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UNIVERSITY OF CALIFORNIA, SAN DIEGO

Synthetic Studies towards the Total Synthesis of Norzoanthamine

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in

Chemistry

by

Fatima R. Rivas

Committee in charge:

Professor Emmanuel A. Theodorakis, Chair
Professor Laurence L. Brunton
Professor Kyriacos C. Nicolaou
Professor Susan Taylor
Professor Michael VanNieuwenhze

2006

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The dissertation of Fatima R. Rivas is approved, and it is acceptable in quality and form for publication on microfilm.

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Chair

University of California, San Diego

2006

DEDICATION

To my family, and TT: I thank you for your love, and support.

EPIGRAPH

The end of the road,

While no one can go back and change the past to make a marvelous beginning, everyone can make an amazing ending.

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LIST OF SYMBOLS AND ABBREVIATIONS

Ac	acetyl
ACN	acetonitrile
Boc (t-BOC)	tert-butoxycarbonyl
Bu	butyl
calcd	calculated
CAN	ceric ammonium nitrate
CCDC	Cambridge Crystallographic Data Center
CI	chemical ionization
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCM	dichloromethane
DEA	diethylaniline
DIBAL	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMA	N,N-dimethylacetamide
DMAP	N,N-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMP	Dess – Martin periodinane
DMS	dimethylsulfide

DMSO	dimethylsulfoxide
ED_{50}	mean effective dose
Et	ethyl
FAB	fast atom bombardment
FT-IR	Fourier transform-infrared
[H]	reduction
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
LTA	lead tetraacetate
m-CPBA	m-chloroperoxybenzoic acid
Me	methyl
MEM	methoxy ethoxy methyl
MOM	methoxymethyl
MHz	megahertz
NBS	N-bromosuccinimide
NIS	N-iodosuccinimide

NMO	4-methylmorpholine N-oxide
NMR	nuclear magnetic resonance
[O]	oxidation
ORTEP	Oak Ridge thermal ellipsoid plot
PG	protecting group
Piv	pivaloyl
Ph	phenyl
PMA	phosphomolybdic acid
PPTS	pyridinium p-toluenesulfonate
R_f	retention factor
SAR	structure – activity relationship
TBAF	tetrabutylammonium fluoride
TBABr	tetrabutylammonium bromide
TBS	t-butyldimethylsilyl
TEA	triethylamine
TES	triethylsilyl
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
TFE	trifluoroethanol
TFAA	trifluoroacetic anhydride
TFPA	trifluoroperacetic acid
THF	tetrahydrofuran

TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl
UV	ultraviolet

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PUBLICATIONS:

1. Rivas, F.; Ghosh, S.; Theodorakis, E. A. Synthetic studies toward the zoanthamine alkaloids: synthesis of the fully functionalized BC ring motif. *Tetrahedron Lett* **2005**, *46*, 5281-5284.

2. Rivas, F.; Gonzalez, M. A.; Theodorakis, E. A. Studies toward the total synthesis of norzoanthamine. Abstracts of Papers, 229th ACS National Meeting, San Diego, CA, United States, March 13-17, 2005 (**2005**),

3. Gonzalez, M. A.; Ghosh, S.; Rivas, F.; Fischer, D.; Theodorakis, E. A. Synthesis of (+) - and (-)-isocarvone. *Tetrahedron Lett* **2004**, *45*, 5039-5041.

4. Ghosh, S.; Rivas, F.; Fischer, D.; Gonzalez, M. A.; Theodorakis, E. A. Stereoselective Synthesis of the ABC Ring System of Norzoanthamine. *Org Lett* **2004**, *6*, 941-944.

5. Ling, T.; Rivas, F.; Theodorakis, E. A. Stereoselective synthesis of the fully functionalized core fragment of terpentecin. *Tetrahedron Lett* **2002**, *43*, 9019-9022.

ABSTRACT OF THE DISSERTATION

Synthetic Studies towards the Total Synthesis of Norzoanthamine

by

Fatima Rivas

Doctor in Philosophy in Chemistry

University of California, San Diego

Professor Emmanuel A. Theodorakis, Chair

The work presented herein is the conclusion of synthetic studies toward the total synthesis of norzoanthamine. This dissertation on the norzoanthamine synthetic studies will be divided into 3 sections: (1) an introduction describing the norzoanthamine family along with their biological significance and previous studies; (2) a stereoselective synthesis of the ABC ring system, and the crucial development of the fully functionalized C ring; (3) a biomimetic approach towards norzoanthamine; which will discuss studies to create the C ring from a polyene system through a Diels-Alder reaction, studies to synthesize the A ring through a sigmatropic rearrangement, studies to generate the BC ring through an intramolecular Diels-Alder reaction from

carvone as a chiral pool, development of isocarvone, and studies of 2-acylamino 1,3 dienes as a viable synthon to form the BC ring through a [4+2] cycloaddition reaction.

CHAPTER 1

AN INTRODUCTION TO THE NORZOANTHAMINE FAMILY

Section 1.1 Natural Origins of Norzoanthamine

Norzoanthamine belongs to a new alkaloid family (known as the zoanthamine) found in the Zoanthus genus (Zoanthus Nymphaeus and Zoanthus species, Phylum Cnidaria), a known Class Anthozoa, a kind of sea anemones, Order Zoanthidea, Family Zoanthidae)[1]. These marine cnidarians, most commonly known as corals, are small sea anemone-like polyps, typically forming colonies of many individuals. A coral's "head" is formed of many individual polyps. Each polyp is only a few millimeters in diameter (Figure 1.1).[1b] They have a cylindrical body with a broad base and rows of hollow tentacles around the upper disk, a central sac, and a space between the outer and inner sac, which is divided by walls called mesenteries.[1d] A colony of polyps functions essentially as a single organism by sharing nutrients via a well-developed gastrovascular network, and the polyps also shared the same genetic structure (Figure 1.2).[1] Each polyp generation grows on the skeletal remains of a previous generation, forming a structure that has a shape characteristic of each species, but naturally subject to environmental changes. Normally, the zoanthids are soft, contractile and sensitive. They can quickly transform from a beautiful flower form to a shapeless, unattractive mass.[1,3d]

Even though sea anemones eat fish and other items and corals eat plankton, they obtain much of their nutrient requirement from symbiotic unicellular dinoflagellates called zooxanthellae.[1e] The reason why they are usually found not far beneath the surface is because they are dependent upon growing in sunlight. Corals can grow in clear waters at depths of 60 m (200 ft).[1h] Other corals, notably the cold-

water genus Lophelia, do not have associated algae, and can live in much deeper water with recent finds as deep as 3000 m.[1d] The hexacorals that produced the zoanthamine compounds are almost exclusively tropical in distribution. They are found in areas such as India and the Canary Islands (Figure 1.2).[2e]

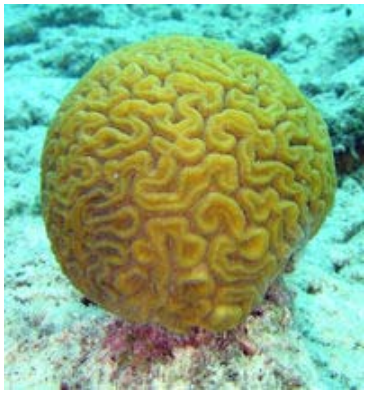


Figure 1.1: Head of a coral of the Class Anthozoa, subclass: Zoantharia

The known secondary metabolites isolated from zoanthids are mainly alkaloids. They are grouped into two classes: the alkaloids of the zoanthoxanthin class, natural tetrazacyclopentazulene fluorescent pigments, and the alkaloids of the zoanthamine class which have a complex carbon skeleton.[1c] Most chemical substances coming from marine invertebrate are purported to be defensive secretions. For instance, if these corals are threatened, they eject jets of water containing the zoanthamine-type compounds. They can cause irritation to the attacker's sensitive membrane systems such as the eyes.[2a]

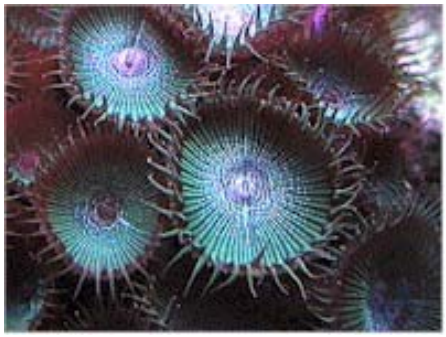



Figure 1.2: Zoanthid colonies from India and Canary Island respectively.

Section 1.2 Phytochemistry

Section 1.2.1 Isolated Natural Products and Structural Analysis

In 1984, zoanthamine (**6**, Figure 1.3) was the first of five novel alkaloids of this family to undergo isolation, and structural determination via X-ray diffraction by Faulkner's group in collaboration with Clardy.[2a] These zoanthamines were isolated from an unidentified colonial zoanthid Zoanthus sp. collected at the Visakhapatnam coast of India. Its complex structure revealed that this family of molecules was unrelated to any previously known alkaloid structure.[2] Currently, seventeen related molecules have been described. Figure 1.3 illustrates the structural complexity found among these natural metabolites.[2] As shown in Figure 1.3, these alkaloid structures conserve the BCD ring core with various oxidation states at the A ring as well as the EFG rings. Norzoanthamine, along with 4 other members, was first isolated from the Amami Islands by Uemura.[2d] The absolute stereochemistry of these compounds was first reported by Uemura's group[4] through an extensive analysis of norzoanthamine, and based on those studies the entire family has been presumed to have the same

absolute stereochemistry due to their ABC core similarities. They are characterized not only by their unique array of structural and stereochemical complexity, but also

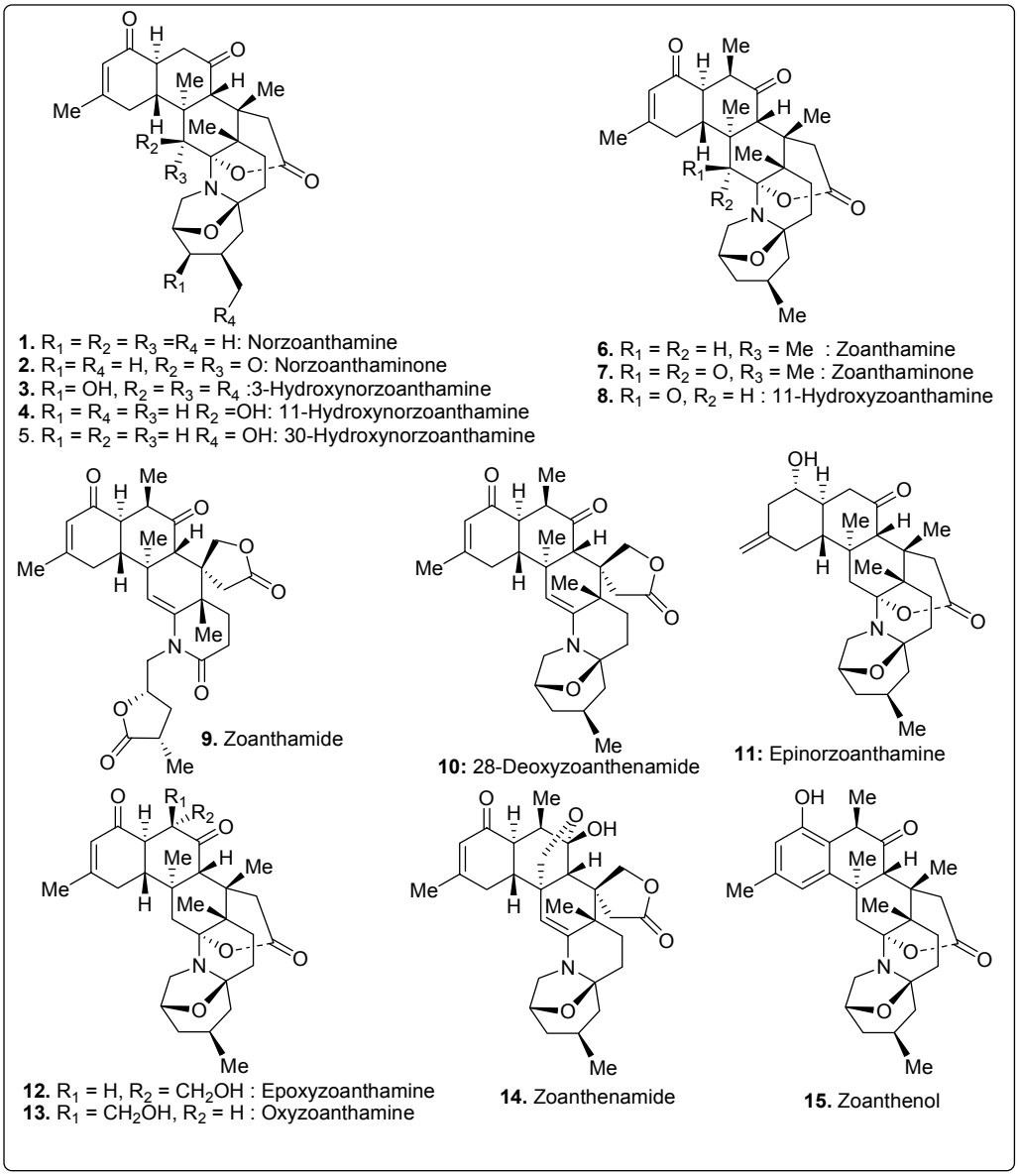


Figure 1.3: Variety and similarity of the zoanthamines natural products.

by their important and interesting pharmacological activities. The absolute stereochemistry of norzoanthamine was determined by a modified Mosher's method

(R) and (S) MTPA esters. Norzoanthamine was treated with $NaBH_4$ to reduced C-17 followed by treatment with (R)-MTPACl.[4,5g] Interestingly, this reduction induced enamine activity. It opened the G ring to produced C-7/C-24 bond, followed by iminium development and reduction to form compound **16** (Figure 1.4).

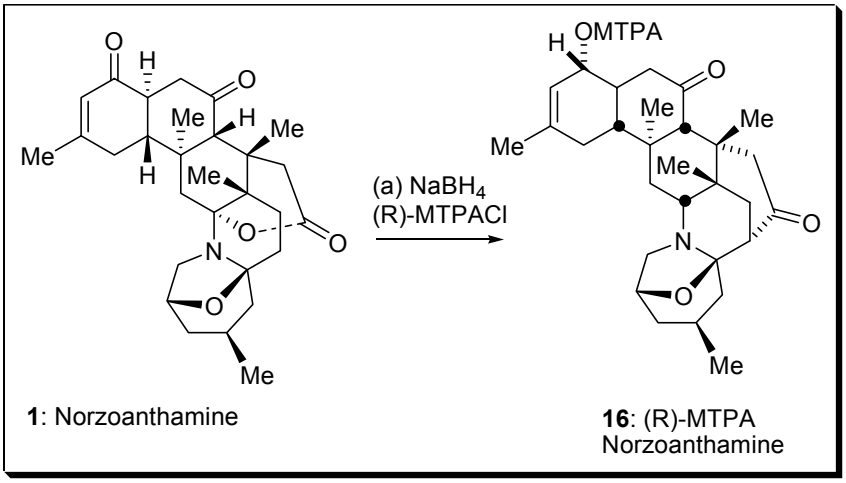
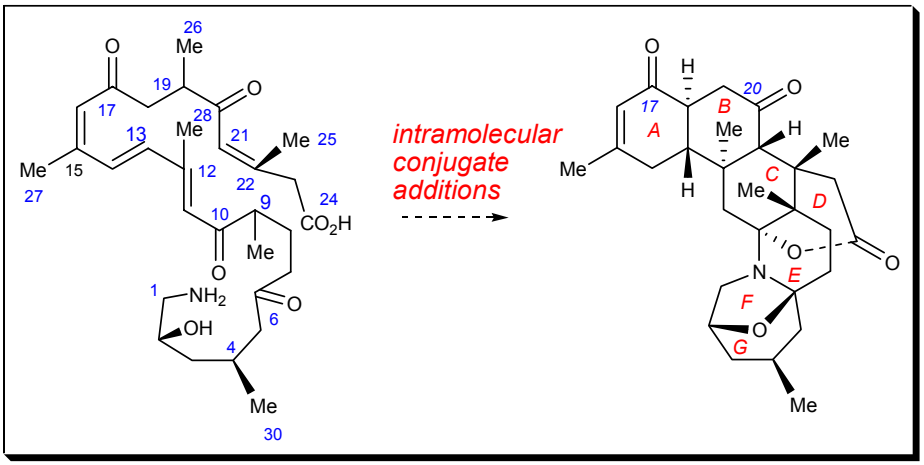


Figure 1.4: Reductive trasformation that led to the absolute configuration of norzoanthamine.

Uemura was able to determine the absolute configuration to be 2R, 4S, 6S, 9S, 10R, 12S, 13R, !8S, 21S, and 22S. In addition, based on NMR analysis, it was deduced that zoanthamine, oxyzoanthamine, norzoanthaminone, cyclozoanthamine, epinorzoanthamine and norzoanthamine alkaloids isolated from the zoanthid *Zoanthus sp.* have the same absolute chemistry.[4]

Section 1.2.2 Biosynthesis

The zoanthamine alkaloids contain a complex skeleton defined by its highly functionalized heptacyclic/hexacyclic structure and three quaternary carbon centers (C-9, C-12, and C-22).



Scheme 1.1: Proposed biosynthesis of the zoanthamines by Uemura**.**

The zoanthamine natural products may be suspected to be tripenoids because the carbon skeleton is composed of thirty carbon atoms. However, it is not possible to understand its biogenesis by the general isoprene rule.[4b] Uemura and et al.[5g] proposed that zoanthamine, shown in Scheme **1.1**, could undergo a sophisticated polyketide biogenetic pathway.[5g] This scheme also shows the correct numbering usage to describe these alkaloids and it will be used throughout the dissertation. Although, a very attractive proposal, only Uemura[7] and our research group has attempted such a risky endeavor. This polyketide system could undergo a series of conjugate additions, like a "zipper-type" cyclization reaction. In addition, it was also postulated by Uemura that norzoanthamine arises from oxidation of C-26, which undergoes a retro-aldol type reaction to provide norzoanthamine.[1d]

We speculated that if such series of reactions could occur from a polyene synthon containing the C-4 center, it would establish chirality and stereocontrol to the overall transformation. Such a proposal is very intriguing and could be a remarkable chemical pathway for the biosynthesis of the zoanthamines, but it is a very risky

approach. Recently, Uemura's group has reported the construction of a precursor to this polyene system, demonstrating an efficient synthetic approach to this intermediate, but its cyclization remains unknown.[7]

Section 1.3 Biological Activity

These interesting polycyclic alkaloids are unquestionably to be the subject of intense biological and chemical investigations because they have shown good pharmacological activities.[5,6] Over the past twenty-two years, more than 14 of these compounds have been reported.[6c] They are characterized by their unique array of structural and stereochemical complexity. Preliminary studies demonstrated that some of these compounds (as shown in Figure 1.3) such as zoanthenamide (14), zoanthamide (9), and 28-deoxyzoanthenamide (10) possess anti-inflammatory properties, inhibiting phorbol myristate acetate (PMA) induced inflammation in mouse ears[5f], and demonstrated potent analgesic effects.[5g] Subsequently, norzoanthamine (1), norzoanthaminone (2), epinorzoanthamine (11), and oxyzoanthamine (13) were found to inhibit the growth of P-388 murine leukemia cell lines, with IC50 values of 24, 1.0, 2.6, and 7.0 mg/mL, respectively.[5g,6c]

In addition, to anti-inflammatory properties, norzoanthamine was found to have a very selective property. It was active against osteoporosis. While antitumor effects of defensive substances of marine origin are known, the norzoanthamines' prevention/treatment of osteoporosis was unexpected.[5i]

Osteoporosis, or porous bone, is a disease characterized by low bone mass and structural deterioration of bone tissue.[6] A bone is not a hard and lifeless structure. It

is a complex, living tissue that provides structural support for muscles. It protects vital organs and stores calcium. It is essential for bone density and strength.[6b] If osteoporosis is left untreated, it can progress painlessly until a bone breaks. Although, any bone can be affected, fractures occur especially at the hip, spine and wrist. Osteoporosis is often called a "silent disease" because bone loss occurs without symptoms. An individual may not be aware that he/she has osteoporosis until their bones become so weak that they fracture or a vertebra collapses.[6c] It is estimated that out the 10 million Americans that suffer from this disease, eight million are women and two million are men.[5b] In women, bone loss accelerates after menopause, when the ovaries stop producing estrogen - the hormone that protects against bone loss. The only way to determine bone density and fracture risk for osteoporosis is to have a bone mass measurement (also called bone mineral density or BMD test). Although, there is no cure for osteoporosis, the following medications are approved by the FDA for postmenopausal women to prevent and/or treat osteoporosis: bisphosphonates, estrogen/hormone therapy, and selective estrogen receptor modulators (SERMs).[5f]

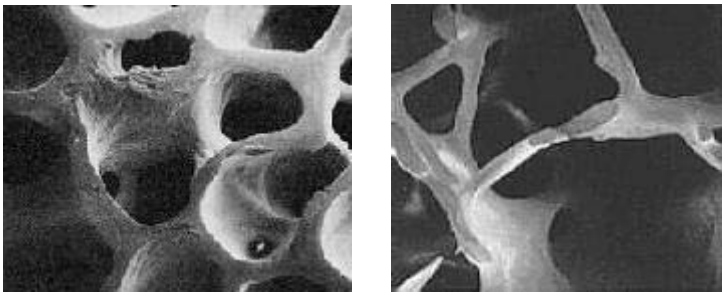


Figure 1.5: Normal bone (left) and osteoporatic bone (right).

Figure 1.5 shows the effects of osteoporosis on a bone.[5h-k] The left picture shows the texture of a normal and healthy bone while the right side shows the damage

bone by osteoporosis.[6h] Norzoanthamine hydrochloride showed to osteoporosis-inhibition properties through testing its effect on bone weight and strength in ovariectomized mice (an animal model of postmenopausal osteoporosis).[5h-m]

Norzoanthamine significantly suppressed the decrease infemoral weight caused by ovariectomy without an increase in uterine weight when administered at daily doses of 0.8 mg/Kg over a period of four weeks. Such data suggested that the mode of action of norzoanthamine hydrochloride differs from that of estrogen.[5m] Furthermore, the failure load and yield energy of the femurs were maintained by the administration of norzoanthamine hydrochloride at a low dose of 0.016 to 0.4 mg/kg/day (p.o.). In addition, it is known that ovariectomy causes a decrease in humeralis trabeculae, but treatment with norzoanthamine hydrochloride significantly suppressed this decrease in a dose- dependent manner as shown in Figure 1.6 in pictures C, D, and E respectively. In ovariectomized mice treated with norzoanthamine, the primary spongiosa did not significantly increase, and the morphology of the metaphysis remained nearly normal.[6e,l] Also, the formation of osteoclasts, which produce osteocalcin, a protein controlling the re-absorption of preexisting bone, is stimulated by interleukin IL-6. Investigators have shown that norzoanthamine and norzoanthamine hydrochloride inhibit IL-6 induction with IC50 values of 13 and 4.7 μg/mL, respectively. These studies clearly suggest that norzoanthamine can be used as a preventive or treatment method for osteoporosis.[6f] SAR studies of norzoanthamine derivatives on IL-6 induction in MC3T3-E1 cells suggested that the double bond (C-15/C-16) and lactone moiety (D ring) were responsible for the biological activity.[5g]

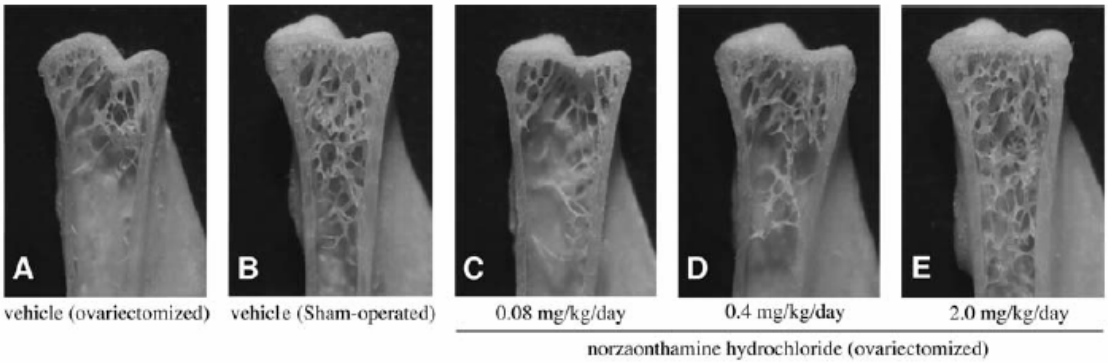


Figure 1.6: Effects of norzoanthamine hydrochloride on humeralis morphology in ovariectomized mice by Uemura's group.

Recent findings by Jimenez' group[6c] indicate that the zoanthamines show platelet aggregation activity. Platelet aggregation plays a crucial role in physiological hemostasis and pathological thrombosis. In fact, platelet thrombus formation is implicated in both venous thrombosis such as pulmonary embolism, deep vein thrombosis, disseminated intravascular coagulation, and in arterial thrombosis. The latter being responsible for myocardial infarction, stroke, and other cardiovascular diseases.[6a] Moreover, it is an established fact in the medical community that platelet deposition on the arterial wall significantly contributes to the progress of atherosclerotic lesions, which may result in the occlusion of the vessel.[6b] Recently, antiplatelet drugs, specifically inhibitors of platelet aggregation, have become essential tools in the therapy of arterial thrombotic disorders. Jimenez' group study that the in vitro effects of the zoanthamine alkaloids[6c] on washed human platelet aggregation, to evaluate the pro-aggregate activity and the antiplatelet effects of the alkaloids on the aggregation induced by either thrombin (0.075 UI/mL), collagen (12.5 mg/ mL) or arachidonic acid (15 mM). In this study, the zoanthamines behaved as a heterogeneous group of compounds in terms of their effect on platelet reactivity, both

at rest and with activated platelets. 3-hydroxynorzoanthamine (**3**), 11-hydroxynorzoanthamine (**12**), 30-hydroxynorzoanthamine (**4**), 11-hydroxyzoanthamine (**8**), and a synthetic derivative of norzoanthamine (methyl ester of **1** at C-24), showed a clear inhibitory activity on the aggregation induced by all three stimulating agents employed.

Jimenez'group[6] has made preliminary observations suggesting that the A ring containing the C-15/C-16 double bond as well as the lactone ring D are important for their biological activity. The obtained findings indicated that the introduction of an oxidized functionality in combination with the presence or absence of the methyl group at C-26 in this class of alkaloids were two of the fundamental factors related to the modulation of the inhibitory platelet aggregation induced because the most active zoanthamine-type alkaloids have this position in an oxidized form: 11-hydroxyzoanthamine and norzoanthamine are active agents against aggregation induced by all three stimulating agents, compound 11-hydroxynorzoanthamine against collagen- and AA-induced aggregation, and compound zoanthaminone is a potent aggregant agent. On the other hand, neither zoanthamine (1mM) nor norzoanthamine (1mM) showed activity in this essay. Finally, this study confirms the utility of the zoanthamine-type alkaloids as good model systems for rational drug design.[6c]

Section 1.4 Synthetic Studies of Norzoanthamine

The complex chemical structure of the norzoanthamine alkaloids as well as its biological profile has triggered strong research interest from several synthetic groups, including those of D. Williams,[9] S. Kobayashi,[10] D. Tanner,[11] and M. Miyashita,[12]

whose groups have made keystone contributions in the development of norzoanthamine and zoanthamine. The chemical synthesis of the zoanthamine alkaloids remained an unmet challenge for many years. Despite great synthetic efforts by the various groups mentioned above, no total synthesis had been published until recent efforts by Miyashita's group resulted in the first total synthesis of norzoanthamine.[12b] The zoanthamine alkaloids are very structurally complex compounds owing to their densely functionalized stereostructures.

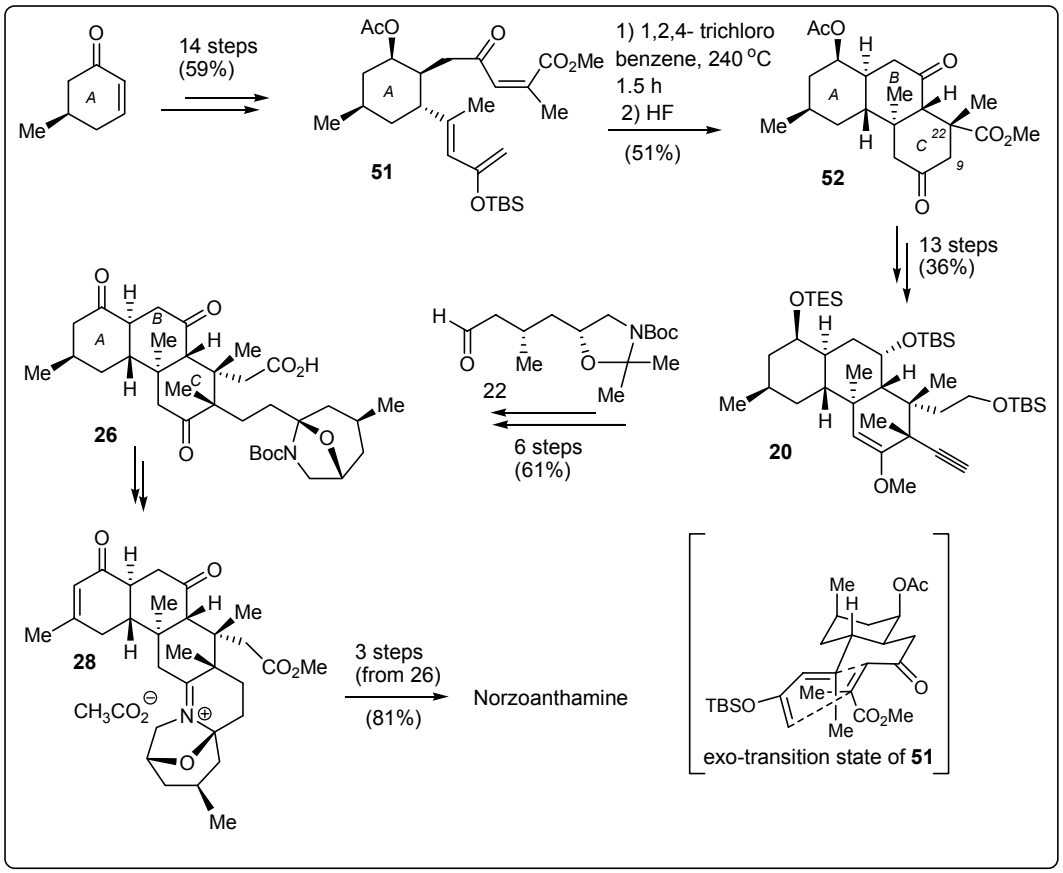
The major synthetic challenges posed by norzoanthamine (**1**) and some of its derivatives lie in the construction of the stereochemically dense C ring that has three adjacent quaternary asymmetric carbon atoms at the C-9, C-12, and C-22 positions. In addition, the stereoselective synthesis of the ABC carbon framework consisting of the *trans*-*anti*-*trans*-fused perhydrophenanthren skeleton and the stereoselective construction of two novel aminoacetal structures, which includes a bridged -lactone.

The advanced intermediates created by these groups have potential to be used as intermediates to complete the total synthesis of norzoanthamine. Their synthesis is critically highlighted in Scheme 1.2-1.5. These groups share one theme in common, the employment of a Diels-Alder reaction to construct either the AB or ABC ring fragments of the target molecule.

Of particular significance is the contribution by the Miyashita group[12] (Scheme 1.2) in which the monocyclic compound **51** underwent a Diels-Alder reaction to form compound **52.** This IMDA reaction gives rise to the desired exo product because the endo transition state is disfavored because of the 1,3-diaxial interaction between C-29

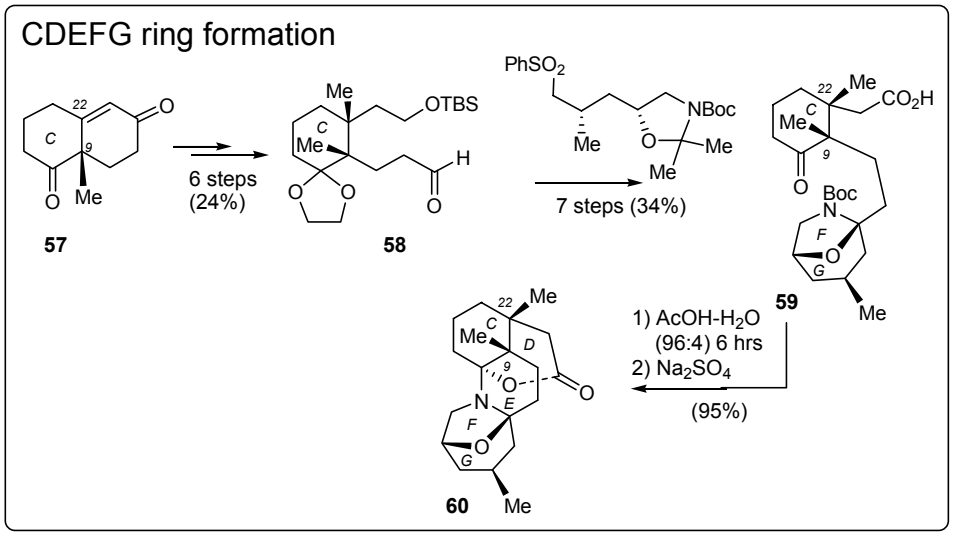
and C-25 (TS of **51** shown in Scheme 1.2). This approach provides a way to install the quaternary asymmetric carbon center at C-12 and C-22 positions of the B and C ring, respectively. The desired stereochemistry was confirmed by X-ray crystallographic analysis. The stereoselective construction of the remaining, most difficult quaternary asymmetric carbon center at the C-9 position at the C ring, was accomplished through a methyl alkylation of a β-keto lactone via its methyl enol ether form. The series of maneuvers from **52** to **20** was 13 steps in an overall 36% yield. This event was followed by side chain extension at C-9, C-22 carbon centers, and the final A ring functionalization. The construction of the DEFG ring system featuring a critical bis-aminoacetalization reaction similar to the previous work carried out by Kobayashi,[10c] culminated in Miyashita's first total synthesis of norzoanthamine.

Kobayashi's approach[45] (Scheme 1.3) uses the Wieland-Mischer enone **57** as the starting material for the formation of the C-ring analogue **58**, which contains both quaternary asymmetric carbon centers at the C-9, C-22 positions, in 6 steps in an overall 24 % yield .



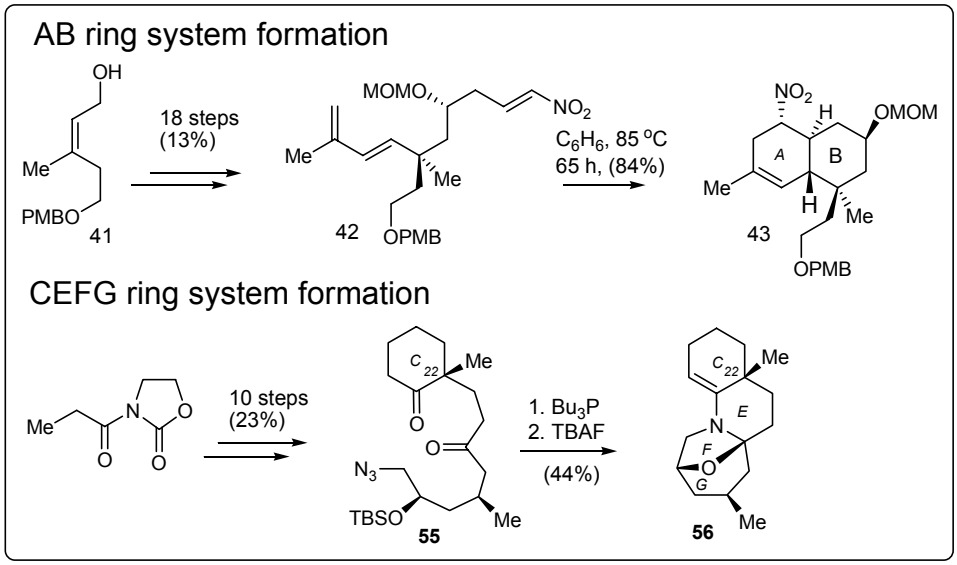
Scheme 1.2: Miyashita's approach to the total synthesis of norzoanthamine.

Sulfone **70** was synthesized in 7 steps with an overall yield of 34%. Further functionalization of the C-9 side chain produced compound **59,** which upon deprotection, cleanly cyclized to form the CDEFG ring system under acidic conditions in 95% yield.



Scheme 1.3: Kobayashi's approach to the CDEFG ring system of norzoanthamine.

Although highly informative, this approach delivers a pentacyclic system that is unlikely to be converted to the final product, due to the absence of functionality groups within the C ring and the difficulties associated with the introduction of appropriate functional groups from compound **57**.

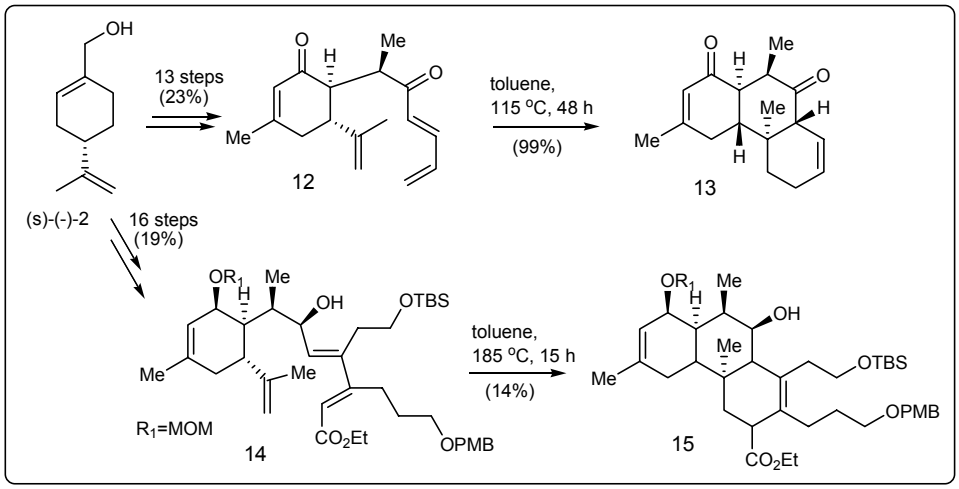


Scheme 1.4: William's synthetic approach to the AB ring system and CEFG ring system respectively.

The William's group has reported a synthetic strategy toward the AB ring system of norzoanthamine and the CEFG scaffold (Scheme 1.4). The latter contribution demonstrated that it is possible to form the fused aminal motif in structure **56**, following a similar approach to Kobayashi's method. However, this approach leaves unanswered questions regarding further functionalization at the C ring of the tetracyclic system. Their approach to the AB ring formation is quite promising, but unfortunately requires several steps **19**, in an overall yield of 10% from **41** to **43**. Because of the modest yields, it is unlikely to be pursued as a total synthesis approach.

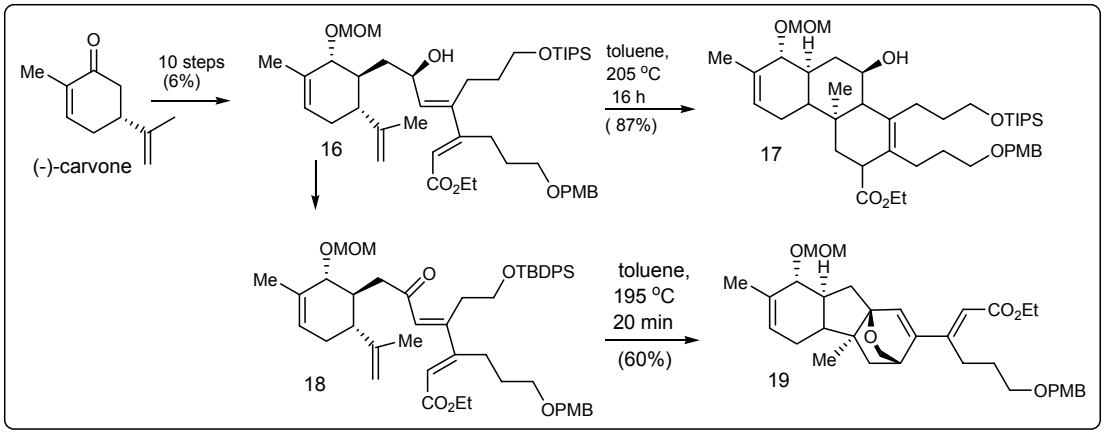
The Tanner group has carried out various studies in developing the ABC core of norzoanthamine. They accomplished the conversion of compound **12** (from perillyl alcohol in 13 steps, 23% overall yield) to tricycle **13** via an intramolecular cycloaddition reaction that proceeded in quantitative yield (Scheme **1.5**)[10]. However, compound **13** can be difficult to functionalize. At that point, the Tanner group started to investigate more elaborated systems, but found that the IMDA proceeded in poor yields under a regular IMDA reaction. Making the diene electronically deficient (compound **14**), it underwent an inverse Diels- Alder reaction in a promising 14% yield (compound **15**). Their synthetic approach was lengthy when using perillyl alcohol, but when they switched to carvone as a model system (shown in Scheme 1.6), they were able to produce larger quantities of intermediate **16**, and **18** in very good yields. They also observed that the stereochemistry of the hydroxyl group at C-17 was responsible for the low yield of **14** since **17**, a similar compound produced the DA

product in 87% yield. Attempts to enhance the inverse DA reaction by oxidizing C-20 resulted in TBDPS elimination followed by cyclization of **18** to **19** in 60% yield.



Scheme 1.5: Tanner's synthetic approach to the ABC ring system using perillyl alcohol as a starting material.

Although promising work has been performed by Tanner, important challenging questions remain to be addressed such as the construction of the vicinal C-9, C-22 quaternary asymmetric carbon centers and the installation of the fused DEFG ring system.



Scheme 1.6: Tanner's synthetic approach to the ABC ring using carvone as a starting material.

Section 1.4 Conclusion

The zoanthamines have shown a broad spectrum of biological activity. Its discovery 22 years ago, changed the perspective of which potential drugs can come from the sea since no osteoporotic-inhibitor had been isolated from the ocean.[5h] The complex chemical structure of the norzoanthamine alkaloids together with their biological profile makes them appealing targets for total synthesis and several groups have extensively studied these remarkable molecules.

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CHAPTER 2

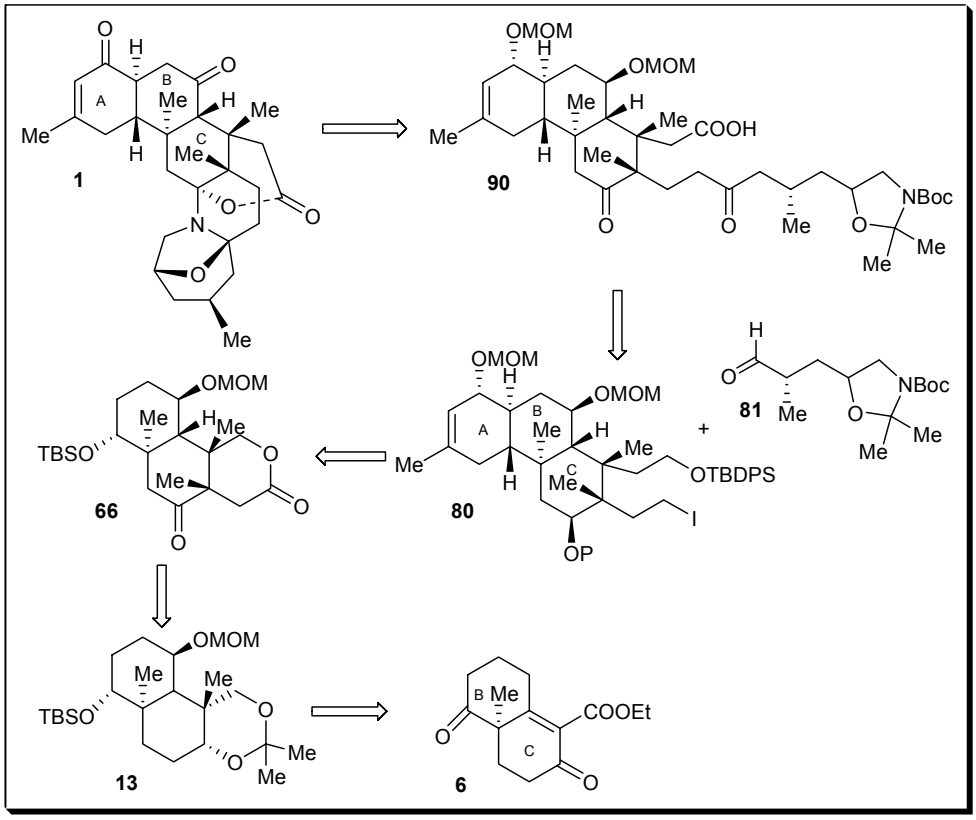
ABC RING CONSTRUCTION AND FUNCTIONALIZATION OF THE BC RING SYSTEM OF NORZOANTHAMINE

Section 2.1 Introduction

After analyzing the previous synthetic studies, we realized that the ABC core system of norzoanthamine could be constructed utilizing a new linear approach such as the one presented in Scheme 2.1. This scheme represents the overall idea of synthesizing this complicated structure in a concise way.

The retrosynthetic analysis of norzoanthamine, **1**, is shown in Scheme 2.1. Norzoanthamine can easily rise from the acid catalysized deprotection of **90**, as previously studied by Miyashita and Kobayashi. Therefore, the fragile aminal system needed to be developed at the end of the synthesis. Intermediate **90** can be developed from nucleophilic attack of aldehyde **81** by compound **80**, which can be synthesized from natural amino acid. Intermediate **80** could be formed from the elaboration of **66**. Intermediate **66** is the most challenging precursor because it posses a dense core with three quaternary centers. Finally, intermediate **13** can be synthesized from the known Wieland-Miescher enone **6**. Taking advantage of the ample chemistry available to manipulate structure **6**, we reasoned that this approach was a feasible route to produce large quantities of norzoanthamine rapidly in an efficient manner, and would contribute to the studies of the zoanthamines since no similar approach had been attempted.

This chapter will discuss the efforts made to stereoselectively synthesized the ABC ring system and the fully functionalized BC ring system of norzoanthamine by starting from bicyclic **6**.



Scheme 2.1: Proposed total synthesis of norzoanthamine.

Section 2.2 Stereoselective Synthesis of the ABC Ring of Norzoanthamine

The synthetic plan for the ABC ring of norzoanthamine proposes to construct intermediate **24** as shown in Scheme 2.2. We envisioned that development of the A ring of **24** could invoke conjugate reduction of enone **22** followed by functionalization of the C-15 and C-17 centers (zoanthamine numbering). Compound **22** could be synthesized by implementing a Robison annulation strategy.[1] It was believed that enone **15** could be formed from intermediate **8** after C-20 oxidation. Representing the

BC ring system is intermediate **6**. The trans-decalin system of **6** was projected to arise from annealing 2-methyl-1,3-cyclohedanedione **5** with Nazarov reagent **4.**[2]

The synthesis began with readily available synthon **4**, which was prepared by reaction of ethyl acetate with LDA and quenching of the anion with acrolein. The resulting alcohol was subsequently oxidized to ketone **4** by using Jones oxidation.[3] Synthon **6** was prepared by a KF-induced condensation of ketoester **4** with diketone **5** as previously described.[3] Stereoselective reduction of the C-13 carbonyl group of **6**[4] and silylation of the resulting alcohol gave rise to enone 13 (two steps, 89% overall yield). This silylation was problematic because under conventional conditions, where imidazole or pyridine are used, silyl ether **8** was contaminated with a disilylated adduct arising from concomitant reaction with the enone functionality in ratio of 1:10 in favor of the desired compound. However, usage of NH_4NO_3 in combination with

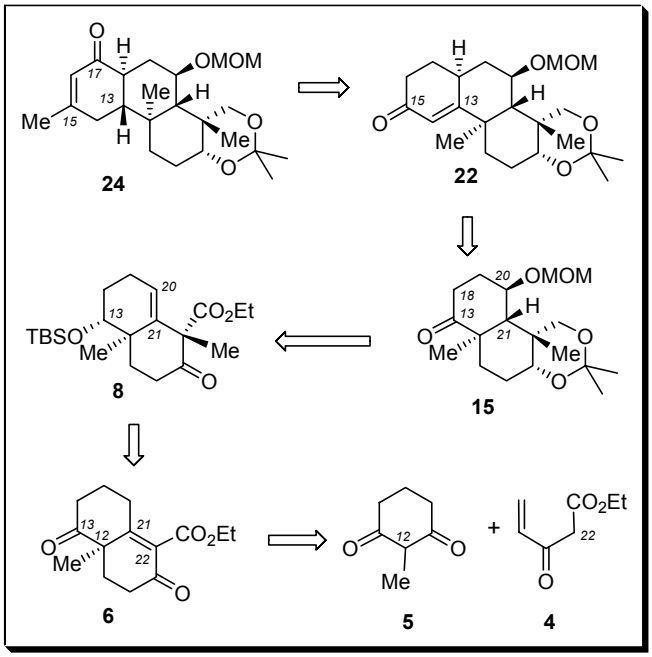
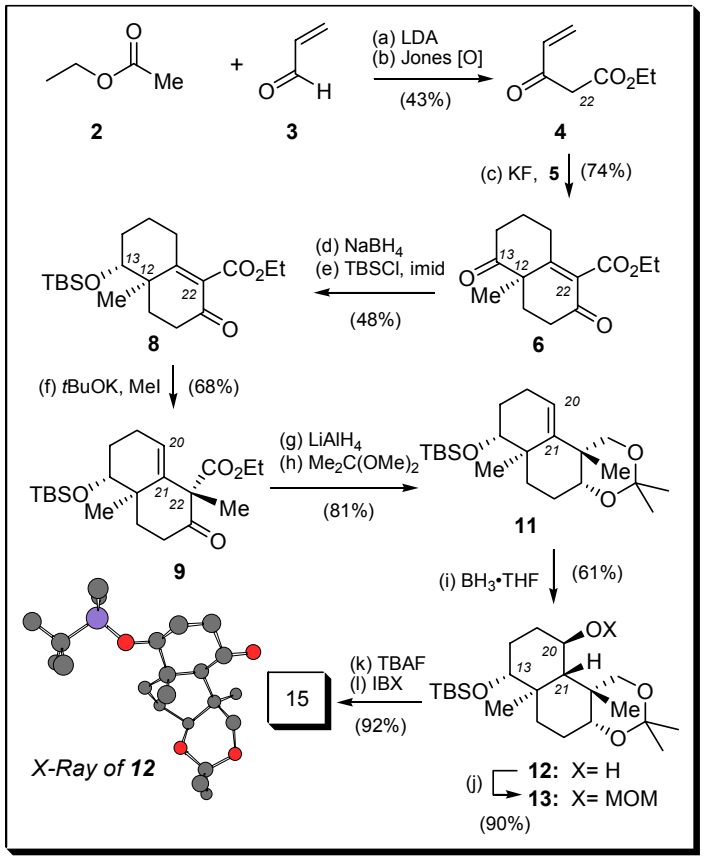


Figure 2.1: Retrosynthetic analysis of norzoanthamine.

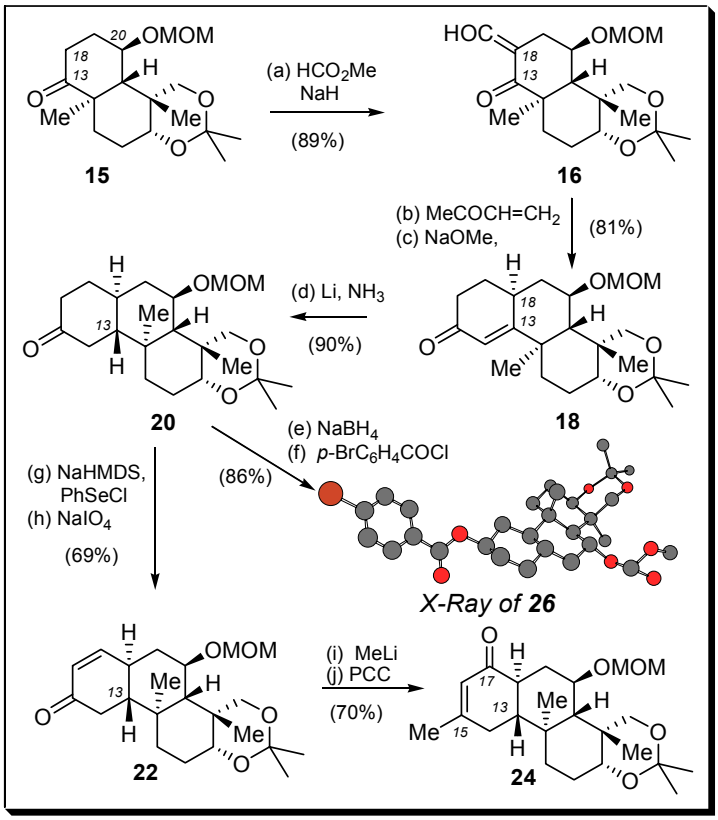
TBS-Cl led to exclusive formation of **8**, which was isolated in 99% yield.[5] Treatment of this enone with potassium *tert*-butoxide produced the extended enolate that upon reaction with methyl iodide formed compound **9** as a single isomer at the C-22 center (68% yield). The *β*-ketoester functionality of **9** was then reduced with $LiAlH_4$[6] and the resulting diol was converted to the corresponding acetonide **11** (two steps, 81% combined yield). Hydroxylation of the C-20/C-21 double bond (BH_3.THF/H_2O_2) occurred predominantly from the more accessible, *β*-face of **11** and afforded the desired trans-fused bicyclic motif of **12** together with its cis isomer (3:2 isomeric ratio in favor of **12**).[7] Gratifyingly, the two isomers were easily separable by column chromatography and the relative stereochemistry of the major product **12** was unequivocally confirmed by X-ray analysis (Scheme 2.2).[8]

Treatment of **12** with DIPEA followed by MOM-Cl produced adduct **13,** which after desilylation and oxidation gave rise to ketone **15** (three steps, 83% combined yield). The conversion of ketone **15** to enone **24** is highlighted in Scheme 2.3. Our initial plan to alkylate the enolate of **15** with methyl vinyl ketone en route to a Robinson annulation sequence gave rise to a mixture of products, including isomers at the C-18 center. This problem was circumvented by alkylating **15** with methyl formate to produce the *β*-ketocarbonyl adduct **16**, which underwent a smooth Michael addition in the presence of methyl vinyl ketone and triethylamine.[9]



Scheme 2.2: Synthesis of synthon **15**.

Subsequent treatment with NaOMe led to a Robinson annulation with concomitant removal of the formyl group, thereby affording **18** as a single isomer at the C-18 center (72% combined yield). Reduction of enone **18** with lithium in liquid ammonia gave rise to ketone **20** (90% yield). Unambiguous structural proof of compound **20** was obtained after derivatization to the corresponding *p*-bromobenzoate **26**, which upon recrystallization from methanol/water yielded crystals suitable for X-ray analysis (Scheme 2.3).[8] This study confirmed the desired trans-anti-trans stereo-relation of the tricyclic motif of **26**. Introduction of the desired functionalities on the A ring of **20** was accomplished by a NaHMDS-promoted phenylselenylation followed by oxidation



Scheme 2.3: Synthesis of the ABC ring core of norzoanthamine.

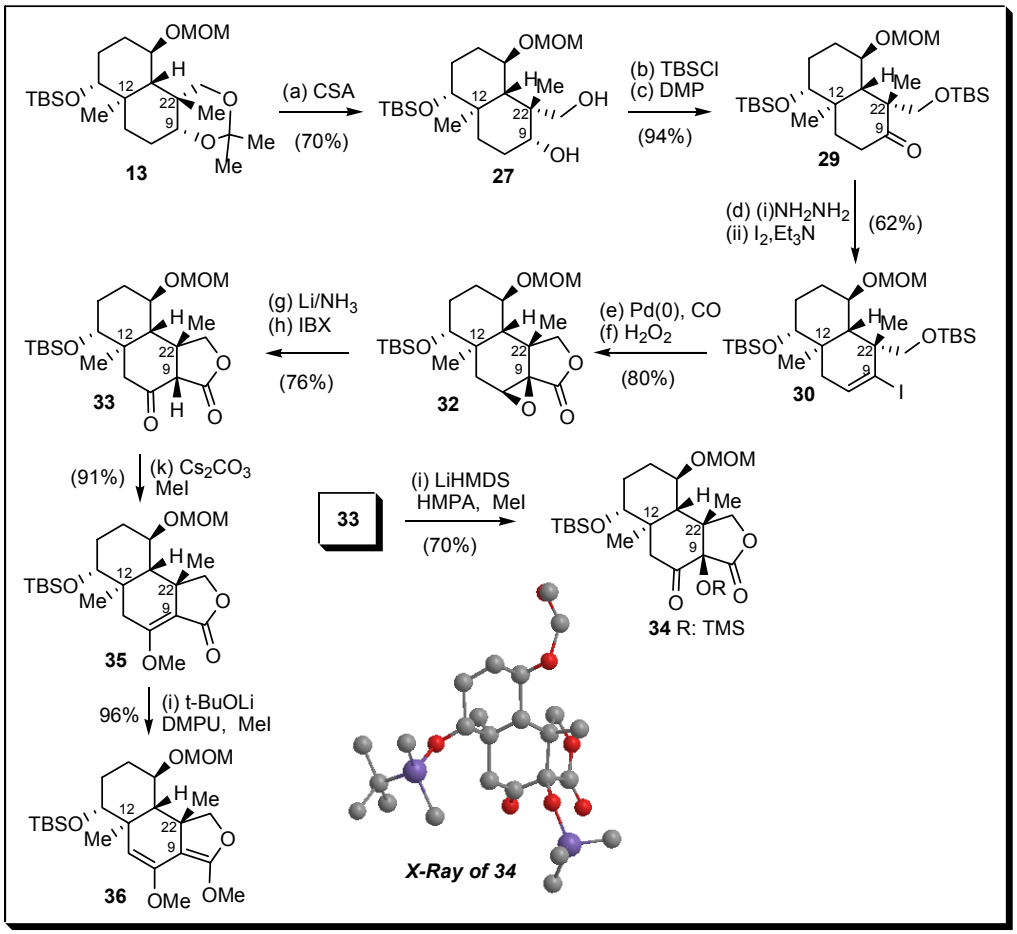
and elimination of the resulting selenide to produce enone **20** in 69% yield.[10] The latter compound was treated with methyl lithium and the resulting tertiary alcohol was subjected to a PCC-mediated oxidative rearrangement to produce enone **24** (two steps, 70% combined yield),[11] which represents a fully functionalized ABC tricyclic motif of norzoanthamine.

At this point, we can conclude that an efficient and versatile approach to the ABC ring framework **24** of norzoanthamine. The approach rests upon a stereocontrolled methylation of *β*-ketoester **8**, thus establishing the critical C-22 quaternary center. Additional key steps include the stereoselective hydroxylation of

alkene **11** and the modified Robinson annulation that set the desired relative stereochemistry of scaffold **18**.

Section 2.3 Synthesis of the Fully Functionalized BC Ring Motif

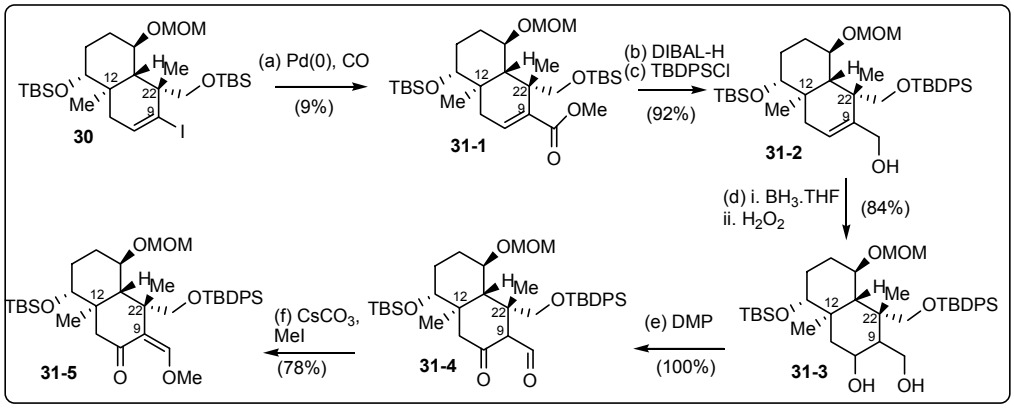
One of the most challenging aspects of the norzoanthamine structure is the C ring, which features four contiguous stereocenters, three of which are quaternary. Although, we had a feasible approach to make the ABC ring core of norzoanthamine, an intensive study to functionalize the C ring needed to be performed, and it was clear that the A ring was an unnecessary appendage and could be added after the successful development of the C ring. It was decided that compound **13** (Scheme 2.2) could be used to start the synthesis since it already contained appropriate functionality for conversion to the norzoanthamine framework. At the onset of this study, we envisioned that conversion of **13** to a suitable β-keto lactone motif such as **33** (Scheme 2.4) would allow the construction of the C-9 stereocenter with the desired configuration. The synthesis began with transformation of compound **13** to ketone **29** via a three step sequence including acetonide deprotection, silylation of the primary hydroxyl group, and oxidation of the C-9 alcohol (66% overall yield). Treatment of **29** with hydrazine produced the corresponding hydrazone that, upon reaction with I_2/Et_3N,[12] afforded vinyl iodide **30** (two steps, 62% overall yield). A Pd (0)-catalyzed carbonylation[13] followed by in situ deprotection of the primary silyl ether, immediately lactonized to give the corresponding tricyclic system, which after epoxidation of the C-9/C-10 double bond proceeded exclusively from the β-face of the tricyclic motif and produced compound **32** (two steps, 80% yield).



Scheme 2.4: Attempts to methylate intermediate **33**.

Reductive opening[14] of the epoxide functionality of **32** with Li/NH_3 and IBX oxidation of the resulting alcohol formed β-keto lactone **33** in 76% yield.[15] Unfortunately, attempts to introduce the C-9 methyl group during the reductive opening of epoxy lactone **32** were unsuccessful. Moreover, all efforts to methylate the C-9 stereocenter of **33** met with failure. Screening of a large variety of bases (LDA, NaHMDS, KHMDS, t-BuOK, Cs_2CO_3, and K_2CO_3) with or without co-solvents (DMPU and HMPA) led to O-methylation at C-10 (compound **35**) or produced bis-O-methylated compound **36** in fairly good yields. Interestingly, treatment of compound **33** with LiHMDS and HMPA followed by quenching with MeI afforded a new crystalline

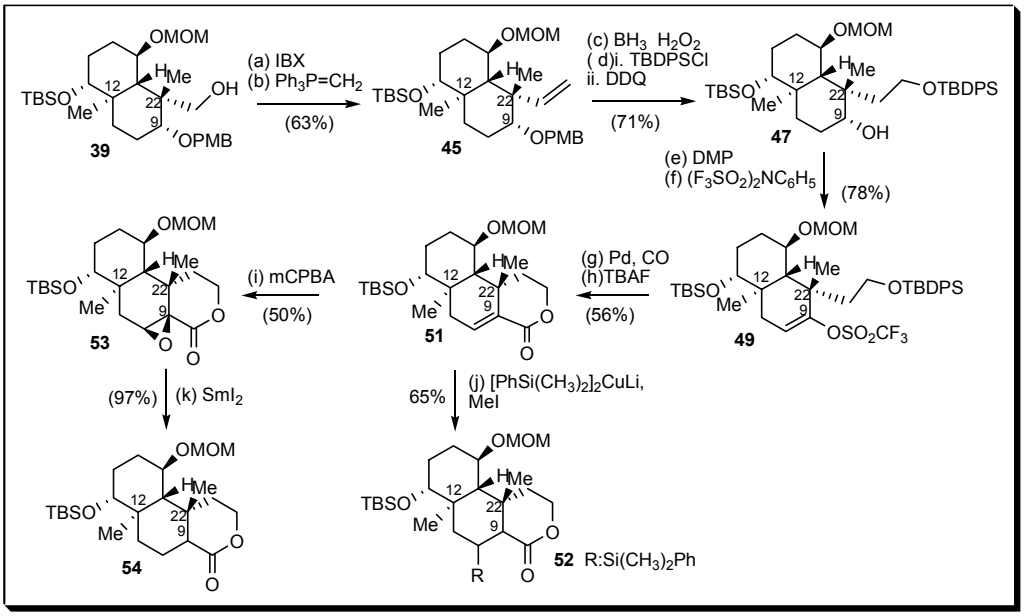
compound, whose structure was unambiguously assigned as that of compound **34** from its X-ray analysis.[15a,24] Presumably, the enolate was oxidized and silylated by HMDS to afford the undesired compound **34**.



Scheme 2.41: Attempts to methylate intermediate **31-4**.

Compound **30** also afforded **31-1** in 9% yield as shown in Scheme 2.41. The resultant ester was reduced with DIBAL-H in 92% yield, but it also cleaved the TBS ether, apparently during the quenching with tartaric acid. The compound was reprotected with TBDPS-Cl to afford compound **31-2**, which was hydroborated/oxidized to give compound **31-3** in 84% yield. This resultant diol was oxidized with DMP to afford quantitatively the keto-aldehyde **31-4**, and was treated with $CsCO_3$ to give compound **31-5** as the only product in 78%. A variety of bases was also evaluated, but no C-alkylation was observed.

These observations raised the question whether a 6-member β-keto lactone instead of the 5-member β-keto lactone **33**, could allow the C-9 axial methylation. It was postulated that **33**, being concave disfavor the methylation attack.



Scheme 2.5: Attempts to construct 6- member β-keto lactone.

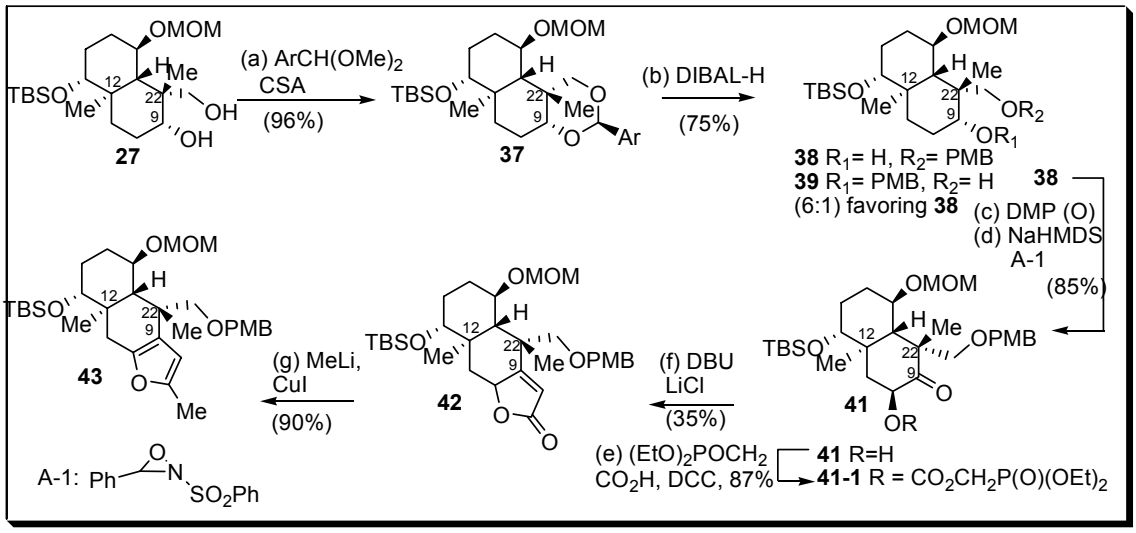
Therefore, compound **39** was oxidized with IBX followed by Wittig reaction to yield compound **45** in 63% yield. Hydroboration/oxidation of **45** produced the primary alcohol, which was protected with TBDPS-Cl. The resultant compound was PMB deprotected with DDQ to afford **47** in 71% yield. Dess Martin treatment of **47** followed by triflation of the ketone provided **49** in a combined 78% yield. Carbonylation[13] and desilylation of **49** gave **51** in 56% yield. Attempts to silylate C-10 and methylate C-9 by adding the known silyl cuprate[15b] followed by MeI only afforded **52** in 55% yield. Surprisingly, Fleming-Tamao oxidation of the silyl group only afforded decomposition.[15c] However, C-9 methylation could also be carried out from the β-keto lactone. Treatment of compound **51** with m-CPBA afforded the corresponding epoxide in 50% yield. However, reductive opening with Li/NH_3 only provided the desired the β-hydroxyl lactone in 5% yield. Attempts to open epoxide **59** under SmI_2 treatment only afforded the complete reduced compound **54** in 97%

yield.[15d] Due to the poor yields, we were unable to synthesize material and test our hypothesis that a 6-member β-keto lactone could be alkylated from the β face.

The failure to methylate the C-9 stereocenter of **33** under electrophilic alkylation conditions led us to explore nucleophilic alkylations, such as a conjugate addition of substrate **42** (Scheme 2.6).

To evaluate this strategy, compound **27** was first converted to p-methoxy benzylidene acetal **37** (96% yield). Reductive cleavage of the acetal ring with DIBAL-H gave rise to PMB ethers **38** and **39** in a 6:1 ratio in favor of **38** in a 75% combined yield. Oxidation of **38** followed by α-hydroxylation (NaHMDS, Davis' oxaziridine),[16] proceeded exclusively from the β-face and produced α-hydroxyketone **41** in 85% yield. Esterification of **41** with $(EtO)_2P(O)CH_2CO_2H$ and DCC produced, after treatment with DBU and LiCl, the corresponding α,β-unsaturated lactone **42** in a combined modest yield of 30%.[15,17]

Efforts to introduce the methyl group at the C-9 position were unsuccessful, presumably due to the steric hindrance of the adjacent quaternary center. In fact, under forcing conditions, we observed formation of the methyl furan system **43**, which is proposed to arise via methylation at

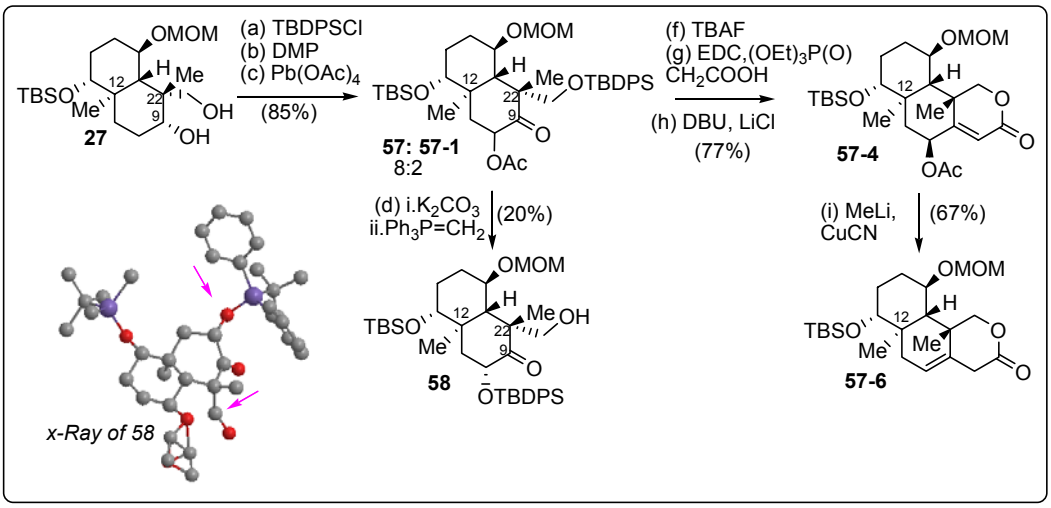


Scheme 2.6: Synthesis of synthon **42.**

the carbonyl group of the lactone, followed by aromatization of the derived hemiketal.[18]

We also tried to functionalize the C-9 via a Wittig reaction of an α-hydroxyl enone such as **57** (Scheme 2.7). This approach started by selectively protecting the primary alcohol **27** with TBDPS-Cl followed by DMP mediated oxidation, and treatment with lead tetraacetate under refluxing conditions afforded **57** in 85 % yield. Compound **57** was obtained in a 8:2 ratio of equatorial/axial hydroxyl, presumably due to the acidity of lead tetraacetate since under Davis' oxaziridine treatment only the β-hydroxyl was observed. Compound **57** was treated with Wittig reagent to afford 20% yield of a crystalline compound, which was unequivocally assigned as **58** through its X-ray analysis.[24] The migration of the large TBDPS group occurred only from the α-face. The remaining unreacted compound was the pure β-hydroxyl isomer. This observation led us to postulate that an intramolecular alkylation could be performed by

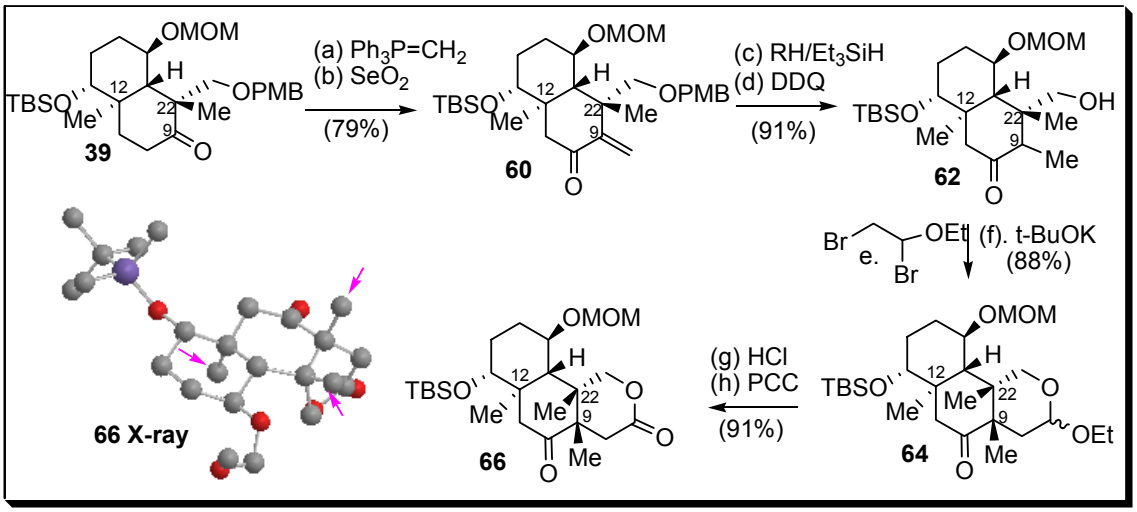
taking advantage of the hydroxyl on C-23. In addition, compound **57** was deprotected with TBAF and coupled with phosphonoacetic acid and EDC to give the corresponding phosphonoacetate in good yield. Using intramolecular Wittig Olefination conditions (DBU and LiCl), the phosphonoacetate was converted to the lactone **57-4**, which was treated with Gilman type cuprate attempting to functionalize the C-9, which only afforded compound **57-6** in 67%.



Scheme 2.7: Synthesis of synthon **58**.

Our collected findings prompted us to explore the possibility of forming the C-9 quaternary center via an intramolecular alkylation (Scheme 2.8). To this end, enone **39** underwent Wittig olefination, and SeO_2-mediated allylic oxidation[19] to afford **60** in a combined 79% yield. Wilkinson reduction of the exocyclic alkene,[20] followed by DDQ-mediated deprotection of the p-methoxybenzyl ether gave rise to ketone **62** in combined 91% yield. Alkylation of **62** with 1,2-dibromo-1-ethoxy-ethane produced the corresponding α-bromo acetal,[21] that upon exposure to t-BuOK[22] underwent intramolecular cyclization at the C-9 position, affording tricycle **64** in a combined

88% yield. To confirm the stereochemistry of the newly formed quaternary center, acetal **64** was subjected to acid catalyzed deprotection[23] and subsequent oxidation, producing lactone **66** in 91% yield.[13] A single crystal X-ray analysis of **66** established unambiguously the stereochemistry at the C-9 center.[24]



Scheme 2.8: Synthesis of synthon **66**.

In conclusion, this section describes a concise synthesis of the fully functionalized BC ring system of norzoanthamine as well as our initial studies to install the C-9 quaternary center. The successful approach to the functionalization of the BC ring rests upon an intramolecular cyclization of an α-bromo acetal on the C-9 enolate center. Further elaboration of this motif could potentially yield norzoanthamine and its related alkaloids.

Section 2.4 Conclusion

This linear sequence features the development of the ABC ring system of norzoanthamine by a stereospecific methylation at C-22, and a hydroboration across double bond C-20/C-21 as well as a critical Robinson annelation reaction that gives rise to the A ring. In addition, we were able to introduce the challenging C-9 quaternary center and overcome the difficulties related to the construction of the vicinal quaternary centers of the C-ring of zoanthamines. The developed strategy could be applied to the synthesis of the entire zoanthamine motif. Moreover, the investigated synthetic maneuvers can be applied to other natural products of similar chemical structure. However, comparison of our strategy to that of Miyashita revealed that both approaches are equally lengthy and difficult to streamline. This observation led us to pursue an alternative and potentially more efficient synthesis toward the zoanthamine alkaloids.

Section 2.5 Experimental Section

Section 2.5.1 General Techniques

All reagents were commercially obtained (Aldrich, Acros) at 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 using flame-dried glassware within an argon atmosphere in dry, freshly distilled solvents, unless otherwise noted. Tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), toluene ($PhCH_3$) and benzene (PhH) were purified by passage through a bed of activated alumina, N,N-diisopropylethylamine (DIPEA), diisopropylamine, pyridine, triethylamine (TEA) and boron trifluoride etherate were distilled from calcium hydride prior to use.[i] Dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) were distilled from calcium hydride under reduced pressure (20 mmHg) and stored over 4Å molecular sieves until needed. Yields refer to chromatographically and spectroscopically (1H 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-

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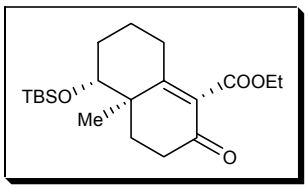
[i] Perrin, D. D.; Armarego, W. L. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Oxford, **1988**.

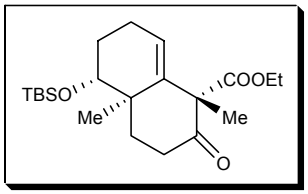
254) using UV light as the visualizing agent and 10% ethanolic phosphomolybdic acid (PMA) or p-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Varian Mercury 300, 400 and/or Unity 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 VG 7070 HS mass spectrometer under chemical ionization (CI) conditions or on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions. X-ray data were recorded on a Bruker SMART APEX 3kW Sealed Tube X-ray diffraction system.

Section 2.5.2 Experimental Procedures and Data

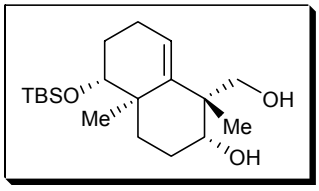


Ester 8: To a stirred solution of enone **6** (11.2 g, 44.7 mmol) in dry EtOH (180 mL) at -78 ^{o}C was added $NaBH_4$ (413 mg, 11.1 mmol) portionwise (4 x 100 mg). The reaction mixture was stirred at that temperature for 1 h and was quenched with glacial acetic acid (2 mL). After evaporation of EtOH under reduced pressure, the residue was extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (2 x 100 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 40:60 ethyl acetate in hexanes) to give the corresponding C13 alcohol (10.39 g, 41.1 mmol 92%), as a white solid R_f = 0.25 (50% EtOAc: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 (2H, q, J = 7.0 Hz), 3.45 (1H, m), 2.51-2.00 (6H, m), 1.91-1.78 (3H, m), 1.72 (1H, m), 1.41 (1H, m), 1.90 (3H, t, J = 7.0 Hz), 1.20 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 166.9, 164.7, 131.9, 77.5, 61.3, 41.5, 33.3, 33.2, 29.8, 29.0, 22.7, 15.6, 14.2. A solution of the alcohol obtained in the above step (10.0 g, 39.63 mmol) and dry DMF (70 mL) was treated with ammonium nitrate (9.5 g, 118.9 mmol) and TBSCl (8.9 g, 59.4 mmol) at 0 ^{o}C. The mixture was warmed to 25 ^{o}C and stirred for 12 h. The reaction mixture was quenched with a saturated solution of aqueous ammonium chloride (30 mL) and extracted with EtOAc (2 x 150 mL). The combined organic extracts were washed with brine (2 x 100 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 6:94 EtOAc: hexane), to give **8** (13.07 g, 35.65 mmol, 90%). **8:** White solid: R_f = 0.47 (20% EtOAc: hexane); ^{1}H NMR (400

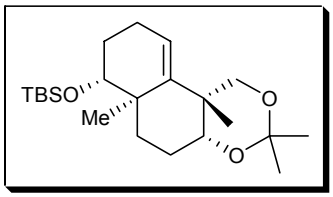
MHz, $CDCl_3$) δ 4.27 (2H, q, J = 7.2 Hz), 3.44 (1H, dd, J = 4.8, 11.2 Hz), 2.50-2.40 (2H, m), 2.35-2.10 (2H, m), 2.10 (1H, m), 1.86 (1H, m), 1.80-1.66 (3H, m), 1.42 (1H, m), 1.31 (3H, t, J = 7.2 Hz), 1.21 (3H, s), 0.90 (9H, s), 0.06 (3H, s), 0.045 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 166.5, 164.0, 131.7, 78.1, 60.8, 41.7, 33.5, 33.2, 30.1, 28.7, 25.6, 25.5, 22.3, 17.8, 15.6, 14.0, -4.1, -5.0; HRMS calcd. for $C_{20}H_{34}O_4Si$ (M+ Na^+) 389.2124, found 389.2103.



Ester 9: A solution of compound **9** (10.0 g, 27.28 mmol) was added to a suspension of potassium tert-butoxide (3.36 g, 30 mmol) in dry benzene (100 mL) at 0 ^oC. After stirring at 25 ^oC for 30 min, it was cooled to 0 ^oC and treated with excess methyl iodide (5 mL, 80.31 mmol). After stirring for 12 h at 25 ^oC, the reaction mixture was quenched with saturated solution of aqueous ammonium chloride (30 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 4:96 EtOAc: hexane) to give **9** (7.05 g, 18.7 mmol, 68% yield). **9:** White solid: R_f = 0.5 (20% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 5.52 (1H, t, J = 3.8 Hz), 4.20-4.06 (2H, m), 3.47 (1H, dd, J = 11.6, 3.6, Hz), 2.70 (1H, m), 2.42 (1H, m), 2.20-2.04 (3H, m), 1.78 (1H, m), 1.73-1.63 (3H, m), 1.43 (3H, s), 1.22 (3H t, J = 6.8 Hz), 1.08 (3H, s), 0.90 (9H, s), 0.07 (3H, s), 0.04 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4, 172.6, 141.8, 123.6, 76.0, 61.4, 60.3, 39.9, 34.9, 32.7, 26.6, 25.9, 24.8, 22.7,18.3, 18.1, 14.0, -3.8, -4.7; HRMS calcd. for $C_{21}H_{36}O_4Si$ (M+ Na^+) 403.2281, found 403.2270.

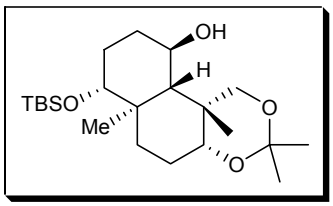


Alkene 10: Lithium aluminum hydride (1.36 g, 36.8 mmol) was added to a stirred solution of compound **7** (7.0 g, 18.4 mmol) in dry tetrahydrofuran (100 mL) at 0 ^{o}C. The mixture was stirred at 0 ^{o}C for 2h and at 25 ^{o}C for 6h. After cooling to 0 ^{o}C, the reaction mixture was quenched with saturated solution of aqueous Na_2SO_4 (20 mL) and was extracted with ethyl acetate (3 x 100 mL), the combined organic extracts were washed with brine (2 x 50 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 35:65 EtOAc: hexane) to give the corresponding diol (5.32 g, 15.6 mmol, 85% yield) as a white solid: R_f = 0.5 (70% EtOAc: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (1H, dd, J = 4.0, 3.6 Hz), 4.06 (1H, dd, J = 5.5, 10.6 Hz), 3.46 (1H, d, J = 10.8 Hz), 3.40-3.30 (2H, m), 2.37 (1H, dd, J = 5.6 Hz), 2.28 (1H, m), 2.17-2.14 (2H, m), 1.97-1.86 (2H, m), 1.81-1.75 (1H, m), 1.69-1.63 (2H, m), 1.57 (1H, m), 1.32 (3H, s), 1.07 (3H, s), 0.90 (9H, s), 0.06 (3H, s), 0.04 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 123.8, 78.6, 78.2, 67.5, 46.3, 39.2, 35.2, 27.4, 26.5, 26.0, 25.2, 21.9, 19.8, 18.2, -3.8, -4.6; HRMS calcd. for $C_{19}H_{36}O_3Si$ (M+ Na^+) 363.2331, found 363.2361.



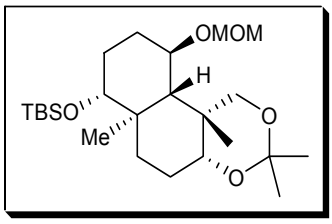
Alkene 11: A stirred solution of diol (5.0 g, 14.7 mmol) in CH_2Cl_2 (30 mL) was treated with excess 2,2-dimethoxy propane (10 mL, 81.32 mmol) and CSA (34 mg, 0.146 mmol) at 0 ^{o}C. After stirring for 30 min the reaction mixture was quenched with a saturated solution of sodium bicarbonate (10 mL) and extracted with DCM (100 mL). The organic layer was washed with brine (30 mL), dried over $MgSO_4$, concentrated

under reduced pressure and purified by flash chromatography (silica, 2:98 EtOAc: hexane) to give **11** (5.3 g, 13.9 mmol, 95% yield). **11:** White solid; R_f = 0.8 (10% EtOAc: hexane).^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 (1H, t, J = 3.6 Hz), 3.92 (1H, d, J = 11.6 Hz), 3.67 (1H, t, J = 5.6 Hz), 3.39 (1H dd, J = 12.0, 3.6 Hz), 3.30 (1H, d, J = 11.6 Hz), 2.23-2.09 (2H, m), 1.91-1.73 (4H, m), 1.62 (1H, m), 1.42 (3H, s), 1.41 (3H, s), 1.26 (1H, m), 1.23 (3H, s), 1.12 (3H, s), 0.90 (9H, s), 0.06 (3H, s), 0.05 (3H, s), ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 121.0, 98.4, 77.3, 74.2, 68.8, 39.0, 38.9, 30.7, 26.9, 26.6, 26.3, 26.0, 24.8, 24.5, 23.7, 20.3, 18.2 -3.7, -4.6; HRMS calcd. for $C_{22}H_{40}O_3Si$ (M+ Na^+) 403.2644, found 403.2674.

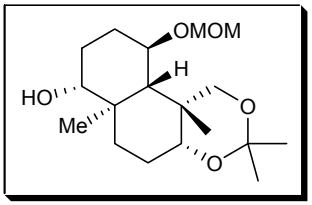


Alcohol 12: A stirred solution of compound **11** (6.0 g, 15.8 mmol) in dry THF (40 mL) at 0 ^{o}C was treated with 1 M BH_3:THF solution (31.6 mL, 31.6 mmol). The mixture was kept at 0 ^{o}C for 6 h and then 25 ^{o}C overnight. A mixture of aqueous NaOH (3N, 42 mL) and H_2O_2 (30%, 42 mL) was added at 0 ^{o}C and the reaction was stirred for 6h. The reaction mixture was extracted with EtOAc (2 x 150 mL), the combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (silica, 8:92 EtOAc: hexane) to give **12** (3.39 g, 8.5 mmol, 54 % yield). **12:** White solid; R_f = 0.45 (30% EtOAc: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ (4.02, 1H, d, J = 11.2 Hz), 3.84(1H, m), 3.63(1H, d, J = 11.2 Hz), 3.45(1H, dd, J = 6.0, 3.2 Hz), 3.19(1H, dd, J = 9.6, 5.0 Hz), 1.93 (1H, m), 1.80 (1H, m), 1.72-1.56 (5H, m), 1.43 (3H, s), 1.37 (3H, s), 1.33 (1H, m), 1.34 (3H, s), 1.21 (3H, s), 1.05 (1H, d, J = 10.8), 0.95 (1H, d, J = 6.0

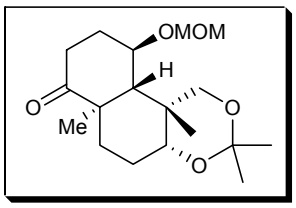
Hz), 0.87 (9H, s), 0.05(3H, s), 0.03 (3H, s). ^{13}C NMR (100 M Hz, $CDCl_3$) δ 99.8, 80.2, 75.6, 68.5, 64.6, 52.7, 39.3, 38.4, 36.0, 32.9, 29.7, 28.6, 25.9, 25.3, 24.6, 23.0, 18.2, 15.9, -3.5, -4.7; HRMS calcd. for $C_{22}H_{42}O_4Si$ (M+ Na^+) 421.2750, found 421.2781.



Alcohol 13: A stirred solution of compound **12** (3 g, 7.53 mmol) in dry dichloromethane (30 mL) was treated at 0 ^oC with DIPEA (5.32 mL, 30.12 mmol) followed by MOMCl (1.71 mL, 22.59 mmol). After stirring at 25 ^oC for 24 h the reaction mixture was quenched with aqueous ammonium chloride and extracted with EtOAc (2 x 75 mL), the combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (silica, 6:94 EtOAc: hexane), to give **13** (2.99 g, 6.8 mmol, 90% yield). **13:** Colorless liquid; R_f = 0.55 (30% EtOAc: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.47 (1H, d, J = 6.8 Hz), 4.60 (1H, d, J = 6.8 Hz), 3.96 (1H, d, J = 11.2 Hz), 3.62 (1H, dt, J = 10.8, 4.4Hz), 3.47 (1H, d, J = 11.2 Hz), 3.43 (1H, m), 3.36 (3H, s), 3.18 (1H, dd, J = 10.8, 4.4 Hz), 2.17 (1H, m), 1.78 (1H, m), 1.71-1.46 (4H, m), 1.42 (3H, s), 1.40-1.25 (2H, m,) 1.36 (3H, s), 1.31 (3H, s), 1.21 (3H, s), 1.05 (1H, d, J = 10.8 Hz), 0.87 (9H, s), 0.04 (3H, s), 0.02 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 99.8, 96.1, 80.2, 76.3, 75.5, 64.5, 56.1, 51.6, 39.4., 38.5, 32.9, 32.0, 29.5, 28.1, 25.9, 25.1, 24.6, 22.8, 18.2, 16.0, -3.5, -4.8; HRMS calcd. for $C_{24}H_{46}O_5Si$ (M+ Na^+) 465.3012, found 465.3032.

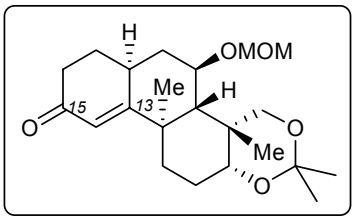


Alcohol 14: A stirred solution of compound **12** (2.9 g, 6.56 mmol) in anhydrous THF (15 mL) was treated at 0 ^{o}C with 1M TBAF in THF (13.10 mL, 13.10 mmol). The resulting mixture was heated at 50 ^{o}C for 48 h and then quenched with aqueous ammonium chloride and extracted with EtOAc (2 x 70 mL) the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (silica, 16:84 EtOAc: hexane) to give the alcohol (2.04 g, 6.23 mmol, 95% yield): R_f = 0.25 (30% EtOAc: hexane).



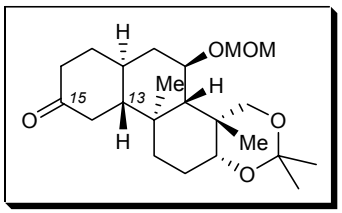
Ketone 15: To a stirred solution of the corresponding alcohol **13** (2.0 g, 6.0 mmol) in dry CH_2Cl_2:DMSO (4:1) (15 mL) at 0 ^{o}C was added IBX (4.6.g, 12.0 mmol). The resulting mixture was stirred at 25 ^{o}C for 24 h and then quenched with aqueous sodium thiosulfate (15 mL) and extracted with CH_2Cl_2 (2 x 70 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (silica,16:84 EtOAc: hexane), to give **15** (1.99 g, 5.82 mmol, 97 % yield). **15:** White solid; R_f = 0.5 (30% EtOAc: hexane); IR (film) ν_{max} 2936, 1710, 1037; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (1H, d, J = 6.8 Hz), 4.64 (1H, d, J = 6.8 Hz) 4.08 (1H, ddd, J = 10.4, 10.0, 4.4 Hz), 3.99 (1H, d, J = 11.2 Hz), 3.53 (1H, d, J= 11.2Hz), 3.45 (1H, m), 3.38 (3H, s), 2.68 (1H, m), 2.48-2.41 (2H, m), 2.3 1 (1H, m), 1.78 (1H, m), 1.66-1.57 (2H, m), 1.54 (1H, d, J =10.8 Hz), 1.51 (3H, s), 1.39 (3H, s), 1.35 (3H, s), 1.33 (1H, m), 1.26 (3H, s); ^{13}C

NMR (100 M Hz, $CDCl_3$) δ 212.7, 100.23, 96.4, 75.2, 74.3, 64.7, 56.3, 50.81, 47.25, 39.7, 35.0, 32.1, 27.4, 25.3, 24.4, 24.3, 24.0, 22.2; HRMS calcd. for $C_{18}H_{30}O_5$ (M+ Na^+) 349.1991, found 349.1984.



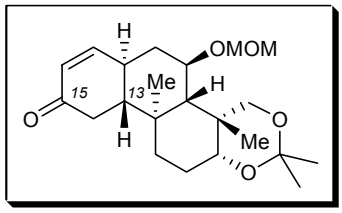
Enone 18: A solution of **15** (1.5g, 4.6 mmol) in dry toluene (15 mL) and dry THF (5 mL), was treated at 0 ^oC with 60% NaH (258 mg, 6.44 mmol) added portion wise. After stirring for 15 min excess HCOOMe (3mL, 48.66 mmol) was added to the reaction mixture. After stirring at 0 ^oC for 2 h then at 25 ^oC for 12 h the reaction mixture was quenched with a saturated solution of aqueous ammonium chloride (10 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography to give **16** (1.4 g, 4.0 mmol, 89%), which was used in the next step. Compound **16** (1.4 g, 4.0 mmol) was treated with methyl vinyl ketone (1.38 mL, 16.6 mmol) and Et_3N (1.28 mL, 9.2 mmol) at 0 ^oC. After stirring for 4 h, the reaction mixture was poured into water and extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with water and brine, then dried over $MgSO_4$. Removal of the solvent in vacuo gave a residue, which was dissolved in dry MeOH (5 mL) under argon at 0 ^oC and treated with a solution of NaOMe in methanol (23 mL, 1 M). After stirring at 0 ^oC for 4 h, the reaction mixture was allowed to warm to 25 ^oC and stirred overnight. Then the reaction mixture was quenched with water (10 mL), methanol was removed under reduced pressure and the residue was extracted with EtOAc (2 x 50 mL). The combined organic extracts were

washed with brine, dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 35:65.ethyl acetate in hexanes) to give **18** (1.05 g, 2.8 mmol, 72% yield). **18:** White solid R_f = 0.45 (50% EtOAc: hexane); IR (film) ν_{max} 2937, 1662; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (1H, s), 4.76 (1H, d, J = 6.8 Hz), 4.72 (1H, d, J = 6.8 Hz) 4.14 (1H, m), 4.03 (1H, d, J = 11.6 Hz), 3.61 (1H, d, J = 11.6, Hz), 3.45 (1H, m), 3.41 (3H, s), 2.70 (1H, m), 2.53 (1H, dd, J = 14.0, 3.6 Hz), 2.39 (1H, m), 2.08-1.99 (3H, m), 1.90-1.72 (3H, m), 1.69 (3H, s), 1.64 (3H, s), 1.61 (1H, m), 1.48 (1H, d, J = 10.8 Hz), 1.39 (3H, s), 1.38 (3H, s), 1.26 (1H, m). ^{13}C NMR (100 M Hz, $CDCl_3$) δ 200.1, 170.6, 124.0, 99.7, 96.4, 75.3, 73.4, 69.5, 64.2, 56.2, 53.2, 48.4, 41.2, 39.2, 38.6, 33.2, 32.4, 29.0, 26.6, 25.4, 25.2, 23.5; HRMS calcd. for $C_{22}H_{34}O_5$ (M+ Na^+) 401.2304, found 401.2334.



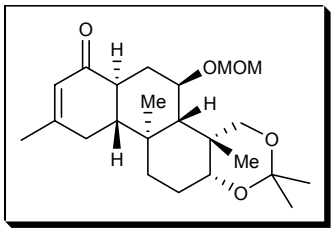
Ketone 20: A solution of **18** (500 mg, 1.32 mmol) in dry THF (3 mL) and dry EtOH (0.2 mL) was added drop wise to liq. NH_3 (8 mL) at -78 ^{o}C under argon. The resulting solution was treated with lithium (184 mg, 26.4 mmol) portion wise (4 x 46 mg) over 1 h. After stirring for 4 h solid NH_4Cl was added and the mixture was warmed slowly to 25 ^{o}C allowing the excess ammonia to be evaporated. The resulting mixture was diluted with water (5 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over $MgS0_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 22:78 EtOAc: hexane) to give **20** (449 mg, 1.18 mmol, 90% yield). **20:** White solid; R_f = 0.5 (50% EtOAc: hexane); IR (film) ν_{max}

2918, 1665, 1034; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (1H, d, J = 6.8 Hz), 4.65 (1H, d, J = 6.8 Hz), 3.95 (1H, d, J =11.6Hz), 3.73 (1H, dt, J = 11.2, 4.0 Hz), 3.52 (1H, d, J = 11.6 Hz), 3.46 (1H, dd, J = 4.8, 3.2 Hz), 3.39 (3H, s), 2.40-2.27 (4H, m), 2.09 (1H, t, J = 13.6 Hz), 2.0 (1H, m), 1.83-1.64 (3H, m), 1.51 (1H, m), 1.38-1.25 (3H, m), 1.40 (3H, s), 1.36 (3H, s), 1.30 (3H, s), 1.25 (3H, s).1.21-1.03 (3H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ 212.3, 100.1, 96.3, 76.2, 74.6, 64.7, 56.2, 55.7, 53.8, 41.4, 41.2, 40.94, 38.7, 37.0, 34.7, 33.6, 32.8, 28.4, 24.5, 24.5, 22.5, 17.5; HRMS calcd. for $C_{22}H_{37}O_5$ (M+ Na^+) 404.2539, found 404.2509.



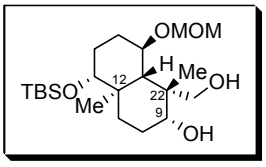
Enone 22: A solution of **20** (400 mg, 1.05 mmol) in dry THF (4 mL) was treated with 1 M NaHMDS in THF (1.5 mL), drop wise at -78 ^{o}C under argon. The mixture was stirred for 30 min and then treated with a solution of PhSeCl (401 mg, 2.1 mmol) in THF (2 mL). After stirring for 1 h the reaction mixture was quenched with saturated solution of aqueous ammonium chloride (2 mL) and extracted with ethyl acetate (2 x 8 mL), the combined organic extracts were washed with brine (3 mL), and dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 12:88 EtOAc: hexane) to give the selenide (417 mg, 0.78 mmol, 75% yield) This selenide was dissolved in THF:H_2O (2:1) (4 mL) and treated with $NaIO_4$ (333 mg, 1.56 mmol) at 0 ^{o}C and stirred for 2 h at room temperature. Then, the reaction mixture was diluted with water (2 mL) and extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried over $MgS0_4$, concentrated under reduced pressure and

purified by flash chromatography (silica, 20:80 EtOAc: hexane) to give **22** (265 mg, 0.70 mmol, 90%). **22:** White solid; R_f = 0.5 (50% EtOAc: hexane); IR (film) ν_{max} 2937, 1682, 1038; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (1H, dd, J = 9.6, 1.6 Hz), 5.95(1H, dd, J = 9.6, 2, Hz), 4.76 (1H, d, J = 6.8 Hz), 4.64 (1H, d, J = 6.8 Hz), 3.92 (1H, d, J = 11.2 Hz), 3.78 (1H, ddd, J = 10.8, 10.4, 4.4 Hz), 3.51-3.47 (2H, m), 3.40 (3H, s) 2.54-2.38 (2H, m), 2.14 (1H, dd, J = 16.0, 14.4 Hz), 1.85-1.66 (3H, m), 1.62-1.48 (2H ,m), 1.43-1.21 (3H, m), 1.40 (3H, s), 1.36 (3H, s), 1.30 (3H, s), 1.29 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 154.1, 128.5, 100.3, 96.5, 76.6, 74.4, 64.6, 56.2, 53.8, 53.6, 39.7, 38.9, 38.6, 36.5, 35.8, 32.2, 28.3, 24.4, 24.3, 22.2, 18.3; HRMS calcd. for $C_{22}H_{34}O_5$ (M+ Na^+) 401.2298, found 401.2307.



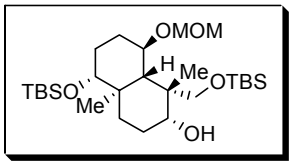
Enone 24: To a solution of **22** (200 mg, 0.52 mmol) in dry ether (4 mL) at 0 ^oC was added MeLi (1.04 mL, 1 M in ether). The mixture was stirred for 30 min and was quenched with a saturated solution of aqueous ammonium chloride (2 mL) and extracted with EtOAc (2 x 5 mL), the combined organic extracts were washed with brine (4 mL), dried over $MgSO_4$, and purified by flash chromatography to give the tertiary alcohol (182 mg, 0.46 mmol, 90%). This alcohol (182 mg, 0.46 mmol) was dissolved in anhydrous DCM (3 mL), containing MS 3A (40 mg) and treated with PCC (198 mg, 0.92 mmol) at 0 ^oC. After stirring for 2 h the reaction mixture was filtered through silica gel, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (22:78 EtOAc: hexane) to give **24** (148 mg, 0.35 mmol, 78% yield). **24:** White solid; R_f = 0.45 (45% EtOAc:

hexane); IR (film) ν_{max} 2925, 1666; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (1H, s), 4.77 (1H, d, J = 6.8 Hz), 4.64 (1H, d, J = 6.8Hz), 3.95 (1H d, J= 11.6 Hz), 3.73 (1H, ddd, J = 11.2, 10.4, 4.4 Hz), 3.59 (1H, d, J = 11.6 Hz), 3.47 (1H, dd, J = 5.2, 3.2 Hz), 3.42 (3H, s), 2.77 (1H, m), 2.26-2.13 (3H, m), 1.96 (3H, s), 1.89-1.51 (6H, m), 1.41 (3H, s), 1.37 (3H, s), 1.32 (3H, s), 1.27 (3H, s), 1.22 (1H, m); ^{13}C NMR (100 M Hz, $CDCl_3$) δ 200.1, 161.4, 125.3, 100.0, 95.7, 75.6, 74.8, 64.6, 56.6, 53.9, 52.0, 43.8, 38.6, 37.0, 34.0, 33.0, 31.2, 29.8, 28.7, 24.7, 24.6, 22.7, 18.1; HRMS calcd. for $C_{23}H_{36}O_5$ (M+ Na^+) 415.2455, found 415.2468.

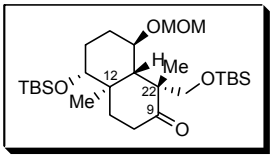


Compound 27: To a solution of compound **13** (10.5 g, 23.71 mmol) in CH_2Cl_2 (200 mL), MeOH (5 mL) and 0.01 equiv of CSA (0.55g, 2.3 mmol) was added at 0 ^oC. The reaction mixture was allowed to stir for 5 h and quenched with a saturated solution of aqueous sodium bicarbonate. The reaction mixture was extracted with CH_2Cl_2 (3 X 100 mL). The combined organic layer was washed with brine (100 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (30% EtOAc/hexane) to give **27** (10.16 g, 70% yield) as a white solid: R_f = 0.33 (35% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (d, J = 6.8 Hz, 1H), 4.62 (d, J = 6.8 Hz, 1H), 4.22 (dd, J = 2.0, 11.2 Hz, 1H), 3.63 (dt, J = 4.4, 10.8 Hz, 1H), 3.57 (t, J = 9.2 Hz, 1H), 3.30-3.50 (m, 4H), 3.15 (br s, 1H), 3.06 (dd, J = 4.4, 11.2 Hz, 1H), 2.92 (br s, 1H), 2.11 (m, 1H), 1.65-1.85 (m, 3H), 1.61 (m, 1H), 1.35-1.52 (m, 4H), 1.28 (m,1H), 1.19 (d, J = 10.4 Hz, 1H), 0.75-1.05(m, 13H),

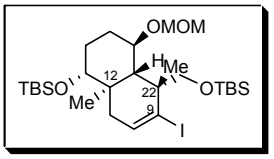
0.0(m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 96.1, 81.3, 80.0, 76.2, 64.4, 56.5, 55.86, 42.7, 40.9, 36.6, 32.1, 29.7, 27.4, 26.0, 25.2, 18.2, 14.5, -3.8, -4.6; HRMS calcd for $C_{21}H_{42}NaO_5Si$ ($M+Na^+$) 425.2699, found 425.2695.



Compound 28: A solution of diol **27** (1.0 g, 2.48 mmol) in CH_2Cl_2 (50 mL) was treated with imidazole (0.338 g, 4.96 mmol) and TBSCl (0.45g, 2.98 mmol) at 0 ^oC. The reaction mixture was stirred at 25 ^0C for 12 hr and quenched with a saturated solution of aqueous ammonium chloride (50 mL). The reaction mixture was extracted with CH_2Cl_2 (3 X 100 mL). The combined organic layer was washed with brine (100 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (5% EtOAc: hexane,) to give **28** (1.28 g, 97% yield) as a colorless solid: R_f = 0.72 (20% EtOAc: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.68 (d, J = 6.40 Hz, 1H), 4.62 (d, J = 6.8 Hz, 1H), 4.48 (d, J = 7.6 Hz, 1H), 4.26 (d, J = 9.6 Hz, 1H), 3.63 (dd, J = 1.2, 10.0 Hz, 1H), 3.60 (dt, J = 4.4, 10.4 Hz, 1H), 3.37 (s, 3H), 3.23 (m, 1H), 3.08 (dd, J = 4.4, 11.2 Hz, 1H), 2.12 (m, 1H), 2.13 (m, 1H), 1.70-1.85 (m, 2H), 1.50-1.70 (m, 2H), 1.35-1.50 (m, 4H), 1.34 (m, 1H), 1.19 (d, J = 10.4 Hz, 1H), 0.96 (m, 1H), 0.70-0.91 (m, 21H), 0.0-0.15(m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 96.5, 81.1, 80.0, 77.0, 65.9, 56.3, 56.1, 42.7, 41.1, 36.9, 32.7, 29.9, 28.2, 26.2, 26.1, 25.6, 18.4, 15.0, -3.5, -4.3, -5.2; HRMS calcd for $C_{27}H_{57}O_5Si_2$ ($M+H^+$) 517.3745, found 517.3747.

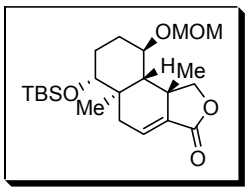


Compound 29: To a solution of alcohol **28** (0.7 g, 1.35 mmol) in CH_2Cl_2 (60 mL) was added Dess Martin periodinane (1.13 g, 1.76 mmol) at 0 ^oC and the mixture was stirred at 25 ^oC for 5 h. A solution of aqueous saturated sodium bicarbonate and sodium thiosulfate (15 mL) was added and extracted with CH_2Cl_2 (3 X 100 mL). The collected organic layer was washed with brine (50 mL), dried over $MgSO_4$, concentrated under reduced pressure and the residue purified by flash chromatography (4% EtOAc: hexane) to give **29** (0.67g, 97% yield) as a white foam: R_f = 0.68 (15% EtOAc: hexane) ^1H NMR (400 MHz, $CDCl_3$) δ 4.68 (s, 2H), 3.95 (d, J = 10.0 Hz, 1H), 3.90 (m, 1H), 3.80 (d, J = 10.0 Hz, 1H), 3.36 (s, 3H), 3.24 (t, J = 8.0 Hz, 1H), 2.44 (m, 2H), 2.25 (m, 1H), 2.05 (m, 1H), 1.74 (d, J = 10.8 Hz, 1H), 1.59 (m, 2H), 1.20-1.45 (m, 2H), 1.12 (s, 3H), 0.75-0.90 (m, 21H), 0.04 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.2, 96.7, 79.1, 76.9, 66.2, 56.8, 56.2, 52.9, 40.3, 34.9, 34.8, 32.6, 31.9, 29.2, 27.4, 26.3, 26.2, 23.1, 18.8, 18.5, 14.6, 13.5, -3.5, -4.4, -5.1, -5.2; HRMS calcd for $C_{27}H_{55}O_5Si_2$ ($M+H^+$) 515.3588, found 515.3591.



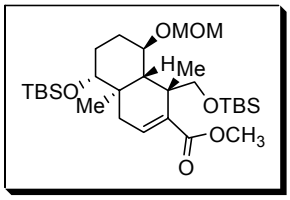
Compound 30: A solution of ketone **29** (0.6 g, 1.16 mmol) in EtOH (20 mL) was treated with anhydrous NH_2NH_2 (1.22 g, 3.84mmol) and Et_3N (0.44g, 4.0 mmol) at 25 ^oC. The reaction mixture was heated at 50 ^oC for 5 h and then concentrated under reduced pressure and dried under high vacuum. The neat light yellow oil was dissolved in Et_2O (20 mL) and cooled to 0 ^oC. Then, DBU (1.06 g,

6.90 mmol) was added followed by slow addition of a solution of I_2 (2.94 g, 11.6 mmol) in Et_2O. The reaction mixture was quenched with a saturated aqueous solution of sodium thiosulfate (10 mL) and sodium bicarbonate (10 mL), and extracted with EtOAc (3 X 25 mL). The organic layer was washed with brine, dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (1% EtOAc: hexane) to give **30** (0.45 g, 62% yield) as a colorless oil : R_f = 0.77 (3% EtOAc: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (dd, J = 1.6, 7.2 Hz, 1H), 4.69 (m, 2H), 3.70-3.90 (m, 2H), 3.58 (d, J = 11.2 Hz, 1H), 3.36 (s, 3H), 3.20 (t, J = 7.6 Hz, 1H), 2.28 (m, 1H), 2.0 (dd, J = 7.2, 16.4 Hz, 1H), 1.80 (d, J = 10.4 Hz, 1H), 1.72 (d, J = 14.0 Hz, 1H), 1.56 (m, 2H), 1.30 (m, 1H), 1.14 (s, 3H), 0.97 (s, 3H), 0.80-0.95 (m, 18H), 0.00-0.10 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 116.6, 96.4, 79.1, 77.9, 68.2, 56.0, 54.0, 46.5, 42.8, 39.7, 31.7, 29.7, 29.7, 28.8, 26.1, 25.9, 25.8, 18.4, 18.0, 14.6, 1.8, 1.0, 0.6, -3.9, -5.0, -5.2; HRMS calcd for $C_{27}H_{54}IO_4Si_2$ ($M+H^+$) 625.2605, found 625.2609.

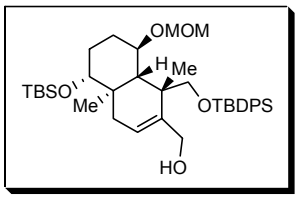


Compound 31: To a solution of vinyl iodide **30** (0.310 g, 0.49 mmol) in degassed DMF (4.2 mL) and MeOH (1.60 mL) was treated with Pd $(PPh_3)_4$ (0.0286 g, 0.0248 mmol) and Et_3N (0.150 g, 0.21 mL, 1.48 mmol) at room temperature. The reaction mixture was heated at 70 ^{o}C and kept under CO atmosphere for 18 h. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography (25% EtOAc: hexane) to give **31** (0.17 g, 83% yield) as a

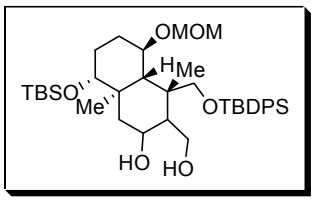
colorless oil: R_f = 0.10 (20% EtOAc: hexane) and **31-1** (0.025 g, 9% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (dd, J = 3.2, 8.4 Hz, 1H), 4.70 (d, J = 6.4 Hz, 1H), 4.60 (d, J = 6.4 Hz, 1H), 4.15 (d, J = 8.4 Hz, 1H), 4.08 (d, J = 8.4, 1H), 3.56 (dt, J = 4.4 10.4 Hz, 1H), 3.30-3.45 (m, 4H), 2.46 (dd, J = 8.4, 16.4 Hz, 1H), 2.25 (m, 1H), 1.45-1.80 (m, 5H), 0.80-1.0 (m, 9H), 0.74 (s, 3H), 0.03 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 136.9, 133.1, 96.1, 78.2, 76.3, 74.9, 56.4, 56.4, 54.5, 43.4, 42.1, 37.7, 31.8, 30.8, 29.8, 26.5, 26.3, 26.2, 18.4, 12.8, -3.5, -4.3; HRMS calcd for $C_{22}H_{39}O_5Si$ ($M+H^+$) 411.2567, found 411.2571.



Compound 31-1: (0.025 g, 9% yield) as a colorless oil: R_f = 0.32 (20% EtOAc/hexane) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (dd, J = 2.0, 7.2 Hz, 1H), 4.72 (d, J = 6.4 Hz, 1H), 4.66 (d, J = 6.4 Hz, 1H), 4.10 (d, J = 10.8 Hz, 1H), 3.83 (d, J = 10.4 Hz, 1H), 3.80 (dt, J = 4.8, 10.8 Hz, 1H), 3.66 (s, 3H), 3.37 (s, 3H), 3.22 (t, J = 8.0 Hz, 1H), 2.20-2.35 (m, 2H), 1.70 (br d, J = 17.6 Hz, 1H),1.50-1.65 (m, 3H), 1.40 (s, 3H), 1.35 (m, 1H), 0.70-1.0 (m, 21H), 0.00 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 138.4, 137.2, 96.4, 79.7, 77.5, 64.6, 56.3, 56.1, 51.3, 43.1, 39.4, 39.1, 31.7, 29.9, 29.2, 29.1, 26.13, 26.1, 26.0, 18.5, 18.3, 14.5, -3.7, -4.6, -5.3, -5.5; HRMS calcd for $C_{29}H_{57}O_6Si_2$ ($M+H^+$) 557.3694, found 557.3689.

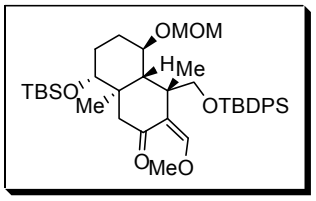


Compound 31-2 : To a solution of vinyl ester **31-1** (0.05 g, 0.075 mmol) in DCM (2.5 mL) DIBAL-H (0.22 mL, 0.22 mmol) was added at -78 ^{o}C and stirred for 30 min. Then, it was stirred at 0 ^{o}C for an additional 15 min. The reaction mixture was quenched with 0.2 mL of MeOH and a saturated solution of sodium potassium tartrate (2 mL) and stirred for 2 h. It was extracted with EtOAc (3 X 5 mL), the organic layer was washed with brine, dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (12% EtOAc: hexane) to give **31-2** (0.045 g, 92% yield) as a colorless oil : R_f = 0.2 (10% EtOAc: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (d, J = 4.8 Hz, 1H), 4.73 (d, J = 6.8 Hz, 1H), 4.69 (d, J = 6.8 Hz, 1H), 4.30 (d, J = 11.6 Hz, 1H), 3.97 (d, J = 10.4 Hz, 1H), 3.77 (t, J = 8.4 Hz, 1H), 3.70 (d, J = 10.0 Hz, 1H), 3.65 (dt, J = 4.4, 10.8 Hz, 1H), 3.57 (m, 1H), 3.37 (s, 3H), 3.20 (dd, J = 4.8, 11.2 Hz, 1H), 2.28 (m, 1H), 2.14 (dd, J = 6.40, 17.2 Hz, 1H), 1.30-1.75 (m, 5H), 1.25 (s, 3H), 0.6-1.0 (m, 21H), -0.03-0.10 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 126.4, 96.3, 79.8, 77.6, 76.9, 65.9, 65.1, 55.9, 54.7, 42.7, 39.7, 39.2, 31.7, 29.2, 27.2, 29.1, 26.07, 18.3, 14.2, -3.8, -4.6, -5.1, -5.2; HRMS calcd for $C_{21}H_{42}O_5Si$ ($M+H^+$) 459.1802, found 459.1819



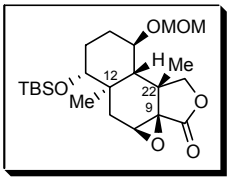
Compound 31-3: To a solution of allylic alcohol **31-2** (0.07 g, 0.107 mmol) in THF (10 mL) was added BH_3.THF (1 M in THF, 0.214 g, 0.214

mmol) at 0^{o}C and stirred at 25 ^{o}C for 12 h. It was treated with H_2O_2 (30% wt, 0.1mL) NaOH (3N, 0.1 mL) and stirred for 2 h. The reaction mixture was extracted with EtOAc (3 X 15 mL), and the organic layer was washed with brine (15 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (10% EtOAc: hexane) to give **31-3** (0.06 g, 84% yield) as a white foam: R_f = 0.26 (20% EtOAc: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (m, 4H), 7.42 (m, 6H), 3.97-4.25 (m, 4H), 3.92 (d, J = 10.4 Hz, 1H), 3.81 (d, J = 7.2 Hz, 1H), 3.32 (d, J = 10.4 Hz, 1H), 3.05-3.25 (m, 5H), 1.95-2.15 (m, 2H), 1.10-.1.70 (m, 10H), 0.90-1.10 (m, 10H), 0.75-0.90 (m, 9H), 0.74 (s, 3H), -0.00 (m, 6H); HRMS calcd for $C_{21}H_{42}O_5Si$ ($M+H^+$) 459.1802, found 459.1819.



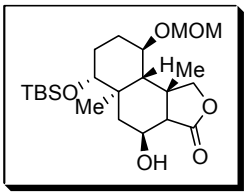
Compound 31-5: To a solution of allylic alcohol **31-3** (10.0 mg,0.002 mmol)in DCM (2 mL) was added DMP (23.0 mg, 0.005 mmol) at 25 ^{o}C. After stirring for 1h, the reaction mixture was quenched with a solution of sodium bicarbonate and extracted with DCM (3 X 3 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure to give the clean diketo system, which was taken to the next step without further purification. The resultant ketoaldehyde **31-4** (5.0 mg, 0.008 mmol) was dissolved in acetonitrile (0.6 mL) and was treated with Cs_2CO_3 (0.02 g, 0.03 mmol) at 0 ^{o}C and stirred at 25 ^{o}C for 1 h. The reaction mixture was treated with CH_3I (0.002g, 0.015mmol) and stirred for an additional 1 h at 25 ^{o}C. The reaction mixture was quenched with a saturated

solution of aqueous ammonium chloride, and extracted with EtOAc (3 X 5 mL). The collected organic layer was washed with brine (5 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (5% EtOAc: hexane) to give **33-5** (4.0 mg, 78% yield) as a colorless oil: R_f = 0. 33 (23% EtOAc: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (m, 4H), 7.37 (m, 6H), 4.33 (d, J = 6.0 Hz, 1H), 4.29 (d, J = 6.4 Hz, 1H), 4.14 (d, J = 10.8 Hz, 1H), 3.70-3.80 (m, 2H), 3.45 (s, 3H), 3.28 (dd, J = 4.4, 10.8 Hz, 1H), 3.20 (s, 3H), 2.60 (d, J = 16.0 Hz, 1H), 2.20 (m, 1H), 1.85 (d, J = 16.0 Hz, 1H), 1.66 (d, J = 10.8 Hz, 1H), 1.10-1.63 (m, 10H), 0.95-1.10 (m, 9H), 0.8-0.95 (m, 9H), -0.00 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 159.6, 136.5, 136.4, 134.0, 129.8, 129.7, 127.7, 127.5, 119.9, 96.2, 78.4, 76.7, 65.5, 62.0, 56.5, 55.9, 52.2, 43.7, 40.7, 31.7, 29.9, 29.1, 28.7, 27.4, 26.2, 19.4, 18.3, 15.3, -3.8, -4.5; HRMS calcd for $C_{21}H_{42}O_5Si$ ($M+H^+$) 459.1802, found 459.1819.



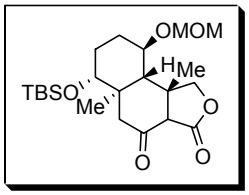
Compound 32: To a solution of allylic system **31** (0.02 g, 0.049 mmol) in MeOH (1 mL) was added H_2O_2 (30% wt, 0.05 mL) and NaOH (3 N, 0.05 mL) at 25 ^{o}C and stirred for 5 h. The reaction mixture was diluted with H_2O (1 mL) and extracted with EtOAc (3 X 5 mL). The organic layer was washed with brine, dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (12% EtOAc: hexane) to give **32** (0.02 g, 96% yield) as a white solid : R_f = 0.45 (40% EtOAc: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (d, J = 7.2 Hz, 1H), 4.59 (d, J = 6.8 Hz, 1H), 4.42 (d, J = 9.2 Hz, 1H), 4.30 (d, J = 9.2 Hz, 1H), 3.50-

3.60 (m, 2H), 3.36 (s, 3H), 3.11 (dd, J = 4.8, 11.2 Hz, 1H), 2.42 (dd, J = 7.2, 14.8 Hz, 1H), 2.17 (m, 1H), 1.61 (m, 1H), 1.35-1.55(m, 4H), 1.28 (m, 1H), 1.15 (d, J = 11.2 Hz, 1H), 1.02 (d, J = 13.6 Hz, 1H), 0.8-0.90 (m, 12H), -0.01 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 95.9, 77.7, 76.1, 74.4, 61.2, 57.6, 56.5, 50.4, 42.1, 37.7, 37.1, 31.2, 29.2, 26.5, 26.3, 26.2, 26.1, 18.4, 13.2, -3.5, -4.3, -4.4; HRMS calcd for $C_{22}H_{39}O_6Si$ ($M+H^+$) 427.2516, found 427.2517.

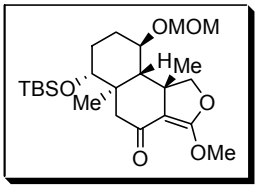


Compound 33-1: At -78 ^{o}C collected liquid ammonia (10 mL) in a three-neck round bottom flask mounted with a cold finger, then added lithium (8.0 mg, 1.17mmol) under argon and stirred for 5 min. Epoxi-lactone **95** (0.10 g, 0.49 mmol) in THF (2 mL) and EtOH (0.2 mL) was added into the reaction flask and stirred for 2 min. The reaction mixture was immediately quenched with solid ammonium chloride and the ammonia was allowed to evaporate at 25 ^{o}C. The reaction mixture was diluted with H_2O and extracted with EtOAc (3 X 5 mL). The organic layer was washed with brine, dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (25% EtOAc: hexane) to give **33-1** (0.09 g, 83% yield) as a white foam: R_f = 0.31 (60% EtOAc: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (d, J = 6.4 Hz, 1H), 4.58 (d, J = 7.2 Hz, 1H), 4.37 (d, J = 9.2 Hz, 1H), 4.13 (d, J = 9.2 Hz, 1H), 3.92 (m, 1H), 3.58 (m, 1H), 3.36 (s, 3H), 3.26 (m, 1H), 2.69 (s, 1H), 2.18 (m, 2H), 2.09 (d, J = 9.6 Hz, 1H), 1.50-1.80 (m, 2H), 1.46(s, 3H), 1.20-1.41 (m, 2H), 0.99 (d, J = 12.4 Hz, 1H), 0.95 (s, 3H), 0.86 (m, 9H), 0.04 (m, 6H); ^{13}C NMR

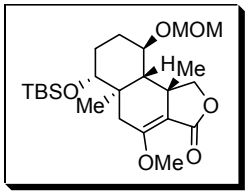
(100 MHz, $CDCl_3$) δ 179.7, 96.0, 78.4, 76.0, 66.1, 58.7, 56.4, 52.4, 42.7, 42.4, 42.3, 33.6, 31.8, 29.2, 26.1, 18.2, 13.8, -3.8, -4.5; HRMS calcd for $C_{22}H_{41}O_6Si$ ($M+H^+$) 429.2672, found 429.2669.



Compound 33-2: To a stirred solution of **33-1** (0.05 g, 0.12 mmol) in CH_2Cl_2 (10 mL) and DMSO (3 mL) was added IBX (0.113 g, 0.41mmol) and stirred at 50 ^oC for 18 h. An aqueous saturated sodium bicarbonate (5 mL) and sodium thiosulfate (5 mL) was added and extracted with DCM (3 x 10 mL). The organic layer was collected, dried over $MgSO_4$, concentrated under reduced pressure and the residue was purified by flash chromatography (30% EtOAc: hexane) to give **33-2** (0.045 g, 91% yield) as a white solid: R_f = 0.42 (40% EtOAc: hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 4.73 (d, J = 8.0 Hz, 1H), 4.60 (d, J = 7.2 Hz, 1H), 4.49 (d, J = 9.6 Hz, 1H), 4.15 (d, J = 9.6 Hz, 1H), 3.71 (m, 2H), 3.38 (s, 3H), 2.60 (d, J = 14.0 Hz, 1H), 2.50 (d, J = 13.2 Hz, 1H), 2.17 (m, 1H), 1.78 (d, J = 10.8 Hz, 1H), 1.70 (m, 1H), 1.30-1.65 (m, 5H), 0.98 (s, 3H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6, 174.0, 95.8, 81.9, 78.8, 75.2, 73.6, 56.6, 51.7, 49.4, 47.8, 44.8, 31.4, 29.4, 26.2, 24.3, 18.4, 14.6, -3.6, -4.3; HRMS calcd for $C_{22}H_{39}O_6Si$ ($M+H^+$) 427.2516, found 427.2519.

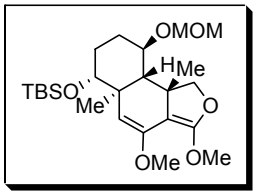


Compound 35: To a solution of diketone **33-2** (0.010 g, 0.023 mmol) in acetonitrile (1 mL) was treated with Cs_2CO_3 (0.0286 g, 0.0248 mmol) at 25 ^oC for 1 h. Then, CH_3I (0.0067 g, 0.047 mmol) was added and stirred for 30 min. The reaction mixture was concentrated under reduced pressure and the yellow residue purified by flash chromatography (15% EtOAc: hexane) to give **35** (9.2 mg, 91% yield) as a colorless oil: R_f= 0.58 (40% EtOAc: hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 4.69 (d, J = 6.8 Hz, 1H), 4.58 (d, J = 7.2 Hz, 1H), 4.27 (d, J = 9.2 Hz, 1H), 4.01 (d, J = 9.6 Hz, 1H), 3.55-3.70 (m, 4H), 3.47 (m, 1H), 3.37 (s, 3H), 2.62 (d, J = 10.8 Hz, 1H), 2.40 (d, J = 10.8 Hz, 1H), 2.20 (m, 1H), 1.85 (d, J = 10.8 Hz, 1H), 1.72 (m, 1H), 1.20-1.60 (m, 5H), 0.94 (s, 3H), 0.88 (m, 9H), 0.05 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.7, 173.0, 97.0, 95.9, 86.9, 78.4, 75.3, 71.9, 56.5, 56.4, 54.2, 51.4, 50.6, 47.7, 47.1, 31.9, 31.8, 29.4, 26.0, 25.9, 24.6, 18.2, 15.6, 14.0, -3.8, -4.5; HRMS calcd for $C_{23}H_{41}O_6Si$ ($M+H^+$) 441.2672, found 441.2668.

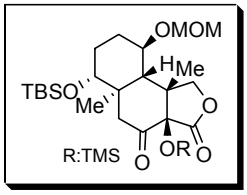


Compound 35-1: To a solution of diketone **33-2** (6.0 mg, 0.0141 mmol) in THF (0.3 mL) and DMPU (0.3 mL) lithium tert-butoxide (1M in THF, 0.0141 mmol) was added and stirred at 25 ^oC for 1 h. Then, CH_3I (20.0 mg, 0.141 mmol) was added and stirred for an additional 30 min. The reaction mixture was concentrated under reduced pressure and the yellow residue purified by flash

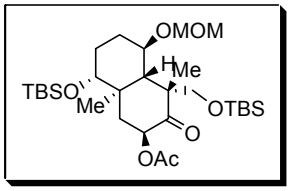
chromatography (15% EtOAc: hexane) to give **35-1** (5.0 mg, 83% yield) as a colorless oil: R_f= 0.59 (40% EtOAc: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (s, 1H), 4.75 (d, J = 6.8 Hz, 1H), 4.65 (d, J = 7.2 Hz, 1H), 4.04 (d, J = 10.8 Hz, 1H), 3.20-3.50 (m, 4H), 3.73 (m, 1H), 3.58 (s, 3H), 3.38 (s, 3H), 2.17 (m, 1H), 1.90 (d, J = 10.8 Hz, 1H), 1.15-1.80 (m, 4H), 1.04 (s, 3H), 1H), 0.9-1.0 (m, 12H), 0.05 (m, 6H); HRMS calcd for $C_{23}H_{41}O_6Si$ ($M+H^+$) 441.2672, found 441.2676.



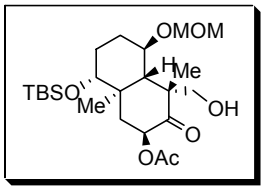
Compound 36: To a solution of **33-2** (0.01 g, 0.034 mmol) in THF (1 mL) and DMPU (1 mL) lithium tert-butoxide (1.0 M in THF, 0.051 mmol) was added and stirred at 25 ^{o}C for 1 h. The reaction mixture was then treated with CH_3I (0.032 g, 0.226 mmol) and stirred at for 2 hr. The reaction mixture was diluted with water and extracted with EtOAc (3 X 5 mL). The organic layer was washed with brine, dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (12% EtOAc: hexane) to give **36** (0.02 g, 96% yield) as a white solid : R_f = 0.6 (40% EtOAc: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (s, 1H), 4.72 (m, 2H), 4.58 (d, J = 10.8 Hz, 1H), 4.42 (d, J = 10.4 Hz, 1H), 3.82 (m, 1H), 3.73 (s, 3H), 3.56 (s, 3H), 3.42 (m, 1H), 3.38 (s, 3H), 2.32 (m, 1H), 1.94 (d, J = 11.2 Hz, 1H), 1.70 (m, 1H), 1.13-1.65 (m, 2H), 1.10 (s, 3H), 0.8-1.0 (m, 12H), 0.06 (m, 6H); HRMS calcd for $C_{24}H_{43}O_6Si$ ($M+H^+$) 455.2829, found 455.2831.



Compound 34: To a solution of ketolactone **33-2** (15.0 mg, 0.035mmol) in THF (1 mL) at -78 ^{o}C was added lithium bis(trimethylsilyl) amide (1.0M in THF, 0.038 mL, 0.039 mmol) along with hexamethylphosphoramide (HMPA, 0.012g, 0.07 mmol)), and stirred for 15 min. The reaction mixture was brought to -40 ^{o}C and CH_3I (0.025g, 0.176 mmol) was added and stirred for 15 min. The reaction mixture was quenched with a solution of ammonium chloride and extracted with EtOAc (3 X 5 mL). The organic layer was washed with brine, dried over $MgSO_4$, concentrated under reduced pressure and the yellow residue purified by flash chromatography (20% EtOAc: hexane) to give **34** (13.0 mg, 72% yield) as colorless needles: R_f = 0.56 (40% EtOAc: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (d, J = 7.2 Hz, 1H), 4.58 (d, J = 6.8 Hz, 1H), 4.30 (d, J = 9.2 Hz, 1H), 4.07 (d, J = 9.6 Hz, 1H), 3.65 (m, 1H), 3.40-3.50 (m, 1H), 3.38 (s, 3H), 2.73 (d, J = 11.2 Hz, 1H), 2.32 (d, J = 11.2 Hz, 1H), 2.20 (m, 1H), 1.65-1.70 (m, 2H), 1.45-1.60 (m, 1H), 1.41 (s, 3H), 1.34 (d, J = 16.8 Hz, 1H), 0.92 (s, 3H), 0.88 (s, 9H), 0.19 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.9, 173.4, 135.8, 129.8, 127.9, 122.9, 95.9, 85.7, 78.5, 75.5, 72.1, 56.4, 51.1, 50.6, 46.9, 46.7, 31.7, 29.4, 26.0, 24.6, 18.2, 13.9, 1.8, -3.9, -4.6; HRMS calcd for $C_{25}H_{47}O_7Si_2$ ($M+H^+$) 515.2860, found 515.2865.

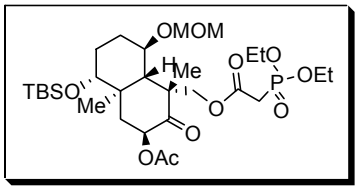


Compound 57-00: To a stirred solution of **29** (0.100 g, 0.162 mmol) in benzene (10 mL) was added $Pb(OAc)_4$ (0.359 g, 0.81mmol) and refluxed for 25 h. A solution of aqueous saturated sodium bicarbonate (10 mL) was added, and then extracted with EtOAc (3 X 10 mL). The organic layer was collected, dried over $MgSO_4$, concentrated under reduced pressure and the residue was purified by flash chromatography (5% EtOAc/hexane) to give 26 (0.09 g, 94% yield) as a white solid: R_f = 0.52 (40% Et_2O/hexane). HRMS calcd for $C_{29}H_{56}O_7Si_2$ ($M+H^+$) 595.3457, found 595.3461.

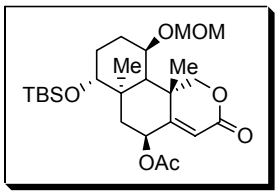


Compound 57-2: To a solution of **57-00** (0.500 g, 0.873 mmol) in CH_2Cl_2 (20 mL) and MeOH was added camphorsulphonic acid (CSA, 0.020 g, 0.087mmol) at 0 ^oC. The reaction mixture was stirred at 25 ^oC for 3 h. A saturated solution of sodium bicarbonate (20 mL) was added, and extracted with CH_2Cl_2 (3 X 25 mL), dried over $MgSO_4$ and purified by flash chromatography (10 % EtOAc: hexane) to give **57-2** (0.36 g, 90% yield) as a colorless solid: R_f = 0.16 (20% Et_2O: hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 5.56 (dd, J = 6.8, 11.6 Hz, 1H), 4.71 (d, J = 6.8 Hz, 1H), 4.63 (d, J = 7.2 Hz, 1H), 4.09 (d, J = 11.6 Hz, 1H), 3.75 (m, 1H), 3.63 (m, 1H), 3.37 (s, 3H), 3.32 (dd, J = 4.0, 10.8 Hz, 1H), 3.22 (m, 1H), 2.24 (m, 2H), 2.15 (s, 3H), 1.75 (dd, J = 6.8, 14.0 Hz, 1H), 1.56 (m, 1H), 1.51 (s, 3H), 1.20-1.43 (m, 3H),

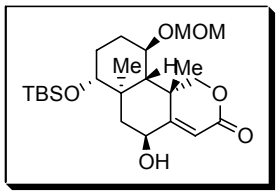
0.85 (s, 9H), 0.83 (s, 3H), 0.05 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.9, 170.2, 95.9, 79.9, 75.2, 70.4, 65.0, 56.6, 55.1, 50.7, 43.9, 40.3, 31.2, 28.8, 26.2, 25.9, 21.1, 18.4, 15.8, -3.3, -4.4; HRMS calcd for $C_{23}H_{43}O_7Si$ ($M+H^+$) 459.2778, found 459.2779.



Compound 57-3: To a solution of alcohol **57-2** (0.500 g, 1.12 mmol) in DCM (10 mL) was added diethyl phosphonoacetic acid (0.67 g, 3.30 mmol) and EDC·HCl (0.344 g, 1.78 mmol) at 0 ^{o}C. The reaction mixture was stirred at 25 ^{o}C for 18 h and quenched with a saturated solution of sodium bicarbonate (10 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (60% EtOAc: hexane) to give **57-3** (0.68 g, 95% yield) as colorless oil: R_f = 0.08 (50% EtOAc: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.44 (dd, J = 6.0, 14.0 Hz, 1H), 4.85 (d, J = 10.8 Hz, 1H), 4.70 (d, J = 6.8 Hz, 1H), 4.62 (d, J = 7.2 Hz, 1H), 4.10-4.25 (m, 4H), 3.82 (dt, J = 4.0, 10.8 Hz, 1H), 3.36 (s, 3H), 3.21 (dd, J = 4.8, 10.8 Hz, 1H), 3.0 (s, 1H), 2.96 (s, 1H), 2.32 (s, 1H), 2.32 (dd, J = 5.6, 12.8 Hz, 1H), 2.24 (m, 1H), 2.12 (s, 3H), 1.50-1.76 (m, 3H), 1.20-1.50 (m, 15), 0.87 (s, 9H), 0.03 (s, 6H), 0.05 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.9, 169.8, 165.9, 96.1, 79.1, 75.4, 72.6, 67.2, 62.9, 57.2, 56.6, 52.8, 42.9, 41.6, 34.8, 33.5, 32.2, 29.3, 26.2, 23.6, 21.1, 18.4, 16.7, 16.7, 15.1, -3.3, -4.4; HRMS calcd for $C_{29}H_{54}O_{11}PSi$ ($M+H^+$) 637.3173, found 637.3169.

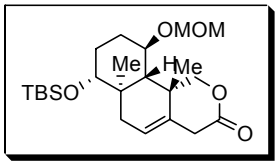


Compound 57-4 : To a solution of **57-3** (0.500 g, 0.785 mmol) in THF (50 mL) was added LiCl (0.133g, 3.14mmol), and 8-diazabicyclo [5,4,0] undec-7-ene (DBU, 0.478 g, 3.14 mmol) at 0 ^{o}C. The reaction mixture was stirred at 25 ^{o}C for 6 h and quenched with a saturated solution of aqueous ammonium chloride and extracted with EtOAc (3 X 50 mL). The collected organic layer was washed with brine (50 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (35% EtOAc: hexane) to give **57-4** (0.170 g, 45% yield) as a white solid: R_f = 0.20 (50% EtOAc: hexane) and **57-5** (0.170 g, 45% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (s, 1H), 5.56 (dd, J = 3.2, 9.2 Hz, 1H), 4.77 (d, J = 6.8 Hz, 1H), 4.64 (d, J = 6.8 Hz, 1H), 4.54 (d, J = 10.8 Hz,1H), 4.46 (d, J = 10.4 Hz, 1H), 3.55 (m, 1H), 3.40 (s, 3H), 3.26 (dd, J = 4.0, 10.8 Hz, 1H), 2.40 (dd, J = 9.6, 15.6 Hz, 1H), 2.25 (m, 1H), 2.06 (s, 3H), 1.87 (d, J = 10.8 Hz, 1H), 1.10-1.70 (m, 7H), 0.70-1.0 (m, 12H), 0.04 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 164.3, 162.1, 118.7, 95.7, 79.7, 74.7, 74.3, 70.4, 56.7, 52.5, 43.6, 40.2, 36.9, 30.8, 29.9, 28.5, 27.9, 26.1, 26.0, 21.6, 18.2, 15.3, -3.6, -4.6; HRMS calcd for $C_{23}H_{42}O_7Si$ ($M+H^+$) 483.2773, found 483.2761.



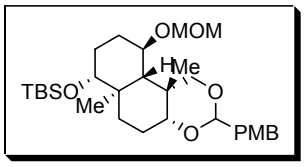
Compound 57-5: (0.170 g, 45% yield) as a white foam: R_f = 0.16 (50% EtOAc: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (s, 1H), 4.77 (d, J =

6.4 Hz, 1H), 4.63 (d, J = 6.8 Hz, 1H), 4.40-4.60 (m, 3H), 3.45-3.60 (m, 2H), 3.40 (s, 3H), 3.27 (dd, J = 4.0, 10.8 Hz, 1H), 2.33 (dd, J = 8.8, 14.8 Hz, 1H), 2.25 (m, 1H), 2.0 (d, J = 10.8 Hz, 1H), 1.05-1.75 (m, 8H), 0.87 (s, 9H), 0.84 (s, 3H), 0.04 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 164.9, 115.7, 95.6, 79.8, 75.0, 74.6, 69.6, 56.7, 52.1, 45.9, 40.5, 37.1, 30.9, 28.8, 28.7, 26.2, 18.4, 15.5, -3.4, -4.4; HRMS calcd for $C_{22}H_{41}O_6Si$ ($M+H^+$) 441.2667, found 441.2673.

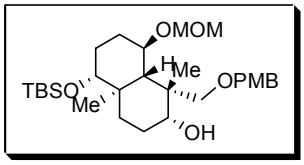


Compound 57-6: To a suspension of CuCN (0.018 g, 0.21 mmol) in Et_2O (5 mL) added methyl lithium (1.6 M in THF, 0.264 mL, 0.422mmol) at -78 ^oC and stirred for 30 min. Then, a solution of **57-4** (34.01 mg, 0.070 mmol) in Et_2O (0.25 mL) was added to the above reaction mixture and stirred at 0 ^oC for 30 min. A saturated solution of aqueous sodium bicarbonate (25 mL) was added and extracted with Et_2O (3 X 5 mL). The organic layer was washed with brine (10 mL), dried ($MgSO_4$), concentrated and purified by flash chromatography (7% EtOAc: hexane) to give **57-6** (0.02 g, 67% yield) as a colorless oil: R_f= 0.3 (50% EtOAc: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 (d, J = 6.8 Hz, 1H), 4.76 (d, J = 6.4 Hz, 1H), 4.62 (d, J = 6.8 Hz, 1H), 4.42 (dd, J = 10.8, 14.0 Hz, 2H), 3.54 (dt, J = 4.4, 10.4 Hz, 1H), 3.46 (m, 1H), 3.39 (s, 3H), 3.10-3.30 (m, 2H), 2.25 (m, 1H), 2.10 (dd, J = 6.8, 16.4 Hz, 1H), 1.20-1.70 (m, 8H), 0.85 (m, 12H), 0.03 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 133.0, 120.4, 95.7, 78.9, 75.5, 73.5, 56.8, 53.2, 40.5, 37.6, 36.9,

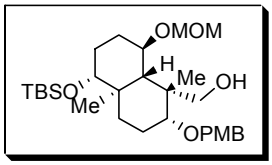
36.5, 31.4, 29.3, 26.2, 25.4, 18.4, 13.6, -3.5, -4.4; HRMS calcd for $C_{23}H_{41}O_5Si$ ($M+H^+$) 425.2718, found 425.2725.



Compound 37: To a solution of diol **27** (10.0 g, 24.86 mmol) in DCM (100 mL) was added anysaldehyde dimethylacetal (6.34g, 34.00mmol), CSA (0.057 g, 0.03 mmol) at 0 ^oC and stirred at 25 ^oC for 7 h. The reaction mixture was quenched with a saturated solution of aqueous sodium bicarbonate (50 mL), and extracted with DCM (3 X 50 mL). The collected organic layer was washed with brine (35 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (5% EtOAc: hexane) to give **37** (12.4 g, 96% yield) as a colorless solid: R_f = 0. 42 (20% EtOAc: hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.73 (s, 1H), 4.71 (d, J = 6.8 Hz, 1H), 4.61 (d, J = 7.2 Hz, 1H), 4.30 (d, J = 11.2 Hz, 2H), 3.86 (d, J = 11.2 Hz, 1H), 3.78 (s, 3H), 3.62 (m, 2H), 3.38 (s, 3H), 3.12 (dd, J = 4.8, 11.2 Hz, 1H), 2.35 (m, 1H), 2.17 (m, 1H), 1.90 (m, 1H), 1.20-1.80 (m, 8H), 1.02(s, 3H), 0.99 (m, 1H), 0.80-0.88 (m, 12H), 0.02 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 131.8, 127.7, 113.9, 96.3, 95.3, 81.9, 79.6, 76.1, 69.8, 56.6, 55.6, 41.1, 37.0, 35.6, 32.5, 29.9, 29.2, 26.3, 21.4, 18.5, 14.6, -3.5, -4.6; HRMS calcd for $C_{29}H_{49}O_6Si$ ($M+H^+$) 521.3298 , found 521.3295.

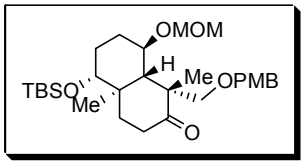


Compound 38: To a solution of **37** (10.0 g, 19.20 mmol) in DCM (200 mL) was added DIBAL-H (1 M in toluene, 38.46 mL, 38.00 mmol) at 78 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 7 h. It was quenched with a saturated solution of sodium potassium tartrate and stirred for 2 h. It was extracted with DCM (3 X 75 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (10% EtOAc: hexane) to give **38** (6.0 g, 63% yield) as a light yellow oil: R_f = 0. 34 (15% EtOAc: hexane) and **39** (1.25 g, 12% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 6.8 Hz, 2H), 6.88 (d, J = 6.4 Hz, 2H), 4.60 (d, J = 6.8 Hz, 1H), 4.35-4.50 (m, 3H), 4.02 (d, J = 7.2 Hz, 1H), 3.95 (d, J = 8.8, 1H), 3.80 (s, 3H), 3.55 (dt, J = 4.0, 10.4 Hz, 1H), 3.48 (d, J = 8.8 Hz, 1H), 3.32 (s, 3H), 3.19 (m, 1H), 3.06 (dd, J = 4.4, 10.8 Hz, 1H), 2.07 (m, 1H), 1.74 (d, J = 11.6 Hz, 2H), 1.35-1.65 (m, 7H), 1.25 (m, 1H), 1.17 (d, J = 10.4 Hz, 1H), 0.95 (m, 1H), 0.85 (s, 9H), 0.80 (s, 3H), -0.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 129.9, 129.6, 114.0, 96.0, 80.6, 80.0, 76.5, 73.5, 72.2, 56.4, 56.2, 55.5, 42.5, 41.0, 36.8, 32.2, 29.7, 27.8, 26.1, 25.8, 18.2, 14.5, -3.7, -4.6; HRMS calcd for $C_{29}H_{51}O_6Si$ ($M+H^+$) 523.3455, found 523.3452.



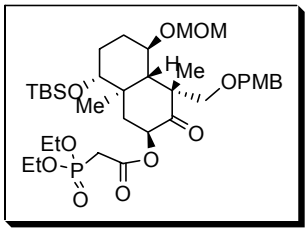
Compound 39: (1.25 g, 12.5% yield) as a colorless oil: R_f = 0. 24 (15% EtOAc:hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 6.80 Hz, 2H),

6.85 (d, J = 6.80 Hz, 2H), 4.71 (d, J = 7.2 Hz, 1H), 4.60 (m, 2H), 4.30 (d, J = 10.8 Hz, 1H), 4.15 (d, J = 10.4, 1H), 3.78 (s, 3H), 3.65 (dt, J = 4.0, 10.8 Hz, 1H), 3.30-3.50 (m, 4H), 3.10 (ddd, J = 4.4, 12.0, 16.4 Hz, 2H), 2.10 (m, 1H), 1.92 (m, 1H), 1.82 (m, 1H), 1.31-1.75 (m, 6H), 1.10-1.31 (m, 2H), 0.70-1.0 (m, 14H), -0.01 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 130.5, 129.5, 114.1, 96.0, 89.2, 80.0, 76.9, 75.8, 72.1, 63.9, 56.6, 56.2, 55.5, 43.3, 40.8, 36.4, 32.0, 29.7, 26.1, 25.5, 22.6, 18.2, 14.4, -3.7, -4.6; HRMS calcd for $C_{29}H_{51}O_6Si$ ($M+H^+$) 523.3455, found 523.3454.



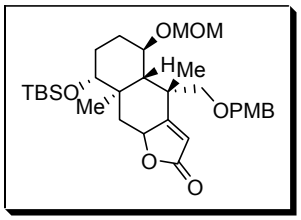
Compound 38-1: To a solution of alcohol **38** (0.5 g, 0.96 mmol) in CH_2Cl_2 (50 mL) was added Dess Martin periodinane (0.85 g, 2.01 mmol) at 0 ^oC and stirred at 25 ^oC for 5 h. The reaction mixture was quenched with a saturated solution of aqueous sodium bicarbonate (20 mL) and sodium thiosulfate (20 mL) and extracted with DCM (3 X 50 mL). The collected organic layer was washed with brine (50 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (8% EtOAc: hexane) to give **38-1** (0.49 g, 98% yield) as a white foam: R_f = 0.56 (15% EtOAc: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 4.52 (d, J = 6.4 Hz, 1H), 4.45 (m, 2H), 4.28 (d, J = 11.6 Hz, 1H), 3.79 (s, 3H), 3.70 (d, J = 9.2 Hz, 1H), 3.65 (d, J = 8.8 Hz, 1H), 3.30 (s, 3H), 3.21 (m, 1H), 2.47 (dd, J = 5.2, 10.0 Hz, 2H), 2.17 (m, 1H), 2.01 (m, 1H), 1.70 (d, J = 10.4 Hz, 1H), 1.50-1.65 (m, 3H), 1.21-1.50 (m, 2H), 1.18 (s, 3H), 0.86 (m, 12H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.6, 159.2, 130.8, 129.5, 113.8,

96.5, 79.3, 76.9, 73.2, 72.8, 56.8, 56.1, 55.5, 51.9, 40.3, 35.1, 34.7, 32.3, 29.1, 27.1, 26.1, 18.2, 12.9, -3.7, -4.6; HRMS calcd for $C_{29}H_{49}O_6Si$ ($M+H^+$) 521.3298, found 521.3296.



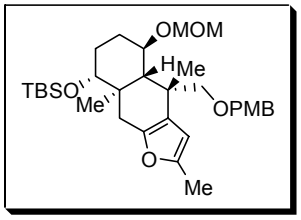
Compound 41-1: To a solution of **38-1** (1.10 g, 2.11 mmol) in THF (50 mL) was added sodium bis(trimethylsilyl) amide (1.0 M in THF,2.32 mmol) at -78 ^oC and stirred for 30 min. Then, a solution of 2-(phenylsulfonyl)-3-phenyloxaziridine (0.551 g, 2.11 mmol) in THF (8mL) was added at -78 ^oC and stirred for 1hr. The reaction mixture was quenched with a saturated solution of ammonium chloride (50 mL) and extracted with EtOAc (3 X 25 mL). The organic layer was dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (10% EtOAc: hexane) to afford the corresponding α- hydroxy ketone (1.0g, 88% yield) as a white solid: $R_f = 0.34$ (20% EtOAc: hexane). A solution of this compound (60.01 mg, 0.11mmol) was dissolved in DCM (15 mL) added diethyl phosphonoacetic acid (21.57 mg, 0.11 mmol), DCC (34.00 mg, 0.165 mmol) and DIPEA (0.04mL, 0.22mmol) at 0 ^0C. The reaction mixture was stirred at 25 ^0C for 18 h and then quenched with a saturated solution of sodium bicarbonate (5 mL) and extracted with CH_2Cl_2 (3 X 10 mL). The organic layer was washed with brine (15 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (60% EtOAc: hexane) to give **41-1** (0.07 g, 87% yield) as colorless

oil: R_f = 0.06 (20% EtOAc: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 5.54 (dd, J = 5.6, 13.6 Hz, 1H), 4.54 (d, J = 6.8 Hz, 1H), 4.41 (m, 2H), 4.33 (d, J = 11.6 Hz, 1H), 4.05-4.27 (m, 4H), 3.78 (s, 3H), 3.65-3.77 (m, 1H), 3.37 (d, J = 9.2 Hz, 1H), 3.27 (s, 3H), 3.22 (dd, J = 5.2, 10.8 Hz, 1H), 3.0-3.10 (m, 2H), 2.30 (dd, J = 5.6, 12.4 Hz, 1H), 2.20 (m, 1H), 1.20- 1.70 (m, 12H), 1.16 (s, 3H), 0.85 (m, 12H), 0.00 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.4, 164.9, 159.4, 130.1, 129.7, 113.9, 96.3, 79.3, 75.9, 74.7, 73.4, 72.9, 62.9, 56.8, 56.3, 55.5, 53.8, 41.9, 41.3, 32.3, 29.2, 26.0, 24.6, 18.1, 16.6, 14.4, -3.8, -4.6 ; HRMS calcd for $C_{35}H_{59}NaO_{11}PSi$ ($M+Na^+$) 737.3462, found 737.3465.



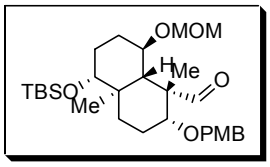
Compound 42: To a solution of phosphonoester **41-1** (0.247 g, 0.338 mmol) in THF (10 mL) was added LiCl (16.10 mg, 0.380 mmol), 8-diazabicyclo [5,4,0] undec-7-ene (DBU, 0.05 mL, 0.380mmol) at -78 ^{o}C for 30 min and then it was stirred at 25 ^{o}C for 4 h. The reaction mixture was quenched with a saturated solution of aqueous ammonium chloride, and extracted with EtOAc (3 X 15 mL). The organic layer was washed with brine (15 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (2% EtOAc: hexane) to give **42** (70.0 mg, 35% yield) as a colorless oil: R_f = 0.34 (20% EtOAc: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.0 Hz, 2H), 5.79 (s, 1H), 4.78 (dd, J = 6.0, 12.4 Hz, 1H), 4.62 (d, J = 6.8 Hz, 1H), 4.51 (d, J = 6.8 Hz, 2H), 4.43 (d, J = 12.0 Hz, 1H), 4.31 (d, J = 12.0 Hz, 1H), 3.80 (s,

3H), 3.71 (m, 3H), 3.61 (d, J = 8.8 Hz, 1H), 3.47 (d, J = 9.2 Hz, 1H), 3.32 (s, 3H), 3.12 (dd, J = 4.8, 10.8 Hz, 1H), 2.55 (d, J = 5.6, 12 Hz, 2H), 2.16 (brd, J = 11.6 Hz, 1H), 1.05-1.80 (m, 8H), 0.60-1.05 (m, 12H), 0.00 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.5, 173.6, 159.6, 129.9, 129.6, 114.9, 114.1, 96.3, 79.2, 78.7, 76.3, 73.1, 71.9, 56.5, 56.4, 55.6, 45.1, 44.6, 41.9, 32.1, 29.1, 26.1, 26.0, 18.2, 14.9, -3.8, -4.6 ; HRMS calcd for $C_{31}H_{48}NaO_7Si$ ($M+Na^+$) 583.3067 found 583.3065.

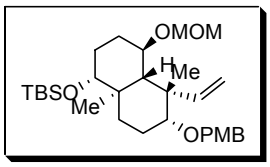


Compound 43: To a suspension of CuCN (0.006 g, 0.071 mmol) in THF (1 mL) added methylmagnesium bromide (1.4 M in toluene, 0.102 mL, 0.143 mmol) and stirred at -78 ^{o}C for 30 min. Then, a solution of unsaturated enone **65** (0.02 mg, 0.036 mmol) in THF (0.25 mL) was added to the above reaction mixture and stirred at 0 ^{0}C for 30 min. A saturated solution of aqueous sodium bicarbonate (25 mL) was added and extracted with Et_2O (3 X 5 mL). The organic layer was collected, dried over $MgSO_4$, concentrated and purified by flash chromatography (7% EtOAc: hexane) to give **43** (0.015 g, 75% yield) as a colorless oil: R_f= 0.6 (20% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 6.02 (s, 1H), 4.59 (d, J = 7.2 Hz, 1H), 4.52 (d, J = 6.8 Hz, 1H), 4.47 (d, J = 12.4 Hz, 2H), 4.37 (d, J = 12.4 Hz, 1H), 3.81 (s, 3H), 3.60 (m, 3H), 3.33 (s, 3H), 2.61 (d, J = 16.4 Hz, 1H), 2.10-2.35 (m, 4H), 1.20-1.65 (m, 9H), 0.89 (m, 12H), 0.00 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 149.3, 146.4, 131.4, 129.2, 123.9, 113.8, 106.9, 96.5, 79.5, 74.2, 73.3, 56.3, 55.5, 54.7, 42.7, 39.4, 37.1, 31.8, 30.1, 29.9,

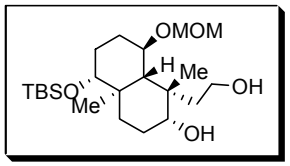
29.1, 26.1, 18.3, 14.8, 13.9, -3.7, -4.6; HRMS calcd for $C_{32}H_{51}O_6Si$ ($M+H^+$) 559.3455, found 559.3457.



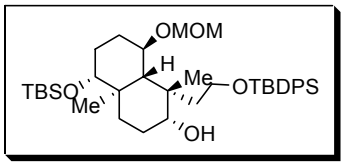
Compound 40: To a solution of alcohol **39** (0.350 g, 0.670 mmol) in CH_2Cl_2 (60 mL) was added Dess Martin periodinane (0.426 g, 1.01 mmol) at 0 ^oC. The reaction mixture was stirred at 25 ^oC for 1 h. It was quenched with a saturated solution of aqueous sodium bicarbonate and sodium thiosulfate and extracted with CH_2Cl_2 dichloromethane (3 X 50 mL). The collected organic layer was washed with brine (50 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (8% EtOAc: hexane) to give **40** (0.250 g, 72% yield) as a colorless oil: R_f = 0.43 (20% EtOAc: hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 10.1(s, 1H), 7.22 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 4.85 (d, J = 6.4 Hz, 1H), 4.66 (m, 2H), 4.40 (d, J = 11.6 Hz, 1H), 3.80 (s, 3H), 3.71(m, 1H), 3.34 (s, 3H), 3.11 (m, 2H), 2.0-2.10 (m, 2H), 1.92 (m, 1H), 1.77 (m, 1H), 1.10-1.65 (m, 7H), 0.98 (m, 1H), 0.86 (m, 9H), 0.77 (s, 3H), 0.02 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.3, 159.3, 130.7, 129.3, 113.9, 97.8, 84.4, 79.3, 76.9, 71.6, 56.8, 55.9, 55.5, 53.3, 41.0, 35.8, 33.4, 29.5, 26.1, 24.1, 23.9, 18.3, 14.4, -3.7, -4.6; HRMS calcd for $C_{29}H_{49}O_6Si$ ($M+H^+$) 521.3298, found 521.3295.



Compound 45: To a suspension of methyltriphenylphosphonium bromide (0.679 g, 1.92 mmol) in THF (25 mL) drop-added sodium bis(trimethyl silyl) amide (1M in THF, 1.92 mL, 1.92 mmol) and stirred at 0 ^{o}C for 15 min. Then, aldehyde **40** (0.250 g, 0.480 mmol) in THF (7 mL) was added to the above reaction mixture and stirred at 50 ^{o}C for 3 h. A saturated solution of aqueous sodium bicarbonate (25 mL) was added and extracted with Et_2O (3 X 50 mL) was added to the reaction mixture. The organic layer was collected, dried ($MgSO_4$), concentrated and purified by flash chromatography (3% EtOAc: hexane) to give **45** (0.220 g, 88% yield) as a colorless oil: R_f= 0.52 (20% EtOAc: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 6.15 (dd, J = 10.8, 17.2 Hz, 1H), 5.16 (m, 2H), 4.60 (m, 3H), 4.40 (d, J = 11.6 Hz, 1H), 3.79 (s, 3H), 3.57 (m, 1H), 3.33 (s, 3H), 3.09 (dd, J = 5.2, 10.4 Hz, 1H), 2.94 (dd, J = 4.0, 12.0 Hz, 1H), 2.14 (m, 1H), 1.84 (m, 2H), 1.25-1.70 (m, 8H), 1.18 (d, J = 10.8 Hz, 1H), 0.8-1.0 (m, 12H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 140.5, 131.5, 129.3, 115.7 113.8, 97.7, 86.4, 79.9, 78.5, 76.9, 71.4, 56.7, 55.9, 55.5, 45.9, 41.0, 36.6, 32.9, 29.7, 26.6, 26.1, 22.7, 18.3, 14.1, -3.7, -4.6; HRMS calcd for $C_{30}H_{51}O_5Si$ ($M+H^+$) 519.3506, found 519.3509.

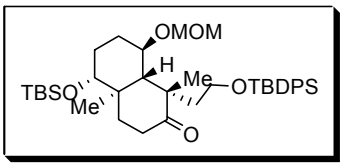


Compound 46: To a solution of **45** (0.160 g, 0.309 mmol) in THF (15 mL) was added BH_3·THF (0.96 mL, 0.96 mmol) and stirred at 0°C for 6 h. Then, the reaction mixture was stirred at 25 °C for 6 h. The reaction mixture was then treated with H_2O_2 (30% wt, 0.247 mL) and NaOH (3N, 0.247 mL) and stirred for 2 h. It was quenched with a saturated solution of aqueous ammonium chloride (15 mL), and it was extracted with EtOAc (3 X 20 mL). The collected organic layer was washed with brine (25 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (30% EtOAc: hexane) to give **46** (0.100 g, 75% yield) as a white solid: R_f = 0.21 (40% EtOAc: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (d, J = 6.8 Hz, 1H), 4.63 (d, J = 6.8 Hz, 1H), 3.70-3.80 (m, 3H), 3.67 (dd, J = 2.0, 4.0 Hz, 1H), 3.37 (s, 3H), 3.21 (dd, J = 4.8, 11.2 Hz, 1H), 2.15 (m, 1H), 1.82-1.95 (m, 2H), 1.78 (m, 1H), 1.15-1.68 (m, 12H), 0.95 (s, 3H), 0.87 (s, 9H), -0.00 (m, 6H); HRMS calcd for $C_{22}H_{45}O_5Si$ ($M+H^+$) 417.3036, found 417.3040.

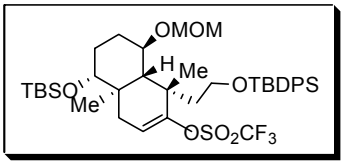


Compound 47: A solution of diol **46** (1.0 g, 2.40 mmol) in dichloromethane (25 mL) was added imidazole (0.396 g, 5.75 mmol) and TBDPSCl (0.739 mL, 2.40 mmol) at 0°C. The reaction mixture was stirred at 0 °C for 12 h and quenched with a saturated solution of aqueous ammonium chloride (50 mL). The reaction mixture was extracted with EtOAc (3 X 25 mL). The combined organic layer

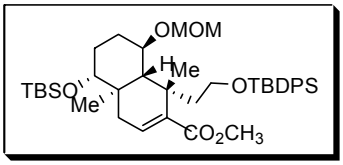
was washed with brine (50 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (5% EtOAc: hexane) to give **47** (1.50 g, 95% yield) as a white foam: R_f = 0.17 (15% EtOAc: hexane). HRMS calcd for $C_{38}H_{63}O_5Si$ ($M+H^+$) 655.4214, found 655.4209.



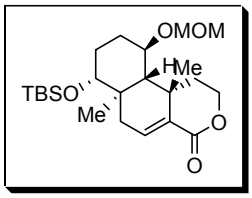
Compound 48: To a solution of alcohol **35** (2.40 g, 3.66 mmol) in dichloromethane (50 mL) was added Dess Martin periodinane (1.81 g, 4.26 mmol) at 0 ^oC. The reaction mixture was stirred at 25 ^oC for 3 h. It was quenched with a saturated solution of aqueous sodium bicarbonate and sodium thiosulfate and extracted with DCM (3 X 50 mL). The collected organic layer was washed with brine (50 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (5% EtOAc: hexane) to give **48** (2.20 g, 92% yield) as a colorless foam: R_f = 0.34 (15% EtOAc: hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (m, 4H), 7.40 (m, 6H), 4.64 (d, J = 6.8 Hz, 1H), 4.57 (d, J = 6.8 Hz, 1H), 3.80 (dt, J = 4.4, 10.4 Hz, 1H), 3.63 (m, 1H), 3.55 (m, 1H), 3.34 (s, 3H), 3.14 (dd, J = 4.4, 10.4 Hz, 1H), 2.56 (dt, J = 5.6, 14.4 Hz, 1H), 2.10-2.30 (m, 3H), 2.04 (m, 1H), 1.80 (m, 1H), 1.44-1.70 (m, 2H), 1.42 (d, J = 10.8 Hz, 1H), 1.20-1.40 (m, 5H), 1.06 (s, 3H), 1.02 (s, 9H), 0.87 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.4, 135.9, 135. 8, 134.0, 133.9, 129.8, 129.7, 127.9, 96.4, 79.7, 76.2, 60.9, 58.7, 56.4, 50.5, 40.9, 38.1, 36.8, 35.4, 32.1, 29.6, 27.1, 26.0, 24.3, 19.3, 18.2, 13.8, -3.7, -4.6; HRMS calcd for $C_{38}H_{61}O_5Si_2$ ($M+H^+$) 653.4058, found 653.4061.



Compound 49: To a solution of **48** (0.089 g, 0.136 mmol) in THF (10 mL) was added sodium bis(trimethylsilyl) amide (1.0 M, 0.226mL, 0.226mmol) at -78 ^{o}C and stirred for 30 min. Then, the reaction mixture was treated with a solution of phenyl trifluromethanesulfonamide (0.047g, 0.133mmol) at -78 ^{o}C and stirred for 30 min. The reaction mixture was warmed to 25 ^{o}C and quenched with a saturated solution of aqueous ammonium chloride (15mL), and extracted with EtOAc (3 X 10 mL). The collected organic layer was washed with brine (15 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (2% EtOAc: hexane) to give **49** (0.09 g, 85% yield) as a colorless oil: R_f = 0.48 (15% EtOAc: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.70 (m, 4H), 7.30-7.50 (m, 6H), 5.59 (m, 1H), 4.60 (d, J = 6.8 Hz, 1H), 4.56 (d, J = 6.8 Hz, 1H), 3.73-3.90 (m, 2H), 3.68 (m, 1H), 3.36 (s, 2H), 3.16 (m, 1H), 2.20-2.30 (m, 3H), 1.88 (m, 2H), 1.34 (s, 3H), 1.05 (s, 9H), 0.87 (s, 9H), 0.84 (s, 3H), 0.02 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 135.8, 135.7, 134.3, 134.2, 129.8, 127.8, 127.7, 113.5, 96.3, 79.3, 76.8, 61.7, 56.3, 55.5, 39.8, 39.6, 37.6, 36.3, 31.3, 29.9, 29.0, 27.2, 27.1, 26.5, 26.1, 26.0, 19.4, 18.3, 13.9, -3.7, -4.6; HRMS calcd for $C_{39}H_{60}F_3O_7SSi_2$ ($M+H^+$) 785.3550, found 785.3545.

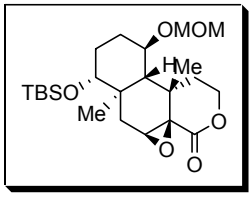


Compound 50: To a solution of vinyl triflate **49** (0.091 g, 0.1159 mmol) in DMF (1 mL) and MeOH (0.2 mL) was added $Pd(OAc)_2$ (6.87 mg, 0.036 mmol), PPh_3 (16.03 mg, 0.0612 mmol) and DIPEA (0.05mL, 0.306 mmol) at 25^{o}C and stirred for 30 min under CO atmosphere. Then, the reaction mixture was heated at 70 ^{o}C for 3 h and quenched with a saturated solution of aqueous ammonium chloride, and extracted with EtOAc (3 X 5 mL). The organic layer was washed with brine (5 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (4% EtOAc: hexane) to give **50** (0.055 g, 68% yield) as a colorless oil: R_f = 0.46 (20% EtOAc: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (m, 4H), 7.37 (m, 6H), 6.70 (d, J = 5.6 Hz, 1H), 4.45 (s, 2H), 3.86 (m, 1H), 3.50-3.70 (m, 4H), 3.32 (s, 3H), 3.16 (dd, J = 4.0, 10.8 Hz, 1H), 2.10-2.30 (m, 3H), 2.04 (m, 1H), 1.66 (d, J = 18.4 Hz, 1H), 1.20-1.62 (m, 8H), 1.02 (s, 9H), 0.86 (s, 9H), 0.70 (s, 3H), 0.01 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 139.1, 135.7, 135.9, 134.5, 129.6, 127.8, 96.6, 79.7, 76.9, 62.9, 56.3, 56.1, 51.4, 39.5, 39.1, 38.4, 36.9, 31.6, 30.3, 29.1, 27.1, 26.1, 19.4, 18.3, 13.8, -3.7, -4.6; HRMS calcd for $C_{40}H_{63}O_6Si_2$ ($M+H^+$) 695.4163, found 695.4165.



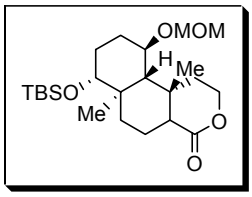
Compound 51: To a solution of vinyl ester **50** (0.100 mg, 0.1438 mmol) in THF (20 mL) was added TBAF (1M in THF, 0.158 mL, 0.158 mmol) at

0°C. The reaction mixture was stirred at 25 °C for 4 h and was quenched with a saturated solution of aqueous ammonium chloride, and extracted with EtOAc (3 X 15 mL). The organic layer was washed with brine (25 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (20% EtOAc: hexane) to give **51** (0.05 g, 82% yield) as a colorless oil: R_f = 0.5 (70% EtOAc: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (d, J = 6.0 Hz, 1H), 4.73 (d, J = 6.8 Hz, 1H), 4.62 (d, J = 6.8 Hz, 1H), 4.45 (m, 1H), 4.35 (m, 1H), 3.67 (m, 1H), 3.36 (s, 3H), 3.27 (dd, J = 4.0, 11.2 Hz, 1H), 2.35 (dd, J = 7.2, 17.6 Hz, 1H), 2. 27 (m, 1H), 2.10 (m, 1H), 2.02 (m, 1H), 1.74 (d, J = 18 Hz, 1H), 1.42-1.70 (m, 4H), 1.37 (s, 3H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 135.9, 135.8, 96.6, 78.9, 76.1, 66.2, 56.4, 54.4, 40.8, 38.4, 36.1, 31.0, 29.6, 29.2, 29.1, 26.0, 18.2, 12.8, -3.7, -4.6; HRMS calcd for $C_{23}H_{41}O_5Si$ ($M+H^+$) 425.2723, found 425.2719.

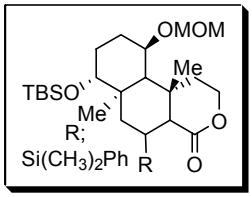


Compound 53: To a solution of unsaturated lactone **51** (3.0 mg, 0.0071 mmol) in DCM (2 mL) was added m-CPBA (5.0 mg, 0.029 mmol), and saturated aqueous $NaHCO_3$ (1.0 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 3 h and quenched with a saturated solution of $Na_2S_2O_4$ (1.5mL) and $NaHCO_3$ (1 mL). Then, the reaction mixture was extracted with DCM (3 X 3 mL). The collected organic layer was washed with brine (5 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (20% EtOAc: hexane) to give **53** (2.0 mg, 64% yield) as a white solid: R_f = 0. 43 (40% EtOAc: hexane). ^{1}H NMR

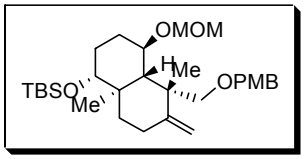
(400 MHz, $CDCl_3$) δ 4.74 (d, J = 6.8 Hz, 1H), 4.60 (d, J = 7.2 Hz, 1H), 4.55 (dt, J = 3.20, 12.4 Hz, 1H), 4.44 (m, 1H), 3.66 (dt, J = 4.4, 10.8 Hz, 1H), 3.60 (d, J = 5.60 Hz, 1H), 3.36 (s, 3H), 3.10 (dd, J = 4.0, 11.2 Hz, 1H), 2.41 (m, 1H), 2.0-2.30 (m, 2H), 1.10-1.70 (m, 9H), 0.93 (s, 3H), 0.88 (s, 9H), 0.03 (s, 6H); HRMS calcd for $C_{23}H_{41}O_6Si$ ($M+H^+$) 441.2672, found 441.2671.



Compound 54: To a solution of epoxide **53** (1.50 mg, 0.0045 mmol) in degassed THF (0.25 mL) was added DMAE (0.0016 g, 0.018 mmol), hexamethylphosphoramide (HMPA, 0.0032 g, 0.018 mmol), SmI_2 (0.1M in THF, 0.0009 mL, 0.0091 mmol) at -78 ^oC and stirred at -45 ^oC for 10 min. The reaction mixture was quenched with a saturated solution of aqueous ammonium chloride (0.5 mL), and extracted with EtOAc (3 X 5 mL). The collected organic layer was washed with brine (5 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (10% EtOAc: hexane) to give **54** (1.50 mg, 78% yield) as a colorless oil: R_f = 0. 54 (40% EtOAc: hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 4.70 (d, J = 7.2 Hz, 1H), 4.60 (d, J = 7.2 Hz, 1H), 4.24-4.45 (m, 2H), 3.74 (m, 1H), 3.35 (s, 3H), 3.12 (dd, J = 4.8, 11.2 Hz, 1H), 2.10-2.30 (m, 3H), 1.85 (d, J = 12 Hz, 2H), 1.20-1.80 (m, 8H), 1.15 (d, J = 11.2 Hz, 1H), 0.99 (m, 1H), 0.94 (s, 3H), 0.86 (s, 9H) 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 96.6, 79.7, 76.9, 66.9, 56.6, 55.8, 53.3, 41.1, 37.5, 35.2, 31.8, 31.7, 29.8, 26.2, 26.1, 23.9, 18.4, 14.4, -3.7, -4.6; HRMS calcd for $C_{23}H_{43}O_5Si$ ($M+H^+$) 427.2880, found 427.2879.

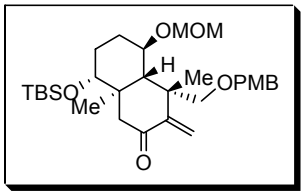


Compound 52: To a suspension of CuCN (7.59 mg, 0.084 mmol) in THF (1 mL) dimethyl phenylsilyl lithium (1M in THF, 0.168 mL, 0.168 mmol) was added and stirred at 0 ^{o}C for 30 min. Then, a solution of unsaturated lactone **51** (18.0 mg, 0.042 mmol) in THF (0.6 mL) was added at -25 ^{o}C and stirred for 10 min. Methyl iodide (29.8mg, 0.211mmol) was added and stirred for 20 min. The reaction mixture was quenched with a saturated solution of aqueous ammonium chloride, and extracted with EtOAc (3 X 5 mL). The collected organic layer was washed with brine (2 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (10% EtOAc: hexane) to give **52** (10.0 mg, 42% yield) as a colorless oil: R_f = 0. 33 (20% EtOAc: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (m, 2H), 7.30 (m, 3H), 4.50-4.60 (m, 3H), 4.24 (m, 1H), 3.68 (dt, J = 5.2, 12.0 Hz, 1H), 3.22 (s, 3H), 3.10 (dd, J = 4.8, 10.4 Hz, 1H), 2.13 (m, 1H), 1.90-2.10 (m, 2H), 1.00-1.70 (m, 11H), 0.85 (s, 3H), 0.65 (s, 9H), 0.15 (s, 3H), -0.02 (s, 3H), -0. 20 (s, 3H); HRMS calcd for $C_{31}H_{53}O_5Si_2$ ($M+H^+$) 561.3431, found 561.3429.



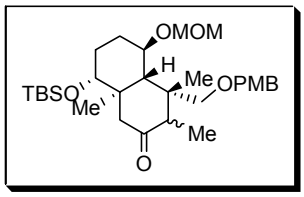
Compound 59: To a suspension of methyltriphenylphosphonium (34.32 g, 96.00 mmol) in THF (150 mL) drop-added potassium tert-butoxide (1M in toluene, 48.00 mL, 48.00 mmol) and stirred at 25 ^{o}C for 30 min. Then, ketone **38-1**(5.00g, 9.60 mmol) in THF (50 mL) was added to the

above reaction mixture and stirred at 50 ^{o}C for 18 h. A saturated solution of aqueous sodium bicarbonate (75 mL) and extracted with EtO_2 (3 X 100 mL) was added to the reaction mixture. The organic layer was collected, dried ($MgSO_4$), concentrated and the yellow residue was purified by flash chromatography (5% EtOAc: hexane) to give **50** (4.90 g, 98% yield) as a light yellow oil: R_f= 0.82 (30% Et_2O: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 4.84 (m, 2H), 4.54 (m, 2H), 4.39 (m, 2H), 3.80 (s, 3H), 3.73 (m, 1H), 3.53 (m, 2H), 3.30 (s, 3H), 3.09 (dd, J = 5.2, 11.2 Hz, 1H), 2.27 (m, 1H), 2.05-2.20 (m, 2H), 1.81 (m, 2H), 1.12-1.60 (m, 6H), 1.05 (dt, J = 5.2, 12.8 Hz, 1H), 0.92 (s, 3H), 0.85 (s, 9H), 0.02 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 155.1, 131.1, 129.4, 113.8, 113.7, 109.1, 96.8, 80.3, 76.9, 73.5, 73.1, 71.0, 56.9, 56.1, 55.5, 44.9, 41.4, 40.7, 32.8, 29.9, 29.7, 26.2, 26.1, 25.7, 18.3, 14.8, -3.7, -4.6; HRMS calcd for $C_{30}H_{51}O_5Si$ ($M+H^+$) 519.3506, found 519.3509.



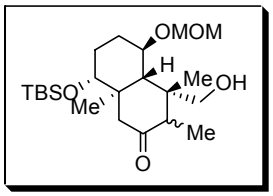
Compound 60: To a solution of olefin **59** (0.486 g, 0.936 mmol) in dioxane (55 mL) added selenium (IV) oxide (0.62 mL, 5.59 mmol) and heated at 50 ^{o}C for 5 h. The reaction mixture was cooled down to 25 ^{o}C, and filtered through celite. The filtrate was dried ($MgSO_4$), concentrated under reduced pressure and subjected to flash chromatography (10% EtOAc: hexane) to give **60** (0.402 g, 81% yield) as a light yellow oil: R_f = 0.38 (25% Et_2O: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 8.0 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 6.07 (s, 1H), 5.36 (s, 1H),

4.60 (d, J = 6.0 Hz, 1H), 4.51 (d, J = 6.4 Hz, 1H), 4.39 (m, 2H), 3.87 (d, J = 10.0 Hz, 1H), 3.81 (s, 3H), 3.50 (d, J = 10.0 Hz, 1H), 3.35 (s, 3H), 3.25 (m, 1H), 2.64 (d, J = 17.6 Hz, 1H), 2.20 (m, 1H), 1.94 (d, J = 17.6 Hz, 1H), 1.68 (d, J = 10.4 Hz, 1H), 1.05-1.60 (m, 7H), 0.70-0.95 (m, 12H), 0.04 (m, 6H); HRMS calcd for $C_{30}H_{49}O_6Si$ ($M+H^+$) 533.3298, found 533.3295.

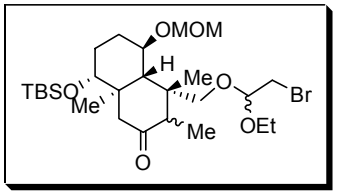


Compound 61: To a solution unsaturated enone **60** (9.0 mg, 0.0168 mmol) in THF (1 mL) was added chlorotris-(triphenylphosphine) rhodium (I) (1.5 mg, 0.0017 mmol) along with Et_3SiH (5.8 mg, 0.05 mmol) and stirred at 60 ^oC for 4 h. Then, the reaction mixture was concentrated under reduced pressure and dried under high vacuum for 10 min. The brown residue was dissolved in MeOH (0.5 mL) and acetone (0.5 mL) and K_2CO_3 (20 mg, excess) was added. The reaction mixture was stirred for 4 h. The reaction mixture was concentrated under reduced pressure, diluted with EtOAc-H_2O and extracted with EtOAc (3 X 5 mL). The organic layer was washed with brine, dried over $MgSO_4$, concentrated under reduced pressure and the brown residue purified by flash chromatography (20% EtOAc: hexane) to give **61** (13.0 mg, 100% yield) as colorless oil: R_f = 0.37 (25% Et_2O: hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 6.8 Hz, 2H), 6.87 (d, J = 6.8 Hz, 2H), 4.51 (d, J = 6.4 Hz, 1H), 4.40-4.49 (m, 2H), 4.31 (d, J = 11.6, 1H), 3.85 (d, J = 9.2 Hz, 1H), 3.80 (s, 3H), 3.62 (d, J = 9.2 Hz, 1H), 3.31 (s, 3H), 3.26 (dd, J = 6.4, 10.0 Hz, 1H), 2.30 (d, J = 14.0 Hz, 1H), 2.21 (m, 1H), 2.0 (t, J = 5.6 Hz, 1H), 1.70 (d, J = 13.6 Hz, 1H), 1.19-1.62

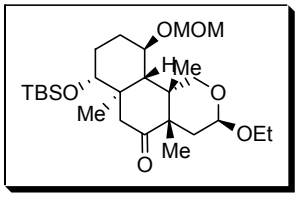
(m, 8H), 0.88 (s, 9H), 0.80 (s, 3H), 0.03 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.4, 159.2, 130.1, 129.5, 113.8, 96.6, 79.1, 76.9, 73.2, 72.8, 72.7, 56.3, 56.1, 55.5, 51.1, 50.1, 38.9, 32.0, 30.5, 29.9, 29.7, 29.5, 28.5, 26.1, 18.3, 14.5, -3.7, -4.7; HRMS calcd for $C_{30}H_{51}O_6Si$ ($M+H^+$) 535.3455, found 535.3451.



Compound 62: To a solution of **61** (0.420 g, 0.787 mmol) in DCM (20 mL) and four drops of H_2O was added DDQ (0.714 g, 3.15 mmol) at 0 ^{o}C. The reaction mixture was stirred for 3 h. The reaction mixture was concentrated under reduced pressure and the yellow residue purified by flash chromatography (20% Et_2O: hexane) to give **62** (0.325 g, 99% yield) as a colorless oil: R_f= 0.50 (50% Et_2O: hexane). HRMS calcd. for $C_{23}H_{36}O_5$ (M+ Na^+) 415.2455, found 415.2468. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (m, 2H), 3.97 (m, 1H), 3.83 (d, J = 11.2 Hz, 1H), 3.60 (d, J = 11.6, 1H), 3.38 (s, 3H), 3.26 (dd, J = 4.4, 11.2 Hz, 1H), 2.90 (m, 1H), 2.43 (m, 1H), 2.0-2.30 (m, 3H), 1.20-1.70 (m, 3H), 1.15 (s, 3H), 1.05 (d, J = 6.4 Hz, 1H), 1.01 (d, J = 6.8 Hz, 3H), 0.96 (s, 3H), 0.86 (s, 9H), 0.03 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.5, 96.4, 96.1, 80.8, 79.9, 76.8, 66.2, 64.9, 57.4, 56.3, 54.9, 54.1, 53.6, 52.3, 48.3, 45.3, 42.7, 32.1, 31.5, 29.3, 28.8, 27.5, 26.0, 24.2, 18.2, 16.4, 13.9, 10.1, -3.6, -3.8, -4.6; HRMS calcd for $C_{22}H_{43}O_5Si$ ($M+H^+$) 415.2880, found 415.2883.

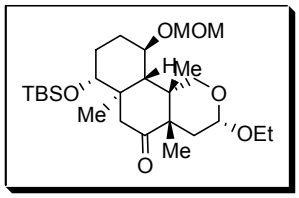


Compound 63: To a solution of alcohol **62** (13.0 mg, 0.0314 mmol) in DCM (1 mL) was treated with N,N-dimethylaniline (0.152 g, 1.25 mmol) and dibromoacetal (2.69 M in DCM, 0.23 mL, 0.628 mmol) at -78 ^{0}C. The reaction mixture was stirred at 25 ^{o}C for 1 h. The reaction mixture was diluted with H_2O (1 mL) and extracted with EtOAc (3 X 5mL). The organic layer was washed with brine (1.5 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (5% EtOAc/hexane) to give **63** (10.0 mg, 57% yield) as a yellow oil : R_f = 0.76 (25% Et_2O/hexane). HRMS calcd for $C_{26}H_{50}BrO_6Si$ ($M+H^+$) 565.2560, found 565.2555.

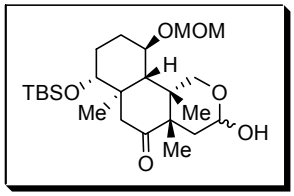


Compound 64-1: To a solution of bromoacetal **63** (10.0 mg, 0.018 mmol) in toluene (1 mL) was added potassium tert- butoxide (0.5 M, 0.035 mL, 0.035 mmol) at 25 ^{o}C and then it was heated to 65 ^{o}C for 12 h. The reaction mixture was quenched with a solution of ammonium chloride and extracted with EtOAc (3 X 5 mL). The organic layer was washed with brine, dried over $MgSO_4$, concentrated under reduced pressure and the residue purified by flash chromatography (20% EtOAc: hexane) to give **64-1** (5.0 mg, 71% yield) as a colorless oil: R_f = 0.39 (10% EtOAc: hexane) and **64-2** (3.0 mg, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (m, 2H), 4.60 (d, J = 7.2 Hz, 1H), 3.69-3.85 (m, 2H), 3.64 (d, J = 12 Hz, 1H), 3.45-3.60 (m,

2H), 3.30-3.40 (m, 4H), 2.25-2.40 (m, 2H), 2.15-2.25 (m, 2H), 1.90 (d, J = 10.4, 1H), 1.66 (m, 1H), 1.30-1.55 (m, 6H), 1.19 (t, J = 7.2 Hz, 3H), 1.08 (s, 3H), 0.96 (s, 3H), 0.90 (m, 9H), 0.01 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.3, 99.2, 96.3, 79.8, 79.5, 75.8, 67.1, 64.2, 56.5, 51.9, 51.5, 49.1, 45.0, 35.1, 31.9, 29.9, 29.3, 26.0, 25.0, 23.9, 18.2, 15.5, 14.5, 1.3, -3.8, -4.5; HRMS calcd for $C_{26}H_{48}O_6Si$ ($M+Na^+$) 507.3117, found 507.3105.

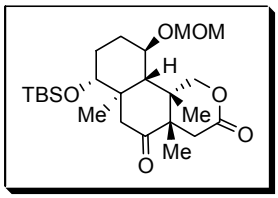


Compound 64-2: (3.0 mg, 24%) as a colorless oil: R_f = 0.32 (10% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67-4.77 (m, 2H), 4.64 (d, J = 6.8 Hz, 1H), 4.06 (d, J = 11.6 Hz, 1H), 3.71 (m, 1H), 3.58, (m, 1H), 3.40 (s, 3H), 3.25-3.35 (m, 2H), 2.51 (d, J = 14.4 Hz, 1H), 2.40 (d, J = 14.0 Hz, 1H), 2.15-2.30 (m, 2H), 1.93 (d, J = 10.8, 1H), 1.62 (m, 2H), 1.30-1.55 (m, 3H), 1.18 (t, J =6.8 , 3H), 1.07 ((s, 3H), 0.97 (s, 3H), 0.86 (m, 9H), 0.02 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.3, 96.4, 96.1, 79.2, 75.8, 63.2, 62.2, 56.6, 51.8, 49.6, 49.0, 43.9, 43.1, 32.2, 31.9, 29.2, 26.7, 26.1, 25.1, 18.2, 15.7, 15.3, -3.8, -4.5; HRMS calcd for $C_{26}H_{48}O_6Si$ ($M+Na^+$) , 507.3117 found 507.3115.

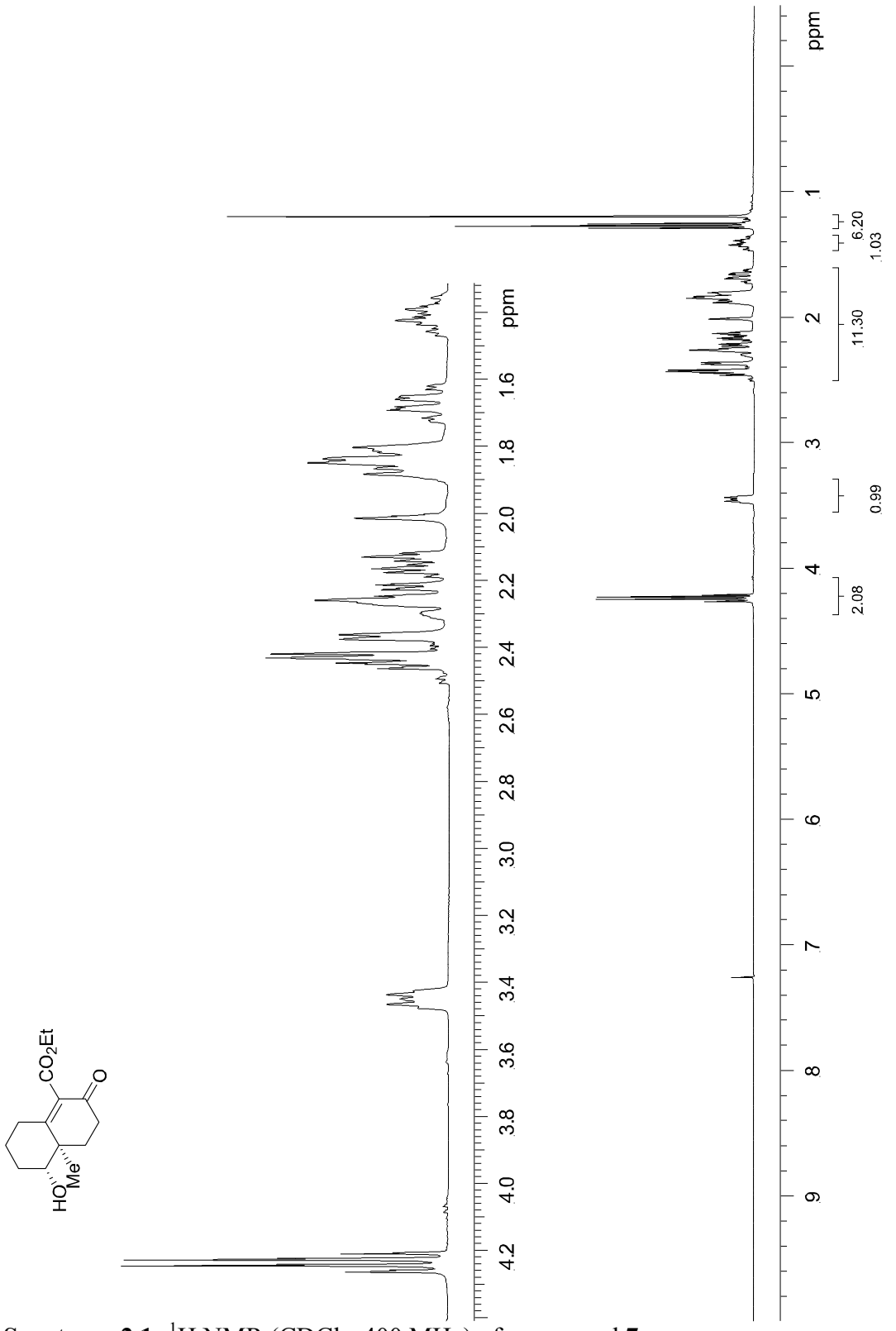


Compound 65: To a solution of **64-1** (10.0 mg, 0.020 mmol) in THF (1.5 mL) was added HCl (0.10 M, 0.5 mL) at 0 ^{o}C and stirred at 25 ^{o}C for 18 h. The reaction mixture was diluted with H_2O and extracted with EtOAc (3 X 5 mL).

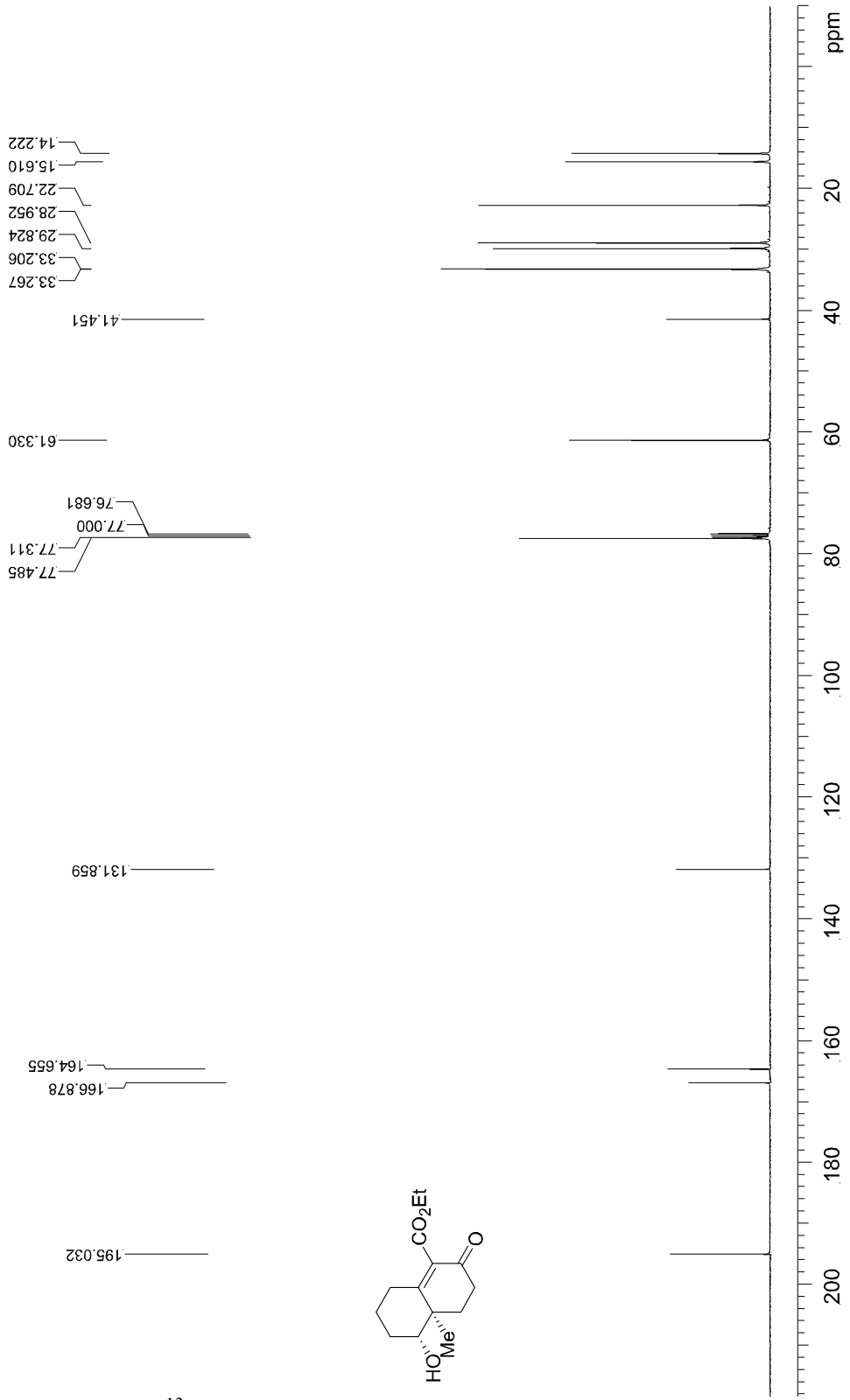
The organic layer was washed with a solution of sodium bicarbonate, dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (25% Et_2O: hexane) to give **44** (7.00 mg, 77% yield) as a white solid : R_f = 0.20 (65% Et_2O: hexane). HRMS calcd for $C_{24}H_{42}O_6Si$ ($M+H^+$) 457.2985, found 457.2980.



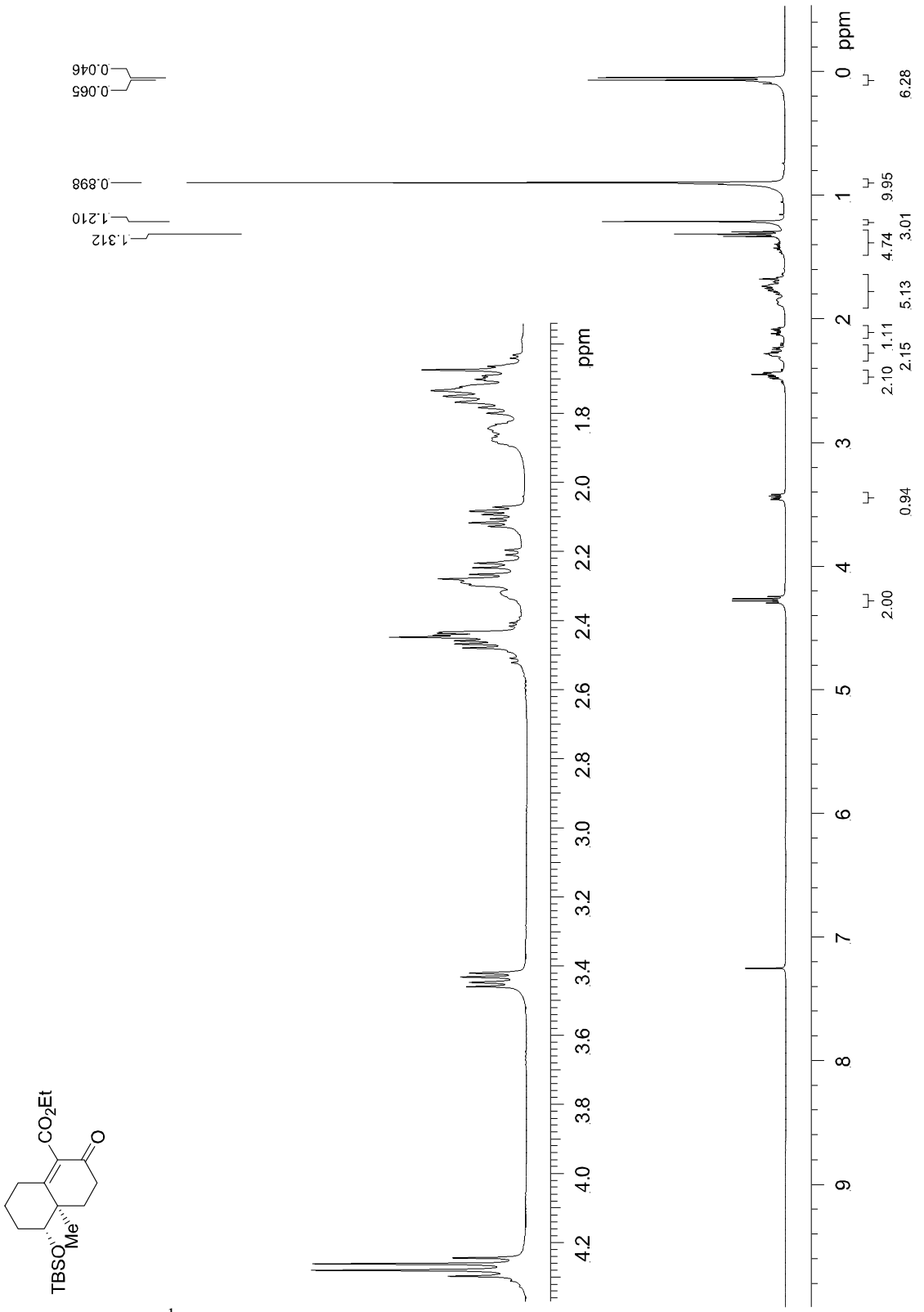
Compound 66: To a solution of lactol **65** (3.0 mg, 0.0066 mmol) in DCM (0.5 mL) and 4Å molecular sieves (10 mg) was added PCC (2.0 mg, 0.0099 mmol) at 0 ^{0}C and stirred at 25 ^{o}C for 18 h. The reaction mixture was diluted with DCM, filtered through celite, and concentrated under reduced pressure. The brown-yellow residue was purified by flash chromatography (20% Et_2O: hexane) to give **43** (2.90 mg, 97% yield) as colorless needles: R_f = 0.3 (65% Et_2O: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (d, 7.2 Hz, 1H), 4.57 (d, J = 7.2 Hz, 1H), 4.23 (d, J = 11.6 Hz, 1H), 4.05 (d, J = 11.6 Hz, 1H), 3.75 (m, 1H), 3.47 (d, J = 17.6 Hz, 1H), 3.39 (s, 3H), 3.36 (m, 1H), 2.41 (s, 2H), 2.22 (m, 1H), 2.18 (s, 2H), 2.0 (d, J = 10.8, 1H), 1.70 (m, 1H), 1.56 (s, 3H), 1.50 (m, 1H), 1.43 (s, 3H), 1.25 (s, 3H), 0.87 (s, 9H), 0.06 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.7, 172.6, 95.6, 78.9, 74.6, 71.4, 56.9, 52.8, 52.4, 48.1, 45.0, 44.9, 35.6, 31.2, 31.1, 29.1, 26.0, 25.0, 23.9, 18.3, 14.5, -3.8, -4.5; HRMS calcd for $C_{24}H_{43}O_6Si$ ($M+H^+$) , 455.2829 found 455.2828.



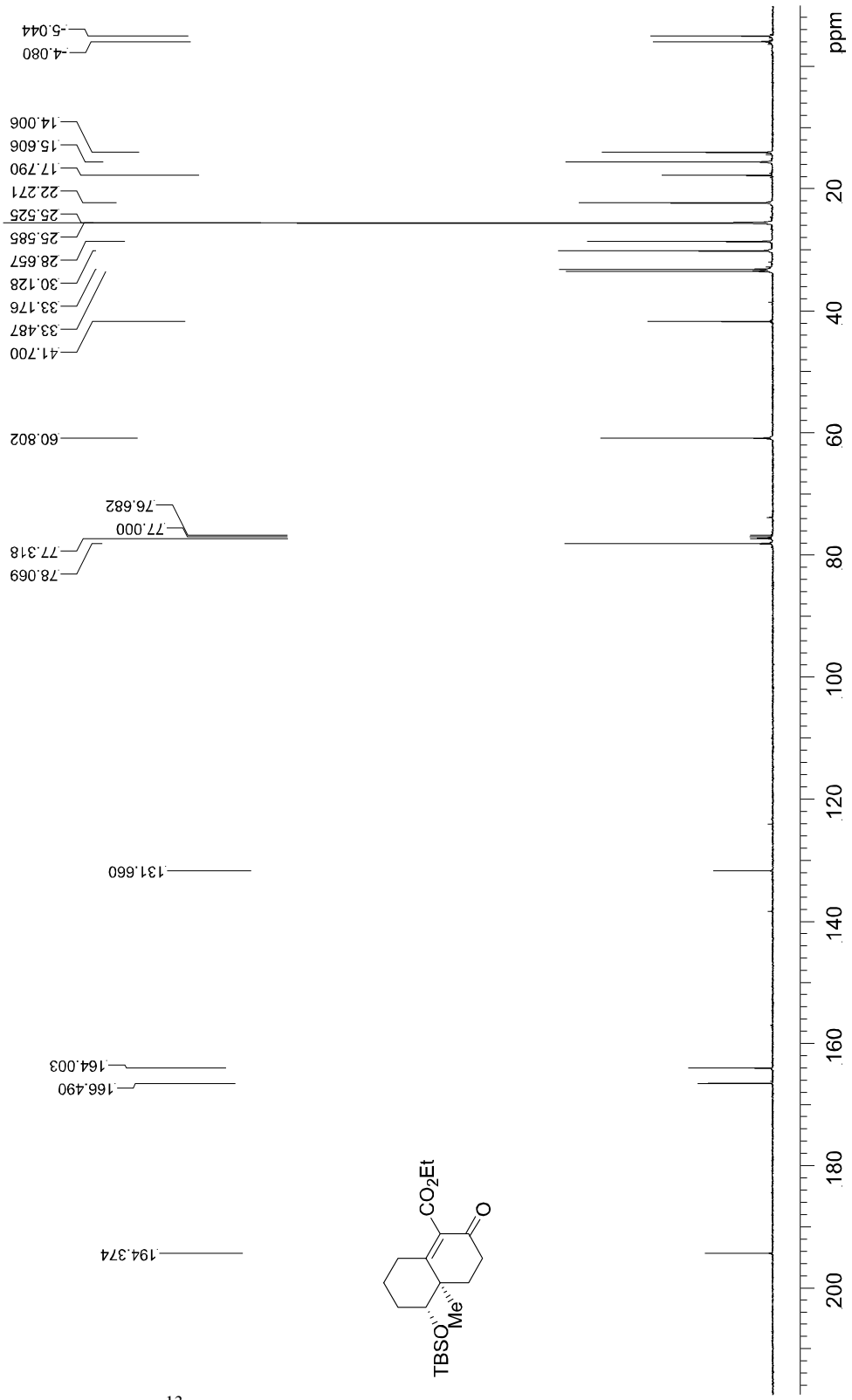
Spectrum 2.1: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **7**



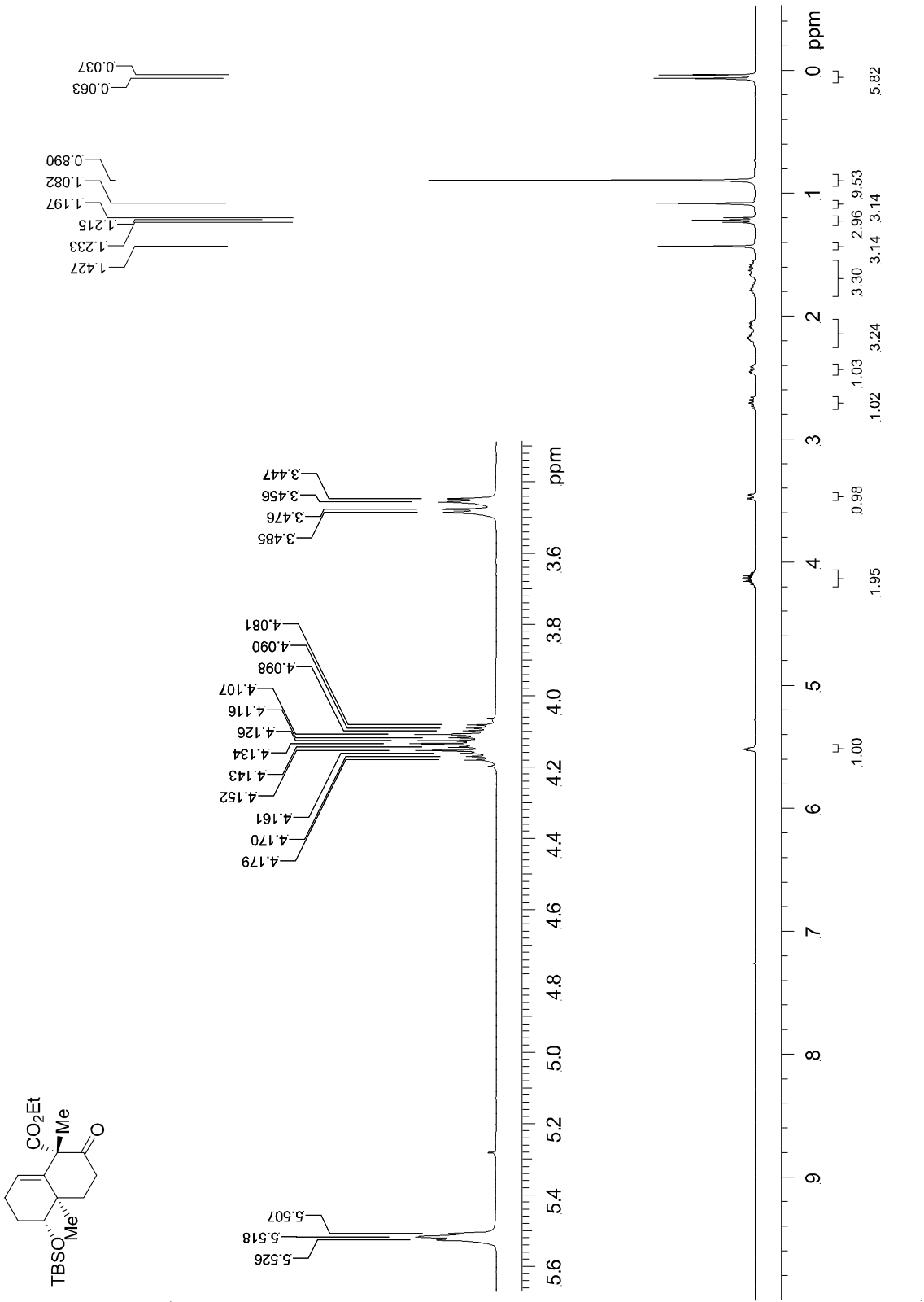
Spectrum 2.2: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **7**



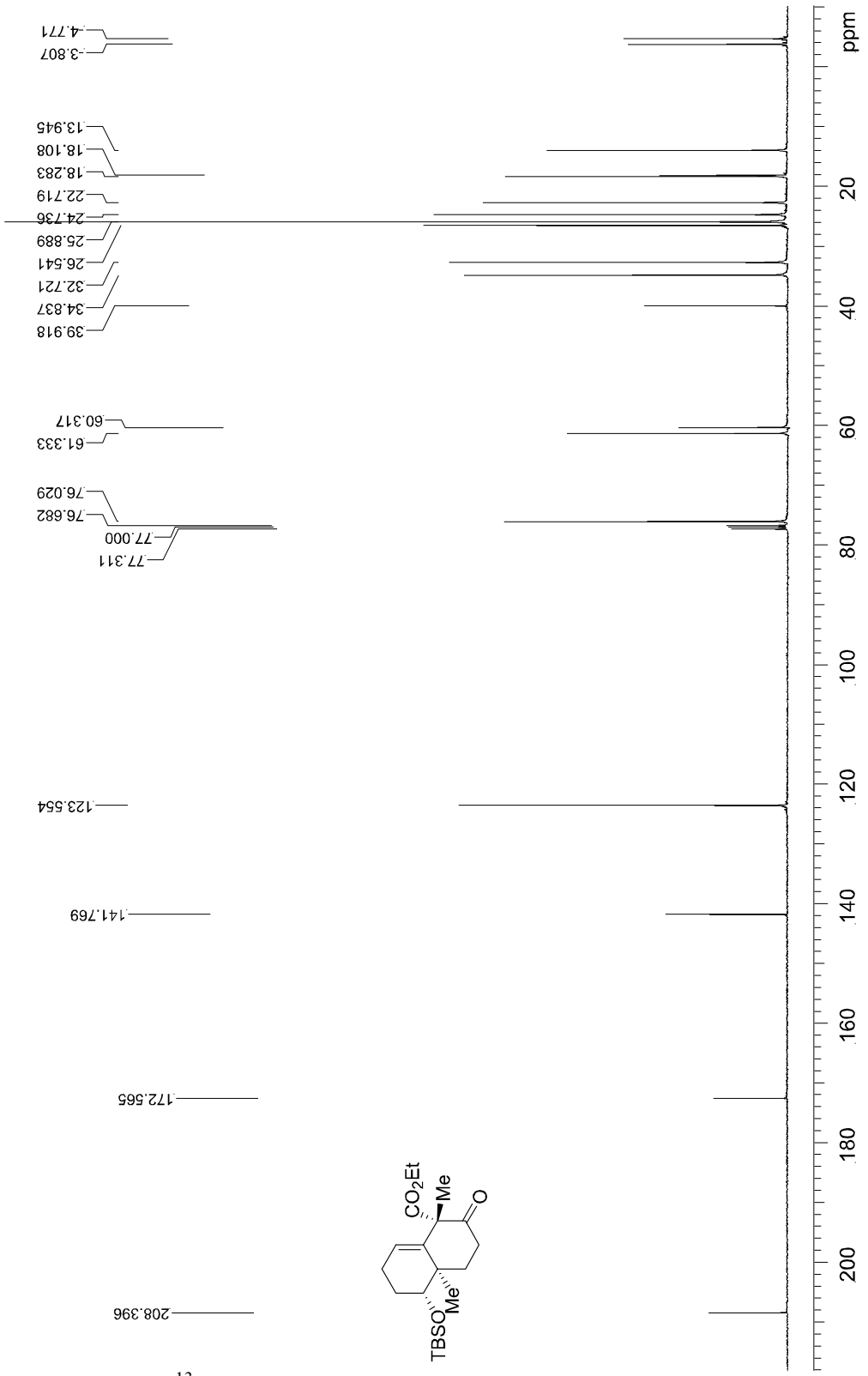
Spectrum 2.3: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **8**



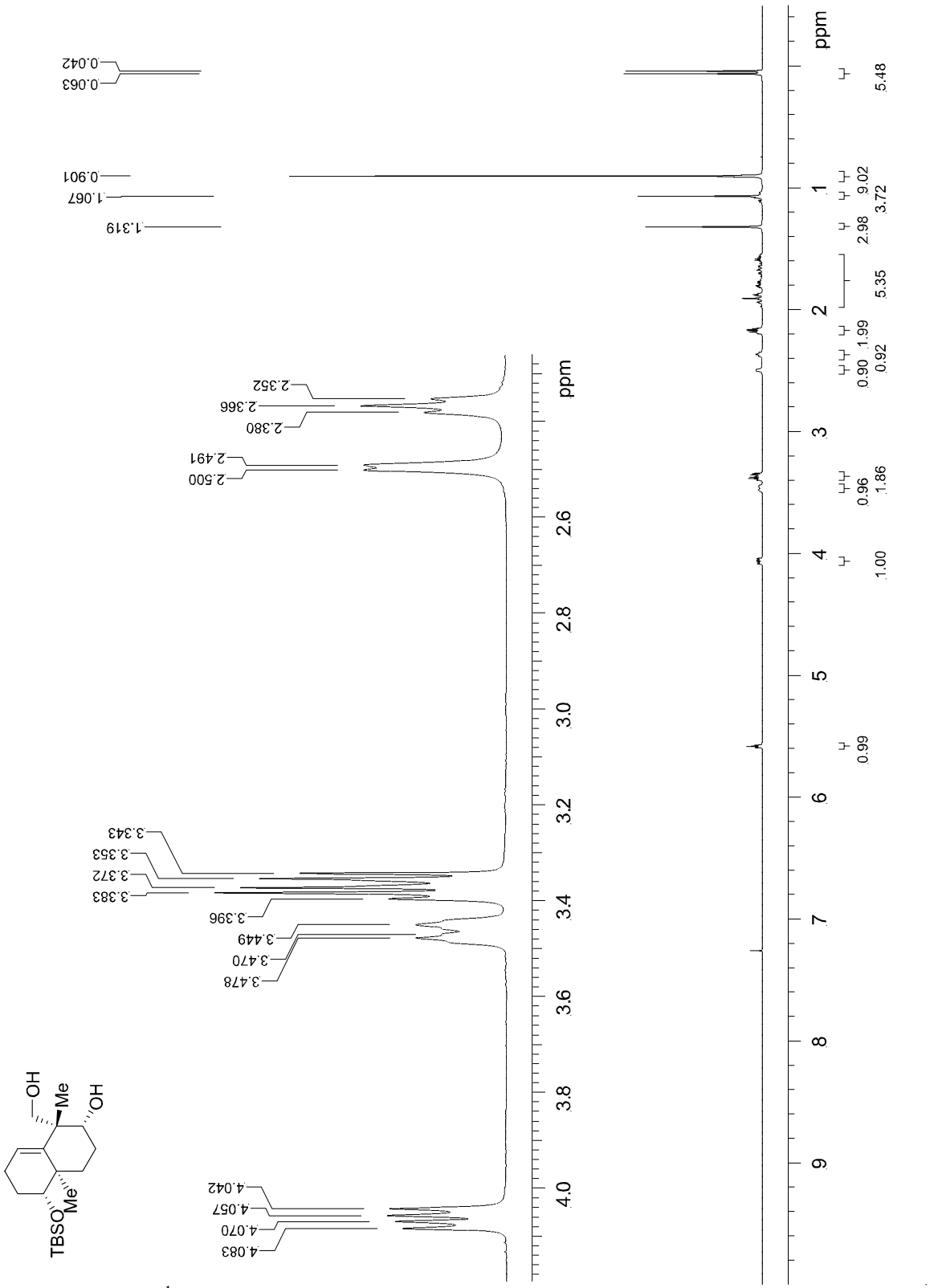
Spectrum 2.4: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **8**



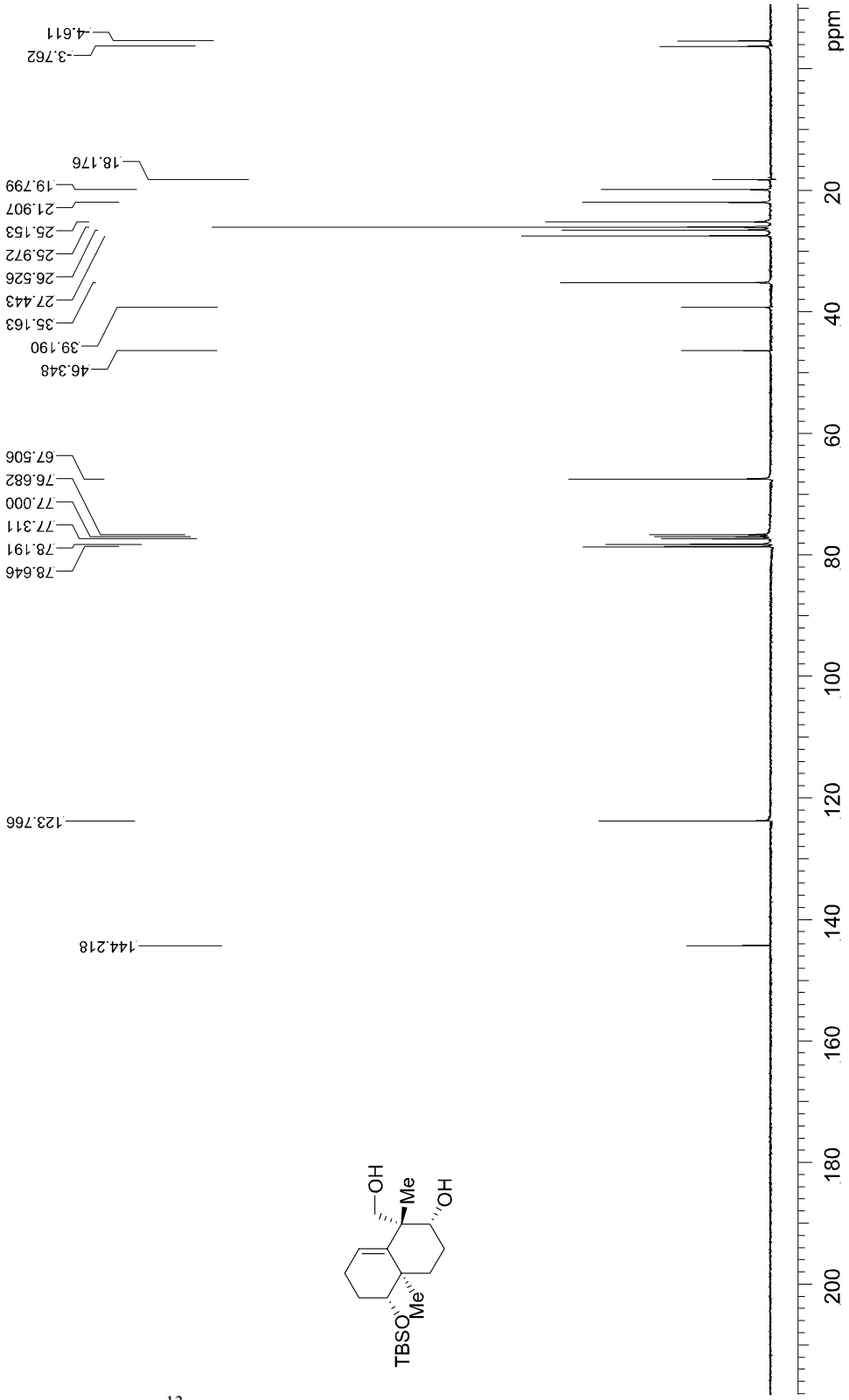
Spectrum 2.5: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **9**



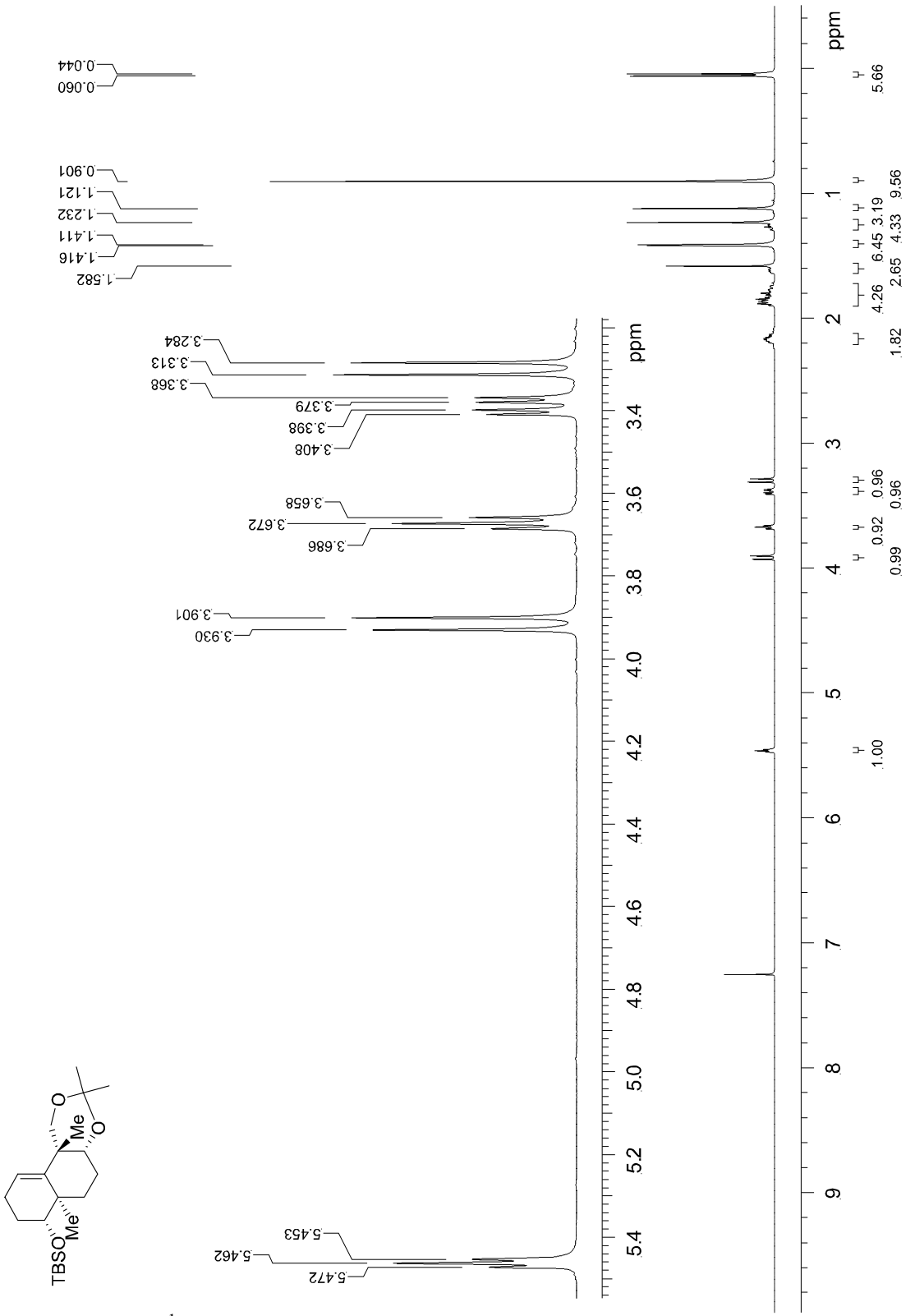
Spectrum 2.6: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **9**



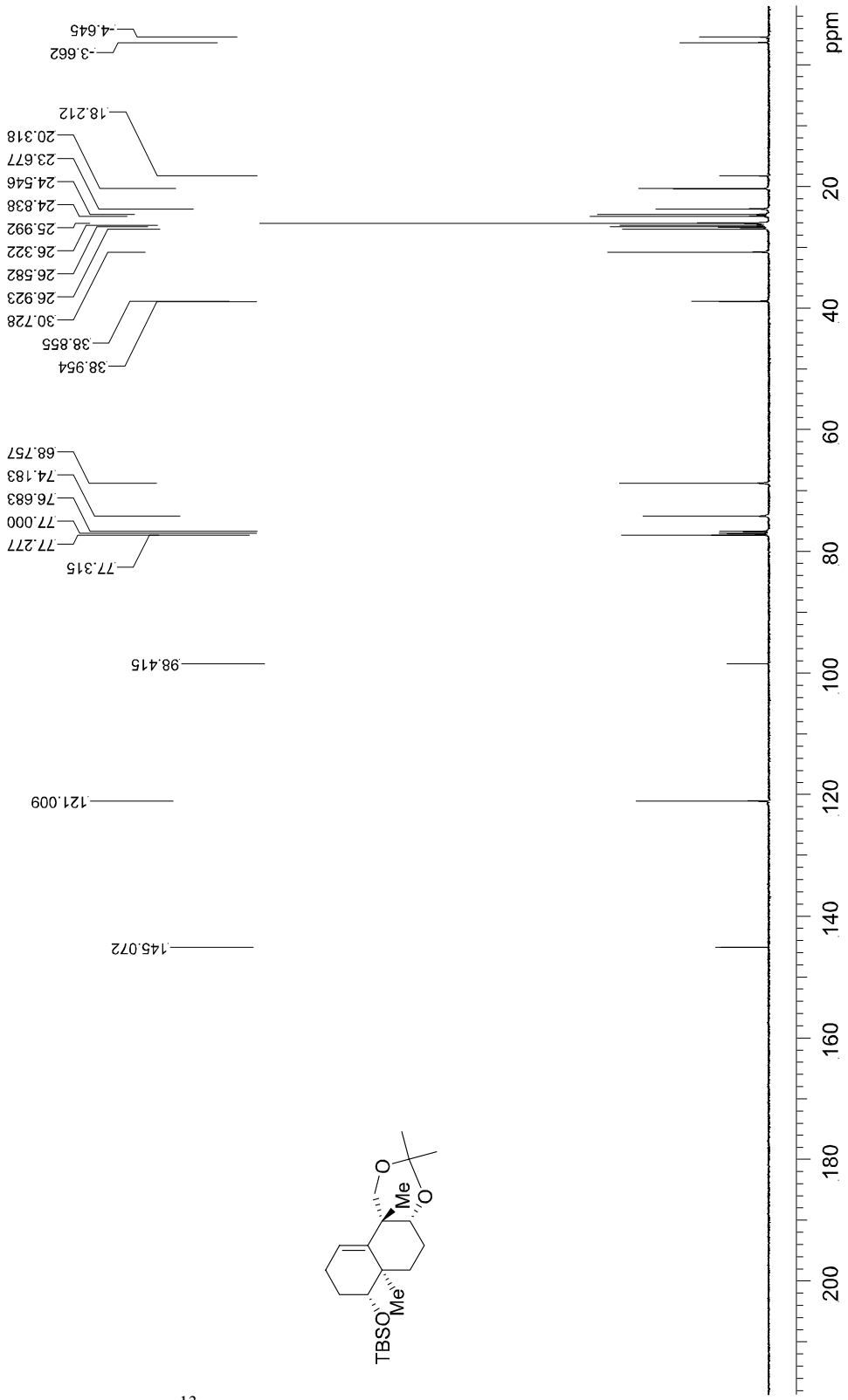
Spectrum 2.7: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **10**



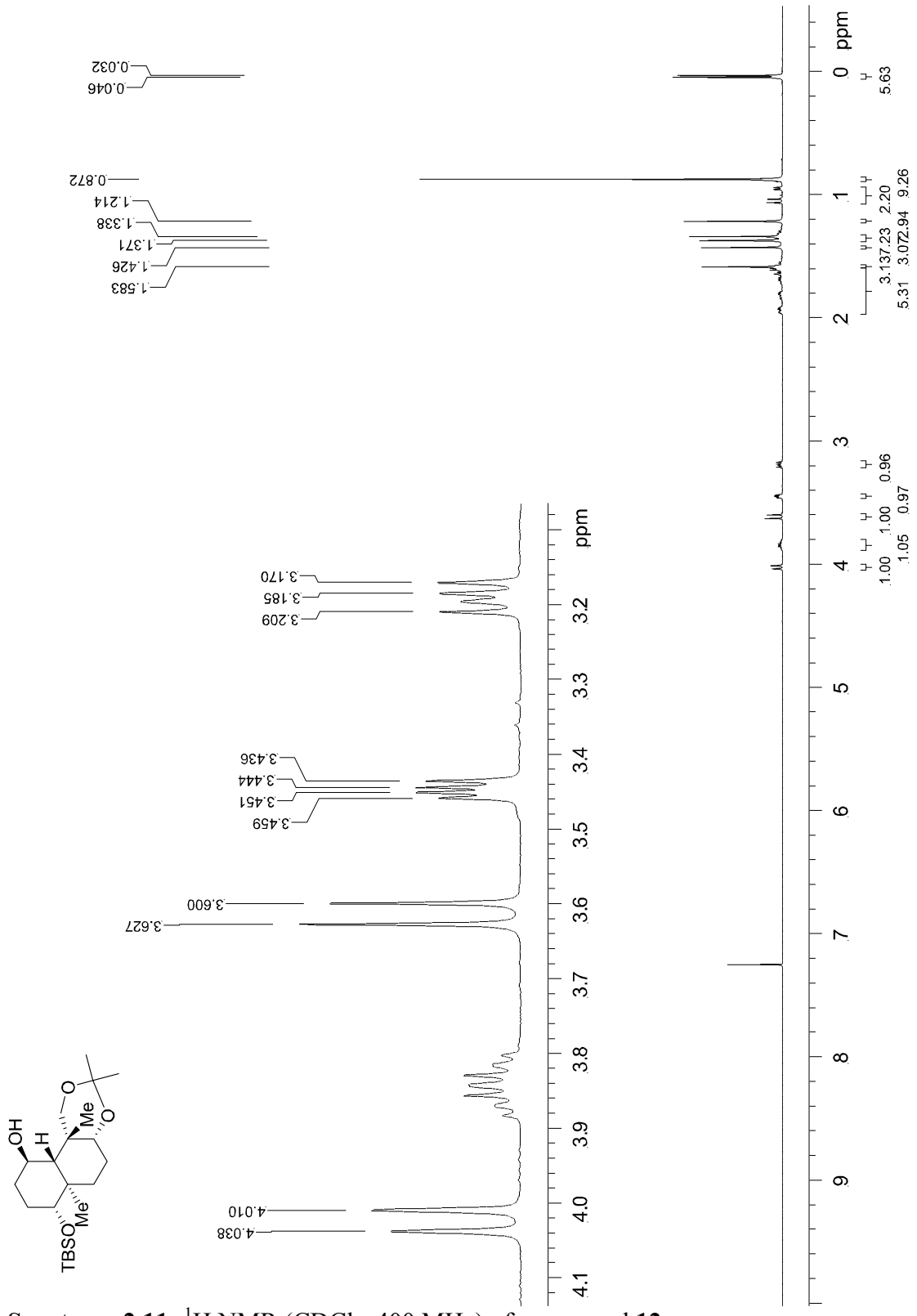
Spectrum 2.8: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **10**



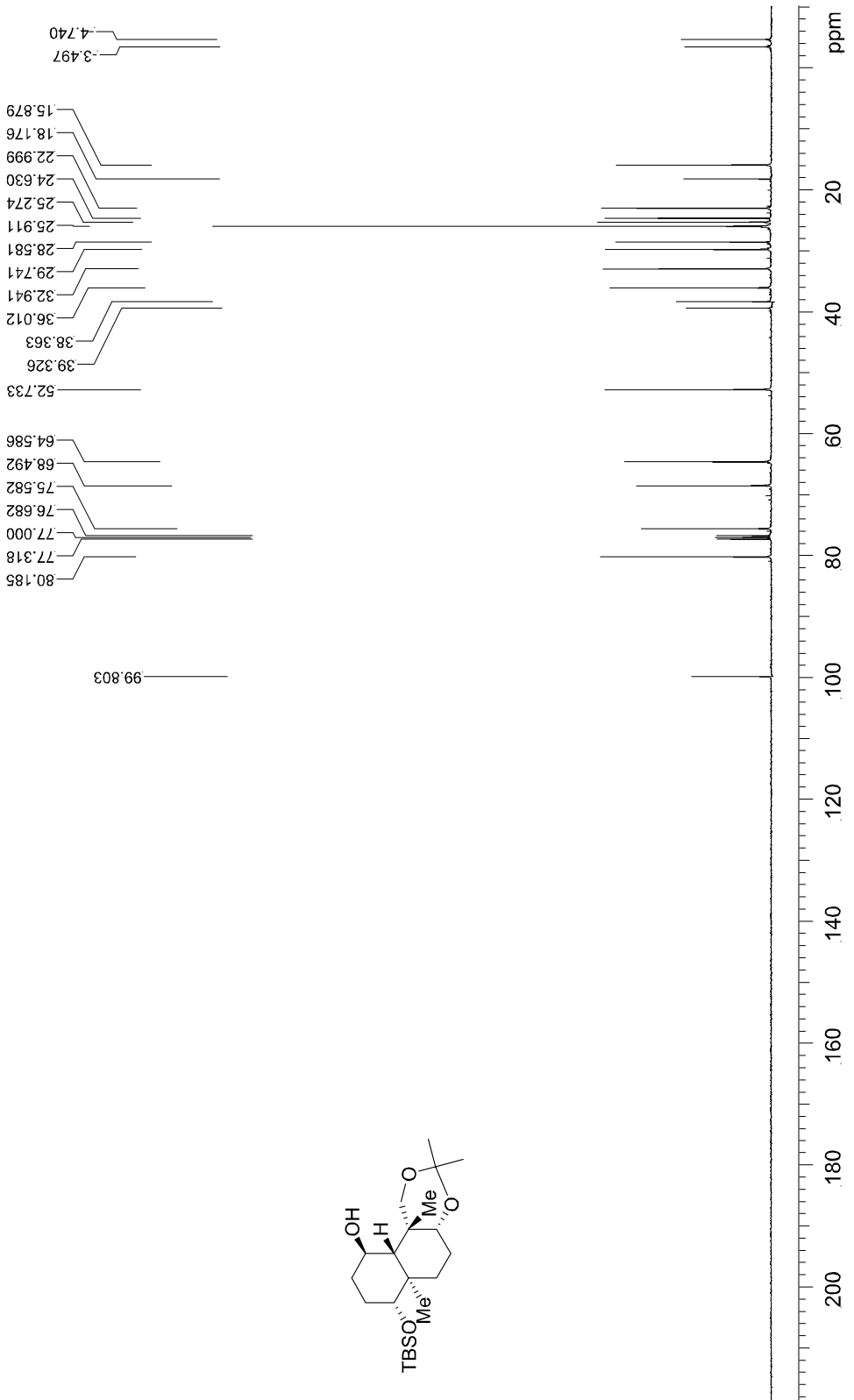
Spectrum 2.9: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **11**



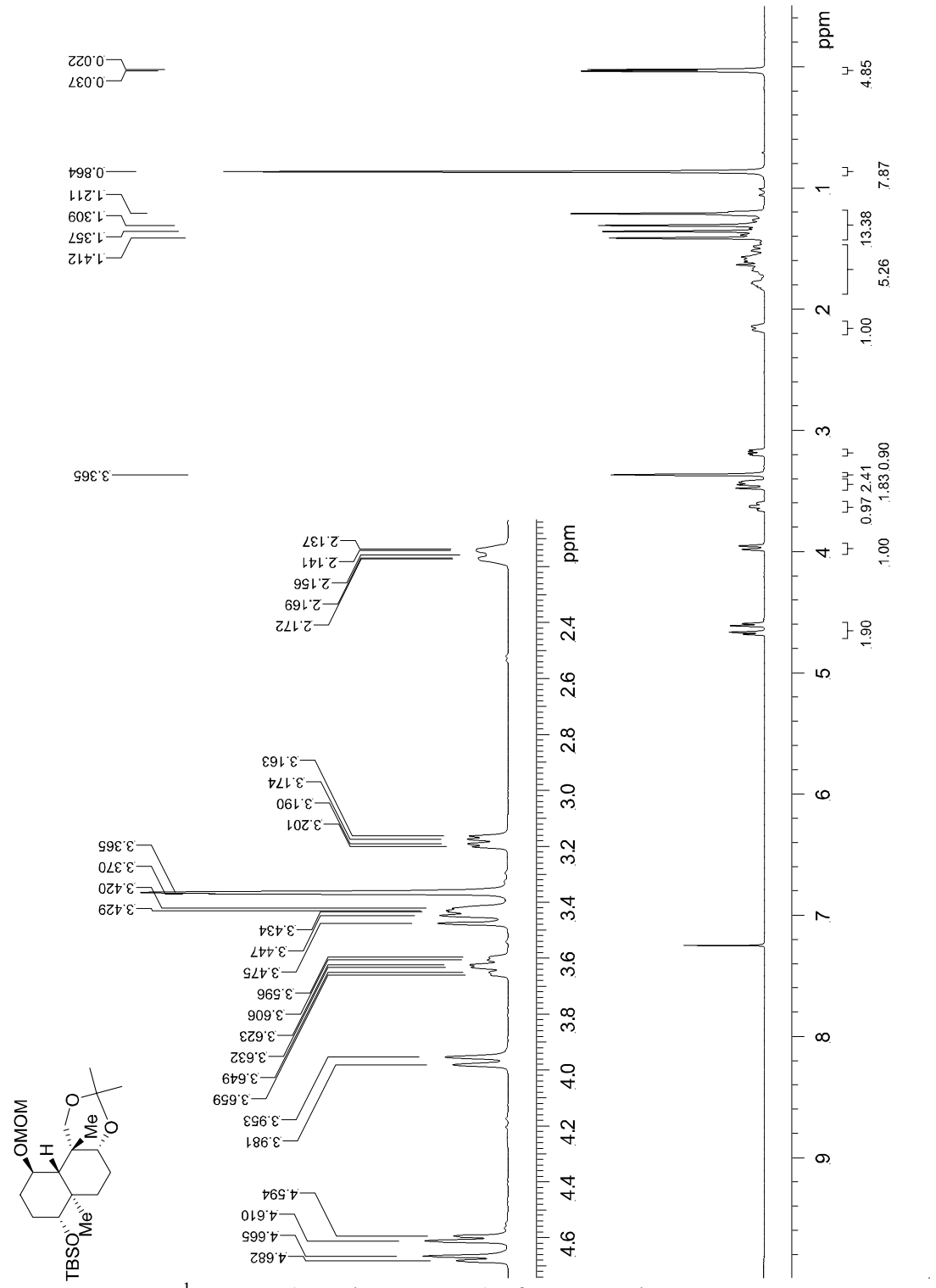
Spectrum 2.10: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **11**



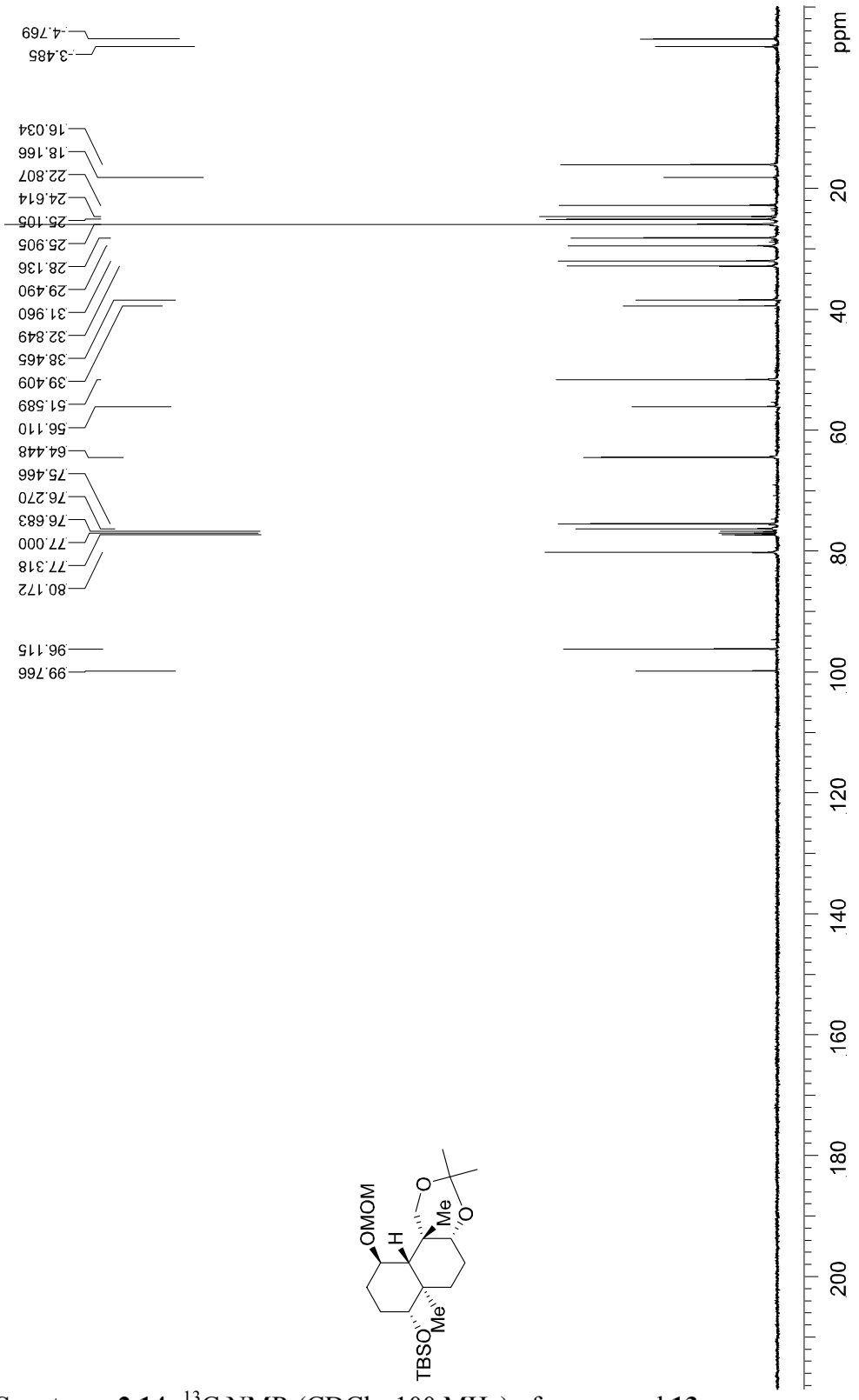
Spectrum 2.11: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **12**



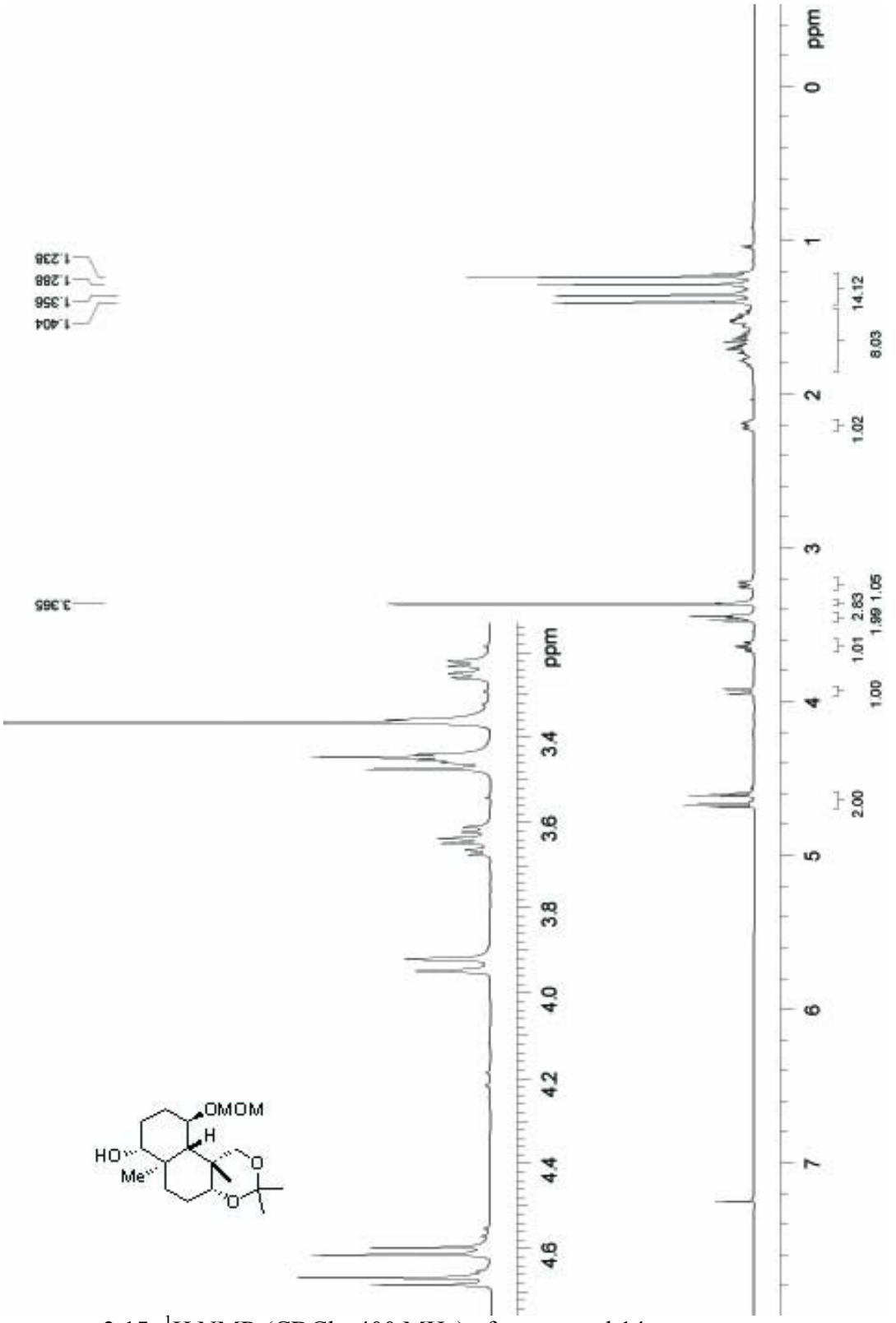
Spectrum 2.12: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **12**



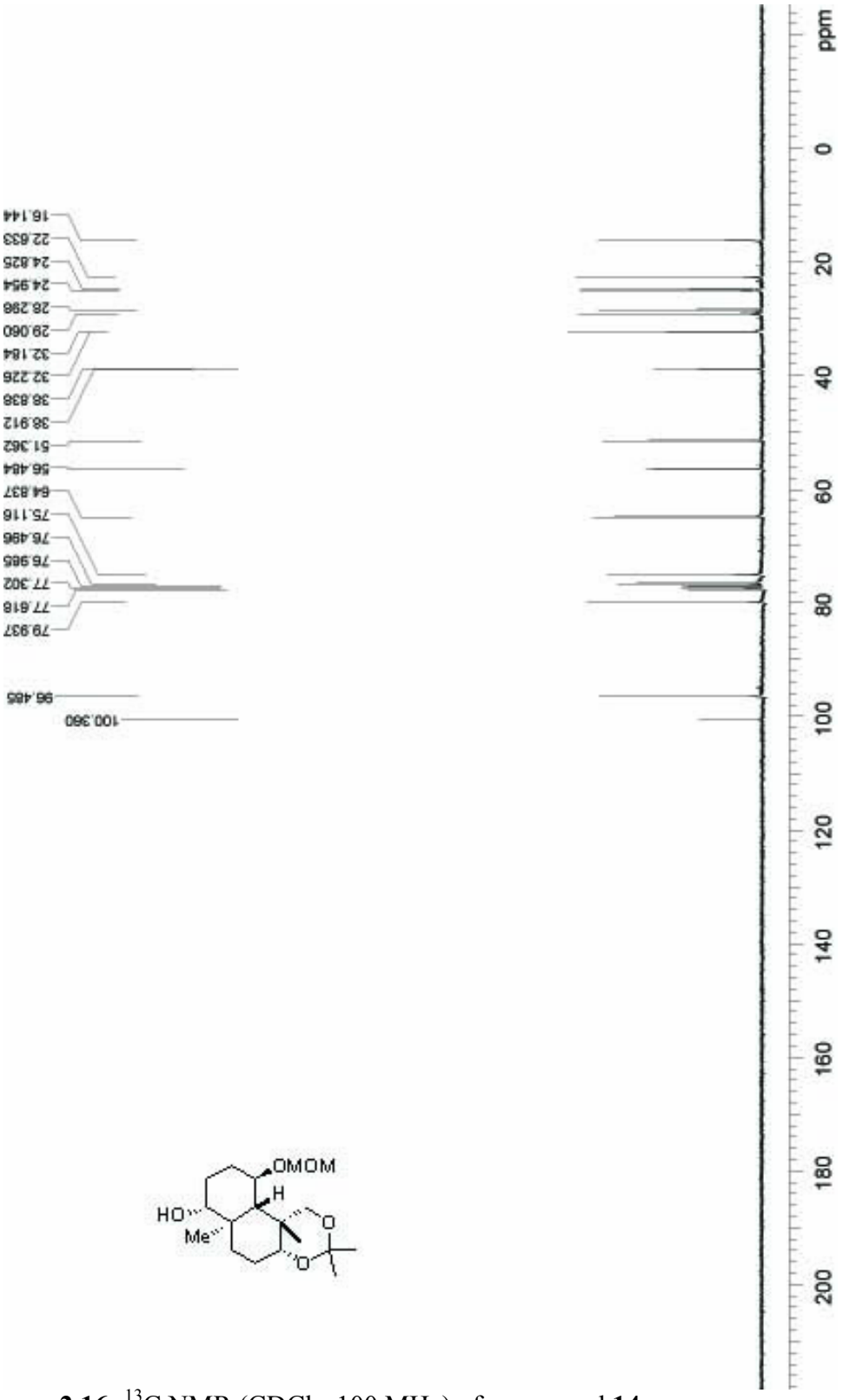
Spectrum 2.13: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **13**



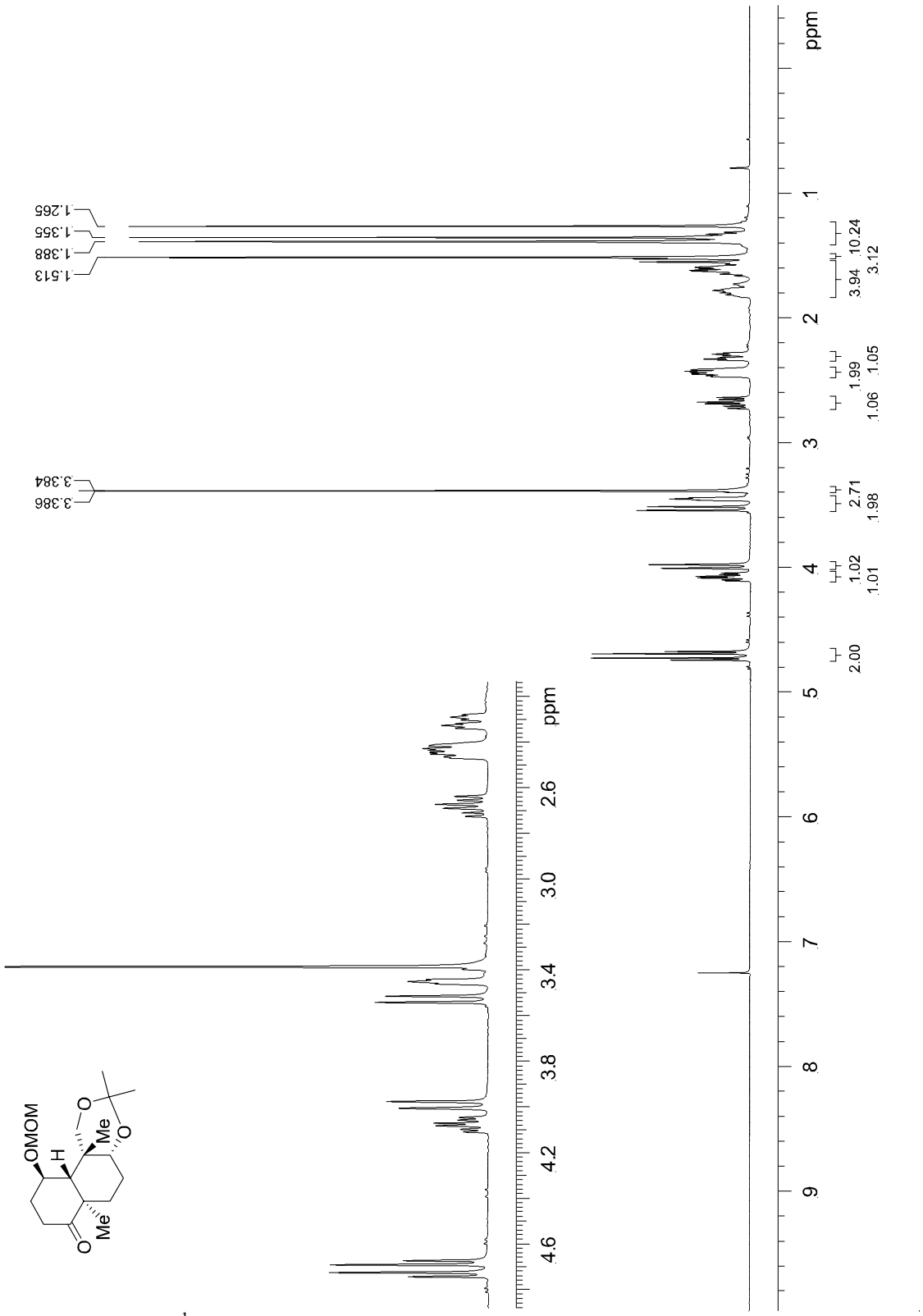
Spectrum 2.14: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **13**



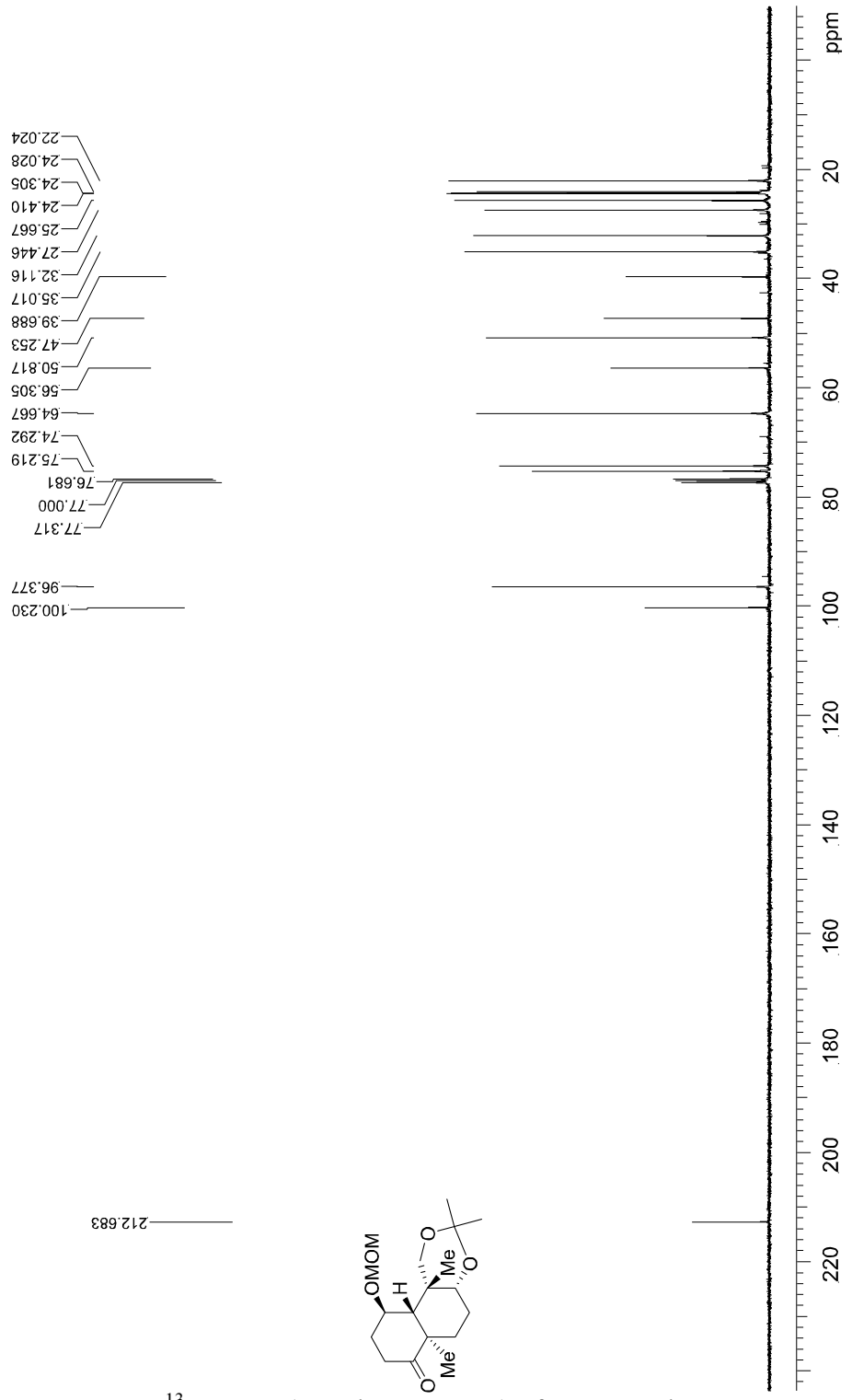
Spectrum 2.15: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **14**



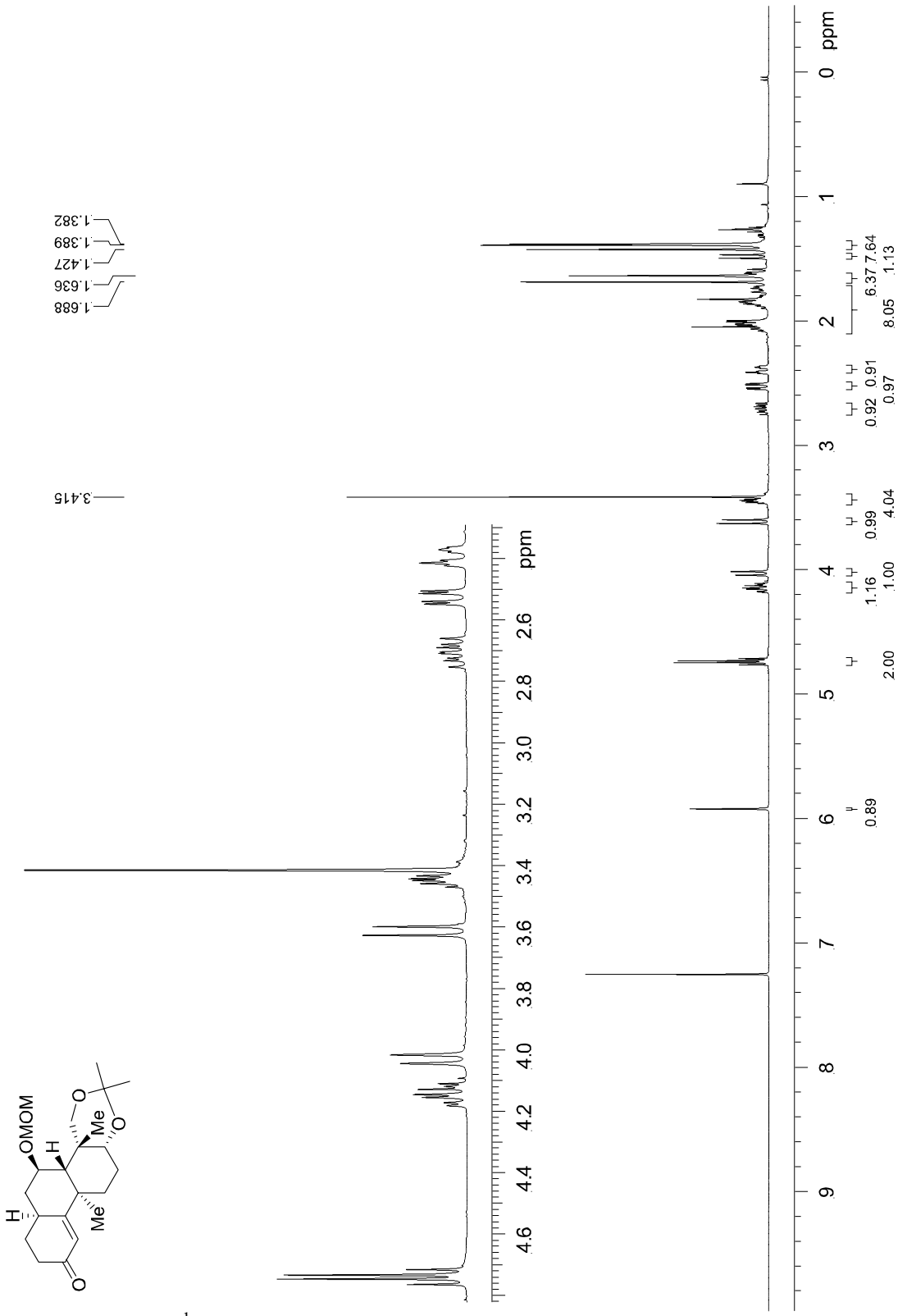
Spectrum 2.16: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **14**



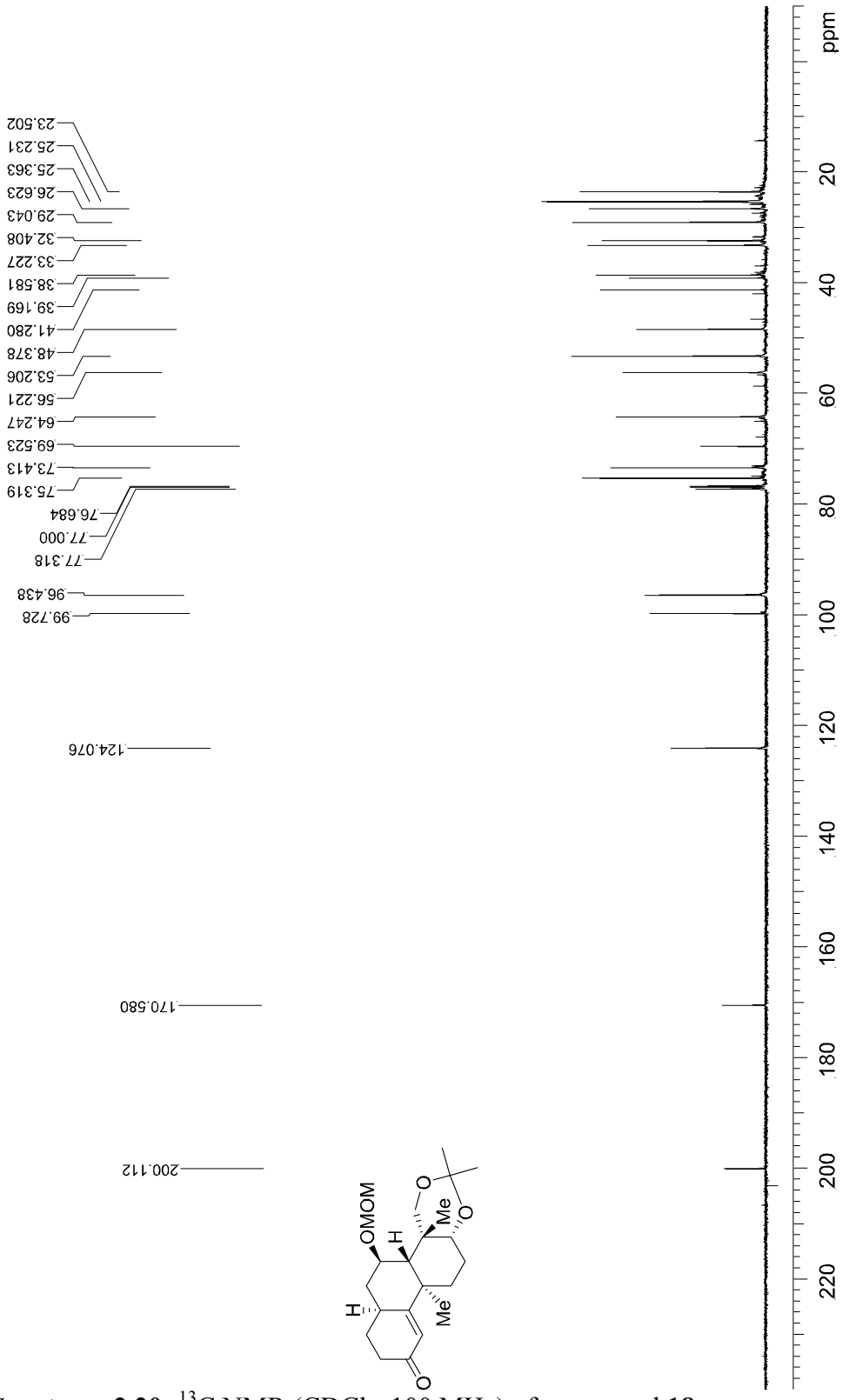
Spectrum 2.17: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **15**



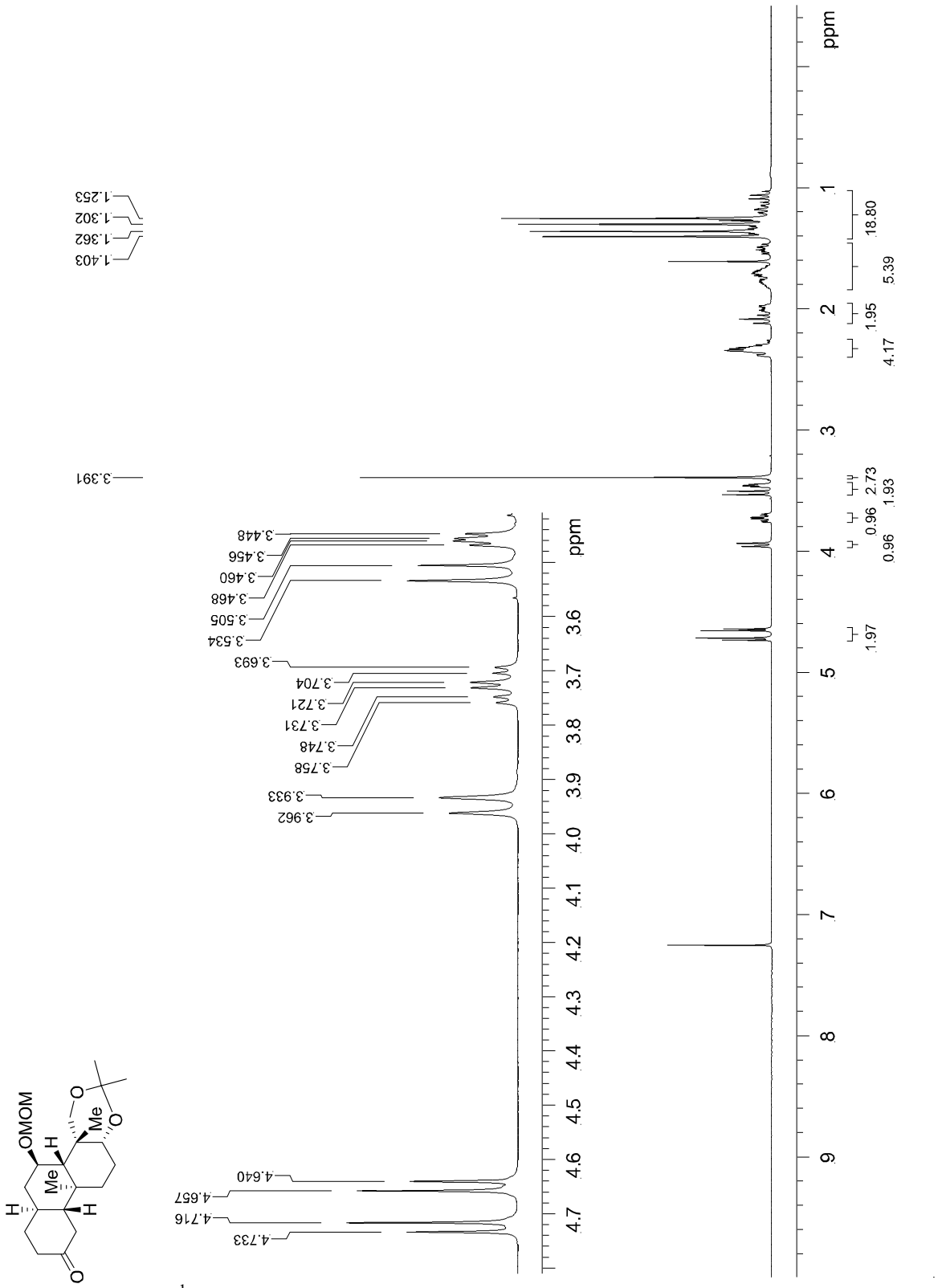
Spectrum 2.18: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **15**



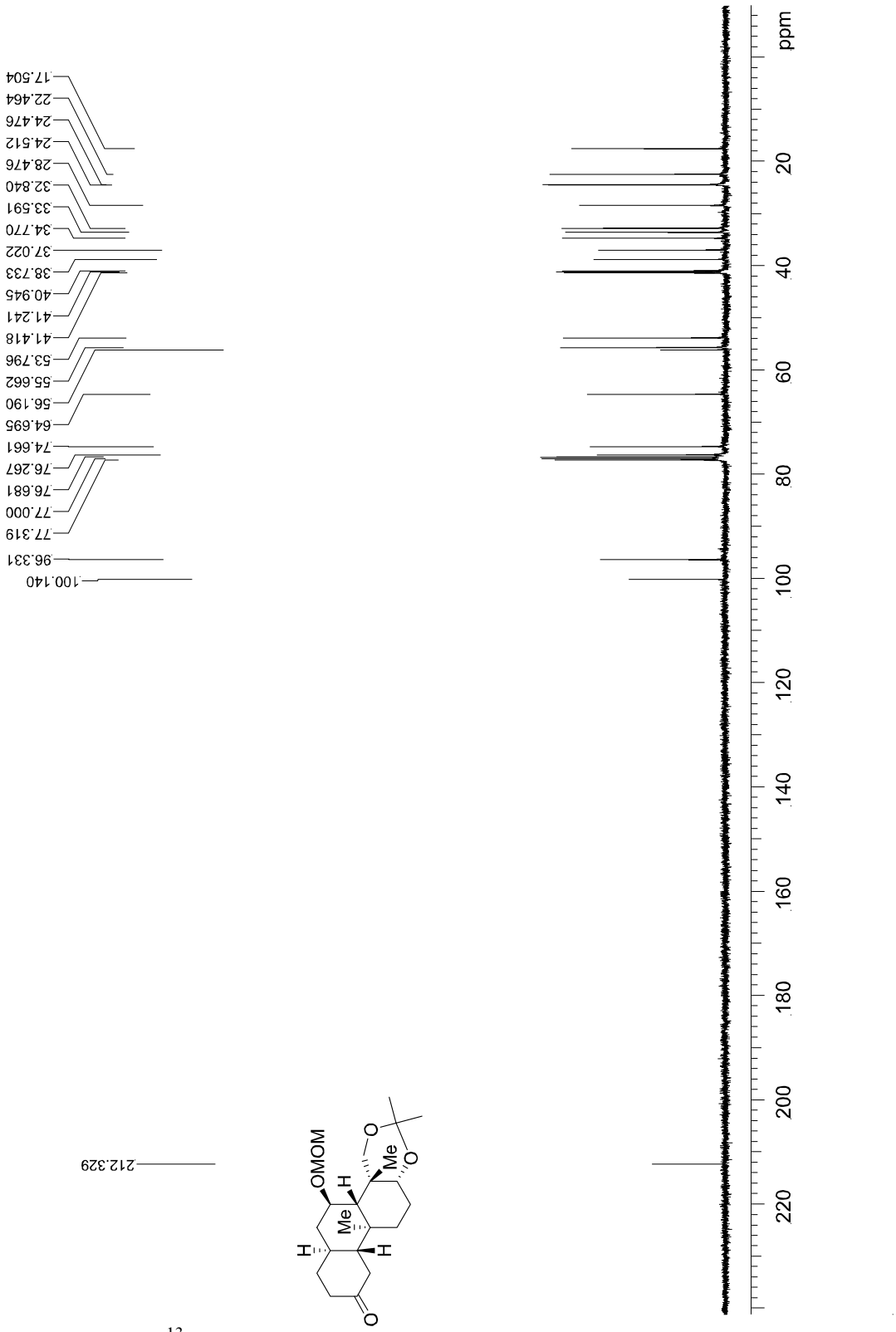
Spectrum 2.19: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **18**



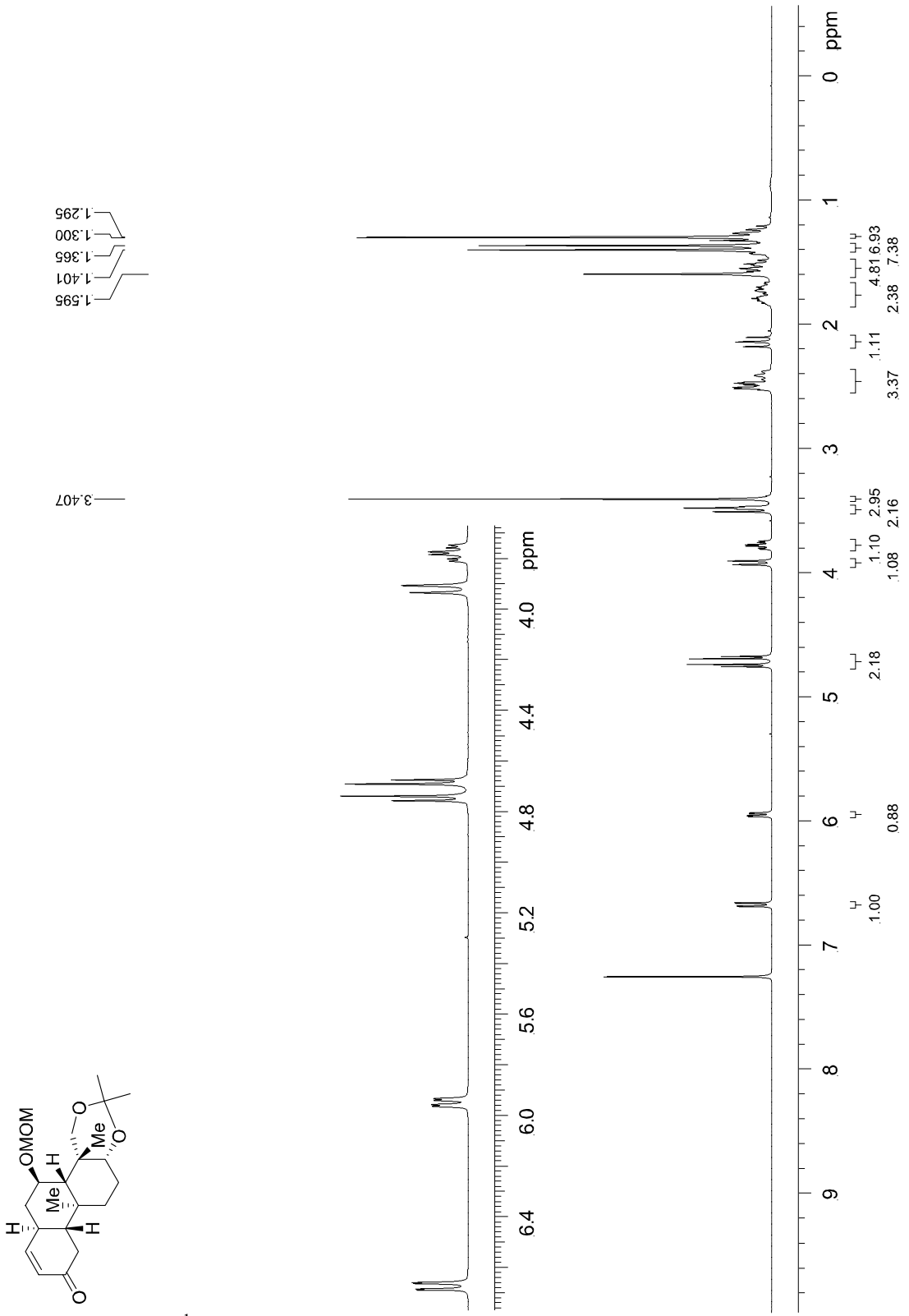
Spectrum 2.20: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **18**



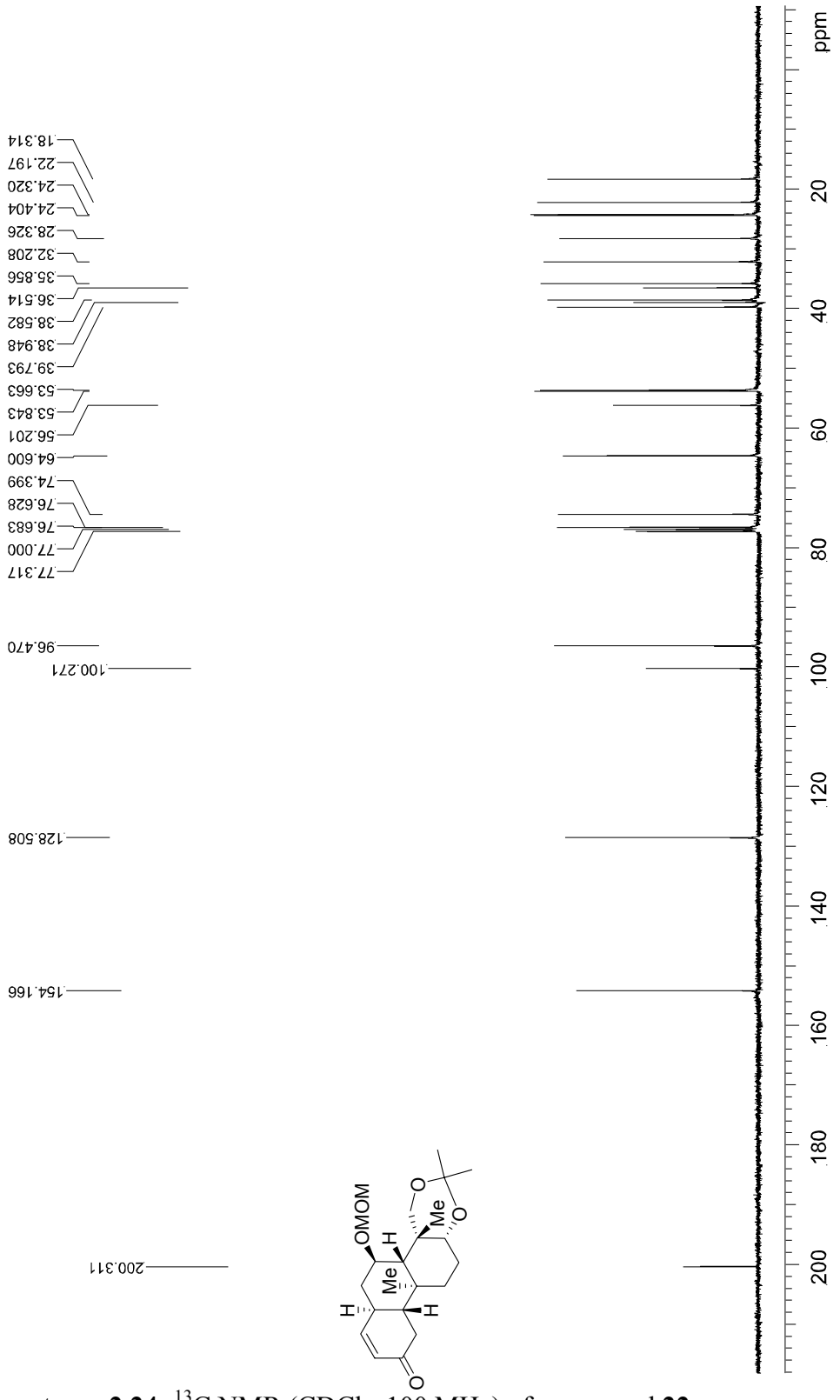
Spectrum 2.21: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **20**



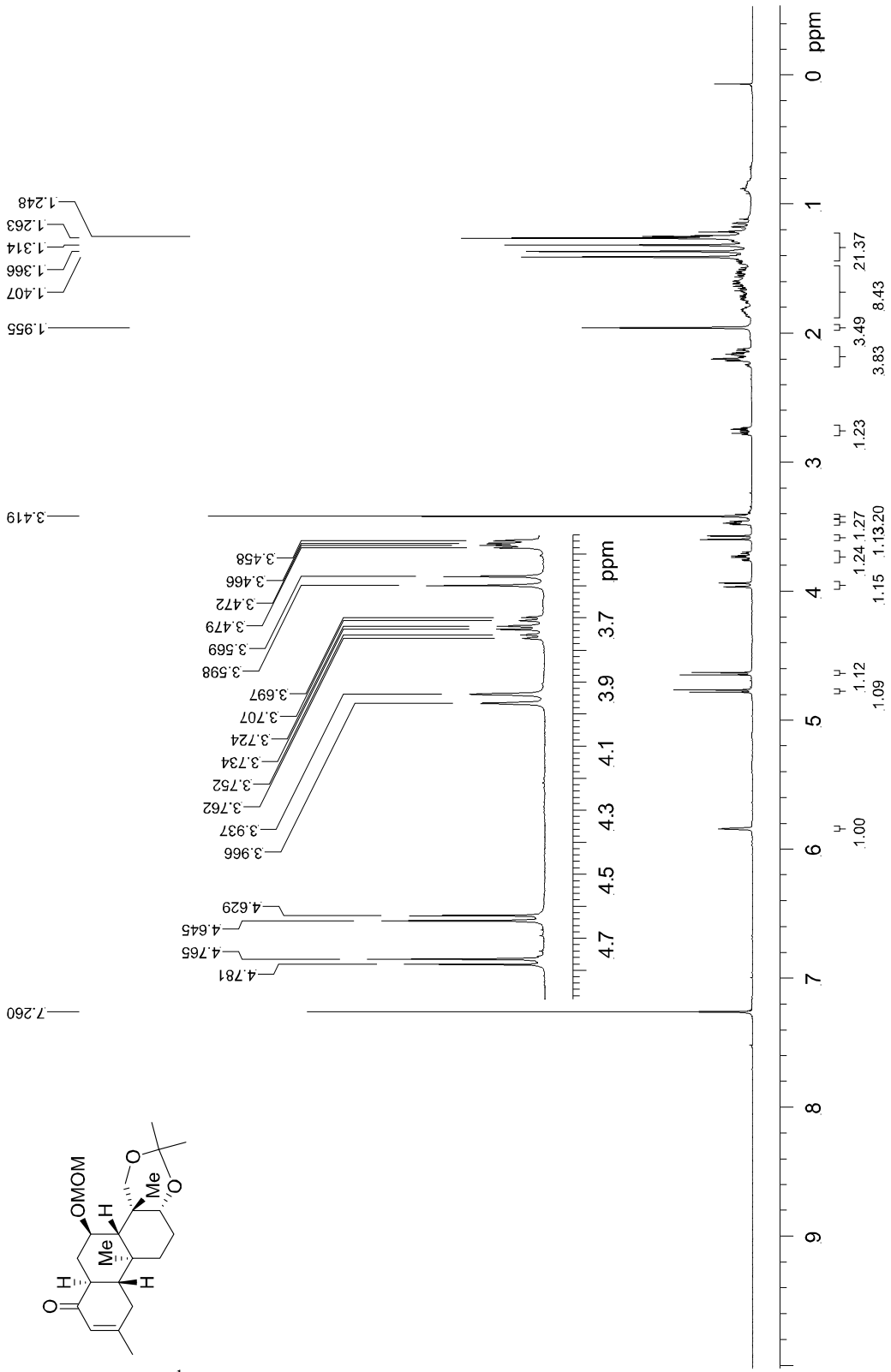
Spectrum 2.22: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **20**



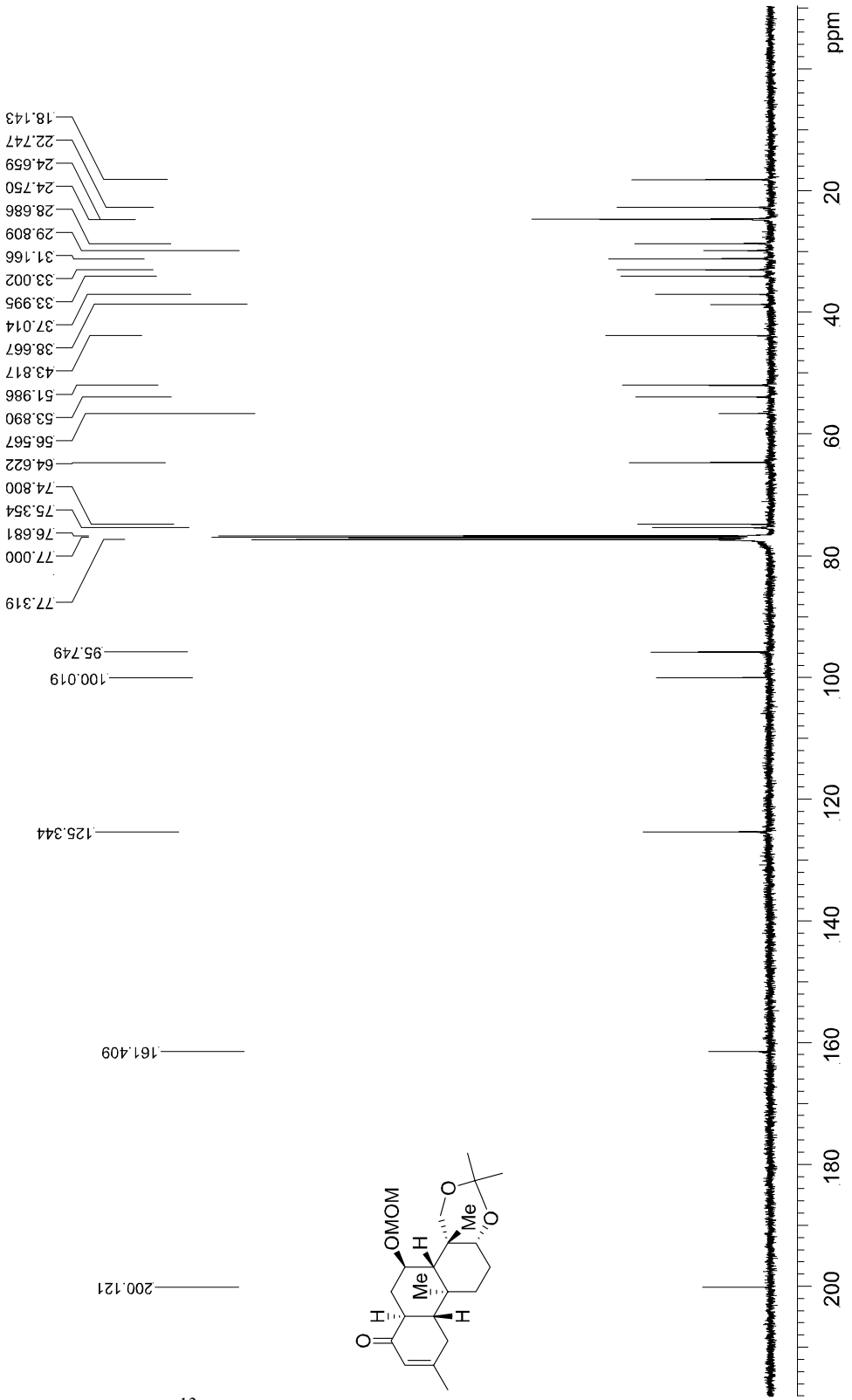
Spectrum 2.23: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **22**



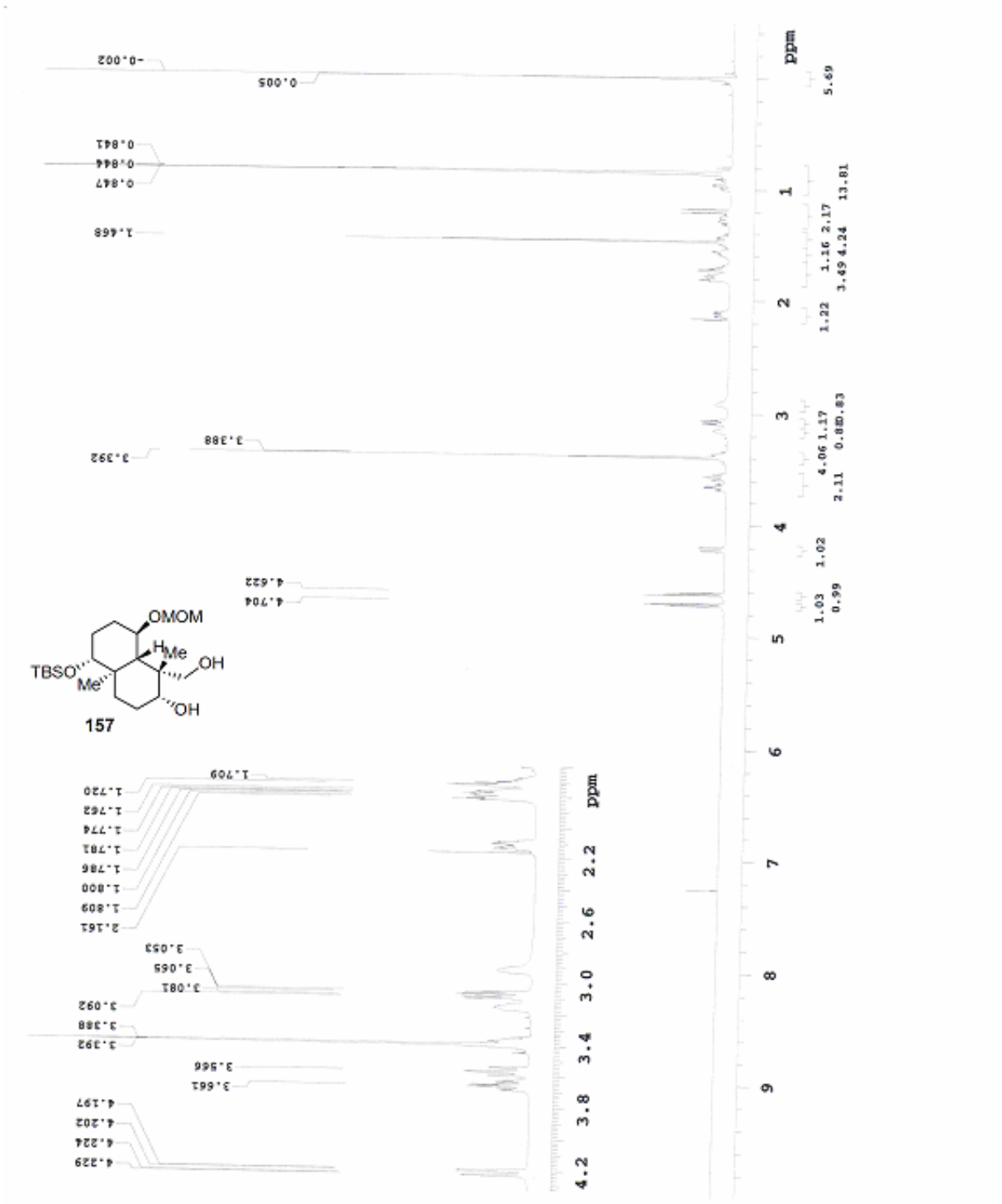
Spectrum 2.24: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **22**



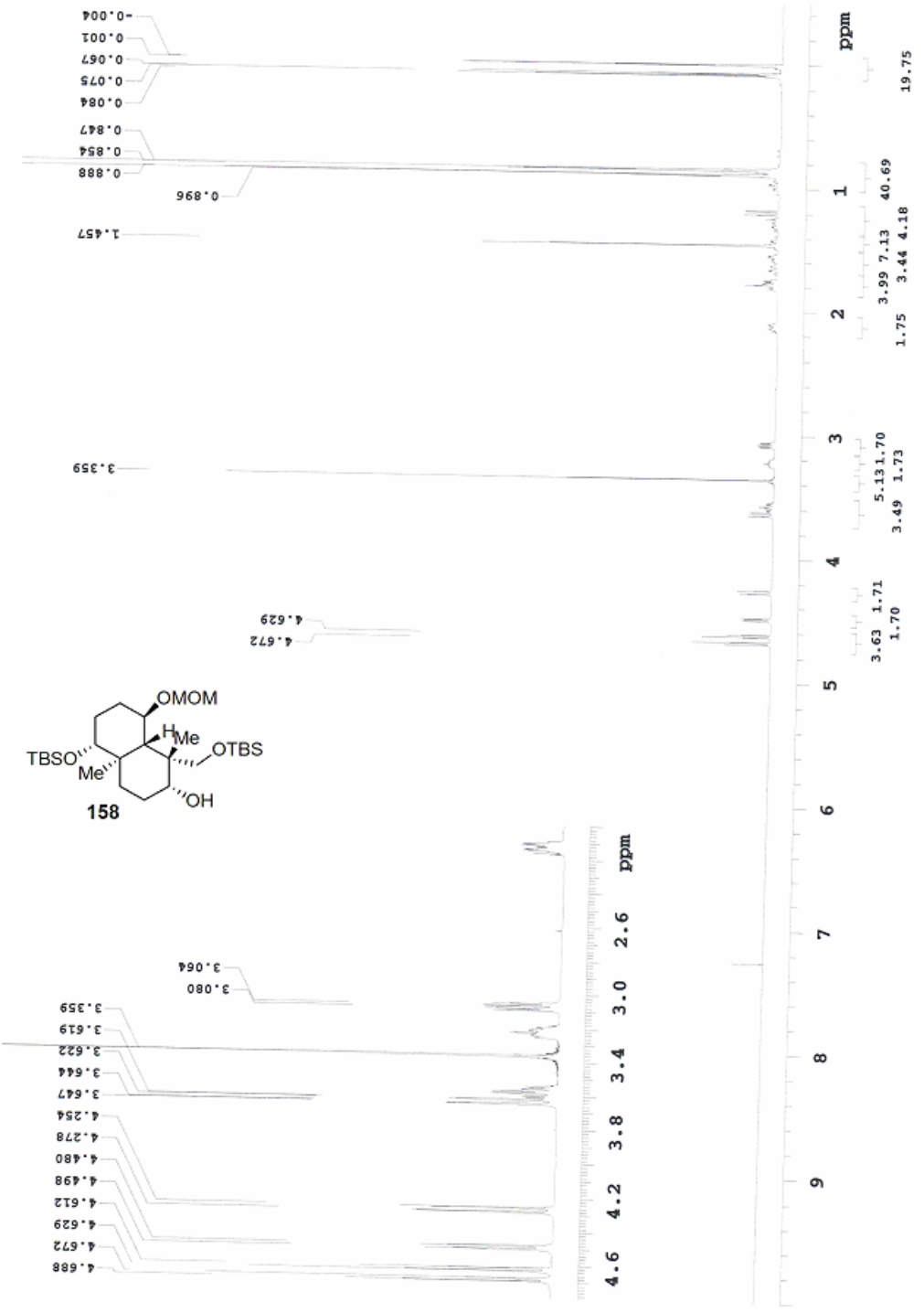
Spectrum 2.25: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **24**



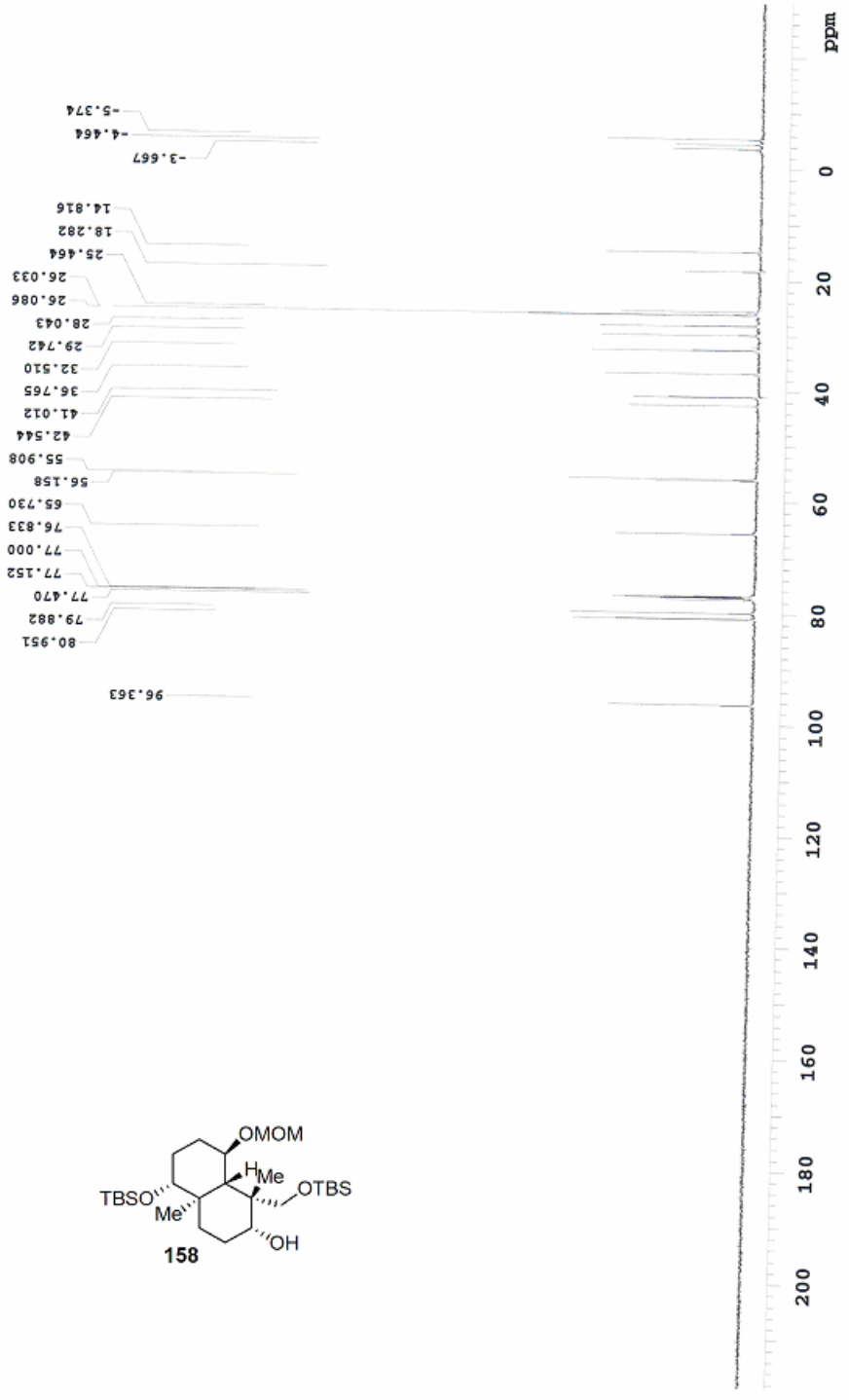
Spectrum 2.26: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **24**



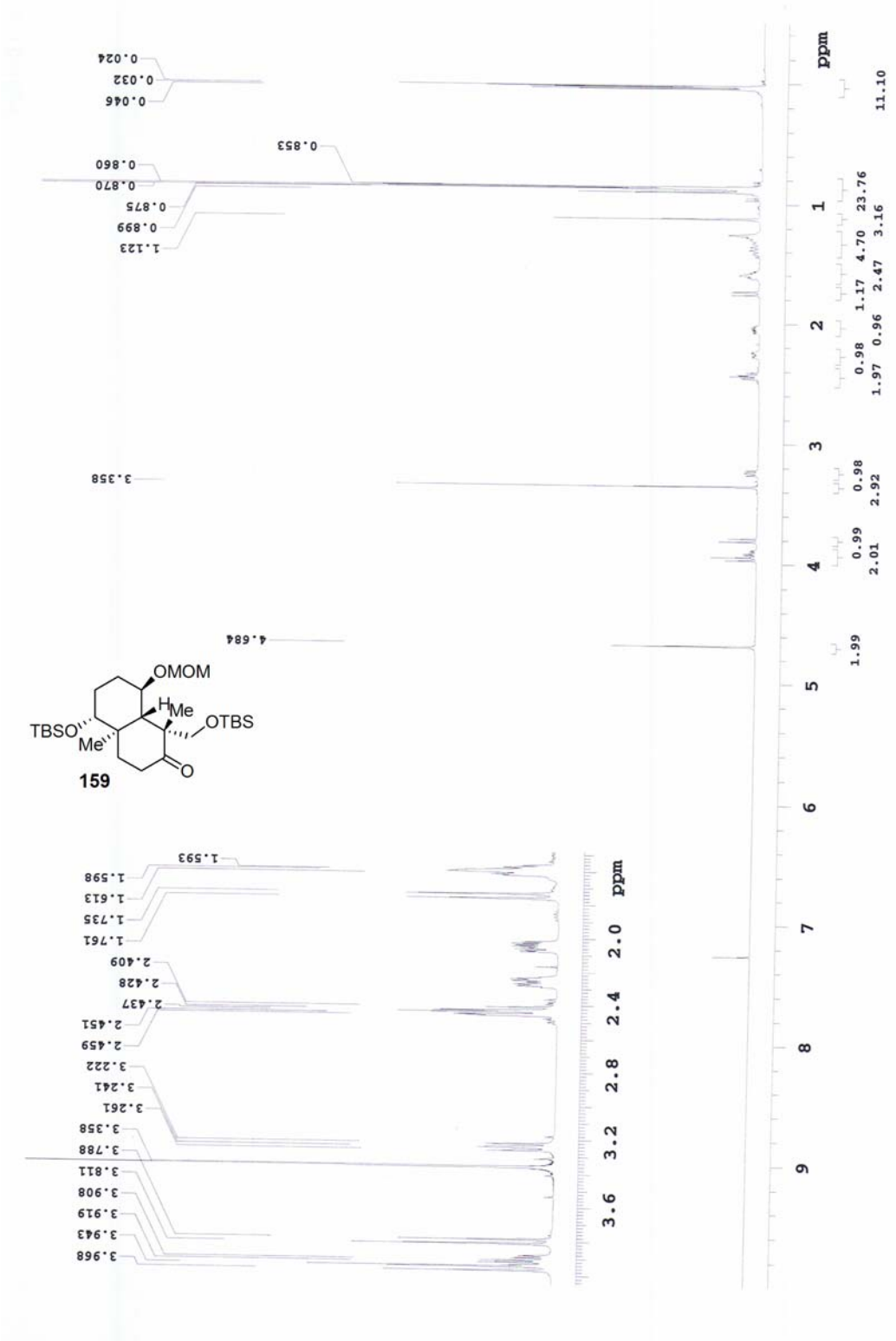
Spectrum 2.27: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **27**



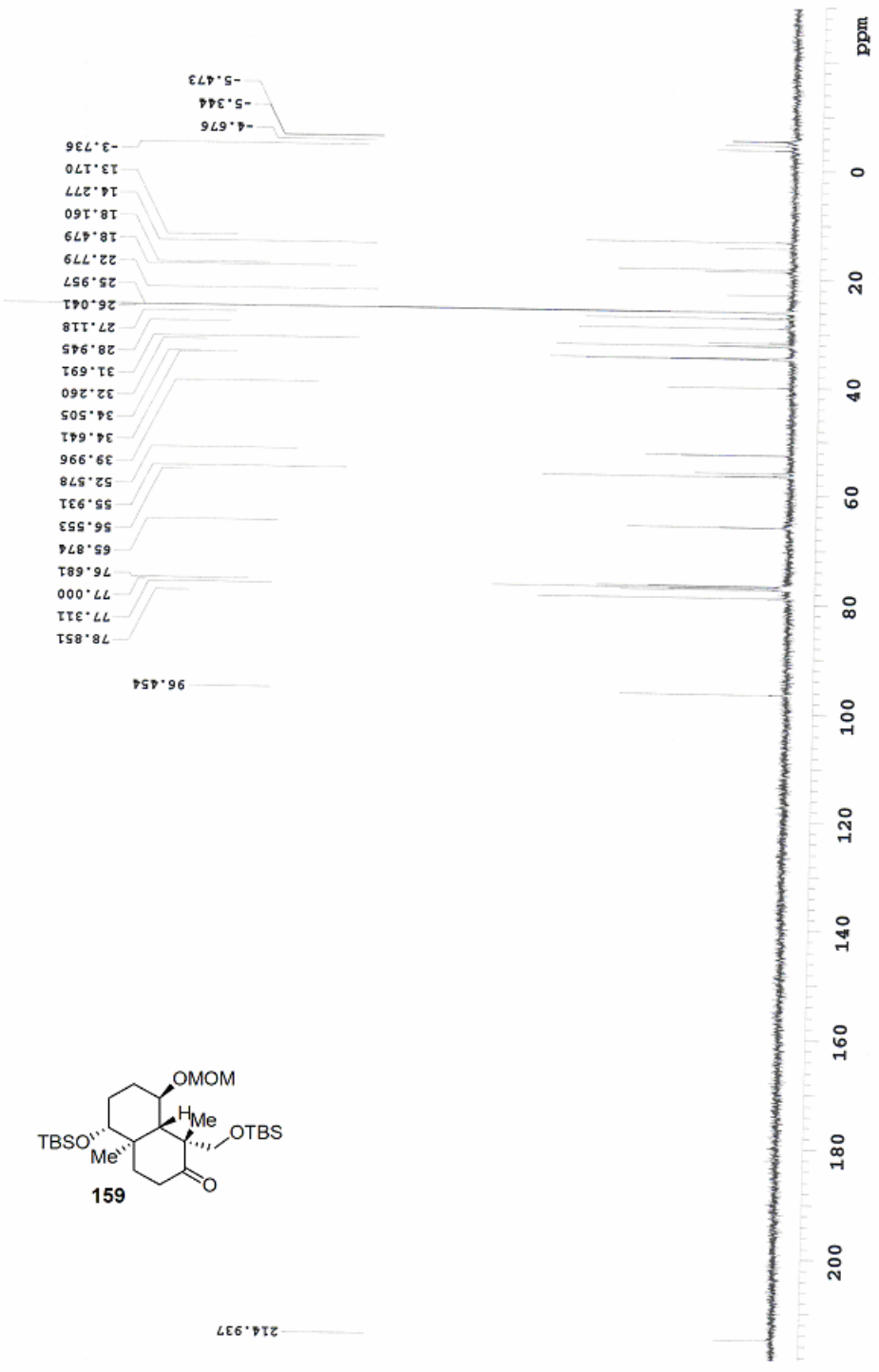
Spectrum 2.28: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **28**



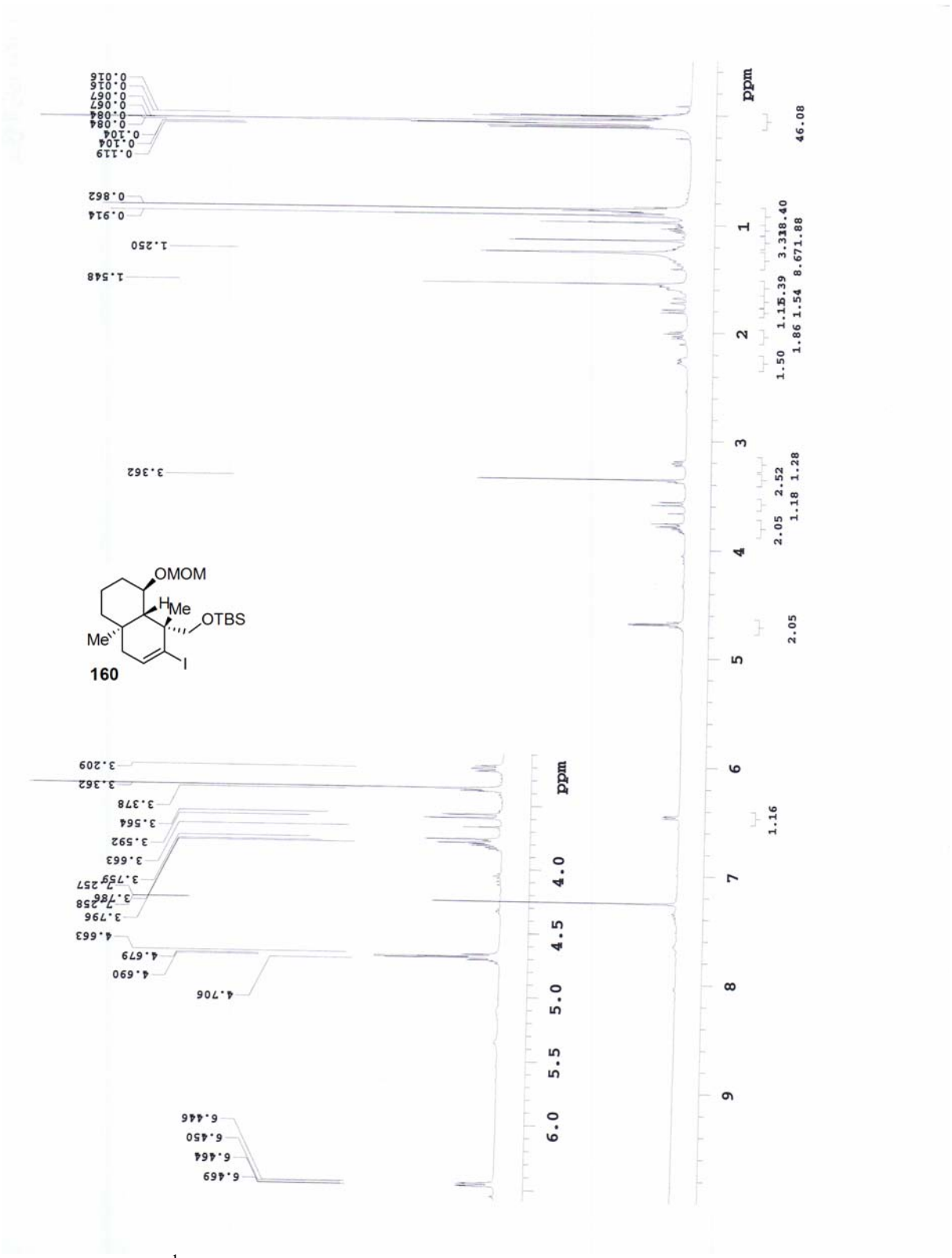
Spectrum 2.29: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **28**



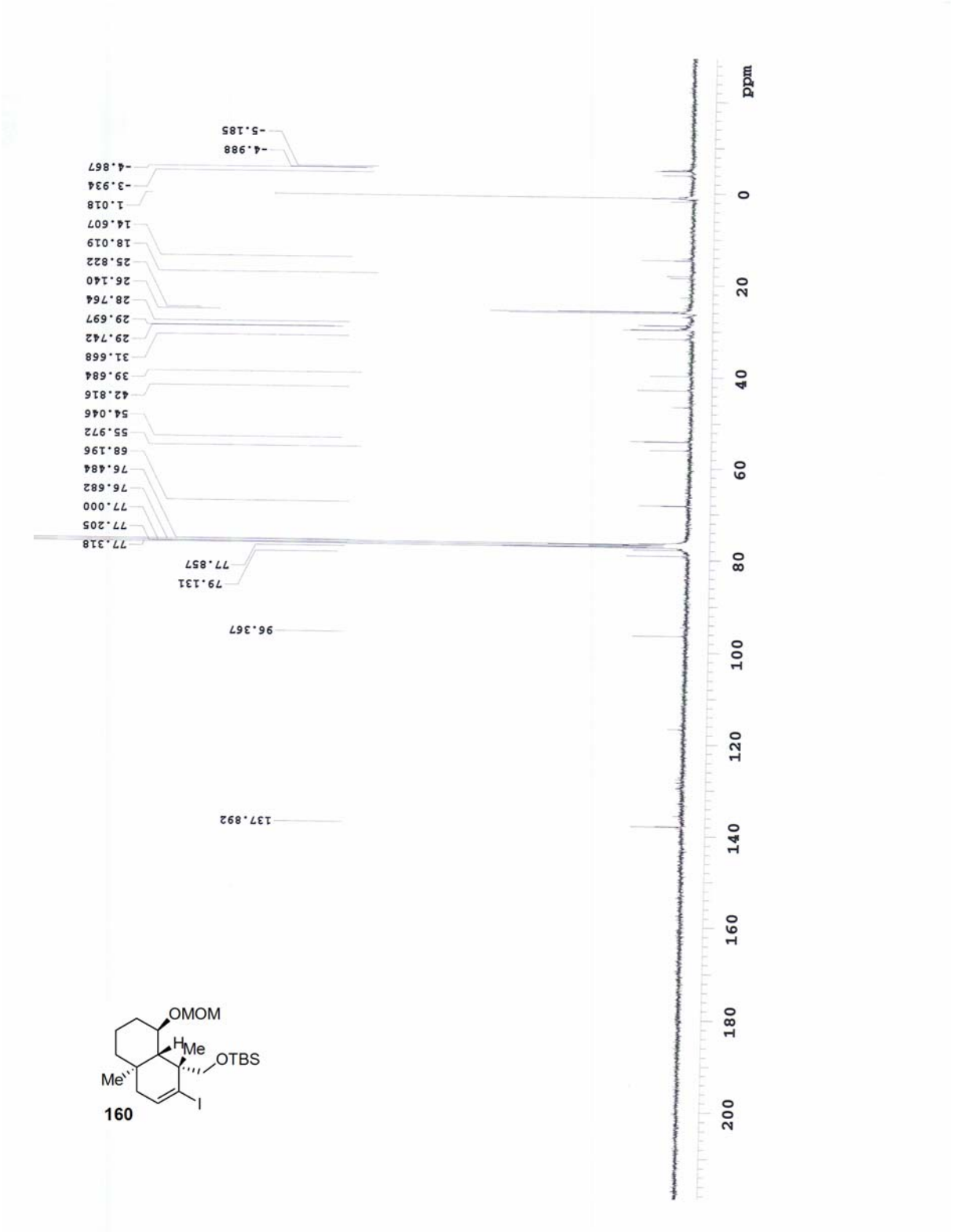
Spectrum 2.30: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **29**



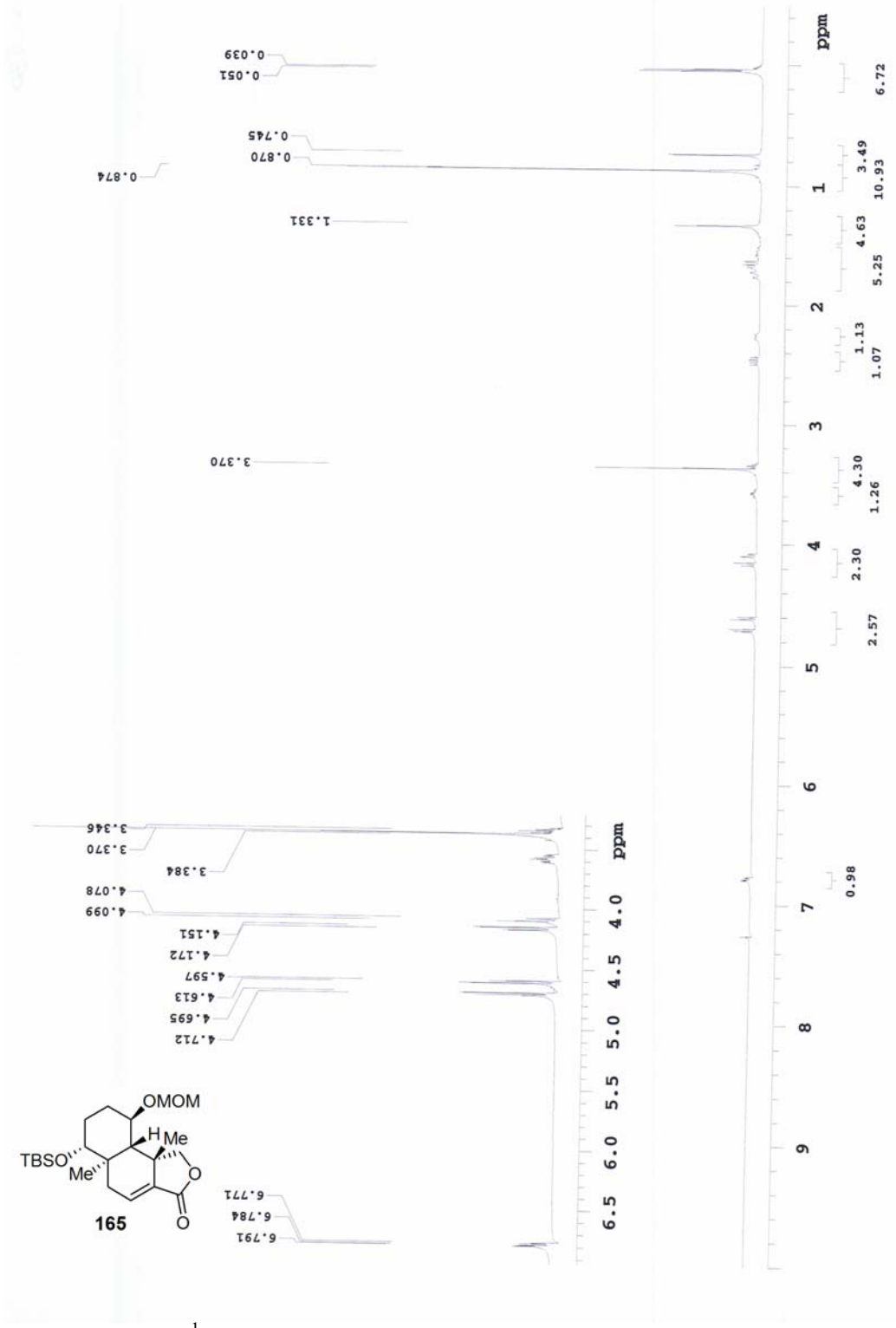
Spectrum 2.31: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **29**



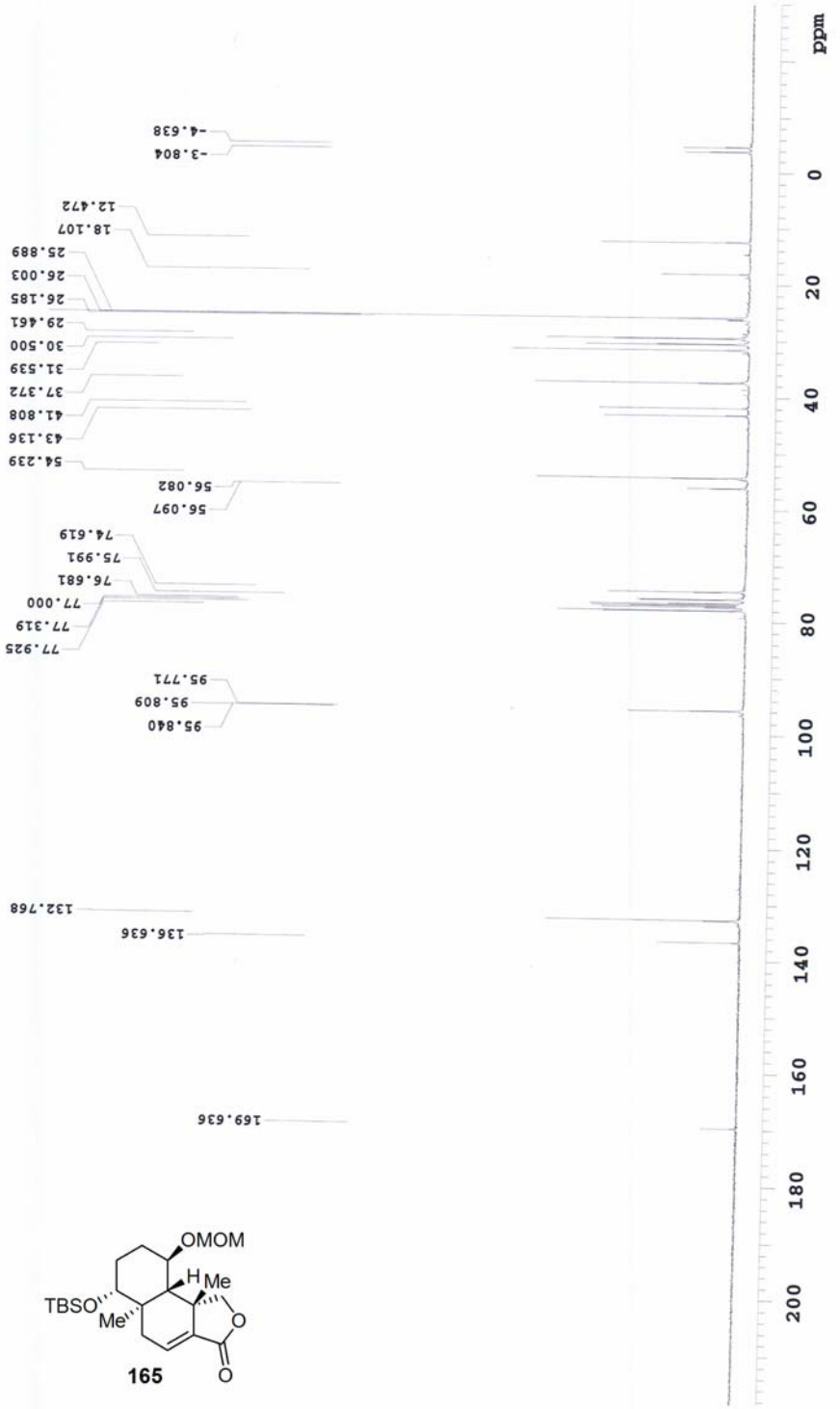
Spectrum 2.32: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **30**



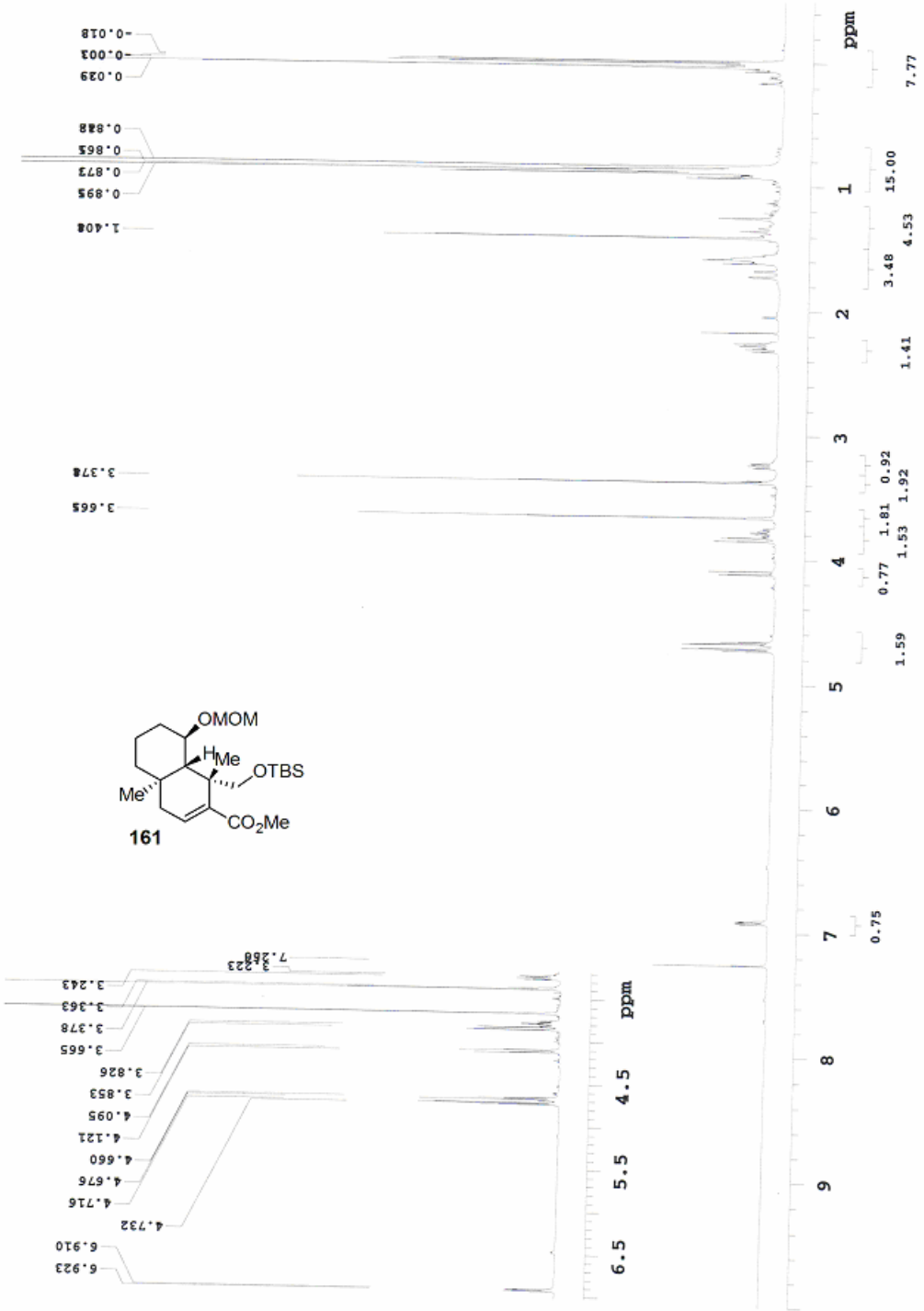
Spectrum 2.33: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **30**



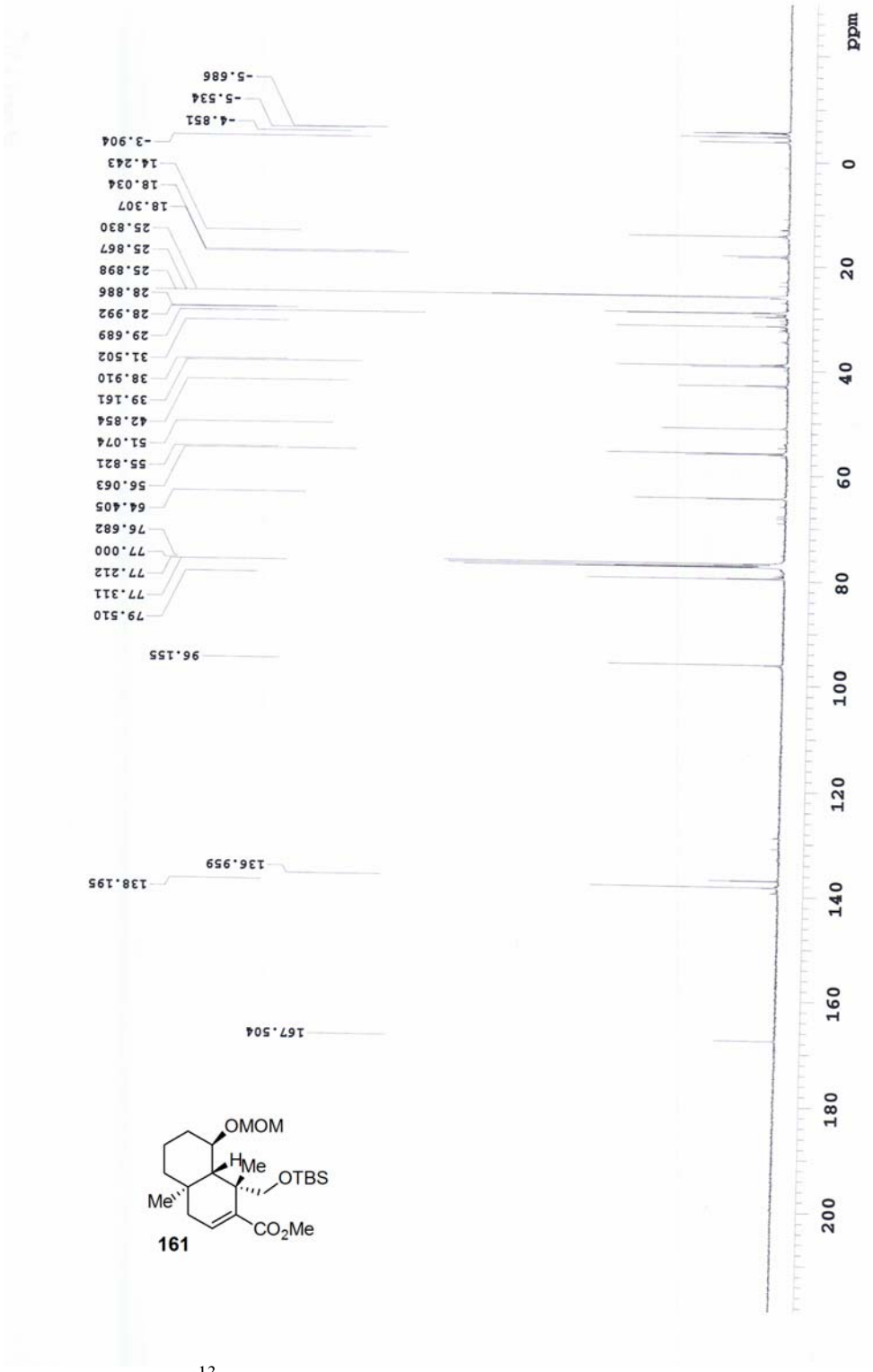
Spectrum 2.34: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **31**



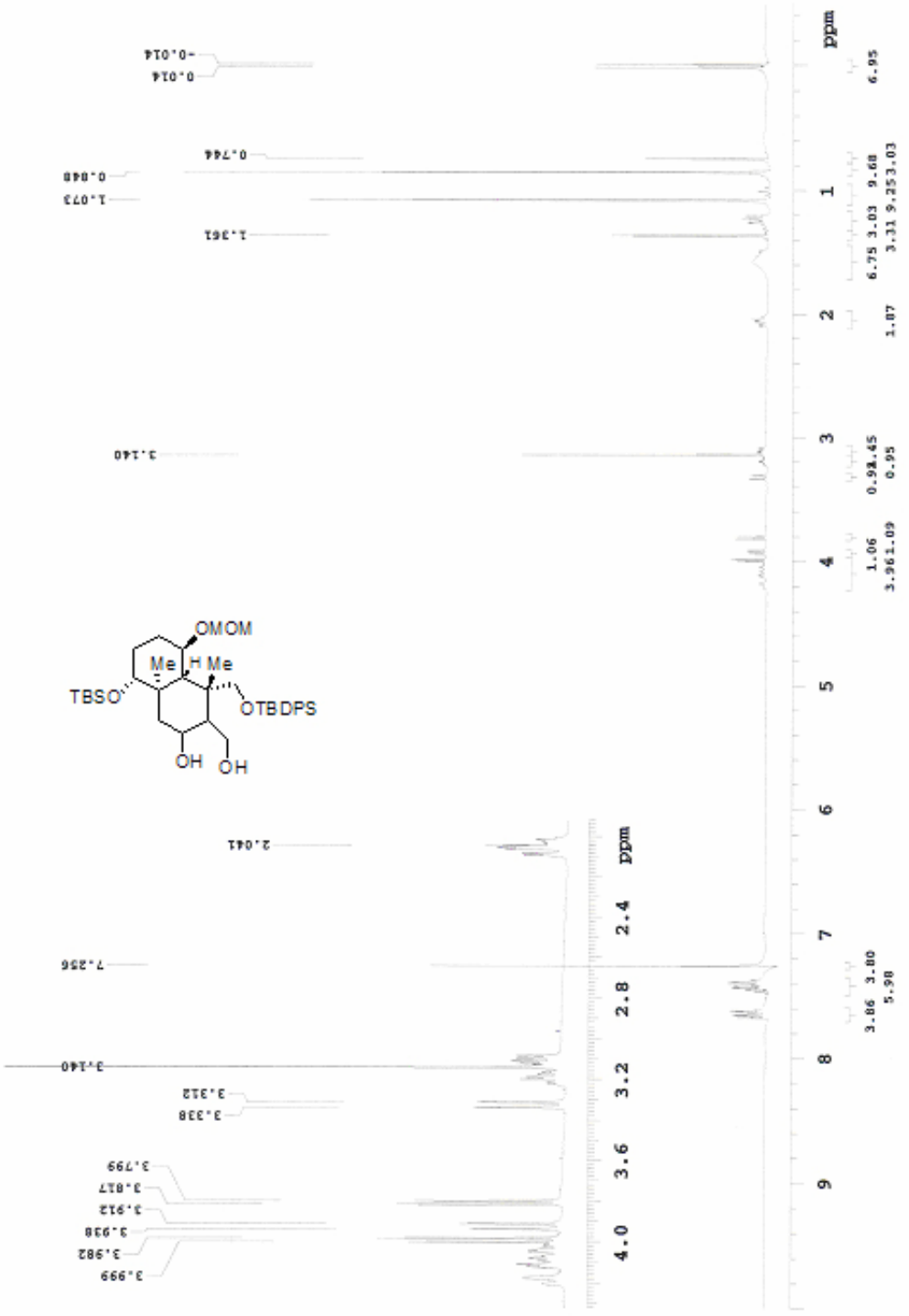
Spectrum 2.35: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **31**



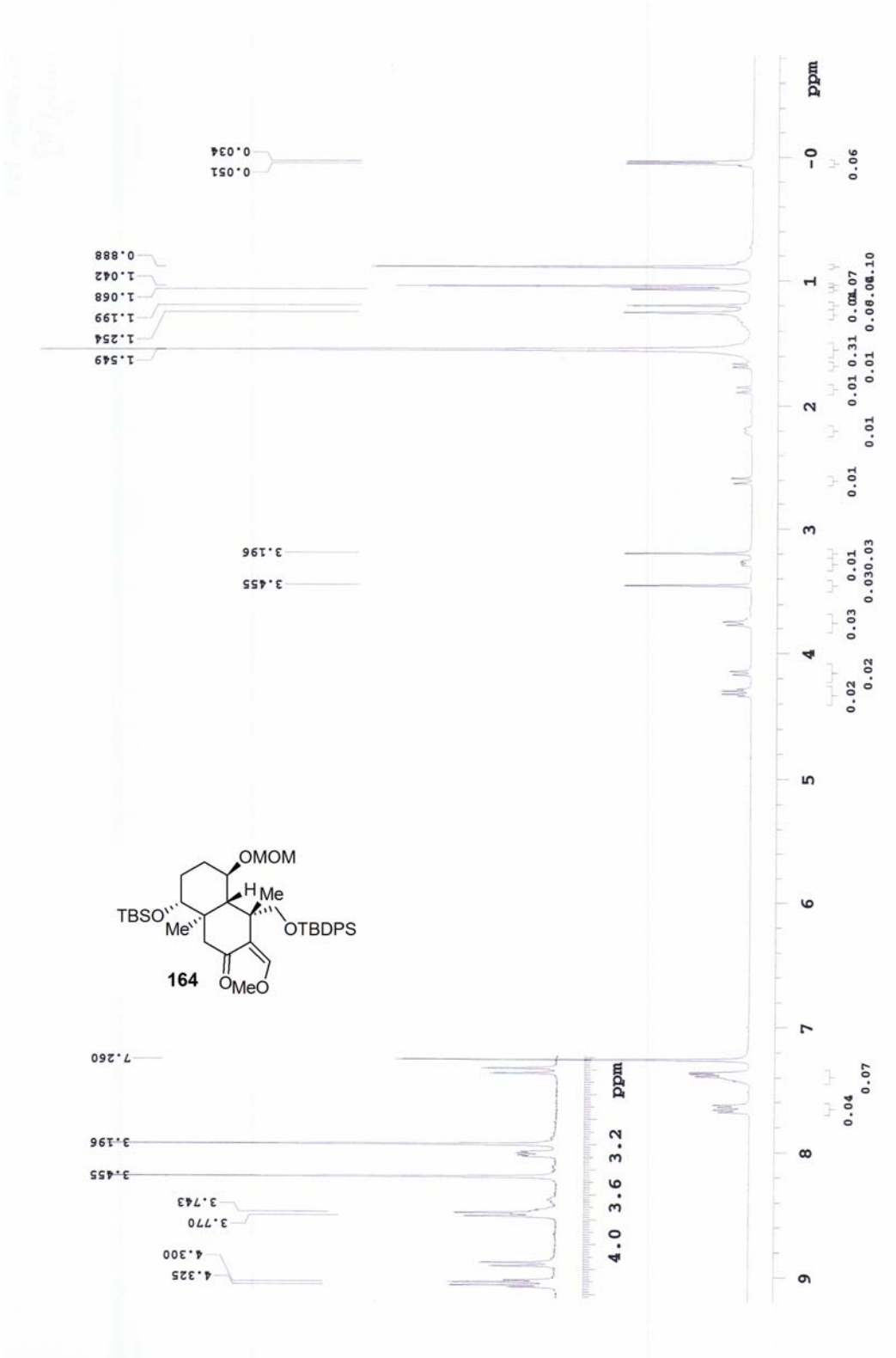
Spectrum 2.36: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **31-1**



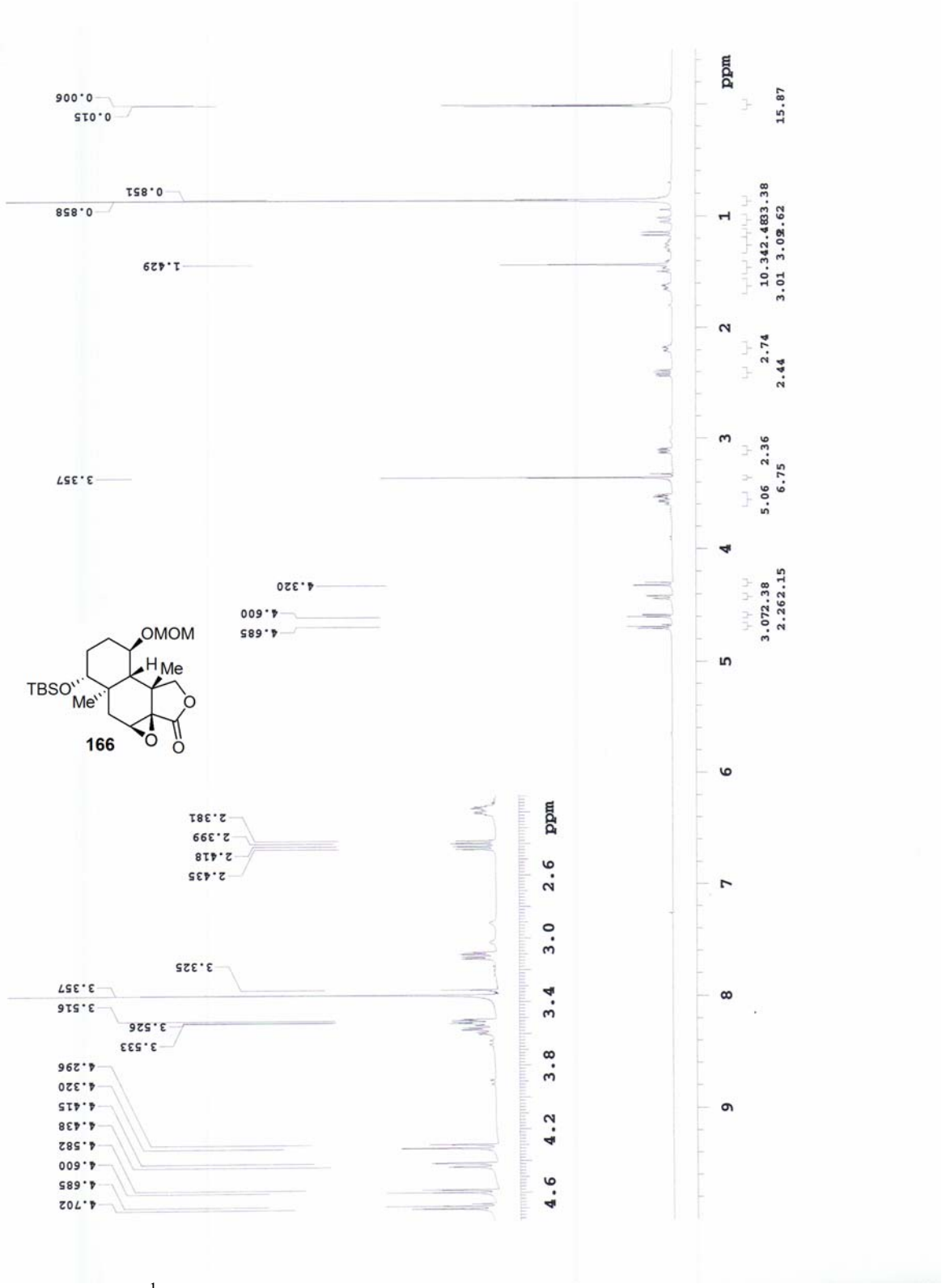
Spectrum 2.37: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **31-1**



Spectrum 2.39: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **31-3**

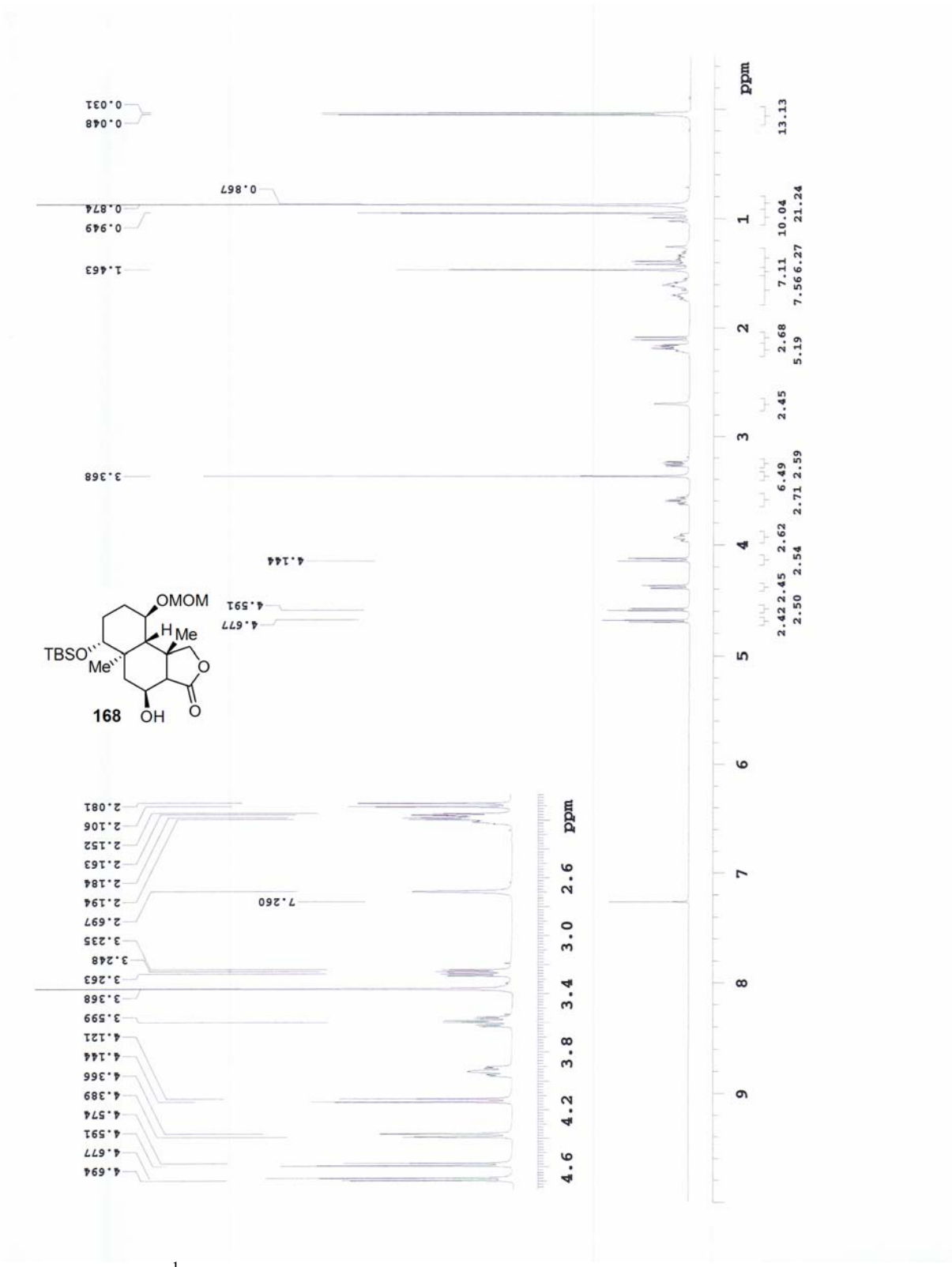


Spectrum 2.38: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **31-5**

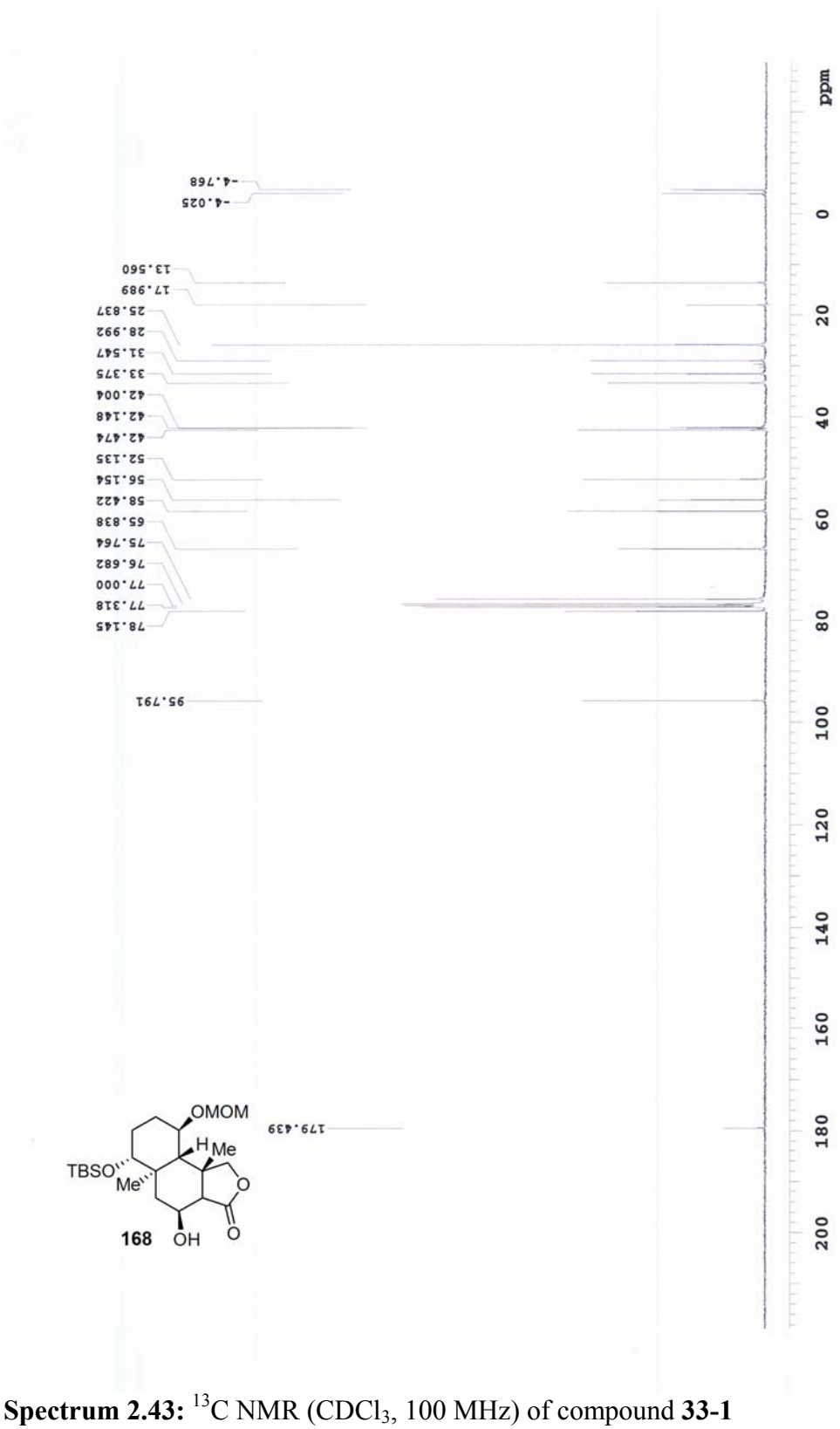


Spectrum 2.40: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **32**

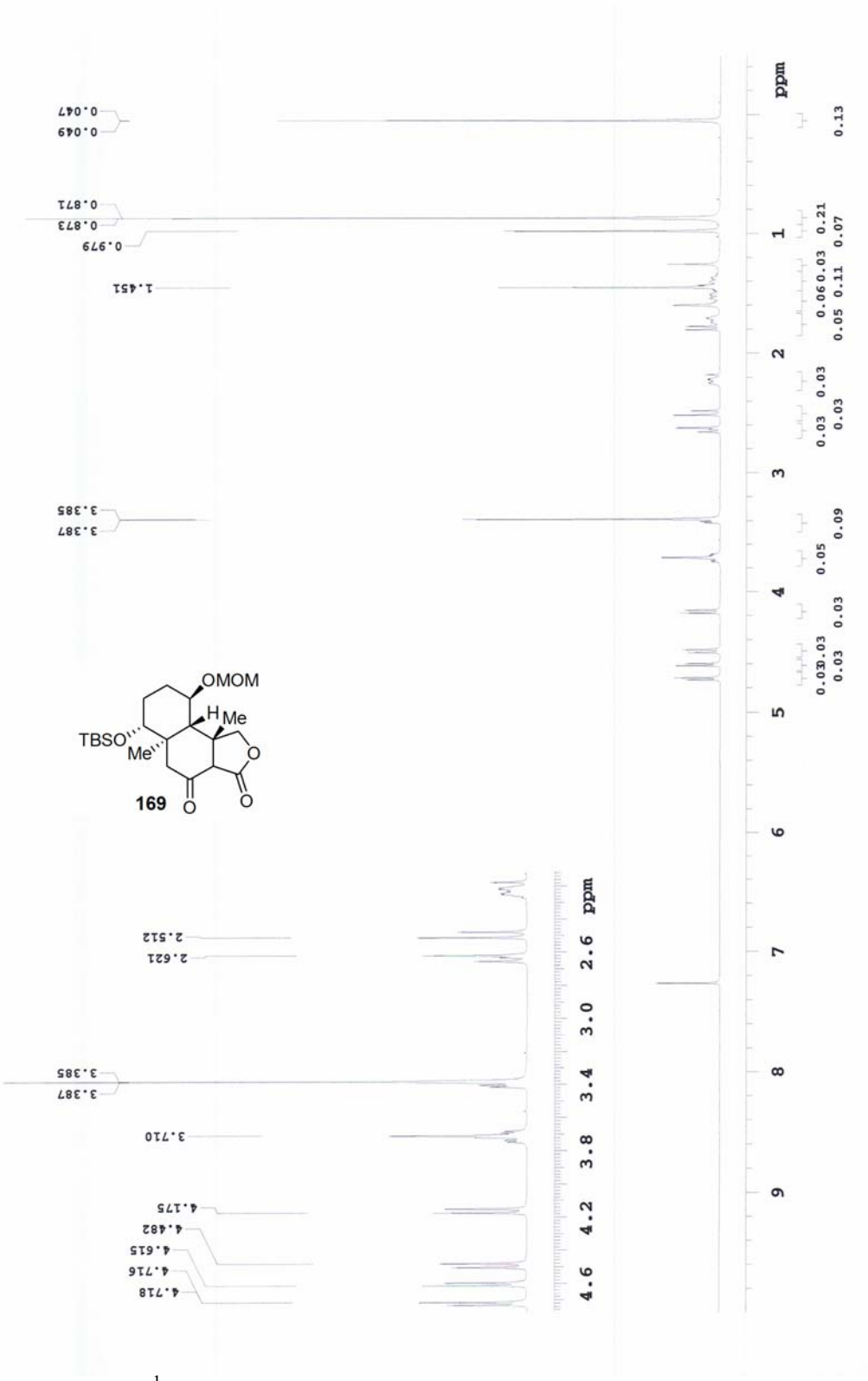
Spectrum 2.41: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **32**



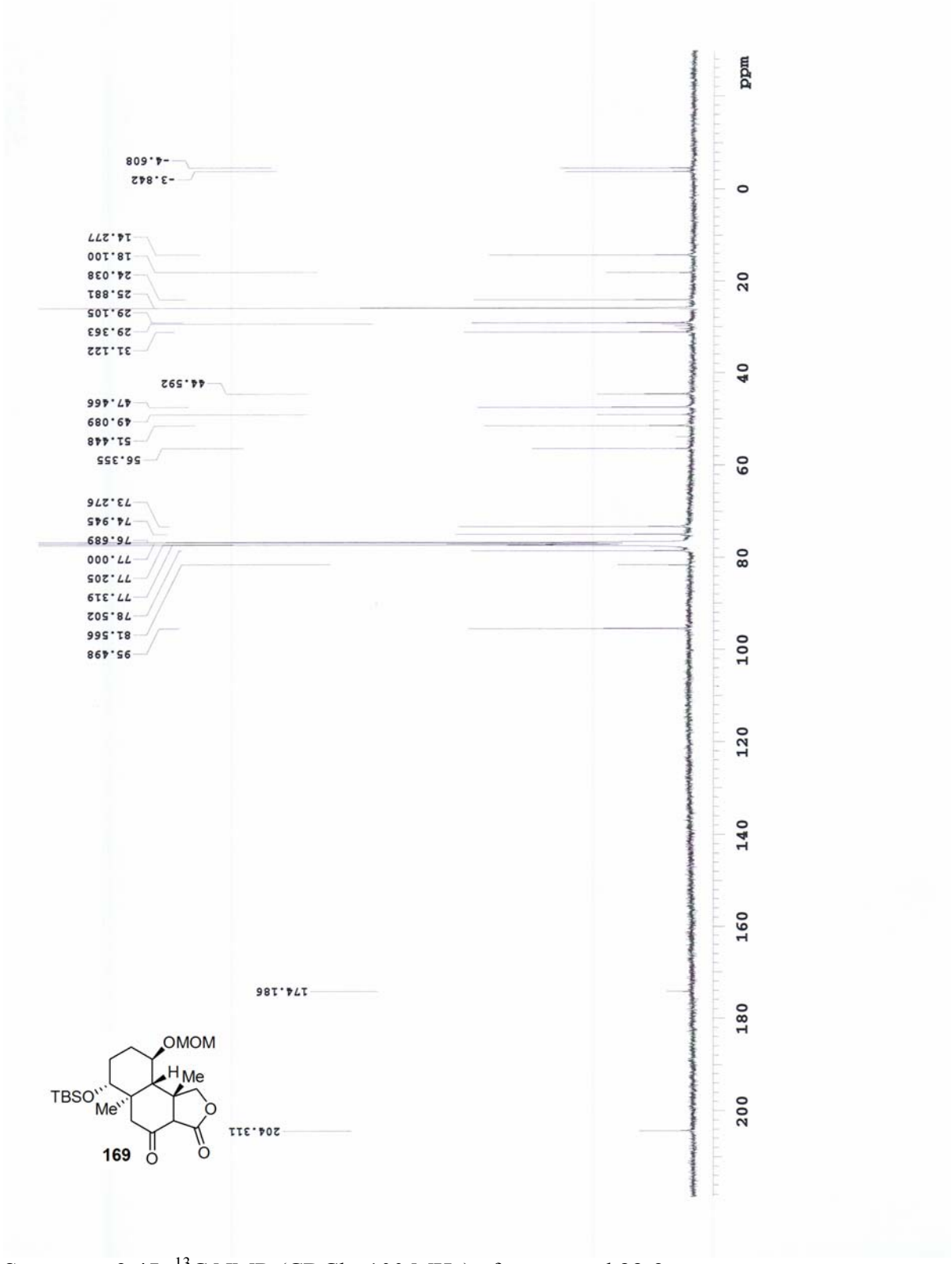
Spectrum 2.42: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **33-1**



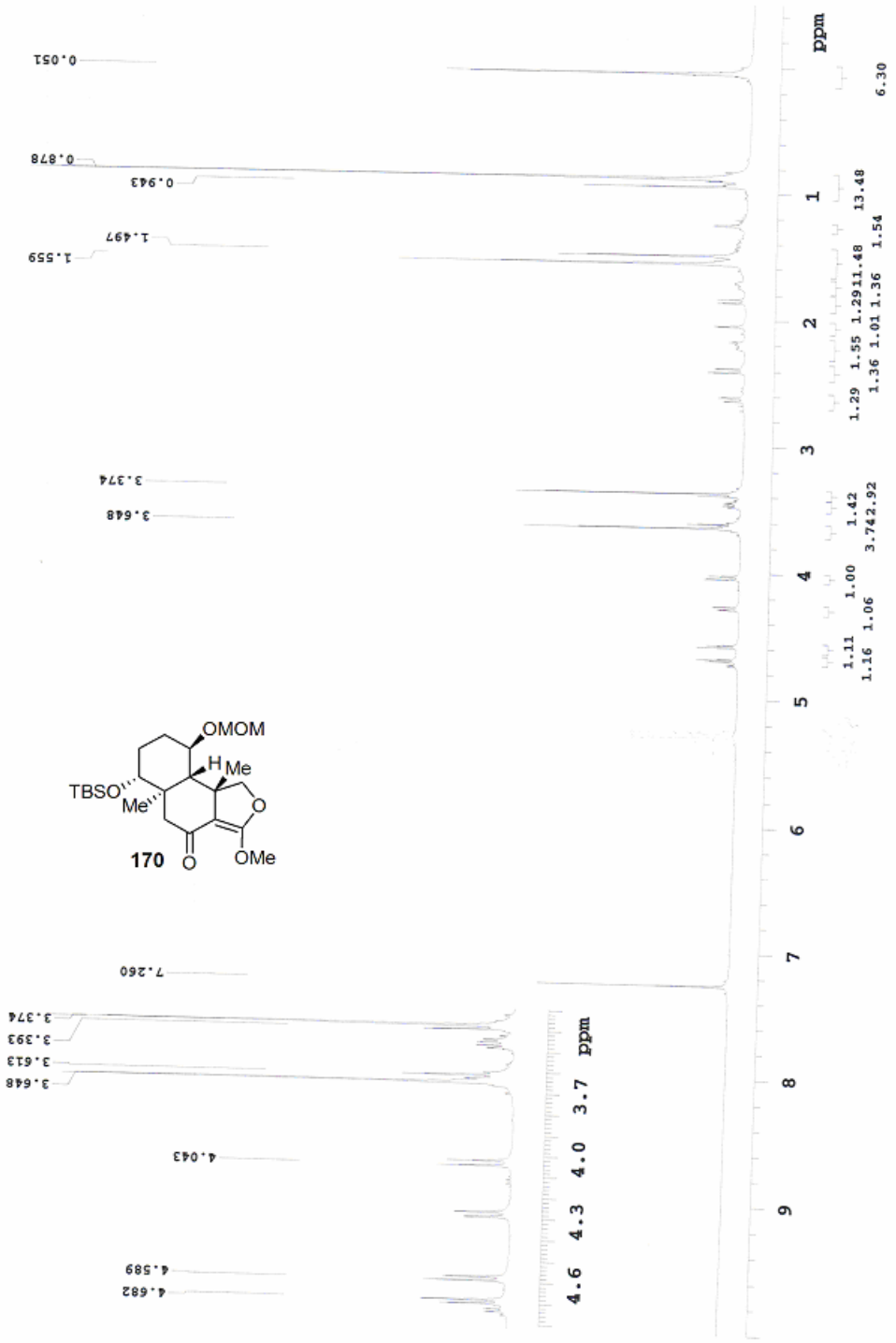
Spectrum 2.43: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **33-1**



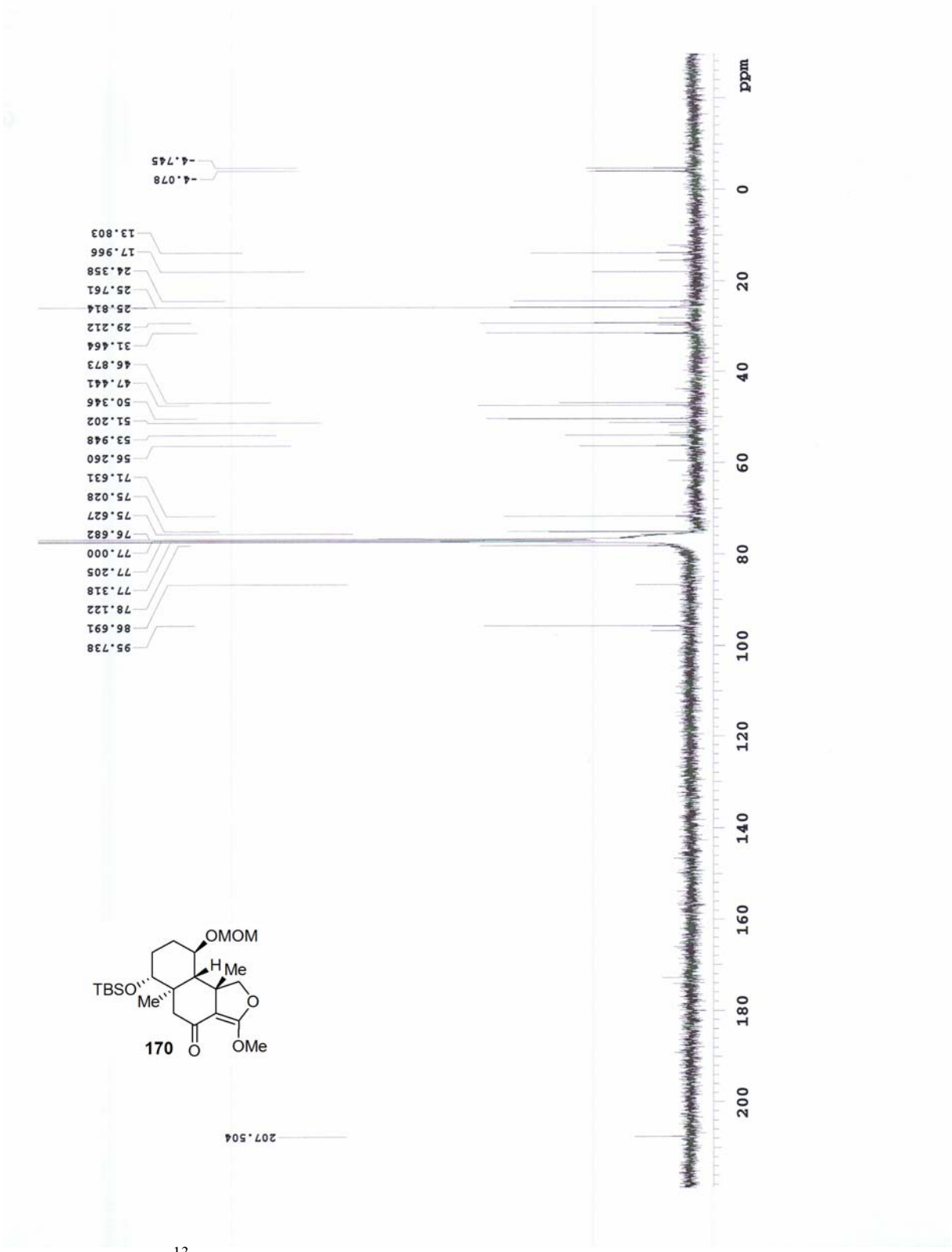
Spectrum 2.44: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **33-2**



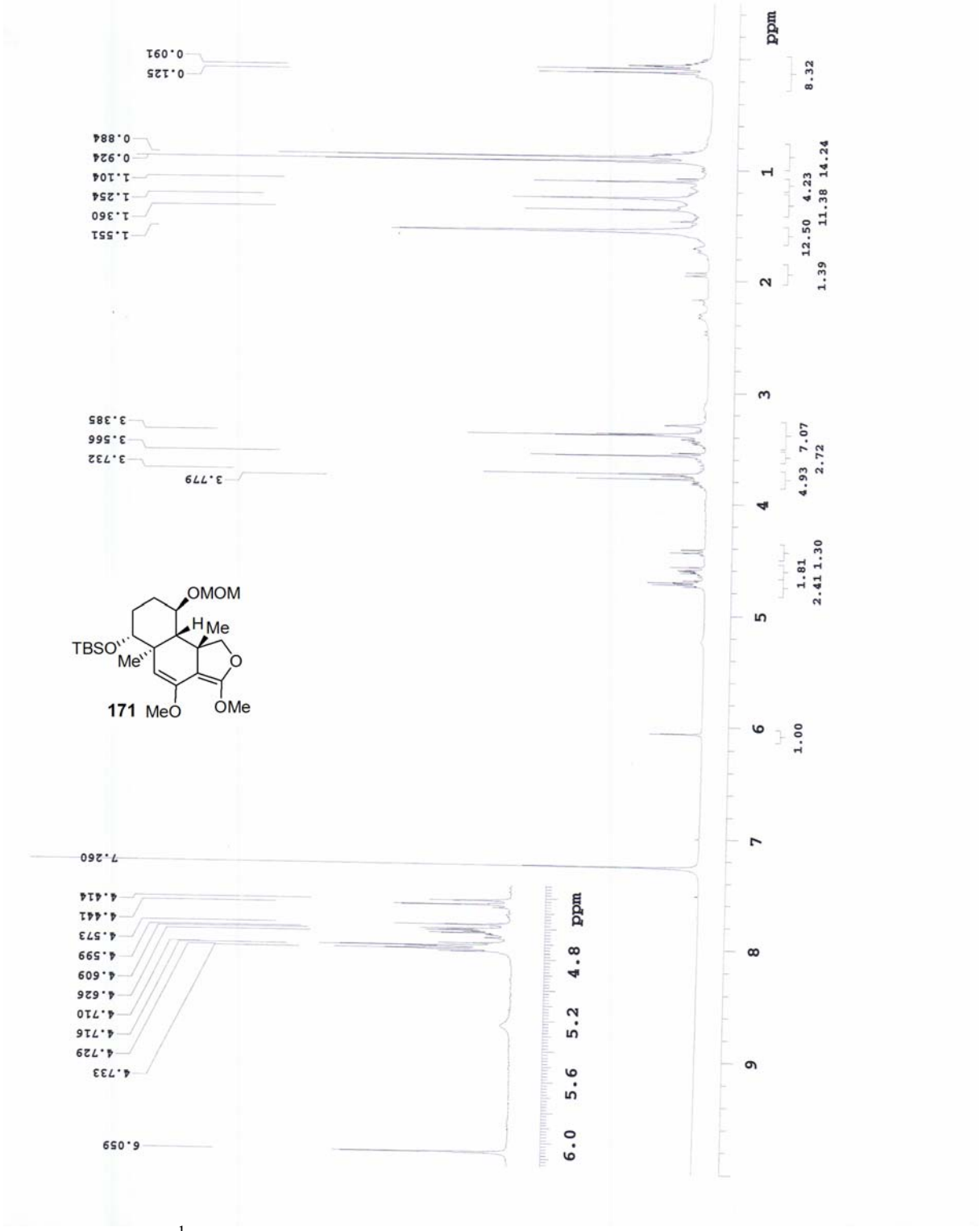
Spectrum 2.45: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **33-2**



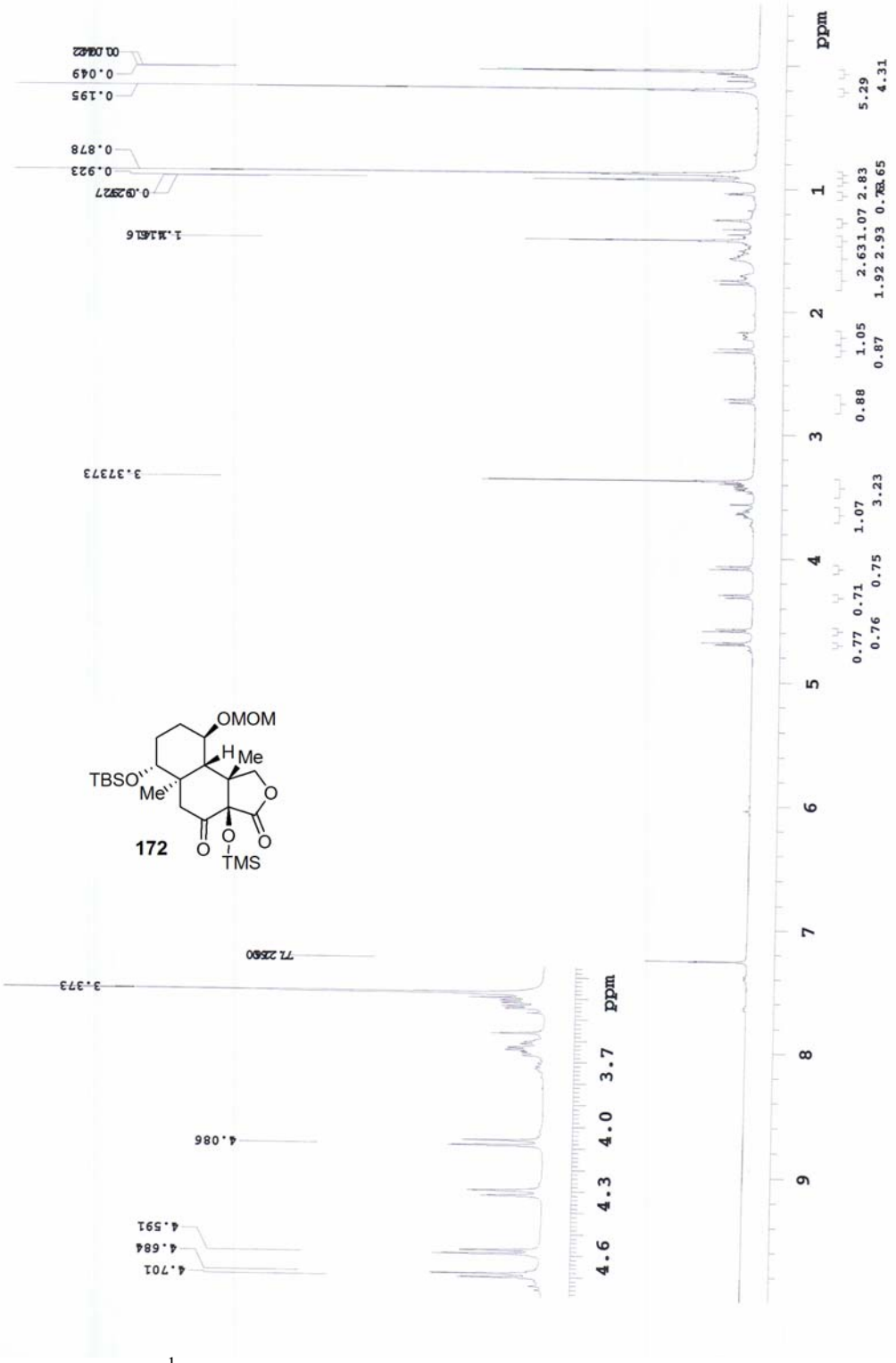
Spectrum 2.46: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **35**



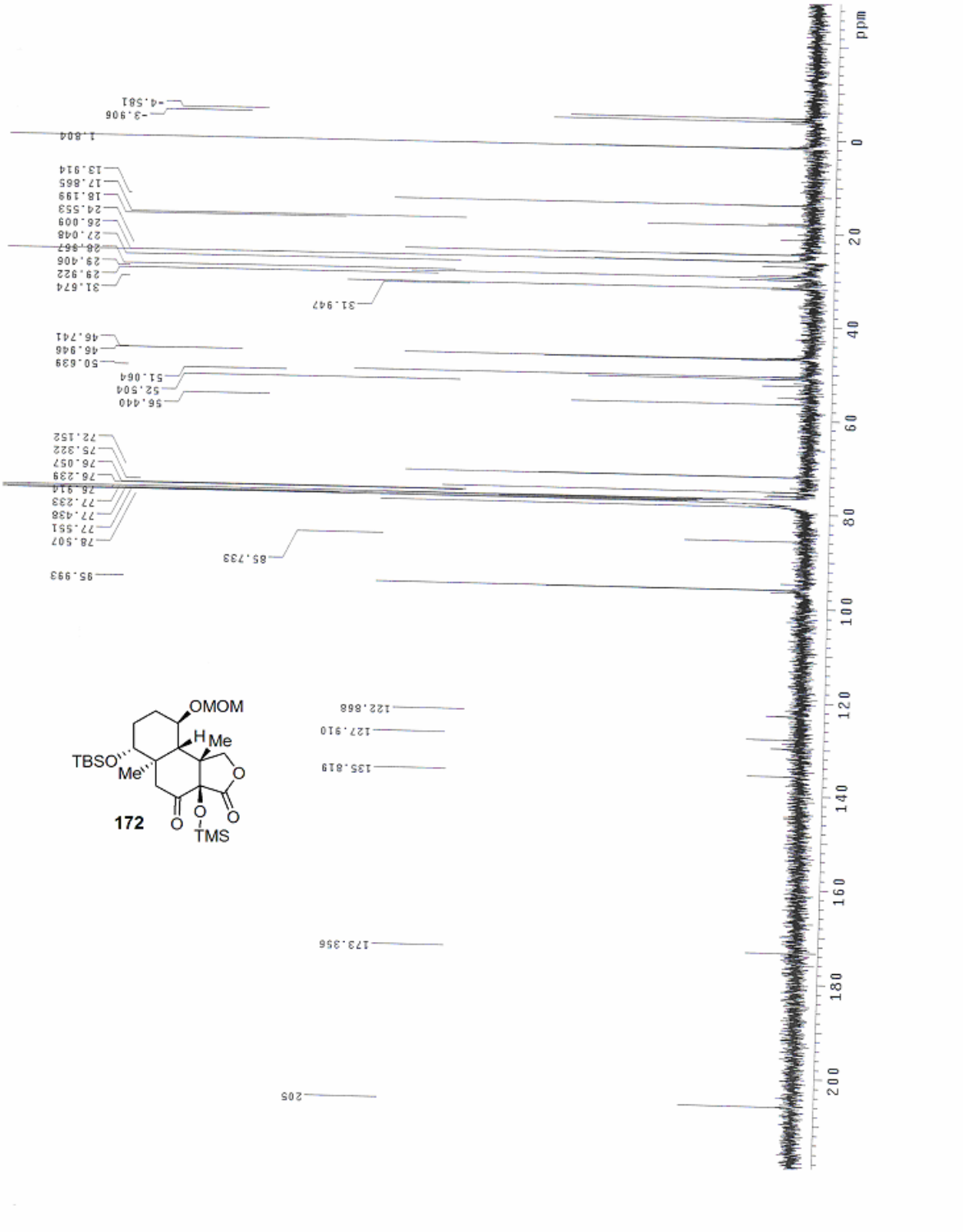
Spectrum 2.47: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **35**



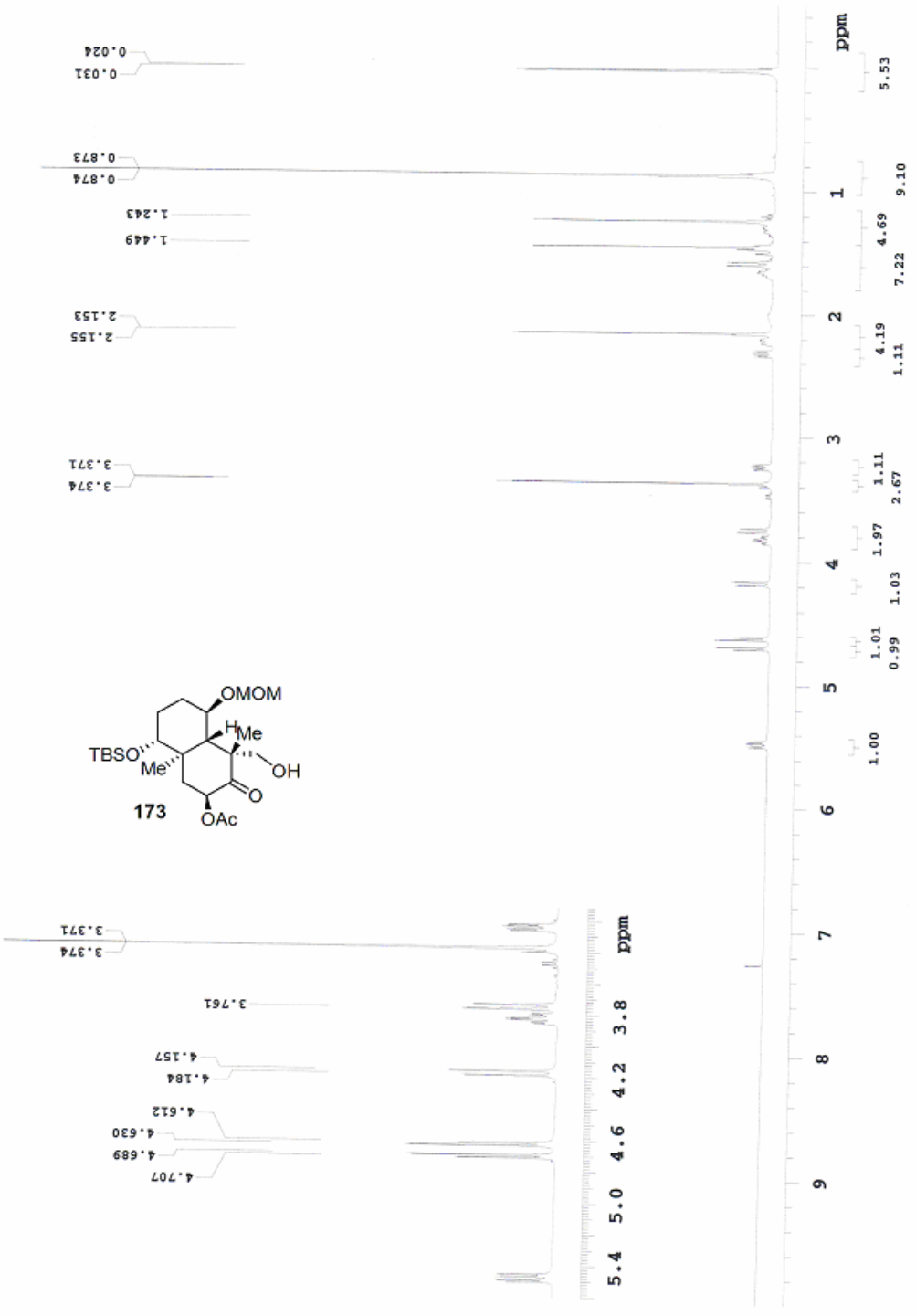
Spectrum 2.48: ^{1}H NMR ($CDCl_3$, 100 MHz) of compound **36**



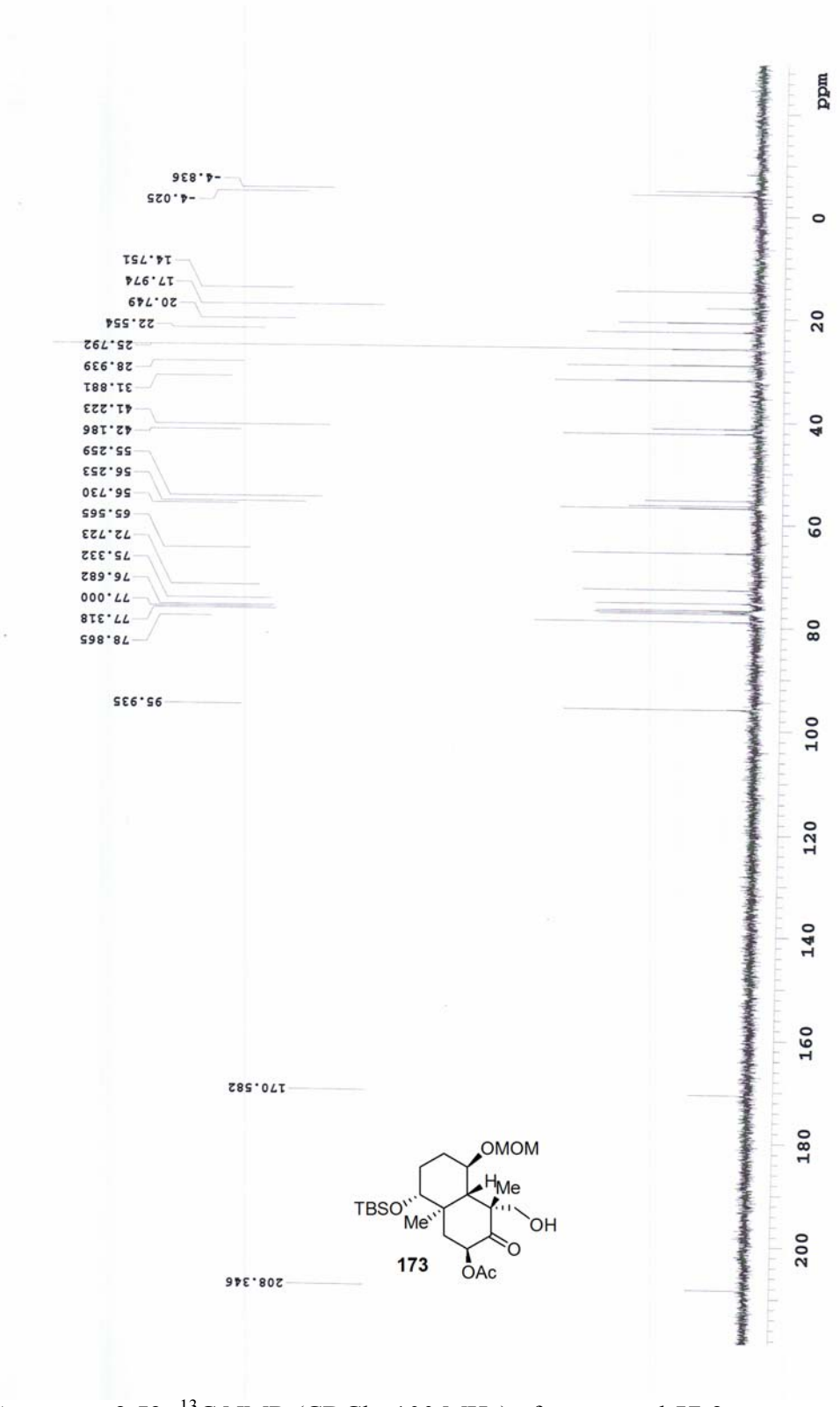
Spectrum 2.49: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **34**



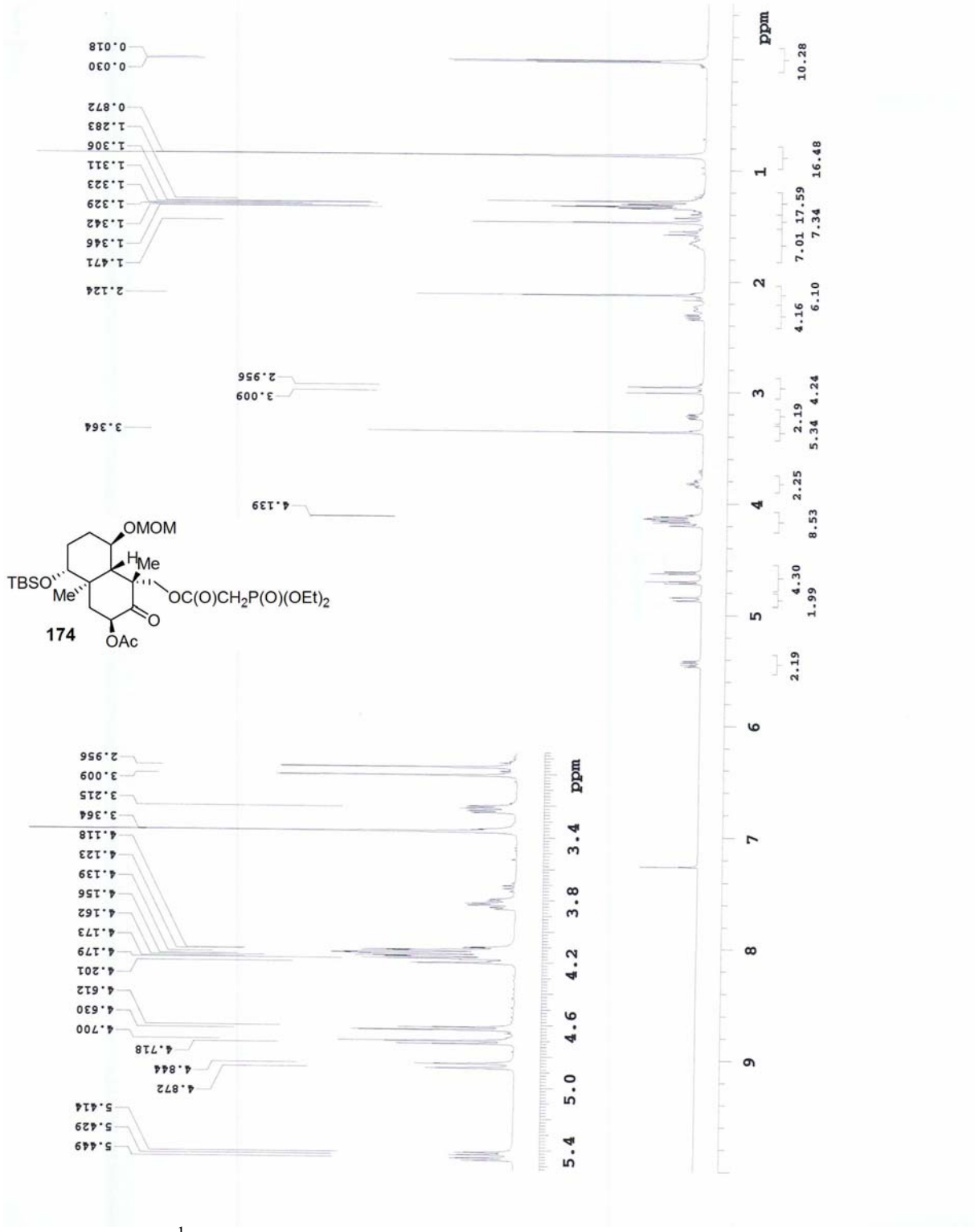
Spectrum 2.50: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **34**



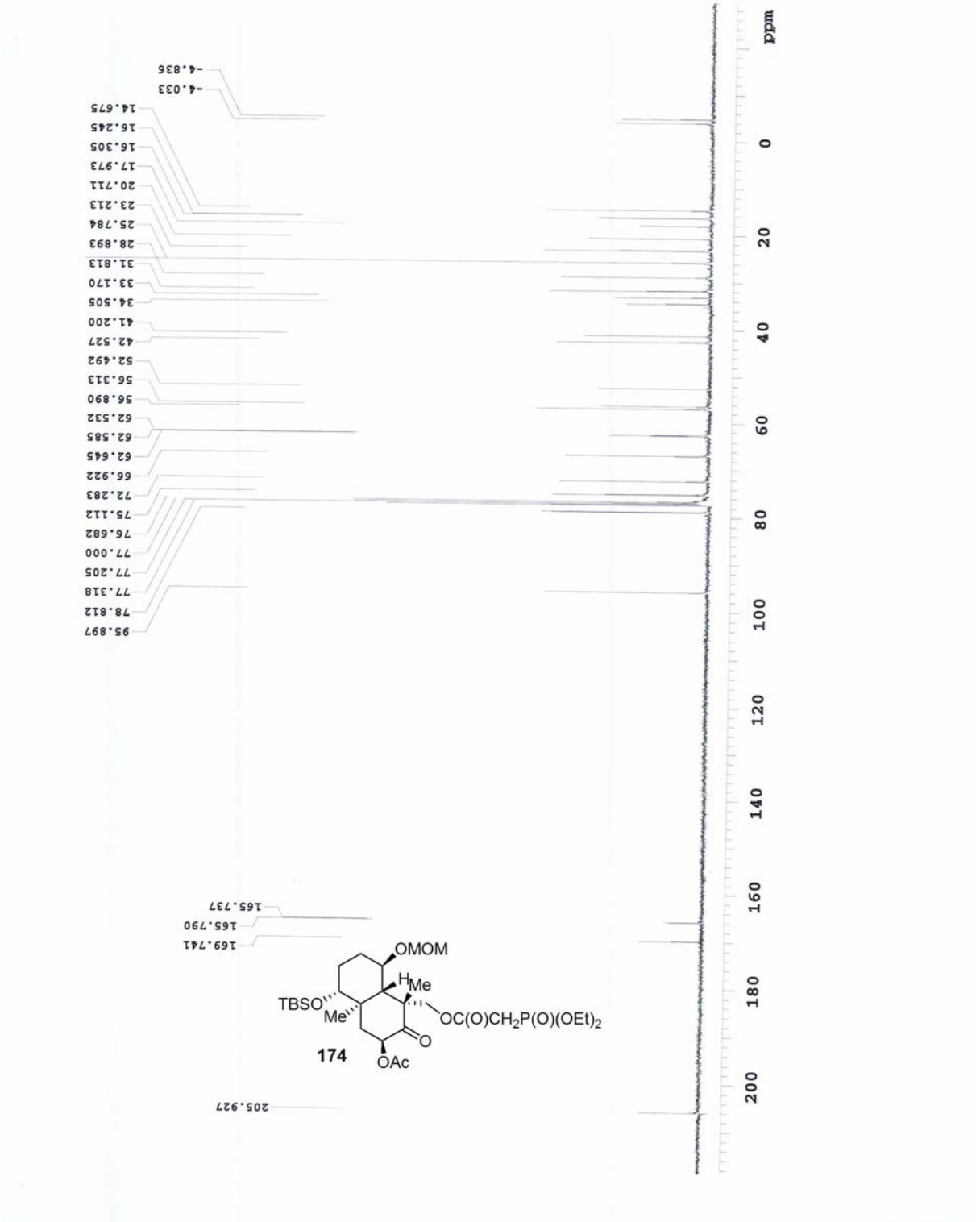
Spectrum 2.51: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **57-2**



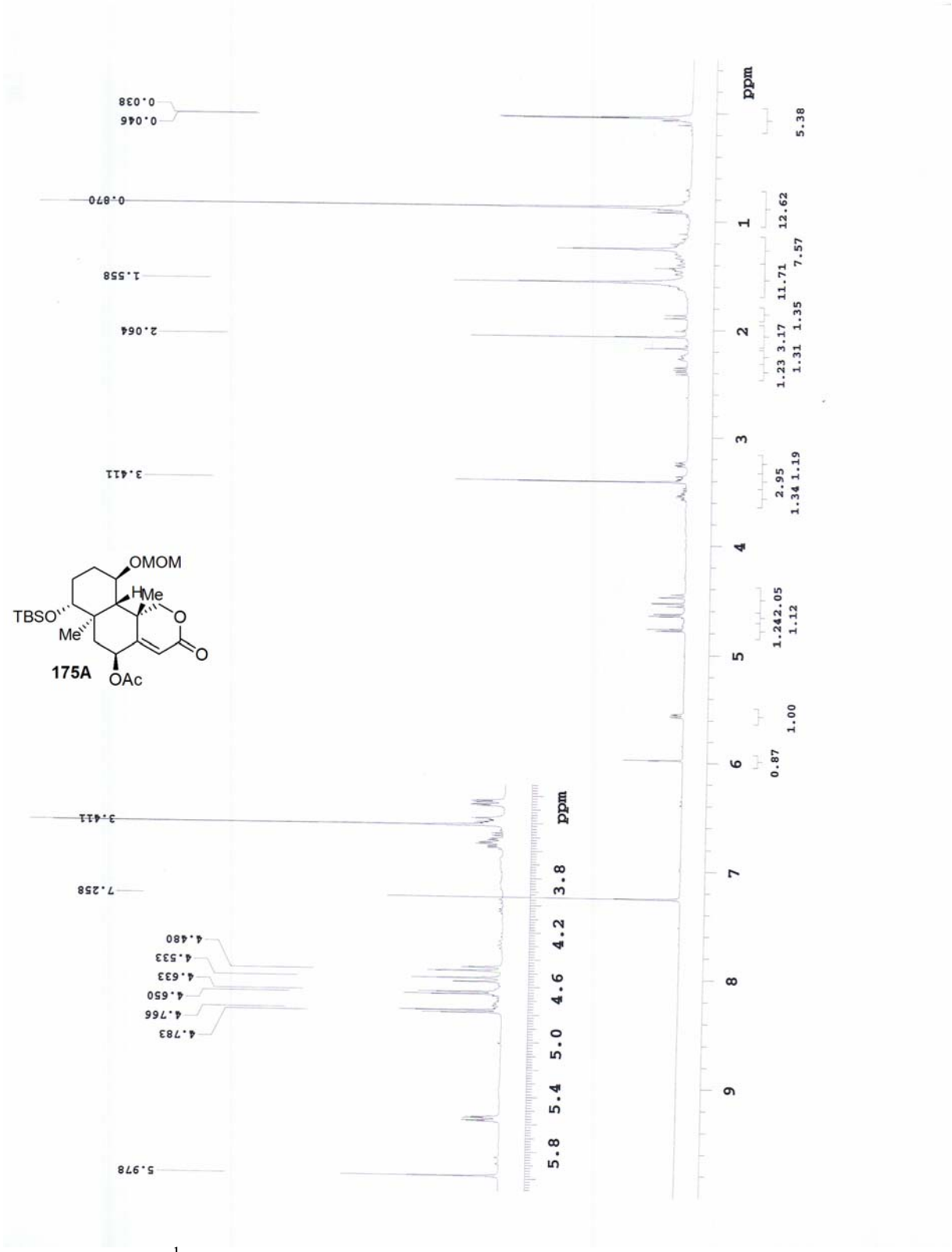
Spectrum 2.52: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **57-2**



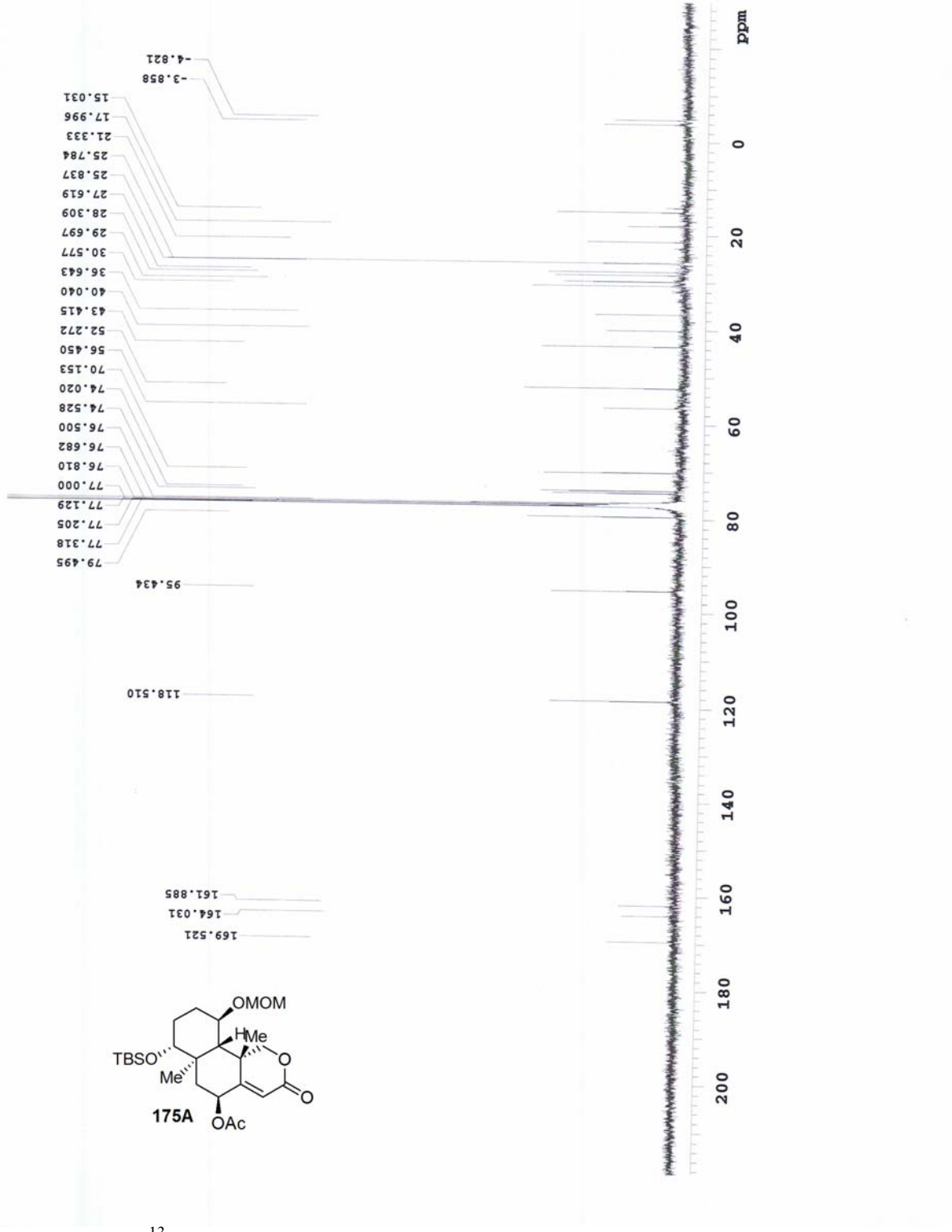
Spectrum 2.59: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **57-3**



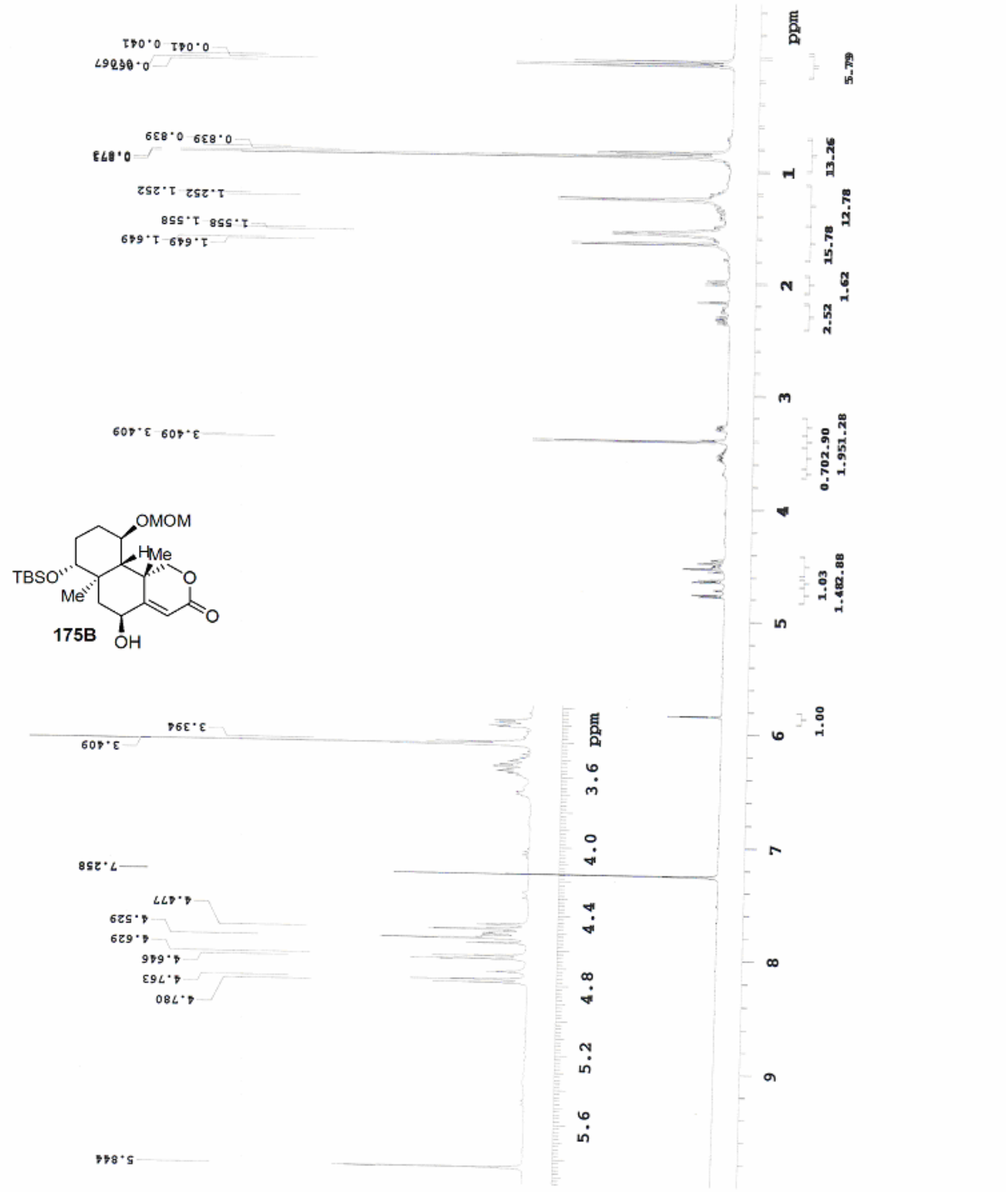
Spectrum 2.60: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **57-3**



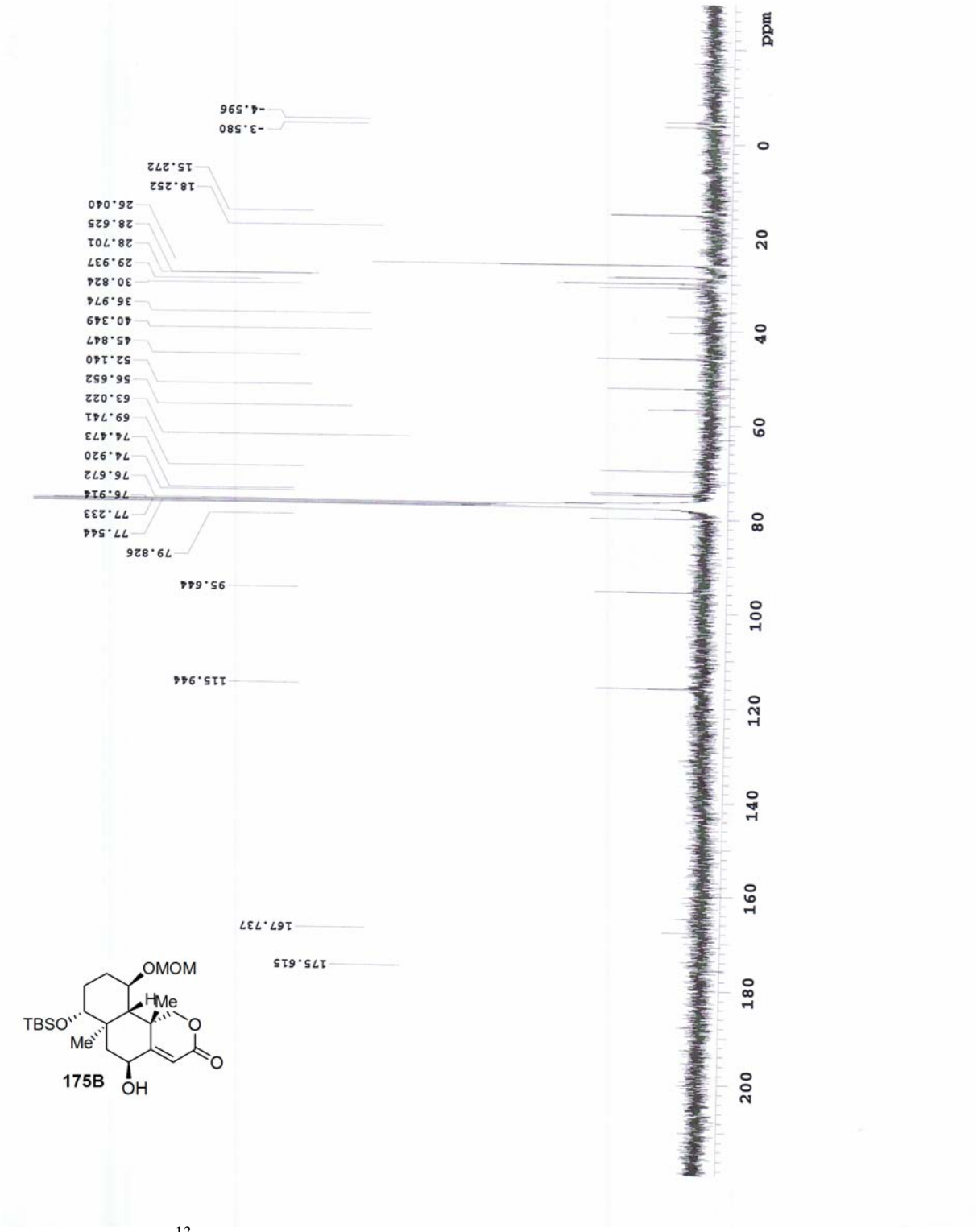
Spectrum 2.53: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **57-4**



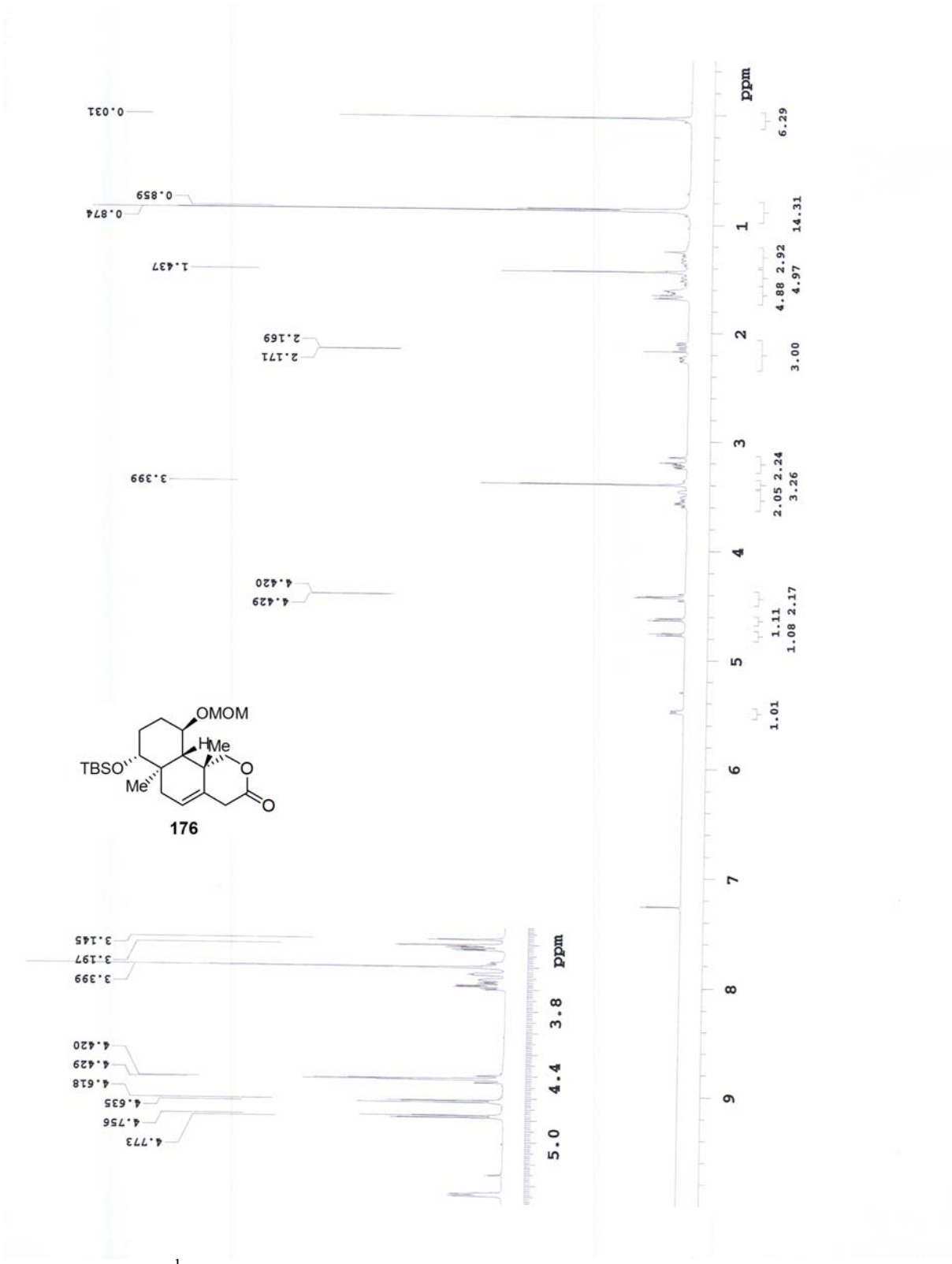
Spectrum 2.54: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **57-4**



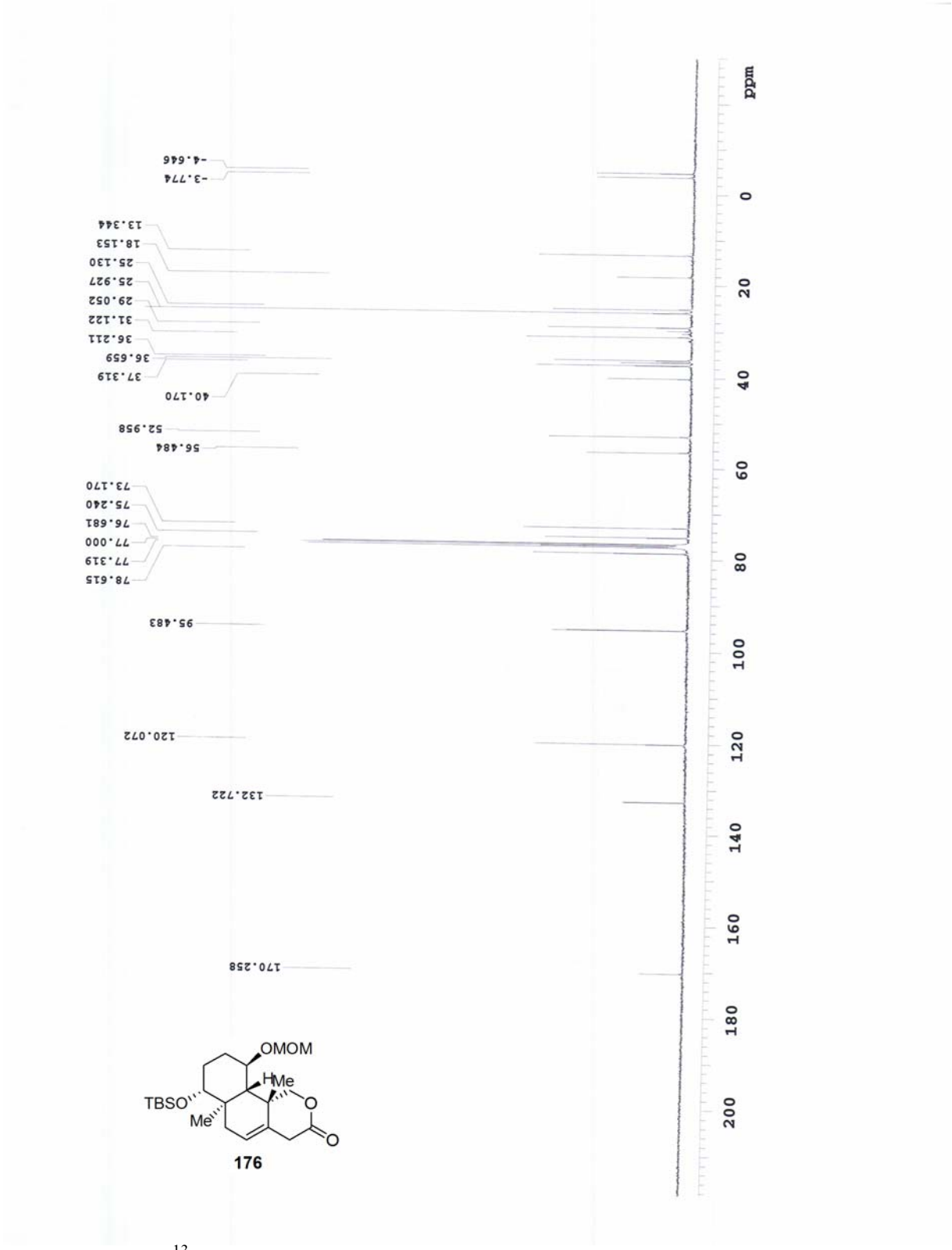
Spectrum 2.55: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **57-5**



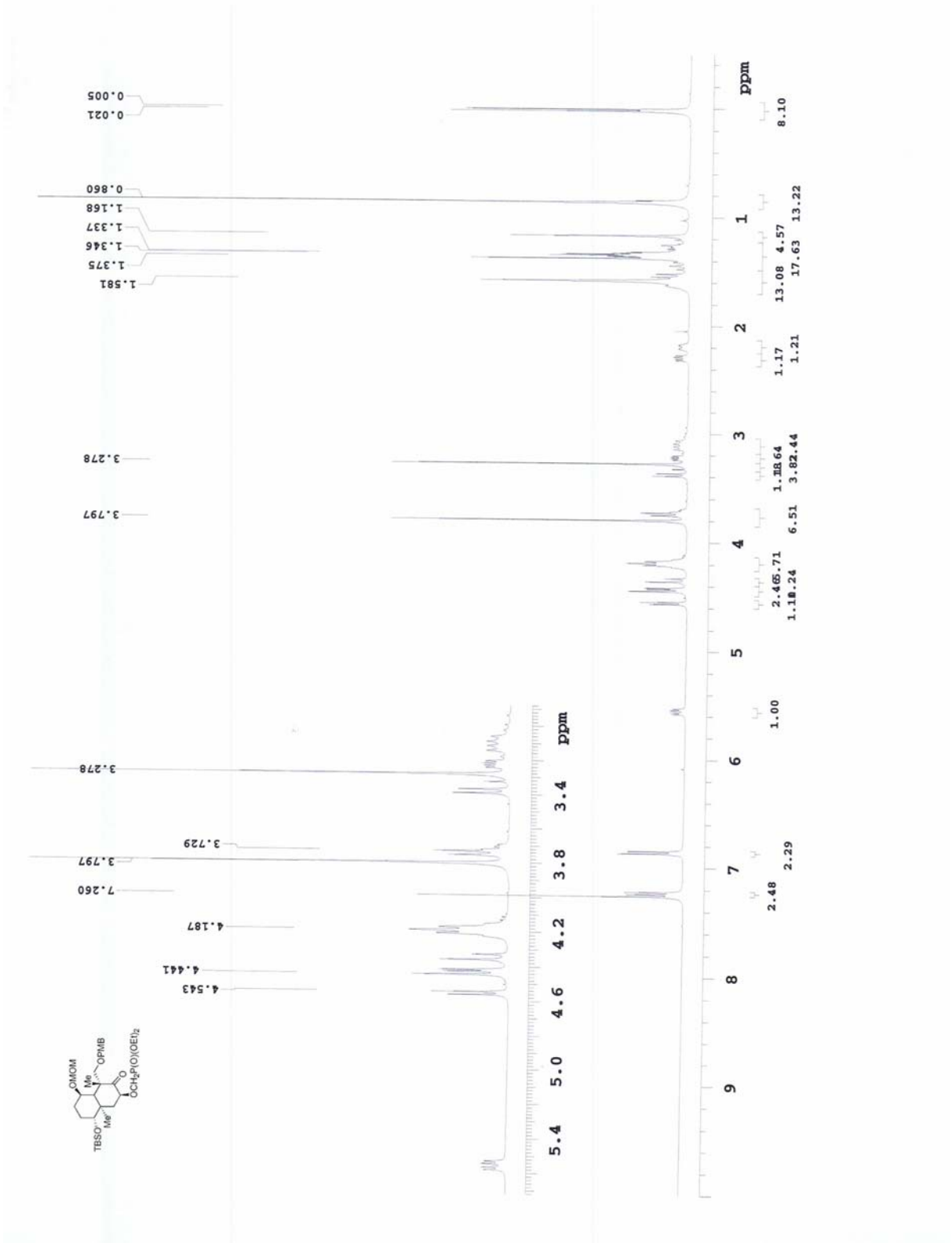
Spectrum 2.56: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **57-5**



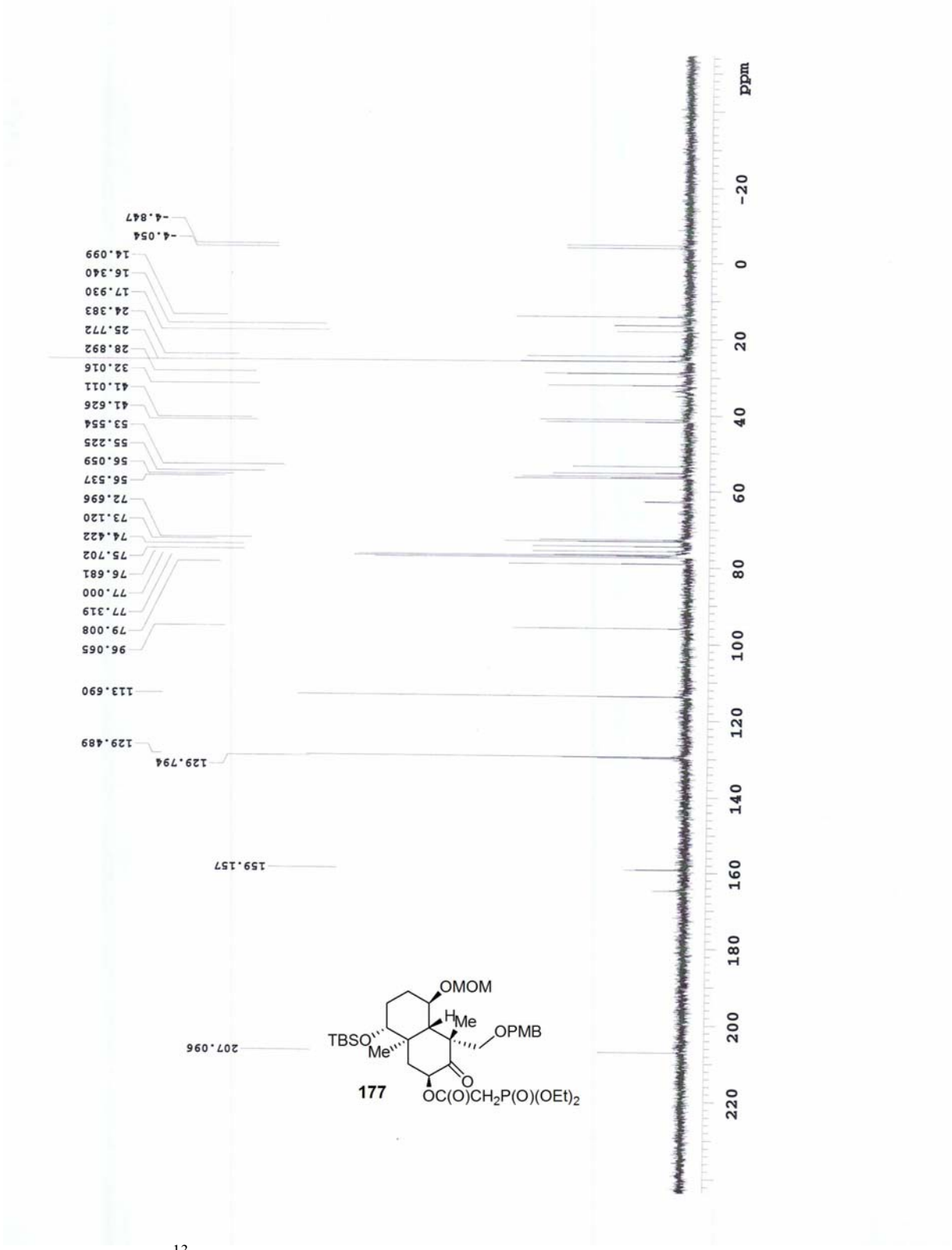
Spectrum 2.57: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **57-6**



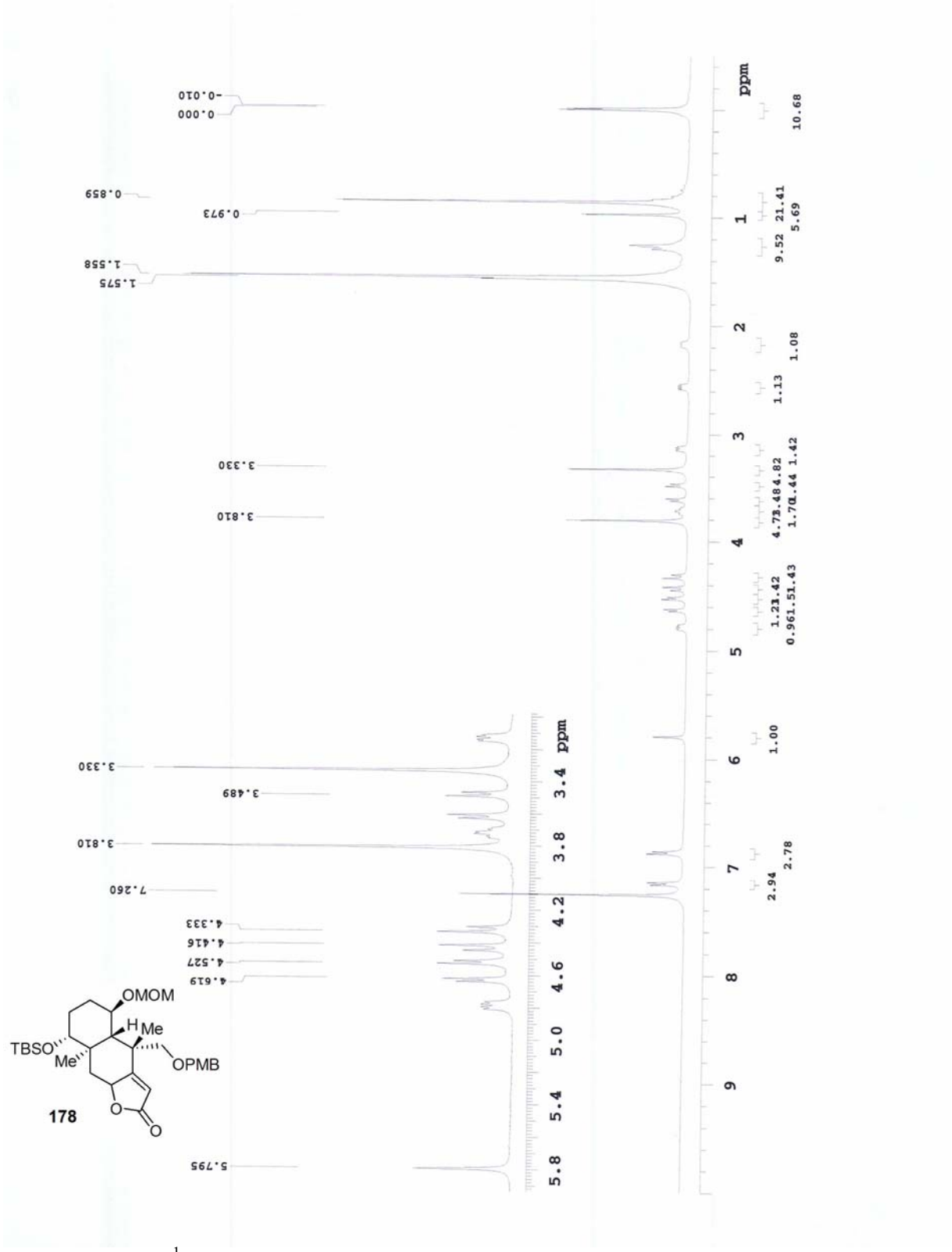
Spectrum 2.58: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **57-6**



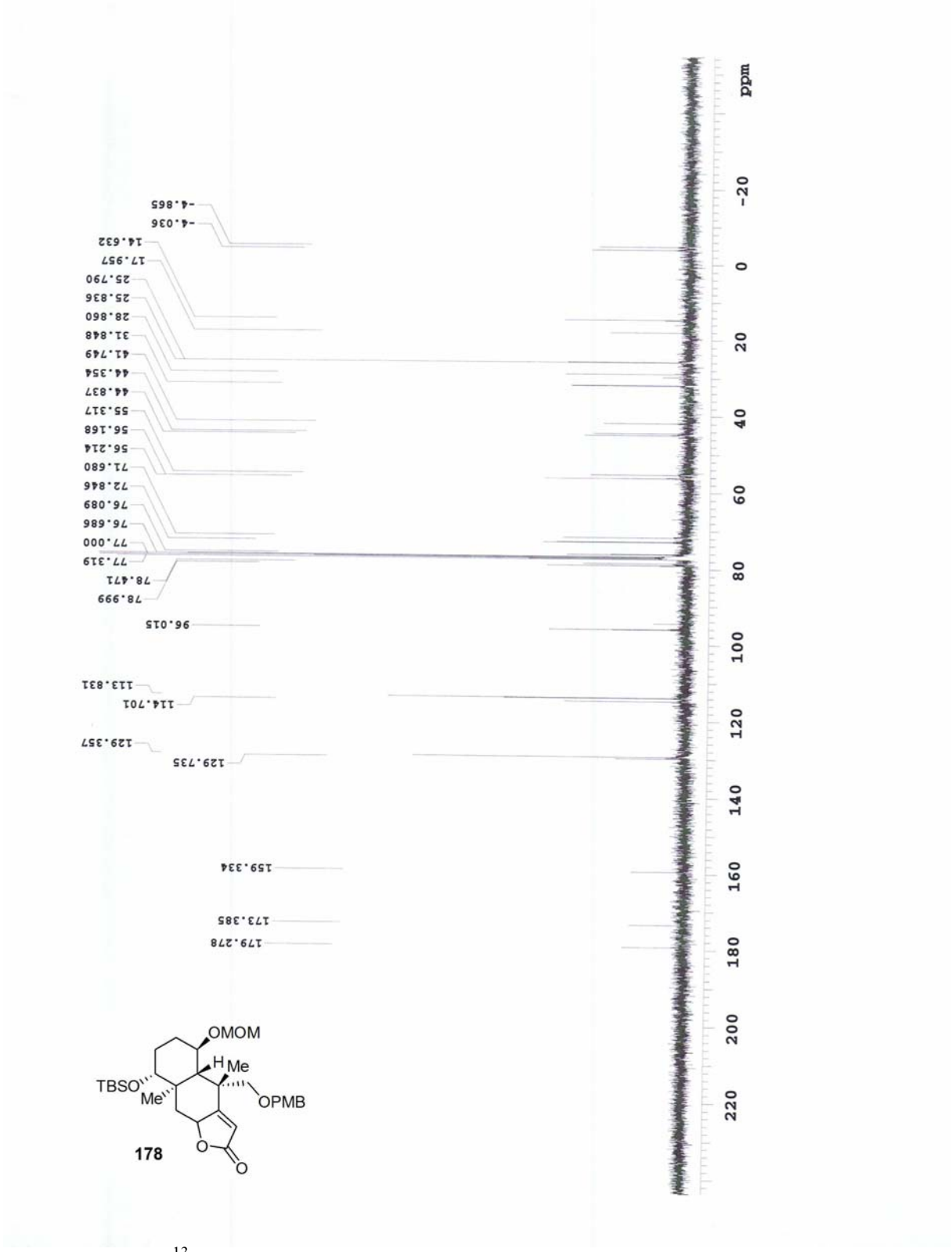
Spectrum 2.59: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **41-1**



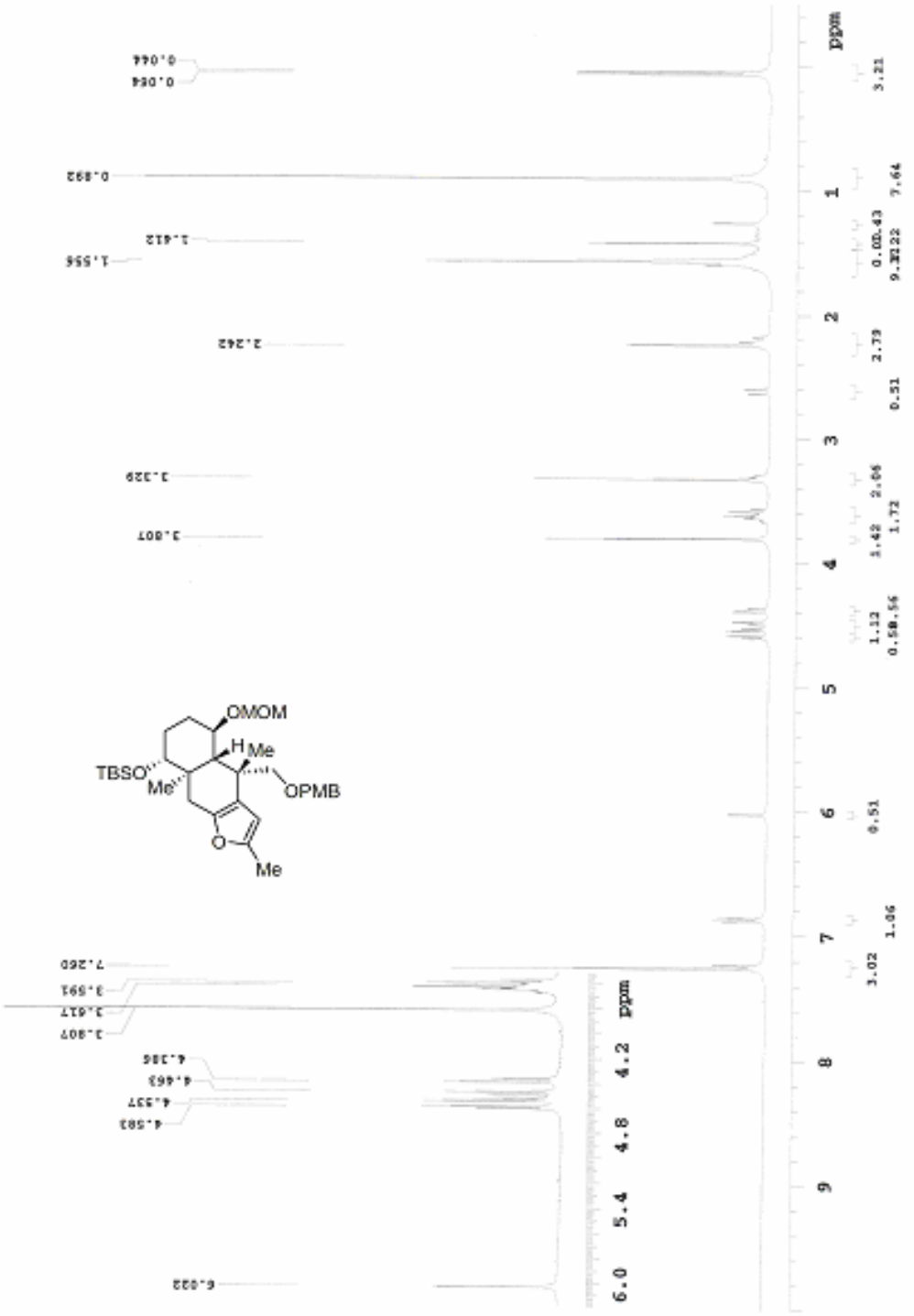
Spectrum 2.62: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **41-1**



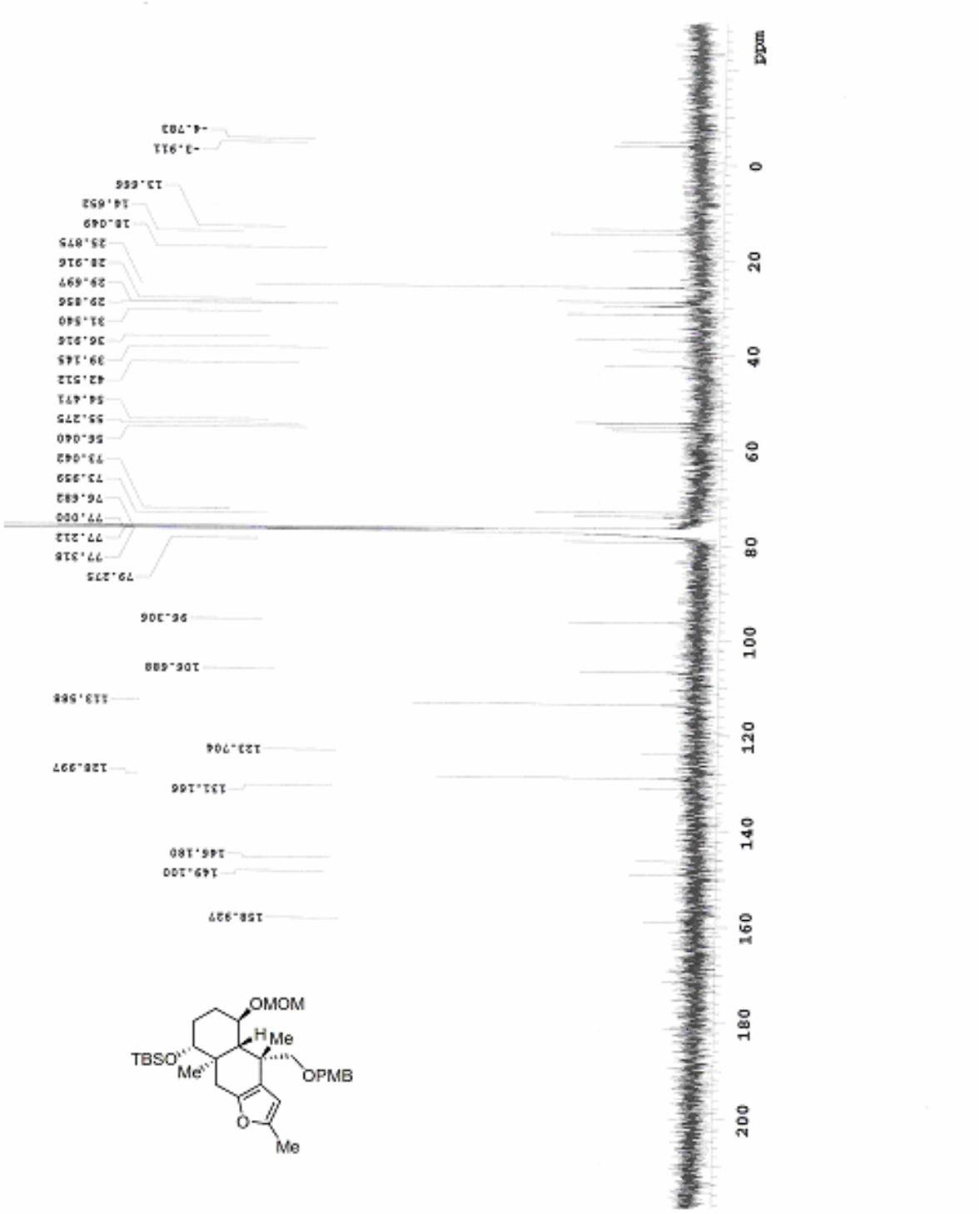
Spectrum 2.63: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **42**



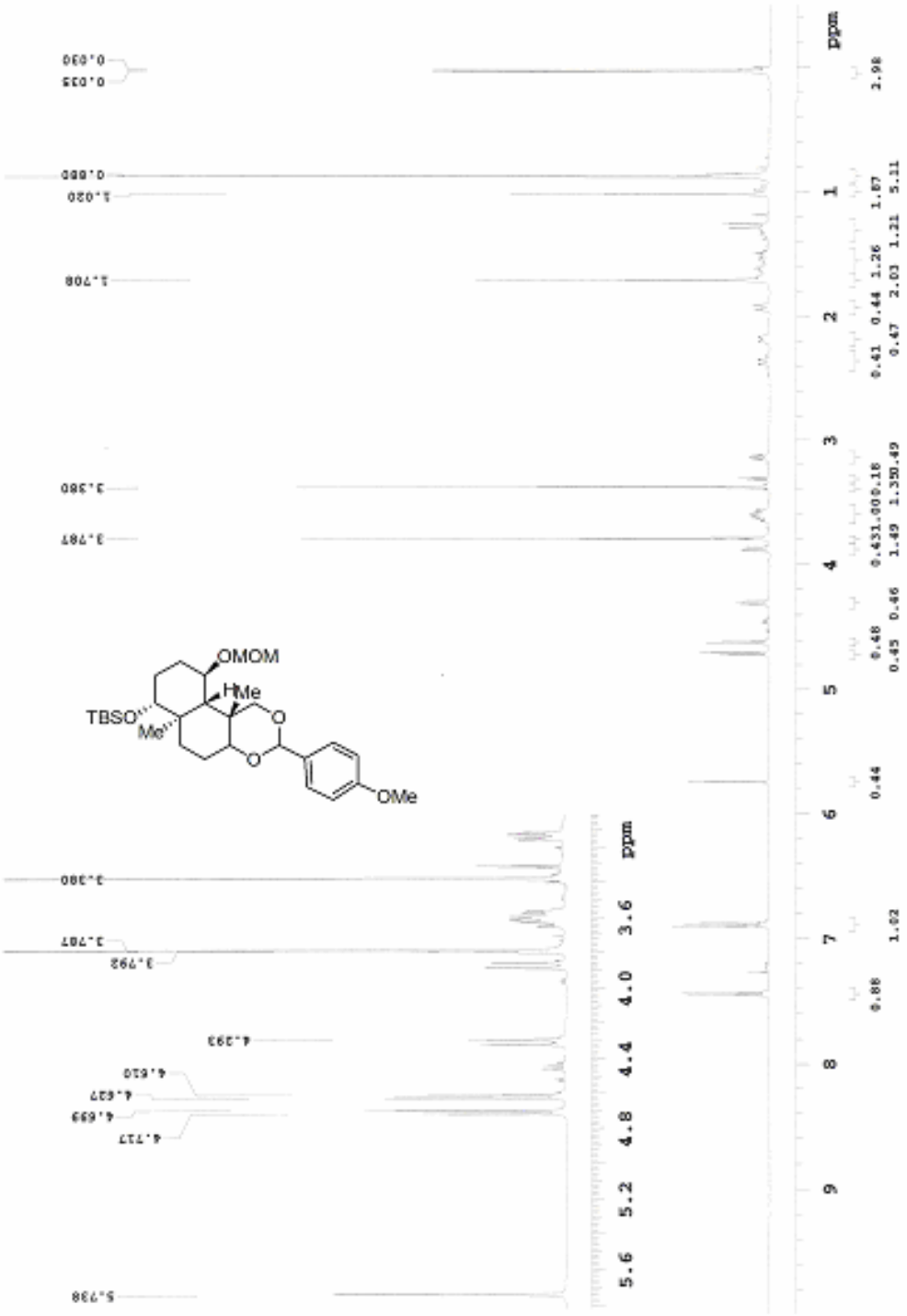
Spectrum 2.64: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **42**



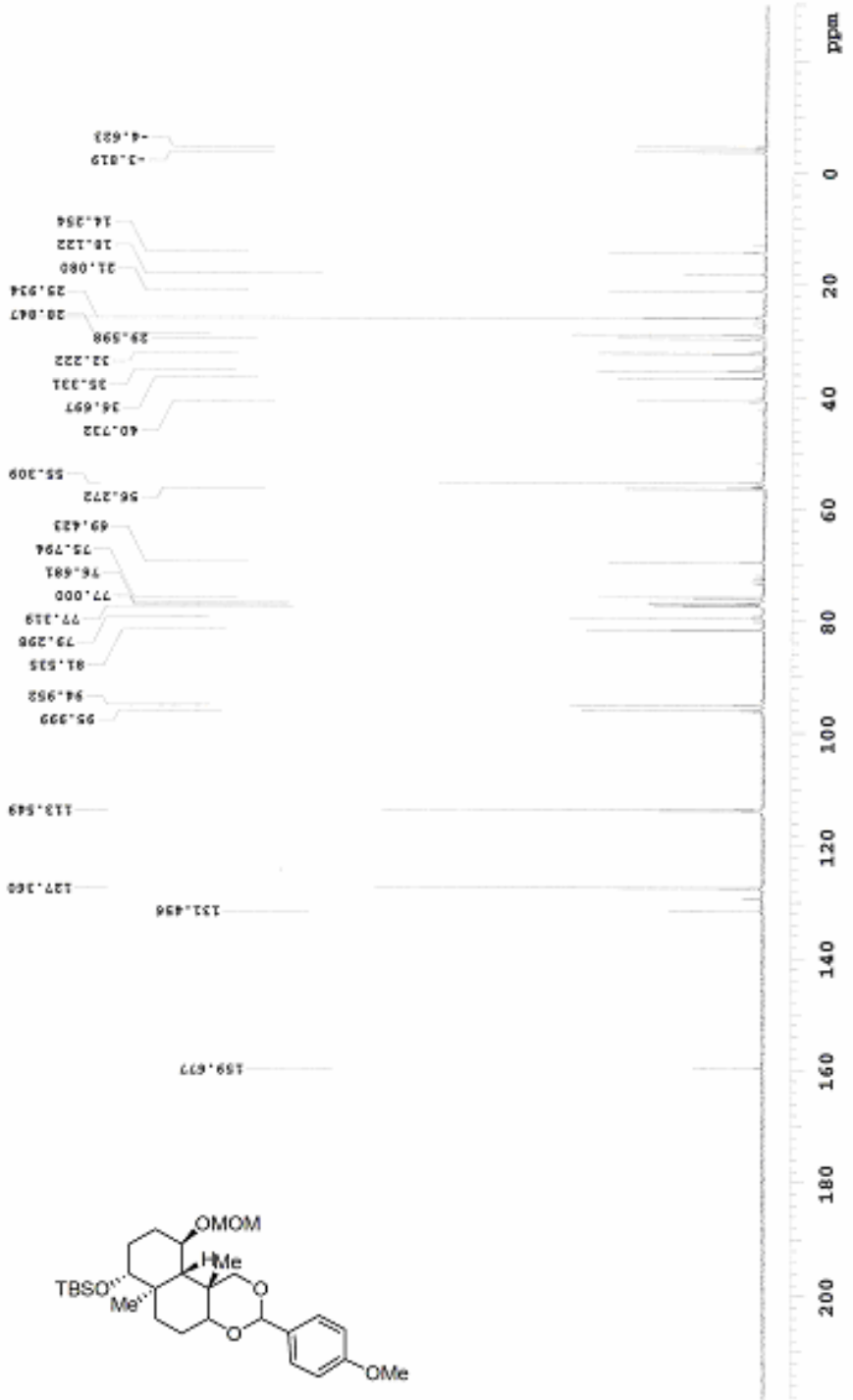
Spectrum 2.65: ^{1}H NMR ($CDCl_3$, 100 MHz) of compound **43**



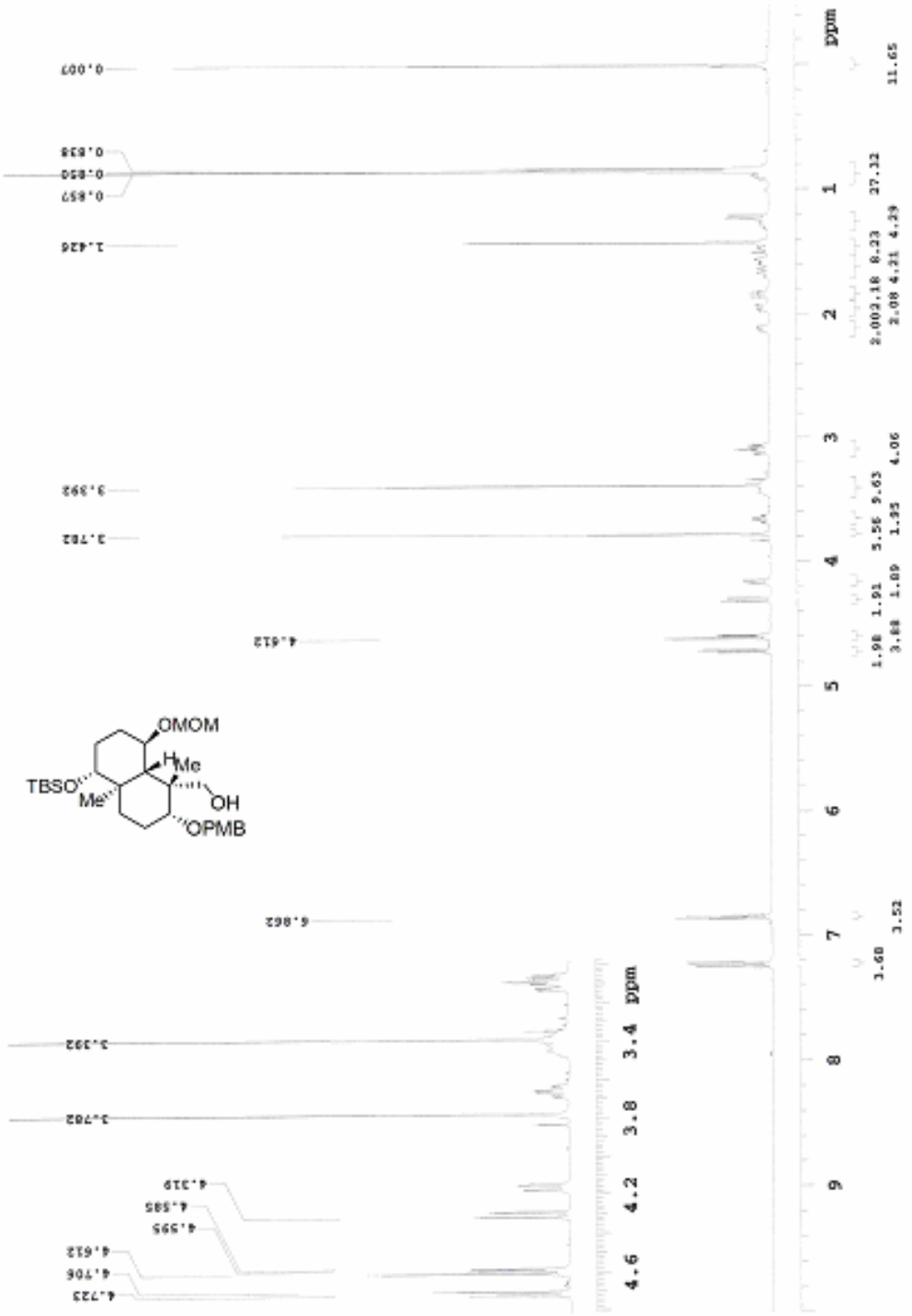
Spectrum 2.66: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **43**



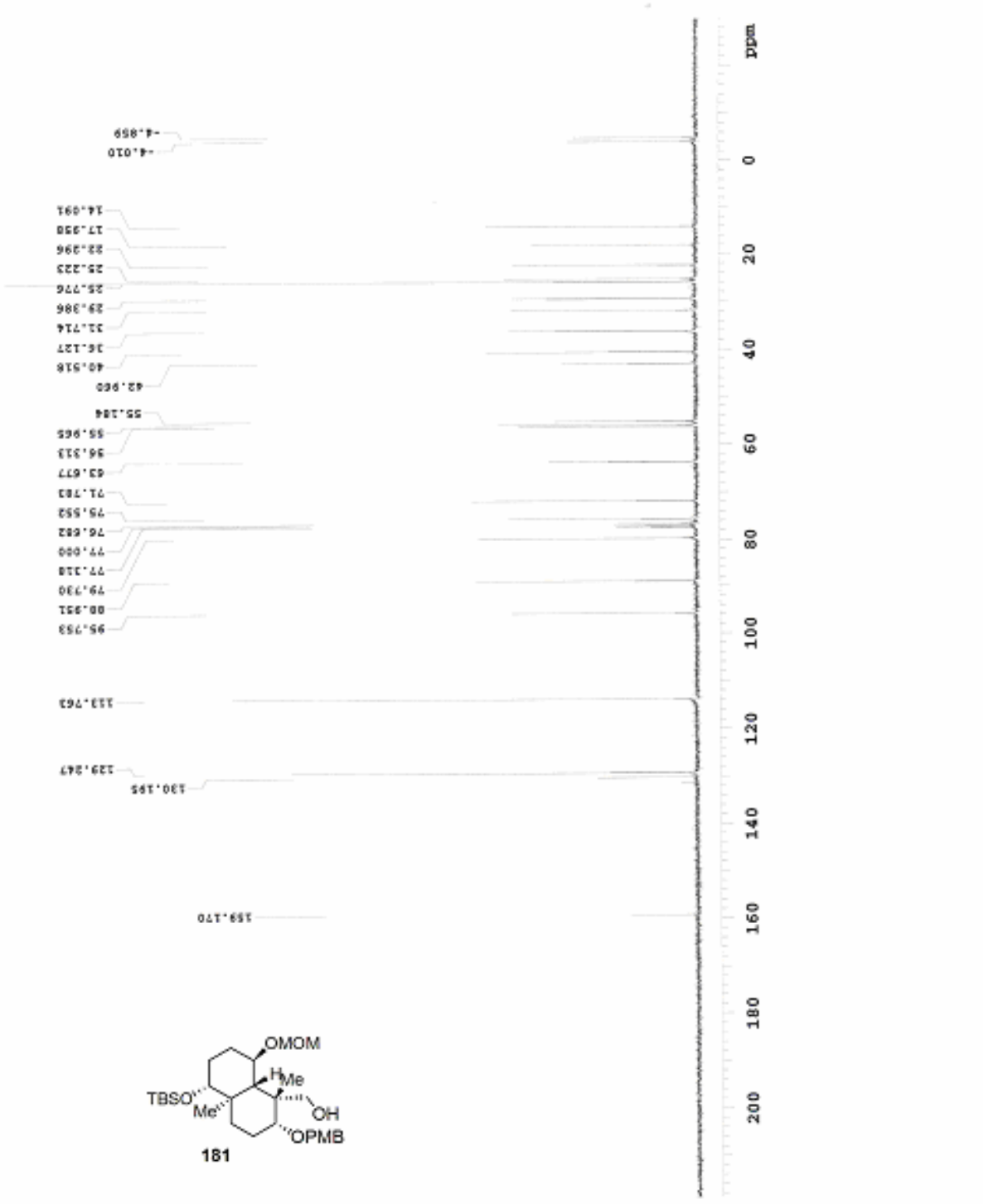
Spectrum 2.67: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **37**



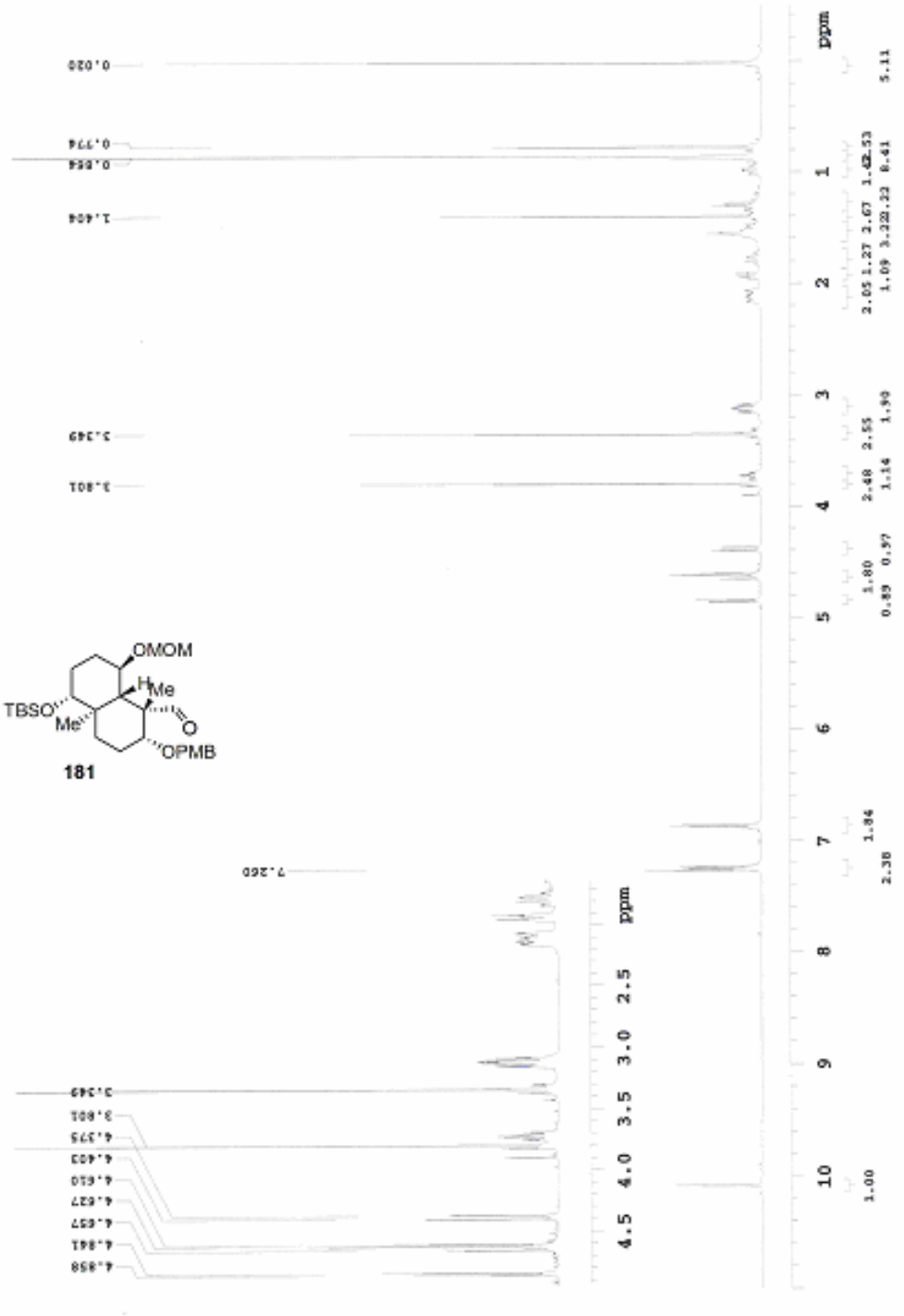
Spectrum 2.68: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **37**



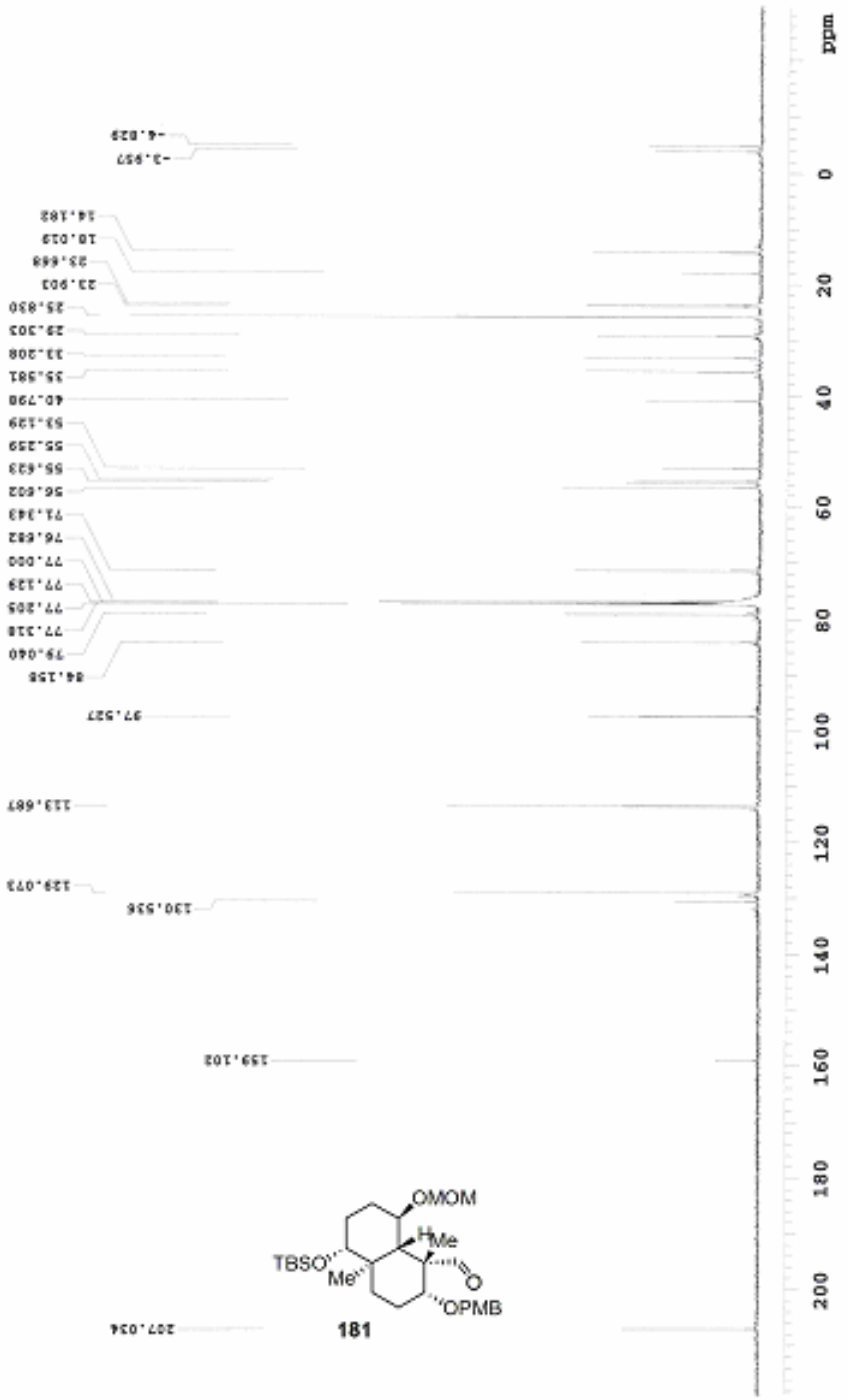
Spectrum 2.69: ^{1}H NMR ($CDCl_3$, 100 MHz) of compound **39**



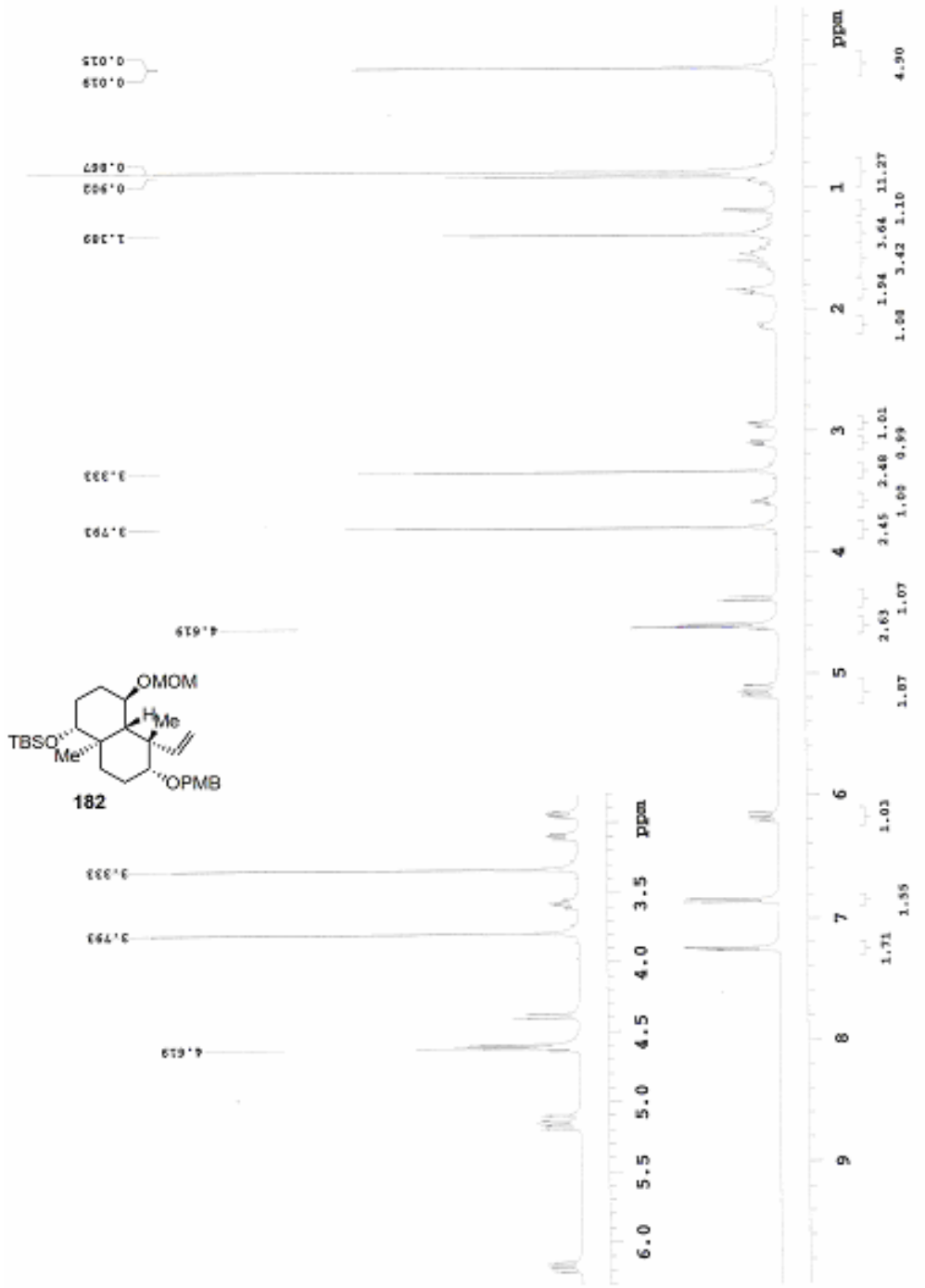
Spectrum 2.70: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **39**



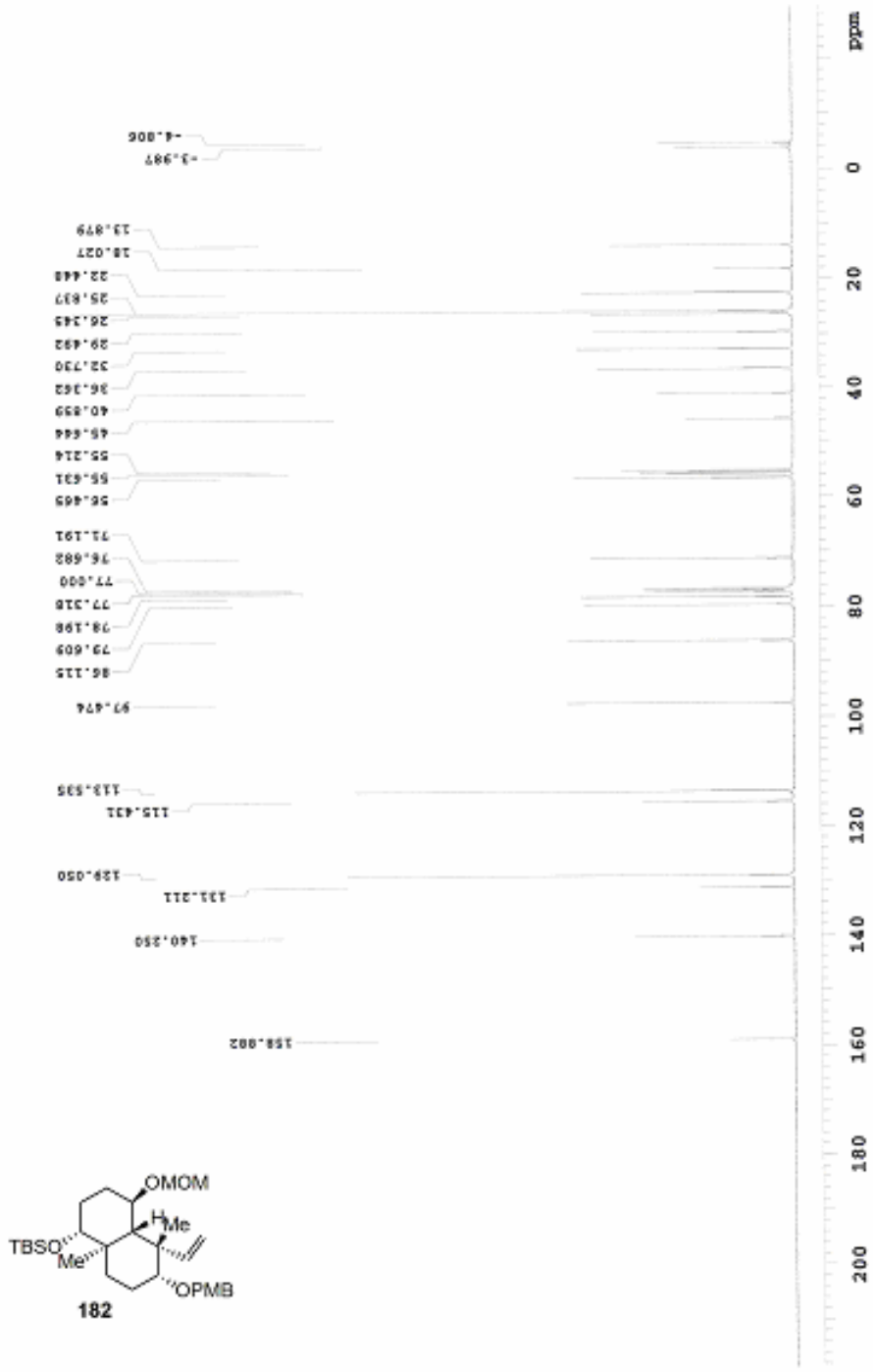
Spectrum 2.71: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **44**



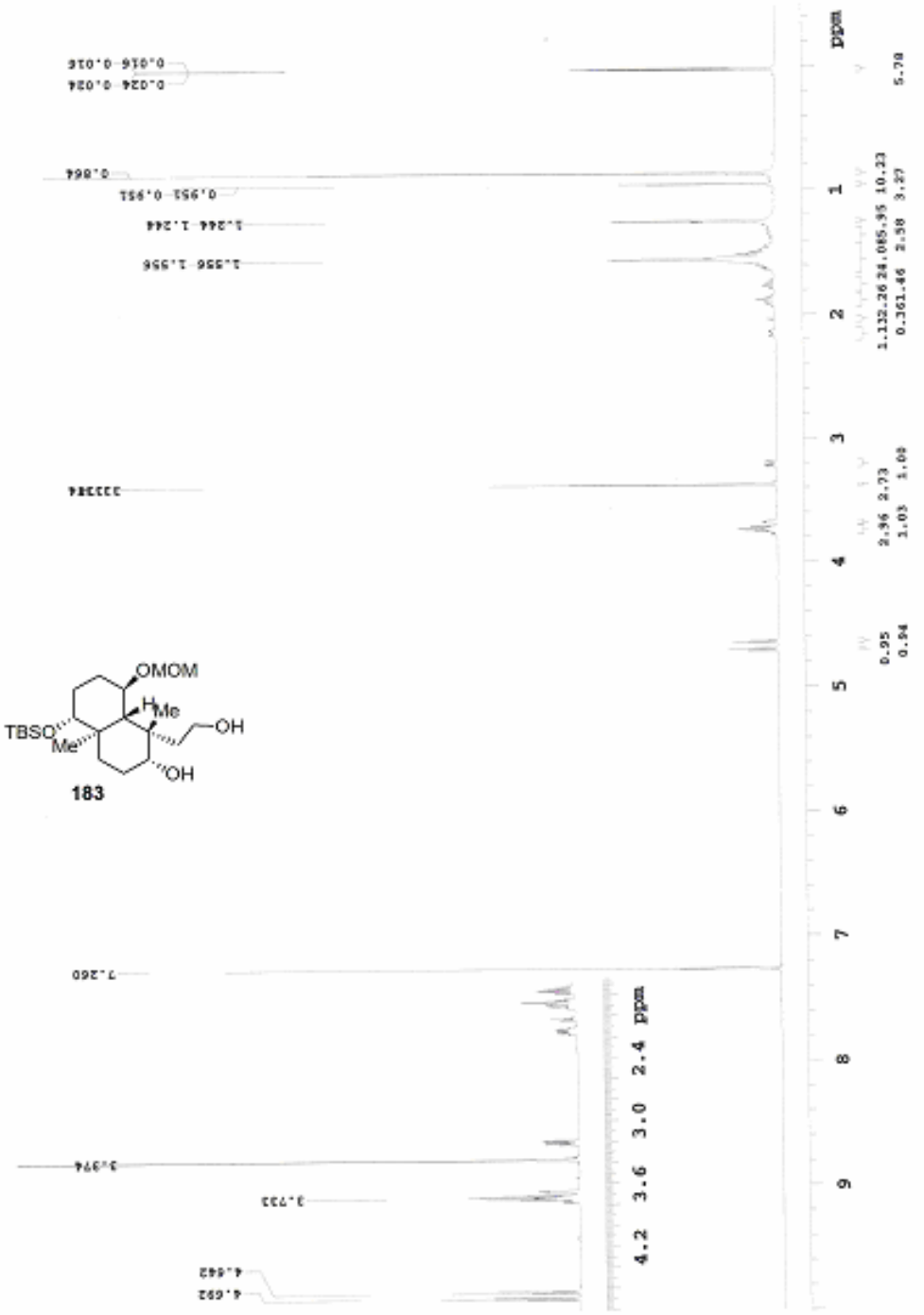
Spectrum 2.72: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **44**



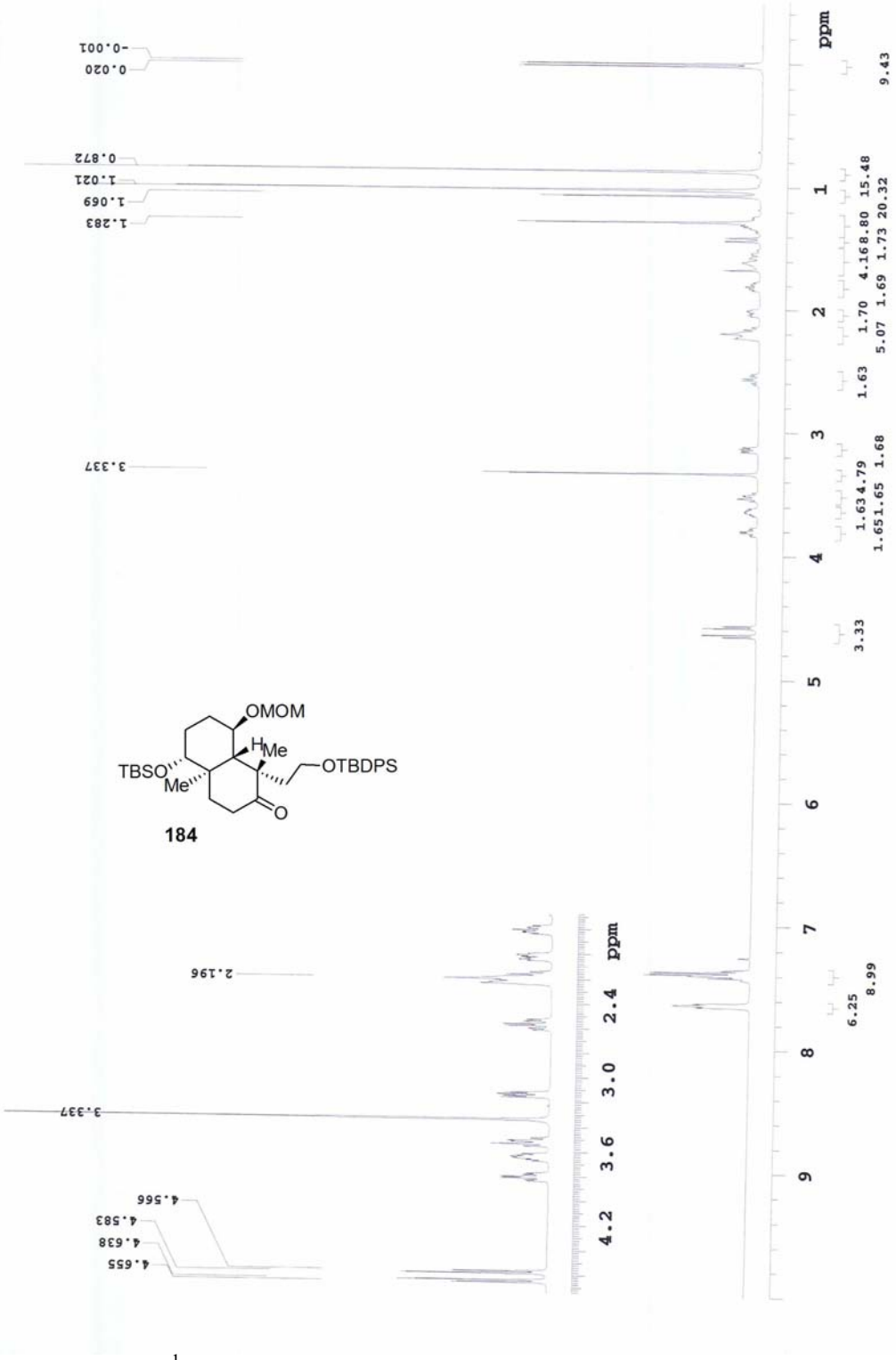
Spectrum 2.73: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **45**



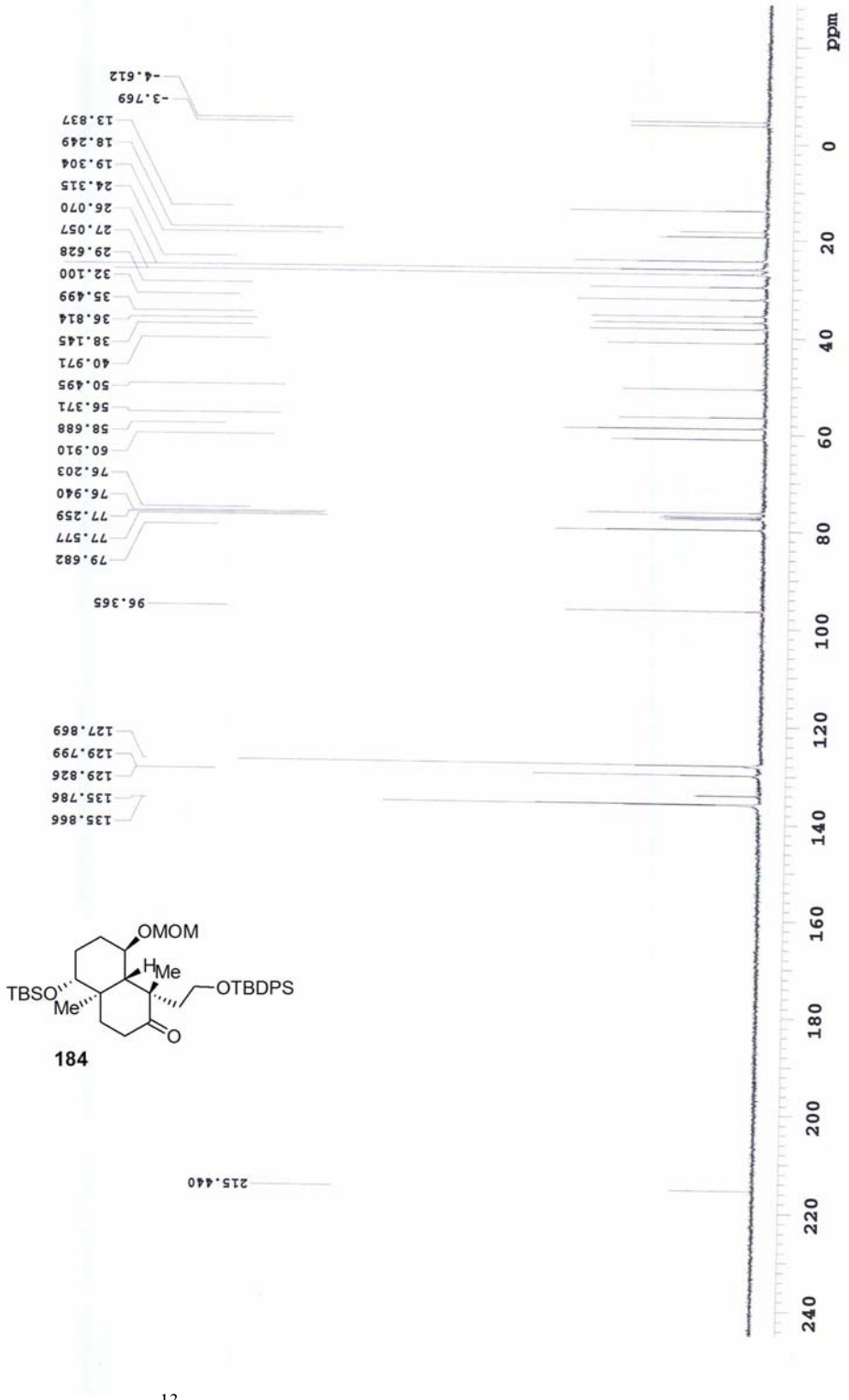
Spectrum 2.74: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **45**



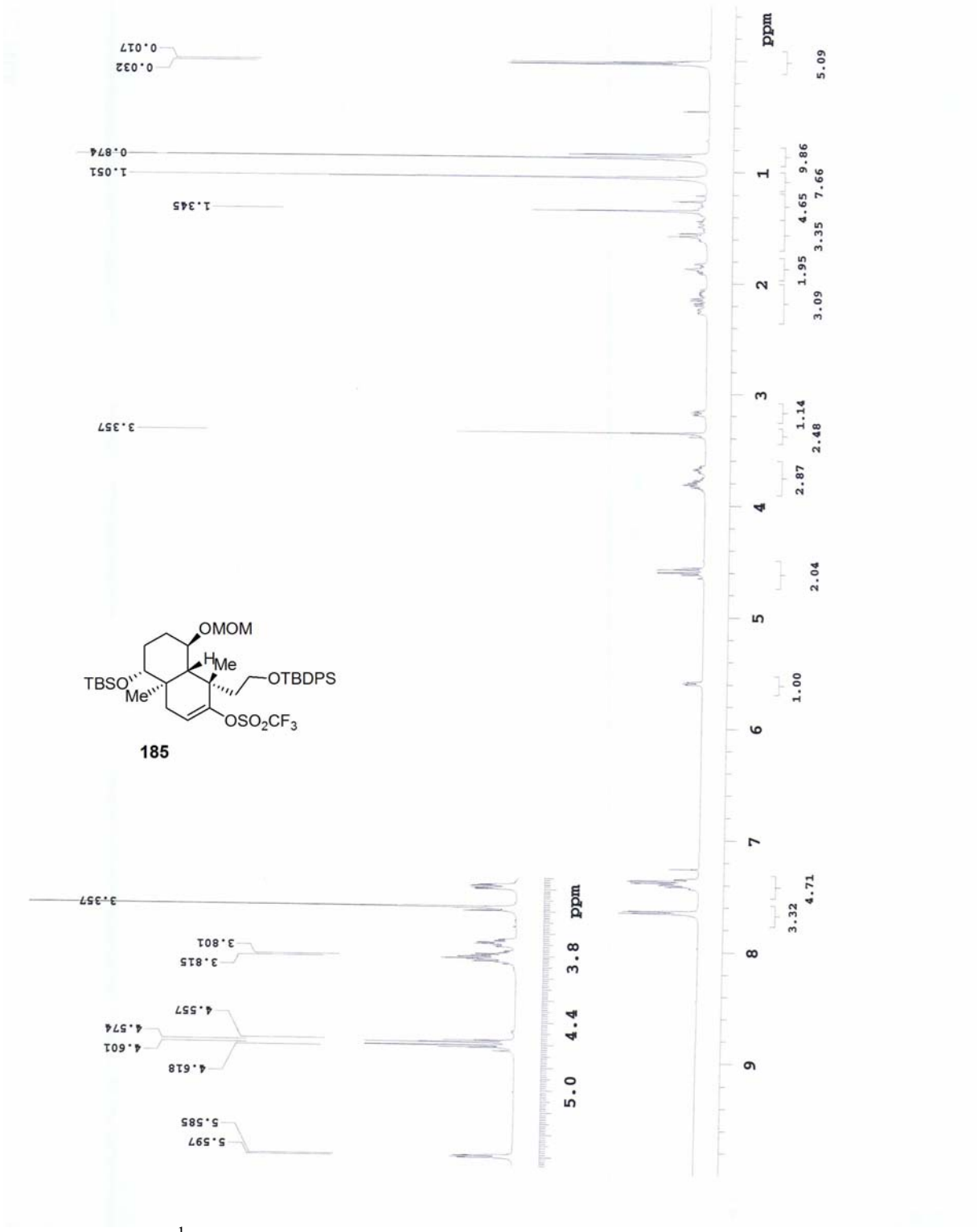
Spectrum 2.75: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **46**



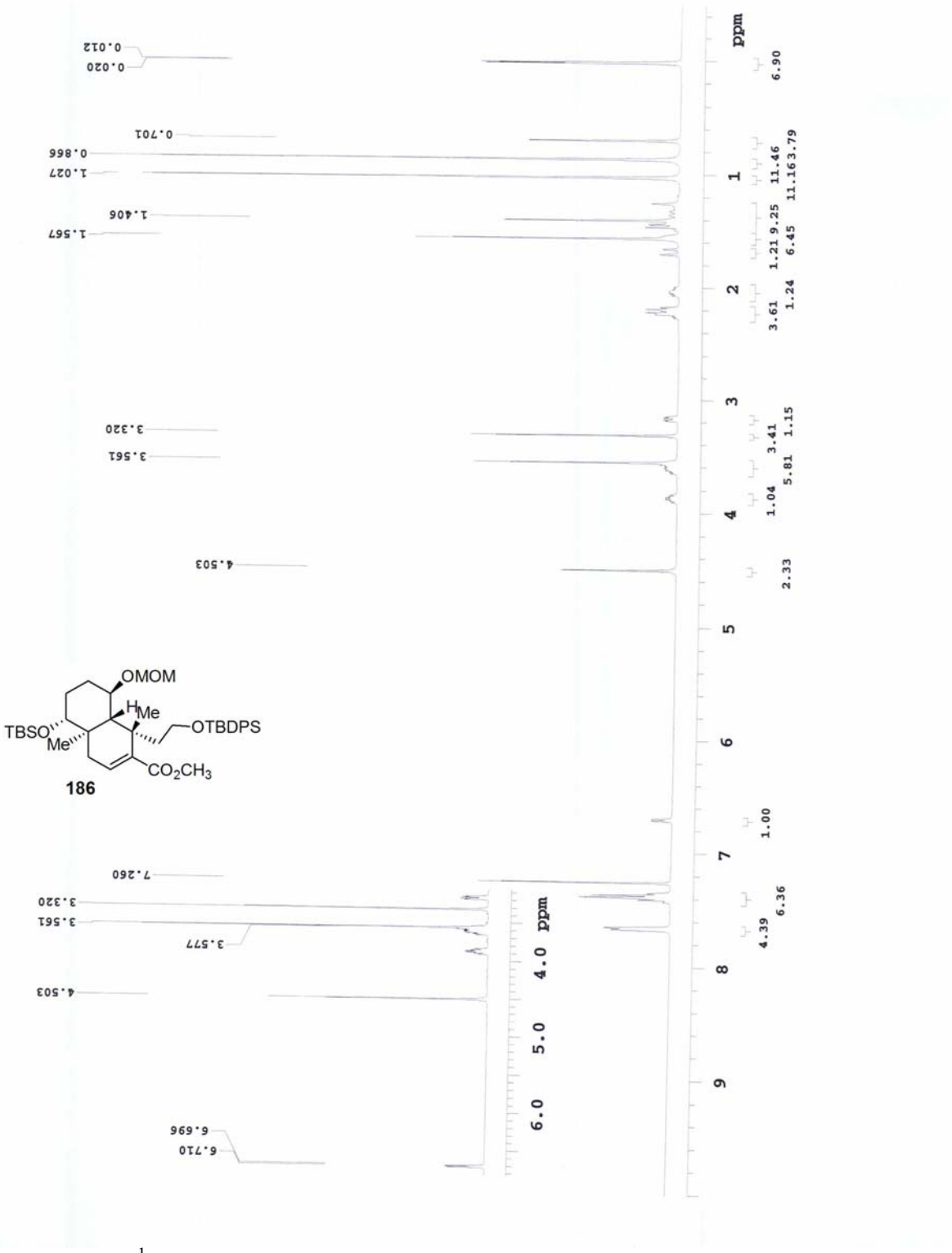
Spectrum 2.76: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **48**



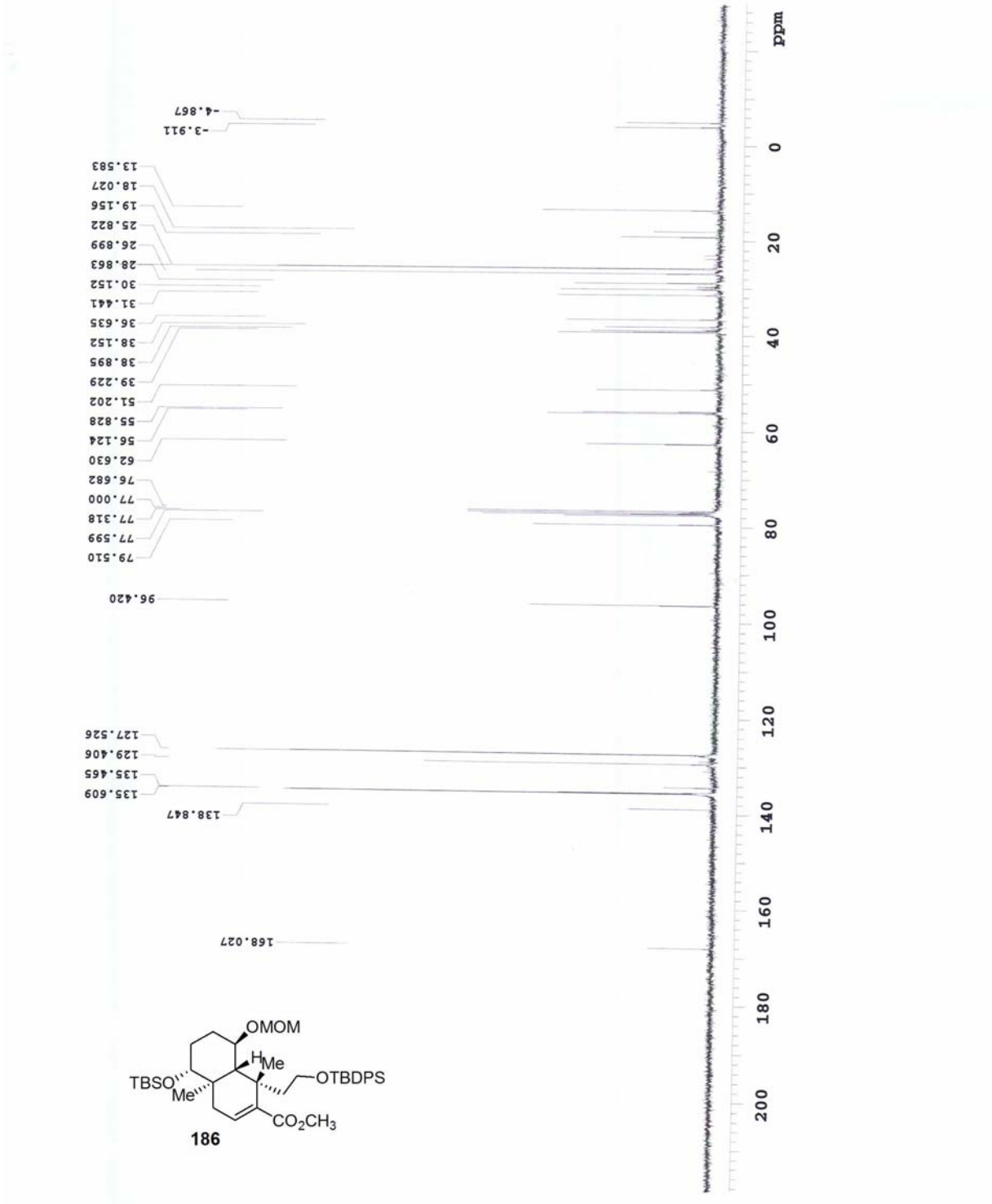
Spectrum 2.77: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **48**



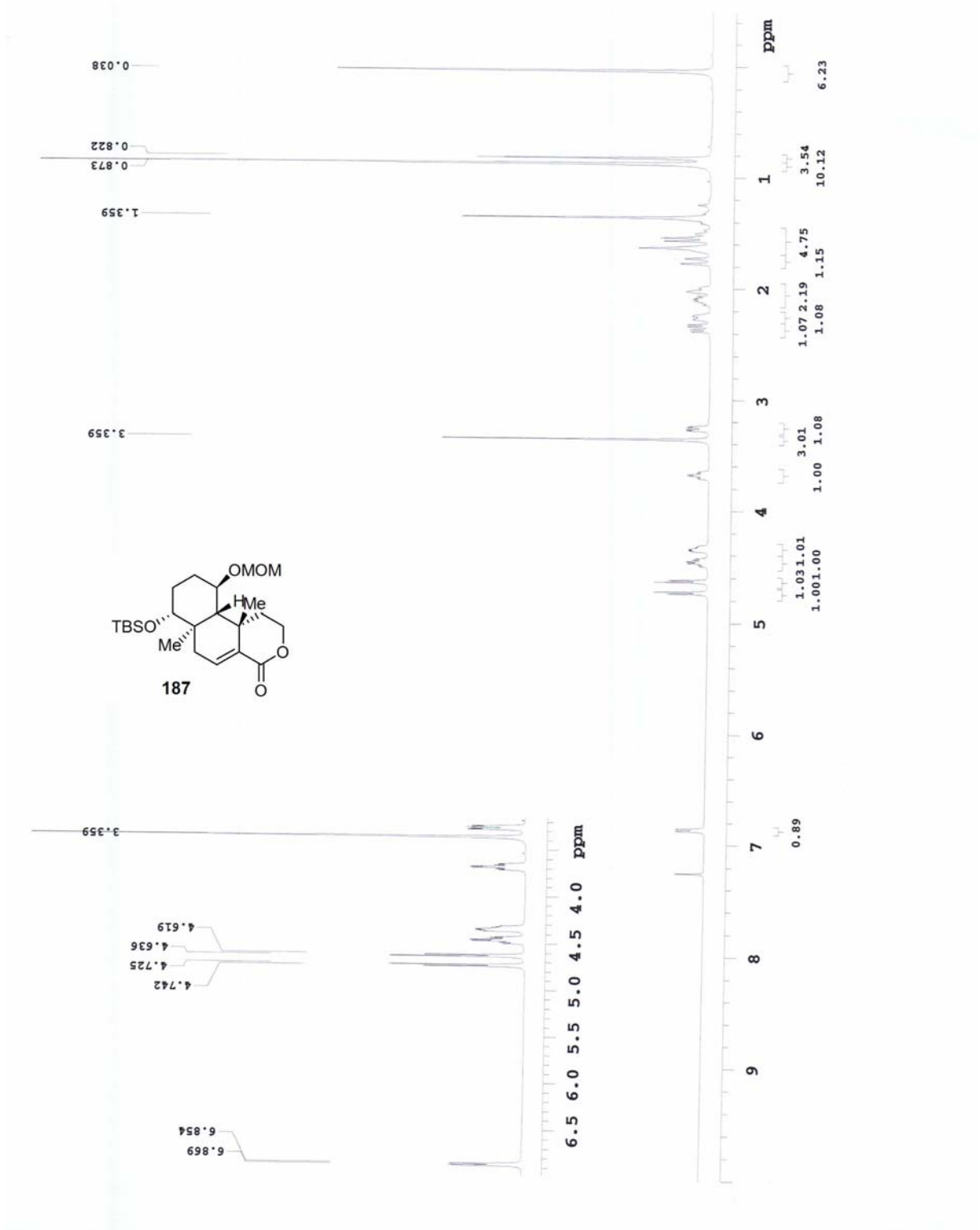
Spectrum 2.78: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **49**



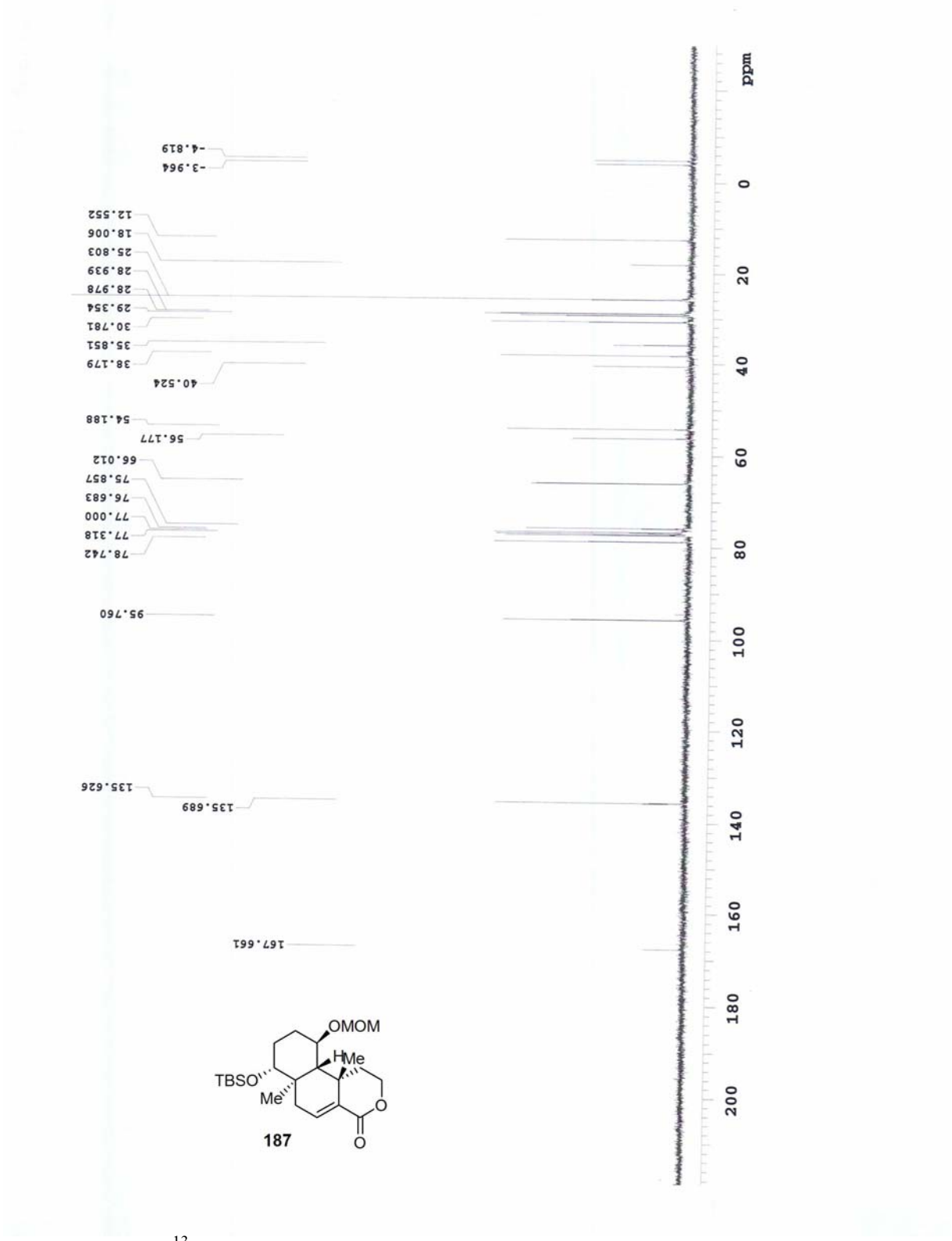
Spectrum 2.79: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **50**



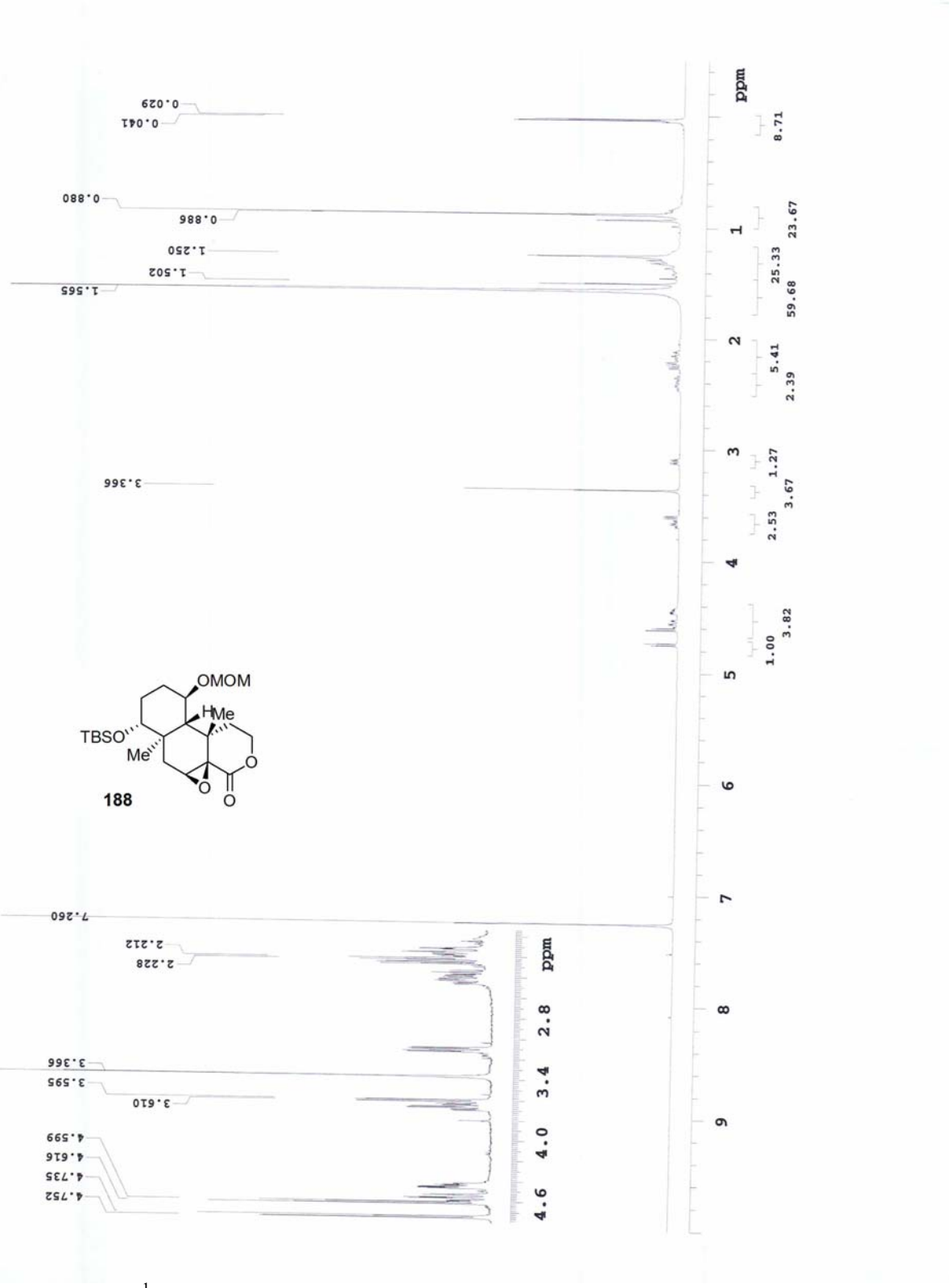
Spectrum 2.80: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **50**



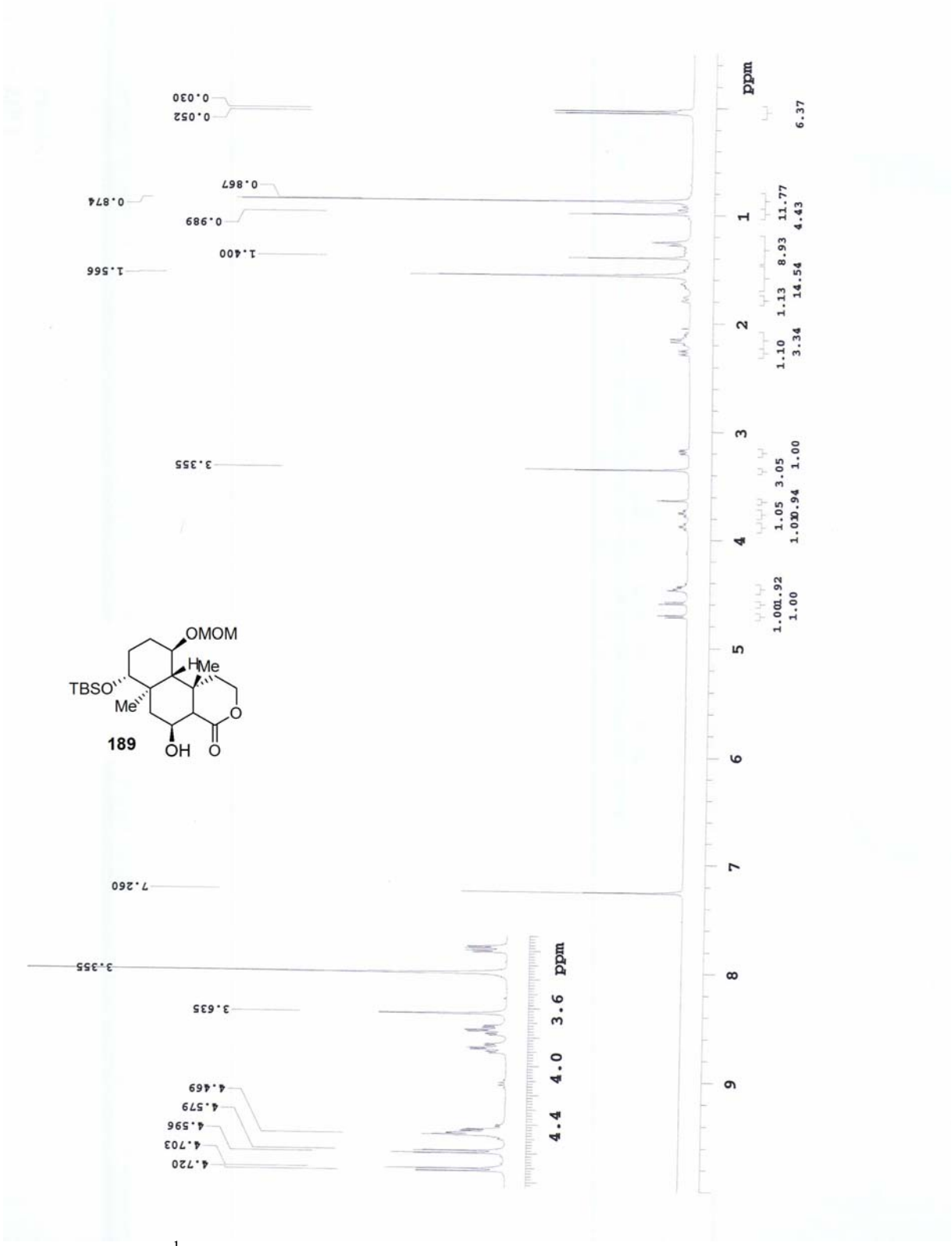
Spectrum 2.81: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **51**



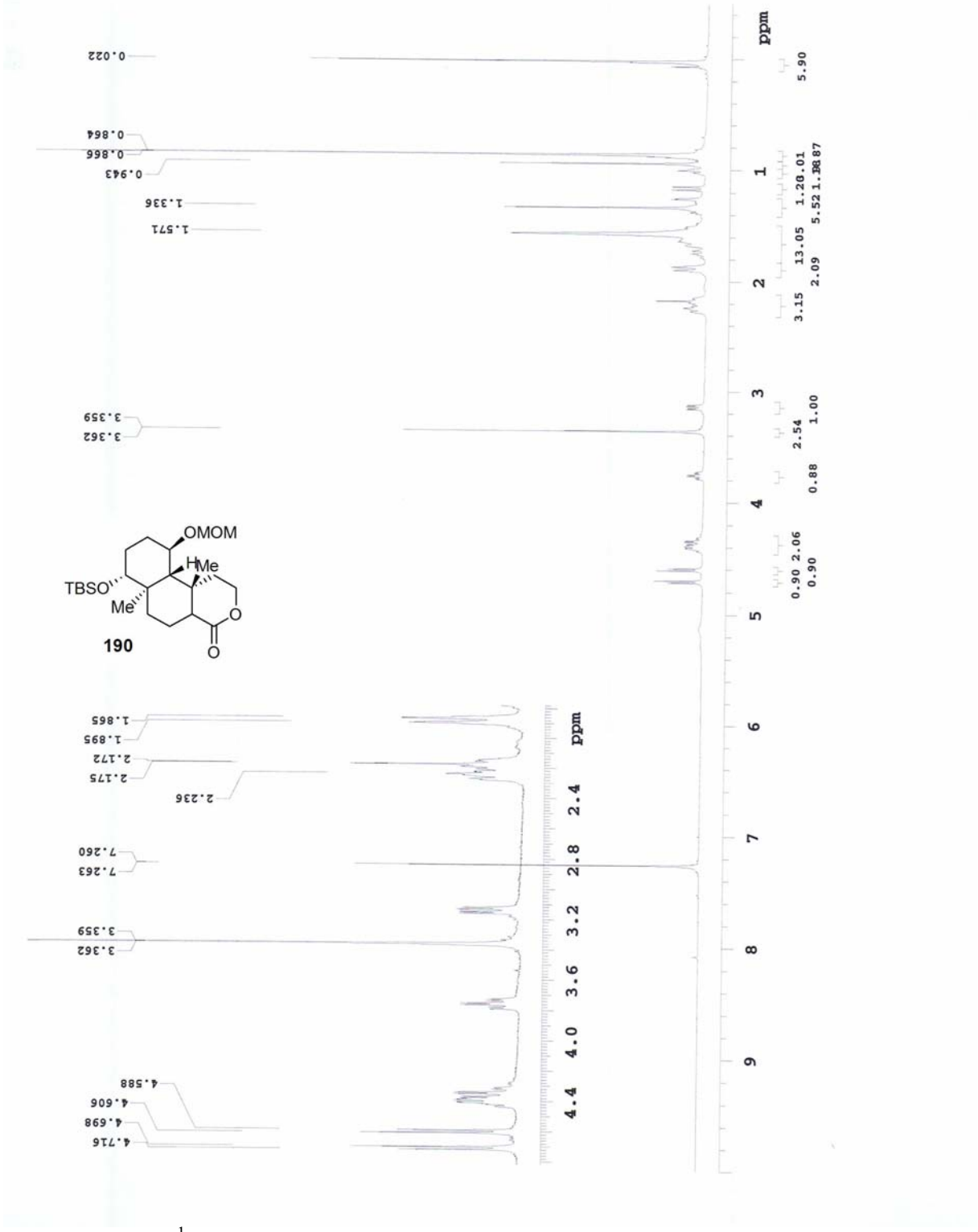
Spectrum 2.82: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **51**



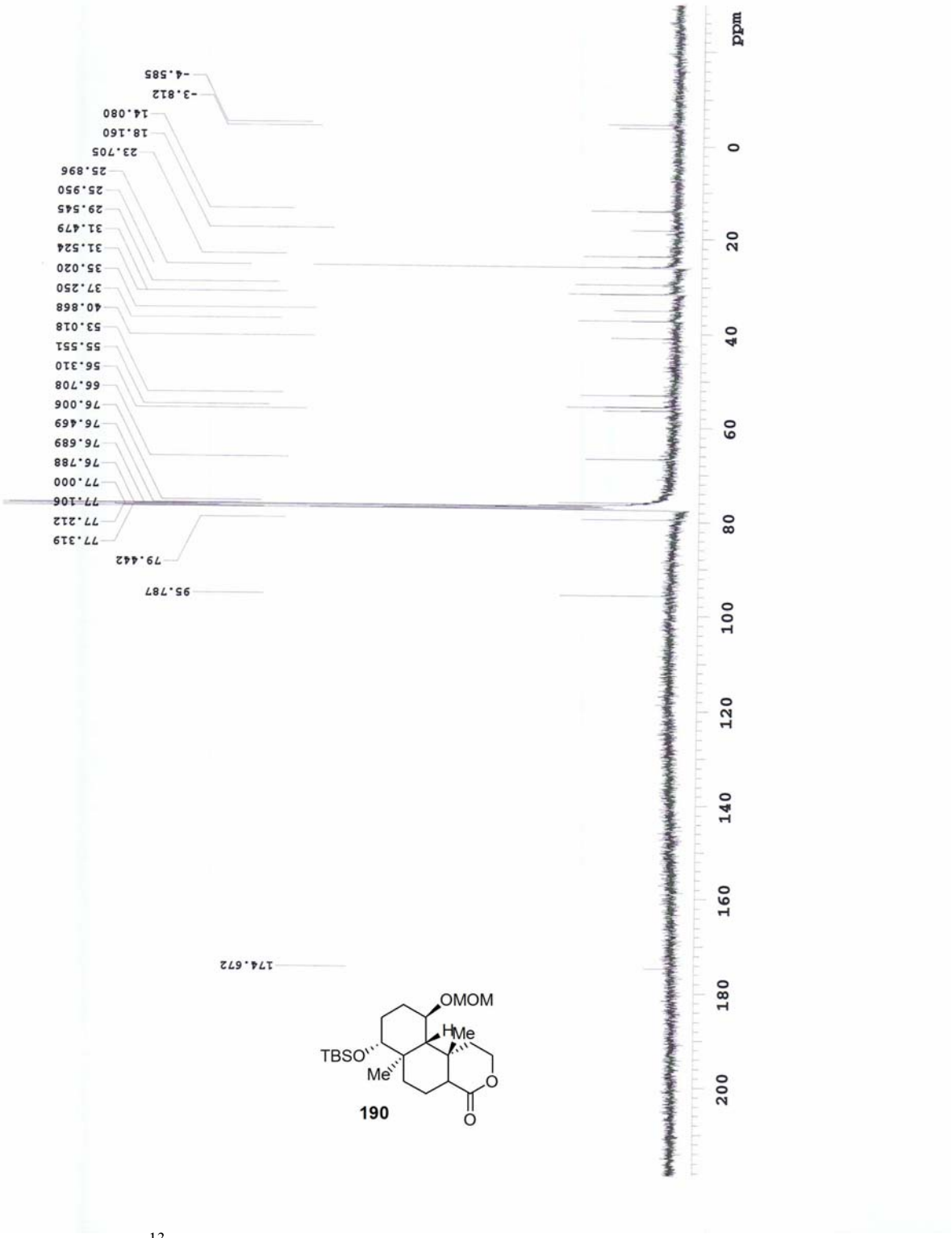
Spectrum2.83: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **53**



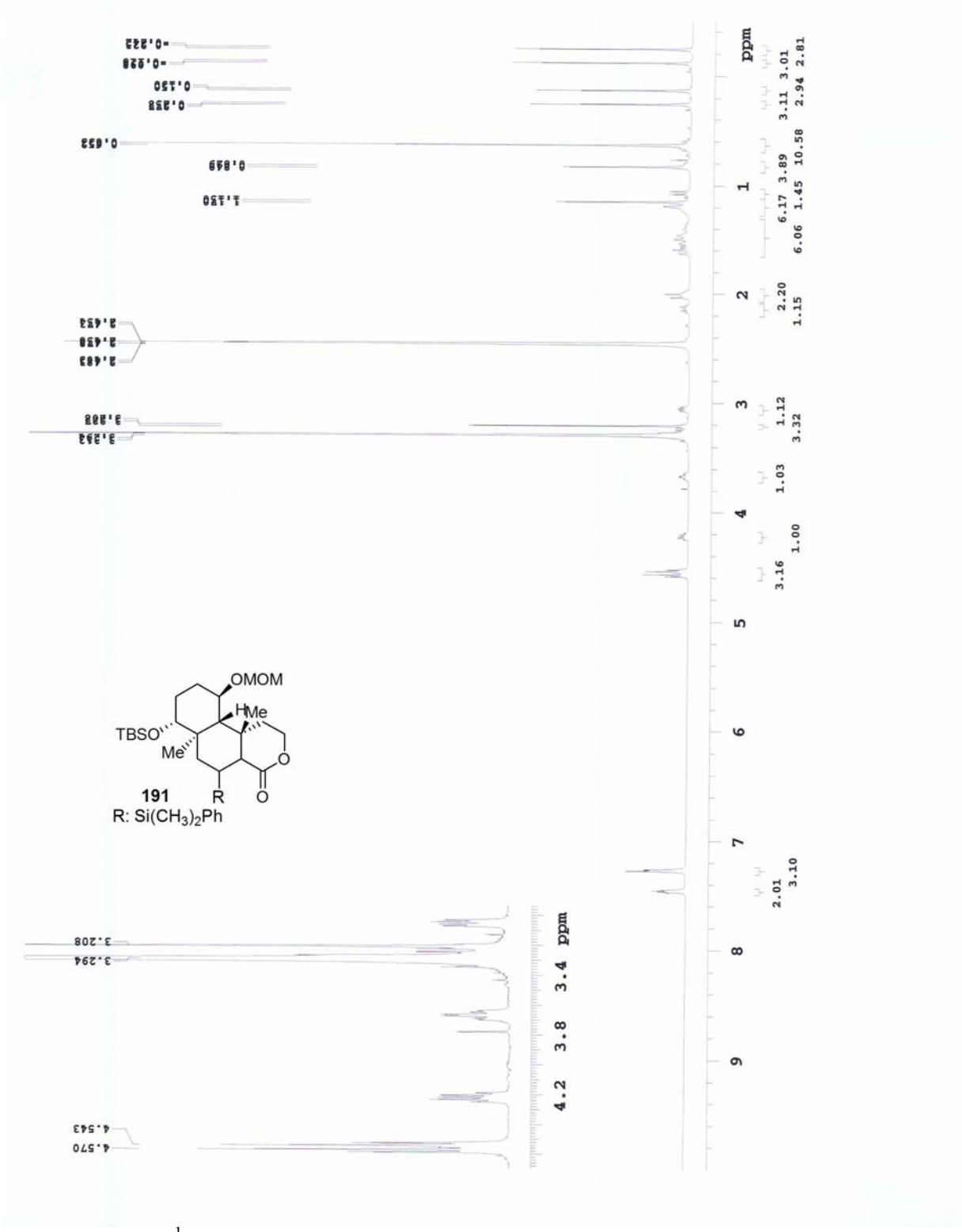
Spectrum 2.84: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **53-1**



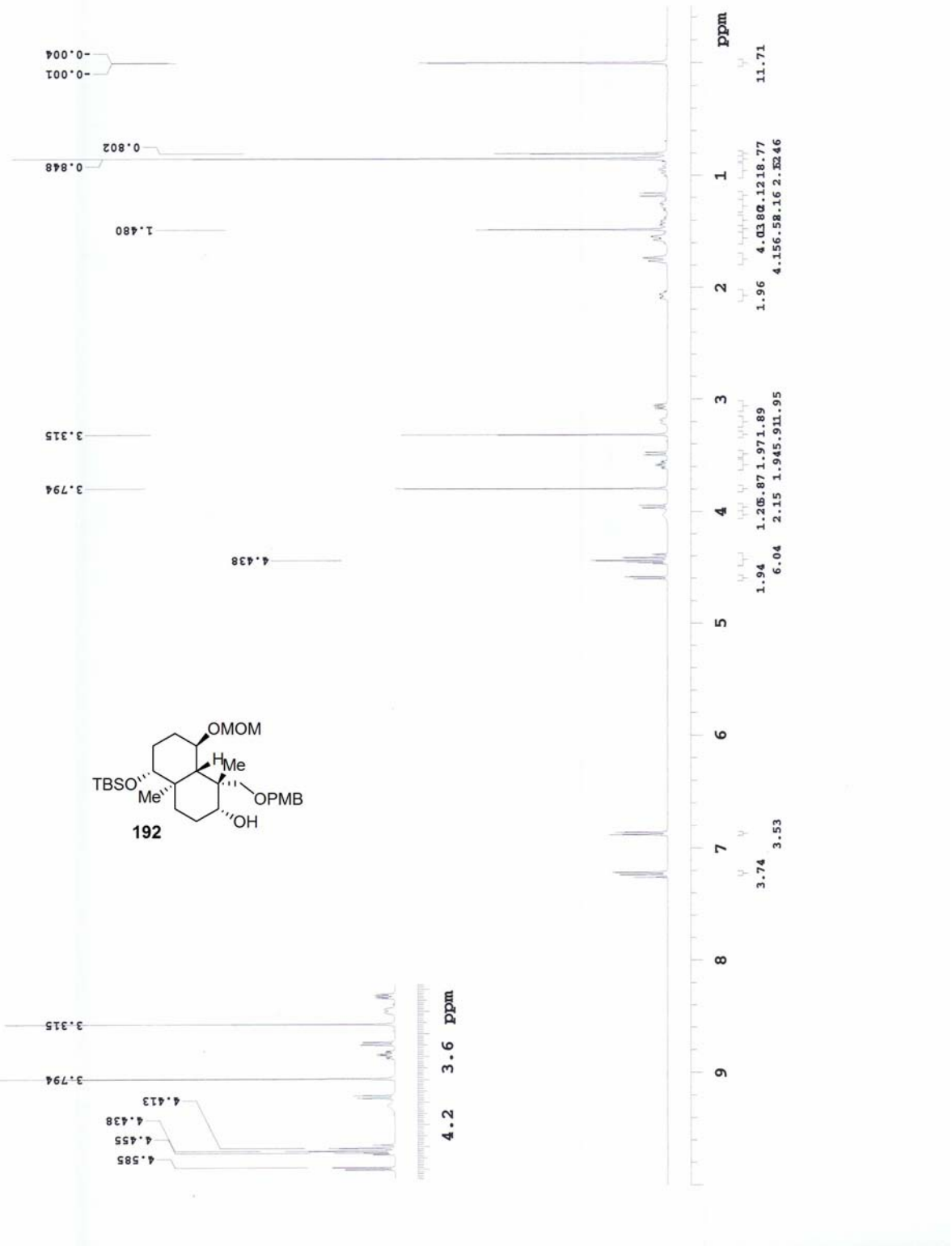
Spectrum 2.85: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **54**



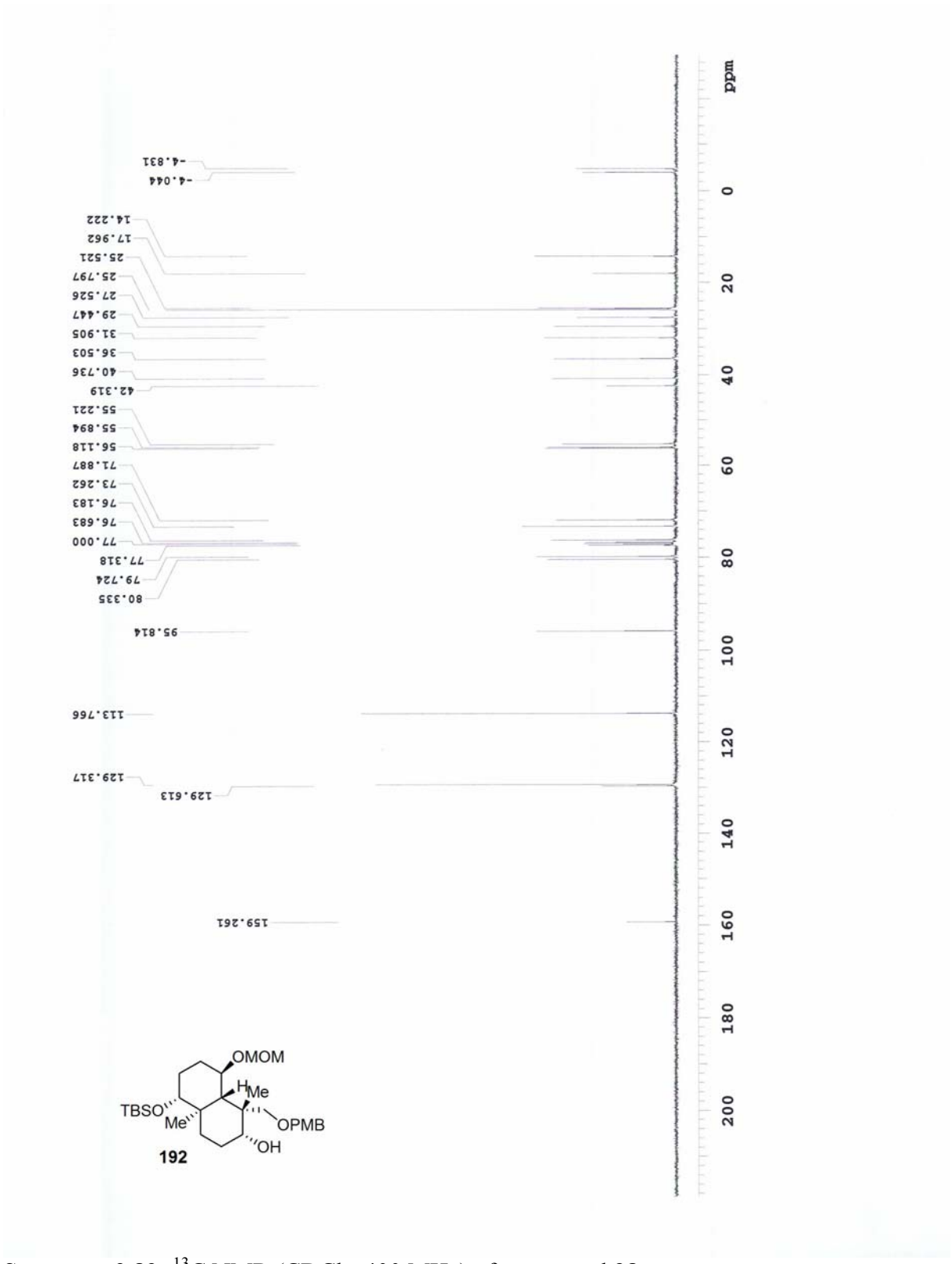
Spectrum 2.86: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **54**



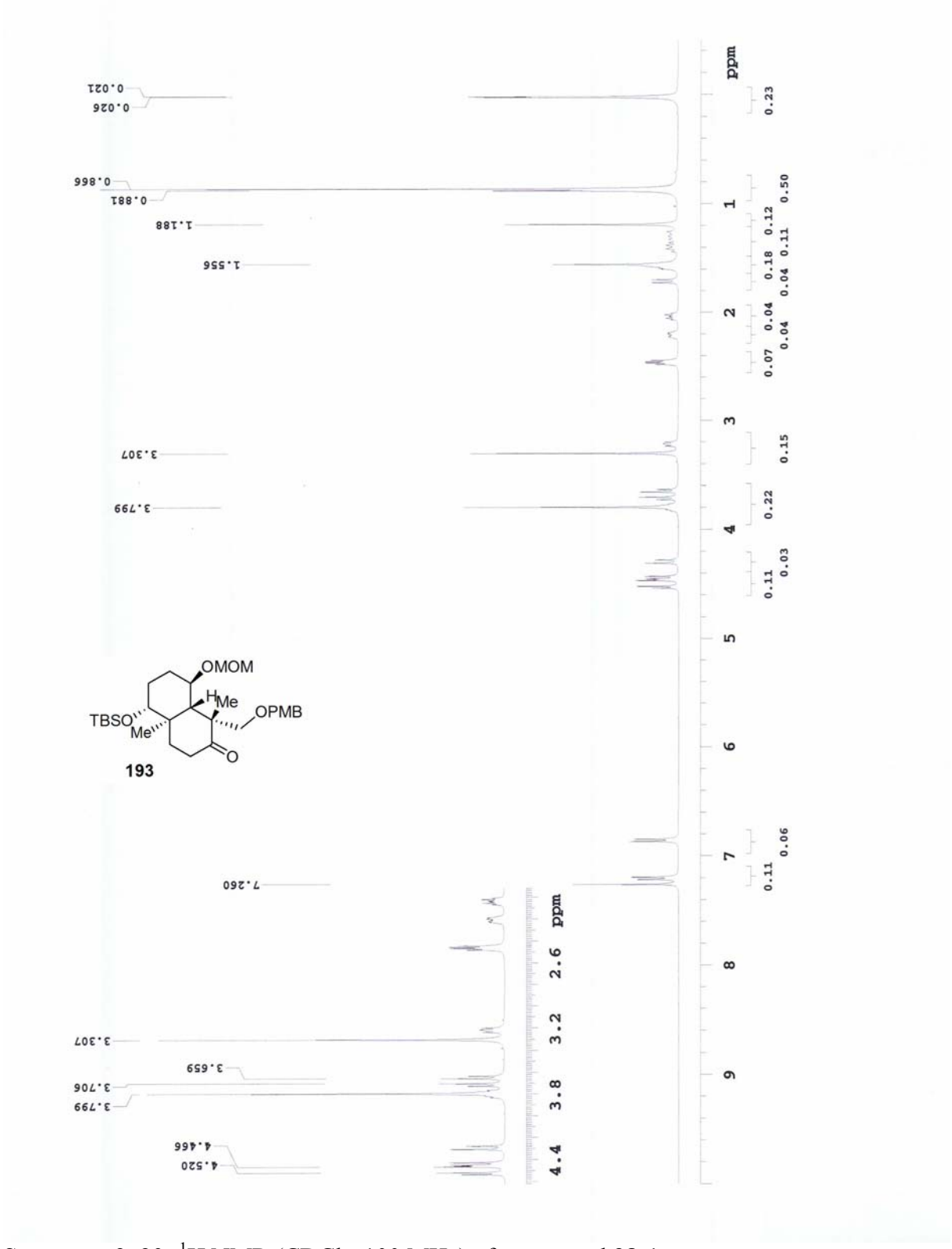
Spectrum 2.87: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **52**



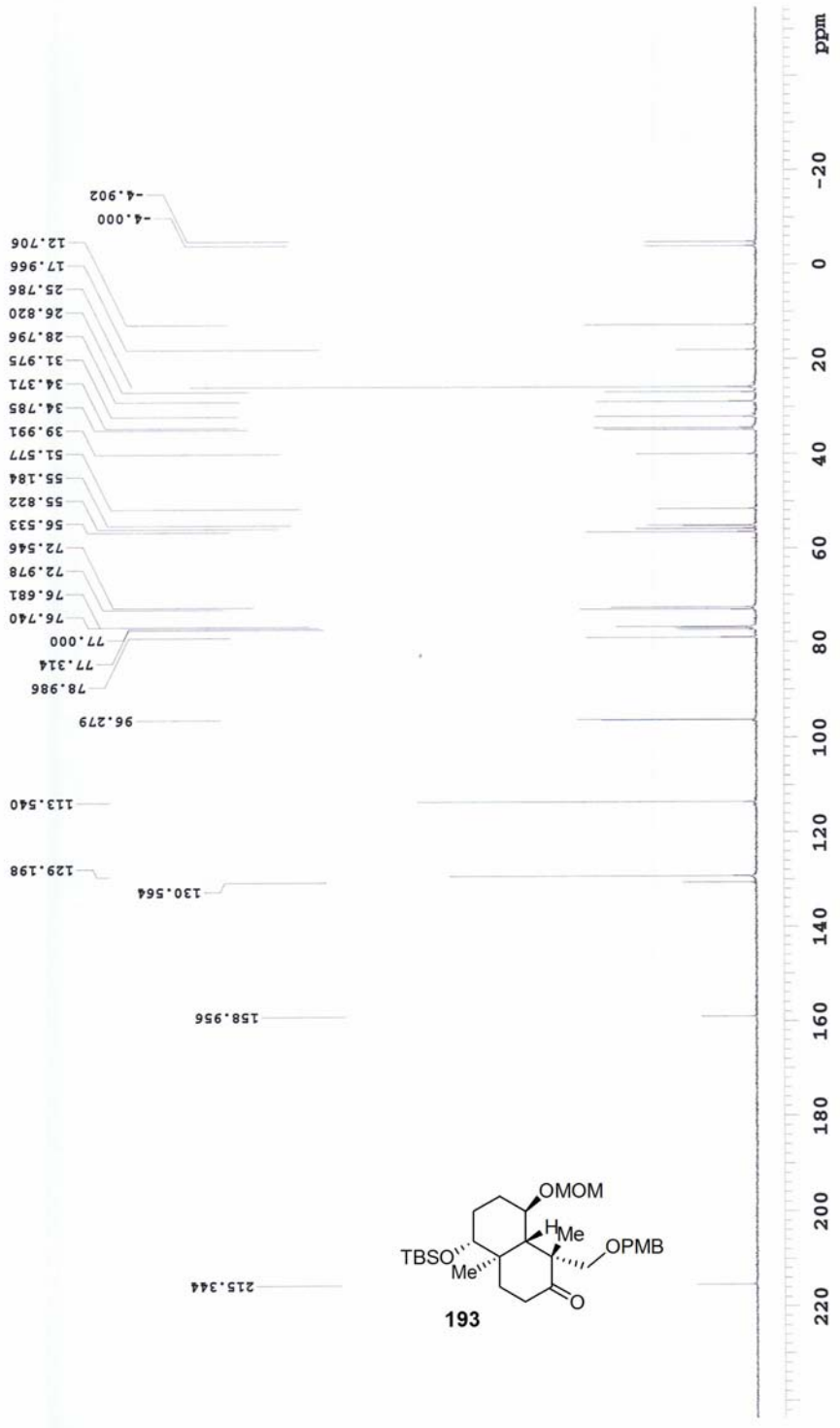
Spectrum 2.88: ^{1}H NMR ($CDCl_3$, 100 MHz) of compound **38**



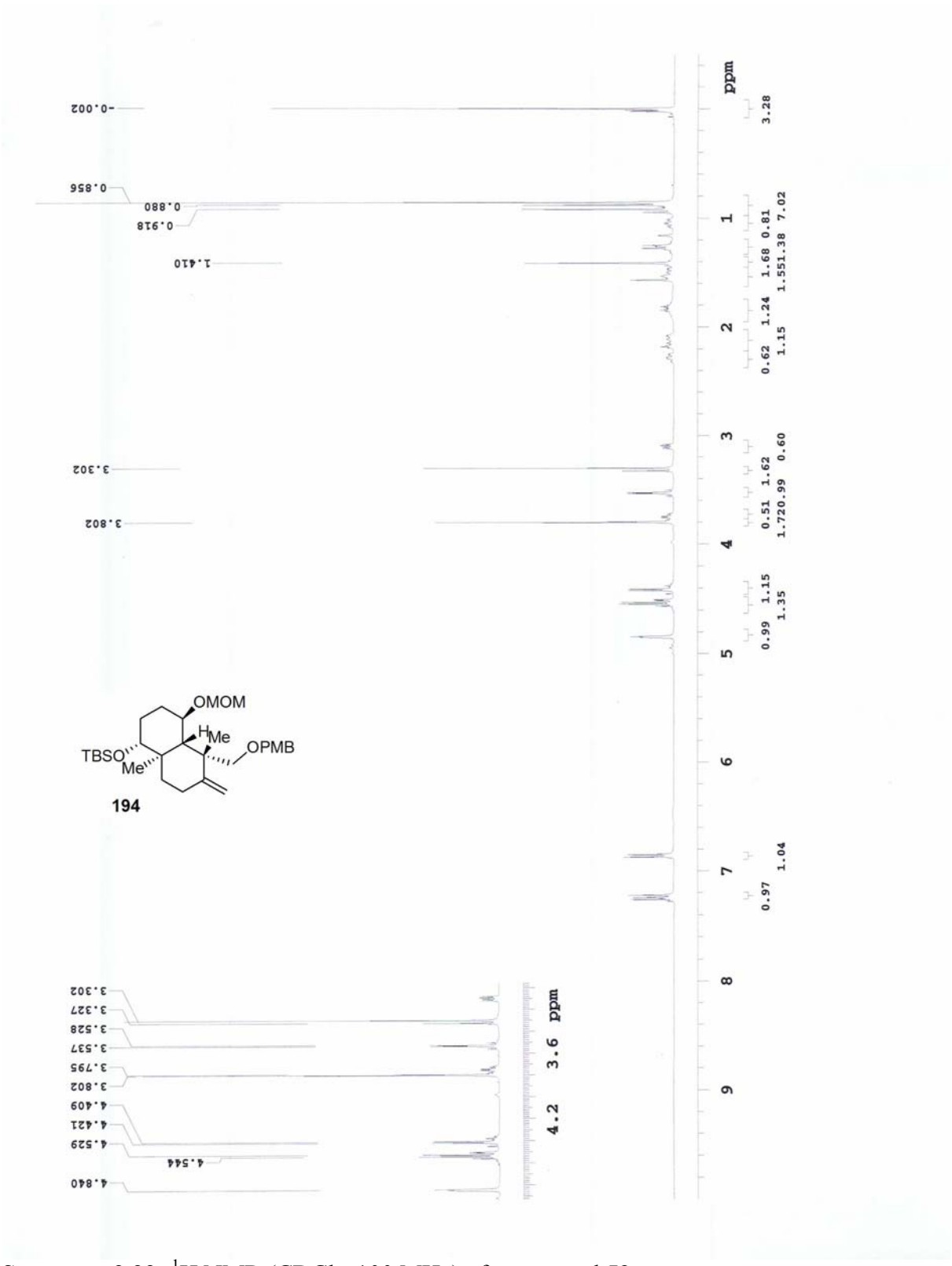
Spectrum 2.89: ^{13}C NMR ($CDCl_3$, 400 MHz) of compound **38**



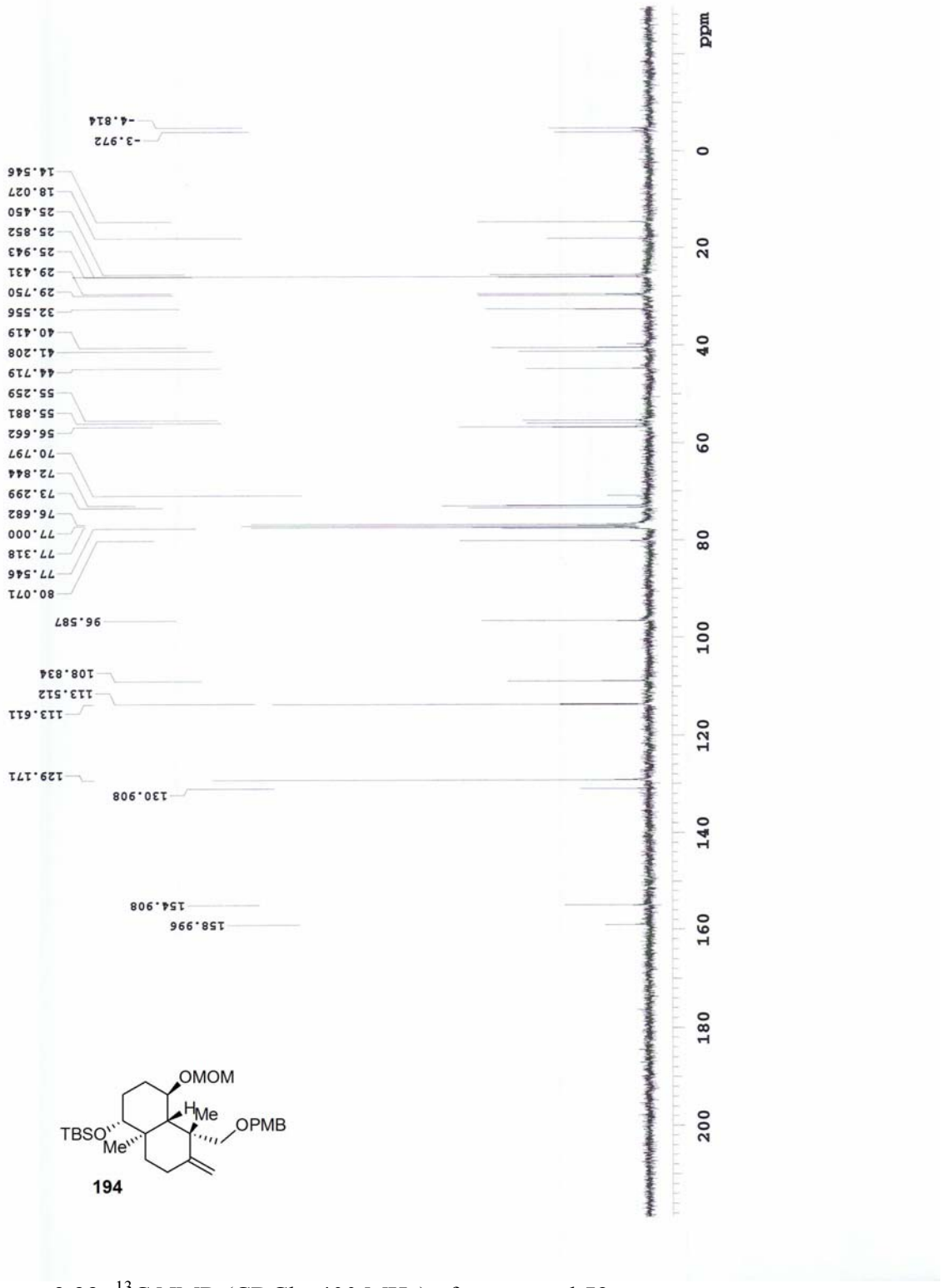
Spectrum 2. 90: ^{1}H NMR ($CDCl_3$, 100 MHz) of compound **38-1**



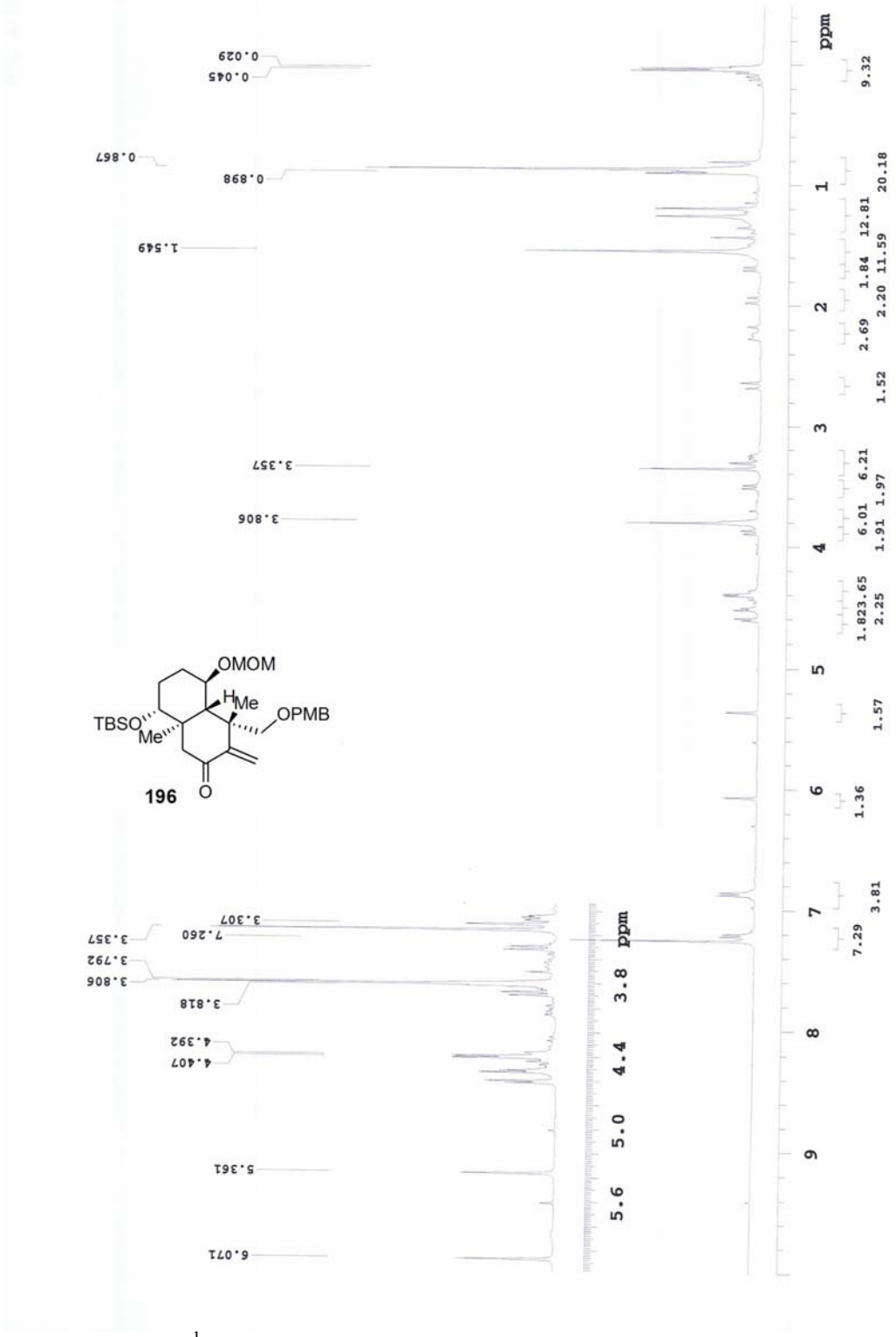
Spectrum 2.91: ^{13}C NMR ($CDCl_3$, 400 MHz) of compound **38-1**



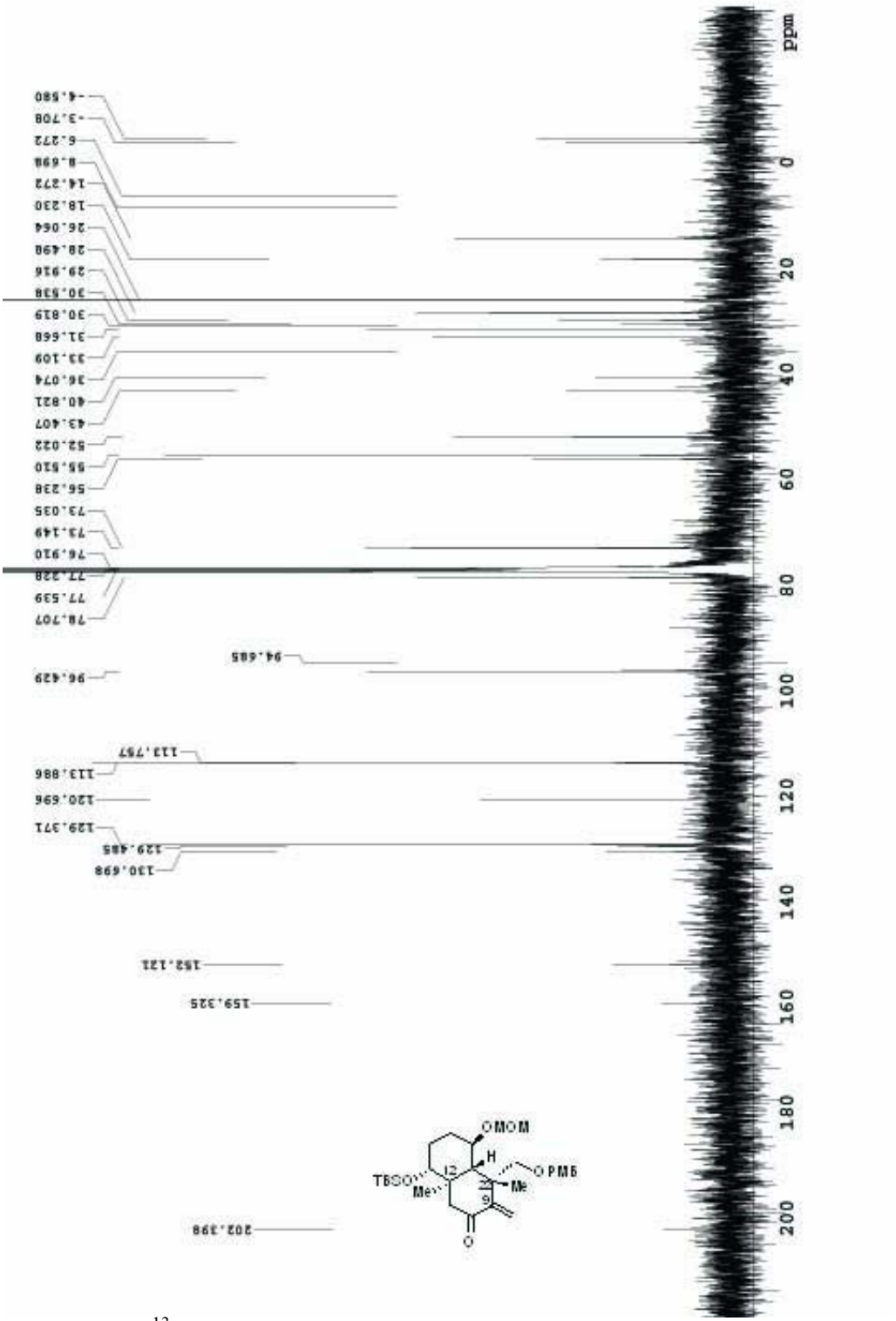
Spectrum 2.92: ^{1}H NMR ($CDCl_3$, 100 MHz) of compound **59**



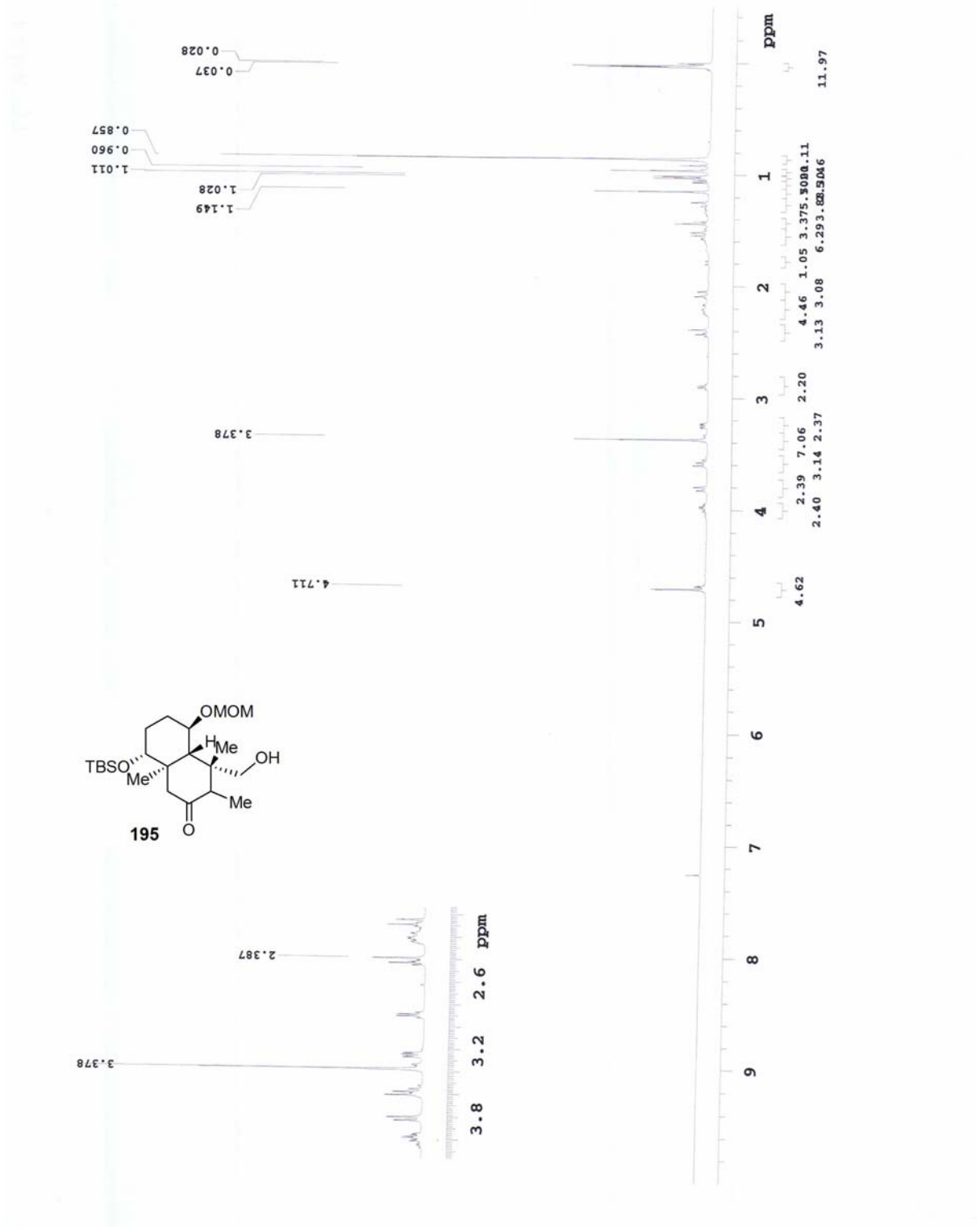
Spectrum 2.93: ^{13}C NMR ($CDCl_3$, 400 MHz) of compound **59**



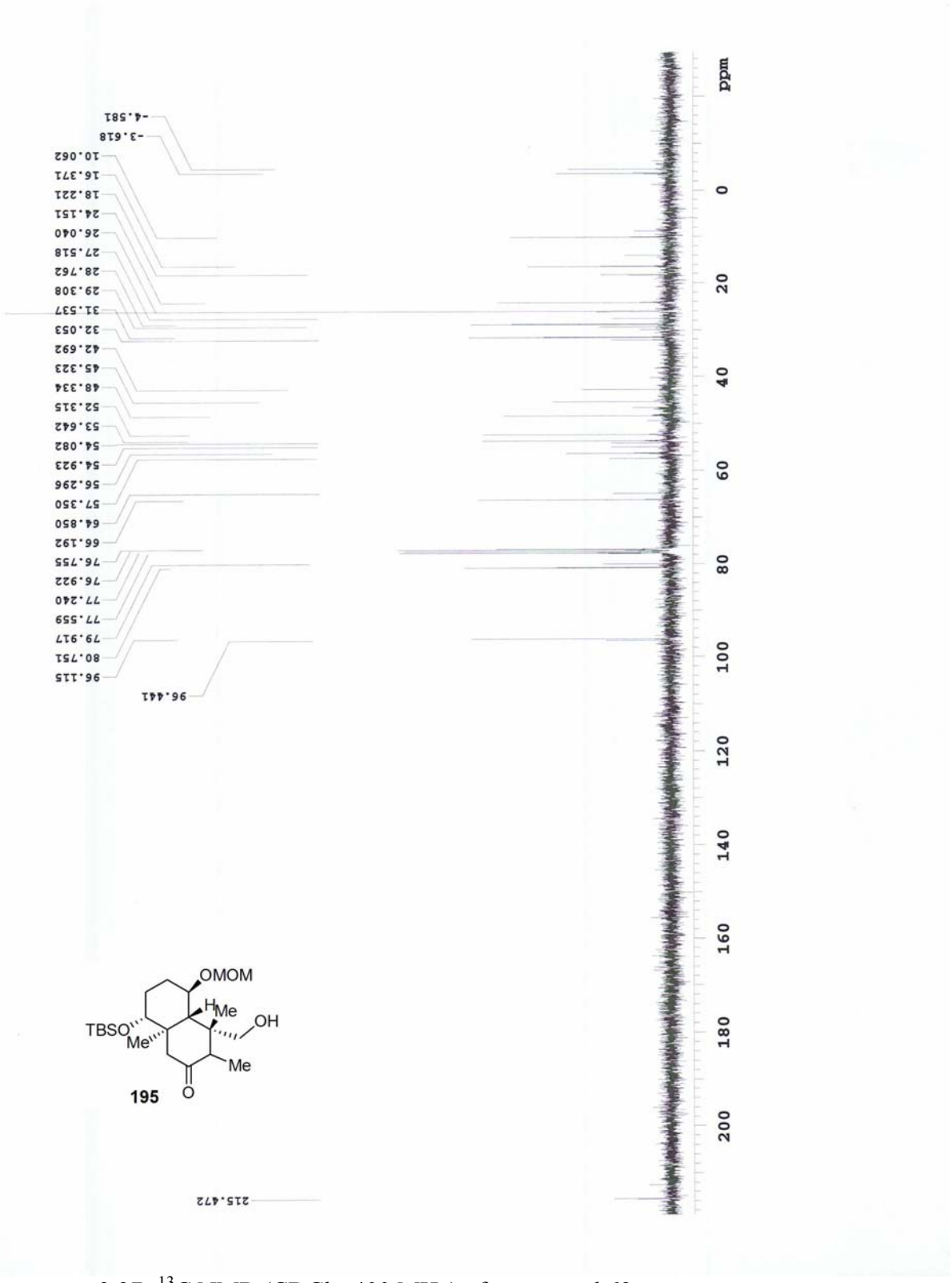
Spectrum 2.94: ^{1}H NMR ($CDCl_3$, 100 MHz) of compound **60**



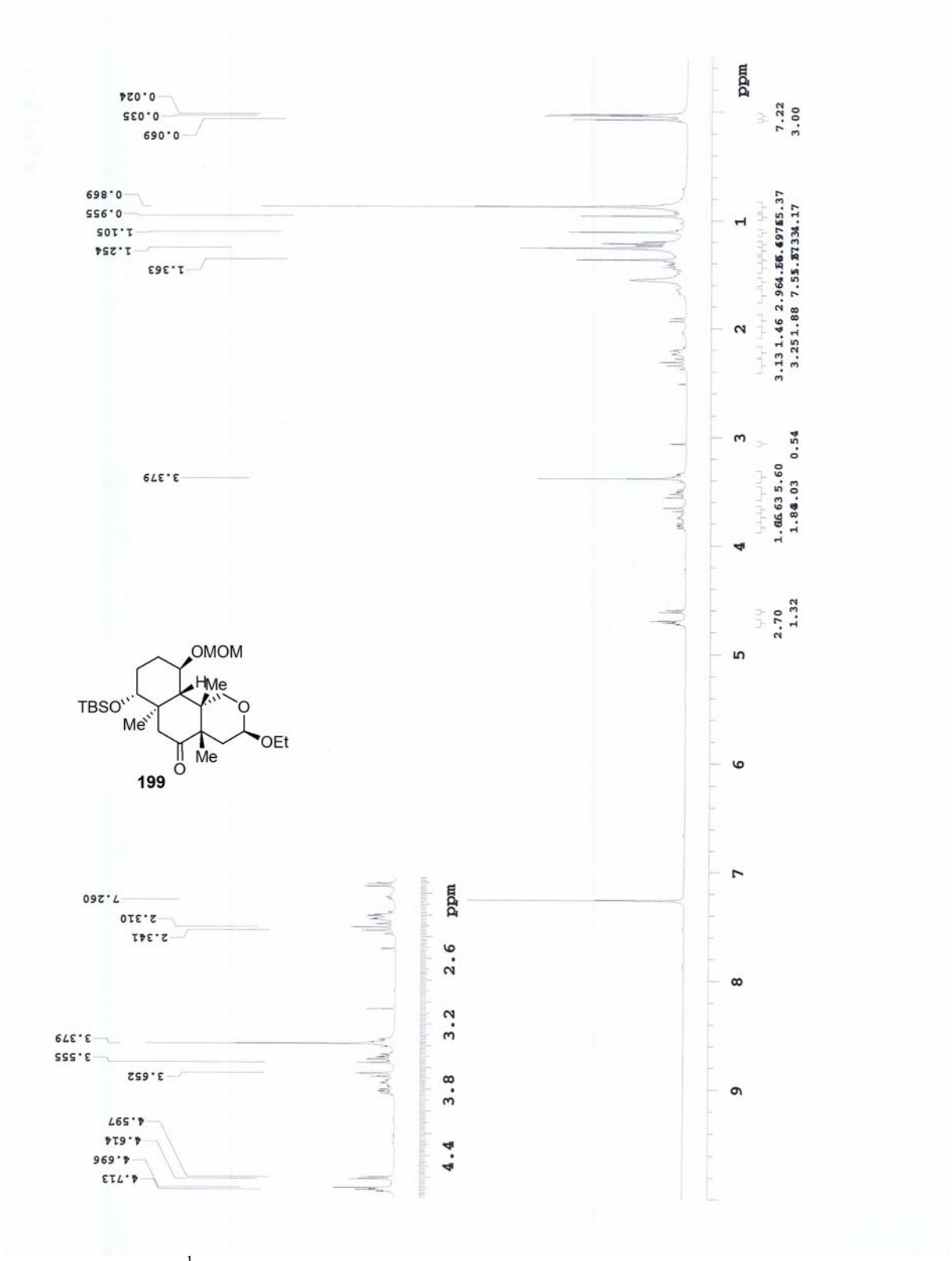
Spectrum 2.95: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **60**



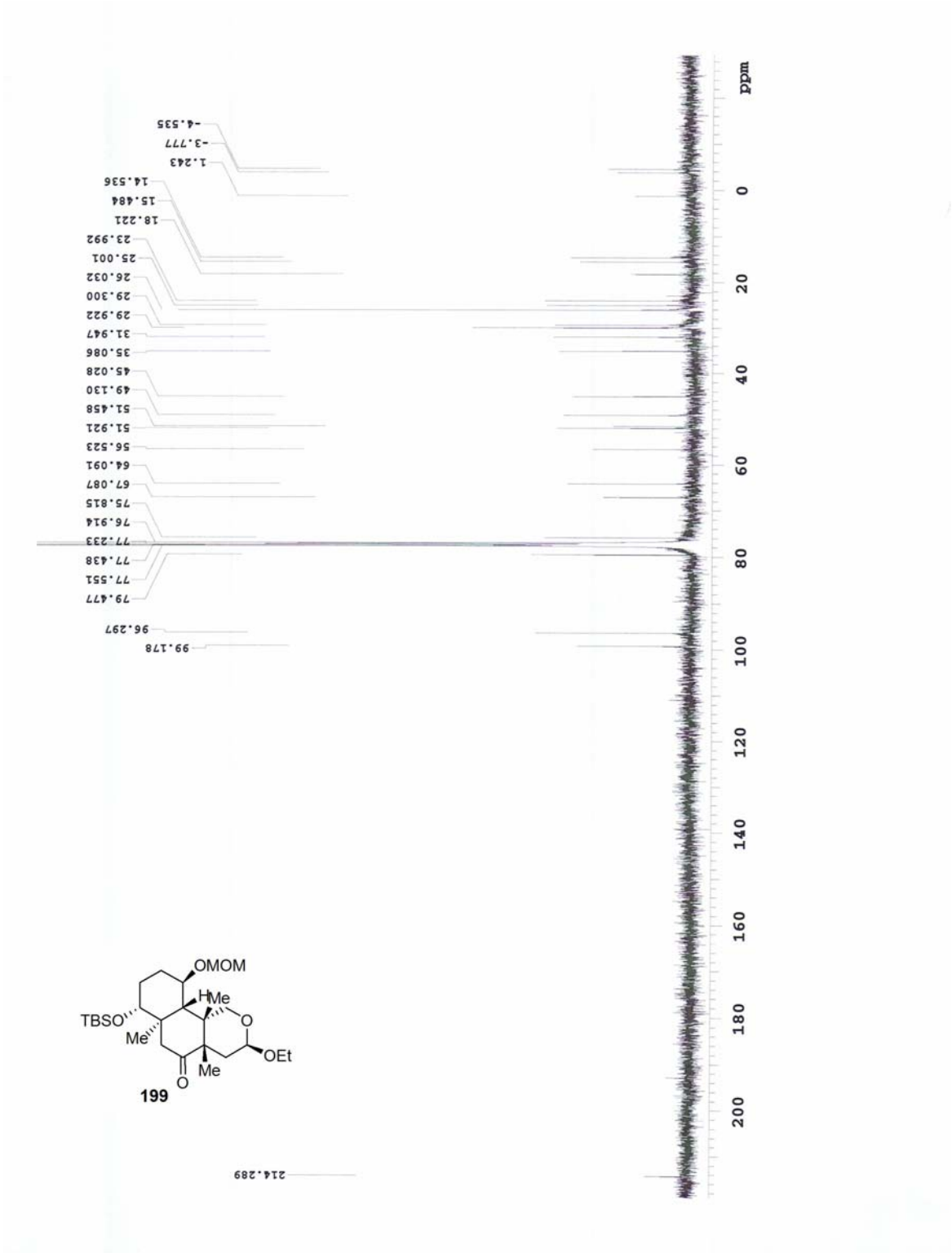
Spectrum 2.96: ^{1}H NMR ($CDCl_3$, 100 MHz) of compound **62**



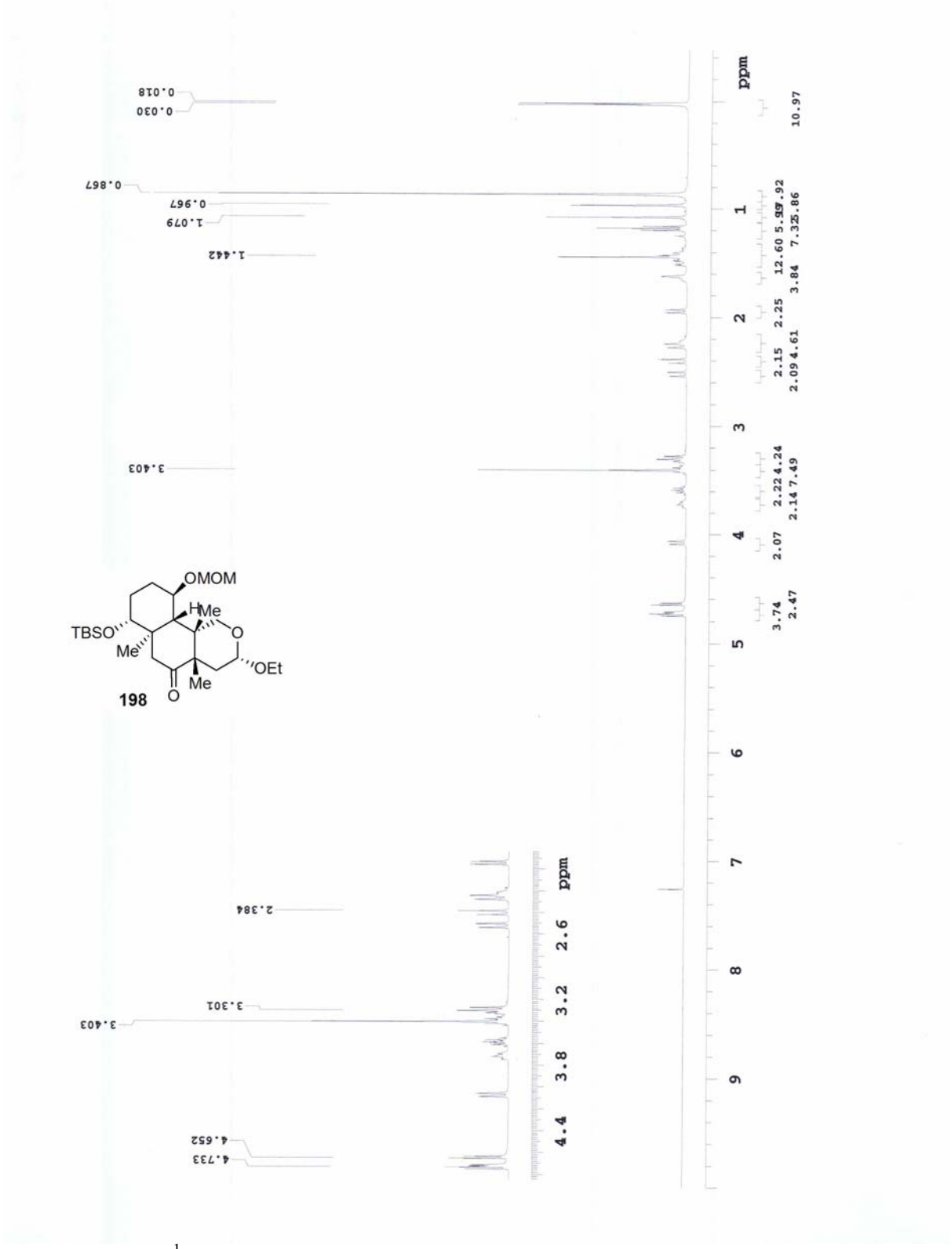
Spectrum 2.97: ^{13}C NMR ($CDCl_3$, 400 MHz) of compound **62**



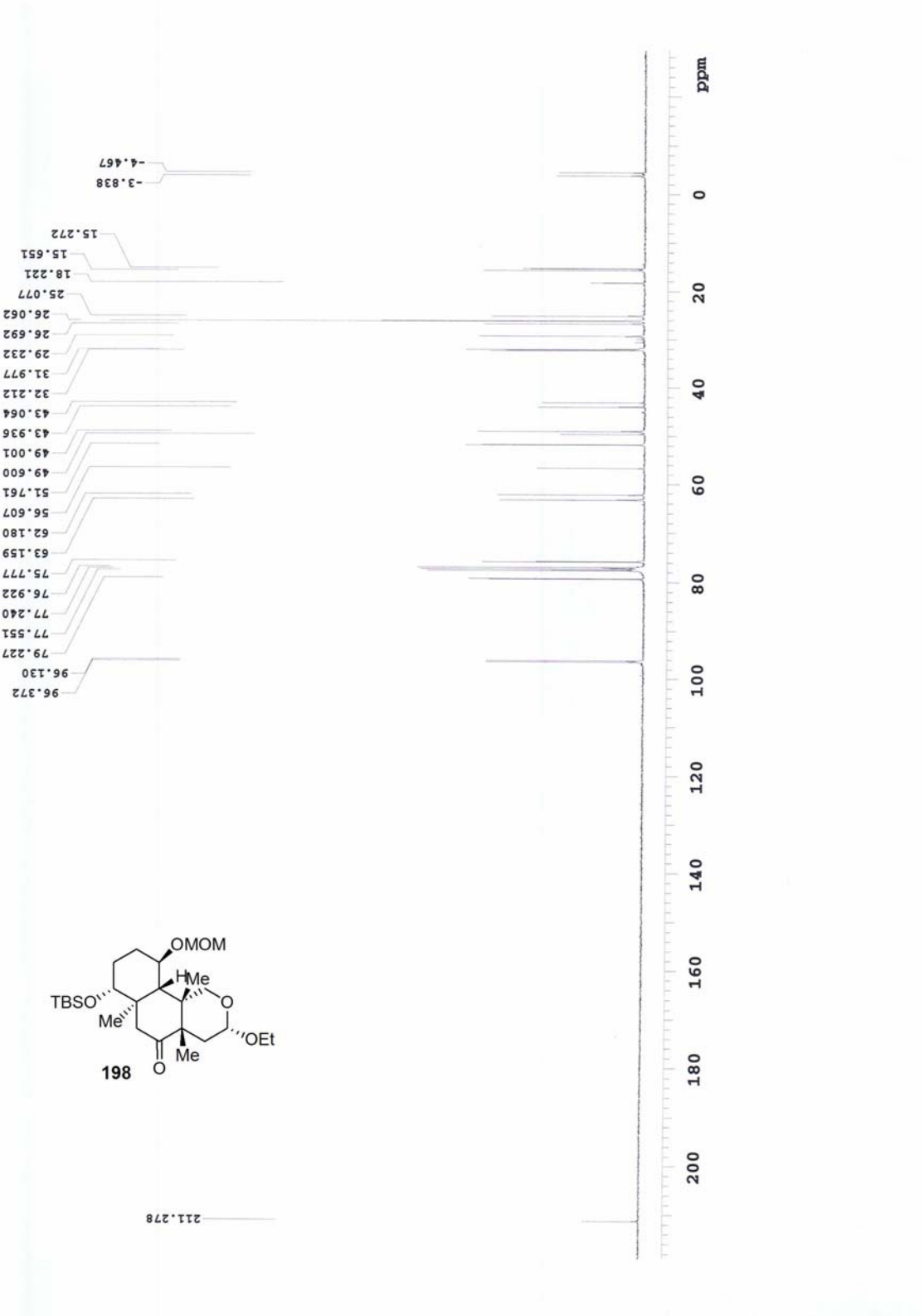
Spectrum 2.100: ^{1}H NMR ($CDCl_3$, 100 MHz) of compound **64-1**



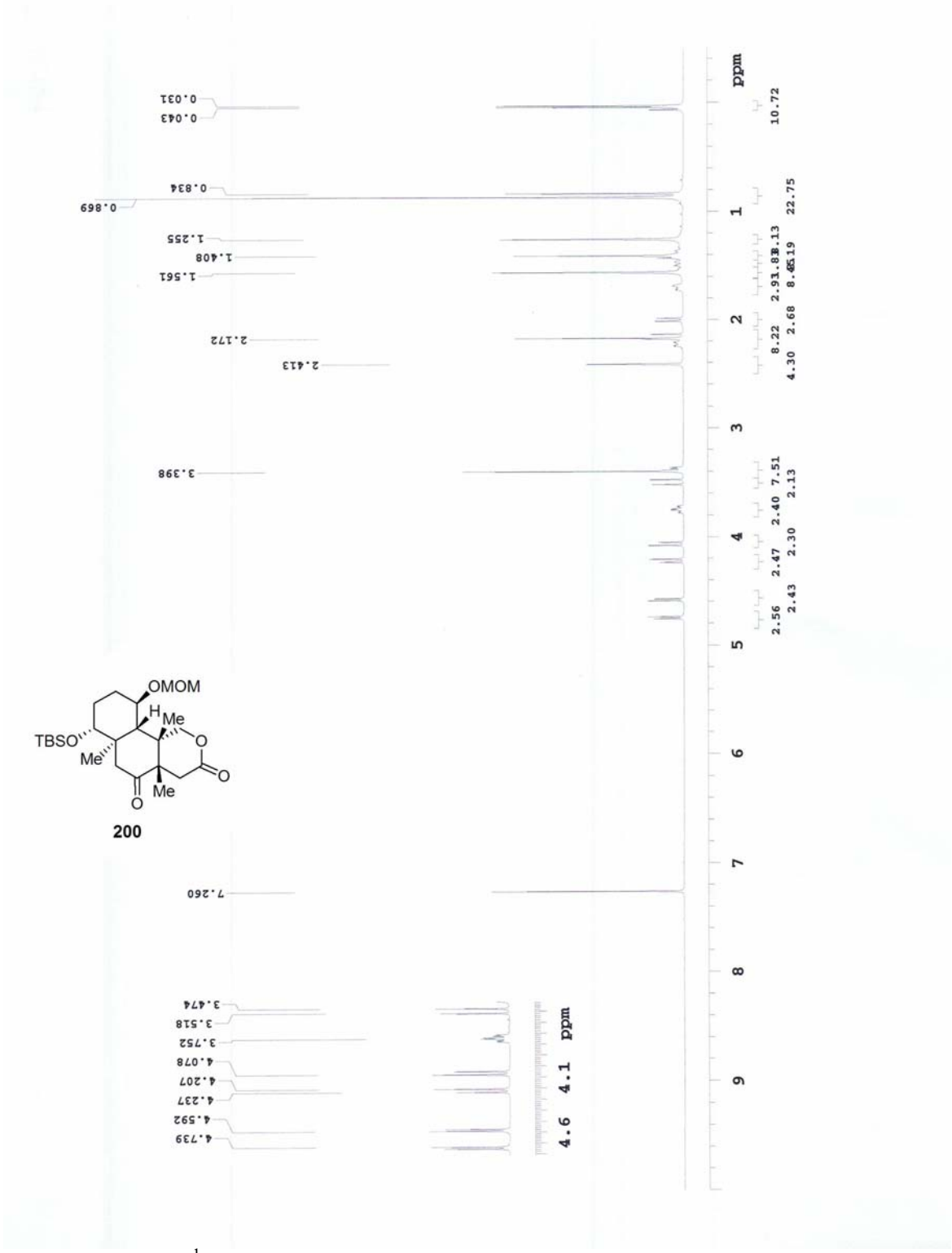
Spectrum 2.101: ^{13}C NMR ($CDCl_3$, 400 MHz) of compound **64-1**



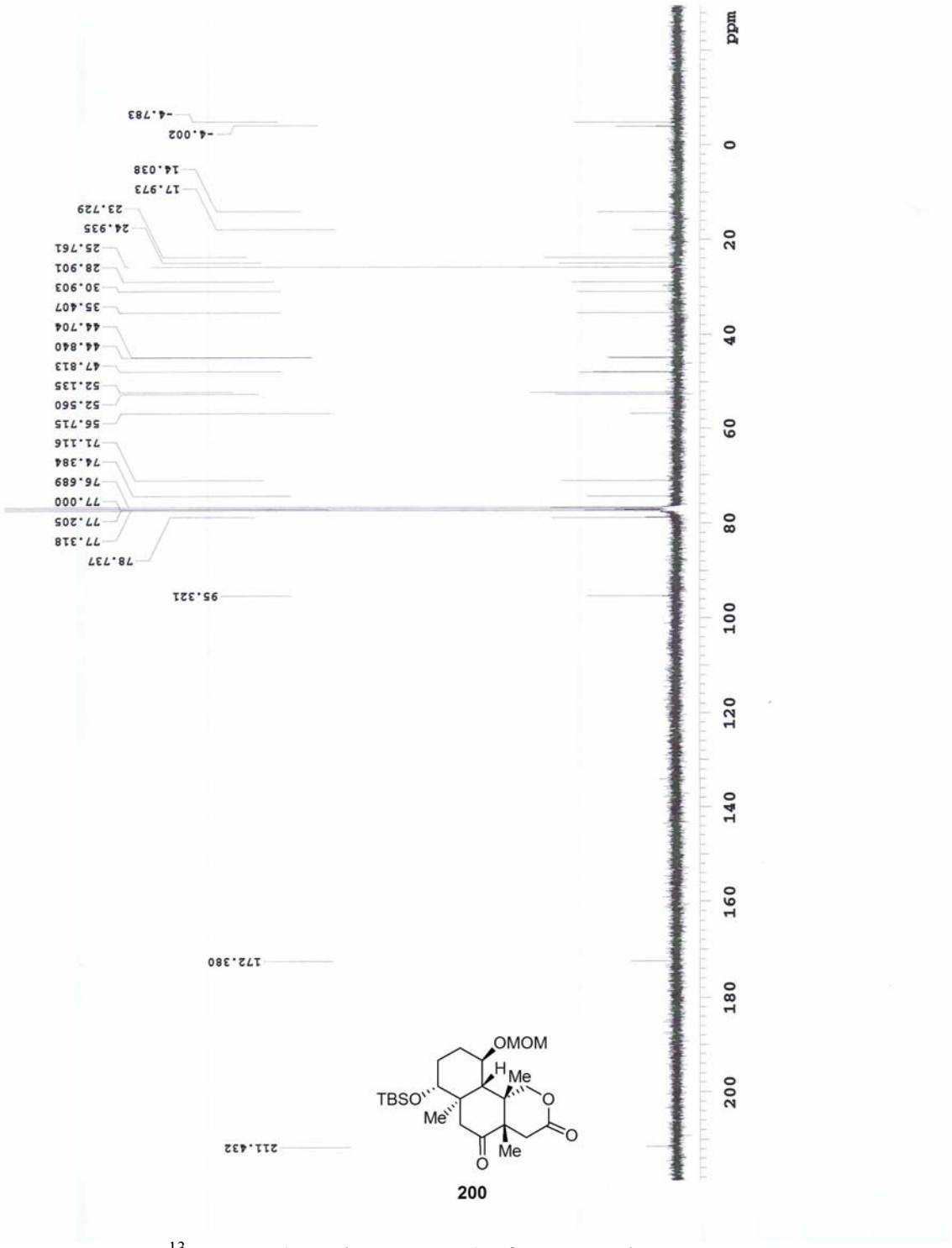
Spectrum 2.98: ^{1}H NMR ($CDCl_3$, 100 MHz)of compound **64-2**



Spectrum 2.99: ^{13}C NMR ($CDCl_3$, 400 MHz) of compound **64-2**



Spectrum 2.102: ^{1}H NMR ($CDCl_3$, 100 MHz) of compound **66**



Spectrum 2.103: ^{13}C NMR ($CDCl_3$, 400 MHz) of compound **66**

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24. CCDC-269730 (**34**), CCDC-615070 (**58**) and CCDC-269731 (**66**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk).

CHAPTER 3

A BIOMIMETIC APPROACH TOWARD THE TOTAL SYNTHESIS OF NORZOANTHAMINE

Section 3.1 Introduction

The proposed biomimetic approach is also an attractive synthetic route to the zoanthamine alkaloids because a cascade reaction can set several rings in a single synthetic operation.[1a] It could produce sufficient quantities of norzoanthamine and its family members who share a similar core skeleton in a more efficient way. We decided to pursue this tempting, but risky approach by looking at various possible connectivities that could arise from a biogenetically inspired pathway (Fig 3.1). This chapter will be divided into three sections. Each one highlights the carbon-carbon disconnections of the different pathways that were studied. Our goal was to develop a feasible synthetic plan that could yield not only norzoanthamine, but also other members of this family in a concise manner.

Our first approach called for an intramolecular Diels-Alder reaction (IMDA) or a Transannular Diels-Alder reaction (TADA). This approach intended to investigate the formation of the C ring, followed by the development of the A/B ring junction through a sigmatropic rearrangement.

Our second generation approach consisted on studying the BC ring formation through an IMDA reaction starting from a chiral synthon containing the A ring, thus adding rigidity to the system as well as introducing chirality. Our model of choice was carvone due to its structure similarity to the A ring of norzoanthamine except for the methyl group at C-16 (norzoanthamine numbering). The removal of this methyl led us to develop a feasible synthesis to isocarvone from carvone.

Lastly, our collected synthetic studies led us to postulate that perhaps the BC ring of norzoanthamine could be formed through an intramolecular [4+2] cycloaddition of an 2-amino-1,3-diene as our third approach. An acyclic precursor to the norzoanthamine alkaloids could experience an intramolecular aminal formation, follow by equilibration to the 2-amino 1,3-diene, which could undergo an intramolecular [4+2] to form the C ring followed by sigmatropic reaction to close the AB ring junction as shown in Figure 3.1. The studies of the [4+2] cycloaddition of 2-amino- 1,3-dienes will conclude our efforts toward the synthesis of norzoanthamine.

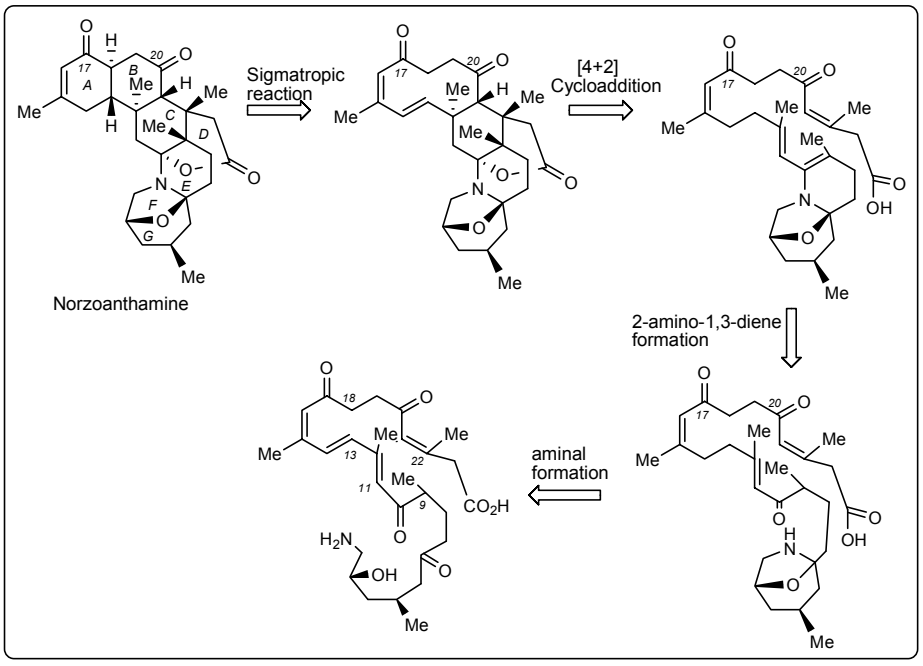


Figure 3.1: Our key proposed disconnections based on the proposed biogenesis of zoanthamine.

Section 3.2 Synthesis of a Polyene System

Our first synthetic approach toward the structurally complex zoanthamine alkaloids was to synthesize a polyene system, which could potentially react via an

intramolecular Diels-Alder (IMDA) or a transannular Diels-Alder (TADA) reaction. For a normal Diels-Alder reaction to take place the diene and dienophile have to be in a boat conformation. For a TADA reaction, the favorable chair-boat-chair transition state is expected, but it can go via boat-boat-chair conformation. This restriction is stereoelectronic in nature and in some cases, it is sterically impossible for a TADA reaction to take place when such conformation cannot be formed. Highly activated dienophiles or Lewis acid catalysis promotes the endo transition state (TS) formation versus the exo TS. As the bridge between the diene and the dienophile is increased, the geometric outcome of the cyclization varies because there are more possible stable conformers. However, predictions of the TADA reaction have become more approachable due to extensive studies performed by Deslongchamps in the late 1980s.[2b] Based on theoretical analysis and experimental observations, Deslongchamp's group proposed a set of rules for the TADA reaction depending on the triene geometry. These rules are powerful tools, and few cases have not followed the rules due to steric factors.[2a] Various factors determine the relative configuration of the new asymmetric centers created during the TADA or IMDA cyclization such as the triene geometry, and diastereomeric control by remote chiral centers. It has been experimentally observed that in general olefin geometry is maintained during the course of cyclization, but a few reported cases reported isomerizations at elevated temperatures.[2a] Similar to a normal DA reaction, the endo TS is usually favored, but many examples examined by Deslongchamps provided mixtures of both possible products.[2b] In fact, not until very recently, an exo selective TADA has been published

by Mulzer[2c] and it is the first one according to the authors (private communication, Figure 3.2, example 1). They claimed that it is difficult to predict the outcome of this reaction without lengthy theoretical calculations. However, inspections of a 3D-molecular model suggests exo TS and according to Deslongchamp's rules endo TS is not possible for this type of triene system. For a synthetically useful TADA reaction, high stereo selectivity is desired. This macrocycle (Fig. 3.2, example 1) could possibly afford both possible exo TS products, but a single compound was isolated in 70% yield. Mulzer attributes their successful results to molecular strain coming from the tether tran-fused lactol (Figure 3.2, example 1). Our macrocyclic system possesses many degrees of freedom, but a restricting factor would be the conjugation of the diene to the other two double bonds, thus minimizing the many possible conformations (Figure 3.3).

Diastereomeric control by remote chiral centers has been obtained after rigorous analysis of possible transition states and controlling the constituents such as recent work performed by the Roush's group. The degree of chiral induction is directly related to the steric bulk of the substituents.[2a]

A survey of the current TADA literature showed that several studies involving large macrocycle systems had been efficient strategies for the synthesis of complex polyclic systems. For instance Shing and Yang[2b] approached the tricyclic system of (-)-oblongolide lactone via TADA reaction, which favored the endo TS to give the corresponding TAC stereochemistry (shown in Figure 3.2, example 2). If the reaction was performed on the corresponding open polyene system (via IMDA), various ratios

of TAC and CAT products were observed. The observed high level of selectivity for the TADA reaction was attributed to the pseudo-equatorial orientation of the methyl group, which controls the diastereoselectivity via a chair like conformation of the A ring as shown its TS (Fig. 3.2, example 2). Besides, the methyl group on the dienophile would have an unfavorable interaction with the diene, if this macrocyclic system assumes the exo TS.

Lastly, Roush and et al.[2b] approached the synthesis of the skeleton of nargenicin A1 (Fig. 3.2, example 3) using a TADA reaction. Having a TTT triene geometry both TAC and CAT were possible, but the TAC configuration was favored. The compound was isolated in 66% yield along with 13% yield of the C-10 epimer and no CAT product. This approach was risky because of the difficulties associated with the prediction of the TS due to the many functional groups embedded within the macrocycle, but theoretical studies supported the formation of the desired stereochemistry. As shown in Figure 3.2, the Br atom in the TS assumes the syn orientation with respect to the C-8 proton and the C-16 is eclipsed with the C-14/C-15 unsaturation, a situation preferable to the C-16 methyl group, which is in the pseudo-equatorial orientation.

The successful synthesis of these complex molecules led us to propose the strategy shown in Figure 3.3. The key to our retrosynthetic analysis focuses on the coupling of synthons **13** and **24**, which formed a 17-member lactone **29**, which upon heating would afford the C core of norzoanthamine, compound **30**. Since our starting material was a racemic mixture, containing two chiral centers, the proposed TADA

reaction could potentially afford sixteen possible stereoisomers, eight of which are shown in Figure 3.31 along with their heat of formation energies predicted by

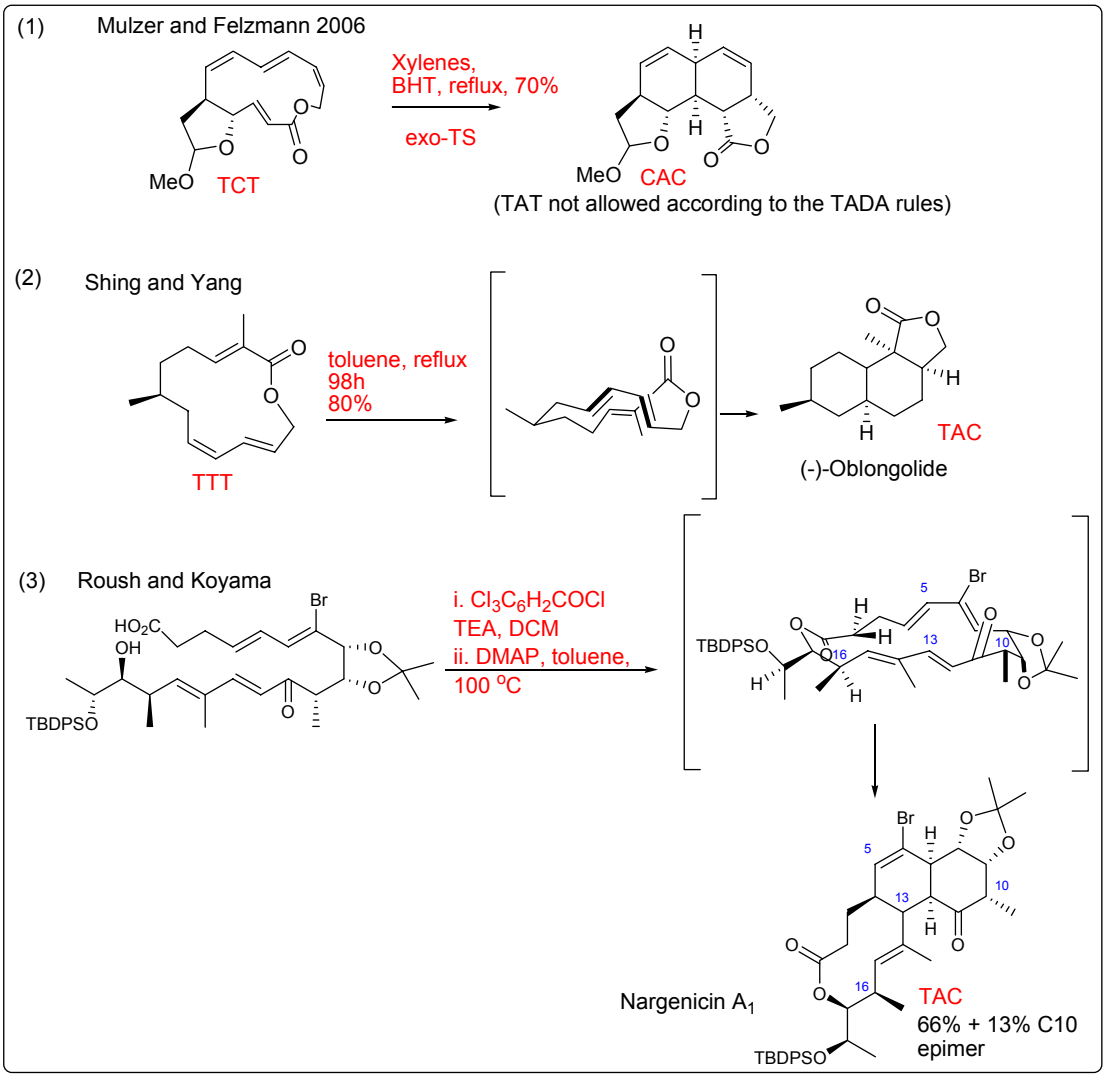


Figure 3.2: Successful applications of the TADA reaction.

Gaussian 1993 computational program. However, we planned to deprotect and to oxidize C-17 and C-20 (norzoanthamine numbering), once the DA reaction had taken place. Having the TTT triene geometry, we expected both TAC and CAT products, but we preferred the TAC product. We figured that both C-21 and C-22 centers could

be epimerized under basic conditions, but the proton at C-12, had to be anti to the proton on C-21. The CAT-configuration product would have afforded the syn junction at C-12/C-21 an undesirable situation. However, it needs to be emphasized that this simple model system was built to assess the synthesis of a polyene system and its reactivity profile. Since norzoanthamine has a methyl group at C-12 , its corresponding most favorable TS could have been different.

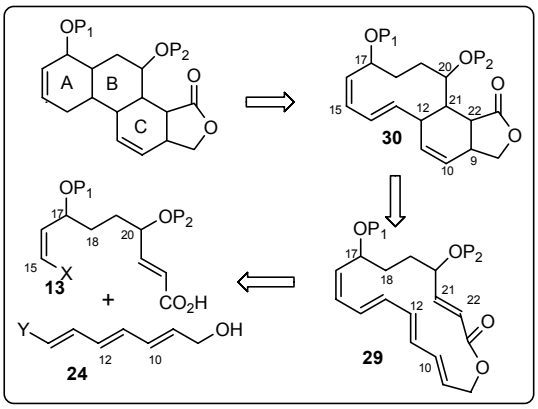


Figure 3.3: Proposed model system toward the C ring formation of norzoanthamine.

The proposed polyene model system contained no large R groups on the dienophile, a factor that is known to favor the exo TS, however, inspection of a 3D-molecular model suggested that both exo and endo transition states would be highly strained. Figure 3.31 describes two possible transition states for the TADA reaction, where the protecting groups at C-17 and C-20 are methyl groups to simplify the calculations. Free energies for these possible transition states (B3LYP/6-31G(d) geometries with selected bond distances for both transitions states: exo TS sum of electronic and thermal free energies = -991.904070 and endo TS -991.863211 in a.u. units) predicted similar energies with a difference of 25.64 kcal/mol. The theoretical

calculations were performed using Gaussian 1993[2d] and thermal zero point energies and thermal energies for the two shown possible transition states (Fig. 3.31) were also predicted (endo TS sum of electronic and zero-point Energies = -991.813424, sum of electronic and thermal Energies = -991.792398, and for the Exo TS sum of electronic and zero-point Energies = -991.892713, and sum of electronic and thermal Energies = -991.881509 a.u.). Simple steric energies suggest that the exo TS has a lower local minimum than the endo TS with energies of 40.3703 and 71.2880 respectively. Close inspection of the distances between the reacting carbon centers showed shorter proximity for the endo TS C(21)-C(12), C(22)-C(9) 3.7155, 2.9615 Å than for the exo TS 4.1335, 2.8635 Å. In addition, Figure 3.31 shows the postulated resultant products TAC and CAT. Although, the steric energy/free energy is lower for the exo TS, the corresponding distances are slightly shorter for the endo, and it is possible that a mixture of products would be obtained.

The heat of formations for the TAC products are slightly lower to those obtained for the CAT products as demonstrated in Figure 3.32.

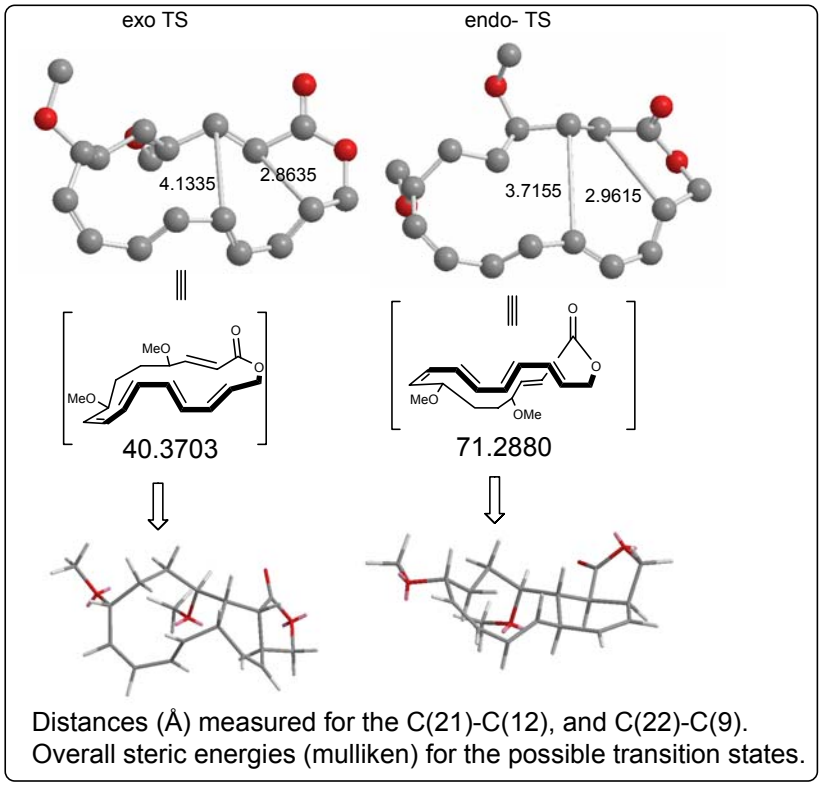


Figure 3.31: Possible transition states for the TADA reaction.

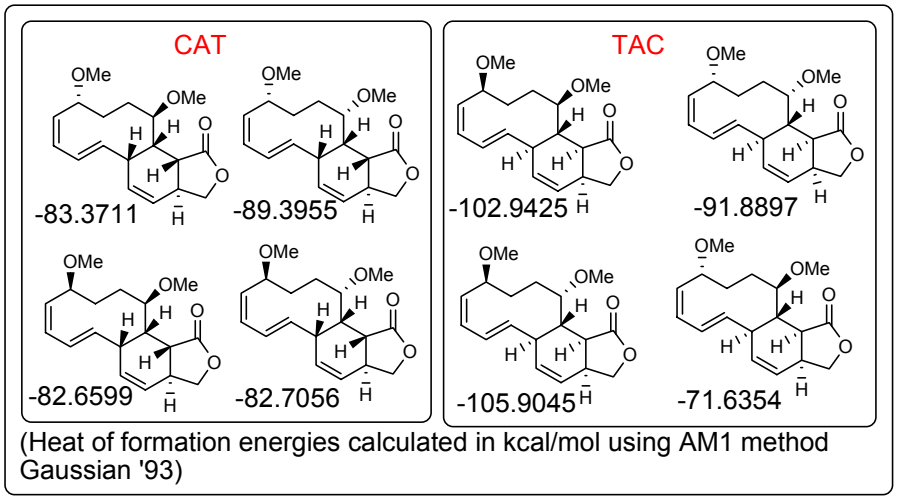
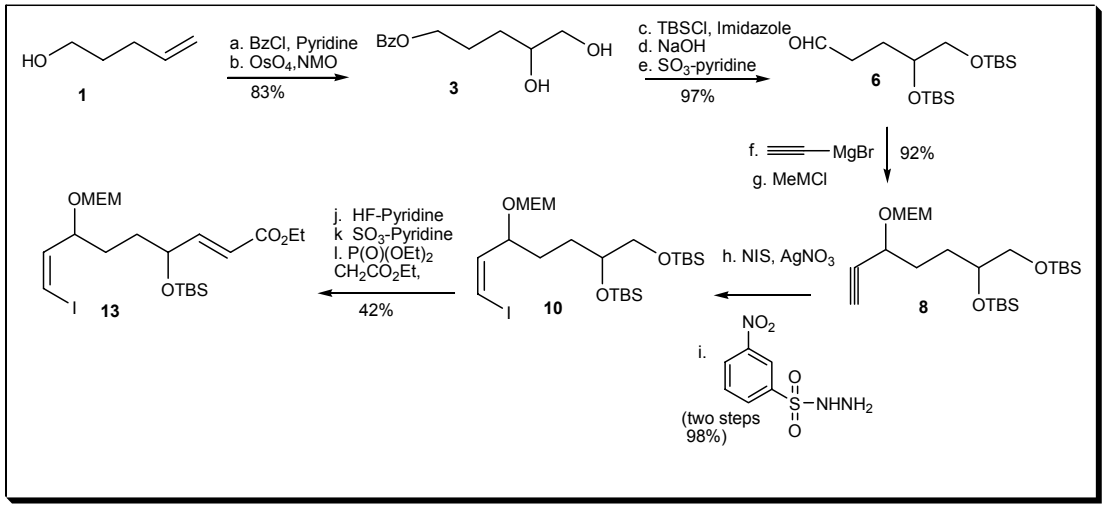


Figure 3.32: Possible stereoisomers and their corresponding heat of formation energies via the two most probable transition states that give rise to the CAT and TAC products.

Section 3.2.1 Attempts to Construct the C Ring of Norzoanthamine via an Intramolecular Diels-Alder Reaction

Our model polyene system did not incorporate the methyl groups at the C-15 and C-12 (norzoanthamine numbering) since we assumed that their presence would not affect the ability of the polyene system to react via an IMDA or TADA reaction.

The synthesis began with protection of commercially available 1-penten-5-ol with benzoyl chloride, followed by osmium-mediated dihydroxylation. The resultant diol was protected with TBS and the Bz protecting group was cleaved with NaOH in MeOH to afford the corresponding alcohol.[3a] This primary alcohol was oxidized with SO_3-pyridine in DMSO[3c] to afford aldehyde **6**, which was treated with ethynyl magnesium bromide to afford the corresponding propargylic alcohol (C-17, 1:1 mixture) that was protected with MEM-Cl to give **8** in 92% yield (two steps).

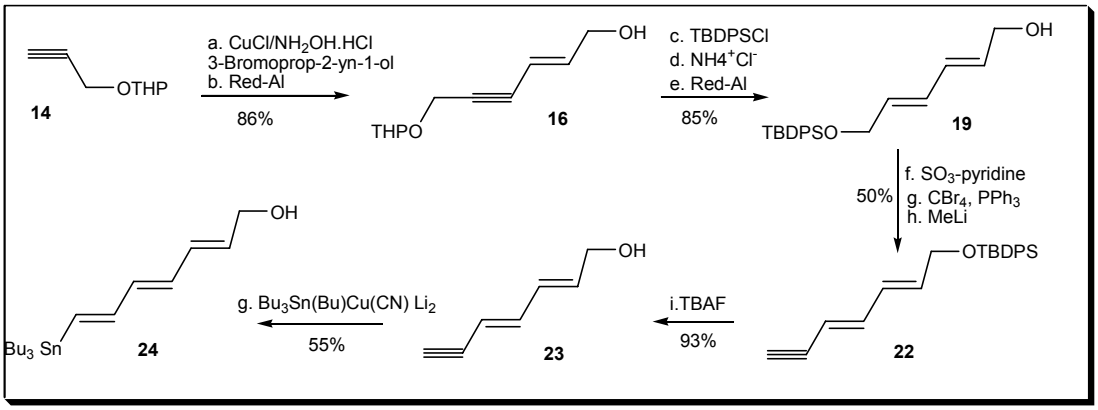


Scheme 3.1: Synthesis of synthon **13**.

The alkyne was treated with NIS in the presence of $AgNO_3$, to afford the iodoalkyne, which was treated with 3-nitrobenzenesulfonohydrazide to produce the (*Z*)-alkenyl

iodide in 98 % yield.[3b] Selective deprotection of the primary alcohol with HF.pyridine complex afforded the free primary alcohol in good yield, which was subsequently oxidized to the corresponding aldehyde. Triethyl phosphonoacetate anion was added to this aldehyde to generate fragment **13** in 42% overall yield (from **10**).

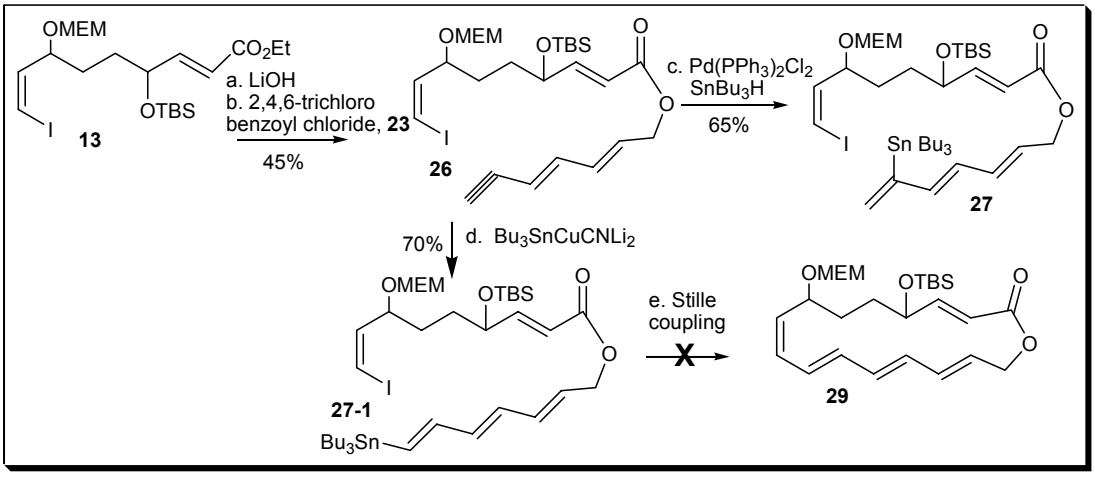
The synthesis of synthon **24** commenced with copper-mediated coupling of 2-(prop-2-ynyloxy)-tetrahydro-2H-pyran and 3-bromoprop-2-yn-1-ol[4a] as shown in Scheme 3.2. Hydroxyl directed reduction of the free propargyl unit afforded **16** in



Scheme 3.2: Synthesis of synthon **24.**

almost quantitative yield. This allylic alcohol was protected with TBDPS and the THP ether was cleaved with ammonium chloride in refluxing methanol. Reduction of the propargyl alcohol afforded the desired trans-alkene **19** in 85% yield from compound **16**. The free hydroxyl group was oxidized with SO_3-pyridine and treated with carbon tetrabromide-triphenylphosphine reagent[4b] followed by treatment with MeLi to afford the terminal acetylene in 50% overall yield. This last step, acetylene formation from the dibromo olefin was problematic since very low yields were obtained when the reaction was carried out at -78 ^{o}C as called by the known protocol. However, the problem was solved by slow addition of MeLi, while maintaining the

temperature at -90 ^{o}C until the reaction was done according to TLC analysis. The resultant alkyne was desilylated with TBAF to afford a light and temperature sensitive compound **23** in 93% yield. Compound **23** would undergo isomerization and decomposition upon standing at 25 ^{o}C. Reductive stannylation[5a,7c] of acetylene **23** afforded a mixture of distal and proximal isomers in similar ratios, but after intensive experimentation, the desired compound **24** could be solely synthesized by treatment with mixed stannylcuprate[5c] in 55% yield. Having both fragments available, it was possible to either carry out an intra-molecular Stille coupling reaction after esterification of **13** with alcohol **24** or perform an intermolecular Stille coupling reaction follow by macrolactonization reaction.



Scheme 3.3: Attempts to construct the C ring of norzoanthamine.

The intramolecular Stille coupling reaction was attempted first since intramolecular Stille coupling reactions have been shown to proceed in good yields.[4c] Saponification of **13** under LiOH treatment, followed by coupling with **23** by DCC or Yamaguchi conditions[6] afforded **26** in 46% yield (2 steps). Reductive stannylation of **26** under typical palladium-mediated conditions led to the formation of the internal (also

described as proximal in the literature) stannane **27** as the only regioisomer in 65% yield.

Mechanistic studies of hydrostannylation reactions mediated by palladium have shown that this is a syn addition (a widely accepted concept), leading to vinylstannane compounds of the *E*-configuration. The regioselectivity of this reaction is a little bit complicated since a few factors such solvent, temperature and most important substrate constituents can influence the outcome.[4c,5d] Changing the size of the ligands on the palladium has no effect in regioselectivity, and studies using Mo as the metal (instead of Pd) also showed similar regioselectivity.[5d] For propargyl alcohols, it is common knowledge that the terminal distal vinylstannanes are typically obtained (Figure 3.4, example 1), but when R_3 as shown in example 1, is not an alkyl group, a mixture of regioisomers are observed depending on the protecting group on the alcohol. For di-alkyne systems the proximal isomer is favored presumably via the prefer internal Pd complex, however when there is an alkyl group on the terminal acetylene, or this one is not symmetric, a mixture of regioisomers is observed (Fig. 3.3, example 2). Hydrostannylation of alkynes in conjugation with olefins can favor (shown in Figure 3.3, example 3) the distal regioisomer, presumably via the less crowded Pd(0) complex, which was isolated in 60% yield along with its corresponding proximal isomer in 40% yield.[4c] Based on this information, our conjugated polyene system was unlikely to favor the desired distal isomer, but a possible mixture was expected. However, we did not observe the proximal isomer under our treatment. After screening solvents, and temperatures (similar results were obtained), it was

found that $Bu_3Sn(Bu)Cu(CN)Li_2$ afforded **27-1** in 70% yield.[5c] It is known that stannylcupration reactions are influence by many factors, but they mostly depend on the electronic composition of the starting alkynes or en-ynes, to afford different regio, and stereoselectivities.[5d] For conjugated systems, the stannylcuprate adds in a 1,4-Michael addition similar to Gilman-type Grignard reagents, but for simple alkynes, the possible products are more difficult to predict (Figure 3.4, example 4-6). However, cis addition of the cyanocuprate to the alkyne gives the two regioisomeric proximal and distal tin derivatives (Figure 3.4, example 6)[5d].

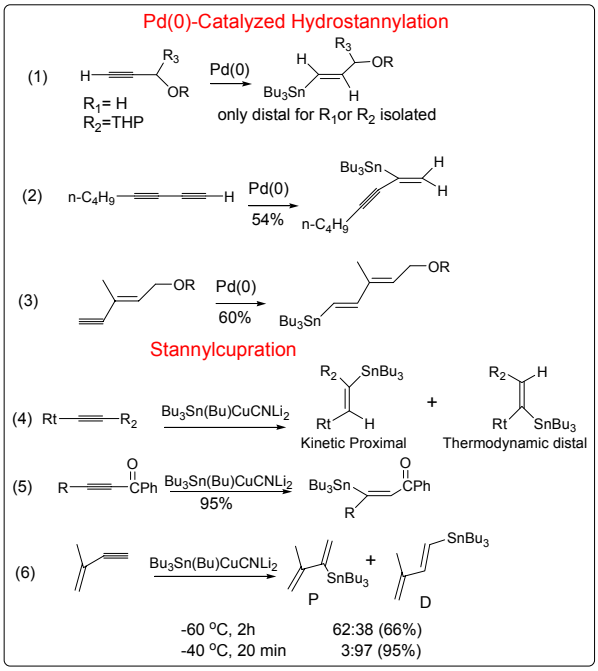
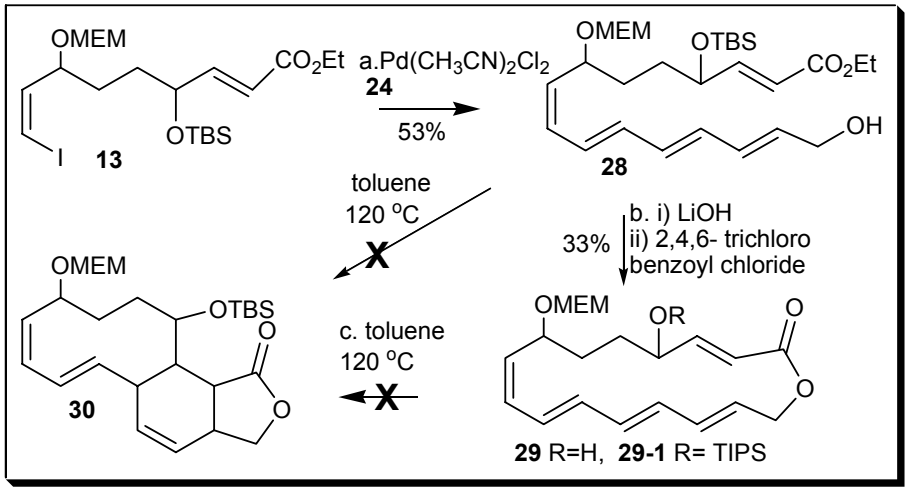


Figure 3.4: Palladium-mediated hydrostannylation versus stannylcupration: regioselectivity.

This reaction can be directed to form either isomer by changing the solvent, temperature or changing the stannylcuprate reagent, but as best described by Richard Taylor "No general guidance can yet be given about how to choose a stannylcopper or

stannylcuprate -it is probably best to follow the closest analogy in the literature…since they (reactants) do differ in their reactivity and selectivity".[5e] We treated compound **27** following careful thermodynamic conditions (THF, -40 ^{o}C, 15 min.)[5d] and we did not observe the corresponding proximal stannane isomer.

Having the stannane **27-1** available the intramolecular Stille coupling reaction was attempted without success. This Stille coupling reaction was conducted under several sets of reaction conditions using either Pd(0) or Pd(II), but only the reduced compound or saponification of the starting material was obtained.[6a] From these findings, it was decided to couple **13** with **24** under Stille conditions,[6b] which afforded the corresponding ester **28** in 53% yield (Scheme 3.4). An extensive study of the free (*E, E, E)*-trienol, compound **28**, showed that it was unstable under various IMDA conditions. Only decomposed starting material was recovered after heating even at low temperatures in toluene (such as 60 ^{o}C).



Scheme 3.4: Synthesis of synthon **29**.

Therefore, compound **28** saponification was carried out with LiOH to afford the corresponding acid in 90% yield. Attempts to lactonize it by DCC or EDC

mediated esterification met with failure, but Yamaguchi conditions provided compound **29** successfully in 49% yield. Interestingly, under Yamaguchi treatment, the TBS group was also cleaved. This resultant alcohol was treated with various oxidizing agents, in an effort to oxidize C-20, but only complicated mixtures, and isomerized compounds were observed. Unable to oxidized C-20, it was decided to protect it with TIPS-Cl and attempted the proposed TADA reaction. Heating compound **29** to 120 ^{o}C in toluene only afforded decomposition. More concerning yet, was the realization that compound **29** would decompose upon standing at room temperature overnight.

Since we were unable to apply the TADA reaction to the polyene system **29**, we decided to modify the strategy. We realized that the polyene system was too unstable and introduction of the necessary methyl groups at C-15, C-12 was a possible solution to the problem, but the introduction of the A ring could provide a much more rigid system that would facilitate the proposed IMDA or TADA reaction.

Section 3.2.2 Attempts to Form the A Ring through a Sigmatropic Reaction.

Under the influence of heat or light, a conjugated system can undergo bond isomerization to form a cyclic compound via an electrocyclic reaction. The reaction is completely stereoselective and completely stereospecific. For instance, under thermal conditions trans,cis,trans-2,4,6-Octatriene gives cis-5,-6-dimethyl-1,3-cyclohexatriene, but the corresponding trans isomer is obtained under photochemical conditions[8e] as shown in Figure 3.5. Although, cycloadditions containing enols/enolates as part of the

hexatriene system are not very common, we decided to investigate the possibility of a 6π cyclization to form the A ring via a trimethylsilyloxyhexatriene (SOH) derivative. Although, theoretical calculations by carpenter suggested that electron donating groups were unlikely to promote the cyclization of hexatriene,[11b] but the few examples present in the literature motivated us to attempt the construction of the A ring of norzoanthamine via 6π cyclization.

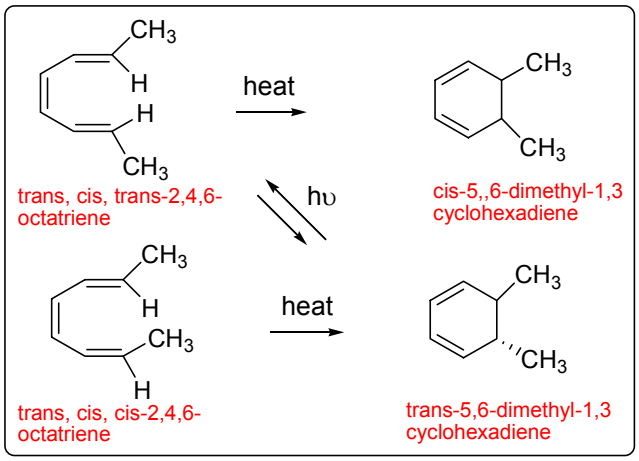


Figure 3.5: Electrocyclization reactions.

A system such as **50-1** (shown in Figure 3.6) could be the elaborated product of a 6π cycloaddition reaction mediated by hν/heat,[8a] or Pd catalysis[8b] from TMS-oxy-hexatriene compound **49**. In turn, compound **49** could rise from enolate-trapping of the corresponding enone (C-17), after oxidation/TBS deprotection (C-17), and C-12 elaboration **43**. Compound **43** can be easily synthesized from system **35**, which can be prepared from commercially available 5-penten-1-ol.

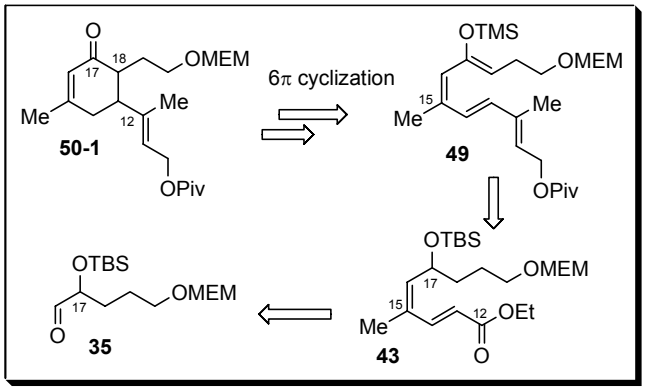
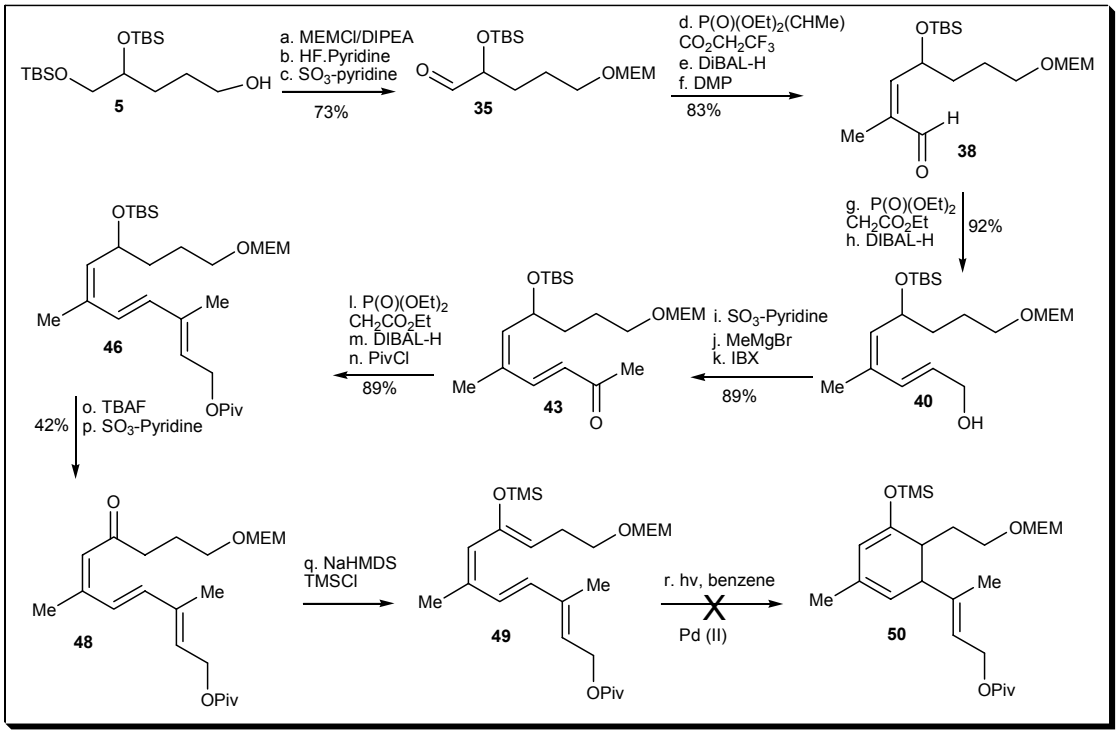


Figure 3.6: Proposed construction of the A ring system of norzoanthamine.

The synthesis began with compound **5** (synthesized as shown in Scheme 3.1), which was treated with MEM-Cl, mono-desilylated with HF-pyridine complex and oxidized with SO_3-pyridine to give **35** in 73% overall yield. Aldehyde **35** was transformed to the (*Z*)-alkene using Still-Gennari protocol in excellent yield.[9a] The corresponding ester was reduced with DIBAL-H and subsequently oxidized with Dess-Martin periodinane[9c] to afford **38** in 83% overall yield (from **35**). Horner-Wadsworth-Emmons olefination[9b] of **38** followed by DIBAL-H reduction afforded the (*Z*, *E*)-diene **40**. A three-step sequence of oxidation, nucleophilic methylation and oxidation provided methyl ketone **43** in 89% overall yield. Horner-Wadsworth-Emmons olefination in refluxing THF afforded the corresponding (*E*)-ester with traces of the (*Z*)-isomer.[9b] Reduction of this ester with DIBAL-H, followed by Piv-Cl treatment of the primary alcohol provided intermediate **46** in 89% yield from compound **43**. Removal of the TBS group with TBAF, SO_3-pyridine oxidation, and enolate trapping provided the unstable compound **49** in 42% yield as a inseparable mixture of C-17/C-18 (*E*:*Z*). This TMS enol ether was extremely acid labile, and even

on standing (neat), it transform back to the parent enone. Attempts to cyclize **49** (dissolved in benzene) thermally or photochemically did not afford compound **50.**[8a] It was postulated that in addition to the lack of reactivity towards the proposed cycloadditon, the (*Z*)-alkene across C-15/C-16 had undergone partial isomerization to the (*E*)-alkene, a scenario that would not allow the reaction to proceed.

As an alternative, Pd(II)-mediated cyclization reaction was also investigated. In addition, several novel metal complexes were tested in collaboration with the O'Connor group at UCSD, but only olefin isomerizations, unreacted starting material (compound **48**) and unidentified compounds were observed.[8d]



Scheme 3.5: Synthesis of synthon **49**.

A survey of the literature showed that compounds such as 1, 3, and 5 (Figure 3.7) participate in thermal or photochemical cyclization reactions in modest yields.

From these published results, it was not clear to what extent the substituents on the hexatriene influence the cycloaddition reaction. Figure 3.7 shows that both electron donating and electron withdrawing groups were embedded in the reactant systems and both cases (example 1 and 2) afford the corresponding products. When compound **1** (Fig. 3.7, example 1) was dissolved in MeOH and exposed to light, it afforded compound **2** in good yields, presumably via intermediate **1-1**. Upon heating compound **3-1** (in toluene) was converted to compound **4** in 34% yield, also unreacted compound **3** was isolated (the low yield was attributed to the competing thermal decomposition of the TMS ether to its corresponding parent molecule, enone **3**). Alternatively to the use of photochemical/thermal conditions, a palladium-mediated reaction had already shown promise since compound **5** (Fig. 3.7, example 3) afforded **6** in 84% yield.

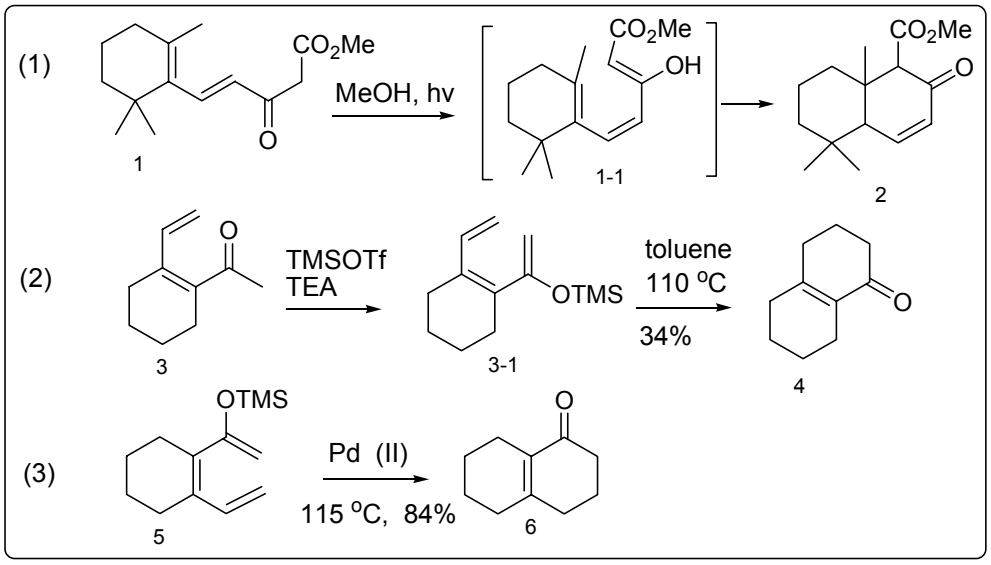
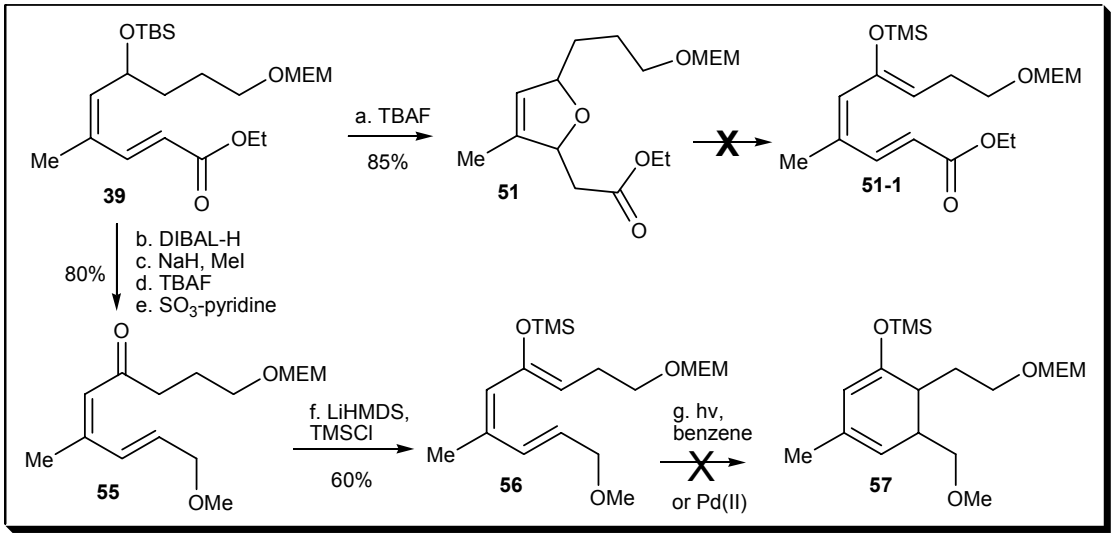


Figure 3.7: Previous studies to form the 6π cyclization via heat or palladium-mediated reaction.

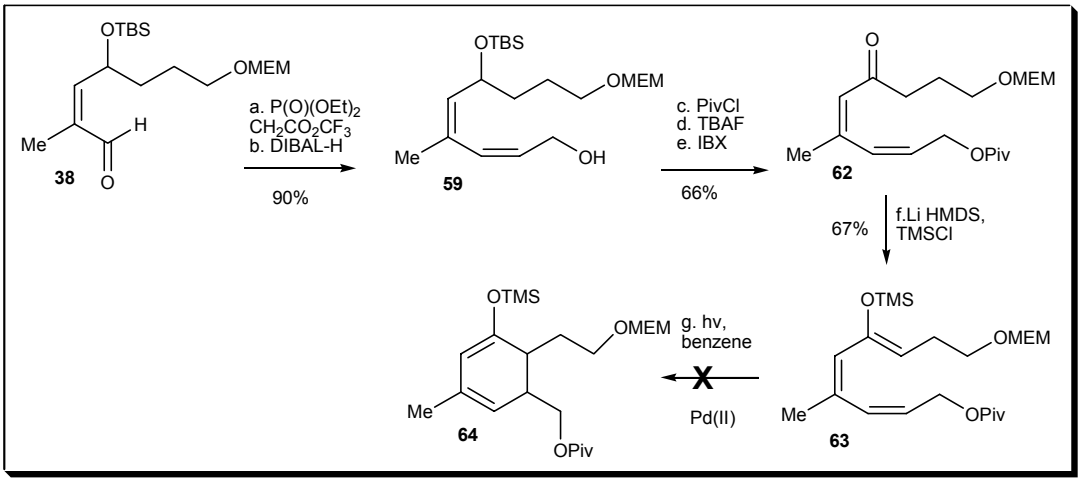
We observed that during the cyclization attempts under Pd catalysis, the Piv group would fall apart (possibly via palladium mediated deprotection since this group is not known to cleave under thermal conditions) and substantial amounts of starting material (compound **48**) would be recovered (due to the thermal TMS-ether decomposition to the parent enone). It was decided that a different protecting group should be evaluated as well as the extra C-12/C-11 olefin to avoid any palladium coordination to that site, this new route is shown in Scheme 3.6. The synthesis of the oxyhexatriene could be constructed from compound **39**, if it could be desilylated and oxidized to give the corresponding keto-ester **51-1**. However, when intermediate **39** was treated with TBAF, the dihydro-furan **51** was produced in 85% yield. It was realized that to create such a desired intermediate **51-1** more steps would be required so the approach was abandoned. Instead, ester **39** was reduced with DIBAL-H followed by O-methylation, removal of TBS with TBAF, and oxidation gave **55** in 80% yield. Enolization of **55** with LiHMDS, followed by quenching with TMS-Cl afforded compound **56** in 60% yield as a mixture C-17/C-18 TMS-enol ether isomers (*E*:*Z* in favor of the *Z* isomer). Rigorous studies such as solvent screening (benzene, halogenated benzene, DMF, DME, etc.) and studying different photochemical conditions (variation of time, temperature, and wavelength) to afford the cyclized compound **57** met with failure. Some thermal decomposition was observed, but mostly unreacted compound **55** was recovered. Changing the protecting group at C-12 (Piv to Me) did not solve the problem, although no cleavage of the protecting group was observed even under palladium-mediated reaction. Concurrently, we were also

evaluating the olefin configuration[8e] at C-14/C-13. Scheme 3.7 describes the approach we took to synthesize the cis olefin across C-14/C-13. Compound **38** was further functionalized by introducing its (*Z*, *Z*) olefin through an application of Still-Gennari protocol[9a] in good yield, followed by reduction of the resultant ester with DIBAL-H to afford **59** in 90% yield (two steps). Protection of the allylic alcohol with Piv-Cl, followed by desilylation, and IBX oxidation of the C-17 afforded compound **62**.



Scheme 3.6: Synthesis of synthon **56**.

TMS enolate trapping of enone **62** occurred in 67% yield C-17/C-18 TMS-enol ether isomers (*E*:*Z* in favor of the *Z* isomer).[11a] Again, attempts to conduct the 6π reaction proved challenging and only unreacted compound **62**, and unidentified mixtures were obtained. Theoretical studies had pointed that electron-donating groups will disfavor a concerted thermal hexatriene cyclization,[11b] but there were was literature precedent for such cyclizations so there was only a few possible explanations. Either, we did not find the right combination of variables for optimization of this reaction or we simply



Scheme 3.7: Synthesis of synthon **63**.

did not have the desired system. Although, we had ^{1}H, ^{13}C NMR spectra, mass spectra, we had no 2D NMR analysis and there was a very logical possibility suggested by Professor K.C. Nicolaou that the C-15/C-16 had isomerized during the oxidation of C-17, and indeed careful analysis of the ^{1}H NMR showed that there was two compounds present (approximately 95:5). At that time, it was thought that this was a minor compound, was just an impurity that could not be separated because it shared the same R_f value. It is possible that the minor compound was the desired (*E*, *Z, E*,)-hexatriene, but the major, the possibly more stable compound had the undesired (*E*, *E*, *E*)-hexatriene in which case the reaction was prone to fail. We cannot know with certainty unless 2D NMR analysis is performed to study the proton on C-16 and the protons on the methyl at C-15.

The failure to conduct the 6π cyclization under palladium catalysis led us to revisit the proposed mechanism for this reaction (Figure 3.8).[8c] Theoretically, this reaction involves the transmetallation of the O-Si bond of **7** to form an (oxyallyl)-palladium species and TMSCl as shown in Figure 3.8. Equilibration to the π-allyl

complex **12** followed by addition across the terminal double bond affords the σ-alkylpalladium species **13**, which forms **14**. In principal, **14** can undergo β-hydride elimination and produce phenol **9**. Indeed, experimental analysis of the byproducts of this $Pd(PPh_3)_2Cl_2$-mediated cyclization reaction have observed compound **9** in small amounts (10-20% yield).

The lack of annulated product from our triene system can be also be due to the prior isomerization of C-15/C-16 to the (*E*) stereochemistry as postulated before in which the cyclization would be unfavorable. Studies of such a (*Z*, *E*, *E*) hexatriene have shown no annulated product even under forcing conditions such as compound **15**

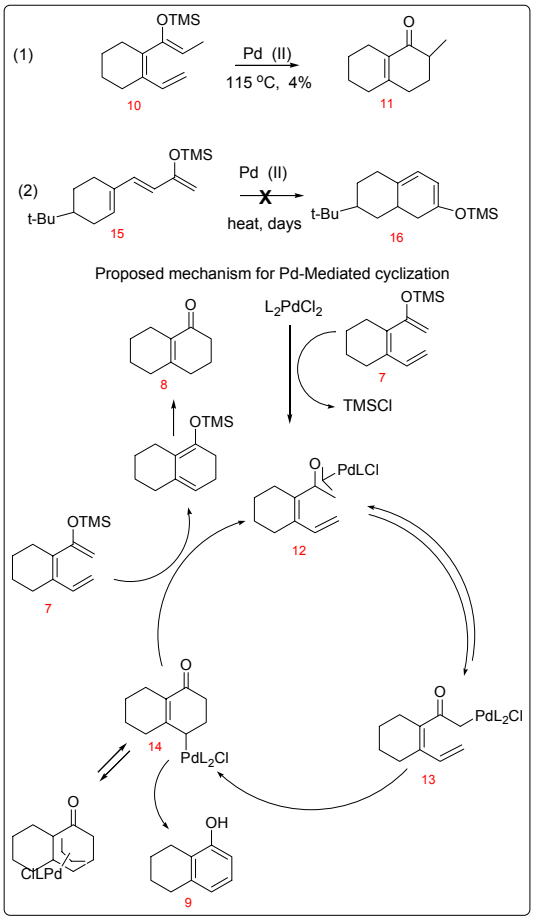


Figure 3.8: Proposed mechanism for the palladium-mediated 6π reaction.

To form compound **16**.[8c] In addition, this mechanistic studies showed that terminal substituted alkenes interfere with this cycloaddition such as compound **10** affording **11** in only 4% yield under forcing conditions.

After evaluating this approach, it was decided to abandon the strategy because further investigation and possibly new methodology needed to be developed in order to cyclize our hexatriene system.

Section 3.3 Model System Using Carvone as the A ring of Norzoanthamine

Carvone (**65**), commercially available in both enantiomeric forms, is one of the most common natural monoterpenes, used in the food and perfume industries, and is also used as a chiral starting material in the synthesis of natural products.[12] A scan of the past years' chemical literature reveals over 4,000 hits for the keyword 'carvone', many of which exemplify and validate its use in synthesis as a chiral building block. Due to its appealing features as a precursor to the A ring of the zoanthamines, we realized that transforming carvone to isocarvone (**75**) was a task that we could pursue in order to test the validity of our hypothesis that intermediate **94** could undergo an intramolecular Diels-Alder reaction. We had evidence that our proposed IMDA reaction had a high probability of working since Zaragoza[13a,b] had conducted an IMDA reaction on a similar system arising from carvone (shown in Scheme 3.12) that only lacked the oxygen at C-20 (norzoanthamine numbering). More recently Tanner and et al. has reported similar work (shown in Scheme 3.12) .[13c]

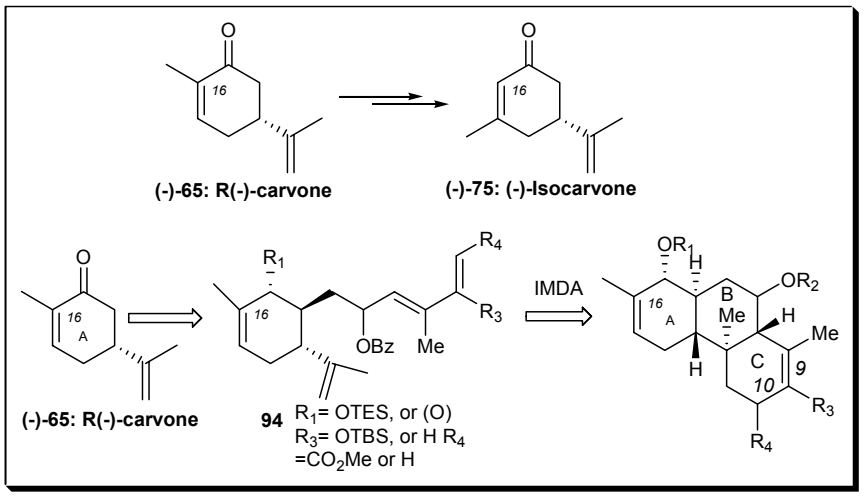


Figure 3.9: Proposed formation of the ABC ring of norzoanthamine from R-(-)-carvone.

Section 3.3.1 Synthesis of (-)-Isocarvone and (+)-Isocarvone

Despite the plethora of chemical transformations based on **65**, the chemistry of its methyl positional isomer, referred to herein as isocarvone (**75**: 5-isopropenyl-3-methyl-cyclohex-2-enone), remains virtually unknown (Figure 3.5). In fact, only one racemic synthesis of isocarvone (**75**) has been described by Stetter and Simons in 1985 using an aldol condensation as key step,[14] and there are no reported syntheses of **75** in enantiomerically pure form. Therefore, we decided to investigate an efficient synthesis of both (–)-**75** and (+)-**75** using as a common starting material the readily available R-(-)-carvone.

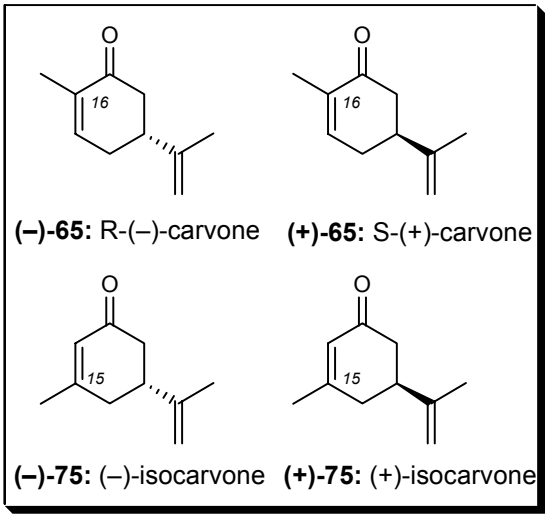


Figure 3.10: Natural carvone and its potential isomers.

The retrosynthetic analysis toward (–) and (+) isocarvone is highlighted in Figure 3.6. We anticipated that intramolecular olefination of β-ketophosphonate **74** would produce (–)-**75**, while methylation of ketone **80**,[15] followed by an oxidative carbonyl transposition would form (+)-**75**. Both **74** and **80** could be available from acid **68**, which is known to derive from manipulation of R-(–)-carvone as reported by the Deslongchamp group.[16]

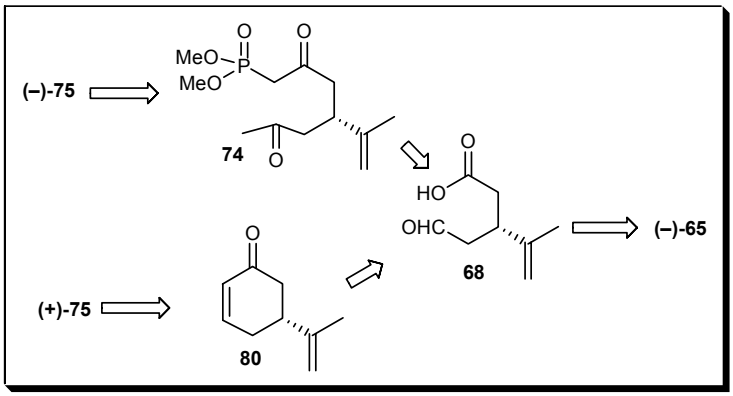
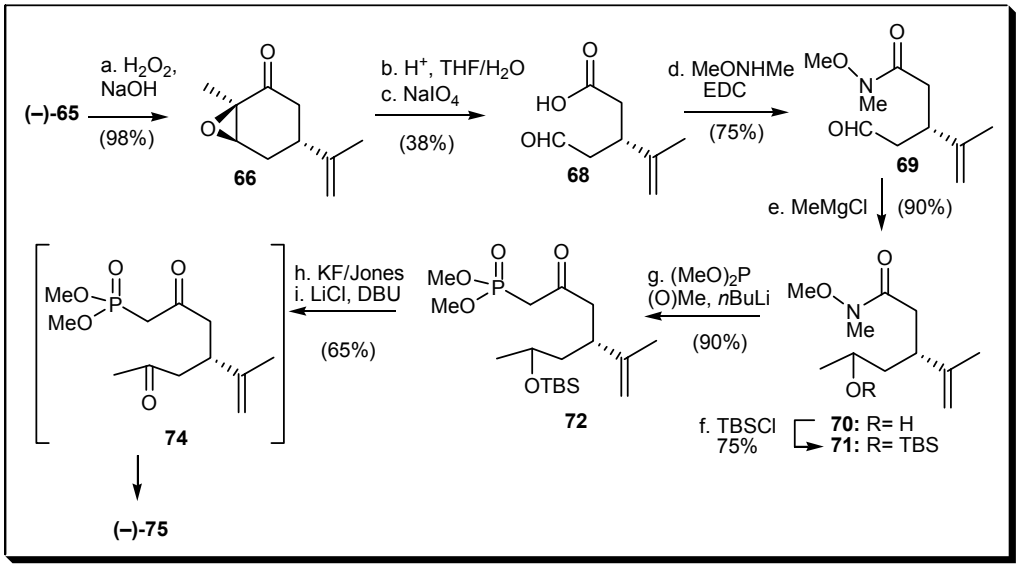


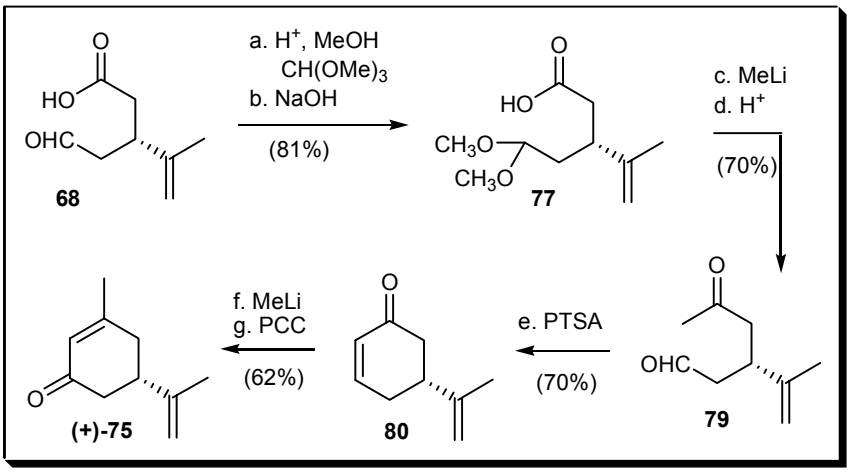
Figure 3.11: Retrosynthetic analysis of (-)-isocarvone and (+)-isocarvone.

The synthesis of (–)-isocarvone began with epoxidation of **65**, in the presence of basic hydrogen peroxide, to produce diastereoselectively epoxide **66** in 98% yield (Scheme 3.8).[16] Compound **66** was treated with aqueous H_2SO_4 in THF to produce a 1:1 mixture of *cis* and *trans* diols that were separated by column chromatography. The *cis* diol was subjected to oxidative cleavage with $NaIO_4$ to produce the known carboxylic acid **68**[16] in 38% overall yield (from **66**). Coupling of **68** with MeO-NHMe•HCl proceeded in best yields using EDC•HCl and Et_3N and afforded Weinreb amide **69** (75% yield). Alkylation of **69** with MeMgCl in THF proceeded selectively at low temperature (–50 to –10 ºC) and generated the secondary alcohol **70**,[17] which was converted to the corresponding silyl ether **71** in 68% overall yield. Treatment of **71** with the anion of dimethoxymethylphosphonate at –78 ºC formed β-ketophosphonate **72** in 90% yield. Deprotection of silyl ether **72** was found to be unexpectedly difficult. Several reagents were tried (TBAF•THF, TBAF on alumina, PTSA, CSA, HCl), but led in most cases to decomposition. After much experimentation, a one-pot procedure using KF and Jones' reagent as oxidant[18] gave the required methyl ketone **74**. Without purification, compound **74**,[19] was subjected to an intermolecular Horner-Wadsworth-Emmons olefination under Masamune-Roush conditions (LiCl, DBU)[20] to afford the desired isocarvone (–)-**75** in 65% overall yield (Scheme 3.8).



Scheme 3.8: Synthesis of (-)-Isocarvone **(75).**

The synthesis of (+)-**75** isocarvone is highlighted in Scheme 3.9. Acid **68** was treated with $(MeO)_3CH$ in MeOH under acid catalysis to produce, after hydrolysis of the resulting methylester, ketal **77** in 81% overall yield. Alkylation of acid **77** using MeLi/TMSCl followed by deprotection of the carbonyl group afforded ketoaldehyde **79** (70% yield), which was subjected to an acid-catalyzed intramolecular aldol condensation reaction to form enone **80** (70% yield). Treatment of **80** with MeLi produced the corresponding tertiary alcohol, which underwent a PCC induced oxidative rearrangement to form (+)-**75** isocarvone in 62% overall yield.

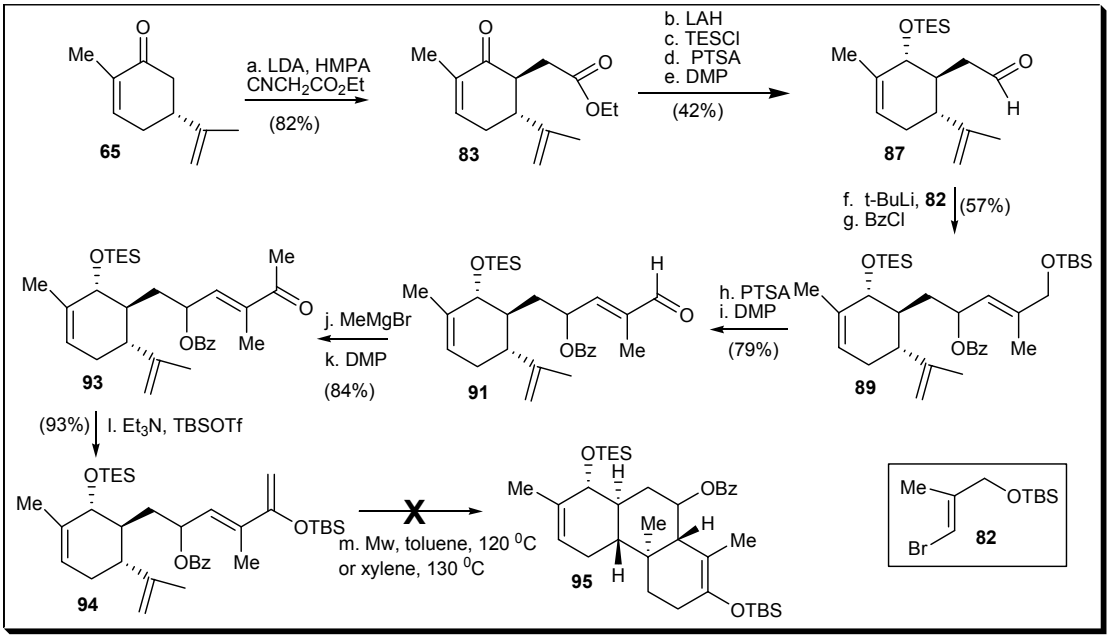


Scheme 3.9: Synthesis of (+)-isocarvone.

In conclusion, we developed an efficient approach for the synthesis of both enantiomers of 5-isopropenyl-3-methyl-cyclohex-2-enone, (isocarvone) (**75**). Both synthetic sequences depart from carboxylic acid **68**, which is readily available from R-(–)-carvone. This approach represents the first entry into both enantiomers of isocarvone and opens the way for their application as chiral building blocks in organic synthesis.[21]

Section 3.3.2 Attempts to synthesize the BC ring via a Diels- Alder reaction using carvone as a model system

Although, we had developed a simple approach to isocarvone, it was decided that our investigation could be performed using carvone as a model system. This approach, if successful, could result in an enantioselective synthesis of the tricyclic system of norzoanthamine enantioselectively.

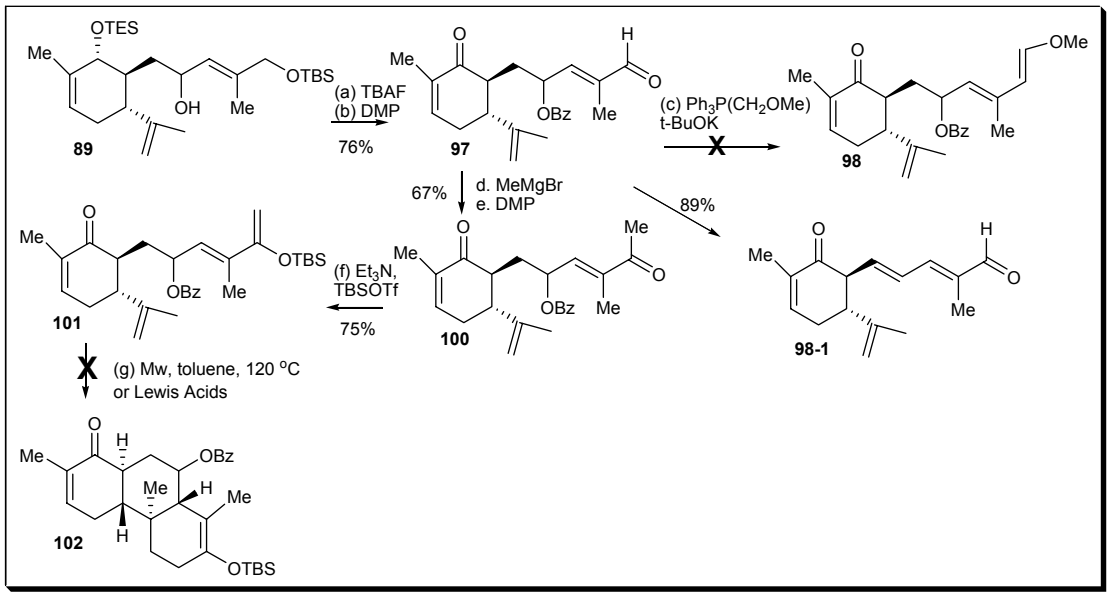


Scheme 3.10: Synthesis of **94.**

The synthesis of a suitable precursor for the IMDA such as compound **94** containing diene-dienophile system is shown in Scheme 3.10. Compound **65** was steroselective alkylated[22] with ethyl 2-cyanoacetate in 82% yield, and the resultant diketo ester was reduced with LAH to afford the corresponding diol, which was protected with TES-Cl. The deprotected diol was mono-desilylated with p-TSA and the primary alcohol was oxidized with Dess-Martin periodinane to give **87** in good yield. Lithiation of **82**[23] with t-BuLi was followed by its addition to aldehyde **87**, to provide the corresponding alcohol (1:1 mixture at C-20, norzoanthamine numbering). The newly generated secondary alcohol was protected with Bz-Cl to afford compound **89** in 57% yield. Selective removal of the primary TBS alcohol with p-TSA, and subsequent DMP oxidation produced aldehyde **91** in 79% yield. Nucleophilic methylation of aldehyde **91** follow by oxidation provided enone **93** in 84% yield.

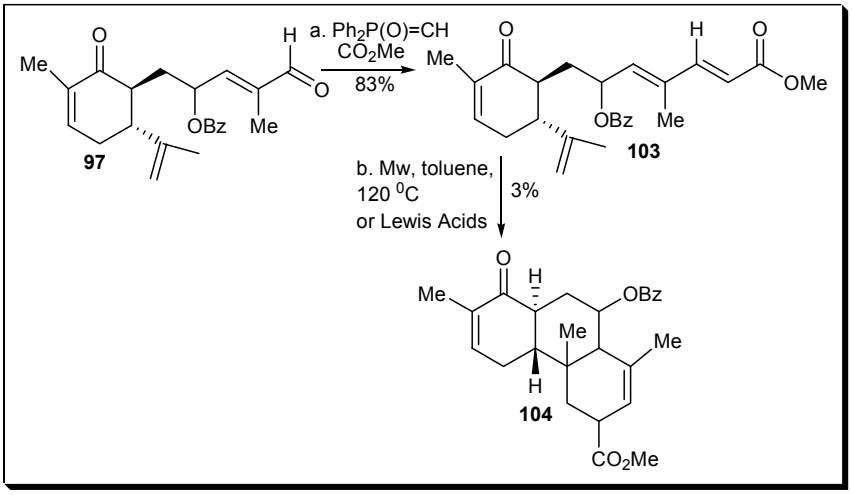
Enone **93** was treated with TEA and TBSOTf at -78 ^{o}C to provide compound **94** in excellent yield (93%). An extensive investigation was carried out with compound **94**. We tried several reaction conditions such as refluxing in toluene, xylene, acetonitrile, and microwave heating in NMP, acetonitrile, and DMSO/H_2O without any success.[24a] In addition, a large number of Lewis acids were screened.[24b] It was observed that the TES group would cleave under high temperatures. In addition, small amounts of the benzoyl group would eliminate, and the trapped TBS enol ether would cleave. It was difficult to analyze the mixtures of recovered material since protecting group scrambling also occurred (observations made through NMR analysis). These experimental results suggested that C-17, C-20 needed modification and that the TBS-enolate should be re-evaluated. A revised synthesis is shown in Scheme 3.11.

Compound **89** was treated with TBAF followed by Dess-Martin oxidation conditions to afford **97** in 76% yield. Attempts to produce **98** under typical Wittig conditions[25a] met with failure since it only produced conjugated aldehyde **98-1**, which arose from the elimination of the protected benzoate group in 89% yield.



Scheme 3.11: Synthesis of compound **101.**

Therefore, methyl magnesium bromide was added to ketoaldehyde **97** and the resultant alcohol was oxidized under Dess- Martin conditions to provide compound **100** in 67% yield. Treatment of compound **100** with TEA and TBSOTf at -78 ^{o}C provided **101** in 75% yield. Heating in toluene, xylene, DMF, in a sealed tube or microwave heating in NMP, acetonitrile, DMSO and Lewis acid catalysis afforded decomposition and the TBS enol ether cleaved. Having compound **97** at hand, it was treated with the commercially available stabilized phosphorane $Ph_3P{=}CHCO_2Me$ under neutral conditions,[25b] which afforded **103** in 83% yield (Scheme 3.12). Heating of **103** in toluene or xylene only provided starting material back with small amounts of Bz elimination.



Scheme 3.12: Synthesis of compound **103.**

However, usage of Lewis acids such as $TiCl_4$[24b] or $LiClO_4$[24c] or $Yb(OTf)_3$[24d] gave trace amounts of the desired compound enough to obtained high resolution mass and ^1H NMR, but insufficient amounts for further analysis. We decided to abandon this strategy since we had encountered poor reactivity. Primarily, we were concerned with our inability to predict whether the problem was due to steric effects, or electronic effects. Previous studies by Zaragaoza[13a,b] supported our proposed IMDA reaction as shown in Figure 3.12, his group had obtained the tricyclic system is 92% yield. However, recent studies reported by Tanner's group using a similar approach to ours

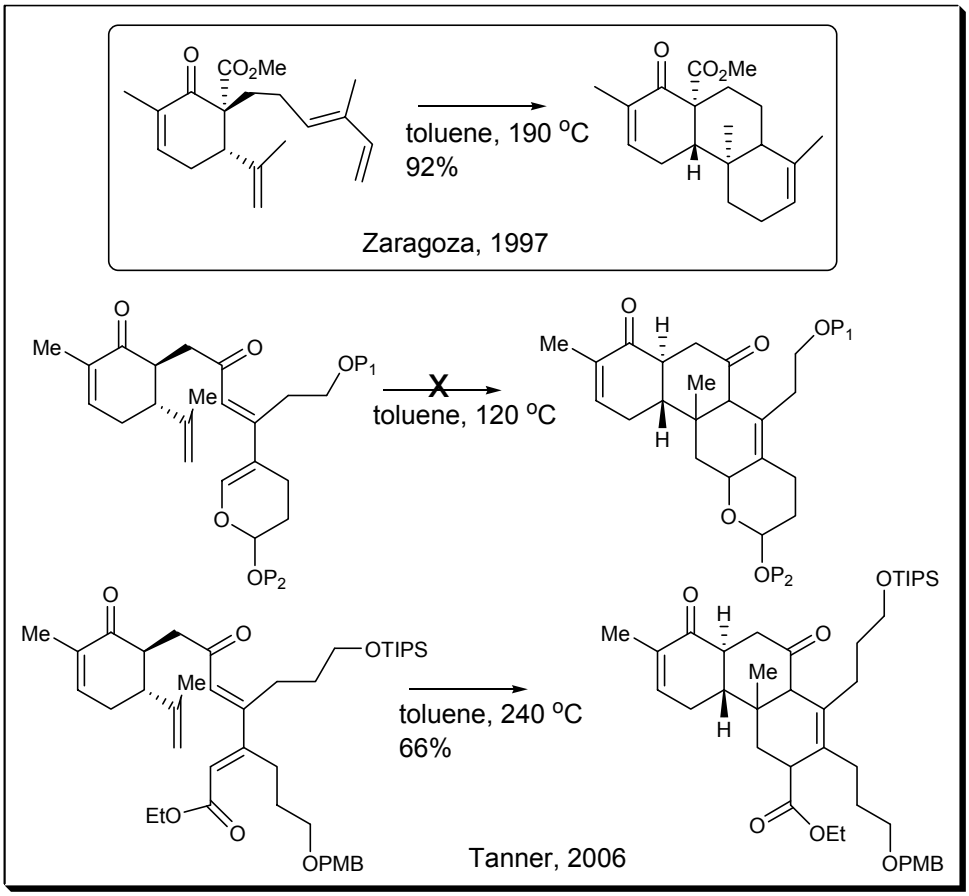


Figure 3.12: Diels-Alder reaction studies by Zaragoza and Tanner.

confirmed our findings that the IMDA for "Normal DA systems" does not take place, but it readily undergoes cyclization via "inverse DA" when the diene is very electronically deficient.[13c]

Having evaluated this approach, we realized that an alternative to form the BC ring would be via a [4+2] cycloaddition using the upper part of the molecule as the dienophile and the lower part as a diene.

Section 3.4 A Study of [4+2] Cycloaddition Reactions of 2-amino 1,3-Dienes: Access to the BC Ring of the Zoanthamines

Section 3.4.1 Introduction

The C ring of norzoanthamine could be formed by a [4+2] cycloaddition of a 2-amino 1,3-diene system (Figure 3.13). Cycloaddition reactions of 2-amino 1,3-dienes have been studied sporadically, but Barluenga[26a] has investigated their reactivity profile in more detail.

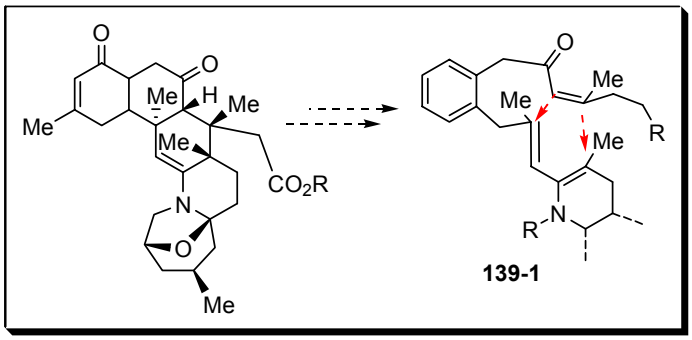


Figure 3.13: Proposed C ring formation of norzoanthamine via a 2-amino 1,3-diene cycloaddition.

Our last approach consists of creating an aminodiene system such as the one shown in Figure 3.13, which can potentially undergo an IMDA reaction or a double Michael addition due to the nucleophilicity of the enamine.

Our previous findings suggested that the presence of the A ring was necessary to add rigidity to system so a model system such as **139-1** (Fig. 3.13) was a suitable precursor to test the [4+2] cycloaddition. In addition, such a model system has potential to be further functionalized to the ABC core of norzoanthamine.

Section 3.4.2 Bio-inspired Model System toward the BC Ring of the Zoanthamines

We postulated that a [4+2] cycloaddition of a 2-amino 1,3-diene could afford the BC core of norzoanthamine (Figure 3.14). We hypothesized that compound **139-2** could be the product of a [4+2] cycloaddition of 1,3- (amino) diene **139**. In principal, as described in Figure 3.14, in a biogenetic pathway, compound **139** could form by dehydration of compound **137**, which could arise from isomerization of its initial formed iminium ion intermediate (Figure 3.15). Compound **137** could derive from aldehyde **128**, after undergoing a Grignard addition. The latter structure can be synthesized by palladium-mediated coupling[27a] of stannane **108** (or **113**) and commercially available 2-(2-bromophenyl)ethanol (compound **114**).

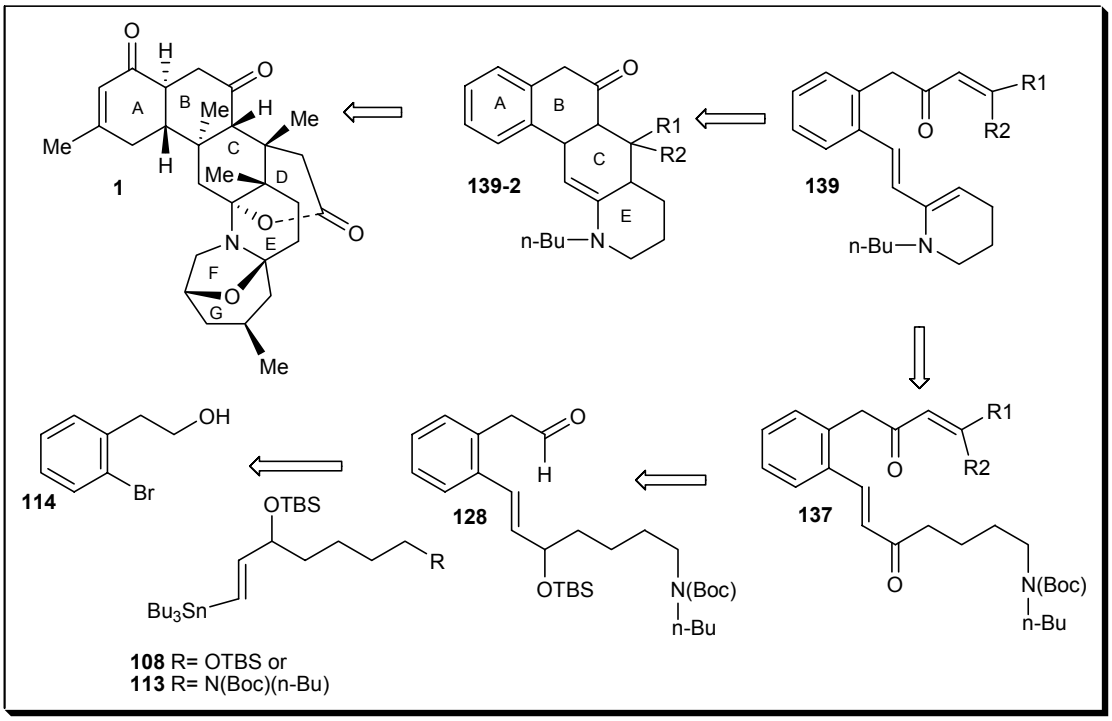


Figure 3.14 Proposed model study to the ABCE ring of norzoanthamine.

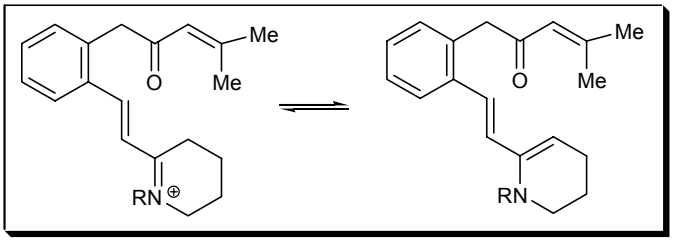
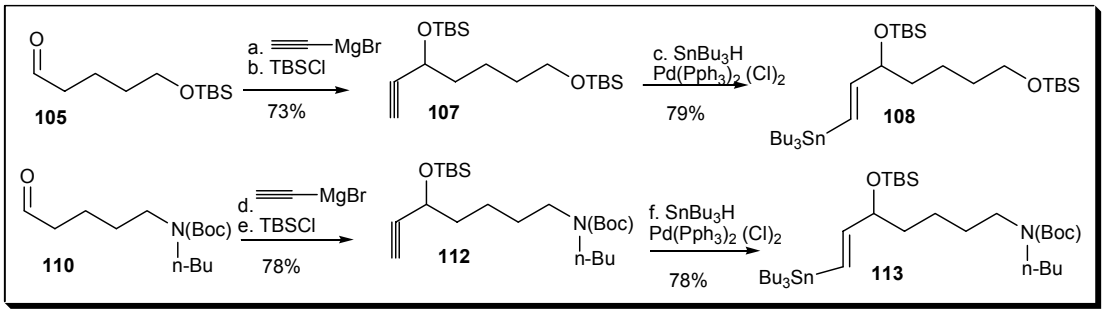


Figure 3.15: Expected enamine isomerization.

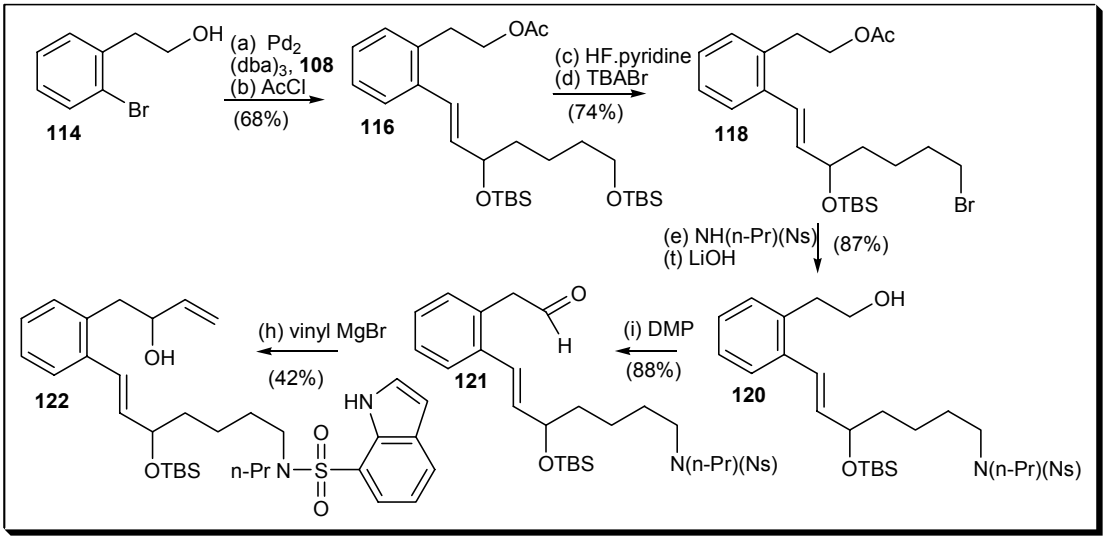
The preparation of synthon **108** and **113** are described in Scheme 3.13. Aldehyde **105** was treated with vinyl magnesium bromide, followed by TBS protection of the newly generated alcohol, to afford compound **107** (73% yield, two steps). The (*E*)-vinylstannane compound **108** was generated from vinyl alcohol compound **107**, which was treated with tributyl tin hydride and Pd(II) in 79% yield.[27b] Alternatively, aldehyde **110**[28a] was treated with vinyl magnesium bromide, followed by TBS protection of the newly generated alcohol to afford compound **112** (78.% yield, two steps). The (*E*)-vinylstannane compound **113** was generated from treatment of the vinyl alcohol compound **112** with tributyl tin hydride and Pd(II) in 78% yield.[27b]



Scheme 3.13: Synthesis of synthon **108** and **113**.

Once synthons **108** and **113** were synthesized, the investigation of the coupling reactions commenced as described in Scheme 3.14 and Scheme 3.16. Coupling of 2-

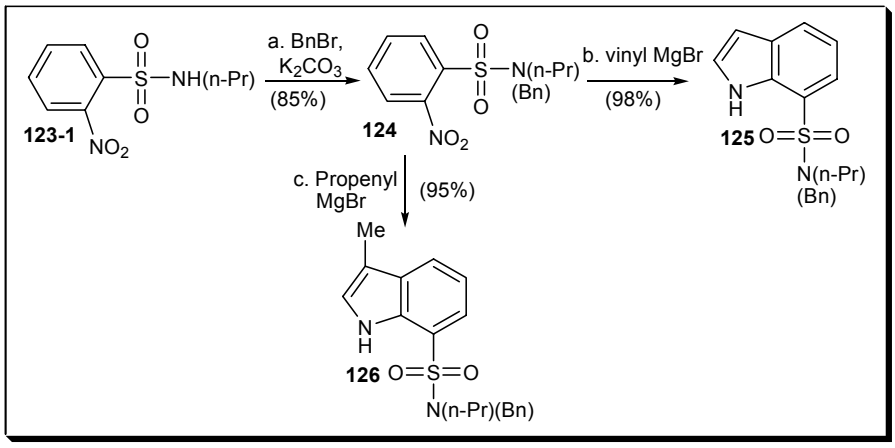
(2-bromophenyl)ethanol, **114**, with (*E*)-vinylstannane **108** catalyzed by $Pd_2(dba)_3$, followed by acetylation of the primary alcohol to afford compound **116** in 68% yield



Scheme 3.14: Use of Ns as a protecting group: Indole formation**.**

over two steps. Selective mono-deprotection of primary alcohol with HF.pyridine followed by bromination under neutral conditions with tetrabutyl ammonium bromide (TBABr)[29] afforded bromo compound **118** in 74% yield (two steps). Compound **118** was converted to the corresponding compound **120** by displacement of the bromide with Ns protected secondary amine under either basic conditions[30] or Mitsunobu conditions[30] followed by acetate removal with LiOH to afford alcohol **120** in 87% yield over two steps. Compound **120** was oxidized to aldehyde **121** with Dess-Martin periodinane in 88% yield and the resultant aldehyde was treated with vinyl magnesium bromide to afford the corresponding adduct **122**. However, we noticed that compound **122** was less polar than expected (characterized by a very peculiar orange tint). In addition, NMR analysis indicated that not only the aldehyde had reacted with the Grignard reagent, but also that the nosyl group had changed. The nosyl (Ns)

protecting group was unexpectedly converted to its corresponding indole adduct. Although the reaction was carried out at -78 ^{o}C, there was not discrimination between



Scheme 3.15: Applications of the indole formation**.**

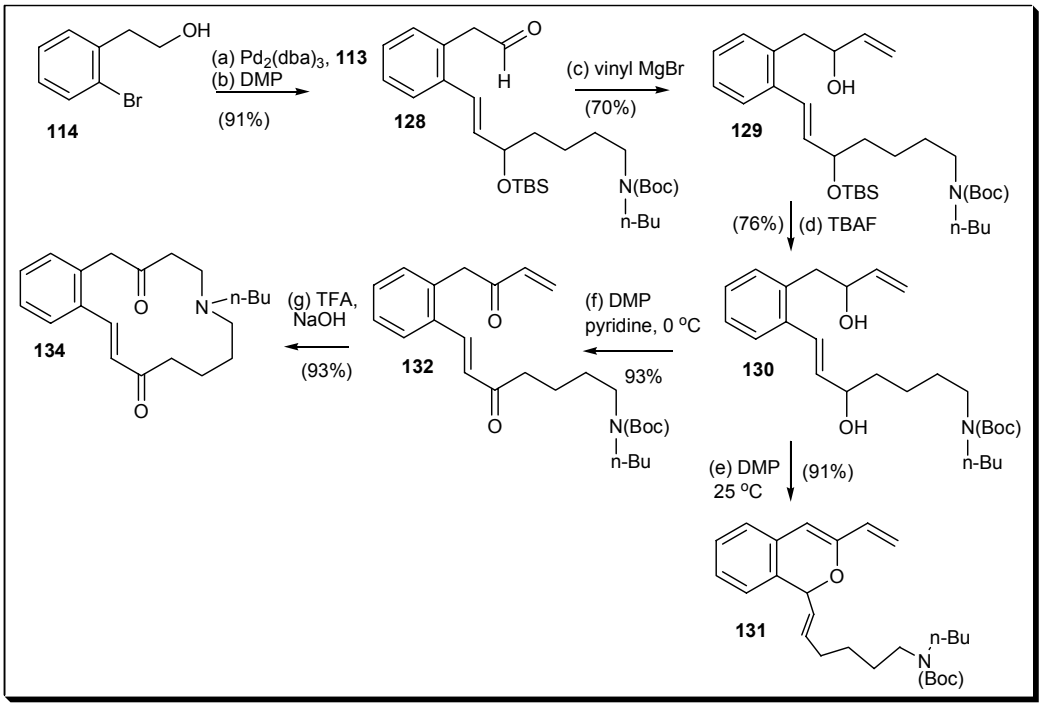
the aldehyde and nitro group, both were attacked concurrently to give **122** in 42% yield along with unreacted starting material. We had used 2.5 equivalents of the Grignard reagent and we found that limiting the amount to one equivalent of Grignard reagent only gave mixtures of the desired alkylated compound, compound **122** in a combined yield of 20%, and the remaining starting material contaminated with decomposed aldehyde. In addition, the purification of the desired product and compound **122** proved problematic since they shared very similar R_f values. Nonetheless, the synthesis of compound **122** motivated us to investigate the applications of this reaction. The Bartoli reaction has been studied for many years,[31] and it is one the shortest methods available to synthesized indoles. However, the reaction suffers from certain drawbacks such as the reaction only works for ortho-substituted aryl compounds and the substituent can have a negative effect on the reaction. The synthesis of sulfamoylindoles via Bartoli reaction has not been reported.

In fact, the various studies of elaborated sulfamoyindoles such as the examples shown here start with the indole moiety and require several steps that proceed with moderate to poor yields.[31b,c] We decided to briefly investigate this reaction. As described in Scheme 3.15, the sulfamoylindole compound **125** and **126** was formed smoothly from compound **124** when using either vinyl magnesium bromide or propenyl magnesium bromide in 98% and 95% yield respectively. The construction of sulfamoylindoles through this reaction would take advantage of the commercially availability of the nosyl protecting group (Ns), whose nitrogen can be either alkylated or protected. This chemical transformation should be of use to the development of complex sulfamoylindoles.

Although, this route provided us with valuable information regarding sulfamoylindoles, a different protecting group had to be investigated for the nitrogen atom. One immediate solution was to use a Boc protecting group. Similar examples[32a,b] suggested that the deprotection of Boc group with TFA would favor the proposed six member ring iminium ion formation via dehydration, followed by base treatment to afford the desired amino diene compound **139** (Fig 3.8).

Scheme 3.16 describes our approach to solve the protecting group problem. The approach commenced by coupling reaction of **114** and **113** under our previous Stille coupling conditions,[27a] to afford the corresponding alcohol, which was oxidized with Dess-Martin periodinane to give aldehyde **128** in good yield (90% yield, two steps). Treatment of aldehyde **128** with vinyl magnesium bromide at -78 ^{o}C afforded the desired compound in low yields due to enolization of the benzylic carbon as well

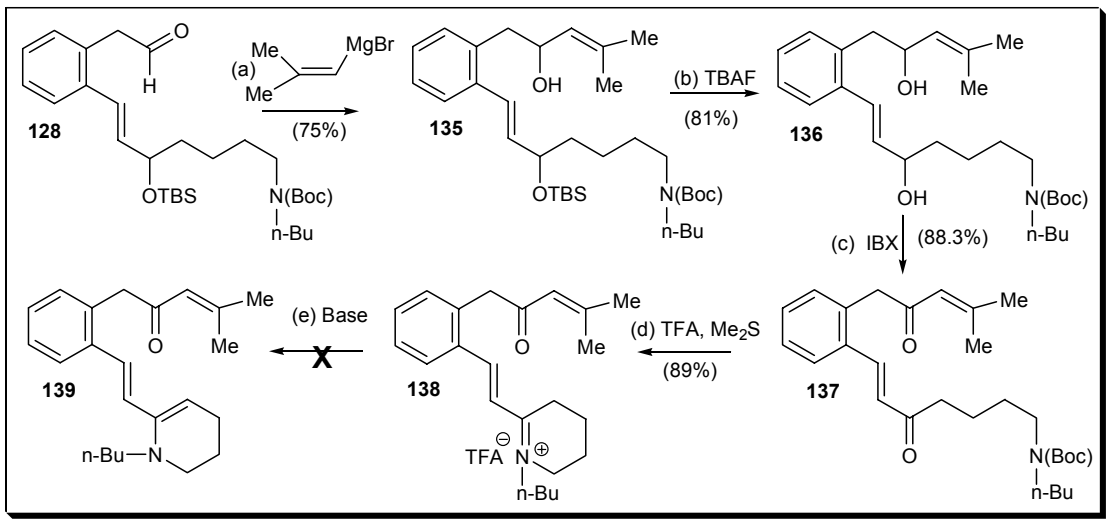
as Boc protecting group incompatibility. However, we found that on lowering the temperature to -90 ^{o}C and with slow addition of the Grignard reagent, we could obtain compound **129** in a satisfying 70% yield. Removal of the TBS group with TBAF, provided us with **130** in 76% yield. The diol was oxidized with Dess-Martin periodinane at 25 ^{o}C and provided only compound **131** in 91% yield. This unexpected transformation can be explained by considering an initial oxidation of the C-20 allylic alcohol, which is rapidly isomerized to the corresponding enol due to extended conjugation with the phenyl ring. Nucleophilic addition (S_N2') of the enol oxygen at the allylic C-8 center, followed by elimination of the allylic hydroxyl group, likely pre-complexed with the periodinane would form the tetrahydropyran structure **131**.



Scheme 3.16: Construction of synthon **132**.

We hypothesized that the increasing acidity of the oxidizing reagent would accelerate the enolization and thus would favor this cyclization. To avoid this side-reaction, we oxidized diol **130** with Dess-Martin periodinane in the presence of pyridine at 0 ^{o}C to afford the desired diketone compound **132** in very good yield. Compound **132** was treated with TFA followed by neutralization with NaOH to afford only Michael adduct **134**, instead of the desired amino diene compound **139**. It was believed that if the α,β-unsaturated system of the upper periphery was substituted, this undesired Michael addition could be prevented.

Alternatively, as described in Scheme 3.17, treatment of aldehyde compound **128** with (2-methylprop-1-enyl) magnesium bromide at -78 ^{o}C produced compound **135** in 75% yield. Removal of the TBS group with TBAF afforded diol **136** in 81% yield, which was treated with IBX at 25 ^{o}C to afford the diketone compound **137**, which upon treatment with TFA yielded the azadiene compound **138** as the TFA salt.



Scheme 3.17: Synthesis of synthon **137**.

However, upon further treatment of compound **138** with various bases (Et_3N, KHMDS, NaHMDS, LiHMDS, DBU, tBuOK; KOH, NaOH, K_2CO_3, $NaHCO_3$, NaH_2PO_4) no traces of the desired dieneamine compound **139** were observed, rather fast decomposition, even at low temperatures, was observed. We postulated that the benzylic carbon was responsible for our failure. It was believed that this benzylic carbon underwent fast enolization upon treatment with base propagating a series of undesired side reactions.

Our current strategy indicated that the imine formation was not as difficult as expected, but the resultant amino diene could not be isolated in its pure form under our conditions. It was decided to synthesize the 2-amino-1,3- diene using a different synthetic approach, one that did not involved an intramolecular dehydration to form the D ring, but one that already contained such functionality.

Section 3.4.3 Studies of the Cycloaddition Reaction of 2-(-N- Acylamino) 1, 3-dienes: An intermolecular study

Having gathered sufficient information on the feasibility of a more bio-inspired approach such as the [4 + 2] cycloaddition of an amino diene to form the C ring, it was decided to synthesize a more robust model amino diene system such as acylamino diene **141** (Figure 3.16).

Our last approach deals with creating an amino diene model system such as **141** to test the proposed intermolecular [4+2] cycloaddition reaction.

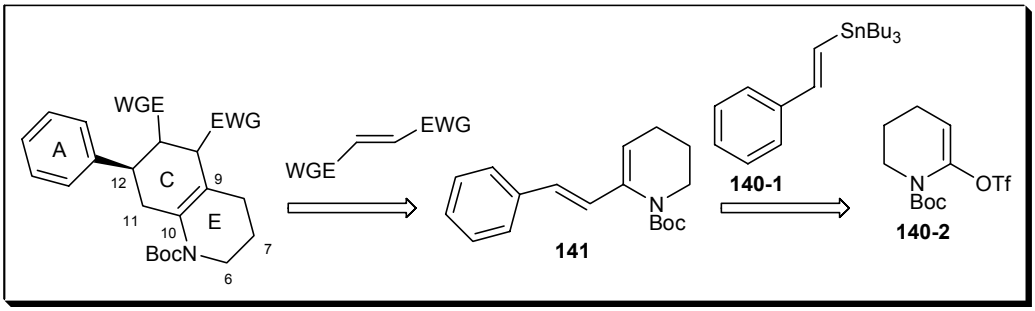


Figure 3.16: Bond disconnection of an intermolecular model system.

As previously stated 2-amino-1,3 dienes have been studied over the past few years with an emphasis on N,N-dialkylamino dienes,[26,33] but their counterparts, N-acylamino 1,3-dienes have not been broadly reported until recently.[33] Amino dienes have proven useful for applications in alkaloid synthesis. For instance, within the past few years several total synthesis of complex alkaloid systems have been carried out by using either 1,2 or 1,3 dieneamines.[34]

However, 2-(N-acylamino) 1,3- dienes have received less attention from the synthetic community, until recent pioneer work by Speckamp, Ha, and Sulikowski respectively.[33c-h, 36a] Their investigations included 5-, 6-, and 7-member ring cyclic 2-amino 1,3-dienes. This sudden interest on cyclic 2-(N-acylamino)-1, 3-dienes was due to the development of 1,3 amino dienes using Stille cross-coupling reactions of lactam derived enol triflates[35] or phosphates[35] with the corresponding stannane partners and Suzuki cross coupling reactions as well. In addition, theoretical studies had suggested that 1,3-amino dienes were poor dienes[36b] and unlikely to react in a [4+2] cycloaddition. This theoretical interpretation was later supported by an elegant study conducted by Sulikowski, whose observations indicated that in the piperidine dieneamide the plane of the carbamate nitrogen was twisted by 38^{o} relative to the

diene,[36a] emphasizing the lack of participation of the nitrogen electron lone pair to the conjugated system, but not necessarily diminishing its potential as a diene.

For *N*,*N*-dialkylated amino dienes, it is possible for their cycloaddition reaction to follow a concerted Diels-Alder reaction or a two step Michael type reaction pathway since the nitrogen electron lone pair is available to direct such a reaction. This two step mechanism would not be expected from the N-acylamino diene because being a carbamate resonance delocalization diminishes the nitrogen's nucleophilicity, making it a more stable diene or unreactive diene.[36c] If the nitrogen has little or no influence on the diene's reactivity, then we would expect the corresponding cycloaddition reaction to follow a normal concerted Diels-Alder reaction, which shows little if any solvent effect.[37]

It is established that the rates of reactions that involve isopolar activated complexes, that are neither dipolar nor radical, normally are not solvent-dependent3[36] and this statement has been repeatedly used as a criterion for establishing the mechanism of the Diels Alder reaction and 1,3- dipolar cycloaddition reactions.[37] The role of the solvent has been assumed to be static in a Diels-Alder reaction, hence its effect is basically given through the contribution of the solvation energy to the total free energy of the reactants and the transition structures.[37a]

A few studies on the cycloaddition reaction of 2-amino 1,3-dienes have been conducted prior to our work, and they showed high regioselectivity and stereoselectivity.[33,36] FMO theory predicts preference for the endo TS for amino

dienes containing 5, and 6 member rings as for the 7-member ring, the exo TS is expected.[36a]

Our synthesis began with Stille coupling reaction of **140-2** and **140-1** to afford amino diene **141** in 87% yield (Figure 3.17). The [4+2] cycloaddition of **141** with benzylmaleimide in benzene or in MeOH afforded white crystal on standing and its structure was unequivocally assigned through its X-ray analysis.[38] We immediately noticed that there was a substantial solvent dependency for the reaction rate in benzene. We became interested in understanding the parameters that could enhance this reaction without using forcing conditions.[39] We turned our attention to the solvent effect of **141** with N-benzylmaleimide (NBMI). Table 3.1 summarizes the results of this reaction in a broad range of solvents. The cycloaddition reaction occurred immediately in MeOH or DMSO at 25 ^{o}C and proceeded to 80% conversion in 6 h, eventually reaching completion in 9 h. Interestingly, we observed that the reaction in TFE would be completed in 7 h at 25 ^{o}C and upon heating it would be completed in 1.5 h. The experiment was also conducted in ethylene glycol, dioxane, DME, DMF, DMSO, and CH_3CN.

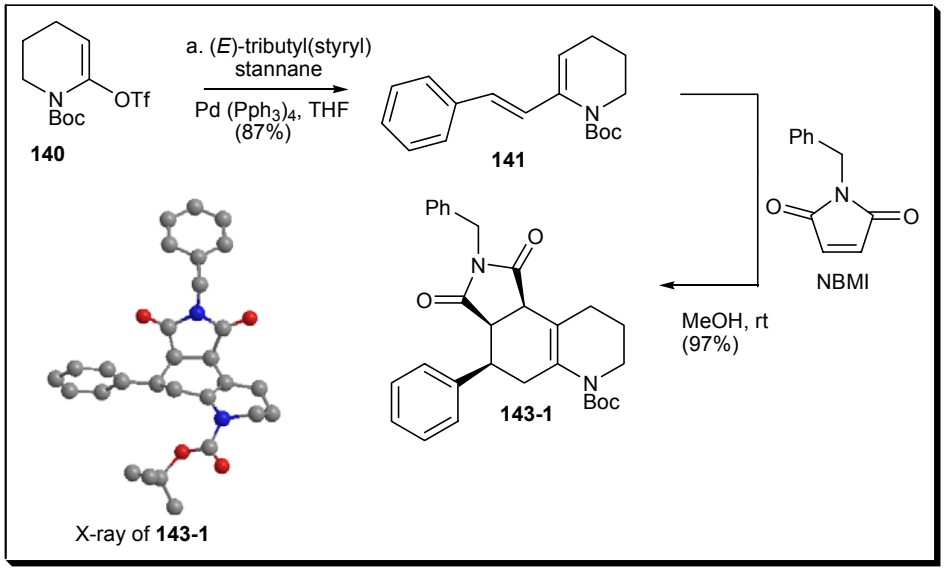


Figure 3.17. Preparation of 2-(-N-acyl-amino)-1,3-diene **141** and its cycloaddition reaction with N-benzylmaleimide (NBMI).

These latter solvents showed similar reaction rates for the cycloaddition, thus taking place slowly at 25 ^{o}C, but upon heating (90 ^{o}C), the cycloadduct was produced in 2 h.

Table 3.1: Solvents, times and NMR yields for reaction of **141** with NBMI.

Solvent	25 ^{o}C (h)	Yield	90 ^{o}C (h)	Yield
C_6H_6	154	90	9	89
$CHCl_3$	100	88	6	90
CH_3CN	18	87	2	87
Dioxane	12	79	2	76
DME	12	80	2	78
DMF	12	88	2	85
DMSO	9	91	2	90
CH_3OH	9	99	2	99
CF_3CH_2OH	7	95	1.5	99

The obtained findings raised the question whether our observed cycloaddition was taking place via a Diels-Alder reaction or a two-step Michael addition that would be enhanced by solvent coordination to the anionic intermediate.

As stated above, stepwise cycloaddition reactions for N, N-dialkyl amino 1,3-dienes are possible[33a] and even intermediates of the Michael addition reaction have been isolated,[37e] but very little is known about the 2-acyl amino 1,3-dienes. Attempts to isolate an intermediate by NMR experiments at low temperatures in polar solvents proved unsuccessful. It is possible that such intermediate exists, but its isolation or observation by NMR is not feasible.

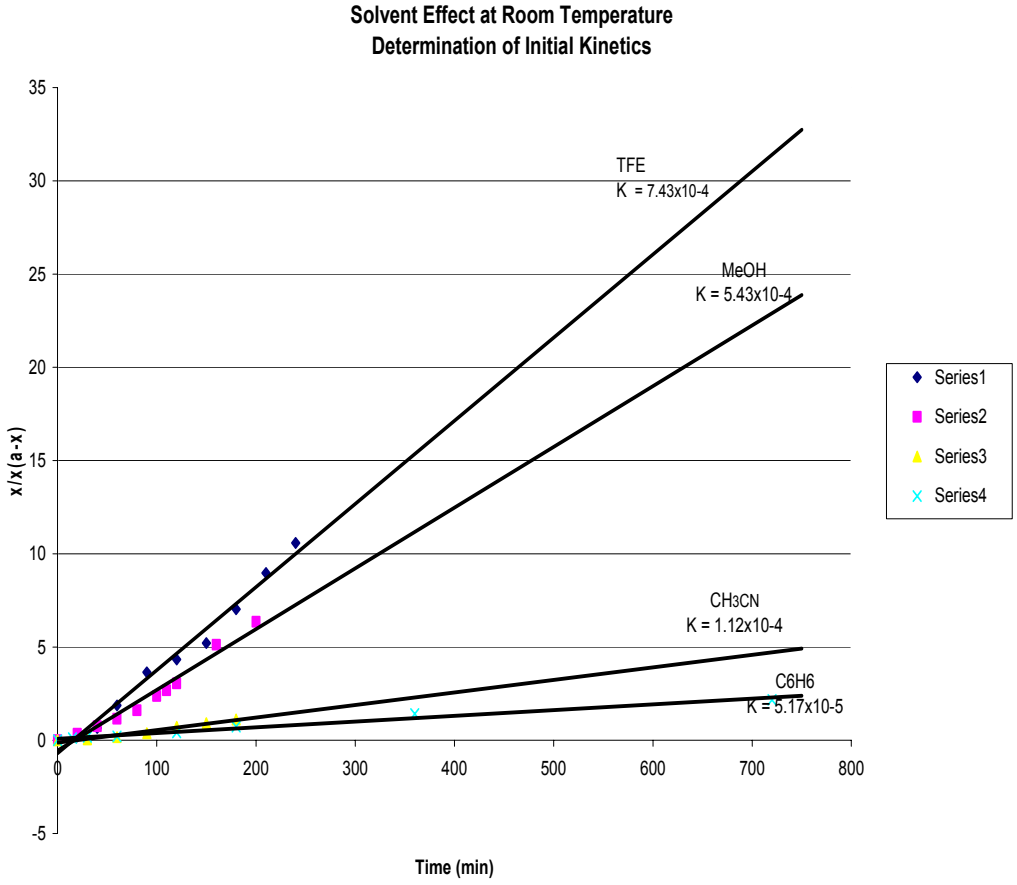
We decided to determine the initial rates of the reaction **141** by using the second order reaction, first order with respect to each reactant, diene and dienophile with equal initial concentrations (1:1 ratio). This situation of equal initial concentrations is equivalent mathematically to a second order reaction of one reactant, which is shown in Equation **1** when *a* represents the initial concentration and *x* is the

$1/c-1/c_0 = kt$ which becomes $1/(a-x)-1/a = x/[a(a-x)]= kt$ **Equation 1**

dependent variable. The obtained results are shown in Graph 3.1 and 3.2 respectively, indicating the initial rates of the reaction at different temperatures. The initial rates of the reaction reflected a bimolecular second order overall reaction with respect to each molecule as shown in the graphs.[43] The overall rate of the reaction showed fluctuation as the reaction proceeded to completion and it deviated from linearity indicating that the reaction was affected by product inhibition, solubility factors, and concentration

factors. Graph 3.1 shows the reaction for CD_3OD, CF_3CD_2OD, CD_3CN, C_6D_6 at 25 ^oC. The reaction was the fastest in CF_3CD_2OD followed closely by CD_3OD and the slowest in C_6D_6. The initial rates of the reaction, k_i, were $CF_3CD_2OD = 7.43x10^{-4}$, $CD_3OH = 5.43x10^{-4}$, $CD_3CN = 1.12x10^{-4}$, $C_6D_6 = 5.17x10^{-5}$.

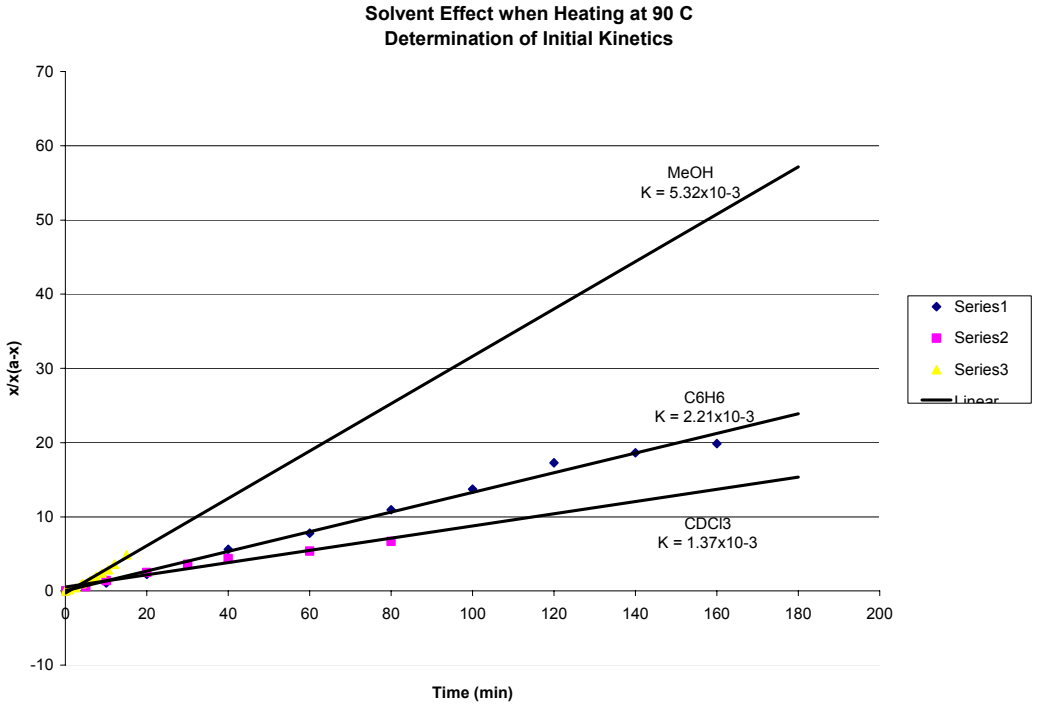
Graph 3.1: Solvent effect of the cycloaddition reaction of **141** with NBMI at 25 ^oC.



The same experiment was carried out at 90 ^oC in sealed tubes using $CDCl_3$, CD_3OD, and C_6D_6 and the results are shown in Graph 3.2. The initial rates of the cycloaddition reaction at 90 ^oC showed that the reaction was the fastest in CD_3OD followed by C_6D_6 and $CDCl_3$ with values of $5.32x10^{-3}$, $2.21x10^{-3}$, $1.37x10^{-3}$ respectively. Although, the initial rate of the reaction in C_6D_6 was faster than $CDCl_3$,

the overall rate of reaction slows down rapidly over time with a completion time of 9 h, while the reaction in chloroform diminishes at a slower rate with a completion time of 6h.

Graph 3.2: Solvent effect of cycloaddition reaction **141** with NBMI at 90 ^{o}C.



Our cycloaddition reaction of 2-acyl-amino 1,3-diene showed great solvent dependency because heating was unnecessary when polar solvents, which are categorized as high electron pair acceptor solvents, were used. Studies of the Diels-Alder reaction rates with empirical solvent parameters such as the electron pair acceptor (EPA) properties are rare, but these studies could help us understand our experimental observations.[41,42] For instance, Teconi's group[42] carried out a cycloaddition reaction between 2,3-dimethylbutadiene with 1,4-naphthoquinone, whose kinetic rate constant was measured in a series of solvents. Their obtained values

did not show suitable linear correlations with classical polarity parameters**,** however, when log**k** values were plotted against the Gutmann's **AN** (Acceptor Number) parameters, a smooth hyperbolic correlation was obtained showing that this reaction belonged to the normal electron-demand type, HOMO-LUMO, and it was controlled by the coordination of the EPA solvent at the carbonyl oxygen atom of the naphthoquinone, which lowered its LUMO energy. At room temperature, the initial rates for polar solvents identified the following trend CF_3CD_2OD >CD_3OD>CD_3CN>C_6D_6, the reactions were completed in 7 h, 9 h, 18 h, 154 h respectively. This reaction accelerating trend is complementary to the increasing EPA numbers of these solvents (as shown in table 3.2); CF_3CD_2OD = 53.3, CD_3OD = 41.5, $CDCl_3$ = 23.1, CD_3CN = 18.9, C_6D_6 = 8.20.

Our studies indicate that the increasing rate is enhanced by the acidity of the solvent and that a Diels-Alder reaction is responsible for the [4+2] cycloaddition.

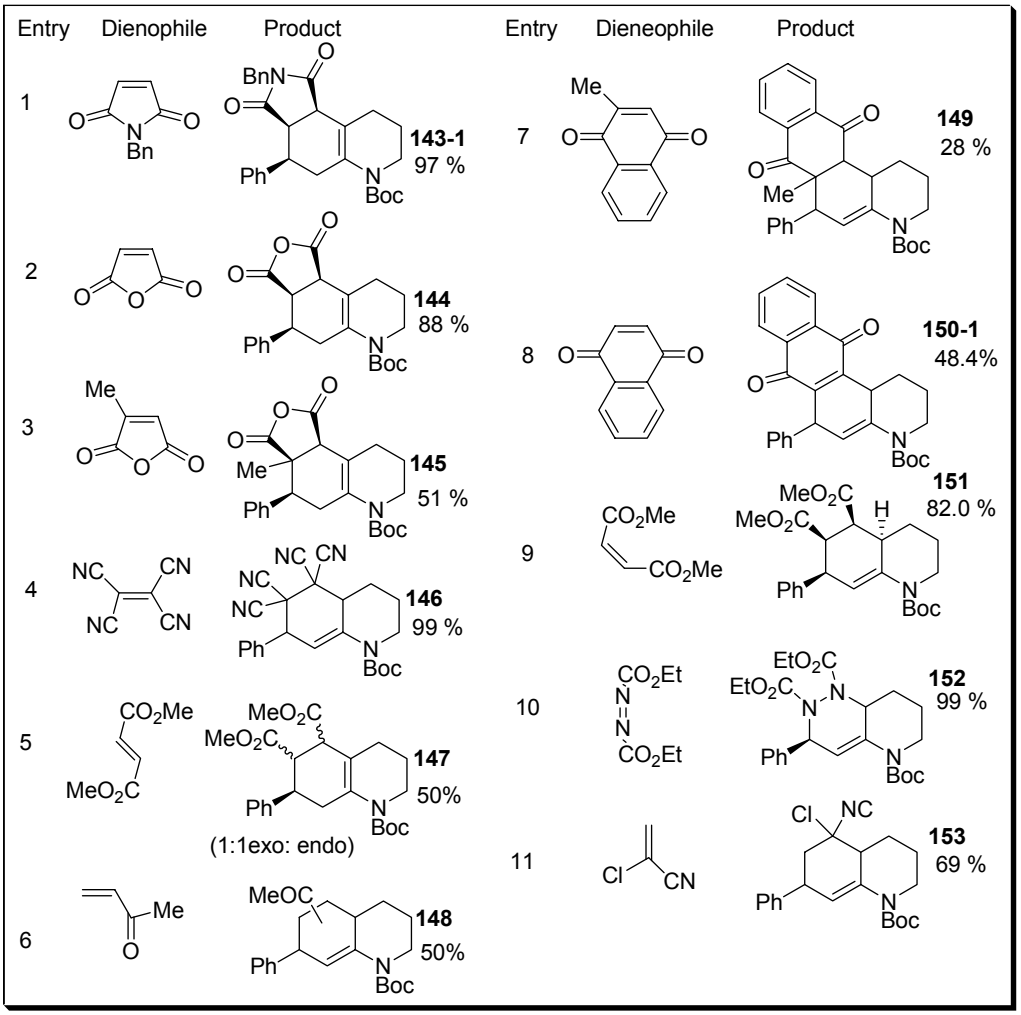
Table 3.2: Initial K versus EPA

Solvent	Initial k	EPA value
CF_3CH_2OH	7.43x10-4	53.3
CH_3OH	5.43x10-4	41.5
CH_3CN	1.12x10-4	18.9
C_6H_6	5.17x10-5	8.2

In addition, we decided to test the reactivity profile of diene **141** with several dienophiles, which provided the corresponding cycloadducts in moderate to good yields (shown in Table 3.3). These experimental results demonstrated the utility of acyl amino dienes to provide complex cycloadducts under mild conditions.[38] The endo TS was favored for these cycloadducts as previously observed in similar

systems.[35] Most of the dienophiles used to carry out the reaction (shown in Table 3.3) are considered highly activated, and the less activated dienophiles such as methyl vinyl ketone resisted cycloaddition under our mild conditions. It is possible that under high pressure and high temperature, the less activated dienophiles can react in moderate yields. As shown in Table 3.1, the yields range from 28% for the congested

Table 3.3. Cycloaddition Reactions of 2-(N-acylamino) 1,3-diene **141** with various dienophiles.



methyl naphthoquinone to almost quantitative (99% yield) for the reactive tetracyano ethylene dienophile. Most of the products were isolated as single compounds with the exception of entry 5, which gave inseparable mixture the endo/exo products. As indicated above, methyl vinyl ketone resisted reacting in benzene at 90 ^{o}C over a 10-day period, and even in MeOH after 48 h, there was no reaction, only starting materials were recovered. However, when the reaction was carried out in ethylene glycol after 6 h, it afforded a mixture of endo/exo cycloadducts in 50% yield. This result supported our findings that the more polar solvents (display Lewis acid properties) speed up the reaction, therefore enhance reactivity. In addition, it was observed that the yields were generally higher in MeOH than in benzene. Some of these cycloadducts also showed interesting reactivity; for instance, compound **150** was oxidized to compound **150-1** in quantitative yield, presumably under air-oxidation (Figure 3.18), while **143** isomerized to compound **143-1** on standing in $CDCl_3$ or neat at room temperature. The isomerization of the resulting double bond in adduct **143** to give the more substituted and thus more stable endo alkene could be use since it is a requirement for the proposed synthesis of norzoanthamine.

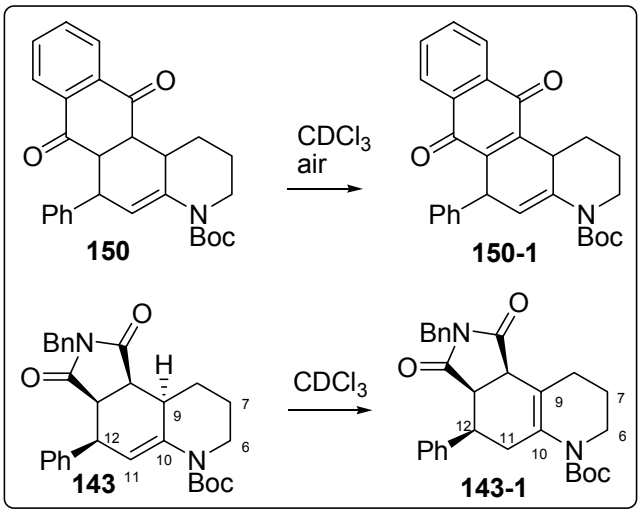


Figure 3.18: Air oxidation of **150** to **150-1** and acid catalyzed bond isomerization of **143** to **143-1.**

In summary, we performed an efficient kinetic study on the cycloaddition of **141** with N-benzylmaleimide and a reactivity survey of the cycloaddition of 2-(N-acylamino)-1,3-diene **141** with various dienophiles. This information is useful not only to the development of the C ring of norzoanthamine, but also to the understanding of [4+2] cycloadditions of 2-(N-acylamino)- 1,3-dienes.

Section 3.5 Experimental Section

Section 3.5.1 General Techniques

All reagents were commercially obtained (Aldrich, Acros) at 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 using flame-dried glassware within an argon atmosphere in dry, freshly distilled solvents, unless otherwise noted. Tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), toluene ($PhCH_3$) and benzene (PhH) were purified by passage through a bed of activated alumina(1), *N,N*-diisopropylethylamine (DIPEA), diisopropylamine, pyridine, triethylamine (TEA) and boron trifluoride etherate were distilled from calcium hydride prior to use.[ii] Dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) were distilled from calcium hydride under reduced pressure (20 mmHg) and stored over 4Å molecular sieves until needed. Yields refer to chromatographically and spectroscopically (1H 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-

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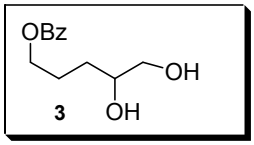
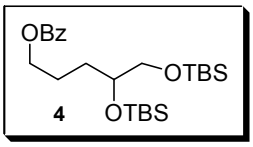
[ii] Perrin, D. D.; Armarego, W. L. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Oxford, **1988**.

254) using UV light as the visualizing agent and 10% ethanolic phosphomolybdic acid (PMA) or p-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Varian Mercury 300, 400 and/or Unity 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. Optical rotations were recorded on a Jasco P-1010 polarimeter and values are reported as follows: $[\alpha]_D$: (c: g/100ml, solvent). High-resolution mass spectra (HRMS) were recorded on a VG 7070 HS mass spectrometer under chemical ionization (CI) conditions or on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions. X-ray data were recorded on a Bruker SMART APEX 3kW Sealed Tube X-ray diffraction system.

Section 3.5.2 Experimental Procedures and Data

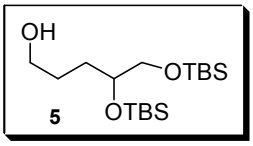


Compound 3: To a stirred solution of compound **2** (21.10 g, 0.1106 mol) in t-BuOH-H_2O (200:30 mL) at 25 ^oC, NMO (40.29 g, 0.344 mol) was added. Then, OsO_4 (11.24 mL, 1.1 mmol) was added and the reaction was allowed to stir at 25 ^oC for 16 h. The reaction mixture was quenched with a solution of NH_4Cl (150 mL) and extracted with DCM (3 x 150 mL). The combined organic extracts were washed with brine (2 x 150 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 25:75 Et_2O : hexane) to give the corresponding diol 3 (22.0 g, 0.096 mmol, 87.24% yield), as a white solid R_f = 0.65 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (m, 2H), 7.51 (m, 1H), 7.39 (m, 2H), 4.33 (tr, J = 6.40 Hz, 2H), 3.75 (d, J = 5.60 Hz, 1H), 3.63 (d, J = 11.20 Hz, 1H), 3.44 (m, 1H), 3.39 (s, 1H), 3.25 (s, 1H), 1.94 (m, 1H), 1.82 (m, 1H), 1.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.86, 133.14, 130.31, 129.68, 128.52, 72.07, 67.03, 65.15, 29.80, 25.40; HRMS calcd. for $C_{12}H_{16}O_4$ (M+ H^+) 225.1127, found 225.1124.



Compound 4: To a stirred solution of compound **3** (20.0 g, 87.7 mmol) in dry DCM (180 mL) at 0 ^oC was added imidazole (18.0 g, 263.00 mmol) followed by DMAP (cat). After 10 min, TBSCl (32.89 g, 219.00 mmol) was added and the reaction was allowed to stir at 25 ^0C for 16 h. The reaction mixture was quenched with a solution of NH_4Cl (150 mL) and extracted with DCM (3 x 150 mL). The combined organic extracts were washed with brine (2 x 150 mL), dried over $MgSO_4$, concentrated under reduced pressure and

purified by flash chromatography (silica, 5:95 Et_2O : hexane) to give the corresponding protected alcohol 4 (39.59g, 87.6 mmol, 99.89% yield), as a white solid R_f = 0.65 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (m, 2H), 7.54 (m, 1H), 7.42 (m, 2H), 4.33 (m, 2H), 3.73 (m, 1H), 3.56 (dd, J = 5.60, 10.0 Hz, 1H), 3.43 (dd, J = 6.80, 9.60, 1H), 2.0-1.70 (s, 3H), 1.65 (m, 1H), 1.0-0.80 (m, 18H), 0.2-0.0 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.70, 132.92, 130.61, 129.70, 128.44, 72.85, 67.33, 65.55, 31.10, 26.34, 26.28, 24.77, 18.74, 18.55, -3.79, -4.26, -4.85, -4.90; HRMS calcd. for $C_{24}H_{44}O_4Si_2$ (M+ H^+) 453.2856, found 453.2854.



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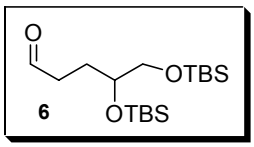
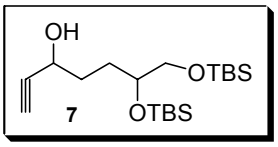
Alcohol 5: To a stirred solution of compound **4** (39.60 g, 87.6 mmol) in MeOH (80 mL) at 0 ^oC was added NaOH (0.35 g, 8.75 mmol). The reaction mixture was stirred for 6 h, and quenched with a solution of NH_4Cl (100 mL) and extracted with DCM (3 x 150 mL). The combined organic extracts were washed with brine (2 x 150 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 Et_2O : hexane) to give the corresponding alcohol 6 (30.10g, 86.50 mmol, 99.0% yield), as a colorless oil R_f = 0.60 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 3.74 (m, 1H), 3.62 (m, 2H), 3.54 (dd, J = 5.60, 10.0 Hz, 1H), 3.44 (dd, J = 6.80, 10.0, 1H), 2.05 (s, 1H), 1.80-1.50 (m, 4H), 1.0-0.80 (m, 18H), 0.2-0.0 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.03, 67.01, 63.49, 31.17, 28.43, 26.36, 26.25, 18.76, 18.55, -3.90, -4.31, -4.84, -4.91; HRMS calcd. for $C_{17}H_{40}O_3Si_2$ (M+ H^+) 349.2594, found 349.2592.

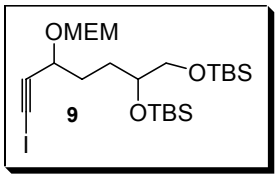


Aldehyde 6: To a stirred solution of compound **5** (30.0 g, 86.15 mmol) in dry DCM: DMSO (145:120 mL) at 0 ^{0}C was added TEA (48.23g, 477.00 mmol) followed by SO_3-pyridine complex (60.80g, 152.96 mmol). The reaction mixture was stirred for 2 h at 25 ^{o}C. The reaction mixture was quenched with a solution of NH_4Cl (150 mL) and extracted with EtOAc (3 x 150 mL). The combined organic extracts were washed with brine (2 x 150 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 5:95 Et_2O : hexane) to give the corresponding aldehyde 6 (29.33g, 85.0 mmol, 99.0% yield), as a colorless oil R_f = 0.65 (50% Et_2O: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 3.72 (m, 1H), 3.53 (dd, J = 4.80, 9.60 Hz, 1H), 3.37 (dd, J = 7.20, 10.0 Hz, 1H), 2.49 (m, 2H), 1.95 (m, 1H), 1.73 (m, 1H), 0.87 (m, 18H), 0.05 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.76, 146.57, 72.06, 66.94, 39.79, 26.95, 26.31, 26.22, 18.72, 18.47, -3.89, -4.32, -4.90, -4.95; HRMS calcd. for $C_{17}H_{38}O_3Si_2$ (M+ H^+) 347.2437, found 347.2438.

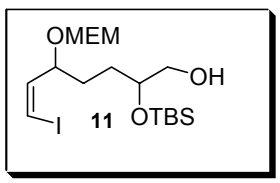


Alcohol 7: To a stirred solution of compound **6** (15.0 g, 43.35 mmol) in dry THF (100 mL) at -45 ^{o}C was added ethynyl magnesium bromide (1.0M, 86.7 mL, 86.70 mmol). The reaction mixture was stirred at 25 ^{o}C for 1 h, and it was quenched with a solution of NH_4Cl (150 mL) and extracted with EtOAc (3 x 150 mL). The combined organic extracts were washed with brine (2 x 150 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 6:94 Et_2O : hexane) to

give the corresponding protected alcohol (15.25 g, 41.0 mmol, 95.0% yield), as a colorless oil R_f = 0.50 (50% Et_2O: hexane).

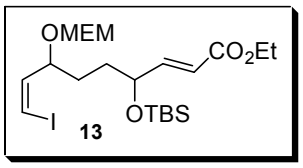


Alcohol 9: To a stirred solution of compound **7** (6.19 g, 30.65 mmol) in dry THF (60 mL) was added DIPEA (5.94 g, 45.99 mmol) followed by MEMCl (5.34 g, 42.9 mmol) at 0 ^{0}C. The reaction mixture was stirred at 25 ^{o}C for 16 h, and it was quenched with a solution of NH_4Cl (80 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (2 x 100 mL), dried over $MgSO_4$, concentrated under reduced pressure to give the protected alcohol (8.5 g, 29.6 mmol, 97% yield), which was dissolved in acetone (100 mL), and was treated with $AgNO_3$ (2.0 g,11.84 mmol) and NIS (9.95g, 44.4 mmol) at 25 ^{o}C. The reaction mixture was stirred at that temperature for 1 h and the solvent was evaporated under reduced pressure and purified by flash chromatography (silica, 5:95 EtOAc : hexane) to give the corresponding iodide (17.23 g, 29.4 mmol, 99.0% yield), as a colorless oil R_f = 0.58 (50% Et_2O: hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.98 (d, J = 7.20 Hz, 1H), 4.70 (d, J =7.20 Hz, 1H), 4.48 (m, 1H), 3.80-3.60 (m, 3H), 3.60-3.50 (m, 3H), 3.45-3.30 (m, 4H), 1.90-1.40 (m, 4H), 1.0-0.80 (m, 18H), 0.20-0.0 (m, 12H); HRMS calcd. for $C_{23}H_{47}IO_5Si_2$ (M+ Na^+) 609.1904, found 609.1905.



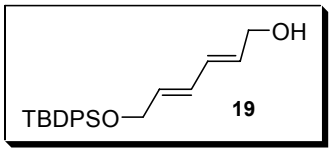
Alcohol 11: Compound **9** (13.0 g, 22.19 mmol) in dry THF: iPrOH (1:1, 50 mL) was treated with TEA (7.18g, 71.0 mmol) followed by NBSH (10.5 g, 48.8 mmol) at 25 ^{o}C. The reaction mixture was stirred at 25 ^{o}C for 16 h and it was quenched with a solution of

NH_4Cl (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (2 x 100 mL), dried over $MgSO_4$, concentrated under reduced pressure to give the reduced compound 10 (12.9 g, 21.94 mmol, 99% yield). Compound 10 (2.20 g, 3.74 mmol) was dissolved in dry THF (25 mL) and HF-pyridine (1.0 M, 3.74 mL) was added at 0 ^oC. The reaction mixture was stirred at 0 ^0C for 4h, then it was quenched with a saturated solution of $NaHCO_3$ (50 mL), and extracted with EtOAc (3x 50mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 20:80 Et_2O : hexane) to afford compound 11 (0.90 g, 1.90 mmol, 50.0% yield), as a colorless film R_f = 0.46 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 6.42 (d, J = 7.60 Hz, 1H), 6.16 (trd, J = 3.60, 8.0 Hz, 1H), 4.80-4.60 (m, 2H), 4.38 (m, 1H), 3.80-3.70 (m, 2H), 3.66 (m, 1H), 3.60-3.51 (m, 3H), 3.48 (m, 1H), 3.39 (s, 3H), 1.70-1.50 (m, 5H), 0.88 (s, 9H), 0.08 (s, 6H); HRMS calcd. for $C_{17}H_{35}IO_5Si$ (M+ Na^+) 497.1196, found 497.1194.



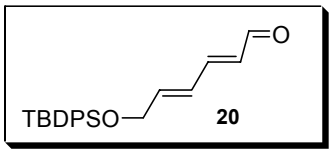
Compound 13: To a stirred solution of compound 11 (6.10 g, 12.87 mmol) in DCM:DMSO (3:1, 100mL) was added TEA (6.4 g, 63.5 mmol) at 0 ^oC. After 15 min, SO_3-pyridine was added and the reaction mixture was stirred at 25 ^oC for 1 h. Then, it was quenched with a saturated solution of NH_4Cl, and extracted with DCM (3x 150). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The aldehyde 12 was carried to the next step without further purification. To a stirred solution of triethylphosphonoacetate (12.8 g, 57.00 mmol) in THF (75 mL) was added

NaH (0.85g, 35.59 mmol) at 0 ^{o}C. After 15 min, the aldehyde 12 (6.0 g, 12.69 mmol) in THF (20 mL) was added via cannula at 0 ^{o}C. The reaction mixture was stirred at 25 ^{o}C for 2 h, and it was quenched with a solution of NH_4Cl (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (2 x 100 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 Et_2O: hexane) to give the corresponding protected alcohol (15.25 g, 41.0 mmol, 95% yield), as a colorless oil R_f = 0.50 (50% Et_2O: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (dd, J = 4.80, 17.30 Hz, 1H), 6.42 (d, J = 8.20 Hz, 1H), 6.14 (trd, J = 1.82, 7.30 Hz, 1H), 6.0 (dd, J = 1.82, 17.30 Hz, 1H), 4.80-4.60 (m, 2H), 4.45-4.25 (m, 2H), 3.80-3.50 (m, 9H), 3.40 (s, 3H), 1.80-1.40 (m, 4H), 1.0-0.80 (m, 9H), 0.10-0.0 (m, 6H); HRMS calcd. for $C_{21}H_{39}IO_6Si$ (M+ H^+) 543.1638, found 543.1639.

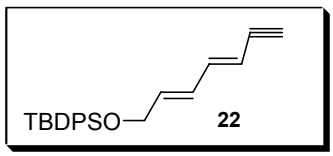


Compound 19: To a stirred solution of compound **18** (35.0 g, 0.1 mol) in dry Et_2O (250 mL) was added Red-Al (44.03 g, 0.2 mol) at -45 ^{o}C. After stirring for 2 h at 25 ^{o}C, the reaction mixture was quenched with a solution of NH_4Cl (150 mL) and extracted with EtOAc (3 x 150 mL). The combined organic extracts were washed with brine (2 x 150 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 Et_2O : hexane) to give the corresponding protected alcohol (15.25 g, 41.0 mmol, 95.0% yield), as a colorless oil R_f = 0.59 (50% Et_2O: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (m, 4H), 7.50-7.30 (m, 6H), 6.26 (m, 2H), 5.81 (m, 2H), 4.25 (d, J = 5.60 Hz, 2H), 4.19 (d, J = 6.0 Hz,

2H), 1.44 (br s, 1H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.65, 133.75, 133.00, 131.51, 131.22, 129.80, 128.96, 127.81, 64.28, 63.71, 27.21, 19.66; HRMS calcd. for $C_{22}H_{28}O_2Si$ (M+ H^+) 353.1937, found 353.1936.

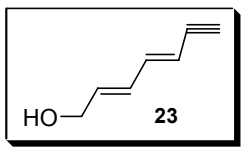


Compound 20: To a stirred solution of compound **19** (15.0 g, 42.00 mmol) in dry DCM:DMSO (80:20 mL) was added TEA (29.05 mL, 210.00 mmol) at 0 ^{0}C. Then, SO_3-pyridine was added and the reaction mixture was stirred at 0 ^{o}C for 30 min. The reaction mixture was quenched with a solution of 1N HCl (150 mL) and extracted with DCM (3 x 150 mL). The combined organic extracts were washed with brine (2 x 150 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 6:94 Et_2O : hexane) to give the corresponding aldehyde 20 (14.52 g, 41.50 mmol, 99% yield), as a colorless oil R_f = 0.63 (50% Et_2O: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (d, J = 7.80 Hz, 1H), 7.80-7.60 (m, 4H), 7.55-7.30 (m, 6H), 7.14 (dd, J = 10.80, 15.30 Hz, 1H), 6.67 (m, 1H), 6.28 (m, 1H), 6.16 (dd, J = 8.10, 15.0 Hz, 1H), 4.36 (m, 2H), 1.09 (s, 9H);^{13}C NMR (100 MHz, $CDCl_3$) δ 194.01, 151.93, 144.06, 135.64, 133.21, 131.46, 130.08, 128.00, 127.02, 63.87, 27.15, 19.67; HRMS calcd. for $C_{22}H_{26}O_2Si$ (M+ H^+) 351.1780, found 351.1780.



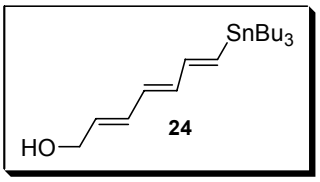
Compound 22: A solution of CBr_4 (11.93 g, 36.0 mmol) in dry DCM (60 mL) was treated with Ph_3P (18.8 g, 12.0 mmol) at 0 ^{o}C. After 5 min, Et_3N (24.9 mL, 180.0 mmol) was added followed by a solution of **20** (3.15 g, 9.0 mmol). The reaction was stirred for 10 minutes at 25 ^{o}C, and then concentrated and the residue (16.38 g,

32.5 mmol) was dissolved in THF (100 mL) and placed in a -90 ^{o}C bath. MeLi (1.4 M, 58.00 mL, 81.25 mmol) was added slowly and it was stirred for 20 min at -78 ^{o}C. The reaction mixture was quenched with a solution of NH_4Cl (100 mL) and extracted with EtOAc (3 x 150 mL). The combined organic extracts were washed with brine (2 x 150 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 Et_2O: hexane) to give the corresponding protected compound 22 (15.25 g, 41.0 mmol, 95% yield), as a colorless oil R_f = 0.63 (50% Et_2O: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.60 (m, 4H), 7.58-7.30 (m, 6H), 6.67 (dd, J = 10.80, 15.60 Hz, 1H), 6.36 (m, 1H), 5.88 (m, 1H), 5.54 (d, J = 16.50 Hz, 1H), 4.27 (d, J = 4.20 Hz, 2H), 3.02 (d, J = 2.40 Hz, 1H), 1.07 (s, 9H); HRMS calcd. for $C_{23}H_{26}OSi$ (M+ H^+) 347.1831, found 347.1830.

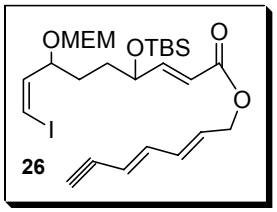


Compound 23: To a stirred solution of compound **22** (6.0 g, 16.92 mmol) in dry THF (10 mL) at 0 ^{o}C, was added AcOH (0.96, 16.92 mmol). Then, TBAF (1M, 33.84 mmol) was added. The reaction mixture was stirred at 25 ^{o}C for 1 h, and quenched with a saturated solution of NH_4Cl (15 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine (2 x 15 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 6:94 Et_2O : hexane) to give the corresponding alcohol (1.7 g, 15.74 mmol, 93% yield), as a colorless oil R_f = 0.42 (50% Et_2O: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (dd, J = 10.80, 15.60 Hz, 1H), 6.29 (m, 1H), 5.97 (m, 1H), 5.58 (dd, J = 2.0, 15.6

Hz, 1H), 4.22 (tr, J = 6.0 Hz, 2H), 3.03 (d, J = 2.0 Hz, 1H), 1.62 (m, 1H); HRMS calcd. for C_7H_8O (M+ H^+) 109.0653, found 109.0652.

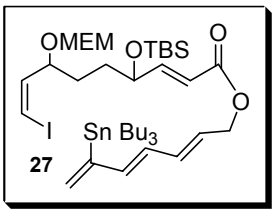


Compound 24: To a suspension of CuCN (0.99g, 11.10 mmol) in anhydrous THF, n-BuLi (8.8 mL, 22.20 mmol) was added at – 78 ^oC. The temperature was increased to -40 ^oC, and the reaction mixture was stirred for 15 min. Then, the mixture was placed back to the -78 ^oC bath and $SnBu_3H$ (5.98 mL, 22.20 mmol) was added, and the temperature brought to -40 ^0C for 15 min, and then it was cooled to -78 ^oC. At this point, a solution of compound **23** (0.60 g, 5.55 mmol) in dry THF (10 mL) was added and stirred at -78 ^oC for 30 min. The reaction mixture was quenched with a solution of NH_3-NH_4Cl (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine (2 x 15 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 30:70 EtOAc: hexane) to give the corresponding alcohol **24** (1.21 g, 3.05 mmol, 55.0% yield), as a colorless oil R_f = 0.44 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 6.59 (dd, J = 9.60, 18.80 Hz, 1H), 6.40-6.10 (m, 4H), 5.89 (m, 1H), 4.20 (m, 2H), 1.70-0.60 (m, 28H); HRMS calcd. for $C_{19}H_{36}OSn$ (M+ Na^+) 423.1686, found 423.1688.



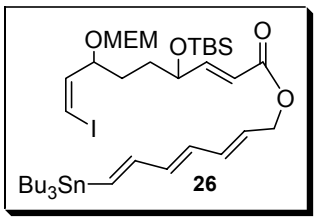
Compound 26: Compound **13** (0.30 g, 0.568 mmol) was dissolved in dry THF: MeOH (1:1, 10 mL), and was treated with LiOH (54.4 mg, 2.27 mmol) and it was allowed to stir for 6 h at 25 ^oC. The pH was adjusted to 2.0 with 1 N HCl and it was extracted with EtOAc (3x 10 mL). The solvent was evaporated under reduced

pressure to give the acid (0.26 g, 0.51 mmol, 90.0%), which was dissolved in dry DCM (10 mL) and treated with compound **23** (0.055 g, 0.51 mmol). Then, DCC (0.105 g, 0.51 mmol) was added and the reaction mixture was stirred at 25 ^{o}C for 16 h. The reaction was quenched with a solution of NH_4Cl (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine (2 x 15 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 EtOAc: hexane) to afford 26 (0.158 g, 0.255 mmol, 50.0% yield), as a colorless film R_f = 0.50 (50% EtOAc: hexane). 1:1 mixture of stereoisomers.

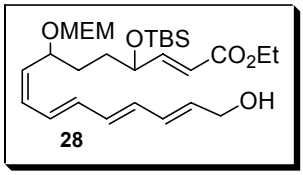


27

Compound 27: To a suspension of CuCN (5.19 mg, 0.058 mmol) in anhydrous THF (8 mL), was added n-BuLi (2.5 M, 0.046 mL, 0.116 mmol) was added at – 78 ^{o}C. The temperature was increased to -40 ^{o}C, and the reaction mixture was stirred for 15 min, then placed back to -78 ^{o}C and $SnBu_3H$ (0.031 mL, 0.116 mmol) was added. The mixture was brought to -40 ^{o}C for 15 min and then cooled to -78 ^{o}C. At this point, a solution of compound **26** (18.0 mg, 0.029 mmol) in dry THF (1 mL) was added and the reaction mixture was stirred at -40 ^{o}C for 1 h. It was quenched with a solution of NH_3-NH_4Cl (15 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (2 x 15 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 6:94 Et_2O : hexane) to give the corresponding protected alcohol (17.29 mg, 0.019 mmol, 65.0% yield), as a light yellow oil R_f = 0.40 (45% EtOAc: hexane).

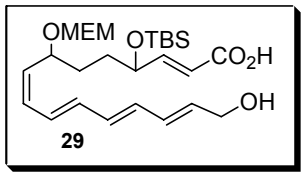


Compound 26: To a suspension of CuCN (0.125 g, 1.25 mmol) in anhydrous THF, n-BuLi (1.1 mL, 2.8 mmol) was added at – 78 ^{o}C. The temperature was increased to -40 ^{o}C, and the reaction mixture was stirred for 15 min. Then, the mixture was placed back to the -78 ^{o}C bath and $SnBu_3H$ (0.75 mL, 2.8 mmol) was added, and the temperature brought to -40 ^{0}C for 15 min, and then it was cooled to -78 ^{o}C. At this point, a solution of compound **13** (0.30 g, 0.568 mmol) was dissolved in dry THF(1 mL) was added and stirred at -40 ^{o}C for 15 min. The reaction mixture was quenched with a solution of NH_3-NH_4Cl (1 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (2 x 10 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 EtOAc: hexane) to afford **26** (0.158 g, 0.255 mmol, 50.0% yield), as a colorless film R_f = 0.50 (50% EtOAc: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (dd, J = 4.10, 16.0 Hz, 1H), 6.55 (dd, J = 9.10, 18.70 Hz, 1H), 6.40-6.10 (m, 5H), 6.01 (dd, J = 2.30, 16.0 Hz, 1H), 5.80 (m, 1H), 4.98 (dd, J = 1.60, 6.56 Hz, 1H), 4.75-4.60 (m, 4H), 4.42-4.30 (m, 2H), 3.80-3.69 (m, 2H), 3.68-3.60 (m, 2H), 3.59-3.50 (m, 2H), 3.39 (s, 3H), 1.90-0.70 (m, 58H), 0.15-0.0 (m, 6H); HRMS calcd. for $C_{38}H_{69}IO_6SiSn$ (M+ H^+) 897.3008, found 897.3007.



Compound 28: To a stirred solution of compound **13** (0.500 g, 0.92 mmol) and compound **23** (0.550 mmol, 1.38 mmol) in dry DMF (20 mL) was added $Pd(CH_3CN)_2Cl_2$ (0.023g, 0.092 mmol). The reaction mixture was stirred at 25 ^{o}C for 10 h in the dark. The

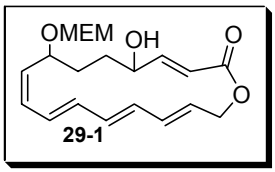
reaction mixture was diluted with Et_2O and filtered through celite. Then, it was washed with brine (2 x 15 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 30:70 EtOAc: hexane) to give the corresponding compound 28 (g, 41.0 mmol, 53.0% yield), as a colorless oil R_f = 0.33 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 6.88 (dd, J = 0.40, 15.60 Hz, 1H), 6.51 (m, 1H), 6.40-6.10 (m, 5H), 5.95 (dd, J = 2.40, 17.60 Hz, 1H), 5.89 (m, 1H), 5.25 (tr, J = 13.1 Hz, 1H), 4.69 (d, J = 7.20 Hz, 1H), 4.60 (d, J = 7.20 Hz, 1H), 4.51 (m, 1H), 4.32 (m, 1H), 4.25-4.10 (m, 4H), 3.79 (m, 1H), 3.65-3.50 (m, 3H), 3.39 (s, 3H), 1.75-1.40 (m, 5H), 1.27 (tr, J = 7.20 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); HRMS calcd. for $C_{28}H_{48}O_7Si$ (M+ Na^+) 547.3067, found 547.3066.



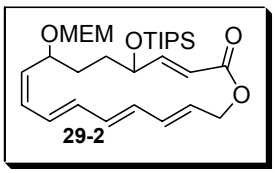
29

Compound 29: To a stirred solution of compound **28** (0.740 g, 1.41 mmol) in THF:MeOH (1:1, 10 mL) was added LiOH (0.168 g, 7.05 mmol). The reaction mixture was stirred at 25 ^oC for 6 h, and it was quenched with a solution of NH_4Cl (15 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine (2 x 15 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 40:60 Et_2O: hexane) to give the corresponding acid (0.56 g, 1.13 mmol, 80.0% yield), as a colorless film R_f = 0.29 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 6.90 (m, 1H), 6.51 (m, 1H), 6.40-6.10 (m, 5H), 5.99 (d, J = 16.0 Hz, 1H), 5.81 (m, 1H), 5.25 (m, 1H), 4.90-4.40 (m, 5H), 4.30 (m, 1H), 3.79 (m, 1H), 3.62 (m, 1H), 3.57 (m, 2H), 3.39 (s, 3H), 1.90-1.20

(m, 5H), 1.0-0.80 (m, 9H), 0.10-0.0 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 1; HRMS calcd. for $C_{26}H_{43}O_7Si$ (M+ H^-) 495.2777, found 495.2778.

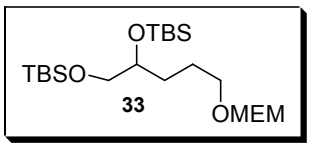


Compound 29-1: To a stirred solution of compound **29** (0.250 g, 0.44 mmol) in dry THF (2 mL) was added 2, 4, 6-trichlorobenzyl chloride (0.069 mL, 0.44 mmol) was added followed by TEA (0.073 mL, 0.53 mmol) at 0 ^oC. After stirring the mixture for 1 h at 25 ^oC, the mixture was added via syringe pump at a 10 mL/h rate to a pre-warmed benzene solution (20 mL) containing DMAP (2.20 mmol). Once the addition was complete the mixture was heated at 50 ^oC for 30 min. The reaction mixture was quenched with a solution of NH_4Cl (15 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine (2 x 15 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:9 EtOAc: hexane) to give the corresponding compound 29 (15.25 g, 41.0 mmol, 41.0% yield), as a light yellow film R_f = 0.45 (50% Et_2O: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (dd, J = 5.60, 16.60 Hz, 1H), 6.50 (tr, J = 11.1 Hz, 1H), 6.40-6.20 (m, 5H), 6.08 (dd, J = 1.60, 15.60 Hz, 1H), 5.80 (m, 1H), 5.29 (tr, J = 11.1 Hz, 1H), 4.85-4.50 (m, 4H), 4.38 (br s, 1H), 3.86 (m, 1H), 3.65-3.50 (m, 2H), 3.39 (s, 3H), 1.90-1.20 (m, 7H); HRMS calcd. for $C_{20}H_{28}O_6$ (M+ H^+) 365.1964, found 365.1963.



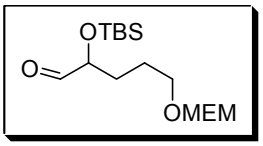
Compound 29-2: To a stirred solution of compound **29** (0.250 g, 0.44 mmol) in dry THF (2 mL) was added 2, 4, 6-trichlorobenzyl chloride (0.069 mL, 0.44 mmol) was added

followed by TEA (0.073 mL, 0.53 mmol) at 0 ^{o}C. After stirring the mixture for 1 h at 25 ^{o}C, the mixture was added via syringe pump at a 10 mL/h rate to a pre-warmed benzene solution (20 mL) containing DMAP (2.20 mmol). Once the addition was completed the mixture was heated at 50 ^{o}C for 30 min. The reaction mixture was quenched with a solution of NH_4Cl (15 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine (2 x 15 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:9 EtOAc: hexane) to give the corresponding compound 29 (15.25 g, 41.0 mmol, 41.0% yield), as a light yellow film R_f = 0.45 (50% Et_2O: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (m, 1H), 6.51 (m, 1H), 6.40-6.10 (m, 5H), 6.0 (d, J = 15.10 Hz, 1H), 5.81 (m, 1H), 5.28 (m, 1H), 4.80-4.30 (m, 6H), 3.78 (m, 1H), 3.60 (m, 1H), 3.55 (m, 2H), 3.39 (s, 3H), 1.90-0.90 (m, 25H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 1; HRMS calcd. for $C_{29}H_{48}O_6Si$ (M+ H^+) 521.3298, found 521.3297.

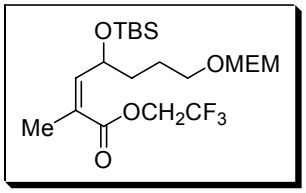


Compound 33: To a stirred solution of alcohol **5** (2.60 g, 7.47 mmol) in DCM (30 mL) at 0 ^{o}C was added DIPEA (3.37 g, 26.00 mmol) followed by MEMCl (2.76g 29.0 mmol). The reaction mixture was stirred for 16 h at 25 ^{o}C, and was quenched with a solution of NH_4Cl (25 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 Et_2O : hexane) to give the corresponding protected alcohol (29.58g, 85.0 mmol, 97.0% yield), as a colorless oil R_f = 0.60 (50% Et_2O: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ

4.71 (s, 2H), 3.67-3.42 (m, 9H), 3.39 (m, 3H), 1.80-1.30 (s, 4H), 1.0-0.80 (m, 18H), 0.10-0.0 (m, 12H); HRMS calcd. for $C_{21}H_{48}O_5Si_2$ (M+ H^+) 437.3119, found 437.3118.

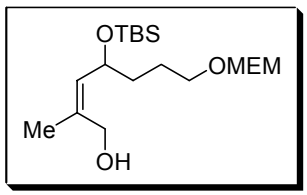


Aldehyde 35: To a stirred solution of compound **33** (2.00 g, 4.93 mmol) in dry THF (40 mL) at 0 ^oC was added HF-pyridine (1 M, 4.93 mL, 4.93 mmol). The reaction mixture was stirred for 6.3 h at 0 ^oC, and quenched with a solution of $NaHCO_3$ (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 Et_2O : hexane) to give the corresponding alcohol **34** (1.4 g, 4.80 mmol, 97.41% yield), as a colorless oil R_f = 0.40 (50% Et_2O: hexane). The alcohol (1.4 g, 4.80mmol) was dissolved in DCM (20 mL) and treated with DMP (2.65 g, 6.24mmol). The reaction was stirred for 1.5 h at 0 ^oC and quenched with a solution of $NaHCO_3$ (20 mL) and extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with brine (2 x 25 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 Et_2O : hexane) to give the corresponding aldehyde as a colorless oil (1.3 g, 4.48 mmol, 93.4% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 4.69 (s, 2H), 3.99 (m, 1H), 3.67(m, 2H), 3.60-3.45 (m, 4H), 3.38 (s, 3H), 1.80-1.60 (m, 4H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ; HRMS calcd. for $C_{15}H_{32}O_5Si$ (M+ H^+) 321.2097, found 321.2098.



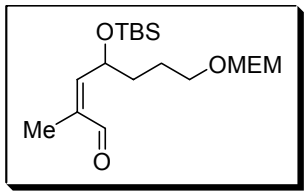
Ester 36: Ethyl 2-((bis(2,2,2-trifluoroethoxy))phosphoryl)

propionate (3.30g, 9.53 mmol) was dissolved THF along with 18 crown-6 (2.51g, 9.51 mmol) on a -78 ^{o}C. Then, KHMDS (12.71 mL, 6.35 mmol) was added and stirred for 60 min. Aldehyde **35** (0.92g, 3.17 mmol) was dissolved in THF and added via cannula to the phosphonate at – 78 ^{o}C. The reaction was allowed to stir for 1.3 h at -78 ^{o}C and it was quenched with a saturated solution of NH_4Cl and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 20:80 EtOAc: hexane) to give compound 36 (1.34 g, 2.93 mmol 92% yield) as a colorless oil R_f = 0.35 (50% Et_2O: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (dd, J = 1.60, 8.40 Hz, 1H), 5.0 (dd, J =7.20, 14.40, 1H), 4.68 (s, 2H), 4.17 (m, 2H), 3.66 (m, 2H), 3.55-3.45 (m, 4H), 3.37 (s, 3H), 1.87 (s, 3H), 1.80-1.40 (m, 4H), 0.80-0.95 (m, 9H), -0.03-0.05 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.45, 146.57, 125.87, 95.65, 72.10, 69.71, 68.30, 66.92, 60.66, 59.33, 34.54, 26.25, 26.01, 20.77, 18.55, 14.70, -4.013, -4.40; HRMS calcd. for $C_{20}H_{37}F_3O_6Si$ (M+ H^+) 459.2289, found 459.2288.

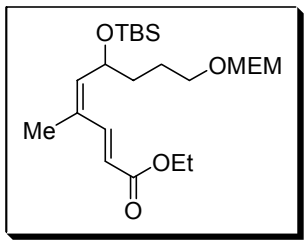


Alcohol 37: To a stirred solution of **36** (1.23 g, 3.2 mmol) in dry THF (30 mL) was added DIBAL-H (6.58 mL, 6.58 mmol) at -78 ^{o}C. The reaction mixture was stirred at -30 ^{o}C for 1.5 h, and it was quenched with a solution of Rochelle's salt (30 mL). It was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (2 x 40 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 EtOAc: hexane) to give the

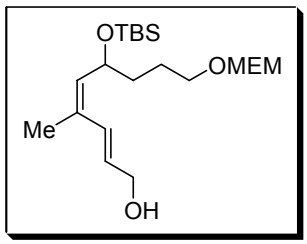
corresponding Alcohol (1.09 g, 3.0 mmol 94% yield), as a white foam R_f = 0.32 (50% EtOAc: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.26 (dd, J = 1.20, 7.20 Hz, 1H), 4.70 (s, 2H), 4.30 (m,1H), 4.11 (s, 2H), 3.68 (m, 2H), 3.62-3.50 (m, 4H), 3.39 (s, 2H), 1.78 (s, 3H), 1.70-1.40 (m, 5H), 1.0-0.80 (m, 9H), 0.0-0.10 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.62, 131.92, 95.70, 72.07, 69.11, 68.34, 67.01, 62.25, 59.34, 35.88, 26.27, 26.06, 21.69, -3.79, -4.27; HRMS calcd. for $C_{18}H_{38}O_5Si$ (M+ Na^+) 385.2386, found 385.2384.



Aldehyde 38: To a stirred solution of **37** (1.0 g, 3.08 mmol) in dry DCM-DMSO (3:1, 15mL) was added TEA (1.55 g, 15.0 mmol) followed by SO_3–Pyridine (2.0 g, 12.3 mmol) at 0 ^{o}C. The reaction mixture was stirred at 25 ^{o}C for 1 h and was quenched with a solution of NH_4Cl (15 mL) and was extracted with DCM (3 x 20 mL). The combined organic extracts were washed with brine (2 x 15 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 EtOAc : hexane) to give the corresponding aldehyde (1.07 g, 2.99 mmol 97% yield), as a light yellow oil R_f = 0.36 (50% Et_2O: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (s, 1H), 6.35 (d, J = 10.80 Hz, 1H), 5.06 (m, 1H), 4.68 (s, 2H), 3.66 (m, 2H), 3.60-3.45 (m, 4H), 3.37 (s, 3H), 1.77 (s, 3H), 1.76-1.44 (m, 4H), 1.00-0.80 (m, 9H), 0.03 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.03, 151.18, 134.89, 95.69, 72.05, 67.88, 67.28, 67.03, 59.33, 35.84, 26.14, 25.86, 18.51, 16.67, -3.83, -4.23; HRMS calcd. for $C_{18}H_{36}O_5Si$ (M+ Na^+) 383.2229, found 383.2230.

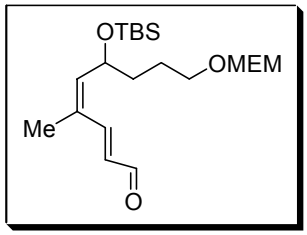


Ester 39: To a stirred solution triethylphosphonoacetate (2.80 g, 12.4 mmol) in THF (30 mL) was added NaH (0.37g, 7.76 mmol) at 0 ^{o}C. The mixture was stirred for 15 min and a solution of **38** (1.0 g, 2.7 mmol) in dry THF (15 mL) at 0 ^{o}C was added via cannula. The reaction mixture was stirred at 25 ^{o}C for 1 h and was quenched with a saturated solution of NH_4Cl (20 mL). It was extracted with EtOAc (3 x 50 mL) and washed with brine (2 x 20 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 EtOAc: hexane) to give the corresponding Ester (1.12 g, 2.6 mmol 96% yield), as a colorless oil R_f = 0.35 (50% EtOAc: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 15.20 Hz, 1H), 5.90 (d, J = 15.60 Hz, 1H), 5.62 (d, J = 9.20 Hz, 1H), 4.69 (s, 2H), 4.67 (m, 1H), 4.21 (m, 2H), 3.67 (s, 2H), 3.60-3.3.40 (m, 4H), 3.38 (s, 3H), 1.84 (s, 3H), 1.70-1.40 (m, 4H), 1.30 (tr, J = 7.20 Hz, 3H), 0.85 (s, 9H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.20, 141.97, 140.58, 130.03, 119.52, 95.67, 72.07, 68.56, 68.16, 66.96, 60.68, 59.33, 35.59, 26.22, 25.93, 20.34, 18.53, 14.71, -3.76, -4.25; HRMS calcd. for $C_{22}H_{42}O_6Si$ (M+ H^+) 431.2829, found 431.2830.



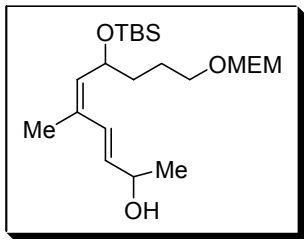
Alcohol 40: Compound **39** (1.0 g, 2.32 mmol) in dry THF (20 mL) was added DIBAL-H (5.8 mL, 5.8 mmol) at -78 ^{o}C. The reaction was allowed to stir for 30 min at -78 ^{o}C and was quenched with a 10% solution of tartaric acid. It was extracted with EtOAc (3 x 25 mL), washed with brine (2 x 100 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography

(silica, 15:85 EtOAc: hexane) to give the corresponding Alcohol (0.87 g, 2.23 mmol 96% yield), as a colorless film R_f = 0.30 (50% EtOAc: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (d, J = 15.60 Hz, 1H), 5.84 (m, 1H), 5.29 (d, J = 8.40 Hz, 1H), 4.69 (s, 3H), 4.56 (m, 1H), 4.22 (m, 2H), 3.66 (m, 2H), 3.60-3.40 (m, 4H), 3.37 (s, 3H), 1.81 (s, 3H), 1.80-1.40 (m, 4H), 0.95-0.70 (m, 9H), 0.04-(-0.04) (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.80, 130.75, 129.66, 127.83, 95.66, 72.06, 68.55, 68.26, 66.88, 64.09, 59.32, 35.50, 26.26, 26.20, 26.05, 25.98, 20.80, 18.57, -3.68, -4.25; HRMS calcd. for $C_{20}H_{40}O_5Si$ (M+ H^+) 389.2723, found 389.2722.

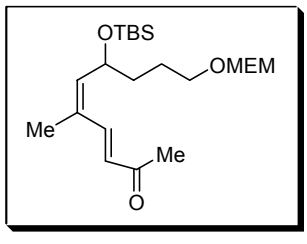


Aldehyde 41: To a stirred solution of **40** (1.0 g, 2.57 mmol) in dry DCM: DMSO (3:1, 20 mL) was added TEA (1.3 g, 12.86) SO_3-pyridine (1.64g, 10.3 mmol) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 1 h and was quenched with a solution of NH_4Cl (20 mL). It was extracted with DCM (3 x 40 mL) and the combined organic extracts were washed with brine (2 x 100 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 EtOAc: hexane) to give the corresponding Aldehyde (0.97 g, 2.52 mmol 98% yield), as a light yellow oil R_f = 0.35 (50% EtOAc: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (dd, J = 2.0, 8.0 Hz, 1H), 7.53 (d, J = 15.60 Hz, 1H), 6.17 (dd, J = 7.60, 15.60 Hz, 1H), 5.75 (d, J = 8.40 Hz, 1H), 4.69 (s, 2H), 4.65 (m, 1H), 3.67 (m, 2H), 3.43-3.60 (m, 4H), 3.35 (s, 3H), 1.88 (s, 3H), 1.80-1.40 (m, 4H), 0.86 (s, 9H), 0.03 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.00, 148.23, 143.93, 130.45,

129.92, 95.71, 72.06, 68.83, 68.06, 67.04, 59.34, 35.56, 26.18, 25.95, 20.37, 18.53, -3.75, -4.23; HRMS calcd. for $C_{20}H_{38}O_5Si$ (M+ Na^+) 409.2386, found 409.2383.

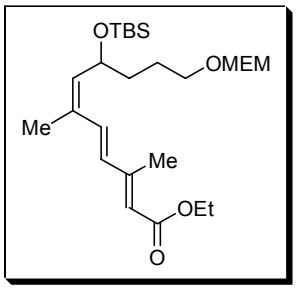


Alcohol 42: To a stirred solution of aldehyde **41** (1.0 g, 2.5 mmol) in dry THF (30 mL) was added MeMgBr (3.70 mL, 5.1 mmol) at -78 ^oC. The reaction mixture was stirred at – 30 ^oC for 1 h, and it was quenched with a solution of NH_4Cl. The mixture was extracted with EtOAc (3 x 50 mL), and the combined organic extracts were washed with brine (2 x 20 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 EtOAc: hexane) to give the corresponding Alcohol (0.97 g, 2.3 mmol, 92% yield), as a light yellow oil R_f = 0.32 (50% EtOAc: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 6.51 (m, 1H), 5.74 (m, 1H), 5.28 (d, J = 8.80 Hz, 1H), 4.69 (s, 2H), 4.56 (m, 1H), 4.40 (m, 1H), 3.68 (m, 2H), 3.60-3.42 (m, 4H), 3.38 (s, 3H), 1.80 (s, 3H), 1.98-1.40 (m, 5H), 1.30 (d, J = 6.80 Hz, 3H), 1.00-0.8 (m, 9H), 0.02-(-0.04); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.74, 130.84, 126.41, 95.66, 72.05, 69.41, 68.55, 68.50, 68.26, 66.96, 66.93, 59.32, 35.52, 26.27, 26.05, 23.93, 20.86, 18.57, -3.69, -4.25; HRMS calcd. for $C_{21}H_{42}O_5Si$ (M+ Na^+) 425.2699, found 425.2697.



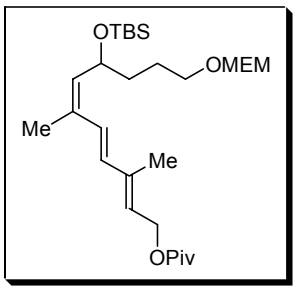
Compound 43: To a stirred solution of **42** (1.2 g, 2.9 mmol) in dry DCM (60 mL) was added DMP (2.53 g, 5.97 mmol) at 0 ^oC, and was stirred for 1 h. The reaction mixture was quenched with a solution of $NaHCO_3$ and $Na_2S_2O_3$ (40 mL), and was extracted with DCM (3 x 50 mL). The combined organic extracts were

washed with brine (2 x 30 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 EtOAc: hexane) to give the corresponding ketone (1.14 g, 2.86 mmol 99% yield), as a colorless oil R_f = 0.35 (50% EtOAc: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 16 Hz, 1H), 6.18 (d, J = 16.00 Hz, 1H), 5.68 (d, J = 8.80 Hz, 1H), 4.69 (s, 2H), 4.65 (m, 1H), 3.66 (m, 2H), 3.60-3.40 (m, 4H), 3.36 (s, 3H), 2.29 (s, 3H), 1.85 (s, 3H), 1.70-1.40 (m, 4H), 0.95-0.80 (m, 9H), 0.04-(-0.04) (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.47, 142.93, 139.08, 130.36, 128.10, 95.71, 72.06, 68.65, 68.10, 66.99, 59.33, 35.58, 28.26, 26.20, 25.95, 20.39, 18.54, -3.74, -4.22; HRMS calcd. for $C_{21}H_{40}O_5Si$ (M+ Na^+) 423.2542, found 423.2543.



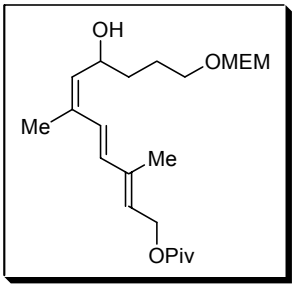
Compound 44: To a stirred solution of triethylphosphonoacetate (1.39 g, 6.24 mmol) in dry THF (15 mL) was added NaH (0.089 g, 3.74 mmol) and it was stirred at 0 ^{o}C for 15 min. Then, ketone **43** (0.5 g, 1.2 mmol) in 5 mL of dry THF was added via cannula at 0 ^{o}C. The reaction mixture was stirred for 10 h at 40 ^{o}C and was quenched with a solution of NH_4Cl (20 mL). The mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (2 x 25 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 8:92 EtOAc hexane) to give the corresponding ester (0.53 g, 1.14 mmol, 95% yield), as a colorless oil R_f = 0.38 (50% EtOAc: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (d, J = 15.60 Hz, 1H), 6.26 (d, J = 16.00 Hz, 1H), 5.82 (s, 1H), 5.46 (d, J = 8.80 Hz, 1H), 4.70 (s,

2H), 4.63 (m, 1H), 4.15 (m, 2H), 3.66 (m, 2H), 3.60-3.45 (m, 4H), 3.38 (s, 3H), 2.32 (s, 3H), 1.86 (s, 3H), 1.75-1.40 (m, 4H), 1.25 (tr, J = 6.80 Hz, 3H), 1.0-0.80 (m, 9H), 0.1-(-0.05) (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.07, 152.27, 132.93, 131.87, 131.31, 130.73, 119.99, 95.70, 72.07, 68.61, 68.20, 66.99, 60.05, 59.33, 35.59, 26.25, 26.07,20.77, 20.70, 18.59, 14.75, 14.17, -3.68, -4.24; HRMS calcd. for $C_{25}H_{46}O_6Si$ (M+ Na^+) 493.2961, found 493.2961.

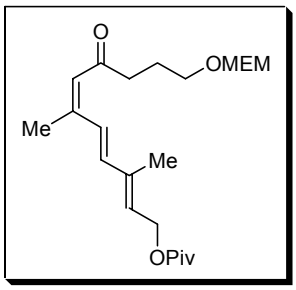


Compound 46: To a stirred solution of **44** (0.3 g, 0.638 mmol) in dry THF (10 mL) was added DIBAL-H (1.59 mL, 1.59 mmol) at -78 ^{o}C and it was allowed to stir for 1.5 h. The reaction mixture was quenched with a solution of 10% tartaric acid (7 mL) and was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (2 x 10 mL), dried over $MgSO_4$, concentrated under reduced pressure to give the clean alcohol 45 (0.26 g, 0.61 mmol, 96% yield). Then, alcohol 45 (0.10g, 0.23 mmol) was dissolved in dry DCM (10 mL) and treated with Pyridine (0.08g, 1.17 mmol) and DMAP (cat) at 0 ^{o}C. After 10 min, PivCl (0.08 g, 0.69 mmol) was added at 0 ^{o}C and the reaction was allowed to stir for 10 h at 25 ^{o}C. The reaction mixture was quenched with a saturated solution of $NaHCO_3$ and extracted with DCM (3 x 25 mL). The combined organic extracts were washed with brine (2 x 10 mL), dried over $MgSO_4$, concentrated under reduced pressure, and purified by flash chromatography (silica, 5:95 EtOAc: hexane) to afford compound 46 (0.109 g, 0.212 mmol 92% yield), as colorless film R_f = 0.39 (50% EtOAc: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (d, J = 15.60 Hz, 1H), 6.27 (d, J

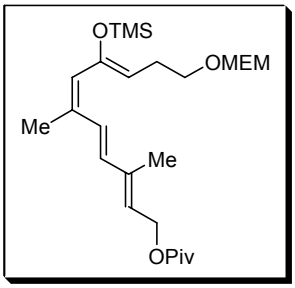
= 15.60 Hz, 1H), 5.65 (tr, J = 6.40 Hz, 1H), 5.32 (d, J = 8.80 Hz, 1H), 4.80-4.63 (m, 4H), 4.61 (m, 1H), 3.67 (m, 2H), 3.60-3.43 (m, 4H), 3.38 (s, 3H), 1.86 (s, 3H), 1.84 (s, 3H), 1.70-1.40 (m, 4H), 1.19 (s, 9H), 0.86 (s, 9H), 0.02 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.97, 138.37, 135.80, 135.04, 131.62, 127.51, 126.10, 125.67, 125.52, 124.26, 95.67, 72.07, 68.61, 68.26, 66.96, 61.53, 59.34, 35.60, 27.60, 27.40, 26.28, 26.13, 20.85, 18.61, 13.18, -3.64, -4.26; HRMS calcd. for $C_{28}H_{52}O_6Si$ (M+ H^+) 513.3611, found 513.3612.



Alcohol 47: To a stirred solution of **46** (0.100 g, 0.195 mmol) in THF (8 mL) was added TBAF (1M, 0.39 mL) at 0 ^{o}C. The reaction mixture was allowed to stir at 25 ^{o}C for 12h. Then, it was quenched with a saturated solution of NH_4Cl (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (2 x 10 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 15:85 EtOAc: hexane) to give the corresponding alcohol (0.58 g, 0.146 mmol, 75% yield), as a white foam R_f = 0.28 (50% EtOAc: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (m, 1H), 6.25 (d, J = 15.60 Hz, 1H), 5.58 (tr, J = 6.40 Hz, 1H), 5.30 (d, J = 8.80 Hz, 1H), 4.75-4.60 (m, 6H), 4.56 (m, 1H), 3.60 (m, 2H), 3.48 (m, 2H), 3.30 (s, 3H), 2.49 (br s, 1H), 1.79 (s, 6H), 1.70-1.40 (m, 4H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.55, 138.36, 134.14, 133.95, 133.56, 126.30, 125.22, 124.36, 95.56, 71.97, 68.10, 67.30, 61.44, 59.21, 58.28, 39.08, 34.87, 27.50, 26.05, 20.80, 18.63, 13.10; HRMS calcd. for $C_{22}H_{38}O_6$ (M+ H^+) 399.2746, found 399.2747.

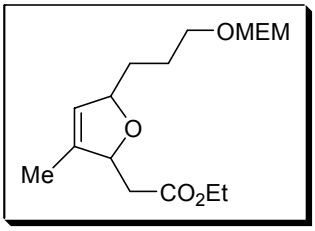


Ketone 48: To a stirred solution of **47** (0.10 g, 0.25 mmol) in dry DCM (10 mL) was added DMP (0.212 g, 0.50 mmol) at 0 ^{o}C. The reaction mixture was stirred for 12 h at 25 ^{o}C and was quenched with a solution of $NaHCO_3$ (10 mL). The reaction mixture was extracted with DCM (3 x 10 mL) and the combined organic extracts were washed with brine (2 x 10 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 EtOAc: hexane) to give the corresponding (0.099 g, 0.25 mmol, 99% yield), as a light yellow oil R_f = 0.31 (50% EtOAc: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) major δ 7.85 (d, J = 16.40 Hz, 1H), 6.65 (d, J = 16.0 Hz, 1H), 6.05 (s, 1H), 5.77 (tr, J = 6.40 Hz, 1H), 4.74 (m, 2H), 4.72 (s, 2H), 3.67 (m, 2H), 3.65-3.50 (m, 4H), 3.39 (s, 3H), 2.57 (m, 2H), 2.03 (s, 3H), 1.92 (m, 5H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.62, 149.32, 140.52, 138.80, 132.34, 129.60, 127.12, 126.91, 124.99, 95.66, 72.03, 67.24, 61.38, 60.33, 59.26, 41.50, 27.54, 24.45, 21.15, 14.31, 13.01; HRMS calcd. for $C_{22}H_{36}O_6$ (M+ H^+) 397.2590, found 397.2592.

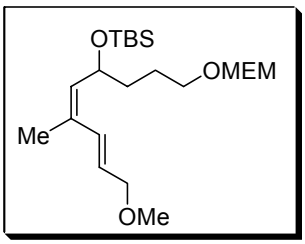


Compound 49: Compound **48** (0.02 g, 0.05 mmol) in dry THF (4 mL) was treated with NaHMDS at -78 ^{o}C. The reaction mixture was stirred for 30 min and TMSCl (0.011g, 0.1 mmol) was added at -78 ^{o}C. The mixture was quenched with a solution of $NaHCO_3$ (3 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (2 x 10 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash

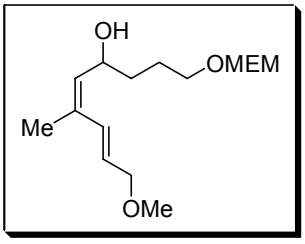
chromatography (pretreated silica gel with 5% TEA-hexane, 10:90 EtOAc: hexane) to give the corresponding trapped enolate (0.013 g, 0.0286 mmol, 57% yield), as a yellow oil R_f = 0.42 (50% EtOAc: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) major δ 7.34 (d, J = 16.0 Hz, 1H), 6.25 (d, J = 16.0 Hz, 1H), 5.77 (s, 1H), 5.64 (m, 1H), 4.92 (m, 1H), 4.64 (d, J = 7.20 Hz, 2H), 4.58 (m, 2H), 3.52 (m, 4H), 3.31 (m, 2H), 3.08 (s, 3H), 2.54 (m, 2H), 1.71 (s, 3H), 1.69 (s, 3H), 1.14 (s, 9H) 0.12 (m, 9H); HRMS calcd. for $C_{25}H_{44}O_6Si$ (M+ H^+) 469.2985, found 469.2987.



Furan 51: To a stirred solution of **43** (1.0 g, 2.50 mmol) in dry THF (20 mL) at 0 ^{o}C was added TBAF (1 M, 5.00 mmol). The reaction mixture was stirred at that temperature for 2 h and was quenched with NH_4Cl (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (2 x 10 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 20:80 EtOAc: hexane) to give the corresponding furan (0.68 g, 2.25 mmol 92% yield), as a light yellow oil R_f = 0.30 (50% EtOAc: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (br s, 1H), 4.97 (m, 1H), 4.69 (m, 3H), 4.16 (m, 2H), 3.67 (m, 2H), 3.60-3.45 (m, 4H), 3.38 (s, 3H), 2.60 (m, 1H), 2.40 (m, 1H), 1.69 (s, 3H), 1.65-1.50 (m, 4H), 1.25 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.51, 137.92, 125.32, 95.65, 85.33, 84.34, 72.02, 68.12, 66.90, 60.74, 59.20, 41.27, 33.67, 25.69, 14.44, 12.59; HRMS calcd. for $C_{16}H_{28}O_6$ (M+ H^+) 317.1964, found 317.1962.

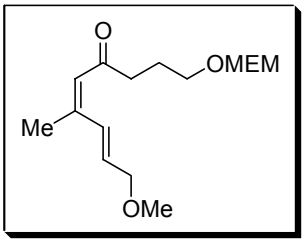


Compound 53: Compound **40** (0.5 g, 1.29 mmol) was dissolved in THF (15 mL) and was treated with NaH (0.067g, 2.57 mmol) at 0 ^{o}C. This mixture was stirred for 10 min, and MeI (1.83 g, 12.86 mmol) was added. The reaction was allowed to stir for 5h at 50 ^{o}C. The reaction mixture was cooled to 25 ^{o}C and quenched with a solution of NH_4Cl (10 mL), and extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine (2 x 10 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 EtO_2: hexane) to afford compound 53 Alcohol (0.5 g, 1.26 mmol, 98% yield), as a light yellow oil R_f = 0.35 (50% Et_2O: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (d, J = 15.60 Hz, 1H), 5.75 (m, 1H), 5.30 (d, J = 8.80 Hz, 1H), 4.70 (s, 2H), 4.57 (m, 1H), 4.01 (d, J = 6.40 Hz, 2H), 3.68 (m, 2H), 3.60-3.45 (m, 4H), 3.39 (s, 3H), 3.35 (s, 3H), 1.82 (s, 3H), 1.75-1.40 (m, 4H), 0.86 (s, 9H), 0.02 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.90, 130.92, 129.50, 127.02, 95.69, 73.59, 72.04, 68.55, 68.24, 66.89, 59.32, 58.18, 35.46, 29.92, 26.10, 26.07, 20.63, 18.38, -3.92, -4.50; HRMS calcd. for $C_{21}H_{42}O_5Si$ (M+ H^+) 403.2879, found 403.2881.

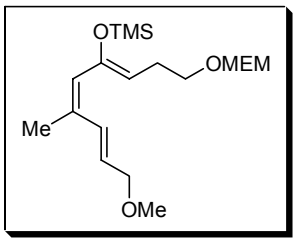


Alcohol 54: To a stirred solution of **53** (0.4 g, 0.99 mmol) in dry THF (20 mL) was added TBAF (1M, 1.99 mmol) at 0 ^{o}C. The reaction mixture was stirred at 25 ^{o}C for 3 h and was quenched with a saturated solution of NH_4Cl (10 mL). Then, the mixture was extracted with EtOAc (3 x 10 mL), and he combined organic extracts were washed with brine (2 x 10 mL), dried over $MgSO_4$, concentrated under

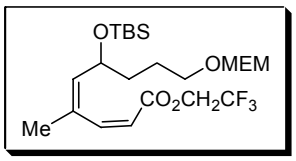
reduced pressure and purified by flash chromatography (silica, 20:80 EtOAc: hexane) to give the corresponding Alcohol 54 (0.26 g, 0.92 mmol, 92% yield), as a light yellow oil R_f = 0.25 (50% EtOAc:: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (d, J = 16.0 Hz, 1H), 5.82 (m, 1H), 5.36 (d, J = 8.80 Hz, 1H), 4.71 (s, 2H), 4.62 (m, 1H), 4.0 (d, J = 5.60 Hz, 2H), 3.56 (m, 2H), 3.65-3.50 (m, 4H), 3.39 (s, 3H), 3.35 (s, 3H), 1.85 (s, 3H), 1.80-1.50 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.17, 129.08, 127.90, 95.66, 72.06, 68.09, 67.35, 59.33, 34.82, 29.91, 25.98, 25.90, 24.45, 20.56, 13.92; HRMS calcd. for $C_{15}H_{28}O_5$ (M+ Na^+) 311.1834, found 311.1835.



Ketone 55: To a stirred solution of **54** (0.25 g, 0.868 mmol) in dry DCM (30 mL) was added DMP (0.74 g, 1.73 mmol) at 0 ^{o}C. The reaction mixture was stirred at 25 ^{o}C for 2.5 h and was quenched with a solution of $NaHCO_3$ and $Na_2S_2O_3$ (20 mL). The mixture was extracted with DCM (3 x 30 mL). The combined organic extracts were washed with brine (2 x 20 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 EtOAc: hexane) to give the corresponding ketone (0.246 g, 0.86 mmol, 99% yield), as a yellow oil R_f = 0.38 (50% EtOAc: hexane); ^{1}H NMR (400 MHz, C_6D_6) δ 8.37 (d, J = 16.40 Hz, 1H), 6.21 (m, 1H), 5.89 (s, 1H), 4.75 (s, 2H), 3.98 (d, J = 6.0 Hz, 2H), 3.77 (m, 2H), 3.65 (tr, J = 6.40, 2H), 3.54 (tr, J = 5.20 Hz, 2H), 3.31 (s, 3H), 3.26 (s, 3H), 2.50 (m, 2H), 2.08 (m, 2H) 1.82 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 199.05, 134.92, 129.92, 125.29, 95.50, 72.90, 72.08, 67.04, 66.94, 58.50, 57.71, 41.08, 24.53, 20.49; HRMS calcd. for $C_{15}H_{26}O_5$ (M+ H^+) 287.1858, found 287.1859.

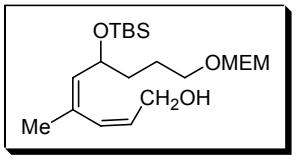


Compound 56: To a stirred solution of **55** (0.060 g, 0.21 mmol) in dry THF (8 mL) was treated with LiHMDS (1 M, 0.83 mmol) at -78 ^{o}C. The reaction was stirred for 30 minutes at -78 ^{o}C and TMSCl (0.091 g, 0.84 mmol) was added. After 15 min, the reaction was warmed to 0 ^{o}C and quenched with a solution of $NaHCO_3$ (5 mL). The reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (2 x 5 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (pretreated silica gel with 5% TEA: hexane, 10:90 EtOAc: hexane) to give the corresponding compound 56 (0.072 g, 0.2 mmol, 95% yield), as a yellow oil R_f = 0.40 (50% EtOAc: hexane); ^{1}H NMR (400 MHz, C_6D_6) δ 7.39 (d, J = 16.0 Hz, 1H), 5.73 (m, 2H), 4.93 (tr, J = 7.60 Hz, 1H), 4.59 (s, 2H), 3.85 (d, J = 6.0 Hz, 1H), 3.58 (m, 5H), 3.33 (tr, J = 4.80 Hz, 2H), 3.09 (s, 6H), 2.52 (dd, J = 6.8 Hz, 2H), 1.69 (s, 3H), 0.23 (m, 9H); ^{13}C NMR (100 MHz, C_6D_6) δ 148.53, 133.40, 130.96, 112.48, 95.57, 73.28, 72.08, 67.53, 67.05, 58.49, 57.58, 27.12, 20.66, 5.76, 5.48, 5.20, 0.51; HRMS calcd. for $C_{18}H_{34}O_5Si$ (M+ H^+) 359.2254, found 359.2253.



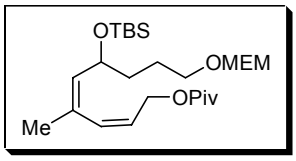
Compound 58: Ethyl 2-((bis(2,2,2-trifluoroethoxy)) phosphoryl)acetate (4.50g, 14.00 mmol) was dissolved THF (80 mL) along with 18 crown-6 (5.28 g, 20.0 mmol) at -78 ^{o}C. Then, KHMDS (0.5 M, 10.5 mmol) was added and stirred for 30 min. Aldehyde 35 (2.50 g, 7.08 mmol) was dissolved in THF (30 mL) and added via cannula to the phosphonate at – 78 ^{o}C. The reaction was allowed to stir for 1.3 h at -78 ^{o}C and it was

quenched with a saturated solution of NH_4Cl (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 EtOAc: hexane) to give the corresponding ester (3.15 g, 6.5 mmol, 92% yield), as a light yellow oil R_f = 0.35 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 6.63 (dd, J = 12.0 Hz, 1H), 5.80 (d, J = 12.00 Hz, 1H), 5.34 (d, J = 8.80 Hz, 1H), 4.68 (s, 2H), 4.21 (m, 1H), 3.80-3.60 (m, 4H), 3.60-3.45 (m, 4H), 3.38 (s, 3H), 1.87 (s, 3H), 1.75-1.30 (m, 4H), 0.92-0.75 (m, 9H), 0.03-(-0.03) (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.37, 142.39, 134.74, 131.38, 120.82, 95.68, 95.65, 72.03, 69.95, 68.17, 66.90, 66.87, 59.22, 51.55, 34.81, 34.68, 26.05, 25.72, 22.27, 18.33, -4.04, -4.64; HRMS calcd. for $C_{22}H_{39}F_3O_6Si$ (M+ Na^+) 507.2365, found 507.2366.

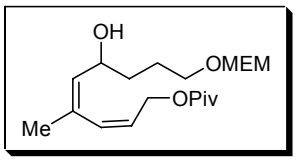


Alcohol 59: To a stirred solution of **58** (1.0 g, 2.07 mmol) in dry THF (50 mL) was added DIBAL-H (1 M, 4.13 mmol) at -78 ^oC and it was allowed to stir for 1.5 h. The reaction mixture was quenched with a solution of 10% tartaric acid (30 mL) and was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (2 x 25 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 20:80 EtOAc: hexane) to give the corresponding Alcohol (0.723 g, 2.02 mmol, 98% yield), as a light yellow oil R_f = 0.30 (50% EtOAc: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 6.13 (d, J = 11.60 Hz, 1H), 5.52 (d, J = 8.80 Hz, 1H), 4.69 (s, 2H), 4.59 (m, 2H), 4.23 (m, 2H), 3.67 (m, 2H), 3.60-3.45 (m, 4H),

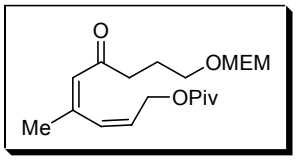
3.37 (s, 3H), 1.82 (s, 3H), 1.75-1.35 (m, 2H), 0.90-0.80 (m, 9H), 0.03-(-0.03) (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.37, 131.74, 131.07, 129.50, 95.60, 72.02, 69.79, 67.93, 66.96, 60.11, 59.23, 34.61, 26.07, 26.05, 25.79, 24.27, 18.34, -3.86, -4.45; HRMS calcd. for $C_{19}H_{38}O_4Si$ (M+ H^+) 359.2617, found 359.2619.



Compound 60: The alcohol 59 (3.0g, 7.7 mmol) was dissolved in dry DCM (100 mL) and treated with Pyridine (2.89 g, 38.60 mmol) and DMAP (cat) at 0 ^{o}C. After 10 min, PivCl (2.78 g, 23. 0mmol) was added at 0 ^{o}C and the reaction was allowed to stir for 3.5 h at 25 ^{o}C. The reaction mixture was quenched with a saturated solution of $NaHCO_3$ (50 mL) and extracted with DCM (3 x 100 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over $MgSO_4$, concentrated under reduced pressure, and purified by flash chromatography (silica, 5:95 EtOAc: hexane) to give the corresponding compound (3.58g, 7.6 mmol, 99% yield), as a yellow oil R_f = 0.35 (50% EtOAc: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δδ 6.12 (d, J = 11.60 Hz, 1H), 5.53 (m, 1H), 5.29 (d, J = 8.80 Hz, 1H), 4.69 (s, 2H), 4.60 (m, 2H), 4.21 (m, 1H), 3.66 (m, 2H), 3.60-3.40 (m, 4H), 3.37 (s, 3H), 1.82 (s, 3H), 1.70-1.40 (m, 4H), 1.18 (s, 9H), 0.85 (s, 9H), 0.02 (s, 3H), -0.03(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.63, 136.54, 131.20, 131.05, 124.40, 95.64, 72.02, 69.62, 68.18, 68.14, 66.87, 61.77, 61.56, 59.21, 38.87, 34.74, 27.38, 27.26, 26.07, 25.90, 23.99, 18.33, -3.97, -4.54; HRMS calcd. for $C_{24}H_{48}O_6Si$ (M+ Na^+) 495.3118, found 495.3118.

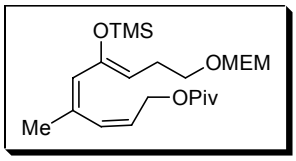


Compound 61: To a stirred solution of **60** (3.2 g, 6.7 mmol) in dry THF (100 mL) was added TBAF (1M, 14.23 mmol) at 0 ^{o}C. The reaction mixture was stirred at 25 ^{o}C for 10 h and was quenched with a saturated solution of NH_4Cl (80 mL). Then, the mixture was extracted with EtOAc (3 x 100 mL), and he combined organic extracts were washed with brine (2 x 50 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 25:70 EtOAc: hexane) to give the corresponding Alcohol **61** (1.79 g, 5.0 mmol, 75% yield), as a light yellow oil R_f = 0.25 (50% EtOAc:: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (d, J = 12.0 Hz, 1H), 5.57 (m, 1H), 5.34 (d, J = 8.80 Hz, 1H), 4.69 (s, 2H), 4.66 (m, 1H), 4.56 (m, 1H), 4.21 (m, 1H), 3.67 (m, 2H), 3.60-3.50 (m, 4H), 3.38 (s, 3H), 1.81 (s, 3H), 1.70-1.45 (m, 5H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.63, 136.24, 133.84, 132.04, 125.86, 95.67, 72.00, 68.76, 68.08, 66.96, 65.10, 61.49, 59.20, 38.92, 34.23, 27.34, 25.95, 24.14; HRMS calcd. for $C_{18}H_{34}O_6$ (M+ H^+) 359.2433, found 359.2434.

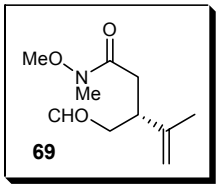


Ketone 62: To a stirred solution of **61** (2.1 g, 5.8 mmol) in dry DCM (100 mL) was added DMP (4.96 g, 11.7 mmol) at 0 ^{0}C. The reaction mixture was stirred at 25 ^{o}C for 10 h and was quenched with a solution of $NaHCO_3$ and $Na_2S_2O_3$ (50 mL). The mixture was extracted with DCM (3 x 10 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 EtOAc: hexane) to give the corresponding ketone (1.84 g, 5.19 mmol, 89% yield), as a yellow oil R_f = 0.30 (50%

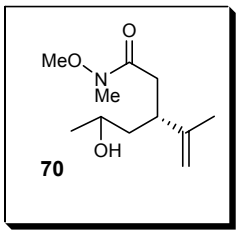
EtOAc: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 16.40 Hz, 1H), 6.16 (m, 1H), 6.06 (s, 1H), 4.69 (m, 2H), 4.68 (s, 2H), 3.66 (m, 2H), 3.60-3.50 (m, 4H), 3.38 (s, 3H), 2.55 (m, 2H), 1.98 (s, 3H), 1.89 (m, 2H), 1.20 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.48, 178.44, 147.66, 132.07, 129.07, 125.73, 95.66, 72.02, 67.19, 66.99, 64.66, 59.24, 41.29, 27.42, 27.38, 24.45, 24.31, 21.09; HRMS calcd. for $C_{18}H_{32}O_6$ (M+ H^+) 357.2272, found 357.2273.



Alcohol 63: To a stirred solution of **62** (0.099 g, 0.27 mmol) in dry THF (10 mL) was treated with LiHMDS (1 M, 0.55 mmol) at -78 ^{o}C. The reaction was stirred for 30 minutes at -78 ^{o}C and TMSCl (0.09 g, 0.83 mmol) was added. After 15 min, the reaction was warmed to 0 ^{o}C and quenched with a solution of $NaHCO_3$ (5 mL). The reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (2 x 5 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (pretreated silica gel with 5% TEA: hexane, 10:90 EtOAc: hexane) to give the corresponding compound 56 (0.078 g, 0.22 mmol, 81% yield), as a yellow oil R_f = 0.4 (50% EtOAc: hexane);

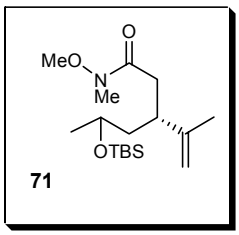


Amide 69: Compound **68** (1.0 g, 6.40 mmol) was dissolved in dry DCM (25 mL), and placed on a -30 ^{o}C bath. Then, (MeO)N(Me).HCl (0.62 g, 6.40 mL) was added slowly followed by TEA (0.92 mL, 6.40 mmol), and EDC.HCl (1.23 g, 6.40 mmol). The reaction was allowed to warm up to 25 ^{o}C and stirred for 16 h. The reaction mixture was quenched with a saturated solution of aqueous NH_4Cl (15 mL) and was extracted with DCM (3 x 25 mL), the combined organic extracts were washed with brine (2 x 10 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 20:80 Et_2O: hexane) to give the corresponding amide **69** (0.955 g, 4.80 mmol, 75% yield) as a light yellow-orange oil; R_f= 0.3 (50% EtOAc: hexane); $[\alpha]^{25}_{D}$= –1.7 (c 0.7, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ 9.65 (1H, br s, C*H*O), 4.80 (2H, m, C=CH_2), 3.68 (3H, s, *Me*O), 3.16 (3H, s, MeN), 2.57-2.44 (4H, m), 1.74 (3H, s, Me); ^{13}C NMR (100MHz, $CDCl_3$) δ201.2, 171.9, 145.6, 111.6, 61.1, 46.7, 36.8, 35.7, 31.9, 20.3; IR (film) ν_{max} 2940, 1721, 1652, 1457, 1420, 1177, 1001, 898; HRMS calcd for $C_{10}H_{17}NO_3$ (M+Na^+) 222.1106, found 222.1126.



Alcohol 70: Compound **69** (1.10 g, 5.53 mmol) was dissolved in dry THF (12 mL), and placed on -50 ^{o}C bath. MgMgCl (3M, 2.03 mL, 6.08mmol) was added dropwise and warmed to -10 ^{o}C for 2.5 h. The reaction mixture was quenched with a saturated solution of aqueous NH_4Cl (25 mL) and was extracted with EtOAc (3 x 20 mL), the combined organic extracts were washed with brine (2 x 15 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica,

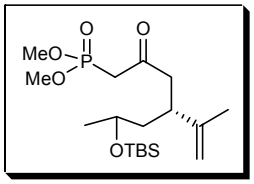
25:75 Et_2O: hexane) to give the corresponding compound **70** (1.07 g, 4.98 mmol, 90% yield) as a yellow oil: R_f = 0.25 (50% EtOAc: hexane); ^{1}H NMR (400MHz, $CDCl_3$) δ 4.81 (1H, br s, C=CH_2), 4.76 (1H, br s, C=*C*H_2), 3.68 (3H, s, MeO), 3.18 (3H, s, *Me*N), 2.84 (1H, m), 2.50 (2H, m), 1.74 (3H, s, *Me*), 1.62 (1H, m), 1.45 (1H, m), 1.16 (3H, d, *J*= 6.0, CH*Me*); ^{13}C NMR (100MHz, $CDCl_3$) δ 148.3, 111.1, 65.7, 61.2, 43.7, 39.1, 36.3, 23.2, 19.9; IR (film) ν_{max} 3500-3300, 2970, 2937, 1732, 1647, 1441, 1383.



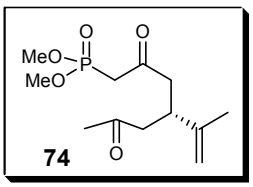
71

Alcohol 71: Compound **70** (0.26 g, 1.21 mmol) was dissolved in dry DCM (4 mL), and placed on an ice bath. Then, TEA (0.2 mL, 1.82 mmol), and DMAP (30.0 mg, 0.242 mmol) were added followed by TBSCl (0.225 g, 1.45 mmol). The reaction mixture was brought to 25 ^{o}C and stirred for 16 h. was added along with dropwise and warmed to -10 ^{o}C for 2.5 h. The reaction mixture was quenched with a saturated solution of aqueous NH_4Cl (10 mL) and was extracted with DCM (3 x 10 mL), the combined organic extracts were washed with brine (2 x 10 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 15:85 Et_2O: hexane) to give the corresponding compound **71** (0.3 g, 0.91 mmol, 75% yield) as a colorless oil, R_f = 0.4 (20% EtOAc: hexane); ^{1}H NMR (400MHz, $CDCl_3$) δ 4.75 (2H, m), 3.66 (3H, s, MeO), 3.14 (3H, s, MeN), 1.70 (3H, s, Me) and 1.67 (s, Me diastereomer), 1.15 (3H, d, *J*= 5.7, CHMe) and 1.13 (d, *J*= 5.7, CHMe diastereomer), 0.87 (9H, br s, Si*C*Me_3), 0.02 (6H, br s, $SiMe_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.09, 146.57, 145.66, 111.83, 111.55, 110.50, 66.69, 61.21, 43.36, 39.71, 34.80, 2

6.01, 25.71, 23.1, 18.13, –4.35, –4.58.. IR (film) ν_{max} 2957, 2932, 2857, 1737, 1670, 1380, 1253. HRMS calcd. for $C_{17}H_{35}NO_3Si$ (M+ Na^+) 352.2284, found 352.2282.

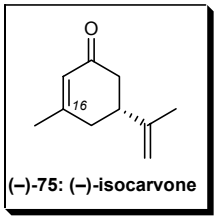


Phosphonate 72: $MeO)_2P(O)CH_3$ (12.5 g, 101.0 mmol) was dissolved in THF (60 mL) treated with *n*BuLi (40.7 mL, 101.0 mL) at –78 ^oC for 30 min. Then, Compound **71** (11.3 g, 33.9 mmol) dissolved in THF (20 mL) was added via syringe. The reaction mixture was brought to 25 ^oC and stirred for 16 h. The reaction mixture was quenched with a saturated solution of aqueous NH_4Cl (50 mL) and was extracted with EtOAc (3 x 50 mL), the combined organic extracts were washed with brine (2 x 30 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 5:95 EtOAc: hexane) to give the corresponding phosphonate (12.09 g, 30.0 mmol, 90.0% yield) as a colorless oil, R_f = 0.3 (50% EtOAc: hexane); ^1H NMR (400MHz, $CDCl_3$) δ 4.73 (2H, m), 3.76 (3H, s, MeO), 3.73 (3H, s, *Me*O), 3.68 (1H, m), 3.05 (2H, m), 1.66 (3H, s, Me) and 1.62 (s, Me diastereomer), 1.10 (3H, d, *J*= 6.0, CH*Me*) and 1.08 (d, *J*= 6.0, CH*Me* diastereomer), 0.86 (9H, s, Si*CMe*$_3$) and 0.84 (s, Si*C*Me$_3$ diastereomer), 0.02 (6H, s, $SiMe_2$) and 0.00 (s, $SiMe_2$ diastereomer);. ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.27, 146.06, 145.84, 112.36, 111.76, 79.03, 66.34, 52.99, 49.01, 43.14, 40.50, 38.96, 23.23, 18.99, 18.11, -3.75, -4.63; HRMS calcd. for $C_{17}H_{35}O_5PSi$ (M+ Na^+) 401.1889, found 401.1891.



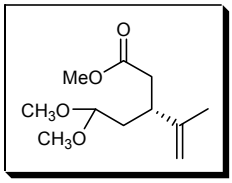
Ketone 74: Phosphonate **72** (0.50 g, 1.26 mmol) was dissolved in acetone (5 mL) and treated with KF (0.146g, 2.52 mmol) and Jones' reagent (8N, 0.60 mL) at 0 ^oC. The reaction was warmed

to 25 ^{o}C and stirred for 5h. The residue was filtered through a celite pad, and washed with a saturated solution of aqueous $NaHCO_3$ (4 mL) and was extracted with DCM (3 x 10 mL), the combined organic extracts were washed with brine (2 x 10 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 Et_2O: hexane) to give the corresponding ketone (0.247 g, 0.89 mmol, 71% yield) as a colorless oil: R_f = 0.3 (50% Et_2O : hexane); ^{1}H NMR (300MHz, $CDCl_3$) δ 4.77-4.75 (2H, m, C=C*H*$_2$), 3.79 (3H, s, *Me*O), 3.75 (3H, s, *Me*O), 3.11-3.04 (3H, m, C*H*$_2$P=O and C*H*C=CH$_2$), 2.74-2.68 (2H, m), 2.52 (2H, d, *J*= 6.9 Hz), 2.11 (3H, s, *Me*), 1.71 (3H, s, *Me*); HRMS calcd. for $C_{11}H_{19}O_6P$ (M+ H^+) 263.1048, found 263.1045.

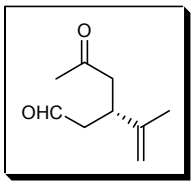


(–)-75: (–)-isocarvone

(-)-Isocarvone 75: Diketophosphonate **253** (7.0 g, 23.0 mmol) was dissolved in anhydrous THF (50 mL), LiCl (0.97 g, 23.0 mmol) was added followed by DBU (3.5 g, 23.0 mmol) at -78 ^{o}C. The reaction mixture was warmed to 25 ^{o}C and stirred for 16 h. Then, the reaction mixture was concentrated under reduced pressure and purified by flash chromatography (silica, 25:75 EtOAc: hexane) to give (–)-isocarvone (3.22 g, 21.46 mmol, 92.0% yield) light yellow oil; R_f = 0.4 (30% Et_2O: hexane); $[\alpha]^{25}_D$= –60.9 (c 0.41, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ 5.85 (1H, br s, =C*H*), 4.78 (1H, br s, C=CH$_2$), 4.73 (1H, br s, C=CH$_2$), 2.65 (1H, m), 2.45 (1H, dd, J = 16.0, 3.6), 2.32-2.20 (3H, m), 1.95 (3H, s, Me), 1.72 (3H, s, Me); ^{13}C NMR (100MHz, $CDCl_3$) δ199.2, 161.6, 146.2, 126.0, 110.5, 41.9, 41.8, 36.2, 24.5, 20.5; IR (film) ν_{max} 2916, 1667, 1439, 1379; HRMS calcd for $C_{10}H_{14}O$ (M+Na^+) 173.0943, found 173.0983.

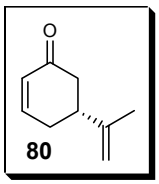


Ester 69: To a stirred solution of **68** (2.0 g, 12.80 mmol) in MeOH: $CH(OMe)_3$ (1:1, 20 mL) was added p-TSA (31.0 mg, 1.28 mmol). The reaction mixture was refluxed for 2 h, and was then cooled to 25 ^oC and quenched with a solution of $NaHCO_3$ (10 mL). It was extracted with DCM (3 x 15 mL), the combined organic extracts were washed with brine (2 x 10 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 20:80 EtOAc: hexane) to give the corresponding compound (0.045 g, 0.076 mmol, 90% yield) as a colorless oil: R_f = 0.35 (50% Et_2O: hexane); HRMS calcd. for $C_{11}H_{20}O_4$ (M+ H^+) 217.1439, found 217.1440.



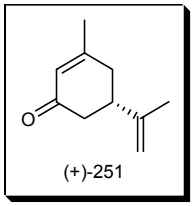
Compound 79: To a stirred solution of compound **69** (3.0 g, 14.83 mmol) in MeOH: THF (1:2, 30 mL) was added 3N NaOH (14.88 mL, 44.4 mmol). The reaction mixture was stirred at 25 °C for 5 h, and was quenched with a saturated solution of NH_4Cl (30 mL). It was extracted with EtOAc (3 x 20 mL), the combined organic extracts were washed with brine (2 x 20 mL), dried over $MgSO_4$, concentrated under reduced pressure to give the crude compound as a colorless oil (2.70g, 13.4 mmol, 90% yield). The acid (10.0 g, 53.39 mmol) was dissolved in dry THF (100 mL) and treated with MeLi (82.5 mL, 132.0 mmol) followed by TMSCl (6.65 mL, 53.39 mmol) at 0 ^oC. The reaction mixture was stirred at 25 ^oC for 1 h and was quenched with a saturated solution of NH_4Cl (50 mL). It was extracted with EtOAc (3 x 100 mL), the combined organic extracts were washed with brine (2 x 50 mL), dried over $MgSO_4$, concentrated

under reduced pressure and dissolved in THF (100 mL). HCl (1 M, 5.3 mmol) was added to the mixture, and it was allowed to stir at 25 ^{o}C for 30 min. The reaction mixture was quenched with a saturated solution of $NaHCO_3$ (50 mL) and extracted with EtOAc (3 x 100 mL), the combined organic extracts were washed with brine (2 x 50 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 20:80 Et_2O: hexane) to give the corresponding compound 80 (5.7 g, 37.5 mmol, 70% yield for two steps) as a colorless oil: R_f = 0.21 (50% Et_2O : hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 8.0 (m, 1H), 7.65 (m, 2H), 7.58 (m, 1H), 7.48 (d, 1H, J= 8.0 Hz), 7.40-7.20 (m, 2H), 7.16 (1H, J= 7.20 Hz), 6.60 (d, 1H, J= 15.6 Hz), 6.03 (dd, 1H, J= 6.40, 16.0 Hz), 4.24 (m, 1H), 3.75 (s, 2H), 3.40-3.15 (m, 4H), 1.70-0.80 (m, 20 H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ; HRMS calcd. for $C_9H_{14}O_2$ ($M+ H^+$) 155.1072, found 155.1073.

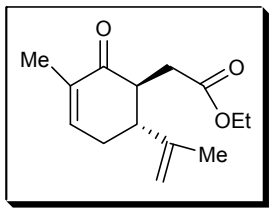


Compound 80: To a stirred solution of compound **79** (5.0 g, 32.46 mmol) in dry $PhCH_3$ (150 mL) was added PTSA (0.618 g, 3.21 mmol). The reaction flask was set up with a Dean stark apparatus and was reflux for 1 h. After cooling to 25 ^{o}C, the reaction mixture was quenched with a saturated solution of aqueous $NaHCO_3$ (50 mL) and was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 Et_2O: hexane) to give the corresponding compound (2.5 g, 22.50 mmol, 70% yield) as a white solid: Rf = 0.45 (50% Et_2O: hexane); 1H NMR (400 MHz, $CDCl_3$) δ 7.0 (m, 1H), 6.03 (dd, J = 2.80, 10.0 Hz, 1H), 4.82 (s, 1H), 4.77

(s, 1H), 2.71 (m, 1H), 2.60-2.20 (m, 4H), 1.76 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 200.2 , 149.60, 146.22, 124.41, 110.66, 43.08, 42.09, 31.05, 20.60; HRMS calcd. for $C_9H_{12}O$ (M+ Na^+) 159.0785, found 159.0786.

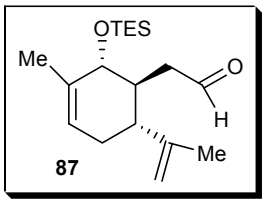


(+)-Isocarvone 75: Compound 254 (1.9 g, 14.70 mmol) was dissolved in anhydrous Et_2O (50 mL) and placed on an ice bath and MeLi (1.6 M, 13.80 mL, 22.0 mmol) was added dropwise. The reaction was stirred for 2.0 h, and it was quenched with a saturated solution of NH_4Cl (30 mL). The mixture was extracted with EtOAc (2x 50 mL), and dried over $MgSO_4$. After evaporating the solvent, the crude material was dissolved in DCM (40 mL), and MS 3A^o (1.0g), PCC (6.30 g, 29.4 mmol) were added at 25 ^{o}C. The reaction mixture was stirred for 3 h, and the solvent was removed under reduced pressure and purified by flash chromatography (silica, 25:75 Et_2O: hexane) to give the corresponding (+)-isocarvone (1.30g, 8.60 mmol, 62% yield) with the same spectroscopic measurements as (-)-isocarvone with the exception of its $[\alpha]_D$. (+)-Isocarvone: $[\alpha]^{25}_D$= + 62.1 (c 0.42, $CHCl_3$).



Keto-ester 83: R (-)-Carvone **65** (10.0 g, 66.0 mmol) was dissolved in anhydrous THF (50 mL) and treated with LDA (2.5M, 32.0 mL, 80.0 mmol) at -78 ^{o}C. The reaction was stirred for 1.0 h at -78 ^{o}C, and HMPT (12.1 mL, 66.0 mmol) was added followed by ethyl bromoacetate (11.0g, 66.0 mmol). The reaction was stirred at -45 ^{o}C for 1h and was quenched with a saturated solution of aqueous NH_4Cl (50 mL) and was extracted with EtOAc (3 x 100 mL), the combined organic extracts were washed with brine (2 x

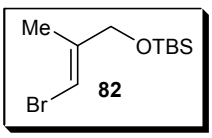
50 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 Et_2O: hexane) to give the corresponding compound (12.8 g, 54.3 mmol, 82% yield) as a colorless oil: R_f = 0.45 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 6.64 (m, 1H), 4.80 (s, 1H), 4.81 (s, 1H), 4.20-4.0 (m, 2H), 2.82 (m, 1H), 2.71 (m, 1H), 2.55-2.35 (m, 3H), 2.25 (m, 1H), 1.71 (m, 2H), 1.65 (s, 3H), 1.20 (tr, J = 7.20 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.75, 172.84, 144.53, 142.62, 134.92, 114.43, 60.67, 48.60, 45.60, 32.69, 31.62, 18.57, 16.40, 14.59; HRMS calcd. for $C_{14}H_{20}O_3$ (M+ H^+) 237.1491, found 237.1491.



87

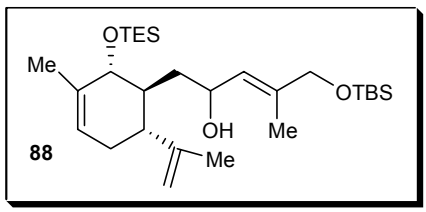
Compound 87: A solution of compound **83** (0.53 g, 2.24 mmol) was dissolved in THF and treated with LAH (1.0M, 6.96mL) at -78 ^oC. The reaction mixture was stirred at -78 ^oC for 1 h and was quenched with a solution of 5% tartaric acid. It was extracted with EtOAc (3 x 25 mL), and concentrated under reduced pressure to give the diol as a white solid (0.350 g, 1.65 mmol, 74%). The diol (0.350g, 1.65 mmol) was dissolved in DCM (20.0 mL) and cooled to -78 ^oC. Then, 2, 6-lutidine (0.71g, 6.66mmol) was added to the reaction mixture followed by TES-Triflate (0.88g, 3.34 mmol). The reaction was allowed to stir at -78 ^oC for 1 h and was quenched with a saturated solution of $NaHCO_3$ (20.0 mL). The mixture was extracted with DCM (3 x 25 mL) and the combined organic extracts were washed with brine (2 x 25 mL), dried over $MgSO_4$, concentrated under reduced pressure to give the crude diprotected material as a colorless oil (0.6 g, 1.45 mmol, 87.2% yield). This di-TBS-protected compound (0.6 g, 1.45 mmol) was dissolved in dry THF (20 mL) in a polystyrene

flask and was treated with HF-Pyridine (1 M, 1.45 mL) at 0 ^{o}C. The reaction mixture stirred for 1 h at 0 ^{o}C and was quenched with a saturated solution of $NaHCO_3$ and extracted with EtOAc (3x 25 mL). The combined organic extracts were washed with brine (2 x 25 mL), dried over $MgSO_4$, concentrated under reduced pressure to give the crude mono-TBS-protected compound **86** as a colorless oil (0.30 g, 0.97 mmol, 67% yield). A solution of **86** (0.041g, 0.13mmol) was dissolved in anhydrous DCM: DMSO (3:1, 3 mL), and treated with TEA at 0 ^{o}C. Then, SO_3-pyridine (0.083g, 0.52 mmol) was added and the reaction was allowed to stir at 0 ^{o}C for 1 h. It was quenched with a saturated solution of NH_4Cl (5 mL) and extracted with DCM (3 x 10 mL) and the combined organic extracts were washed with brine (2 x 5 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 Et_2O: hexane) to give the corresponding compound **87** (0.045g, 0.126 mmol, 97.1% yield) as a colorless oil: R_f = 0.5 (50% Et_2O: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (m, 1H), 5.48 (m, 1H), 4.77 (s, 2H), 4.14 (d, J = 8.80 Hz, 1H), 2.55-2.45 (m, 2H), 2.37 (ddd, J = 4.80, 11.2, 11.6 Hz, 1H), 2.19 (m, 2H), 1.92 (m, 1H), 1.70 (s, 3H), 1.62 (s, 3H), 1.05-0.90 (m, 9H), 0.80-0.55 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.97, 146.87, 135.92, 123.83, 123.79, 114.04, 76.2, 76.13, 46.86, 45.5, 42.33, 30.77, 20.98, 19.11, 19.07, 7.58, 6.15; HRMS calcd. for $C_{18}H_{32}O_2Si$ (M+ H^+) 309.2249, found 309.2251.



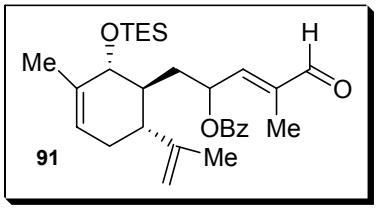
Compound 82: (*E*)-ethyl 3-bromo-2-methylacrylate (2.0 g, 10.0 mmol) was dissolved in anhydrous DCM (25 mL) and was treated with DIBAL-H (1 M, 21.0 mmol) at -78 ^{o}C. The reaction was

stirred at -78 ^{o}C for 2.5 h and quenched with a solution of 5% tartaric acid (25 mL) and was extracted with DCM (3 x 100 mL), the combined organic extracts were washed with brine (2 x 50 mL), dried over $MgSO_4$, concentrated under reduced pressure to afford a white semi-solid (1.49 g, 9.9 mmol, 99% yield). This alcohol (1.49 g, 9.9 mmol) was dissolved in dry DCM (25 mL) and was treated with imidazole (1.35 g, 19.8 mmol) and DMAP (cat). Then, TBSCl (1.5 g, 10.0 mmol) was added at 0 ^{o}C. The reaction mixture was stirred at 25 ^{o}C for 10 h and was quenched with a saturated solution of NH_4Cl (15 mL) and extracted with DCM (3 x 30 mL). Then, the combined organic extracts were washed with brine (2 x 25 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 5:95 Et_2O: hexane) to give compound 82 (2.61 g, 9.85 mmol, 99% yield) as a colorless oil: R_f = 0.5 (50% Et_2O: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (s, 1H), 4.07 (s, 2H), 1.76 (s, 3H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.93, 103.03, 102.94, 67.04, 26.24, 26.10, 18.73, -4.94; HRMS calcd. for $C_{10}H_{22}BrOSi$ (M+ H^+) 265.0623, found 265.0621.



Compound 88: A solution of (E)-(3-bromo-2 methylallyloxy)(tert-butyl)dimethylsilane **82** (3.28 g, 14.0 mmol) was dissolved in THF and treated with t-BuLi (1.7 M, 8.5 mL) at -78 ^{o}C for 30 min. Then, it was stirred at -40 ^{o}C for 30 min and cooled back to -78 ^{o}C followed by the addition of the aldehyde 87 (1.5 g, 4.86 mmol in 20mL of THF) via cannula. The reaction mixture was stirred at -78 ^{o}C for 1 hr and was quenched with a saturated

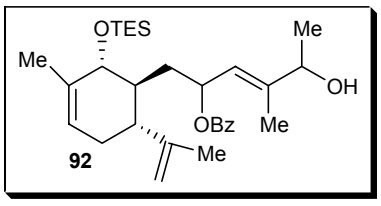
solution of NH_4Cl (25 mL). The mixture was extracted with EtOAc (3 x 50 mL), and the combined organic extracts were washed with brine (2 x 50 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 Et_2O: hexane) to give the corresponding alcohol 89 (1.63 g, 3.3 mmol, 68% yield) as a white solid: R_f = 0.4 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 5.50-5.40 (m, 2H), 4.80-4.70 (m, 1H), 4.41 (m, 1H), 4.20 (d, J = 8.0 Hz, 1H), 4.01 (s, 2H), 2.35 (m, 1H), 2.30-1.20 (m, 13H), 1.10-0.80 (m, 18H), 0.15-0.0 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 137.23, 135.43, 127.75, 127.71, 123.83, 123.43, 112.81, 111.99, 75.64, 67.93, 66.53, 48.06, 44.95, 42.03, 40.25, 38.23, 30.68, 29.80, 26.31, 21.64, 21.31, 20.02, 19.46, 18.81, 6.15, 6.07, -4.85; HRMS calcd. for $C_{28}H_{54}O_3Si_2$ (M+ Na^+) 517.3509 found 517.3510.



91

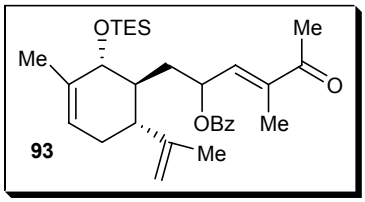
Compound 91: Then, alcohol **88** (0.85 g, 1.7 mmol) was dissolved in dry DCM (30 mL) and was treated with Pyridine (0.19 g, 2.3 mmol) and DMAP (cat) at 0 ^oC. After 10 min, benzoyl chloride (0.31 g, 2.2 mmol) was added at 0 ^oC and the reaction was allowed to stir for 10 h at 25 ^oC. The reaction mixture was quenched with a saturated solution of NH_4Cl and extracted with DCM (3 x 30 mL). The combined organic extracts were washed with brine (2 x 15 mL), dried over Mg SO_4, and concentrated under reduced pressure to afford compound 89 (0.96 g, 1.66 mmol, 98% yield). Compound 89 (0.10 g, 0.17 mmol) was dissolved in dry DCM (5 mL) and p-TSA (0.003 g, 0.017 mmol) was added at 0 ^oC. The reaction mixture was stirred at 0 ^oC for 1.5 h, and was quenched with a saturated solution of $NaHCO_3$ (5

mL). The reaction mixture was extracted with DCM (3x 15) and dried over $MgSO_4$ to afford the corresponding alcohol 90 (0.056 g, 0.12 mmol, 70% yield). Alcohol **90** (0.071 g, 0.16 mmol) was dissolved in anhydrous DCM (10 mL) and treated with DMP (0.145 g, 0.34 mmol). The reaction was stirred at 25 ^oC for 2.5 h. The reaction mixture was quenched with a saturated solution of aqueous $NaHCO_3$ (5 mL) and a solution of $Na_2S_2O_3$ (5 mL). The mixture was extracted with DCM (3 x 10 mL), the combined organic extracts were washed with brine (2 x 5 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 15:85 Et_2O: hexane) to give compound 91 (0.061 g, 0.148 mmol, 91.2% yield) as a light yellow oil: R_f = 0.43 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.10-7.95 (d, J = 8.0 Hz, 2H), 7.56 (m, 1H), 750-7.35 (tr, J = 7.60 Hz, 2H), 6.35 (d, J = 8.0 Hz, 1H), 6.05 (m, 1H), 5.48 (s, 1H), 4.86 (s, 2H), 4.14 (d, J = 6.0 Hz, 1H), 2.40-1.92 (m, 2H), 1.91-1.50 (m, 10H), 1.10-0.80 (m, 9H), 0.80-0.50 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ; HRMS calcd. for $C_{29}H_{44}O_3Si$ ($M+ H^+$) 469.3138, found 469.3139.



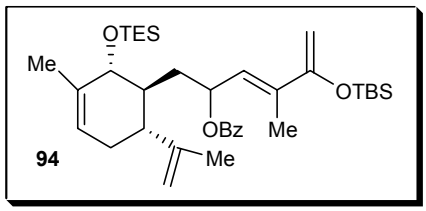
Compound 92: To a stirred solution of compound 91 (0.10 g, 0.214 mmol) was dissolved in dry THF (10 mL) and methyl magnesium bromide (1.4 M, 0.257 mmol) was added at -78 0 ^oC. The reaction mixture was stirred at -50 ^oC for 1.5 h and it was quenched with a saturated solution of NH_4Cl (5 mL) and extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with brine (2 x 10 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash

chromatography (silica, 10:90 EtOAc: hexane) to give the corresponding compound **92** (0.09 g, 0.187 mmol, 87% yield) as colorless oil: R_f = 0.39 (30% EtOAc: hexane); ^{1}H NMR (400 MHz, $CDCl_3$); δ 8.10-7.95 (d, J = 8.50 Hz, 2H), 7.53 (m, 1H), 7.40 (tr, J = 7.60 Hz, 2H), 5.90 (m, 1H), 5.50 (m, 2H), 4.81 (m, 2H), 4.20 (m, 1H), 4.0 (m, 1H), 2.30 (m, 1H), 2.20-1.20 (m, 16H), 1.10-0.80 (m, 9H), 0.80-0.60 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ;HRMS calcd. for $C_{30}H_{46}O_4Si$ (M+ Na^+) 521.3063, found 521.3264.

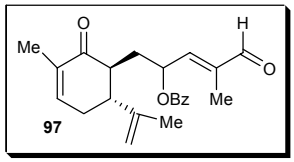


Compound 93: To a stirred solution of compound **92** (0.10 g, 0.20 mmol) in dry DCM (10 mL) was added DMP (0.131 g, 0.31 mmol) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 2.5 h and was quenched with a saturated solution of aqueous $NaHCO_3$ (5 mL) and $Na_2S_2O_3$ (2 mL). It was extracted with DCM (3 x 15 mL), and the combined organic extracts were washed with brine (2 x 15 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 30:70 Et_2O: hexane) to give the corresponding compound **93** (0.095 g, 0.192 mmol, 96% yield) as a yellow oil: R_f = 0.28 (50% Et_2O: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (m, 1H), 8.10-8.00 (d, J = 8.30 Hz, 2H), 7.55 (m, 1H), 7.50-7.40 (tr, J = 8.20, 2H), 6.44 (dd, J = 1.20, 8.40 Hz, 1H), 5.98 (m, 1H), 5.48 (s, 1H), 4.85 (s, 2H), 4.10 (d, J = 6.0 Hz, 1H), 2.32 (s, 3H), 2.20-1.95 (m, 4H), 1.93 (d, J = 1.20 Hz, 3H), 1.85-1.20 (m, 8H), 1.10-0.90 (m, 9H), 0.75-0.60 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.70, 165.81, 147.20, 140.73, 139.13, 134.76, 133.12, 129.93, 129.75, 128.76, 128.53, 128.42, 125.66, 123.70, 112.60, 75.17, 70.75, 44.35, 42.07,

33.52, 30.70, 30.08, 26.08, 20.60, 20.51, 12.38, 7.71, 7.56, 6.38, 5.98; HRMS calcd. for $C_{30}H_{44}O_4Si$ (M+ Na^+) 519.2907, found 519.2906.

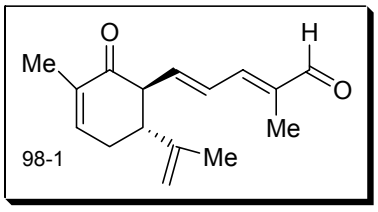


Compound 94: Compound **93** (0.048 g, 0.097 mmol) was dissolved in dry DCM (1.4 mL) and was treated with TEA (0.029 g, 0.29 mmol) at -78 ^oC followed by TBSOTF (0.038 g, 0.145 mmol). The reaction was stirred at -78 ^oC for 1.5 h, and was quenched with a solution of $NaHCO_3$ (0.3mL). It was then extracted with pentane (3 x 5 mL), and the combined organic extracts were washed with brine (2 x 5 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 Et_2O: pentane) to give the corresponding trapped enolate (0.055g, 0.09 mmol, 93% yield) as a colorless oil: R_f = 0.38 (50% Et_2O: pentane); ^1H NMR (400 MHz, $CDCl_3$) δ 8.01-7.95 (d, J = 14.2 Hz, 2H), 7.55 (m, 1H), 7.55 (m, 1H), 7.45-7.35 (tr, J = 12.0 Hz, 2H), 6.05 (m, 1H), 6.00 (d, J = 14.30, 1H), 5.45 (br s, 1H), 4.90 (s, 1H), 4.83 (s, 1H), 4.52 (s, 1H), 4.33 (s, 1H), 4.12 (d, J = 9.20 Hz, 1H), 2.30 (m, 1H), 2.20-0.80 (m, 38H), 0.20-0.0 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.09, 156.67, 147.56, 134.84, 134.54, 132.89, 130.88, 129.70, 128.41, 126.66, 123.67, 112.14, 93.73, 75.01, 71.17, 46.48, 43.48, 42.11, 35.09, 34.50, 30.08, 29.53, 26.17, 26.01, 22.73, 21.58, 20.42, 18.66, 14.47, 14.25, 11.89, 7.56, 6.01, -3.15, -4.23, -4.39; HRMS calcd. for $C_{39}H_{58}O_4Si_2$ (M+ H^+) 611.3952, found 611.3952.



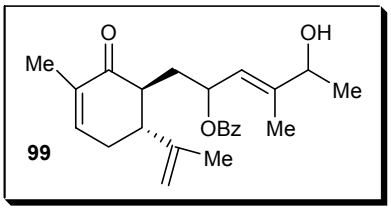
Compound 97: To a stirred solution of compound **89** (0.10 g, 0.20 mmol) in dry THF (5 mL) was added TBAF (1 M,

0.45 mmol) at 0 ^{o}C. The reaction mixture was stirred at 25 ^{o}C for 1.5 h, and was quenched with a saturated solution of NH_4Cl (5 mL). The reaction mixture was extracted with DCM (3x 15) and dried over $MgSO_4$ to afford the corresponding alcohol (0.059 g, 0.16 mmol, 80% yield). Alcohol (0.059 g, 0.16 mmol) was dissolved in anhydrous DCM (5 mL) and treated with DMP (0.271 g, 0.64 mmol). The reaction was stirred at 25 ^{o}C for 2.5 h. The reaction mixture was quenched with a saturated solution of aqueous $NaHCO_3$ (5 mL) and a solution of $Na_2S_2O_3$ (5 mL). The mixture was extracted with DCM (3 x 10 mL), the combined organic extracts were washed with brine (2 x 5 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 Et_2O: hexane) to give compound (0.051 g, 0.14 mmol, 88% yield) as a light yellow oil: R_f = 0.35 (50% Et_2O: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) (major) δ 9.41 (d, J = 9.60 Hz, 1H), 8.10-7.95 (m, 2H), 7.60 (m, 1H), 7.50-7.40 (d, J = 13.6 Hz, 2H), 6.63 (m, 1H), 6.40 (d, J = 13.6 Hz, 1H), 6.20 (m, 1H), 4.95 (s, 1H), 4.90 (s, 1H), 2.70-2.20 (m, 5H), 2.02 (m, 3H), 1.95-1.60 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.30, 196.81, 157.75, 155.70, 139.92, 135.26, 134.27, 131.64, 130.50, 128.04, 127.75, 126.88, 122.97, 122.86, 79.30, 49.22, 47.16, 46.84, 40.77, 31.17, 30.80, 28.90, 28.87, 28.26, 21.89, 21.38, 20.43, 14.35; HRMS calcd. for $C_{23}H_{26}O_4$ (M+ H^+) 367.1909, found 367.1910.



Compound 98-1: To a stirred solution of $PPh_3CH_2OCH_3Cl$ (0.49 g, 1.43 mmol) in dry THF (15 mL) was added t-BuOK (1 M, 1.2 mmol) at 0 ^{o}C. After 30 min of stirring, the aldehyde (0.35 g, 0.95

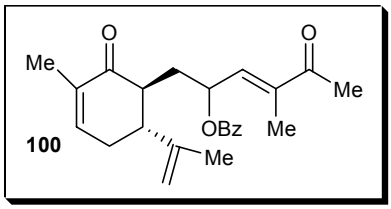
mmol in 5 mL of THF) was added at -45 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 1 h. The reaction mixture was quenched with saturated solution of aqueous NH_4Cl (10 mL) and was extracted with EtOAc (3 x 25 mL), the combined organic extracts were washed with brine (2 x 15 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 Et_2O: hexane) to give the corresponding compound (0.217 g, 0.89 mmol, 94% yield) as a white solid: R_f = 0.4 (50% Et_2O: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.02 (d, J = 10.0 Hz, 1H), 6.70 (m, 1H), 6.31 (m, 1H), 6.20 (d, J = 16.8 Hz, 1H), 5.85 (d, J = 9.60 Hz, 1H), 4.89 (s, 1H), 4.80 (s, 1H), 2.75-2.60 (m, 2H), 2.60-2.25 (m, 4H), 2.21 (s, 3H), 1.80 (s, 3H), 1.71 (s, 3H); HRMS calcd. for $C_{16}H_{20}O_2$ (M+ Na^+) 267.1361, found 267.1361.



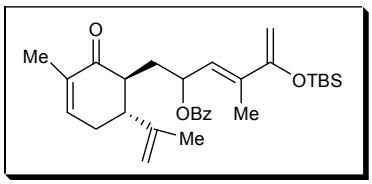
99

Compound 99: A solution of aldehyde (0.418 g, 1.0 mmol) anhydrous THF (20 mL) was treated with MeMgBr (1.4 M, 1.1 mmol) at -78 ^{o}C. The reaction mixture was allowed to stir at -78 ^{o}C for 1.5 h and was quenched with a saturated solution of aqueous NH_4Cl (10 mL) and was extracted with EtOAc (3 x 20 mL), the combined organic extracts were washed with brine (2 x 15 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 25:75 Et_2O: hexane) to give the corresponding compound (0.286 g, 0.75 mmol, 75% yield) as a light yellow oil: R_f = 0.26 (50% Et_2O: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05-7.95 (m, 2H), 7.50 (m, 1H), 7.45-7.35 (m, 2H), 6.63 (m, 1H), 6.01 (m, 1H), 4.90 (s, 1H), 4.82 (s, 1H), 4.19 (m, 1H), 2.60 (m, 1H), 2.50-2.20 (m, 4H), 2.16 (s, 3H), 2.0-1.60 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

200.67, 165.79, 145.22, 144.23, 143.06, 135.10, 132.81, 130.85, 129.75, 128.42, 123.70, 123.20, 114.30, 72.57, 54.14, 48.69, 35.02, 32.84, 31.27, 21.08, 15.67, 15.67, 23.04, 13.42 ; HRMS calcd. for $C_{24}H_{30}O_4$ (M+ H^+) 383.2222, found 383.2225.

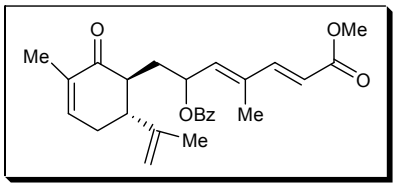


Compound 100: To a stirred solution of alcohol 4a (0.250 g, 0.65 mmol) anhydrous DCM (20 mL) was added DMP (0.297 g, 0.70 mmol) at 0 ^oC. The reaction was stirred at 25 ^oC for 1.5 hr. The reaction mixture was quenched with saturated solution of aqueous $NaHCO_3$ (10 mL) and a solution of $Na_2S_2O_3$ (10 mL) and was extracted with DCM (3 x 30 mL). The combined organic extracts were washed with brine (2 x 15 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 20:80 Et_2O: hexane) to give the corresponding diketone (0.228 g, 0.60 mmol, 92% yield) as a light yellow film: R_f = 0.41 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) major δ 8.10-7.95 (m, 2H), 7.55 (m, 1H), 7.42 (m, 2H), 6.66 (m, 1H), 6.40 (d, J = 8.80 Hz, 1H), 6.08 (dd, J = 7.20, 14.40 Hz, 1H), 4.92 (s, 1H), 4.87 (s, 1H), 2.64 (m, 1H), 2.57-2.38 (m, 2H), 2.38-2.20 (m, 4H), 1.91 (s, 3H), 1.87-1.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.31, 199.73, 165.76, 145.17, 143.50, 143.41, 140.25, 139.80, 139.38, 135.21, 130.21, 129.78, 114.64, 71.30, 48.81, 45.19, 32.18, 31.64, 31.36, 26.08, 19.02, 18.48, 16.56, 12.40; HRMS calcd. for $C_{24}H_{28}O_4$ (M+ H^+) 381.2066, found 381.2066.



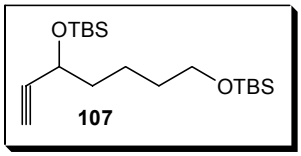
Compound 101: Compound **100** (0.050 g, 0.132 mmol) was dissolved in dry DCM (1 mL) and was treated with TEA (0.019 g, 0.198 mmol) at -78 ^oC

followed by TBSOTF (0.036 g, 0.135 mmol). The reaction was stirred at -78 ^{o}C for 1 h, and was quenched with a solution of $NaHCO_3$ (0.5 mL). It was then extracted with pentane (3 x 5 mL), and the combined organic extracts were washed with brine (2 x 5 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 5:95 Et_2O: pentane) to give the corresponding trapped enolate (0.054 g, 0.11 mmol, 83% yield) as a light yellow oil: R_f = 0.5 (50% Et_2O: pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20-8.05 (m, 2H), 7.20-6.90 (m, 3H), 6.80-6.60 (m, 2H), 6.25 (d, J = 16.0 Hz, 1H), 5.96 (m, 1H), 4.74 (s, 1H), 4.65 (s, 1H), 4.48 (s, 1H), 4.33 (s, 1H), 2.50 (m, 1H), 2.40-1.40 (m, 13H), 1.0-0.80 (m, 9H), 0.2-0.0 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.42, 165.41, 156.85, 145.56, 145.44, 142.37, 142.24, 136.02, 134.75, 132.62, 132.41, 131.23, 126.52, 113.96, 93.68, 72.11, 71.57, 49.18, 48.41, 45.67, 45.24, 33.54, 33.10, 31.34, 30.90, 26.03, 18.65, 18.53, 18.00, 16.50, 16.44, 14.40, -4.37, -4.65; HRMS calcd. for $C_{30}H_{42}O_4Si$ (M+ Na^+) 517.2750, found 517.2751.

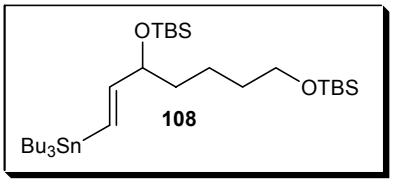


Compound 103: To a stirred solution of aldehyde (0.10 g, 0.272 mmol) in anhydrous DCM (10 mL) was added ylide (0.228 g, 0.68 mmol) at 0 ^{o}C. The reaction was allowed to stir at 25 ^{o}C for 1.5 h at this temperature. The reaction mixture was quenched with saturated solution of aqueous $NaHCO_3$ (10 mL) and was extracted with EtOAc (3 x 25 mL), the combined organic extracts were washed with brine (2 x 15 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 Et_2O: hexane) to give the

corresponding ester (0.110 g, 0.26 mmol, 96% yield) as a white foam: R_f = 0.39 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) major δ 8.05-7.91 (m, 1H), 7.51(m, 1H), 7.45-7.35 (m, 2H), 7.23 (m, 1H), 6.62 (m, 1H), 6.15 (m, 1H), 5.91 (d, J = 15.0 Hz, 1H), 5.80 (d, J = 9.00 Hz, 1H), 4.87 (s, 1H), 4.82 (s, 1H), 3.71 (s, 3H), 2.70-2.20 (m, 5H), 2.05 (s, 3H), 1.90-1.60 (m, 8H); HRMS calcd. for $C_{26}H_{30}O_5$ (M+ Na^+) 445.1991, found 445.1989.

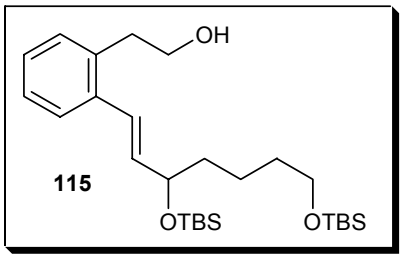


Compound 107: Hept-6-yne-1, 5-diol (4 g, 31.0 mmol) was dissolved in dry DCM (100 mL) along with imidazole (10.63 g, 156.0 mmol), and DMAP (cat). The reaction mixture was cooled to 0 ^oC and TBSCl (11.70g, 78.0 mmol) was added. The reaction mixture was stirred at 25 ^oC for 12 h. It was then quenched with a solution of NH_4Cl (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (2 x 100 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 5:95 Et_2O : hexane) to give compound 107 (10.57 g, 29.7 mmol, 96% yield), as a colorless oil R_f = 0.65 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 4.33 (dd, J = 6.0, 8.0 Hz, 1H), 3.61 (dd, J =1.60 Hz, 2H), 2.37 (tr, J = 1.60 Hz, 1H), 1.69 (m, 2H), 1.60-1.40 (m, 4H), 0.96-0.85 (m, 18H), 0.20-0.0 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 94.55, 85.91, 72.21, 63.35, 63.04, 38.76, 32.83, 31.98, 26.37, 26.17, 21.97, 18.77, 18.64, -4.10, -4.60, -4.81; HRMS calcd. for $C_{19}H_{40}O_2Si_2$ (M+ H^+) 357.2645, found 357.2644.



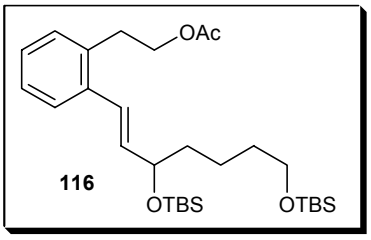
Compound 108: To a stirred solution of compound **107** (0.36 g, 1.09 mmol) in dry THF (10 mL) was

added Pd $(PPh_3)_2Cl_2$ (0.007 g, 0.009 mmol) and was cooled to -78 ^oC. Then, Bu_3SnH (0.35g, 1.2 mmol) was added via syringe and the mixture was stirred for 45 min at -78 ^oC. It was quenched with a solution of NH_4Cl (150 mL) and extracted with EtOAc (3 x 150 mL). The solvent was concentrated under reduced pressure and purified by flash chromatography (silica, 2:98 Et_2O: hexane) to give the corresponding stannane (0.55 g, 0.86 mmol, 79.0% yield), as a colorless oil R_f = 0.75 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 5.99 (d, J = 19.2 Hz, 1H), 5.89 (dd, J = 5.60, 18.80 Hz, 1H), 4.0 (dd, J = 5.20, 11.20 Hz, 3H), 3.58 (tr, J = 6.0 Hz, 2H), 1.62-0.75 (m, 51H), 0.10-0.0 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.98, 126.56, 63.60, 38.29, 33.28, 29.51, 27.65, 26.39, 26.34, 26.28, 22.21, 18.78, 18.75, 14.16, 9.86, -3.81, -4.30, -4.80; HRMS calcd. for $C_{31}H_{68}O_2Si_2Sn$ (M+ H^+) 649.3858, found 649.3859.

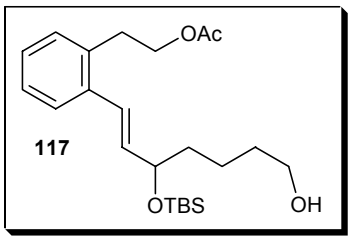


Compound 115: Commercial available 2-(2-bromophenylethanol) **114** (2.21g, 10.9 mmol) was dissolved in dry toluene along with Pd_2dba_3 (1.0g, 1.09 mmol), and tri-tert-butyl phosphine (2.85g, 1.12mmol). The reaction mixture was degassed and stannane 108 (7.14g, 10.9 mmol) was added. The reaction mixture was heated at 80 ^oC for 15 h. The solvent was concentrated under reduced pressure and purified by flash chromatography (silica, 25:75 Et_2O: hexane) to give the corresponding compound 115 (3.3 g, 6.8 mmol, 68.9 % yield) as a colorless oil: R_f = 0.35 (50% Et_2O:hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (m, 1H), 7.30-7.10 (m, 3H), 6.76 (d, 1H, J= 15.6 Hz), 6.05 (dd, 1H, J=6.0, 15.6 Hz), 4.28 (m, 1H), 3.79 (tr, 2H, J= 7.20 Hz), 3.59 (m, 2H), 2.95 (tr, 2H, J= 6.40 Hz),

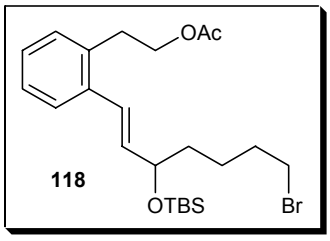
1.80–1.30 (m, 6H), 0.92 (s, 9H), 0.88 (s, 9H), 0.09-0.01 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.71, 135.84, 135.63, 130.47, 127.53, 127.08, 126.59, 126.26, 73.77, 63.54, 63.39, 38.63, 36.94, 33.25, 26.37, 26.29, 22.06, 18.79, 18.67, -3.79, -4.24, -4.79 ; HRMS calcd. for $C_{27}H_{50}Si_2$ (M+ H^+) 479.3377, found 479.3379 .



Compound 116: Compound **115** (50.0 mg, 0.1 mmol) was dissolved in dry DCM (5 mL) and pyridine (83.0 mg, 1.0 mmol) was added at 0 ^{o}C. Then, acetyl chloride (41.0mg, 0.5 mmol) was added drop wise and the mixture stirred at 25 ^{o}C for 2.5 h. The reaction mixture was quenched with a saturated solution of aqueous NH_4Cl (5 mL) and was extracted with DCM (3 x 15 mL), the combined organic extracts were washed with brine (2 x 10 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 Et_2O: hexane) to give the corresponding compound 116 (51.0 mg, 0.09 mmol, 98% yield) as a colorless oil: R_f = 0.4 (50% Et_2O: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (m, 1H), 7.35-7.10 (m, 3H), 6.76 (d, 1H, J= 16.0 Hz), 6.10 (dd, 1H, J= 6.0, 15.6 Hz), 4.29 (m, 1H), 4.20 (m, 2H), 3.60 (m, 2H), 2.99 (m, 2H), 2.03 (s, 3H), 1.70-1.20 (m, 6H), 1.0-0.8 (m, 18H), 0.20-0.0 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170, 136.68, 136.12, 134..86, 130.20, 127.53, 127.19, 126.47, 125.94, 73.73, 64.63, 63.47, 38.66, 33.28, 32.74, 31.98, 26.37, 26.30, 22.03, 21.38, 18.78, 18.66, -3.82, -4.25, -4.25, -4.802 ; HRMS calcd. for $C_{29}H_{52}O_4Si_2$ (M+ Na^+) 543.3302, found .543.3300.

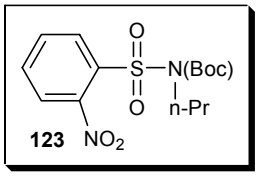


Compound 117: Compound **116** (50.0 mg, 0.096 mmol) was dissolved in dry THF in a plastic flask at 0 ^{o}C. HF-Pyridine (1M, 0.15 mL, 0.096 mmol) was added and stirred at 0 ^{o}C for 5h. The reaction mixture was quenched with a saturated solution of aqueous $NaHCO_3$ (5 mL) and was extracted with EtOAc (3 x 10 mL), the combined organic extracts were washed with brine (2 x 10 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 20:80 Et_2O: hexane) to give the corresponding compound (29.0 mg, 0.072 mmol, 75% yield) as a colorless oil: R_f = 0.25 (50% Et_2O: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 1H), 7.35-7.10 (m, 3H), 6.75 (d, 1H, J= 16.0 Hz), 6.08 (dd, 1H, J= 6.0, 15.6 Hz), 4.31 (m, 1H), 4.20 (m, 2H), 3.62 (tr, 2H, J= 6.80 Hz), 2.99 (tr, 2H, J= 7.60 Hz), 2.03 (s, 3H), 1.70-1.50 (m, 4H),1.45-1.35 (m, 2H), 0.92 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ; HRMS calcd. for $C_{23}H_{38}O_4Si$ (M+ H^+) 407.2618 , found 407.2620.



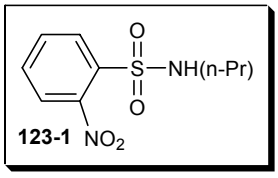
Compound 118: DDQ (11.0 mg, 0.049 mmol) and PPh_3 (13.0 mg, 0.049 mmol) were dissolved in anhydrous DCM (2.50 mL), and after 2 min TBABr (16.0 mg, 0.049 mmol) was added. Then, the alcohol **117** (10.0 mg, 0.025 mmol) in DCM (1.0 mL) was added via cannula at 25 ^{o}C. After 2 min of stirring, the reaction was completed by TLC. The solvent was evaporated and the orange residue was purified by flash chromatography (silica, 10:90 Et_2O: hexane) to give the corresponding bromide (11.0 mg, 0.023 mmol, 94.0 % yield) as a light yellow oil: R_f =

0.4 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (m, 1H), 7.35-7.10 (m, 3H), 6.80 (d, 1H, J= 16.0 Hz), 6.06 (dd, 1H, J= 6.40, 15.6 Hz), 4.31 (m, 1H), 4.20 (tr, 2H, J= 7.20 Hz), 3.42 (tr, 2H, J= 6.80 Hz), 3.0 (tr, 2H, J= 7.60 Hz), 2.04 (s, 3H), 1.88 (tr, 2H, J= 7.20 Hz), 0.70-0.20 (m, 4H), 0.95 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.99, 136.55, 135.71, 134.88, 132.19, 130.27, 127.63, 127.25, 126.47, 126.33, 73.46, 64.62, 37.79, 34.17, 33.18, 32.80, 26.28, 24.27, 21.40, 18.64, -3.80, -4.25; HRMS calcd. for $C_{23}H_{37}BrO_3Si$ (M+ H^+)469.1774, found 469.1772.

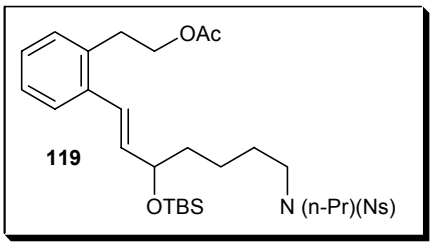


Compound 123: Commercially available 2-nitrobenzenesulfonamide (2.08 g, 10.30 mmol) was dissolved in dry DCM (20 mL), and treated with TEA (2.69 g, 15.4 mmol) and DMAP (0.126g, 1.03 mmol). After 10 min, $(Boc)_2O$ (2.69 g, 12.4 mmol) was added and the reaction mixture was stirred for 10 hr at 25 ^oC. The mixture was quenched with a saturated solution of aqueous $NaHCO_3$ (12 mL) and was extracted with EtOAc (3 x 25 mL), the combined organic extracts were washed with brine (2 x 15 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 30:70 Et_2O: hexane) to give the corresponding protected amine (2.57 g, 10.0 mmol, 97% yield) as a white solid. Then, the protected amine (2.0g, 7.7 mmol) was dissolved in anhydrous DMF (20 mL), and K_2CO_3 (5.37 g, 38.8 mmol) was added. The mixture was cooled to 0 ^oC and 1-bromopropane (1.43g, 1.0 mL) was added. The reaction mixture was heated to 50 ^oC for 4 h. The mixture was quenched with a solution of NH_4Cl (20 mL) and extracted with DCM (3x 40 mL).

The combined organic extracts were dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 40:60 Et_2O: hexane) to give compound 123 (1.93 g, 7.5 mmol, 97% yield) as an off white solid : R_f = 0.4 (50% Et_2O: hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (m, 1H), 7.80-7.62 (m, 3H), 3.74 (tr, J = 7.20 Hz, 2H), 1.90-1.70 (m, 2H), 1.35 (s, 9H), 0.98 (tr, J = 7.20 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.10, 133.38, 131.78, 131.41, 124.41, 84.99, 49.98, 28.24, 23.85, 11.51; HRMS calcd. for $C_{14}H_{20}N_2O_6S$ (M+ H^+) 345.1120, found 345.1119.

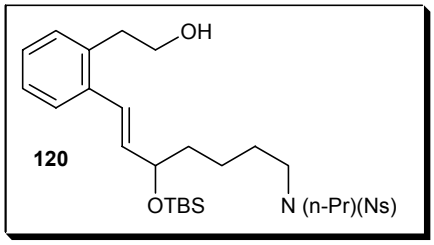


Compound 123-1: To a stirred solution of compound **123** (0.50 g, 1.45 mmol) in dry THF (10 mL) was treated with TFA (0.25g, 2.17 mmol) at 0 ^oC. The reaction mixture was stirred at 25 ^oC for 6 h. The solvent was concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 Et_2O: hexane) to give compound 123-1 (0.045 g, 0.15 mmol, 88.53% yield) as a white solid: R_f = 0.2 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (m, 1H), 7.83 (m, 1H), 7.73 (m, 2H), 5.30 (tr, J = 5.20 Hz, 1H), 2.03 (m, 2H), 1.52 (dd, J = 7.60, 14.40 Hz, 2H), 0.87 (tr, J = 7.20 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.79, 132.99, 131.15, 125.50, 45.93, 23.32, 11.47; HRMS calcd. for $C_9H_{12}N_2O_4S$ (M+ H^+) 245.0596, found 245.0597.



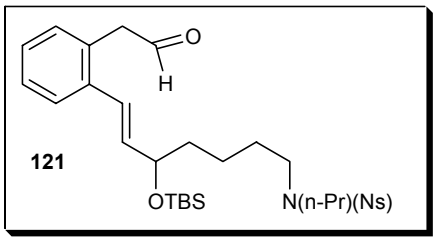
Compound 119: Compound **118** (0.010g, 0.021 mmol) was dissolved in anhydrous DMF (2 mL), 2-nitro-N-propylbenzenesulfonamide (0.005 g, 0.021mmol) was added followed by K_2CO_3

(0.015g, 0.1 mmol). The reaction mixture was stirred for 12 h and then quenched with 3N HCl (1.0 mL) and extracted with EtOAc (3 x 5 mL), the combined organic extracts were washed with brine (2 x 5 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 25:75 EtOAc: hexane) to give compound 119 (0.012 g, 0.019 mmol, 90% yield) as a colorless oil: R_f = 0.18 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 8.0 (m, 1H), 7.70-7.50 (m, 3H), 7.43 (m, 1H), 7.30-7.10 (m, 3H), 6.76 (d, 1H, J= 12.4 Hz), 6.03 (dd, 1H, J= 4.80, 12.8 Hz), 4.27 (m, 1H), 4.21 (tr, 2H, J= 7.20 Hz), 3.35-3.20 (m, 4H), 2.99 (tr, 2H, J= 7.60 Hz), 2.04 (s, 3H), 1.70-1.10 (m, 8H), 0.91 (s, 9H), 0.85 (m, 3H), 0.08-0.05 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.97, 136.51, 134.03, 133.31, 130.81, 130.27, 127.63, 127.24, 126.22, 124.24; HRMS calcd. for $C_{32}H_{48}N_2O_7SSi$ (M+ H^+) 633.3029, found 633.3030 .

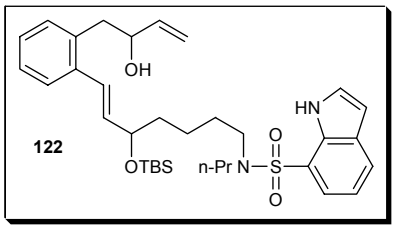


Compound 120: Compound **119** (0.050 g, 0.079 mmol) was dissolved in THF: MeOH (2:1, 1.75 mL), and K_2CO_3 (0.055 g, 0.40 mmol) was added. The reaction mixture was stirred at 25 ^oC for 3 hr. The reaction was quenched with H_2O (2.0 mL) and was extracted with DCM (3 x 5 mL), the combined organic extracts were washed with brine (2 x 5 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 30:70 EtOAc: hexane) to give the corresponding compound (0.045 g, 0.076 mmol, 96.4% yield) as a colorless oil: R_f = 0.15 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (m, 1H), 7.75-7.55 (m, 3H), 7.42 (m, 1H), 7.35-7.10 (m, 3H),

6.77 (d, 1H, J= 12.4 Hz), 6.02 (dd, 1H, J= 4.80, 12.8 Hz), 4.29 (m, 1H), 3.81 (tr, 2H, J= 7.20 Hz), 3.40-3.20 (m, 4H), 2.97 (tr, 2H, J= 7.60 Hz), 1.80-1.10 (m, 8H), 0.91 (s, 9H), 0.84 (m, 3H), 0.20-0.0 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ; HRMS calcd. for $C_{30}H_{46}N_2O_6SSi$ (M+ H^+) 591.2924, found 591.2925.

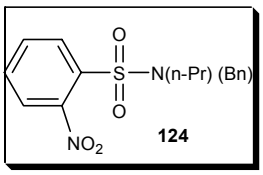


Aldehyde 121: Alcohol **120** (0.03 g, 0.05 mmol) was dissolved in anhydrous DCM (4 mL) and treated with DMP (0.043 g, 0.1 mmol) at 0 ^{o}C. The reaction was stirred for 2.5 hr at 25 ^{o}C and was quenched with a saturated solution of aqueous $NaHCO_3$ (4 mL) and was extracted with DCM (3 x 10 mL). The combined organic extracts were washed with brine (2 x 10 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 Et_2O: hexane) to give the corresponding aldehyde (0.026 g, 0.044 mmol, 88.3% yield) as a colorless oil: R_f = 0.21 (50% Et_2O : hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 8.0 (m, 1H), 7.65 (m, 2H), 7.58 (m, 1H), 7.48 (d, 1H, J= 8.0 Hz), 7.40-7.20 (m, 2H), 7.16 (1H, J= 7.20 Hz), 6.60 (d, 1H, J= 15.6 Hz), 6.03 (dd, 1H, J= 6.40, 16.0 Hz), 4.24 (m, 1H), 3.75 (s, 2H), 3.40-3.15 (m, 4H), 1.70-0.80 (m, 20 H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ; HRMS calcd. for $C_{30}H_{44}N_2O_6SSi$ (M+ Na^+) 611.2587, found 611.2583.



Compound 122: To a stirred solution of compound **121** (0.03 g, 0.05 mmol) in dry THF (5 mL) was added ethynyl magnesium bromide (0.076 mL, 0.076 mmol) at -78 ^{o}C. The reaction was allowed to stir at

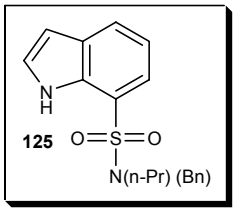
-78 ^{o}C for 1 h. The reaction mixture was quenched with a saturated solution of aqueous NH_4Cl (2 mL) and was extracted with EtOAc (3 x 5 mL), the combined organic extracts were washed with brine (2 x 5 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 20:80 Et_2O: hexanes) to give compound **122** (0.016 g, 0.026 mmol, 53% yield) as an orange foam: R_f = 0.19 (50% Et_2O: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (s, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 7.20 Hz, 1H), 7.43 (m, 1H), 7.39-7.10 (m, 5H), 6.78 (dd, J = 2.80, 15.20 Hz, 1H), 6.60 (s, 1H), 6.10-5.85 (m, 2H), 5.25 (dd, J = 1.60, 9.20 Hz, 1H), 5.10 (dd, J = 1.60, 9.20 Hz, 1H), 4.32 (m, 1H), 4.24 (m, 1H), 3.20-3.0 (m, 4H), 3.0-2.80 (m, 2H), 1.70-0.70 (m, 21 H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.29, 140.25, 135.41, 135.33, 135.20, 131.12, 130.15, 127.52, 127.16, 126.75, 126.62, 126.52, 126.01, 125.66, 121.49, 119.49, 115.04, 103.07, 73.54, 73.30, 53.75, 50.27, 48.50, 41.47, 41.32, 38.27, 29.11, 26.31, 22.70, 22.71, 22.29, 18.65, 11.59, -3.73, -4.25; HRMS calcd. for $C_{34}H_{50}N_2O_4SSi$ (M+ Na^+) 633.3158, found 633.3157.



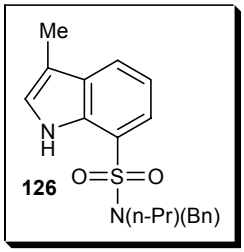
124

Compound 124: To a stirred solution of compound **123-1** (0.290 g, 1.0 mmol) in dry DMF (10 mL), was added K_2CO_3 (0.69 g, 5.0 mmol) and BnBr (0.25 g, 1.5 mmol). The reaction mixture was stirred at 50 ^{o}C for 4.5 h. After cooling to 25 ^{o}C, the reaction mixture was quenched with a saturated solution of aqueous NH_4Cl (10 mL) and was extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine (2 x 15 mL), dried over $MgSO_4$, concentrated

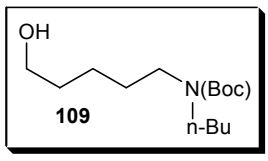
under reduced pressure and purified by flash chromatography (silica, 30:70 Et_2O: hexane) to give the corresponding compound (0.30 g, 0.9 mmol, 90% yield) as a white solid: R_f = 0.3 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 8.0 (d, J = 7.6 Hz, 1H), 7.6 (m, 3H), 7.24 (m, 5H), 4.5 (s, 2H), 3.2 (t, J = 7.6 Hz, 2H), 1.4 (m, 2H), 0.73 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.93, 134.12, 133.53, 131.79, 130.97, 128.80, 128.30, 128.01, 124.35, 51.38, 49.18, 21.23, 11.35; HRMS calcd. for $C_{16}H_{18}N_2O_4Si$ (M+ Na^+) 357.0885, found 357.0884.



Compound 125: Compound **124** (0.05 g, 0.15 mmol) was dissolved in dry THF (3 mL), and was treated with vinyl magnesium bromide (1M, 0.25 mmol) at -78 ^oC. The reaction mixture was stirred at -45 ^oC for 1.5 h, and was quenched with a saturated solution of aqueous NH_4Cl (2 mL) and was extracted with EtOAc (3 x 5 mL). Then, the combined organic extracts were washed with brine (2 x 5 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 20:80 Et_2O: hexane) to give compound **125** (0.046 g, 0.14 mmol, 93% yield) as an orange oil: R_f = 0.4 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.89 (d, J = 7.86 Hz, 1H), 7.62 (d, J = 7.42 Hz, 1H), 7.36-7.25 (m, 7H), 6.67 (tr, J = 2.17 Hz, 1H), 4.39 (s, 2H), 3.15 (tr, J = 6.16 Hz, 2H), 1.37 (dd, J = 7.54, 15.20 Hz, 2H), 0.70 (tr, J = 7.39 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ; 136.57, 130.24, 128.68, 128.28, 127.88, 127.88, 126.12, 125.90, 122.32, 121.68, 119.60, 103.18, 52.08, 50.15, 21.66, 11.51; HRMS calcd. for $C_{18}H_{20}N_2O_2S$ (M+ H^+) 329.1323, found 329.1324.

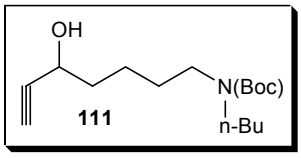


Compound 126: Compound **124** (0.05 g, 0.15 mmol) was dissolved in dry THF (3 mL), and was treated with 1-propenyl magnesium bromide (0.5 M, 0.45 mmol) at -78 ^{o}C. The reaction mixture was stirred at -45 ^{o}C for 1.5 h, and was quenched with a saturated solution of aqueous NH_4Cl (2 mL) and was extracted with EtOAc (3 x 5 mL). Then, the combined organic extracts were washed with brine (2 x 5 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 15:85 Et_2O: hexane) to give compound 126 (0.048 g, 0.14 mmol, 93% yield) as bright yellow oil: R_f = 0.42 (50% Et_2O: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (s, 1H), 7.80 (d, J = 7.60 Hz, 1H), 7.58 (d, J = 7.60 Hz, 1H), 7.40-7.19 (m, 6H), 7.08 (s, 1H), 4.36 (s, 2H), 3.11 (tr, J = 7.60, 15.20 Hz, 2H), 2.36 (s, 3H), 1.32 (dd, J = 7.60, 15.20 Hz, 2H), 0.66 (tr, J = 7.60 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.67, 132.69, 130.67, 128.67, 128.30, 127.84, 123.99, 123.61, 121.99, 121.58, 118.87, 112.18, 52.12, 50.18, 21.68, 11.54, 9.99; HRMS calcd. for $C_{19}H_{22}N_2O_2S$ (M+ H^+) 343.1480, found 343.1481.

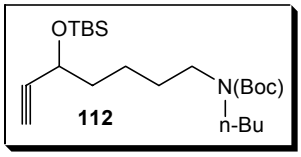


Alcohol 109: Commercial available 5-aminopentan-1-ol was Boc protected according to reference (3a). The mono protected compound (5.0 g, 24.60 mmol) was dissolved in dry EtOH and treated with buteryldehyde (2.31 g, 31.98 mmol) at 0 ^{o}C. The reaction mixture was stirred at 25 ^{o}C for 1 h, then it was cooled to 0 ^{o}C, and $NaBH_4$ (0.47 g, 12.3 mmol) was added. The reaction was allowed to stir at 25 ^{o}C for 10 h. The solvent was removed under reduced pressure and purified by flash chromatography

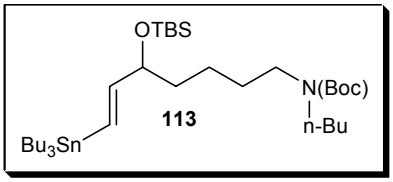
(silica, 10:90 Et_2O: hexane) to afford compound **109** (6.22 g, 24.0 mmol, 98% yield) as a colorless oil: R_f = 0.41 (50% Et_2O:hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 3.61 (m, 2H), 3.30-3.05 (m, 4H), 1.70-1.20 (m, 20H), 1.0-0.80 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.13, 47.15, 32.79, 28.88, 20.46, 14.33; HRMS calcd. for $C_{14}H_{29}NO_3$ (M+ H^+) 260.2226, found 260.2225.



Alcohol 111: To a stirred solution of compound **109** (2.5g, 9.62 mmol) in DCM (45 mL) was added DMP (6.11g, 14.42 mmol) at 0 ^oC. The reaction was allowed to stir for 2.5 h at 0 ^oC and was quenched with a solution of $NaHCO_3$ and $Na_2S_2O_3$ (50 mL)). It was extracted with DCM (3x 50 mL), washed with brine (2 x 50 mL), dried over $MgSO_4$, and concentrated under reduced pressure to afford the aldehyde (2.4 g, 9.3 mmol, 97% yield), which was dissolved in THF (40 mL) and placed in a -78 ^oC bath. Ethynyl magnesium bromide (05 M, 20.5 mL, 10.25 mmol) was added via syringe at -78 ^oC, and then it was allowed to stir at -30 ^oC for 2 h. The reaction mixture was quenched with a saturated solution of NH_4Cl (50 mL). It was extracted with EtOAc (3x 50 mL), washed with brine (2 x 50 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 15:85 Et_2O: hexane) to give the corresponding compound 111 (2.05 g, 7.06 mmol, 76% yield) as a colorless oil: R_f = 0.35 (50% Et_2O:hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 4.37 (tr, J= 6.0 Hz, 1H), 3.30-3.0 (m, 4H), 2.45 (s, 1H), 1.90-1.20 (m, 20H), 0.88 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ; HRMS calcd. for $C_{16}H_{29}NO_3$ (M+ Na^+) 306.2045, found 306.2044.

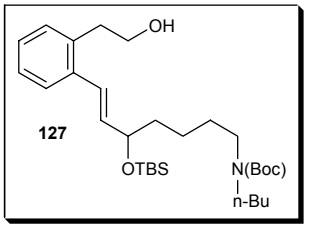


Compound 112: To a stirred solution of compound **111** (4.0 g, 14.10 mmol) in dry DCM (60 mL) at 0 ^{o}C was added imidazole (2.41 g, 35.00 mmol) followed by DMAP (cat). After 10 min, TBSCl (3.18 g, 21.00 mmol) was added and the reaction was allowed to stir at 25 ^{o}C for 16 h. The reaction mixture was quenched with a solution of NH_4Cl (50 mL) and extracted with DCM (3 x 50 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 5:95 Et_2O : hexane) to give the corresponding protected alcohol (5.40 g, 13.60 mmol, 96% yield), as a colorless oil R_f = 0.4 (50% Et_2O: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (m, 1H), 3.25-3.0 (m, 4H), 2.39 (s, 1H), 1.80-1.20 (m, 19H), 1.0-0.80 (m, 12H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -3.78, -4.23; HRMS calcd. for $C_{22}H_{43}NO_3Si$ (M+ H^+) 398.3091, found 398.3090.

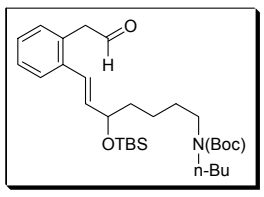


Compound 113: To a stirred solution of compound 112 (5.0 g, 12.5 mmol) was dissolved in dry THF (50 mL) along with Pd $(Pph_3)_2Cl_2$ (0.88 g, 1.25 mmol). The reaction mixture was cooled to -65 ^{o}C, and $SnBu_3H$ (3.70 mL, 13.80 mmol) was added slowly, and the reaction mixture was allowed to stir at that temperature for 30 min. The solvent was removed under reduced pressure and purified by flash chromatography (silica, 25:75 Et_2O: hexane) to give the corresponding compound (0.045 g, 0.082 mmol, 97% yield) as a colorless oil: R_f = 0.39 (50% Et_2O:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 (d, J = 19.50 Hz, 1H),

5.88 (dd, J = 7.0, 19.0 Hz, 1H), 3.30-3.0 (m, 4H), 1.80-0.80 (m, 59H), 0.20-0.0 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -3.78, -4.23; HRMS calcd. for $C_{34}H_{71}NO_3SiSn$ (M+ Na^+) 712.4123, found 712.4122.

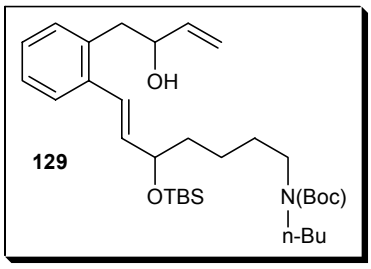


Alcohol 127: Commercial available 2-(2-bromophenylethanol) (0.017 g, 0.085 mmol) was dissolved in dry toluene along with Pd_2dba_3 (0.007 g, 0.0085 mmol), and tri-tert-butyl phosphine (0.02 g, 0.009 mmol). The reaction mixture was degassed and stannane **113** (0.05 g, 0.085 mmol) was added. The reaction mixture was heated at 80 ^oC for 18 h. After cooling to 25 ^oC, the solvent was removed under reduced pressure and purified by flash chromatography (silica, 25:75 Et_2O: hexane) to give the corresponding compound 127 (0.045 g, 0.082 mmol, 97% yield) as a colorless oil: R_f = 0.39 (50% Et_2O:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, 1H, J= 8.0 Hz), 7.44 (m, 1H), 7.35-7.05 (m, 2H), 6.76 (d, 1H, J= 15.6 Hz), 6.02 (m, 1H), 4.30 (m, 1H), 3.89 (m, 1H), 3.85-3.70 (m, 2H), 3.20-2.90 (m, 8H), 1.70-0.80 (m, 29H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.81, 136.56, 133.09, 130.49, 128.36, 127.59, 127.03, 126.49, 79.37, 73.73, 63.38, 62.34, 47.25, 47.09, 39.71, 38.36, 37.20, 31.18, 30.81, 28.87, 28.61, 27.23, 26.30, 22.89, 20.44, 18.68, 14.36, 14.07, -3.78, -4.23; HRMS calcd. for $C_{30}H_{53}NO_4Si$ (M+ Na^+) 542.3642, found 542.3641.



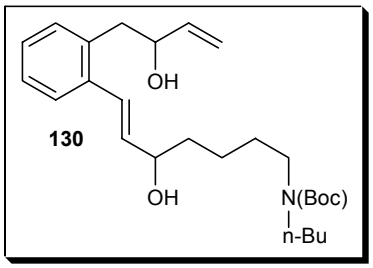
Aldehyde 128: Alcohol **127** (4.0 g, 7.70 mmol) was dissolved in anhydrous DCM (75 mL) and treated with DMP (6.53 g, 15.0 mmol). The reaction was stirred for 2.5 h at 25 ^oC. The

reaction mixture was quenched with a saturated solution of aqueous $NaHCO_3$ (100 mL) and was extracted with DCM (3 x 100 mL), the combined organic extracts were washed with brine (2 x 50 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 20:80 Et_2O: hexane) to give the corresponding aldehyde (3.7 g, 7.15 mmol, 93% yield) as a colorless oil: R_f = 0.43 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 9.68 (m, 1H), 7.48 (d, 1H, J= 6.80 Hz), 7.30-7.20 (m, 2H), 7.15 (d, 1H, J= 6.80 Hz), 6.60 (d, 1H, J= 15.6 Hz), 6.06 (dd, 1H, J= 6.0, 15.6 Hz), 4.25 (m, 1H), 3.74 (m, 2H), 3.20-3.0 (m, 4H), 1.70-1.20 (m, 19H), 0.90 (s, 9H), 0.85 (tr, 3H, J= 7.20 Hz), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.23, 155.69, 137.34, 136.94, 131.04, 129.62, 128.17, 127.98, 126.88, 125.83, 79.19, 79.50, 48.77, 47.18, 38.50, 31.23, 29.22, 28.87,28.89, 28.29, 22.96, 20.43, 18.66, 14.36, -3.81, -4.26; HRMS calcd. for $C_{30}H_{51}NO_4Si$ (M+ Na^+) 540.3485, found 540.3483 .

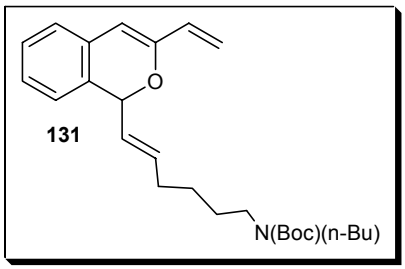


Alcohol 129: Aldehyde **128** (0.03 g, 0.058 mmol) was dissolved in dry THF (3 mL) and cooled to -78 ^oC, and treated with vinyl magnesium bromide (1.0 M, 0.087 mL, 0.087 mmol). The reaction mixture was stirred at that temperature for 1 hr. The reaction mixture was quenched with saturated solution of aqueous NH_4Cl (2 mL) and was extracted with ethyl acetate (3 x 5 mL), the combined organic extracts were washed with brine (2 x 5 mL), dried over $MgSO_4$, concentrated under reduced pressure to give a light yellow oil (0.022 g, 0.04 mmol, 70% yield) as a light yellow oil: R_f = 0.4 (50% Et_2O: hexane); ^1H NMR (400

MHz, $CDCl_3$) δ 7.60-7.40 (m, 1H), 7.40-7.0 (m, 3H), 6.77 (d, J = 15.6 Hz, 1H), 6.05 (m, 1H), 5.92 (m, 1H), 5.23 (d, J = 17.2, 1H), 5.10 (d, J = 9.6 Hz, 1H), 4.29 (m, 2H), 3.20-3.0 (m, 4H), 3.0-2.80 (m, 2H), 1.80-0.8 (m, 31H), 0.08 (s, 3H), 0.06 (s, 3H); HRMS calcd. for $C_{32}H_{55}NO_{24}Si$ (M+ Na^+) 568.3798, found 568.3796.

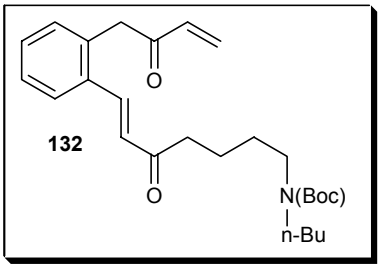


Compound 130: To a stirred solution of compound **129** (0.02 g, 0.038 mmol) was dissolved in dry THF (2 mL), and was treated with HF-Pyridine (1 M, 0.13 mmol) at 0 ^oC. The reaction mixture was stirred at 25 ^oC for 1 h and was quenched with a saturated solution of aqueous $NaHCO_3$ (2 mL) and was extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were washed with brine (2 x 5 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 30:70 Et_2O: hexane) to give the corresponding diol (0.012 g, 0.029 mmol, 76% yield) as a white foam: R_f = 0.3 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (tr, J = 3.60 Hz, 1H), 7.30-7.10 (m, 3H), 6.87 (dd, J = 2.40, 15.20 Hz, 1H), 6.10 (m, 1H), 5.91 (m, 1H), 5.21 (m, 1H), 5.10 (m, 1H), 4.21 (m, 2H), 3.30-3.0 (m, 4H), 2.91 (d, J = 16.40 Hz, 2H), 1.80-0.70 (m, 24H); HRMS calcd. for $C_{26}H_{41}NO_4$ (M+ H^+) 432.3113, found 432.3114.



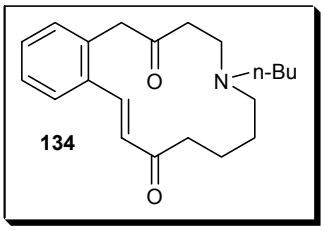
Compound 131: Alcohol **4** (0.071 g, 0.16 mmol) was dissolved in anhydrous DCM (10 mL) and treated with DMP (0.145 g, 0.34 mmol). The reaction was stirred for 2.5 h at 25 ^oC. The reaction mixture was quenched with a saturated solution of aqueous $NaHCO_3$ (5 mL) and a

solution of $Na_2S_2O_3$ (5 mL). The mixture was extracted with DCM (3 x 10 mL), the combined organic extracts were washed with brine (2 x 5 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 20:80 Et_2O: hexane) to give compound (0.061 g, 0.148 mmol, 91% yield) as a light yellow oil: R_f = 0.41 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.10 (m, 2H), 7.07-6.95 (m, 2H), 6.23 (dd, 1H, J= 10.5, 17.0 Hz), 5.81 (s, 1H), 5.80- 5.65 (m, 3H), 5.52 (d, 1H, J= 6.0 Hz), 5.20 (d, 1H, J= 10.5 Hz), 3.25-3.0 (m, 6H), 2.20-2.0 (m, 4H), 1.60-1.20 (m, 10H), 1.0-0.80 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.76, 133.31, 131.62, 131.11, 128.15, 126.81, 124.62, 124.04, 115.35, 105.67, 79.24, 78.74, 49.06, 47.11, 34.14, 32.33, 30.57, 30.11, 29.77, 28.88, 27.09, 26.63, 23.11, 14.59, 11.75, 1.49 ; HRMS calcd. for $C_{26}H_{37}NO_3$ (M+ H^+) 412.2852, found 412.2848.

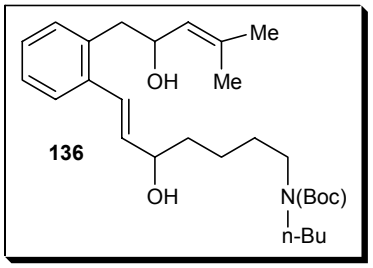


Diketone 132: Compound **130** (0.10 g, 0.23 mmol) was dissolved in anhydrous DCM (75 mL) and was treated with DMP (0.197g, 0.46 mmol) and Pyridine (0.003 g, 0.046 mmol) at 0 ^oC. The reaction mixture was stirred at 0 ^oC for 1 h and was quenched with a saturated solution of solution of aqueous $NaHCO_3$ (5 mL) and a solution of $Na_2S_2O_3$ (5 mL). It was extracted with DCM (3 x 10 mL), and the combined organic extracts were washed with brine (2 x 50 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 EtOAc: hexane) to give the corresponding ketone (0.085 g, 0.2 mmol, 87% yield) as a colorless film: R_f = 0.45 (50% Et_2O: hexane); ^1H

NMR (400 MHz, $CDCl_3$) δ 7.75-7.60 (m, 2H), 7.45-7.25 (m, 2H), 7.20 (d, 1H, J= 7.20 Hz), 6.64 (d, 1H, J= 15.6 Hz), 6.50-6.30 (m, 2H), 5.86 (dd, 1H, J= 1.20, 10.0 Hz), 4.05 (s, 2H), 3.30-3.0 (m, 4H), 2.75-2.60 (tr, 2H, J= 6.40 Hz), 1.70-1.40 (m, 17H), 0.86 (tr, 3H, J= 7.60 Hz); HRMS calcd. for $C_{26}H_{37}NO_4$ (M+ H^+) 428.2800, found 428.2801 .

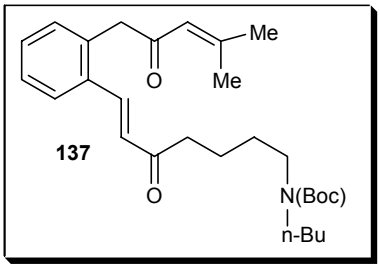


Compound 134: A solution of diketone (0.015g, 0.036 mmol) in DCM (0.5 mL) was placed on an ice bath. Then, DMS (0.025 mL) was added followed by TFA (0.05 mL). The reaction was stirred at 25 ^oC for 6 h. The reaction mixture was quenched with NaOH (1M, 0.05 mL) and extracted with DCM (3 x 5 mL), the combined organic extracts were washed with brine (2 x 5 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 60:40 Et_2O: hexane) to give compound 134 (0.011 g, 0.033 mmol, 93% yield) as a colorless oil: R_f = 0.12 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (m, 1H), 7.56 (d, J = 16.40 Hz, 1H), 7.34 (m, 1H), 7.24 (m, 1H), 7.15 (m, 1H), 7.10 (m, 1H), 6.46 (d, J = 16.40 Hz, 1H), 4.06 (s, 2H), 3.63 (d, J = 9.20 Hz, 2H), 3.20-0.60 (m, 18H); HRMS calcd. for $C_{21}H_{29}NO_2$ (M+ Na^+)350.2096, found 350.2094.



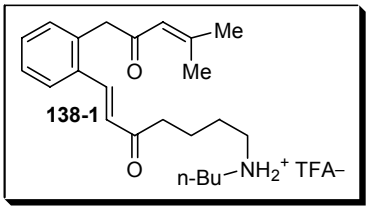
Compound 136: Compound **128** (2.0 g, 3.8 mmol) was dissolved in dry THF (30 mL) and cooled to -78 ^oC. The mixture was treated with 2-methyl-1-propenyl magnesium bromide (0.5 M, 5.79 mmol). The reaction mixture was stirred at -78 ^oC for 1 h. The reaction mixture was quenched with saturated solution of aqueous NH_4Cl (20 mL)

and was extracted with EtOAc (3 x 50 mL), the combined organic extracts were washed with brine (2 x 50 mL), dried over $MgSO_4$, concentrated under reduced pressure to give a light yellow oil (1.63 g, 2.85 mmol, 75%). The crude compound (0.1 g, 0.174 mmol) was dissolved in dry THF (5 mL) and cooled to 0 ^oC. It was treated with HF-Pyridine (1 M, 0.20 mmol), and allowed to stir for 6 h. The reaction mixture was quenched with a solution of aqueous $NaHCO_3$ (5 mL) and was extracted with EtOAc (3 x 10 mL). The colorless residue was purified by flash chromatography (silica, 30:70 Et_2O: hexane) to give the corresponding compound 136 (0.065 g, 0.142 mmol, 81% yield) as a colorless oil: R_f = 0.32 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (m, 1H), 7.35-7.05 (m, 3H), 6.90 (d, 1H, J= 15.2 Hz), 6.07 (m, 1H), 5.20 (d, 1H, J= 7.20 Hz), 4.50 (m, 1H), 4.27 (br s, 1H), 3.25-3.05 (m, 4H), 2.93 (m, 1H), 2.77 (m, 1H), 1.80-1.20 (m, 25H), 0.90 (tr, 3H, J= 7.20 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.78, 135.47, 134.24, 130.79, 127.54, 127.16, 126.76, 126.70, 126.55, 125.97, 79.08, 72.58, 69.22, 46.79, 46.53, 41.60, 36.93, 30.84, 30.45, 28.55, 28.03, 25.80, 22.96, 22.53, 20.09, 18.17, 14.03; HRMS calcd. for $C_{28}H_{44}NO_4$ (M+ H^+) 459.3348, found 459.3349.

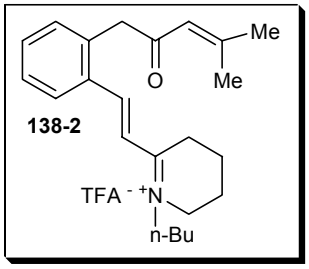


Diketone 137: A solution of Diol **136** (0.80 g, 1.74 mmol) in anhydrous DCM: DMSO (3:1, 30 mL) was treated with IBX (1.22 g, 4.35 mmol) at 0 ^oC. The reaction was allowed to stir for 1.5 hr at 0 ^oC and was quenched with a saturated solution of aqueous $NaHCO_3$ (20 mL) and a solution of $Na_2S_2O_3$ (10 mL) and was extracted with EtOAc

(3 x 25 mL), the combined organic extracts were washed with brine (2 x 15 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 15:85 Et_2O: hexane) to give the corresponding diketone (0.70 g, 1.5 mmol, 88% yield) as a colorless oil: R_f = 0.38 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, 1H, J= 16.0 Hz), 7.62 (dd, 1H, J= 1.20, 7.60 Hz), 7.40-7.25 (m, 2H), 7.21 (d, 1H, J= 7.60 Hz), 6.64 (d, 1H, J= 15.6 Hz), 6.11 (m, 1H), 3.86 (s, 2H), 3.30-3.10 (m, 4H), 2.67 (tr, 2H, J= 6.80 Hz), 2.12 (s, 3H), 1.87 (s, 3H), 1.70-1.40 (m, 13H), 1.40-1.20 (m, 4H), 0.92 (tr, 3H, J= 7.20 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.30, 196.81, 157.75, 155.70, 139.92, 135.26, 134.27, 131.64, 130.50, 128.04, 127.75, 126.88, 122.97, 122.86, 79.30, 49.22, 47.16, 46.84, 40.77, 31.17, 30.80, 28.90, 28.87, 28.26, 21.89, 21.38, 20.43, 14.35; HRMS calcd. for $C_{28}H_{41}NO_4$ (M+ Na^+) 478.2933, found 478.2930.



Compound 138-1: To a stirred solution of **137** (0.05g, 0.109mmol) was added DMS (0.012 mL) and TFA (0.25 mL) at 0 ^oC. The reaction mixture was stirred for 2 h, and TLC showed no more starting material. The solvent was concentrated under reduced pressure to give the pure TFA salt (0.046 g, 0.100 mmol, 92% yield) as a light yellow salt: R_f = 0.1 (90% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 15.80, 1H), 7.64 (m, 1H), 7.50-7.10 (m, 3H), 6.64 (d, J = 16.0 Hz, 1H), 6.12 (s, 1H), 3.89 (s, 2H), 3.15-2.90 (m, 4H), 2.90-2.70 (m, 4H), 2.11 (s, 3H), 1.89 (s, 3H), 1.82-1.2 (m, 11H), 0.94 (m, 3H); HRMS calcd. for $C_{25}H_{34}F_3NO_4$ (M+) 469.2439, found 469.2440 .



Compound 138-2: To a stirred solution of 137 (0.05g, 0.109mmol) was added DMS (0.012 mL) and TFA (0.25 mL) at 0 ^{o}C. The reaction mixture was stirred for 18 h at 25 ^{o}C and TLC showed no more starting material. The solvent was concentrated under reduced pressure to give the pure TFA salt (0.046 g, 0.100 mmol, 91.7% yield) as an off-white film: R_f = 0.15 (90% EtOAc: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 16.0 Hz, 1H), 7.35 (m, 1H), 7.05-6.90 (m, 2H), 6.84 (d, J = 7.20 Hz, 1H), 6.45 (d, J = 15.60 Hz, 1H), 5.77 (s, 1H), 3.49 (s, 2H), 2.40-2.20 (m, 2H), 1.94 (s, 6H), 1.60-0.90 (m, 12H), 0.70 (tr, J = 7.20 Hz, 3H) ; HRMS calcd. for $C_{25}H_{32}F_3NO_3$ (M+) 451.2334, found 451.2332.

Section 3.5.3 Experimental Procedures and Kinetic Studies

Kinetic Studies [iii]

A representative procedure for kinetics studies is as follows: 1**41 dieneamide** (10 mg, 0.0351 mmol) was added to a calibrated double precision NMR tube containing N-Benzyl maleimide (NBMI) (6.6 mg, 0.0352mmol). Then, 0.4 mL of deuterated chloroform (degassed and dried over 4 Å molecular sieves) was added under argon and CH_2Cl_2 (as an internal standard for 1H NMR measurements, 0.3 mg, 0.0035mmol). The NMR tube was sealed and its contents vortex for at least two minutes. We noticed that when the DA reactions were conducted entirely in the NMR tube without thoroughly stirring with a vortex apparatus, the reactions became partially diffusion-controlled and the orders of the reaction could not be unambiguously determined. ^{1}H NMR spectra was recorded every 20 or 30 minutes. The experiments were carried out at room temperature or heat was applied 90 ^{o}C inside the NMR instrument. The bimolecular rate constants were obtained from the plots $1/(B_0-A_0)\ln[(A_0B) / (B_0A)]$ against the elapsed time, where A_0 and B_0 are the initial concentrations of the reactants, and x is the reactant concentration that is consumed at any given time, and by the very similar slope values of the plots at different initial reactant concentrations.

When the initial concentrations of the two reactants are equal, x / A (A- x) is plotted against time instead. Two such plots are shown in Figures S1 and S2. The bimolecular

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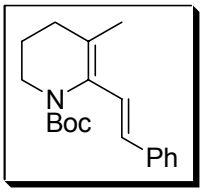
[iii] Fu, Y.S.;Tsai, S.C.;Huang, C.H.;Yen, S.Y.;Hu, W.P.;Yu, S.J. *J.Org. Chem*. **2003**, 68, 3068-3072

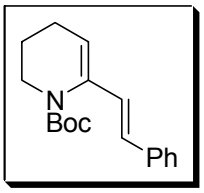
initial rate constants are equal to the slopes of these plots. The slopes were obtained using a linear least square fit to the first six or eight data points.

Data: x/a(a-x) vs time

Time (min)	TFE (25C)	MeOH (25C)	CH_3CN (25C)	$CDCl_3$ (90C)	C_6H_6 (90C)	MeOH (90C)	C_6H_6 (25C)
0	0	0	0	0	0	0	0
1						0.17384	
2.5						0.447948	
4						0.992654	
5				0.584955	0.705687		
6						1.4109	
7.5						2.0145	
9						2.42148	
10				1.41091	1.0767		
10.5						2.85388	
12						3.6049	
15						4.89237	0.1153
17							
20	0.209	0.352504		2.4889	2.236		
30			0.05736	3.58665			0.18
40	0.666953	0.761035		4.36637	5.594		
60	1.8646	1.15803	0.1738	5.37201	7.776		0.215
80		1.61584		6.65757	10.9558		
90	3.64633		0.3769				
100		2.37765			13.73		
110		2.69084					
120	4.32786	3.05436	0.728069		17.278		0.414
130							
140					18.625		
150	5.21791		0.925613				
160		5.11887			19.8589		
180	7.02636		1.1174				0.729
200		6.3565					
210	8.96934		1.198				
220							
240	10.5827						
260							
280							
300							
330							
360							1.41
390							
420							
450							
690							
720							2.17

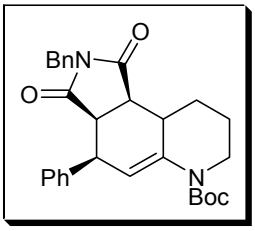


Compound 142-1: (0.053g, 0.17 mmol) was dissolved in dry THF (2 mL), and (*E*)-tributyl(styryl)stannane (0.202g, 0.514 mmol) was added along with $Pd(PPh_3)_4$ (0.010g, 0.0085 mmol). Finally, LiCl (0.1799 g, 4.28 mmol) was added and the reaction mixture was refluxed for 18 h. After cooling to room temperature, the reaction mixture was quenched with saturated solution of aqueous $NaHCO_3$ (2 mL) and was extracted with EtOAc (3 x 5 mL), the combined organic extracts were washed with brine (2 x 5 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica, 10:90 Et_2O: hexane) to give the corresponding dieneamine (0.045 g, 0.15 mmol, 89% yield) as a white solid: R_f = 0.5 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.25 (m, 4H), 7.21 (m, 1H), 6.9 (d, J = 15.6 Hz, 1H), 6.48 (d, J = 16.0 Hz, 1H), 3.56 (m, 2H), 2.20 (m, 2H), 1.80 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 138.0, 133.3, 131.7, 131.3, 128.8, 128.1, 127.6, 126.4, 123.6, 81.03, 44.8, 30.6, 28.6, 28.5, 28.2, 24.1, 19.1; HRMS calcd. for $C_{19}H_{25}NO_2$ (M+ Na^+) 299.1883, found 299.1885.

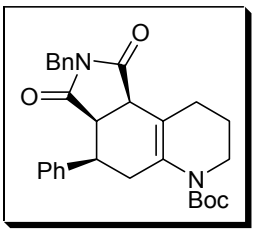


Compound 141: (0.100 g, 0.3 mmol) was dissolved in dry THF (4 mL), and (*E*)-tributyl(styryl)stannane (0.29 g, 0.75 mmol) was added along with $Pd(PPh_3)_4$ (0.017 g, 0.015 mmol). Finally, lithium chloride (0.319 g, 7.5 mmol) was added and the reaction mixture was refluxed for 15 h. After cooling to 25 ^oC , the reaction mixture was quenched with saturated solution of aqueous $NaHCO_3$ (4 mL) and was extracted with EtOAc (3 x 15 mL), the combined organic extracts were washed with brine (2 x 10 mL), dried over $MgSO_4$,

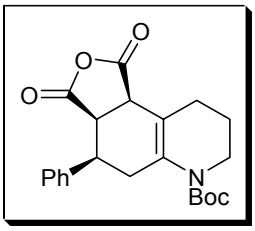
concentrated under reduced pressure and purified by flash chromatography (silica, 8:90:2 Et_2O: hexane :TEA) to give the corresponding dieneamine (0.075 g, 0.26 mmol, 88% yield) as a white solid: R_f = 0.39 (50% Et_2O : hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 2H), 7.30 (m, 2H), 7.20 (t, J = 6.8 Hz, 1H), 6.62-6.53 (m, 2H), 5.46 (t, J = 4.0 Hz, 1H), 3.59 (m, 2H), 2.25 (m, 2H), 1.82 (m, 2H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 138.8, 137.5, 128.7, 127.8, 127.3, 126.4, 116.0, 80.8, 44.7, 28.7, 24.1, 23.8; HRMS calcd. for $C_{18}H_{23}O_2N$ (M+ H^+) 285.1728, found 285.1731.



Compound 143: To a solution of 2-(N-acylamino) 1, 3-diene **141** (10.00 mg, 0.035 mmol) in dry CD_3CN (0.4 mL) was added N-benzylmaleimide (7.0 mg, 0.037 mmol) at 25 ^oC. The reaction mixture was allowed to stand for 18 h and the solvent removed. The white precipitate was collected to afford the corresponding compound **143** (14.5 mg, 0.0307 mmol, 88% yield), as a white solid R_f = 0.25 (50% Et_2O:hexane); ^1H NMR (400 MHz, CD_3CN) δ 7.50-7.10 (m, 10H), 6.39 (m, 1H), 4.53 (d, J = 14.40 Hz, 1H), 4.42 (d, J = 16.80 Hz, 1H), 3.72 (m, 1H), 3.59 (m, 1H), 3.44 (m, 1H), 3.36 (m, 1H), 3.25 (dd, J = 5.20, 8.0 Hz, 1H), 2.75 (m, 1H), 2.29 (m, 1H), 1.95 (m, 1H), 1.69 (m, 1H), 1.60-1.20 (m, 10H); ^{13}C NMR (100 MHz, CD_3CN) δ 176.0, 175.9, 153.6, 140.8, 136.0, 135.9, 129.0, 128.7, 128.6, 128.4, 128.0, 127.9, 127.0, 114.4, 81.2, 46.6, 45.6, 44.6, 42.4, 41.0, 32.3, 30.1, 28.8, 26.9, 23.8; HRMS calcd. for $C_{29}H_{32}O_4N_2$ (M+ H^+) 473.2440, found 473.2441.

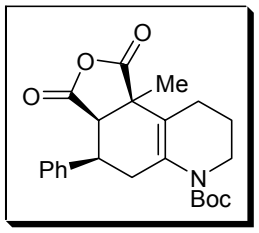


Compound 143-1: To a solution of 2-(N-acylamino) 1, 3-diene **141** (10.00 mg, 0.035 mmol) in dry MeOH (0.4 mL) was added N-benzylmaleimide (7.0 mg, 0.037 mmol) at 25 ^{o}C. The reaction mixture was allowed to stand for 9 h and the solvent was decanted. The white precipitate was collected to afford the corresponding compound 143-1 (16.5 mg, 0.0349 mmol, 99% yield), as a white solid R_f = 0.25 (50% Et_2O:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.40 (m, 10H), 4.50 (s, 2H), 3.93 (m, 1H), 3.45 (m, 2H), 3.25 (m, 2H), 2.85 (dd, J = 10.4, 15.2 Hz, 2H), 2.70 (d, J =15.6 Hz, 1H), 2.10 (m, 1H), 1.80-1.95 (m, 2H), 1.45 (s, 9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 175.9, 153.6, 140.8, 136.0, 135.9, 129.0, 128.7, 128.6, 128.4, 128.0, 127.9, 127.0, 114.4, 81.2, 46.6, 45.6, 44.6, 42.4, 41.0, 32.3, 30.1, 28.8, 26.9, 23.8; HRMS calcd. for $C_{29}H_{32}O_4N_2$ (M+) 472.2357, found 472.2363.

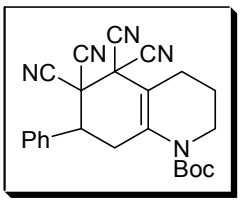


Compound 144: To a solution of 2-(N-acylamino) 1, 3-diene **141** (10.00 mg, 0.035 mmol) in dry benzene (0.4 mL) at rt was added maleic anhydride (4.0 mg, 0.037 mmol). The reaction mixture was heated at 90 ^{o}C for 7 h and the solvent was evaporated. The white precipitate was collected to afford the corresponding compound **144** (11.75 mg, 0.030 mmol, 88% yield), as a white solid R_f = 0.32 (50% Et_2O: hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10-7.40 (m, 5H), 3.80 (m, 1H), 3.25 (m, 2H), 2.70-2.90 (m, 4H), 2.60 (d, J = 17.6 Hz, 1H), 1.50- 1.80 (m, 3H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6) δ 170.0, 169.51, 163.95, 152.96, 139.7, 136.73, 134.2, 128.82, 128.6, 128.45, 128.08, 128.0, 127.83, 127.59, 127.25, 111.5, 80.7,

46.95, 45.69, 44.45, 38.76, 31.66, 28.26, 28.17, 27.52, 26.42, 25.93, 23.28; HRMS calcd. for $C_{22}H_{25}O_5$ (M+ Na^+) 383. 1727, found 383.1724.

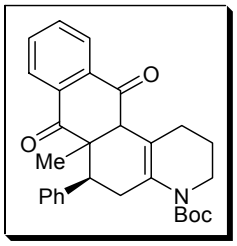


Compound 145: To a solution of 2-(N-acylamino) 1, 3-diene **141** (10.00 mg, 0.035 mmol) in dry benzene (0.4 mL) was added citraconic anhydride (4.0 mg, 0.0356 mmol). The reaction mixture was heated at 90 ^oC for 48 h and the solvent was evaporated. The compound was purified by flash chromatography (silica, 35:65 Et_2O: hexanes) to give the corresponding compound 145 (7.1 mg, 0.0179 mmol, 51% yield) as a white solid: R_f = 0.45 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.20-7.40 (m, 5H), 3.73 (m, 1H), 3.54 (m, 1H), 3.24 (s, 1H), 2.96 (t, J = 4.40 Hz, 1H), 2.91 (s, 2H), 2.75 (m, 1H), 2.01 (m, 1H), 1.90 (m, 2H), 1.52 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 169.50, 153.60, 138.87, 136.5, 129.80, 129.16, 128.82, 128.72, 128.65, 128.35, 128.21, 111.80, 81.54, 53.58, 49.56, 45.03, 32.24, 28.55, 28.51, 28.34, 26.72, 24.11, 23.38, 23.31, 11.69; HRMS calcd. for $C_{23}H_{27}O_5N$ (M+ H^+) 397.1884, found 397.1885.

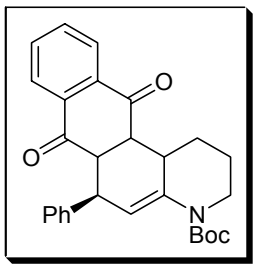


Compound 146: To a stirred solution of 2-(N-acylamino) 1,3-diene **141** (10.00 mg, 0.035 mmol) in benzene at 25 ^oC was added tetracyanoethylene (3.30 mg, 0.038 mmol). The resulting mixture was stirred for 2 min at 25 ^oC. The solvent was evaporated and purified by column chromatography (12:88 Et_2O: hexane), to give **146** (14.3 mg, 0.034 mmol, 99% yield). Yellow solid; R_f = 0.5 (30% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.60 (m, 5H), 5.95 (s, 1H) 4.43 (t, J = 2.0 Hz, 1H), 4.31 (d, J = 12.8 Hz, 1H),

2.95-3.15 (m, 2H), 2.45 (m, 1H) 2.36 (dd, J=3.60, 17.2 1H), 2.0 (m, 1H), 1.83 (m, 1H), 1.47 (s, 9H); ^{13}C NMR (100 M Hz, CDC l_3) δ 153.05, 136.34, 133.11, 130.62, 129.99, 129.55, 119.53, 111.44, 111.11, 110.06, 109.39, 81.99, 46.58, 46.18, 43.85, 43.35, 42.16, 29.92, 29.61, 28.41, 25.14, 17.75; HRMS calcd. for $C_{24}H_{23}N_5O_2$ (M+ Na^+) 413.1849, found 413.1851.

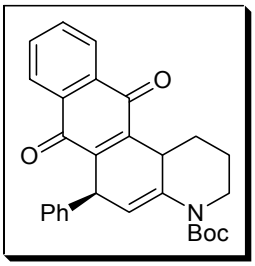


Compound 149: To a solution of 2-(N-acylamino) 1,3-diene **141** (10.00 mg, 0.035 mmol) in dry benzene (0.4 mL) was added 2-methyl-1, 4-naphthoquinone (4.0 mg, 0.037 mmol). The reaction mixture was heated at 90 ^{o}C for 52 h and the solvent was evaporated. The brown residue was purified by flash chromatography (silica, 30:70 Et_2O: hexane) to give the corresponding compound **149** (4.5 mg, 0.0098 mmol, 28% yield) as a dark yellow oil: R_f = 0.5 (50% Et_2O: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.0 (m, 1H), 7.90 (m, 1H), 7.62-7.75 (m, 1H), 7.2-7.4 (m, 5H), 5.73 (bs, 1H), 4.95 (m, 1H), 4.21 (m, 1H), 3.50 (m, 1H), 2.94 (m, 5H), 2.67 (m, 1H), 1.93 (m, 1H), 1.82 (m, 1H), 1.52-1.70 (m, 2H), 1.45 (s, 9H);). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0, 197.3, 153.90, 140.2, 135.13, 134.34, 134.18, 133.90, 133.74, 130.40, 130.2, 129.0, 128.7, 128.3, 128.11, 128.0, 127.8, 127.6, 127.3, 126.9, 126.8, 125.9, 121.7, 117.8, 80.8, 61.1, 51.50, 49.3, 44.6, 32.4, 31.9, 29.70, 29.40, 29.35, 28.44, 28.3, 28.1, 27.9, 24.2, 23.7, 23.2, 22.7, 14.1, 1.02; HRMS calcd. for $C_{29}H_{31}NO_4$ (M+H^+) 457.2248, found 457.2252.

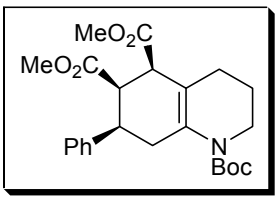


Compound 150: To a solution of 2-(N-acylamino) 1, 3-diene **141** (10.00 mg, 0.035 mmol) in dry benzene (0.4 mL) at rt was

added 1,4-napthtoquinone (4.0 mg, 0.037 mmol). The reaction mixture was heated at 90 ^{o}C for 48 h and the solvent was evaporated. The bright orange residue was purified by flash chromatography (silica, 30:70 Et_2O:hexanes) to give the corresponding compound **150** (7.5 mg, 0.0169 mmol, 48% yield) as a red-orange oil; R_f = 0.45 (30% Et_2O: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.0 (m, 1H), 7.90 (m, 1H), 7.62-7.75 (m, 1H), 7.2-7.4 (m, 5H), 5.73 (bs, 1H), 4.95 (m, 1H), 4.21 (m, 1H), 3.50 (m, 1H), 2.94 (m, 5H), 2.67 (m, 1H), 1.93 (m, 1H), 1.82 (m, 1H), 1.52-1.70 (m, 2H), 1.45 (s, 9H); HRMS calcd. for $C_{28}H_{29}NO_4$ (M+ Na^+) 443.1997, found 443.1995.

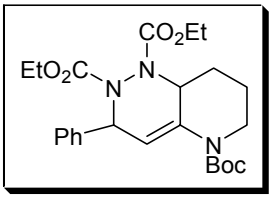


Compound 150-1: Compound **150** on standing at room temperature became compound **150-1** (7.4 mg, 0. 0167 mmol, 99%). **150-1:** Red oil; R_f = 0.5 (30% Et_2O:hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.0-8.20 (m, 2H), 7.60-7.80 (m, 2H), 7.15- 7.40 (m, 5H), 4.48 (d, J = 8.0 Hz, 1H), 3.67 (m, 1H), 3.18-3.40 (m, 2H), 3.05 (m, 1H), 2.82 (d, J = 16.8 Hz, 1H), 2.40 (m, 1H), 1.96 (m, 1H), 1.65 (m, 2H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.5, 183.6, 153.11, 142.4, 141.37, 140.4, 138.27, 133.61, 133.36, 133.12, 132.38, 128.74, 127.62, 127.16, 126.50, 126.11, 117.31, 82.03, 45.6, 35.23, 34.74, 29.92, 28.53, 25.08, 23.21; HRMS calcd. for $C_{28}H_{27}NO_4$ (M+ Na^+) 441.1935, found 421.1929.

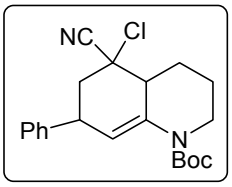


Compound 151: To a solution of 2-(N-acylamino) 1, 3-diene **141** (10.00 mg, 0.035 mmol) in dry benzene (0.4 mL) at rt was added dimethyl maleic ester (4.0 mg, 0.037 mmol). The reaction mixture was heated at 90 ^{o}C for h and the solvent was

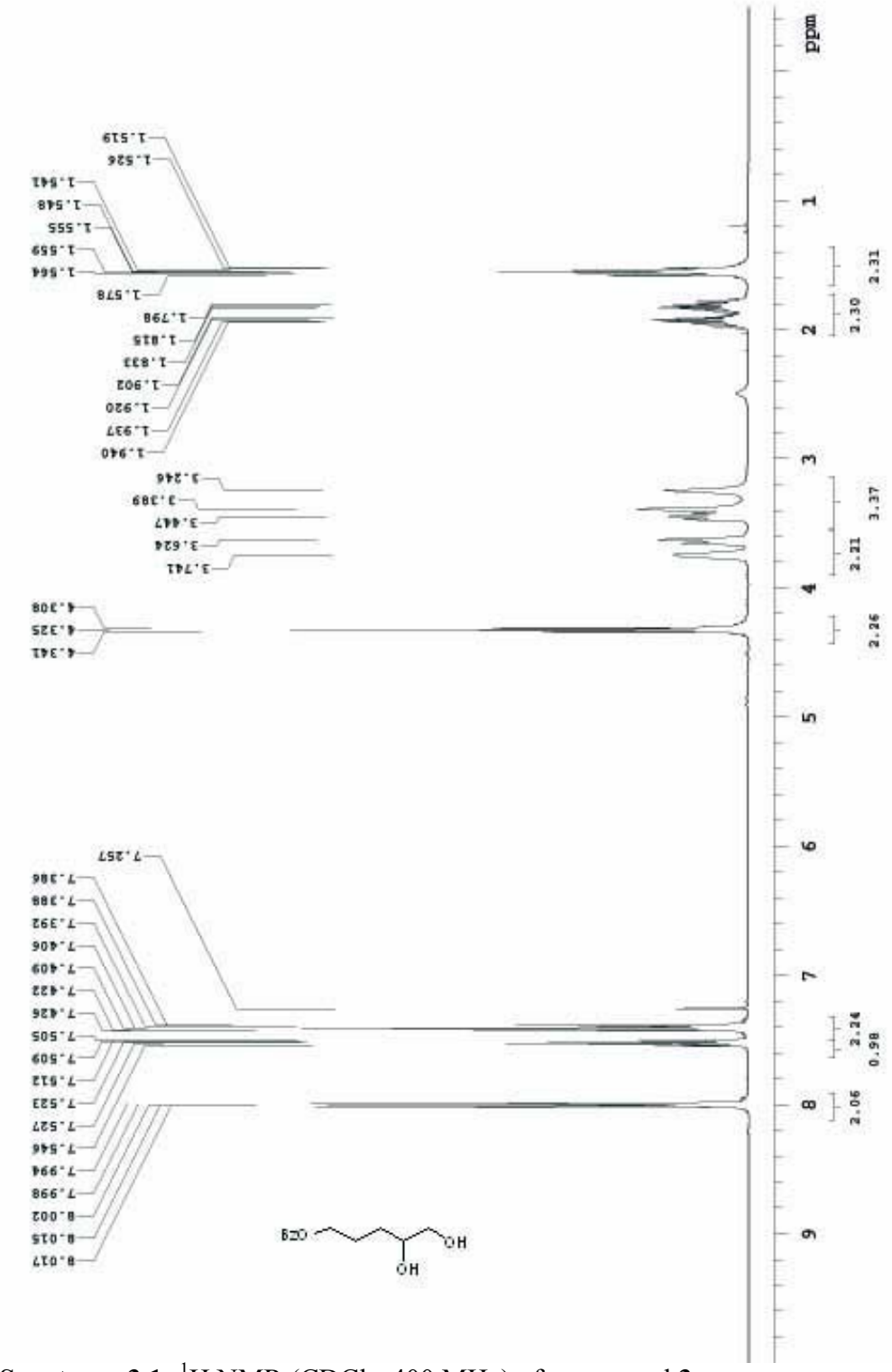
evaporated. The light yellow precipitate was collected to afford the corresponding compound 151 (12 mg, 0.030 mmol, 82% yield), as a white solid R_f = 0.29 (50% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.20-7.40 (m, 5H), 5.56 (d, J = 5.6 Hz, 1H), 4.36 (d, J = 12 Hz, 1H), 4.27 (bs, 1H), 3.70 (s, 3H), 3.60 (s, 3H), 3.28 (d, J = 1.6 Hz, 1H), 2.90-2.80 (d, J = 2.85 Hz, 1H), 2.71 (m, 1H), 2.51 (m, 1H), 2.37 (dd, J = 3.6, 9.2 Hz, 1H) 1.75 (m, 1H), 1.41 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.50, 172.37, 142.50, 140.55, 128.87, 128.51, 127.25, 126.77, 119.96, 79.8, 52.25, 52.06, 48.80, 46.70, 43.01, 42.0, ,35.77, 33.60, 29.92, 28.56, 25.74; HRMS calcd. for $C_{24}H_{31}O_6N$ (M+) 429.2146, found 429.2141.



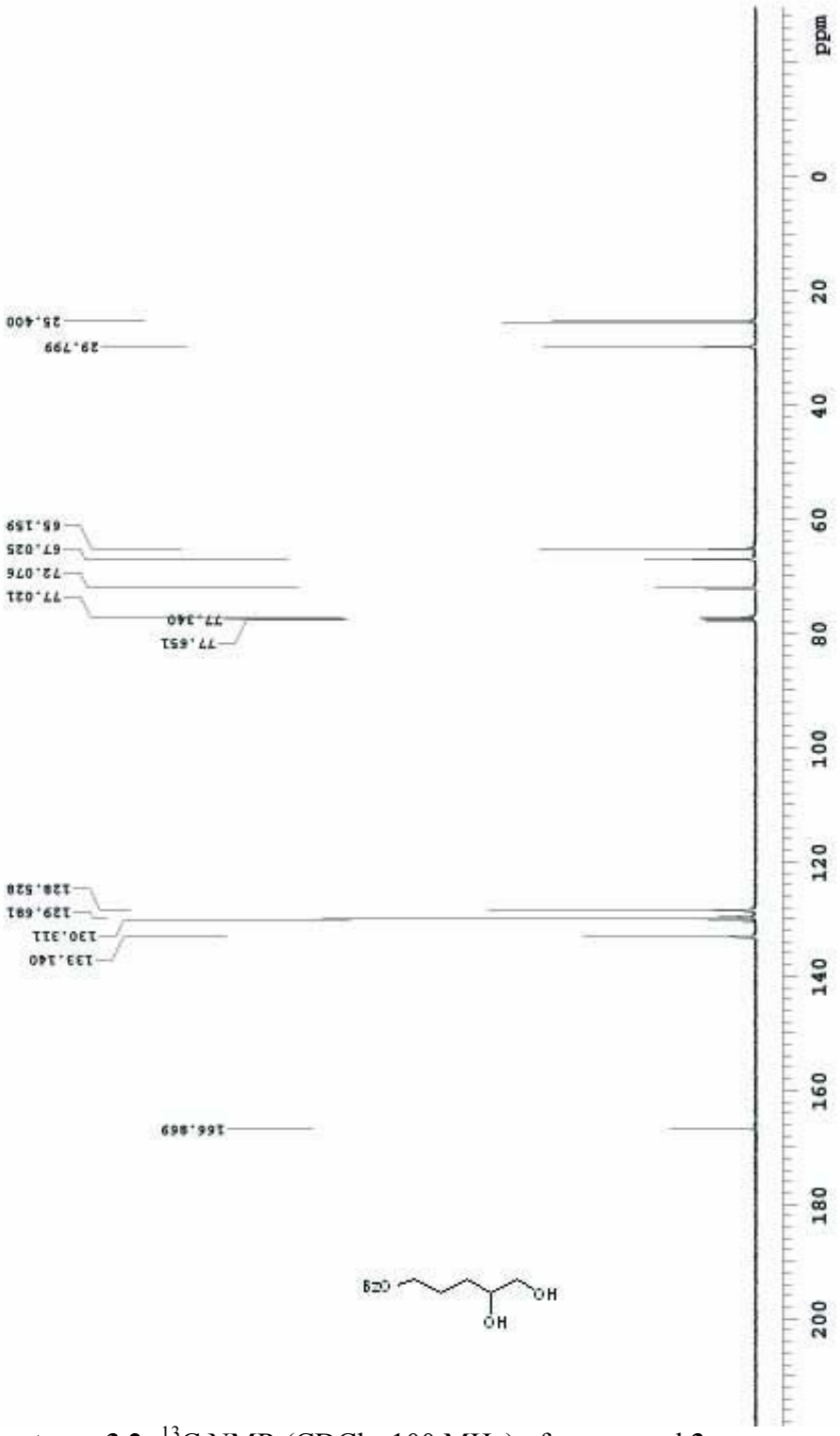
Compound 152: To a stirred solution of 2-(N-acylamino) 1,3-diene **141**(10.00 mg, 0.035 mmol) in DCM at 25 ^oC was added DEAD (3.30 mg, 0.038 mmol). The resulting mixture was stirred for 5 min at 25 ^oC. The solvent was evaporated and purified by column chromatography (12:88 Et_2O: hexane), to give **152** (14.3 mg, 0.034 mmol, 99% yield). Yellow oil; R_f = 0.5 (30% Et_2O: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 7.20 Hz, 2H), 7.38-7.20 (m, 3H), 6.10-5.70 (m, 2H), 4.40-3.80 (m, 5H), 3.21 (br s, 1H), 2.85 (trd, J = 3.60, 12.80 Hz, 1H), 1.90-0.80 (m, 19H); ^{13}C NMR (100 M Hz, CDC l_3) δ 206.92, 155.92, 153.97, 138.02, 128.60, 128.52, 128.52, 128.27, 128.20, 127.86, 121.31, 80.59, 63.24, 62.91, 61.67, 57.20, 56.47, 46.66, 31.31, 29.64, 28.66, 28.58, 24.34, 15.00, 14.92; HRMS calcd. for $C_{24}H_{33}N_3O_6$ (M+ H^+) 460.2447, found 460.2448.



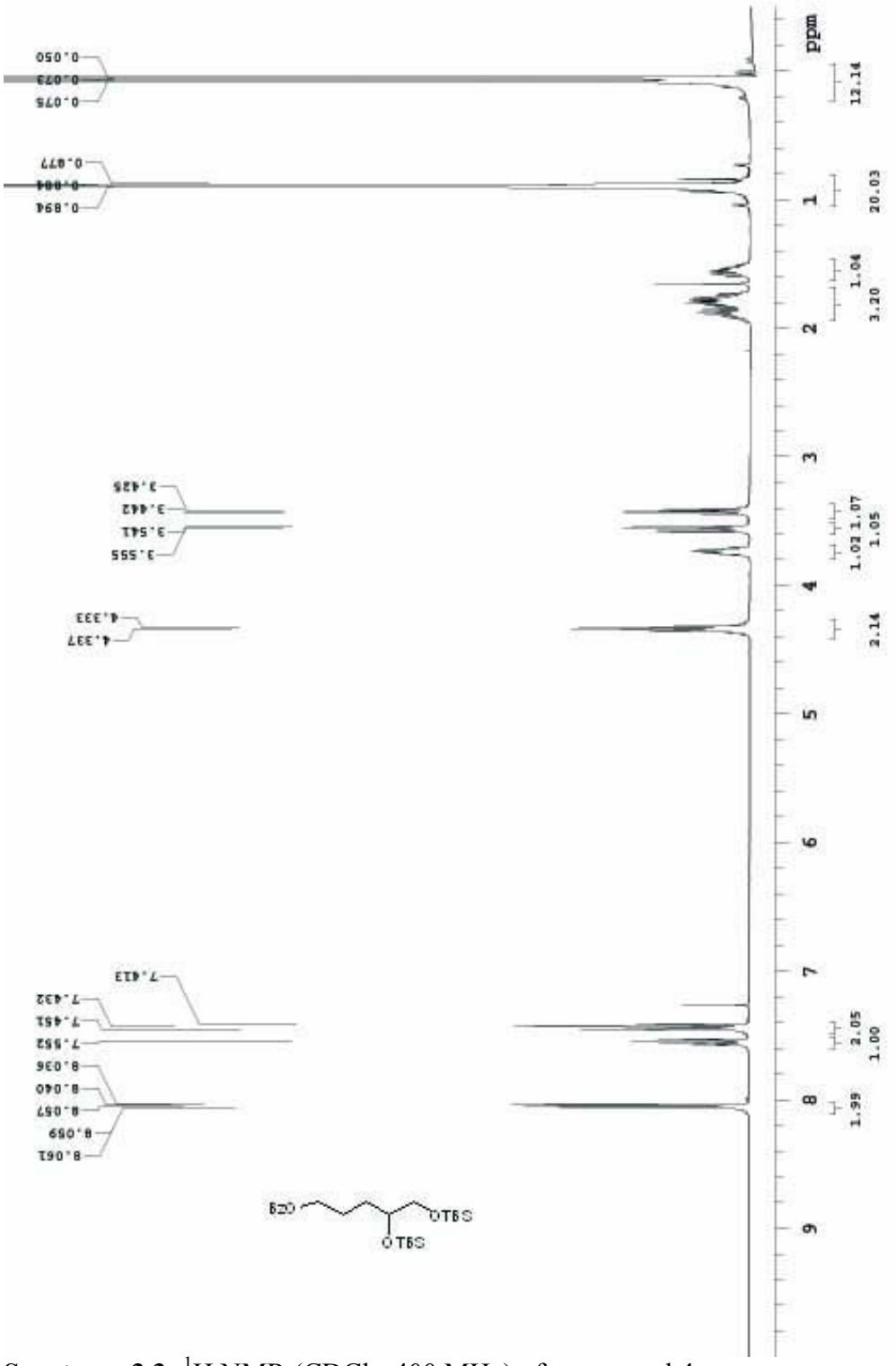
Compound 153: A stirred solution of 2-(N-acylamino) 1,3-diene **141** (10.0 mg, 0.035 mmol) in anhydrous benzene (5 mL) was treated with 1-cyano-chloroethylene (4.90 mg, 0.035 mmol) and heated at 90 ^{o}C for 18 h. The solvent was removed and the residue purified by column chromatography (silica, 10:90 Et_2O: hexane) to give compound **153** (9.0 mg, 0.029 mmol, 69% yield): light yellow solid; R_f = 0.25 (30% Et_2O: hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20-7.60 (m, 5H), 3.80 (m,1H), 3.25-3.50 (m, 4H), 2.95 (s, 2H), 2.0-2.20 (m, 2H), 1.80-2.0 (m, 2H), 3.36 (3H, s), 3.18 (1H, dd, J = 10.8, 4.4 Hz), 2.17 (1H, m), 1.78 (1H, m), 1.71-1.46 (4H, m), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.85, 138.50, 132.5, 129.32, 128.83, 128.72, 128.6, 128.5, 118.4, 115.8, 81.22, 76.66, 59.0, 51.25, 48.84, 46.17, 44.94, 34.97, 29.92, 28.56, 27.93, 27.88, 23.5, 23.33; HRMS calcd. for $C_{21}H_{26}N_2O_5$ (M+) 372.1601, found 372.1603.



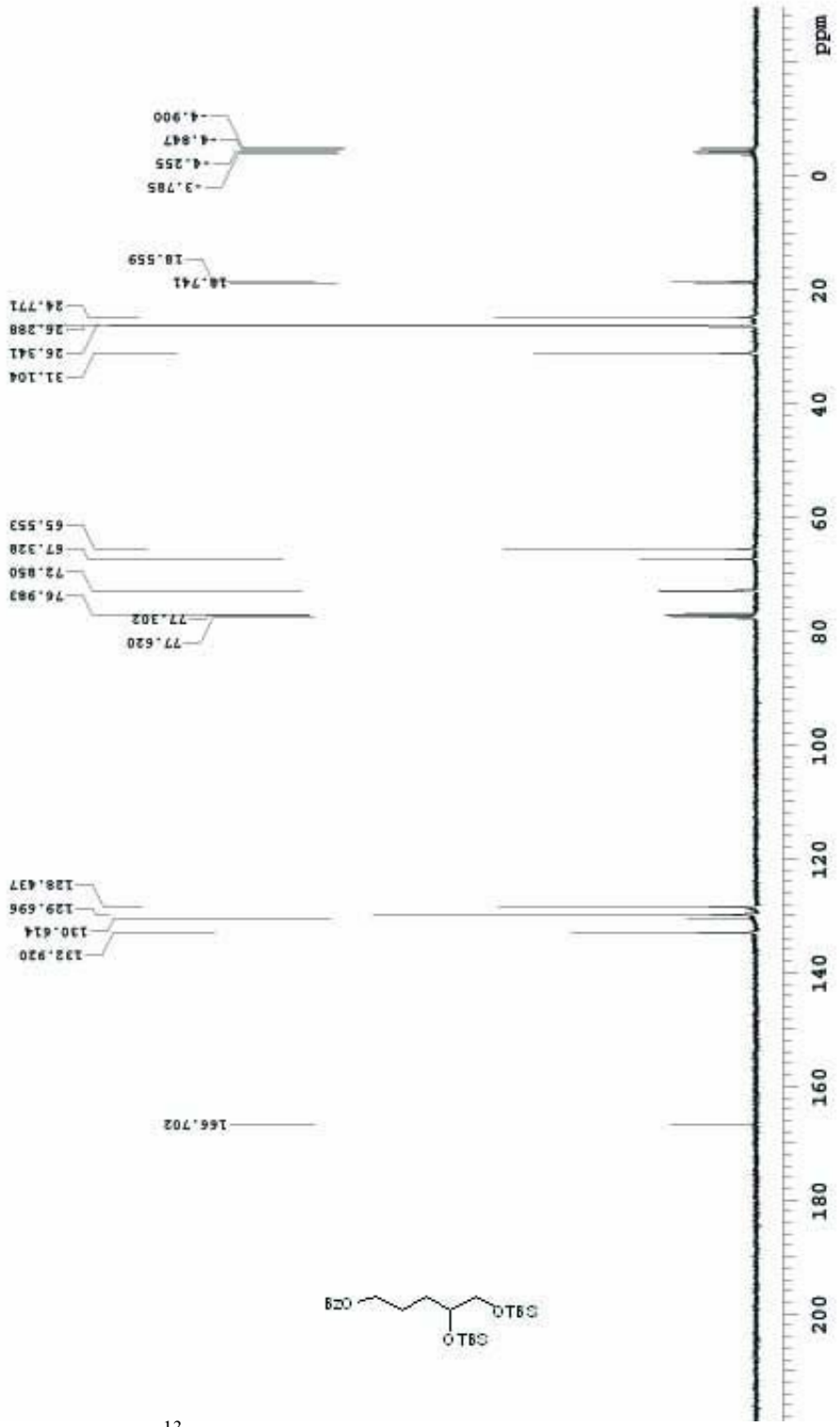
Spectrum 3.1: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **3**



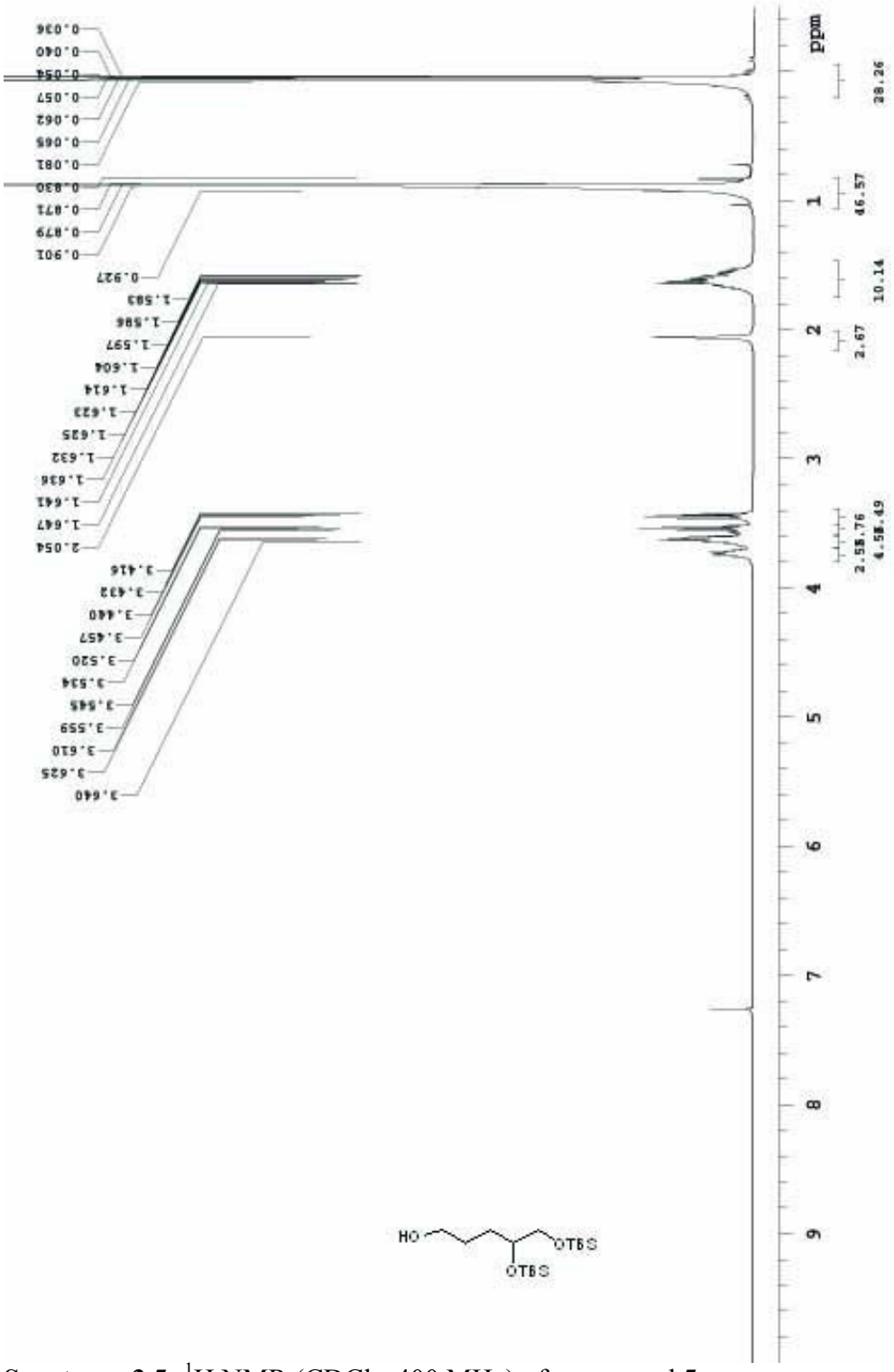
Spectrum 3.2: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **3**



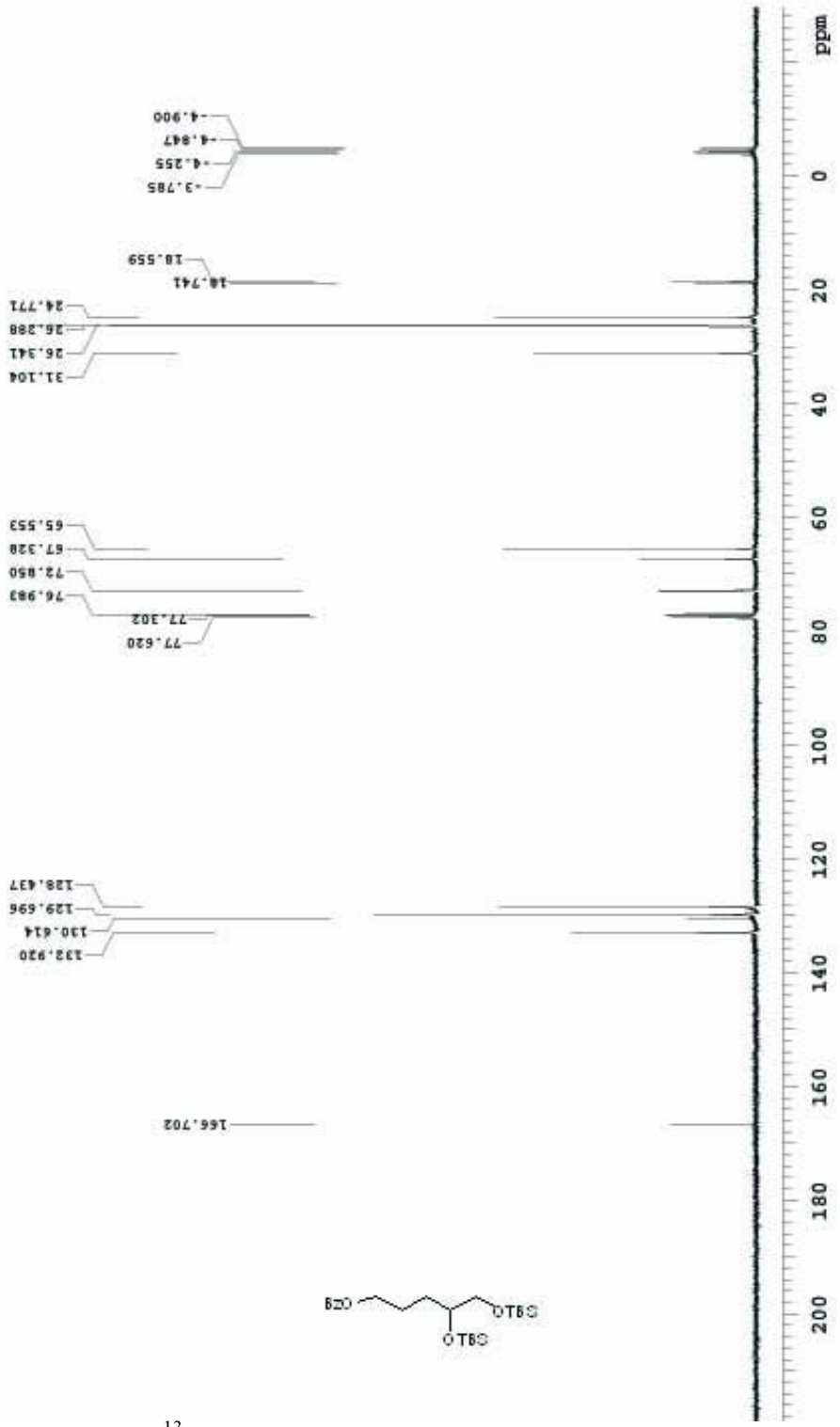
Spectrum 3.3: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **4**



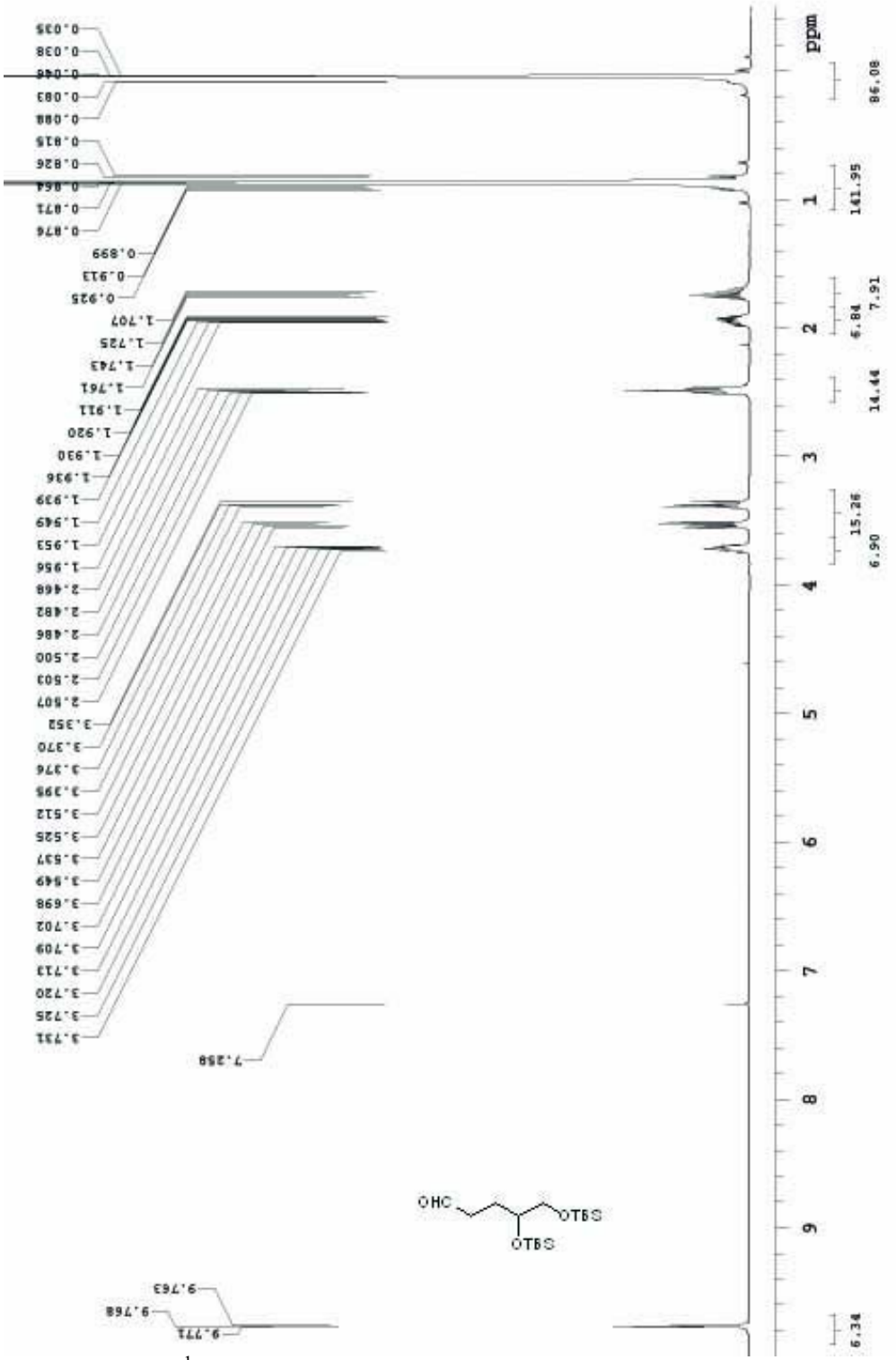
Spectrum 3.4: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **4**



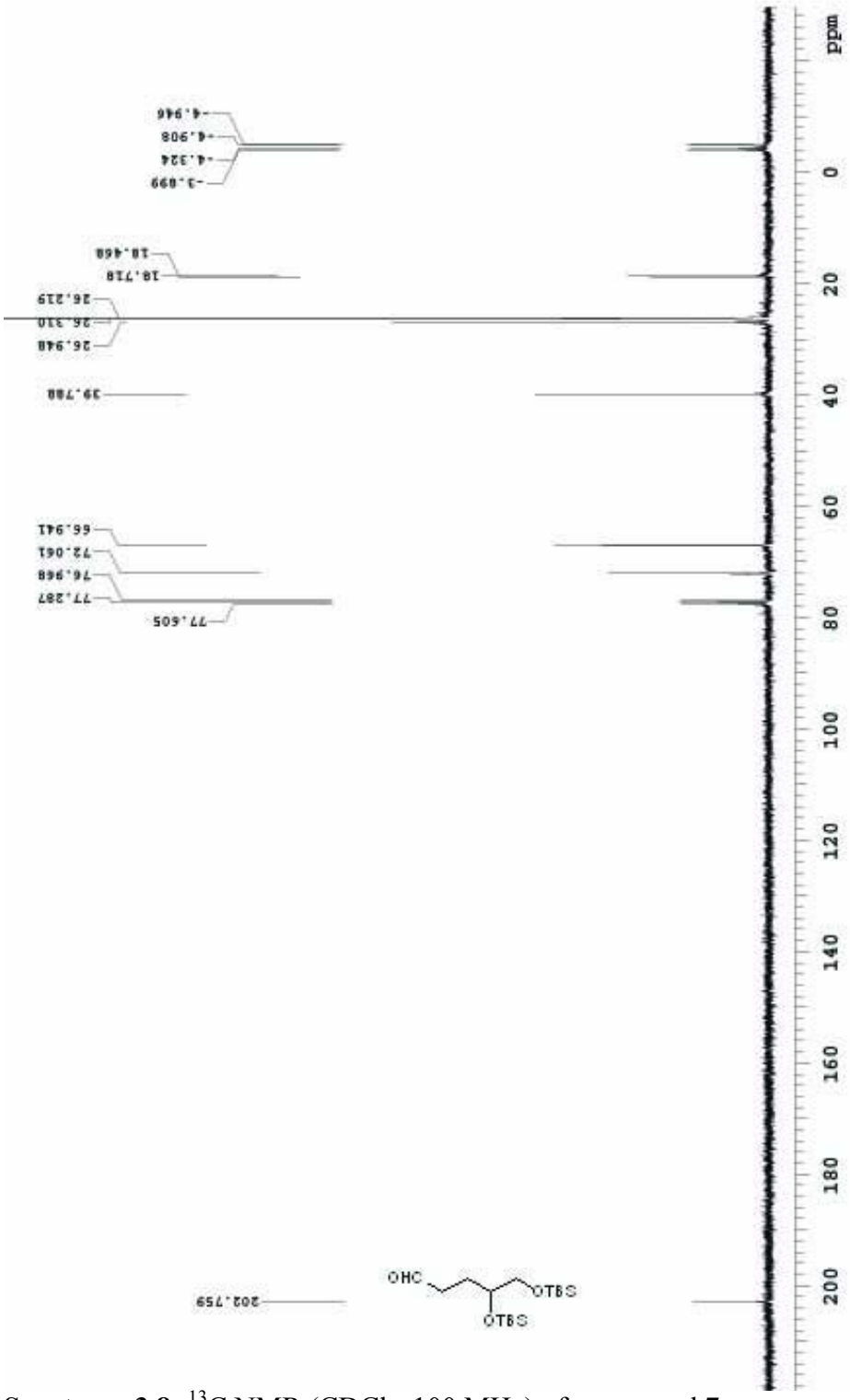
Spectrum 3.5: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **5**



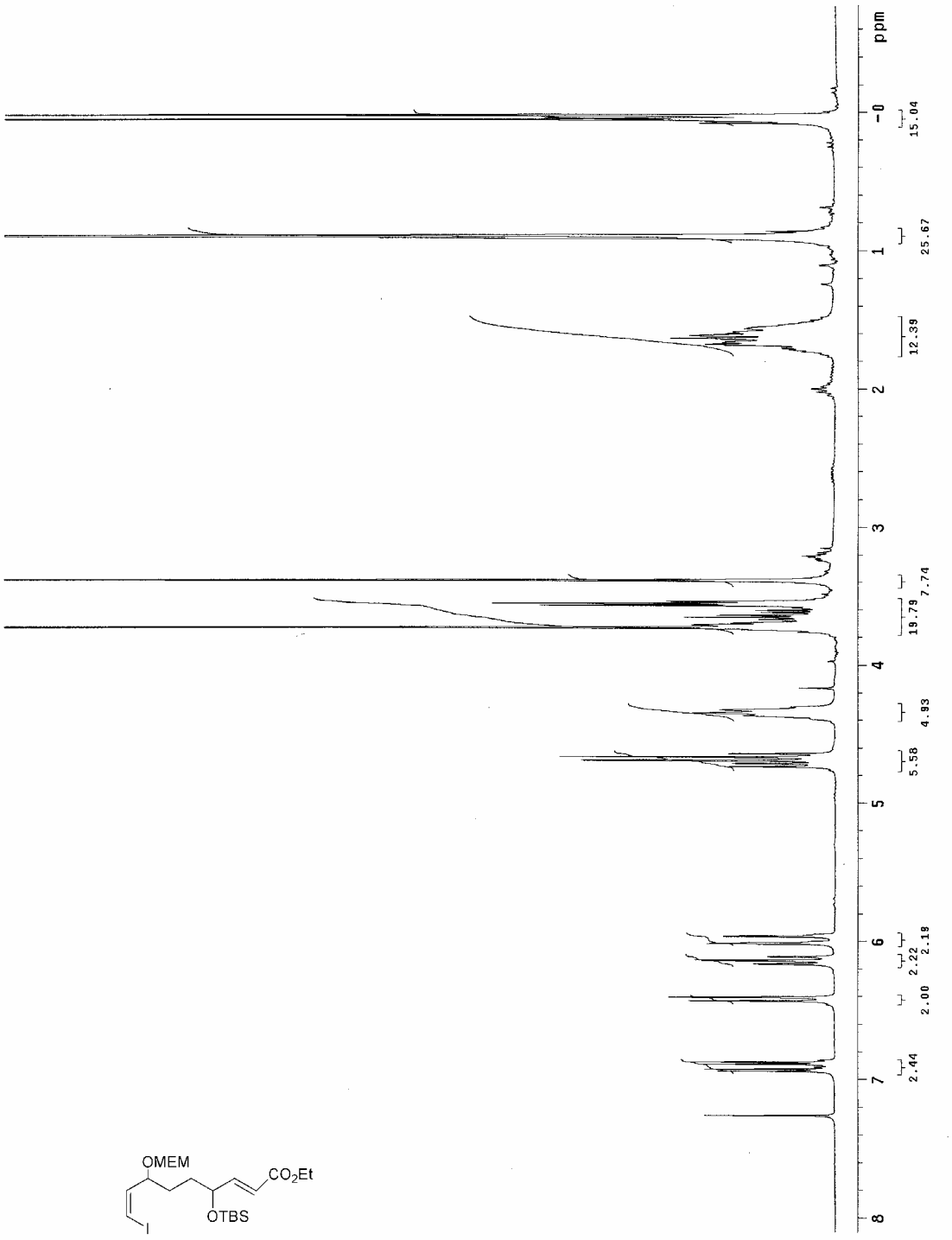
Spectrum 3.6: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **5**



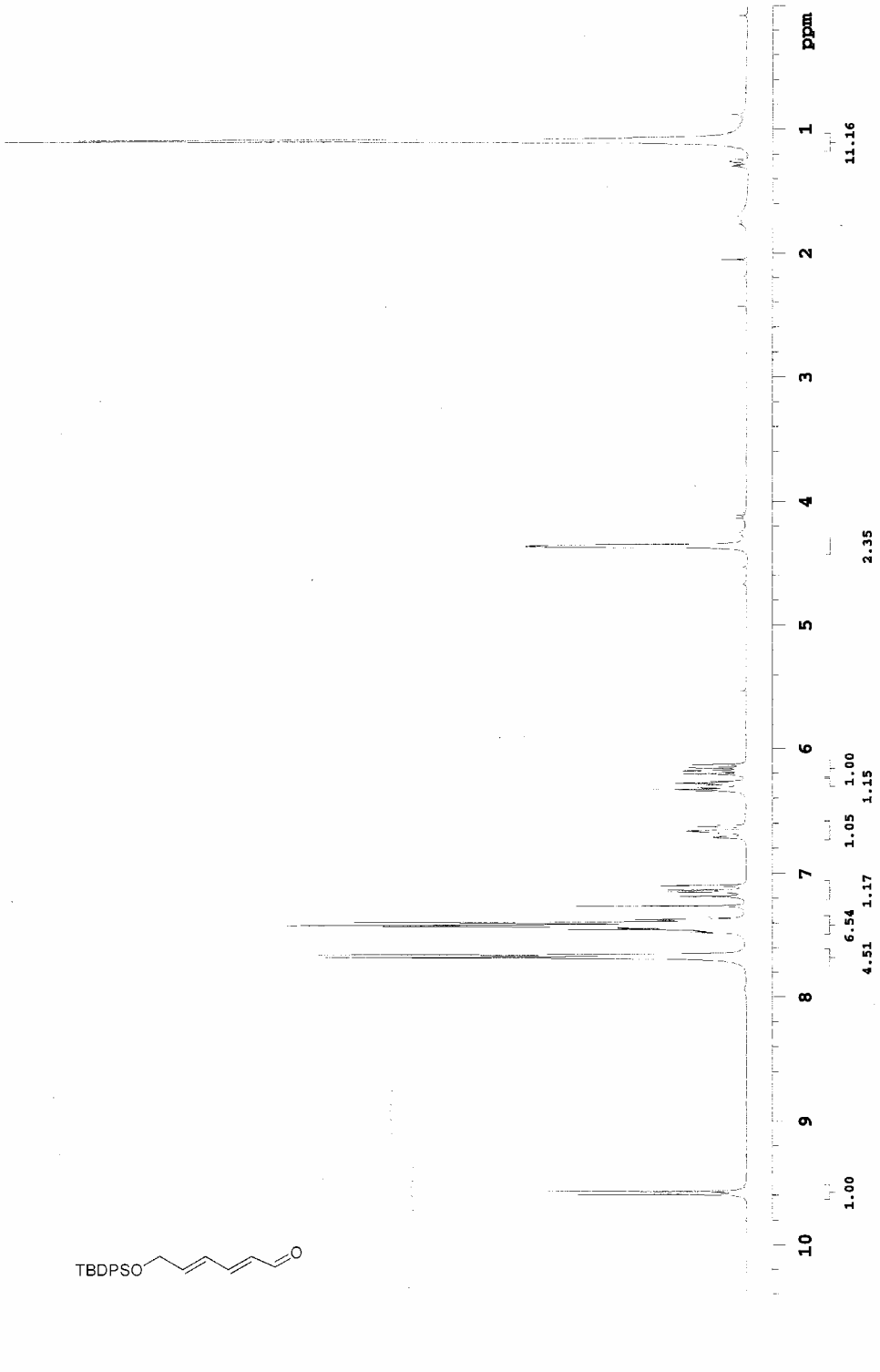
Spectrum 3.7: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **7**



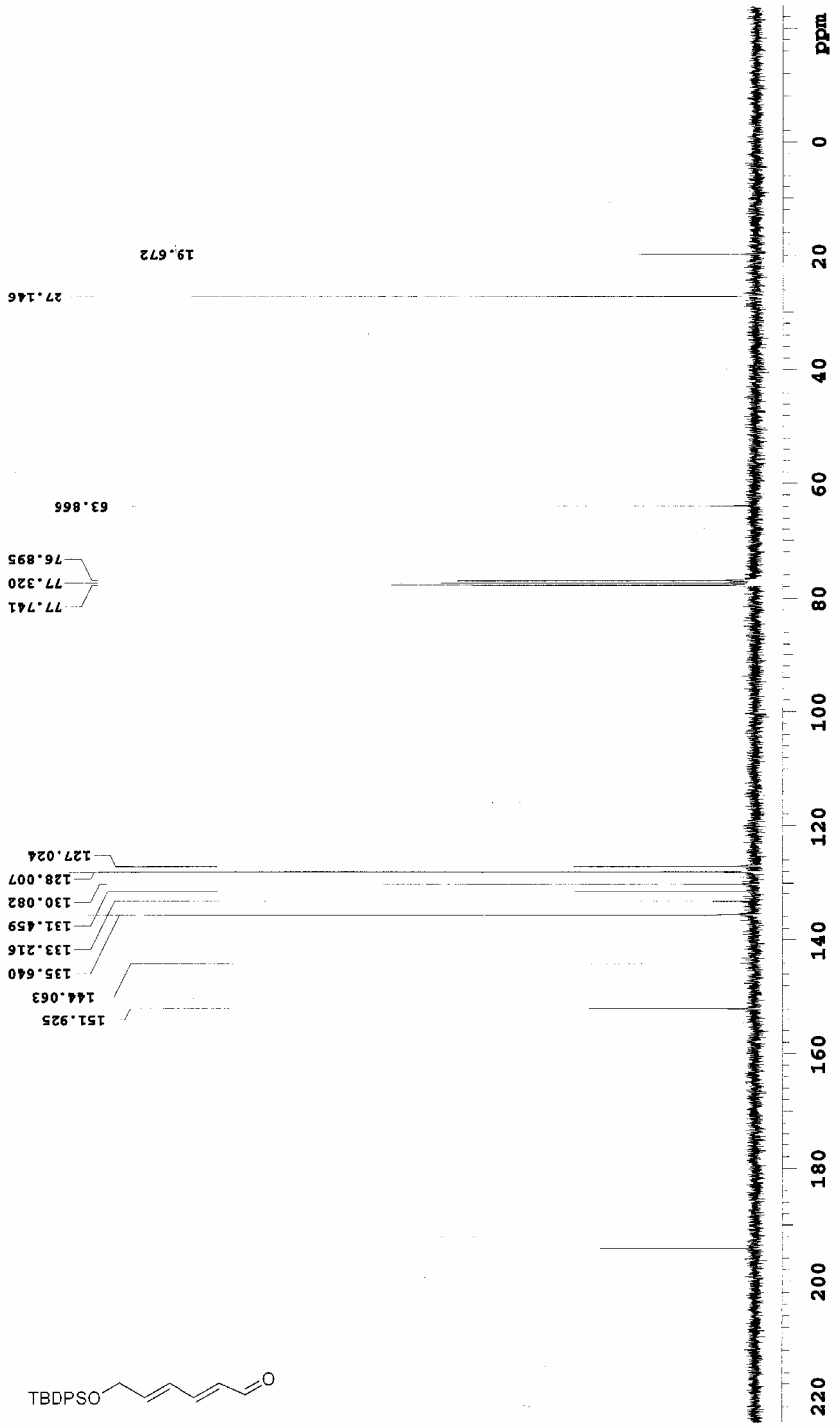
Spectrum 3.8: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **7**



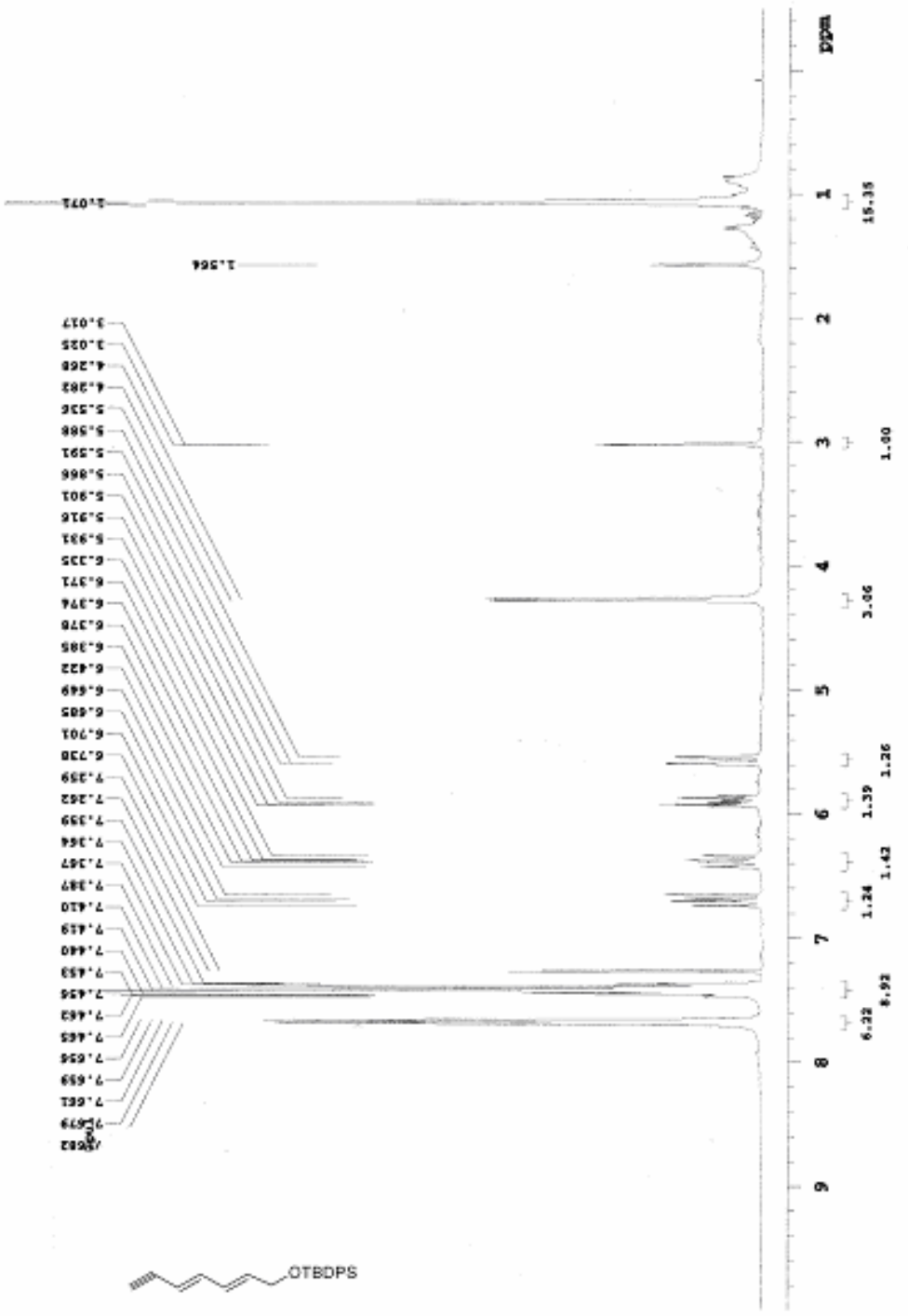
Spectrum 3.9: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **13**



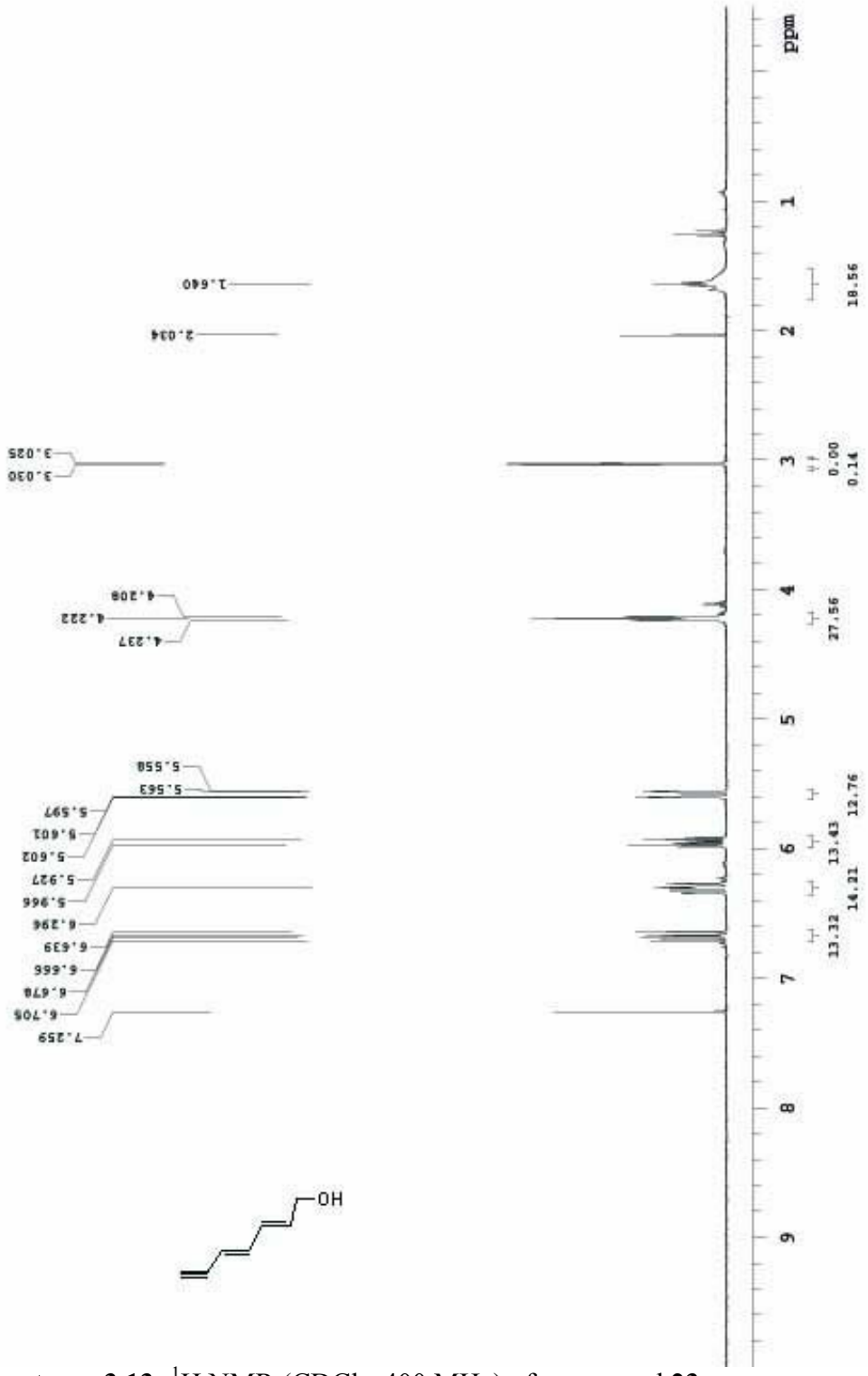
Spectrum 3.10: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **20**



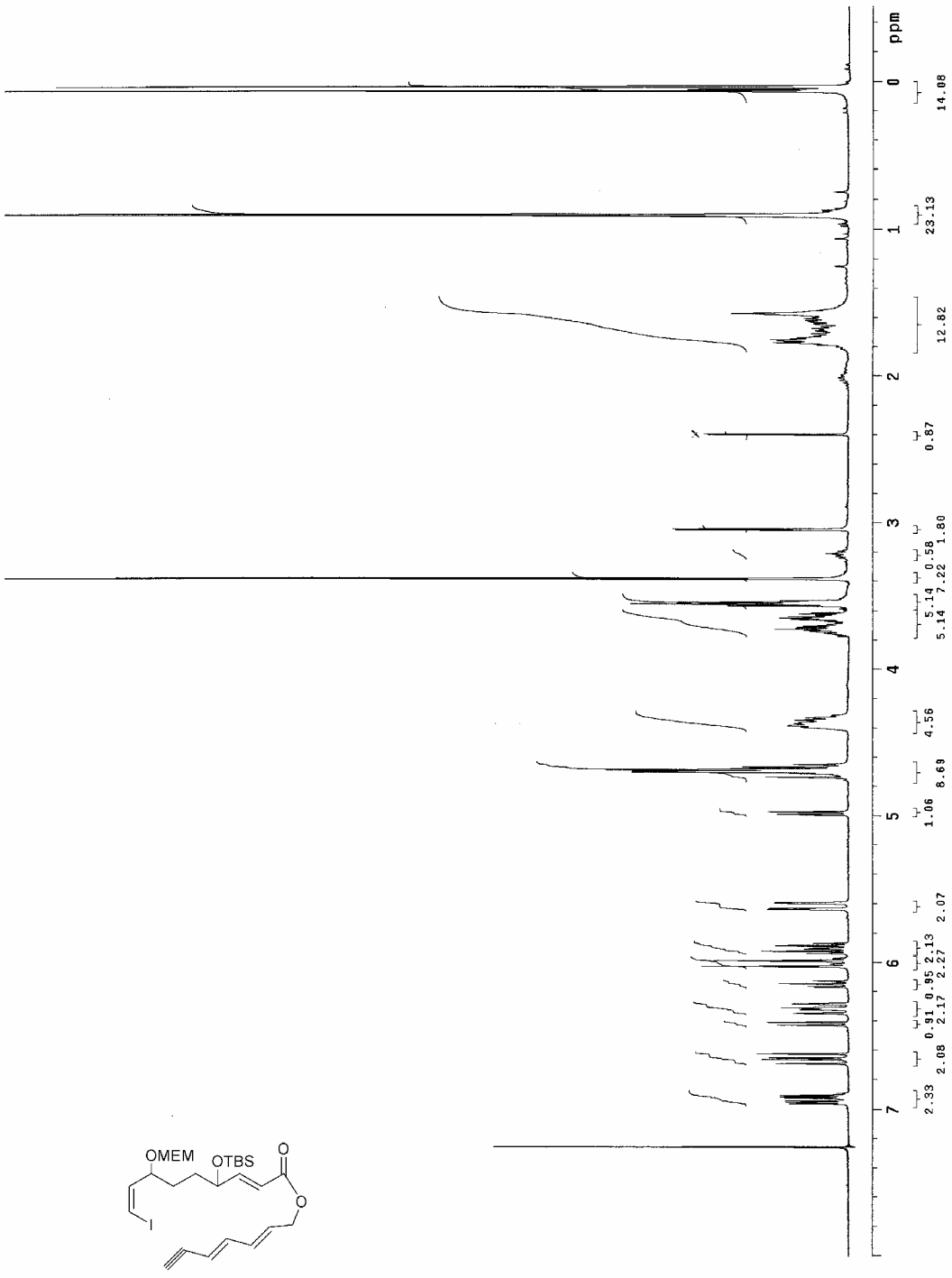
Spectrum 3.11: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **20**



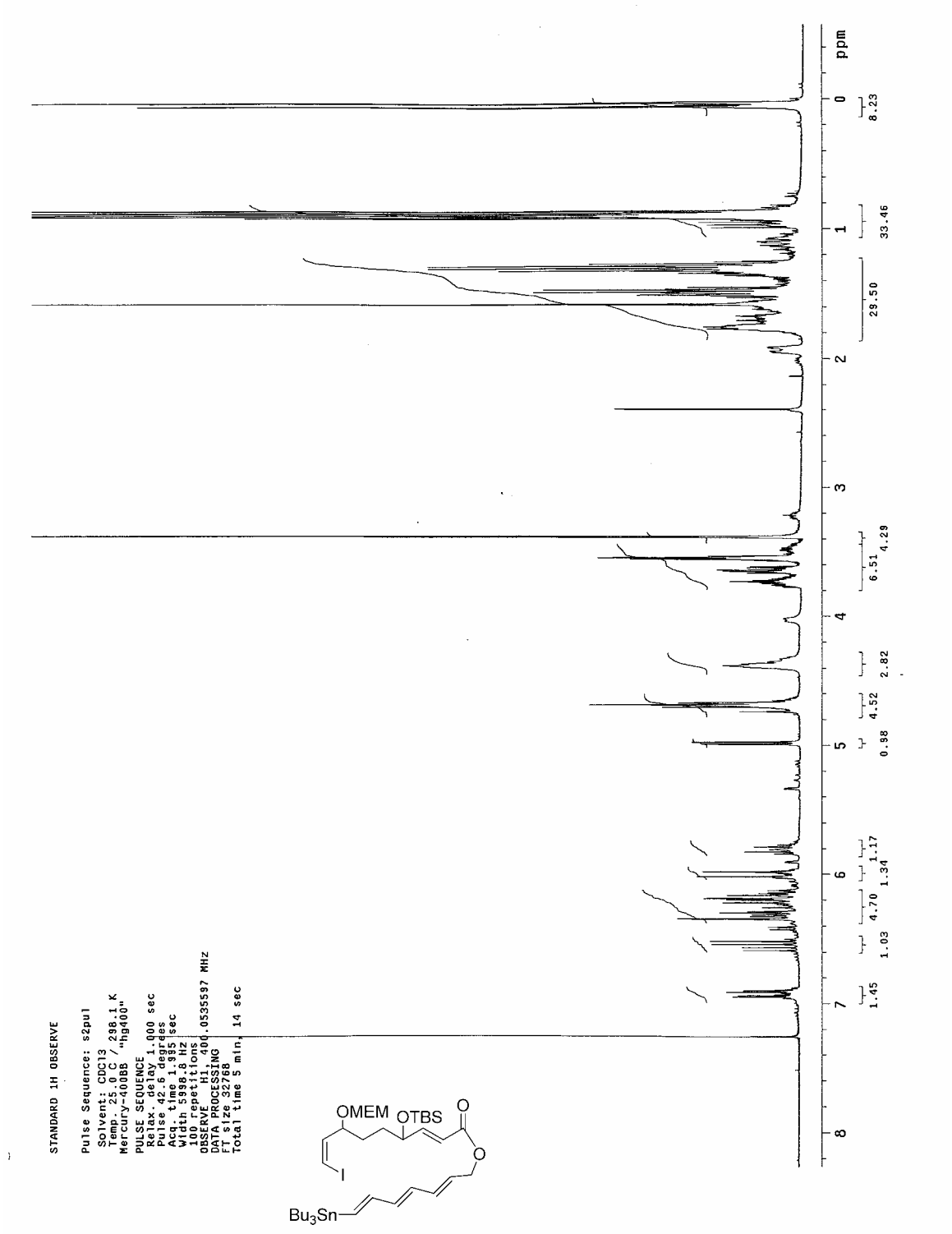
Spectrum 3.12: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **22**



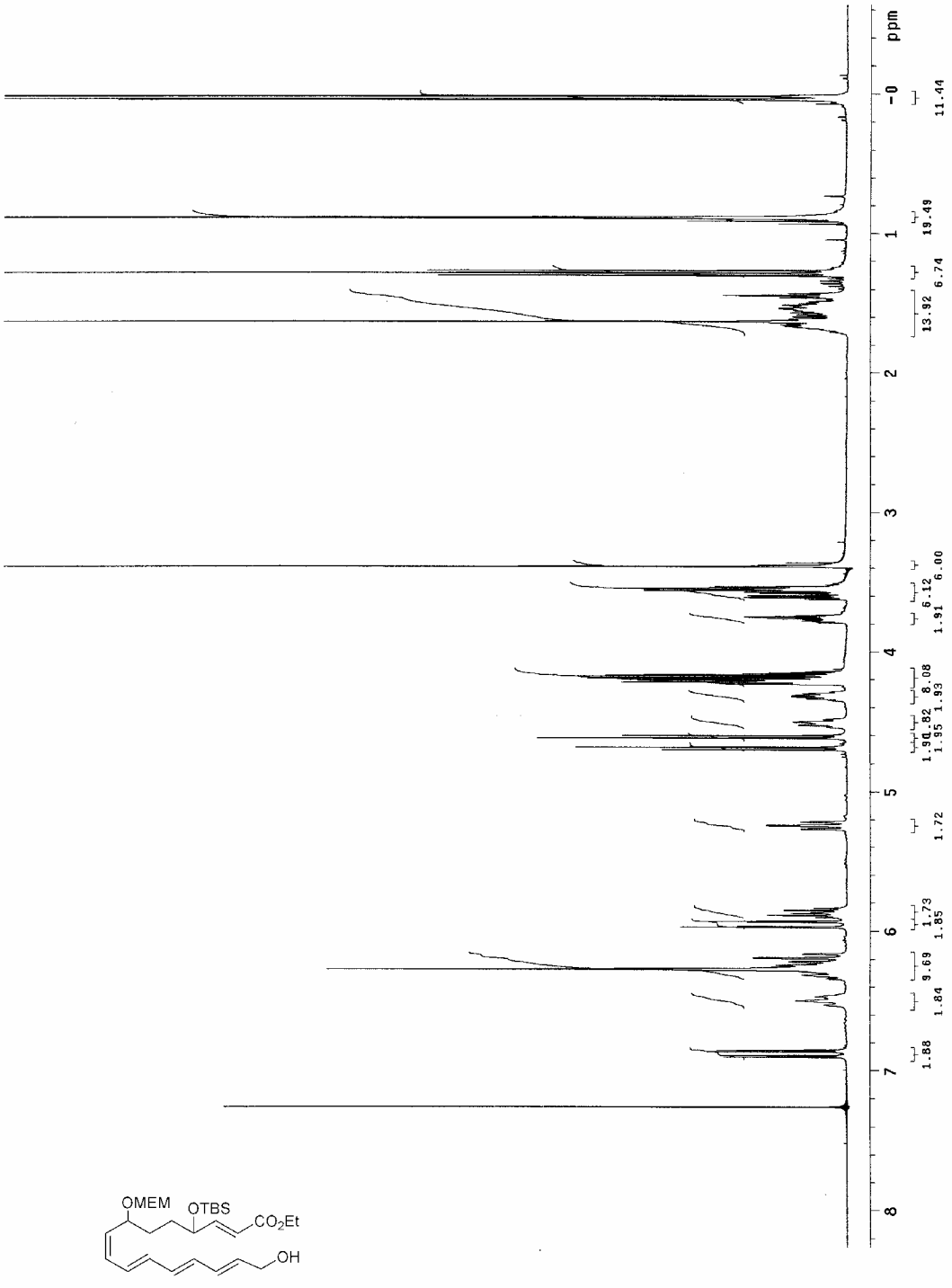
Spectrum 3.13: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **23**



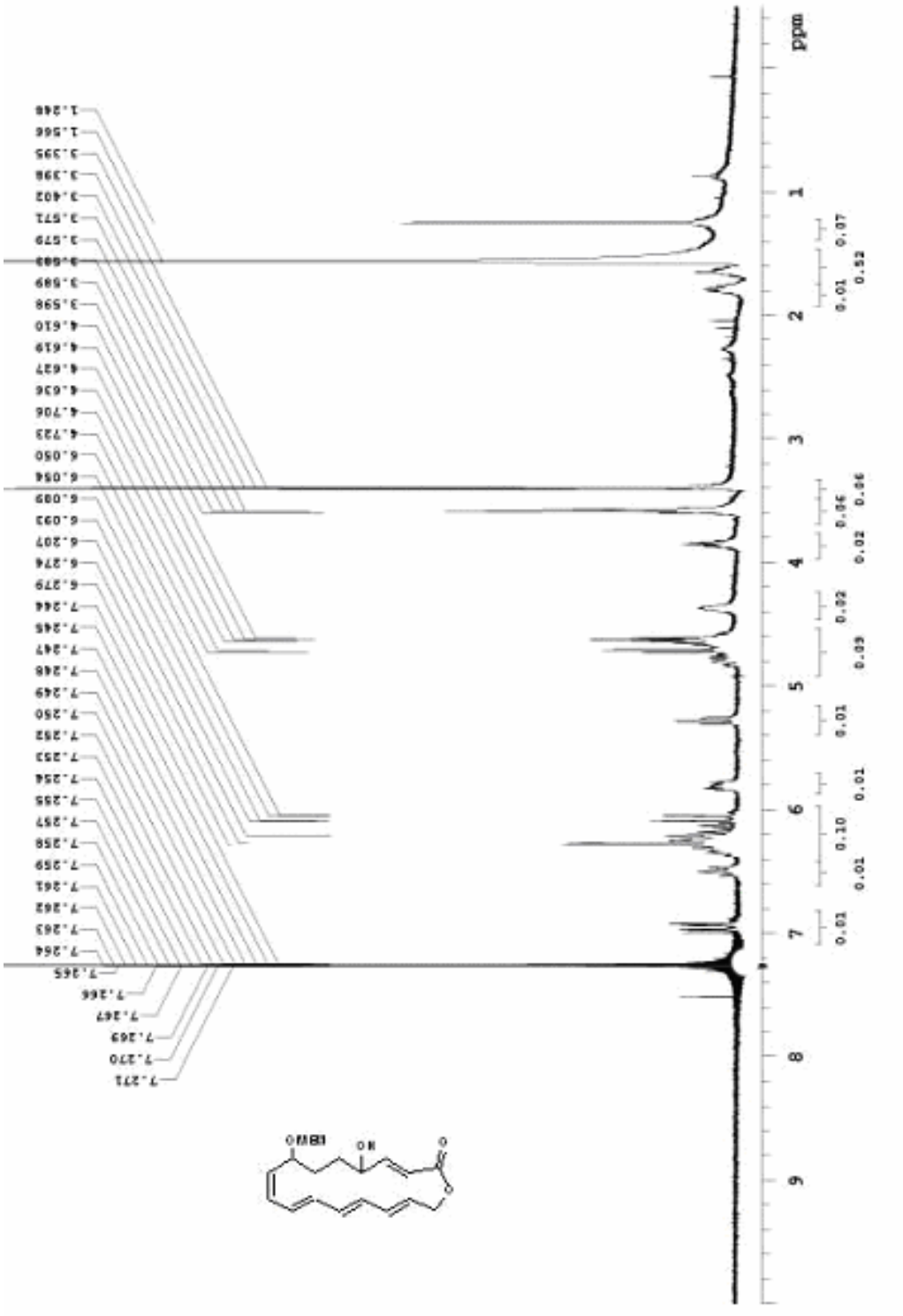
Spectrum 3.14: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **26**



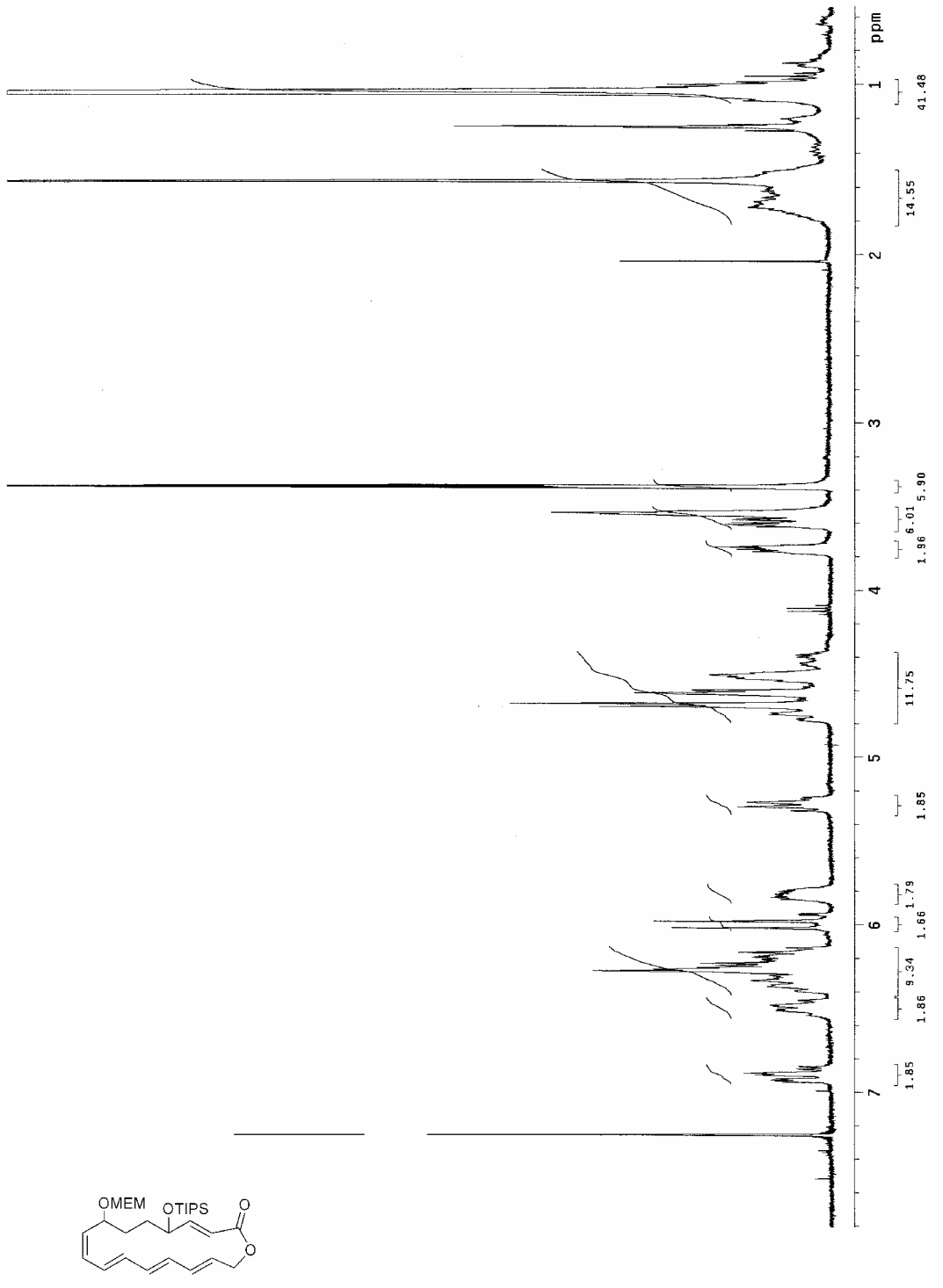
Spectrum 3.15: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **27-1**



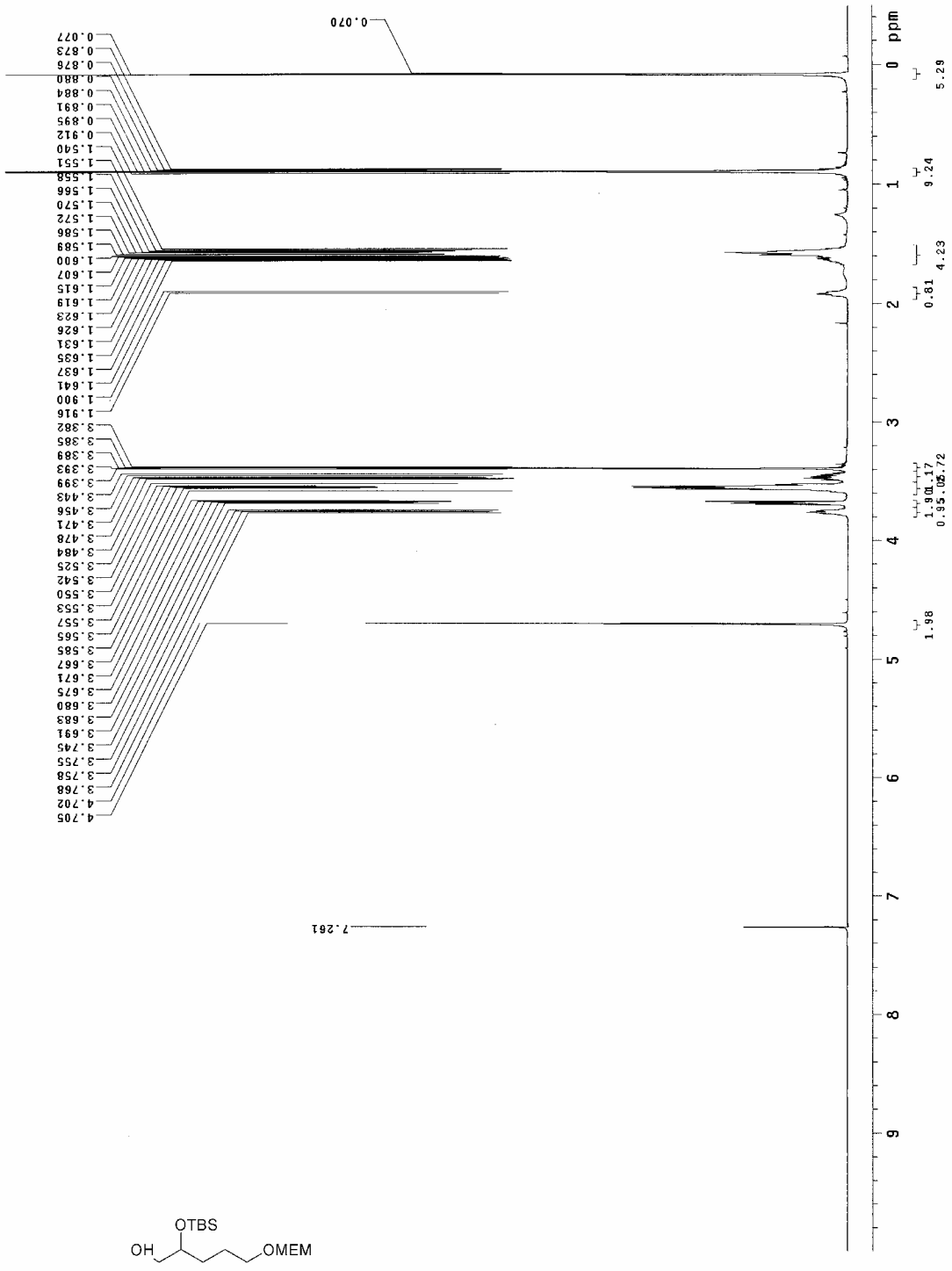
Spectrum 3.16: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **28**



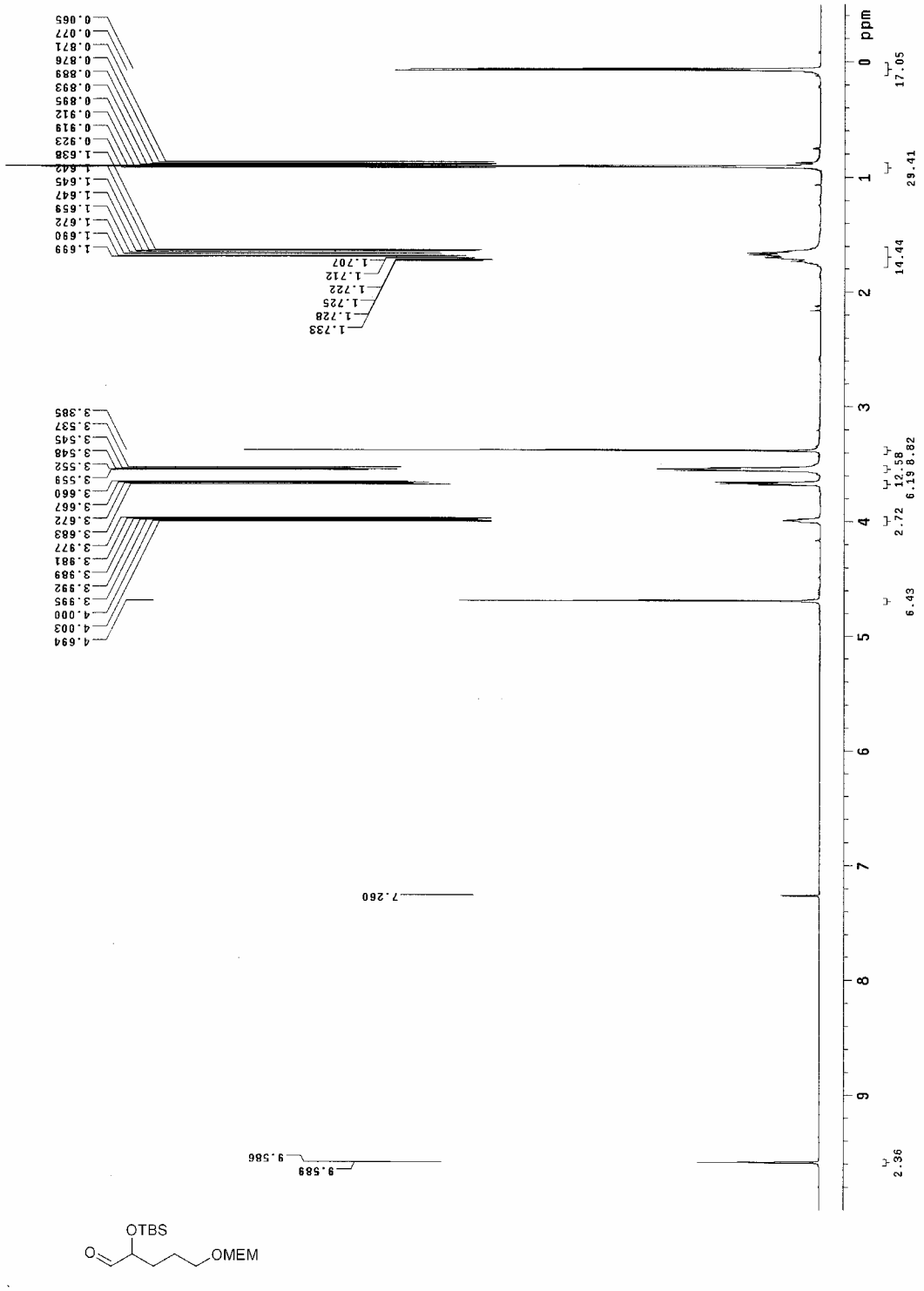
Spectrum 3.17: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **29-1**



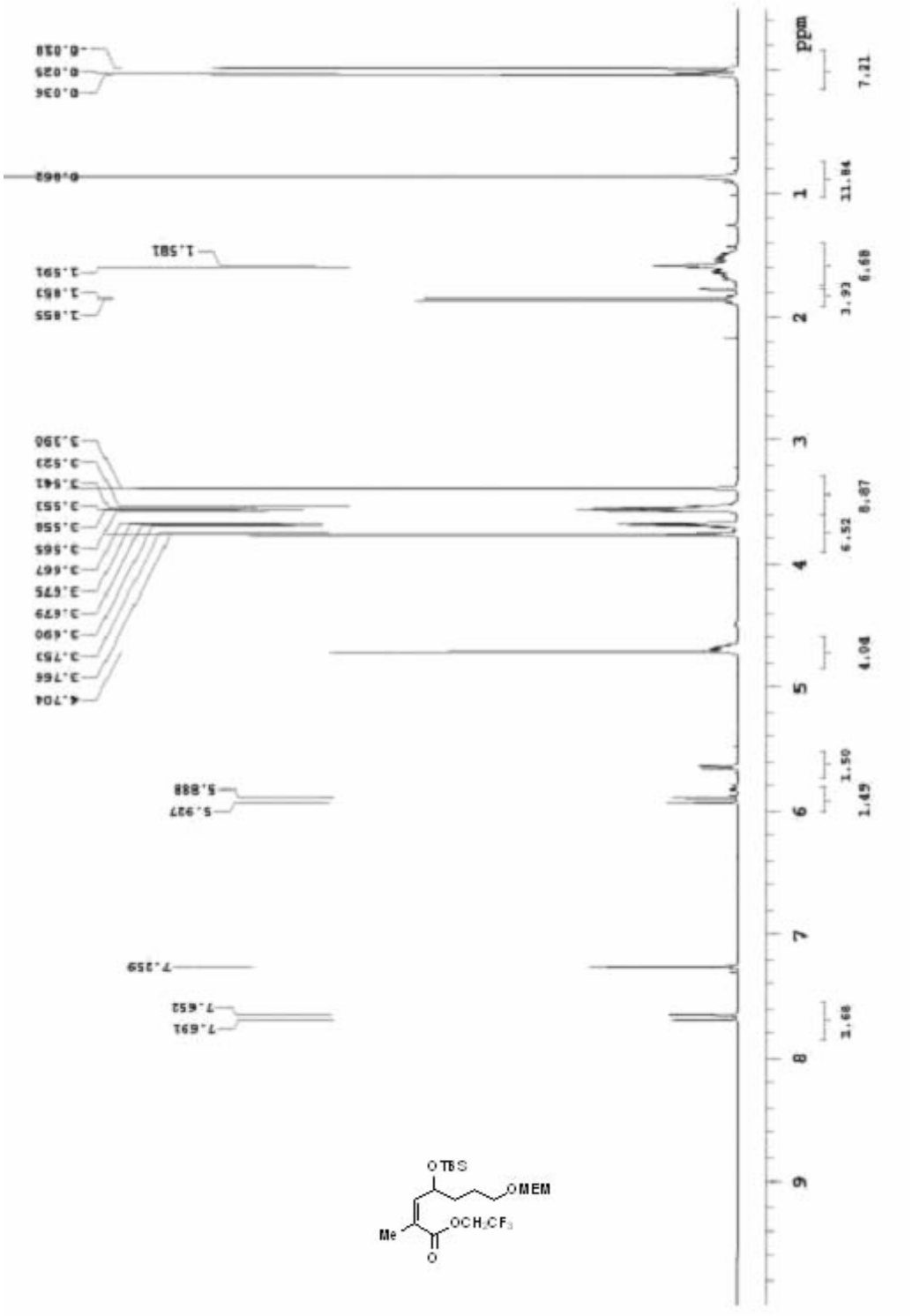
Spectrum 3.18: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **29-2**



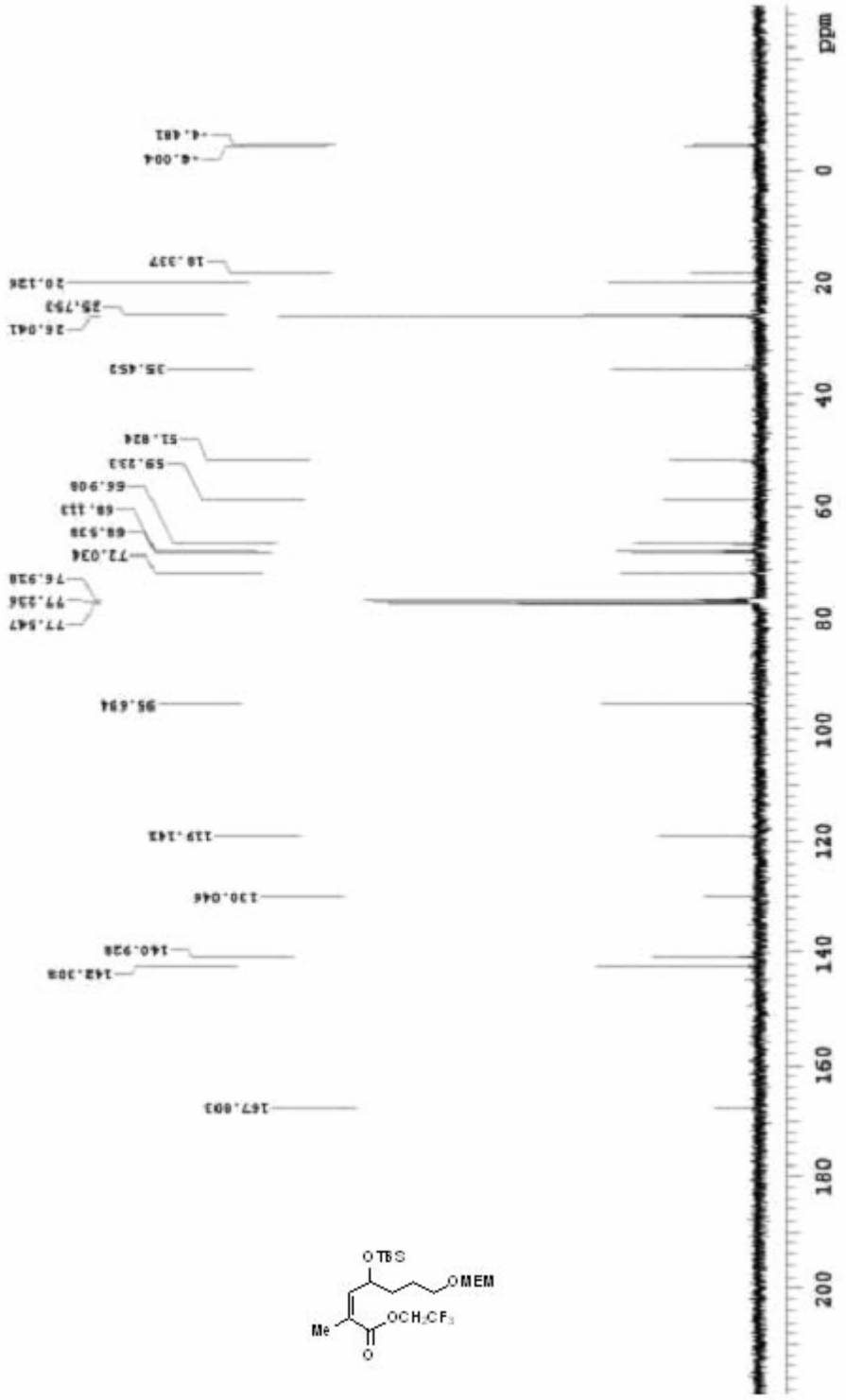
Spectrum 3.19: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **34**



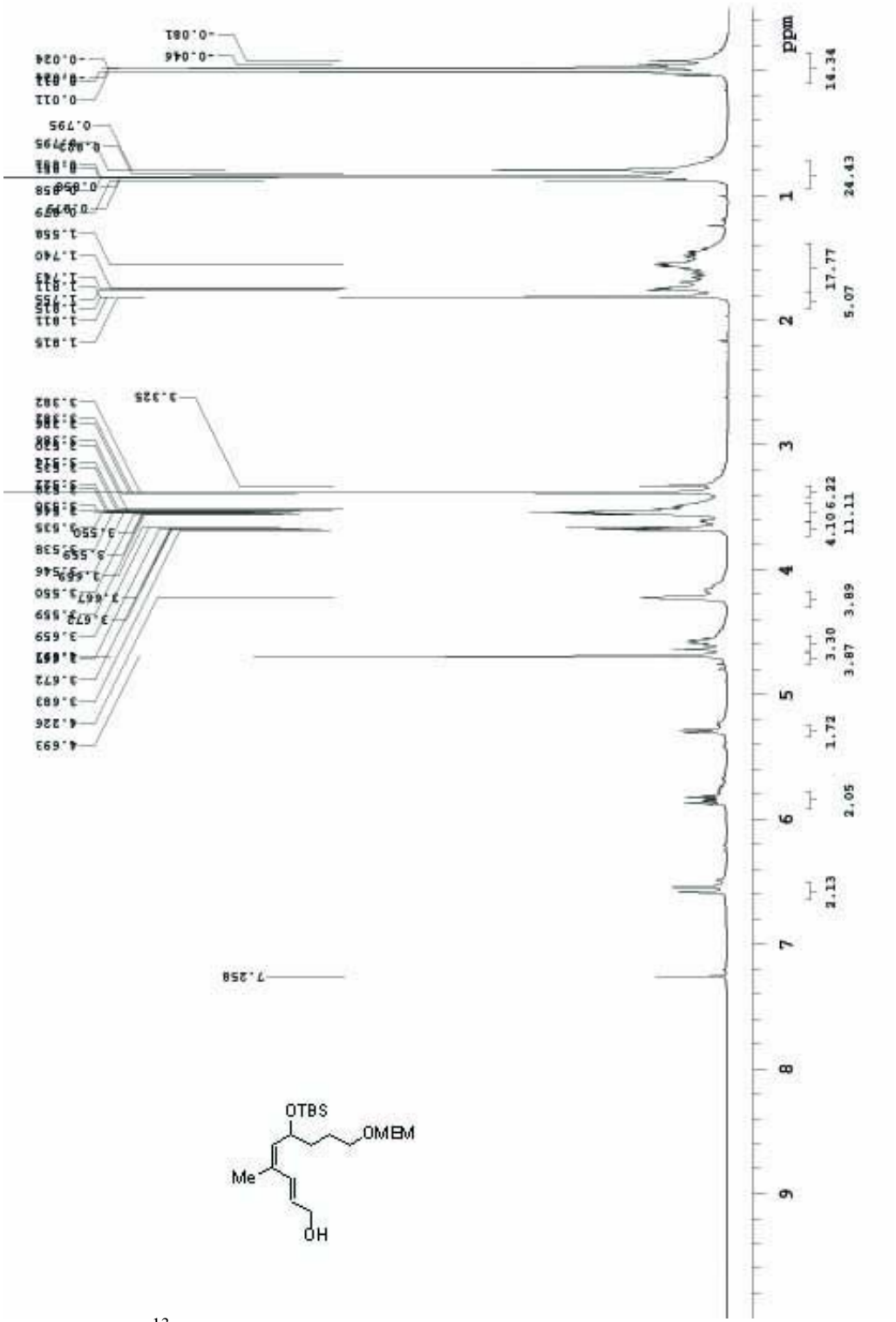
Spectrum 3.20: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **35**



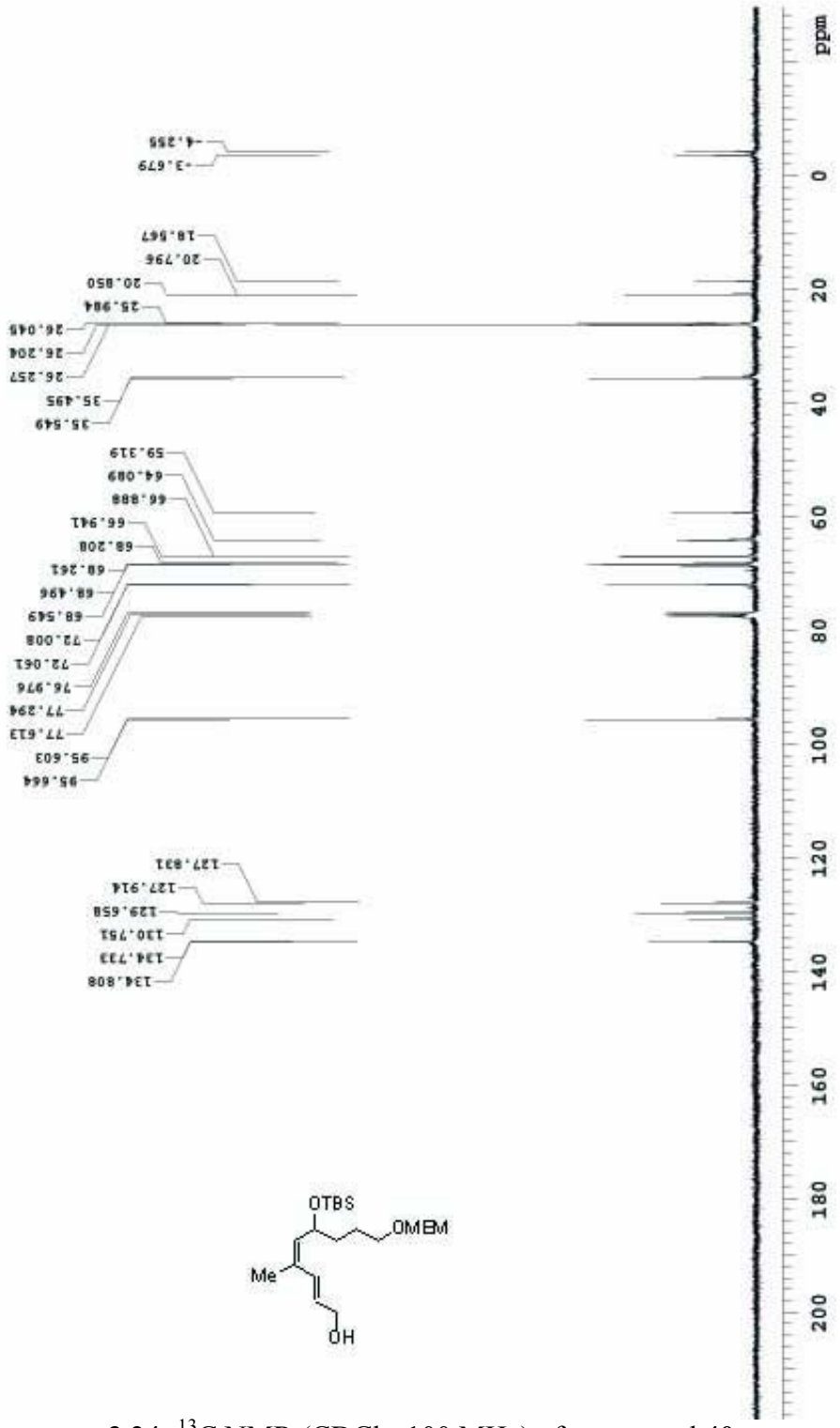
Spectrum 3.21: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **36**



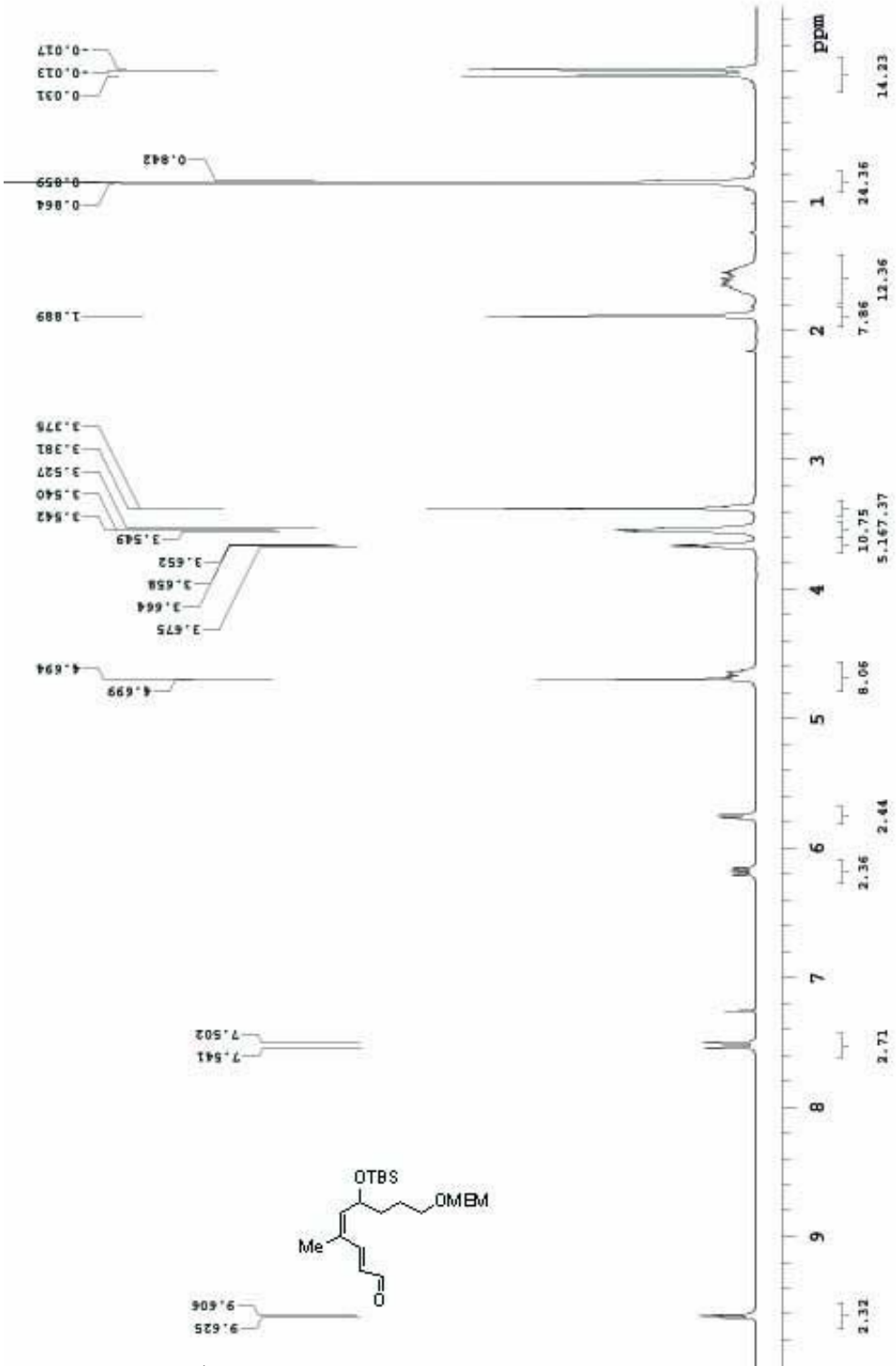
Spectrum 3.22: ^{1}H NMR ($CDCl_3$, 100 MHz) of compound **36**



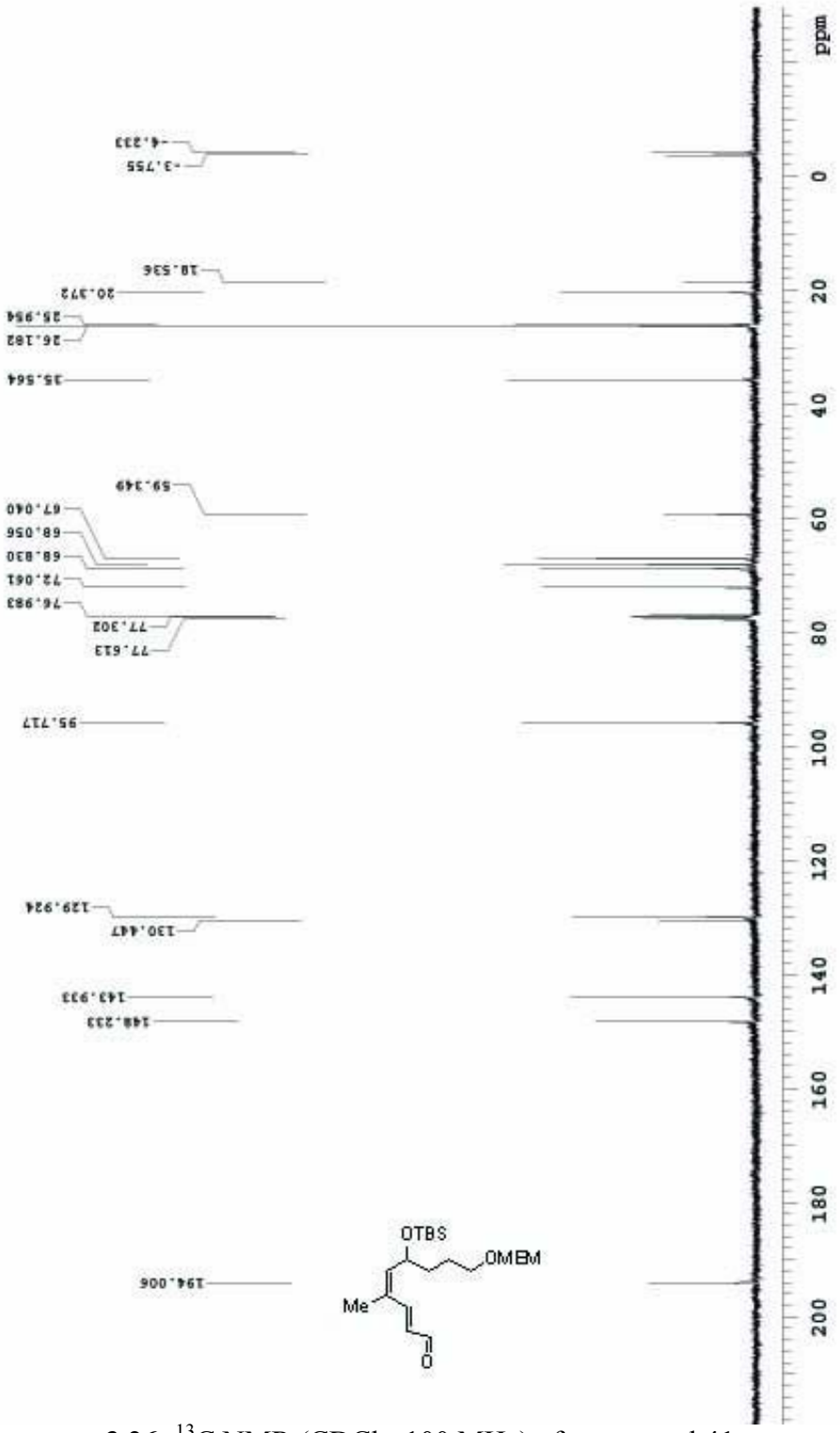
Spectrum 3.23: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **40**



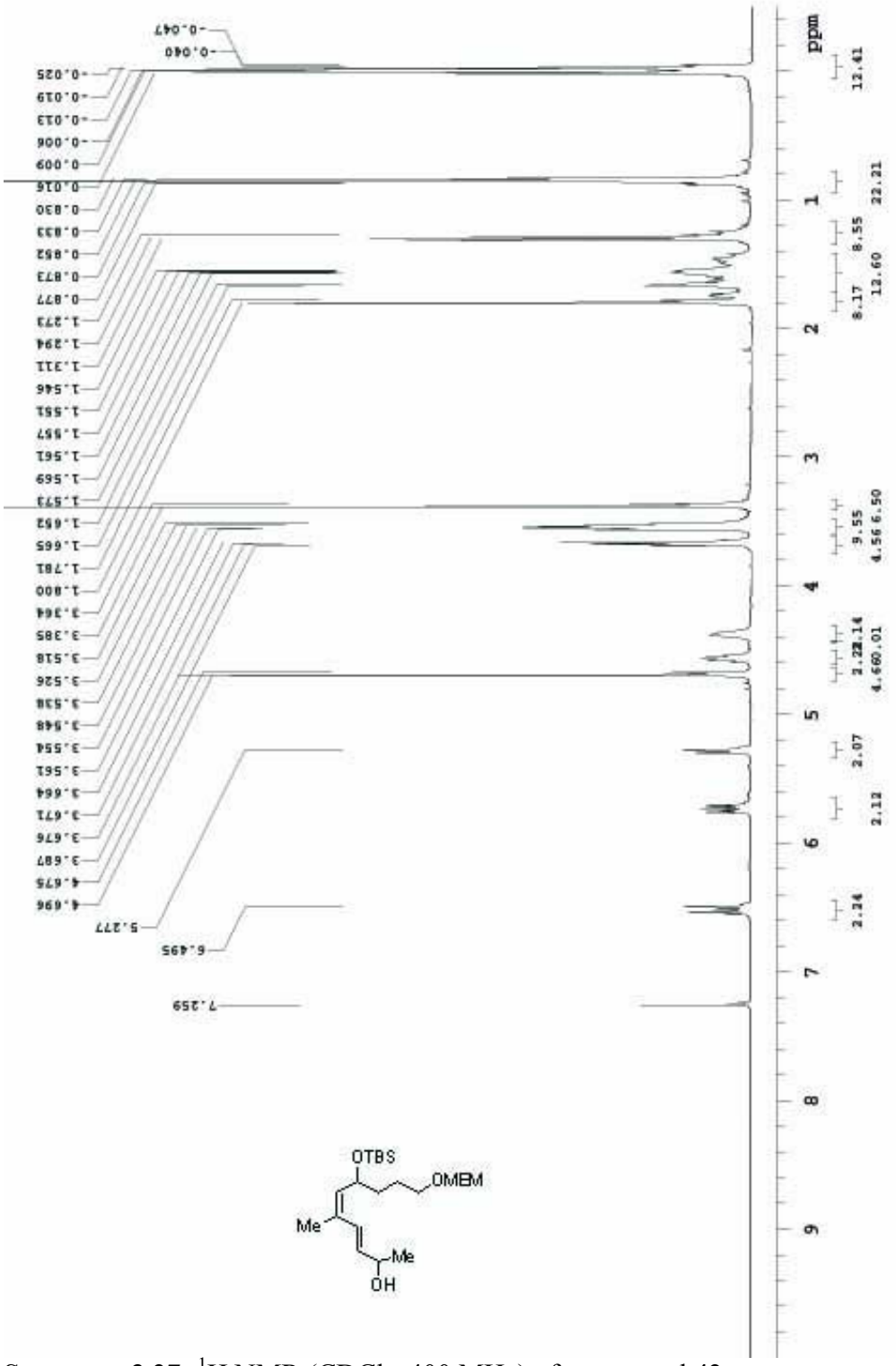
Spectrum 3.24: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **40**



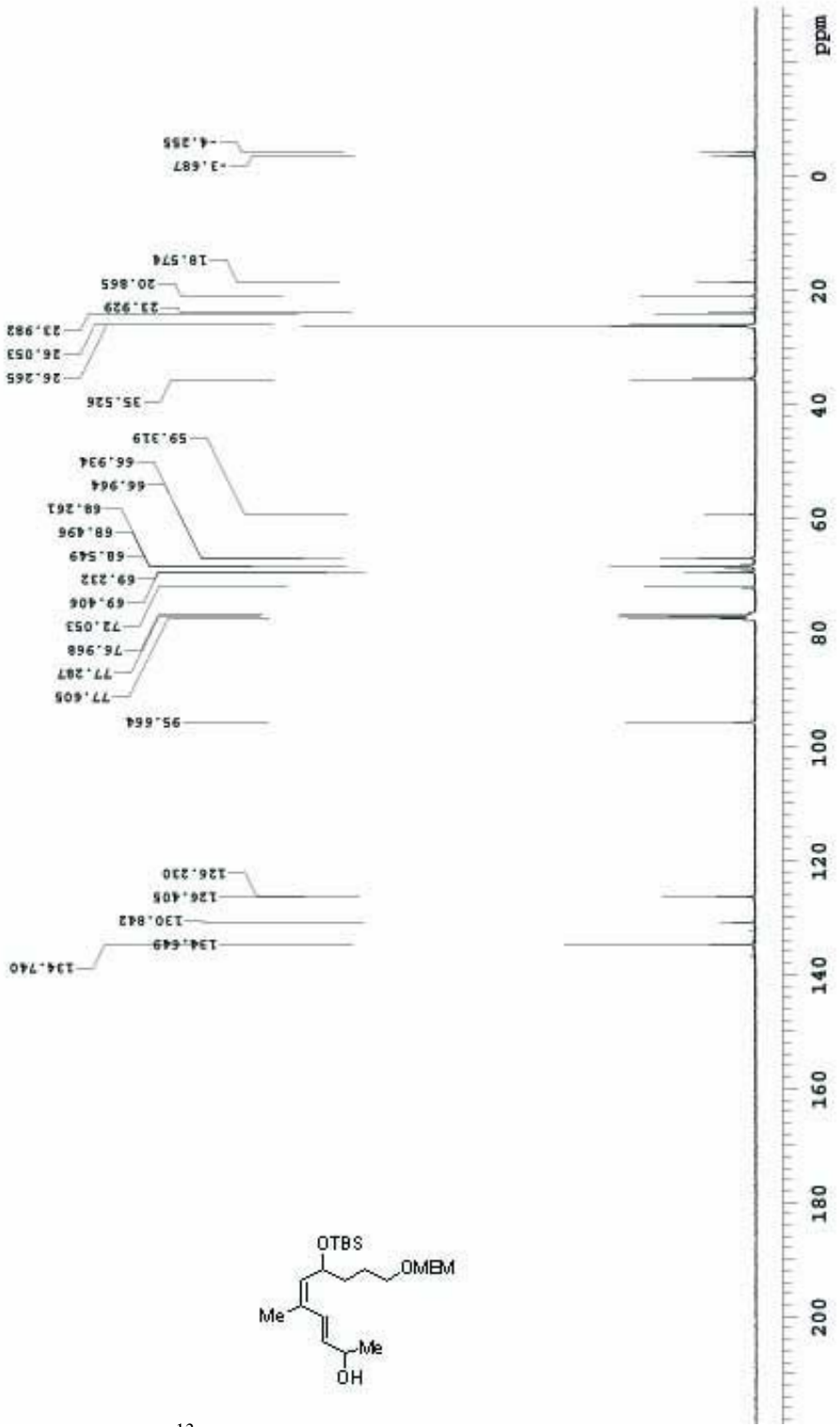
Spectrum 3.25: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **41**



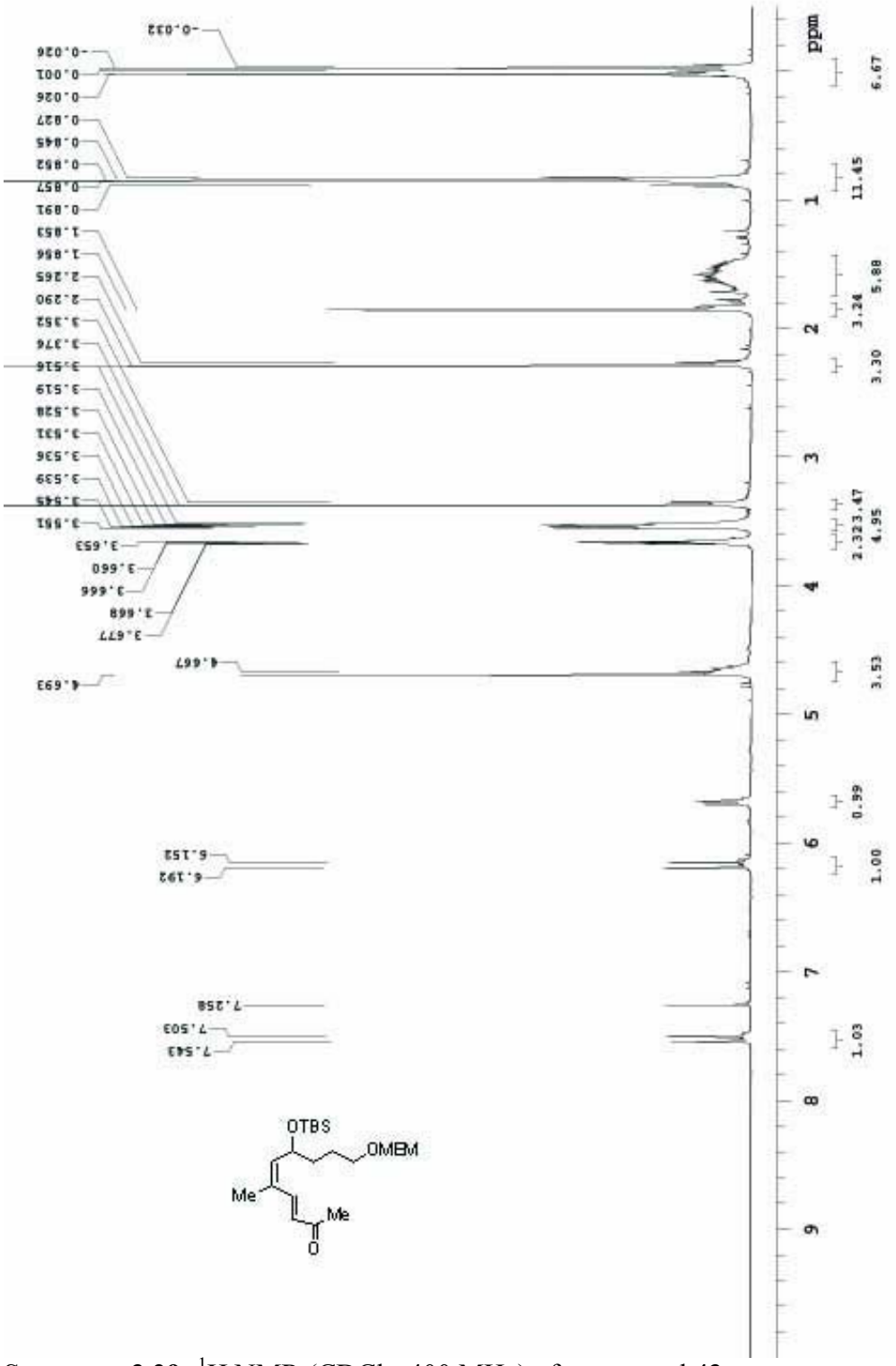
Spectrum 3.26: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **41**



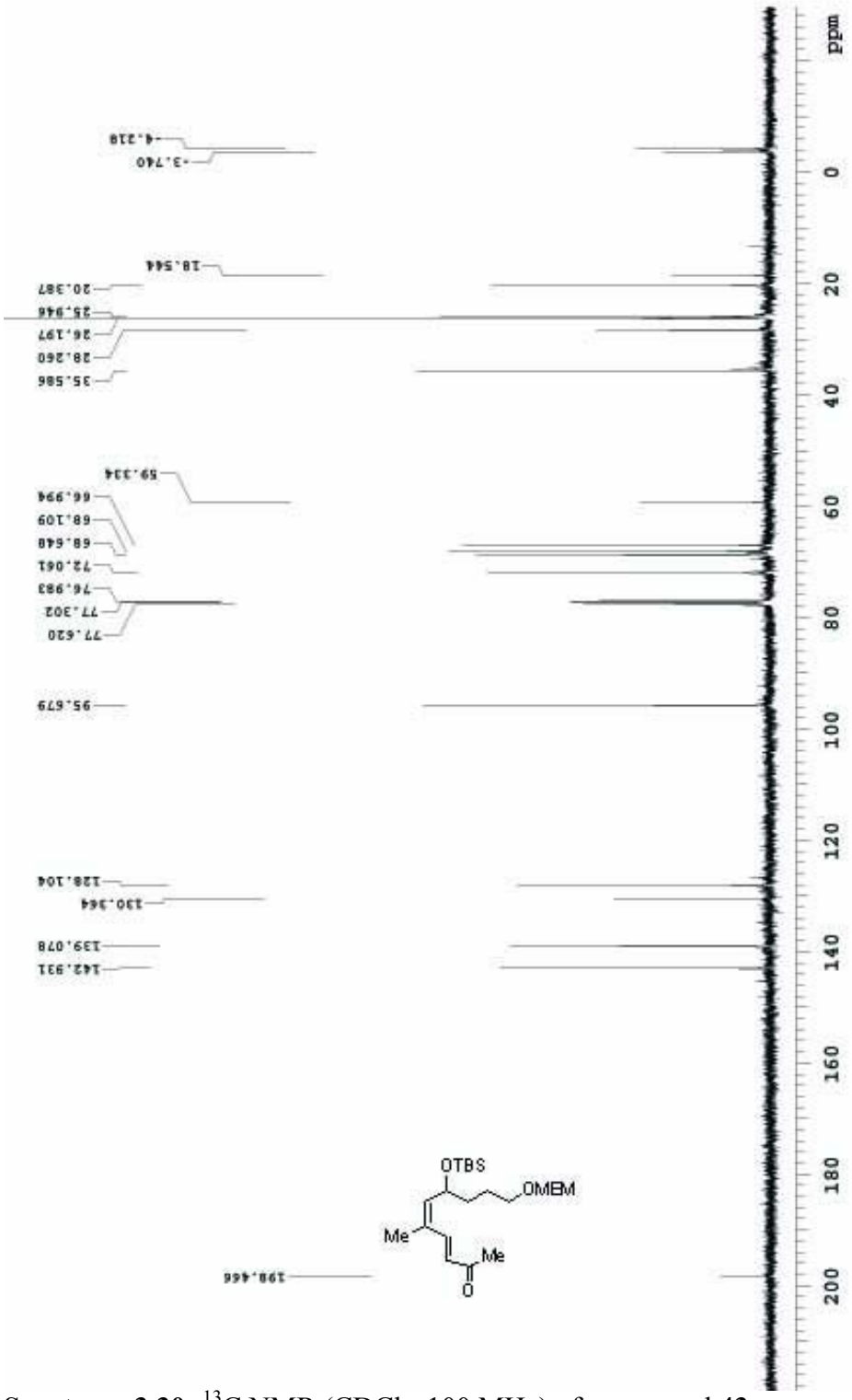
Spectrum 3.27: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **42**



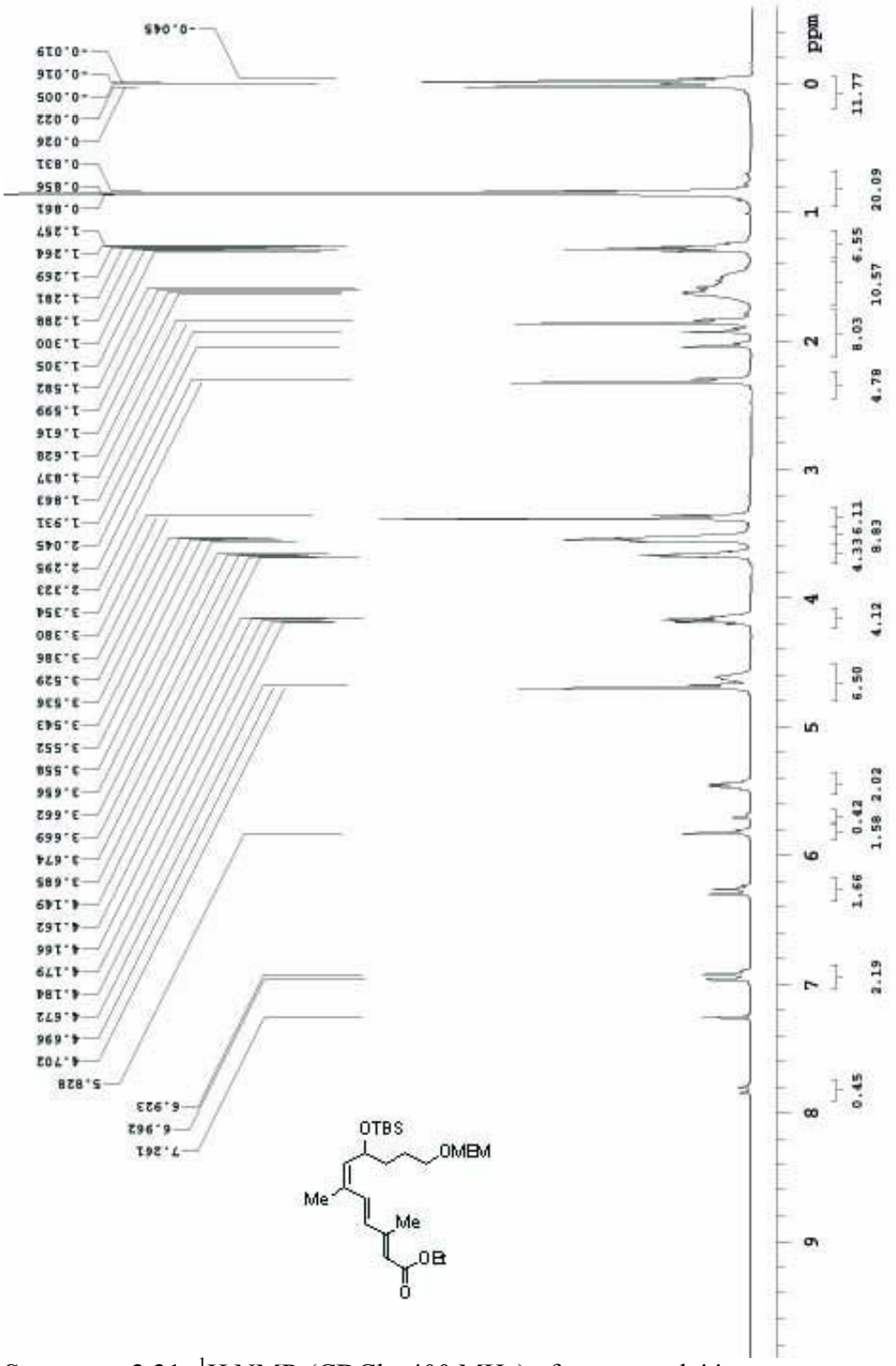
Spectrum 3.28: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **42**



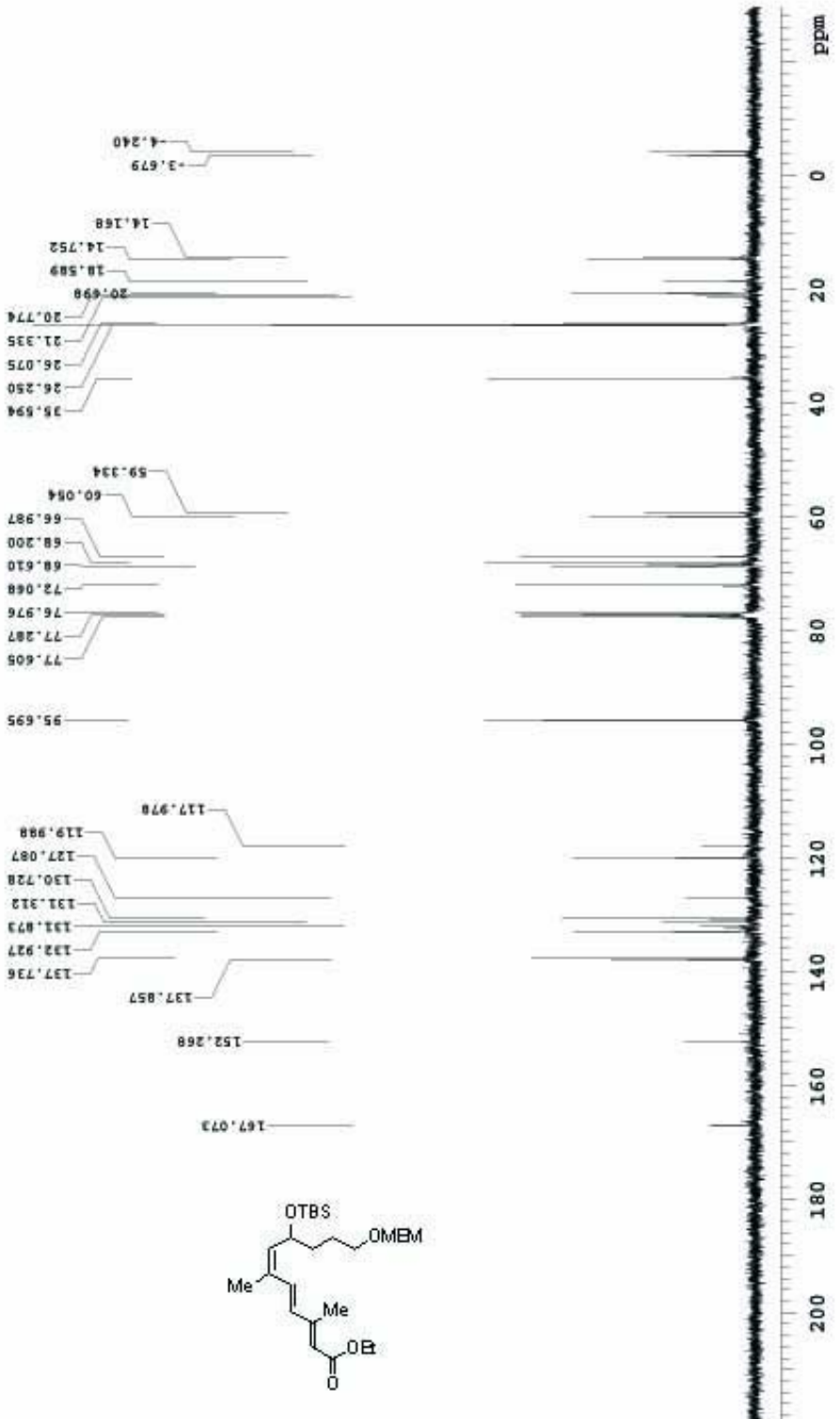
Spectrum 3.29: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **43**



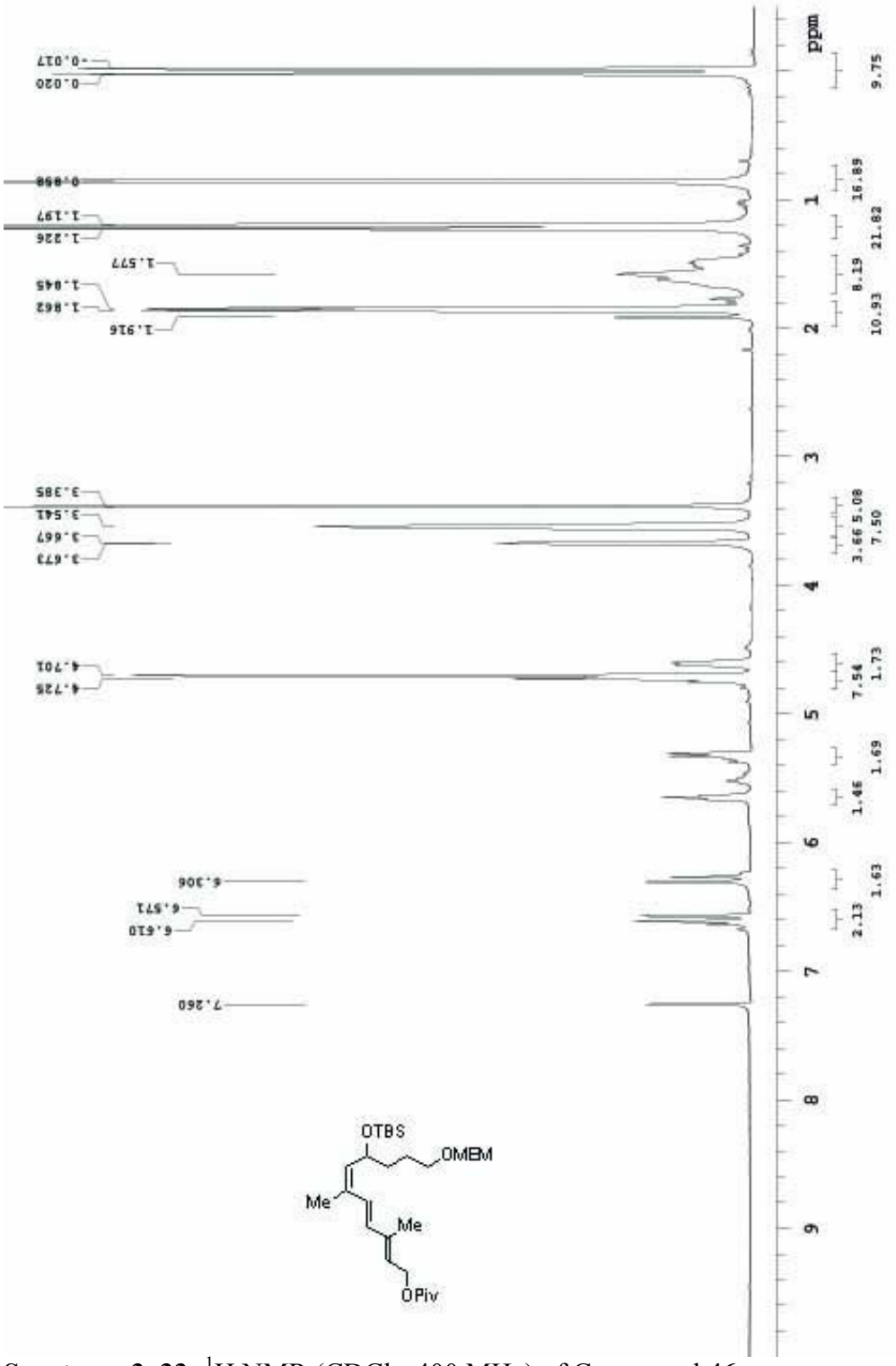
Spectrum 3.30: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **43**



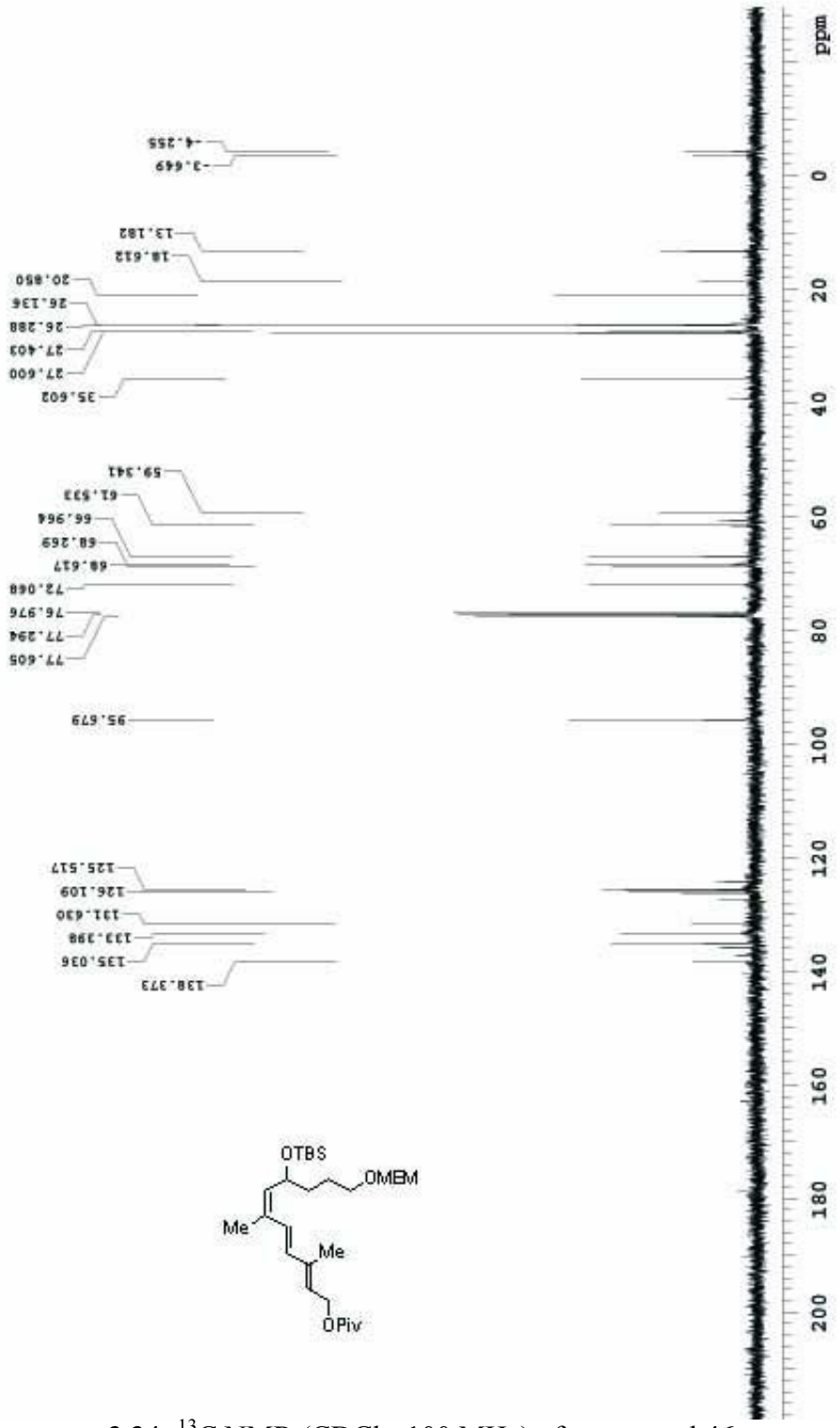
Spectrum 3.31: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **44**



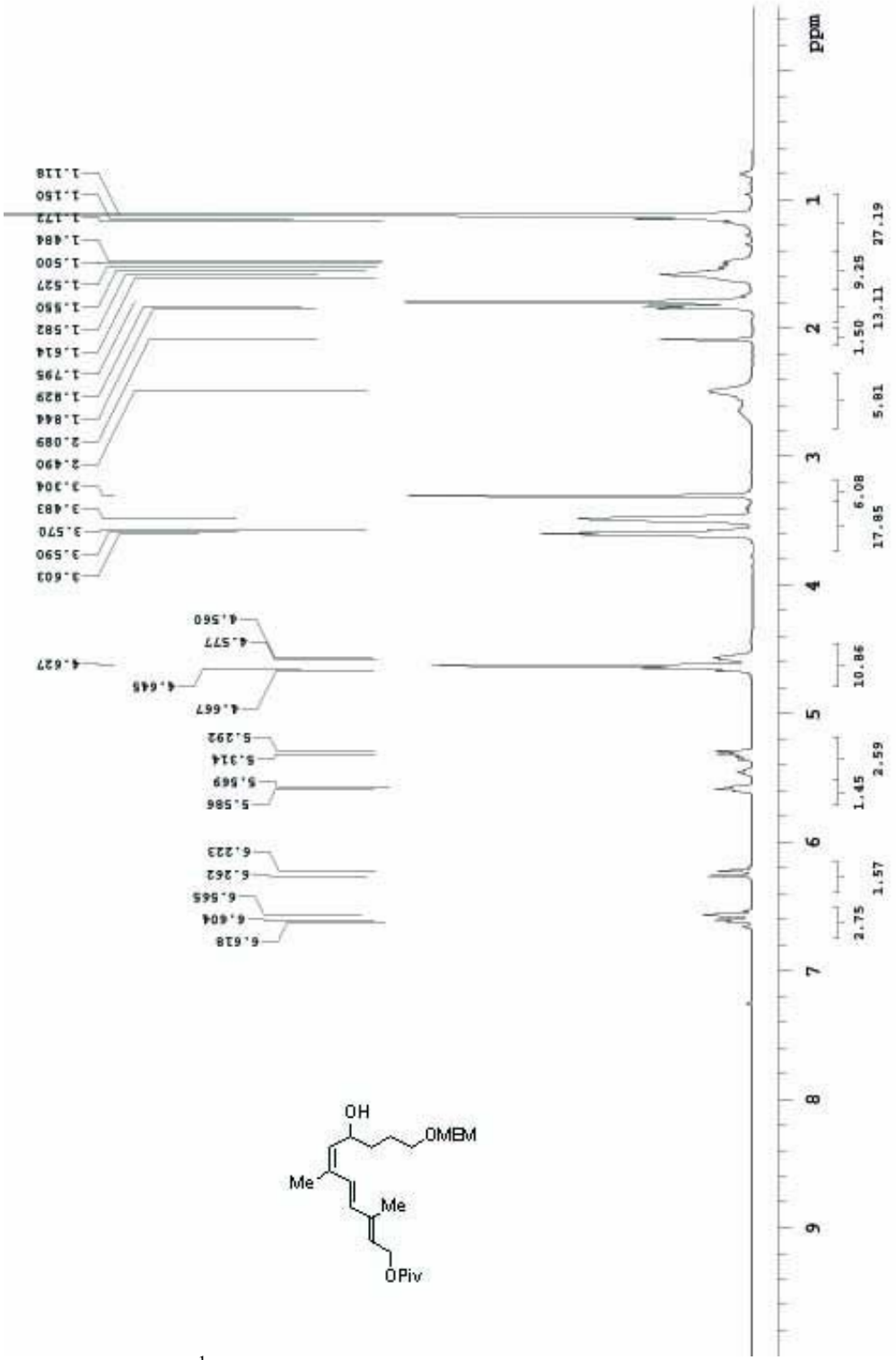
Spectrum 3.32: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **44**



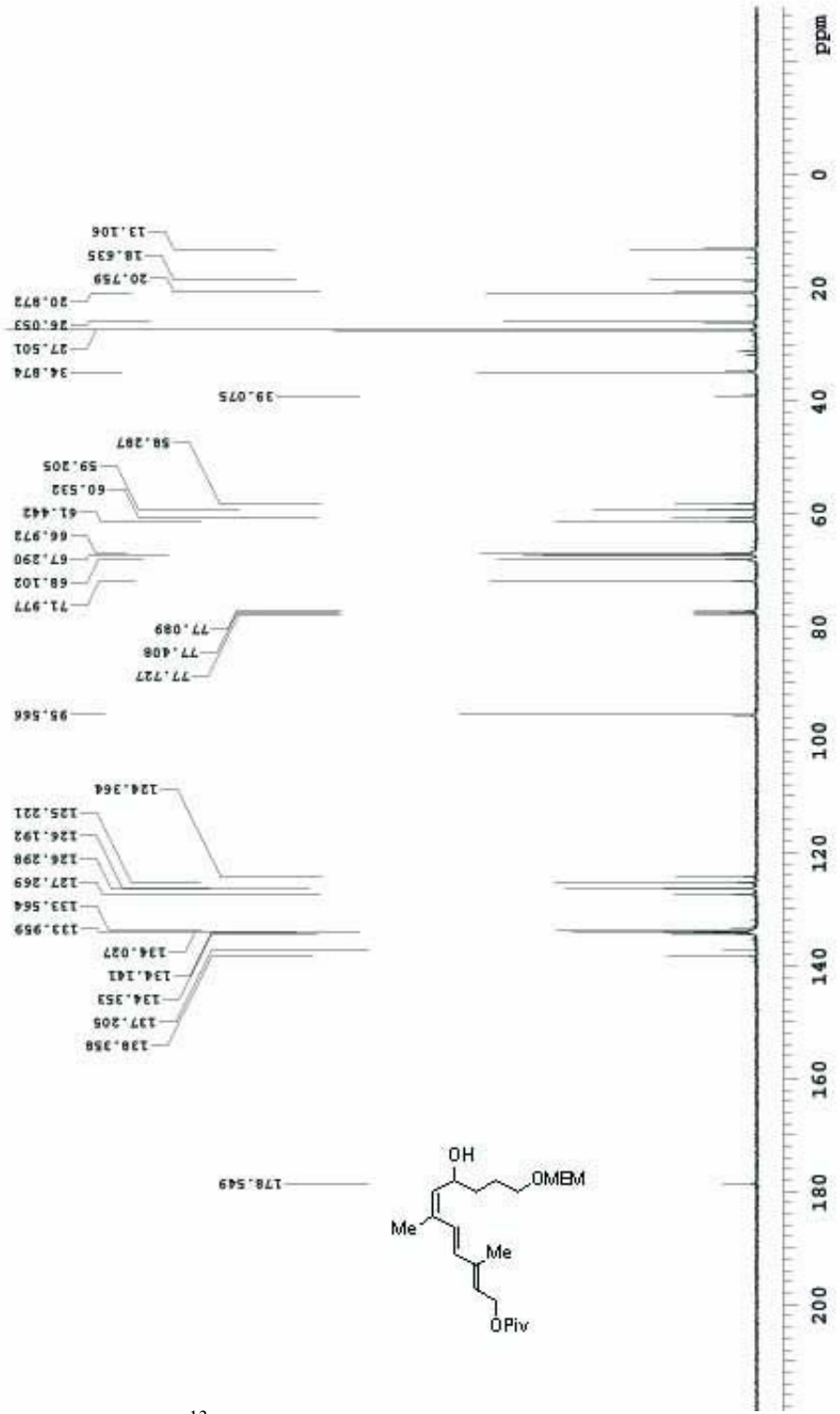
Spectrum 3. 33: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **46**



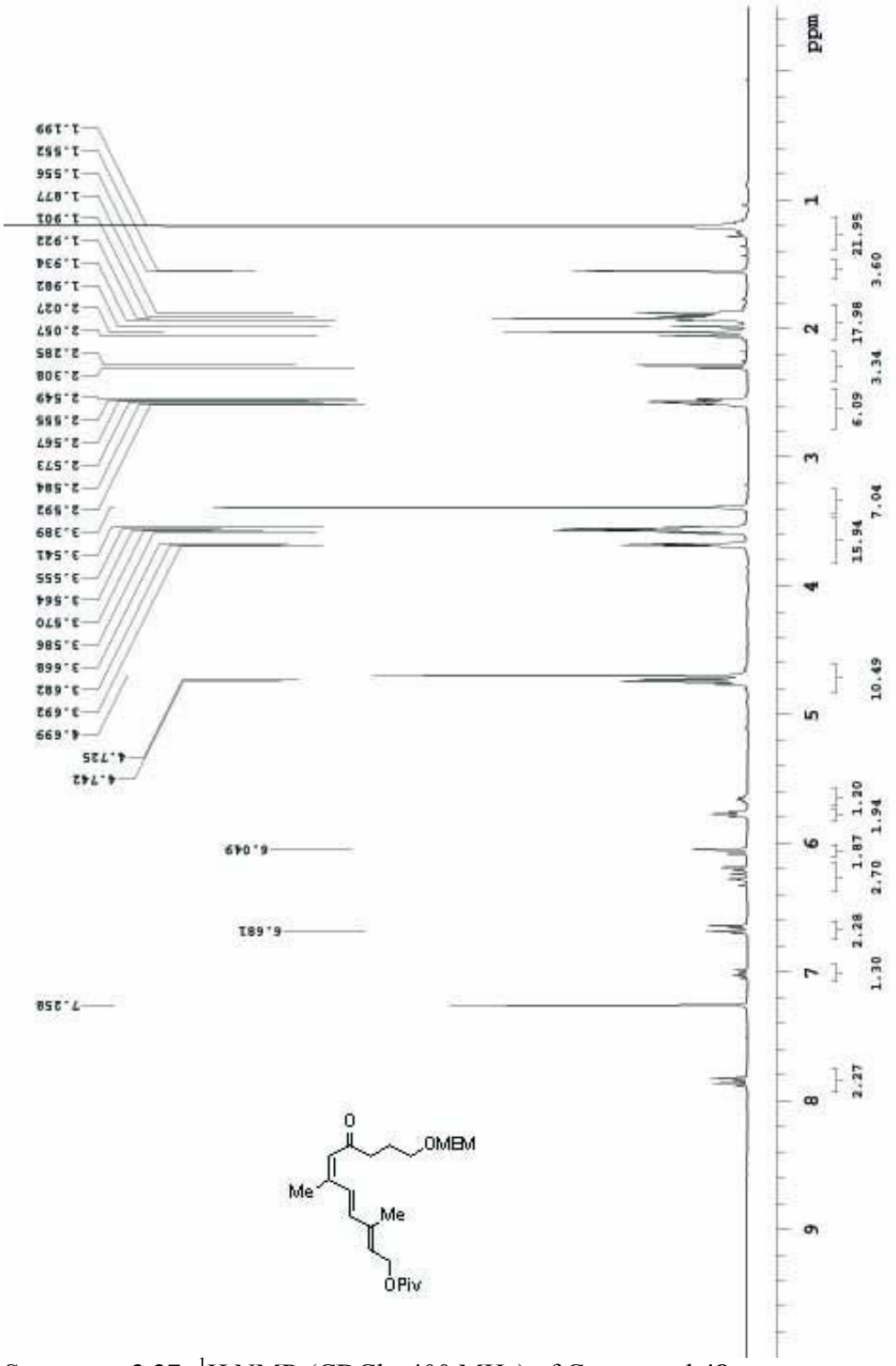
Spectrum 3.34: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **46**



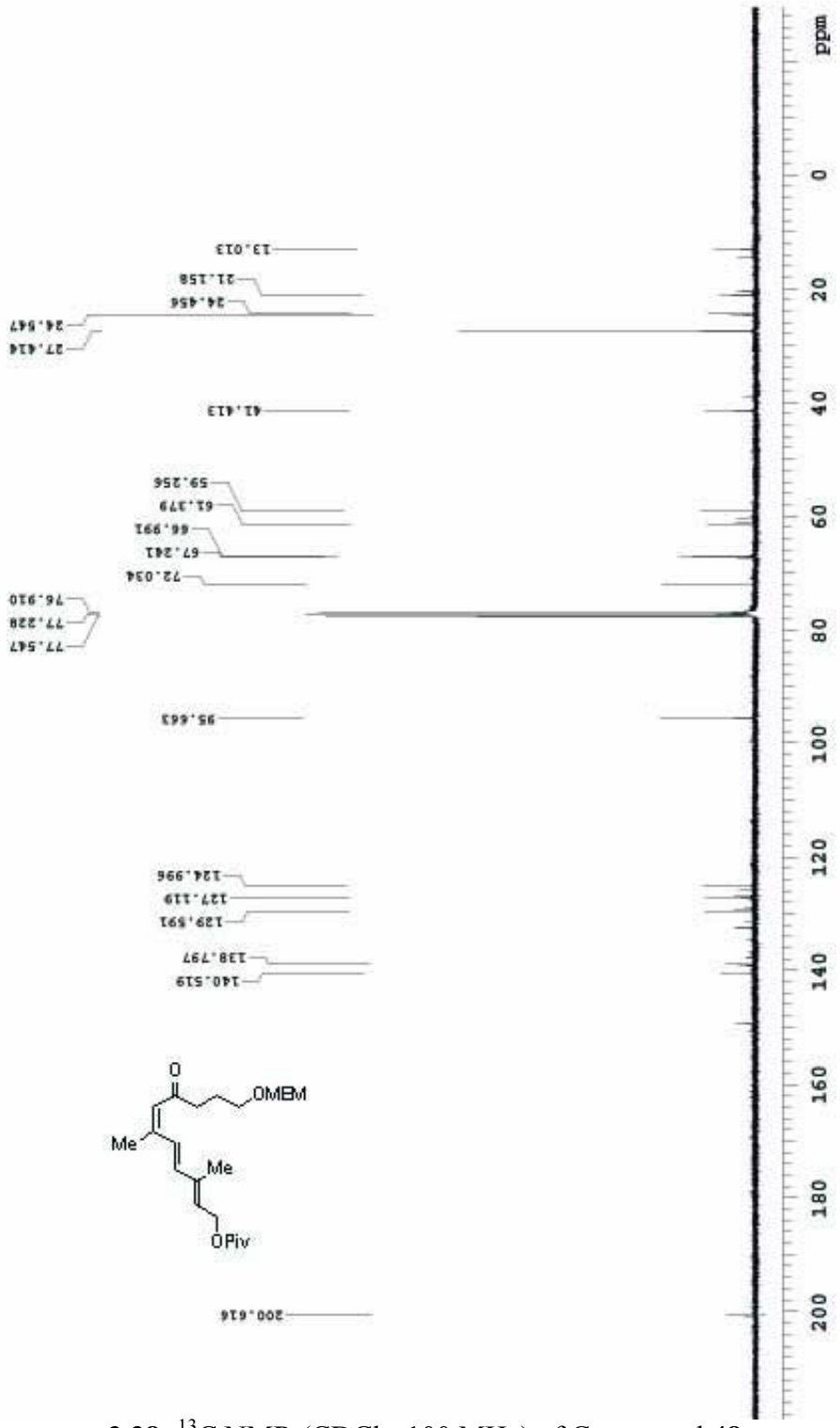
Spectrum 3.35: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **47**



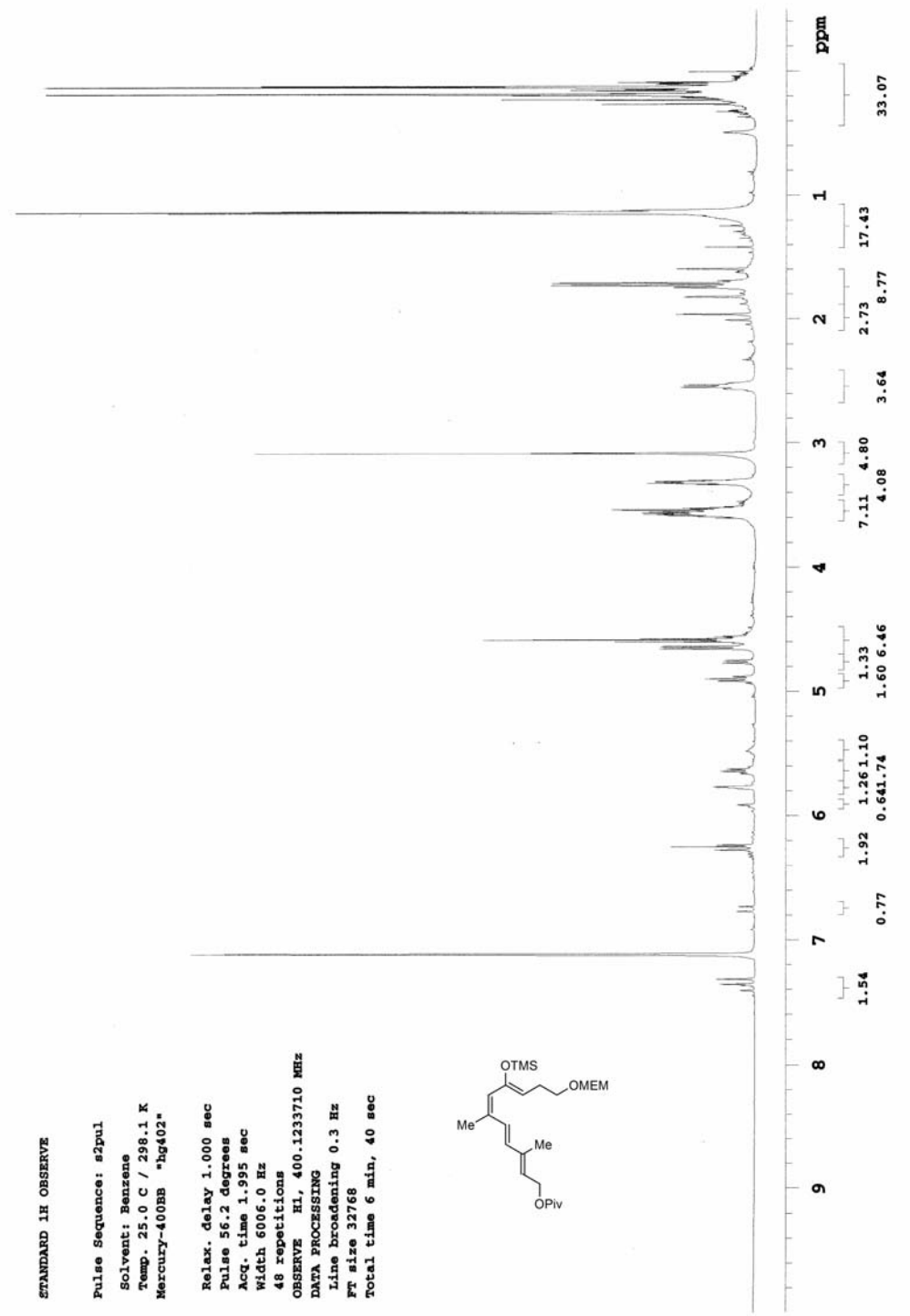
Spectrum 3. 36: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **47**



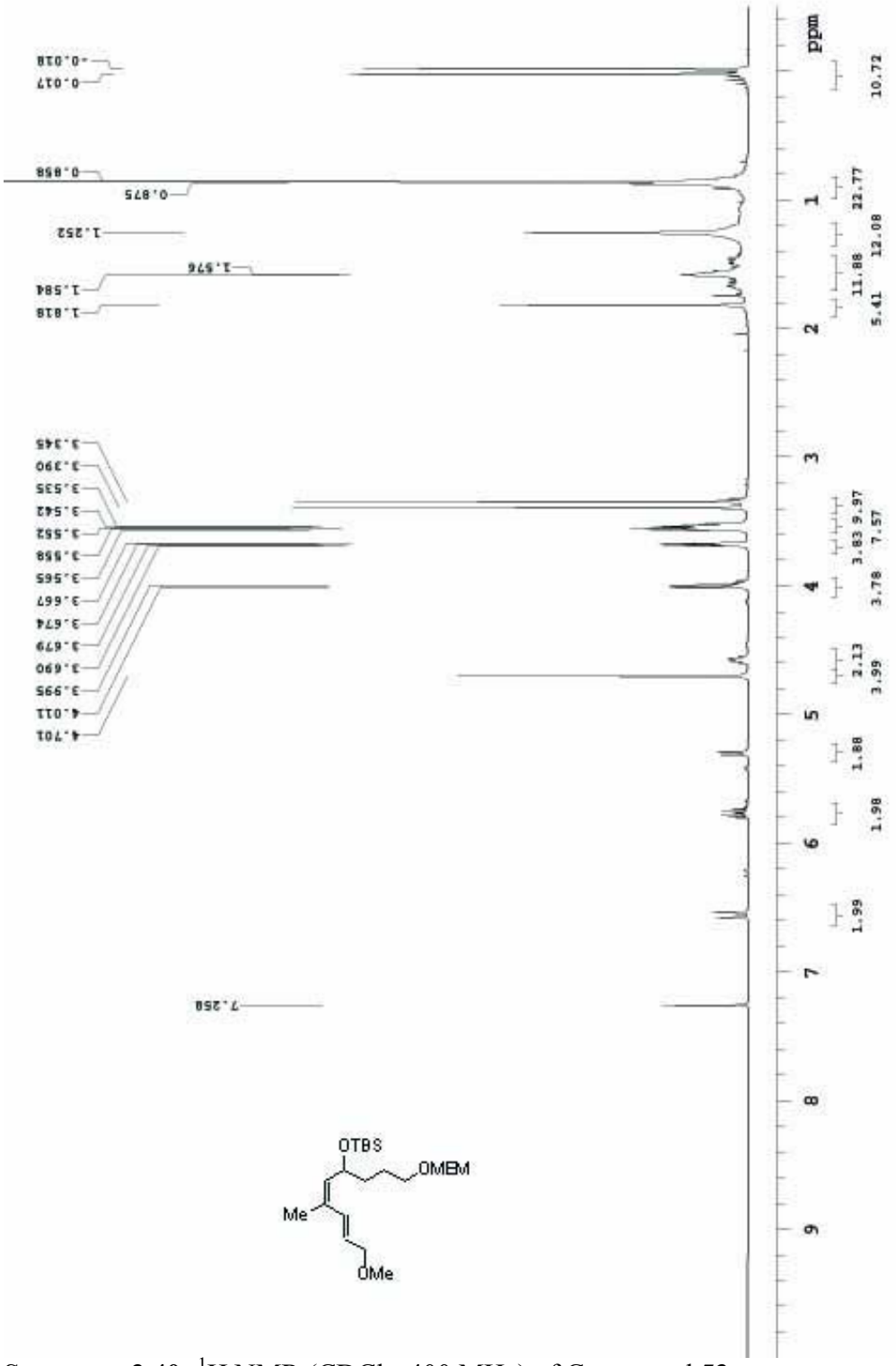
Spectrum 3.37: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **48**



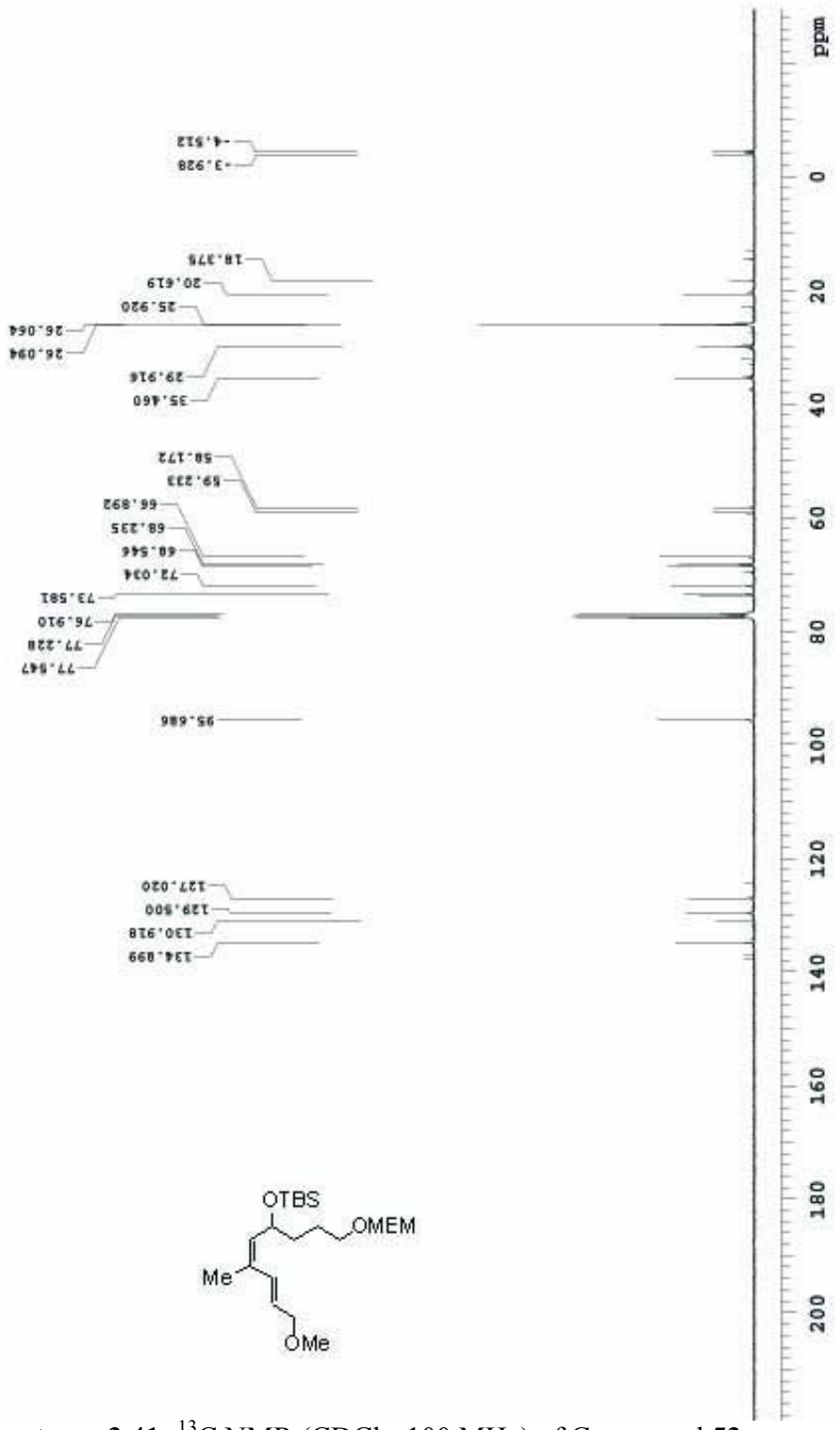
Spectrum 3.38: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **48**



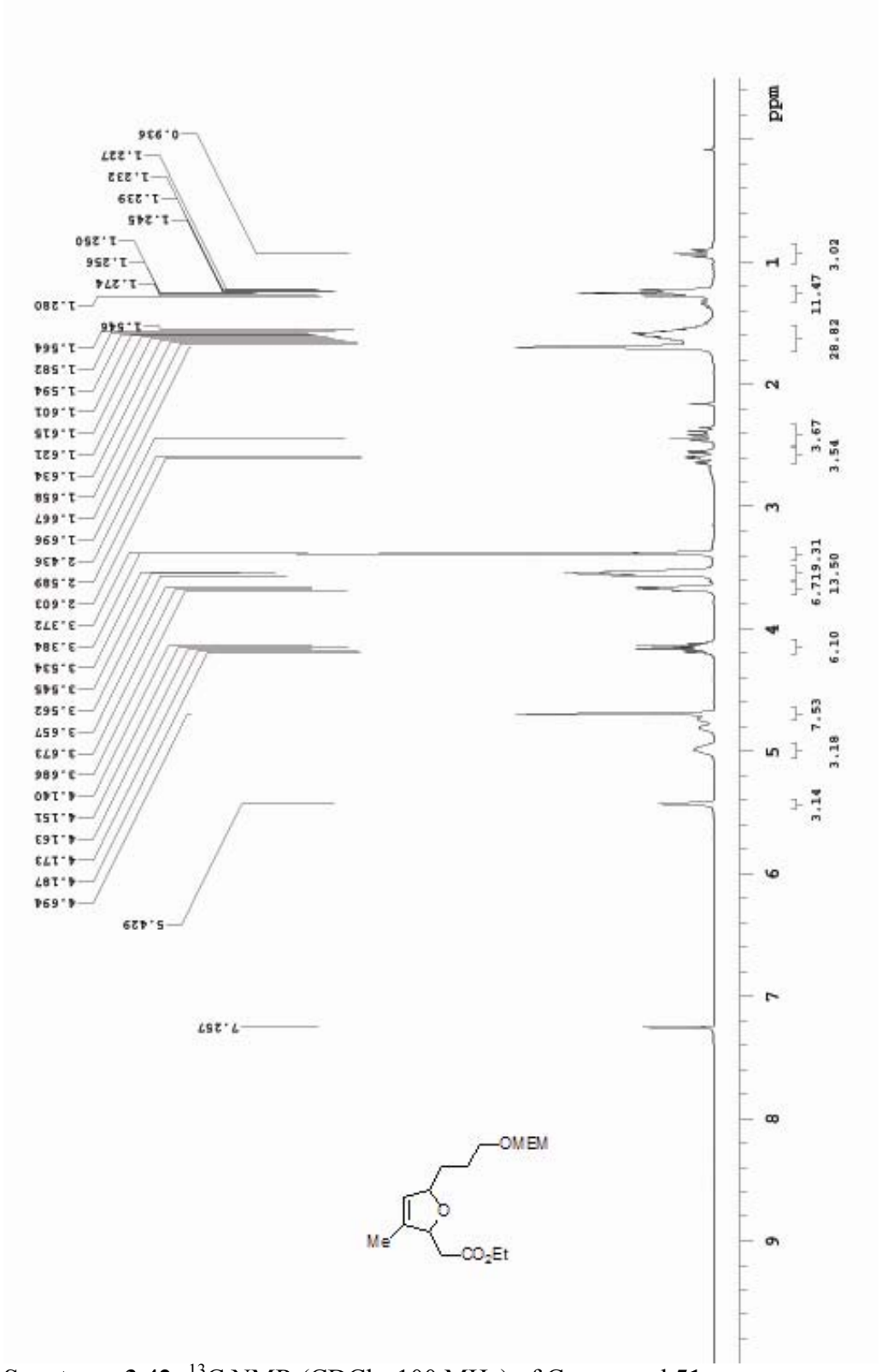
Spectrum 3.39: ^{13}H NMR ($CDCl_3$, 400 MHz) of Compound **49**



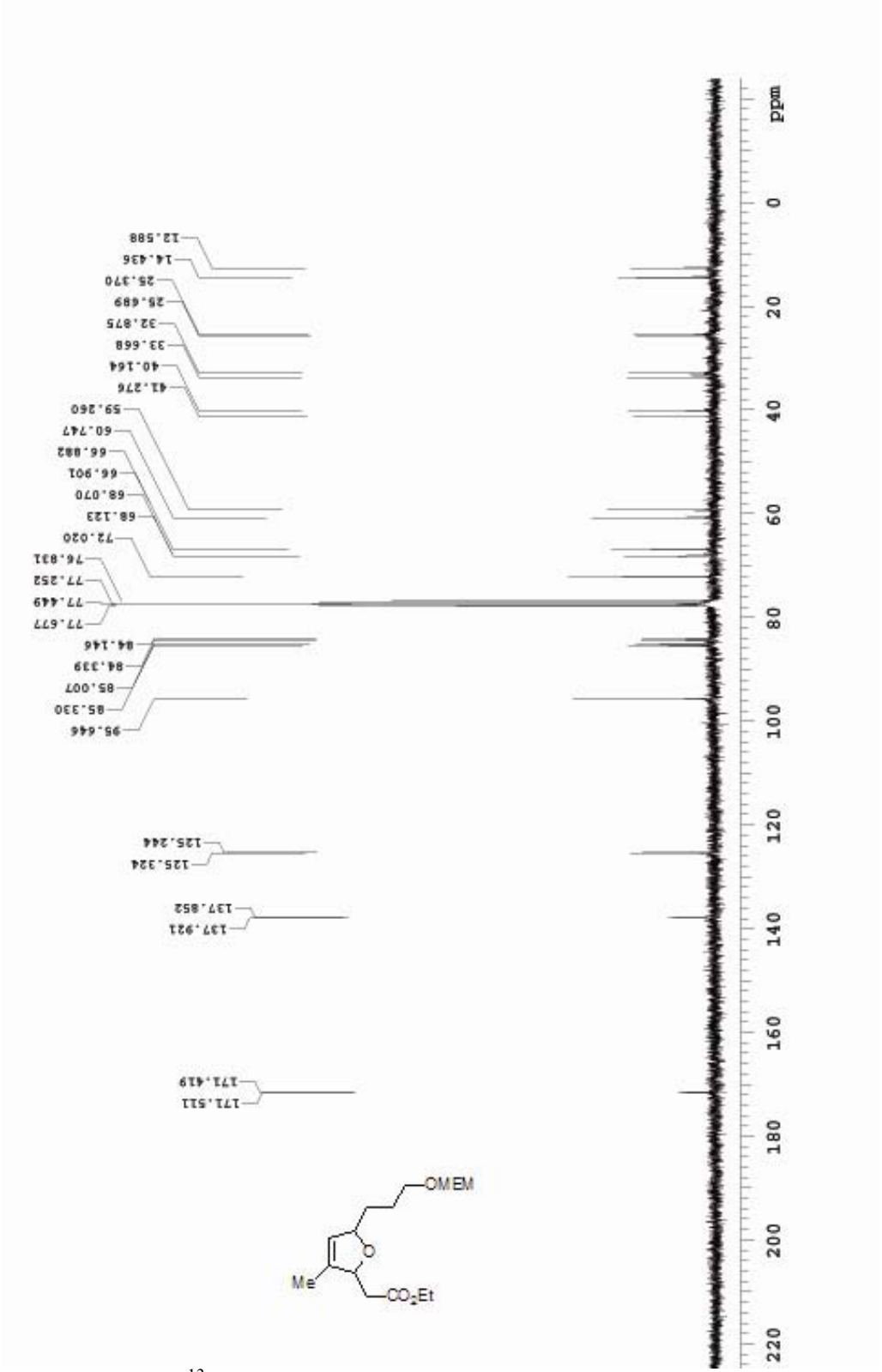
Spectrum 3.40: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **53**



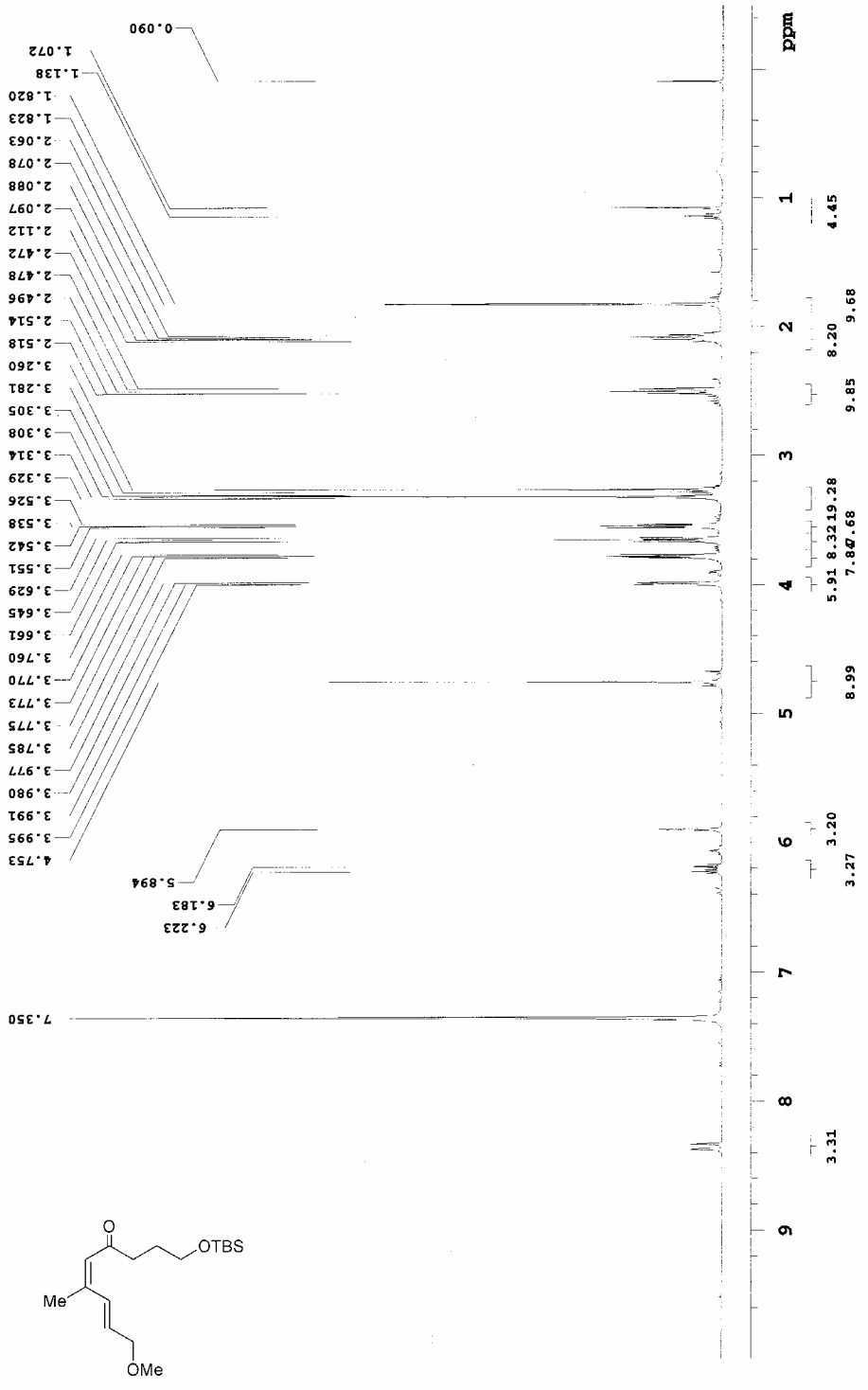
Spectrum 3.41: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **53**



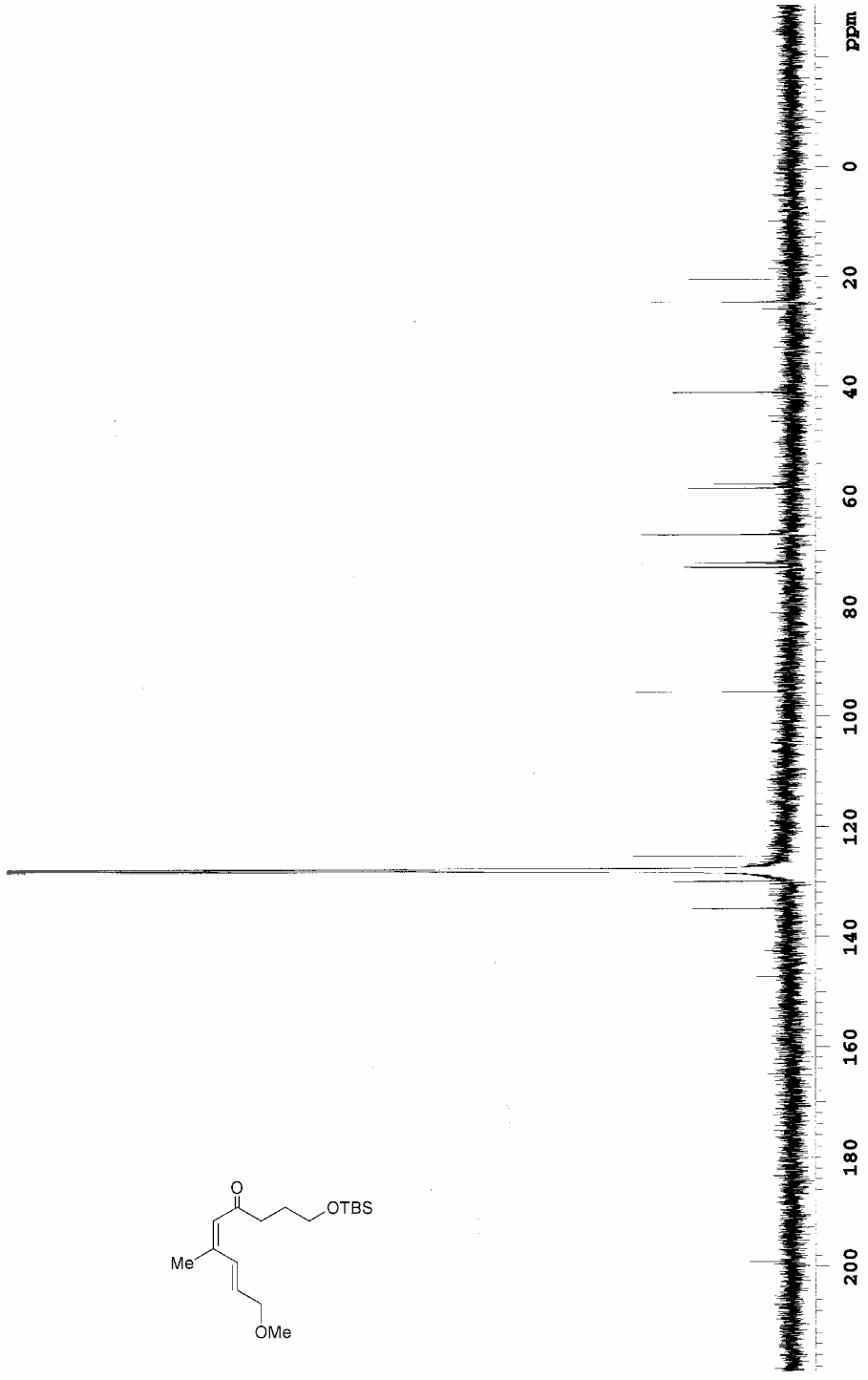
Spectrum 3.42: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **51**



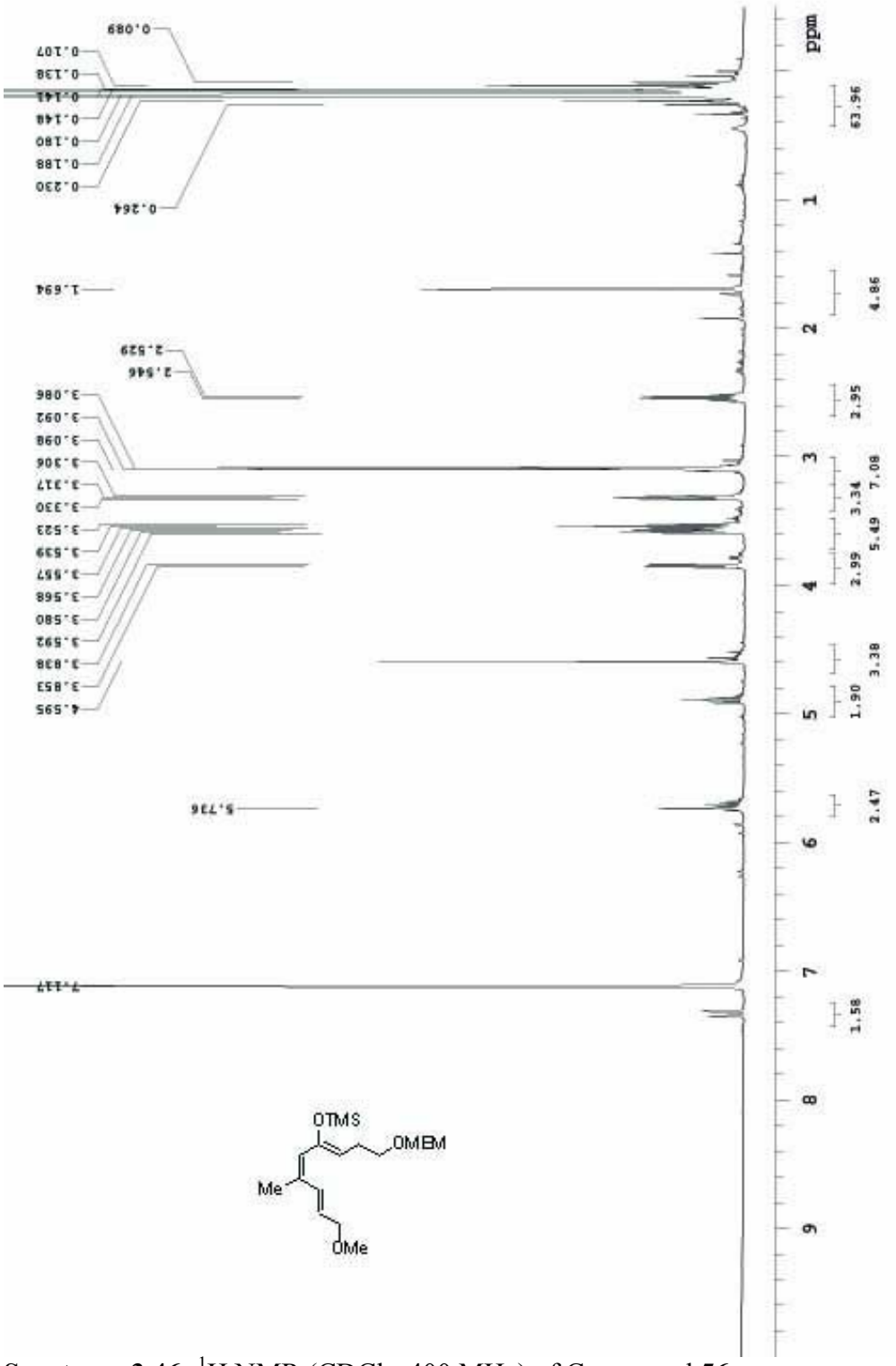
Spectrum 3.43: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **51**



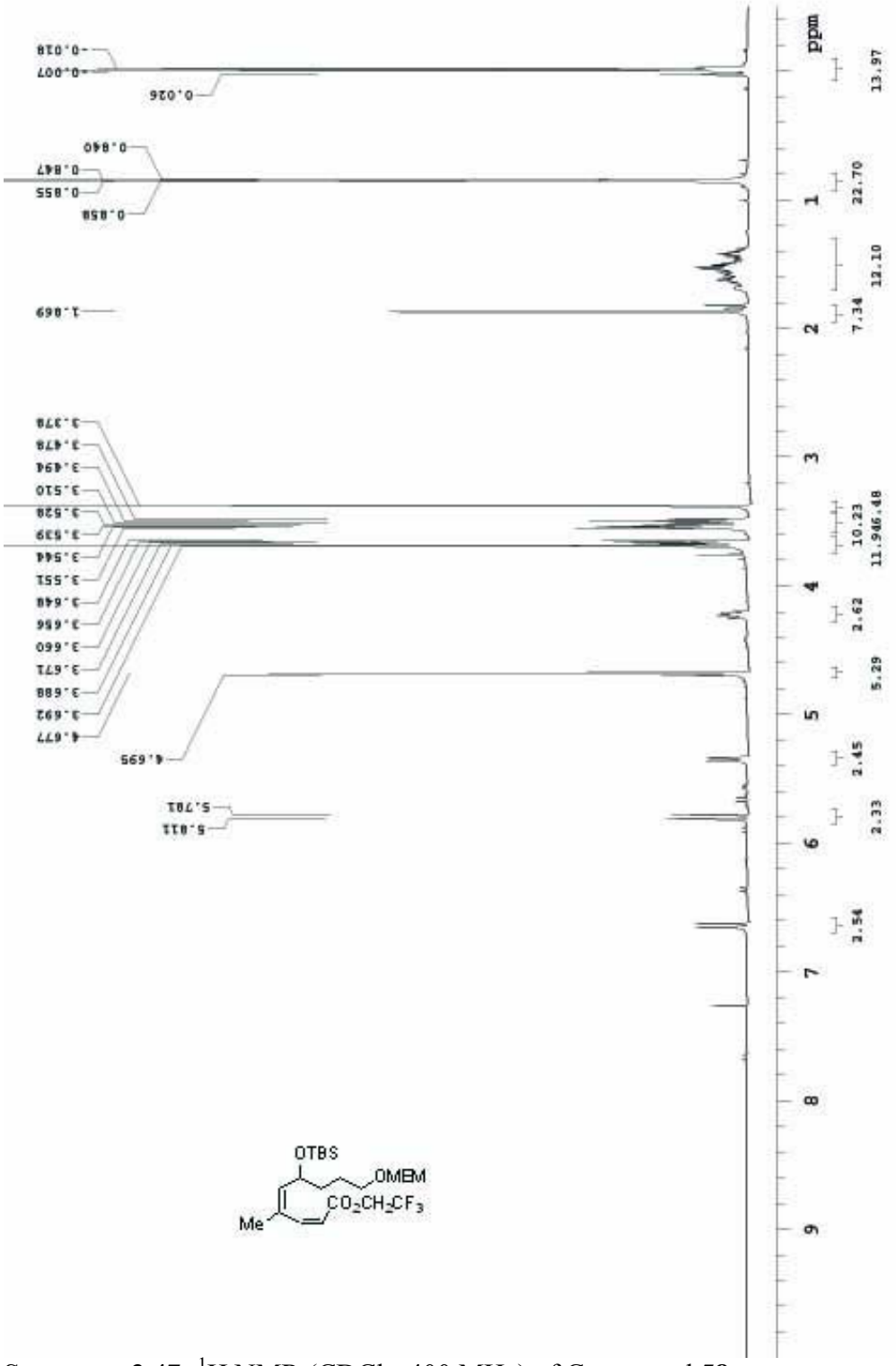
Spectrum 3.44: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **55**



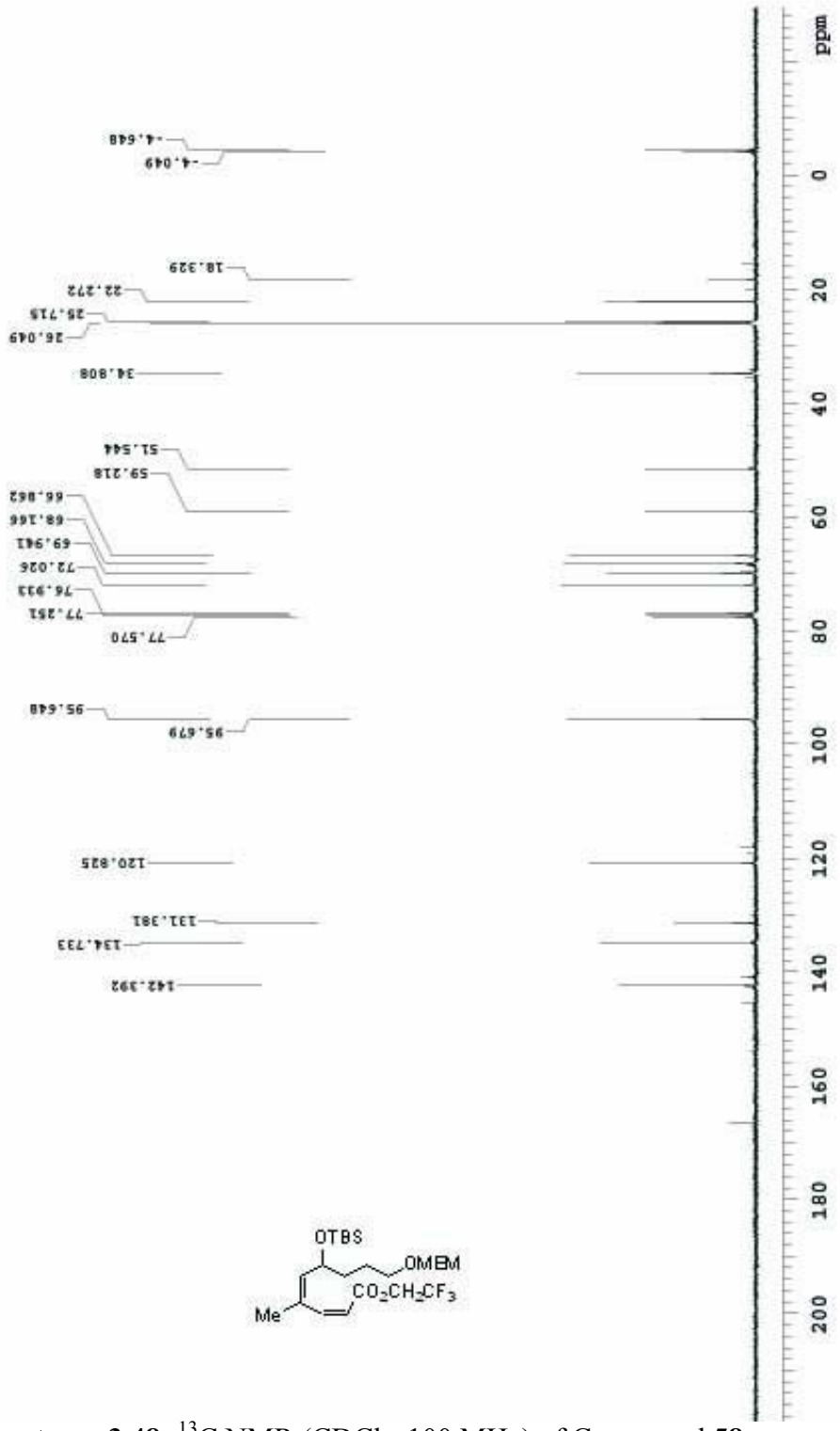
Spectrum 3.45: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **55**



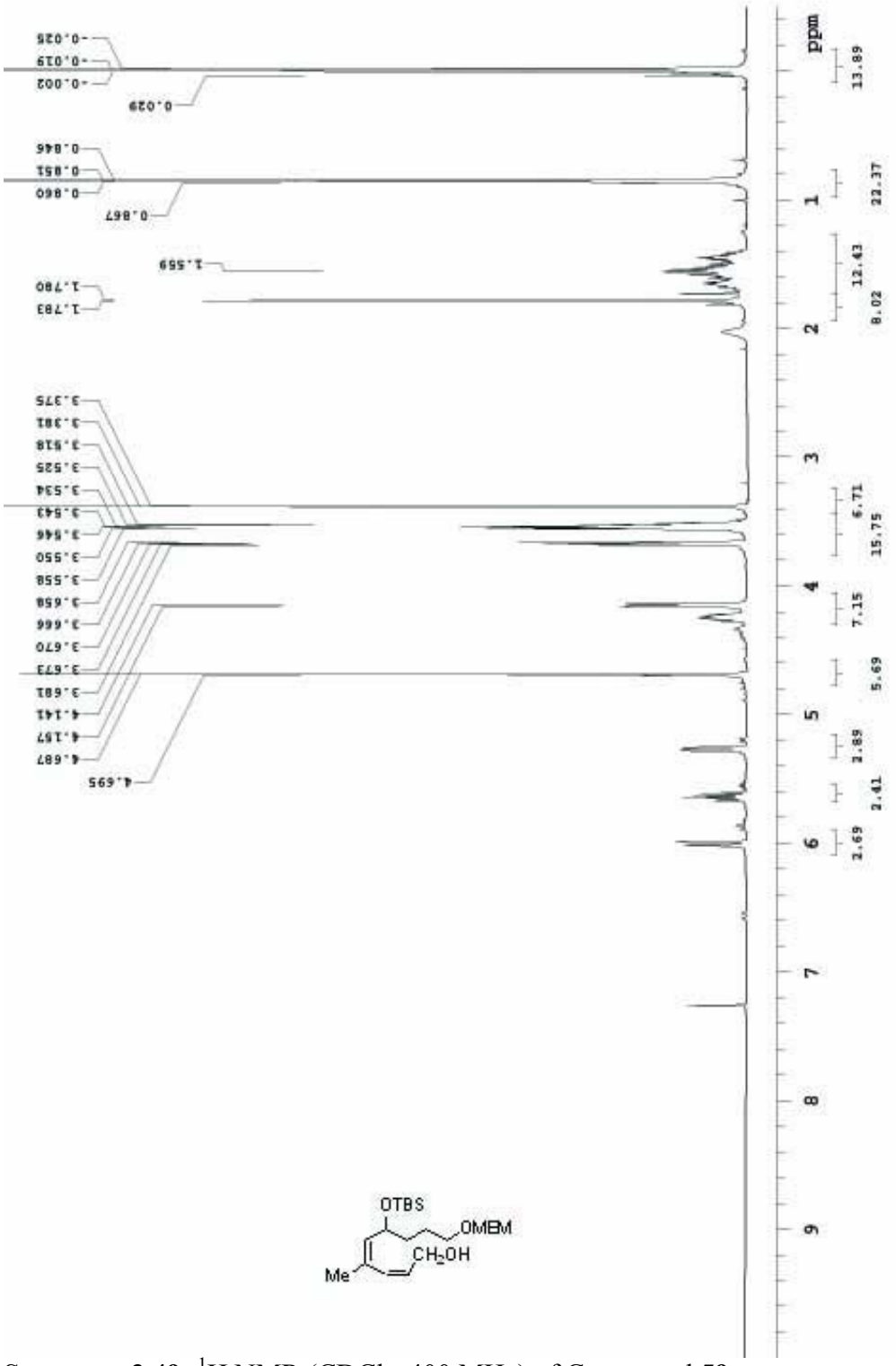
Spectrum 3.46: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **56**



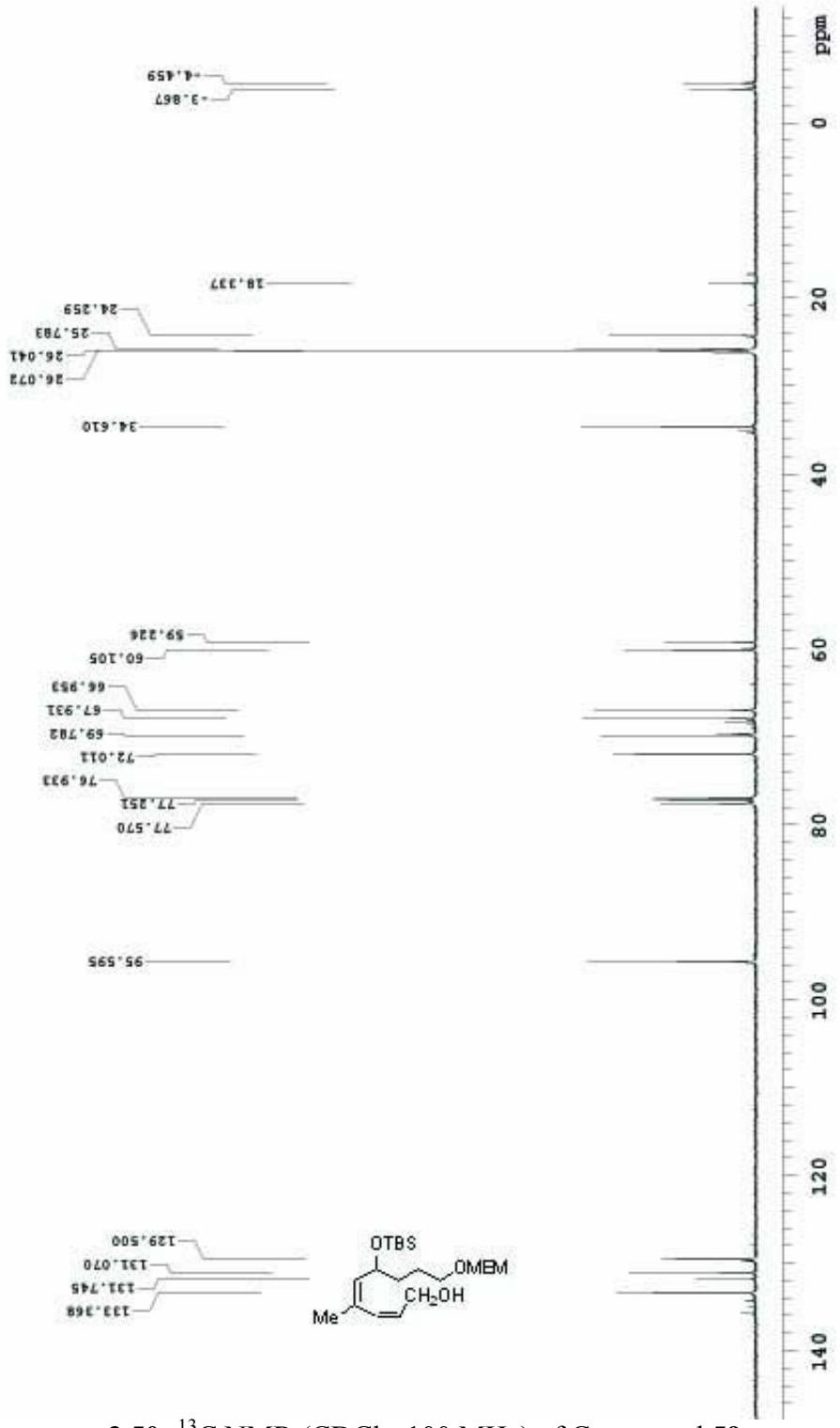
Spectrum 3.47: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **58**



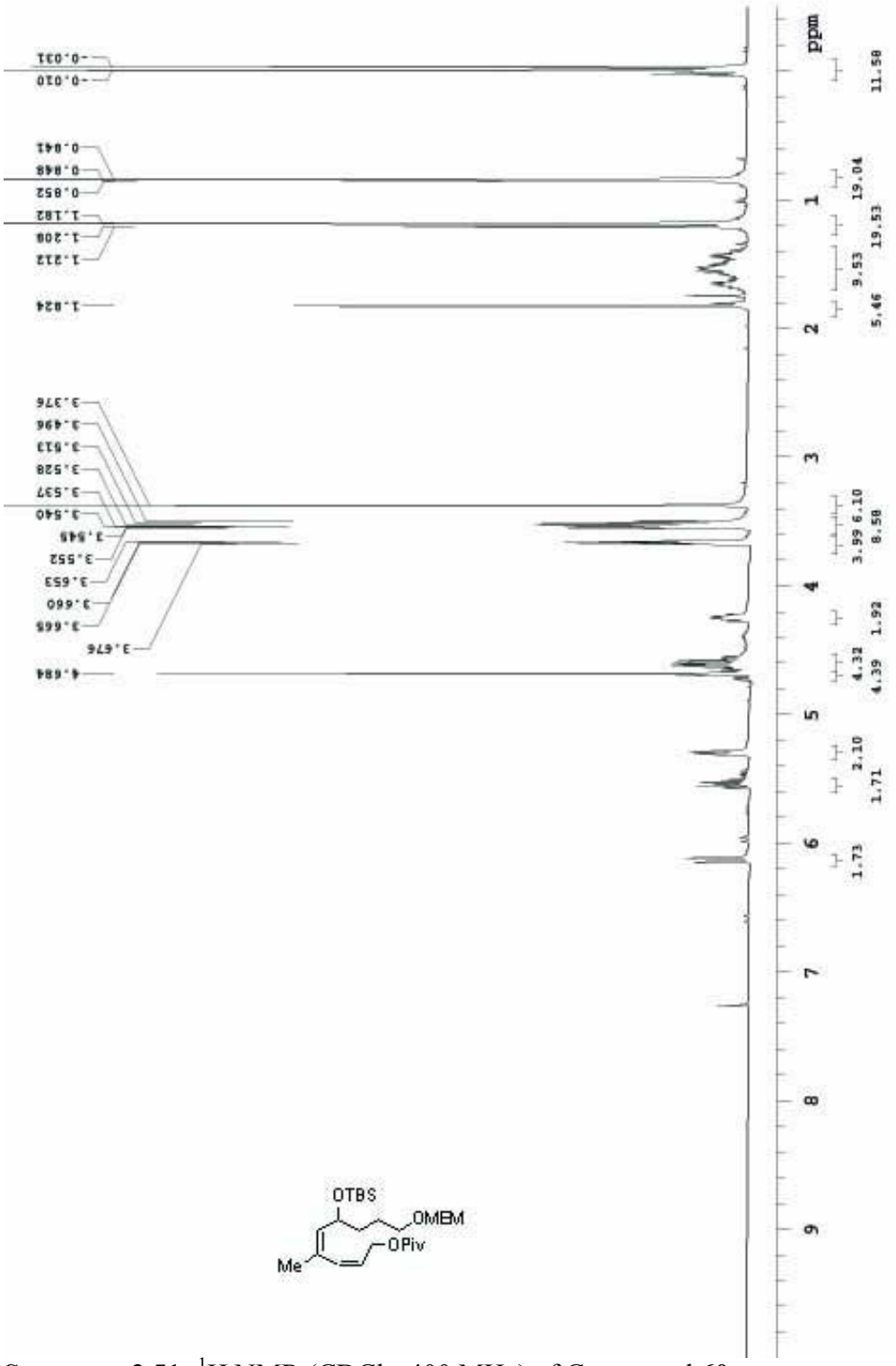
Spectrum 3.48: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **58**



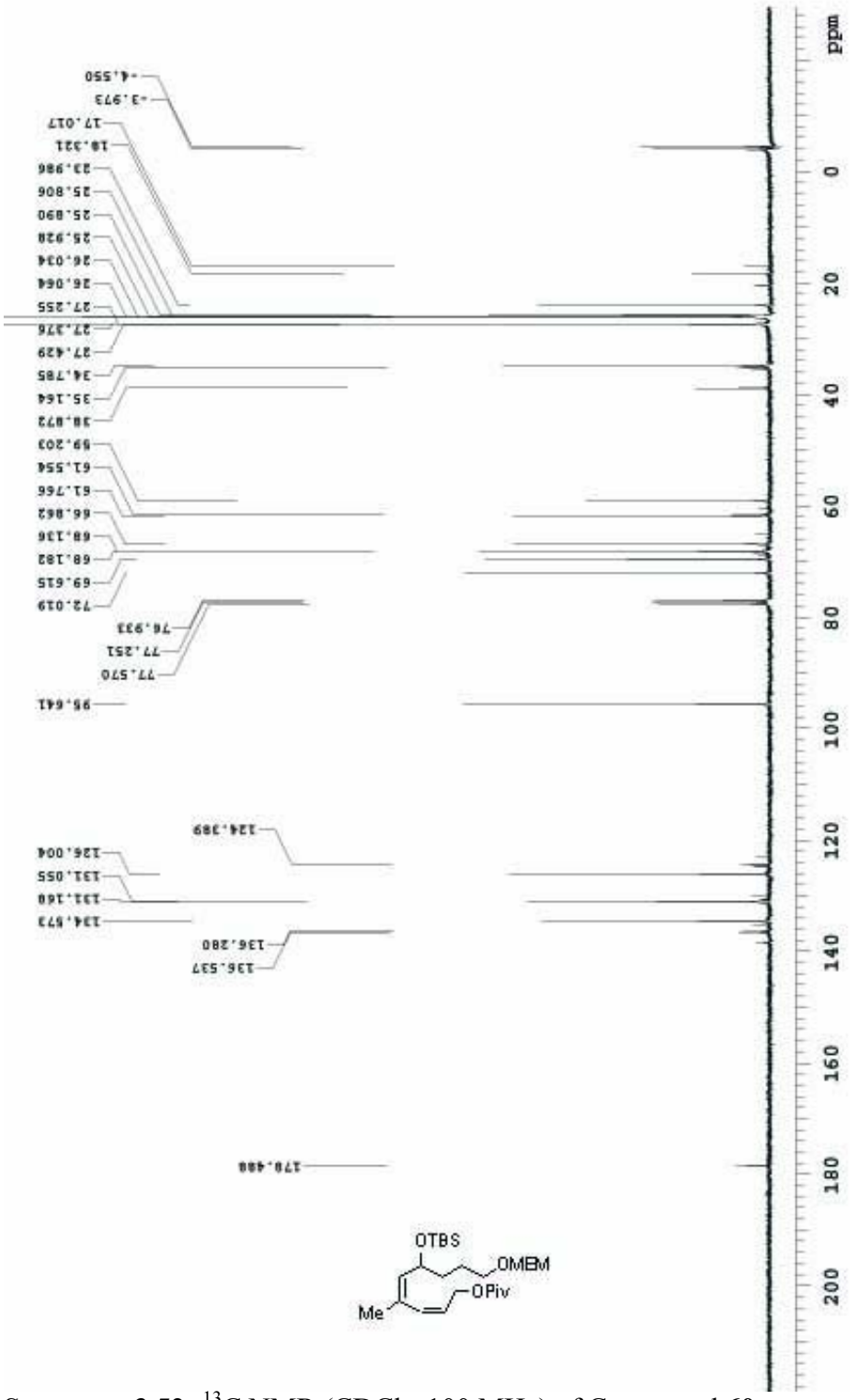
Spectrum 3.49: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **59**



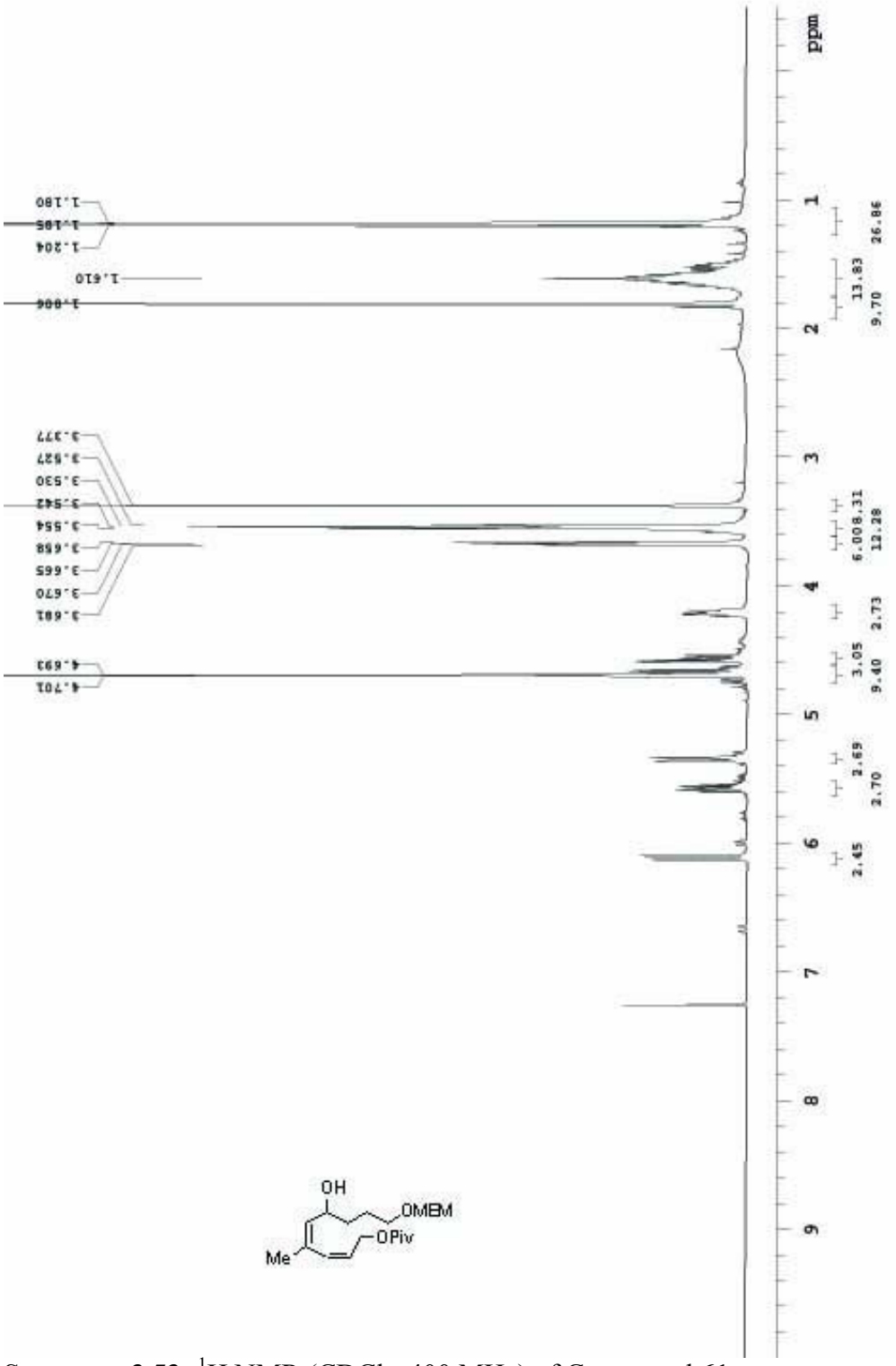
Spectrum 3.50: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **59**



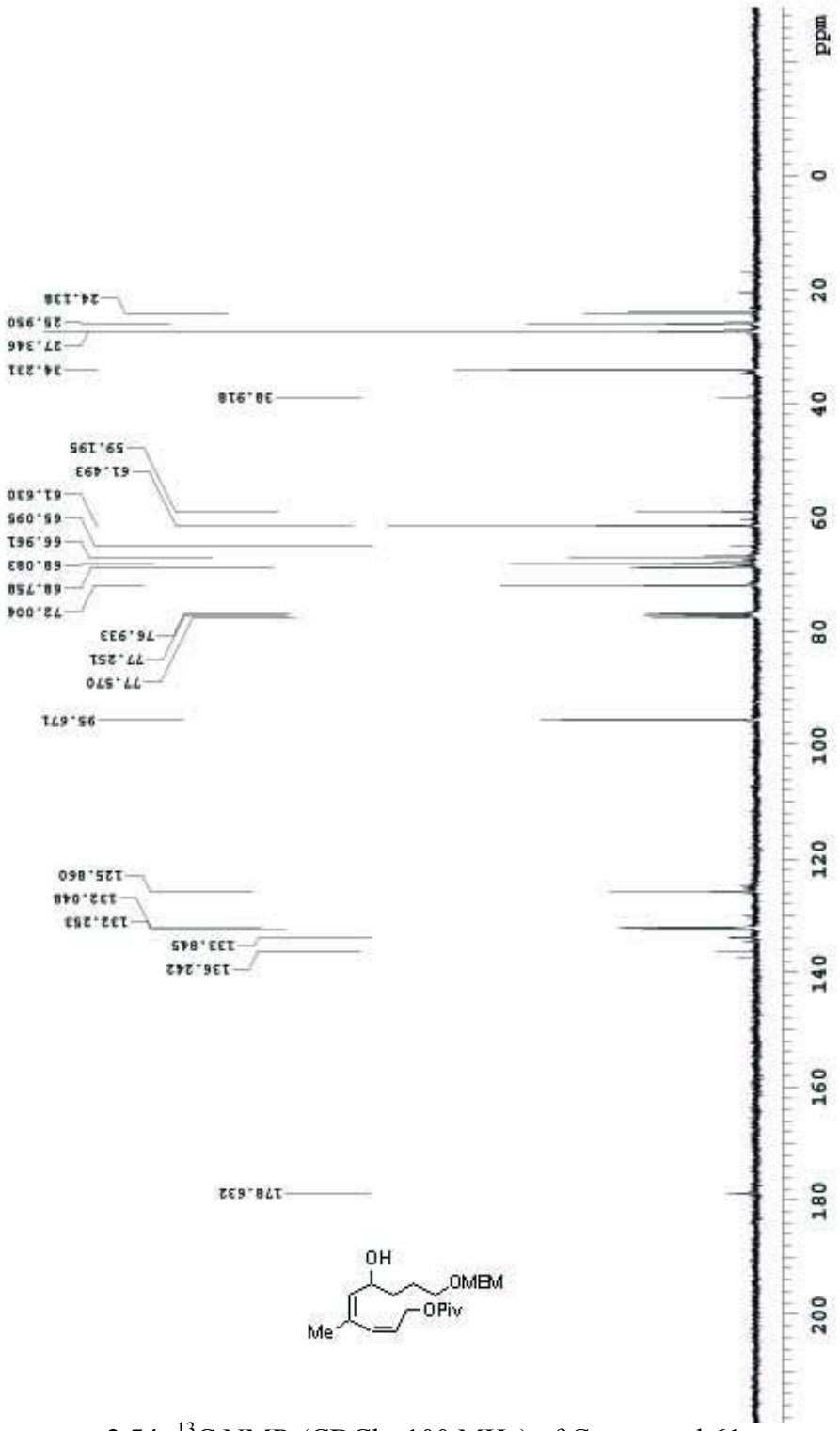
Spectrum 3.51: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **60**



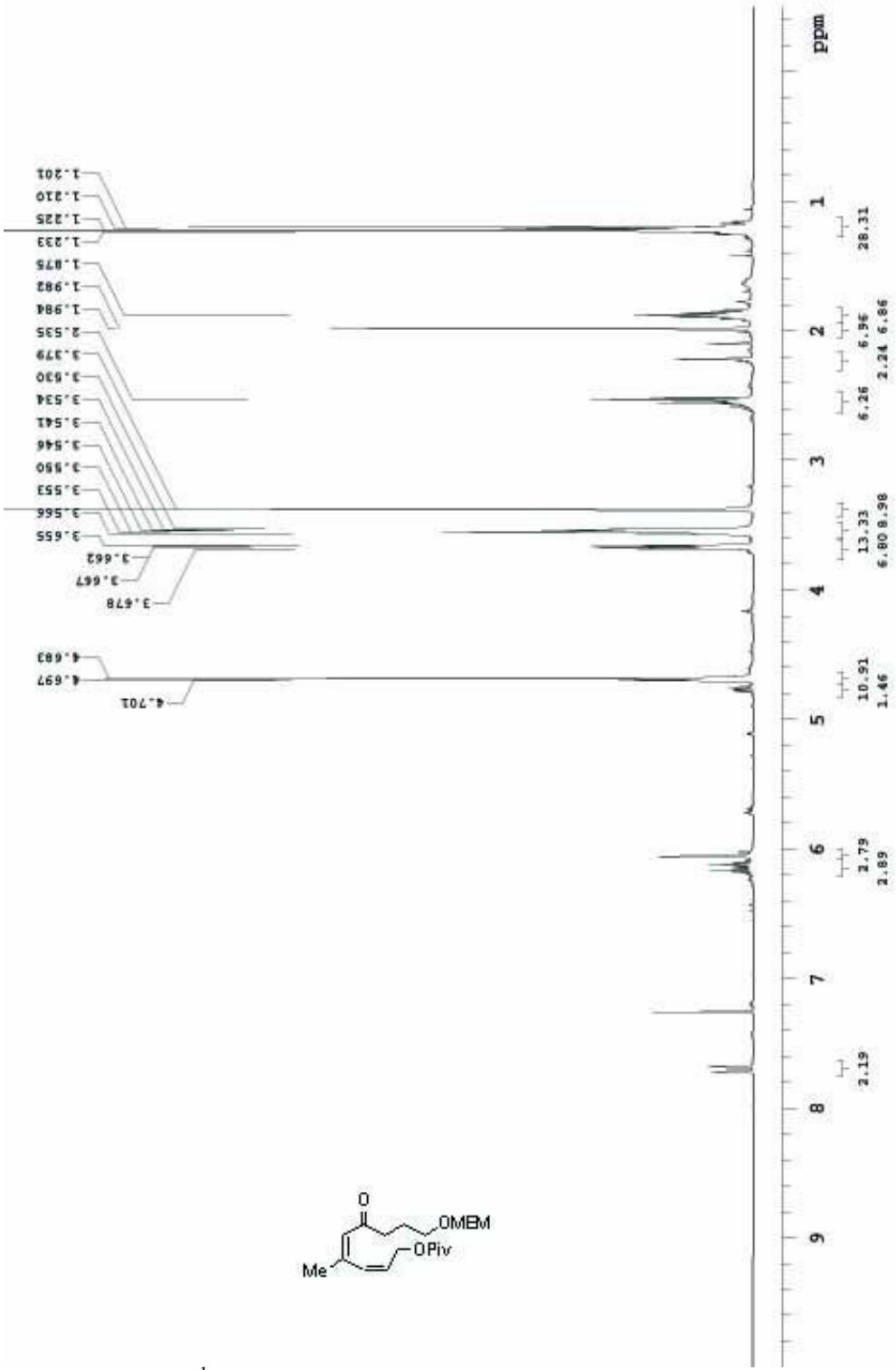
Spectrum 3.52: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **60**



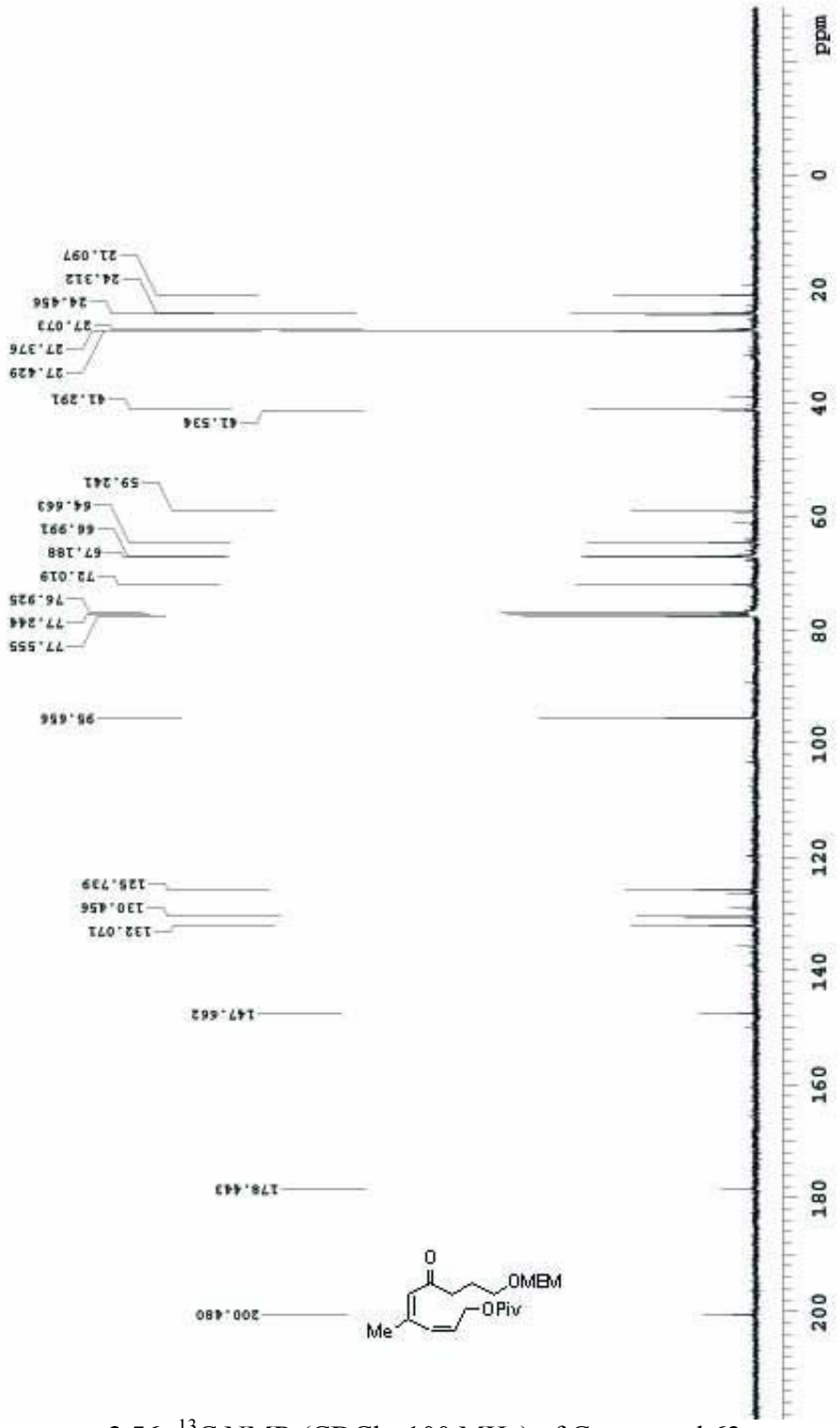
Spectrum 3.53: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **61**



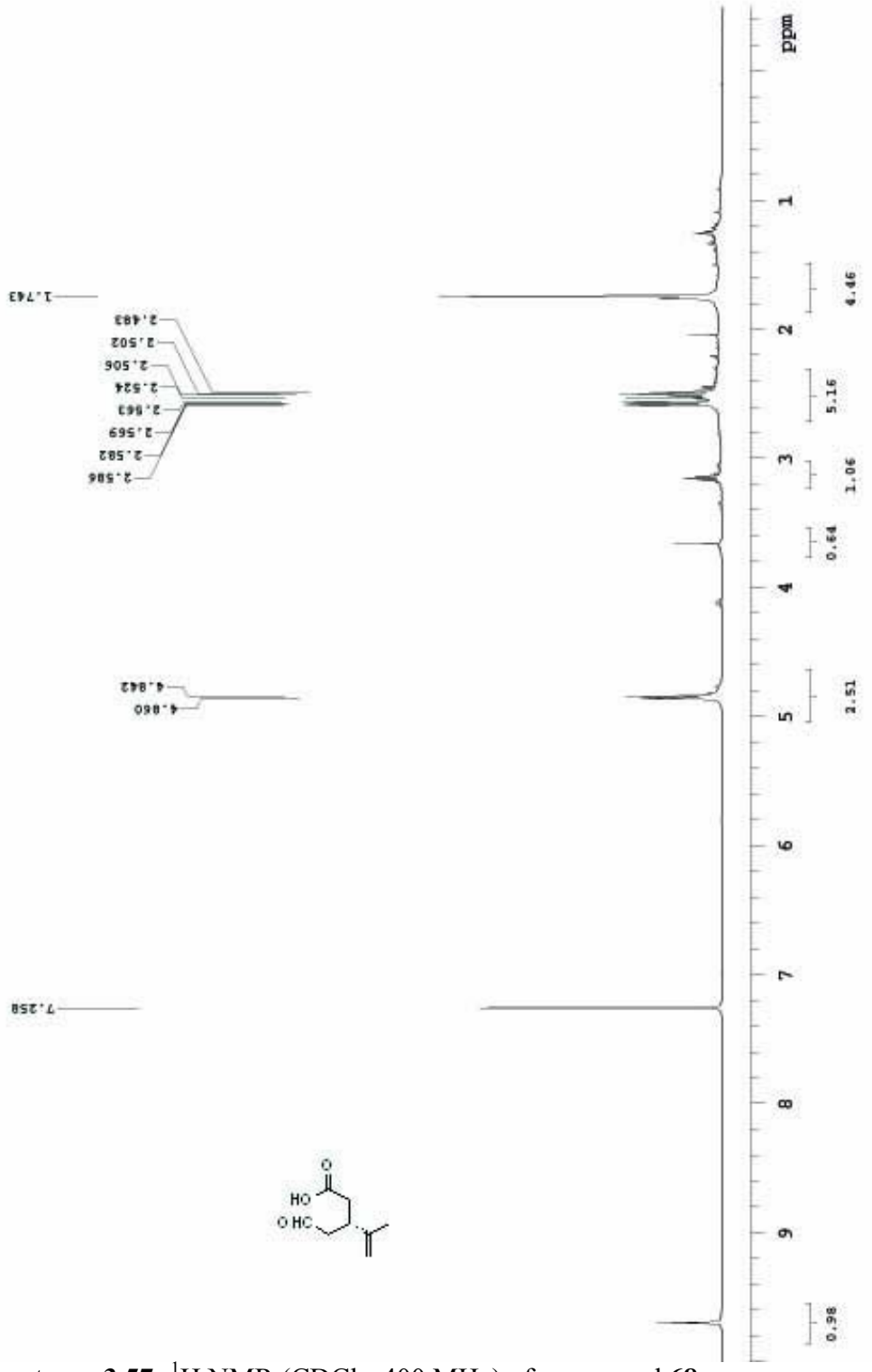
Spectrum 3.54: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **61**



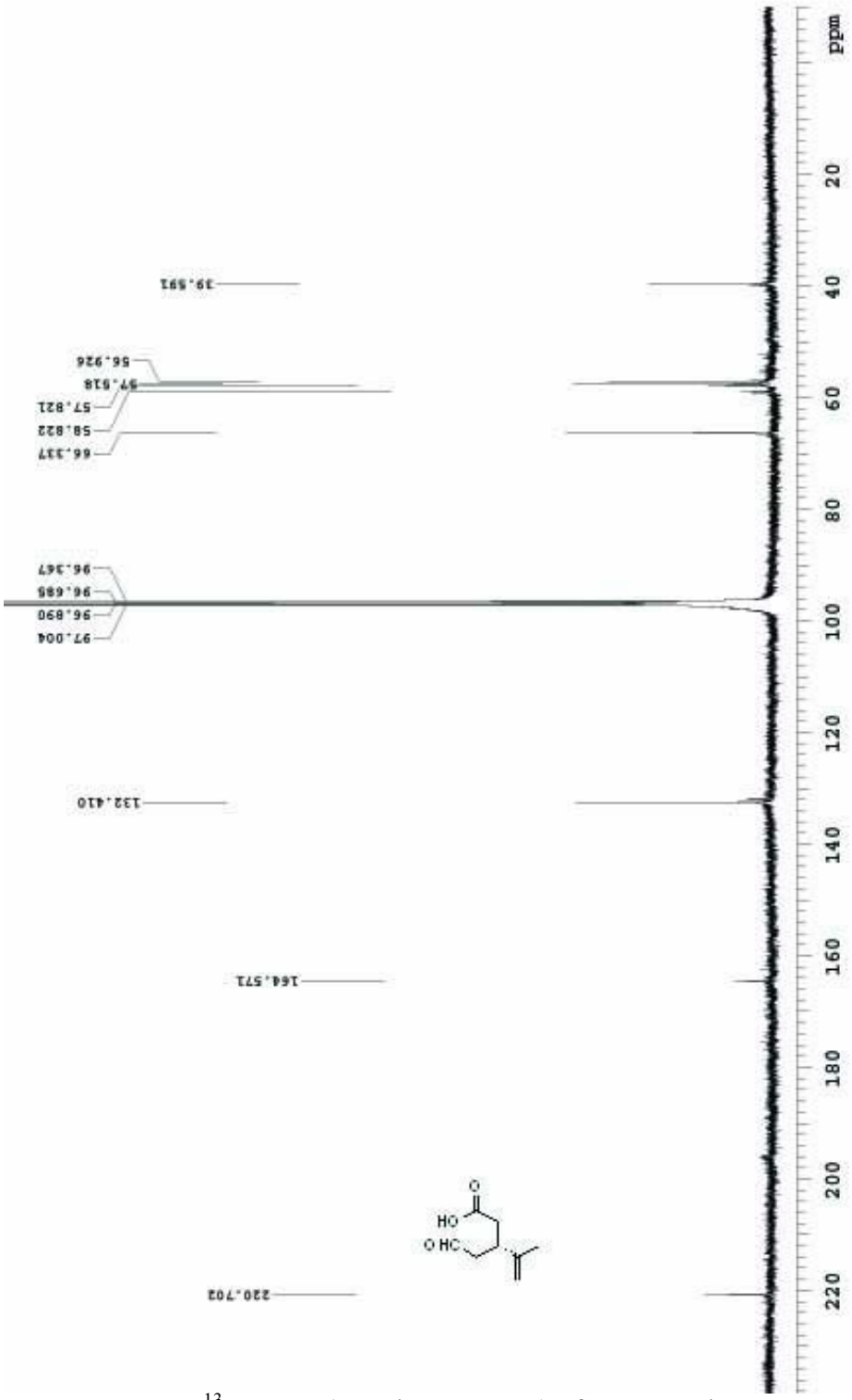
Spectrum 3.55: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **62**



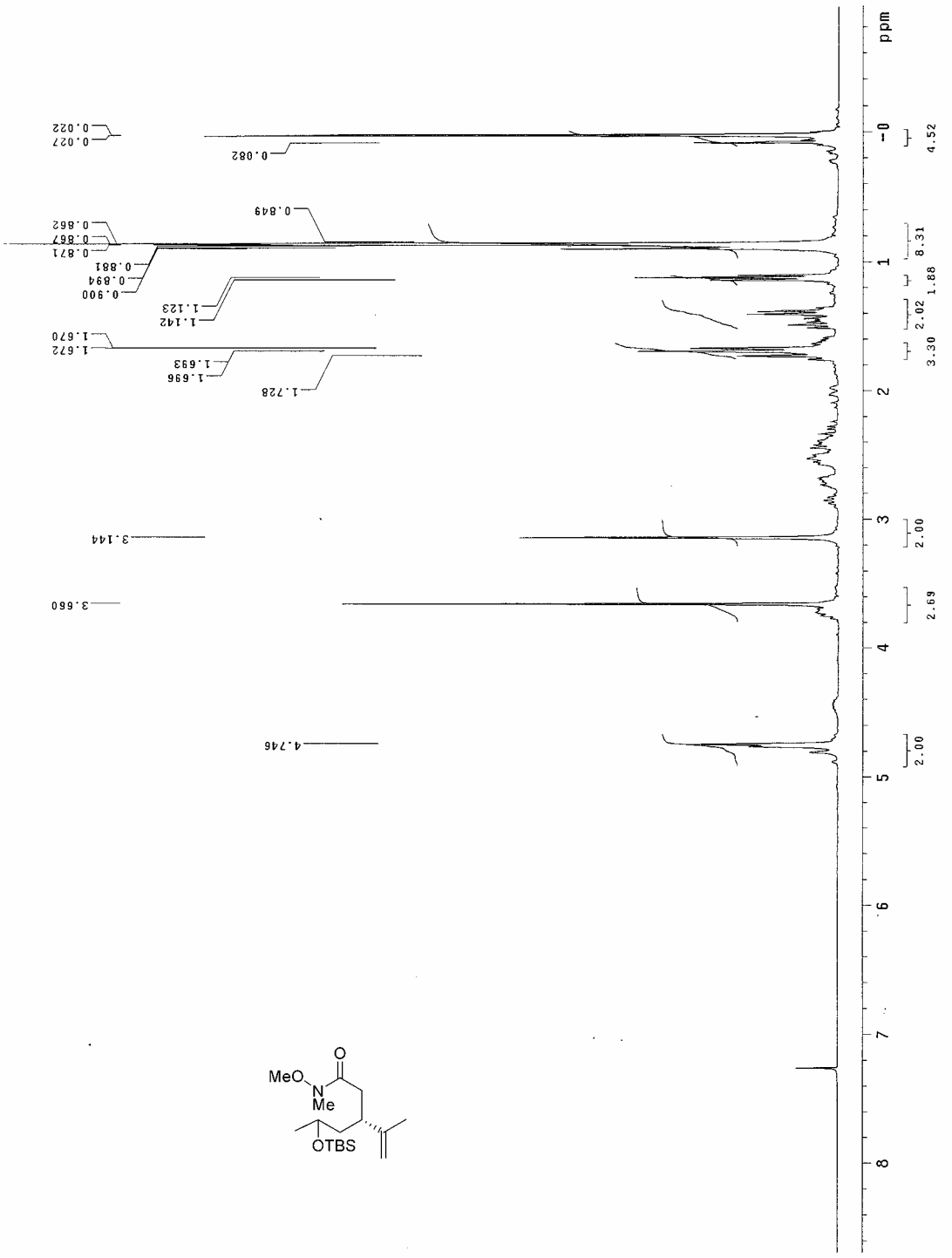
Spectrum 3.56: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **62**



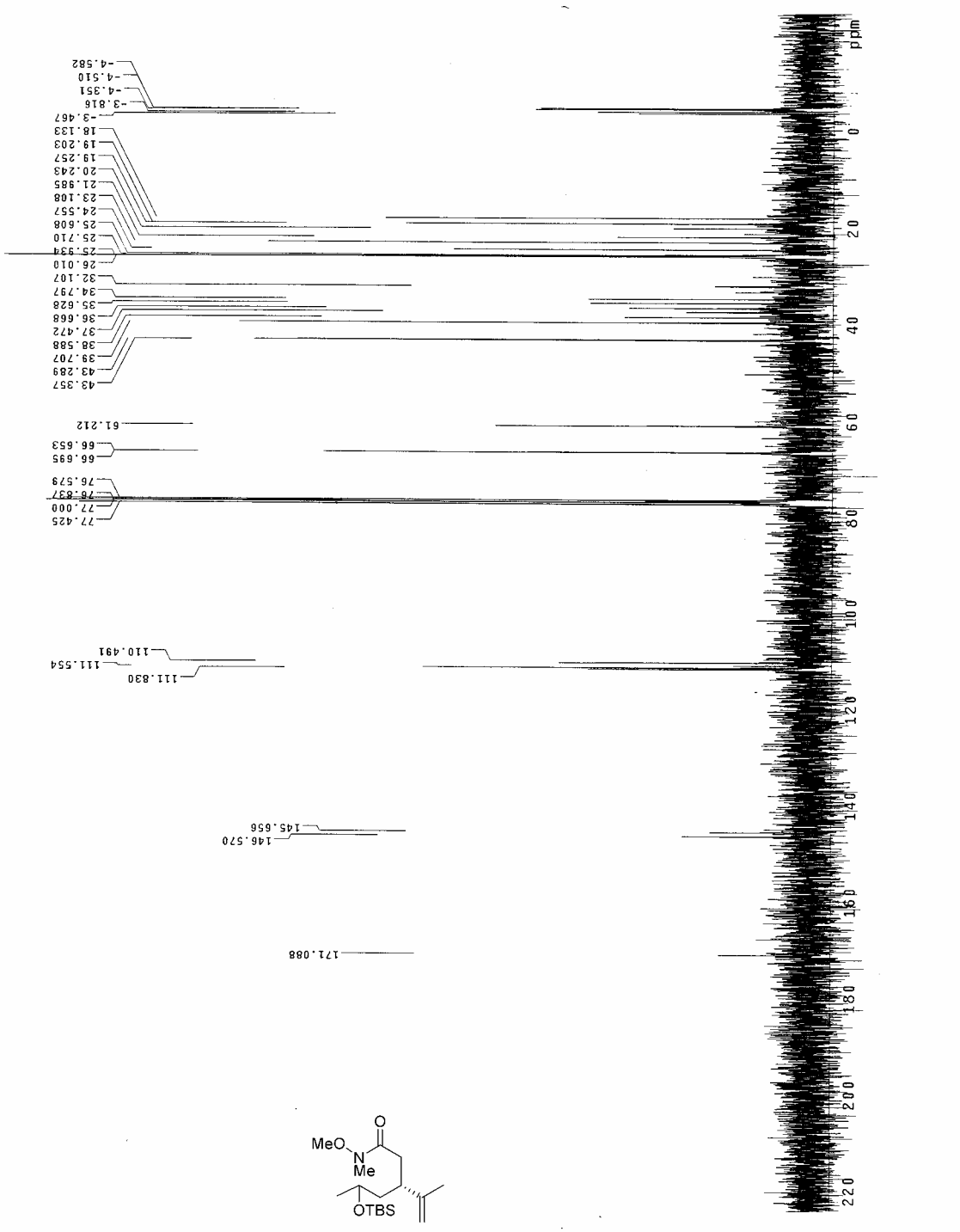
Spectrum 3.57: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **68**



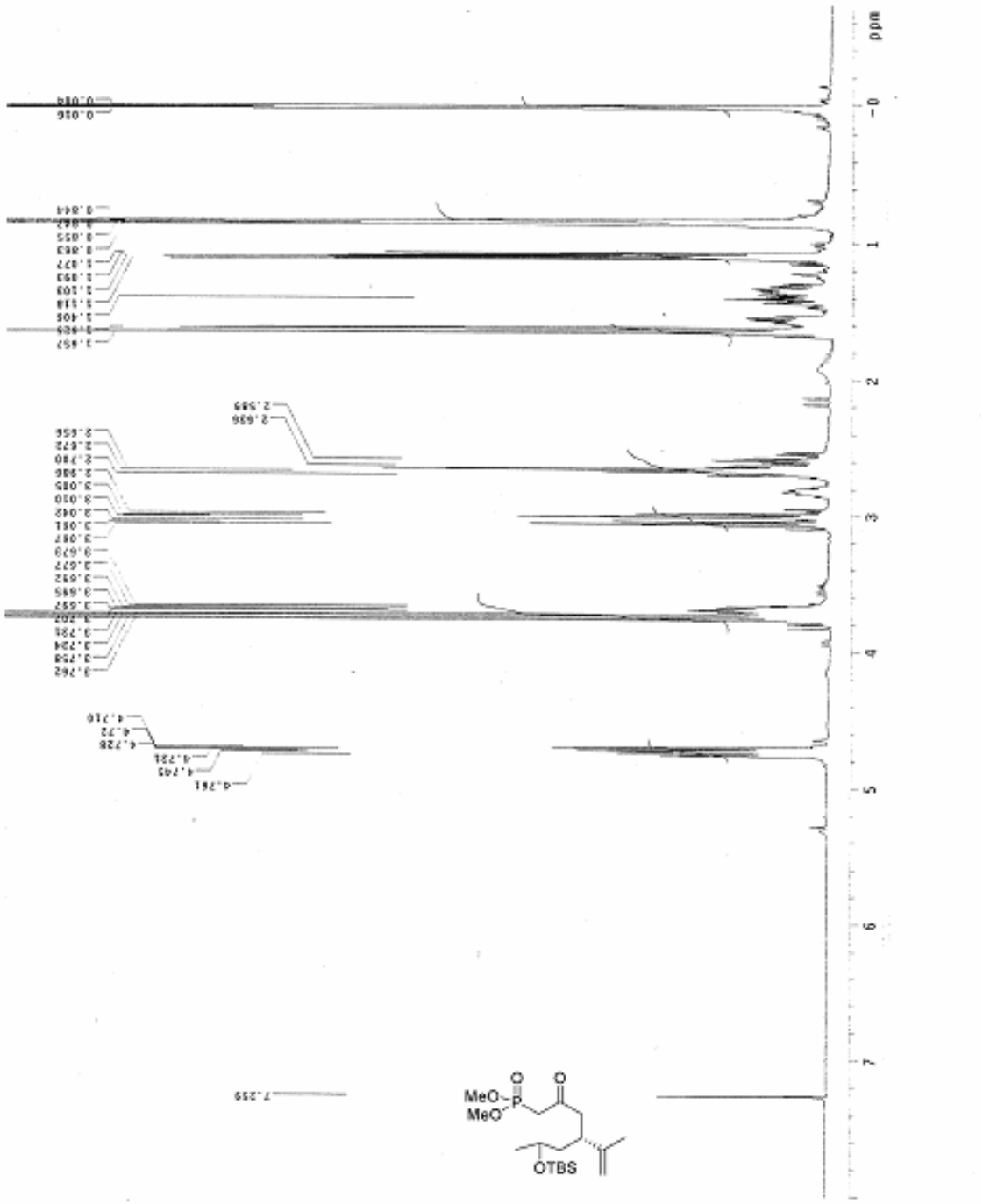
Spectrum 3.58: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **68**



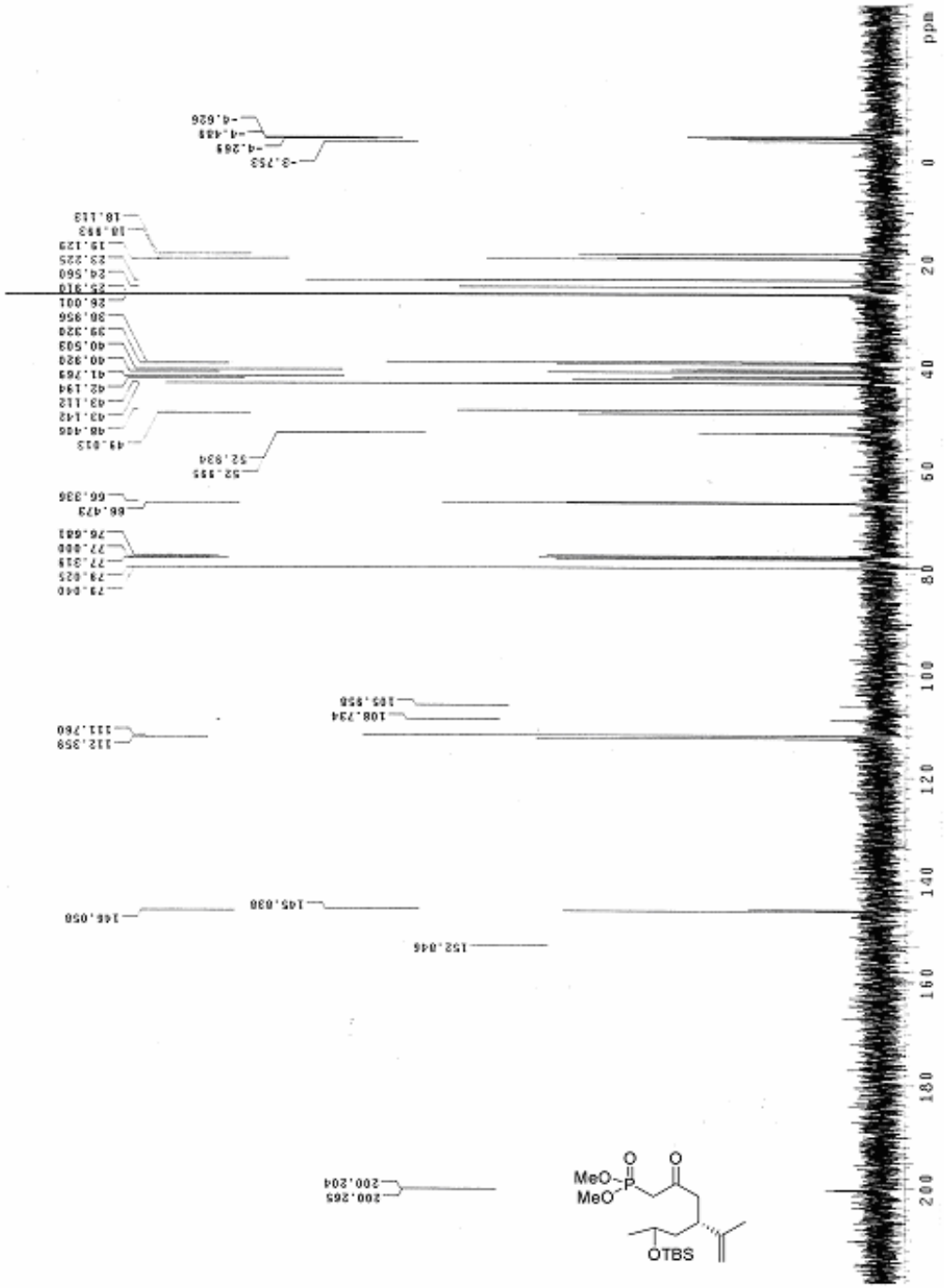
Spectrum 3.59: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **71**



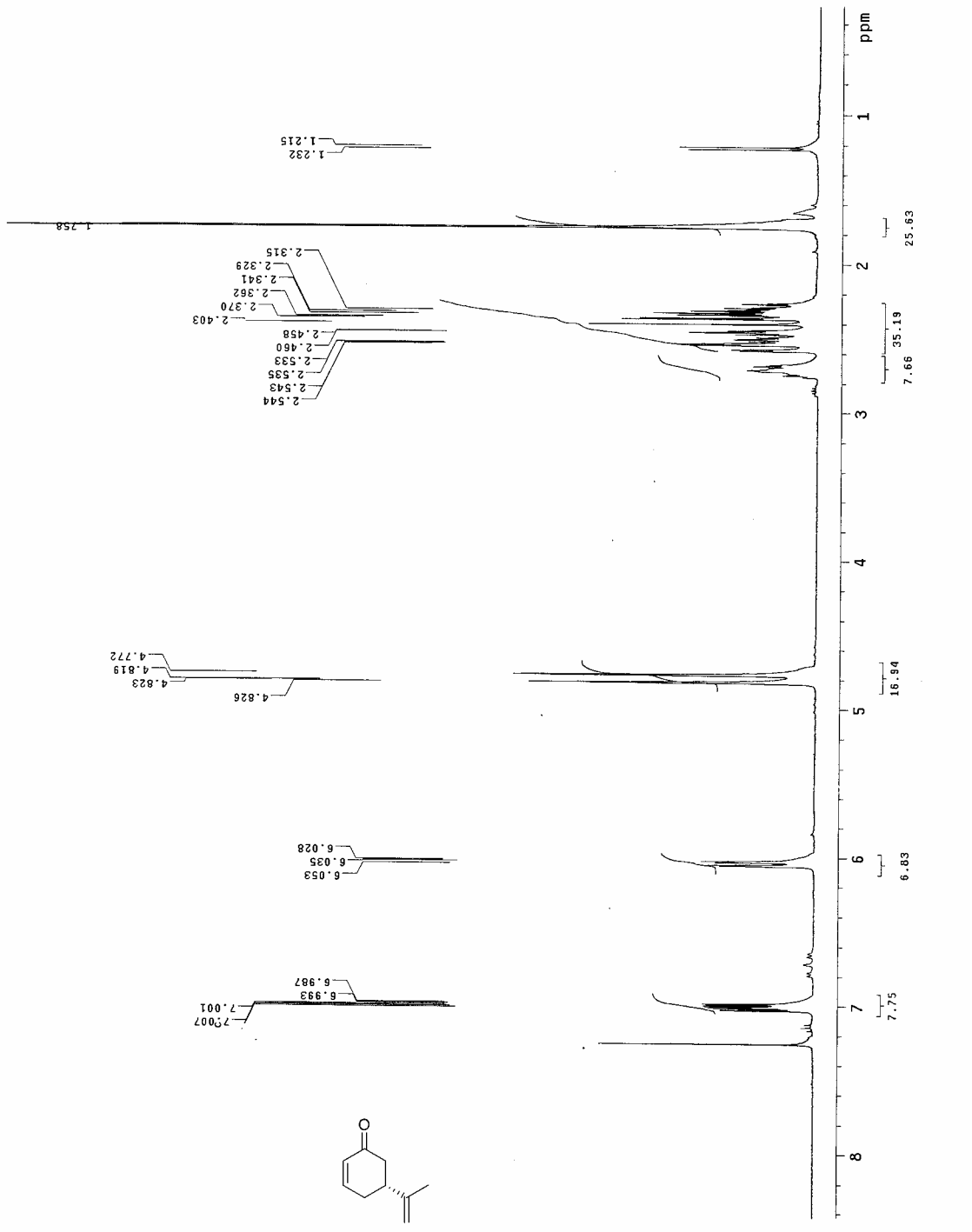
Spectrum 3.60: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **71**



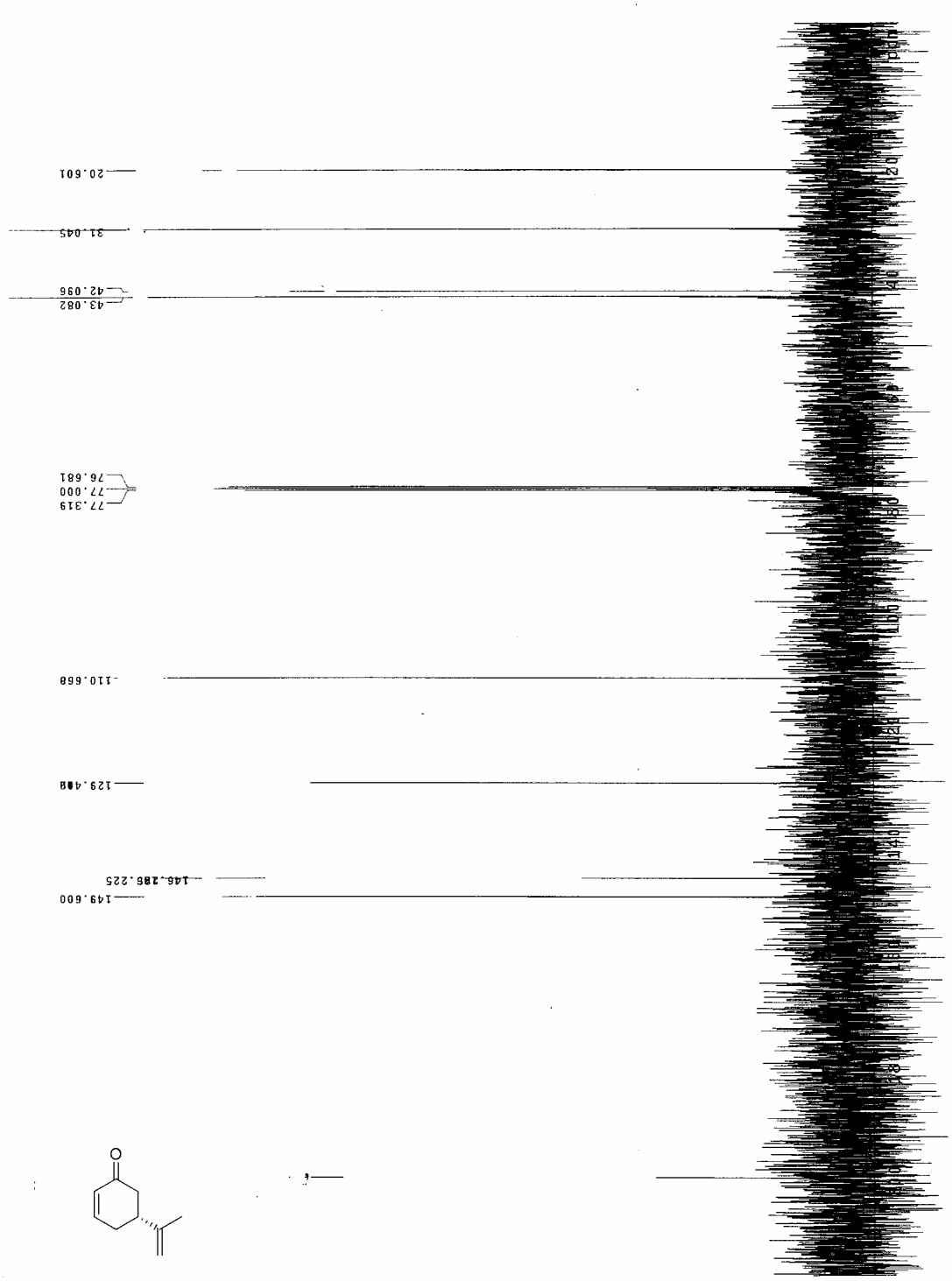
Spectrum 3.61: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **72**



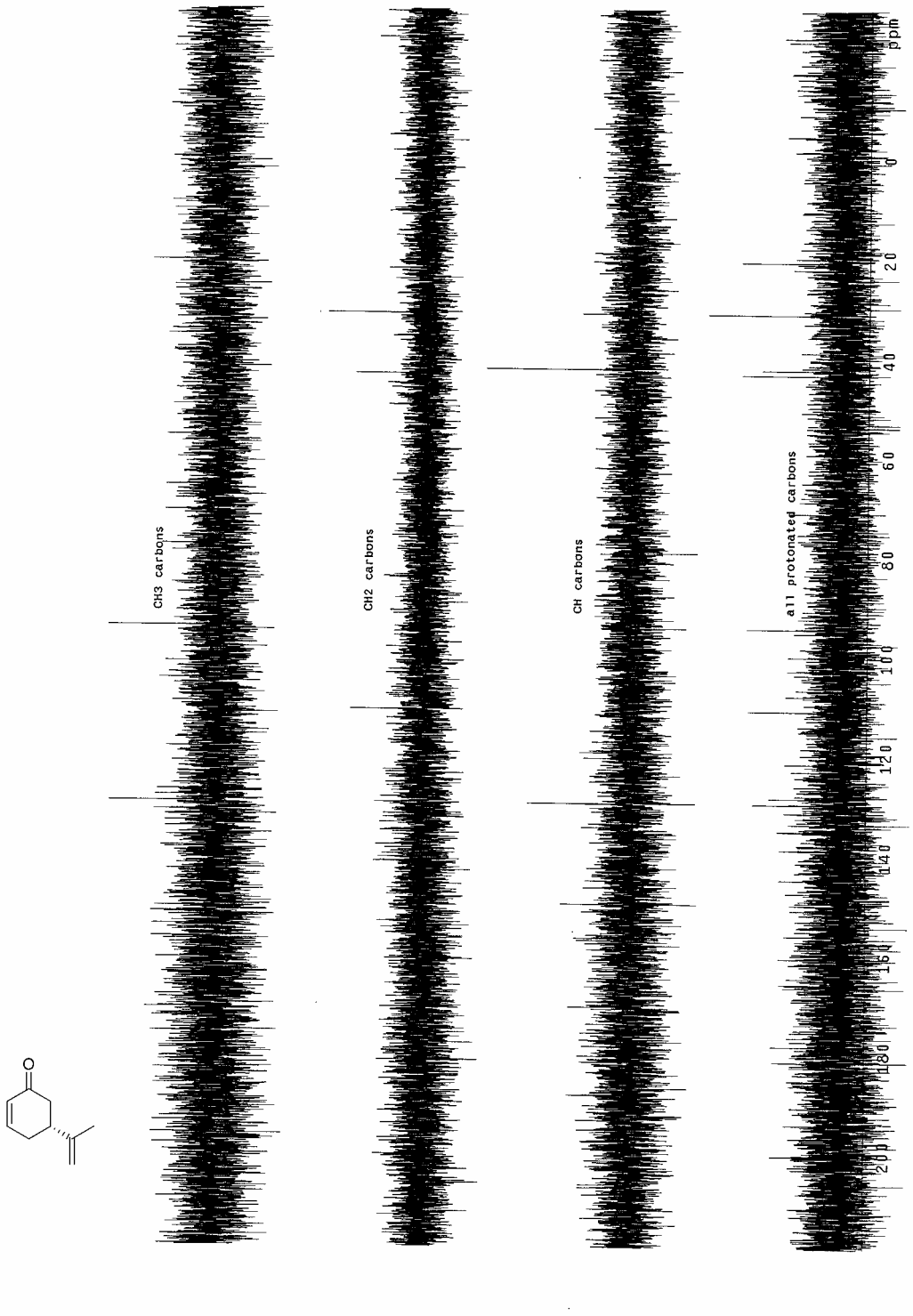
Spectrum 3.62: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **72**



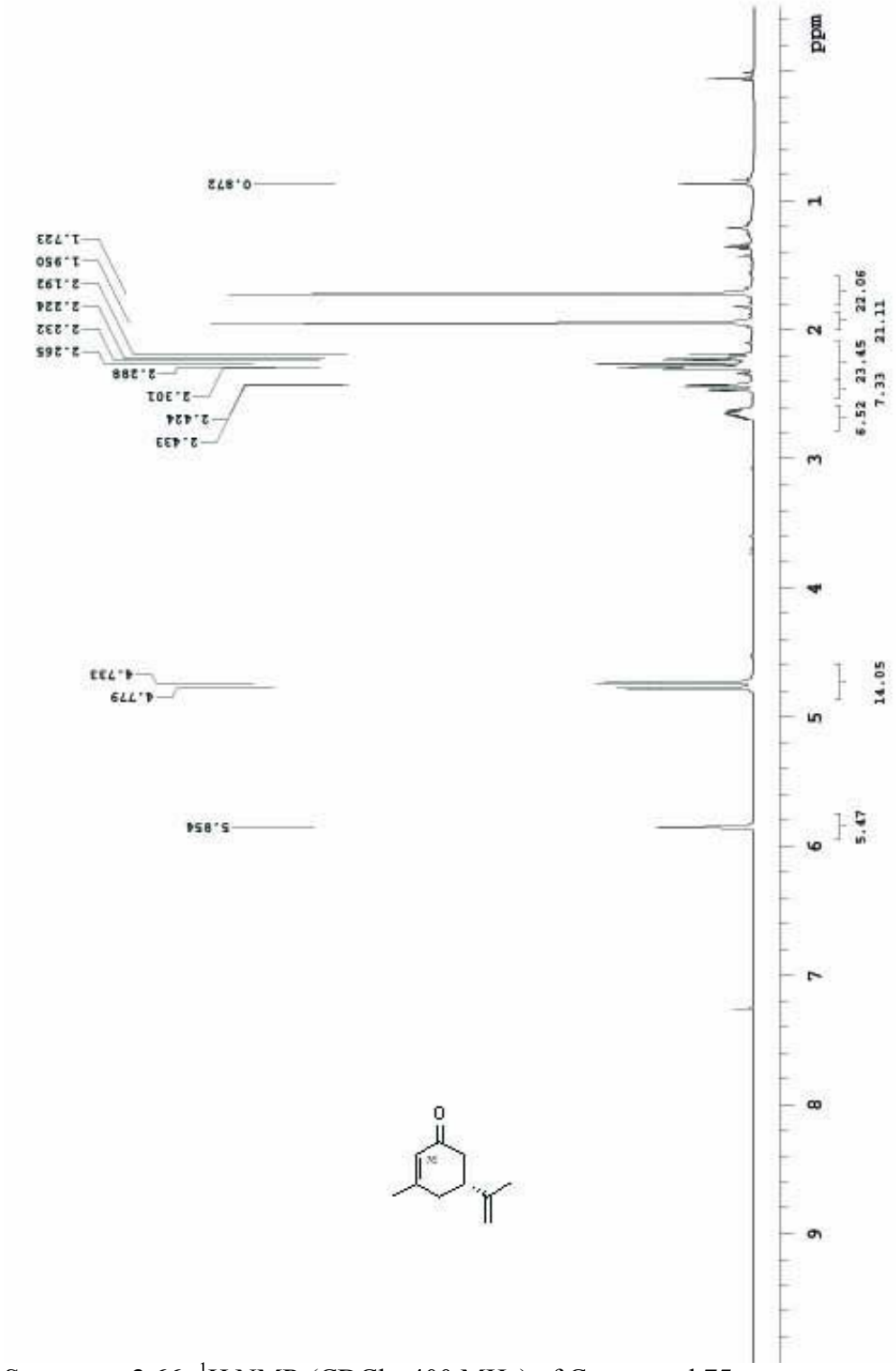
Spectrum 3.63: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **80**



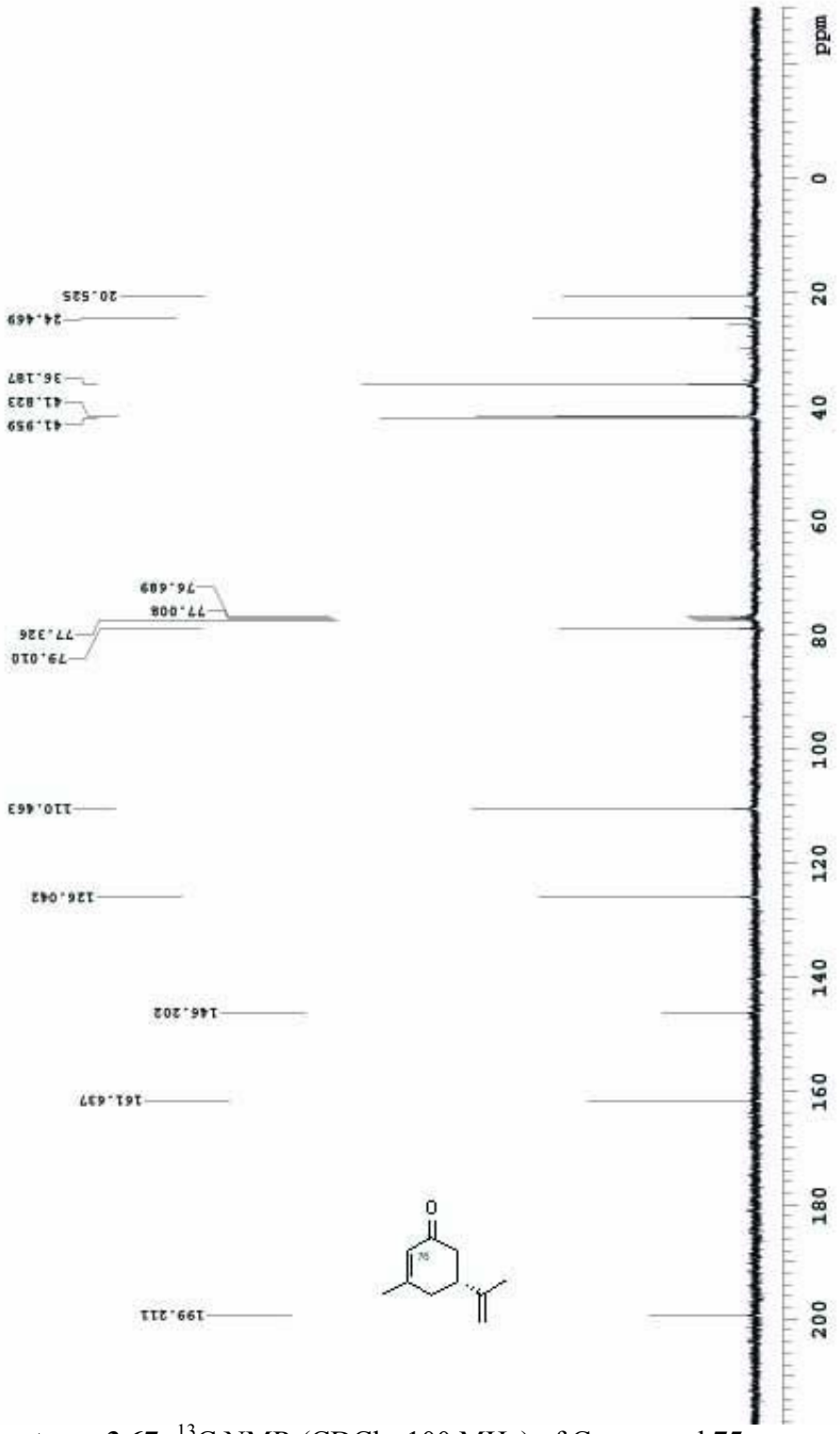
Spectrum 3.64: ^{2}D NMR ($CDCl_3$, 400 MHz) of Compound **80**



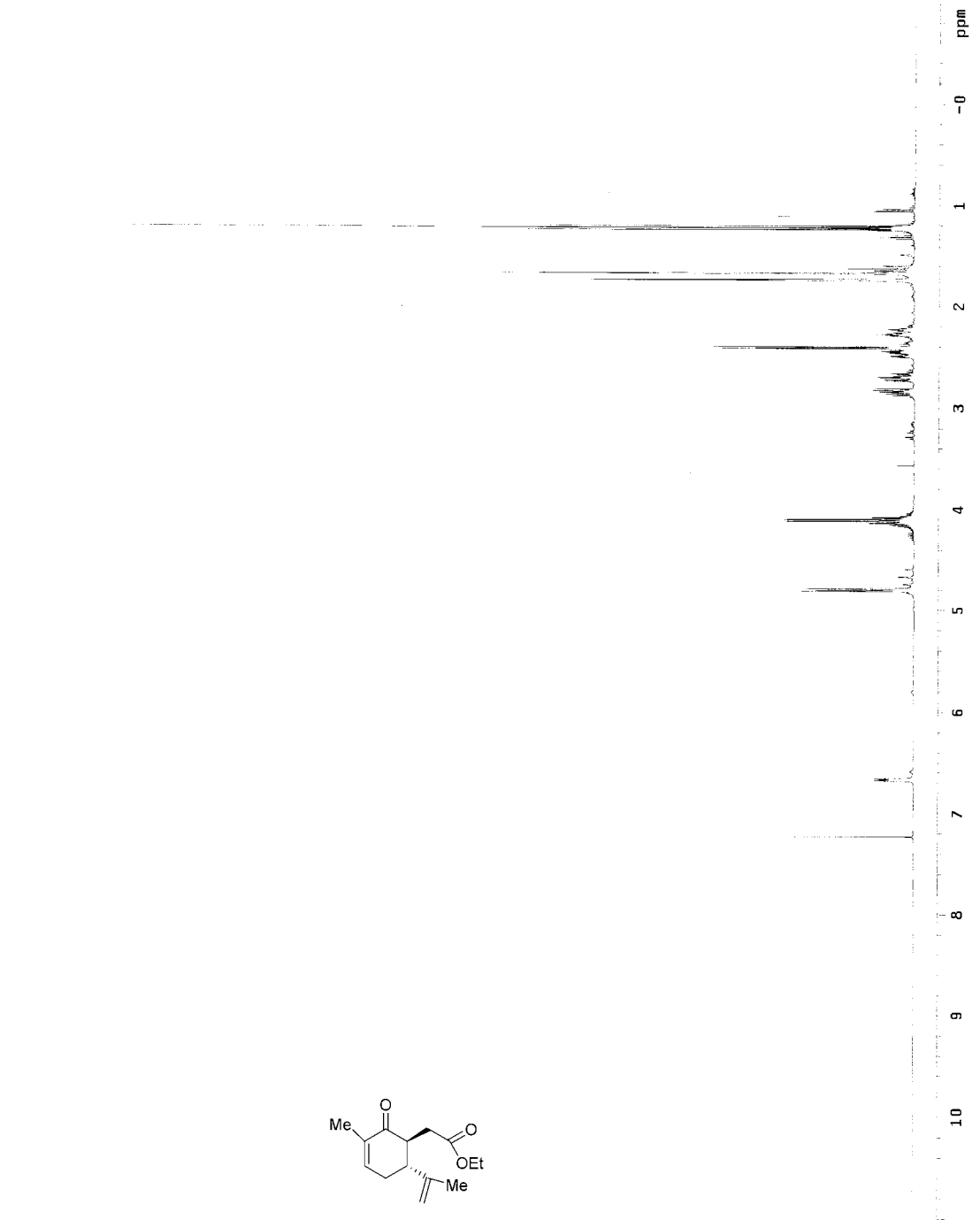
Spectrum 3.65: 2D NMR ($CDCl_3$, 100 MHz) of compound **80**



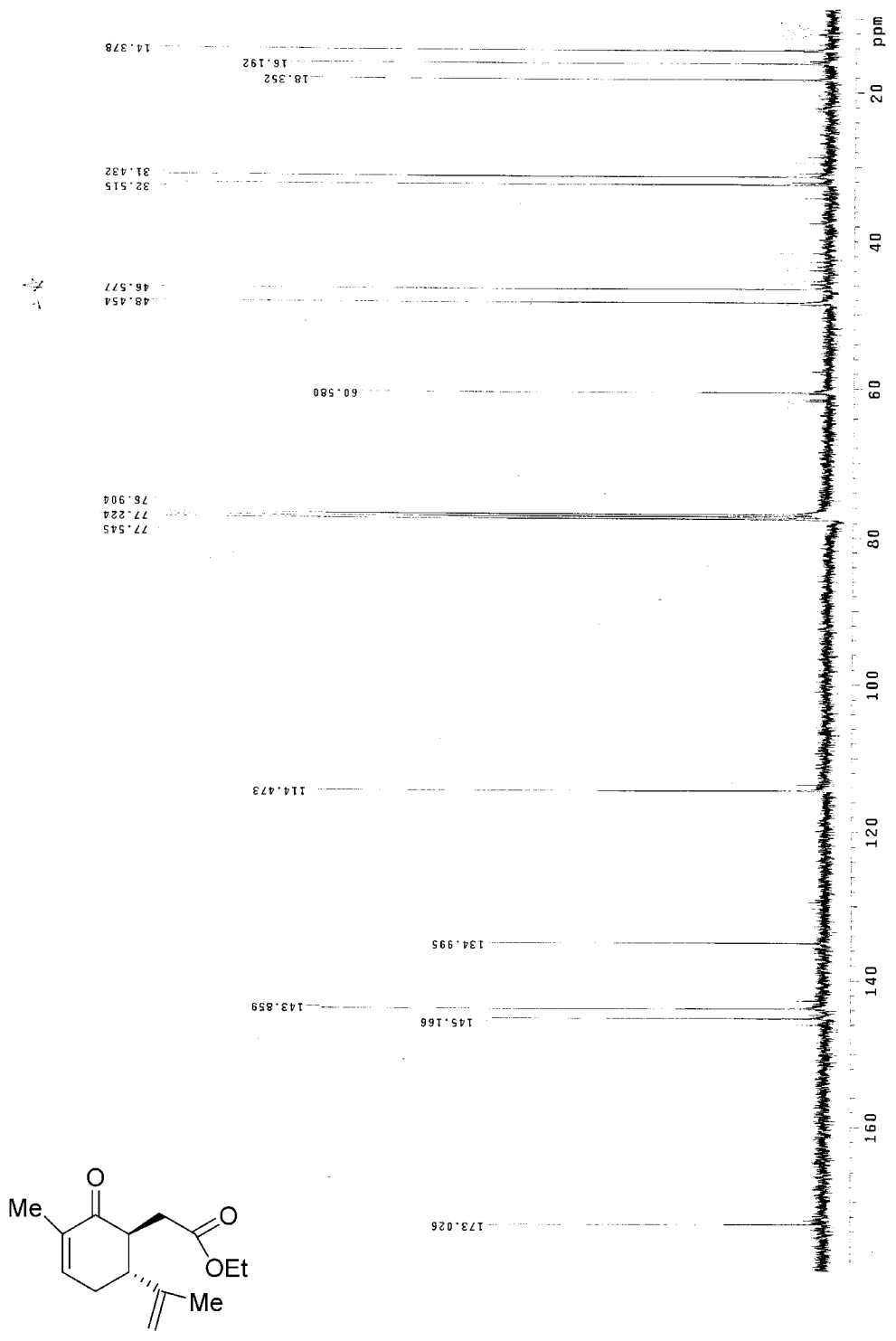
Spectrum 3.66: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **75**



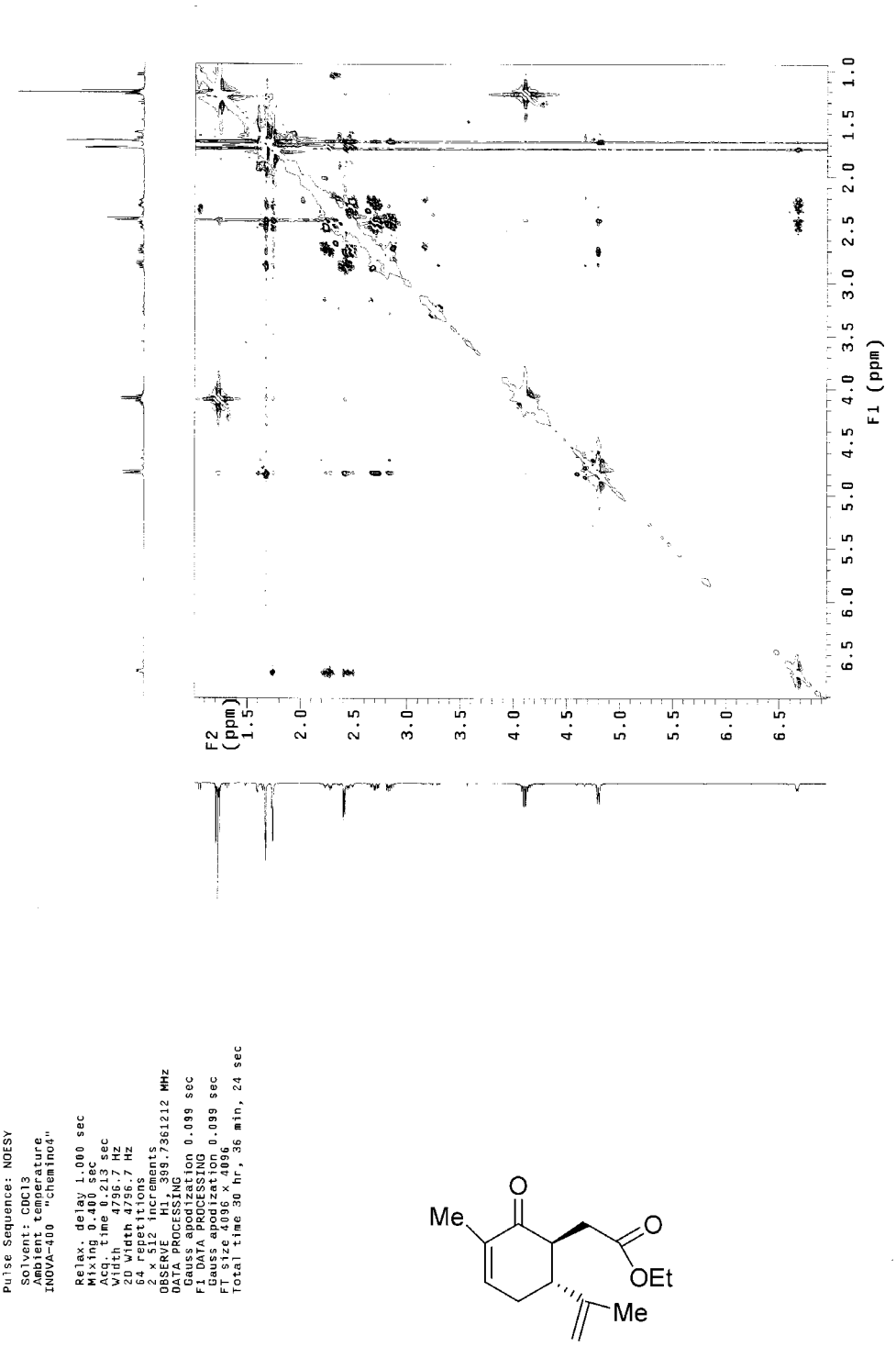
Spectrum 3.67: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **75**



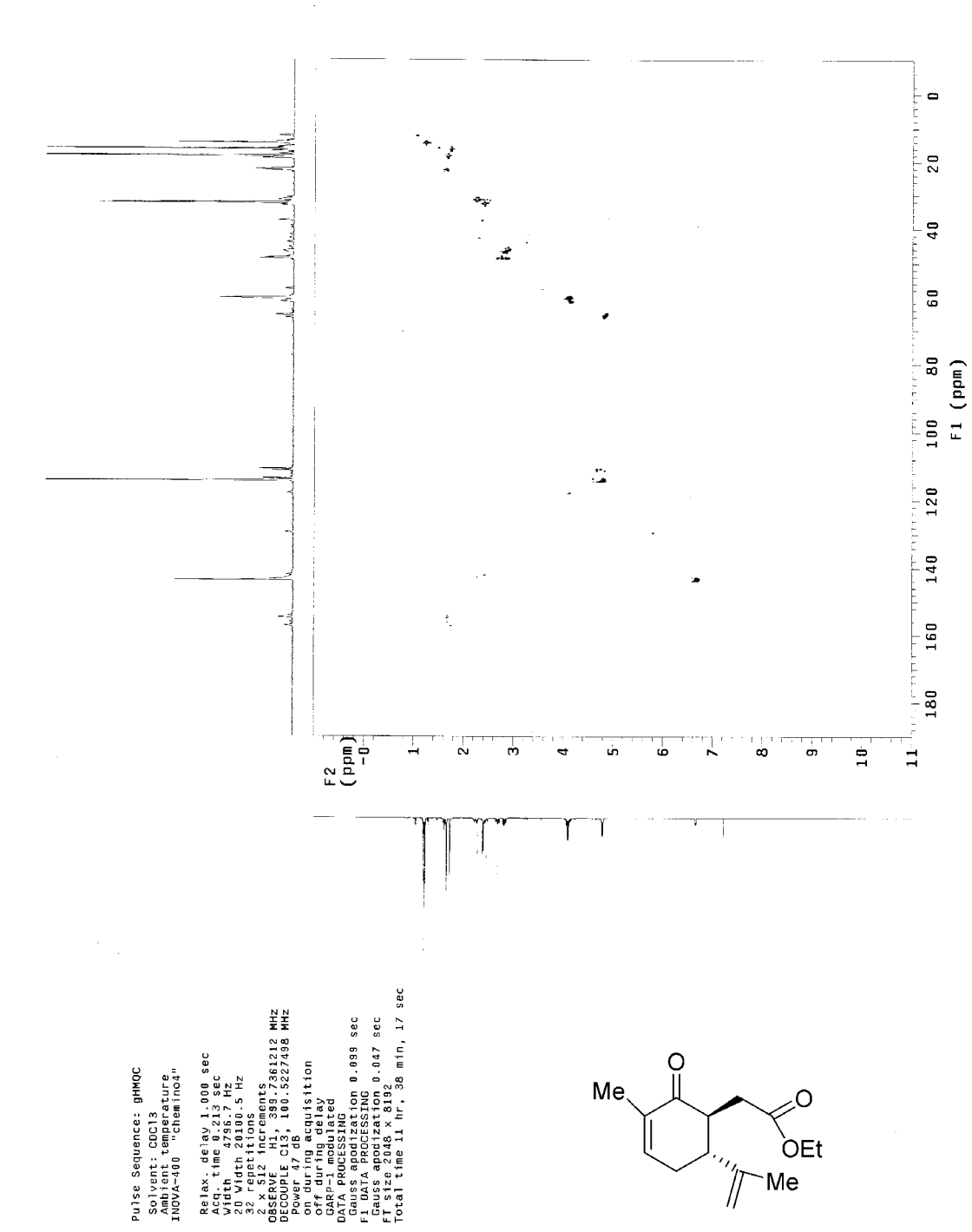
Spectrum 3.68: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **83**



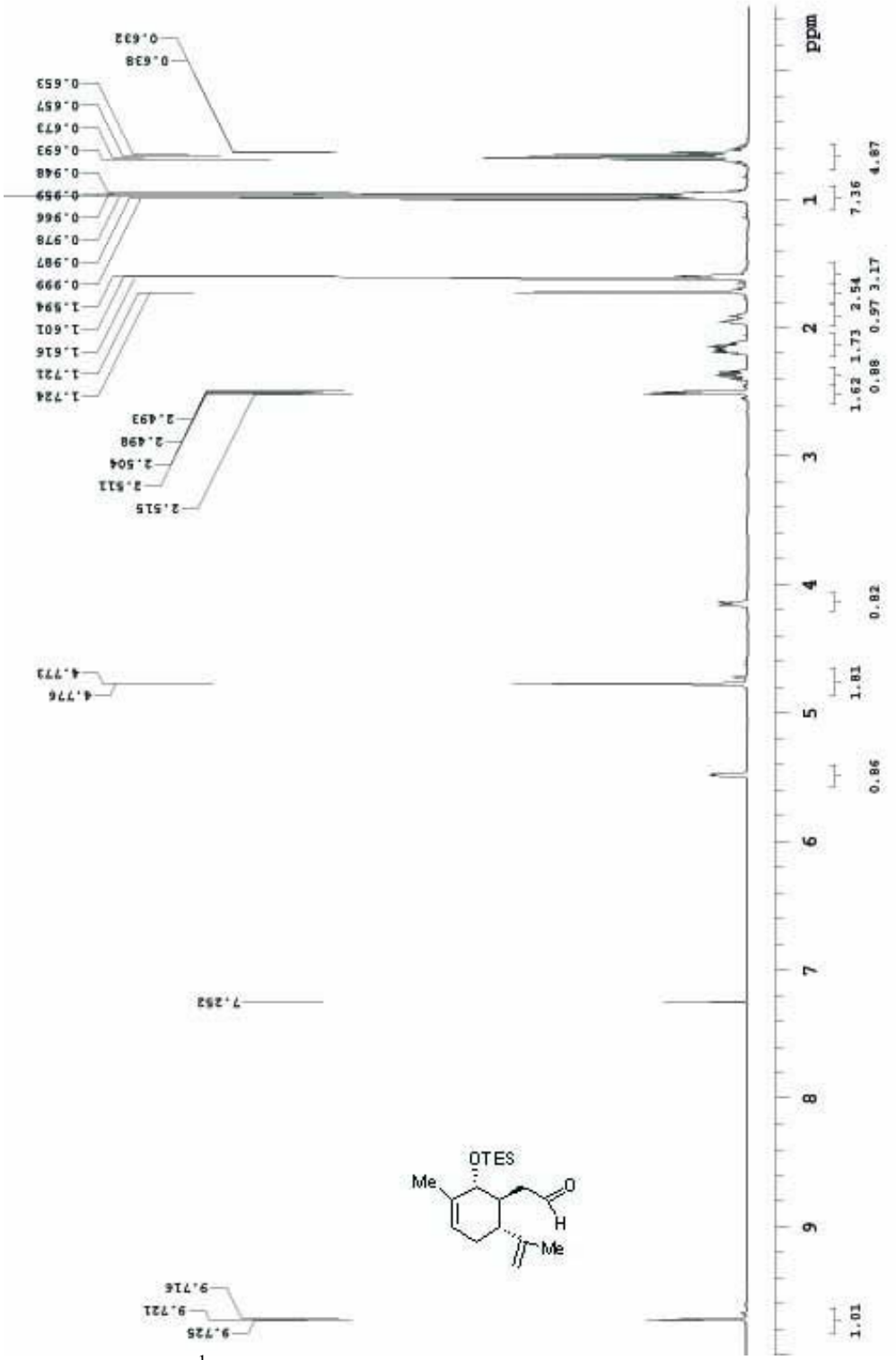
Spectrum 3.69: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **83**



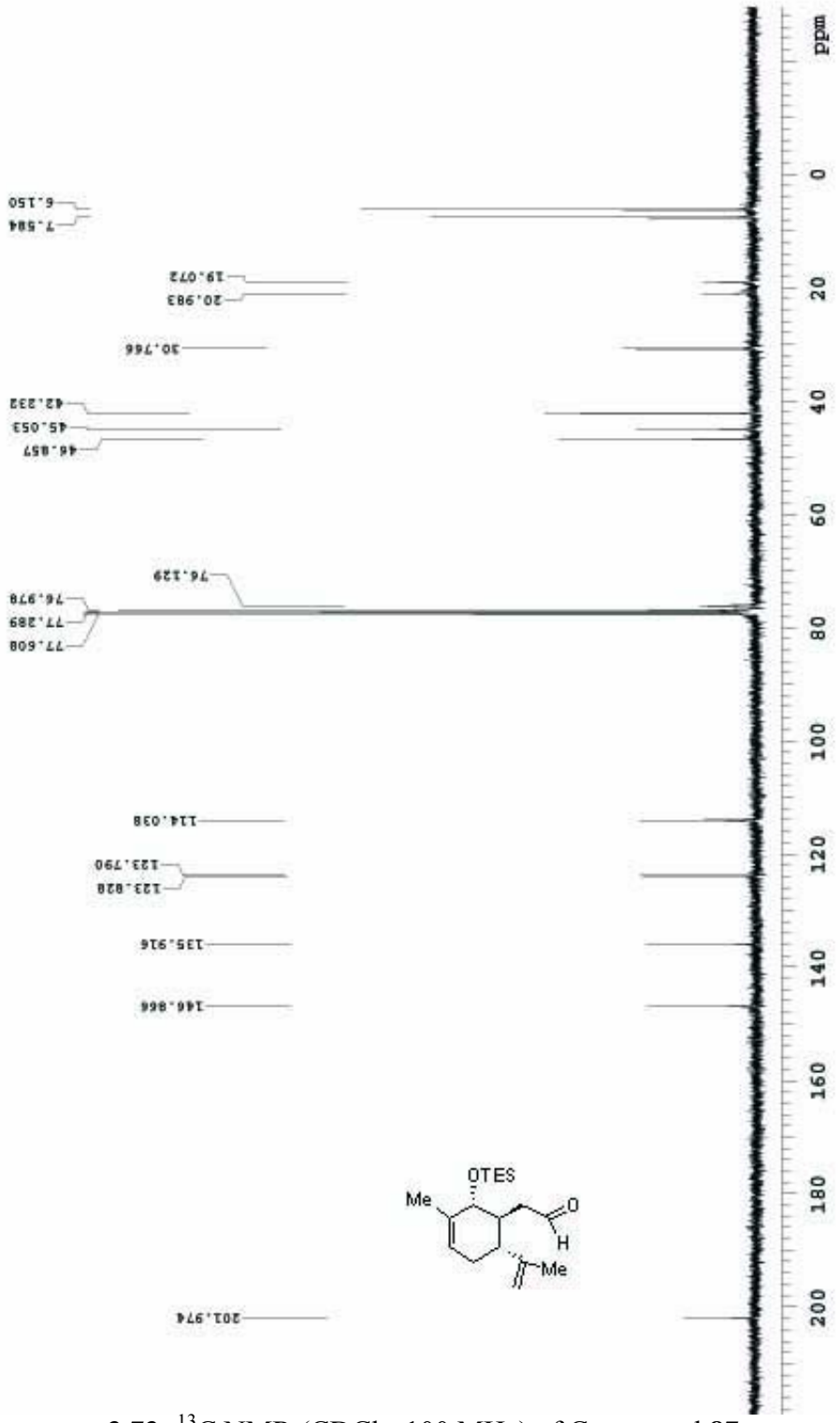
Spectrum 3.70: 2D NMR ($CDCl_3$, 400 MHz) of Compound **83**



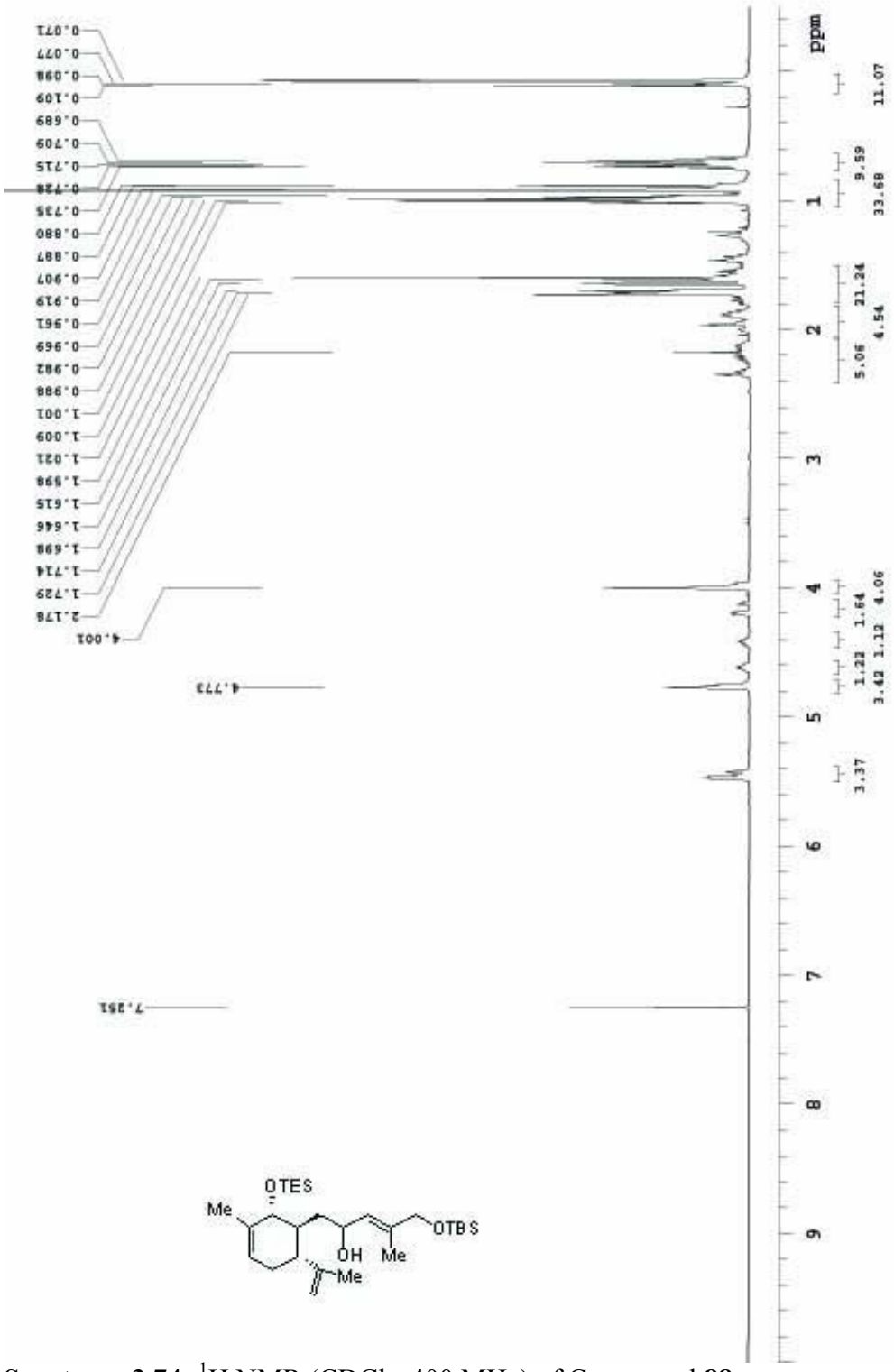
Spectrum 3.71: 2D NMR ($CDCl_3$, 400 MHz) of Compound **83**



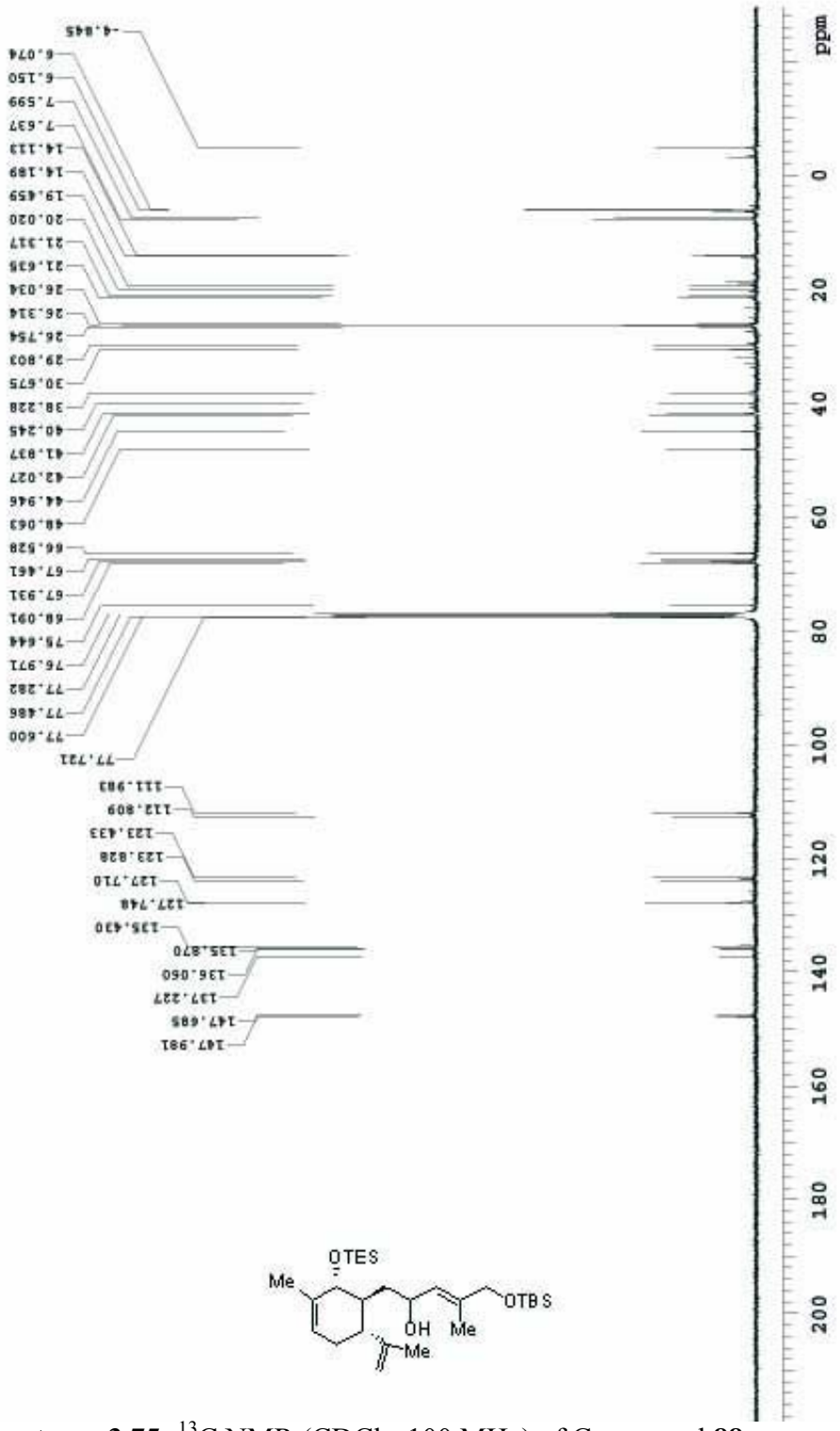
Spectrum 3.72: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **87**



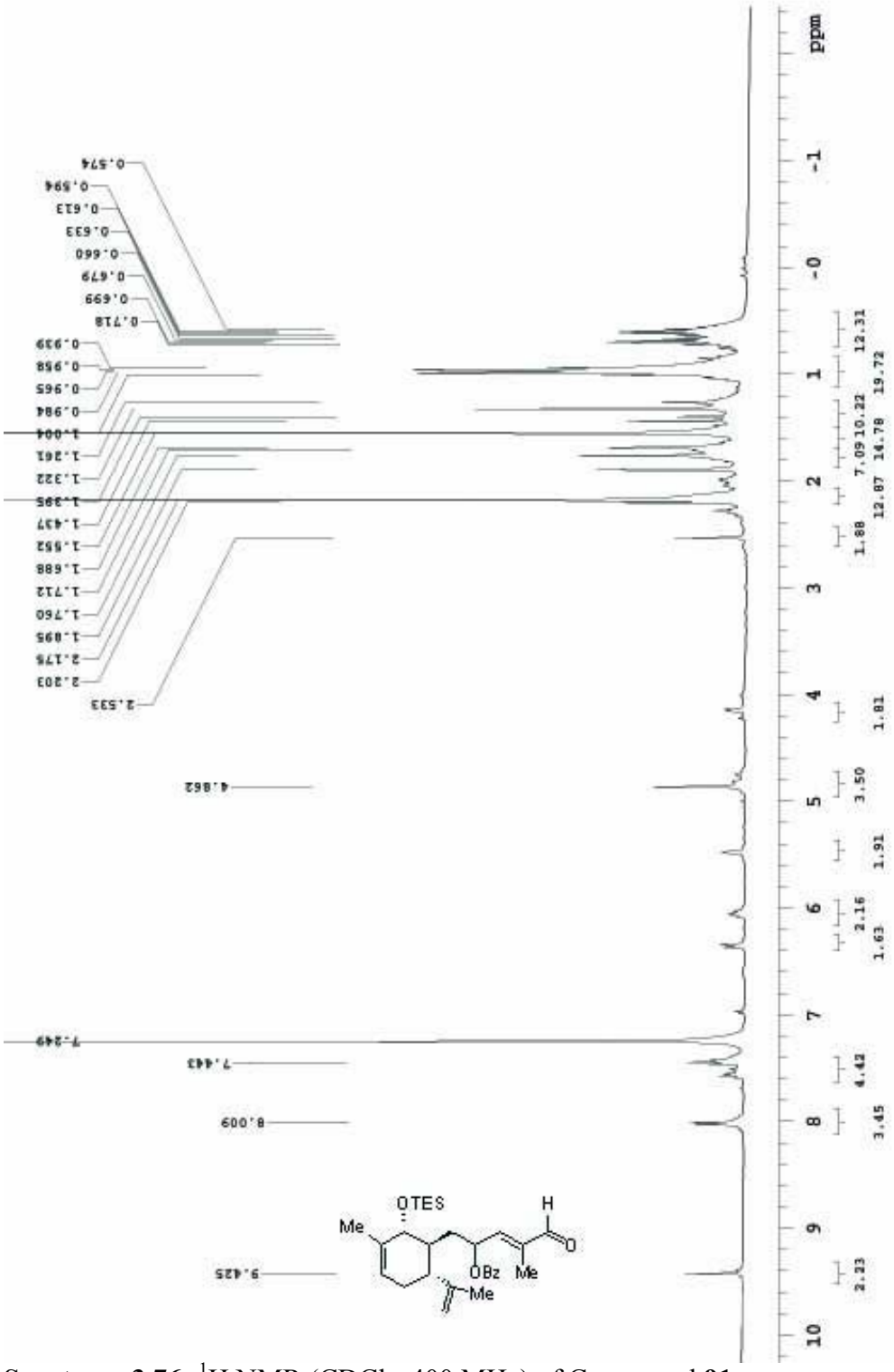
Spectrum 3.73: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **87**



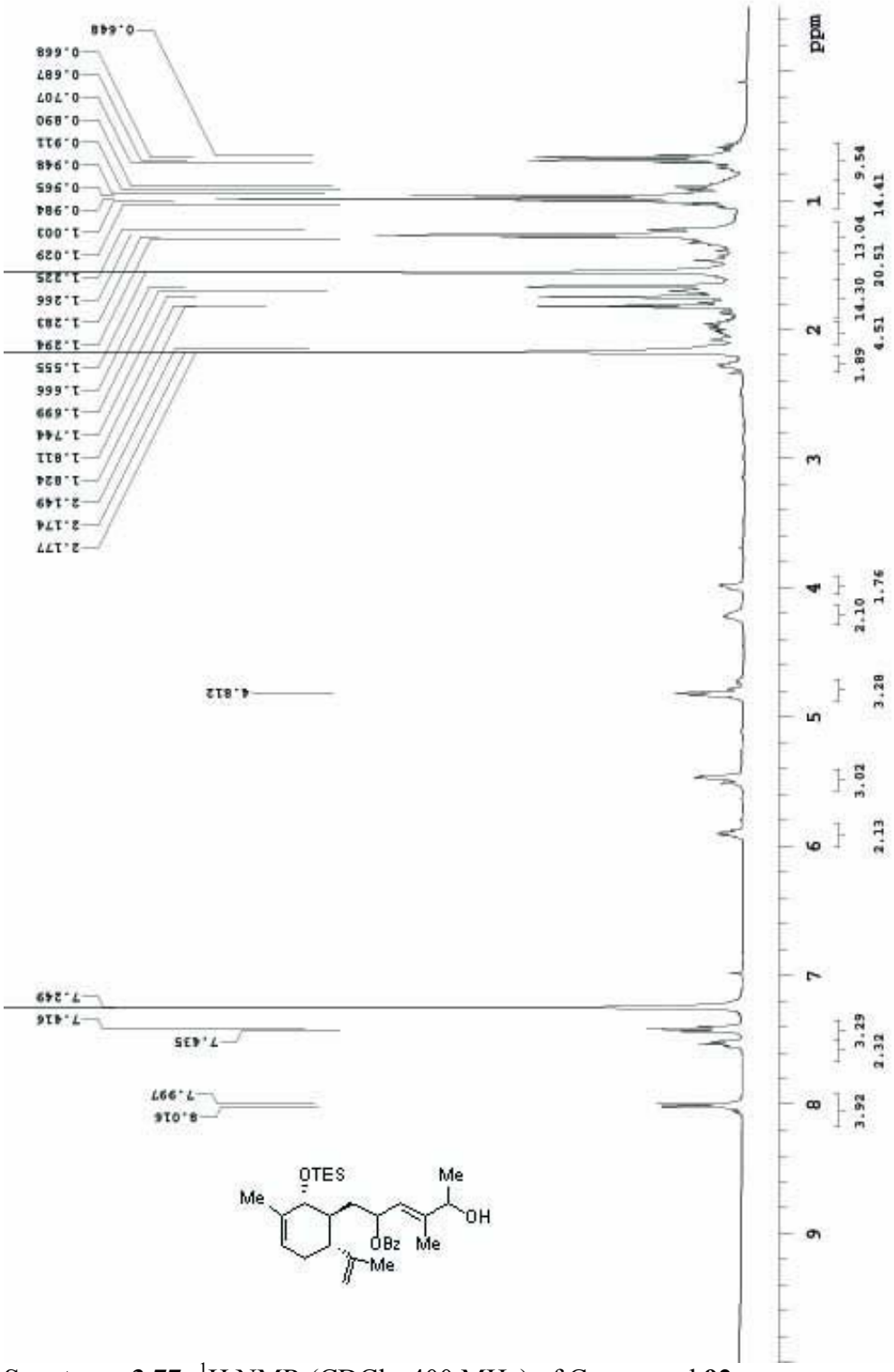
Spectrum 3.74: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **88**



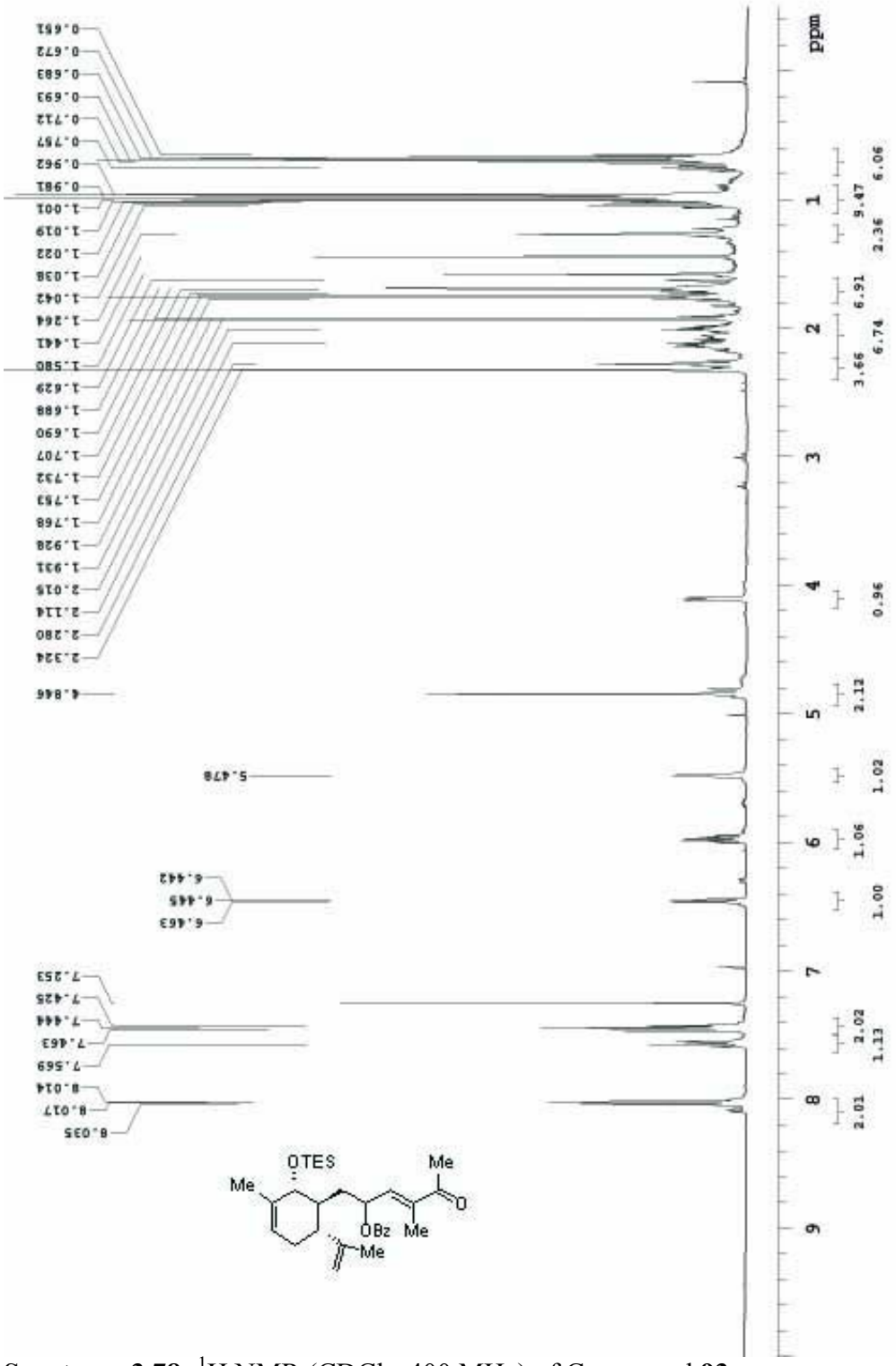
Spectrum 3.75: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **88**



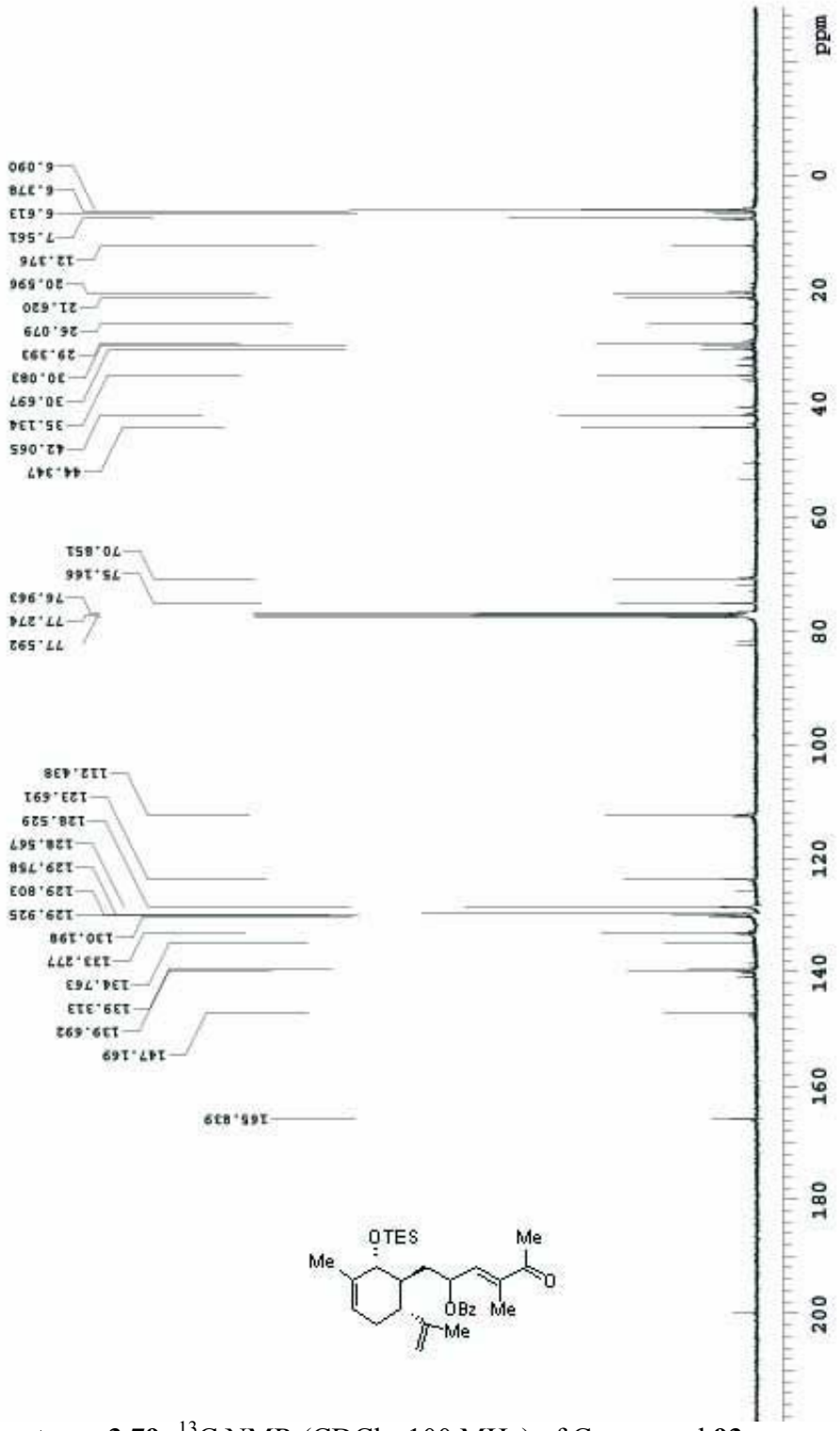
Spectrum 3.76: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **91**



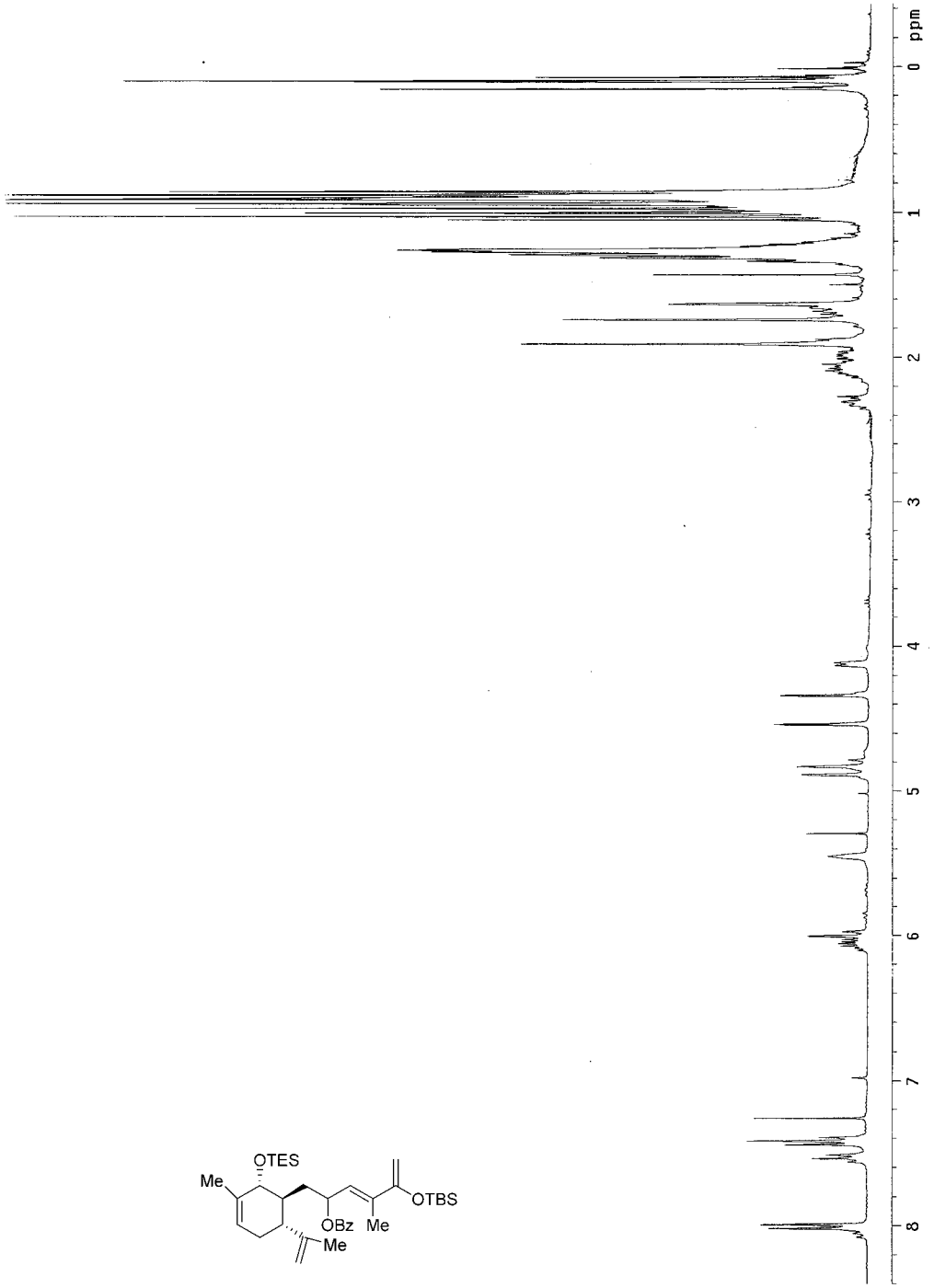
Spectrum 3.77: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **92**



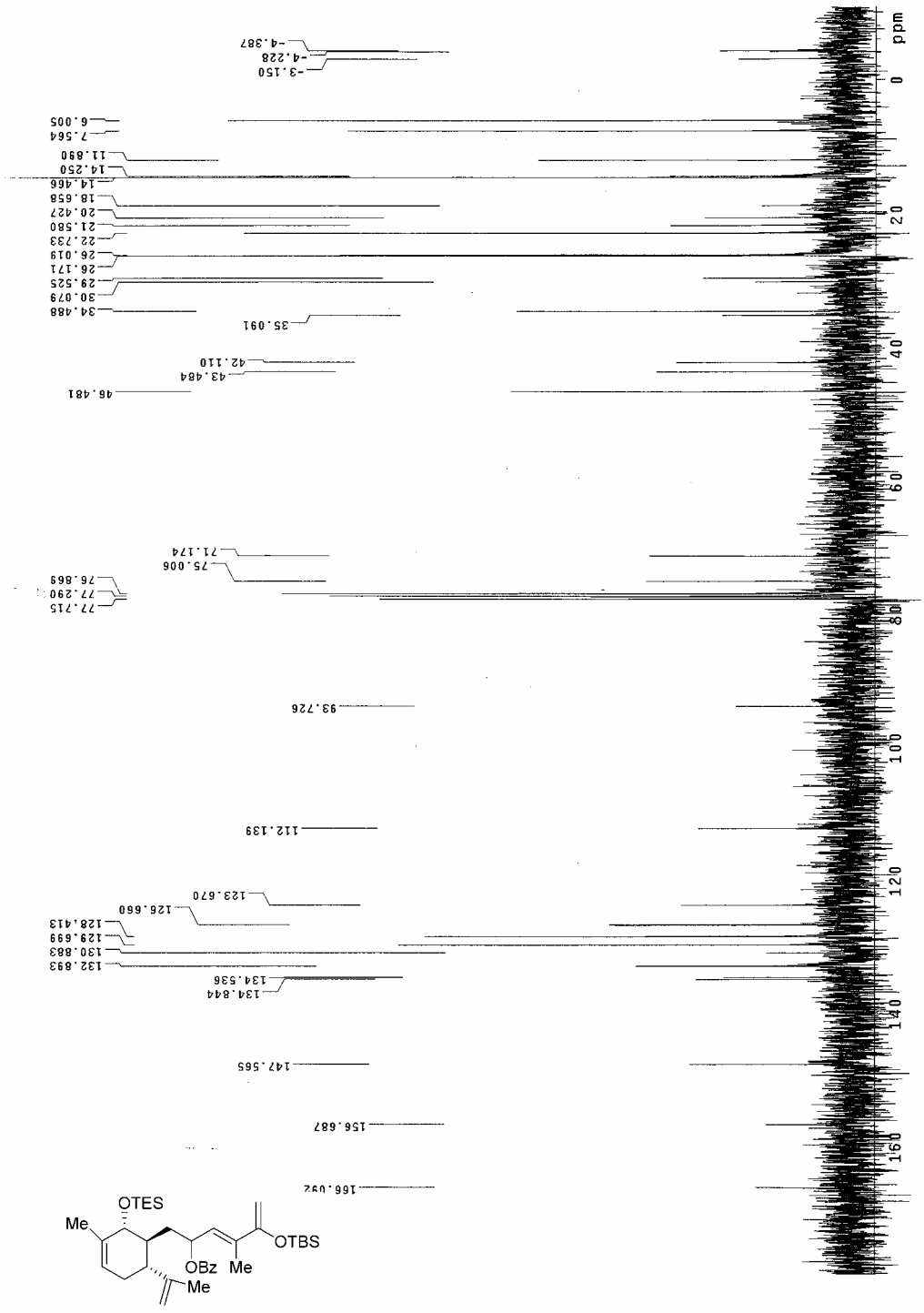
Spectrum 3.78: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **93**



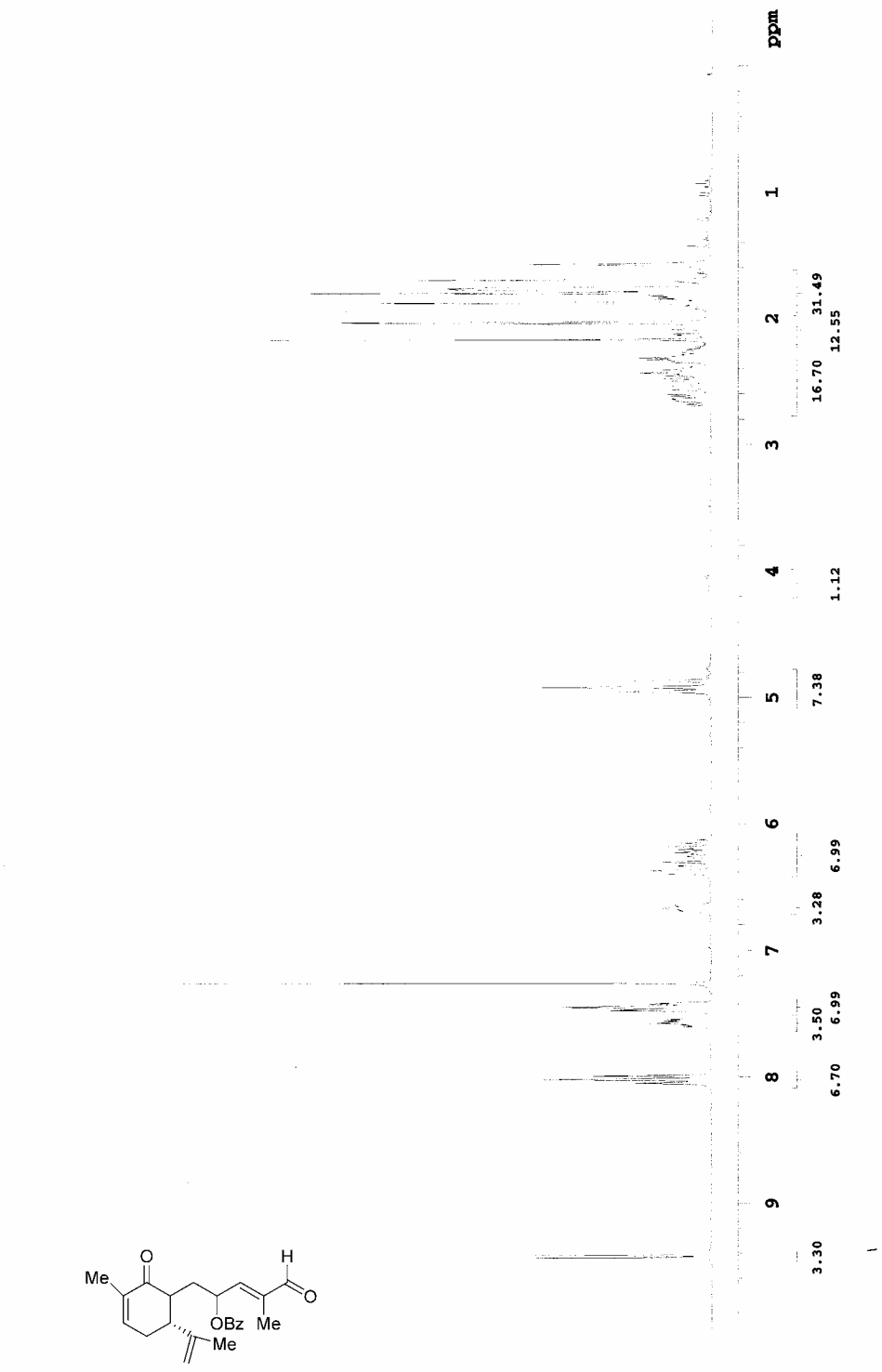
Spectrum 3.79: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **93**



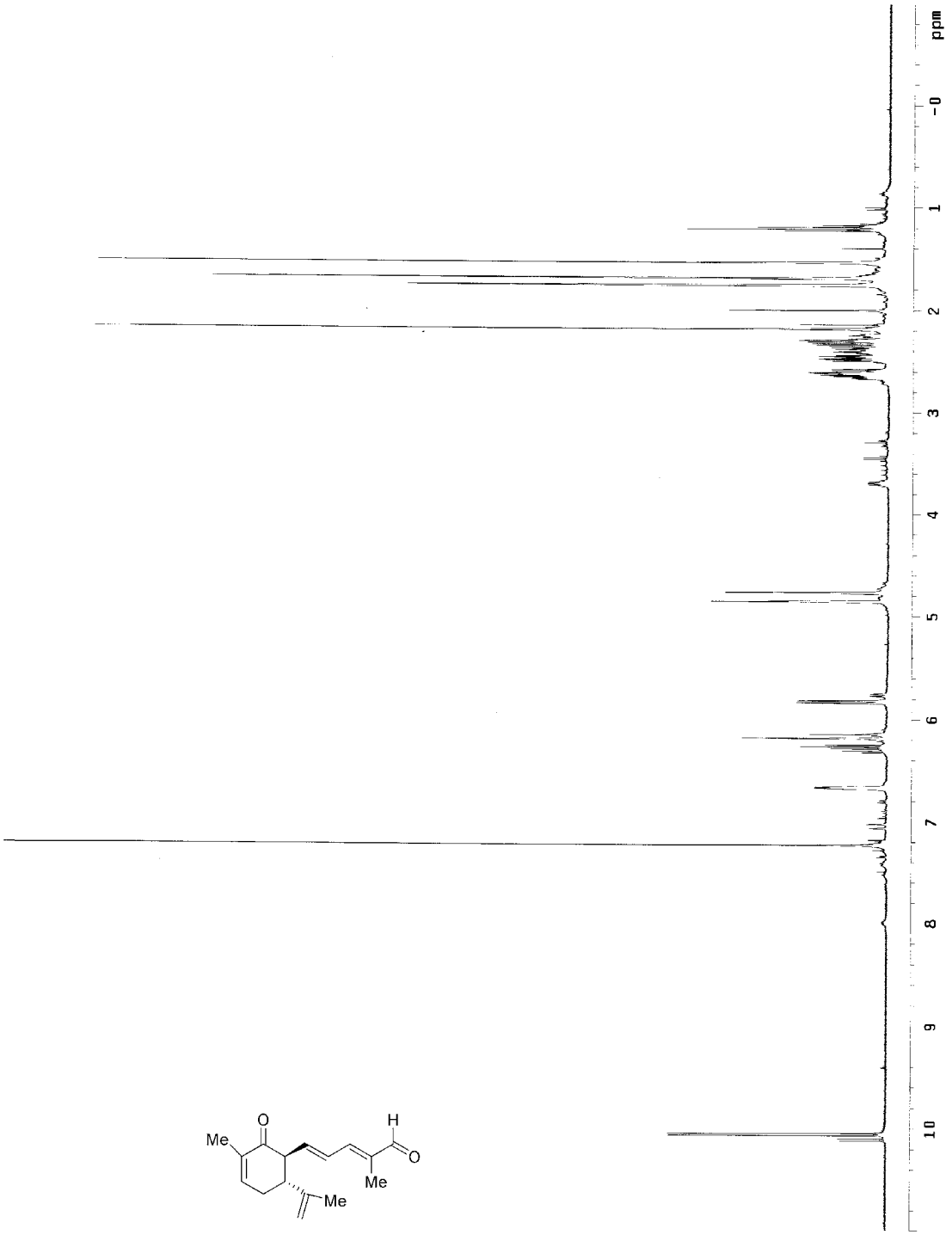
Spectrum 3.80: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **94**



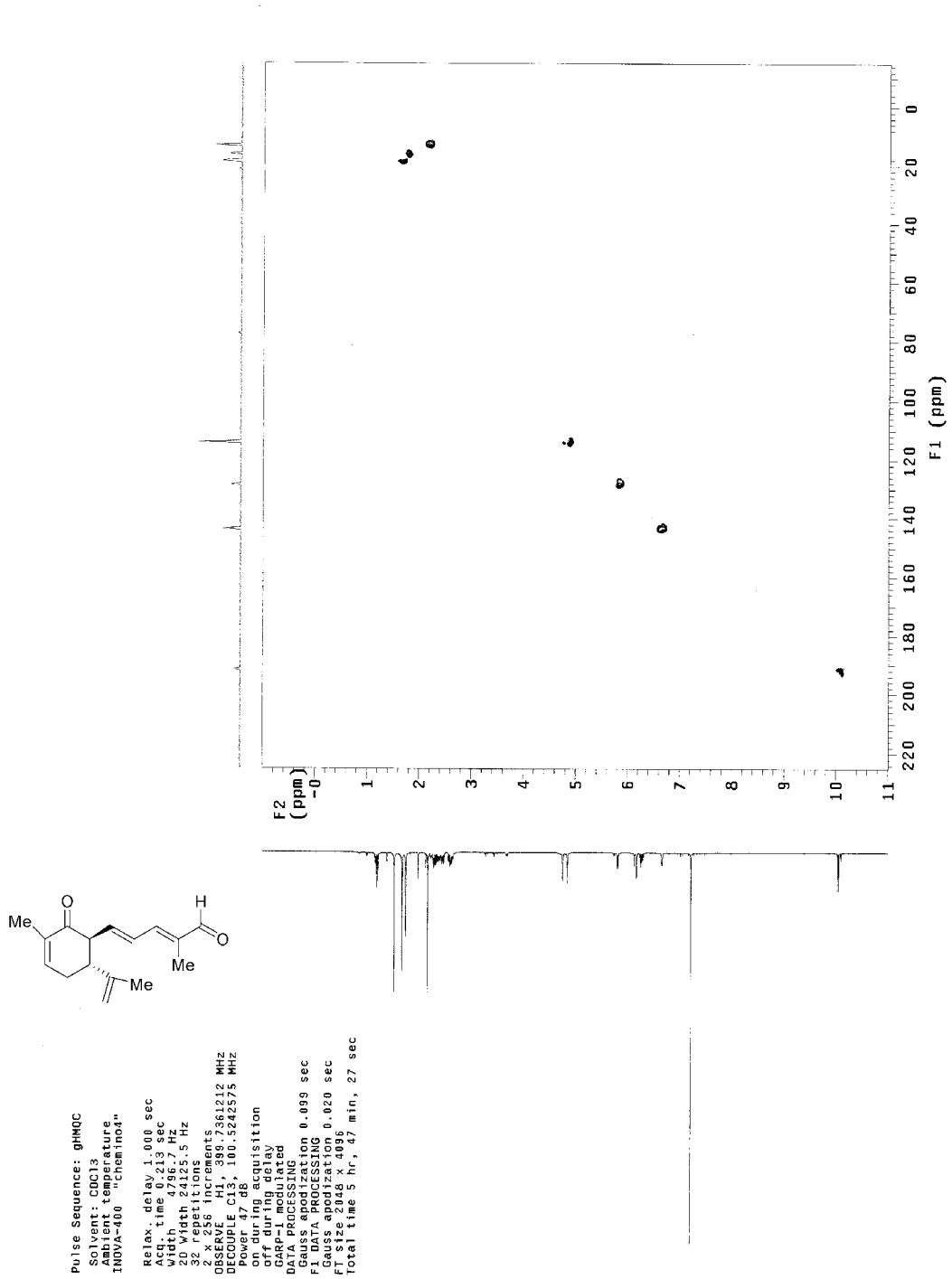
Spectrum 3.81: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **94**



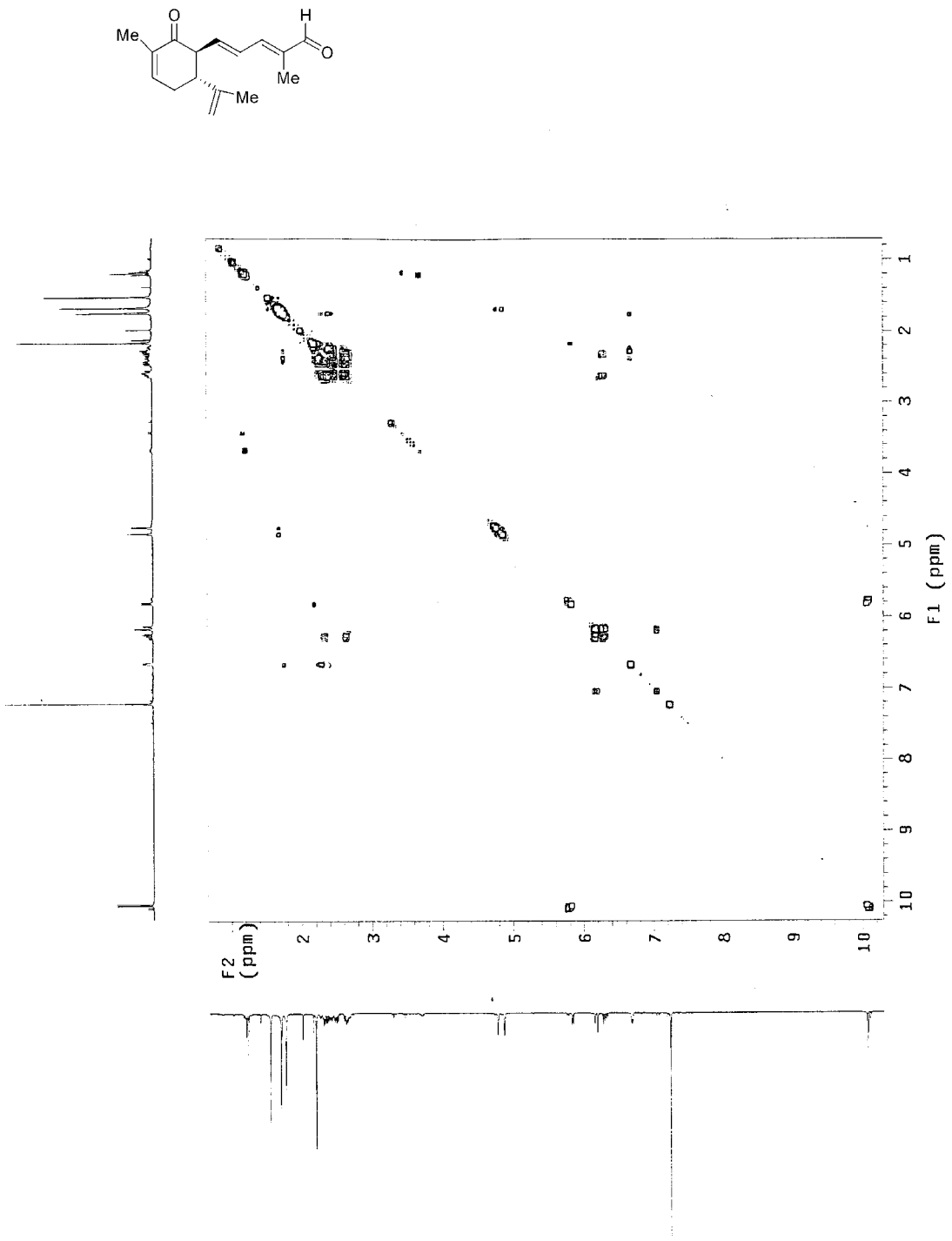
Spectrum 3.82: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **97**



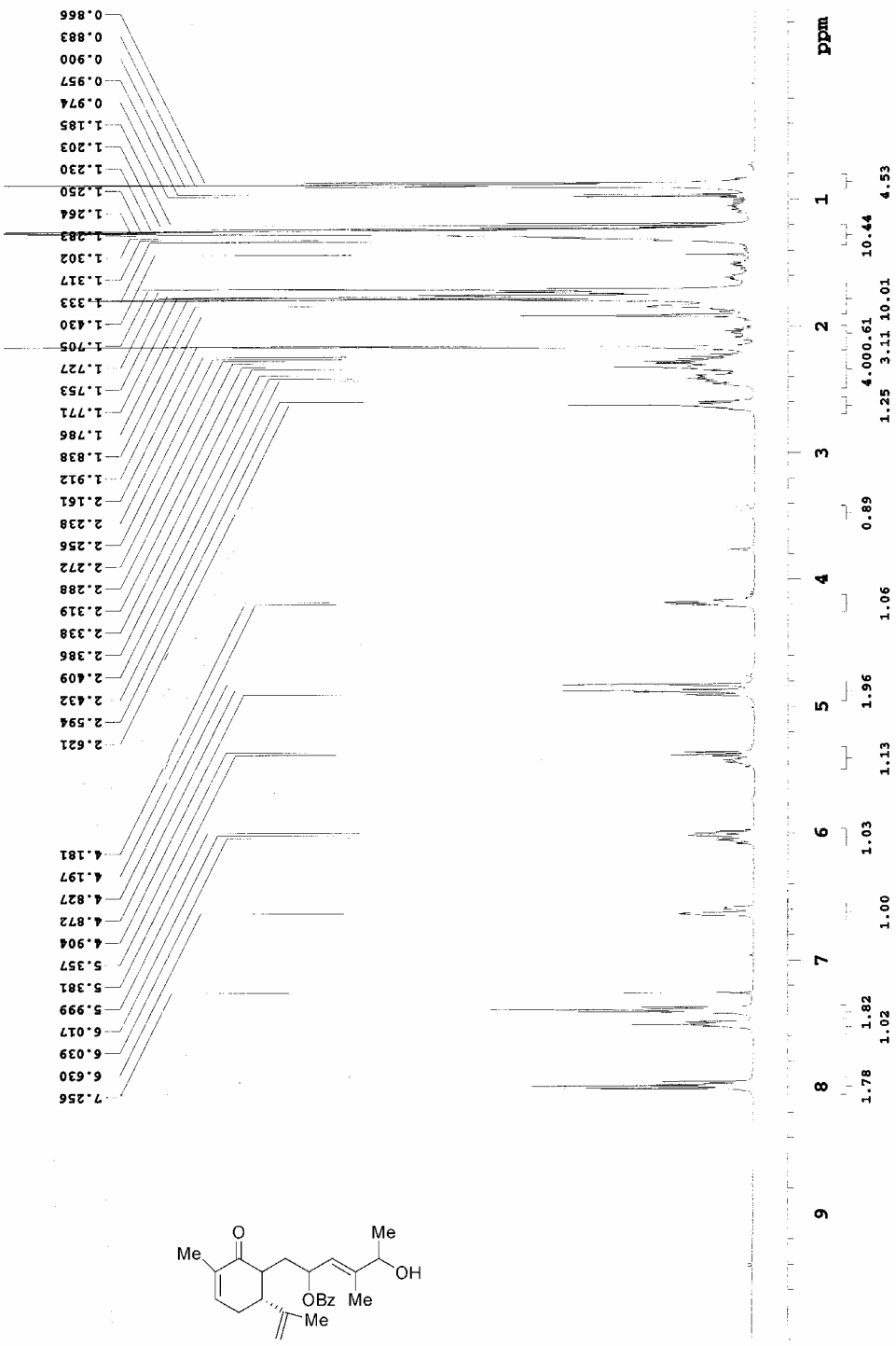
Spectrum 3.83: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **98-1**



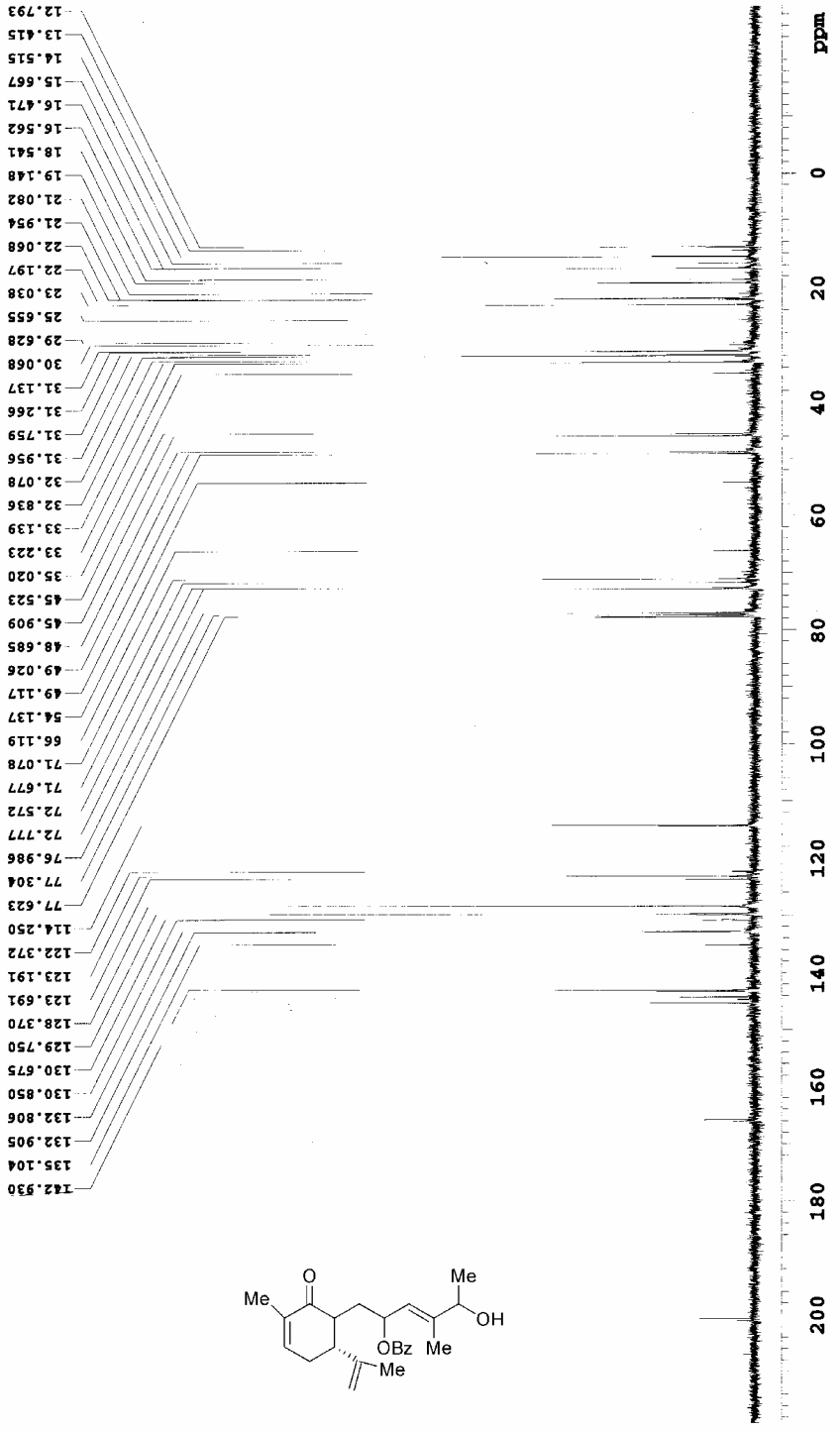
Spectrum 3.84: 2D NMR ($CDCl_3$, 400 MHz) of Compound **98-1**



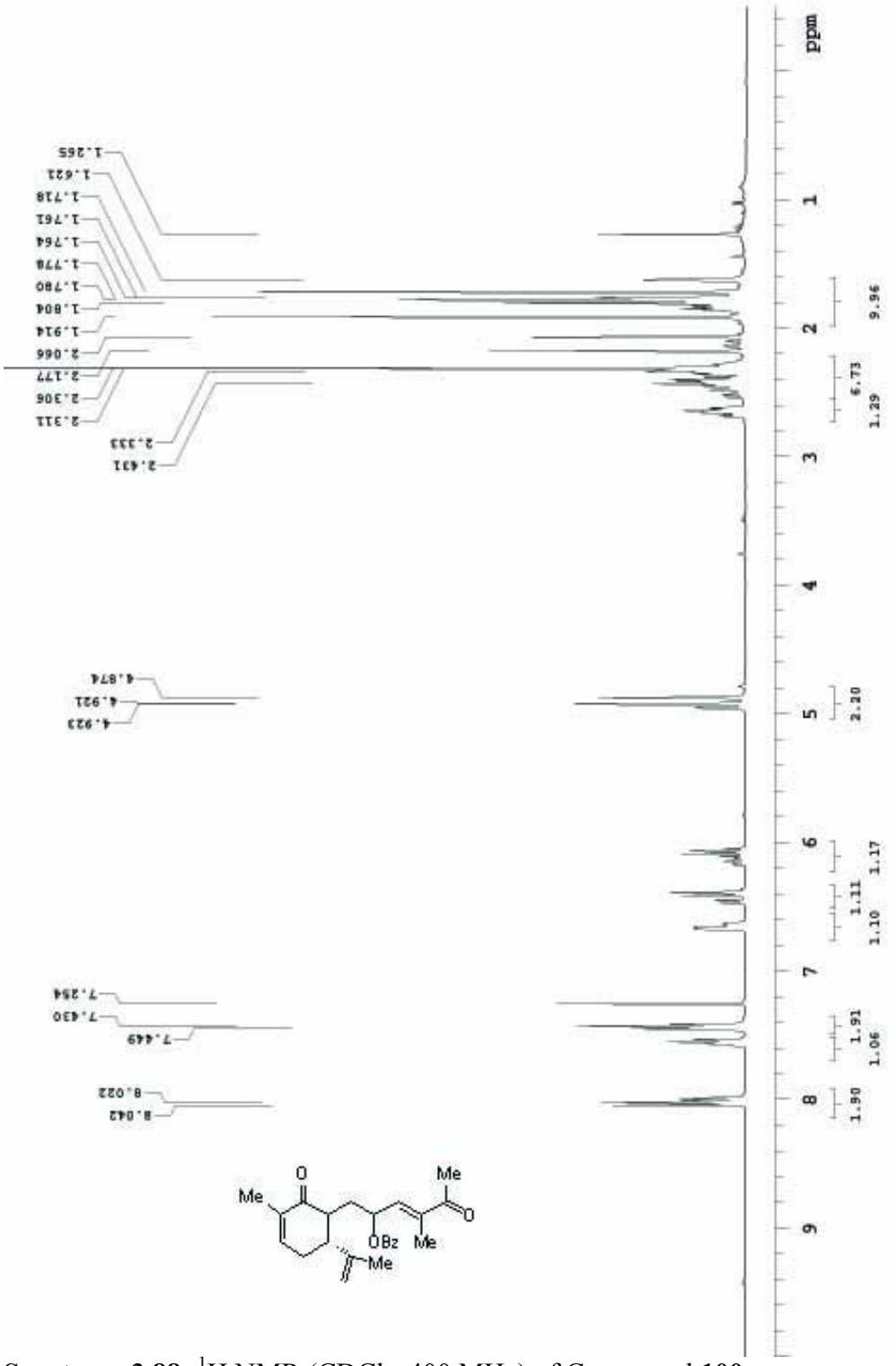
Spectrum 3.85: 2D NMR ($CDCl_3$, 400 MHz) of Compound **98-1**



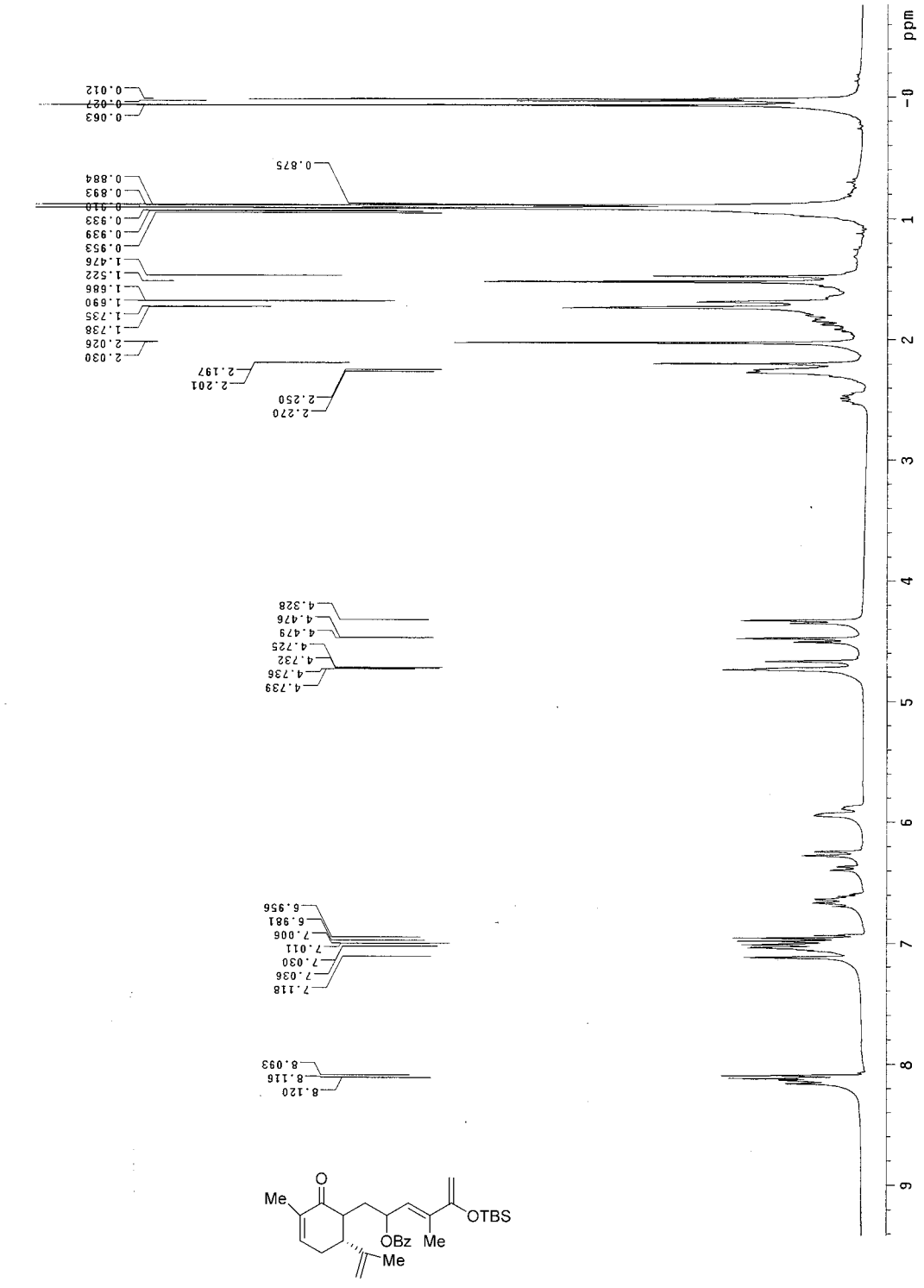
Spectrum 3.86: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **99**



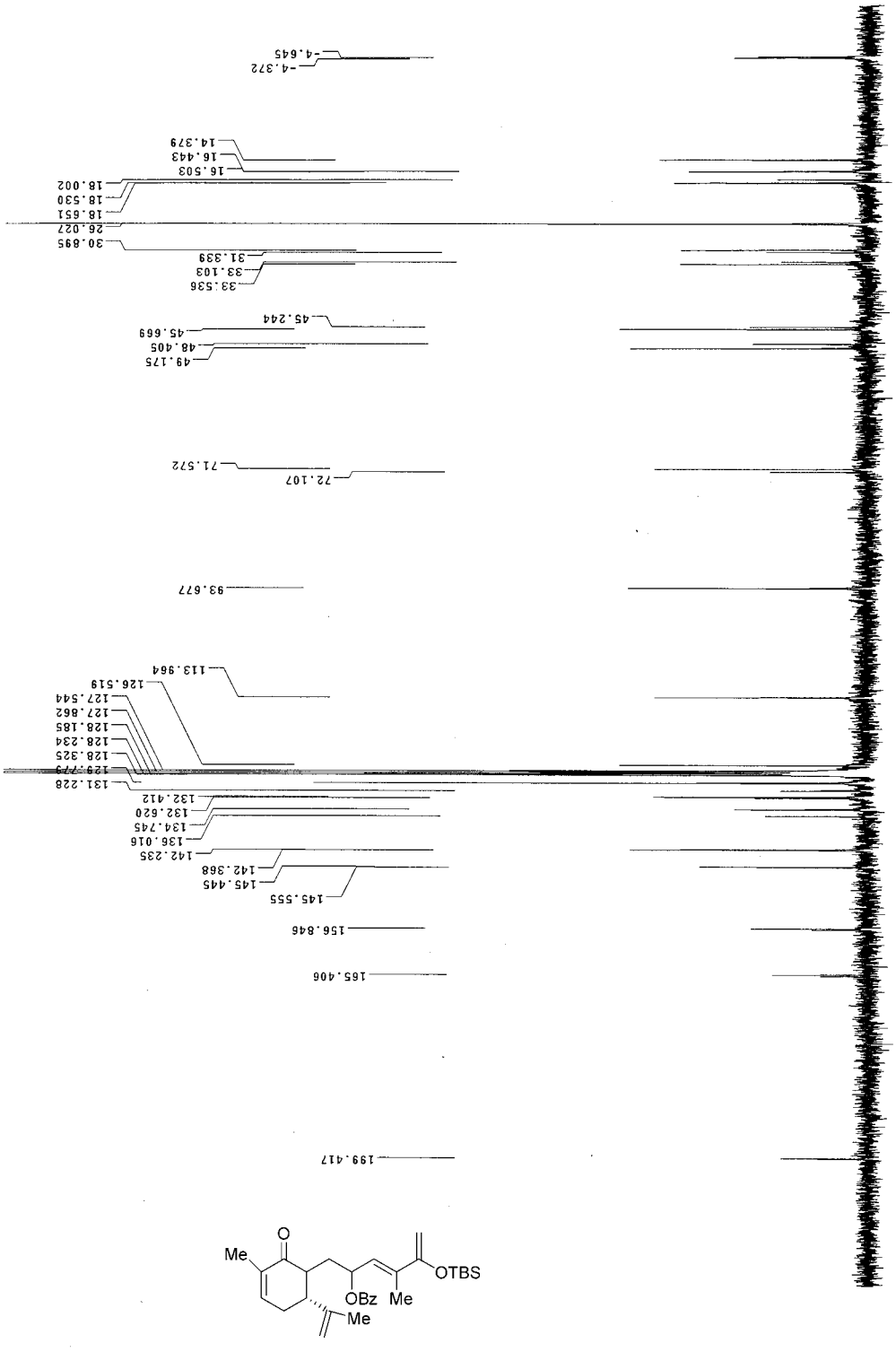
Spectrum 3.87: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **99**



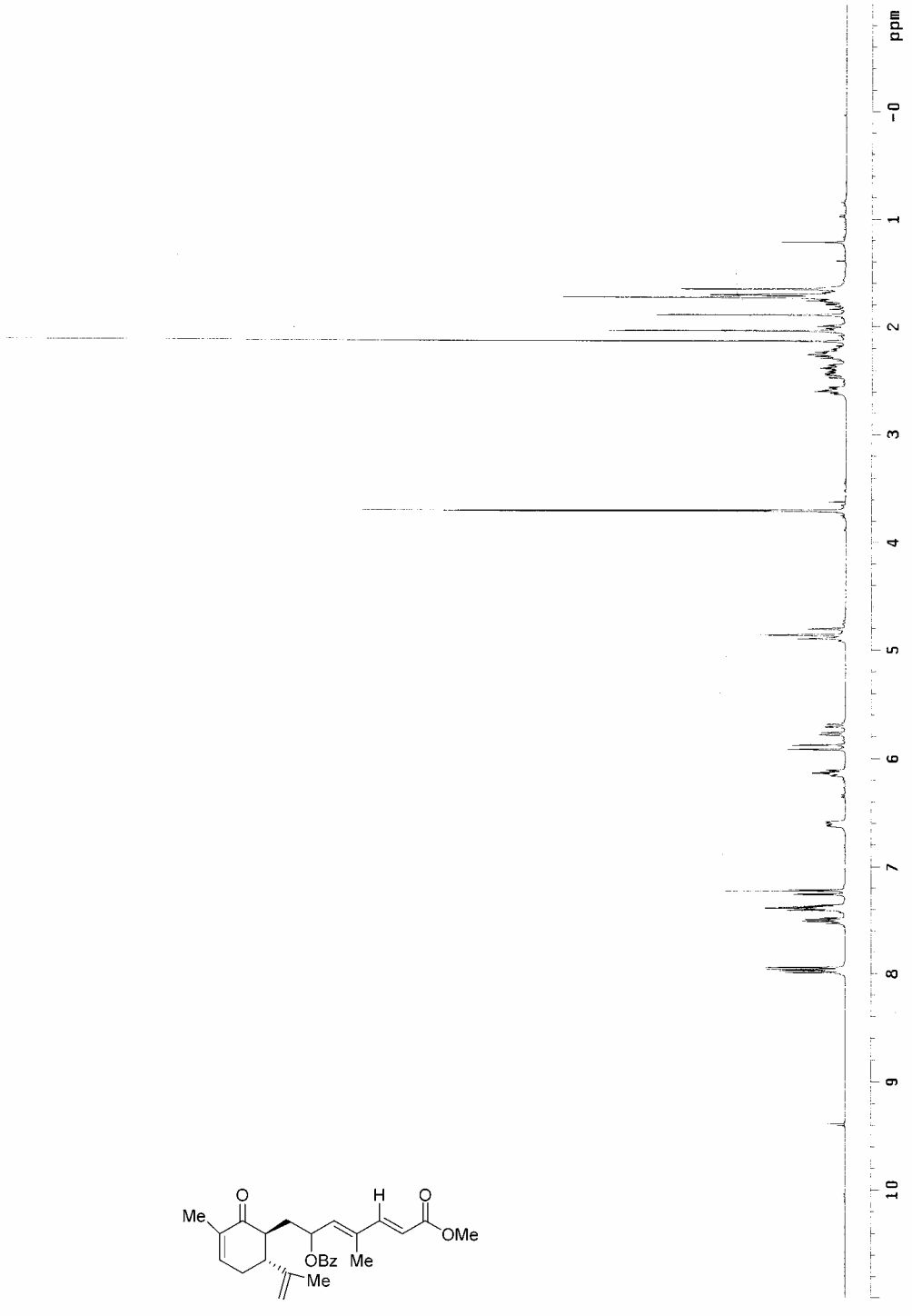
Spectrum 3.88: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **100**



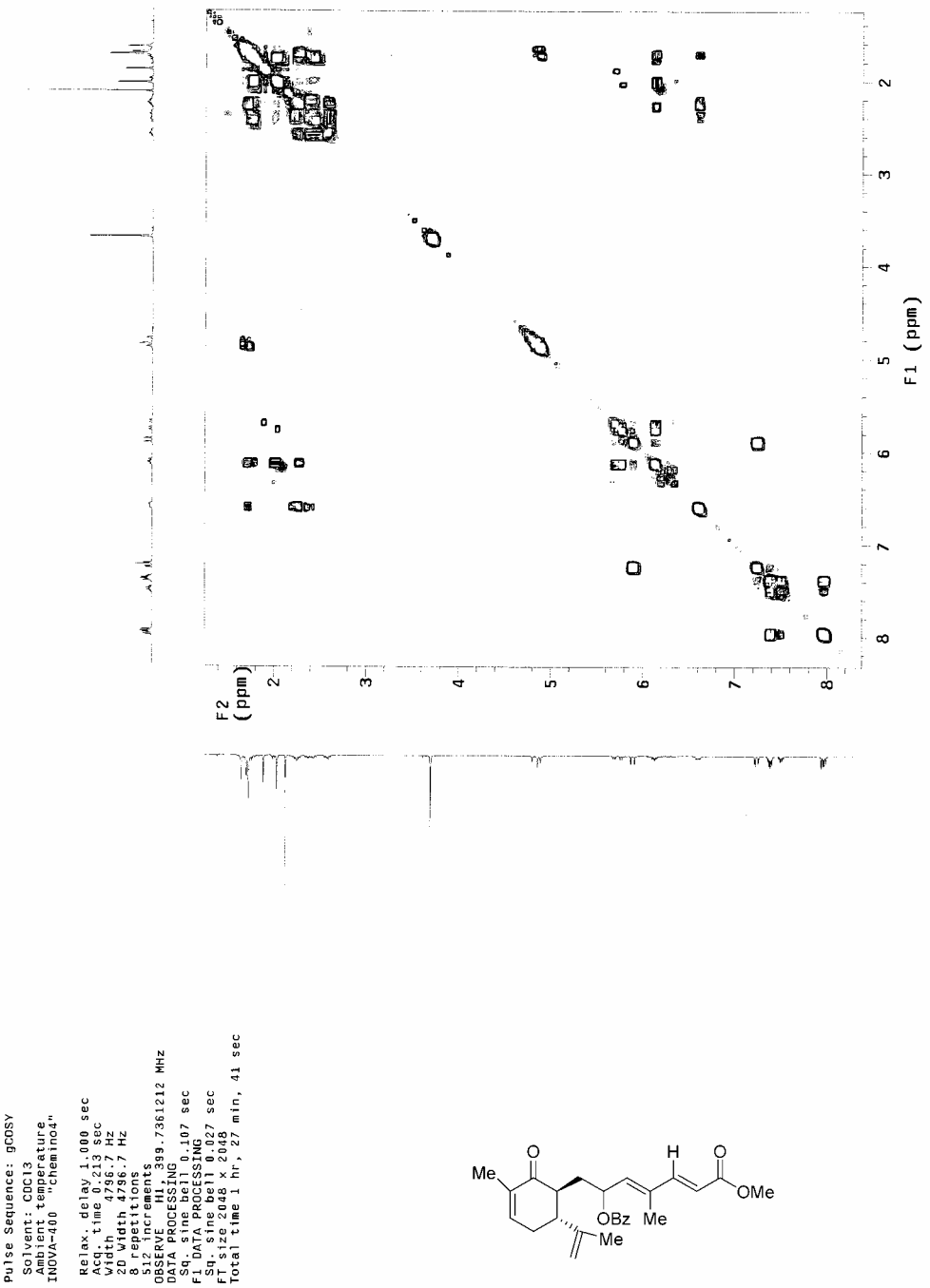
Spectrum 3.89: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **101**



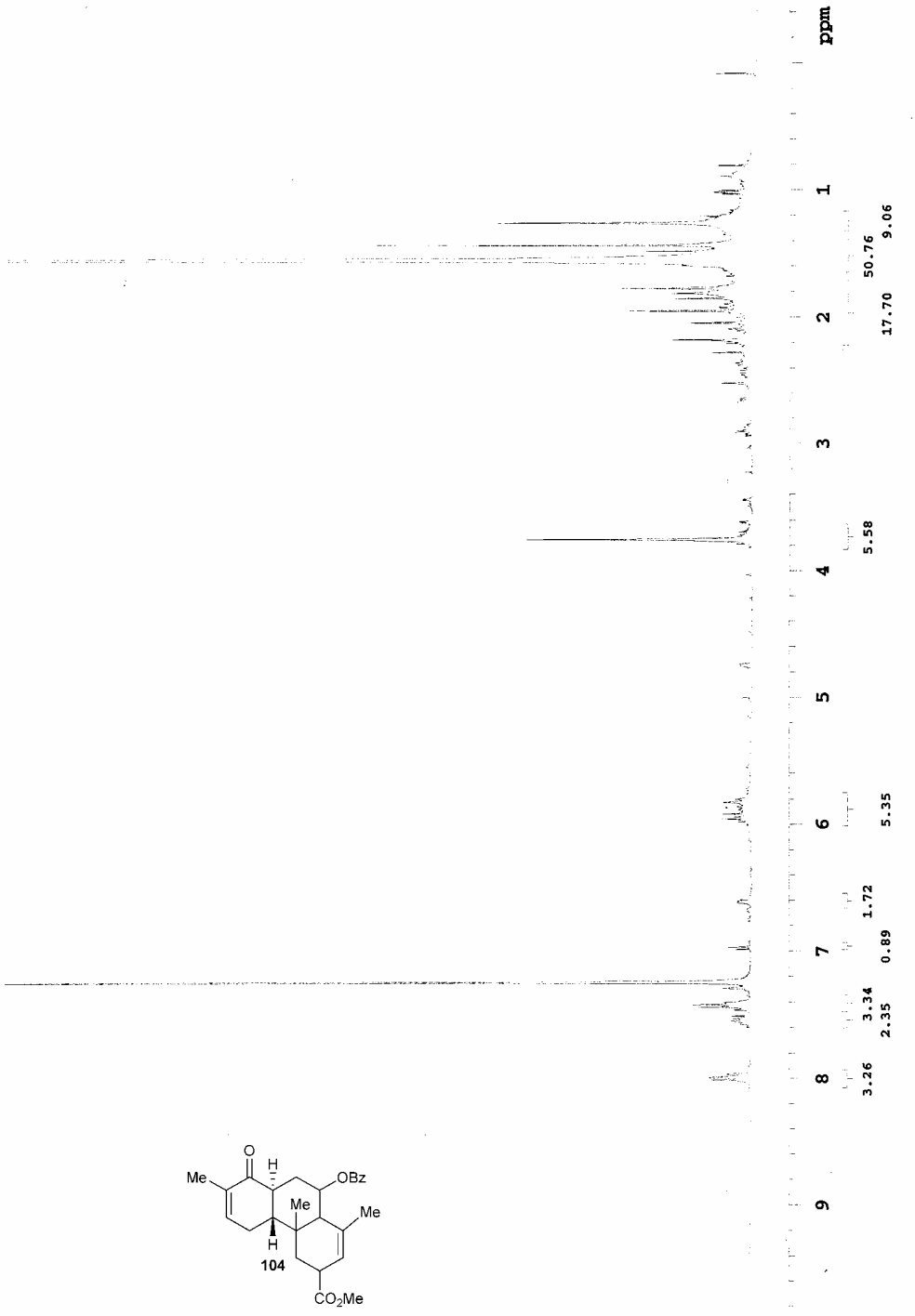
Spectrum 3.90: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **101**



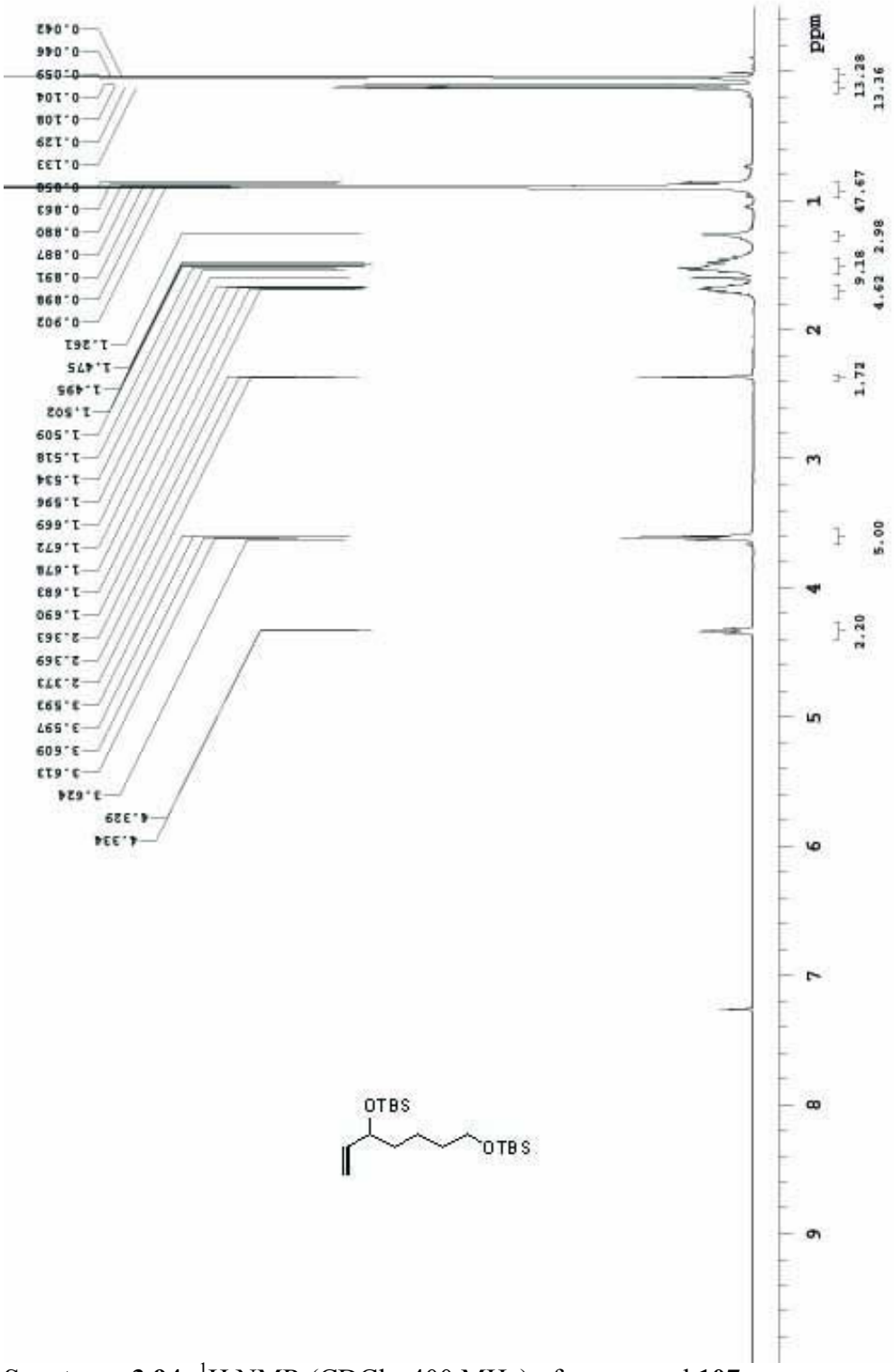
Spectrum 3.91: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **103**



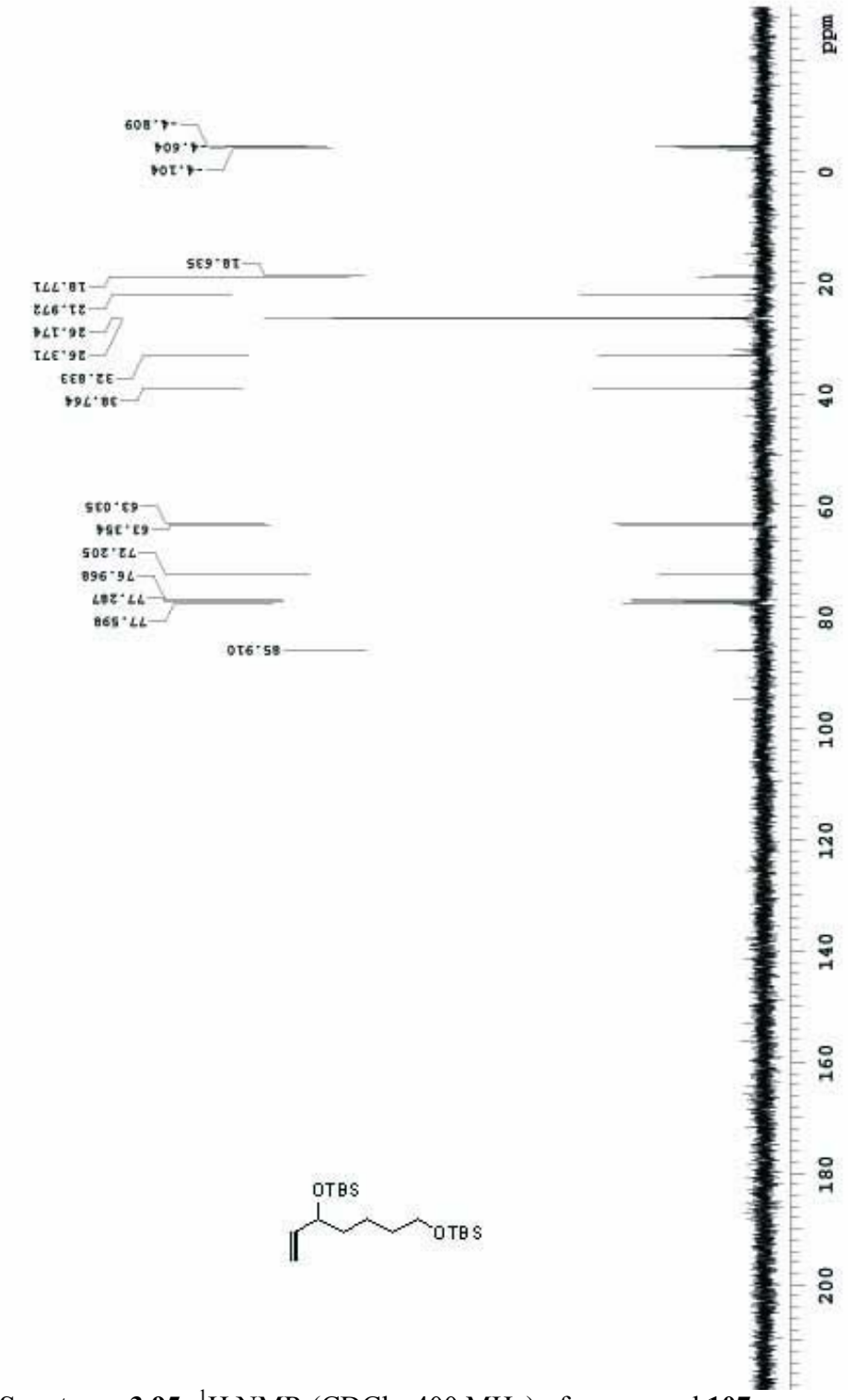
Spectrum 3.92: 2D NMR ($CDCl_3$, 400 MHz) of Compound **103**



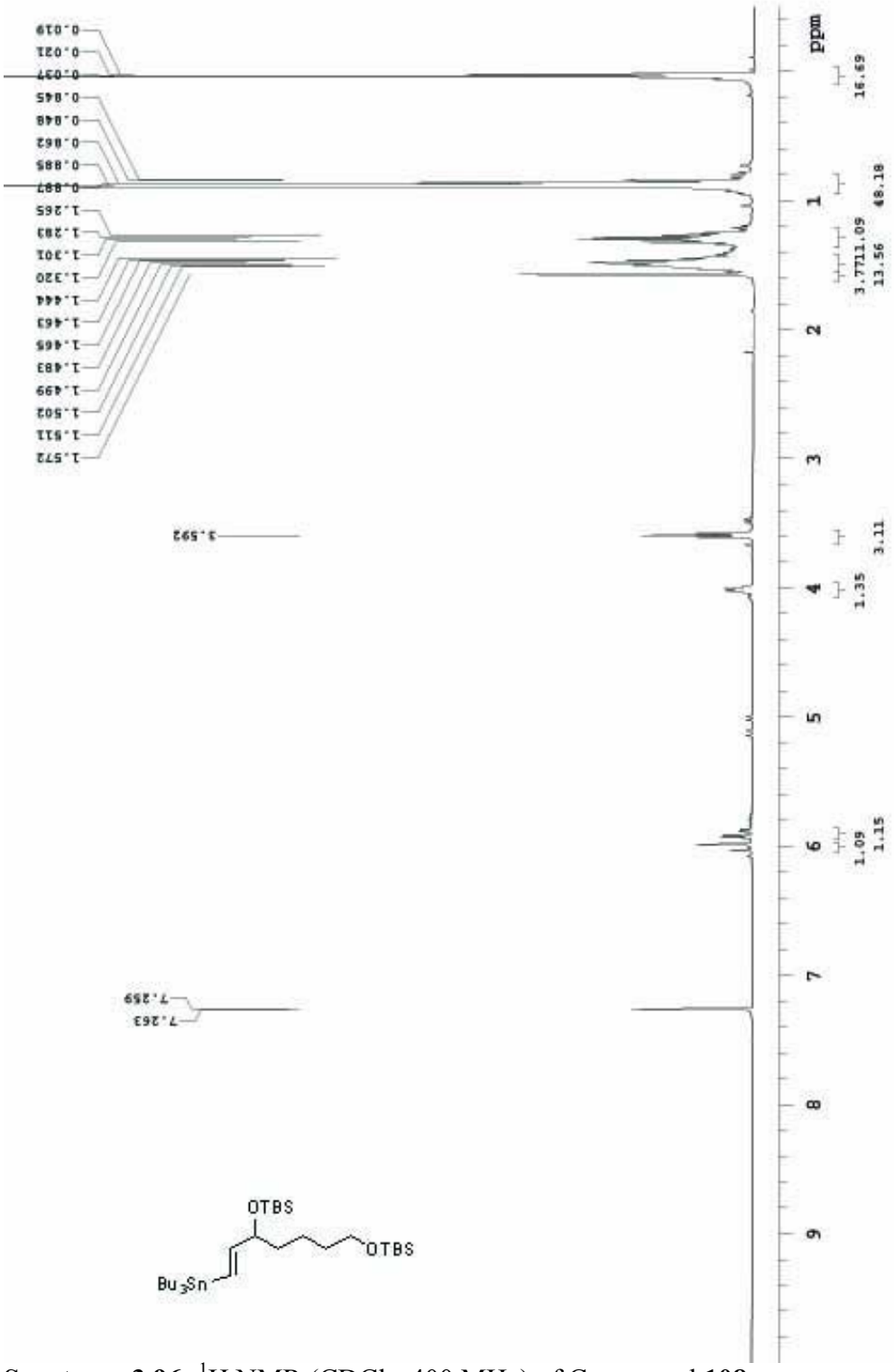
Spectrum 3.93: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **104**



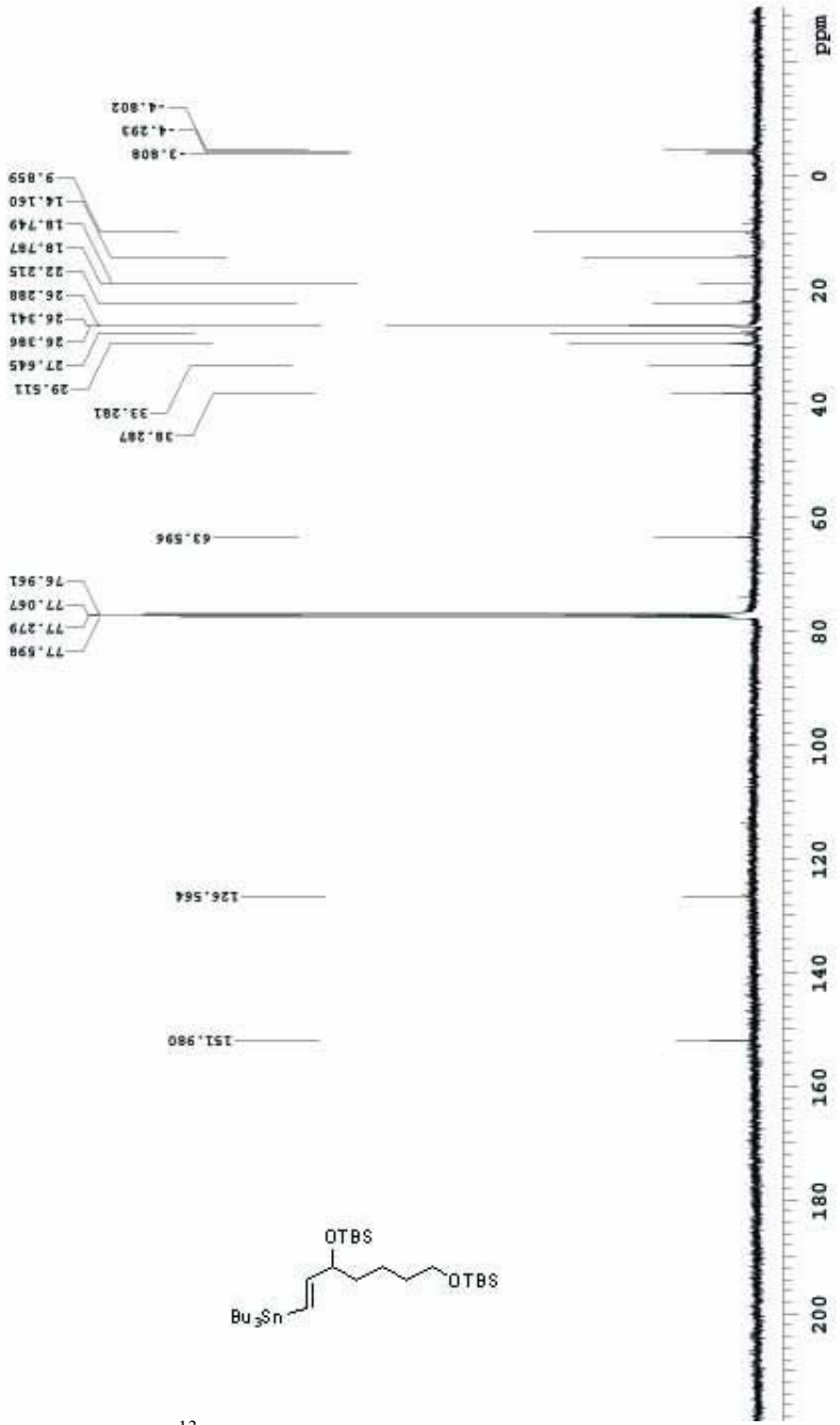
Spectrum 3.94: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **107**



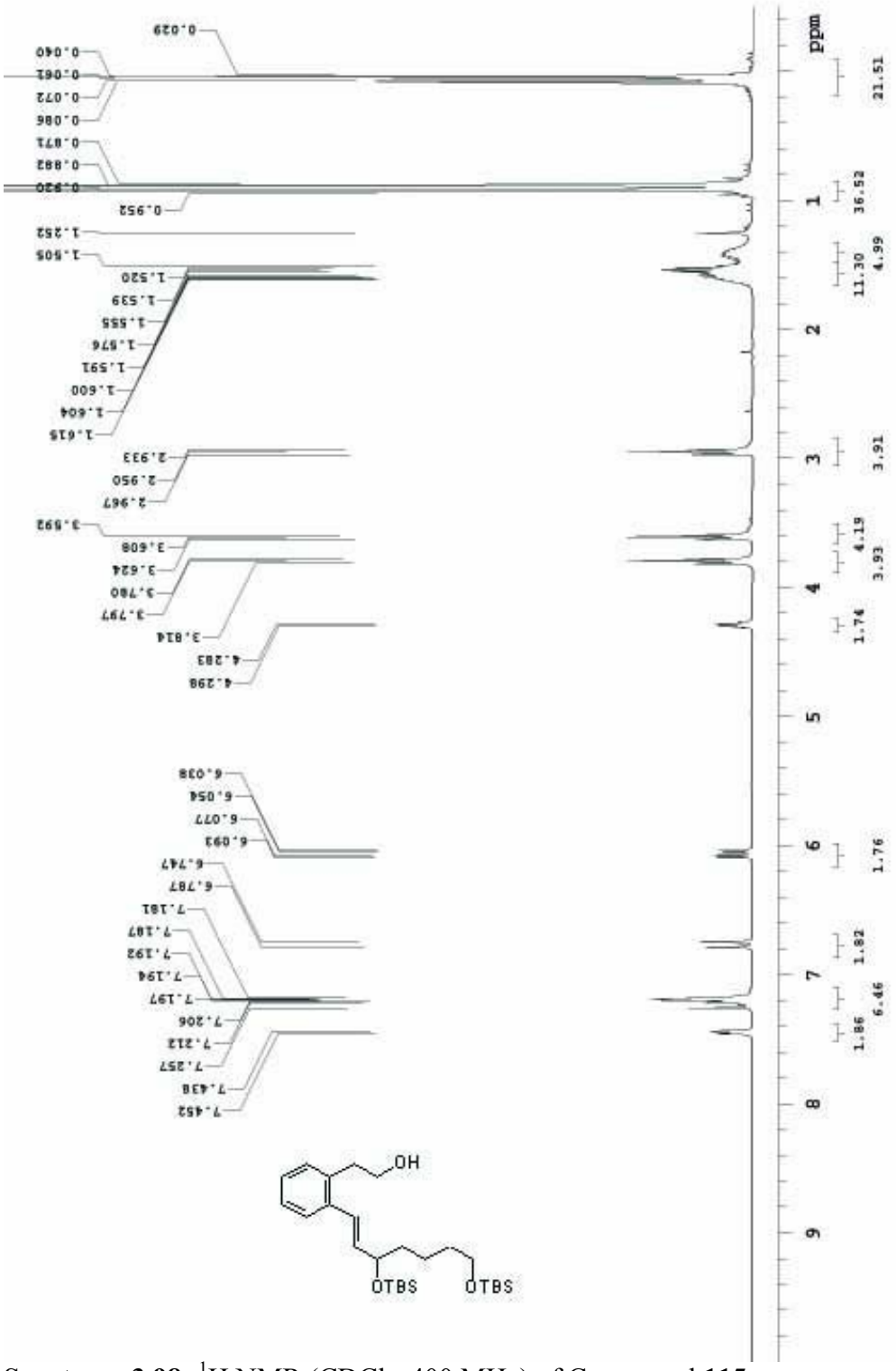
Spectrum 3.95: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **107**



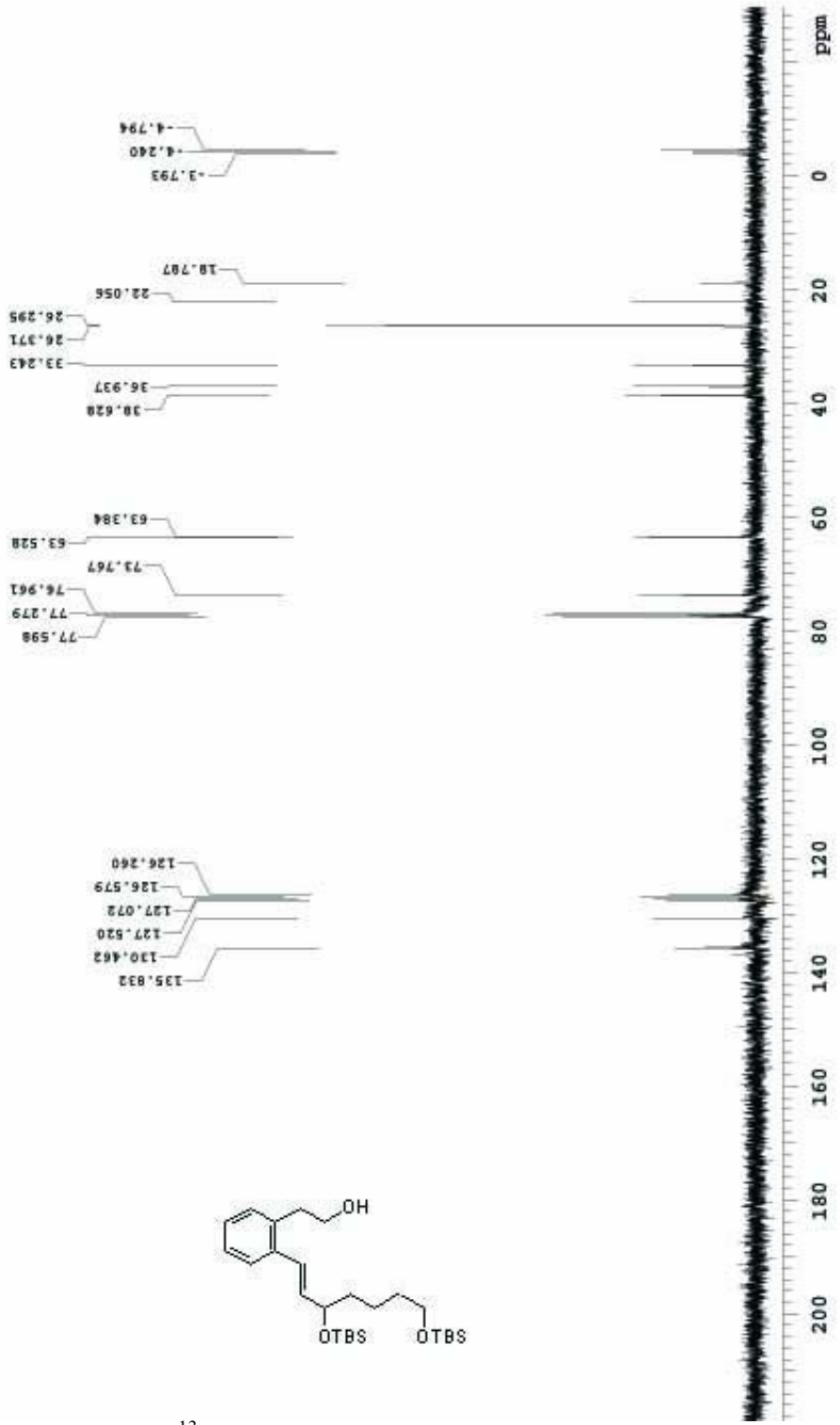
Spectrum 3.96: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **108**



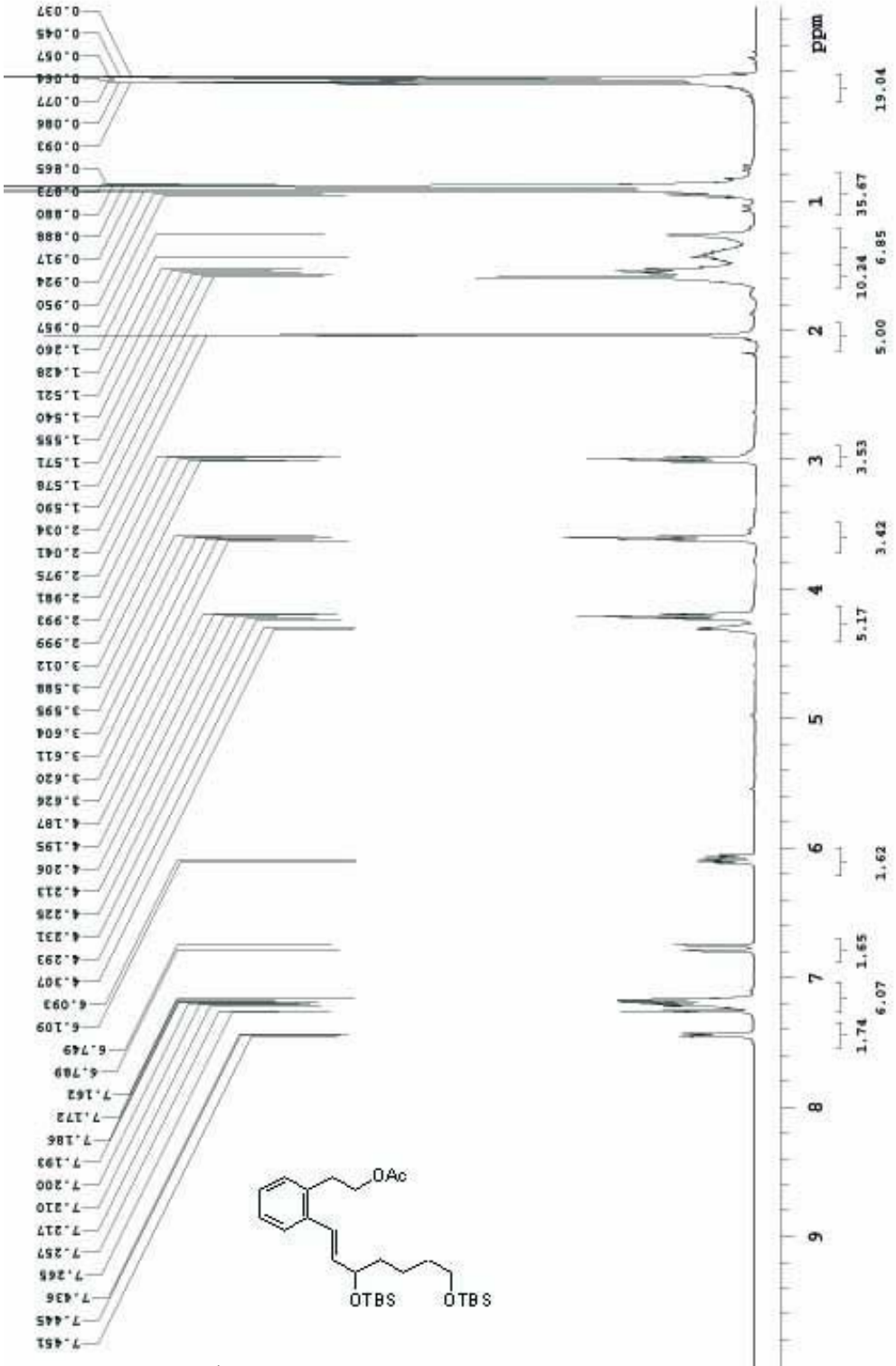
Spectrum 3.97: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **108**



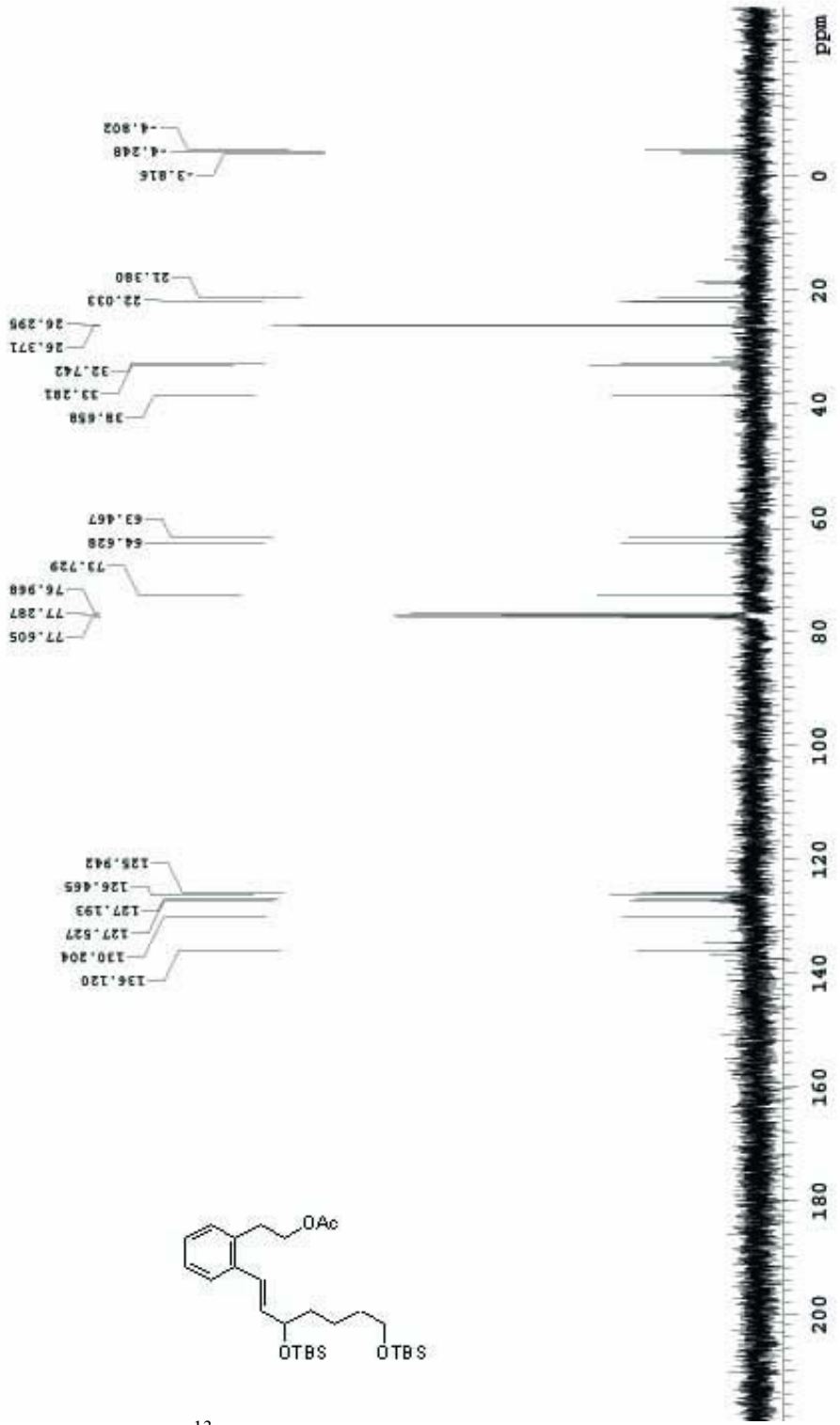
Spectrum 3.98: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **115**



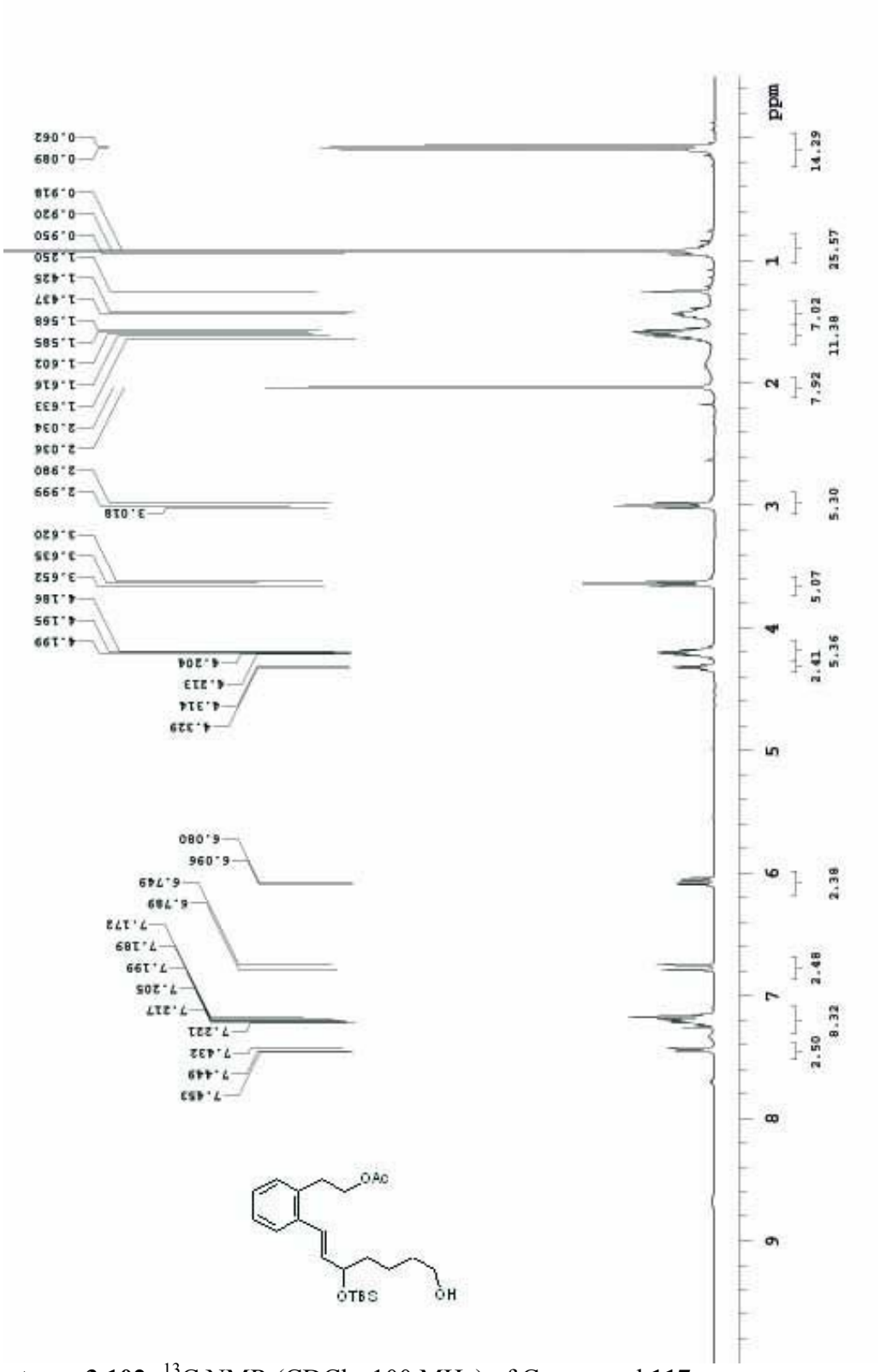
Spectrum 3.99: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **115**



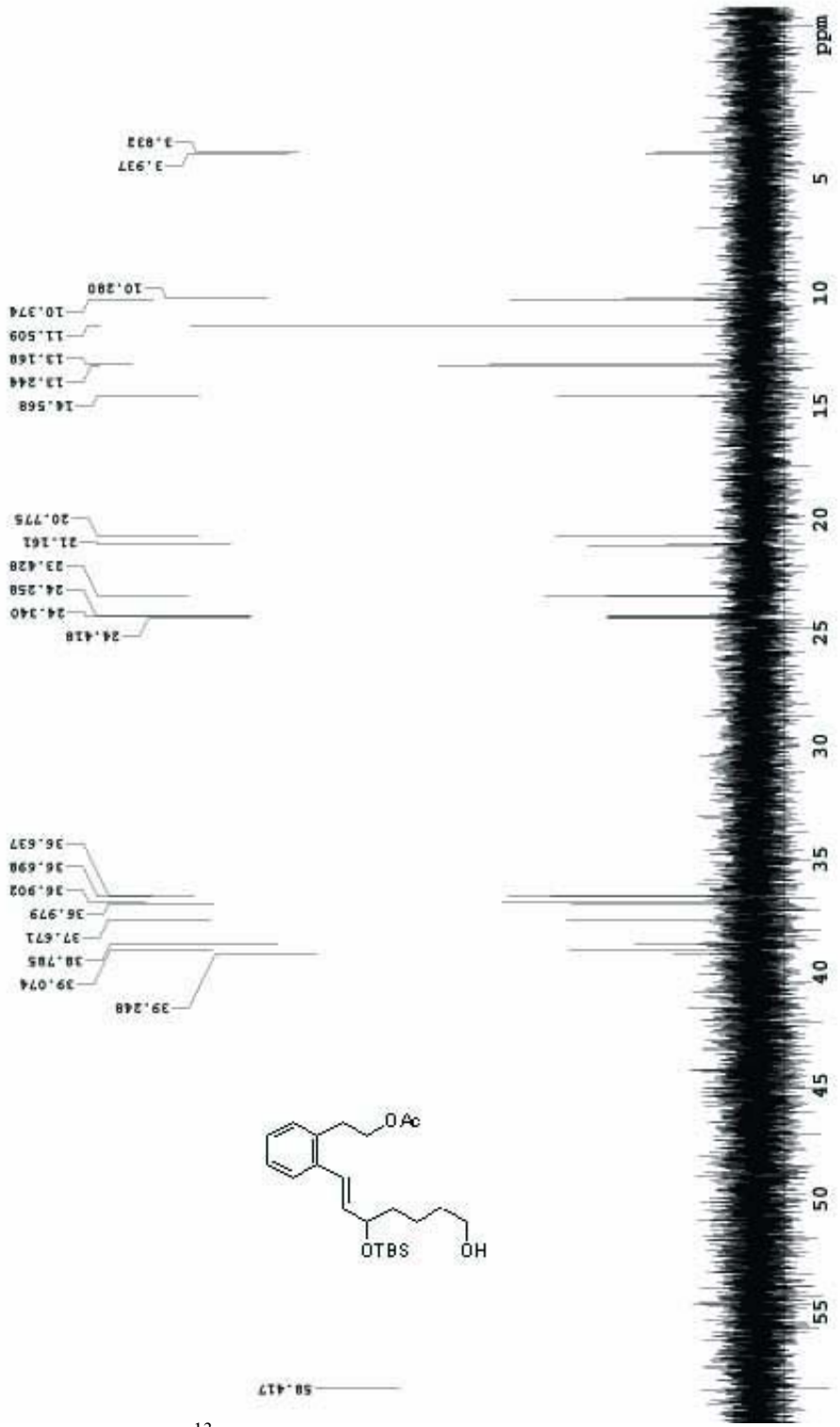
Spectrum 3.100: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **116**



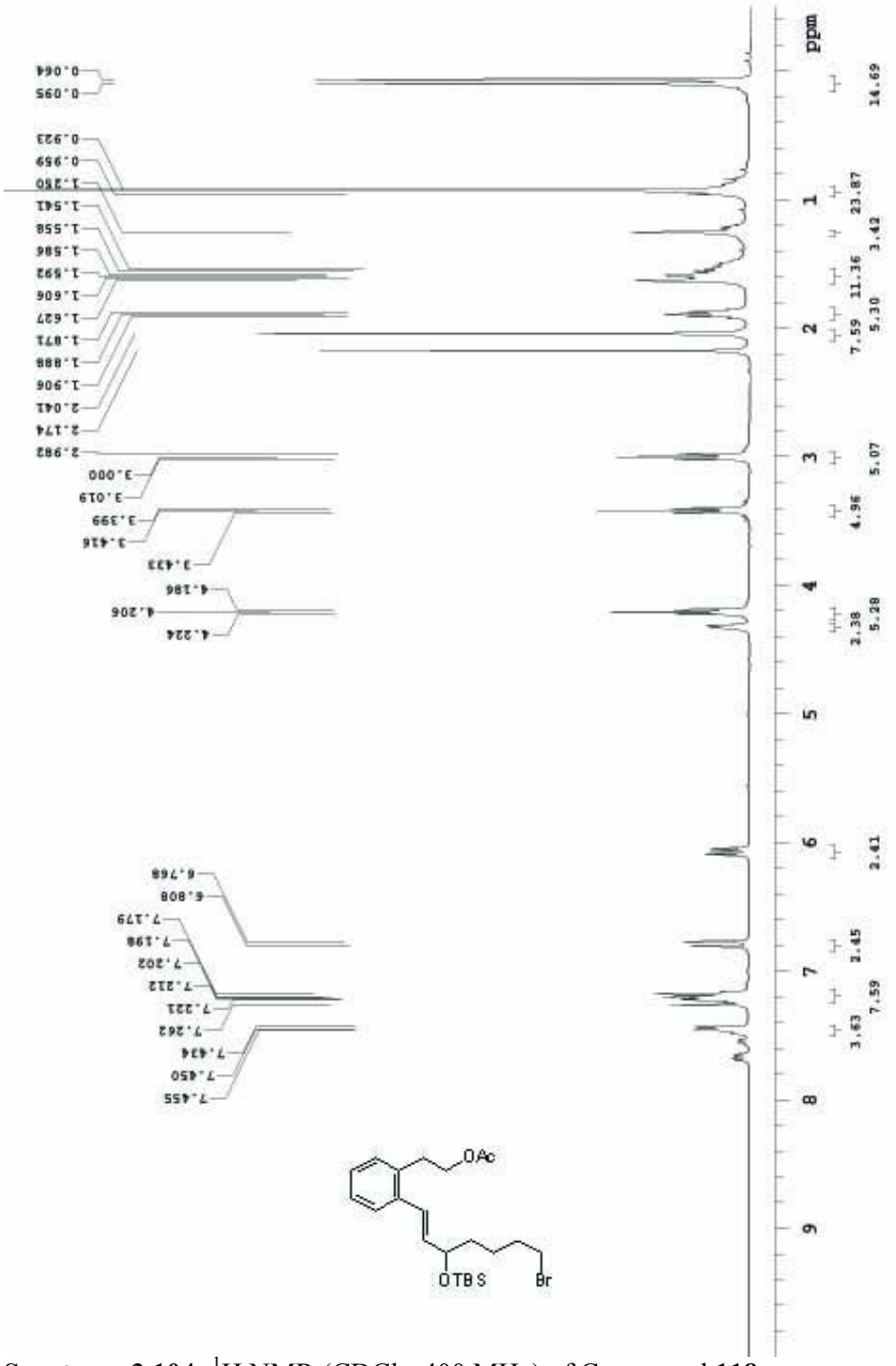
Spectrum 3.101: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **116**



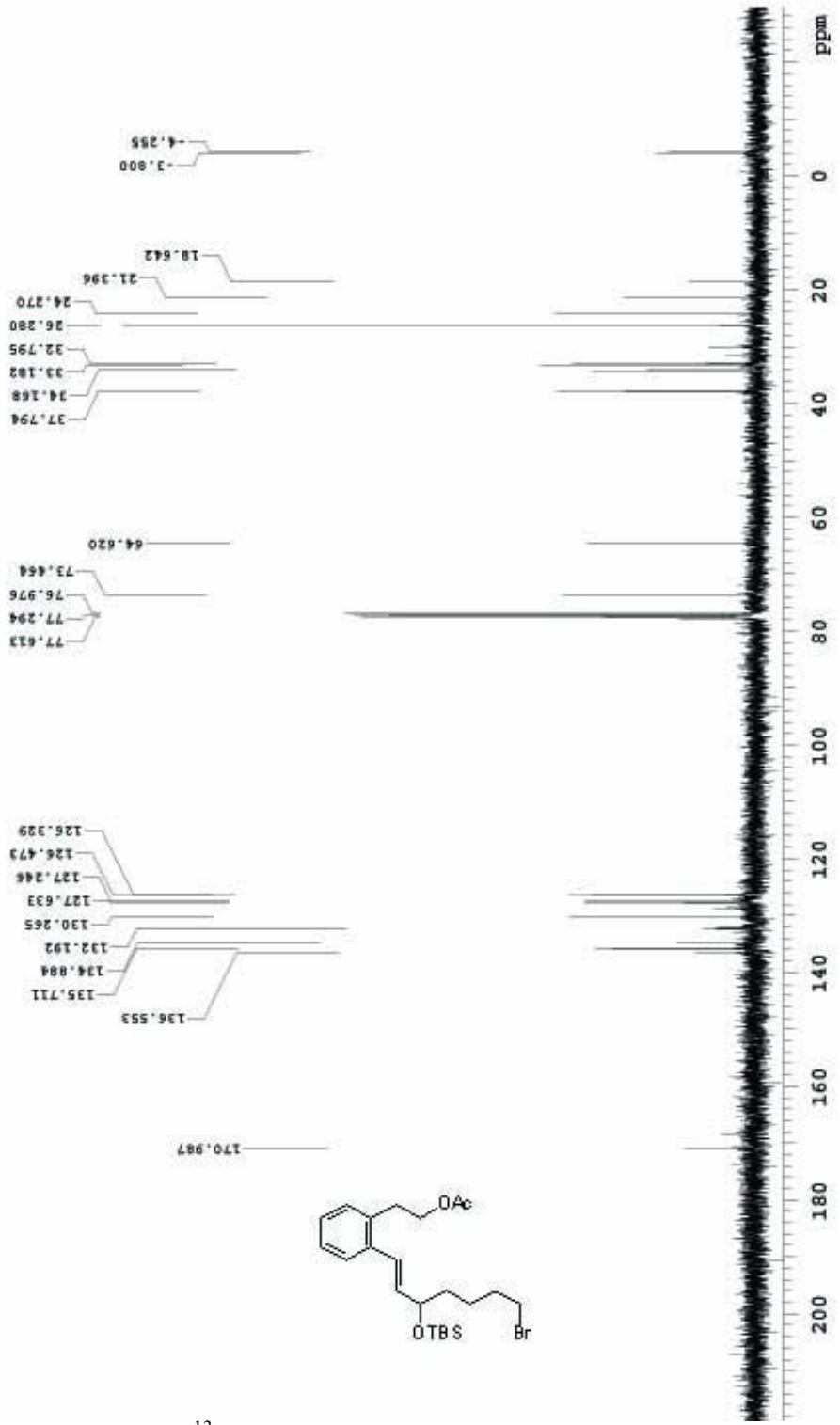
Spectrum 3.102: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **117**



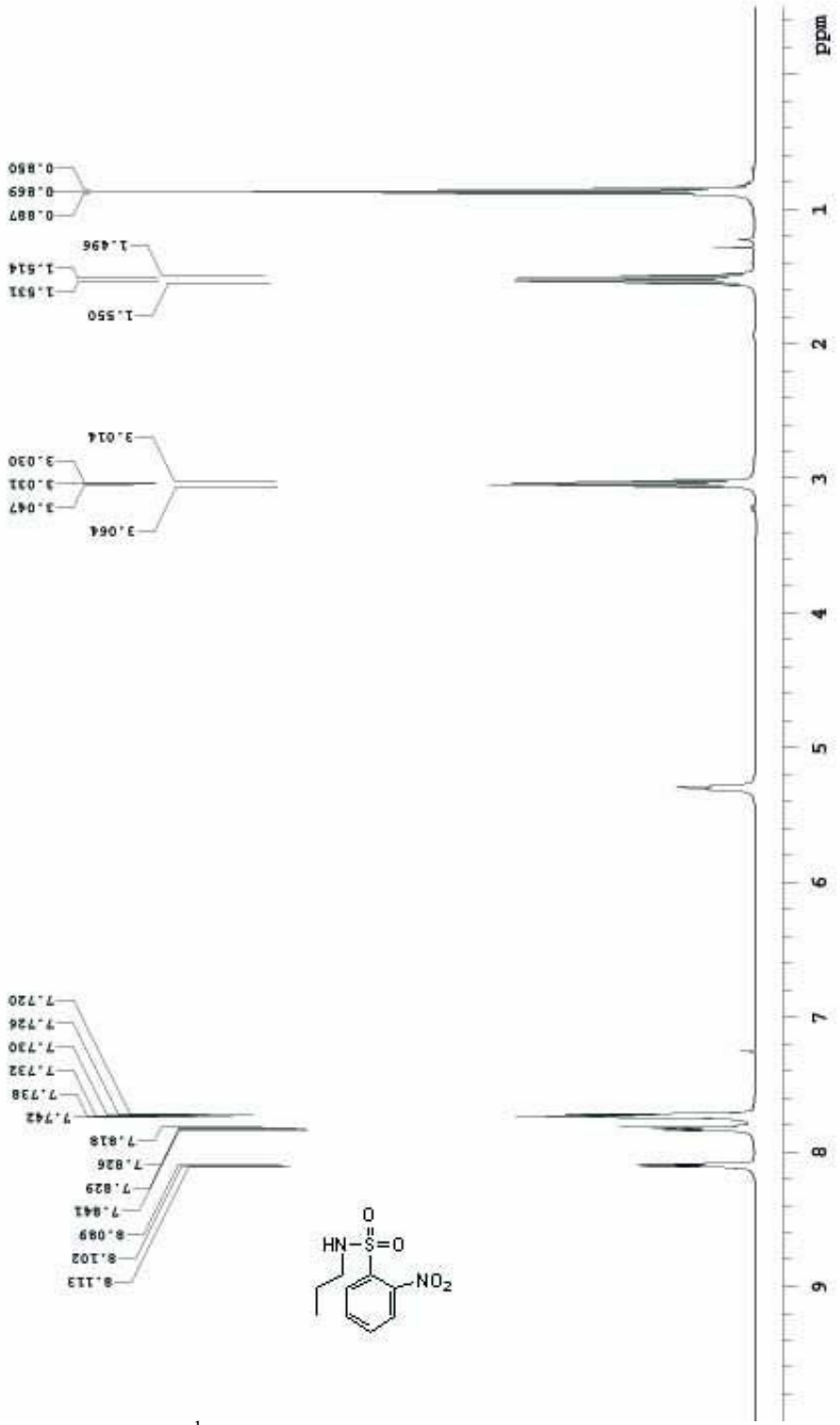
Spectrum 3.103: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **117**



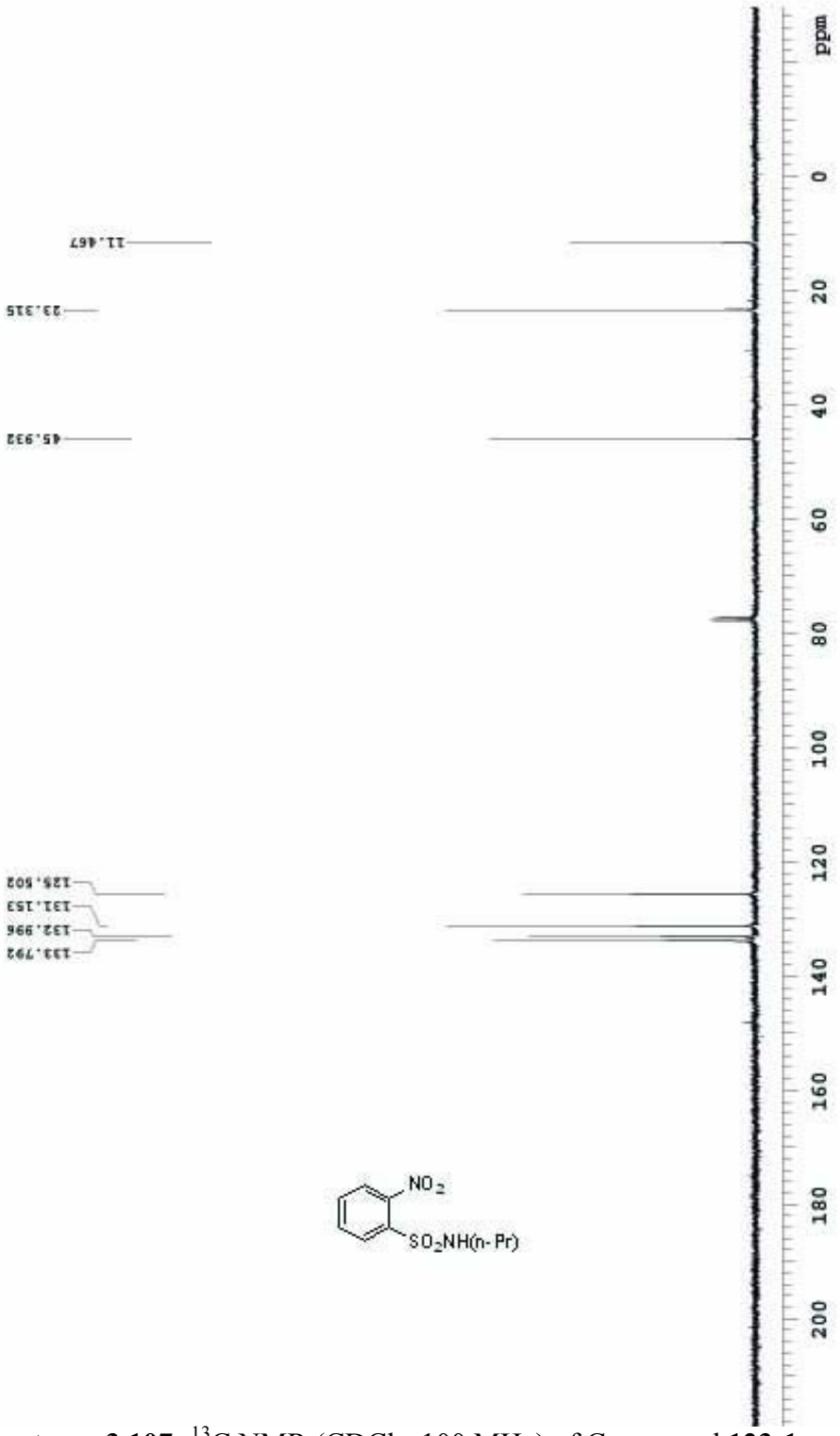
Spectrum 3.104: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **118**



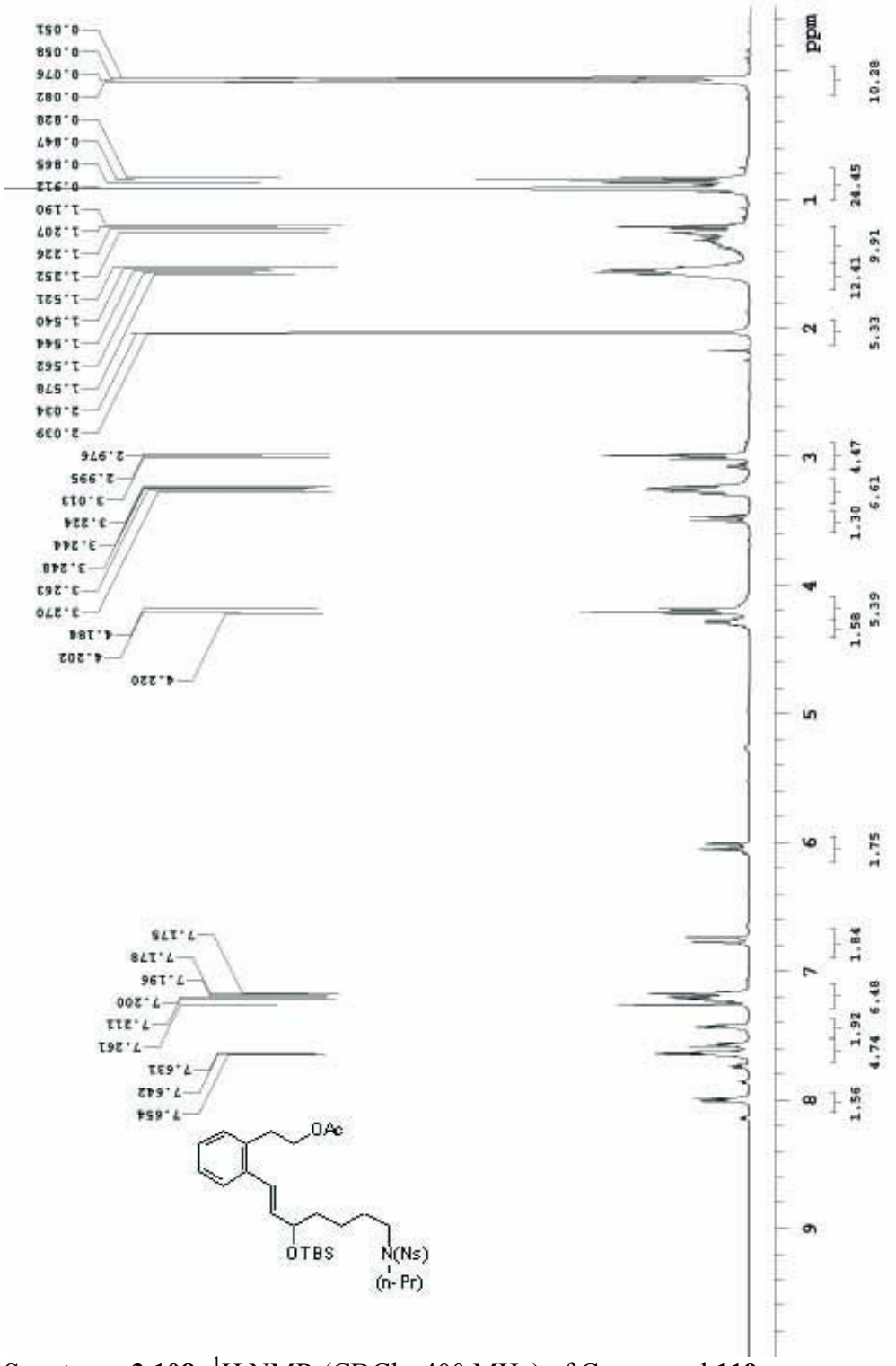
Spectrum 3.105: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **118**



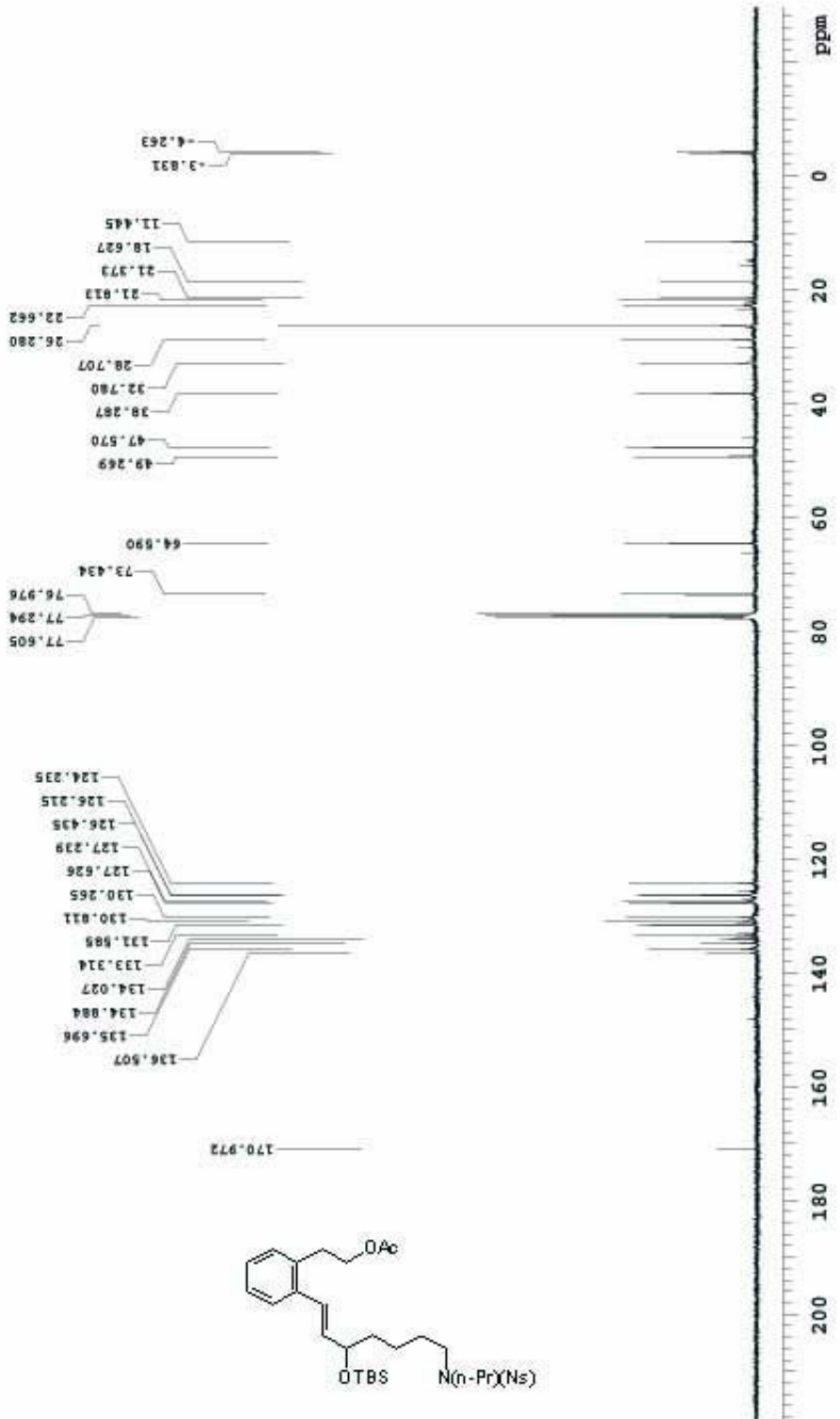
Spectrum 3.106: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **123-1**



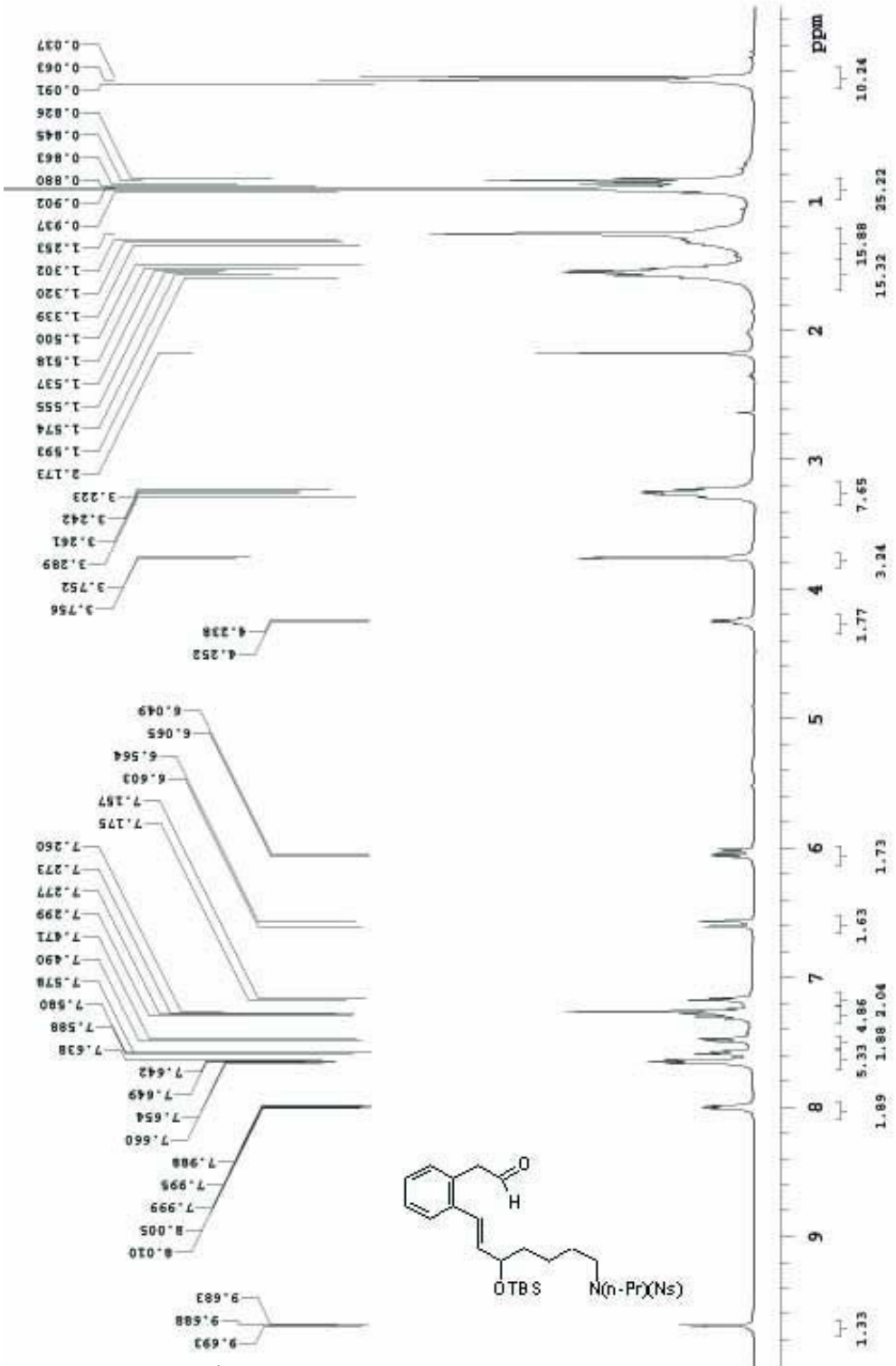
Spectrum 3.107: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **123-1**



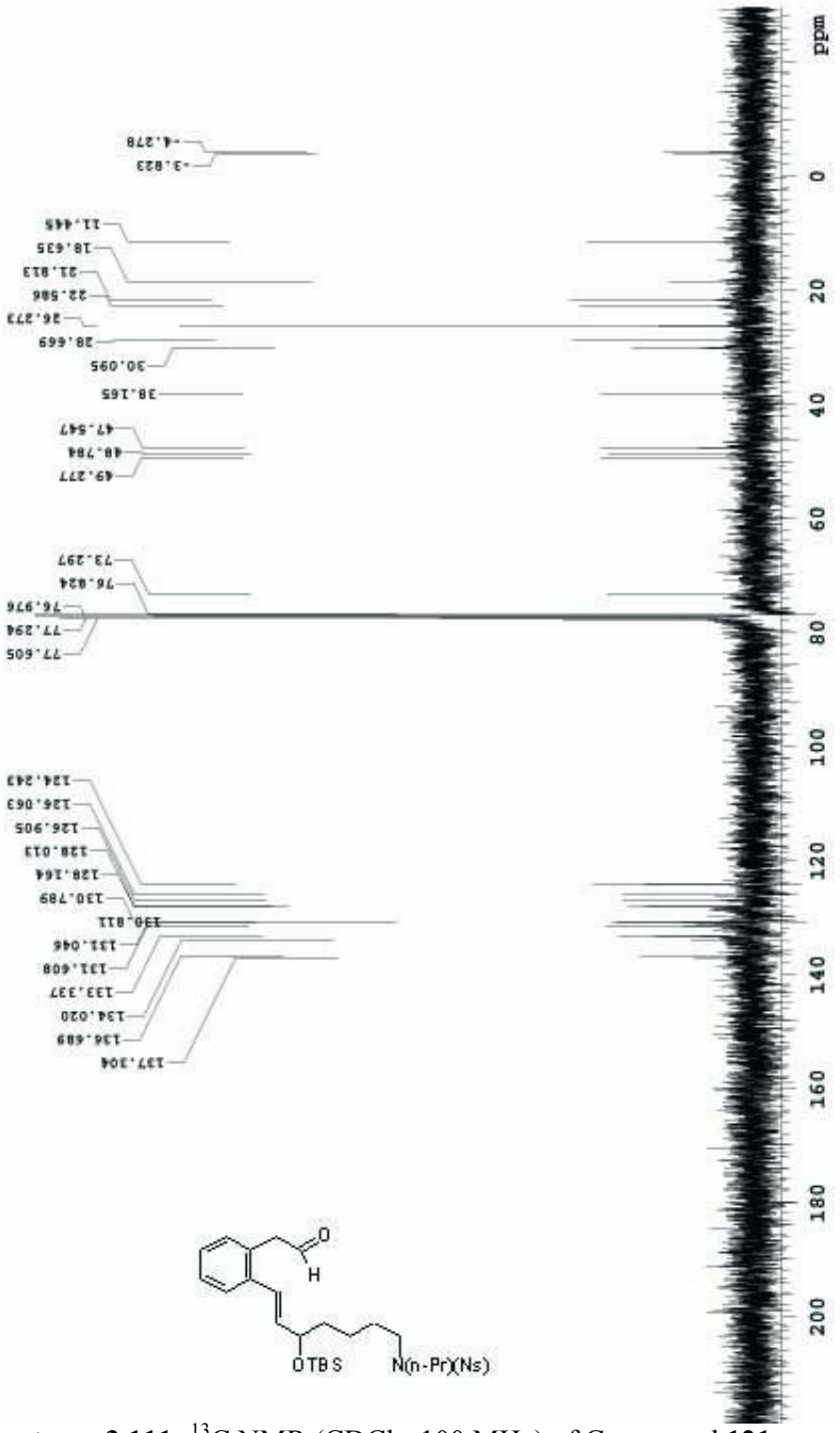
Spectrum 3.108: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **119**



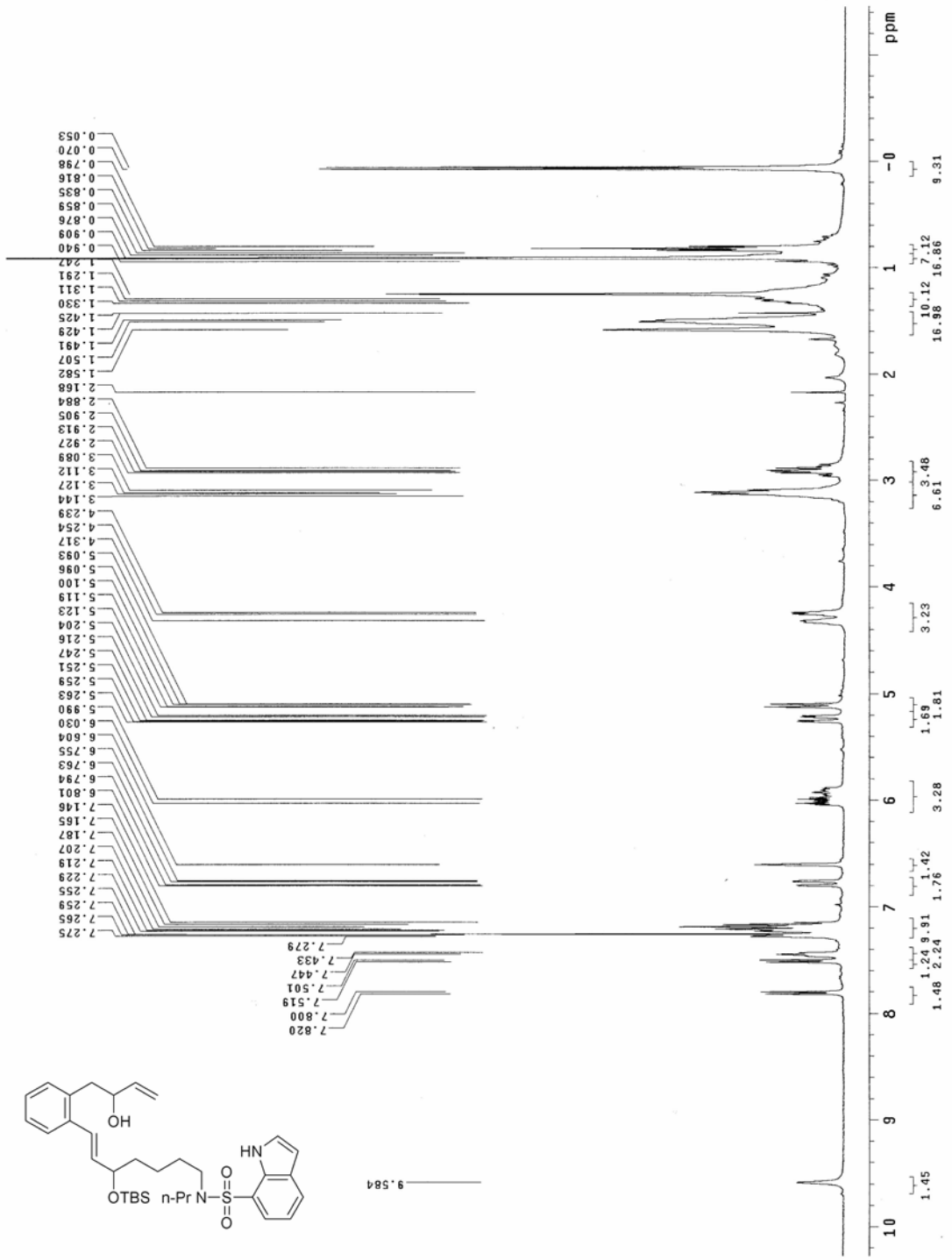
Spectrum 3.109: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **119**



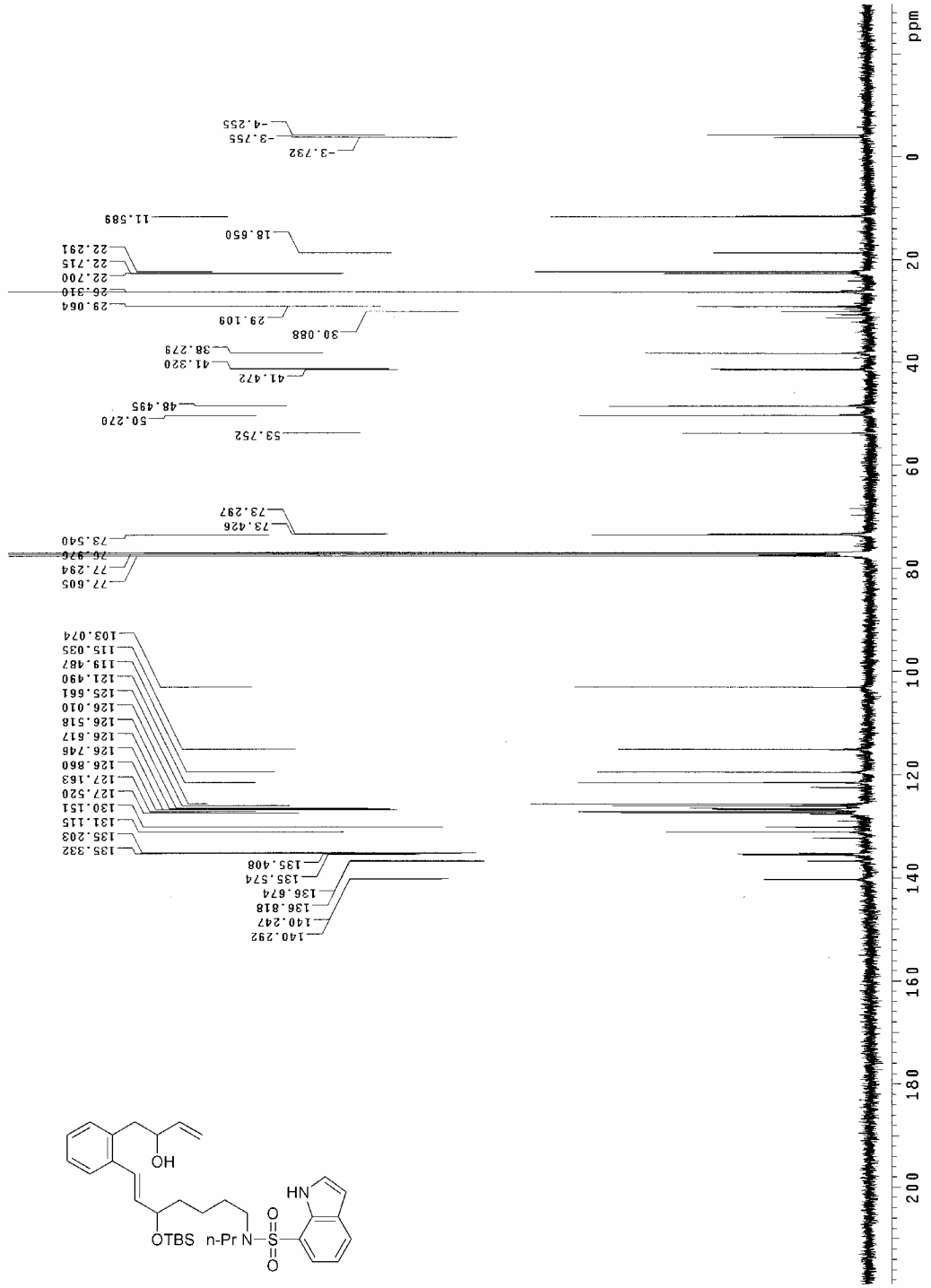
Spectrum 3.110: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **121**



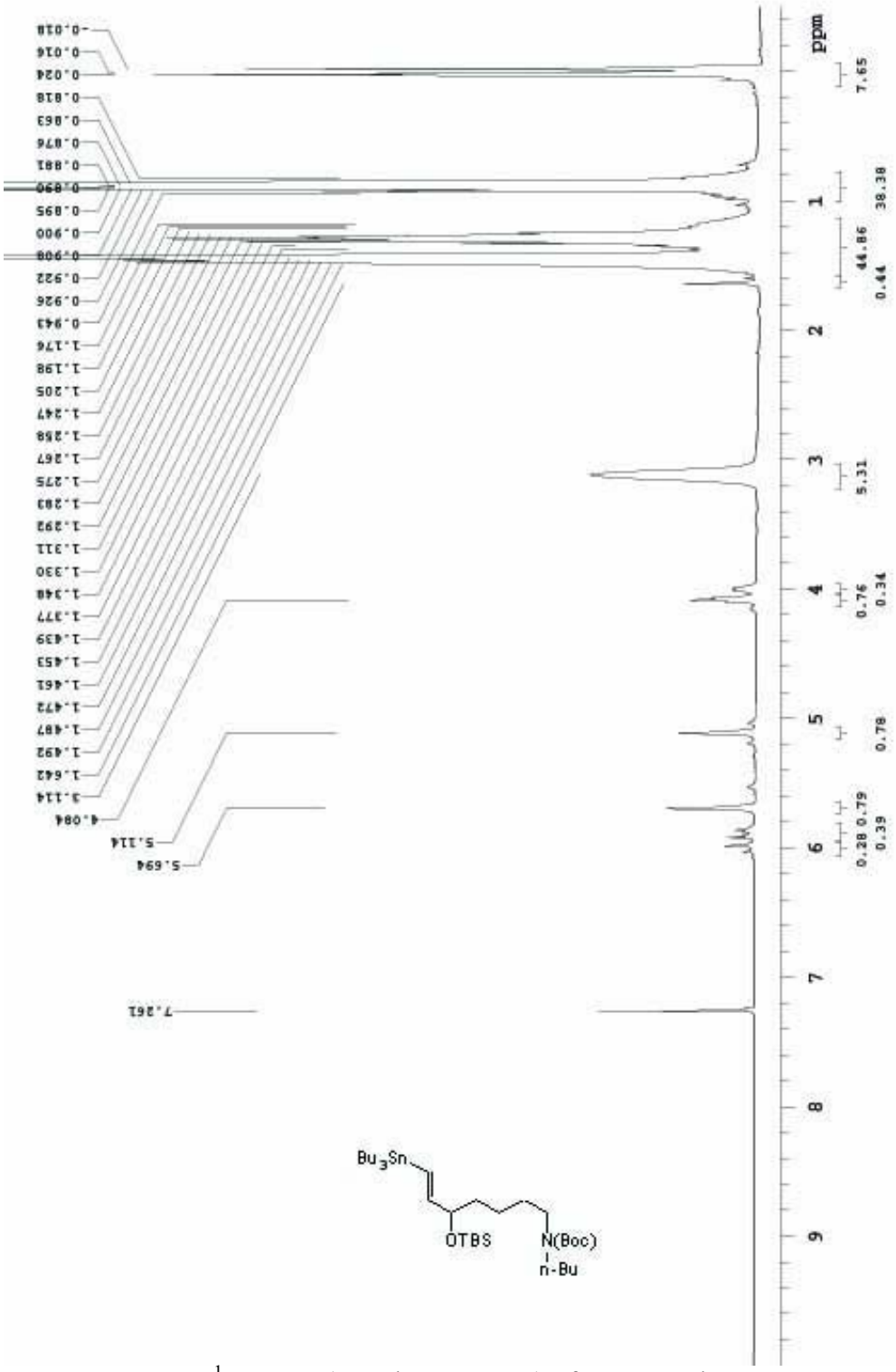
Spectrum 3.111: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **121**



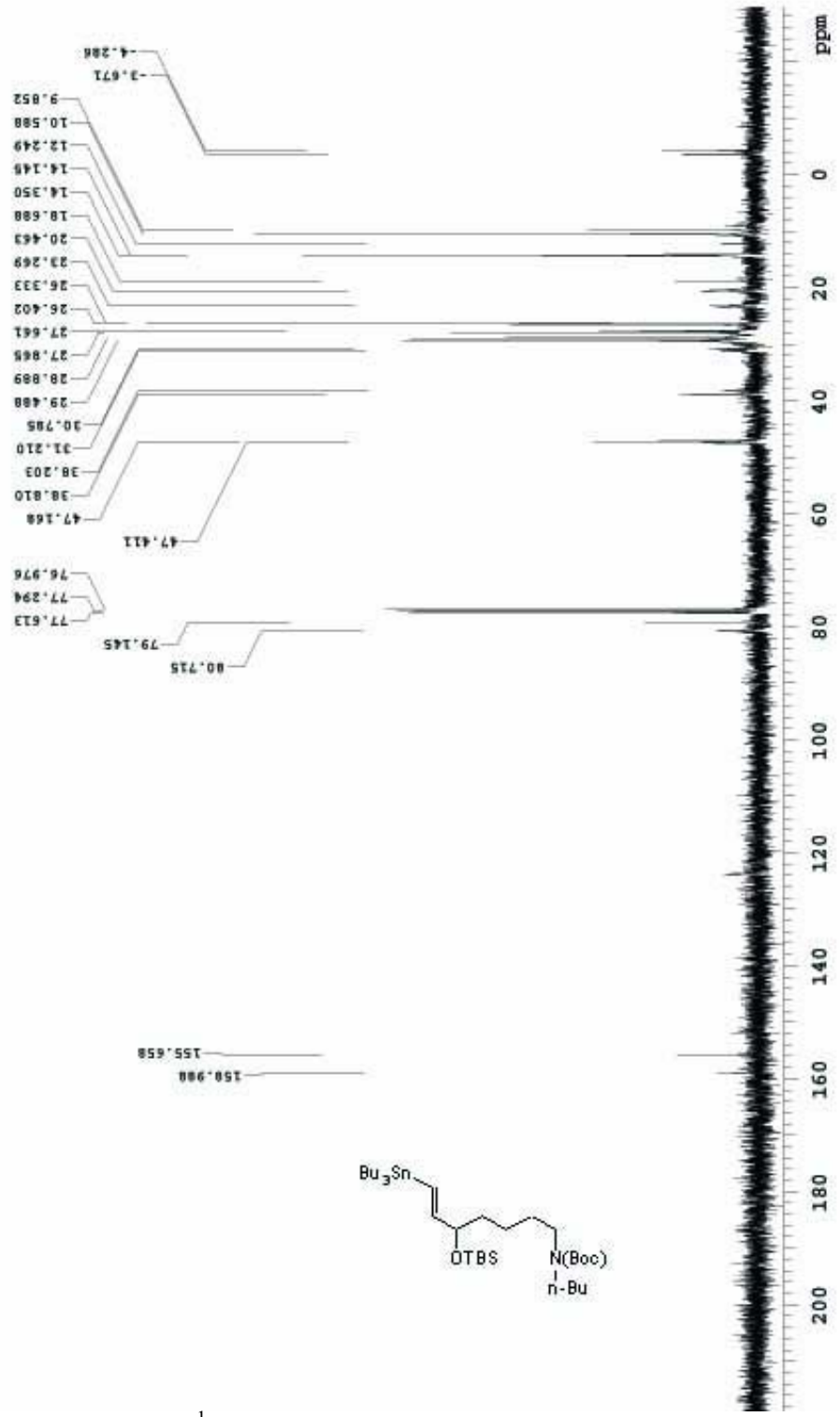
Spectrum 3.112: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **122**



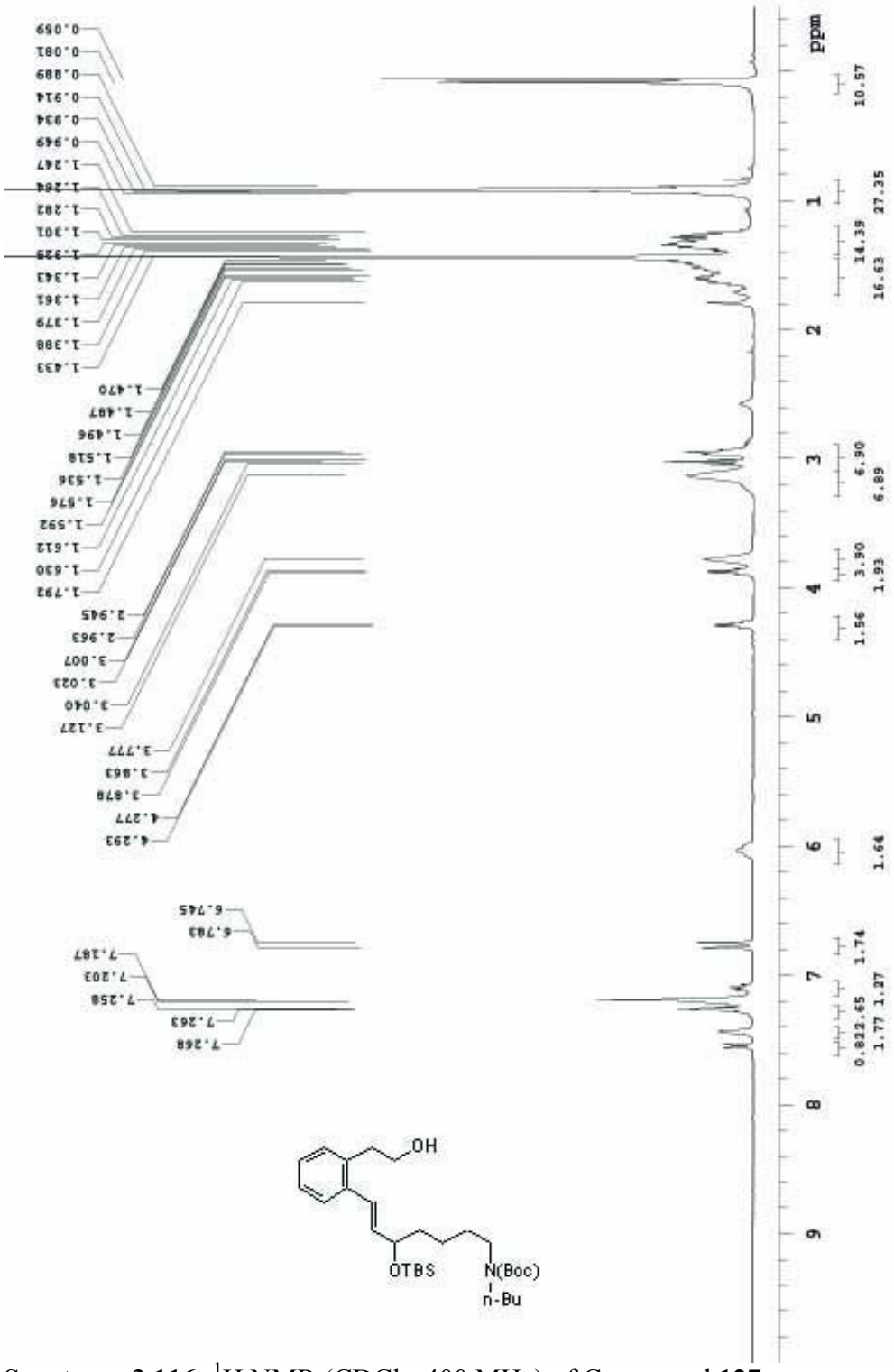
Spectrum 3.113: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **122**



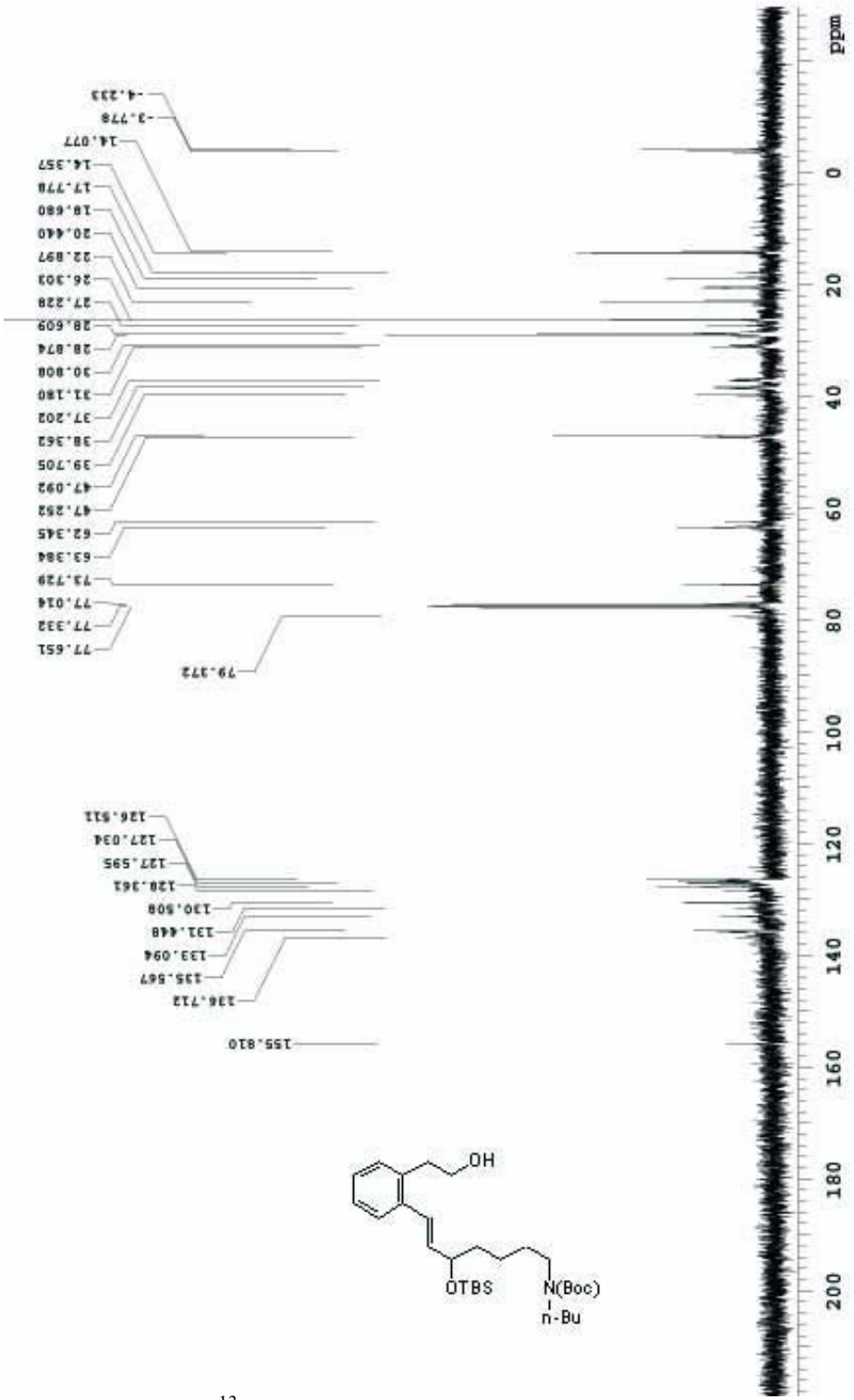
Spectrum 3.114: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **113**



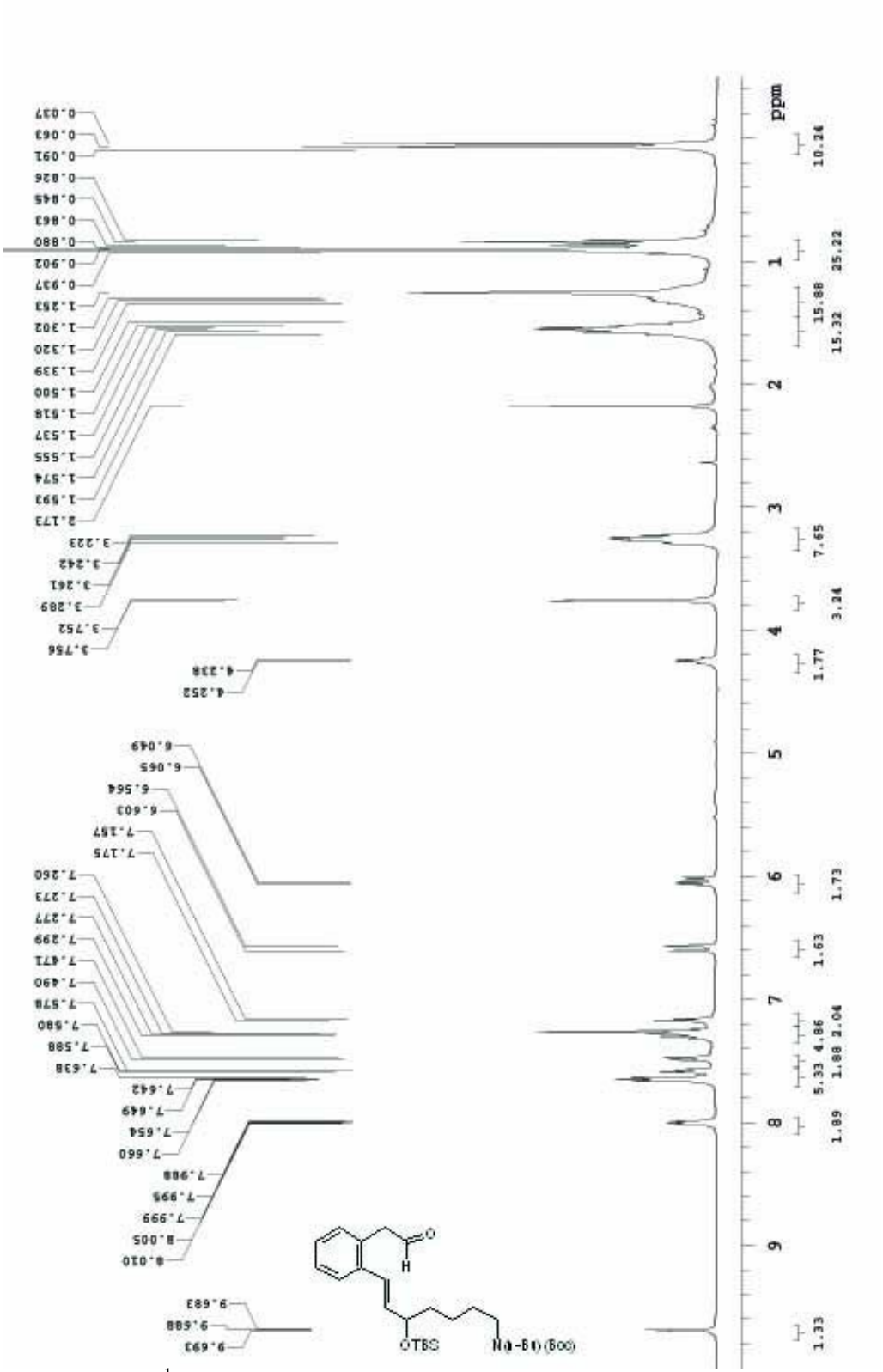
Spectrum 3.115: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **113**



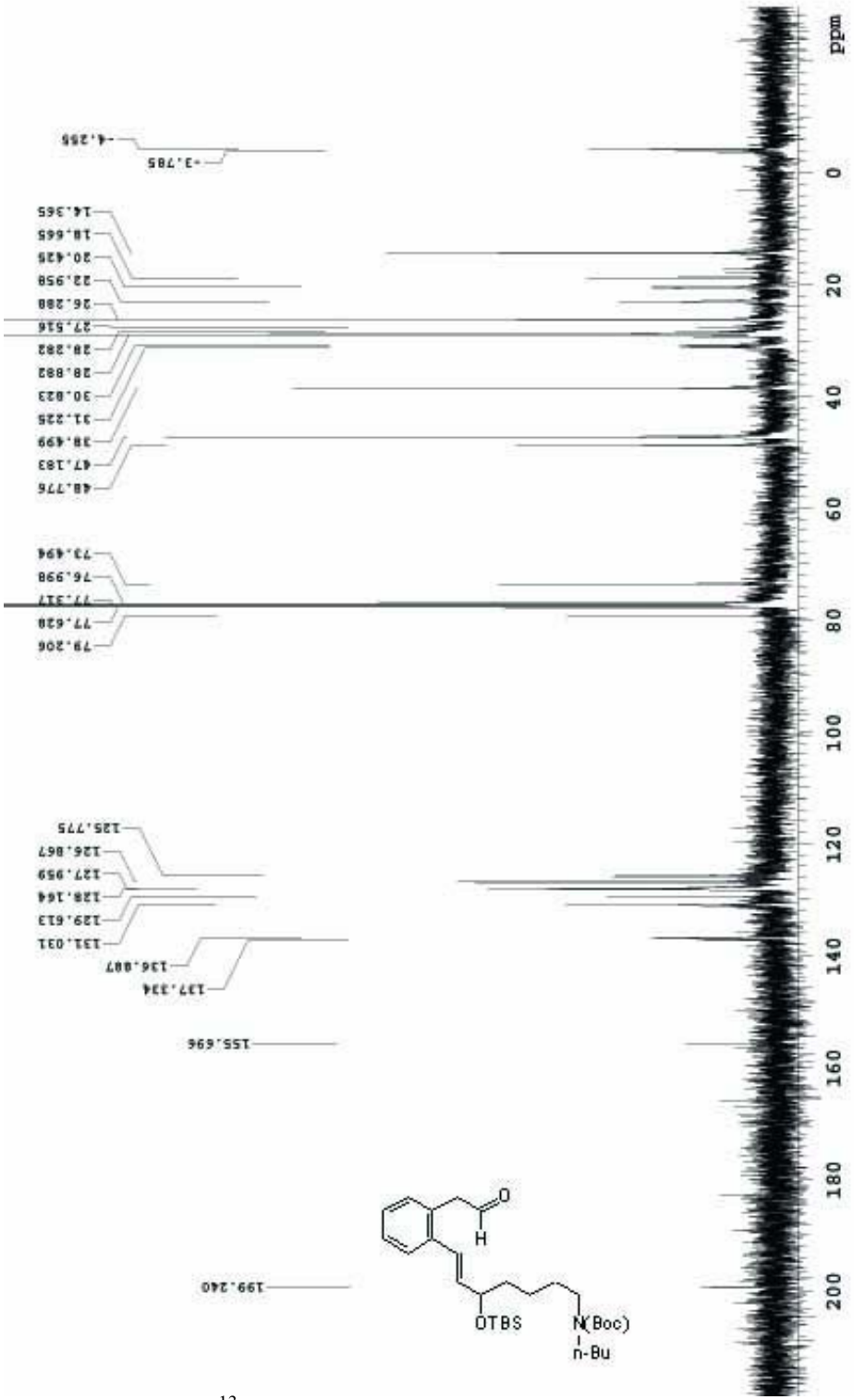
Spectrum 3.116: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **127**



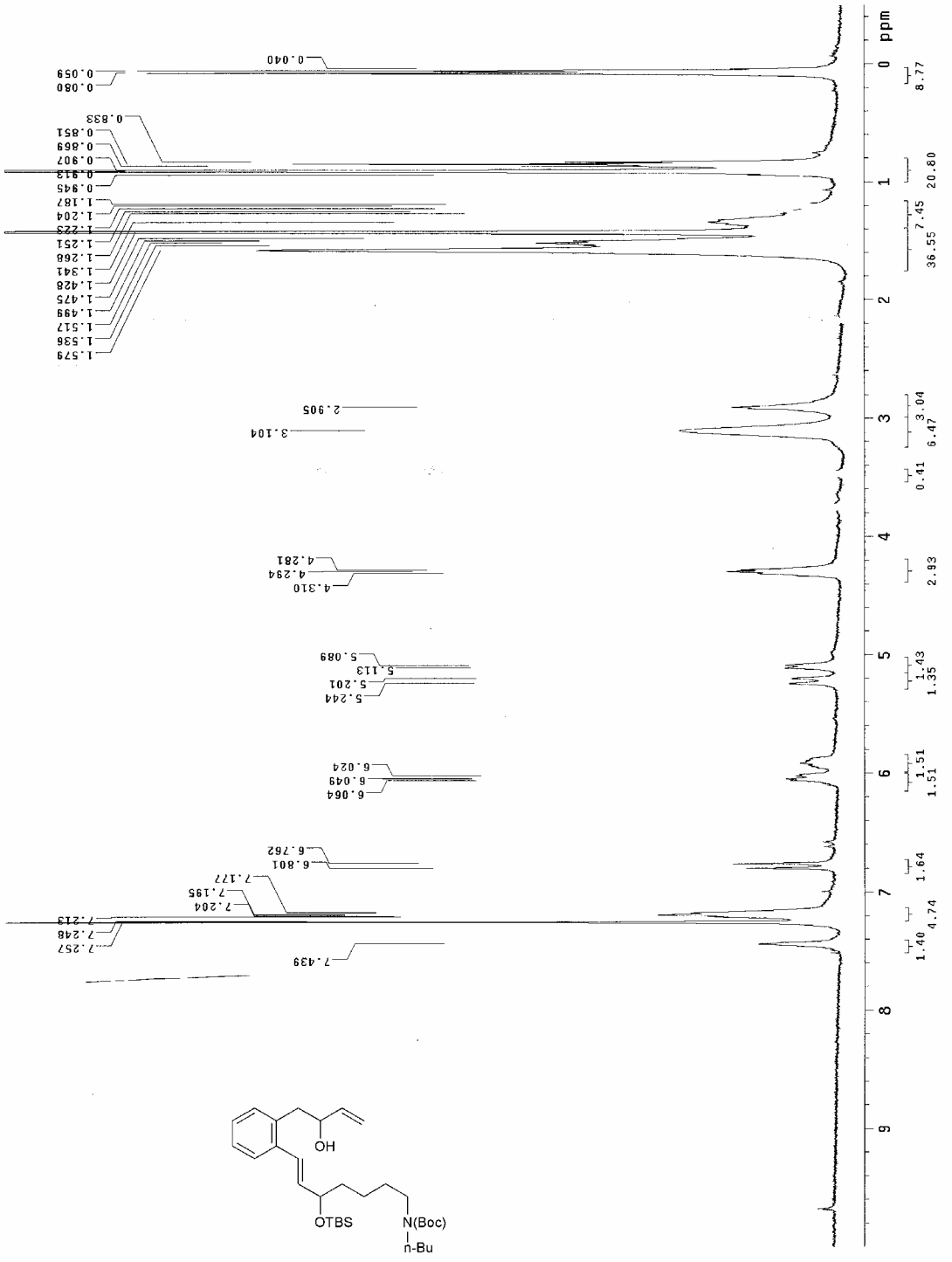
Spectrum 3.117: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **127**



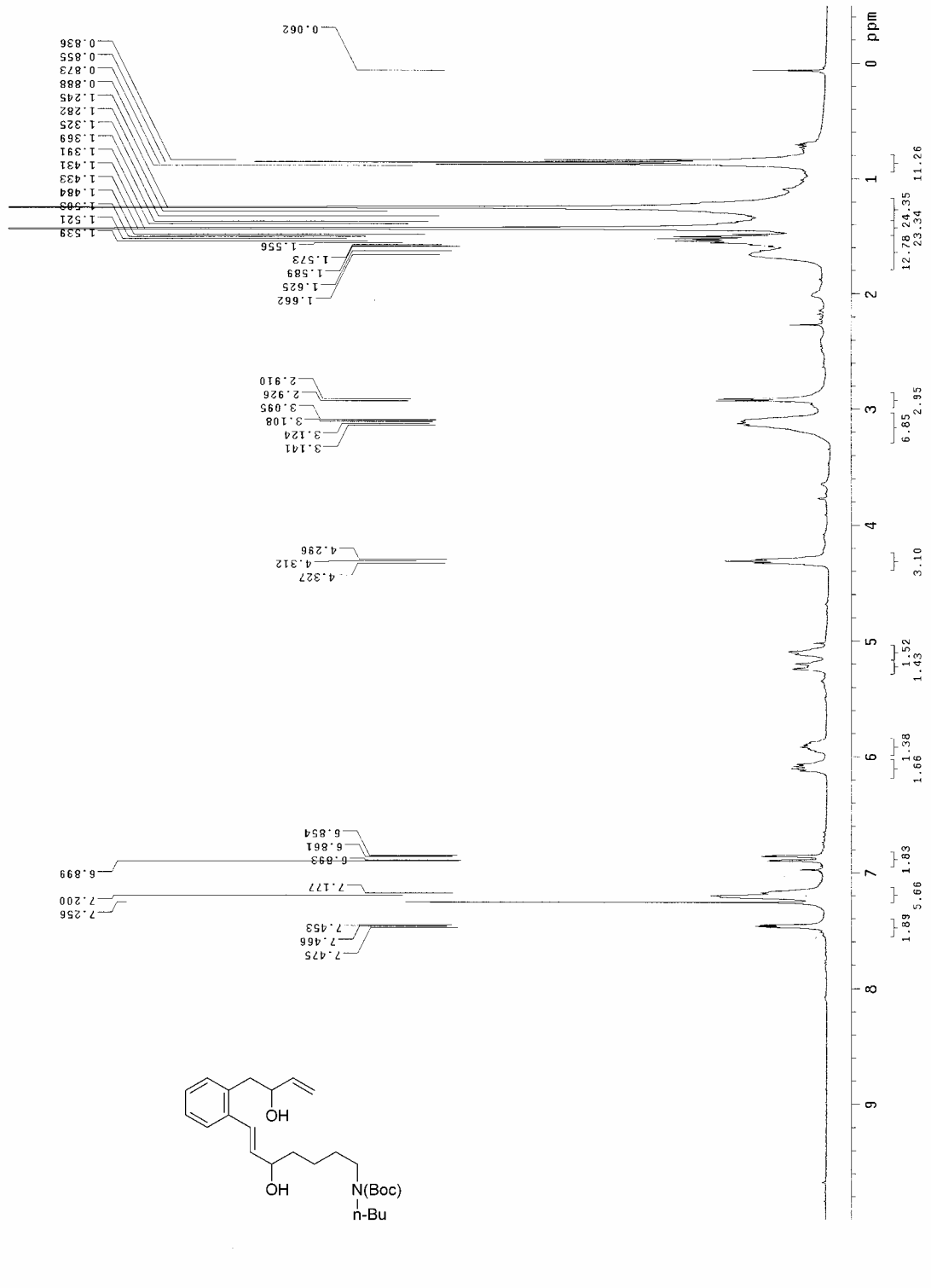
Spectrum 3.118: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **128**



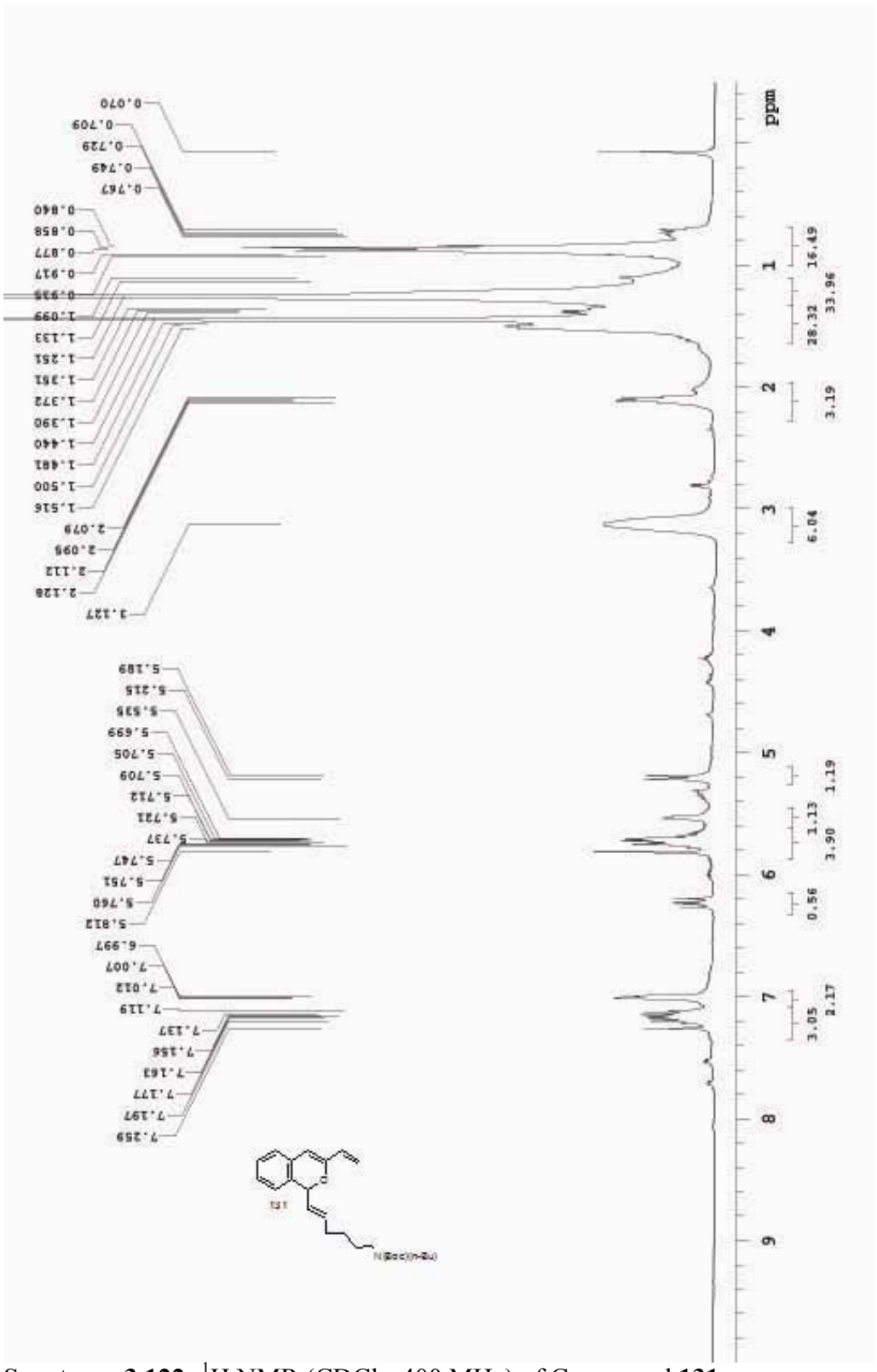
Spectrum 3.119: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **128**



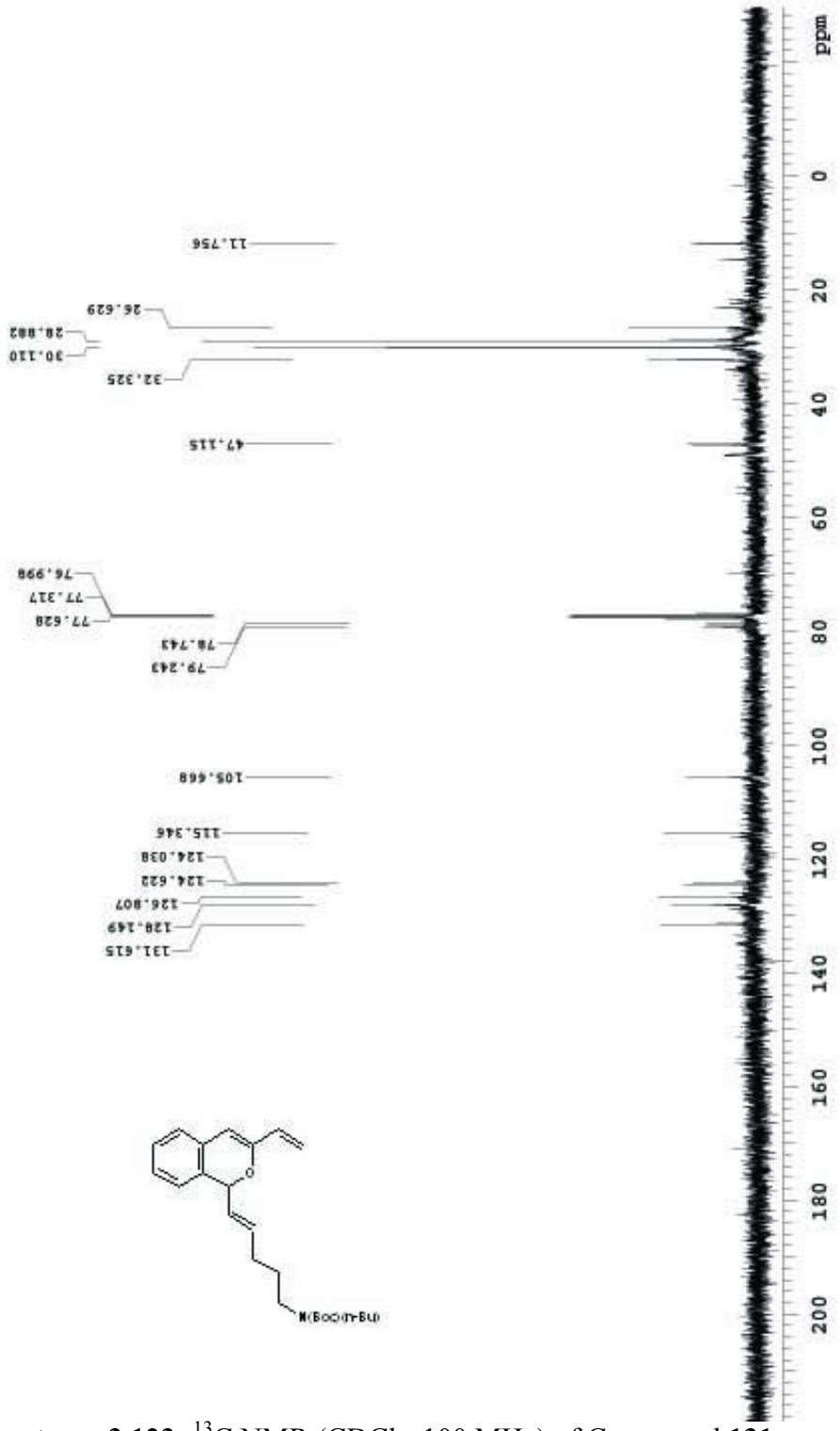
Spectrum 3.120: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **129**



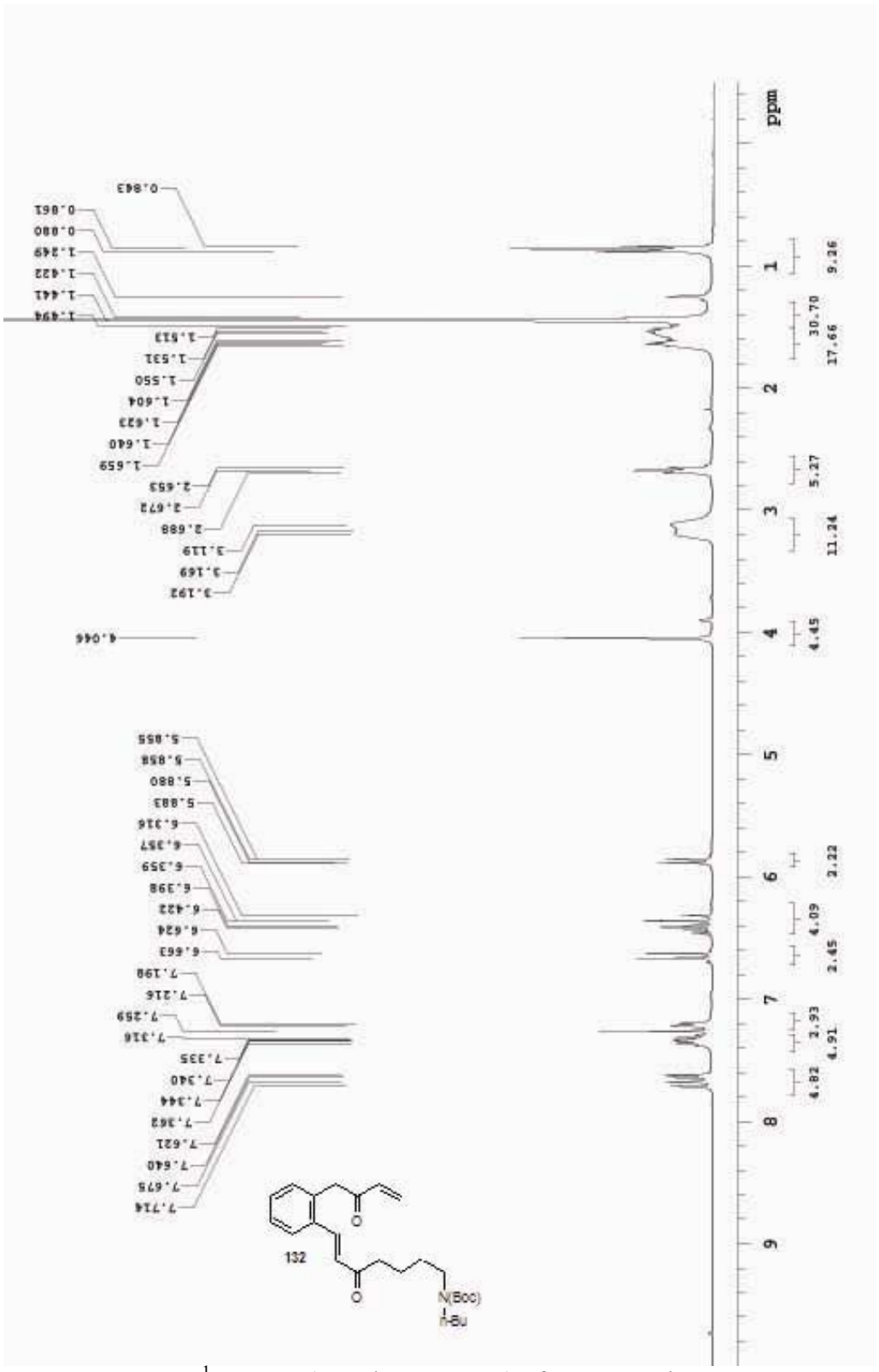
Spectrum 3.121: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **130**



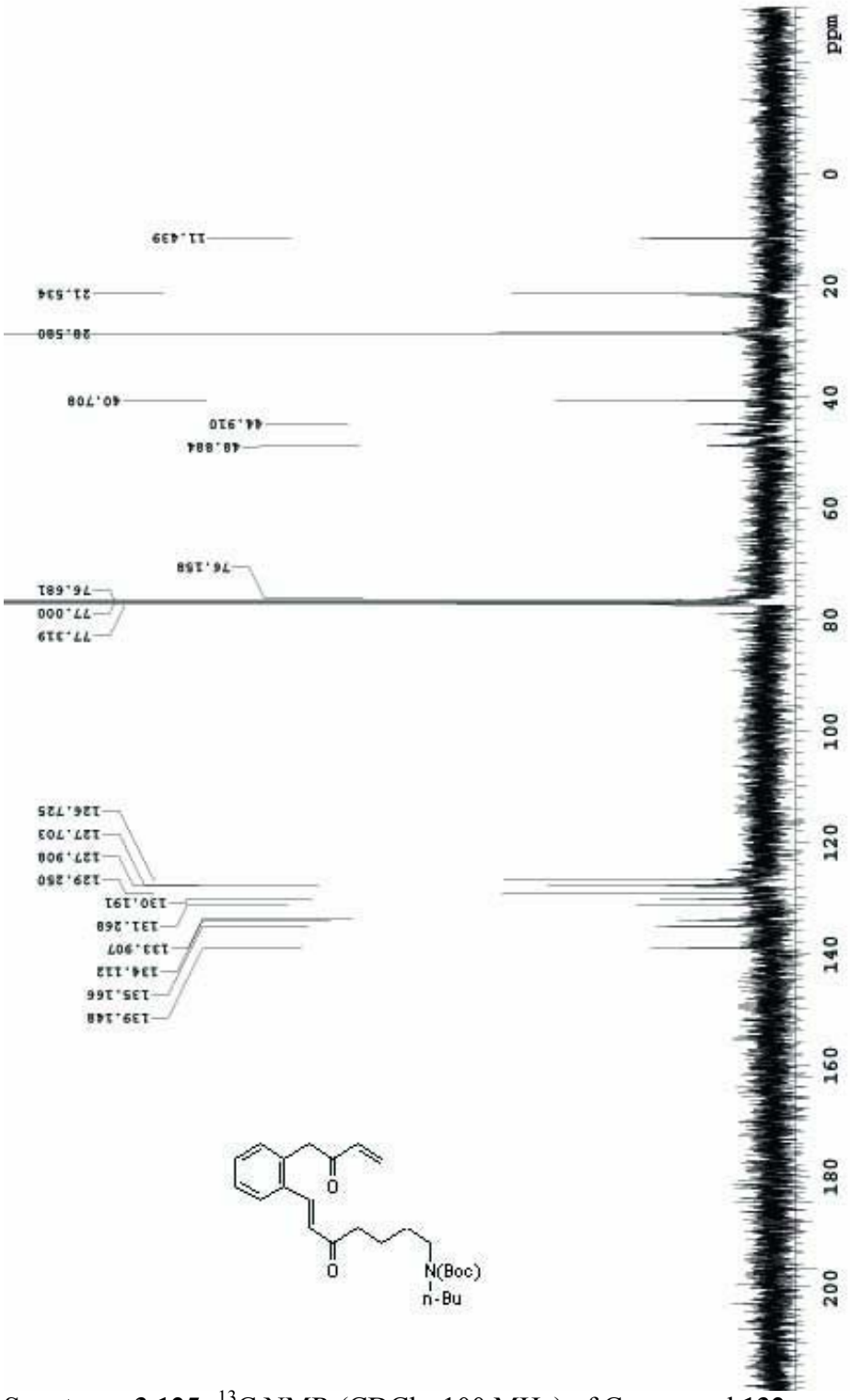
Spectrum 3.122: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **131**



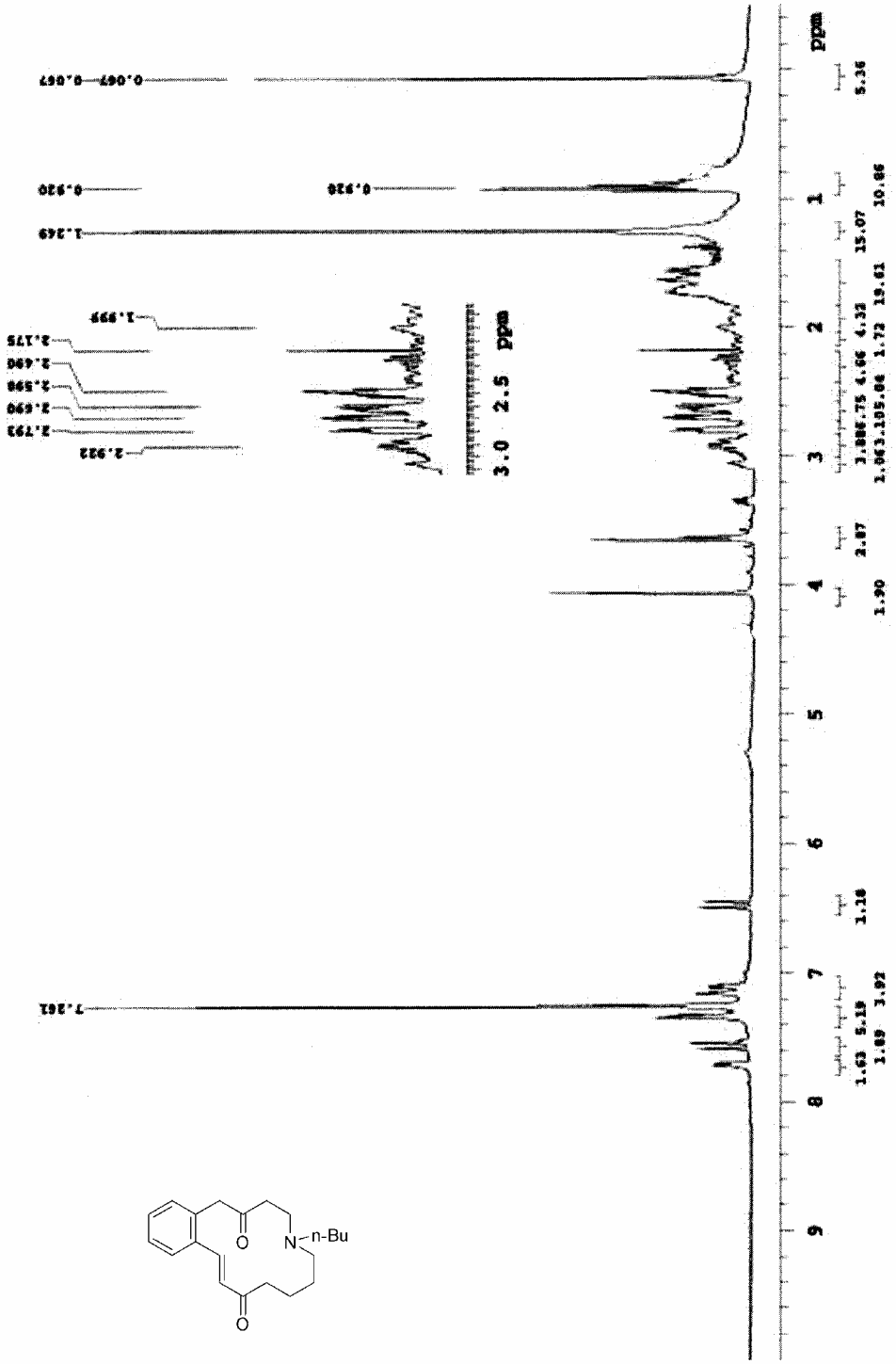
Spectrum 3.123: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **131**



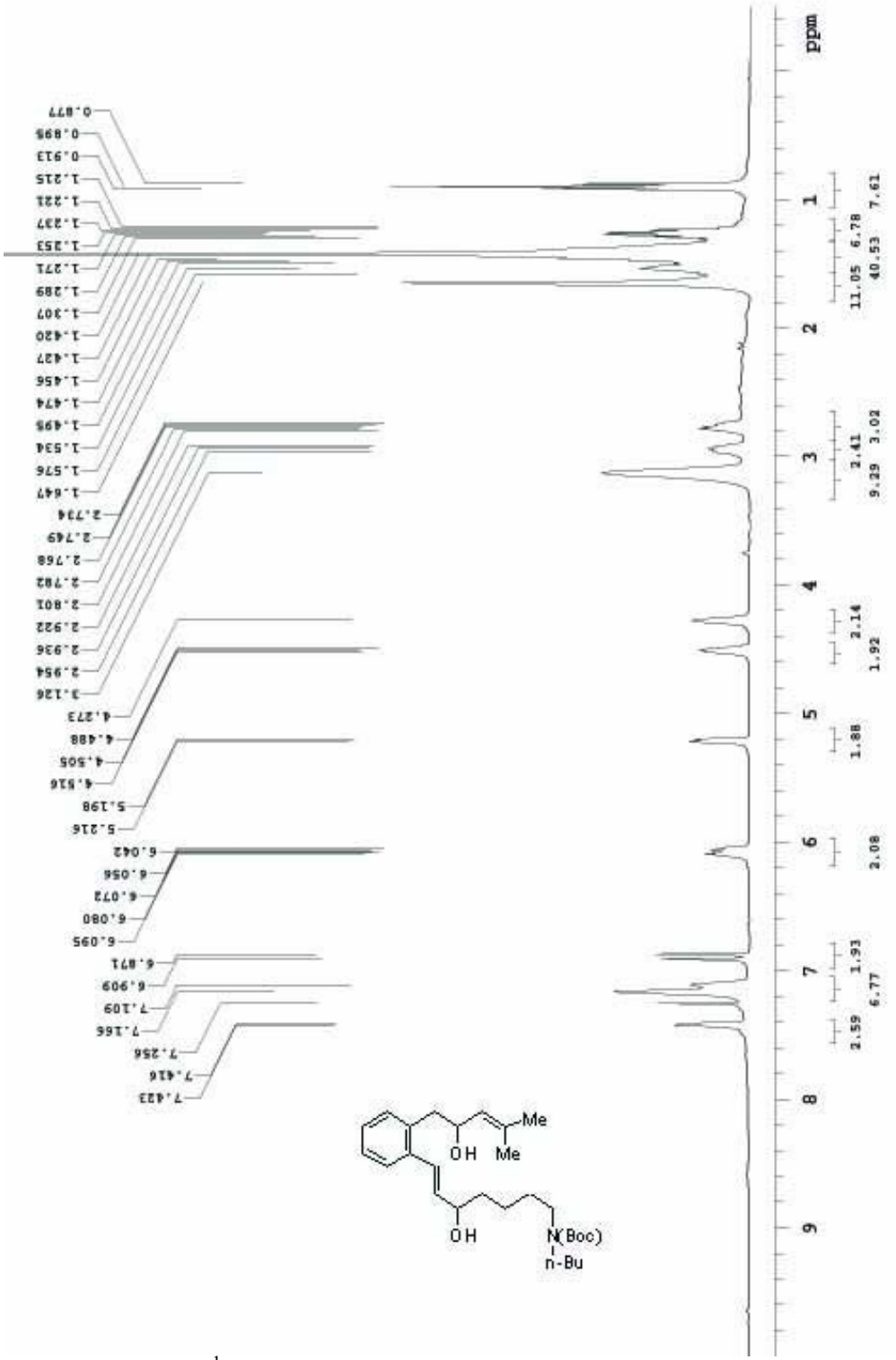
Spectrum 3.124: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **132**



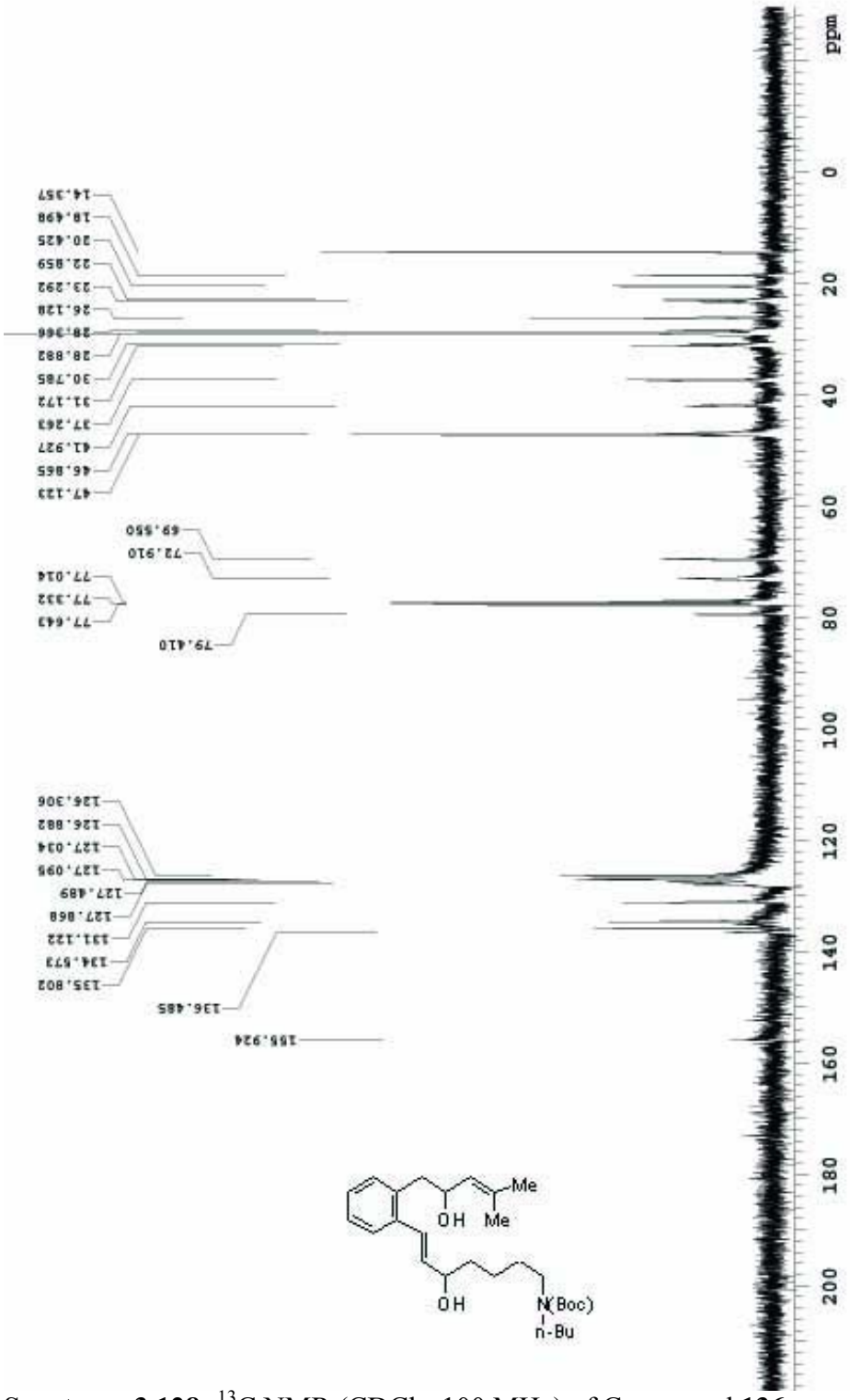
Spectrum 3.125: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **132**



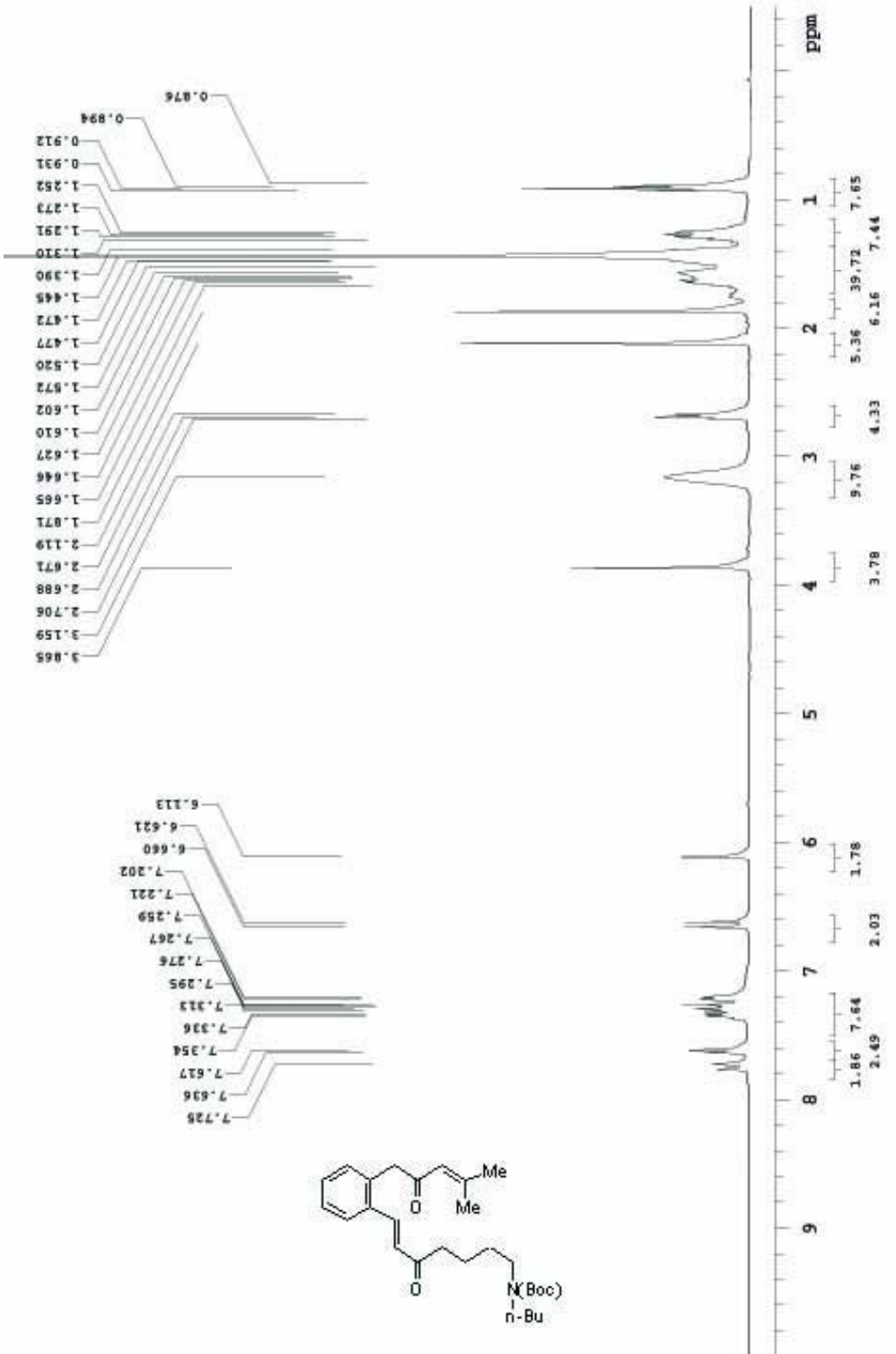
Spectrum 3.126: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **134**



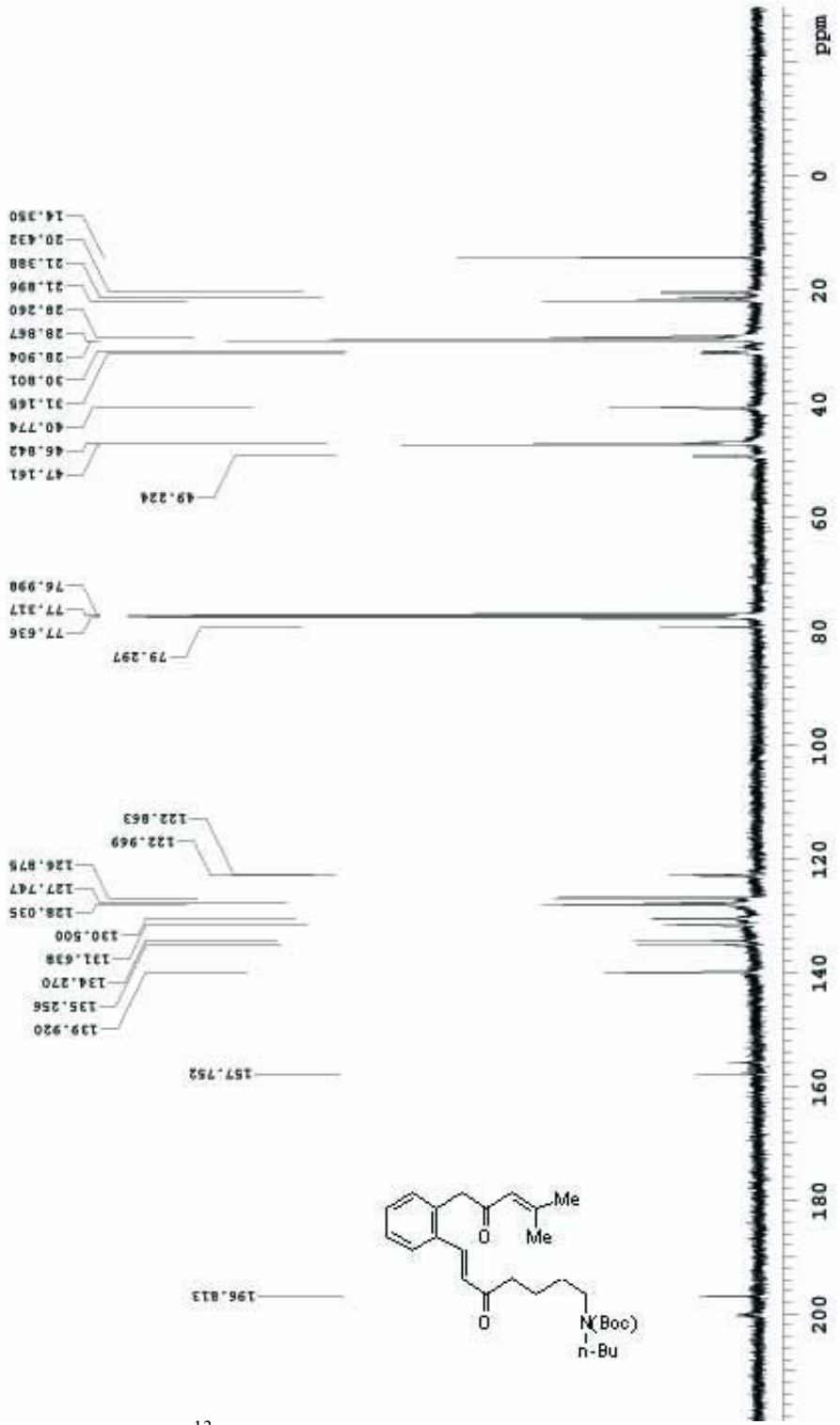
Spectrum 3.127: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **136**



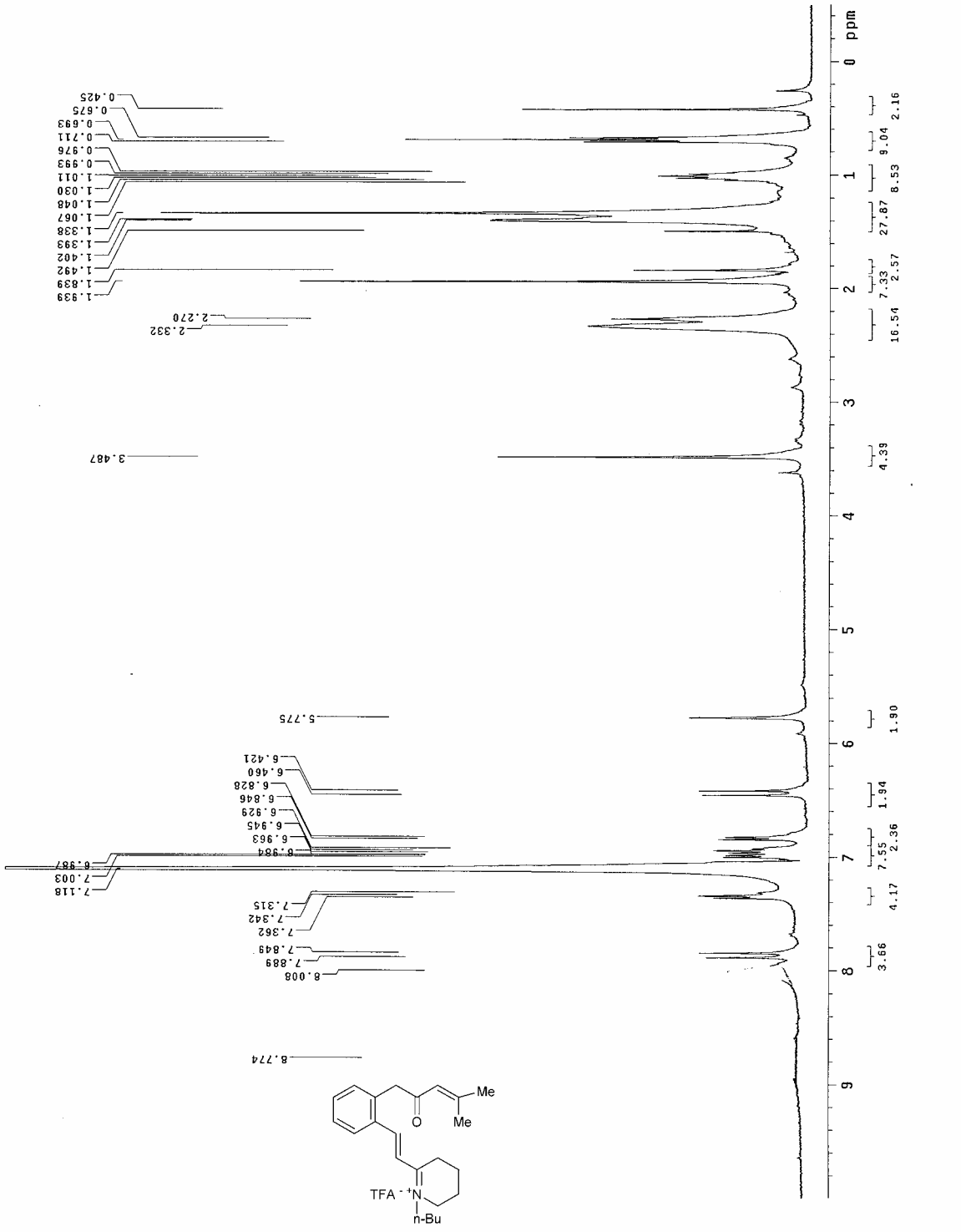
Spectrum 3.128: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **136**



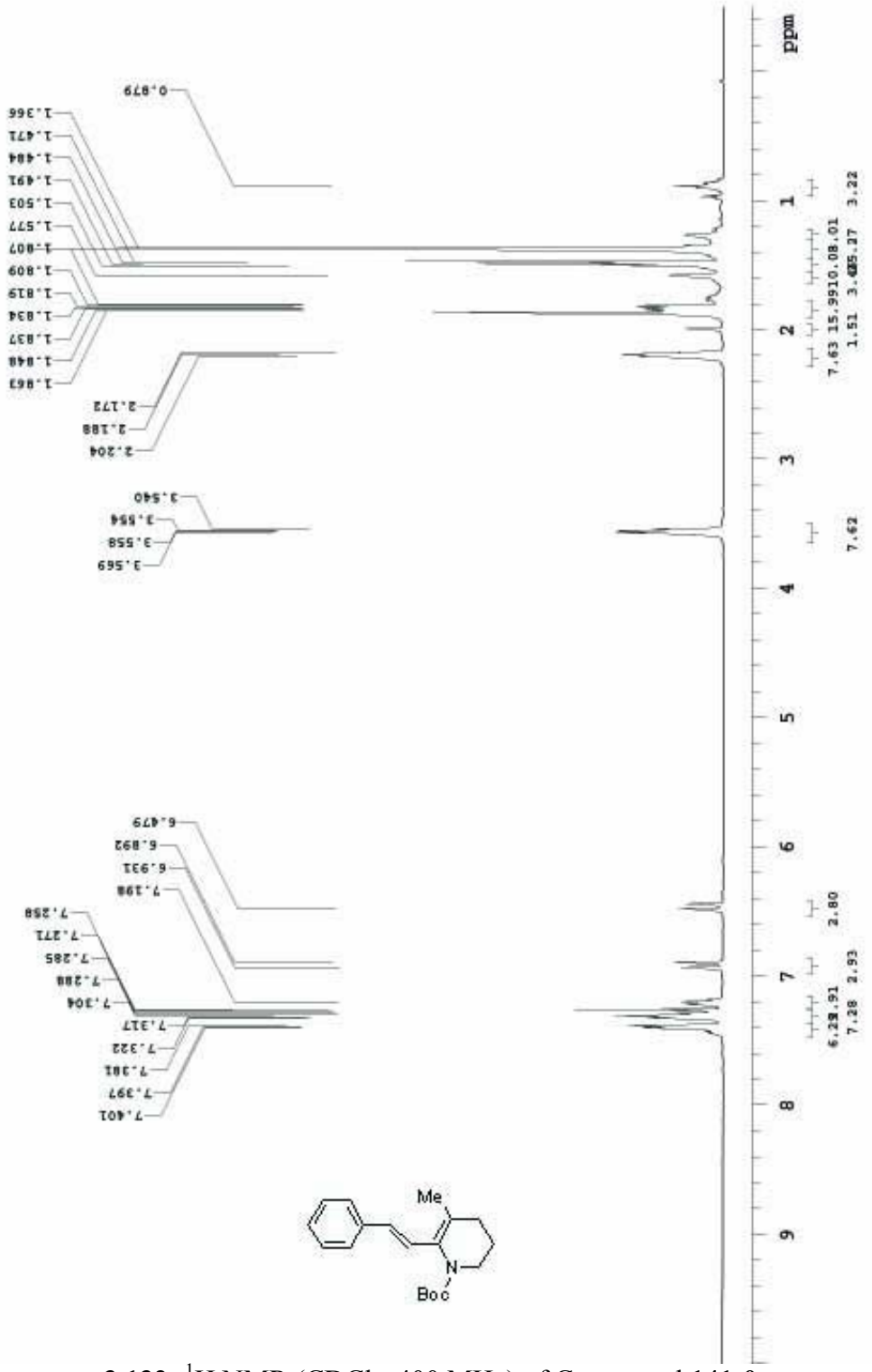
Spectrum 3.129: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **137**



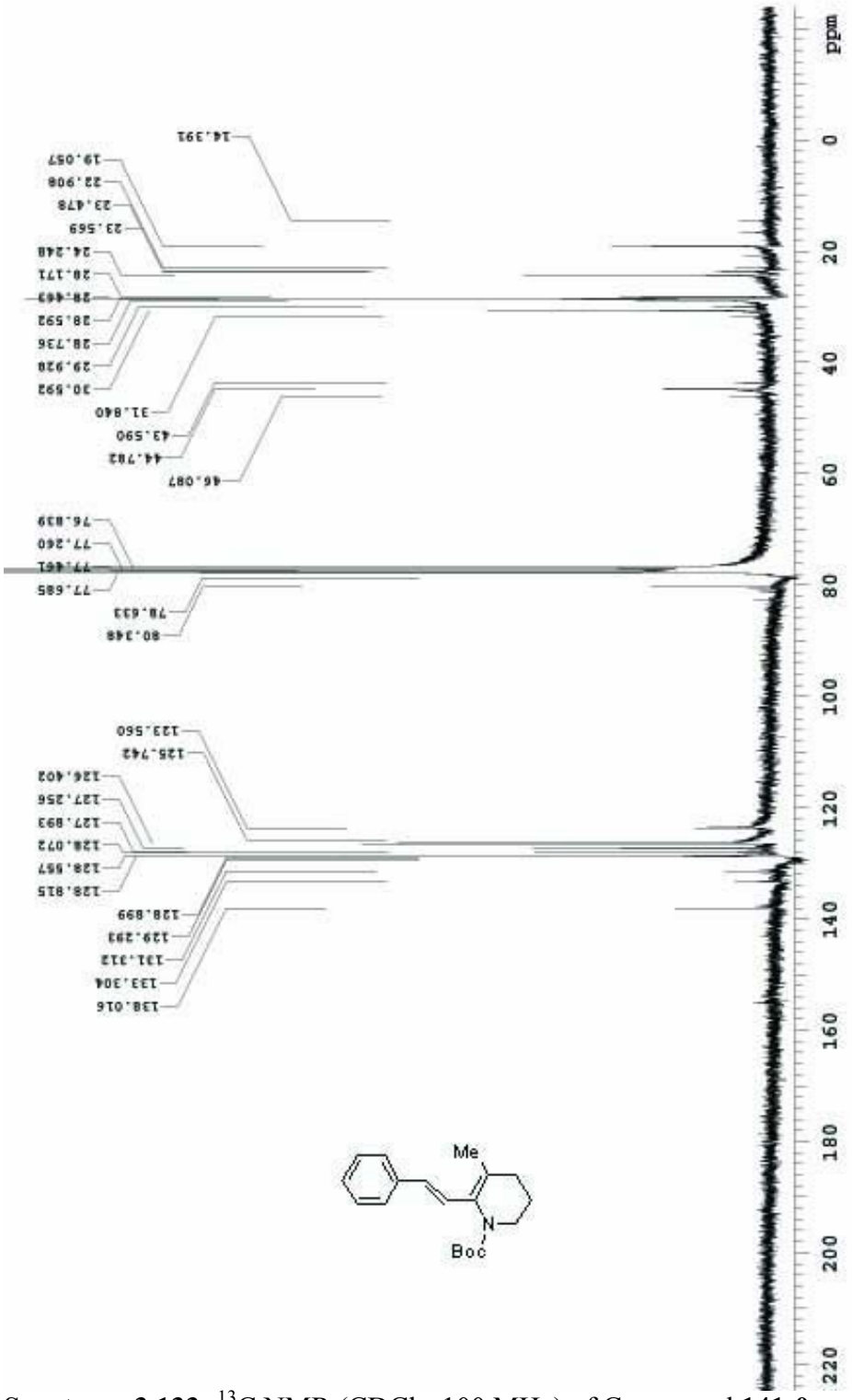
Spectrum 3.130: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **137**



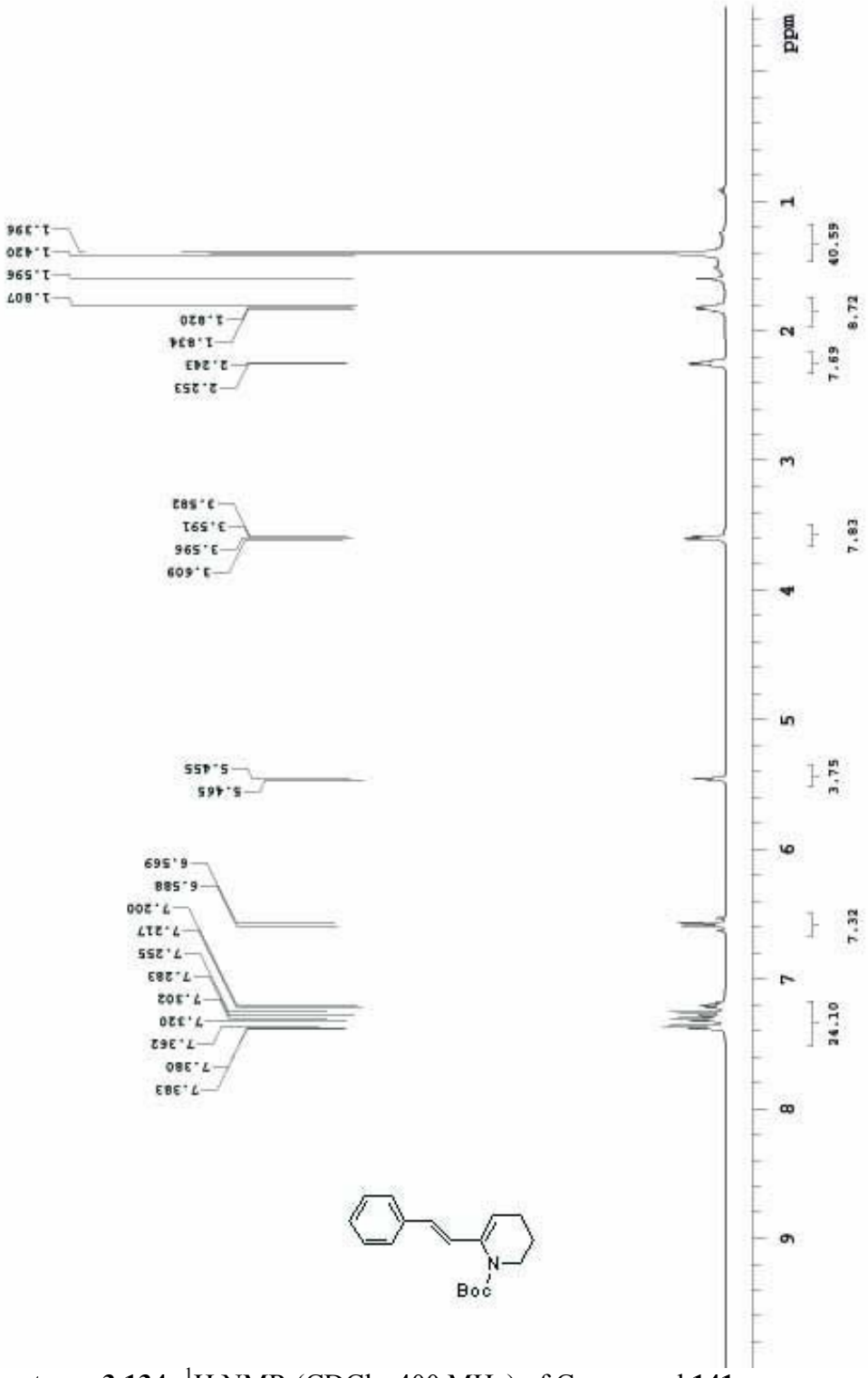
Spectrum 3.131: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **138-2**



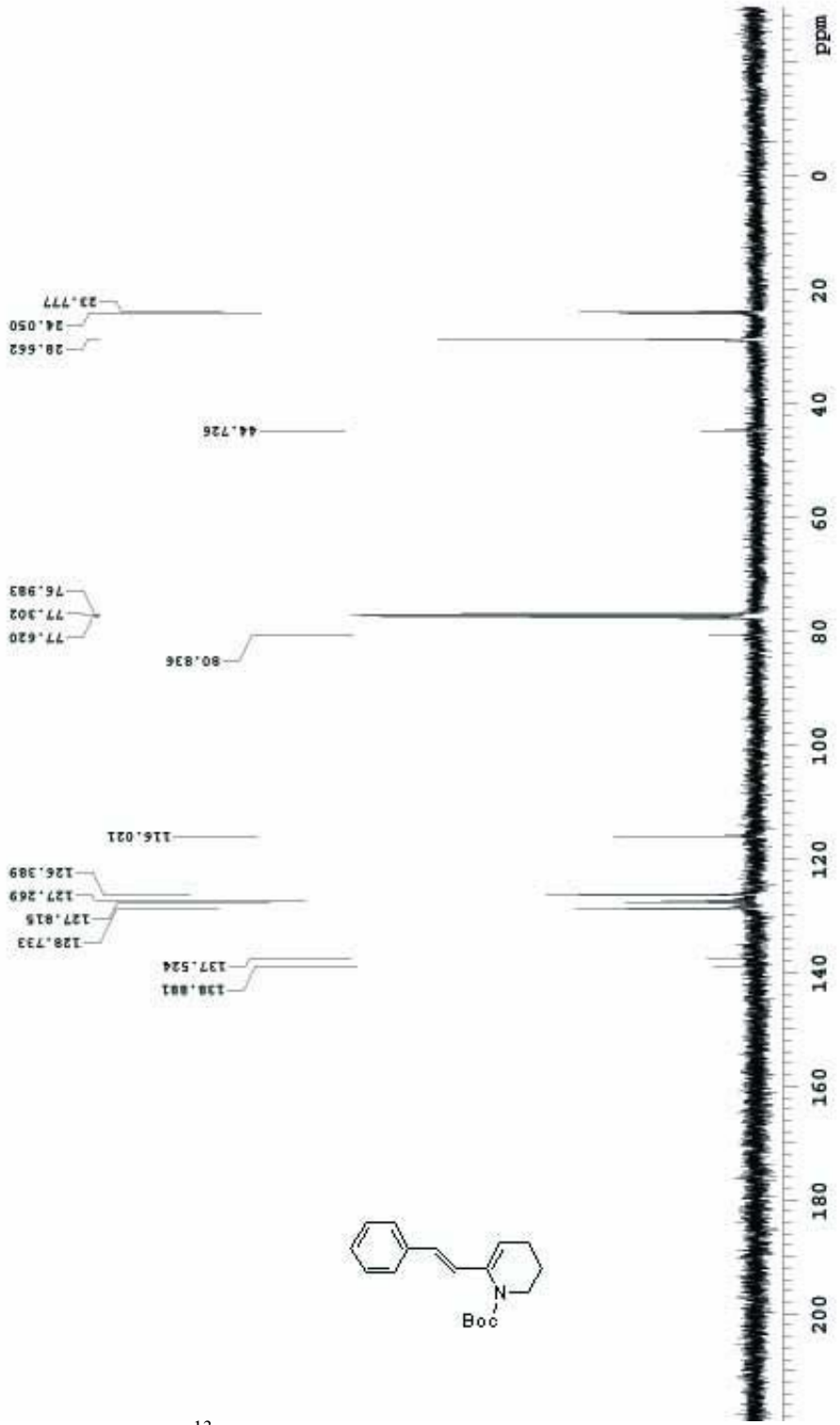
Spectrum 3.132: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **141-0**



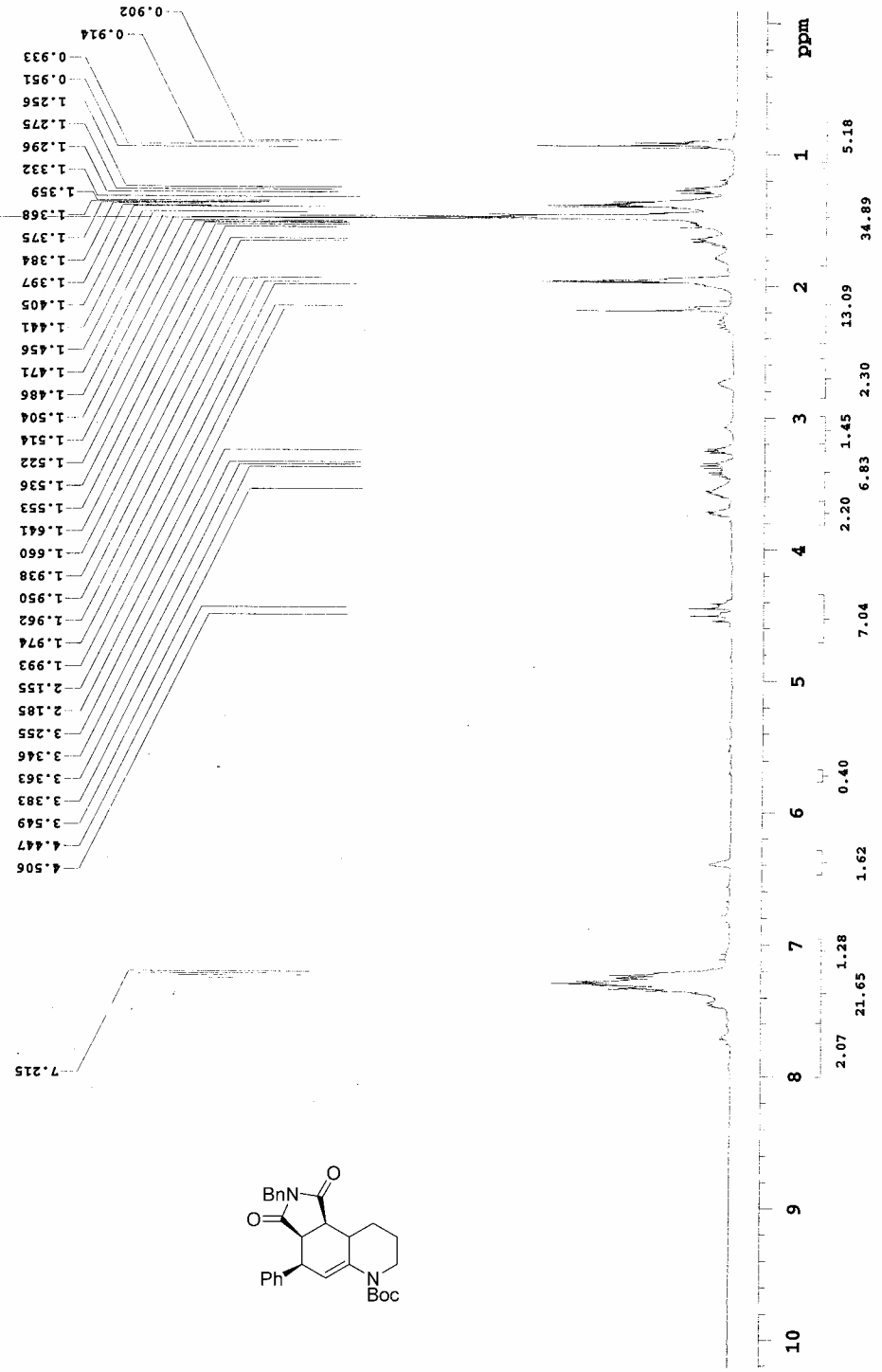
Spectrum 3.133: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **141-0**



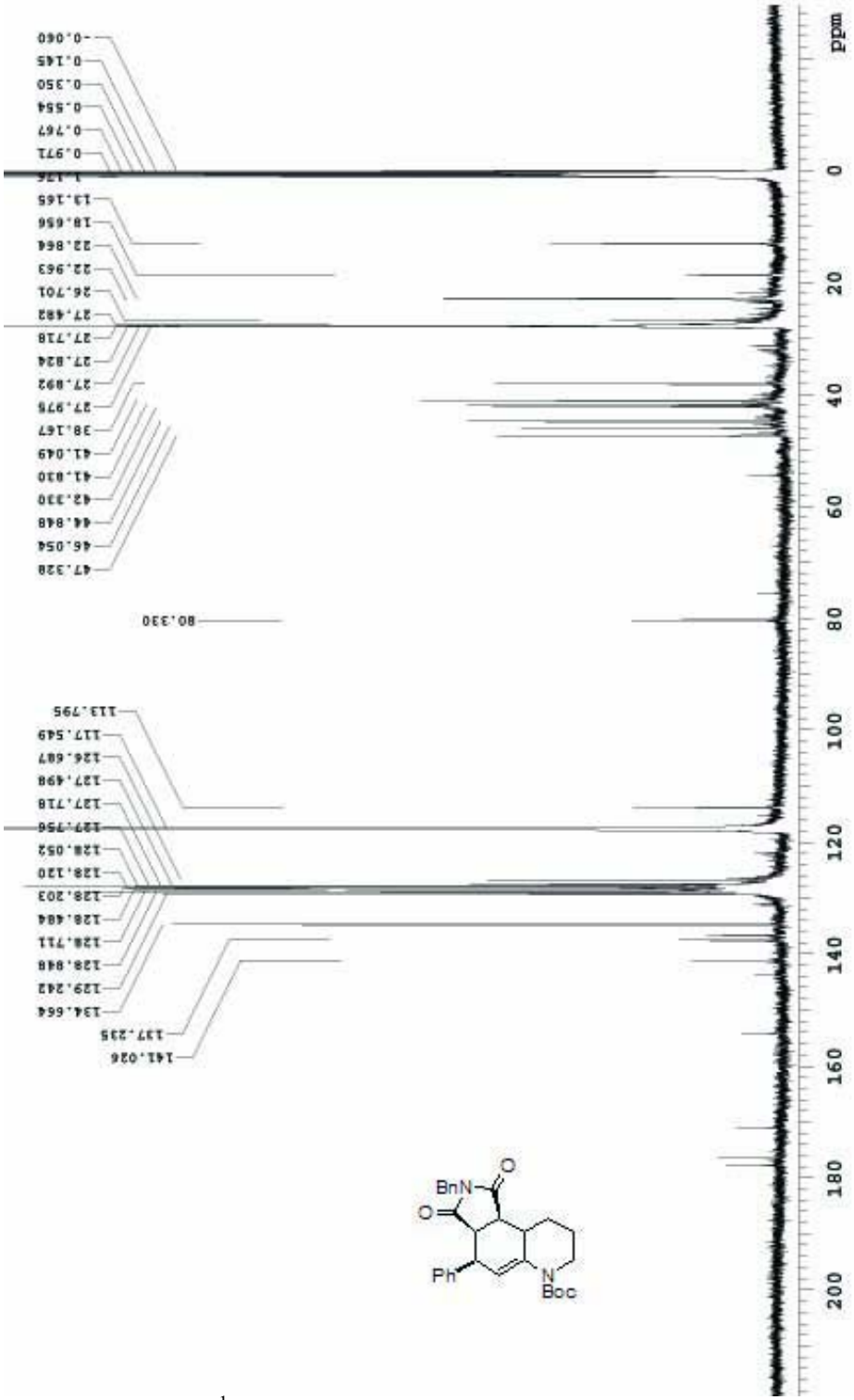
Spectrum 3.134: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **141**



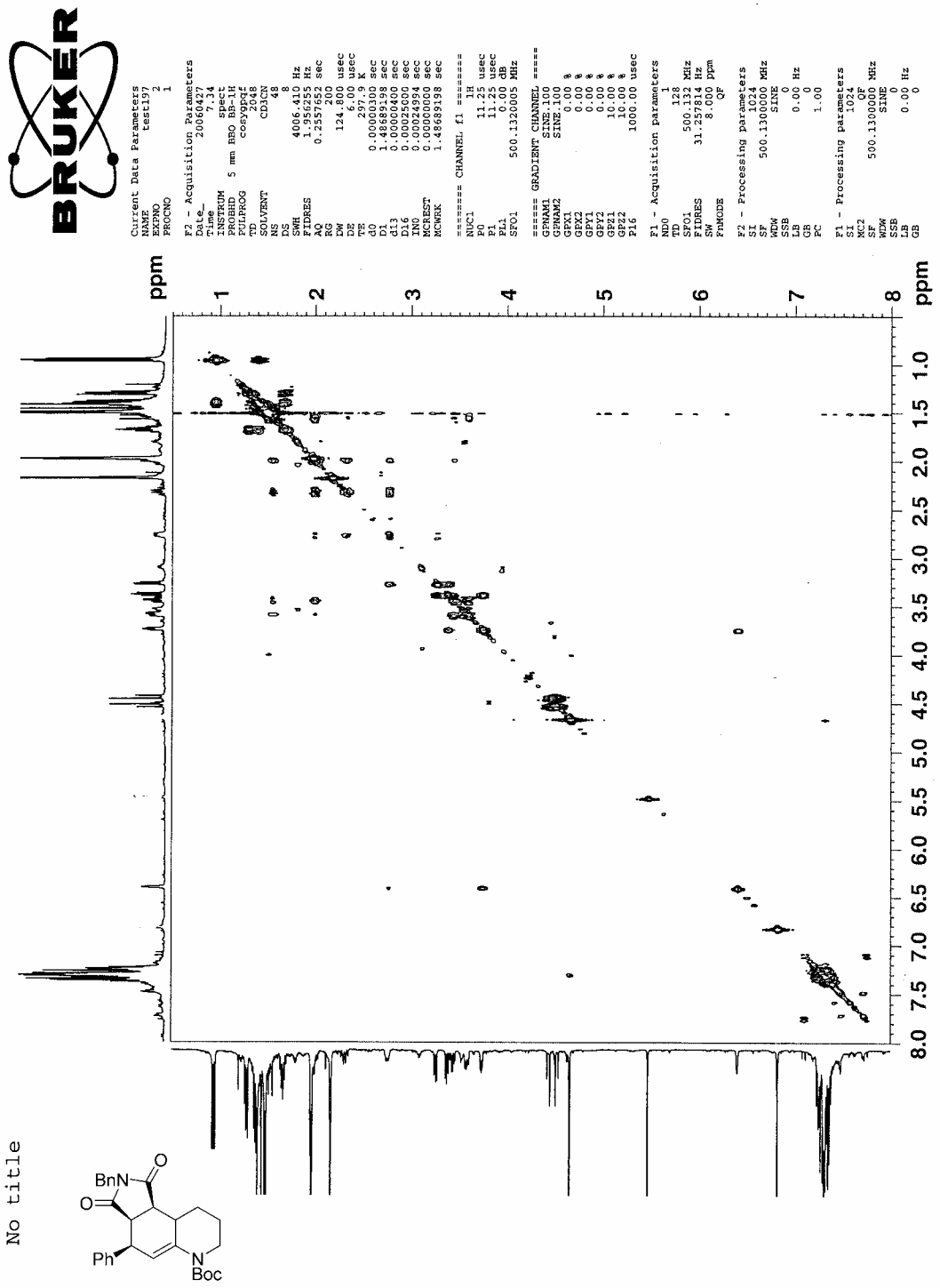
Spectrum 3.135: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **141**



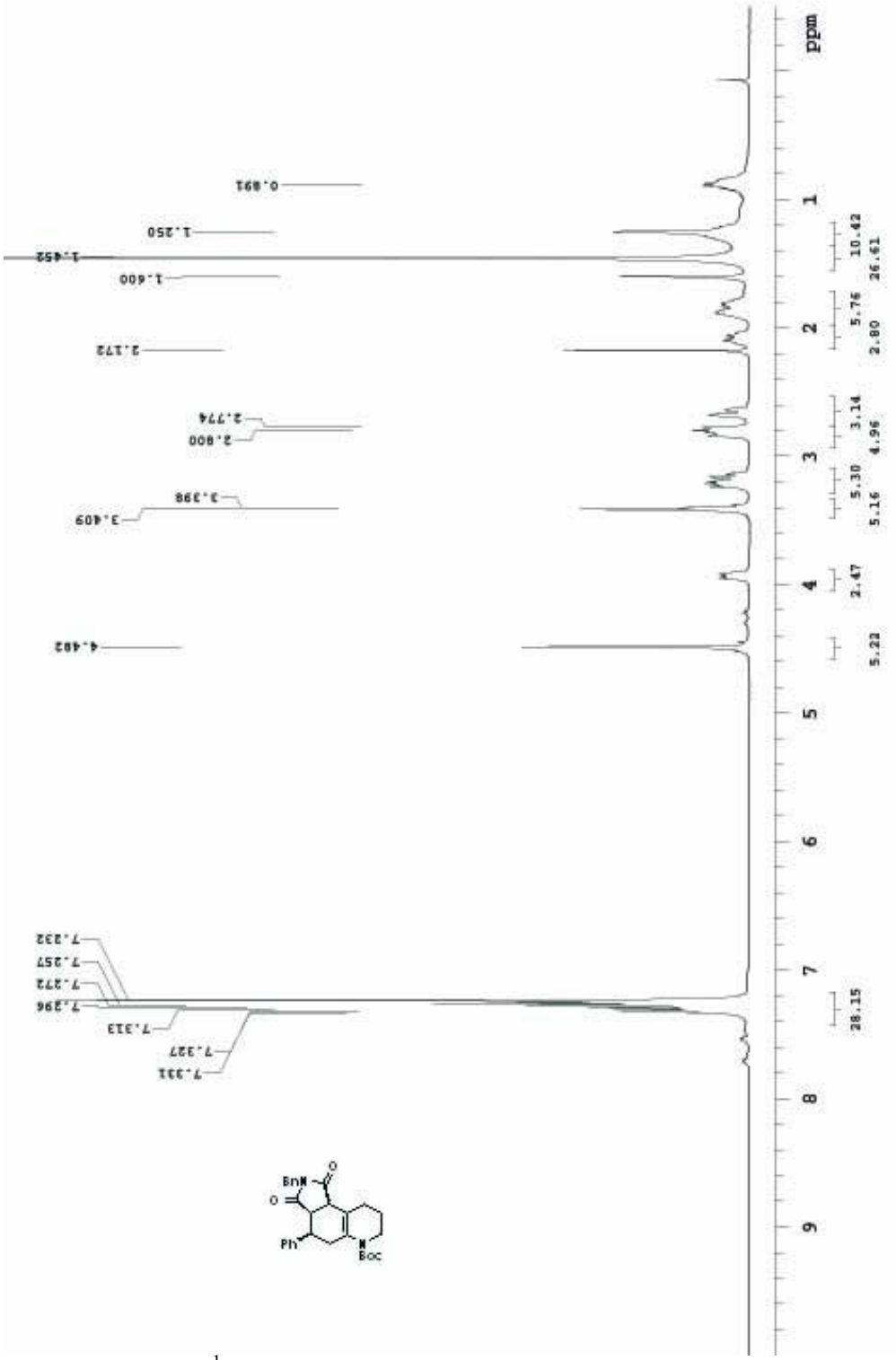
Spectrum 3.136: ^{1}H NMR (CD_3CN, 400 MHz) of Compound **143**



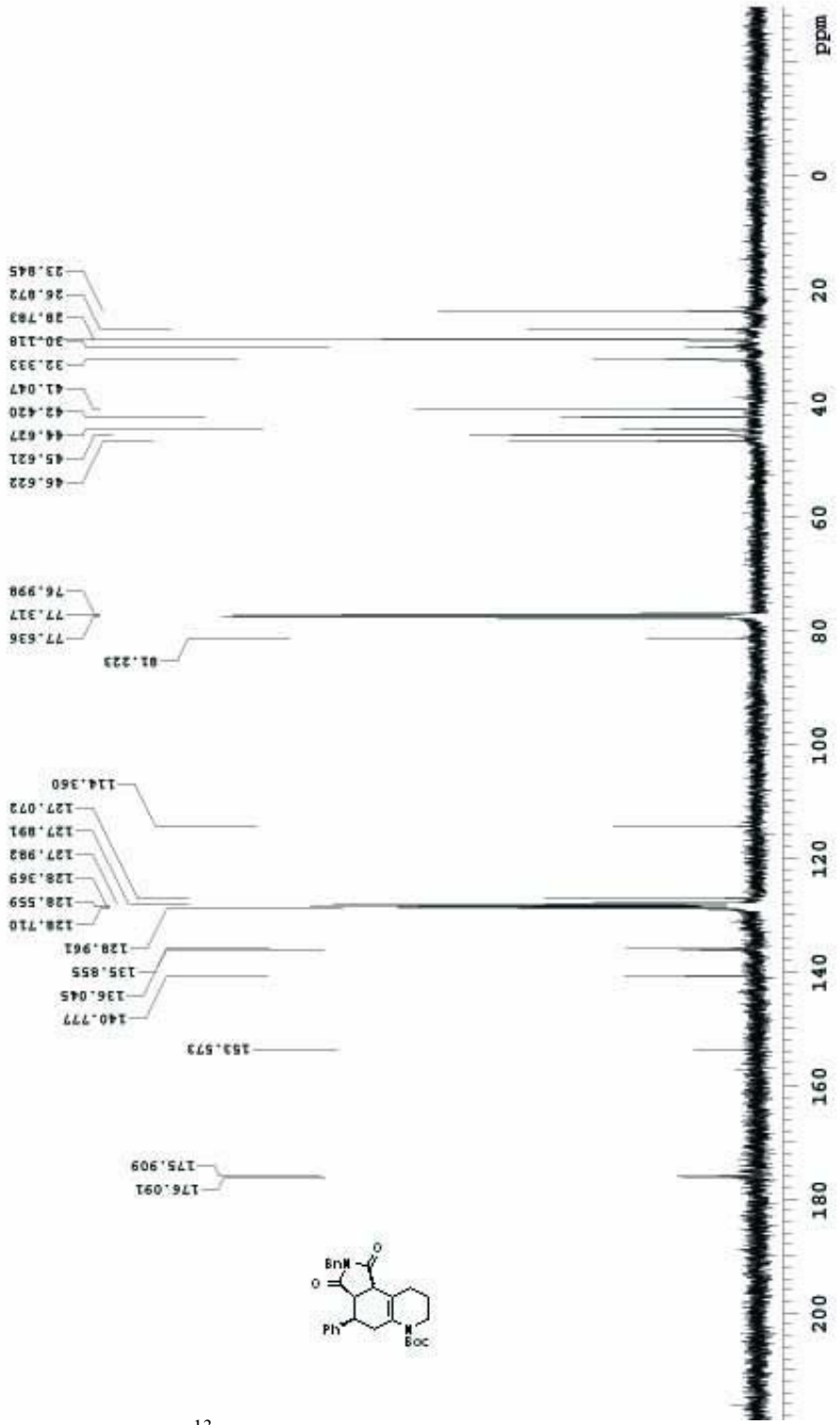
Spectrum 3.137: ^{1}H NMR (CD_3CN, 100 MHz) of Compound **143**



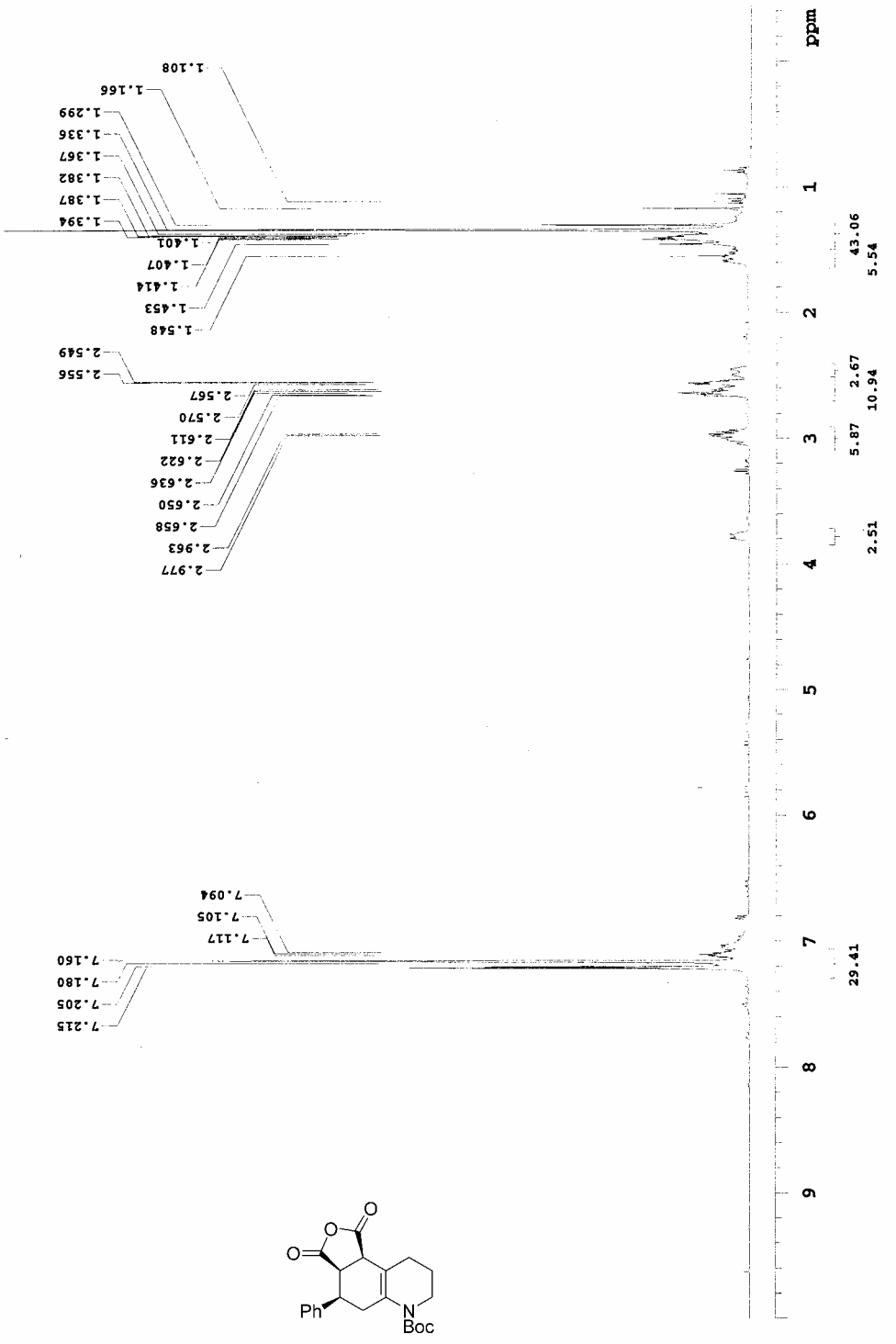
Spectrum 3.138: 2D NMR (CD_3CN, 400 MHz) of Compound **143** (cont.).



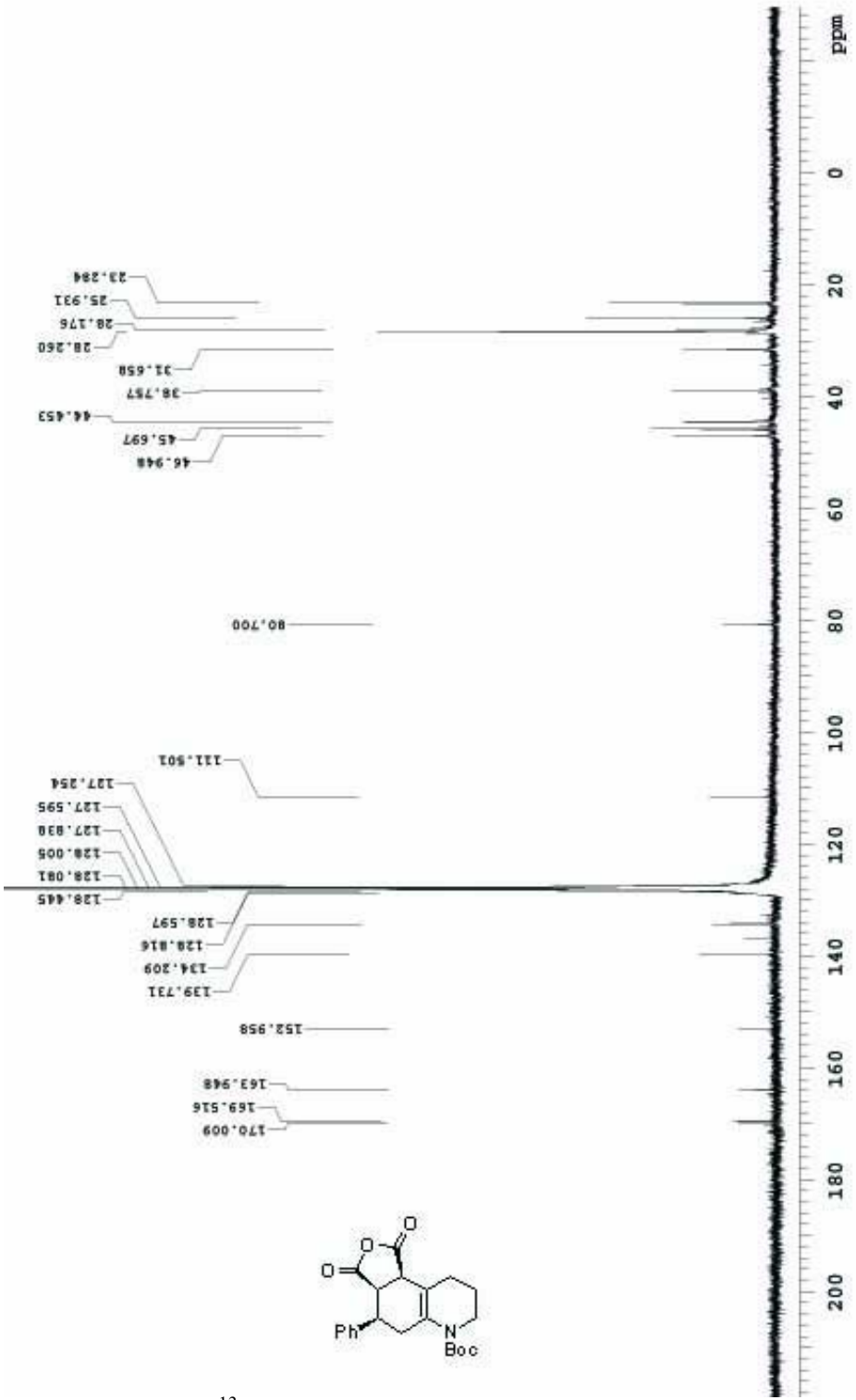
Spectrum 3.139: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **143-1**



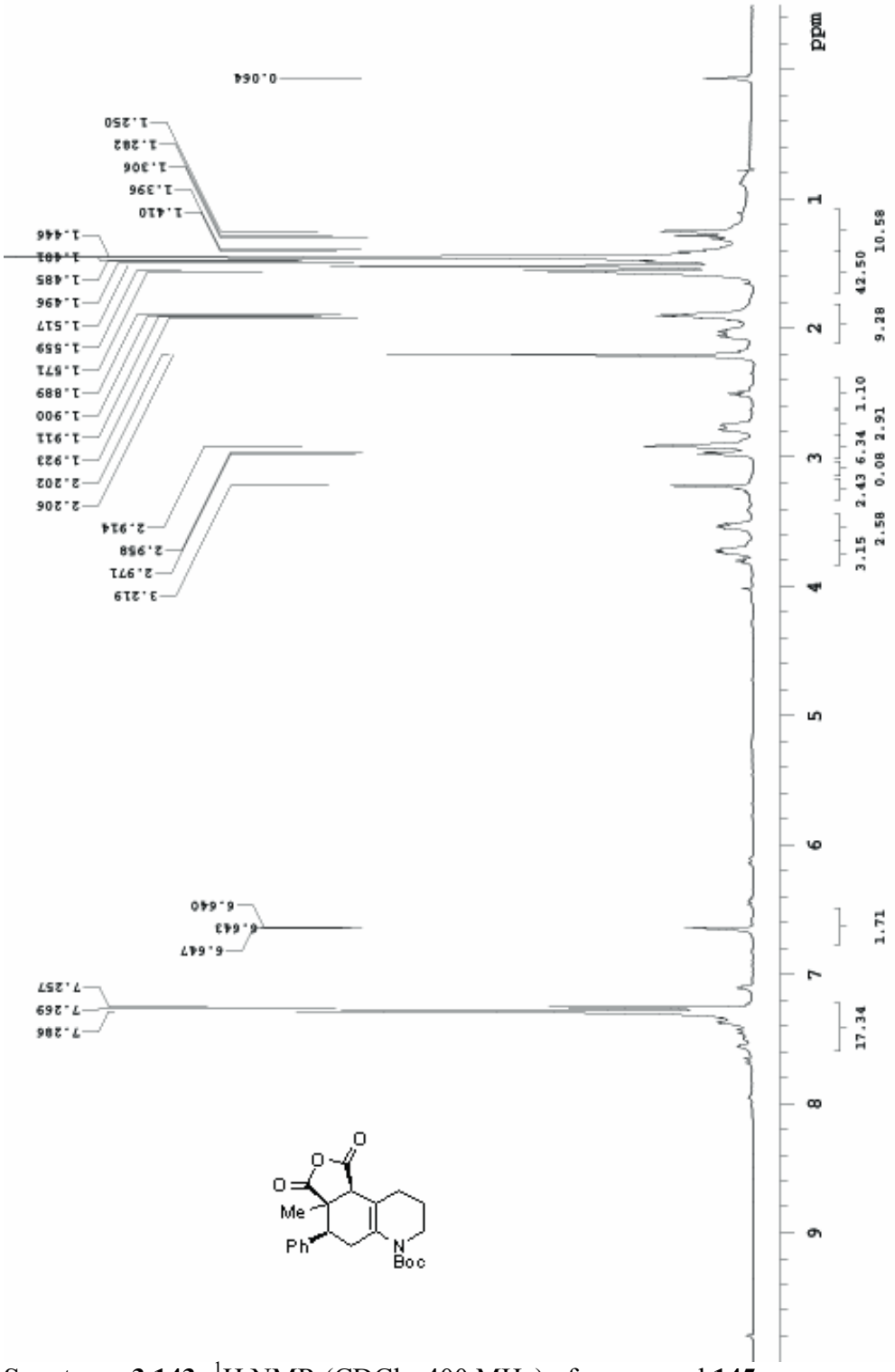
Spectrum 3.140: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **143-1**



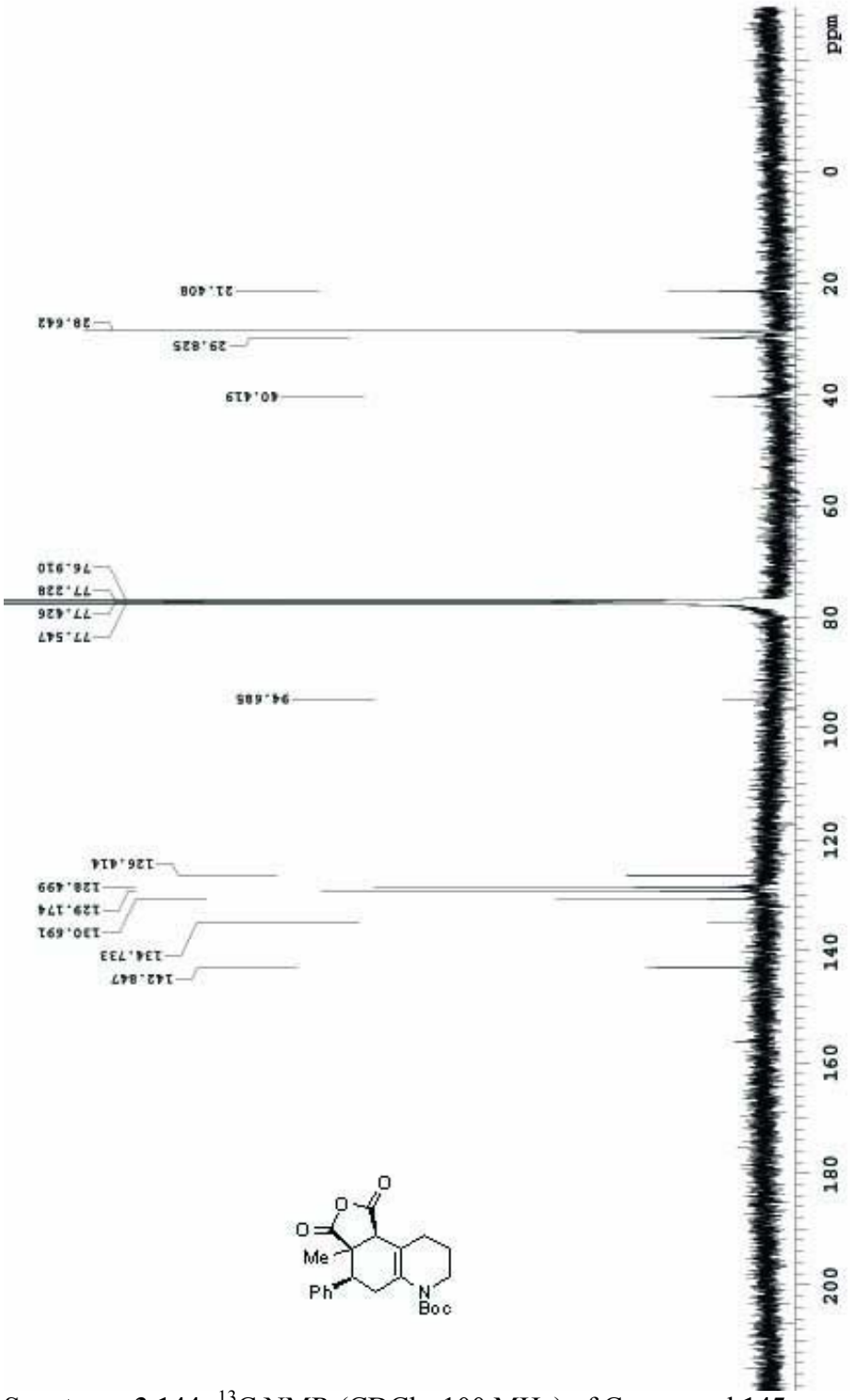
Spectrum 3.141: ^{1}H NMR (C_6D_6, 400 MHz) of Compound **144**



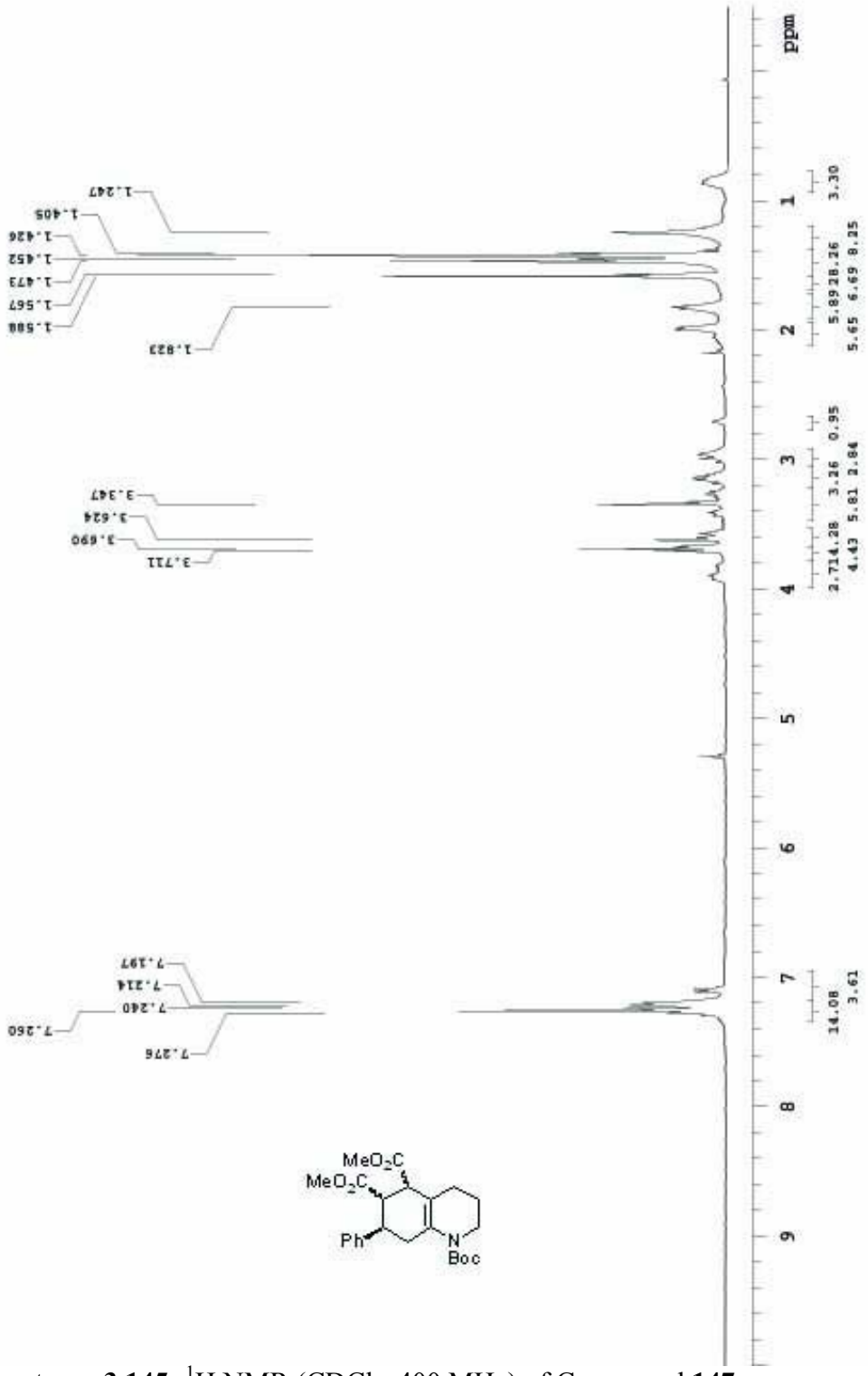
Spectrum 3.142: ^{13}C NMR (C_6D_6, 100 MHz) of Compound **144**



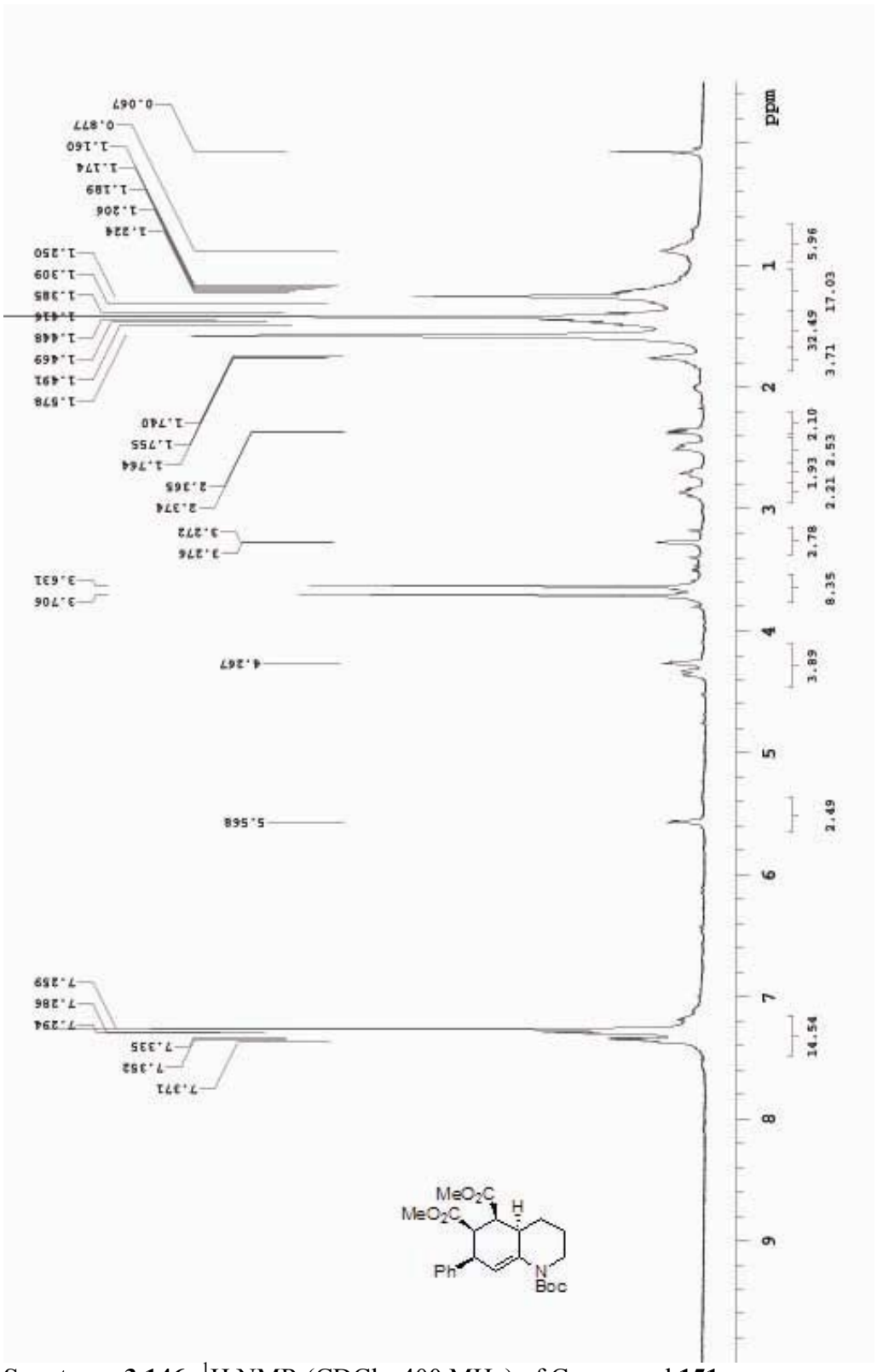
Spectrum 3.143: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **145**



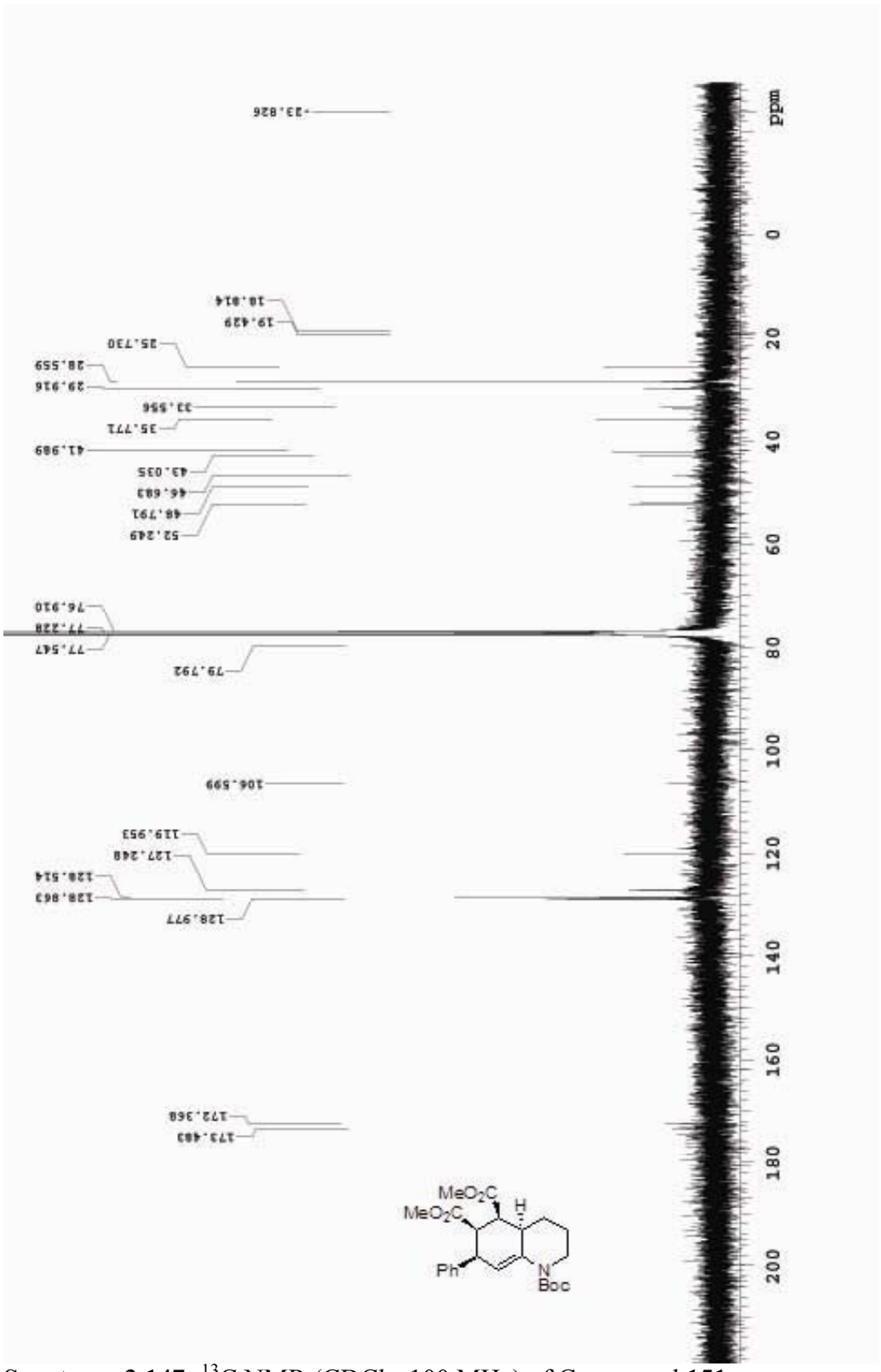
Spectrum 3.144: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **145**



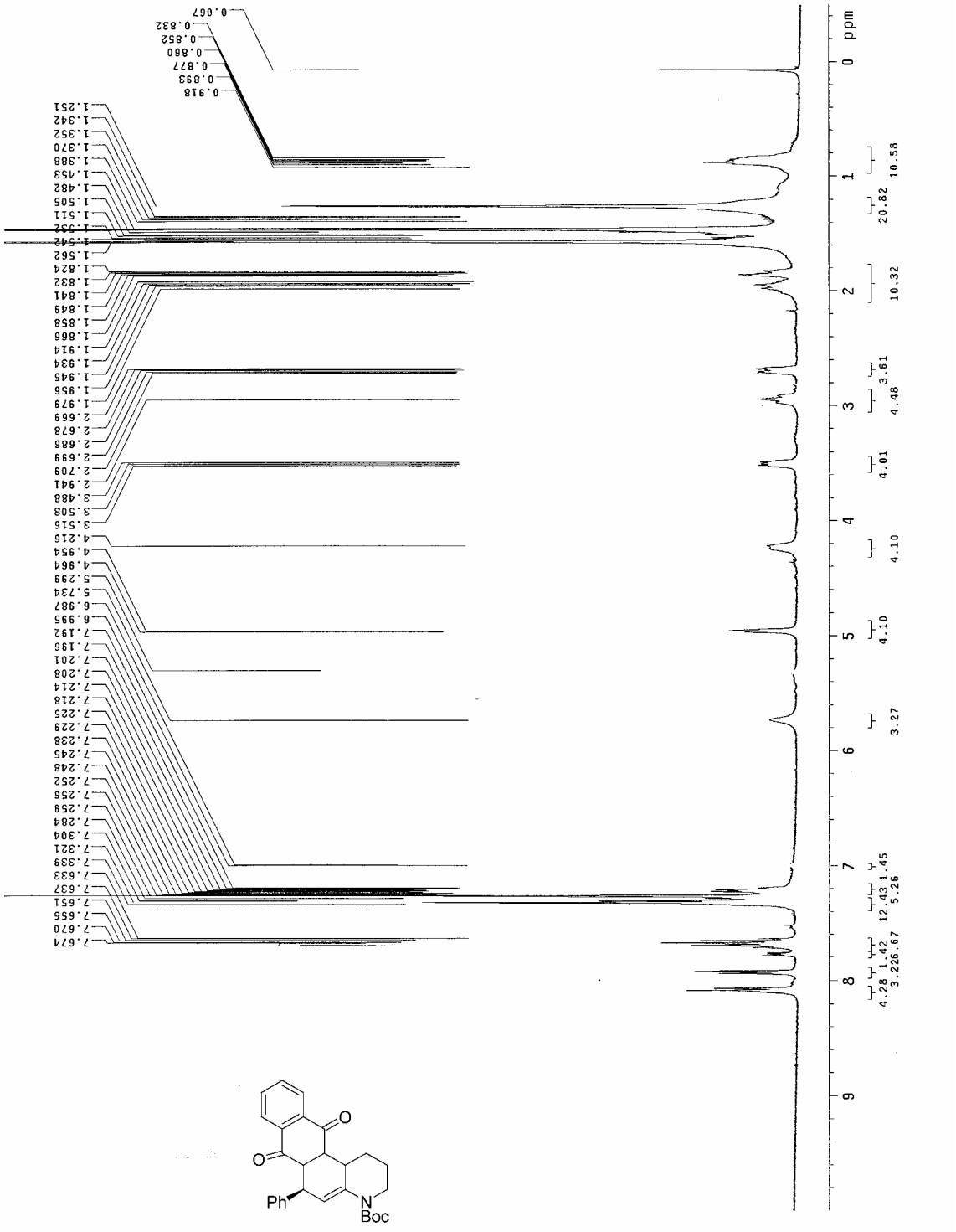
Spectrum 3.145: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **147**



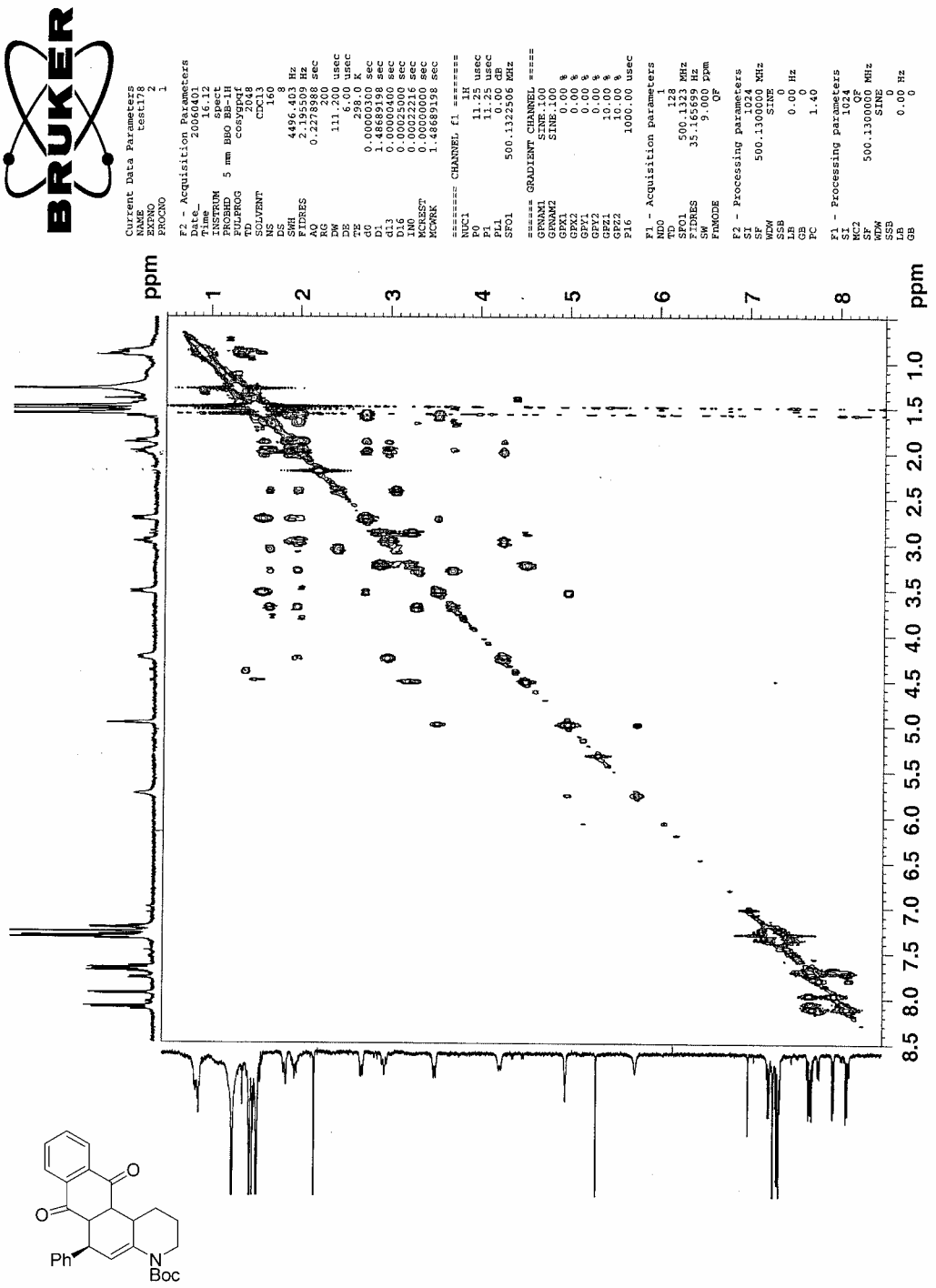
Spectrum 3.146: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **151**



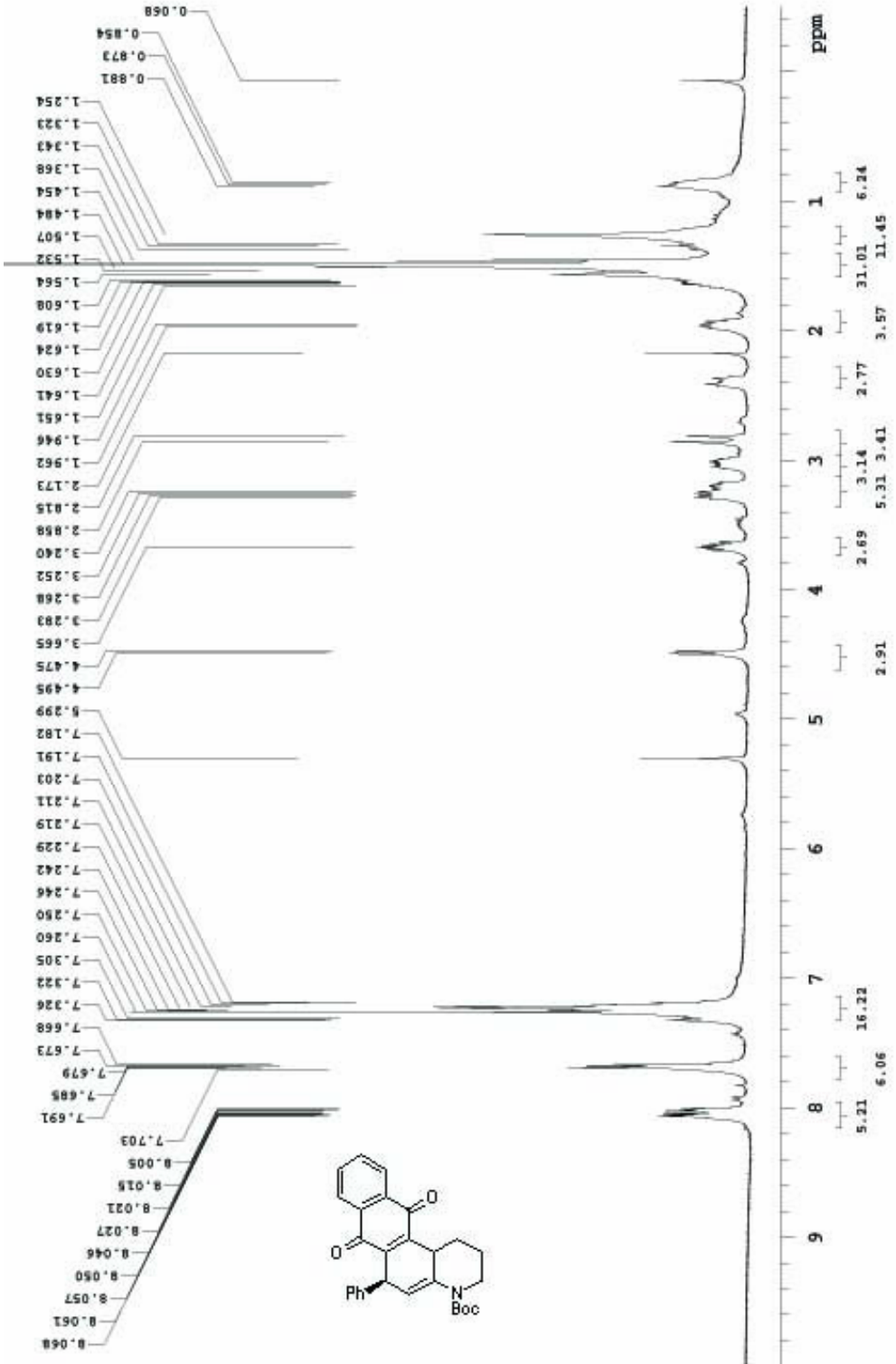
Spectrum 3.147: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **151**



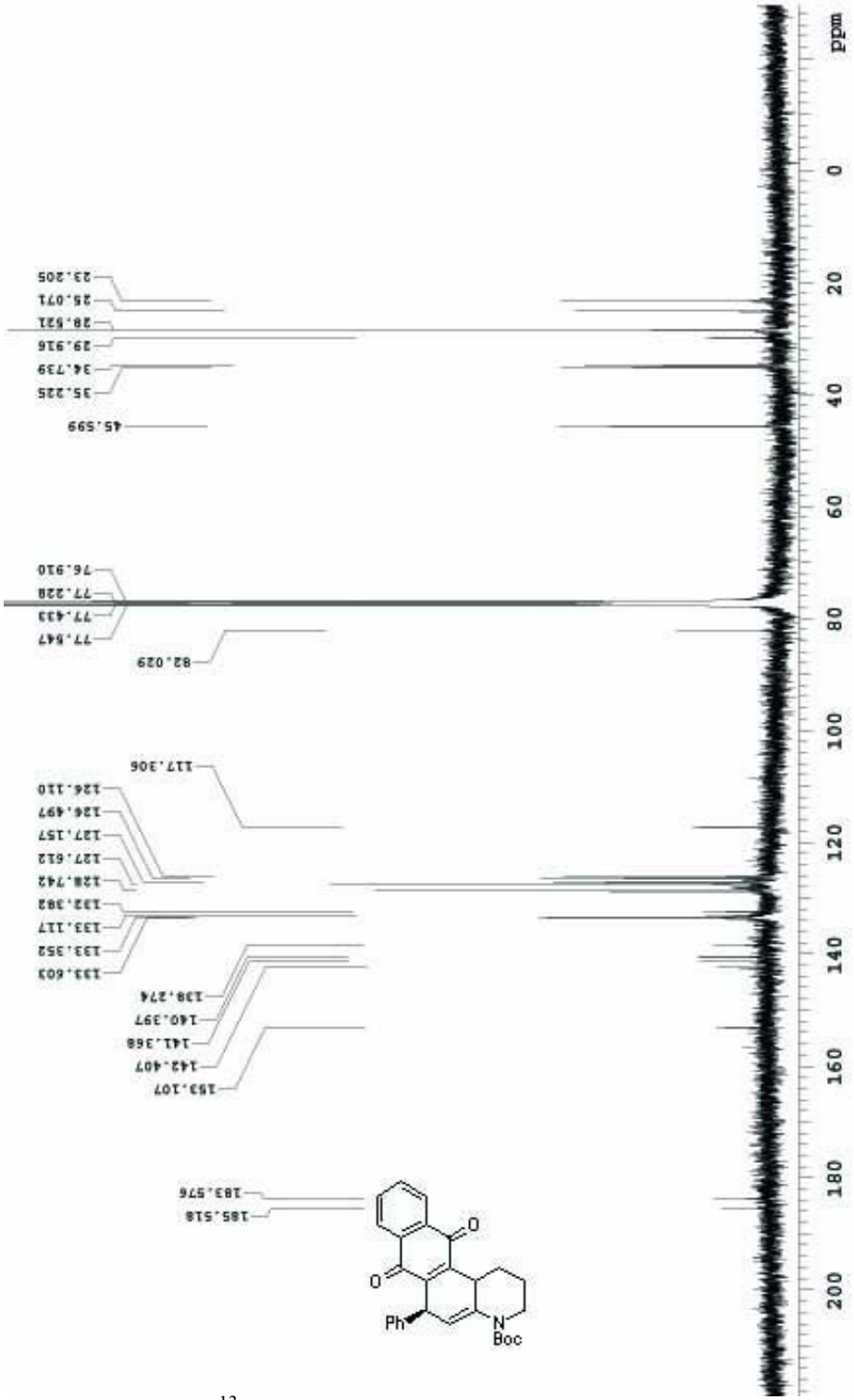
Spectrum 3.148: ^{13}H NMR ($CDCl_3$, 400 MHz) of Compound **150**



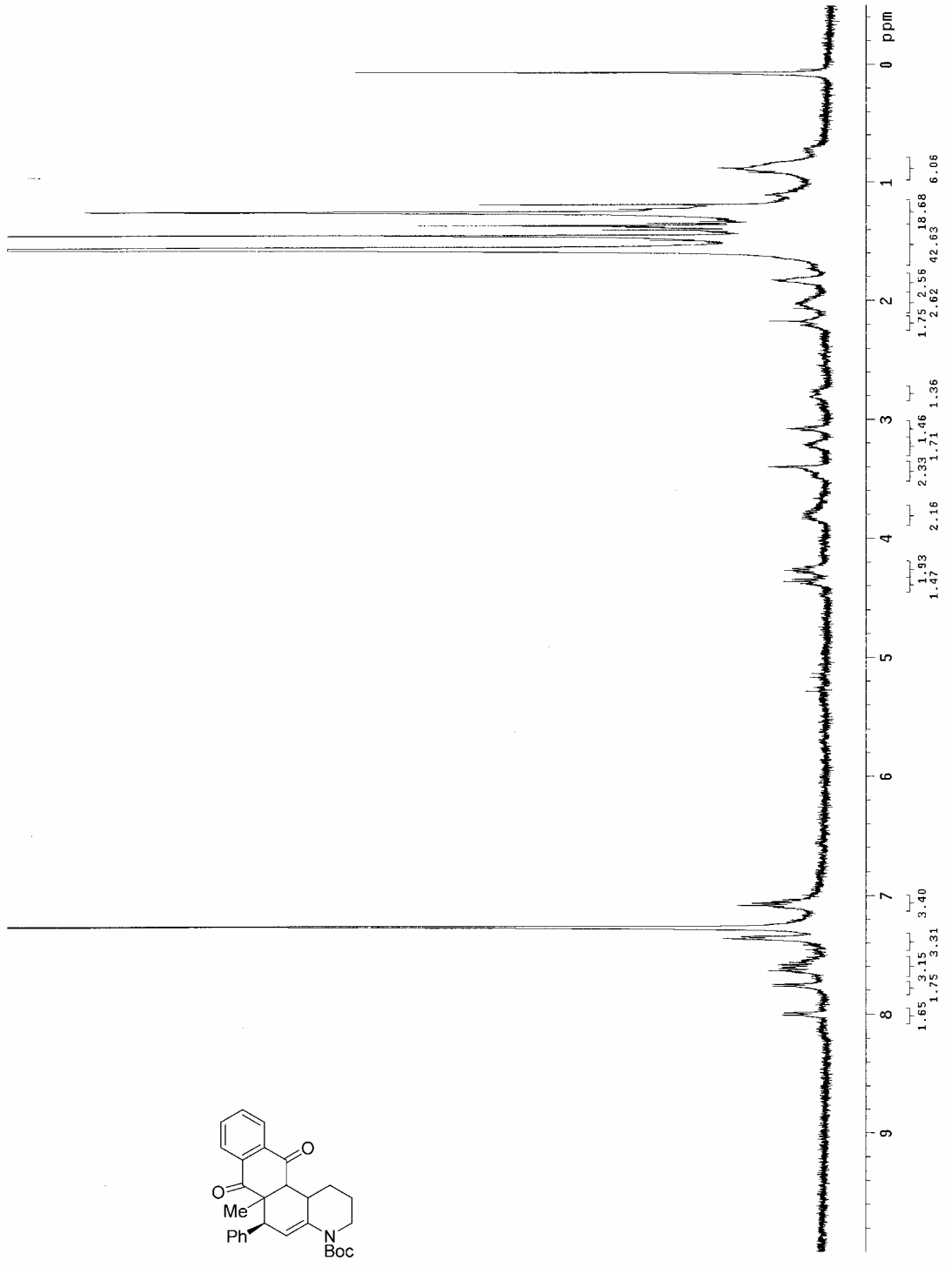
Spectrum 3.149: 2D NMR ($CDCl_3$, 400 MHz) of Compound **150**



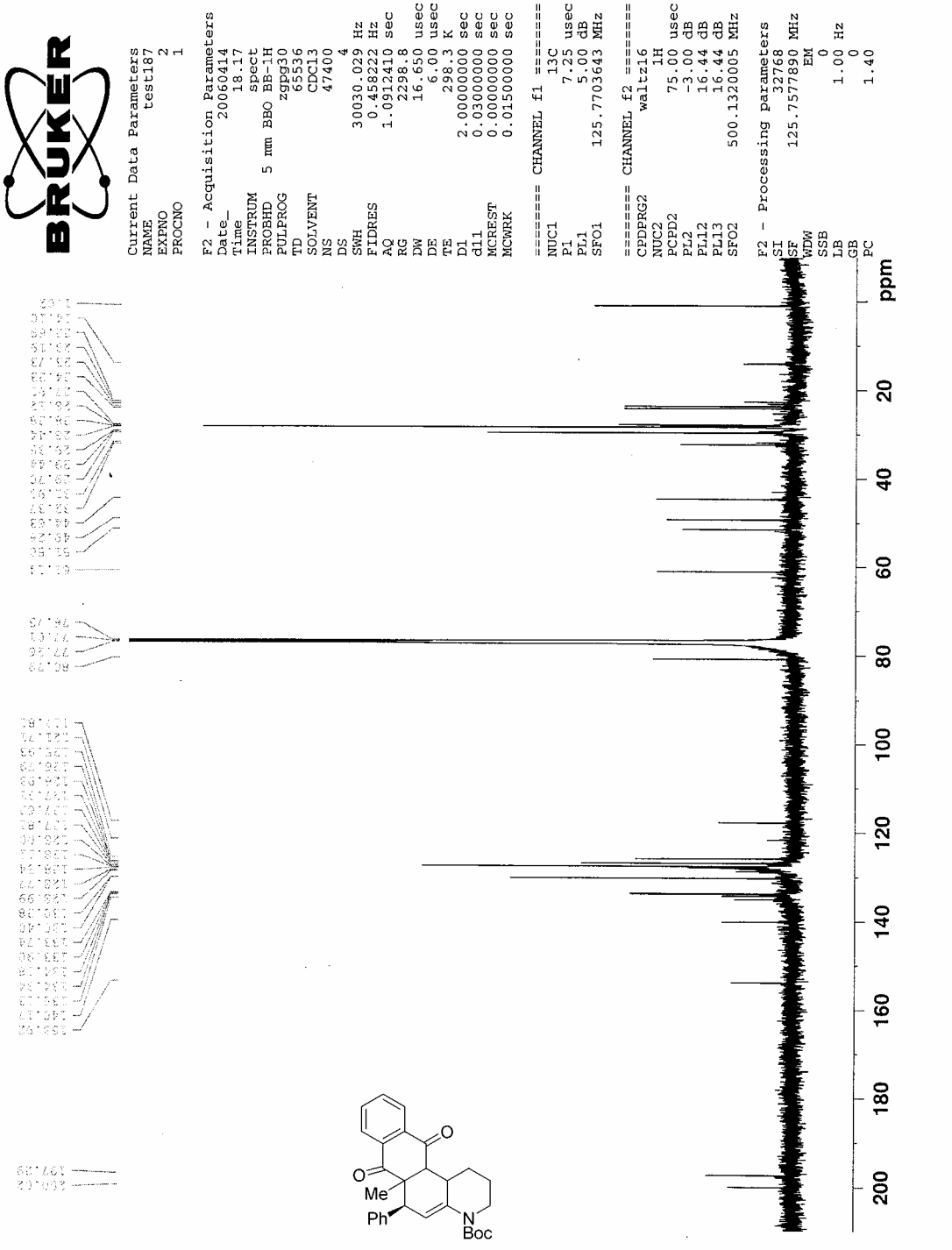
Spectrum 3.150: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **150-1**



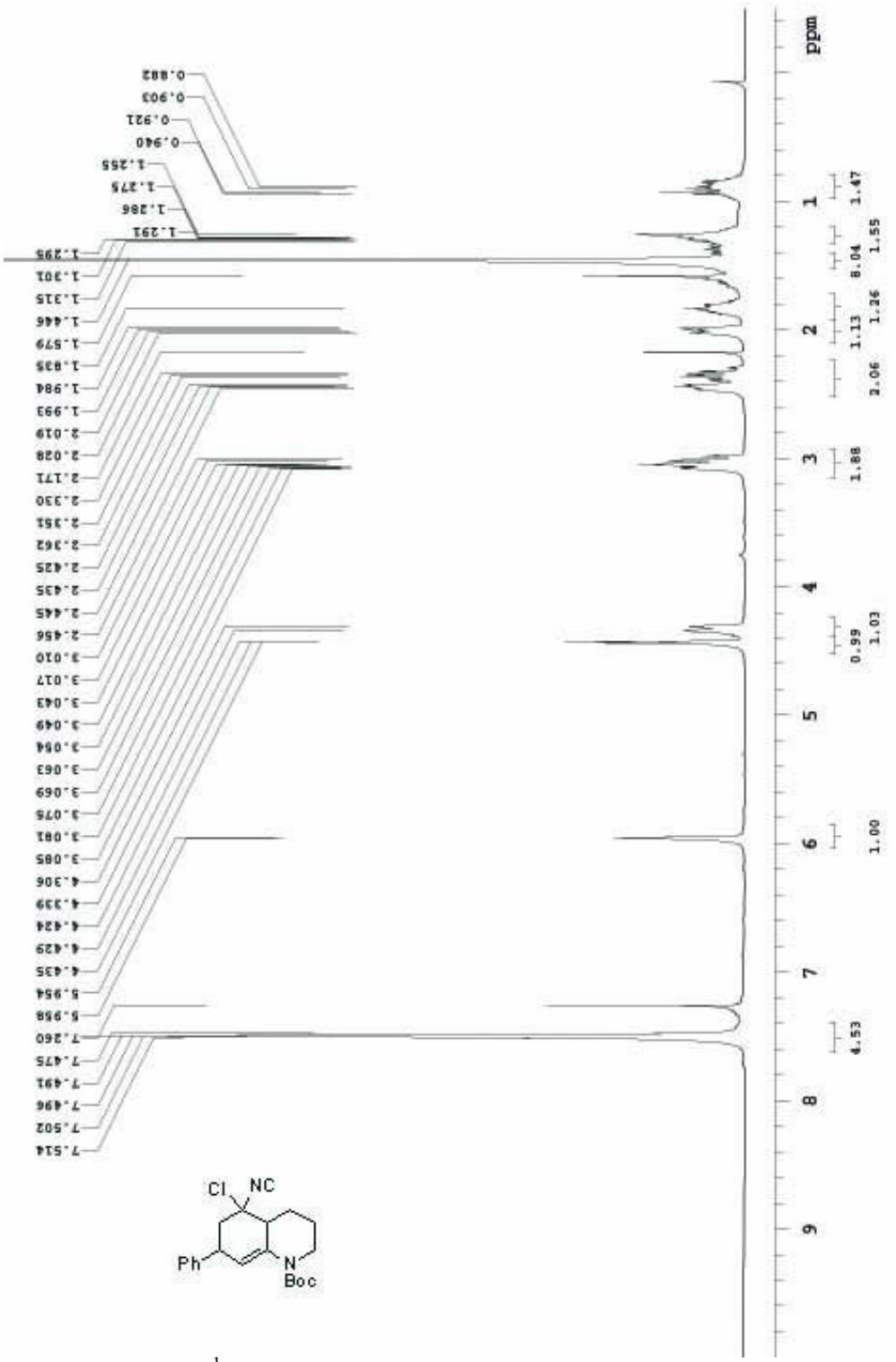
Spectrum 3.151: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **150-1**



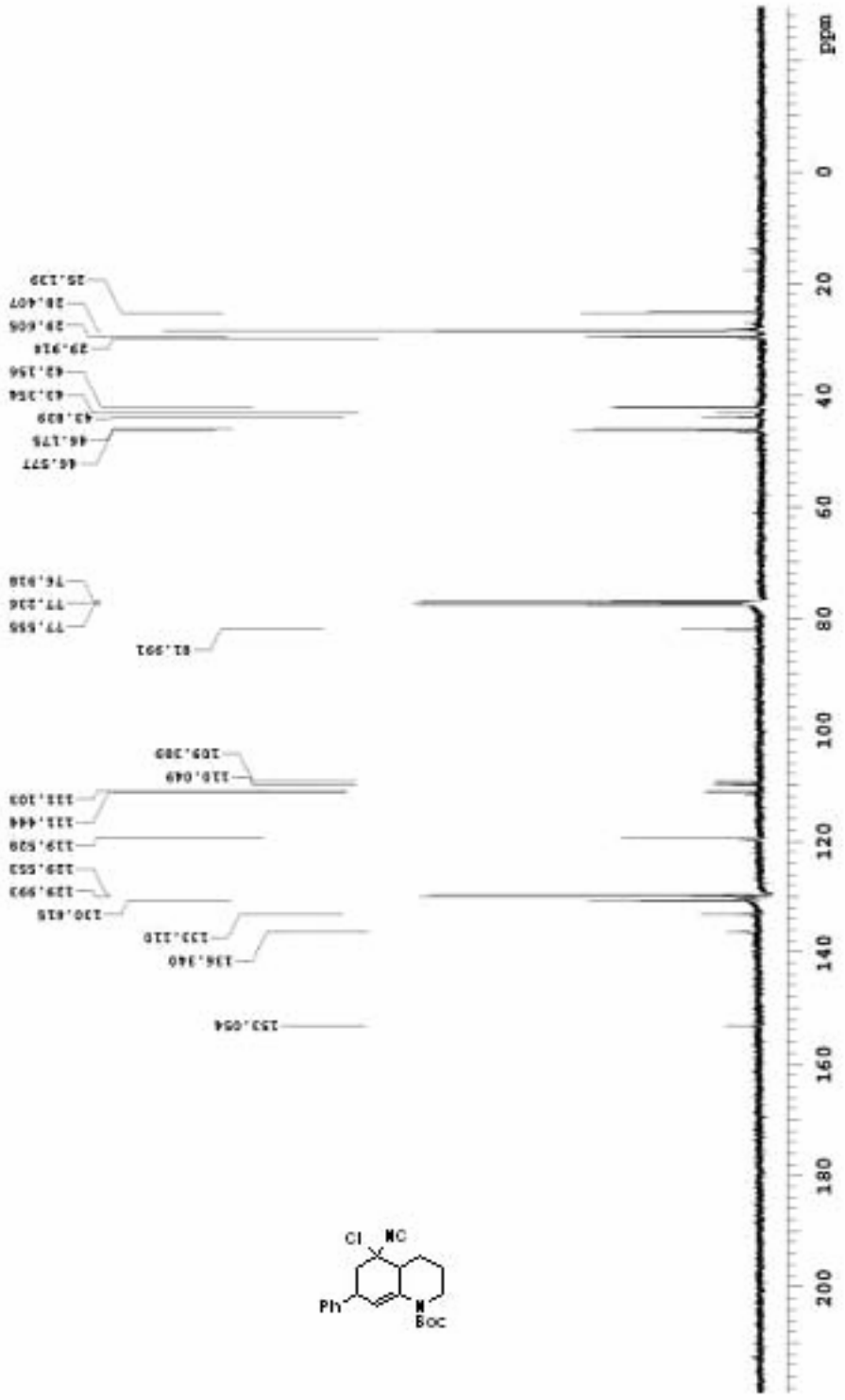
Spectrum 3.152: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **149**



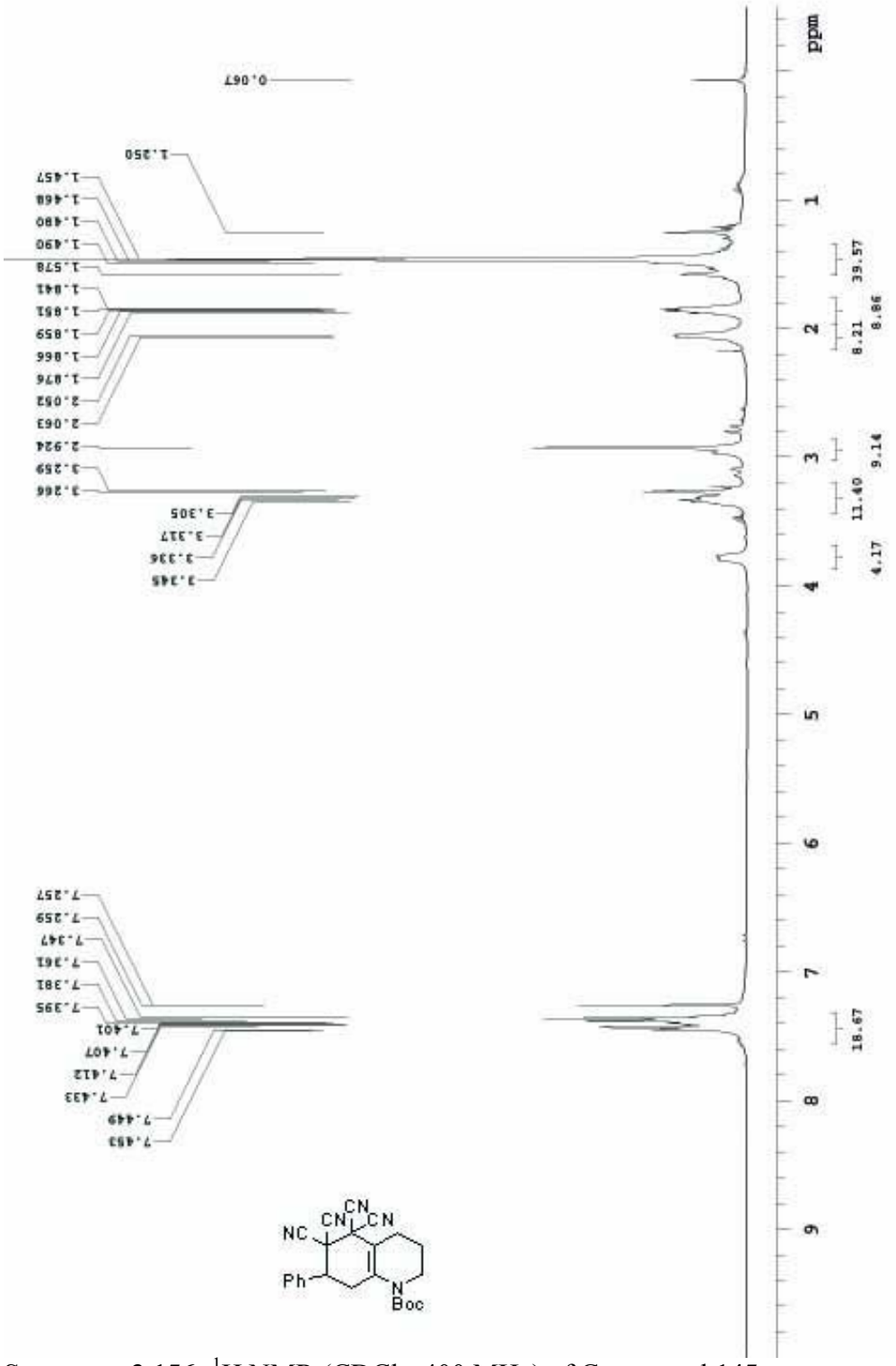
Spectrum 3.153: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **149**



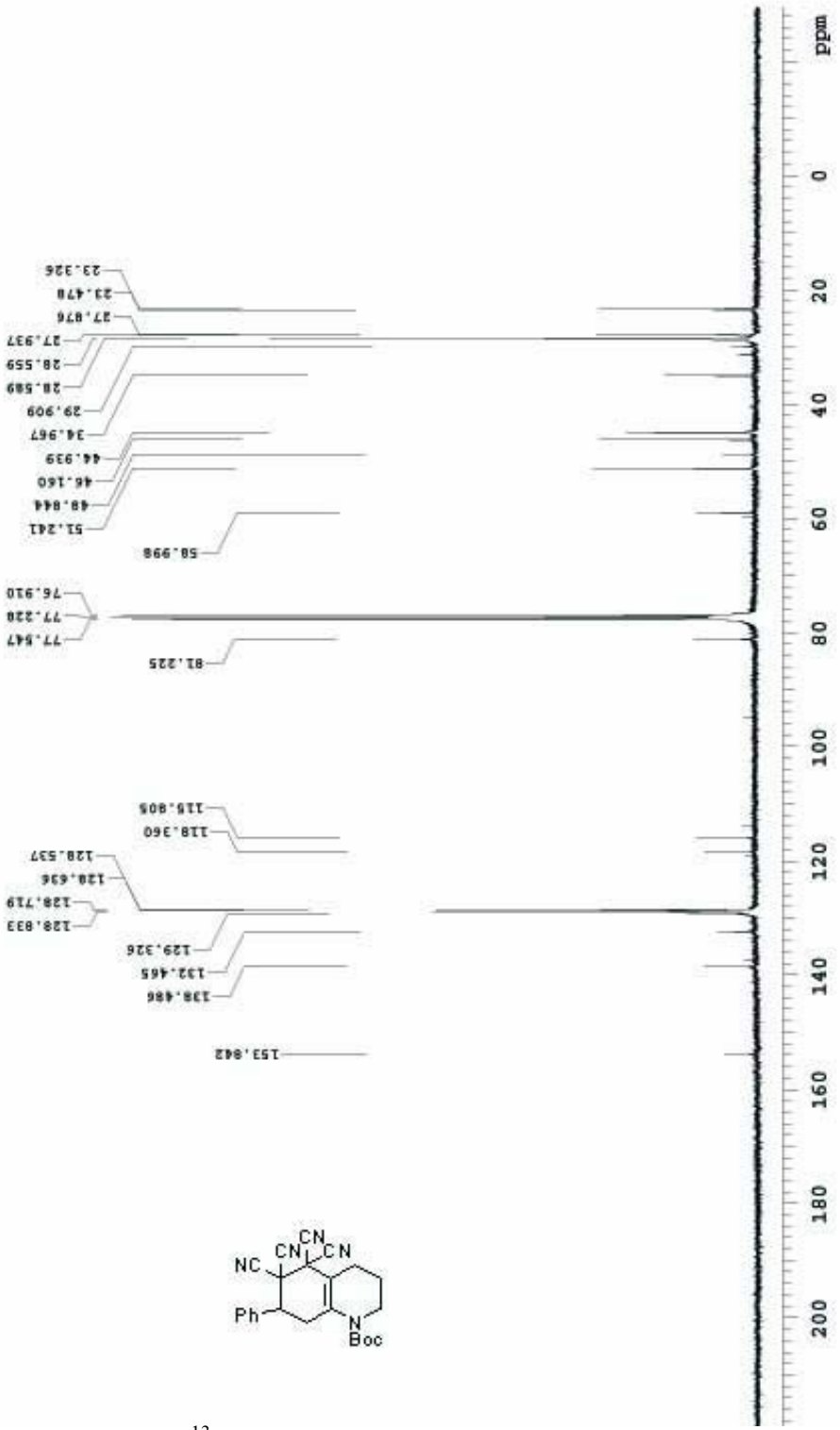
Spectrum 3.154: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **153**



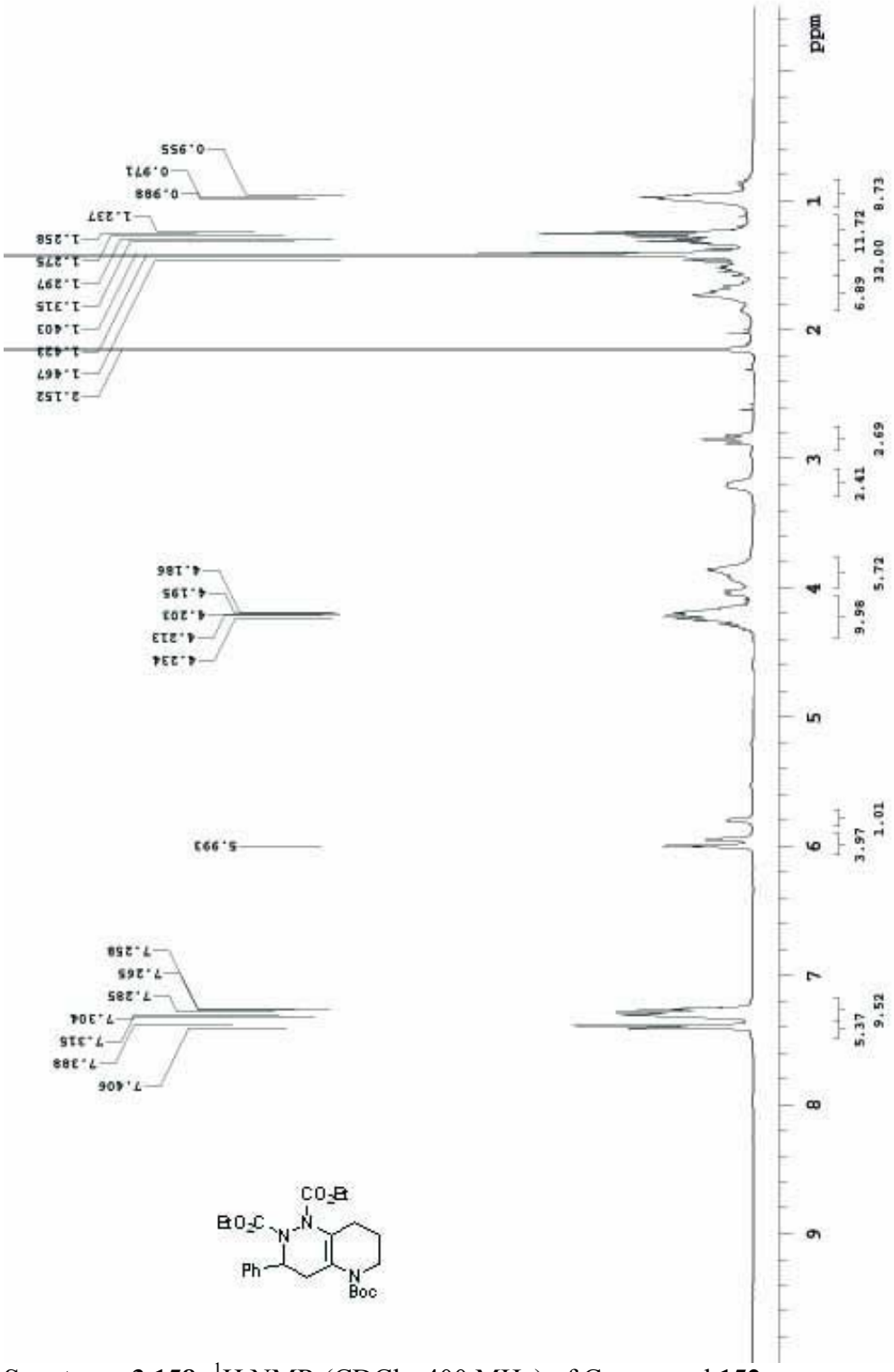
Spectrum 3.155: ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **153**



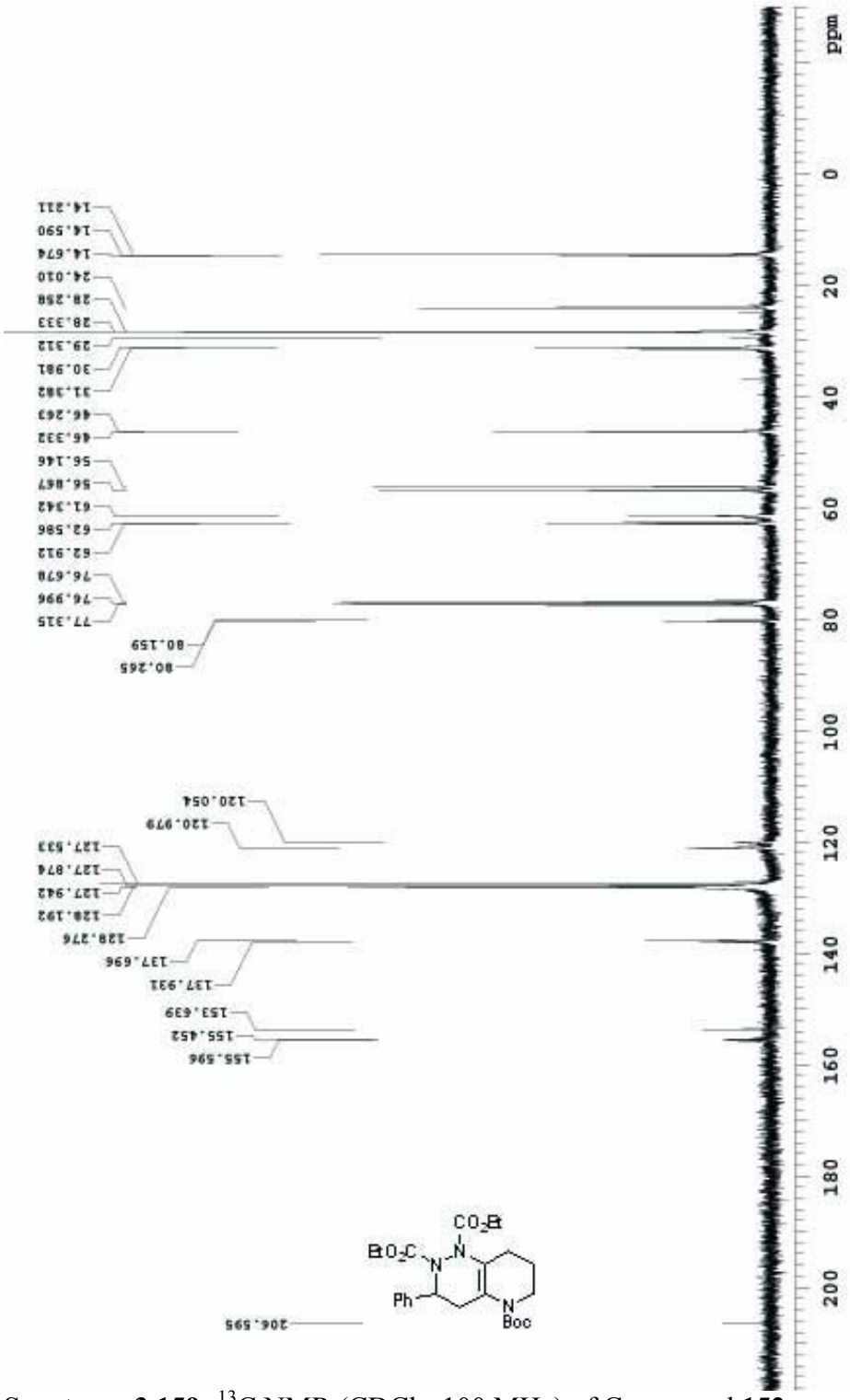
Spectrum 3.156: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **145**



Spectrum 3.157: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **145**



Spectrum 3.158: ^{1}H NMR ($CDCl_3$, 400 MHz) of Compound **152**



Spectrum 3.159: ^{13}C NMR ($CDCl_3$, 100 MHz) of Compound **152**

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www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

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CHAPTER 4

CONCLUSION

Section 4.1 Conclusion

In conclusion, we studied a variety of strategies toward the total synthesis of norzoanthamine and related alkaloids. The studies included both a biomimetic approach and a linear approach. The latter led to the synthesis of the ABC ring system of zoanthamines including the installation of the fully functionalized C-ring. This strategy can now be applied to the synthesis of the zoanthamine alkaloids and related polycyclic natural products.

We also studied a potentially biomimetic approach toward the zoanthamines that involves polyene cyclization. This approach includes formation of the C ring via a Diels-Alder reaction and construction of the A ring through a 6 π cycloaddition. Along these lines we developed a synthesis of (-) and (+)-isocarvone and evaluated an intramolecular Diels-Alder reaction. In addition, we studied the reactivity of 1,3-amino dienes as substrates for this cycloaddition using external electrophiles. We found that this reaction is accelerated in the presence of polar solvents and favors formation of the endo cycloadduct. This approach can lead to an efficient synthesis of the BCE ring of norzoanthamine, which represents the most challenging part of this structure. These synthetic studies set the foundation for a concise, potentially biomimetic, total synthesis of the norzoanthamine family of natural products.