the southern fragment,[22] in addition to research focused northern fragments.[23,24] Initial studies directed toward the southern fragment were conducted with the reported butyrolactone **196** (Scheme 2.6) assembled through Evans aldol methodology.[22a] The iodo butyrolactone (**196**) was converted to the corresponding azide, which was then reduced to the diol with borane. Di-TBS protection and mild deprotection of the primary alcohol provided alcohol **197** in good overall yield. Mesylate formation and displacement with iodide gave primary iodide **198**. Deprotonation of cyanohydrin **199** and addition of iodide **198** formed enone **200** in excellent yield after hydrolysis. A diastereoselective conjugate addition was achieved by addition of the tautomer of known imine **201** to enone **200**. The chiral auxiliary was hydrolyzed with aqueous acid to give diketone **202**. The Staudinger reaction was then utilized to reduce the azide and efficiently provided imine **203**, which was treated with TBAF. TBS cleavage resulted in hydroxyl attack of the imine and condensation of the resultant amine with the C10 ketone to form enamine **204**. The synthesis of enamine **204** constitutes rings C, E, F, and G of the zoanthamine alkaloids and offers an alternative to aminal formation under acidic conditions.



Scheme 2.6 Williams' southern fragment synthesis.

Unfortunately, subsequent studies with more functionalized substrates failed to provide the aminal ring system (Scheme 2.7).[22b] Methods similar to those used to produce diketone **202** were used to build diketoesters **205** and **206**, substrates equal in functional complexity to those reported by Kobayashi. The Aza-Wittig reaction of **205** and **206** proceded well, as previously reported. Treatment of methyl ester **207** with TBAF provided the free alcohol **210** which failed to cyclize in the manner previously observed. And treatment of **207** or **208** with TFA resulted in isolation of a compound tentatively identified as **211**. The researchers claimed that ammonium salt **209** was formed, but that hydrolysis occurred upon neutralization to provide **211**. This was an

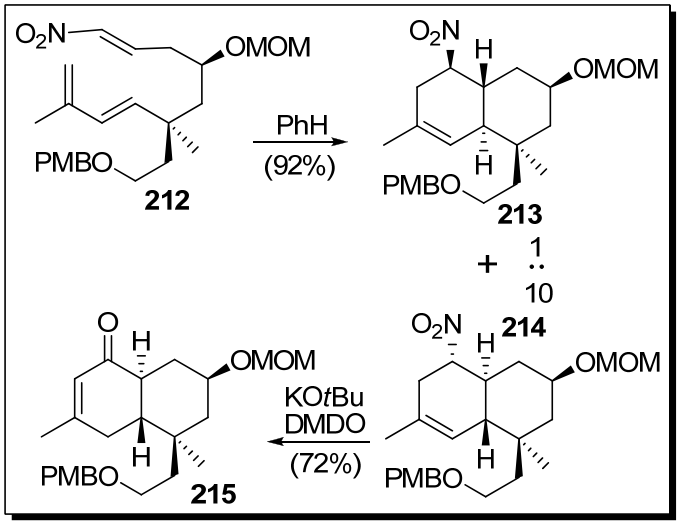
unexpected result since the intermediate ammonium salt (**209**) was presumably the identical intermediate in the acid catalyzed cyclization reported by Kobayashi (Scheme 2.4). This particular report therefore serves as an indicator of the fastidious nature of this cyclization where multiple hydrolysis, condensation, and solvolysis reactions may exist in equilibrium.



Scheme 2.7 Williams' southern fragment analog cyclization attempts.

The Williams group has reported a Diels-Alder approach to the AB ring system (Scheme 2.8).[23] Nitrotriene **212** was constructed in approximately 21 steps utilizing Evans aldol methodology to install chirality. After a 65 hour treatment in refluxing benzene, two endo isomers (decalins **213** and **214**) were isolated in favorable diastereoselectivity from the IMDA reaction. While increased diastereoselectivity (95:5

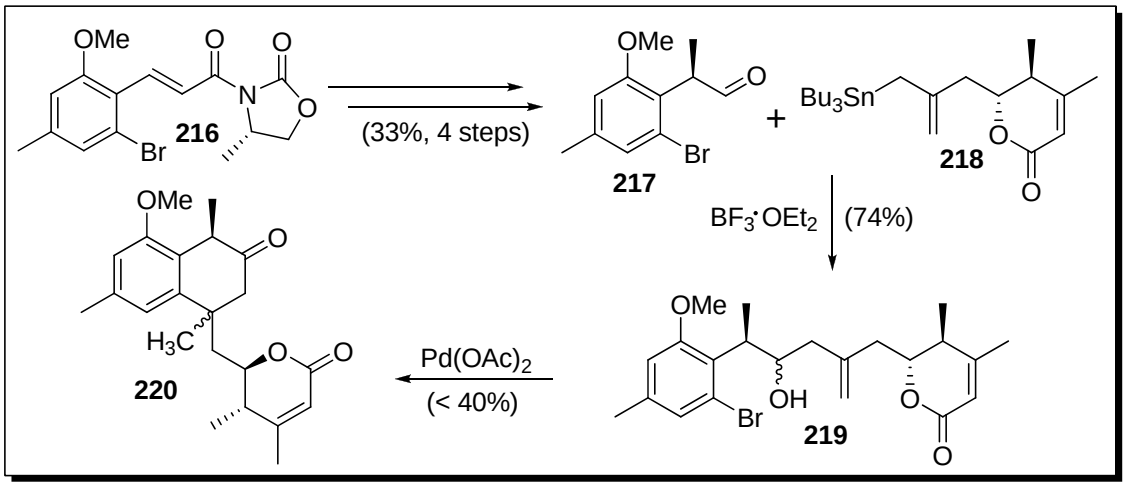
in acetonitrile) was achieved in some solvents, reduced overall yield of the desired decalin (**214**) was observed. When **214** was treated under oxidative Nef reaction conditions, enone **215** was produced in 60% yield from nitrotriene **212**. The enone (**215**) represents the fully functionalized A ring with correct ring junction and C12 methyl stereochemistry of the zoanthamines.



Scheme 2.8 Williams' AB ring forming Diels-Alder sequence.

An approach to the AB ring system of zoanthenol (**163**) has also been published by Williams (Scheme 2.9).[24] Related studies by Williams and coworkers allowed synthesis of aldehyde **217** through a directed cuprate addition to oxazolidinone **216** followed by cleavage of the chiral auxiliary and manipulations (oxidation/elimination then ozonolysis) leading to the aldehyde (**217**). A Lewis acid mediated coupling with stannane **218** gave Heck reaction substrate **219**. Unoptimized Heck conditions provided the AB ring system (**220**) of zoanthenol (**163**) as a mixture of C12 epimers. While the efficiency of this reaction is not clear, the obtained yield was less than 40% based on

recovery of starting material and isolation of a side product. Nonetheless, the fully functionalized A and functionalized B rings were formed through this process.

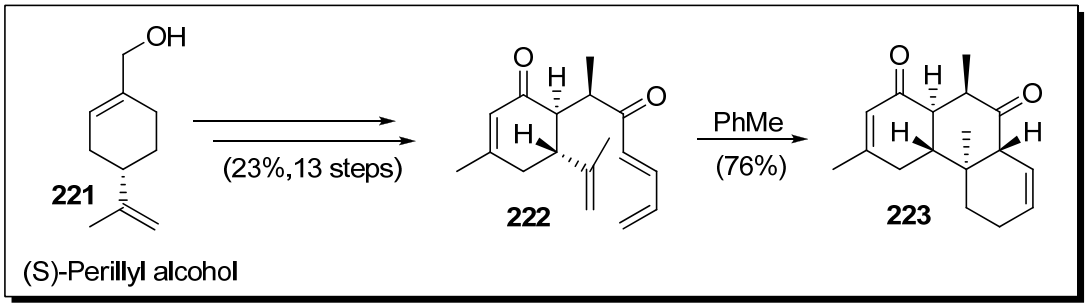


Scheme 2.9 Williams' approach to the AB ring system of zoanthenol (**163**).

Publications related to the zoanthamine alkaloids from the Williams group have spanned 1998 to 2007 and describe unique approaches to both the northern and southern hemispheres. The work on the northern portion has utilized a [4+2] cycloaddition to simultaneously build rings A and B and palladium coupling methodology was used to form ring B of their zoanthenol (**163**) model. An efficient approach to the southern portion resulted in formation of ring E,F, and G in 2 steps to yield an enamine adduct, but failed when analogs designed to incorporate ring D were studied.

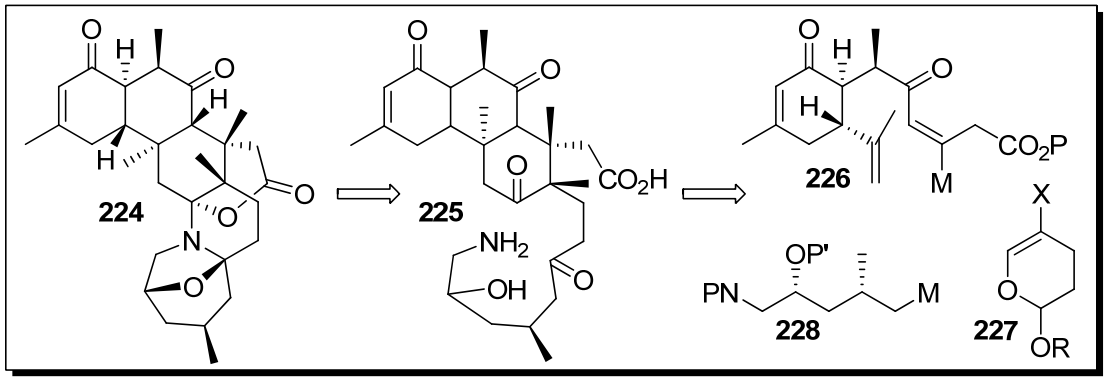
The Tanner group research has been focused on developing a Diels-Alder reaction to close rings B and C to provide a functionalized ABC ring system.[25] The group's first publication detailed a Diels-Alder reaction applied to a model system encompassing the ABC zoanthamine (**163**) ring system (Scheme 2.10). The synthetic work began with

inexpensive perillyl alcohol, which was converted to triene **222** in 13 steps with a good overall yield. The chiral Diels-Alder substrate underwent cyclization upon prolonged mixing in refluxing toluene to form a single adduct, **223**. Diketone **223** represents the fully functionalized zoanthamine (**163**) AB ring system. Inspired by the success of this highly efficient Diels-Alder reaction, Tanner worked toward more functionalized cycloaddition substrates.



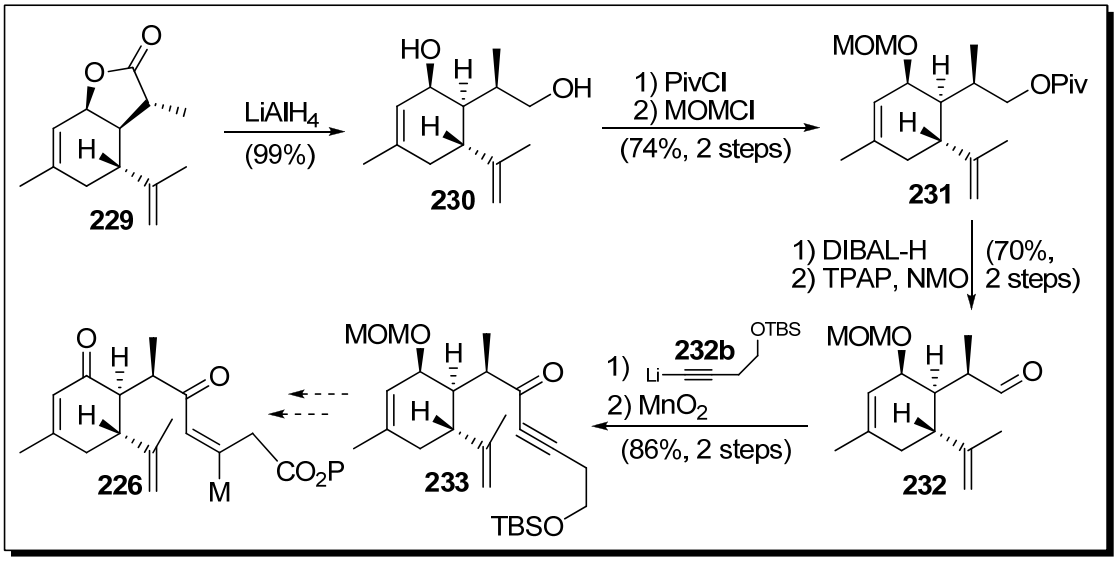
Scheme 2.10 Tanner's early Diels-Alder approach to the ABC ring system.

The second publication from Tanner outlined the general approach to zoanthamine alkaloid synthesis that has guided subsequent work (Scheme 2.11).[25b] Fragments **226**, **227**, and **228** were viewed as potential precursors to a functionalized ABC system (**225**) capable of cyclizing to zoanthamine (**150**). Coupling of fragments **227** and **226** would provide a triene for intramolecular cyclization. Fragment **228** would presumably be appended through organometallic means after coupling and cyclization of fragments **228** and **227**. This sequence in conjunction with the appropriate deprotection steps would theoretically provide aminal cyclization substrate **225**.



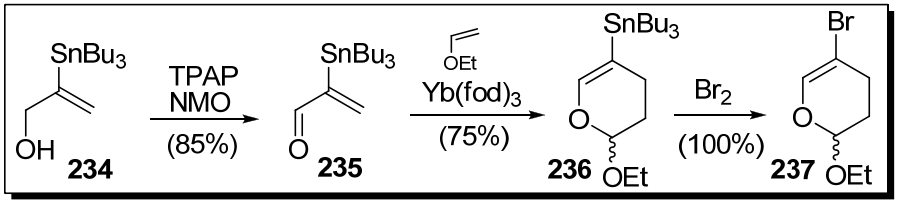
Scheme 2.11 Tanner's retrosynthetic approach to zoanthamine (**150**).

Fragment analogs were prepared with this approach in mind. The previously reported lactone (**229**), prepared from perillyl alcohol, was reduced to the diol (**230**) with $LiAlH_4$ and the alcohols differentiated by protection with pivaloyl chloride and MOMCl (Scheme 2.12). Deprotection of the pivaloate ester (**231**) and oxidation provided aldehyde **232**. Addition of Lithium acetylide **232b** and allylic oxidation with MnO_2 provided the fragment **226** precursor (**233**). Stannylcupration, MOM deprotection, and C17 oxidation remained to form fragment **226**.



Scheme 2.12 Tanner's synthesis of fragment **233**.

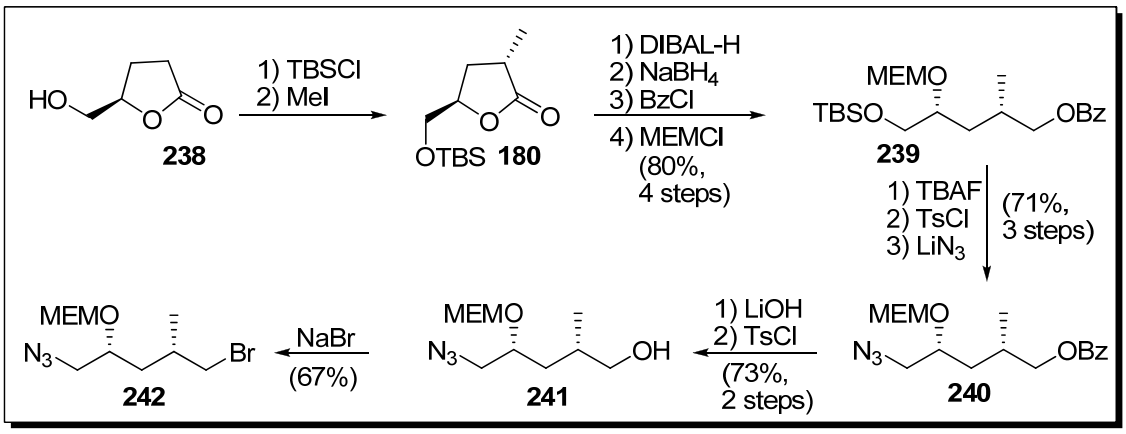
Fragment **237**, analogous to **227**, was produced expeditiously from the reported stannane (**234**) (Scheme 2.13). Oxidation followed by an ytterbium catalyzed hetero Diels-Alder provided the sensitive hydropyran (**236**), which was treated with bromine directly to access fragment **237**.



Scheme 2.13 Tanner's synthesis of fragment **237**.

Synthesis of the **228** analog (**242**) began from the commercially available hydroxymethyl-butyrolactone (**238**) and followed a reported procedure for TBS protection and alkylation to give **180** (Scheme 2.14).[26] Consecutive reductions opened

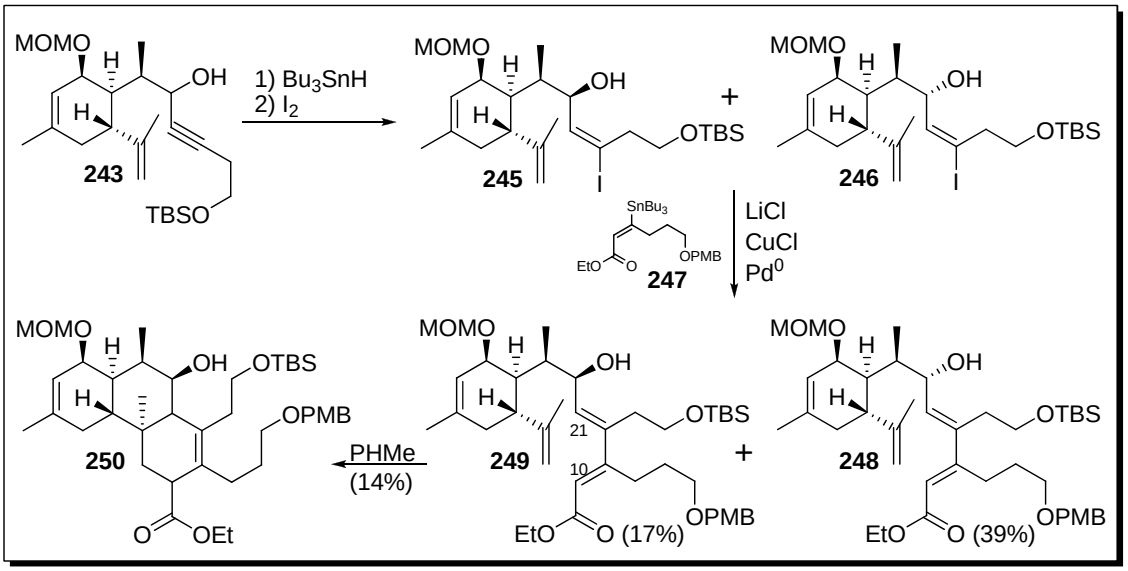
the ring and primary alcohol protection as the benzyloyl ester followed by secondary alcohol protection as the MEM ether provided **239**. Silyl ether cleavage with TBAF, conversion to the primary tosylate, and displacement with lithium azide gave azide **240**. Saponification and tosylation of the resultant alcohol gave **241**, which was displaced with sodium bromide to provide fragment **242**. While this particular publication did not address fragment coupling reactions, subsequent publications have detailed the attempts at assembling the fragments.



Scheme 2.14 Tanner's synthesis of fragment **242**.

In 2002, Tanner described the complete synthesis of fragment **245**, an analog of **226** (Fig. 2.15).[25c] A 2006 publication discusses coupling of fragments **245** and **237** as well as related cycloaddition reactions (Fig 2.15).[25d] Unfortunately, cycloaddition attempts with a fragment **237** variant (benzyl stabilized instead of ethyl) failed. It was speculated that the enone diene system was polarized in the wrong direction. Therefore the strategy was modified to use a linear diene system activated at C10 instead of C21. Vinyl iodides (**245** and **246**) were produced by hydrostannylation of alkyne **243**

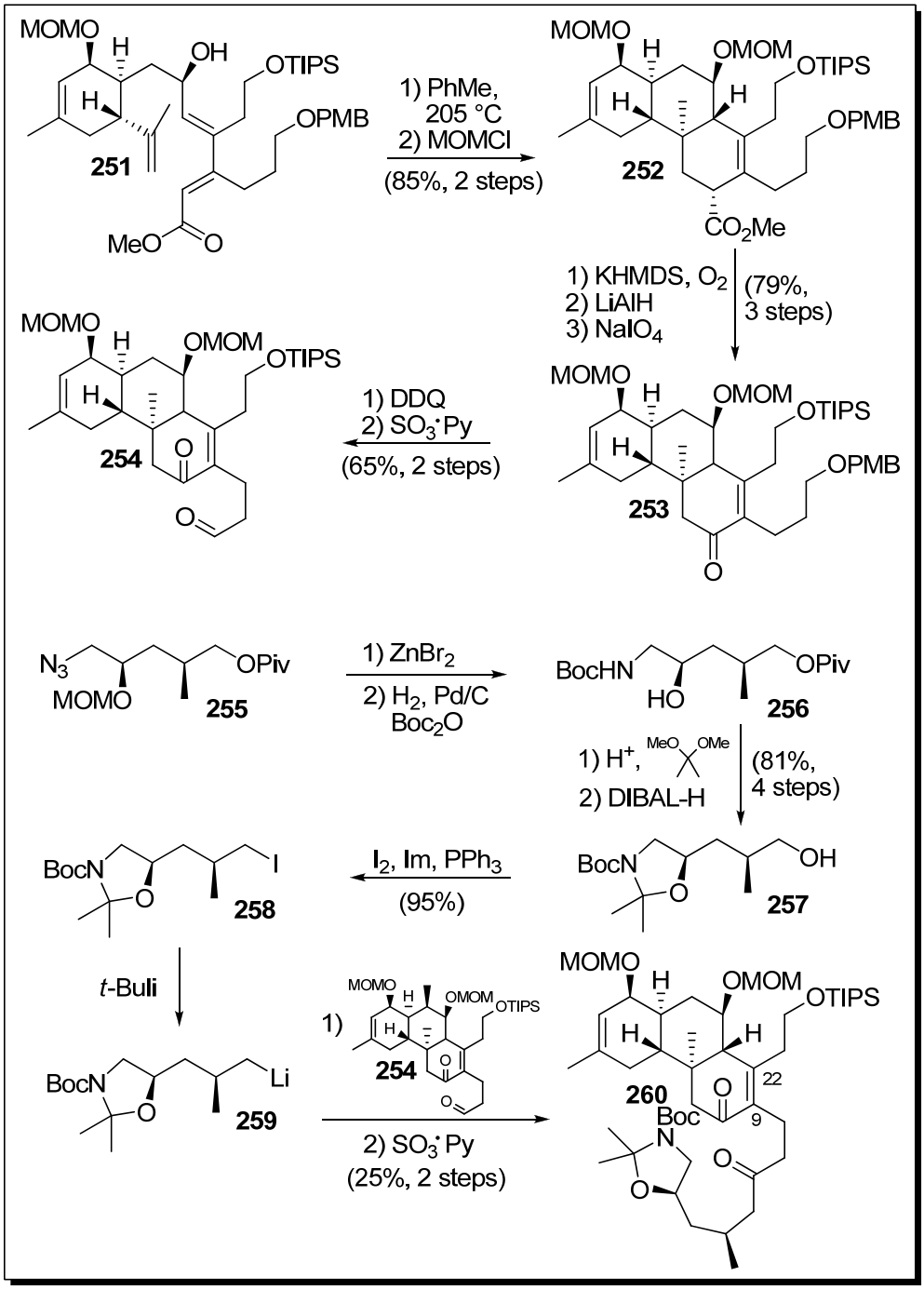
followed by treatment with iodine. The diastereomeric mixture (**245** and **246**) was coupled to stannane **247**. The resultant diastereomers were separated and isolated as **249** and **248** in 17% and 39% yields, respectively. When **248** was heated with toluene, an unexpected product resulting from elimination of the allylic MOM ether and cyclization of the C20 hydroxyl at the C17 cation was isolated in 43% yield without observation of the desired Diels-Alder reaction. The elimination-cyclization process predominated when **249** was heated in toluene as well, however the desired Diels-Alder adduct (**250**) was isolated in 14% yield. Tanner attributed the elimination to unfavorable conformational effects.



Scheme 2.15 Tanner's initial Diels-Alder reaction toward a functionalized C ring.

A highly advanced intermediate in the synthesis of norzoanthamine (**151**) was reported in Tanner's most recent publication (Scheme 2.16).[25e] Accordingly, modifications were made to the Diels-Alder substrate by removing the C19 methyl

group, changing the ethyl ester to a methyl ester, and replacement of the TBS group with a TIPS group.[25d] The IMDA reaction proved much more efficient with triene **251**, and the exo Diels-Alder adduct (**252**) was formed in 85% yield under thermal conditions. After protection of the C20 hydroxyl as a MOM ether, an oxidative decarbonylation involving α-hydroxylation, ester reduction and diol cleavage provided C10 ketone **253**. Deprotection of the PMB ether and oxidation gave aldehyde **254**.

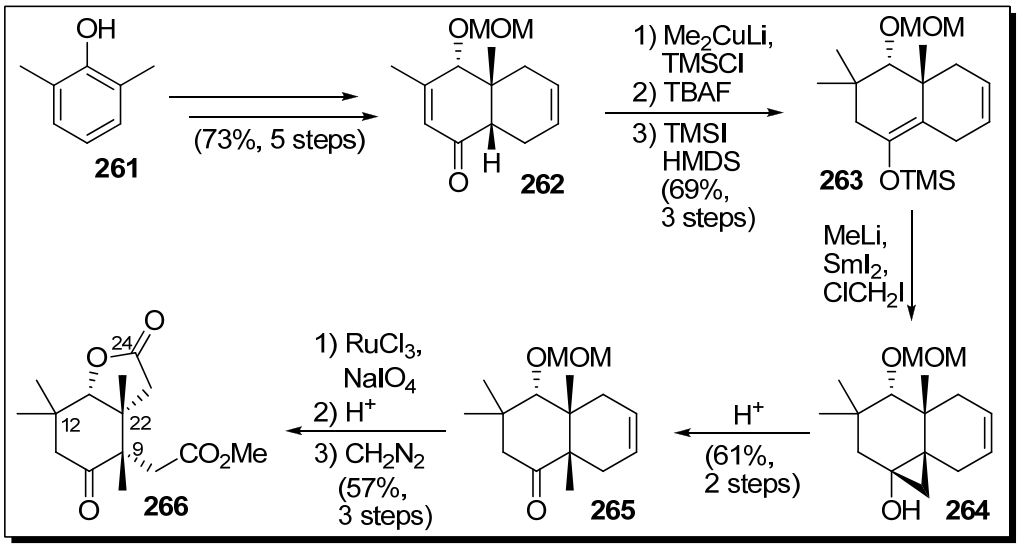


Scheme 2.16 Tanner's synthesis of norzoanthamine (**151**) intermediate **260**.

The coupling partner for aldehyde **254** was prepared from azide **255** by protecting group manipulation and iodination. After cleavage of the MOM ether with zinc bromide, azide **255** was reduced to the corresponding amine in the presence of Boc anhydride to provide alcohol **257**. The amine and hydroxyl groups were protected as the N,O ketal and the pivaloyl ester cleaved by reduction. The primary alcohol was converted to alkyl iodide **258** by treatment with imidazole, triphenylphosphine, and iodine. The alkyl lithiate (**259**) was formed by treatment of **258** with *t*-BuLi and was subsequently quenched with aldehyde **254**. Oxidation of the diastereomeric mixture gave ketone **260**, which represents a nearly fully functionalized norzoanthamine (**151**) precursor. In the event that an aminal cyclization as reported by Kobayashi (Schemes 2.4 and 2.5) was to be executed, methyl installation at the adjacent C9 and C22 positions in addition to oxidations C17, C20, and C24 would be necessary. It is not known whether the cyclization has been attempted, but based on the significant advancement toward total synthesis of the natural product, it is assumed that positive results would be available in the literature at this time.

Hirama and coworkers have published approaches to the C ring of zoanthamine, the ABC ring system of zoanthenol (**163**), as well as the common CDEFG ring system.[14, 27] Reported work with an early C ring model system disclosed an interesting method for developing the adjacent C9 and C22 methyl connections (Scheme 2.17).[27a] Oxidation of **261** to the corresponding quinone, [4+2] cycloaddition with 1,3 butadiene, stereo and regioselective reduction of the C13 enone, and protection of the resultant allylic alcohol as the MOM ether gave enone **262**. Conjugate methyl addition and thermodynamic

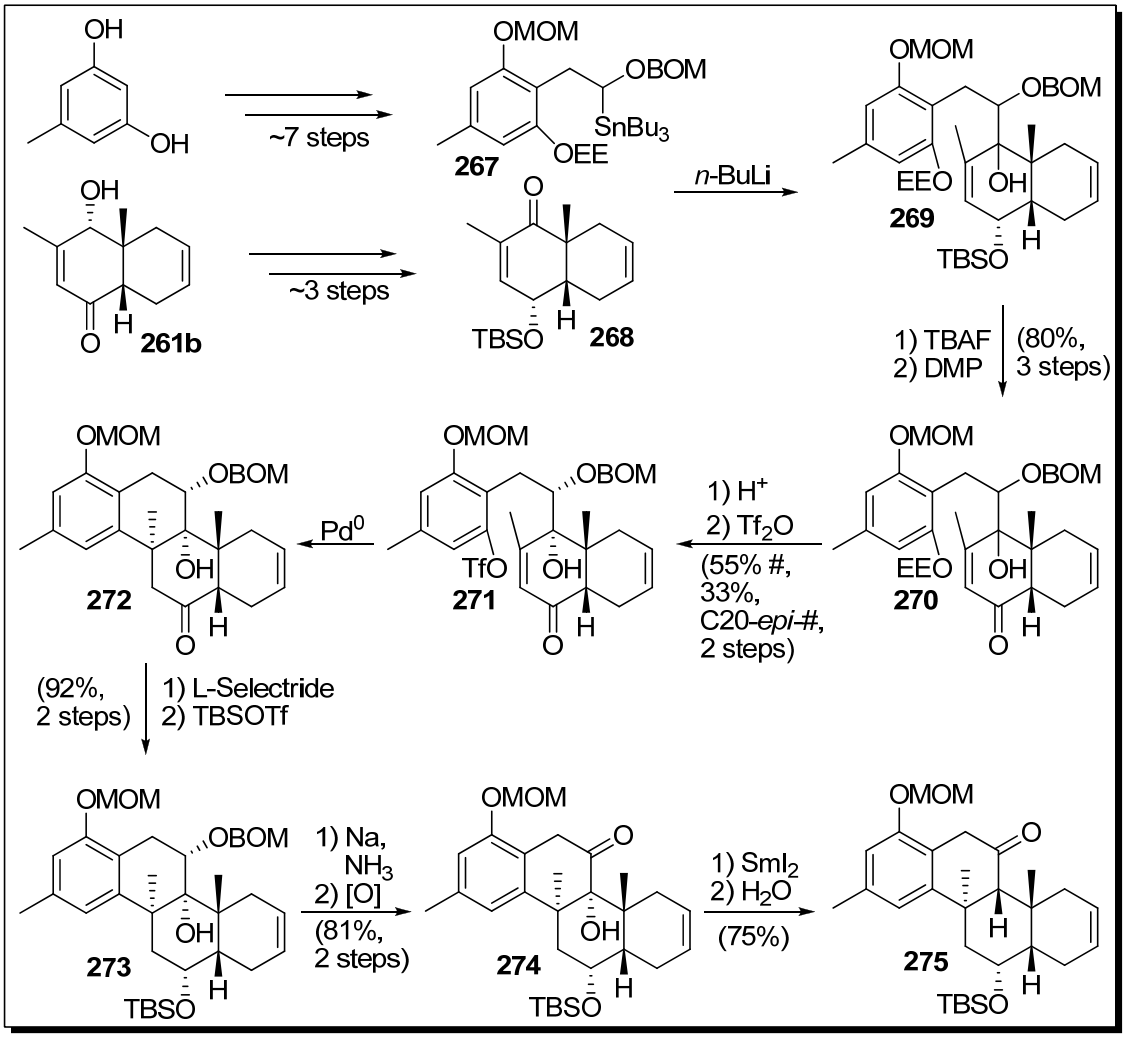
enolate trapping as the vinyl TMS ether efficiently provided **263**. Samarium mediated cyclopropanation gave tertiary alcohol **264**, while acid treatment opened the cyclopropane and returned the C10 ketone (**265**), demonstrating a unique and elegant method for C9 methyl installation. Oxidative cleavage of the cyclohexene and acid removal of the MOM ether allowed lactonization, and subsequent diazomethane treatment gave methyl ester **266**. The petite nature of this model betrayed its advanced nature. Quaternary centers C9, C12, and C22 were formed, a handle attached to C9 for southern fragment functionalization, and a C24 carboxyl group in the form of a butyrolactone were all constructed.



Scheme 2.17 Hirama's C ring model system.

Hirama and coworkers have also published approaches to the zoanthenol (**163**) ABC ring system.[27b-d,14] Optimization of initial work is presented in Scheme 2.18. Orcinol was protected and functionalized through ortho-lithiation at C18 to provide stannane

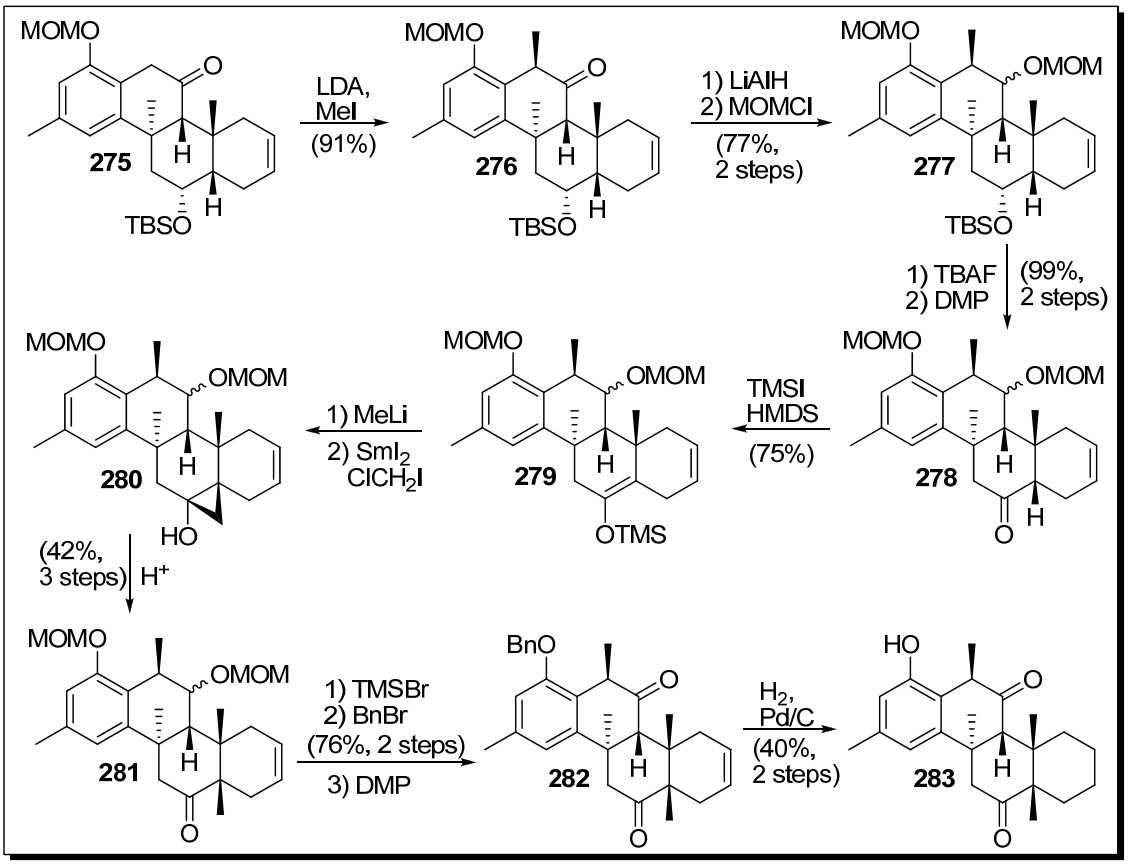
267. Decalin **261b**, a precursor to decalin **262** previously reported by Hirama, was converted to **268** through oxidation, selective reduction, and silyl ether formation. Stannane **267** was lithiated and treated with enone **268** to provide an inseparable diastereomeric mixture of alcohols (**269**). The silyl ether of this mixture was deprotected with TBAF and oxidized with Dess-Martin periodinane to enone **270**. The ethoxyethyl ether was cleaved and converted to the corresponding triflate (**271**). The epimers were separated at this stage to reveal a 44% yield of **271** from stannane **267**. A $Pd(dppb)Cl_2$ mediated reductive Heck coupling provided the zoanthenol (**163**) ABC ring scaffold. Enone reduction with L-Selectride followed by TBS protection gave silyl ether **273** in excellent yield. Then removal of the BOM group and oxidation gave ketone **274**, also in excellent yield. Samarium mediated deoxygenation provided **275**, represents an advanced zoanthenol (**163**) ABC model.



Scheme 2.18 Hirama's approach to the zoanthenol (**163**) ABC system.

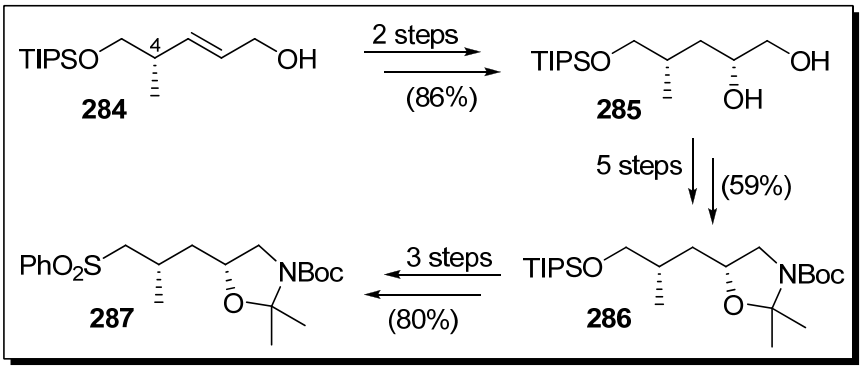
Additional work was performed to convert **273** to the fully functionalized zoanthenol (**163**) northern fragment (Scheme 2.19). Stereoselective C19 alkylation was achieved through LDA induced enolization and methyl iodide quenching. Reduction of the C20 ketone and protection as the MOM ether proceeded well, and **277** was obtained as a mixture of diastereomers. TBAF treatment and oxidation of the C10 alcohol proceeded in a highly efficient manner, giving ketone **278** in 99% combined yield. Ketone **278**

was enolized and then treated with TMSI to give the silyl enol ether **279**. Silyl ether **279** was de-silylated with methyl lithium and the resultant lithium enolate was subjected to samarium controlled cyclopropanation conditions to selectively provide cyclopropanol **280**. Cyclopropane cleavage was performed by treatment with toluenesulphonic acid, thereby installing the C9 quaternary methyl group. Ketone **281** represents the fully functionalized ABC Zoanthenol (**163**) system. Further modifications at C17, C20, and cyclohexene hydrogenation were performed as shown for SAR studies.[14]



Scheme 2.19 Hirama's fully functionalized zoanthenol (**163**) ABC system.

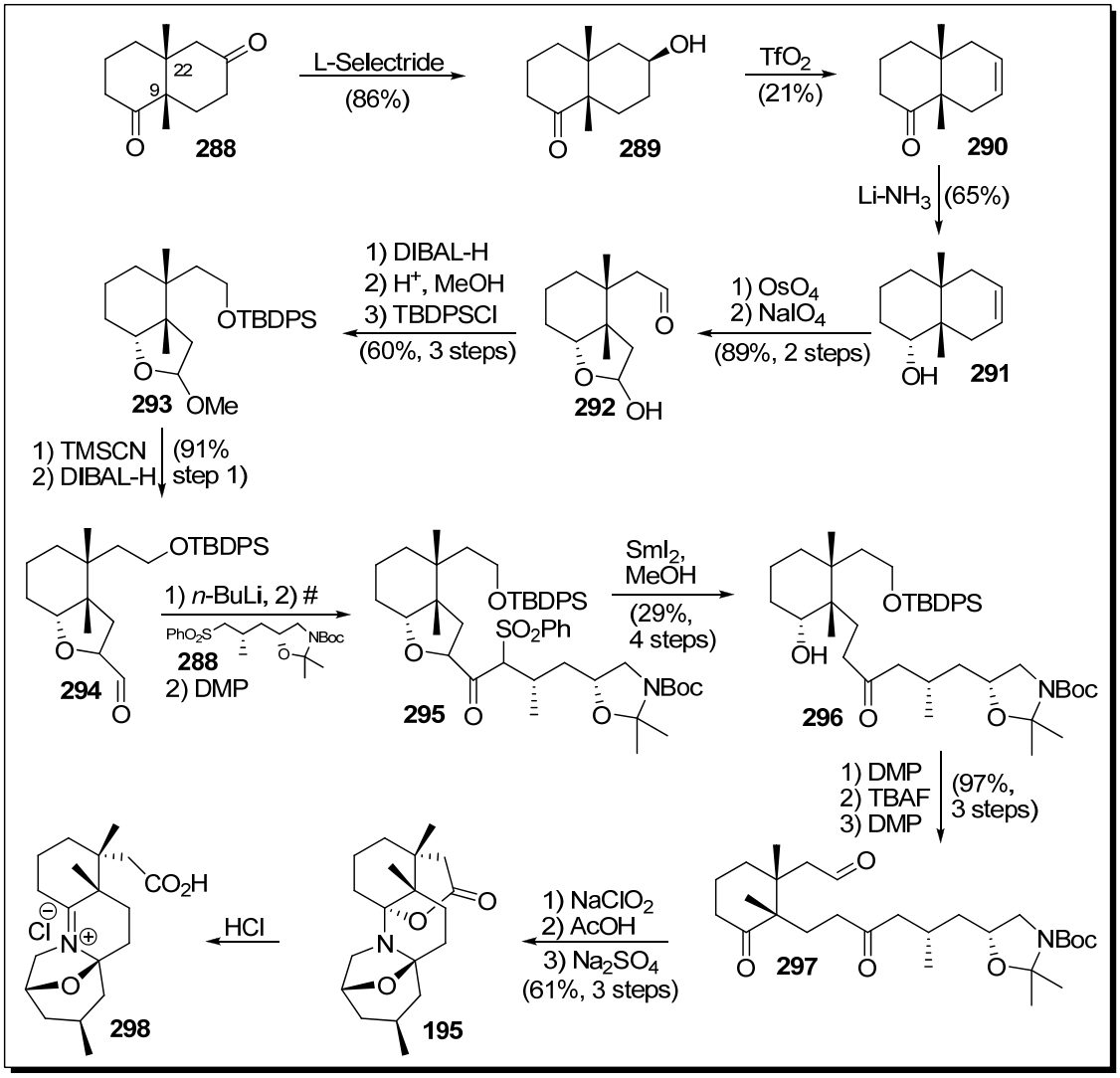
Contributions of the Hirama group extend to a functionalized southern fragment.[14] The sulfone, **287**, was synthesized through a route alternative to that previously reported by the Kobayashi group used to build the C1- C5 fragment (Scheme 2.20). Allyl alcohol **284** was synthesized from a chiral (C4 methyl) hydroxyl ester as previously reported.[27] Sharpless epoxidation and DIBAL-H treatment provided diol **285**. Diol **285** was converted to the N,O ketal through a series of manipulations similar to that used by Tanner. Selective tosylation and conversion to the primary azide followed by reduction to the amine, Boc protection, and acidic treatment with 2,2-dimethoxypropane gave N,O ketal **286** in good overall yield. TBAF deprotection of silyl ether **286**, conversion to the phenyl thiol, and oxidation to the sulfone was performed to access **287**.



Scheme 2.20 Hirama's sulfone (**287**) synthesis.

With the sulfone (**287**) available (its constituents comprising the F and G rings), the necessary coupling partner (**294**) (comprising the C,D, and E rings) was constructed (Scheme 2.21). The known chiral Wieland-Miescher ketone (**288**), possessing cis C22 and C9 quaternary methyl groups, was reduced by hydride attack at the more accessible

ketone and converted to cyclohexene **290** by elimination of the C24 triflate. Reduction of the remaining ketone, dihydroxylation and oxidative cleavage with $NaIO_4$ provided lactol **292**. Aldehyde reduction, mixed methyl ketal formation, and primary alcohol protection with TBDPS gave ketal **293**. Ketal **293** was treated with TMSCN to convert the ketal to a cyanohydrin, and the nitrile group was reduced with DIBAL-H to give C6 aldehyde **294**. Aldehyde **294** was treated with the lithiated sulfone (**288**) then oxidized to provide ketone **295**. Samarium iodide was utilized for desulfonation and hydrofuran cleavage to give alcohol **296**. This alcohol was oxidized to the ketone prior to deprotection of the primary silyl ether and successive oxidations to access the carboxylic acid. The acid was heated with acetic acid then neutralized to give the fully functionalized southern fragment (**195**) previously reported by Kobayashi, which was then converted to the HCl salt for SAR studies.[14]

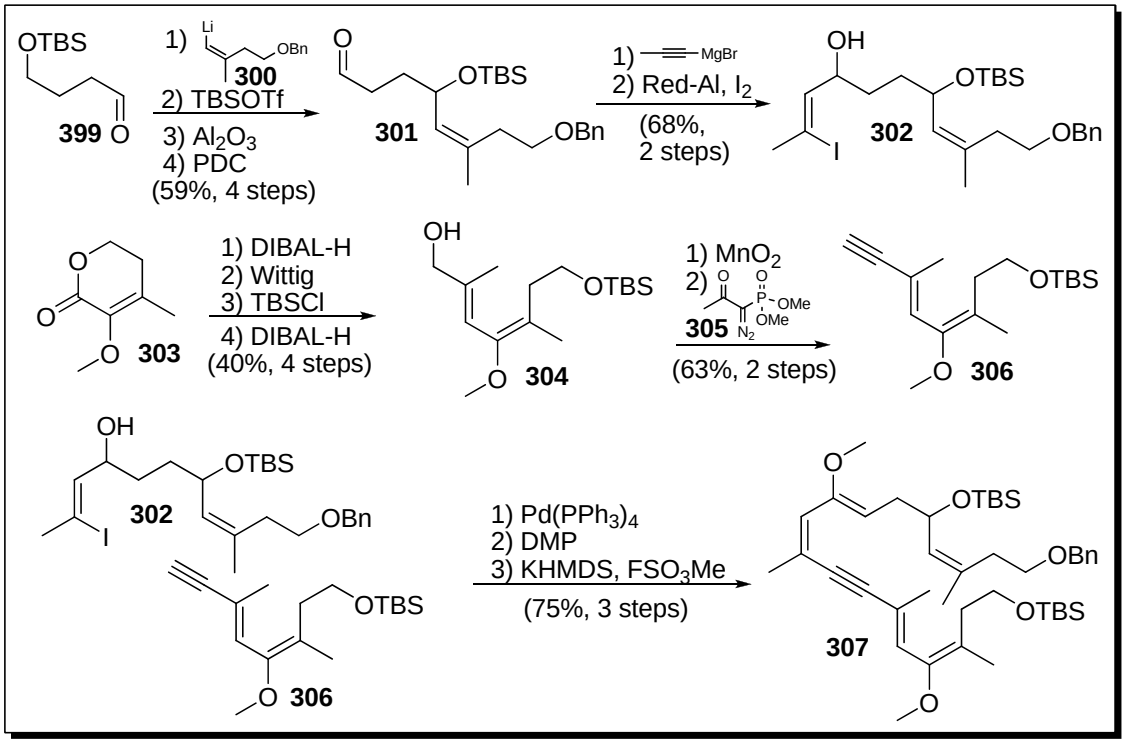


Scheme 2.21 Hirama's zoanthamine southern fragment synthesis.

The Hirama group has made significant strides in the zoanthamine alkaloid synthetic effort, demonstrating an approach to the functionalized zoanthenol (**163**) ABC ring system amenable to addition of a southern fragment as well as achieving a formal synthesis of the southern fragment. Of particular interest to us is the manner in which

the C9 methyl group has been installed. The use of a labile cyclopropanol moiety is a clever alternative to standard enolate alkylations.

The Uemura group has published a substrate designed to test their biosynthetic proposal (Scheme 2.22).[28] Polyene **307** synthesis was envisaged to arise from the coupling of fragments **302** and **306**. To this end, aldehyde **399** was treated with vinyl lithiate **300**, di-protected, selectively deprotected, and oxidized to provide aldehyde **301**. Aldehyde **301** was treated with propynyl magnesium bromide, then hydroalumination and iodination gave vinyl iodide **302**.

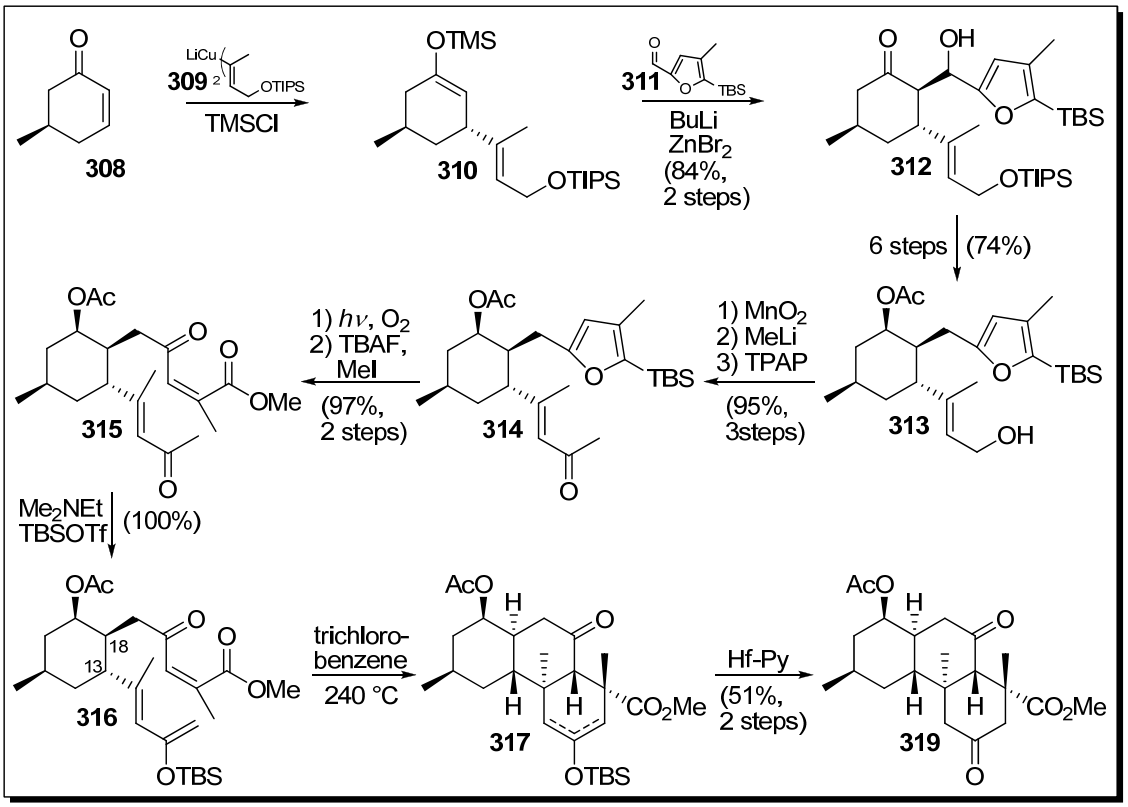


Scheme 2.22 Uemura's biosynthetic cyclization substrate.

Alkyne fragment **306** synthesis began from the reported enone (**303**). Reduction to the lactol, ethylpropionate-ylide homologation, TBS protection, and reduction of the ethyl ester gave alcohol **304**. Oxidation of the allylic alcohol to the corresponding aldehyde and treatment with Bestmanns (**305**) reagent gave alkyne **306**. Polyene fragment **307** was constructed by coupling vinyl iodide **302** and alkyne **306** through a Sonogashira coupling. It is not known if conditions for selective alkyne to alkene reduction were explored in order to provide the proposed intermediate scaffold, or if studies have been performed on polyene alkyne **307** directly.

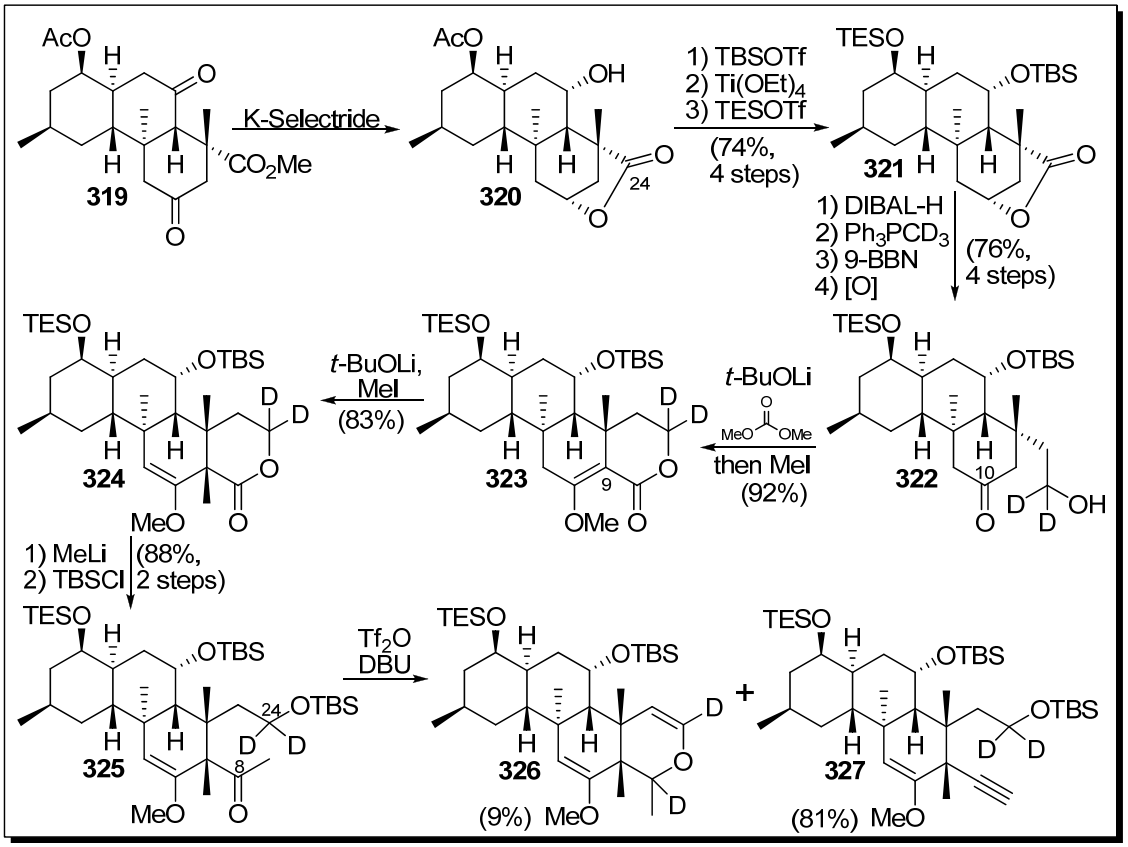
The only total syntheses of Zoanthamine alkaloids to date have been reported by Miyashita and coworkers in 2004 and 2007.[29] Early synthetic studies resulted in a reported Diels-Alder, which allowed construction of the norzoanthamine (**151**) ABC ring skeleton.[30] After demonstrating the effectiveness of the key [4+2] reaction in a model system, the cycloaddition substrate was further elaborated as outlined in Scheme 2.23. Work began from the reported enone (**308**). Conjugate addition of cuprate **309**, prepared by transmetallation of the reported stannane, to **308** and quenching with TMSCl provided silyl enol ether **310**. BuLi and $ZnBr_2$ treatment of **310** provided the zinc enolate, which was mixed with furaldehyde **311** to give a mixture of alcohols (**312**). Thiocarbonyldiimidazole-mediate dehydration, hydrosilylation, and resultant silyl enol ether cleavage preceded stereoselective C17 reduction, subsequent protection, and TIPS ether cleavage to give primary alcohol **313**. Oxidation, methyl lithium treatment, and TPAP oxidation provided methyl ketone **314**. Rose Bengal-photosensitized oxidation of furan **314** with molecular oxygen gave the corresponding

silyl ester, which was immediately converted to the methyl ester by treatment with TBAF and methyl iodide to give the Z, ketoester (**315**). The C10 enolate of ketoester **315** was trapped as the TBS enol ether to provide the Diels-Alder substrate (**316**). Heating in trichlorobenzene at 240 °C for 1.5 hours gave a mixture of endo/exo adducts in 98% yield. Removal of the TBS group with HF·Py, provided desired exo adduct **319** in 51% over 2 steps. The C13-C18 trans substitution apparently controlled facial selectivity while the regiochemistry was most likely controlled by factors related to diene/dienophile proximity.



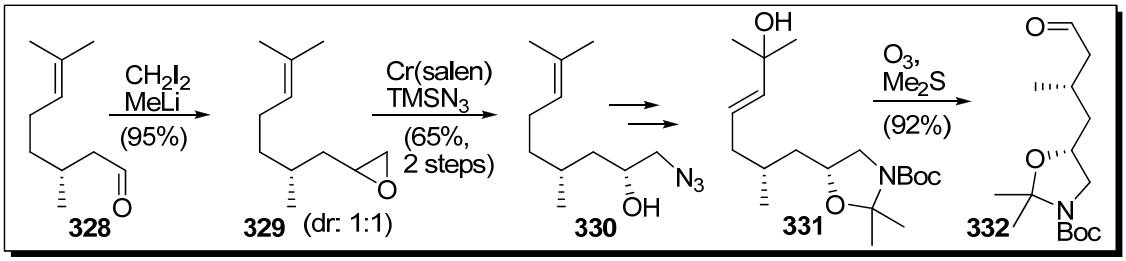
Scheme 2.23 Route to Miyashita's, BC ring forming, Diels-Alder reaction.

With a scalable route to diketone **319** realized, the Miyashita group focused on substituting the C ring in preparation for further functionalization (Scheme 2.24). Stereoselective reduction of both ketones (C10 and C20) followed by lactonization at C24 gave lactone **320**. Protecting group manipulation provided lactone **321**, which was reduced to the corresponding lactol and treated with deuterated methyl phosphonium ylide. The resultant olefin was subjected to hydroboration and oxidized at C10 chemoselectively with ammonium molybdate and hydrogen peroxide to give ketone **322**. Methylation at C9 began by trapping of the C9 thermodynamic enolate as the vinyl methoxy ether after dimethyl carbonate incorporation at C9 and transesterification to give lactone **323**. Continued base treatment and quenching with methyl iodide installed the C9 methyl stereoselectively, and lactone **324** was subsequently isolated in excellent yield. Conversion of the lactone to a methyl ketone and protection of the resultant primary alcohol provided ketone **325**. The enolized ketone was trapped as the triflic enol ether and eliminated to give the desired alkyne (**327**). A significant side product (the undeuterated analog of vinyl ether **326**) had been observed when this reaction was performed with the undeuterated equivalent of ketone **325** as a result of presumed 1,5-hydride shift (C24 to C8) prior to triflate displacement by the C8 alcohol. Use of deuterium apparently exploited a kinetic isotope effect by reducing side product formation from 30% to 9%.



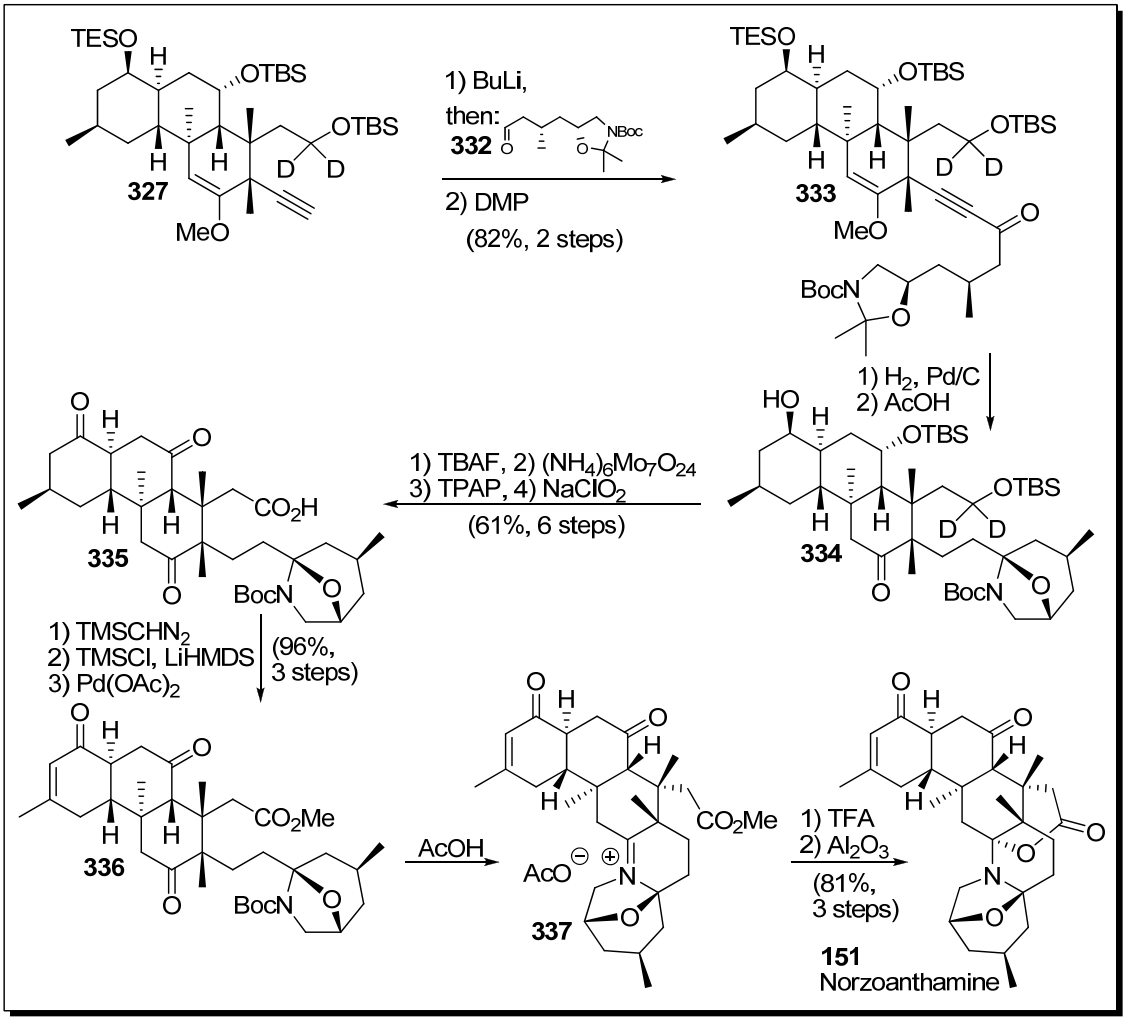
Scheme 2.24 Miyashita's C ring functionalization and C9 methyl installation.

The C1-C6 fragment was prepared from (*R*)-citronellal with the initial modification being epoxidation (Scheme 2.25).[29b] Epoxide opening by treatment with a chiral chromium salen complex and TMS azide provided azide **330**. The epoxidation was reported to proceed without selectivity and the resolution was reported to proceed in greater than 50%, without explanation. Perhaps the diastereomeric mixture (**329**) was purified to a single enantiomer or a sample enriched in the desired enantiomer. Undisclosed reduction of the azide, hydration/olefin migration, and protection steps were performed in an undisclosed manner to provide tertiary alcohol **331**. Reductive ozonolysis gave C1-C6 fragment **332** in high yield.



Scheme 2.25 Miyashita's synthesis of C1-C6 fragment (**332**).

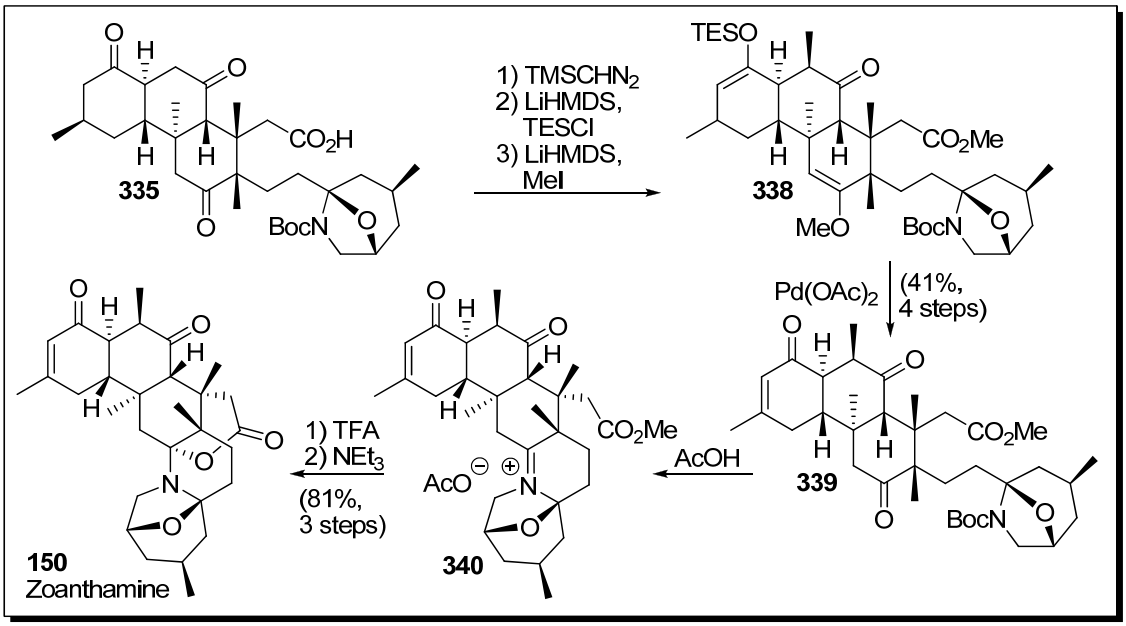
The C1-C6 fragment was coupled to the northern fragment by deprotonation of alkyne **327** and exposure to C1-C6 aldehyde **332** (Scheme 2.26). Subsequent oxidation gave unsaturated ketone **333**. Complete reduction of the alkyne through hydrogenation preceded cleavage of the vinyl methyl ether and cyclization of rings F and G prompted by heating in acetic acid, which provided aminal **334**. Global desilylation then secondary alcohol oxidation with ammonium molybdate and hydrogen peroxide followed by sequential oxidation of the primary alcohol to the carboxylic acid yielded **335**. Esterification with TMSdiazomethane was performed prior to introduction of the C15-C16 double bond by the Ito-Saegusa method. Chemoselective enolization of C17 was achieved by treating **335** with LiHMDS at low temperature and the enolate was then trapped as the silyl enol ether with TMSCl. Reaction with palladium acetate provided enone **336** in extraordinary yield from carboxylic acid **335**. Heating in acetic acid reportedly freed the amino group, which spontaneously condensed at C10 to form the acetic acid salt **337**. Additional heating with trifluoroacetic acid hydrolyzed the methyl ester, allowing cyclization at C10, and neutralization allowed isolation of norzoanthamine (**151**) in impressive yield from enone **336**.



Scheme 2.26 Miyashita's total synthesis of norzoanthamine (**151**).

Three years after the total synthesis of norzoanthamine (**151**), Miyashita reported the total synthesis of zoanthamine (**150**) (Scheme 2.27).[30] Norzoanthamine (**151**) synthetic intermediate **335** was esterified with TMSdiazomethane and converted to the C16-C17 TES silyl enol ether. Alkylation at C19 was achieved by treatment with LiHMDS and quenching with methyl iodide. The silyl enol ether (**338**) was converted to enone **339** as reported in the norzoanthamine (**151**) synthesis. Consecutive acid treatments as

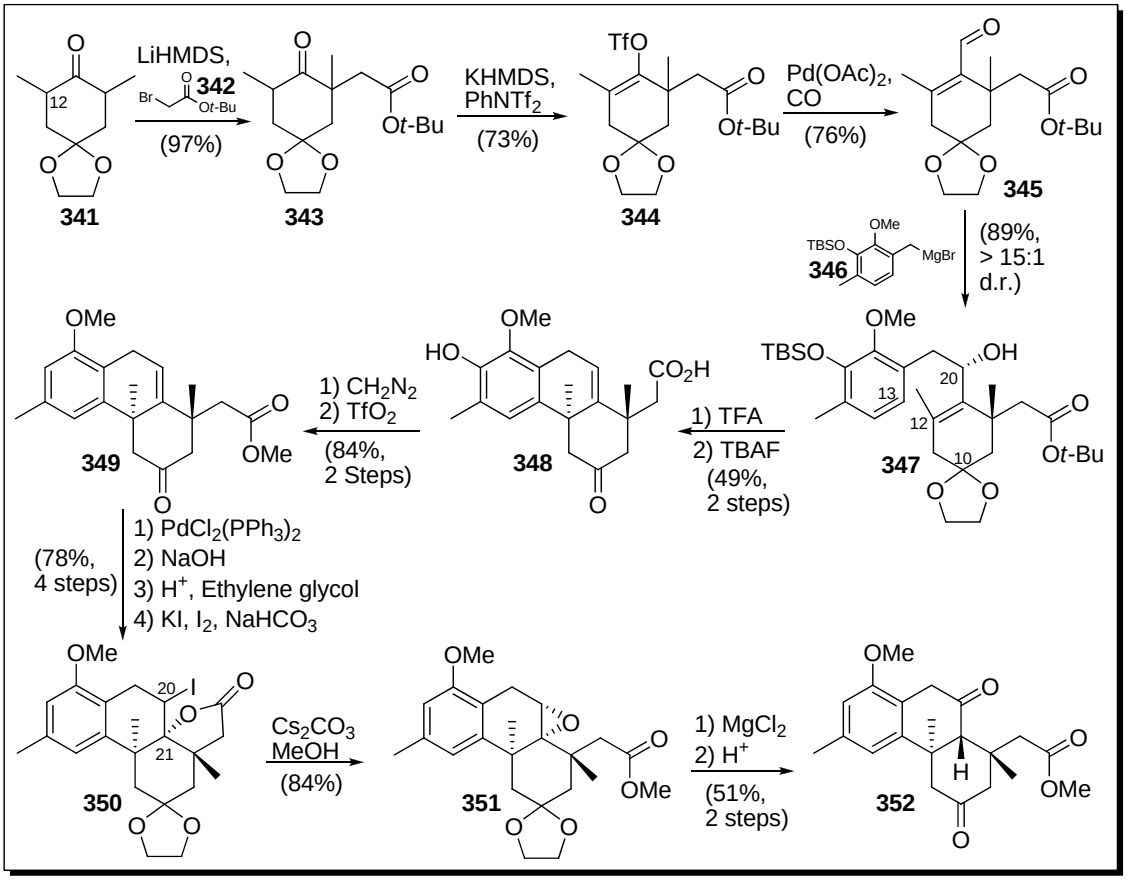
performed in the norzoanthamine (**151**) synthesis and neutralization gave zoanthamine (**150**).



Scheme 2.27 Miyashita's total synthesis of zoanthamine (**150**).

The synthetic effort(s) reported by Miyashita are highlighted by the ingenious dienophile formation through furan oxidation and the subsequent Diels-Alder reaction. Two quaternary centers were formed with good selectivity demonstrated for the exo transition state. The 41-step synthesis of norzoanthamine (**151**) corroborated the previously proposed absolute stereochemistry and the zoanthamine (**150**) synthesis has now done the same. The total syntheses of these natural products stand as impressive achievements and examples of what modern synthetic chemistry can accomplish. The fact that twenty years passed from the isolation of zoanthamine (**150**) to the total synthesis of norzoanthamine (**151**) may serve as a testament to this statement.

The most recently published entry into zoanthamine synthetic studies has come from the Stoltz lab (Scheme 2.28).[31] The Stoltz group's strategy toward the zoanthenol (**163**) ABC ring system was centered around a Friedel-Crafts cyclization to form the C12-C13 bond. Fragment synthesis began from the known dimethyl ketone (**341**). Enolate formation and alkylation provided **343**, which was subjected to a second base treatment and trapped as the vinyl triflate (**344**). Reductive carbonylation gave aldehyde **345**, which was treated with benzyl Grignard **346** to provide allylic alcohol **347** with good stereoselectivity. The Friedel-Crafts cyclization in TFA was expected to proceed by initially cleaving the protecting groups and instigating an olefin migration to form a C10-C12 enone, then cyclizing through a conjugate addition at the C10 enone system, leaving the necessary hydroxyl functionality at C20. Under the described conditions, in addition to dioxolane deprotection and hydrolysis of the *t*-butyl ester, elimination of the C20 alcohol occurred. The elimination would have likely created an allylic cation ideally positioned for 6-endo cyclization instead of the proposed 6-exo cyclization. The properties of TFA seem ideally suited to promoting this particular reaction as weaker and stronger acids failed to promote cyclization, as did dilution of TFA with methylene chloride, benzene, or acetic acid.



Scheme 2.28 Stoltz's zoanthenol (**163**) ABC ring system synthesis.

The TBS group of the cycloadduct was cleaved with TBAF to give **348**. Tricycle **348** was further functionalized by converting the acid to the corresponding methyl ester and deoxygenation of C16 was achieved by palladium insertion and formic acid treatment. After deoxygenation, the methyl ester was saponified to the acid and the C10 ketone protected again as a dioxolane. Typical epoxide formation procedures failed to oxidize the C20-C21 olefin, presumably due to steric hindrance created in part by the adjacent methyl groups. An alternative method was devised for olefin oxidation involving iodolactonization and iodine displacement. Iodolactonization provided

lactone **350** in excellent yield. Lactone methanolysis formed the C24 methyl ester and freed the C21 oxygen for iodide displacement. Epoxide opening and C20 hydride shift mediated by magnesium chloride formed the C20 ketone. Subsequent acid treatment cleaved the dioxolane to give the zoanthenol (**163**) ABC ring moiety, **352**. Only alkylation of C19 remained to form the fully functionalized northern fragment, but this reaction may be slated for a later stage similar to the alkylation demonstrated by Miyashita and coworkers.

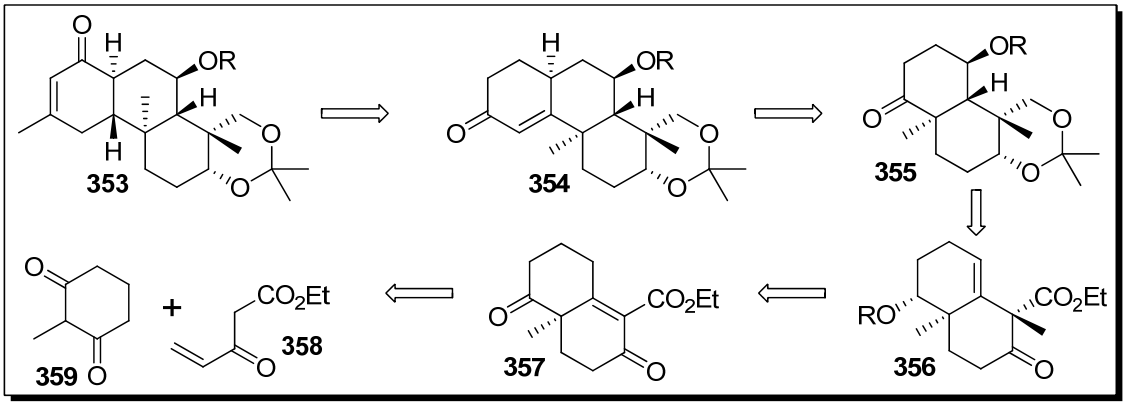
To further validate this approach, the Stoltz group has developed a procedure for producing ketoester **343** enantioselectively through their asymmetric decarboxylative allylation chemistry making an asymmetric zoanthenol (**163**) synthesis within reach. To summarize, the Stoltz approach is focused on a Friedel-Crafts cyclization reaction to create the quaternary C12 center and has resulted in an advanced tricyclic intermediate (**348**, or its ketal precursor) potentially capable of further functionalization.

Research performed by our group has resulted in the synthesis of the functionalized ABC ring system and helped guide an alternative and truly novel approach to zoanthamine alkaloid synthesis. The work resulting in the ABC ring system (1st generation strategy) will be presented prior to discussing the initial results of the 2nd generation strategy.

Section 2.4 1st Generation Strategy Toward Zoanthamine Alkaloids

Early studies in the lab focused on development of a model system for a trans-annular Diels-Alder as well as a scaffold to study the BC ring system forming Diels-

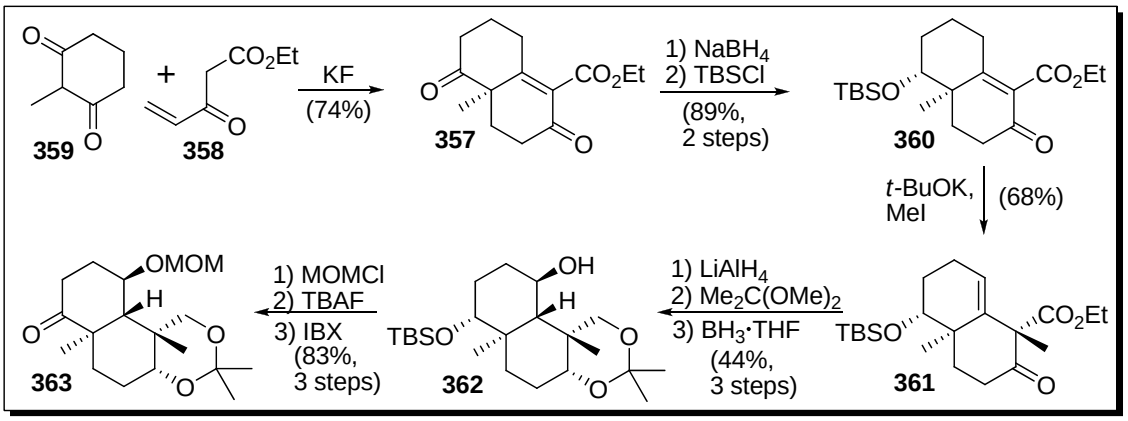
Alder reaction. When these reactions proved problematic, a plan was devised that involved appending the A ring to a BC decalin system arrived at through Robinson annelation chemistry and appropriately functionalized (Scheme 2.29).[32] Enone **353** represents a highly functionalized ABC ring model, requiring only C10 oxidation and C9 functionalization to become a viable synthetic intermediate. We felt the C17 ketone moiety of **353** could be placed in position through methylation and an oxidative rearrangement of enone **354**. Robinson annelation chemistry was expected to provide enone **354** by reacting methyl vinyl ketone with bicyclic ketone **355**, which was expected to arise from a correctly oxygenated cyclohexene such as ester **356**. Ester **356** would presumably be accessed from the reported enone (**357**), a Robinson annelation product of dione **359** and enone **358**.



Scheme 2.29 1st generation ABC ring retrosynthetic plan.

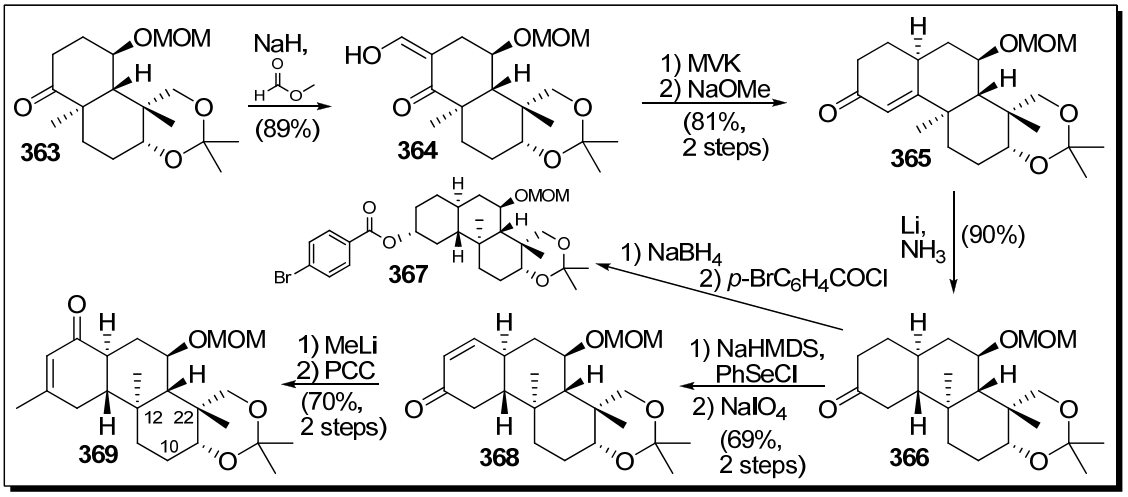
The synthesis of tricycle **353** began by synthesizing ketoester **358** through a LDA mediated reaction of ethyl acetate and acrolein (Scheme 2.30). Robinson annelation of dione **359** and ester **358** proceeded in good yield, 74%, as previously reported.[33]

Stereoselective C13 reduction was achieved with sodium borohydride and protection of the secondary alcohol as the TBS ether proceeded smoothly with ammonium nitrate and TBSCl to provide enone **360**. Stereoselective alkylation through an extended enolate gave ester **361** in 68% yield. Reduction of the ester and ketone functionalities preceded protection of the resultant diol as the corresponding acetonide in 80% yield over the two steps. Hydroboration of the C20-C21 olefin produced a mixture of separable diastereomers (3:2 in favor of **362**) in 90% overall yield and stereochemical assignments associated with major product **362** were confirmed by single crystal x-ray analysis of **362**. Attempts to improve the selectivity of this reaction revealed the importance of C13 substitution (R-OTBS) as a directing group. When a corresponding ketal was subjected to hydroboration, only the cis decalin was isolated. Protection of the C20 hydroxyl as a MOM ether, deprotection of the C13 silyl ether, and oxidation of C13 to ketone **363** was achieved in high yield over three steps (88%).



Scheme 2.30 Synthesis of decalin intermediate (**363**).

With a route to the BC ring analog discovered, attention was turned to appending the A ring (Scheme 2.31). Direct reaction to tricycle **365** through Robinson annelation of ketone **363** and methyl vinyl ketone resulted in a complex mixture of products. Due to the undesired reactivity of **363**, it was converted to enol **364** by enolization and quenching with methyl formate.[34] Treatment with triethylamine promoted 1-4 addition to methyl vinyl ketone and subsequent sodium methoxide treatment instigated the cyclization/elimination step with concomitant loss of the formyl group to provide enone **365**. Lithium/ammonia reduction of enone **365** provided ketone **366** in excellent yield. The desired stereochemical outcome of was confirmed by derivitizing **366** to the corresponding bromo-benzoate (**367**) and obtaining x-ray crystal analysis.



Scheme 2.31 Synthesis of functionalized ABC ring system analog (**369**).

Unsaturation (C16-C17) was formed through conversion of **366** to the phenylselenide then oxidation to the sulfoxide and requisite elimination to provide

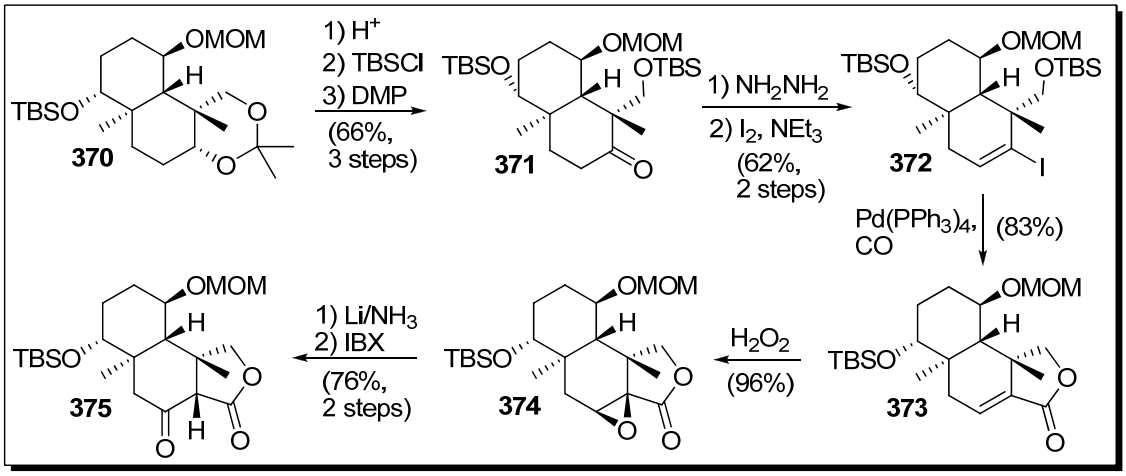
enone **368**. Methyl lithium treatment of enone **369** gave the necessary tertiary alcohol and exposure to PCC prompted the desired rearrangement to enone **369**.

Enone **369** contains fully functionalized A and B norzoanthamine (**151**) rings, including the all-carbon quaternary C12 and C22 centers, as well as a nearly fully functionalized C ring. C12 and C22 of the C ring contained the necessary functionalization in correct stereochemistry, but C10 needed oxygenation and C9 required deoxygenation and alkyl connections. These issues were resolved indirectly through studies on a BC ring motif.

As mentioned, three challenges remained to complete the ABC ring system; oxygenation of C10, installation of a quaternary methyl group at C9, and further alkyl functionalization of C9. Having developed a method for A ring formation, the remaining questions were addressed with a scaffold more amenable to expedient troubleshooting. The BC ring system analog **370** was utilized in studies performed primarily by Fatima Rivas to answer the vital questions.[67]

The first approach is outlined in Scheme 2.32 and involved a strategy similar to that used by Miyashita to stereoselectively install the C9 quaternary methyl group on a similarly functionalized substrate. Investigation began by deprotecting the acetonide functionality of **370**, selective primary alcohol protection with TBSCl, and oxidation of the C9 alcohol gave ketone **371**. Ketone **371** was converted to C9 vinyl iodide **372** by formation of a hydrazone and subsequent treatment with triethylamine and iodine.[35] Palladium mediated carbonylation provided lactone **373** without the need for discrete

deprotection of the C24 silyl ether. Hydrogen peroxide induced epoxidation of the olefin was achieved in excellent yield, after which reductive epoxide opening with lithium/ammonium gave the corresponding C10 alcohol. IBX oxidation supplied the alkylation substrate (**375**).

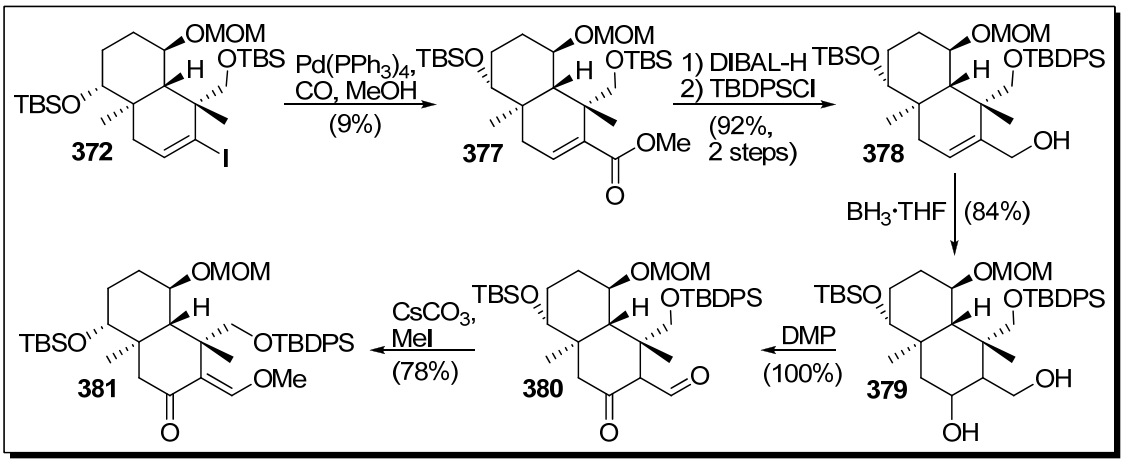


Scheme 2.32 Attempted methyl installation through a 1,3 dicarbonyl alkylation.

Methylation attempts, either simultaneous to the epoxide opening or through the C9 enolate were unsuccessful. Only O-methylation products were observed from the enolate alkylation attempts. Although the C9 methyl group was not installed, this method demonstrated a route to oxygenate C10 and provided alkyl substitution at C9 in the form of the butyrolactone, which could be used as a handle for attachment of a southern fragment.

A clear explanation for the failed alkylation did not present itself. It was speculated that a larger lactone ring or a non-cyclic 1,3-dicarbonyl functionality could create important conformational freedom necessary for adequate electrophile approach. Two

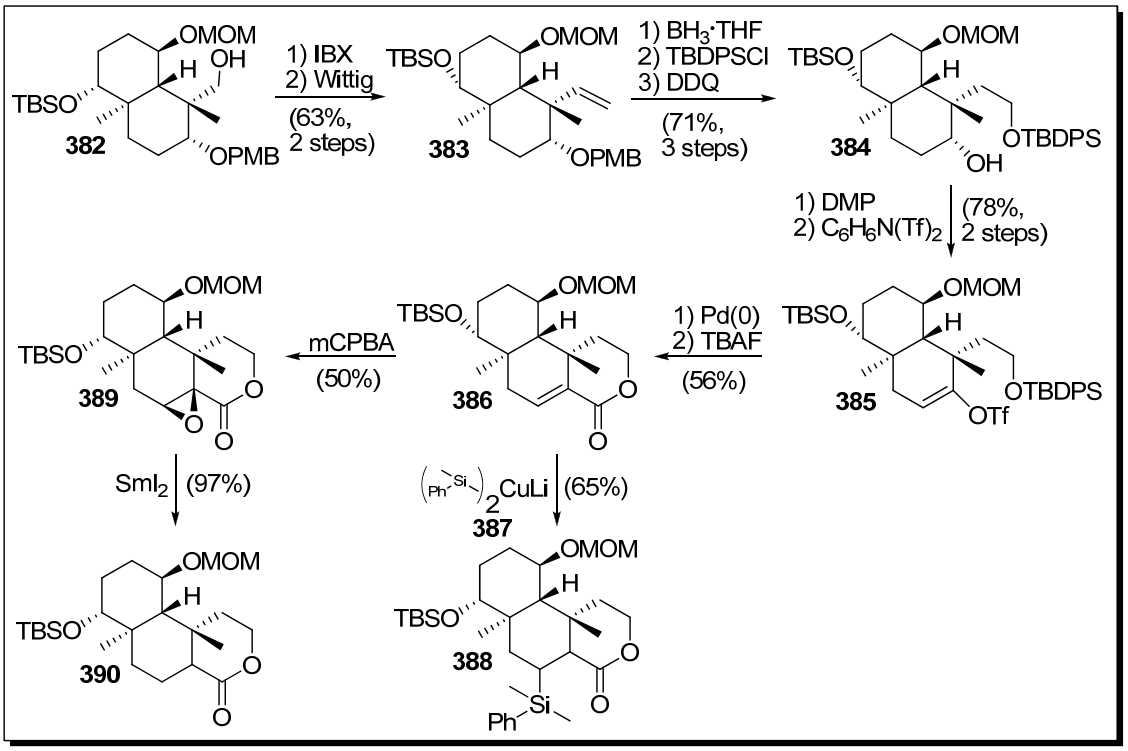
analogous substrates were prepared for study. An aldehyde 1,3-dicarbonyl BC system (**380**) was prepared as described in Scheme 2.33. Intermediate, vinyl iodide **372**, was carbonylated in low yield to methyl ester **377**. Ester reduction resulted in cleavage of the primary silyl ether, which was protected in preference to the allylic alcohol with the more robust TBDPSCl to provide alcohol **378**. Hydroboration gave a mixture of diastereomers. One-pot oxidation of both hydroxyl groups provided ketoaldehyde **380**. Unfortunately only the vinyl methoxy moiety (**381**) was isolated under a variety of alkylation conditions.



Scheme 2.33 Synthesis of ketaldehyde alkylation substrate **380**.

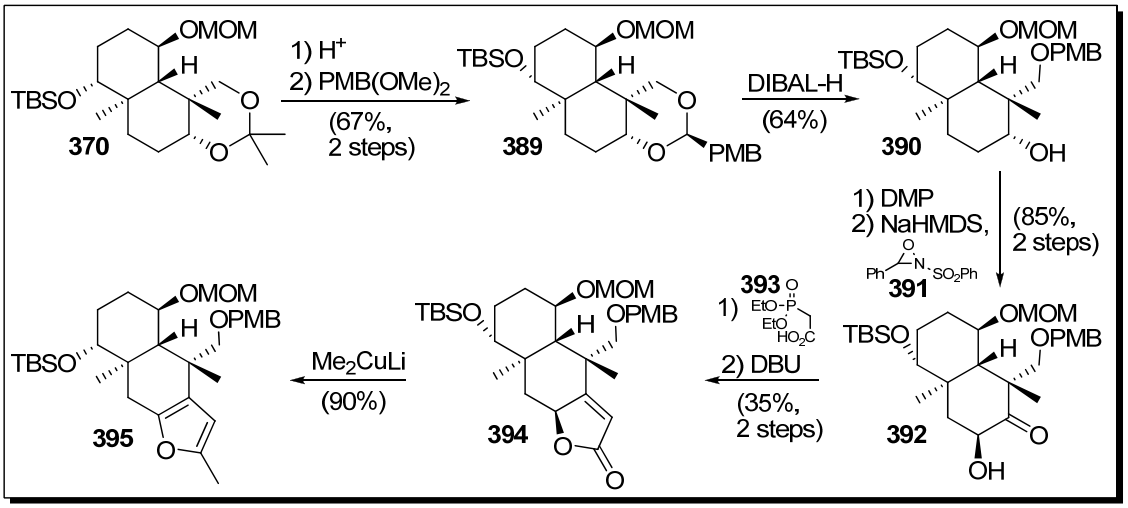
Attention was turned to synthesizing a keto-valerolactone tricyclic system for C9 alkylation (Scheme 2.34). Primary alcohol **382** (a product of PMB acetal cleavage described in Scheme 2.5) was oxidized and homologated to alkene **383**. Hydroboration, subsequent TBDPS cleavage, and PMB ether deprotection gave secondary alcohol **384**. Oxidation and enolate trapping as the vinyl triflate provided **385**. Palladium mediated

carbonylation and silyl ether deprotection provided enone **386**. Simultaneous silylcuprate addition and methylation resulted only in cuprate 1-4 addition, giving only adduct **388**. Attempts to manipulate the C10 silicon bond to the corresponding ketone were unsuccessful. Consequently, enone **386** was oxidized to epoxide **389** with mCPBA, but reductive epoxide opening with Li/NH_3 gave an unacceptable yield of the desired hydroxylactone (~5%). Samarium iodide treatment provided only the fully reduced tricycle **390**. Further study of this particular route was prevented by limited material due to the lengthy route and less than ideal yields.



Scheme 2.34 Attempt at 1,3-keto-valerolactone synthesis for alkylation studies.

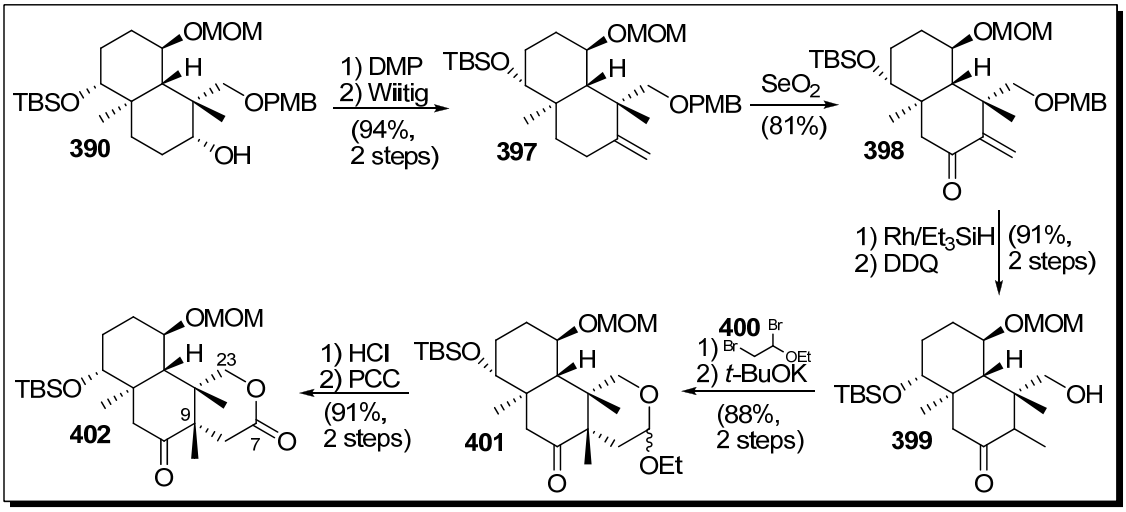
An approach involving nucleophilic attack of a methyl group at C9 was being pursued concurrently (Scheme 2.35). Conversion of acetonide **370** to the corresponding PMB acetal was performed prior to acetal cleavage. In this manner the free secondary alcohol (**390**) was isolated in 43% over three steps. C9 oxidation and C10 hydroxylation with the Davis oxaziridine[36] provided alcohol **392** in excellent yields. Esterification with phosphonate **393** and intramolecular cyclization under Masamune-Roush conditions provided unsaturated butyrolactone **394** in modest yield.[37] Butyrolactone **394** was treated with methyl cuprate in attempt to effect a 1-4 addition at C9. Unfortunately, 1-2 addition followed by aromatization, predominated and **395** was isolated as the major product.



Scheme 2.35 C9 nucleophilic methylation attempt of lactone **394**.

With important lessons learned, a strategy involving intramolecular cyclization at C9 with an attached methyl group was devised (Scheme 2.36). Oxidation and single carbon Wittig homologation of secondary alcohol **390** provided alkene **397**. Allylic

oxidation with selenium dioxide was achieved in good yield to give enone **398**. Wilkinson reduction and PMB ether deprotection gave ketone **399** in excellent yields.[38] Treatment of **399** with *N*,*N*-dimethylaniline and 1,2-dibromo-1-ethoxy-ethane (**400**) gave the corresponding α-bromoacetal, which was reacted with *t*-BuOK to provide the cyclized product (**401**). Conversion to the hemiketal and oxidation gave lactone **402**, representing the fully functionalized C ring.



Scheme 2.36 Completion of the C9 methylated BC fragment.

In the manner described above, the crucial C9 quaternary methyl group was installed in an innovative manner, providing the fully functionalized C ring. The valerolactone moiety represents functionalizable substitution at C24 and provides a handle at C7 (potential aldehyde functionality) for elaboration of the southern hemisphere.

In summary, we have developed chemistry allowing stereoselective construction of the ABC ring system of the zoanthamine alkaloids. Formation of the BC ring system

skeleton was accomplished through Robinson annelation chemistry, as well as the subsequent appendage of the A ring. After much experimentation, installation of the C9 methyl group was achieved through an intramolecular alkylation/cyclization process. The chemistry developed appears to be a viable approach to the complete, fully functionalized, ABC ring system with a good likelihood of achieving the total synthesis of norzoanthamine (**151**) given enough time and effort. However, the route involving this chemistry would most likely involve a late-stage intermediate identical to, or strongly resembling, one already reported by Miyashita in the total synthesis of norzoanthamine (**151**). Additionally, our route would require a similar number of manipulations to that utilized by Miyashita. We were unable to justify continuation of this route based on these observations and changed focus to a fresh approach for the synthesis of zoanthamine alkaloids.

Section 2.5 2nd Generation Strategy; an Amino-diene Approach

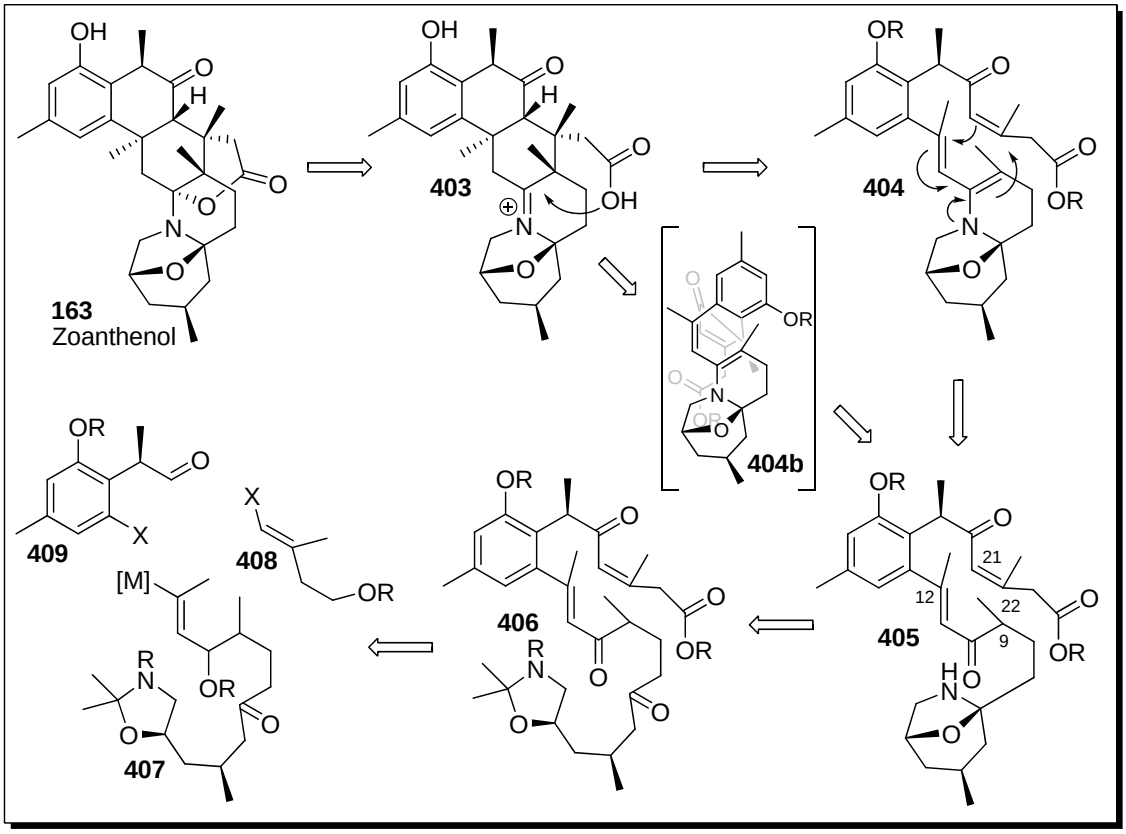
Section 2.5.1 Expanded Biosynthetic Proposal and Key Disconnections

The length and scale of the Miyashita norzoanthamine total synthesis demonstrates the shortcomings of a linear, step-wise, approach to synthesis of complex natural products such as the zoanthamine alkaloids. A more convergent and efficient synthetic route would be necessary for complete biological studies, including thorough SAR studies. Moreover, a shorter and more efficient route increases the likelihood of a natural product becoming a drug. With these concepts in mind and in consideration of the shortcomings associated with linear synthetic approaches, we devised a risky but

potentially rewarding approach to the zoanthamine alkaloids (Scheme 2.37). The approach centers on a cyclization reaction of a fully functionalized linear precursor to form the B and C rings simultaneously. We imagined the final cyclization (formation of the D ring lactone) would could occur from an iminium ion such as **403**, as demonstrated previously by the Kobayashi, Hirama, and Miyashita groups.[19,14,29] The key step of this proposal is formation of imminium **403** or its enamine equivalent from a linear precursor such as **406**. The [4+2] cyclization would form 3 quaternary centers and close 2 rings in one step, making it a very appealing tactic. However, we recognized a Diels-Alder pathway would not provide the desired stereochemical outcome, unless a high-energy hindered transition state could be achieved (**404b**). Triene **404b** indicates the necessary diene stereochemistry for the desired stereochemical reaction outcome. The extended conjugation between the aromatic A ring and the diene system would favor a rigid, planar arrangement for carbons C18-C9. However, steric effects, due to C9 and C12 substitutions would likely prevent the desired confirmation. Additionally, conformational analysis by traditional plastic model systems suggested the cis olefin arrangement at C12 of **404b** would place the dienophile distant from the diene system, while the trans conformation indicated by **404** located the diene and dienophile proximal to each other. The diene-dienophile distance was also shorter in the exo transition state without the need for destroying C9-C18 planarity than in the corresponding endo transition state, as indicated by models.

We did see the potential for an alternative cyclization pathway though. It is plausible that the enamine (C9) (**404**) could act as a Michael donor through nucleophilic

attack at C22 of the enone system, thereby inducing formation of a C21 enolate and a conjugated 1,4 imminium system (C10-C12). If this intermediate could be achieved, it was suspected that the enolate (C21) would likely cyclize at the highly activated C12 position to contract the 10-membered intermediate ring system to a more favorable 6,6 system such as **403**.



Scheme 2.37 2nd generation retrosynthetic analysis of zoanthenol (**163**).

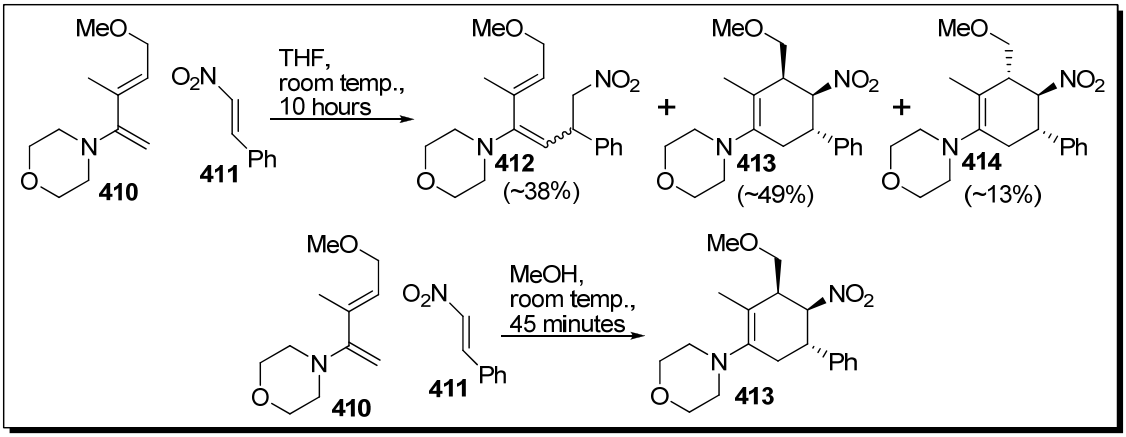
The 2-amino-1,3-butadiene cyclization substrate (**404**) could be formed through condensation of the C1 amino and the C10 ketone. Previous synthetic work suggests an aminal system such as **405**, would likely add to C10 under acidic conditions to form a

C10 imminium ion with concomitant loss of water.[14,19,29] We felt formation of the imminium ion in this manner, followed by neutralization, could form the dieneamine system (**404**). It was also thought that the process of imminium formation, neutralization to the dienamine tautomer, and cyclization may have even been feasible as a one-pot reaction.

Precedent also exists for formation of an N-carbamate aminal analog of **405** by acid treatment of a linear N,O-ketal such as **406**.[14,19,29] We felt N,O-ketal **406** could be synthesized in a convergent manner from three fragments; aryl halide aldehyde **409**, vinyl organometalic fragment **407**, and vinyl halide **408**. It was foreseeable that vinyl halide **408** could be lithiated, and added to aldehyde **409** to construct the C13-C24 northernmost fragment. Palladium mediated cross coupling of the resultant aryl halide (or aryl triflate) with stannane **407** was expected to provide an intermediate resembling **406**.

This plan was recognized as very ambitious from the onset of the research. However, strong literature precedent involving formation of the EFG ring system through our proposed aminal chemistry buoyed our confidence. However, the question as to whether the reactive dieneamine could be formed remained, as previous studies formed the imminium aminal with an internal nucleophile capable of trapping the reactive imminium in situ. At the onset we were most concerned as to whether we could obtain cyclization of the dienamine and whether it would proceed through a step-wise mechanism expected from consecutive conjugate additions or a concerted mechanism assumed of Diels-Alder reactions.

Fortunately, examples of 2-amino-1,3 butadienes as cyclization substrates were easily found in the literature. Examples of single Michael addition reactions from C1 of 2-amino-1,3-butadienes forming linear products as well as cyclization reactions have been reported by several different research groups.[39] Barluenga and coworkers made a particularly interesting finding when dienamine **410** was reacted with nitrostyrene (**411**) (Scheme 2.38).[40] A mixture of products was obtained when the reaction was performed with THF as a solvent. Single Michael addition adduct **412** was isolated in roughly 38% yield along with cyclized products **413** (49% yield) and **414** (13%). Barluenga argued that the cyclized products (**413** and **414**) are likely the result of sequential conjugate additions rather than Diels-Alder adducts. The strongest evidence being that the single Michael addition adduct (**412**) was isolated and is arguably an intermediate in the formation of the cyclized compounds. However, it was not stated whether or not further heating of **412** resulted in formation of **413** and/or **414**. Additional evidence supporting the step-wise mechanism was found when reaction of nitrostyrene and dieneamine **410** in methanol resulted in a single product, **412**. A polar solvent, such as methanol, can presumably better stabilize polarized intermediate(s) in a sequential conjugate addition pathway. The rate of this cyclization was also significantly increased with methanol as the solvent.



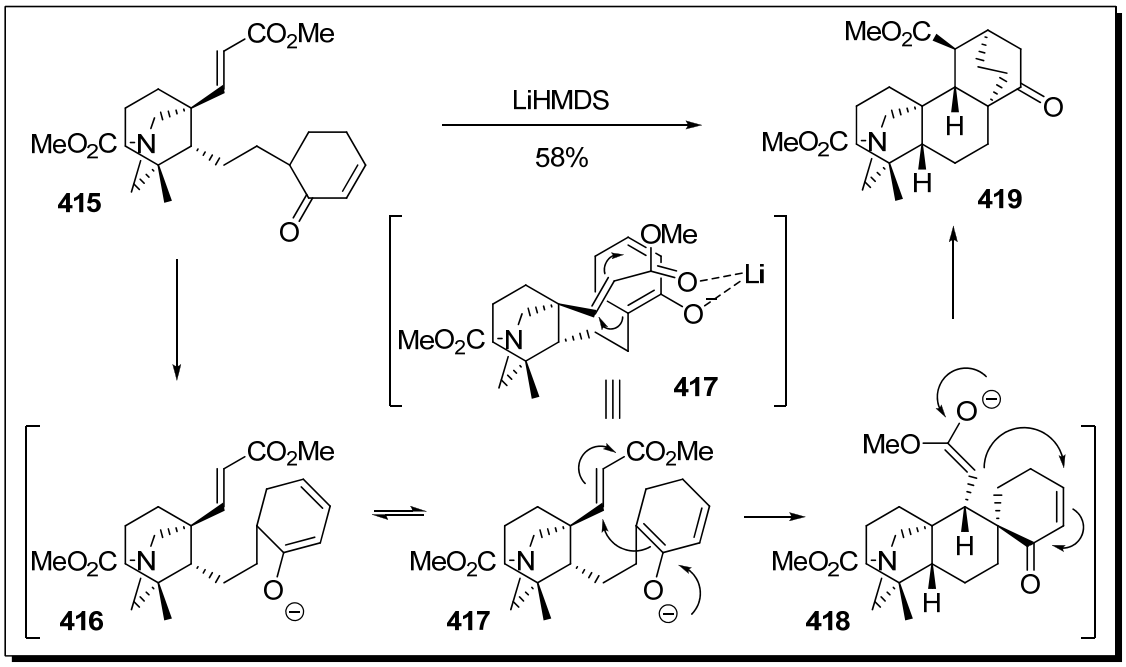
Scheme 2.38 Enamine reactions with nitrostyrene by Barluenga's group.

Enantioselective dieneamine cyclizations related to our proposal have also been reported.[41] To the best of our knowledge, the amine portion of the dienamine has served as the chiral controller in all cases. This observation may lend support to our hope that the chiral aminal portion could provide asymmetric induction and create enantioselectivity in a [4+2] reaction.

The growing field of organocatalysis has taken advantage of this methodology by using amines (chiral or otherwise) to form reactive intermediates in the form of imminium ions or enamines. Numerous examples of aldol, Mannich, Michael, and Diels-Alder reactions using this reactive, tautomeric, intermediate moiety have been reported.[42] In their sum these findings set an important precedent, seemingly supporting our proposed cyclization. Additionally, reports of asymmetric reactions were exciting, as we intended to use a chiral aminal (southern fragment) to effect an asymmetric cyclization. Furthermore, an observation pertaining to the existing literature was that

nearly all cyclizations, enantioselective or otherwise, involved an activated dienophile (or Michael acceptor/donor) such as nitrostyrene.

A search of the literature also revealed examples of cyclization reactions involving dienolates as diene equivalents. An excellent example of this type of reaction is the key step of the atisine total synthesis published by Ihara and coworkers (Scheme 2.39).[43] It is not clear whether this reaction follows a concerted or step-wise pathway. Nonetheless, this reaction represents a [4+2] cyclization relevant to our proposal as it suggests our proposed cycloadduct may be accessed in a step-wise manner through enolate chemistry. The Ihara example therefore offered us an alternative cyclization reaction to apply to our dienone substrate.

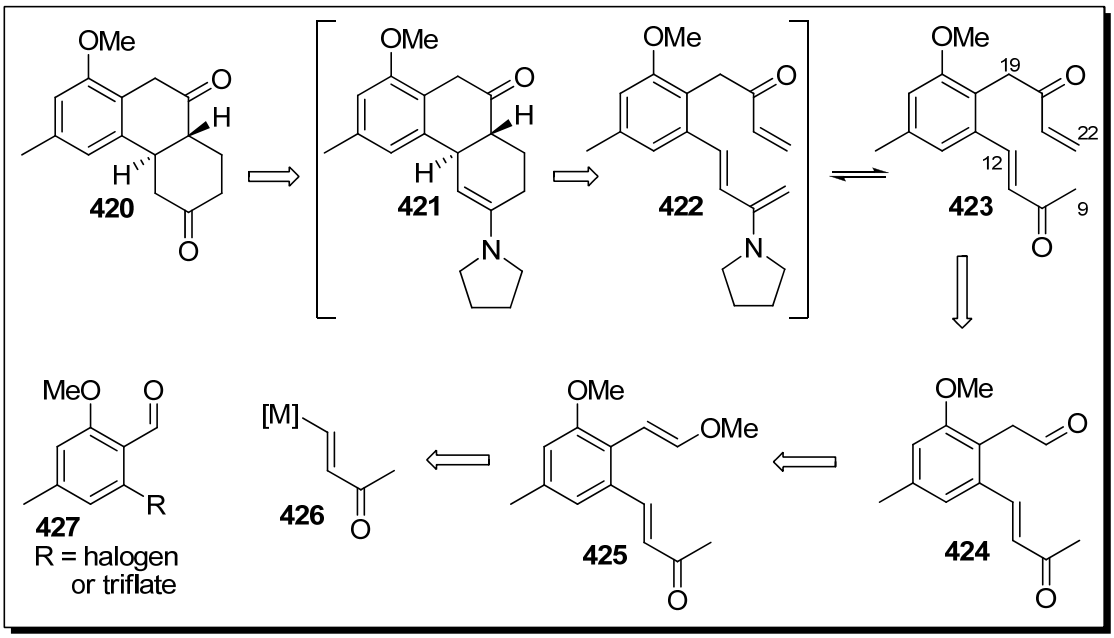


Scheme 2.39 Dienolate cyclization reaction demonstrated by Ihara's group.

While we felt sufficient literature precedent existed to justify our proposal, we decided to explore the key cyclization reaction with model systems prior to attempting the reaction with a valuable, advanced zoanthamine intermediate. Several model systems were designed with this in mind and will be discussed.

Section 2.5.2 Attempted In-situ Intermolecular Amino-diene Formation and Intramolecular [4+2], an Unexpected Michael-Aldol Cascade

We sought to test our proposed dienamine cyclization initially in a simple model sstem to prove the viability. To this end, dienone **420** was targeted as a cyclization substrate (Scheme 2.40).



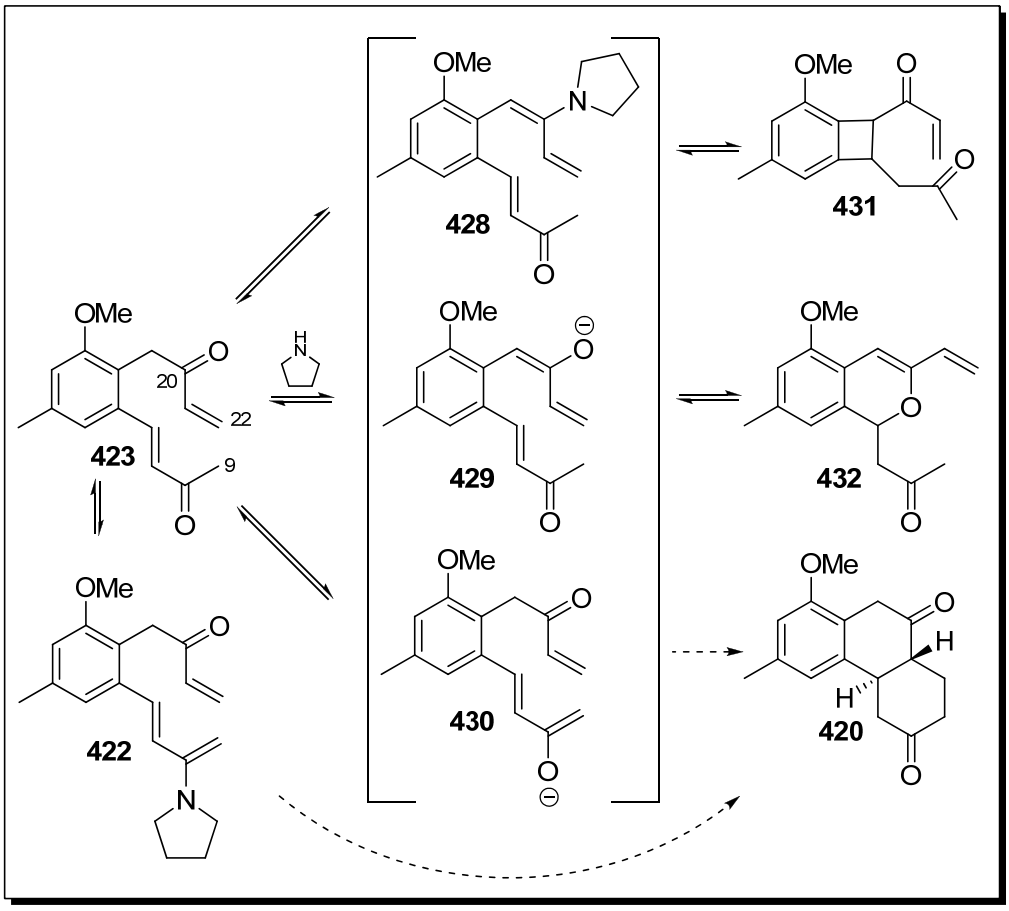
Scheme 2.40 In-situ intramolecular amino-diene formation and cyclization plan.

Condensation of a secondary amine, such as pyrrolidine, at C10 of **423** would produce 2-amino-1,3-diene **422**, hopefully instigating a cyclization reaction. Exposure to mild acid was expected to provide the cyclized product as the C10 tricyclic ketone (**420**).

A convergent synthetic plan allowing for varied functionalization of C9, C19, C12, and C22 was desirable, particularly if studies showed the cyclization to be plausible in the less functionalized system. We felt an aldehyde such as **424** would allow for nucleophilic addition of vinyl anions with the desirable C22 functionalization. We also felt the aldehyde functionality could be installed through Wittig olefination performed on a benzaldehyde such as **427**. A halogen or triflate at the C13 position of the benzaldehyde would provide a coupling partner for appropriately functionalized stannanes or boronic esters representing the C12-C9 fragment (**426**).

We recognized the cyclization to be potentially problematic as multiple reaction pathways leading to undesired products were seen as plausible. However, most reactions were viewed as reversible, allowing for equilibration to dieneamine **422** and subsequent cyclization to **420**. Scheme 2.41 outlines some of the expected side reactions. We felt that acid base chemistry could operate through enolate formation to form enolate **429** or **430**. Interestingly, enolate **430** could potentially cyclize to give the same product as the desired cyclization of dieneamine **422**. Enolate **429** is capable of cyclizing in Michael fashion to form enol ether **432**, which we felt would be converted back to starting material with extended reaction times. We also felt that a dieneamine could be formed at C20, but any further reaction of **428** would result in high-energy

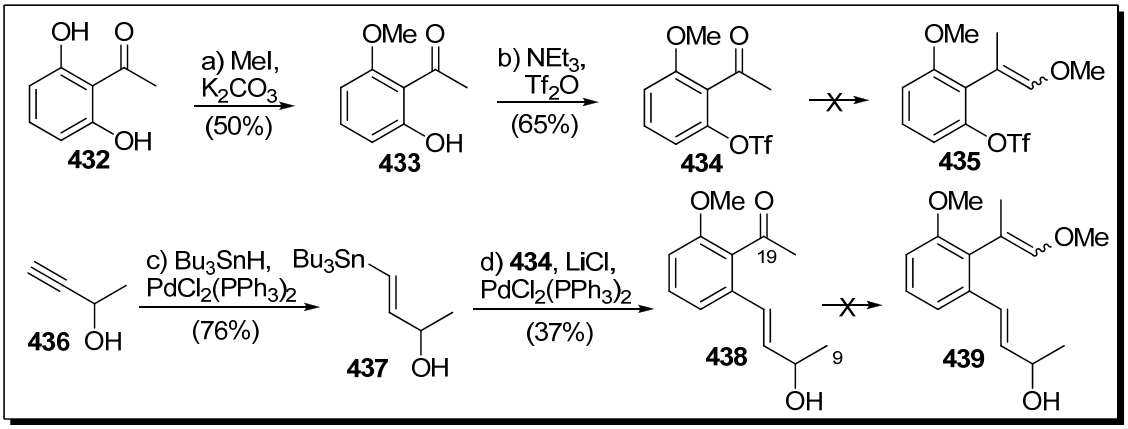
products, precipitating conversion back to starting material and cycling through lower energy pathways. It was also felt that the base itself could act as a Michael donor by reacting at C22.



Scheme 2.41 Potential reaction pathways of dienone **423**.

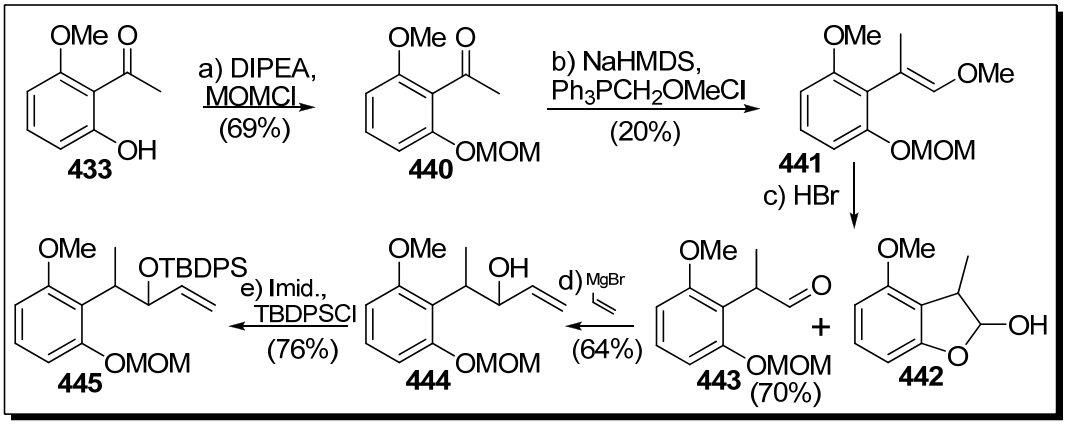
The previously reported synthesis of bromo benzaldehyde **427** (**427a**) involved the use of harsh reagents and required five steps with an overall yield of 35%.[44] Due to the issues associated with synthesis of benzaldehyde **427a**, an alternative route to a similar benzaldehyde was explored concurrently with synthesis of benzaldehyde **427a**.

Synthesis of a benzaldehyde **427a** analog began with diphenol **432** (Scheme 2.42). Diphenol **432** lacks the C15 methyl group, but we felt this group to be unnecessary for our model studies as it is not proximal to reactive centers and was expected to have minimal electronic effects. This model would also have allowed us to evaluate any effect the C19 benzylic methyl group might have had on the planned manipulations. Treatment of **432** with K_2CO_3 and methyl iodide in refluxing acetone resulted in a mixture of products, with phenol **433** easily isolable in 50% yield. Conversion to the corresponding aryl triflate (**434**) was accomplished by treatment of phenol **433** with Hunig's base followed by addition of triflic anhydride. Attempted homologation to the aldehyde equivalent, **435**, was unsuccessful. However, it was found that aryl triflate **434** could be coupled to the known stannane (**437**) to provide the C9-C19 fragment (**438**). Stannane **437** was synthesized in the manner reported by Lee and Kim.[4] With a method for constrtuction of the C12-C13 bond through a Stille coupling in place, Wittig homologation to the aldehyde equivalent (**439**) was attempted without success.



Scheme 2.42 Synthesis of C10-C19 fragment **438**.

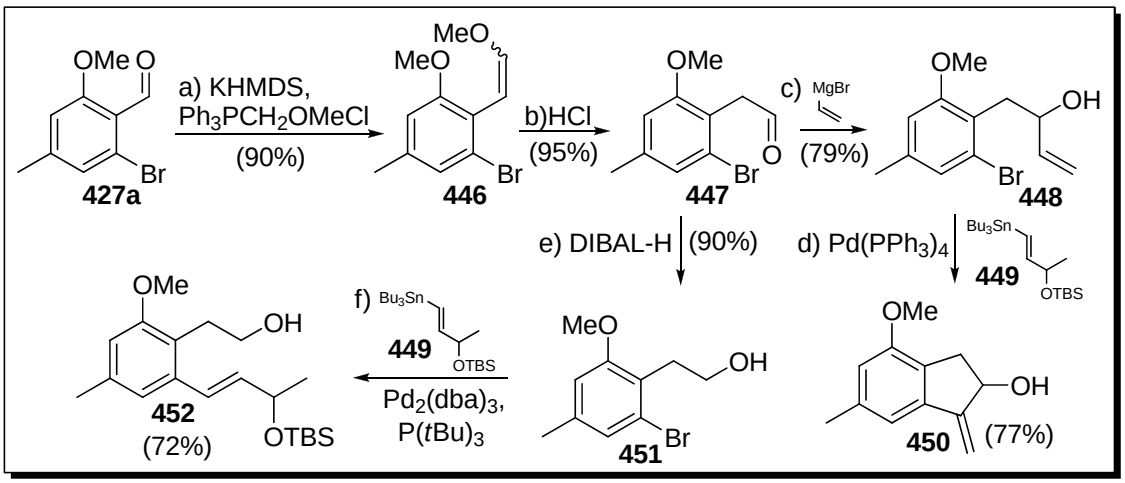
Focus was shifted to installing the C20 aldehyde functionality prior to performing the Stille coupling (Scheme 2.43). To this end, phenol **433** was protected as the MOM ether. Wittig homologation to the methoxy enol ether (**441**) was achieved without optimization in low yield (20%). Then treatment with acid gave the desired aldehyde (**443**) as well as observable MOM cleavage which resulted in formation of a compound tentatively identified as lactol **442**. Grignard reaction with vinyl magnesium bromide gave allylic alcohol **444** as a mixture of diastereomers, and the mixture was protected as the TBDPS ether (**445**). Attempts to deprotect the MOM ether with bromocatecholborane resulted in complex product mixtures. Although this route showed promise, we chose to use the reported benzaldehyde (**427a**) as it represents the fully functionalized A ring and we had achieved its synthesis in yields similar to that reported by Gould and coworkers.



Scheme 2.43 Synthesis of C13-C22 fragment **445**.

The synthesis of dienone **423** therefore began from benzaldehyde **427a** (Scheme 2.44). Wittig homologation to **446** worked well when performed at room temperature

in toluene with excess phosphonium salt (1.6 eq.), and subsequent acid treatment of the vinyl ether revealed the C20 aldehyde (**447**) in excellent yield. The aldehyde was then converted to allylic alcohol **448** by treatment with vinyl magnesium bromide. Unfortunately, when the Stille coupling of allylic alcohol **448** and stannane **449** was attempted, only Heck adduct **450** was isolated. The same result was obtained even when the reaction was performed with large excess of stannane **449** in concentrated solutions.

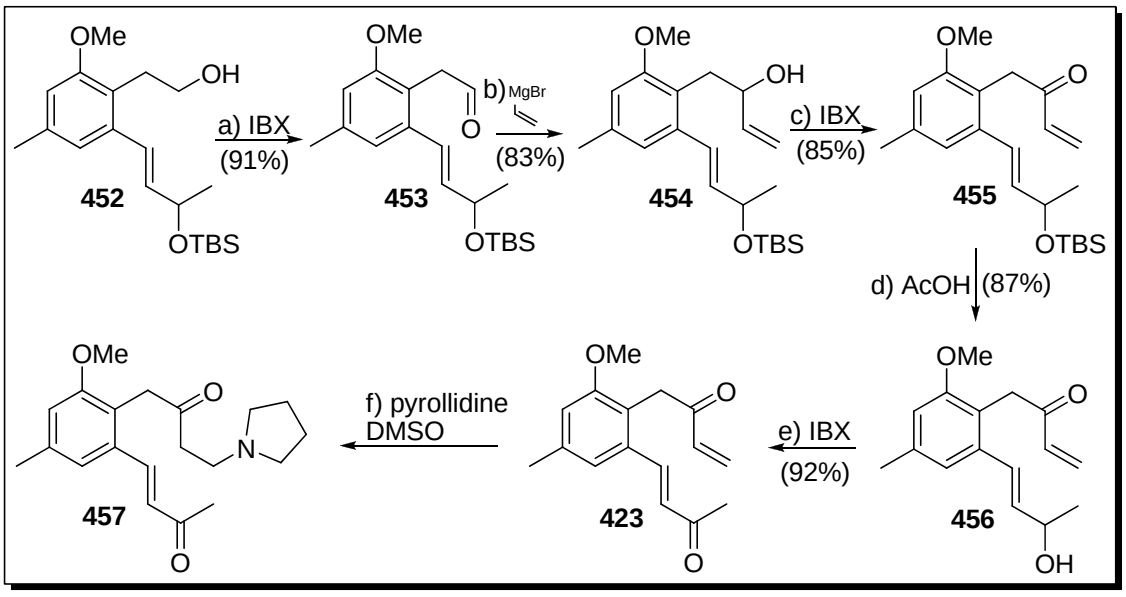


Scheme 2.44 Synthesis of C9-C20 fragment **452**.

Coupling reactions also failed when aldehyde **447** was used as a Stille partner. However, the coupling issue was resolved by reducing aldehyde **447** to the corresponding alcohol (**451**). Early coupling attempts of aryl bromide **451** and stannane **449** resulted in little or no reaction when traditional catalyst systems were used, such as $Pd(PPh_3)_4$ and $Pd(PPh_3)_2Cl_2$ with or without additives such as lithium chloride or copper iodide. Success was achieved when a catalytic system ($Pd_2(dba)_3/P(tBu)_3$) developed

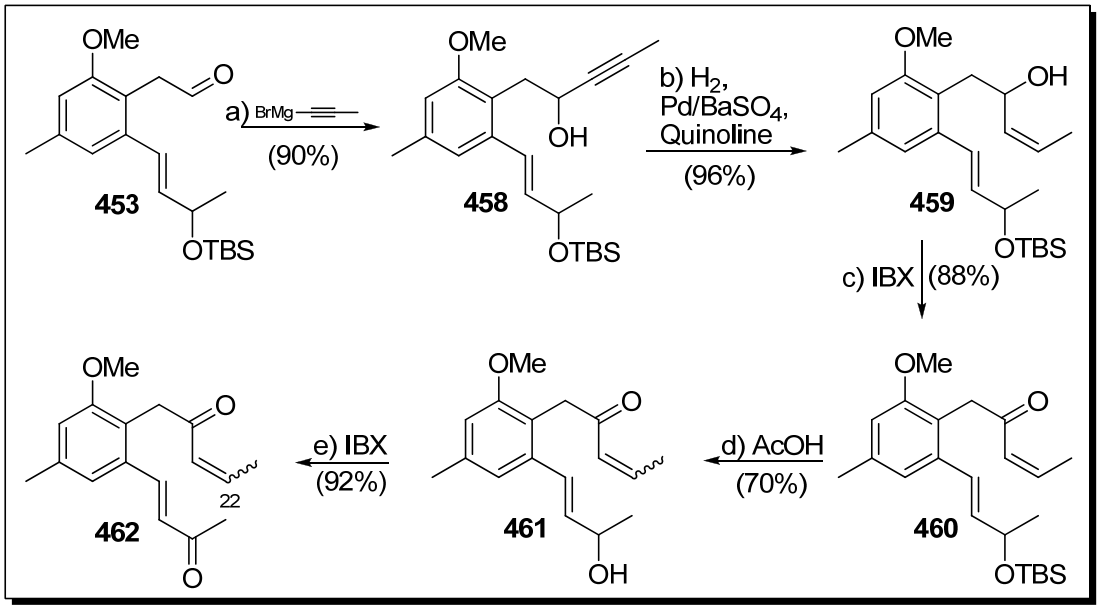
by the Fu research group was utilized.[46] We suspected the bulky tri-*t*-butyl ligands enhanced the oxidative addition step by increasing access of the aryl bromide to the reactive Pd^0 species. Simply put, we felt four *t*-butyl ligands could not coordinate to palladium simultaneously as with triphenylphosphine and other ligands.

Having found a solution to sluggish reactivity associated with the Stille coupling reaction, attention was turned to the remaining functionalization reactions (Scheme 2.45). Oxidation of **452** to the corresponding aldehyde (**453**) and Grignard reaction provided allylic alcohol **454**. Oxidation (IBX) and deprotection of the C10 silyl ether gave allylic alcohol **456** in good yields. A final IBX oxidation provided dienone **423** in high yield. When dienone **423** was treated with pyrollidine in DMSO at room temperature or with mild heating, only Michael adduct **457** was observed. Complex mixtures were formed when more forcing conditions were applied (increased heat).



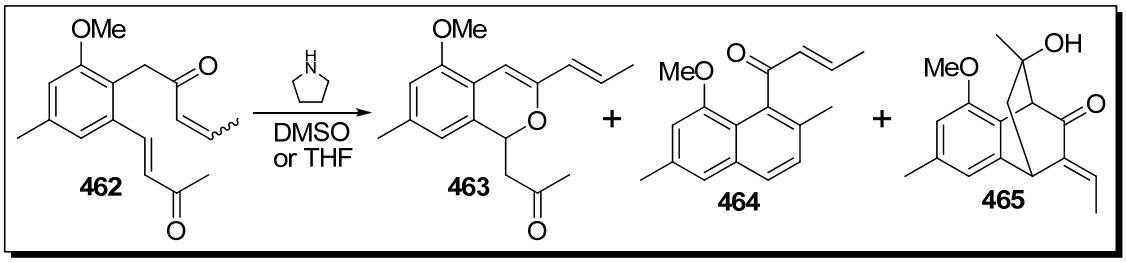
Scheme 2.45 Synthesis of C9-C22 fragment **423**.

Having observed rapid Michael addition of pyrollidine to dienone **423**, we felt substitution at C22 might have slowed the Michael addition and increased the likelihood of dieneamine formation. For this reason, aldehyde **453** was treated with 1-propynyl magnesium bromide to form propargyl alcohol **458** (Scheme 2.46). Poisoned hydrogenation of propargyl alcohol **458** gave allylic alcohol **459** in excellent yield, then oxidation with IBX efficiently provided enone **460**. Deprotection of the TBS ether with acetic acid in THF and water, followed by oxidation with IBX provided cyclization substrate **462**. It should be noted that slow isomerization of the C21-C22 olefin was observed, particularly during the acid mediated TBS cleavage reaction. Although the *E,Z* isomers were not typically separated, separation was achievable with column chromatography.



Scheme 2.46 Synthesis of C22-methyl C9-C22 fragment **462**.

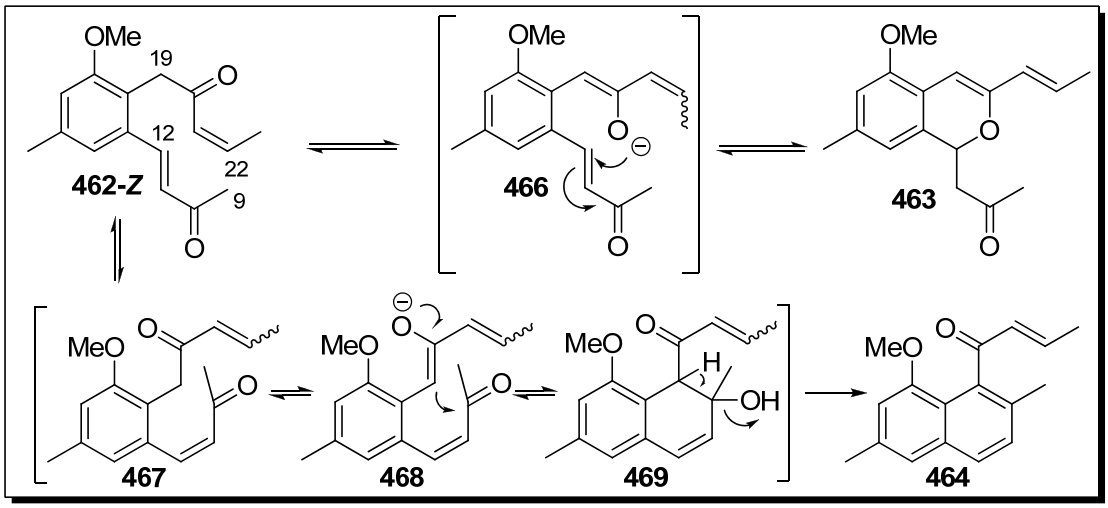
We felt the solvent choice to be important for the consecutive conjugate addition reaction of **462**, with polar solvents more likely to bias the pathway to a stepwise mechanism though stabilization of the charged intermediates. For this reason, DMSO was initially picked as the solvent of choice (Scheme 2.47). Treatment of dienone **462** with pyrrolidine at 50 °C for varied lengths of time inevitably provided a mixture of products. The three major components were *tentatively* identified as; enol ether **463**, naphthalene **464**, and tricycle **465**. Attempts to modulate the reactivity of pyrrolidine by adding camphorsulfonic acid as a buffer led to the same mixture of products, in different yields and ratios.



Scheme 2.47 Attempted cyclization of C9-C22 fragment **462**, an unexpected Michael-aldol cascade.

The products suggested several reaction pathways were operating. We believed enol ether **463** was formed through enolization of C19-C20 (**466**) (Scheme 2.48). The C19 protons were expected to be the most acidic due to conjugation with the aromatic ring, and the mechanism therefore likely involved enolization and Michael addition of the enolate to the C12 enone. We assumed this process to be reversible, and confirmed our

suspension by observing that re-treatment of **463** with pyrrolidine provided the same mixture of products originally observed (**463**, **464**, and **465**).

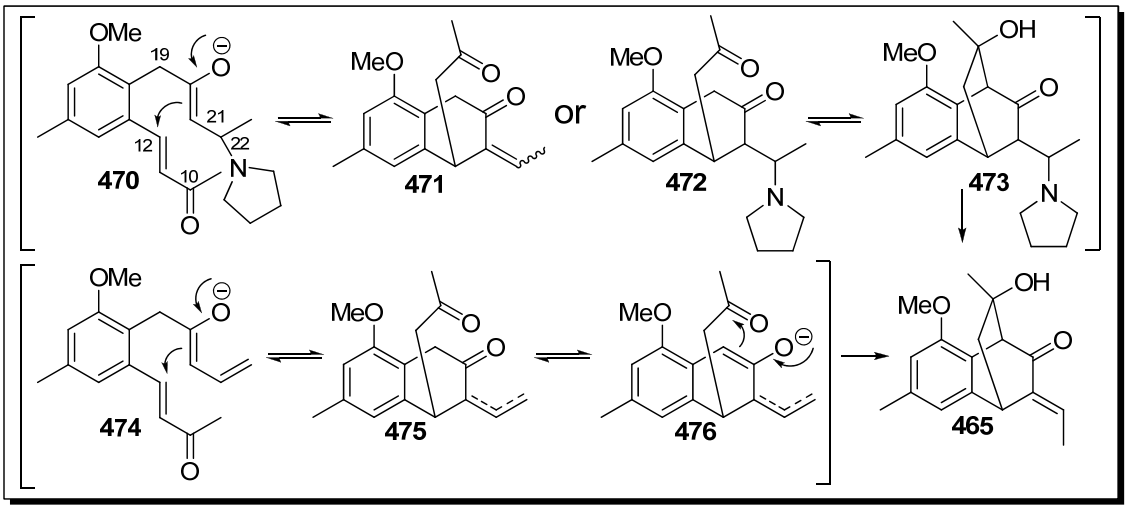


Scheme 2.48 Proposed mechanism for formation of enol ether **463** and naphthalene **464**.

Formation of naphthalene **464** was expected to arise from initial isomerization of the C12-C22 olefin (**467**) (Scheme 2.48). Enolization at C19 and 1,2 attack of the C19 enolate at the C10 ketone likely provided the intermediate allylic alcohol (**469**). Aromatization through C10 hydroxyl group elimination was suspected of being the final manipulation which provided naphthalene **464**.

Of the three major products, tricycle **465** was the most interesting to us. The mechanism was not clear, but we felt the initial step involved charge development at C21 through Michael addition of pyrrolidine at C22 (**470**) via a Bayliss-Hillman type mechanism or formation of an extended enolate by deprotonation at C22 (**474**) (Scheme

2.49). Michael addition of C21 to C12 would form a cyclohexane ring, such as **471** or **475**. Subsequent C19 enolization and 1-2 addition would form the second cyclohexane ring. It is not clear at what stage isomerization of the C22-C23 olefin to C21-C22 would occur if the extended enolate pathway was in operation. Likewise, elimination of pyrrolidine to regenerate the C21-C22 olefin could have feasibly occurred at any stage after C21-C12 bond formation if the reaction followed a Bayliss-Hillman mechanism.

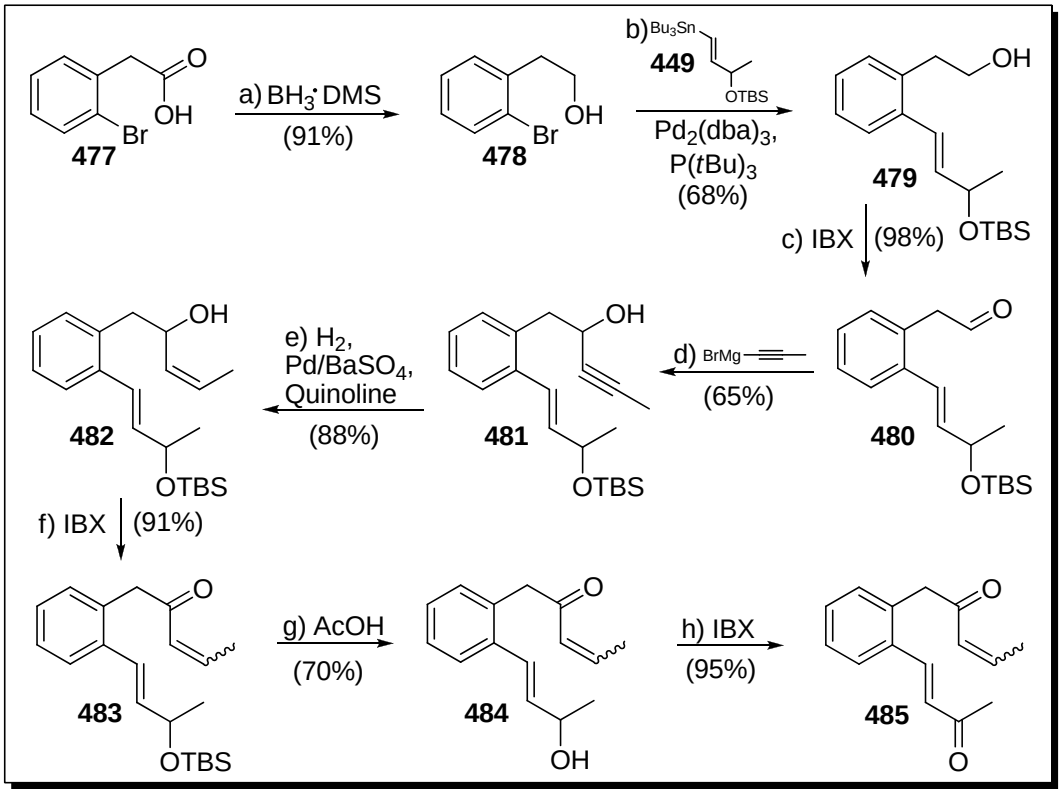


Scheme 2.49 Proposed mechanisms for formation of tricycle **465**.

Although no useful intermediates such as **471**, **472**, or **475** were isolated, we felt modified reaction conditions may have allowed for manipulation of the reaction pathways. We understood that installation of the C19 methyl group would prevent formation of naphthalene **464** by C11 elimination, due to the lack of β hydrogen atoms. If our proposed mechanism(s) for tricycle **465** was correct, it suggested C12 to be a good Michael acceptor and C21 to be a good Michael donor. The desired C12-C21

bond had been formed, but subsequent reactivity from C19 converted the intermediate to undesired material. It seemed that we may have been able to tune this reaction to provide the desired tricyclic structure if the enolizability of C19 could be mitigated. Additionally, it was thought that we may have been able to use a Bayliss-Hillman reaction to form the C12-C21 bond and intercept a useful intermediate such as **471**, prior to any additional reactions.

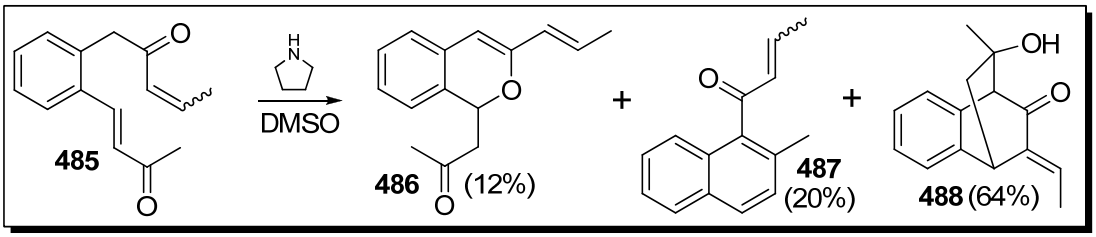
We decided to use a further simplified model system to expedite the additional studies. 2-bromo-phenethyl alcohol (**478**) was used as a starting point (Scheme 2.50). Although commercially available, we found borane reduction of the inexpensive carboxylic acid (**477**) to phenethyl alcohol **478** to be convenient.[47] Coupling of stannane **449** gave **479** in yields similar to those observed for the construction of **452**. Oxidation to the corresponding aldehyde, Grignard reaction, and poisoned alkyne hydrogenation gave allylic alcohol **482**, which was oxidized to enone **483**. Mild deprotection of silyl ether **484** and oxidation of the resultant allylic alcohol provided dienone **485** as a separable mixture of C22 isomers favoring the cis isomer. Additionally, the *E* isomer (**485*E***) could be isolated via trituration as an amorphous solid.



Scheme 2.50 Synthesis of dienone **485**.

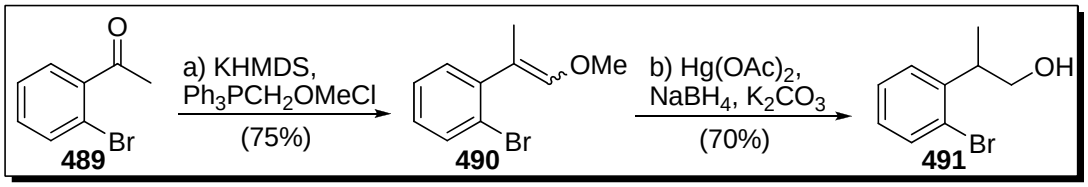
Unfortunately, attempted cyclizations of dienone **485** were unsuccessful under an expanded set of conditions. All modifications provided only enol ether **486**, naphthalene **487**, and tricycle **488** as isolable products (Scheme 2.51). Reactions in DMSO with pyrrolidine, morpholine, proline, prolinol, or methoxymethyl prolinol (SAMP) all gave similar product distributions. Reactions in toluene gave the same product mixture, as judged by crude NMR. Furthermore, no optical activity was observed for products obtained from proline or proline derivatives, which was suggestive of a lack of involvement of an enamine mechanism. All reaction conditions produced tricycle **488** as a mixture of diastereomers, with the indicated stereochemistry

preferred, as judged by NMR. The major diastereomer of **488** provided a crystal suitable for single crystal x-ray analysis, which supported the indicated structure (Scheme 2.51).



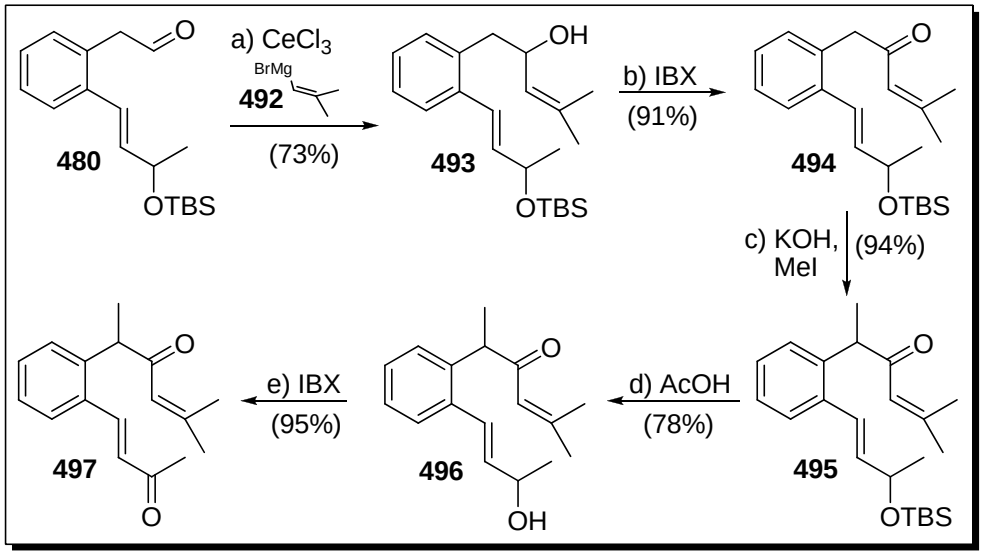
Scheme 2.51 Attempted cyclization of dienone **485**.

At this stage we decided it was necessary to install the C19 methyl group prior to cyclization, in order to prevent aromatization and to limit the ability of C19 to act as a nucleophile in the aldol reaction. We also decided to install a second methyl group at C22 for two reasons; to represent the desired C22 tertiary center at C22 of the zoanthamine alkaloids, and to increase C22 steric hindrance to minimize a Bayliss-Hillman mechanism. To this end, two methods were explored for installing the C19 methyl group. One method involved Wittig extension of a methyl ketone (Scheme 2.52). Wittig homologation was performed on 2-bromoacetophenone (**489**) to yield a mixture of methoxy enol ethers (**490**). Methoxy enol ether **490** was converted directly to alcohol **491** by a one-pot oxymercuration/reduction procedure using $Hg(OAc)_2$, $NaBH_4$, and K_2CO_3 in wet THF.[48] Alcohol **491** was not tested as a coupling partner due to limited quantities and the success of an alternative approach.



Scheme 2.52 Synthesis of aryl bromide **491**.

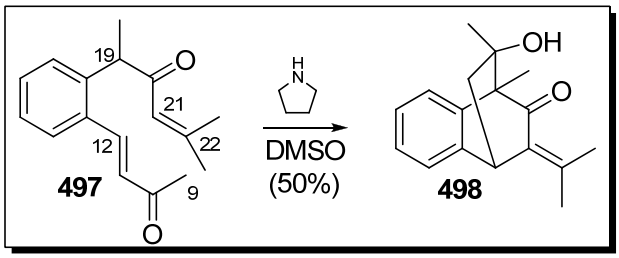
Standard Grignard additions of 3-methyl-propenyl magnesium bromide (**492**) to aldehyde **480** proved to be low-yielding and provided erratic results under different conditions (Scheme 2.53). We suspected the enolizability of aldehyde **480** increased the likelihood of polymerization pathways, so cerium chloride was used to form the less basic and more oxophilic organocerium reagent.[49] This modification resulted in acceptable and reproducible yields of allylic alcohol **493**. Oxidation with IBX provided alkylation substrate **494**. Enolization with potassium hydroxide in the presence of methyl iodide gave C19 alkylation, and enone **495** was constructed in this manner. Deprotection as previously described with acetic acid and oxidation with IBX gave dienone **497**.



Scheme 2.53 Synthesis of dienone **497**.

Numerous cyclization conditions were evaluated for dienone **497**. Heating with pyrrolidine in DMSO provided a complex mixture of products, with only tricycle **498** isolated (Scheme 2.54) as a diastereomeric (C10) mixture. Reaction condition modifications included temperature and solvent variation. Reactions were performed at low temperature (-78 °C, 0 °C) as well as temperatures up to 75 °C under standard thermal conditions and up to 150 °C in a microwave reactor. Several solvents were tested; toluene, benzene, THF, and DMSO, without significant change in the reaction outcomes. Cyclization initiated through enolization was unsuccessfully attempted by treating dienone **497** with non nucleophilic bases KHMDS and LiHMDS. Although the base promoted reactions (HMDS) resulted in particularly complex reaction mixtures, tricycle **498** was observed in crude reaction mixture analyses. This finding suggested

the mechanism involved initial formation of an extended enolate followed by Michael addition and an aldol reaction between C19 and C10.



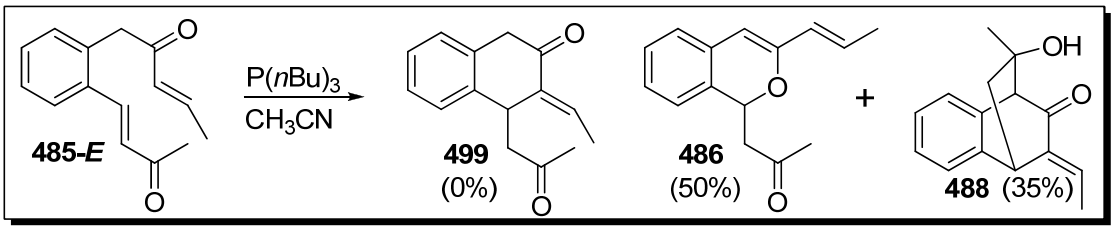
Scheme 2.54 Attempted cyclization of dienone **497**.

One potential hindrance to the desired cyclization was the fact that the desired reaction pathway involved formation of a ten-membered ring system via formation of a C9-C22 bond. The more favorable path to tricycles **465**, **488**, and **498** apparently involved initial cyclization to a cyclohexane ring and rapid formation of a second cyclohexane ring. Additionally, the acidity of the C19 proton(s) apparently prevented us from intercepting any direct products of the initial C9-C22 bond forming event.

Regardless of the disappointing results, we felt the reaction merited continued investigation. Two final experiments were devised. The first approach involved promotion of a Bayliss-Hillman reaction through the use of a nucleophilic tertiary phosphine instead of a secondary amine base such as pyrrolidine, feeling that the enhanced reagent nucleophilicity and reduced basicity[50] may have allowed for isolation of the Bayliss-Hillman adduct (**499**) (Scheme 2.55). We felt the Bayliss-Hillman adduct could be subsequently converted to the desired cycloadduct through a Michael addition of C9 to C22. In this manner we could potentially have achieved consecutive

conjugate additions, albeit in two steps, and possibly elucidated the reaction mechanism for formation of the caged tricyclic compounds.

Surprisingly, when dienone **485-*E*** was treated with tributylphosphine in acetonitrile, enol ether **486** and tricycle **488** were isolated (Scheme 2.55).[51] All evidence suggested the desired cyclization would not be achieved with an enolizable C19 position, so a final approach to address the issue was attempted.

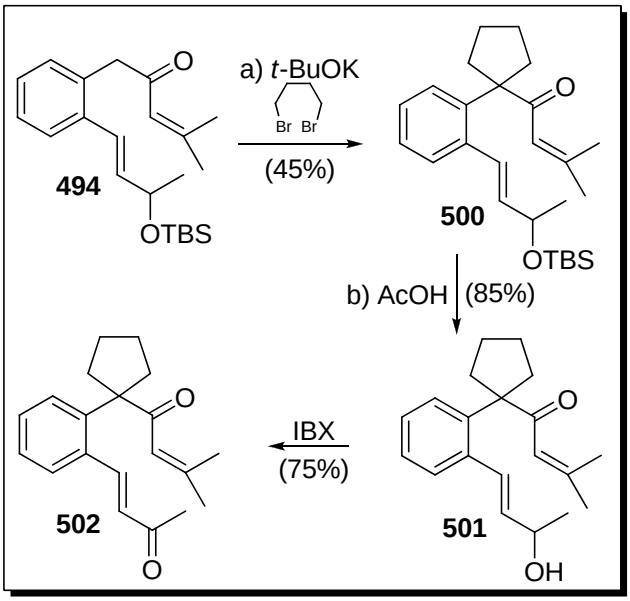


Scheme 2.55 Attempted Bayliss-Hillman reaction of dienone **485-*E***.

In order to nullify the enolizability of C19, we planned to alkylate the C19 carbon twice. If the dialkylation approach was successful, we felt we could apply the concept to a zoanthenol (**163**) synthesis with a cleavable protecting group at C19 capable of preventing enolization.

Di-methylation at C19 of enone **494** was unsuccessful. The first alkylation occurred at C19 as desired, but the second methylation appeared to occur at C21 by way of an extended enolate. Due to this disappointment, C19 addition to a single moiety capable of a second, intramolecular, alkylation reaction was concocted (Scheme 2.56). Enone **494** was treated with base and 1,4dibromobutane. Extended reaction times and heating provided cyclopentane **500**. In this manner the enolizability of C19 was quashed.

Deprotection of the silyl ether and oxidation as previously performed resulted in cyclization substrate **502**. Regrettably, a limited amount of dienone **502** was prepared and two small-scale exploratory reactions showed little promise for a clean cyclization reaction.

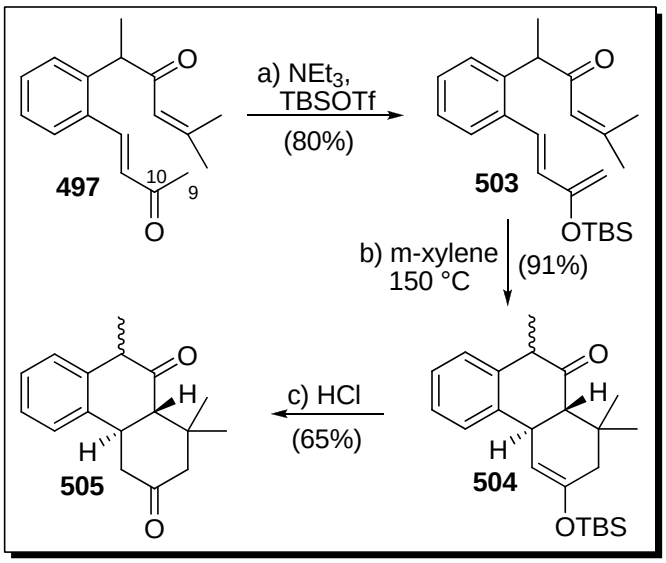


Scheme 2.56 Synthesis of non-enolizable C19 cyclization substrate **502**.

While we did not attain the desired consecutive conjugate reaction sequence, an interesting Michael-aldol cascade was discovered. We gained knowledge pertaining to the ease of enolizability of the benzylic C19 carbon that proved useful in analyzing reactions of a related project. We also overcame a troublesome Stille coupling and observed an efficient Heck reaction in the formation of **450**.

Section 2.5.3 Intramolecular [4+2] Cyclization of a Silyl-enol Ether

Unwilling to concede the developed chemistry, an alternative cyclization method was attempted to form the B and C rings simultaneously (Scheme 2.57). Dienone **497** was trapped as silyl enol ether **503** with unexpected efficiency. Despite the problems associated with C19 enolizability, low temperature treatment of **497** with triethylamine produced the kinetic C9-C10 enolate. Also worthy of note is the observation that C9 was enolized but failed to cyclize in a Michael addition to C22, instead an oxygen-silicon bound was formed from a bimolecular reaction.



Scheme 2.57 Synthesis of the minimized zoanthenol (**163**) ABC ring System.

An intramolecular [4+2] reaction of triene **503** performed well with m-xylene as a solvent when heated at 150 °C for 14 hours. The conditions described, produced cycloadduct **504** as a mixture of C19 isomers in 91% yield. Subsequent deprotection of the silyl enol ether to reveal the C10 ketone generated tricycle **505** in 65% yield.

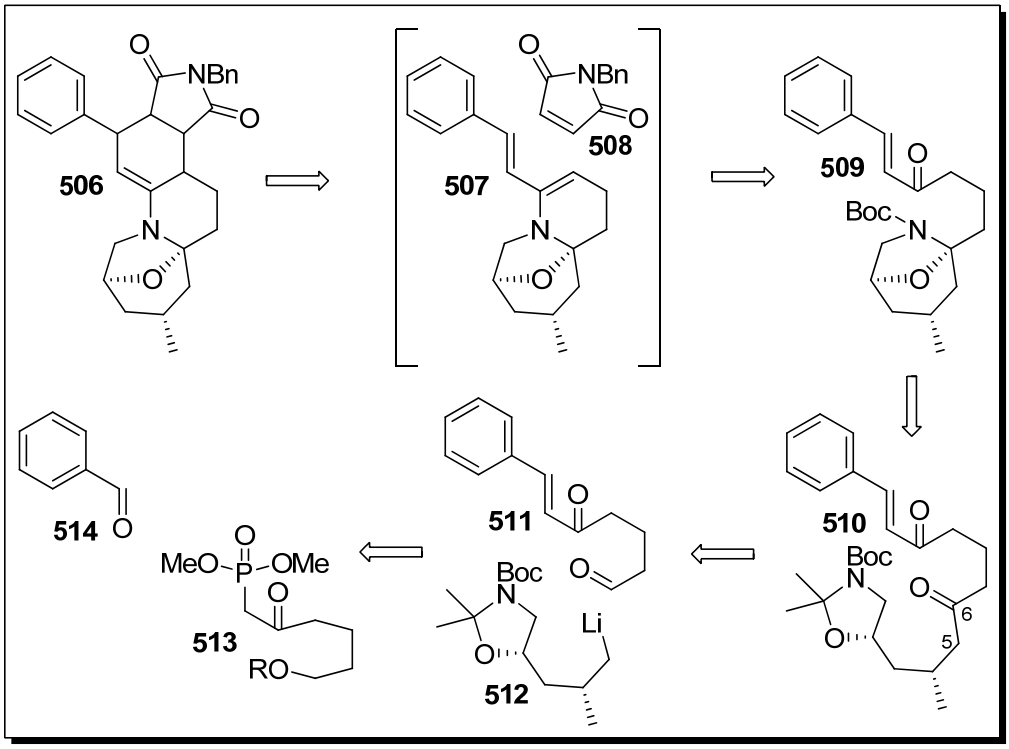
Limited attempts to epimerize the C19 methyl group by enolization to provide a single diastereomer resulted in little or no conversion to a single isomer.

Tricycle **505** represents a minimized ABC zoanthenol (**163**) ring system. Of particular note is the fact that only the exo isomer was isolated and a quaternary center was set at C22. We suspected functionalization of the aromatic ring at C15 and C17 would have little effect if such a substrate was subjected to the cycloaddition reaction conditions, and we previously developed chemistry amenable to the construction of such a substrate. Methyl substitutions at C9 and C12 are also necessary for this approach to be considered viable. Miyashita has already demonstrated a similar cycloaddition with methyl substitution at C12[29a], and we felt the results may be applicable to our system, allowing for cyclization with the C12 methyl group preinstalled. Functionalization of C9 remains unresolved, but it was thought perhaps the C1-C8 fragment could have been tethered to C9 and the challenging C9 methyl group could have been installed at a later time using a previously developed alkylation method or through an enamine alkylation.

Section 2.5.4 Attempted In Situ Intramolecular Aminal-diene Formation and Intermolecular [4+2] Cyclization

Based on the conclusion that products from the previous studies were almost certainly not produced by dieneamine intermediates and the lack of evidence of a dieneamine intermediate from NMR tube reactions, we felt a model system involving an internal amine capable of cyclizing to a dieneamine would hold more promise.

Consequently, we designed a model system which included an internal secondary amine in the form of the southern portion of the zoanthamine alkaloids. In order to simplify and expedite the studies, we designed a system with the purpose of testing the cycloaddition reaction with an external, activated dienophile (or Michael acceptor/donor) such as maleimide. This was designed primarily to evaluate whether formation of the desired dieneamine was viable, due to the assumption that the dieneamine intermediate could be trapped with a sufficiently reactive dienophile.



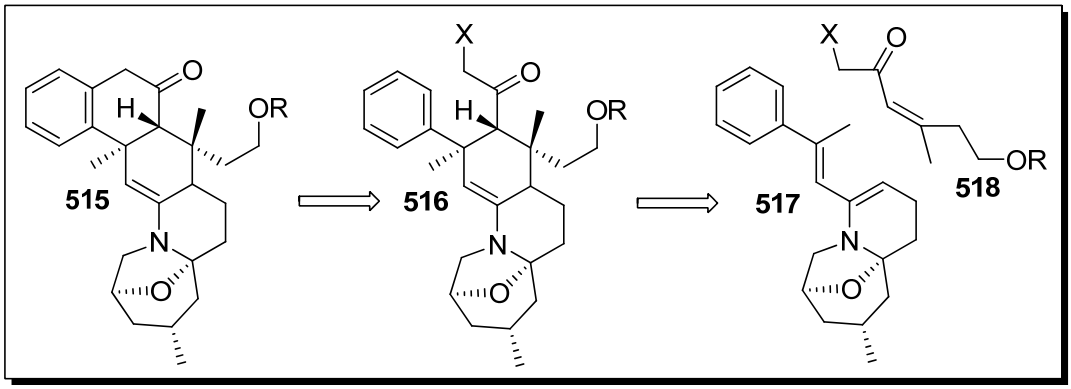
Scheme 2.58 Retrosynthetic analysis of the intermolecular aminal-diene approach.

We believed an enamine such as **506** could be formed from the cycloaddition reaction of a dieneaminal resembling **507** with a reactive dienophile (Scheme 2.58).

Dieneaminal **507** was expected to arise from condensation of an aminal, which could be formed from a protected amine such as **508**. Previous work by the Kobayashi[19], Hirama[14], and Miyashita[29] research groups suggested the Boc group to be a prudent N-protecting group choice as subsequent acid catalyzed deprotection afforded the corresponding iminium in their cases. It was believed that dieneaminal **507** could be accessed through neutralization of the corresponding iminium.

Aminal **509** was anticipated to form upon deprotection of a suitably substituted substrate such as aminal **510**. The C5-C6 bond of aminal **510** was chosen as a disconnection, with a lithiate addition of a chiral fragment such as **512** to an aldehyde resembling **511** in mind for the bond development. The chiral aminal piece (**512**) would theoretical arise from chemistry similar to that used by Kobayashi and coworkers[19], and the aldehyde (**511**) could be formed through homologation of benzaldehyde with a suitably functionalized phosphonate such as **513**.

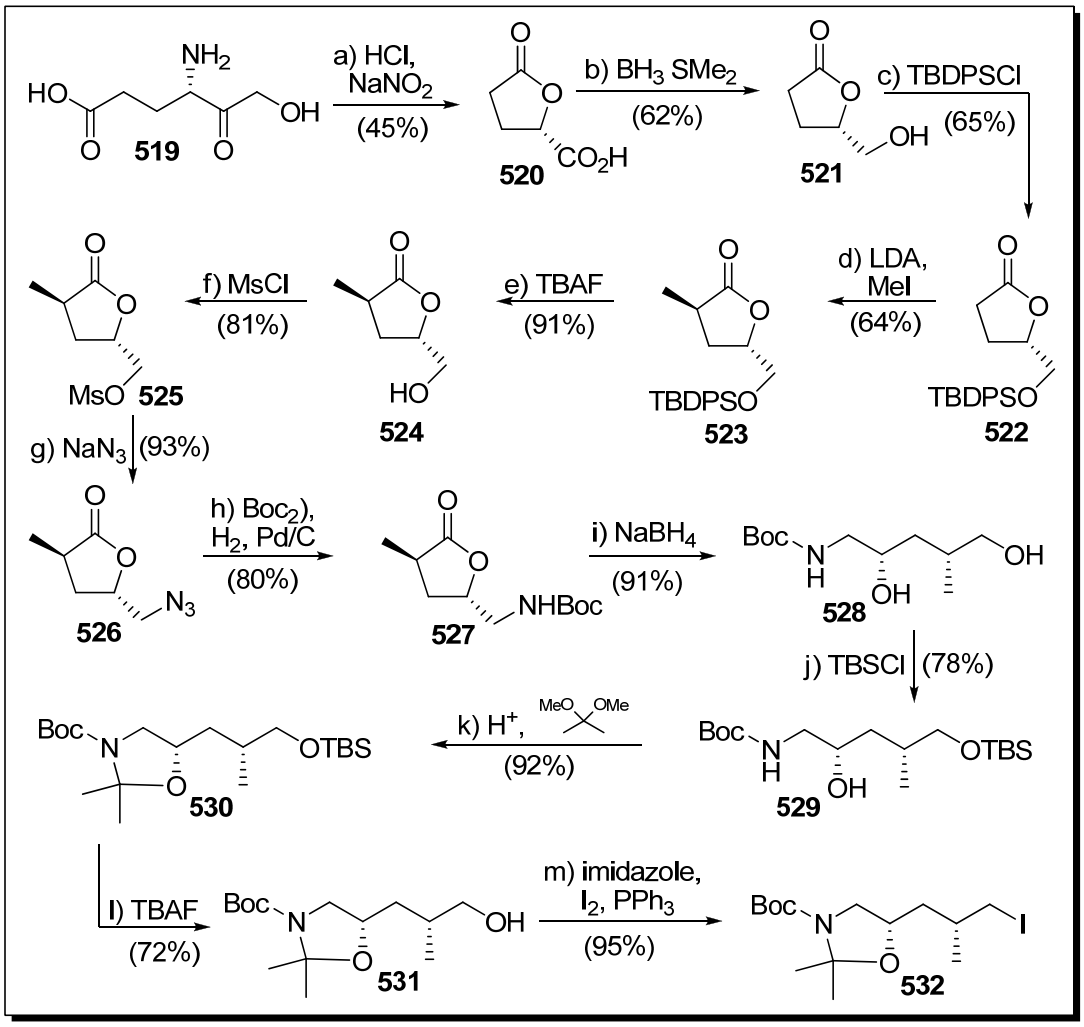
If the cycloaddition reaction proved feasible with activated dienophiles, we felt the intermolecular cyclization could be applied as a method for zoanthenol (**163**) total synthesis. The ABCEFG skeleton of zoanthenol (**163**) could arise from a Friedel-Crafts acylation reaction between C18 and C19 as shown in Scheme 2.59. α-haloketone **516** could result from an exo cycloaddition between dienophile **518** and dieneaminal **516**. If exo adduct forming conditions could not be found and endo product(s) predominated, we felt subsequent epimerization at C21 could potentially provide the necessary B-C trans ring junction, and the geometry of the dienophile (C22) could be altered as needed.



Scheme 2.58b Retrosynthetic analysis of the intermolecular cycloaddition / Friedel-Crafts approach to zoanthenol (**163**).

Synthesis of the chiral C1-C5 fragment (**532**) began from glutamic acid (Scheme 2.60). Although it contains the opposite requisite stereochemistry, we chose to use L-glutamic acid (**519**) based primarily on an abundant laboratory supply. Nitrosation of L-glutamic acid (**519**) gave butyrolactone **520** via the reported method.[52] Reduction to the primary alcohol with borane provided **521** in acceptable yield,[52a,b] and typical reaction conditions provided the bulky TBDPS silyl ether (**522**).[20] A diastereoselective alkylation was achieved using conditions similar to those originally reported by Hanessian and coworkers.[53] Chromatographic separation showed alkylation from the α face predominated, yielding methyl butyrolactone **523** in 64%. Cleavage of the silyl ether with TBAF as reported by Kobayashi[20] gave the primary alcohol (**524**), which was converted to the corresponding mesylate by utilizing reaction conditions previously reported by Herdeis and Lutsch.[54] Mesylate displacement by treatment with sodium azide followed by a one-pot procedure involving azide reduction to the corresponding amine and in-situ protection as the Boc carbamate proceeded as originally described by

Herdei and Lutsch.[54] Mild reduction conditions developed by the Soai research group provided linear diol **528** in excellent yield when applied to butyrolactone **527**.[55]

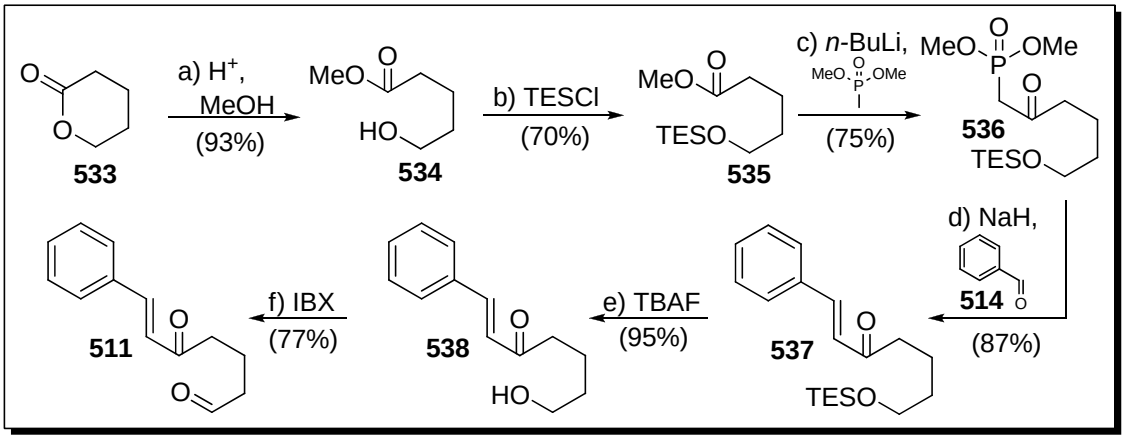


Scheme 2.59 Synthesis of chiral C1-C5 fragment (**532**).

Attempts to protect the 1,2 amino-alcohol functionality under acidic conditions with dimethoxypropane at this stage failed to effectively supply the desired N,O-ketal under several conditions. Aminodiol **528** was therefore converted to the primary TBS ether (**532**) in order to circumvent the amino-alcohol protection problems. Ketalization of

amino-alcohol **530** proceeded with excellent yield once the primary alcohol was protected. Deprotection of **530** and conversion of the resultant primary alcohol (**531**) to the corresponding iodide (**532**) proved an efficient method. Primary alcohol **531** and iodide **532** provided spectroscopic data identical to the enantiomer subsequently reported by the Tanner research group.[25e] It should be noted that NMR spectra of N,O ketal **530** and all subsequent C1-C5 fragment-containing compounds indicated the presence of two stable rotamers. This observation was in accordance with expermintal data reported by Tanner and Miyashita for similar and/or identical compounds.[25e, 29a]

With a proven route to iodide **532** in hand, focus was switched to building an aldehyde coupling partner. We felt the most expedient route to the desired cyclization substrate would involve selective addition of lithiated **532** to a ketoaldehyde such as **511** (Scheme 2.61). Therefore, we decided a Horner-Wadsworth-Emmons reaction to be an excellent method for introducing the α,β-unsaturated ketone central to keto-aldehyde **511**. Consequently, valerolactone (**533**) was converted to the methyl ester (**534**) by treatment with acid in methanol, and the primary alcohol was quickly protected as the triethylsilyl ether **535**. Formation of stabilized phosphonate **536** occurred upon exposure of the dimethyl methylphosphonate anion to methyl ester **536**. Deprotonation with sodium hydride and mixing with benzaldehyde gave trans-alkene **537** in excellent yield as the only product isolated. Deprotection and oxidation afforded coupling partner, ketoaldehyde **511**.

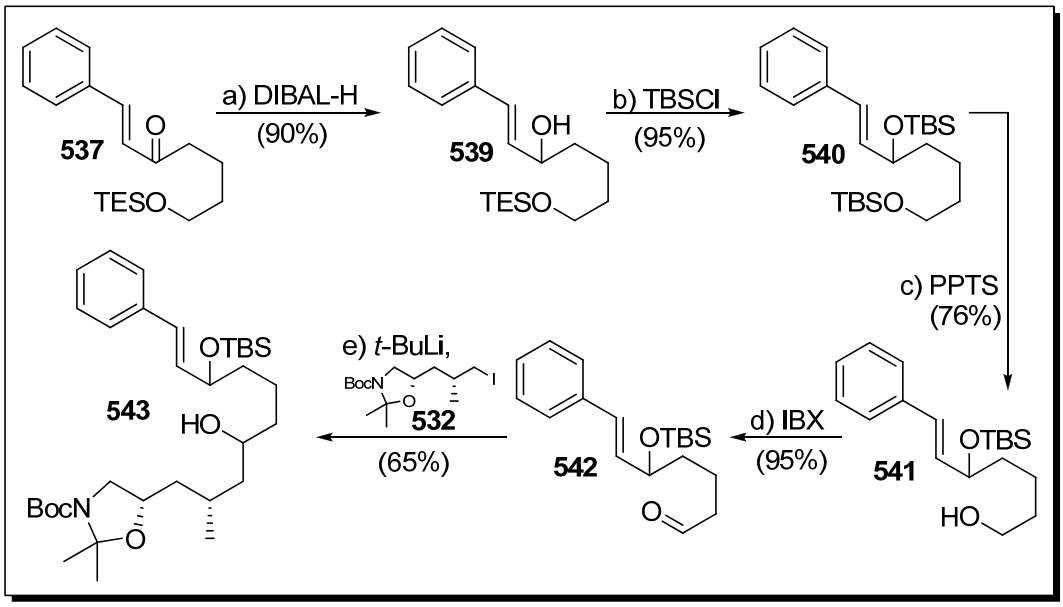


Scheme 2.60 Synthesis of keto-aldehyde **511**.

Coupling attempts with ketoaldehyde failed under numerous conditions. Treatment of iodide **532** with *t*-BuLi to form the lithiate and exposure to ketoaldehyde **511** produced complex mixtures of inseparable products. Similar results were obtained when transmetallation of the lithiate to organozinc and organotitanium nucleophiles was performed. We suspected the product had been formed to some degree (this suspicion was supported by mass and NMR spectral analysis but that a subsequent cyclization to form the C6-C10 lactol, as well as enolization at C9 probably complicated the reaction. Oxidation of the presumed mixture of lactols unfortunately did not assist in characterization.

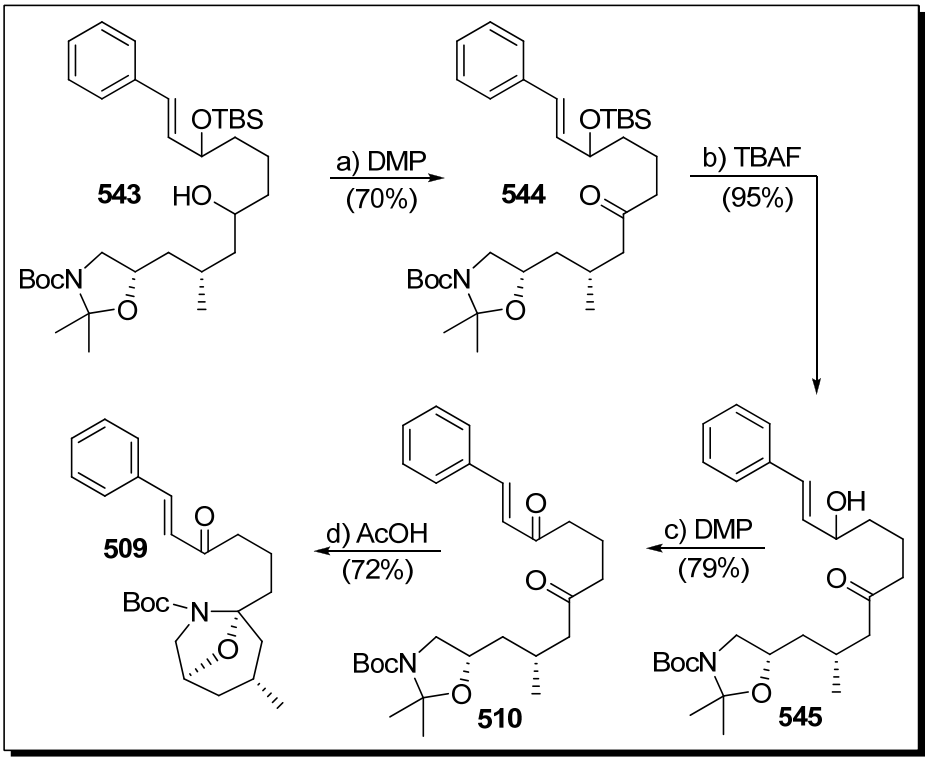
Having observed problems with the coupling presumably arising from the α,β-unsaturated ketone functionality, enone **537** was reduced to the allylic alcohol (**539**) and protected as the TBS ether (**540**) (Scheme 2.61). Selective deprotection with pyridinium p-toluenesulfonic acid gave primary alcohol **541**, which was oxidized to aldehyde **542**. Lithiate formation from **532** and addition to aldehyde **542** provided a

mixture of diastereomers (**543**) in 65% overall yield, reinforcing the idea that the C10 enone had interfered with the earlier coupling attempts.



Scheme 2.61 Synthesis of alcohol **543**.

Formation of diketone **510** was accomplished by oxidation of alcohol **543**, deprotection of the C10 silyl ether with TBAF, and C10 oxidation with Dess-Martin periodinane, respectively (Scheme 2.62). Transaminalization of diketone **510** to aminal **509** was accomplished by heating at 50 °C in an acetic acid/water (1:1) solution for 1 hour.



Scheme 2.62 Synthesis of aminal **509**.

Results for attempted aminal-diene formation and subsequent cyclization of **509** with N-benzylmaleimide were ambiguous at best. Treatment with an acetic acid/water (1:1) solution at 100 °C in the presence of excess N-benzylmaleimide (**508**) resulted in a complex mixture of products. However, NMR spectra of semi-purified material revealed the presence of a peak at 5.4 ppm, within the typical enamine range, and other peaks consistent with the expected product. However, analysis of splitting patterns and integration suggested a mixture of diastereomers, in addition to many other reaction products.

A similar procedure was performed in deuterated benzene with p-toluenesulphonic acid substituted for acetic acid. All traces of starting material had disappeared, by NMR, within three hours of heating at 45 °C. However, only decomposition was observed. In contrast to toluenesulphonic acid, when pyridinium p-toluenesulphonic acid was used with deuterated benzene as the solvent, limited reaction was observed after 20 hours at 65 °C. After 24 hours additional heating at 100 °C, starting material was observed by NMR in conjunction with a complex mixture of products.

Two reactions were performed in the absence of a dienophile order to determine whether the enamine and/or its tautomeric iminium species had been formed. Aminal **509** was treated with TFA and dimethyl sulfide at room temperature in deuterated methylene chloride. Spectral data obtained immediately (approximately 2 minutes) after TFA addition suggested the starting material had been consumed. Of significant note was the downfield shift of the C12 proton, suggestive of increased conjugation as would be expected from iminium formation. After twenty minutes had passed, an apparent triplet, suggestive of an enamine proton appeared at 5.25 ppm. There were additional products, however, and no compound was isolated for characterization.

We felt the desired iminium had been formed upon Boc deprotection, but alternative reaction pathways lead to decomposition before the desired cyclization could be effected. Therefore, we sought to confirm iminium formation by acid treatment of **509** followed by treatment with sodium cyano borohydride to reduce the iminium intermediate to a more stable and isolable tri-substituted amine. As with the other experiments, no single product was isolated from this reaction.

From the limited number of reactions performed to explore the cycloaddition potential of aminal-diene **507**, we learned that, while a tentative argument for iminium and/or aminal-diene formation could have been made based on spectroscopic evidence, the reactions mainly followed alternative pathways. We could not exclude the possibility that small amounts of cycloadducts had been formed, as reactions were typically performed on 1-3 milligrams of aminal **509**. We also expected several products to arise from the desired cycloaddition reaction as a result of limited facial selectivity and uncertainty about endo/exo preference. In addition, we expected some isomerization of the C10-C11 enamine olefin of the desired product(s) to the more substituted C10-C22 position. The small scale of the studies in conjunction with the numerous reaction possibilities prevented us from isolating a single product.

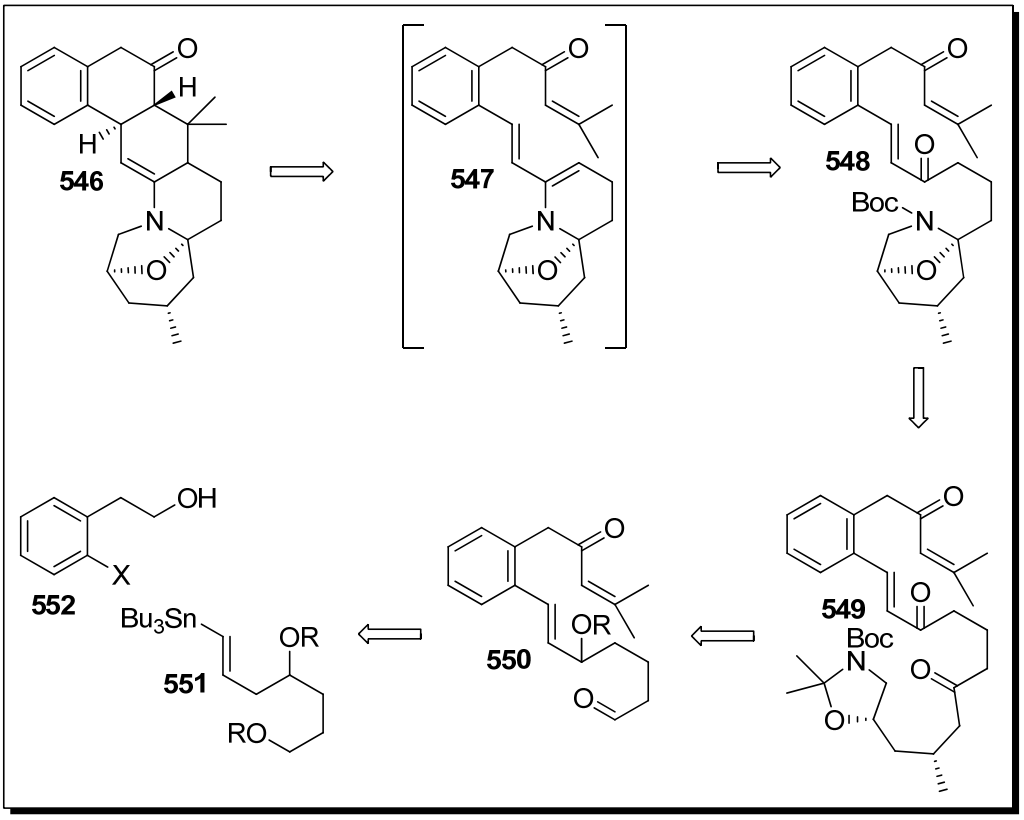
In-light of the problems encountered with this approach to studying the aminal-diene cyclization, we decided to install an internal dienophile. This was designed to increase endo/exo selectivity, and potentially facial selectivity. The proximity of the diene and dienophile systems was also expected to be increased in an intramolecular reaction system, thereby increasing the likelihood of cyclization.

Section 2.5.5 Attempted In Situ Aminal-diene Formation and Intramolecular [4+2] Cyclization

Installation of an internal dienophile allowed us to more accurately assess the viability of the cyclization reaction as applied to our planned zoanthenol (**163**) synthesis. We felt it important to demonstrate formation of the quaternary C22 center

through the intended cycloaddition and therefore planned on building a β-dimethyl enone dienophile (Scheme 2.63). Although methyl substitutions at C9 and C12 were desirable, the increased steric bulk at the reaction centers was expected to hinder our initial studies. It was decided to exclude substitution at these centers until the desired reactivity had been fundamentally proven.

It was believed that the hexacyclic cycloadduct, **546**, could arise from an intermediate aminaldiene such as **547**, which was expected to form through N-deprotection of aminal **548** and subsequent condensation at C10 (Scheme 2.63). We expected difficulties at this stage as we had previously failed to observed conclusive evidence of iminium or aminaldiene formation in the intermolecular model. We were, however, optimistic that an intramolecular cyclization pathway was more prone to occur.

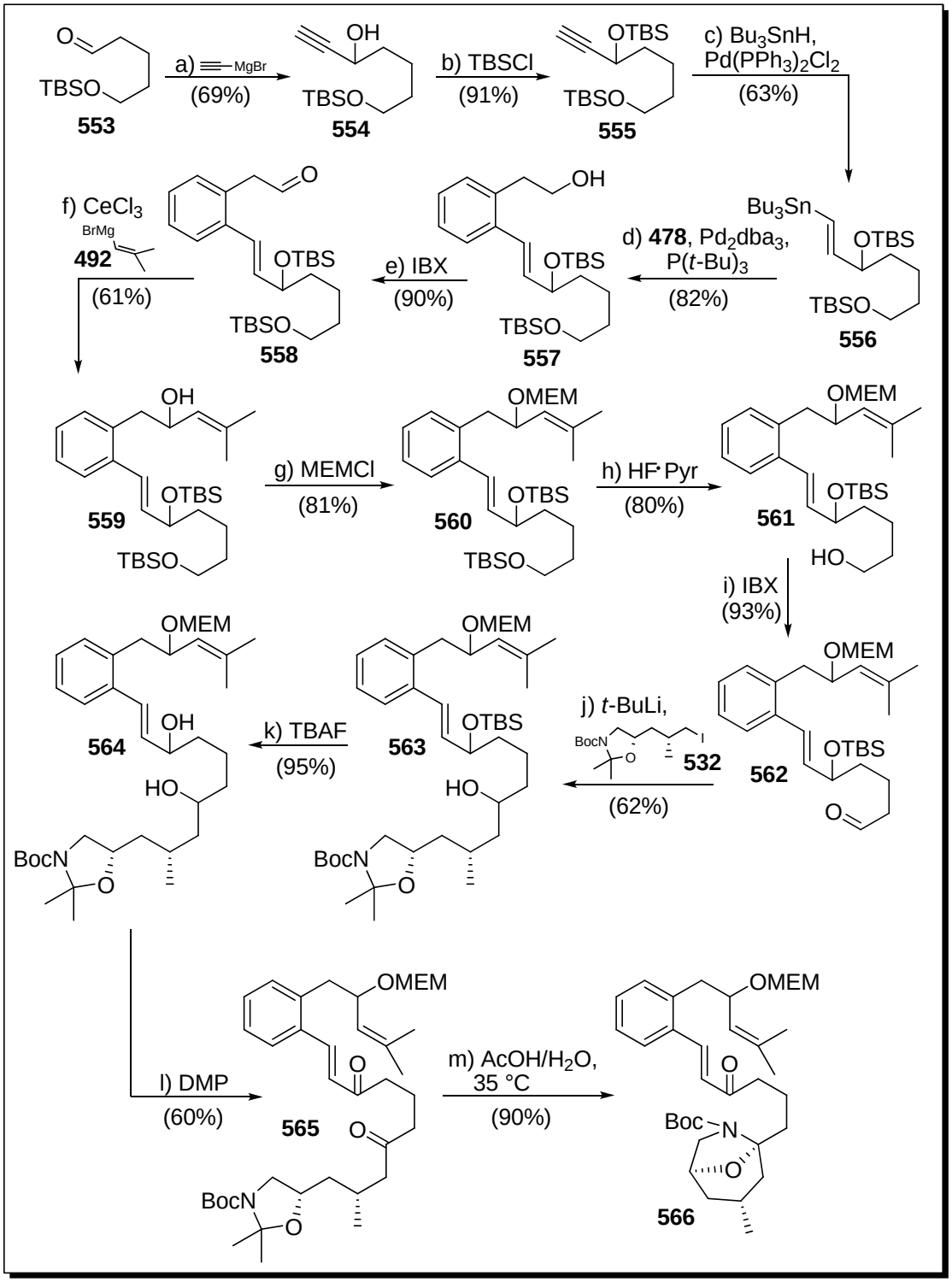


Scheme 2.63 Retrosynthetic analysis of intramolecular aminal cyclization.

We believed the chemistry developed in our intermolecular study for the formation coupling of the C1-C5 fragment could be applied to the synthesis of dienone (**548**). Consequently, we planned to synthesize an aldehyde resembling **550** for the lithiate coupling reaction. It was assumed that the enone functionality would necessarily be masked as a group inert to the highly basic coupling conditions. We also drew on previous experience for formation of aldehyde **550**, deciding to use a Stille coupling to connect aryl bromide **552** and a suitably protected C6-C12 fragment (**551**).

The synthesis of aminal **566** began with mono protection of 1,5-pentane diol[56] and oxidation under Swern conditions to aldehyde **553**[57] as previously reported (Scheme

2.64). Treatment of aldehyde **553** with ethynyl magnesium bromide provided propargyl alcohol **554**. Palladium catalyzed hydrostannylation of propargyl alcohol **555** at low temperature provided a mixture of stannanes. The *E*-stannane (**556**) could be isolated in 63% yield by column chromatography, but it was discovered that the difficult separation could be avoided and the crude stannane mixture was used in the Stille coupling, as only the desired *E*-stannane (**556**) coupled to aryl bromide **478** under the chosen conditions. Oxidation of primary alcohol **557** with IBX to the corresponding aldehyde (**558**) proceeded in high yield without the need of purification. Nucleophilic addition of the requisite organocerium reagent provided allylic alcohol **559** as an inseparable mixture of diastereomers. Protection as the MEM ether and subsequent selective deprotection of the primary TBS group gave alcohol **561** in good yield. IBX mediated oxidation provided the coupling substrate, aldehyde **562**.



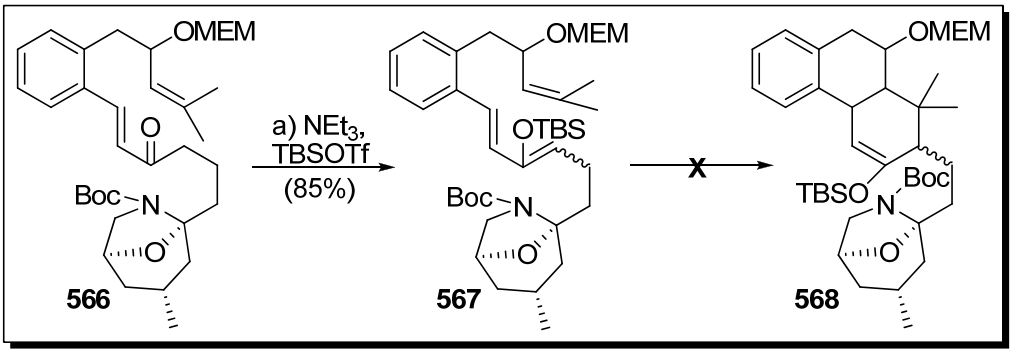
Scheme 2.64 Synthesis of aminal **566**.

Lithiation of alkyl iodide **532** followed by addition of aldehyde **562** gave the desired aminal **563** in 62% yield as a mixture of diastereomers. This reaction returned unreacted aldehyde (**562**) under several different reaction conditions, even when alkyl iodide **532** was used in excess (2 equivalents). Deprotection of the silyl ether with TBAF provided diol **564**, which was oxidized to the diketone (**565**) by Dess-Martin Periodinane. Simultaneous oxidation proved less than ideal, as previously observed in the intermolecular aminal study, and a stepwise process was adopted for subsequent studies.

Gentle heating of aminal **565** in an acetic acid/water (1:1) solution cleaved the acetonide N,O protecting group and provided the rearranged aminal (**566**). We unfortunately did not find conditions for the MEM ether deprotection. We planned to cleave the MEM group with $ZnBr_2$ or bromocatechol borane, feeling the Boc group would be stable to these reagents, but were unable to realize the deprotection with these or any other reagents. A product lacking the MEM group was produced in the acetic acid reaction used to form aminal **566**, and we felt that continued heating in the acetic acid/water solution may have provided the free allylic alcohol. Unfortunately, heating in acetic acid over extended time frames coupled with close reaction monitoring resulted only in complex reaction mixtures. The Boc group unfortunately proved to be more labile than the MEM group under all deprotection conditions attempted.

Reluctant to surrender the valuable material, aminal **566** was converted to the TBS enol ether as an alternative cyclization substrate (Scheme 2.65). The enolate trapping reaction gave a mixture of products tentatively assigned as an *E/Z* mixture (**567**).

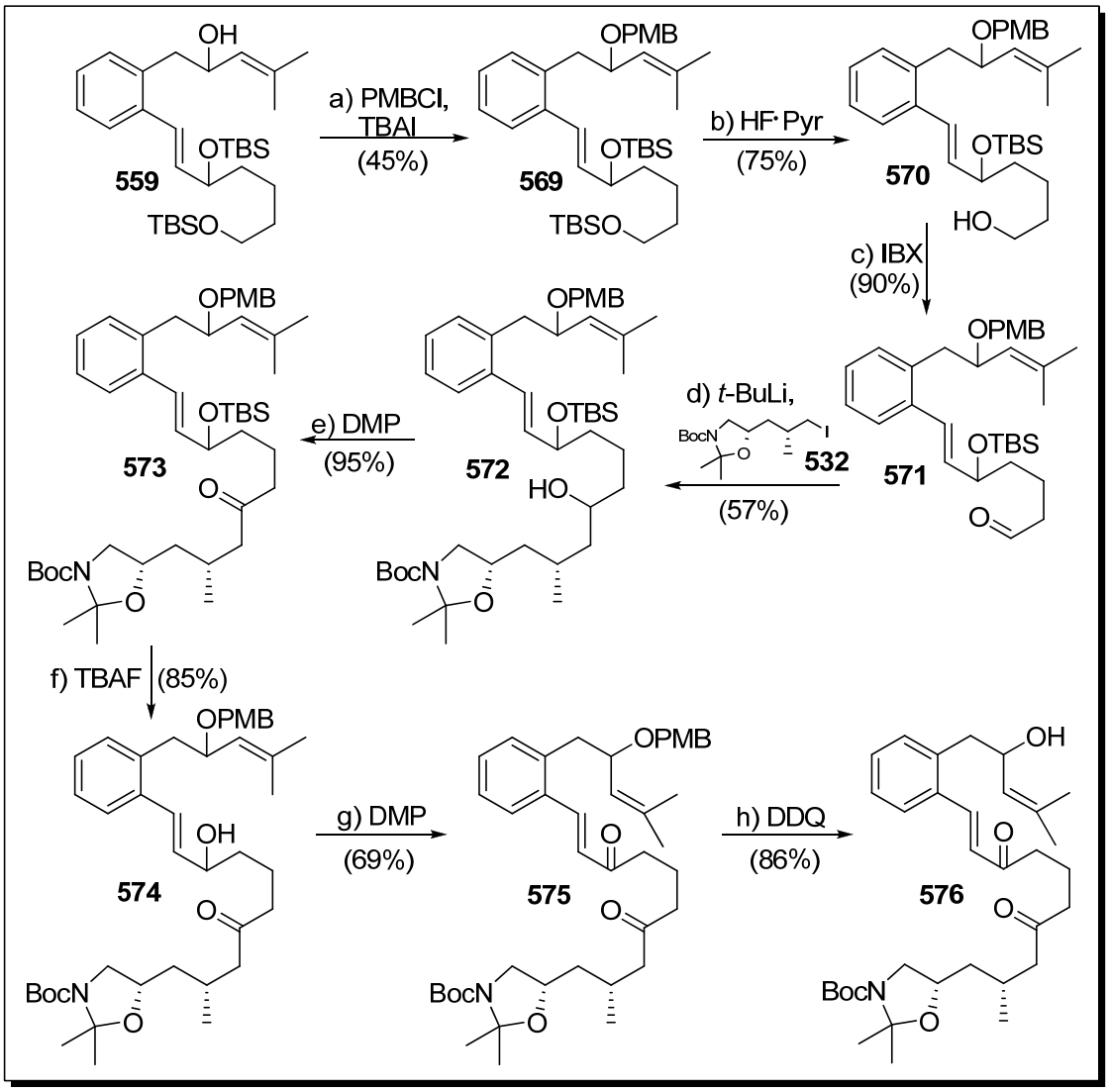
Heating of **567** in deuterated benzene from 100 °C to 205 °C over a period of 40 hours resulted in no discernable spectral (NMR) changes. When a Lewis acid was used, $ZnBr_2$, only decomposition was observed. Efforts to deprotect the MEM group at this stage resulted in decomposition of the silyl enol ether. Although we failed to deprotect the MEM ether and synthesize the desired cycloaddition substrate (**547**), we developed chemistry to advanced intermediates.



Scheme 2.65 Attempted cyclization of silyl enol ether **567**.

Having developed a reliable route to aminal **566**, we decided to utilize the same chemistry with an alternative protecting group at C20 (Scheme 2.66). Allylic alcohol **559** was therefore protected as the PMB ether (**569**) as we felt oxidative cleavage of the C20 protecting group to be compatible with conservation of the Boc functionality. Selective deprotection of the primary TBS ether and oxidation to the corresponding aldehyde (**571**) was achieved in good yield over two steps. Coupling of lithiated alkyl iodide **532** provided aminal **572** in yield similar to that observed for the analogous MEM ether. Oxidation of the C6 hydroxyl group and deprotection of the C10 TBS ether provided allylic alcohol **574** in 80% overall yield. Oxidation of the allylic alcohol

(**574**) with Dess-Martin Periodinane gave diketone **575** in 60% yield under unoptimized reaction conditions.

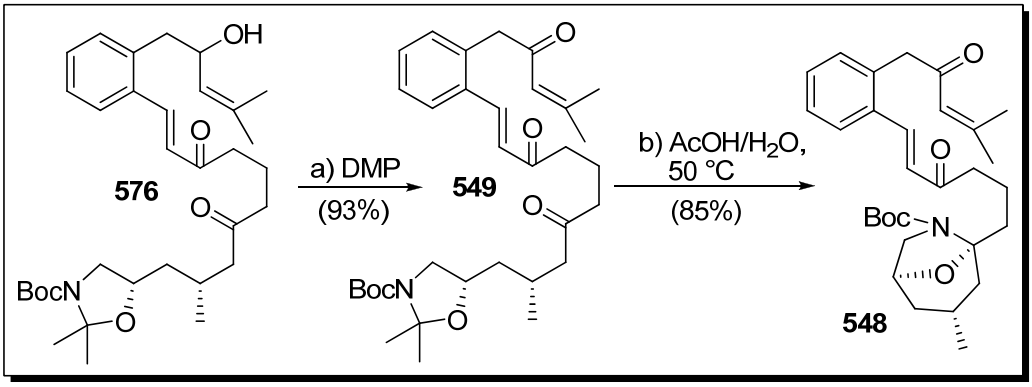


Scheme 2.66 Synthesis of diketone **576**.

We hoped oxidative deprotection of PMB ether **575** would immediately precede a DDQ mediated one-pot oxidation of the allylic alcohol to afford the C20 ketone in a fashion similar to that previously reported for allylic alcohols.[58] While we were unable

to realize the one-pot deprotection/oxidation reaction, DDQ mediated deprotection provided allylic alcohol **576** in 85% yield.

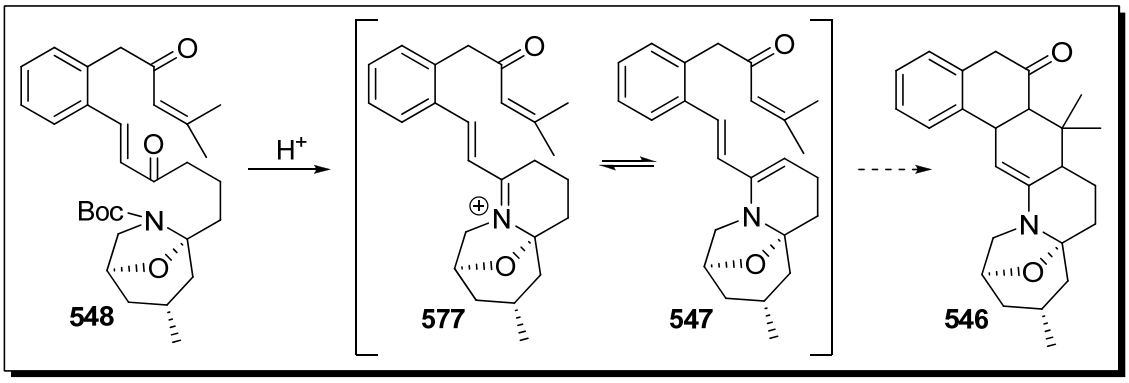
Oxidation of allylic alcohol **576** with Dess-Martin Periodinane gave aminal triketone **549** in excellent yield (Scheme 2.67). Unfortunately, attempts to effect the cycloaddition reaction directly from triketone aminal **549** by heating in acetic acid/water at 100 °C were fruitless. However, heating in acetic acid at a more moderate temperature provided aminal dienone **548** in surprisingly good yield. The deprotection was performed at 50 °C, as we felt the Boc group would be labile in acetic acid/water at higher temperatures, based on the similar Boc deprotection reaction reported by Miyashita and coworkers.[29a]



Scheme 2.67 Synthesis of dienone aminal **548**.

Numerous attempts, employing different methodologies to induce the desired cycloaddition of **548** were unsuccessful. We expected the reaction to follow the pathway depicted in Scheme 2.68. Acid induced Boc deprotection was expected to initiate condensation at C10 and produce iminium **577**. Tautomerization to dienamine

547 and reaction in an intramolecular cycloaddition reaction was considered, but we suspected the equilibrium would remain far towards the iminium form under acidic conditions. Reactions in acetic acid/water at 100 °C clearly cleaved the Boc group, but failed to provide easily isolable products. Neutralization with sodium carbonate or DBU proved unhelpful. It is interesting to note that mass spectroscopic analysis of reactions performed with acetic acid returned a molecular weight consistent with the iminium ion (378.2), as the major product. This mass happens to correspond to [M+H] for the predicted enamine, as well as the cycloadduct. Regardless of what it actually represented, the MS data strongly suggested the Boc group had been cleaved and an oxygen atom had been lost, both consistent with our proposed route (Scheme 2.68).

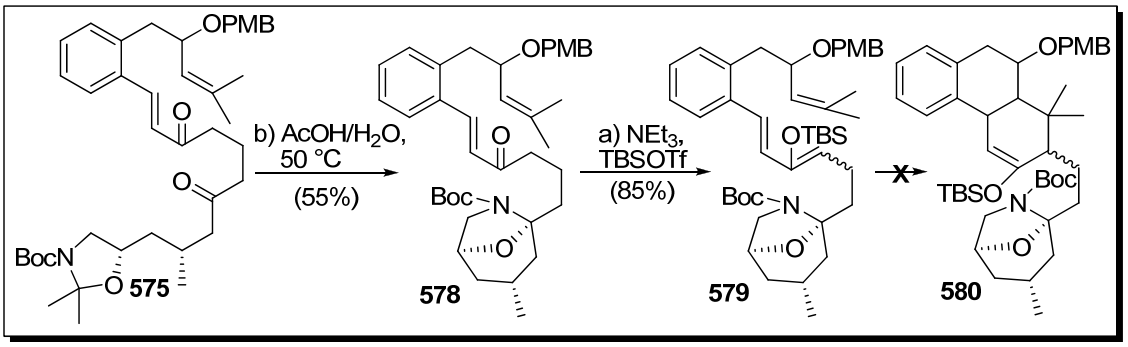


Scheme 2.68 Proposed acid induced cyclization pathway.

Stronger acids such as HCl, TSOH, and TFA, failed to provide an isolable product, as did PPTS. Having previously observed Boc cleavage from exposure of Boc aminal **566** to $ZnBr_2$, an attempt to utilize the Lewis acid as a Boc cleavage reagent and subsequent cycloaddition catalyst was unsuccessful. As with the intermolecular

approach to aminal diene cyclization, interception of the iminium intermediate (**577**) by reduction with sodium cyanoborohydride was not successful.

As with the corresponding MEM ether, PMB ether **578** (derived from transaminalization of **575)** was converted to the silyl enol ether (**579**) in order to ascertain it's suitability as a cycloaddition substrate (Scheme 2.69). Treatment of the *E/Z* mixture (**579**) dissolved in deuterated benzene at 185 °C, in a sealed NMR tube over 13 hours, generated no reaction. Continued heating at 250 °C resulted in decomposition within a few hours. In consideration of the fact that silyl enol ether **503** underwent an efficient intramolecular cycloaddition reaction, we felt the dienophile of aminal **579** needed to be activated as the corresponding enone. We sought to cleave the PMB ether of **579** and oxidize the resultant allylic alcohol to the corresponding enone. Unfortunately, all attempts at PMB deprotection lead to decomposition of the silyl enol ether functionality.



Scheme 2.69 Attempted cyclization of silyl enol ether **579**.

The root cause of the failed aminal diene (**547**) cyclization attempts was not established. However, we have considered the possibility that the aminal diene tautomer (**547**) was never formed under the reaction conditions explored. We expected the iminium form (**577**) to predominate under acidic conditions as previously demonstrated by the Kobayashi, Hirama, and Miyashita groups.[14,19,29] Yet, we were unsuccessful in attempts to isolate the intermediate iminium or aminal diene by neutralization and iminium reduction with sodium cyano borohydride. It is possible that acid catalyzed enolization of the C20 ketone could have prompted a conjugate addition at the activated C12 β carbon of the iminium functionality, as we have observed similar pyran rings to be stable (Schemes 2.47 and 2.51).

We have also speculated that the iminium/dienamine (**547**/**577**) compound may have been produced and undesired reactivity, more favorable than the desired cycloaddition, immediately followed. For instance, it is possible that the iminium was trapped by an acetate molecule in the reactions utilizing acetic acid. The reactions demonstrated by Kobayashi,[14] Hirama,[19] and Miyashita[29] involved iminium formation followed by nucleophilic attack of an internal nucleophile at C10 to form the D ring upon neutralization. It is therefore plausible that C10 attack of an acetate molecule has occurred at C10 of iminium **577**.

Additional conjecture involves imine formation at C6. Perhaps the conjugation inherent in the aromatic enone system (C10-C18) thwarted the condensation of the free amine at C10. A lower energy route may have involved imine formation at C6 and opening of the F ring to give the free C2 alcohol. This particular idea may have

precedent. The Williams research group performed a similar reaction with a proposed intermediate iminium similar to our expected intermediate, but was unable to isolate the desired D ring adduct although an internal nucleophile was present (Scheme 2.7)[22b], as in the case of work reported by Kobayshi,[14] Hirama,[19] and Miyashita[29].

We also considered that the dienophile was possibly too hindered at C22 and was not sufficiently electronically activated. Though aminal diene **547** may have been formed, it is suspected that the withdrawing effect of the C6 aminal position would mitigate the nucleophilicity of the C9 enamine. If this supposition is true, the diene system would not have the activation we hoped for of a dieneamine system.

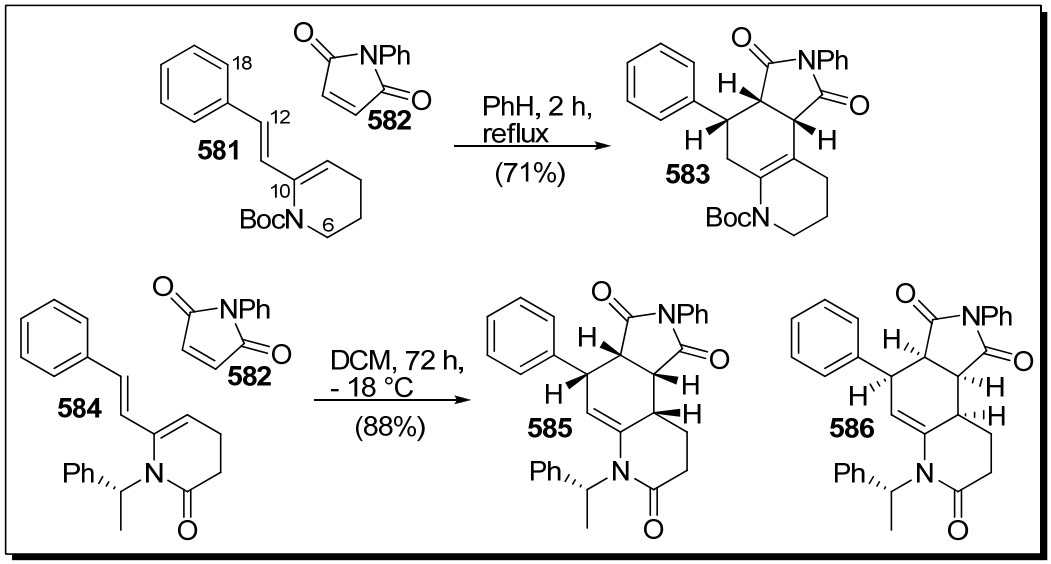
We sought to explore the question of dienophile activation and dienamine deactivation through more predictable chemistry. To this end we decided to work with substrates with unambiguous and easily characterizable dienamine functionalities, as well as substrates designed to probe the level of necessary dienamine nucleophilicity/activation.

Section 2.5.6 Intermolecular [4+2] Cyclizations of Carbamate and Amide stabilized 2-Amino-1,3-Dienes

Based on the inconclusive results of previous reactions and failure to confirm 2-amino-1,3-diene formation in any cases, we opted for an approach which allowed unambiguous construction of the 2-amino-1,3-diene moiety. The reactivity inherent in enamines which makes them prone to undesired hydrolysis and polymerization reactions can be mitigated by introducing conjugation with π systems. For instance,

many indoles are air stable and easily handled due to conjugation of the aromatic ring. The ability of the enamine nitrogen to donate electron density to the enamine olefin can be diminished by attachment of electron withdrawing groups α to the nitrogen atom. Removal of electron density from the enamine system, while stabilizing the enamine functionality, was expected to render the enamine less nucleophilic and presumably less reactive. However, a search of the literature revealed N-carbamate and N-acyl dienamines capable of cyclizing in a [4+2] manner with activated dienophiles. Moreover, in contrast to unstabilized enamines and dieneamines, the stabilized 2-amino-1,3-dienes appeared to be stable to typical work up and purification techniques such as aqueous extraction and silica chromatography.

Examples of stabilized dienamine systems resembling the C6-18 fragment of zoanthenol (**163**) have been reported to behave well as dienes in [4+2] reactions (Scheme 2.70). For example, in 2000 Occhiato and coworkers reported cyclization of N-Boc stabilized 2-amino-1,3-diene **581** with an activated dienophile, N-phenyl maleimide (**582**).[59] The endo cycloadduct (**583**) was isolated in good yield (71%) from the cyclization of **581** and **582**. The fact that the direct cycloadduct containing a C10-C11 olefin was not isolated is worthy of note as isomerization of the olefin to C9-C10 offers the possibility for functionalization at C9. The cycloaddition reportedly occurred in a short time frame (2 hours) in concentrated refluxing benzene. Furthermore, the diene was ostensibly stable to typical organic laboratory methods although decomposition to the ring-opened C10 enone was observed upon standing in chloroform solutions



Scheme 2.70 Carbamate and amide stabilized 2-amino-1,3-diene cyclizations from the Occhiato group.

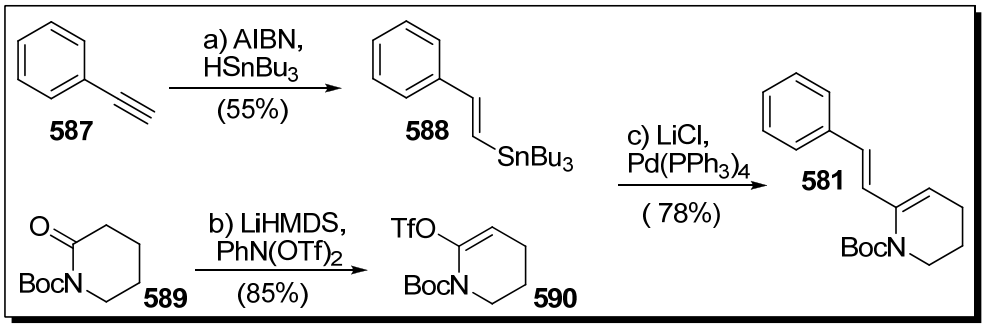
The Occhiato research group has also the reported the cyclization of N-acyl-2-amino-1,3-dienes with phenyl maleimide (**582**) (Scheme 2.70).[60] Chiral diene **584** produced a mixture of endo cycloadducts (**585** and **586**), as well as small amounts of exo cycloadducts, when treated with **582** in cold methylene chloride for extended time periods. After recrystallization, cycloadduct **586** was isolated in 61% yield. The amide (**584**) reactivity was particularly exciting as the carbonyl functionality at C6 provided a potential handle for further functionalization leading to the F and G ring system of zoanthenol (**163**). We were also pleased to see that the remote chiral center induced some facial selectivity. Another aspect of significance to us was the fact that the stabilized diene synthons were both assembled via palladium mediated cross coupling reactions which allowed for diene formation under neutral or basic conditions.

We were also encouraged by additional reports of N-carbamate-2-amino-1,3-diene cycloadditions[61], as well as other reported N-acyl-2-amino-1,3-diene cyclizations.[62] Most of the reports involved highly activated dienophiles such as maleimides, maleic anhydride, fumarates, and maleates, with endo products predominating. In addition to the intermolecular cycloaddition reactions of N-stabilized-2-amino-1,3-dienes, two intramolecular reactions of N-carbamate stabilized 2-amino-1,3-dienes were discovered in recent literature reports.[63]

We were curious as to whether N-stabilized-2-amino-1,3-dienes retained sufficient enamine nucleophilicity to effect stepwise cyclizations as is assumed of some N-alkyl-2-amino-1,3-dienes[39,40] previously discussed. We also felt the simplicity and synthetic brevity of the diene substrates would have allowed us to rapidly build analogs with substitution at C9 and/or C12 to probe the effect of increasing steric hindrance within the diene system, as well as investigating steric effects of dienophiles. Initial research involved solvent studies, with the hope that polar solvents may have allowed us to observe linear Michael (single addition) adducts and/or cycloadducts containing stereochemistry impossible to achieve from concerted mechanisms.

N-Boc-stabilized-2-amino-1,3-diene (**581**) synthesis was achieved by a palladium mediated cross coupling of reported stannane **588** and a N-Boc lactam derived vinyl triflate (**590**) (Scheme 2.71). Stille coupling of stannane **588** and vinyl triflate (**590**) provided the diene (**581**) in yields similar to the Suzuki coupling of a styryl boronic ester and vinyl triflate **590** reported by Occhiato and coworkers, as well as identical spectral data.[64] Stannane **588**[65] and vinyl triflate **590**[66] were prepared as previously

reported from phenyl acetylene (**587**) and Boc protected valerolactam (**589**), respectively. We were happy to find diene **581** easily characterized and stable to silica chromatography.

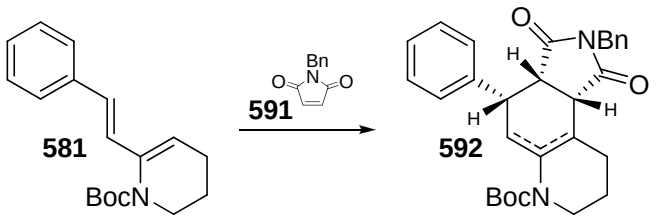


Scheme 2.71 Synthesis of stannane **581**.

As previously reported, we found diene **581** a capable [4+2] diene when reacted with N-protected maleimide (**591**) (Table.20). Cycloaddition was accompanied by olefin isomerization from C10-C11 to C9-C10 of the cycloadduct in some cases. We were also pleased when a solvent effect was observed in the cycloaddition of diene **581** and N-benzylmaleimide (**591**) (Table 2.0).[67] Reactions performed at room temperature displayed a loose correlation between relative solvent polarity and reaction rate, with increased solvent polarity resulting in reduced reaction times. It was also interesting to observe rapid reactions in protic solvents such as methanol and trifluoroethanol, as we expected some degree of diene decomposition under protic conditions. Although no intermediates (single Michael addition adducts) were isolated or observed, we initially felt the correlation to solvent polarity suggested a polarized diene transition state. Other researchers have observed similar polarity effects, particularly when protic solvents

were used in catalytic amounts, as co-solvents, or as the lone solvent.[68] Explanations of this effect generally involve the concept of diene and/or dienophile activation through stabilization of developing charges at reactivity centers. The argument is supported it part by computational studies[68b] which indicated protic solvents can act as Lewis acids by activating enone dienophiles toward cycloaddition reactions through hydrogen bonding.

Table 2.0 Effect of Solvent on the cyclization of **581** to **592**.



Solvent	Time (25 °C)	Yield	Time (90 °C)	Yield
TFE	7h	95%	1.5h	99%
MeOH	9h	99%	2h	99%
DMSO	9h	91%	2h	90%
DMF	12h	88%	2h	85%
DME	12h	80%	2h	78%
Dioxane	12h	79%	2h	76%
CH_3CN	18h	87%	2h	87%
$CHCl_3$	100h	88%	6h	90%
C_6H_6	154h	90%	9h	89%

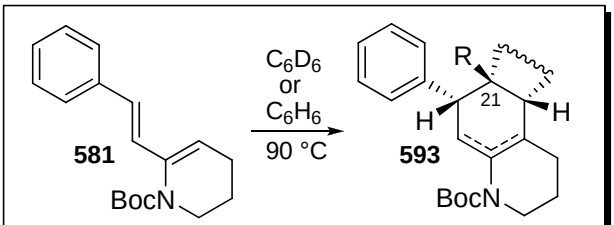
The solvent effect was unfortunately not general. Diene or dienophile decomposition was observed in many cases when additional dienophiles were screened.[67] In summary, when more sterically hindered or less activated dienophiles were studied, alternative reaction pathways involving reactions of diene **581** and/or dienophiles with the solvent predominated. For instance, use of maleic anhydride as a dienophile in protic solvents resulted in poor yields of cycloadduct **593b** (Table 2.1).

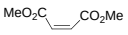
However, high yields of the maleic anhydride cycloadduct (**593b**) were achieved when benzene was used as a solvent.

We also learned that substituents on the dienophile olefin decreased isolated yields. Methyl substitution of maleic anhydride (Table 2.1, entry c) reduced cycloadduct yield relative to maleic anhydride in benzene. The same trend was found to be true for naphthoquinone (Table 2.1, entry d) and methyl-naphthoquinone (Table 2.1, entry e). Although we observed decreased reactivity with substituted dienophiles, we did learn that all isolated cycloadducts fit the expected regiochemical outcome, with the dienophile alkyl substitution (methyl groups) at the C21 position.

This study also revealed that less activated dienophiles such as methyl vinyl ketone (Table 2.1, entry f) did not cyclize in refluxing benzene or other standard solvents. However, a mixture of cycloadduct **593f** isomers was obtained when the cycloaddition of **581** and methyl vinyl ketone was performed in ethylene glycol at 80 °C.[67] In the course of this study, diene **581** was demonstrated capable of facile cycloaddition reactions with highly activated dienophiles. Only endo adducts were isolated and the expected regiochemistry was typically observed. Additionally, isomerization of the C10-C11 olefin of the cycloadducts to the C9-C10 position occurred in a seemingly random fashion.

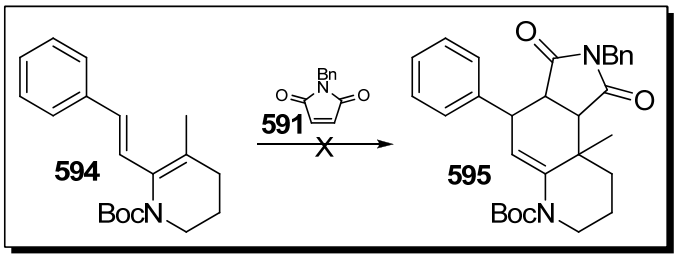
Table 2.1 Cycloaddition reactions of diene **581** with various enone dienophiles.



Entry	Dienophile	Time	Yield #
a		48h	82%
b		7h	88%
c		48h	51%
d		48h	48%
e		52h	28%
f		6h	50%

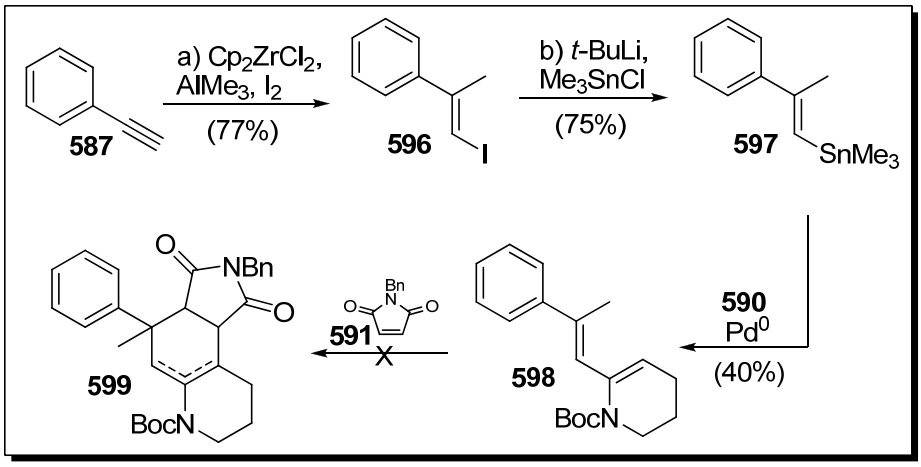
*ethylene glycol

Having observed a steric effect with substituted dienophiles, we became curious as to whether diene substitution would inhibit cyclization reactions. Unfortunately, cyclization reactions of benzylmaleimide (**591**) and substituted diene **594** were unsuccessful under a variety of conditions (Scheme 2.72).[67]



Scheme 2.72 Attempted cyclization of diene **594** with maleimide **591**.

We also tested the effect of diene substitution at C12. Synthesis of diene **598** began with methyl-alumination of phenyl acetylene followed by an iodine quench as reported by the Wipf research group.[69] This sequence gave vinyl iodide **596** in 77% yield. Lithium-halogen exchange and exposure to Me_3SnCl gave stannane **597** as reported by the Curran research group (Scheme 2.73).[70] Coupling of **597** with vinyl triflate **590** gave diene **598** in an unoptimized yield of 40%. Unfortunately, cycloaddition reactions between diene **598** and maleimide **591** were unsuccessful under our standard conditions, refluxing methanol or benzene as well as in a variety of other solvents. When more forcing conditions were applied, (sealed tube reactions at higher temperatures) decomposition was observed without clear indication of cycloadduct **599** formation.

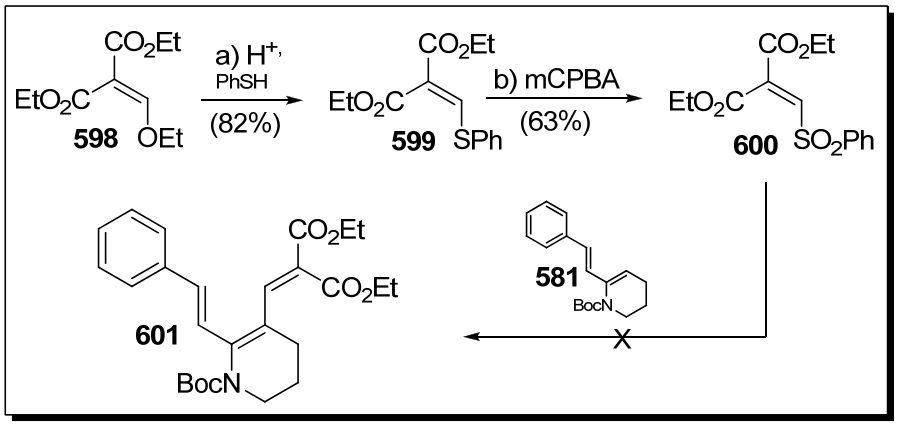


Scheme 2.73 Attempted cyclization of diene **599** with maleimide **591**.

The reactions with diene **581** taught us that activated or highly activated dienophiles were necessary for [4+2] addition under thermal conditions, and methyl substitution at any of the reaction centers hindered or prevented cyclization. We had hoped that

increased substitution, particularly at the β position (C12) of the diene, would have allowed potentially us to isolate a Michael addition intermediate as we felt the second Michael addition would be slowed by increased substitution at the Michael acceptor. This hope was not realized, and we observed no evidence that the reactions followed a consecutive conjugate addition pathway. A final attempt to induce a conjugate addition from the N-Boc-2-amino-1,3-diene (**581**) was attempted.

We felt an enone dienophile with a β leaving group may have allowed us to isolate a linear Michael adduct (Scheme 2.74). To this end, the reported vinyl sulfone (**600**) was prepared as described from diethyl malonate derivative **598**.[71] Treatment of **598** with catalytic toluenesulphonic acid and excess thiophenol gave sulfide **599**, which was easily oxidized to the corresponding sulfone (**600**) with mCPBA.



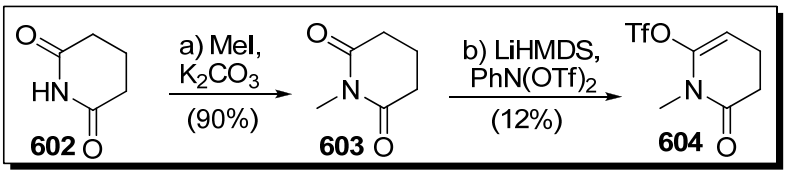
Scheme 2.74 Attempt at single Michael adduct trapping.

We were curious if stabilized dienamine **581** retained enough nucleophilic character to add to sulfone malonate **600** and displace the sulfone moiety in an addition-

elimination sequence. Unfortunately, neither the desired linear Michael adduct, **601**, nor the [4+2] cycloadduct was obtained from reaction of the stabilized dienamine (**581**) and sulfone (**600**).

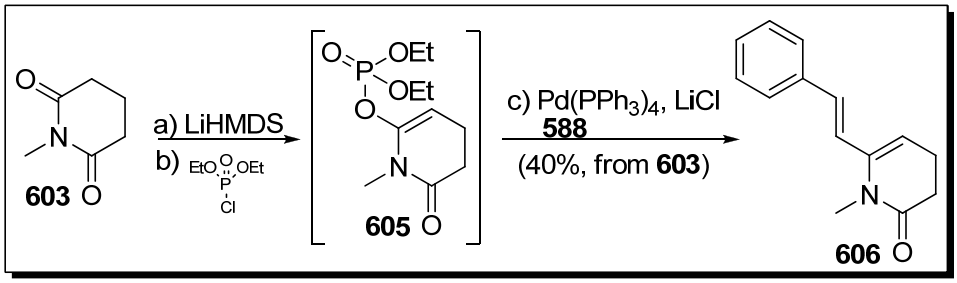
Having explored the reactivity of the N-Boc-stabilized-2-amino-1,3-diene (**581**), we turned our attention to construction of a corresponding amide diene to further probe cyclization reactivity. The Stille coupling had proven a reliable method for formation of the dienamine functionality in the construction of diene **581**, and we felt it prudent to continue with proven chemistry.

However, construction of the desired amido-vinyl triflate (**604**) proved problematic (Scheme 2.75). Glutarimide (**602**) was N-alkylated with methyl iodide as previously described, and provided N-methylglutarimide (**603**) in good yield.[72] Formation of the corresponding triflate (**604**) under the conditions utilized to construct vinyl triflate **590** was realized in 12% yield. No improvement was observed when alternative triflating reagents were evaluated. This finding is consistent with the observation for a similar N-alkylglutarimide published by Jotham Coe.[73] Coe reported yields below 10% when trapping of a lithium N-alkylglutarimide enolate was attempted with several triflating reagents.



Scheme 2.75 Synthesis of vinyl triflate **604**.

However, Coe was able to trap the N-alkylglutarimide enolate as an enolphosphonate and subsequently perform a palladium-mediated Heck reaction. Quantitative conversion to the enolphosphonate and isolation by simple solvent evaporation under an inert atmosphere was reported. Inspired by the Coe report, we explored the enolphosphonate chemistry with our N-alkylglutarimide system. Initial attempts at isolation of the enolphosphonate, **605**, proved problematic. Although reaction aliquots analyzed by NMR strongly suggested the desired product had been formed, attempted isolation provided only the starting material (**603**), presumably due to hydrolysis of **605**. In response to this problem, a one pot procedure was developed for the coupling of enolphosphonate **605** and stannane **588**, thereby circumventing the problematic isolation (Scheme 2.76). Low temperature enolization of **603** in THF with LiHMDS and subsequent addition of diethylchlorophosphate gave intermediate **605**. The solution was warmed to room temperature and stannane **588**, lithium chloride, and $Pd(PPh_3)_4$ were rapidly added.



Scheme 2.76 Synthesis of enol-phosphonate **605** and coupling with stannane **588**.

Stirring at reflux several hours typically provided amide-stabilized dienamine **606** in 35-40% yield after hurried silica chromatography. In this manner, diene **606** was

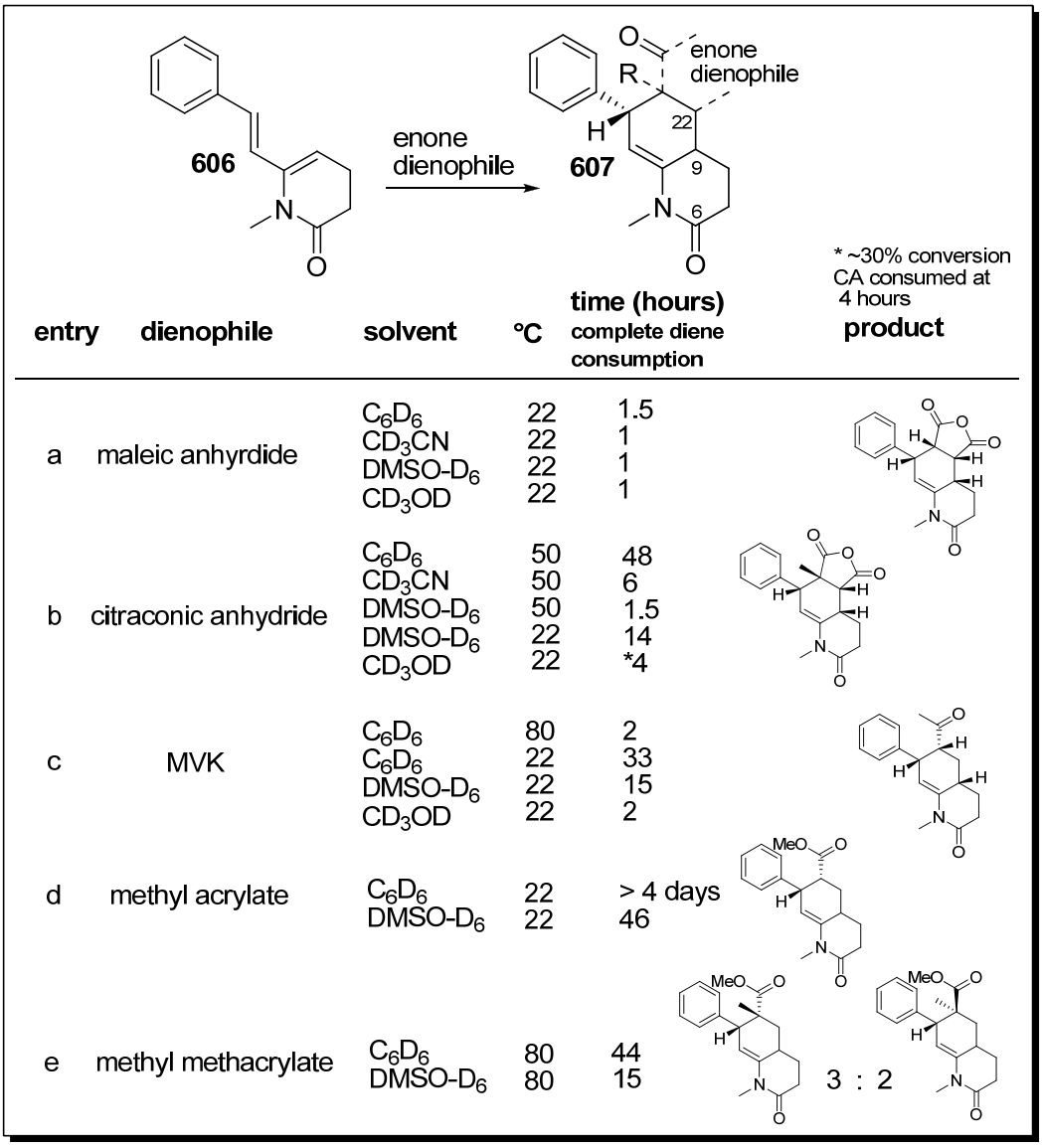
constructed in a total of three reactions beginning from commercially available glutarimide (**602**) and phenylacetylene (**587**).

The viability of 2-amido-1,3-dienamine **606** as a cycloaddition partner was explored through reactions with a variety of dienophiles. Our approach to zoanthenol (**163**) required an enone dienophile and we therefore screened a number of enone cycloaddition partners to assess associated dienophile steric and electronic effects, as well as regioselectivity (Table 2.2). We were surprised to observe good reactivity with a broader range of dienophiles than observed for N-Boc-stabilized-2-amino-1,3-diene **581**. When between two and 4 equivalents dienophile were used, entries a through e provided products isolated in 70-90% yields in relatively short time frames.

Cyclization with maleic anhydride to **607a**, judged by complete consumption of diene **606** according to NMR analysis, occurred in less than 1.5 hours in methanol, dimethylsulfoxide, acetonitrile, and benzene at room temperature. The corresponding reaction of N-Boc-stabilized-2-amino-1,3-diene **581** required 7 hours in refluxing benzene. Increased dienophile bulk slowed the cyclization, as demonstrated by the reaction performed with citraconic anhydride (Table 2.2, entry b). The citraconic anhydride reaction was complete in 14 hours when performed at room temperature in DMSO, but required heating with other, less polar, solvents to access useful reaction times. Heating at 50 °C in DMSO reduced the reaction time to 1.5 hours and reactions in benzene at this temperature were judged complete within 48 hours. Decomposition of citraconic anhydride with methanol or trifluoroethanol as solvents was observed at room temperature and 50 °C. In methanol at room temperature, diene conversion to

607b was judged at approximately 30% after 4 hours, at which time the citraconic anhydride had been completely consumed. The decomposition pathway of citraconic anhydride with methanol involving ring-opening-monoesterification under neutral conditions has been previously documented by other reasearchers.[74] Regardless of the solvent or temperature, only the endo adduct containing the predicted regiochemistry was isolated. Single crystal x-ray analysis of **607b** confirmed the structural assignment of **607b** made by 2D NMR techniques. All other major cycloadducts displayed similar 2D NMR results, and have been assigned as endo cycloadducts.

Table 2.2 Reactivity of diene **606** with various dienophiles.



Reaction with methyl vinyl ketone, a less activated enone, also proved facile. As observed with the anhydride dienophiles, only the endo adduct containing the predicted regiochemistry (**607b**) was isolated. A similar rate trend was also observed, with rapid reaction in methanol at room temperature (2 hours) compared to more sluggish reaction

in benzene at the same temperature (33 hours). Heating at 80 °C in benzene decreased the reaction time to 2 hours, but did not change exo/endo or regioselectivity as compared to room temperature reactions. The cyclization with methyl vinyl ketone in DMSO, benzene, and methanol at room temperature was exceptionally interesting as the cyclization of N-Boc-diene **581** with methyl vinyl ketone failed in refluxing benzene.

Cyclization attempts of N-Boc-diene **581** with acrylates were unsuccessful. However we observed cyclization of N-amide diene **606** with methyl acrylate (Table 2.2, entry d) and methyl methacrylate (entry e). Room temperature reactions in DMSO and benzene required 46 hours and greater than 4 days, respectively, to reach completion. In addition to the endo cycloadduct, formation of a trace amount of a product tentatively identified as the exo isomer was observed. The diastereomeric product ratio did not change when the reaction was performed at 80 °C in DMSO.

Reactions with methylmethacrylate required heating when performed in DMSO or benzene. In this case, a mixture of endo/exo isomers was obtained. The solvent did not affect the endo selectivity, as very similar product ratios were obtained from reactions in DMSO and benzene. The reduced endo selectivity associated with acrylates has been reported[74] and we attribute this phenomenon to decreased secondary orbital interactions due to the delocalization of electron density associated with esters relative to ketones and anhydrides. As with other enones, only the predicted regiochemistry was observed.

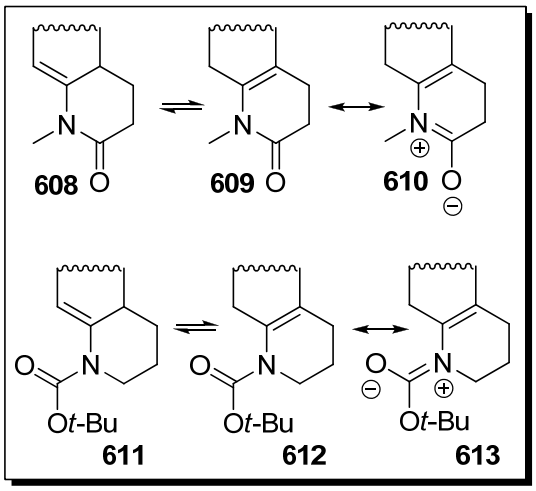
Strong regioselectivity was observed for all reactions with N-Amide-diene **606**. We ascribe this to the polarization of the diene, as bond formation between the electron-rich diene C9 and electron-poor dienophile C22 was expected to be favored.

We also observed decreased reaction rates with increased dienophile substitution (Table 2.2, entries b and e). Reactions with mesityl oxide (4-methylpent-3-en-2-one) and 2,3-dimethylmaleic anhydride, designed to demonstrate formation of a quaternary C22 position, proved problematic. Forcing conditions (high temperatures and sealed tubes) were necessary to observe reaction with these hindered dienophiles, and only complex mixtures were obtained. This was a disappointing discovery as we intended to form a quaternary center (C22) through an intramolecular dienamine cyclization.

Another interesting observation was the lack of olefin isomerization from C10-C11 to C9-C10 in the amide products, although commonly observed in the N-Boc-dieneamine reactions. Rapid decomposition to a complex mixture was observed when isomerization of the maleic anhydride adduct (**607a**) was attempted by room temperature solvation with deuterated chloroform. This is in contrast to the N-Boc-dieneamine adducts, as clean isomerization was commonly induced under this condition. Decomposition during silica chromatography was also extensive for the **607** cycloadducts.

We do not currently have an explanation for the failure of olefin isomerization to a more substituted position. However, we have speculated that a cyclic enamide structure containing an endocyclic olefin (C9-C10) could induce ring strain as the resonance

structure of the amide creates partial olefin character between the nitrogen and C6 carbonyl (Scheme 2.78). Resonance form **610** contains a conjugated cyclohexyl diene system, which would necessarily perturb the typical valerolactam bond angles. Perhaps this particular resonance form was responsible for increased reaction rates relative to the N-Boc-dienamines. Strain associated with the resonance form would limit the electron-withdrawing effect of the amide carbonyl, and presumably reduce stability of the dienamide system. If significant in the reactive diene, the strained resonance form could potentially have been relieved through cyclization. This presumably would have been manifested through increased reaction rates.



Scheme 2.77 Tautomeric and resonance forms of enamide **608** and enecarbamate **611**.

The analogous resonance form of the N-Boc-diene adducts (**613**) would not create a transient endocyclic double bond, but rather an exocyclic bond. Experiments involving cycloaddition with an analogous acetamide diene system (exocyclic amide) and subsequent olefin isomerization experiments could shed light on this proposal.

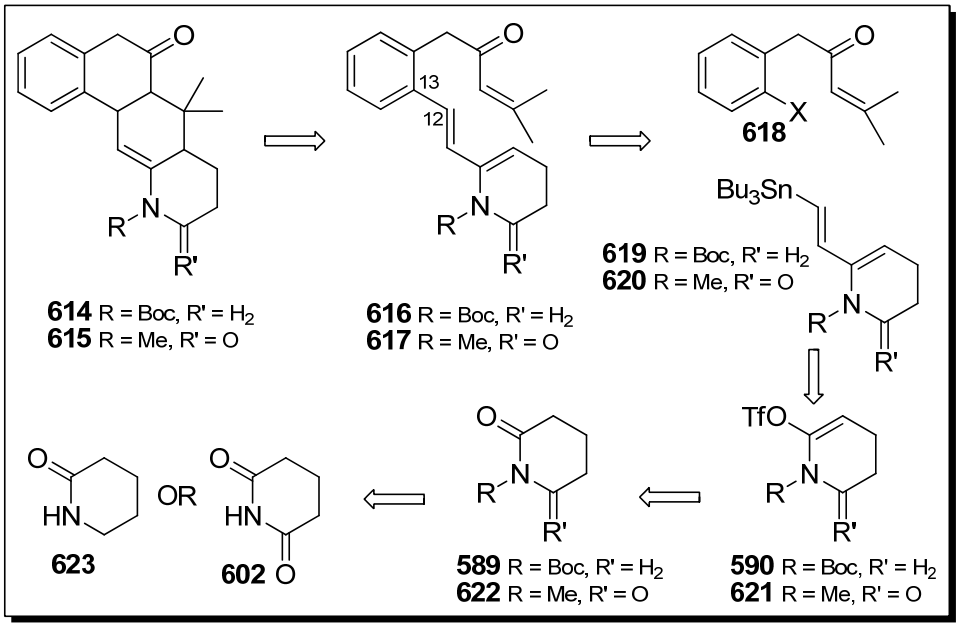
It is worthy of note that carbamate vinyl triflate **590** was isolated in good yield and could be stored for extended time periods in the absence of acid. The corresponding amide vinyl triflate (**604**) was isolated in only 12% yield and decomposed completely within several days when stored at -30 °C.

In summary, both carbamate and amide stabilized-2-amino-1,3-dienamines exhibited cycloaddition reactivity. Dienophile activation as an enone, anhydride, or maleimide was necessary. Diene decomposition, particularly with the carbamate-stabilized dieneamine, frequently occurred in reactions with less activated dienophiles as heating for extended time periods was typically necessary. We were also unable to set a C22 quaternary center with these diene systems.

Section 2.5.7 Intramolecular [4+2] Cyclizations of Carbamate and Amide stabilized 2-Amino-1,3-Dienes

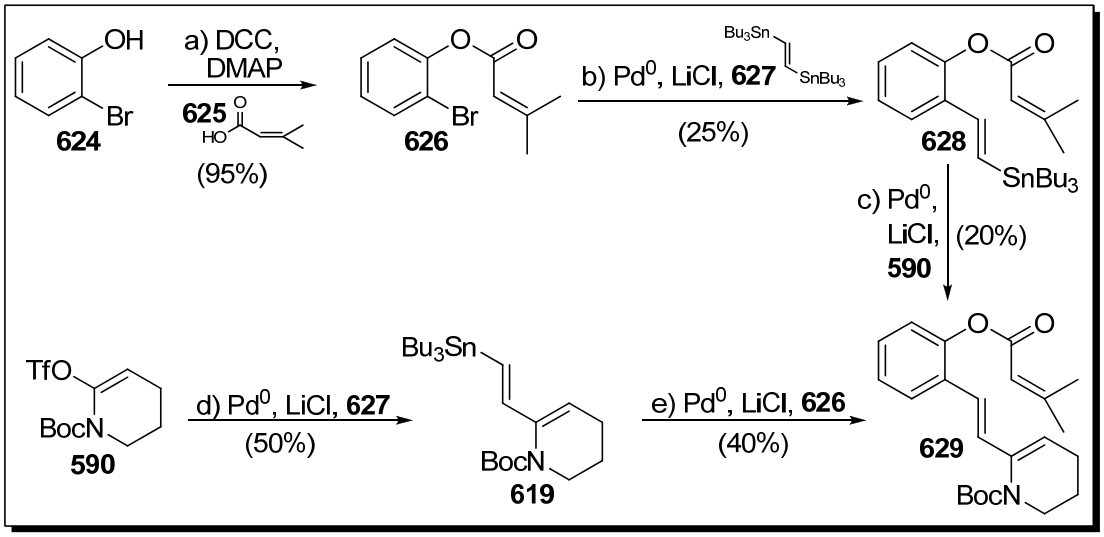
We continued studies with stabilized dienamine systems to ascertain the practicality of their use in intramolecular cycloaddition reactions. We considered intramolecular reactions likely to increase diene and dienophile proximity, and thereby allow the use of less activated and more sterically hindered dienophiles. Additionally, we felt cyclization of a C6 amide would justify the reaction as an approach to the synthesis of zoanthamide (**165**). The E ring of zoanthamide (**165**) contains a C6 amide and N-alkyl substitution, just as in our proposed cycloadduct. We also felt it was important to maintain continuity with the intermolecular studies and compare reaction rates.

We felt tetracyclic cycloadducts **614** and **615** could have arisen from triene systems **616** and **617** (Scheme 2.79). We planned to form the important C12-C13 bond as previously done in the initial zoanthenol (**163**) studies (Section 2.5.2) through a palladium-mediated cross coupling reaction utilizing aryl halide or aryl triflate **618** as a common intermediate for each substrate. We planned to construct stannane **619** from the easily accessible vinyl triflate **590** through a Stille coupling with a 1,2-bis-trialkyltin ethene moiety. A similar approach for the amide analog (**620**) was planned, although we understood the vinyl triflate (**621**) would have most likely been replaced by a phosphonate functionality, based on results from the intermolecular studies. We planned to build the vinyl triflate and/or vinyl phosphonate coupling partners (**590**/**621**) as previously described (Section 2.5.6).



Scheme 2.78 Retrosynthetic plan for stabilized diene intramolecular cyclizations.

We devised a plan outlined in Scheme 2.80 with the aim of addressing whether or not IMDA reactions would render, otherwise unreactive dienophiles capable of the thermal cycloaddition with stabilized dienamines. We had previously determined acrylates to be insufficiently activated to react with a N-carbamate stabilized dienamine (**581**) under typical thermal Diels-Alder conditions and felt pursuing an analogous intramolecular reaction could provide insight into diene/dienophile reactivity thresholds. Consequently, we devised a simple synthetic route for rapid development of triene **629**. 2-Bromophenol (**624**) was coupled to β-disubstituted acrylic acid (**625**) to provide acrylate **626** with excellent efficiency. Coupling of acrylate **626** and trans-1,2-Bis(tri-n-butylstannyl)ethylene (**627**) provided stannane **628** in poor yield (25%). Although stannane **628** was the only compound isolated from two reaction attempts, we did not have a clear explanation for the low yield. We felt the use of excess **627** would limit the amount of Heck adduct and curb dimerization of **628** and **626**. Nonetheless, the coupling of **628** and vinyl triflate **590** was evaluated. The reaction produced the cyclization substrate, triene **629** in low yield.

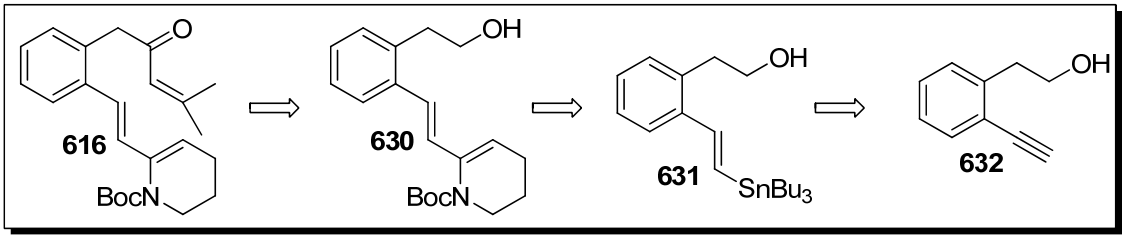


Scheme 2.79 Synthesis of acrylate triene **629**.

The coupling yields were unacceptably low, so an alternative route to triene **629**, also relying on Stille coupling chemistry, was implemented (Scheme 2.80). Vinyl triflate **590** was coupled to bis stannane **627** in order to access diene stannane **619**. Diene stannane **619** was isolated in modest yield (50%) although spectroscopic reaction monitoring had suggested the reaction operated more effectively. The purification was problematic and likely responsible for material loss. Purification attempts with triethylamine-neutralized silica and neutral alumina failed to provide better results than were obtained with typical silica chromatography. Unfortunately, these reactions were performed on small scale, making distillation difficult. Nevertheless, stannane **619** did serve as an acceptable Stille coupling partner with acrylate **626**. Triene **629** was assembled in slightly better yield via this particular coupling, but triene **629** failed to cyclize when heated in deuterated benzene or deuterated DMSO. When temperatures of 160 °C (benzene) and 130 °C (DMSO) were reached, decomposition to complex

mixtures was observed. The intramolecular acrylate cyclization remains largely unstudied due to limited availability of **629** and interest in more promising chemistry. The limited data did however suggest that an activated dienophile would be necessary for clean cyclization.

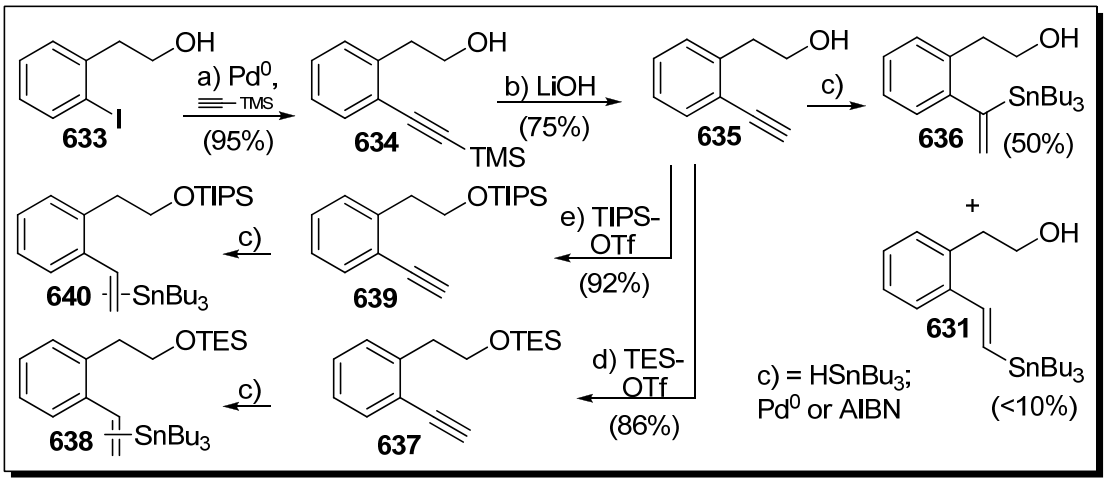
We also learned that coupling of bis-stannane (**627**) or diene stannane (**619**) to aryl bromide (**626**) was problematic with regard to scalability. Having previously observed coupling of styryl stannane **588** and vinyl triflate **590** to be efficient with production of a relatively easily purified diene (**581**), we modified the synthetic route to incorporate styryl stannane **631** derived from phenyl acetylene (**632**) (Scheme 2.81). We felt diene **630** could be constructed in sufficient quantity based on previous experience and hoped triene **616** could be constructed via oxidation and Grignard reactions without destroying the 2-aminodiene moiety if acidic reaction conditions could be avoided.



Scheme 2.80 Alternative retrosynthetic plan to triene **616**.

Aryl iodide (**633**) was prepared by borane-mediated reduction of the corresponding carboxylic acid or via a nickel-mediated transhalogenation from the analogous aryl bromide (**478**) (Scheme 2.82). Sonogashira coupling with TMSacetylene and subsequent TMS removal provided phenyl acetylene **635** in excellent yields. Unfortunately, geminal stannane (**636**) was isolated as the major product from

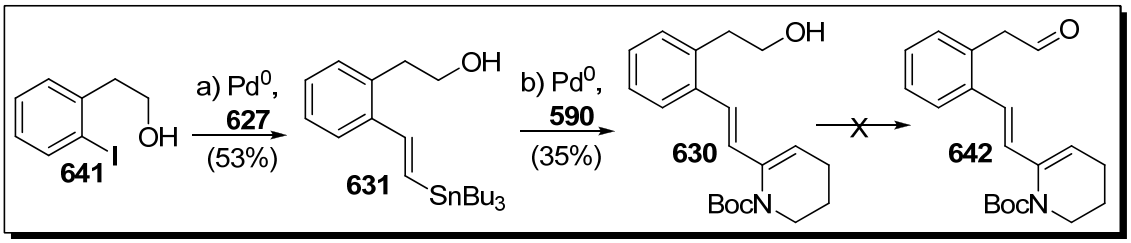
palladium or radical mediated hydrostannylation attempts, and the desired trans stannane (**631**) was never isolated in greater than 10%. We suspected the C20 alcohol may have played role by directing the hydrostannylation. For this reason, the alcohol was protected with silyl protecting groups of different bulk and stability (**637** and **639**). Palladium and radical mediated hydrostannylation of protected phenyl alkynes **637** and **639** produced similar mixtures of stannanes, with the geminal stannane the predominant isomer. Although the desired trans-stannane was a minor constituent, the stannane mixture was used in coupling attempts with vinyl triflate **590**. We were disappointed when no coupling was observed under the previously developed Pd^0/LiCl conditions.



Scheme 2.81 Attempted synthesis of styryl stannane **631**.

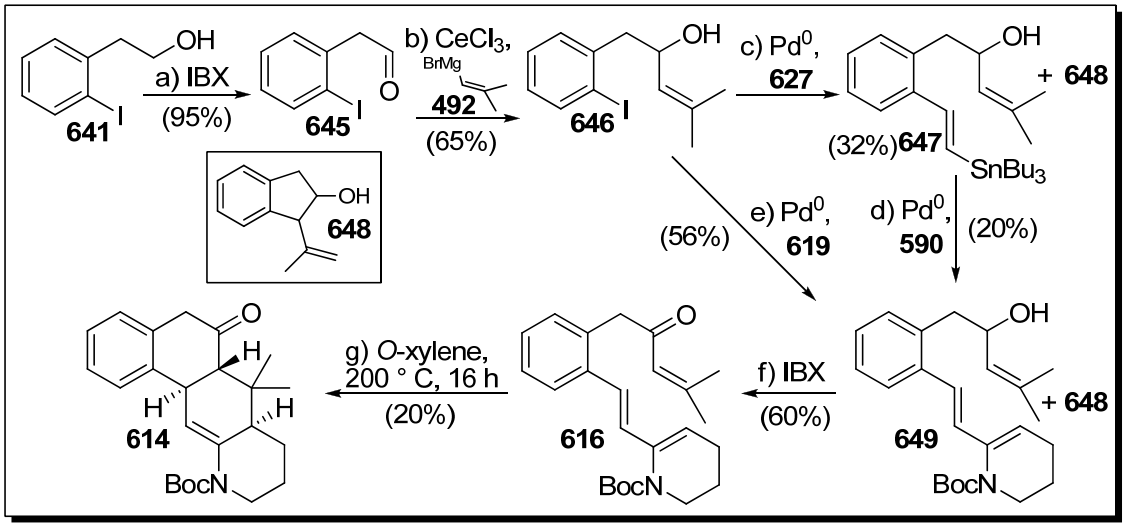
In light of the difficulty producing the desired styryl stannane, we opted for a more promising alternative route to diene **630** (Scheme 2.83). Coupling of aryl iodide **641** with bis-stannane **627** gave styryl stannane **631** in an unoptimized yield of 53%. A single attempt at coupling of **631** with vinyl triflate **590** resulted in a surprisingly low yield of the desired diene, **630**. Sufficient material was however synthesized for

unsuccessful pyridine-buffered oxidation attempts with IBX and Dess-Martin periodinane. Instead of observing aldehyde (**642**) formation, only complex mixtures due to diene decomposition were observed.



Scheme 2.82 Synthesis of diene **630**.

Diene decomposition (**630**) under mild oxidation conditions influenced our decision to functionalize the dienophile prior to installing the diene moiety as in the synthesis of the acrylate triene (**629**) (Scheme 2.84). Aryl iodide **641** was efficiently oxidized to the corresponding aldehyde (**645**) by IBX in refluxing acetonitrile without the need for purification after filtration through fluorosil. The less-costly Swern oxidation conditions provided the aldehyde (**645**) in low yields as a minor component of complex mixtures. Conversion of the Grignard reagent (**492**) to the equivalent organocerium reagent and aldehyde addition provided allylic alcohol **646** in useful yields. Coupling of allylic alcohol **646** and bis-stannane **627** gave stannane **647** in low yield, along with Heck adduct **648**. Stannane **647** was coupled with vinyl triflate **590** with success similar to that previously observed (conversion of **631** to **630**, Scheme 2.83).



Scheme 2.83 Synthesis of tetracycle **614**.

Significant optimization led to conditions that allowed for isolation of **649** in 56% yield as the product of Stille coupling between **646** and **619**. Excess stannane (1.5 – 2.0 equivalents **619**) and solventless reactions provided the best results. Triene **616** was isolated in 60% yield as the IBX oxidation product of allylic alcohol **649**.

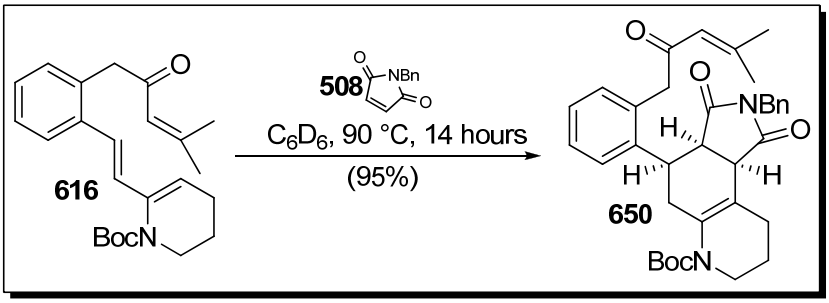
The intramolecular cycloaddition of **616** was studied in a number of solvents. High temperatures (typically 200 °C or more) and non polar solvents (xylenes) gave the best results when reactions were performed in sealed NMR tubes. More polar solvents (trifluoroethanol, acetonitrile, methanol, and DMSO) failed to provide the cycloadduct **614** as judged by NMR, and instead prompted extensive triene decomposition. This was surprising as we had previously observed dramatic rate increases with these specific solvents in intermolecular reactions (Tables 2.0 and 2.2). Limited attempts to

increase cyclization efficiency with Lewis acids ($ZnCl_2$ and $ZnBr_2$) were unsuccessful, as mixtures of Boc-deprotected products were obtained.

Reactions performed in deuterated xylene appeared, by NMR monitoring, to produce the cycloadduct (**614**) relatively cleanly at lower temperatures, but the reaction rate was prohibitively slow. At higher temperatures (190 °C and greater) Boc cleavage was observed and isolated yields were low, typically around 20%. As previously observed, material loss was observed in the form of extensive decomposition during purification.

It should be noted that the stereochemical assignment of **614** relies heavily on observance of a large coupling constant, indicative of axial proton coupling, between the protons of C12 and C21. 2D proton and carbon experiments were utilized to assign a clearly visible doublet at 1.7 ppm to the C21 proton. The coupling constant of 12 Hz suggested a trans ring junction as pictured in Scheme 2.84.

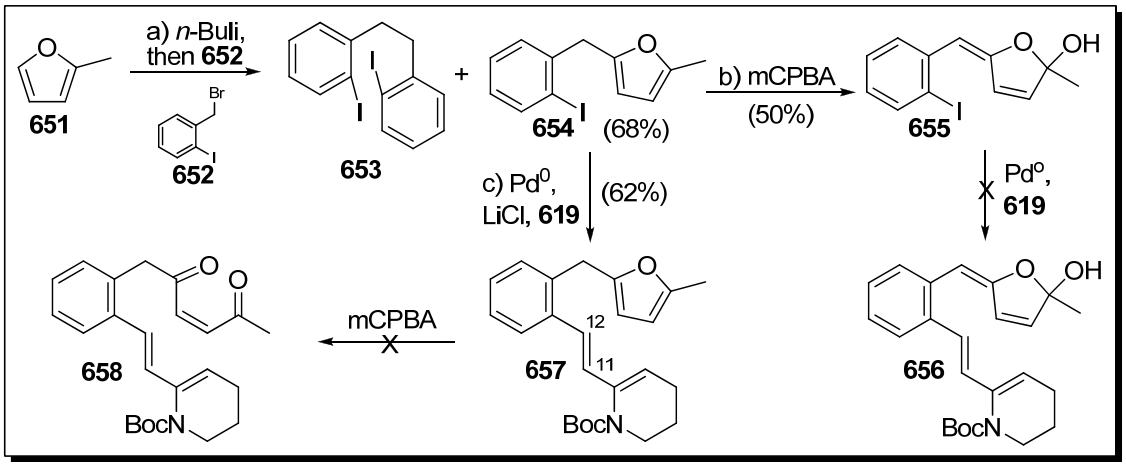
When triene **616** was heated in benzene with two equivalents benzyl maleimide (**508**), relatively quick cyclization to the corresponding endo cycloadduct (**650**) was observed at 90 °C (Scheme 2.85). This reactivity was very similar to the cycloaddition observed between **581** (**616** analog without the C19-C23 enone side chain) and benzyl maleimide **508** (Table 2.0). This finding suggested the enone dienophile, although an intramolecular reactant, was not sufficiently activated to allow efficient cyclization under mild thermal conditions.



Scheme 2.84 Dienophile competition experiment of triene **616**.

The belief, based on the maleimide (**508**) competition experiment, that the enone dienophile would not provide sufficient reactivity and failure of rate promotion by polar solvents prompted us to design an internal dienophile with increased electronic activation in attempt to encourage cycloaddition at lower temperatures. We believed a 1,4 diketo-enone dienophile, such as triene **658**, could greatly increase cyclization efficiency (Scheme 2.86). The attempted synthesis of **658** began by lithiation of methyl furan (**651**) and addition of the lithiate to benzyl bromide **653**. Benzyl furan **654** was obtained in acceptable yield in this manner, along with dimerization product **653**. Oxidative furan opening with mCPBA of **654** provided a more polar compound as the major product tentatively identified as lactol **655**. We believed the lactol (**655**) tautomer of the desired 1,4 diketone predominated due to the enolizability of the C20 ketone position, which extends conjugation to the aromatic ring. However, a minor product was isolated and tentatively identified as the desired 1,4 diketone based on proton NMR comparison to the known, corresponding des-iodo compound (see experiemental section for details).[76] Attempted coupling of **619** and lactol **655** was

unsuccessful under typical coupling conditions. Unfortunately, no products were isolated from the single coupling attempt so reaction optimization was not possible.

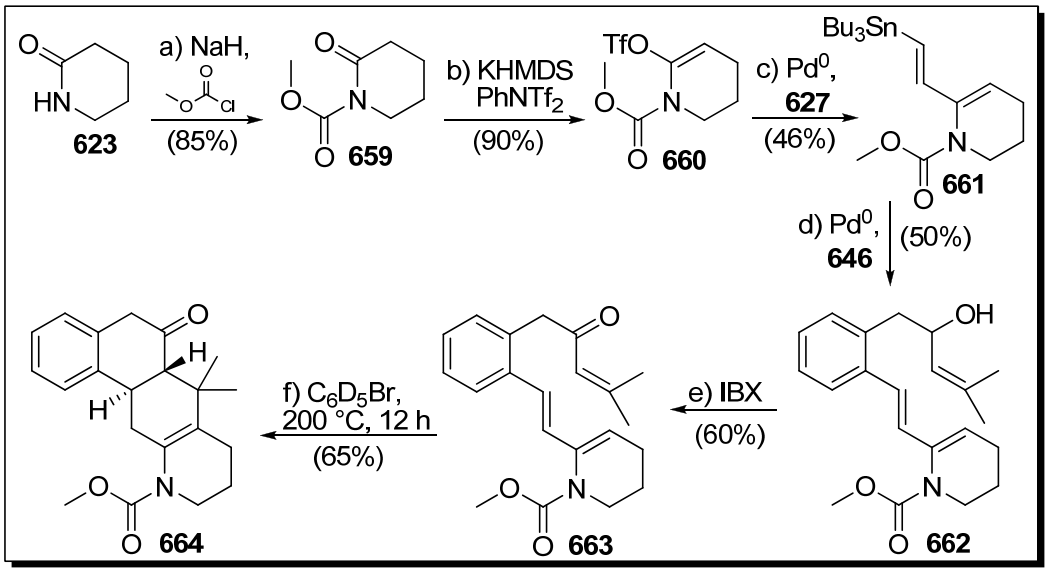


Scheme 2.85 Attempted synthesis of triene **658**.

Furtunately, coupling at an earlier stage, **654**, was successful. Diene **657** was formed in good yield (62%) under standard coupling conditions with stannane **619**. Unfortunately, oxidative opening of the furan moiety contained in **657** was not realized. Crude reaction analysis of two reactions performed with mCPBA revealed the loss of the C11-C12 olefin, which lead us to suspect epoxidation had occurred across the C11-C12 olefin.

Work being conducted simultaneously to circumvent the problems attributed to Boc lability showed promise (Scheme 2.87). Valerolactam (**623**) was protected as the methyl carbamate as previously reported.[77] The corresponding triflate was synthesized in the same manner as previously described for the Boc analog (**590**) and gave spectroscopic data identical to that previously reported.[78] Palladium coupling with bis-

stannane **627** provided stannane **661**, which was coupled to aryl iodide **646** with yields similar to those obtained for the analogous Boc compounds. IBX oxidation of coupling adduct **662**, provided triene **663** in acceptable yield. Cyclization of **663** was more efficient than reaction of the corresponding Boc analog (**614**). Treatment in deuterated bromobenzene at 200 °C over 11 hours provided cycloadduct **664** in 65% isolated yield. Reaction monitoring by NMR showed the methyl carbamate group to be stable at 200 °C and suggested clean formation of cycloadduct **664**. Unfortunately, purification was again problematic, however neutral alumina chromatography allowed for reasonable product isolation.

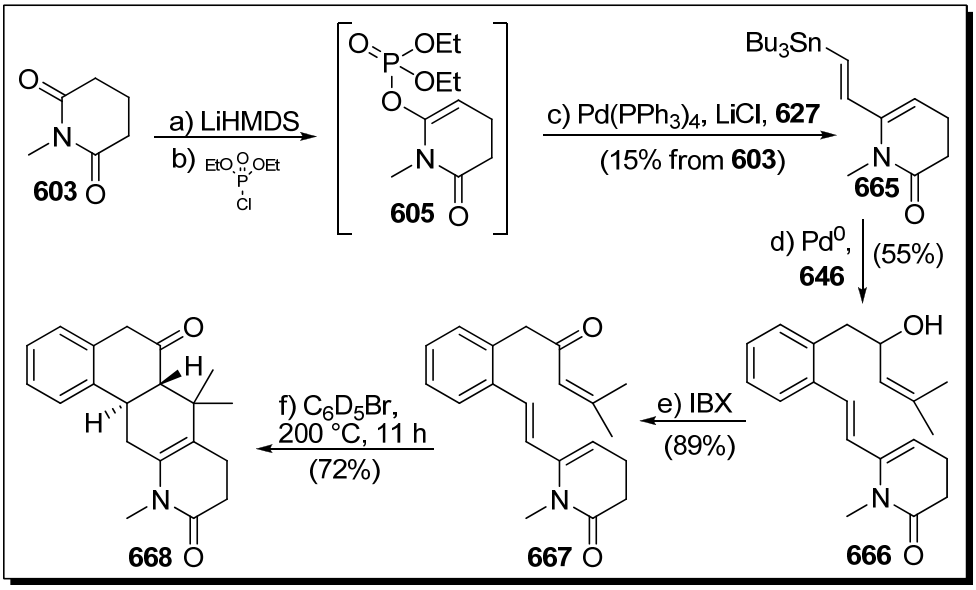


Scheme 2.86 Synthesis of methyl carbamate tetracycle **664**.

Interestingly, only the isomerized cycloadduct (C9-C10 olefin) was isolated. The reason for this is not clear, however we suspect the internal, tetrasubstituted, olefin (C9-C10) to be more stable than the trisubstituted exo olefin (C10-C11). In addition to

increased carbamate thermal stability, we partially attribute the higher isolated yield of cycloadduct **664** to more rapid in situ olefin isomerization. In each case, only the exo cycloadducts were isolated.

In order to explore the intramolecular amide cyclization reaction, we employed the methodology developed for construction of dienamine **606** (Scheme 2.88). Vinyl phosphonate **605** was prepared in the same manner as previously discussed and Stille coupling with bis-stannane **627** via a one-pot procedure provided diene stannane **665**. Several reactions at varied concentrations and ratios of stannane **627** to N-methylglutarimide (**603**) failed to provide the desired product (**665**) in yield greater than 15%. However, neat coupling of aryl iodide **646** with diene stannane **665** gave triene alcohol **666** reliably in 55% yield, and IBX oxidation of allylic alcohol **666** provided triene **667** in excellent yield. It should be noted that IBX oxidation of the analogous carbamate trienes (**616** and **663**) typically provided yields in the 60% range. This observation was interesting as we viewed the dienamide and N-carbamate-dienamine functionalities as moieties distant from the C20 allylic alcohol and unlikely to effect the oxidation reaction.



Scheme 2.87 Synthesis of amide tetracycle **668**.

Triene **667** was found to be more prone to cyclization at lower temperature than the analogous carbamates (**616** and **663**). Synthetically useful reaction progress was observed in reactions performed at 150 °C in deuterated bromobenzene, while no cyclization was detected at this temperature in trienes **616** and **663**. Additionally, cyclization occurred in acetonitrile, although not as cleanly as when performed in bromobenzene. However, reactions performed in deuterated acetone, methanol, and DMSO failed to provide the cyclization adduct **668**, instead producing complex mixtures of products. Isomerization of the C10-C11 olefin cycloadduct to the C9-C10 olefin cycloadduct could be followed by NMR. While cyclization occurred at lower temperatures, we found reaction in bromobenzene at 200 °C to be ideal for promoting the cyclization and the subsequent olefin isomerization within a twelve hour time period. Structural assignment of enamide **668** by 2D NMR techniques was supported

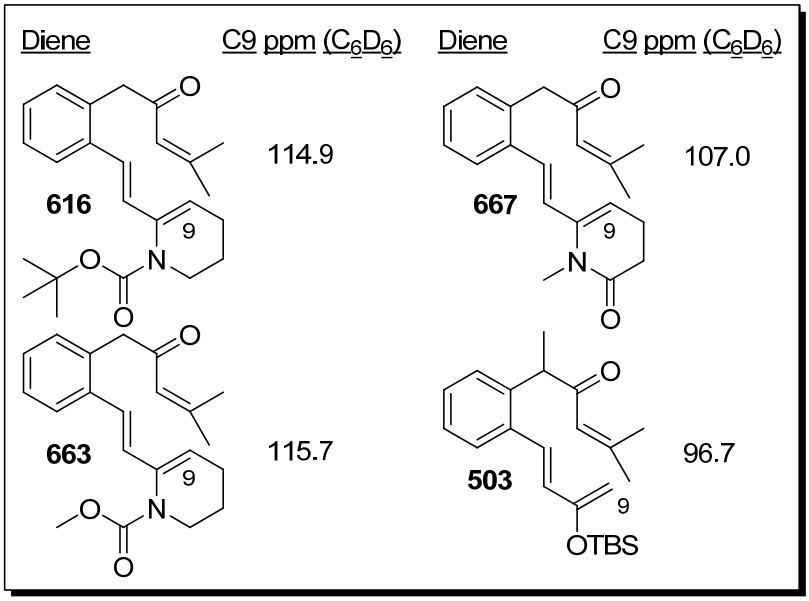
by single crystal x-ray diffraction analysis. As with the corresponding N-carbamate dienamines, isolation proved problematic, and only the exo product was isolated.

Exo Cycloaddition of carbamate stabilized 2-amino-1,3-dienamines **616**, **663**, and **667** to tetracycles **614**, **664** ,and **668** provided proof of concept for an intramolecular cycloaddition approach to zoanthenol (**163**). Our cyclization substrates lack methyl substitution at C9 and C12, and therefore represent minimized model systems. Importantly, the C22 quaternary center was constructed through this methodology and we suspect modifications at C22 to an enone more appropriately functionalized (containing components of the D ring lactone) for zoanthenol (**163**) synthesis would not inhibit cycloaddition. Installation of the C12 methyl group prior to cyclization would likely hinder the cyclization and require more forcing conditions, but may be feasible as we have observed significant reactivity with the dienamido system.

Once again we were surprised by the dramatic difference in reactivity between an amide diene and analogous carbamate dienes. Simple electron pushing suggests the very groups which stabilize the amino-diene functionality would limit the amount of electronic donation into the diene system by the nitrogen lone pair. The amide group is assumed to have a more significant withdrawing effect than carbamate groups, yet we observed increased reactivity with the amido diene substrates. However, empirical data collected over the course of this research creates doubt as to which group, amide or carbamate, displayed a more significant withdrawing effect (Table 2.3). Carbon NMR may be used as a method for assessing relative electronic wealth for individual carbon atoms as demonstrated by chemical shift. The relative chemical shift of the C9 carbon

of diene systems **616**, **663**, **667**, and **503** correlates with observed cycloaddition efficiency. Diene systems with greater electron density at C9, as determined by ^{13}C chemical shift, displayed shorter reaction times and higher isolated yields. The most efficient [4+2] reaction was achieved with silylenol ether diene **503** as the triene system. Not coincidentally, triene **503** also displayed the furthest upfield signal for C9, 96.7 ppm. The fact that amide **667** displays a C9 signal at 107.0 ppm, vs. ~115 ppm for the carbamate analogs, suggests the nitrogen atom of amide **667** actually funnels more electron density into the diene system than the corresponding carbamates (**616** and **663**).

Table 2.3 Diene **616**, **663**, **667**, and **503** C9 ^{13}C NMR shifts.



The chemical shift data is not in accordance with our predictions related to relative C9 electron density and therefore intimates that a rationalization will require additional parameters beyond simple arrow pushing to evaluate the degree of electron withdrawal

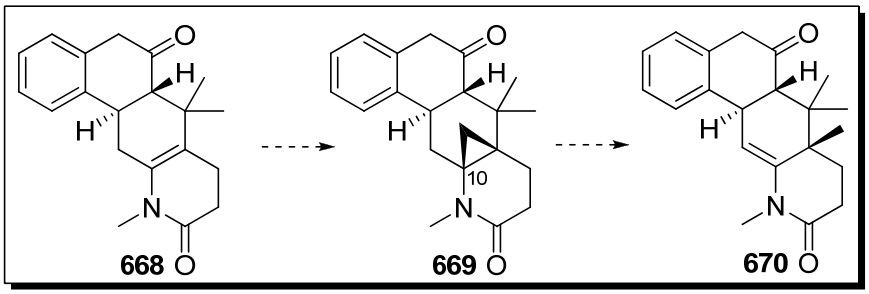
of the stabilizing groups. As previously discussed, conformational effects related to the cyclic amide may mitigate the degree of electron withdrawal. Unfortunately, examples of appropriate acyclic 2-amido-1,3-diene systems for ^{13}C NMR comparison could not be found in the literature.

Section 2.6 Concluding Remarks

While we were initially concerned about biasing the reaction toward a stepwise consecutive conjugate addition route, C10-C11 olefin isomerization to C9-C10 has mitigated this concern, as isomerization destroys the C9 stereocenter formed in the cycloaddition reaction. In fact, if the C9 methyl group could be installed at a later time, a concerted cycloaddition mechanism may be preferable as it allows for easily predicted stereochemical outcome and would allow for appropriate functionalization (*E*/*Z*) at the C22 olefin center in the cycloaddition substrate(s).

Alkylation at C9 through enamine methodology could potentially be utilized to install the C9 methyl group, although attempts to alkylate enamide **668** by heating in the presence of excess methyl iodide failed to provide reaction at moderate temperatures, and resulted in decomposition when heated in a sealed tube at 100 °C. An interesting alternative would be to borrow methodology demonstrated by the Hirama research group (Schemes 2.17 and 2.19).[27] Cyclopropanation of enamide **668** would give a cyclopropane ring with an attached electron donating group, in the form of the C10 nitrogen atom (**669**) (Scheme 2.89). The nitrogen atom could presumably direct an acid-mediated regioselective cyclopropane opening to give C9-methylate tetracycle **670**

as demonstrated by Hirama with an analogous C10 tertiary alcohol functionality. The question of stereoselectivity involving a potential cyclopropanation is not easily answered as the solid state confirmation of **668**, as demonstrated by single crystal x-ray analysis, suggests equal facial accessibility. Perhaps stereoselective reduction of the C20 ketone to an alcohol would allow the alcohol, or a derivative thereof, to serve as a directing group. Fortunately, numerous examples of stereoselective enamide cyclopropanation exist in the literature.[79] Further exploration of these ideas would require optimization of the current route or development of an alternative, more scalable route to triene cyclization substrate **667**.



Scheme 2.88 Proposed cyclopropanation methodology to install C9 methyl group.

Two approaches to zoanthamine alkaloids have been presented. The 1st generation approach established a stereoselective route to the ABC ring system of zoanthamines **150**, **151**, **154**, and **155**. The strategy, which relied heavily on Robinson annelation chemistry, allowed construction of an advanced tricyclic intermediate (**369**) containing the fully functionalized A and B rings. Functionalization of two C-ring stereocenters (C10 carbonyl and C29 methyl) was lacking. These issues were resolved after much experimentation using a BC ring system model. The penultimate BC ring system model

(**402**) included a fully functionalized C ring (including the C10 ketone and stereochemically correct C9 methyl group) with substituents amenable to further functionalization toward the D and E rings, as well as B ring functionalization previously proven capable of effecting A ring formation.

A second generation strategy designed around a 2-amino-1,3-diene cycloaddition was explored on minimized zoanthenol (**163**) scaffolds. Attempts at in situ formation of the 2-amino-1,3-diene moiety via intermolecular and intramolecular amine condensations were stymied by alternative reactivity and limited material due to lengthy synthetic routes. However, synthetic routes to advanced intermediates have been developed and the groundwork has been layed for future work in this area.

In the course of this study, we observed an efficient silyl-enol ether diene cycloaddition which culminated in a minimized zoanthenol (**163**) ABC ring scaffold. The [4+2] reaction constructed rings B and C in a single step with the desired C12-C21 ring junction stereochemistry via an exo transition state.

Finally, we were able to demonstrate several cycloaddition reactions with N-stabilized 2-amino-1,3-dienes. Of particular note were the intramolecular reactions of carbamates **616**, **663**, and amide **667**. We are aware of only two reported N-carbamate stabilized 2-amino-1,3-diene intramolecular cycloadditions[63] and no previous N-amide stabilized 2-amino-1,3-diene intramolecular cycloaddition reactions. This work therefore represents an early entry into the study of underutilized electron rich diene

moieties. The dienes studied were also shown to demonstrate excellent regiocontrol in both intramolecular and intermolecular reactions.

A subtle, but very important, observation was the cycloadduct olefin isomerization which occurred in many of the [4+2] reactions. The isomerization renders the question of whether the reactions follow a concerted or stepwise mechanism superfluous, as the C9 stereocenter is necessarily destroyed in the isomerization.

Cycloadditions with dienamide moieties proved surpisingly facile, and the intramolecular cyclization of **667** is of synthetic interest. Although our intramolecular model bore an aromatic A ring, we feel the 2-amido-1,3-diene methodology developed to be applicable to a zoanthamide (**165**) total synthesis.

An additional attribute of the intramolecular cycloaddition research was the rapid development of the triene cyclization substrates via concise synthetic routes. Palladium-mediated cross coupling proved a reliable, although not always efficient, method for constructing the compulsary diene functionaliy. Reaction optimization associated with the cross coupling methodology for N-stabilized 2-amino-1,3-diene systems is merited due to the compatibility with convergent synthetic routes and ability to form reactive systems otherwise difficult to access.

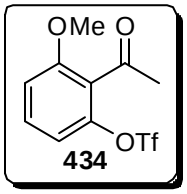
Appendix Experimental Information

Section A.1 General Techniques

All reagents were obtained (Aldrich, Acros) at the highest commercial quality and used without further purification except where noted. Air- and moisture-sensitive

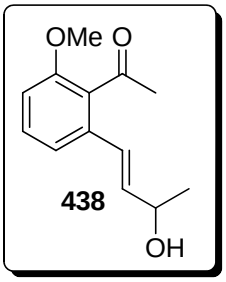
liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 45 °C at approximately 20 mmHg. All non-aqueous reactions were carried out under anhydrous conditions, *i.e.* using flame-dried glassware, under an argon atmosphere and in dry, freshly distilled solvents, unless otherwise noted. Repeated extractions were performed to obtain all products, as judged by TLC. Yields refer to chromatographically and spectroscopically (^{1}H NMR, ^{13}C NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) and visualized under UV light and/or developed by dipping in solutions of cerric ammonium molybdate (CAM) or p-anisaldehyde and applying heat. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. NMR spectra were recorded on Varian Mercury 300, 400, Varian Unity 500, and/or Jeol eca 500 MHz instruments and calibrated using the residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. IR spectra were recorded on a Nicolet 320 Avatar FT-IR spectrometer and values are reported in cm^{-1} units. High resolution mass spectra (HRMS) were recorded on a ThermoFinnigan MAT900XL under fast atom bombardment (FAB) conditions with 3-nitrobenzyl alcohol matrix and polyethylene glycol reference. X-ray data were recorded on a Bruker SMART APEX 3kW Sealed Tube X-ray diffraction system.

Section A.2 Experimental Procedures and Data



434

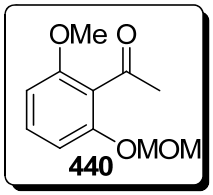
Compound 434: Phenol **433** (440 mg, 3.55 mmol) was dissolved in methylene chloride (5 mL), cooled to -78 °C and NEt_3 (1.6 mL, 12.8 mmol) was added in one portion. Triflic anhydride (0.84 mL, 5.0 mmol) was added dropwise over 5 minutes, and the solution was allowed to warm to room temperature. After 10 hours at room temperature, the solution was cooled to 0 °C. Approximately 1 mL NEt_3 was added prior to diluting with diethyl ether and water. The mixture was washed with aqueous NH_4Cl, dried over $MgSO_4$, and concentrated. Column chromatography provided triflate **434** (689 mg, 65%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.55 (s, 3H), 3.83 (s, 3H), 6.91 (d, J = 8.4 Hz, 1H), 6.97 (d, J =8.4 Hz, 1H), 7.41 (t, J = 8.4 Hz, 1H).



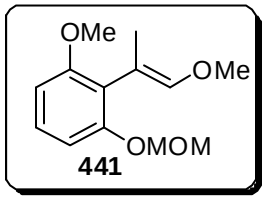
438

Compound 438: Triflate **434** (104 mg, 0.29 mmol) was dissolved in THF (3.0 mL) under argon at room temperature. Stannane **437** (103 mg, 0.35 mmol) was added to **434** under an argon fow. $PdCl_2(PPh_3)_2$ (4 mg, 0.006 mmol) was added to the reaction flask, followed rapidly by LiCl (35 mg, 0.82 mmol). The reaction was

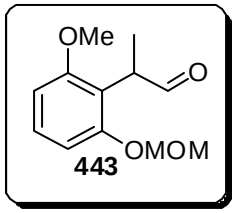
stirred at room temperature 10 hours. A saturated $NaHCO_3$ aqueous solution was added, and a diethyl ether extraction performed. The organic extracts were combined and dried over $MgSO_4$. Concentration and column chromatography provided allylic alcohol 438 as an oil (23 mg, 37%). TLC (ethyl acetate/hexanes 2:3): R_f = 0.1; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (d, J = 6.0 Hz, 3 H), 2.50 (s, 3H), 3.83 (s, 3H), 4.44 (m, 1H), 6.20 (dd, J = 6.4, 15.6 Hz, 1H), 6.49 (d, J = 15.6 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.28 (t, J = 8.0 Hz, 1H); ESI-MS: *m/z* calcd. for $C_{13}H_{16}O_3Na_1$: 243.10, found: 243.12 $[M+Na]^+$.



Compound 440: To a flask containing phenol **433** (459 mg, 2.77 mmol) in methylene chloride (5 mL), was added Hunigs base (1.0 mL, 5.74 mmol) at 0 °C. MOMCl (0.3 mL, 3.95 mmol) was added and the solution was allowed to warm to room temperature. After 13 hours stirring, water was added prior to diluting with diethyl ether and washing with aqueous $NaHCO_3$. The extracts were dried over $MgSO_4$ and concentrated. Column chromatography provided MOM ether **440** (401 mg, 69%). TLC (ethyl acetate/hexanes 3:2): R_f = 0.6; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.49 (s, 3H), 3.45 (s, 3H), 3.80 (s, 3H), 5.15 (s, 2H), 6.59 (d, J = 8.4 Hz), 6.75 (d, J = 8.4 Hz), 7.23 (t, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.5, 156.6, 154.0, 138.2, 130.5, 107.3, 104.8, 94.5, 56.2, 55.8, 32.3; ESI-MS: *m/z* calcd. for $C_{11}H_{14}O_4Na_1$: 233.08, found: 233.08 $[M+Na]^+$.

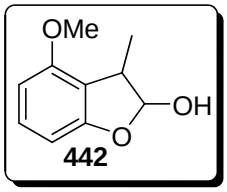


Compound 441: Ph_3PClCH_2OMe (2.0 g, 5.22 mmol) was dissolved in THF (5 mL) under argon and cooled to -78 °C. A 1 M THF solution of NaHMDS (5 mL, 5.0 mmol) was added rapidly. After stirring 2 hours, ketone **440** (186 mg, 0.89 mmol) was added as a THF (2 mL) solution. The reaction mixture was allowed to warm to room temperature after 16 hours at -78 °C, and then stirred an additional 30 hours before the solution was diluted with diethyl ether and quenched with water. Extraction with ether, exposure of the organic layers to $MgSO_4$, concentration, and column chromatography gave enol ether **441** as an oil (42 mg, 20%). TLC (ethyl acetate/hexanes 3:4): R_f = 0.6; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.87 (d, J = 1.6 Hz, 3H), 3.46 (s, 3H), 3.66 (s, 3H), 3.79 (s, 3H), 5.14 (s, 2H), 5.93 (s, 1H), 6.59 (d, J = 8.4 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 7.14 (t, J = 8.4 Hz, 1H).



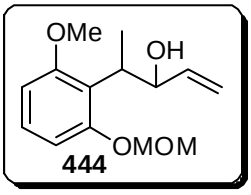
Compound 443: Enol ether **441** (88 mg, 0.37 mmol) was dissolved in acetone (1 mL) and water was added (0.1 mL). 1 drop aqueous HBR (48%) was added to the solution at room temperature. After stirring 50 minutes, the solution was diluted with diethyl ether and a saturated $NaHCO_3$ aqueous solution was

added. Ether extraction, drying of the combined organic layers with $MgSO_4$, concentration, and column chromatography provided aldehyde **443** as an oil (56 mg, 70%). TLC (ethyl acetate/hexanes 1:3): $R_f = 0.4$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (d, J = 6.8 Hz), 3.45 (s, 3H), 3.80 (s, 3H), 3.94 (q, J = 6.8 Hz, 1H), 5.16 (s, 2H), 6.62 (d, J = 8.4 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 7.21 (t, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.9, 158.0, 155.7, 128.7, 117.2, 107.0, 104.8, 94.4, 56.2, 55.7, 42.8, 12.7.



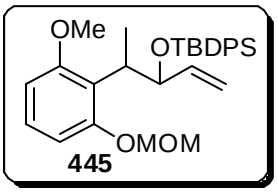
442

Compound 442: Lactol **442** was isolated as a side product of the aldehyde **443** synthesis reaction. TLC (ethyl acetate/hexanes 1:3): $R_f = 0.3$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (d, J = 7.2 Hz, 3H), 3.31 (dq, J = 1.2, 7.2 Hz, 1H), 3.83 (s, 3H), 5.58 (s, 1H), 6.47 (d, J = 8.0 Hz, 1H), 6.51 (d, J = 8.0 Hz, 1H), 7.13 (t, J = 8.0 Hz, 1H); ESI-MS: *m/z* calcd. for $C_{10}H_{12}O_3Na_1$: 203.07, found: 203.08 $[M+Na]^+$.



444

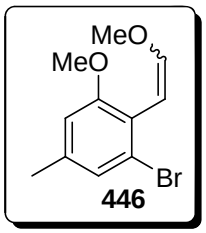
Compound 444: Aldehyde **443** (55 mg, 0.25 mmol) was dissolved in THF (3 mL) and cooled to -78 °C. Vinyl Grignard reagent was added as a 1 M THF solution (0.4 mL, 0.4 mmol) in a rapid dropwise fashion. After stirring 1 hour, water was added, and followed by aqueous NH_4Cl. Extractions with diethyl ether were performed and the combined extracts dried over $MgSO_4$. Column chromatography gave allylic alcohol **444** as an oil (40 mg , 64%). TLC (ethyl acetate/hexanes 1:3): $R_f = 0.2$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (d, J = 7.2 Hz, 3H), 1.36 (d, J = 7.2 Hz, 2H), 3.48 (s, 2H), 3.49 (s, 3H), 3.52-3.59 (m, 0.7H), 3.59-3.67 (m, 1H), 3.81 (s, 2H), 3.83 (s, 3H), 4.51 (m, 1H), 4.58 (m, 0.7H), 4.96 (ddd, J = 1.2, 10.8 Hz, 0.7H), 5.10-5.21 (m, 5H), 5.30 (ddd, J = 1.2, 16.8 Hz, 1H), 5.74-5.83 (m, 0.7H), 5.83-5.92 (m, 1H), 6.57 (d, J = 8.4 Hz, 0.7H), 6.61 (d, J = 8.4 Hz, 1H), 6.72-6.78 (m, 1.7H), 7.08-7.17 (m, 1.7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 156.7, 140.91, 140.86, 128.0, 127.7, 115.7, 114.3, 108.1, 107.7, 105.6, 105.5, 95.0, 94.8, 76.2, 75.8, 56.5, 56.4, 56.0, 55.9, 36.8, 36.5, 15.9, 14.6.



445

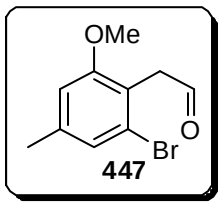
Compound 445: Allylic alcohol **445** (36 mg, 0.14 mmol) was dissolved in methylene chloride (2 mL) at room temperature. Imidazole (20 mg, 0.29 mmol) was added, followed rapidly by TBDPSCl (0.07 mL, 0.27 mmol), and the reaction was allowed to stir 8 hours at room temperature. The reaction was diluted with diethyl ether and acqueous $NaHCO_3$. Repeated extractions with diethyl ether, combination and drying of the organic layers over $MgSO_4$, concentration, and column chromatography gave silyl ether **445** as an oil (53 mg, 76%). TLC (ethyl acetate/hexanes 1:3): $R_f = 0.6$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.08 (s, 9H),

1.08-1.16 (m, 12H), 1.30 (bs, 3H), 3.45 (s, 5H), 3.69 (s, 5H), 4.42-5.15 (m, 11H), 5.55-5.66 (m, 1H), 5.69-5.79 (m, 1H), 6.55 (d, J = 8.2 Hz, 1H), 6.75 (d, J = 8.2 Hz, 0.8H), 7.03 (t, J = 8.2 Hz, 1H), 7.12 (t, J = 8.2 Hz, 1H), 7.25-7.45 (m, 14H), 7.57 (d, J = 7.4 Hz, 2H), 7.74 (d, J = 6.8 Hz, 2H), 7.82 (d, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9, 156.5, 140.7, 140.4, 136.3, 136.1, 136.0, 135.9, 129.1, 129.0, 128.9, 128.87, 128.84, 127.1, 126.93, 126.88, 126.8, 126.7, 116.3, 114.6, 107.5, 104.9, 94.6, 78.1, 77.6, 56.0, 55.3, 36.2, 27.4, 26.7, 19.8, 16.2, 15.1.



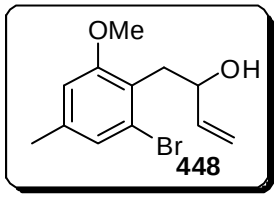
446

Compound 446: The enol ether ylid was prepared by adding KHMDS (13 mL, 6.65 mmol) as a 0.5 M toluene solution to $MeOCH_2PPh_3Cl$ (2.65 g, 7.73 mmol) in toluene (30 mL) at 0 °C under argon. After stirring 30 minutes at 0 °C, then 30 minutes at room temperature, aldehyde **427a** (1.1 g, 4.81 mmol) was added in 10 mL toluene. After mixing 2 hours at room temperature, aqueous NH_4Cl was added and diethyl ether extractions were performed. The combined ether extracts were dried over $MgSO_4$, concentrated and subjected to column chromatography. The cis isomer was collected as an oil (165 mg), as was the trans isomer (945 mg) in a combined yield of 90%. TLC (ethyl acetate/hexanes 1:3): R_f = 0.6; **446-*Z***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.30 (s, 3H). 3.67 (s, 3H), 3.82 (S, 3H), 5.21 (d, J = 7.0 Hz, 1H), 6.19 (d, J = 7.0 Hz, 1H), 6.64 (s, 1H), 7.04, (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.5, 147.9, 138.5, 125.1, 124.5, 122.1, 110.6, 100.4, 59.8, 56.0, 21.4; **446-*E***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.29 (s, 3H). 3.71 (s, 3H), 3.83 (S, 3H), 5.96 (d, J = 13.0 Hz, 1H), 6.63 (s, 1H), 7.04 (s, 1H), 7.40, (d, J = 13.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9, 153.0, 136.5, 125.7, 123.9, 121.7, 110.9, 101.0, 56.2, 55.7, 21.1.



447

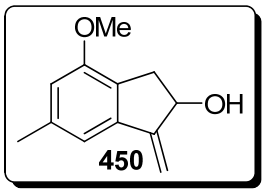
Compound 447: Enol ether **446** (945 mg, 3.68 mmol) was dissolved in acetone (8 mL) and 37% aqueous HCl (10 drops) was added at room temperature. The reaction was allowed to stir 4 hours before hexanes were added. The reaction was then quenched with aqueous $NaHCO_3$. Extraction with diethyl ether was performed and the combined extracts dried over $MgSO_4$. Column chromatography gave aldehyde **447** as an oil (850 mg, 95%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (s, 3H), 3.79 (s, 3H), 3.87 (s, 2H), 6.66 (s, 1H), 7.06 (s, 1H), 9.63 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.8, 158.0, 139.7, 125.5, 125.1, 118.7, 110.5, 55.8, 44.4, 21.4.



448

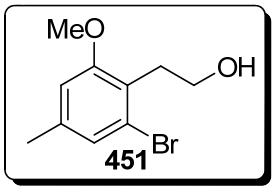
Compound 448: Aldehyde **447** (16 mg, 0.07 mmol) was dissolved in THF (2 ml) and cooled to 0 °C. Vinyl Grignard

reagent was added as a 1 M THF solution (0.15 mL, 0.15 mmol) dropwise over 5 minutes. The ice bath was removed immediately after reagent addition and the reaction was stirred 3 hours prior to addition of diethyl ether and aqueous NH_4Cl. Ether extraction, combination of the organic extracts, $MgSO_4$ treatment, concentration, and column chromatography gave allylic alcohol **448** as an oil (14 mg, 79%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (s, 3H), 3.05 (m, 1H), 3.06 (m, 1H), 3.82 (s, 3H), 4.39 (bs, 1H), 5.09 (dt, J = 1.6, 10.8 Hz, 1H), 5.25 (dt, J = 1.6, 17.2 Hz, 1H), 5.99 (ddd, J = 6.0, 10.8, 17.2 Hz, 1H), 6.64 (s, 1H), 7.03 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 140.1, 138.6, 125.7, 125.6, 123.6, 114.1, 110.7, 72.7, 55.8, 37.2, 21.1.



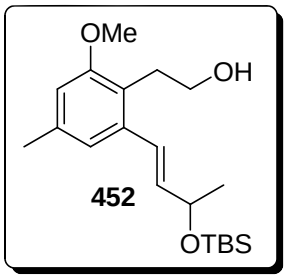
450

Compound 450: Allylic alcohol **450** was isolated as a Heck adduct in the attempted Stille coupling of aryl bromide **448** and stannane **449**. Aryl bromide **448** (43 mg, 0.16 mmol) was dissolved in THF (1 mL) under argon and stannane **449** (184 mg, 0.62 mmol) was added. $Pd(PPh_3)_4$ (17 mg, 0.15 mmol) was added in one portion at room temperature. After 11 hours, the reaction was diluted with hexanes and filtered through celite prior to concentration and column chromatography. Allylic alcohol **450** was obtained as an oil (23 mg, 77%). TLC (ethyl acetate/hexanes 3:2): R_f = 0.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 2.73 (dd, J = 3.6, 16.8 Hz, 1H), 3.25 (dd, J = 7.2, 16.8 Hz, 1H), 3.82 (s, 3H), 4.93 (bs, 1H), 5.30, (d, J = 2.0 Hz, 1H), 5.57 (d, J = 2.0 Hz, 1Hz), 6.58 (s, 1H), 6.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.0, 153.5, 139.8, 138.4, 127.5, 113.6, 111.3, 105.6, 74.6, 55.3, 37.3, 21.9; HRMS: *m/z* calcd. for $C_{12}H_{14}O_2Na_1$: 213.09, found: 213.09 $[M+Na]^+$.

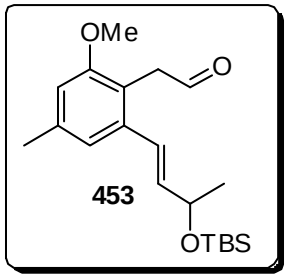


451

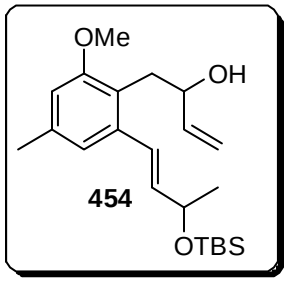
Compound 451: To a stirred solution of aldehyde **447** (904 mg, 3.72 mmol) in methylene chloride (10 mL) at 0 °C was added DIBAL-H (4.9 mL, 4.9 mmol), portionwise over 5 minutes, as a 1 M hexane solution. The ice bath was removed immediately after DIBAL-H addition and the reaction was allowed to warm to room temperature. After stirring 40 minutes, the reaction was cooled to 0 °C and 15 mL of a saturated aqueous Rochelle's salt solution was added. The solution clarified after 2 hours stirring at room temperature. Repeated extractions with methylene chloride were performed and the combined extracts were dried over $MgSO_4$. Column chromatography gave alcohol **451** as an oil (823 mg, 90%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30 (s, 3H), 3.10 (t, J = 7.2 Hz, 2H), 3.78 (t, J = 7.2 Hz, 2H), 3.81 (s, 3H), 6.63 (s, 1H), 7.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 138.3, 125.4, 125.3, 123.6, 110.4, 61.9, 55.8, 32.9, 21.2; HR-EI-MS: *m/z* calcd. for $C_{10}H_{13}O_2Br$: 244.0091, found: 244.0093 $[M]^+$.



Compound 452: Aryl bromide **451** (390 mg, 1.59 mmol) and stannane **449** (540 mg, 1.81 mmol) were mixed under argon and dissolved in toluene (10 mL). The solution was degassed by bubbling argon through the solution with stirring for 10 minutes. $Pd_2(dba)_3$ (150 mg, 0.16 mmol) was added at room temperature, followed rapidly by P(*t*-Bu)$_3$ (32 mg, 0.16 mmol) addition as a 10% hexane solution. The solution was heated to reflux and stirred 8 hours before cooling. The solution was filtered through a silica plug and concentrated for column chromatography. At this stage, dibenzylidene acetone could be precipitated via trituration with ether and hexanes. Column chromatography provided alcohol **452** as an oil (402 mg, 72%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.10 (s, 3H), 0.11 (s, 3H), 0.94 (s, 9H), 1.31 (d, J = 6.4 Hz, 3H), 2.34 (s, 3H), 3.00 (t, J = 6.4 Hz, 2H), 3.74 (t, J = 6.4 Hz, 2H), 3.82 (s, 3H), 4.49 (m, 1H), 6.10 (dd, J = 5.4, 15.0 Hz, 1H), 6.62 (s, 1H), 6.80 (d, J = 15.0 Hz, 1H), 6.92 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.5, 137.6, 136.74, 136.69, 125.3, 121.4, 119.3, 110.1, 69.4, 62.8, 55.5, 29.0, 26.0, 24.8, 21.7, 18.4, -4.4, -4.6; ESI-MS: *m/z* calcd. for $C_{20}H_{34}O_3Si_1Na_1$: 373.22, found: 373.23 $[M+Na]^+$.

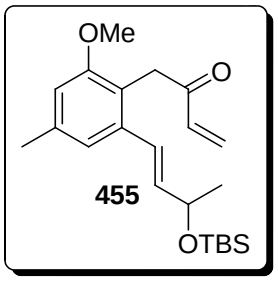


Compound 453: Alcohol **452** (275 mg, 0.78 mmol) was dissolved in methylene chloride (8 mL) and DMSO (2 mL) at room temperature. To the stirred solution was added IBX (645 mg, 2.30 mmol). The reaction was stirred 5 hours, and then diluted with hexanes. Water was added to the resultant slurry and repeated diethyl ether extractions were performed. The combined ether extracts were dried over $MgSO_4$ and concentrated. The crude mixture was filtered through a silica plug to provide aldehyde **453** as an oil (249 mg, 91%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.08 (s, 3H), 0.09 (s, 3H), 0.92 (s, 9H), 1.28 (d, J = 6.4 Hz, 3H), 2.36 (s, 3H), 3.73 (s, 2H), 3.80 (s, 3H), 4.45 (m, 1H), 6.08 (dd, J = 5.6, 15.6 Hz, 1H), 6.60 (d, J = 15.6 Hz, 1H), 6.64 (s, 1H), 6.92 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.9, 157.4, 138.2, 138.0, 137.8, 124.8, 119.5, 115.8, 110.1, 69.2, 55.6, 41.0, 26.0, 24.7, 21.8, 18.4, -4.4, -4.6.

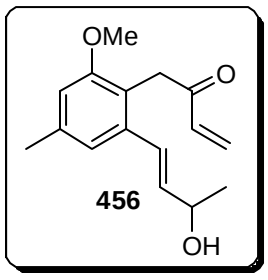


Compound 454: To a stirred THF (3 mL) solution of aldehyde **453** (56 mg, 0.16 mmol) at 0 °C, was added vinyl Grignard reagent (0.32 mL, 0.32 mmol) as a 1 M THF solution dropwise over ~10 seconds. The reaction was stirred 30

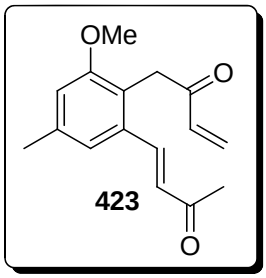
minutes, and then hexanes were added followed by aqueous NH_4Cl. Extraction with diethyl ether was performed, and the combined organic extracts were dried over $MgSO_4$ prior to concentration. Column chromatography gave allylic alcohol **454** as an oil (50 mg, 83%). TLC (ethyl acetate/hexanes 1:4): R_f = 0.3; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.10 (s, 3H), 0.11 (s, 3H), 0.93 (s, 9H), 1.3 (d, J = 6.3 Hz, 3H), 2.34 (s, 3H), 2.94 (m, 2H), 3.82 (s, 3H), 4.31 (m, 1H), 4.48 (m, 1H), 5.03 (d, J = 10.5 Hz, 1H), 5.25 (d, J = 17.1 Hz, 1H), 5.95 (m, 1H), 6.08 (m, 1H), 6.63 (s, 1H), 6.80 (d, J = 15.6 Hz, 1H), 6.92 (s, 1H).



Compound 455: Allylic alcohol **454** (22 mg, 0.06 mmol) was dissolved in methylene chloride (1 mL) and DMSO (1 mL) at room temperature. IBX (68 mg, 0.24 mmol) was added and the reaction was stirred 2 hours before being diluted with hexanes and water. Repeated extraction with diethyl ether was performed and the extracts combined prior to being dried over $MgSO_4$. Column chromatography gave enone **455** as an oil (19 mg, 85%). TLC (ethyl acetate/hexanes 1:4): R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.90 (s, 9H), 1.27 (d, J = 6.4 Hz, 3H), 2.34 (s, 3H), 3.77 (s, 3H), 3.93 (m, 2H), 4.43 (m, 1H), 5.73 (dd, J = 1.0, 10.0 Hz, 1H), 6.06 (dd, J = 5.2, 15.6 Hz, 1H), 6.29 (dd, J = 1.0, 17.6 Hz, 1H), 6.37 (d, J = 10.0 Hz, 1H), 6.57 (d, J = 15.6 Hz, 1H), 6.62 (s, 1H), 6.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 157.2, 137.6, 137.3, 135.3, 127.6, 125.2, 119.4, 118.0, 110.2, 69.3, 55.6, 38.2, 26.0, 24.7, 21.8, 18.4, -4.4, -4.6; ESI-MS: *m/z* calcd. for $C_{22}H_{34}O_3Si_1Na_1$: 397.22, found: 397.24 $[M+Na]^+$.

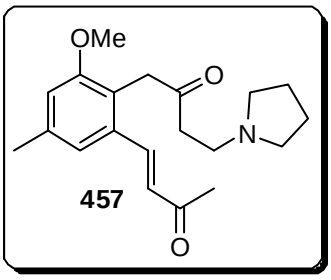


Compound 456: Silyl ether **455** (18 mg, 0.05 mmol) was dissolved in an $AcOH/H_2O/THF$ (13:7:7, 1 mL) solution at room temperature. The solution was stirred 6 hours, and then diluted with diethyl ether. The solution was then neutralized by adding saturated aqueous $NaHCO_3$ followed by solid Na_2CO_3. Repeated ether extractions were performed and the combined extracts were dried over $MgSO_4$. Column chromatography gave allylic alcohol **456** as an oil (11 mg, 87%). TLC (ethyl acetate/hexanes 2:3): R_f = 0.2.

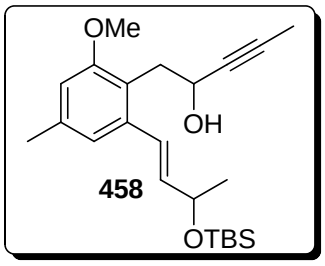


Compound 423: Allylic alcohol **456** (10 mg, 0.04 mmol) was dissolved in methylene chloride (1.5 mL) and DMSO (0.7mL) at room temperature. IBX (43 mg, 0.15 mmol) was added and the solution was stirred 5 hours before dilution with hexanes and water. Repeated diethyl ether extractions were performed and

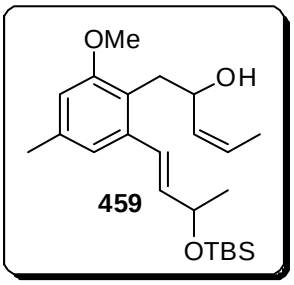
the ether extracts combined, then dried over $MgSO_4$. Column chromatography provided dienone **423** as a white solid after concentration (9 mg, 92%). TLC (ethyl acetate/hexanes 2:3): R_f = 0.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.357 (s, 3H), 2.36 (s, 3H), 3.81 (s, 3H), 4.03 (s, 2H), 5.80 (dd, J = 1.0, 10.0 Hz, 1H), 6.34 (dd, J = 1.5, 17.6 Hz, 1H), 6.43 (dd, J = 10.0, 17.6 Hz, 1H), 6.59 (d, J = 16.0 Hz, 1H), 6.76 (s, 1H), 7.04 (s, 1H), 7.66 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 197.3, 157.2, 140.7, 138.2, 135.3, 135.1, 129.4, 128.5, 120.1, 119.5, 113.0, 55.8, 37.7, 27.6, 21.8; ESI-MS: *m/z* calcd. for $C_{16}H_{18}O_3Na_1$: 281.12, found: 281.13 $[M+Na]^+$.



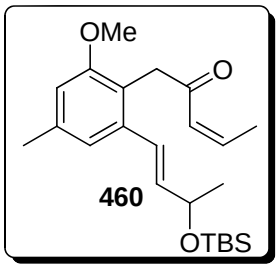
Compound 457: Dienone **423** (4 mg) was dissolved in DMSO-d6 and transferred to a NMR tube. Pyrollidine was added , and the reaction progress was monitored by NMR. After 30 minutes at room temperature, complete conversion to amine **457** was observed. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.76 (m, 4H), 2.43 (s, 3H), 2.45 (s, 3H), 2.62 (m, 4H), 2.73 (m, 4H), 3.87 (s, 3H), 4.05 (s, 2H), 6.77 (d, J = 16.0 Hz, 1H), 7.02 (s, 1H), 7.29 (s, 1H), 7.72 (d, J = 16.0 Hz, 1H).



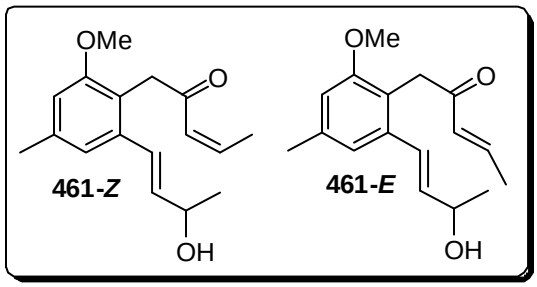
Compound 458: To a stirred THF (1 mL) solution of **453** (62 mg, 0.18 mmol) at 0 °C, was added 1-propynyl magnesium bromide (0.5 mL, 0.27 mmol) as a 0.5 M THF solution. After stirring 30 minutes, aqueous NH_4Cl was added and repeated diethyl ether extractions were performed. Combination of the ether extracts, drying by $MgSO_4$, and column chromatography gave propargyl alcohol **458** as an oil (63 mg, 90%). TLC (ethyl acetate/hexanes 1:4): R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.11 (s, 6H), 0.94 (s, 9H), 1.30 (d, J = 6.8 Hz, 3H), 1.83 (m, 3H), 2.33 (s, 3H), 3.07 (ddd, J = 2.0, 5.2, 14.0 Hz, 1H), 3.17 (dd, J = 8.6, 14.4 Hz, 1H), 3.8 (s, 3H), 4.45-4.55 (m, 1H), 6.08 (dd, J = 5.2, 15.6 Hz, 1H), 6.61 (s, 1H), 6.86 (d, J = 15.6 Hz, 1H), 6.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.5 138.1, 137.2, 136.8, 125.61, 125.56, 120.4, 119.6, 119.5, 110.2, 80.5, 69.34, 69.29, 62.89, 62.87, 55.6, 34.6, 34.5, 26.0, 24.82, 24.80, 21.7, 18.4, 3.8, -4.4, -4.6; ESI-MS: *m/z* calcd. for $C_{23}H_{36}O_3Si_1Na_1$: 411.23, found: 411.24 $[M+Na]^+$.



Compound 459: Propargyl alcohol **458** (27 mg, 0.07 mmol) was dissolved in methanol (2 mL) at room temperature. Quinoline (~ 5 μL) was added, followed by Pd/$BaSO_4$ (5% weight Pd, 3 mg). An atmosphere of hydrogen was created (balloon), and the mixture was stirred 50 minutes, before it was filtered through celite. Column chromatography gave olefin **459** as an oil (26 mg, 96%). TLC (ethyl acetate/hexanes 1:4): R_f = 0.4 (above **458**); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.09 (s, 3H), 0.10 (s, 3H), 0.92 (s, 9H), 1.29 (m, 3H), 1.57 (m, 3H), 2.33 (s, 3H), 2.87 (dd, J = 4.8, 14.0 Hz, 1H), 2.96 (ddd, J = 5.2, 8.8, 14.0 Hz, 1H), 3.82 (s, 3H), 4.46 (m, 1H), 4.68 (m, 1H), 5.45-5.55 (m, 2H), 6.06 (m, 1H), 6.61 (s, 1H), 6.82 (dd, J = 10.4, 15.6 Hz, 1H), 6.9 (d, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 138.0, 136.8, 136.6, 133.9, 133.19. 133.17, 126.1, 125.7, 125.5, 121.2, 119.5, 119.4, 110.2, 69.6, 69.4, 68.1, 68.0, 55.6, 33.64, 33.58, 26.0, 24.8, 21.7, 18.4, 13.3, -4.4, -4.6

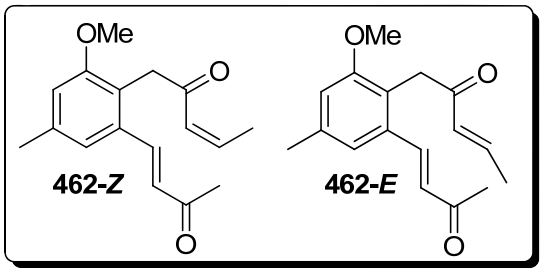


Compound 460: Allylic alcohol **459** (24 mg, 0.06 mmol) was dissolved in methylene chloride (1 mL) and DMSO (1 ml) at room temperature. IBX (52 mg, 0.18 mmol) was added and the solution stirred 4 hours before hexanes were added. Water was then added and repeated diethyl ether extractions were performed. The ether extracts were combined and dried over $MgSO_4$. Column chromatography gave enone **460** as an oil (21 mg, 88%). TLC (ethyl acetate/hexanes 1:4): R_f = 0.6; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.08 (s, 3H), 0.90 (s, 9H), 1.27 (d, J = 6.0 Hz, 3H), 2.08 (d, J = 2.4 Hz, 3H), 2.34 (s, 3H), 3.78 (s, 3H), 3.79 (d, J = 3.2 Hz, 2H), 4.44 (m, 1H), 6.01 (dd, J = 5.6, 16.0 Hz,1H), 6.09-6.16 (m, 1H), 6.55-6.64 (m, 1H), 6.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.9, 157.3, 142.8, 137.9, 137.7, 137.1, 126.7, 125.3, 119.2, 118.5, 110.2, 69.4, 55.6, 41.7, 26.0, 24.7, 21.8, 18.4, 16.0, -4.4, -4.6; ESI-MS: *m/z* calcd. for $C_{23}H_{36}O_3Si_1Na_1$: 411.23, found: 411.23 $[M+Na]^+$.

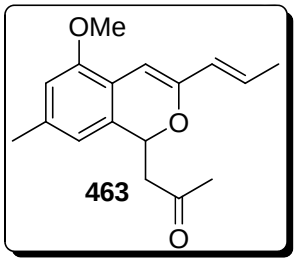


Compound 461: Silyl ether **460** (20 mg, 0.05 mmol) was dissolved in an AcOH/H_2O/THF (13:7:7, 1 mL) solution and THF (1 mL) was added at room temperature. The solution was stirred 28 hours, and then diluted with diethyl ether. The solution was then neutralized by adding saturated aqueous $NaHCO_3$ followed by solid Na_2CO_3. Repeated ether extractions were performed and the combined extracts were dried over $MgSO_4$. Column chromatography gave allylic alcohols **461-*Z*** and **461-*E*** (10 mg, 70% combined yield). TLC (ethyl acetate/hexanes

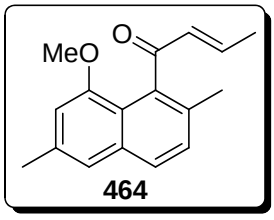
1:4): R_f = 0.2; **461-*Z*** ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.34 (d, J = 6.5 Hz, 3H), 2.07 (d, J = 5.5 Hz, 3H), 2.34 (s, 3H), 3.80 (s, 3H), 3.81 (s, 2H), 4.46 (m, 1H), 6.07-6.17 (m, 3H), 6.63 (s, 1H), 6.66 (d, J = 16.5 Hz, 1H), 6.91 (s, 1H); **461-*E*** ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (d, J = 6.5 Hz, 3H), 1.86 (d, J = 6.5 Hz, 3H), 2.34 (s, 3H), 3.78 (s, 3H), 3.88 (s, 2H), 4.44 (m, 1H), 6.09 (dd, J = 6.5, 15.5 Hz, 1H), 6.16 (d, J = 15.5 Hz, 1H), 6.63 (s, 1H), 6.63 (d, J = 16.0 Hz, 1H), 6.91 (s, 1H), 6.89-6.97 (m, 1H).



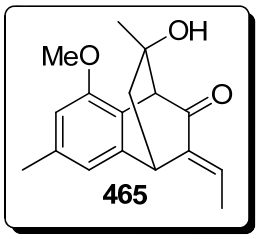
Compound 462: Allylic alcohol **461** (33 mg, 0.12 mmol) was dissolved in methylene chloride (3 mL) and DMSO (1 mL) at room temperature. IBX (100 mg, 0.36 mmol) was added and the solution was stirred. After 3 hours, hexanes were added, followed by water. Repeated diethyl ether extractions were performed and the extracts combined. The extracts were dried over $MgSO_4$ and subjected to column chromatography. Dienones **462-*Z*** and **462-*E*** were obtained (30 mg, 92% combined yield). TLC (ethyl acetate/hexanes 2:3): R_f = 0.4; **462-*Z*** ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.08 (d, J = 5.0 Hz, 3H), 2.36 (s, 3H), 2.37 (s, 3H), 3.82 (s, 3H), 3.91 (s, 2H), 6.14-6.22 (m, 2H), 6.58 (d, J = 16.0 Hz, 1H), 6.08 (s, 1H), 7.04 (s, 1H), 7.69 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 157.2, 143.8, 140.9, 138.0, 135.0, 129.3, 126.6, 120.7, 119.3, 113.0, 55.8, 41.4, 27.5, 21.8, 16.1; **462-*E*** ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.89 (d, J = 6.5 Hz, 3H), 2.35 (s, 3H), 2.36 (s, 3H), 3.81 (s, 3H), 3.98 (s, 3H), 6.18 (m, J = 16 Hz, 1H), 6.58 (d, J = 16.0 Hz, 1H), 6.75 (s, 1H), 6.97 (dq, J = 7, 15.5 Hz, 1H), 7.04 (s, 1H), 7.67 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 196.7, 157.3, 143.0, 140.9, 138.0, 135.1, 130.6, 129.3, 120.6, 119.4, 113.0, 55.8, 38.0, 29.8, 18.5, 14.3; **462-*Z*** HR-FAB-MS: *m/z* calcd. for $C_{17}H_{21}O_3$: 273.1495, found: 273.1485 $[M+H]^{+;}$ **462-*E*** HR-FAB-MS: *m/z* calcd. for $C_{17}H_{21}O_3$: 273.1496, found: 273.1435 $[M+H]^+$.



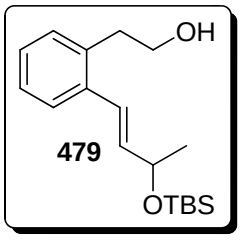
Compound 463: Pyran **463** was isolated at any stage of the reaction conditions which formed naphthalene **464** and enone **465**. Yields of pyran **463** decreased with increased reaction times. TLC (ethyl acetate/hexanes 2:3): R_f = 0.7; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.80 (d, 6.4 Hz, 3H), 2.18 (s, 3H), 2.31 (s, 3H), 2.60 (dd, J = 4.4, 15.6 Hz, 1H), 3.17 (dd, J = 8.8, 15.6 Hz, 1H), 3.83 (s, 3H), 5.61 (dd, J = 4.4, 8.8 Hz, 1H), 5.95 (d, 15.6 Hz, 1H), 6.01 (s, 1H), 6.01-6.10 (m, 1H), 6.46 (s, 1H), 6.57 (s, 1H); ESI-MS: *m/z* calcd. for $C_{17}H_{20}O_3Na_1$: 295.13, found: 295.13 $[M+Na]^+$.



Compound 464: Naphthalene **464** was isolated in varied yields, and its formation was dependent upon specific reaction conditions. Typical conditions are as follows: Dienone **462** (2.3 mg, 0.008 mmol) was dissolved in DMSO-d6 (0.7 mL) and pyrollidine (0.6 μL, 0.007 mmol) was added at room temperature. The solution was heated at 50 °C for 13 hours. The mixture was partitioned between diethyl ether and aqueous NH_4Cl, dried over $MgSO_4$, and purified by column chromatography. Naphthalene **464** was isolated as an oil (< 1mg). TLC (ethyl acetate/hexanes 2:3): $R_f = 0.7$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.83 (dd, J = 1.6, 6.8 Hz, 3H), 2.30 (s, 3H), 2.46 (s, 3H), 3.79 (s, 3H), 6.20 (dq, J = 6.8, 16.0 Hz, 1H), 6.43 (dq, J = 1.6, 16.0 Hz, 1H), 6.64 (s, 1H), 7.20 (s, 1H), 7.26 (m, 1H), 7.62 (d, J = 8.4 Hz, 1H); ESI-MS: *m/z* calcd. for $C_{17}H_{18}O_2Na_1$: 277.12, found: 277.14 $[M+Na]^+$.

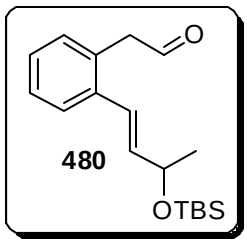


Compound 465: Tricycle **464** was isolated in varied yields, and its formation was dependent upon specific reaction conditions. Typical conditions are as follows: Dienone **462** (2.3 mg, 0.008 mmol) was dissolved in DMSO-d6 (0.7 mL) and pyrollidine (0.6 μL, 0.007 mmol) was added at room temperature. The solution was heated at 50 °C for 13 hours. The mixture was partitioned between diethyl ether and aqueous NH_4Cl, dried over $MgSO_4$, and purified by column chromatography. Tricycle **464** was isolated as an oil (~ 1mg). TLC (ethyl acetate/hexanes 2:3): $R_f = 0.3$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.16 (s, 3H), 1.78 (dd, J = 3.0, 17.5 Hz, 1H), 1.88 (d, J = 7.5 Hz, 3H), 2.03 (dd, J = 3.0, 14.0 Hz, 1H), 2.34 (s, 3H), 3.79 (s, 3H), 4.06 (s, 1H), 4.10 (m, 1H), 6.56-6.68 (m, 3H [includes : 6.65 (s) and 6.57 (s)]); ESI-MS: *m/z* calcd. for $C_{17}H_{20}O_3Na_1$: 295.13, found: 295.15 $[M+Na]^+$.

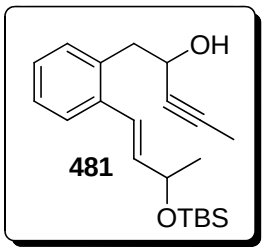


Compound 479: Aryl bromide **477** (930 mg, 4.63 mmol) and stannane **449** (2.08 g, 6.98 mmol) were mixed under argon and dissolved in toluene (15 mL). The solution was degassed by bubbling argon through the solution with stirring for 10 minutes. $Pd_2(dba)_3$ (430 mg, 0.47 mmol) was added at room temperature, followed rapidly by P(*t*-Bu)$_3$ (112 mg, 0.55 mmol) addition as a 10% hexane solution. The solution was placed in an 80 °C oil bath and stirred 12 hours before cooling to room temperature. The solution was then filtered through a silica plug and concentrated for column chromatography. At this stage, dibenzylidene acetone could be precipitated via trituration with ether and hexanes. Column chromatography provided alcohol **452** as an oil (963 mg, 68%). TLC (ethyl acetate/hexanes 1:3): $R_f = 0.3$; ^1H NMR (300 MHz, $CDCl_3$): δ 0.10 (s, 3H), 0.11 (s, 3H), 0.94 (s, 9H), 1.30 d, J = 6.3 Hz, 3H), 2.96 (t, 2H), 3.81 (m, 2H), 4.50 (m, 1H), 6.12 (dd,

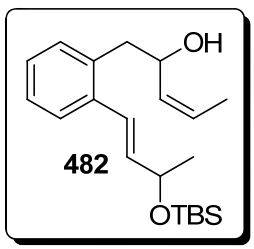
J = 5.4, 16.0 Hz, 1H), 6.81 (d, J = 16.0 Hz, 1H), 7.16-7.24 (m, 3H), 7.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.6, 136.5, 135.5, 130.4, 127.3, 126.9, 126.3, 125.0, 69.3, 63.0, 36.5, 25.9, 24.7, 18.3, -4.6, -4.8; ESI-MS: *m/z* calcd. for $C_{18}H_{31}O_2Si_1$: 307.20, found: 307.21 $[M+H]^+$.



Compound 480: Alcohol **479** (930 mg, 3.03 mmol) was dissolved in methylene chloride (10 mL) and DMSO (5 mL) at room temperature. To the stirred solution was added IBX (2.53 g, 9.04 mmol). The reaction was stirred 3 hours, and then diluted with hexanes. Water was added to the resultant slurry and repeated diethyl ether extractions were performed. The combined ether extracts were dried over $MgSO_4$ and concentrated. The crude mixture was filtered through a silica plug to provide aldehyde **480** as an oil (905 mg, 98%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.6; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.09 (s, 3H), 0.10 (s, 3H), 0.93 (s, 9H), 1.30 (d, 3H), 3.76 (s, 2H), 4.48 (m, 1H), 6.14 (dd, J = 5.4, 15.8 Hz, 1H), 6.65 (d, J = 15.8 Hz, 1H), 7.16 (d, J = 7.6 Hz, 1H), 7.27 (m, 2H), 7.50 (d, J = 7.6 Hz, 1H), 9.69 (t, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.9, 137.7, 137.1, 130.7, 129.4, 127.8, 127.6, 126.6, 124.4, 69.1, 48.4, 26.0, 24.7, 18.4, -4.4, -4.6.

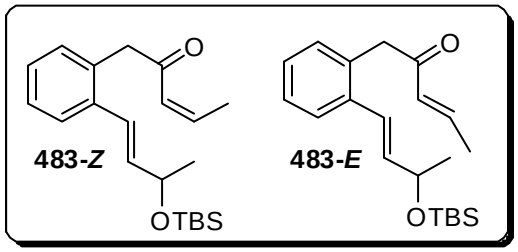


Compound 481: To a stirred THF (10 mL) solution of aldehyde **480** (3.1 g, 10.18 mmol) at 0 °C, was added 1-propynyl magnesium bromide (30.0 mL, 15.0 mmol), dropwise over 5 minutes, as a 0.5 M THF solution. The reaction was stirred 1.5 hours, and then hexanes were added, followed by aqueous NH_4Cl. Extraction with diethyl ether was performed, and the combined organic extracts were dried over $MgSO_4$ prior to concentration. Column chromatography gave propargyl alcohol **481** as an oil (2.3 g, 65%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.11 (s, 6H), 0.94 (s, 9H), 1.31 (d, J = 6.0 Hz, 3H), 1.83 (d, J = 2.0 Hz, 3H), 3.05 (m, 2H), 4.50 (m, 2H), 6.11 (dd, J = 2.4, 15.6 Hz, 1H), 6.84 (d, J = 15.6, 1H), 7.22 (m, 3H), 7.46 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.6, 134.2, 134.1, 131.0, 127.1, 127.0, 126.2, 126.1, 125.1, 125.0, 81.8, 79.7, 69.3, 69.2, 63.0, 62.9, 41.8, 26.0, 24.8, 18.4, 3.754, -4.4, -4.5; HR-EI-MS: *m/z* calcd. for $C_{21}H_{32}O_2Si_1$: 344.2174, found: 344.2166 $[M+H]^+$.

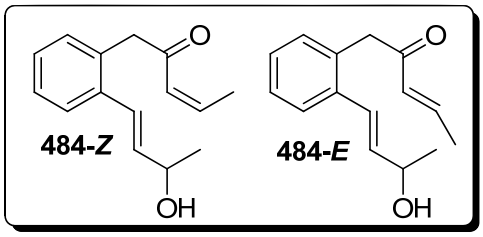


Compound 482: Propargyl alcohol **481** (620 mg, 1.80 mmol) was dissolved in methanol (10 mL) at room temperature. Quinoline (~ 50 μL) was added, followed by Pd/$BaSO_4$ (5%

weight Pd, 40 mg). An atmosphere of hydrogen was created (balloon) and the mixture was stirred 50 minutes, and then filtered through celite. Column chromatography gave olefin **482** as an oil (549 mg, 88%). Mixture of diastereomers: TLC (ethyl acetate/hexanes 1:3): R_f = 0.5; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.10 (s, 6H), 0.11 (s, 6H), 0.93 (s, 18H), 1.31 (dd, J = 1.5, 6.5 Hz, 3H), 1.32 (dd, J = 1.5, 6.5 Hz, 3H), 1.48 (m, 3H), 1.52 (m, 3H), 2.85 (ddd, J = 5.5, 13.0, 13.5 Hz, 2H), 2.94 (ddd, J = 7.5, 13.5, 13.5 Hz, 2H), 4.50 (m, 2H), 4.67 (m, 2H), 5.43-5.58 (m, 4H), 6.11 (m, 2H), 6.85 (m, 2H), 7.12 (m, 6H), 7.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.8, 136.7, 136.6, 135.2, 135.1, 132.3, 131.0, 130.9, 127.21, 127.17, 126.88, 126.87, 126.74, 126.72, 126.3, 126.2, 125.7, 125.2, 69.6, 69.2, 67.8, 41.1, 41.0, 25.9, 24.7, 25.9, 24.7, 18.3, 13.2, 13.155, -4.5, -4.6, -4.7, -4.8; HR-EI-MS: *m/z* calcd. for $C_{21}H_{35}O_2Si_1$: 347.2328, found: 347.2385 $[M+H]^+$.

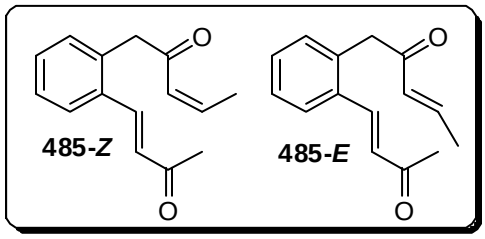


Compound 483: Allylic alcohol **482** (140 mg, 0.40 mmol) was dissolved in methylene chloride (5 mL) and DMSO (2 ml) at room temperature. IBX (300 mg, 1.07 mmol) was added and the solution stirred 5 hours before hexanes were added. Water was then added and repeated diethyl ether extractions were performed. The ether extracts were combined and dried over $MgSO_4$. Column chromatography gave enone mixture **483** as an oil (127 mg, 91%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.7 (**483-*Z*** above **483-*E***); **483-*Z*** ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.08 (s, 3H), 0.09 (s, 3H), 0.92 (s, 9H), 1.29 (d, J = 6.3 Hz, 3H), 2.11 (d, J = 5.7 Hz, 3H), 3.79 (s, 2H), 4.47 (m, 1H), 6.09 (dd, J = 5.4, 15.6 Hz, 1H), 6.15-6.26 (m, 2H), 6.65 (d, J = 15.6 Hz, 1H), 7.11-7.28 (m, 3H), 7.48 m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.4, 144.3, 137.2, 137.0, 132.2, 130.8, 127.5, 127.4, 126.6, 126.4, 125.1, 69.3, 49.0, 25.9, 24.6, 18.3, 16.0, -4.6, -4.8; **483-*E*** ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.28 (d, J = 6.3 HZ, 3H), 1.86 (dd, J = 1.5, 6.9 Hz, 3H), 3.87 (s, 2H), 4.46 (m, 1H), 6.08 (dd, J = 5.1, 15.6 Hz, 1H), 6.16 (dd, J = 1.5, 15.6 Hz, 1H), 6.63 (d, J = 15.6 Hz, 1H), 6.92 (dq, J = 6.9, 15.6 Hz, 1H), 7.10-7.23 (m, 3H), 7.46 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.0, 143.3, 137.2, 137.0, 132.1, 130.64, 130.62, 127.4, 127.3, 126.5, 125.1, 69.2, 45.4, 25.9, 24.6, 18.3, -4.6, -4.8. HR-EI-MS: *m/z* calcd. for $C_{21}H_{32}O_2Si_1$: 344.2172, found: **483-*Z*** 344.2166 $[M]^+$; **483-*E*** 344.2185 $[M]^+$.

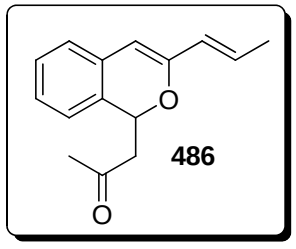


Compound 484: Silyl ether **483** (1.01 g, 2.93 mmol) was dissolved in an AcOH/H_2O/THF (2:1:1, 7 mL) solution. The solution was stirred 9 hours then diluted with diethyl ether and water. Na_2CO_3 was added and the

resultant slurry extracted with diethyl ether. Repeated ether extractions were performed and the combined extracts were dried over $MgSO_4$. Column chromatography gave allylic alcohols **484-*Z*** and **484-*E*** (465 mg, 70% combined yield). TLC (ethyl acetate/hexanes 9:11): R_f = 0.4 (**484-*Z*** above **484-*E***); **484-*Z*** ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.36 (d, J = 6.8 Hz, 3H), 2.10 (d, J = 5.6 Hz, 3H), 3.80 (s, 2H), 4.48 (m, 1H), 6.09-6.25 (m, 3H), 6.69 (d, J = 15.6 Hz, 1H), 7.15-7.26 (m, 3H), 7.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 144.3, 136.5, 136.2, 132.1, 130.7, 127.7, 127.3, 126.5, 126.4, 126.3, 68.8, 49.3, 23.4, 16.1; **484-*E*** ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35 (d, J = 6.5 Hz, 3H), 1.87 (dd, J = 2.0, 7.0 Hz, 3H), 3.87 (s, 2H), 4.47 (m, 1H), 6.12 (dd, J = 6.5, 15.5 Hz, 1H), 6.16 (m, 1H), 6.67 (d, J = 16.0 Hz, 1H), 6.93 (dq, J = 7.0, 15.5 Hz, 1H), 7.13-7.25 (m, 3H), 7.47 (m, 1H); HR-EI-MS: *m/z* calcd. for $C_{15}H_{18}O_2$: 230.1307, found: 230.1311 $[M]^+$.

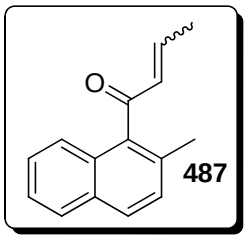


Compound 485: Allylic alcohol **484** (317 mg, 1.38 mmol) was dissolved in methylene chloride (5 mL) and DMSO (3 mL) at room temperature. IBX (940 mg, 3.36 mmol) was added and the solution stirred. The reaction was monitored by TLC, and when the starting material had been consumed, hexanes were added, followed by water. Repeated diethyl ether extractions were performed and the extracts combined. The extracts were dried over $MgSO_4$ and subjected to column chromatography. Dienones **485-*Z*** and **485-*E*** were obtained (299 mg, 95% combined yield). TLC (ethyl acetate/hexanes 2:3): R_f = 0.5; **485-*Z*** ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.09 (d, J = 6.5 Hz, 1H), 2.38 (s, 3H), 3.90 (s, 2H), 6.17-6.29 (m, 2H), 6.62 (d, J = 16.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.63 (d, J = 7.5 Hz, 1H), 7.70 (d, J = 16.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.5, 197.7, 145.2, 140.6, 134.4, 134.1, 131.5, 130.4, 129.0, 127.8, 126.8, 126.3, 49.1, 27.4, 16.0; **485-*E*** ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.90 (d, J = 2.0 Hz, 3H), 2.37 (s, 3H), 3.98 (s, 2H), 6.19 (dd, J = 1.5, 15.5 Hz, 1H), 6.62 (d, J = 16.0 Hz, 1H), 6.98 (dq, J = 7.5, 15.5 Hz, 1H), 7.22 (d, J = 6.0 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.62 (d, J = 7.0 Hz, 1H), 7.69 (d, J = 16.0 Hz, 1H); HR-EI-MS: *m/z* calcd. for $C_{15}H_{16}O_2$: 228.1131, found: 228.1145 $[M]^+$.

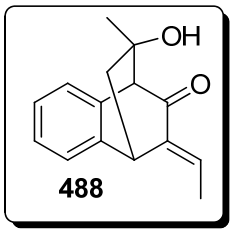


Compound 486 Pyran **486** was isolated at any stage of the reaction conditions which formed naphthalene **487** and enone **488**. Yields of pyran **463** decreased with increased reaction times. TLC (ethyl acetate/hexanes 2:3): R_f = 0.7 (slightly below **487**); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.82 (dd, J = 1.5, 7.0 Hz, 3H), 2.19 (s, 3H), 2.68 (dd, J = 4.0, 16.0 Hz, 1H), 3.20 (dd, J = 9.0, 16.0 Hz, 1H), 5.69 (dd, J = 5.0, 9.0 Hz, 1H), 5.73

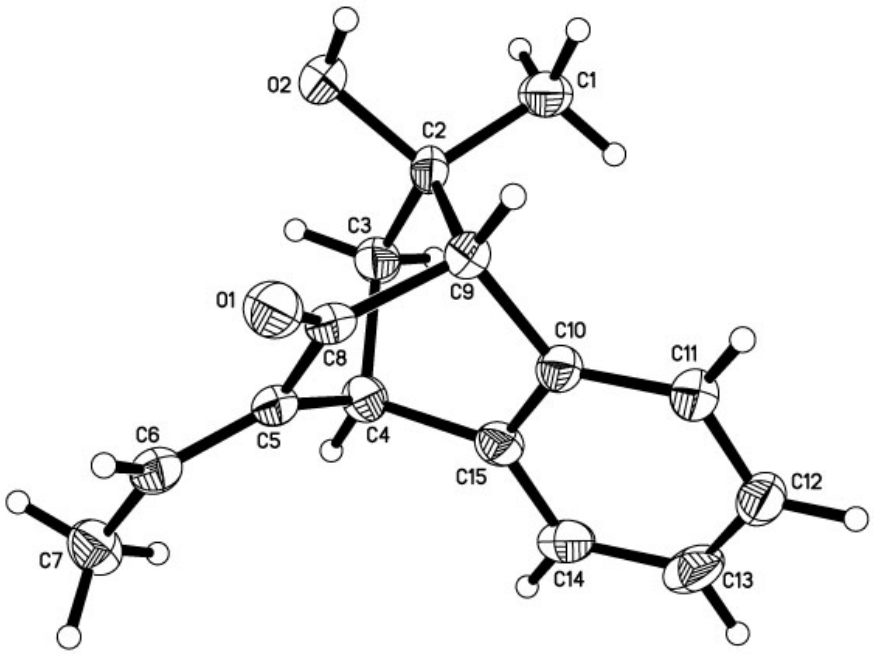
(s, 1H), 5.94 (dd, J = 2.0, 15.0 Hz, 1H), 6.14 (m, 1H [poorly resolved dq, J = 7.0, 15.0 Hz]), 7.0 (app. t, J = 7.0 Hz, 2H), 7.12 (t, J = 7.5 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.2, 150.4, 130.9, 130.4, 128.3, 128.2, 126.4, 125.8, 123.8, 123.7, 103.0, 73.8, 47.4, 31.3, 18.2; ESI-MS: *m/z* calcd. for $C_{15}H_{17}O_2$: 229.12, found: 229.12 $[M+H]^+$.



Compound 487: Naphthalene **487** was isolated in varied yields, and its formation was dependent upon specific reaction conditions. Typical conditions were as follows: Dienone **485** (10 mg, 0.04 mmol) was dissolved in DMSO (1 mL) and pyrollidine (3 mg, 0.04 mmol) was added at room temperature. The solution was heated at 55 °C for 16 hours. The mixture was partitioned between diethyl ether and aqueous NH_4Cl, dried over $MgSO_4$, and purified by column chromatography. Naphthalene **487** was isolated as an oil (2 mg, 20%). TLC (ethyl acetate/hexanes 2:3): R_f = 0.7 (slightly above **486**); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.90 (dd, J = 2.0, 5.5 Hz, 3H), 2.37 (s, 3H), 6.47-6.54 (m, 2H), 7.32 (d, J = 15.5 Hz, 1H), 7.40-7.47 (m, 2H), 7.55-7.60 (m, 1H), 7.76-7.85 (m, 2H [including 7.79 (d, J =15.5 Hz]); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.0, 149.2, 136.3, 134.3, 131.7, 131.6, 130.4, 128.7, 128.4, 128.0, 126.6, 125.3, 124.8, 19.6, 18.6; ESI-MS: *m/z* calcd. for $C_{15}H_{14}O_1Na_1$: 233.09, found: 233.10 $[M+Na]^+$.



Compound 488: Tricycle **488** was isolated in varied yields, and its formation was dependent upon specific reaction conditions. Typical conditions are as follows: Dienone **485** (10 mg, 0.04 mmol) was dissolved in DMSO (1 mL) and pyrollidine (3 mg, 0.04 mmol) was added at room temperature. The solution was heated at 55 °C for 16 hours. The mixture was partitioned between diethyl ether and aqueous NH_4Cl, dried over $MgSO_4$, and purified by column chromatography. Tricycle **488** was isolated as an oil (6-7 mg, 65%). TLC (ethyl acetate/hexanes 2:3): R_f = 0.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (s, 3H), 1.82 (dd, J = 2.8, 13.4 Hz, 1H), 1.90 (d, J = 7.4 Hz, 3H), 2.09 (dd, J = 2.8, 13.4 Hz, 1H), 3.62 (s, 1H), 4.19 (app. t, J = 2.8 Hz, 1H), 6.70 (q, J = 7.4 Hz, 1H), 7.17-7.26 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.7, 141.1, 134.9, 134.8, 130.0, 127.8, 127.0, 126.6, 123.1, 74.2, 66.6, 43.7, 38.6, 30.3, 13.8; ESI-MS: *m/z* calcd. for $C_{15}H_{16}O_2Na_1$: 251.11, found: 251.12 $[M+Na]^+$. A crystal suitable for x-ray analysis was grown and the following data was obtained:



Crystal data and structure refinement for Fischer.

Identification code	DF1	
Empirical formula	C15 H16 O2	
Formula weight	228.28	
Temperature	100 K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pna2(1)	
Unit cell dimensions	a = 16.1749(16) Å	α= 90°.
	b = 8.4717(8) Å	β= 90°.
	c = 17.8514(18) Å	γ = 90°.
Volume	2446.2(4) $Å^3$	
Z	8	
Density (calculated)	1.240 Mg/m^3	
Absorption coefficient	0.081 mm^{-1}	

F(000)	976
Crystal size	0.30 x 0.06 x 0.06 mm^3
Theta range for data collection	2.28 to 25.00°.
Index ranges	-19<=h<=19, -10<=k<=10, -21<=l<=21
Reflections collected	16776
Independent reflections	4314 [R(int) = 0.0511]
Completeness to theta = 25.00°	100.0 %
Absorption correction	None
Max. and min. transmission	0.9952 and 0.9761
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4314 / 1 / 317
Goodness-of-fit on F^2	1.028
Final R indices [I>2sigma(I)]	R1 = 0.0429, wR2 = 0.0924
R indices (all data)	R1 = 0.0645, wR2 = 0.1012
Absolute structure parameter	-0.3(16)
Largest diff. peak and hole	0.182 and -0.161 e.$Å^{-3}$

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for Fischer. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	8509(1)	2751(2)	258(1)	31(1)
O(2)	8470(1)	5070(2)	-1263(1)	30(1)
C(1)	9855(2)	5243(3)	-1766(2)	30(1)
C(2)	9200(2)	4173(3)	-1437(2)	25(1)
C(3)	8931(2)	2850(4)	-1978(2)	29(1)
C(4)	8998(2)	1222(3)	-1600(2)	25(1)
C(5)	8492(2)	1259(3)	-882(2)	24(1)
C(6)	7846(2)	363(3)	-690(2)	27(1)
C(7)	7461(2)	-914(3)	-1141(2)	34(1)
C(8)	8795(2)	2490(3)	-371(2)	25(1)
C(9)	9522(2)	3403(3)	-699(2)	25(1)
C(10)	10181(2)	2199(3)	-897(2)	23(1)
C(11)	10989(2)	2221(3)	-646(2)	28(1)

C(12)	11524(2)	1042(3)	-882(2)	33(1)
C(13)	11248(2)	-149(4)	-1353(2)	37(1)
C(14)	10431(2)	-172(3)	-1596(2)	30(1)
C(15)	9898(2)	1014(3)	-1369(2)	26(1)
O(1A)	9091(1)	7300(2)	-262(2)	32(1)
O(2A)	9115(1)	4987(2)	1256(1)	31(1)
C(1A)	7726(2)	4818(3)	1746(2)	33(1)
C(2A)	8389(2)	5891(3)	1421(2)	24(1)
C(3A)	8663(2)	7214(4)	1960(2)	30(1)
C(4A)	8595(2)	8861(4)	1575(2)	29(1)
C(5A)	9112(2)	8784(3)	878(2)	26(1)
C(6A)	9777(2)	9632(3)	698(2)	32(1)
C(7A)	10184(2)	10849(4)	1169(2)	45(1)
C(8A)	8802(2)	7566(3)	354(2)	24(1)
C(9A)	8073(2)	6670(3)	683(2)	23(1)
C(10A)	7426(2)	7869(4)	868(2)	24(1)
C(11A)	6612(2)	7861(4)	614(2)	33(1)
C(12A)	6074(2)	9042(4)	850(2)	44(1)
C(13A)	6348(2)	10200(4)	1320(2)	45(1)
C(14A)	7165(2)	10233(4)	1576(2)	39(1)
C(15A)	7701(2)	9055(3)	1349(2)	27(1)

Bond lengths [Å] and angles [°] for Fischer.

O(1)-C(8)	1.234(4)
O(2)-C(2)	1.438(3)
C(1)-C(2)	1.513(4)
C(2)-C(3)	1.542(4)
C(2)-C(9)	1.559(4)
C(3)-C(4)	1.540(4)
C(4)-C(5)	1.521(4)
C(4)-C(15)	1.524(4)
C(5)-C(6)	1.337(4)
C(5)-C(8)	1.470(4)

C(6)-C(7)	1.484(4)
C(8)-C(9)	1.524(4)
C(9)-C(10)	1.516(4)
C(10)-C(11)	1.383(4)
C(10)-C(15)	1.388(4)
C(11)-C(12)	1.386(4)
C(12)-C(13)	1.388(4)
C(13)-C(14)	1.389(4)
C(14)-C(15)	1.384(4)
O(1A)-C(8A)	1.216(4)
O(2A)-C(2A)	1.431(3)
C(1A)-C(2A)	1.521(4)
C(2A)-C(3A)	1.542(4)
C(2A)-C(9A)	1.561(4)
C(3A)-C(4A)	1.560(4)
C(4A)-C(5A)	1.500(4)
C(4A)-C(15A)	1.510(4)
C(5A)-C(6A)	1.333(4)
C(5A)-C(8A)	1.480(4)
C(6A)-C(7A)	1.484(4)
C(8A)-C(9A)	1.520(4)
C(9A)-C(10A)	1.496(4)
C(10A)-C(11A)	1.392(4)
C(10A)-C(15A)	1.396(5)
C(11A)-C(12A)	1.391(5)
C(12A)-C(13A)	1.365(5)
C(13A)-C(14A)	1.399(5)
C(14A)-C(15A)	1.383(4)

O(2)-C(2)-C(1)	110.0(2)
O(2)-C(2)-C(3)	106.7(2)
C(1)-C(2)-C(3)	112.9(3)
O(2)-C(2)-C(9)	108.3(2)
C(1)-C(2)-C(9)	110.1(2)

C(3)-C(2)-C(9)	108.6(2)
C(4)-C(3)-C(2)	110.9(3)
C(5)-C(4)-C(15)	106.8(2)
C(5)-C(4)-C(3)	108.2(2)
C(15)-C(4)-C(3)	106.8(2)
C(6)-C(5)-C(8)	120.3(3)
C(6)-C(5)-C(4)	128.7(3)
C(8)-C(5)-C(4)	111.0(2)
C(5)-C(6)-C(7)	127.1(3)
O(1)-C(8)-C(5)	124.5(3)
O(1)-C(8)-C(9)	123.2(3)
C(5)-C(8)-C(9)	112.3(3)
C(10)-C(9)-C(8)	106.9(2)
C(10)-C(9)-C(2)	108.6(2)
C(8)-C(9)-C(2)	106.2(2)
C(11)-C(10)-C(15)	121.2(3)
C(11)-C(10)-C(9)	125.4(3)
C(15)-C(10)-C(9)	113.4(2)
C(10)-C(11)-C(12)	118.8(3)
C(11)-C(12)-C(13)	120.5(3)
C(12)-C(13)-C(14)	120.3(3)
C(15)-C(14)-C(13)	119.4(3)
C(14)-C(15)-C(10)	119.8(3)
C(14)-C(15)-C(4)	126.9(3)
C(10)-C(15)-C(4)	113.2(2)
O(2A)-C(2A)-C(1A)	109.7(2)
O(2A)-C(2A)-C(3A)	106.4(2)
C(1A)-C(2A)-C(3A)	113.5(3)
O(2A)-C(2A)-C(9A)	108.7(2)
C(1A)-C(2A)-C(9A)	110.1(2)
C(3A)-C(2A)-C(9A)	108.3(2)
C(2A)-C(3A)-C(4A)	110.8(3)
C(5A)-C(4A)-C(15A)	108.5(2)
C(5A)-C(4A)-C(3A)	106.7(2)

C(15A)-C(4A)-C(3A)	106.4(2)
C(6A)-C(5A)-C(8A)	119.8(3)
C(6A)-C(5A)-C(4A)	128.8(3)
C(8A)-C(5A)-C(4A)	111.4(2)
C(5A)-C(6A)-C(7A)	126.6(3)
O(1A)-C(8A)-C(5A)	124.7(3)
O(1A)-C(8A)-C(9A)	123.7(3)
C(5A)-C(8A)-C(9A)	111.6(3)
C(10A)-C(9A)-C(8A)	106.8(2)
C(10A)-C(9A)-C(2A)	109.3(2)
C(8A)-C(9A)-C(2A)	106.4(2)
C(11A)-C(10A)-C(15A)	120.4(3)
C(11A)-C(10A)-C(9A)	125.9(3)
C(15A)-C(10A)-C(9A)	113.6(3)
C(12A)-C(11A)-C(10A)	119.3(3)
C(13A)-C(12A)-C(11A)	120.0(3)
C(12A)-C(13A)-C(14A)	121.5(3)
C(15A)-C(14A)-C(13A)	118.9(3)
C(14A)-C(15A)-C(10A)	119.9(3)
C(14A)-C(15A)-C(4A)	127.0(3)
C(10A)-C(15A)-C(4A)	113.1(3)

Symmetry transformations used to generate equivalent atoms:

Anisotropic displacement parameters ($Å^2 x\ 10^3$) for Fischer. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

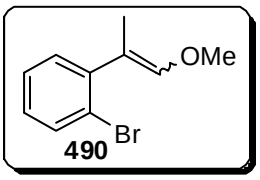
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	32(1)	27(1)	33(2)	-1(1)	7(1)	0(1)
O(2)	23(1)	27(1)	41(1)	3(1)	1(1)	4(1)
C(1)	33(2)	24(2)	35(2)	2(1)	4(1)	2(1)
C(2)	15(1)	26(2)	33(2)	6(1)	2(1)	0(1)
C(3)	25(2)	27(2)	34(2)	8(2)	-3(1)	-1(1)
C(4)	24(2)	25(2)	28(2)	-1(2)	-2(1)	-2(1)

C(5)	22(1)	20(2)	31(2)	6(1)	0(1)	3(1)
C(6)	26(2)	26(2)	29(2)	6(1)	-3(1)	4(1)
C(7)	33(2)	36(2)	33(2)	7(2)	-7(1)	-7(1)
C(8)	24(2)	18(2)	31(2)	4(1)	1(2)	4(1)
C(9)	21(1)	22(1)	31(2)	-1(1)	1(1)	1(1)
C(10)	22(2)	23(1)	25(2)	1(1)	3(1)	2(1)
C(11)	23(2)	28(2)	33(2)	2(2)	0(1)	0(1)
C(12)	23(2)	36(2)	41(2)	14(2)	3(1)	3(1)
C(13)	35(2)	33(2)	42(2)	9(2)	13(2)	15(2)
C(14)	37(2)	23(2)	31(2)	3(1)	6(1)	4(1)
C(15)	27(2)	23(2)	26(2)	5(1)	3(1)	-1(1)
O(1A)	33(1)	26(1)	37(2)	0(1)	8(1)	2(1)
O(2A)	24(1)	25(1)	44(1)	-1(1)	-4(1)	2(1)
C(1A)	34(2)	31(2)	33(2)	2(2)	5(1)	-1(1)
C(2A)	26(2)	17(2)	30(2)	0(1)	-4(1)	3(1)
C(3A)	33(2)	30(2)	25(2)	-4(2)	-4(1)	2(2)
C(4A)	36(2)	21(2)	29(2)	-1(1)	-6(1)	-2(1)
C(5A)	23(2)	21(2)	33(2)	3(1)	-5(1)	5(1)
C(6A)	30(2)	30(2)	35(2)	3(1)	-8(1)	-1(1)
C(7A)	42(2)	43(2)	49(2)	6(2)	-11(2)	-15(2)
C(8A)	21(1)	20(2)	32(2)	4(1)	-4(2)	7(1)
C(9A)	24(2)	22(1)	24(2)	-1(1)	-1(1)	-4(1)
C(10A)	20(2)	26(2)	26(2)	13(2)	2(1)	1(1)
C(11A)	23(2)	36(2)	40(2)	17(2)	4(1)	-1(2)
C(12A)	27(2)	51(2)	55(2)	24(2)	10(2)	8(2)
C(13A)	43(2)	40(2)	53(2)	25(2)	25(2)	21(2)
C(14A)	60(2)	26(2)	32(2)	5(2)	16(2)	9(2)
C(15A)	32(2)	23(2)	25(2)	7(1)	5(1)	4(1)

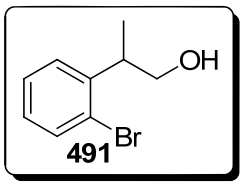
Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for Fischer.

	x	y	z	U(eq)

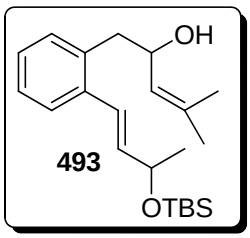
H(1)	8590(19)	5830(40)	-878(19)	52(10)
H(1A)	9648	5711	-2232	46
H(1B)	10354	4628	-1871	46
H(1C)	9985	6084	-1407	46
H(3A)	8353	3033	-2138	34
H(3B)	9286	2872	-2429	34
H(4A)	8812	357	-1942	30
H(6A)	7606	565	-214	33
H(7D)	7801	-1121	-1584	41
H(7E)	6906	-589	-1297	41
H(7F)	7423	-1876	-837	41
H(9A)	9736	4213	-340	29
H(11A)	11175	3029	-318	34
H(12A)	12083	1049	-719	40
H(13A)	11618	-953	-1510	44
H(14A)	10241	-993	-1914	36
H(2)	8892(17)	4250(40)	947(16)	27(8)
H(1AA)	7927	4351	2215	49
H(1AB)	7599	3977	1388	49
H(1AC)	7226	5435	1846	49
H(3AA)	9242	7028	2118	35
H(3AB)	8310	7196	2413	35
H(4AA)	8781	9729	1915	34
H(6AA)	10015	9436	220	38
H(7AF)	9878	10966	1640	54
H(7AD)	10188	11858	901	54
H(7AE)	10753	10525	1276	54
H(9AA)	7859	5861	324	28
H(11B)	6426	7058	283	39
H(12B)	5516	9042	684	53
H(13B)	5976	11002	1476	55
H(14B)	7349	11050	1900	47



Compound 490: $MeOCH_2PPh_3Cl$ (380 mg, 1.11 mmol) was dissolved in toluene (3.5 mL) and cooled to 0 C. KHMDS (2.0 mL, 1.0 mmol) was added in one portion as a 0.5 M toluene solution. After base addition, the ice bath was removed and the solution was stirred 30 minutes before being replaced in the ice bath. Bromoacetophenone **489** (140 mg, 0.70 mmol) was added in one portion. The ice bath was removed and the reaction was stirred at room temperature 1.5 hours. The reaction was then quenched with aqueous NH_4Cl and repeated diethyl extractions were performed. The combined ether extracts were dried over $MgSO_4$ and concentrated. Column chromatography gave enol ether **490** as a mixture of isomers (120 mg, 75%). TLC (ethyl acetate/hexanes 1:9): R_f = 0.3 and 0.4 (cis/trans).

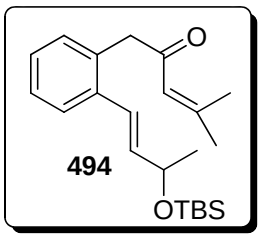


Compound 491: Enol ether **490** (32 mg, 0.14 mmol) was dissolved in THF (0.4 mL) and cooled to 0 °C. $HgOAc_2$ (54 mg, 0.17 mmol) was added in water (0.5 mL). The solution was stirred 1.5 hours, then $NaBH_4$ (23 mg, 0.61 mmol) was added along with 0.5 mL saturated aqueous K_2CO_3. The solution was stirred 15 minutes at 0 °C, then 30 minutes at room temperature. The solution was diluted with diethyl ether and aqueous NH_4Cl. Repeated ether extractions were performed, and the combined extracts were dried over $MgSO_4$. Column chromatography gave alcohol **491** as an oil (23 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (d, 7.0 Hz, 3H), 3.64 (m, 1H), 3.83 (dd, J = 6.0, 10.5 Hz, 1H), 3.93 (dd, J = 6.0, 10.5 Hz, 1H), 7.21 (m, 1H), 7.38-7.45 (m, 2H), 7.70 (d, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.3, 132.9, 127.8, 127.6, 127.5, 125.1, 67.3, 40.8, 17.1; ESI-MS: *m/z* calcd. for $C_9H_{11}O_1Br_1Na_1$: 236.99, 238.99, found: 237.0, 239.0 $[M+Na]^+$.

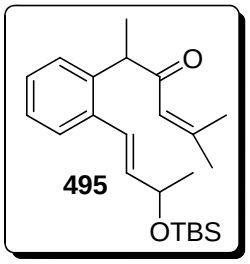


Compound 493: Aldehyde **480** (184 mg, 0.60 mmol) was freshly prepared, dissolved in THF (1 mL), and cooled to -78 °C. Anhydrous $CeCl_3$ (228 mg, 0.93 mmol) was added in one portion and the suspension was vigorously stirred. 2-methyl-1-propenyl-magnesium bromide (1.8 mL, 0.9 mmol) was added dropwise as a 0.5 M THF solution over ~2 minutes. The solution was stirred 3 hours at -78 °C, and then allowed to warm to room temperature over 2 hours. The reaction was quenched with aqueous NH_4CL and diluted further with water. Repeated diethyl ether extractions were performed, the extracts combined, and dried over $MgSO_4$. Column chromatography gave allylic alcohol **493** as an oil (159 mg, 73%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.10-0.13 (m, 6H), 0.93-0.95 (m, 9H), 1.29-1.34 (m, 3H), 1.48-1.54 (m, 3H), 1.68-1.78 (m, 3H), 2.80-2.95 (m, 2H), 4.44-4.59 (m, 2H), 5.21-5.28 (m, 1H), 6.07-6.17 (m, 1H), 6.78-

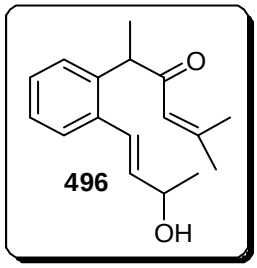
6.90 (m, 1H), 7.13-7.25 (m, 3H), 7.43-7.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.5, 136.3, 136.2, 135.3, 135.25, 130.83, 130.77, 127.0, 126.8, 126.77, 126.6, 126.1, 126.0, 125.6, 125.0, 69.59, 69.56, 69.21, 69.18, 69.0, 41.5, 41.3, 26.0, 25.98, 25.8, 24.8, 18.39, 18.38, -4.3, -4.5, -4.53, -4.6; ESI-MS: *m/z* calcd. for $C_{22}H_{36}O_2Si_1Na_1$: 383.24, found: 383.24 $[M+Na]^+$.



Compound 494: Allylic alcohol **493** (373 mg, 1.04 mmol) was dissolved in methylene chloride (3 mL) and DMSO (2.5 mL) at room temperature. IBX (720 mg, 2.57 mmol) was added and the reaction was stirred 12 hours before being diluted with hexanes and water. Repeated extraction with diethyl ether was performed and the extracts were combined prior to being dried over $MgSO_4$. Column chromatography gave enone **494** as an oil (338 mg, 91%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.6; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.09 (s, 3H), 0.92 (s, 9H), 1.29 (d, 3H), 1.85 (s, 3H), 2.14 (s, 3H), 3.76 (s, 2H), 4.47 (m, 1H), 6.06-6.09 (m, 1H), 6.11 (d, J = 5.6 Hz, 1H), 6.66 (d, J = 16.0 Hz, 1H), 7.11-7.16 (m, 1H), 7.19-7.26 (m, 2H), 7.45-7.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.2, 156.4, 136.84, 136.76, 132.5, 130.6, 127.3, 127.1, 126.22, 126.16, 122.7, 69.3, 49.0, 27.9, 26.0, 24.7, 21.0, 18.4, -4.4, -4.6; HR-EI-MS: *m/z* calcd. for $C_{22}H_{34}O_2Si_1$: 358.2319, found: 358.2323 $[M]^+$.

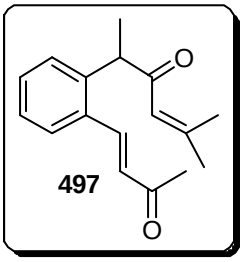


Compound 495: Enone **494** (327 mg, 0.91 mmol) was dissolved in dimethoxy ethane (10 mL) and KOH (113 mg, 2.02 mmol) was added in one portion at room temperature. MeI (0.09 mL, 1.44 mmol) was added in one portion directly after base addition. The reaction was stirred 2 hours, and then partitioned between diethyl ether and aqueous NH_4Cl. The organic extracts were combined and dried over $MgSO_4$. Column chromatography gave enone **495** as an oil (317 mg, 94%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.6 (slightly above **494**); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.10 (s, 3H), 0.11 (s, 3H), 0.93 (s, 9H), 1.30-1.36 (m, 6H), 1.75 (s, 3H), 2.15 (s, 3H), 4.02 (m, 1H), 4.53 (m, 1H), 5.87 (bs, 1H), 6.07-6.15 (m, 1H, [the 2 diastereomers can be differentiated at this peak: 6.09 (dd, J = 5.2, 15.6 Hz, 0.5H) and 6.13 (dd, J = 5.2, 15.6, 0.5H)]), 6.83-6.91 (m, 1H), 7.03-7.08 (m, 1H), 7.17-7.22 (m, 2H), 7.41-7.47 (m, 1H); HR-EI-MS: *m/z* calcd. for $C_{23}H_{36}O_2Si_1$: 372.2484, found: 372.2479 $[M]^+$.

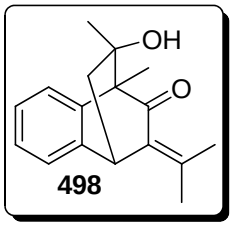


Compound 496: Silyl ether **495** (118 mg, 0.32 mmol) was dissolved in an AcOH/H_2O/THF (2:1:1, 3 mL) solution. The solution was stirred 12 hours and then diluted with diethyl ether and water. EtOAc extractions were performed, and the organic

extracts were combined. The organic extracts were washed with aqueous $NaHCO_3$, concentrated, and dried over $MgSO_4$. Column chromatography gave allylic alcohol **496** (63 mg, 78% combined yield). TLC (ethyl acetate/hexanes 1:3): R_f = 0.1; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (d, J = 7.2 Hz, 3H), 1.39 (d, J = 6.8 Hz, 3H), 1.76 (s, 3H), 2.14 (s, 3H), 3.99 (q, 7.2 Hz, 1H), 4.52 (m, 1H), 5.84 (s, 1H), 6.13 (dd, J = 6.2, 15.6 Hz, 1H), 6.88 (d, J = 15.6 Hz, 1H), 7.06-7.12 (m, 1H), 7.19-7.25 (m, 2H), 7.41-7.47 (m, 1H).

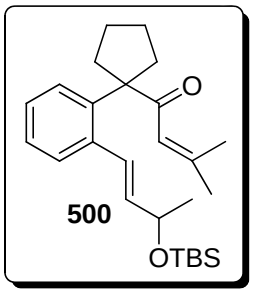


Compound 497: Allylic alcohol **496** (125 mg, 0.048 mmol) was dissolved in methylene chloride (8 mL) and DMSO (2 mL) at room temperature. IBX (400 mg, 1.43 mmol) was added and the solution stirred. The reaction was stirred 2.5 hours, and then hexanes were added, followed by water. Repeated diethyl ether extractions were performed and the extracts were combined. The extracts were dried over $MgSO_4$ and subjected to column chromatography. Dienone **497** was obtained as an oil (117 mg, 95% combined yield). TLC (ethyl acetate/hexanes 2:3): R_f = 0.6; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (d, J = 6.8 Hz, 3H), 1.77 (d, J =1.2 Hz, 3H), 2.14 (d, J = 1.2 Hz, 3H), 2.40 (s, 3H), 4.05 (q, J = 6.8 Hz, 1H), 5.85 (app. t, J = 1.2 Hz, 1H), 6.62 (d, J = 16.4 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.28 (t, J = 8.0 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.58 (d, 7.6 Hz, 1H), 7.88 (d, J = 16.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.6, 198.0, 156.8, 140.7, 140.3, 133.2, 130.5, 129.3, 128.3, 127.2, 122.7, 50.1, 27.9, 27.8, 21.0, 17.5; HR-EI-MS: *m/z* calcd. for $C_{17}H_{20}O_2$: 256.1458, found: 256.1458 $[M]^+$.

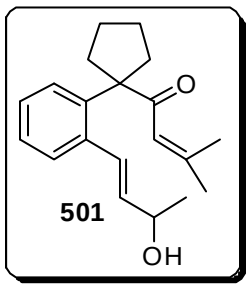


Compound 498: Tricycle **498** was isolated in varied yields, and its formation was dependent upon specific reaction conditions. Typical conditions were as follows: Dienone **497** (2 mg, 0.008 mmol) was dissolved in DMSO-d6 (0.7 mL) and pyrollidine (0.25 mL (0.03 M DMSO-d6 solution), 0.008 mmol) was added at room temperature. The solution was heated at 55 °C for 12 hours, then warmed to 75 °C for an additional 12 hours. The mixture was partitioned between diethyl ether and aqueous NH_4Cl, dried over $MgSO_4$, and purified by column chromatography. Tricycle **498** was isolated as an oil (1 mg, 50%). TLC (ethyl acetate/hexanes 2:3): R_f = 0.5 (likely effected by AcOH); major isomer ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (s, 3H), 1.53 (s, 3H), 1.90 (dd, J = 2.6, 13.6 Hz, 1H), 2.00 (s, 3H), 2.16 (dd, J = 3.2, 13.6 Hz, 1H), 4.19 (app. T, J = 2.8 Hz, 1H), 7.15-7.27 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.3, 145.7, 142.5, 142.1, 138.0, 130.3, 128.6, 127.5,

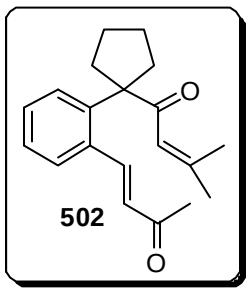
127.1, 126.9, 126.6, 125.0, 123.8, 123.0, 122.7, 75.5, 73.8, 61.93, 60.88, 47.0, 45.5, 40.1, 39.7, 27.2, 26.7, 23.4, 22.5, 9.3, 9.2; HRMS: *m/z* calcd. for $C_{17}H_{20}O_2Na_1$: 279.14, found: 279.14 $[M+Na]^+$.



Compound 500: Enone **494** (17 mg, 0.05 mmol) was dissolved in dimethoxyethane (0.5 mL). *t*-BuOK (12.5 mg, 0.11 mmol) was added in one portion and the reaction vigorously stirred. After 30 minutes, 1-4dibromobutane (9 mg, 0.04 mmol) was added and the reaction was heated to 45 °C. The reaction was quenched with aqueous NH_4Cl after 3 hours reaction. Repeated diethyl ether extractions were performed, the extracts combined, dried over $MgSO_4$, and subjected to column chromatography. Cyclopentane **500** was obtained as an oil (9 mg, 45%). TLC (ethyl acetate/hexanes 1:9): R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.08 (s, 3H), 0.90 (s, 9H), 1.25 (d, J = 6.4 Hz, 3H), 1.63-1.69 (m, 7H), 1.81-1.99 (m, 2H), 2.10 (s, 3H), 2.34-2.51 (m, 2H), 4.39 (m, 1), 5.75 (s, 1H), 5.92 (dd, J = 6.4, 15.6 Hz, 1H), 6.48 (d, J = 15.6 Hz, 1H), 7.16-7.29 (m, 2H), 7.39-7.45 (m, 2H); ESI-MS: *m/z* calcd. for $C_{26}H_{40}O_2Si_1Na_1$: 435.27, found: 435.28 $[M+Na]^+$.

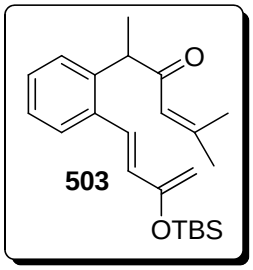


Compound 501: Silyl ether **500** (7 mg, 0.02 mmol) was dissolved in 0.5 mL of an AcOH/THF/H_2O (8:1:1) solution at room temperature. The mixture was stirred 10 hours, and then diluted with diethyl ether and water. Repeated ether extractions were performed and the combined extracts were dried over $MgSO_4$. Column chromatography gave allylic alcohol **501** as an oil (4-5 mg, ~90%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (d, 3H), 1.61-1.73 (m, 7H), 1.85-1.99 (m, 2H) 2.10 (s, 3H), 2.37-2.51 (m, 2H), 4.40 (m, 1H), 5.72 (s, 1H), 5.88 (dd, J = 6.4, 15.6 Hz, 1H), 6.62 (d, J = 15.6 Hz, 1H), 7.20-7.31 (m, 2H), 7.36 (m, 1H), 7.44 (m, 1H).

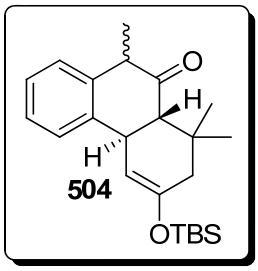


Compound 502: Allylic alcohol **501** (3 mg, 0.01 mmol) was dissolved in methylene chloride (0.5 mL) and DMSO (0.5 mL) at room temperature. IBX (7 mg, 0.03 mmol) was added and the reaction mixture was stirred 4 hours. The reaction was diluted with diethyl ether and water, and then repeated ether extractions were performed. The extracts were combined and dried over MgSO4. Column chromatography gave dienone **502** as an oil (2-3 mg, ~75%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67-1.74 (m, 7H), 1.90-2.02 (m, 2H), 2.09 (s, 3H), 2.38 (s, 3H),

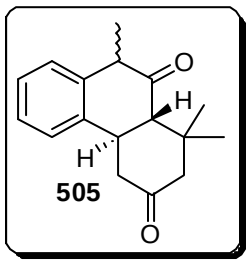
2.46-2.58 (m, 2H), 5.74 (s, 1H), 6.36 (d, J = 16.0 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.51-7.57 (m, 2H), 7.68 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.2, 199.3, 156.7, 143.4, 134.5, 130.0, 129.7, 127.7, 127.2, 126.4, 121.4, 64.4 35.8, 28.0, 26.1, 24.8, 20.9; HR-EI-MS: *m/z* calcd. for $C_{20}H_{24}O_2$: 296.1773, found: 296.1771 $[M]^+$.



Compound 503: Enone **497** (5 mg, 0.02 mmol) was dissolved in methylene chloride (0.5 mL) and cooled to -78 °C. Triethylamine (6 μL, 0.04 mmol) was added, followed by TBSOTf (7 μL, 0.03 mmol). The mixture was stirred 20 minutes, and then placed directly on a neutralized (10% NEt_3/Hexanes) silica column. Elution and concentration provided silyl enol ether **503** as an oil (6 mg, 80%). TLC (ethyl acetate/hexanes 1:3): R_f = ;0.6 ^{1}H NMR (400 MHz, C_6D_6): δ 0.15 (s, 3H), 0.17 (s, 3H), 1.00 (s, 9H), 1.49 (d, J = 6.8 Hz, 3H), 2.09 (s, 3H), 4.18 (q, J = 6.8 Hz, 1H), 4.38 (bs, 1H), 4.44 (bs, 1H), 5.87 (s, 1H), 6.49 (d, J = 15.0 Hz, 1H), 6.92-7.01 (m, 2H), 7.16-7.19 (m, 1H), 7.35-7.38 (m, 1H), 7.57 (d, J = 15.0 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6): δ 199.0, 155.8, 155.1, 140.1, 136.0, 129.5, 128.6, 127.3, 127.0, 123.8, 97.0, 49.9, 27.2, 26.0, 20.7, 18.4, 17.6, -4.5, -4.6.

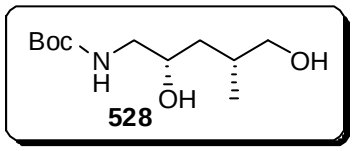


Compound 504: Triene **503** (11 mg, 0.03 mmol) was dissolved in *m*-xylene-d8 (0.7 mL) and transferred to a NMR tube. The reaction was heated at 120 °C for 8 hours, then 150 °C an additional 6 hours. After cooling to room temperature, the reaction mixture was concentrated and subjected to column chromatography. Tricycle **504** was obtained as a mixture of C19 isomers (10 mg, 91%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.6 (no R_f change from **503**, but no longer UV active); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.19-0.25 (m, 12H), 0.96 (s, 9H), 0.97 (s, 9H), 1.10 (s, 3H) 1.16 (s, 3H), 1.25 (s, 3H), 1.30 (s, 3H), 1.43 (d, J = 7.6 Hz, 3H), 1.51 (d, J = 6.8 Hz, 3H), 1.63-1.78 (m, 2H), 1.88 (d, J = 12.0 Hz, 1H), 2.01-2.17 (m, 2H), 2.26 (d, J = 12.8 Hz, 1H), 3.49 (q, J = 7.6 Hz, 1H), 3.57 (q, J =6.8 Hz, 1H), 3.66 (d, J = 12.8 Hz, 1H), 3.80 (d, J = 12.0 Hz, 1H), 5.40 (app. t, J = 2.4 Hz, 2H), 7.16-7.34 (m, 8H).



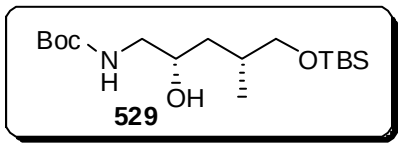
Compound 505: Tricycle **504** (9 mg, 0.024 mmol) was dissolved in THF (4 mL) at room temperature. HCl (1 mL, 1 M aqueous solution) was added and the mixture was stirred 23 hours. The reaction was diluted with diethyl ether and washed with aqueous $NaHCO_3$. The organics were dried over $MgSO_4$ and a small

amount of NEt_3 was added prior to concentration. Column chromatography gave diketone **505** as an oil (4 mg, 65%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (s, 3H), 1.12 (s, 1.5H), 1.37 (s, 4.5H), 1.41 (d, J = 7.2 Hz, 3H), 1.51 (d, J = 6.8 Hz, 3H), 2.15 (dd, J = 2.4, 13.6 Hz, 0.6H), 2.17 (d, J = 12.0 Hz, 1H), 2.24 (dd, J = 2.4, 13.6 Hz, 1H), 2.37 (d, J = 13.6 Hz, 0.6H), 2.43 (d, J = 14.0 Hz, 1H), 2.54 (app. dt, J = 1.2, 13.6 Hz, 0.6H), 2.61 (d, J = 12.8 Hz, 0.6H), 2.67 (app. dt, J = 0.8, 13.6 Hz, 1H), 3.04 (ddd, J = 2.0, 4.4, 13.6 Hz, 1H), 3.16 (ddd, 2.4, 5.2, 14.0 Hz, 0.6H), 7.12-7.34 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.1, 209.6, 208.9, 208.8, 138.8, 137.7, 136.2, 128.0, 127.7, 127.6, 127.2, 124.7, 124.5, 122.9, 58.0, 56.7, 56.62, 56.57, 49.4, 48.3, 45.7, 43.7, 38.7, 38.1, 37.4, 30.5, 30.1, 29.7, 22.0, 21.1, 17.8, 11.0; HR-EI-MS: *m/z* calcd. for $C_{17}H_{20}O_2$: 256.1460, found: 256.1458 $[M]^+$.



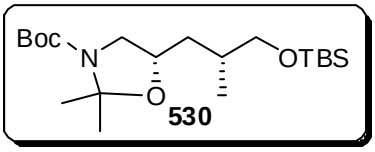
528

Compound 528: Butyrolactone **527** (5.2 g, 22.7 mmol) was dissolved in THF (100 mL) at room temperature. $NaBH_4$ (1.73 g, 45.53 mmol) was added in one portion, followed by MeOH (50 mL). The mixture was heated at 60 °C for 20 minutes, and then cooled to 0 °C and the reaction was quenched with water. The reaction was extracted with EtOAc and the combined organic extracts were dried over $MgSO_4$. Column chromatography gave diol **528** (4.8 g, 91%). TLC (ethyl acetate/hexanes 2:3): R_f = ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (d, J = 6.8 Hz, 3H), 1.41 (s, 9H), 1.44-1.51 (m, 2H), 1.80-1.94 (m, 1H), 2.93-3.05 (m, 1H), 3.19-3.27 (m, 1H), 3.43 (dd, J = 6.8, 10.4 Hz, 1H), 3.52 (dd, J = 4.4, 10.4 Hz, 1H), 3.77-3.90 (m, 2H), 5.0-5.4 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 79.6, 68.5, 67.5, 46.6, 39.1, 32.0, 28.3, 17.2; α_D +8.37 (c = 1.87, $CHCl_3$); HRMS: *m/z* calcd. for $C_{10}H_{15}O_5$: #, found: # $[M+H]^+$.

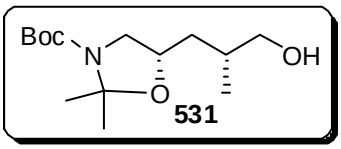


529

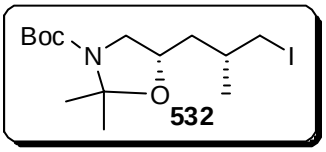
Compound 529: To a stirred solution of diol **528** (3.7 g, 15.88 mmol) in dimethylformamide (50 mL), was added imidazole (2.14 g, 31.47 mmol) and TBSCl (2.65 g, 17.58 mmol) at room temperature. The reaction was stirred overnight, and then diluted with EtOAc and aqueous NH_4Cl. Repeated EtOAc extractions were performed, and the organic extracts were combined before being dried over $MgSO_4$. Column chromatography gave silyl ether **529** as an oil (4.3 g, 78%). TLC (ethyl acetate/hexanes 2:3): R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.85 (s, 9H), 1.38-1.41 (m, 11H), 1.7-1.9 (m, 1H), 2.8-2.95 (m, 1H), 3.15-3.3 (m, 1H), 3.35-3.45 (m, 1H), 3.45-3.55 (m, 1H), 3.6-3.8 (m, 1H), 5.0-5.11 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 79.0, 68.4, 68.2, 46.4, 39.7, 32.1, 28.3, 25.8, 18.2, 17.2, -5.61, -5.63; α_D +12.37 (c = 2.7, $CHCl_3$); HRMS: *m/z* calcd. for $C_{10}H_{15}O_5$: #, found: # $[M+H]^+$.



Compound 530: Alcohol **529** (3.9 g, 11.24 mmol) was dissolved in methylene chloride (300 mL) and cooled to 0 °C. Dimethoxy propane (20 mL) was added followed by camphorsulfonic acid (200 mg). The reaction was allowed to warm to room temperature over 2 hours, at which time the reaction was diluted with aqueous $NaHCO_3$. Repeated methylene chloride extractions were performed, the organic extracts combined, dried over $MgSO_4$, and subjected to column chromatography. N-O ketal **530** was obtained as an oil (4.0 g, 92%). TLC (ethyl acetate/hexanes 2:3): R_f = 0.9; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.02 (s, 6H), 1.8-1.95 (m, 12H), 1.39-1.58 (m, 15H), 1.58-1.7 (m, 2H), 2.89-3.05 (m, 1H), 3.36-3.47 (m, 1H), 3.52-3.62 (m, 1H), 3.62-3.72 (m, 1H), 4.05-4.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 151.8, 93.1, 92.7, 79.8, 79.2, 72.4, 72.1, 68.4, 68.3, 67.8, 51.4, 51.2, 36.7, 36.6, 33.0, 32.8, 28.4, 27.3, 26.2, 25.9, 25.1, 24.2, 18.2, 17.2, 17.1, -5.47, -5.49; α_D +19.5 (c = 1.95, $CHCl_3$); HRMS: *m/z* calcd. for $C_{10}H_{15}O_5$: #, found: # $[M+H]^+$.

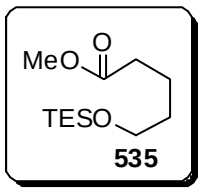


Compound 531: N-O Ketal **530** (3.9 g, 10.06 mmol) was dissolved in THF (50 mL) at room temperature. TBAF (15 mL, 15.0 mmol) was added as a 1 M THF solution at room temperature. The reaction was stirred 1.5 hours then diluted with aqueous $NaHCO_3$. Repeated EtOAc extractions were performed, and the combined extracts dried over $MgSO_4$. Column chromatography gave alcohol **531** as an oil, which crystallized upon standing (1.98 g, 72%). TLC (ethyl acetate/hexanes 2:3): R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (d, J = 7.2 Hz, 3H), 1.42-1.70 (m, 17H), 1.79-1.90 (m, 1H), 2.05-2.31 (m, 1H), 2.97-3.12 (m, 1H), 3.41-3.57 (m, 1H), 3.57-3.76 (m, 2H), 4.13-4.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 151.8, 93.5, 93.0, 80.1, 79.4, 77.2, 71.6, 71.4, 68.1, 67.4, 51.3, 51.1, 51.0, 37.9, 36.4, 34.2, 32.7, 28.4, 27.2, 26.2, 25.1, 24.2, 20.6, 17.7, 16.8, 13.9; α_D +26.0 (c = 1.94, $CHCl_3$); HRMS: *m/z* calcd. for $C_{10}H_{15}O_5$: #, found: # $[M+H]^+$.

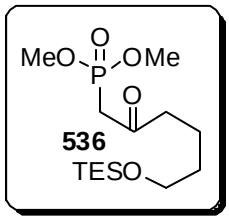


Compound 532: Alcohol **531** (560 mg, 2.05 mmol) was dissolved in benzene (20 mL) and cooled to 0 °C. PPh_3 (1.35 g, 5.14 mmol) and imidazole (349 mg, 5.12 mmol) were added in single portions, followed by I_2 (1.0 g, 3.94 mmol). The reaction was stirred 2 hours, and then diluted with diethyl ether and saturated aqueous $Na_2S_2O_3$. After the solution clarified, repeated ether extractions were performed. The ether extracts were combined, dried over $MgSO_4$, and concentrated. The crude residue was diluted with ether and the solids were filtered off. Column chromatography of the ether filtrate gave iodide **532** as an oil (832 mg, 99%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.7; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.0 (d, J = 6.4 Hz, 3H), 1.42-1.65 (m, 17H), 2.96-3.10 (m, 1H), 3.14-3.34 (m, 2H),

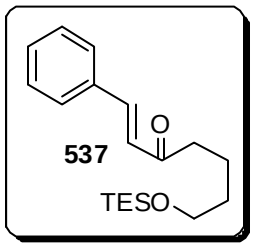
3.58-3.77 (m, 1H), 4.02-4.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 151.7, 93.3, 92.8, 80.0, 79.3, 77.2, 71.4, 71.2, 51.1, 39.5, 31.7, 31.3, 31.2, 28.4, 27.2, 26.2, 25.1, 24.2, 21.1, 20.4, 17.7, 17.5, 17.2; α_D +8.76 (c = 5.0, $CHCl_3$); HRMS: *m/z* calcd. for $C_{10}H_{15}O_5$: #, found: # $[M+H]^+$.



Compound 535: Alcohol **534** (13.4 g, 101 mmol) was dissolved in methylene chloride (70 mL) and cooled to °0 C. Imidazole (17.9 g, 263.2 mmol) and TES-Cl (20 mL, 119.2 mmol) were added in single portions, respectively. The reaction was allowed to warm to room temperature over several hours. After stirring a total of 8.5 hours, the reaction was diluted with hexanes and water. Repeated ether extractions were performed and the combined extracts were dried over $MgSO_4$. Column chromatography gave silyl ether **535** as an oil (17.5 g, 70%). TLC (ethyl acetate/hexanes 2:3): R_f = 0.9; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.59 (q, J = 8.0 Hz, 6H), 0.95 (t, J = 8.0 Hz, 9H), 1.50-1.62 (m, 2H), 1.62-1.74 (m, 2H), 2.34 (t, J = 5.6 Hz, 2H), 3.61 (t, J = 6.4 Hz, 2H), 3.66 (s, 3H).

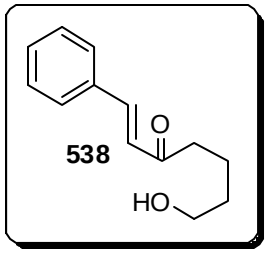


Compound 536: Dimethyl phosphonate (2.6 mL, 24.0 mmol) was dissolved in THF (70 mL) and cooled to -78 °C. *n*-BuLi (8.6 mL, 23.0 mmol) was added as a 2.7 M hexane solution portionwise over several minutes. The reaction mixture was stirred 20 minutes before methyl ester **535** (5.35 g, 21.7 mmol) was added via cannula over 20 minutes. The reaction was stirred an additional 40 minutes before aqueous NH_4Cl was added at -78 °C. The reaction was warmed to room temperature and diluted with hexanes prior to performing ether extractions. The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was passed through a silica plug, and phosphonate **536** was obtained as an oil (5.5g, 75%). TLC (ethyl acetate/hexanes 4:1): R_f = 0.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.58 (q, J = 8.0 Hz, 6H), 0.94 (t, J = 8.0 Hz, 9H), 1.46-1.58 (m, 2H), 1.58-1.69 (m, 2H), 2.64 (t, J = 7.2 Hz, 2H), 3.05 (s, 1H), 3.1 (s, 1H), 3.60 (t, J = 6Hz, 2H), 3.77 (s, 3H), 3.80 (s, 3H).

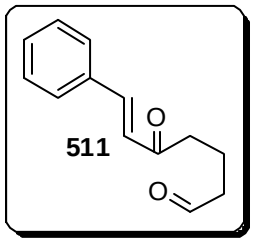


Compound 537: To a stirred suspension of NaH/mineral oil (110mg, 2.75 mmol) in THF (10 mL) at -78 °C, was added phosphonate **536** (785 mg, 2.32 mmol). The mixture was stirred 30 minutes, and then benzaldehyde (0.24 mL, 2.37 mmol) was

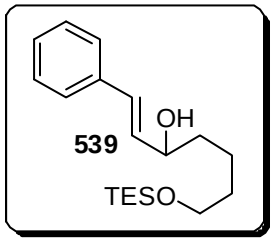
added at -78 °C via cannula over 5 minutes. Immediately after benzaldehyde addition, the reaction was transferred to a 0 °C ice bath and allowed to warm to room temperature over several hours. At the end of 4 hours stirring (from benzaldehyde addition), diethyl ether and aqueous NH_4Cl were added to the reaction. Repeated ether extractions were performed, and the combined ether extracts dried over $MgSO_4$. Column chromatography gave enone **537** as an oil (575 mg, 87%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.8; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.06 (q, J = 8.0 Hz, 6H), 0.96 (t, J = 8.0 Hz, 9H), 1.56-1.64 (m, 2H), 1.70-1.78 (m, 2H), 2.70 (t, J = 7.5 Hz, 2H), 3.64 (t, J = 6.0 Hz, 2H), 6.74 (d, J = 17.0 Hz, 1H), 7.36-7.41 (m, 3H), 7.51-7.57 (m,3H).



Compound 538: Silyl ether **537** (65 mg, 0.204 mmol) was dissolved in THF (1 mL) and cooled to 0 °C. TBAF (0.3 mL, 0.3 mmol) was added as a 1 M THF solution. The mixture was stirred 1.5 hours, and then diluted with diethyl ether and water. Repeated EtOAc extractions were performed, and the combined extracts dried over $MgSO_4$. Column chromatography gave enone **538** as an oil (40 mg, 99%). TLC (ethyl acetate/hexanes 4:1): R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54-1.65 (m, 2H), 1.70-1.81 (m, 2H), 2.54 (bs, 1H), 2.70 (t, J = 7.2 Hz, 2H), 3.64 (t, J = 6.8 Hz, 2H), 6.72 (d, J = 16.0 Hz, 1H), 7.31-7.39 (m, 3H), 7.49-7.57 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.6, 142.6, 134.3, 130.4, 128.8, 128.2, 125.9, 62.0, 40.3, 32.0, 20.1.

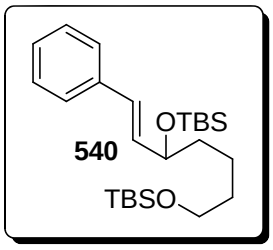


Compound 511: Alcohol **538** (47 mg, 0.23 mmol) was dissolved in acetonitrile (3 mL) at room temperature. IBX (150 mg, 0.53 mmol) was added and the mixture was heated to reflux. The reaction mixture cooled to room temperature and filtered through florisil after 25 minutes at reflux. Aldehyde **511** was obtained in sufficient purity (37mg, 77%). TLC (ethyl acetate/hexanes 2:3): R_f = ; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.98-2.06 (m, 2H), 2.56 (t, J = 7.0 Hz, 2H), 2.75 (t, J = 7.0 Hz, 2H), 6.72 (d, J = 16.0 Hz, 1H), 7.37-7.43 (m, 3H), 7.52-7.59 (m, 3H), 9.80 (bs, 1H).

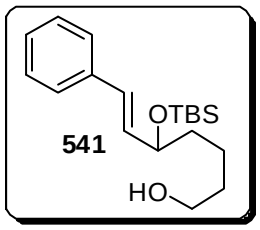


Compound 539: Enone **537** (680 mg, 2.14 mmol) was dissolved in methylene chloride (10 mL) and cooled to -78 C. DIBAL-H (2.1 mL, 2.1 mmol) was added dropwise over 10 minutes as a 1 M methylene chloride solution. The reaction was stirred 1.5 hours at -78 °C, then methanol and an aqueous Rochelle's salt solution was added. The ice bath was removed and the reaction was allowed to stir until it clarified. Repeated

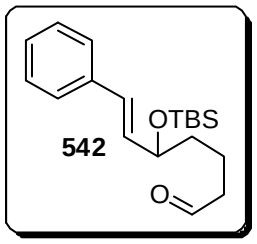
ether extractions, combination of the organic extracts, drying over $MgSO_4$, and column chromatography gave allylic alcohol **539** as an oil (615 mg, 90%). TLC (ethyl acetate/hexanes 1:3): $R_f = 0.5$; ^1H NMR (400 MHz, $CDCl_3$): δ 0.59 (q, J = 8.0 Hz, 6H), 0.95 (t, J = 8.0 Hz, 9H), 1.35-1.73 (m, 6H), 3.62 (t, J = 6.4 Hz, 2H), 4.29 (app. q, J = 6.8 Hz, 1H), 6.22 (dd, J = 7.2, 16.0 Hz, 1H), 6.57 (d, J = 16.0 Hz, 1H), 7.21-7.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.7, 132.5, 130.1, 128.5, 127.5, 126.4, 72.9, 62.7, 37.0, 32.6, 21.7, 6.7, 4.3.



Compound 540: Allylic alcohol **539** (560 mg, 1.75 mmol) was dissolved in dimethylformamide (10 mL) and cooled to 0 °C. Imidazole (712 mg, 10.46 mmol) was added followed by TBSCl (660 mg, 4.38 mmol). The reaction was allowed to slowly warm to room temperature. After stirring 15 hours, the reaction was diluted with diethyl ether and water. Repeated ether extractions were performed, combined, and dried over $MgSO_4$. Column chromatography gave **540** as an oil (724 mg, 95%). TLC (ethyl acetate/hexanes 1:3): $R_f = 0.9$; ^1H NMR (400 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.07 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 0.94 (s, 9H), 1.34-1.69 (m, 6H), 3.63 (t, J = 6.4 Hz, 2H), 4.28 app. q, J = 6.4 Hz, 1H), 6.19 (dd, J = 6.8, 16.0 Hz, 1H), 6.50 (d, J = 16.0 Hz, 1H), 7.21-7.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.2, 133.5, 128.9, 128.5, 127.2, 126.3, 73.6, 63.2, 38.3, 32.8, 26.0, 25.9, 21.7, 18.4, 18.3, -4.4, -5.8, -5.3; ESI-MS: *m/z* calcd. for $C_{25}H_{50}O_2Si_2N_1$: 451.30, found: 451.82 $[M+NH_4]^+$.

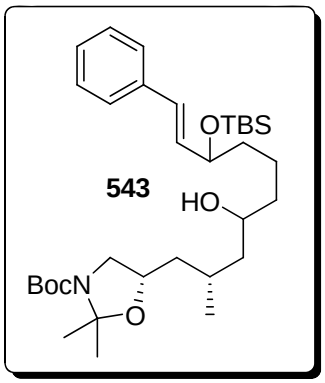


Compound 541: Bis-TBS ether **540** (700 mg, 1.61 mmol) was dissolved in ethanol (10 mL) and PPTS (9 mg) was added at room temperature. The reaction was stirred 13 hours, and then aqueous $NaHCO_3$ and diethyl ether were added. Repeated ether extractions were performed, combined, and dried over $MgSO_4$. Column chromatography gave alcohol **541** as an oil (392 mg, 77%). TLC (ethyl acetate/hexanes 1:3): $R_f = 0.2$; ^1H NMR (400 MHz, $CDCl_3$): δ 0,06 (s, 3H), 0.09 (s, 3H), 0.92 (s, 9H), 1.36-1.70 (m, 6H), 3.64 (t, J = 6.4 Hz, 2H), 4.28 (app. q, J = 6.4 Hz, 1H), 6.17 (dd, J = 6.4, 16.0 Hz, 1H), 6.48 (d, J = 16.0 Hz, 1H), 7.20-7.39 (5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.0, 133.3, 129.0, 128.5, 127.3, 126.3, 73.5, 62.9, 38.1, 32.7, 25.9, 21.4, 18.3, -4.2, -4.8.

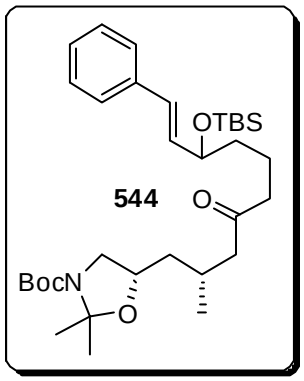


Compound 542: To a stirred acetonitrile (3 mL) solution of **541** (260 mg, 0.811 mmol), was added IBX (700 mg, 2.5 mmol). The mixture was heated to reflux and stirred for 1 hour, then cooled to room temperature and filtered through a silica plug. Aldehyde

542 was obtained without the need for further purification (246 mg, 95%). This material was typically used in the next step immediately after preparation. Therefore, aldehyde **542** was coevaporated at reduced pressure several times with toluene to limit water content. TLC (ethyl acetate/hexanes 1:3): R_f = 0.6; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.05 (s, 3H), 0.08 (s, 3H), 0.92 (s, 9H), 1.57-1.80 (m, 6H), 2.46 (t, J = 6.5 Hz, 2H), 4.30 (app. q, J = 6.5 Hz, 1H), 6.15 (dd, J =7.0, 16.0 Hz, 1H), 6.50 (d, J = 16.0 Hz, 1H), 7.21-7.25 (m, 1H), 7.29-7.38 (m, 4H), 9.76 (bs, 1H).

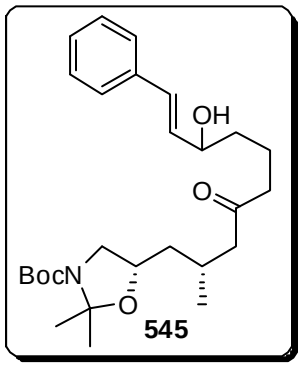


Compound 543: Alkyl iodide **532** (370 mg, 0.97 mmol) was dissolved in diethyl ether (1.8) at room temperature and cooled to -78 °C. *t*-BuLi (1.4 mL, 2.12 mmol) was added as a 1.5 M pentane solution dropwise over 2 minutes. The mixture was stirred 1 minute, and then aldehyde **543** (210 mg, 0.66 mmol) was added via cannula over 5 minutes. The reaction was stirred 4 hours at -78 °C, and then diluted with diethyl ether and water. Repeated diethyl ether extractions were performed and the ether extracts combined and dried over MgSO4. Column chromatography gave secondary alcohol **543** as a mixture of diastereomers and rotamers (247 mg, 65%). TLC (ethyl acetate/hexanes 1:9): R_f = 0.1; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.05 (s, 3H), 0.08 (s, 3H), 0.86-0.99 (m, ~ 18H), 1.31-1.72 (m, ~ 23H), 2.93-3.09 (m, 1H), 3.58-3.78 (m, 2H), 4.06-4.19 (m, 1H), 4.23-4.32 (m, 1H), 4.78-4.93 (m, 1H), 6.16 (dd, J = 6.5, 16.0 Hz, 1H), 6.48 (d, J = 16.0 Hz, 1H), 7.19-7.24 (m, 1H), 7.29-7.38 (m, 4H); ESI-MS: *m/z* calcd. for $C_{33}H_{57}O_5N_1Si_1Na_1$: #, found: 598.32 $[M+Na]^+$.



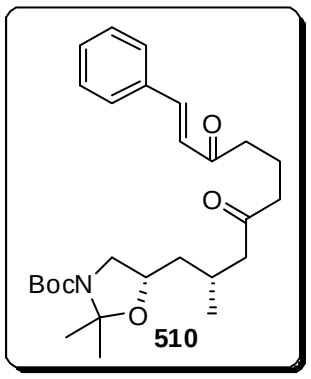
Compound 544: To a stirred methylene chloride (4 mL) solution of alcohol **543** (270 mg, 0.469 mmol), was added Dess-Martin periodinane (380 mg, 0.90 mmol) at room temperature. The reaction was stirred 8 hours at room temperature, and then diluted with diethyl ether. Aqueous $Na_2S_2O_3$ was added and the reaction stirred until it clarified. Repeated ether extractions were performed and the combined ether extracts were dried over $MgSO_4$. Column chromatography provided ketone **544** as an oil (188 mg, 70%). Mixture of diastereomers and rotamers: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.04 (s, 3H), 0.07 (s, 3H), 0.91 (s, 9H), 0.92-0.96 (m, ~ 1H), 1.40-1.76 (m, ~ 18H), 2.06-2.32 (m, 2H), 2.35-2.49 (m, 2H), 2.93-3.10 (m, 1H), 3.54-3.79 (m, 1H), 4.0-4.13 (m, 1H), 4.27 (m, 1H), 6.15 (dd, 1H), 6.48 (d, 1H), 7.18-7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.4, 210.2, 152.3, 151.8, 141.6, 136.9, 133.0, 131.5, 129.2, 128.5, 127.9, 127.3, 126.3, 94.4, 93.3, 92.8, 80.0, 79.4, 77.2,

73.3, 71.9, 71.7, 51.4, 51.1, 50.1, 50.0, 49.8, 43.4, 43.2, 40.3, 39.7, 37.8, 29.7, 28.4, 28.2, 27.9, 27.3, 26.5, 26.3, 26.2, 25.9, 25.2, 24.2, 20.2, 20.1, 19.5, 18.2, -4.0, -4.3, -4.8.



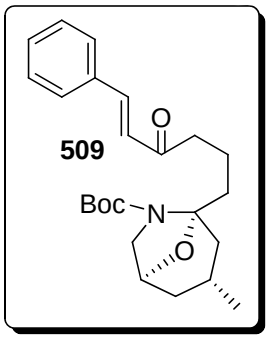
545

Compound 545: To a stirred THF (3 mL) solution of **544** (170 mg, 0.30 mmol) at room temperature, was added TBAF (0.5 mL, 0.5 mmol) as a 1 M THF solution. After stirring 1 hour, additional TBAF (0.2 mL, 0.2 mmol) was added. A third portion of TBAF (0.3 mL, 0.3 mmol) was added 2 hours after the second addition. The reaction was stirred a total of 7 hours from the initial TBAF addition, at which time the reaction was diluted with diethyl ether and aqueous NH_4Cl. Repeated ether extractions were performed, combined, and dried over $MgSO_4$. Column chromatography gave allylic alcohol **545** as an oil (136 mg, 95%). Mixture of diastereomers and rotamers: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (d, J = 6.8 Hz, 3H), 1.23-1.33 (m, 1H), 1.36-1.77 (m, ~ 23H), 2.08-2.33 (m, 2H), 2.36-2.53 (m, 3H), 2.93-3.08 (m, 1H), 3.56-3.75 (m, 1H), 4.01-4.13 (m, 1H), 4.23-4.32 (m, 1H), 6.21 (dd, J = 7.2, 16.0 Hz, 1H), 6.58 (d, J = 16.0 Hz, 1H), 7.17-7.40 (m, 5H).



510

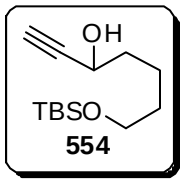
Compound 510: To a stirred methylene chloride (2 mL) solution of **545** (138 mg, 0.3 mmol), was added Dess-Martin periodinane (220 mg, 0.53 mmol) at room temperature. After stirring 3 hours, the reaction was diluted with diethyl ether and aqueous $Na_2S_2O_3$ and then stirred until the solution clarified. The mixture was partitioned between ether and water and the combined organic layers were dried over $MgSO_4$. Column chromatography gave diketone **510** as an oil (106 mg, 79%). Mixture of rotamers: TLC (ethyl acetate/hexanes 1:3): R_f = 0.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (d, J = 6.0 Hz, 3H), 1.39-1.56 (m, ~ 15H), 1.85-1.97 (m, 2H), 2.05-2.35 (m, 2H), 2.40-2.50 (m, 3H), 2.69 (t, J = 6.8 Hz, 2H), 2.92-3.08 (m, 1H), 3.53-3.76 (m, 1H), 3.99-4.16 (m, 1H), 6.70 (d, J = 16.2 Hz, 1H), 7.34-7.39 (m, 3H), 7.49-7.59 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.9, 209.8, 152.2, 151.8, 142.6, 134.3, 130.4, 128.9, 128.2, 126.0, 93.2, 92.8, 79.9, 79.3, 71.8, 71.6, 51.1, 49.9, 49.8, 42.2, 42.1, 39.6, 39.5, 28.4, 27.2, 26.5, 26.3, 26.2, 25.1, 24.2, 20.1, 18.0.



509

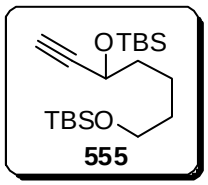
Compound 509: Diketone **510** (60 mg, 0.13 mmol) was dissolved in 1 mL of an AcOH/H_2O (1:1) solution at room temperature. The mixture was heated to 50 °C and stirred 1 hour. After cooling to room temperature, the reaction was

diluted with diethyl ether and aqueous $NaHCO_3$. Solid Na_2CO_3 was added and repeated ether extractions were performed. The combined ether extracts were washed with aqueous $NaHCO_3$ and dried over $MgSO_4$. Column chromatography gave aminal **509** as an oil (36 mg, 72%). Mixture of rotamers: TLC (ethyl acetate/hexanes 1:3): R_f = 0.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (d, J = 6.8 Hz, 1.5H), 0.91 (d, J = 6.8 Hz, 1.5H), 1.17-1.28 (m, 1H), 1.42-1.47 (m, ~ 10H), 1.53-2.32 (m, 7H), 2.60-2.75 (m, 2H), 3.33-3.55 (m, 2H), 4.34-4.42 (bs, 1H), 6.72 (d, J = 16.0 Hz, 0.5H), 6.74 (d, J = 16.0 Hz, 0.5H), 7.37-7.40 (m, 3H), 7.50-7.59 (m, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 198.5, 198.4, 152.6, 152.2, 141.5, 141.2, 135.2, 135.0, 130.0, 129.8, 128.83, 128.76, 128.3, 128.0, 127.8, 126.8, 126.6, 94.4, 94.1, 79.4, 78.7, 72.5, 72.3, 65.8, 51.5, 51.1, 42.4, 41.13, 41.07, 40.95, 37.8, 37.7, 36.3, 35.5, 28.4, 28.3, 24.3., 24.2, 21.6, 21.5, 18.0, 15.5; α_D -41.1 (c = 18, mg/mL, $CHCl_3$); HRMS: *m/z* calcd. for $C_{24}H_{33}O_4N_1Na_1$: 422.23, found: 422.23 $[MNa]^+$.



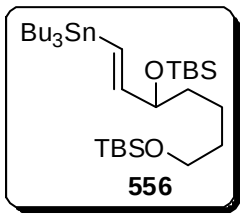
554

Compound 554: To a stirred solution of aldehyde **553** (17 g, 78.7 mmol) in diethyl ether (100 mL) at 0 °C, was added ethynyl magnesium bromide (195 mL, 97 mmol) as a 0.5 M THF solution over fifteen minutes. The reaction was stirred 2 hours, then hexanes and aqueous NH_4Cl were added. Repeated ether extractions were performed, and the combined organic extracts dried over $MgSO_4$. Column chromatography gave propargyl alcohol **554** as an oil (13.2 g, 69%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.6; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.89 (s, 9H), 1.48-1.58 (m, 4H), 1.69-1.78 (m, 2H), 1.91 (d, J = 5.6 Hz, 1H), 2.46 (d, J = 1.6 Hz, 1H), 3.63 (t, J = 6.0 Hz, 2H), 4.38 (ddd, J = 2.0, 6.4, 12.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 84.9, 72.9, 62.9, 62.3, 37.3, 32.3, 25.9, 21.4, 18.3, -5.3.

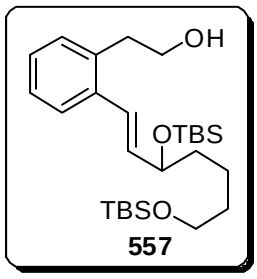


555

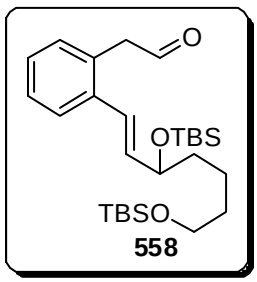
Compound 555: To a stirred dimethylformamide (25 mL) solution of **554** (5.9 g, 24.38 mmol) at 0 °C, was added imidazole (4.1 g, 59.6 mmol), TBSCl (4.5 g, 29.8 mmol), and DMAP (100 mg). The reaction was then allowed to warm to room temperature. After stirring 17 hours, hexanes and water were added. Repeated diethyl ether extractions were performed, and the combined extracts dried over $MgSO_4$. Column chromatography gave **555** as an oil (7.9 g, 91%). TLC (ethyl acetate/hexanes 6:44): R_f = 0.8; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.10 (s, 3H), 0.13 (s, 3H), 0.89 (s, 9H), 0.90 (s, 9H), 1.38-1.57 (m, 3H), 1.60-1.75 (m, 3H), 2.36 (d, J = 2.0 Hz, 1H), 3.61 (t, J = 6 Hz, 2H), 4.33 (dt, J =2.0, 6.8, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 85.7, 77.3, 63.0, 62.7, 38.4, 32.5, 26.0, 25.8, 21.6, 18.3, 18.2, -4.6, -5.1, -5.3.



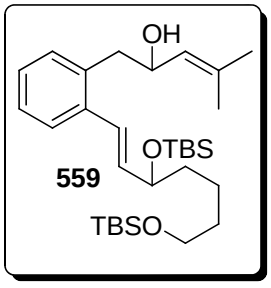
Compound 556: Alkyne **555** (3.8 g, 10.65 mmol) was dissolved in THF (100 mL) and cooled to -78 °C. $Pd(PPh_3)_2Cl_2$ (145 mg, 0.21 mmol) was added, followed by addition of Bu_3SnH (3.15 mL, 11.7 mmol) in one portion. The reaction warmed to -40 °C over three hours, at which time the reaction mixture was concentrated on a rotary evaporator without work up. Column chromatography of the residue gave stannane **556** as an oil (2.56 g, 63%). TLC (ethyl acetate/hexanes 1:99): R_f = 0.1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.00-0.05 (m, 10H), 0.74-1.00 (m, 28H), 1.21-1.65 (m, 16H), 3.59 (t, J = 6.6 Hz, 2H), 3.96-4.05 (m, 1H), 5.72-6.21 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.1, 126.6, 77.6, 63.5, 38.1, 33.1, 29.3, 27.5, 26.2, 26.1, 22.0, 18.6, 18.5, 13.9, 9.6, -4.0, -4.6, -5.1.



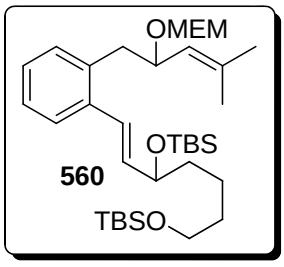
Compound 557: Stannane **556** (5.3 g, 8.18 mmol) and aryl iodide **478** (2.1 g, 10.4 mmol) were mixed under argon. The mixture was diluted with toluene (60 mL) and degassed 20 minutes via bubbling argon. $Pd_2(dba)_3$ (620 mg, 0.68 mmol) was added, followed immediately with addition of P*t*-Bu_3 (267 mg, 1.3 mmol) as a 10 % w/w hexane solution. The reaction was stirred at 80 °C 17 hours, and then cooled to room temperature. The mixture was filtered through a silica plug and concentrated. Column chromatography of the residue gave alcohol **557** as an oil (3.2 g, 82%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.06 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 0.92 (s, 9H), 1.29-1.67 (m, 4H), 2.95 (t, J = 7.2 Hz, 2H), 3.67 (t, J = 6.4 Hz, 2H), 3.80 (app. q, J = 6.4 Hz, 2H), 4.29 (app. q, J = 5.6 Hz, 1H), 6.07 (dd, J = 6.4, 15.6 Hz, 1H), 6.76 (d, 15.6 Hz, 1H), 7.15-7.24 (m, 3H), 7.42-7.48 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.5, 135.6, 135.5, 130.3, 127.3, 126.9, 126.4, 126.1, 73.5, 63.2, 63.0, 38.2, 36.5, 32.8, 26.0, 25.9, 21.6, 18.3, 18.2, -4.3, -4.7, -5.3.



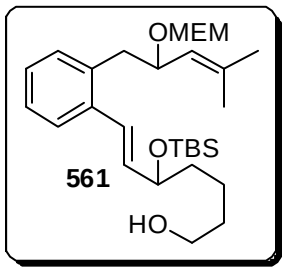
Compound 558: Alohol **557** (2.5 g, 5.2 mmol) was dissolved in acetonitrile (50 mL) and IBX (3.5 g, 12.5 mmol) was added. The solution was heated to reflux and stirred 1 hour. The mixture was cooled to room temperature and filtered through a plug of florisil. Aldehyde **558** was obtained in high purity (2.24 g, 90%). TLC (ethyl acetate/hexanes 2:44): R_f = 0.7; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.05 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 0.91 (s, 3H), 1.30-1.68 (m, 4H), 3.60 (t, J = 6.4 Hz, 2H), 3.74 (d, J = 2.0 Hz, 2H), 4.27 (app. q, J = 6.0 Hz, 1H), 6.09 (dd, J = 6.4, 16.0 Hz, 1H), 6.61 (d, J = 16.0 Hz, 1H), 7.16 (d, J = 7.2 Hz, 1H), 7.23-7.32 (m, 2H), 7.49 (d, J = 7.2 Hz, 1H), 9.69 (t, J = 2.0 Hz, 1H).



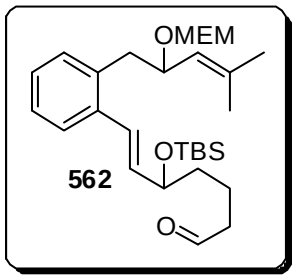
Compound 559: **A** $CeCl_3$ (2.18 g, 8.84 mmol)/THF (15 mL) slurry was prepared and cooled to 0 °C. 2-methyl-1-propenyl-magnesium bromide (15.2 mL, 7.6 mmol) was added in one portion as a 0.5 M THF solution, and the mixture was stirred 1.5 hours. Aldehyde **558** (2.38 g, 4.99 mmol) was dissolved in THF (5 mL) and added to the slurry via cannula over 45 minutes. The reaction was warmed to room temperature 3 hours after aldehyde addition. Hexanes and water were added to the reaction and repeated diethyl ether extractions were performed. The combined organic extracts were dried over $MgSO_4$ and concentrated. Column chromatography gave allylic alcohol **559** as an oil (1.65 g, 61%). TLC (ethyl acetate/hexanes 6:44): $R_f = 0.5$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.02-0.11 (m, 12H), 0.85-0.95 (m, 18H), 1.30-1.71 (m, 12H), 2.79-2.96 (m, 2H), 3.56-3.66 (m, 2H), 4.25-4.37 (m, 1H), 4.49-4.59 (m, 1H), 5.21-5.27 (m, 1H), 6.03-6.13 (m, 1H), 6.77-6.86 (m, 1H), 7.10-7.24 (m,3H), 7.41-7.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.7, 136.6, 135.6, 135.42, 135.39, 135.3, 135.26, 131.0, 130.9, 127.14, 127.11, 127.0, 126.7, 126.6, 126.2, 126.1, 77.1, 73.8, 73.4, 69.04, 69.02, 63.13, 63.09, 41.33, 41.26, 38.3, 32.8, 25.92, 25.87, 25.66, 25.65, 21.64, 18.3, 18.2, 18.12, 18.06, -4.18, -4.27, -4.78, -5.33; HR-EI-MS: *m/z* calcd. for $C_{31}H_{56}O_3Si_2$: 532.3763, found: 532.3764 $[M]^+$.



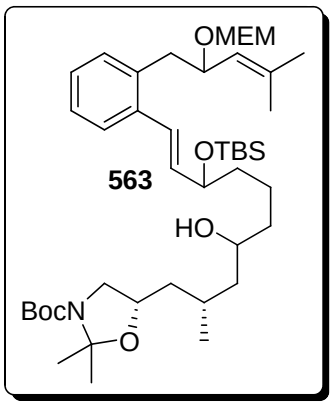
Compound 560: Allylic alcohol **559** (2.05 g, 3.8 mmol) was dissolved in methylene chloride (25 mL) and cooled to 0 °C. Hunig's base (3.4 mL, 19.5 mmol) and MEMCl (1.3 mL, 11.3 mmol) were added. The solution was allowed to warm to room temperature over approximately 1 hour. After 11 hours (from MEMCl addition) additional Hunig's base (1.7 mL, 9.8 mmol) and MEMCl (0.65 mL, 5.7 mmol) were added. Hexanes and aqueous $NaHCO_3$ were added to the reaction after a total of 18 hours stirring at room temperature. Repeated diethyl ether extractions were performed, and the combined ether extracts dried over $MgSO_4$. Column chromatography gave MEM ether **560** as an oil (1.9 g, 81%). 65%). TLC (ethyl acetate/hexanes 1:3): $R_f = 0.6$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.05 (s, 3H), 0.6 (s, 3H), 0.88-0.92 (m, 18H), 1.30-1.73 (m, 12H), 2.69-2.82 (m, 1H), 2.86-3.00 (m, 1H), 3.09-3.33 (m, 6H), 3.60 (t, J = 6.0 Hz, 2H), 4.18-4.31 (m, 1H), 4.41-4.55 (m, 2H), 4.59-4.67 (m, 1H), 5.05-5.13 (m, 1H), 5.95-6.11 (m, 1H), 6.80 (d, J = 16.0 Hz, 0.5H), 6.82 (d, j = 16.0 Hz, 0.5H), 7.08-7.20 (m, 3H), 7.35-7.44 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.61, 136.51, 136.47, 136.2, 136.15, 135.24, 135.08, 131.12, 131.04, 127.08, 126.92, 126.83, 126.49, 126.39, 126.36, 125.85, 125.69, 124.83, 91.98, 91.91, 74.01, 73.60, 72.68, 72.59, 71.63, 66.12, 66.05, 63.14, 58.83, 39.16, 38.4, 32.89, 32.86, 25.95, 25.91, 25.79, 21.77, 18.22, 18.25, 18.21, 18.17, -4.07, -4.19, -4.76, -5.30; HR-EI-MS: *m/z* calcd. for $C_{35}H_{64}O_5Si_2$: 620.4287, found: 620.4293 $[M]^+$.



Compound 561: Silyl ether **560** (600 mg, 0.97 mmol) was dissolved in THF (12 mL) and cooled to 0 °C. Pyridine (3 mL) was added to the cold solution, then Hf·Pyr (1.4 mL, 70% Hf / 30% Pyr solution) was added. The mixture was stirred 2.5 hours, and then transferred to a flask containing diethyl ether and $NaHCO_3$. The solution was then filtered through a silica plug and concentrated. Column chromatography gave alcohol **561** as an oil (391 mg, 80%). TLC (ethyl acetate/hexanes 2:3): R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.08 (s, 3H), 0.91 (s, 9H), 1.40-1.71 (m, 11H), 2.70-2.82 (m, 1H), 2.87-2.98 (m, 1H), 3.08-3.20 (m, 1H), 3.21-3.32 (m, 4H), 3.58-3.67 (m, 1H), 4.24-4.34 (m, 1H), 4.40-4.54 (m, 2H), 4.59-4.65 (m, 1H), 5.04-5.12 (m, 1H), 5.97-6.10 (m, 1H), 6.77-6.80 (m, 1H), 7.08-7.19 (m, 3H), 7.37-7.45 (m, 1H); HR-EI-MS: *m/z* calcd. for $C_{29}H_{50}O_5Si_1$: 506.3422, found: 506.3398 $[M]^+$.

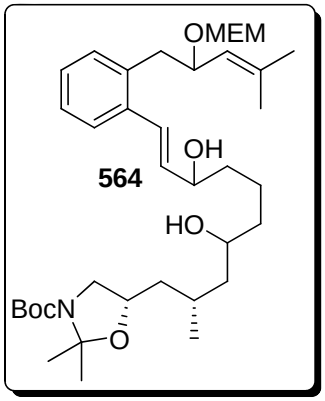


Compound 562: Alcohol **561** (14 mg, 0.03 mmol) was dissolved in acetonitrile (1 mL) and IBX (18 mg, 0.06 mmol) was added. The mixture was stirred under reflux 1.5 hours, and then filtered through florisil. Aldehyde **562** was obtained in good purity (13 mg, 90%). TLC (diethyl ether/hexanes 1:1): R_f = 0.5; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.47-1.79 (m, ~ 10H), 2.42-2.51 (m, 2H), 2.69-2.82 (m, 1H), 2.87-3.01 (m, 1H), 3.10-3.22 (m, 1H), 3.23-3.33 (m, 5H), 4.24-4.36 (m, 1H), 4.42-4.54 (m, 2H), 4.59-4.67 (m, 1H), 5.04-5.13 (m, 1H), 5.96-6.10 (m, 1H), 6.79-6.88 (m, 1H), 7.11-7.20 (m, 3H), 7.35-7.44 (m, 1H), 9.75-9.78 (m, 1H).

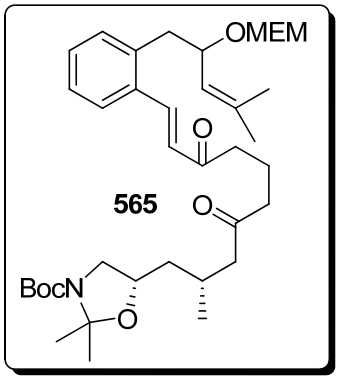


Compound 563: Alkyl iodide **532** (43 mg, 0.11 mmol) was dissolved in diethyl ether (0.5 mL) and cooled to -78 °C. *t*-BuLi (0.17 mL, 0.26 mmol) was added as a 1.5 M pentane solution. The reaction was stirred 3 minutes, then aldehyde **562** (40 mg, 0.08 mmol) was added via cannula over approximately 3 minutes. After stirring 2.5 hours, diethyl ether and aqueous NH_4Cl were added to the reaction mixture, and the mixture was warmed to room temperature. Repeated diethyl ether extractions were performed and the combined extracts were dried over $MgSO_4$. Column chromatography gave alcohol **563** as a mixture of diastereomers and rotamers (37 mg, 62%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.2; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.08 (s, 3H),

0.84-1.01 (m, ~12H), 1.32-1.63 (m, ~ 19H), 1.70 (s, 3H), 2.66-2.84 (m, 1H), 2.84-3.08 (m, 2H), 3.09-3.20 (m, 1H), 3.20-3.35 (m, ~ 5H), 3.55-3.79 (m, 2H), 4.02-4.22 (m, 1H), 4.22-4.36 (m, 1H), 4.39-4.55 (m, 2H), 4.56-4.67 (m, 1H), 5.03-5.15 (m, 1H), 5.96-6.11 (m, 1H), 6.81 (d, J = 15.6 Hz, 0.5H), 6.82 (d, J = 15.6 Hz, 0.5H), 7.08-7.20 (m, 3H), 7.36-7.45 (m, 1H); ESI-MS: *m/z* calcd. for $C_{43}H_{75}O_3N_1Si_1$: 784.51, found: 784.45 $[M+Na]^+$.

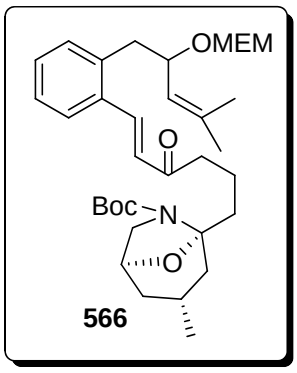


Compound 564: Silyl ether **563** (180 mg, 0.24 mmol) was dissolved in THF (7 mL) at room temperature. TBAF (0.9 mL, 0.9 mmol) was added as a 1 M THF solution and the reaction was stirred 5 hours. The reaction mixture was diluted with diethyl ether and aqueous $NaHCO_3$. Repeated ether extractions were performed, and the combined ether extracts were dried over $MgSO_4$. Column chromatography gave diol **564** as an oil (146 mg, 95%). Mixture of diastereomers and rotamers: TLC (ethyl acetate/hexanes 2:3): R_f = 0.2; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94-1.0 (m, ~ 3H), 1.22-1.73 (m, ~ 30H), 2.66-2.76 (m, 1H), 2.95-3.14 (m, 2H), 3.33 (s, 3H), 3.33-3.45 (m, 5H), 3.57-3.77 (m, 2H), 4.07-4.20 (m, 1H), 4.27-4.39 (m, 1H), 4.47-4.57 (m, 2H), 4.65-4.69 (m, 1H), 5.03-5.08 (m, 1H), 6.06-6.16 (m, 1H), 6.90-6.99 (m, 1H), 7.06-7.19 (m, 3H), 7.38-7.43 (m, 1H); HR-EI-MS: *m/z* calcd. for $C_{37}H_{61}O_8N_1$: 647.4397, found: 670.4393 $[M]^+$.

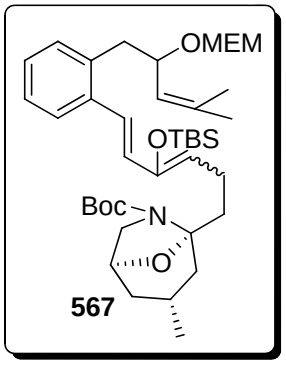


Compound 565: Diol **565** (135 mg, 0.208 mmol) was dissolved in methylene chloride (9 mL) at room temperature. Dess-Martin periodinane (265 mg, 0.63 mmol) was added and the reaction mixture was stirred. Additional Dess-Martin periodinane (250 mg, 0.59 mmol) was added after 2 hours, and the mixture was stirred 2 hours additional (4 hours total reaction time). The reaction was then diluted with diethyl ether and water. Repeated ether extractions were performed and the combined extracts were dried over $MgSO_4$. Column chromatography gave diketone **565** as an oil (81 mg, 60%). Mixture of diastereomers and rotamers: TLC (ethyl acetate/hexanes 2:3): R_f = 0.4; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.08-0.99 (m, ~ 5H), 1.43-1.55 (m, > 15H), 1.58 (s, 3H), 1.67 (s, 3H), 1.91-1.99 (m, 2H), 2.08-2.46 (m, ~ 4H), 2.46-2.53 (m, 2H), 2.67-2.73 (m, 2H), 2.86-2.96 (m, 2H), 2.96-3.08 (m, 2H), 3.20-3.26 (m, 1H), 3.27-3.35 (m, 8H), 3.56-3.76 (m, 2H), 4.03-4.14 (m, 1H), 4.41-4.51 (m, 2H), 4.61-4.66 (m, 1H), 5.04-5.09 (m, 1H), 6.63

(d, J = 16.0 Hz, 1H), 7.16-7.32 (m, 3H), 7.56 (d, J = 7.5 Hz, 1H), 7.97 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ [incomplete, missing Boc carbonyl]): δ 209.76, 199.56, 140.58, 139.48, 138.89, 136.98, 133.7, 131.8, 130.3, 129.83, 127.77, 126.77, 126.16, 124.35, 103.9, 92.85, 92.02, 79.98, 79.39, 72.93, 71.61, 66.21, 58.85, 51.15, 49.87, 42.24, 40.36, 39.74, 39.29, 36.59, 33.61, 31.89, 30.28, 29.67, 28.44, 27.95, 27.29, 26.52, 25.78, 25.16, 24.28, 23.33, 22.67, 20.10, 18.08, 15.24, 14.10; HRMS: *m/z* calcd. for $C_{37}H_{57}O_8N_1Na$: 666.40, found: 666.33 $[M+Na]^+$.

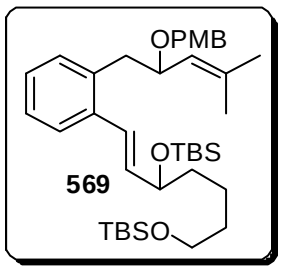


Compound 566: Diketone **565** (2 mg, 0.003 mmol) was dissolved in 0.5 mL of an AcOH/H_2O (1:1) solution. The mixture was heated at 35 °C 12 hours. The mixture was then diluted with diethyl ether and aqueous $NaHCO_3$. Repeated ether extractions were performed and the combined extracts were dried over $MgSO_4$. Rapid column chromatography with neutralized silica gave aminal **566** as an oil (2 mg, 90%). TLC (ethyl acetate/hexanes 2:3): R_f = 0.7; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86-0.94 (m, 3H), 1.02-1.08 (m, 1H), 1.37-1.87 (m, ~ 20H), 2.0-2.38 (m, 3H), 2.59-2.75 (m, 2H), 2.84-2.93 (m, 1H), 2.96-3.05 (m, 1H), 3.17-3.40 (m, 5-6H), 3.47-3.77 (m, 2H), 4.35-4.41 (m, 1H), 4.60-4.65 (d, J = 6.8 Hz, 1H), 5.02-5.09 (m, 1H), 6.63 (2 adjacent 16.0 Hz doublets, 1H total), 7.10-7.33 (m, 3H), 7.56 (m, 1H), 7.93 (d, J = 16.0 Hz, 0.5H), 7.95 (d, J = 16.0 Hz, 0.5 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.18, 199.88, 152.69, 152.24, 140.36, 140.23, 140.06, 138.8, 137.01, 133.96, 133.86, 131.8, 129.71, 129.60, 129.14, 127.23, 127.11, 126.74, 126.19, 125.98, 124.66, 124.37, 94.12, 92.12, 80.07, 79.31, 78.09, 77.21, 72.92, 72.72, 72.56, 72.35, 71.63, 67.95, 66.22, 58.85, 51.09, 42.01, 41.05, 40.94, 40.69, 39.57, 39.31, 37.68, 35.87, 35.04, 29.68, 28.50, 28.42, 28.20, 25.79, 25.58, 24.07, 21.52, 18.17, 18.10, 17.67, 17.59; HR-EI-MS: *m/z* calcd. for $C_{34}H_{51}O_7N_1$: 585.3660, found: 585.3659 $[M]^+$.

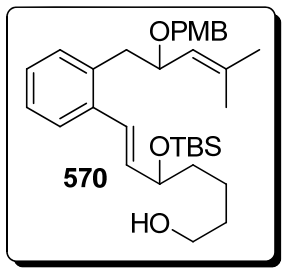


Compound 567: Aminal **567** (7 mg, 0.12 mmol) was dissolved in methylene chloride (1 mL) and cooled to -78 °C. Triethylamine (180 μL, 1.3 mmol) was added, followed by TBSOTf (several drops, ~ 1 eq.). The reaction was stirred 45 minutes, and then diluted with diethyl ether and aqueous $NaHCO_3$. Repeated ether extractions were performed and the combined ether extracts were dried over $MgSO_4$. Rapid column chromatography with neutralized silica provided a mixture of silyl enol ethers (8 mg, 85%). Mixture of diastereomers and rotamers: TLC (ethyl acetate/hexanes 1:3):

R_f = 0.4; ^{1}H NMR (400 MHz, C_6D_6): δ 0.19-0.31 (m, 6-7H), 0.64-0.75 (m, 2H), 0.80-0.96 (m, ~ 3H), 1.09-1.14 (m, ~ 9H), 1.20-1.67 (m, ~ 15H), 1.97-3.01 (m, ~ 6H), 3.08-3.58 (m, ~ 11H), 3.9-4.06 (m, 1H), 4.52-4.57 (m, 1H), 4.71-4.81 (m, 2H), 5.0-5.28 (m, 2H), 6.51-6.61 (m, 1H), 6.92-7.11 (m, 3H), 7.21-7.89 (m, ~5H); ESI-MS: *m/z* calcd. for $C_{40}H_{65}O_7N_1Si_1Na_1$: 722.44, found: 722.42 $[M+Na]^+$; and *m/z* calcd. for $C_{40}H_{65}O_7N_1Si_1N_1H_4$: 717.14, found: 717.12 $[M+NH_4]^+$.

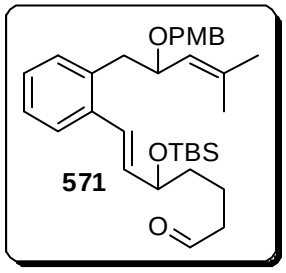


Compound 569: Allylic alcohol **559** (685 mg, 1.29 mmol) was dissolved in dimethylformamide (7 mL) and NaH (43 mg, 1.79 mmol) was added at room temperature as a mineral oil dispersion. After stirring several minutes, PMBCl (0.25 mL, 1.84 mmol) was added, followed by TBAI (40 mg, 0.11 mmol). The reaction was stirred 8.5 hours, and then diluted with diethyl ether and aqueous NH_4Cl. Repeated ether extractions were performed and the combined extracts were dried over $MgSO_4$. Column chromatography gave PMB ether **569** as an oil (378 mg, 45%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.7; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.04-0.08 (m, 12H), 0.90 (s, 9H), 0.92 (s, 9H), 1.25-1.77 (m, ~ 12H), 2.68-2.82 (m, 1H), 2.99-3.12 (m, 1H), 3.57-3.65 (m, 2H), 3.78 (s, 3H), 4.16-4.29 (m, 2H), 4.43-4.50 (m, 1H), 5.12-5.19 (m, 1H), 5.96-6.05 (m, 1H), 6.73-6.83 (m, 3H), 7.05-7.20 (m, 5H), 7.40 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.83, 136.52, 136.09, 135.97, 135.90, 135.14, 135.07, 131.21, 131.03, 130.49, 128.96, 128.89, 128.79, 126.89, 126.82, 126.77, 126.63, 126.5, 126.33, 125.8, 125.76, 125.58, 113.56, 113.53, 75.52, 75.42, 73.94, 73.63, 69.39, 65.50, 63.14, 55.18, 39.45, 38.40, 32.92, 32.88, 32.36, 25.95, 25.90, 25.77, 25.75, 25.36, 21.71, 21.66, 18.32, 18.21, 18.12, 18.02, -4.09, -4.18, -4.73, -4.76, -5.31.

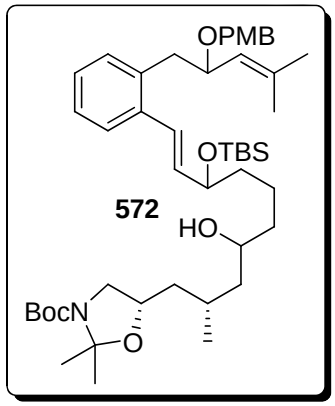


Compound 570: Silyl ether **569** (40 mg, 0.06 mmol) was dissolved in THF (2 mL) and cooled to 0 °C. Pyridine (0.35 mL) then HF·Pyr (0.15 mL) was added. After 5 hours stirring at 0 °C, diethyl ether and aqueous $NaHCO_3$ were added. Repeated ether extractions were performed and the combined ether extracts were dried over $MgSO_4$. Column chromatography gave alcohol **570** as an oil (25 mg, 75%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.2; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.04-0.08 (m, 6H), 0.91 (s, 9H), 1.28-1.35 (m, 3H), 1.35-1.60 (m, 6H), 1.68-1.71 (m, 3H), 2.69-2.78 (m, 1H), 2.99-3.11 (m, 1H), 3.58-3.66 (m, 2H), 3.78 (s, 3H), 4.16-4.27 (m, 3H), 4.43-4.50 (m, 1H), 5.11-5.17 (m, 1H), 5.94-6.03 (m, 1H), 6.72-6.81 (m, 3H), 7.04-7.20 (m, 5H), 7.37-7.41 (d, J = 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.77, 136.45, 136.23, 136.18, 136.00, 135.91, 134.91, 134.82, 131.24, 131.22, 131.08, 131.03, 128.98, 128.90, 127.08, 126.89, 126.86, 126.35, 125.80, 125.74, 125.52, 113.58, 113.56, 75.47, 75.38, 73.82, 73.58, 69.36, 69.26, 62.89, 62.87,

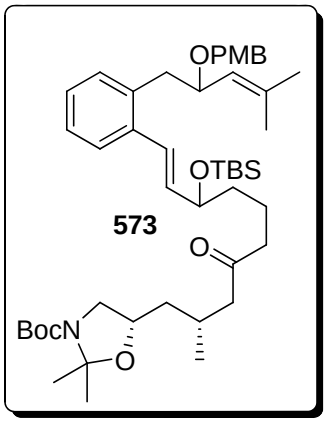
55.23, 39.48, 38.20, 32.77, 32.74, 29.69, 25.91, 25.79, 25.77, 21.44, 21.39, 18.22, 18.13, 18.04, -4.08, -4.17, -4.72; ESI-MS: *m/z* calcd. for $C_{33}H_{50}O_4Si_1Na_1$: 561.34, found: 561.37 $[M+Na]^+$.



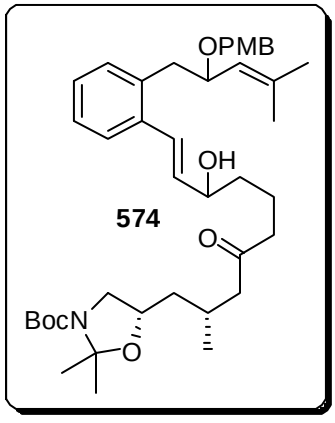
Compound 571: Alcohol **570** (360 mg, 0.67 mmol) was dissolved in acetonitrile (10 mL) and IBX (550 mg, 1.96 mmol) was added. The reaction was stirred at reflux 1 hour, cooled to room temperature, and rapidly filtered through a silica plug. Aldehyde 571 was isolated in good purity (324 mg, 90%). TLC (ethyl acetate/hexanes 1:3): $R_f = 0.5$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.04-0.07 (m, 6H), 0.91 (s, 9H), 1.29-1.35 (m, 3H), 1.48-1.72 (m, 7H), 2.39-2.47 (m, 2H), 2.69-2.80 (m, 1H), 3.00-3.10 (m, 1H), 3.78 (s, 3H), 4.16-4.29 (m, 3H), 4.42-4.50 (m, 1H), 5.10-5.18 (m, 1H), 5.94-6.01 (m, 1H), 6.74-6.82 (m, 3H), 7.01-7.21 (m, 5H), 7.39 (d, J = 7.5 Hz, 1H), 9.73 (t, J = 2.0 Hz, 0.5H), 9.75 (t, J = 2.0 Hz, 0.5H).



Compound 572: Alkyl iodide **532** (385 mg, 1.0 mmol) was dissolved in diethyl ether (3 mL) and cooled to -78 °C. *t*-BuLi (1.45 mL mL, 2.175 mmol) was added as a 1.5 M pentane solution dropwise over 2 minutes. The reaction was stirred 1 minute, then a diethyl ether (1 mL) solution of aldehyde **562** (352 mg, 0.61 mmol) was added via cannula over approximately 3 minutes. After stirring 5 hours, diethyl ether and aqueous NH_4Cl were added to the reaction mixture, and the mixture was warmed to room temperature. Repeated diethyl ether extractions were performed and the combined extracts were dried over $MgSO_4$. Column chromatography gave alcohol **572** as a mixture of diastereomers and rotamers (274 mg, 57%). TLC (ethyl acetate/hexanes 1:3): $R_f = 0.3$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.03-0.13 (m, 6H), 0.84-1.0 (m, 11H), 1.23-1.83 (m, ~ 27H), 2.68-2.80 (m, 1H), 2.95-3.11 (m, 2H), 3.57-3.78 (m, 1H), 3.78 (s, 3H), 4.07-4.27 (m, 3H), 4.42-4.50 (m, 1H), 5.11-5.18 (m, 1H), 5.95-6.04 (m, 1H), 6.72-6.82 (m, 3H), 7.04-7.21 (m, 5H), 7.36-7.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.78, 152.2, 151.8, 136.46, 136.14, 135.97, 135.87, 134.92, 134.82, 131.18, 131.06, 131.01, 128.96, 128.87, 127.72, 127.05, 126.83, 126.32, 125.79, 125.74, 125.52, 113.54, 93.2, 92.9, 80.0, 79.3, 77.21, 75.51, 75.41, 75.33, 73.80, 73.61, 73.56, 71.99, 69.45, 69.35, 69.30, 69.24, 55.18, 51.27, 51.03, 45.04, 44.77, 40.96, 40.82, 39.44, 39.21, 38.50, 38.42, 37.85, 29.65, 28.41, 28.25, 27.25, 26.99, 26.53, 26.20, 25.89, 25.81, 25.77, 25.15, 24.25, 21.43, 21.33, 18.19, 18.11, -4.08, -4.18, -4.73; HRMS: *m/z* calcd. for $C_{47}H_{75}O_7N_1Si_1Na$: 815.92, found: 816.44 $[M+Na]^+$.

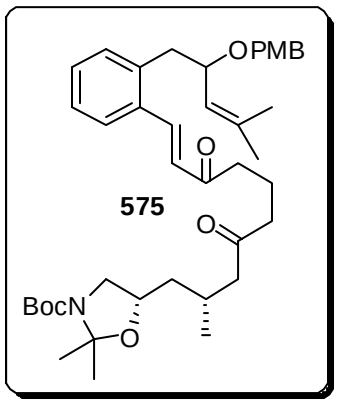


Compound 573: Alcohol **572** (3 mg, 0.004 mmol) was dissolved in methylene chloride (0.7 mL) at room temperature. Dess-Martin periodinane (5 mg, 0.012 mmol) was added and the reaction mixture stirred 2 hours. The solution was then diluted with diethyl ether and aqueous $Na_2S_2O_3$, and then stirred until the mixture clarified. Repeated ether extractions were performed and the combined extracts were dried over $MgSO_4$. Column chromatography gave ketone **573** as an oil (3 mg, 95%). Mixture of diastereomers and rotamers: TLC (ethyl acetate/hexanes 1:3): $R_f = 0.5$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.03-0.10 (m, 3H), 0.88-0.98 (m, 12H), 1.27-1.73 (m, 23H), 2.06-2.31 (m, 2H), 2.33-2.49 (m, 3H), 2.68-2.80 (m, 1H), 2.93-3.11 (m, 2H), 3.58-3.75 (m, 1H), 3.78 (s, 3H), 4.01-4.12 (m, 1H), 4.15-4.28 (m, 3H), 4.42-4.49 (m, 1H), 5.11-5.18 (m, 1H), 5.94-6.03 (m, 1H), 6.72-6.83 (m, 3H), 7.03-7.20 (m, 5H), 7.35-7.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.18, 210.01, 158.84, 158.80, 136.39, 136.36, 136.15, 136.04, 135.95, 134.63, 134.56, 131.21, 131.10, 131.06, 128.98, 128.91, 127.25, 126.99, 126.94, 126.89, 126.36, 125.81, 125.76, 125.60, 125.57, 113.59, 113.55, 93.31, 92.81, 79.94, 79.43, 77.21, 75.58, 75.45, 73.68, 73.43, 71.96, 71.74, 69.40, 69.31, 55.20, 51.41, 51.17, 49.98, 43.35, 39.81, 39.43, 37.96, 29.68, 28.45, 27.32, 26.50, 26.38, 26.26, 25.90, 25.80, 25.77, 25.20, 24.28, 20.13, 19.63, 19.59, 18.20, 18.14, 18.04, -4.07, -4.17, -4.73, -4.75; ESI-MS: *m/z* calcd. for $C_{47}H_{73}O_7N_1Si_1Na_1$: 814.50, found: 814.45 $[M+Na]^+$.

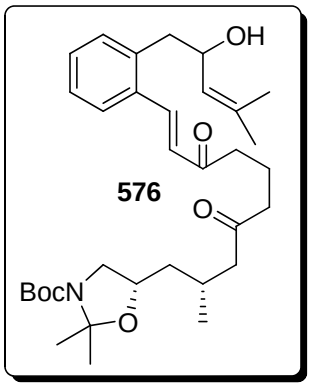


Compound 574: Silyl ether **573** (75 mg, 0.10 mmol) was dissolved in THF (2 mL) at room temperature. TBAF (0.25 mL, 0.25 mmol) was added as a 1 M THF solution and the reaction mixture was stirred 4.5 hours. The reaction mixture was diluted with diethyl ether and aqueous $NaHCO_3$. Repeated ether extractions were performed, and the combined ether extracts were dried over $MgSO_4$. Column chromatography gave diol **574** as an oil (54 mg, 85%). Mixture of diastereomers and rotamers: TLC (ethyl acetate/hexanes 1:3): $R_f = 0.1$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92-0.97 (m, 3H), 1.23-1.78 (m, 27H), 2.08-2.32 (m, 2H), 2.38-2.51 (m, 3H), 2.69-2.77 (m, 1H), 2.95-3.08 (m, 2H), 3.57-3.74 (m, 1H), 3.78 (s, 3H), 4.02-4.22 (m, 4H), 4.42-4.50 (m, 1H), 5.10-5.18 (m, 1H), 5.94-6.03 (m, 1H), 6.73-6.84 (m, 3H), 7.02-7.20 (m, 5H), 7.35-7.41 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.23, 210.07, 158.86, 158.84, 152.21, 151.83, 136.17, 136.13, 136.01, 135.96, 133.59, 131.25, 131.01, 129.05, 128.33, 127.18, 126.37, 125.79, 125.74, 125.54, 125.46, 113.53, 93.27, 92.80, 79.96, 79.39,

77.31, 75.10, 75.07, 72.77, 72.73, 72.71, 71.89, 71.71, 69.22, 69.19, 55.20, 51.15, 49.88, 43.00, 39.75, 39.57, 36.66, 30.27, 29.65, 28.42, 27.27, 26.52, 26.39, 26.24, 25.77, 25.75, 25.18, 24.25, 20.16, 19.51, 18.03, 18.00.

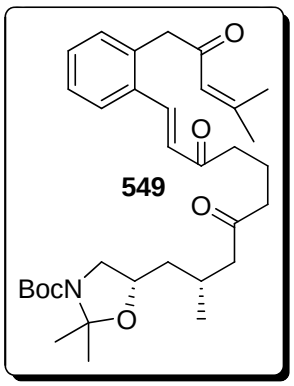


Compound 575: Alcohol **574** (54 mg, 0.08 mmol) was dissolved in methylene chloride (1 mL) at room temperature. Dess-Martin periodinane (65 mg, 0.15 mmol) was added and the reaction mixture was stirred 2.5 hours. The reaction was diluted with diethyl ether and aqueous $Na_2S_2O_3$, and then stirred until the mixture clarified. Repeated ether extractions were performed and the combined extracts dried over $MgSO_4$. Column chromatography gave ketone **574** as an oil (37 mg, 69%). Mixture of diastereomers and rotamers: TLC (ethyl acetate/hexanes 1:3): R_f = 0.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (d, J = 6.4 Hz, 3H), 1.33 (s, 3H), 1.42-1.58 (m, 15H), 1.68 (s, 3H), 1.85-1.96 (m, 2H), 2.09-2.33 (m, 2H), 2.40-2.49 (m, 2H), 2.56-2.63 (m, 2H), 2.87 (dd, J = 6.0, 13.6, 1H), 2.96-3.11 (m, 2H), 3.57-3.75 (m, 1H), 3.78 (s, 3H), 4.02-4.21 (m, 3H), 4.45 (d, J = 11.6 Hz, 1H), 5.13 (d, J = 8.8 Hz, 1H), 6.53 (d, J = 16.0 Hz, 1H), 6.77 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 7.16-7.32 (m, 3H), 7.54 (d, J = 7.2 Hz, 1H), 7.91 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.90, 209.73, 199.63, 158.87, 152.25, 151.89, 140.86, 138.86, 136.42, 133.81, 131.82, 130.79, 129.77, 129.07, 128.96, 126.95, 126.70, 126.20, 125.48, 125.30, 113.55, 93.31, 92.84, 79.95, 79.39, 77.21, 75.71, 71.92, 71.70, 69.38, 55.22, 51.42, 51.18, 50.23, 49.98, 49.86, 42.35, 42.18, 40.39, 39.79, 39.54, 39.38, 30.29, 29.68, 28.46, 27.30, 26.54, 26.27, 25.83, 25.20, 24.29, 20.14, 18.07, 18.03.

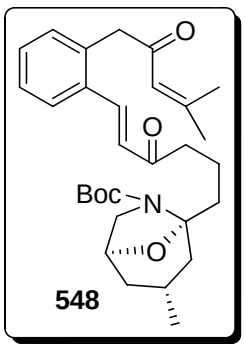


Compound 576: PMB ether **575** (22 mg, 0.033 mmol) was dissolved in methylene chloride (1.6 mL) and cooled to 0 °C. Water (0.07 mL) was added, then DDQ (8 mg, 0.035 mmol). The reaction was stirred 2.5 hours, and then diluted with diethyl ether and aqueous $NaHCO_3$. Repeated ether extractions were performed and the combined extracts dried over $MgSO_4$. Column chromatography gave allylic alcohol 576 as an oil (16 mg, 86%). Mixture of diastereomers and rotamers: TLC (ethyl acetate/hexanes 2:3): R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (d, J = 6.8 Hz, 3H), 1.25 (s, 3H), 1.38-1.58 (m, 19H), 1.65 (s, 3H), 1.90-2.00 (m, 1H), 2.10-2.23 (m, 1H), 2.43-2.55 (m, 2H), 2.65-2.73 (m, 2H), 2.89-3.11 (m, 2H), 3.56-3.76 (m, 1H), 4.01-4.13 (m, 1H), 4.49-4.59 (m, 1H), 5.21 (m, 1H), 6.63 (d, J = 16.0 Hz, 1H),

7.20-7.35 (m, 3H), 7.60 (d, J = 8.0 Hz, 1H), 8.01 (d, J =16.0 Hz, 1H); ESI-MS: *m/z* calcd. for $C_{33}H_{49}O_6N_1Na_1$: 578.35, found: 578.38 $[M+Na]^+$.

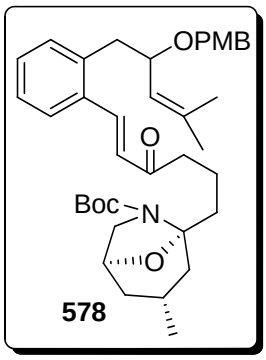


Compound 549: Allylic alcohol **576** (14 mg, 0.025 mmol) was dissolved in methylene chloride (1 mL) at room temperature. Dess-Martin periodinane (17 mg, 0.04 mmol) was added and the reaction mixture stirred 2 hours. The reaction was diluted with diethyl ether and aqueous $Na_2S_2O_3$, and then stirred until the mixture clarified. Repeated ether extractions were performed and the combined extracts were dried over $MgSO_4$. Column chromatography gave ketone **549** as an oil (13 mg, 93%). Mixture of rotamers: TLC (ethyl acetate/hexanes 2:3 [developed 2X]): R_f = 0.7; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (d, J = 6.8 Hz, 3H), 1.42-1.64 (m, ~ 16H), 1.87 (s, 3H), 1.89-1.98 (m, 1H), 2.12 (d, J = 1.2 Hz, 3H), 2.22-2.36 (m, 2H), 2.41-2.54 (m, 3H), 2.65-2.73 (m, 2H), 2.95-3.11 (m, 1H), 3.56-3.75 (m, 1H), 3.88 (s, 2H), 4.02-4.14 (m, 1H), 6.09-6.14 (bs, 1H), 6.62 (d, J = 16.0 Hz, 1H), 7.19-7.39 (m, 3H), 7.62 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 16.0 Hz, 1H); ^{1}H NMR (400 MHz, C_6D_6): δ 0.73-0.80 (m, 3H), 1.18-2.13 (m, ~ 32H), 2.37-2.47 (m, 2H), 2.90-3.08 (m, 1H), 3.46-3.55 (bs, 2H), 3.64-3.92 (m, 2H), 5.79 (s, 1H), 6.48 (d, J = 16.0 Hz, 1H), 6.89-7.03 (m, 3H), 7.30 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6): δ 208.41, 198.72, 195.85, 156.40, 152.01, 139.71, 135.84, 134.84, 131.75, 130.19, 129.94, 127.62, 126.96, 125.87, 123.27, 123.09, 93.79, 92.93, 79.25, 79.04, 72.48, 72.16, 51.95, 51.65, 49.67, 49.31, 42.21, 42.06, 39.99, 39.73, 32.35, 30.46, 30.23, 29.85, 28.61, 28.45, 27.76, 27.30, 26.77, 26.70, 25.53, 24.52, 23.15, 20.73, 20.32, 18.63, 14.41; ESI-MS: *m/z* calcd. for $C_{33}H_{47}O_6N_1Na_1$: 576.33, found: 576.25 $[M+Na]^+$.

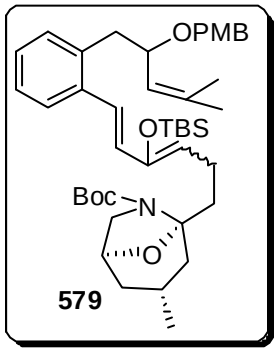


Compound 548: Triketone **549** (14 mg, 0.025 mmol) was dissolved in 0.5 mL of an AcOH/H_2O (1:1) solution. The mixture was heated at 50 °C 1 hour. The mixture was then diluted with diethyl ether and aqueous $NaHCO_3$. Repeated ether extractions were performed and the combined extracts were dried over $MgSO_4$. Rapid column chromatography with neutralized silica gave aminal **548** as an oil (11 mg, 85%). Mixture of rotamers: TLC (ethyl acetate/hexanes 2:3 [developed 2X]): R_f = 0.7 (directly above **549**); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88-0.94 (m, 3H), 1.42-1.50 (m, 9H), 1.72-2.38 (m, 14H [includes 1.88 (s, 3H) and 2.12 (s, 3H)]), 2.62-2.72 (m, 2H), 3.5-3.54 (m, 1H), 3.86 (s, 2H), 4.36-4.41 (m, 1H), 6.11 (bs, 1H), 6.63 (d, J = 16.0 Hz, 1H), 7.16-7.38 (m, 3H), 7.62 (d, J = 7.2 Hz, 1H), 7.71 (d, J = 16.0 Hz, 0.5H), 7.74 (d, J = 16.0 Hz, 0.5H); ^{1}H NMR (400 MHz, C_6D_6): δ 0.66 (d, J = 6.4 Hz, 3H), 1.02-1.37 (m, ~ 14H), 1.40-1.49 (m, 9H), 1.55-1.71 (m, 2H),

1.80-1.92 (m, 1H), 1.92-2.14 (m, 6H), 2.16-2.26 (m, 1H), 2.33 (dd, J = 4.8, 12.8 Hz, 1H), 2.42-2.57 (m, 2-3H), 3.09-3.14 (m, 1H), 3.24-3.34 (m, 1H), 3.39-3.51 (m, 3H), 3.88-3.97 (m, 1H), 5.78 (bs, 1H), 6.49 (app. t, J =16.0 Hz, 1H) 6.89-7.02 (m, 3H), 7.28 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 16.0 Hz, 0.5H), 7.92 (d, J = 16.0 Hz, 0.5H); ^{13}C NMR (100 MHz, C_6D_6 [poor phasing may have led to additional peaks]): δ 198.79, 195.83, 195.79, 156.20, 156.05, 152.67, 152.30, 139.25, 138.90, 135.82, 135.76, 134.96, 134.90, 131.63, 131.54, 130.13, 130.02, 129.85, 128.49, 127.53, 127.44, 127.31, 126.96, 126.79, 125.69, 123.25, 123.11, 94.52, 94.24, 79.50, 78.84, 72.59, 72.37, 51.61, 51.21, 49.19, 48.94, 42.50, 41.38, 41.02, 40.97, 37.88, 36.43, 35.56, 30.43, 35.56, 30.43, 30.19, 30.11, 29.81, 29.64, 28.55, 28.44, 27.24, 24.44, 24.34, 23.10, 21.68, 21.62, 20.67, 18.18, 18.14, 14.35; α_D -41.6 (c = 6, mg/mL, $CHCl_3$); ESI-MS: *m/z* calcd. for $C_{30}H_{41}O_5N_1Na_1$: 518.29, found: 518.28 $[M+Na]^+$.

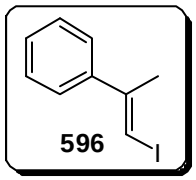


Compound 578: Diketone **575** (12 mg, 0.018 mmol) was dissolved in 0.5 mL of an AcOH/H_2O (1:1) solution. The mixture was heated at 50 °C 3 hours. The mixture was then diluted with diethyl ether and aqueous $NaHCO_3$. Repeated ether extractions were performed and the combined extracts were dried over $MgSO_4$. Rapid column chromatography with neutralized silica gave aminal **578** as an oil (6 mg, 55%). Mixture of diastereomers and rotamers: TLC (ethyl acetate/hexanes 1:3): R_f = 0.2 (directly above **575**); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88-0.94 (m, 4-5H), 1.18-1.88 (m, < 32H), 1.97-2.30 (m, 2H), 2.55-2.64 (m, 2H), 2.83-2.91 (m, 1H), 3.02-3.10 (m, 1H), 3.37-3.55 (m, 2H), 3.78 (s, 3H), 4.10-4.18 (m, 1H), 4.18 (d, J = 11.5 Hz, 1H), 4.34-4.39 (m, 1H), 4.45 (d, J = 11.5 Hz, 1H), 5.08-5.15 (m, 1H), 6.55 (m, 1H), 6.73-6.80 (m, 2H), 7.01-7.08 (m, 2H), 7.14-7.32 (m, 3H), 7.49-7.57 (m, 1H), 7.83-7.93 (m, 1H); ESI-MS: *m/z* calcd. for $C_{38}H_{51}O_6N_1Na_1$: 640.36, found: 640.39 $[M+Na]^+$.

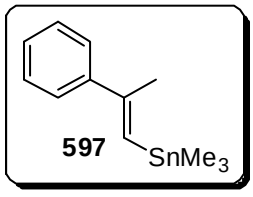


Compound 579: Aminal **578** (5 mg, 0.008 mmol) was dissolved in methylene chloride (1 mL) and triethylamine (50 μL, 0.04 mmol) was added at room temperature. The mixture was cooled to 0 °C after stirring 5 minutes at room temperature. TBSOTf (several drops, ~ 1.5 eq.) was added and the reaction mixture was stirred 30 minutes, and then diluted with diethyl ether and aqueous $NaHCO_3$. Repeated ether extractions were performed and the combined ether extracts dried over $MgSO_4$. Rapid column chromatography with neutralized silica provided a mixture of silyl enol ethers (5 mg, 85%). Mixture of diastereomers and rotamers: TLC (ethyl acetate/hexanes 1:3): R_f = 0.4; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.09-0.2 (m, ~ 9H), 0.84-1.06 (m, ~ 24H), 1.16-1.26 (m, ~ 14H), 1.38-

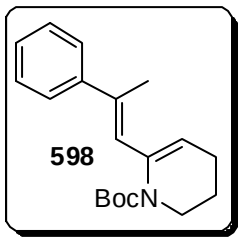
1.53 (m, ~ 19H), 1.64-1.89 (m, ~ 11H), 1.97-2.41 (m, ~ 6H), 2.70-2.80 (m, 1H), 3.00-3.12 (m, 1H), 3.38-3.56 (m, 3H), 3.78 (s, 3H), 4.15-4.24 (m, 3H), 4.34-4.46 (m, 2H), 4.84-4.95 (m, 1H), 5.09-5.17 (m, 1H), 6.37 (m, 1H), 6.76-6.80 (m, 2H), 7.04-7.17 (m, 6H), 7.39-7.43.



Compound 596: To a stirred methylene chloride (42 mL) solution of dichlorozirconocene (7.85 g, 26.89 mmol), was added $AlMe_3$ (5.15 mL, 66.4 mmol) at room temperature in 1 mL portions over 10 minutes. After stirring 15 minutes, phenylacetylene (5.65 mL, 24.16 mmol) was added in 1 mL portions. The reaction mixture was stirred 25 hours, and then cooled to 0 °C. I_2 (8g) was added in THF (50 mL). The reaction was stirred 1 hour, the ice bath was removed, and stirring was continued 10 minutes at room temperature. The mixture was then diluted with hexanes and water. Repeated ether extractions were performed and the extracts combined. The organic extracts were washed with aqueous $Na_2S_2O_3$, then the precipitate was filtered and the extracts were dried over MgSO4. Column chromatography gave vinyl iodide **596** as an oil (5.1 g, 77%). TLC (ethyl acetate/hexanes 1:9): R_f = 0.6; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.86 (s, 3H), 6.52 (bs, 1H), 7.26-7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.2, 141.4, 128.4, 127.8, 126.0, 79.1, 24.4.

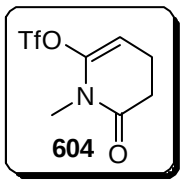


Compound 597: To a stirred THF (30 mL) solution of vinyl iodide **596** (1.38 g, 5.66 mmol) at -78 °C, was added *t*-BuLi (11.2 mL, 19.0 mmol) as a 1.7 M pentane solution. The reaction was stirred 1.5 hours, and then $ClSnMe_3$ (7.5 mL, 7.5 mmol) was added as a 1 M THF solution. The reaction was stirred 1 hour after $ClSnMe_3$ addition, and then the mixture was diluted with hexanes and water. Repeated ether extractions were performed and the extracts were dried over $MgSO_4$. Rapid column chromatography gave stannane **597** as an oil (1.18g, 75%). TLC (ethyl acetate/hexanes 1:9): R_f = 0.7; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.204-0.67 (m, 9H), 2.03-2.57 (m, 3H), 6.18-6.34 (m, 1H), 7.21-7.26 (m, 1H), 7.28-7.34 (m, 2H), 7.43-7.47 (m, 2H).



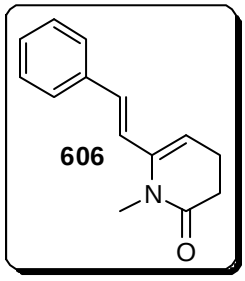
Compound 598: Stannane **597** (290 mg, 1.0 mmol) and vinyl triflate **590** (256 mg, 0.77 mmol) were mixed under argon. The mixture was diluted with degassed dioxane (10 mL) and $Pd(PPh_3)_4$ (50 mg, 0.043 mmol) was added, followed rapidly by LiCl (180 mg, 4.29 mmol). The mixture was heated 20 hours at 60 °C. After cooling to room temperature, the mixture was diluted with diethyl ether and filtered through a silica plug. The filtrate was concentrated and subjected to column chromatography. Diene **598** was obtained as an

oil (231 mg, 75%). TLC (ethyl acetate/hexanes 1:9): R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (s, 9H), 1.80-1.89 (m, 2H), 2.20-2.28 (m, 2H), 3.57-3.66 (m, 2H), 5.13 (app. t, J = 3.6 Hz, 1H), 6.23 (bs, 1H), 7.16-7.36 (m, 4H), 7.42-7.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 143.3, 136.6, 133.7, 128.2, 127.0, 126.7, 125.5, 115.3, 80.1, 43.8, 28.4, 28.2, 23.4, 17.1.



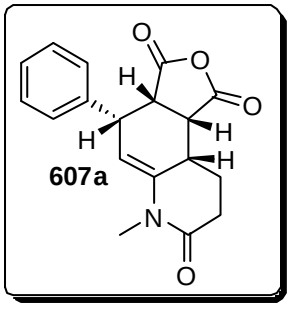
604

Compound 604: N-methyl glutarimide **603** (180 mg, 1.42 mmol) was dissolved in THF (4 mL) and cooled to -78 °C. KHMDS (3.4 mL, 1.7 mmol) was added as a 0.5 M THF solution over 5 minutes. The reaction mixture was warmed to 0 C, and stirred 30 minutes. The resultant slurry was diluted with THF (3 mL) and cooled to -78 °C. N-phenyltriflimide (601 mg, 1.68 mmol) was added in one portion, and the reaction was transferred to a 0 °C ice bath after stirring 1 hour at -78 °C. The mixture was stirred 45 minutes at 0 °C, and then diluted with diethyl ether and 15% $NaOH/H_2O$. Repeated ether extractions were performed, and the combined extracts dried over $MgSO_4$. Rapid column chromatography with neutralized silica gave vinyl triflate **604** as an oil (44 mg, 12%). TLC (ethyl acetate/hexanes 2:3): R_f = 0.5; ^{1}H NMR (400 MHz, C_6D_6): δ 1.21-1.33 (m, 2H), 1.85-1.94 (m, 2H), 2.73 (s, 3H), 4.52-4.60 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6): δ 168.5, 141.5, 118.8 (q, J = 318 Hz), 96.1, 30.6, 27.2, 17.0.

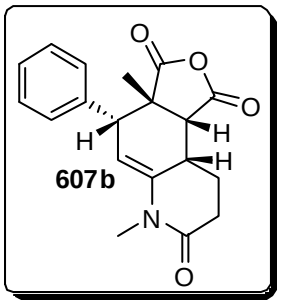


606

Compound 606: N-methyl glutarimide **603** (1.4 g, 11.02 mmol) was dissolved in THF (20 mL) and cooled to 0 °C. LiHMDS (11.2 mL, 11.2 mmol) was added as a 1 M THF solution over 2.5 minutes. The solution was removed from the ice bath and stirred at room temperature 10 minutes before cooling to -78 °C. Diethylchlorophosphate (1.6 mL, 11.04 mmol) was added as a THF solution (10 mL) via cannula over 10 minutes. After stirring 20 minutes, the mixture was transferred to a 0 °C ice bath. Styryl stannane **588** (2.9 g, 7.4 mmol) was added followed quickly by $Pd(PPh_3)_4$ (650 mg, 0.56 mmol) and LiCl (4.8 g, 114.3 mmol). The reaction mixture was then heated at 60 °C 5 hours. The mixture was then diluted with hexanes and decanted to remove solids. The solids were stirred with diethyl ether and decanted again. The combined organics were washed with 0.5 M LiOH, and the aqueous layer was back-extracted with ether. The combined organic extracts were dried over K_2CO_3. Column chromatography on neutralized silica gave diene **606** as an oil (631 mg, 40%). TLC (ethyl acetate/hexanes 2:3): R_f = 0.5; ^{1}H NMR (400 MHz, C_6D_6): δ 1.72-1.79 (m, 2H), 2.26 (app. t, J = 7.6 Hz, 2H), 2.89 (s, 3H), 5.02 (app. t, J = 5.2 Hz, 1H), 6.24 (d, J = 16.0 Hz, 1H), 6.53 (d, J = 16.0 Hz, 1H), 7.01-7.18 (m, 5H); ^{13}C NMR (100 MHz, C_6D_6 [1 peak obscured by C_6H_6]): δ 169.8, 141.5, 137.0, 131.2, 128.9, 126.9, 123.5, 105.6, 31.7, 30.4, 19.8.

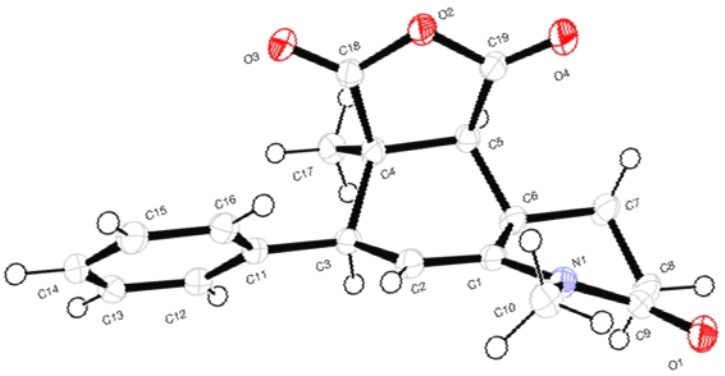


Compound 607a: Similar yields were obtained with a variety of solvents at different temperatures. For effect of solvent and temperature on relative reaction rate, see Table 2.2. A reaction performed in C_6D_6 is described. Diene **606** (5.5 mg, 0.026 mmol) was transferred to a NMR tube containing maleic anhydride (3.5 mg, 0.036 mmol) and diluted with C_6D_6 (0.7 mL). The reaction was monitored by NMR and deemed complete after 75 minutes. The reaction mixture was transferred to a vial and diluted with a hexanes/diethyl ether (1:1) solution. The solids were filtered off and the filtrate was concentrated. Expedient column chromatography on neutralized silica gave cycloadduct **607a** as an oil (7 mg, 90%), which crystallized upon storage at reduced temperature. TLC (ethyl acetate/hexanes 4:1): R_f= 0.5; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 2.10-2.17 (m, 1H), 2.30-2.41 (m, 1H), 2.61-2.74 (m, 2H), 2.86-2.95 (m, 1H), 3.10 (s, 3H), 3.56-3.68 (m, 2H), 3.76-3.81 (m, 1H), 5.39 (app. t, J = 3.0 Hz, 1H), 7.32-7.46 (m, 5H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 171.4, 170.1, 169.6, 142.8, 139.1, 129.2, 129.0, 128.1, 103.9, 48.8, 46.0, 41.9, 35.3, 32.6, 29.8, 21.0.



Compound 507b: Similar yields were obtained with a variety of solvents at different temperatures. For effect of solvent and temperature on relative reaction rate, see Table 2.2. A reaction performed in C_6D_6 is described. Diene **606** (5 mg, 0.023 mmol) was transferred to a NMR tube containing citraconic anhydride (5 mg, 0.045 mmol) and diluted with C_6D_6 (0.7 mL). The reaction was heated to 50 °C and monitored by NMR. The reacition was deemed complete after 48 hours. The reaction mixture was then transferred to a vial and diluted with a hexanes/diethyl ether (1:1) solution. An aqueous $NaHCO_3$ wash was performed and the organic layer was concentrated after drying over $MgSO_4$. Expedient column chromatography on neutralized silica gave cycloadduct **607b** as an oil (6 mg, 80%), which crystallized upon storage at reduced temperature. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 1.50 (s, 3H), 2.05-2.12 (m, 1H), 2.36-2.44 (m, 1H), 2.68-2.85 (m, 3H), 3.07 (s, 3H), 3.16-3.20 (m, 1H), 3.32-3.36 (m, 1H), 5.17 (bs, 1H), 7.21-7.27 (m,2H), 7.34-7.42 (m, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 173.1, 170.7, 169.5, 143.8, 139.4, 130.1, 128.9,

128.4, 105.2, 52.8, 51.0, 34.3, 32.7, 30.2, 29.6, 21.9, 21.6. A crystal suitable for single crystal x-ray analysis was grown:



Crystal data and structure refinement for theod28.

X-ray ID	theod28	
Sample/notebook ID	DEF11-6	
Empirical formula	C19 H19 N O4	
Formula weight	325.35	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 11.0173(4) Å	α= 90°.
	b = 11.7765(4) Å	β= 111.718(2)°.

	c = 12.9144(4) Å γ = 90°.
Volume	1556.64(9) $Å^3$
Z	4
Density (calculated)	1.388 Mg/m^3
Absorption coefficient	0.799 mm^{-1}
F(000)	688
Crystal size	0.14 x 0.12 x 0.08 mm^3
Crystal color/habit	colorless block
Theta range for data collection	4.52 to 68.15°.
Index ranges	-13<=h<=12, -11<=k<=14, -14<=l<=15
Reflections collected	7953
Independent reflections	2797 [R(int) = 0.0301]
Completeness to theta = 67.00°	98.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9388 and 0.8964
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2797 / 0 / 220
Goodness-of-fit on F^2	1.131
Final R indices [I>2sigma(I)]	R1 = 0.0406, wR2 = 0.1012
R indices (all data)	R1 = 0.0521, wR2 = 0.1071
Extinction coefficient	0.0012(3)
Largest diff. peak and hole	0.218 and -0.200 $e.Å^{-3}$

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for theod28. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)

C(1)	2663(2)	1866(2)	-414(2)	20(1)
C(2)	2888(2)	757(2)	-230(1)	20(1)
C(3)	3556(2)	371(2)	963(1)	20(1)
C(4)	2865(2)	873(2)	1746(1)	20(1)
C(5)	2382(2)	2089(2)	1383(1)	20(1)
C(6)	2970(2)	2633(2)	590(2)	21(1)
C(7)	2565(2)	3861(2)	286(2)	25(1)
C(8)	2982(2)	4192(2)	-676(2)	28(1)
C(9)	2291(2)	3474(2)	-1689(2)	22(1)
C(10)	1524(2)	1591(2)	-2434(2)	24(1)
C(11)	3784(2)	-900(2)	1087(1)	20(1)
C(12)	4926(2)	-1311(2)	1907(2)	23(1)
C(13)	5150(2)	-2469(2)	2067(2)	26(1)
C(14)	4250(2)	-3233(2)	1389(2)	28(1)
C(15)	3124(2)	-2833(2)	556(2)	27(1)
C(16)	2888(2)	-1674(2)	417(2)	23(1)
C(17)	3789(2)	807(2)	2968(2)	25(1)
C(18)	1613(2)	233(2)	1587(1)	21(1)
C(19)	911(2)	1977(2)	838(2)	22(1)
N(1)	2118(2)	2354(1)	-1489(1)	20(1)
O(1)	1897(1)	3872(1)	-2634(1)	29(1)
O(2)	533(1)	885(1)	996(1)	23(1)
O(3)	1464(1)	-685(1)	1909(1)	27(1)
O(4)	114(1)	2663(1)	356(1)	33(1)

Bond lengths [Å] and angles [°] for theod28.

C(1)-C(2)	1.333(3)	C(1)-C(6)	1.512(2)
C(1)-N(1)	1.416(2)	C(2)-C(3)	1.511(2)

C(2)-H(2)	0.9500	C(10)-H(10A)	0.9800
C(3)-C(11)	1.516(2)	C(10)-H(10B)	0.9800
C(3)-C(4)	1.588(2)	C(10)-H(10C)	0.9800
C(3)-H(3)	1.0000	C(11)-C(16)	1.387(3)
C(4)-C(18)	1.518(2)	C(11)-C(12)	1.397(3)
C(4)-C(17)	1.531(2)	C(12)-C(13)	1.388(3)
C(4)-C(5)	1.539(2)	C(12)-H(12)	0.9500
C(5)-C(19)	1.514(2)	C(13)-C(14)	1.384(3)
C(5)-C(6)	1.540(2)	C(13)-H(13)	0.9500
C(5)-H(5)	1.0000	C(14)-C(15)	1.390(3)
C(6)-C(7)	1.522(2)	C(14)-H(14)	0.9500
C(6)-H(6)	1.0000	C(15)-C(16)	1.388(3)
C(7)-C(8)	1.526(3)	C(15)-H(15)	0.9500
C(7)-H(7A)	0.9900	C(16)-H(16)	0.9500
C(7)-H(7B)	0.9900	C(17)-H(17A)	0.9800
C(8)-C(9)	1.507(3)	C(17)-H(17B)	0.9800
C(8)-H(8A)	0.9900	C(17)-H(17C)	0.9800
C(8)-H(8B)	0.9900	C(18)-O(3)	1.191(2)
C(9)-O(1)	1.226(2)	C(18)-O(2)	1.384(2)
C(9)-N(1)	1.370(2)	C(19)-O(4)	1.186(2)
C(10)-N(1)	1.461(2)	C(19)-O(2)	1.390(2)

C(2)-C(1)-N(1)	123.80(16)	C(2)-C(3)-C(4)	111.66(14)
C(2)-C(1)-C(6)	117.67(16)	C(11)-C(3)-C(4)	113.58(14)
N(1)-C(1)-C(6)	118.50(15)	C(2)-C(3)-H(3)	105.6
C(1)-C(2)-C(3)	117.71(16)	C(11)-C(3)-H(3)	105.6
C(1)-C(2)-H(2)	121.1	C(4)-C(3)-H(3)	105.6
C(3)-C(2)-H(2)	121.1	C(18)-C(4)-C(17)	109.83(15)
C(2)-C(3)-C(11)	113.84(15)	C(18)-C(4)-C(5)	103.08(14)

C(17)-C(4)-C(5)	112.59(14)	O(1)-C(9)-C(8)	121.89(17)
C(18)-C(4)-C(3)	110.80(14)	N(1)-C(9)-C(8)	115.94(16)
C(17)-C(4)-C(3)	110.13(14)	N(1)-C(10)-H(10A)	109.5
C(5)-C(4)-C(3)	110.24(14)	N(1)-C(10)-H(10B)	109.5
C(19)-C(5)-C(4)	104.50(14)	H(10A)-C(10)-H(10B)	109.5
C(19)-C(5)-C(6)	111.60(15)	N(1)-C(10)-H(10C)	109.5
C(4)-C(5)-C(6)	113.96(15)	H(10A)-C(10)-H(10C)	109.5
C(19)-C(5)-H(5)	108.9	H(10B)-C(10)-H(10C)	109.5
C(4)-C(5)-H(5)	108.9	C(16)-C(11)-C(12)	118.61(17)
C(6)-C(5)-H(5)	108.9	C(16)-C(11)-C(3)	122.08(16)
C(1)-C(6)-C(7)	113.31(15)	C(12)-C(11)-C(3)	119.30(16)
C(1)-C(6)-C(5)	107.79(14)	C(13)-C(12)-C(11)	120.90(18)
C(7)-C(6)-C(5)	114.28(15)	C(13)-C(12)-H(12)	119.6
C(1)-C(6)-H(6)	107.0	C(11)-C(12)-H(12)	119.6
C(7)-C(6)-H(6)	107.0	C(14)-C(13)-C(12)	119.91(18)
C(5)-C(6)-H(6)	107.0	C(14)-C(13)-H(13)	120.0
C(6)-C(7)-C(8)	107.75(15)	C(12)-C(13)-H(13)	120.0
C(6)-C(7)-H(7A)	110.2	C(13)-C(14)-C(15)	119.62(18)
C(8)-C(7)-H(7A)	110.2	C(13)-C(14)-H(14)	120.2
C(6)-C(7)-H(7B)	110.2	C(15)-C(14)-H(14)	120.2
C(8)-C(7)-H(7B)	110.2	C(16)-C(15)-C(14)	120.31(19)
H(7A)-C(7)-H(7B)	108.5	C(16)-C(15)-H(15)	119.8
C(9)-C(8)-C(7)	110.85(16)	C(14)-C(15)-H(15)	119.8
C(9)-C(8)-H(8A)	109.5	C(11)-C(16)-C(15)	120.61(18)
C(7)-C(8)-H(8A)	109.5	C(11)-C(16)-H(16)	119.7
C(9)-C(8)-H(8B)	109.5	C(15)-C(16)-H(16)	119.7
C(7)-C(8)-H(8B)	109.5	C(4)-C(17)-H(17A)	109.5
H(8A)-C(8)-H(8B)	108.1	C(4)-C(17)-H(17B)	109.5
O(1)-C(9)-N(1)	122.17(18)	H(17A)-C(17)-H(17B)	109.5

C(4)-C(17)-H(17C)	109.5	O(4)-C(19)-C(5)	129.93(17)
H(17A)-C(17)-H(17C)	109.5	O(2)-C(19)-C(5)	109.88(15)
H(17B)-C(17)-H(17C)	109.5	C(9)-N(1)-C(1)	122.56(15)
O(3)-C(18)-O(2)	119.65(17)	C(9)-N(1)-C(10)	119.03(15)
O(3)-C(18)-C(4)	129.73(17)	C(1)-N(1)-C(10)	117.74(15)
O(2)-C(18)-C(4)	110.60(14)	C(18)-O(2)-C(19)	110.53(14)
O(4)-C(19)-O(2)	120.17(17)		

Symmetry transformations used to generate equivalent atoms:

Anisotropic displacement parameters ($Å^2 x\ 10^3$)for theod28. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	18(1)	21(1)	21(1)	0(1)	8(1)	0(1)
C(2)	22(1)	20(1)	21(1)	-2(1)	8(1)	-1(1)
C(3)	19(1)	20(1)	21(1)	-1(1)	8(1)	0(1)
C(4)	21(1)	19(1)	20(1)	-1(1)	8(1)	0(1)
C(5)	21(1)	17(1)	21(1)	-1(1)	8(1)	0(1)
C(6)	23(1)	19(1)	22(1)	-2(1)	9(1)	-2(1)
C(7)	34(1)	17(1)	26(1)	-2(1)	15(1)	-2(1)
C(8)	38(1)	18(1)	31(1)	0(1)	18(1)	-3(1)
C(9)	24(1)	20(1)	27(1)	3(1)	13(1)	6(1)
C(10)	25(1)	26(1)	20(1)	-2(1)	6(1)	1(1)
C(11)	22(1)	19(1)	22(1)	1(1)	11(1)	0(1)
C(12)	21(1)	23(1)	26(1)	1(1)	10(1)	0(1)
C(13)	24(1)	27(1)	31(1)	7(1)	14(1)	7(1)
C(14)	33(1)	18(1)	41(1)	3(1)	24(1)	3(1)

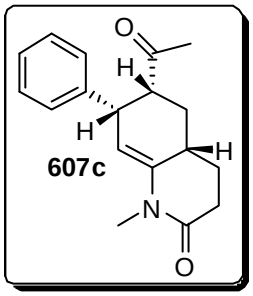
C(15)	31(1)	21(1)	34(1)	-5(1)	18(1)	-4(1)
C(16)	23(1)	23(1)	25(1)	0(1)	10(1)	0(1)
C(17)	26(1)	27(1)	20(1)	0(1)	7(1)	3(1)
C(18)	24(1)	21(1)	19(1)	-1(1)	10(1)	2(1)
C(19)	24(1)	21(1)	23(1)	1(1)	10(1)	0(1)
N(1)	23(1)	20(1)	19(1)	0(1)	8(1)	1(1)
O(1)	35(1)	26(1)	26(1)	7(1)	14(1)	8(1)
O(2)	20(1)	21(1)	26(1)	2(1)	7(1)	0(1)
O(3)	31(1)	20(1)	34(1)	4(1)	17(1)	0(1)
O(4)	26(1)	30(1)	42(1)	12(1)	11(1)	6(1)

Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3)

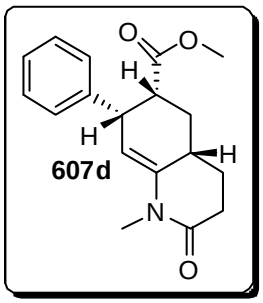
for theod28.

	x	y	z	U(eq)
H(2)	2636	229	-828	25
H(3)	4445	722	1227	23
H(5)	2597	2576	2062	24
H(6)	3941	2629	985	25
H(7A)	2993	4361	935	30
H(7B)	1607	3940	59	30
H(8A)	2776	5003	-862	33
H(8B)	3938	4093	-446	33
H(10A)	1251	2027	-3129	37
H(10B)	760	1221	-2366	37
H(10C)	2161	1013	-2441	37
H(12)	5558	-790	2362	27

H(13)	5919	-2737	2641	31
H(14)	4402	-4026	1492	33
H(15)	2513	-3354	80	32
H(16)	2105	-1409	-143	28
H(17A)	3353	1119	3443	37
H(17B)	4581	1247	3072	37
H(17C)	4026	13	3171	37

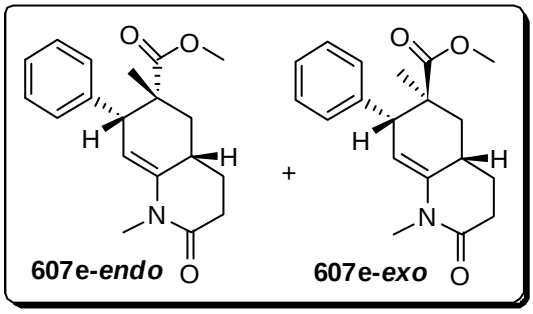


Compound 607c: Similar yields were obtained with a variety of solvents at different temperatures. For effect of solvent and temperature on relative reaction rate, see Table 2.2. A reaction performed in C_6D_6 is described. Diene **606** (7 mg, 0.032 mmol) was transferred to a NMR tube containing methyl vinyl ketone (5 mg, 0.071 mmol) and diluted with C_6D_6 (0.7 mL). The reaction was heated to 80 °C and monitored by NMR. The reaction was deemed complete after 2 hours. The reaction mixture was then transferred to a vial and diluted with a hexanes/diethyl ether (1:1) solution. An aqueous $NaHCO_3$ wash was performed and the organic layer was concentrated after drying over $MgSO_4$. Expedient column chromatography on neutralized silica gave cycloadduct **607c** as an oil (7 mg, 75%), which crystallized upon storage at reduced temperature. ^{1}H NMR (400 MHz, C_6D_6): δ 0.89-1.01 (m, 1H), 1.12-1.19 (m, 1H), 1.20-1.28 (m, 1H), 1.45 (s, 3H), 1.49-1.59 (m, 1H), 2.03-2.14 (m, 1H), 2.34-2.47 (m, 2H), 2.87 (s, 3H), 3.66-3.73 (m, 1H), 4.51-4.57 (d, 1H), 6.98-7.04 (m, 3H), 7.05-7.10 (2H); ^{13}C NMR (100 MHz, C_6D_6): δ 207.7, 167.8, 141.3, 141.0, 129.6, 128.4, 127.3, 104.6, 51.7, 42.7, 34.5, 33.1, 29.5, 28.4, 27.3, 26.8.

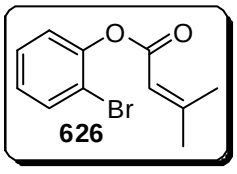


Compound 607d: Similar yields were obtained with a variety of solvents at different temperatures. For effect of solvent and temperature on relative reaction rate, see Table 2.2. A reaction performed in C_6D_6 is described. Diene **606** (7 mg, 0.032 mmol) was transferred to a NMR tube containing methyl acrylate (6 mg, 0.070 mmol) and diluted with C_6D_6 (0.7 mL). After 5 days at room temperature, the reaction was deemed complete. The

reaction mixture was then transferred to a vial and diluted with a hexanes/diethyl ether (1:1) solution. An aqueous $NaHCO_3$ wash was performed and the organic layer was concentrated after drying over $MgSO_4$. Expedient column chromatography on neutralized silica gave cycloadduct **607d** as an oil (7 mg, 71%), which crystallized upon storage at reduced temperature. ^{1}H NMR (400 MHz, C_6D_6): δ 0.86-1.00 (m, 1H), 1.07-1.15 (m, 1H), 1.44-1.57 (m, 3H), 1.96-2.08 (m, 1H), 2.34-2.43 (m, 1H), 2.60-2.67 (m, 1H), 2.85 (s, 3H), 3.19 (s, 3H), 3.87 (app. t, J = 5.2 Hz, 1H), 4.54 (d, J = 4.8 Hz, 1H), 7.04-7.16 (m, 5H); ^{13}C NMR (100 MHz, C_6D_6 [1 carbon obscured by C_6H_6]): δ 172.8, 167.8, 141.5, 141.2, 129.8, 127.4, 104.1, 50.7, 44.5, 42.6, 34.3, 33.0, 29.4, 27.1, 26.5.

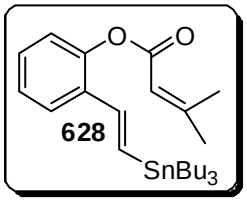


Compound 607e: Similar yields were obtained with a variety of solvents at different temperatures. For effect of solvent and temperature on relative reaction rate, see Table 2.2. A reaction performed in C_6D_6 is described. Diene **606** (45 mg, 0.21 mmol) was transferred to a NMR tube containing methyl methacrylate (36 mg, 0.36 mmol) and diluted with C_6D_6 (1.0 mL). The reaction was heated to 80 °C and monitored by NMR. The reacition was deemed complete after 44 hours. The reaction mixture was transferred to a vial and diluted with a hexanes/diethyl ether (1:1) solution. An aqueous $NaHCO_3$ wash was performed and the organic layer was concentrated after drying over $MgSO_4$. Expedient column chromatography on neutralized silica gave cycloadduct **607e** as a mixture of diastereomers (45 mg, 68%), which formed an amorphous solid upon storage at reduced temperature. TLC (ethyl acetate/hexanes 3:2): R_f = 0.6; ^{1}H NMR (400 MHz, C_6D_6): δ 0.74 (s, 2.7H), 0.94-1.24 (m, ~ 4.7H), 1.29 (s, 6H), 1.35-1.43 (m, 2.6H), 1.64-2.47 (m, ~ 15H), 2.84 (s, 2.7H, ***exo***), 2.85 (s, 5H, ***endo***), 3.04 (s, 5H, ***endo***), 3.35 (s, 2.5H, ***exo***), 3.44 (d, J = 5.2 Hz, 1.8H, ***endo***), 4.29 (d, J = 5.6 Hz, 1H, ***exo***), 4.53 (d, J = 5.6 Hz, 1.8H, ***endo***), 4.77 (d, J = 5.2 Hz, 1H, ***exo***), 6.92-7.27 (m, 14H); ^{13}C NMR (100 MHz, C_6D_6 [1 carbon obscured by C_6H_6]): δ 176.8, 175.4, 167.83, 167.80, 141.9, 141.6, 140.7, 139.8, 130.7, 129.9, 128.2, 127.3, 127.1, 105.1, 103.0, 51.8, 50.8, 49.9, 46.3, 45.8, 44.6, 34.5, 33.2, 33.1, 32.5, 32.2, 31.2, 29.4, 29.3, 27.4, 27.2, 25.7, 23.3.

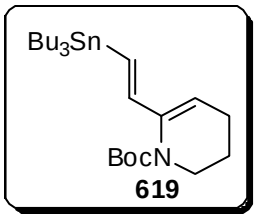


Compound 626: Phenol **624** (149 mg, 0.8623 mmol), 3-methyl-2-enoic acid (**625**) (124 mg, 1.24 mmol), DCC (270 mg, 1.3 mmol), and DMAP (10 mg, 0.08 mmol) were dissolved in methylene chloride (4 mL) at 0 °C. The reaction was allowed to warm to room temperature and then stirred 18 hours. The solids were filtered, washed with ether, and the combined organics (filtrate) were concentrated for column chromatrography. Acrylate **626** was obtained as an oil (220 mg, 99%). TLC

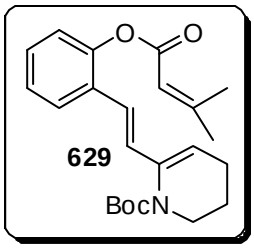
(ethyl acetate/hexanes 1:3): $R_f = 0.6$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.01 (s, 3H), 2.25 (s, 3H), 5.98-6.01 (bs, 1H), 7.08-7.17 (m, 2H), 7.30-7.36 (m, 1H), 7.59-7.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 161.2, 148.2, 133.2, 128.3, 127.0, 124.0, 116.4, 114.5, 27.7, 20.6.



Compound 628: Aryl bromide **626** (32 mg, 0.13 mmol) and bis stannane **627** (138 mg, 0.23 mmol) were mixed under argon. The mixture was then diluted with degassed toluene (0.2 mL). $Pd(PPh_3)_4$ (9 mg, 0.008 mmol) was added, and the mixture was placed in a 50 °C oil bath for 6 hours. The crude mixture was loaded directly onto a silica column and eluted. Stannane **628** was obtained as an oil (15 mg, 25%). TLC (ethyl acetate/hexanes 1:9): $R_f = 0.9$; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87-0.96 (m, ~ 19H), 1.25-1.36 (m, ~ 16H), 1.48-1.54 (m, ~ 5H), 2.00 (s, 3H), 2.23 (s, 3H), 5.96-5.98 (bs, 1H), 6.82-6.97 (m, 2H), 7.02-7.05 (m, 1H), 7.18-7.26 (m, 2H), 7.58-7.62 (m, 1H).

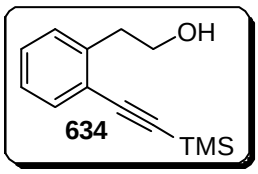


Compound 619: Bis stannane **627** (195 mg, 0.32 mmol) and vinyl triflate **590** (60 mg, 0.18 mmol) were mixed under argon and diluted with toluene (0.1 mL). $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) was added at room temperature and the reaction flask was transferred to a 50 °C oil bath. After stirring 3 hours, the reaction was cooled to room temperature and loaded directly onto a silica column. Stannane **619** was obtained as an oil (45 mg, 50%). TLC (ethyl acetate/hexanes 1:9): $R_f = 0.4$; ^{1}H NMR (400 MHz, C_6D_6): δ 0.85-1.05 (m, 11H), 1.29-1.46 (m, 14H), 1.51-1.70 (m, 5H), 1.70-1.79 (m, 2H), 3.45-3.52 (m, 2H), 5.17 (app. t, J = 4 Hz, 1H), 6.35-6.74 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6): δ 154.15, 145.6, 141.1, 124.4, 114.7, 80.0, 44.6, 129.7, 29.6, 29.5, 28.4, 27.8, 23.7, 23.5, 13.9, 9.8, [29.7, 29.6, and 29.5 are signals from a single carbon coupled to Sn, as are 11.5, 11.4, 9.8, 8.2, and 8.1].



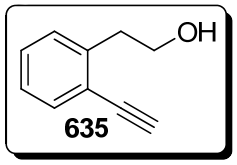
Compound 629: Stannane **619** (9 mg, 0.018 mmol) and aryl bromide **626** (10 mg, 0.040mmol) were mixed under argon and diluted with toluene (0.5 mL). $Pd(PPh_3)_4$ (1 mg, 0.001 mmol) was added at room temperature and the reaction flask was transferred to a 50 °C oil bath. After stirring 2 hours, the reaction was cooled to room temperature and loaded directly onto a silica column. Stannane **629** was obtained as an oil (2-3 mg, 40%). ^{1}H

NMR (400 MHz, $CDCl_3$): δ 1.55 (s, 9H + H_20 protons), 1.78-1.85 (m, 2H), 2.0 (s, 3H), 2.22 (s, 3H), 2.22-2.27 (m, 2H), 3.56-3.60 (m, 2H), 5.43 (app. t, J = 4.0 Hz, 1H), 5.96 (bs, 1H), 6.97-7.0 (m, 1H), 7.03-7.06 (m, 1H), 7.15-7.26 (m, 3H), 7.54-7.58 (m, 1H).



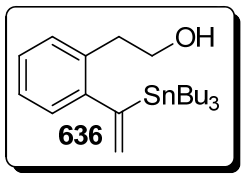
634

Compound 634: Aryl iodide **633** (2.65 g, 10.69 mmol) was dissolved in dimethylformamide (30 mL) and triethylamine (30 mL). The solution was degassed with argon 30 minutes, and then TMS acetylene (10.5 mL, 74.5 mmol) was added. $Pd(PPh_3)_4$ (990 mg, 0.86 mmol) was added at room temperature followed by CuI (112 mg, 0.59 mmol), and the reaction flask was transferred to a 35 °C oil bath. The reaction was stirred 5 hours, and then cooled to room temperature. Aqueous 0.5 M HCl was added and repeated diethyl ether extractions were performed. The combined ether extracts were dried over $MgSO_4$. Column chromatography gave alkyne **634** as an oil (2.3 g, 95%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.7; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.25 (s, 9H), 3.05 (t, J = 8.0, 2H), 3.9 (t, J = 8.0 2H), 7.14-7.30 (m, 3H), 7.41-7.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.7, 132.5, 129.5, 128.5, 128.3, 126.2, 122.8, 103.6, 62.7, 38.1, 0.1; HR-FAB-MS: *m/z* calcd. for $C_{13}H_{19}O_1Si_1$: 219.1200, found: 219.1203 $[M+H]^+$.



635

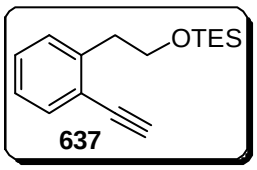
Compound 635: TMS alkyne **634** (1.2 g, 5.5 mmol) was dissolved in THF (14 mL) and water (2 mL) was added at room temperature. Solid LiOH (240 mg, 10mmol) was then added and after stirring 6 hours, the reaction was quenched with aqueous NH_4Cl and diethyl ether. Repeated ether extractions were performed and the combined ethereal extracts were dried over $MgSO_4$. Column chromatography gave alkyne **635** as an oil (620 mg, 77%). TLC (ethyl acetate/hexanes 2:3): R_f = 0.5; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.08 (t, J = 7.0 Hz, 2H), 3.26 (s, 1H), 3.90 (t, J = 7.0 Hz, 2H), 7.17-7.34 (m, 3H), 7.49-7.54 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.0, 133.1, 129.6, 128.9, 126.4, 121.9, 82.1, 81.0, 62.8, 37.8; ESI-MS: *m/z* calcd. for $C_{10}H_{10}O_1Na_1$: 169.06, found: 169.11 $[M+Na]^+$.



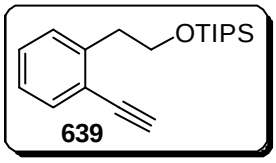
636

Compound 636: Alkyne **635** (21 mg, 0.14 mmol) was dissolved in THF (0.4 mL) and $Pd(PPh_3)_2Cl_2$ (2 mg, 0.003 mmol) was added at room temperature. $HSnBu_3$ (0.06 mL, 0.22 mmol) was added and the reaction was allowed to stir 15 minutes before being concentrated under reduced pressure. Stannane **636** was isolated as the major product after column chromatography (31 mg, 50%). TLC (ethyl acetate/hexanes 1:3): R_f= 0.7; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81-0.98 (m, 15H), 1.20-1.56 (m, 14H), 2.81 (t, J = 6.8 Hz, 2H), 3.76 (t, J = 6.8 Hz, 2H), 5.45-5.61 (including

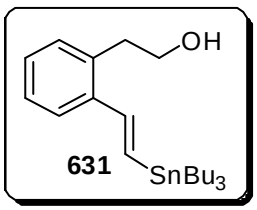
5.54 d, J = 3.0 Hz, 1H), 5.61-5.5.95 (including d, J = 3.0 Hz, 1H), 6.86-6.92 (m, 1H), 7.09-7.19 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7, 147.3, 129.4, 128.0, 127.0., 126.1, 125.5, 63.6, 36.8, 29.1, 29.0, 28.9, 27.4, 27.1, 13.8, 12.1, 12.0, 10.4, 8.9, 8.8; ESI-MS: *m/z* calcd. for $C_{22}H_{39}O_1Sn_1$: 439. 19, found: 438.85 $[M+H]^+$.



Compound 637: Alkyne **635** (38 mg, 0.26 mmol) was dissolved in methylene chloride (2 mL) and cooled to 0 °C. Pyridine (0.05 mL, 0.62 mmol), DMAP (2 mg, 0.02 mmol), and TESOTf (0.06 mL, 0.27 mmol), were added respectively. The reaction was stirred 5 minutes, and was then treated with aqueous $NaHCO_3$. Repeated ether extractions were performed and the combined extracts were dried over $MgSO_4$. Column chromatography gave silyl ether **637** as an oil (59 mg, 87%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.7; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.57 (q, J = 8.0 Hz, 6H), 0.93 (t, J = 8.0 Hz, 9H), 3.05 (t, J = 7.5 Hz, 2H), 3.23 (s, 1H), 3.83 (t, J = 7.5 Hz, 2H), 7.14-7.19 (m, 1H), 7.23-7.30 (m, 2H), 7.45-7.50 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.4, 132.8, 129.9, 128.7, 126.2, 121.8, 82.2, 80.5, 63.0, 38.2, 6.7, 4.3; HR-EI-MS: *m/z* calcd. for $C_{16}H_{24}O_1Si_1$: 260.1591, found: 260.1597 $[M]^+$.

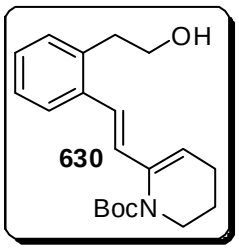


Compound 639: Alkyne **635** (44 mg, 0.30 mmol) was dissolved in methylene chloride (1 mL) and cooled to 0 °C. Lutidine (0.09 mL, 0.77 mmol), and TIPSOTf (0.1 mL, 0.37 mmol), were added respectively. The reaction was stirred 4 hours, and then diluted with hexanes and aqueous $NaHCO_3$. Repeated ether extractions were performed and the combined extracts dried over $MgSO_4$. Column chromatography gave silyl ether **639** as an oil (80 mg, 88%). TLC (ethyl acetate/hexanes 1:9): R_f = 0.7; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00-1.08 (m, 21H), 3.06 (t, J = 7.2 Hz, 2H), 3.22 (s, 1H), 3.91 (t, J = 7.2 Hz, 2H), 7.13-7.19 (m, 1H), 7.25-7.28 (m, 2H), 7.45-7.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.6, 132.8, 130.1, 128.6, 126.1, 121.8, 82.3, 80.5, 63.5, 38.2, 18.0, 11.9; HR-EI-MS: *m/z* calcd. for $C_{19}H_{30}O_1Si_1$: 302.2060, found: 302.2062 $[M]^+$.

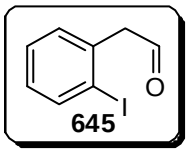


Compound 631: Procedure A: Stannane **631** was isolated as a minor product from the reaction conditions described for the synthesis of **636**. **Procedure B:** Aryl iodide **641** (44 mg, 0.18 mmol) was mixed with bis stannane **627** (155 mg, 0.26 mmol) and diluted with dioxane (1 mL). $Pd(PPh_3)_4$ (18 mg, 0.02 mmol) and LiCl (60 mg, 1.4 mmol) were added, and the reaction was heated at 80 °C. After 2.5 hours, the reaction was cooled to room temperature and filtered through celite. The filtrate was concentrated and subjected to column

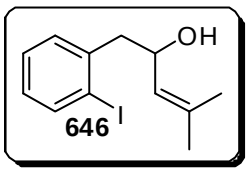
chromatography. Stannane **631** was obtained as an oil (41 mg, 53%). TLC (diethyl ether/hexane 1:9 then ethyl acetate/hexanes 1:3): R_f = 0.6; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88-1.01 (m, 14H), 1.29-1.40 (m, 7H), 1.47-1.65 (m, 6H), 3.0 (t, J = 6.5 Hz, 2H), 3.81-3.88 (m, 2H), 6.67-6.86 (incuding 6.76 d, J = 19.5 Hz, 1H), 7.14-7.27 (m, 4H), 7.50-7.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.,4 138.6, 134.7, 132.5, 130.2, 127.4, 126.8, 125.9, 63.1, 36.5, 29.3, 27.4, 13.9, 9.9; HR-EI-MS: *m/z* calcd. for $C_{22}H_{38}O_1Sn_1$: 438.1939, found: 438.1944 $[M]^+$.



Compound 630: Stannane **631** (31 mg, 0.08 mmol) was mixed with vinyl triflate **590** (45 mg, 0.14 mmol) under argon and diluted with dioxane (0.8 mL). $Pd(PPh_3)_4$ (9 mg, 0.008 mmol) and LiCl (45 mg, 1.07 mmol) were added, and the reaction was heated at 110 °C. After 3 hours, the reaction was cooled to room temperature and filtered through celite. The filtrate was concentrated and subjected to column chromatography. Stannane **630** was obtained as an oil (9 mg, 35%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.1; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 9H), 1.77-1.87 (m, 2H), 2.22-2.29 (m, 2H), 2.96 (t, J = 6.8 Hz, 2H), 3.57-3.63 (m, 2H), 3.81 (t, J = 6.8 Hz, 2H), 5.48 (app. t, J = 3.8 Hz, 1H), 6.49 (d, J = 16.0 Hz, 1H), 6.82 (d, J = 16.0 Hz, 1H), 7.16-7.24 (m, 3H), 7.46-7.50 (m, 1H); HR-EI-MS: *m/z* calcd. for $C_{20}H_{27}O_3N_1$: 329.1985, found: 329.1989 $[M]^+$.

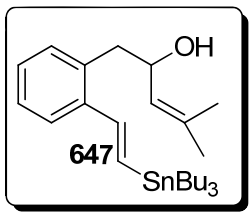


Compound 645: Alcohol **633** (4.85 g, 19.56 mmol) was dissolved in acetonitrile (60 mL) and IBX (16.0 g, 57.1 mmol) was added at room temperature. The mixture was stirred under reflux 1 hour and then cooled to room temperature. The mixture was then filtered through a large cotton plug, and the filtrate was concentrated. The filtrate was then purified through a silica plug. Aldehyde **645** was obtained as an oil (4.8g, 99%). TLC (ethyl acetate/hexanes 2:3): R_f = 0.6; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.89 (s, 2H), 7.01 (t, J = 7.5 Hz, 1H), 7.23 (d, J = 7.5 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.89 (d, J = 7.5 Hz, 1H), 9.78 (bs, 1H).

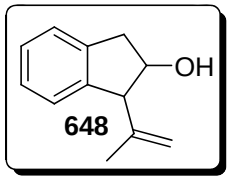


Compound 646: A THF (65 mL) solution of 2-methyl-1-propenyl magnesium bromide (32 mmol) was cooled to 0 °C. Aldehyde **645** (4.85 g, 19.5 mmol) was added in THF (10 mL) via cannula, over 40 minutes. The reaction was allowed to warm to room temperature over several hours. The reaction was then diluted with hexanes and aqueous NH_4Cl after stirring a total of 18 hours. Repeated diethyl ether extractions were performed and the combined extracts were dried over $MgSO_4$. Column chromatography gave allylic alcohol **646** as an oil (3.5 g, 59%). TLC

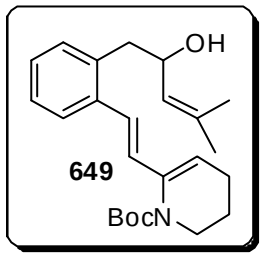
(ethyl acetate/hexanes 2:3): R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.55 (s, 3H), 1.71 (s, 3H), 2.86-2.99 (m, 2H), 4.64-4.72 (m, 1H), 5.27 (d, J = 8.8 Hz, 1H), 6.88-6.94 (m, 1H), 7.20-7.30 (m, 2H), 7.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.9, 139.5, 135.6, 131.3, 128.2, 128.0, 126.6, 101.1, 68.2, 48.3, 25.7, 18.3; HR-EI-MS: *m/z* calcd. for $C_{12}H_{15}O_1I_1$: 302.0162, found: 302.0159 $[M]^+$.



Compound 647: Aryl iodide **646** (70 mg, 0.23 mmol) was mixed with bis stannane **627** (0.195 mL, 0.37 mmol) and diluted with dioxane (0.1 mL). $Pd(PPh_3)_4$ (25mg, 0.022 mmol) and LiCl (87 mg, 2.07 mmol) were added, and the reaction was heated at 90 °C. After 5 hours, the reaction was cooled to room temperature, diluted with methylene chloride and filtered through celite. The filtrate was diluted with hexanes and washed with aqueous 0.5 M LiOH, then concentrated and subjected to column chromatography. Stannane **647** was obtained as an oil (36 mg, 32%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.7; ^{1}H NMR (400 MHz, C_6D_6): δ 0.92 (app. t, J = 7.2 Hz, 7H), 0.99-1.09 (m, 4H), 1.31 (s, 3H), 1.32-1.43 (m, 5H), 1.56-1.69 (m, 8H), 2.84 (dd, J = 5.6, 13.6 Hz, 1H), 3.00 (dd, J = 6.8, 13.6 Hz, 1H), 4.49-4.55 (m, 1H), 5.19-5.24 (d, 1H), 6.81-6.89 (m, 1H), 6.98-7.09 (m, 3H), 7.43-7.59 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6): δ 145.3, 139.3, 135.7, 133.9, 131.6, 131.2, 128.5, 127.6, 127.0, 126.2, 69.5, 41.7, 29.6, 27.7, 25.7, 18.1, 14.0, 9.9; HR-EI-MS: *m/z* calcd. for $C_{26}H_{43}O_1Sn_1$: 491.2330, found: 491.2318 $[M-H]^+$.

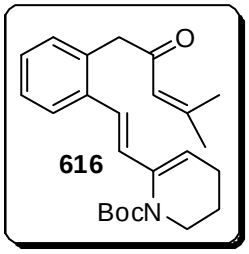


Compound 648: Alcohol **648** was isolated in varied yields from the reactions described to produce stannane **647** and diene **649**. TLC (ethyl acetate/hexanes 1:3): R_f = 0.3; ^{1}H NMR (400 MHz, C_6D_6): δ 1.51 (bs, 3H), 2.63 (dd, 6.0, 16.0 Hz, 1H), 2.96 (dd, J = 6.8, 16.0 Hz, 1H), 3.53 (d, J = 6.2 Hz, 1H), 4.15 (app. q, J = 6.4 Hz, 1H), 4.77-4.79 (m, 1H), 4.83-4.86 (m, 1H), 6.96-7.05 (m, 4H); EI-MS: *m/z* calcd. for $C_{12}H_{14}O_1$: 174.10, found: 174.10 $[M]^+$.

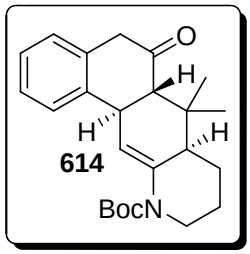


Compound 649: Procedure A: Stannane **647** (35 mg, 0.07 mmol) was mixed with vinyl triflate **590** (59 mg, 0.18 mmol) and diluted with dioxane (0.1 mL). $Pd(PPh_3)_4$ (8mg, 0.007 mmol) and LiCl (25 mg, 0.6 mmol) were added, and the reaction was heated at 105 °C. After 5.5 hours, the reaction was cooled to room temperature, diluted with diethyl ether, and filtered through celite. The filtrate was concentrated and subjected to column chromatography. Triene **649** was obtained as an oil (5-6 mg, 20%). **Procedure B:** Aryl iodide **646** (77 mg, 0.26 mmol) was mixed with stannane **619** (257 mg, 0.52

mmol), and $Pd(PPh_3)_4$ (25 mg, 0.022 mmol), then LiCl (105 mg, 2.5 mmol) were added. The reaction was heated at 95 °C for 10.5 hours. After cooling to room temperature, the reaction was diluted with diethyl ether, and filtered through celite. The filtrate was concentrated and subjected to column chromatography. Triene **649** was obtained as an oil (55 mg, 56%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.3; ^{1}H NMR (400 MHz, C_6D_6): δ 1.35 (bs, 12H), 1.38-1.46 (m, 2H), 1.51 (s, 3H), 1.75-1.82 (m, 2H), 2.86 (dd, J = 5.2, 13.6 Hz, 1H), 3.00 (dd, J = 7.2, 13.6 Hz, 1H), 3.32-3.41 (m, 1H), 3.55-3.66 (m, 1H), 4.54-4.63 (m, 1H), 5.21-5.28 (m, 2H), 6.60 (d, J = 16.0 Hz, 1H), 6.98-7.17 (m, 4H), 7.48-7.52 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6): δ 154.2, 140.0, 137.5, 136.6, 133.6, 131.7, 13.0, 128.7, 127.31, 127.26, 127.0, 126.0, 124.6, 115.2, 80.1, 69.6, 44.7, 42.2, 28.3, 25.7, 23.7, 23.6, 18.1.

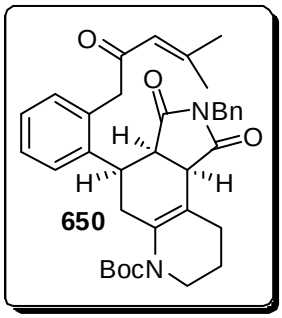


Compound 616: Allylic alcohol **649** (9 mg, 0.02 mmol) was dissolved in methylene chloride (0.6 mL) and DMSO (0.4 mL) at room temperature. IBX (15 mg, 0.05 mmol) was added and the solution stirred. The reaction was monitored by TLC, and when the starting material had been consumed, hexanes were added, followed by water. Repeated diethyl ether extractions were performed and the extracts were combined. The extracts were dried over $MgSO_4$ and subjected to column chromatography. Dienone **616** was obtained as an oil (5 mg, 60%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.5; ^{1}H NMR (400 MHz, C_6D_6): δ 1.32 (s, 3H), 1.35-1.43 (m, 11H), 1.70-1.77 (m, 2H), 2.02 (s, 3H), 3.48-3.53 (m, 2H), 3.62 (s, 3H), 5.29 (app. t, J = 4.0 Hz, 1H), 5.88 (bs, 1H), 6.63 (d, J = 16.0 Hz, 1H), 6.96-7.07 (m, 4H), 7.50-7.54 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6 [atoms obscured by C_6H_6]): δ 196.5, 155.4, 154.1, 139.6, 137.8, 133.6, 131.4, 131.0, 127.5, 126.1, 123.9, 123.3, 114.9, 80.0, 49.6, 44.5, 28.3, 27.2, 23.7, 23.5, 20.7; HR-EI-MS: *m/z* calcd. for $C_{24}H_{31}O_3N_1$: 381.2298, found: 381.2302 $[M]^+$.

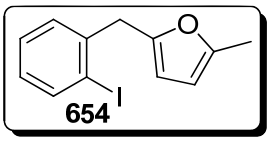


Compound 614: Triene **616** (12 mg, 0.03 mmol) was dissolved in *0*-xylene-d8 (0.7 mL) and transferred to a NMR tube. The tube was sealed and heated to 205 °C. After 12 hours, the reaction was cooled to room temperature, concentrated, and purified on a neutral alumina column. Tetracycle **614** was obtained as an oil (2-3 mg, 20%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.5 (slightly higher than **616**); ^{1}H NMR (400 MHz, C_6D_6): δ 0.87 (s, 3H), 1.32 (s, 3H), 1.46 (s, 9H), 1.60-1.66 (m, 2H), 1.71-1.77 (m, 2H), 2.78-2.90 (m, 1H), 2.97-3.06 (m, 1H), 3.07-3.16 (m, 1H), 3.30 (bs, 2H), 3.67-3.78 (m, 1H), 4.21-4.22 (m, 1H), 6.77 (d, J = 7.6 Hz, 1H), 6.98 (t, J = 7.2 Hz, 1H), 7.07 (t, J = 7.2 Hz, 1H), 7.19 (d, J = 8Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6 [incomplete, signals obscured by C_6H_6]): δ 209.2, 153.8, 140.0, 133.3, 127.3, 127.0, 124.3, 79.6, 56.1, 49.0, 44.7, 39.4, 35.4, 33.7, 30.1,

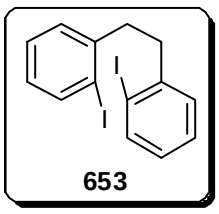
28.4, 26.5, 24.4, 21.7, 21.6; HR-ESI-TOF-MS: *m/z* calcd. for $C_{24}H_{32}O_3N_1Na_1$: 404.2195, found: 404.2196 $[M+Na]^+$.



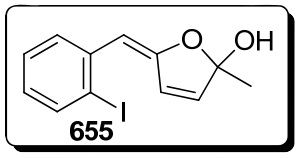
Compound 50: Triene **616** (2 mg, 0.005 mmol) was mixed with N-benzylmaleimide (2 mg, 0.01 mmol), dissolved in C_6D_6 (0.7 mL), and transferred to a NMR tube. The mixture was heated at 90 °C 14 hours. The reaction was then diluted with diethyl ether and filtered. The filtrate was concentrated and subjected to silica chromatography. Cycloadduct **650** was isolated as an oil, which formed an amorphous solid upon standing (3 mg, 95%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.2; ^{1}H NMR (400 MHz, C_6D_6): δ 1.30 (m, ~ 14H), 1.61-1.74 (m, 1H), 1.99 (s, 3H), 2.53-2.60 (m, 1H), 2.76-2.96 (m, 3-4H), 3.06-3.17 (m, 1H), 3.31-3.38 (m, 1H), 3.48 (d, J = 15.2 Hz, 1H), 3.62 (d, J = 15.2 Hz, 1H), 3.79-3.87 (m, 1H), 4.28 (bs, 2H), 5.92 (bs, 1H), 6.9-7.10 (m, 6H), 7.26 (d, J = 7.6 Hz, 2H), 7.59 (d, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6 [atoms obscured by C_6H_6]): δ 197.3, 175.6, 175.3, 156.2, 153.6, 140.3, 136.8, 133.6, 130.9, 129.7, 123.1, 114.6, 80.1, 49.8, 46.8, 44.2, 43.9, 41.8, 37.4, 33.3, 28.3, 27.2, 26.5, 23.6, 20.6; HR-FAB-MS: *m/z* calcd. for $C_{35}H_{41}O_5N_2$: 569.3010, found: 569.3005 $[M+H]^+$.



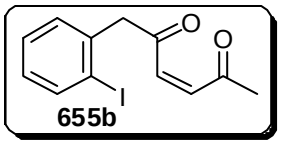
Compound 654: Methyl furan **651** (0.7 mL, 7.76 mmol) was dissolved in THF (8 mL) and cooled to -78 °C. *n*-BuLi (2.5 mL, 7 mmol) was added as a 2.8 M hexane solution and the mixture was then stirred at 0 °C for 2 hours. Iodobenzylbromide (2 g, 6.7 mmol) was added in THF (5 mL) via cannula over 15 minutes. The reaction was stirred an additional 3 hours, then diluted with hexanes and quenched with water. Repeated hexane extractions were performed, and the combined extracts were dried over $MgSO_4$. Column chromatography gave furan **654** as an oil (1.36 g, 68%). TLC (ethyl acetate/hexanes 1:9): R_f = 0.6; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.26 (s, 3H), 4.02 (s, 2H), 5.86-5.90 (m, 2H), 6.89-6.95 (m, 1H), 7.16-7.20 (m, 1H), 7.26-7.31 (m, 1H), 7.81-7.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.2, 151.0, 141.1, 139.4, 129.8, 128.3, 128.2, 107.9, 106.1, 100.6, 39.7, 13.6; APCI-MS: *m/z* calcd. for $C_{12}H_{12}O_1I$: 298.99, found: 298.92 $[M+H]^+$.



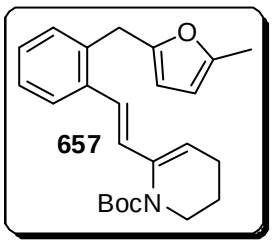
Compound 653: Aryl iodide **653** was isolated as a minor product of the reaction conditions used for the synthesis of **654**. TLC (ethyl acetate/hexanes 1:9): R_f = 0.6 (directly above **654**); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.98-3.01 (bs, 4H), 6.88-6.95 (m, 2H), 7.20-7.31 (m, 4H), 7.82-7.86 (m, 2H).



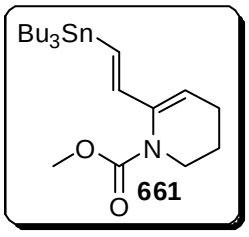
Compound 655: Furan **654** (100 mg, 0.34 mmol) was dissolved in methylene chloride (3 mL) and cooled to 0 °C. mCPBA (65 mg, 0.38 mmol) was added, and the reaction mixture was stirred 2 hours. Water was then added to the mixture, followed by aqueous $Na_2S_2O_3$. Repeated diethyl ether extractions were performed, and the combined organic extracts were then dried over $MgSO_4$ and Na_2CO_3. Column chromatography gave aryl iodide **655** as an oil (53 mg, 50%). TLC (ethyl acetate/hexanes 2:3): R_f = 0.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (s, 3H), 4.27 (bs, 1H), 6.30 (d, J = 5.8 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.97 (t, J = 8.0 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.52 (d, J = 6.0 Hz, 1H), 7.90 (d, 8.0 Hz, 1H; ESI-MS: *m/z* calcd. for $C_{12}H_{12}O_2I$: 314.98, found: 314.93 $[M+H]^+$.



Compound 655b: A compound isolated from the reaction conditions described for the synthesis of **655** has been tentatively identified as **655b**. ^{1}H NMR (400 MHz, **C_6D_6**): δ 1.75 (s, 3H), 3.65 (s, 2H), 5.42 (d, 1H), 5.65 (d, 1H), 6.41 (m, 1H), 6.81 (m, 1H), 6.98 (m, 1H), 7.55 (m, 1H).

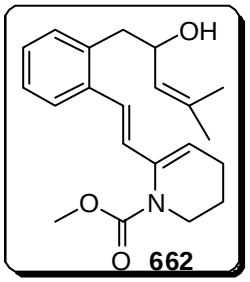


Compound 657: Furan **654** (29 mg, 0.010 mmol) and stannane **661** (100 mg, 0.22 mmol) were mixed under argon. $Pd(PPh_3)_4$ (13 mg, 0.011 mmol) and LiCl (50 mg, 1.2 mmol) were added, and the mixture was heated at 90 °C 10 hours. After the reaction cooled to room temperature, hexanes and and diethyl ether were added. The mixture was filtered through a cotton plug and concentrated. Chromatography through an alumina column gave diene **657** as an oil (20 mg, 62%). TLC (ethyl acetate/hexanes 1:9): R_f = 0.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1 ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 1.

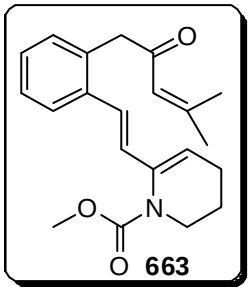


Compound 661: Bis stannane **627** (2.9 mL, 5.5 mmol) and vinyl triflate **660** (1.6 g, 5.5 mmol) were mixed under argon and diluted with dioxane (15 mL). $Pd(PPh_3)_4$ (640 mg, 0.55 mmol) was added at room temperature followed by LiCl (2.4 g, 57.14 mmol) and the reaction flask was transferred to a 100 °C oil bath. After stirring 2 hours, the reaction was cooled to room temperature and diluted with hexanes. The solution was filtered through celite and the filtrate was concentrated for chromatography through neutralized silica. Stannane **661** was obtained as an oil (1.15 g, 46%). TLC (ethyl acetate/hexanes 1:9): R_f = 0.4; ^{1}H NMR (400 MHz, C_6D_6): δ 0.89 (t, J = 7.2 Hz, 9H), 0.93-1.04 (m, 4H), 1.29-1.40 (m,

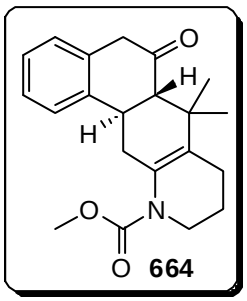
8H), 1.49-1.69 (m, 5H), 1.69-1.75 (m, 2H), 3.42-3.48 (m, 2H), 3.48 (s, 3H), 5.19 (app. t, J = 4Hz, 1H), 6.34-6.72 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6): δ 155.4, 145.0, 140.8, 125.0, 114.7, 52.2, 44.9, 29.7, 29.5, 29.4, 28.0, 27.7, 27.4, 23.5, 23.4, 13.9, 9.8.



Compound 662: Aryl iodide **646** (78 mg, 0.26 mmol) and stannane **661** (251 mg, 0.55 mmol) were mixed under argon. $Pd(PPh_3)_4$ (30 mg, 0.025 mmol) was added at room temperature followed by LiCl (98 mg, 2.33 mmol), and the reaction flask was transferred to a 100 °C oil bath. After stirring 4.5 hours, the reaction was cooled to room temperature and diluted with hexanes and diethyl ether. The solution was filtered through celite and the filtrate concentrated for chromatography through neutralized silica. Allylic alcohol **662** was obtained as an oil (44 mg, 50%). TLC (ethyl acetate/hexanes 3:2): R_f = 0.6; ^{1}H NMR (400 MHz, C_6D_6): δ 1.31 (s, 3H), 1.33-1.40 (m, 2H), 1.50 (s, 3H), 1.70-1.78 (m, 2H), 2.80 (dd, J = 6.0, 13.6 Hz, 1H), 3.01 (dd, J = 6.8, 13.6 Hz, 1H), 3.24-3.36 (m, 1H), 3.44 (s, 3H), 3.52-3.61 (m, 1H), 4.54-4.63 (m, 1H), 5.21-5.28 (m, 1H), 6.58 (d, J = 16.0 Hz, 1H), 6.98-7.12 (m, 4H), 7.46-7.50 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6): δ 155.5, 139.6, 137.5, 136.8, 133.6, 131.6, 129.3, 128.7, 127.3, 126.9, 126.3, 125.2, 116.1, 69.6, 52.5, 45.0, 42.4, 25.7, 23.5, 23.4, 18.0.

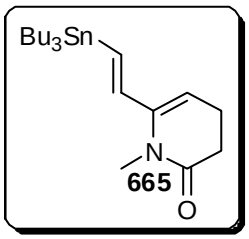


Compound 663: Allylic alcohol **662** (15 mg, 0.04 mmol) was dissolved in methylene chloride (0.5 mL) and DMSO (0.5 mL) at room temperature. IBX (30 mg, 0.11 mmol) was added and the solution was stirred at room temperature. The reaction was monitored by TLC, and when the starting material had been consumed, hexanes were added, followed by water. Repeated diethyl ether extractions were performed and the extracts combined. The extracts were dried over $MgSO_4$ and subjected to column chromatography. Triene **663** was obtained as an oil (9 mg, 60%). TLC (ethyl acetate/hexanes 2:3): R_f = 0.9; ^{1}H NMR (400 MHz, C_6D_6): δ 1.27-1.38 (m, 5H), 1.67-1.76 (m, 2H), 2.02 (s, 3H), 3.39-3.46 (m, 2H), 3.46 (s, 3H), 3.60 (s, 2H), 5.26-5.34 (m, 1H), 5.88 (bs, 1H), 6.63 (d, J = 16.0 Hz, 1H), 6.98-7.10 (m, 4H), 7.48-7.54 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6): δ 196.5, 155.3, 139.3, 137.8, 133.6, 131.3, 129.9, 127.5, 127.4, 126.3, 124.4, 123.1, 52.3, 49.7, 44.8, 27.1, 23.5, 23.2, 20.6.

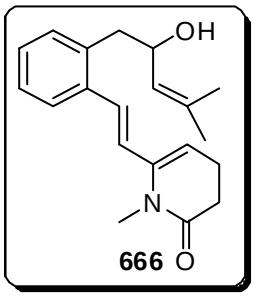


Compound 664: Triene **663** (8 mg, 0.02 mmol) was dissolved in bromobenze-d5 (0.7 mL) and transferred to a NMR tube. The tube was sealed and heated to 200 °C. After 11 hours, the reaction was cooled to room temperature, concentrated, and purified on a

neutral alumina column. Tetracycle **664** was obtained as an oil (5 mg, 65%). TLC (ethyl acetate/hexanes 1:3): $R_f = 0.5$; ^{1}H NMR (400 MHz, C_6D_6): δ 0.86 (s, 3H), 1.22-1.31 (m, 2H), 1.33 (s, 3H), 1.37-1.50 (m, 2H), 1.57-1.63 (m, 2H), 1.69 (d, J = 12.0 Hz, 1H), 2.76-2.85 (m, 2H), 2.93-3.03 (m, 1H), 3.08-3.16 (m, 1H), 3.26-3.30 (m, 2H), 3.50 (s, 3H), 3.53-3.64 (m, 1H), 6.76 (d, J = 7.2 Hz, 1H), 6.98 (t, J = 7.2 Hz, 1H), 7.06 (t, J = 7.2 Hz, 1H), 7.13-7.15 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6 [1 carbon obscured by C_6H_6]): δ 209.3, 155.1, 139.9, 133.3, 130.9, 127.6, 127.3, 127.1, 124.6, 56.0, 52.2, 49.0, 44.8, 39.4, 35.3, 33.1, 26.6, 24.3, 21.7, 21.6; HR-ESI-TOF-MS: *m/z* calcd. for $C_{21}H_{26}O_3N_1$: 340.1907, found: 340.1898# $[M+H]^+$.

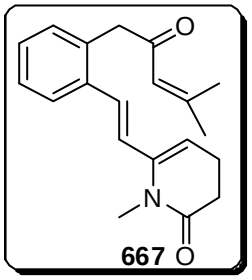


Compound 665: N-methyl glutarimide **603** (1.3 g, 10.24 mmol) was dissolved in THF (8 mL) and cooled to 0 °C. LiHMDS (10.2 mL, 10.2 mmol) was added as a 1 M THF solution over 4 minutes. The solution was removed from the ice bath and stirred at room temperature 30 minutes before cooling to -78 °C. Diethylchlorophosphate (1.77 g, 10.2 mmol) was added as a THF solution (5 mL) via cannula over 8 minutes. After stirring 15 minutes, the mixture was transferred to a 0 °C ice bath and stirred 50 minutes. The ice bath was removed and the reaction was stirred 30 minutes at room temperature. Bis stannane **627** (7.2 g, 11.9 mmol) was added followed quickly by $Pd(PPh_3)_4$ (400 mg, 0.35 mmol) and LiCl (4.1 g, 98 mmol). The reaction mixture was then heated at reflux 4 hours. The mixture was then diluted with hexanes and decanted to remove solids. The solids were stirred with diethyl ether and decanted again. The combined organics were subjected to column chromatography on neutralized silica. Stannane **665** was obtained as an oil (655 mg, 15%). TLC (ethyl acetate/hexanes 1:3): $R_f = 0.5$; ^{1}H NMR (400 MHz, C_6D_6): δ 0.82-1.01 (m, 15H), 1.23-1.62 (m, 13H), 1.71-1.78 (m, 2H), 2.23 (app. t, J = 7.2 Hz, 2H), 3.01 (s, 3H), 5.07 (app. t, J = 5.2 Hz, 1H), 6.20-6.60 (including: [6.30, d, J = 19.2 Hz, 1H] and [6.49, d, J = 19.2 Hz, 1H]); ^{13}C NMR (100 MHz, C_6D_6): δ 169.8, 143.5, 141.5, 132.2, 105.4, 31.6, 30.3, 29.4, 27.5, 19.6, 13.8, 9.7.



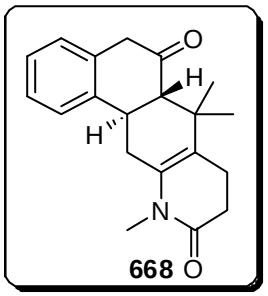
Compound 666: Aryl iodide **646** (305 mg, 1.0 mmol) and stannane **665** (515 mg, 1.21 mmol) were mixed under argon. $Pd(PPh_3)_4$ (50 mg, 0.0.04 mmol) was added at room temperature followed by LiCl (500 mg, 11.9 mmol), and the reaction flask was transferred to a 95 °C oil bath. After stirring 2.5 hours, the reaction was diluted with methylene chloride while still warm, and then diluted with hexanes and filtered through neutralized silica. Fractions of interest were combined for chromatographic purification. Allylic alcohol **666** was obtained as an oil after column chromatography (176 mg, 55%). TLC (ethyl acetate/hexanes 2:3): $R_f = 0.1$; ^{1}H NMR (400 MHz, C_6D_6): δ 1.23 (s, 3H), 1.46 (s, 3H), 1.70-1.80 (m, 2H), 2.25 (app. t, J =

7.6 Hz, 2H), 2.73 (dd, J = 6.0, 13.6 Hz, 1H), 2.91 (dd, J = 7.6, 13.6 Hz, 1H), 2.96 (s, 3H), 4.38-4.47 (m, 1H), 5.11-5.17 (m, 2H), 6.18 (d, J = 16.0 Hz, 1H), 7.01-7.14 (m, 3H), 7.28-7.32 (m, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 171.1, 141.6, 136.9, 136.2, 134.8, 131.6, 129.5, 128.0, 127.7, 126.9, 126.0, 124.6, 106.6, 69.5, 41.6, 31.6, 30.8, 25.7, 19.9, 18.0.



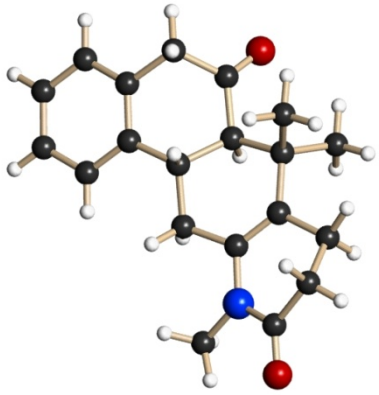
667

Compound 667: Allylic alcohol **666** (105 mg, 0.34 mmol) was dissolved in EtOAc (10 mL) and IBX (420 mg, 1.5 mmol) was added at room temperature. The reaction mixture was heated to reflux and stirred 2.5 hours. After cooling to room temperature, the reaction mixture was rapidly filtered through florisil. Triene **667** was obtained as an oil (93 mg, 89%). TLC (ethyl acetate/hexanes 3:2): R_f = 0.4; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 1.88 (s, 3H), 2.13 (s, 3H), 2.26-2.35 (m, 2H), 2.48 (app. t, J = 7.6 Hz, 2H), 3.12 (s, 3H), 3.82 (s, 2H), 5.54 (app. t, J = 4.8 Hz, 1H), 6.15 (bs, 1H), 6.51 (d, J = 15.6 Hz, 1H), 7.14-7.33 (m, 3H), 7.52-7.57 (m, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 197.3, 171.1, 157.0, 141.5, 136.6, 133.8, 131.4, 129.0, 128.3, 127.6, 126.2, 125.3, 123.0, 107.0, 49.4, 30.8, 30.3, 27.8, 20.8, 19.9.



668

Compound 668: Triene **667** (5.5 mg, 0.18 mmol) was dissolved in 1,2-dichlorobenzene (1 mL) and heated at 195 °C 10 hours. The reaction mixture was cooled to room temperature and diluted with EtOAc. The EtOAc solution was washed with water and dried over $MgSO_4$. The extracts were concentrated and rapidly passed through a neutralized silica column. The fractions of interest were concentrated and cycloadduct **668** was obtained as a solid via trituration with a hexanes/diethyl ether solution (4 mg, 72%). TLC (ethyl acetate/hexanes 3:2): R_f = 0.3; ^{1}H NMR (500 MHz, CD_2Cl_2): δ 1.14 (s, 3H), 1.29 (s, 3H), 1.89 (d, J = 11.5 Hz, 1H), 2.14-2.23 (m, 2H), 2.30 (ddd, J = 7.5, 13.7, 22 Hz, 1H), 2.46 (app. dt, J = 4.0, 15.5 Hz, 1H), 2.50-2.57 (m, 1H), 2.81-2.87 (m, 1H), 3.14 (s, 3H), 3.39 (ddd, J = 5.0, 11.5, 16.5 Hz, 1H), 3.47 (d, 14.3 Hz, 1H), 3.73 (d, J = 14.9 Hz, 1H), 7.14 (d, J = 7.4 Hz, 1H), 7.21-7.25 (m, 1H), 7.28-7.31 (m, 2H); ^{13}C NMR (125 MHz, CD_2Cl_2 [1 alkene C signal missing, a C_6D_6 sample revealed a peak (100.4 ppm) absent in the CD_2Cl_2 sample]): δ 210.1, 170.1, 139.1, 133.2, 130.6, 127.6, 127.3, 123.0, 122.9, 55.6, 49.1, 39.1, 35.0, 32.0, 29.0, 29.8, 24.9, 22.0, 20.3; HR-ESI-TOF-MS: *m/z* calcd. for $C_{20}H_{24}O_2N_1$: 310.1801, found: 310.1800 $[M+H]^+$. A crystal suitable for single crystal x-ray analysis was grown:



Crystal data and structure refinement for theod30.

Identification code	theod30	
Empirical formula	C20 H23 N O2	
Formula weight	309.39	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 12.1707(11) Å	α= 90°
	b = 8.9538(8) Å	β= 90°
	c = 28.545(3) Å	γ = 90°
Volume	3110.7(5) $Å^3$	
Z	8	
Density (calculated)	1.321 g/cm^3	
Absorption coefficient	0.085 mm^{-1}	
F(000)	1328	
Crystal size	0.24 x 0.14 x 0.08 mm^3	

Theta range for data collection	1.43 to 25.35°
Index ranges	-14<=h<=13, -10<=k<=8, -34<=l<=29
Reflections collected	15463
Independent reflections	2848 [R(int) = 0.0598]
Completeness to theta = 25.00°	100.0 %
Absorption correction	Multi-scan
Max. and min. transmission	0.9933 and 0.9800
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2848 / 0 / 208
Goodness-of-fit on F^2	1.026
Final R indices [I>2sigma(I)]	R1 = 0.0530, wR2 = 0.1240
R indices (all data)	R1 = 0.0788, wR2 = 0.1395
Largest diff. peak and hole	0.479 and -0.413 e $Å^{-3}$

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)for theod30. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	-954(1)	167(2)	7496(1)	29(1)
O(2)	2276(1)	1824(2)	4881(1)	29(1)
N(1)	819(2)	1559(2)	5373(1)	21(1)
C(1)	1882(2)	1293(3)	5240(1)	22(1)
C(2)	2510(2)	278(3)	5564(1)	26(1)
C(3)	2254(2)	626(3)	6073(1)	25(1)
C(4)	1029(2)	571(3)	6152(1)	19(1)
C(5)	620(2)	120(3)	6636(1)	19(1)
C(6)	-645(2)	379(3)	6666(1)	17(1)
C(7)	-1162(2)	-291(3)	7104(1)	20(1)

C(8)	-2016(2)	-1483(3)	7020(1)	21(1)
C(9)	-2855(2)	-811(2)	6693(1)	18(1)
C(10)	-3970(2)	-792(3)	6800(1)	19(1)
C(11)	-4716(2)	-156(3)	6492(1)	21(1)
C(12)	-4344(2)	472(3)	6081(1)	21(1)
C(13)	-3222(2)	513(3)	5977(1)	20(1)
C(14)	-2469(2)	-122(2)	6286(1)	17(1)
C(15)	-1237(2)	-111(3)	6213(1)	17(1)
C(16)	-865(2)	906(3)	5818(1)	19(1)
C(17)	373(2)	991(3)	5802(1)	19(1)
C(18)	158(2)	2512(3)	5063(1)	26(1)
C(19)	1196(2)	1115(3)	7002(1)	22(1)
C(20)	899(2)	-1523(3)	6740(1)	22(1)

Bond lengths [Å] and angles [°] for theod30.

O(1)-C(7)	1.217(3)	C(6)-C(7)	1.524(3)
O(2)-C(1)	1.228(3)	C(6)-C(15)	1.543(3)
N(1)-C(1)	1.369(3)	C(7)-C(8)	1.509(3)
N(1)-C(17)	1.434(3)	C(8)-C(9)	1.509(3)
N(1)-C(18)	1.468(3)	C(9)-C(10)	1.391(3)
C(1)-C(2)	1.504(4)	C(9)-C(14)	1.399(3)
C(2)-C(3)	1.519(4)	C(10)-C(11)	1.386(3)
C(3)-C(4)	1.509(3)	C(11)-C(12)	1.378(3)
C(4)-C(17)	1.333(3)	C(12)-C(13)	1.397(3)
C(4)-C(5)	1.524(3)	C(13)-C(14)	1.392(3)
C(5)-C(20)	1.539(3)	C(14)-C(15)	1.513(3)
C(5)-C(19)	1.542(3)	C(15)-C(16)	1.519(3)
C(5)-C(6)	1.559(3)	C(16)-C(17)	1.508(3)

C(1)-N(1)-C(17)	122.2(2)	O(1)-C(7)-C(6)	122.4(2)
C(1)-N(1)-C(18)	116.9(2)	C(8)-C(7)-C(6)	115.7(2)
C(17)-N(1)-C(18)	120.84(19)	C(9)-C(8)-C(7)	106.40(19)
O(2)-C(1)-N(1)	122.1(2)	C(10)-C(9)-C(14)	120.3(2)
O(2)-C(1)-C(2)	123.3(2)	C(10)-C(9)-C(8)	122.0(2)
N(1)-C(1)-C(2)	114.6(2)	C(14)-C(9)-C(8)	117.6(2)
C(1)-C(2)-C(3)	111.1(2)	C(11)-C(10)-C(9)	120.4(2)
C(4)-C(3)-C(2)	109.8(2)	C(12)-C(11)-C(10)	119.5(2)
C(17)-C(4)-C(3)	118.1(2)	C(11)-C(12)-C(13)	120.8(2)
C(17)-C(4)-C(5)	124.0(2)	C(14)-C(13)-C(12)	120.0(2)
C(3)-C(4)-C(5)	117.8(2)	C(13)-C(14)-C(9)	119.0(2)
C(4)-C(5)-C(20)	110.9(2)	C(13)-C(14)-C(15)	124.3(2)
C(4)-C(5)-C(19)	108.23(19)	C(9)-C(14)-C(15)	116.7(2)
C(20)-C(5)-C(19)	108.74(19)	C(14)-C(15)-C(16)	113.62(19)
C(4)-C(5)-C(6)	109.35(19)	C(14)-C(15)-C(6)	110.49(19)
C(20)-C(5)-C(6)	110.50(19)	C(16)-C(15)-C(6)	108.15(19)
C(19)-C(5)-C(6)	109.11(19)	C(17)-C(16)-C(15)	110.5(2)
C(7)-C(6)-C(15)	112.50(19)	C(4)-C(17)-N(1)	120.9(2)
C(7)-C(6)-C(5)	113.1(2)	C(4)-C(17)-C(16)	124.1(2)
C(15)-C(6)-C(5)	112.00(19)	N(1)-C(17)-C(16)	115.0(2)
O(1)-C(7)-C(8)	121.8(2)		

Anisotropic displacement parameters ($Å^2 x\ 10^3$) for theod30. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}

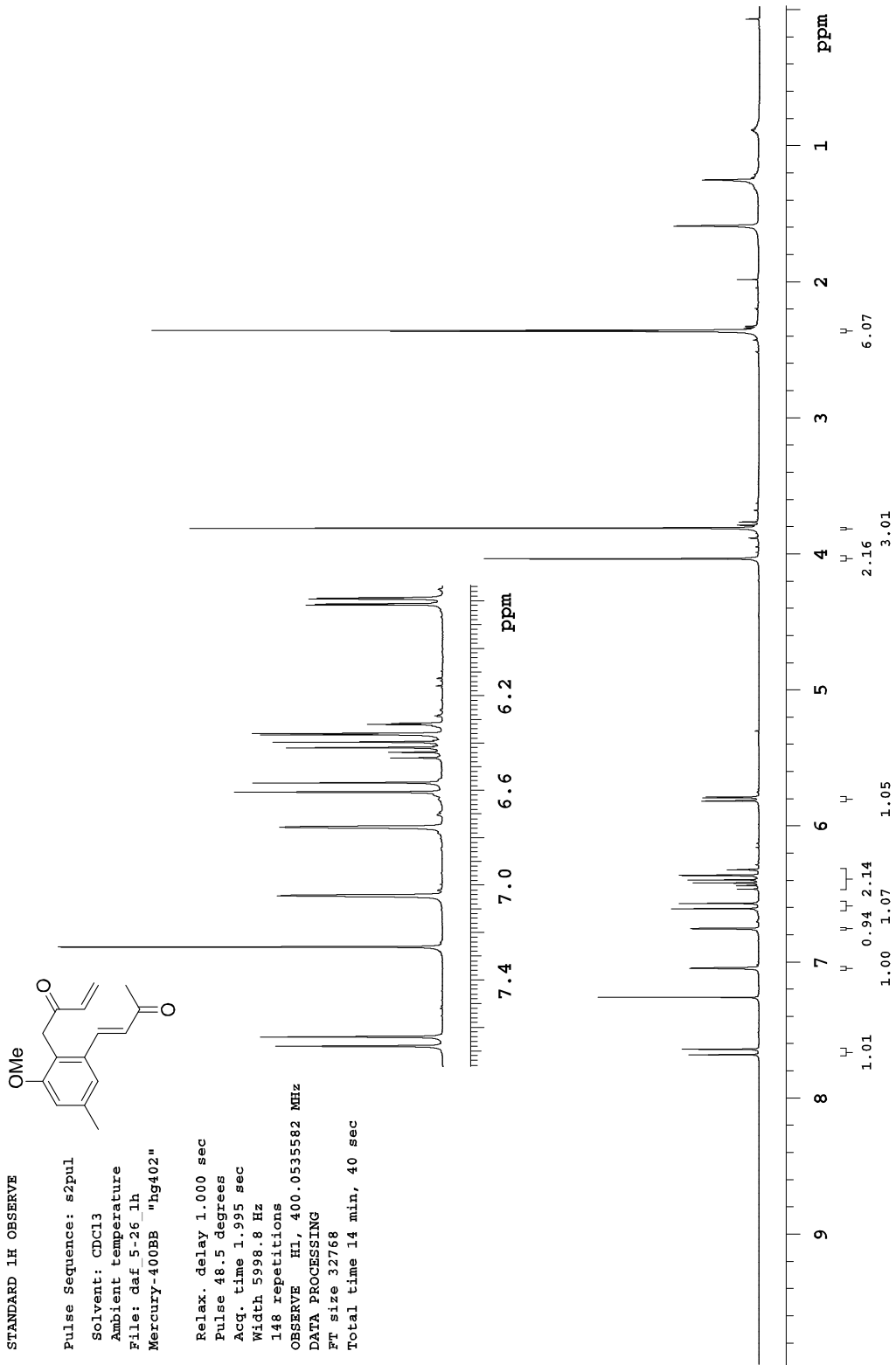
O(1)	28(1)	40(1)	18(1)	-3(1)	-2(1)	0(1)
O(2)	27(1)	34(1)	26(1)	-2(1)	7(1)	-5(1)
N(1)	20(1)	25(1)	19(1)	3(1)	1(1)	-1(1)
C(1)	20(1)	25(1)	21(1)	-6(1)	3(1)	-6(1)
C(2)	17(1)	33(2)	28(2)	-2(1)	2(1)	-2(1)
C(3)	20(1)	30(1)	25(2)	0(1)	-1(1)	-2(1)
C(4)	15(1)	19(1)	22(1)	-4(1)	0(1)	-1(1)
C(5)	17(1)	21(1)	19(1)	-2(1)	-3(1)	-1(1)
C(6)	18(1)	16(1)	17(1)	-2(1)	-3(1)	0(1)
C(7)	17(1)	23(1)	20(2)	-1(1)	-2(1)	8(1)
C(8)	23(1)	23(1)	18(1)	2(1)	2(1)	0(1)
C(9)	20(1)	14(1)	19(1)	-1(1)	0(1)	0(1)
C(10)	23(1)	16(1)	18(1)	-2(1)	2(1)	0(1)
C(11)	17(1)	20(1)	26(2)	-3(1)	3(1)	-1(1)
C(12)	21(1)	23(1)	20(1)	0(1)	-4(1)	3(1)
C(13)	21(1)	22(1)	17(1)	-1(1)	0(1)	-1(1)
C(14)	18(1)	17(1)	16(1)	-4(1)	0(1)	0(1)
C(15)	16(1)	17(1)	19(1)	-1(1)	0(1)	1(1)
C(16)	17(1)	23(1)	18(1)	-1(1)	-3(1)	-1(1)
C(17)	19(1)	19(1)	20(1)	-1(1)	1(1)	-1(1)
C(18)	27(1)	30(1)	22(2)	8(1)	2(1)	0(1)
C(19)	19(1)	24(1)	23(1)	-3(1)	-3(1)	0(1)
C(20)	20(1)	22(1)	25(2)	-1(1)	-3(1)	3(1)

Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for theod30.

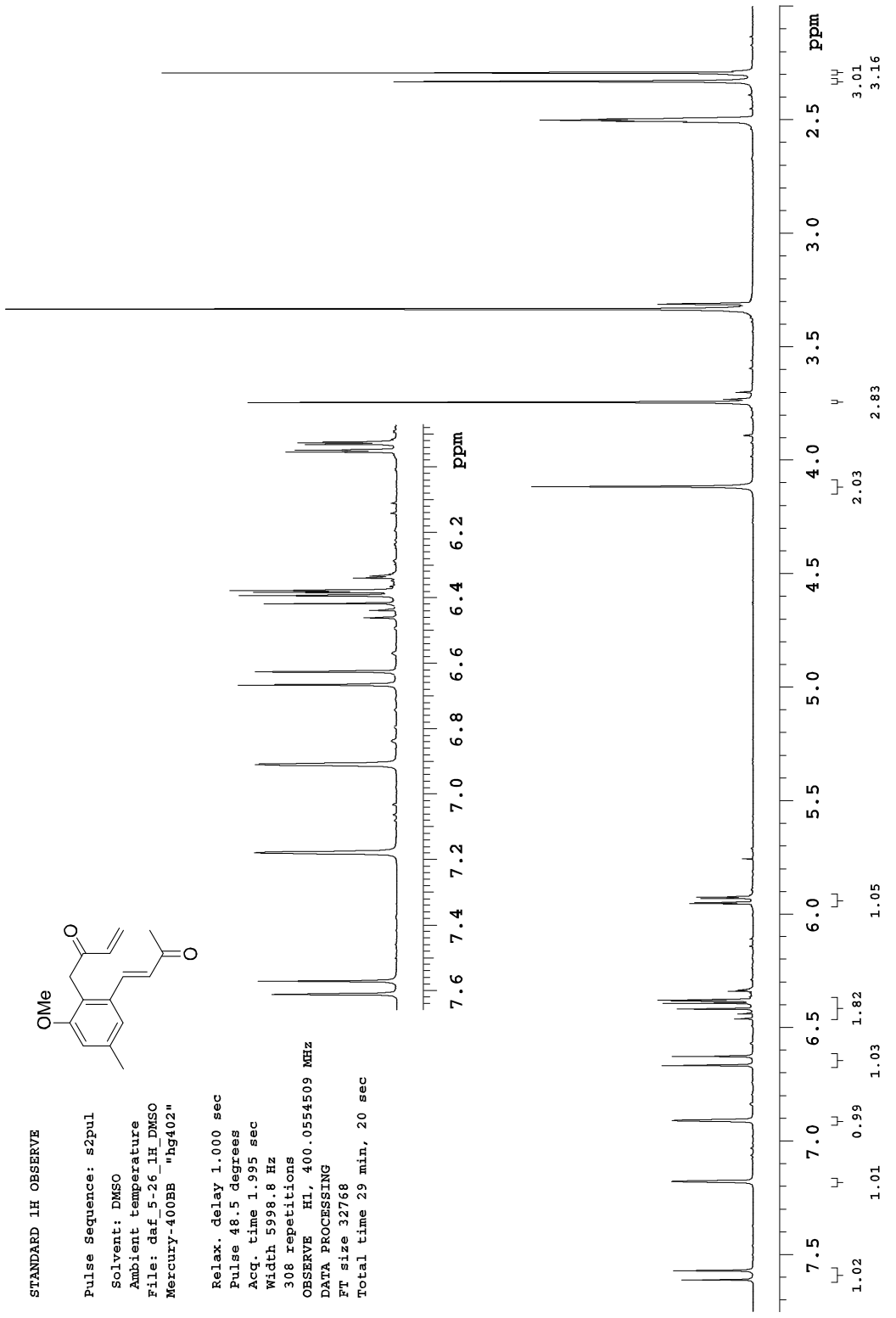
	x	y	z	U(eq)

H(2A)	3308	400	5508	31
H(2B)	2314	-773	5496	31
H(3A)	2622	-111	6278	30
H(3B)	2536	1631	6153	30
H(6A)	-751	1483	6690	21
H(8A)	-1676	-2377	6877	25
H(8B)	-2366	-1779	7319	25
H(10A)	-4222	-1219	7085	23
H(11A)	-5478	-152	6563	25
H(12A)	-4856	882	5865	26
H(13A)	-2973	974	5697	24
H(15A)	-999	-1152	6137	21
H(16A)	-1144	519	5516	23
H(16B)	-1172	1919	5866	23
H(18A)	594	2790	4788	40
H(18B)	-62	3416	5233	40
H(18C)	-499	1965	4963	40
H(19A)	1992	961	6985	33
H(19B)	936	851	7316	33
H(19C)	1027	2166	6939	33
H(20A)	1696	-1668	6719	34
H(20B)	531	-2168	6512	34
H(20C)	649	-1780	7057	34

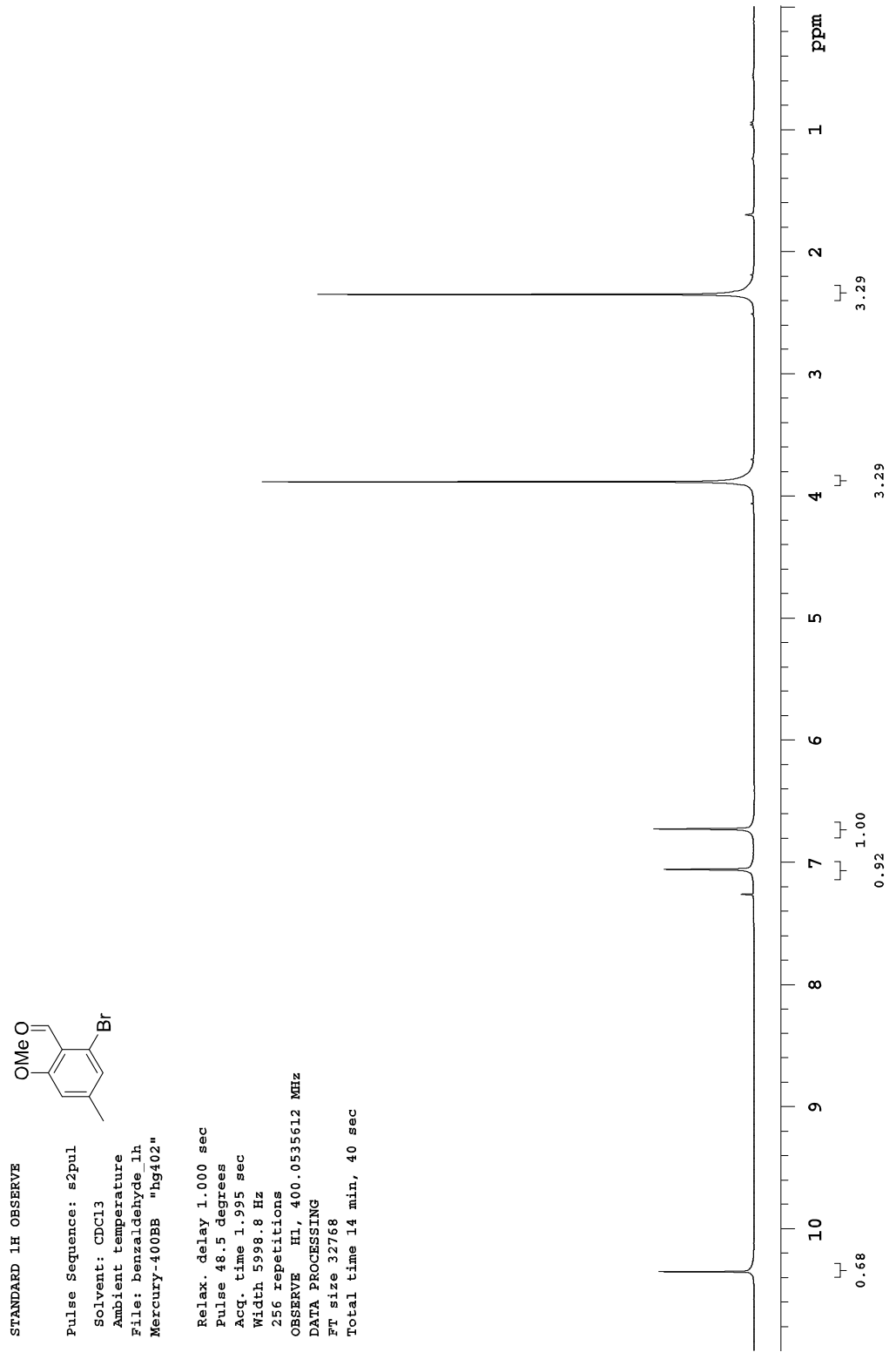
Section A.3 Selected NMR Spectra



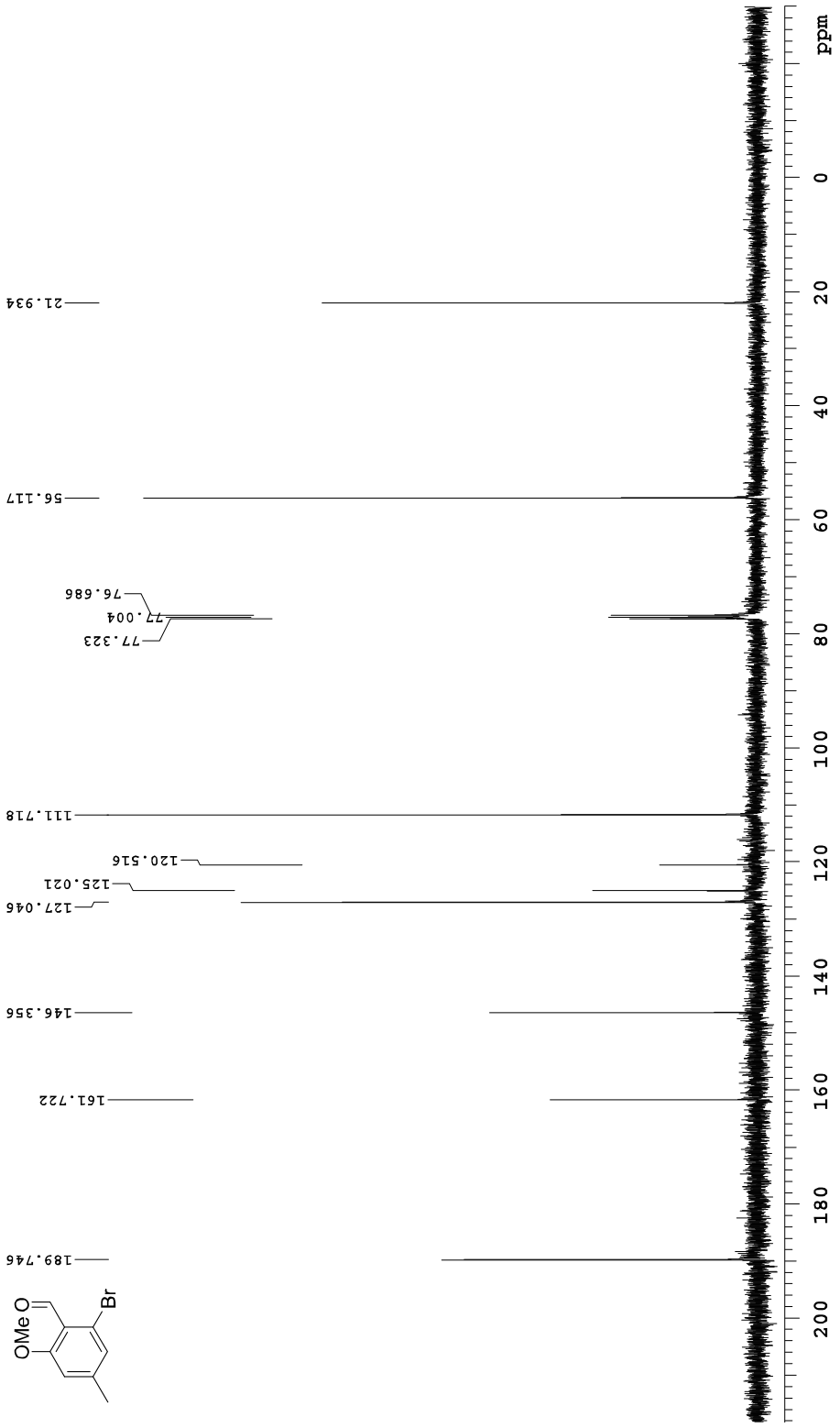
Spectrum 2.0 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **423**



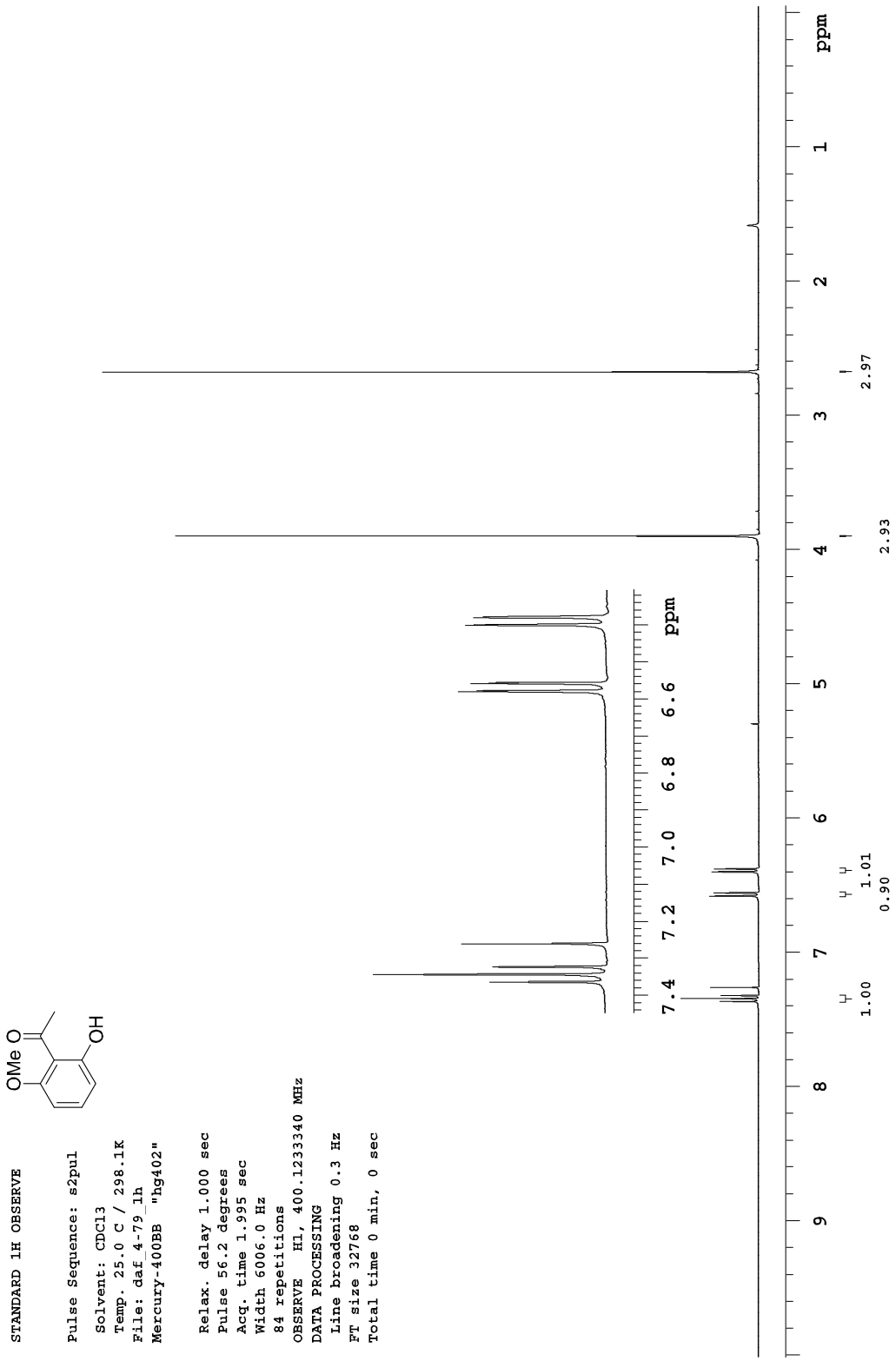
Spectrum 2.1 ^{1}H NMR (DMSO-d6, 400 MHz) of compound **423**



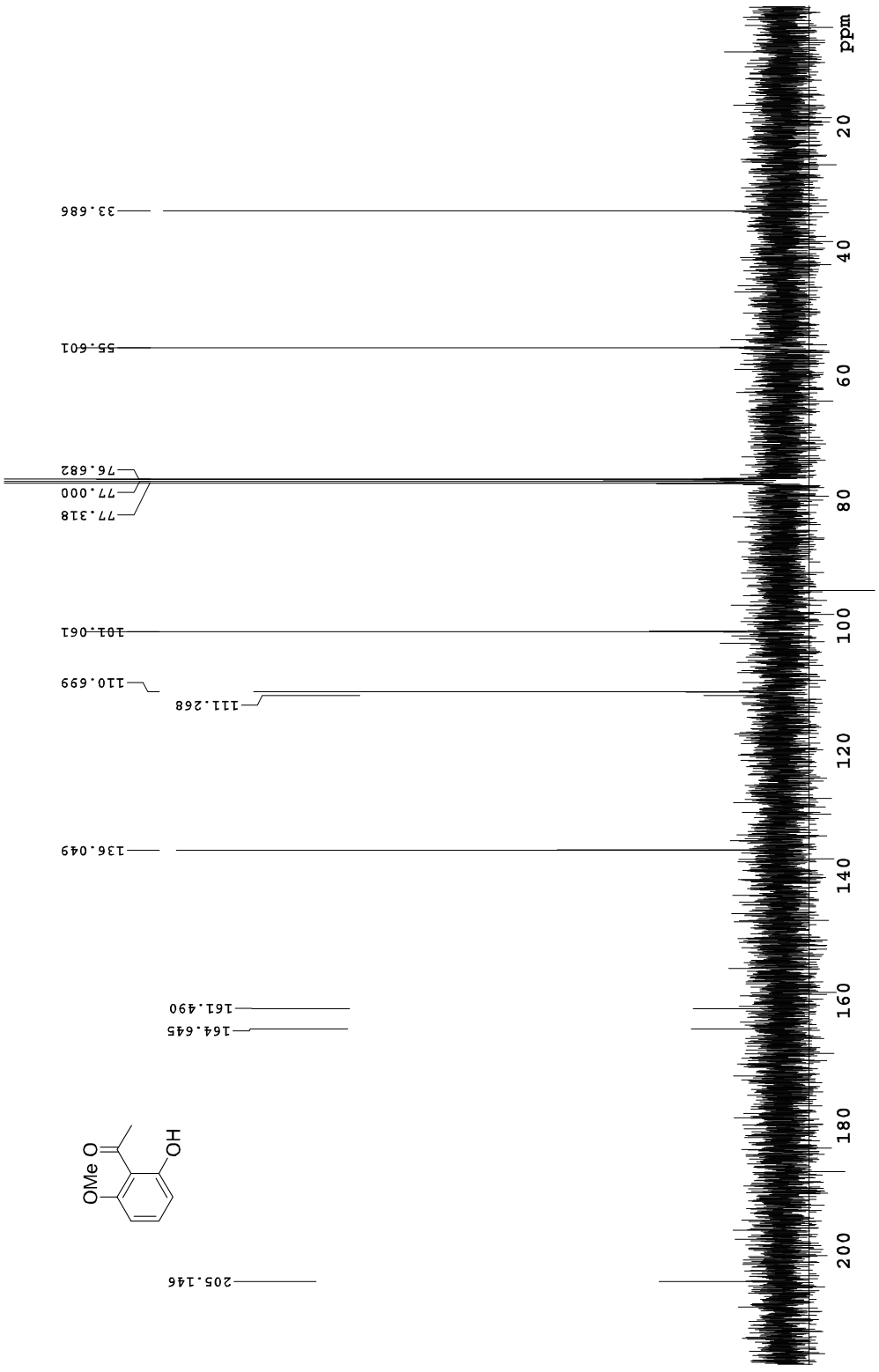
Spectrum 2.2 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **427**



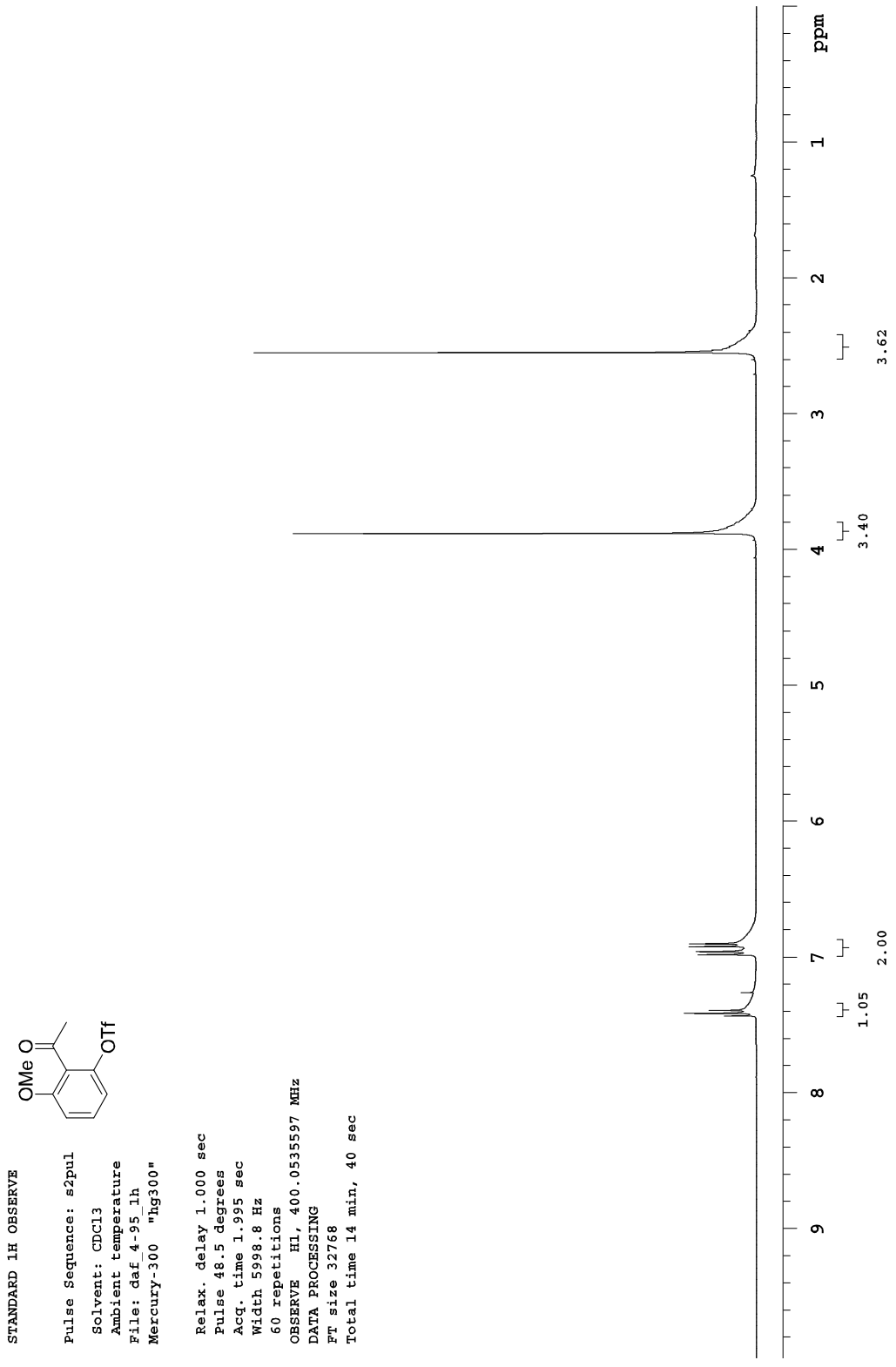
Spectrum 2.3 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **427**



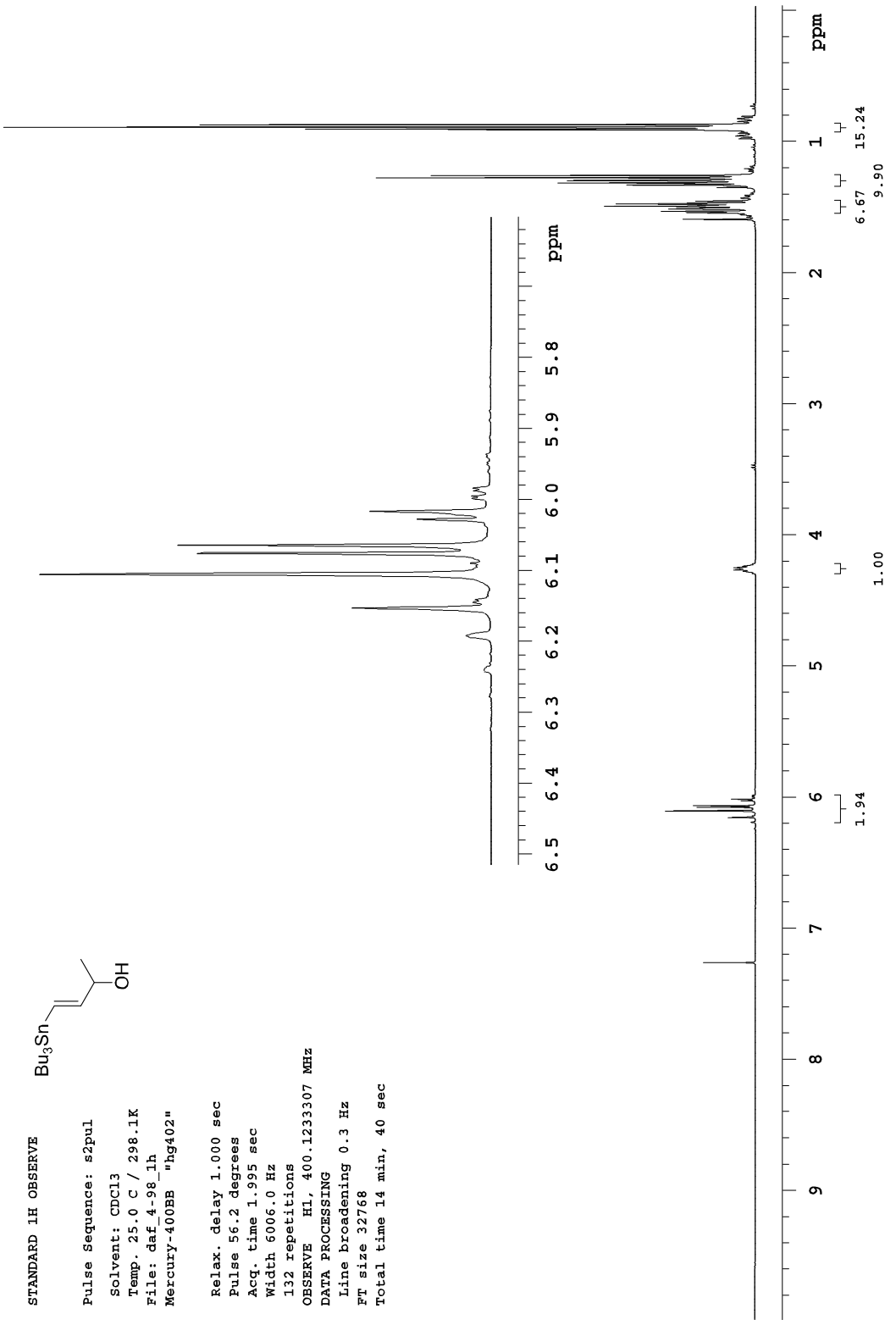
Spectrum 2.4 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **433**



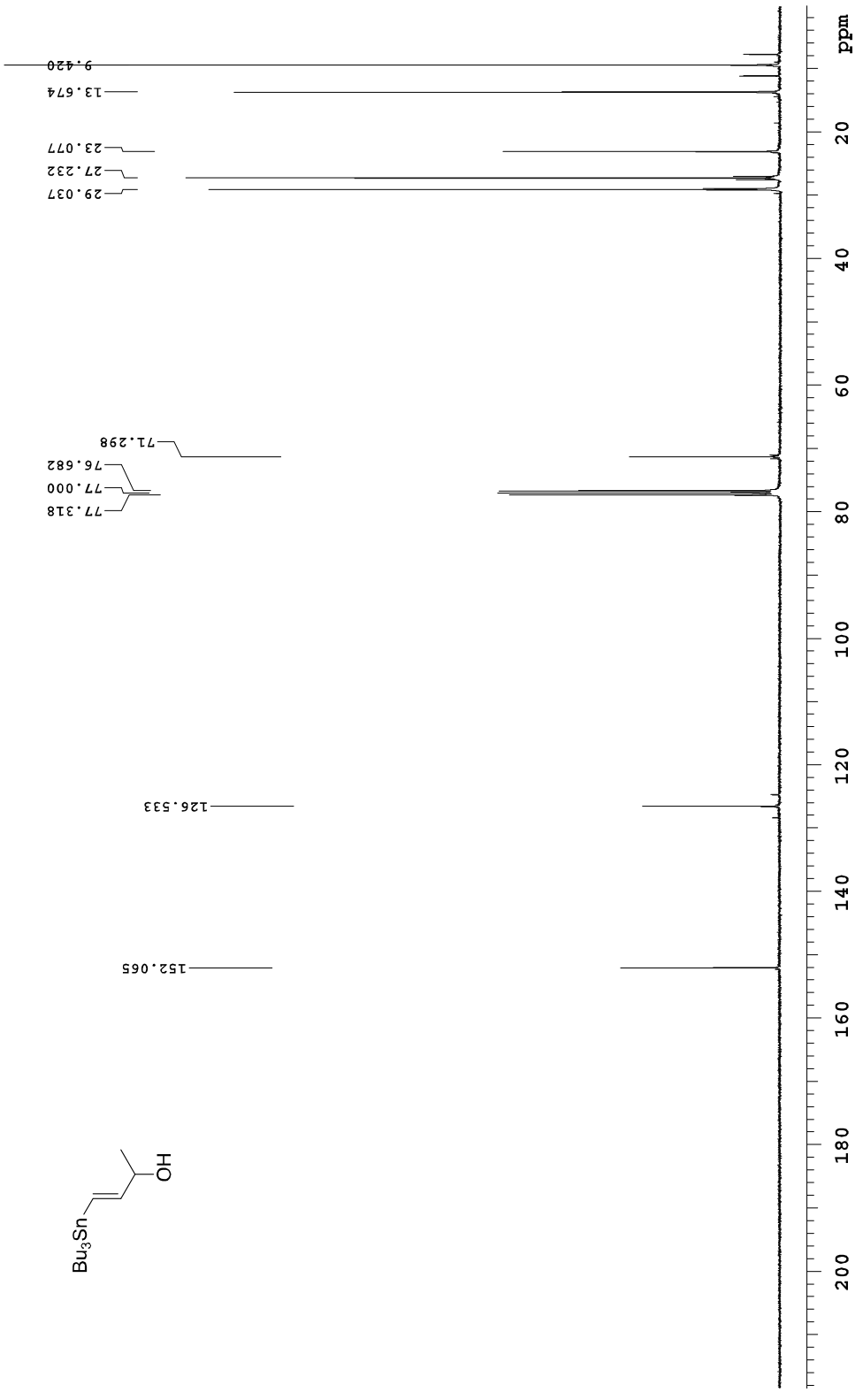
Spectrum 2.5 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **433**



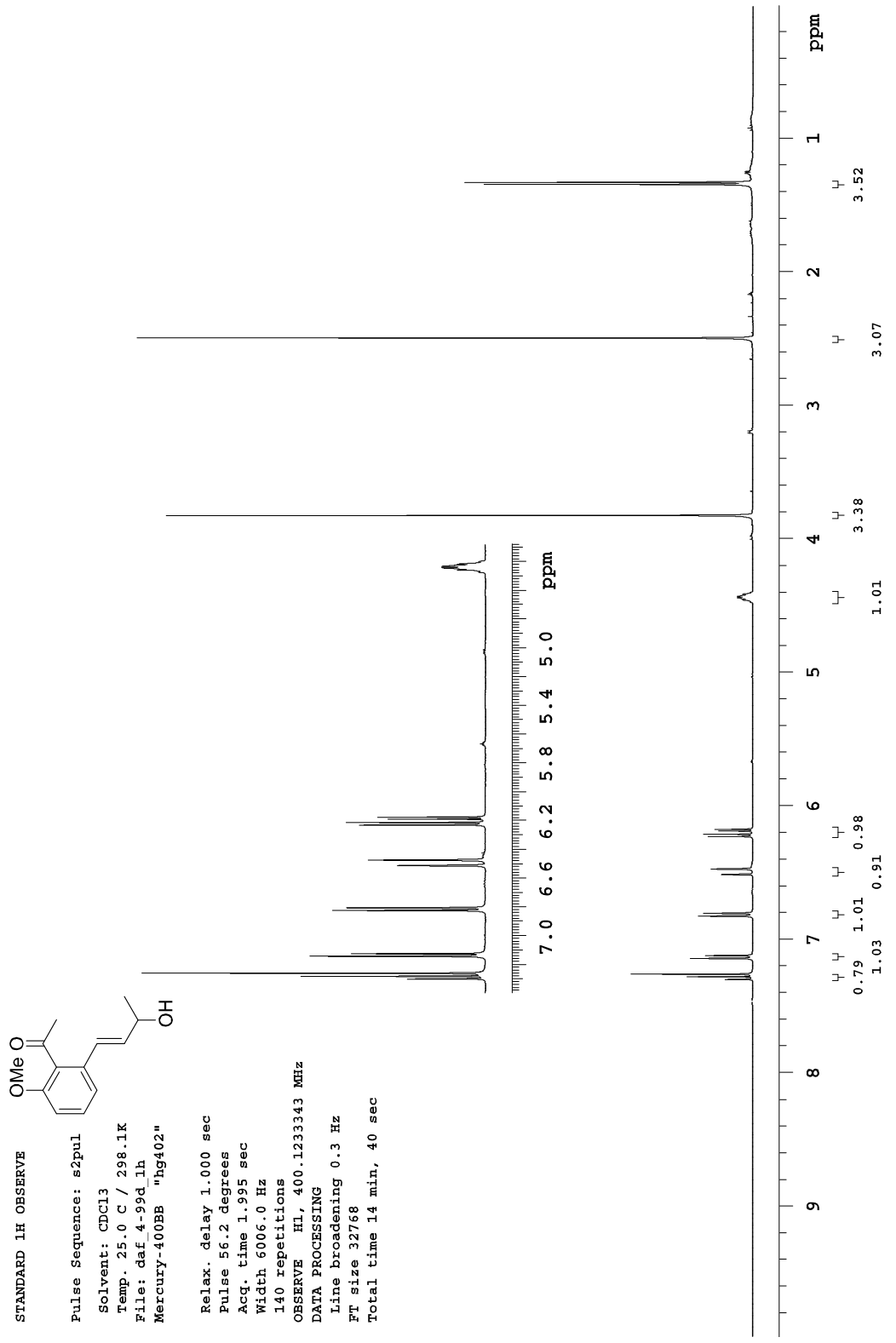
Spectrum 2.6 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **434**



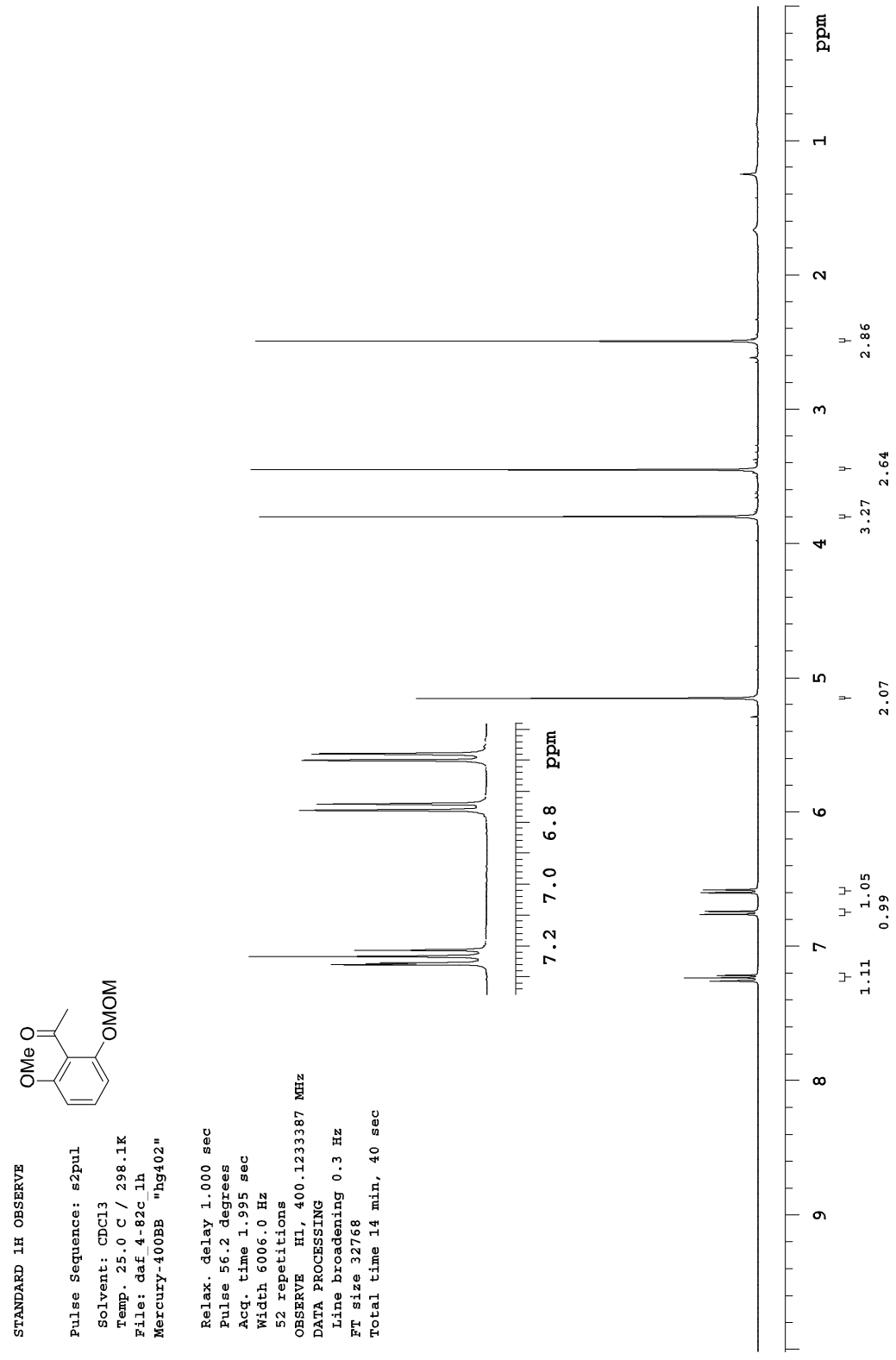
Spectrum 2.7 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **437**



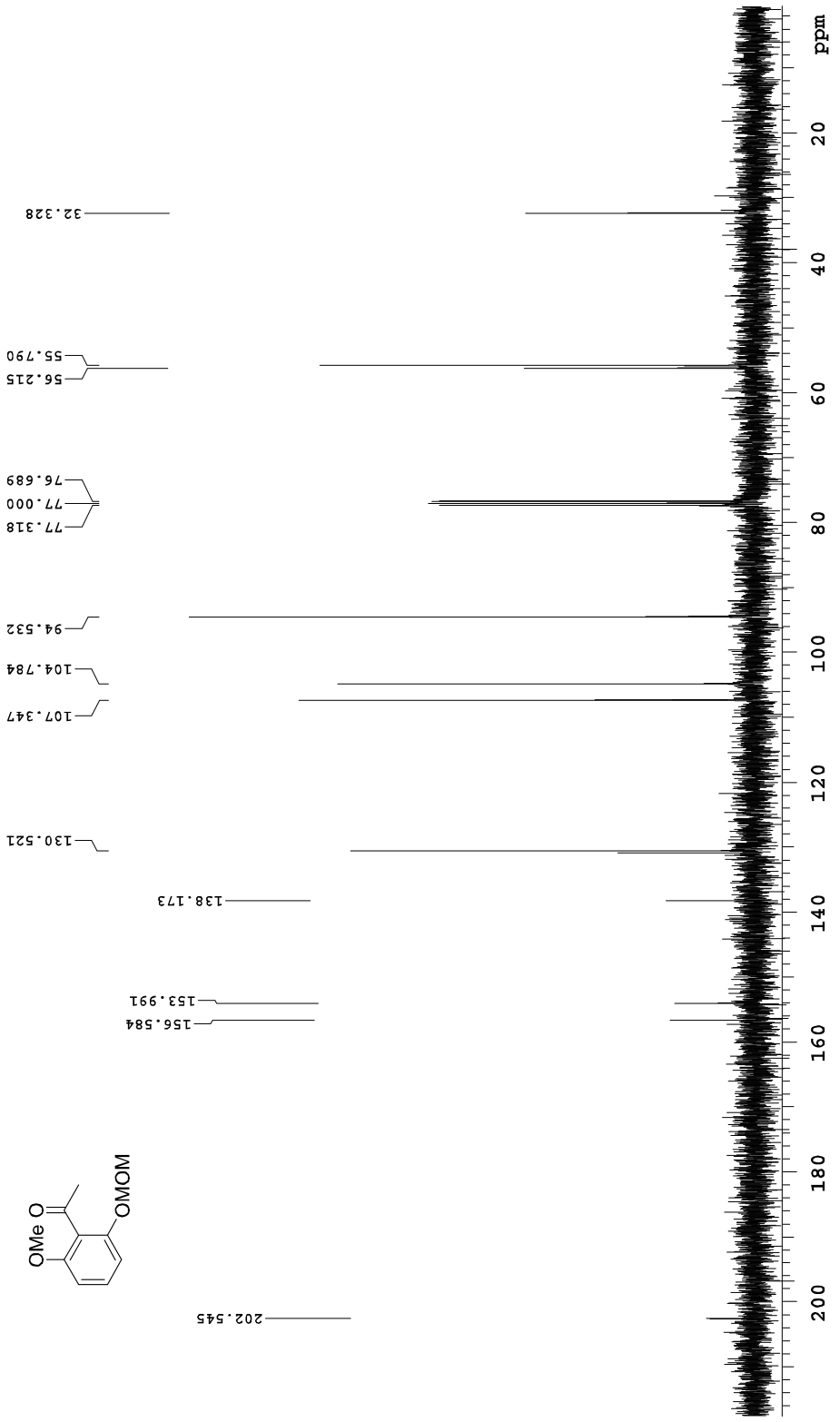
Spectrum 2.8 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **437**



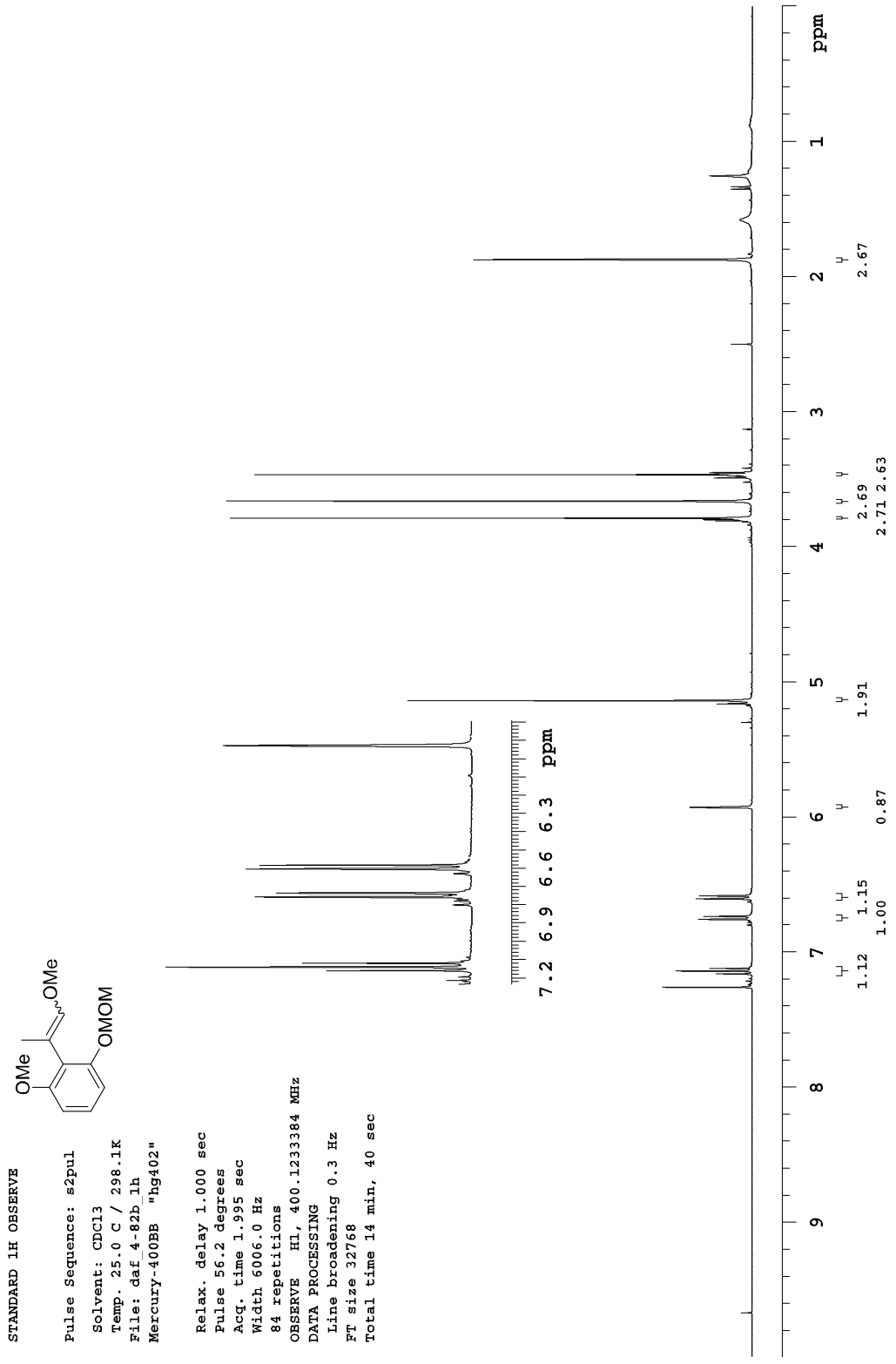
Spectrum 2.9 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **438**



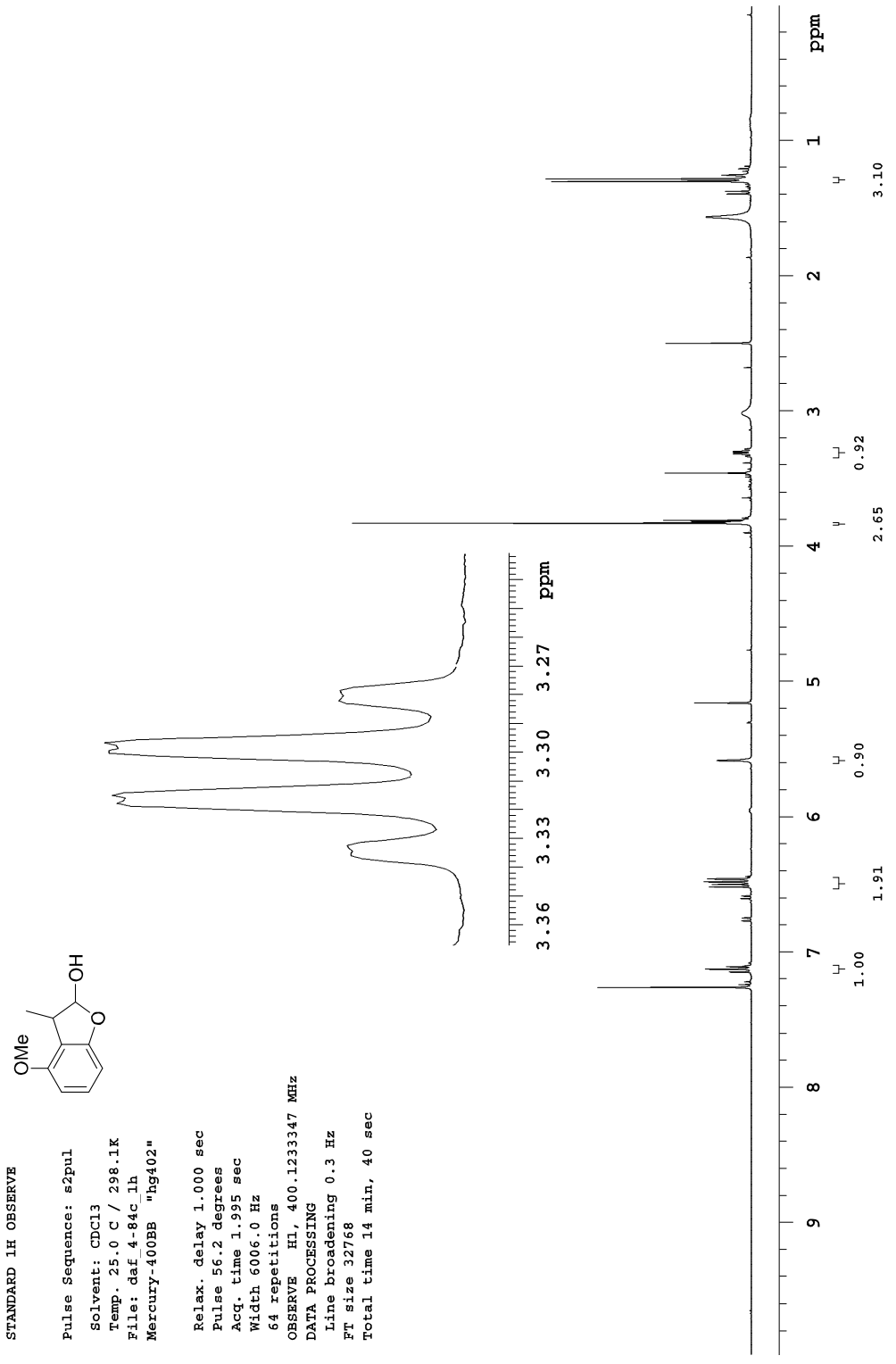
Spectrum 2.10 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **440**



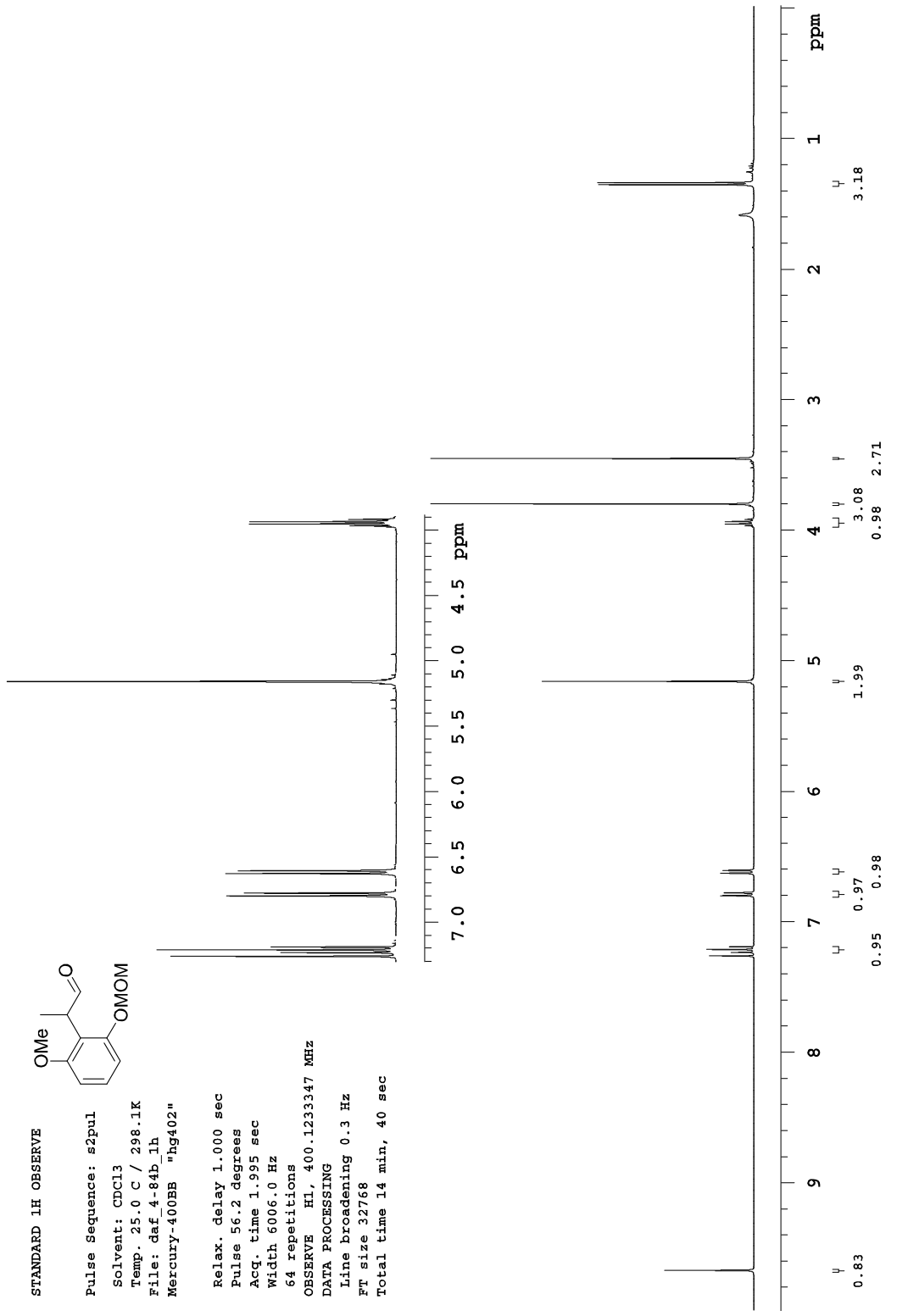
Spectrum 2.11 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **440**



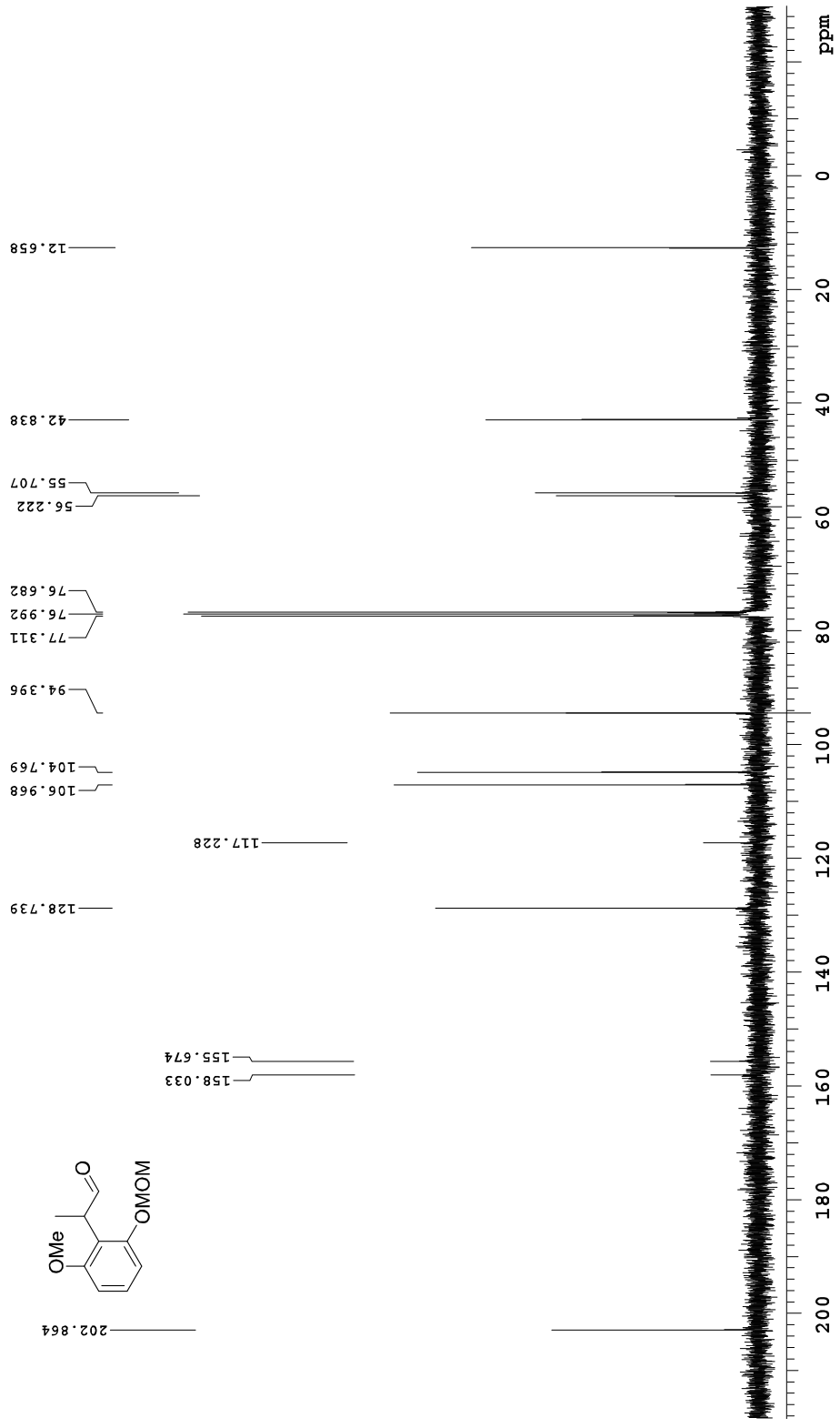
Spectrum 2.12 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **441**



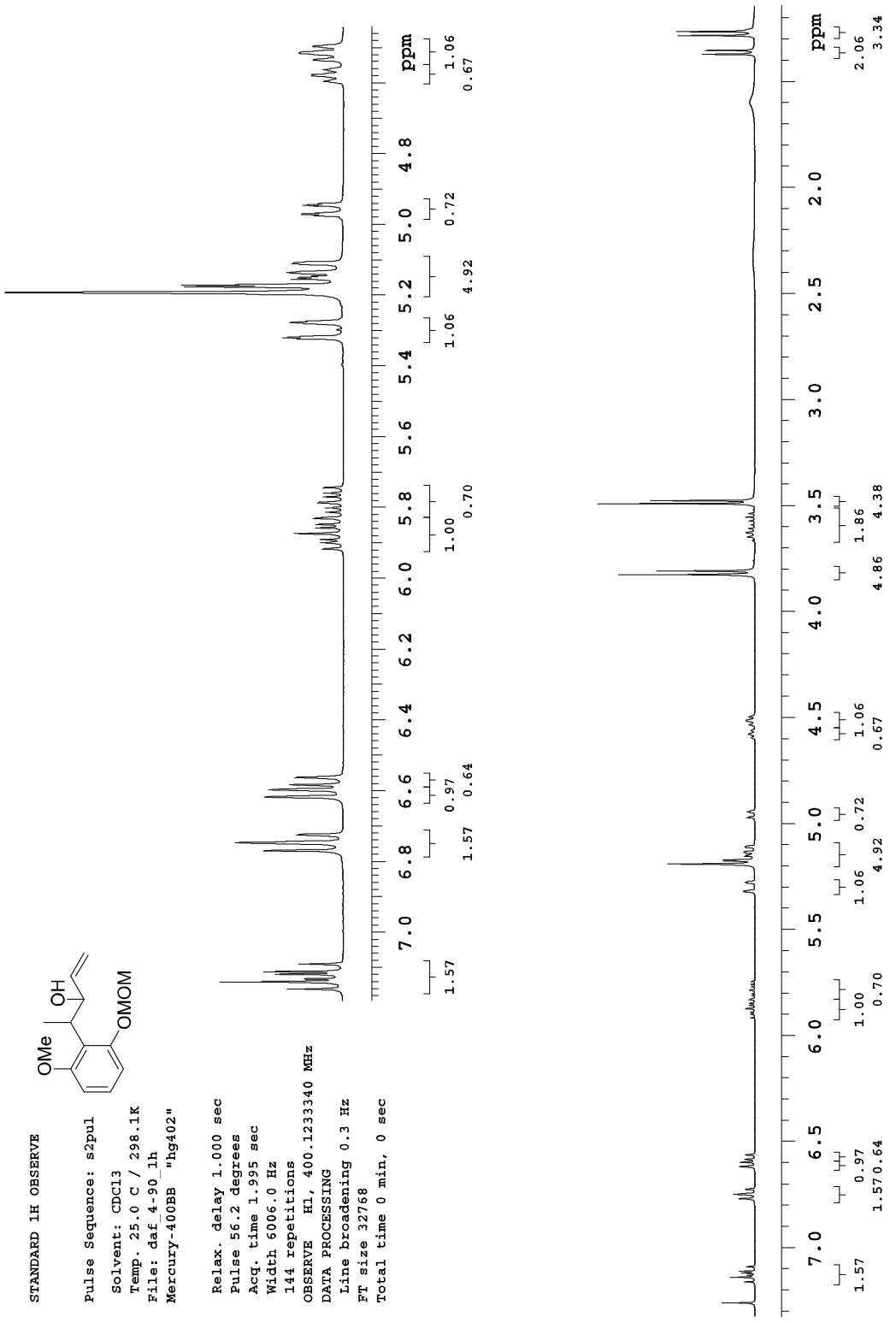
Spectrum 2.13 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **442**



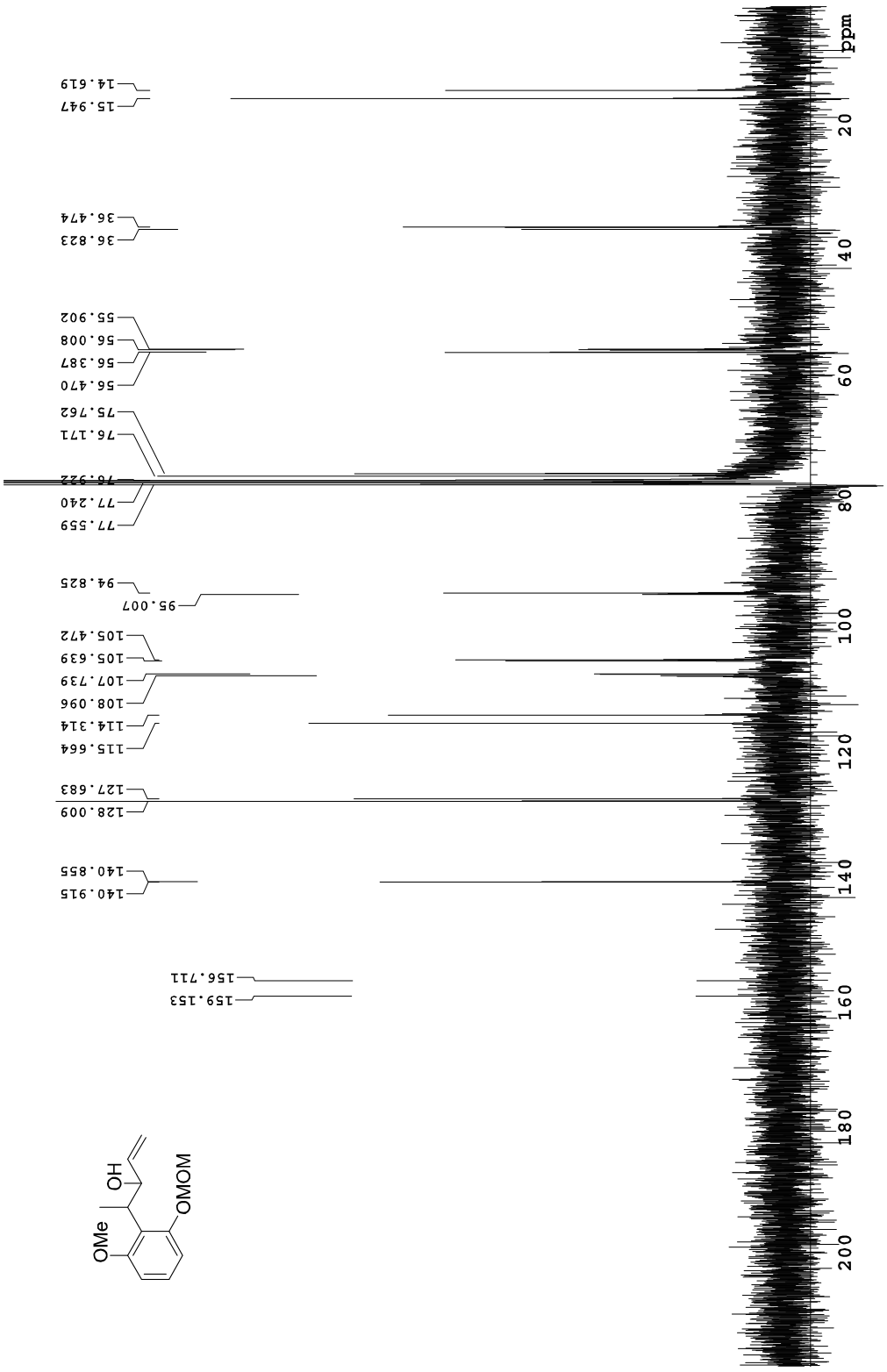
Spectrum 2.14 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **443**



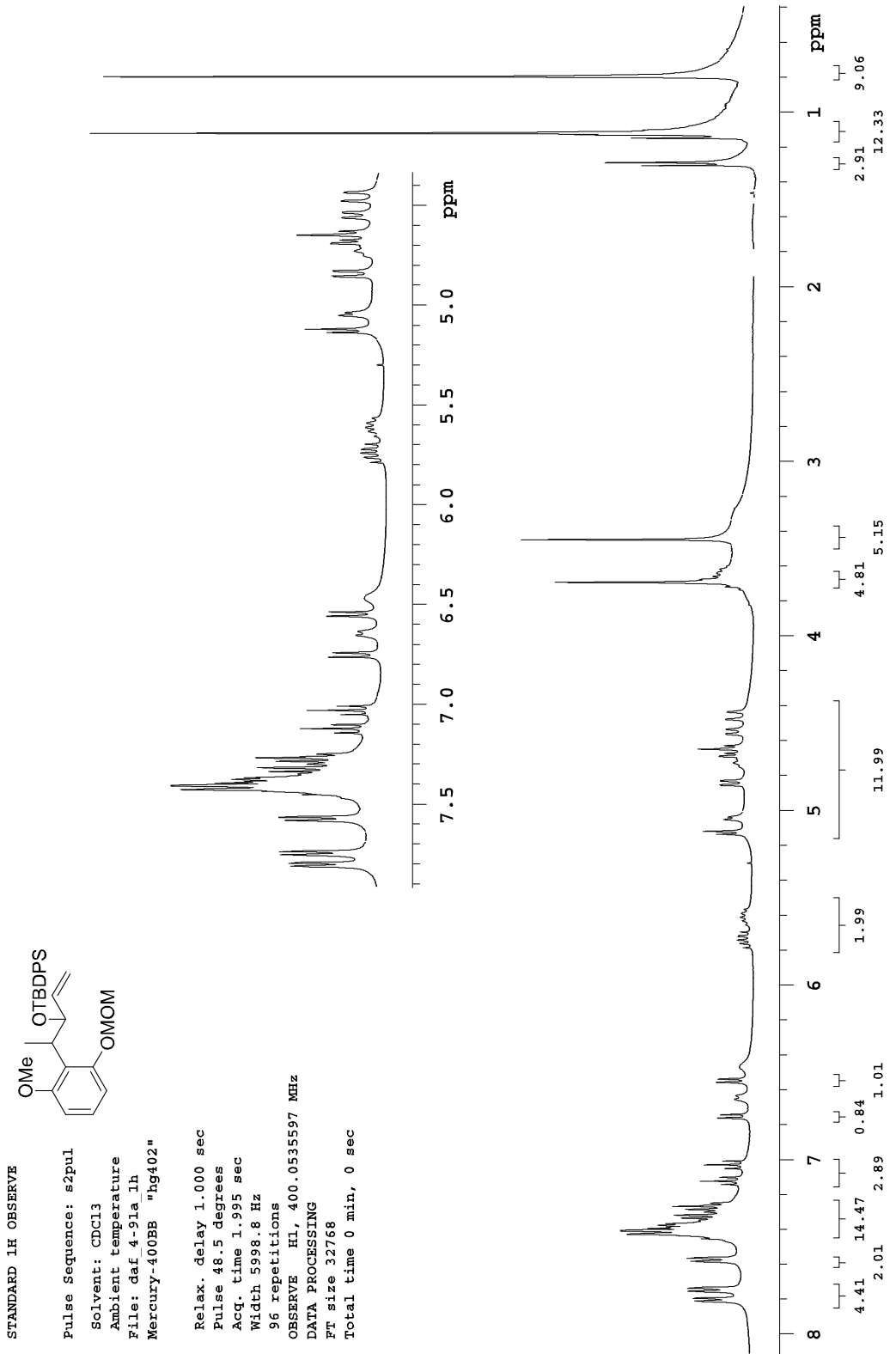
Spectrum 2.15 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **443**



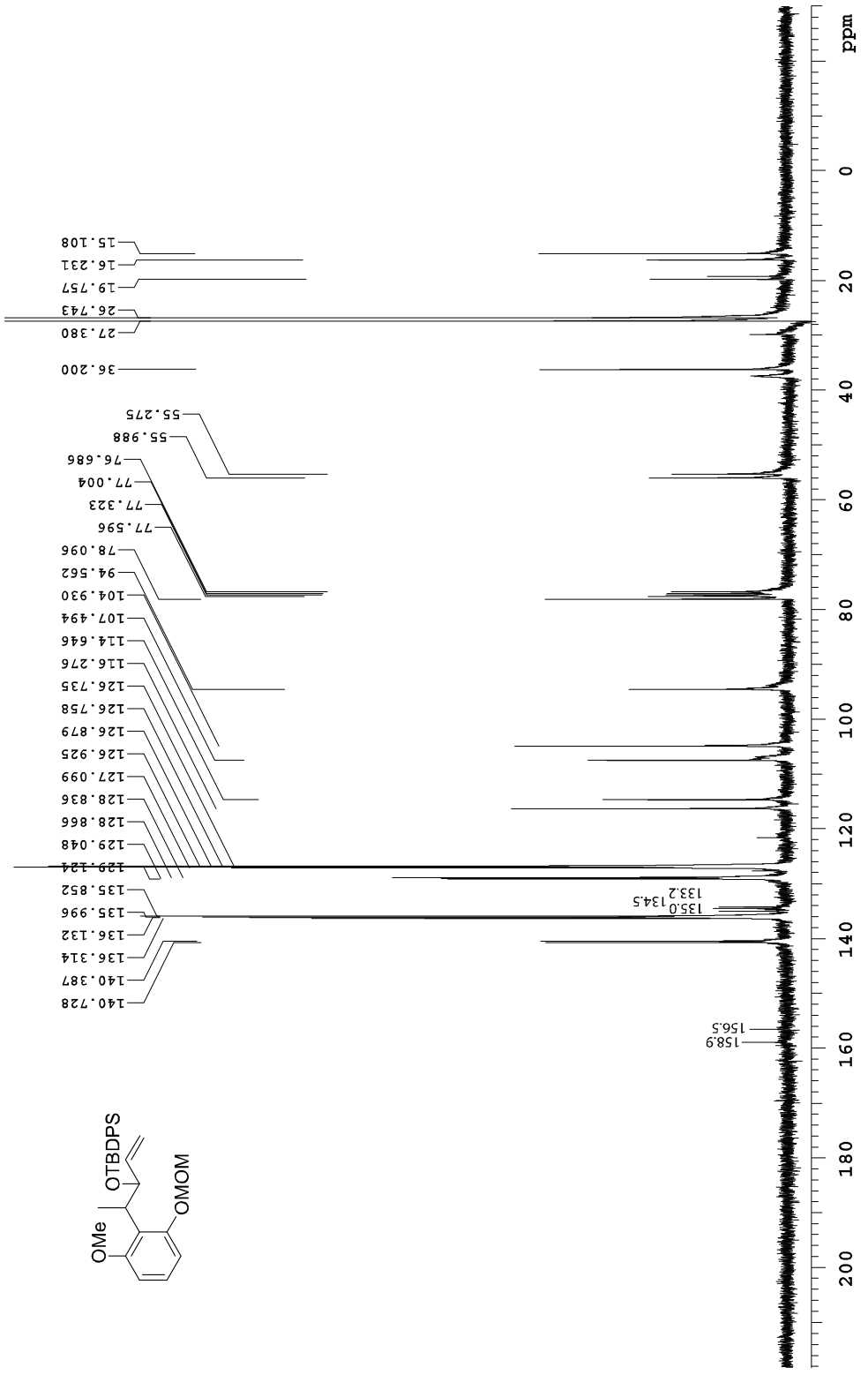
Spectrum 2.16 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **444**



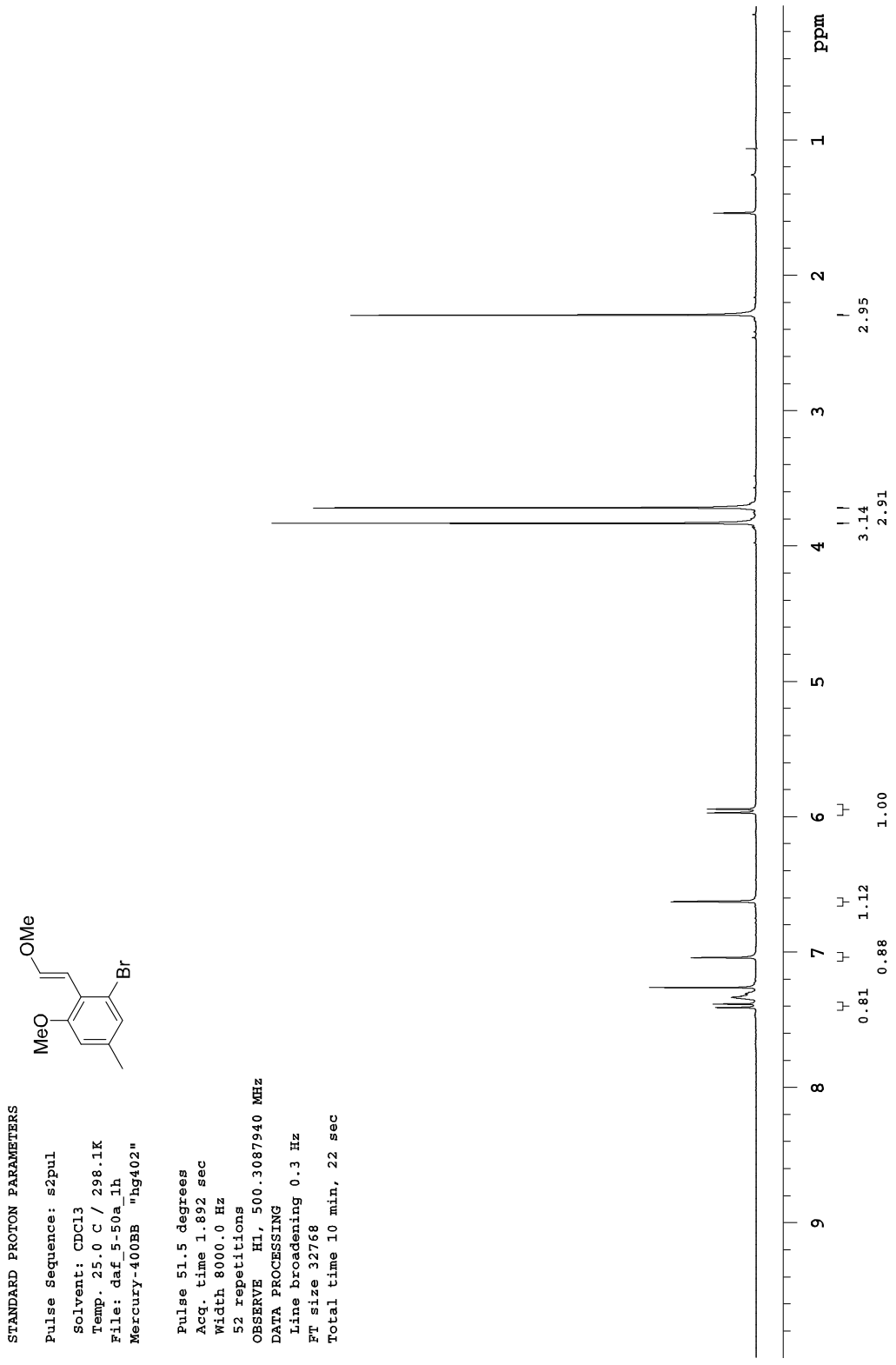
Spectrum 2.17 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **444**



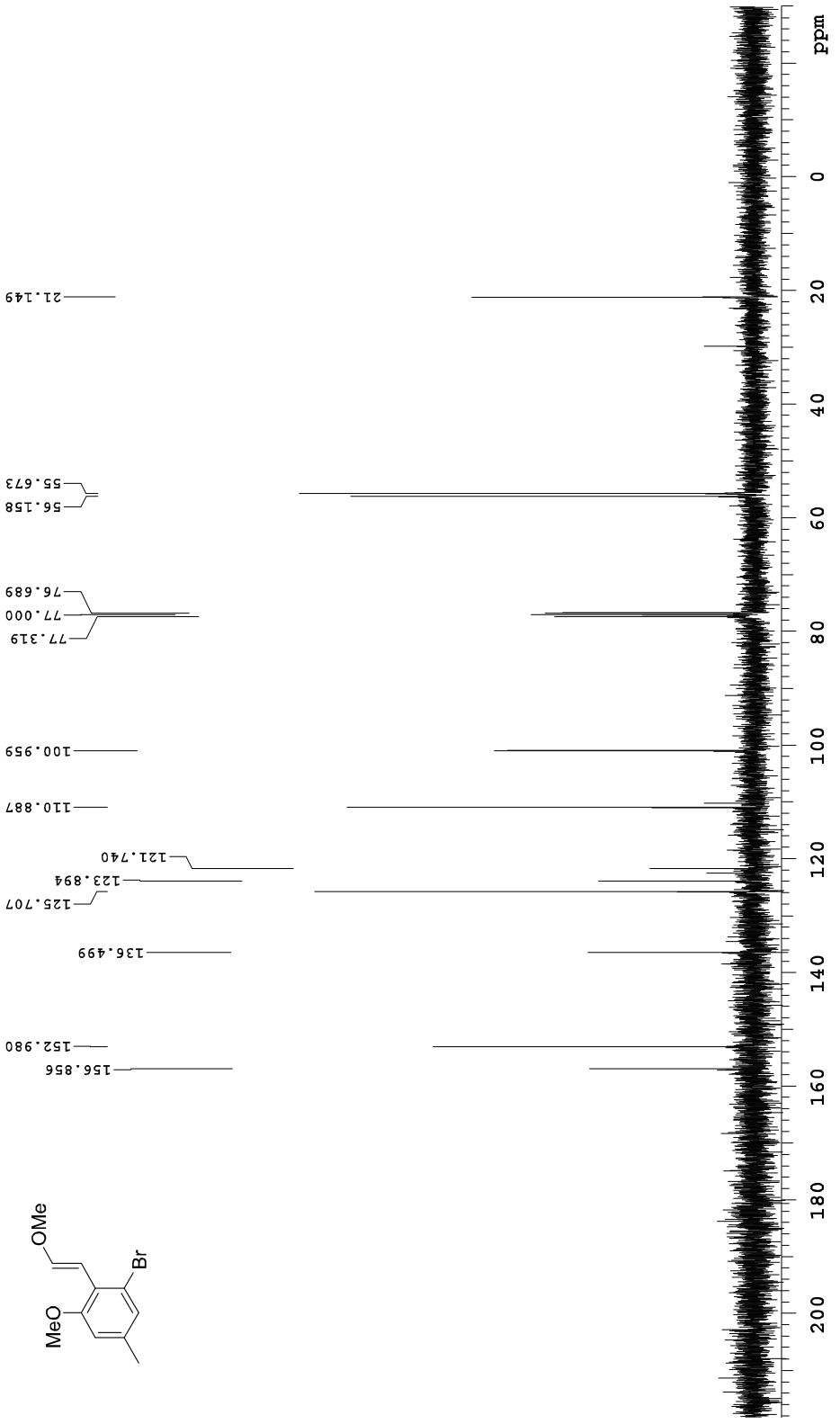
Spectrum 2.18 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **445**



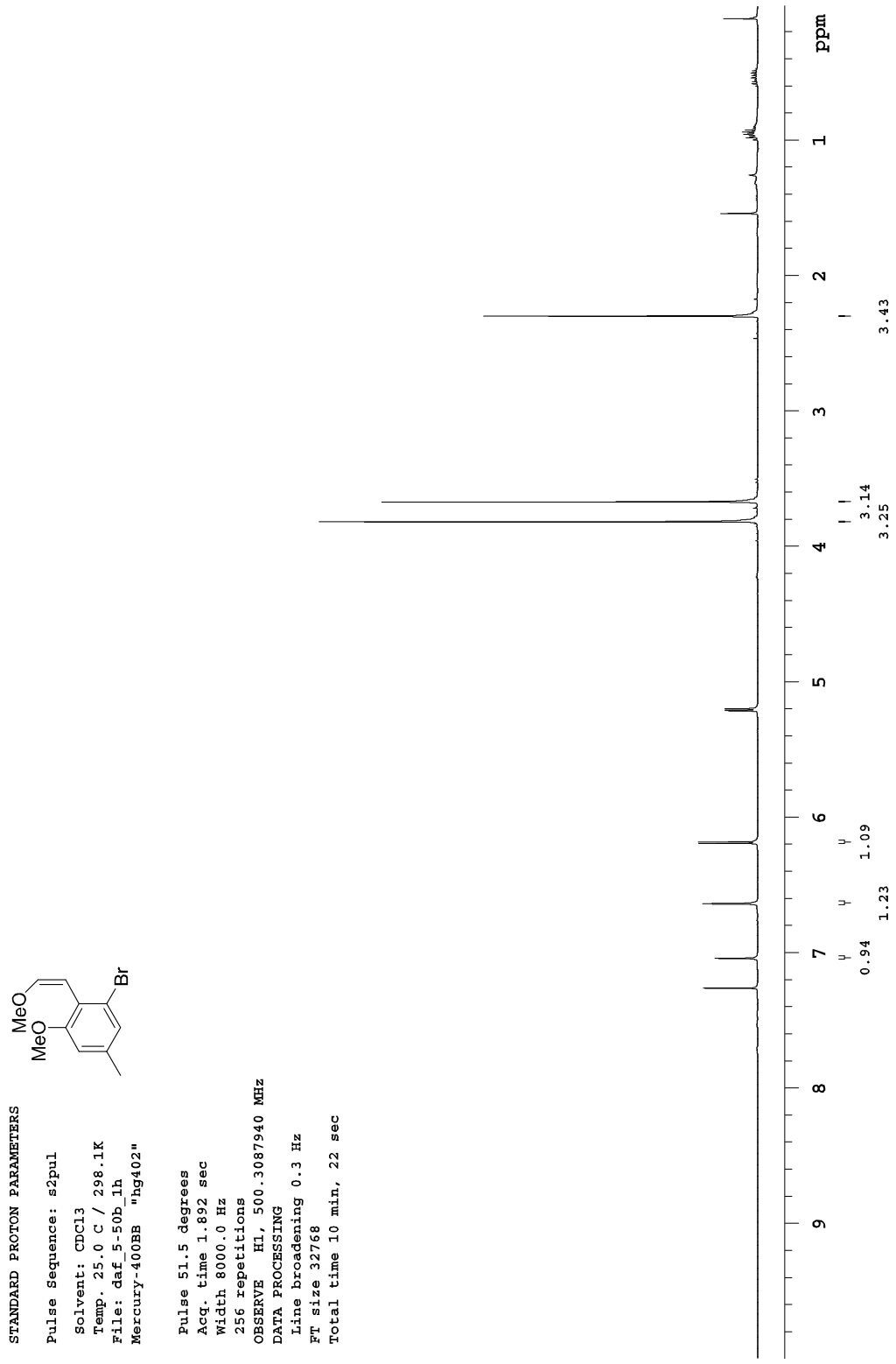
Spectrum 2.19 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **445**



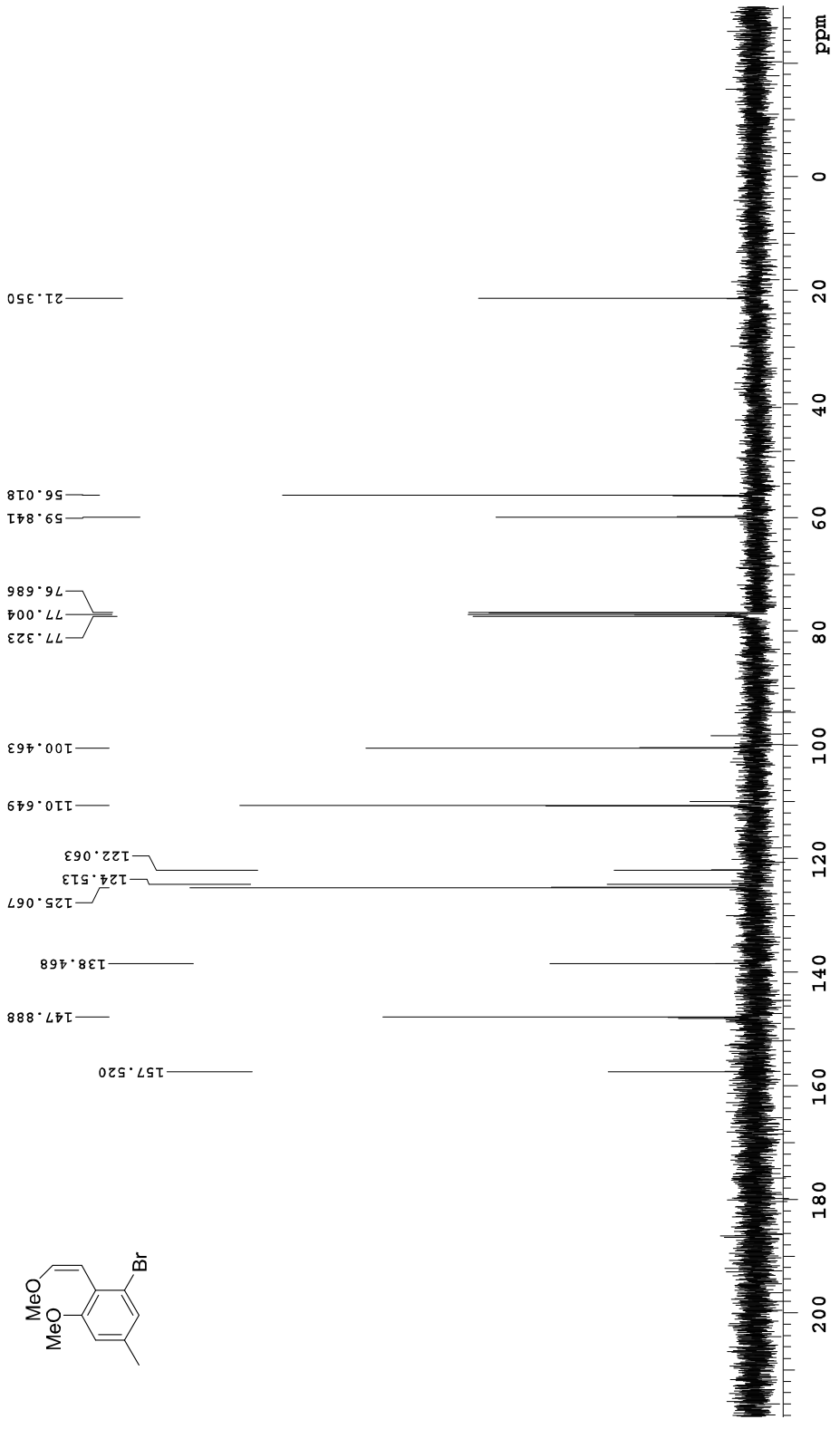
Spectrum 2.20 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **446E**



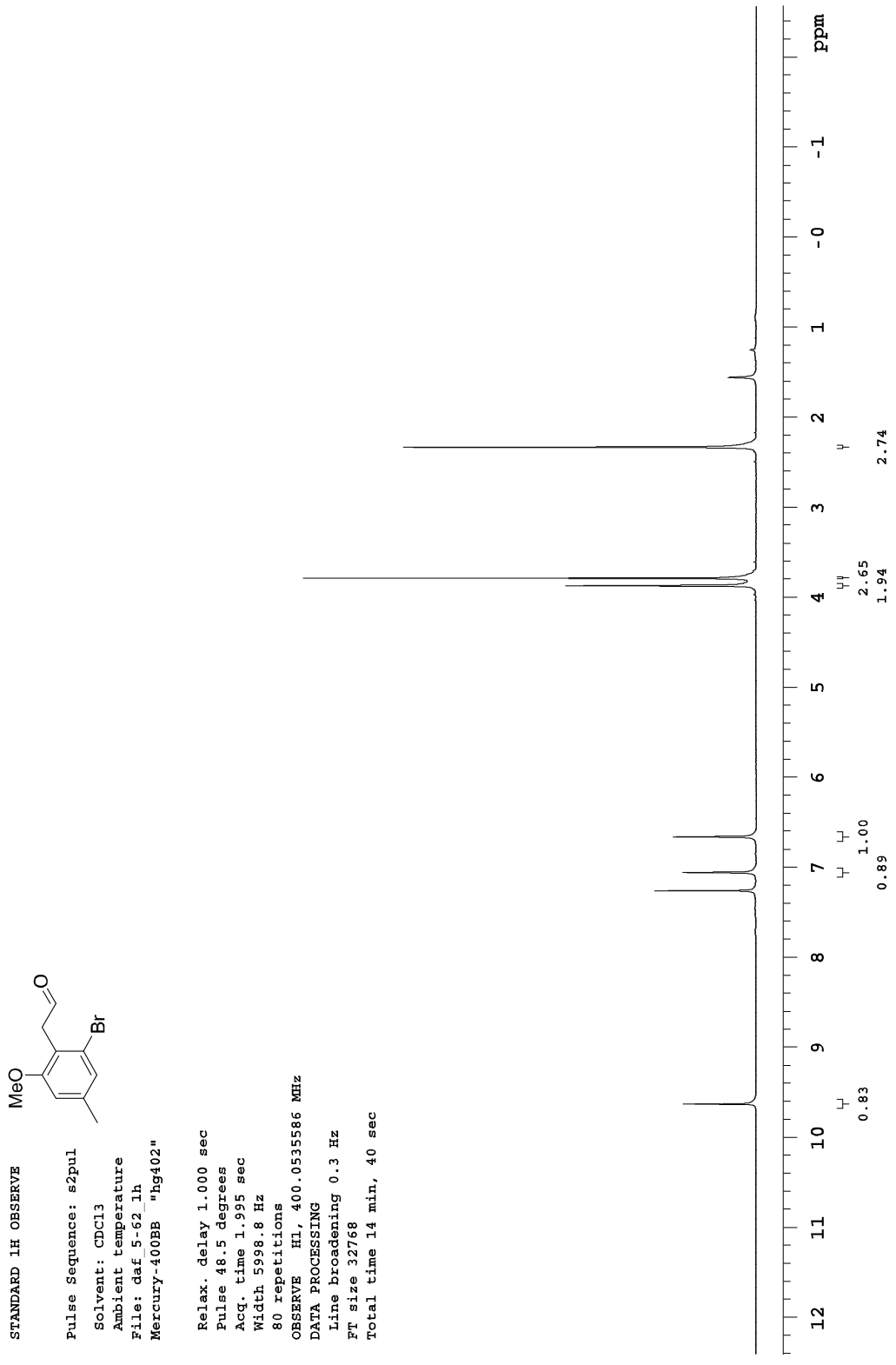
Spectrum 2.21 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **446E**



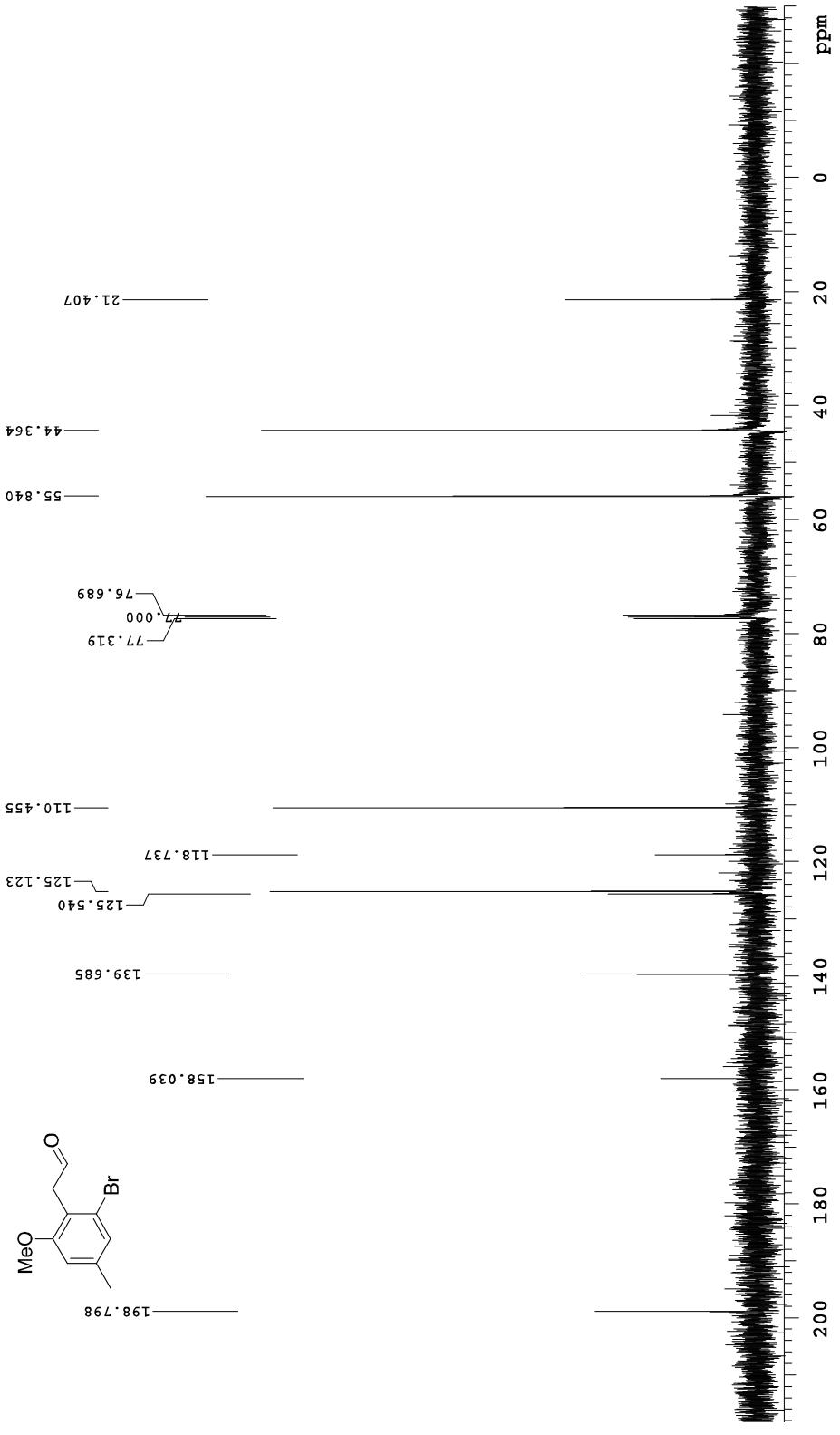
Spectrum 2.22 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **446Z**



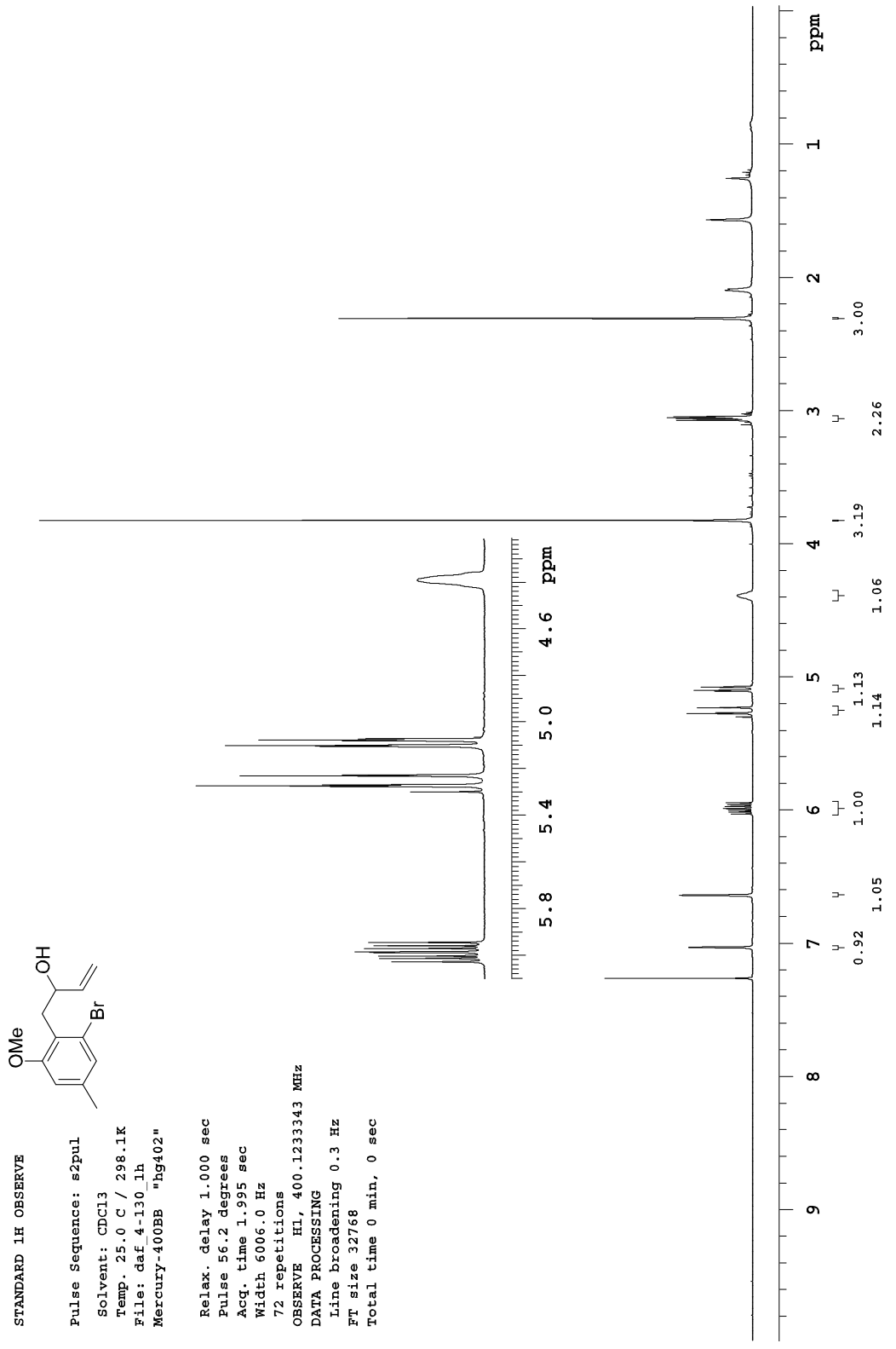
Spectrum 2.23 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **446Z**



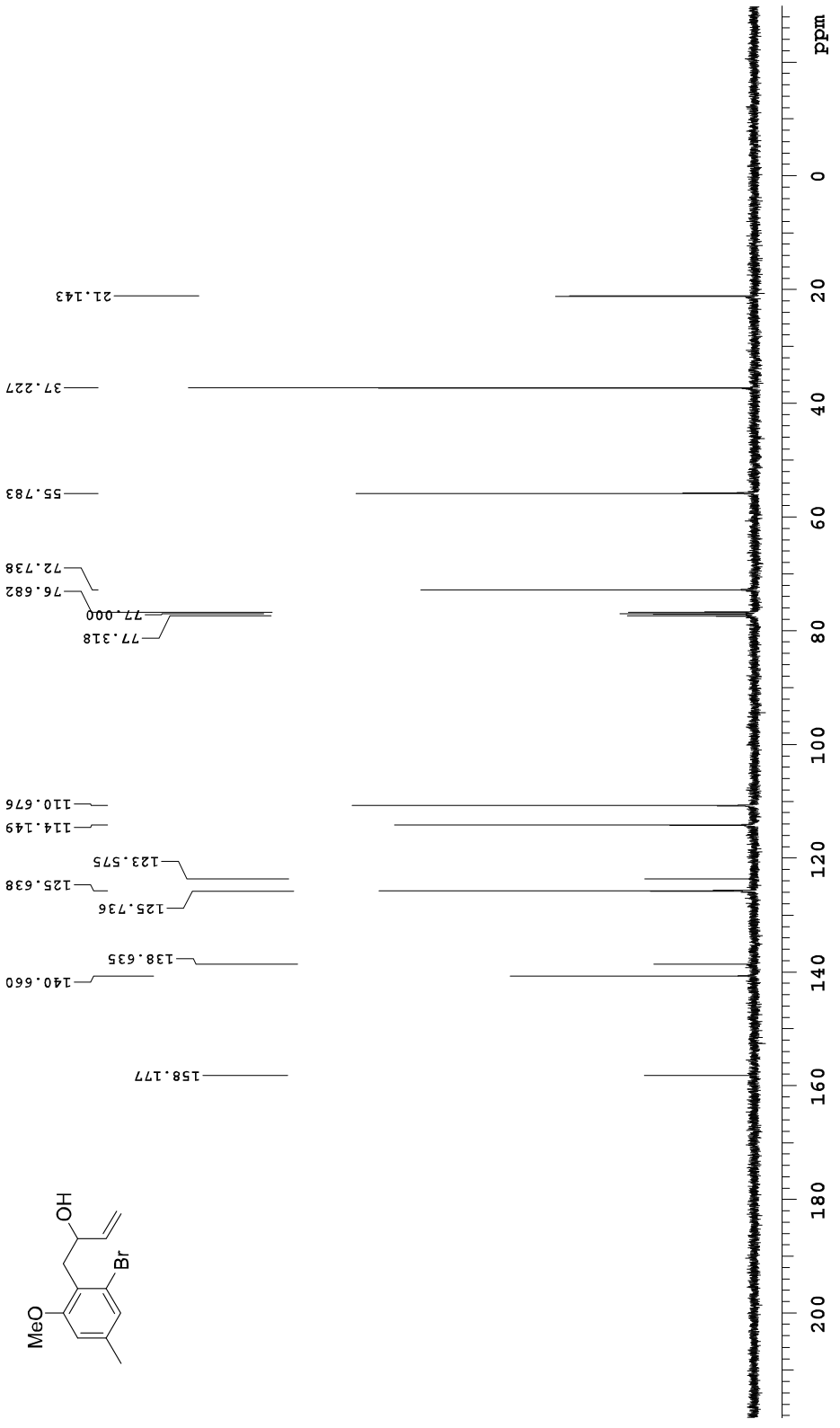
Spectrum 2.24 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **447**



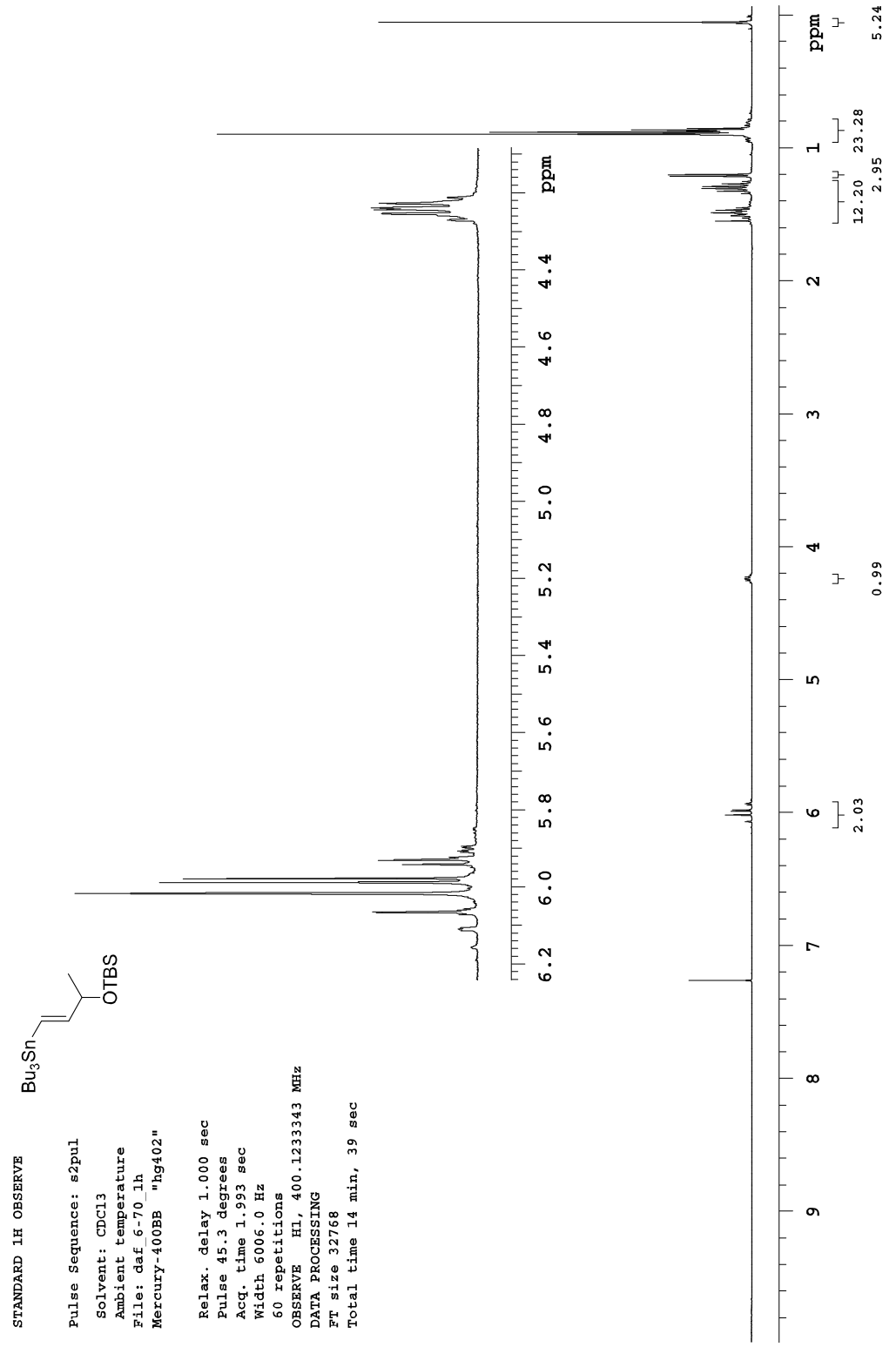
Spectrum 2.25 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **447**



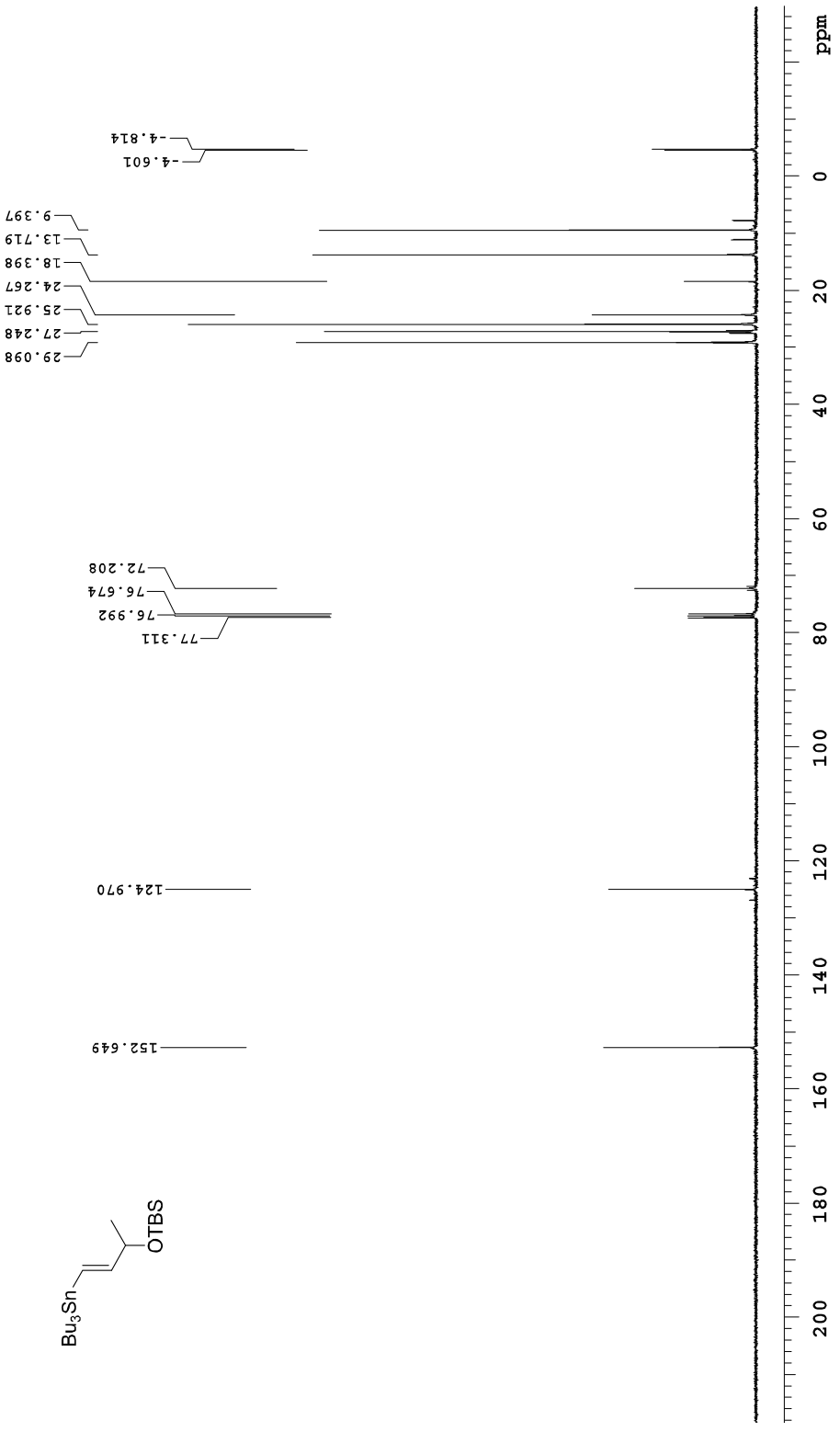
Spectrum 2.26 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **448**



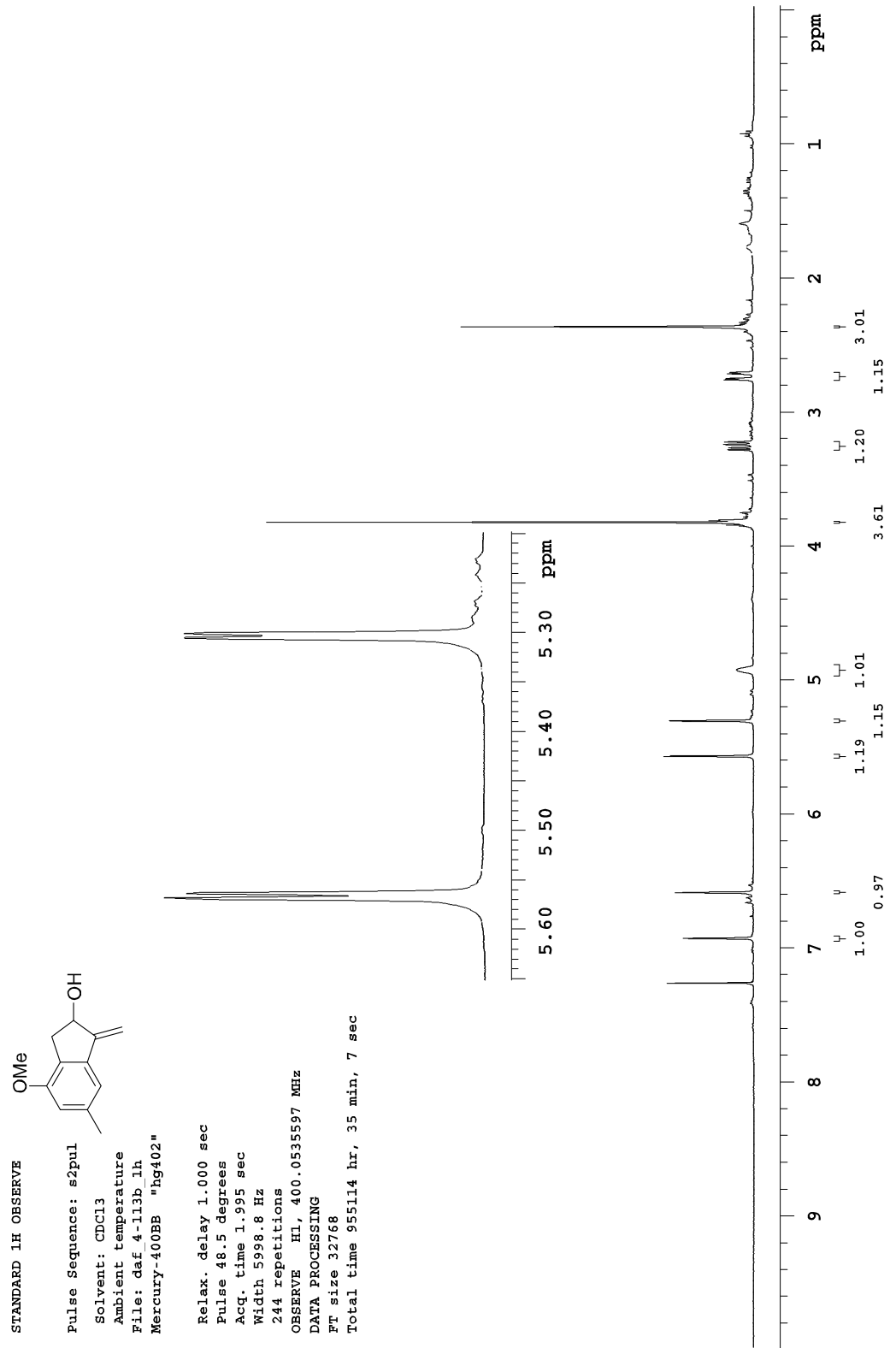
Spectrum 2.27 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **448**



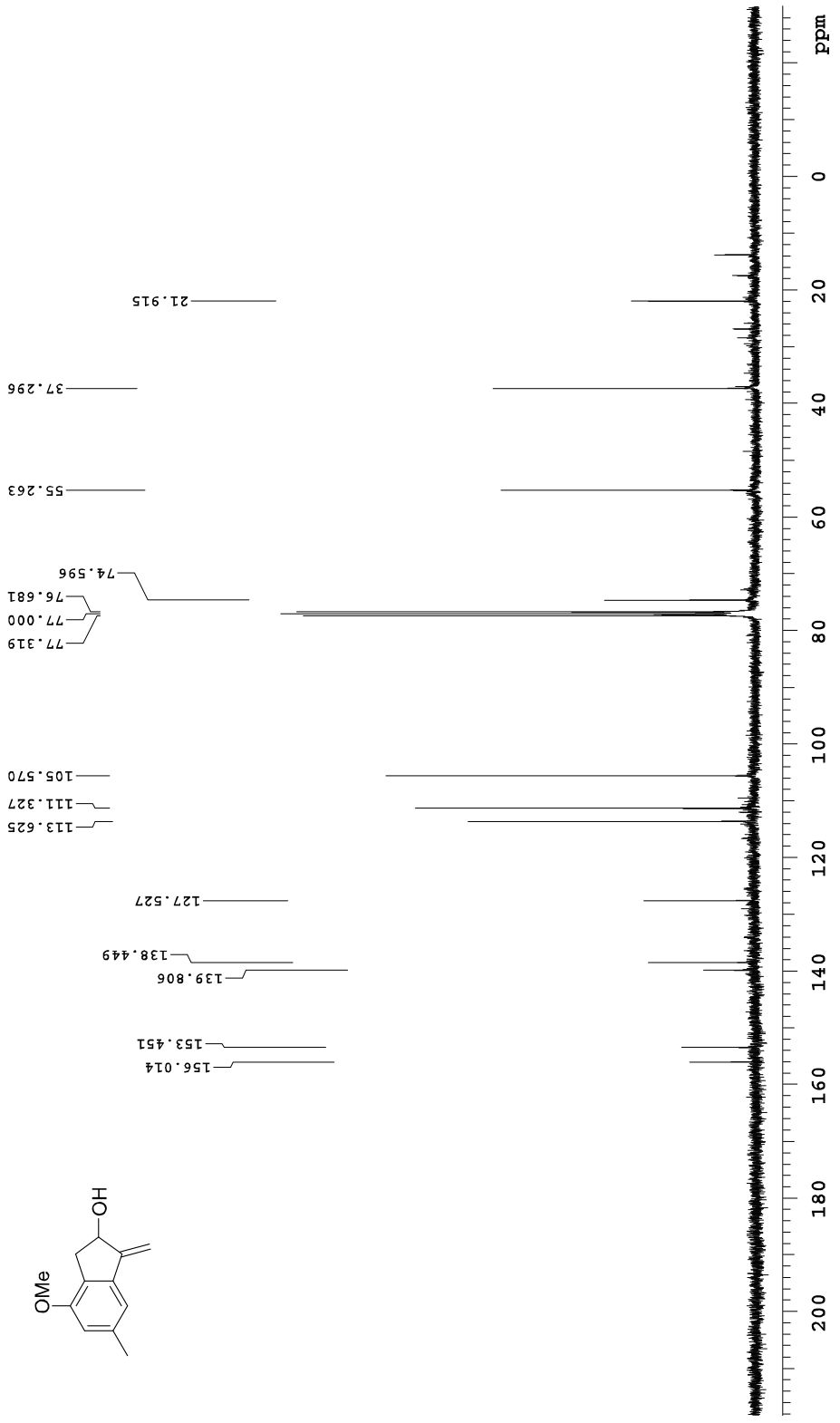
Spectrum 2.28 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **449**



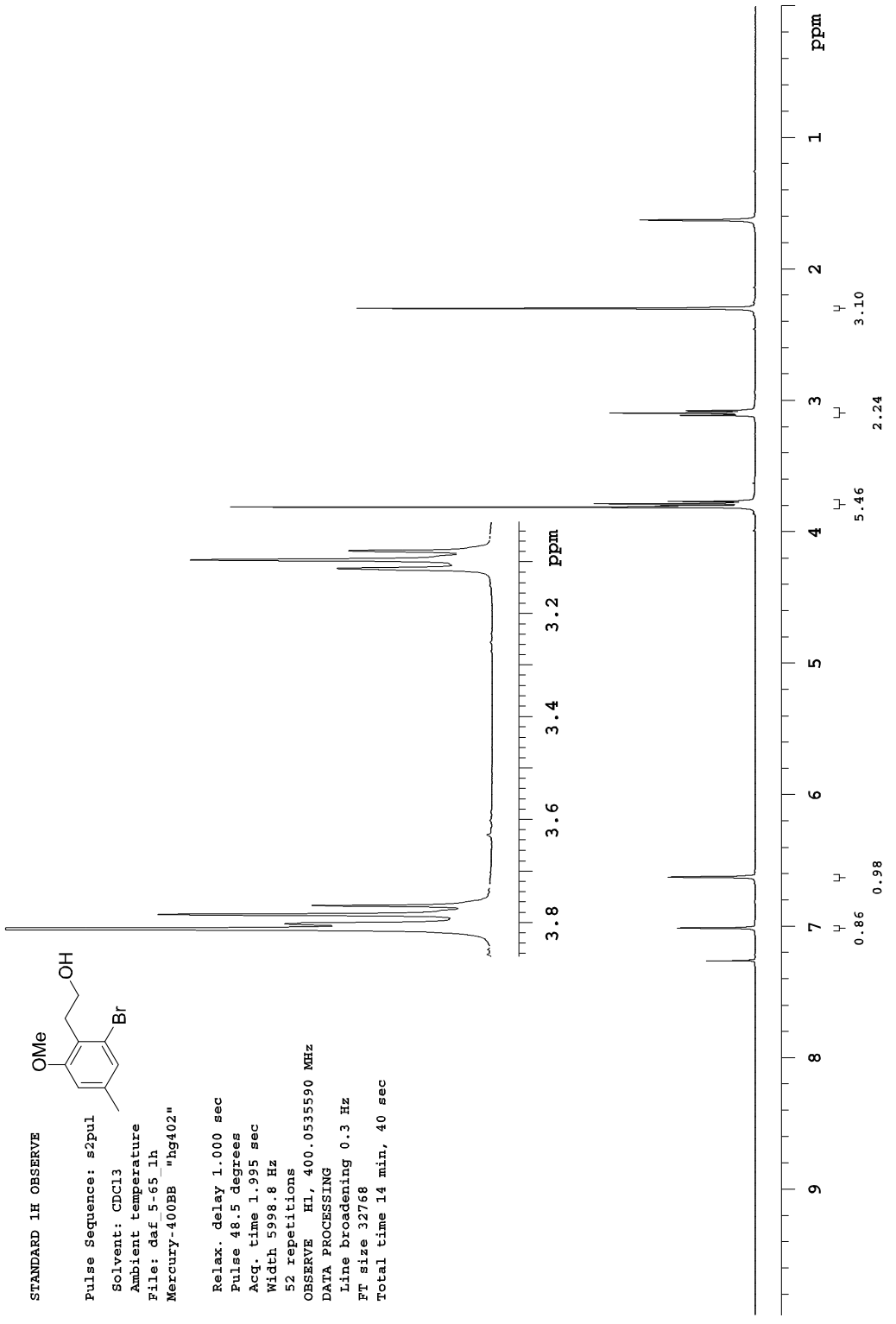
Spectrum 2.29 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **449**



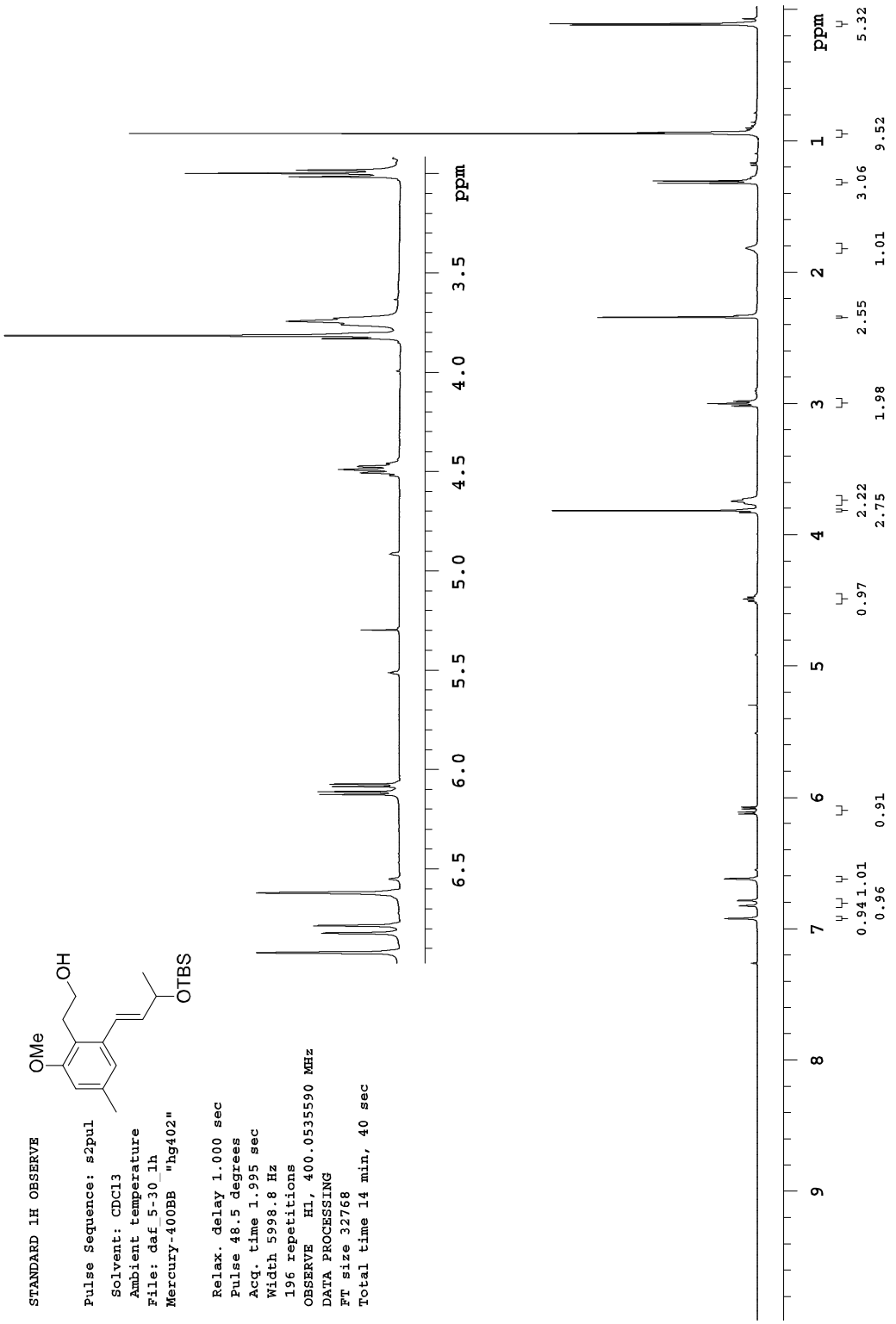
Spectrum 2.30 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **450**



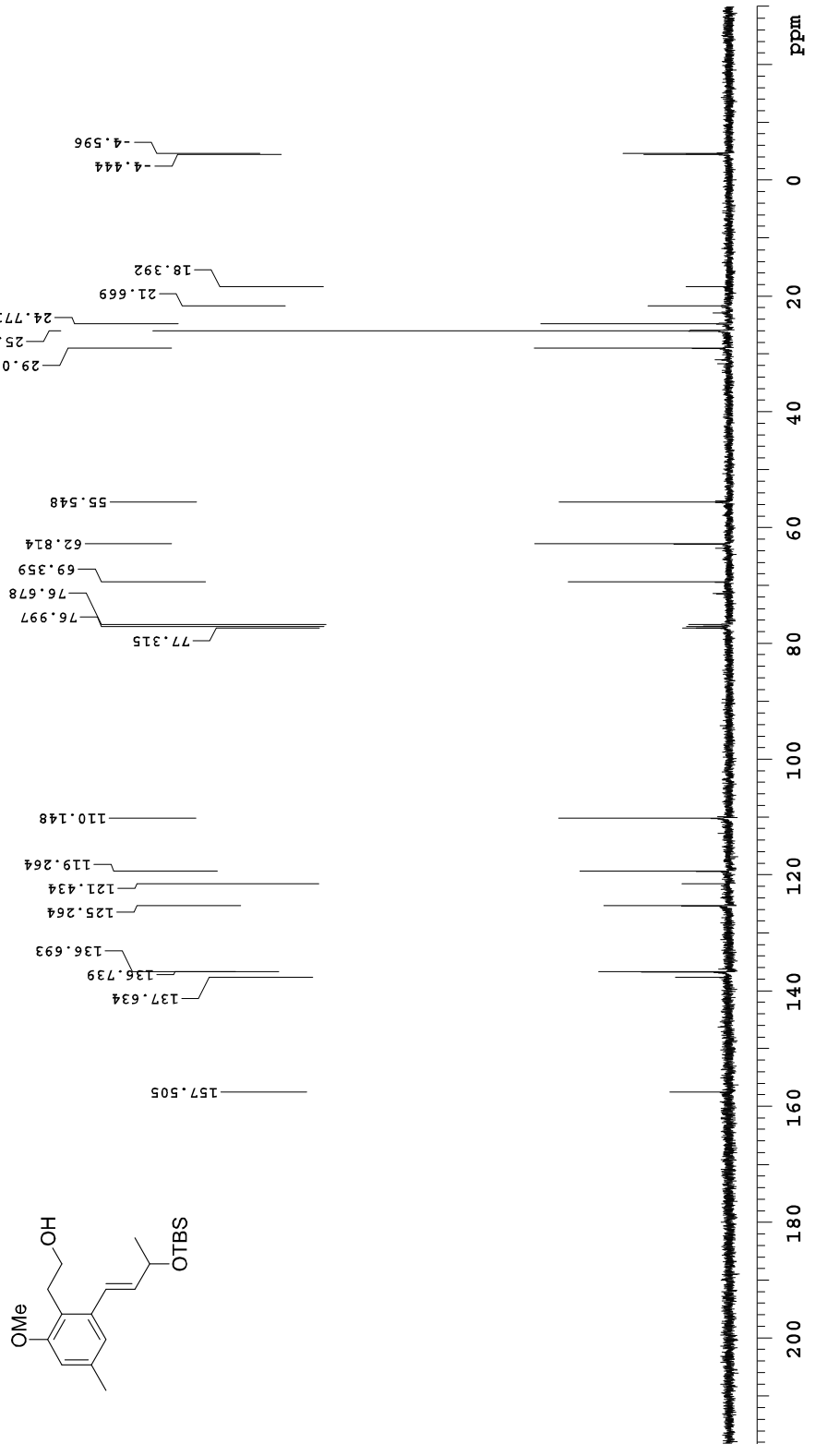
Spectrum 2.31 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **450**



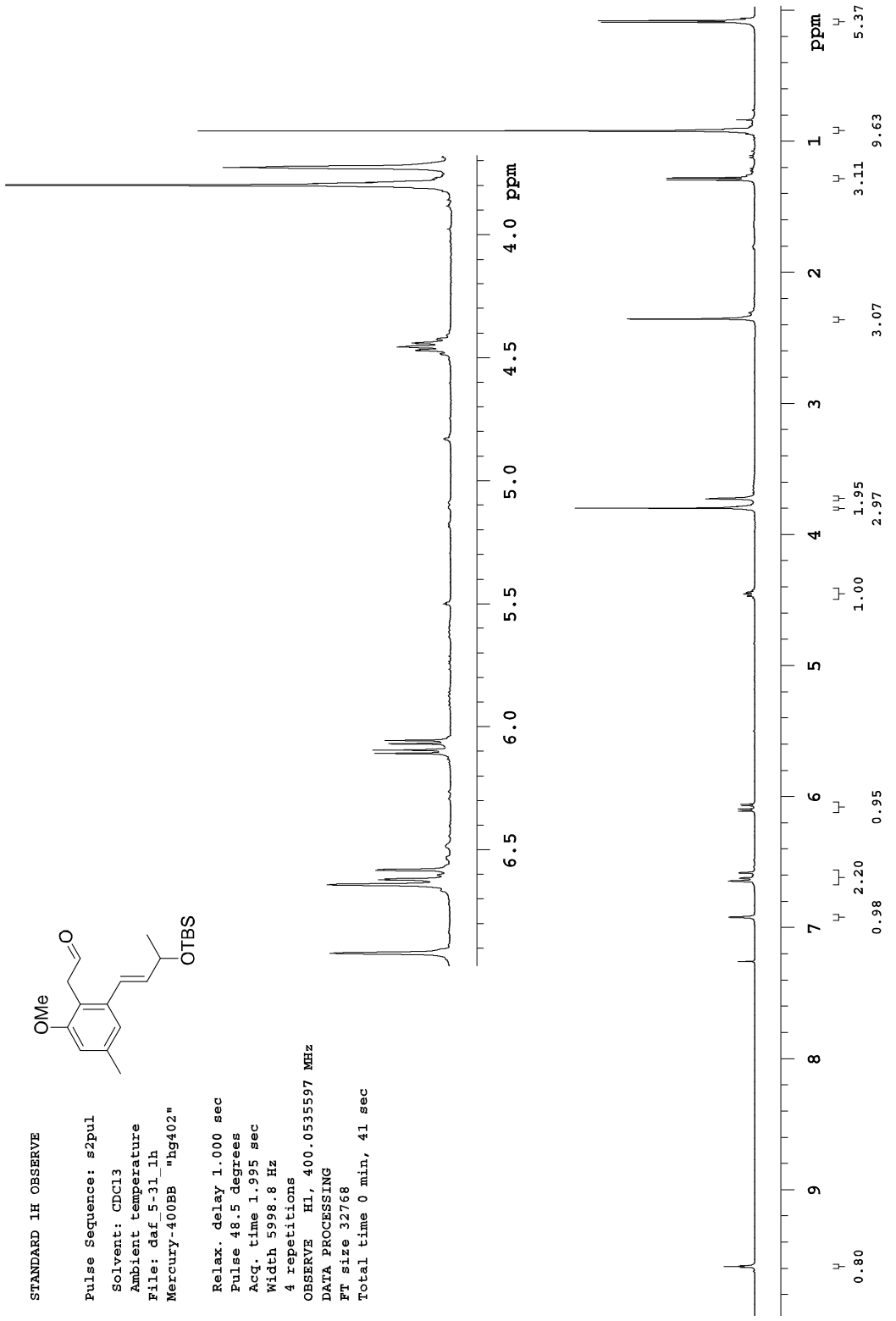
Spectrum 2.32 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **451**



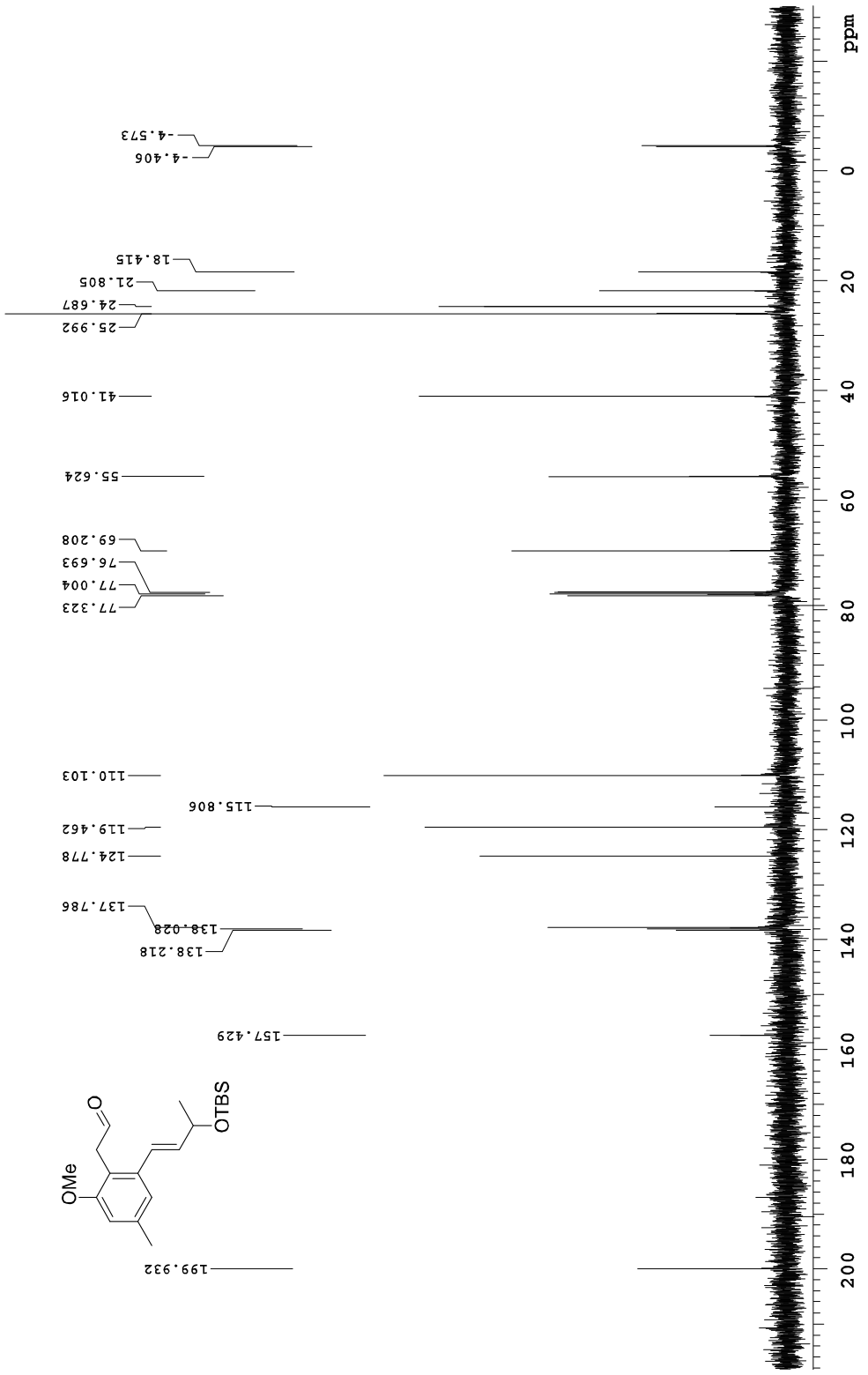
Spectrum 2.33 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **452**



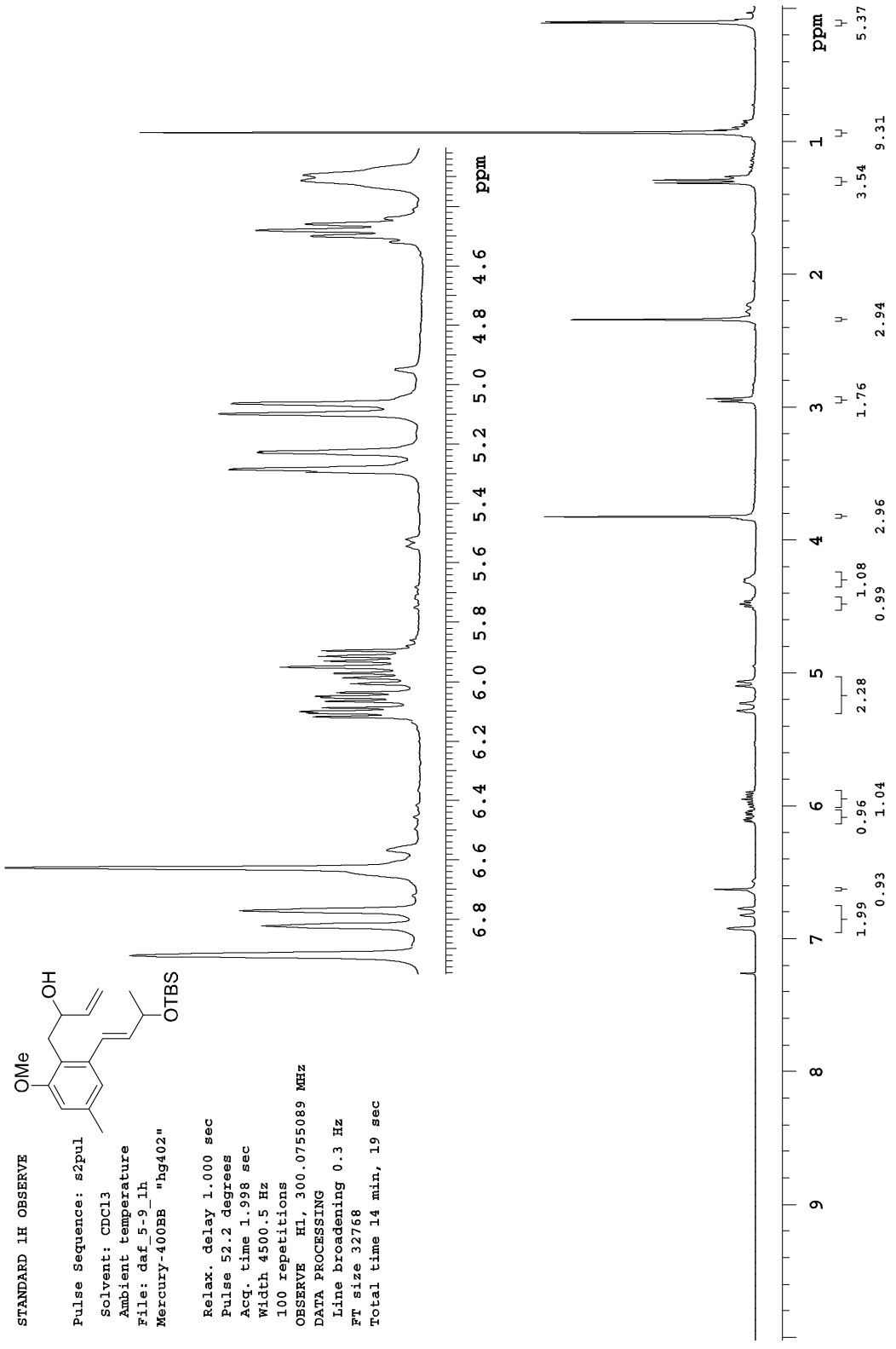
Spectrum 2.34 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **452**



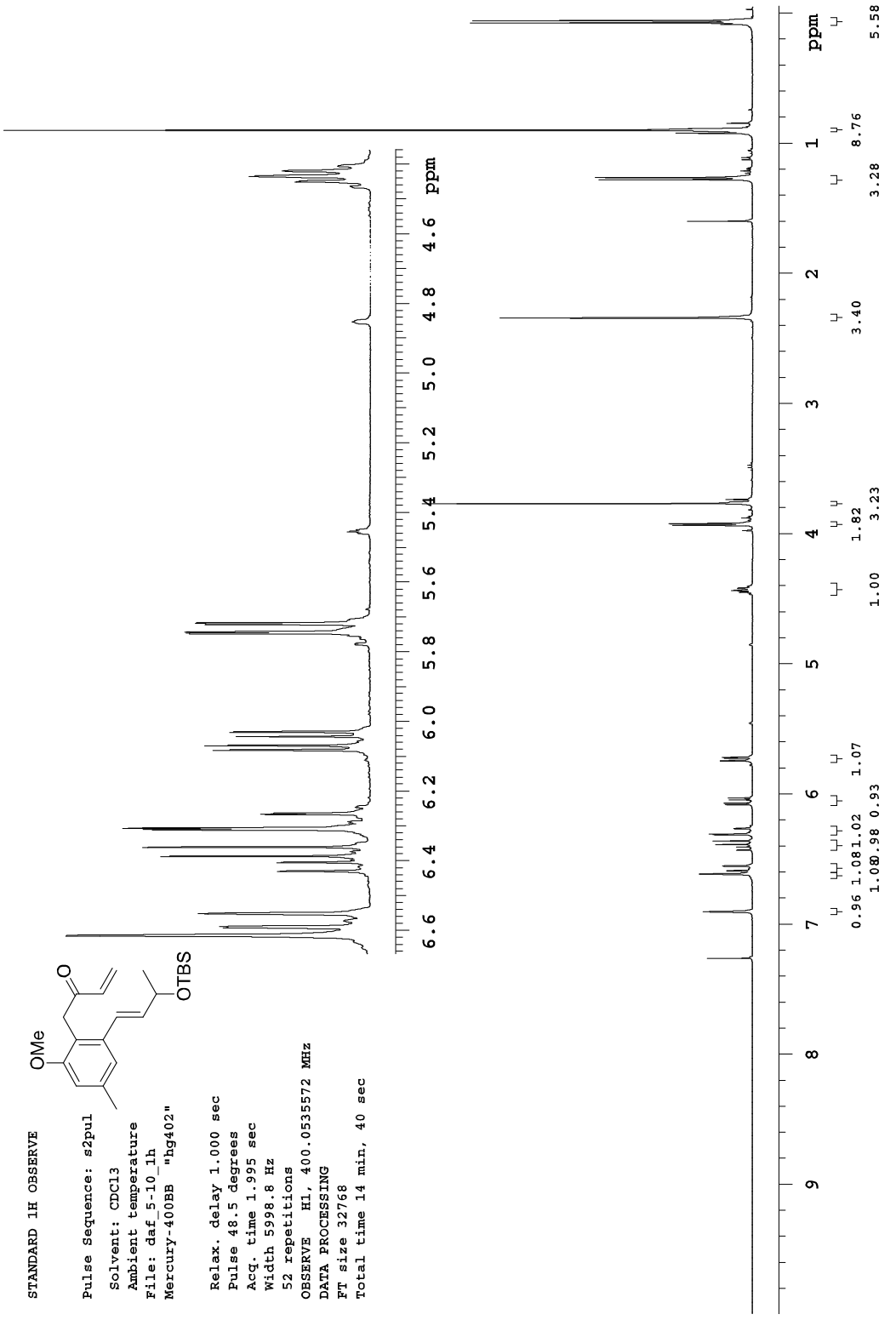
Spectrum 2.35 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **453**



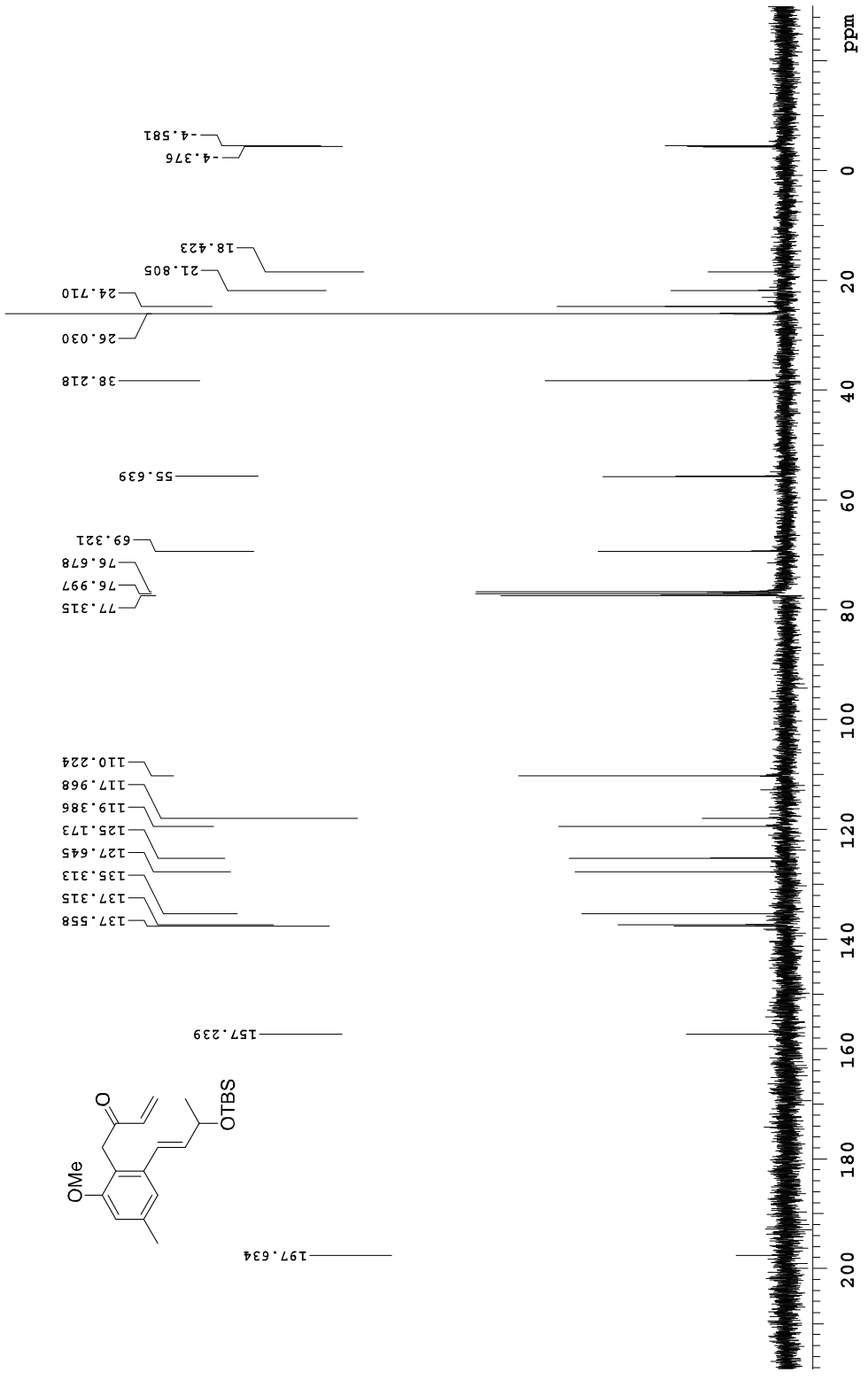
Spectrum 2.36 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **453**



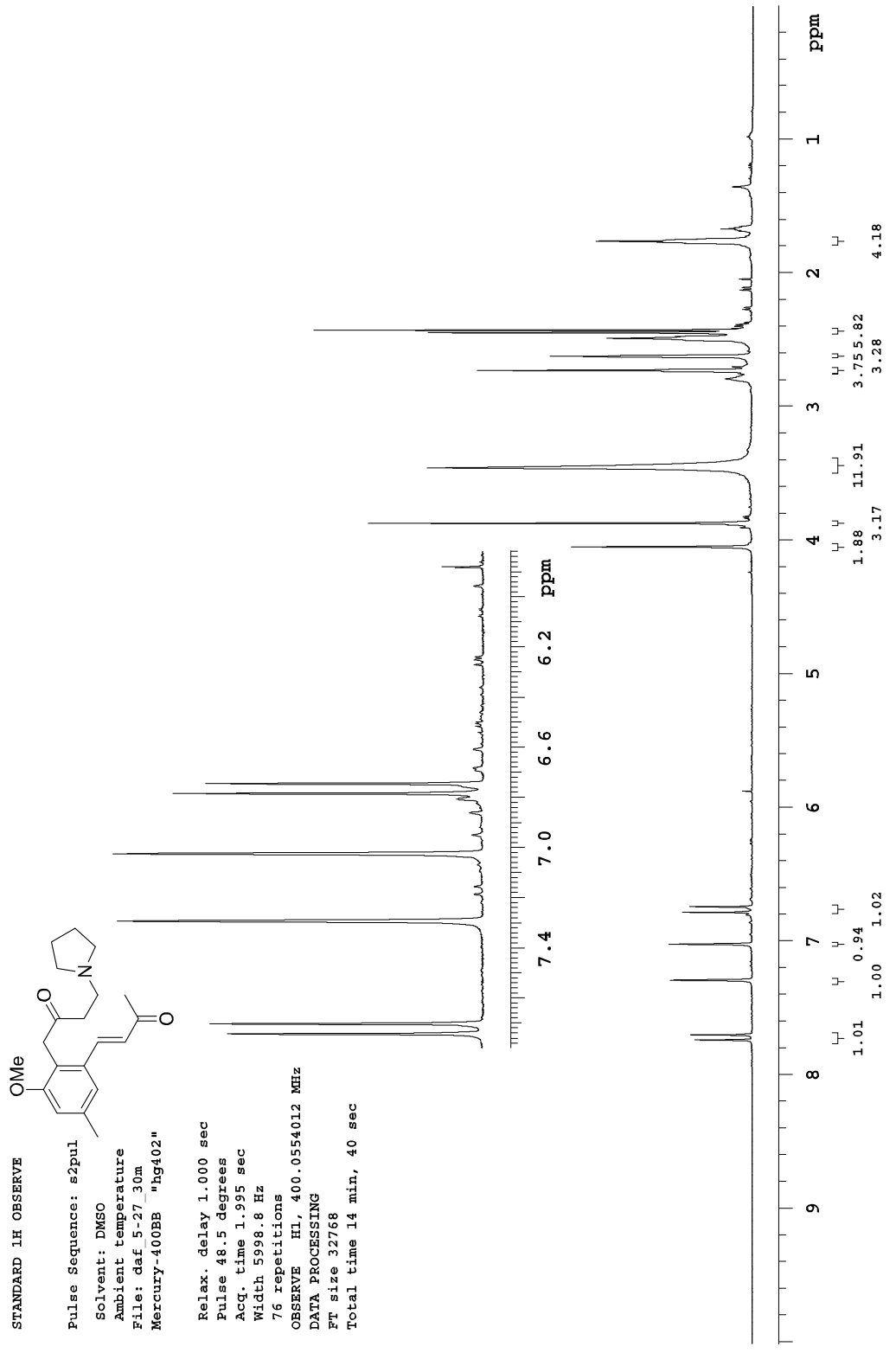
Spectrum 2.37 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **454**



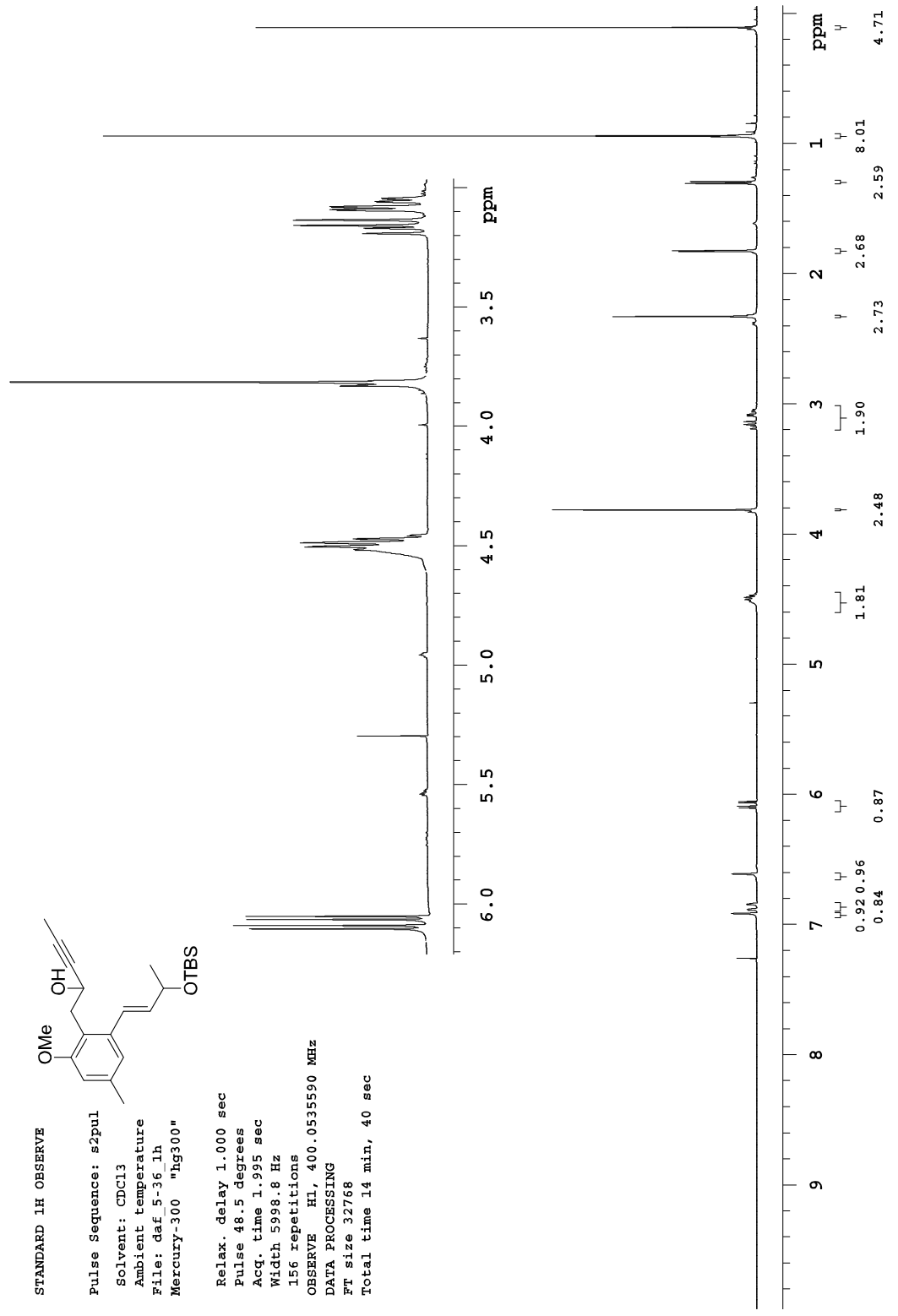
Spectrum 2.38 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **455**



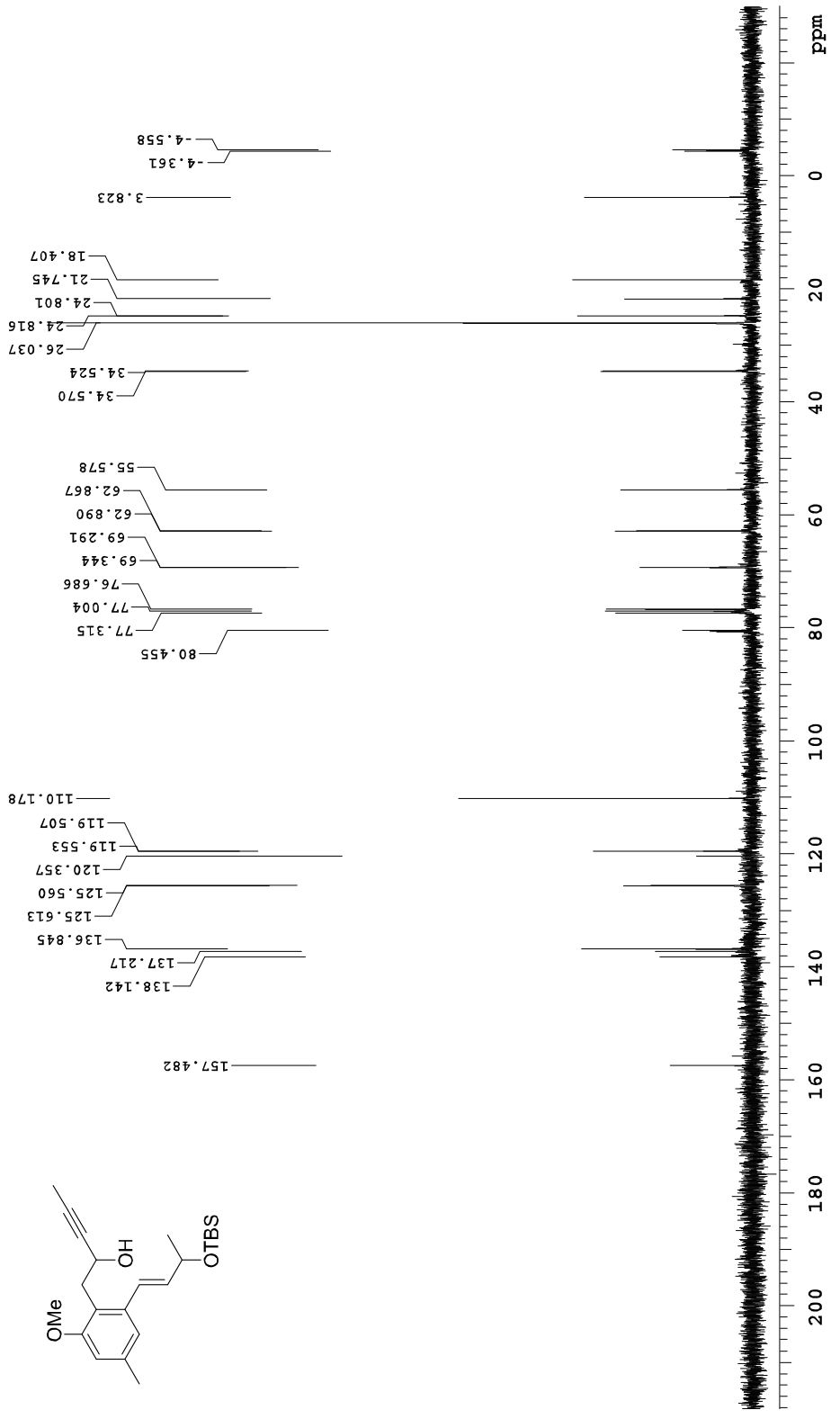
Spectrum 2.39 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **455**



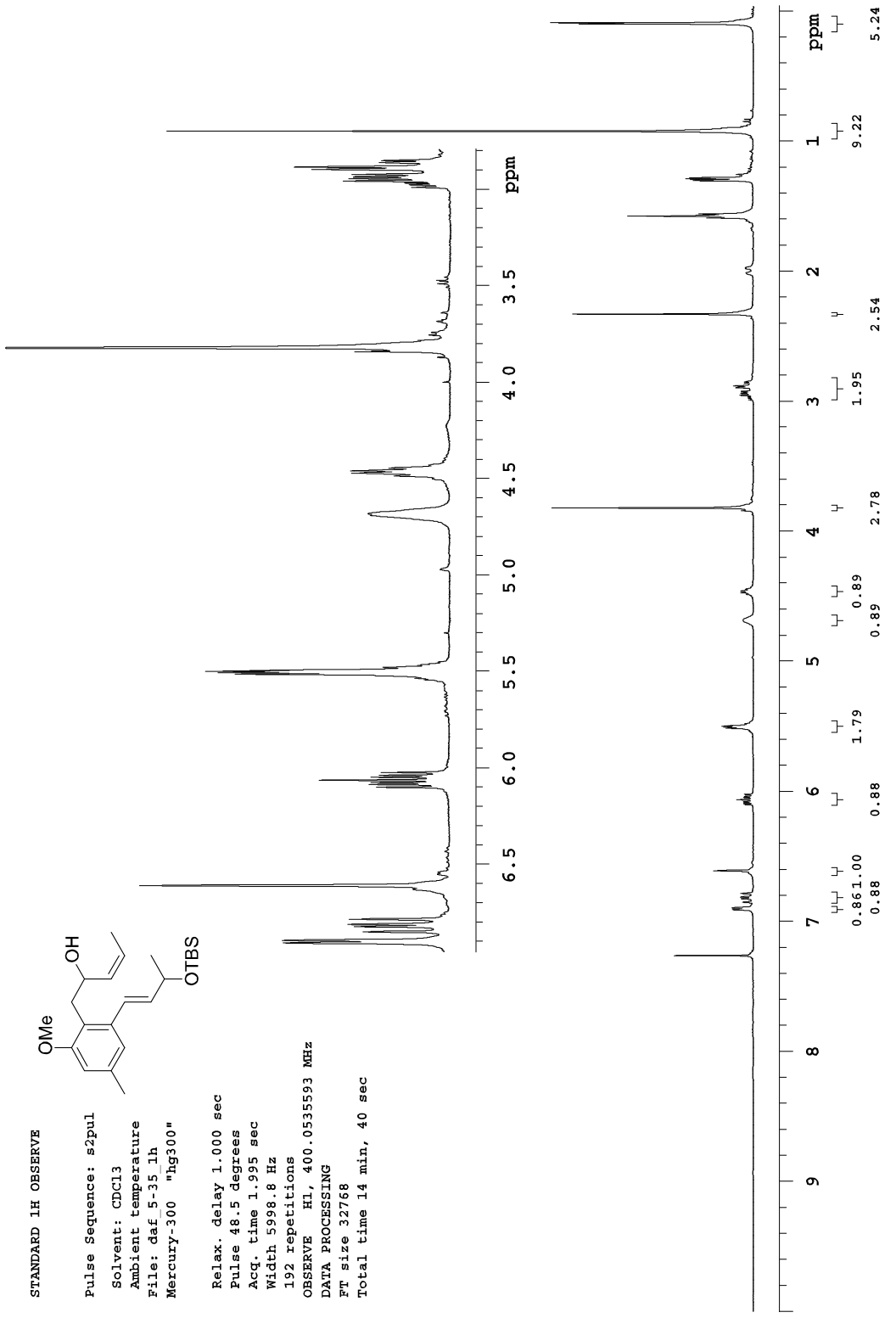
Spectrum 2.40 ^{1}H NMR (DMSO-d6, 400 MHz) of compound **457**



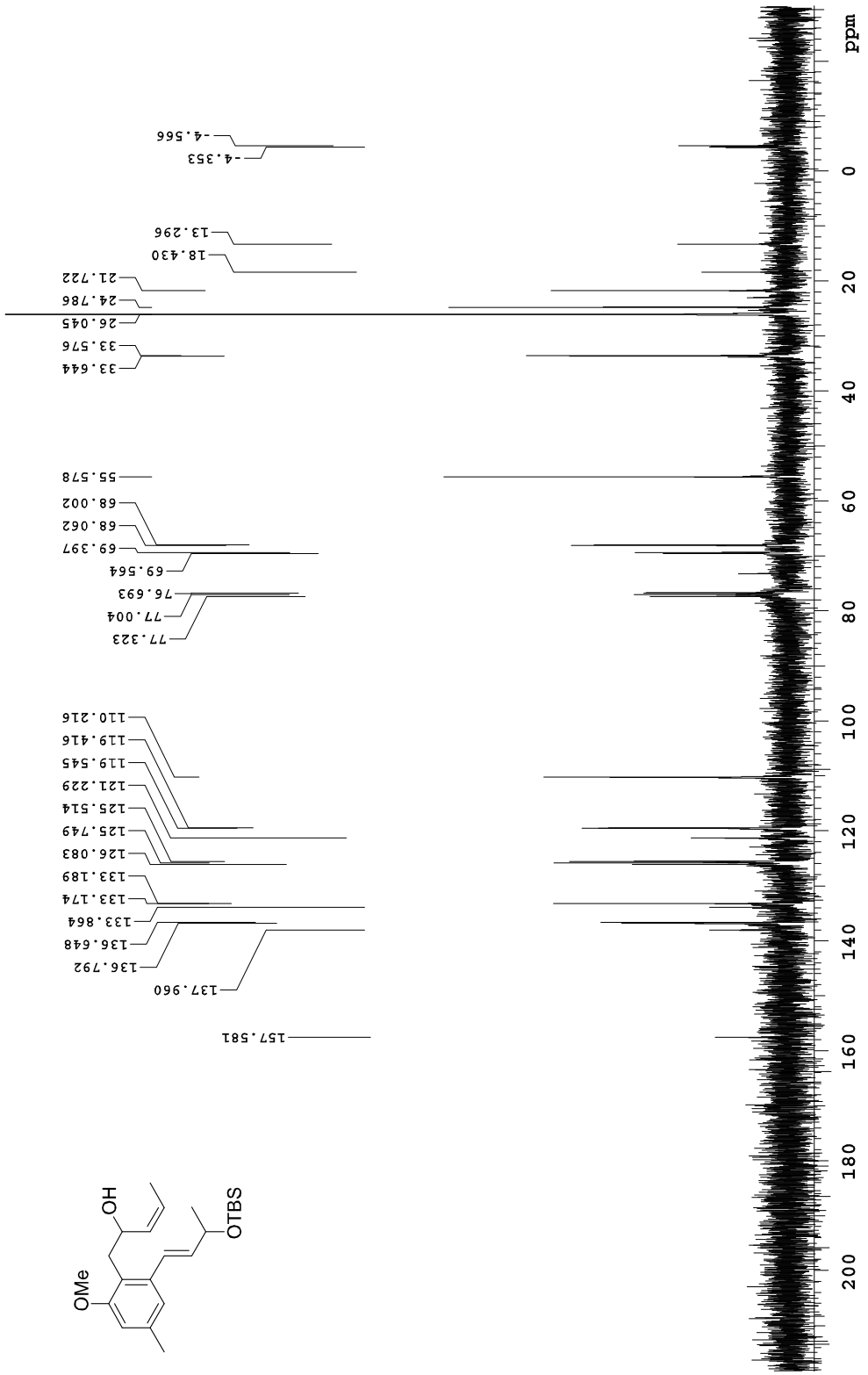
Spectrum 2.41 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **458**



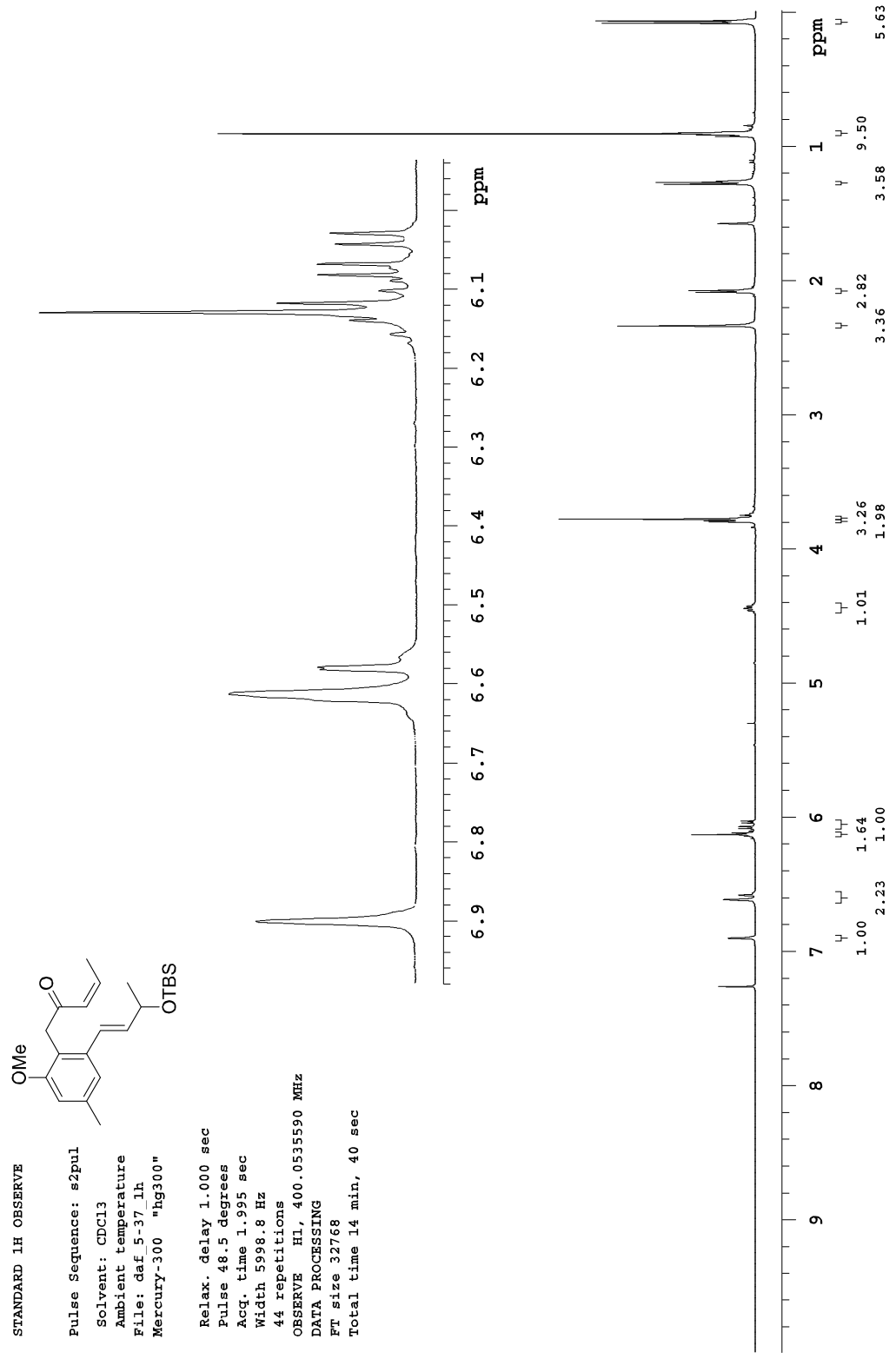
Spectrum 2.42 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **458**



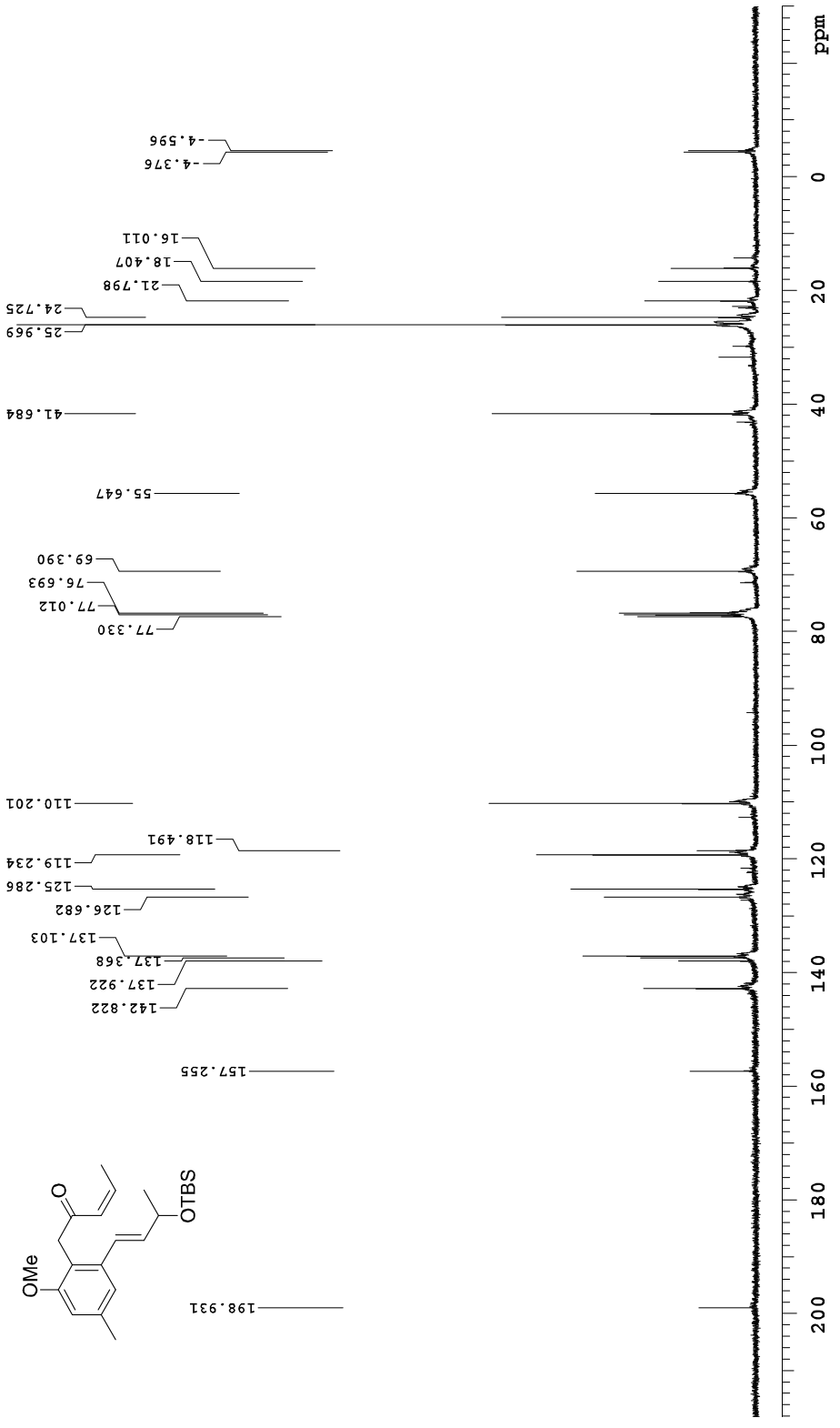
Spectrum 2.43 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **459**



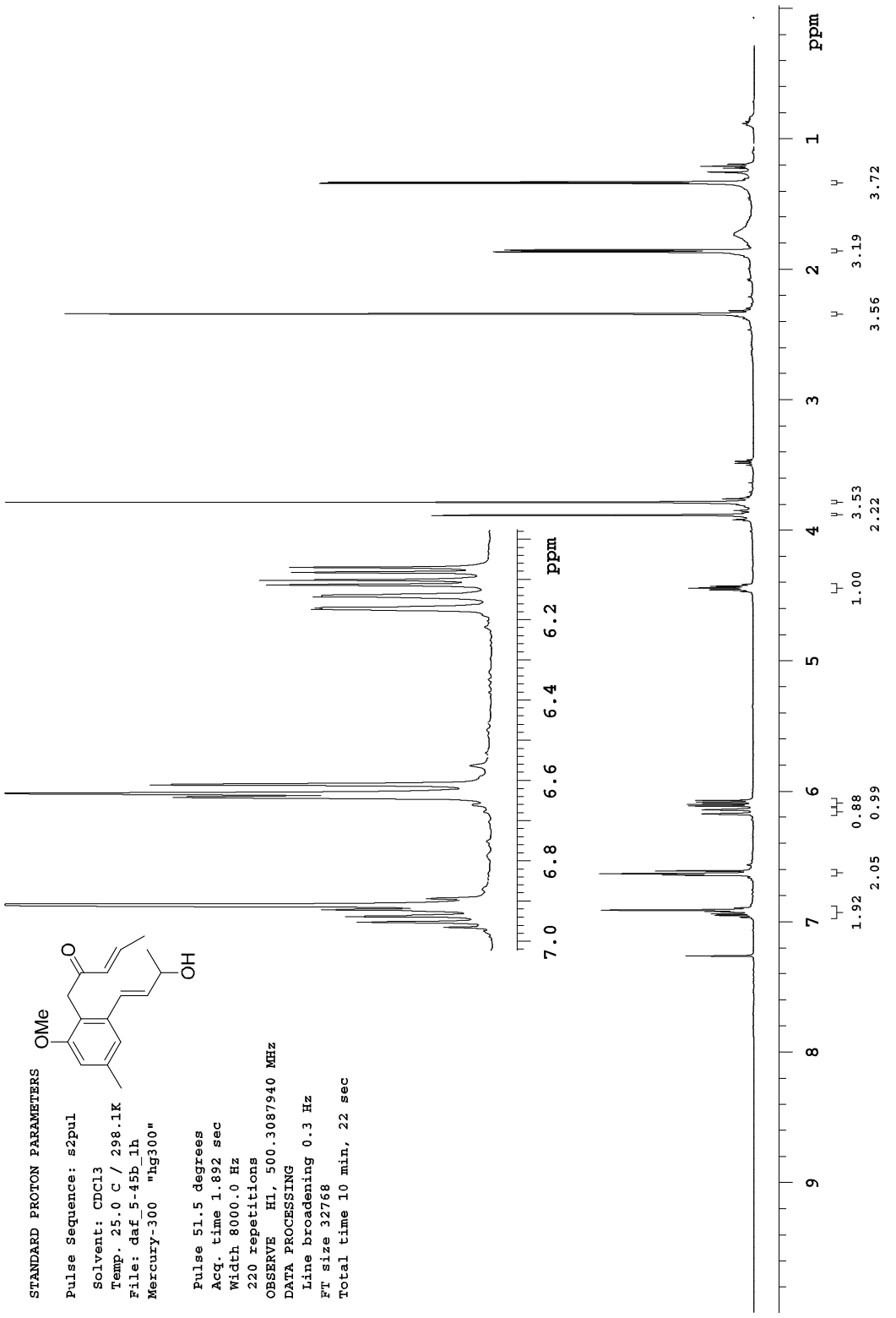
Spectrum 2.44 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **459**



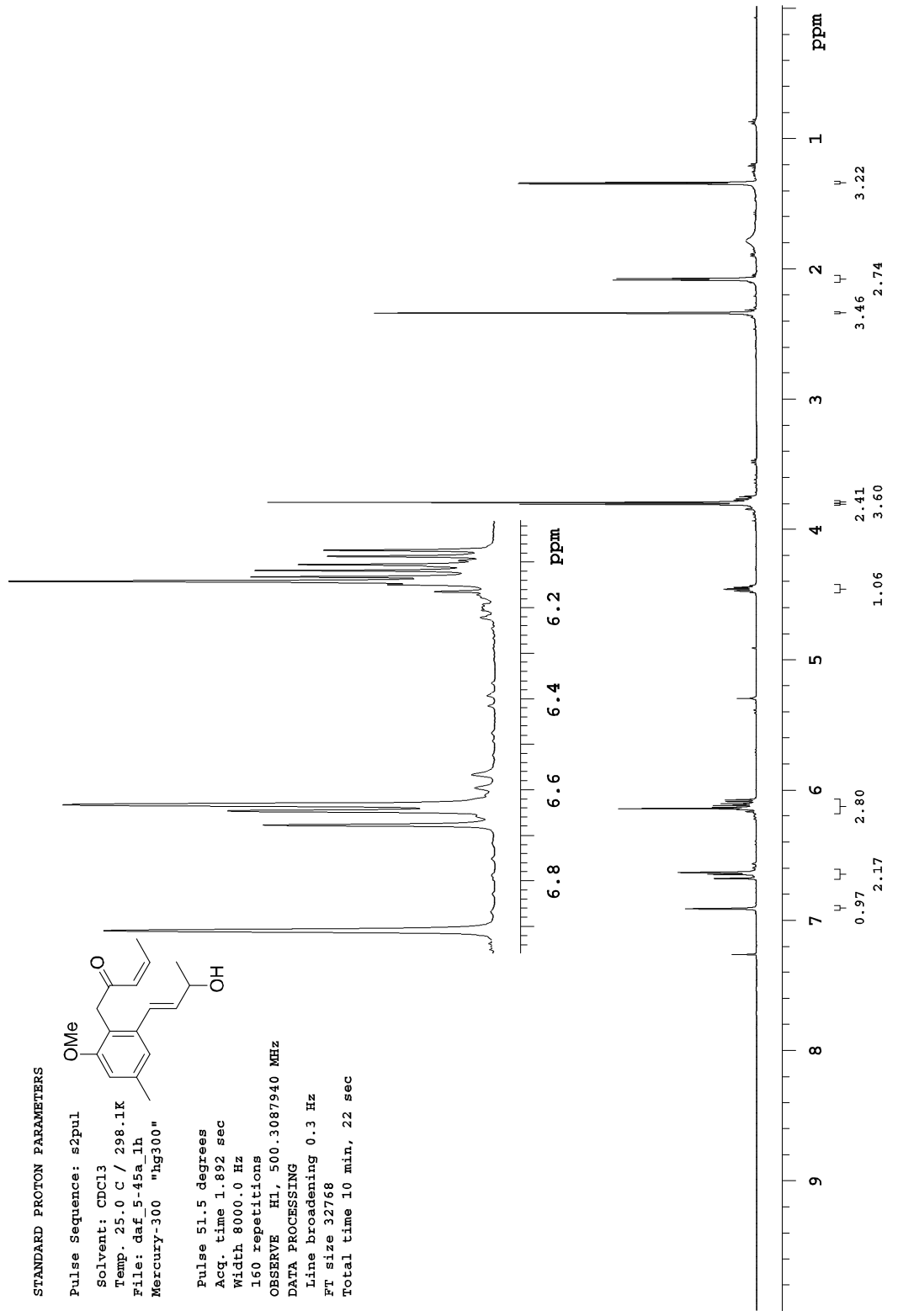
Spectrum 2.45 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **460**



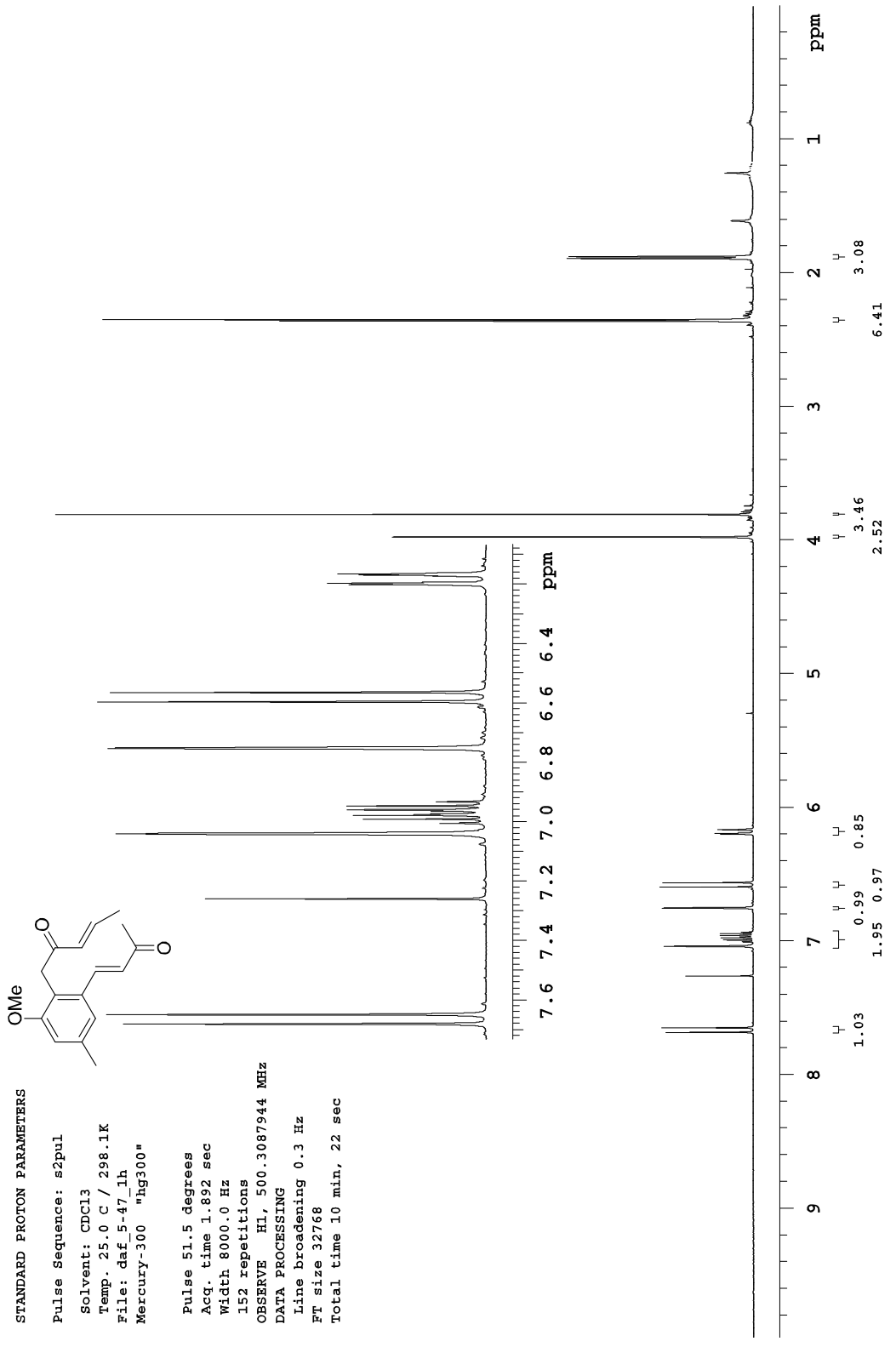
Spectrum 2.46 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **460**



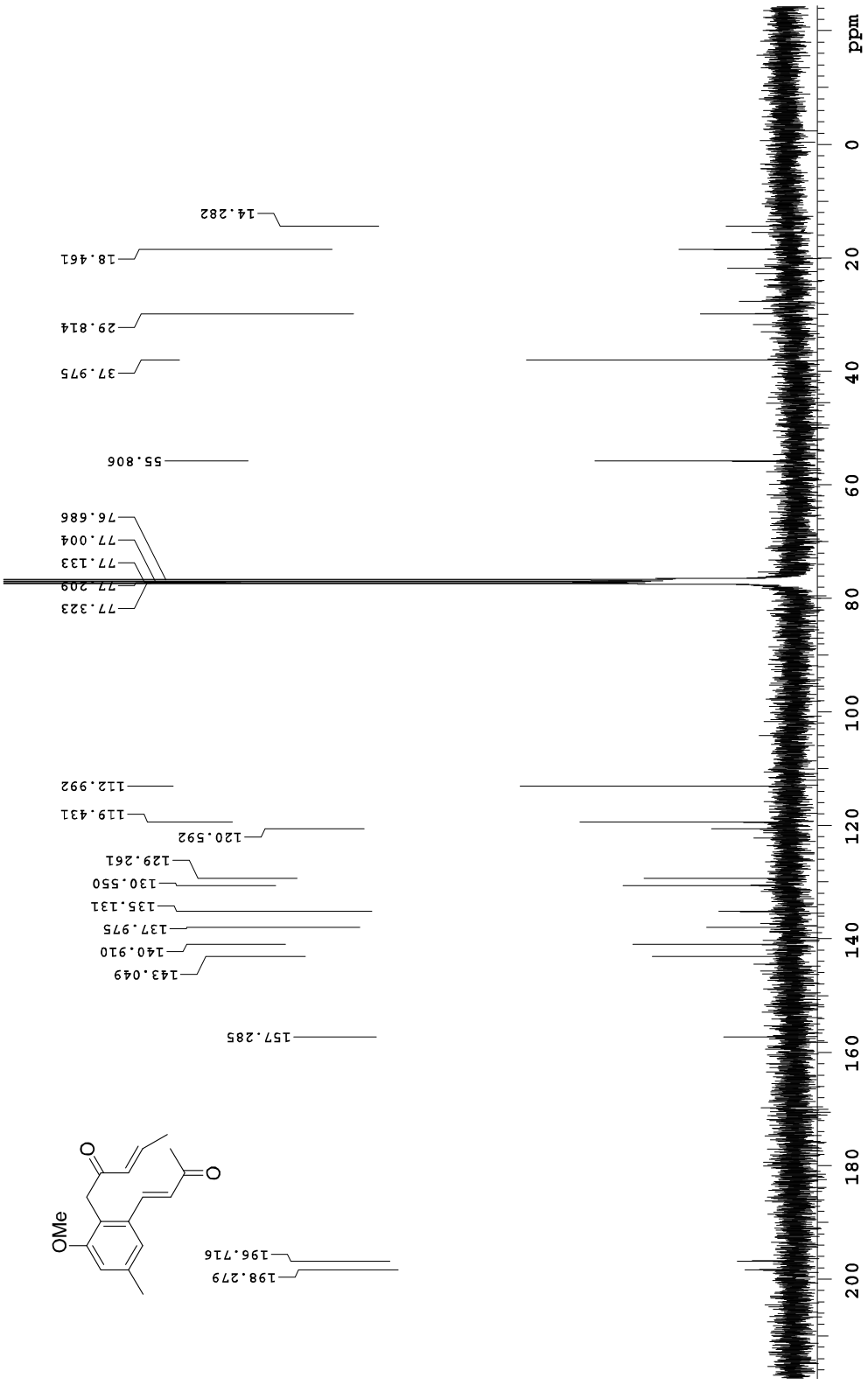
Spectrum 2.47 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **461E**



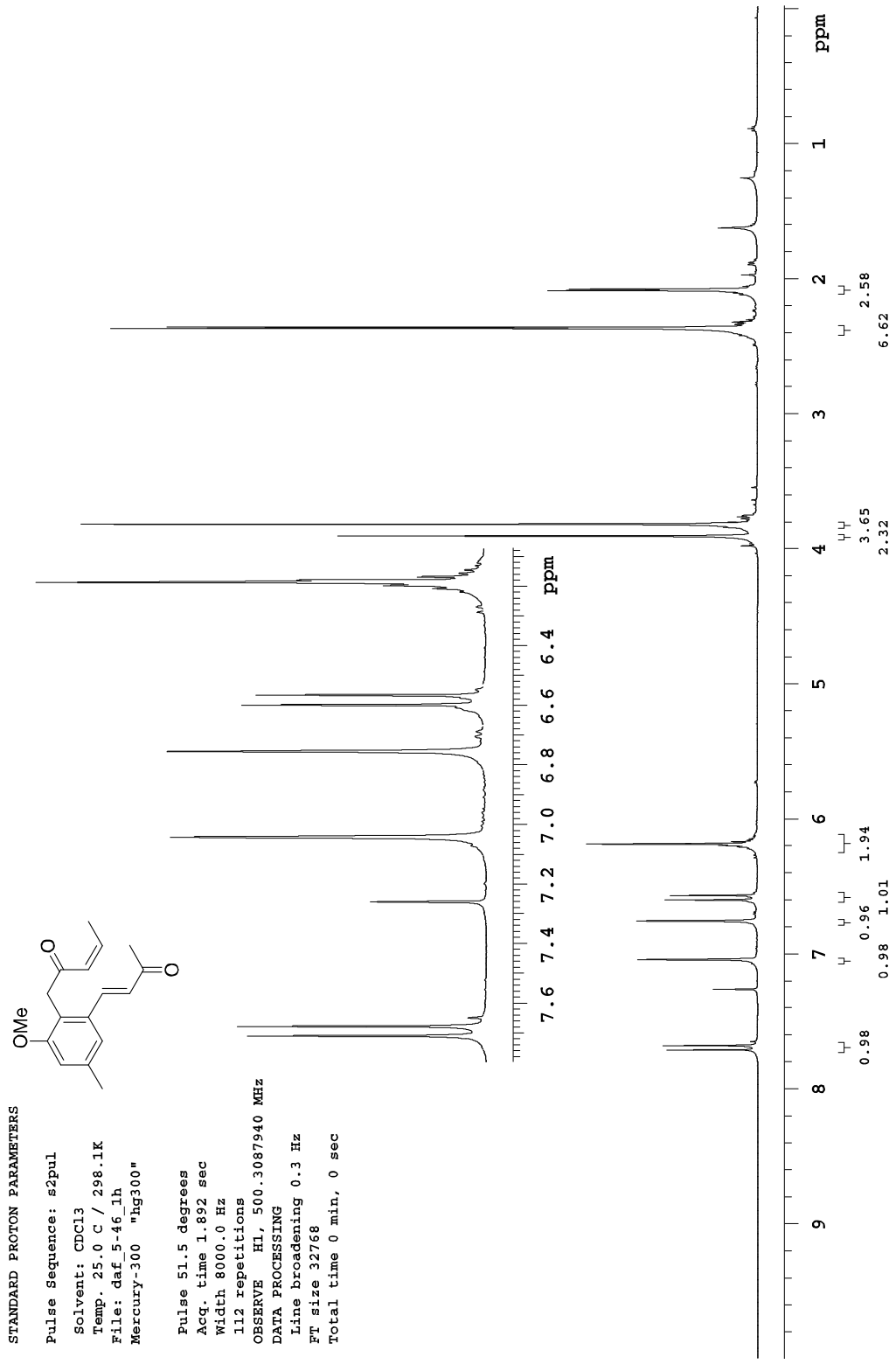
Spectrum 2.48 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **461Z**



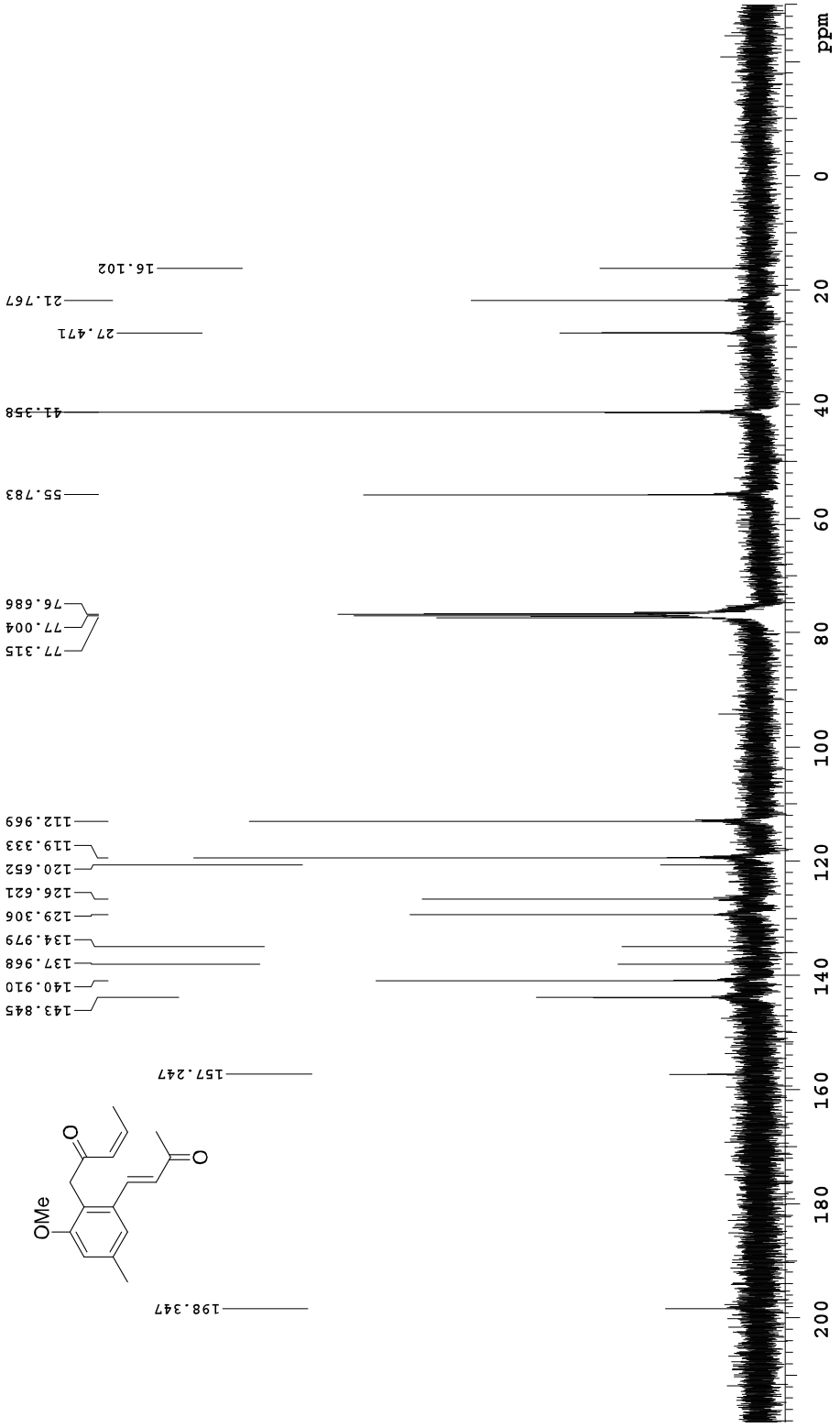
Spectrum 2.49 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **462E**



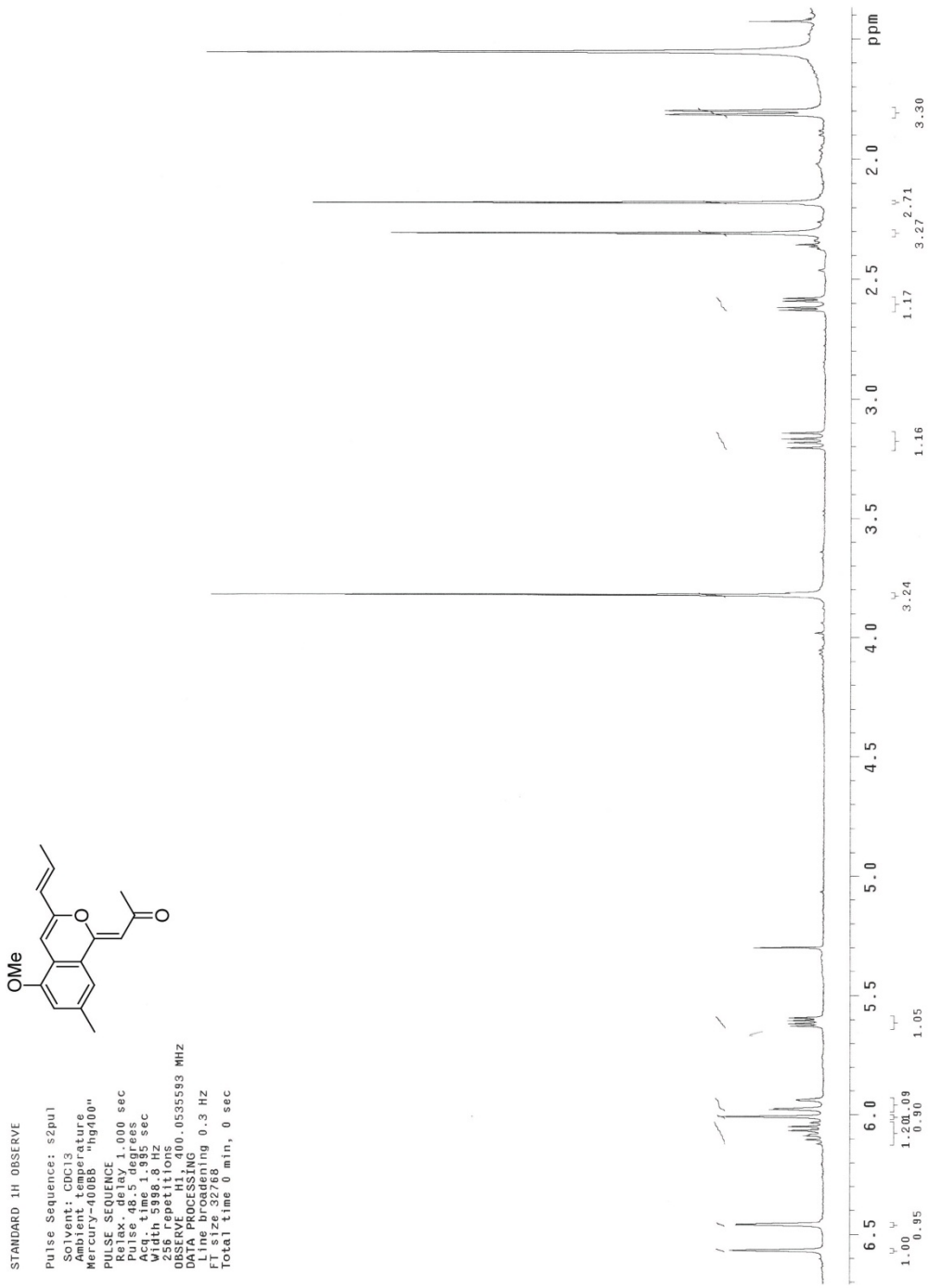
Spectrum 2.50 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **462E**



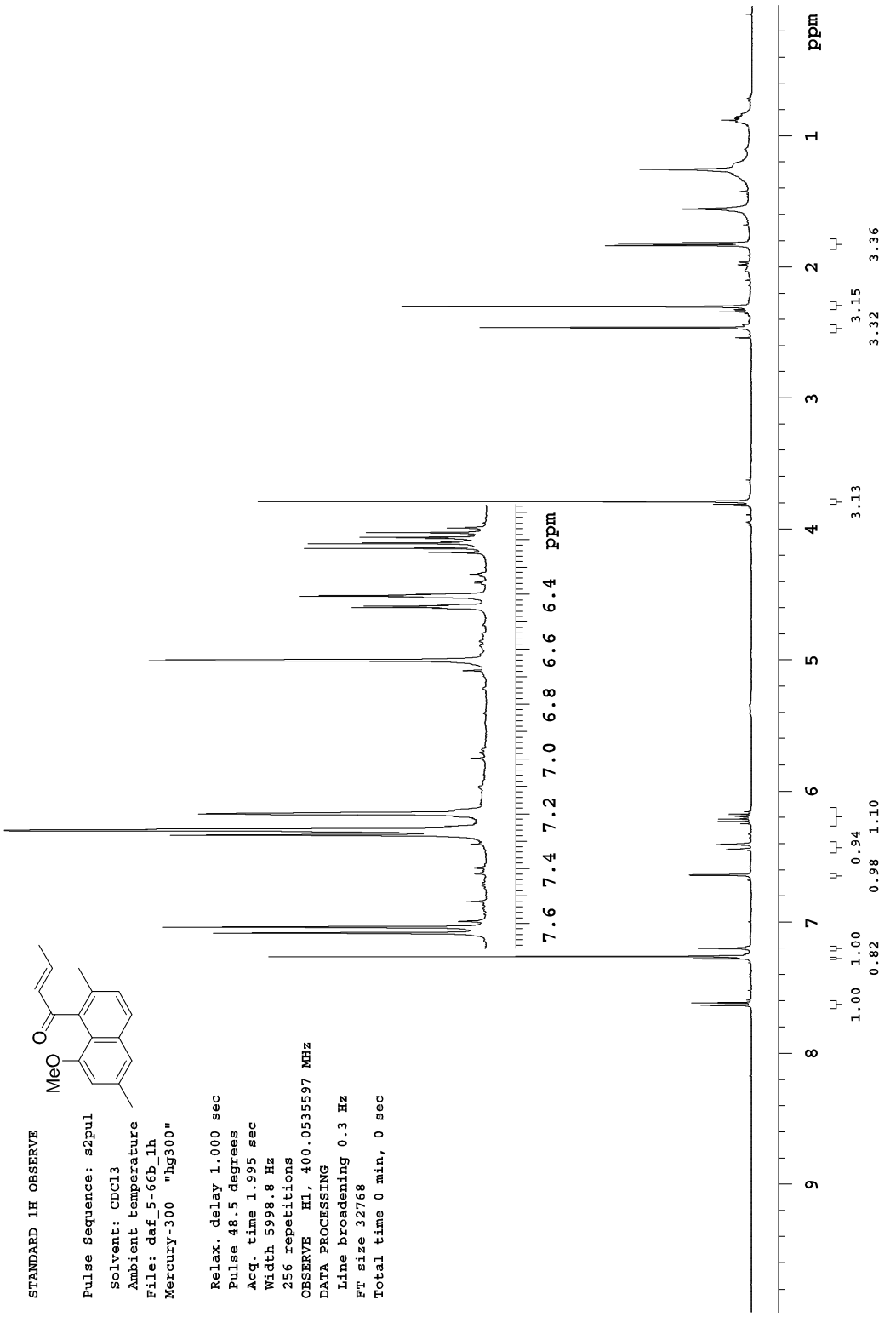
Spectrum 2.51 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **462Z**



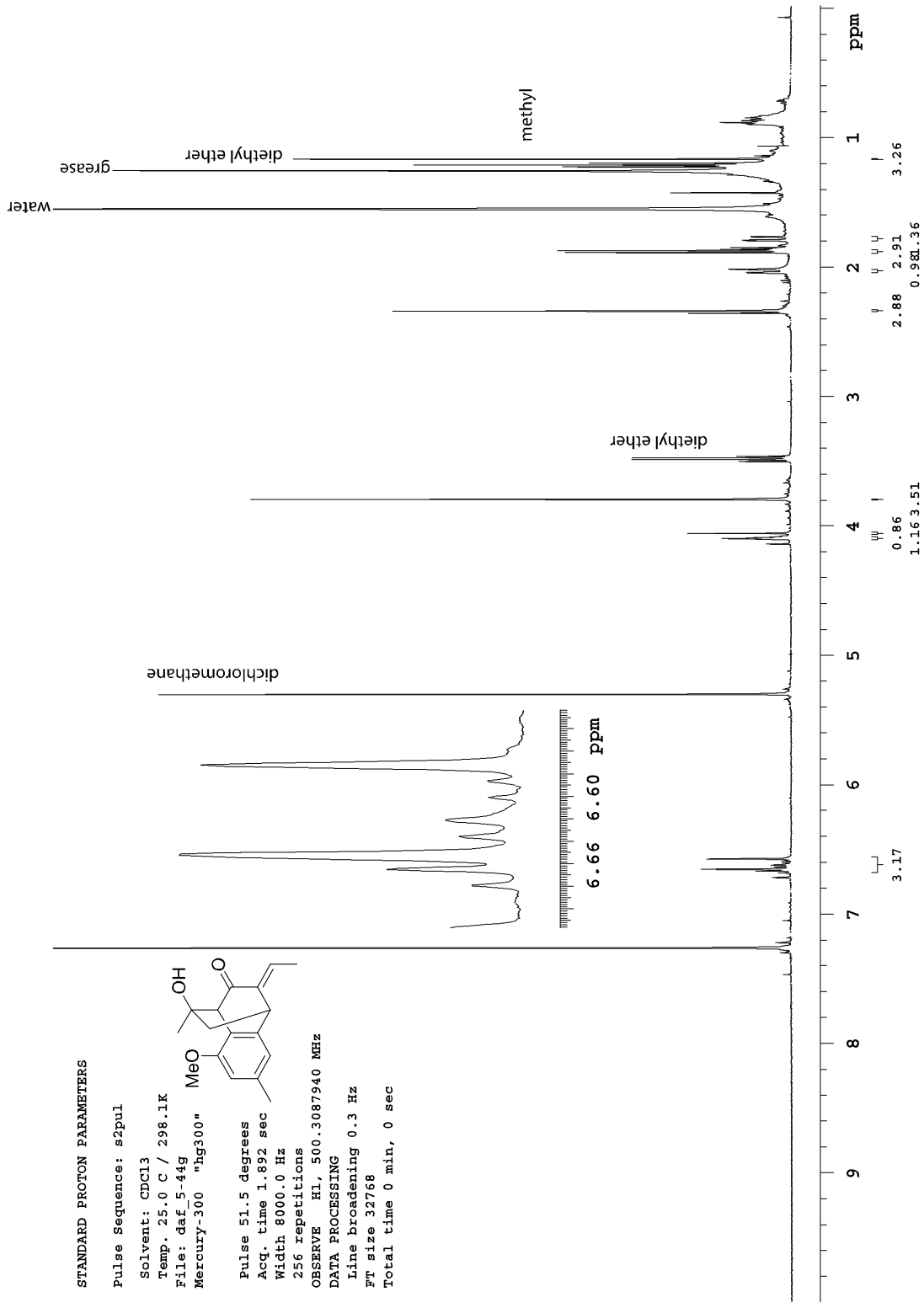
Spectrum 2.52 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **462Z**



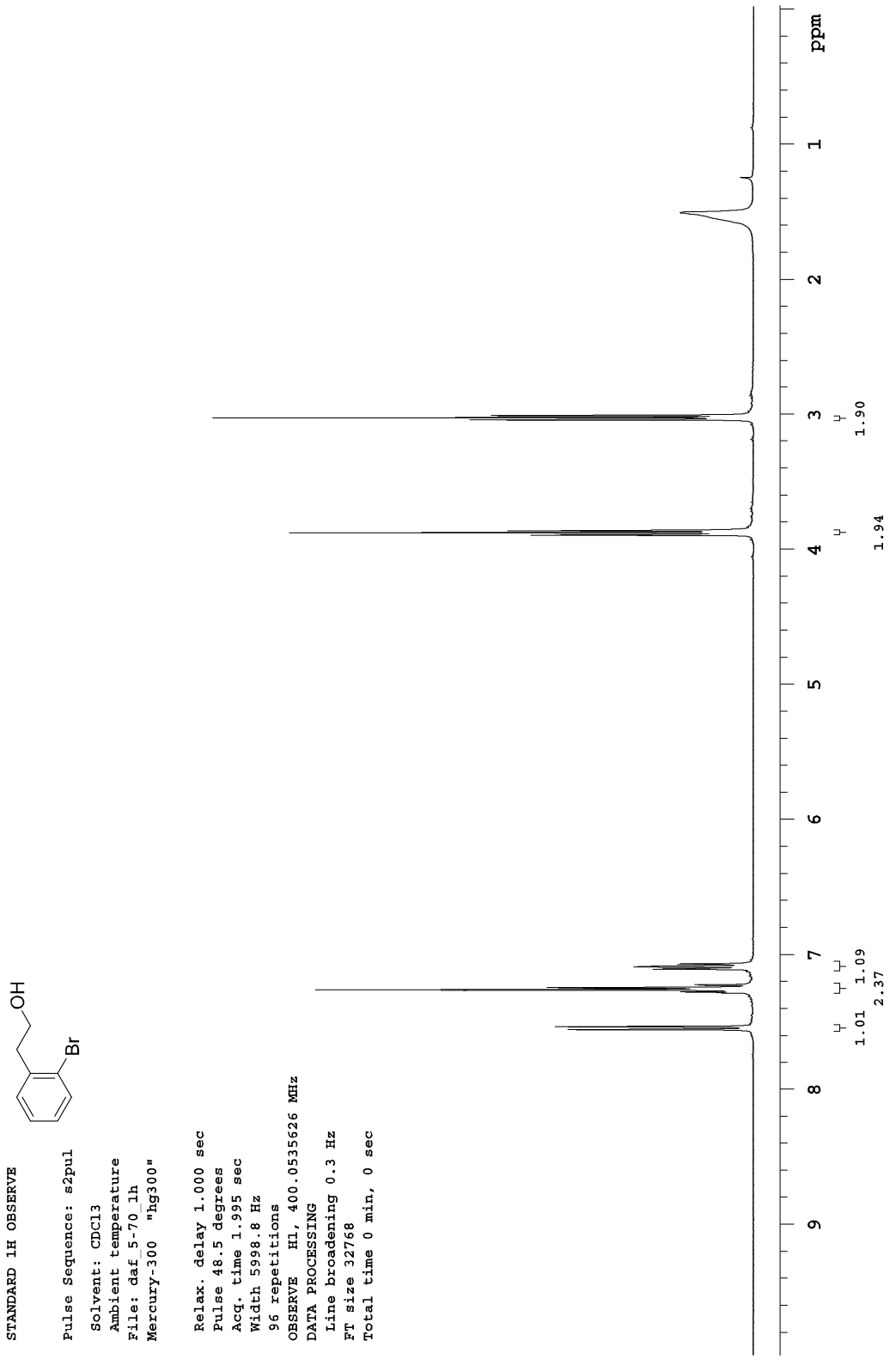
Spectrum 2.53 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **463**



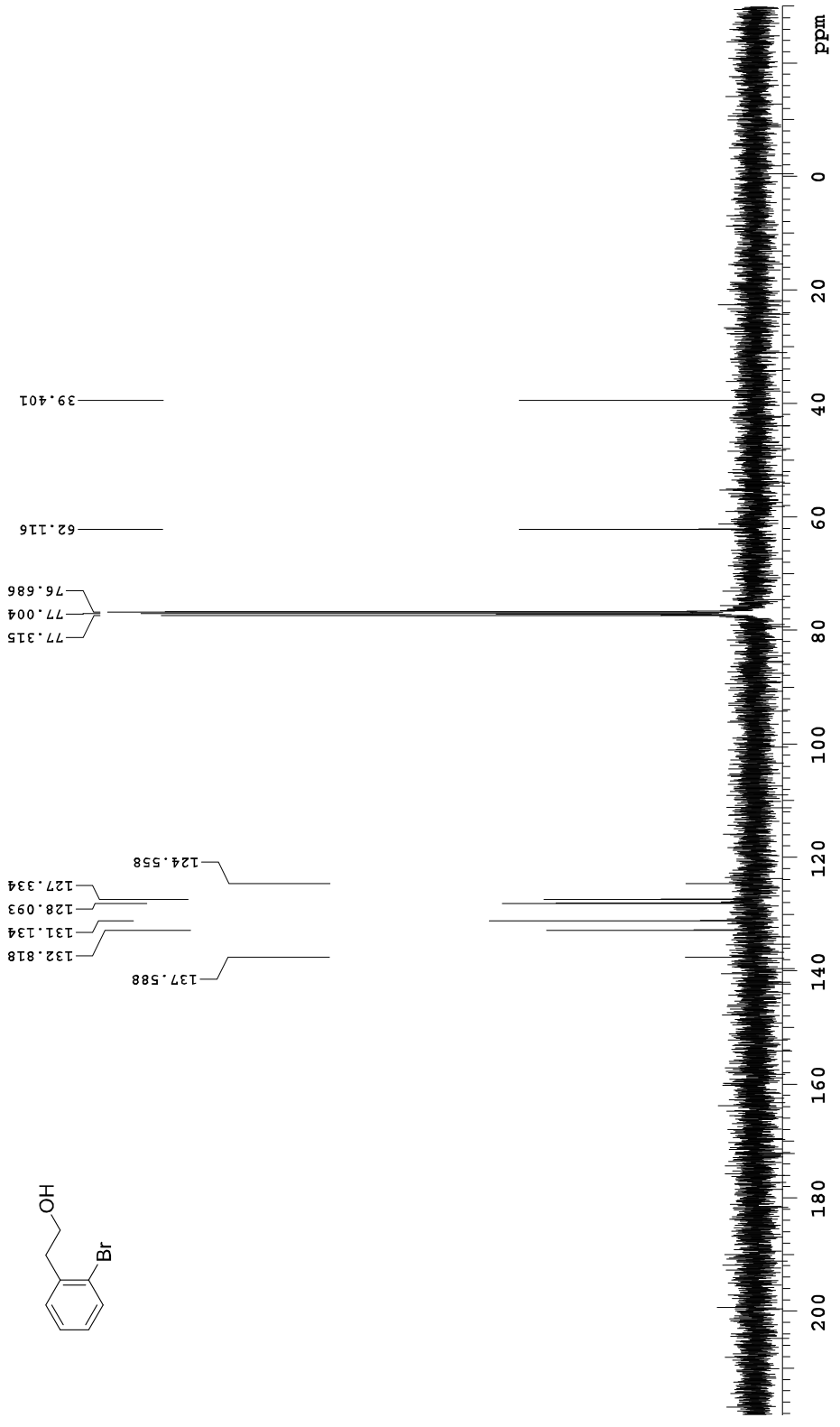
Spectrum 2.54 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **464**



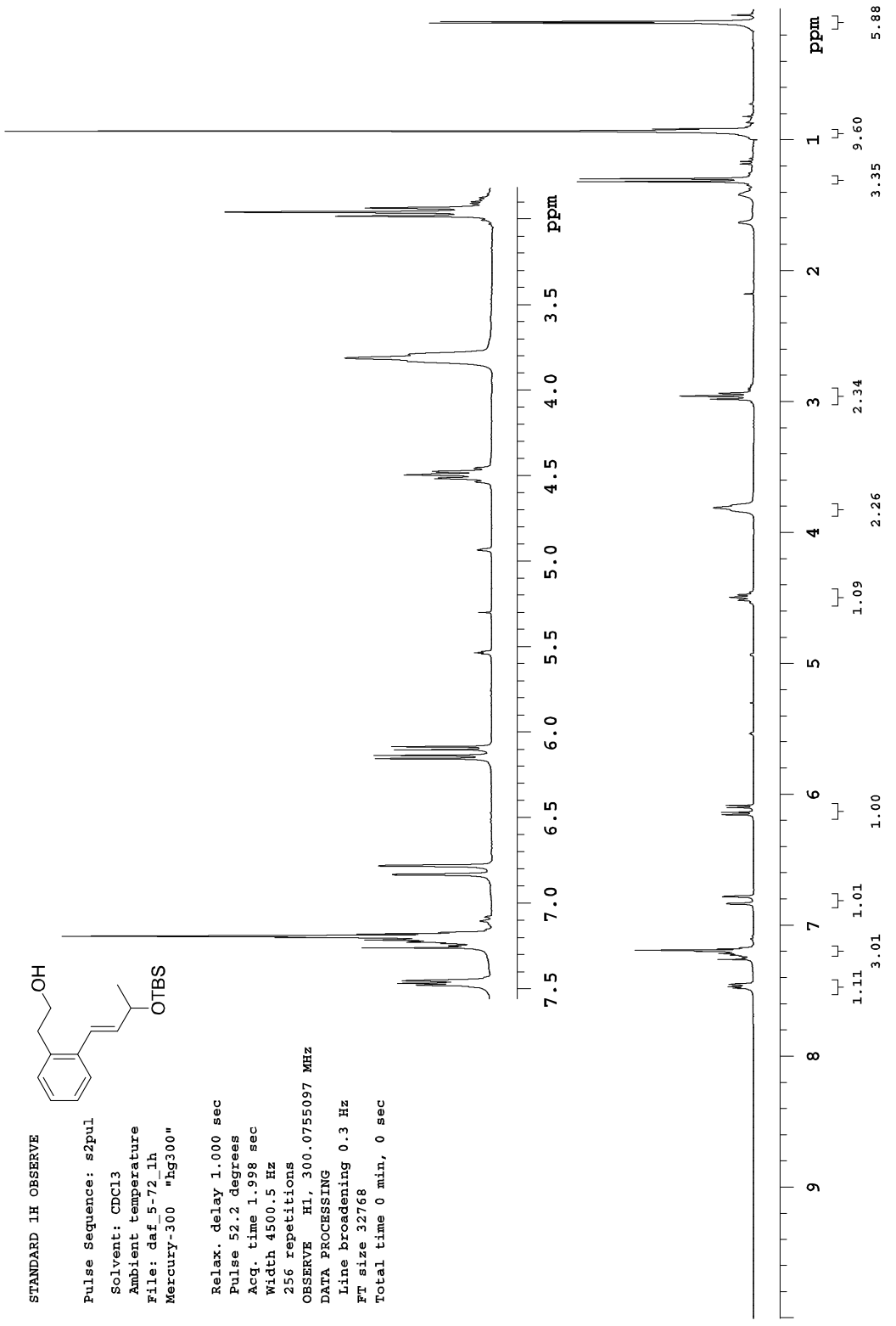
Spectrum 2.55 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **465**



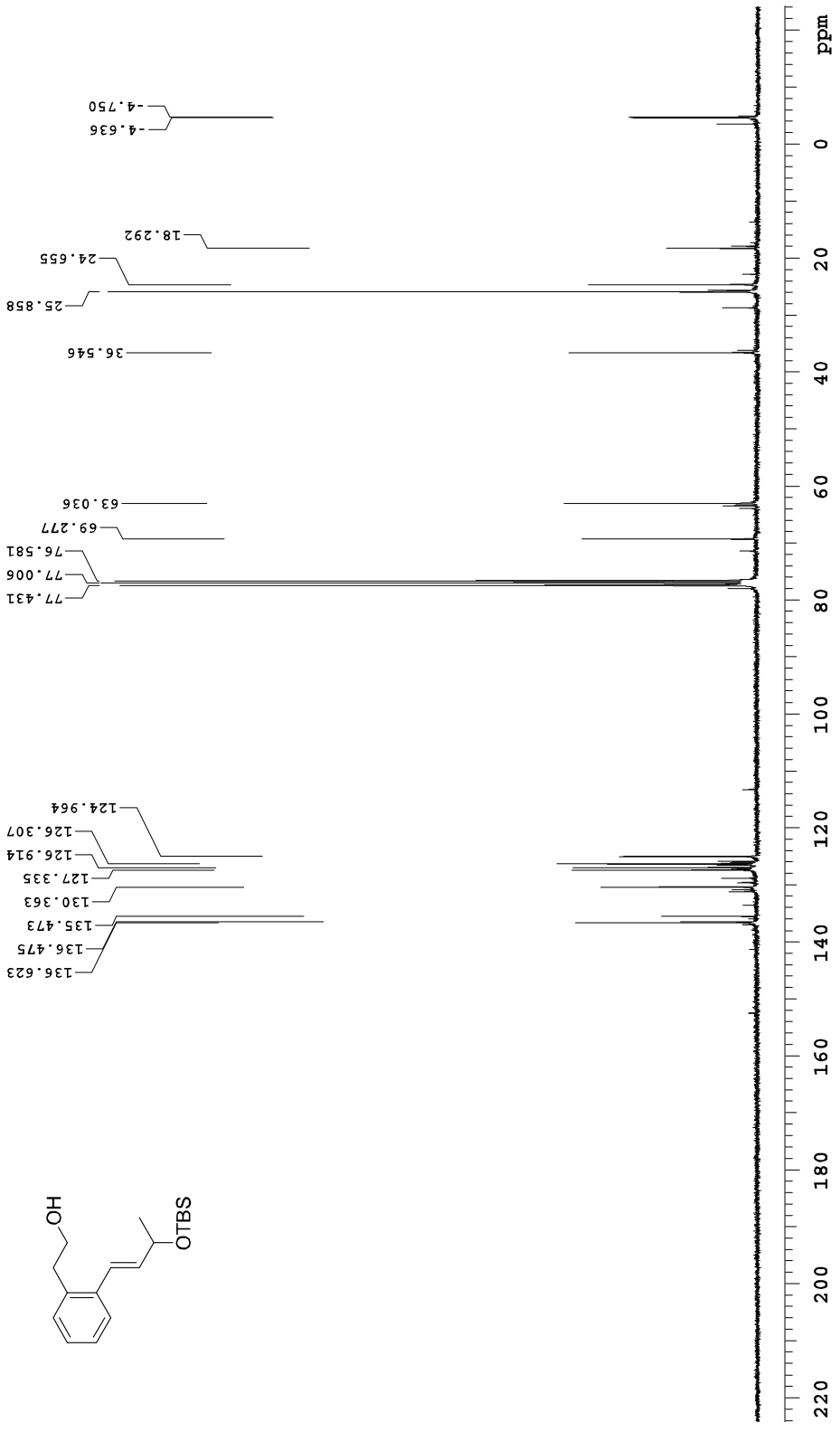
Spectrum 2.56 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **478**



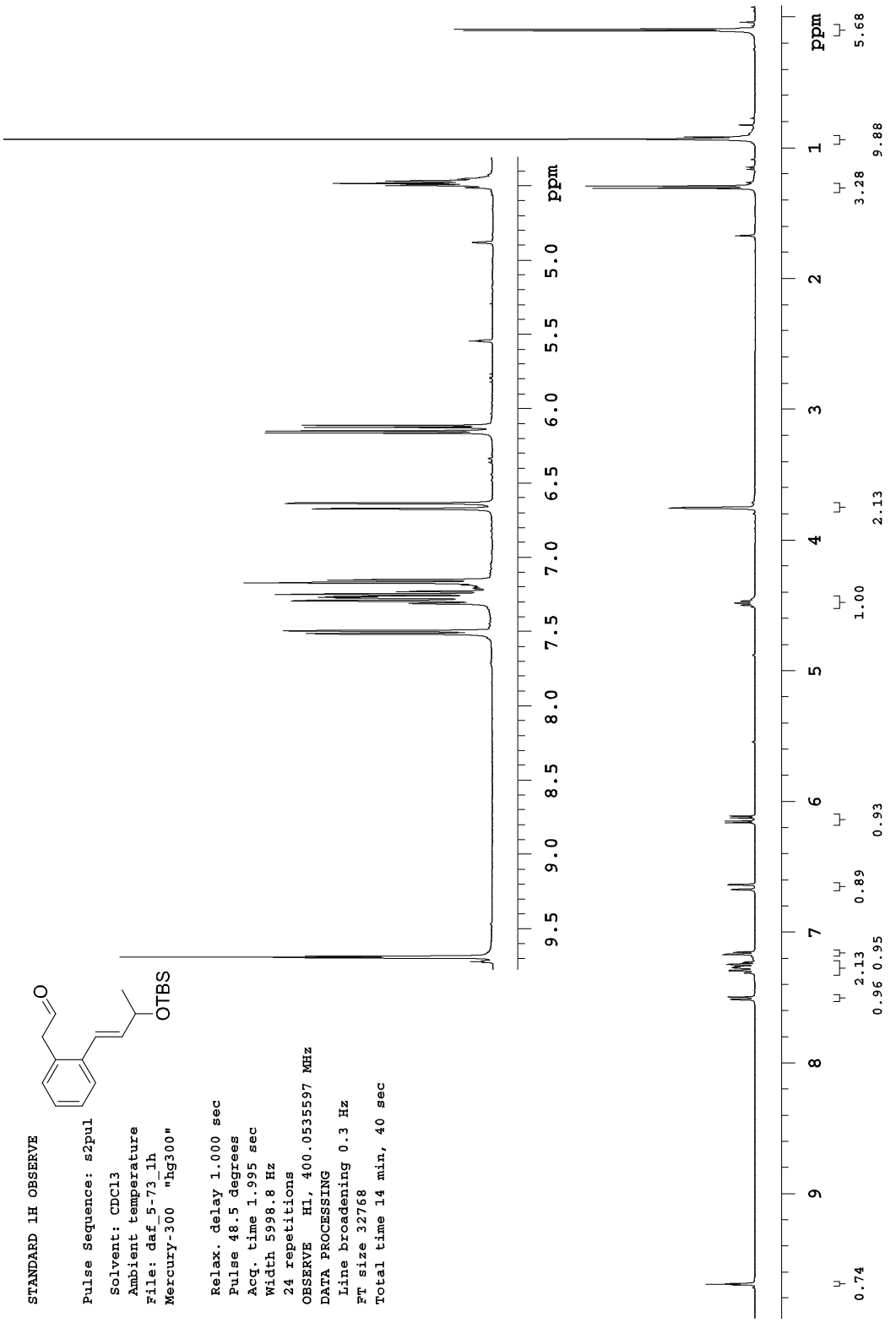
Spectrum 2.57 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **478**



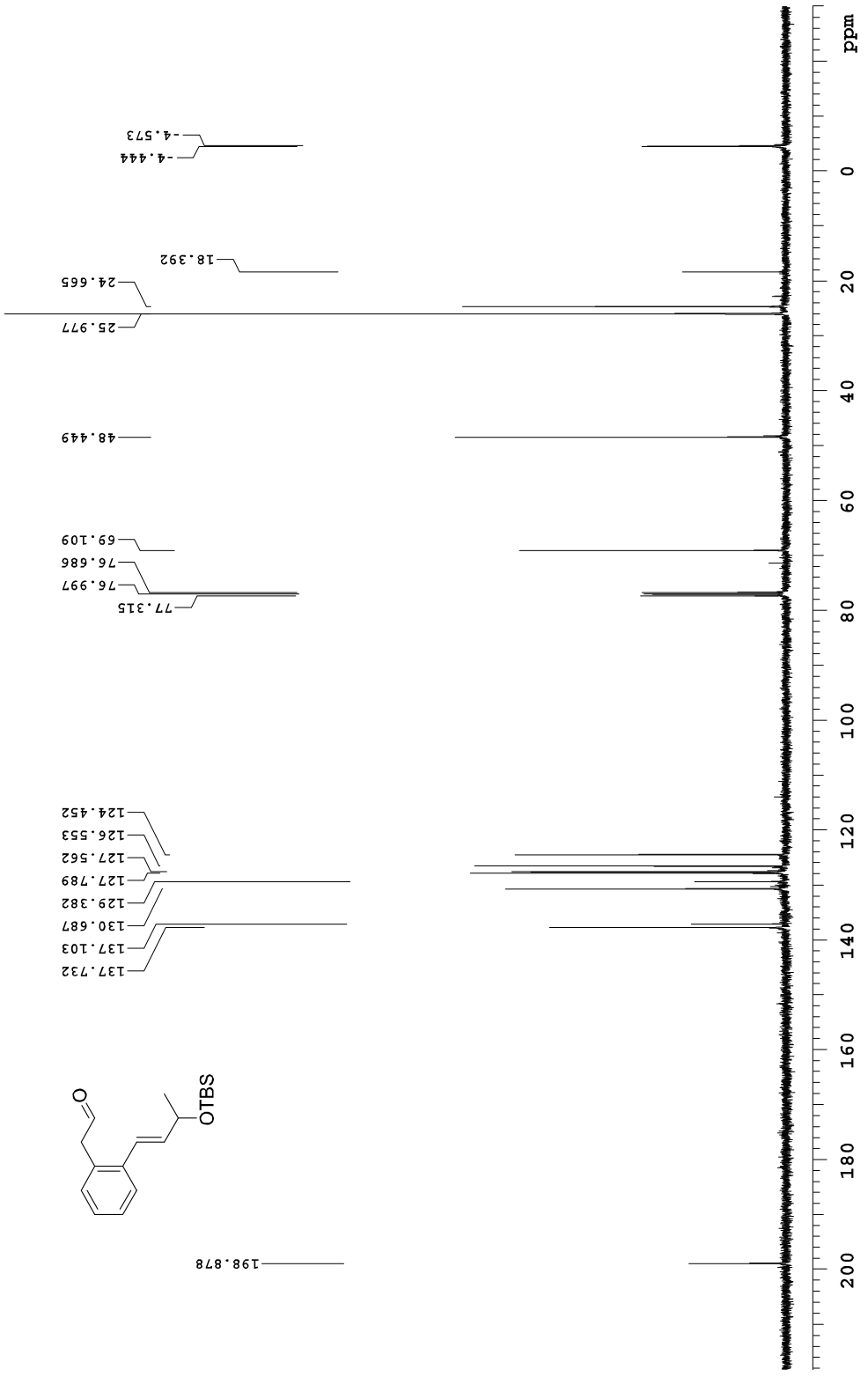
Spectrum 2.58 ^{1}H NMR ($CDCl_3$, 300 MHz) of compound **479**



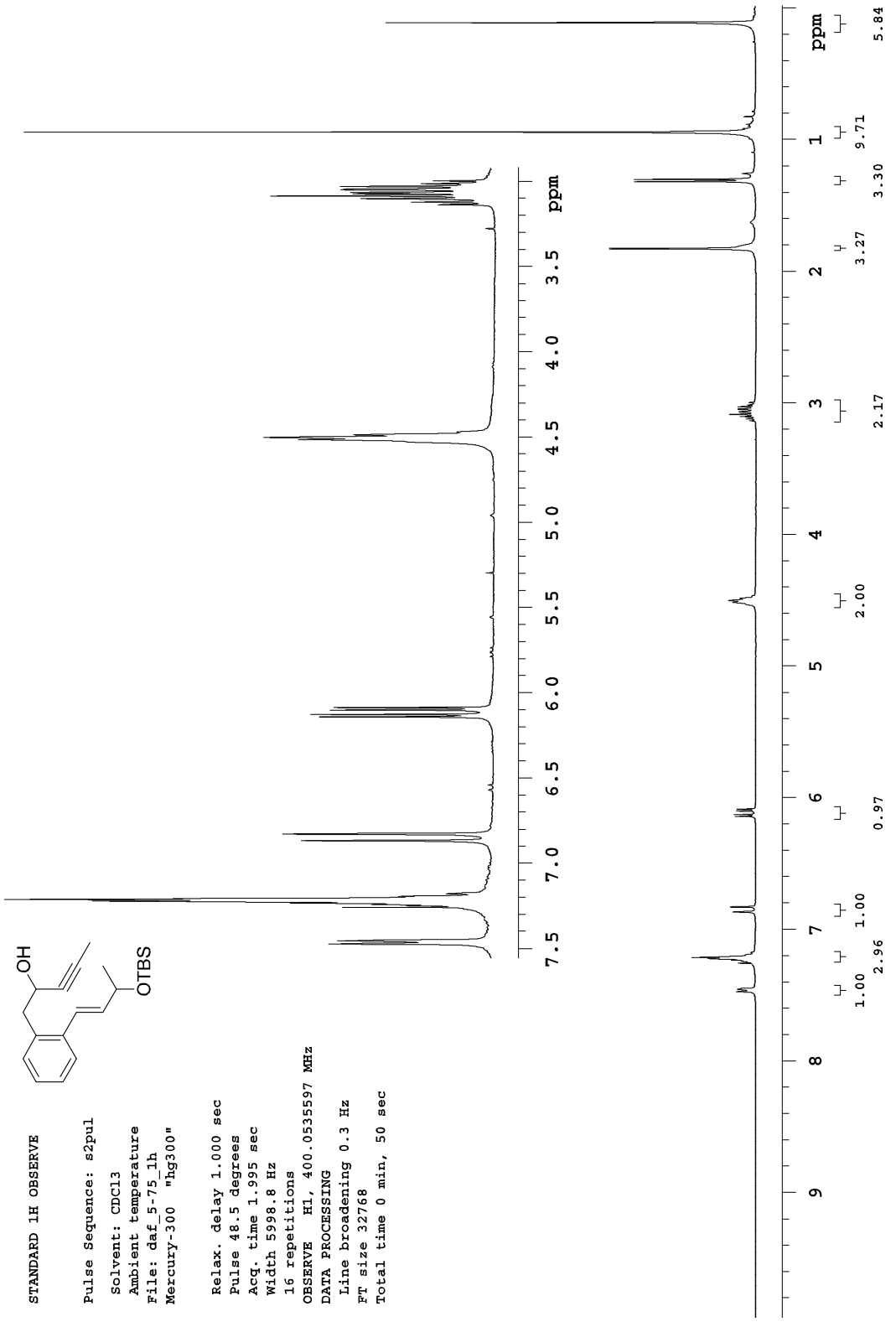
Spectrum 2.59 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **479**



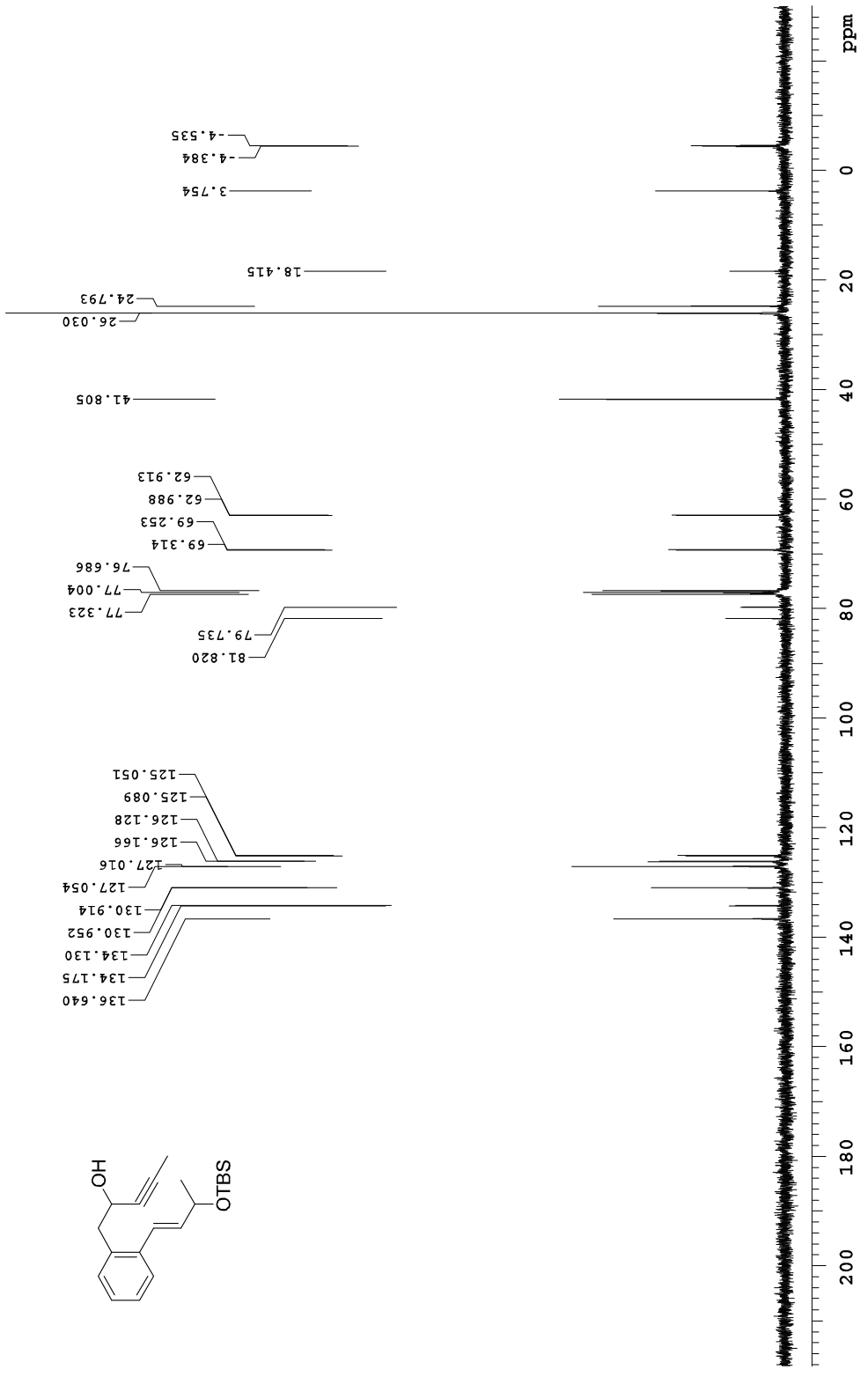
Spectrum 2.60 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **480**



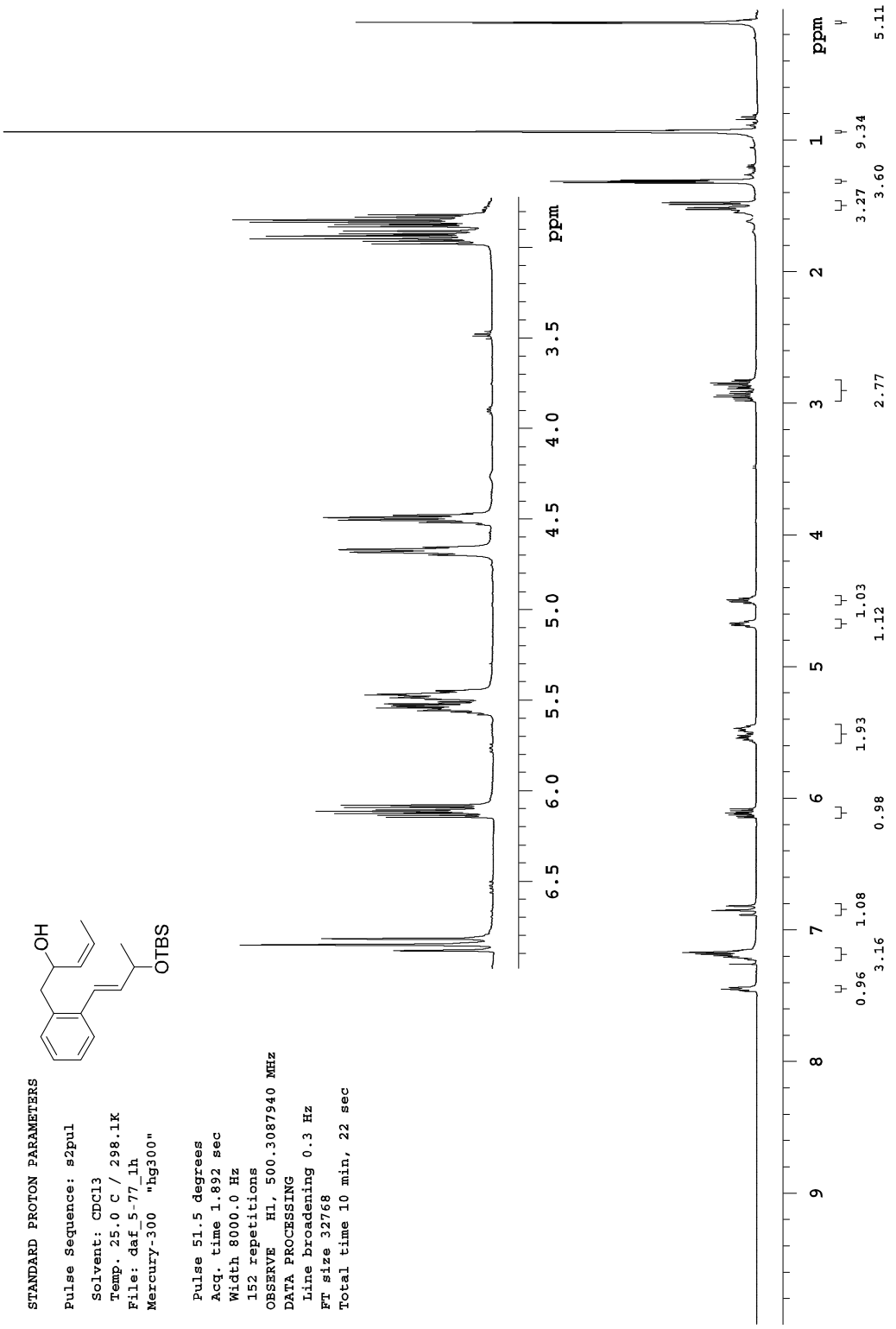
Spectrum 2.61 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **480**



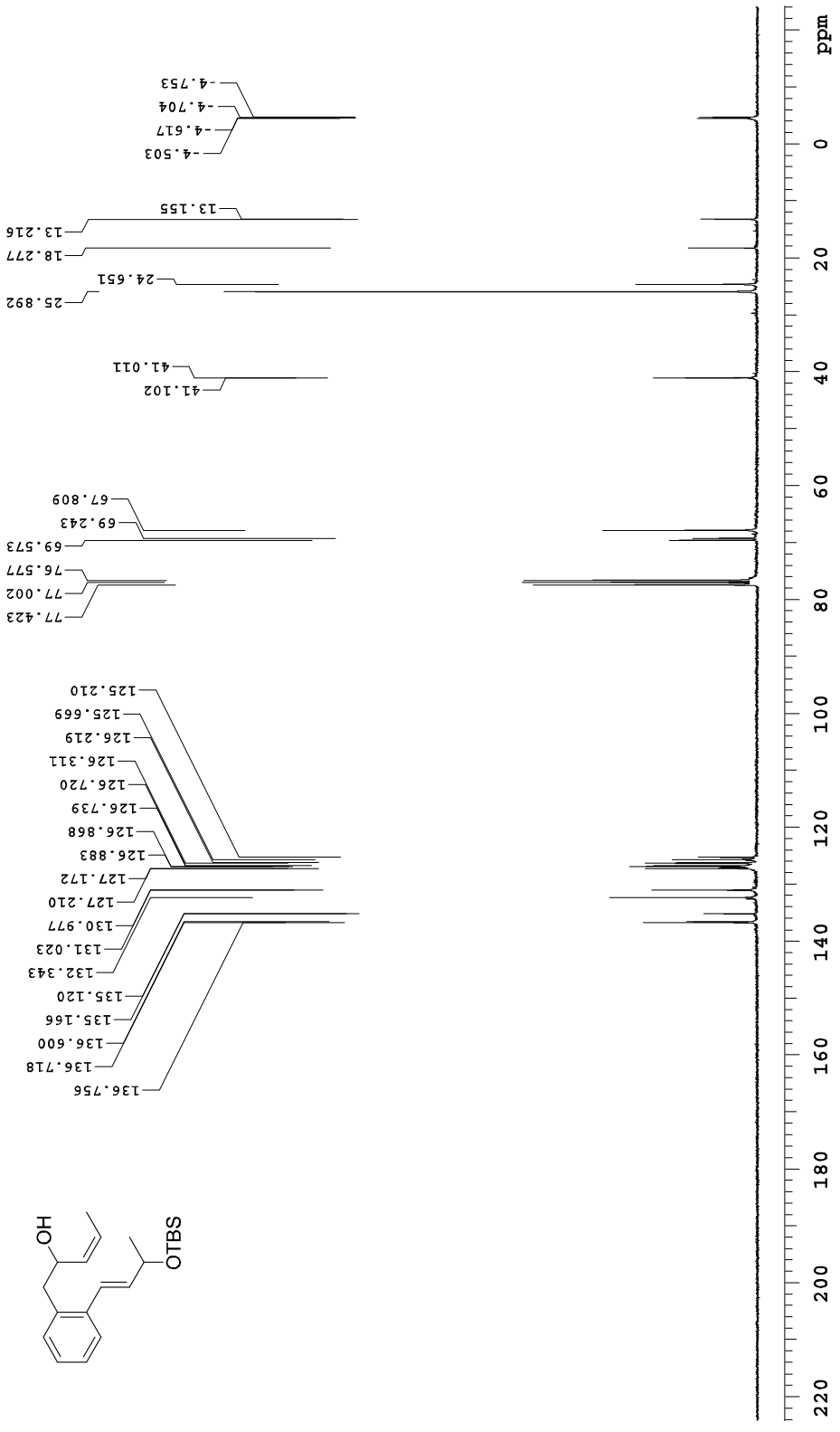
Spectrum 2.62 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **481**



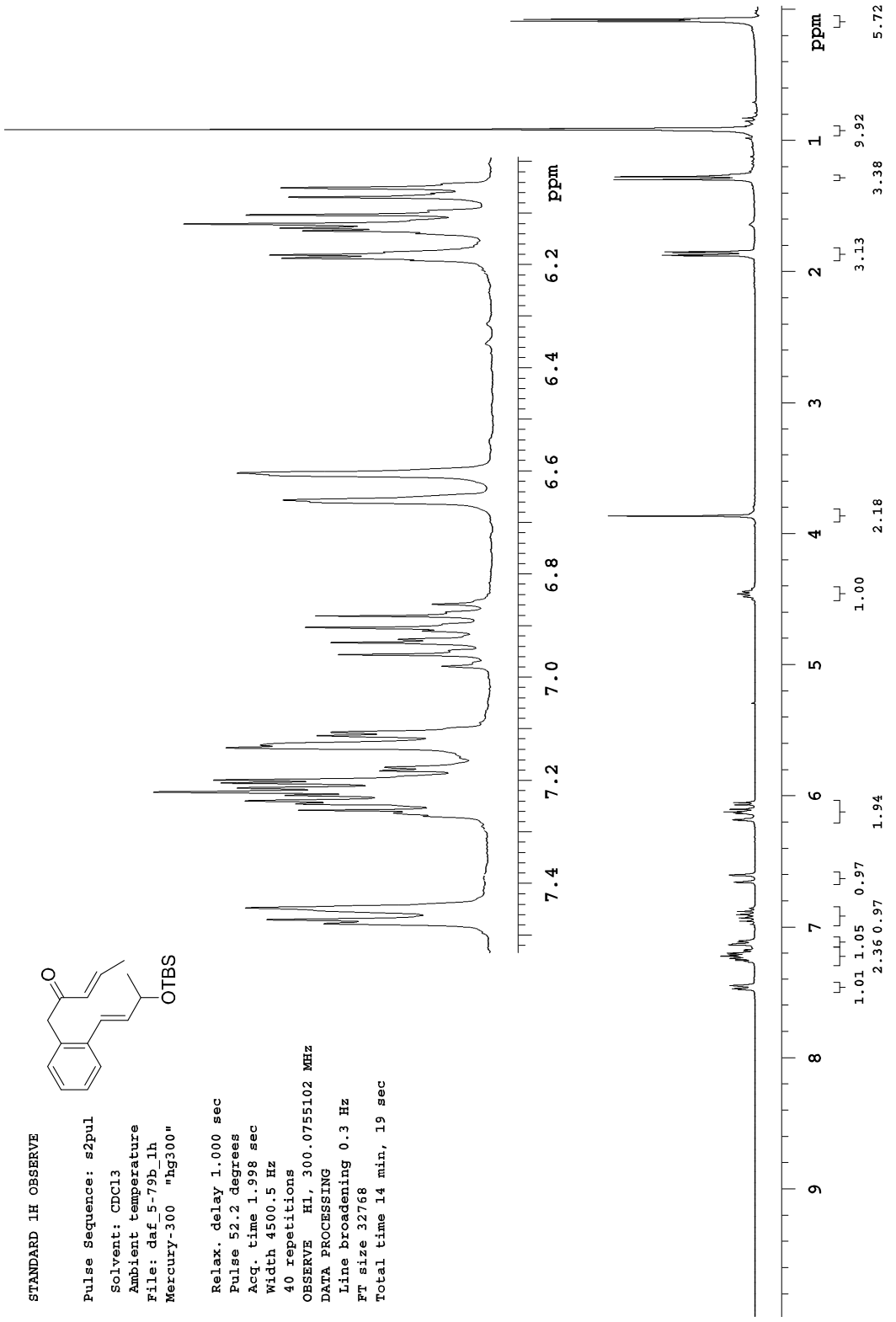
Spectrum 2.63 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **481**



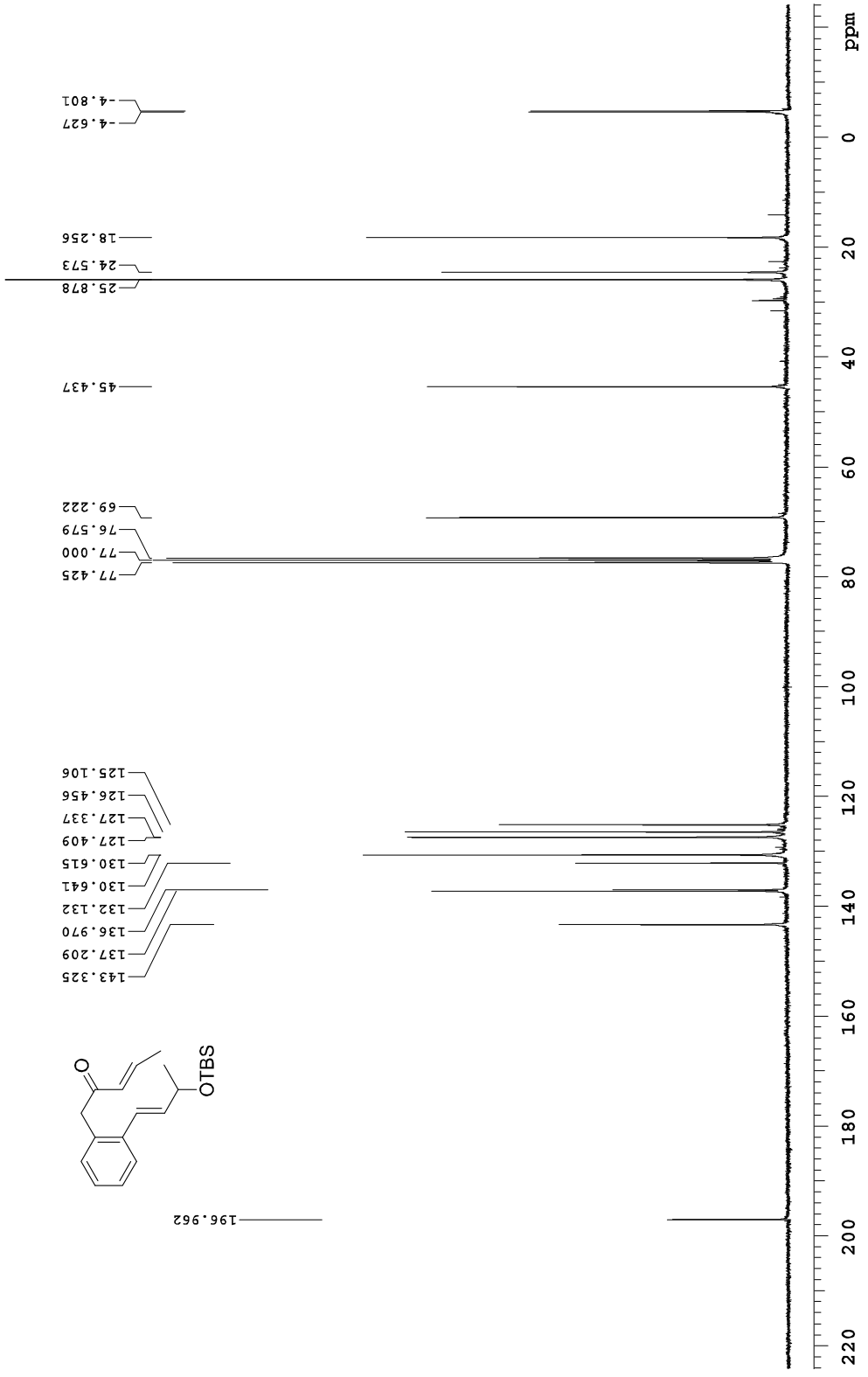
Spectrum 2.64 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **482**



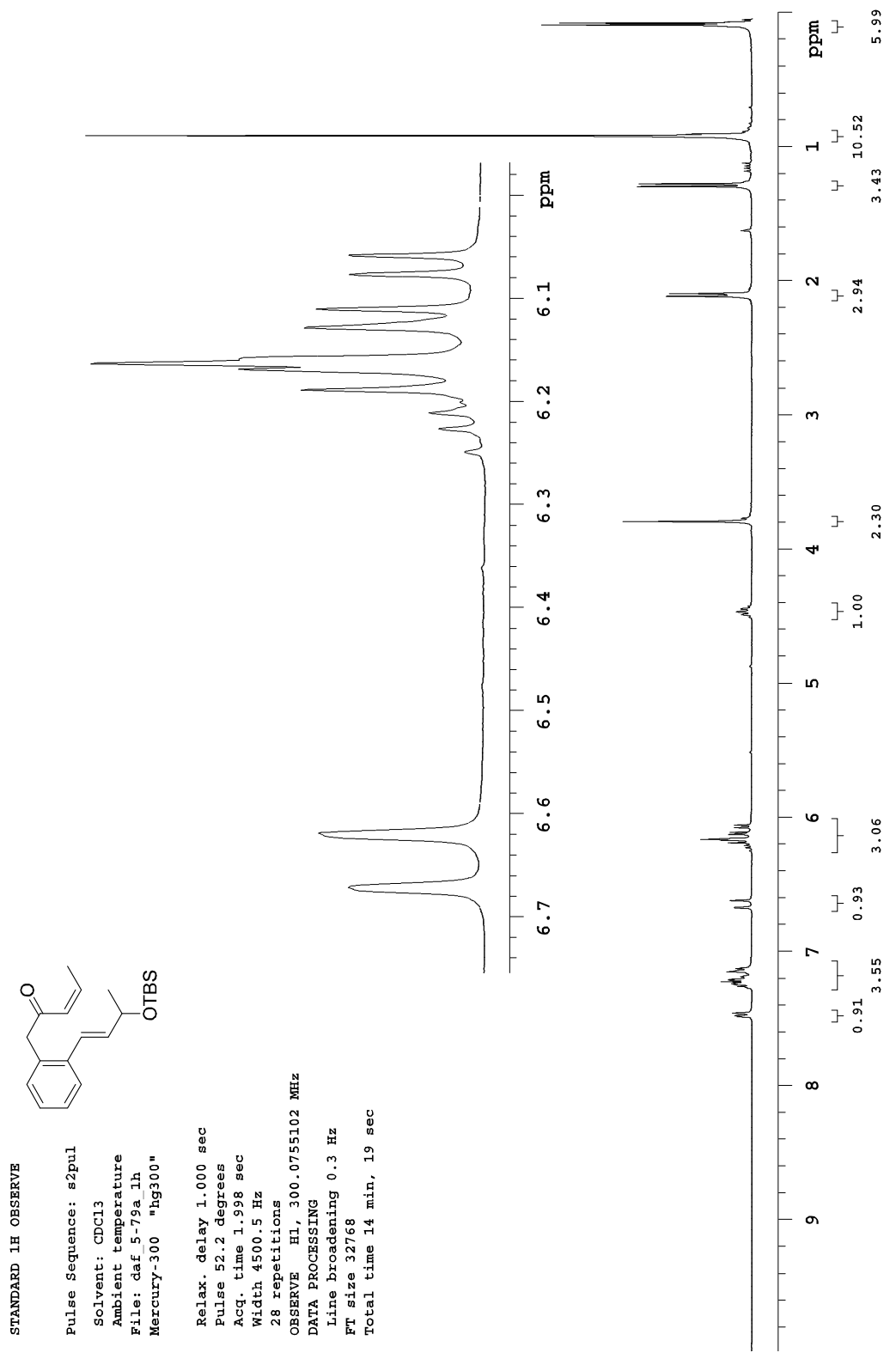
Spectrum 2.65 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **482**



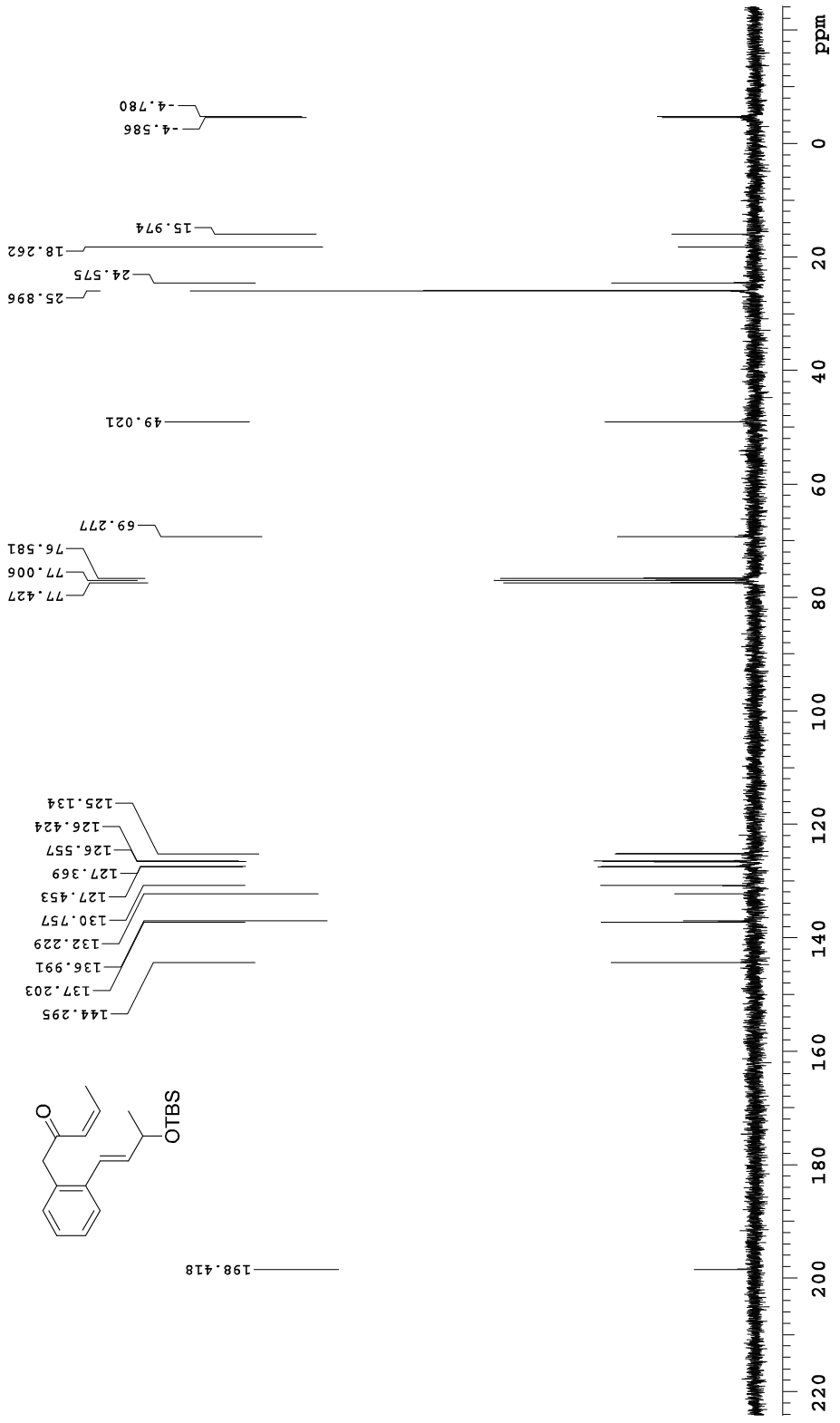
Spectrum 2.66 ^{1}H NMR ($CDCl_3$, 300 MHz) of compound **483E**



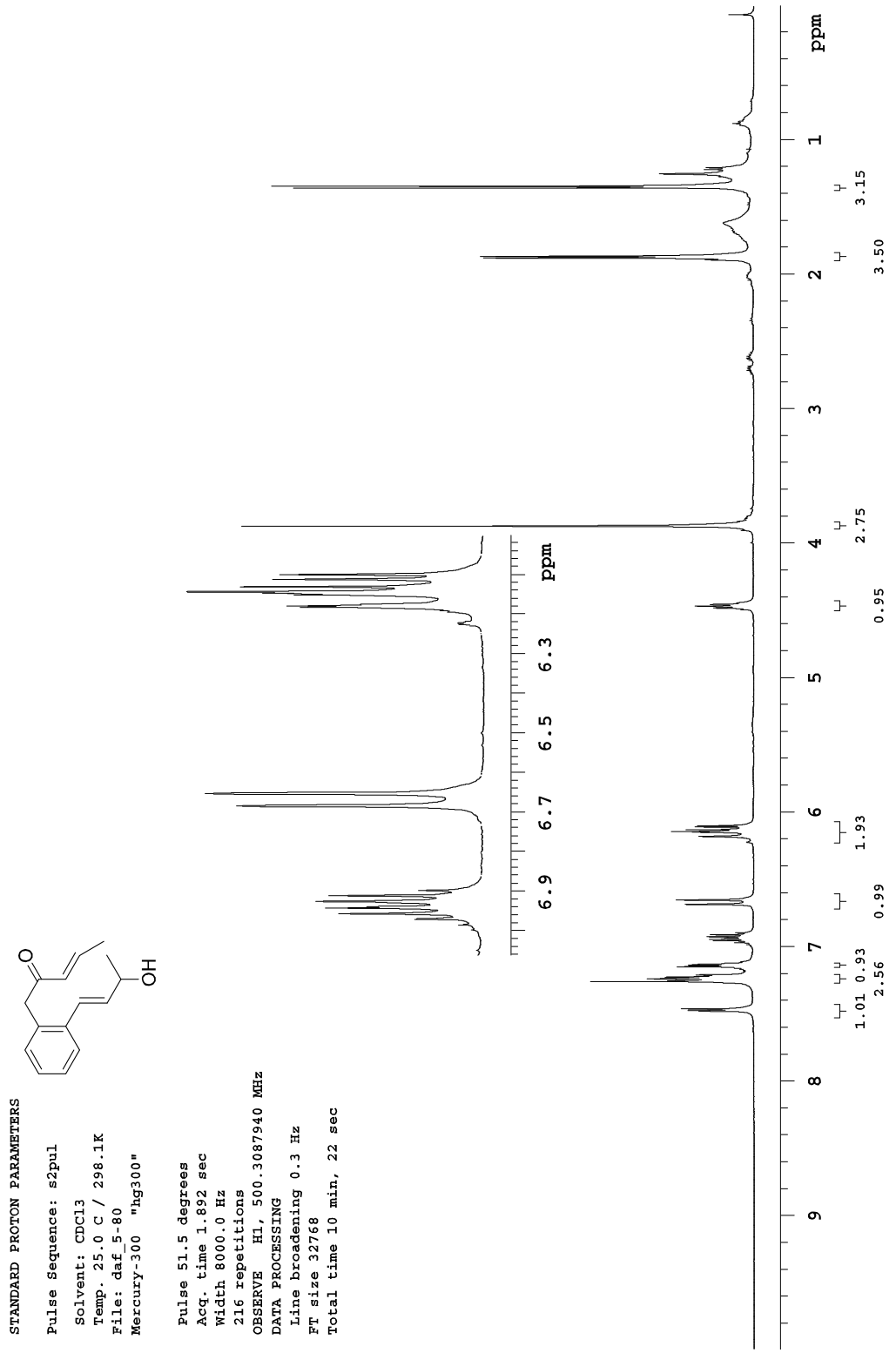
Spectrum 2.67 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **483E**



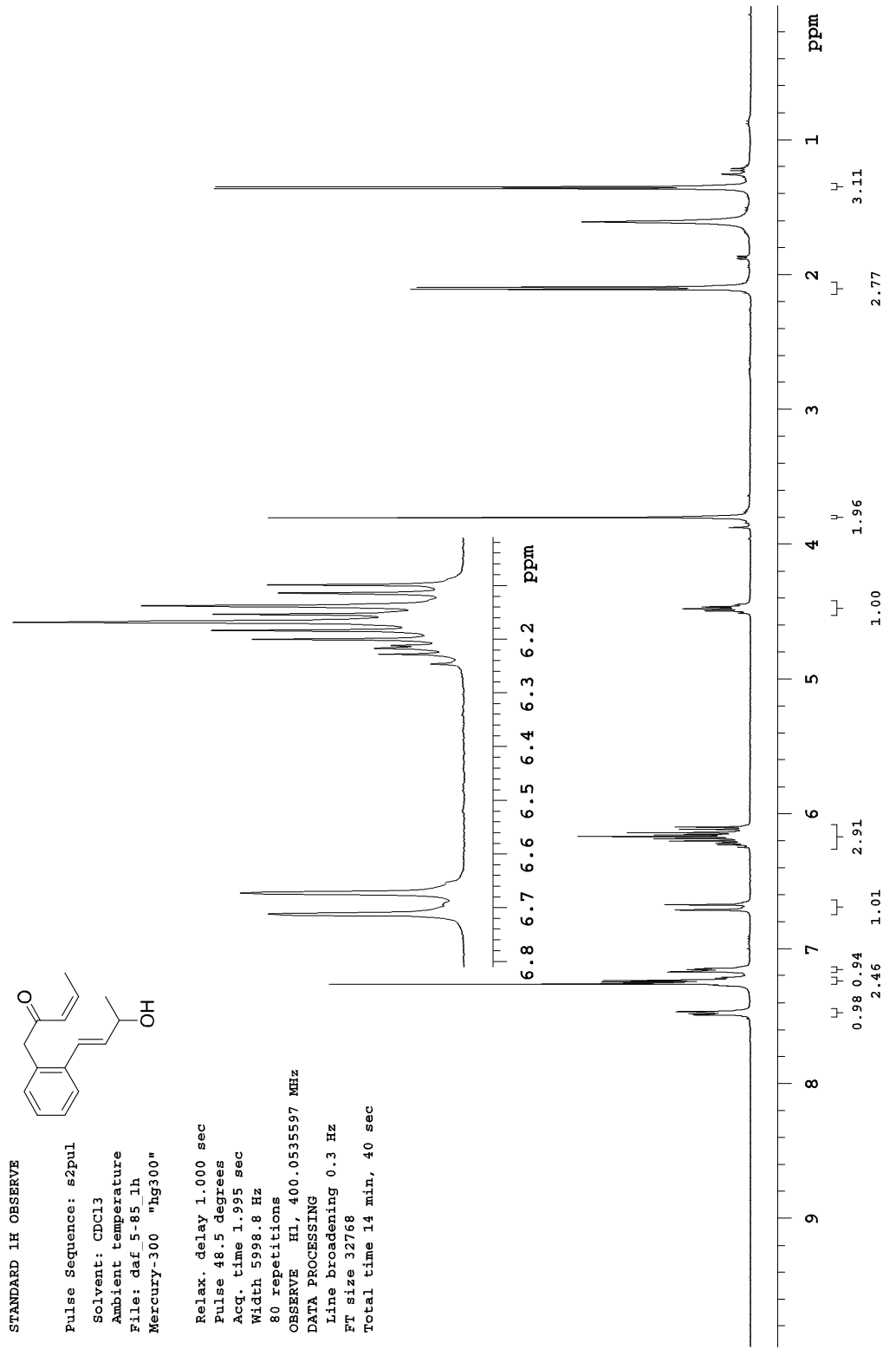
Spectrum 2.68 ^{1}H NMR ($CDCl_3$, 300 MHz) of compound **483Z**



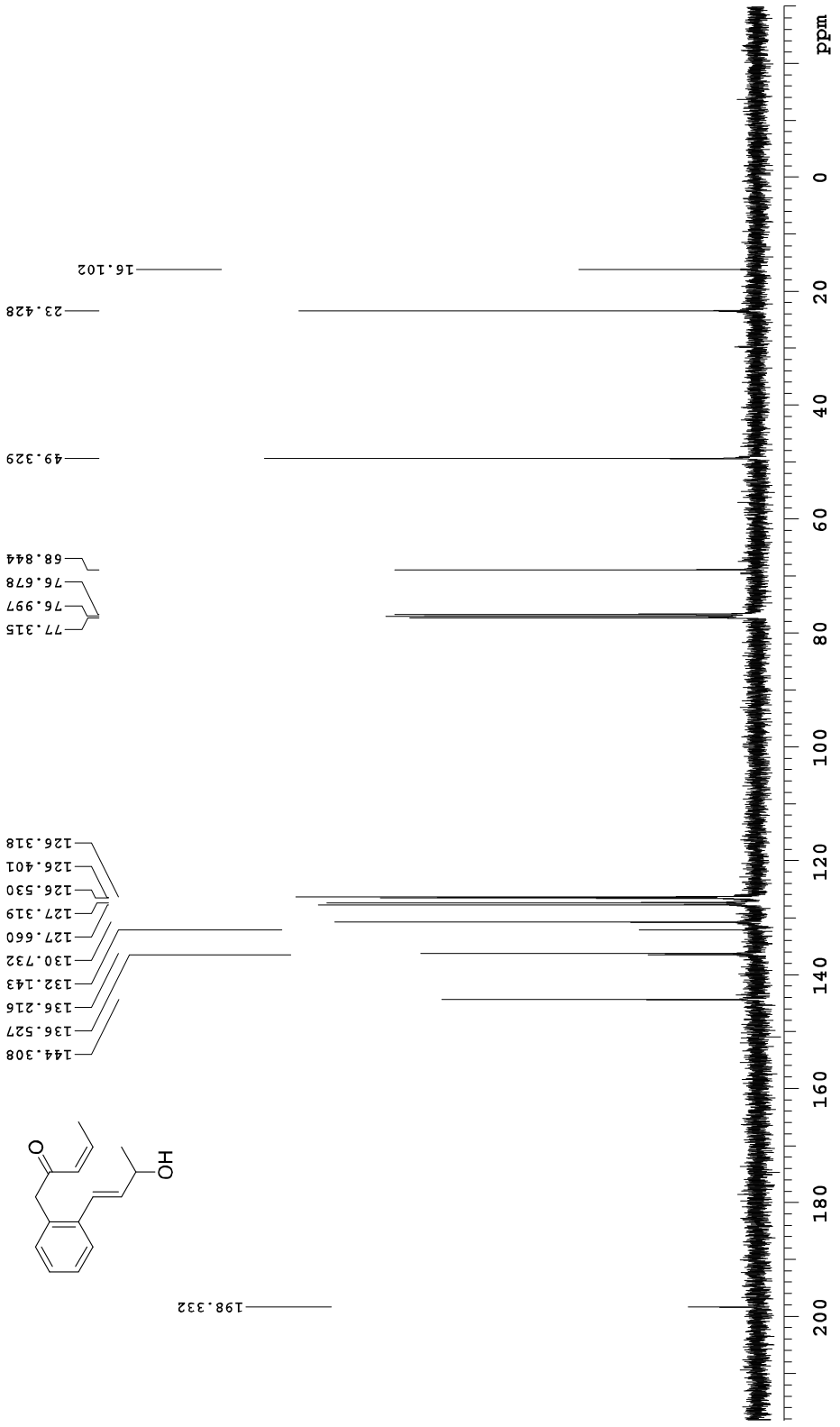
Spectrum 2.69 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **483Z**



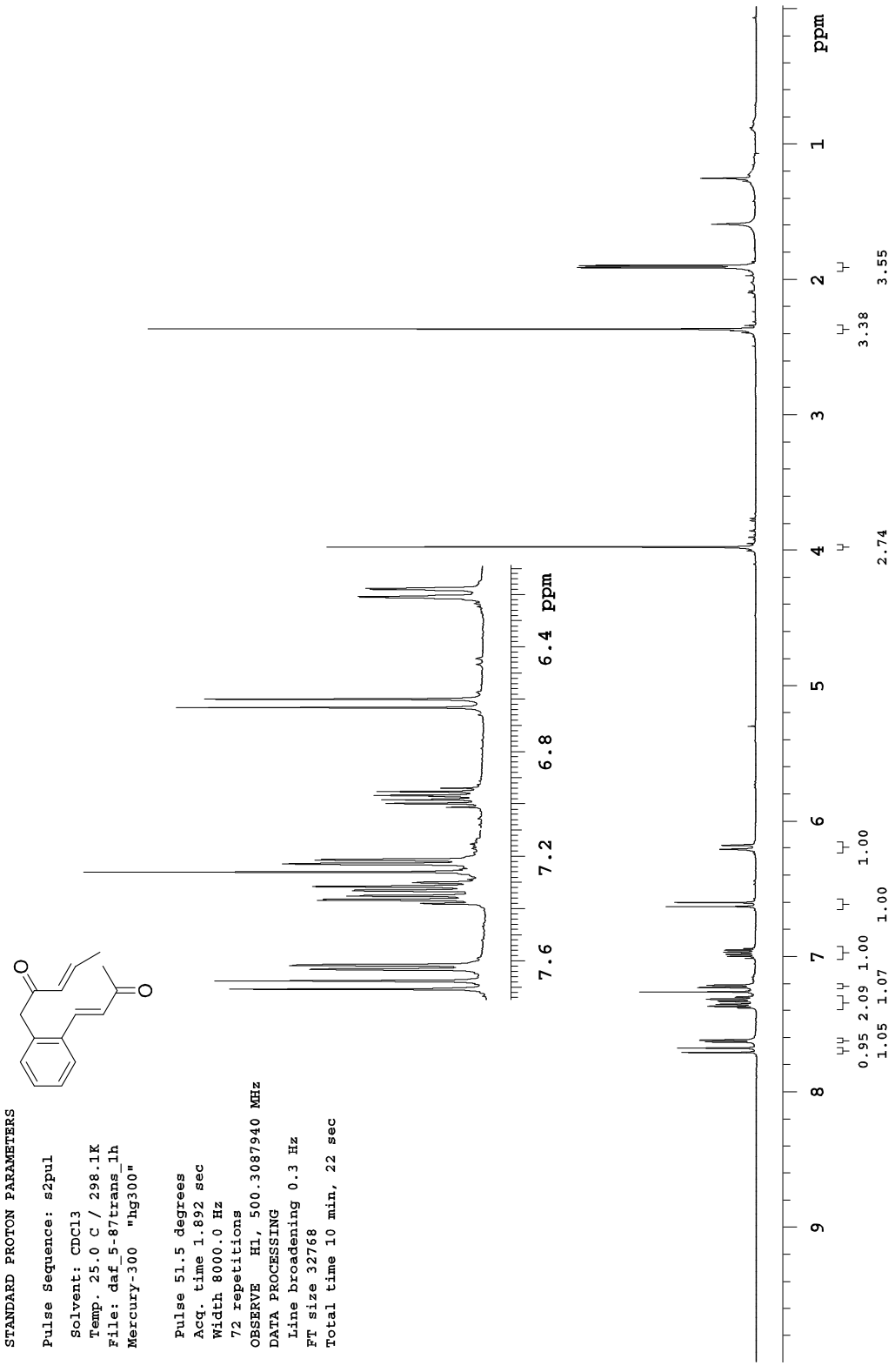
Spectrum 2.70 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **484E**



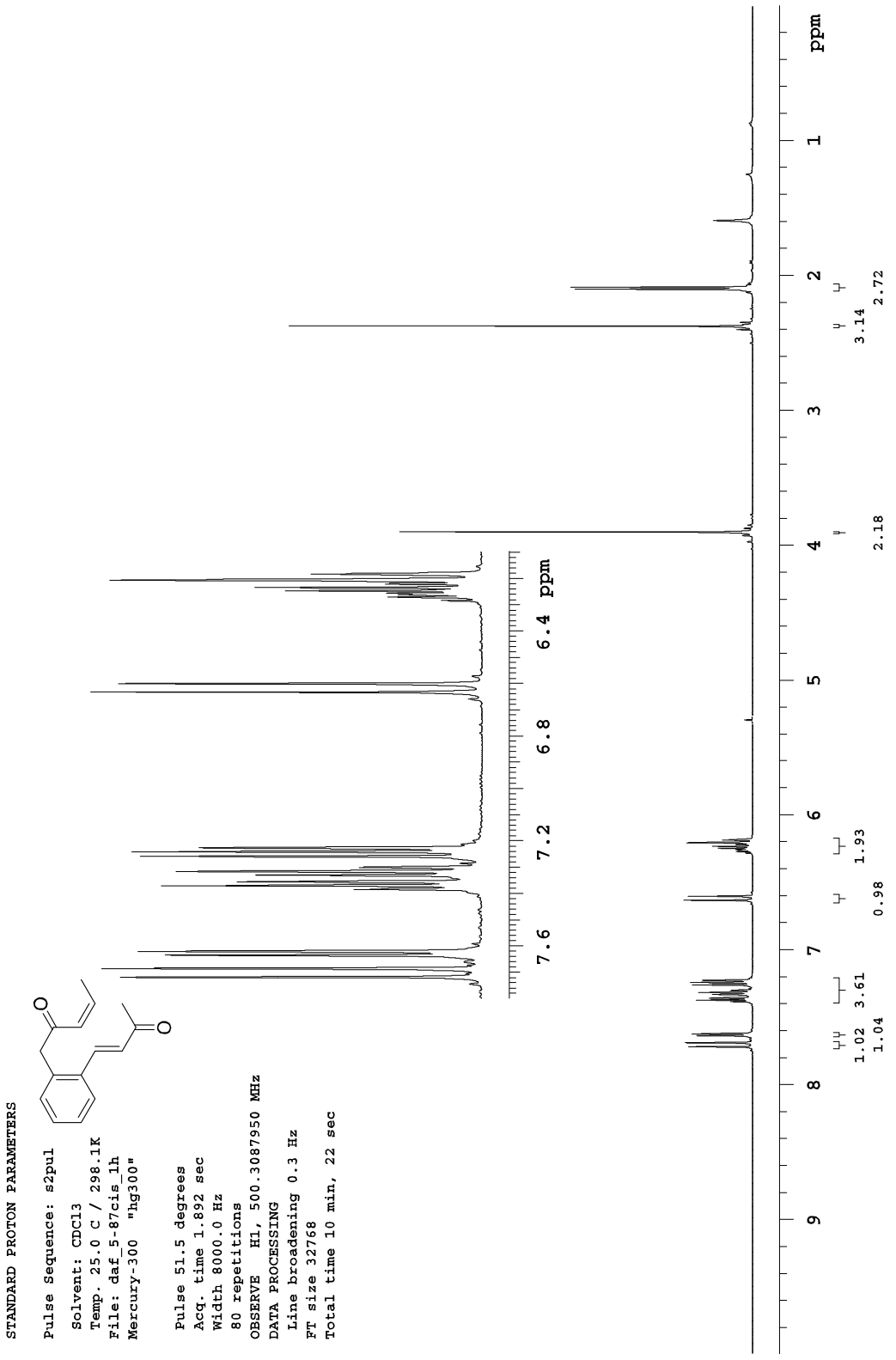
Spectrum 2.71 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **484Z**



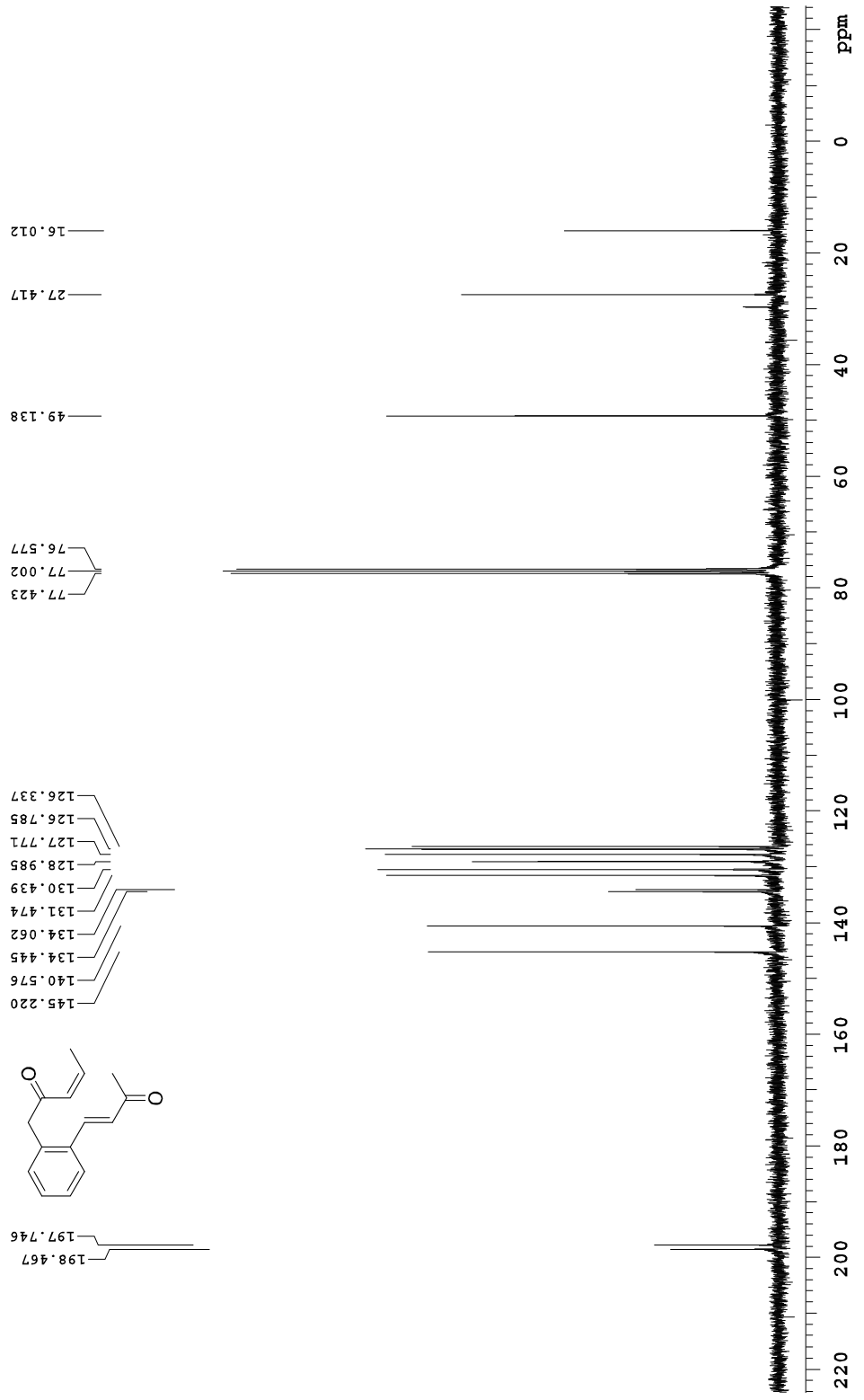
Spectrum 2.72 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **484Z**



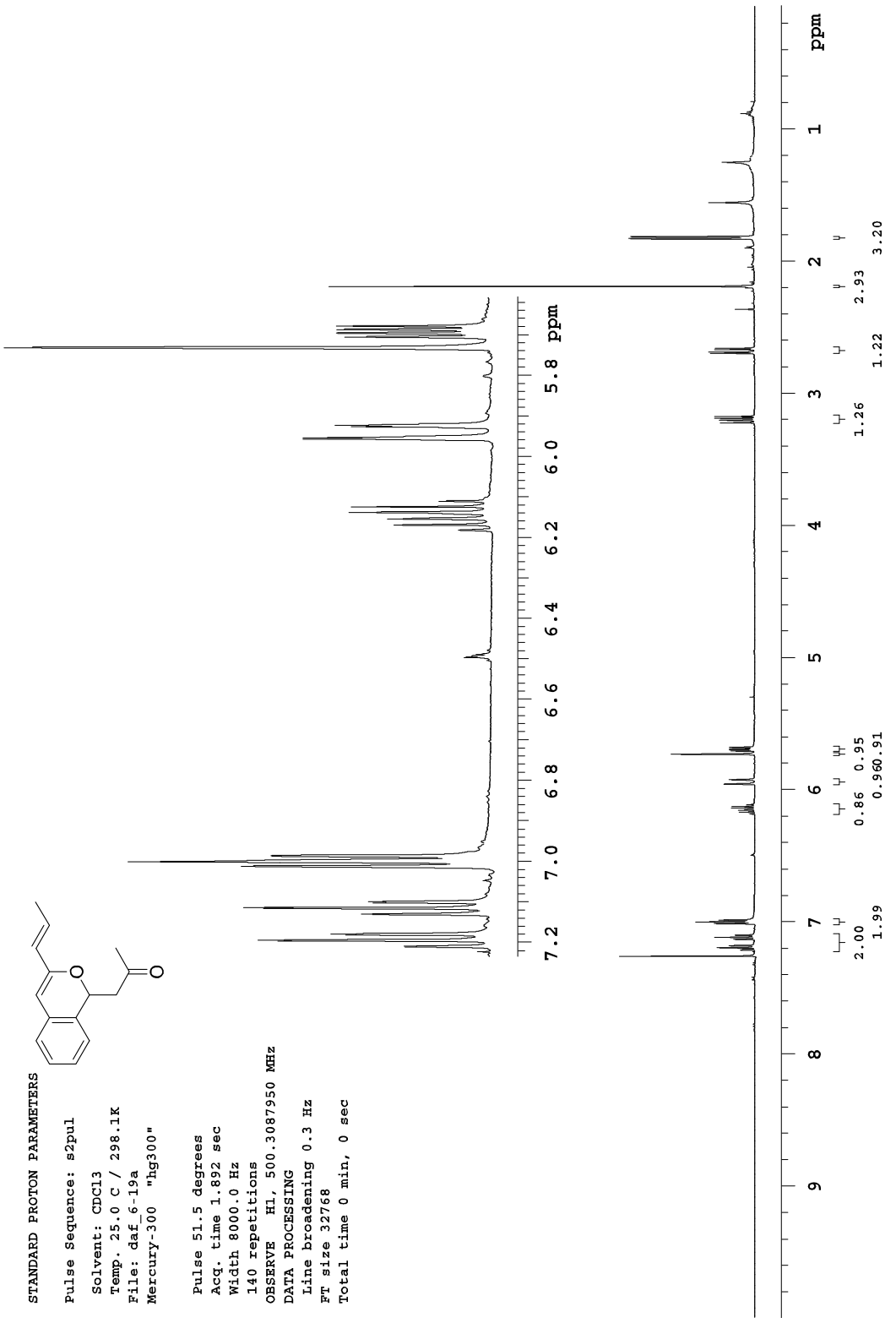
Spectrum 2.73 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **485E**



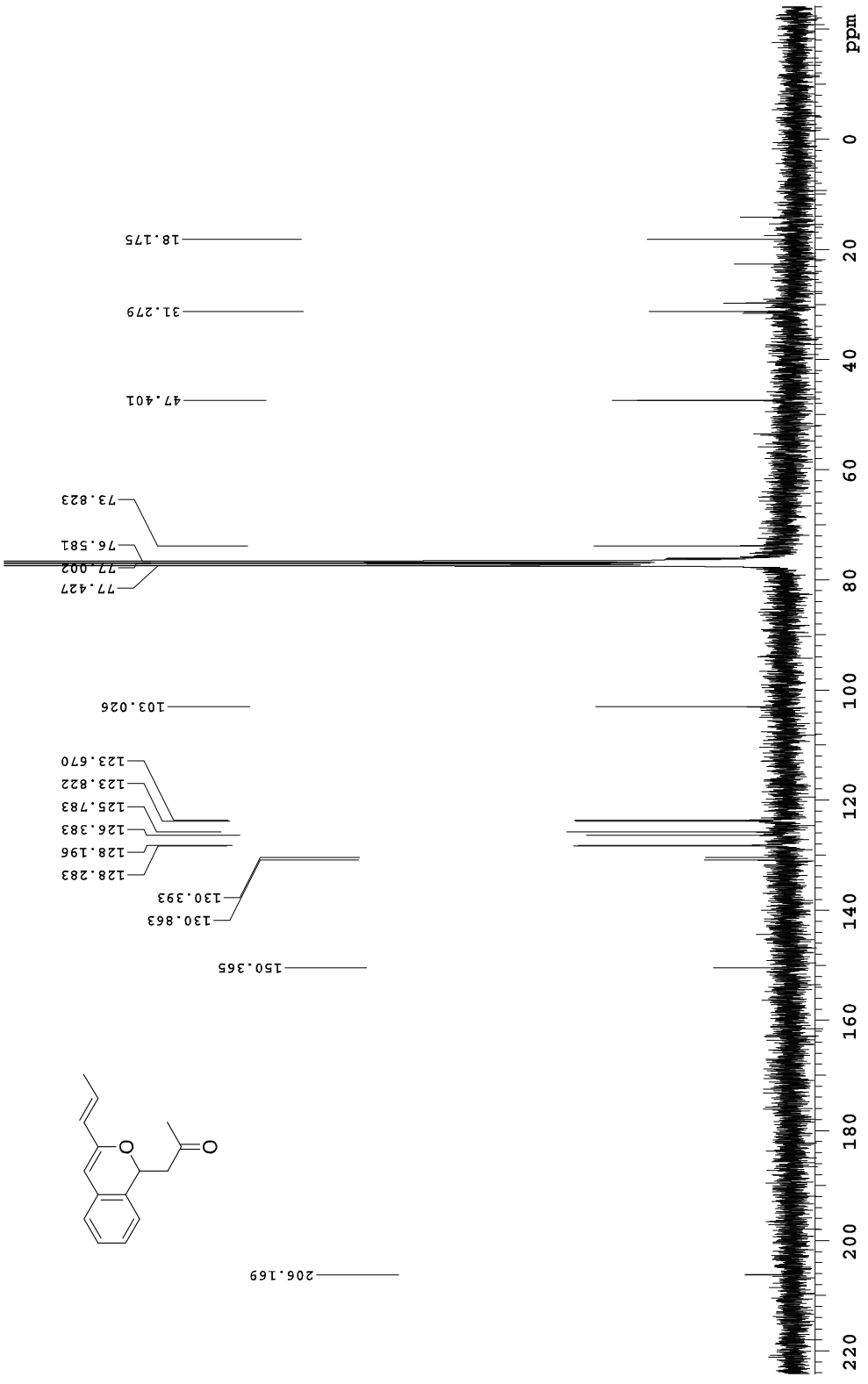
Spectrum 2.74 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **485Z**



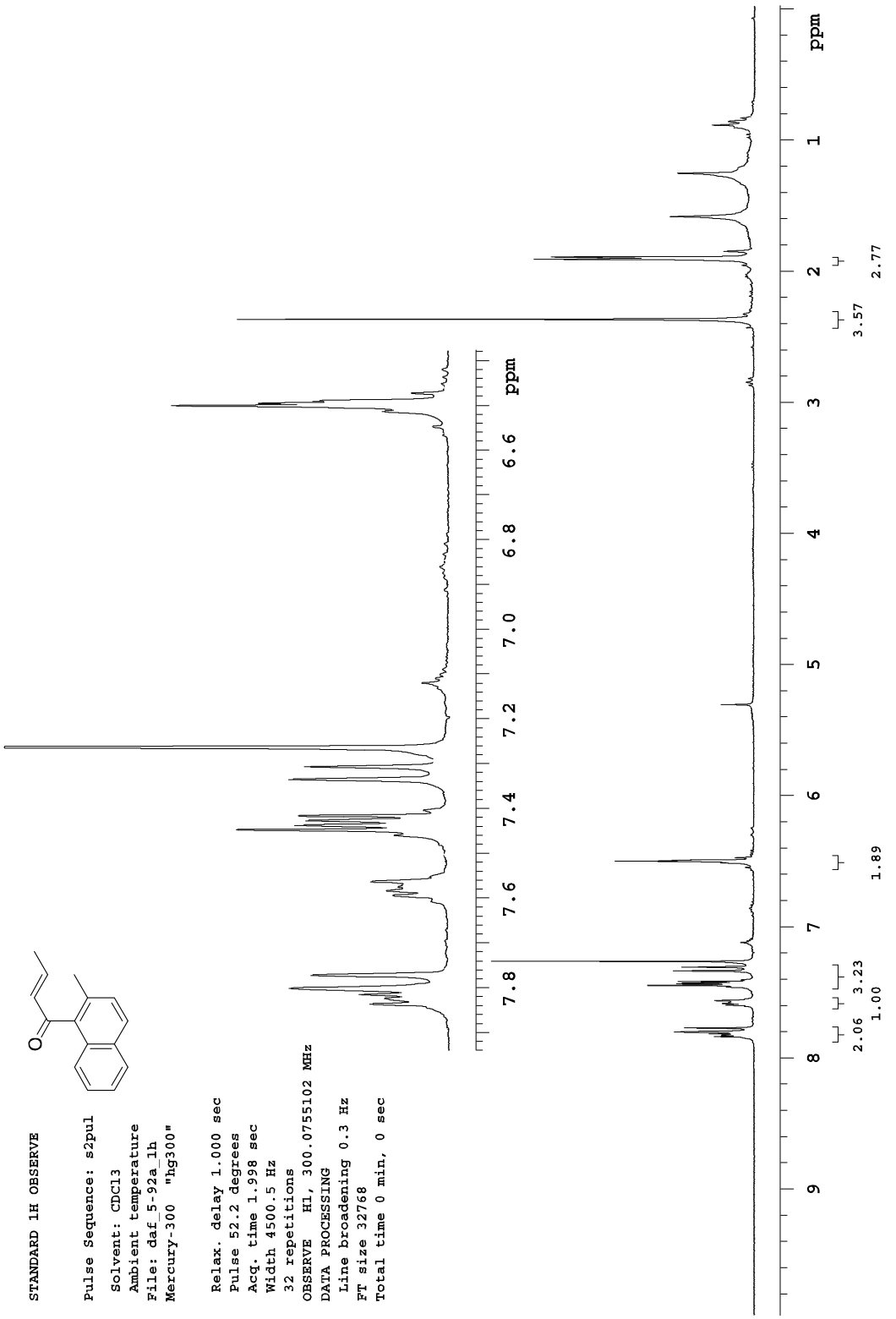
Spectrum 2.75 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **485Z**



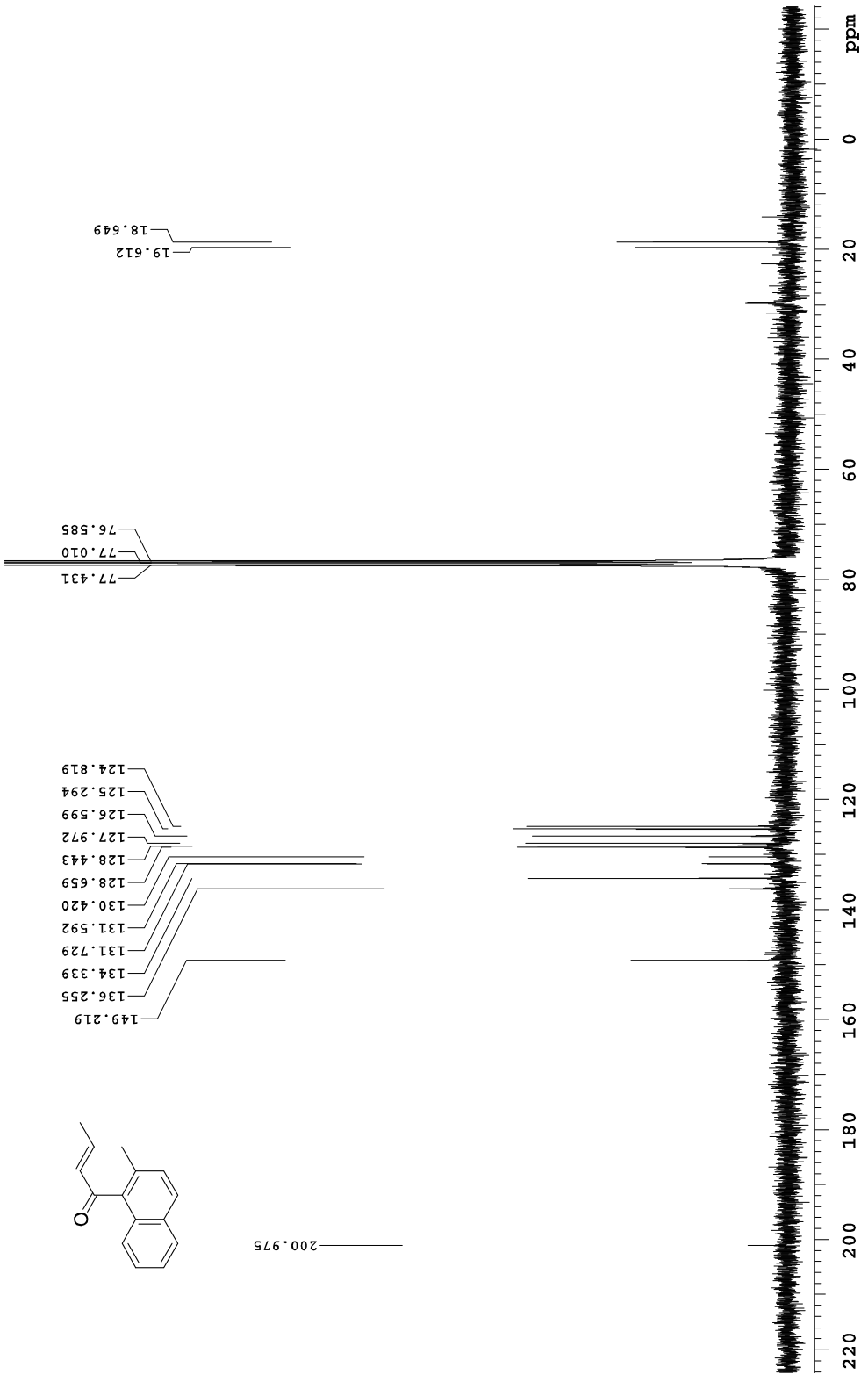
Spectrum 2.76 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **486**



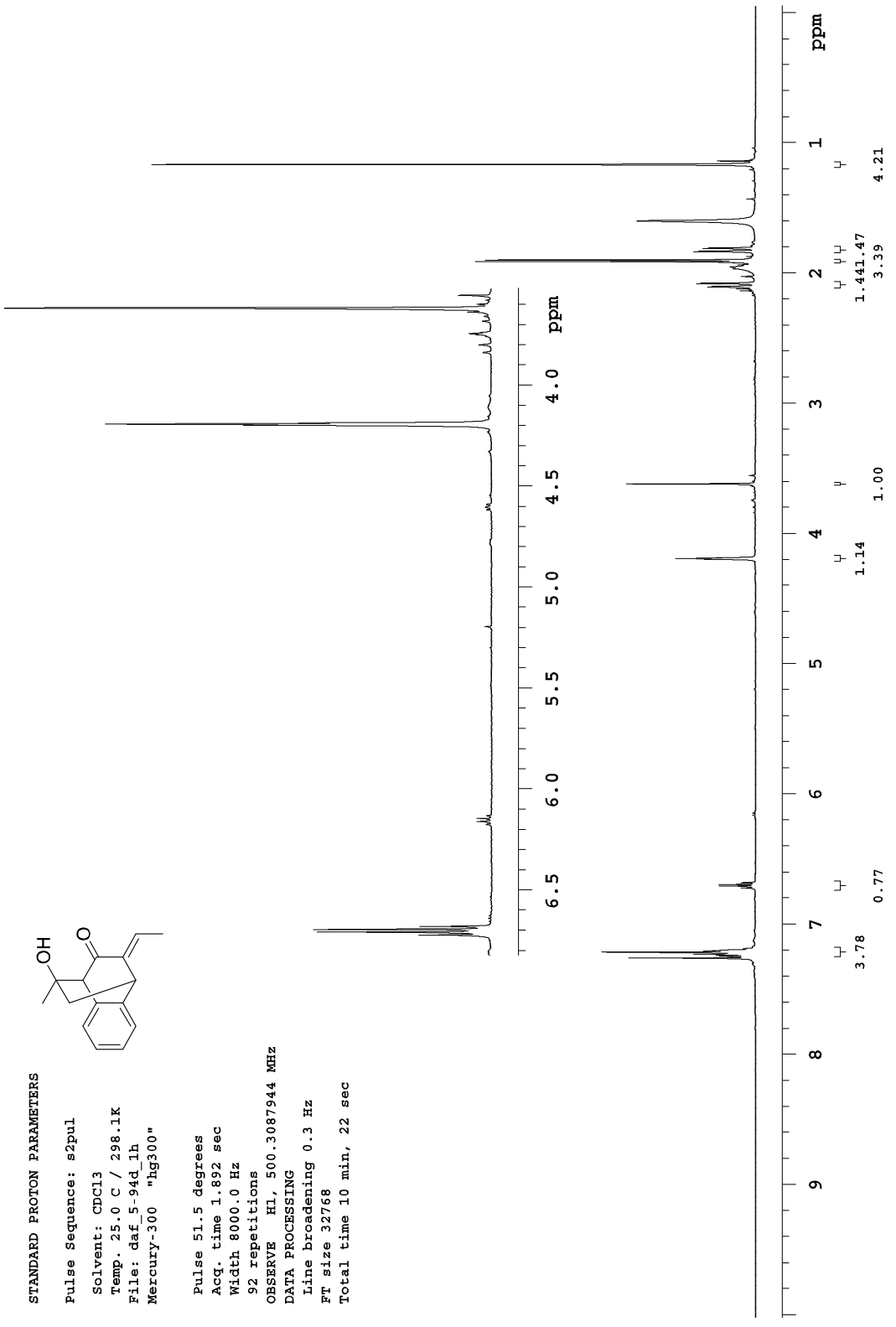
Spectrum 2.77 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **486**



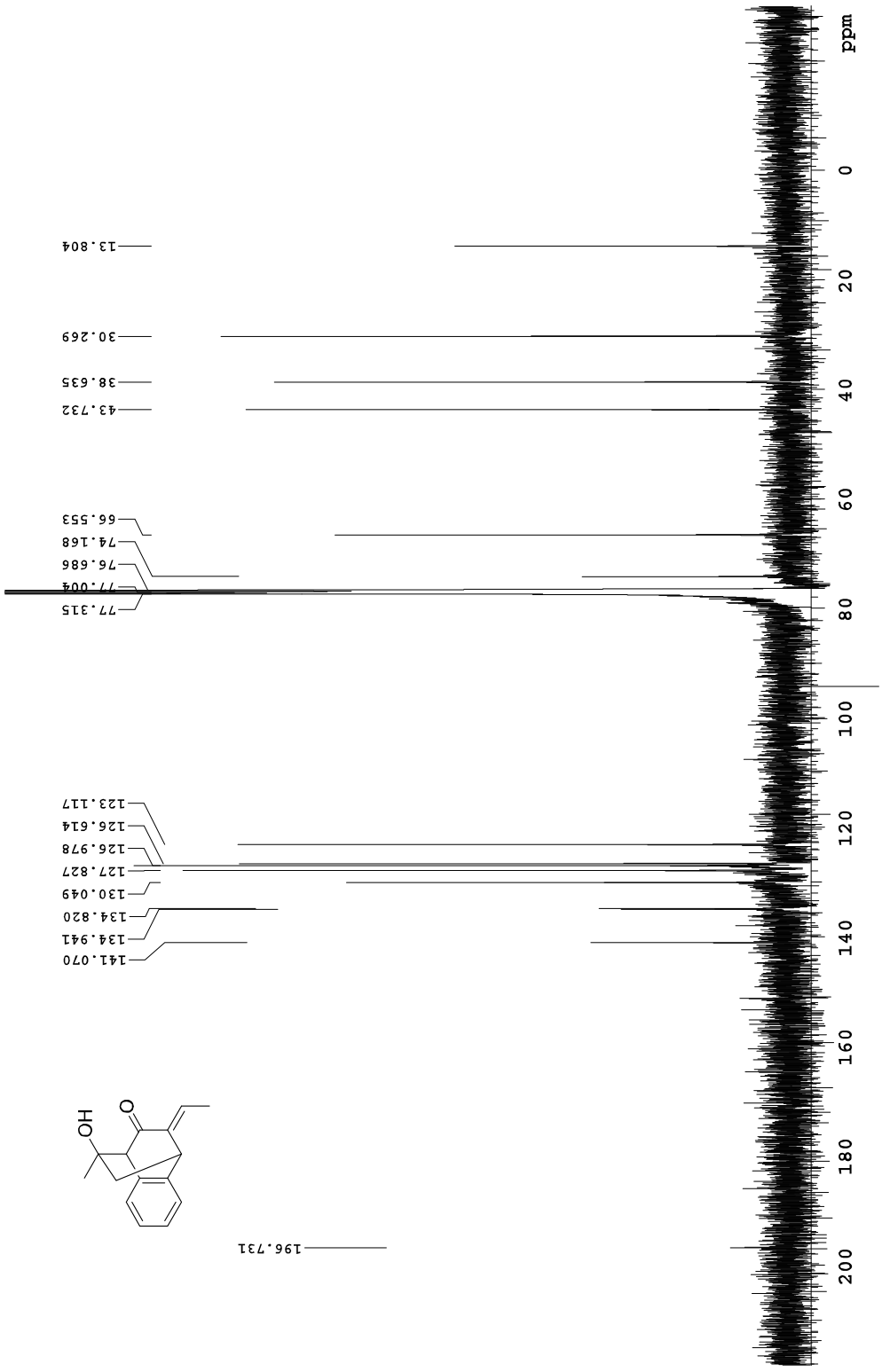
Spectrum 2.78 ^{1}H NMR ($CDCl_3$, 300 MHz) of compound **487**



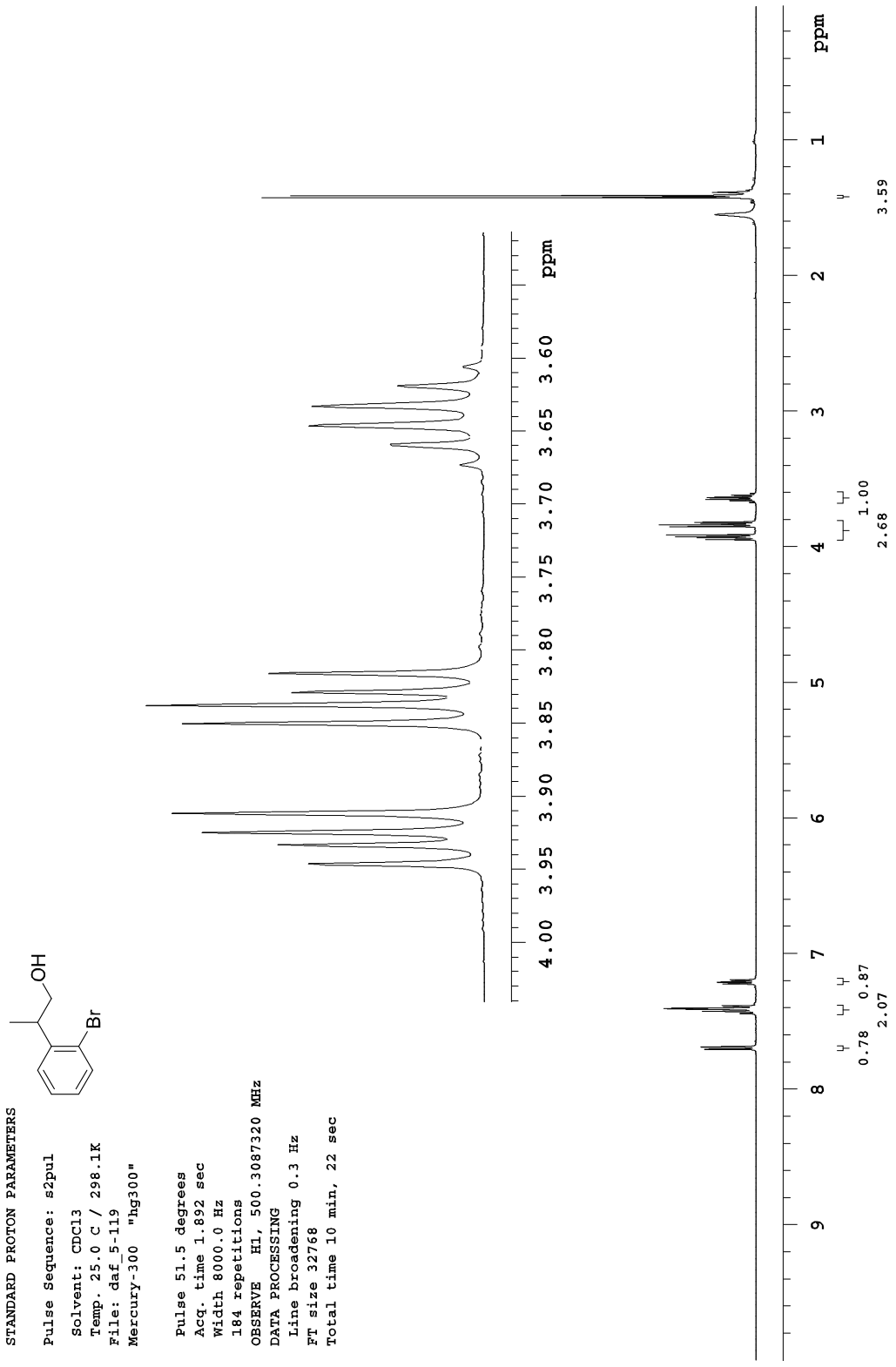
Spectrum 2.79 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **487**



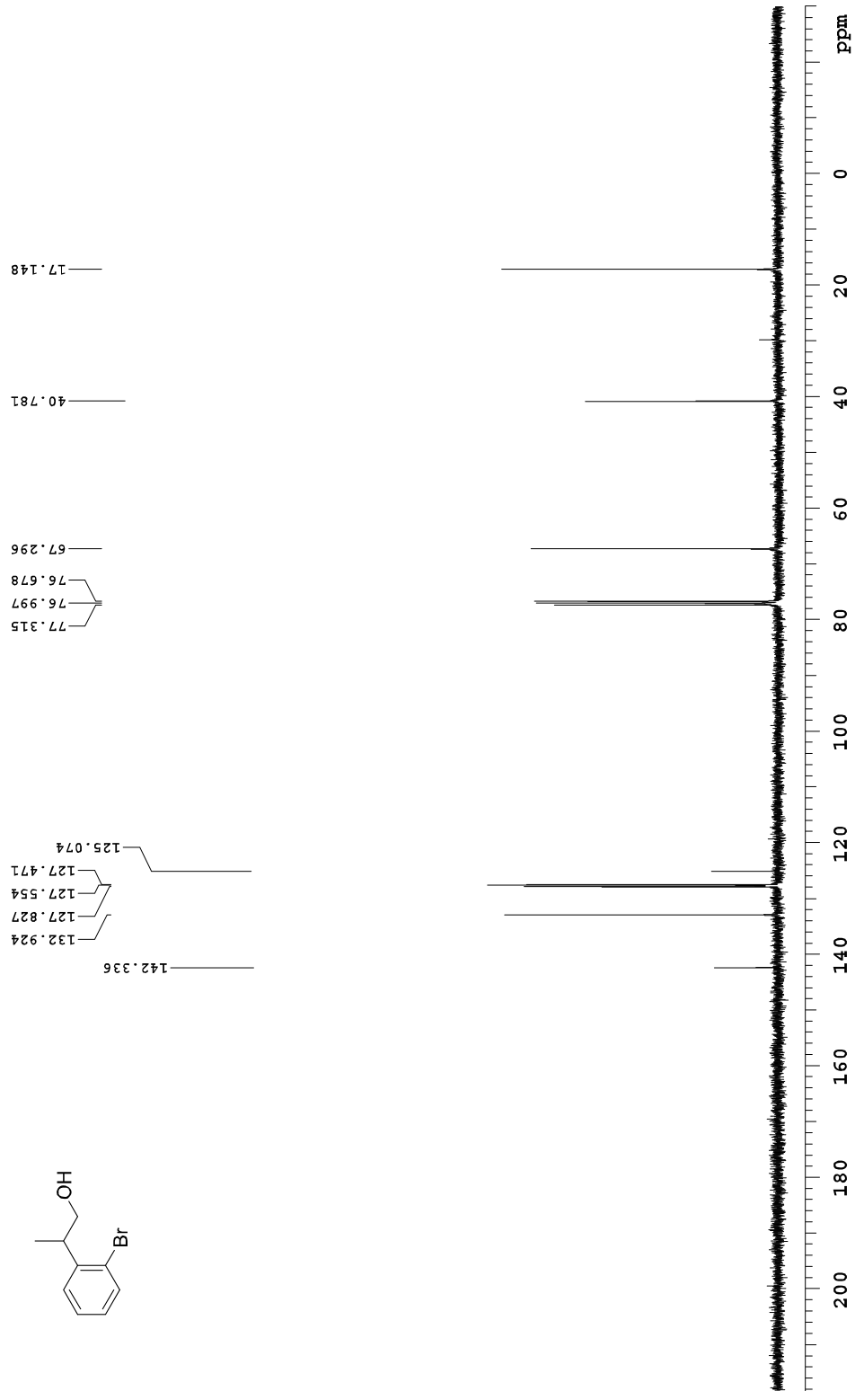
Spectrum 2.80 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **488**



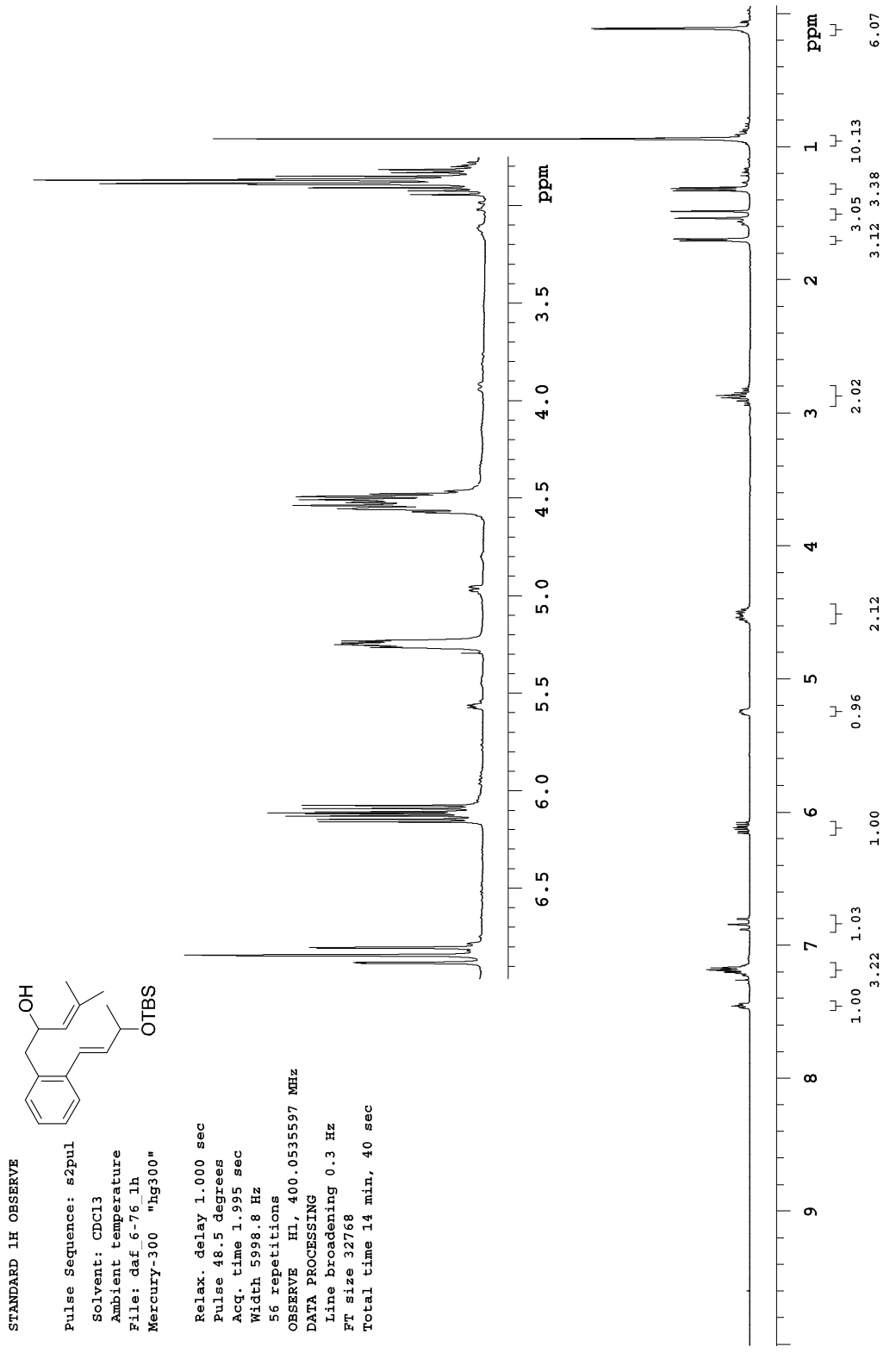
Spectrum 2.81 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **488**



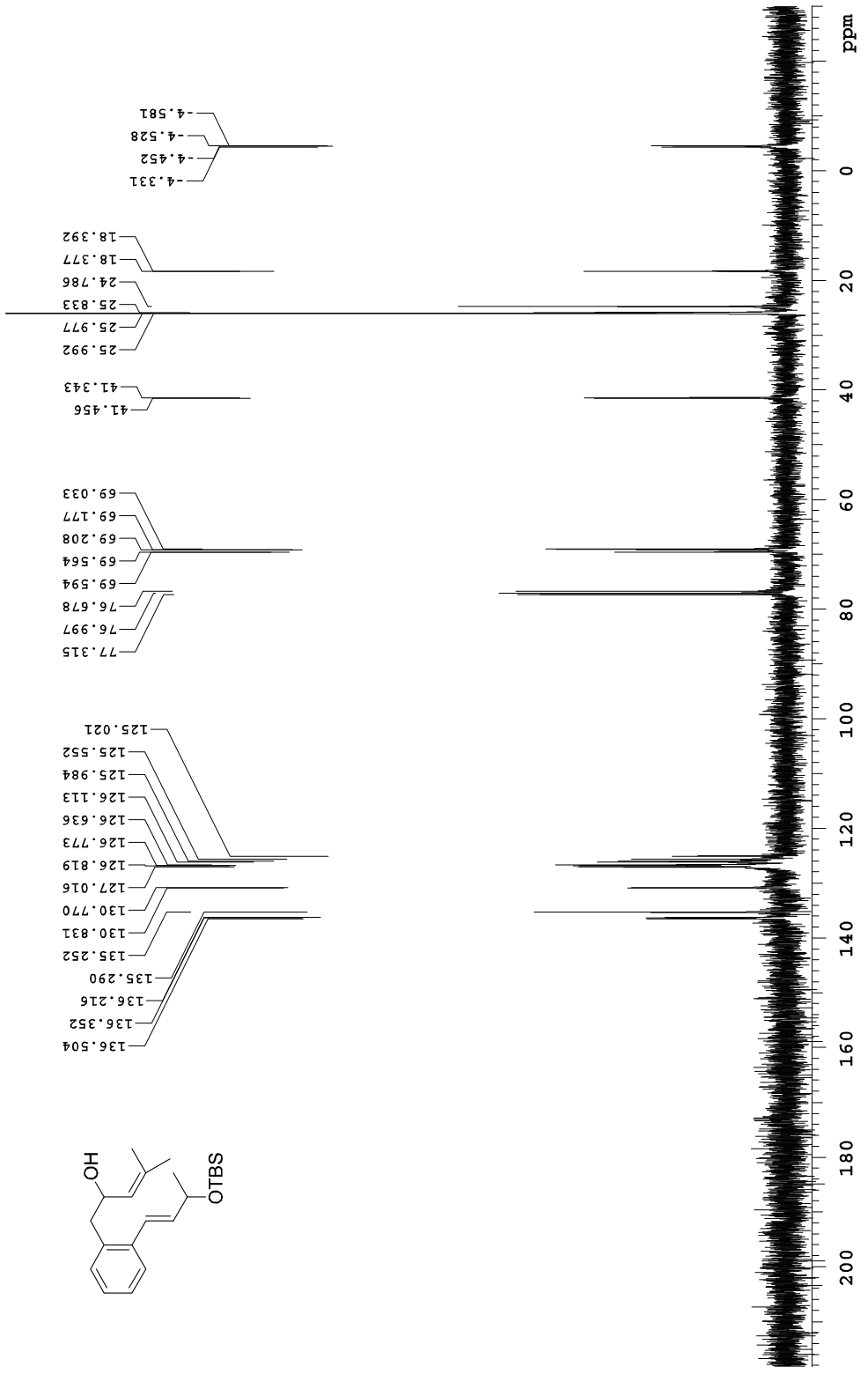
Spectrum 2.82 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **491**



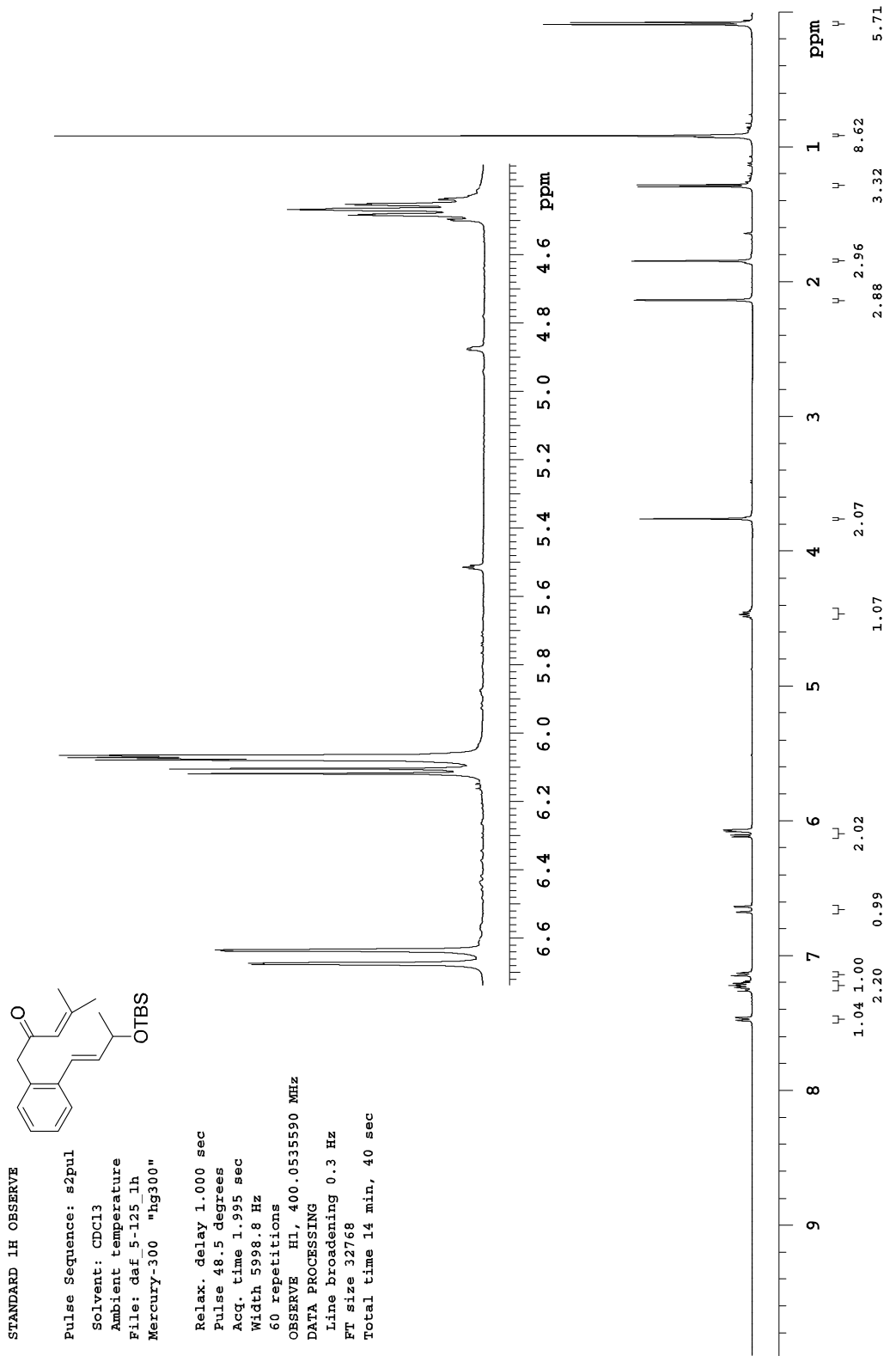
Spectrum 2.83 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **491**



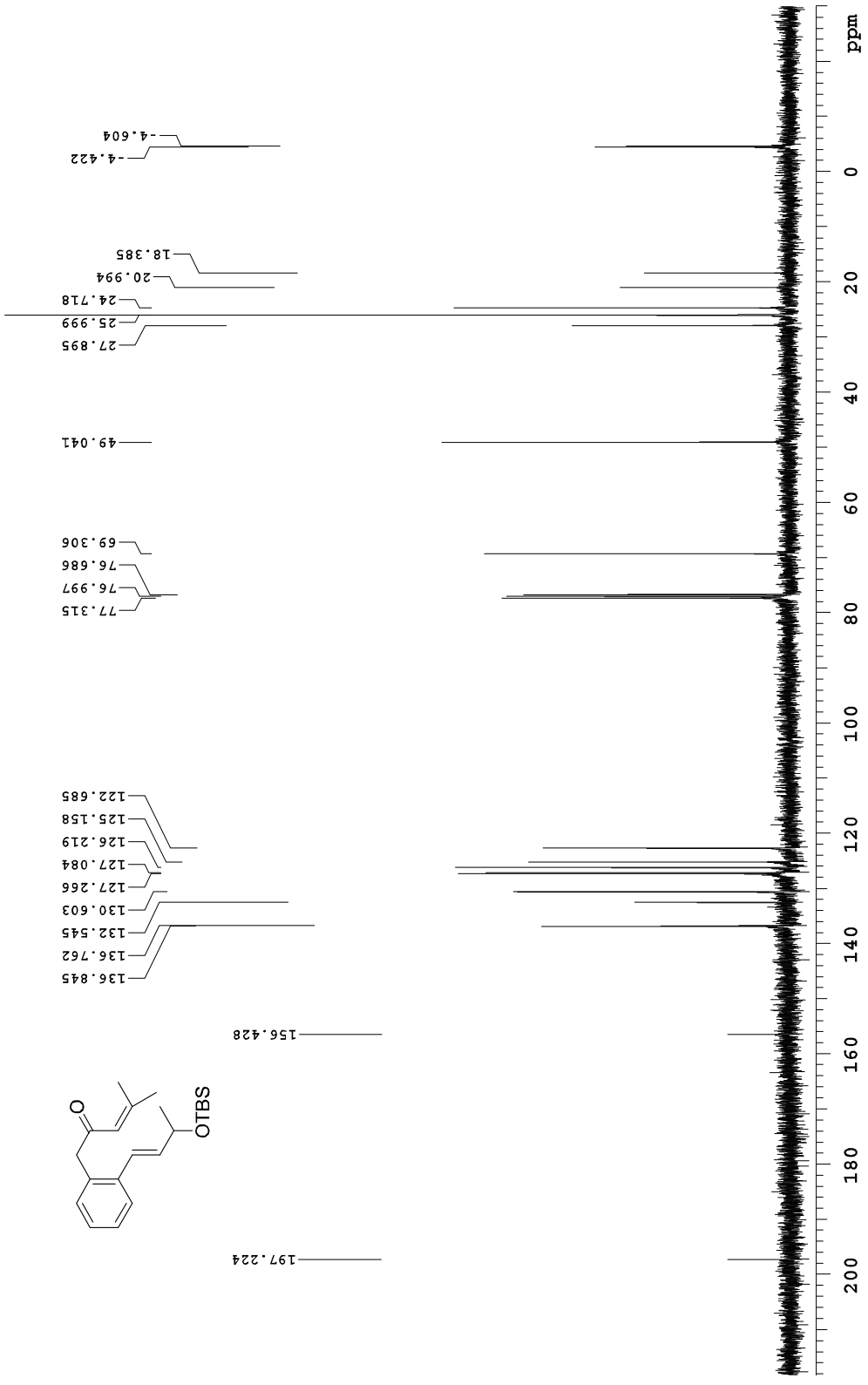
Spectrum 2.84 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **493**



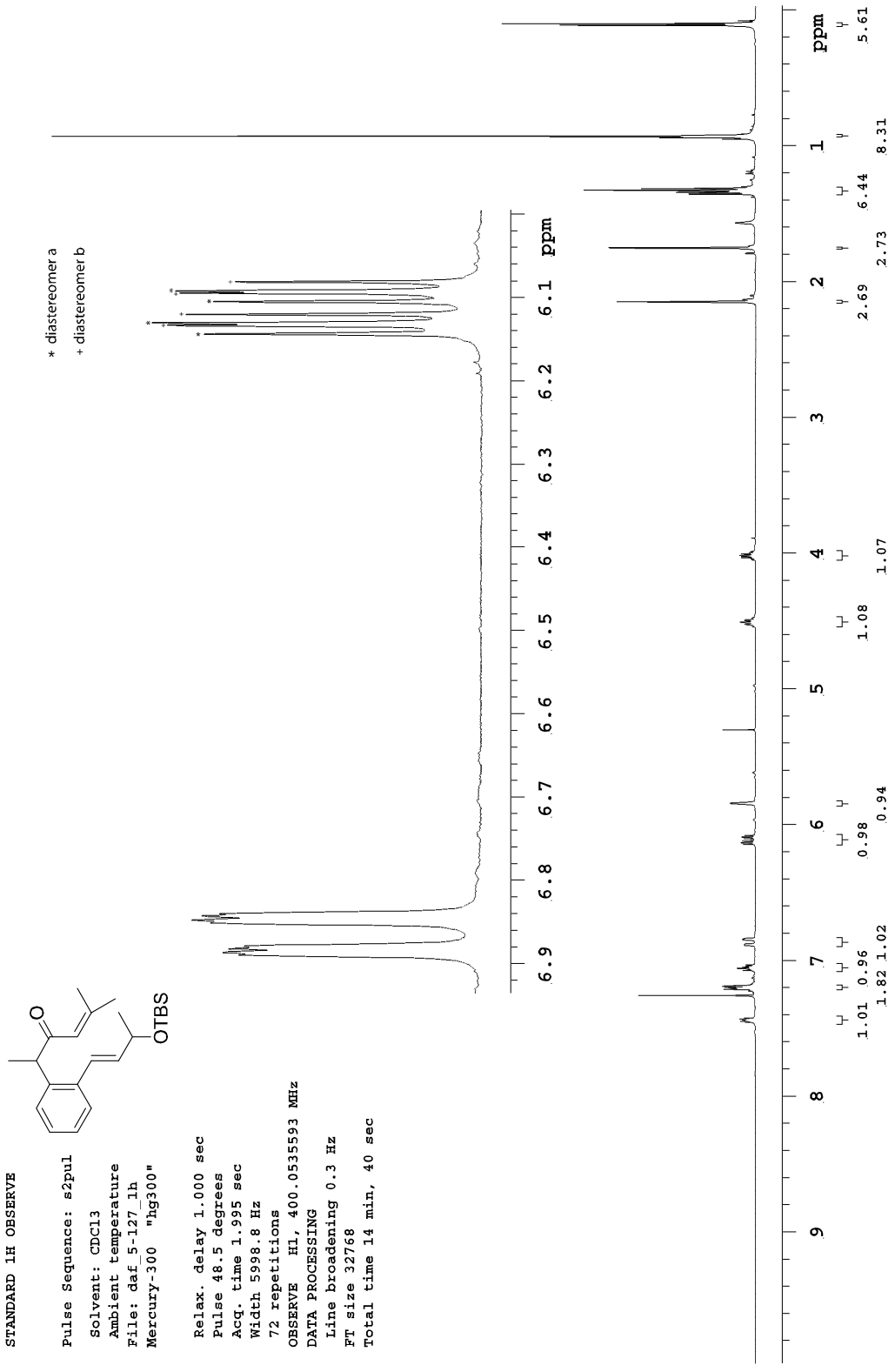
Spectrum 2.85 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **493**



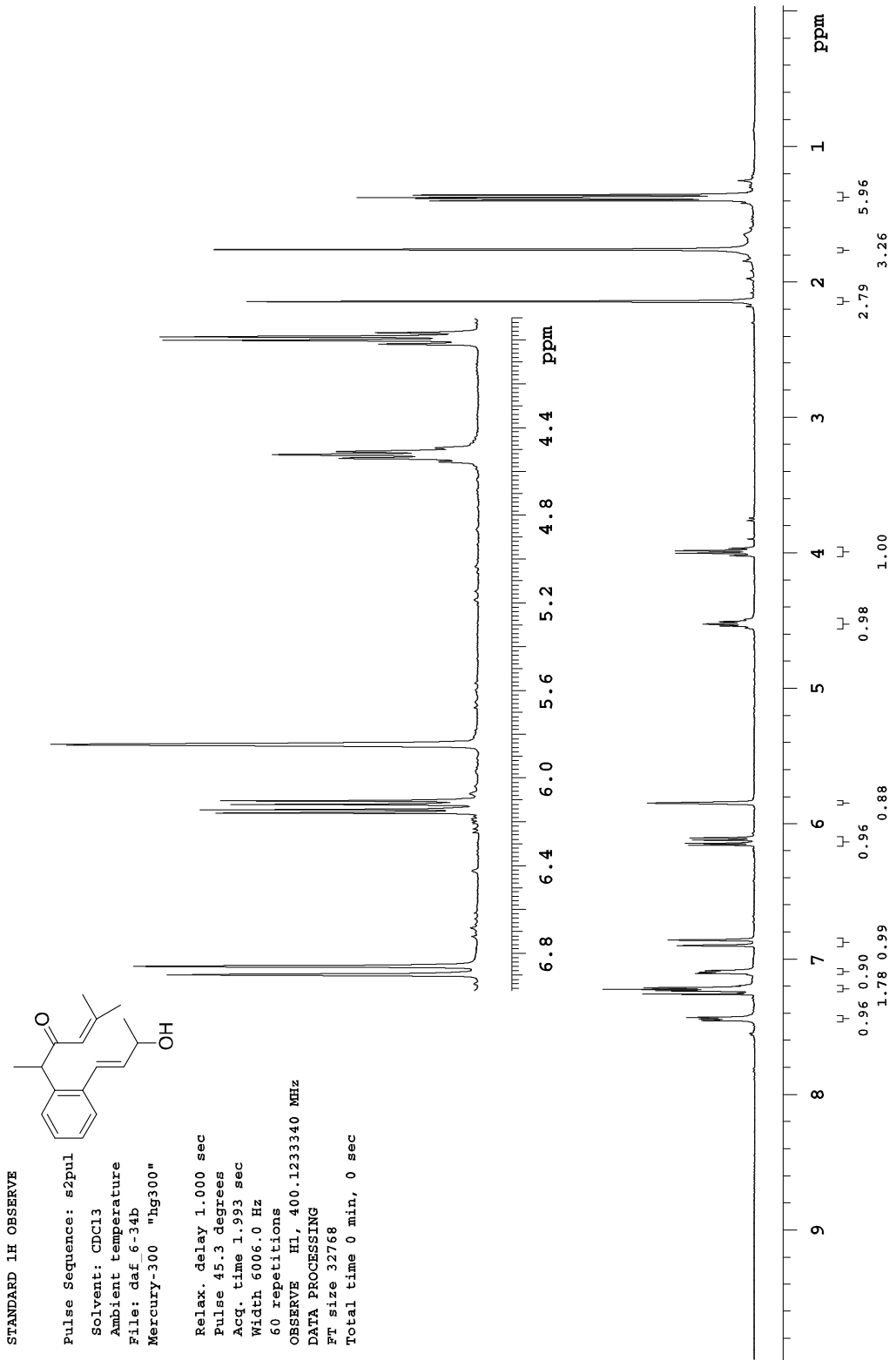
Spectrum 2.86 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **494**



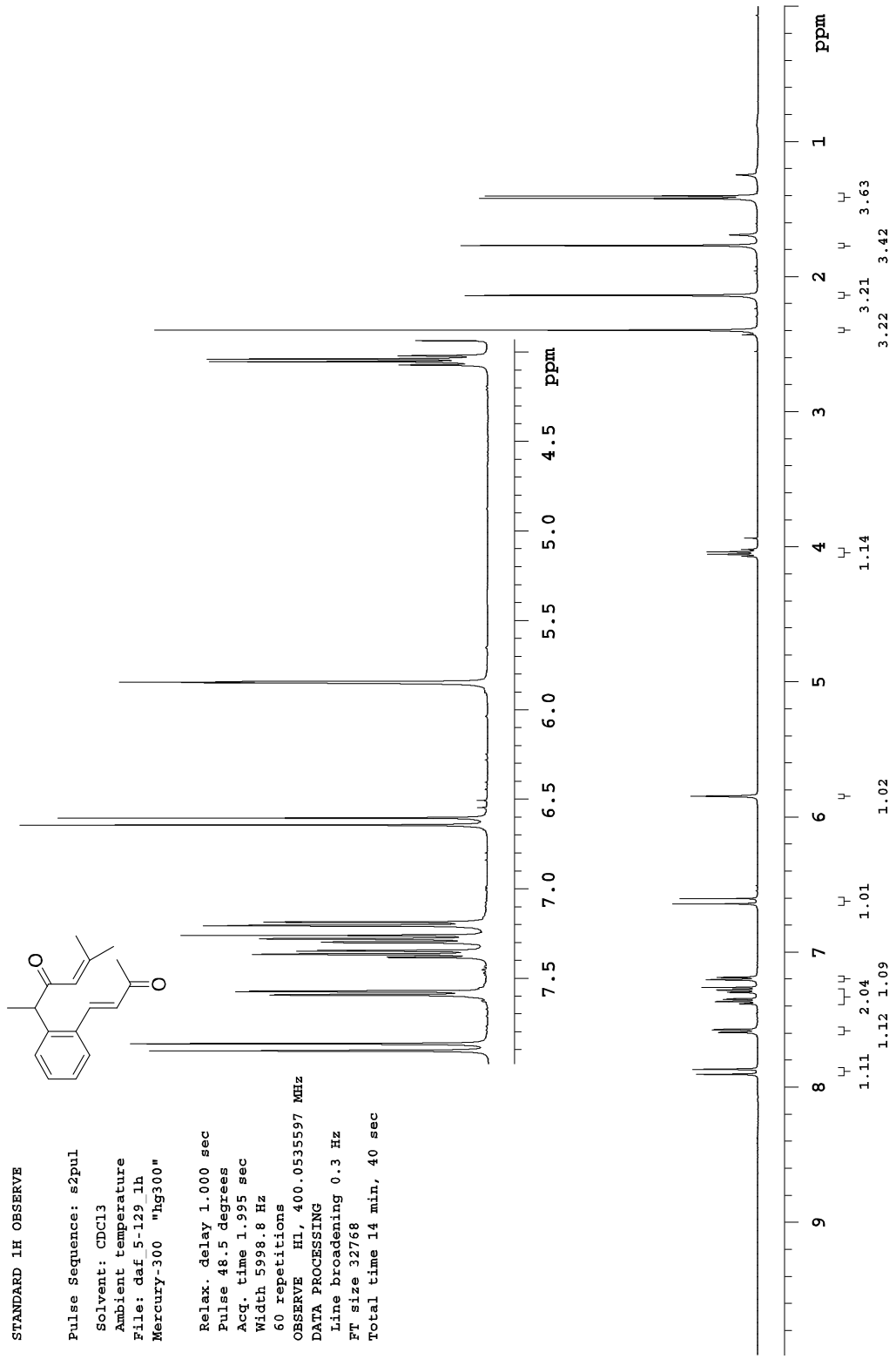
Spectrum 2.87 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **494**



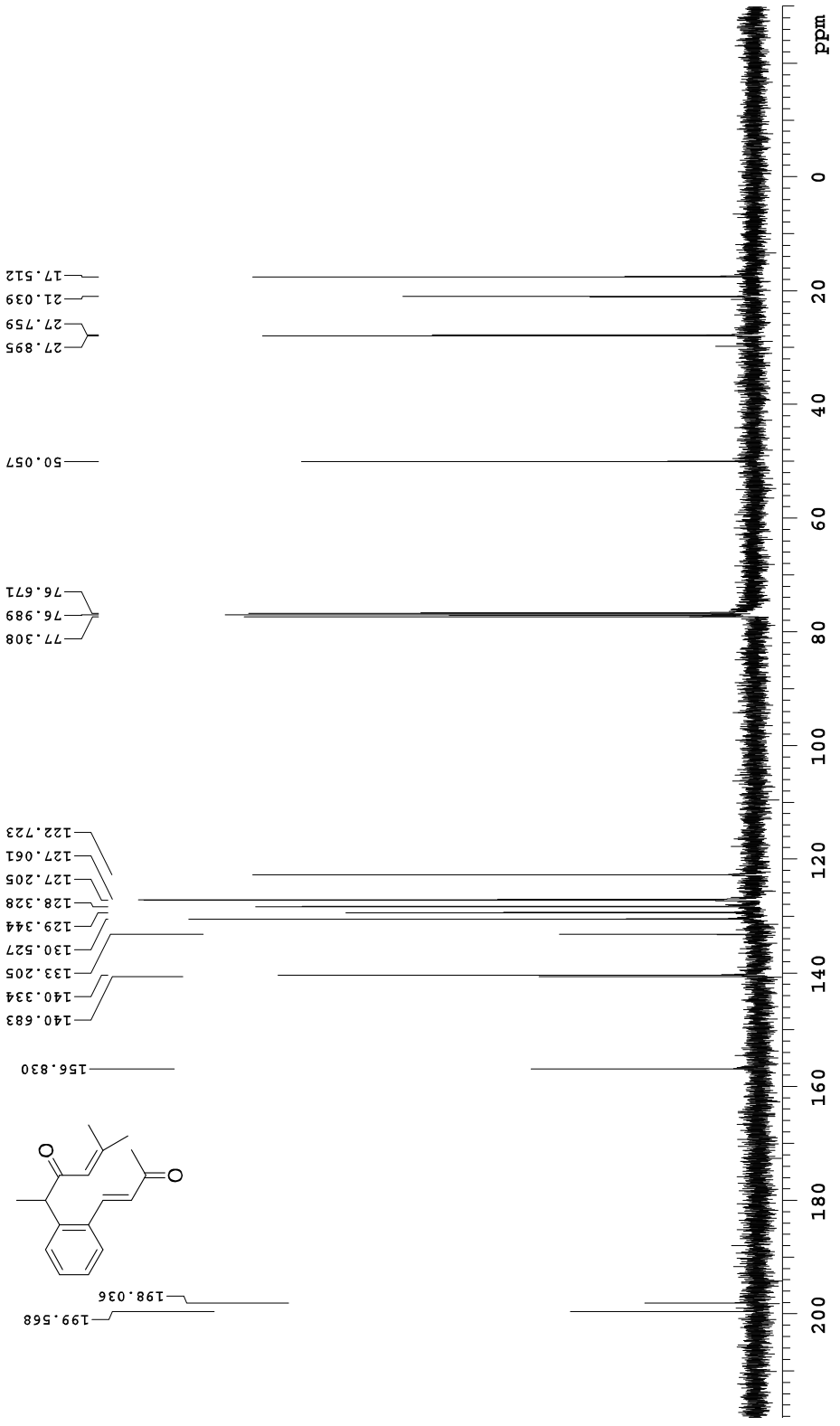
Spectrum 2.88 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **495**



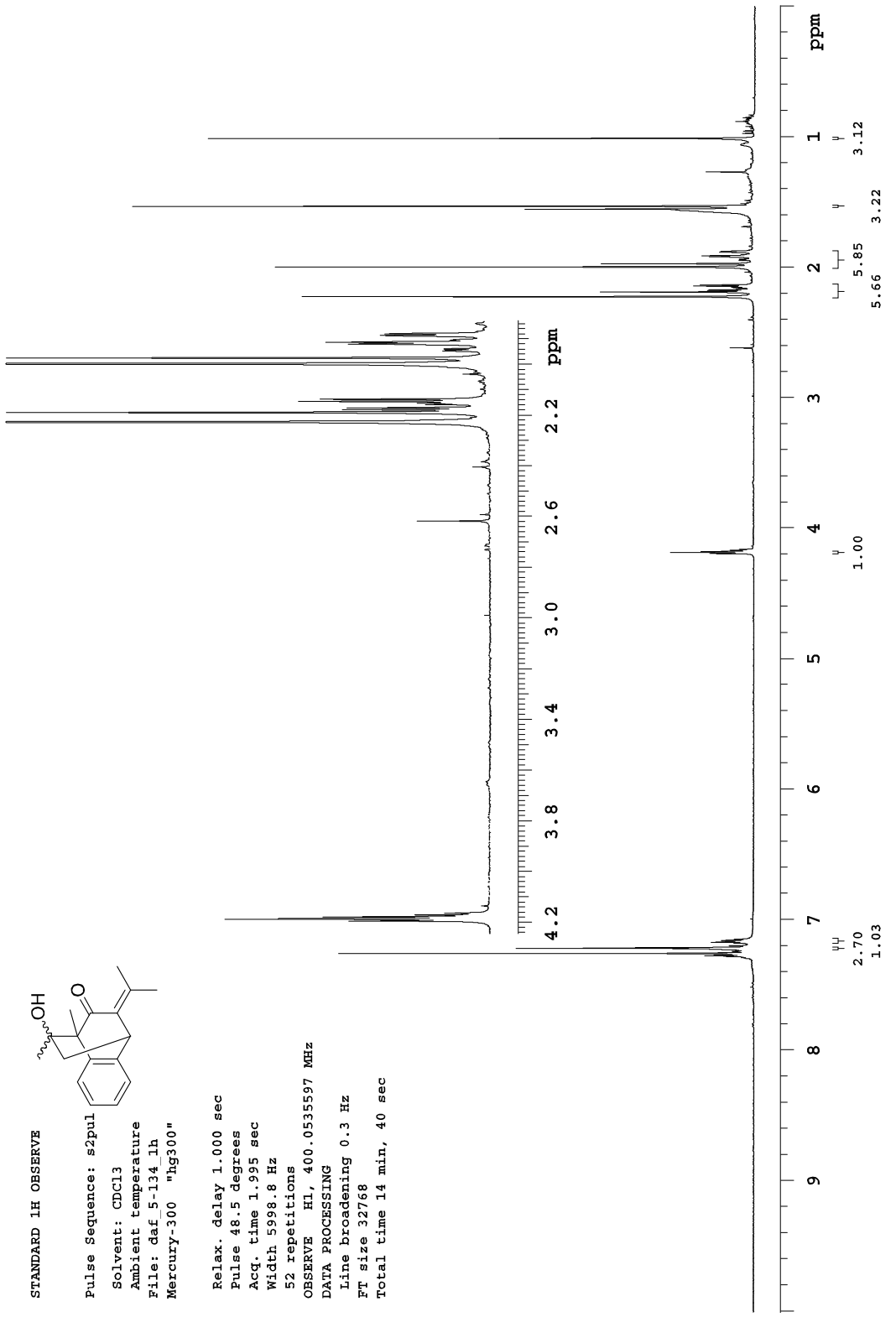
Spectrum 2.89 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **496**



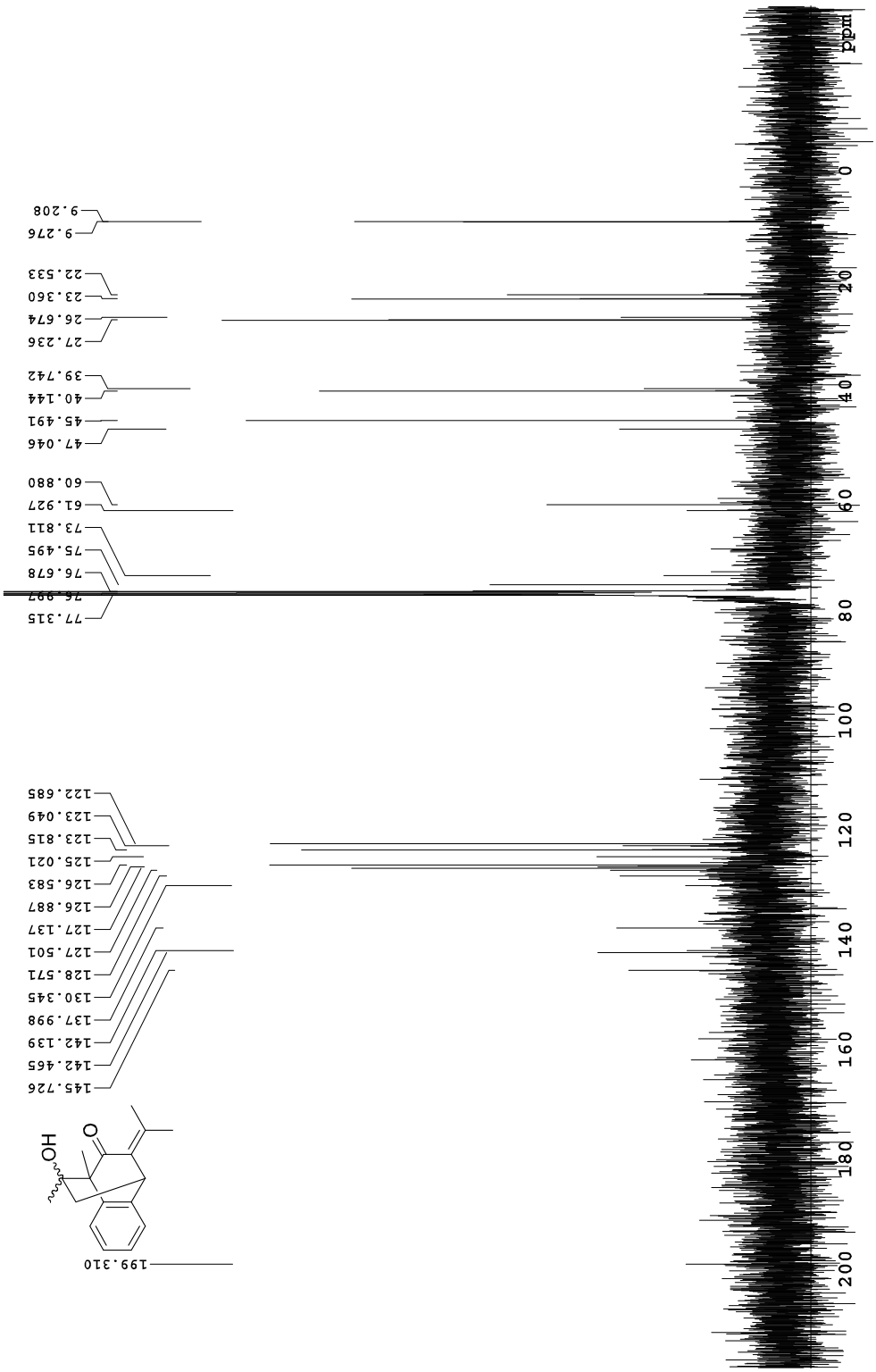
Spectrum 2.90 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **497**



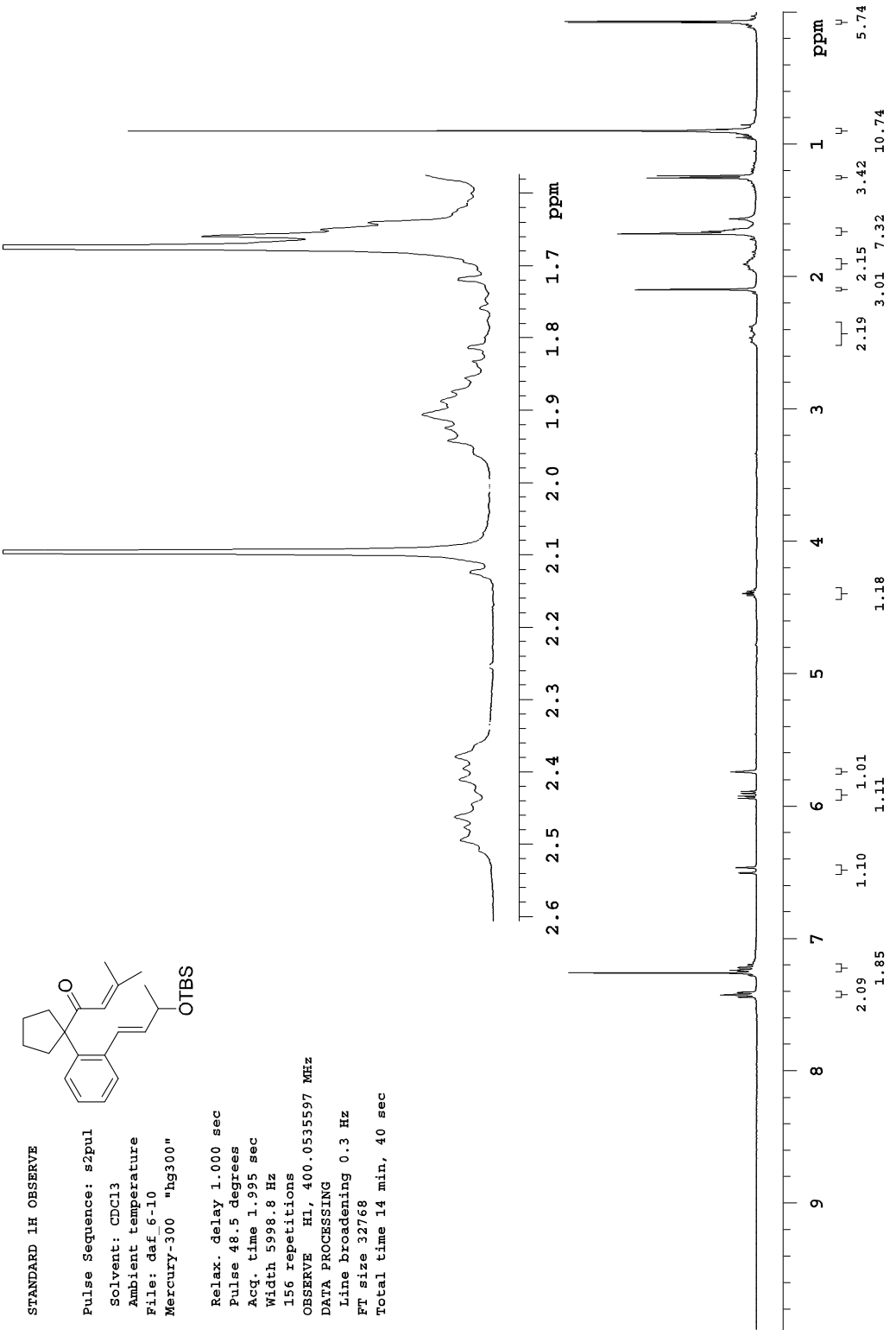
Spectrum 2.91 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **497**



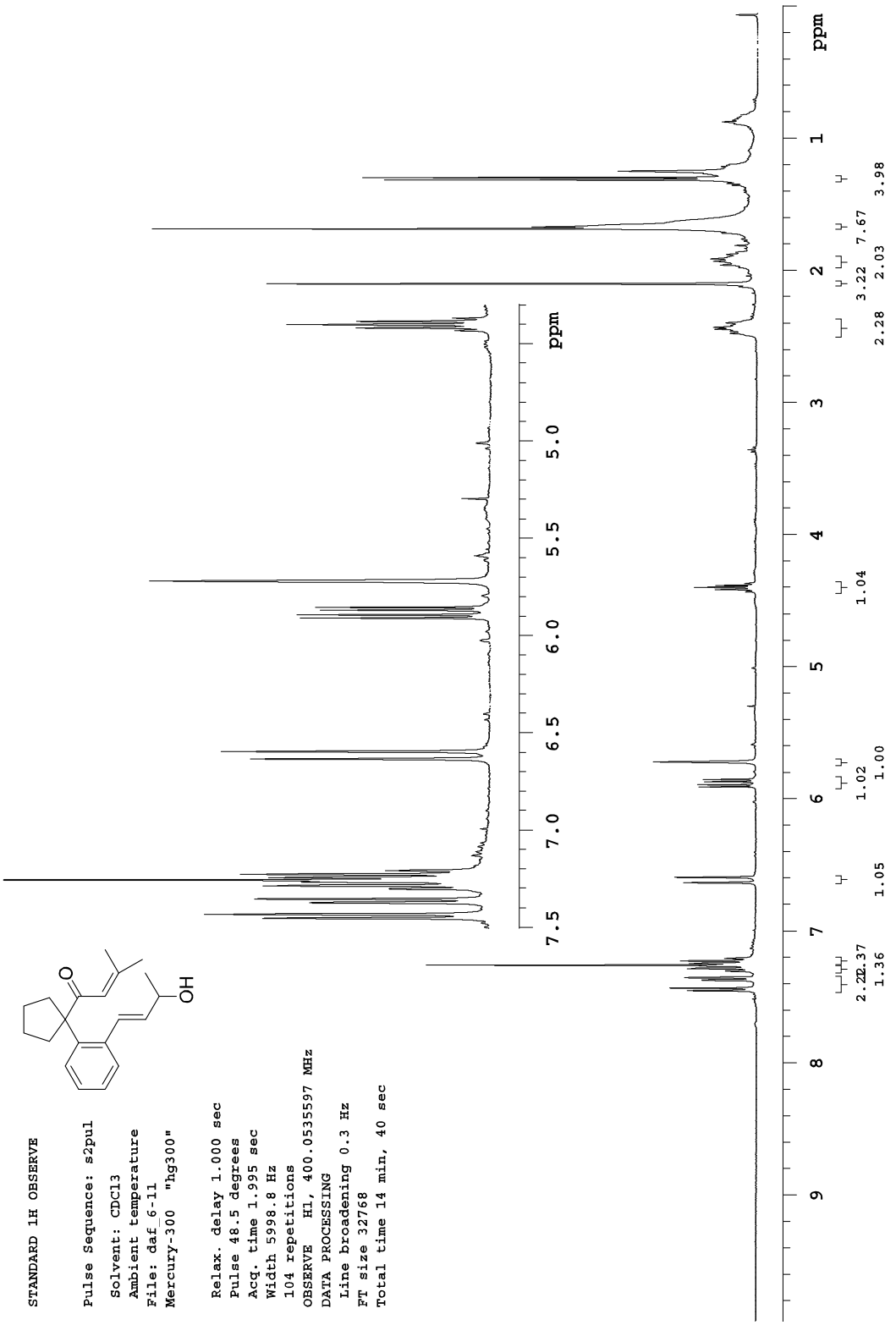
Spectrum 2.92 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **498**



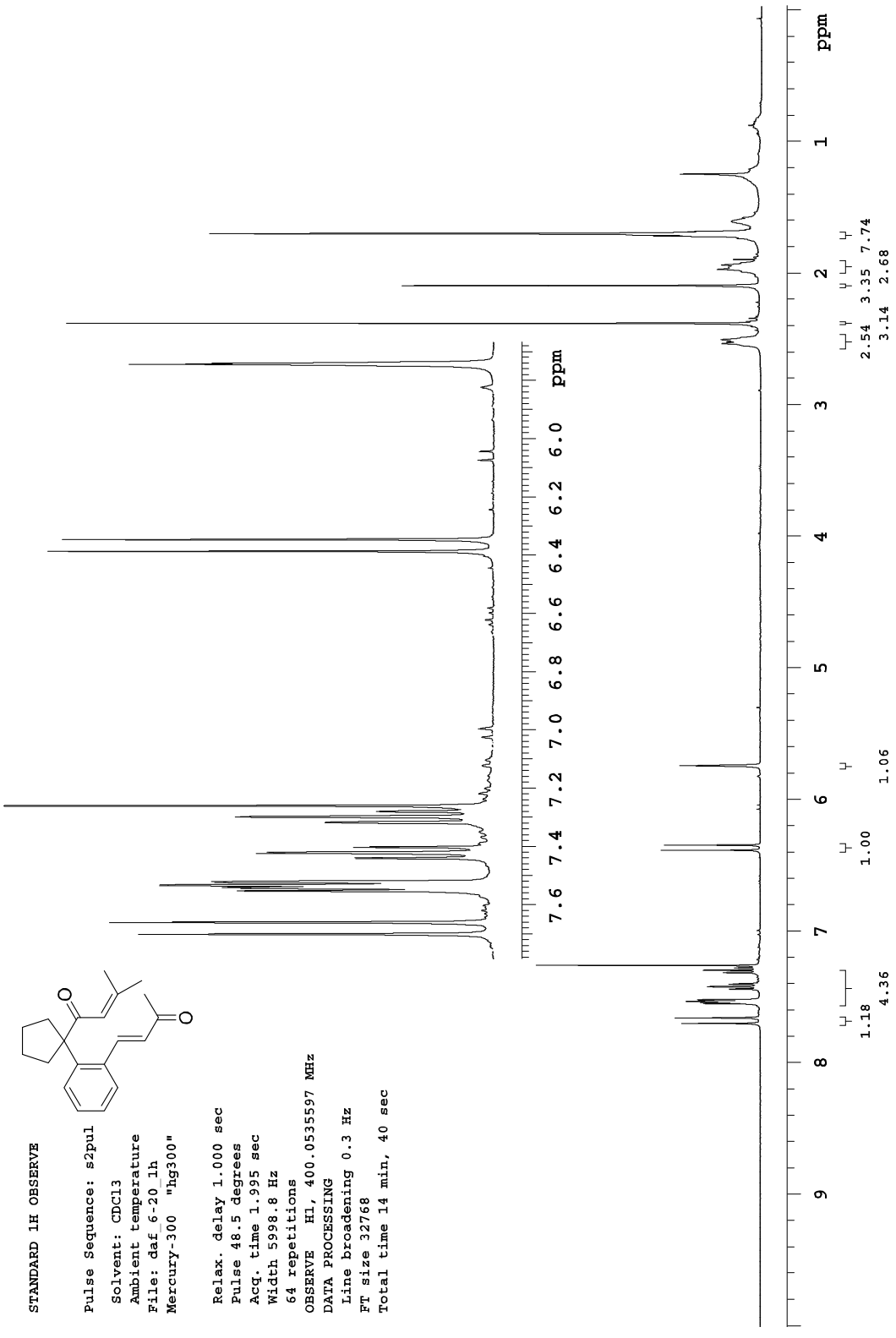
Spectrum 2.93 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **498**



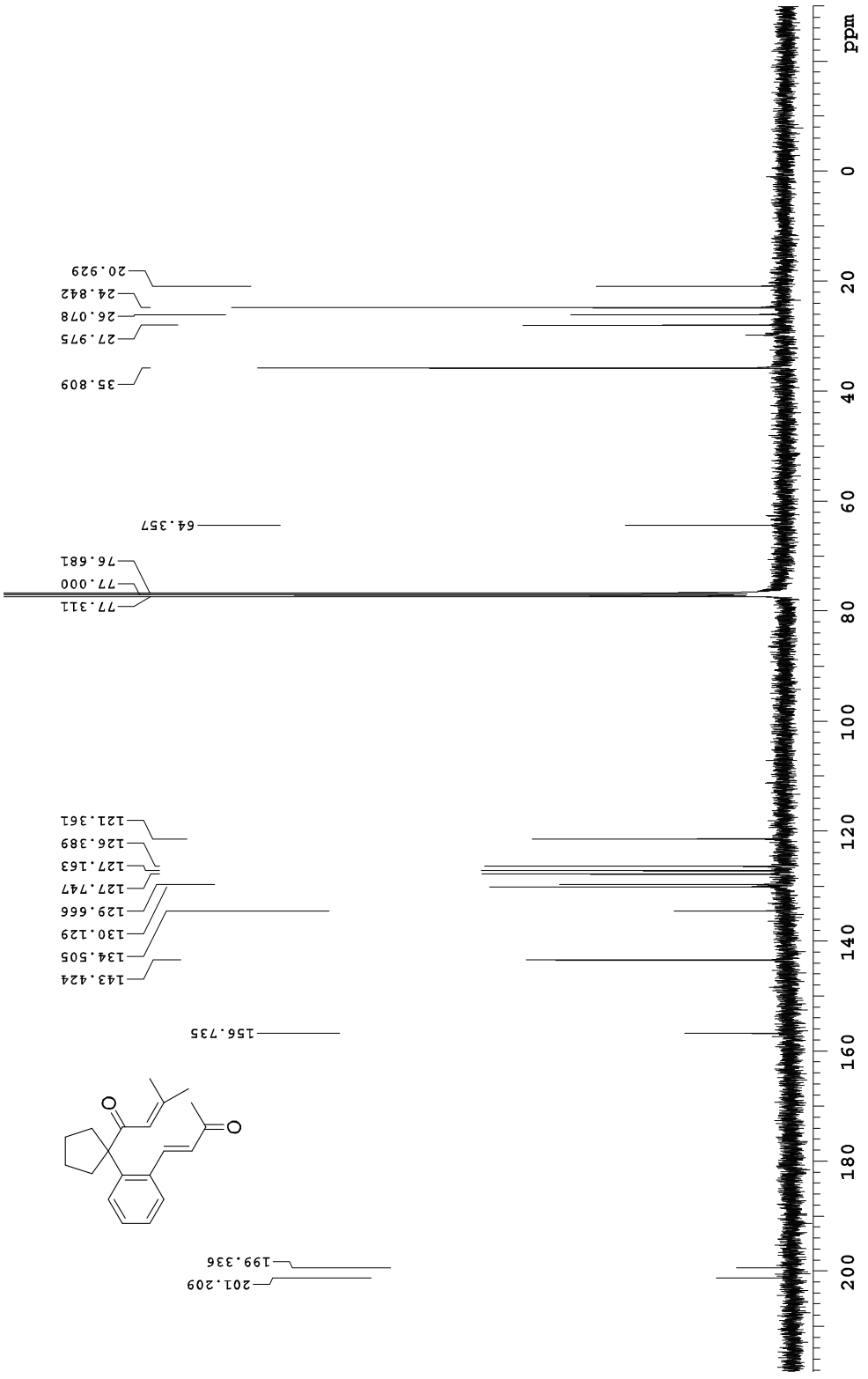
Spectrum 2.94 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **500**



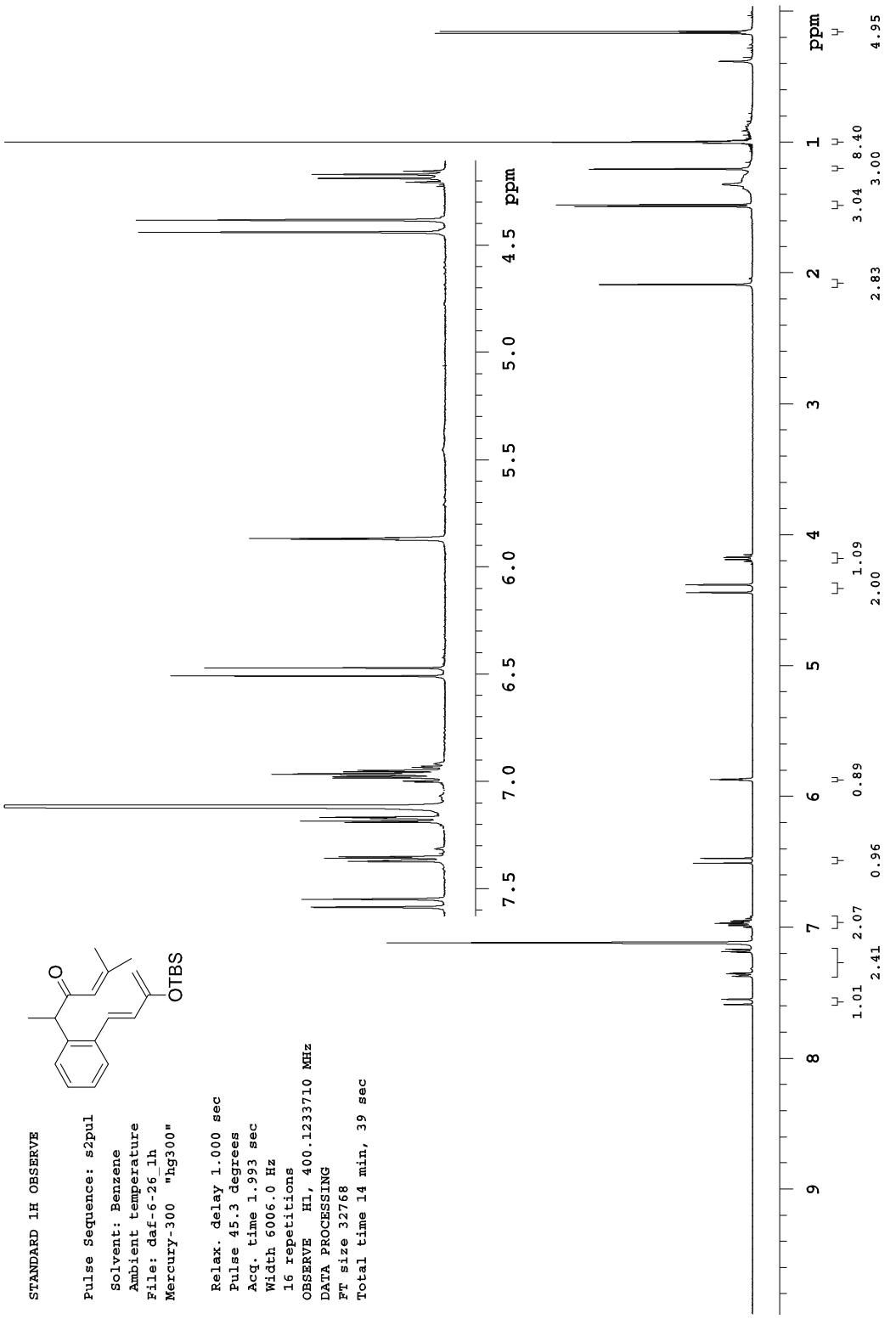
Spectrum 2.95 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **501**



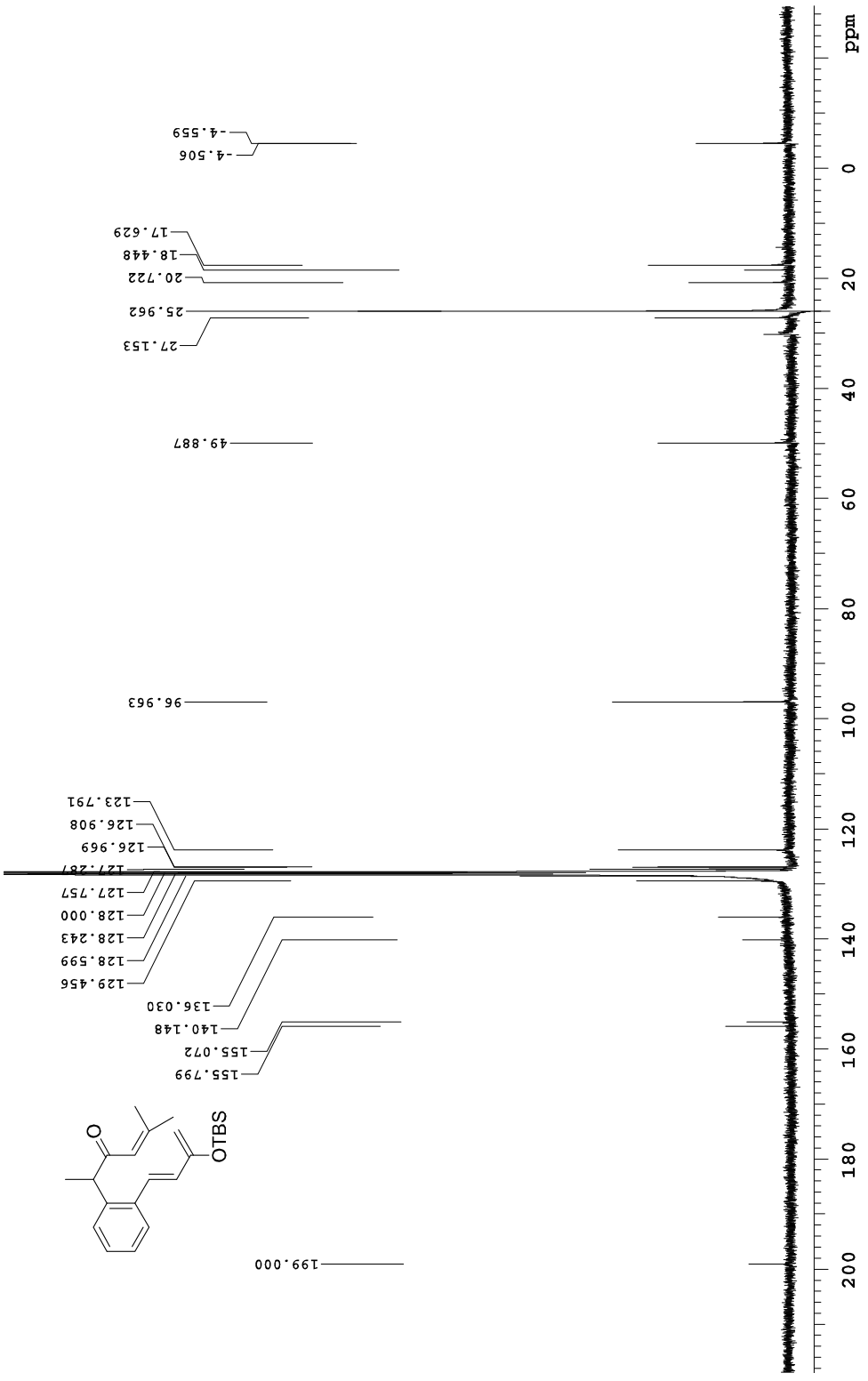
Spectrum 2.96 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **502**



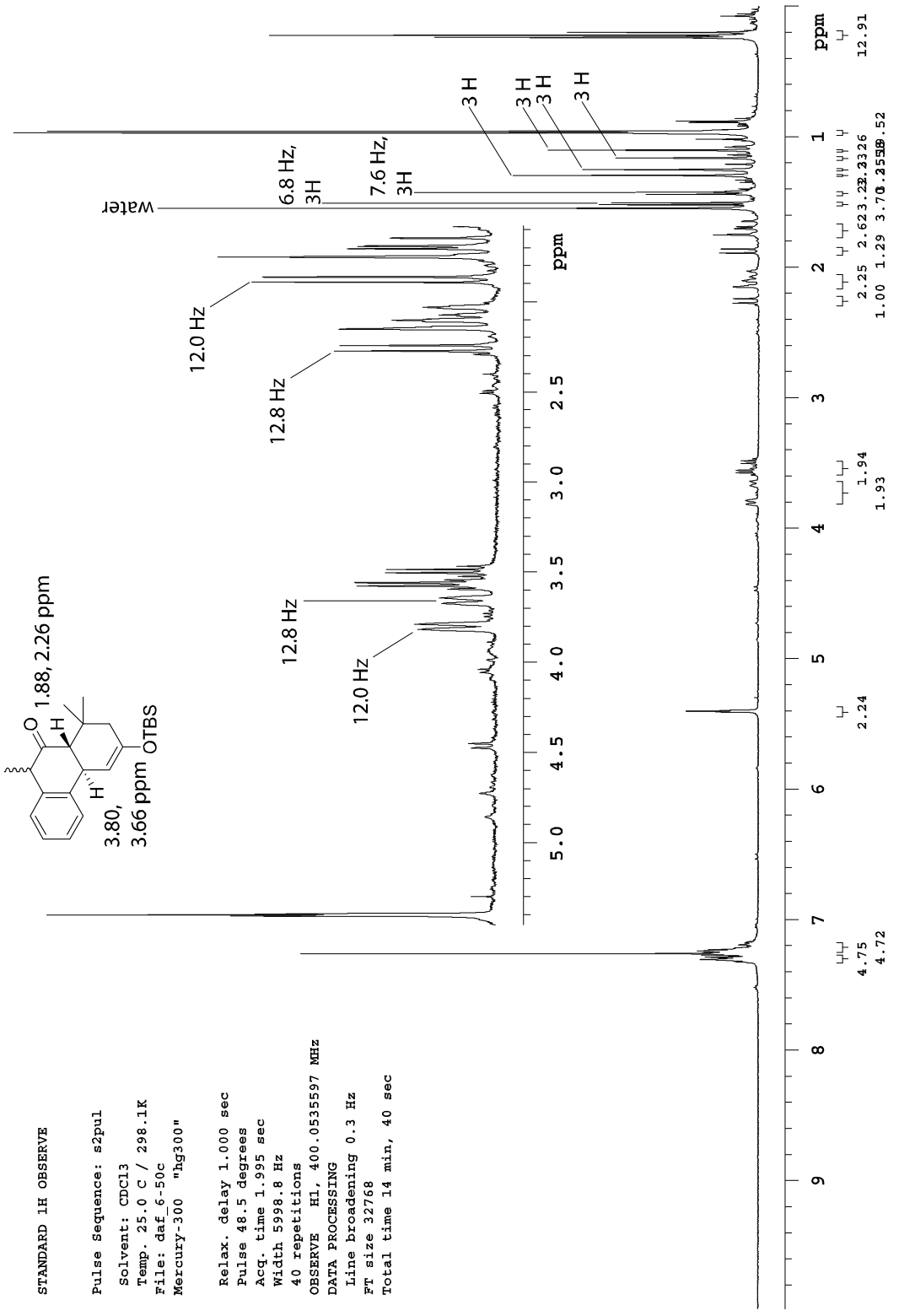
Spectrum 2.97 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **502**



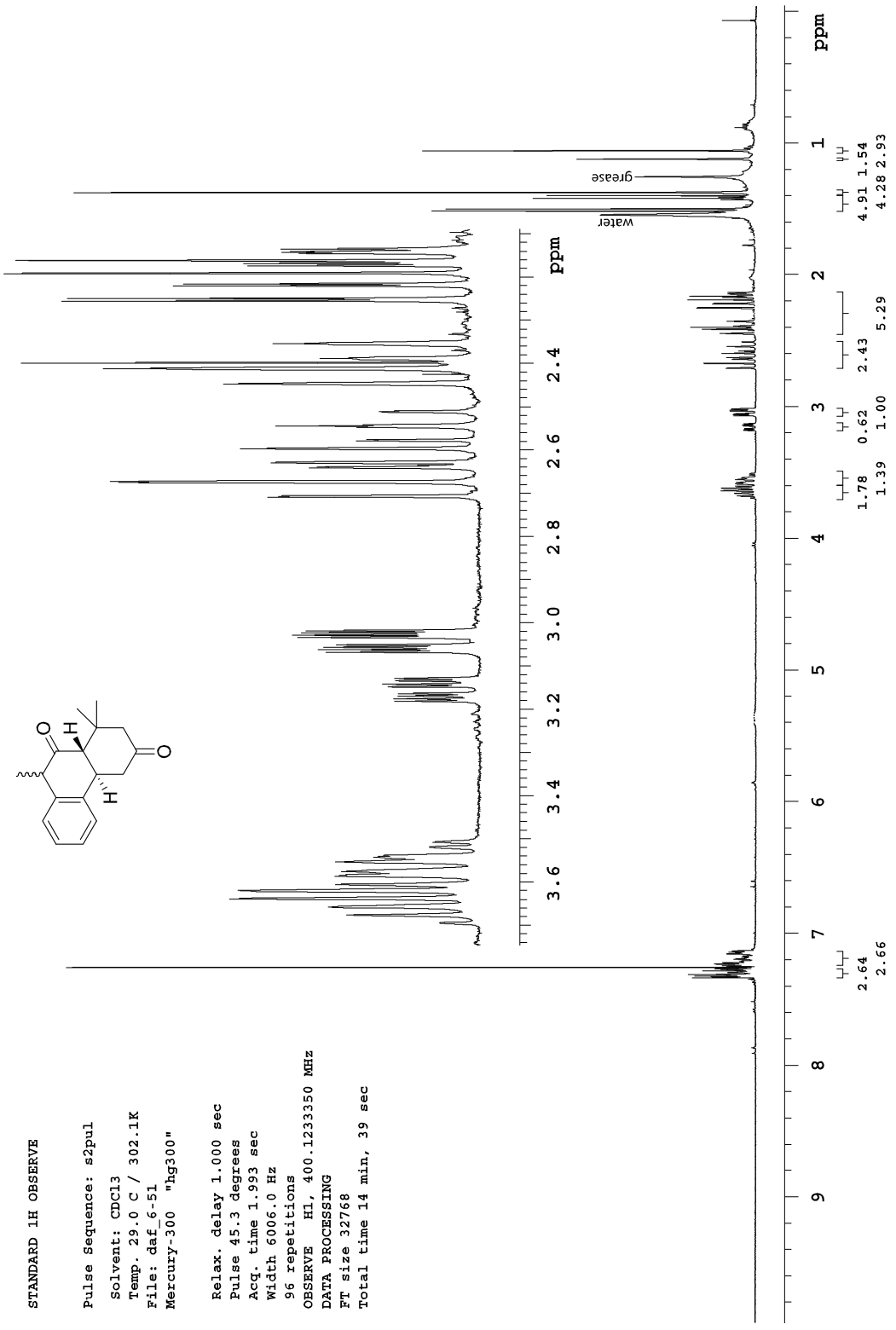
Spectrum 2.98 ^{1}H NMR (C_6D_6, 400 MHz) of compound **503**



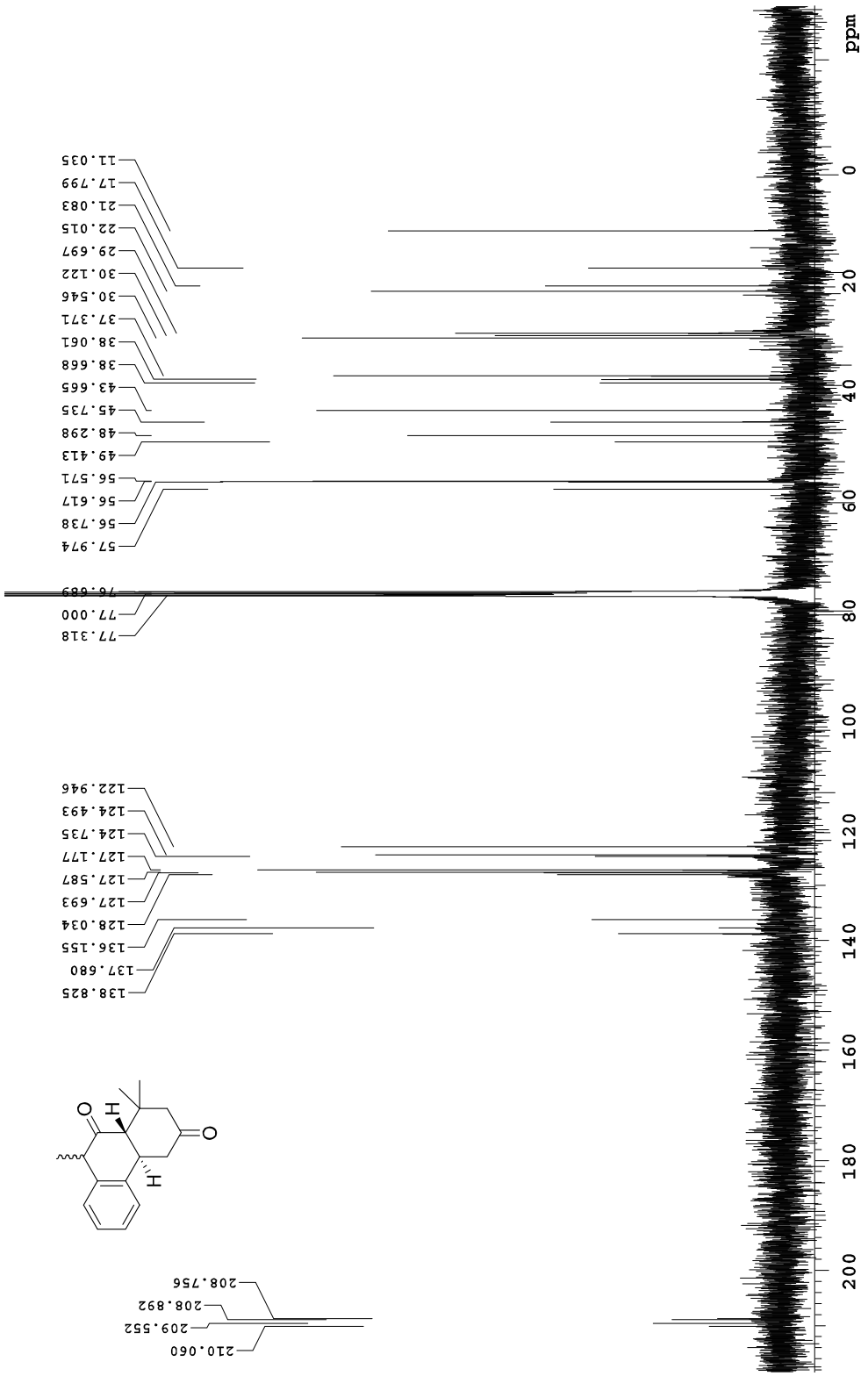
Spectrum 2.99 ^{13}C NMR (C_6D_6, 100 MHz) of compound **503**



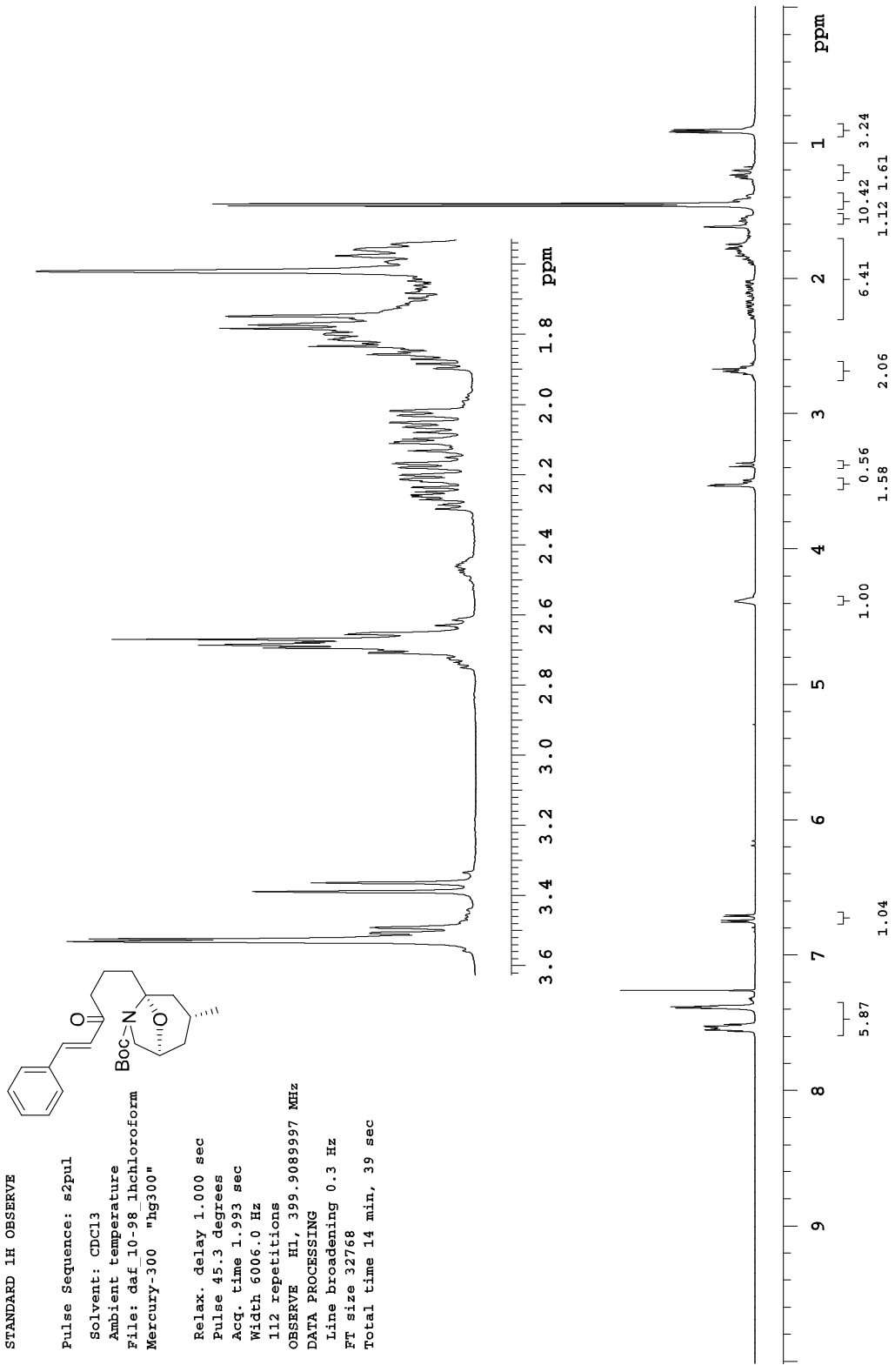
Spectrum 2.100 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **504**



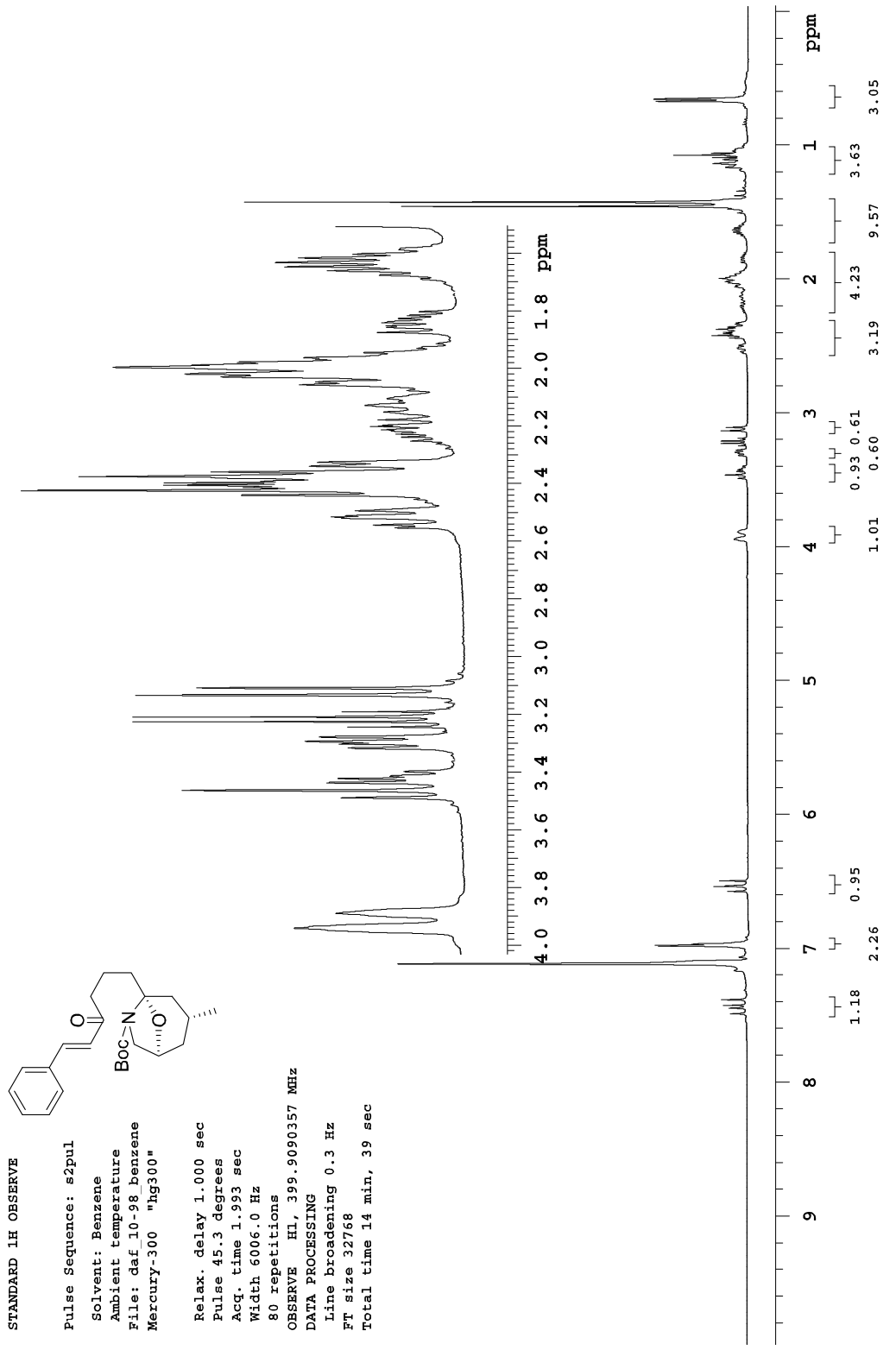
Spectrum 2.101 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **505**



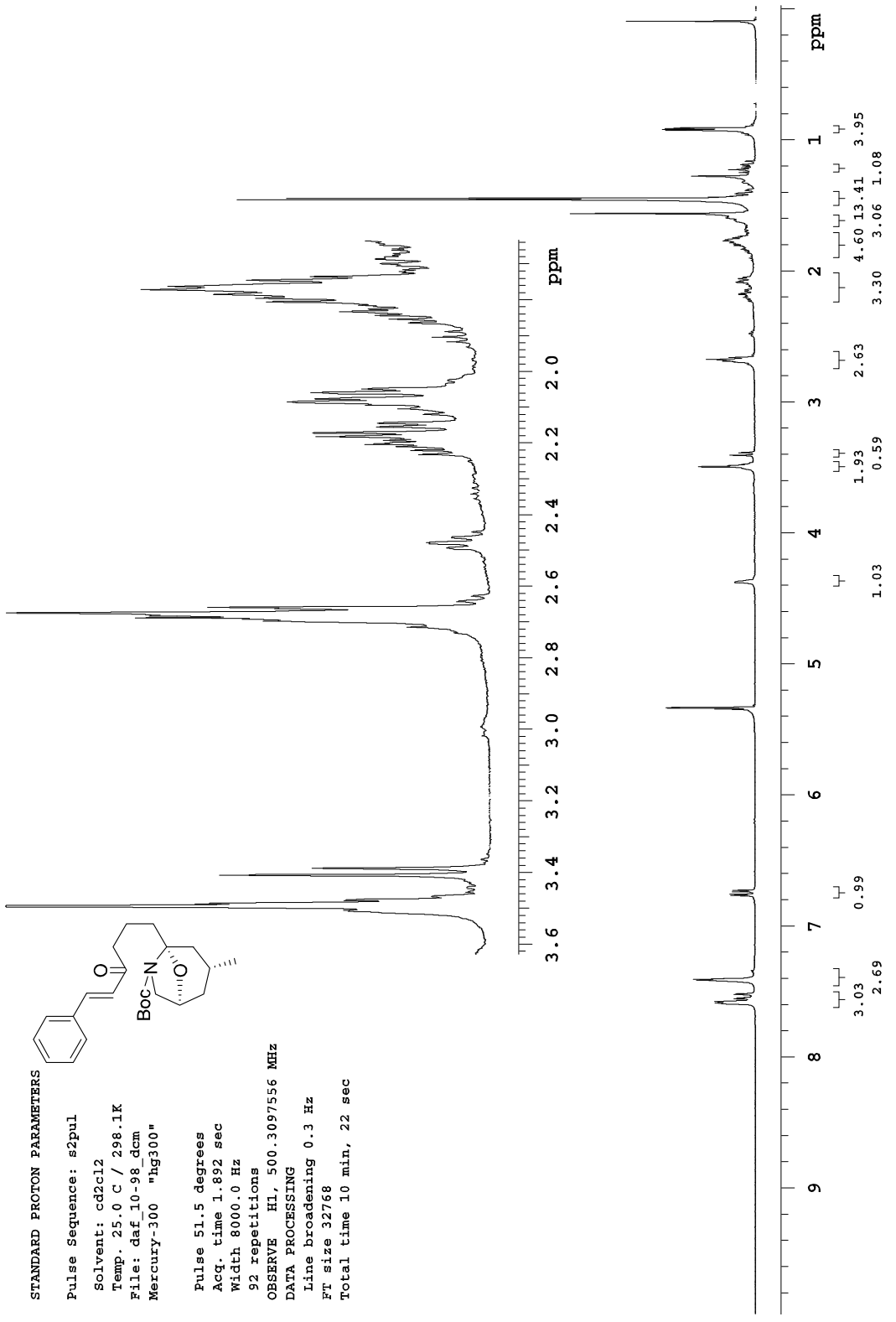
Spectrum 2.102 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **505**



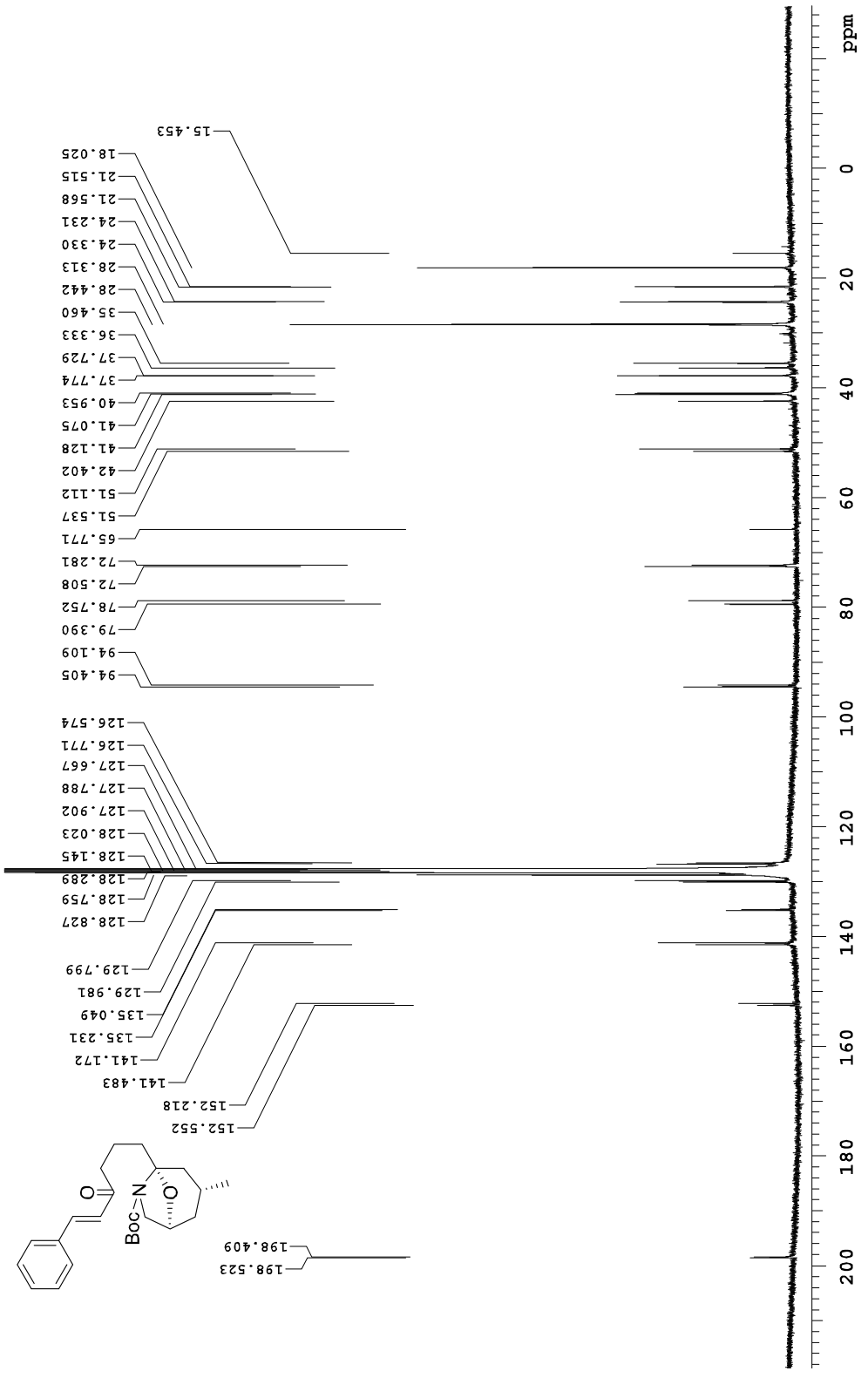
Spectrum 2.103 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **509**



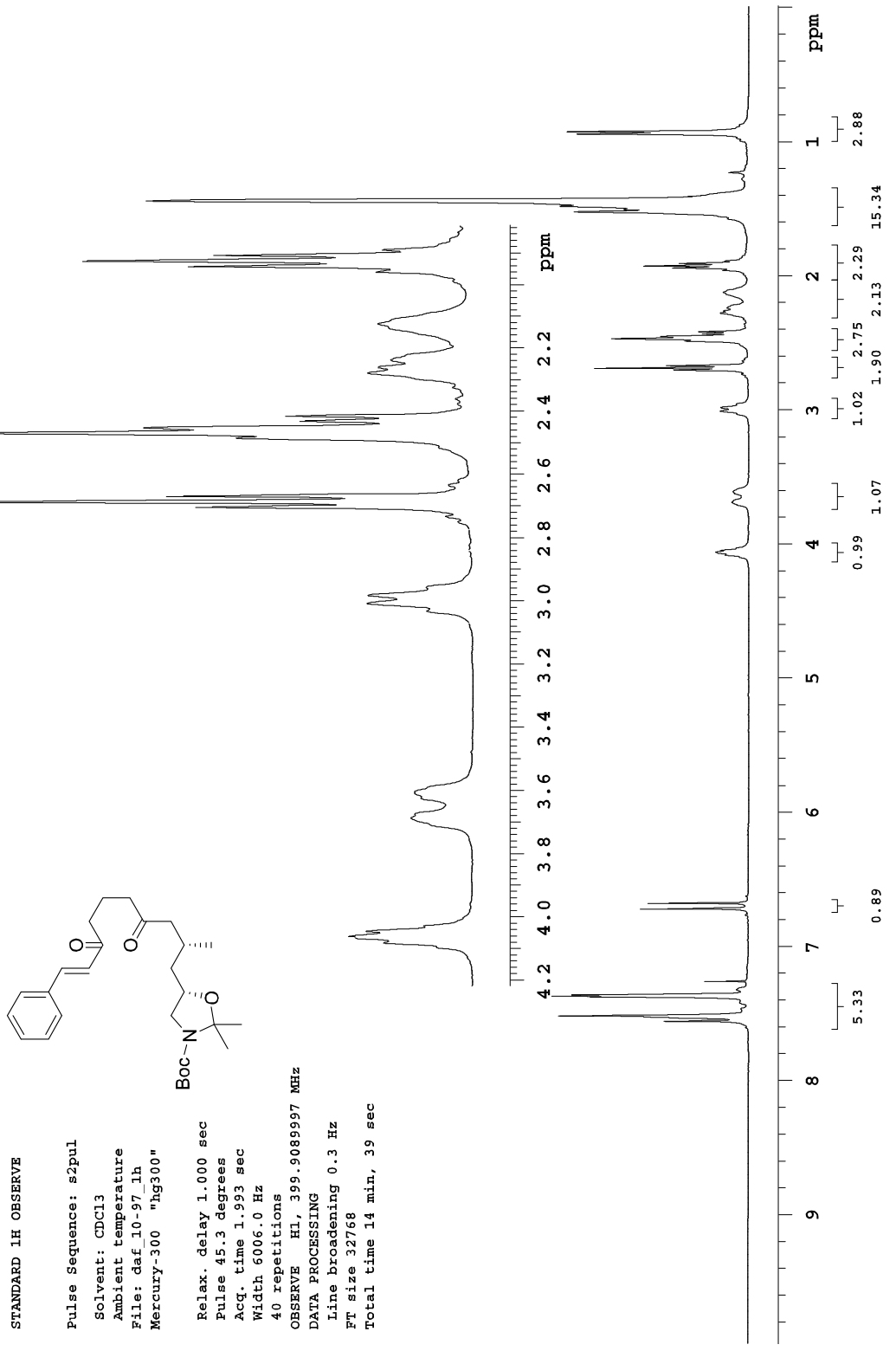
Spectrum 2.104 ^{1}H NMR (C_6D_6, 400 MHz) of compound **509**



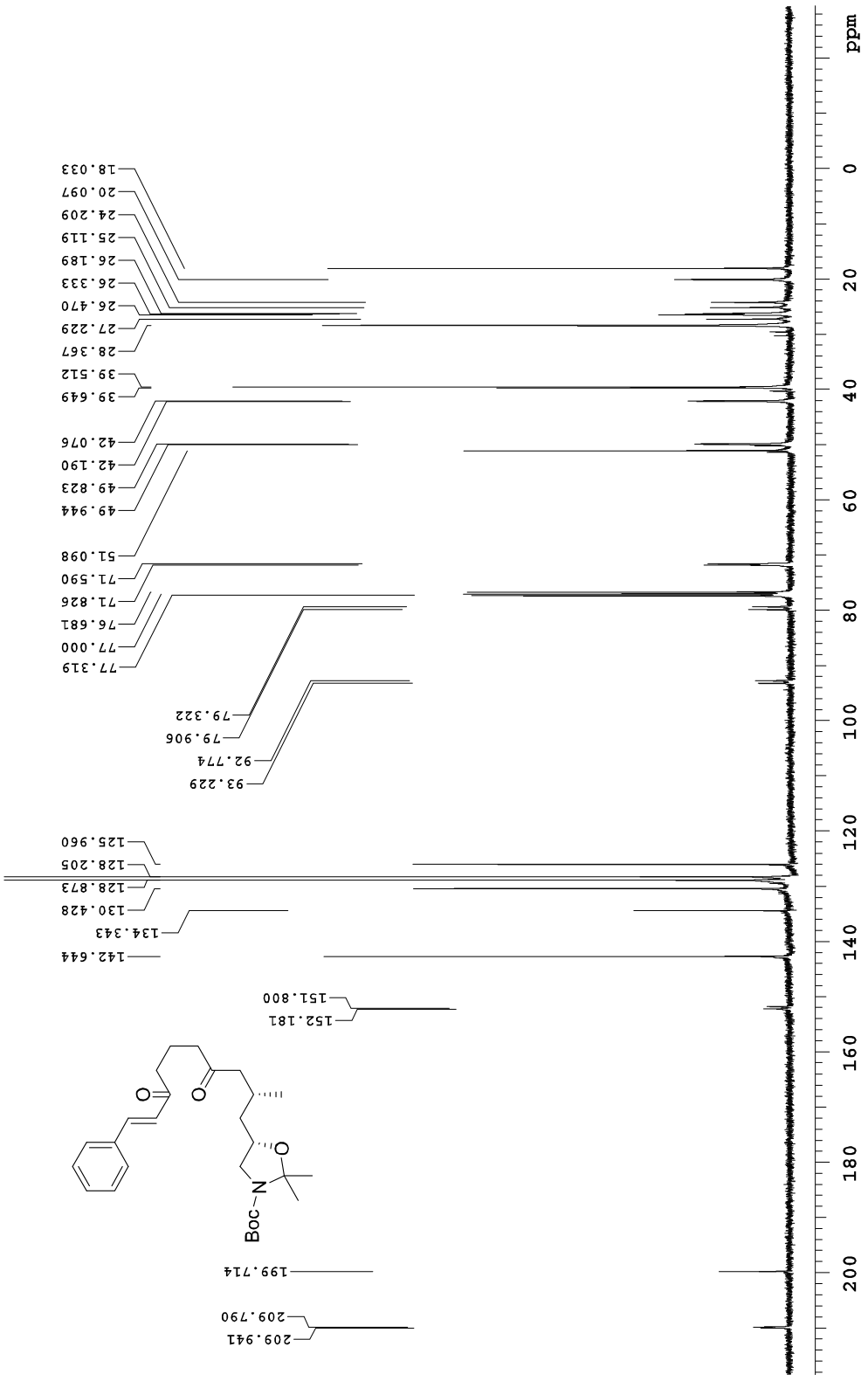
Spectrum 2.105 ^{1}H NMR (CD_2Cl_2, 500 MHz) of compound **509**



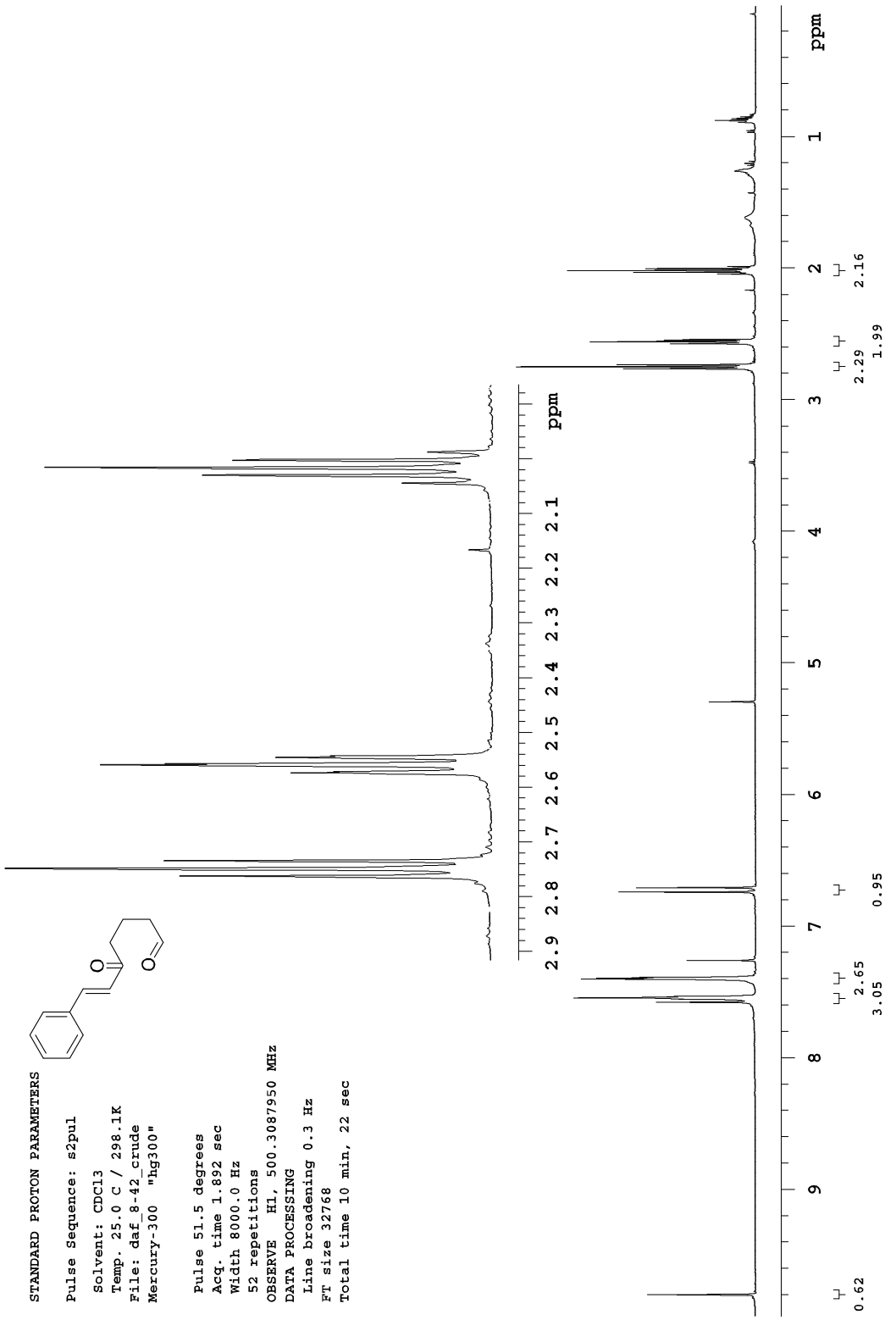
Spectrum 2.106 ^{13}C NMR (C_6D_6, 100 MHz) of compound **509**



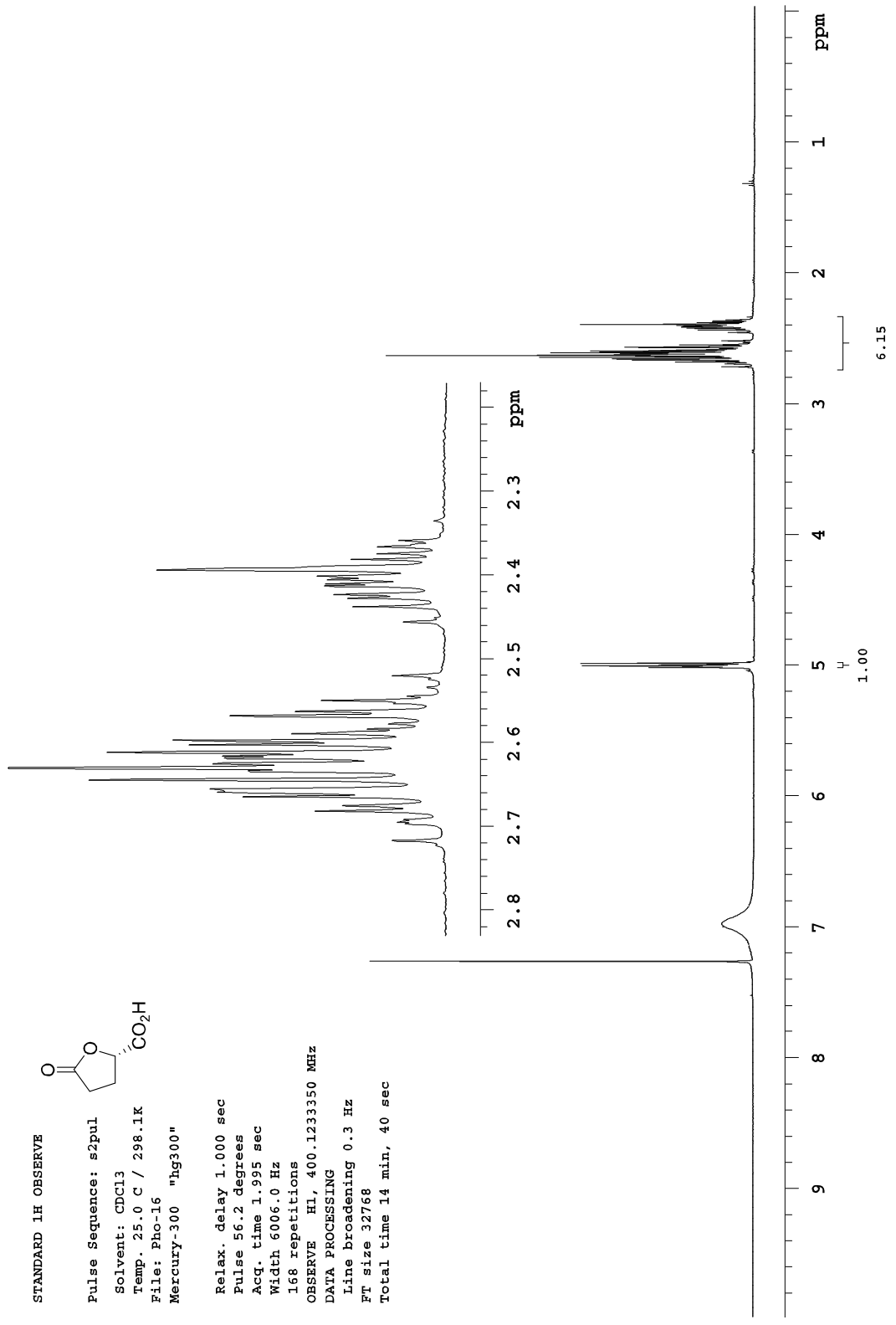
Spectrum 2.107 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **510**



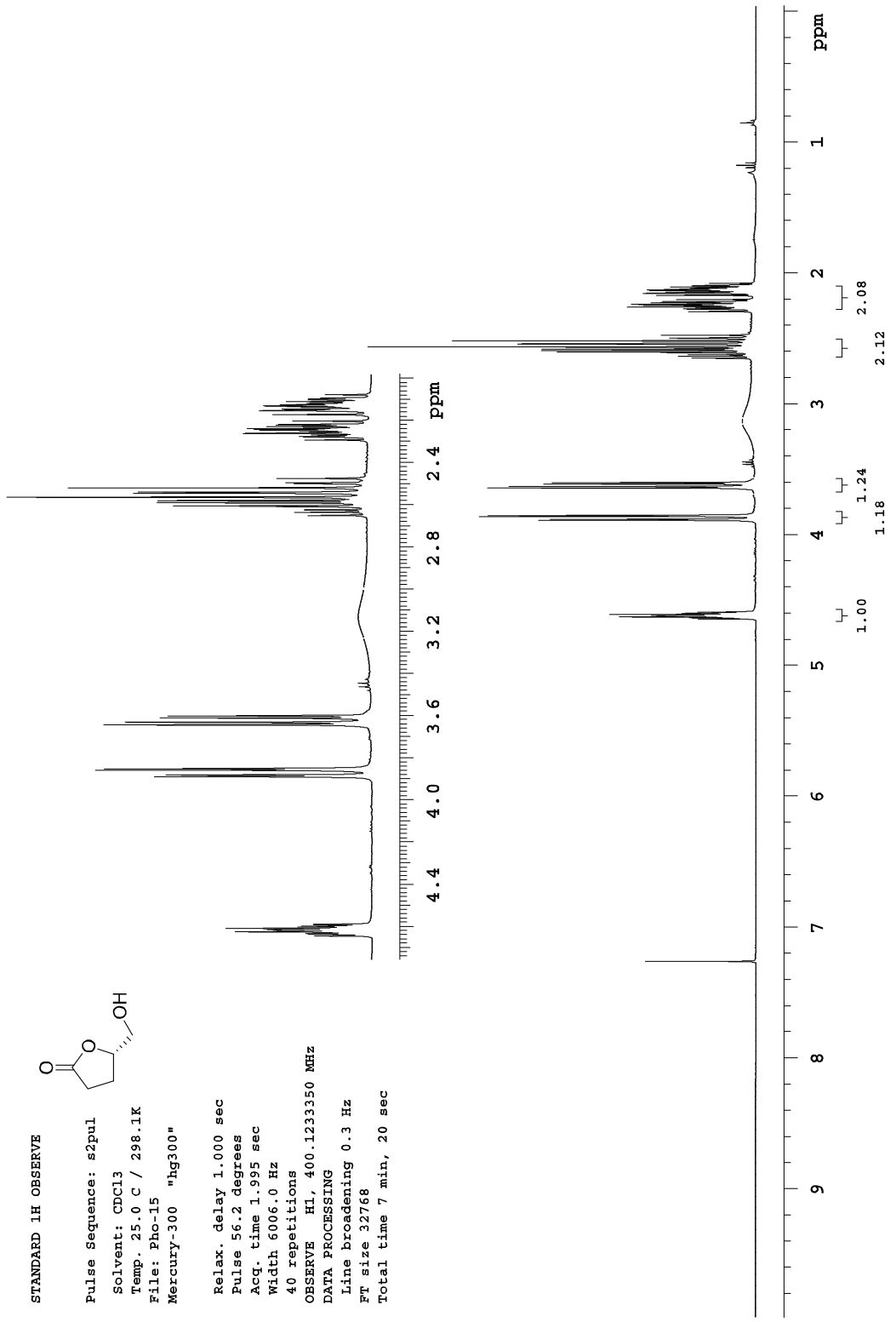
Spectrum 2.108 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **510**



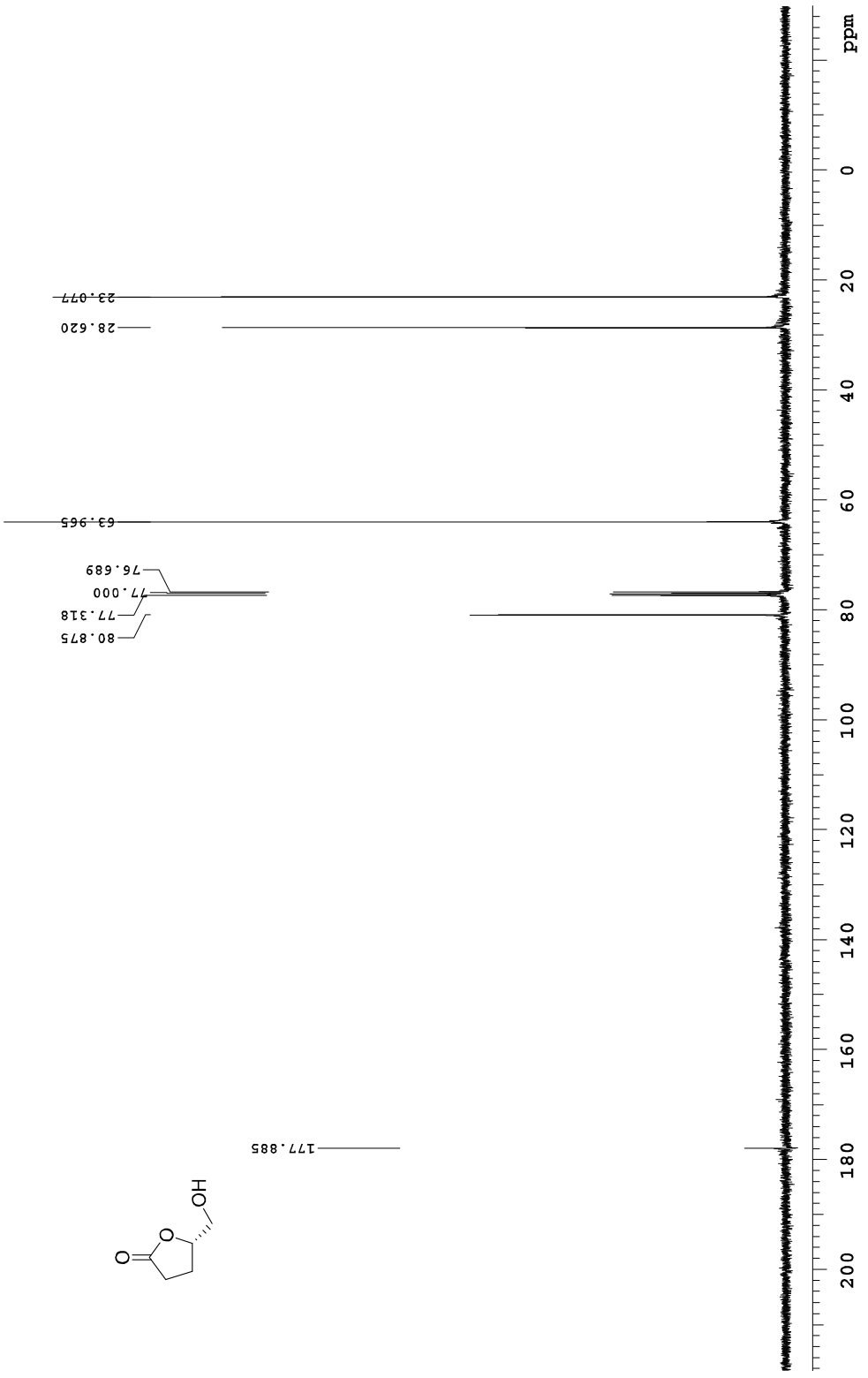
Spectrum 2.109 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **511**



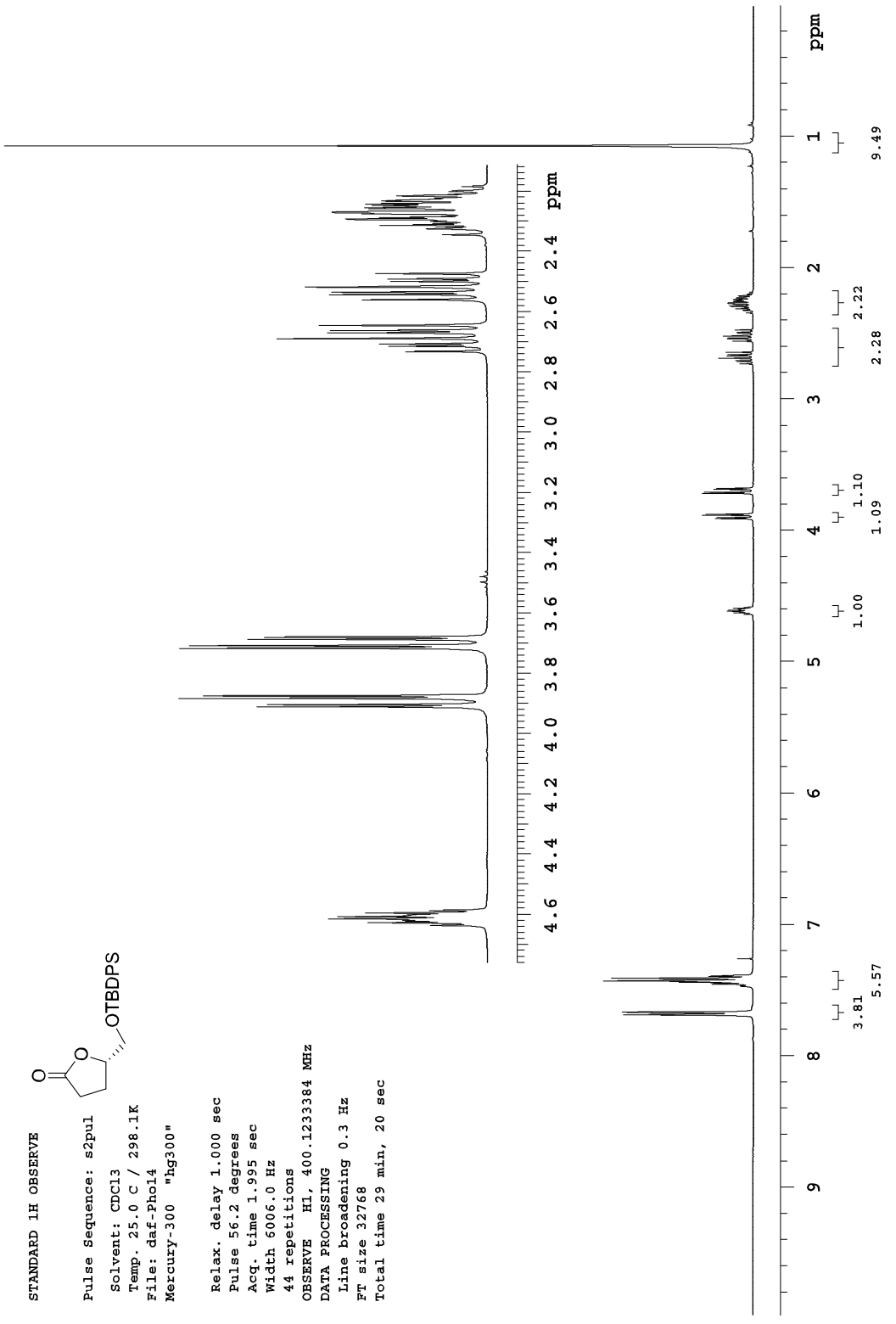
Spectrum 2.110 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **520**



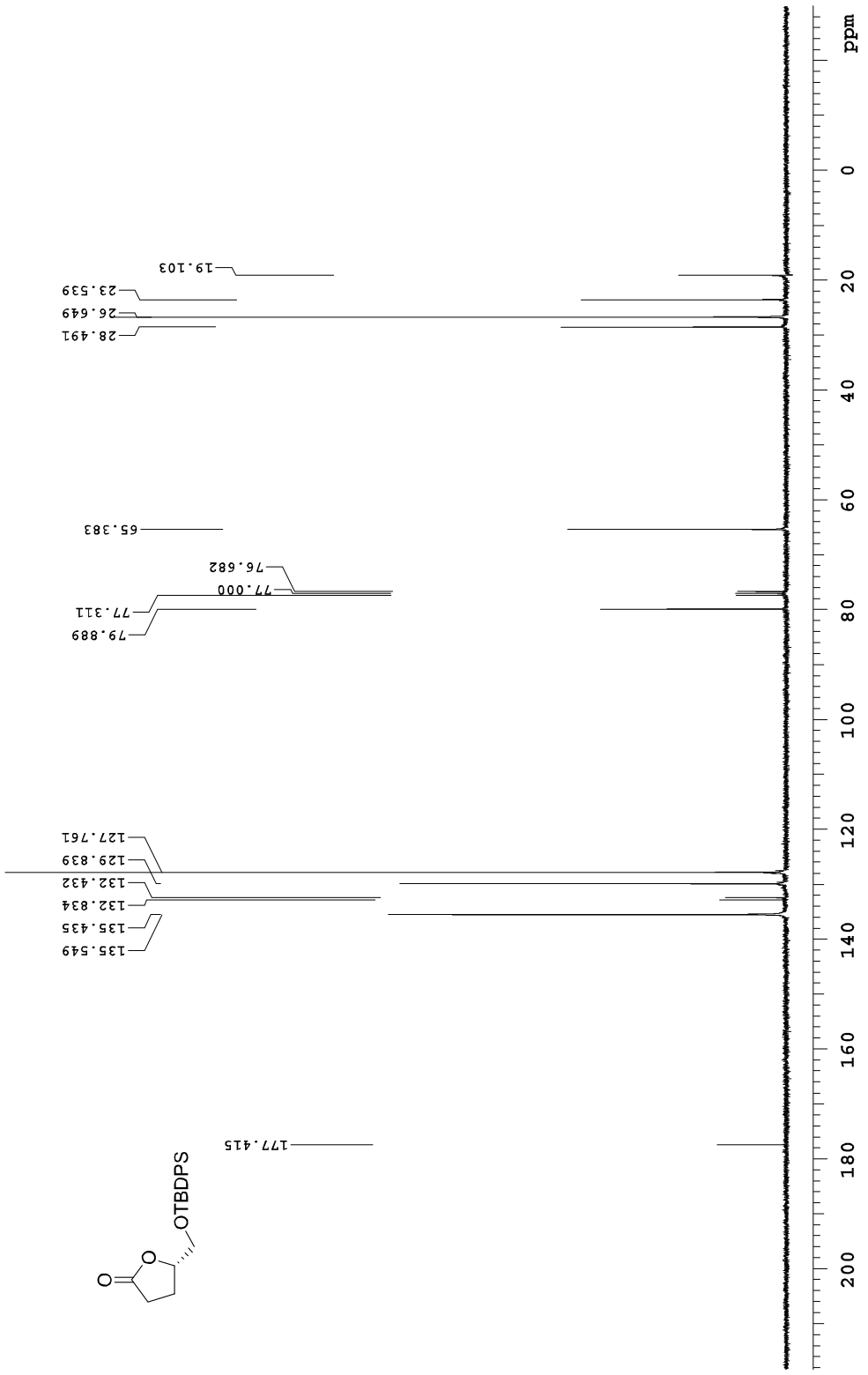
Spectrum 2.111 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **521**



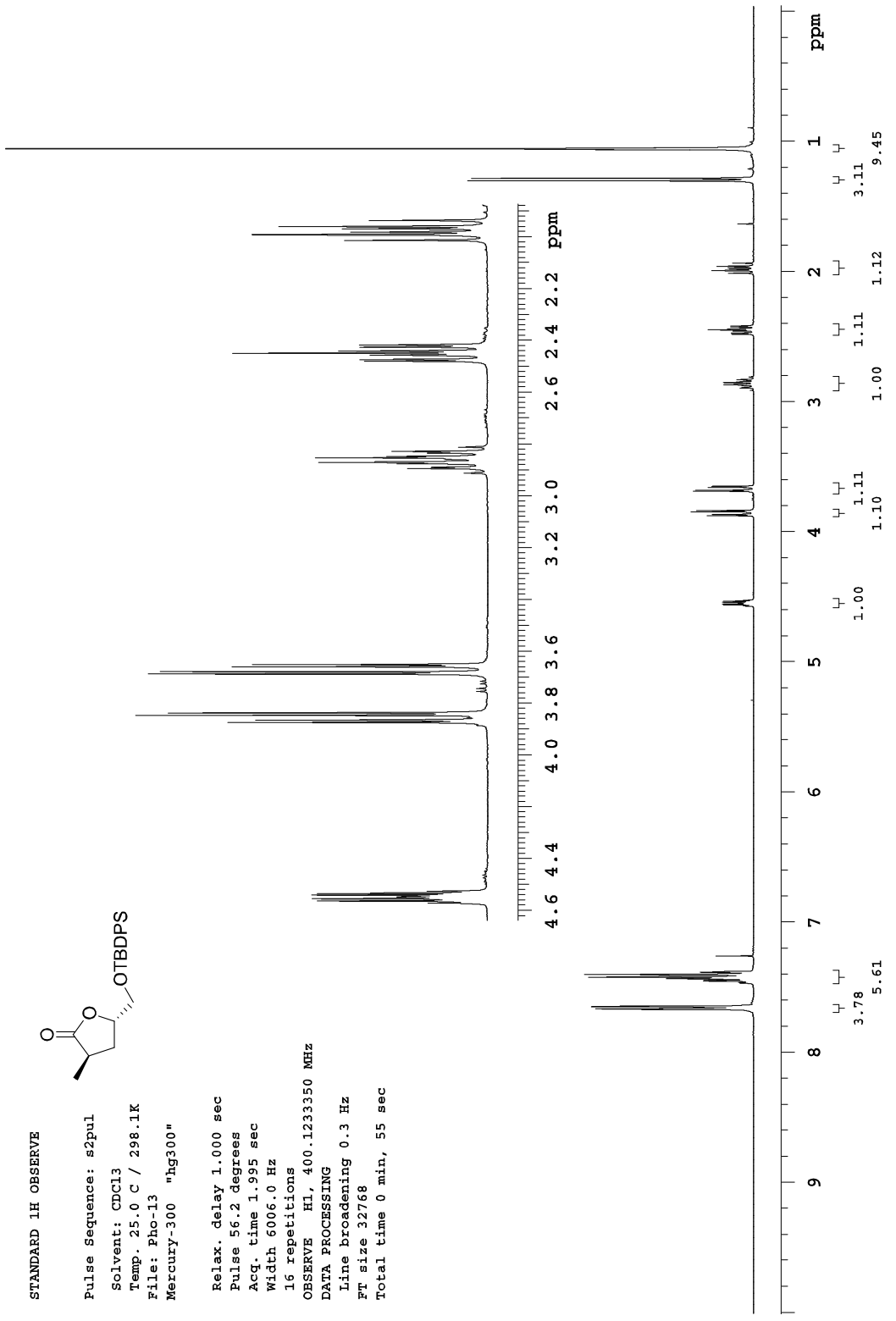
Spectrum 2.112 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **521**



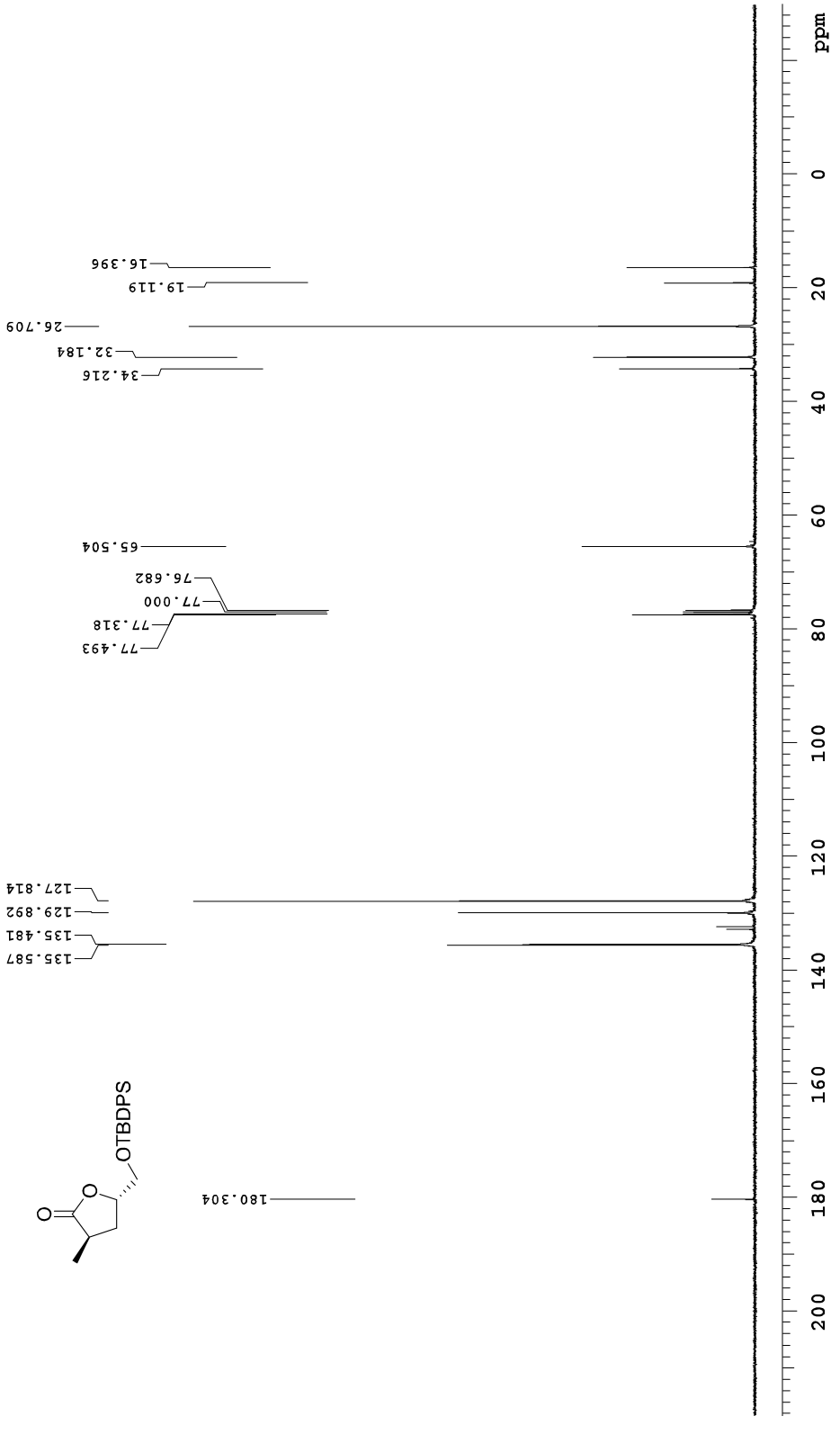
Spectrum 2.113 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **522**



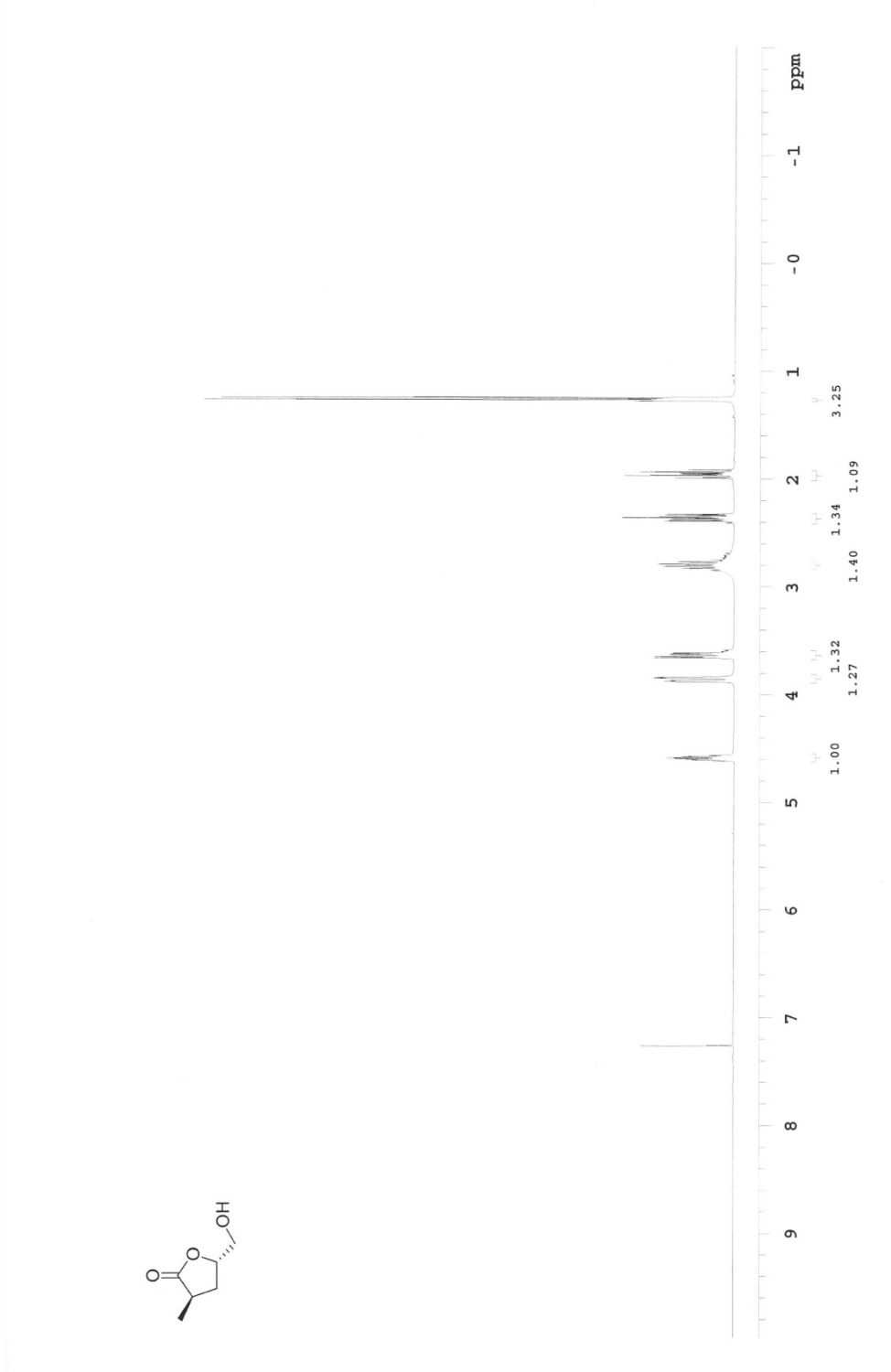
Spectrum 2.114 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **522**



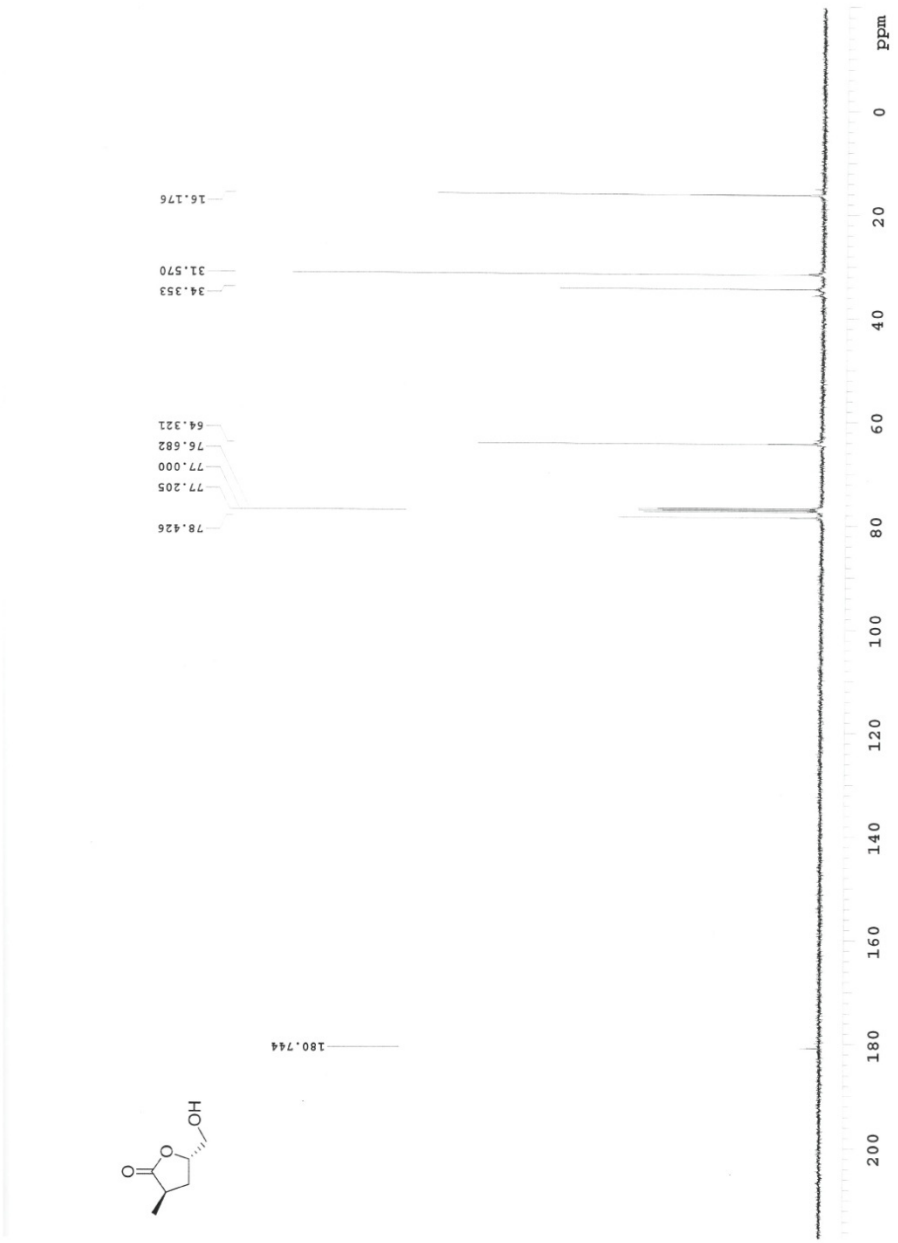
Spectrum 2.115 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **523**



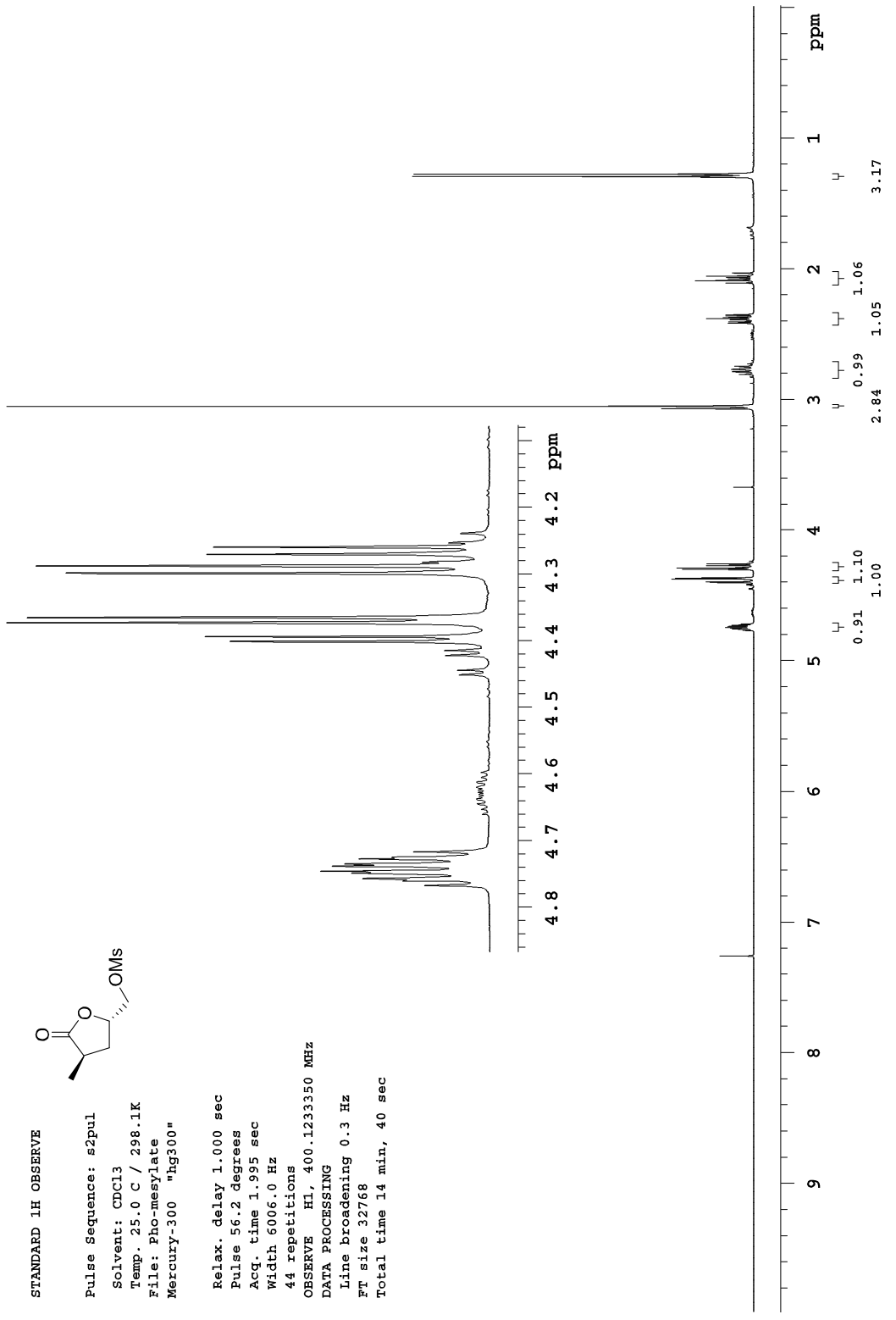
Spectrum 2.116 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **523**



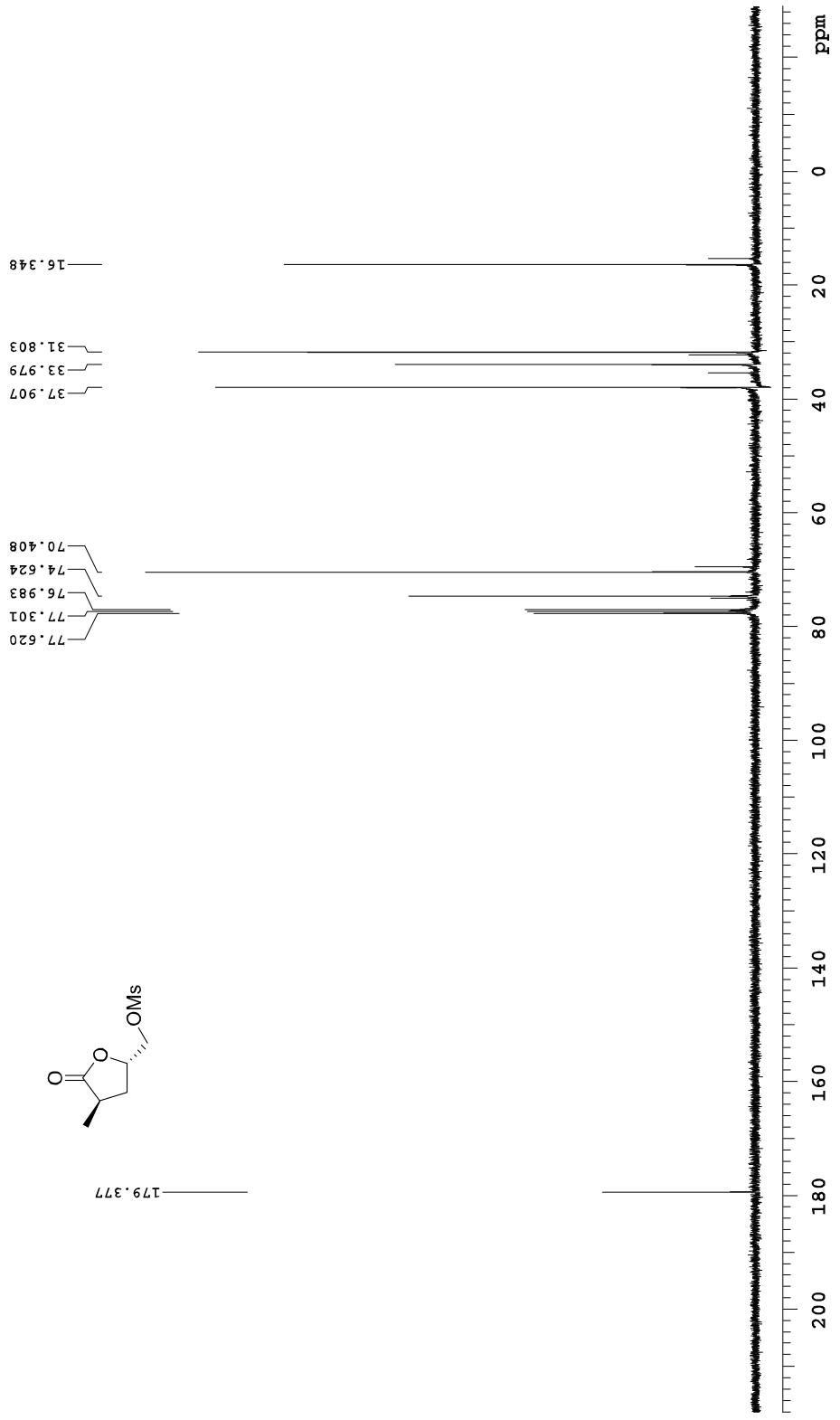
Spectrum 2.117 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **524**



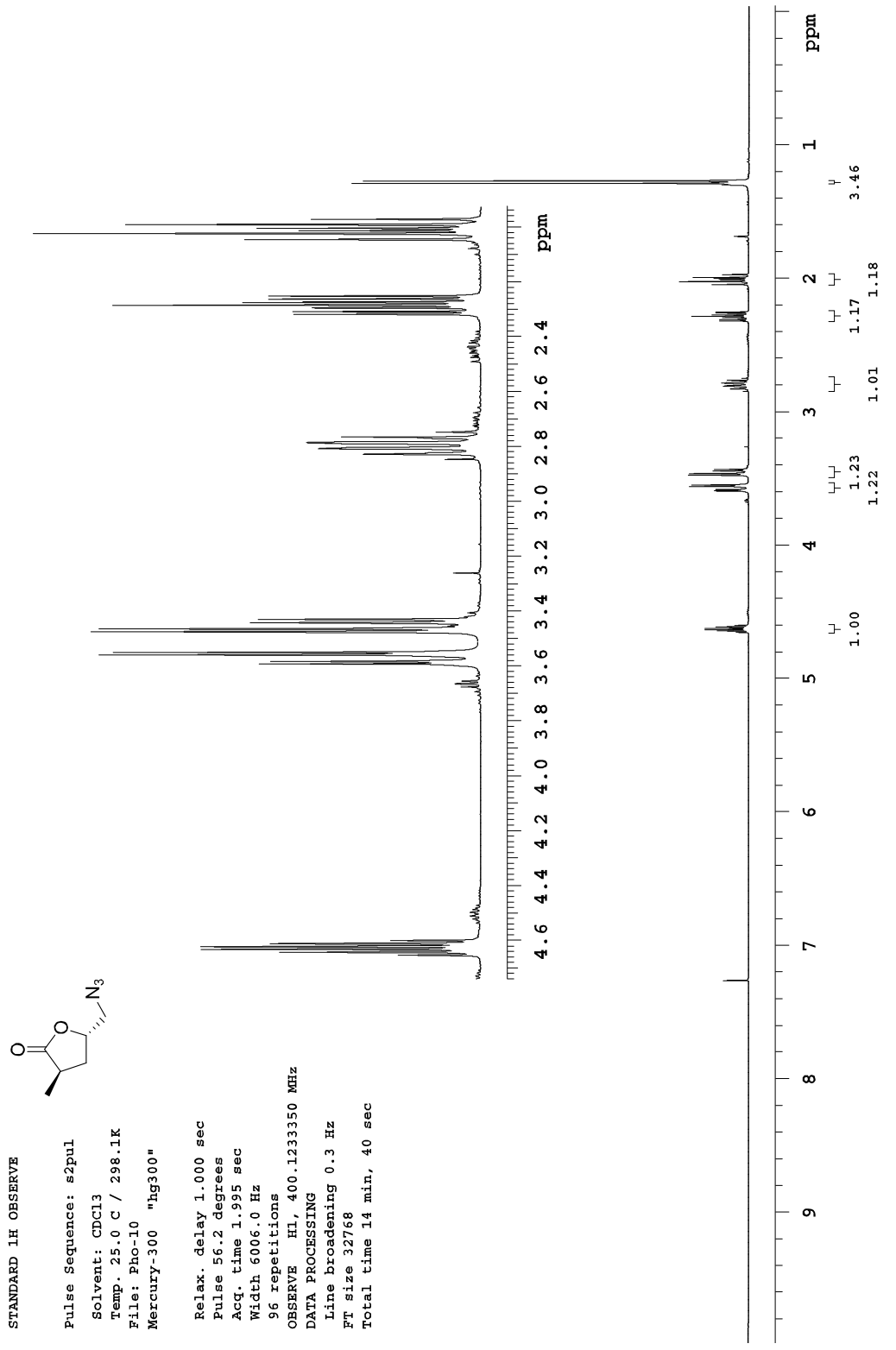
Spectrum 2.118 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **524**



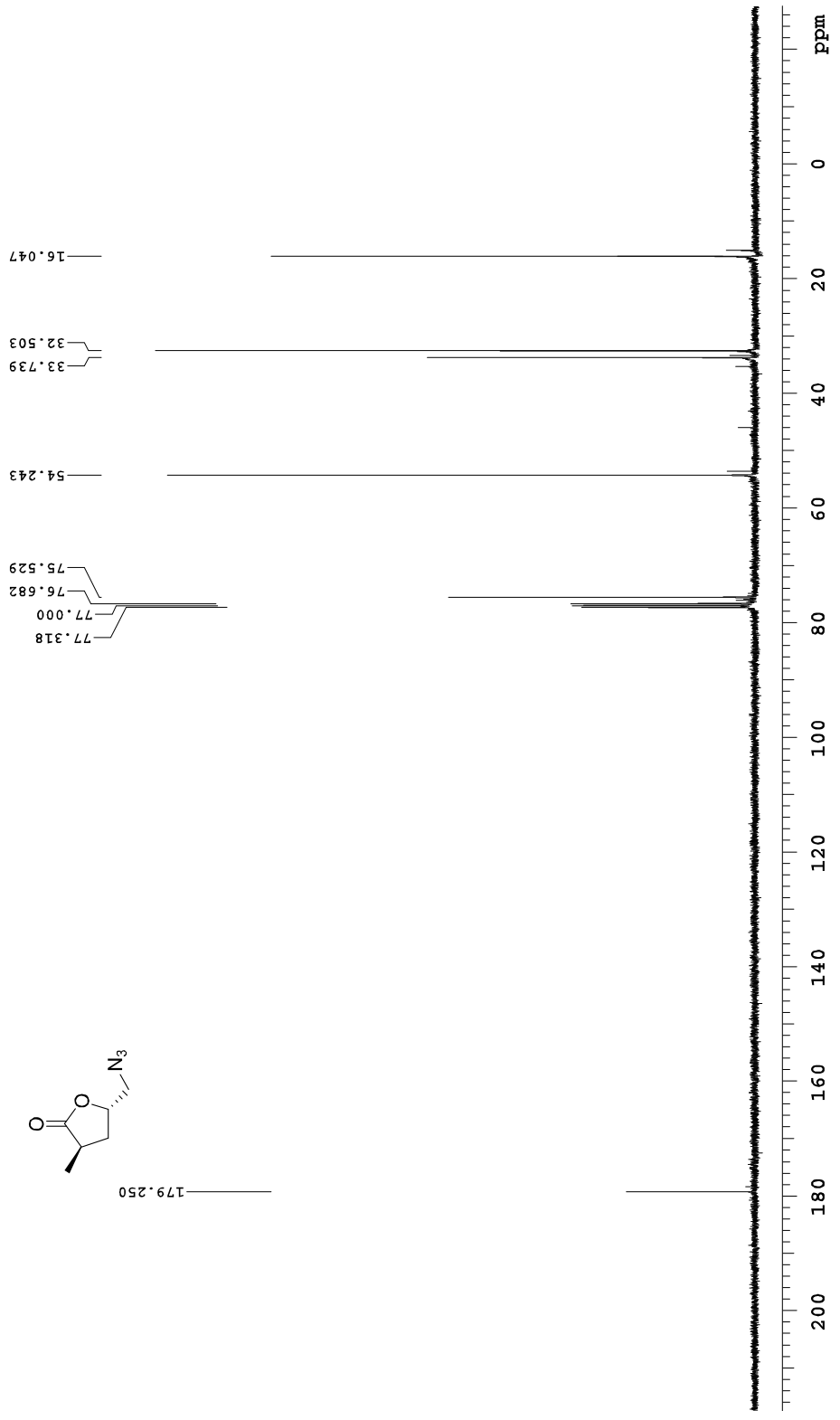
Spectrum 2.119 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **525**



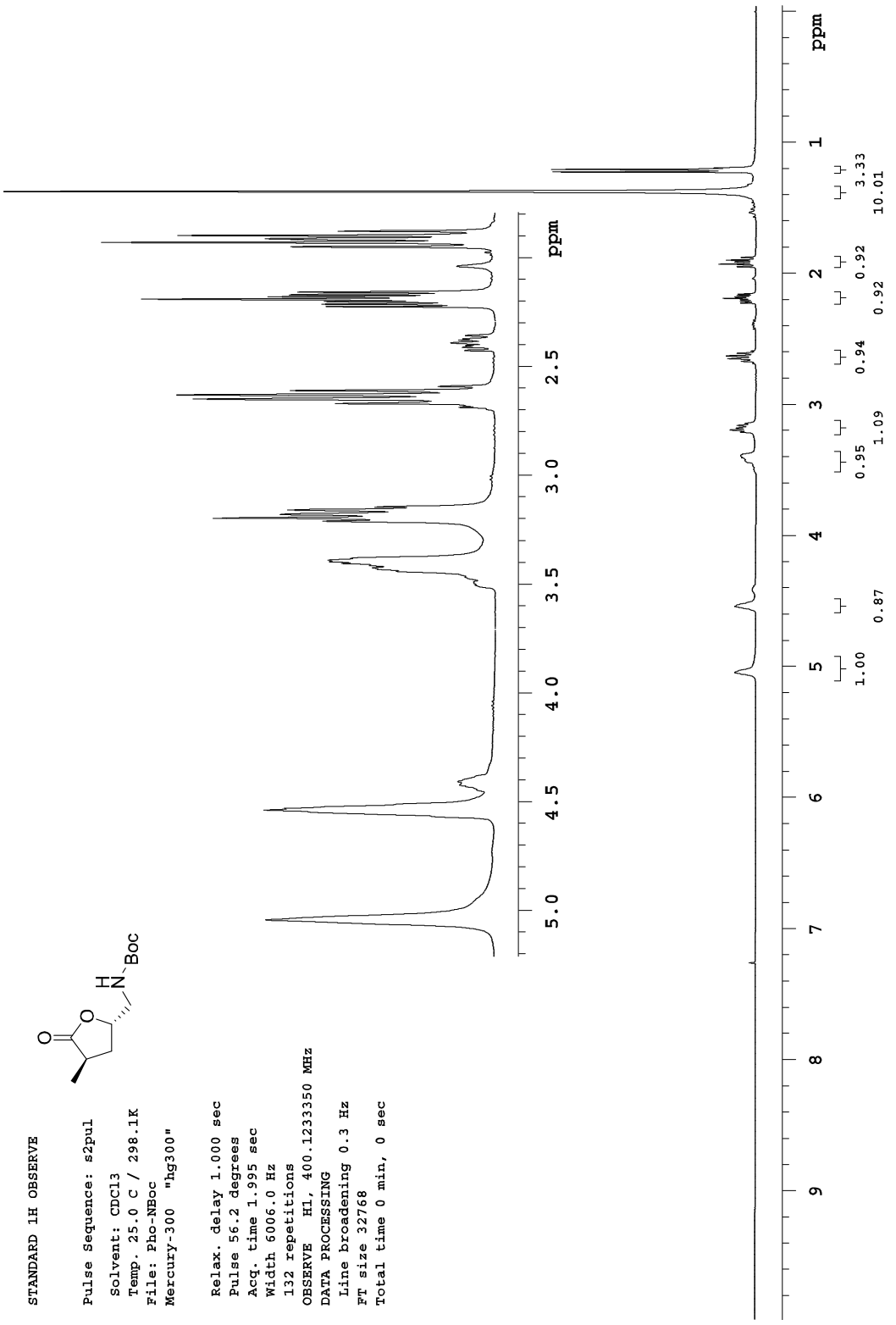
Spectrum 2.120 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **525**



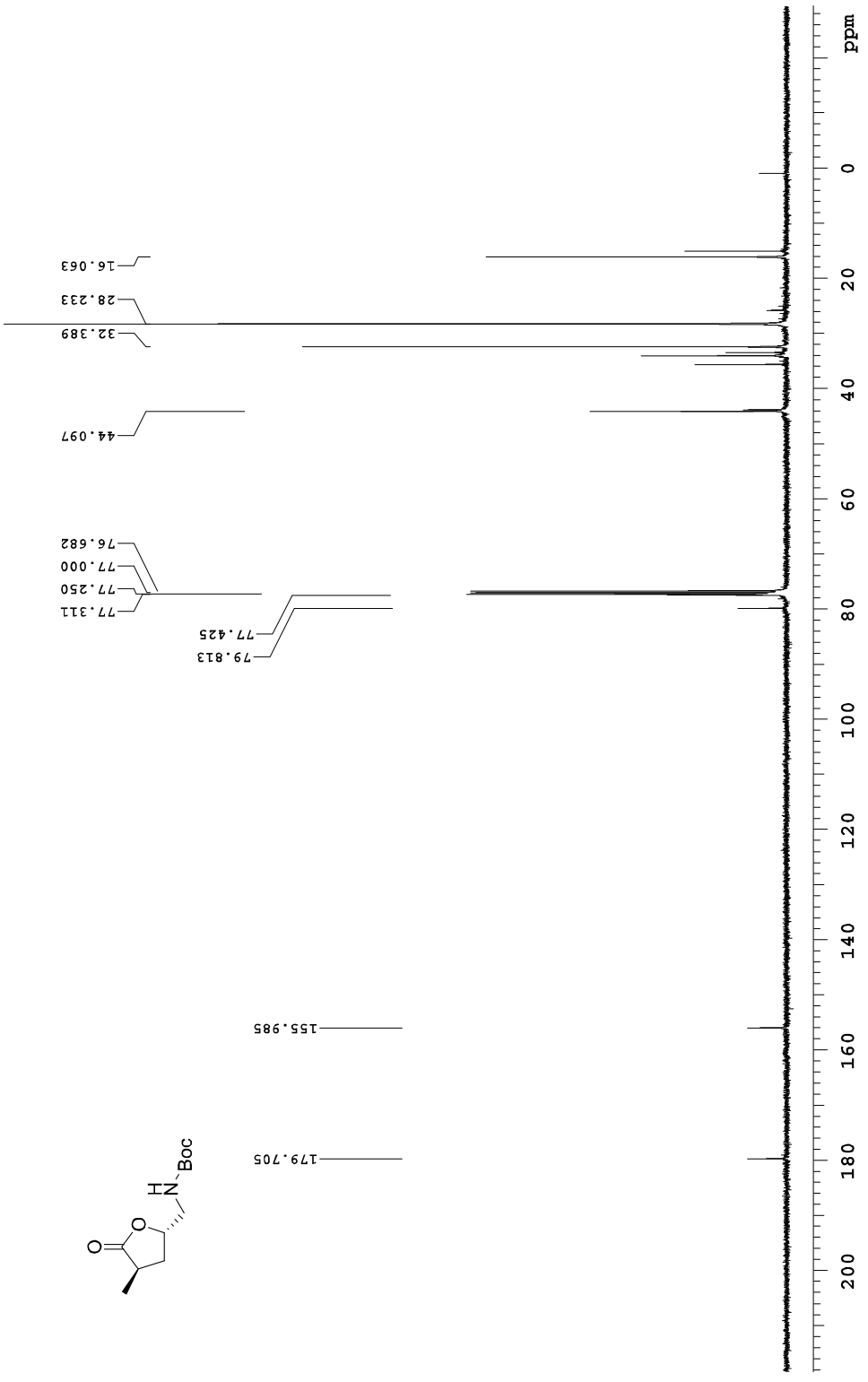
Spectrum 2.121 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **526**



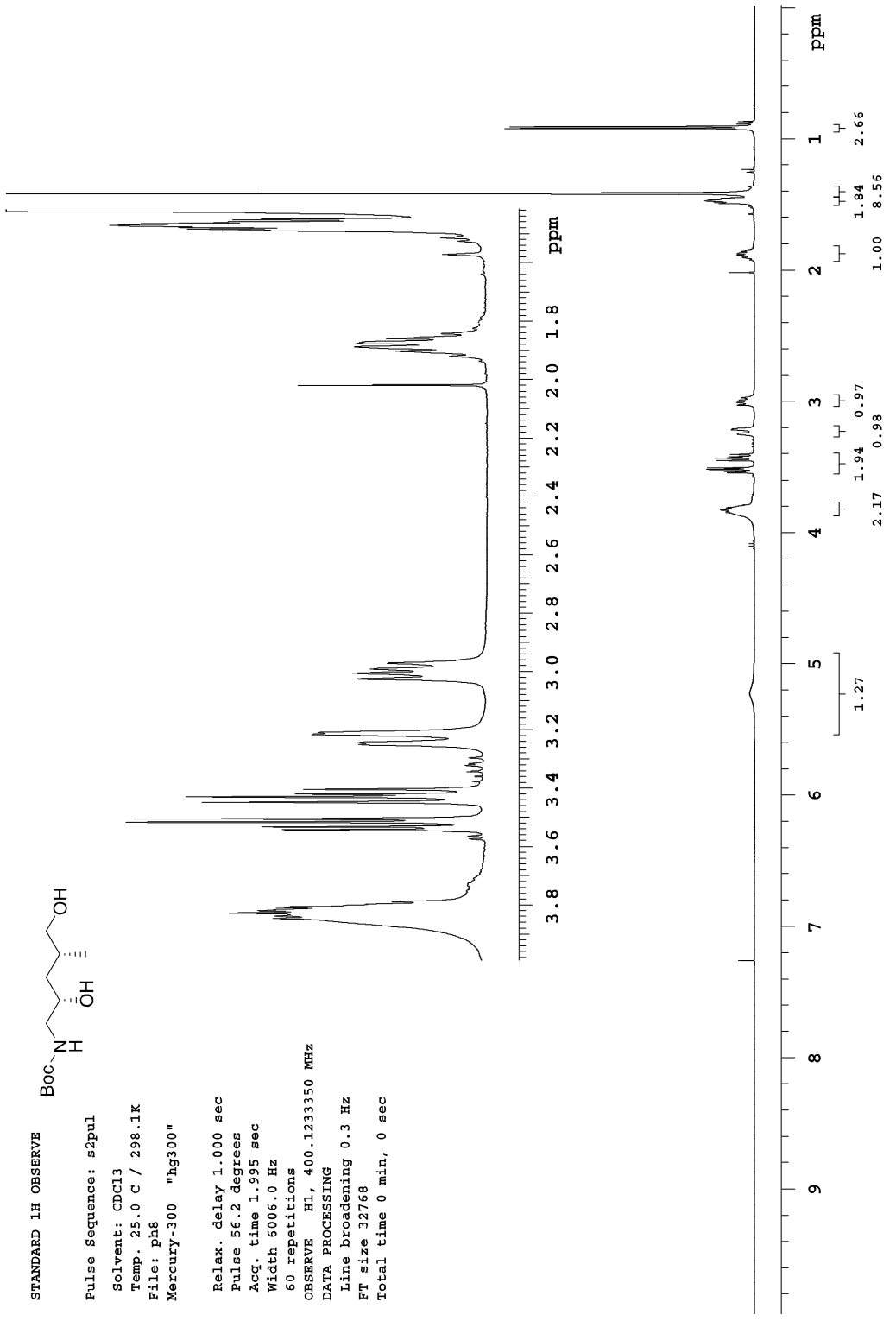
Spectrum 2.122 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **526**



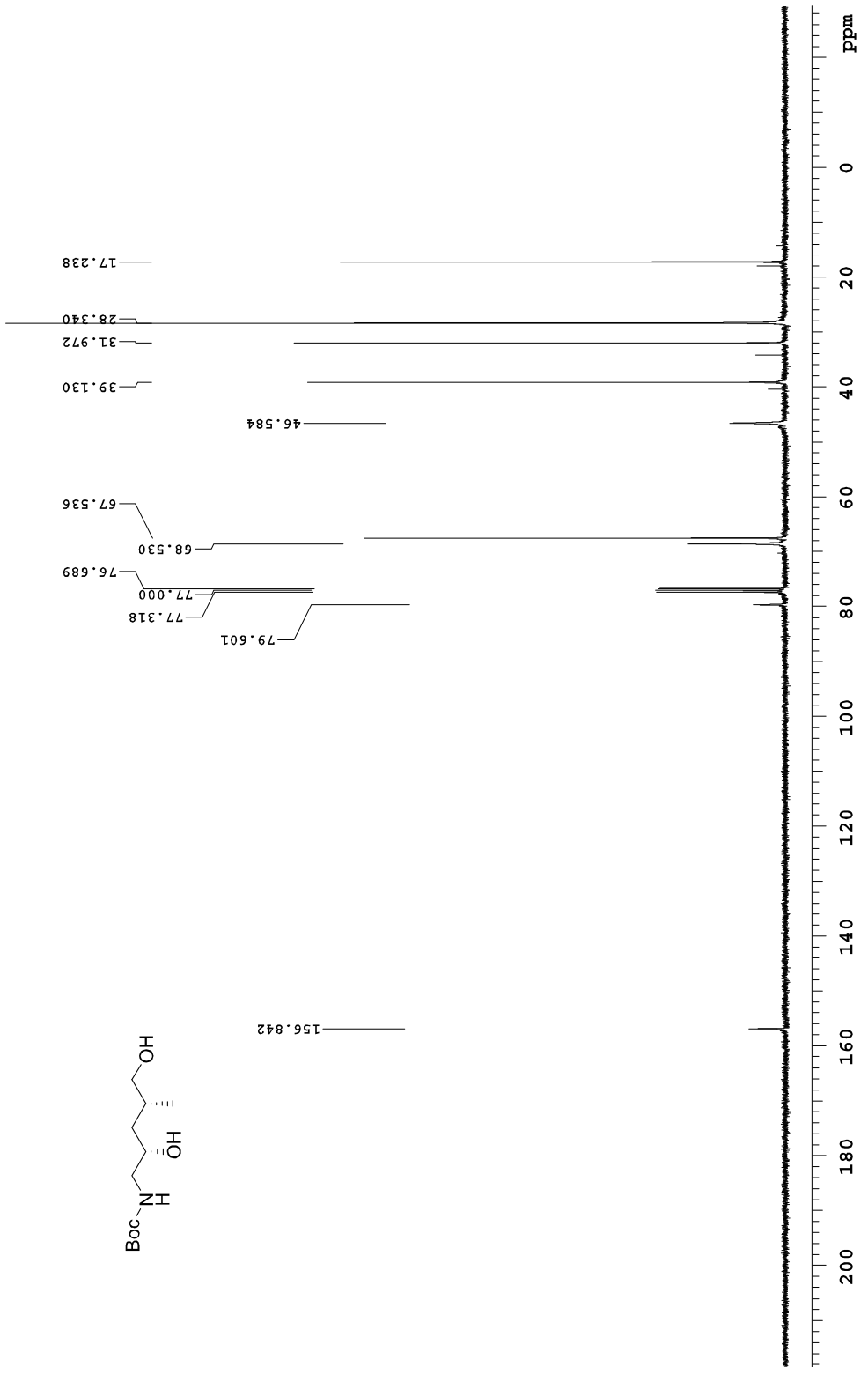
Spectrum 2.123 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **527**



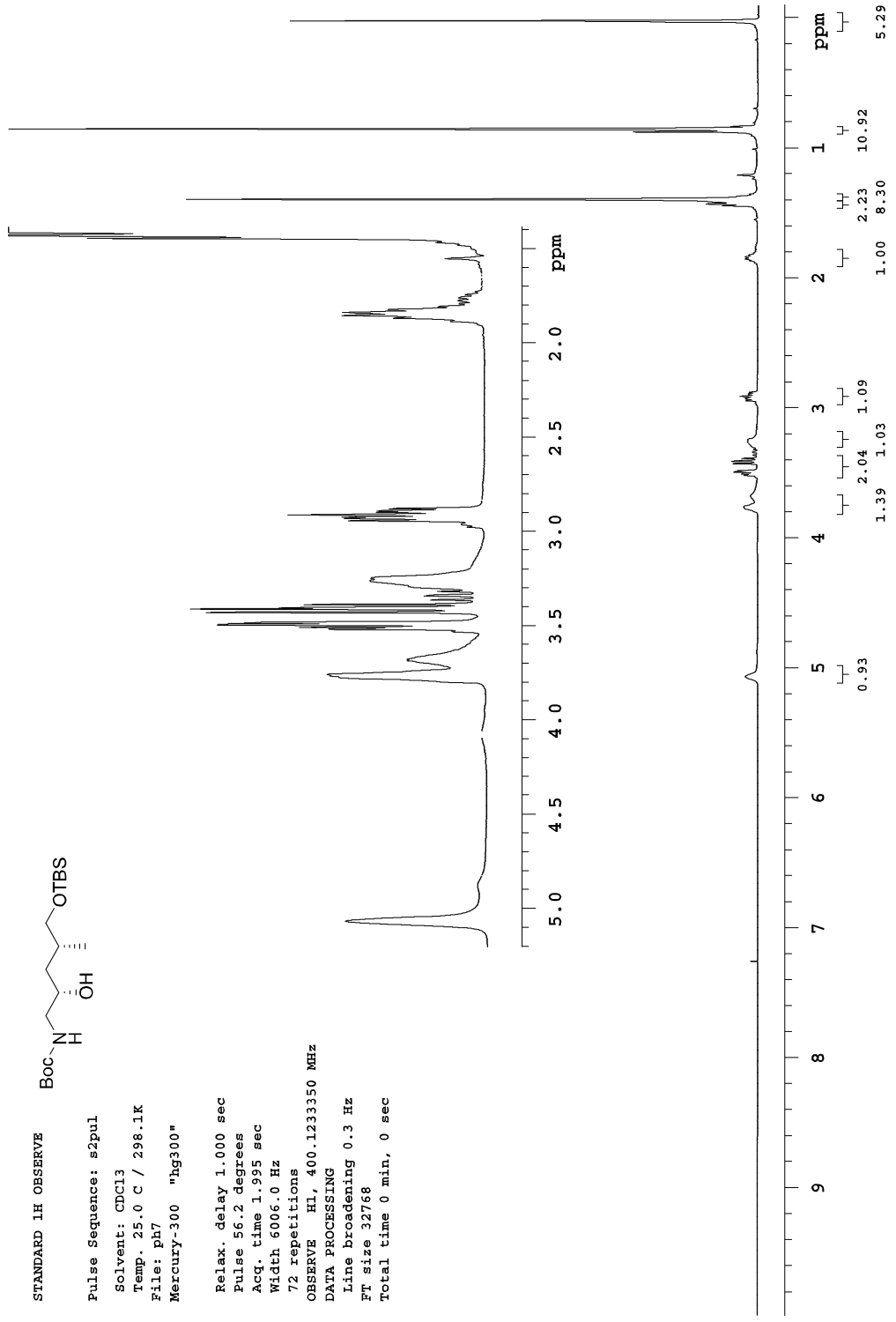
Spectrum 2.124 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **527**



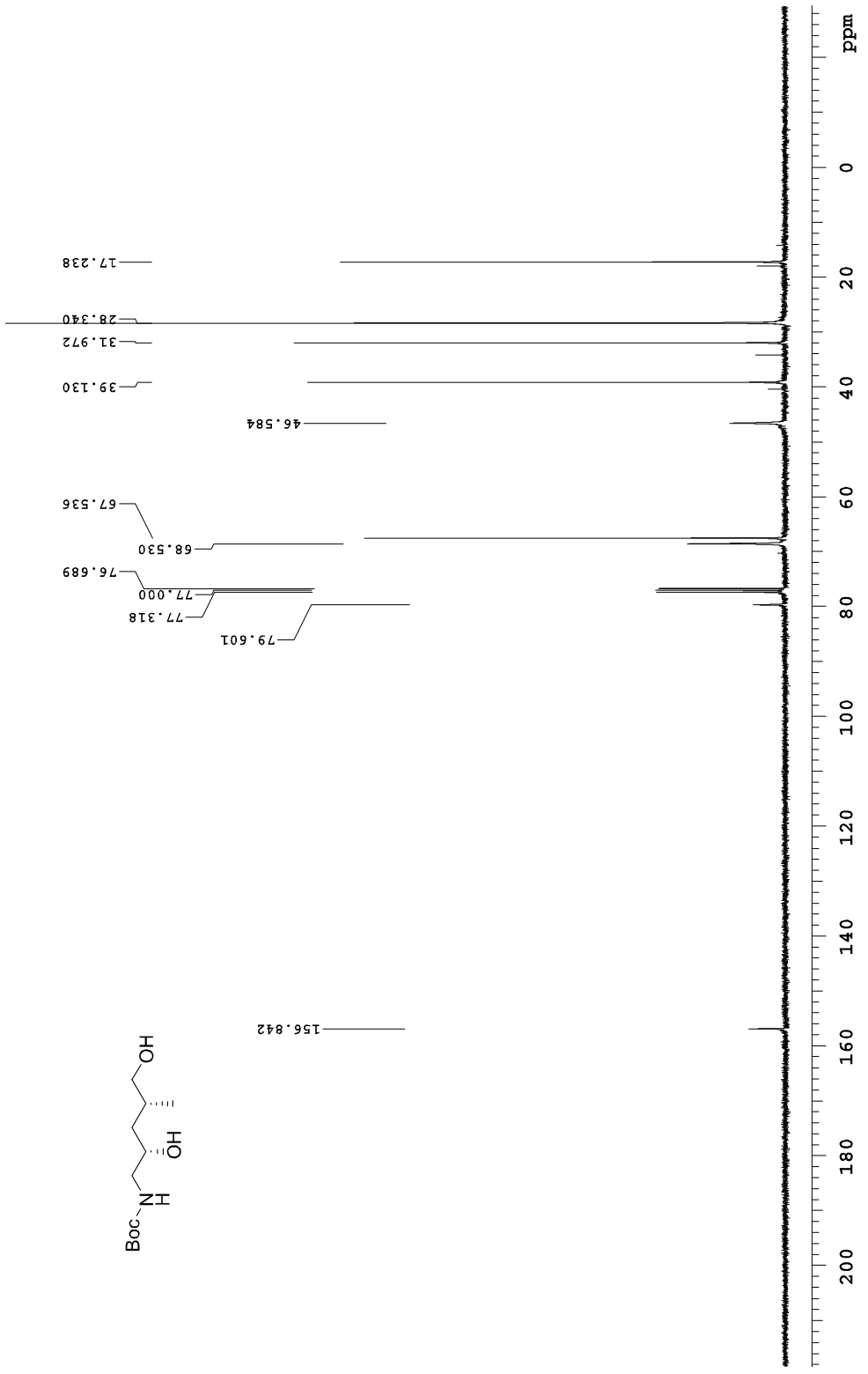
Spectrum 2.125 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **528**



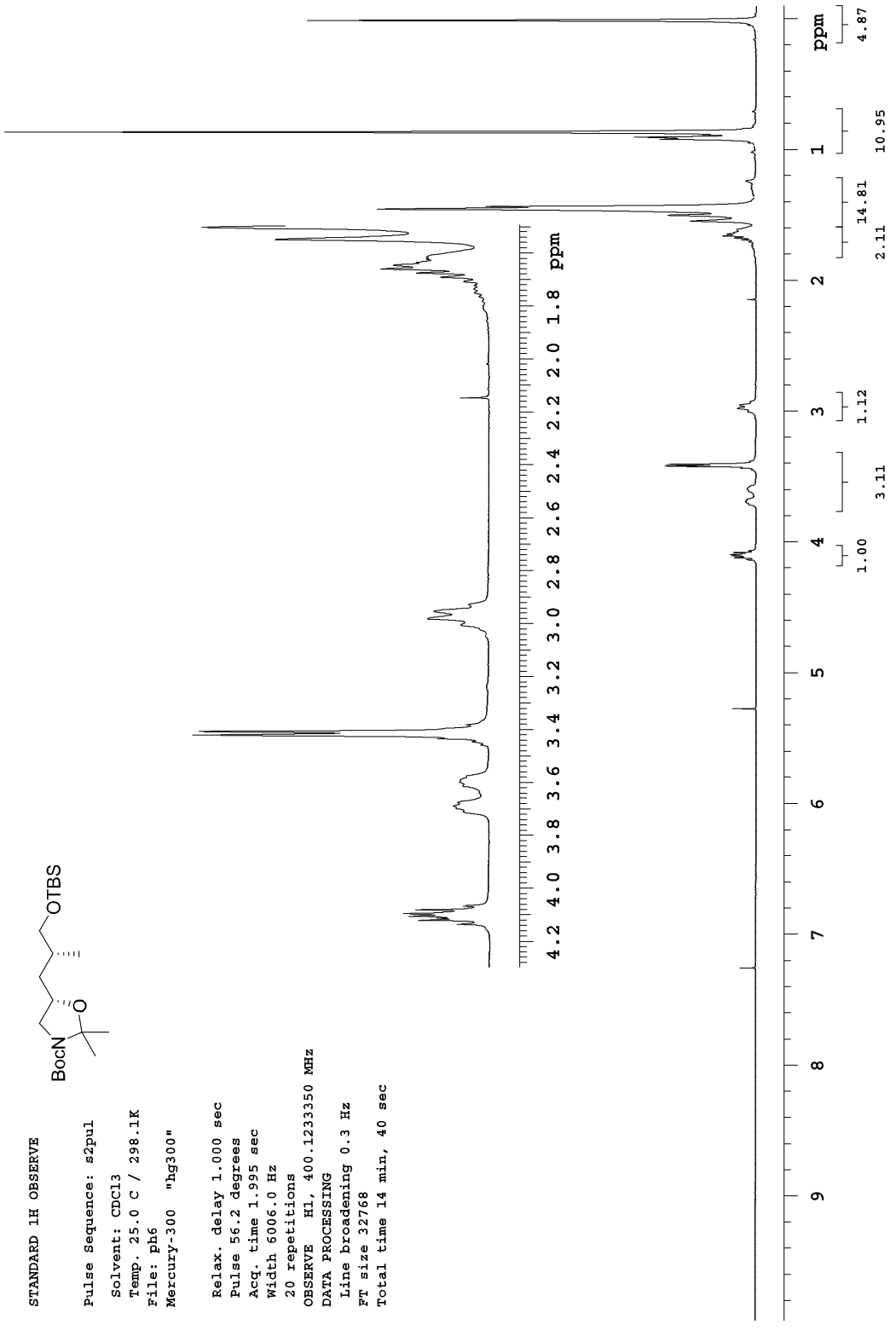
Spectrum 2.126 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **528**



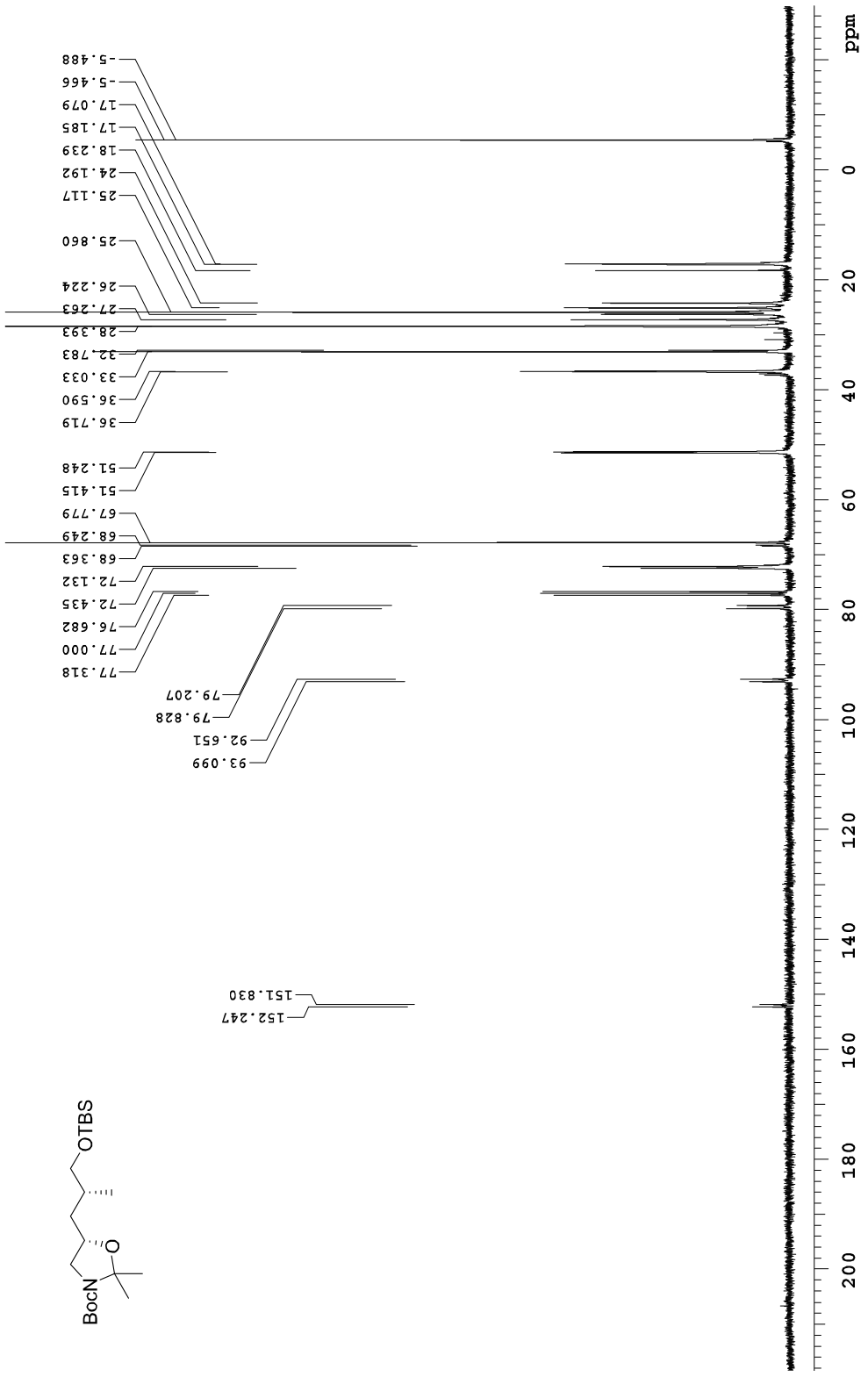
Spectrum 2.127 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **529**



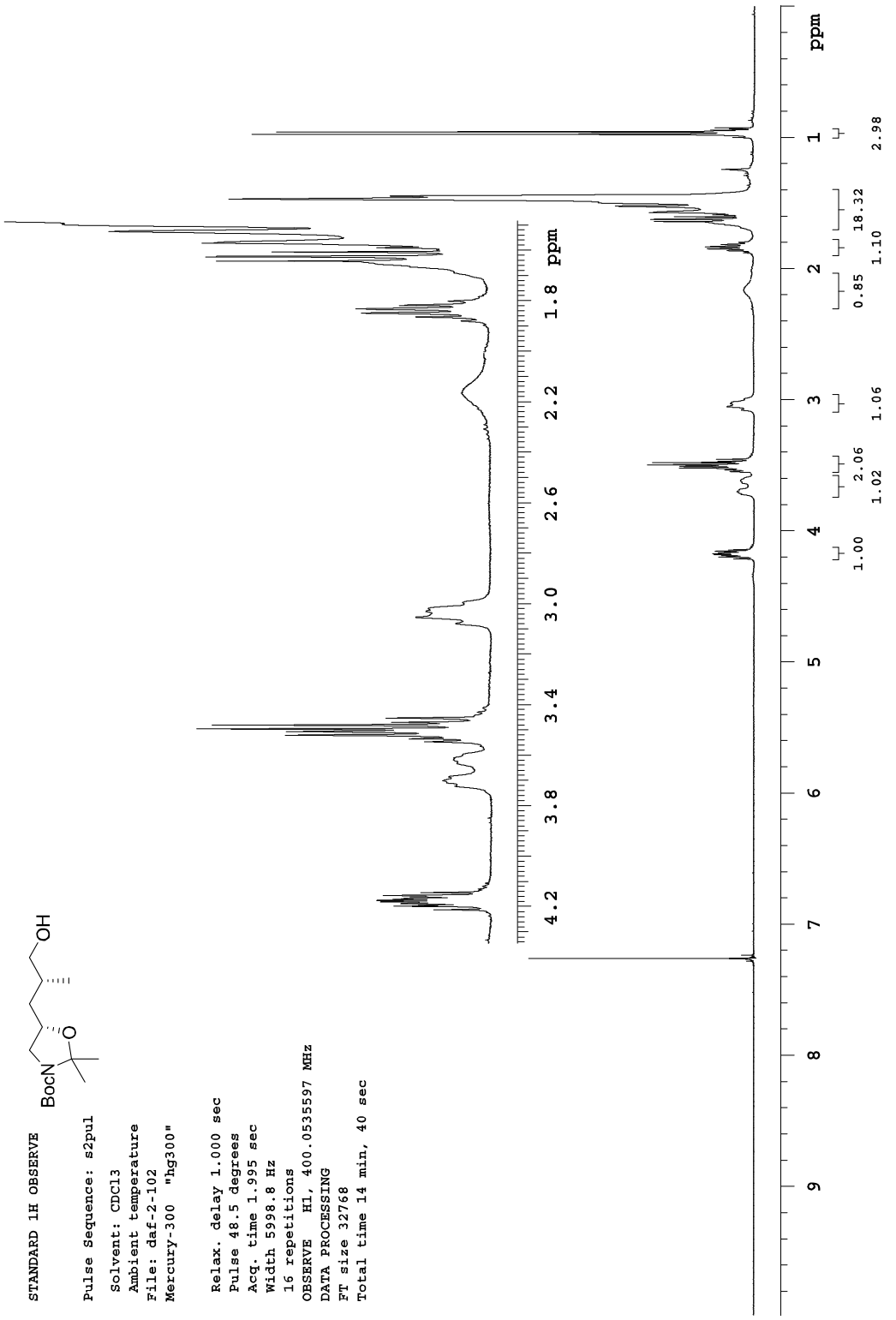
Spectrum 2.128 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **529**



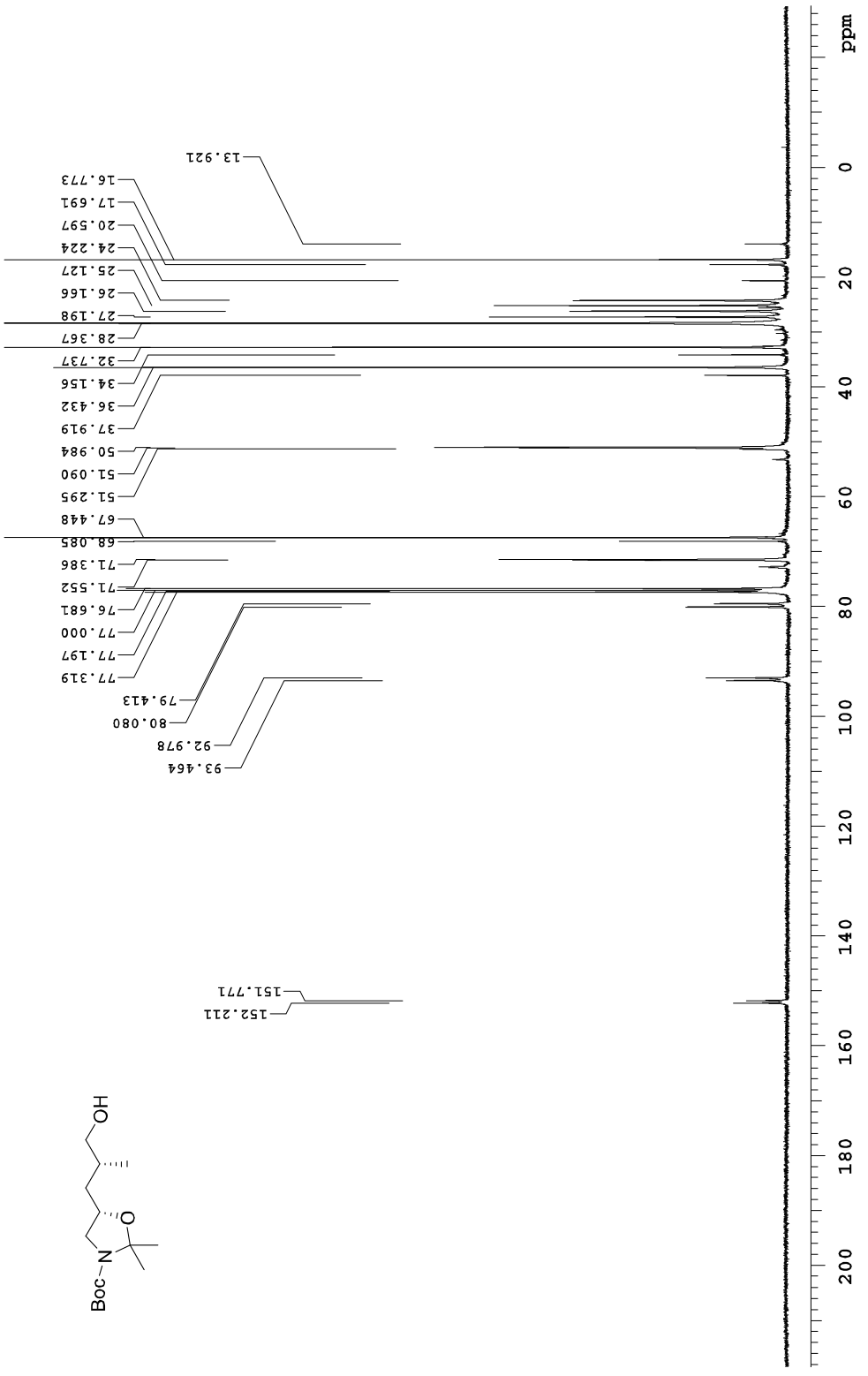
Spectrum 2.129 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **530**



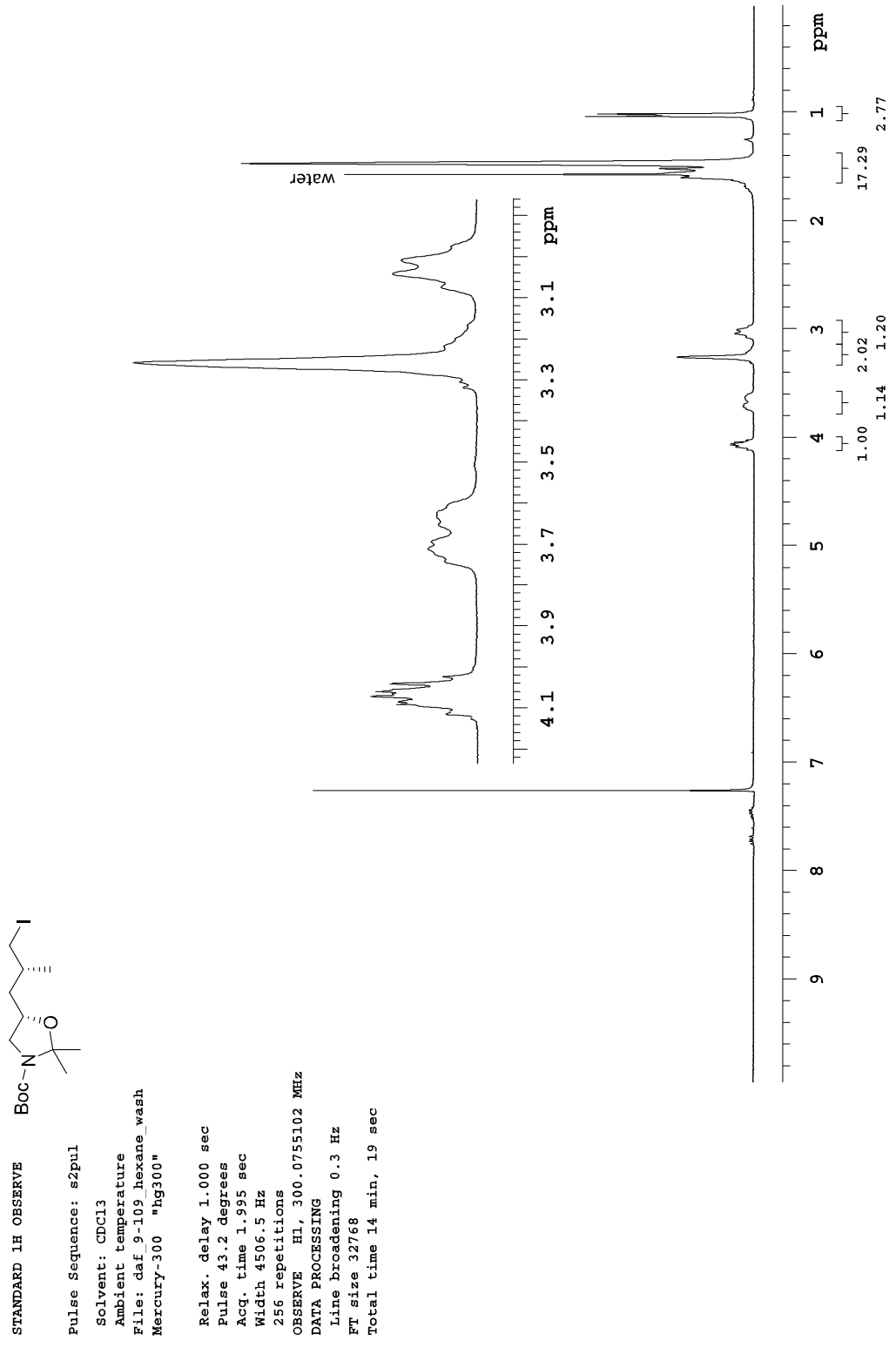
Spectrum 2.130 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **530**



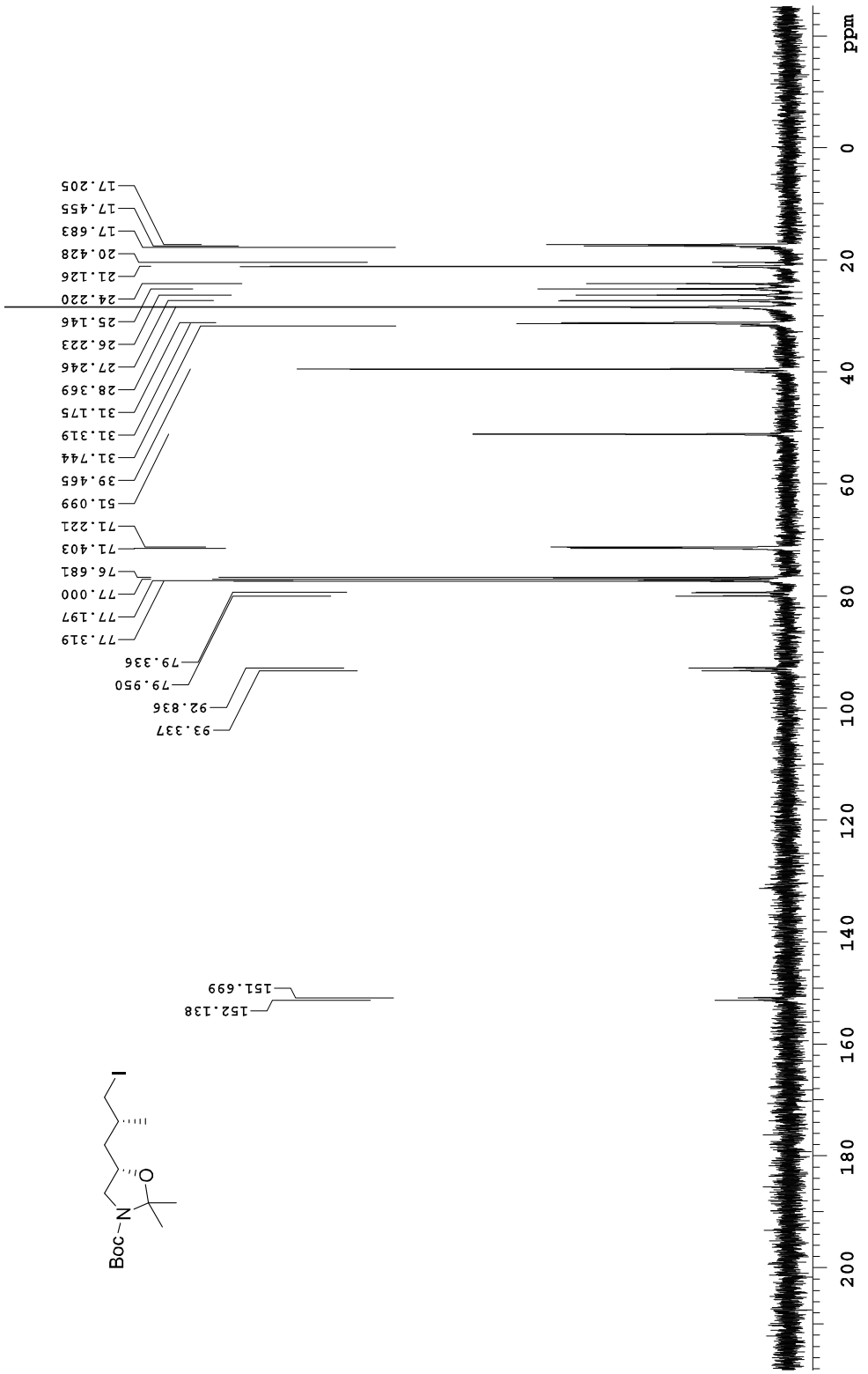
Spectrum 2.131 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **531**



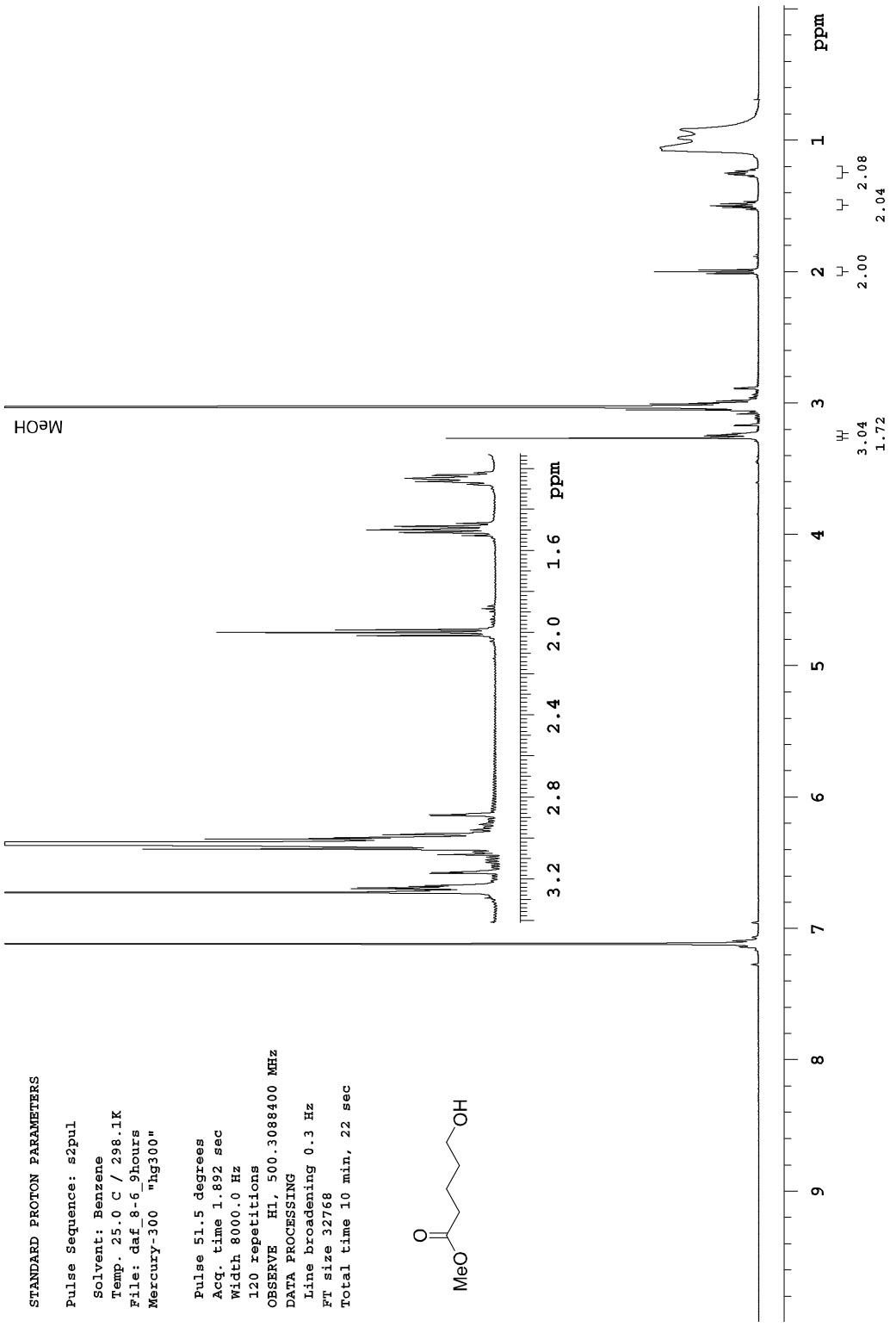
Spectrum 2.132 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **531**



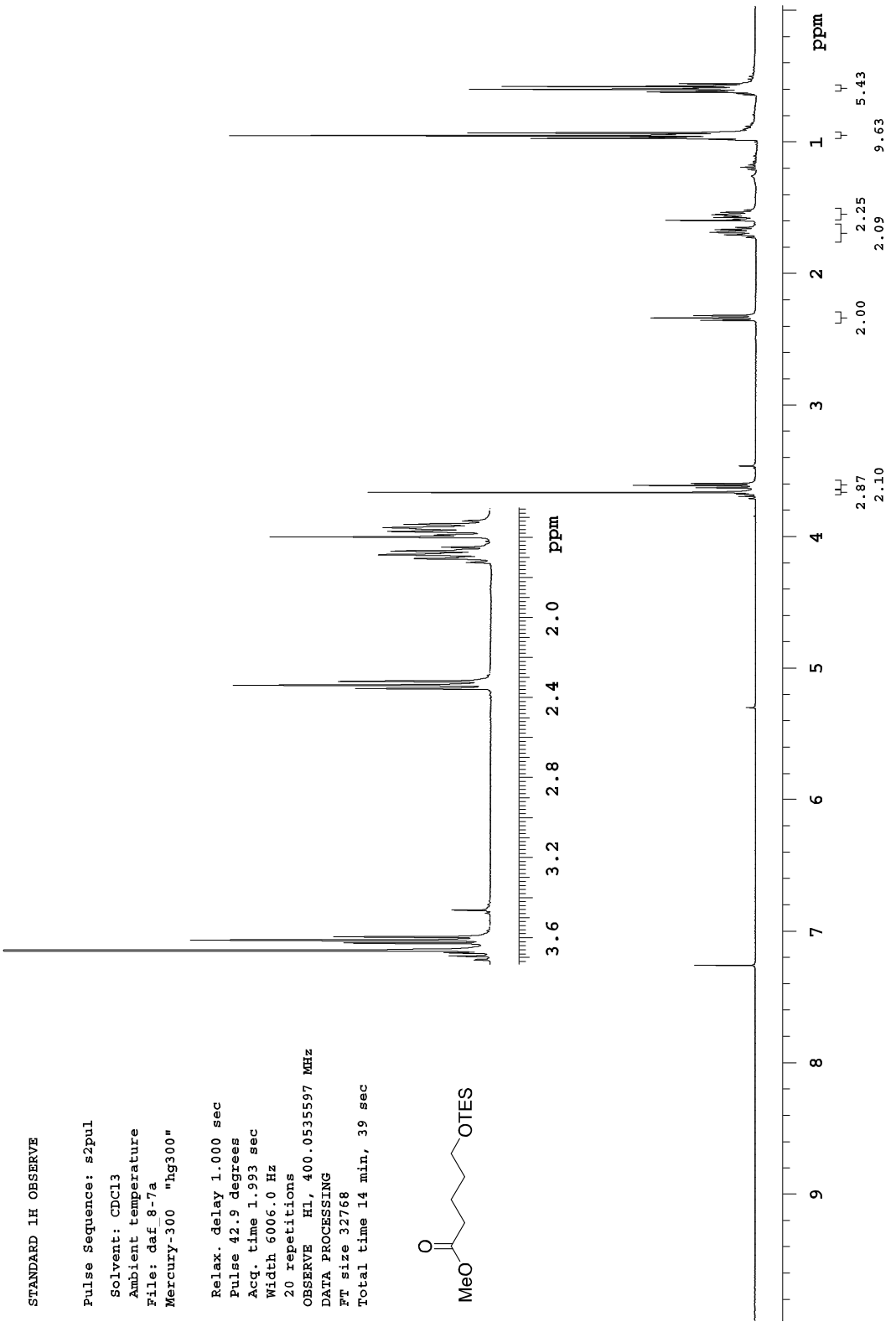
Spectrum 2.133 ^{1}H NMR ($CDCl_3$, 300 MHz) of compound **532**



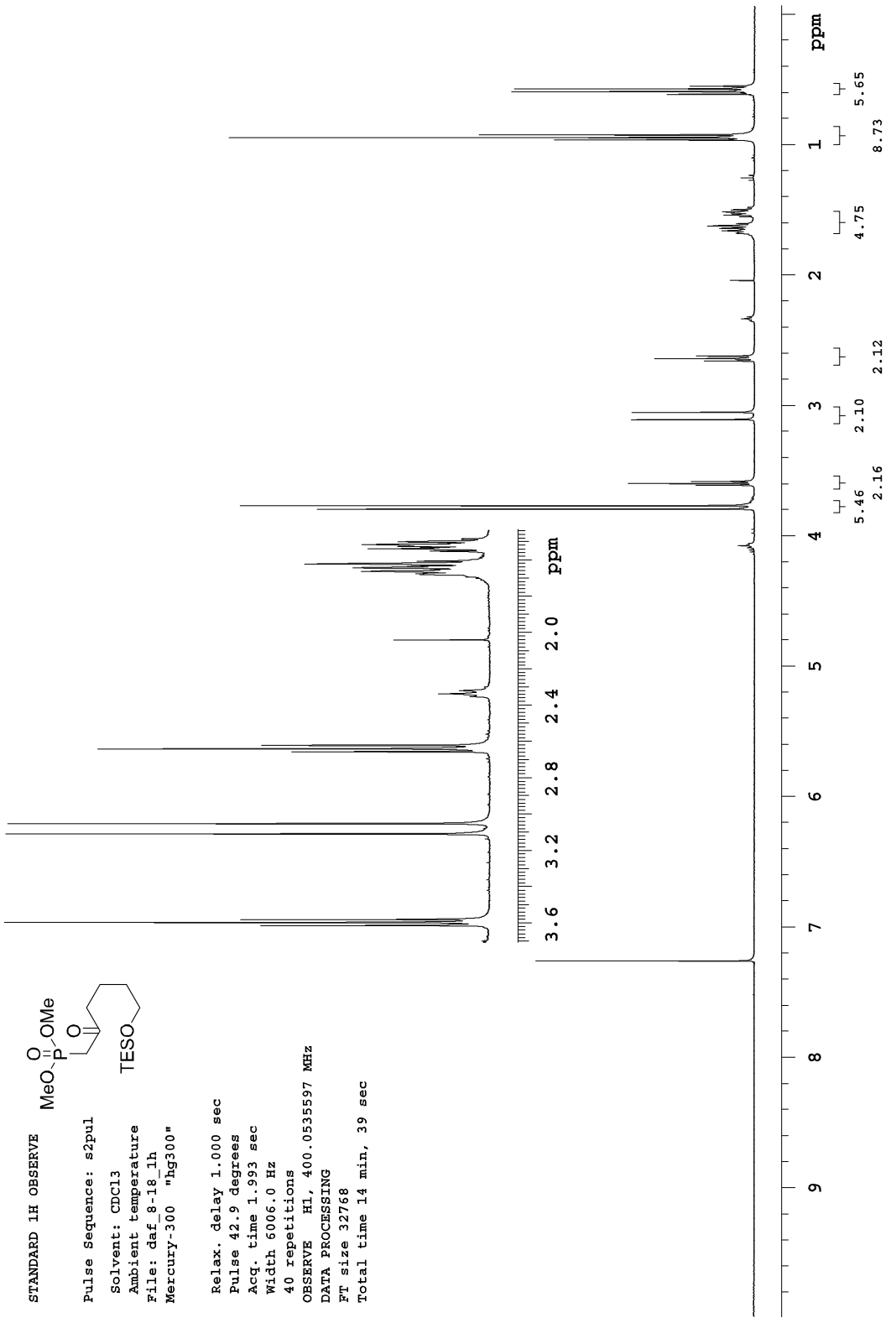
Spectrum 2.134 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **532**



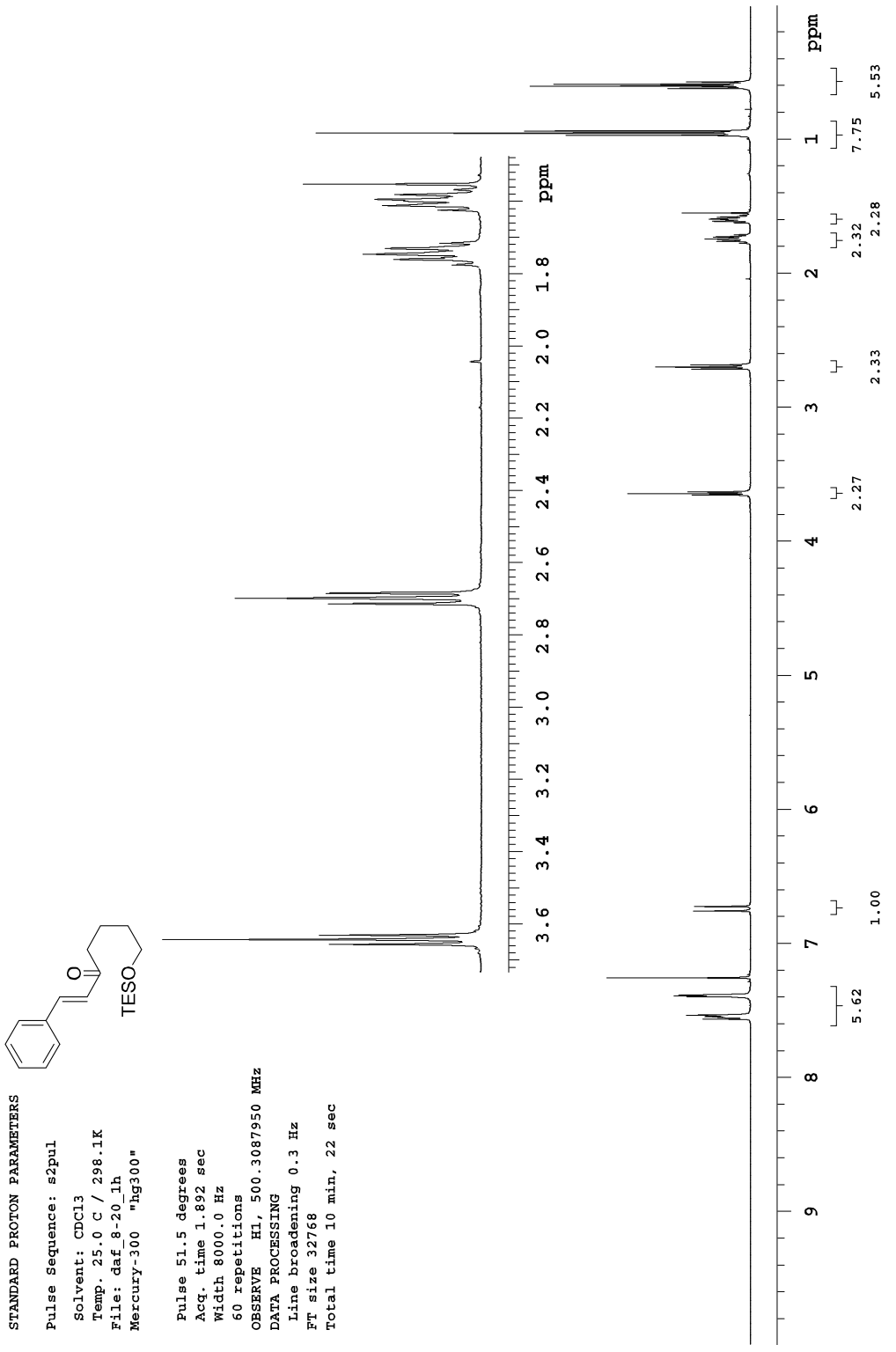
Spectrum 2.135 ^{1}H NMR (C_6D_6, 500 MHz) of compound **534**



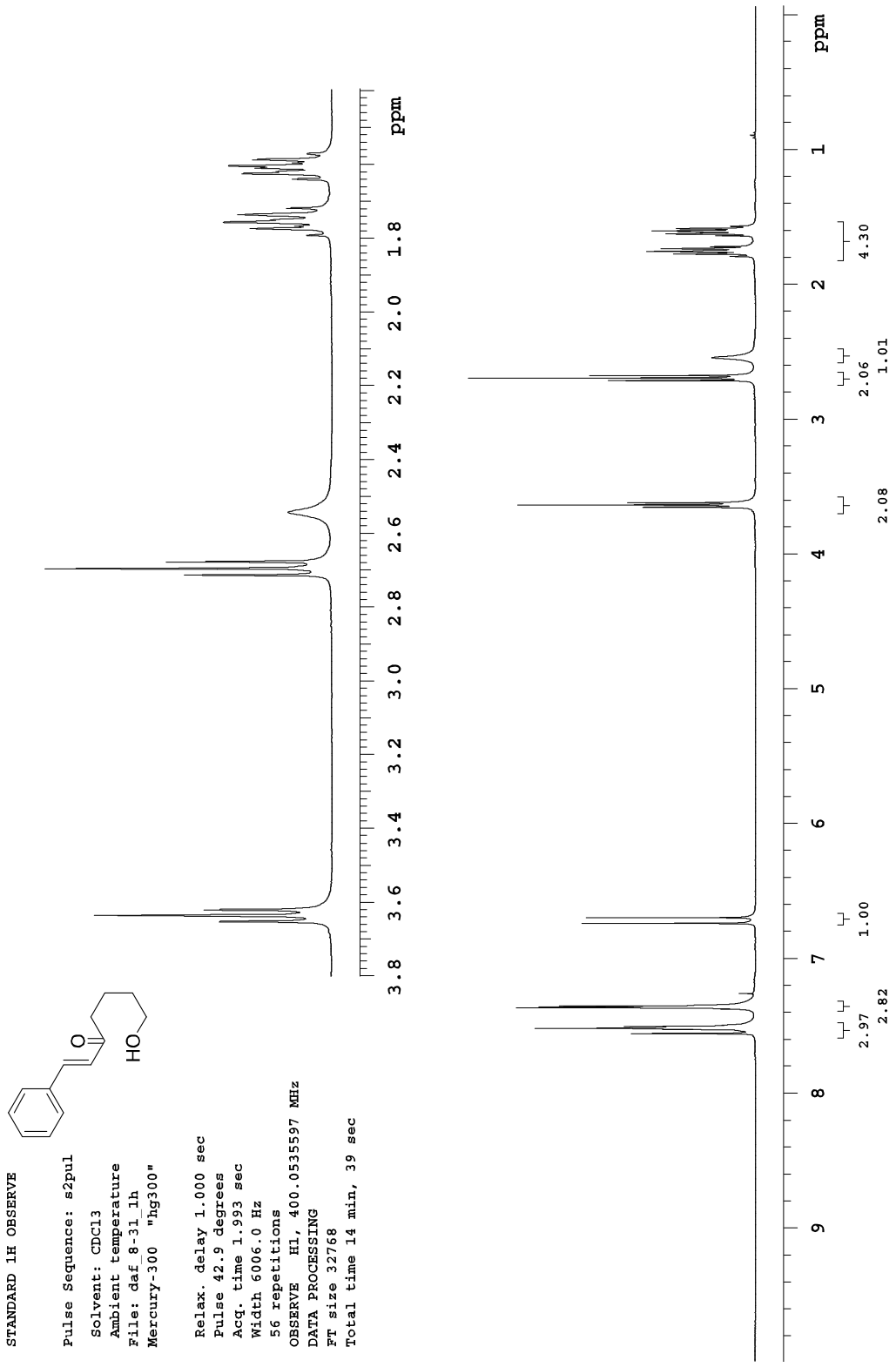
Spectrum 2.136 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **535**



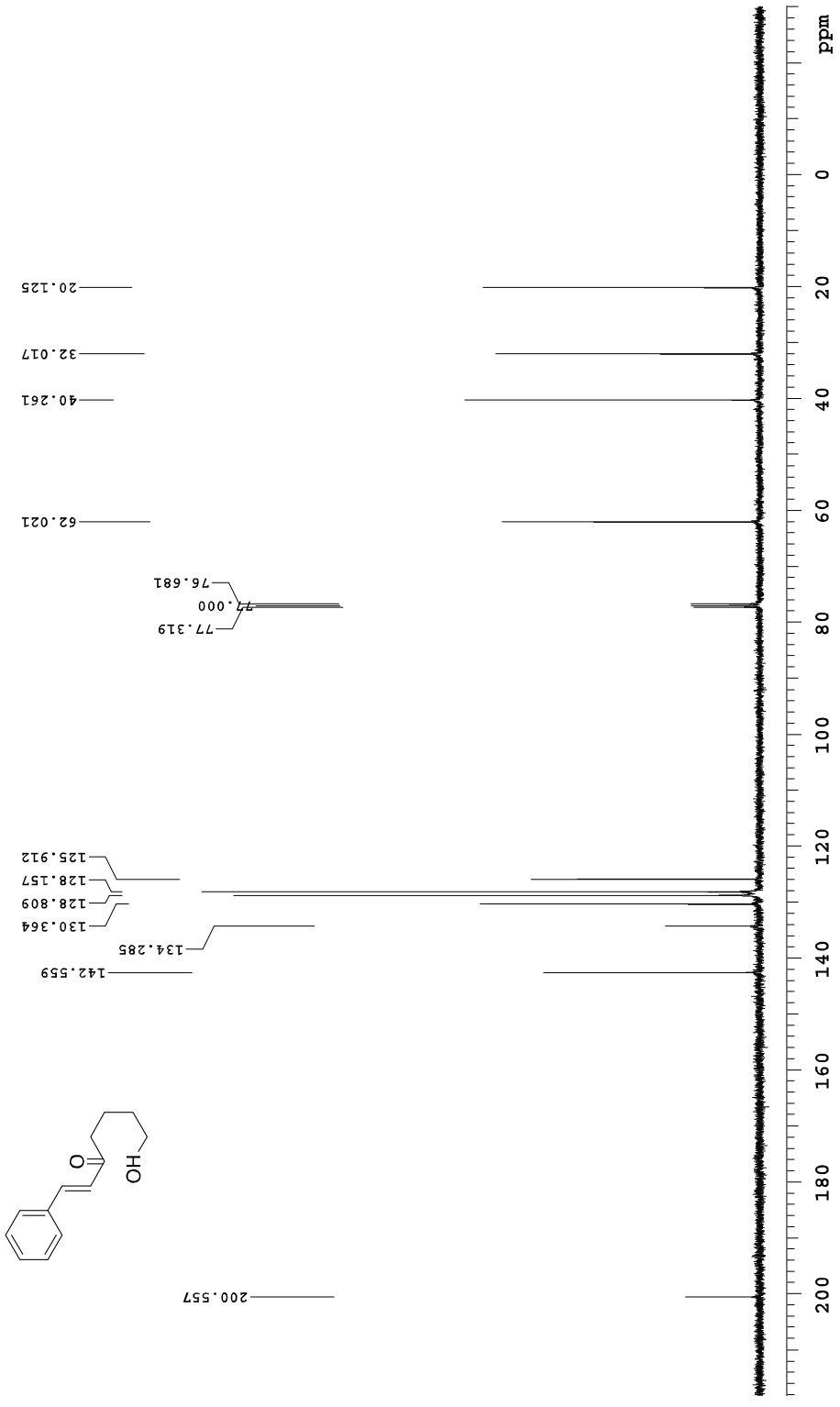
Spectrum 2.137 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **536**



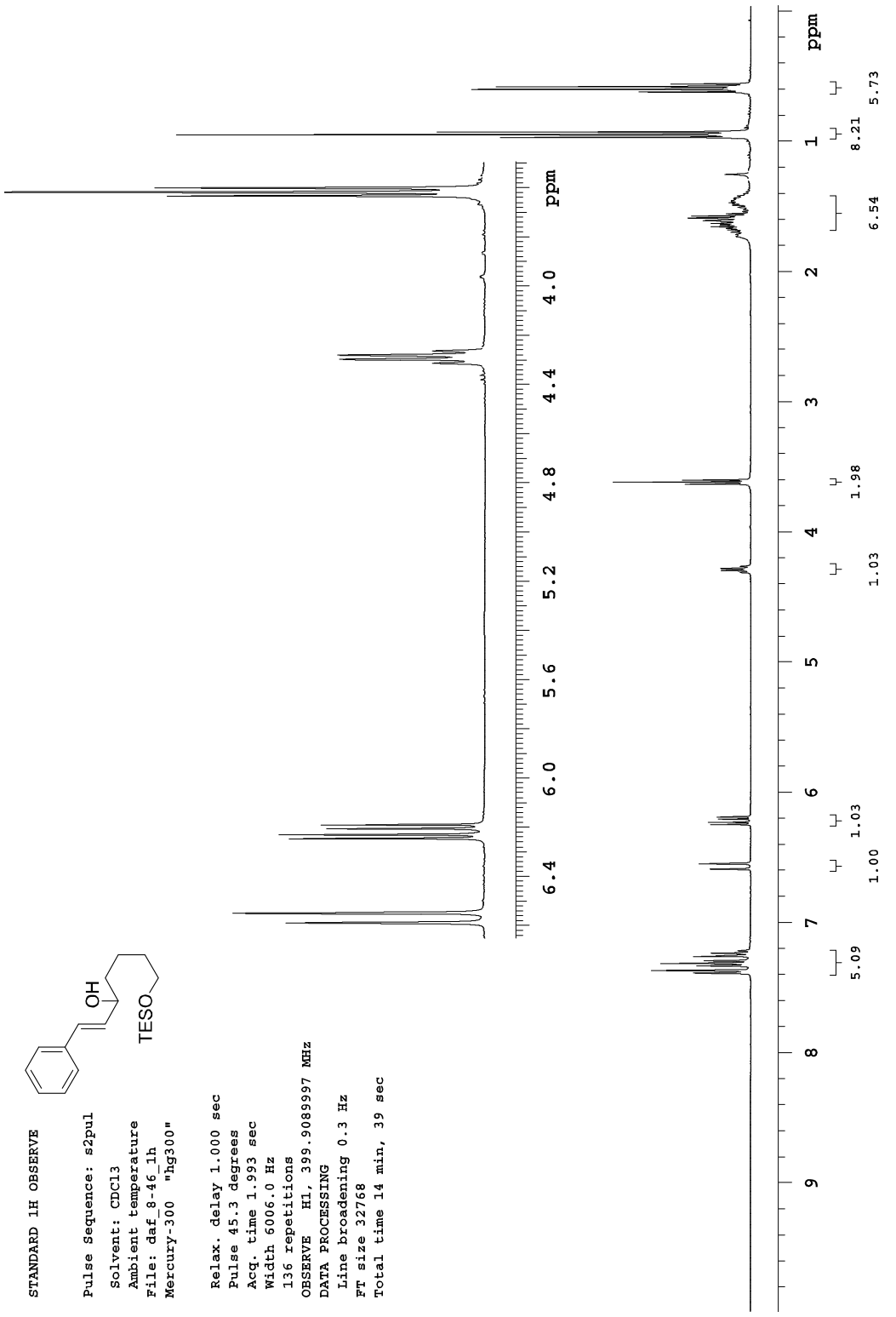
Spectrum 2.138 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **537**



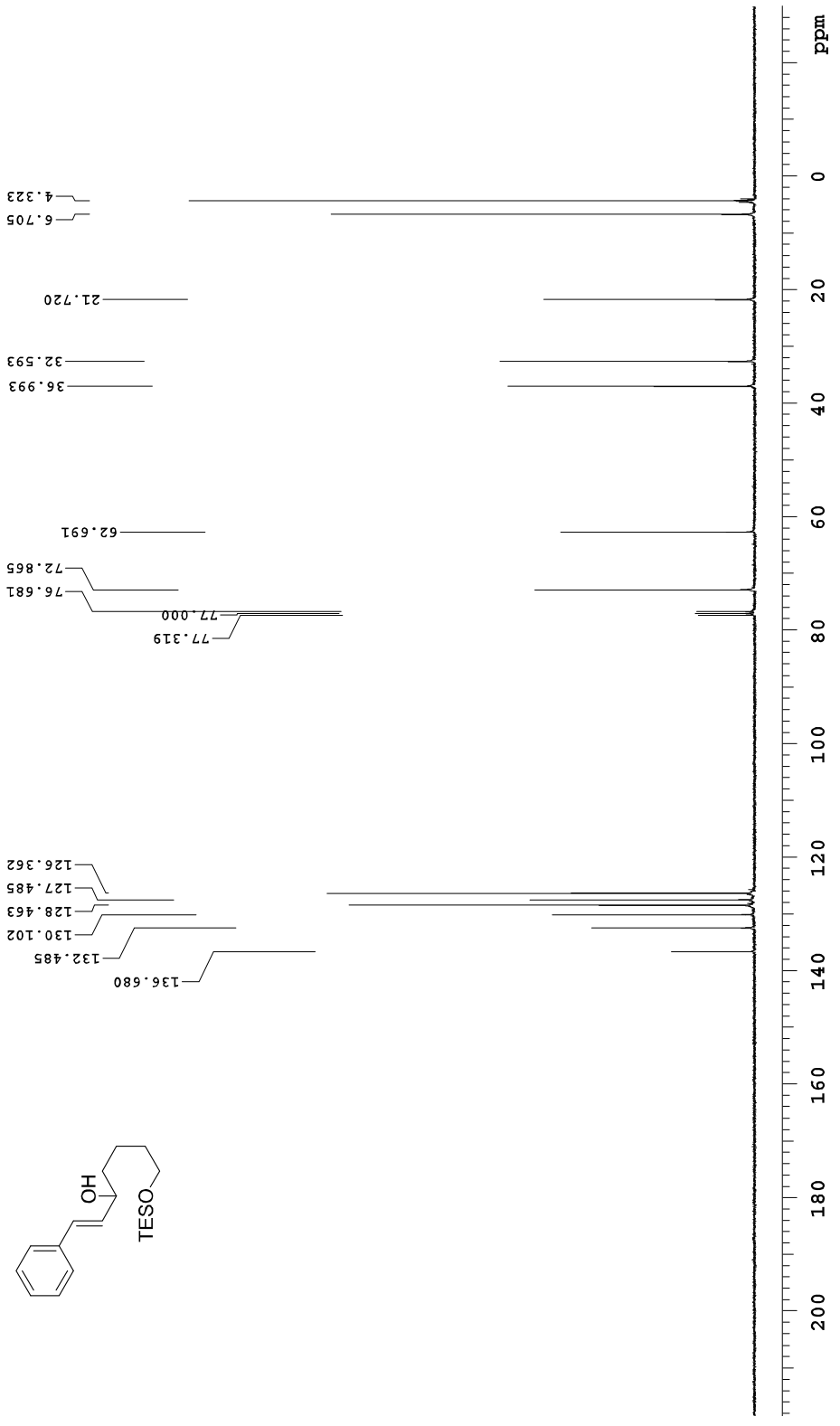
Spectrum 2.139 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **538**



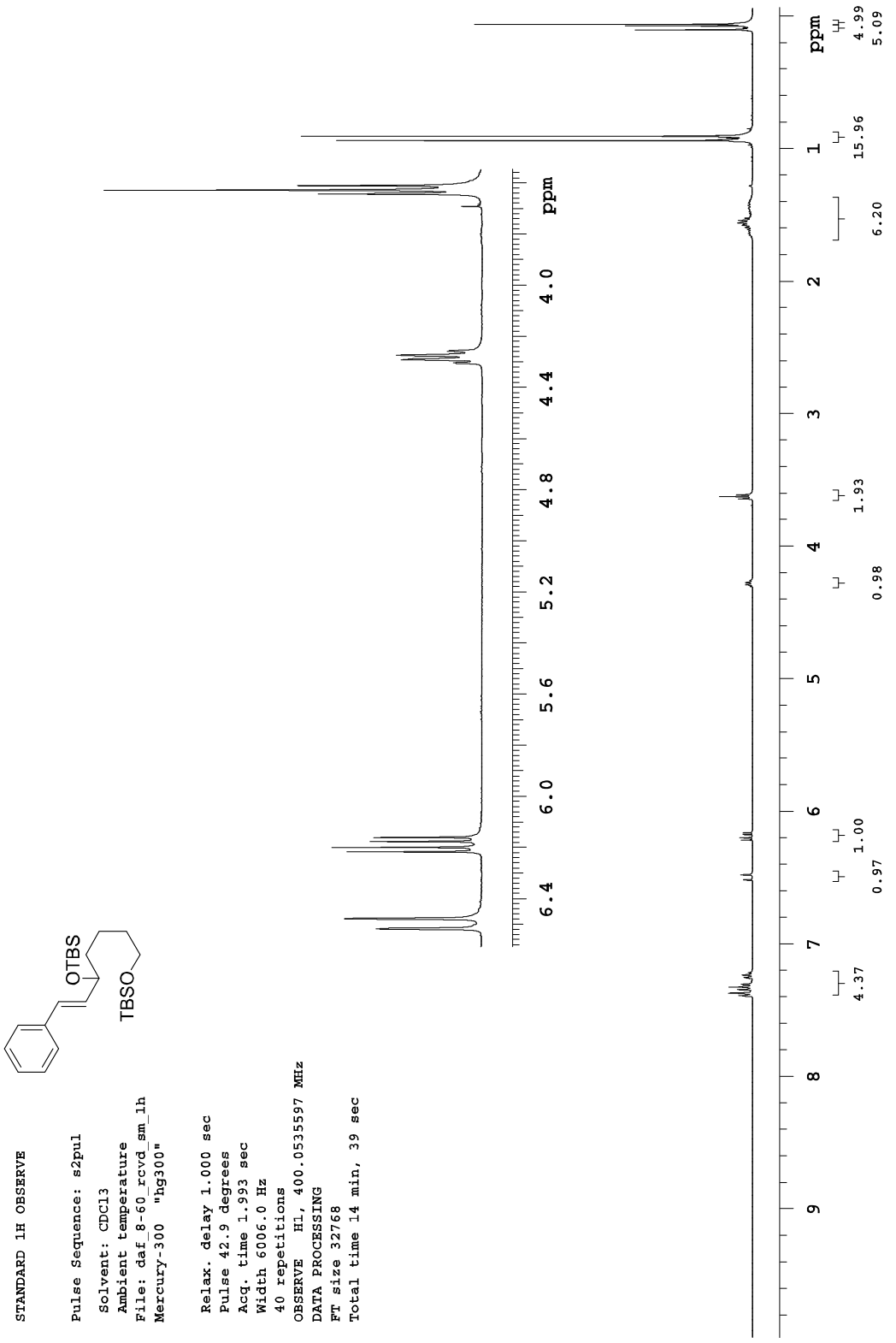
Spectrum 2.140 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **538**



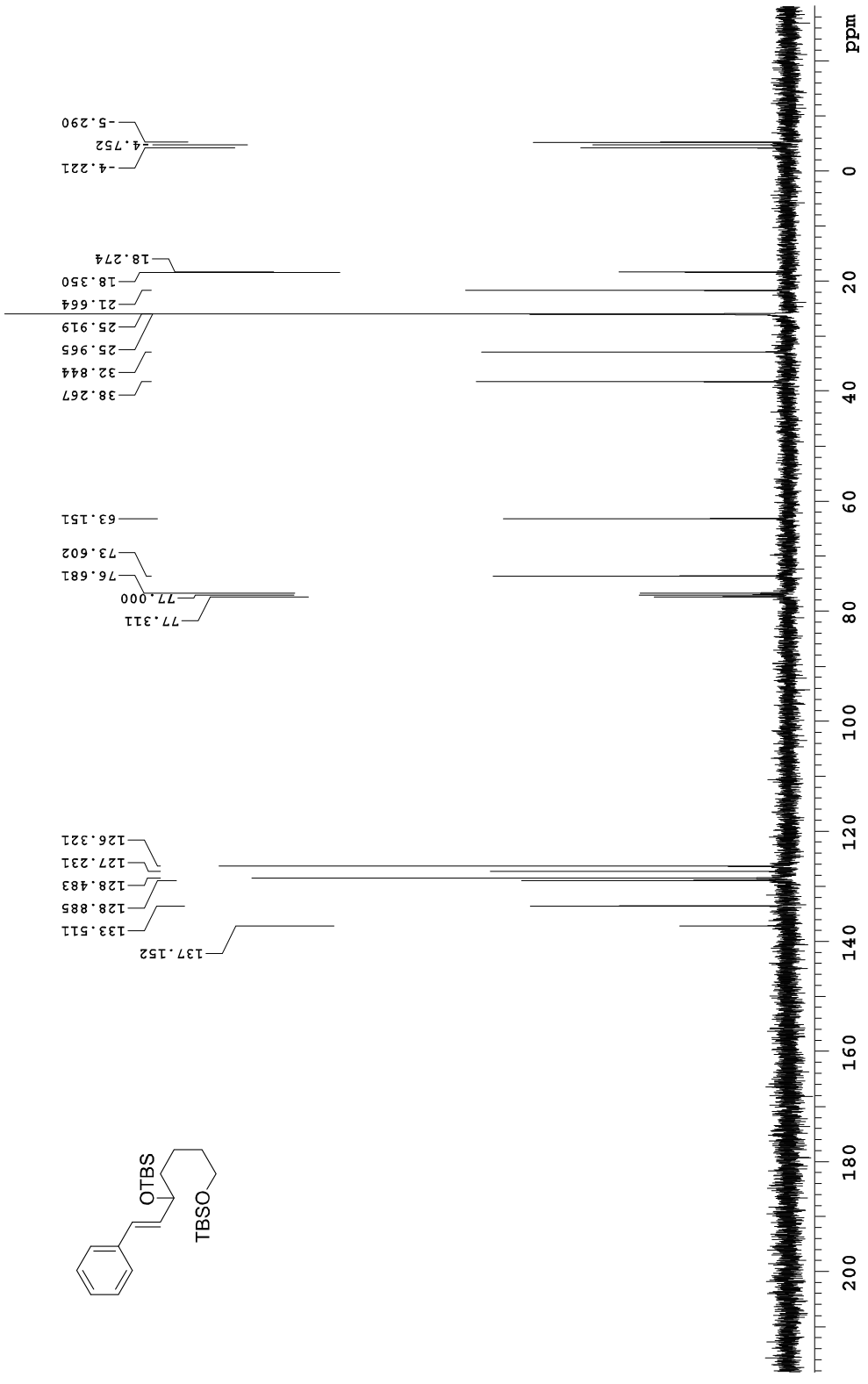
Spectrum 2.141 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **539**



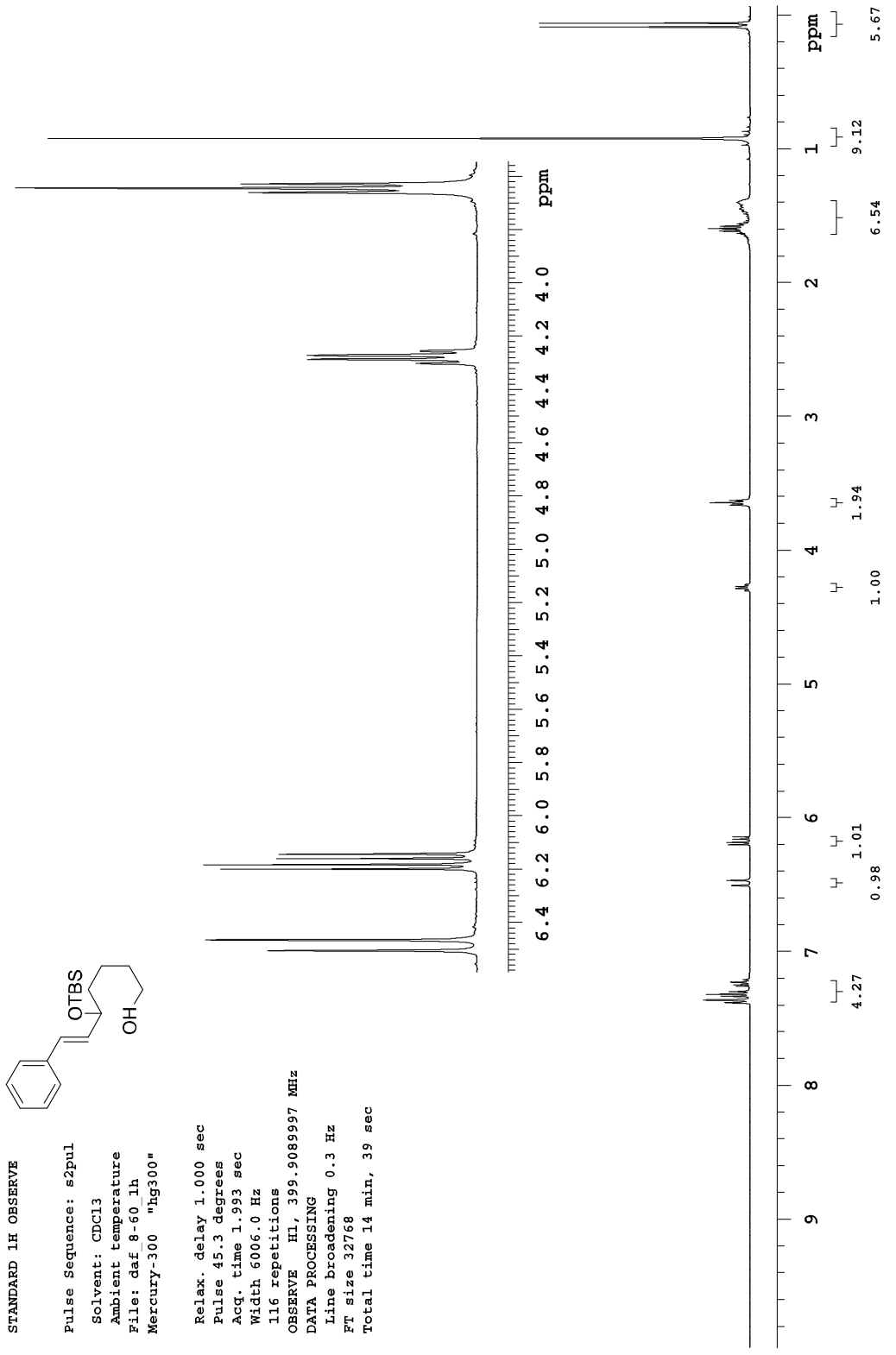
Spectrum 2.142 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **539**



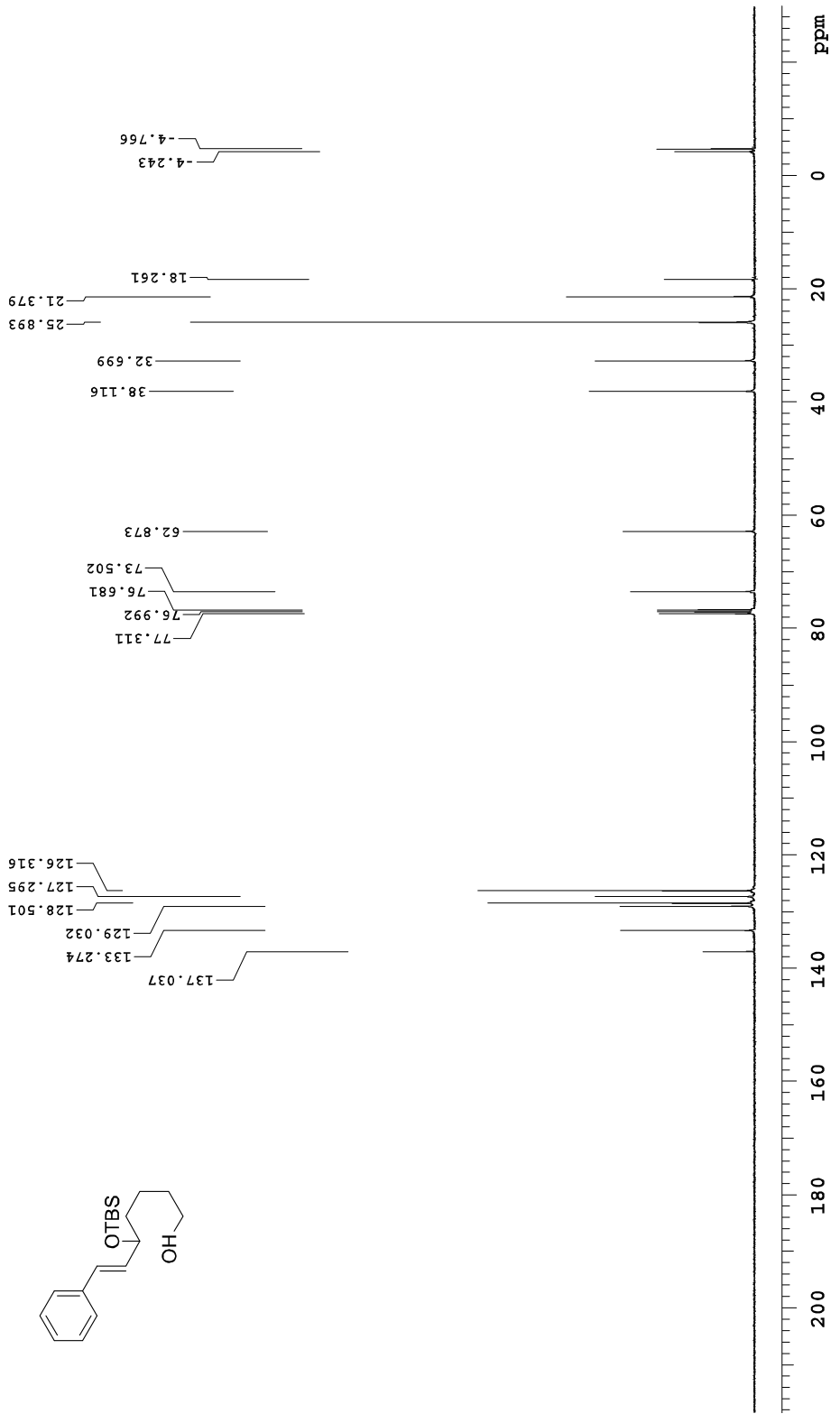
Spectrum 2.143 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **540**



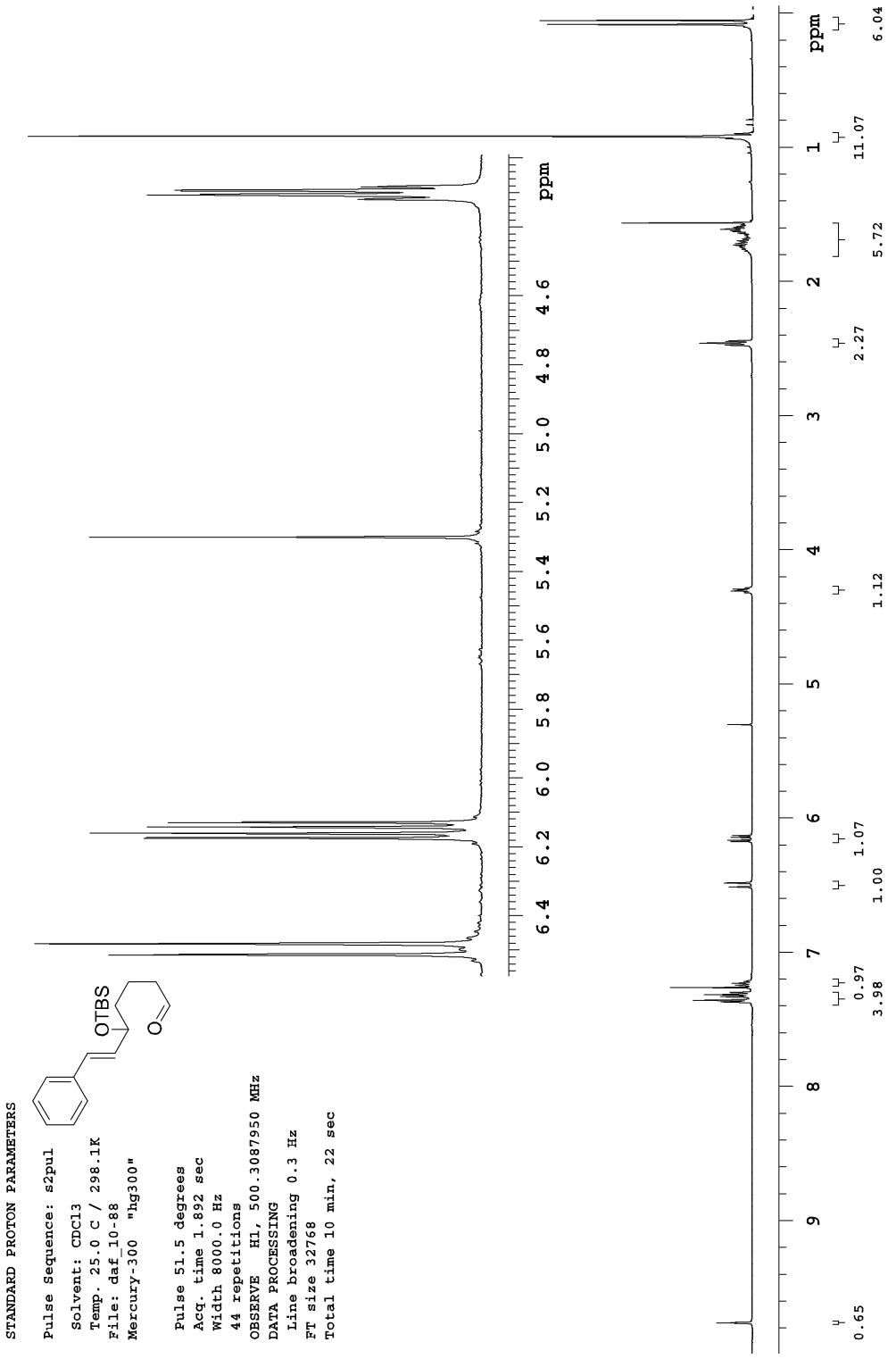
Spectrum 2.144 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **540**



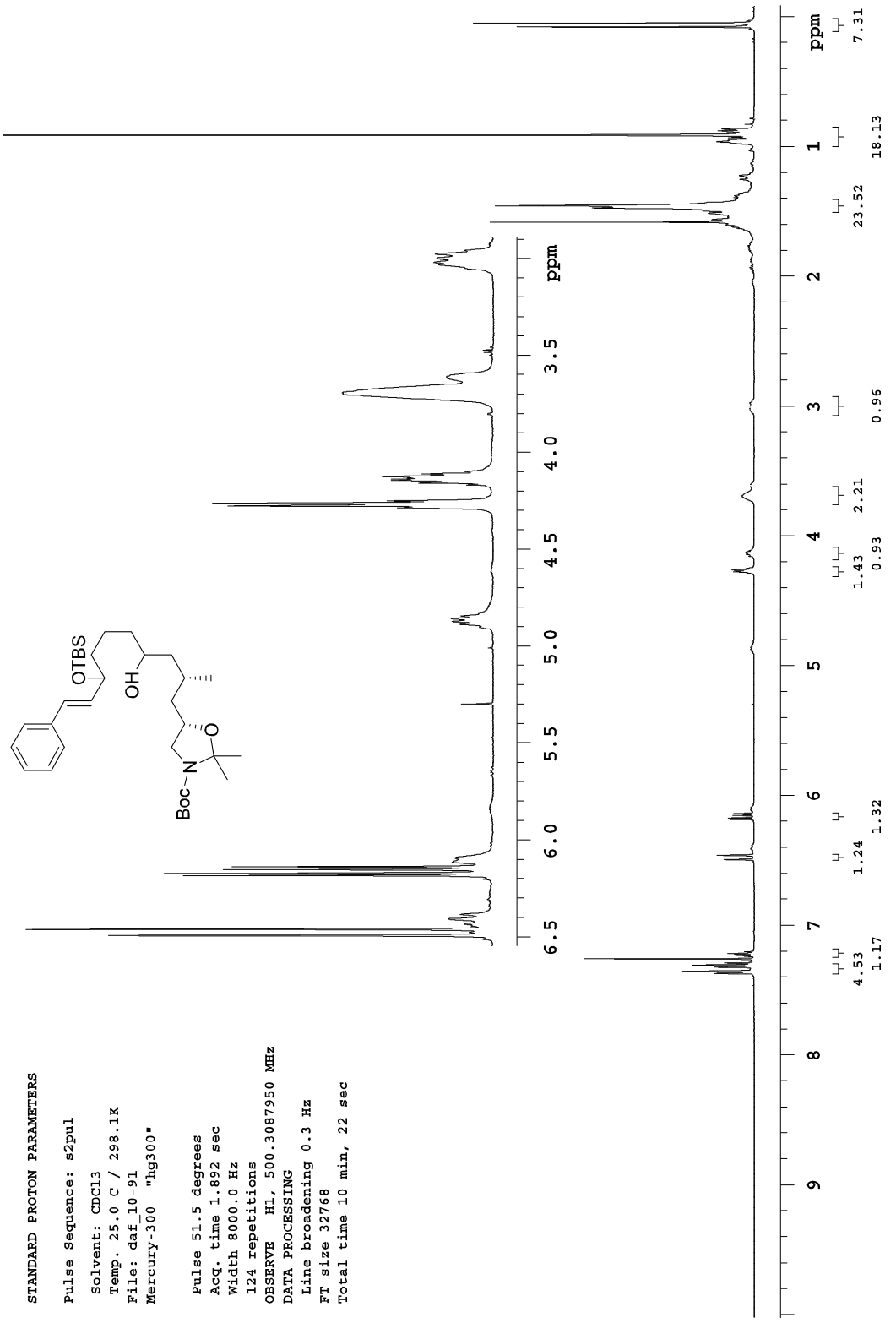
Spectrum 2.145 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **541**



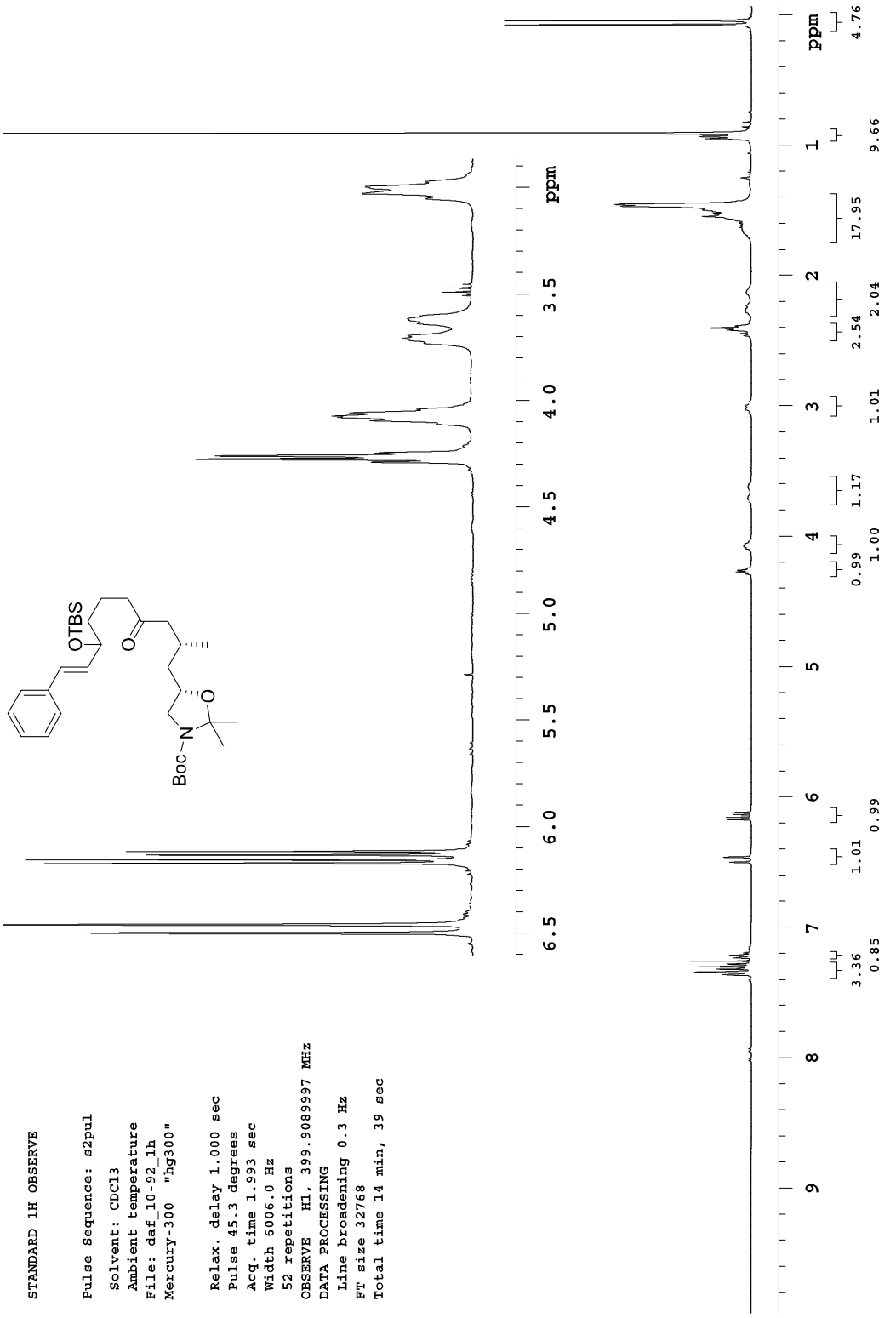
Spectrum 2.146 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **541**



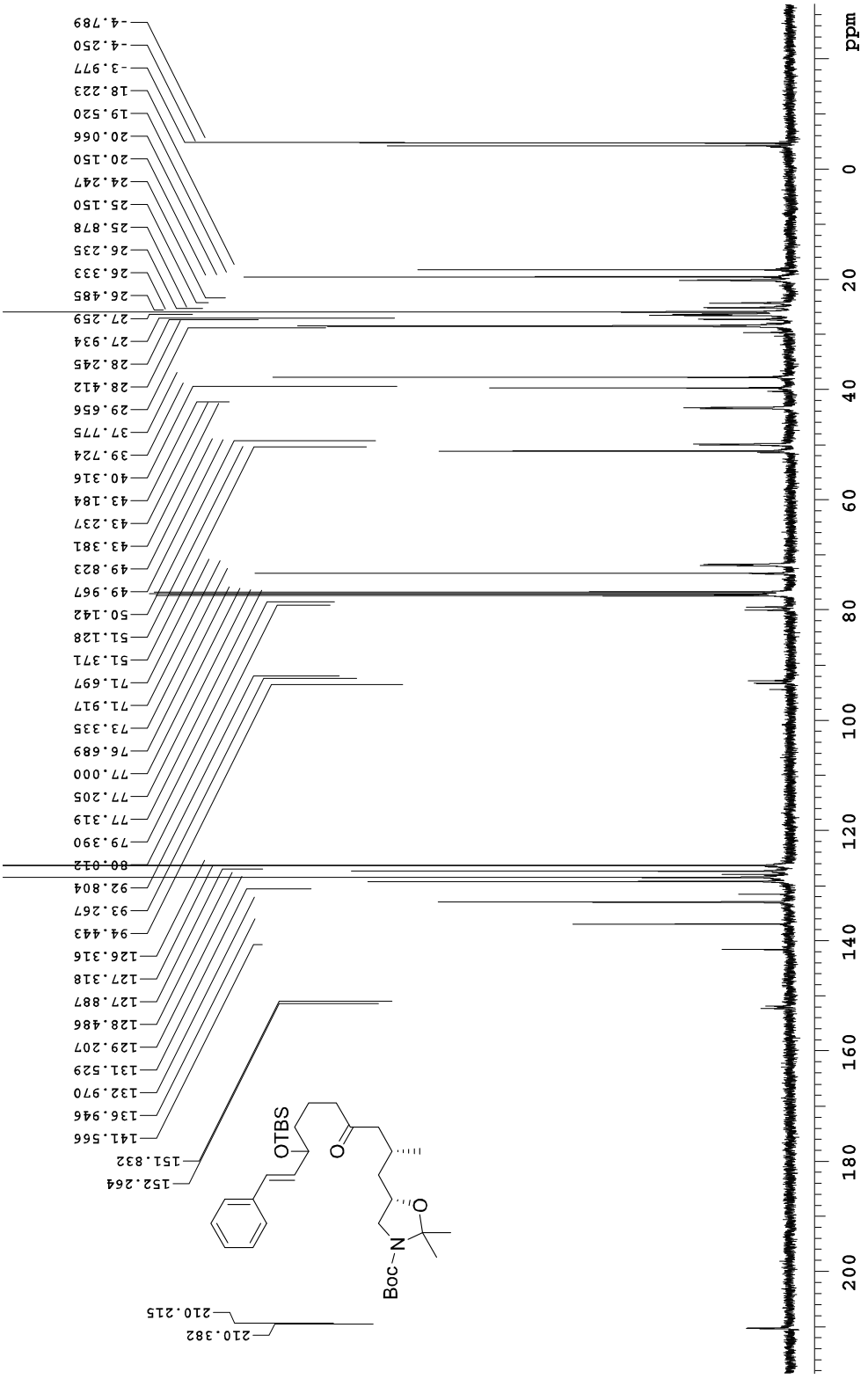
Spectrum 2.147 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **542**



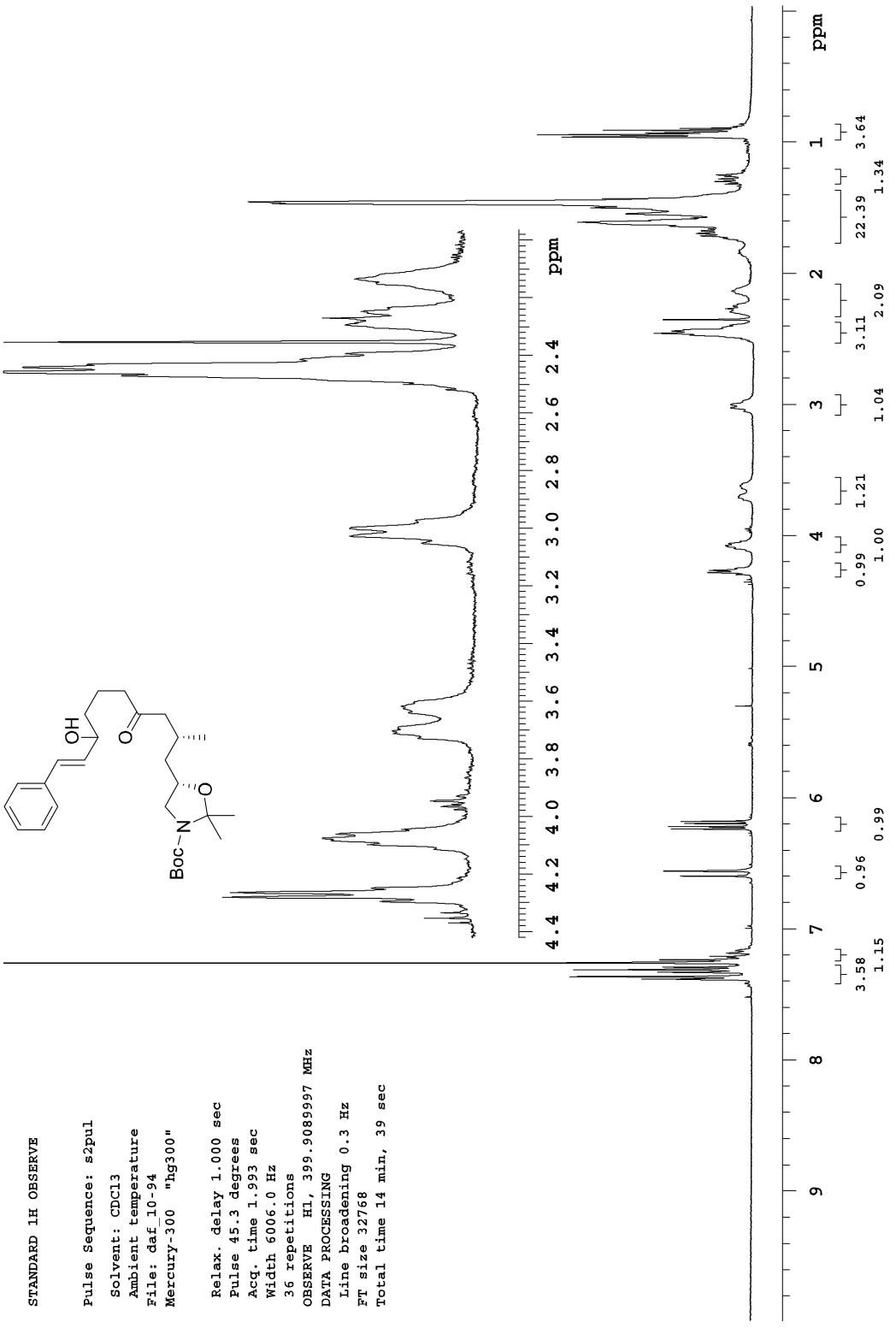
Spectrum 2.148 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **543**



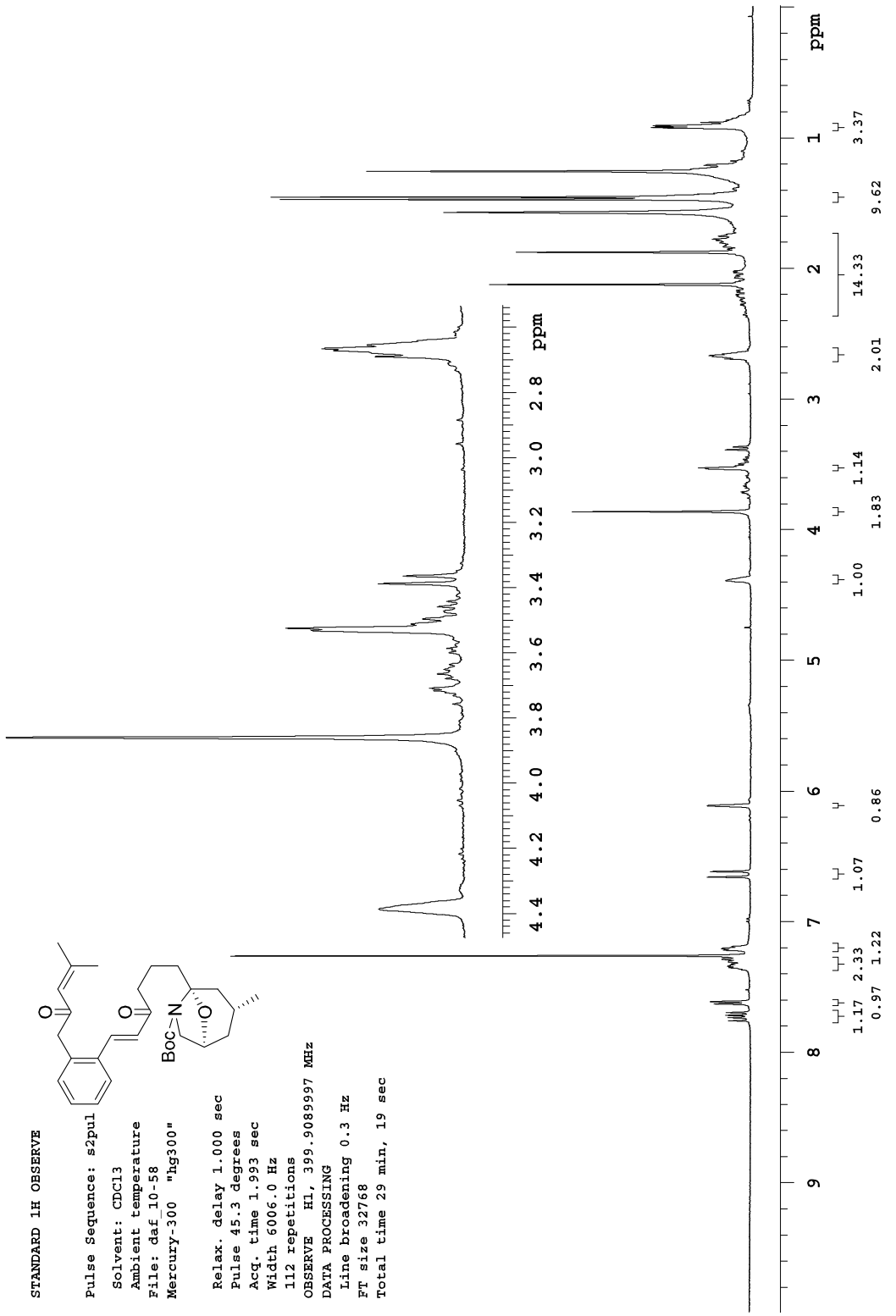
Spectrum 2.149 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **544**



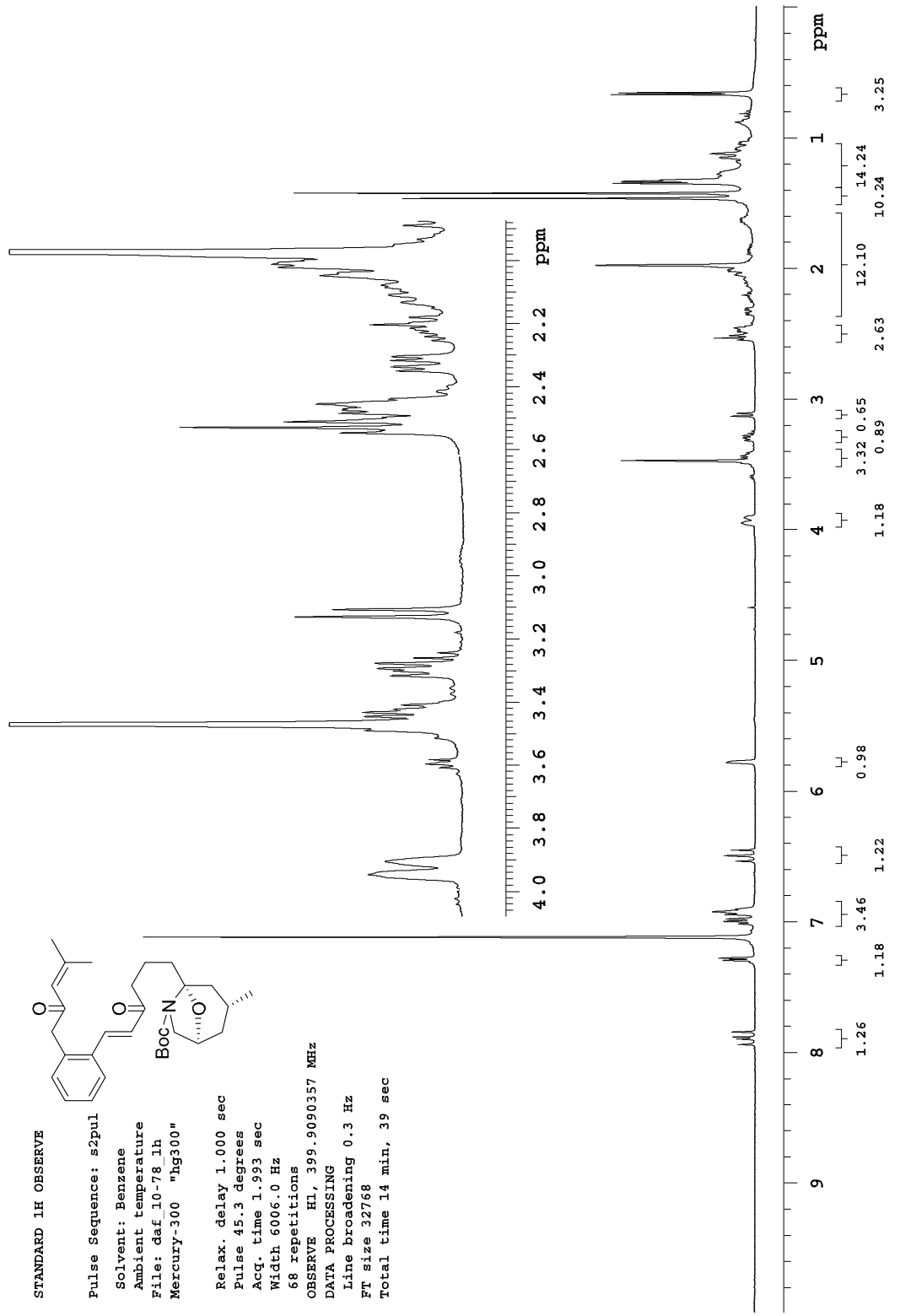
Spectrum 2.150 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **544**



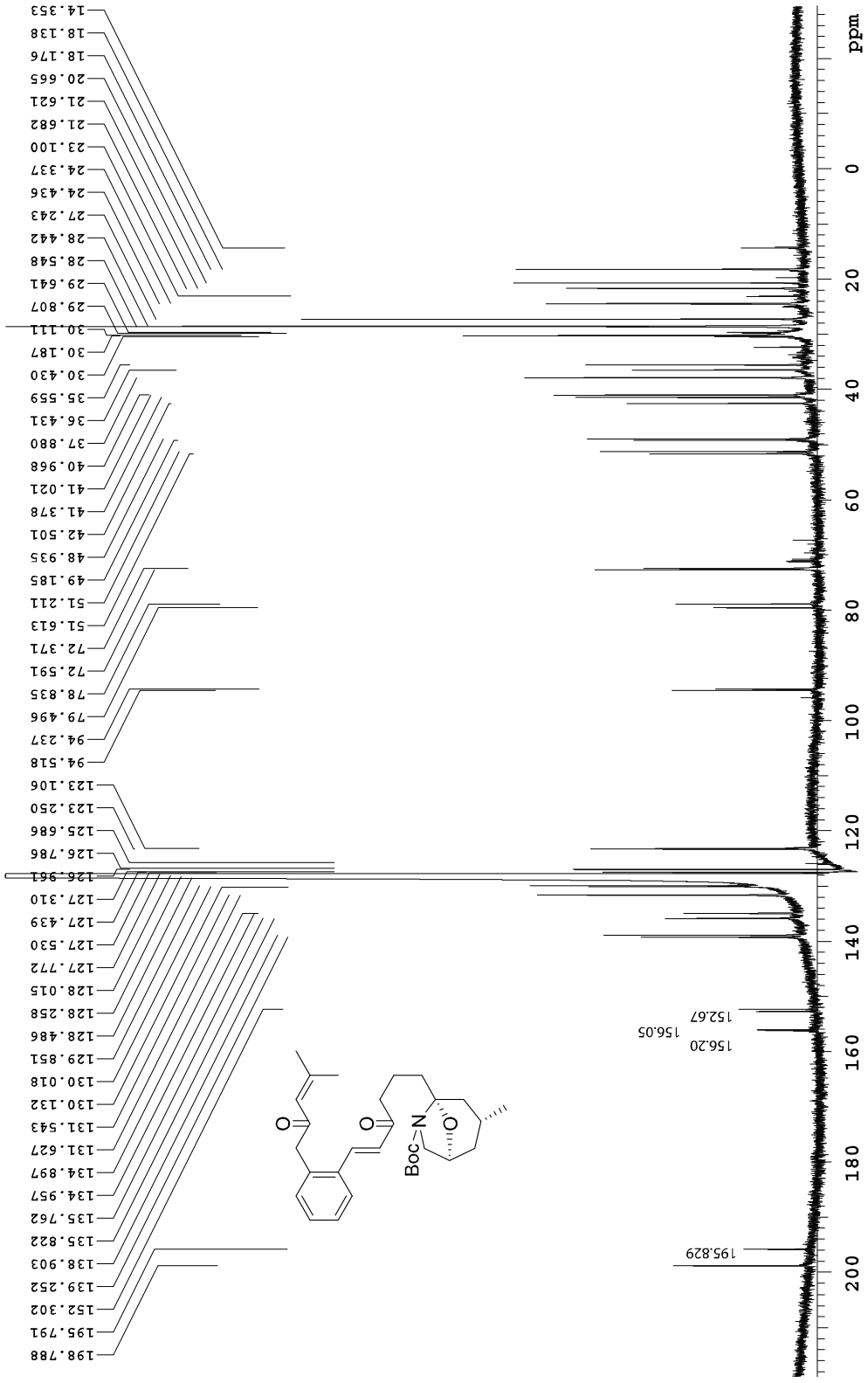
Spectrum 2.151 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **545**



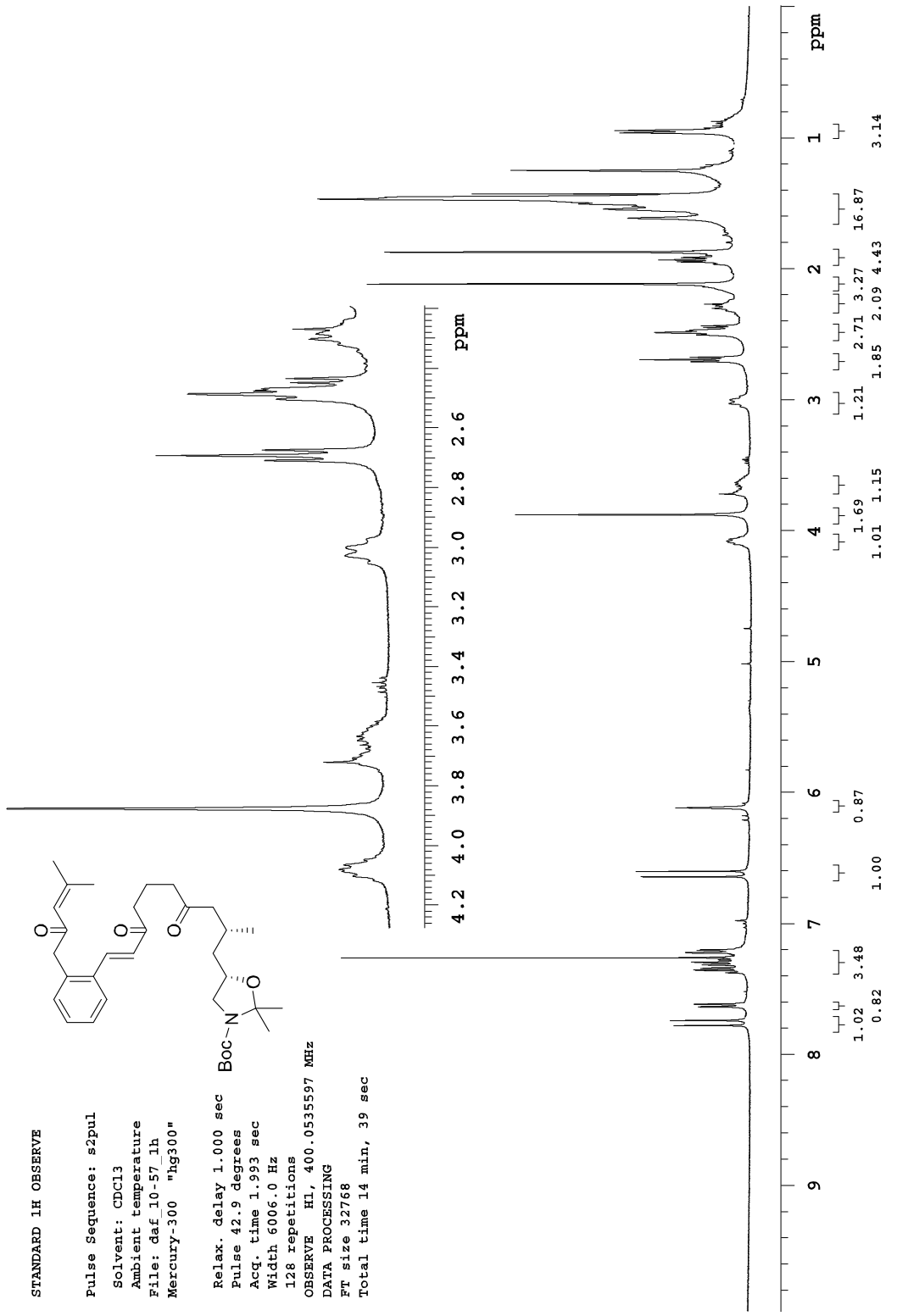
Spectrum 2.152 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **548**



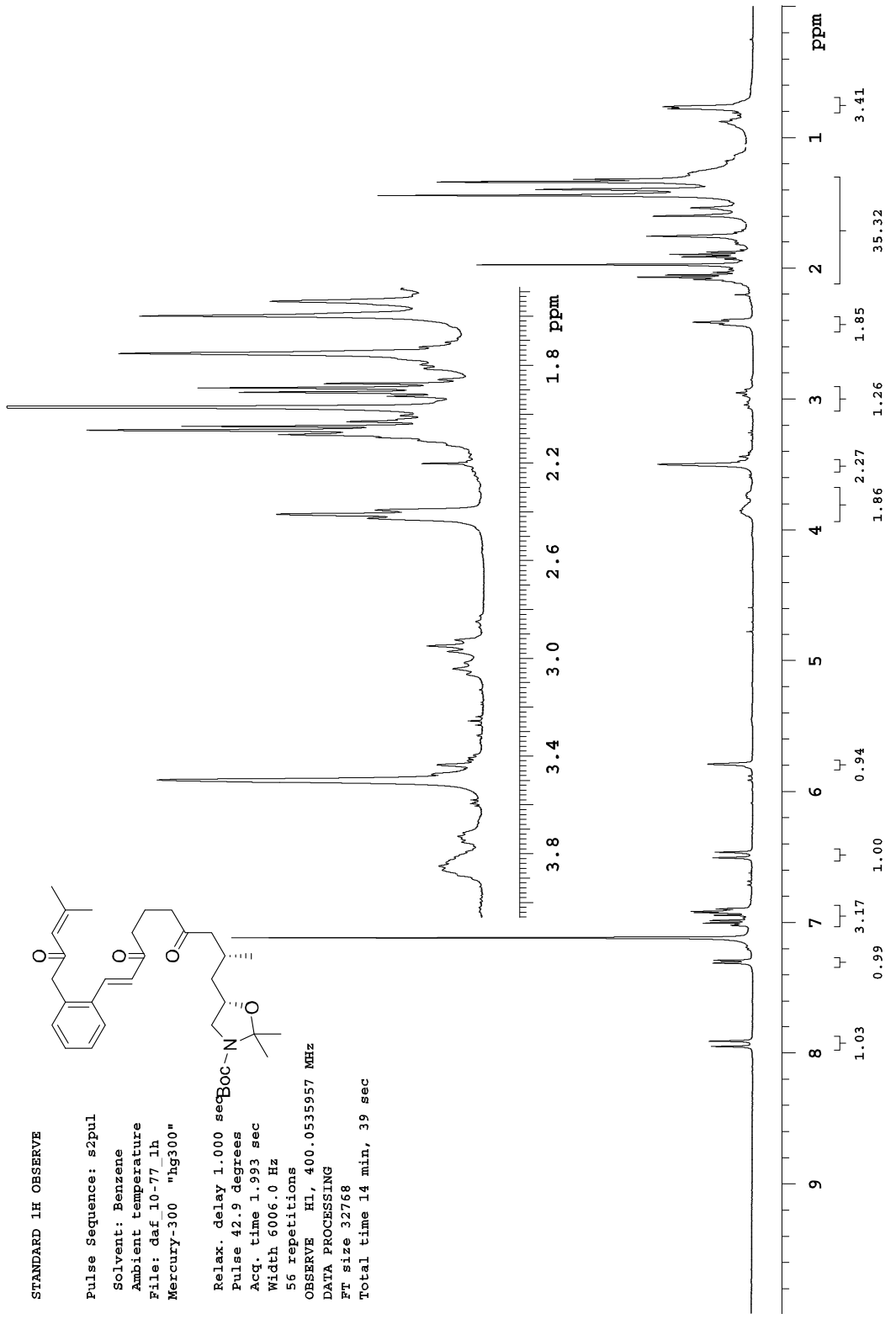
Spectrum 2.153 ^{1}H NMR (C_6D_6, 400 MHz) of compound **548**



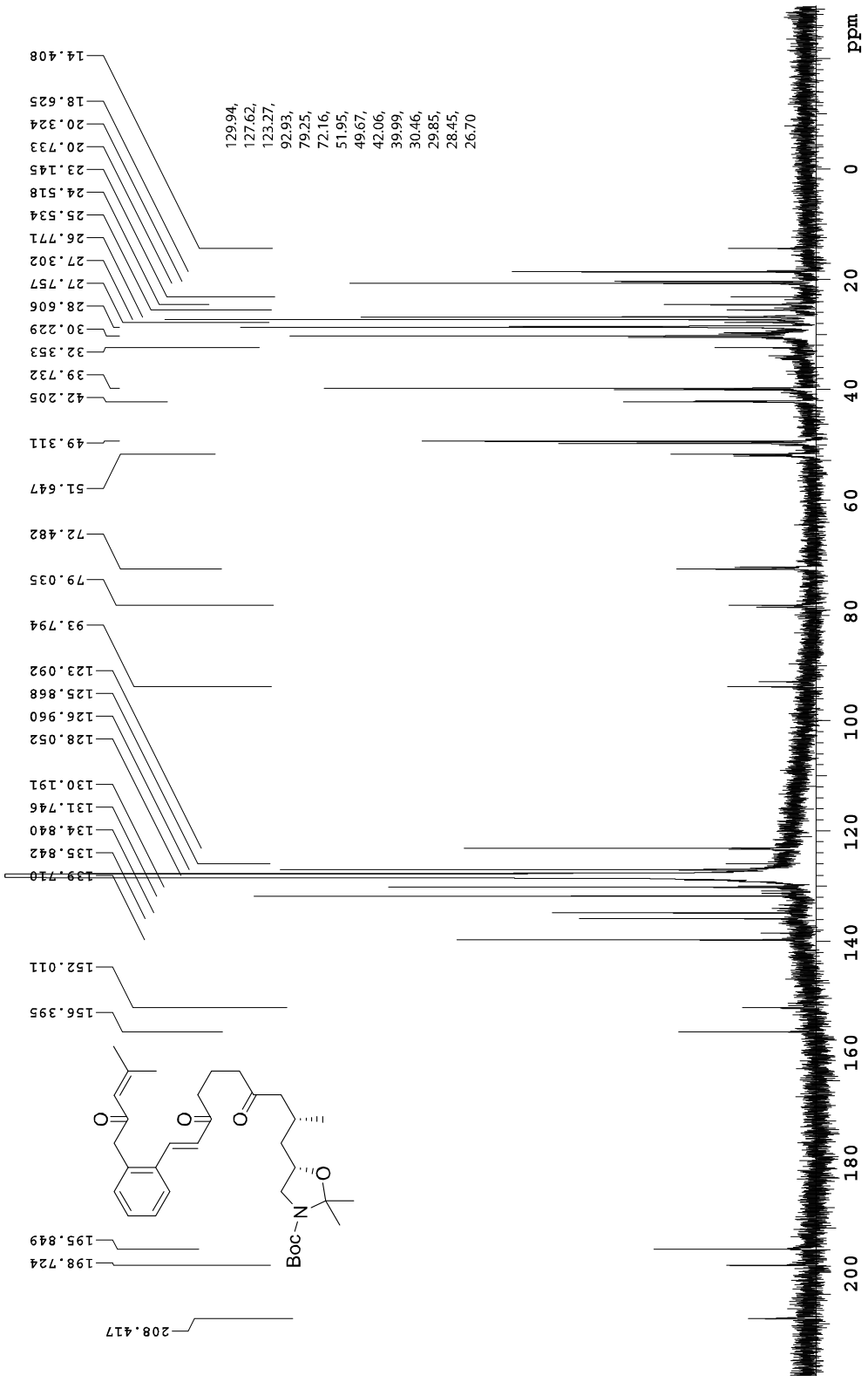
Spectrum 2.154 ^{13}C NMR (C_6D_6, 100 MHz) of compound **548**



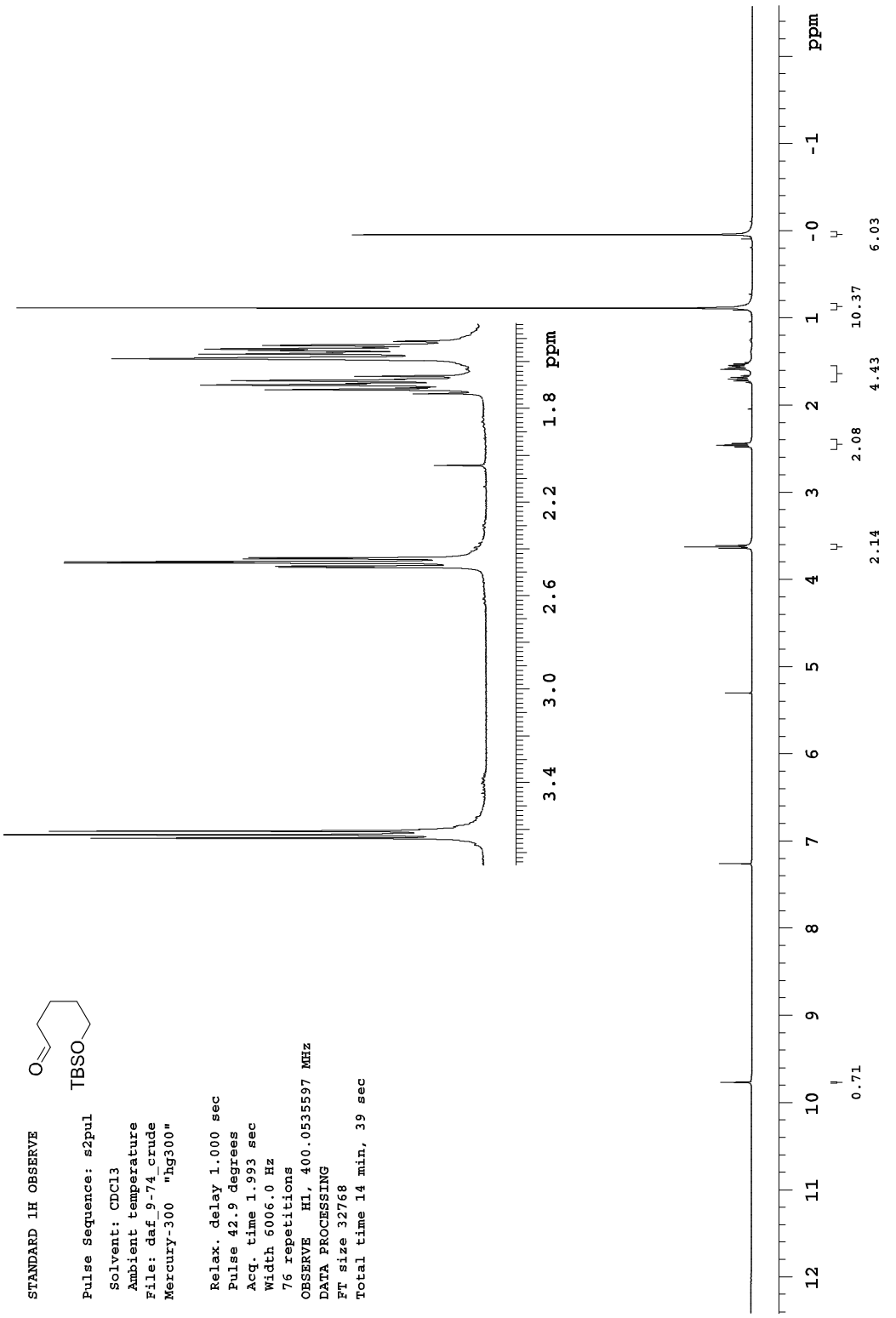
Spectrum 2.155 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **549**



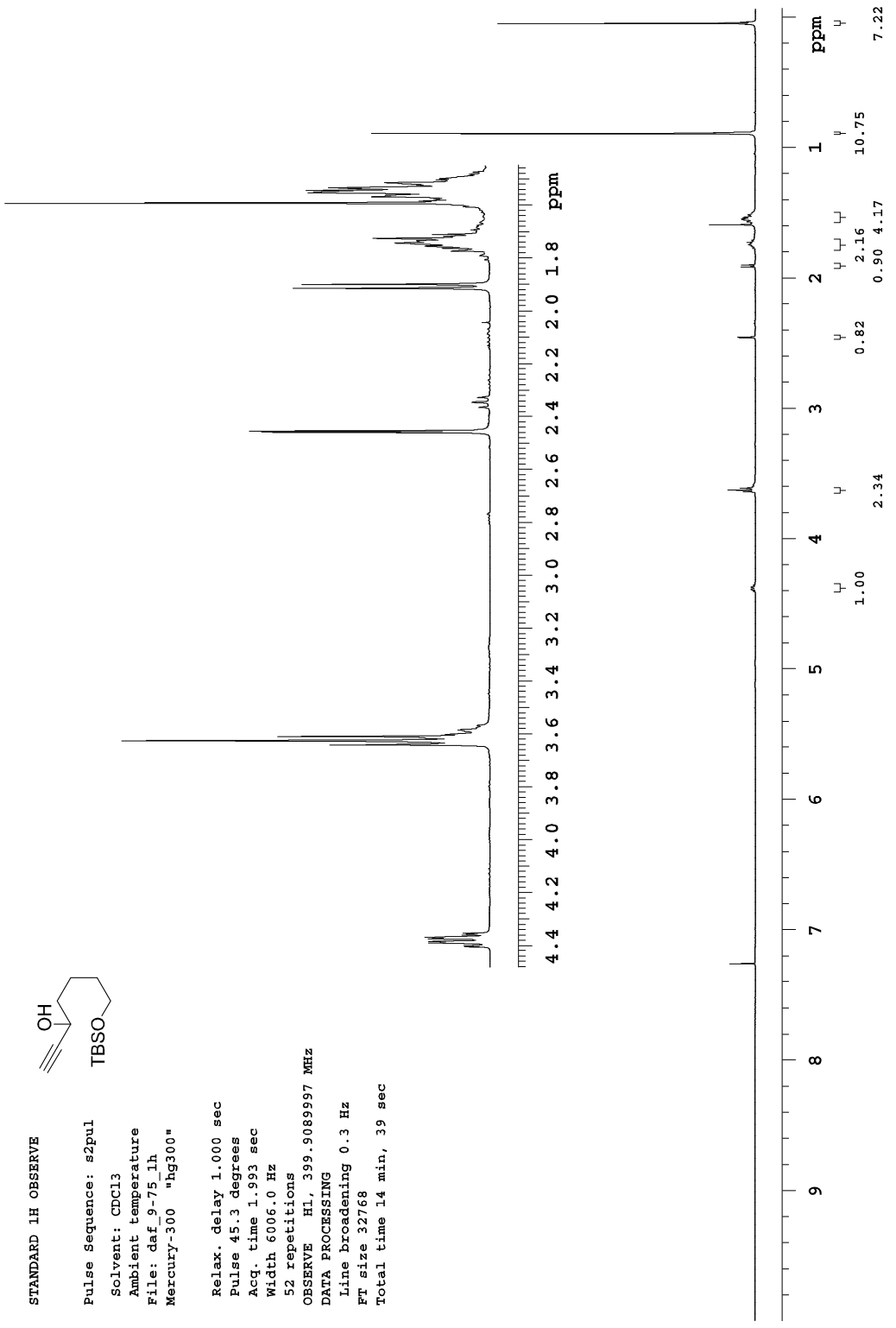
Spectrum 2.156 ^{1}H NMR (C_6D_6, 400 MHz) of compound **549**



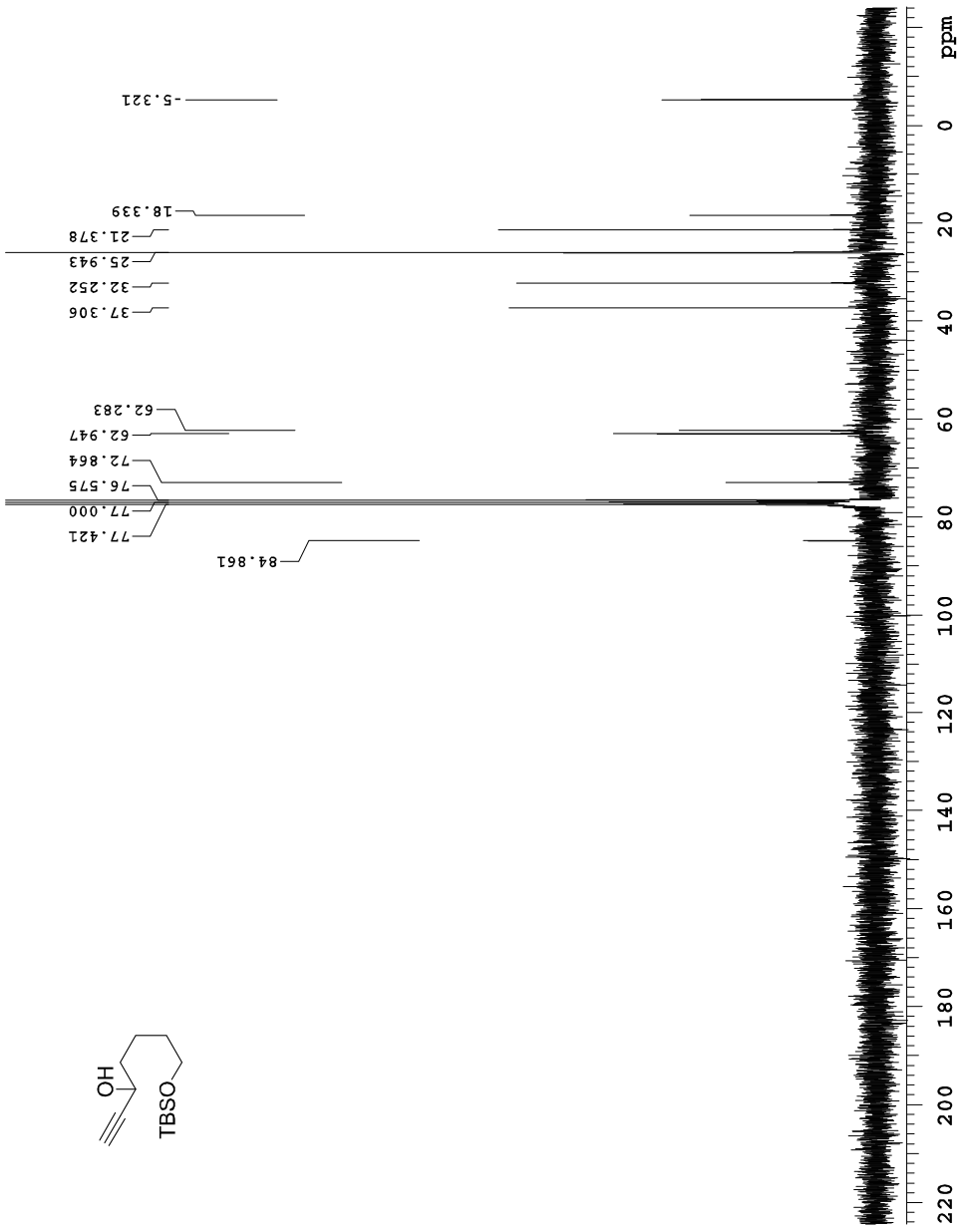
Spectrum 2.157 ^{13}C NMR (C_6D_6, 100 MHz) of compound **549**



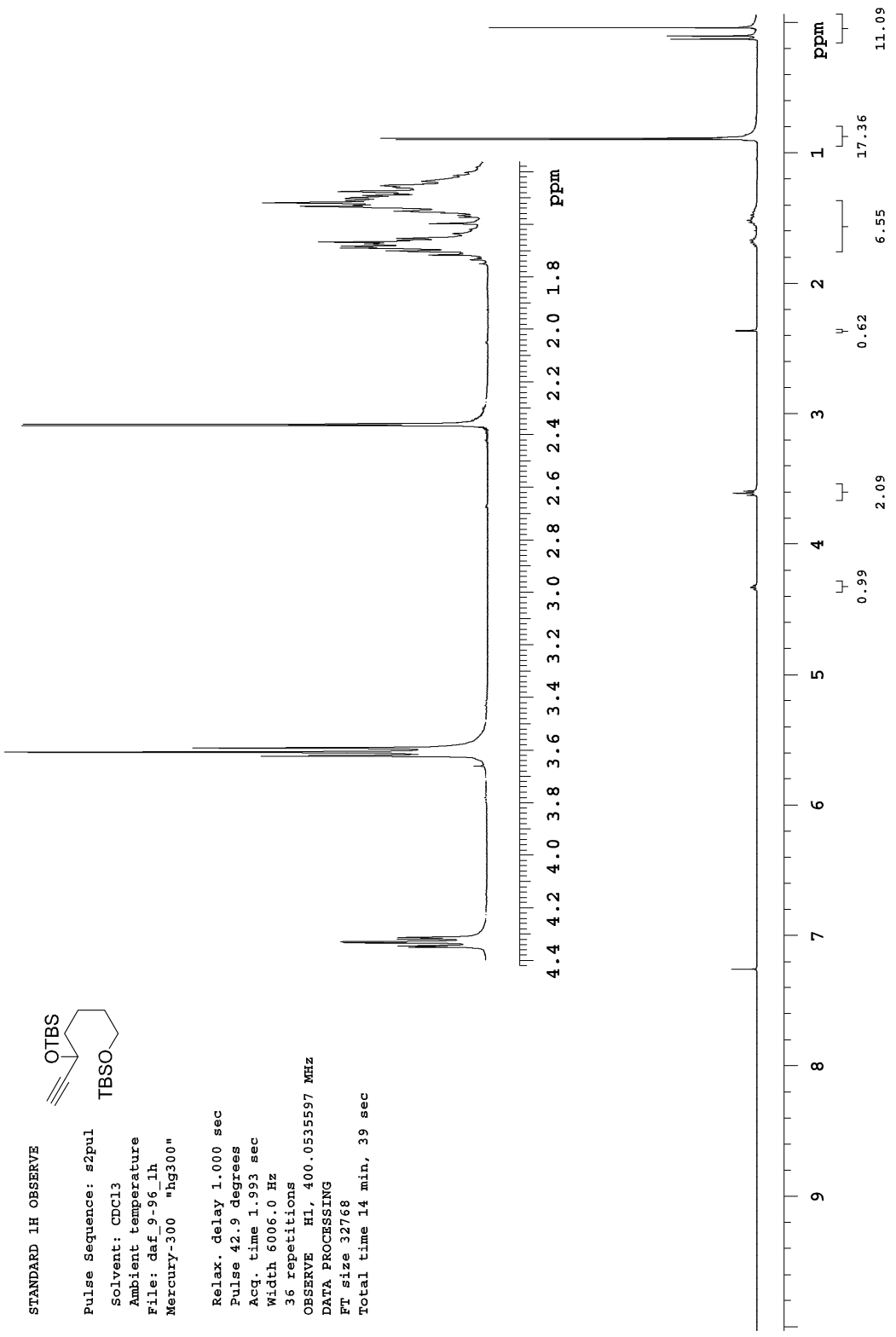
Spectrum 2.158 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **553**



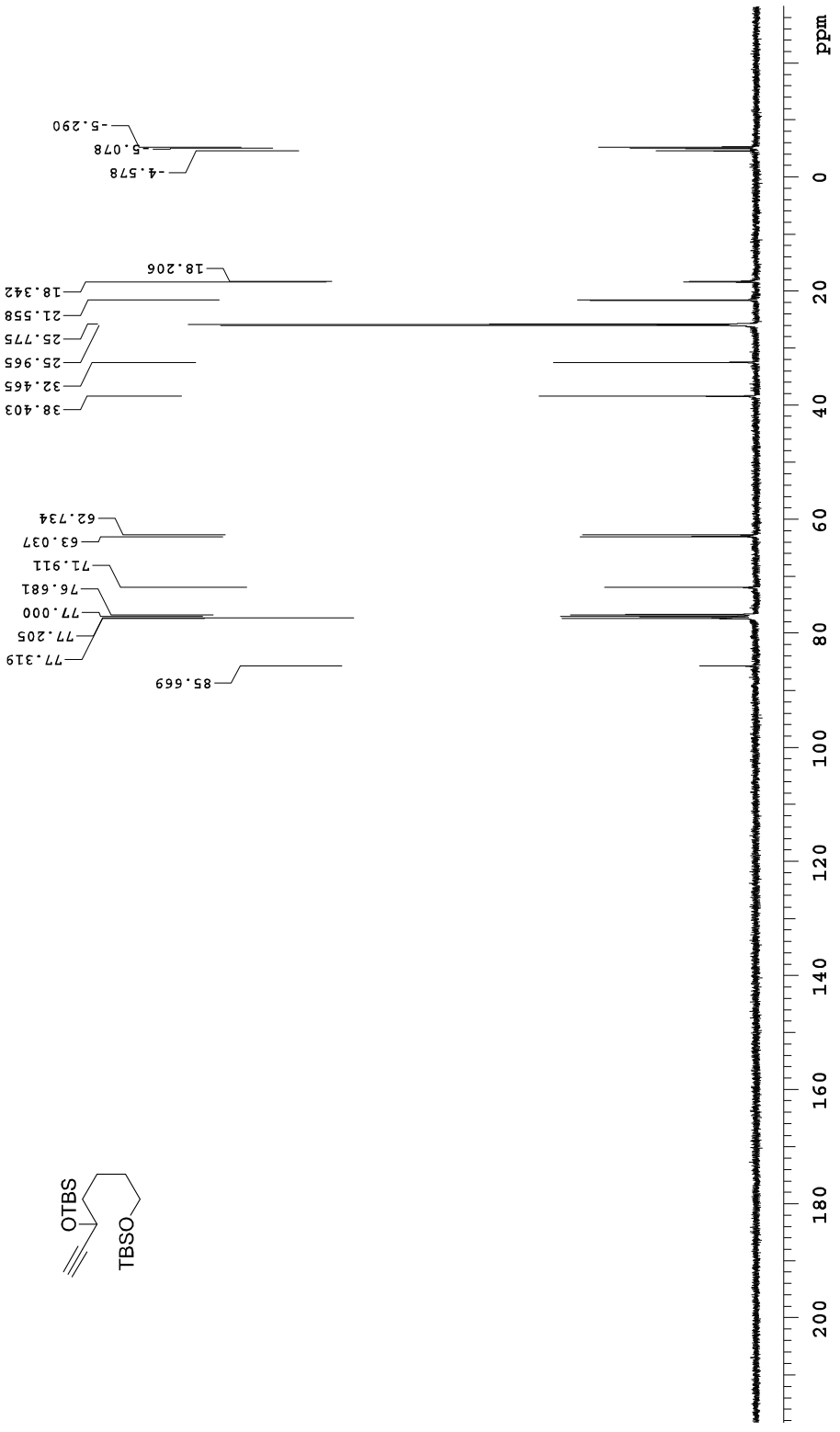
Spectrum 2.159 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **554**



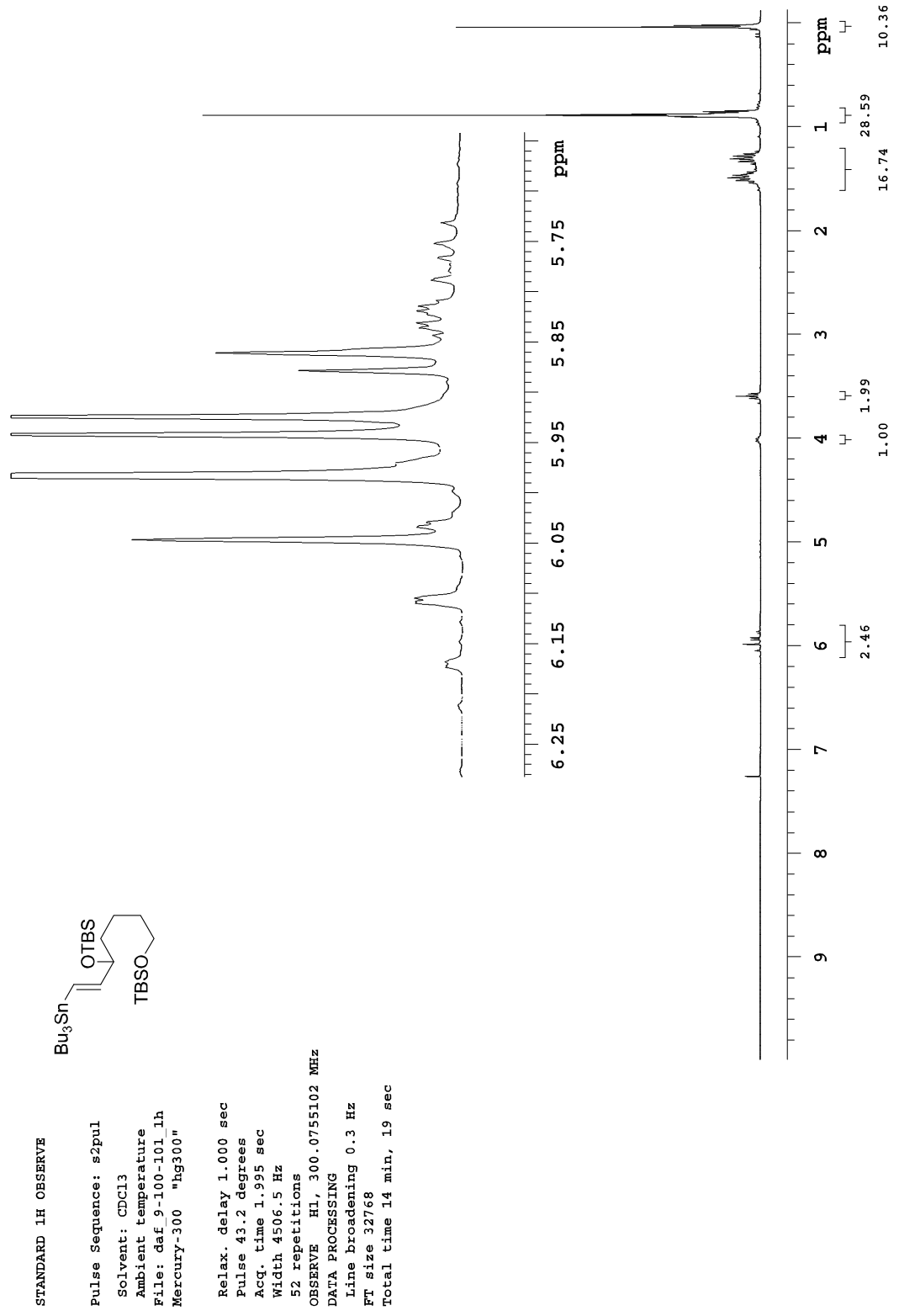
Spectrum 2.160 ^{13}C NMR ($CDCl_3$, 75 MHz) of compound **554**



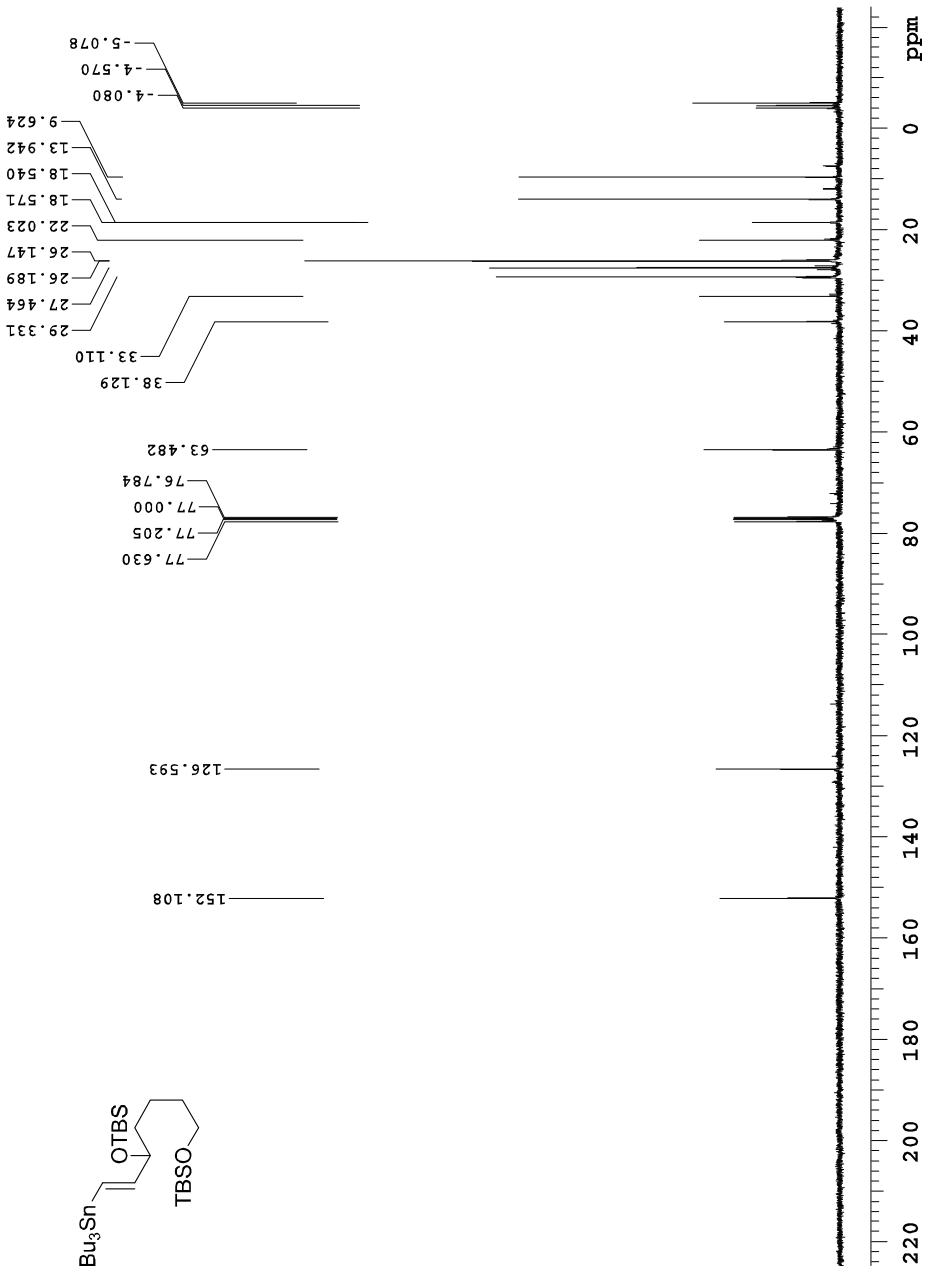
Spectrum 2.161 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **555**



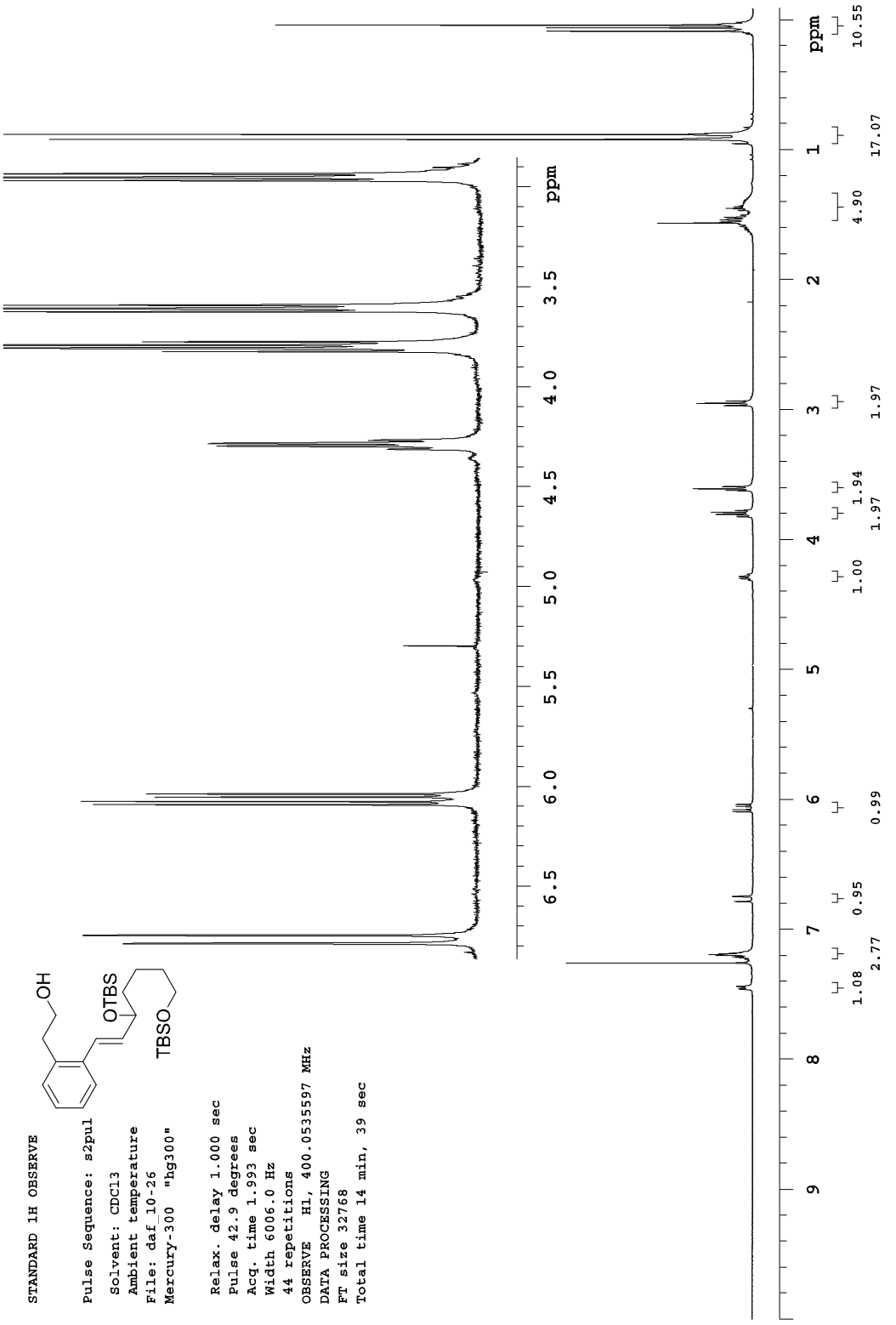
Spectrum 2.162 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **555**



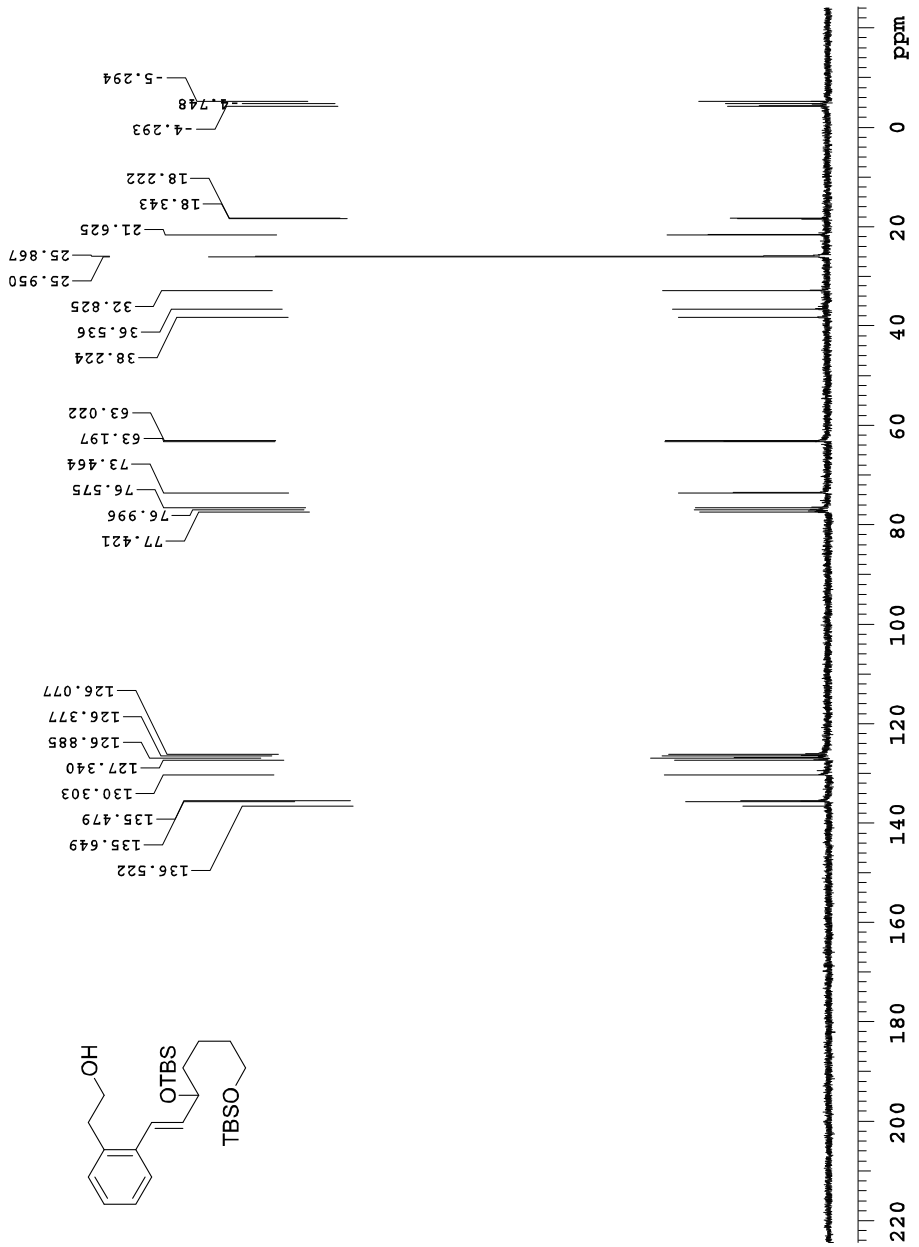
Spectrum 2.163 ^{1}H NMR ($CDCl_3$, 300 MHz) of compound **556**



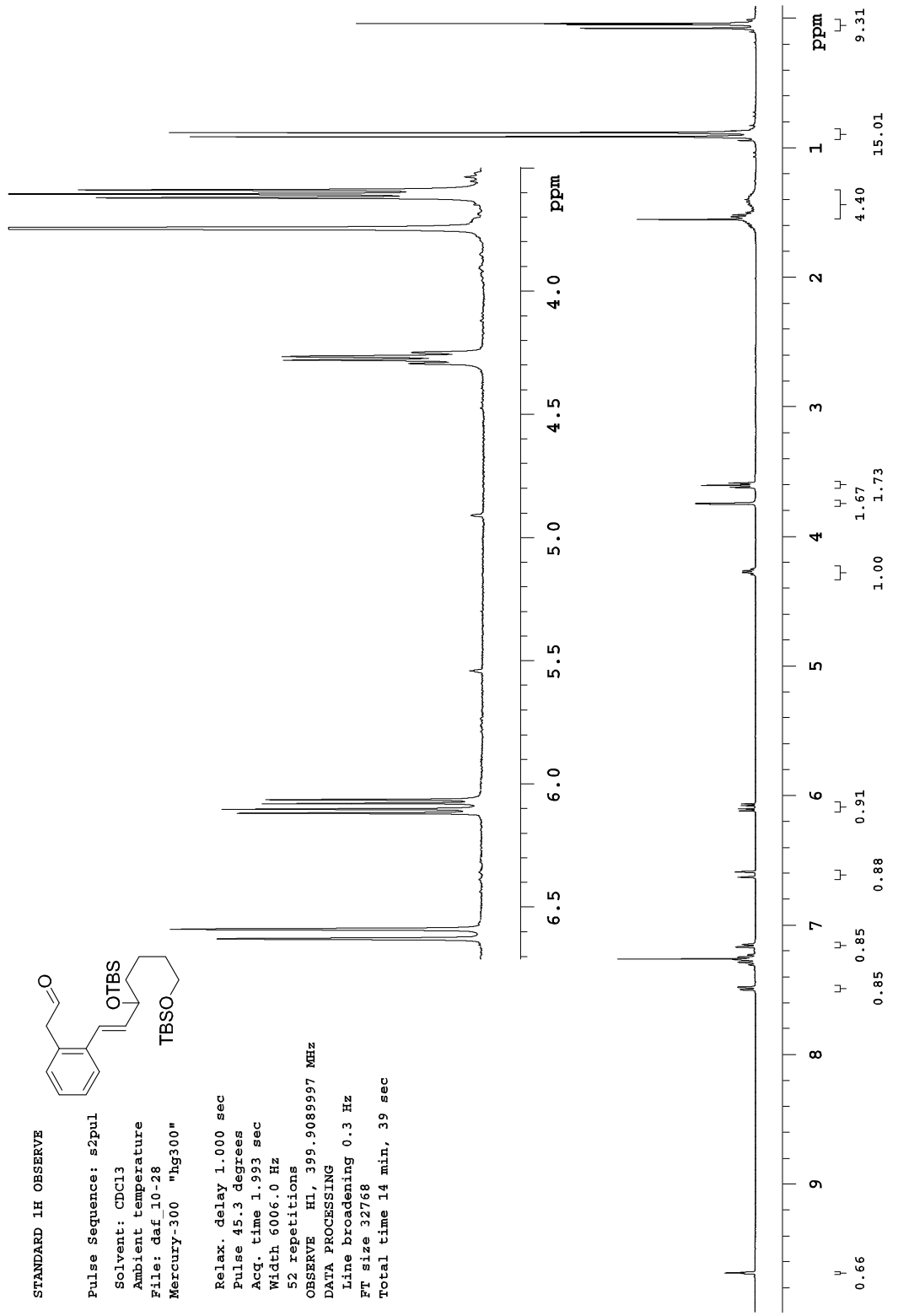
Spectrum 2.164 ^{13}C NMR ($CDCl_3$, 75 MHz) of compound **556**



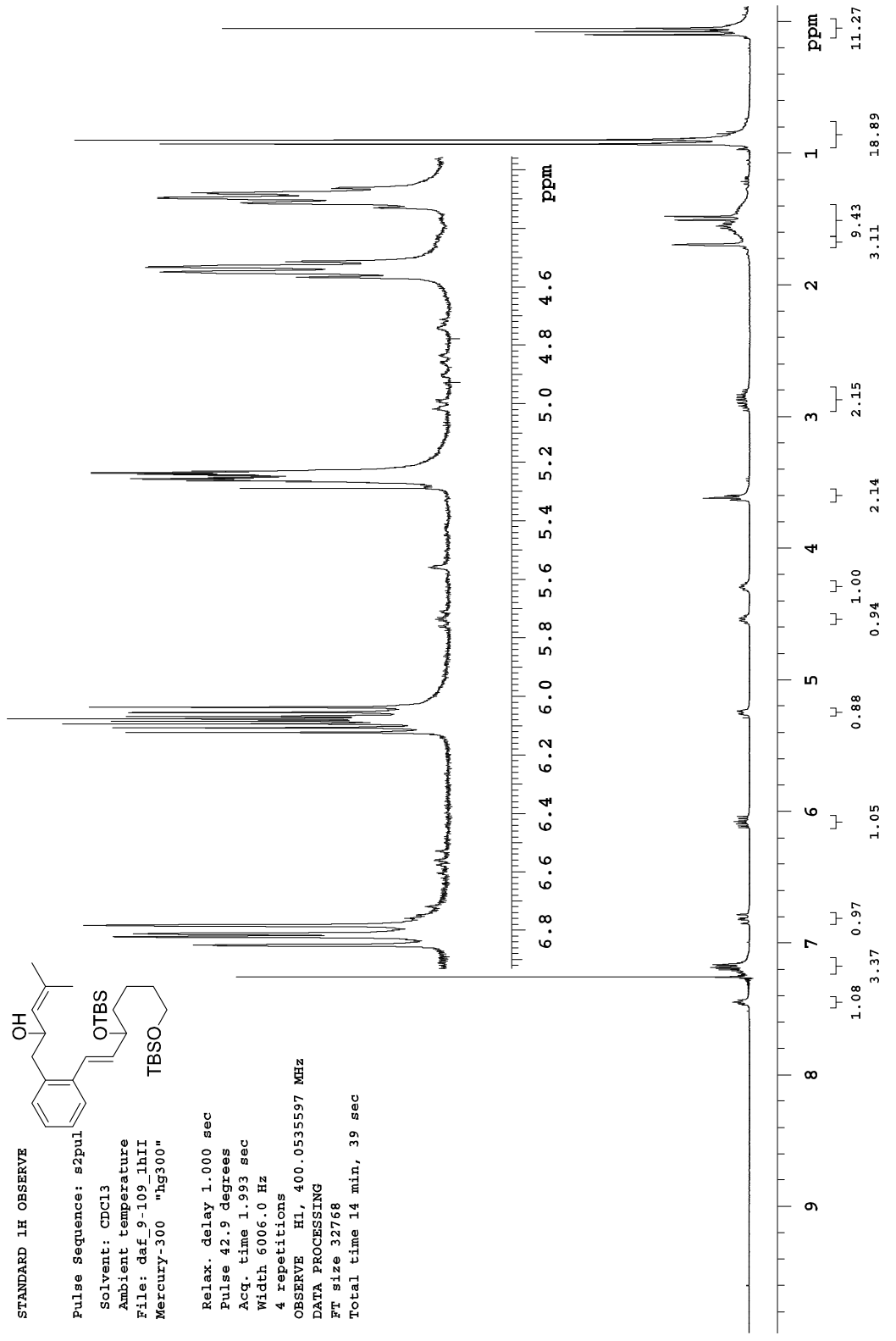
Spectrum 2.165 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **557**



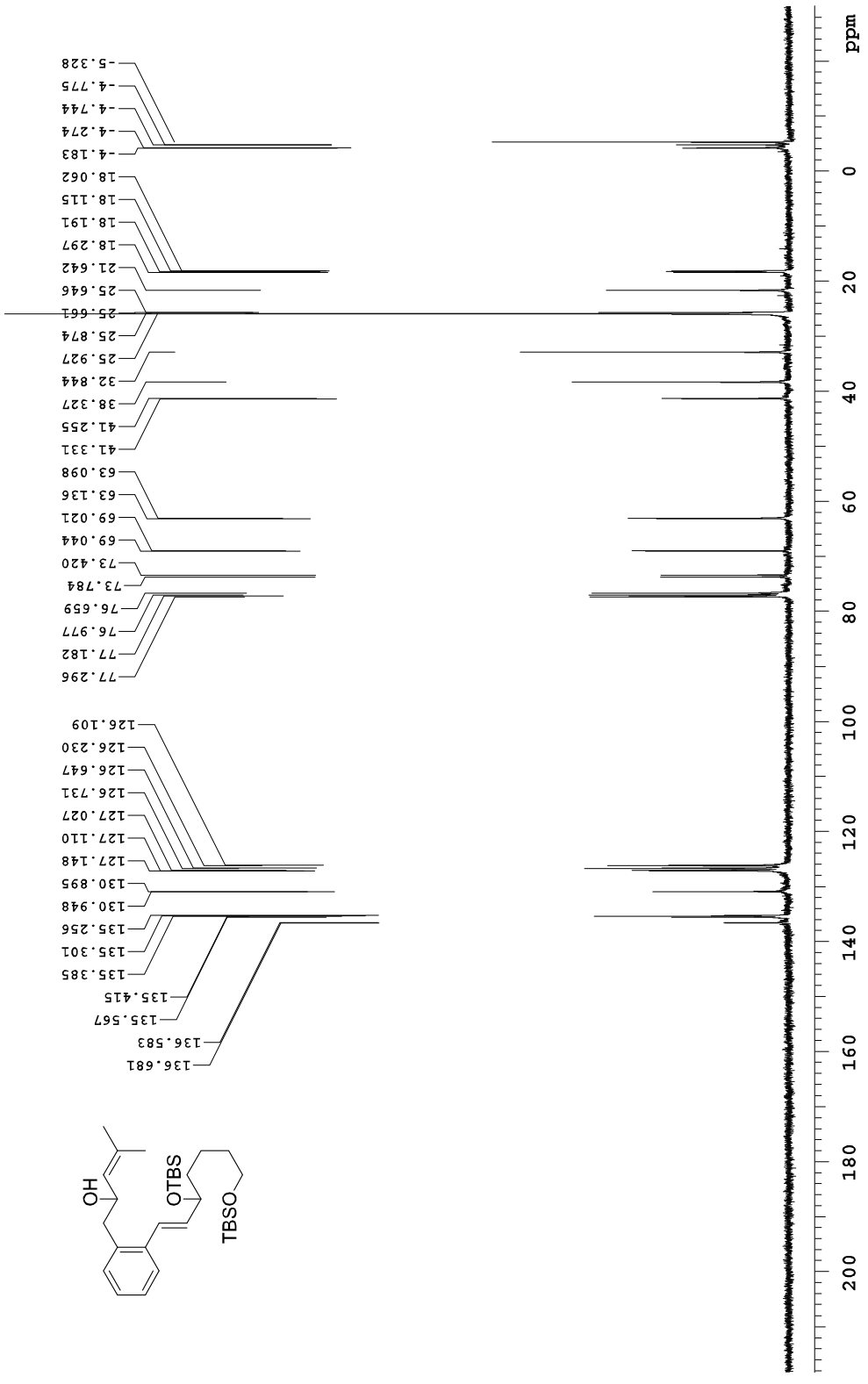
Spectrum 2.166 ^{13}C NMR ($CDCl_3$, 75 MHz) of compound **557**



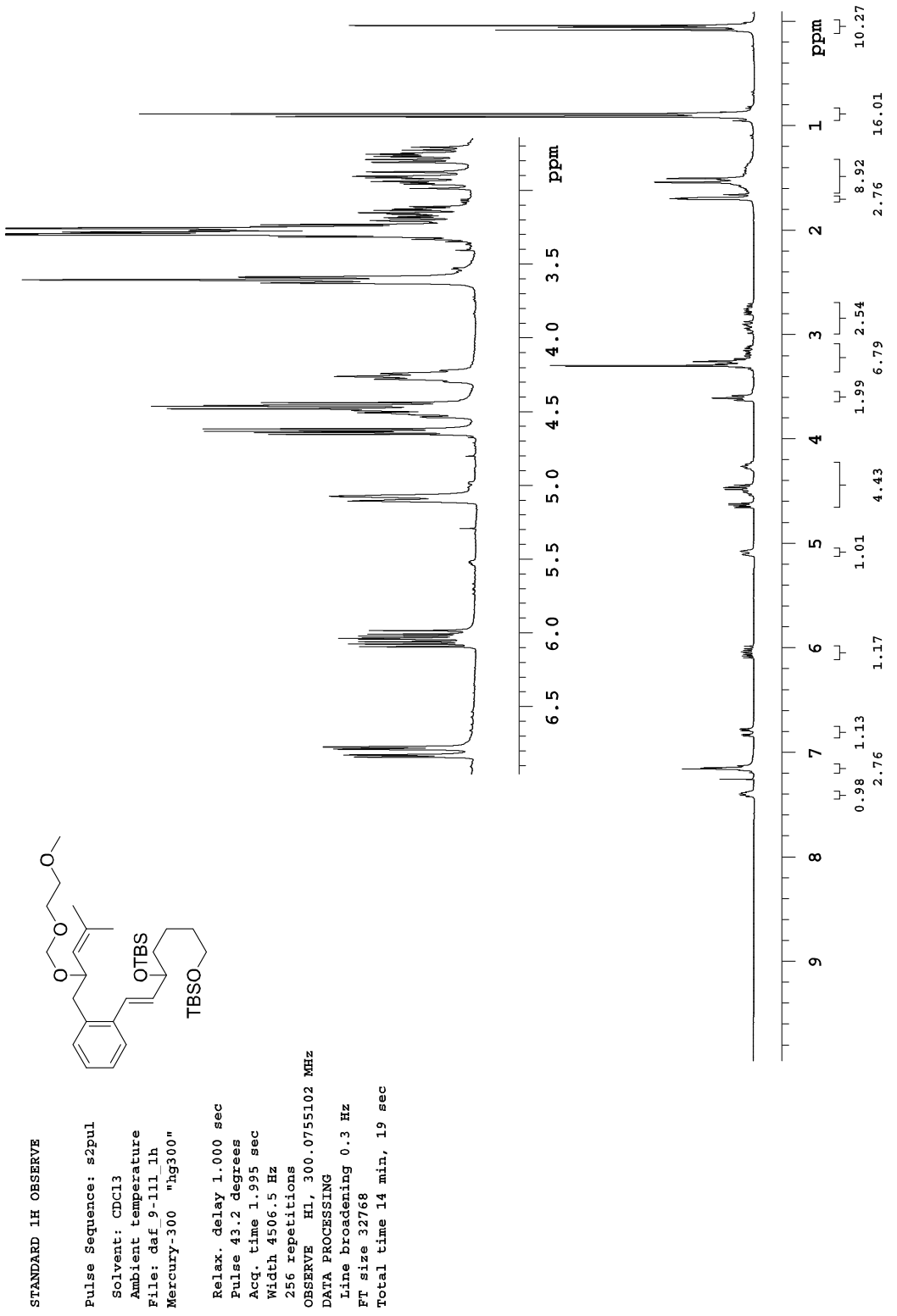
Spectrum 2.167 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **558**



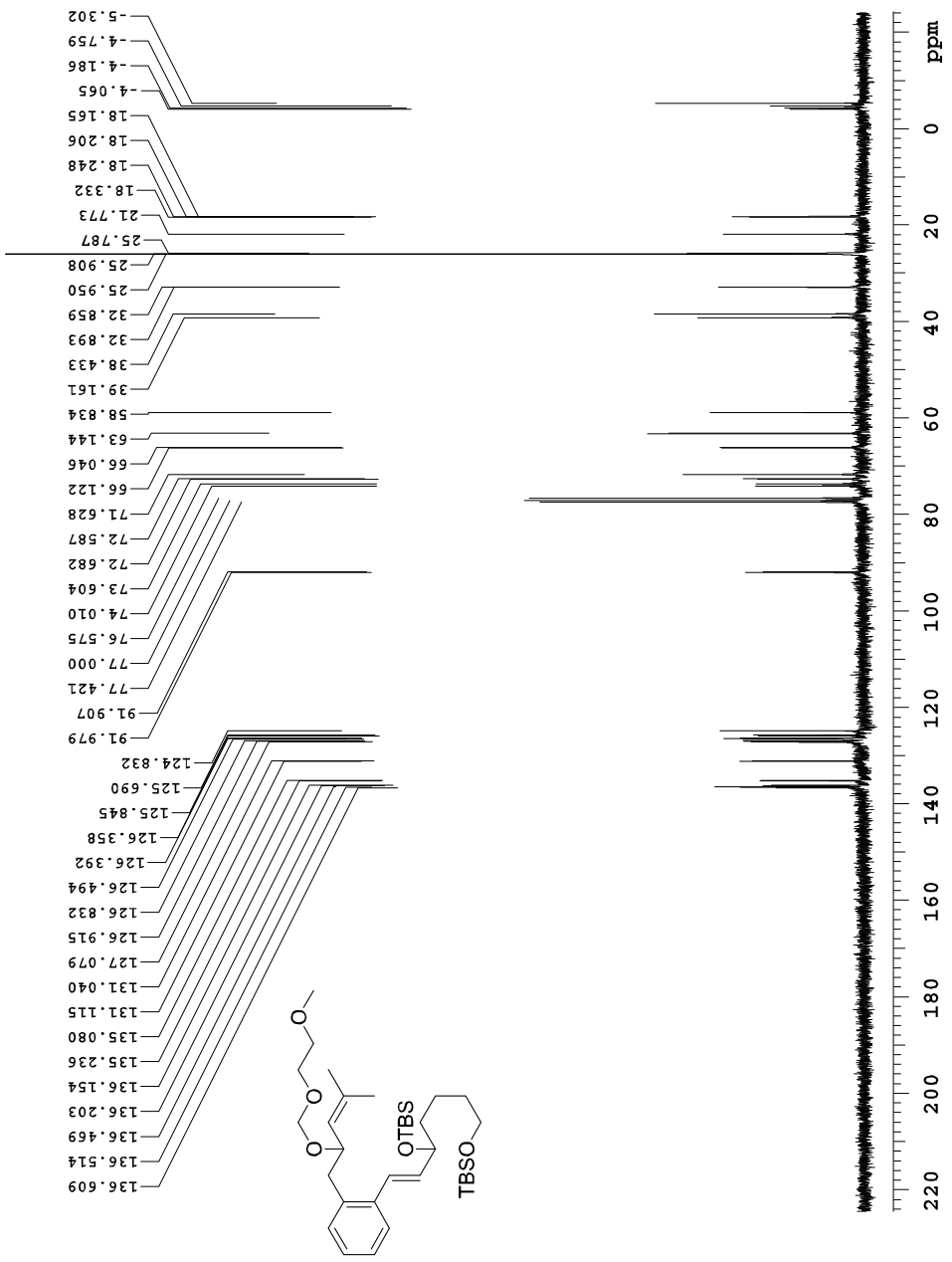
Spectrum 2.168 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **559**



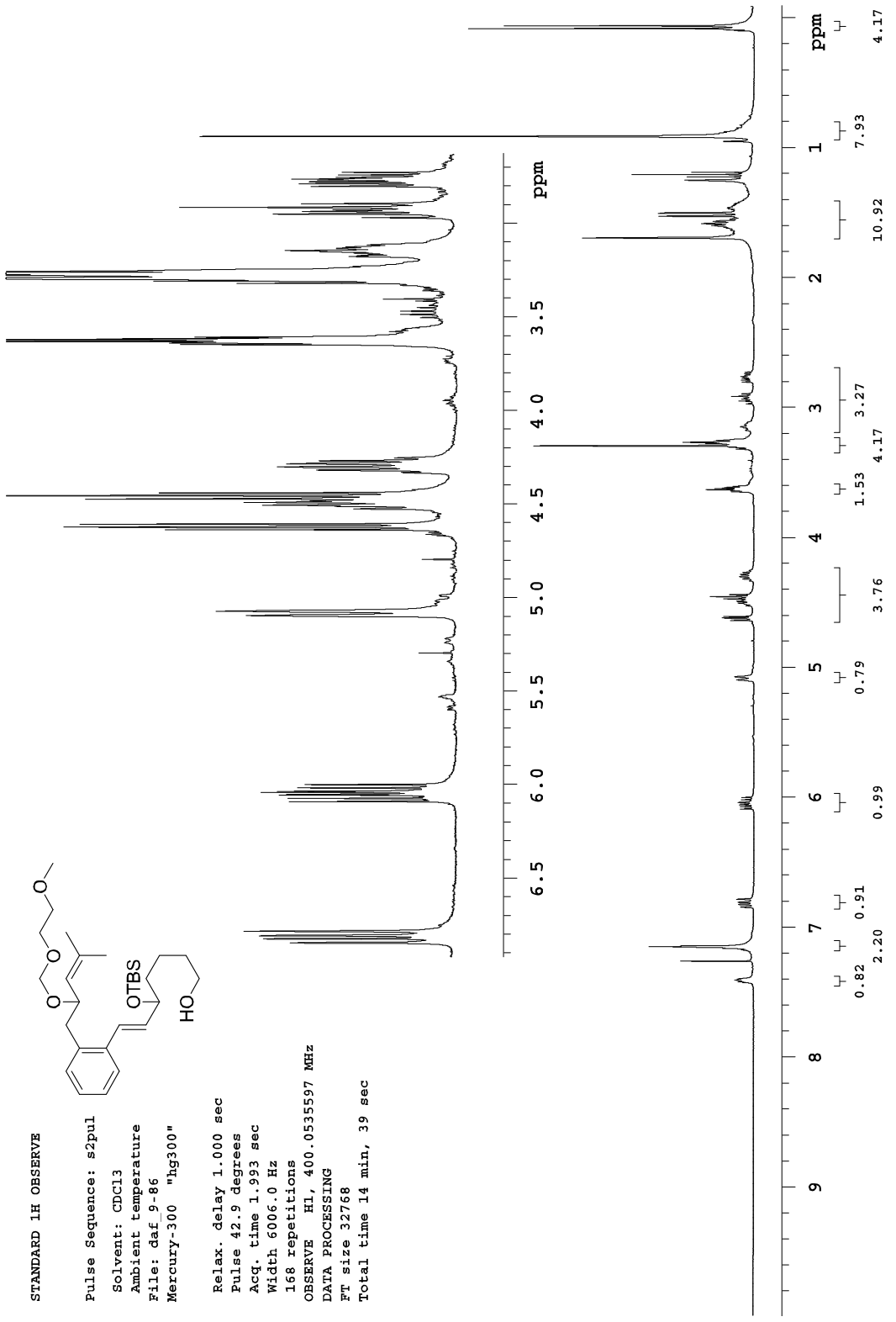
Spectrum 2.169 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **559**



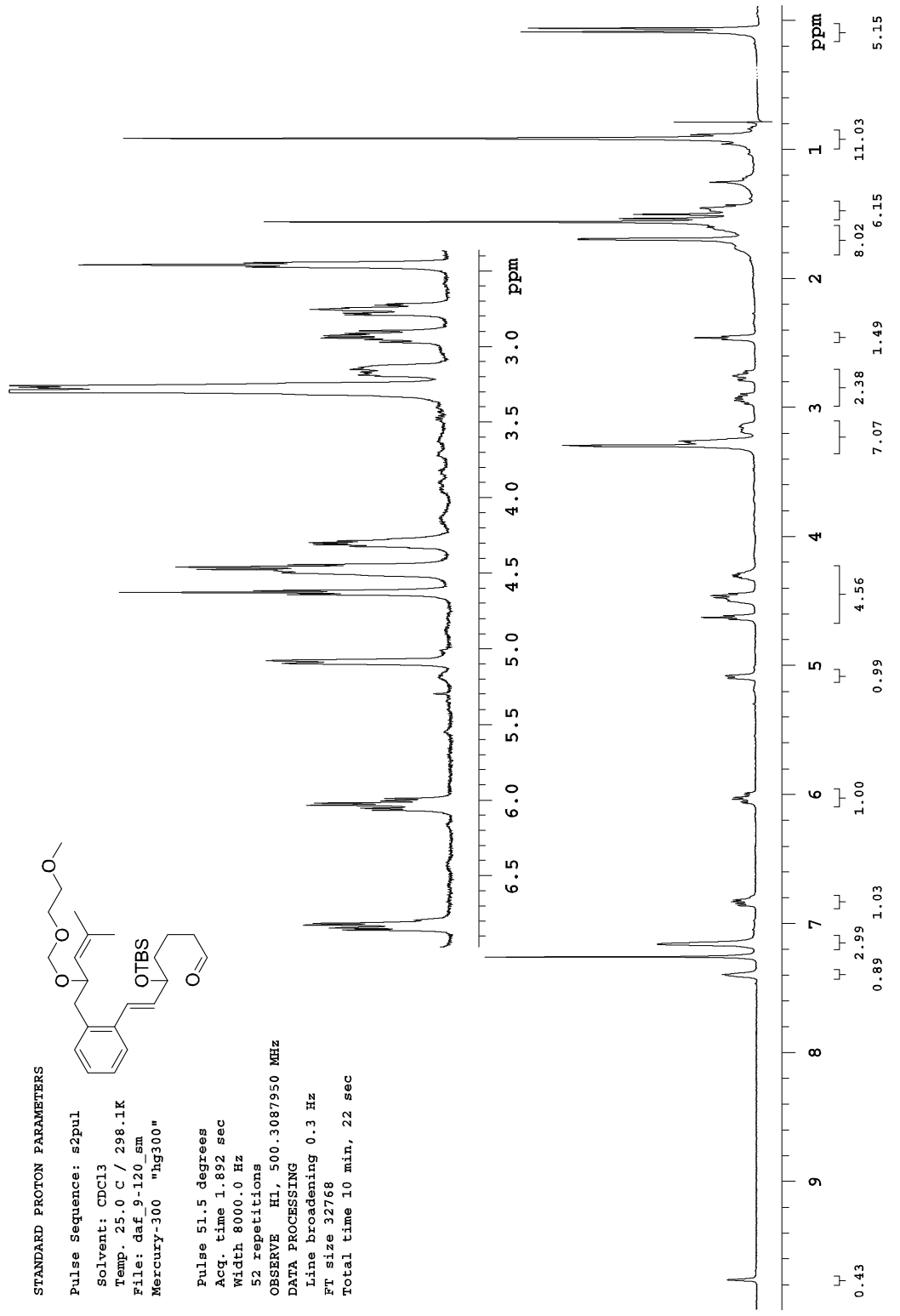
Spectrum 2.170 ^{1}H NMR ($CDCl_3$, 300 MHz) of compound **560**



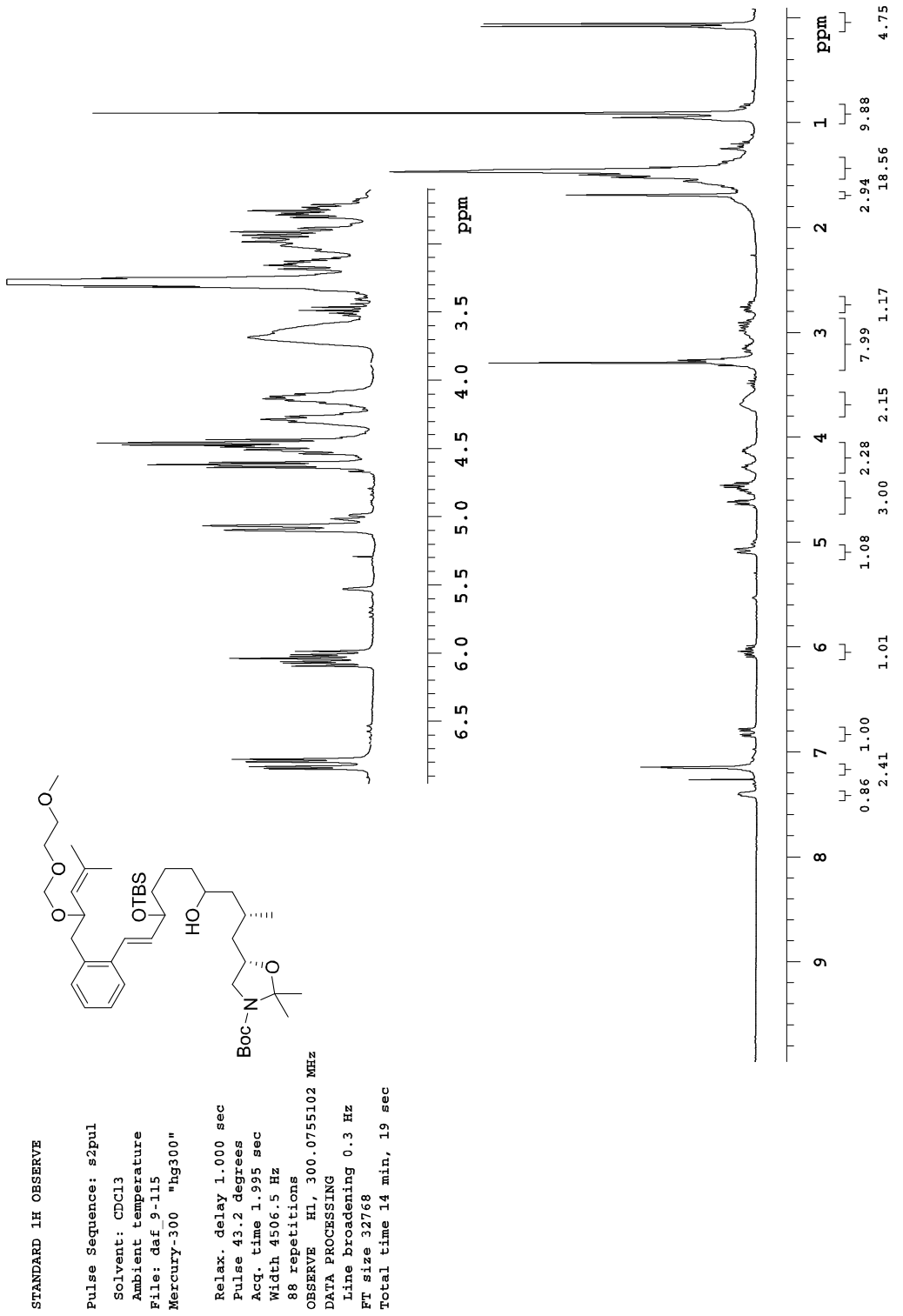
Spectrum 2.171 ^{13}C NMR ($CDCl_3$, 75 MHz) of compound **560**



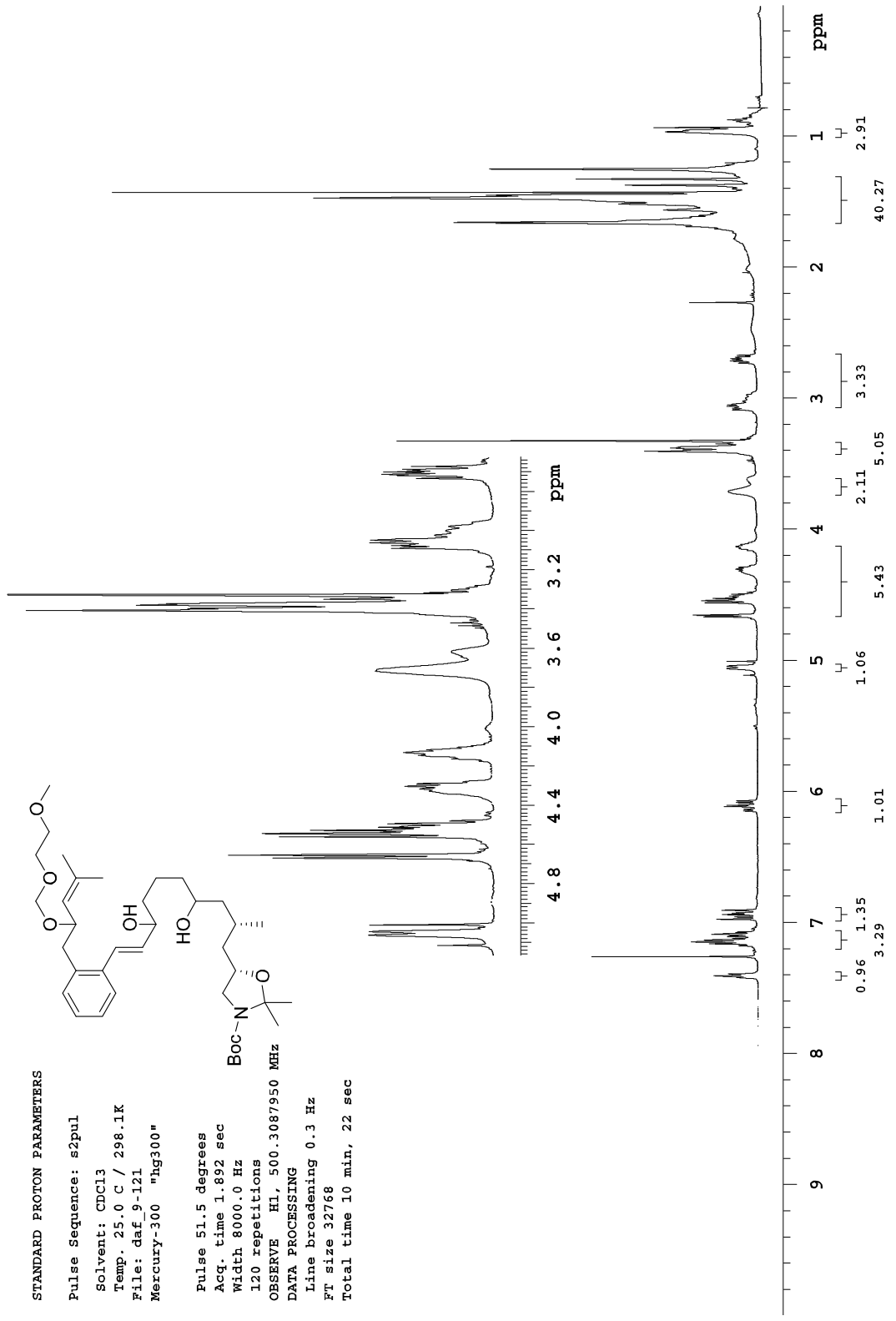
Spectrum 2.172 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **561**



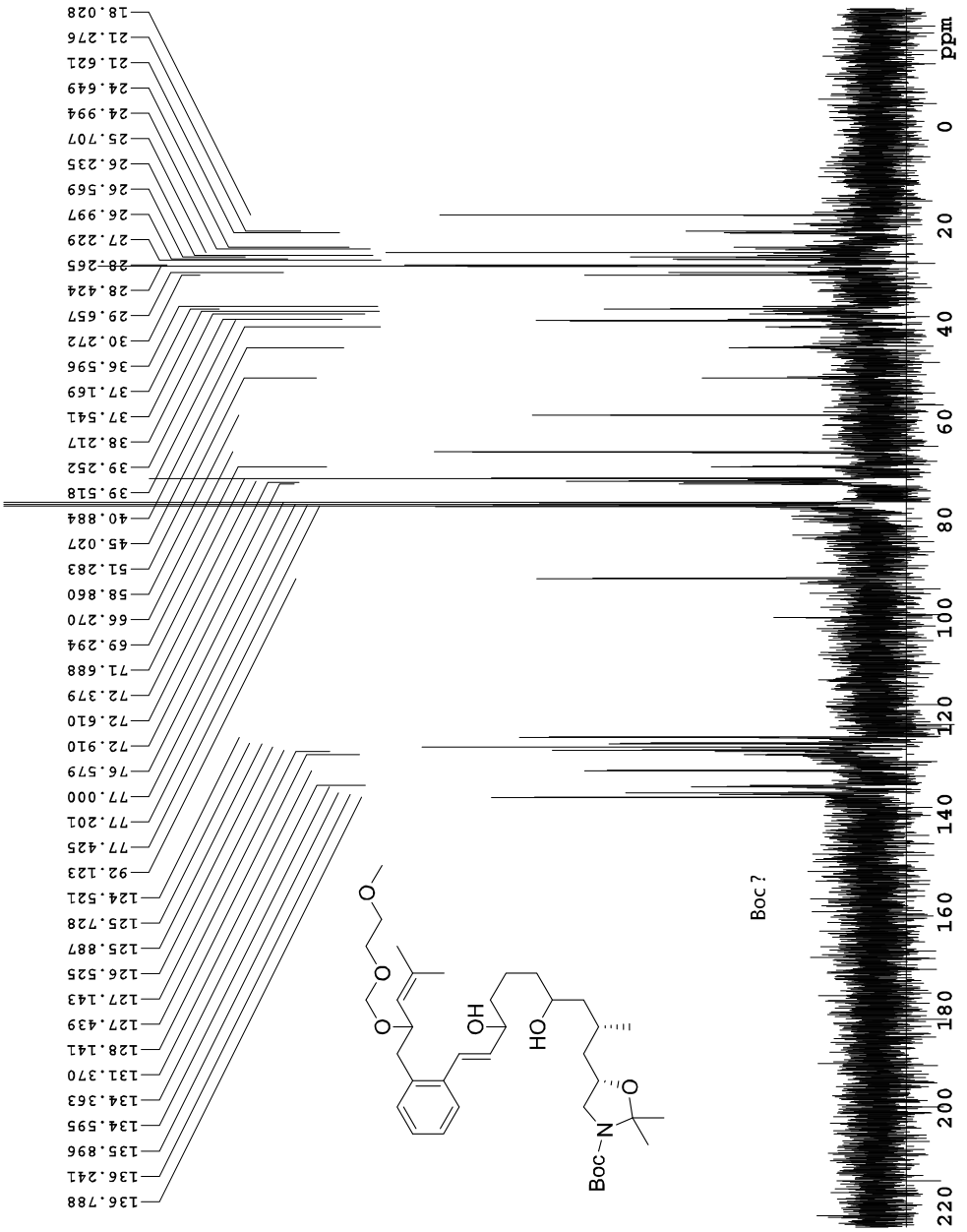
Spectrum 2.173 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **562**



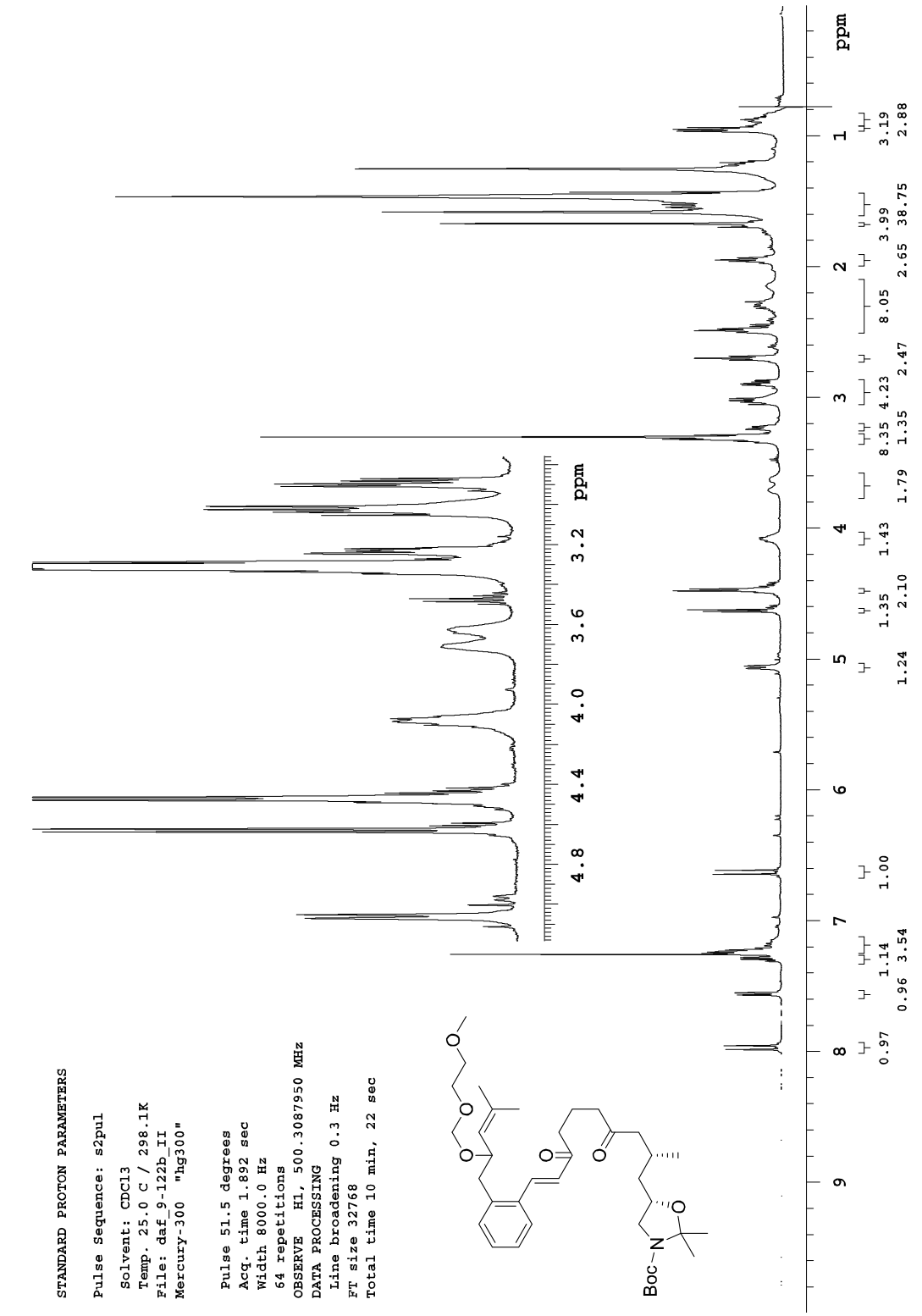
Spectrum 2.174 ^{1}H NMR ($CDCl_3$, 300 MHz) of compound **563**



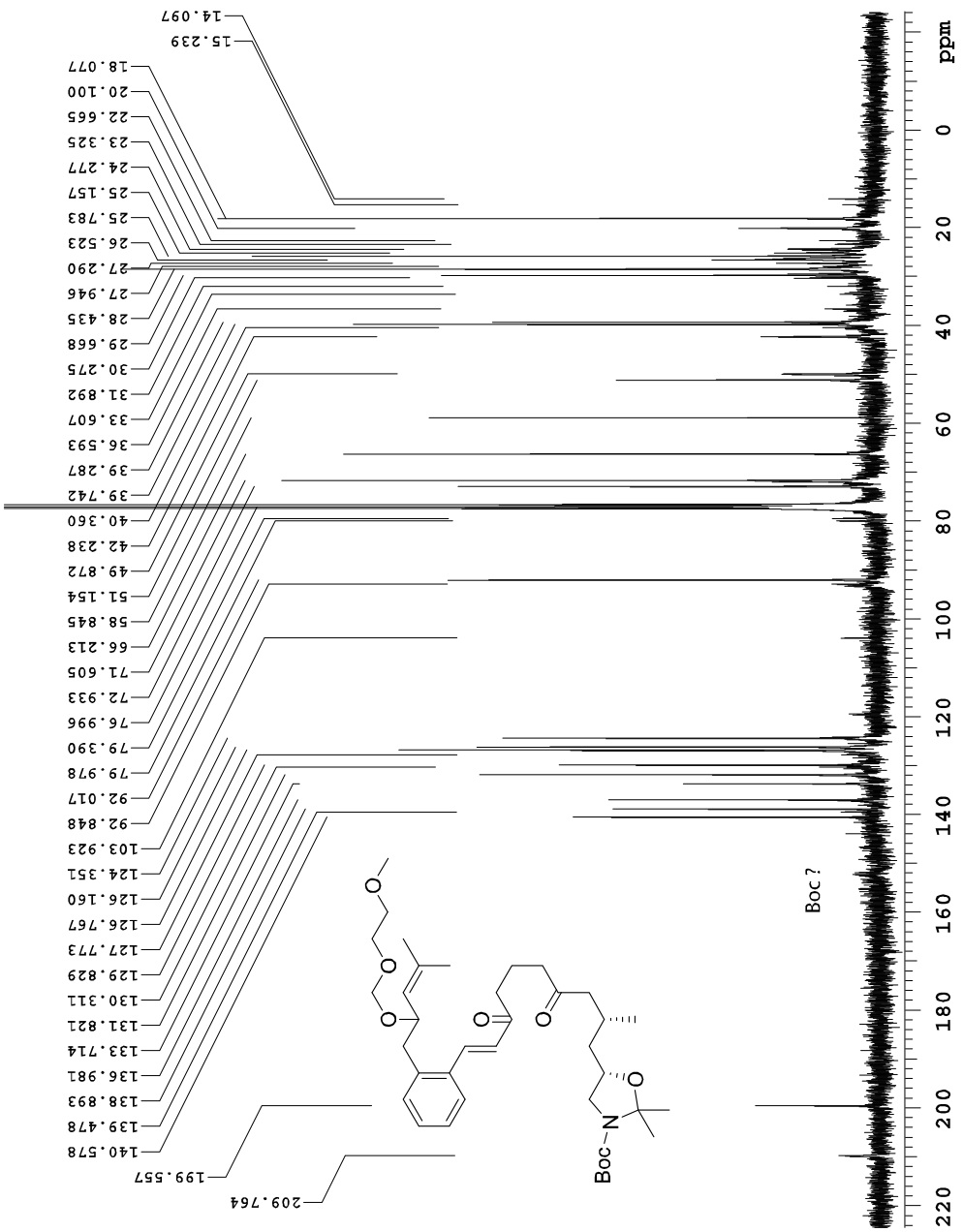
Spectrum 2.175 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **564**



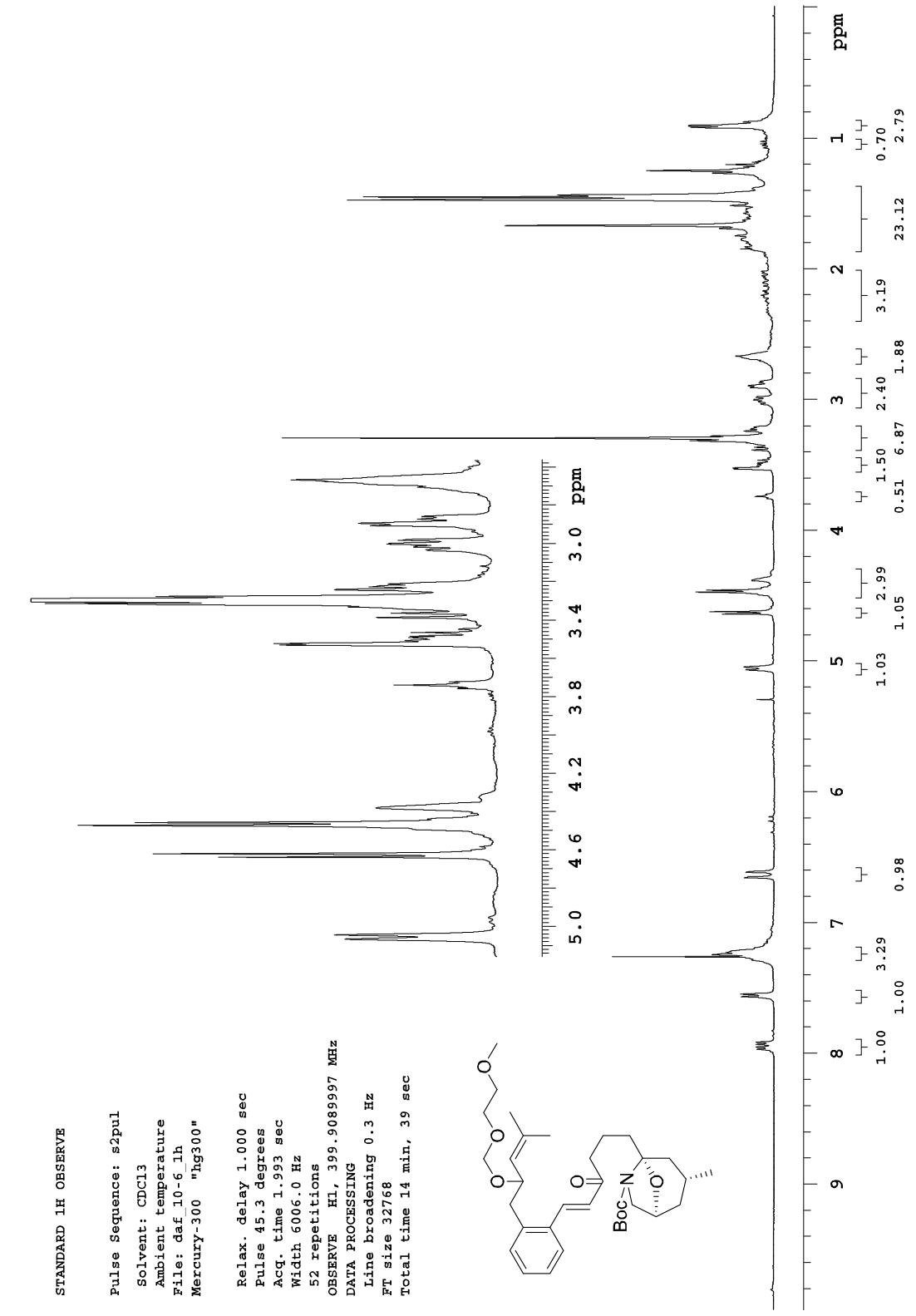
Spectrum 2.176 ^{13}C NMR ($CDCl_3$, 75 MHz) of compound **564**



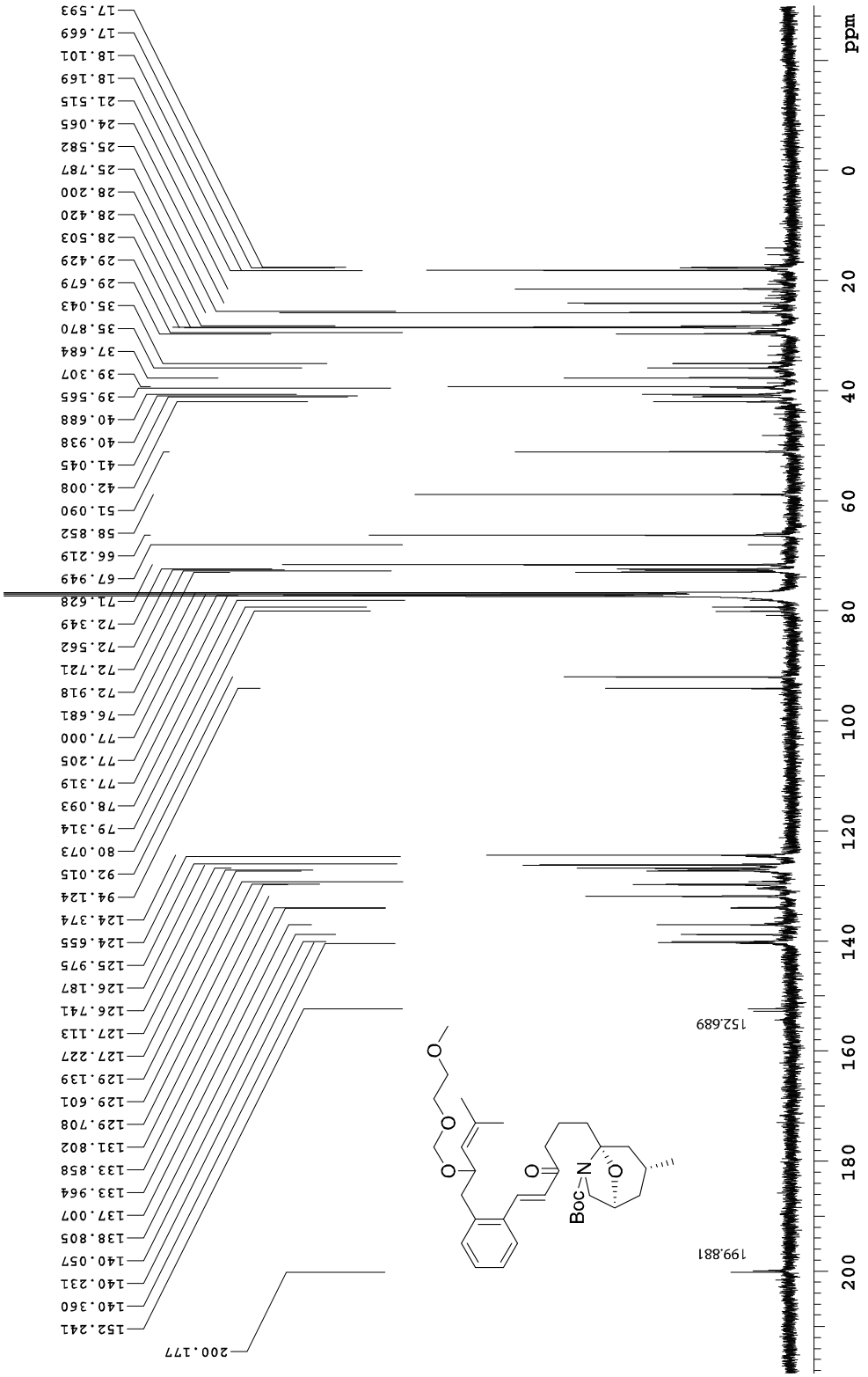
Spectrum 2.177 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **565**



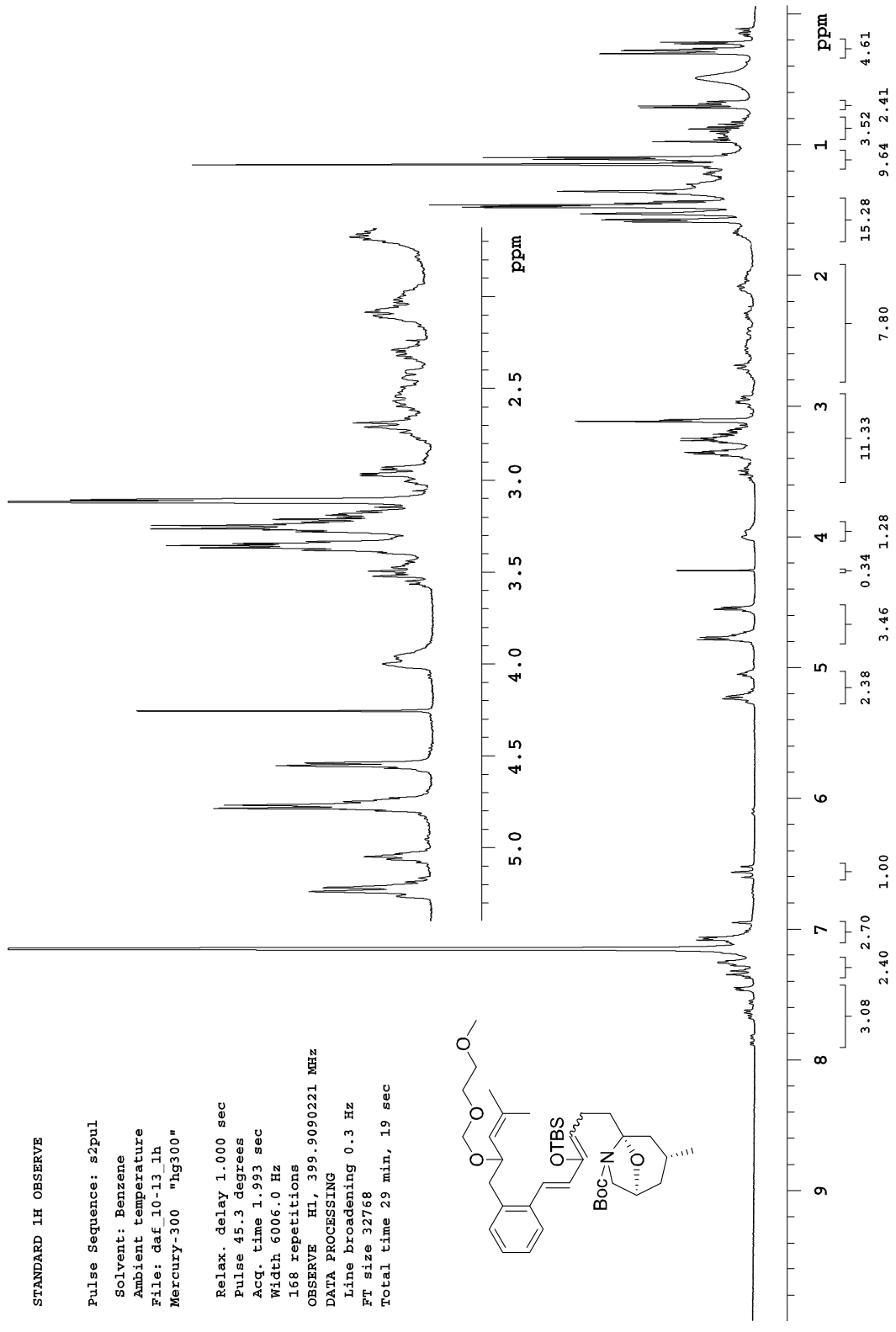
Spectrum 2.178 ^{13}C NMR ($CDCl_3$, 75 MHz) of compound **565**



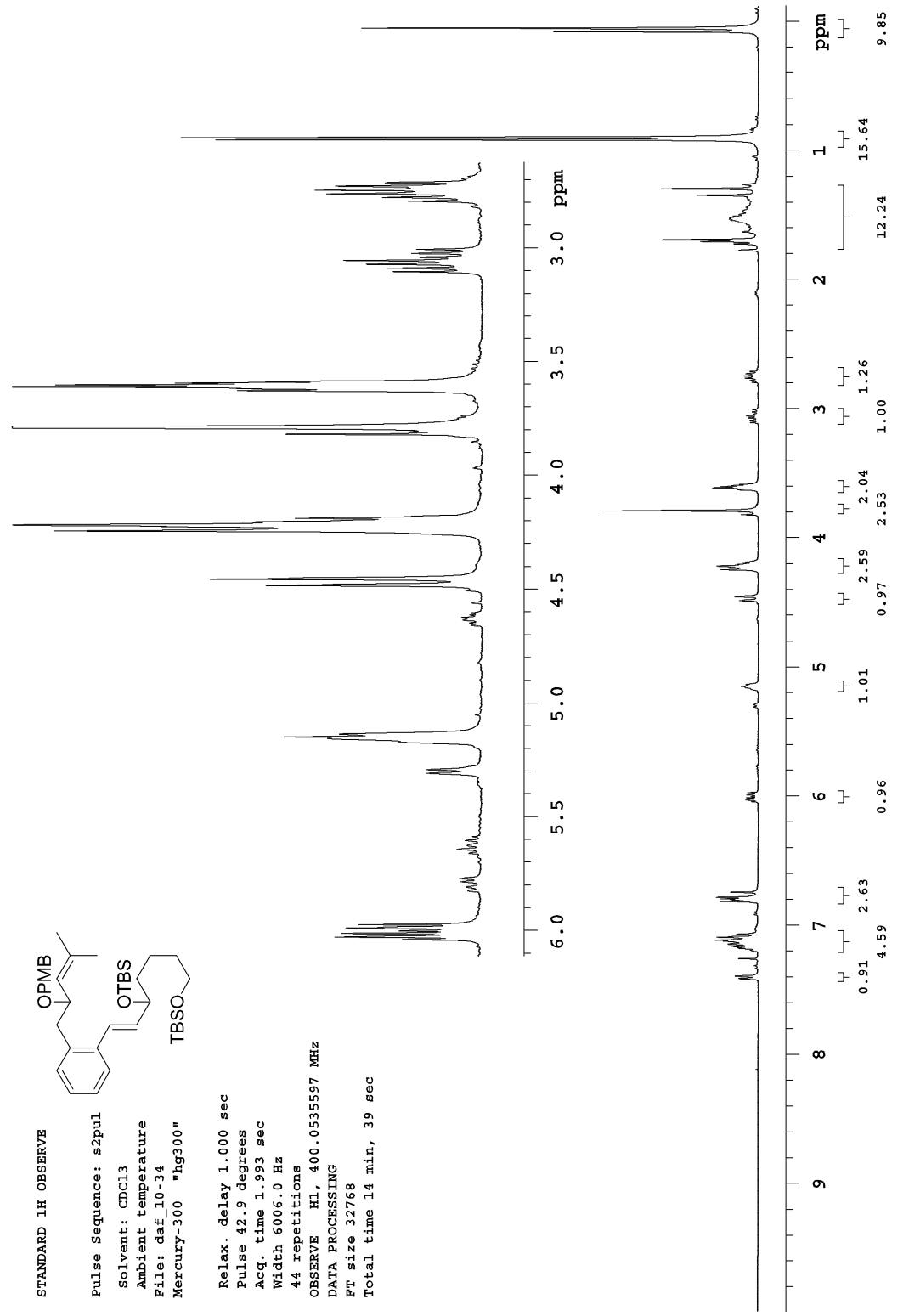
Spectrum 2.179 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **566**



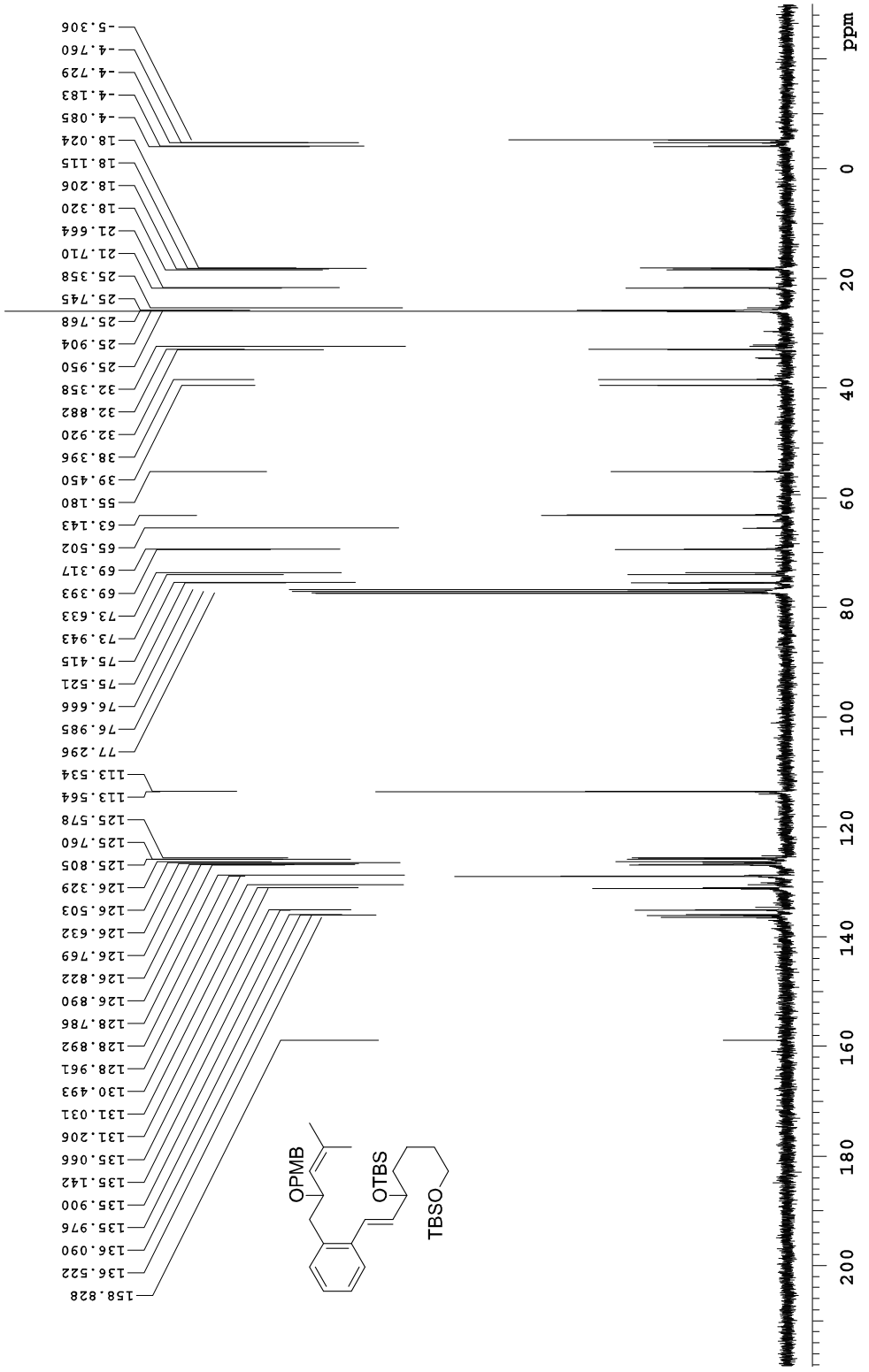
Spectrum 2.180 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **566**



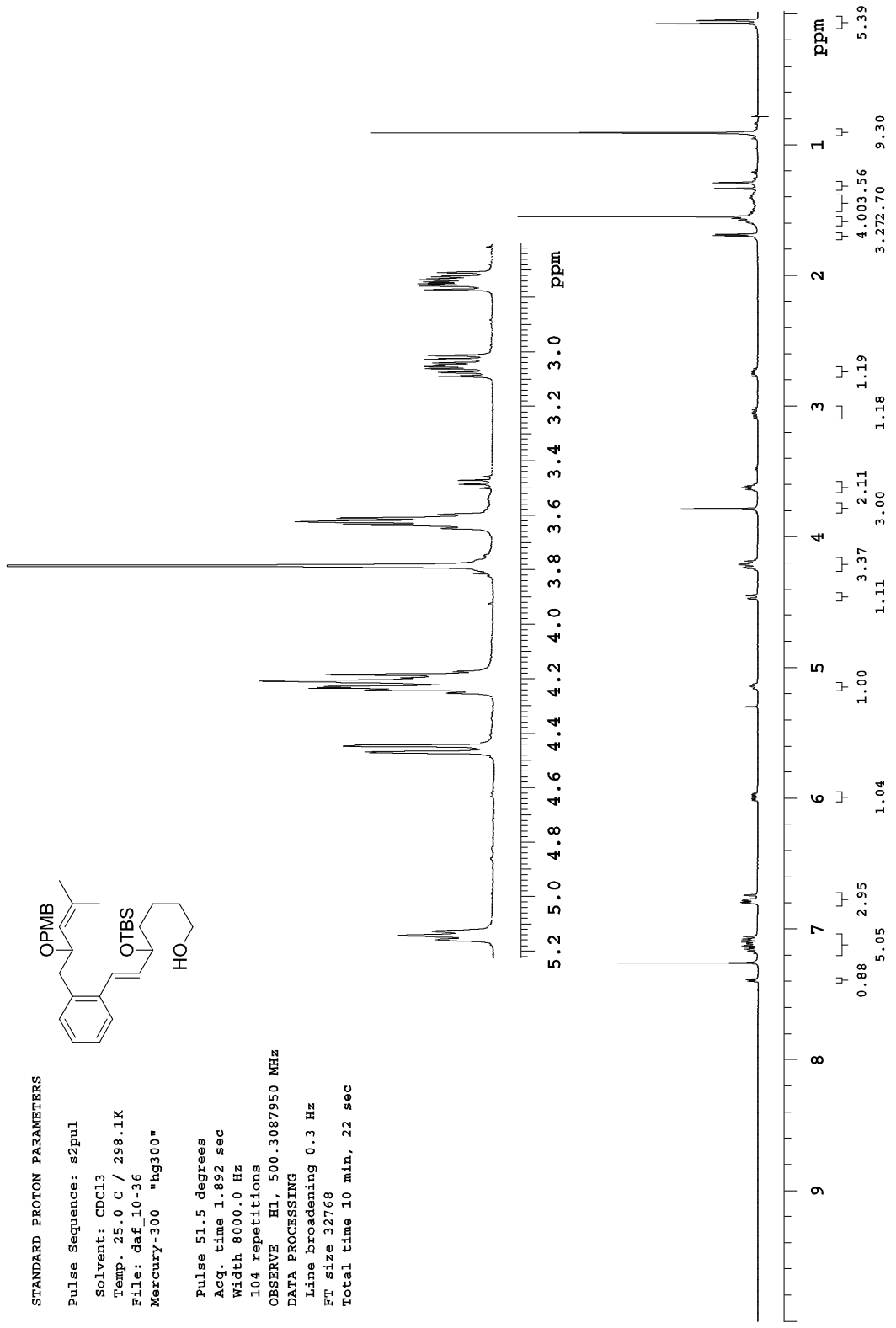
Spectrum 2.181 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **567**



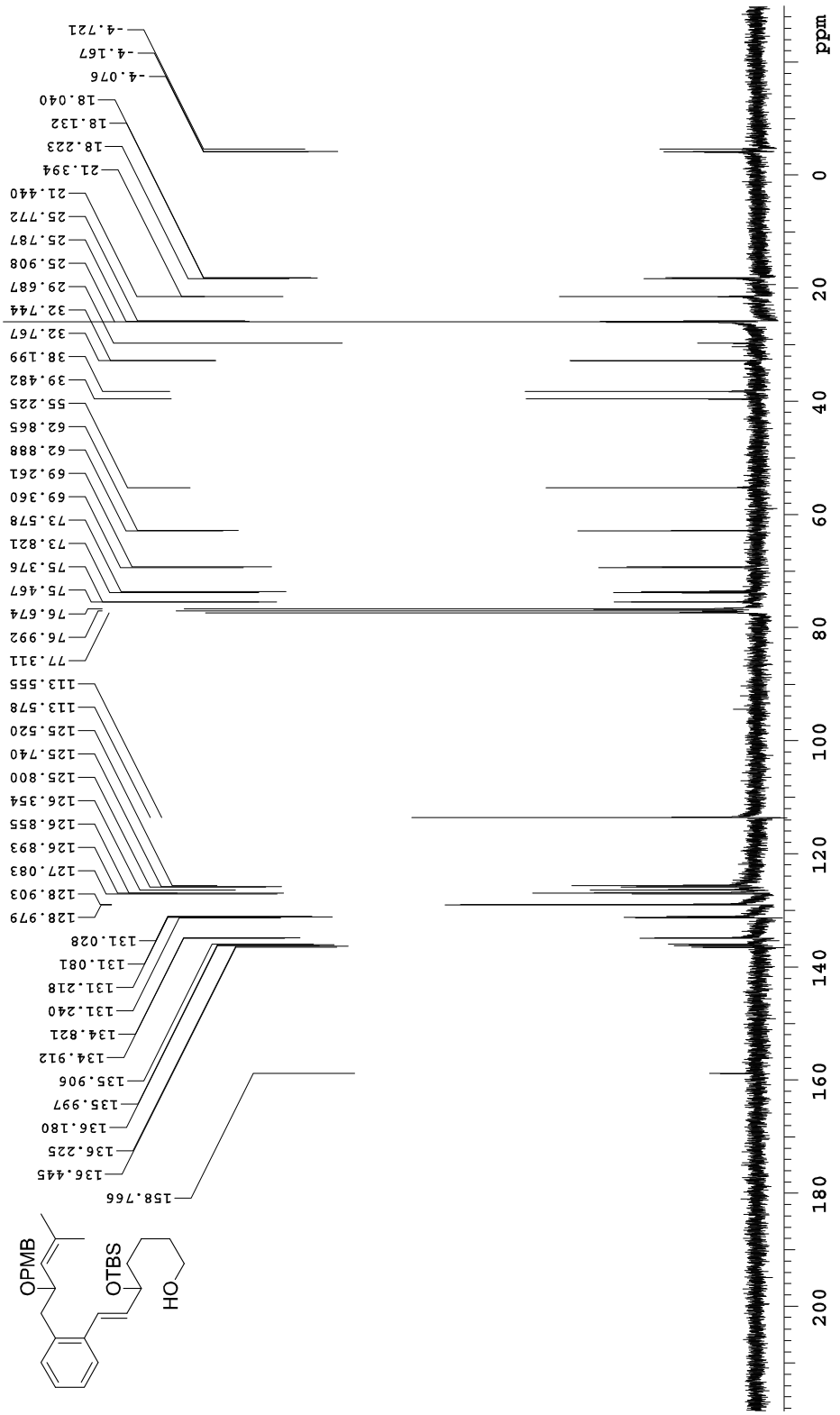
Spectrum 2.182 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **569**



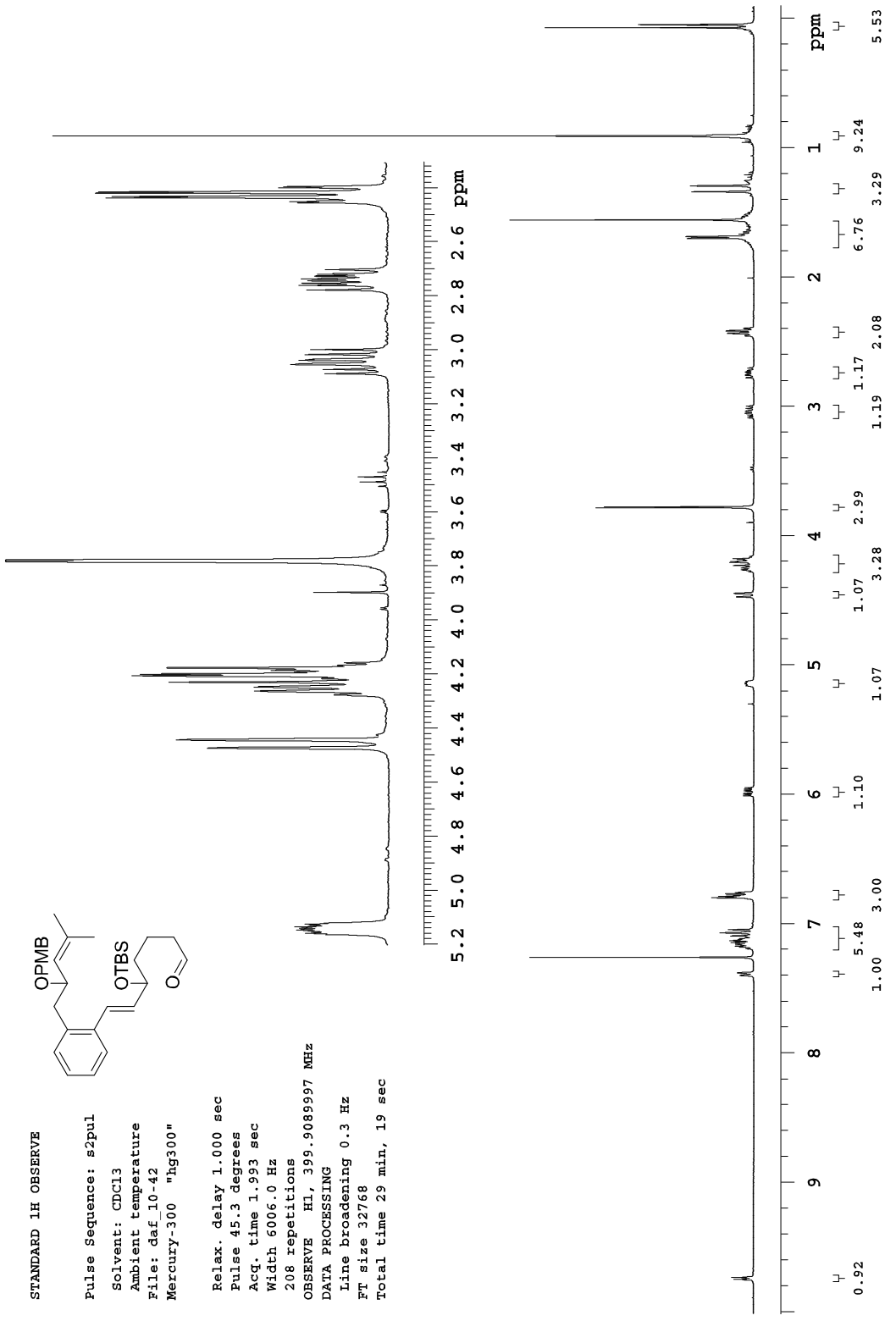
Spectrum 2.183 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **569**



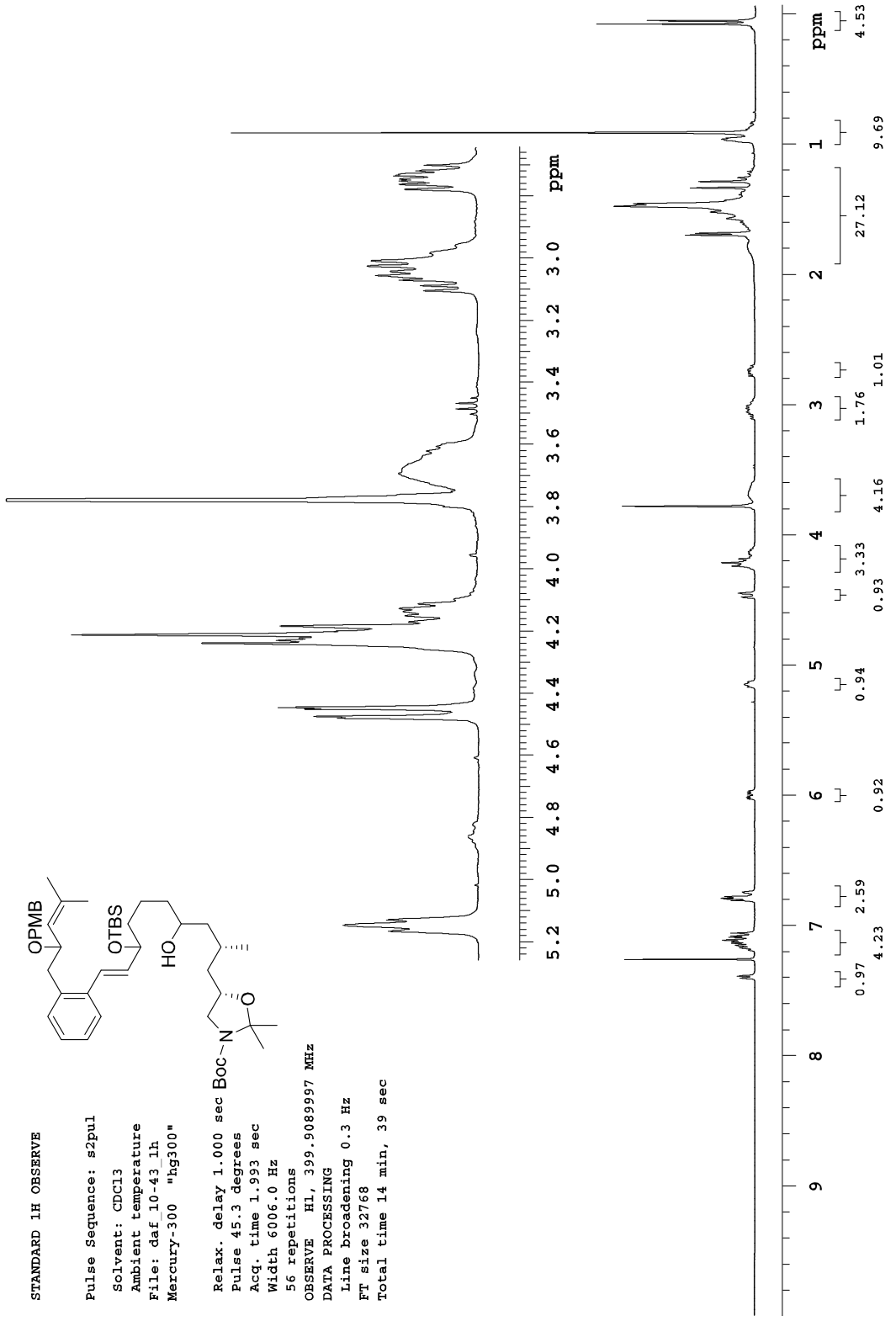
Spectrum 2.184 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **570**



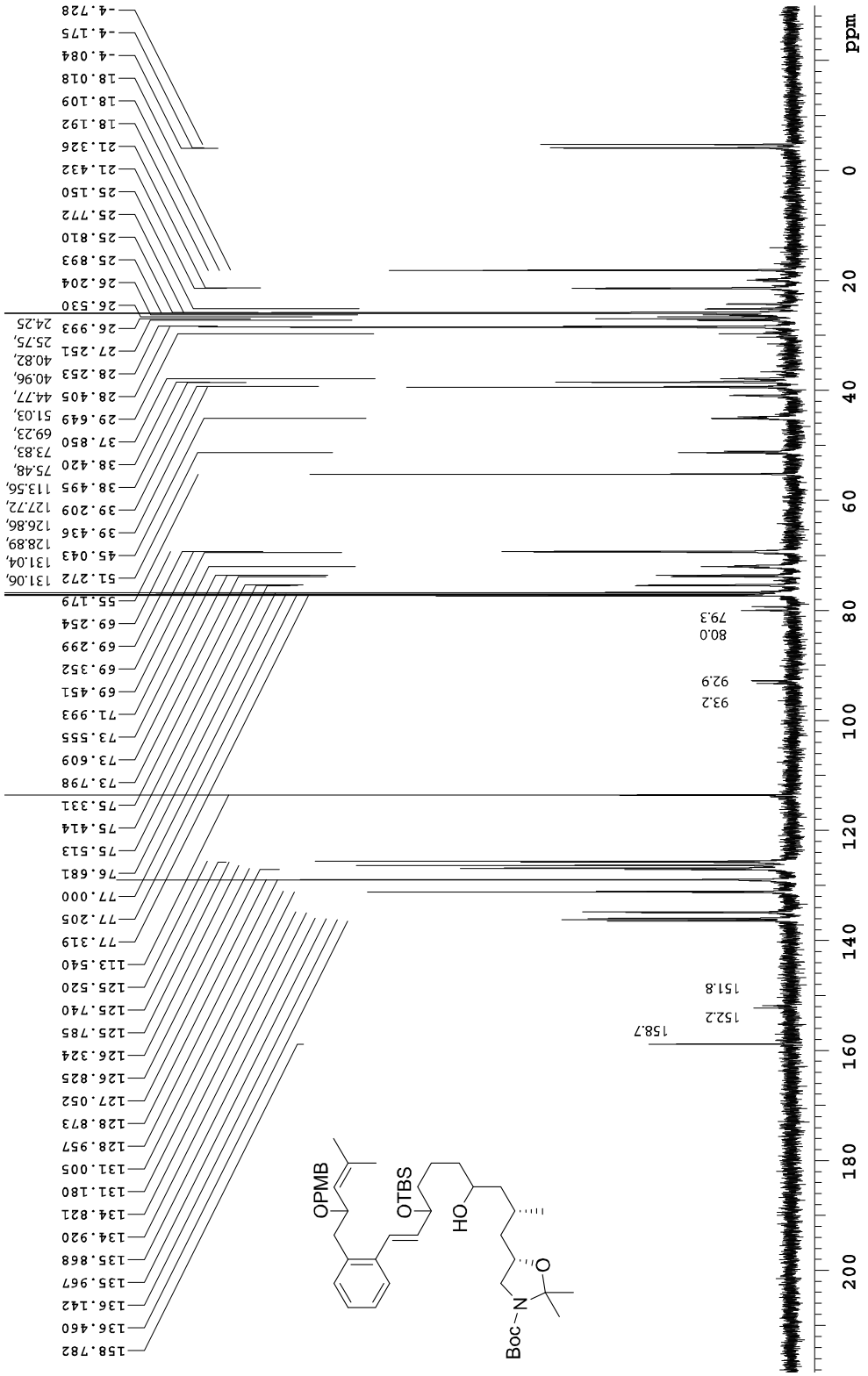
Spectrum 2.185 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **570**



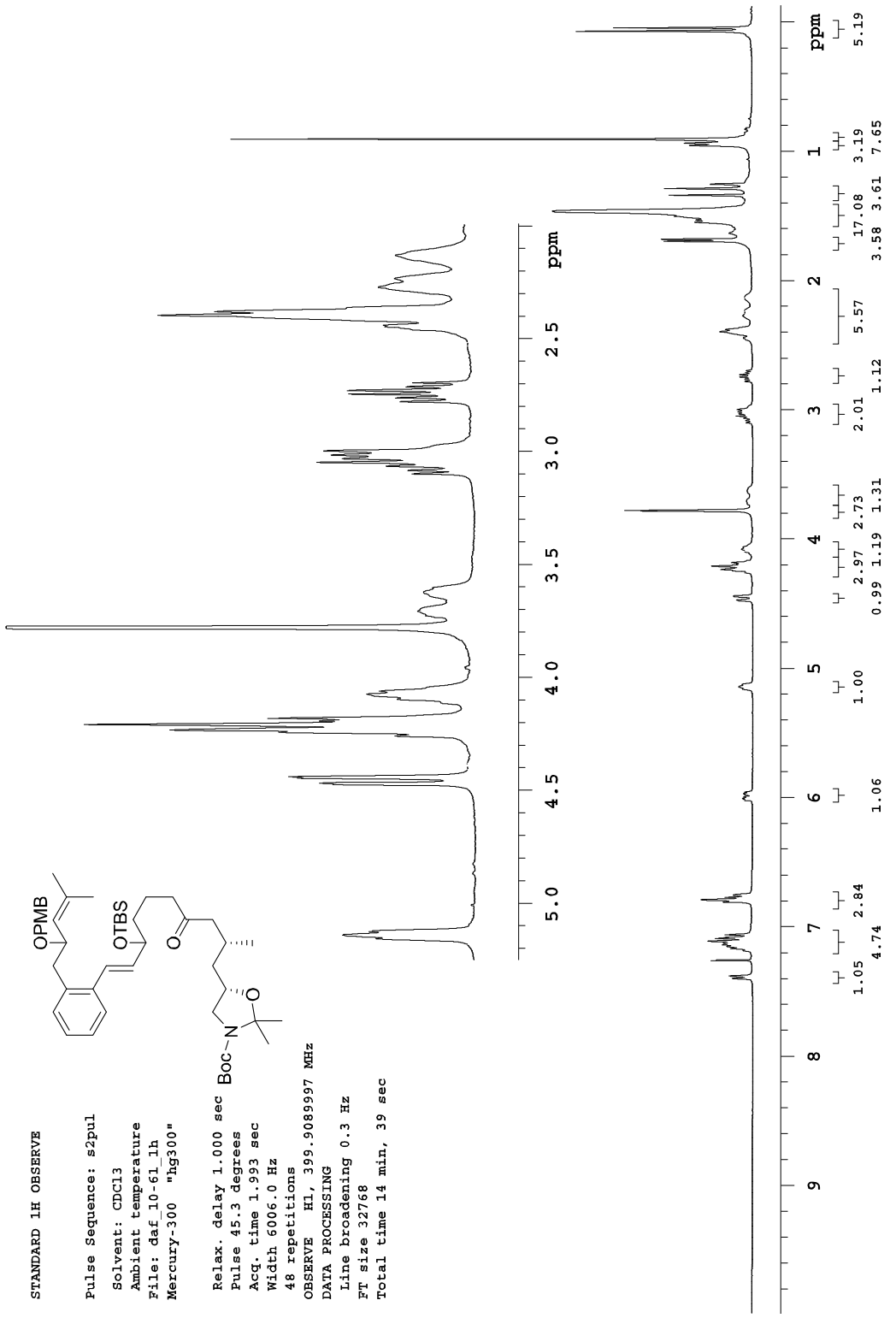
Spectrum 2.186 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **571**



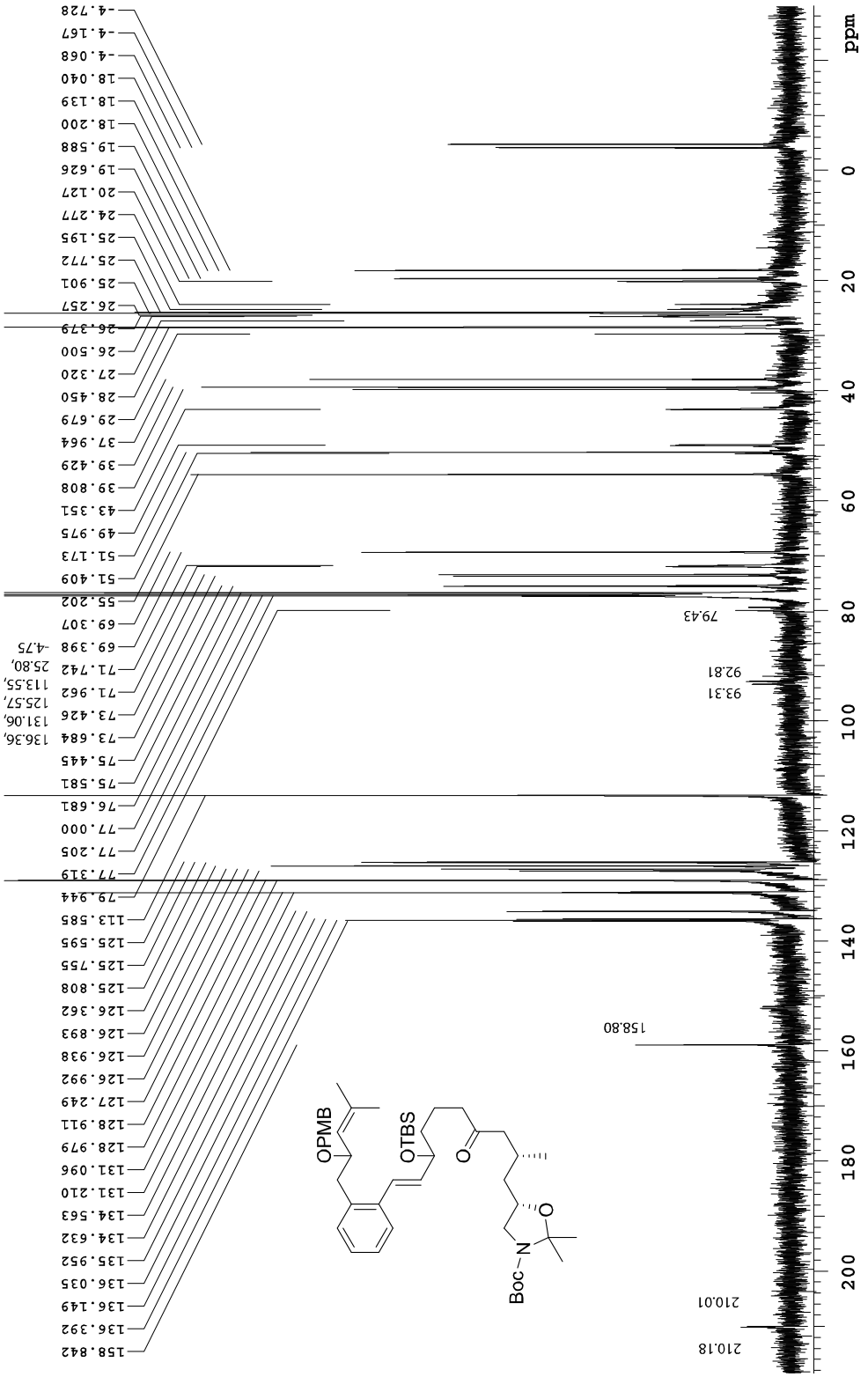
Spectrum 2.187 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **572**



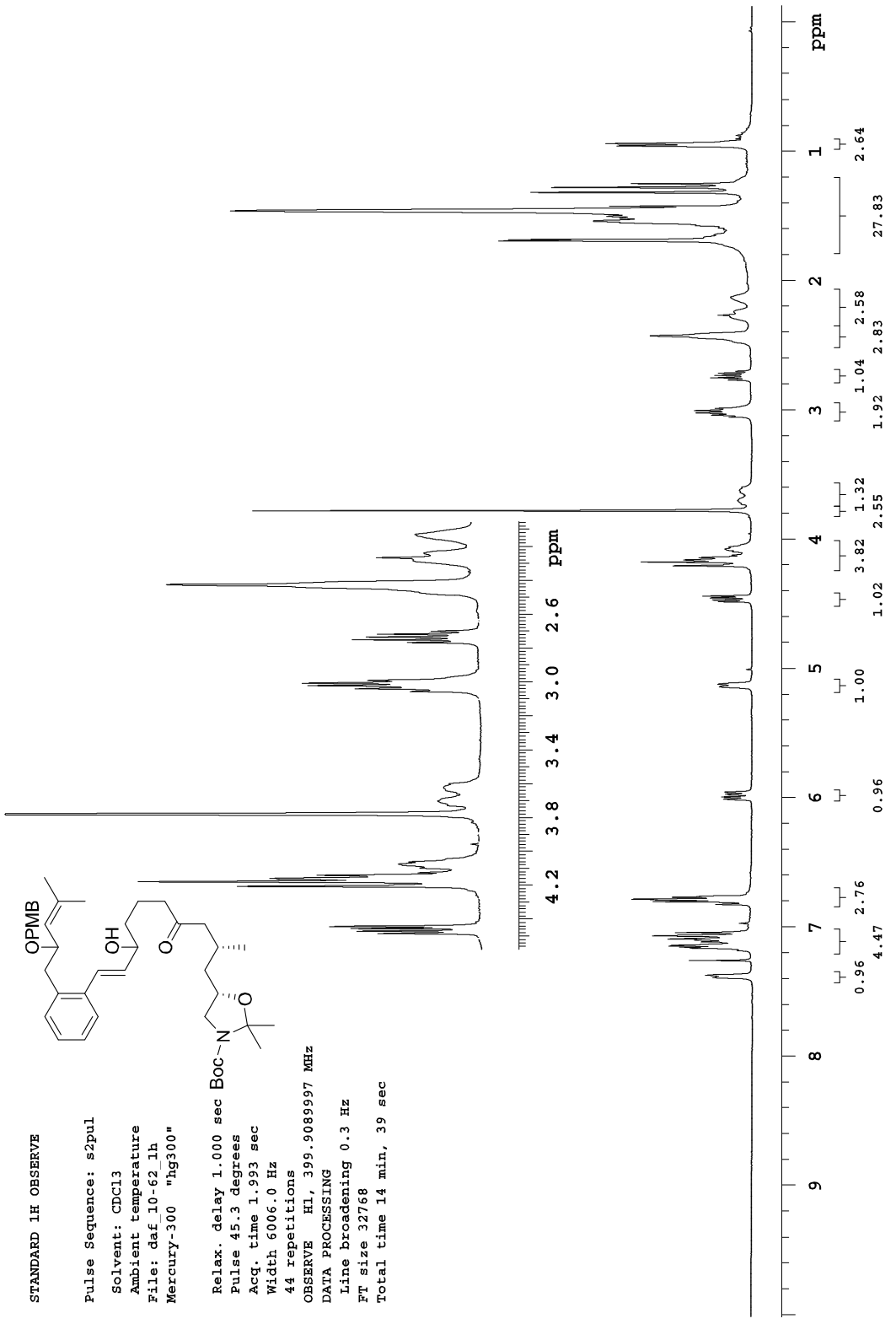
Spectrum 2.188 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **572**



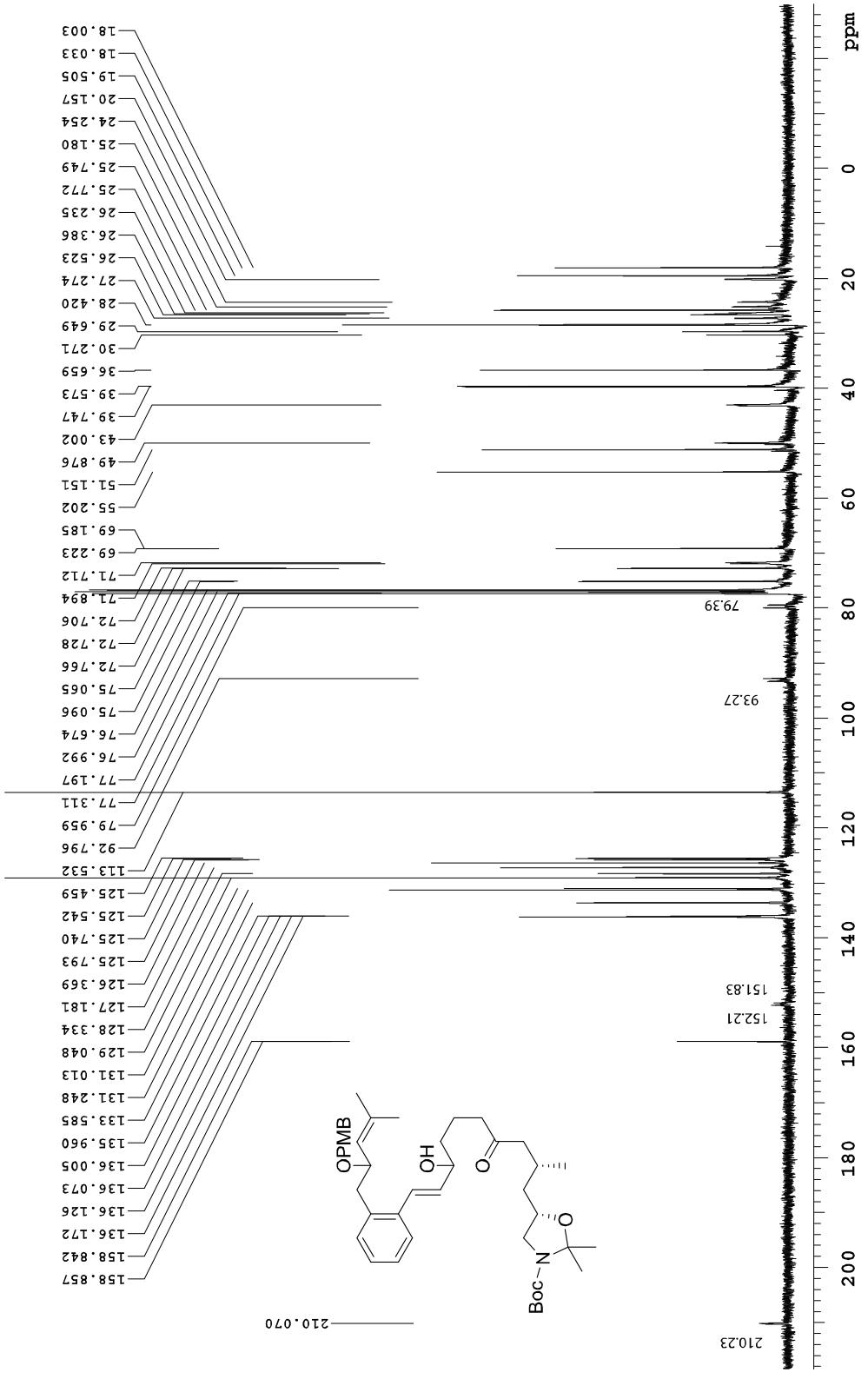
Spectrum 2.189 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **573**



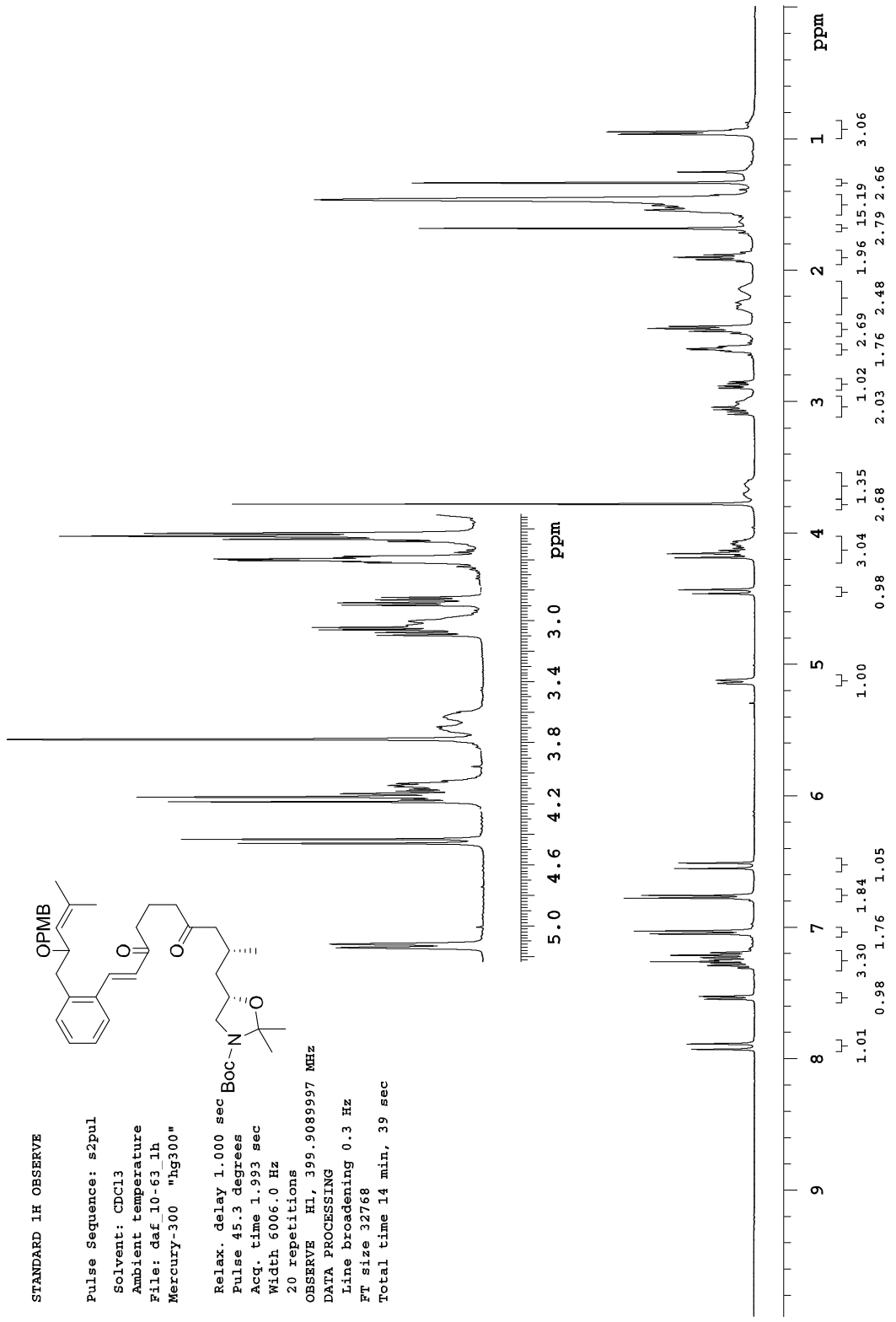
Spectrum 2.190 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **573**



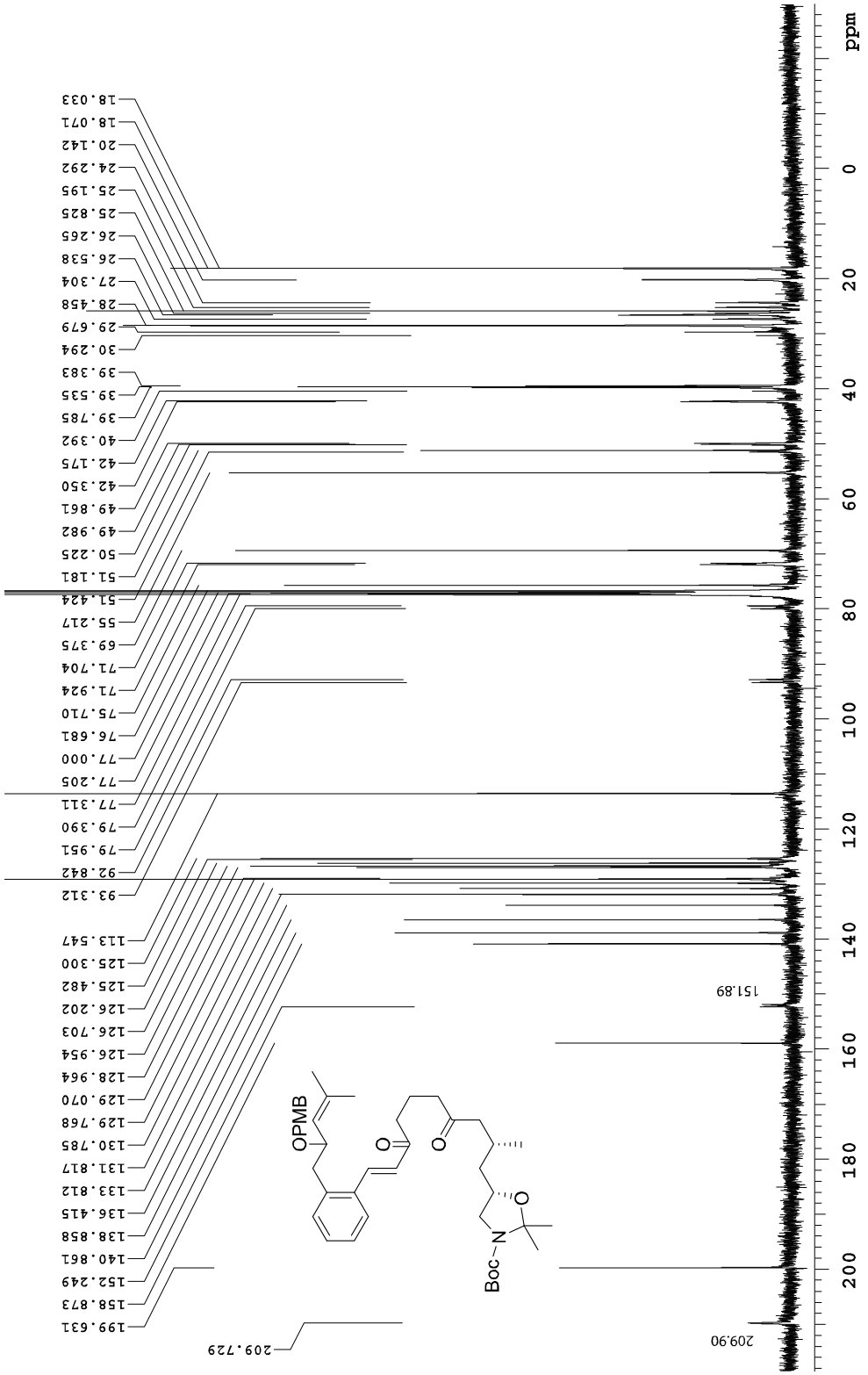
Spectrum 2.191 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **574**



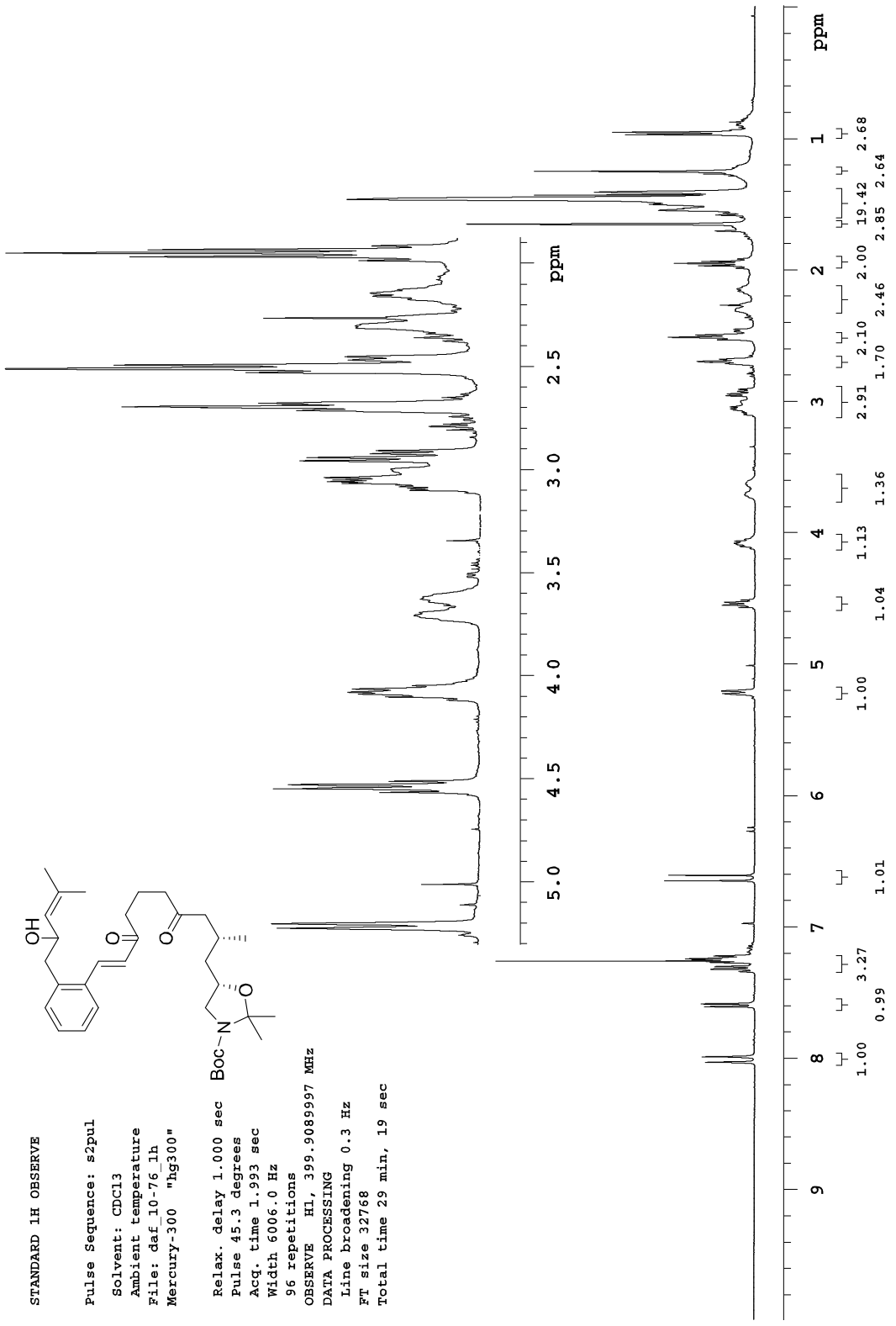
Spectrum 2.192 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **574**



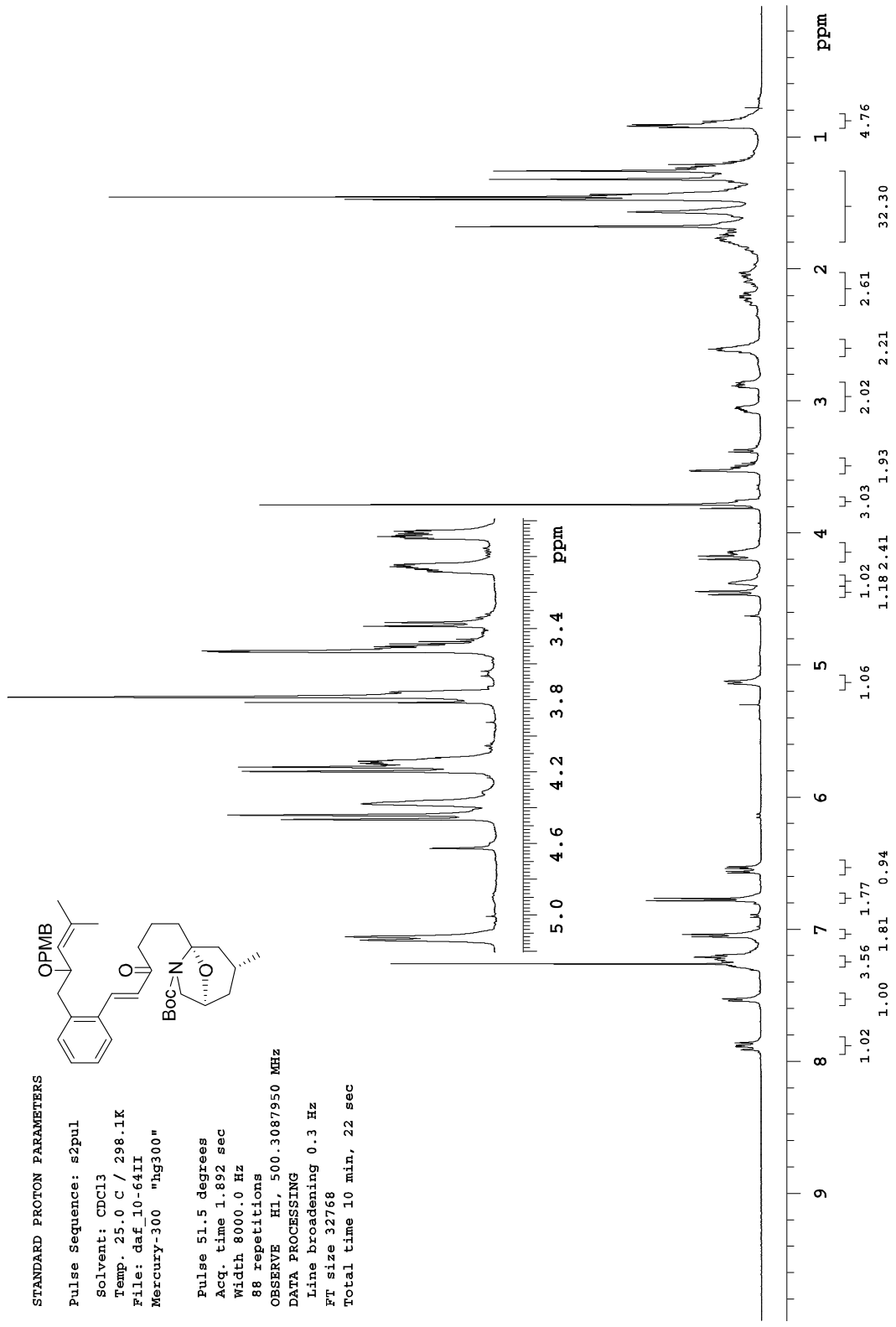
Spectrum 2.193 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **575**



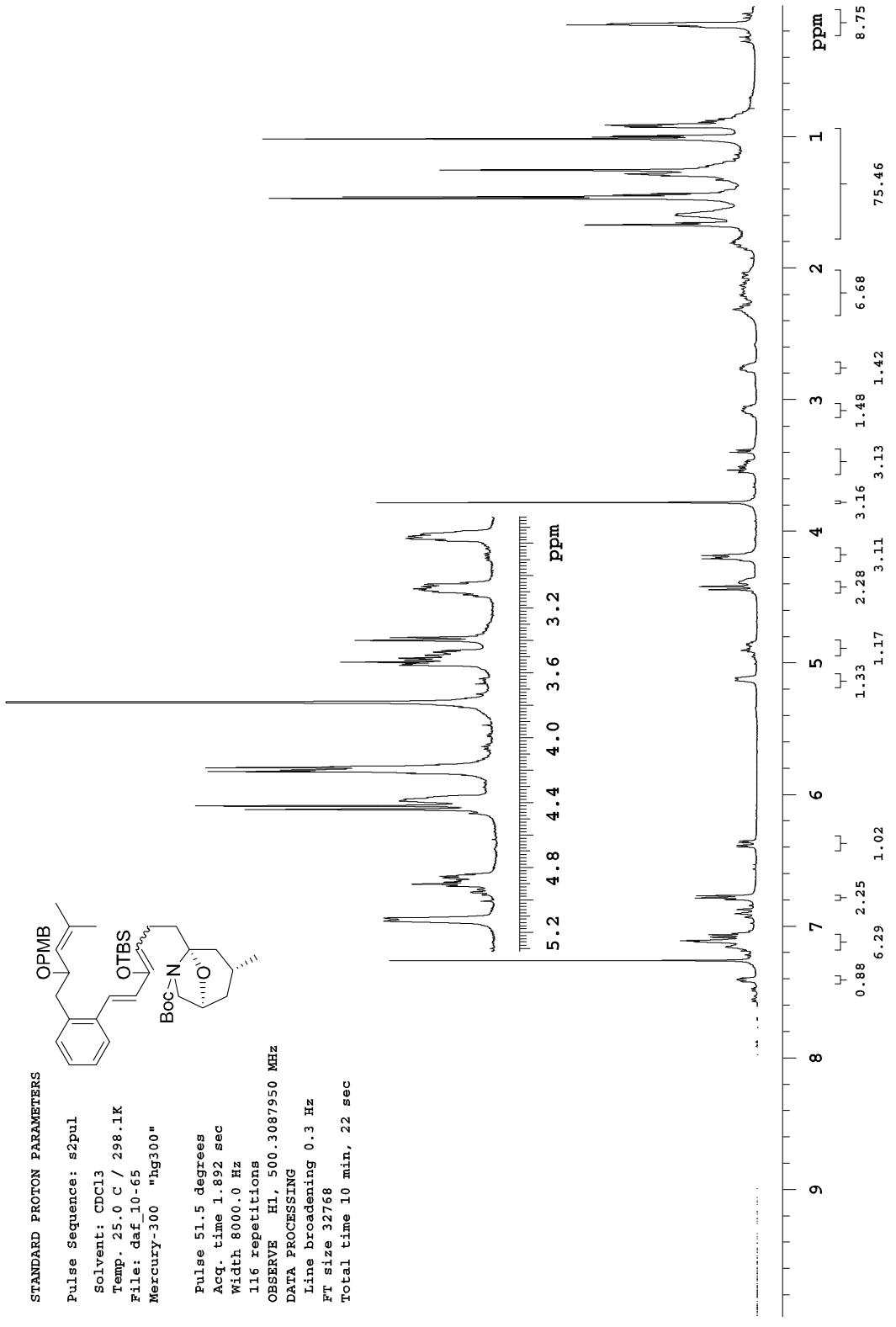
Spectrum 2.194 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **575**



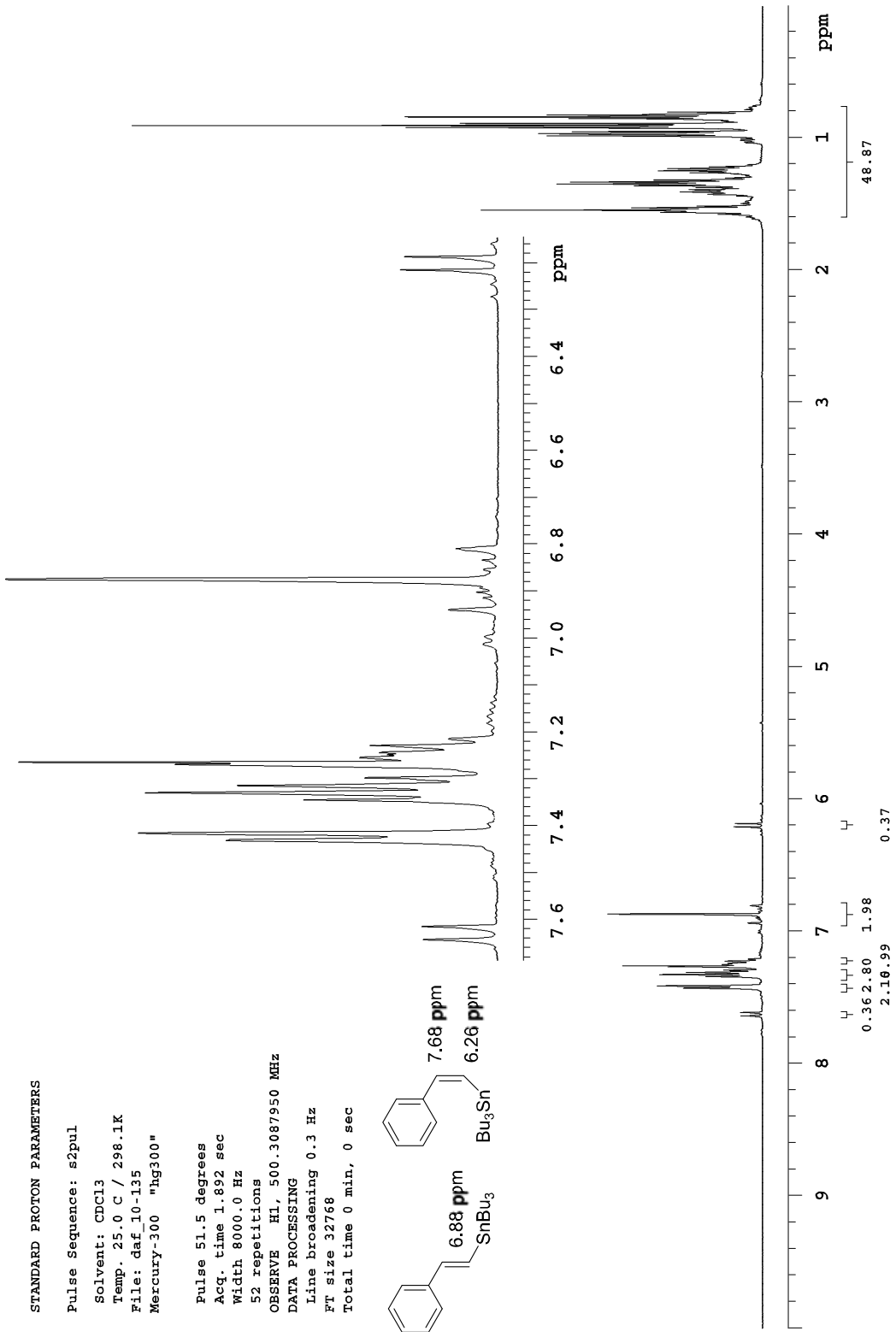
Spectrum 2.195 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **576**



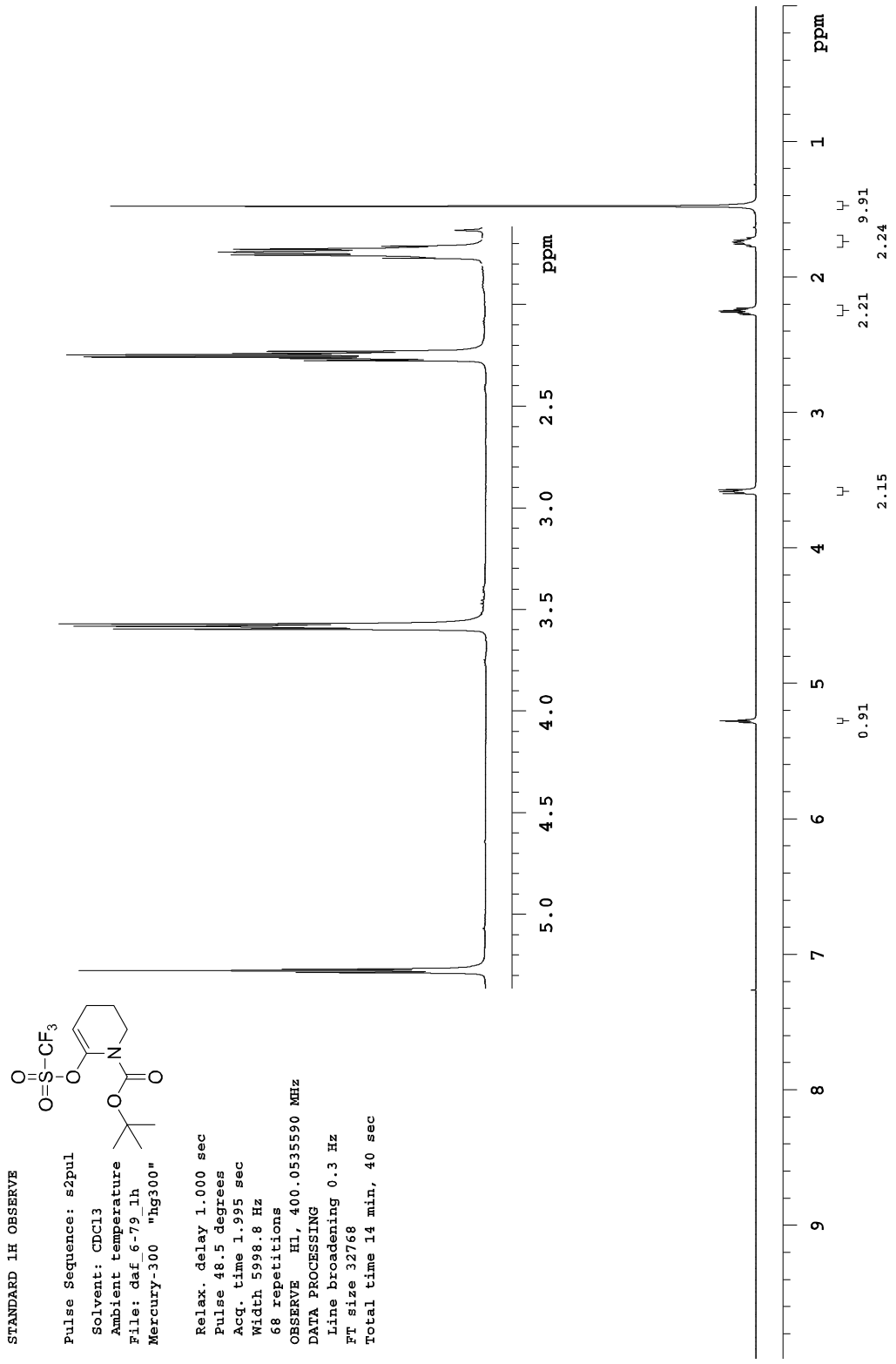
Spectrum 2.196 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **578**



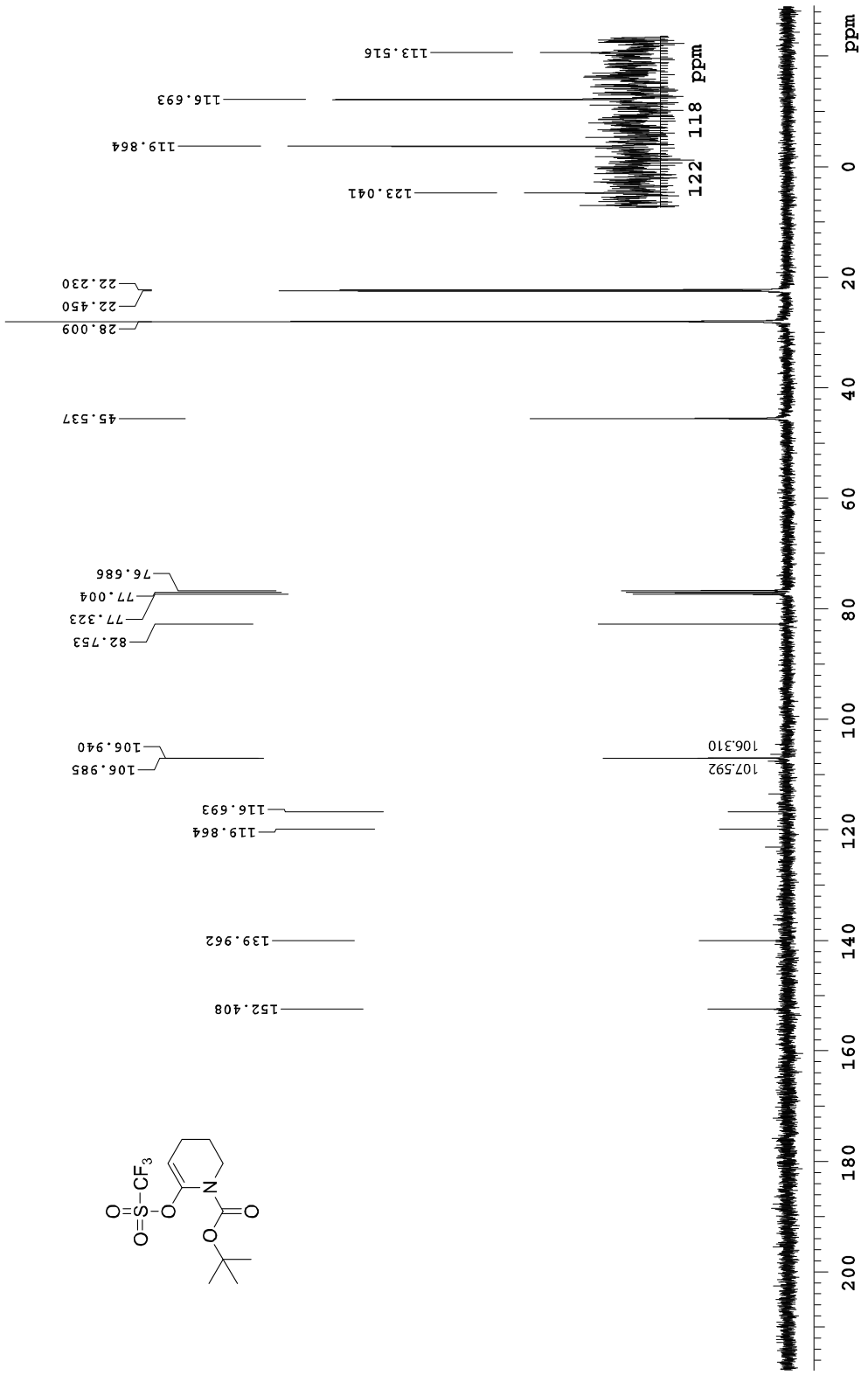
Spectrum 2.197 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **579**



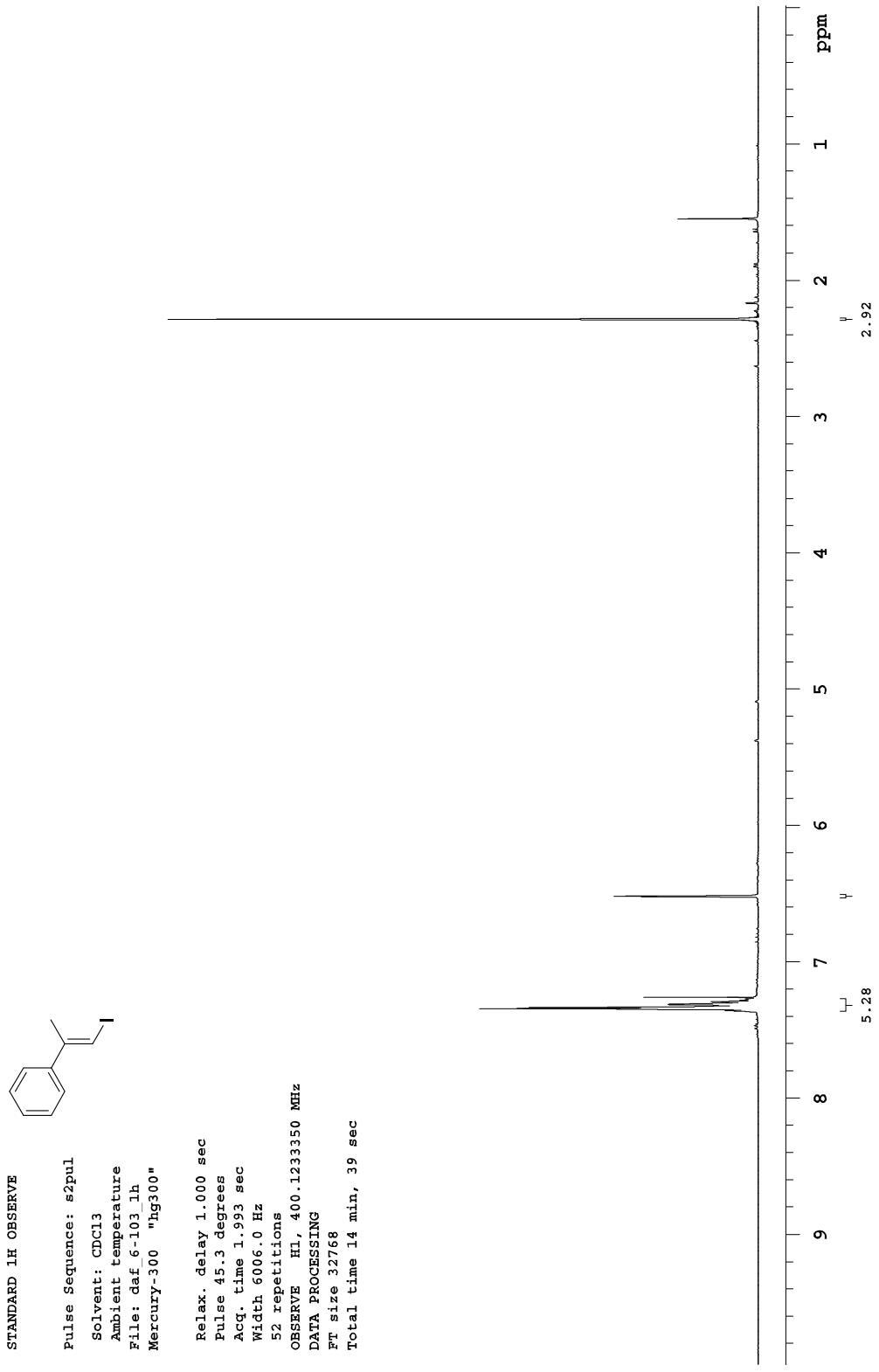
Spectrum 2.198 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **588**



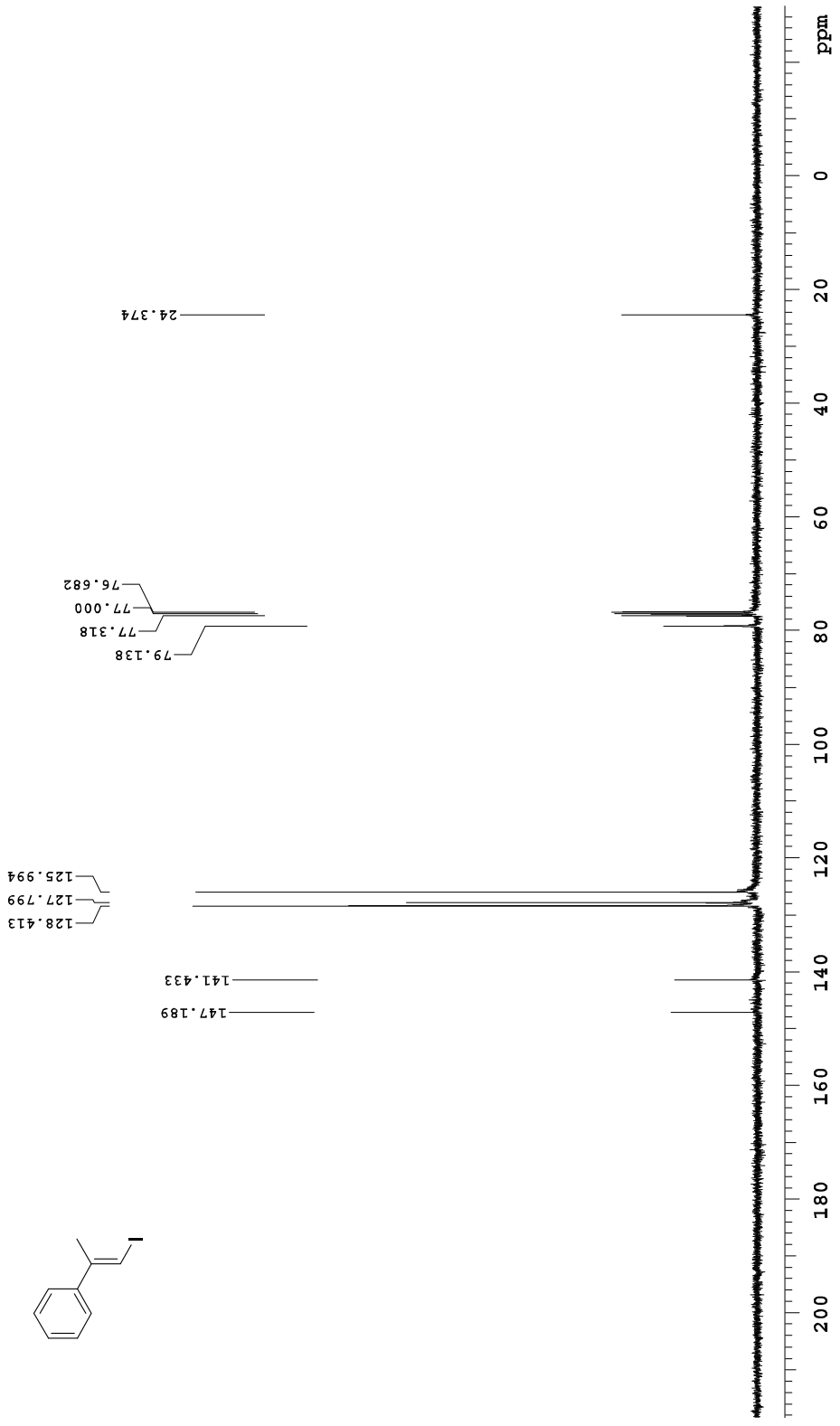
Spectrum 2.199 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **590**



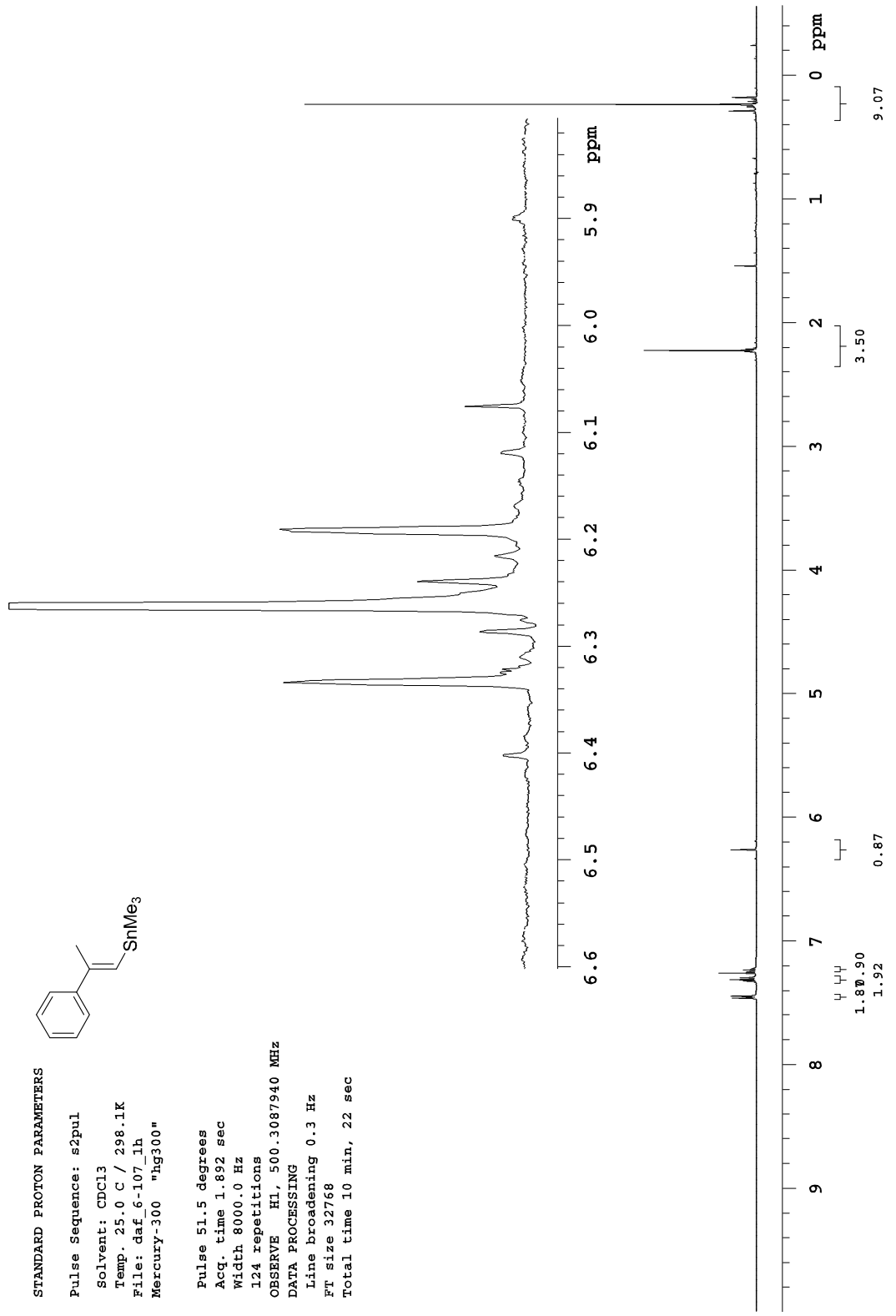
Spectrum 2.200 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **590**



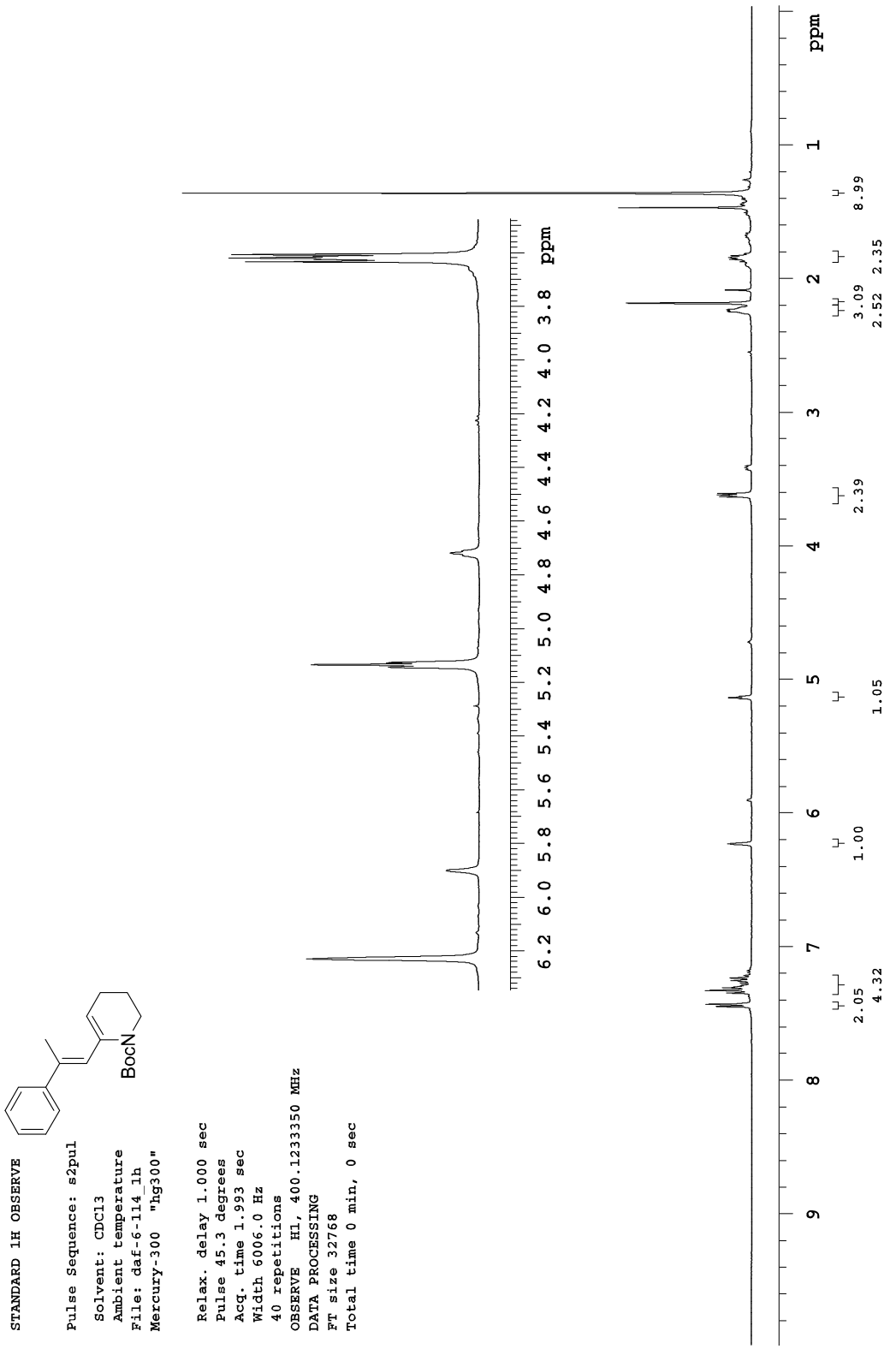
Spectrum 2.201 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **596**



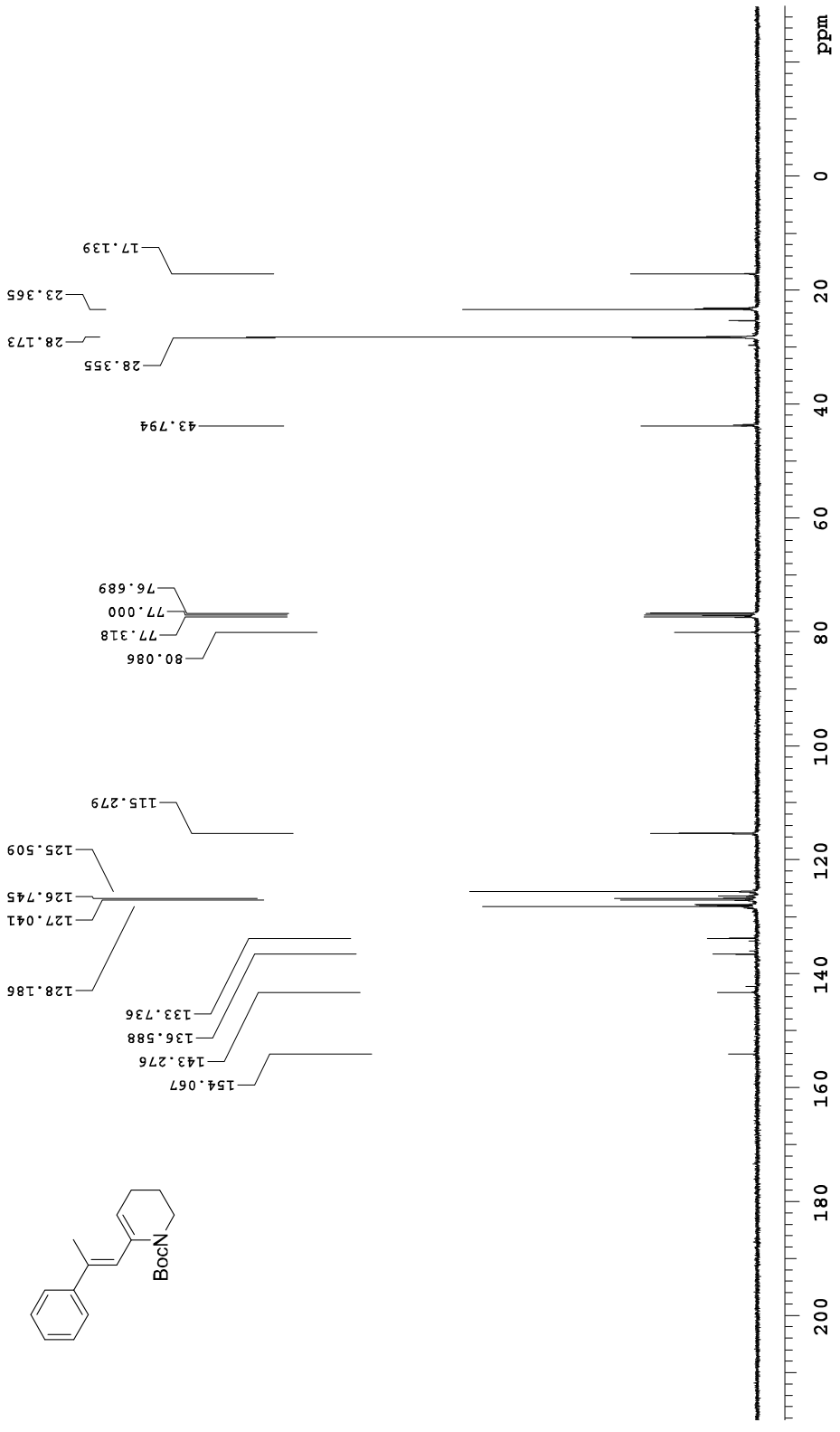
Spectrum 2.202 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **596**



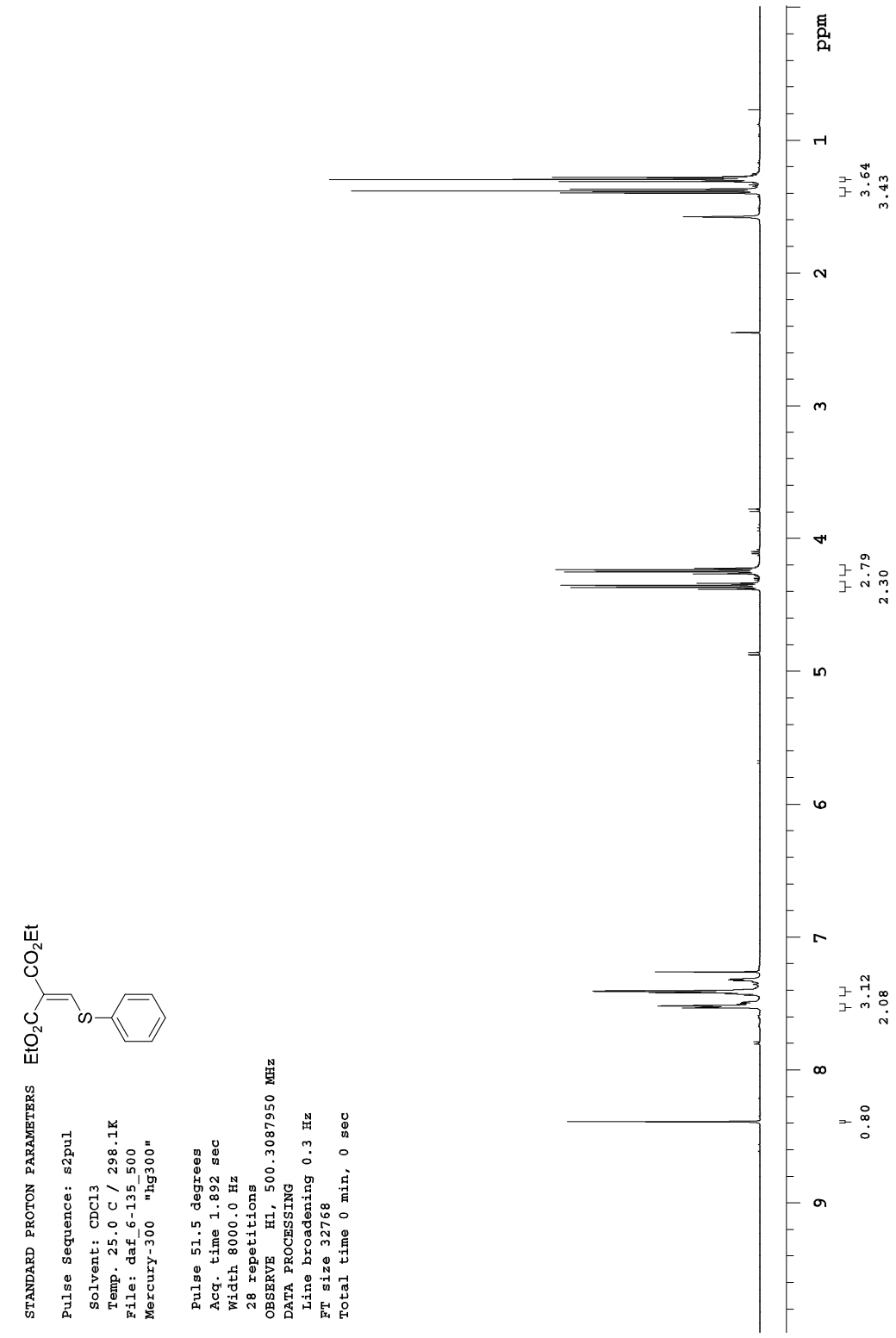
Spectrum 2.203 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **597**



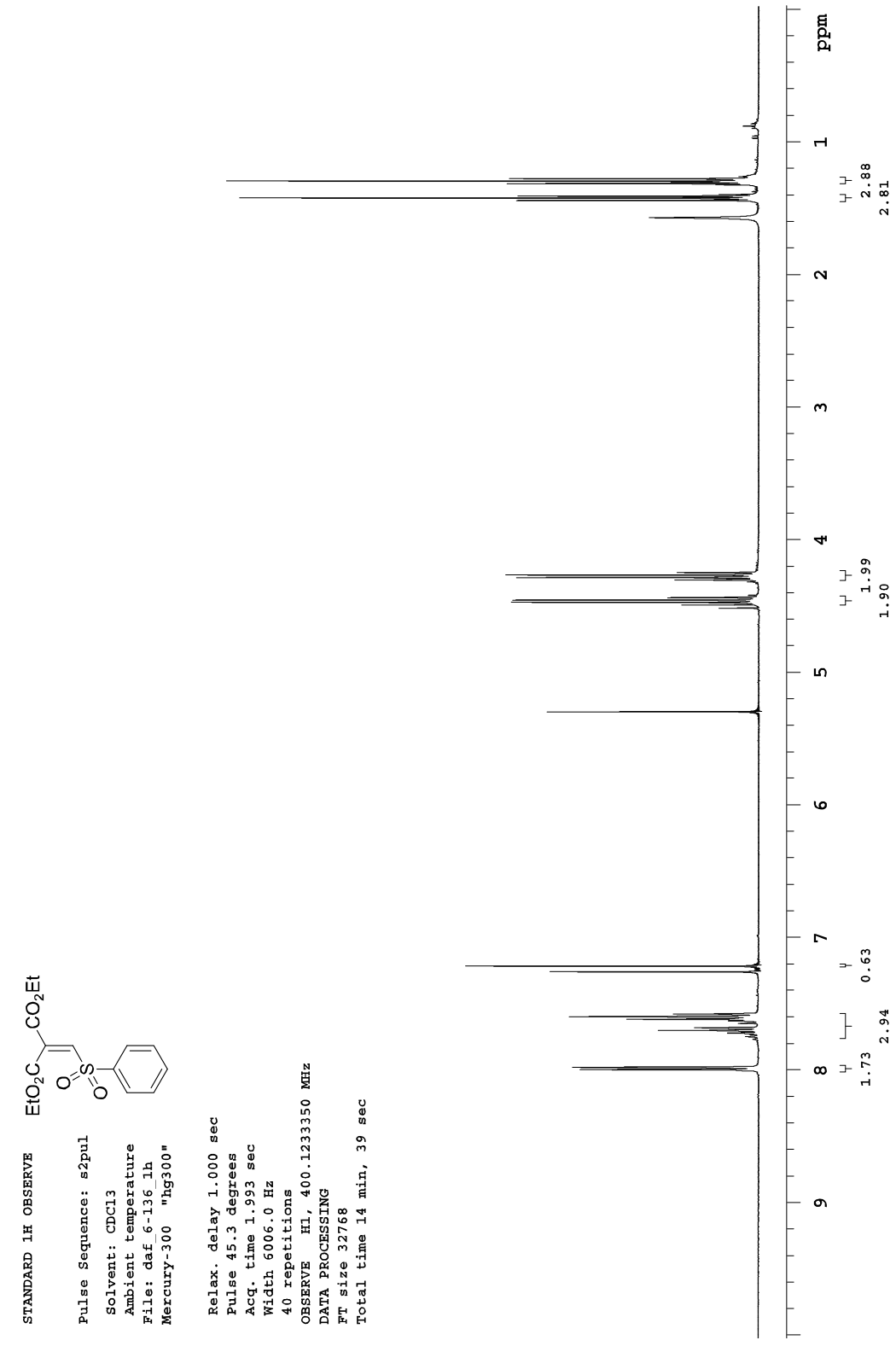
Spectrum 2.204 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **598**



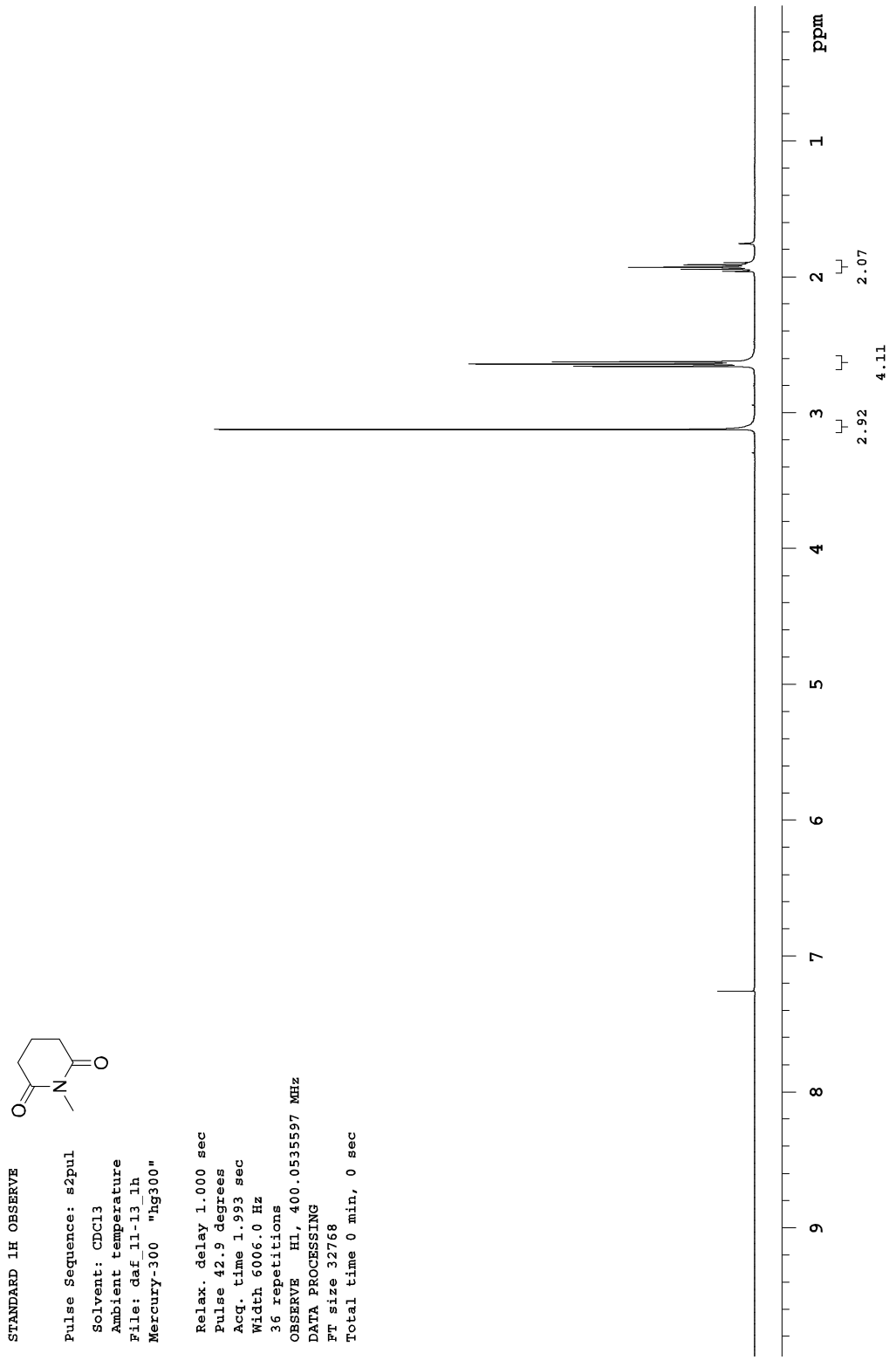
Spectrum 2.205 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **598**



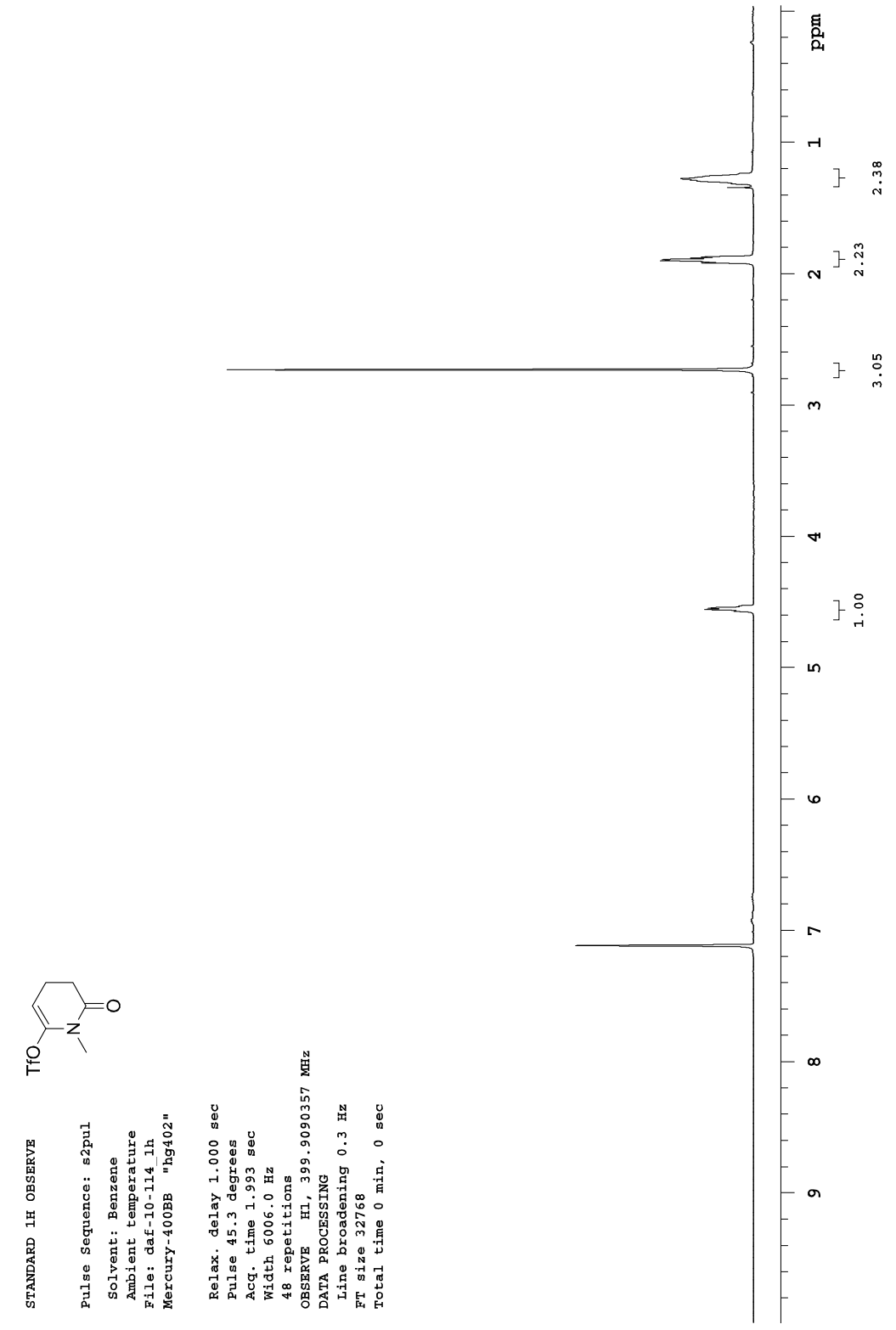
Spectrum 2.206 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **599**



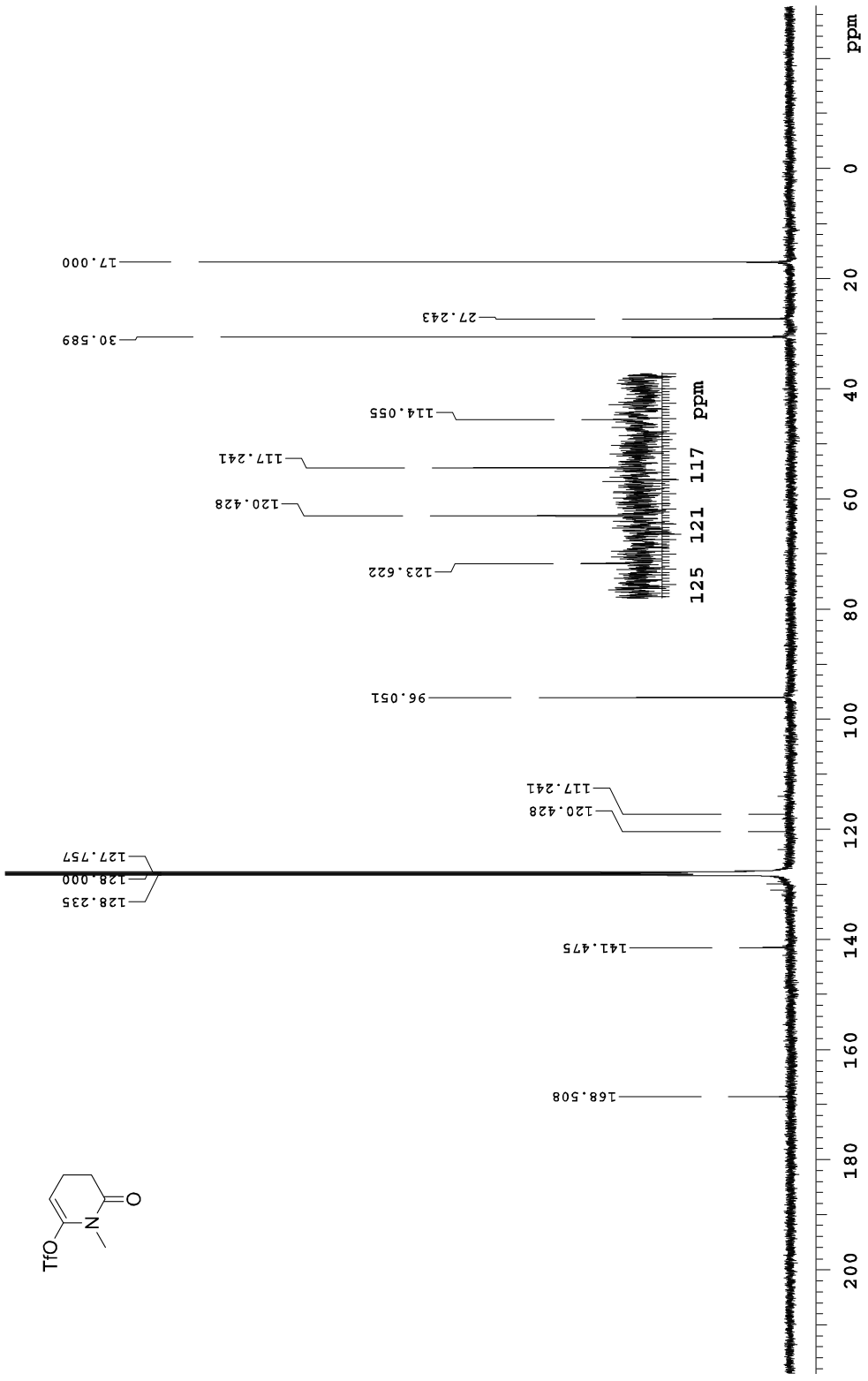
Spectrum 2.207 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **600**



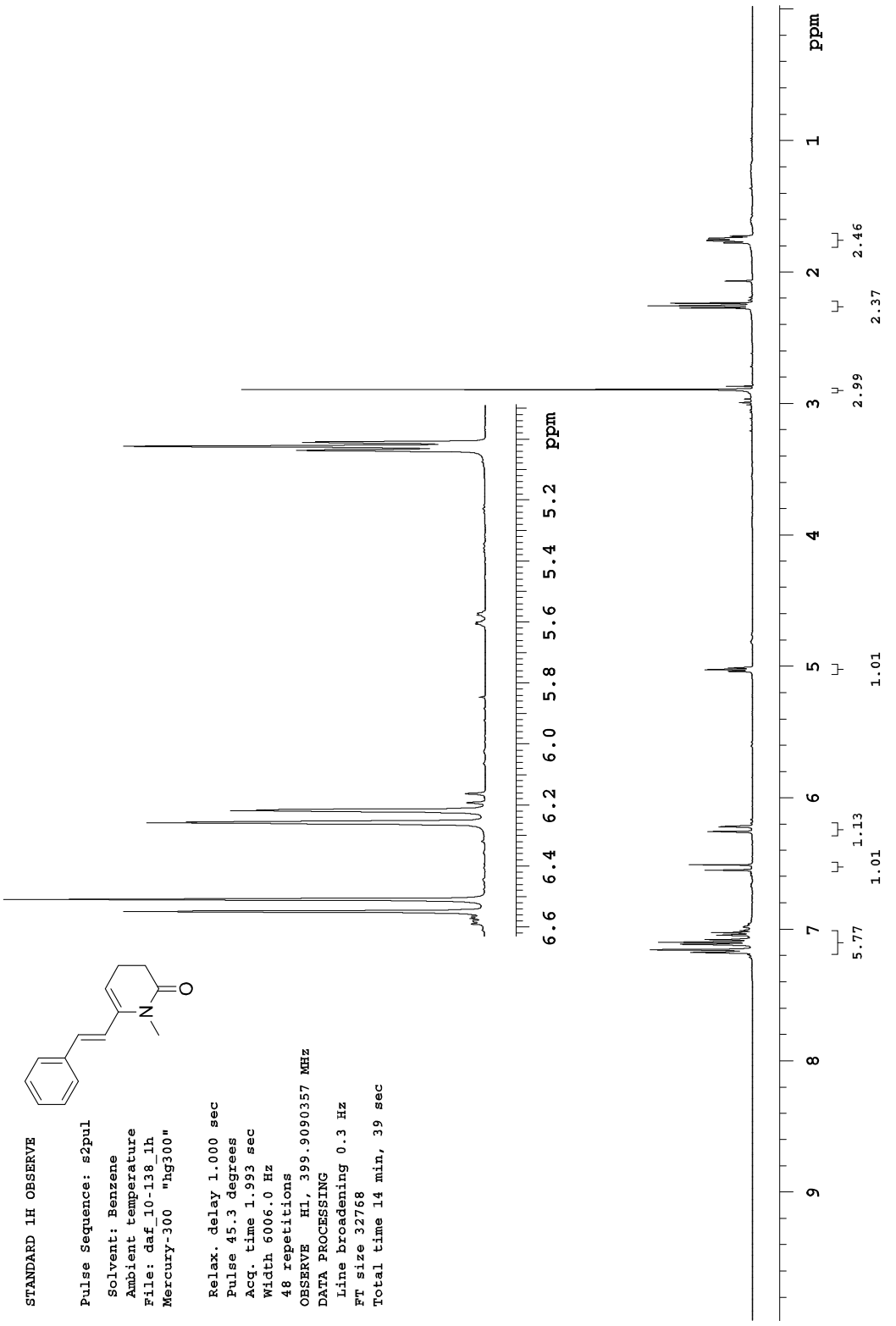
Spectrum 2.208 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **603**



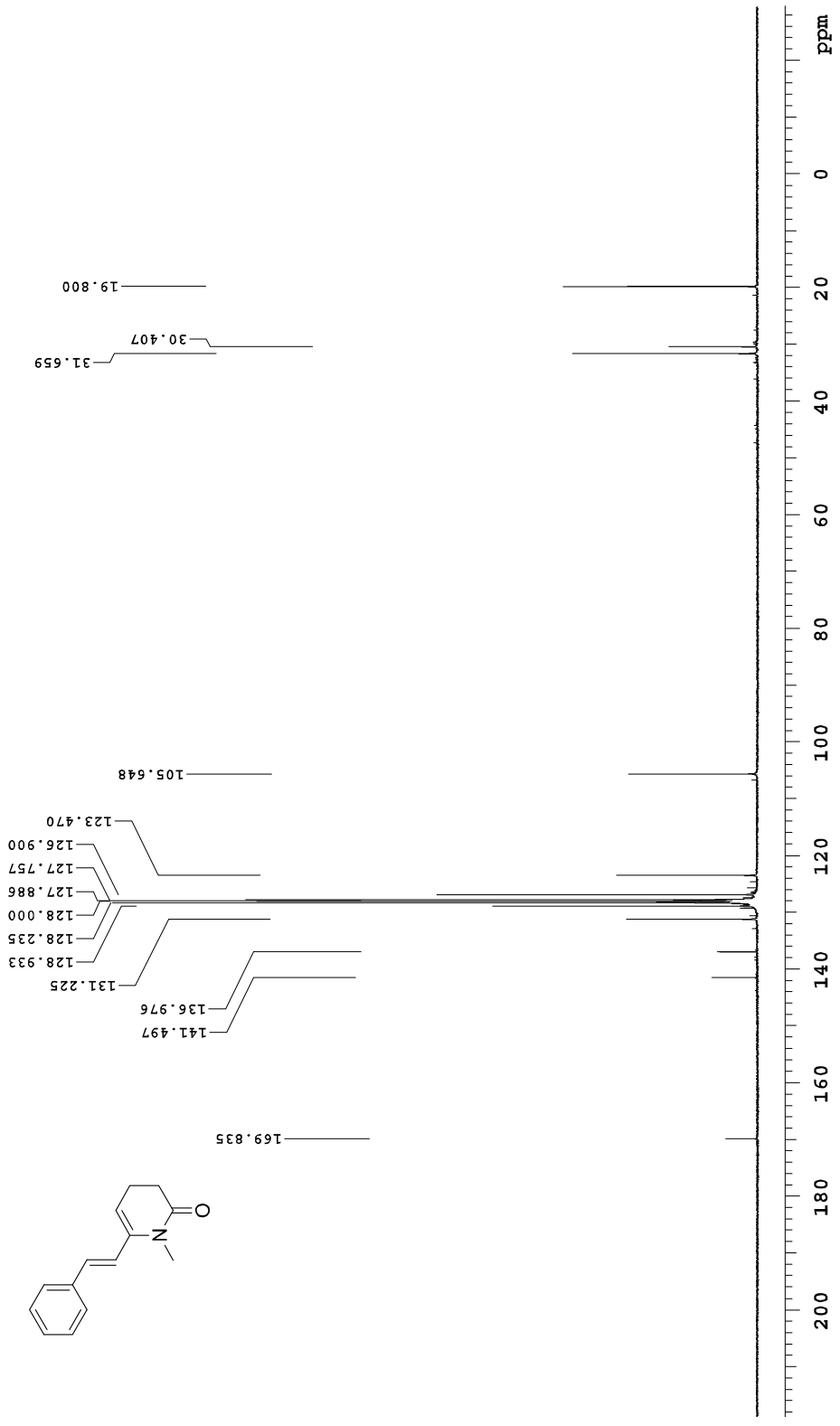
Spectrum 2.209 ^{1}H NMR (C_6D_6, 400 MHz) of compound **604**



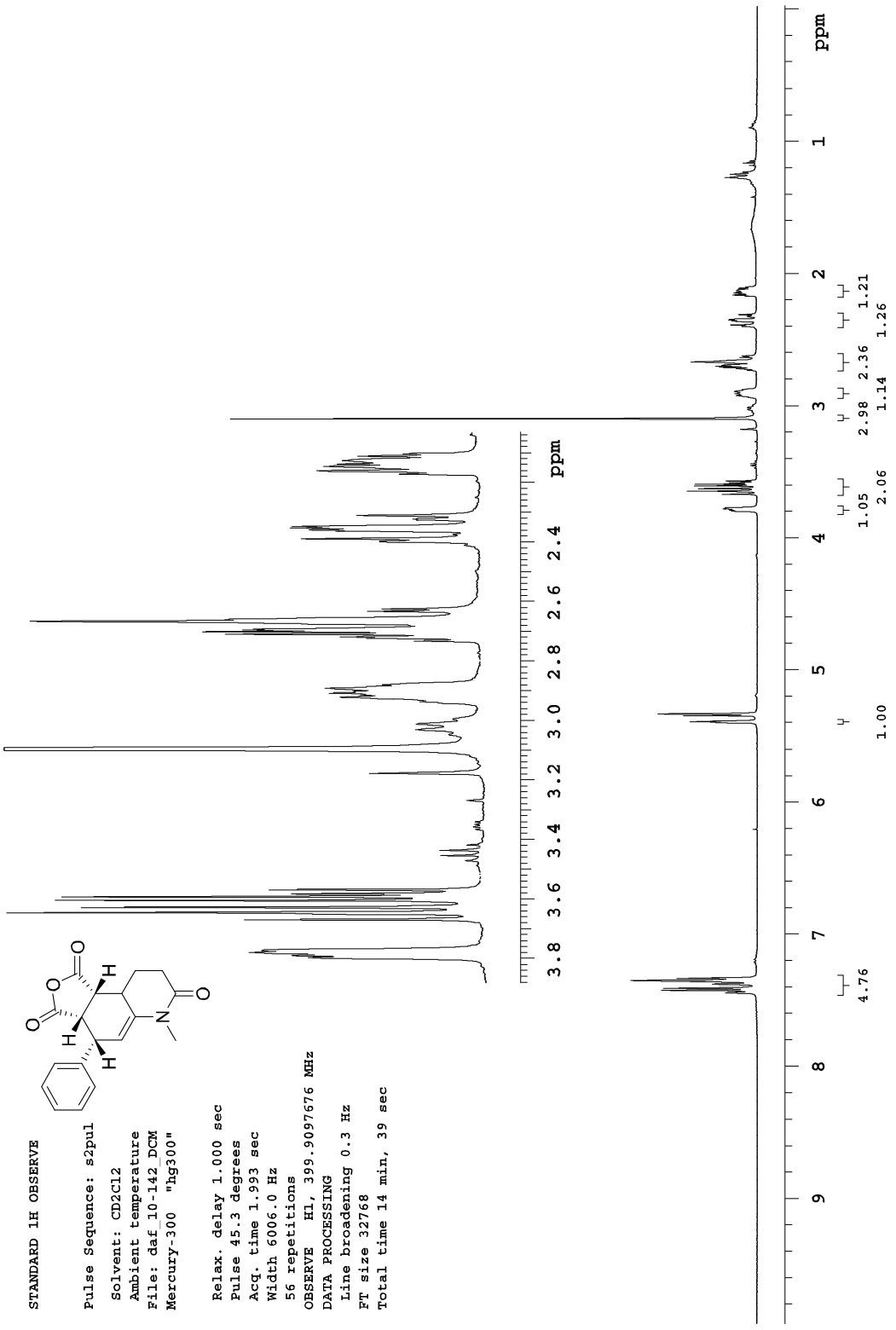
Spectrum 2.210 ^{13}C NMR (C_6D_6, 100 MHz) of compound **604**



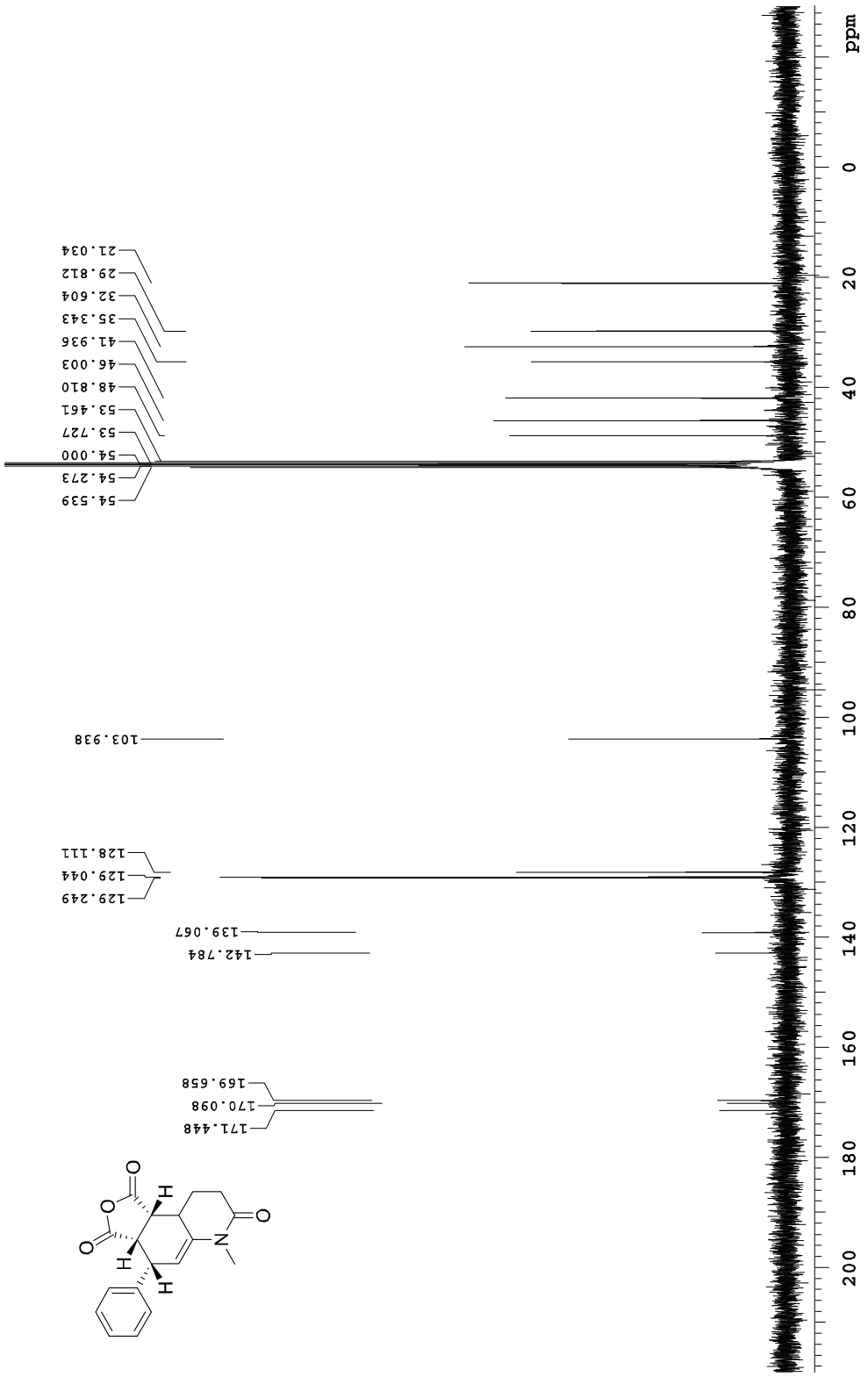
Spectrum 2.211 ^{1}H NMR (C_6D_6, 400 MHz) of compound **606**



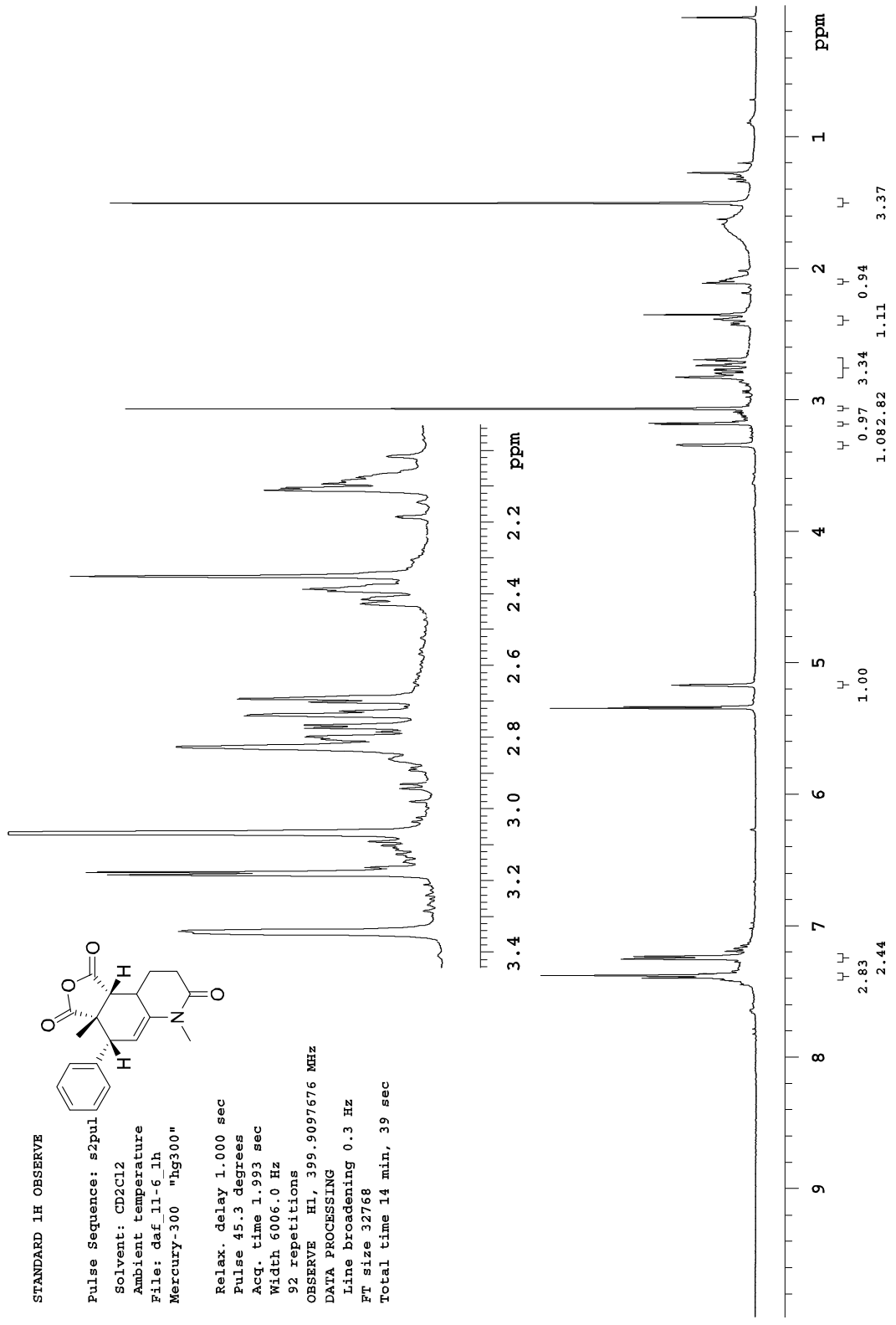
Spectrum 2.212 ^{13}C NMR (C_6D_6, 100 MHz) of compound **606**



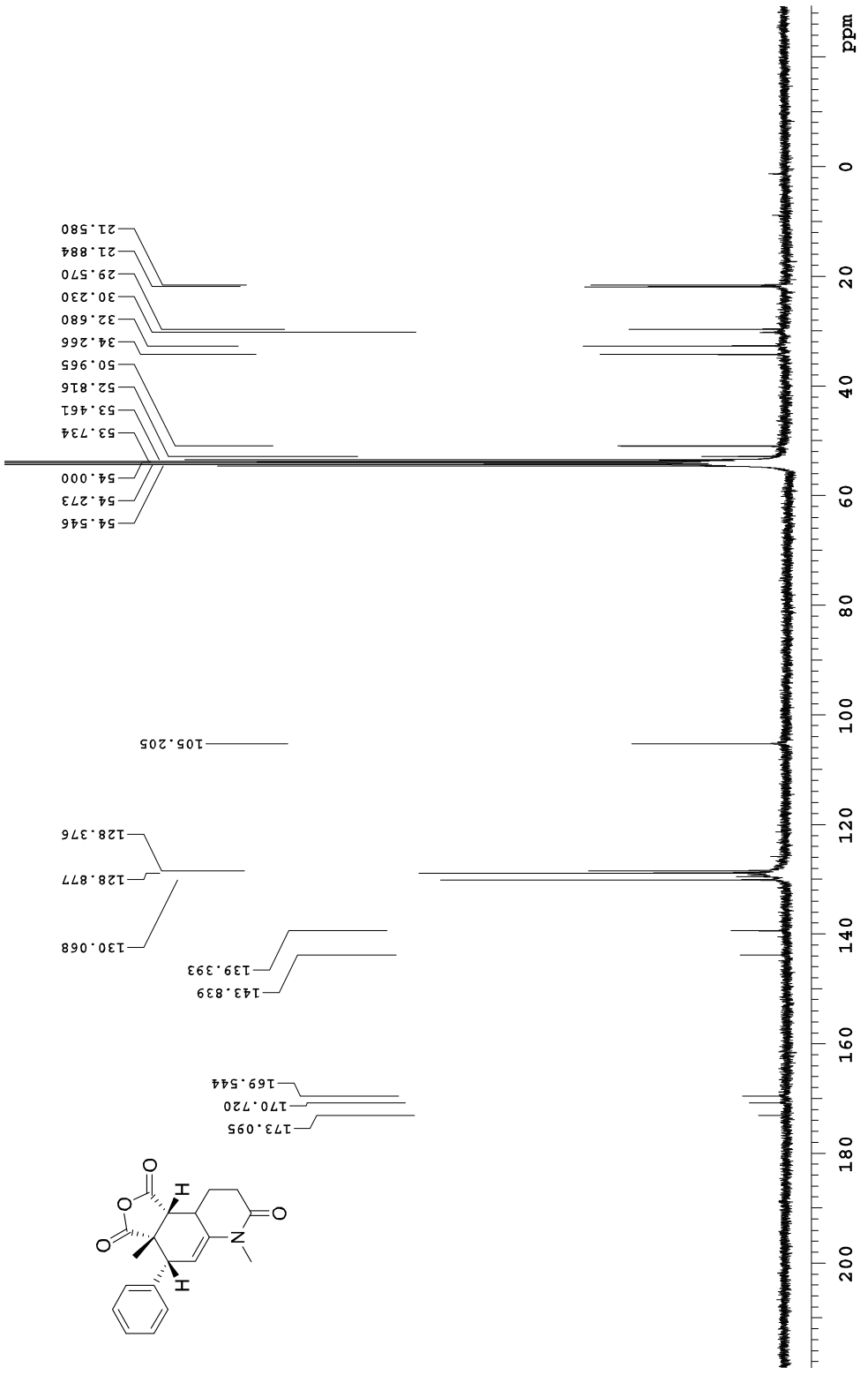
Spectrum 2.213 ^{1}H NMR (CD_2Cl_2, 400 MHz) of compound **607a**



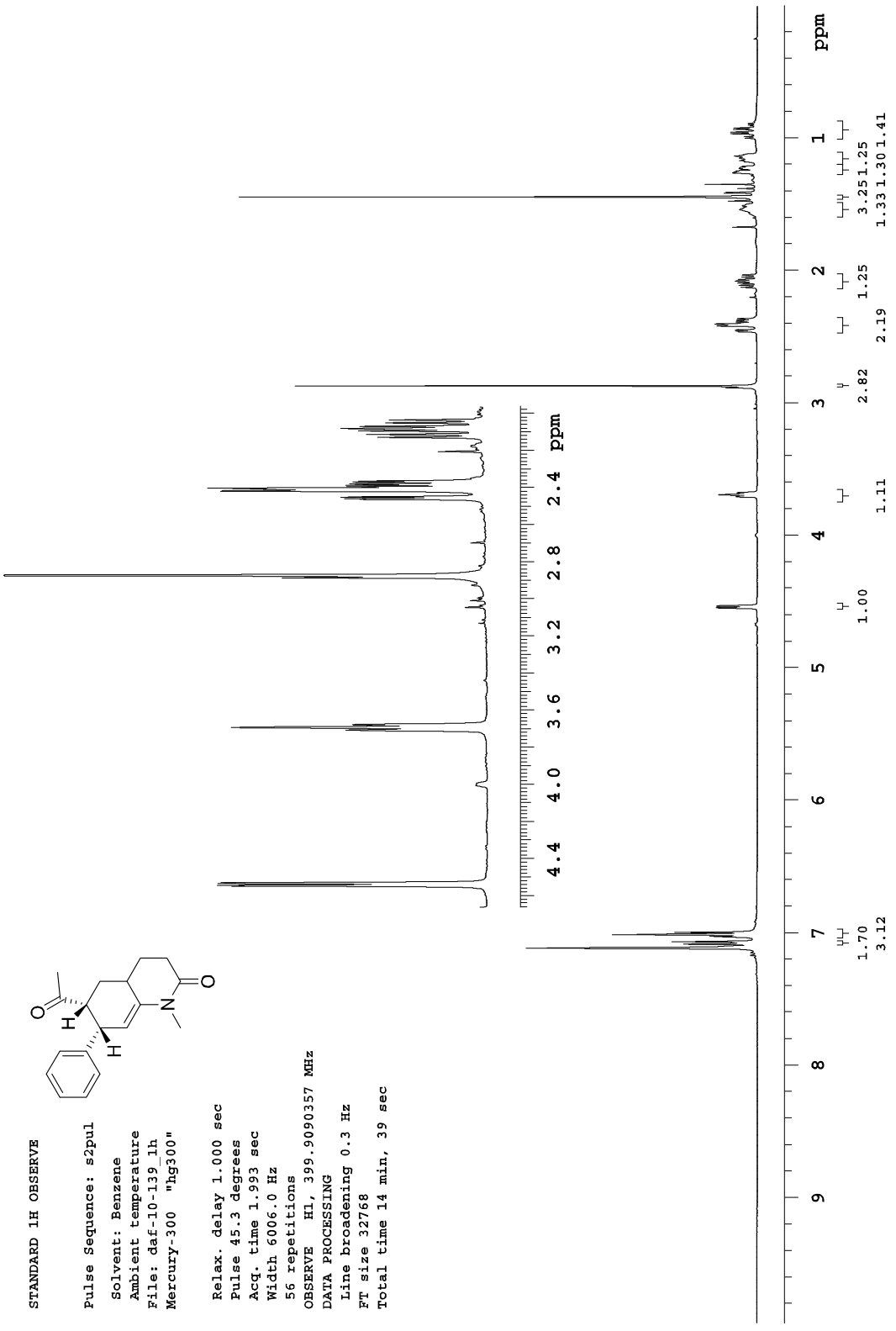
Spectrum 2.214 ^{13}C NMR (CD_2Cl_2, 100 MHz) of compound **607a**



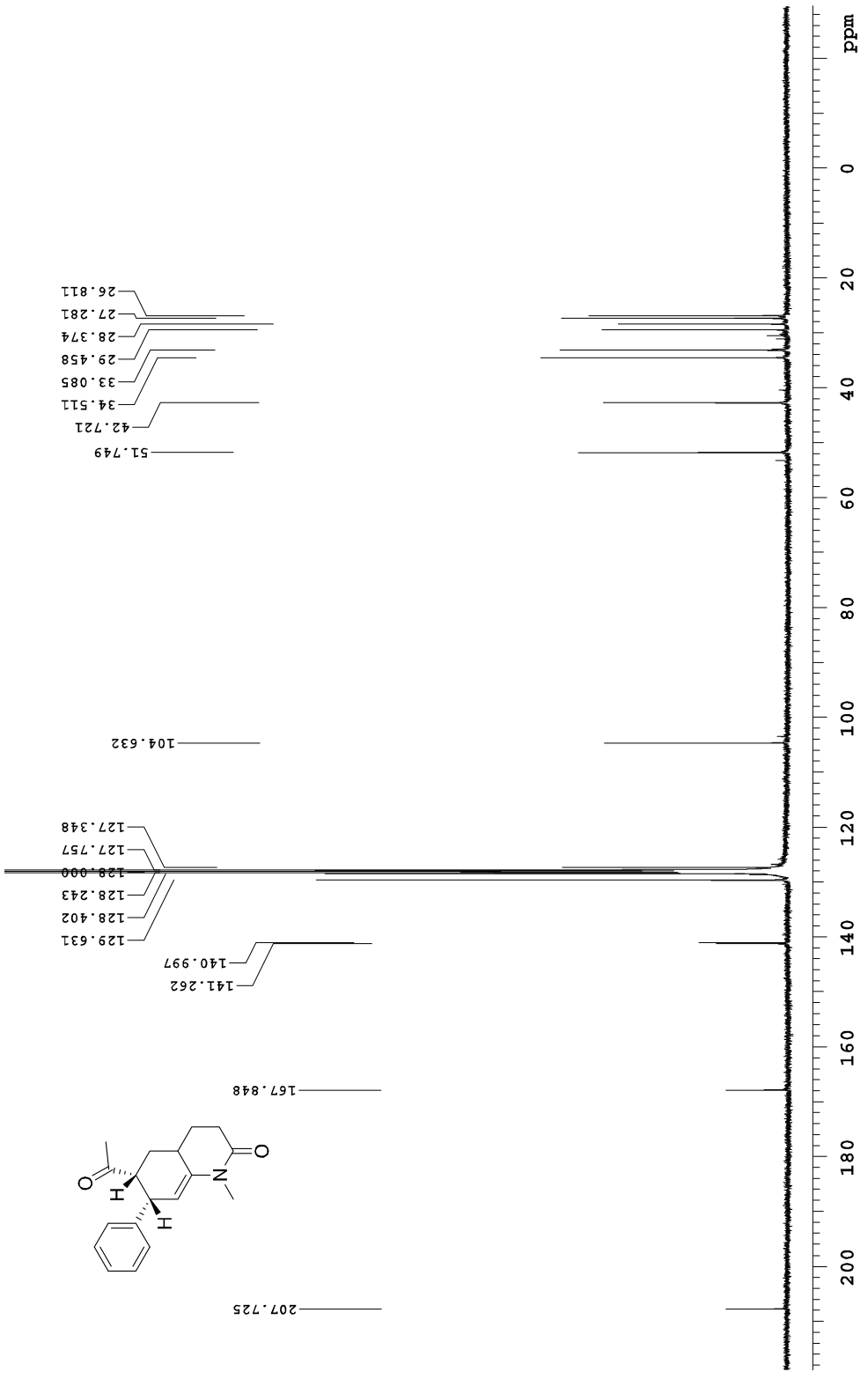
Spectrum 2.215 ^{1}H NMR (CD_2Cl_2, 400 MHz) of compound **607b**



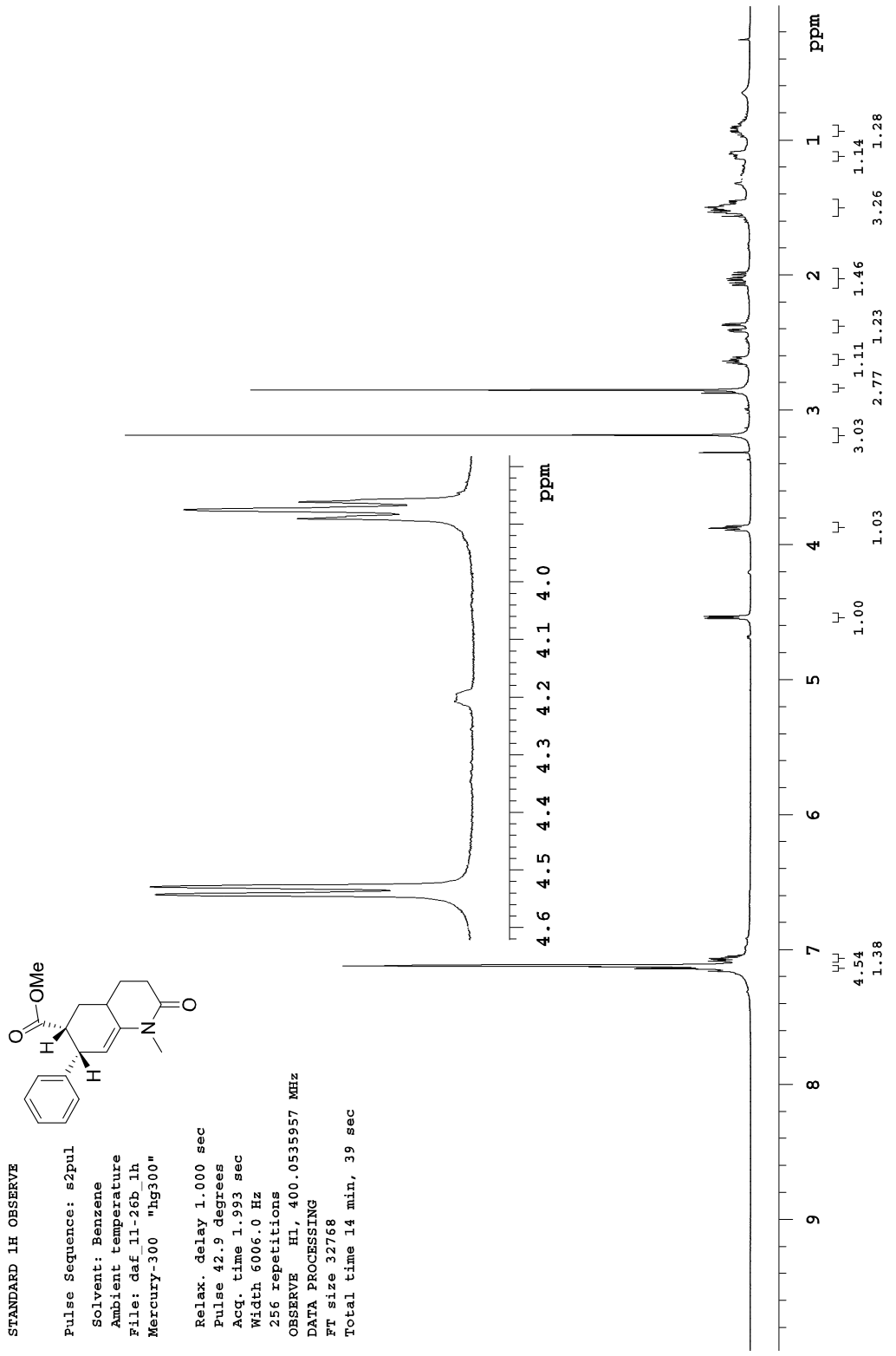
Spectrum 2.216 ^{13}C NMR (CD_2Cl_2, 100 MHz) of compound **607b**



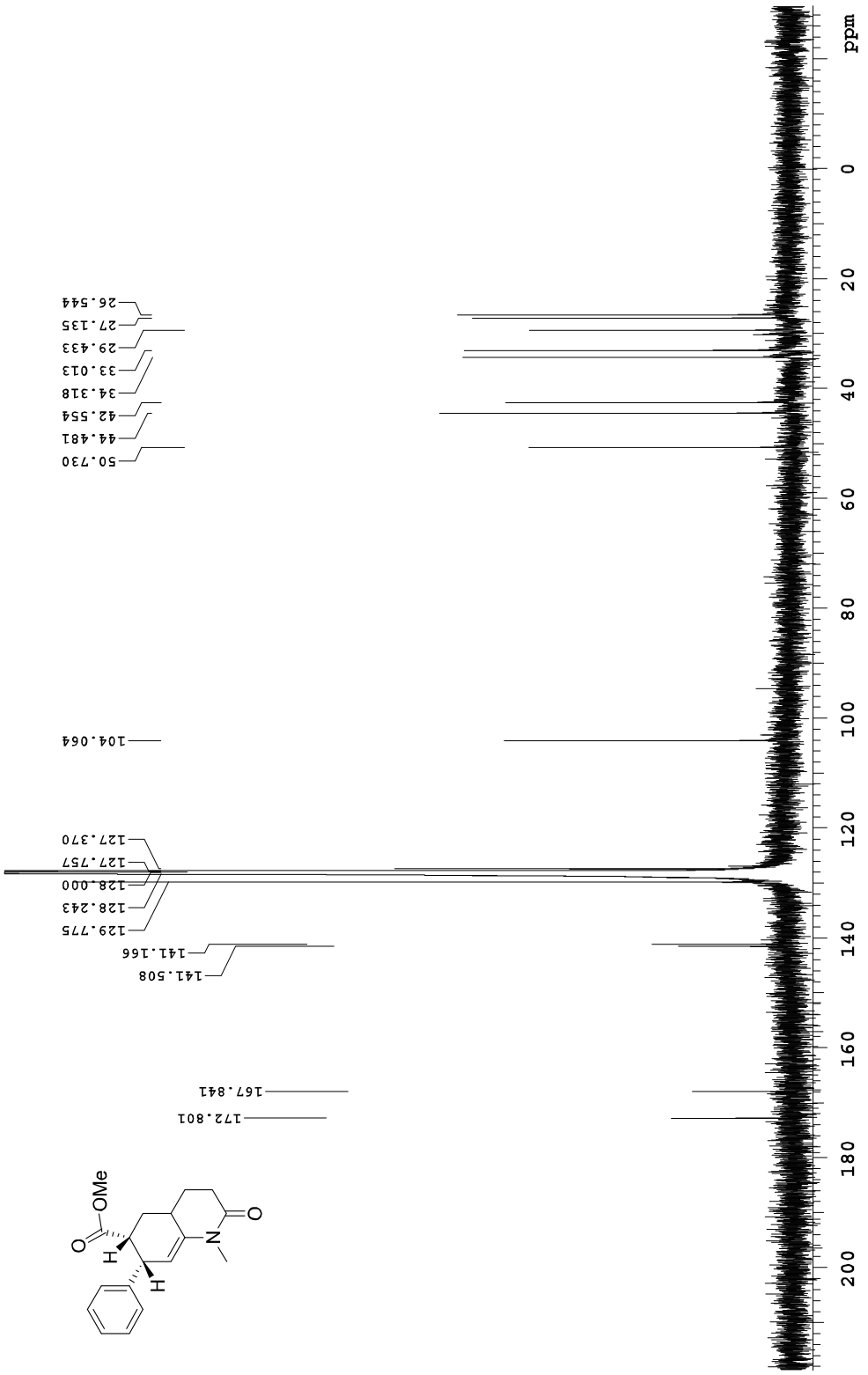
Spectrum 2.217 ^{1}H NMR (C_6D_6, 400 MHz) of compound **607c**



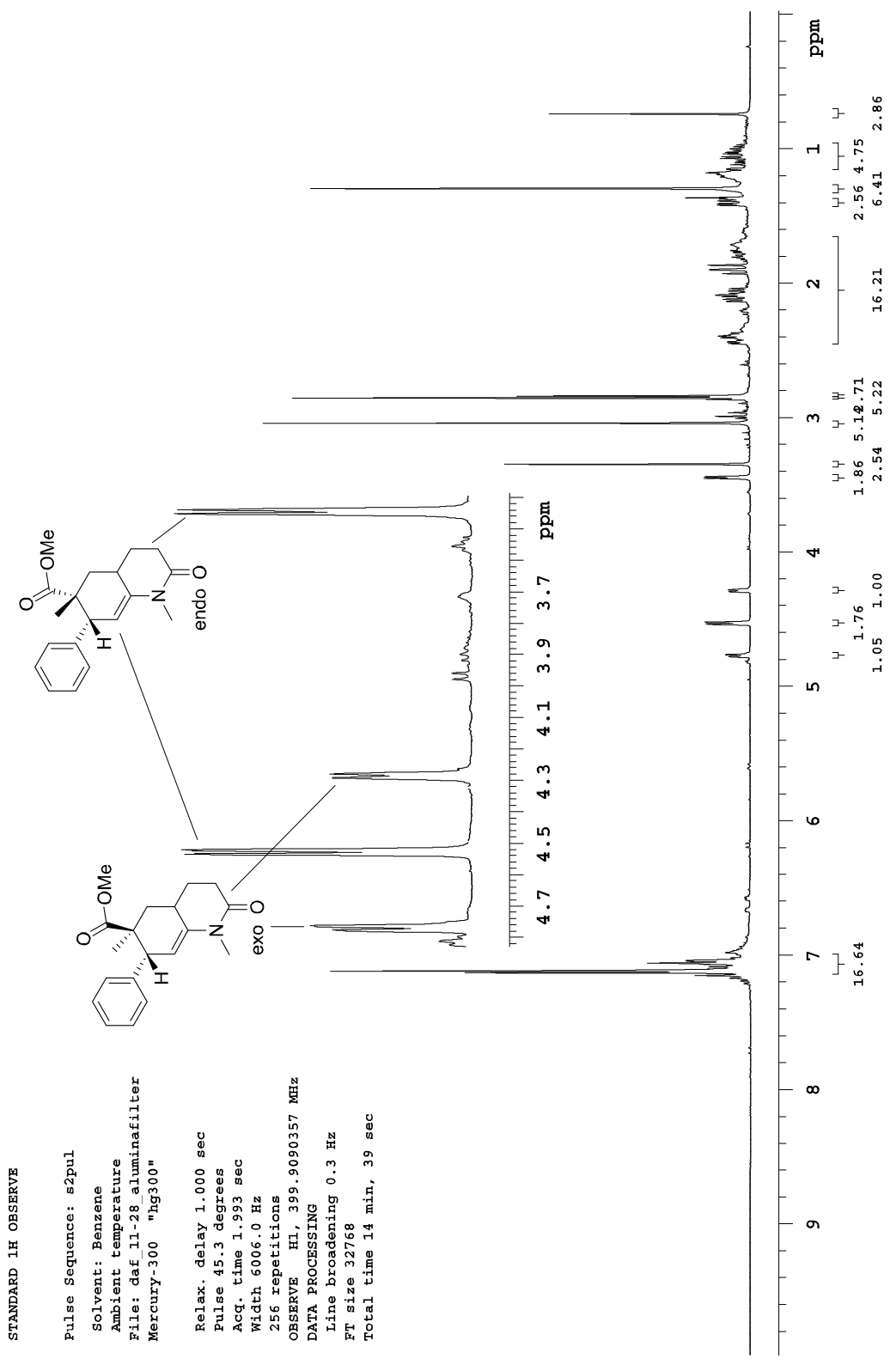
Spectrum 2.218 ^{13}C NMR (C_6D_6, 100 MHz) of compound **607c**



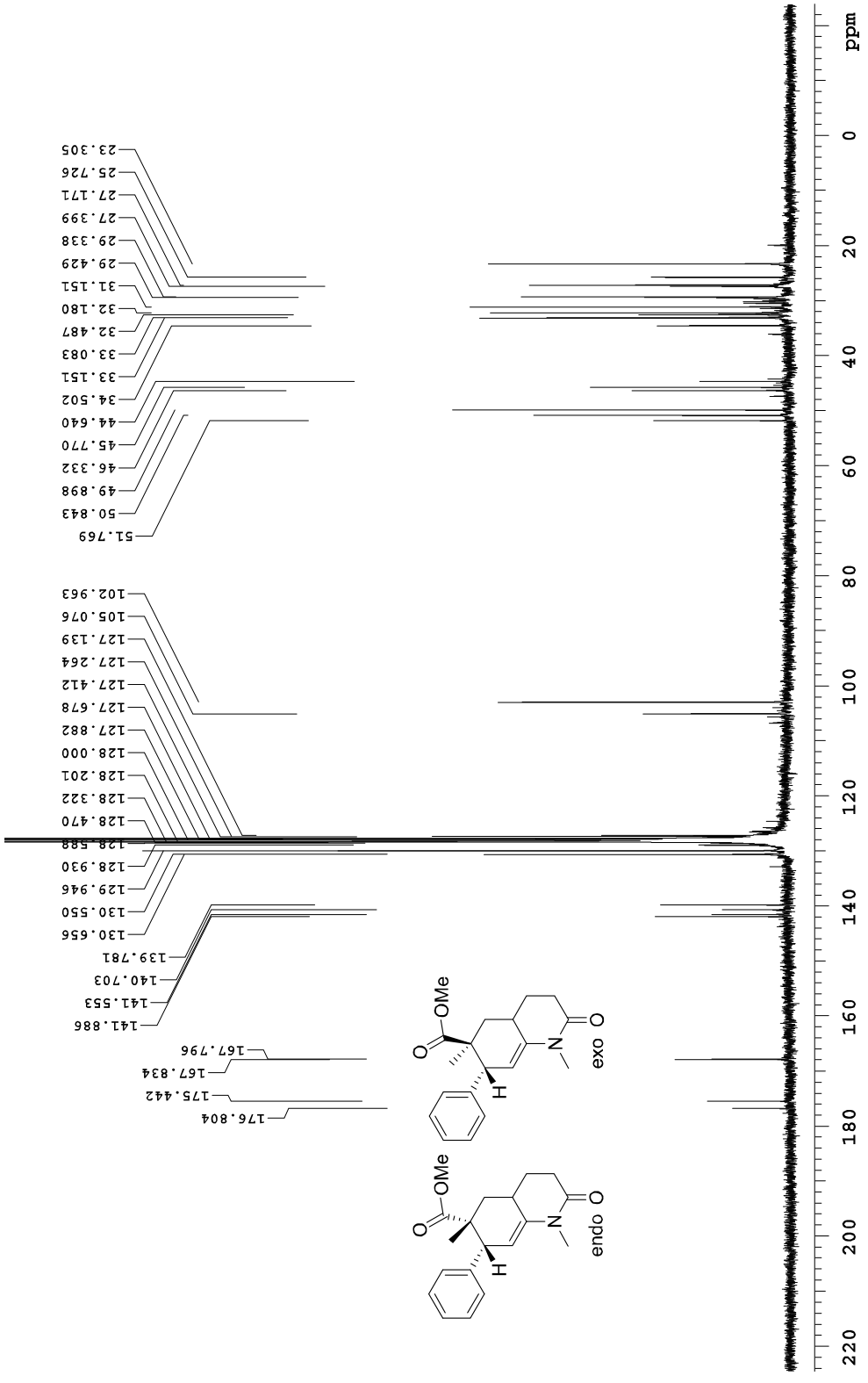
Spectrum 2.219 ^{1}H NMR (C_6D_6, 400 MHz) of compound **607d**



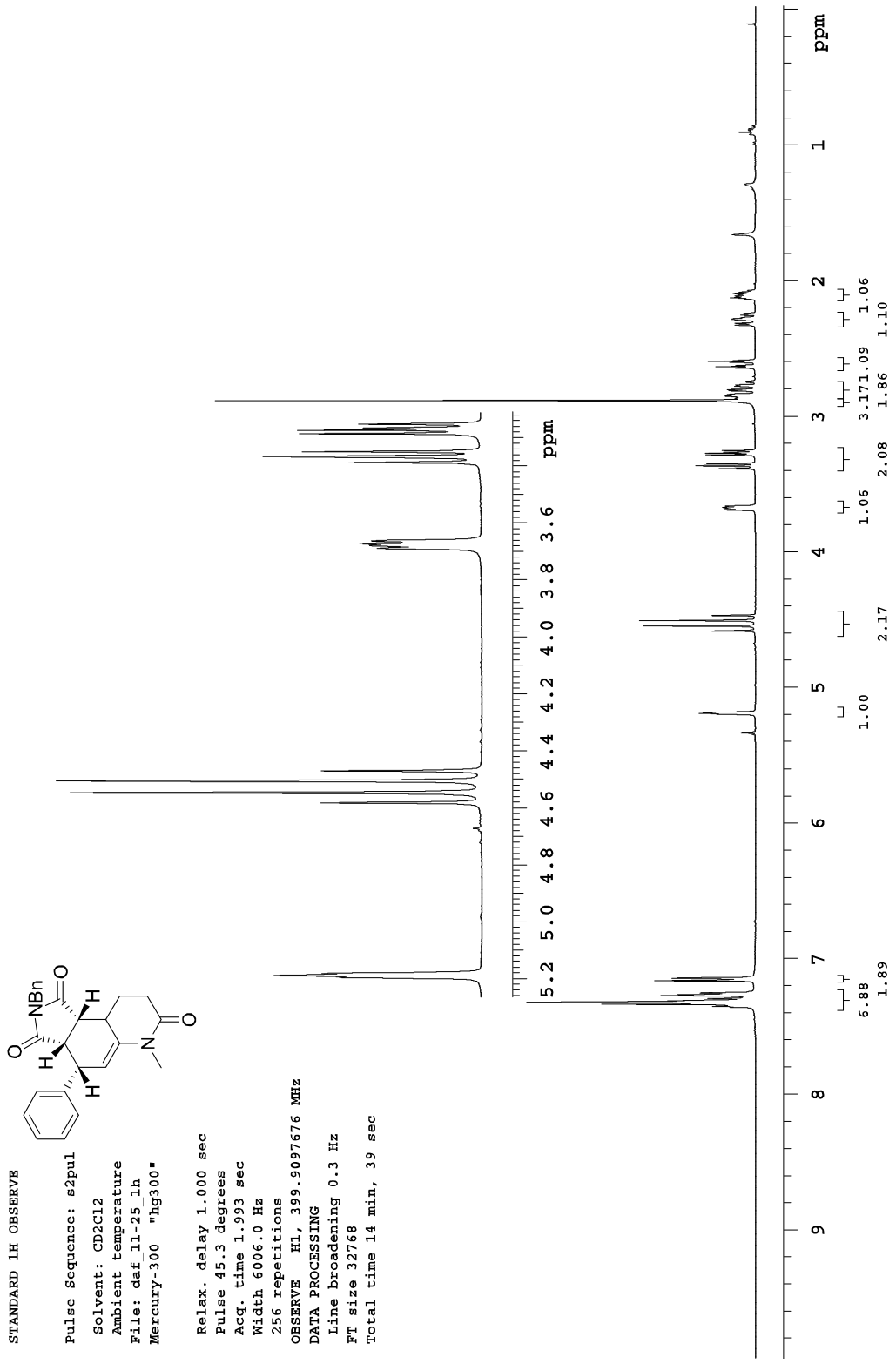
Spectrum 2.220 ^{13}C NMR (C_6D_6, 100 MHz) of compound **607d**



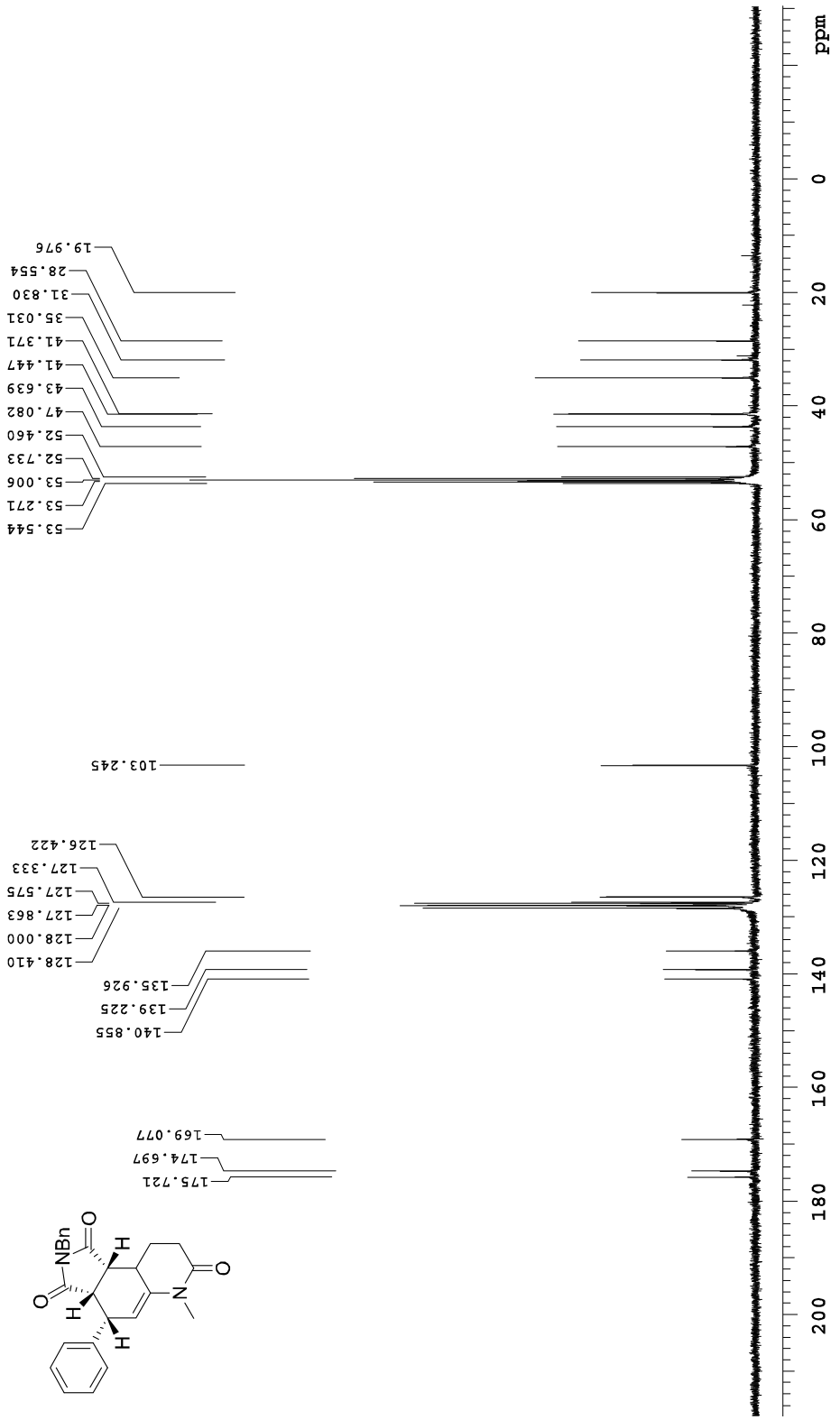
Spectrum 2.221 ^{1}H NMR (C_6D_6, 400 MHz) of compound **607e**



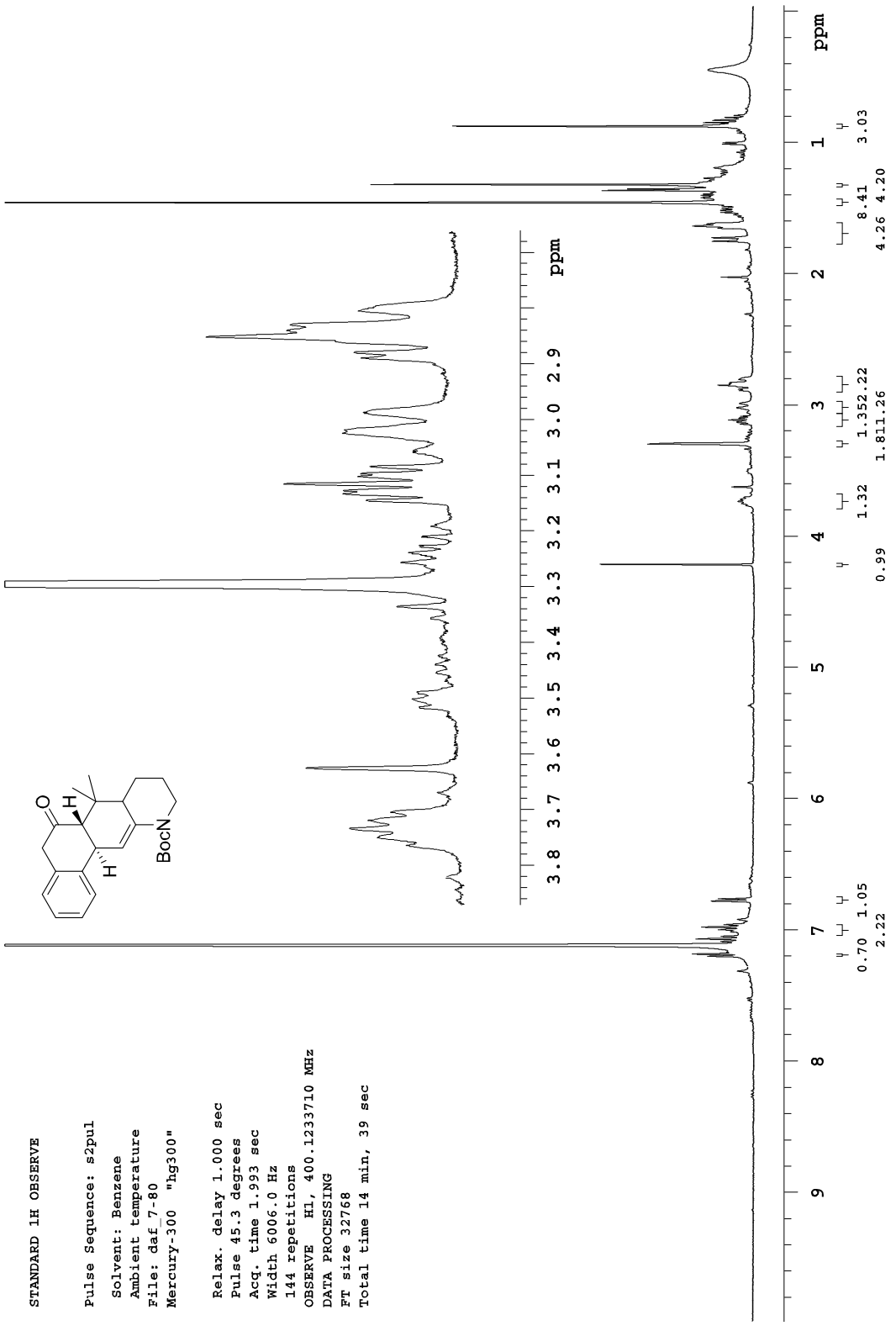
Spectrum 2.222 ^{13}C NMR (C_6D_6, 100 MHz) of compound **607e**



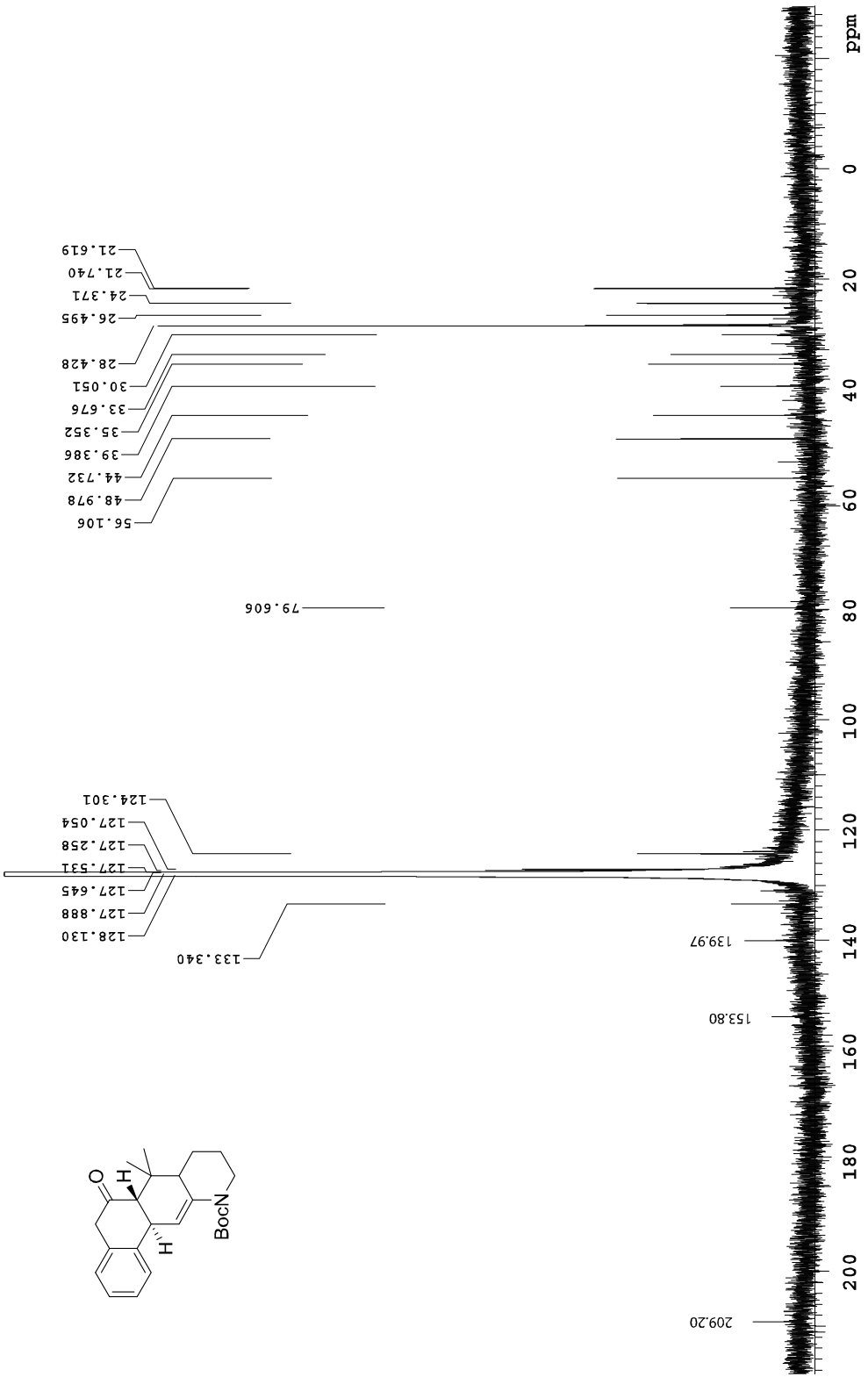
Spectrum 2.223 ^{1}H NMR (CD_2Cl_2, 400 MHz) of compound **607nbn**



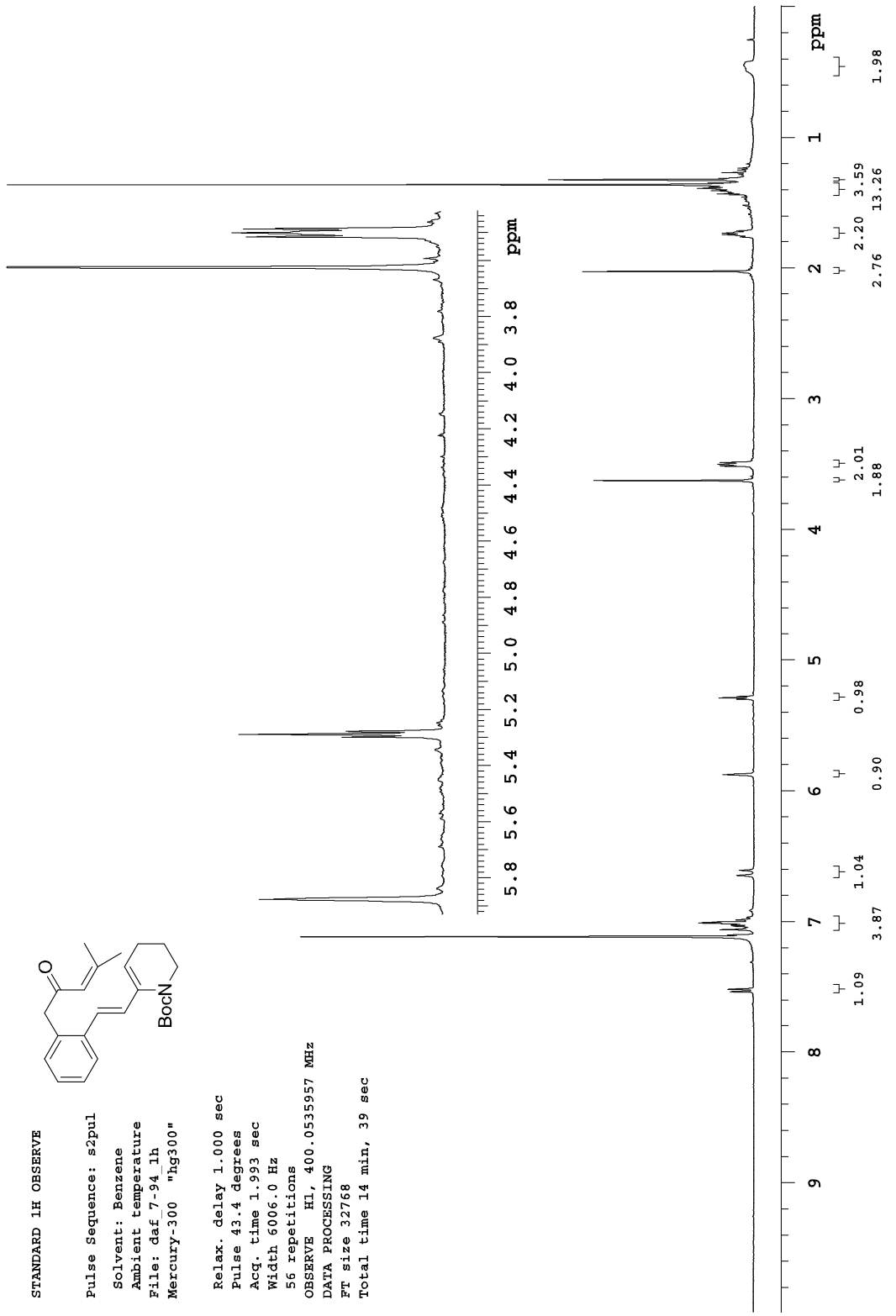
Spectrum 2.224 ^{13}C NMR (CD_2Cl_2, 100 MHz) of compound **607nbn**



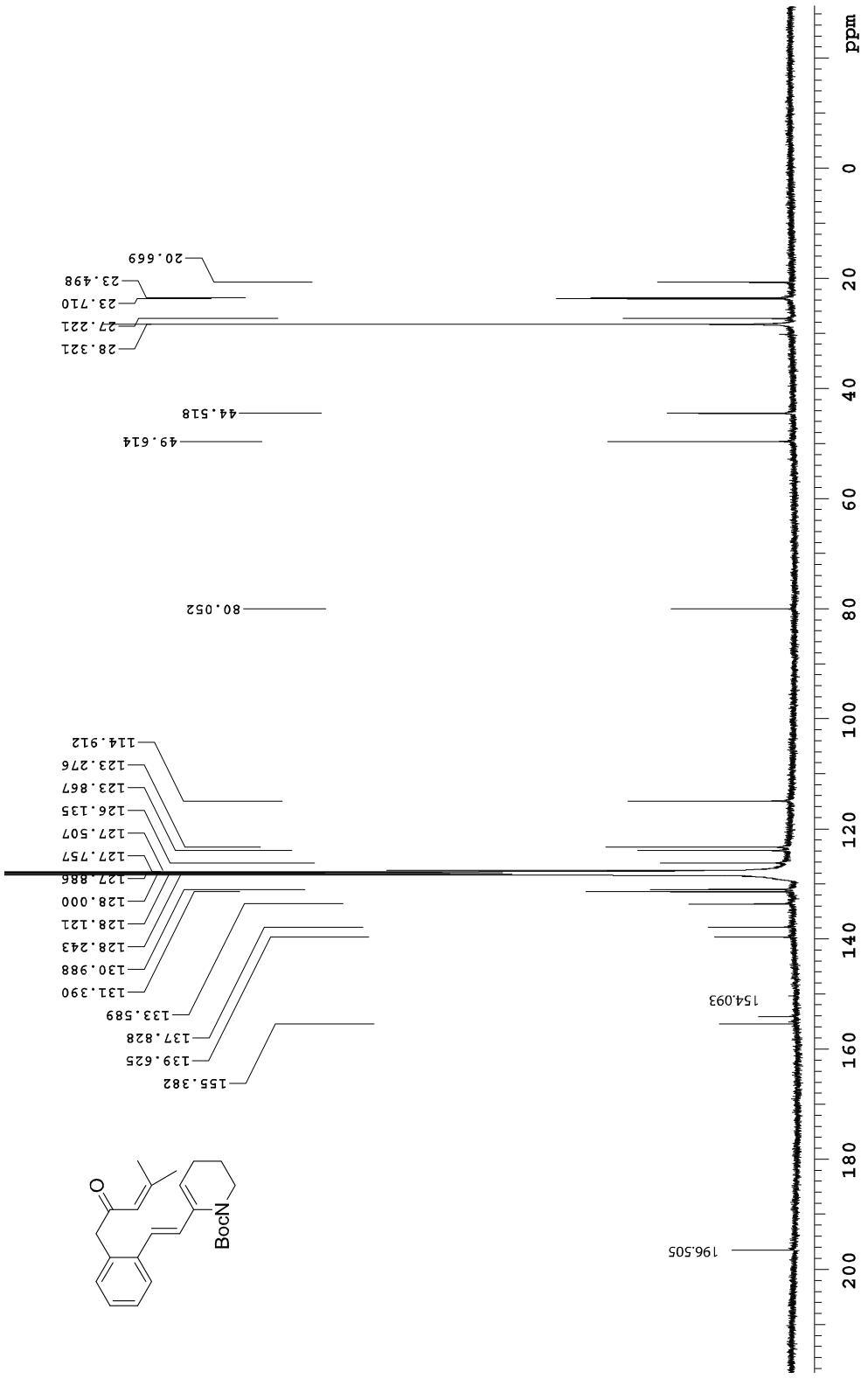
Spectrum 2.225 ^{1}H NMR (C_6D_6, 400 MHz) of compound **614**



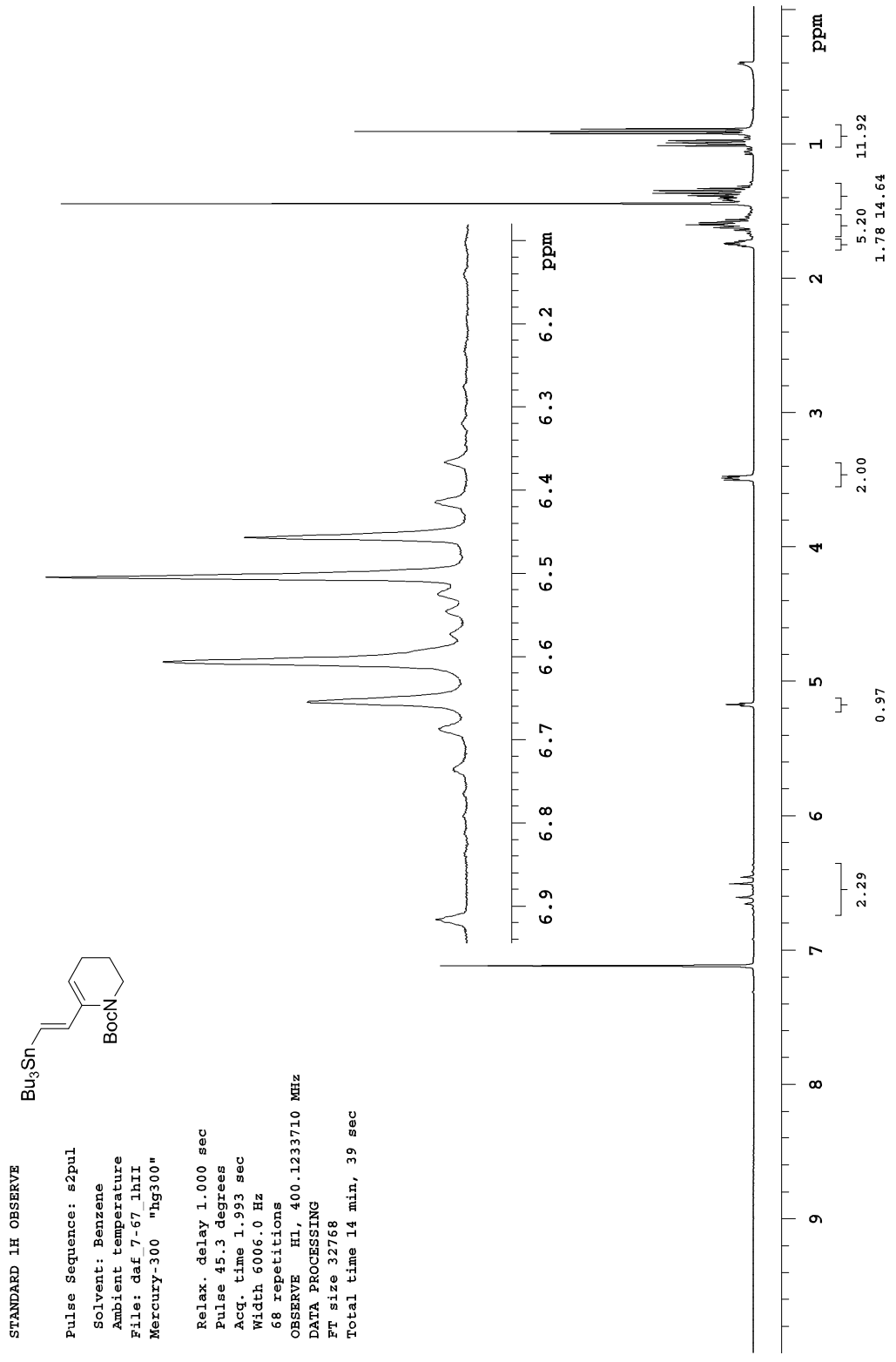
Spectrum 2.226 ^{13}C NMR (C_6D_6, 100 MHz) of compound **614**



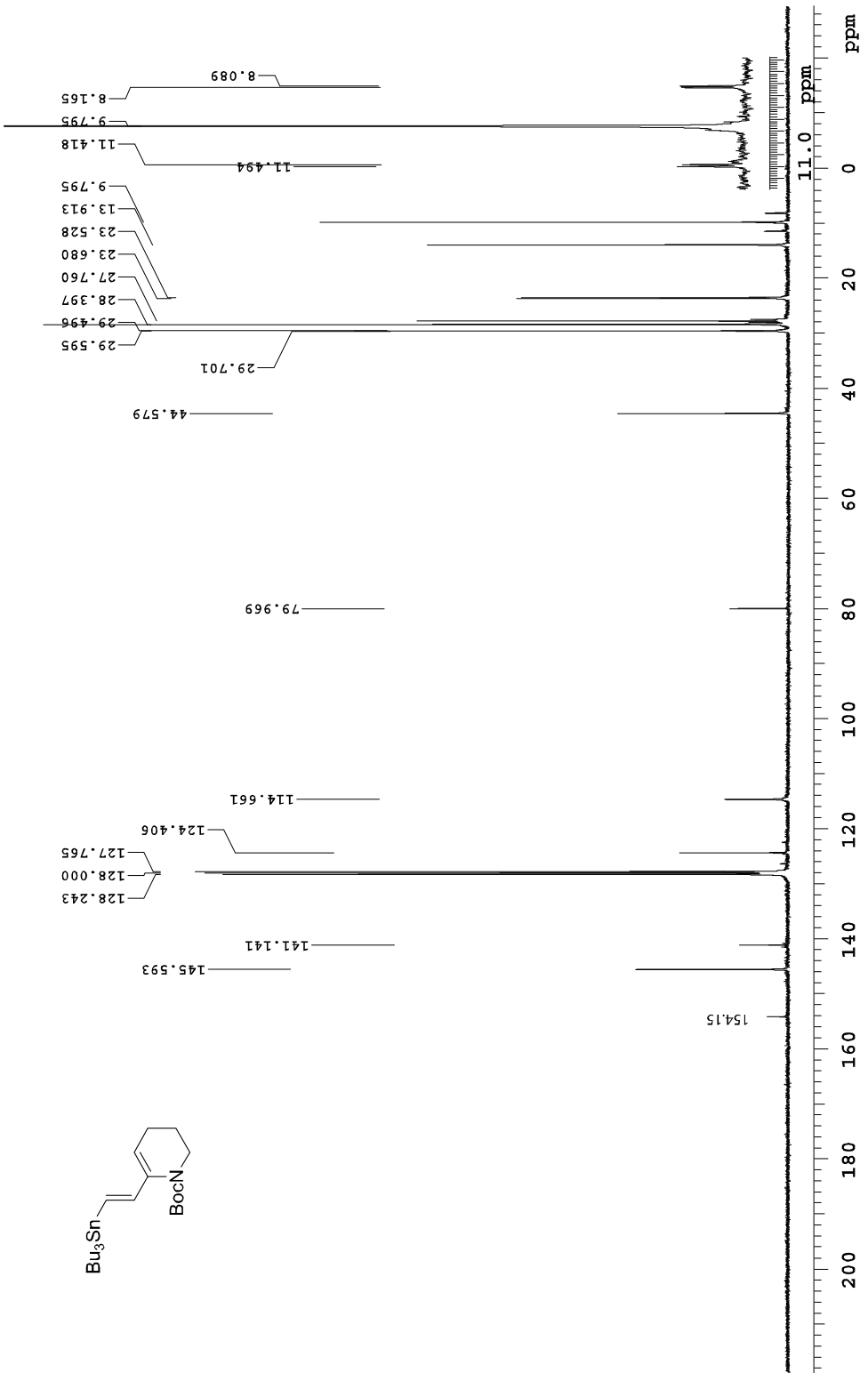
Spectrum 2.227 ^{1}H NMR (C_6D_6, 400 MHz) of compound **616**



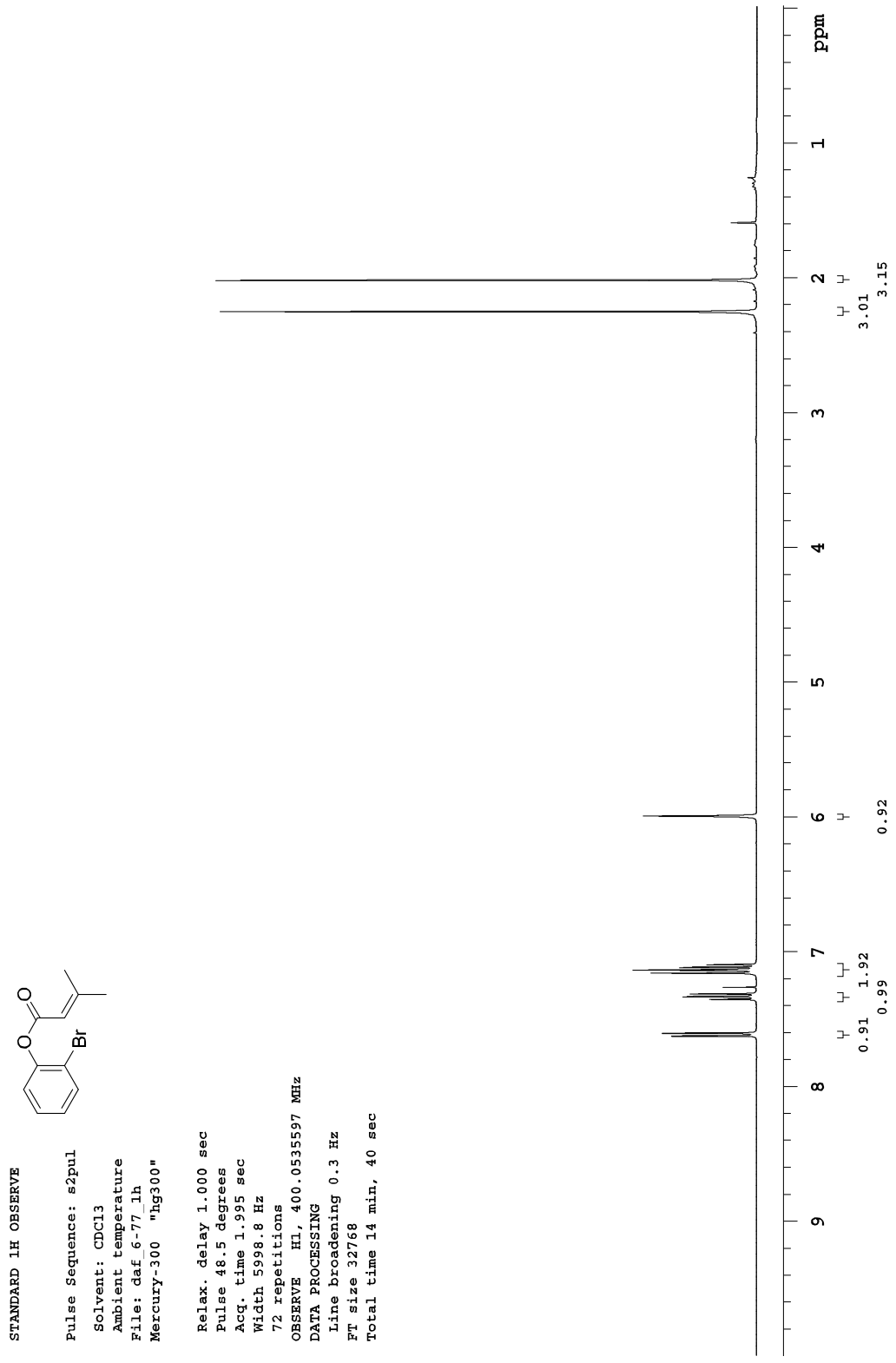
Spectrum 2.228 ^{13}C NMR (C_6D_6, 100 MHz) of compound **616**



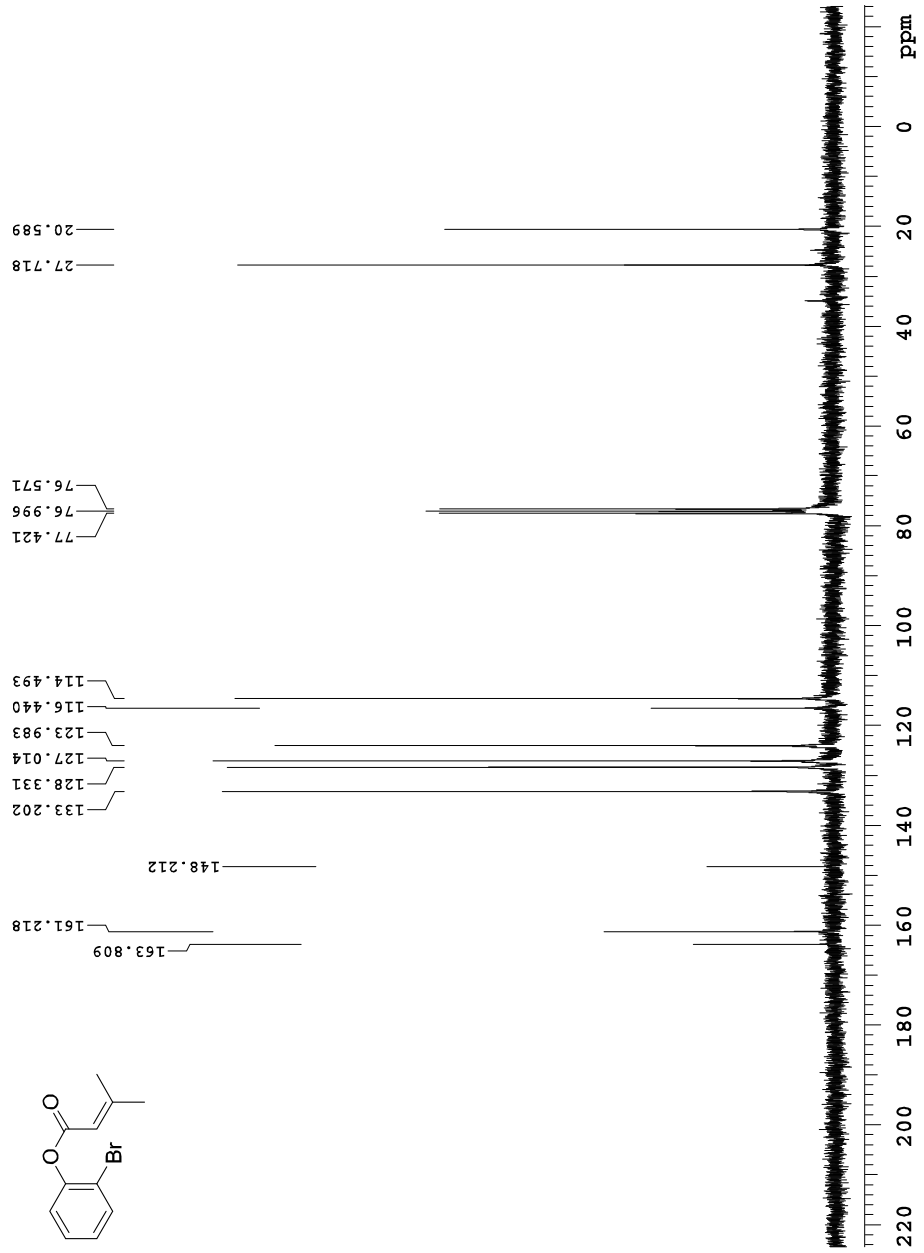
Spectrum 2.229 ^{1}H NMR (C_6D_6, 400 MHz) of compound **619**



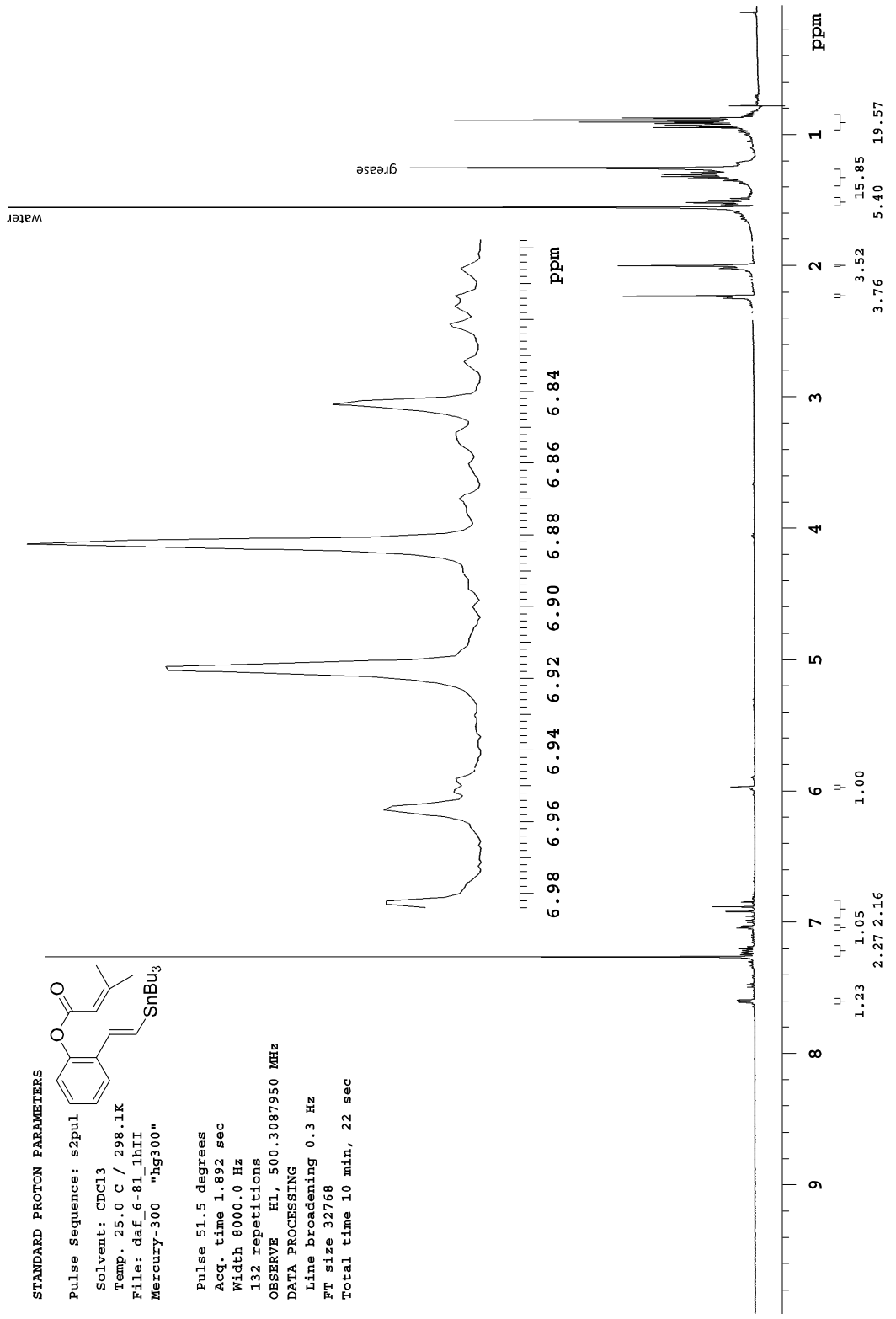
Spectrum 2.230 ^{13}C NMR (C_6D_6, 100 MHz) of compound **619**



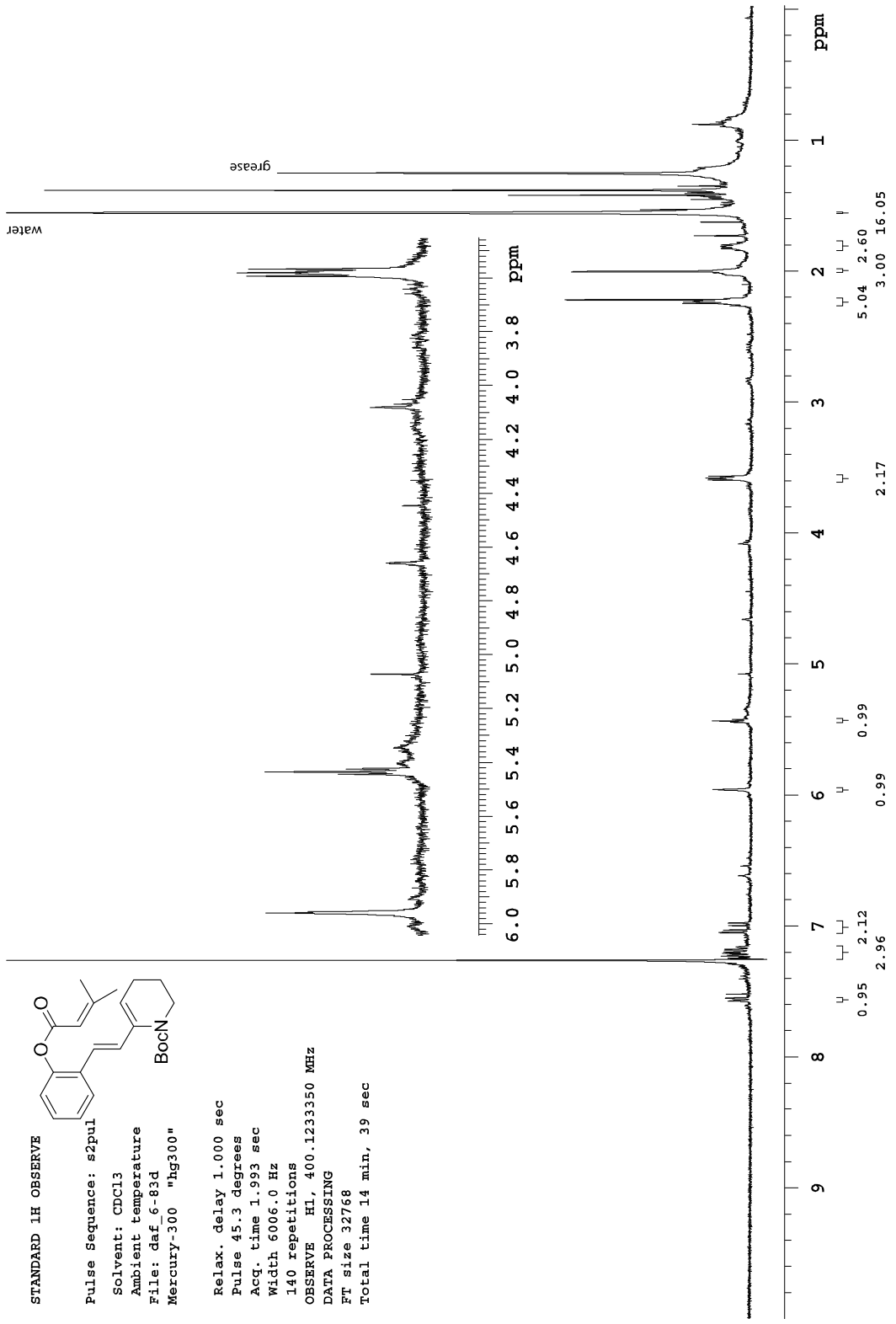
Spectrum 2.231 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **626**



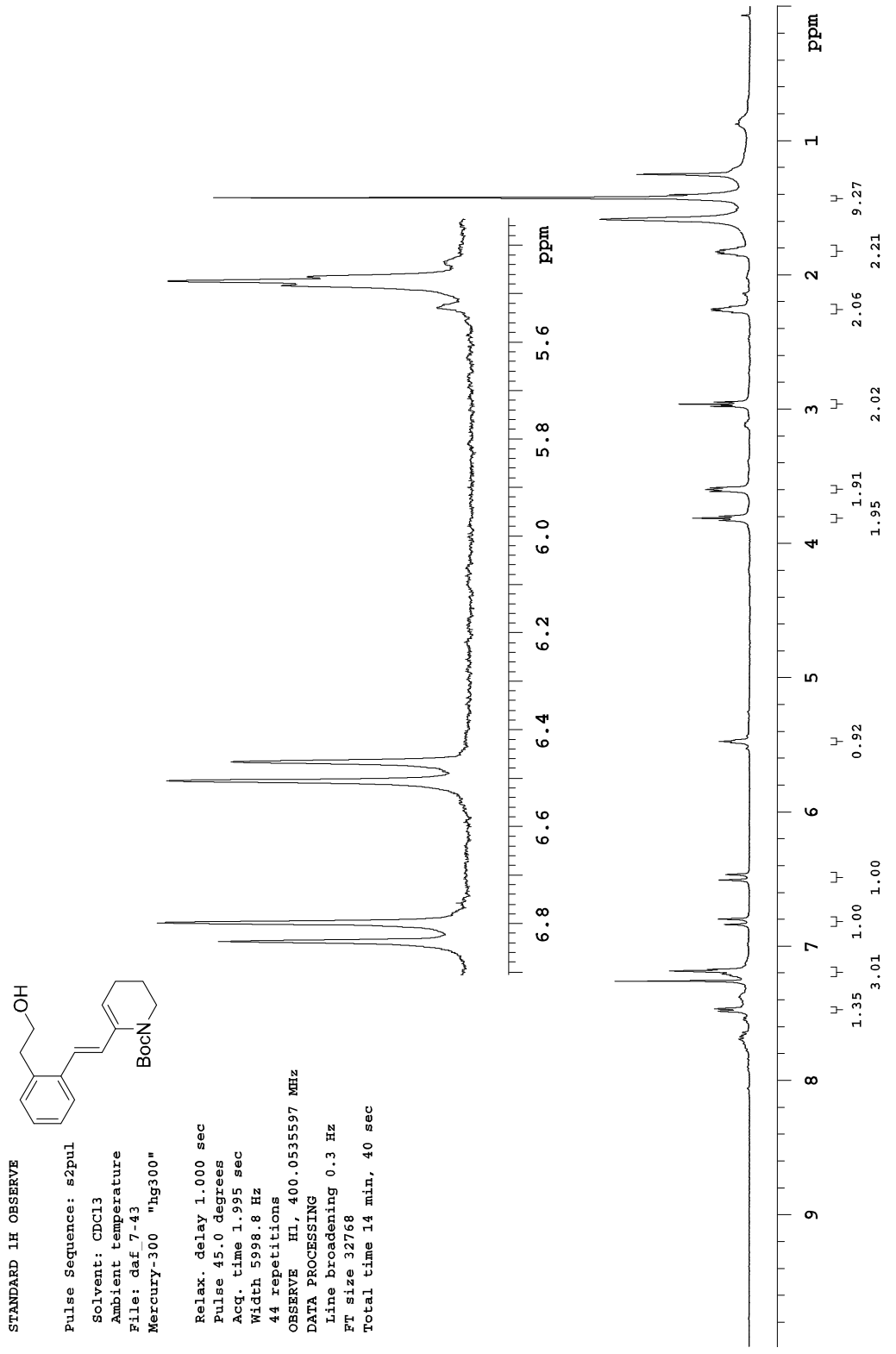
Spectrum 2.232 ^{13}C NMR ($CDCl_3$, 75 MHz) of compound **626**



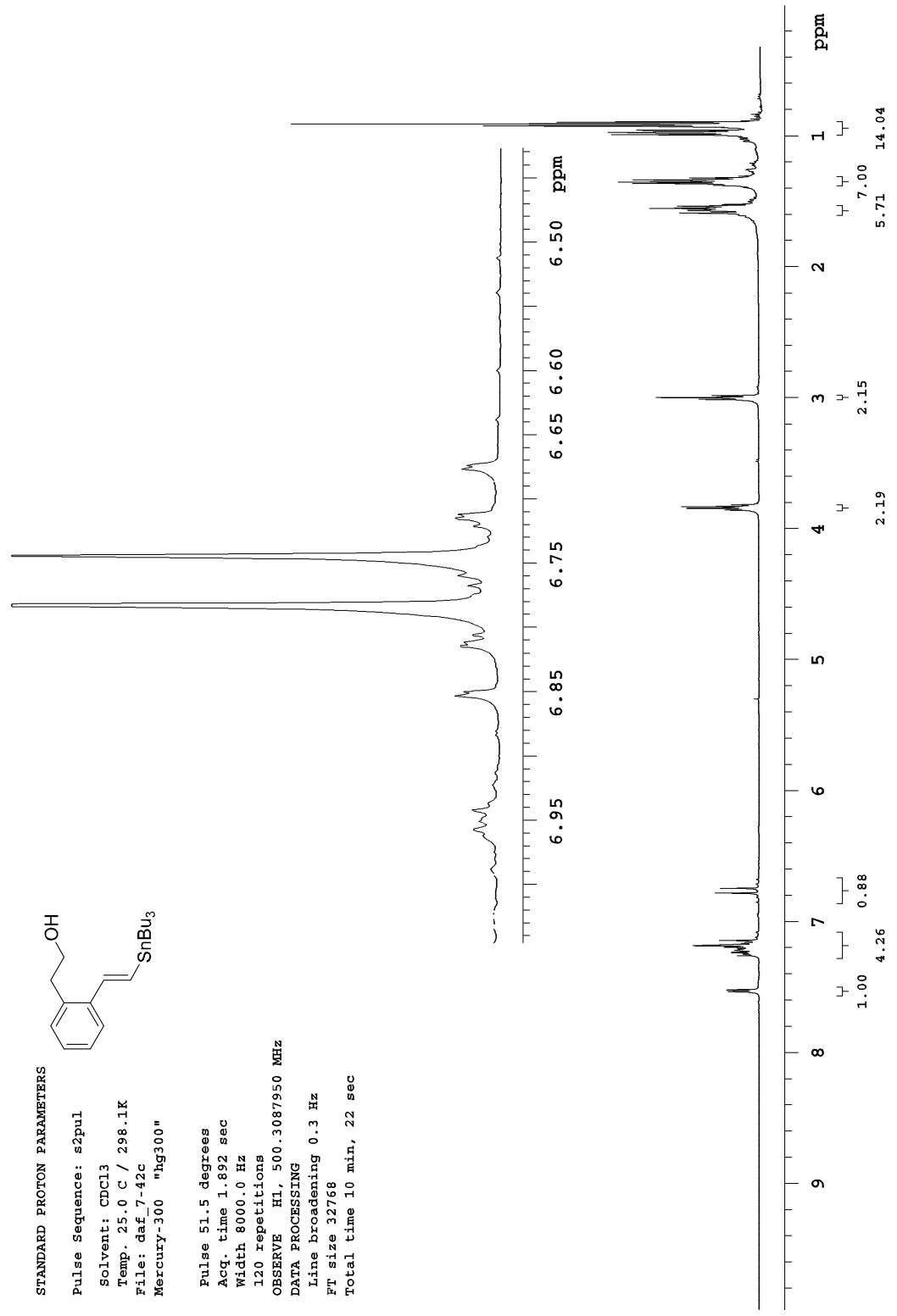
Spectrum 2.233 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **628**



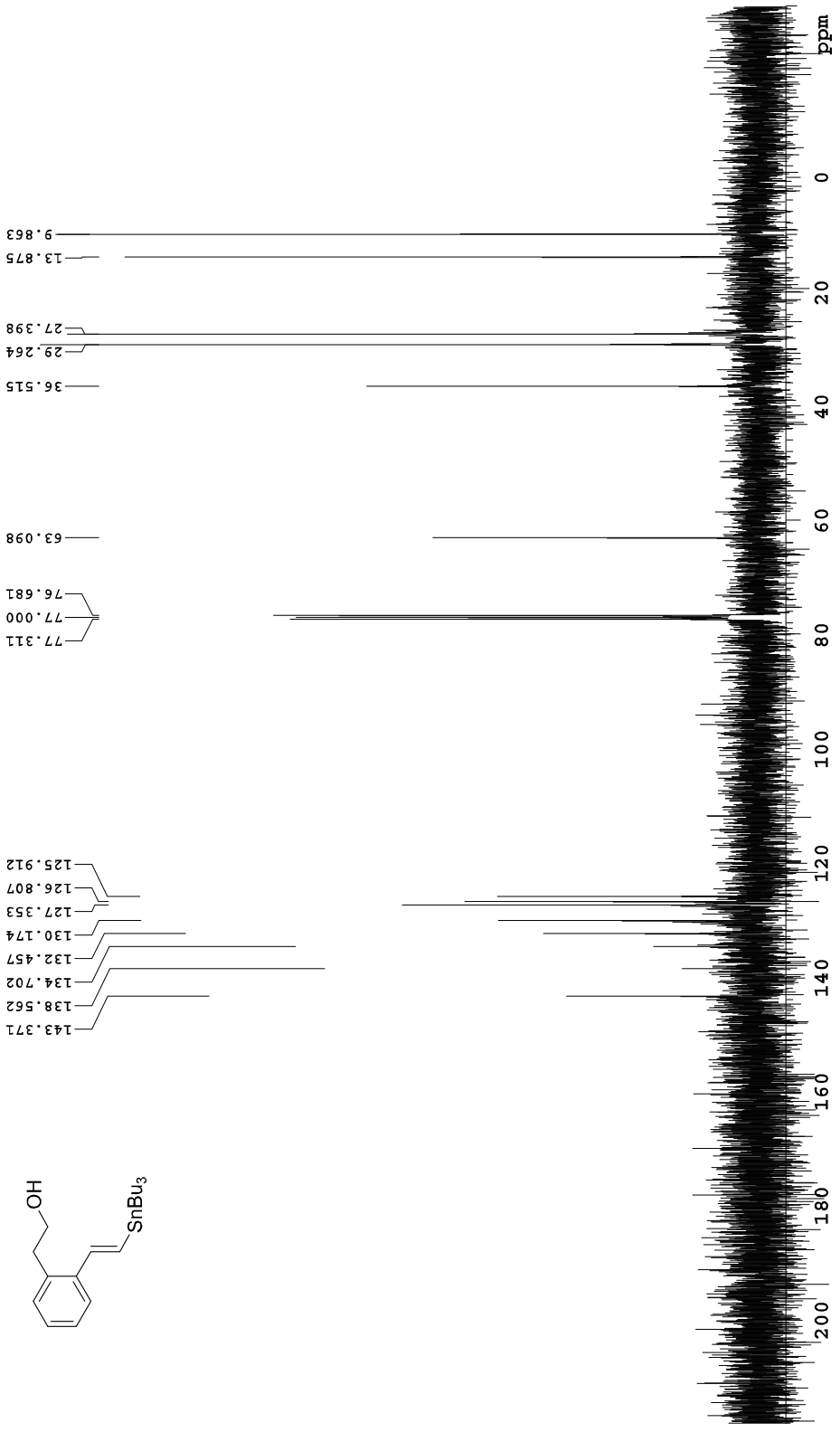
Spectrum 2.234 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **629**



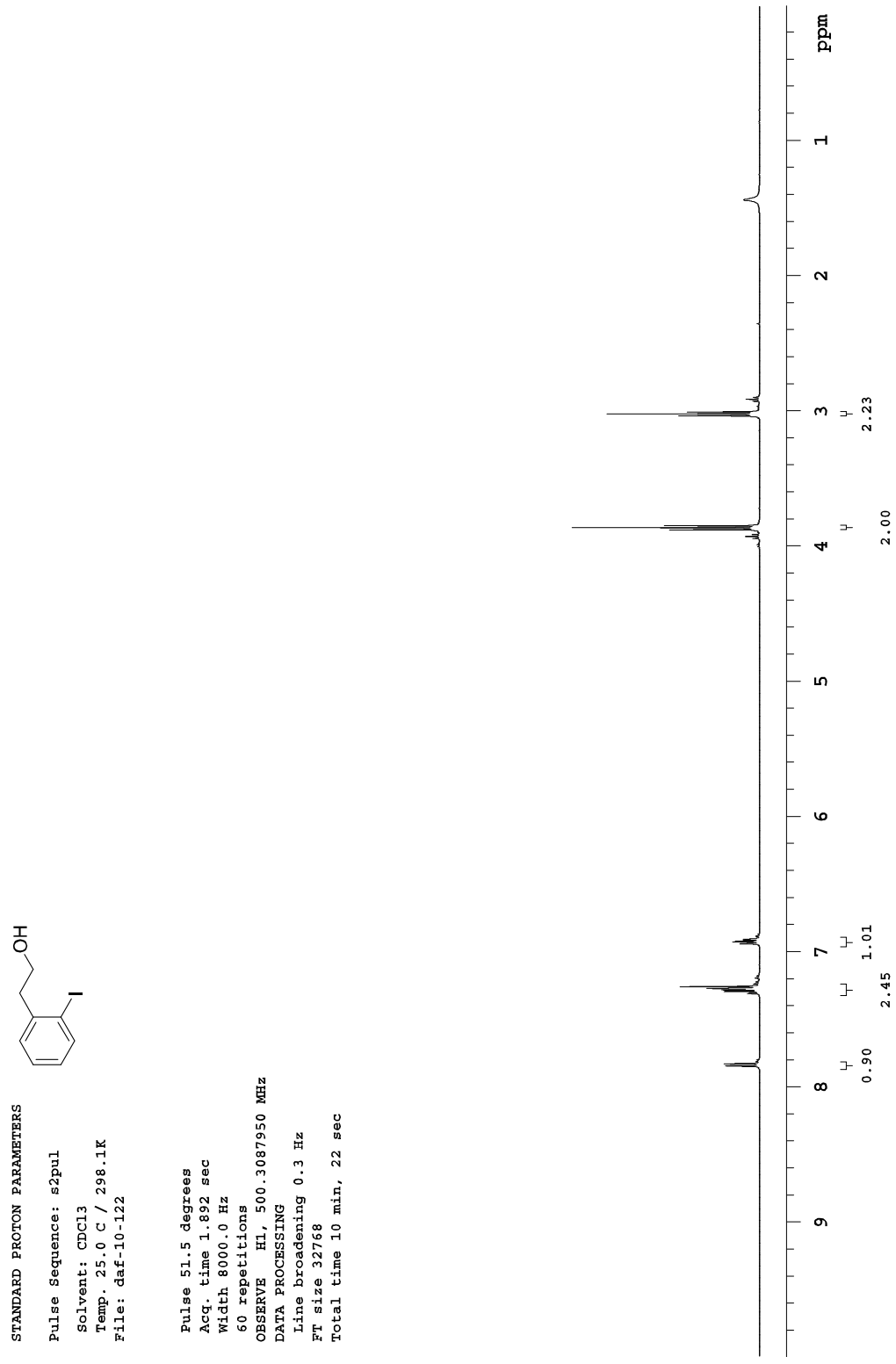
Spectrum 2.235 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **630**



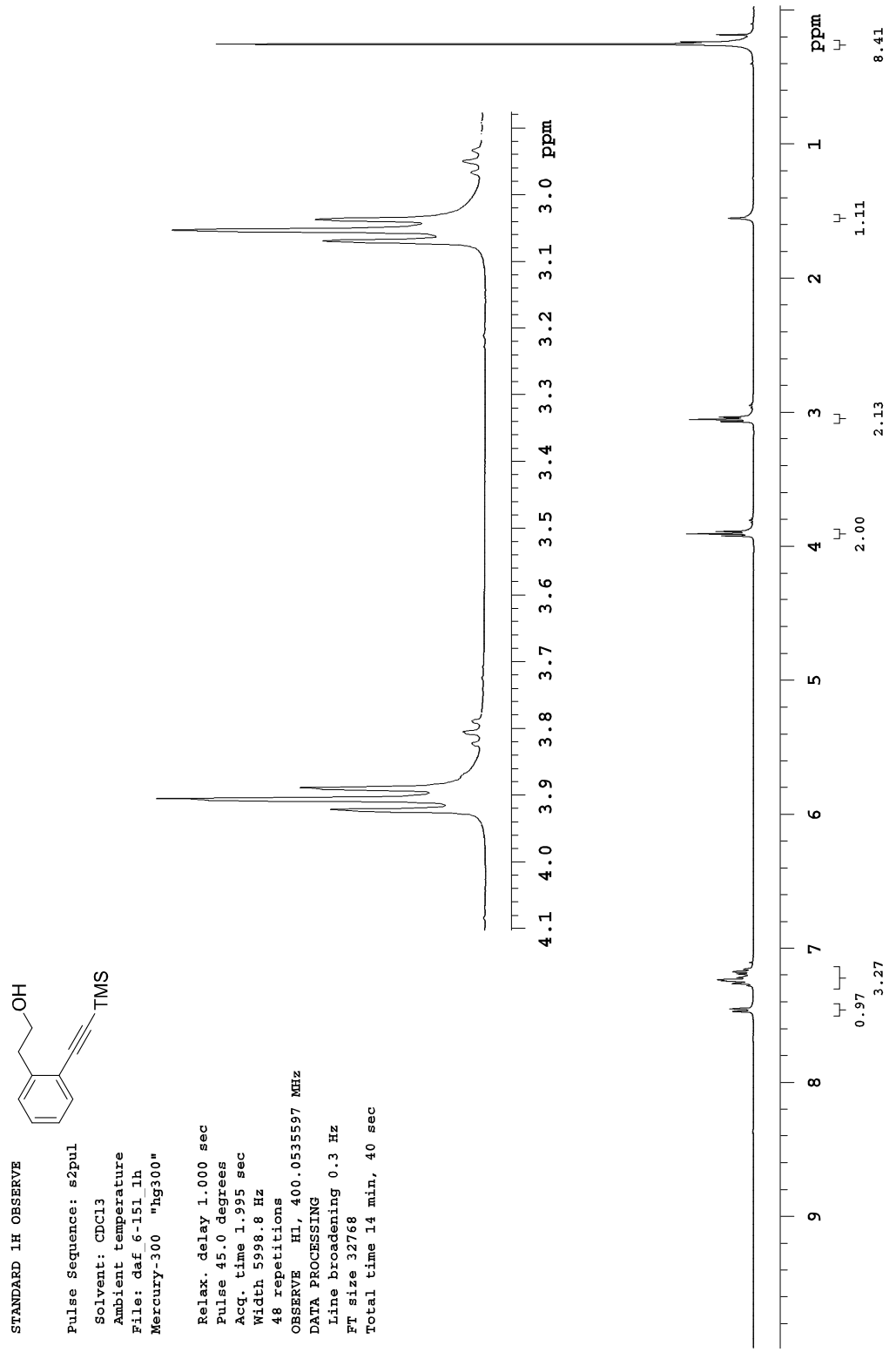
Spectrum 2.236 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **631**



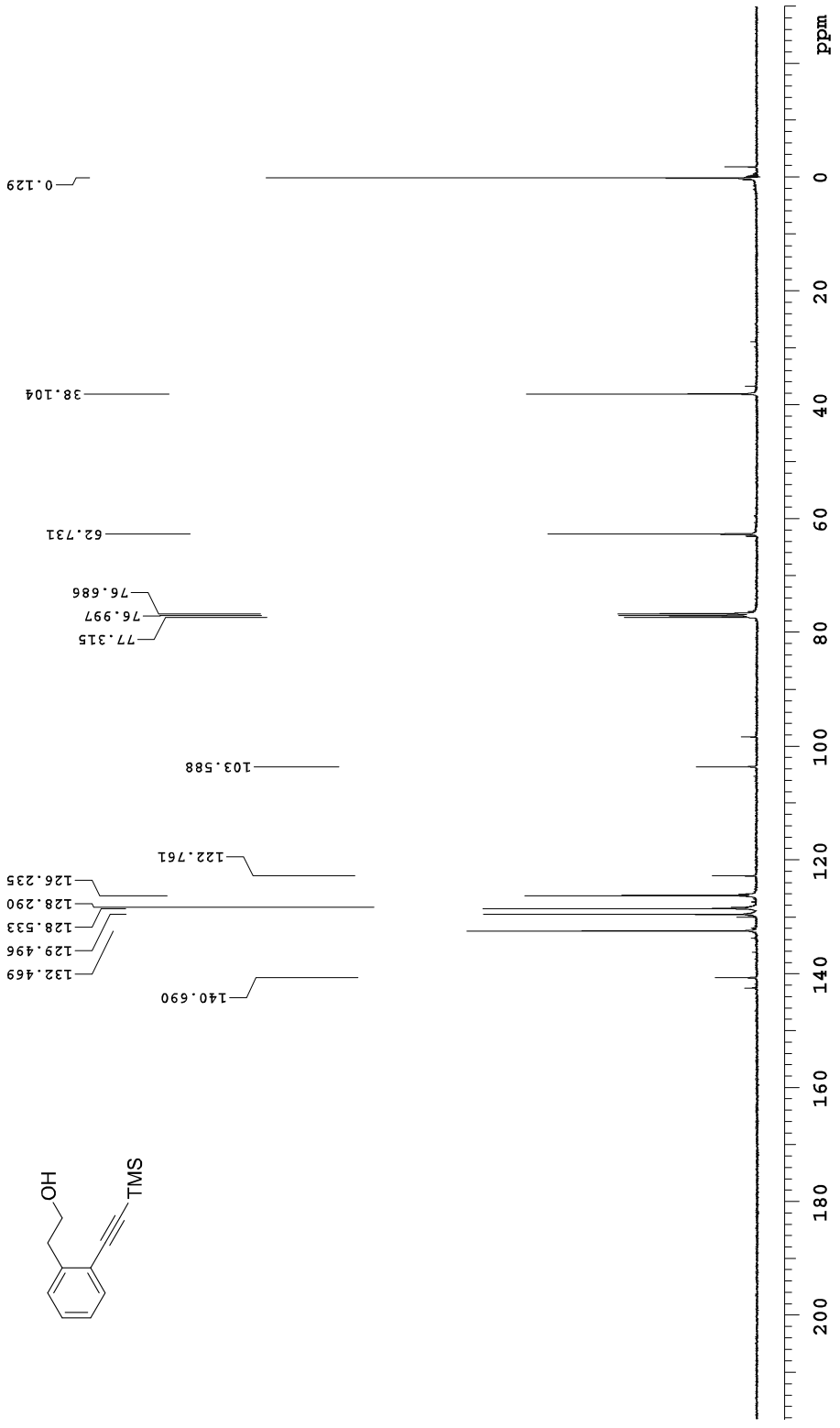
Spectrum 2.237 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **631**



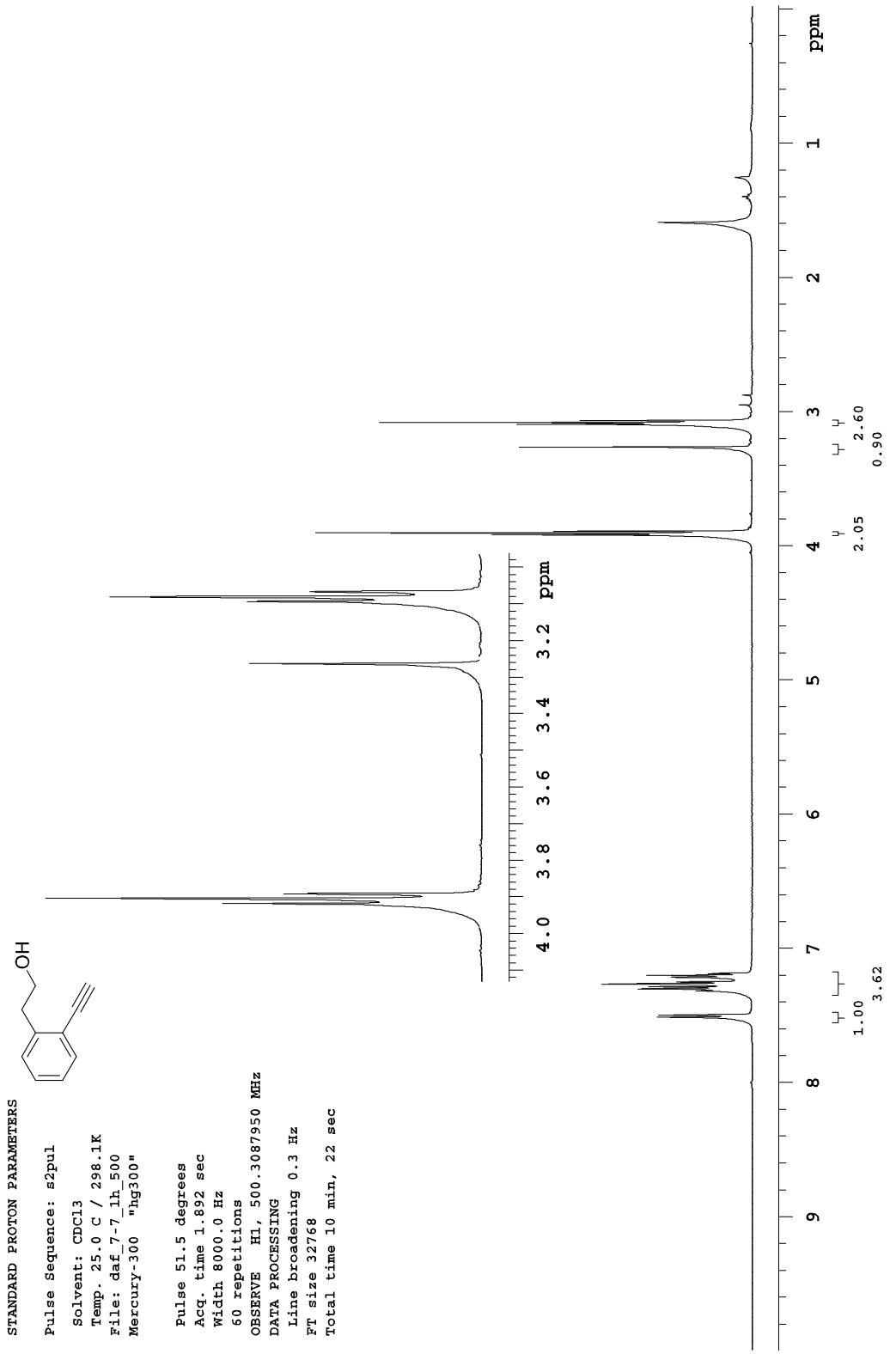
Spectrum 2.238 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **633**



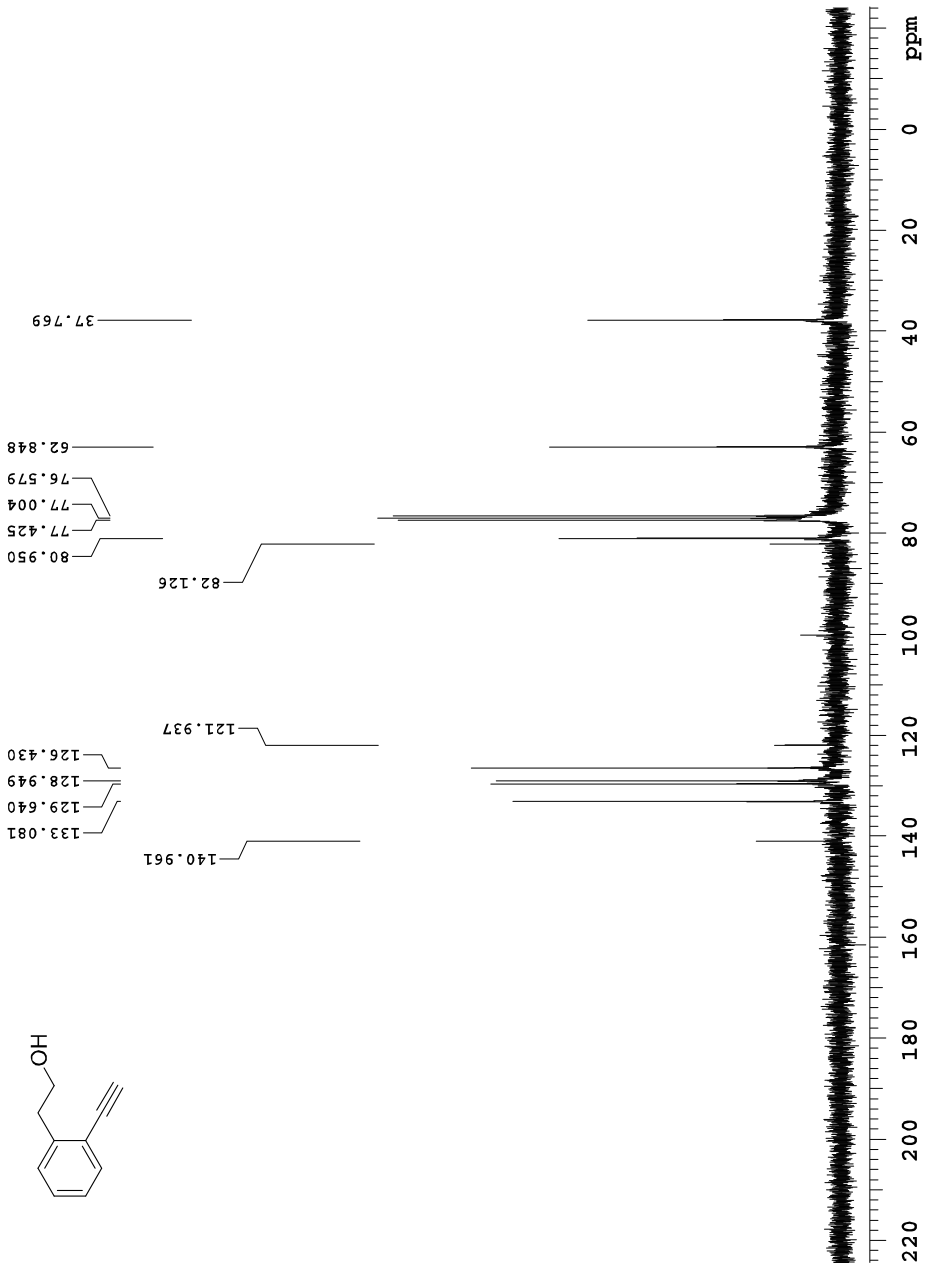
Spectrum 2.239 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **634**



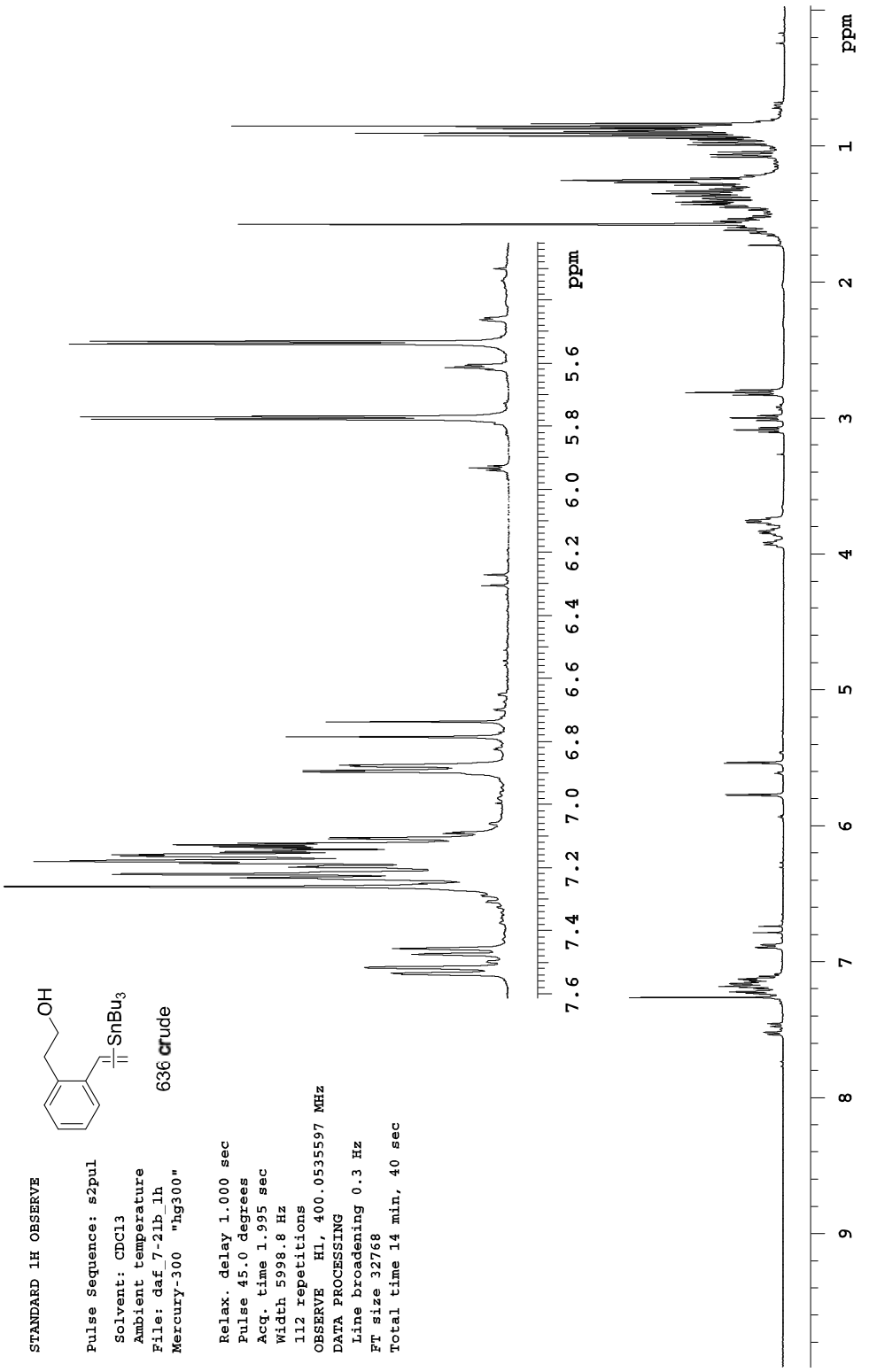
Spectrum 2.240 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **634**



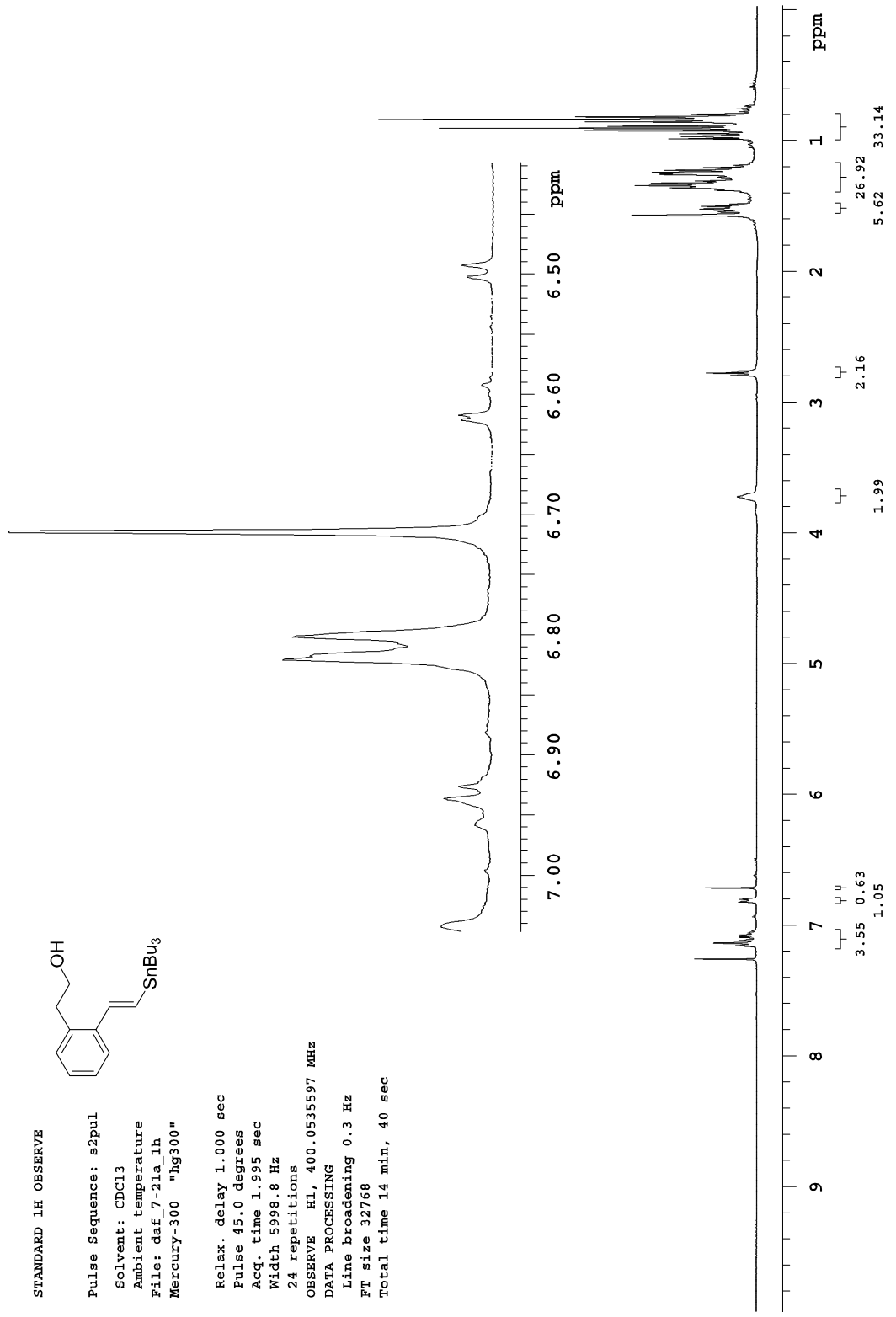
Spectrum 2.241 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **635**



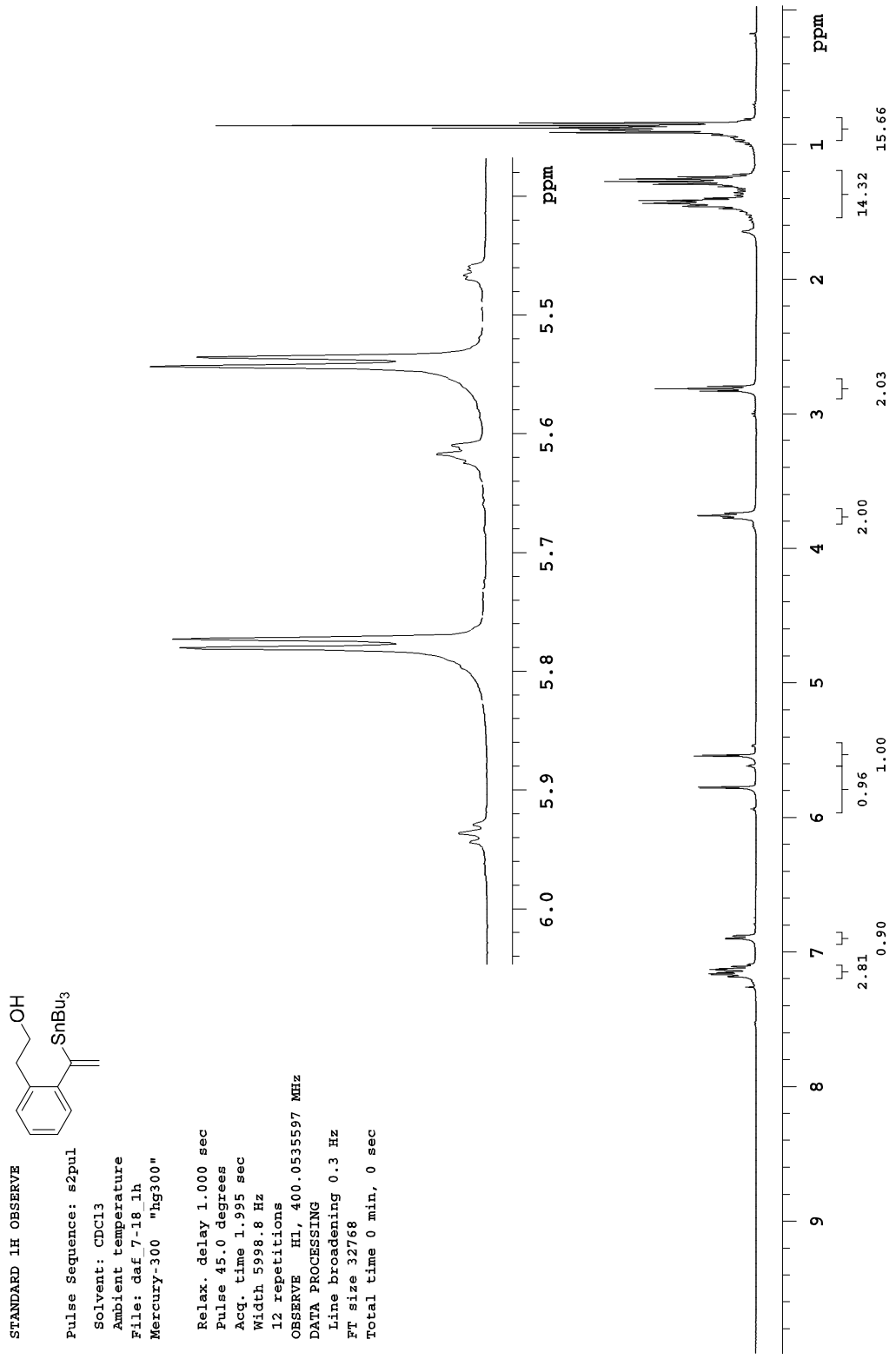
Spectrum 2.242 ^{13}C NMR ($CDCl_3$, 75 MHz) of compound **635**



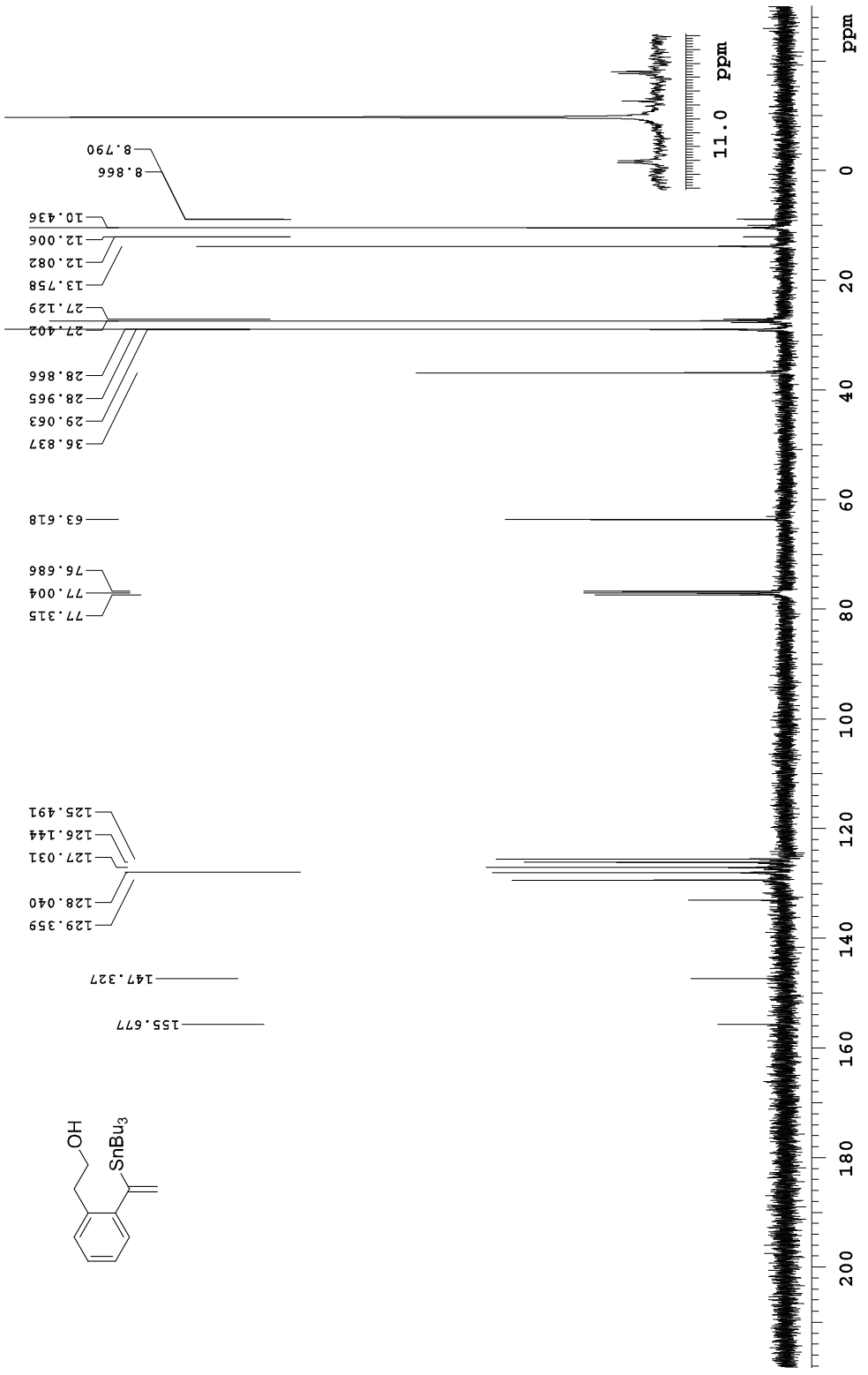
Spectrum 2.243 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **636 crude**



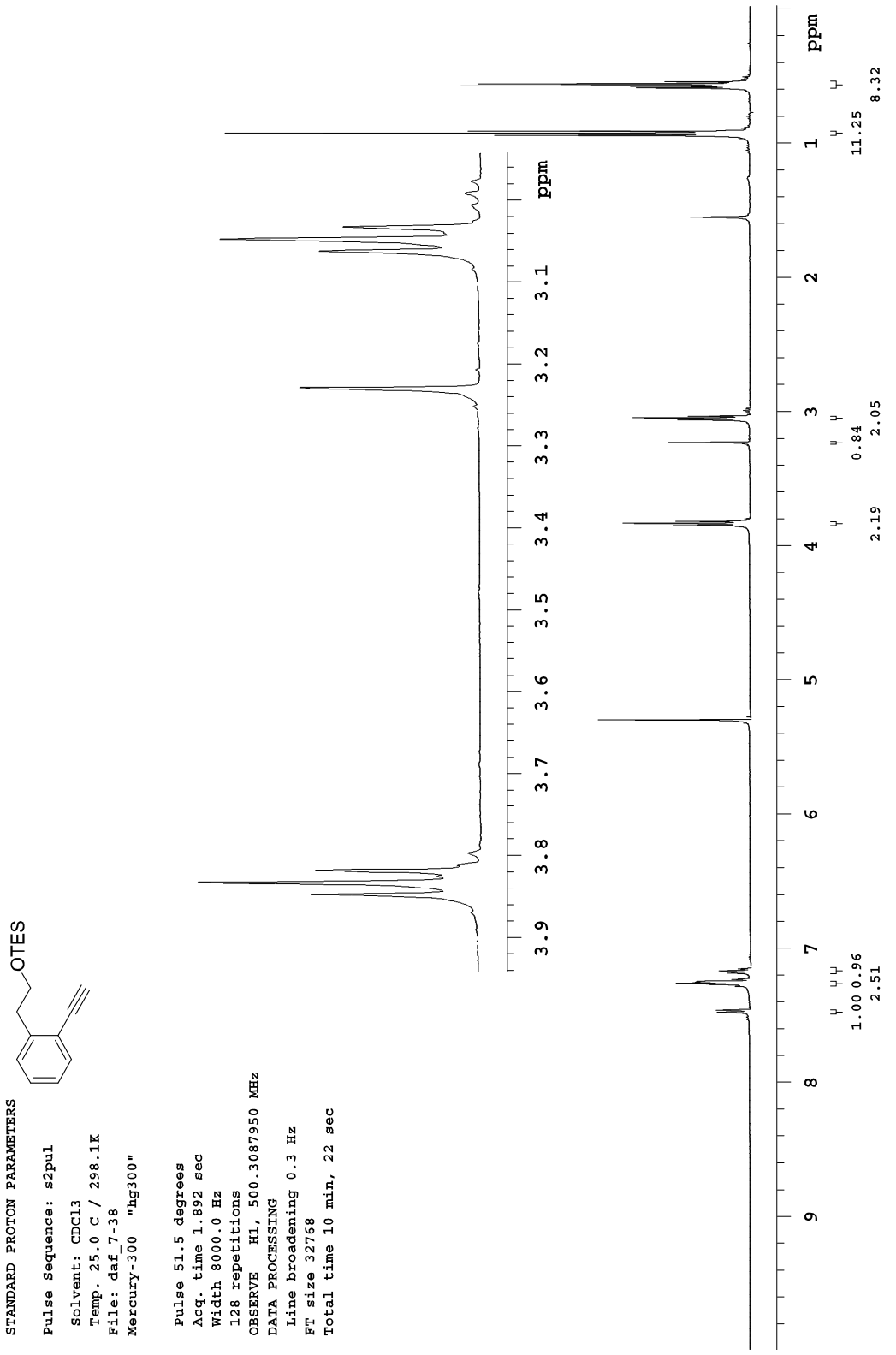
Spectrum 2.244 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **636a**



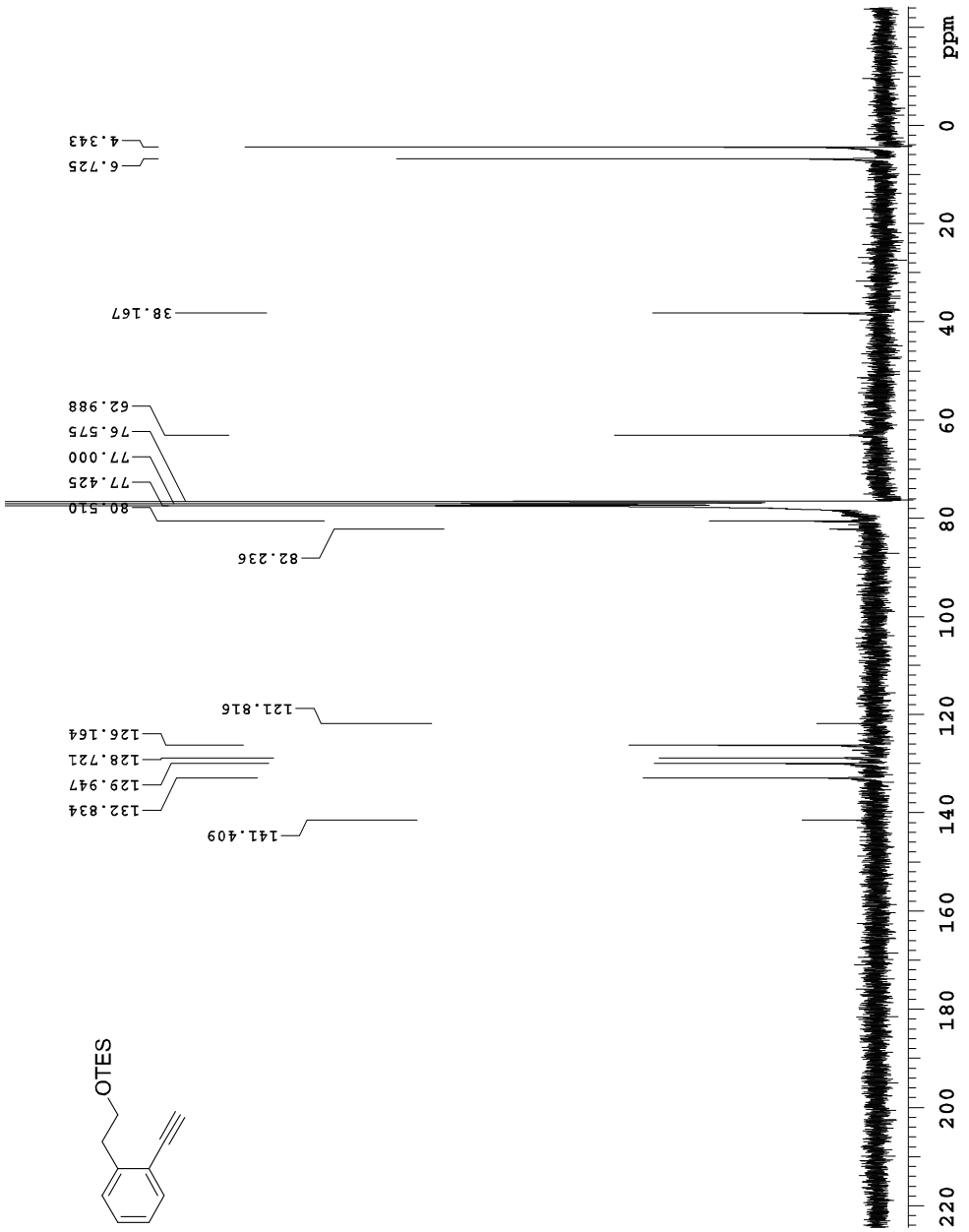
Spectrum 2.245 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **636b**



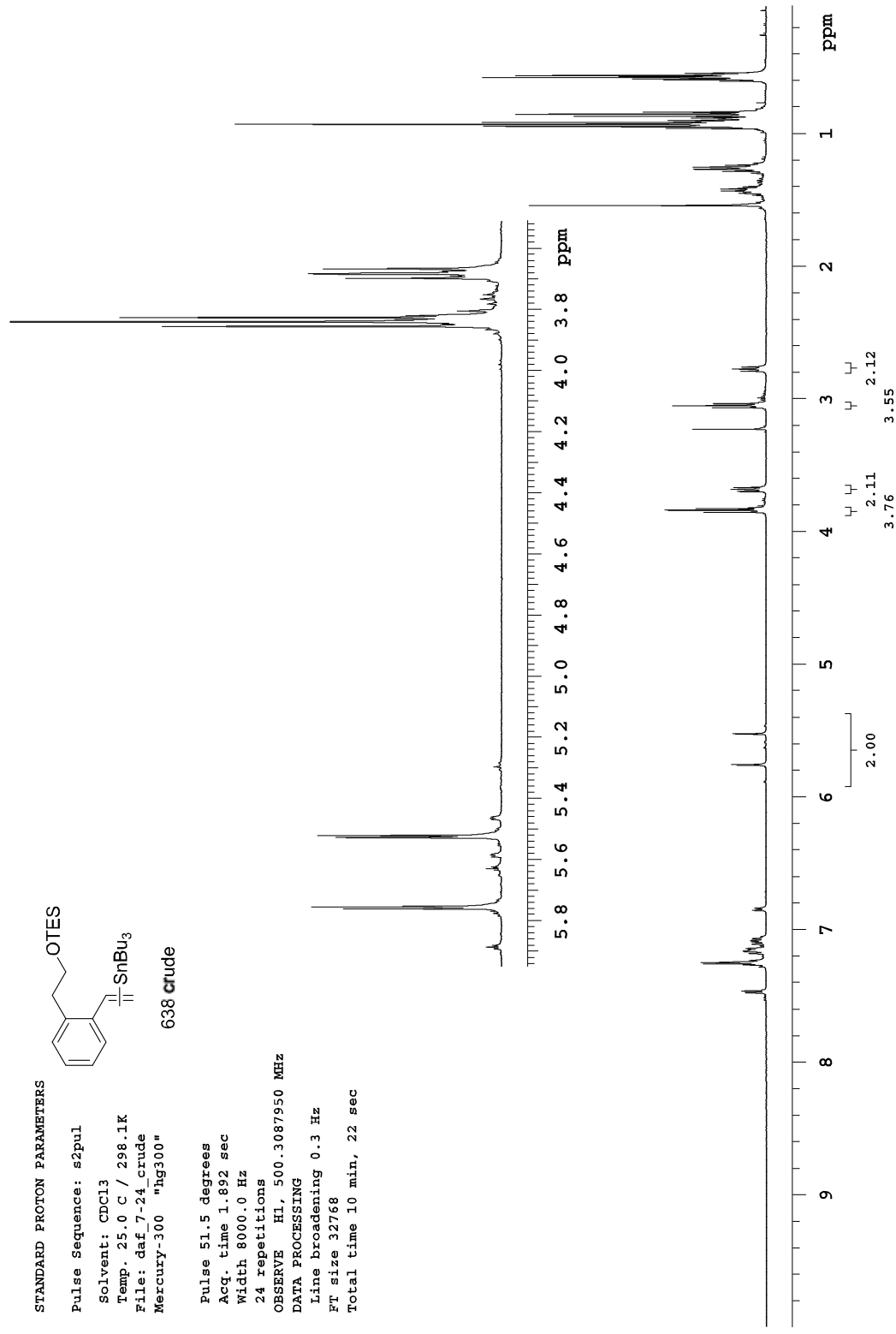
Spectrum 2.246 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **636b**



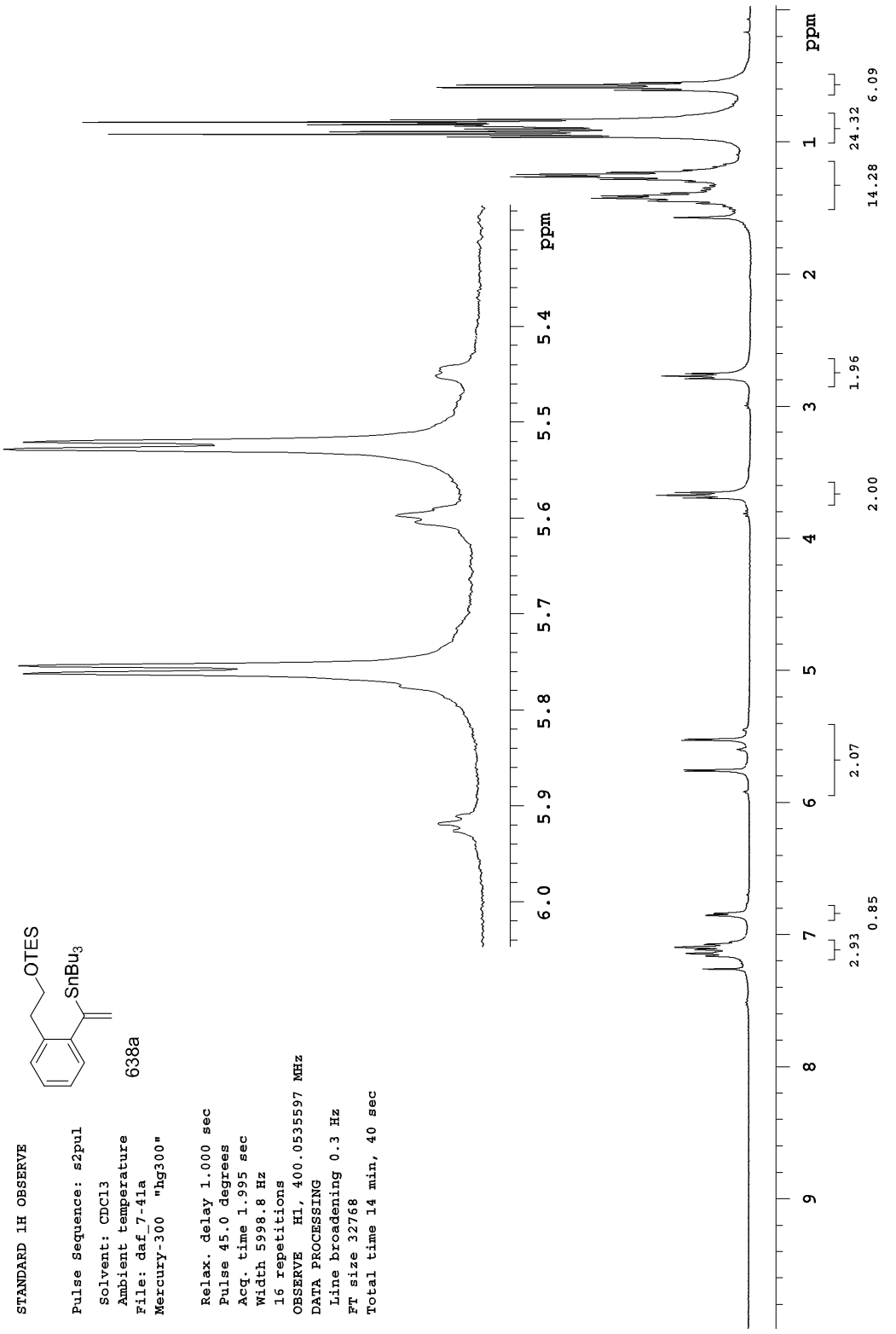
Spectrum 2.247 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **637**



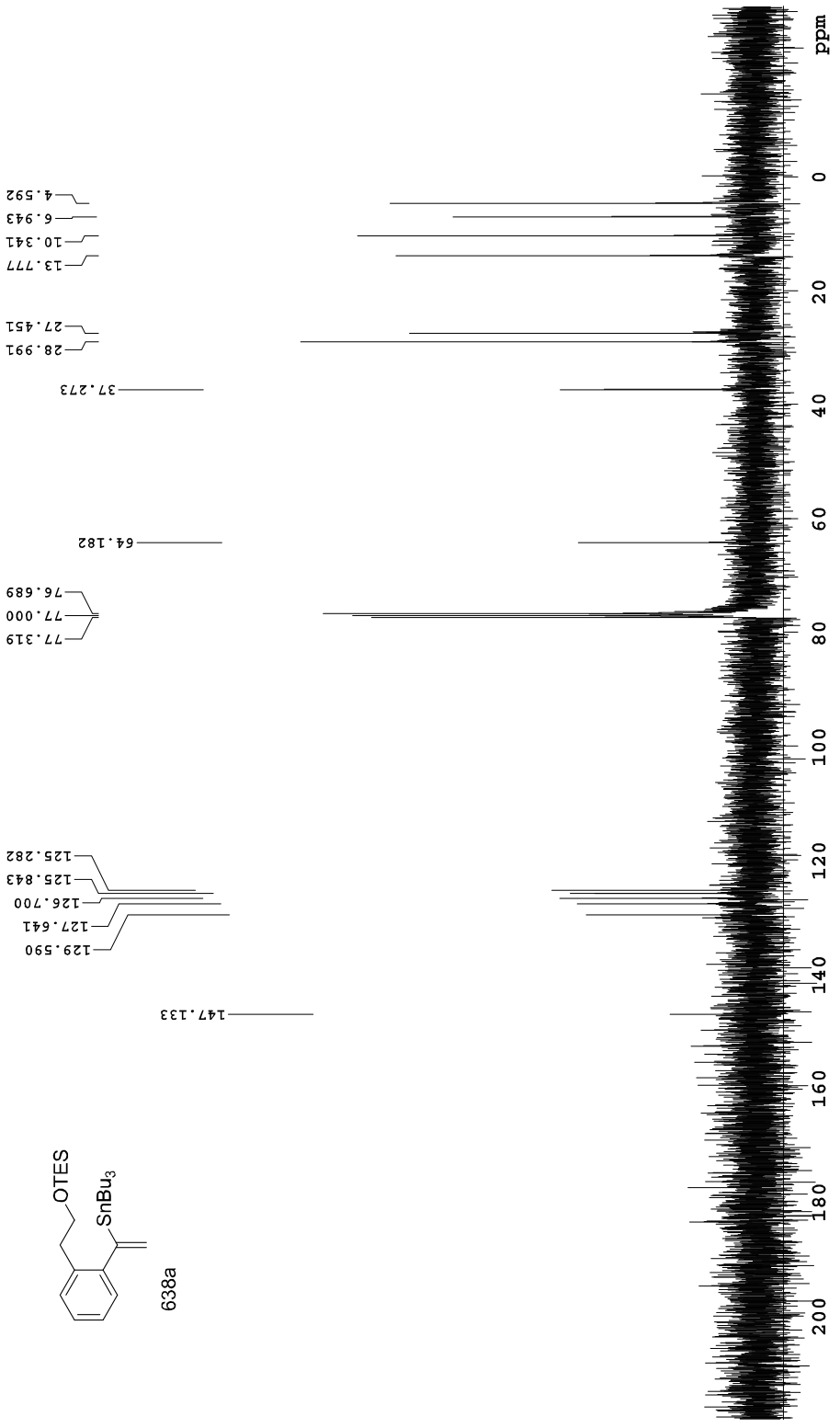
Spectrum 2.248 ^{13}C NMR ($CDCl_3$, 75 MHz) of compound **637**



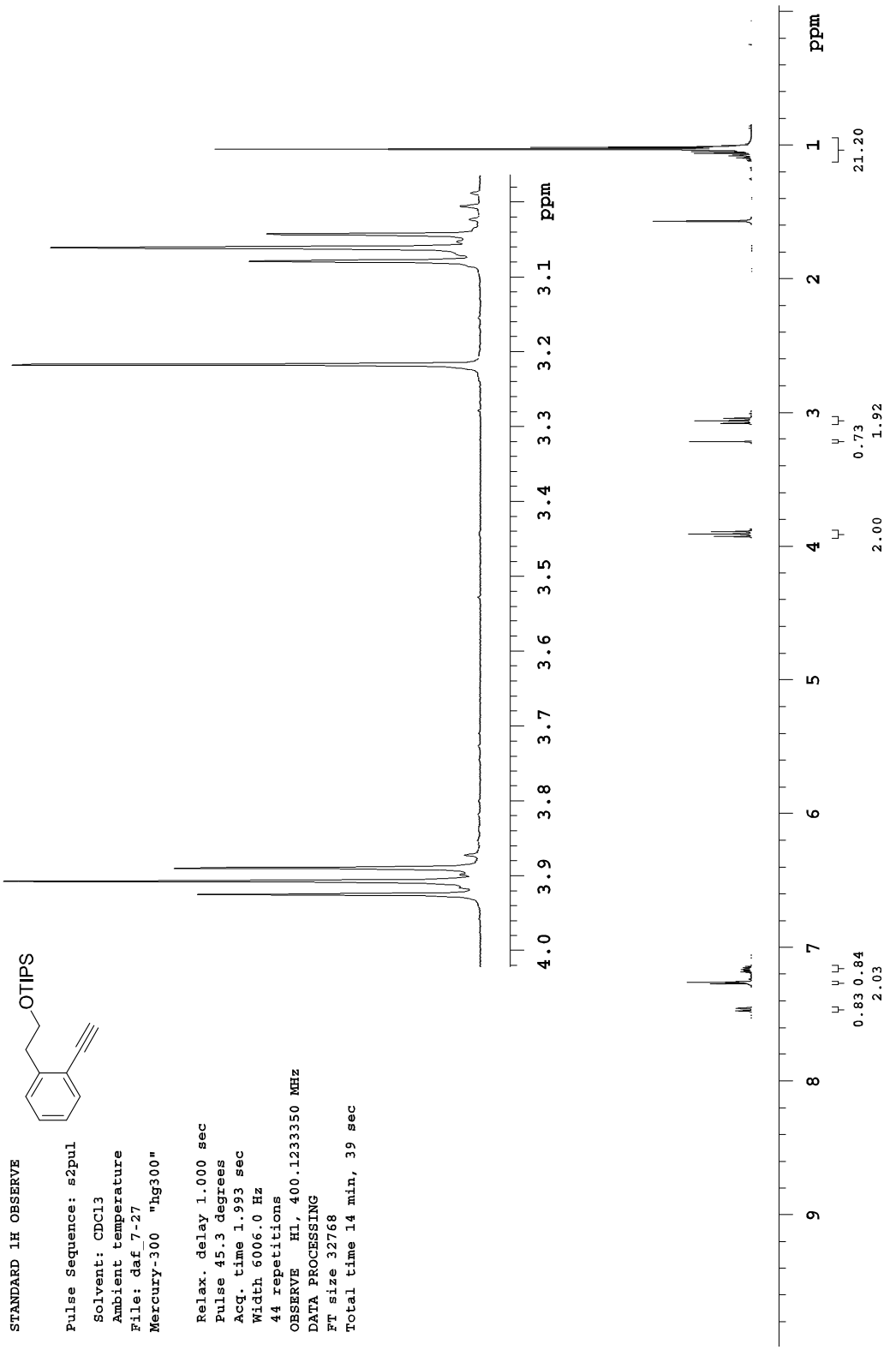
Spectrum 2.249 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **638 crude**



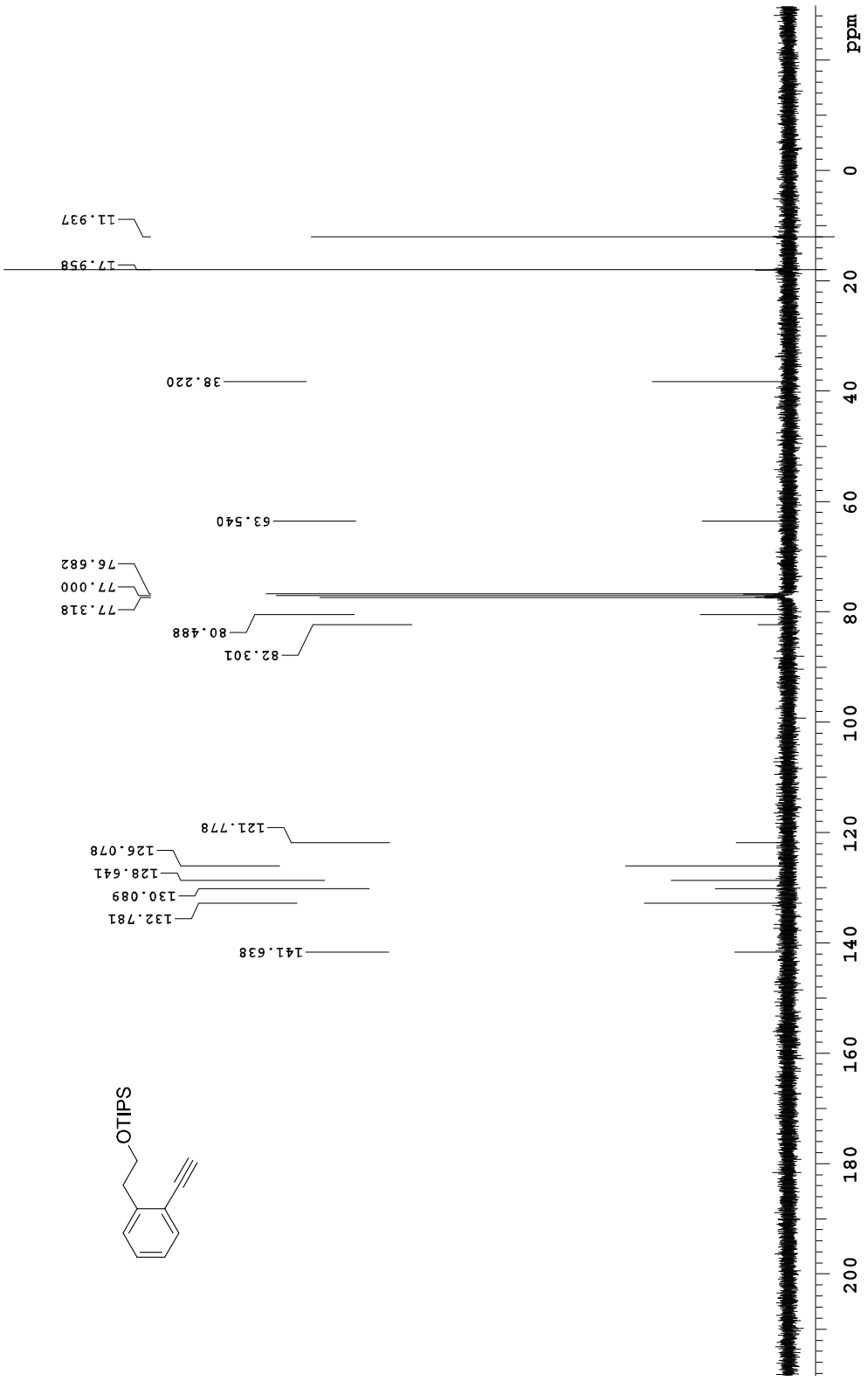
Spectrum 2.250 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **638a**



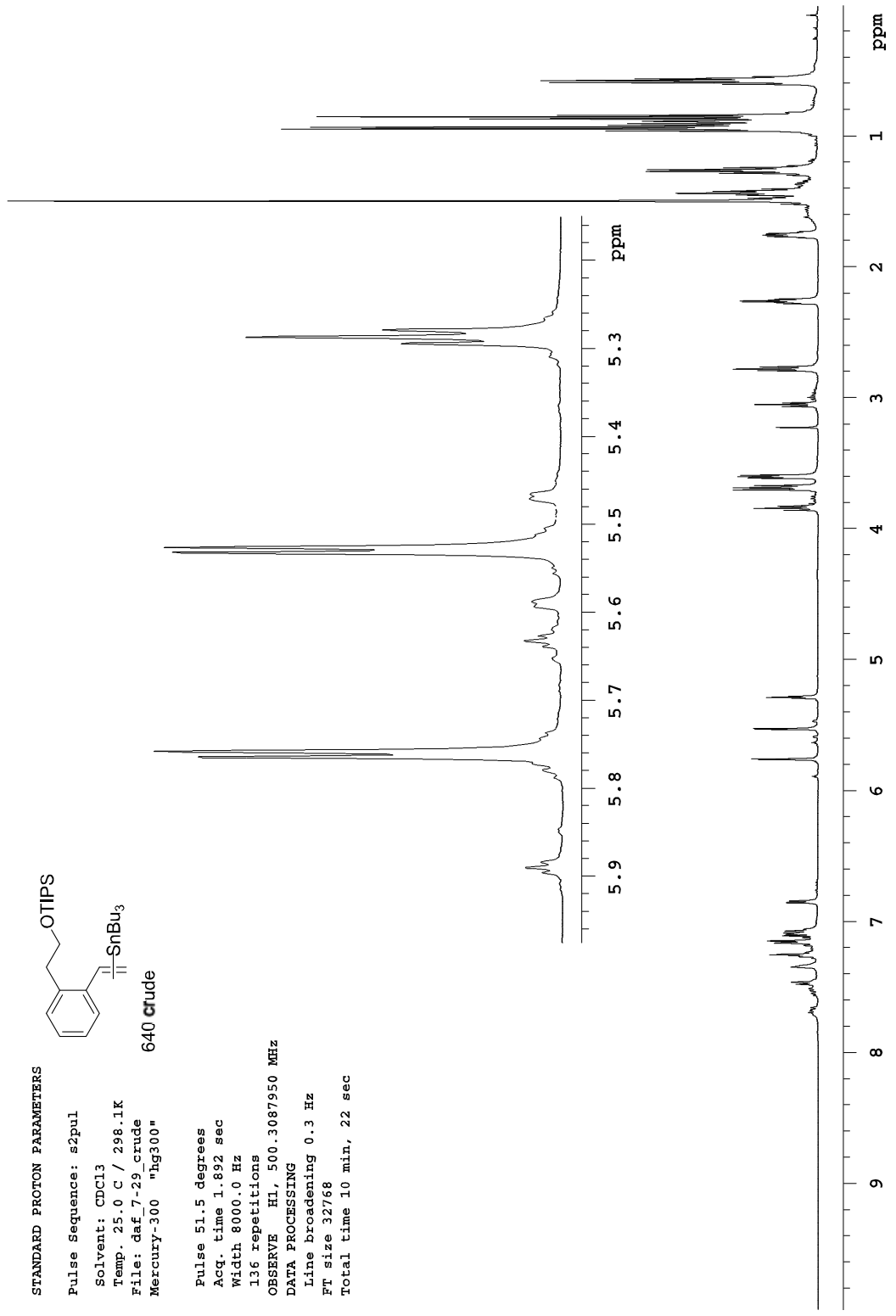
Spectrum 2.251 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **638a**



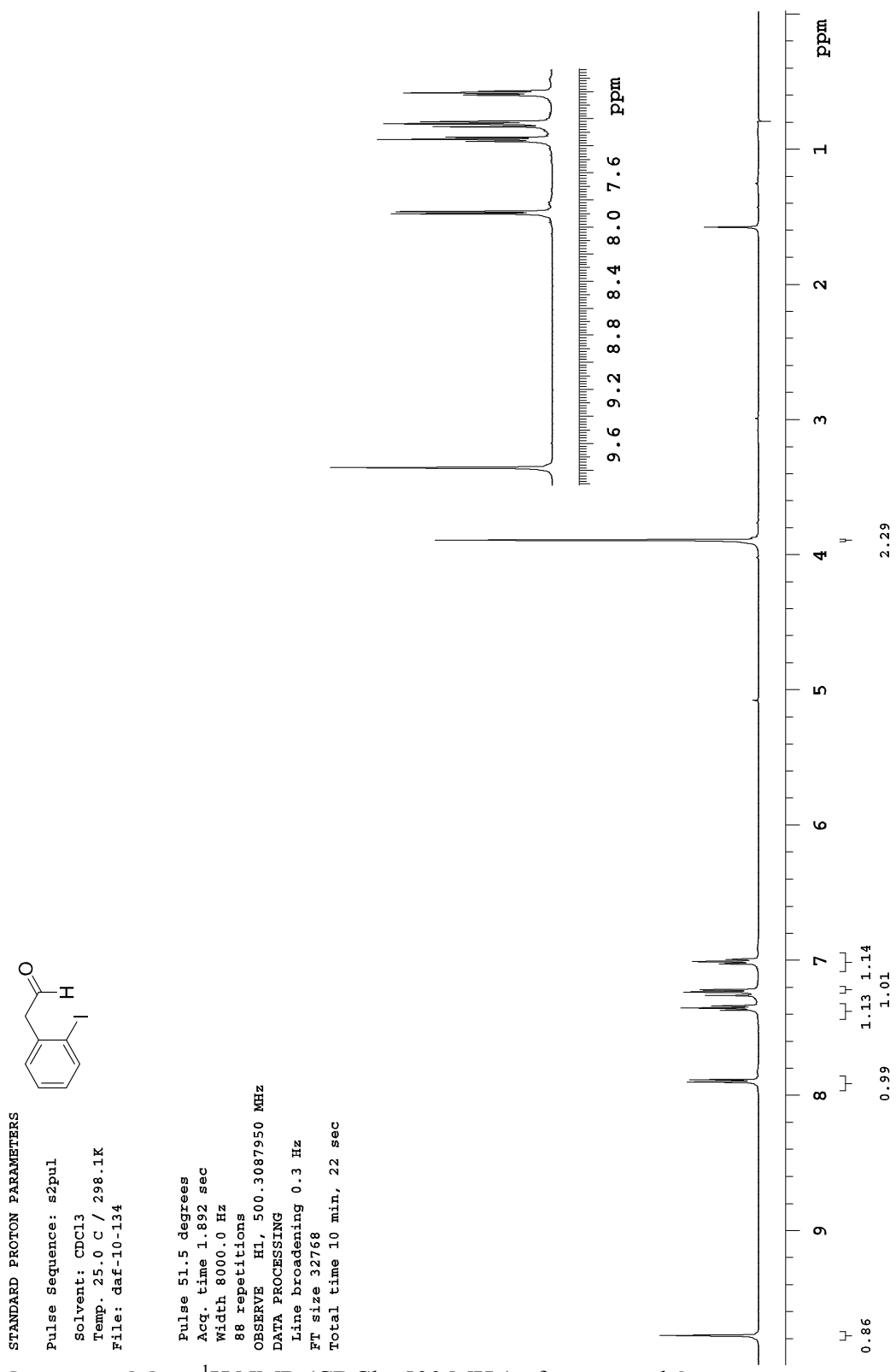
Spectrum 2.252 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **639**



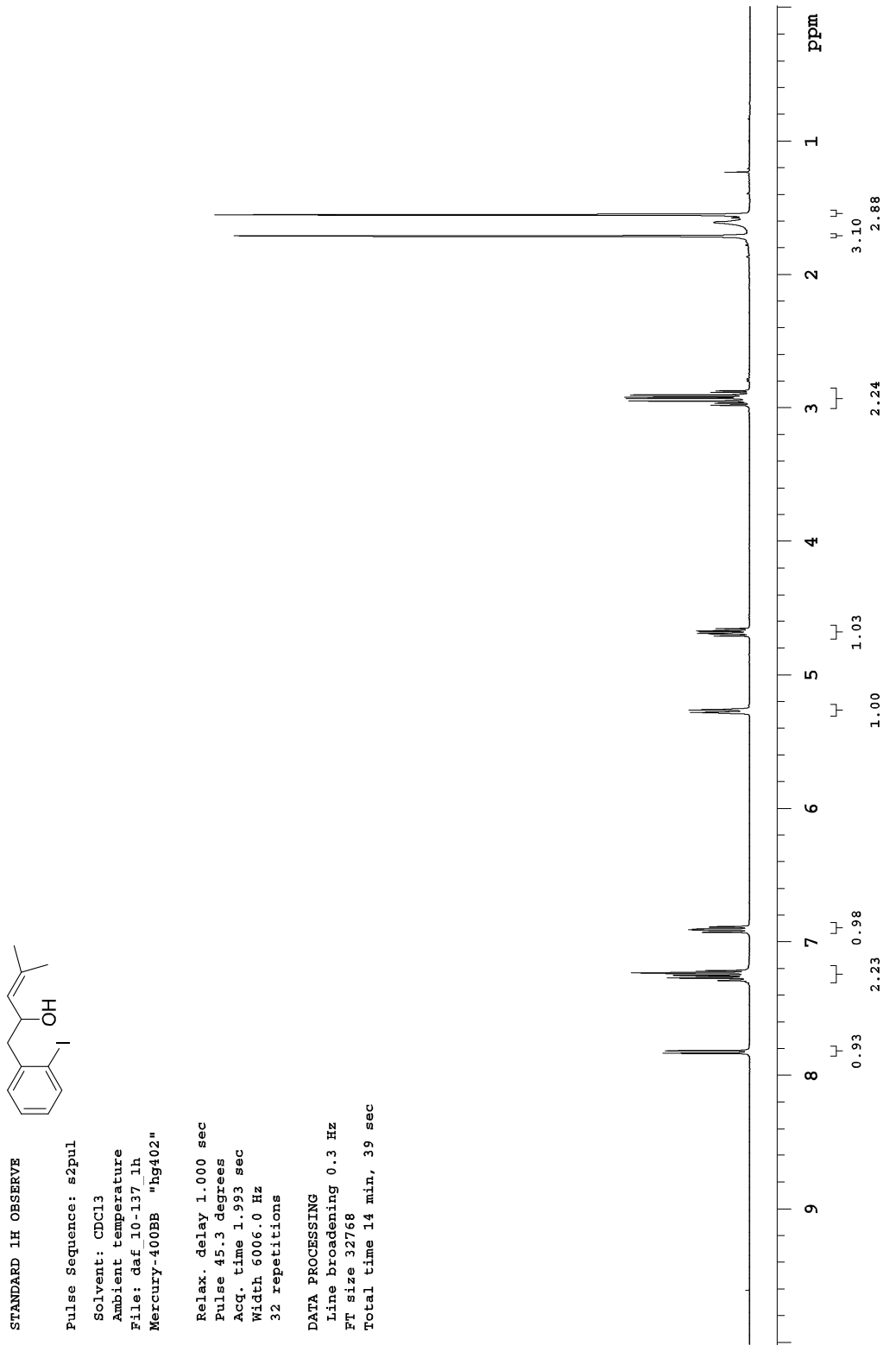
Spectrum 2.253 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **639**



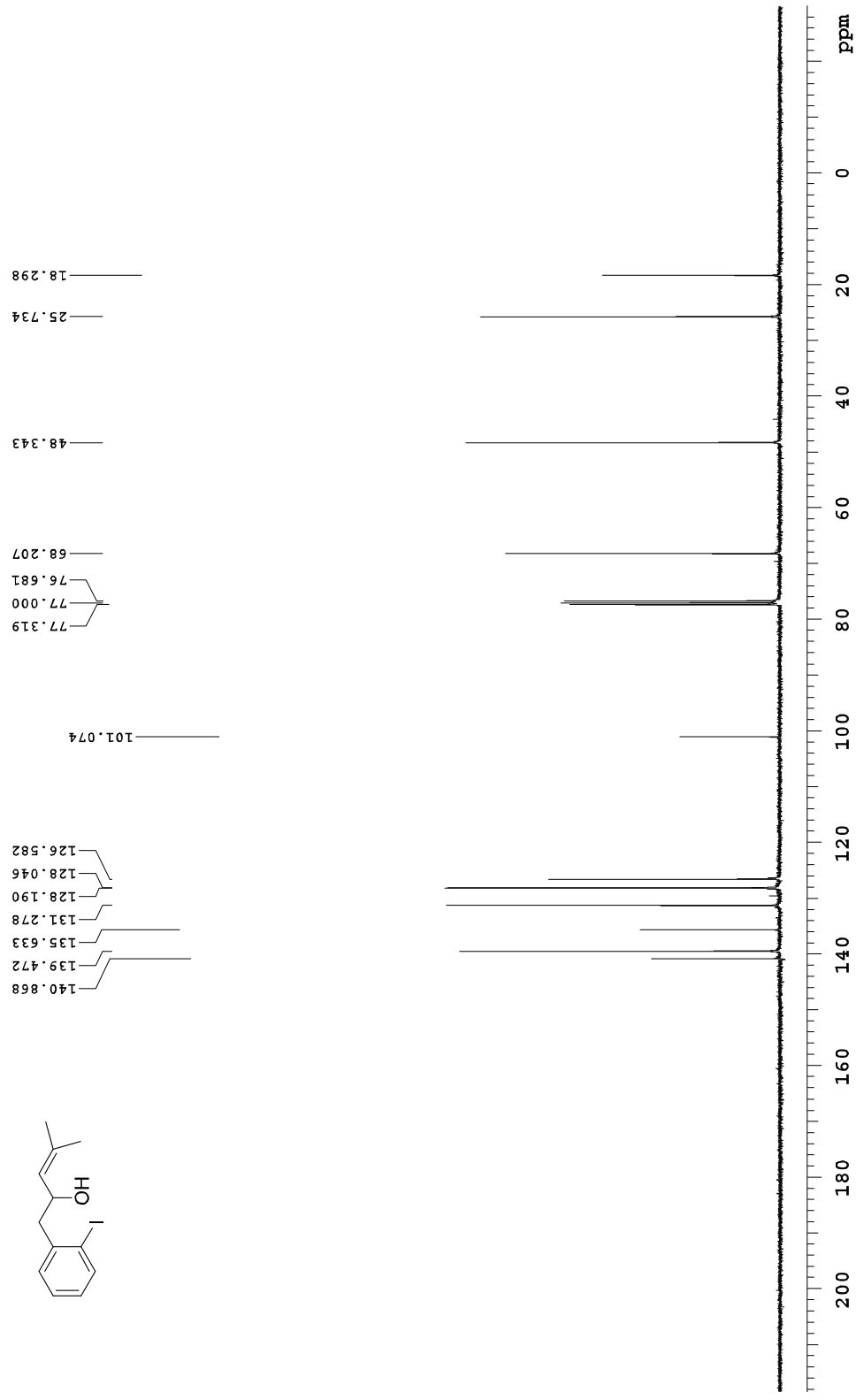
Spectrum 2.254 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **640 crude**



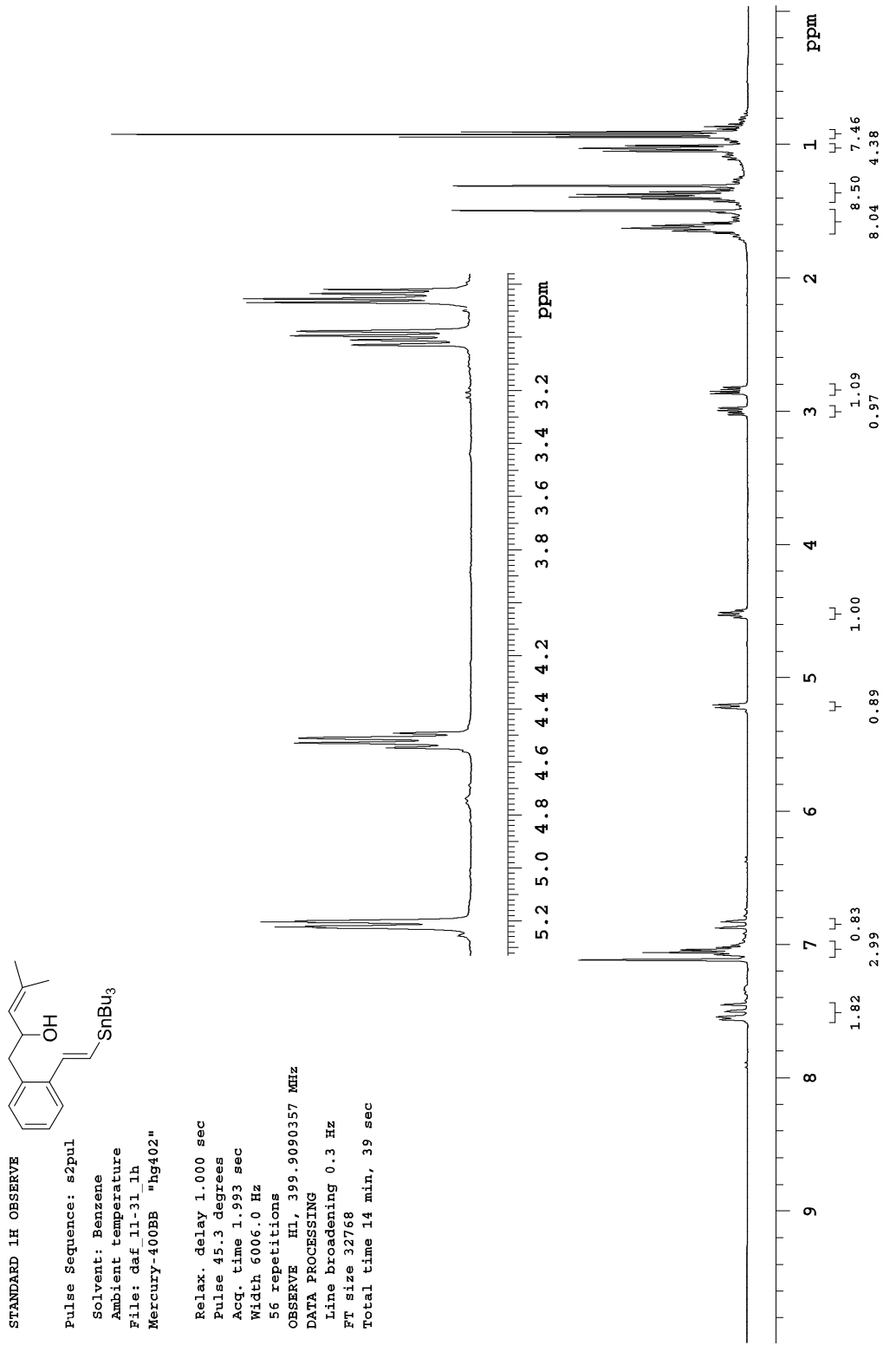
Spectrum 2.255 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **645**



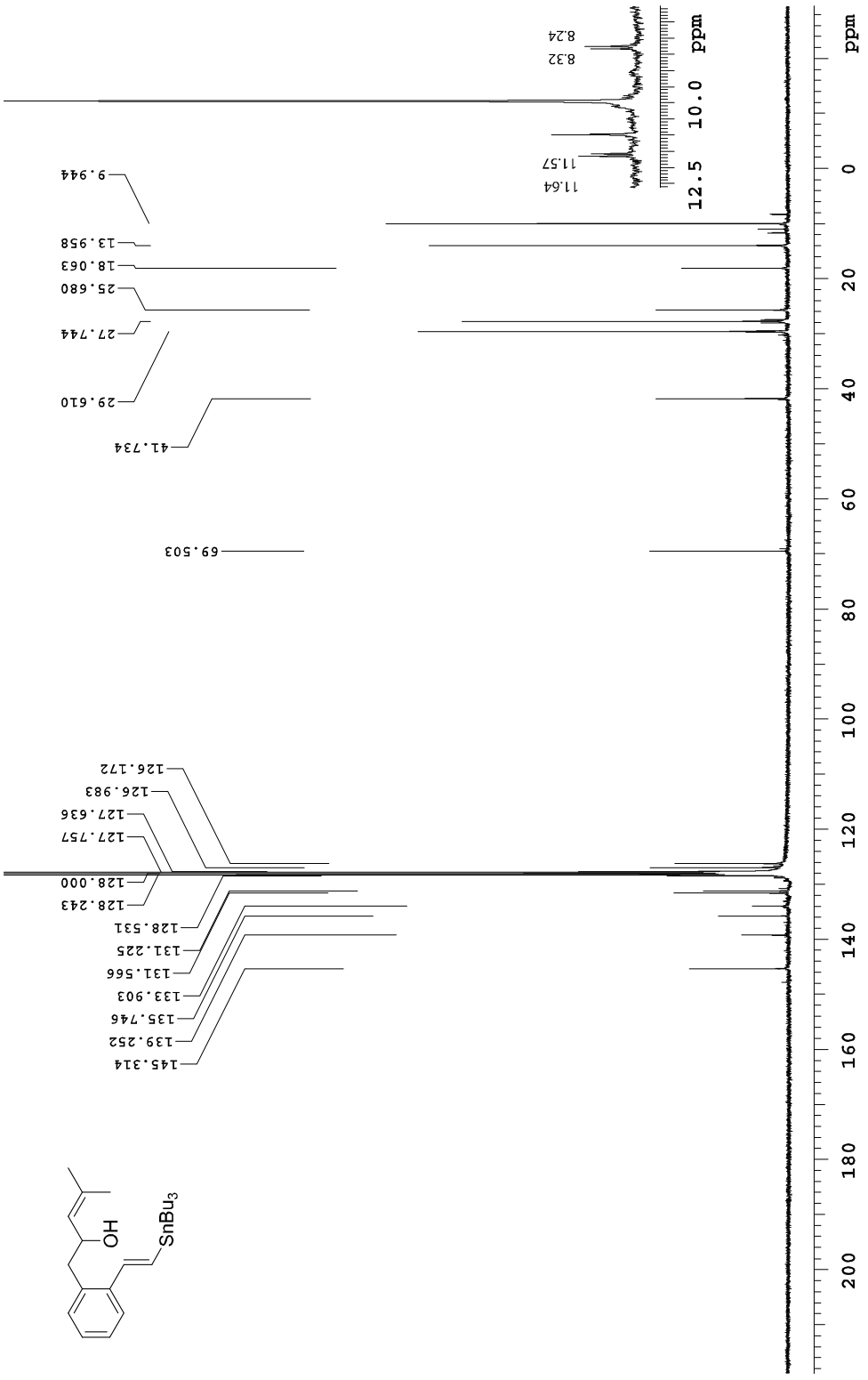
Spectrum 2.256 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **646**



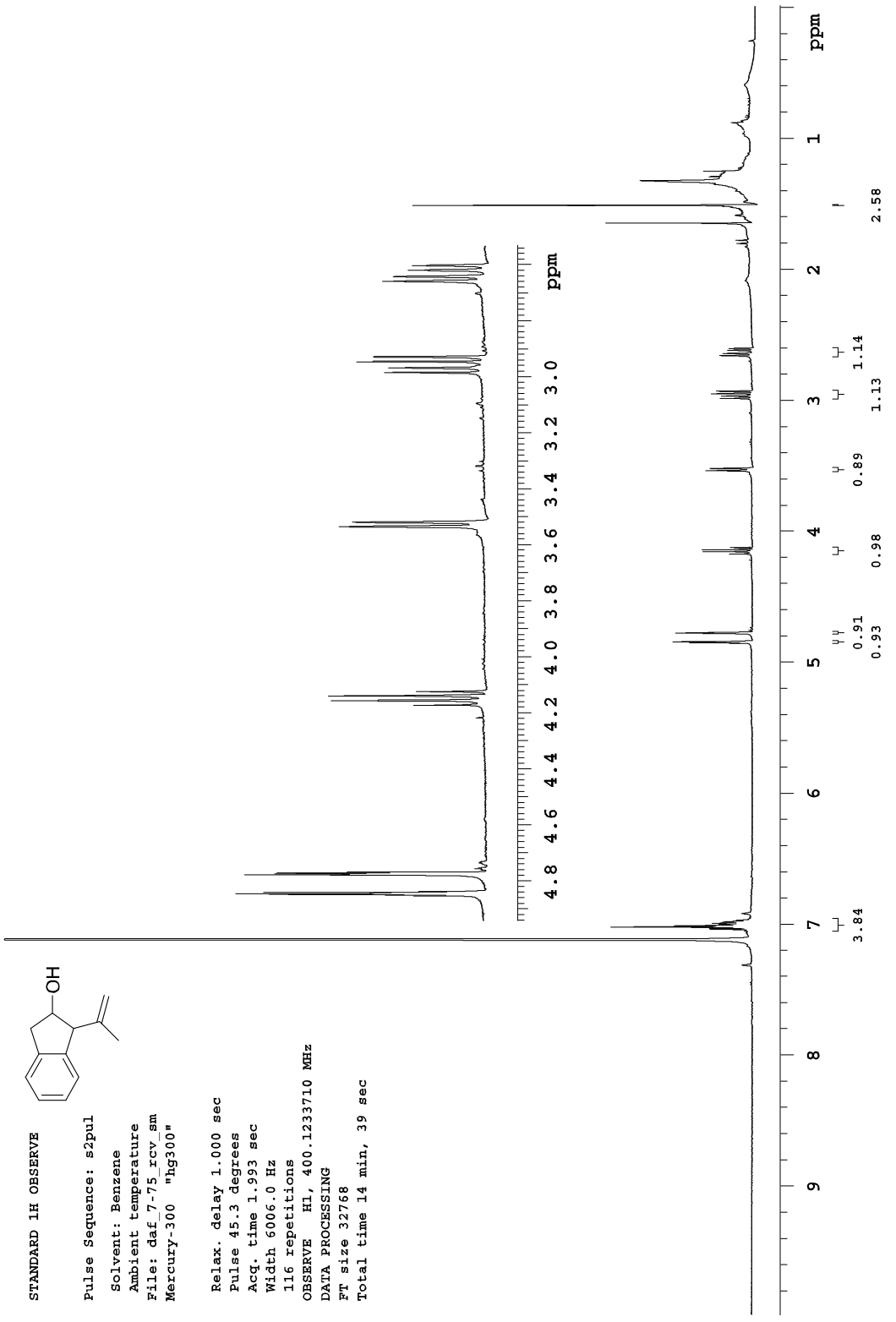
Spectrum 2.257 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **646**



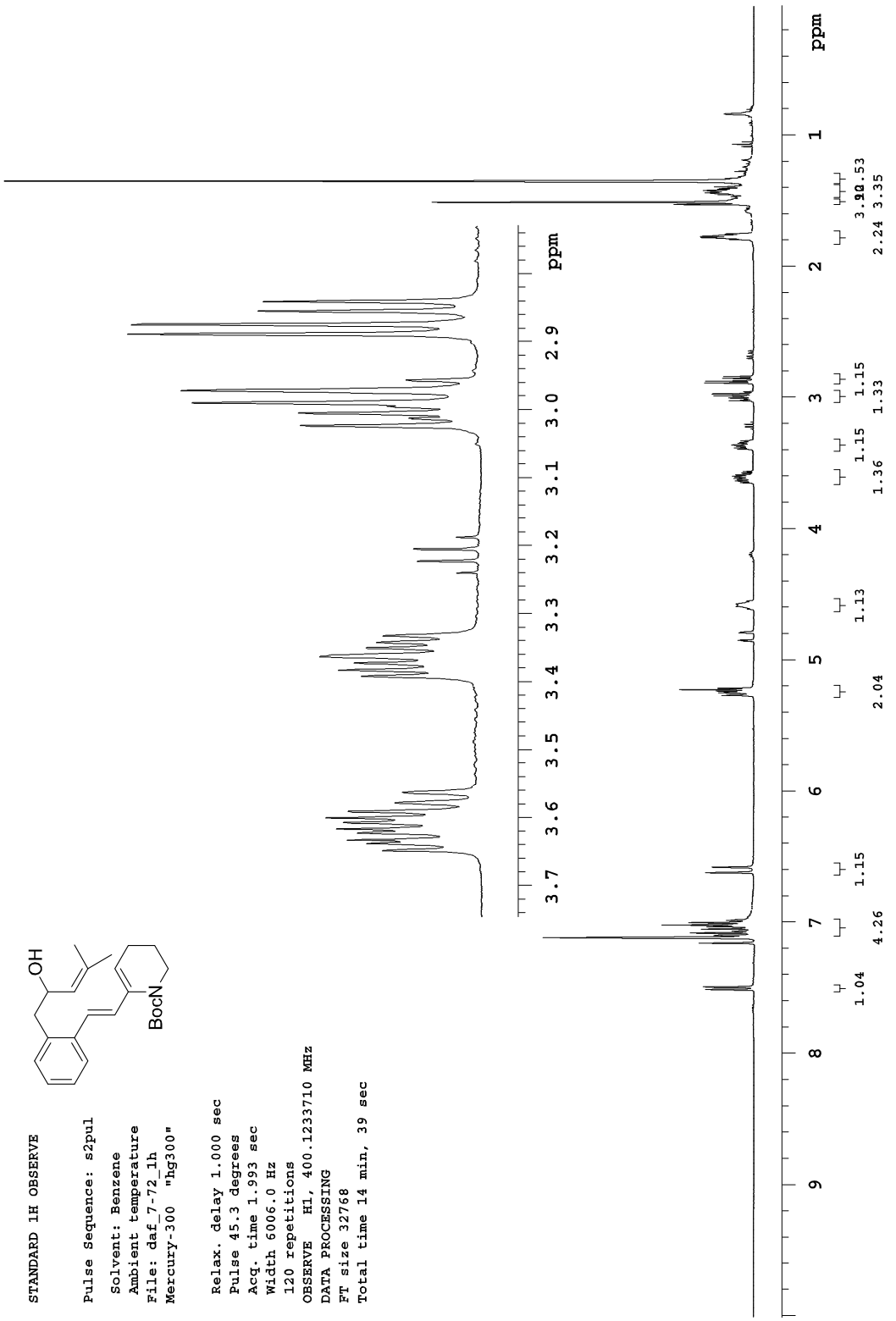
Spectrum 2.258 ^{1}H NMR (C_6D_6, 400 MHz) of compound **647**



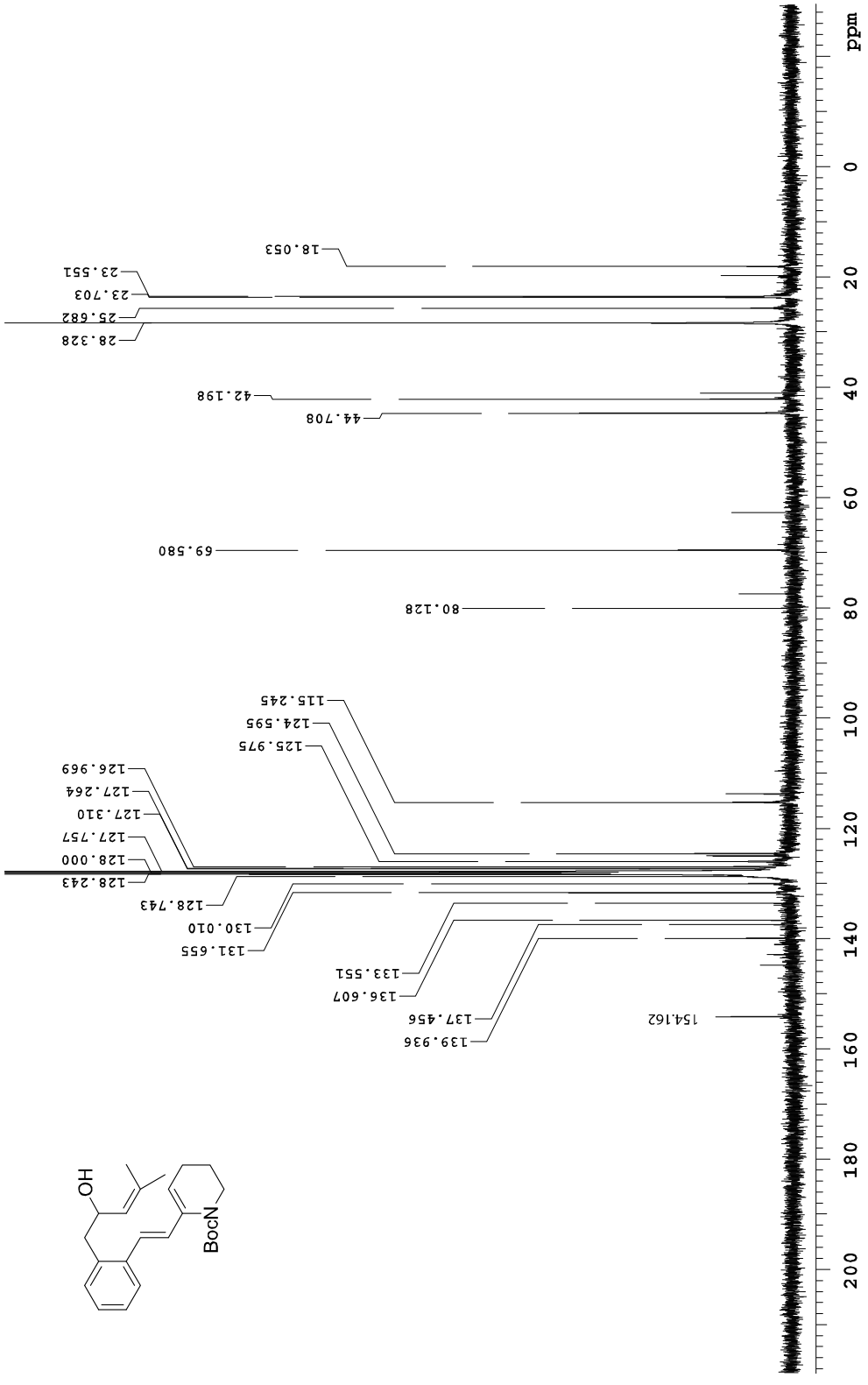
Spectrum 2.259 ^{13}C NMR (C_6D_6, 100 MHz) of compound **647**



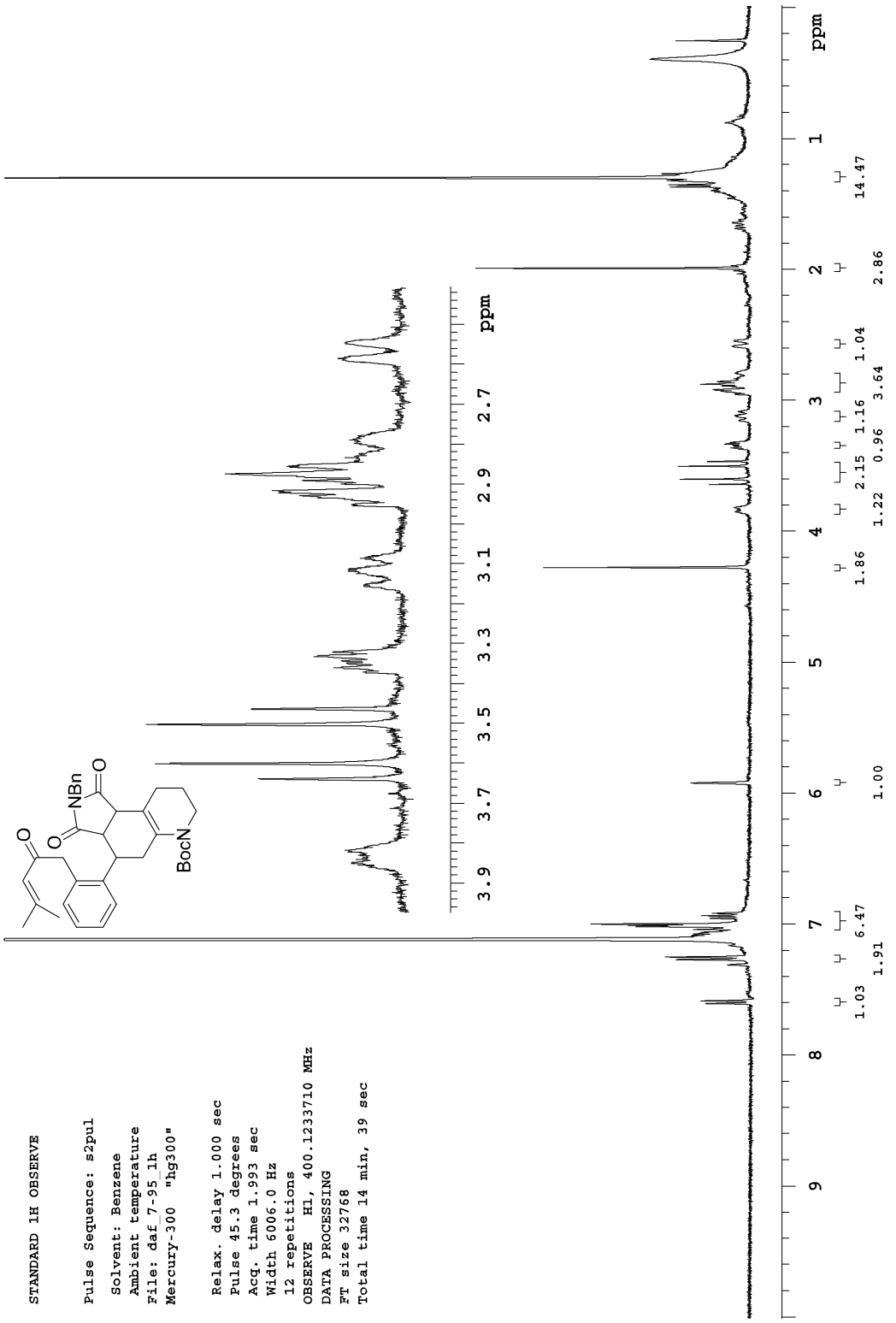
Spectrum 2.260 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **648**



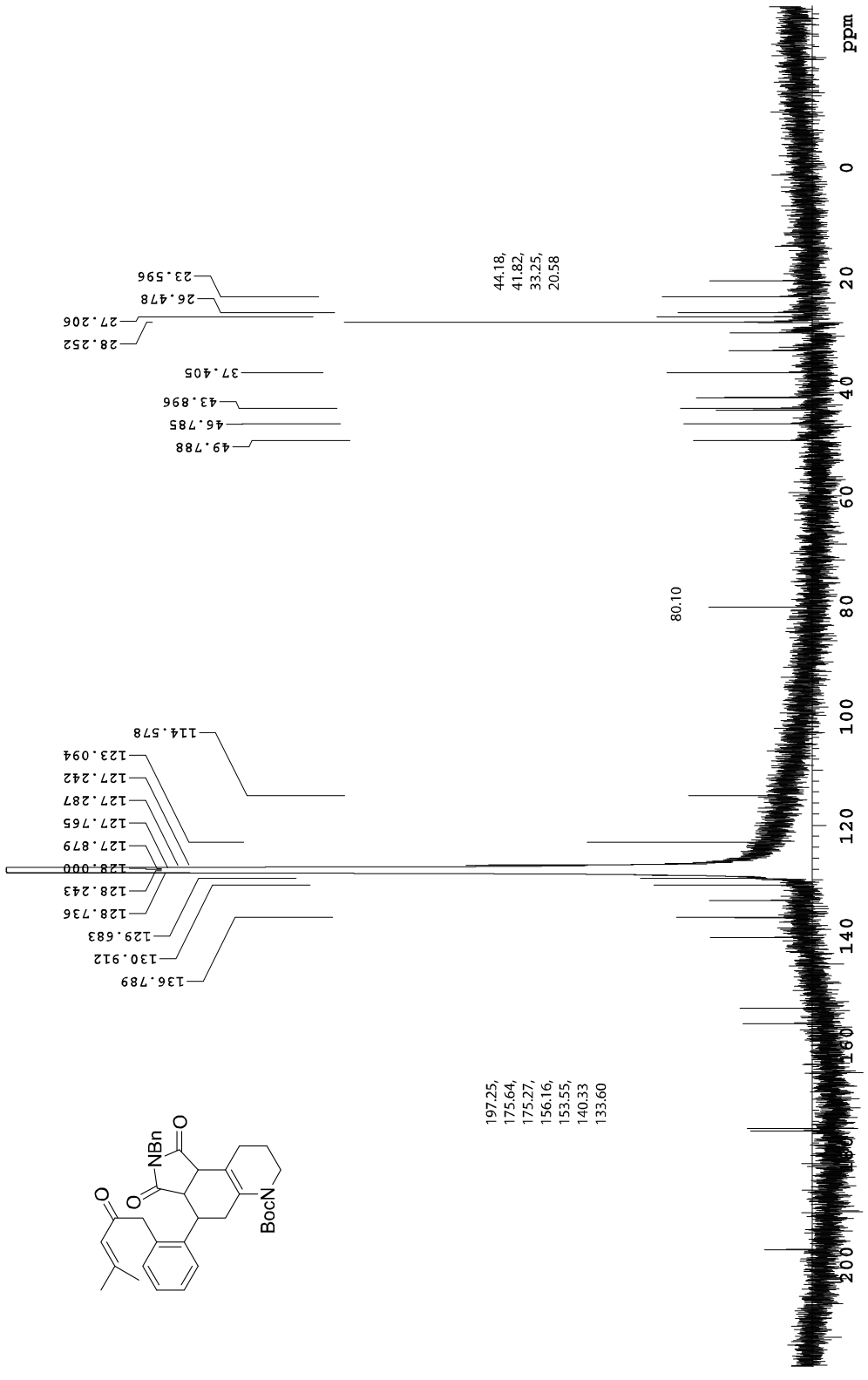
Spectrum 2.261 ^{1}H NMR (C_6D_{63}, 400 MHz) of compound **649**



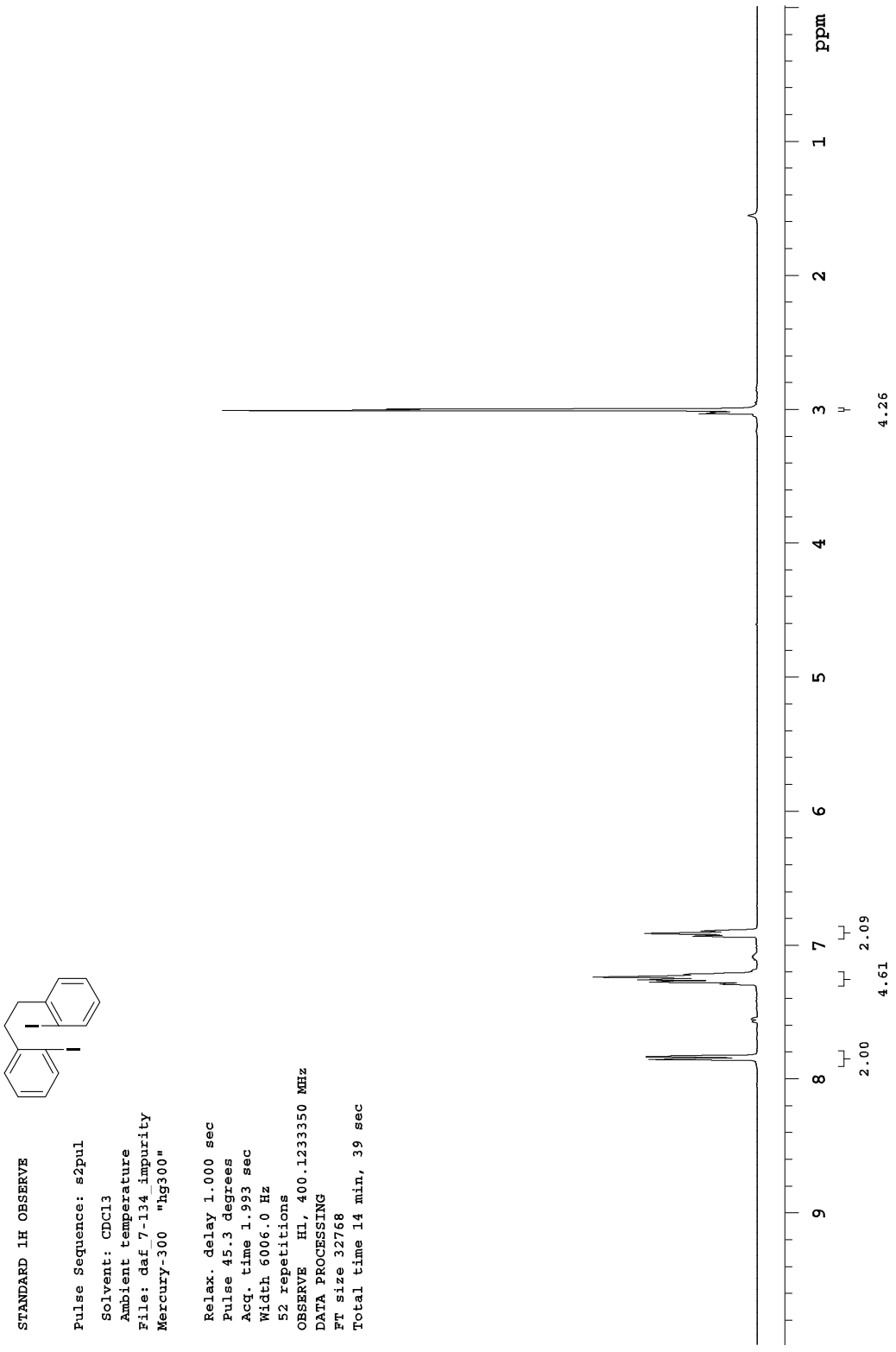
Spectrum 2.262 ^{13}C NMR (C_6D_6, 100 MHz) of compound **649**



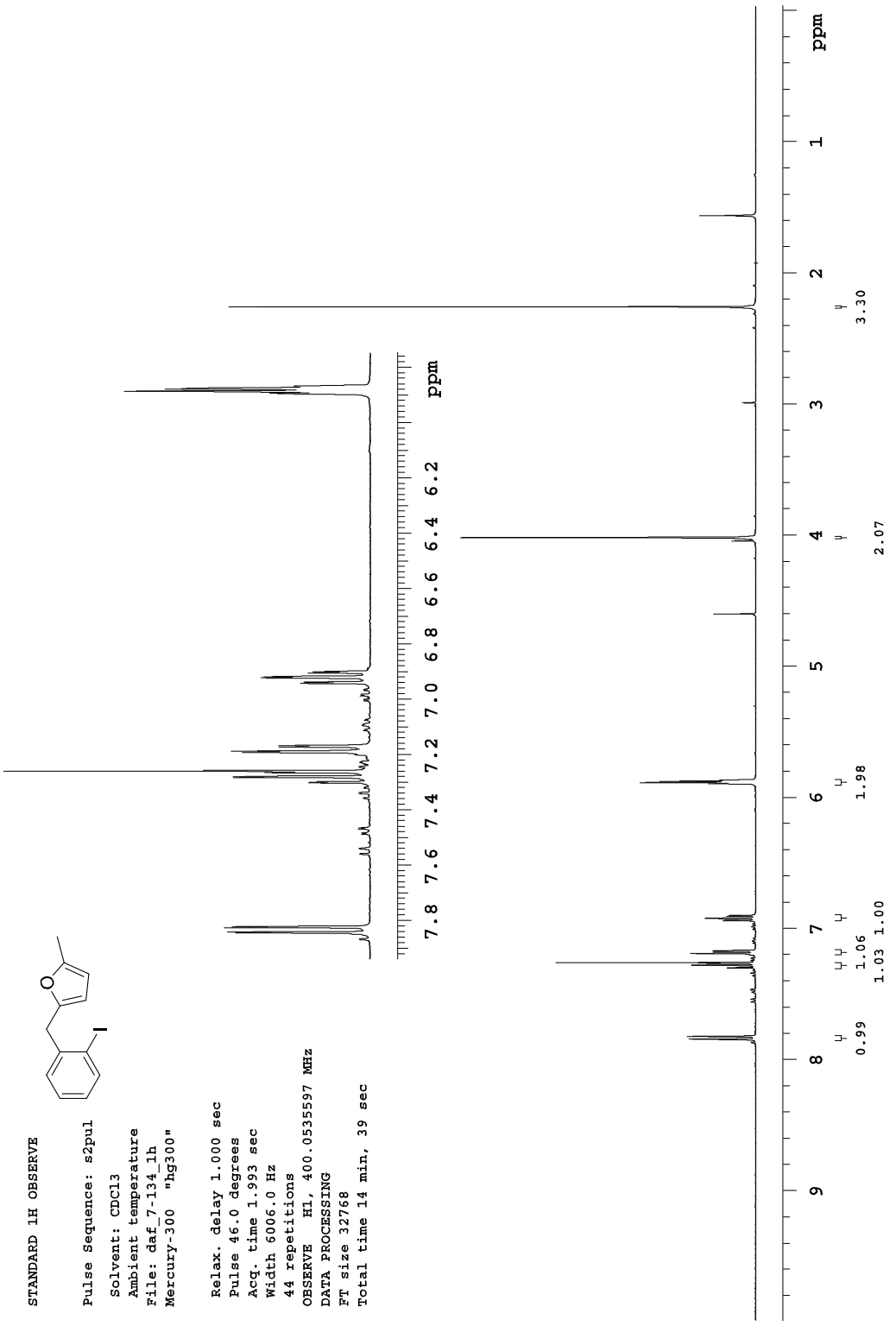
Spectrum 2.263 ^{1}H NMR (C_6D_6, 400 MHz) of compound **650**



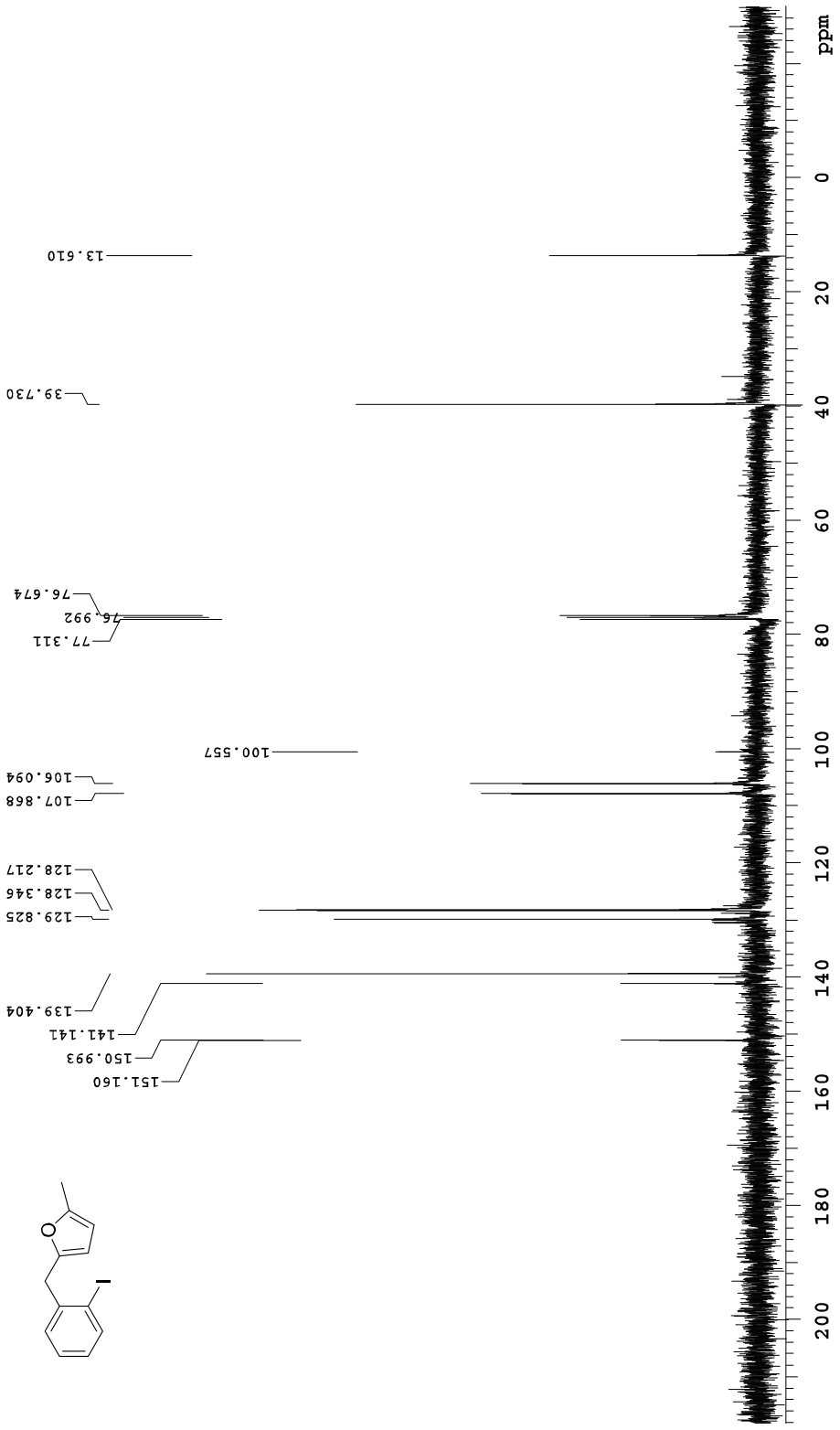
Spectrum 2.264 ^{13}C NMR (C_6D_6, 100 MHz) of compound **650**



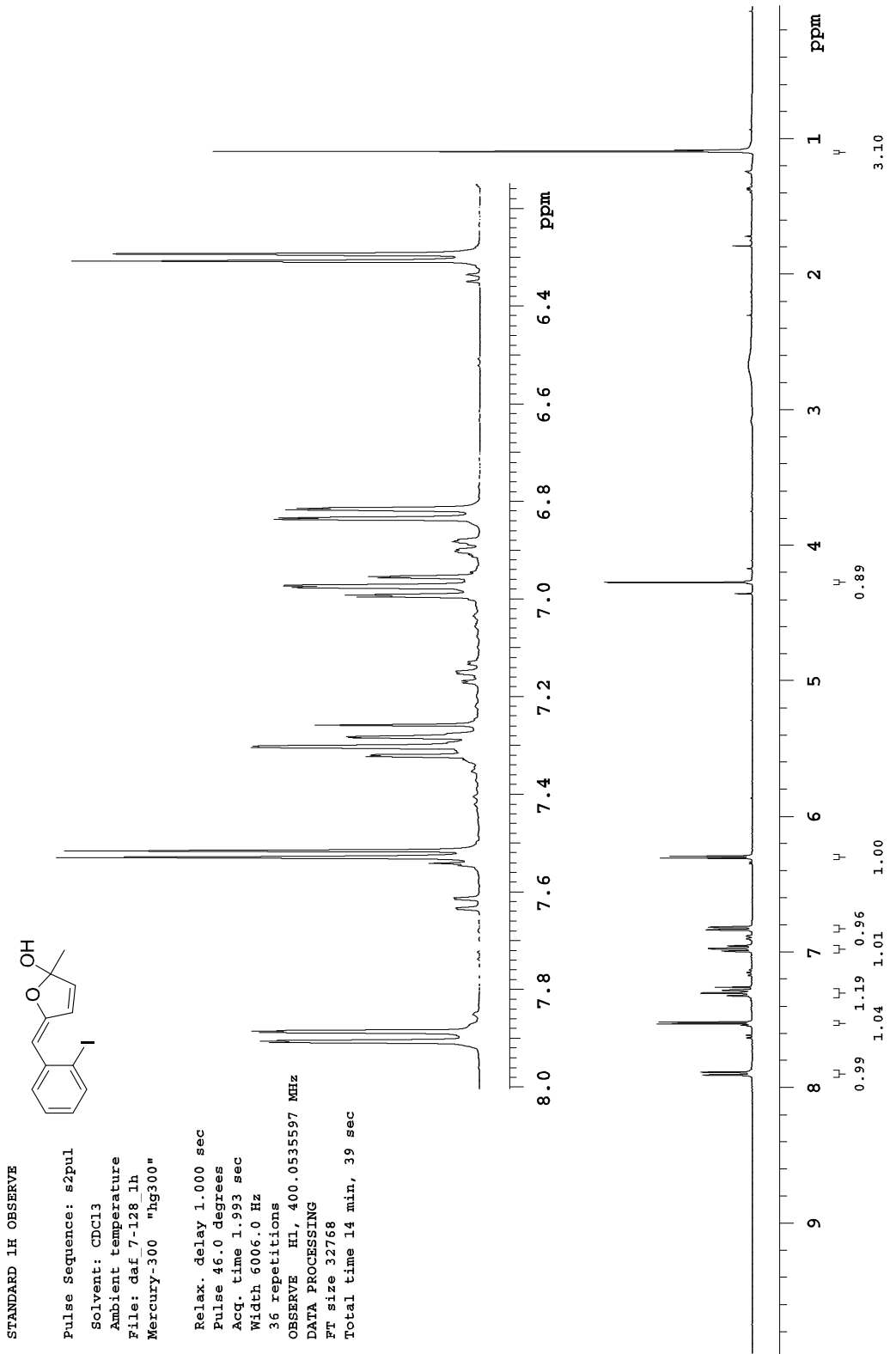
Spectrum 2.265 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **653**



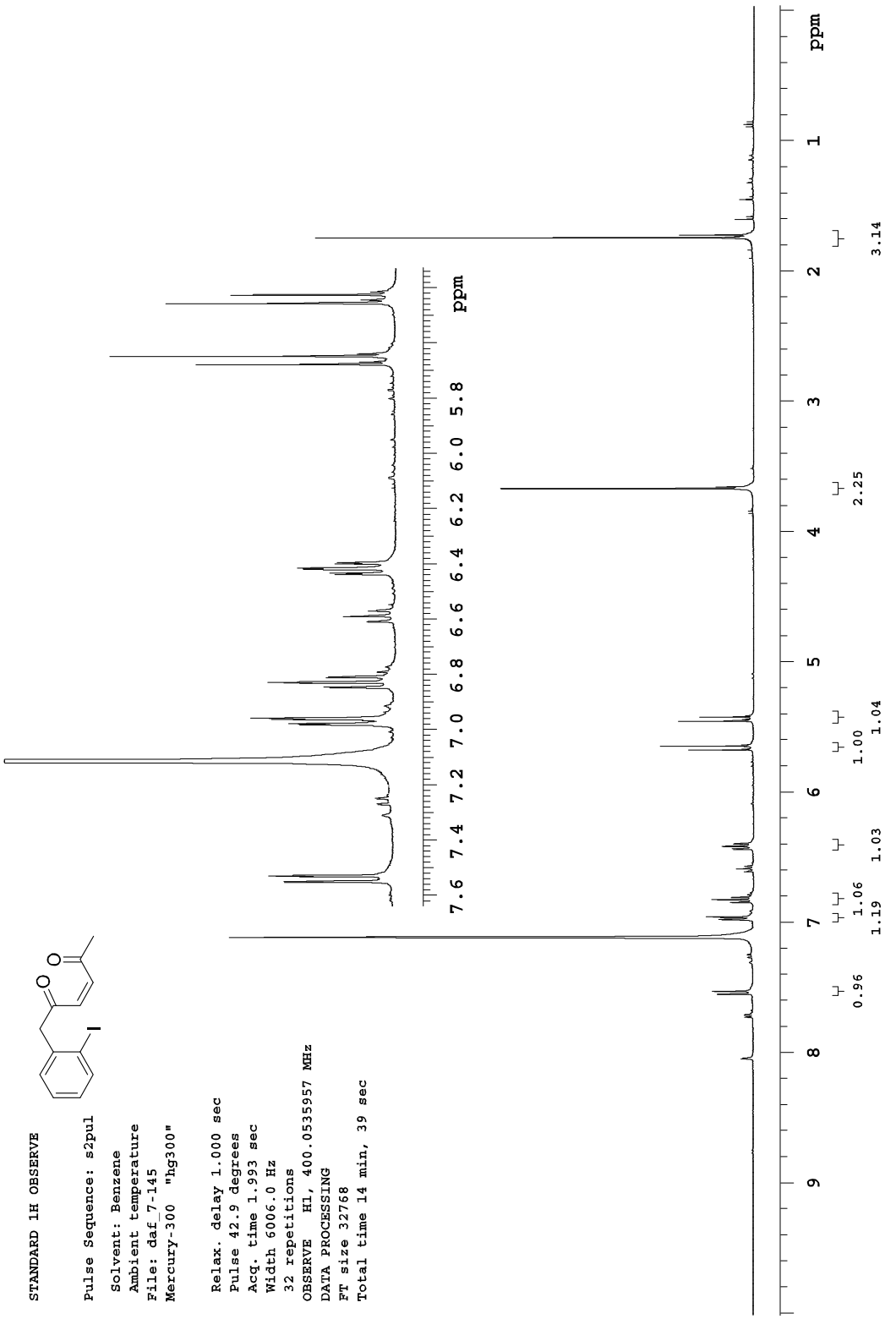
Spectrum 2.266 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **654**



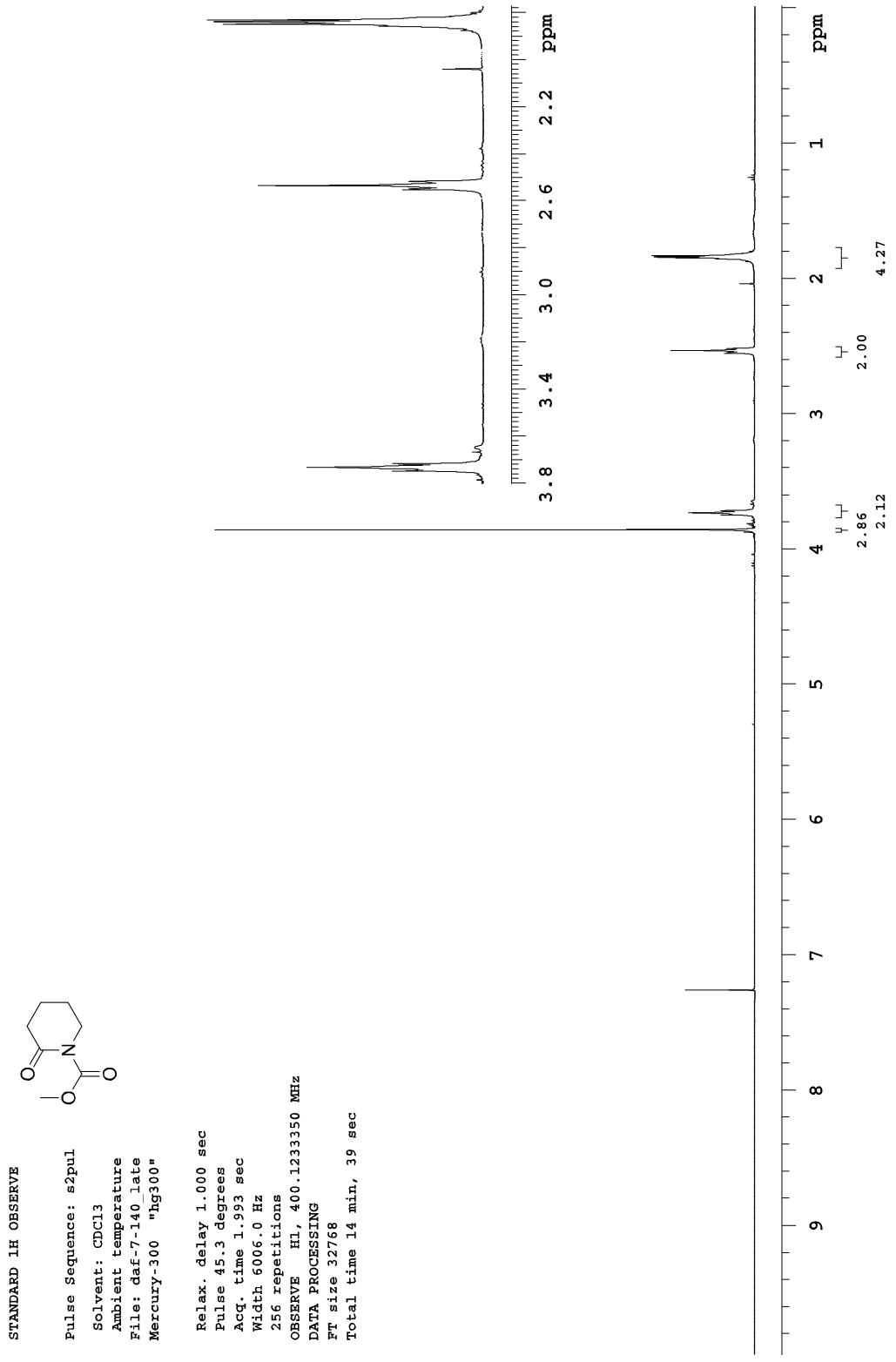
Spectrum 2.267 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **654**



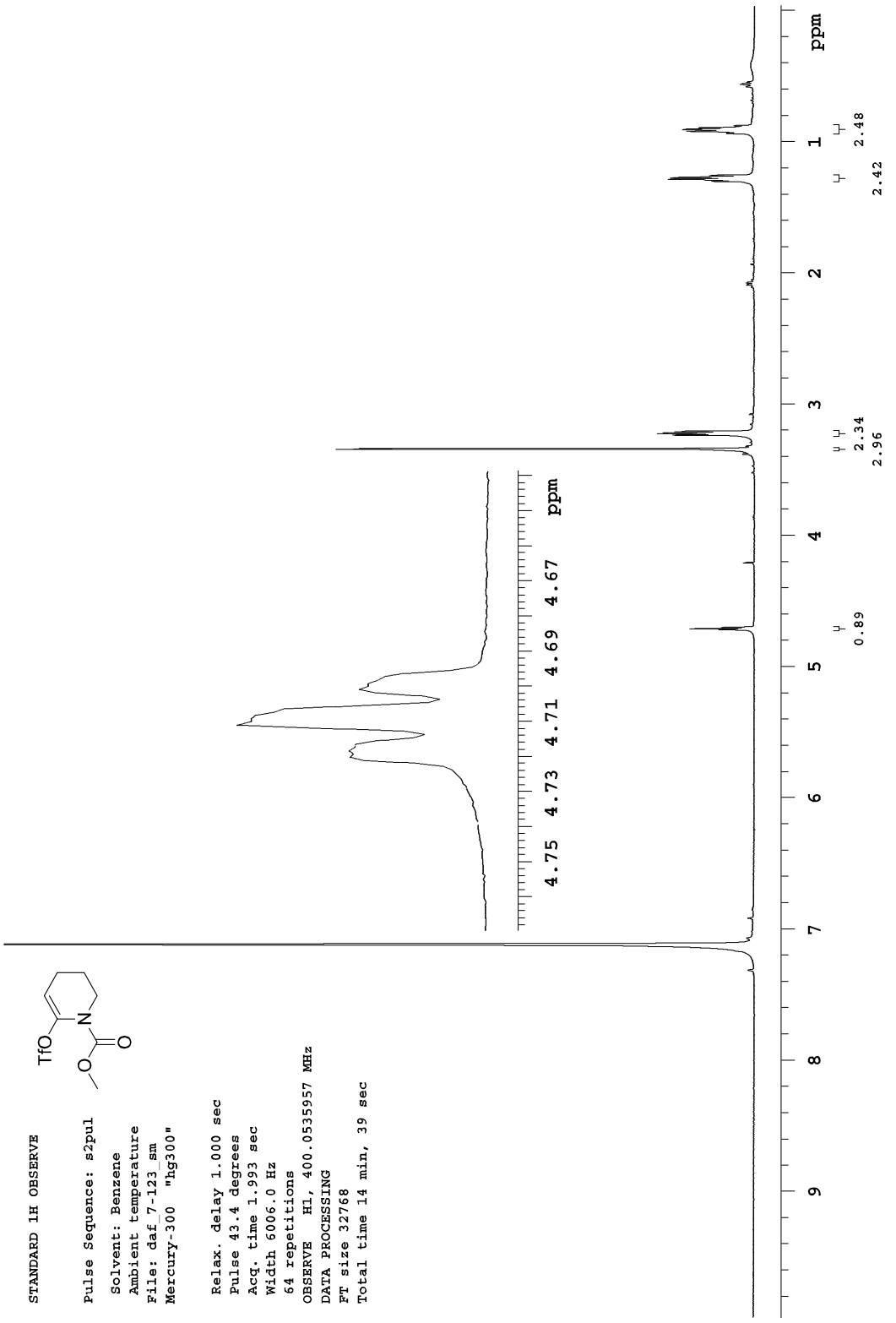
Spectrum 2.268 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **655**



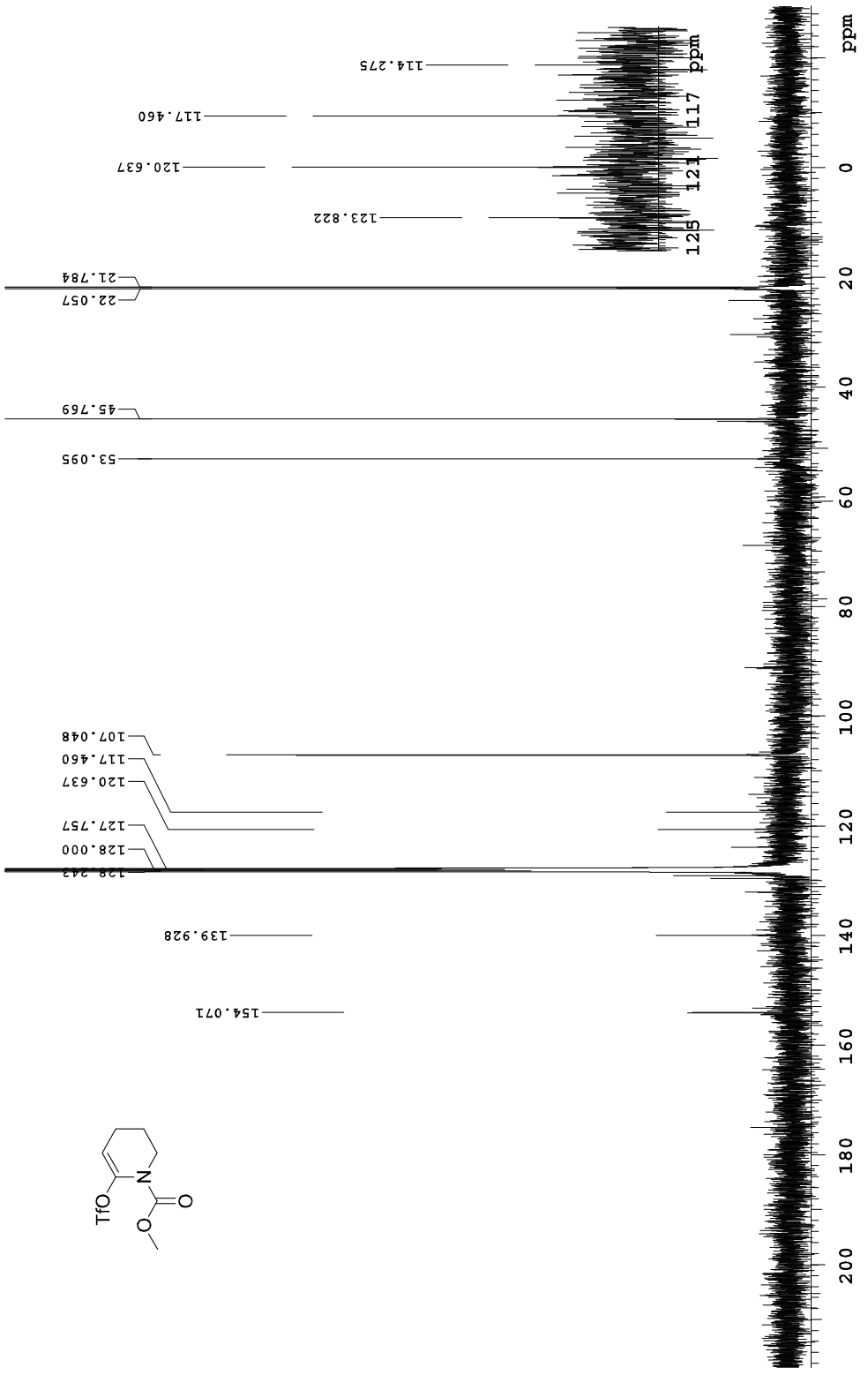
Spectrum 2.269 ^{1}H NMR (C_6D_6, 400 MHz) of compound **655b**



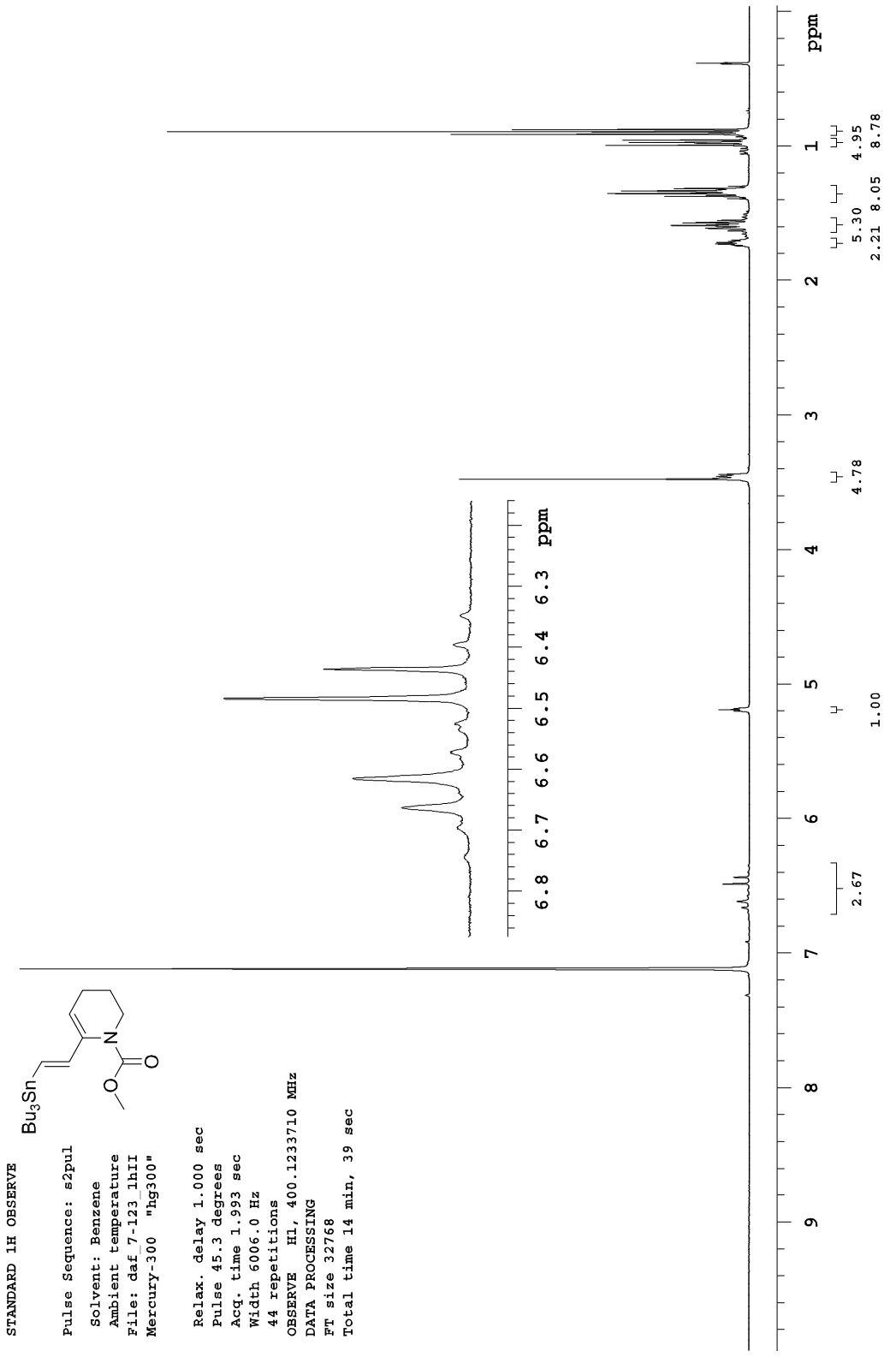
Spectrum 2.270 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **659**



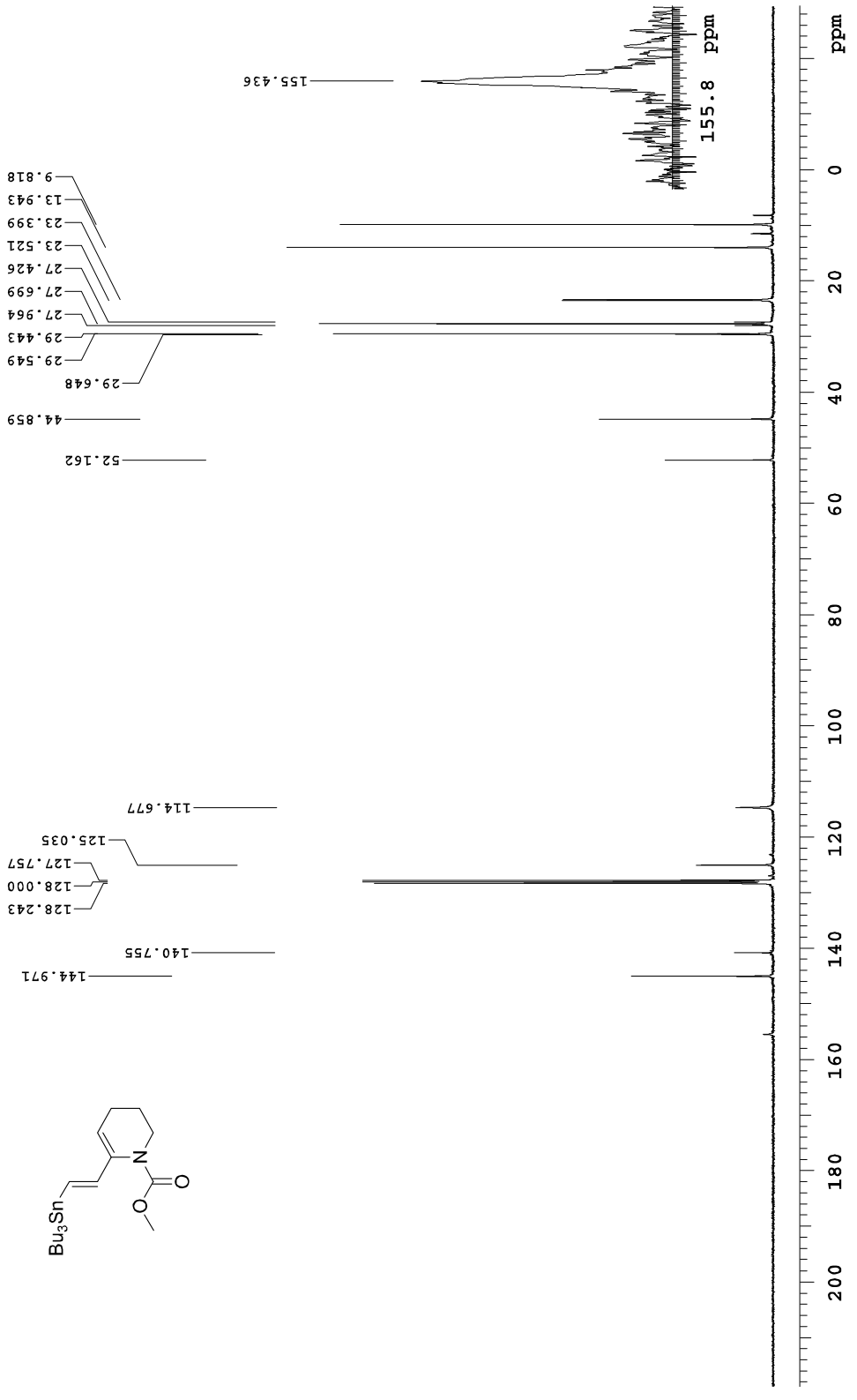
Spectrum 2.271 ^{1}H NMR (C_6D_6, 400 MHz) of compound **660**



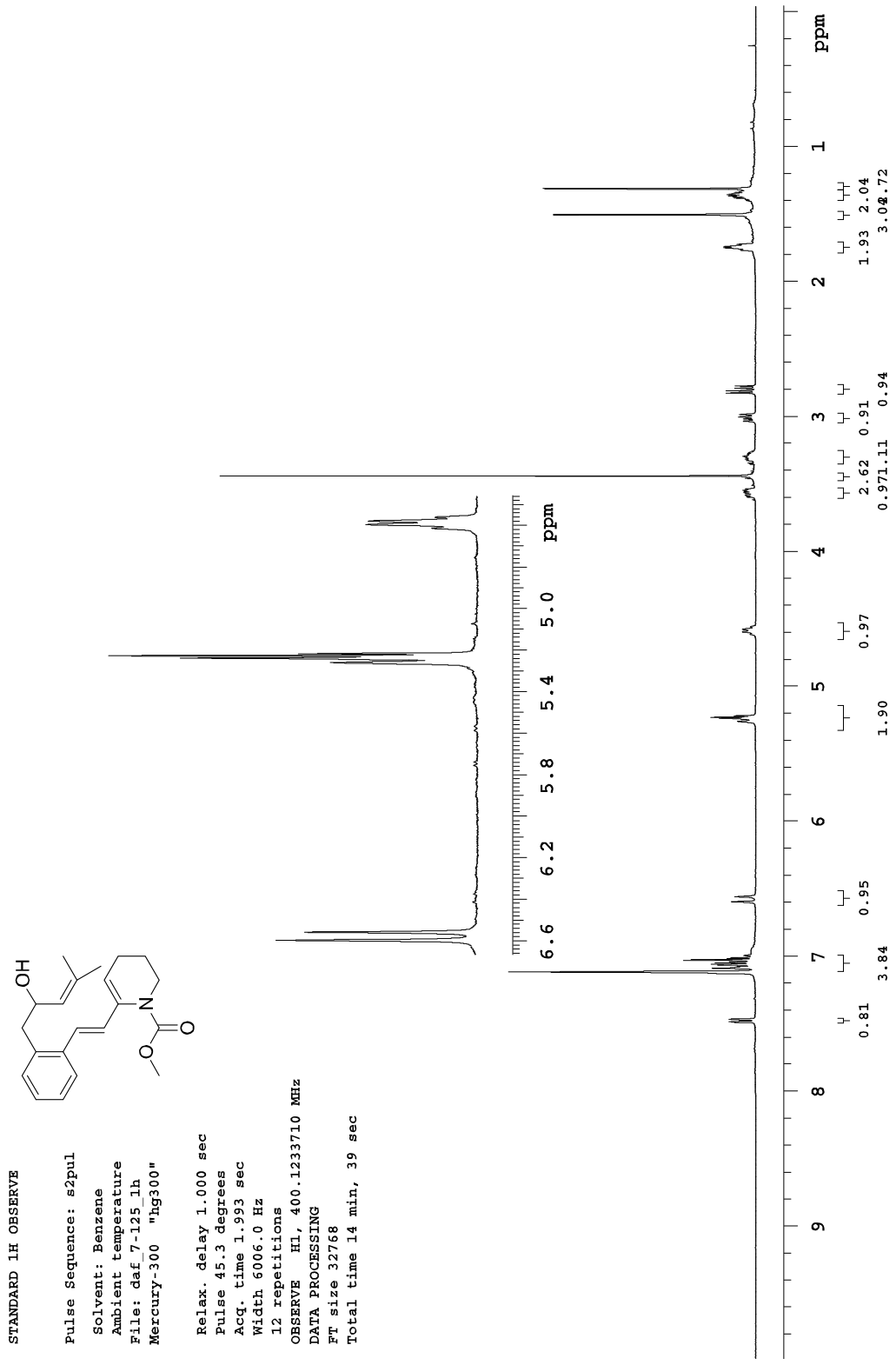
Spectrum 2.272 ^{13}C NMR (C_6D_6, 100 MHz) of compound **660**



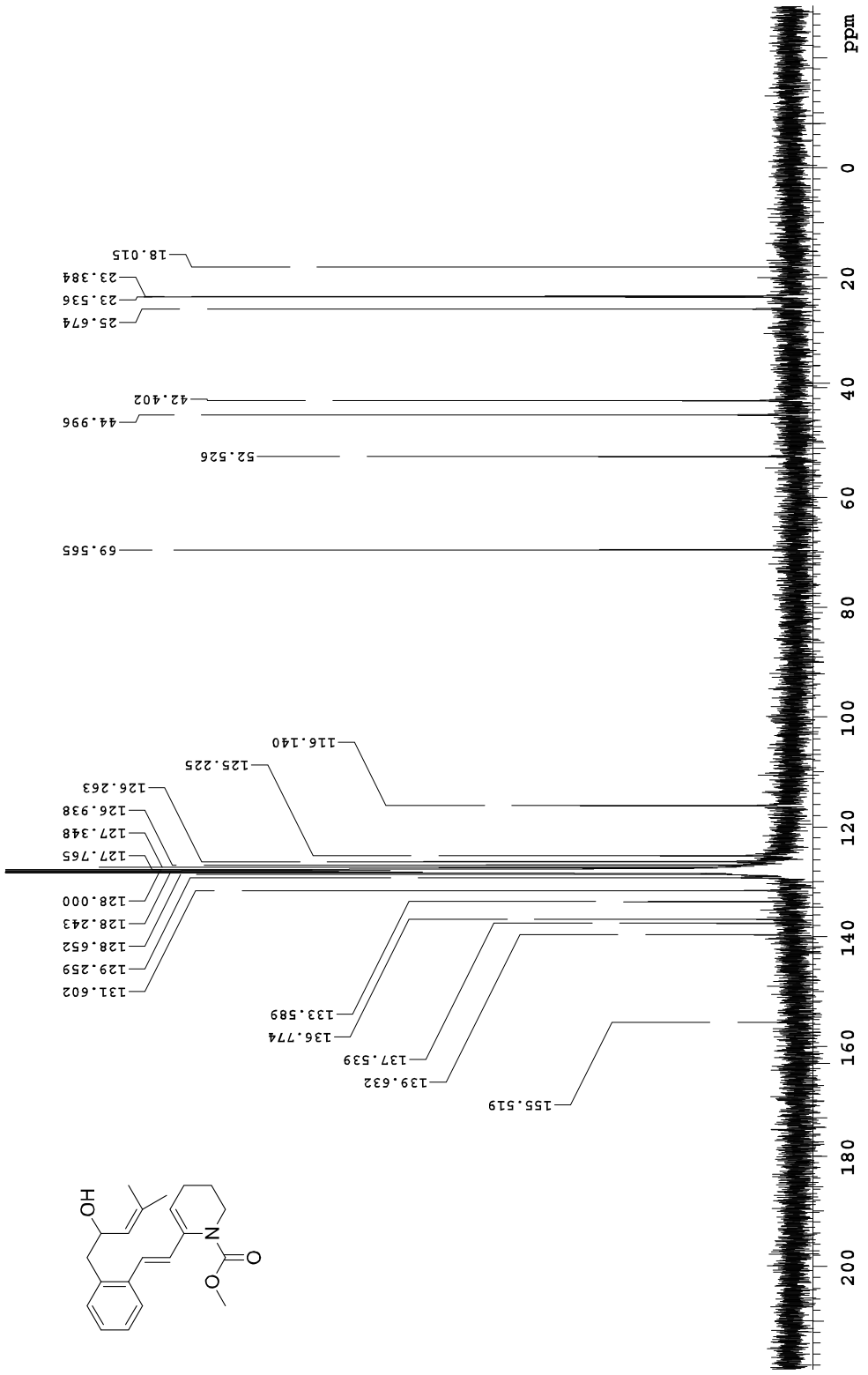
Spectrum 2.273 ^{1}H NMR (C_6D_6, 400 MHz) of compound **661**



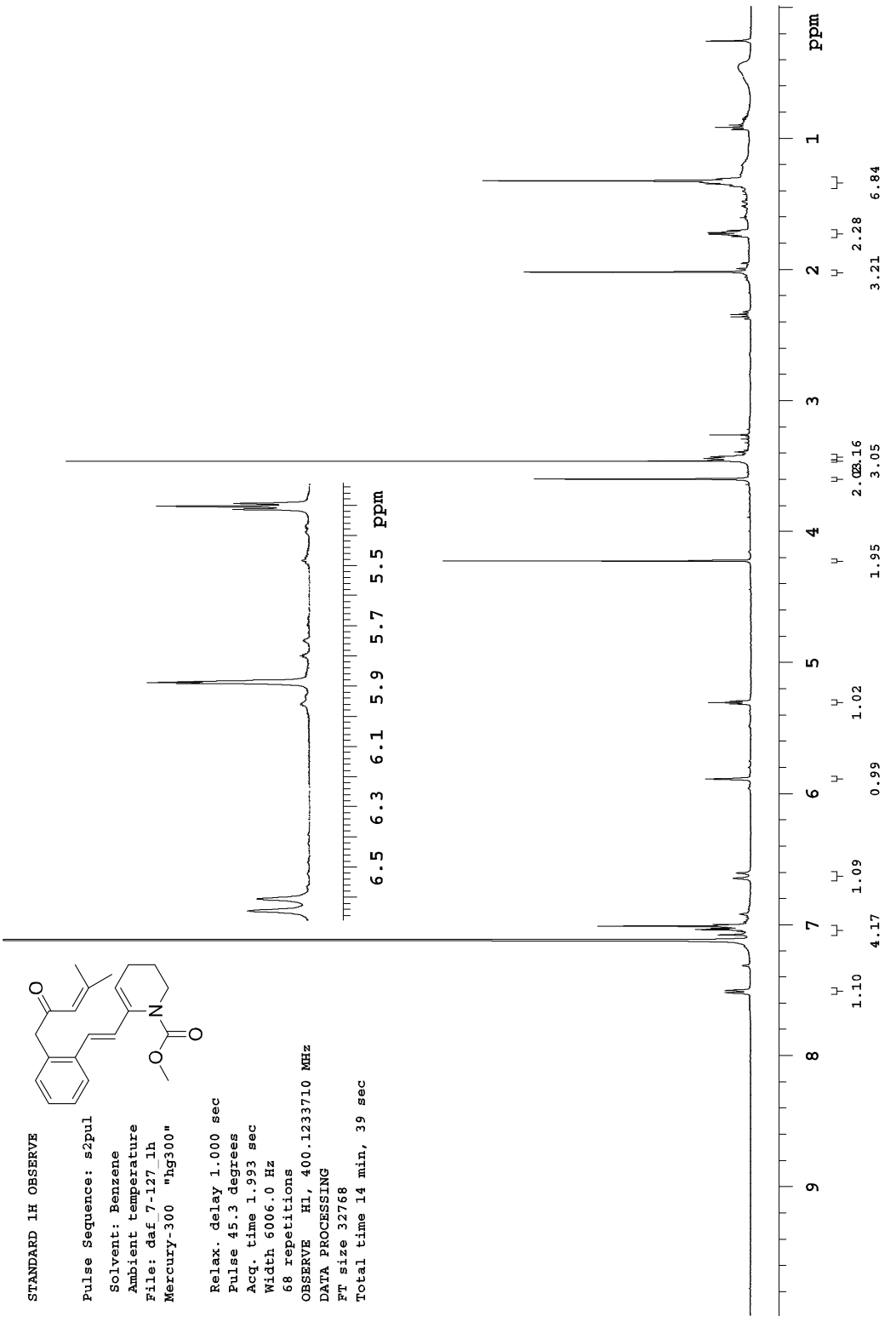
Spectrum 2.274 ^{13}C NMR (C_6D_6, 100 MHz) of compound **661**



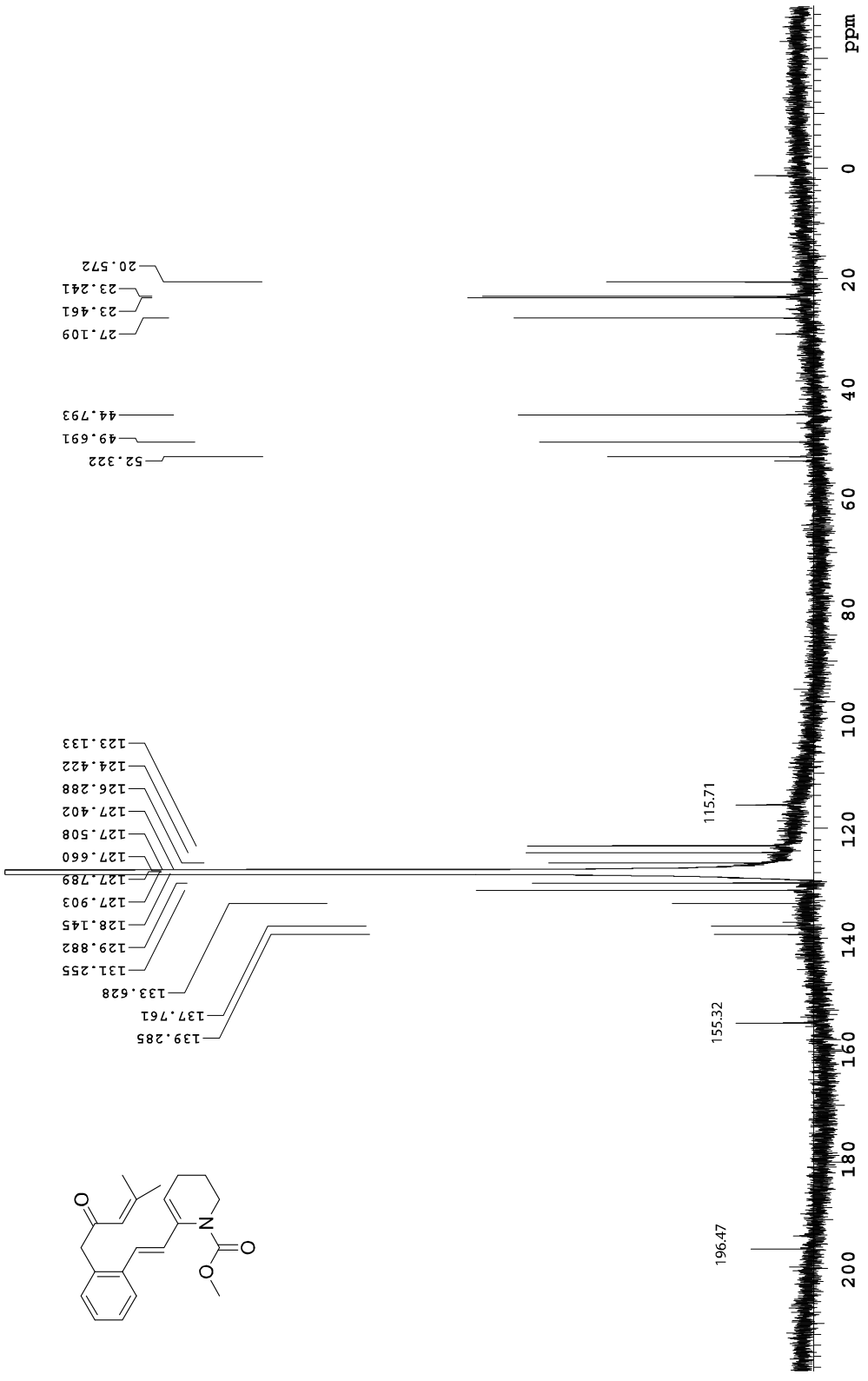
Spectrum 2.275 ^{1}H NMR (C_6D_6, 400 MHz) of compound **662**



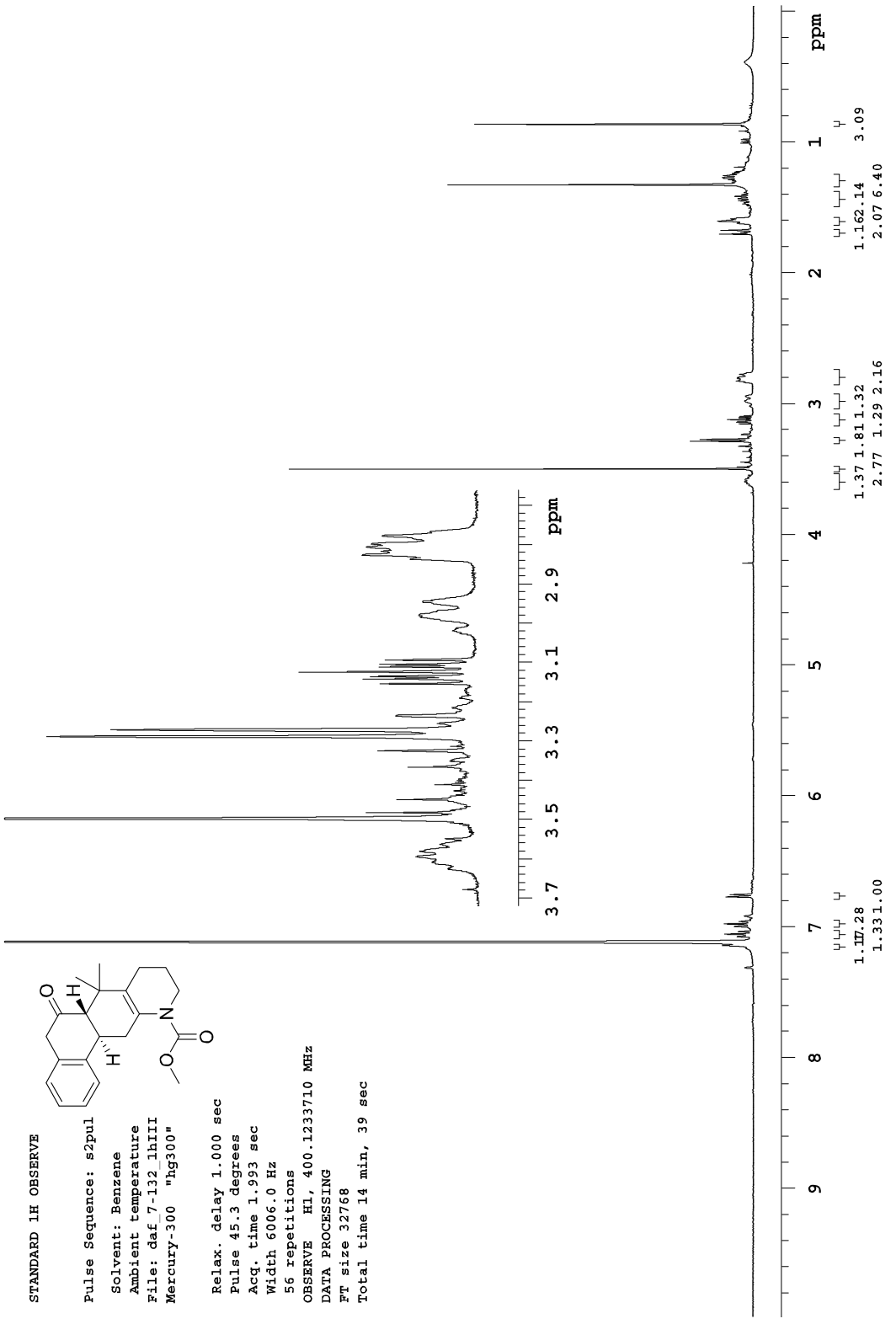
Spectrum 2.276 ^{13}C NMR (C_6D_6, 100 MHz) of compound **662**



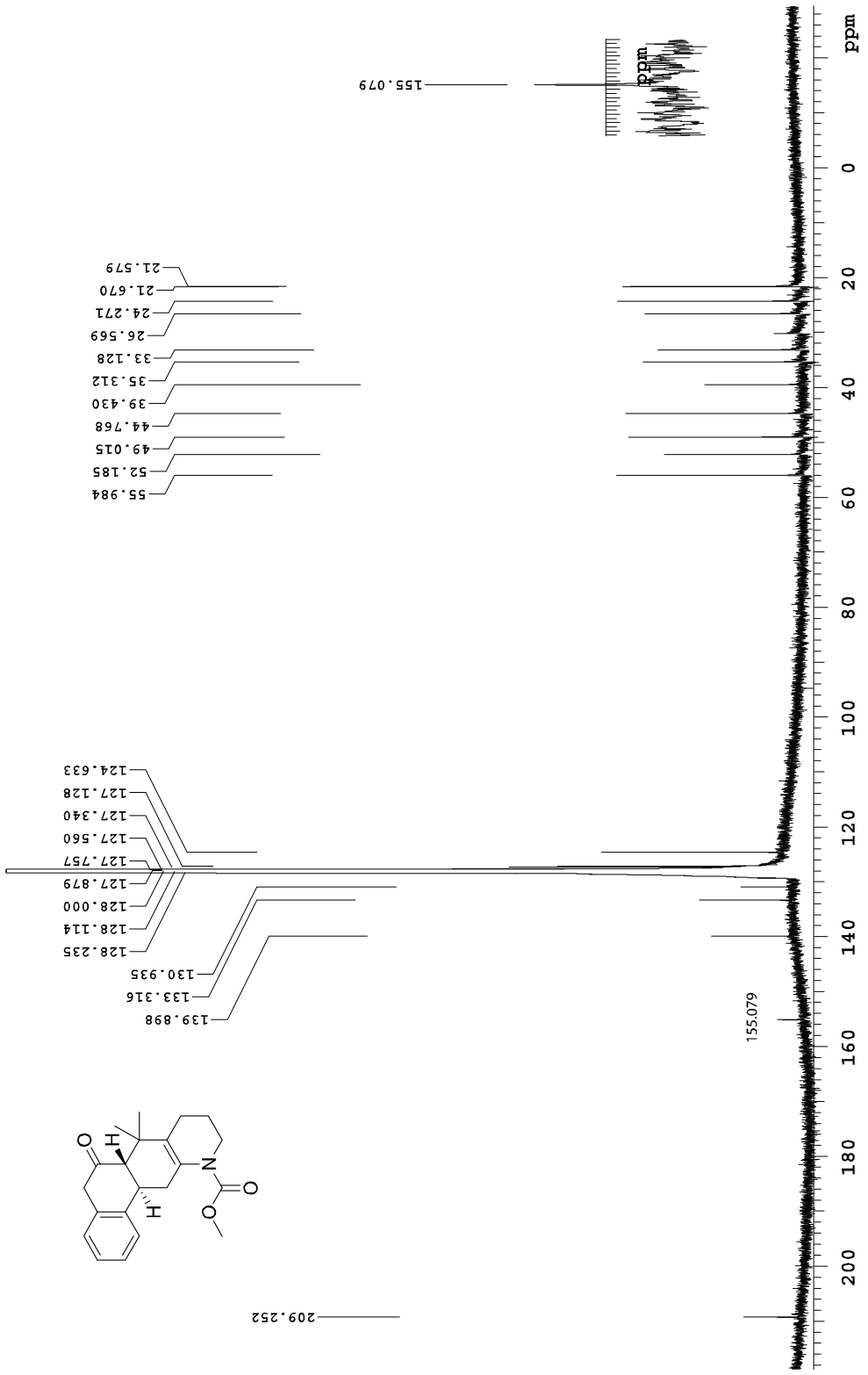
Spectrum 2.277 ^{1}H NMR (C_6D_6, 400 MHz) of compound **663**



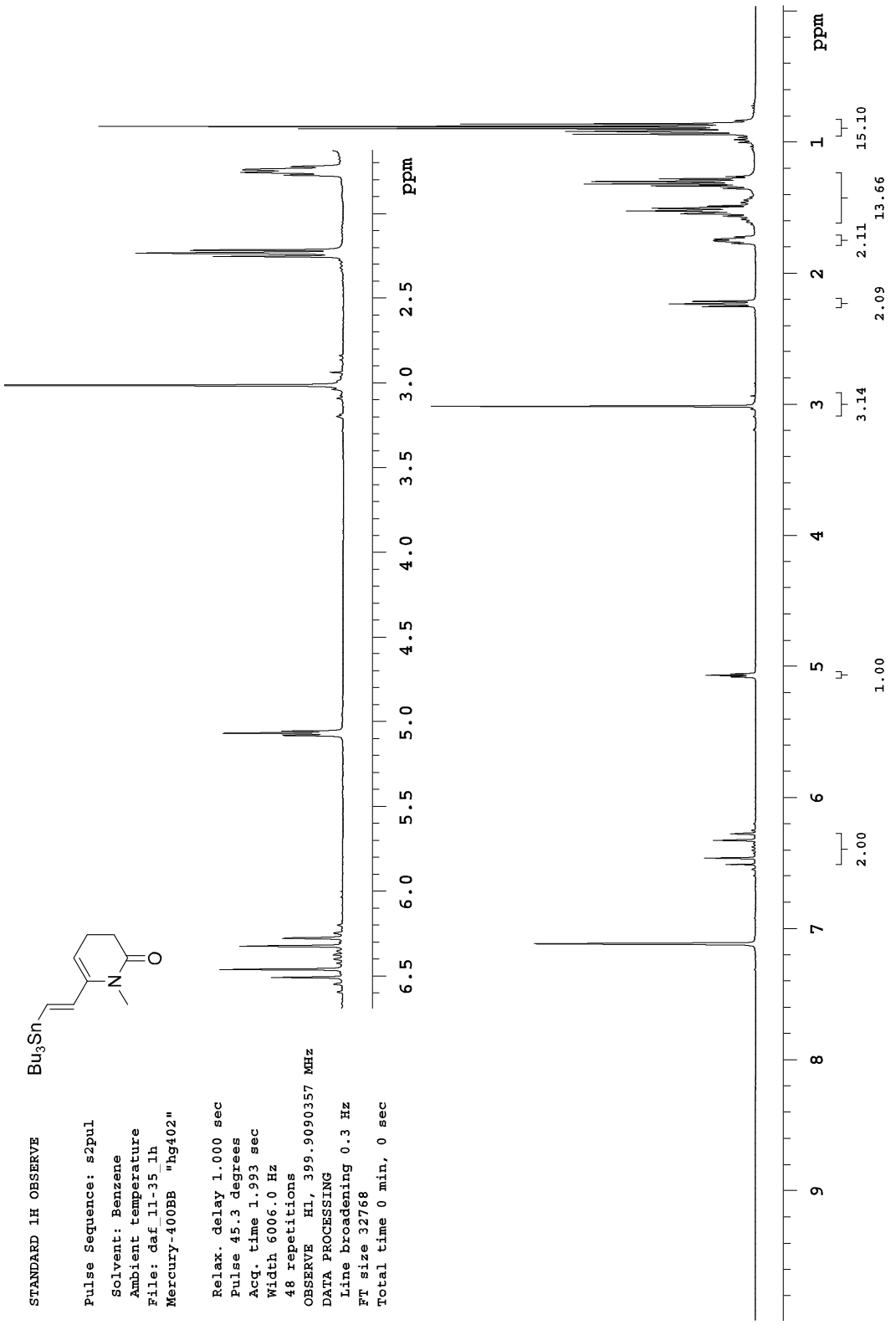
Spectrum 2.278 ^{13}C NMR (C_6D_6, 100 MHz) of compound **663**



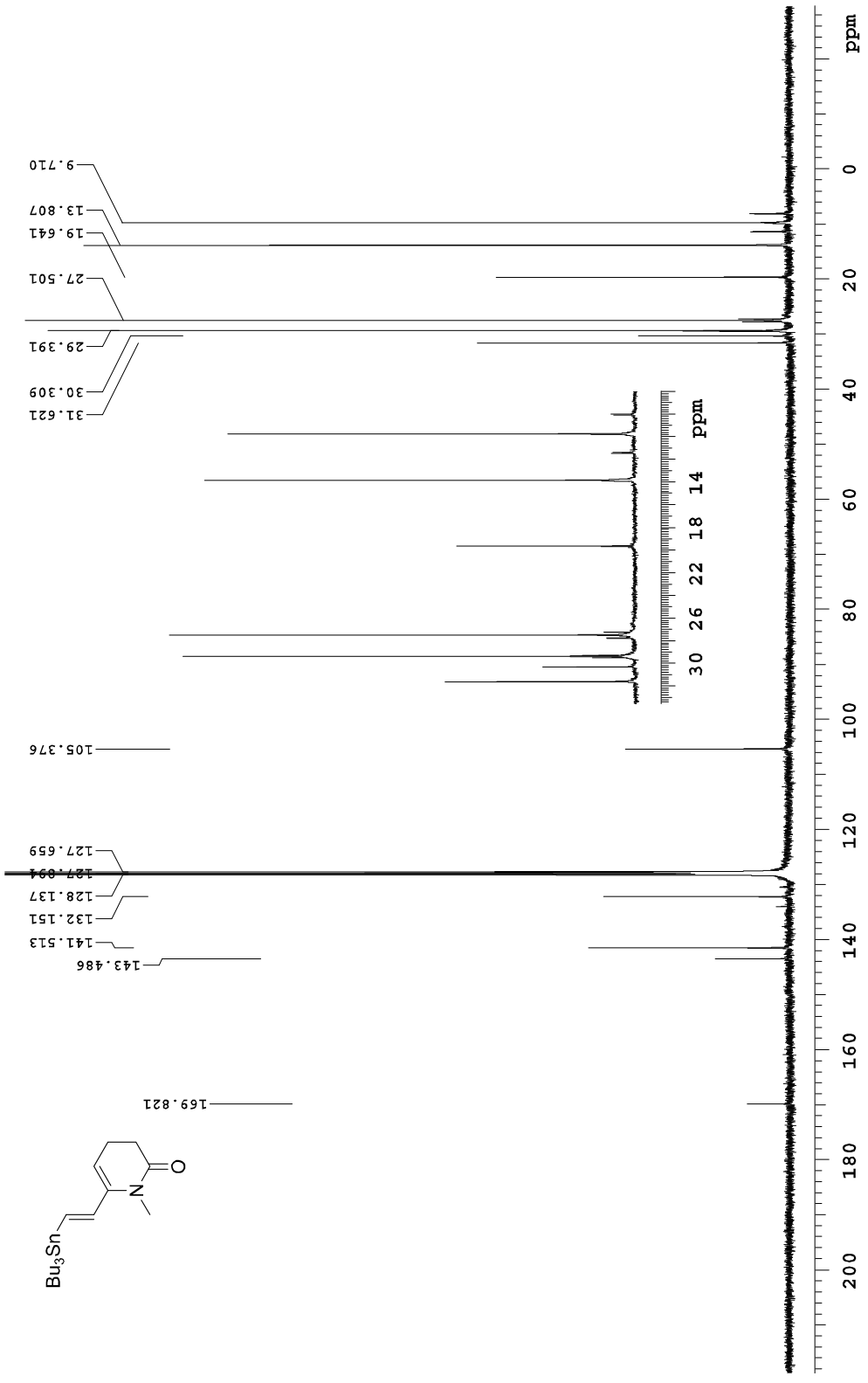
Spectrum 2.279 ^{1}H NMR (C_6D_6, 400 MHz) of compound **664**



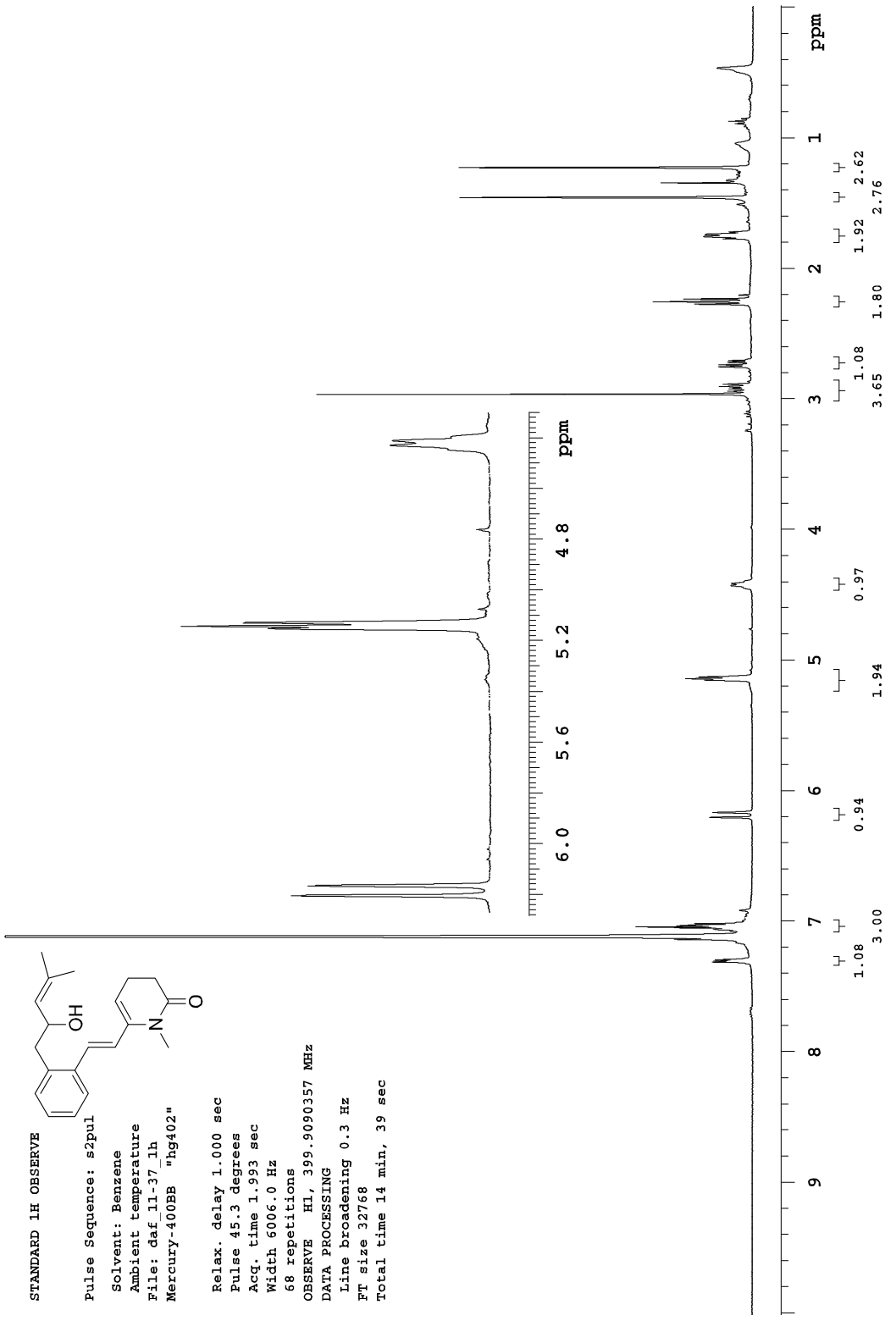
Spectrum 2.280 ^{13}C NMR (C_6D_6, 100 MHz) of compound **664**



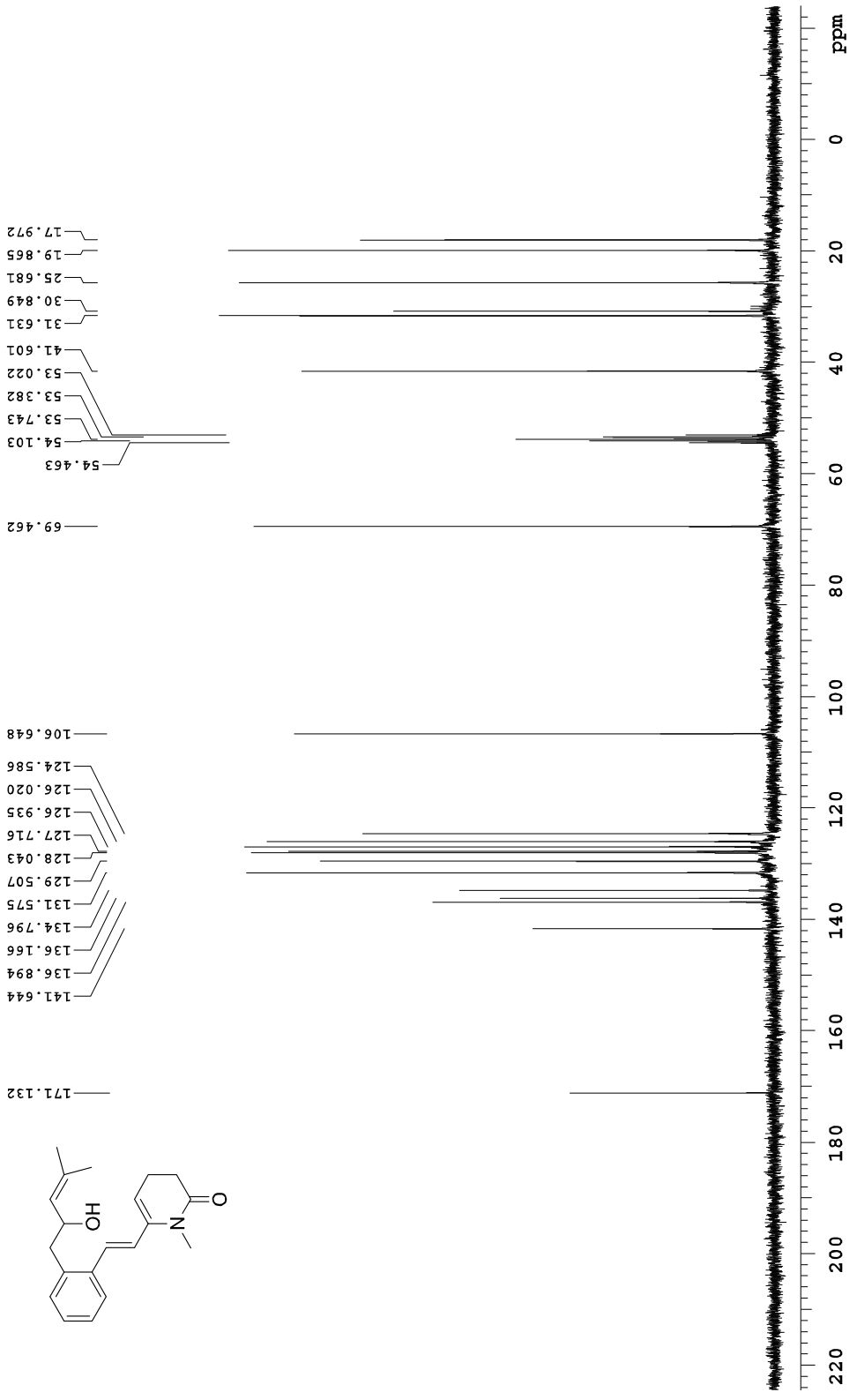
Spectrum 2.281 ^{1}H NMR (C_6D_6, 400 MHz) of compound **665**



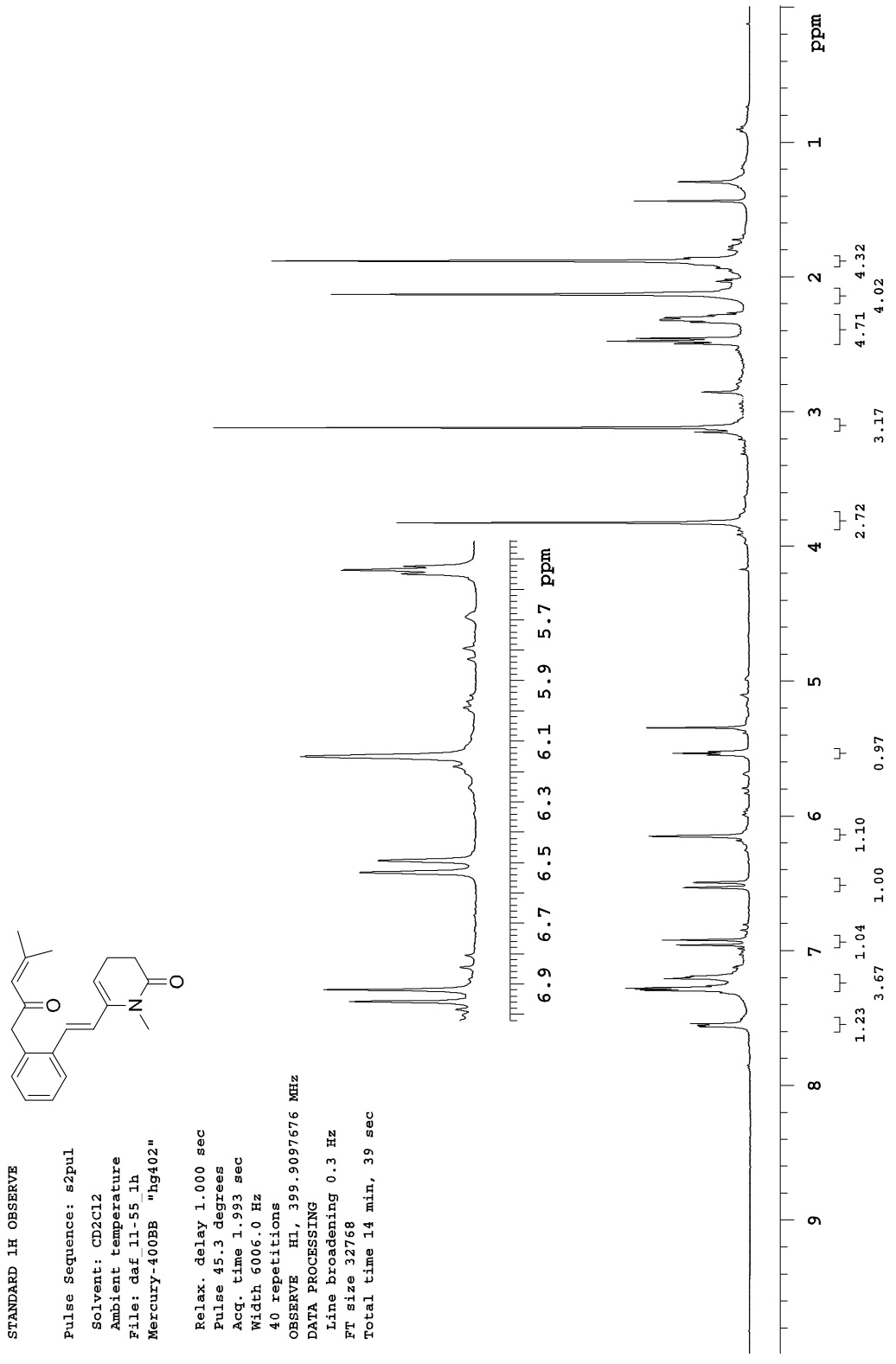
Spectrum 2.282 ^{13}C NMR (C_6D_6, 100 MHz) of compound **665**



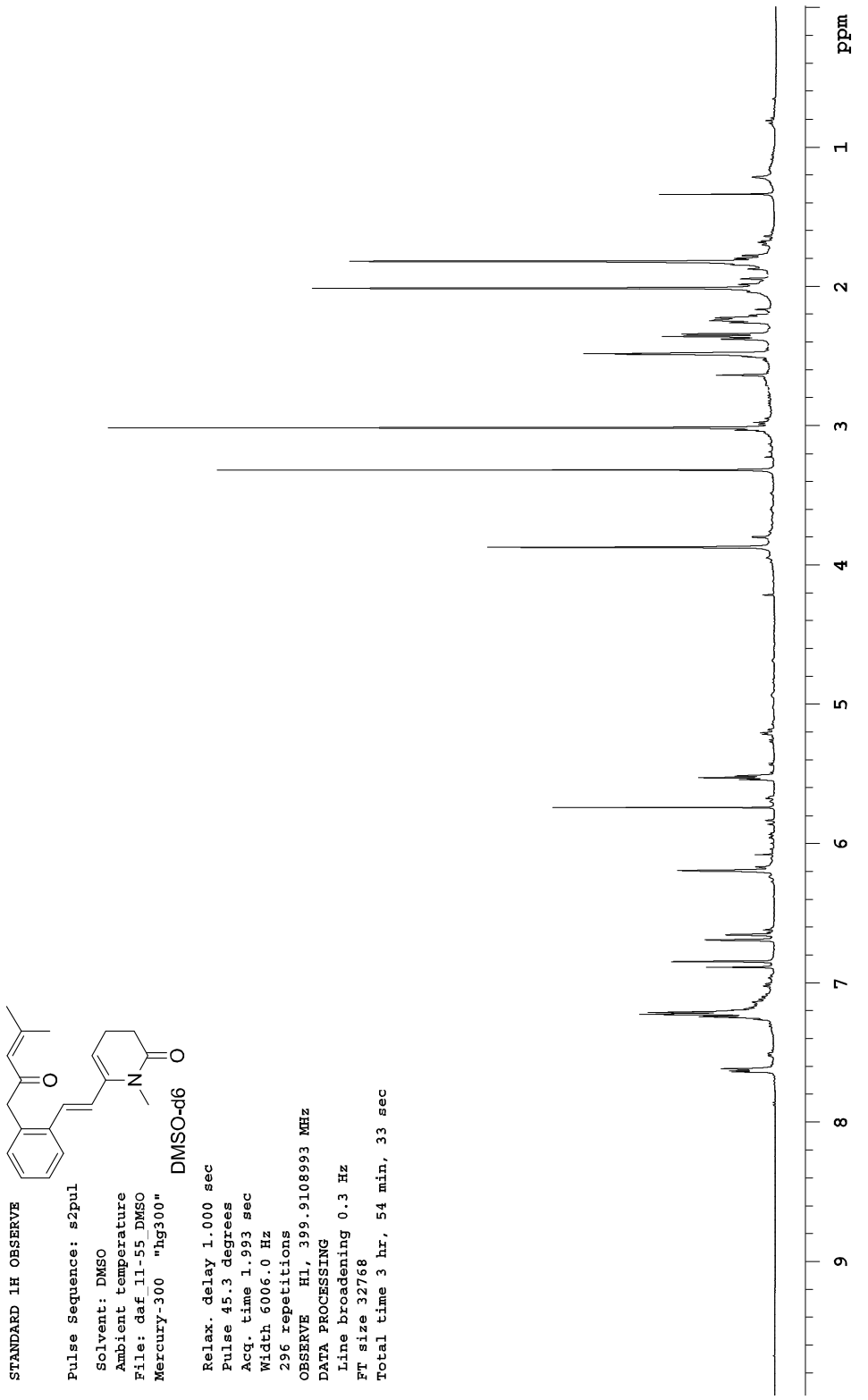
Spectrum 2.283 ^{1}H NMR (C_6D_6, 400 MHz) of compound **666**



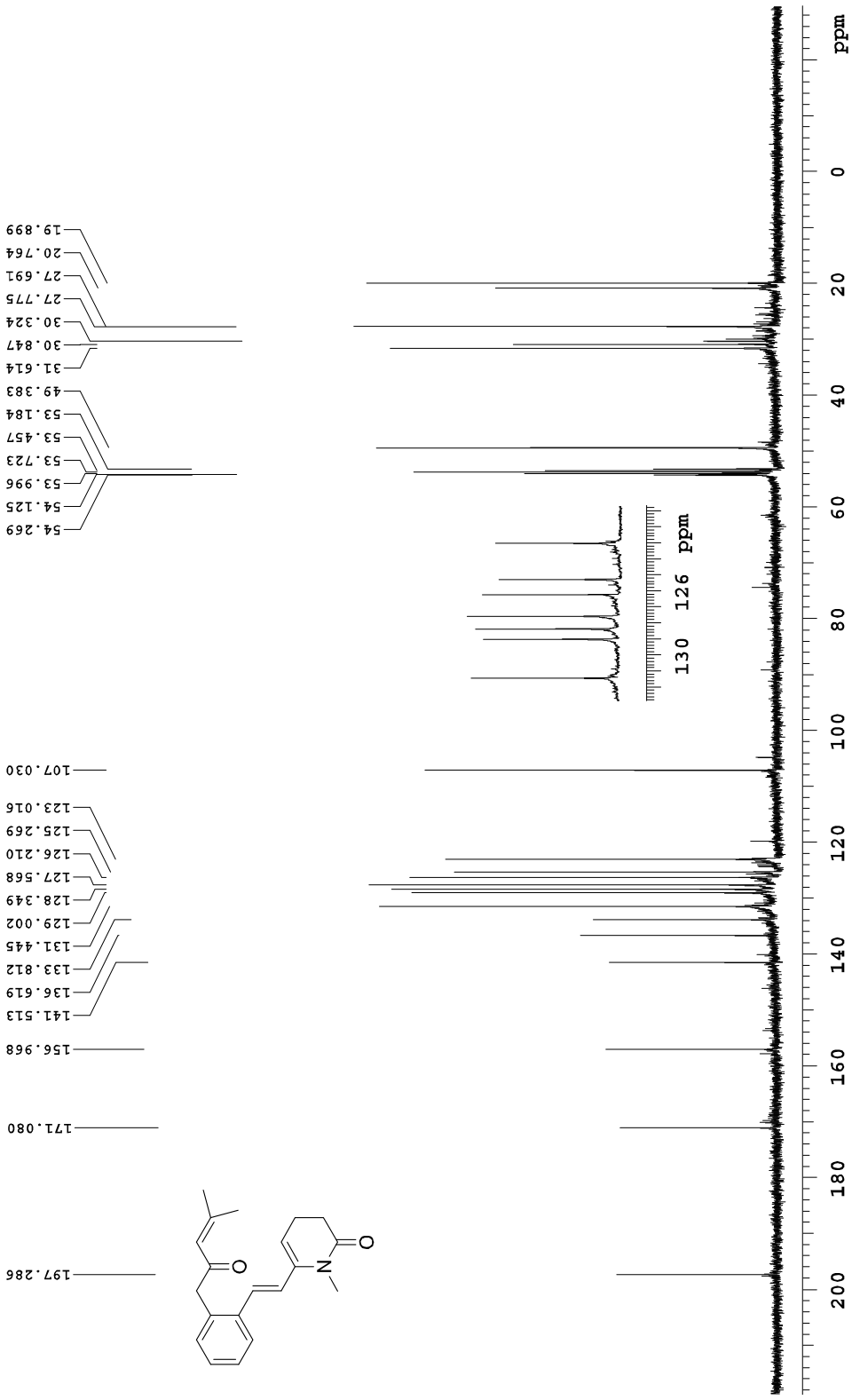
Spectrum 2.284 ^{13}C NMR (C_6D_6, 100 MHz) of compound **666**



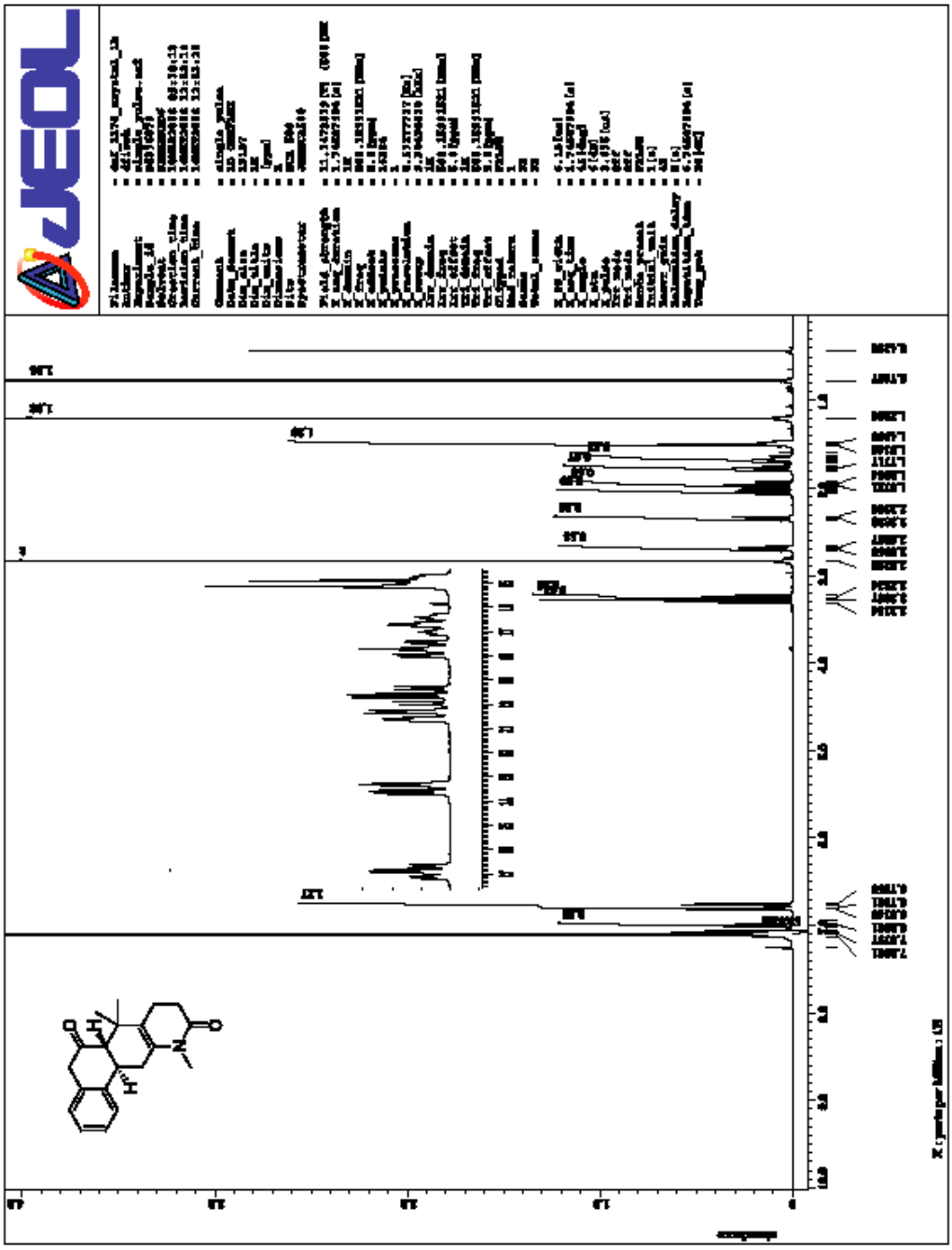
Spectrum 2.285 ^{1}H NMR (CD_2Cl_2, 400 MHz) of compound **667**



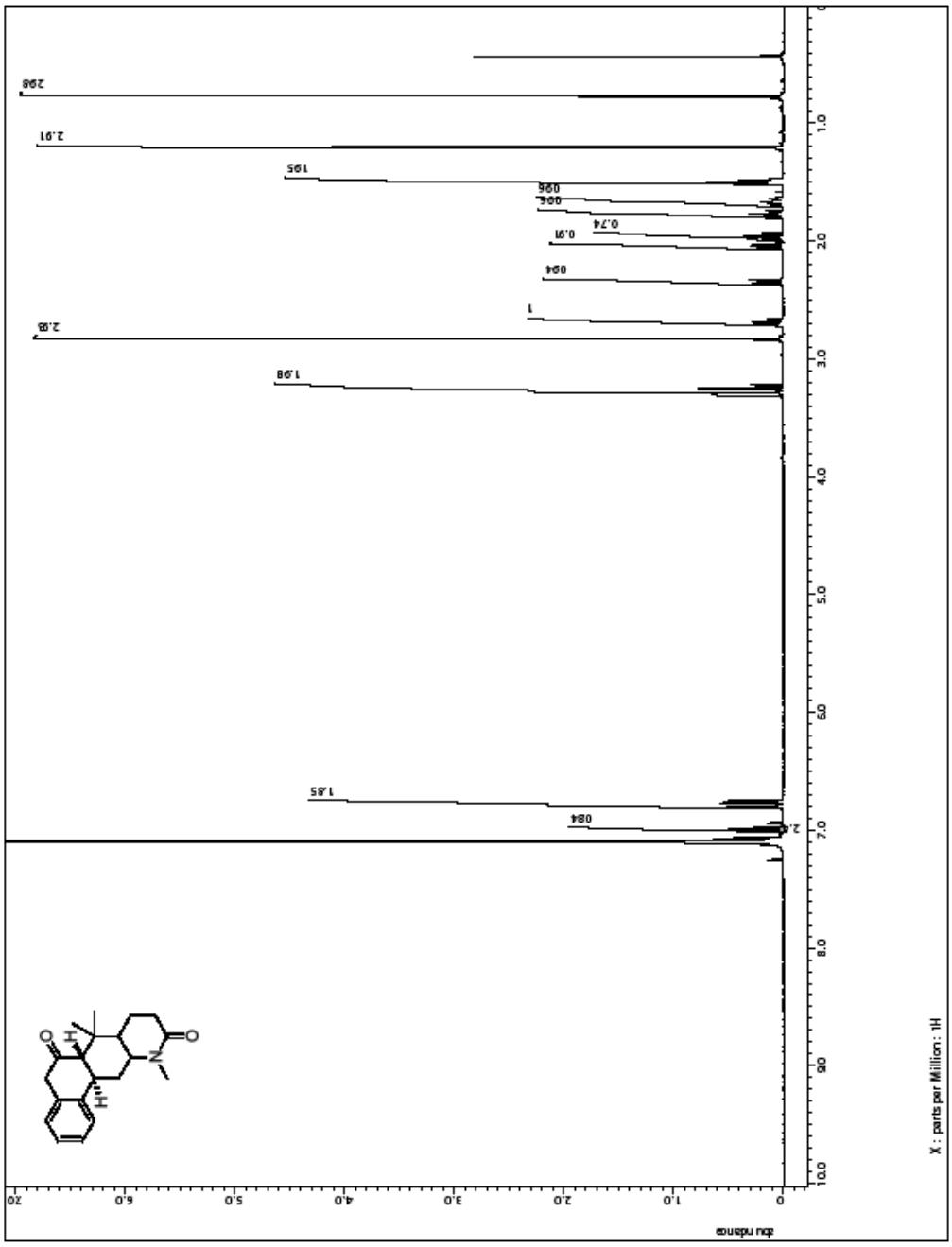
Spectrum 2.286 ^{1}H NMR (DMSO-d6, 400 MHz) of compound **667**



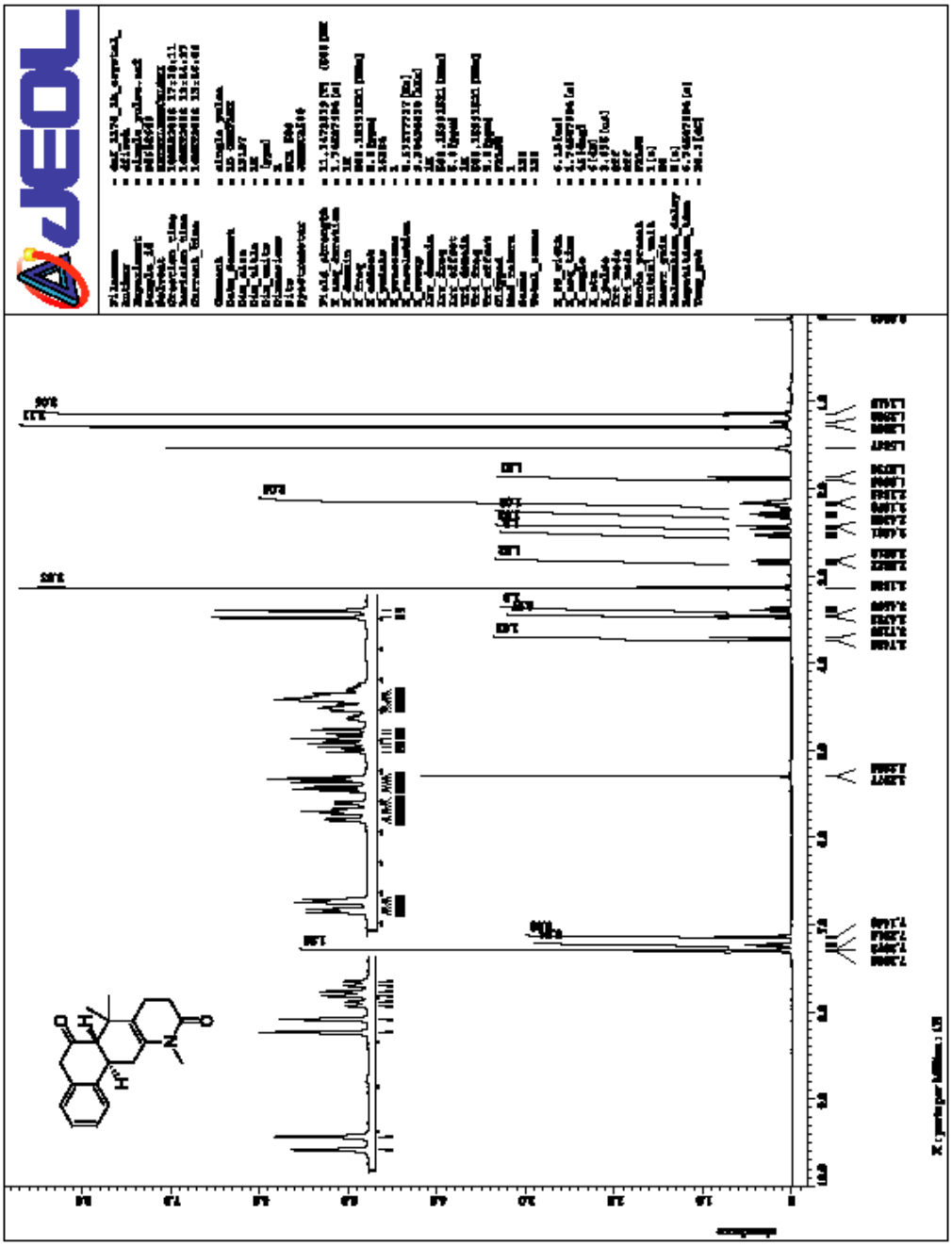
Spectrum 2.287 ^{13}C NMR (CD_2Cl_2, 100 MHz) of compound **667**



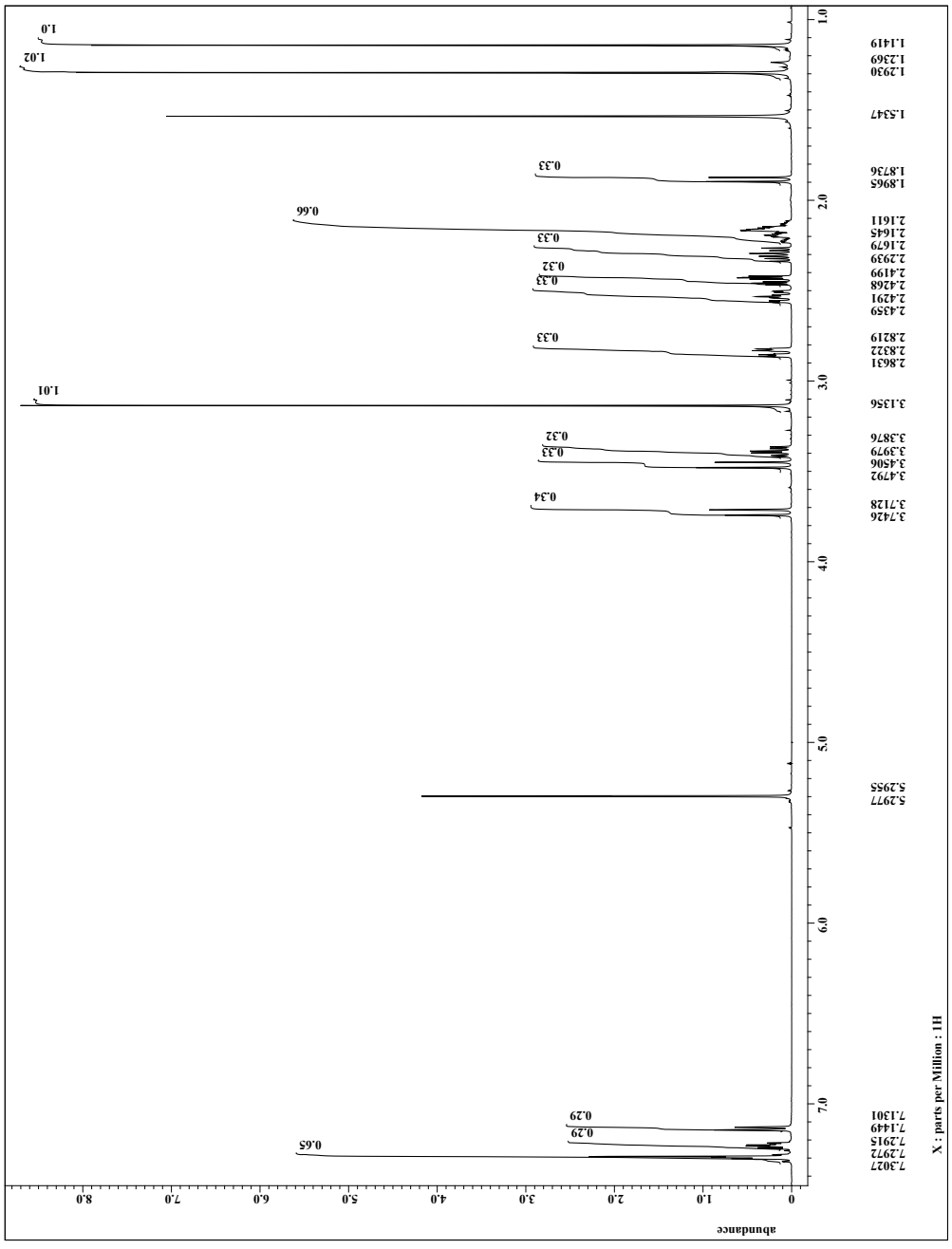
Spectrum 2.288 ^{1}H NMR (C_6D_6, 500 MHz) of compound **668**



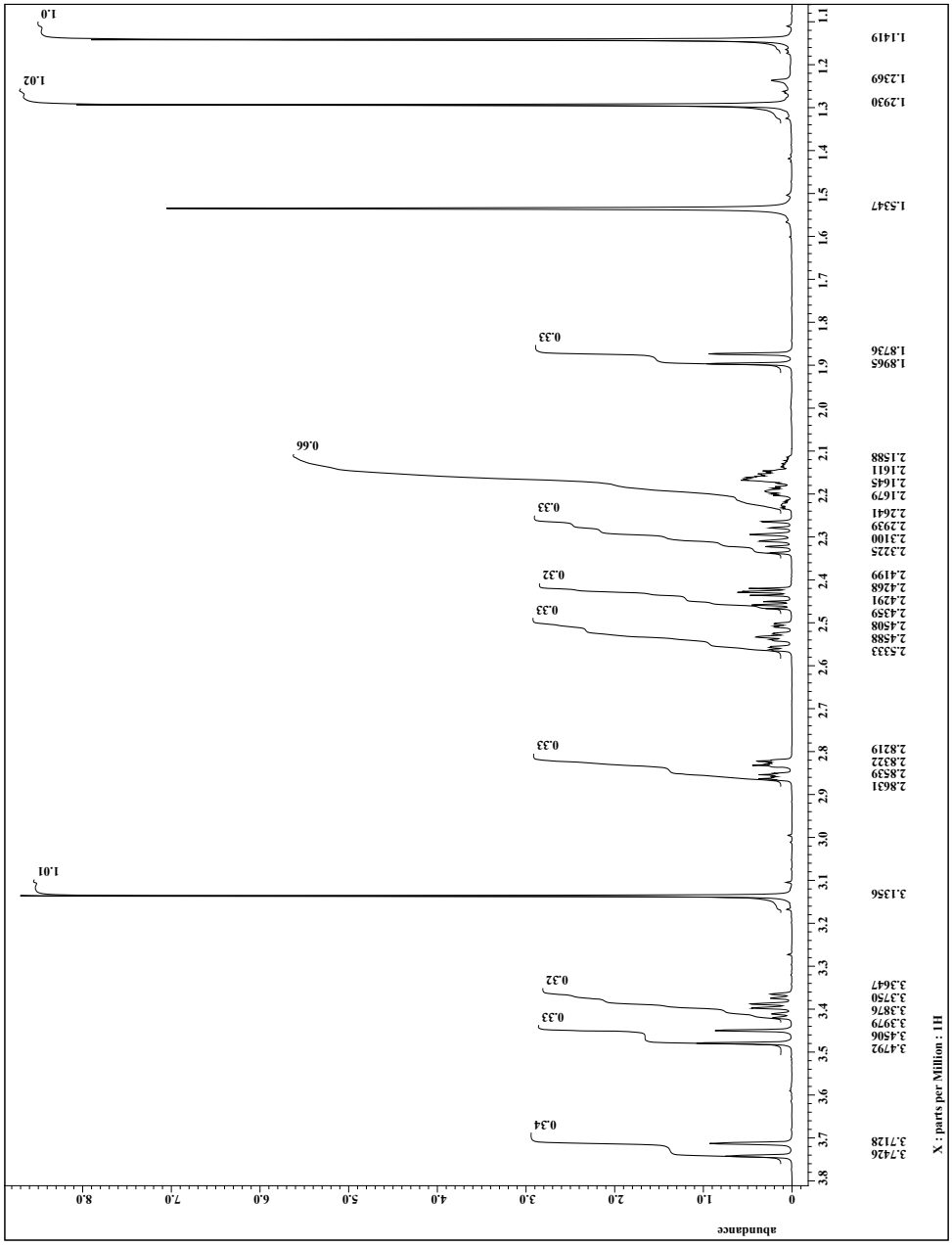
Spectrum 2.289 ^{1}H NMR (C_6D_6, 500 MHz) of compound **668**



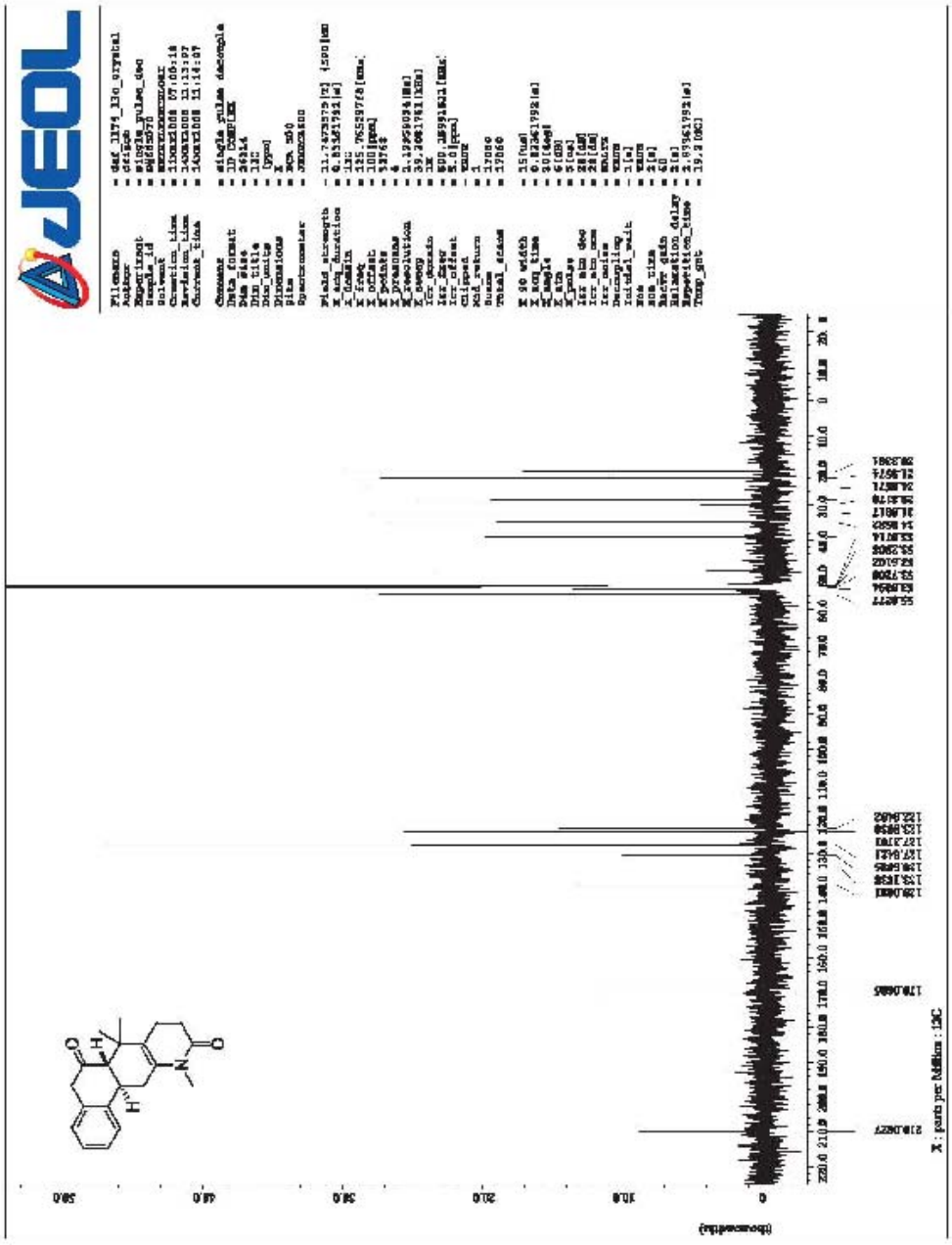
Spectrum 2.290 ^{1}H NMR (CD_2Cl_2, 500 MHz) of compound **668**



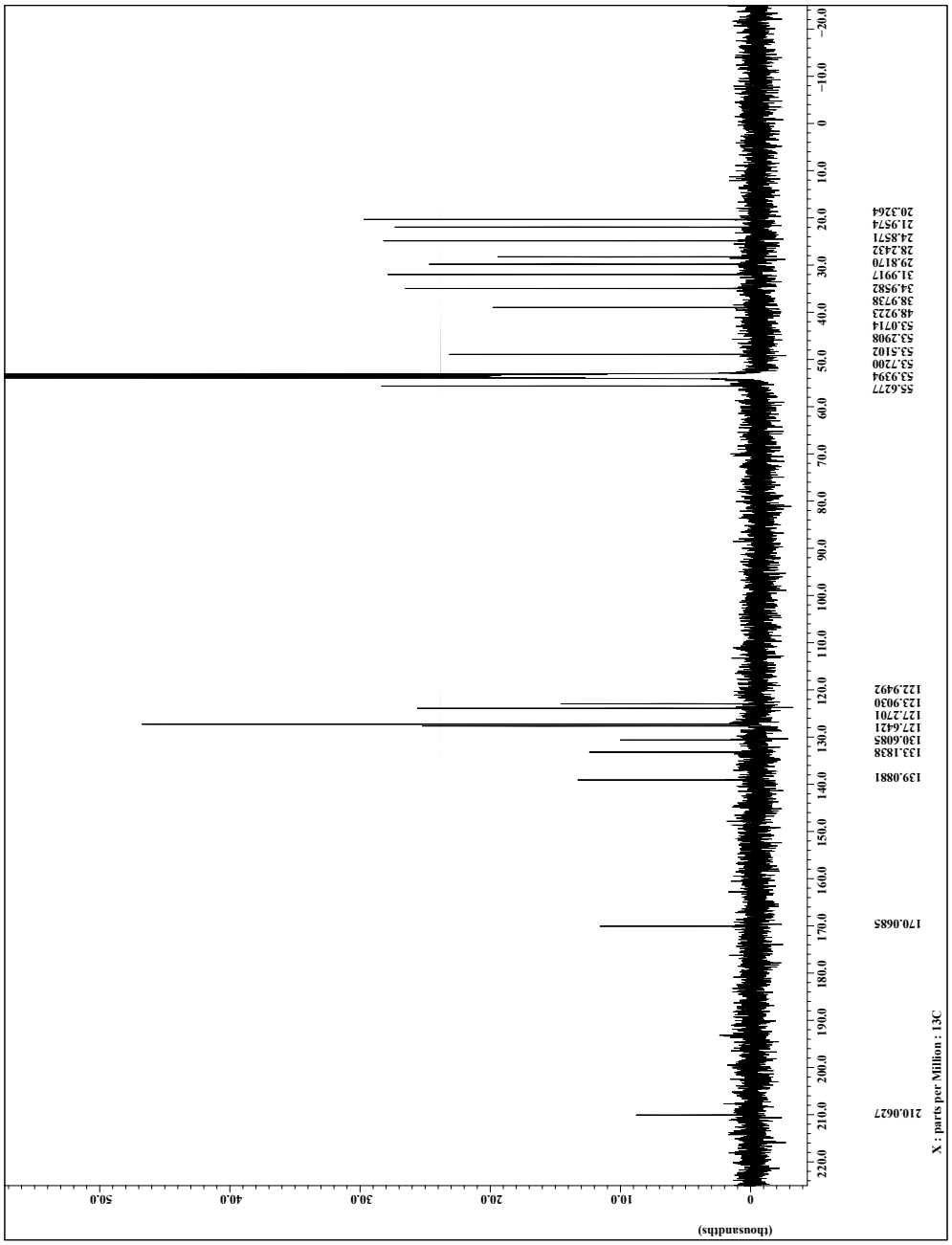
Spectrum 2.291 ^{1}H NMR (CD_2Cl_2, 500 MHz) of compound **668**



Spectrum 2.292 ^{1}H NMR (CD_2Cl_2, 500 MHz) of compound **668**



Spectrum 2.293 ^{13}C NMR (CD_2Cl_2, 125 MHz) of compound **668**



Spectrum 2.294 ^{13}C NMR (CD_2Cl_2, 125 MHz) of compound **668**

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