BETA-LACTONES AS SYNTHETIC VEHICLES IN NATURAL PRODUCT SYNTHESIS: TOTAL SYNTHESES OF SCHULZEINES B & C AND OMPHADIOL, AND STUDIES TOWARD THE TOTAL SYNTHESES OF SCABROLIDES A & B AND SINULOCHMODIN C

A Dissertation

by

GANG LIU

Submitted to the Office of Graduate Studies of
Texas A&M University
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

December 2011

Major Subject: Chemistry

Beta-Lactones as Synthetic Vehicles in Natural Product Synthesis:

Total Syntheses of Schulzeines B & C and Omphadiol, and

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Approved by:

Chair of Committee,	Daniel Romo
Committee Members,	Brian Connell
	Jiong Yang
	Hongmin Qin
Head of Department,	David Russell

December 2011

Major Subject: Chemistry

ABSTRACT

Beta-Lactones as Synthetic Vehicles in Natural Product Synthesis:

Total Syntheses of Schulzeines B & C and Omphadiol, and

Studies toward the Total Syntheses of

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(December 2011)

Gang Liu, B.S., Wuhan University;

M.S., Wuhan University

Chair of Advisory Committee: Dr. Daniel Romo

β-Lactones are a class of structurally unique compounds. The versatile reactivity patterns offered by β-lactones have enabled chemists to utilize them as powerful synthetic vehicles in complex molecule synthesis.

In the total syntheses of the naturally occurring, α-glucosidase inhibitors schulzeines B & C, a readily available trichloromethyl β-lactone was used as a versatile masked surrogate for bishomoserine aldehyde, which led to a highly efficient construction of the core structures through a pivotal Pictet-Spengler condensation and a Corey-Link reaction.

The first total synthesis of (+)-omphadiol was achieved in ten steps from (*R*)-carvone. This synthesis features a three-step synthesis of a bicyclic β-lactone, which

constitutes the key intermediate for the highly stereocontrolled introduction of the six contiguous stereogenic centers in the natural product.

In efforts toward the total syntheses of scabrolides A & B and sinulochmodin C via transannular C-H insertions, β-lactones served as the key intermediates for the synthesis of complex macrocyclic model substrates. These model studies provided valuable insights into the reactivity and selectivity issues for transannular C-H insertion reactions.

DEDICATION

To my family

ACKNOWLEDGEMENTS

First and foremost, I would like to thank Professor Daniel Romo for being my advisor for the past six years. Daniel is a great mentor, who not only taught me knowledge about chemistry, but problem-defining and solving skills. Working in his lab was definitely a unique and rewarding experience in my life; it is his guidance and support that shaped me into a well-rounded chemist and independent thinker.

I would like to thank several professors with whom I have had the fortune to interact during my years at Texas A&M. In particular, I would like to thank Professor Brian Connell. His organometallics class in my first year was probably the best class I've ever had. His teaching style and insight on chemistry were truly enlightening. It is a great honor to have had such a knowledgeable scholar around during my whole graduate study. In addition, I am indebted to Professor Jiong Yang for being approachable at this turning point in my life. His journey to Texas A&M was a great source of inspiration to me. His advice and support were definitely invaluable to my future career. I also would like to extend a wholehearted thank you to Professor Hongmin Qin, who has always been very kind and helpful serving on my committee. My sincere gratitude goes to Professor Kevin Burgess for his support.

I would like to thank all of the former and current members of the Romo group for their support. A very special one is Dr. Ke Kong. He is by far the most persistent and meticulous person I know. His commitment to excellence set me an example to follow. Thanks to Dr. Yonggang Wang and Dr. Chunxiao Xu for sharing their lives with me in

the Romo group. I have learned a lot from their self-motivation and work ethic. I would like to thank Morgan Shirley and Alfred Tuley for making me laugh and teaching me English. With them, chemistry is much more fun. Special thanks to Ta Chamni and JC Reyes. To me, they are just like my younger sister and brother who came from the other side of the earth with me. Their presence made my time here much more enjoyable. Thanks are also due to Mikail Abbasov for his help on chemical calculations and graphic designs. It is lucky for me to have such a talented and helpful person in the group. Sincere thanks to all other group members who helped me along the way: Natalie Harvey, Rae Lynn McFarlin, Dr. Sreekumar Vellalath, Dr. Omar Robles, Dr. Carolyn Levertt, Andrea Matla, Dr. Fang Li, Dr. Vikram Purohit, Dr. Sung Wook Cho, Dr. Andy Mitchell, Dr. Shaohui Wang, Dr. Richard Duffy, Dr. Cong-Ying Zhou, Dr. Xinzhong Lai, Dr. Wei Zhang, Dr. Gil Ma, Dr. Mahesh Peddibhotla, Dr. Liang Tang, Dr. Manuel Zancanella, Dr. Henry Nguyen, Dr. Kay Morris, and Dr. Changsuk Lee.

For all their help in making my life in graduate school a whole lot easier, I would like to thank the chemistry graduate student office: Sandy Manning, Prof. Simon North, Julie Wilson, and Joy Monroe. I am especially grateful to Sandy, who I bothered with numerous questions and from whom I could always get the right answers.

I also would like to thank Dr. Yingcai Wang, my intern mentor in Amgen, Inc. in San Francisco. I am thankful that he offered me a great opportunity to get to know a world-class pharmaceutical company.

Finally, my greatest appreciation goes to my entire family. It is their sacrifice and patience that made this journey possible.

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CHAPTER I

INTRODUCTION: β-LACTONES AS SYNTHETIC VEHICLES IN NATURAL PRODUCT SYNTHESIS

1.1 Introduction

As a class of structurally unique organic compounds, β-lactones (2-oxetanones) have been the focus of much attention in organic synthesis. Such an interest in this structural motif stems from its presence in numerous biologically active natural products and pharmaceutical agents.[1, 2] Moreover, the versatile reactivity, in conjunction with the unusual structural features of these species, has inspired the development of a variety of methodologies involving both the construction of these organic compounds and their applications as important synthetic intermediates for transformations to more advanced structures.[3, 4]

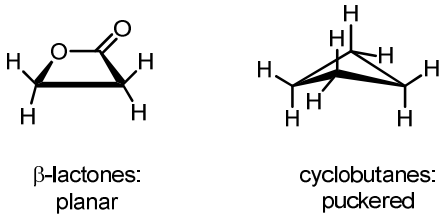

Figure 1.1 Structural Comparison of β-Lactones and Cyclobutanes

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This dissertation follows the style of *Journal of Organic Chemistry*.

From the perspective of organic structure, the uniqueness of β-lactones originates from the planar structure that deviates dramatically from the common puckered conformation of their saturated counterparts such as cyclobutanes (Figure 1.1); incorporation of an ester functionality in a compact four-membered ring leads to the nearly square geometry of the four atoms in the ring, forced by the resonance of the ester bond. This highly strained structure possesses comparable strain energy relative to epoxides (Figure 1.2). [5]

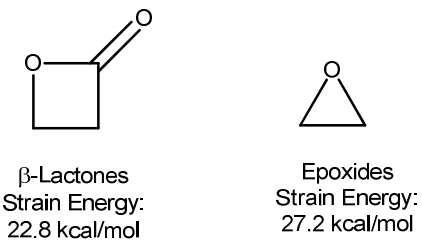


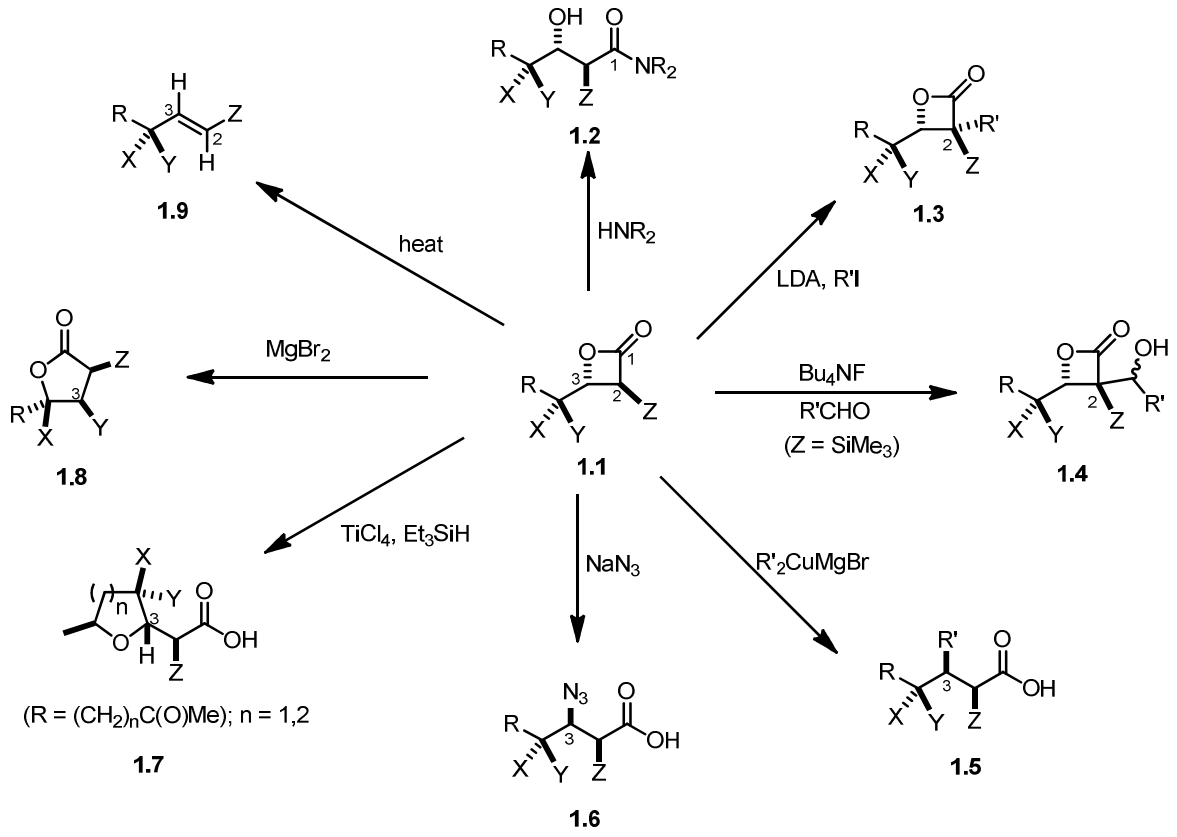
Figure 1.2 Strain Energy of β-Lactones and Epoxides

Imparted by the unusual planar structure and highly strained nature of β-lactones, a unique spectrum of reactivity patterns that lead to distinct reaction pathways could be revealed under different reaction conditions (Scheme 1.1).

Arguably, the most prevalent transformation of β-lactones is the attack at the C1 carbonyl group under the influence of a suitable nucleophile, leading to the ring-opening products. This site (C1) is mostly susceptible to the addition of hard nucleophiles such as alcohols and amines. This transformation readily unmasks lactones under very mild conditions to the corresponding β-hydroxyl esters or amides characteristic of ester or

amide aldol adducts (**1.2**). Thus, the methodologies developed for the β-lactone synthesis through C2-C3 bond formation could be regarded as variants of classic aldol reactions.

Scheme 1.1



The C2 carbon could be manipulated to a nucleophilic site by either direct deprotonation or fluoride-induced C-Si cleavage when a silyl group resident at C2 is available. The strained enolates so formed could be trapped by electrophiles such as

alkyl iodides or aldehydes, giving rise to derived β-lactones (**1.3** and **1.4**). This reaction manifold enables the carbon homologation at the C2 position while maintaining the integrity of the highly strained β-lactone ring system.

The highly strained nature of β-lactones renders C3 a potential reacting site that offers a range of unique reaction manifolds normally unavailable to other lactones and esters. For example, soft nucleophiles such as organocupurates and azides tend to induce the cleavage of the C-O single bond at C3 to afford β-substituted acids with the inversion of stereoconfiguration (**1.5** and **1.6**).

In addition, Lewis acids, such as $TiCl_4$, could activate the C-O single bond to generate a partial cation at C3, which could be intercepted in the presence of a pendant carbonyl group to form a five or six membered oxocarbenium. Ensuing hydride reduction of this transient intermediate by triethyl silane delivers highly substituted furans or pyrans with defined stereoconfigurations(**1.7**).

With certain β-lactones, dyotropic rearrangements could be triggered by Lewis acids. This concerted process leads to ring-expansion from four-membered lactones to five-membered lactones through the antiperiplanar transposition of the C-O bond and the neighboring C-Y bond (**1.8**).

Thermal extrusion of CO_2 to give olefins (**1.9**) is another unique reactivity pattern of β-lactones, even though this transformation is generally undesirable; from the standpoint of synthetic efficiency, this leads to a degradation of structural complexity due to the elimination of two vicinal stereogenic centers. Notably, this event proceeds in a stereospecific fashion to deliver the substituted olefins that retain the relative

stereochemistry of β-lactones, *i.e. cis*-β-lactones give (*Z*)-olefins, while *trans*-β-lactones lead to (*E*) olefins.

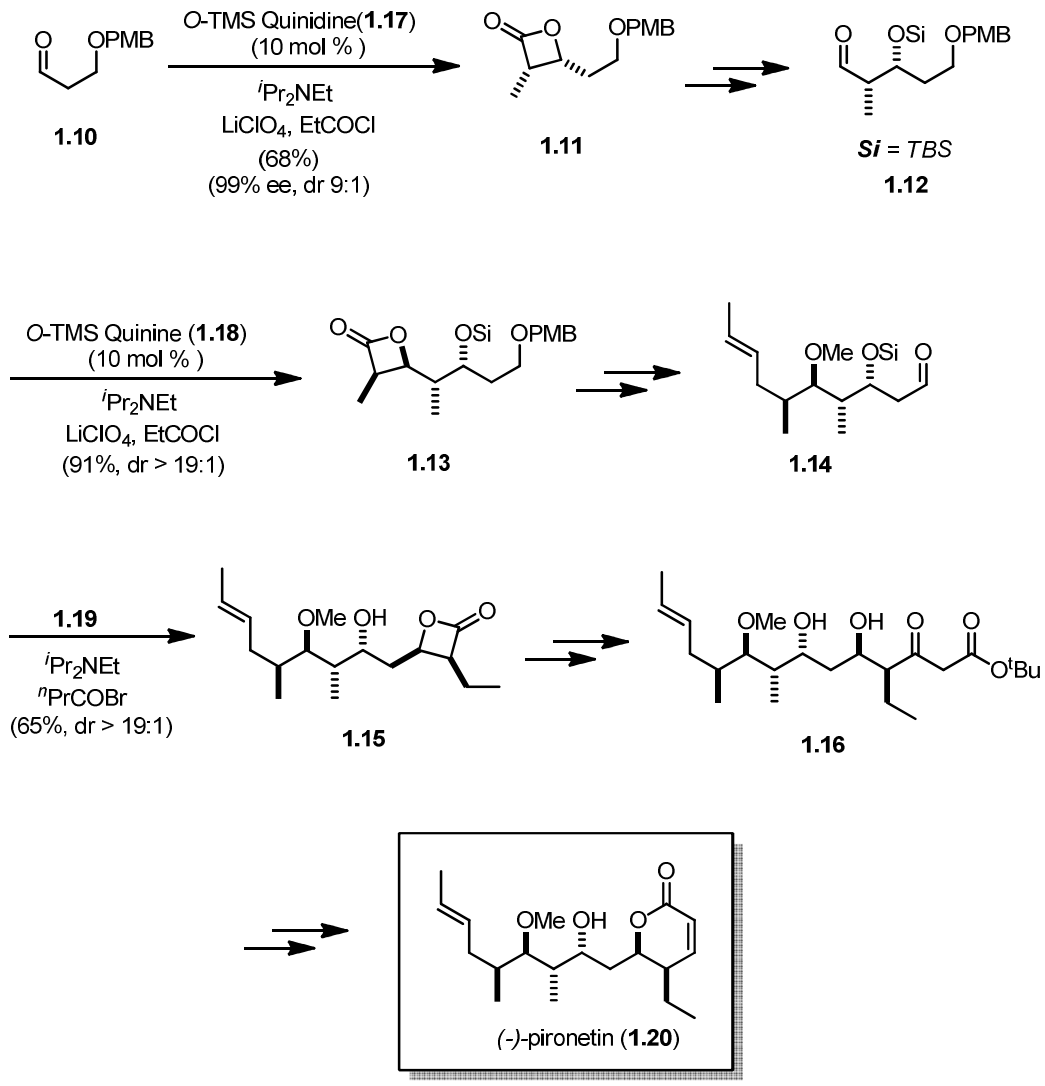
1.2 Application of β-Lactones in Natural Product Total Synthesis

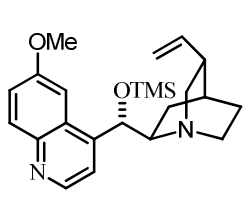
The versatile reactivity patterns available to β-lactones have armed organic chemists with powerful tools that facilitate rapid build-up of structural complexity, which is evidenced by numerous applications of β-lactones as pivotal synthetic vehicles in complex settings, especially in natural product synthesis. This section will focus on the representative examples of natural product synthesis that implement unique β-lactone chemistry as strategic transformations over the last seven years since a relevant review on this topic was published in 2004.[5]

1.2.1 (-)-Pironetin

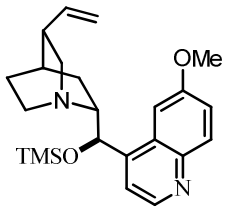
In 2006, the Nelson group reported their total synthesis of (-)-pironetin.[6] This total synthesis highlighted the iterative application of their acid chloride-aldehyde cyclocondensation (AAC) reactions for the catalytic asymmetric synthesis of extended propionate networks (Scheme 1.2).

Scheme 1.2

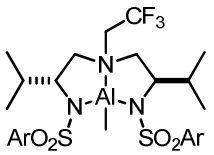




O-TMS Quinidine
1.17



O-TMS Quinine
1.18



Ar = 3,5-$(CF_3)_2C_6H_3$-
1.19

Their AAC technology successfully integrated *in situ* ketene formation and aldehyde cycloaddition to realize the catalytic β-lactone formation employing inexpensive commercially available materials. The β-lactones emerged from these reactions constitute ester or amide aldol adduct from which the characteristic 1,3-hydroxyl ester or amide could be readily unmasked upon ring-opening with alcohols or amines under very mild conditions. Thus, this method serves as a highly efficient variant of catalytic asymmetric cross aldol reactions by addressing the issues of cost and operational simplicity associated with chiral auxiliary-based asymmetric aldol reactions.

The first AAC reaction using 3-*p*-methoxybenzyloxypropanal (**1.10**) and propionoyl chloride as the reaction partners afforded β-lactone **1.11** in excellent enantiomeric excess and diastereomeric ratios, which was subjected to a three-step lactone-to-aldehyde conversion to give *syn* aldehyde **1.12**, positioned for the second iteration of the AAC reaction. It was found that OTMS-quinine catalyzed the AAC homologation of **1.12** in a matched double diastereodifferentiation, providing the *syn, anti, syn* β-lactone **1.13** with high than 19:1 diastereomeric ratio.

Further elaboration of this β-lactone (**1.13**) through an array of straightforward transformations led to aldehyde **1.14**, setting the stage for the last aldol bond forming step. This substrate, however, failed to deliver the cycloaddition product **1.15** under alkaloid-catalyzed conditions.

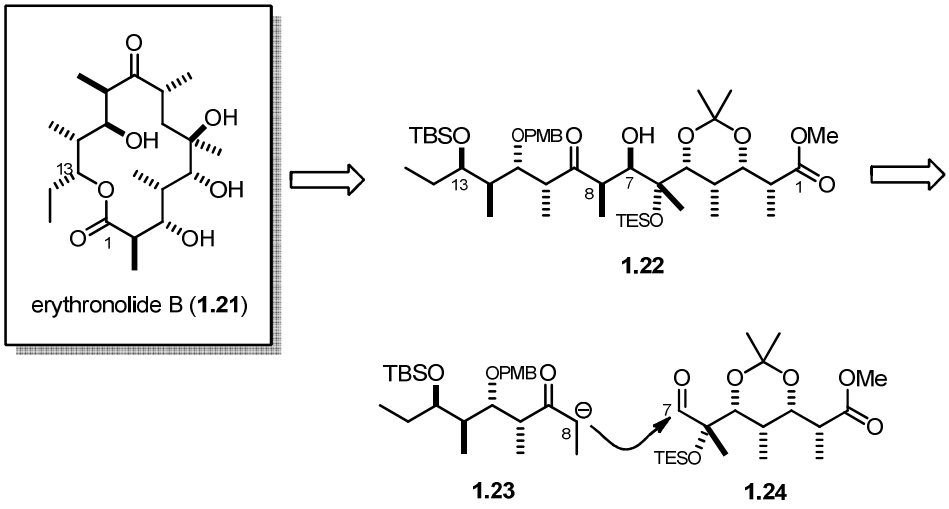
Instead, engaging aldehyde **1.14** in Lewis acid-promoted AAC homologation (50 mol % of **1.19**) employing butyryl bromide as a butanoate enolate equivalent afforded β-lactone **1.15** (65% yield, high than 19:1 diastereomeric ratio), possessing all of the (-)-pironetin stereocenters. This result attests to the complementary nature of the Lewis acid and alkaloid-catalyzed AAC reactions. Ensuing transformations delivered (-)-pironetin without incident.

1.2.2 Erythronolide B

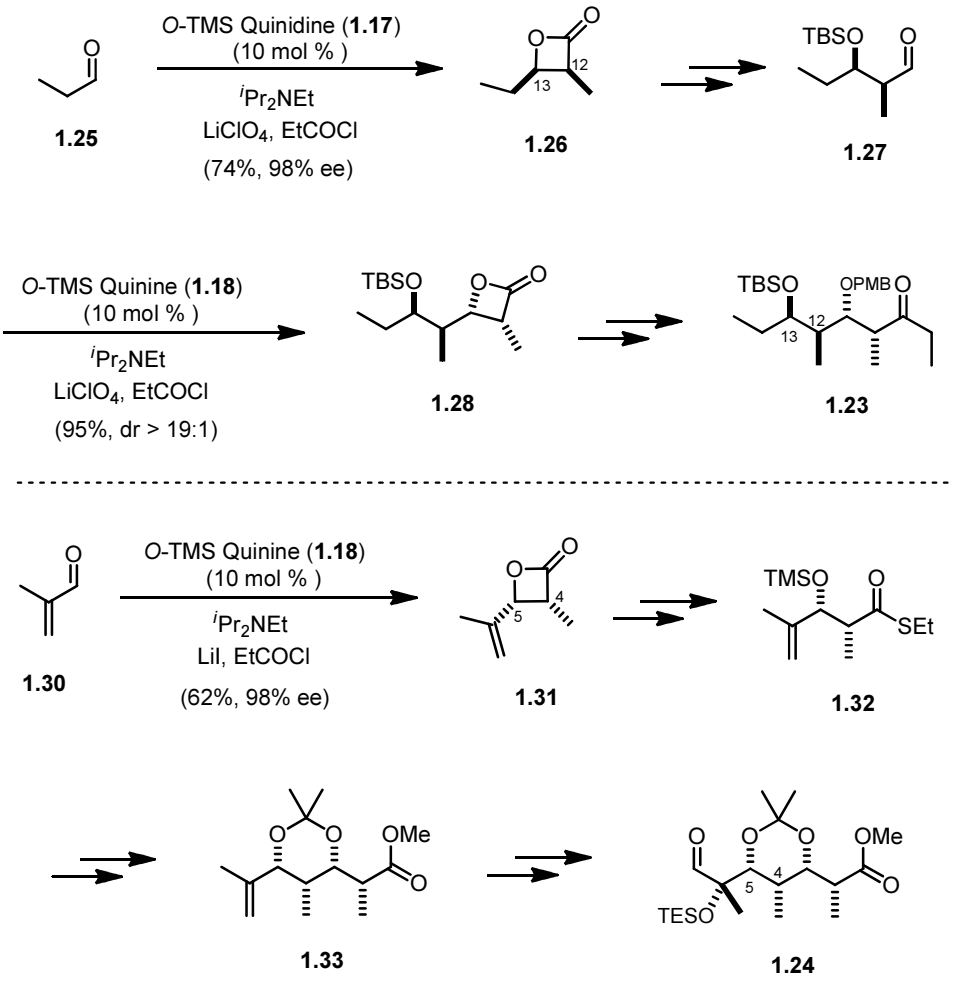
As shown in the previous case, Nelson's acid chloride-aldehyde cyclocondensation reactions provided a uniform strategy for executing asymmetric cross aldol additions on enantioenriched aldehyde substrates. Iterative application of these AAC reactions afforded a rapid entry into stereodefined polypropionate building blocks expressed in numerous polyketide natural products. To further demonstrate the usefulness of this method as a practical surrogate for aldol reactions, the Nelson group extended the application of this strategy to the total synthesis of erythronolide B, a much more complex setting that encompasses a fourteen-membered macrocycle along with eleven stereogenic centers (Scheme 1.3).[7]

The synthesis hinged on the disconnection of target across the C1-O13 and C7-C8 bonds leading to two modified propionate trimer equivalents **1.23** and **1.24**; the construction of both fragments utilized the AAC reactions for key C-C bond forming steps as well as the elaborations of the resultant β-lactone units (Scheme 1.4).

Scheme 1.3



Scheme 1.4



All four stereogenic centers of fragment **1.23** were introduced by AAC reactions. Condensation of propionyl chloride with propionaldehyde catalyzed by OTMS-quinidine provided β-lactone **1.26**, which presents the C12-C13 syn-propionate unit. Modification of this β-lactone through a two-step sequence to aldehyde **1.27** set the stage for the second AAC homologation. In the event, the condensation with propionyl chloride was

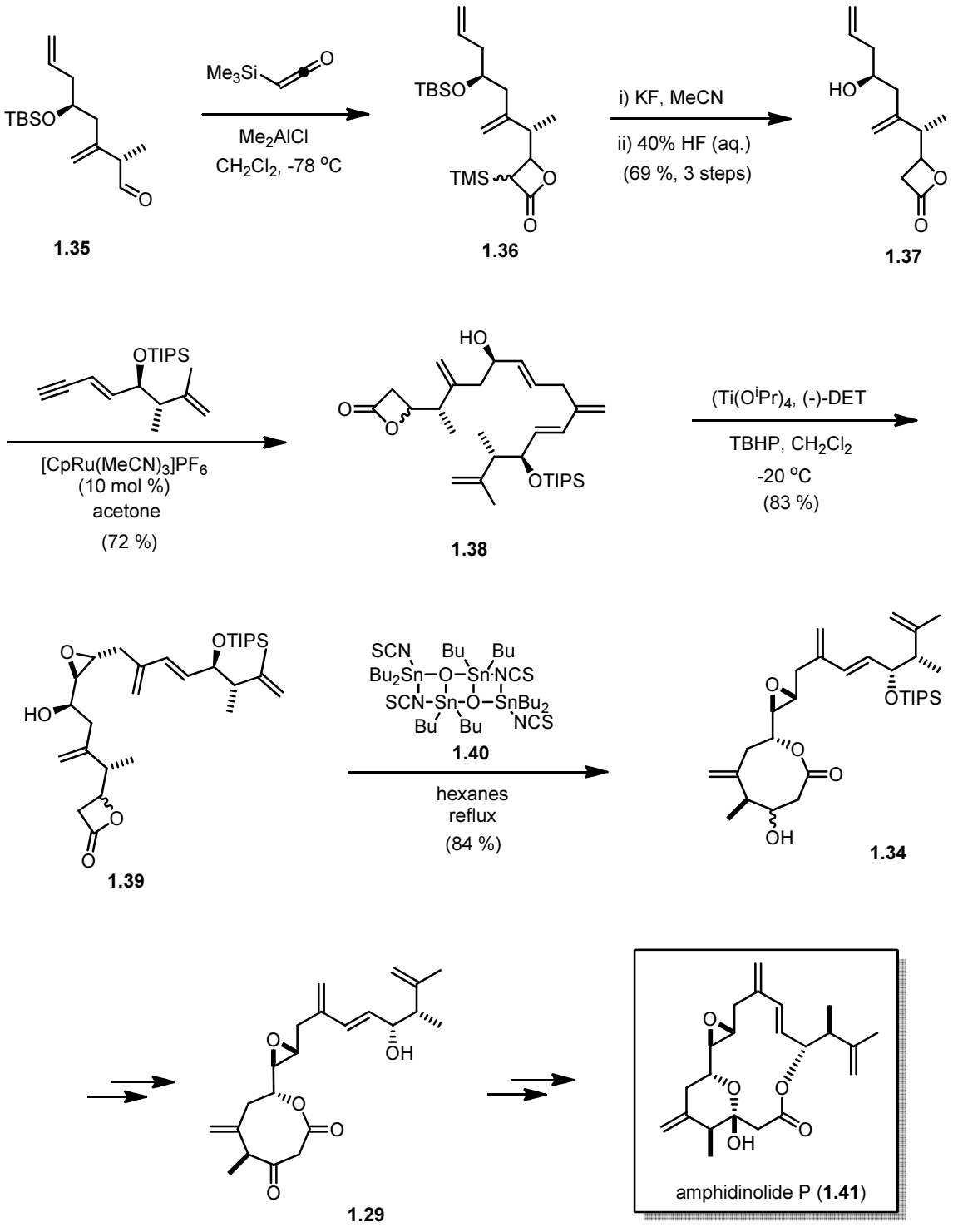
performed in the presence of the quinine-based catalyst **1.18**, affording β-lactone **1.28** with exceptional efficiency (95% yield) and greater than 19:1 diastereomeric ratio. The β-lactone was subsequently elaborated to fragment **1.23**.

The cyclocondensation of α,β-unsaturated aldehyde **1.30** with propionyl chloride catalyzed by OTMS-quinine also proceeded with good yield and excellent enantiomeric excess to give β-lactone **1.31**, which provides the C4-C5 bond in fragment **1.24**. The two stereogenic centers generated in this pivotal aldol bond construction served as the stereochemical control elements in the following introduction of the other three stereogenenic centers, and eventually enabled the assembly of this fragment in a highly substrate-controlled manner.

1.2.3 Amphidinolide P

Amphidinolide P is a member of the amphidinolide family isolated by Kobayashi from a strain of laboratory-cultured symbiotic dinoflagellates of the genus *Amphidinium sp.* This macrolide exhibited cytotoxicity against murin lymphoma L1210 and human epidermoid carcinoma KB cells *in vitro* (IC_{50} = 4.0 and 14.6 μM, respectively). The Trost group disclosed their total synthesis of this natural product employing β-lactone construction as a strategic C-C bond forming step (Scheme 1.5). [8]

Scheme 1.5


TBSO
O
1.35
Me3Si
O
Me2AlCl
CH2Cl2, -78 °C
TBSO
TMS
O
O
1.36
i) KF, MeCN
ii) 40% HF (aq.)
(69 %, 3 steps)
HO
O
O
1.37
OTIPS
[CpRu(MeCN)3]PF6
(10 mol %)
acetone
(72 %)
HO
O
O
OTIPS
1.38
(Ti(OiPr)4, (-)-DET
TBHP, CH2Cl2
-20 °C
(83 %)
OTIPS
O
HO
O
O
1.39
SCN
Bu
Bu
Bu2Sn
O
Sn
NCS
SCN
Sn
O
SnBu2
Bu
Bu
NCS
1.40
hexanes
reflux
(84 %)
O
OTIPS
O
O
OH
1.34
OH
O
O
O
1.29
O
O
OH
O
O
amphidinolide P (1.41)

In the late stage elaborations en route to the final target, they resorted to a Lewis acid mediated silyl ketene-aldehyde cycloaddition reaction to effect the two-carbon homologation at C3. The β-lactone so formed (**1.36**), surprisingly, survived a series of transformations, including desilylation under both acidic and basic conditions, Ru-catalyzed en-yne coupling reaction, and sharpless epoxidation to arrive at the cyclization precursor **1.39**.

Under the influence of a catalytic amount of Otera's catalyst **1.40**, eventually, the β-lactone motif of **1.39** acted as a latent acylation site to cap the pendant secondary hydroxyl group, delivering the eight-membered lactone **1.34**. The ring expansion event was presumably driven by the strain release of the β-lactone to the more flexible eight-membered ring.

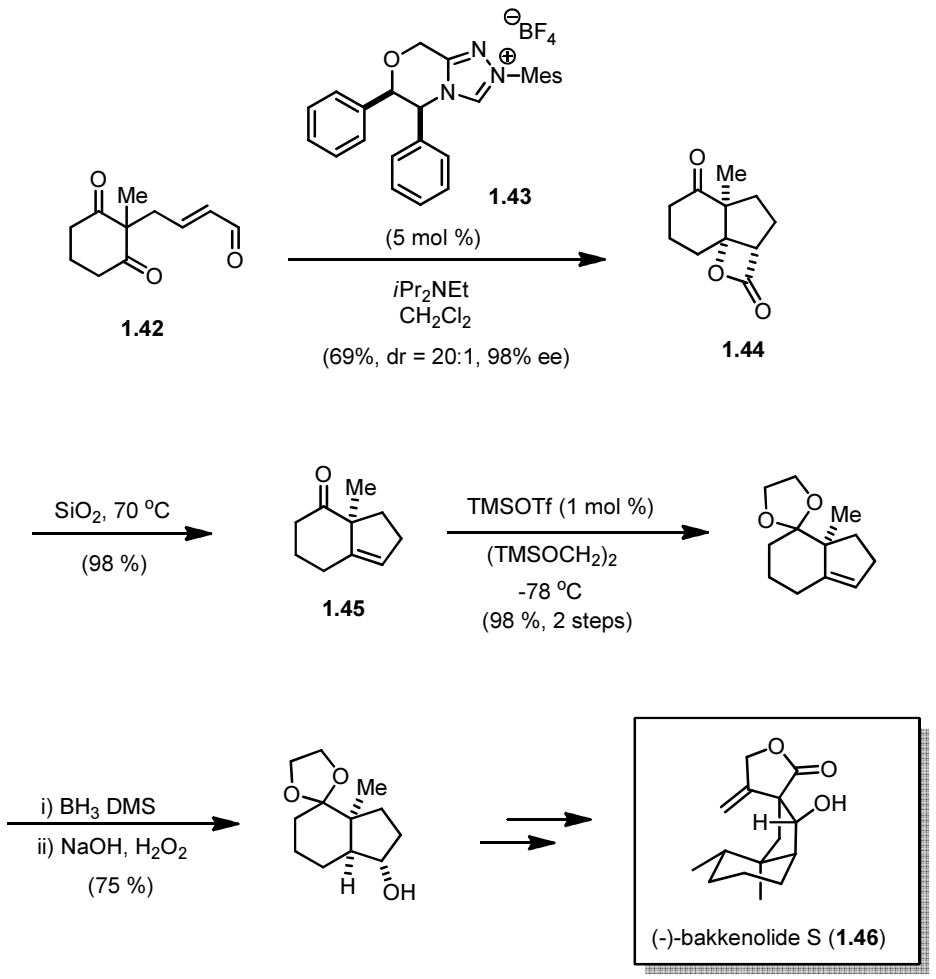
1.2.4 (-)-Bakkenolide S

Bakkenolides belong to a large class of sesquiterpenes containing a characteristic *cis*-fused 6,5-bicyclic core. The Scheidt group developed a general strategy for the catalytic asymmetric syntheses of these natural products (Scheme 1.6). [9]

The desymmetrization of 1,3-diketone **1.42** catalyzed by an N-heterocyclic carbene (NHC) provided a rapid entry into the tricyclic β-lactone **1.44** with excellent relative and absolute stereocontrol. Notably, this process is amenable to large scale synthesis (up to 5 grams) without diminishing stereoselectivity. To adjust the oxidation state at C10 as found in the final target, β-lactone **1.44** was subjected to heated silica gel to effect the elimination of CO_2, generating the trisubstituted double bond with

essentially quantitative yield. Following the protection of the ketone carbonyl group in the form of a ketal, a regioselective hydroboration-oxidation of this olefin was executed at a later stage to properly secure the methine hydrogen at C10 with desired stereoconfiguration.

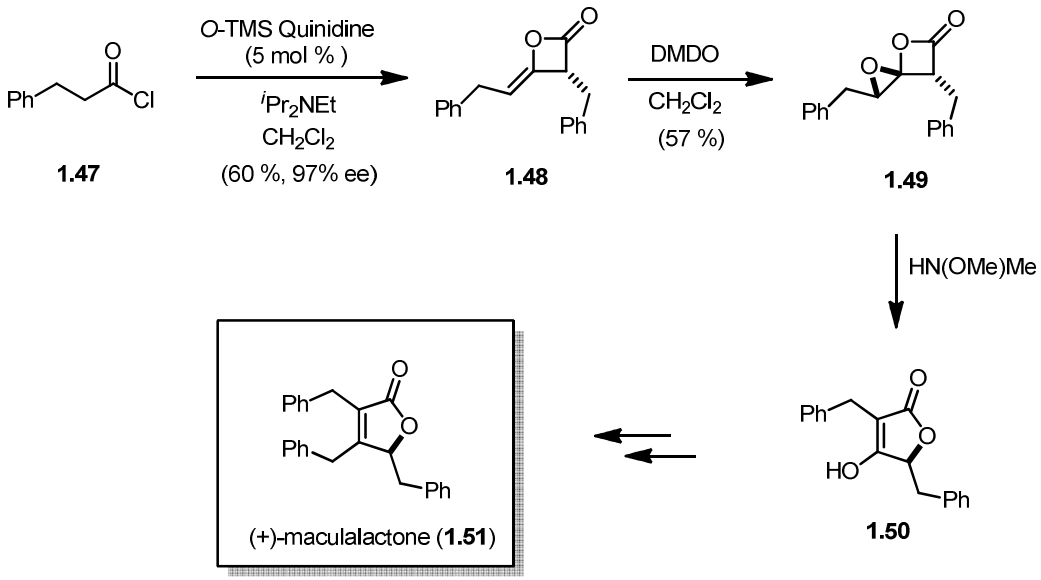
Scheme 1.6



1.2.5 (+)-Maculalactone

Isolated from the marine cyanobacterium *Kyrtuthrix maculans*, maculalactones are unique natural products containing a butenolide moiety. Among this family, maculalactone A was found to be the only member of this family that exhibited biological activity, namely, inhibition of the growth of marine bivalves on rock surfaces (LD_{50} = 4.2 μg/mL).[10]

Scheme 1.7



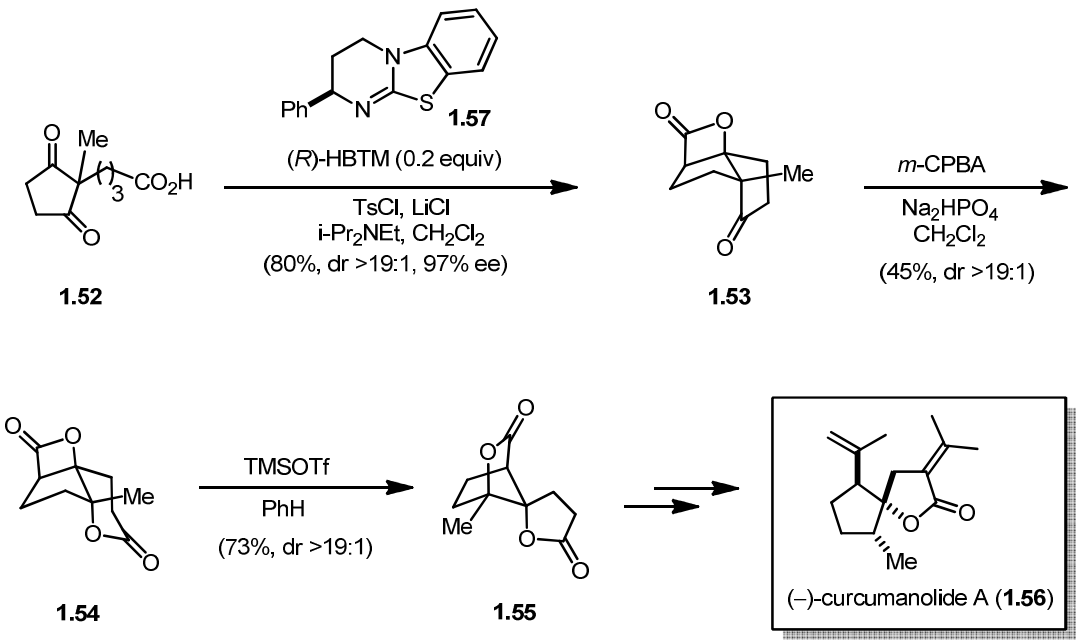
Toward the total synthesis of maculalactone A, the Romo group devised an approach that centered on the application of spiroepoxy-β-lactones, a class of highly strained yet surprisingly stable β-lactones (Scheme 1.7). The asymmetric ketene dimerization catalyzed by OTMS-quinidine afforded the highly enantioenriched ketene

dimer **1.48**. The spiroepoxy-β-lactone **1.49** was subsequently accessed by treatment of this ketene dimer with dimethyldioxirane (DMDO) by preferential delivery of the oxygen atom to the less hindered face of the olefin. Ring opening with N,O-dimethyl hydroxyl amine elicited the rearrangement of this key β-lactone to the butenolide domain, which was elaborated by ensuing transformation to reach the targeted natural product in a highly efficient manner.

1.2.6 (-)-Curcumanolide A

Curcumanolide A was isolated from the crude drug zedoary and other Curcuma species and is expected to possess potential bioactivity.[11]

Scheme 1.8



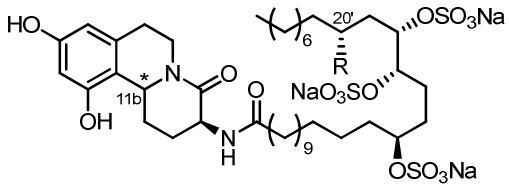
The Romo group developed a practical, catalytic asymmetric nucleophile catalyzed aldol lactonization (NCAL) process of keto-acids that highlights a novel utility of homobenzotetramisole derivative (HBTM, **1.57**) as a chiral nucleophile in conjunction with LiCl as mild Lewis acid co-catalyst, providing bi- and tricyclic β-lactones in excellent enantioselectivities and good to excellent yields (Scheme 1.8). Tricyclic β-lactone **1.53** produced from this reaction was subjected to buffered Baeyer-Villiger conditions; the oxidative ring expansion proceeded smoothly to afford the bis-lactone **1.54** after a prolonged reaction time. The stereospecific dyotropic rearrangement of this intermediate was triggered in the presence of substoichiometic TMSOTf to deliver the spiro-γ-lactone **1.55**, which constitutes the core of curcumanolide A. Subsequent elaborations on this core structure would ultimately lead to the natural product.

CHAPTER II

TOTAL SYNTHESES OF SCHULZEINES B & C*

2.1 Introduction

Schulzeines A-C are members of a new class of marine alkaloids isolated from the marine sponge *Penares schulzei* in 2003 by the Fusetani group (Figure 2.1).[12] Bioassays indicated potent α-glucosidase inhibitory activity of these compounds with IC_{50} values of 48-170 nM. Thus schulzeines are potential drug leads for treatment of diseases such as diabetes, viral diseases, and cancer, since α-glucosidases are involved in a series of important biological processes, such as processing protein glycosylation and controlling oligosaccharide metabolism. [13]



schulzeine A *(*S*), R= Me (**2.1**)
schulzeine B *(*R*), R= H (**2.2**)
schulzeine C *(*S*), R= H (**2.3**)

Figure 2.1 Structures of Marine Alkaloid Schulzeines A-C

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*Reprinted with permission from [Enantioselective Synthesis of Schulzeines B and C via a β-Lactone-derived Surrogate for Bis-homoserine Aldehyde. Liu, G.; Romo, D. *Org. Lett*, **2009**, *11*, 1143-1147.] Copyright [2009] American Chemical Society.

Because of their intriguing bioactivity, schulzeines have attracted considerable attention from the synthetic community. In 2006, the Kuntigyong group reported a synthesis of the tricyclic core structure of schulzeines capitalizing on an N-acyliminium ion cyclization.[14] In 2007, the Gurjar group reported their total syntheses of schulzeines B and C using a strategic Bischler-Napieralski cyclization.[15] More recently, the Wardrop group disclosed their syntheses of all the three members of schulzeines (A-C) employing a pivotal Pictet-Spengler condensation for the construction of the core structure.[16] Their synthetic efforts toward schulzeine A led to the revision of the stereochemical assignment with the inversion of the methyl stereoconfiguration at C20'. All these synthetic approaches relied on the glutamate derivatives as the starting material to forge the core structures. [17]

Prompted by our continued interest in the application of β-lactone chemistry in natural product synthesis, we proposed a distinct approach that is initiated from β-lactone-containing building blocks (Figure 2.2).

Our retrosynthetic analysis of the core structure of schulzeines B and C hinges on the fusion of the six-membered lactam through the amide bond formation of the pendant α-azido acid as in **2.5**. The α-azido acid moiety was envisioned to arise from the trichloromethyl carbinol **2.6** through a Corey-Link reaction. This strategy takes advantage of trichloromethyl carbinols as synthetic equivalents of masked α-amino acids so as to avoid potential epimerization at the α position in the course of multiple manipulations. Simultaneous disconnection of the C11b C-N and C-C bond as in **2.6** suggests a Pictet-Spengler condensation that could greatly simplify the tetrahydro-

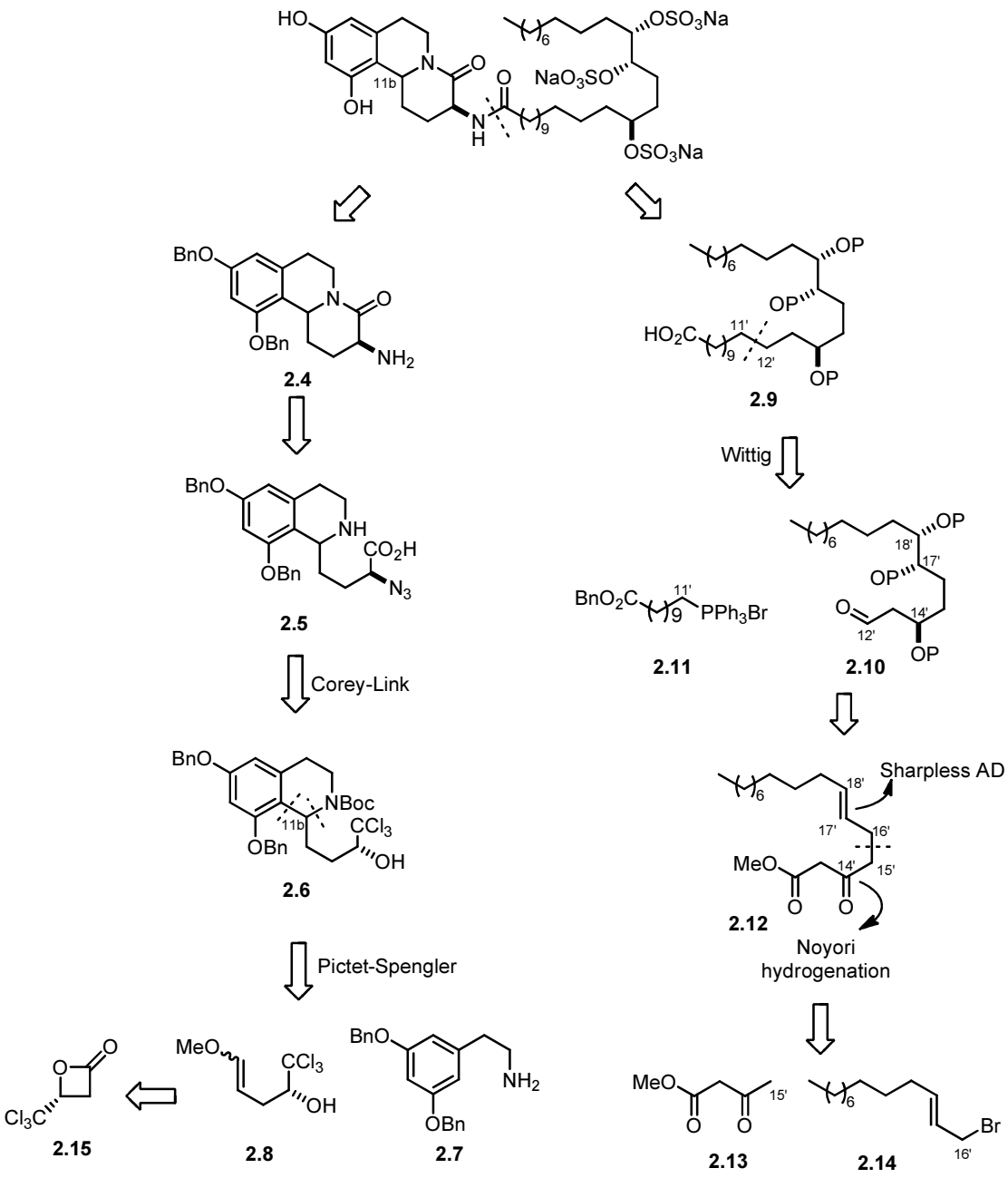


Figure 2.2 Retrosynthetic Analysis of Schulzeines B & C

isoquinoline to the primary amine **2.7** and an aldehyde equivalent **2.8**. The trichloromethyl carbinol unit in **2.8** was further projected to be readily derived from the commercially available β-lactone **2.15**.

Central to the assembly of the side chain is the stereoselective installation of the three stereogenic hydroxyl groups. The difficulty of this task could be easily underestimated by the fact that there exists a wide spectrum of reactions that are readily available for the stereoselective formation of secondary alcohols from various types of precursors. Decades of advancement in the field of organic chemistry has reached a point where the efficiency of a synthetic route, as one of the top priorities for synthetic design, has never been so high as it is today. No longer is the feasibility of a synthetic design the only concern, as the efficiency and elegancy are now added as a significant consideration.

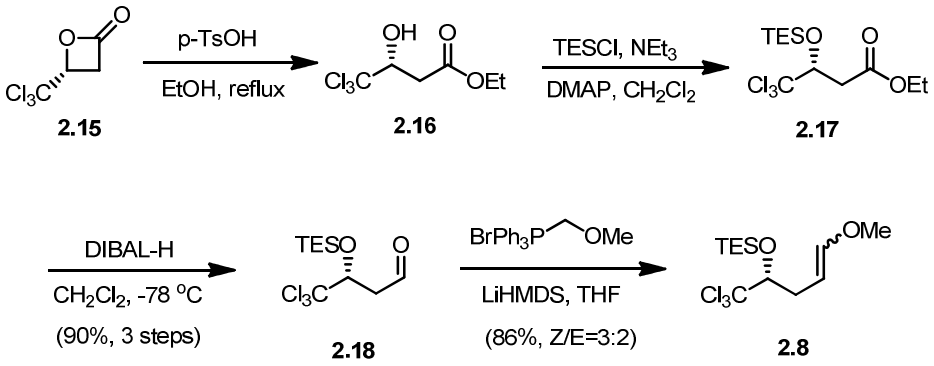
In line with the criteria for an efficient synthetic design, we opted to implement Sharpless asymmetric dihydroxylation (SAD) reaction of an E olefin as in **2.12** to install the vicinal diol and Noyori hydrogenation of the β-ketoester to introduce the isolated hydroxyl group. Both reactions proceed in a catalytic fashion and are known for the high levels of stereocontrol with the substrates of interest. More importantly, the β-keto ester portion that is required for Noyori hydrogenation could act as a dual functional carbon homologation synthon; the E-olefin moiety for the Sharpless AD reaction could be joined by a straightforward dienolate coupling at the γ position, while the ester functionality, after controlled reduction to aldehyde, could serve to extend to the other end of the C28 side chain through a Wittig coupling. This synthetic design was expected

to build up the side chain in a very concise and highly stereoselective manner from readily available materials.

2.2 Synthesis of the Core Structure

Synthesis of the tetrahydroisoquinoline core began with commercially available β-lactone **2.15** (Scheme 2.1). Nucleophilic attack of ethanol to the strained ring system led to smooth ring cleavage. The resultant trichloromethyl carbinol **2.16** was protected with TES to afford the masked β-hydroxyl ester **2.17**. Controlled partial reduction of this ester proceeded uneventfully to afford the corresponding aldehyde **2.18**.[18] Subsequent one carbon homologation via the Wittig reaction gave rise to the vinyl ether **2.8** as an inconsequential 3:2 mixture of *E*/*Z* olefin isomers, which was envisioned to act as an aldehyde surrogate to couple with a primary amine under acid-promoted Pictet-Spengler condensation conditions.

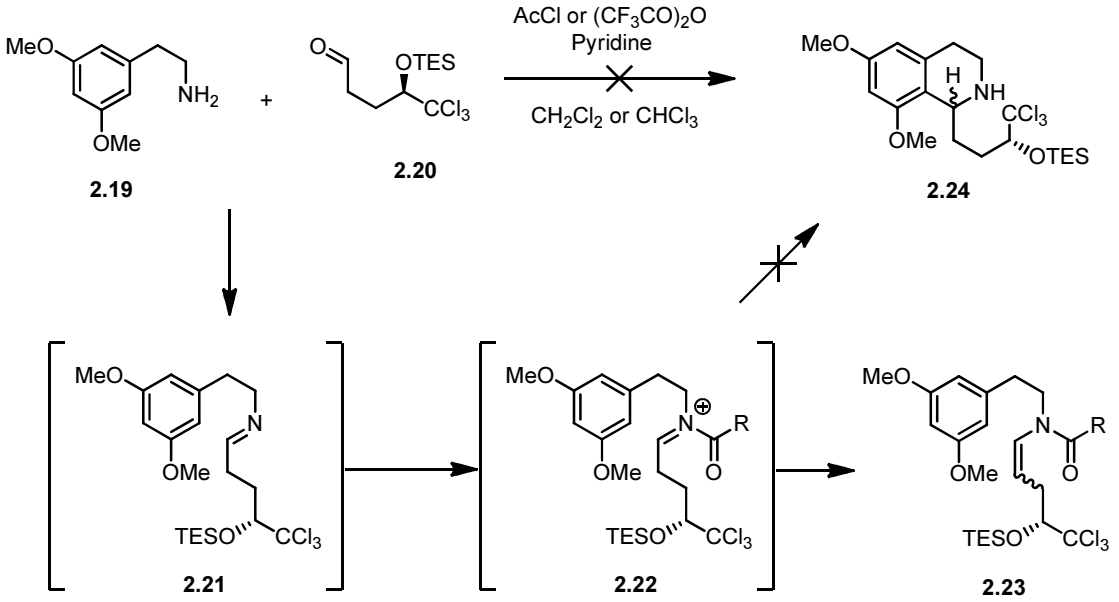
Scheme 2.1



In our initial studies of the Pictet-Spengler process, we employed the commercially available dimethyl catechol amine **2.19** to probe suitable Pictet-Spengler conditions.

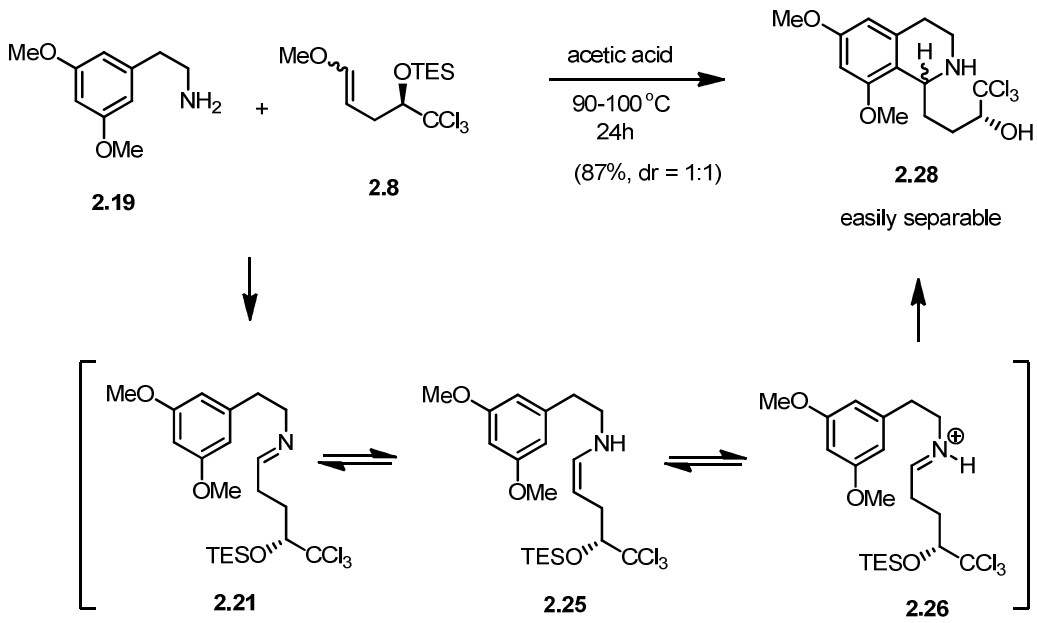
Indeed, the vinyl ether was carefully unmasked under acidic conditions to give the aldehyde **2.20**, which was condensed in aprotic solvent with the primary amine to give an imine intermediate, as confirmed by NMR study (Scheme 2.2). Unfortunately, all attempts to effect the Pictet-Spengler reaction met with failure when acylating reagents (acid chloride or trifluroacetic acid anhydride) were used to activate the putative imine intermediate **2.21**; isomerization of imine to enamine was observed as the dominant reaction pathway in these studies.

Scheme 2.2



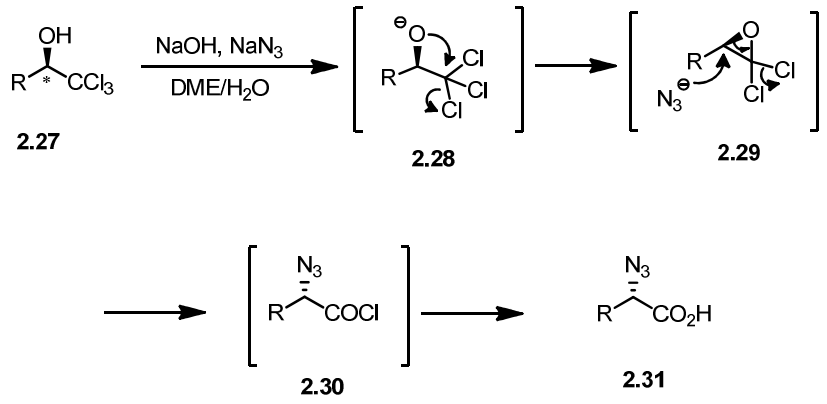
Attention was then directed to using Bronsted acids as the activating species, which does not require unmasking of the aldehyde from the vinyl ether (Scheme 2.3). A wide range of Bronsted acids were screened under conventional conditions at room temperature, but to no avail. Eventually, a condition using acetic acid as the solvent at elevated temperatures was identified to promote the cyclization event with great efficiency: simply by heating the equimolar mixture of vinyl ether and the primary amine in acetic acid to 100 degrees for 24 hours, a 1:1 diastereomeric mixture of tretrahydroisoquinoline **2.28** was obtained with excellent yields. Surprisingly, these two diastereomers could be readily separated by simple flash column chromatography. The efficiency of this protocol was further highlighted by the fact that not only the construction of the C-N and C-O bond at C11b was realized simultaneously but also the protected trichloromethyl carbinol was unveiled concomitantly, immediately setting the stage for the pivotal Corey-Link reaction.

Scheme 2.3



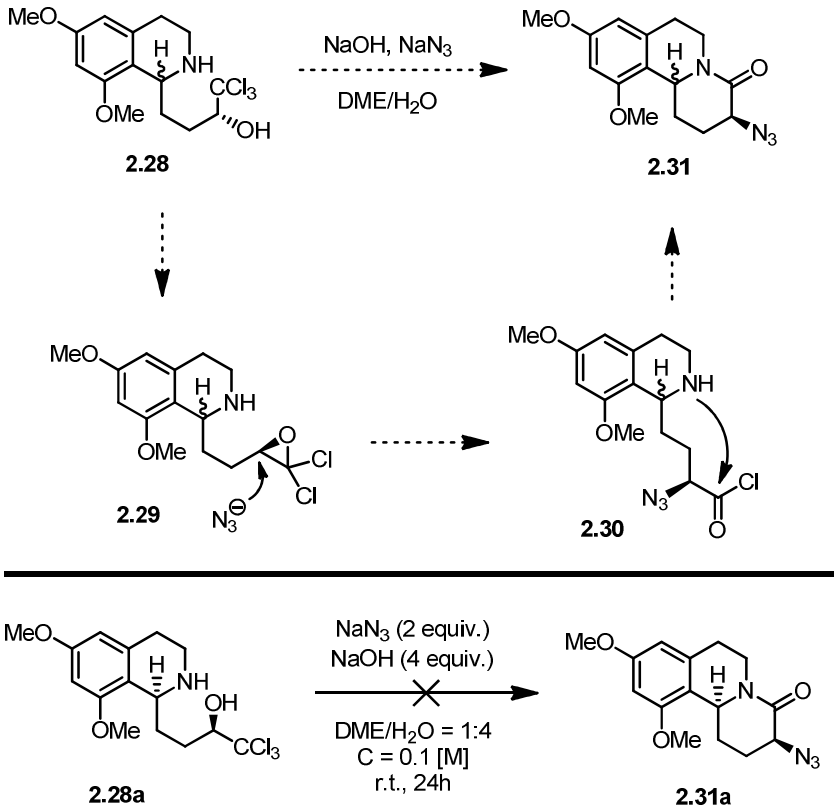
The Corey-Link reaction is the conversion of trichloromethyl carbinols to α-azido acids in the presence of a strong base and an azide species (Scheme 2.4).[19, 20] Mechanistically, the base would deprotonate the secondary alcohol to promote the dichloroepoxide (**2.29**) formation, which in turn could be opened by ensuing nucleophilic attack of the azide with simultaneous 1, 2 shift of the oxygen atom to extrude a chloride ion.[21] The resultant acid chloride would then be hydrolyzed under basic conditions to give a carboxylate. In this transformation, the stereoconfiguration of the trichloromethyl carbinol is inverted due to the stereospecific attack of the azide at the oxirane ring (S_N2 type).

Scheme 2.4



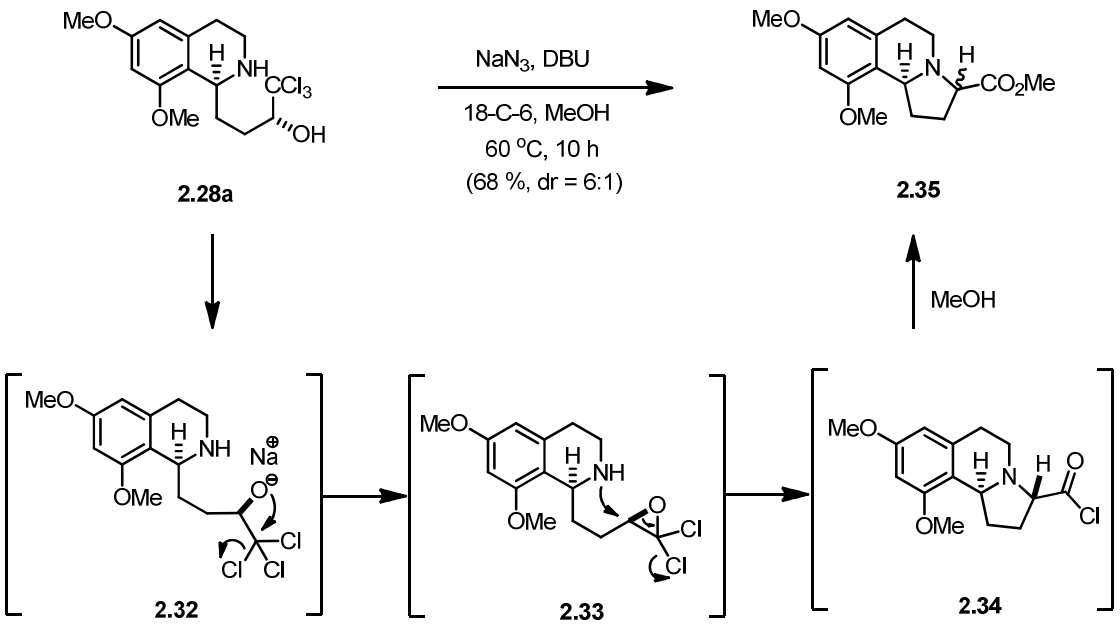
Our initial strategy involved a one-pot conversion of the trichloromethyl carbinol **2.28** to the δ-lactam **2.31** (Scheme 2.5). We envisioned that treatment of the trichloromethylcarbinol **2.28** with sodium hydroxide and sodium azide (standard Corey-Link conditions) would lead to an acid chloride intermediate **2.30** through dichlorooxirane formation and azide attack. The pendant acid chloride so formed could be potentially intercepted by the piperidine nitrogen to provide δ-lactam **2.31** prior to the saponification by sodium hydroxide present, considering that the intramolecular process is a kinetically favored process over the intermolecular one. However, despite extensive experimentation, this strategy was unsuccessful. The reaction proceeded very sluggishly and prolonged reaction time led to very complex mixtures that prevented effective analysis.

Scheme 2.5



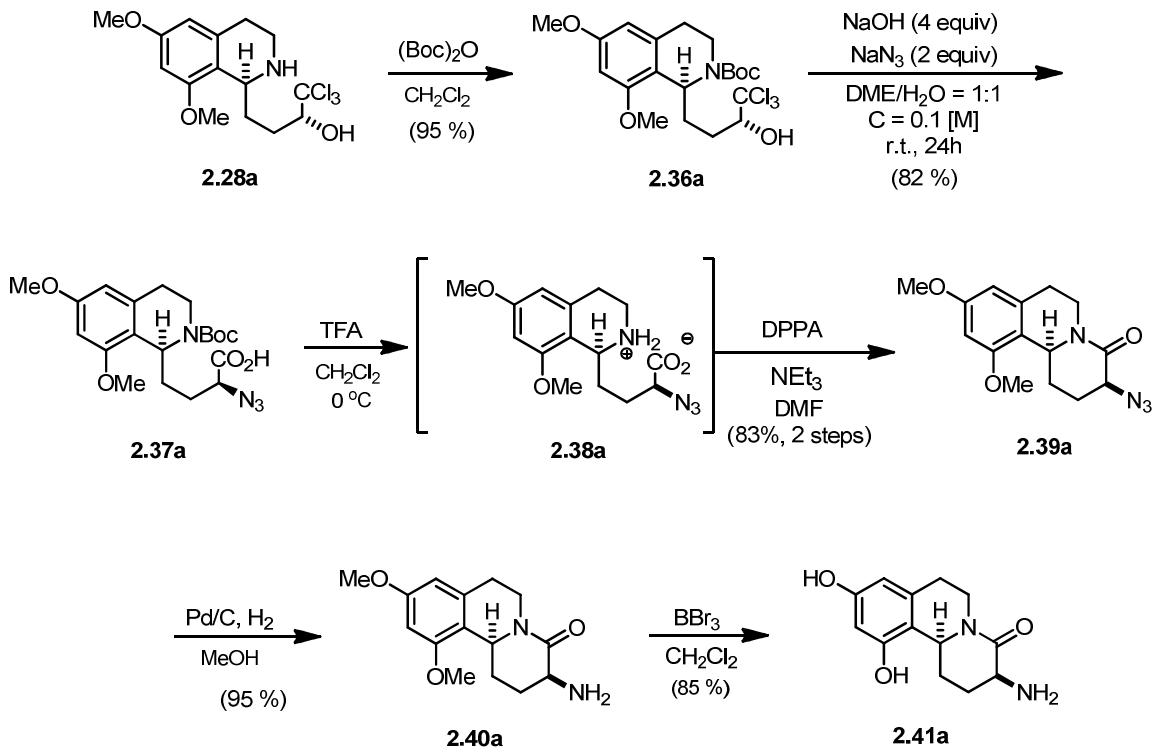
Under one set of conditions employing DBU as base, pyrrolidines **2.35**. were isolated as a ~6:1 mixture of separable diastereomers with 68% combined yield (Scheme 2.6). These products presumably arose from attack of the piperidine nitrogen onto the intermediate dichloroepoxide **2.33** as shown (Scheme 2). In the presence of MeOH, the methyl ester **2.35** is generated from the putative acid chloride intermediate **2.34**.

Scheme 2.6



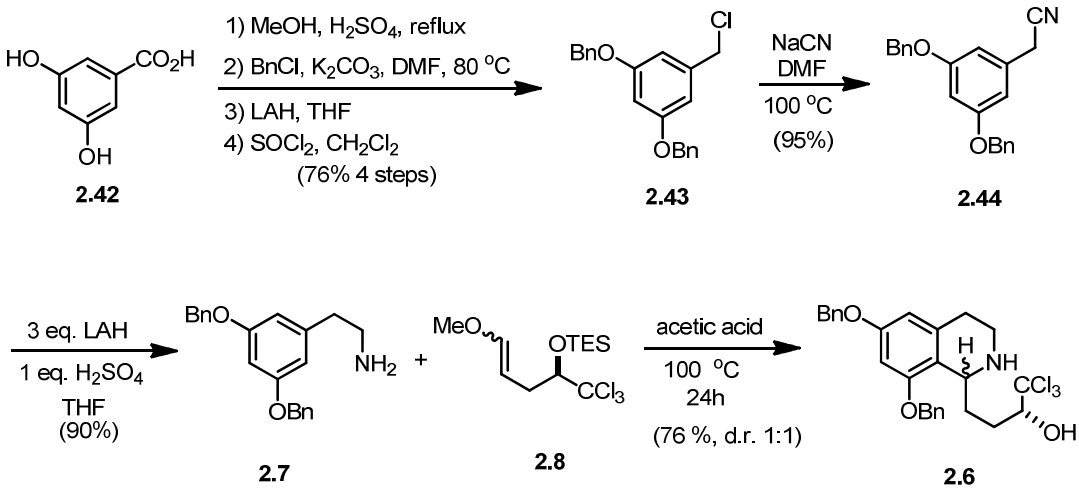
To avoid the premature cyclization, the secondary amine **2.28a** was protected as the corresponding *t*-butyl carbamate (Boc) and then subjected to standard Corey-Link conditions which now proceeded smoothly to give the α-azido acid **2.37a** (Scheme 2.7). Direct Boc deprotection and cyclization to the *δ*-lactam with diphenylphosphoryl azide (DPPA) in DMF gave the azido tricycle **2.39a**. Following azide reduction and demethylation of the protected catechol, the known amino tricycle **2.41a** was obtained, and all spectroscopic data matched those previously reported for the same compound derived from schulzeines degradation.

Scheme 2.7



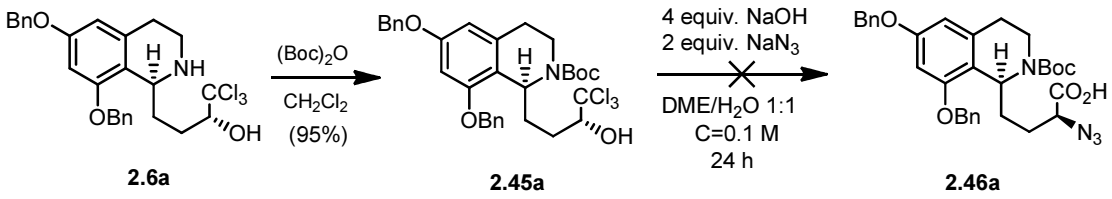
In a second-generation strategy to the tetrahydroisoquinoline core, aiming to simplify final deprotection of the catechol, we employed a dibenzyl-protected catechol derivative **2.6** in the Pictet-Spengler reaction to enable a late stage deprotection by hydrogenation (Scheme 2.8). The required phenethyl amine **2.7** was prepared by reduction of a known cyanide precursor using a slight modification of a literature procedure. Pictet-Spengler condensation of vinyl ether **2.8** and phenethyl amine **2.7** gave the tetrahydroisoquinolines **2.6** (d.r. = 1:1) which were readily separable and could be processed separately to schulzeines B and C.

Scheme 2.8



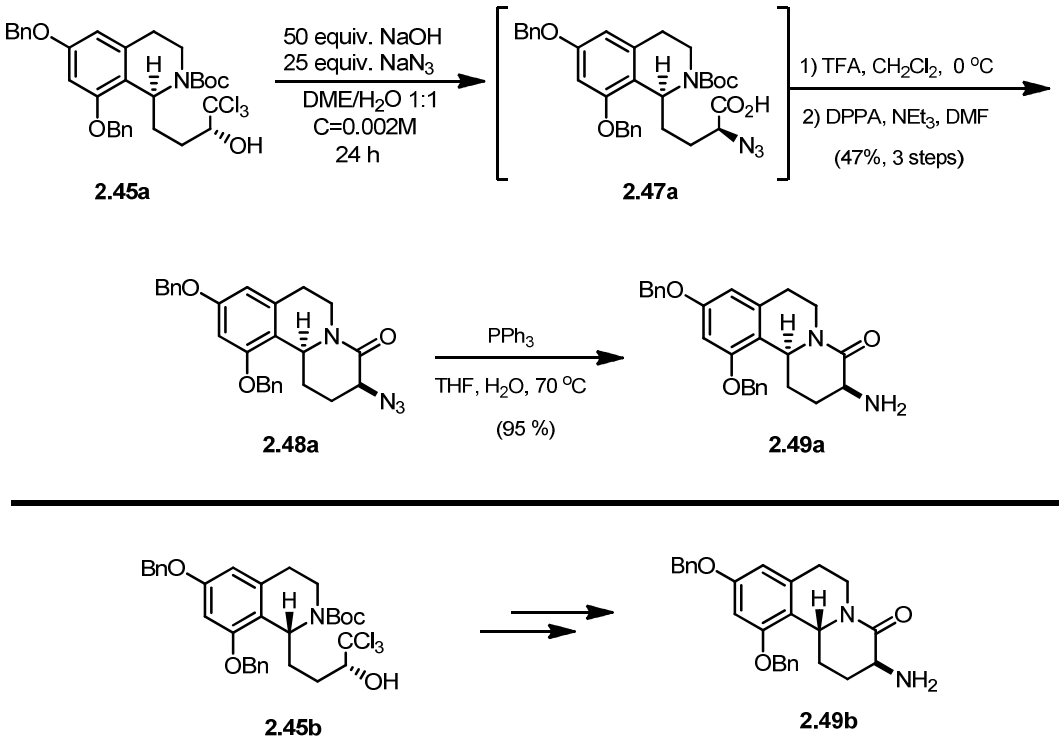
Following the same process developed in the dimethyl series, amine protection with a Boc group was followed by subjection of the resulting trichloromethyl carbinol **2.45a** to the previously employed Corey-Link conditions (Scheme 2.9). However, with this dibenzyl substrate, no reaction was observed under these reaction conditions. We reasoned that this was likely due to a solubility issue of this hydrophobic substrate in the DME/H_2O reaction medium.

Scheme 2.9



Thus, the concentration of reagents ($NaOH/NaN_3$) was maintained (0.4 M/0.2 M), while substrate concentration was significantly lowered (0.008 M) (Scheme 2.10). Under these conditions, the Corey-Link reaction proceeded efficiently to give the desired azido acid **2.47a** which was directly transformed to the tricyclic structure **2.48a** by Boc deprotection and lactamization. Hydrogenolysis of the benzyl ethers with concomitant reduction of the azide enabled correlation to the previously prepared amino catechol **2.41a** and confirmed both relative and absolute stereochemistry identical to the previous sequence. Selective azide reduction of **2.48a** with triphenyl phosphine gave the primary amine **2.49a** ready for coupling to the side chain. Likewise, the diastereomeric tetrahydroisoquinoline **2.45b** was transformed to the corresponding schulzeine C core structure **2.49b** by following the same synthetic sequence.

Scheme 2.10

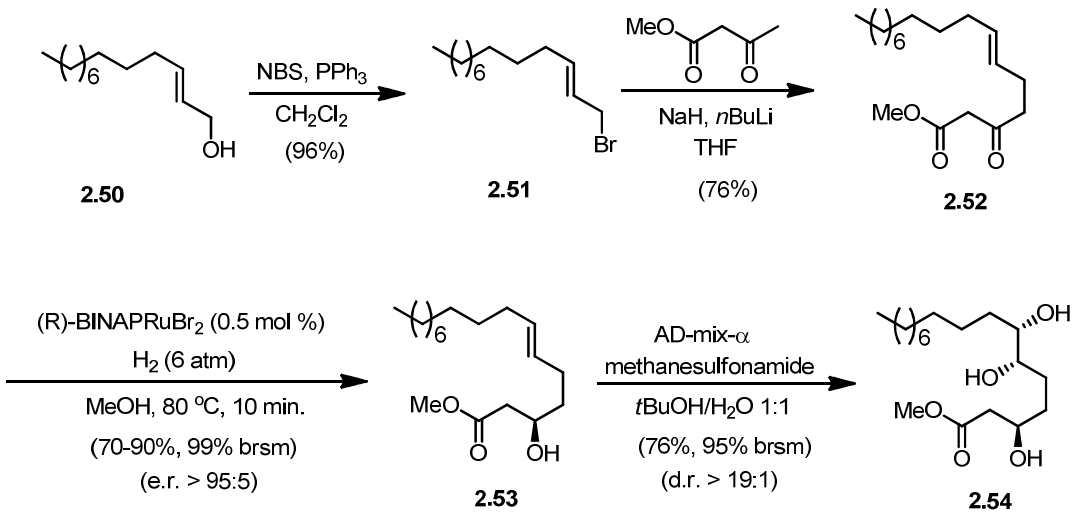


2.3 Synthesis of the Side Chain

The synthesis of the side chain began with alkylation of the dienolate of methylacetoacetate with allyl bromide **2.51** prepared by bromination of the commercially available allylic alcohol **2.50** (Scheme 2.11). The derived β-ketoester **2.52** was subjected to Noyori hydrogenation conditions to give optically active β-hydroxyl ester in good yield and excellent enantioselectivity (e.r. > 95:5). To avoid reduction of the olefin, the hydrogenation was terminated prior to completion, and the starting material was readily separated and recycled. The C17′, C18′ diol was then introduced via

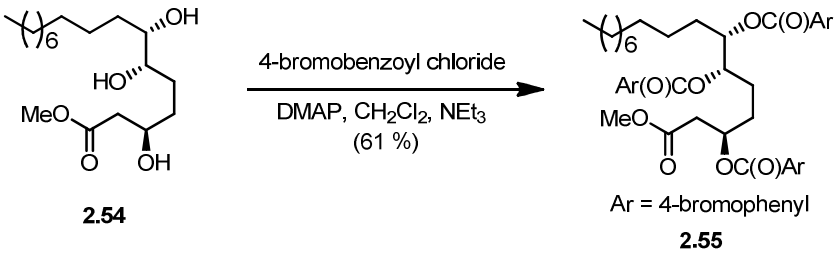
reagent-controlled Sharpless dihydroxylation in excellent yield and diastereoselectivity (d.r. > 19:1).

Scheme 2.11



To confirm the relative stereochemistry, the triol **2.54** was peracylated with *p*-bromobenzoyl chloride to give a crystalline tribenzoate **2.55** enabling confirmation of the relative and absolute stereochemistry by X-ray crystallographic analysis as shown based on heavy atom (Br) anomalous dispersion (Scheme 2.12).

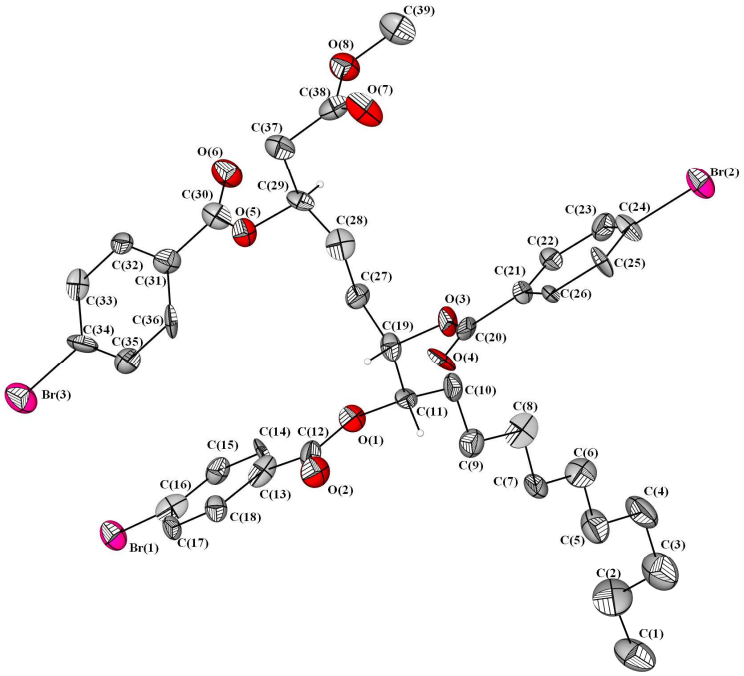
Scheme 2.12



2.54

Ar = 4-bromophenyl

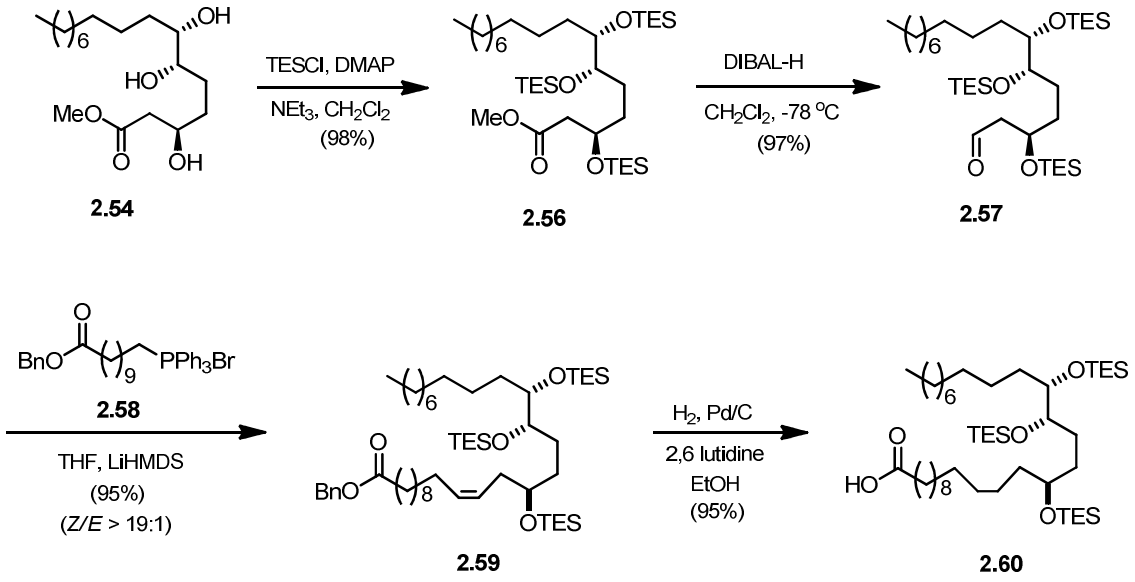
2.55



X-ray Single Crystal Structure of **2.55**

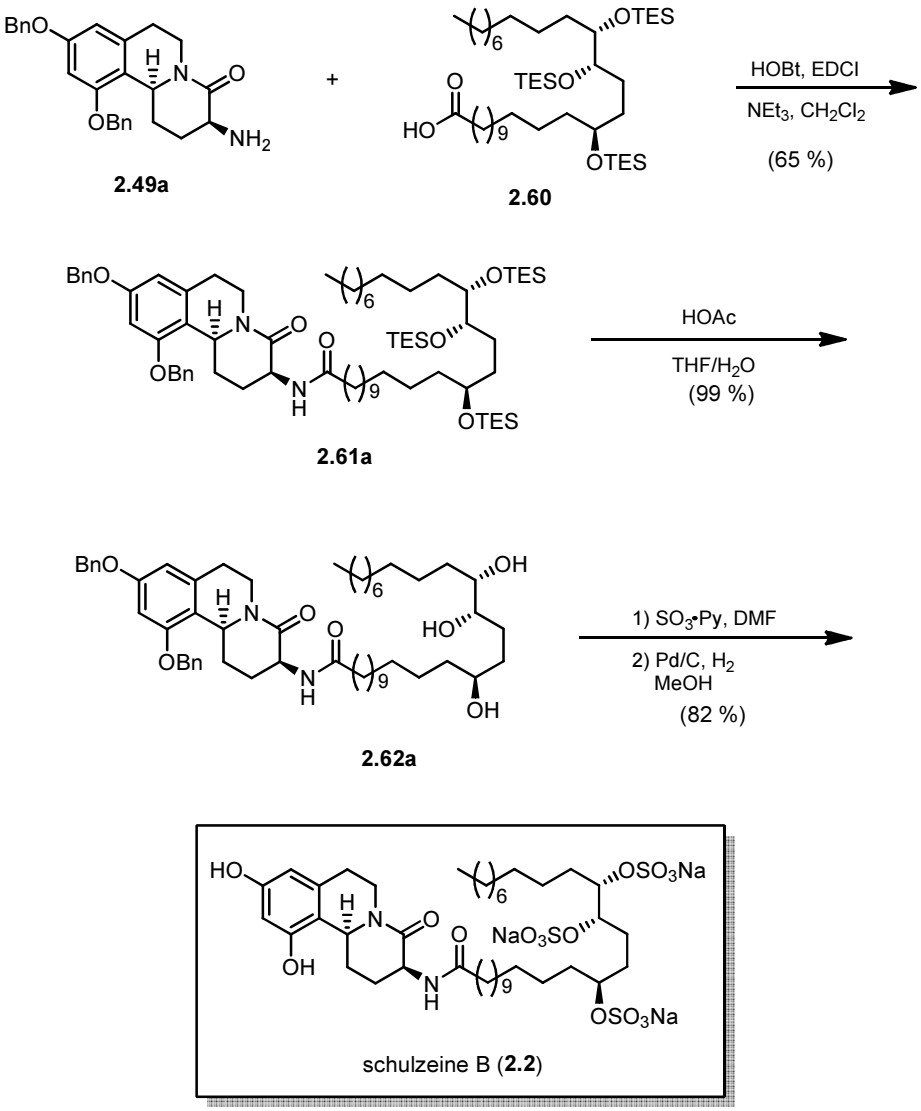
Protection of the triol ester **2.54** as the corresponding tris-triethylsilyl ether **2.56** and partial reduction gave an intermediate aldehyde **2.57** that was directly subjected to olefination with the Wittig reagent derived from phosphonium salt **2.58** (Scheme 2.13). Simultaneous alkene hydrogenation and benzyl hydrogenolysis in the presence of 2,6-lutidine, to avoid TES deprotection, gave the carboxylic acid side chain **2.60**.

Scheme 2.13



2.4 Total Syntheses of Schulzeines B & C

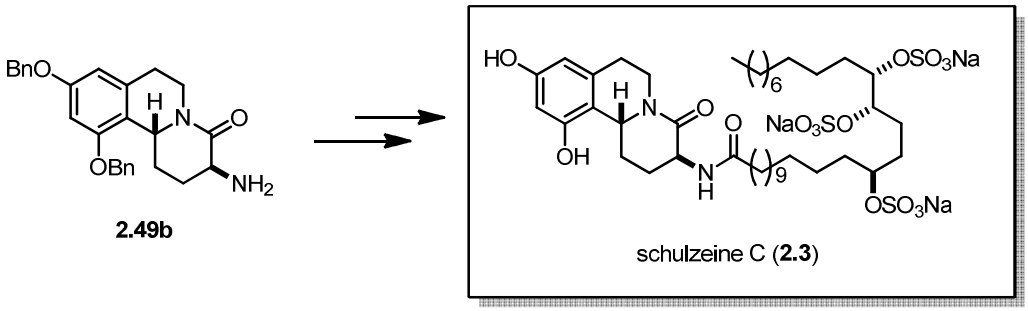
Scheme 2.14



Under typical carbodiimide coupling conditions, the carboxylic acid side chain **2.60** and the amino tetrahydroisoquinoline core **2.49a** were joined to give amide **2.61a** (Scheme 2.14). Cleavage of the TES ethers under mild acidic conditions gave triol **2.62a** which was subjected to sulfation with the SO_3·pyridine complex to provide the trisulfate which was of sufficient purity following rapid purification through silica gel, to carry on to the final step. Hydrogenolysis of the benzyl groups and filtration to remove the Pd catalyst led to schulzeine B (**2.2**) of high purity that was identical in all respects to the natural product including optical rotation (lit. $[\alpha]^D$ -23 (*c* 0.1, MeOH); syn. $[\alpha]^D$ -23.5 (*c* 0.68, MeOH).

Following the same sequence, schulzeine C (**2.3**) was also synthesized from the diastereomeric core structure **2.49b**, and data for the synthetic material matched those previously reported for the diastereomeric natural product including optical rotation (lit. $[\alpha]^D$ +33 (*c* 0.1, MeOH); syn. $[\alpha]^D$ +38.0 (*c* 0.42, MeOH) (Scheme 2.15).

Scheme 2.15



CHAPTER III

TOTAL SYNTHESIS OF (+)-OMPHADIOL*

3.1 Introduction

Omphadiol (**3.1**) is a sesquiterpene isolated from the basidiomycete *omphalotus illudens* and the edible fungus *clavicorona pyxidata*.[22, 23] As a member of the africanane family of sesquiterpenes, which all possess a 5-7-3 tricyclic core, omphadiol contains six contiguous stereogenic centers making it a challenging synthetic target (Figure 3.1).

Comparison to structurally similar terpenoids, including africanol (**3.2**) and pyxidatol (**3.3**), reveals a large family of sesquiterpenes and diterpenes that share a common tetrasubstituted cyclopentane ring. Notably, many of these natural products display potent biological activities. For example, rossinone B (**3.5**) showed anti-inflammatory, antiviral, and antiproliferative activities [24] while tomoeone F (**3.6**) displayed significant cytotoxicity against KB cells. [25] Chinesin (**3.8**) possessed antimicrobial and antiviral activity.[26] While for members of this family synthetic studies including a recent biomimetic synthesis of rossinone B have appeared, no further biological studies have been described. Full biological evaluation of omphadiol was precluded owing to insufficient quantities isolated from natural sources.

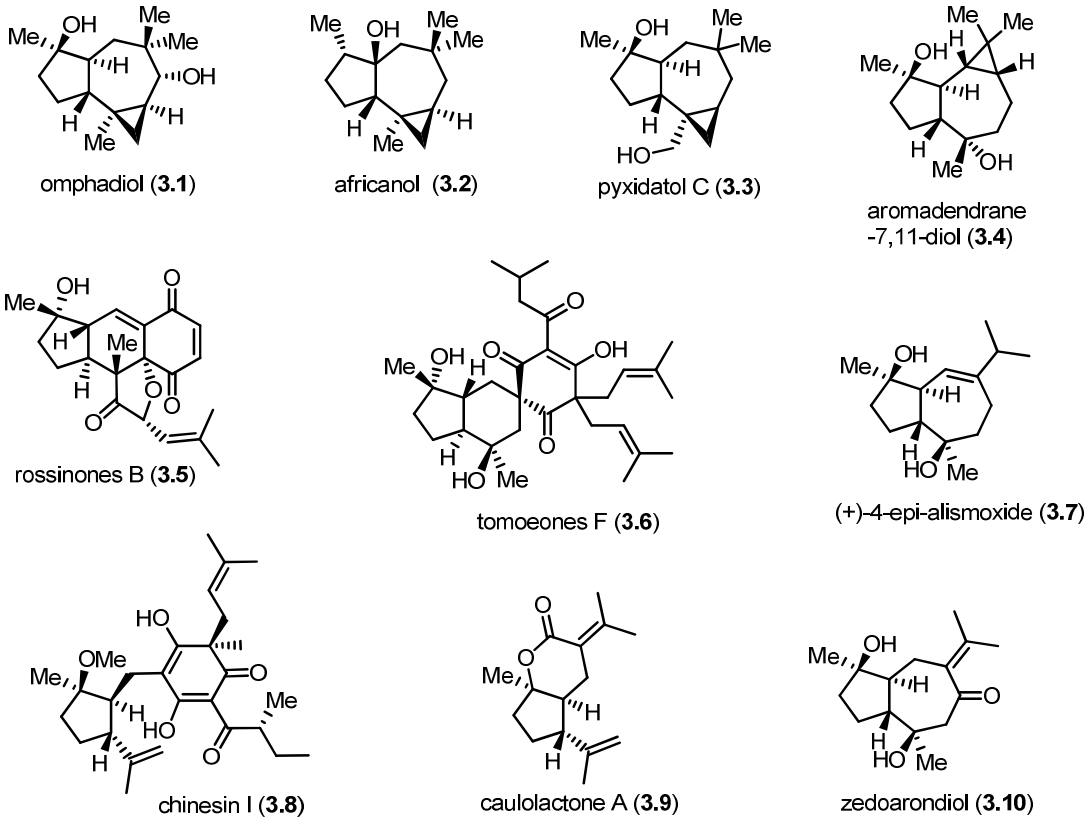


Figure 3.1 Omphadiol and Structurally Related Natural Products

As part of a program demonstrating the utility of β-lactones as synthetic intermediates, we set out to develop a scaleable route to the common cyclopentane core found in these terpenoids, which we believed could be derived from (*R*)-carvone (**3.11**) through a β-lactone intermediate (**3.12**), as a prelude to biological studies and investigations into their likely biosynthetic interconnectivity (Figure 3.2).

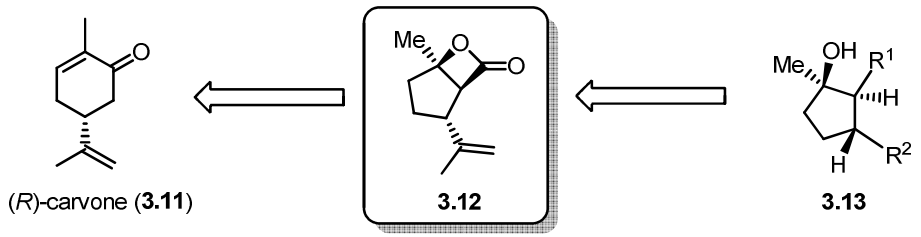


Figure 3.2 Common Cyclopentane Core from a Key β-Lactone Intermediate

Our efforts toward this goal has culminated in a three-step synthesis of a versatile, carvone-derived bicyclic β-lactone, which constitutes the key intermediate for the ten-step synthesis of (+)-omphadiol described in this section.[27] This total synthesis also features several efficient C-C bond-forming reactions, novel single-pot, sequential and tandem processes, and the highly stereocontrolled introduction of all six stereogenic centers.

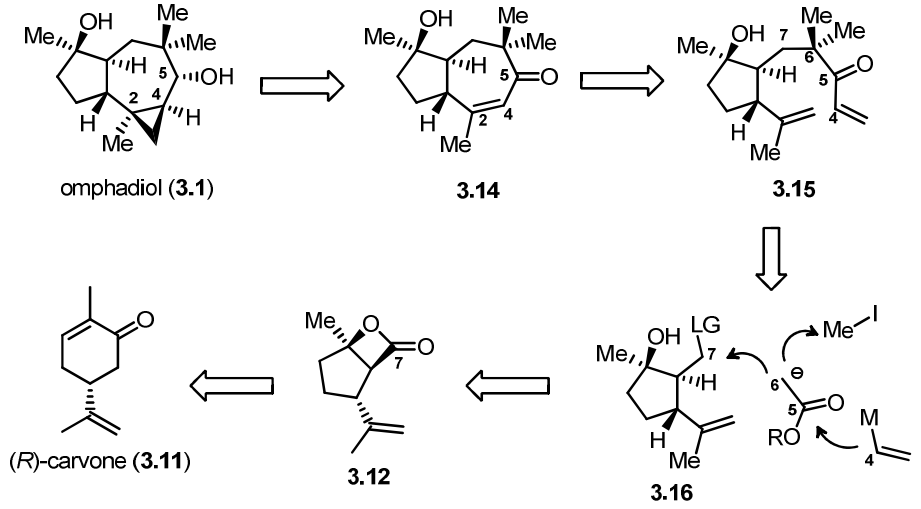


Figure 3.3 Retrosynthetic Analysis of Omphadiol

Our synthetic strategy was premised on a late-stage facial selective cyclopropanation of the C2-C4 double bond governed by the topology of the [5.3.0] bicycle **3.14** (Figure 3.3). The cycloheptenone would in turn be constructed by ring-closing metathesis (RCM) of diene **3.15**, which could be derived from a suitable intermediate **3.16** by a series of carbon homologation events including ester alkylations and carbonyl addition with vinyl metallic regents. The key intermediate for the synthesis of omphadiol and related terpenes was identified as the bicyclic β-lactone **3.12**. We anticipated that this versatile intermediate could be constructed by the reorganization of the carbon skeleton of (*R*)-carvone **3.11** through a nucleophile promoted aldol lactonization process of a derived keto-acid.

3.2 Synthesis of the Core Structure

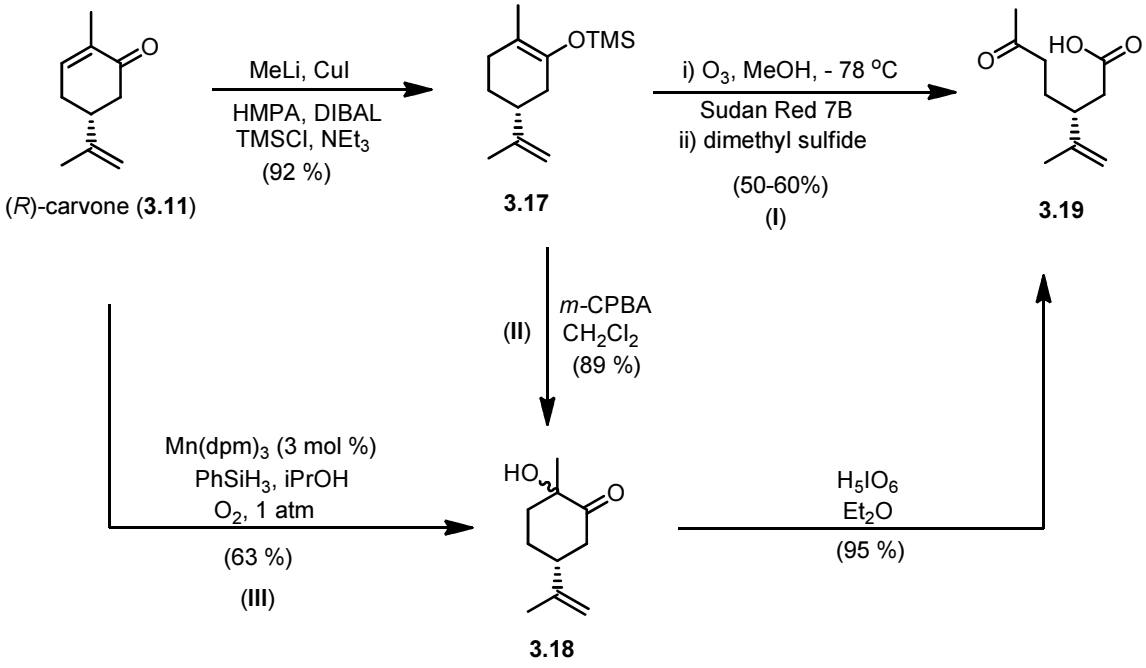
Synthesis of (+)-omphadiol commenced with a [$Mn(dpm)_3$]-catalyzed (dpm=dipivaloylmethanato) formal hydration of the enone moiety of (*R*)-carvone to afford hydroxyl ketone **3.18** in a chemo- and regioselective manner and as an inconsequential mixture of diasteromers (d.r. = 2:1; Scheme 3.1). [28] Subsequent oxidative cleavage of the α-hydroxyketone by periodic acid, delivered keto-acid **3.19** (Scheme 3.1, route III).

Other attempted routes to access this key keto-acid intermediate include CuI catalyzed 1,4-hydrosilylation of the enone moiety and subsequent ozone mediated oxidative C-C bond cleavage (Scheme 3.1, route I); this route proved to be impractical as ozonolysis could not afford satisfactory chemical differentiation between the two

olefins in **3.17** resulting in complex mixtures of oxidation products with poor reproducibility.

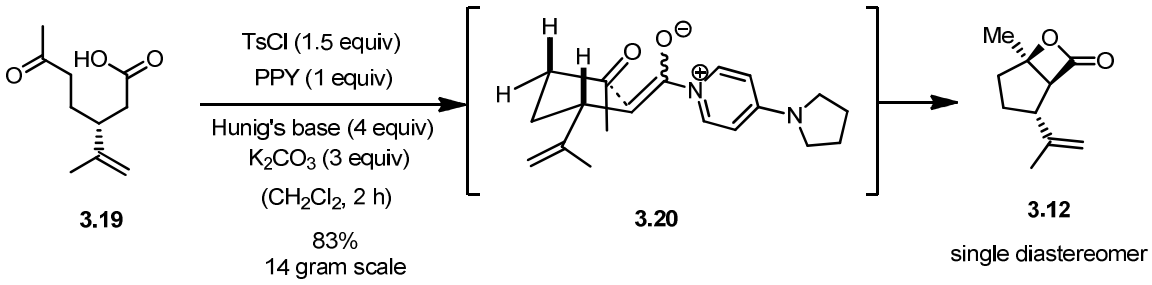
Another route to avoid this non-discriminating oxidation was attempted through a stepwise oxidation sequence, that is the Rubottom oxidation of vinyl silyl ether **3.17** to afford the α-hydroxyl ketone **3.18** followed by oxidative cleavage with periodic acid as before (Scheme 3.1, route II); this route was executed in decagram scale and proved to be reproducible, however, from the perspective of step count, it takes one more step than route I to access keto-acid **3.19**.

Scheme 3.1



With keto-acid **3.19** in hand, attention was then directed to the first pivotal C-C bond forming event, i.e. nucleophile-promoted aldol lactonization (Scheme 3.2).[29] Upon activation of the carboxylic acid with tosyl chloride and addition of 4-PPY (4-pyrrolidinopyridine) as a nucleophilic promoter, keto-acid **3.19** underwent an aldol lactonization to give the desired bicyclic β-lactone **3.12** with high diastereoselectivity (55%, d.r. > 19:1) after 24 hours. Optimization studies revealed that powdered anhydrous K_2CO_3, in combination with iPr_2NEt as a shuttle base, led to a high yield of 83% in 2 hours on a scale greater than 10 grams.[30, 31] The high diastereoselectivity is rationalized by the chair-like transition state **3.20**, wherein the isopropenyl moiety adopts a pseudoequatorial position to avoid 1,3-allylic strain with the ammonium enolate (E/Z geometry undefined) substituent and 1,3-diaxial interaction between the pseudoaxial C-H bond.

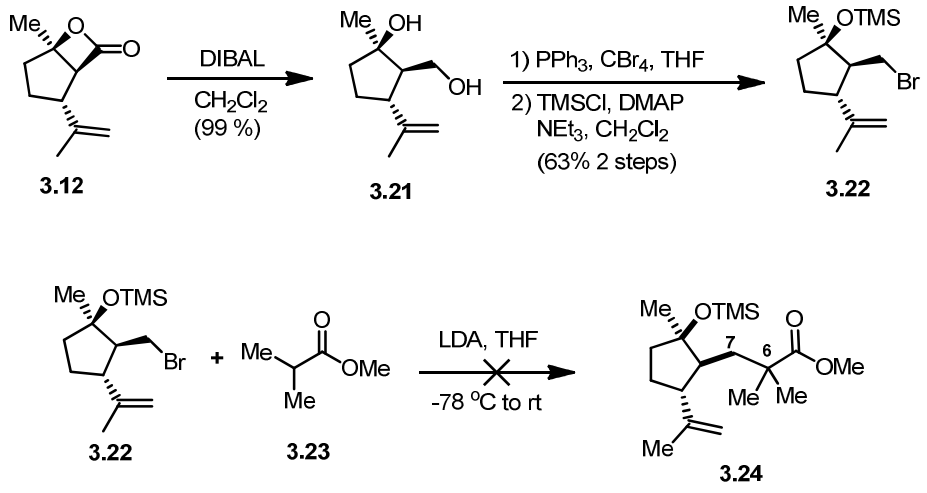
Scheme 3.2



3.3 Carbon Homologation Through Alkylations

The next stage of the planned synthesis entailed a four-carbon homologation at C7 including the introduction of the C6-gemdimethyl moiety (Scheme 3.3). Hence, β-lactone **3.12** was elaborated to primary bromide **3.22** by sequential DIBAL reduction, selective bromination of the primary alcohol, and TMS protection of the tertiary alcohol, setting the stage for the subsequent intermolecular alkylation. However, all attempts to effect this C-C bond formation event returned unreacted starting material.

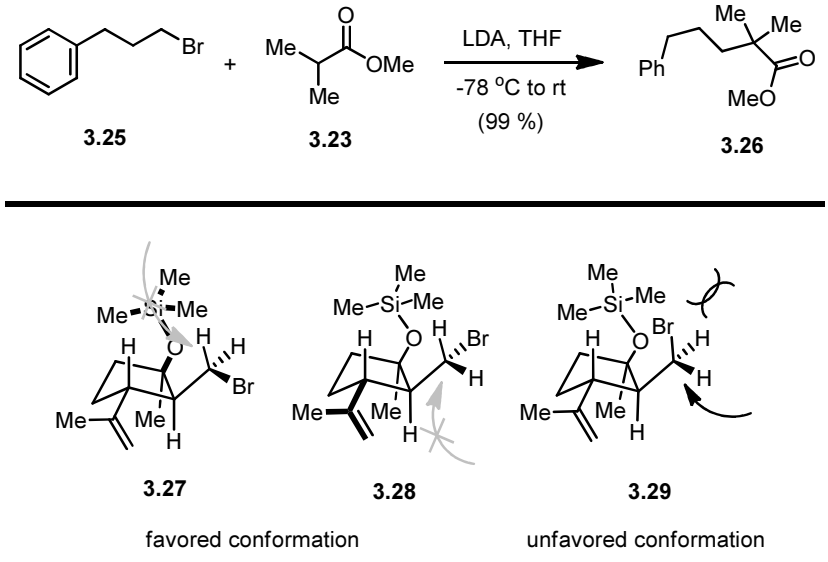
Scheme 3.3



In sharp contrast, a control experiment using a simple primary bromide **3.25** afforded the desired alkylation product **3.26** with essentially quantitative yield (Scheme 3.4). This observation prompted us to take a closer look at the three-dimensional

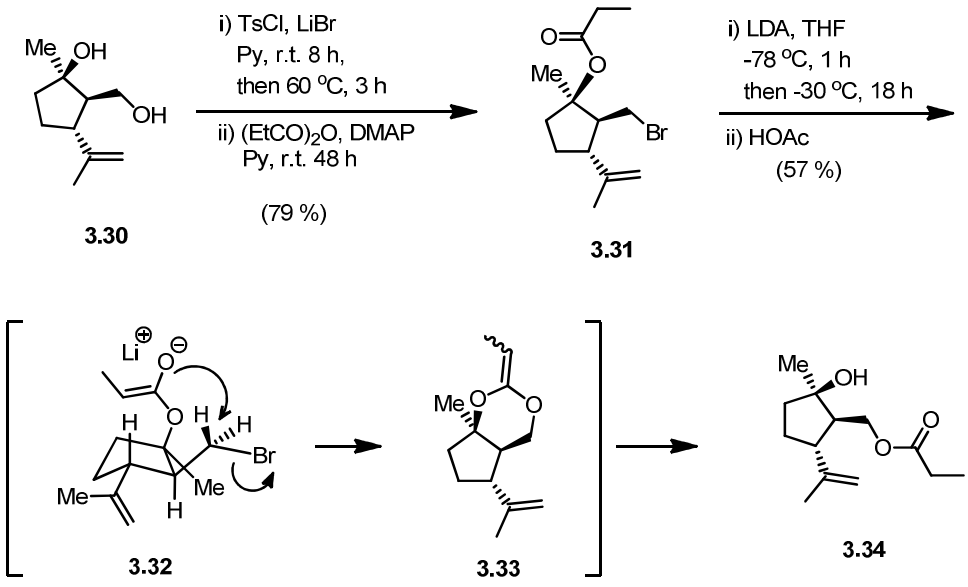
structure of **3.22**. Among the three staggered conformational isomers of **3.36** along the C7-C8 bond, the two relatively stable ones (**3.27** and **3.28**) were unreactive toward the enolate nucleophiles due to the shielding of the trajectories of the incoming nucleophiles by either the TMS ether moiety or the isopropenyl group. The third conformer **3.29** with a readily accessible C-Br σ anti bond was conformationally susceptible to bonding with the incoming nucleophile, however, the steric congestion between the bromine atom and the TMS ether moiety would dramatically increase the ground state energy, rendering this reaction pathway unlikely.

Scheme 3.4



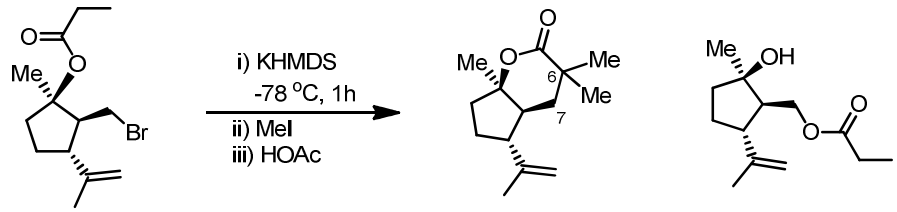
Hampered by this setback, recourse was made to intramolecular alkylations. Hence, a highly efficient process involving a one-pot tosylation-bromination sequence and a subsequent acylation was developed to provide bromo-ester **3.31** (Scheme 3.5). When this substrate was subjected to the action of LDA, surprisingly, ester **3.34** emerged as the product. Similar results were obtained with LiHMDS and NaHMDS. A rationale for this result could be the intramolecular *O*-alkylation of the enolate that gave rise to a putative ketene acetal intermediate **3.33**, which could be hydrolyzed during acidic work-up to yield **3.34**.

Scheme 3.5



Utlimately, a highly efficient process for construction of the C6-C7 bond was identified when KHMDS was used as the base (Scheme 3.6). Treatment of this ester with KHMDS (3 equiv) in THF at -78 ^{o}C, followed by quenching with excess MeI, furnished the bicyclic δ-lactone **3.35** bearing the requisite C6 gem-dimethyl moiety. Thus, two required C-C bonds were formed in one operation. Notably, except the dramatic counter-ion effect on *C*-alkylation and *O*-alkylation pathways in this intramolecular alkylation, solvent also played an important role in this transformation. THF facilitated the desired *C*-alkylation, while toluene tended to favor the *O*-alkylation pathway.

Scheme 3.6



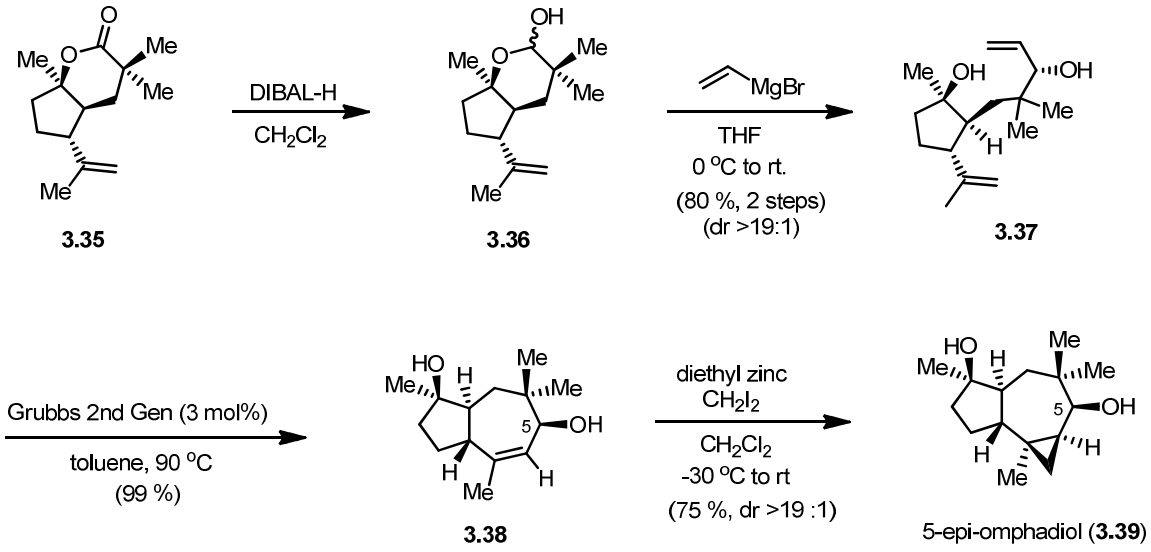
3.31 **3.35** **3.34**

PhMe/THF 1:1	17 %	22 %
THF	78 %	< 5 %

3.4 Synthesis of 5-epi-Omphadiol

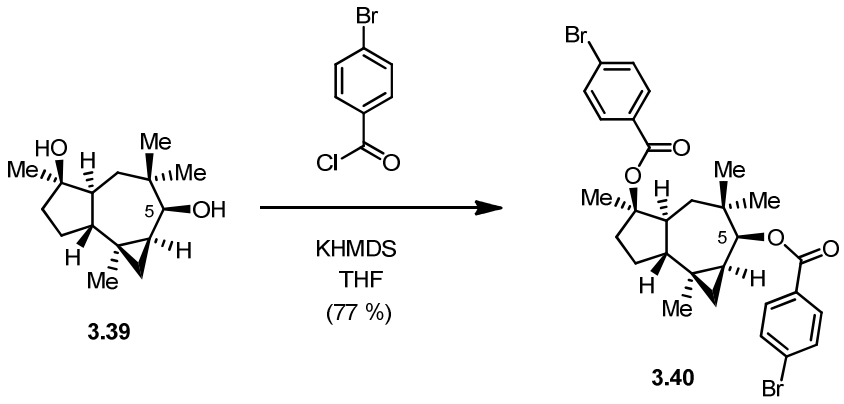
With lactone **3.35** in hand, a two-step sequence involving the reduction to the lactol and vinyl Grignard addition was envisioned to introduce the remaining two carbons required for the ring-closing metathesis (RCM) to form cycloheptene **3.38** (Scheme 3.7). While the degree of diastereoselectivity, if any, for the Grignard addition step was uncertain at this point, lactone **3.35** was reduced to lactol **3.36** by DIBAL and to our surprise, the subsequent addition of vinyl magnesium bromide gave diene **3.37** with high diastereoselectivity (d.r. > 19:1) even at 0 ^{o}C. RCM of diene **3.37** using Grubbs second generation catalyst yielded the desired trans-fused [5.3.0] bicyclic core in nearly quantitative yield.[32] A Simmons–Smith cyclopropanation of allylic alcohol **3.38** delivered cyclopropane **3.39** as the exclusive product (d.r > 19:1).

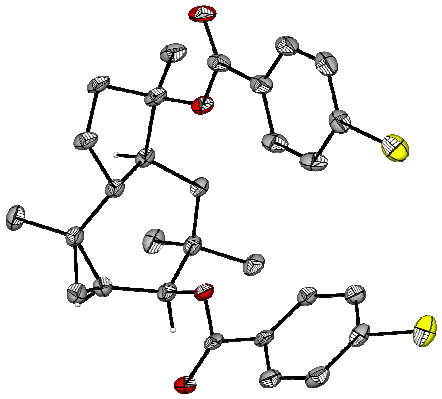
Scheme 3.7



However, comparison of NMR data reported for the natural product suggested that a diastereomer had been produced. X-ray crystallographic analysis of the bis(p-bromophenylester) derivative **3.40** unambiguously determined that diol **3.39** was actually a C5-epimer of omphadiol (Scheme 3.8).

Scheme 3.8

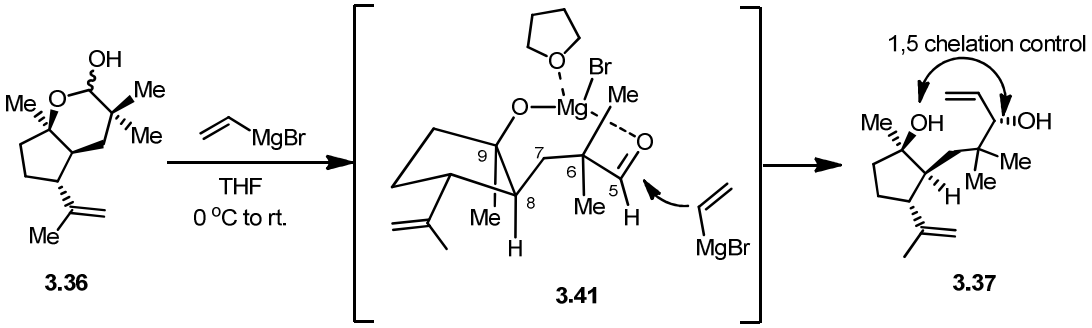




X-ray Structure of **3.40**

The high diastereoselectivity obtained during the vinyl Grignard addition revealed an interesting example of 1,5-stereoinduction (Scheme 3.9).[33, 34] One rationale for this highly selective example of 1,5-stereoinduction invokes chelation control between an *in situ* generated C9-magnesium alkoxide and the C5-aldehyde, thus leading to an eight-membered metallocycle **3.41** that imparts substantial facial bias during nucleophilic addition.

Scheme 3.9

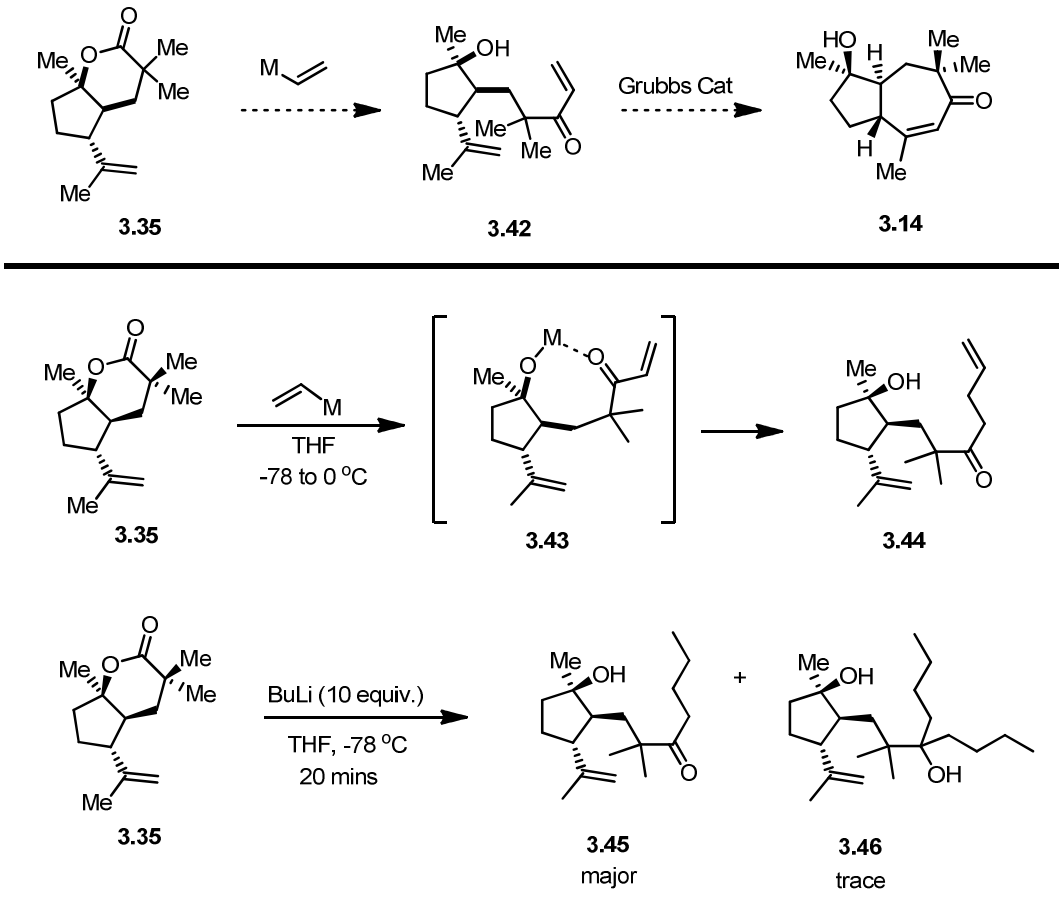


3.5 Synthesis of (+)-Omphadiol

We recognized that one solution to the C5-stereochemical issue would involve a facial selective reduction of enone **3.14**, which can be derived from the RCM of a dienone **3.42** (Scheme 3.10). The seemingly straightforward conversion of the sterically hindered lactone **3.35** into enone **3.14** by the monoaddition of a vinylmetal species (e.g. vinyl lithium, vinyl magnesium bromide, and divinyl zinc), proved challenging. In contrast to the facile partial reduction to lactol **3.36** by DIBAL (Scheme 3.7) and

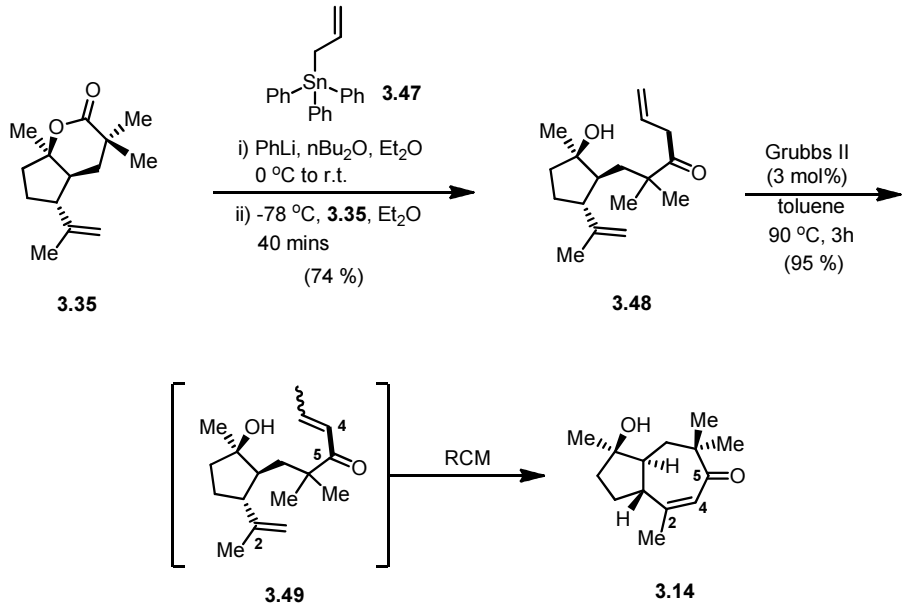
numerous reported successful monoadditions of vinylmetal reagents to δ-lactones, the monoaddition of vinyl metallic species with the sterically congested δ-lactone **3.35** was unsuccessful.[35, 36] The major by-product was derived from the subsequent conjugate addition to the initially formed α,β-enone **3.42**.[37, 38] On the other hand, a control experiment showed that addition of butyllithium afforded predominantly monoaddition product (**3.45**).

Scheme 3.10



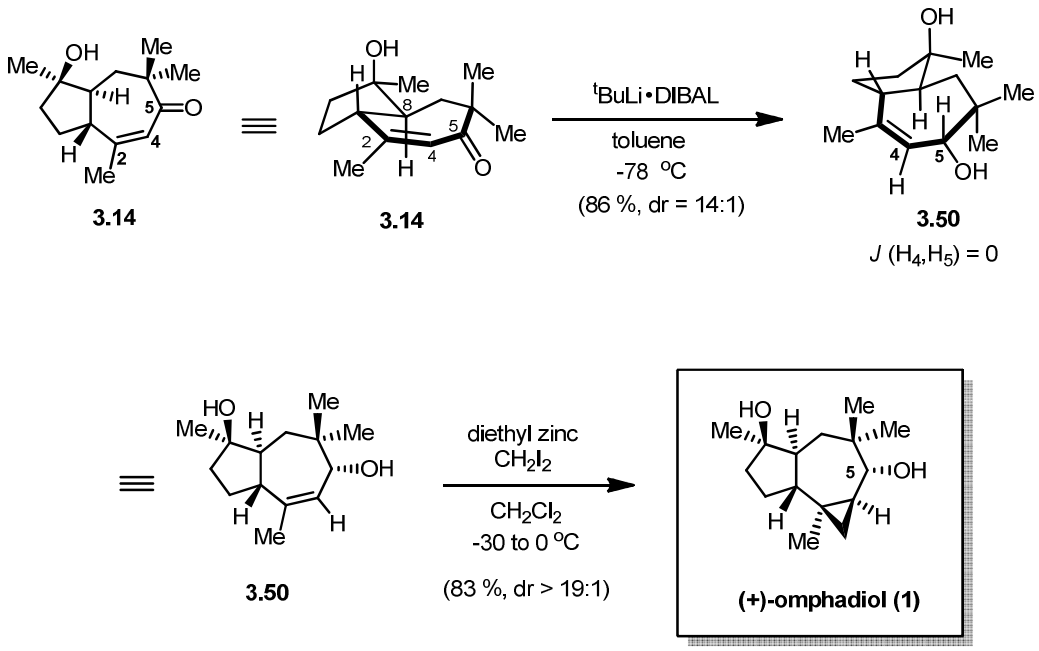
Thus, this problem was circumvented by addition of allyllithium, derived from allyltriphenyltin by transmetallation, to the sterically congested δ-lactone **3.35** to give the β,γ-enone **3.45** (Scheme 3.11).[39] Use of the latter intermediate was premised on a designed tandem isomerization/RCM process guided by the known reluctance of RCM to provide eight-membered rings [40, 41] and the ability of the ruthenium–hydride species generated from the Grubbs catalyst to promote olefin isomerization.[42, 43] As predicted, upon heating diene **3.48** with the second generation Grubbs catalyst in toluene, the desired cycloheptenone was formed in 95% yield indicating that olefin isomerization was faster than RCM; a situation which would have led to a cyclooctenone.

Scheme 3.11



At this juncture, the remaining steps to omphadiol involved the regio- and stereoselective reduction of the enone and a facial selective cyclopropanation (Scheme 3.12). After studying several reaction conditions, enone **3.14** was reduced smoothly to give the desired allylic alcohol **3.50** by treating with a DIBAL·tBuLi complex at -78 ^{o}C in toluene (d.r. = 14:1).[44] Finally, the cyclopropanation of allylic alcohol **3.50** under Simmons–Smith conditions gave (+)-omphadiol with high facial selectivity (d.r. > 19:1). Despite the well-known directing effect of allylic alcohols in seven-membered rings under Simmons–Smith conditions, this was not observed with **3.50**.[45, 46] This avoided the need for protection of the C5-hydroxyl group. The unique conformational constraint of allylic alcohol **3.50**, imposed by the bicyclic structure, places the secondary hydroxyl group in a pseudoequatorial position (in plane with the p bond). This rigid conformation is likely responsible for the unexpected, non-hydroxyl directed but desired facial selectivity. Both DFT calculations and NMR studies ($J_{H4,H5}$ = 0 Hz) of alcohol **3.50** support the conformation shown in Scheme 3.12. Synthetic (+)-omphadiol correlated well spectroscopically with the natural product including optical rotation.

Scheme 3.12


OH
Me
Me
Me
H
5
O
4
H
2
Me
3.14
≡
OH
H
Me
Me
8
5
2
Me
H
4
Me
O
3.14
tBuLi•DIBAL
toluene
-78 °C
(86 %, dr = 14:1)
OH
H
Me
Me
H
H
Me
4
5
Me
OH
H
3.50
J (H4,H5) = 0
≡
HO
H
Me
Me
Me
OH
H
Me
H
3.50
diethyl zinc
CH2I2
CH2Cl2
-30 to 0 °C
(83 %, dr > 19:1)
HO
H
Me
Me
Me
5
OH
H
H
Me
(+)-omphadiol (1)

CHAPTER IV

STUDIES TOWARD THE TOTAL SYNTHESES OF SCABROLIDES A & B AND SINULOCHMODIN C

4.1 Introduction

Since 1999, a class of structurally related terpenoids has been isolated from a variety of natural sources (Figure 4.1). Ineleganolide (**4.6**) was initially isolated by Duh and coworkers from a related soft coral *Sinularia inelegans* in 1999, the structure of which was determined by spectral and single crystal X-ray analysis. [47] Scabrolides A and B (**4.1** and **4.2**) were isolated by Sheu and coworkers from the soft coral in 2002; the structural assignment was made based on extensive spectroscopic studies and the relative stereochemistry was established by NOESY experiments.[48] Sinulochmodin C (**4.3**) was isolated in 2005 from soft coral *Sinularia lochmodes*; the structure was elucidated by NMR studies and a modified Mosher method.[49] Other significant members include verillin (**4.4**) [50] and rameswaralide (**4.5**).[51]

Some members of this family possess interesting biological activities. For example, ineleganolide (**4.5**) displayed cytotoxicity against a P388 cell line with an ED_{50} of 3.82 μg/mL. Rameswaralide (**4.6**) showed potent anti-inflammatory activity (inhibitory activity exhibited against TNF-α, IL-15, IL-5 and Cox_2; IC_{50} 0.5-5 μg/mL).

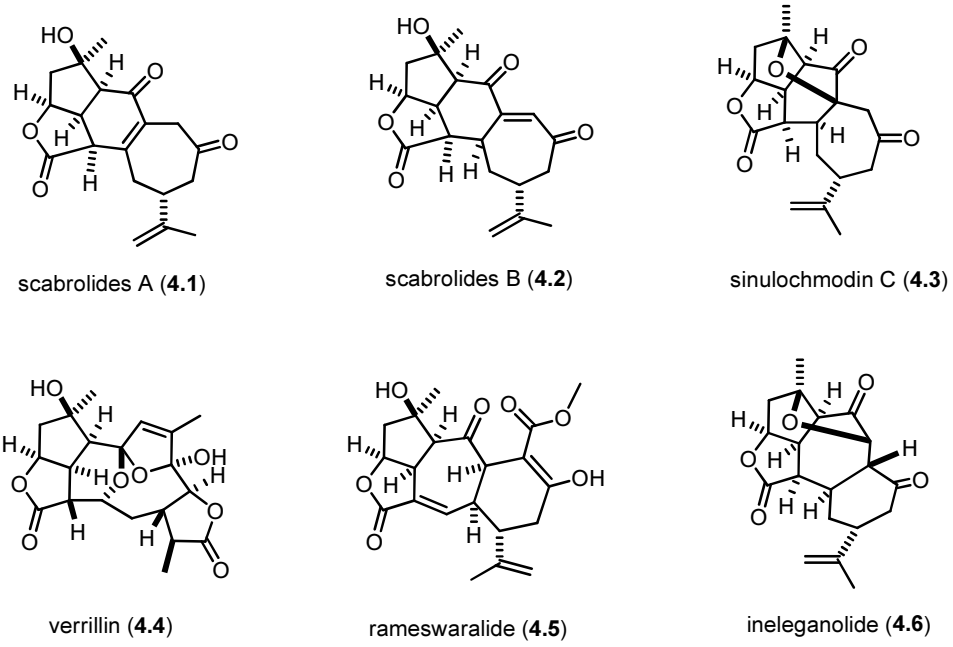


Figure 4.1 Scabrolides and Related Natural Products

From the perspective of chemical structure, these natural products are related by their highly substituted cyclopentane ring fused with a γ-lactone. This common structural motif shared by these natural products inspired us to undertake the total syntheses of scabrolides A & B and sinulochmodin C. We believe that entry into these relatively simple structures could serve as a prelude to the synthetic as well as biological studies of other more complex, biologically significant natural products of this family.

4.2 Retrosynthetic Plan

Retrosynthetically, sinulochmodin C (**4.3**) could be derived from scabrolide B (**4.2**) by an intramolecular oxo-Michael addition of the tertiary alcohol on the enone motif to close the furan ring (Figure 4.2). In turn, the conjugated 1,4-dione motif in scabrolide B (**4.2**) could be rearranged from scabrolide A (**4.1**) through an allyic transposition, taking advantage of thermodynamic stability gained by the extented conjugation. Disconnection of the tetra-substituted C-C double bond in scabrolide A (**4.1**) by a regioselective transannular aldol condensation would lead to macrocyclic trione **4.7**. As a key C-C bond forming step in this synthetic design, we envisioned the γ-lactone moiety could be forged through a transannular C-H insertion of a diazo carbene precursor into the cyclopentyl ring as in **4.8**.[52, 53] This macrocyclic structure **4.8** could be derived from the β-lactone **4.9** fused with a cyclopentane, which has been readily accessed by a nucleophile promoted aldol lactonization process developed in the Romo group.

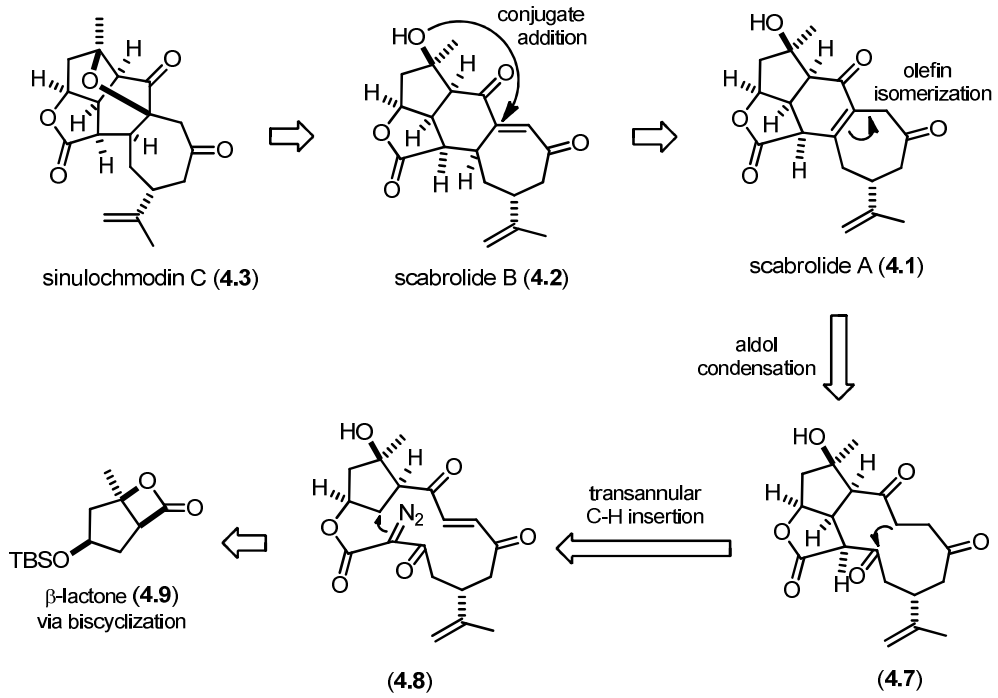


Figure 4.2 Retrosynthetic Plan

4.3 Transannular C-H Insertion Studies on Macrocyclic Systems

The transannular C-H insertion in the context of a macrocycle has rarely been reported. Toward understanding the electronic and conformational factors that control the outcome of transannular C-H insertions, we initiated model studies on various macrocyclic systems.

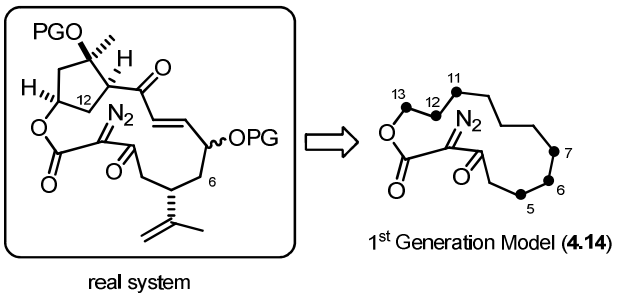
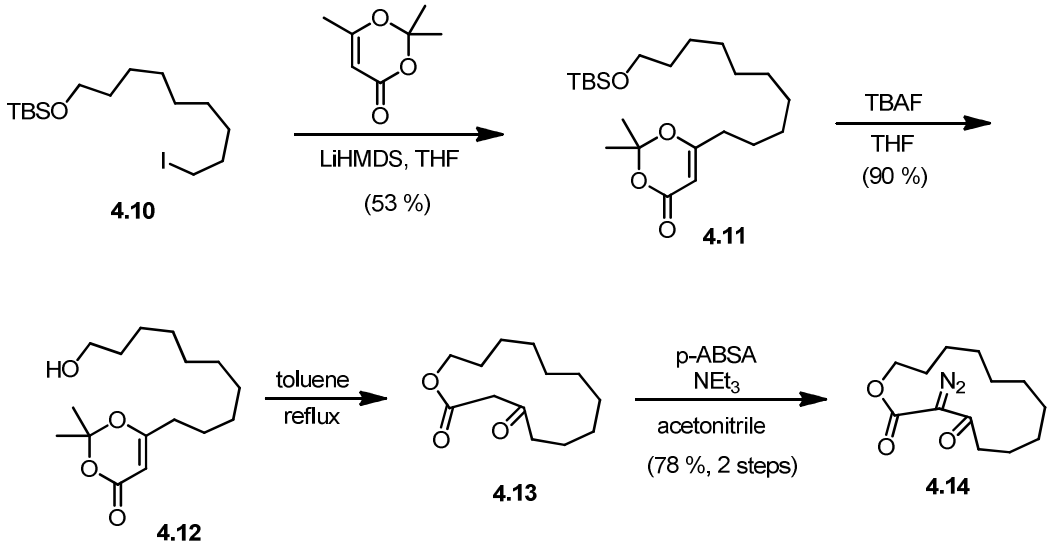


Figure 4.3 Design of the First Generation Model Substrate

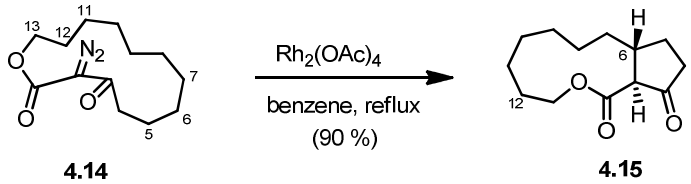
First, macrocycle **4.14**, which contains the requisite 14-membered cyclic β-ketoester to meet the minimal structural requirement of the planned transannular C-H insertion, was designed (Figure 4.3). Synthesis of this substrate started with primary iodide **4.10**. Alkylation with dioxenone led to intermediate **4.11**. Removal of the TBS protection, followed by submission to refluxing toluene to generate a putative acyl ketene that is trapped by the pendant primary alcohol, delivered the macrocyclic β-ketoester **4.13**.[54] Diazo transfer to the α position under conventional conditions (p-ABSA) produced the desired substrate **4.14** for the first transannular C-H insertion. (Scheme 4.1).

Scheme 4.1

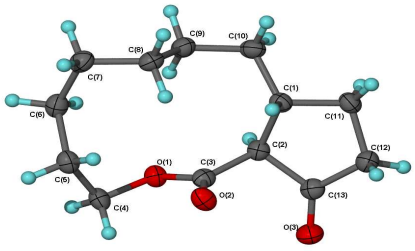


Attempts to effect the C-H insertion with Rh-based catalysts resulted in clean conversion to bicyclic cyclopentanone **4.15**, the structure of which was confirmed by X-ray crystallographic analysis (Scheme 4.2). This reaction is surprisingly site-selective considering that formation of lactones by insertion into C11, C12, or C13 and formation of carbocycles by insertion into C5, C6, or C7 have been well documented in analogous linear systems; [55, 56] in this particular macrocyclic system, only one site (i.e. C6) reacted. [57] Conditions using Cu-based catalysts led to complex mixtures that defied further analysis, while exposure to light (256 nm uv lamp) led to a major product identified as an acid arising from Wolff rearrangement.

Scheme 4.2



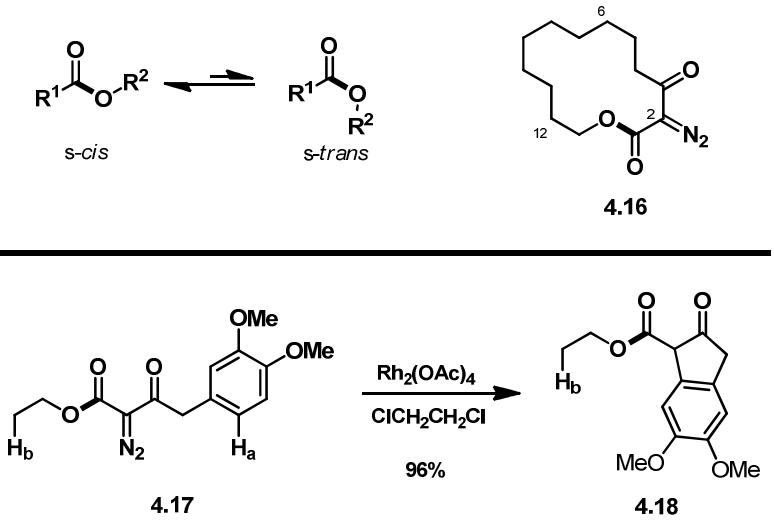
4.14 **4.15**



X-ray Structure of **4.15**

The site-selective C-H insertion could be attributed to the *s-cis* conformation of the ester σ bond present in the 14-membered macrocycle (Scheme 4.3). This forces C12 *trans* to the C2 carbene center and thus C12 is conformationally inaccessible to the C2 carbene center. Another factor that could favor the observed selectivity was the electronic withdrawing nature of the ester functionality, which renders C12 less reactive comparing to C6, as the C-H insertion proceeds through an electrophilic carbenoid wherein the targeted CH bonds act as electron donors. [58, 59] This site-selectivity imparted by both electronic and stereoelectronic effect of the ester functionality could be further supported by many reported cases such as **4.18** where formation of cyclopentanones instead of γ-lactones is the exclusive reaction pathway.[60]

Scheme 4.3



A second model system incorporated the requisite cyclopentane ring in the macrocyclic structure (Figure 4.4). We anticipated that this structural revision would introduce rigidity in the macrocycle and thus perturb the conformation in favor of the desired reaction pathway, i.e. insertion into the C12 C-H bond.

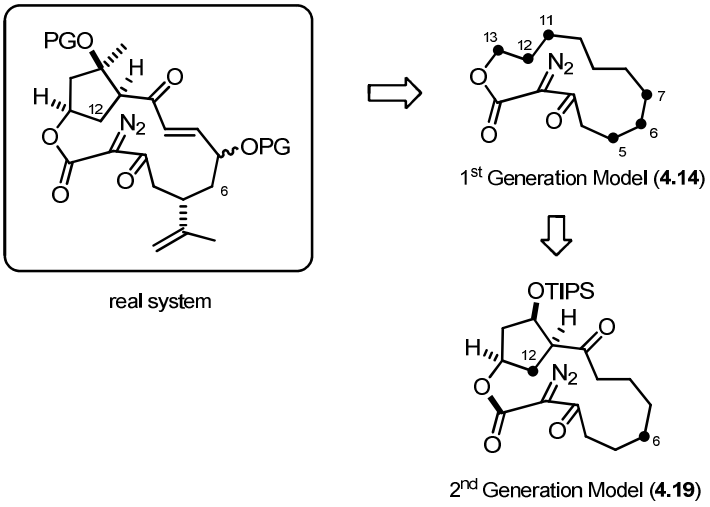
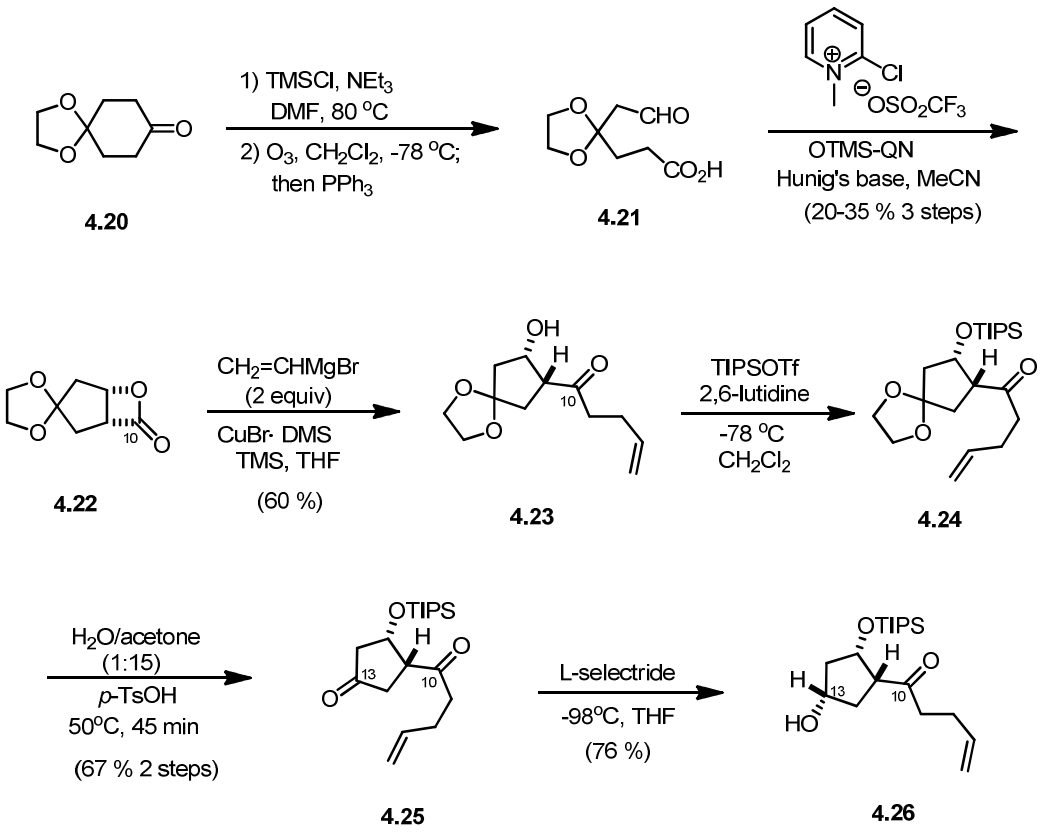


Figure 4.4 Design of the Second Generation Model Substrate

In line with the objective to highlight the application of β-lactones as synthetic vehicles, we opted to implement the NCAL process developed in our group to introduce the substituted cyclopentane ring (Scheme 4.4). Thus, a ring-opening manipulation of the derived cyclohexanone **4.20** was executed by vinyl silyl ether formation and ensuing ozone-mediate oxidative cleavage. The linear aldehyde acid so formed (**4.21**) was subjected to the NCAL conditions, giving rise to a bicyclic β-lactone fused with the

requisite cyclopentane ring (**4.22)**. Subsequent elaborations based on this cyclopentane ring would eventually lead to the desired substrate.

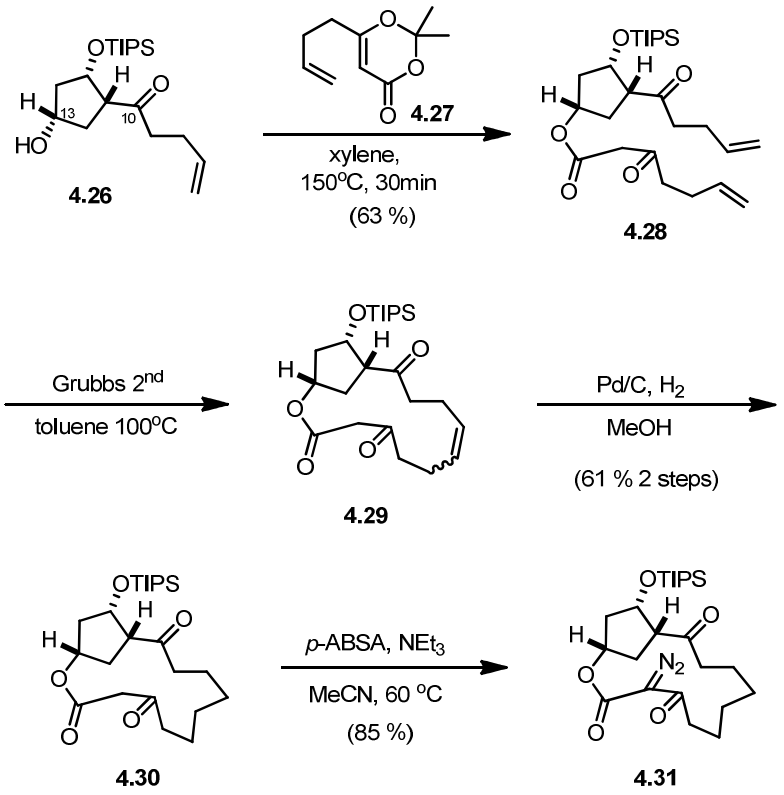
Scheme 4.4



Hence, four carbon homologation at C10 afforded ketone **4.23** through a tandem ring-opening and conjugate addition with vinyl cuprate reagents. Subsequent protection of the secondary alcohol and careful unmasking of the ketal functionality at C13 led to dione **4.25**. Differentiation of the two keto groups through chemoselective reduction

with a sterically demanding hydride species, i.e. L-selectride, at -98 ^{o}C in THF proved to be very successful. This condition selectively reduced the C13 carbonyl group to the corresponding secondary alcohol, with the C10 carbonyl group intact; the facial selective hydride delivery from the less hindered face of the cyclopentyl ring secured the desired diastereoselectivity, affording **4.26** as the exclusive product.

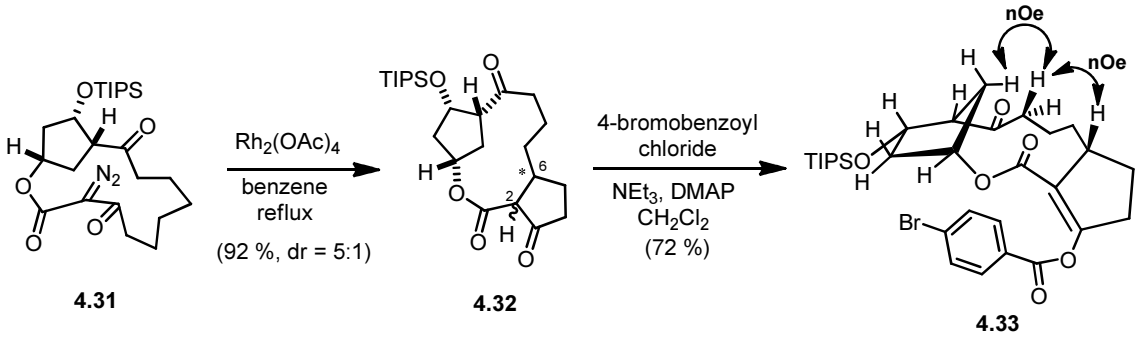
Scheme 4.5



The resulting alcohol was thus coupled with a derived dioxenone **4.27** under thermal conditions to afford diene **4.28** (Scheme 4.5). Exposure of this diene to the 2nd

generation Grubbs catalyst at 100 ^{o}C in toluene completed the construction of the 14-membered macrocyclic β-ketoester bridged to the substituted cyclopentenyl ring. This material was obtained as an inconsequential mixture of olelin *Z/E* isomers, as both were hydrogenated leading to the same intermediate **4.30**. Ensuing diazo transfer to the α position of the β-ketoester moiety as before eventually delivered **4.31**, arriving at the stage for the investigation of the second transannular C-H insertion model system.

Scheme 4.6



Attempted C-H insertions on this substrate, however, returned only discouraging results (Scheme 4.6). Consistent with previous observations with the first generation model study, insertion occurred with the C6 C-H bond of **4.31** to afford the undesired cyclopentanone **4.32** with excellent yields when rhodium acetate was used as the catalyst. All Rh-based catalysts provided similar results without C-H insertion into C12. Other metallic catalysts screened led to either no reaction or complex mixtures without observation of the desired product.

We then turned our attention to a third model system, which incorporated a C8-C9 enone motif (**4.35**) in the macrocycle (Figure 4.5). We anticipated this would further rigidify the macrocycle enforcing an *s-trans* conformation of the ester moiety and thus facilitate the desired C-H insertion.

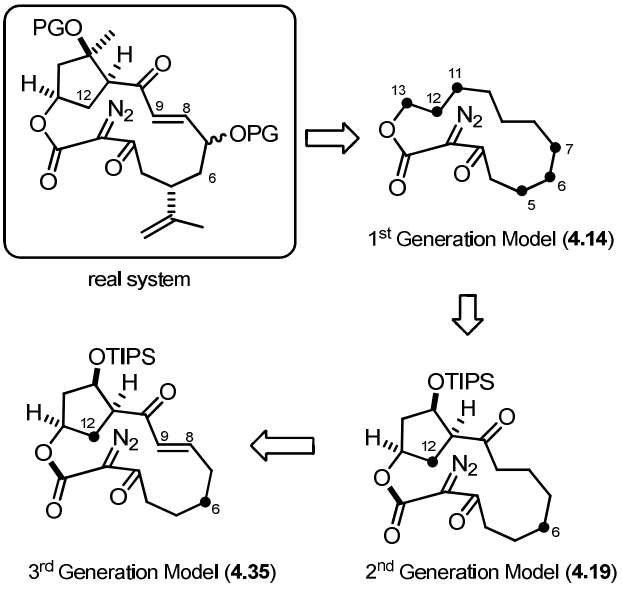
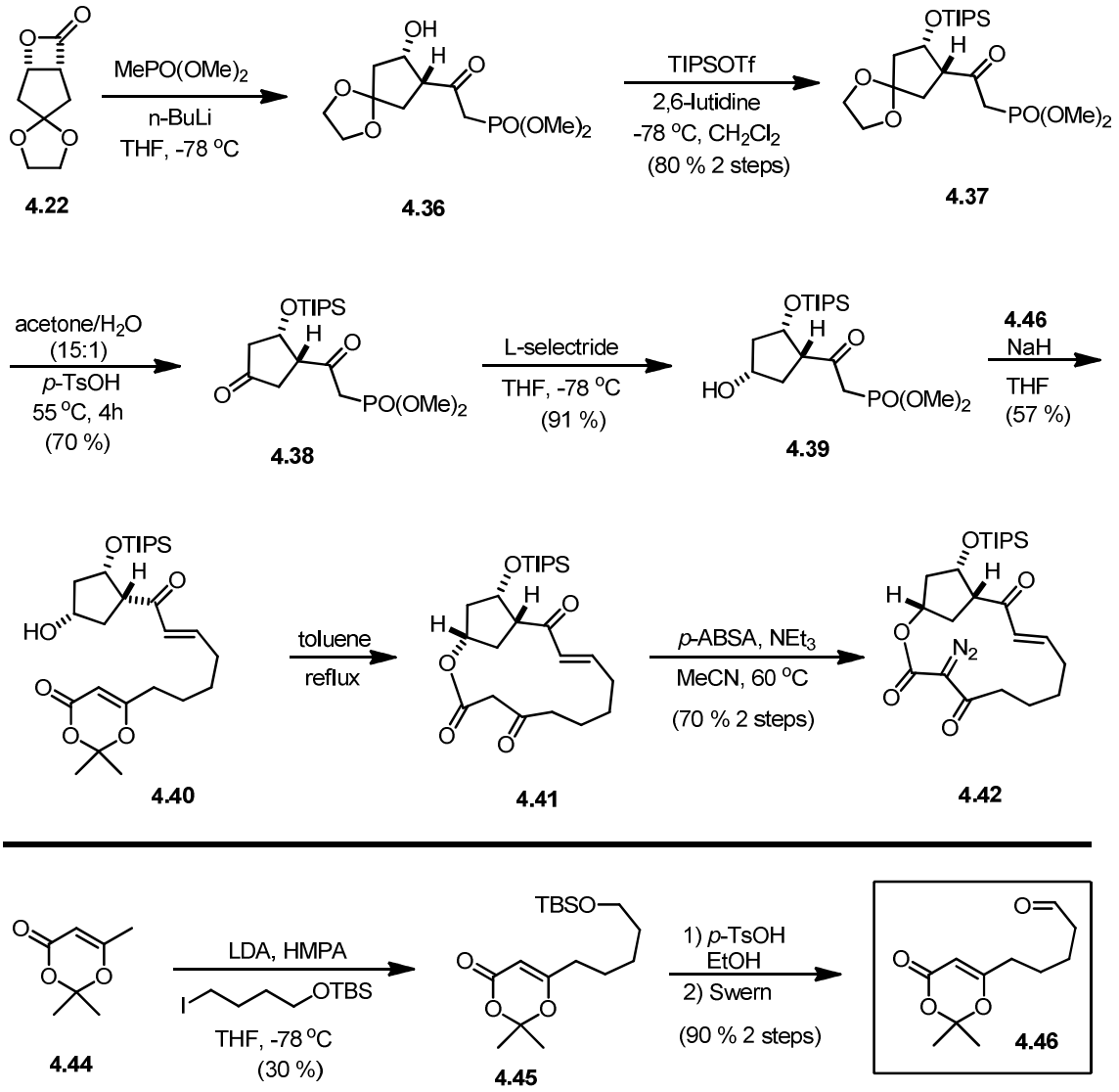


Figure 4.5 Design of the Third Generation Model Substrate

To access this model substrate, bicyclic β-lactone **4.22** was used again as the starting point of the synthetic sequence (Scheme 4.7). The lactone was opened with a lithiated phosphonate to give a secondary alcohol, which was immediately capped with a TIPS group. Careful unveiling of the cyclic ketone from the ketal moiety under acidic conditions delivered dione **4.38**. Site- and facial selective reduction of the dione using L-selectride as before afforded secondary alcohol **4.39**.

Scheme 4.7



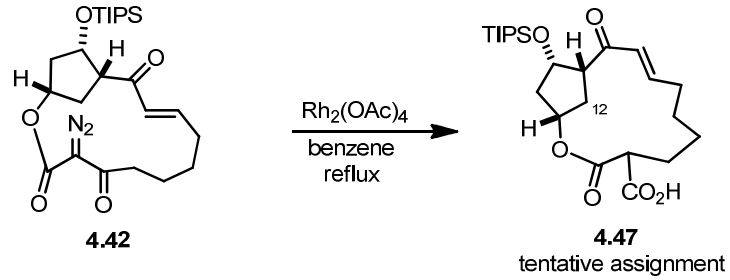
The phosphonate functionality was then utilized as the carbon extension site to react with aldehyde **4.46** (prepared from THF via 5 steps) by a Horner-Wadsworth-Emmons (HWE) reaction. This coupling reaction successfully introduced the *E* enon motif as planned and, at the same time, appended a dioxenone unit ready for the

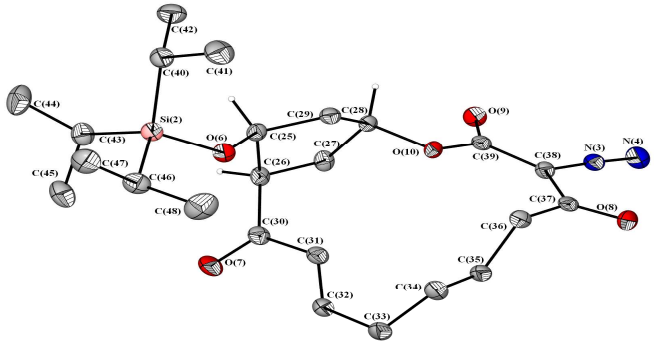
subsequent macrocyclization. The ring-closure event proceeded under thermal conditions (refluxing toluene) via a ketene intermediate to afford the macrocyclic keto-ester **4.41** with good yields. Routine diazo transfer as before delivered the third generation substrate **4.42** for the transannular C-H insertion.

Screening of conditions for C-H insertion with the third generation model substrate was even more challenging (Scheme 4.8). All attempts using various types of metallic catalysts afforded polar complex mixtures. Even with rhodium catalysts, which were proved to be effective in catalyzing the C-H insertion into C6 in the first and second generation model studies, the reactions led to complex mixtures and one of the major components was assigned as a Wolff rearrangment product.

To better understand these results, a single crystal of the diazo substrate **4.42** was obtained. Information drawn from the X-ray diffraction analysis is quite revealing. As is clearly shown by the three dimensional structure of the single crystal, the *s-cis* conformation of the ester moiety was still present; the rigidity conferred by the incorporation of the enone motif in the macrocycle did not reverse the conformational bias of the ester σ bond. On the contrary, the conformational rigidity introduced was able to block the facile C-H insertion into C6 C-H bonds observed in the first and second model studies. The unavailability of CH bond in the local environment of the carbene center led to the manifestation of the Wolff rearrangement pathway, which is normally regarded as trivial under Rh-complexes catalyzed conditions.

Scheme 4.8





X-ray Structure of **4.42**

At this point, all efforts toward transannular C-H insertions on macrocyclic systems were of no avail. The implication from these results is multifold. First, we are dealing with macrocyclic systems, which generally possess considerable flexibility comparing to conformationally stable small rings, such as five and six membered rings. Even though this conformational mobility could be tuned to some extent, prediction of the stable

conformation of macrocyclic systems as to determine whether a conformational bias could be reversed by structural variation in a particular substrate is generally difficult.

Moreover, substituents embedded in the 14-membered macrocyclic framework could give rise to multiple structural variables that are capable of dramatically altering the conformation of the macrocycles in an unpredictable way. These variables could be the positions where the substituents reside, the electronic or steric impact they might impose on the neighboring functionalities, and sometimes even transannular interactions between the substituents that might bring about uncertain conformational bias. This multitude of structural variables in conjunction with the conformationally flexible nature of macrocycles renders envisioning the outcome of the final C-H insertion reactions at the planning stage a very challenging task.

In addition, from the point of practice, each of these macrocyclic substrates took multiple steps to prepare; along the way to each substrates, lots of chemoselectivity and reactivity issues need to be dealt with individually. All these factors added considerably to the difficulties of the progress to the final targets.

4.4 Attempted Transannular C-H Insertion on Medium-sized Systems

The obstacle encountered with the macrocyclic systems forced us to resort to another approach toward C-H insertions. Thus, [4.2.1] bridged diazo substrate (**4.50**) was designed (Figure 4.6). In this strained system, the conformation would force the carbenoid center to be in close proximity to the targeted C-H bond; unlike the flexible macrocyclic systems, this medium-sized bridged substrate has limited conformational

choices and ensure the ester σ bond adopts an *s-cis* conformation. The caged cyclobutanone **4.51** arising from this planned C-H insertion reaction could be readily converted into the 5-5 bicycle **4.52** by a nucleophile initiated retro-Dieckmann cleavage.

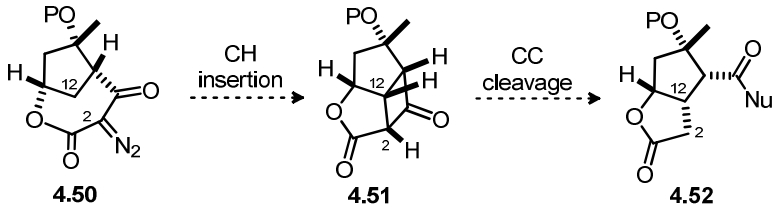


Figure 4.6 Design of a Bridged Diazo Substrate

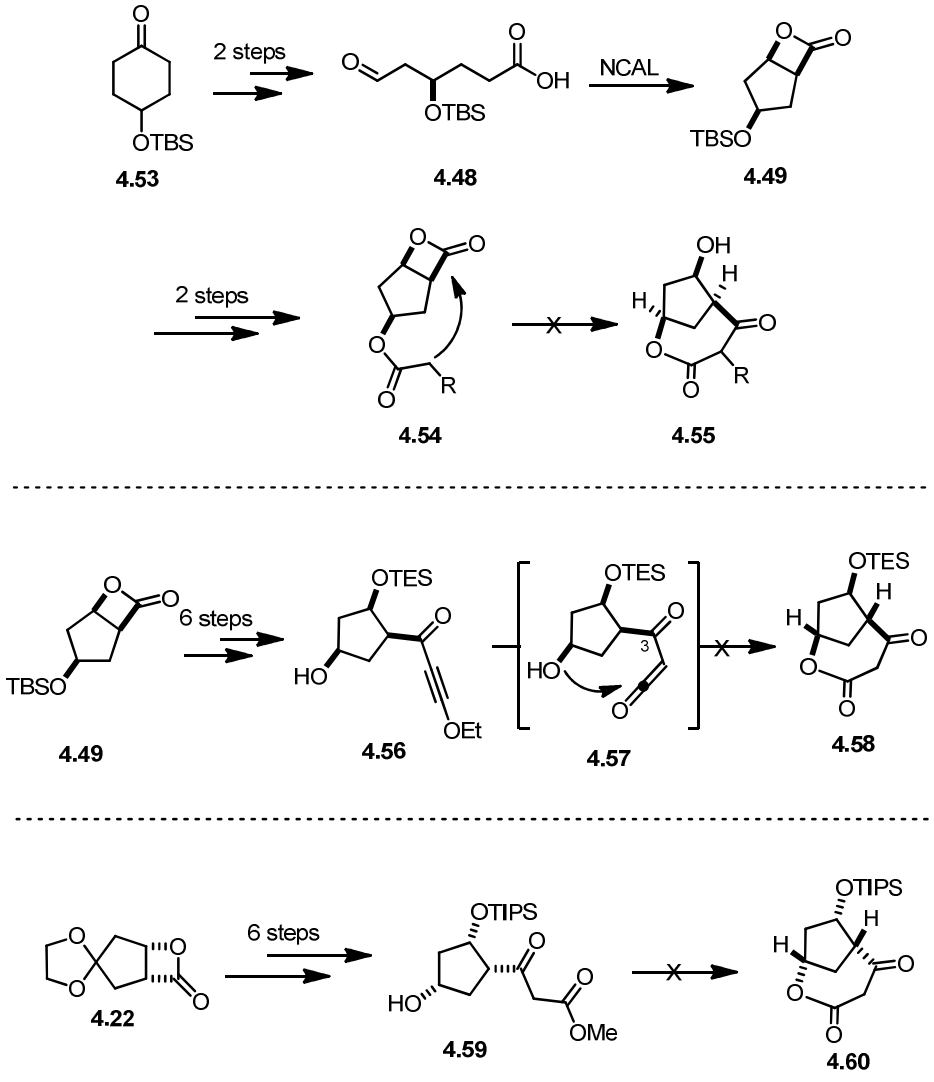
This design raised another question: how to make this bridged structure in an efficient way? As the carbon skeleton of the targeted substrate is an unprecedented structure with considerable strains, it is anticipated that this would not be an easy task.

Indeed, we encountered a maze of obstacles en route to the bridged structure (Scheme 4.9). Thus, the derived bicyclic β-lactone **4.54** was prepared from a derived cyclohexanone **4.53** through a five-step sequence involving a pivotal NCAL reaction.[61] The attempted transannular Dieckman condensation of this substrate under numerous conditions failed to provide the bridged structure.

Attention was then directed to the ring-closure strategy based on lactonization. Hence, after a series of transformations, **4.56** was accessed from **4.53**. Unfortunately, ring-closure through a ketene-trapping strategy under thermal conditions failed to deliver the desired product with practical yields. Another substrate (**4.59**) prepared from **4.22**

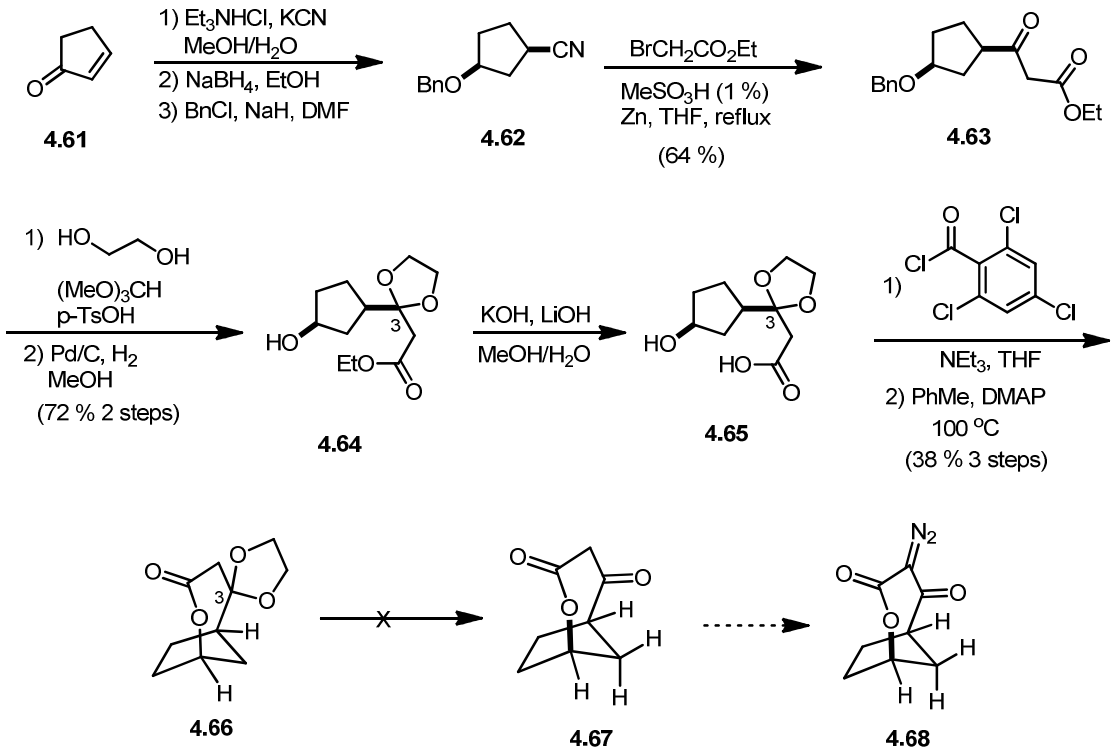
could not be converted to the corresponding bridged lactone **4.60** either. These failed cyclization processes were attributed to the carbonyl group at C3 (**4.57**), the sp^2 hybridization of which added considerably to the rigidity of the resulting bridged system.

Scheme 4.9



Ultimately, a strategy using a pivotal Yamaguchi lactonization emerged as a solution to the construction of the bridged structure (Scheme 4.10). Following a cascade of transformations, cyclopentenone **4.61** was converted to hydroxyl acid **4.65** with the keto group at C3 masked in the form of a ketal; this structural variation would relieve the strain previously posed by the C3 carbonyl group. Cyclization under Yamaguchi esterification conditions proceeded smoothly to yield the desired bridged lactone structure **4.66**. Further advances by ketal removal, unfortunately, are presently unsuccessful, presumably due to the fragile nature of the highly strained structures under the reaction conditions.

Scheme 4.10

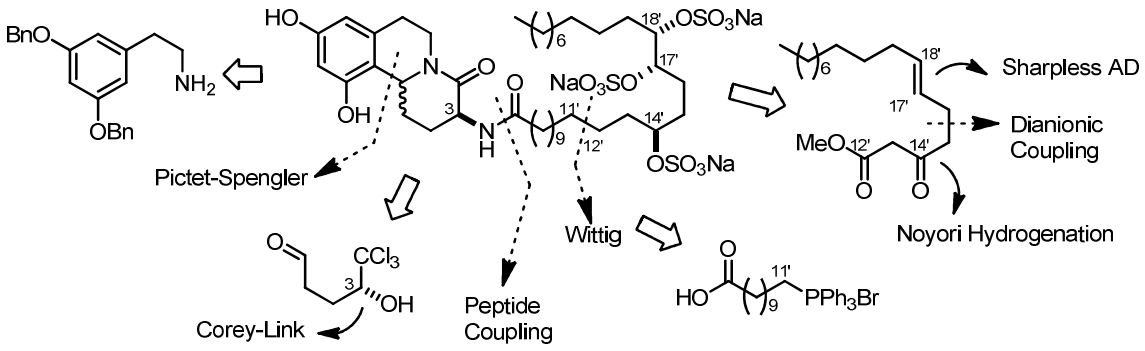


CHAPTER V

CONCLUSIONS

5.1 Total Syntheses of Schulezeines B & C

Scheme 5.1

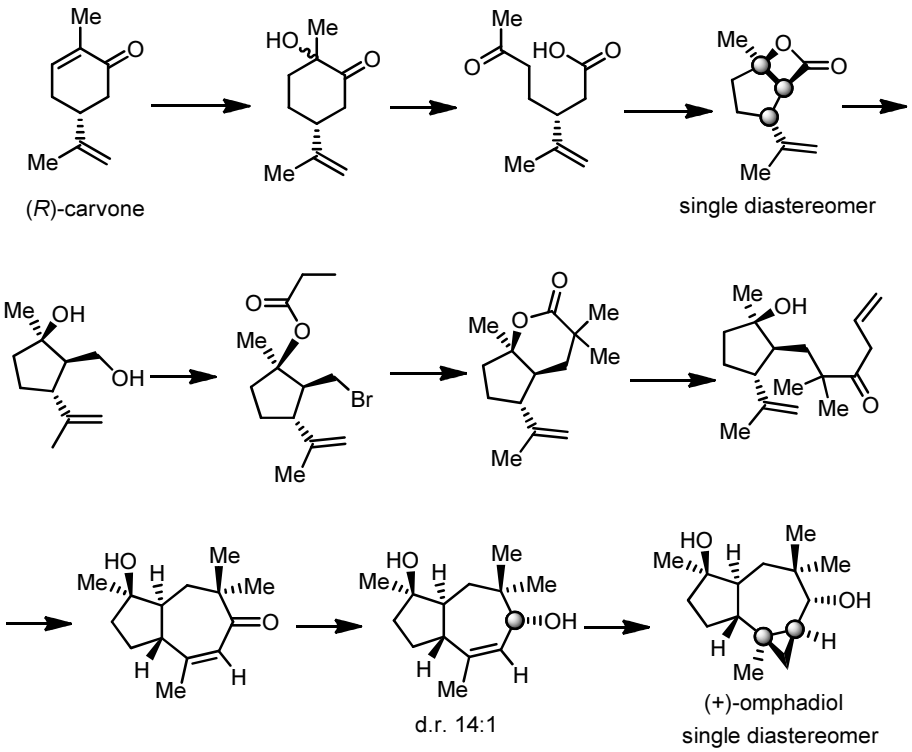


Total syntheses of the naturally occurring, α-glucosidase inhibitors schulzeines B and C have accomplished in a highly convergent manner employing a masked, α-amino acid aldehyde synthon derived from a β-lactone. Key features of the synthesis include a tetrahydroisoquinoline synthesis via a Pictet-Spengler reaction of a masked bishomoserine aldehyde, a Corey-Link process to unmask the α-amino acid, and a highly efficient synthesis of the required optically active, sulfated triol side chain employing a Noyori hydrogenation and Sharpless dihydroxylation sequence. An unexpected pyrrolidine product was obtained under modified Corey-Link conditions with a substrate

bearing a pendant amine and suggests the possiblity of capturing the dichloroepoxide intermediate by other tethered nucleophiles leading to proline and other amino acid derivatives. This synthesis further demonstrates the utility of β-lactones as intermediates in natural product total synthesis, and in particular application of the readily available trichloromethyl β-lactone which, in this instance, leads to a versatile masked surrogate for bishomoserine aldehyde.

5.2 Total Synthesis of (+)-Omphadiol

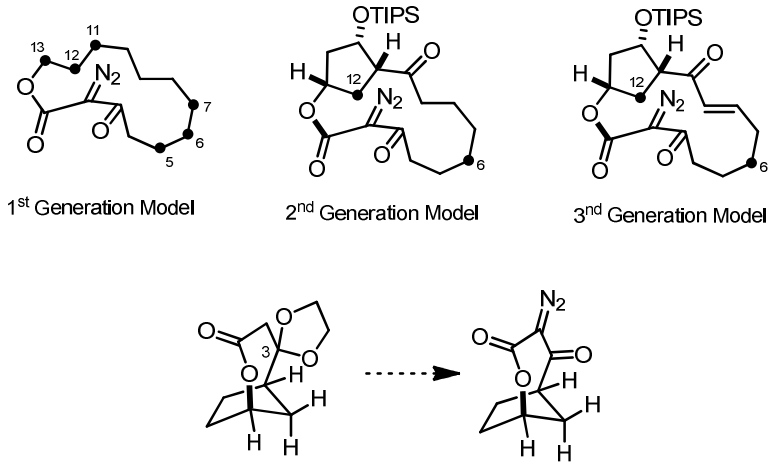
Scheme 5.2



The first total synthesis of (+)-omphadiol has been achieved in ten steps from (*R*)-carvone. This synthesis features the highly stereocontrolled introduction of the six contiguous stereogenic centers exclusively using substrate control from the single stereocenter in (*R*)-carvone. The concise nature of the synthesis derives from a high ratio of C-C bond-forming steps (five of the ten steps) that proceed in a highly efficient manner, the design and implementation of novel single-pot sequential processes, and the absence of protecting groups. This total synthesis paves the way for further biological studies of omphadiol and its congeners. Furthermore, synthetic strategies are now readily envisioned toward other members of this class of terpenes employing the versatile bicyclic β-lactone that is readily prepared on a multigram scale.

5.3 Synthetic Studies toward Scabrolides A & B and Sinulochmodin C

Scheme 5.3



Transannular CH insertion has been investigated on three generations of macrocyclic model substrates. These results revealed that insertion into the C6 C-H bonds is favored over the C12 CH bond to give predominantly cyclopentanone products. The attempted study of transannular C-H insertion on medium-sized bridged structures was hampered by the inaccessibility of the substrates due to the highly strained nature of the structure.

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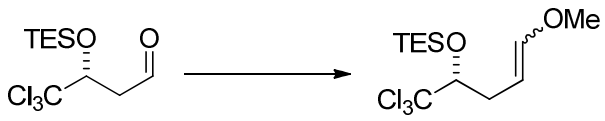
APPENDIX A

EXPERIMENTAL PROCEDURES

A.1 General

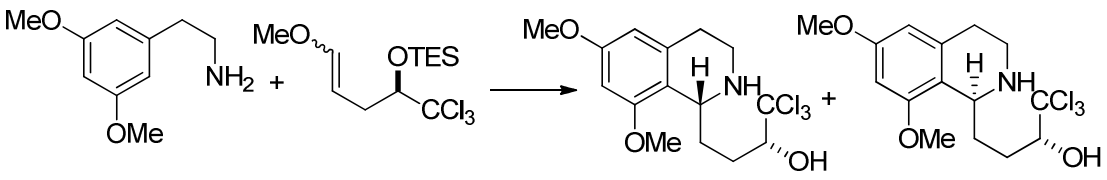
All reactions were carried out under nitrogen atmosphere in flame-dried glassware. Dichloromethane, methanol, and diethyl ether were purified by passage through activated alumina. Tetrahydrofuran was freshly distilled from sodium and benzophenone. All commercial reagents were used as received. $Mn(dpm)_3$ was purchased from Strem Inc. and used as received. ^1H NMR chemical shifts are reported as δ values in ppm relative to $CDCl_3$ (7.26 ppm,), coupling constants (*J*) are reported in Hertz (Hz), and multiplicity follows normal convention. Unless indicated otherwise, deuterochloroform ($CDCl_3$) served as an internal standard (77.16 ppm) for all ^{13}C spectra. Flash column chromatography was performed using 60Å silica gel (Baker, 230-400 mesh or Silacycle, 230-400 mesh) as a stationary phase. Mass spectra were obtained at the Center for Chemical Characterization and Analysis (Texas A&M University). Thin layer chromatography (TLC) was performed using glass-backed silica gel 60_{F254} (Merck, 250 μm thickness).

A.2 Procedure



Vinyl ether 2.8: LiHMDS (1M in THF, 2.4 mL, 2.4 mmol) was added dropwise to a suspension of (methoxymethyl)triphenyl phosphonium chloride (790 mg, 2.3 mmol) in THF (8 mL) at 0 °C. The resulted orange mixture was stirred at 0 °C for 1 h, followed by addition of the solution of aldehyde (470 mg, 1.54 mmol) in THF (8 mL). The mixture was then left to warm up to 23 °C and stirred overnight. The reaction was quenched by addition of 10% potassium carbonate solution, extracted with diethyl ether, dried over anhydrous $MgSO_4$, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, eluting with 100% hexanes) to give the vinyl ether as a clear oil (441 mg, 84%, *Z/E*=2:3). A small amount of material was used for gravity column chromatography to separate the *Z/E* isomer for characterization. ***Z isomer***: $[\alpha]_D^{23}$ +49.1 (*c* 3.5, $CHCl_3$); IR (thin film) 2957, 2880, 1667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.00 (dt, *J* = 6.0, 1.2 Hz, 1H), 4.44 (m, 1H), 4.13 (dd, *J* = 8.1, 3.0 Hz, 1H), 3.61 (s, 3H), 2.82-2.96 (m, 1H), 2.31-2.44 (m, 1H), 0.99 (m, 9H), 0.71 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 103.9, 101.6, 84.0, 59.7, 28.6, 7.0, 5.4; LRMS (ESI+) calcd. for $C_{12}H_{24}Cl_3O_2Si$ (M+H) 333. Found 333. ***E isomer***: $[\alpha]_D^{23}$ +33.6 (*c* 0.72, $CHCl_3$); IR (thin film) 2957, 2881, 1655 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.37 (d, *J* = 12.3 Hz, 1H),

4.73 (m, 1H), 4.03 (m, 1H), 3.55 (s, 3H), 2.66-2.78 (m, 1H), 2.18-2.34 (m, 1H), 0.99 (m, 9H), 0.72 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 103.7, 98.0, 84.9, 56.0, 32.4, 7.0, 5.5; LRMS (ESI+) calcd. for $C_{12}H_{24}Cl_3O_2Si$ (M+H) 333. found 333.

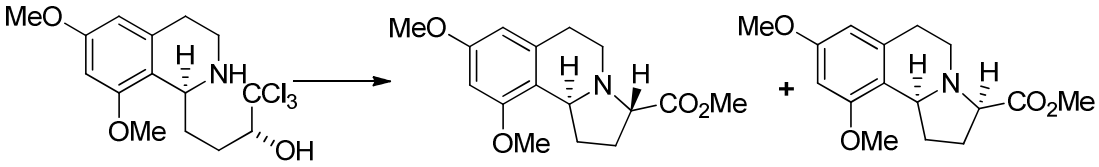


Tetrahydroisoquinoline 2.28: The primary amine (292 mg, 1.64 mmol) and vinyl ether (525 mg, 1.64 mmol) were dissolved in AcOH (10 mL) in a seal tube. The reaction vessel was sealed and placed in an oil bath pre-warmed to 100 °C. The reaction was stirred for 24 h, cooled down to 23 °C, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, eluting with 30%->50% EtOAc/hexanes, 4% Et_3N) to separate the two diastereoisomers as foamy solids:

2.28a: (254 mg, 42%): $[\alpha]_D^{23}$ -28.3 (*c* 0.66, $CHCl_3$); IR (thin film) 3055, 2990, 1261 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.30 (d, *J* = 2.5 Hz, 1H), 6.22 (d, *J* = 2.5 Hz, 1H), 4.04 (dd, *J* = 10.0, 2.0 Hz, 1H), 3.96 (dd, *J* = 10.0, 1.5 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.05-3.20 (m, 2H), 2.65-2.81 (m, 2H), 2.54-2.61 (m, 1H), 2.16-2.24 (m, 1H), 1.76-1.86 (m, 1H), 1.64-1.73 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 157.1, 135.6, 119.6,

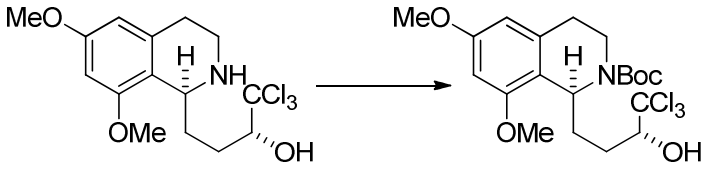
104.6, 104.3, 96.7, 83.5, 55.4, 55.3, 52.4, 36.4, 32.6, 29.8, 28.7; LRMS (ESI+) calcd. for $C_{15}H_{21}Cl_3NO_3$ (M+H) 368. Found 368.

2.28b: (276 mg, 45%): $[\alpha]_D^{23}$ -65.6 (*c* 1.1, $CHCl_3$); IR (thin film) 3061, 2990, 1267 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.32 (d, *J* = 2.5 Hz, 1H), 6.25 (d, *J* = 2.5 Hz, 1H), 4.30 (dd, *J* = 7.5, 3.5 Hz, 1H), 4.19 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.15 (m, 1H), 3.02 (m, 1H), 2.85 (m, 1H), 2.71 (m, 1H), 2.28 (m, 1H), 2.18 (m, 1H), 1.95 (m, 1H), 1.79 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 157.2, 137.0, 119.0, 104.6, 104.5, 96.7, 82.2, 55.4, 55.3, 50.0, 38.9, 29.9, 29.5, 28.6; LRMS (ESI+) calcd. for $C_{15}H_{21}Cl_3NO_3$ (M+H) 368. Found 368.

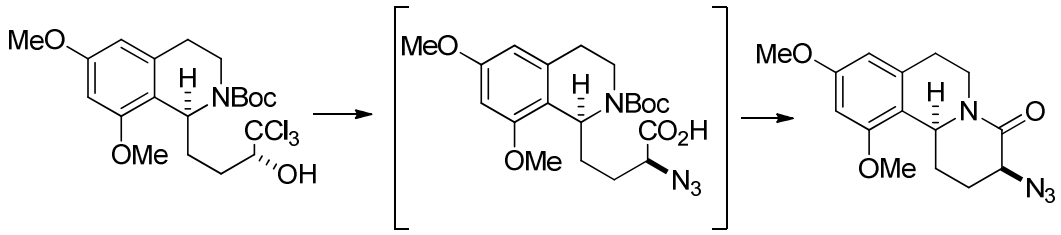


pyrrolidines 2.35: A mixture of amine (50 mg), DBU (0.1 mL), and NaN_3 (27 mg) in MeOH (2.5 mL) was stirred at 60 ^oC for 10 hours, and the mixture was concentrated, diluted with ethyl acetate, washed with saturated NH_4Cl solution, dried over $MgSO_4$, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, eluting with 20% EtOAc/hexanes) to give the major pyrrolidine (23 mg, 58%) and minor (4 mg, 10%):$[\alpha]_D^{23}$ -171 (*c* 0.24, $CHCl_3$); IR (thin film) 2990, 2949, 1738, 1607 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.30 (d, *J* = 2.5 Hz, 1H), 6.22 (d, *J* = 2.5 Hz, 1H), 4.49 (t, *J* =

6.5 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 3.69 (t, *J* = 6.5 Hz, 1H), 3.04 (m, 1H), 2.97 (m, 1H), 2.83 (m, 1H), 2.50-2.64 (m, 2H), 2.10 (m, 1H), 2.01 (m, 1H), 1.62 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 158.6, 157.9, 136.4, 120.4, 103.9, 96.6, 64.3, 57.3, 55.4, 55.3, 52.2, 45.5, 31.6, 28.8, 26.0; LRMS (ESI+) calcd. for $C_{16}H_{22}NO_4$ (M+H) 292. Found 292

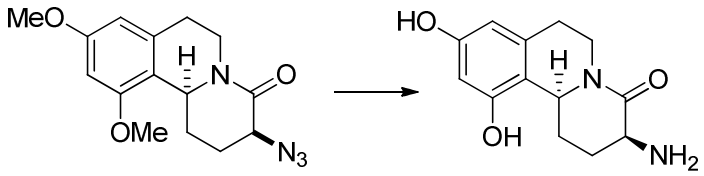


Boc amine 2.36a: A mixture of secondary amine (200 mg, 0.54 mmol) and $(Boc)_2O$ (153 mg, 0.7 mmol) in dichloromethane (2 mL) was stirred at room temperature for 3 hours. The mixture was washed sequentially with saturated sodium bicarbonate and water, dried over $MgSO_4$, concentrated, and purified by flash column chromatography (SiO_2, eluting with 20% EtOAc/hexanes) to give **2.36a** as a foamy solid (242 mg, 95%): $[\alpha]_D^{23}$ +131.0 (*c* 3.3, $CHCl_3$); IR (thin film) 3393, 2975, 2940, 1658, 1670 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), rotamer, see attached figures. ^{13}C NMR rotamer, see attached figures; LRMS (ESI+) calcd. for $C_{20}H_{29}Cl_3NO_5$ (M+H) 468. Found 468

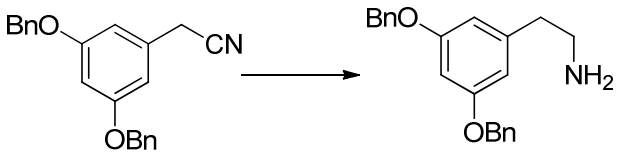


Lactam 2.39a: To a solution of the trichloromethyl carbinol (45 mg, 0.1 mmol) in DME (0.5 mL) was added a solution of NaOH (0.8M) and NaN_3 (0.4M) in water (0.5 mL) with vigorous stirring. The mixture was stirred at room temperature for 24 hours, extracted with ethyl acetate, dried over $MgSO_4$, and concentrated to give the crude acid.

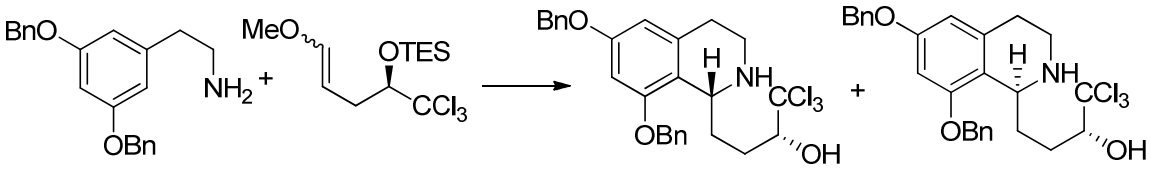
To a solution of the crude acid in dichloromethane (0.6 mL) at 0 ^oC was added TFA (0.3 mL). The mixture was stirred at 0 ^oC for 1 hour. The mixture was then concentrated and dried *in vacuo*. DMF (0.7 mL), triethyl amine (40uL, 0.3 mmol), and DPPA (42uL, 0.2 mmol) were added sequentially to the same vial and the mixture was stirred at room temperature for 8 hours. The mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over $MgSO_4$, concentrated, and purified by flash column chromatography (SiO_2, eluting with 40% EtOAc/hexanes) to give azide **2.39a** as a foamy solid (16 mg, 53% over 3 steps) : $[\alpha]_D^{23}$ -375.8 (*c* 1.0, $CHCl_3$); IR (thin film) 2999, 2102, 1667, 1643 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.35 (d, *J* = 2.0 Hz, 1H), 6.29 (d, *J* = 2.0 Hz, 1H), 4.86 (m, 1H), 4.70 (dd, *J* = 11.0, 3.5 Hz, 1H), 4.15 (dd, *J* = 6.5, 6.5 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 2.79-2.91 (m, 1H), 2.63-2.74 (m, 2H), 2.53-2.61 (m, 1H), 2.08-2.18 (m, 1H), 1.76-1.85 (m, 1H), 1.36-1.48 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 159.4, 157.3, 137.6, 116.9, 104.6, 97.2, 58.4, 55.4, 55.3, 52.7, 39.1, 30.2, 26.3, 25.6; LRMS (ESI+) calcd. for $C_{15}H_{19}N_4O_3$ (M+H) 303. Found 303.



primary amine 2.41a: A mixture of azide (50 mg, 0.16 mmol) and Pd/C 10% w/w in MeOH (1 mL) was stirred under hydrogen for 8 hours. The mixture was then filtered and concentrated to give the crude amine, which was dissolved in dichloromethane (1 mL) and cooled to -78 ^{o}C. Boron tribromide solution (1M, 0.63 mL, 0.63 mmol) was added dropwise. The mixture was then warmed up to room temperature and stirred for 18 hours. The reaction was cooled down to -78 ^{o}C, quenched slowly with MeOH, and warmed up to room temperature slowly. The mixture was dried and purified by flash column chromatography (SiO_2, eluting with 5% MeOH/CH_2Cl_2) to give amine **2.41a** as a foamy solid (33 mg, 85% from azide): $[\alpha]_D^{23}$ -138.7 (*c* 0.73, MeOH); IR (thin film) 3203, 2949, 1673, 1613, 1202, 1140 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 6.25 (d, *J* = 2.5 Hz, 1H), 6.24 (d, *J* = 2.5 Hz, 1H), 4.72 (dd, *J* = 11.5, 4.0 Hz, 1H), 4.41 (dt, *J* = 11.5, 3.5 Hz, 1H), 4.10 (dt, *J* = 10.5, 7.5 Hz, 1H), 2.62-2.74 (m, 3H), 2.28-2.40 (m, 2H), 1.66 (m, 1H), 1.41 (m, 1H) ; ^{13}C NMR (125 MHz, D_2O) δ 168.3, 155.4, 153.8, 138.2, 114.3, 107.0, 101.1, 49.6, 48.7, 39.4, 28.3, 26.9, 22.2; LRMS (ESI+) calcd. for $C_{13}H_{17}N_2O_3$ (M+H) 249. Found 249.



primary amine 2.7: Into a suspension of LAH (2.6g, 68.4 mmol) in THF (40 mL) at 0 ^{o}C was added dropwise concentrated sulfuric acid (1.2 mL, 22.8 mmol) and the mixture was stirred at the same temperature for 30 min. A solution of the nitrile[1] (7.5g, 22.8 mmol) in THF (10 mL) was then added dropwise to the reaction mixture and the reaction was allowed to warm up to room temperature and stirred at room temperature for 1 hour. The mixture was carefully quenched with a mixing solvent of THF and water at 0 ^{o}C, added with 15% NaOH solution, and filtered through a pad of celite. The filtant was concentrated and dried to give **2.7** as a syrup (6.8g, 90%), which is essentially pure and used without further purification. The NMR data matched with the reported.[2]

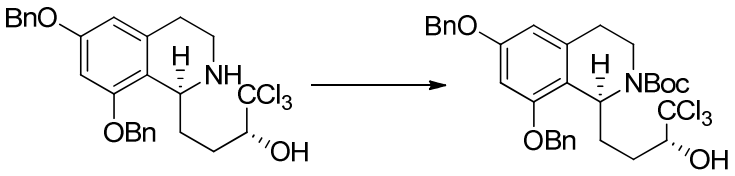


[1] The nitrile was prepared according to the literature procedures: Comber, M.F; Sargent, M; Skelton, B; and White.D; *J. Chem. Soc. Perkin Trans. 1* **1989**; 441–448

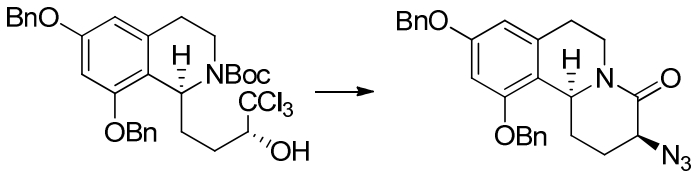
[2] Zhao, H; Neamati, N; Mazumder, A; Sunder, S; Pommier, Y; Burke, T. *J. Med. Chem*, **1997**, *40*, 1186-1194.

tetrahydroisoquinoline 2.6: The primary amine (220 mg, 0.66 mmol) and vinyl ether (265 mg, 0.66 mmol) were dissolved in AcOH (4 mL) in a seal tube. The reaction vessel was sealed and placed in an oil bath pre-warmed to 100 °C. The reaction was stirred for 24 h, cooled down to 23 °C, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, eluting with 30%->50% EtOAc/hexanes, 4% NH_4OH) to separate the two diastereoisomers as foamy solids. **2.6a:** (140 mg, 41%): $[\alpha]_D^{23}$ -2.2 (*c* 2.7, $CHCl_3$); IR (thin film) 3304, 2946, 1601 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43-7.33 (m, 10H), 6.46 (d, *J* = 2.0 Hz, 1H), 6.34 (d, *J* = 2.0 Hz, 1H), 5.08-5.01 (m, 4H), 4.06 (m, 2H), 3.15 (m, 2H), 2.76 (m, 2H), 2.51 (m, 1H), 2.28 (m, 1H), 1.75 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 156.2, 136.9, 136.8, 135.8, 128.8, 128.7, 128.2, 128.1, 127.6, 126.9, 120.2, 105.8, 104.5, 98.6, 83.5, 70.2, 69.8, 52.6, 36.5, 32.4, 30.1, 28.7; LRMS (ESI+) calcd. for $C_{27}H_{29}Cl_3NO_3$ (M+H) 520. Found 520.

2.6b: (114 mg, 33%): $[\alpha]_D^{23}$ -43.6 (*c* 2.0, $CHCl_3$); IR (thin film) 3064, 2937, 1604, 1149 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44-7.32 (m, 10H), 6.48 (d, *J* = 2.0 Hz, 1H), 6.35 (d, *J* = 2.0 Hz, 1H), 5.03-4.98 (m, 4H), 4.33 (dd, *J* = 7.5, 3.0 Hz, 1H), 4.14 (dd, *J* = 9.5, 3.0 Hz, 1H), 3.16 (m, 1H), 3.01 (m, 1H), 2.83 (dt, *J* = 16.5, 5.0, Hz, 1H), 2.70 (m, 1H), 2.29 (m, 1H), 2.12 (m, 1H), 1.94 (m, 1H), 1.77 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta^{13}C$ NMR (125 MHz, $CDCl_3$) δ 158.2, 156.3, 137.2, 136.9, 136.8, 128.7, 128.6, 128.2, 127.7, 127.3, 119.6, 105.9, 104.5, 98.6, 82.1, 70.2, 70.1, 50.2, 38.9, 29.9, 29.6, 28.8; LRMS (ESI+) calcd. for $C_{27}H_{29}Cl_3NO_3$ (M+H) 520. Found 520.

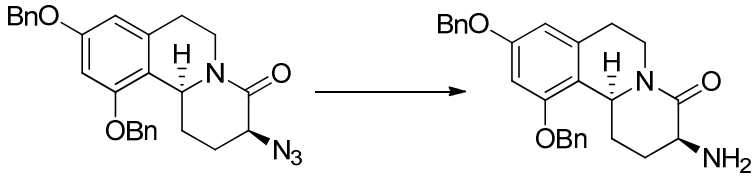


Boc amine 2.45a: A mixture of secondary amine (396 mg, 0.76 mmol) and $(Boc)_2O$ (189 mg, 1.0 mmol) in dichloromethane (3 mL) was stirred at room temperature for 3 hours. The mixture was washed sequentially with saturated sodium bicarbonate and water, dried over $MgSO_4$, concentrated, and purified by flash column chromatography (SiO_2, eluting with 20% EtOAc/hexanes) to give **2.45a** as a foamy solid (433 mg, 92%).$[\alpha]_D^{23}$ +28.5 (*c* 6.7, $CHCl_3$); IR (thin film) 3283, 2978, 2931, 1655 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), rotamer, see attached figures. ^{13}C NMR (125 MHz, $CDCl_3$) rotamer, see attached figures; LRMS (ESI+) calcd. for $C_{32}H_{37}Cl_3NO_5$ (M+H) 620. Found 620



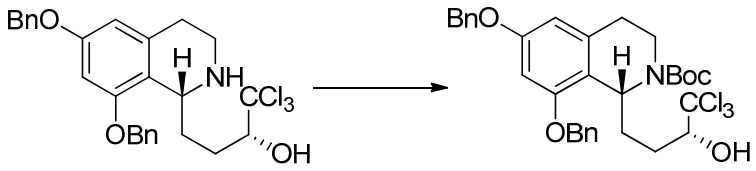
Lactam 2.48a: To a solution of the trichloromethyl carbinol (50 mg, 0.08 mmol) in DME (5.0 mL) was added a solution of NaOH (0.8M) and NaN_3 (0.4M) in water (5.0 mL) with vigorous stirring. The mixture was stirred at room temperature for 24 hours, extracted with ethyl acetate, dried over $MgSO_4$, and concentrated to give the crude acid.

To a solution of the crude acid in dichloromethane (1.0 mL) at 0 ^{o}C was added with TFA (0.5 mL). The mixture was stirred at 0 ^{o}C for 1 hour. The mixture was then concentrated and dried *in vacuo*. DMF (0.8 mL), triethyl amine (40uL, 0.3 mmol), and DPPA (42uL, 0.2 mmol) were added sequentially to the same vial and the mixture was stirred at room temperature for 8 hours. The mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over $MgSO_4$, concentrated, and purified by flash column chromatography (SiO_2, eluting with 40% EtOAc/hexanes) to give **2.48a** as a foamy solid (17 mg, 47% for 3 steps): $[\alpha]_D^{23}$ -375.8 (*c* 1.0, $CHCl_3$); IR (thin film) 2999, 2102, 1667, 1643 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35 (d, *J* = 2.0 Hz, 1H), 6.29 (d, *J* = 2.0 Hz, 1H), 4.86 (m, 1H), 4.70 (dd, *J* = 11.0, 3.5 Hz, 1H), 4.15 (dd, *J* = 13.0, 6.5 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 2.79-2.91 (m, 1H), 2.63-2.74 (m, 2H), 2.53-2.61 (m, 1H), 2.08-2.18 (m, 1H), 1.76-1.85 (m, 1H), 1.36-1.48 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 159.4, 157.3, 137.6, 116.9, 104.6, 97.2, 58.4, 55.4, 55.3, 52.7, 39.1, 30.2, 26.3, 25.6; LRMS (ESI+) calcd. for $C_{27}H_{22}N_4O_3$ (M+H) 455. Found 455.

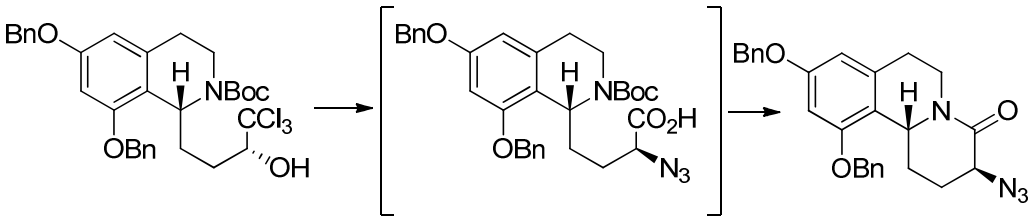


primary amine 2.49a: A mixture of azide (71 mg, 0.16 mmol) and triphenylphosphine (61 mg, 0.24 mmol) in THF (3 mL) and H_2O (20 uL) was stirred at 60 ^{o}C for 12 hours. The mixture was concentrated and purified by flash column chromatography (SiO_2, eluting with 5% MeOH/CH_2Cl_2) to give amine **2.49a** as a solid (72 mg, 93%): $[\alpha]_D^{23}$ -

278.6 (*c* 1.5, $CHCl_3$); IR (thin film) 3369, 2940, 1649, 1610 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.35 (d, *J* = 2.5 Hz, 1H), 6.29 (d, *J* = 2.5 Hz, 1H), 4.76 (m, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.54 (dd, *J* = 12.0, 15.5 Hz, 1H), 2.62-2.88 (m, 3H), 2.22-2.48 (m, 2H), 1.23-1.55 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 159.5, 157.2, 137.7, 117.4, 104.6, 97.2, 55.6, 55.5, 50.4, 50.0, 39.0, 30.1, 28.6, 27.9; LRMS (ESI+) calcd. for $C_{27}H_{29}N_2O_3$ (M+H) 429. Found 429.

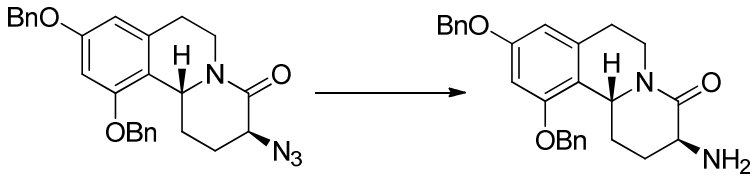


Boc amine 2.45b: A mixture of secondary amine (515 mg, 1.0 mmol) and $(Boc)_2O$ (246 mg, 1.3 mmol) in dichloromethane (3 mL) was stirred at room temperature for 3 hours. The mixture was washed sequentially with saturated sodium bicarbonate and water, dried over $MgSO_4$, concentrated, and purified by flash column chromatography (SiO_2, eluting with 20% EtOAc/hexanes) to give **2.45b** as a foamy solid (590 mg, 95%).$[\alpha]_D^{23}$ -12.1 (*c* 10.0, $CHCl_3$); IR (thin film) 3419, 2975, 2931, 1687, 1664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), rotamer, see attached figures. ^{13}C NMR (125 MHz, $CDCl_3$) rotamer, see attached figures; LRMS (ESI+) calcd. for $C_{32}H_{37}Cl_3NO_5$ (M+H) 620. Found 620.

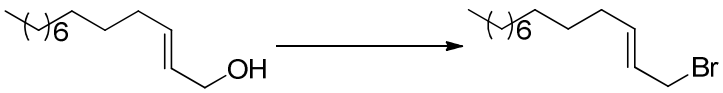


Azide 2.48b: To a solution of the trichloromethyl carbinol **(**50 mg, 0.08 mmol) in DME (5.0 mL) was added a solution of NaOH (0.8M) and NaN_3 (0.4M) in water (5.0 mL) with vigorous stirring. The mixture was stirred at room temperature for 24 hours, extracted with ethyl acetate, dried over $MgSO_4$, and concentrated to give the crude acid.

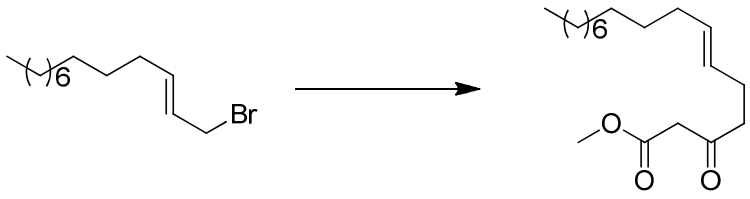
To a solution of the crude acid in dichloromethane (1.0 mL) at 0 ^oC was added with TFA (0.5 mL). The mixture was stirred at 0 ^oC for 1 hour. The mixture was then concentrated and dried *in vacuo*. DMF (0.8 mL), triethyl amine (40uL, 0.3 mmol), and DPPA (42uL, 0.2 mmol) were added sequentially to the same vial and the mixture was stirred at room temperature for 8 hours. The mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over $MgSO_4$, concentrated, and purified by flash column chromatography (SiO_2, eluting with 40% EtOAc/hexanes) to give azide **2.48b** as a foamy solid (14 mg, 39% for 3 steps): $[\alpha]_D^{23}$ +229.2 (*c* 0.82, $CHCl_3$); IR (thin film) 2940, 2102, 1646 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.35 (d, *J* = 2.0 Hz, 1H), 6.27 (d, *J* = 2.0 Hz, 1H), 4.93 (m, 1H), 4.72 (dd, *J* = 10.5, 3.0 Hz, 1H), 4.08 (dd, *J* = 11.5, 7.0 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 2.80-2.93 (m, 2H), 2.59-2.68 (m, 2H), 2.15-2.23 (m, 1H), 1.72-1.82 (m, 1H), 1.26-1.38 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 159.3, 157.7, 137.8, 117.3, 104.7, 97.3, 59.8, 55.5, 55.4, 55.3, 39.3, 30.4, 27.9, 27.0; LRMS (ESI+) calcd. for $C_{27}H_{22}N_4O_3$ (M+H) 455. Found 455.



Primary amine 2.49b: A mixture of azide (185 mg, 0.41 mmol) and triphenylphosphine (160 mg, 0.61 mmol) in THF (8 mL) and H_2O (0.5 mL) was stirred at 60 ^oC for 12 hours. The mixture was concentrated and purified by flash column chromatography (SiO_2, eluting with 5% MeOH/CH_2Cl_2) to give **2.49b** as a solid (170 mg, 87%): $[\alpha]_D^{23}$ +270.8 (*c* 0.62, $CHCl_3$); IR (thin film) 3357, 2937, 1610, 1590, 1456, 1433 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.34 (d, *J* = 2.5 Hz, 1H), 6.26 (d, *J* = 2.5 Hz, 1H), 4.92 (m, 1H), 4.71 (dd, *J* = 11.0, 3.0 Hz, 1H) , 3.79 (s, 3H), 3.77 (s, 3H), 3.33 (dd, *J* = 12.0, 6.5 Hz, 1H), 2.89-2.97 (m, 1H), 2.78-2.88 (m, 1H), 2.54-2.63 (m, 2H), 2.19-2.27 (m, 1H), 1.61-1.72 (m, 1H), 1.29-1.40 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 159.1, 157.7, 137.8, 117.9, 104.7, 97.2, 56.1, 55.4, 55.2, 52.4, 39.3, 30.6, 28.6, 28.2; LRMS (ESI+) calcd. for $C_{27}H_{29}N_2O_3$ (M+H) 429. Found 429.

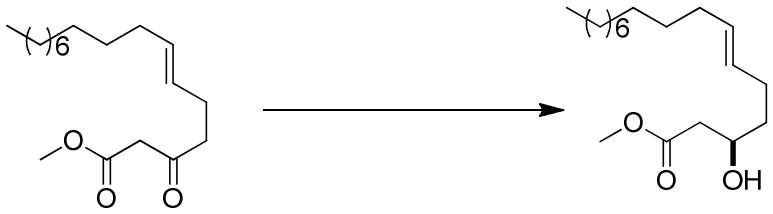


Primary bromide 2.51: To a solution of allylic alcohol (1.0 g, 5.0 mmol) and PPh_3 (1.38 g, 5.3 mmol) in dichloromethane (15 mL) at 0 °C was added NBS (1.05 g, 5.8 mmol) in one portion. The reaction mixture was stirred at °C for 1 hour. The reaction mixture was then left to warm up to room temperature and stirred for another 1 hour. Hexane was added to the mixture and some white precipitate showed up. The mixture was then passed through a silicon gel plug and the filtrate was concentrated to give the bromide **2.51** as a colorless oil (1.27g, 96%): IR (thin film) 2957, 2925, 1673 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.67-5.82 (m, 2H), 3.94 (d, *J* = 7.5 Hz, 2H), 2.05 (m, 2H), 1.33-1.41 (m, 2H), 1.10-1.33 (m, 14H), 0.88 (t, *J* = 6.5Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.9, 126.3, 33.8, 32.2, 32.0, 29.8, 29.7, 29.6, 29.5, 29.3, 28.9, 22.8, 14.2; LRMS (ESI+) calcd. for $C_{13}H_{26}Br$ (M+H) 261. Found 261.



Ketoester 2.52: To a suspension of NaH (132 mg, 3.3 mmol) in THF (5 mL) at 0 °C was added methyl acetoacetate (383 mg, 3.3 mmol) and the mixture was stirred at 0 °C for 15 min before n-butyl lithium was added dropwise. After the addition, the mixture was stirred at 0 °C for another 15 min before the solution of bromide (608 mg, 2.3 mmol) in THF (0.5 mL) was added to the reaction mixture. The reaction was then left to warm up to room temperature, stirred at room temperature for 1 hour, quenched with sat. NH_4Cl,

extracted with ethyl ether, dried over $MgSO_4$, concentrated to give a oily crude, which was purified by flash column chromatography, eluting with 5% EtOAc/hexanes, to give the ketoester **2.52** as a white solid (517 mg, 76%): IR (thin film) 2957, 2928, 2854, 1747, 1720, 1649, 1616, 1462 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.24-5.54 (m, 2H), 3.70 (s, 3H), 3.43 (s, 2H), 2.58 (t, *J* = 7.2 Hz, 2H), 2.25 (m, 2H), 1.95 (m, 2H), 1.14-1.38 (m, 16H), 0.86 (t, *J* = 6.6Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 167.7, 132.1, 127.7, 52.4, 49.1, 43.0, 32.6, 32.0, 29.7, 29.6, 29.5, 29.4, 29.3, 26.6, 22.8, 14.2; LRMS (ESI+) calcd. for $C_{18}H_{33}O_3$ (M+H) 297. Found 297.

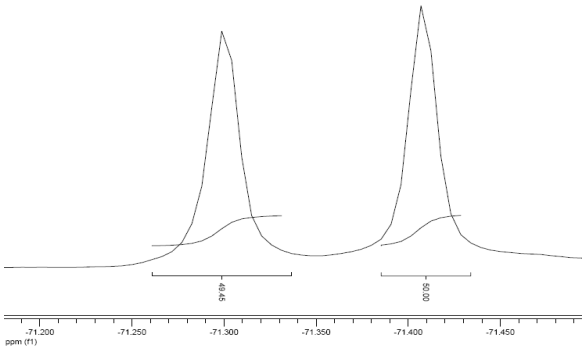


Secondary alcohol 2.53: A vial containing the reaction mixture of newly prepared catalyst (R)-BinapRuBr$_2$ (2.5 mg, 0.5% eq.) and ketoester (172 mg, 0.58 mmol) in MeOH (0.3 mL) was placed in a hydrogen bomb, which was placed in an oil bath pre-warmed to 80 °C. Hydrogen gas was purged through the hydrogen bomb for 5 min, the pressure of hydrogen was then raised to 6 bars, and the mixture began to stir. The stirring was continued for 50 min and reaction was stopped. The reaction mixture was diluted with dichloromethane, passed through a pad of silica gel, concentrated, and purified by flash column chromatography (SiO_2, eluting with 5% EtOAc/hexanes) to

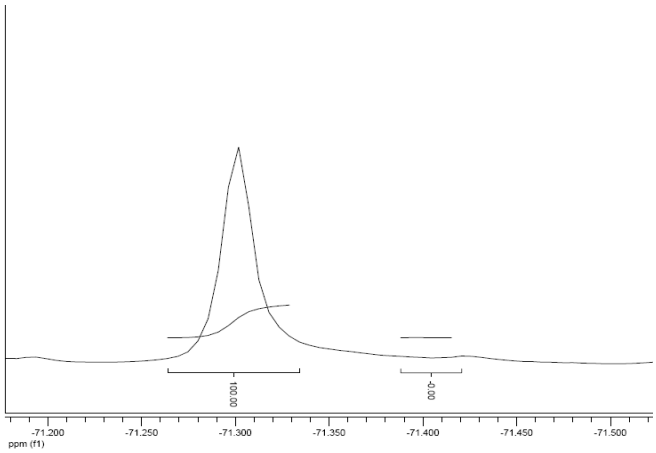
give the alcohol **2.53** as a solid (149 mg, 85%) and also unreacted starting material (24 mg, 14%) : $[\alpha]_D^{23}$ -30.0 (*c* 0.45, $CHCl_3$) IR (thin film) 2919, 2851, 1714, 1471, 1172 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.42 (m, 2H), 4.01 (m, 1H), 3.71 (s, 3H), 2.84 (d, *J* = 4.2 Hz, 1H), 2.36-2.58 (m, 2H), 1.93-2.25 (m, 3H), 1.40-1.65 (m, 2H), 1.10-1.40 (m, 16H), 0.88 (t, *J* =6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 131.5, 129.2, 67.6, 51.8, 41.2, 36.4, 32.7, 32.0, 29.7 (3C), 29.6, 29.5, 29.3, 28.7, 22.8, 14.2; LRMS (ESI+) calcd. for $C_{13}H_{25}BrLi$ (M+Li) 305. Found 305.

•Enantiomeric purity determination by Mosher ester analysis of alcohol (^{19}F NMR, CDCl3)

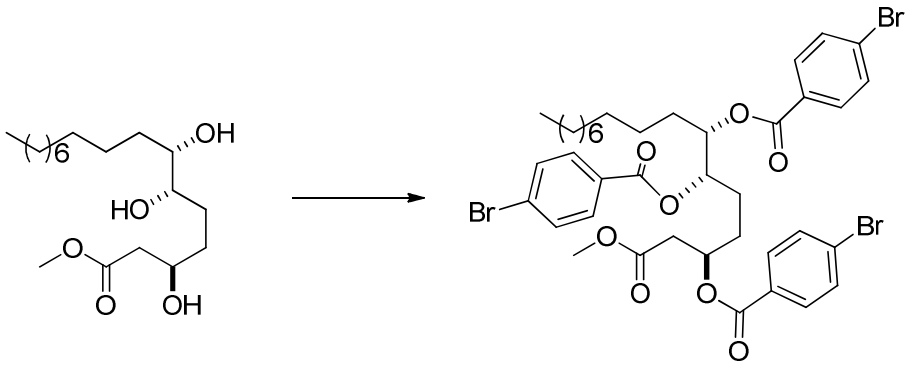
a) racemic



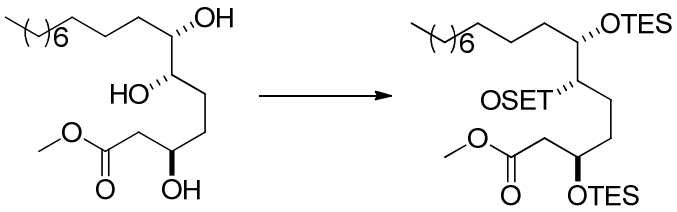
b) optically active



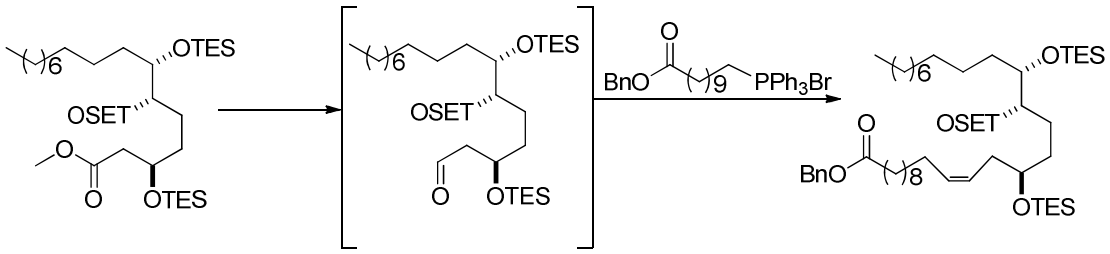
Triol 2.54: To a vial charged with AD-mix-alpha (530 mg, 0.74 mmol) and $MeSO_4NH_2$ (70 mg, 0.74 mmol) was added t-Butyl alcohol (1.5 mL) and water (1.5 mL). The mixture was stirred at room temperature until the mixture turned a yellow-brownish homogeneous solution. The mixture was then cooled to 0 °C and the alkene (147 mg, 0.49 mmol) was added to the reaction mixture. The reaction was then left to warm up to room temperature and stirred at room temperature for 24 hours. The reaction was then quenched by addition of sat. Na_2SO_3, dried *in vacuo*, and purified by flash column chromatography, eluting with 80% EtOAc/hexanes, to give the triol **2.54** as a white solid (123 mg, 76%) and some starting material (30 mg, 20%) was also recovered. $[\alpha]_D^{23}$ -19.5 (*c* 1.5, MeOH) IR (thin film) 3431, 2928, 2857, 1732, 1640, 1456 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 4.05 (m, 1H), 3.67 (s, 3H), 3.37 (m, 2H), 2.39-2.54 (m, 2H), 1.70 (m, 2H), 1.40-1.52 (m, 6H), 1.24-1.40 (m, 16H), 0.89 (t, *J* =7.0Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 173.9, 75.5, 75.3, 52.0, 43.3, 34.8, 33.9, 33.0, 30.9, 30.8 (3C), 30.7, 30.5, 30.2, 27.1, 23.8, 14.5; LRMS (ESI+) calcd. for $C_{18}H_{36}O_5Li$ (M+Li) 339. Found 339.



Tribenzoate 2.55: Pyridine (0.5 mL) was added into a vial charged with the triol (12 mg, 0.036 mmol) and 4-bromobenzoyl chloride (47 mg, 0.21 mmol), and DAMP (2 mg). The white mixture was stirred at 23 ^{o}C for 6 hours. The mixture was then poured into cold water, extracted with ethyl acetate, dried over $MgSO_4$, concentrated to give a crude oil, purified to give a solid (19 mg, 61%), which was crystallized from ethyl ether to give single crystals for X-ray analysis:$[\alpha]_D^{23}$ -1.4 (*c* 2.8, $CHCl_3$) IR (thin film) 3422, 2928, 2851, 1729, 1720, 1696,1649, 1261 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74-7.86 (m, 6H), 7.48-7.57 (m, 6H), 5.54 (m, 1H), 5.33 (m, 2H), 3.60 (s, 3H), 2.73 (dd, *J* = 15.5, 7.0 Hz, 1H), 2.61 (dd, *J* = 15.5, 6.0 Hz, 1H), 1.83 (m, 4H), 1.63 (m, 3H), 1.24-1.33 (m, 15H), 0.86 (t, *J* =7.0Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 165.4, 165.1, 131.9, 131.8 (2C), 131.3, 131.2, 131.1, 128.7, 128.6 (2C), 128.5, 128.4 (2C), 74.5, 74.3, 71.0, 52.0, 39.1, 32.0, 30.8, 29.9, 29.6, 29.5, 29.4 (3C), 26.8, 25.2, 22.7, 14.2; LRMS (ESI+) calcd. for $C_{39}H_{45}Br_3O_8Li$ (M+Li) 885. Found 885.



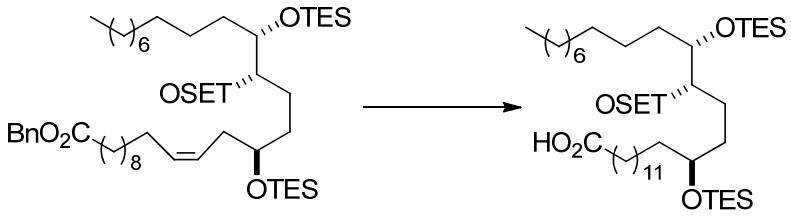
TES protected triol 2.56: To a solution of triol (0.92 g, 2.8 mmol) , TESCl (2.5 g, 16.6 mmol), and DMAP (34 mg, 0.28 mmol) in dichloromethane (40 mL) at 0 °C was added triethylamine (2.7 mL, 19.6 mmol) dropwise. The reaction mixture was then allowed to warm up to room temperature and stirred for 12 h. The reaction was cooled down to 0 °C, quenched with methanol, diluted with ether, washed with water and then brine, dried over $MgSO_4$, concentrated, and purified by flash column chromatography, eluting with 2% EtOAc/hexanes, to give the ester **2.56** as a colorless oil (1.83g, 98%).$[\alpha]_D^{23}$ -38.2 (*c* 0.68, $CHCl_3$); IR (thin film) 2957, 2922, 2880, 1744, 1092 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.13 (m, 1H), 3.66 (s, 3H), 3.50 (m, 2H), 2.45 (d, *J* = 6.5 Hz, 2H), 1.71 (m, 2H), 1.54-1.64 (m, 1H), 1.41-1.50 (m, 1H), 1.33-1.40 (m, 1H), 1.12-1.32 (m, 17H), 0.91-10.01 (m, 27H), 0.86 (t, *J* = 6.5 Hz, 3H), 0.56 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 76.1, 75.6, 70.1, 51.6, 42.8, 35.5, 32.1, 30.2, 29.9, 29.7, 29.8 (m), 29.7, 29.5, 26.8, 26.2, 22.8, 14.3, 7.1 (m), 6.9, 5.3, 5.2 (m), 5.0; LRMS (ESI+) calcd. for $C_{36}H_{78}O_5Si_3Li$ (M+Li) 681. Found 681.



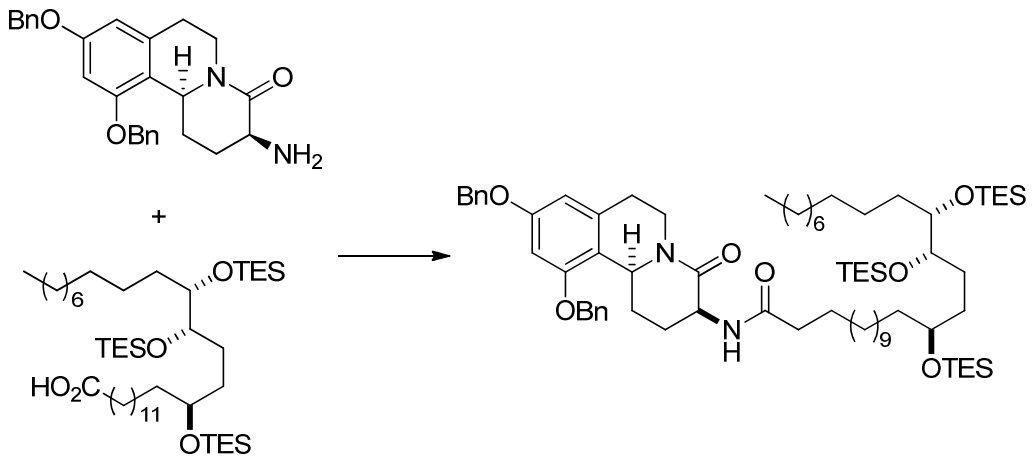
Benzyl ester 2.59: To a solution of ester (533 mg, 0.79 mmol) in dichloromethane (5 mL) at -78 °C was added a solution DIBAL (0.18 mL, 1.0 mmol) in dichloromethane (5 mL) dropwise. The reaction mixture was stirred at -78 °C for 3 hours and then quenched by dropwise addition of methanol before warming up to room temperature slowly. The reaction was then added with 1M Rochelle's salt and pH 7 buffer, stirred overnight, extracted with dichloromethane, dried over $MgSO_4$, and concentrated to give the aldehyde as a yellowish oil, which was used for the next step directly without purification (478 mg, 97%).

To a suspension of the phosphonium salt (137 mg, 0.33 mmol) in THF (1.5 mL) at -78 °C was added KHMDS (0.5M in THF, 0.42 mL, 0.21 mmol) dropwise. The resulted orange mixture was stirred at 0 °C for 1 h, and cooled back to -78 °C before the solution of aldehyde (40 mg, 0.063 mmol) in THF was added dropwise. The reaction mixture was then left to warm up to room temperature and stirred at room temperature for 12 h. The reaction mixture was quenched with water, extracted with ethyl ether, dried over $MgSO_4$, concentrated, and purified by flash column chromatography, eluting with 2% EtOAc/hexane, to give the olefin as a colorless oil (54 mg, 95%, only Z olefin was observed): $[\alpha]_D^{23}$ -22.7 (*c* 0.79, $CHCl_3$); IR (thin film) 2951, 2928, 2854, 1741, 1456,

1092 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (m, 5H), 5.39 (m, 2H), 5.11 (s, 2H), 3.63 (m, 1H), 3.54 (m, 2H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.20 (t, *J* = 1.5Hz, 2H), 2.02 (m, 2H), 1.57-1.80 (m, 5H), 1.40-1.50 (m, 1H), 1.10-1.36 (m, 30H), 0.93-0.98 (m, 27H), 0.88 (t, *J* = 6.5Hz, 3H), 0.53-0.62 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 136.3, 131.6, 128.7, 128.3, 128.2, 125.9, 76.3, 75.7, 73.2, 66.2, 35.7, 34.7, 34.5, 32.1, 30.3, 30.0, 29.8 (m), 29.7 (m), 29.6 (m), 29.5 (m), 29.4 (m), 29.3, 27.6, 26.8, 26.7, 25.1, 22.8, 14.3, 7.1 (m), 7.0, 5.3, 5.2 (m), 5.1; LRMS (ESI+) calcd. for $C_{53}H_{102}O_5Si_3Li$ (M+Li) 909. Found 909.

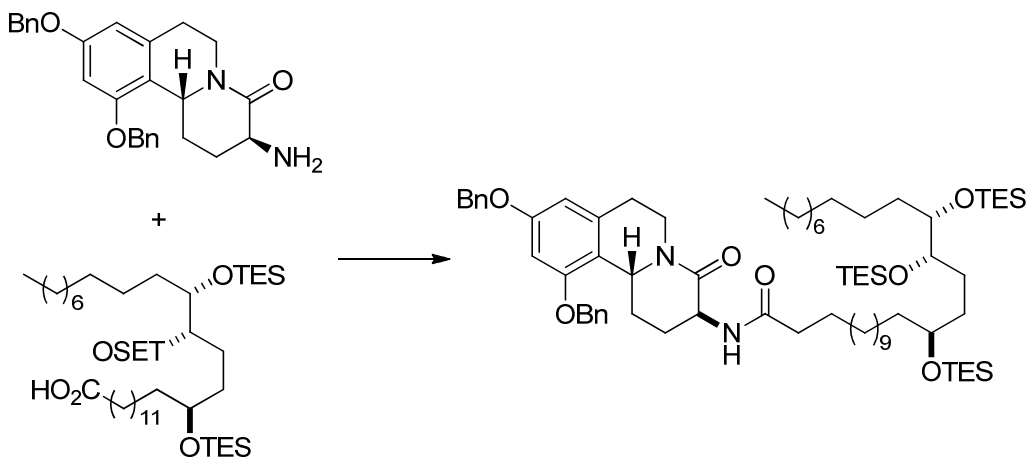


Acid 2.60: A mixture of benzyl ester (173 mg, 0.19 mmol), Pd/C (50 mg, 10%), and 2,6-lutidine (0.045 mL, 0.38 mmol) in EtOH (1 mL) was stirred under hydrogen (10 atm) for 5 hours. The mixture was then filtered through a pad of silica gel and concentrated to give the acid as a colorless oil (147 mg, 95%), which was used immediately in the next step without further purification.



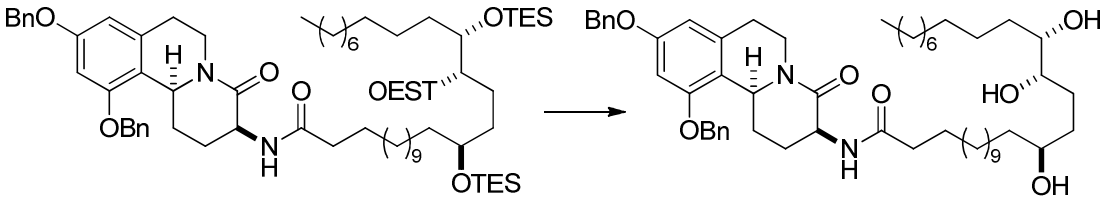
Amide 2.61a: A mixture of amine **(**46 mg, 0.11 mmol), acid (89 mg, 0.11 mmol), HOBt (18 mg, 0.13 mmol), EDCI (26 mg, 0.13 mmol), and NEt_3 (0.025 mL, 0.18 mmol) in CH_2Cl_2 (1.6 mL) was stirred at room temperature for 24 hours. The mixture was then poured into water, extracted with EtOAc, dried over $MgSO_4$, concentrated, and purified by flash column chromatography (SiO_2, eluting with 30% EtOAc/hexanes) to give the amide (88 mg, 65%) as a clear oil: $[\alpha]_D^{23}$ -62.5 (*c* 0.66, $CHCl_3$); IR (thin film) 3304, 2954, 1640, 1607 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.30 (m, 10H), 6.80 (d, *J* = 5.0 Hz, 1H), 6.50 (d, *J* = 2.5 Hz, 1H), 6.37 (d, *J* = 2.5 Hz, 1H), 5.09 (d, J=2.5 Hz, 2H), 4.99 (s, 2H), 4.73 (m, 1H), 4.54 (m, 1H), 3.60 (m, 1H), 3.51 (m, 2H), 3.08 (m, 1H), 2.64-2.88 (m, 4H), 2.48 (m, 1H), 2.25 (t, *J* = 7.0 Hz, 2H), 1.54-1.76 (m, 8H), 1.10-1.50 (m, 38H), 0.95 (t, *J* = 7.5 Hz, 27H), 0.88 (t, *J* = 6.5H, 3H), 0.52-0.62 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 170.6, 158.6, 156.0, 137.3, 136.8, 136.5, 128.9, 128.8, 128.3, 128.2, 127.6, 127.2, 117.3, 105.9, 99.1, 76.3, 75.7, 73.1, 70.3, 70.2, 48.9, 48.8, 39.0, 37.4, 36.9, 35.0, 32.0, 30.2, 30.0, 29.9, 29.8 (3C), 29.7 (3C), 29.6, 29.5 (2C), 29.4,

28.6, 26.8, 26.5, 25.9, 25.7, 25.3, 22.8, 14.2, 7.1, 7.0, 5.3, 5.2; LRMS (ESI+) calcd. for $C_{73}H_{125}N_2O_7Si_3$ (M+H) 1225. Found 1225.



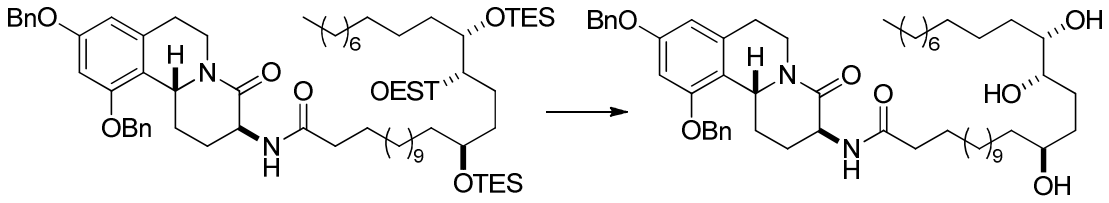
Amide 2.61b: 2.61b was obtained by following the same procedure **(**75 mg, 54%): $[\alpha]_D^{23}$ +48.0 (*c* 0.62, $CHCl_3$); IR (thin film) 3304, 2954, 1640, 1607 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43-7.31 (m, 10H), 6.50 (d, *J* = 2.5 Hz, 1H), 6.37 (d, *J* = 2.5 Hz, 1H), 6.30 (d, *J* = 4.0 Hz, 1H), 5.09-4.98 (m, 4H), 4.88-4.95 (m, 1H), 4.79 (dd, *J* = 3.0, 11.0 Hz, 1H), 4.22 (m, 1H), 3.60 (m, 1H), 3.52 (m, 2H), 3.08 (m, 1H), 2.82-2.92 (m, 1H), 2.54-2.68 (m, 3H), 2.22 (dd, *J* = 7.0, 9.0 Hz, 2H), 1.56-1.88 (m, 8H), 1.38-1.56 (m, 4H), 1.12-1.36 (m, 34H), 0.90-0.98 (m, 27H), 0.86-0.90 (t, 7.5, 3H), 0.52-0.86 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 169.2, 158.6, 157.1, 138.1, 137.0, 136.7, 129.0, 128.9, 128.4, 127.8, 127.5, 118.5, 106.3, 99.4, 76.5, 75.9, 73.3, 70.5, 70.4, 56.5, 52.3, 39.9, 37.6, 37.1, 35.2, 32.2, 30.9, 30.4, 30.2, 30.1, 30.0 (4C), 29.9 (2C), 29.8, 29.7 (2C), 29.6,

28.2, 27.6, 27.0, 26.7, 26.0, 25.9, 23.0, 14.5, 7.3, 7.2, 5.5, 5.4; LRMS (ESI+) calcd. for $C_{73}H_{124}N_2O_7Si_3Na$ (M+Na) 1247. Found 1247.

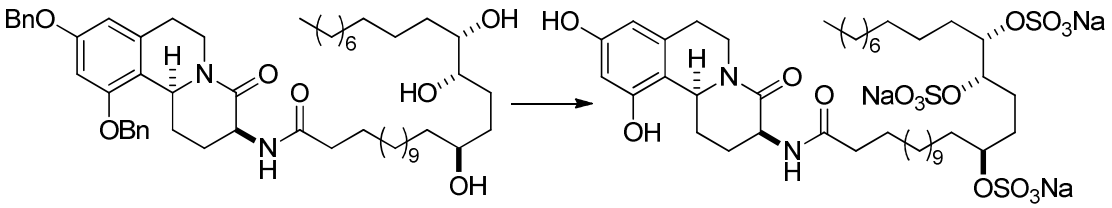


Triol 2.62a: A mixture of amide (80 mg, 0.065 mmol) in a mixing solvent of THF (0.3 mL), HOAc (0.45 mL), and H_2O (0.15 mL) was stirred at room temperature for 3 hours. The volatile was then removed *in vacuo* and the crude was purified by flash column chromatography (SiO_2, eluting with 5% MeOH/CH_2Cl_2) to give triol (57 mg, 99%) as a clear oil: $[\alpha]_D^{23}$ -22.8 (*c* 0.65, $CHCl_3$); IR (thin film) 3307, 2919, 2848, 1667, 1646, 1610, 1465 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44-7.30 (m, 10H), 6.49 (d, *J* = 2.5 Hz, 1H), 6.45 (d, *J* = 5.0 Hz, 1H), 6.36 (d, *J* = 2.5 Hz, 1H), 5.09 (d, J=2.5 Hz, 2H), 4.97-5.05 (m, 4H), 4.90 (m, 1H), 4.79 (m, 1H), 4.22 (m, 1H), 3.64 (m, 1H), 3.42 (m, 2H), 2.63-2.87 (m, 4H), 2.48 (m, 1H), 2.25 (t, *J* = 7.5, 2H), 1.60-1.76 (m, 8H), 1.18-1.60 (m, 4H), 1.12-1.36 (m, 42H), 0.87 (t, 7.5H, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 170.8, 158.7, 156.1, 137.4, 136.9, 136.7, 129.0, 128.9, 128.4, 128.3, 127.7, 127.3, 117.3, 106.0, 99.3, 74.8, 74.6, 72.1, 70.3 (2C), 49.0 (2C), 39.1, 37.7, 37.0, 33.7, 33.3, 32.1, 29.9 (2C),

29.8 (2C), 29.7 (2C), 29.6, 29.5 (2C), 29.4, 28.7, 25.9 (2C), 25.4, 22.9; LRMS (ESI+) calcd. for $C_{55}H_{82}N_2O_7Li$ (M+Li) 889. Found 889.

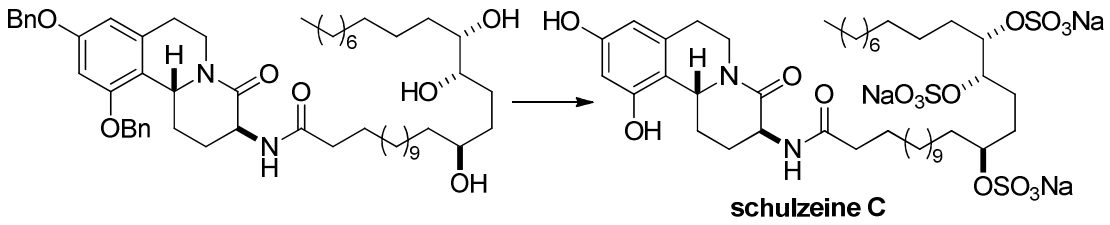


Triol 2.62b: 2.62b was obtained by following the same procedure **(**42 mg, 99%): $[\alpha]_D^{23}$ +34.8 (*c* 0.41, $CHCl_3$); IR (thin film) 3309, 2916, 2846, 1664, 1644, 1615, 1467 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44-7.30 (m, 10H), 6.80 (d, *J* = 5.5 Hz, 1H), 6.47 (d, *J* = 2.5 Hz, 1H), 6.38 (d, *J* = 2.5 Hz, 1H), 5.09 (d, J=2.5 Hz, 2H), 4.99 (s, 2H), 4.93 (m, 1H), 4.72 (m, 1H), 4.54 (m, 1H), 3.66 (m, 1H), 3.43 (m, 2H), 3.06 (m, 1H), 2.86 (m, 1H), 2.63 (m, 1H), 2.52 (m, 1H), 2.21 (t, *J* = 7.5, 2H), 1.60-1.76 (m, 5H), 1.38-1.60 (m, 9H), 1.12-1.36 (m, 32H), 0.87 (t, 7.5H, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 169.1, 158.4, 157.0, 138.0, 136.9, 136.6, 128.9 (2C), 128.3 (2C), 127.8, 127.4, 118.3, 106.2, 99.3, 74.6, 72.0, 70.4, 70.3, 56.4, 52.1, 39.8, 37.7, 36.9, 33.7, 33.3, 32.1, 30.8, 30.0, 29.9 (2C), 29.8, 29.7 (3C), 29.6, 29.5 (2C), 28.1, 27.4, 25.9 (2C), 25.8, 22.9, 14.4; LRMS (ESI+) calcd. for $C_{55}H_{82}N_2O_7Li$ (M+Li) 889. Found 889.



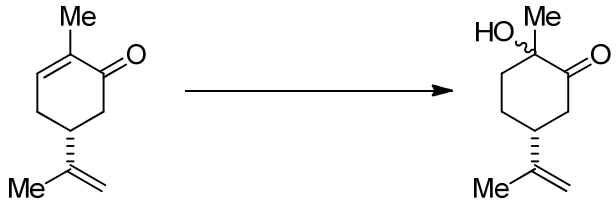
schulzeine B

Schulzeine B: A mixture of triol (50 mg, 0.057 mmol) and sulfur trioxide pyridine complex (135 mg, 0.85 mmol) in DMF (1.5 mL) was stirred at room temperature under nitrogen for 48 h. The mixture was then quenched with sat. $NaHCO_3$ solution and dried under a stream of nitrogen. The crude was passed through a pad of silica gel by eluting with 20% methanol in EtOAc slowly to give an essentially pure product, which was immediately dissolved in a vial charged with MeOH (0.5 mL) and Pd/C (6.7 mg, 10%). Hydrogen balloon was inserted to the vial and the mixture was stirred for 4h. The mixture was then passed through silica gel pad to remove the catalyst and concentrated to give **Schulzeine B (**45 mg, 82% over 2 steps) as a white powder: $[\alpha]_D^{23}$ -23.5 (*c* 0.68, MeOH); IR (thin film) 2925, 2851, 1633, 1599 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.21 (d, *J* = 2.5 Hz, 1H), 6.14 (d, *J* = 2.5 Hz, 1H), 4.87 (dd, *J* = 11.5, 4.0 Hz, 1H), 4.63-4.70 (m, 4H), 4.36 (dt, *J* = 10.5, 5.5 Hz, 1H), 2.68-2.80 (m, 2H), 2.52-2.68 (m, 2H), 2.23-2.34 (m, 3H), 1.92-2.04 (m, 2H), 1.51-1.82 (m, 9H), 1.38-1.47 (m, 3H), 1.22-1.48 (m, 32H), 0.87 (t, *J* = 7.5H, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 171.8, 157.9, 156.2, 138.3, 115.0, 107.2, 101.9, 81.2, 80.0, 79.8, 51.6, 49.5, 40.4, 37.0, 35.5, 31.7, 30.9, 30.8 (3C), 30.7 (2C), 30.6, 30.5, 30.4, 30.3, 29.8, 29.0, 26.9, 26.0, 25.9, 25.8, 23.7, 14.4; LRMS (MALDI+) calcd. for $C_{41}H_{67}N_2Na_4O_{16}$ (M+Na) 1031. Found 1031.

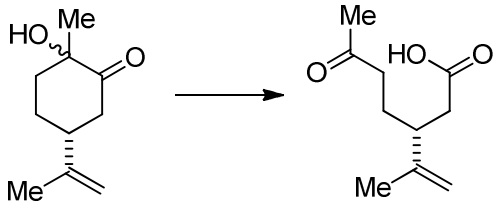


schulzeine C

Schulzeine C was obtained by following the same procedure as **Schulzeine B** (23 mg, 75% over 2 steps): $[\alpha]_D^{23}$ +38.0 (*c* 0.42, MeOH); IR (thin film) 2922, 2851, 1689, 1611 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.20 (d, *J* = 2.5 Hz, 1H), 6.10 (d, *J* = 2.5 Hz, 1H), 4.77-4.85 (m, 2H), 4.62-4.73 (m, 2H), 4.33-4.43 (m, 1H), 4.29 (dd, *J* = 12.0, 6.5 Hz, 1H), 3.09 (dq, *J* = 14, 2.5 Hz, 1H), 2.60-2.79 (m, 2H), 2.50-2.60 (m, 1H), 2.25 (dt, *J* = 7.0, 4.0 Hz, 2H), 2.12 (m, 1H), 1.89-2.04 (m, 3H), 1.52-1.84 (m, 8H), 1.21-1.52 (m, 38H), 0.89 (t, *J* = 7.5H, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 169.3, 156.5, 155.5, 137.4, 114.6, 106.4, 100.9, 80.1, 78.8, 78.7, 56.0, 50.8, 39.6, 35.9, 31.9, 30.6, 29.8, 29.7 (2C), 29.6 (3C), 29.5, 29.4, 29.3, 29.2, 29.1, 28.6, 28.2, 27.3, 25.8, 25.7, 24.8, 24.7, 22.6, 13.3; LRMS (MALDI+) calcd. for $C_{41}H_{67}N_2Na_4O_{16}$ (M+Na) 1031. Found 1031.



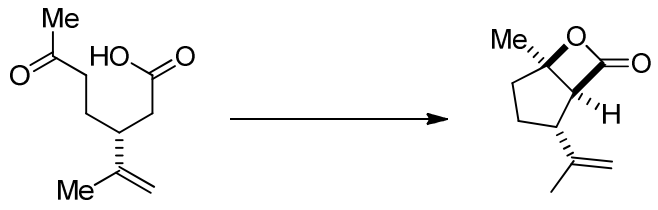
α-Hydroxy ketone 3.18: To a solution of (*R*)-carvone (3.6 g, 24 mmol) and $Mn(dpm)_3$ (435 mg, 0.72 mmol, 0.03 equiv) in *i*-PrOH (120 mL) at 0 °C was added phenylsilane (3.9 g, 4.4 mL, 36 mmol, 1.5 equiv) dropwise over 2 min under an oxygen atmosphere (balloon). The reaction mixture was stirred at 0 ^{o}C for 30 min, then ambient temperature (23 ^{o}C) for 2 h. After removing the oxygen balloon, triethylphosphite (6.0 g, 36 mmol, 1.5 equiv) was added. The mixture was stirred for 30 min, diluted with ethyl acetate, washed with saturated sodium bicarbonate and then brine. The organic layer was dried over sodium sulfate and purified by flash column chromatography (SiO_2, eluting with 10 → 40% EtOAc/hexanes) to afford the ketone as a 2:1 mixture of diastereomers (2.55 g, 63%). NMR data matched that previously reported.[3]



Ketoacid 3.19: A mixture of α-hydroxy ketone (7.36 g, 44 mmol) and periodic acid (20 g, 88 mmol, 2.0 equiv) in Et_2O (200 mL) was vigorously stirred at ambient temperature (23 ^{o}C) until reaction completion (~10 min) as monitored by TLC. The reaction mixture was diluted with ethyl acetate and washed with brine followed by saturated $Na_2S_2O_3$.

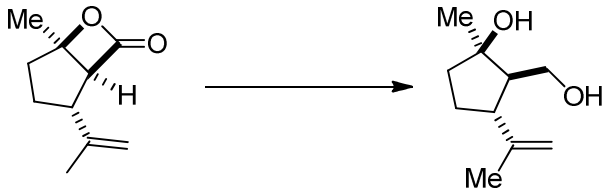
[3] (a) Blair, M.; Tuck, K. L. *Tetrahedron: Asym.* **2009,** *20*, 2149-2153. (b) Kido, F.; Yamaji, K.; Sinha, S. C.; Abiko, T.; Kato, M. *Tetrahedron* **1995,** *51*, 7697-714.

The organic layer was then dried over sodium sulfate and concentrated to afford ketoacid as a colorless liquid (7.71 g, 95%). NMR data matched that previously reported and purity was established by ^{1}H NMR (500 MHz).[4] The crude material was of sufficient purity to be used in the next step without further purification.

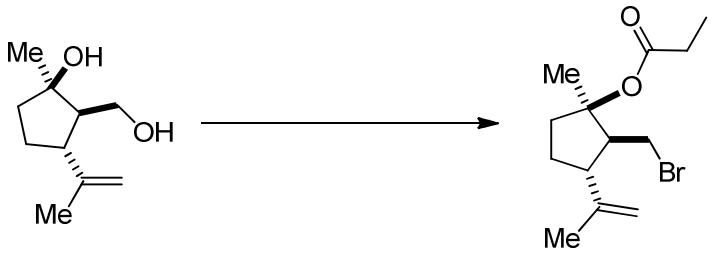


Bicyclic-β-lactone 3.12: To a mixture of TsCl (22 g, 116 mmol, 1.5 equiv), 4-PPY (11.4 g, 77.2 mmol, 1.0 equiv), and diisopropylethyl amine (53.8 mL, 309 mmol, 4.0 equiv) in CH_2Cl_2 (150 mL) was added a solution of ketone **12** (14.2 g, 77.2 mmol) in CH_2Cl_2 (20 mL) dropwise (over 2 min). The reaction mixture was stirred at ambient temperature (23 ^oC) for 10 min and then powdered anhydrous K_2CO_3 (32 g, 232 mmol, 3.0 equiv) was added in one portion. The reaction turned dark brown after stirring at ambient temperature (23 ^oC) for 2 h. The reaction was diluted with hexanes and passed through a pad of silica gel to remove the solids. Concentration by rotary evaporation and purification of the residue by flash column chromatography (SiO_2, eluting with 20→50% EtOAc/hexanes) gave β-lactone as a colorless liquid (10.6 g, 83%), which upon standing became a white solid. $[\alpha]_D^{23}$ +33.8 (*c* 1.4, $CHCl_3$); IR (thin film) 2975, 2937, 1818, 1643 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.76 (s, 1H), 4.41 (s, 1H), 3.47 (s, 1H), 2.84 (d, *J* = 7.0 Hz, 1H), 1.99-2.12 (m, 2H), 1.84-1.92 (m, 1H), 1.73 (s, 3H), 1.68 (s, 3H); 1.62-1.67 (m, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 145.1, 109.8, 87.9, 63.0, 45.7, 33.7, 28.3, 22.5, 21.6; HRMS (ESI+) calcd. for $C_{10}H_{15}O_2$ (M+H) 167.1072. Found 167.1079.

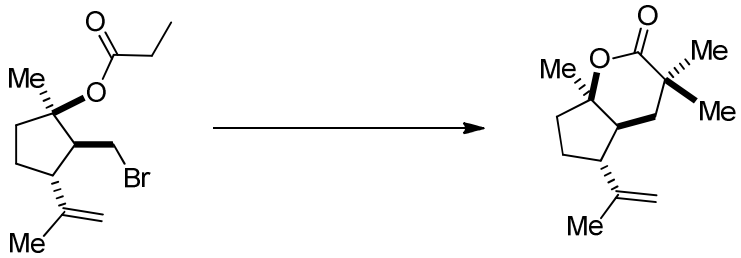
[4] Pinheiro, L.; Marsaioli, A. J. *J. Mol. Cat. B: Enz.* **2007,** *44*, 78-86.



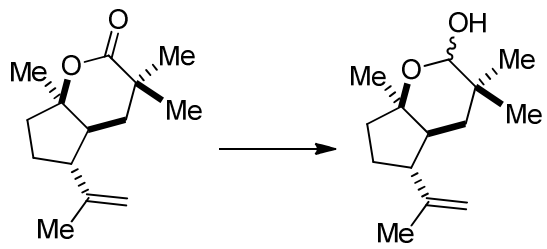
Diol 3.21: To a solution of β-lactone (5.14 g, 31 mmol) in CH_2Cl_2 (200 mL) cooled to -78 °C was added DIBAl-H (16.5 mL, 93 mmol, 3.0 equiv) dropwise over 2 min. The reaction mixture was warmed to 0 °C and stirred for an additional 30 mins. The reaction was quenched by careful and slow addition of 3 mL H_2O at 0 °C. Stirring was continued at the same temperature for 30 min, and then 6 mL 20% aq. NaOH was added and stirring was continued at ambient temperature (23 ^oC) for 3 h. The resulting white precipitate was removed by filtration through a pad of silica gel and the eluent was concentrated to afford diol (5.21 g, 99%) as a colorless oil. $[\alpha]_D^{23}$ -36.0 (*c* 1.0, $CHCl_3$); IR (thin film) 3357, 2966, 2875, 1643 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.77 (s, 1H), 4.74 (s, 1H), 3.90 (dd, *J* = 11.5, 3.0 Hz, 1H), 3.71 (dd, *J* = 11.5, 5.0 Hz, 1H), 3.44 (s, 1H), 3.34 (s, 1H), 2.88 (dd, *J* = 20.0, 9.0 Hz, 1H), 1.89-1.98 (m, 1H), 1.72-1.76 (m, 2H), 1.69 (s, 3H), 1.54-1.59 (m, 1H), 1.44-1.54 (m, 1H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.0, 110.8, 81.7, 60.7, 52.5, 46.9, 41.6, 28.4, 28.1, 19.4; HRMS (ESI+) calcd. for $C_{10}H_{18}O_2Li$ (M+Li): 177.1467. Found 177.1466.



Bromide 3.31: A mixture of diol (2.37 g, 13.9 mmol), TsCl (2.78 g, 14.6 mmol), and LiBr (1.33 g, 15.3 mmol) in freshly distilled pyridine (3.5 mL) was stirred at ambient temperature (23 ^{o}C) for 8 h. The reaction was then heated to 60 °C for 3 h. After cooling to ambient temperature (23 ^{o}C), $(EtCO)_2O$ (20 mL), triethylamine (10 mL), and DMAP (340 mg) was added and the reaction was stirred an additional 48 h. The reaction mixture was then diluted with EtOAc and washed with satd. $NaHCO_3$, followed by 1M HCl and brine. The organic layer was dried over sodium sulfate, concentrated, and purified by flash column chromatography (SiO_2, 0 → 20% EtOAc/hexanes) to afford the bromoester as a light yellow oil (3.16 g, 79%). $[\alpha]_D^{23}$ +40.0 (*c* 0.35, $CHCl_3$); IR (thin film) 2976, 2937, 2879, 1731, 1641 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.77 (s, 2H), 3.62 (t, *J* = 9.5, 1H), 3.37 (dd, *J* = 10.5, 2.5 Hz, 1H), 3.35-3.49 (m, 2H), 2.30 (dd, *J* = 15.0, 7.5 Hz, 2H), 2.00-2.80 (m, 1H), 1.88-1.98 (m, 1H), 1.74-1.82 (m, 1H), 1.70 (s, 6H), 1.40-1.52 (m, 1H), 1.06-1.14 (t, *J* = 7.5, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 145.5, 111.9, 88.8, 55.7, 52.0, 37.5, 30.1, 28.7, 28.2, 24.6, 19.0, 9.2. The parent molecular ion (M^+) could not be detected by available ionization methods.

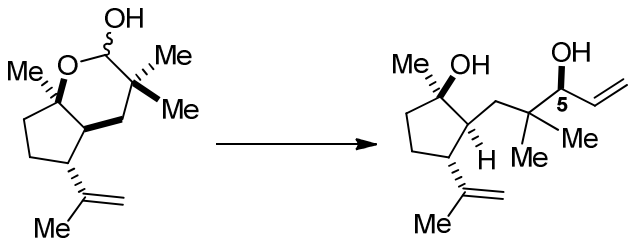


δ-Lactone 3.35: A solution of KHMDS (1M in THF, 43 mL, 43 mmol, 3.0 equiv) was added dropwise by syringe over 5 min to a cooled (-78 °C) THF (50 mL) solution of bromoester **8** (4.15 g, 14.4 mmol, 1.0 equiv). The reaction mixture was stirred for 30 min at -78 °C and then MeI (17.8 mL, 288 mmol, 20 equiv) was added. The mixture was warmed to ambient (23 ^{o}C) temperature, diluted with EtOAc, and washed with brine followed by saturated $Na_2S_2O_3$, dried over sodium sulfate, concentrated, and purified by flash column chromatography (SiO_2, 5 → 15% EtOAc/hexanes) to afford the lactone as a light yellow oil (2.68 g, 84%). $[\alpha]_D^{23}$ +75.0 (*c* 1.1, $CHCl_3$); IR (thin film) 3071, 2968, 2937, 2873, 1728, 1451 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.73 (d, *J* = 1.5 Hz, 1H), 4.71 (s, 1H), 2.45 (dd, *J* = 18.0, 8.0 Hz, 1H), 1.97-2.05 (m, 1H), 1.77-1.93 (m, 3H), 1.69(s, 3H), 1.59-1.66 (m, 1H), 1.44-1.52 (m, 1H), 1.43 (s, 3H), 1.24 (s, 6H), 1.11-1.22 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 145.7, 110.3, 90.3, 52.1, 43.0, 39.7, 38.7, 36.1, 28.7, 28.4, 27.5, 26.4, 20.2.; HRMS (ESI+) calcd. for $C_{14}H_{23}O_2$ (M+H): 223.1698. Found 223.1702.

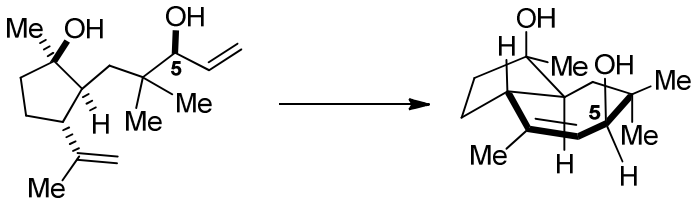


Lactol 3.36: To a solution of lactone (1.22 g, 5.5 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) cooled to -78 °C was added dropwise a solution of DIBAl-H, (1.36 mL, 7.7 mmol, 1.4 equiv) in THF (2 mL). The reaction mixture was stirred at -78 °C for 30 min and then MeOH (0.1 mL) was added carefully at -78 °C and stirred for an additional 30 min. The reaction was quenced by careful addition of 20% aq. NaOH (0.2 mL) at -78 ^{o}C and stirring was continued at this temperature for 8 h. The resulting white precipitate was

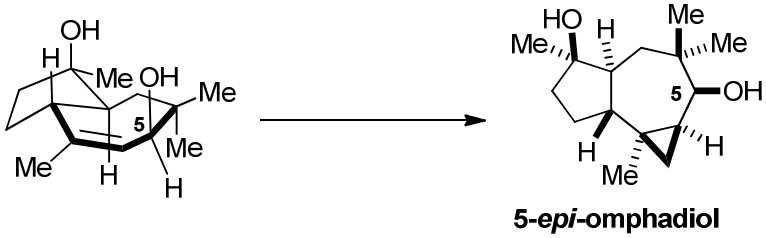
removed by filtration through a pad of silica gel and the eluent was concentrated to afford the lactol as a colorless liquid (1.21 g). This material was carried directly to the next step without further purification.



Diol 3.37: To a solution of freshly prepared lactol (1.21 g, 5.4 mmol) in THF (20 mL) cooled to -78 °C was added dropwise over 2 min, a solution of vinyl magnesium bromide (1M in THF, 16.2 mL, 16.2 mmol). After complete addition, the reaction mixture was warmed to 0 °C and stirred at the same temperature for 1 h. The mixture was then quenched with H_2O, warmed to ambient temperature, diluted with EtOAc, washed with brine, dried over sodium sulfate, concentrated, and purified by flash column chromatography (SiO_2, 20 $\rightarrow$ 50% EtOAc/hexanes) to afford the diol as a colorless oil (1.11 g, 80%). ^{1}H NMR (500 MHz) analysis of the crude reaction mixture revealed a dr >19:1. $[\alpha]_D^{23}$ +8.5 (*c* 0.7, $CHCl_3$); IR (thin film) 3320, 3074, 2962, 2873, 1641, 1462 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (ddd, *J* = 17.5, 10.5, 6.0 Hz, 1H), 5.22 (d, *J* = 17.5 Hz, 1H), 5.15 (d, *J* = 10.5 Hz, 1H), 4.72 (s, 1H), 4.71 (s, 1H), 3.82(d, *J* = 6.0 Hz, 1H), 3.65 (s, 1H), 2.19-2.26 (m, 1H), 1.99 (dd, *J* = 15.0, 7.0 Hz, 1H), 1.74-1.81 (m, 1H), 1.66-1.71 (m, 1H), 1.65(s, 3H), 1.44-1.49 (m, 1H), 1.35-1.40 (m, 1H), 1.33(s, 3H),), 0.97 (dd, *J* = 15.0, 7.0 Hz, 1H), 0.79 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.5, 137.8, 116.3, 111.8, 79.2, 78.5, 57.5, 46.6, 42.7, 39.2, 37.4, 30.6, 28.7, 24.1, 23.1, 18.6.; HRMS (ESI+) calcd. for $C_{16}H_{28}O_2Li$ (M+Li) 259.2249. Found 259.2260.



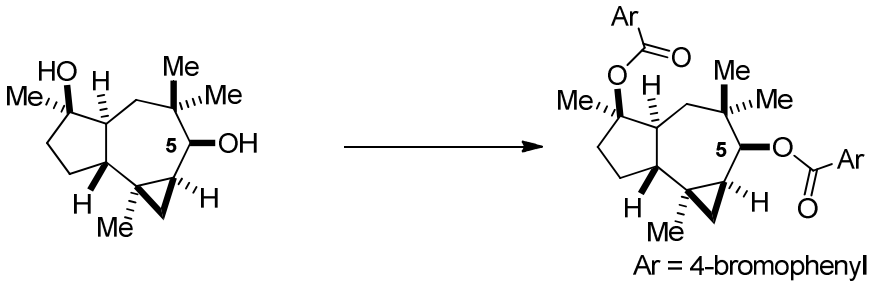
Allylic alcohol 3.38: A solution of dien (136 mg, 1 mmol) and Grubbs Generation II catalyst (21 mg, 0.03 mmol, 3 mol%) in toluene (40 mL) was heated to 90 °C under nitrogen for 3 h. The solvent was then removed under reduced pressure and the residue was purified by flash column chromatography (SiO_2, 20 → 50% EtOAc/hexanes) to afford allylic alcohol as an amorphous solid (222 mg, 99%). $[\alpha]_D^{23}$ +26.9 (*c* 0.5, $CHCl_3$); IR (thin film) 3409, 2962, 2867, 1557 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.47 (d, *J* = 5.5 Hz, 1H), 3.83 (d, *J* = 6.5 Hz, 1H), 2.92 (dd, *J* = 4.5, 6.5 Hz, 1H), 1.86-1.89 (m, 1H), 1.82(t, *J* = 13.0 Hz, 1H), 1.73 (s, 3H), 1.64-1.71 (m, 2H), 1.43-1.54 (m, 2H), 1.32-1.40 (m, 2H), 1.22-1.28 (m, 2H), 1.21 (s, 3H), 0.99 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5, 126.3, 80.3, 76.2, 64.8, 48.9, 46.1, 40.0, 36.6, 35.8, 28.7, 26.8, 26.1, 23.6; HRMS (ESI+) calcd. for $C_{16}H_{24}O_2Li$ (M+Li) 231.1936. Found 231.1932.



5-*epi*-omphadiol

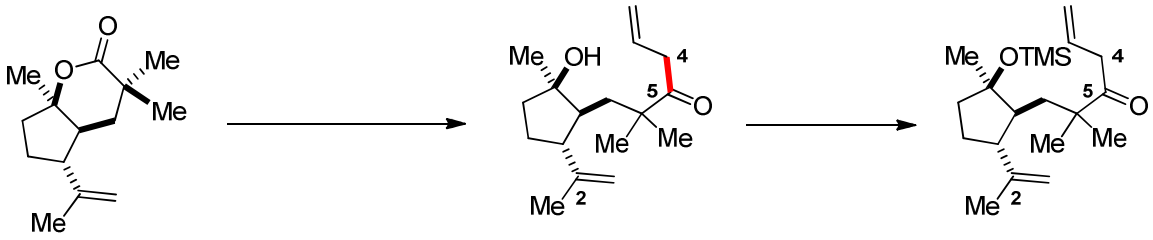
(+)-5-*epi*-omphadiol (3.39). To a solution of allylic alcohol (27.1 mg, 0.12 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) cooled to -30 °C was added diethyl zinc (62 μL, 0.6 mmol, 5.0 equiv) dropwise over 2 min. After stirring for 10 min, CH_2I_2 (68 *u*L, 0.84 mmol, 7.0 equiv) was added dropwise over 2 min and the reaction mixture was slowly warmed to 0°C and stirred at that temperature for an additional 2 h. The reaction was then quenched with H_2O, diluted with EtOAc, washed with 1M NaOH and brine , dried over sodium

sulfate, concentrated, and purified by flash column chromatography (SiO_2, eluting with 20 → 50% EtOAc/hexanes) to afford 5-*epi*-omphadiol as an amorphous solid (21.4 mg, 75%). $[\alpha]_D^{23}$ +57.2 (*c* 1.1, $CHCl_3$); IR (thin film) 3404, 2954, 1456, 1379 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.84 (d, *J* = 4.5 Hz, 1H), 1.81-1.89 (m, 1H), 1.72-1.80 (m, 1H), 1.62-1.69 (m, 2H), 1.55-1.62 (m, 2H), 1.44-1.54 (m, 1H), 1.46(s, 1H), 1.25-1.30 (m, 1H), 1.23 (s, 3H), 1.19 (dd, *J* = 23.0, 11.0 Hz, 1H), 1.06 (s, 3H), 1.01 (s, 3H), 0.99 (s, 3H), 0.62-0.68 (m, 2H), 0.42-0.47 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.1, 76.5, 47.6, 46.7, 41.5, 37.7, 35.5, 31.5, 27.0, 25.6, 24.2, 23.3, 20.8, 19.6, 18.1.; HRMS (ESI+) calcd. for $C_{15}H_{26}O_2Li$ (M+H): 245.2093, Found 245.2087.



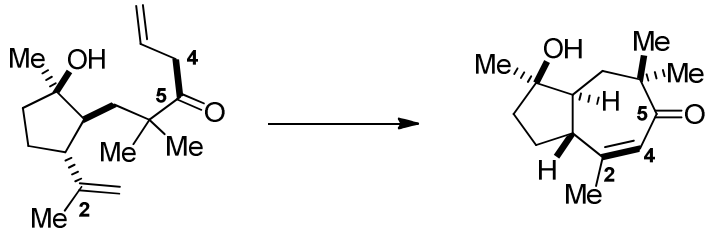
Bis-4-bromophenyl derivative of (+)-5-*epi*-omphadiol. To a solution of the diol (15.1 mg, 0.063 mmol, 1.0 equiv) in THF (1 mL) at 0 °C was added a solution of KHMDS (1M in THF, 0.32 mL, 0.32 mmol, 5.0 equiv) dropwise. After stirring for 30 min at 0 °C, a solution of *p*-BrPhCOCl (83 mg, 0.38 mmol, 6.0 equiv) in THF (0.5 mL) was added and stirring was continued at the same temperature for 3 h. The reaction mixture was then quenched with H_2O, diluted with EtOAc, washed with satd. $NaHCO_3$, dried over sodium sulfate, concentrated, and purified by flash column chromatography (SiO_2, 10 → 40% EtOAc/hexanes) to give the diester as a gummy solid (29.3 mg, 77%). This material was dissolved in a mixed solvent system of Et_2O/MeOH (v/v 1:1, 1 mL) and slow evaporation at ambient temperature (23 ^oC) gave crystals suitable for X-ray analysis; mp 81-82 ^oC (Et_2O/MeOH). $[\alpha]_D^{23}$ +91.2 (*c* 0.97, $CHCl_3$); IR (thin film) 2957, 1717, 1593, 1291, 1273 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.81-7.90 (m, 4H), 7.46-7.55 (m, 4H),

5.38 (d, *J* = 6.0 Hz, 1H), 2.73-2.80 (m, 1H), 1.92-2.09 (m, 2H), 1.80-1.88 (m, 1H), 1.71-1.75 (m, 2H),), 1.69 (s, 3H), 1.60-1.68 (m, 1H), 1.49-1.55 (m, 1H), 1.18 (s, 3H), 1.06 (s, 3H), 1.05 (s, 3H), 0.90 (ddd, *J* = 10.5, 9.5, 5.0 Hz, 1H), 0.60 (dd, *J* = 10.5, 5.0 Hz, 1H), 0.28 (t, *J* = 5.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 164.8, 132.0(2), 131.8(2), 131.1, 130.8(2), 130.6(2), 129.3, 128.1, 127.6, 92.8, 79.3, 50.2, 47.2, 37.4, 37.1, 36.8, 31.0, 25.0, 23.8, 23.5, 21.3, 20.8, 19.7, 19.2; HRMS (ESI+) calcd. for $C_{29}H_{32}Br_2ClO_4$ (M+Cl) 637.0356, Found 637.0335.



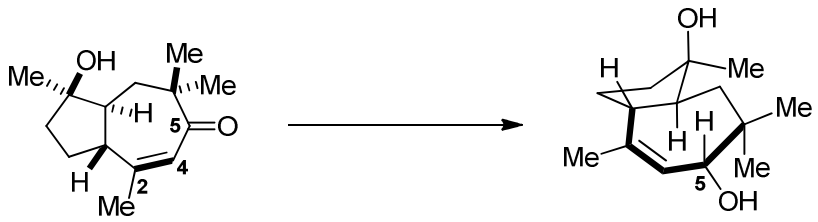
Enone: To a solution of allyl triphenyltin (260 mg, 0.66 mmol, 1.65 equiv) in Et_2O (2 mL) at 0 °C was added a solution of phenyl lithium (1.8 M in Bu_2O, 0.37 mL, 0.67 mmol, 1.65 equiv) dropwise. The mixture was warmed to ambient temperature (23 ^{o}C) and stirred for an additional 20 min. The resulting mixture containing a white precipitate was cooled to -78 °C, and a solution of the lactone (90 mg, 0.4 mmol) in Et_2O (0.5 mL) was added dropwise. After stirring for 40 min, the reaction was quenched with MeOH, diluted with EtOAc, passed through a pad of silica gel to remove the white precipitate, dried over sodium sulfate, concentrated, and purified by flash column chromatography (SiO_2, 0 → 60% EtOAc/hexanes) to afford diene **20** as a colorless liquid (79 mg, 74%). This diene exists as an equilibrium mixture of hydroxy ketone and δ-lactol, therefore to faciliate characterization, a portion of diene was converted to the corresponding TMS-ether ketone. However, the hydroxyketone could be carried directly to the ring-closing metathesis step. The TMS-ether ketone was prepared by dissolving a portion of diene (10 mg, 0.038 mmol) in MeCN (1 mL) and TMSCl (0.1 mL) and imidazole (100 mg)

were added. The mixture was stirred at ambient temperature for 8 h, quenched with MeOH, concentrated, and purified by flash column chromatography (SiO_2, eluting with 0 → 20% EtOAc/hexanes) to afford TMS ether as a colorless liquid (11.7 mg, 92%). $[\alpha]_D^{23}$ +74.3 (*c* 0.4, $CHCl_3$); IR (thin film) 2960, 2925, 1702, 1643, 1462 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.87-5.98 (m, 1H), 5.22 (m, 2H), 4.70 (m, 1H), 4.69 (m, 1H), 3.23-3.36 (d, *J* = 10.5 Hz, 2H), 2.39 (dd, *J* = 12.5, 9.0 Hz, 1H), 1.92-1.97 (m, 1H), 1.79-1.89 (m, 1H), 1.69-1.77 (m, 1H), 1.64 (s, 3H), 1.55-1.63 (m, 2H), 1.32-1.42 (m, 2H), 1.24 (d, *J* = 0.5 Hz, 3H), 1.07 (s, 3H), 1.06 (s, 3H), 0.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.9, 147.9, 132.0, 117.7, 111.1, 83.5, 54.7, 49.0, 47.4, 41.9, 41.0, 39.0, 28.3, 27.6, 25.2, 25.1, 19.2, 2.3(3); HRMS (ESI+) calcd. for $C_{20}H_{37}O_2Si$ (M+H): 337.2563. Found 337.2566



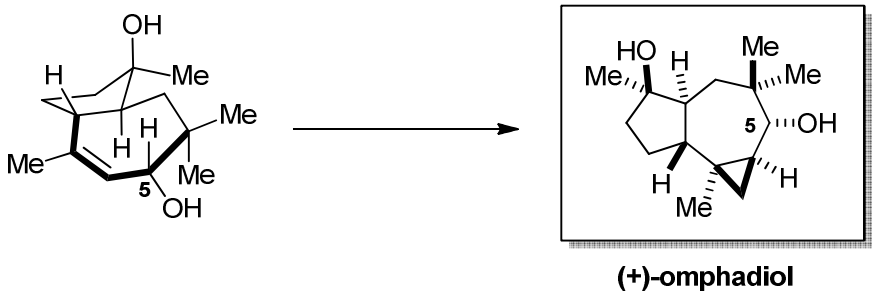
Cycloheptenone 3.14: A solution of diene (136 mg, 0.51 mmol, 1.0 equiv) and Grubbs 2nd generation catalyst (11 mg, 0.013mmol, 3 mol%) in toluene (30 mL) was heated to 90 °C under nitrogen for 3 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (SiO_2, 20 → 50% EtOAc/hexanes) to afford enone as an amorphous solid (108 mg, 95%): $[\alpha]_D^{23}$ -125 (*c* 0.8, $CHCl_3$); IR (thin film) 3443, 2963, 2931, 2869, 1720, 1625, 1456 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.77 (s, 1H), 2.70 (dd, *J* = 14.5, 9.5 Hz, 1H), 2.00-2.10 (m, 1H), 1.87 (s, 3H), 1.76-1.84 (m, 3H), 1.56-1.65 (m, 2H), 1.28-1.35 (m, 2H), 1.27 (s, 3H), 1.15 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.2, 154.3, 126.7, 80.2, 52.3,

51.6, 47.4, 39.0, 36.9, 29.4, 27.6, 26.9, 25.9, 24.6; HRMS (ESI+) calcd. for $C_{14}H_{23}O_2$ (M+H) 223.1698. Found 223.1691.



Allylic alcohol 3.50: A solution of DIBAL/*t*BuLi complex in hexanes/toluene[5] (0.37 M, 5.1 mL, 1.89 mmol, 3.0 equiv) was cooled to -78 °C and a solution of enone (140 mg, 0.63 mmol, 1.0 equiv) in toluene (10 mL) was added dropwise. After stirring at -78 °C for 12 h, the reaction was carefully quenched with MeOH (0.2 mL), diluted with CH_2Cl_2 and 0.4 mL of aq. 20% NaOH was added. The reaction was stirred at ambient temperature (23 ^oC) for 8 h. The resulting white precipitate was removed by filtration through a pad of silica gel and the eluent was concentrated to afford the allylic alcohol as an amorphous solid (121 mg, 86%): $[\alpha]_D^{23}$ +11.4 (*c* 0.5, $CHCl_3$); IR (thin film) 3387, 2963, 2931, 2869, 1652, 1453 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.23 (s, 1H), 4.14 (s, 1H), 2.72 (dd, *J* = 17.5, 10.0 Hz, 1H), 1.82-1.93 (m, 1H), 1.76 (s, 3H), 1.64-1.74 (m, 3H), 1.44-1.62 (m, 3H), 1.24-1.32 (m, 2H), 1.22 (s, 3H), 1.03 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 130.3, 80.7, 77.3, 48.7, 45.7, 42.4, 41.0, 35.7, 29.2, 26.4, 24.6, 22.0, 19.3; HRMS (ESI+) calcd. for $C_{14}H_{24}ClO_2$ (M+Cl) 259.1465. Found 259.1475.

[5] Bian, J.; Van Wingerden, M.; Ready, J. M., *J. Am. Chem. Soc.* **2006,** *128*, 7428-7429.

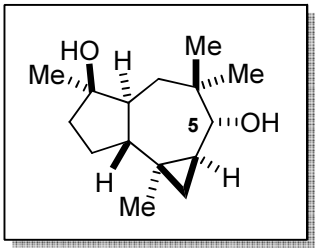


(+)-omphadiol

Omphadiol (1). To a solution of the allylic alcohol (16.2 mg, 0.072 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) cooled to -30 °C was added diethyl zinc (0.36 μL, 0.36 mmol, neat) dropwise. After stirring for 10 mins, CH_2I_2 (0.41 μL, 0.5 mmol) was added dropwise. The reaction mixture was warmed to 0°C slowly and stirred at this temperatute for 2 h. The reaction was then quenched with H_2O, diluted with EtOAc, washed with 1M NaOH and brine, dried over sodium sulfate, concentrated, and purified by flash column chromatography (SiO_2, eluting with 20 $\rightarrow$ 50% EtOAc/hexanes) to afford omphadiol as an amorphous solid (14.3 mg, 83%): $[\alpha]_D^{23}$ $[\alpha]_D^{23}$ +19.4 (*c* 0.31, EtOH); IR (thin film) 3384, 2990, 2951, 2926, 1557, 1538, 1465 cm^{-1}; For ^1H and ^{13}C NMR line listings, see Tables 1 and 2 below; HRMS (ESI+) calcd. for $C_{15}H_{26}NaO_2$ (M+Na) 261.1830. Found 261.1827.

Table 1. Comparison of ^{1}H NMR data of natural (600 MHz)[6] and synthetic (+)-omphadiol (this work, (500 MHz) in $(CD_3)_2CO$

C#	**natural omphadiol** δ (H) (multicity, *J* in Hz)	**synthetic omphadiol** δ (H) (multicity, *J* in Hz)
1	1.45 (overlap)	1.45 (m)
3α	0.62 (dd, *J* = 8.2, 4.0)	0.62 (dd, *J*=8.5, 4.0)
3β	0.34 (t, *J* = 4.4)	0.34 (t, *J*=4.4)
4	0.51-0.55 (m)	0.51-0.55 (m)
5α	3.05 (dd, *J*=9.0, 4.2)	3.05 (dd, *J* =8.5, 4.5)
7α	1.42 (overlap)	1.42 (m)
7β	1.25 – 1.29 (m)	1.23 – 1.29 (m)
8	1.59 (overlap)	1.59 (m)
10α	1.65 (overlap)	1.65 (m)
10β	1.58 (overlap)	1.58 (m)
11α	1.77 – 1.80 (m)	1.75 – 1.82 (m)
11β	1.64 (overlap)	1.64 (m)
12	0.98 (s, 3 H)	0.98 (s, 3 H)
13	0.97 (s, 3 H)	0.97 (s, 3 H)
14	0.94 (s, 3 H)	0.94 (s, 3 H)
15	1.21 (s, 3 H)	1.21 (s, 3 H)
5(OH)	3.40 (d, *J* = 4.2)	3.41 (d, *J* =4.5)
9(OH)	2.90 (s)	2.90 (s)



(+)-omphadiol

[6] Zheng, Y.-B.; Lu, C.-H.; Zheng, Z.-H.; Lin, X.-J.; Su, W.-J.; Shen, Y.-M. *Helv. Chim. Acta.* **2008**, *91*, 2174.

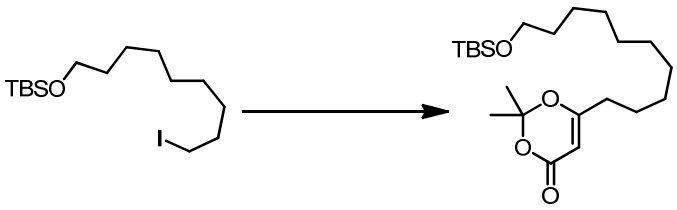
Table 2. Comparison of ^{13}C NMR data of natural (150 MHz) and synthetic (+)-omphadiol (this work, 125 MHz) in $(CD_3)_2CO$.

C#	**natural omphadiol** (δ)	**synthetic omphadiol** (δ)	(Δ **δ**)
1	49.2	49.2	0
2	18.8	18.8	0
3	22.5	22.5	0
4	30.3	30.3	0
5	79.8	79.8	0
6	37.8	37.8	0
7	42.4	42.4	0
8	48.3	48.3	0
9	79.4	79.4	0
10	41.4	41.4	0
11	23.0	23.0	0
12	19.0	19.1	-0.1
13	30.0(*)	28.8	1.2
14	18.9	18.9	0
15	25.0	25.0	0

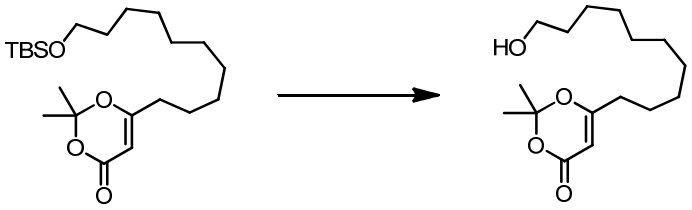
*Zheng *et. al.* inadvertently misassigned this peak.[7]

Note: In general, the ^{1}H and ^{13}C NMR data for our synthetic omphadiol matched well with that reported by Zheng[6] for the natural product. However, there was a discrepancy with one ^{13}C signal (C13, natural: δ 30.0, synthetic: δ 28.8, Δδ 1.2). We determined that the C13 signal in the reported ^{13}C spectrum was actually embedded in the $(CD_3)_2CO$ solvent signals and was thus likely misassigned due to the low concentration of the natural sample (see p. S42). 2D NMR data reported by Zheng[6] also support this conclusion since reported HSQC and HMBC spectra showed C-H correlations with a peak embedded within the solvent acetone signals (~δ 28.8) but not the signal at δ 30.0 (see pp. S45-49). Thus, the correct chemical shift for C13 of omphadiol should be δ 28.8 rather than 30.0(*) in $(CD_3)_2CO$

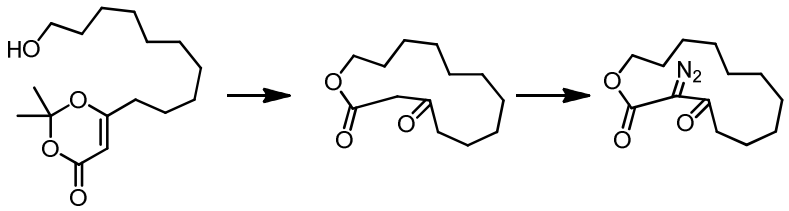
[7] This was confirmed in a private communication with Profs. Zheng and Shen.



Dioxenone 4.11: A solution of *i*-Pr_2NH (134 μL, 0.96 mmol) in THF (1 mL) at -78 °C was added with a solution of *n*-BuLi (2.5 M in hexanes, 0.35 mL, 0.87 mmol). The reaction was stirred at -78 °C for 30 minutes. HMPA (167 μL, 0.96 mmol) was added, followed by a solution of dioxenone (108 μL, 0.82 mmol) in THF (0.5 mL). The mixture was stirred for 1 hour before the addition of iodide (200 mg, 0.52 mmol). After the addition, The reaction was allowed to warm up to room temperature over 3 hours. The reaction was then quenched with saturated NH_4Cl, partitioned between ethyl acetate and water. The organic extract was concentrated to give a crude product and purified by flash column chromatography (SiO_2, eluting with 100% hexanes) to give the dioxeneone as a clear oil (110 mg, 53%). IR (thin film) 2959, 2888, 1721, 1705, 1667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.17 (s, 1H), 3.54 (t, J = 6.0 Hz, 2H), 2.18 (t, J = 8.0 Hz, 2H), 1.44 (m, 4H), 1.28 (m, 18 H), 0.94 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 161.5, 106.2, 93.1, 63.3, 33.6, 32.9, 29.6, 29.4(2), 29.2, 29.0, 26.0(3), 25.8, 25.8, 25.0(2), 18.4, -5.1(2); LRMS (ESI+) calcd. for $C_{22}H_{43}O_4Si$ (M+H) 399. Found 399.

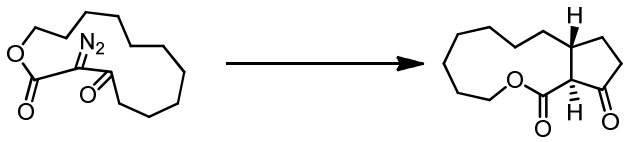


Alcohol 4.12: A reaction mixture of TBS ether (400mg, 1mmol) in THF (8 mL) was added with TBAF(1 mmol, 1.5 mL) at 0 °C. The reaction was stirred for 3 hours at room temperature, diluted with ethyl acetate, washed with saturated NH_4Cl, concentrated, purified by flash column chromatography (SiO_2, eluting with 30%->50% EtOAc/hexanes) to give the alcohol as a clear liquid (255 mg, 90%). IR (thin film) 2959, 2889, 1721, 1705, 1665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.18 (s, 1H), 3.63 (t, *J* = 6.0 Hz, 2H), 2.16 (t, *J* = 8.0 Hz, 2H), 1.45 (m, 4H), 1.28 (m, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 161.6, 106.3, 93.1(2), 63.1, 33.7, 32.8, 29.5, 29.4, 29.4, 29.2, 29.0, 25.8, 25.1(2); LRMS (ESI+) calcd. for $C_{16}H_{29}O_4$ (M+H) 285. Found 285.



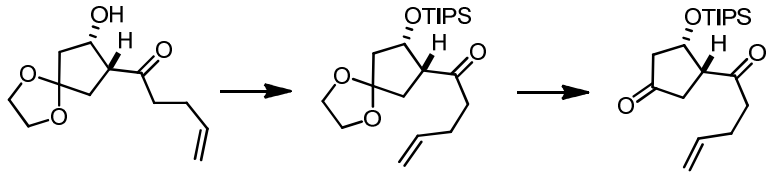
Diazoester 4.14: A solution of primary alcohol (26 mg, 0.09 mmol) in toluene (40 mL) was added dropwise to a refluxing toluene (150 mL) over 3 hours. The reaction mixture

was concentrated to give a crude product (20 mg). This crude was subsequently dissolved in a blending solvent of dichloromethane and acetonitrile (1:1, 0.5 mL) and added with p-ABSA (26 mg, 0.33 mmol) and triethyl amine (24μL, 0.6 mmol). After stirring at 40 ^{o}C for 10 hours, the reaction was diluted with ethyl acetate, washed with saturated NH_4Cl solution, dried over $MgSO_4$, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, eluting with 10-50 % EtOAc/hexanes) to give the diazoester as a solid (18 mg, 78% over 2 steps). IR (thin film) 2995, 2987, 1742, 1708, 1685, 1476 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.37 (t, J = 9.0 Hz, 2H), 2.88 (t, J = 11.0 Hz, 2H), 1.79 (m, 4H), 1.27-1.58 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.0, 162.4, 80.3, 65.5, 38.5, 27.4, 26.8, 25.3, 25.1, 24.9, 24.2(2), 22.7; LRMS (ESI+) calcd. for $C_{13}H_{21}N_2O_3$ (M+H) 253. Found 253.



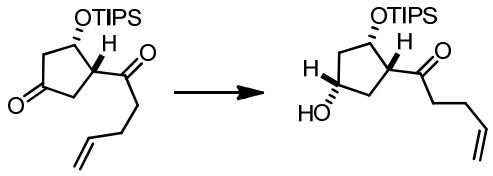
Cyclopentanone 4.15: A mixture of diazo ester (20 mg, 0.0794 mmol) in benzene (1 mL) was added dropwise into refluxing benzene (1 mL) containing $Rh_2(OAc)_4$ (2 mg, 0.0045 mmol) over 4 hours. After the addition the reaction was stirred at the same temperature for another 1 hours. The mixtusre was then concentrated down and purified by flash column chromatography (SiO_2, eluting with 10-50 % EtOAc/hexanes) to give the cyclopentanone as a solid (16 mg, 90%). IR (thin film) 2941, 2139, 1705, 1668 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 (t, *J* = 8.5 Hz, 1H), 4.08 (d, *J* = 10.5 Hz, 1H), 2.83 (m, *J* = 10.5 Hz, 1H), 2.76 (m, 1H), 2.28-2.47 (m, 2H), 2.07-2.16 (m, 1H), 1.79-1.93 (m, 2H), 1.32-1.58 (m, 5H), 1.13-1.27 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.4, 170.5, 66.1, 62.4, 40.3, 38.9, 34.6, 29.2, 27.7, 26.0, 24.6, 23.0, 21.9; LRMS (ESI+) calcd. for $C_{13}H_{21}O_3$ (M+H) 225. Found 225.

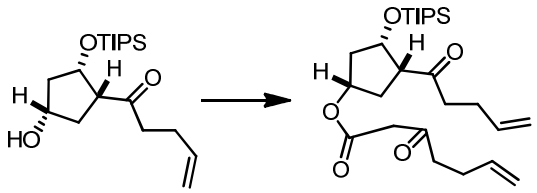


Dione 4.25: To a solution of the ketone (450 mg, 2 mmol) in dichloromethane (15 mL) at -78 °C was added 2,6-lutidine (0.47 mL, 4 mmol) and TIPSOTf (0.59 mL, 2.2 mmol). The reaction was stirred at -78 °C for 30 minutes and then at 0 °C for another 30 minutes before quenched with saturated NH_4Cl. The mixture was diluted with ethyl acetate, washed with 1N HCl, dried over $MgSO_4$, and concentrated to give a clean crude product. This material was then dissolved in a blending solvent of acetone and water (15:1) containing p-TsOH (0.4 M, 0.5 mL, 0.2 mmol) and heated up to 55 °C for 35 minutes. The reaction was then carefully quenched with saturated sodium bicarbonate, diluted with ethyl acetate, washed with water, dried over sodium sulfate, concentrated, and purified by flash column chromatography (SiO_2, eluting with 10-40% EtOAc/hexanes) to give the dione as a colorless oil (452 mg, 67% over 2 steps). $[\alpha]_D^{23}$ -15.3 (*c* 1.0, $CHCl_3$); IR (thin film) 2994, 1719, 1712, 1643 cm^{-1}; ^{1}H NMR (500 MHz,

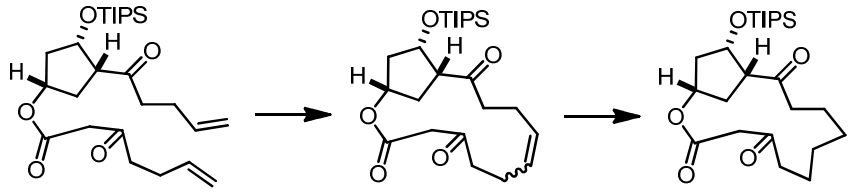
$CDCl_3$) δ 5.91 (m, 1H), 4.96-5.07(m, 2H), 3.36 (dd, *J* = 8.5, 2.5 Hz, 1H), 2.79-2.84 (m, 2H), 2.57-2.63(m, 2H), 2.12-2.21 (m, 3H), 2.06 (m, 2H), 1.05 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.2, 208.2, 137.1, 115.4, 72.5, 54.0, 47.5, 42.6, 38.2, 27.4, 18.1(3), 18.0(3), 12.5(3); LRMS (ESI+) calcd. for $C_{19}H_{35}O_3Si$ (M+H) 339. Found 339.



Alcohol 4.26: A solution of dione (95 mg, 0.28 mmol) in THF at -98 ^oC was added with a solution of L-selectride (1 M in THF, 0.28 mL, 0.28 mmol). The reaction mixture was stirred at -98 ^oC for 40 minutes and acetone was added slowly to quench the reaction. The reaction mixture was then left to warm up to room temperature, quenched with saturated sodium bicarbonate, and diluted with ethyl acetate. The crude product was purified by flash column chromatography (SiO_2, eluting with 20% EtOAc/hexanes) to give the alcohol as a liquid (72 mg, 76%). $[\alpha]_D^{23}$ -12.6 (*c* 0.7, $CHCl_3$); IR (thin film) 2994, 2949, 1713, 1202 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.92 (m, 1H), 4.97 (dd, *J* = 10.5, 5.5 Hz, 2H), 4.49 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.12 (s, 1H), 3.83 (s, 1H), 3.16 (m, 1H), 2.81 (m, 1H), 2.64 (m, 1H), 2.19-2.34 (m, 2H), 1.93 (m, 2H), 1.64 (m, 1H), 1.06 (m, 21H), 0.92 (m, 1H); ^{13}C NMR (125 MHz, D_2O) δ 213.8, 137.2, 115.2, 76.4, 70.4, 55.2, 44.3, 44.3, 35.9, 27.4, 18.1(3), 18.1(3), 12.3(3); LRMS (ESI+) calcd. for $C_{19}H_{37}O_3Si$ (M+H) 341. Found 341.

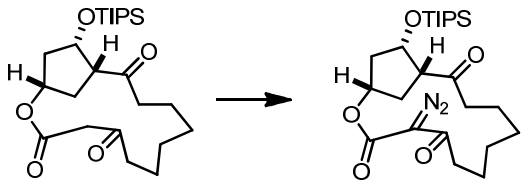


Diene 4.28: A reaction mixture of alcohol (72 mg, 0.21 mmol) and dioxenone (39 mg, 0.21 mmol) in xylene was heated up to 130 ^{o}C. After 30 mins, the reaction was cooled down to 0 ^{o}C, concentrated, and was purified by flash column chromatography (SiO_2, eluting with 20% EtOAc/hexanes) to give the diene as a liquid (62 mg, 63%). $[\alpha]_D^{23}$ -25.8 (*c* 0.2, $CHCl_3$); IR (thin film) 2994, 2949, 1748, 1722, 1712, 1452 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (m, 2H), 4.92-5.09 (m, 5H), 4.78 (dd, *J* = 8.5, 2.0 Hz, 1H), 3.36 (s, 2H), 2.87 (m, 1H), 2.54-2.72 (m, 2H), 2.17-2.42 (m, 4H), 1.96 (m, 2H), 1.14 (m, 1H), 1.06 (m, 21H); ^{13}C NMR (125 MHz, CDCl3) δ 208.3, 201.9, 167.2, 137.4, 136.6, 115.7, 115.2, 74.1, 73.7, 55.8, 49.3, 42.6, 42.2, 41.3, 31.5, 27.5, 27.5, 18.1(3), 18.1(3), 12.6(3); LRMS (ESI+) calcd. for $C_{26}H_{45}O_5Si$ (M+H) 465. Found 465.



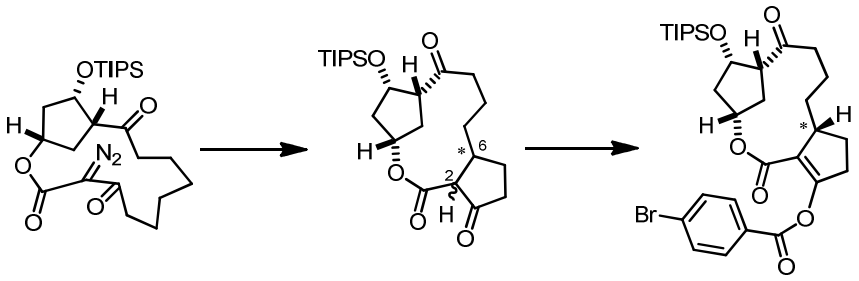
Macrocycle 4.30: A reaction mixture of diene (40 mg, 0.086 mg) and Grubbs catalyst (14 mg, 0.0172 mmol) in toluene (170 mL) was heated to 100 °C for 2 hours. The

reaction mixture was then concentrated by rotary evaporation to give a crude product, which was purified by flash column chromatography (SiO_2, eluting with 10-30% EtOAc/hexanes) to give a product that is identified as a Z/E isomeric mixture. The crude was dissolved in 0.5 mL MeOH and added with Pd/C (10%, 5mg). The reaction mixture was stirred under 1 atm hydrogen (balloon) for 8 hours and concentrated down to give a reaction mixture that is purified by flash column chromatography to give the macrocycle as colorless oil (24 mg, 61%). $[\alpha]_D^{23}$ +7.2 (*c* 0.5, $CHCl_3$); IR (thin film) 2998, 1740, 1721, 1711, 1601 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.18 (m, 1H), 4.45 (m, 1H), 3.52 (d, *J* = 11.5 Hz, 1H), 3.38 (d, *J* = 11.5 Hz, 1H), 2.92 (m, 1H), 2.41-2.63 (m, 5H), 2.21 (m, 2H), 1.93 (d, *J* = 10.5 Hz, 1H), 1.63-1.83 (m, 4H), 1.43-1.52 (m, 1H), 1.13-1.28 (m, 3H), 1.07 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.9, 203.3, 166.3, 74.3, 73.9, 55.6, 49.4, 42.8, 40.7, 40.6, 34.0, 27.1, 26.8, 22.5, 21.7, 18.0(3), 18.0(3), 12.1(3); LRMS (ESI+) calcd. for $C_{24}H_{43}O_5Si$ (M+H) 439. Found 439.



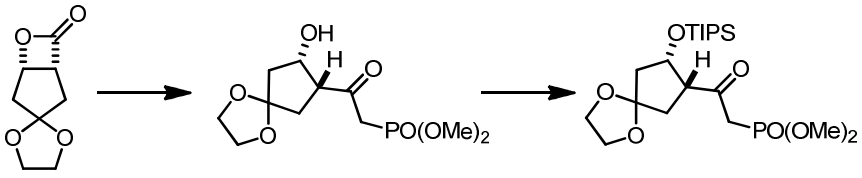
Diazoester 4.31: Keto-ester (4.5 mg, 0.01 mmol) was dissolved in a blending solvent of dichloromethane and acetonitrile (1:1, 0.2 mL) and added with p-ABSA (4.9 mg, 0.02 mmol) and triethyl amine (4.2 μL, 0.03 mmol). After stirring at 40 ^oC for 10 hours, the reaction was diluted with ethyl acetate, washed with saturated NH_4Cl solution, dried

over $MgSO_4$, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, eluting with 10-50 % EtOAc/hexanes) to give the diazoester as a solid (4.0 mg, 85 %). $[\alpha]_D^{23}$ +7.8 (*c* 0.2, $CHCl_3$); IR (thin film) 2975, 2136, 1708, 1667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.36 (m, 1H), 4.48 (m, 1H), 3.09 (t, *J* = 10.5 Hz, 1H), 2.57-2.68 (m, 4H), 2.32-2.51 (m, 4H), 2.21 (d, *J* = 13.0 Hz, 1H), 1.93 (m, 1H), 1.54-1.83 (m, 3H), 1.36-1.52 (m, 3H), 1.06 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.8, 192.5, 162.2, 81.6, 75.6, 74.3, 55.9, 41.1, 40.6, 40.5, 33.7, 26.9, 26.7, 24.0, 21.1, 18.2(3), 18.1(3), 12.2(3); LRMS (ESI+) calcd. for $C_{24}H_{41}N_2O_5Si$ (M+H) 465. Found 465.



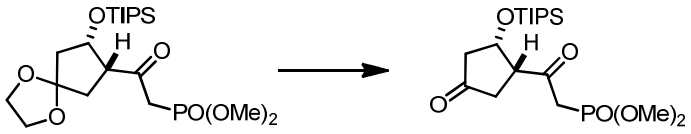
Ester 4.33: A mixture of diazoester (74 mg, 0.16 mmol) in benzene (4 mL) was added dropwise to refluxing benzene (13 mL) containing $Rh_2(OAc)_4$ (3.4 mg, 0.008 mmol) over 4 hours. After the addition the reaction was stirred at the same temperature for another 1 hours. The mixture was then concentrated down purified by flash column chromatography (SiO_2, eluting with 10-50 % EtOAc/hexanes) to give the cyclopentanone as a solid (63 mg, 92%). NMR of this material showed a diastereomeric mixture.

An aliquot of this material (5 mg) was dissolved in 0.5 mL dichloromethane, added with 4-bromobenzoyl chloride (10 mg), DMAP (3 mg) and triethyl amine (0.02 mL). The reaction mixture was stirred at room temperature for 30 mins. TLC showed starting material was consumed. The reaction was quenched with water, filtered through silica gel, and concentrated to give a crude, which was purified by flash column chromatography (SiO_2, eluting with 5-10 % EtOAc/hexanes) to give the ester (4.3mg, 60%) and another diastereomer (1.0 mg, 14 %). $[\alpha]_D^{23}$ -17.8 (*c* 0.3, $CHCl_3$); IR (thin film) 2945, 1744, 1715, 1706, 1663, 1652 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 6.5 Hz, 2H), 7.61 (d, *J* = 6.5 Hz, 2H), 5.26 (t, *J* = 3.5 Hz, 1H), 4.63 (m, 1H), 3.57 (m, 1H), 3.05-3.18 (m, 2H), 2.96 (m, 1H), 2.61-2.72 (m, 3H), 2.31-2.42 (m, 1H), 1.96-2.17 (m, 4H), 1.44-1.73 (m, 4H), 1.06 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.2, 162.4, 161.1, 153.6, 132.3, 131.9, 131.9, 131.8, 129.0, 127.9, 121.7, 74.7, 74.2, 58.5, 41.8, 40.6, 38.9, 36.3, 34.8, 31.8, 28.7, 25.2, 17.9(3), 17.9(3), 11.8(3); LRMS (ESI+) calcd. for $C_{31}H_{43}BrLiO_6Si$ (M+Li) 625. Found 625



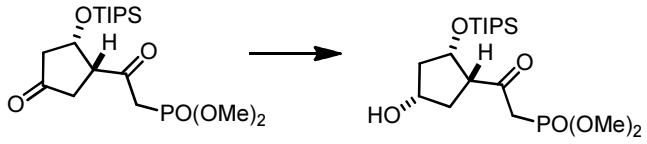
Phosphate 4.37: A mixture of $MePO(OMe)_3$ (220 mg, 1.8 mmol) in THF (1 mL) at -78 ^oC was added with a solution of BuLi (2.17 M, 0.7 mL, 1.5 mmol). The reaction mixture was stirred for 20 minutes and then a solution of latone (100 mg, 0.6 mmol) in THF (1

mL) was added dropwise to the reaction mixture. After stirring at this temperature for 1 hour, TFA (0.11 mL, 2.1 mmol) was added. THF was then removed by rotary evaporation. Dichloromethane was then added at -78 °C, followed by 2,6-lutidine (0.35 mL, 3 mmol) and TIPSOTf (0.644 mL, 2.4 mmol). The reaction was stirred at 0 °C for 1 hour, before quenched with saturated NH_4Cl. The mixture was diluted with ethyl acetate, washed with 1N HCl, dried over $MgSO_4$, concentrated to give a clean crude product, and purified by flash column chromatography (SiO_2, eluting with 50-80% EtOAc/hexanes) to give a colorless liquid (211 mg, 80%): $[\alpha]_D^{23}$ -8.7 (*c* 0.5, $CHCl_3$); IR (thin film) 2940, 1745, 1716, 1649 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.76 (dd, *J* = 8.0, 2.5 Hz, 1H), 3.96 (m, 4H), 3.72 (s, 3H), 3.68 (s, 3H), 3.47 (m, 2H), 3.03 (m, 1H), 2.44 (dd, *J* = 11.0, 3.5 Hz, 1H), 1.92-2.15 (m, 2H), 1.83 (dd, *J* = 8.0, 3.5 Hz, 1H), 1.06 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.4 (201.4 split by P), 114.5, 73.6, 64.7, 64.0, 55.3(55.3 split by P), 53.2(53.1 split by P), 53.0(52.9 split by P), 45.2, 42.3 (41.373split by P), 36.0, 18.1(3), 18.0(3), 12.5(3); LRMS (ESI+) calcd. for $C_{20}H_{40}O_7PSi$ (M+H) 451. Found 451.



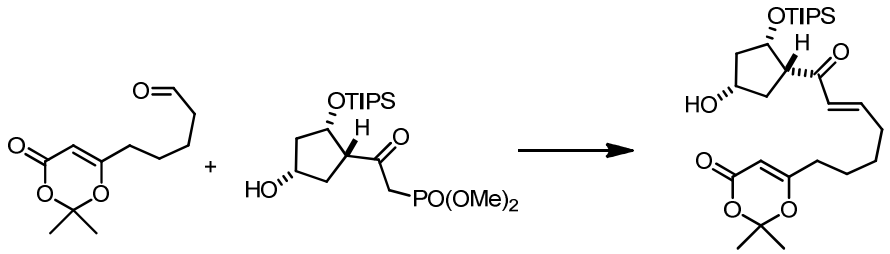
Dione 4.38: The ketal (1.4 g, 3 mmol) was dissolved in a blending solvent of acetone and water (15:1) containing p-TsOH (0.4 M, 6 mL, 2.4 mmol) and heated up to 55 °C for 4 hour. The reaction was then carefully quenched with sodium bicarbonate (200 mg),

dried over sodium sulfate, filtered to remove the solid, and purified by flash column chromatography (SiO_2, eluting with 50-100% EtOAc/hexanes) to give the dione as a colorless oil (880 mg, 70%). $[\alpha]_D^{23}$ -13.8 (*c* 0.4, $CHCl_3$); IR (thin film) 2976, 2931, 1718, 1713, 1664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.01 (dd, *J* = 8.0, 2.0 Hz, 1H), 3.72-3.86 (m, 7H), 3.62 (m, 1H), 3.08 (m, 1H), 2.64 (dd, *J* = 11.0, 3.5 Hz, 1H), 2.37-2.45 (m, 2H), 2.20 (dd, *J* = 15.0, 4.5 Hz, 1H), 1.06 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.7, 200.5, 72.5, 54.7, 53.4(53.3 split by P), 53.1(53.1 split by P), 47.6, 42.1(41.1 split by P), 37.9, 18.1(3), 18.0(3), 12.5(3); LRMS (ESI+) calcd. for $C_{18}H_{36}O_6PSi$ (M+H) 407. Found 407.



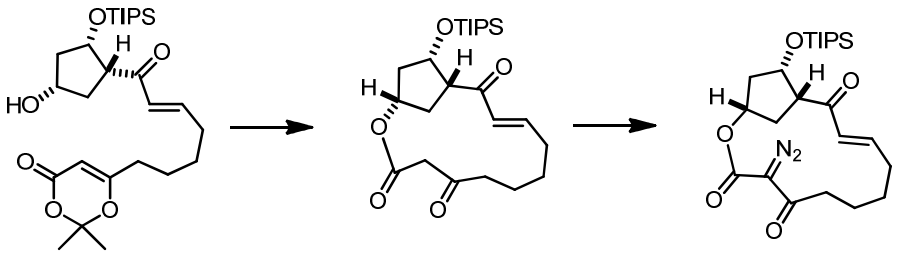
Alcohol 4.39: A solution of dione (1.1 g, 2.7 mmol) in THF at -78 ^oC was added with a solution of L-selectride (1 M in THF, 7 mL, 7 mmol). The reaction mixture was stirred at -78 ^oC for 1 hour and acetone was added slowly to quench the reaction. The reaction mixture was then left to warm up to room temperature, quenched with saturated sodium bicarbonate, and diluted with ethyl acetate. The crude product was purified by flash column chromatography (SiO_2, eluting with 100% EtOAc) to give the alcohol as a liquid (1.03 mg, 91%). $[\alpha]_D^{23}$ +22.5 (*c* 0.2, $CHCl_3$); IR (thin film) 2994, 2949, 1718, 1712, 1613 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.54 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.09 (m, 1H),

3.70-3.89 (m, 7H), 3.41-3.63 (m, 2H), 2.94 (m, 1H), 2.24 (dd, *J* = 12.5, 3.5 Hz, 1H), 1.93 (m, 2H), 1.57 (m, 1H), 1.06 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.1(205.1 split by P), 75.8, 69.9, 55.9 (55.9split by P), 53.1(53.0 split by P), 52.8 (52.8 split by P), 44.0, 43.3 (42.3 split by P), 35.4 (35.3 split by P), 17.9(3), 17.8(3), 12.2(3); LRMS (ESI+) calcd. for $C_{18}H_{38}O_6PSi$ (M+H) 409. Found 409.



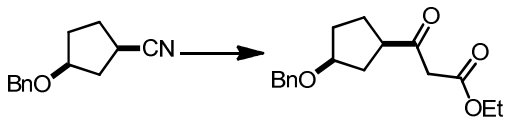
Dioxenone 4.40: To a solution of phosphonate (135 mg, 0.33 mmol) in THF (1 mL) was added NaH powder (13.2 mg, 0.33 mmol) at 0 ^{o}C in one portion. The mixture was stirred at at 0 ^{o}C for 20 minutes and then a solution of aldehyde (70 mg, 0.33 mmol) in THF (1 mL) was added to the reaction mixture dropwise. The reaction was left to warm up to room temperature, stirred for 1 hour, diluted with dichloromethane, concentrated, and purified by flash column chromatography (SiO_2, eluting with 20-50% EtOAc/hexanes) to give the dioxenone (93 mg, 57%). $[\alpha]_D^{23}$ +11.8 (*c* 0.2, $CHCl_3$); IR (thin film) 3356, 2974, 1724, 1708, 1665, 1580 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (ddd, *J* = 11.5, 6.5, 2.0 Hz, 1H), 6.34 (d, *J* = 11.5 Hz, 1H), 4.63 (dd, *J* = 8.5, 2.0 Hz, 1H), 4.17 (m, 1H), 3.74 (d, *J* = 8.5 Hz, 1H), 3.45 (m, 1H), 2.18-2.27 (m, 5H), 1.95-2.07 (m, 3H), 1.77-1.90 (m, 1H), 1.75 (s, 6H), 1.60-1.69 (m, 2H), 1.51-1.59 (m, 2H), 1.06 (m, 21H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 202.0, 171.4, 161.3, 145.9, 131.4, 106.4, 93.4, 76.8, 71.0, 54.1, 44.9, 36.0, 33.5, 32.0, 27.5, 25.4, 25.1(2), 18.1(3), 18.1(3), 12.3(3); LRMS (ESI+) calcd. for $C_{27}H_{47}O_6Si$ (M+H) 495. Found 495.



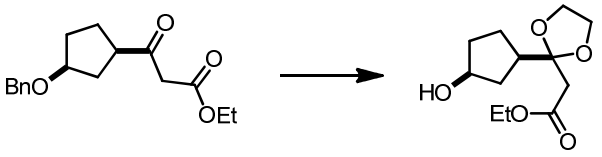
Diazoester 4.42: A solution of alcohol (72 mg, 0.176 mmol) in toluene (10 mL) was added dropwise to a refluxing toluene (240 mL) over 3 hours. The reaction mixture was concentrated to give a crude product (66 mg). This crude was subsequently dissolved in a blending solvent of dichloromethane and acetonitrile (1:1, 1 mL) and added with p-ABSA (73 mg, 0.3 mmol) and triethyl amine (62 μL, 0.45 mmol). After stirring at 45 ^oC for 4 hours, the reaction was diluted with ethyl acetate, washed with saturated NH_4Cl solution, dried over $MgSO_4$, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, eluting with 10-30 % EtOAc/hexanes) to give the diazoester as a solid (57 mg, 70% over 2 steps). This material was crystalized from diethyl ether to give a single crystal (melting point: 96 ^oC). $[\alpha]_D^{23}$ +7.6 (*c* 0.3, $CHCl_3$); IR (thin film) 2996, 2138, 1743, 1708, 1665, 1642 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ

6.91 (ddd, *J* = 11.0, 6.5, 2.0 Hz, 1H), 6.34 (d, *J* = 11.0 Hz, 1H), 5.66 (m, 1H), 4.72 (dd, *J* = 8.5, 3.5 Hz, 1H), (m, 1H), 2.94-3.12 (m, 3H), 2.53-2.64 (m, 3H), 2.23-2.43 (m, 2H), 2.05-2.14 (m, 1H), 1.44-1.87 (m, 4H), 1.06 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.8, 191.7, 162.0, 145.2, 127.7, 81.2, 75.7, 74.3, 56.4, 41.4, 41.3, 35.3, 30.1, 25.7, 25.0, 17.9(3), 17.9(3), 12(3); LRMS (ESI+) calcd. for $C_{24}H_{39}N_2O_5Si$ (M+H) 463. Found 463.

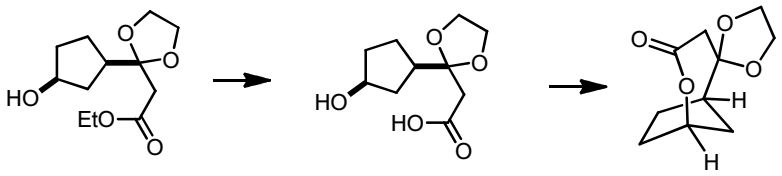


Ketoester 4.63: To a suspension of zinc (1.44 g, 22.1 mmol), nitrile (1.48 g, 7.36 mmol), and methanesulfonic acid (10 μL, 0.15 mmol) in THF (120 mL) at 65 °C was added ethyl bromoacetate (1.64 mL, 14.7 mmol) solution in THF (10 mL) over 1 hour. After addition, the reaction was stirred at 65 °C for another 1 hour. The reaction was then quenched with 3N HCl, stirred at room temperature for 10 hours, diluted with ethyl acetate, washed with saturate sodium bicarbonate, and dried over sodium sulfate. The crude was purified by flash column chromatography (SiO_2, eluting with 10-30 % EtOAc/hexanes) to give the ketoester as a liquid (1.37 g, 64%). IR (thin film) 2957, 2927, 1746, 1720, 1648 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 3H), 7.12 (m, 2H), 4.46 (dd, *J* = 9.5, 3.0 Hz, 2H), 4.13 (q, *J* = 6.5, 2H), 3.93 (m, 1H), 3.54 (s, 2H), 2.96-3.01 (dd, *J* = 9.5, 2.5 Hz, 2H), 1.67-2.08 (m, 5H), 1.21 (t, *J* = 6.5, 3H); ^{13}C NMR (75

MHz, $CDCl_3$) δ 201.4, 165.0, 135.3, 129.0, 126.8, 118.8, 77.6, 67.4, 58.9, 47.6; LRMS (ESI+) calcd. for $C_{17}H_{23}O_4$ (M+H) 291. Found 291.



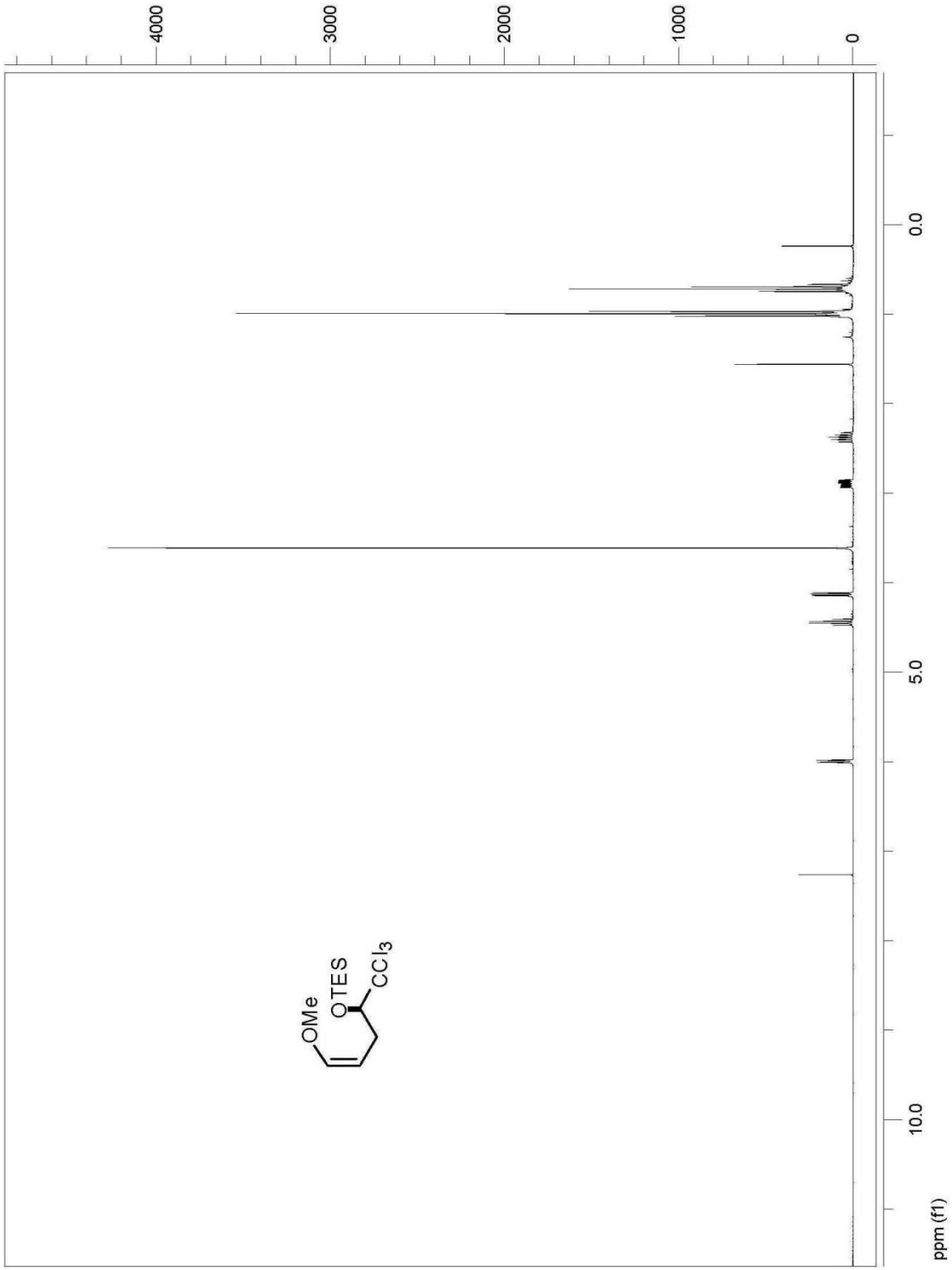
Ketal ester 4.64: A reaction mixture of ethylene glycol (250 mg, 4 mmol), ketoester (290 mg, 1 mmol) , p-TsOH (25 mg, 0.1 mmol), and trimethyl orthoester(212 mg, 2 mmol) was stirred at room temperature for 24 hours. The reaction was then diluted with ethyl acetate, washed with saturate sodium carbonate, and dried over sodium sulfate. The crude was concentrated to give a crude oil. This material was then dissolved in MeOH (3 mL) and added with Pd/C (10%, 20 mg). The reaction was stirred under hydrogen atmosphere (balloon) for 24 hours. The reaction was then concentrated and purified by flash column chromatography (SiO_2, eluting with 10-30 % EtOAc/hexanes) to give the ketal ester as a liquid (175 mg, 72% 2 steps). IR (thin film) 2983, 2924, 1745, 1232 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.01-4.17 (m, 7H), 3.82 (s, 1H), 3.75 (s, 2H), 1.45-2.05 (m, 7H), 1.21 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 110.9, 73.2, 65.5, 65.4, 60.7, 43.8, 41.7, 36.1, 36.0, 24.7, 14.2; LRMS (ESI+) calcd. for $C_{12}H_{21}O_5$ (M+H) 245. Found 245.



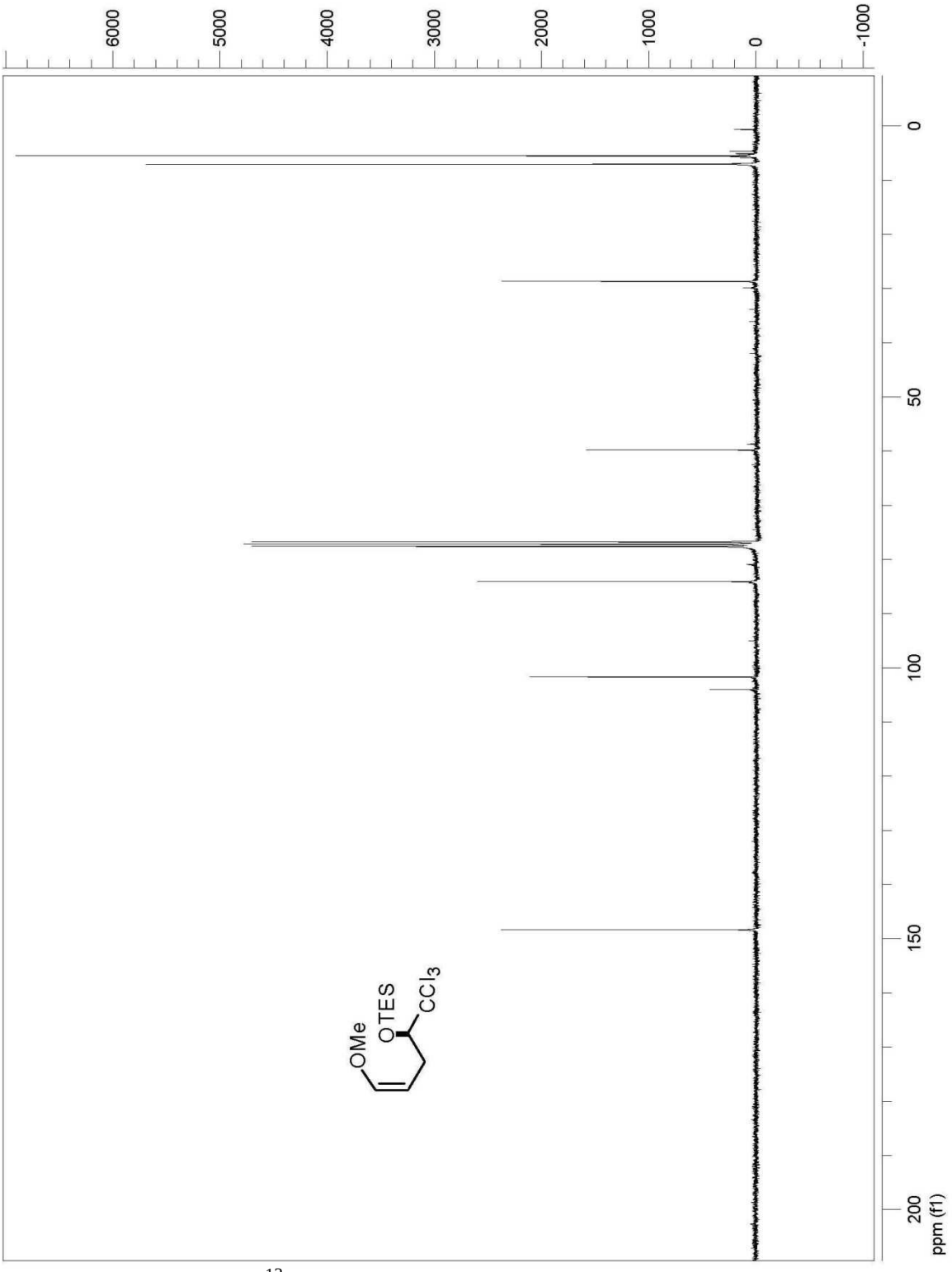
A reaction mixture of the ester (25 mg, 0.1 mmol) and potassium hydroxide/lithium hydroxide 1:1 aqueous solution (2M, 0.1 mL, 0.2 mmol) in methanol (3 mL) was stirred at room temperature for 4 hours. The reaction was then diluted with ethyl acetate, washed with saturate ammonium chloride and 1N HCl, dried over sodium sulfate. The crude was concentrated to give a crude oil. This material was then dissolved in THF (1 mL) and added with Yamaguchi acid chloride (62 mg, 0.3 mmol) and triethyl amine (0.3 mL). The reaction was stirred for 3 hours and diluted with toluene (2 mL). This mixture was added dropwise to a refluxing solvent of toluene (10 mL) over 8 hours. The reaction was then diluted with ethyl acetate, washed with sodium bicarbonate and ammonium chloride, dried over sodium sulfate, and purified by flash column chromatography (SiO_2, eluting with 10-30 % EtOAc/hexanes) to give the bridged structure as an amorphous solid (7.5 mg, 38%). IR (thin film) 2988, 2932, 1749, 1664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.88 (m, 1H), 3.90-4.15 (m, 4H), 2.96 (d, J = 7.5 Hz, 1H), 2.87 (d, J = 7.5 Hz, 1H), 2.23-2.41 (m, 3H), 2.03-2.16 (m, 2H), 1.76-1.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 108.2, 81.1, 65.3, 64.8, 47.3, 43.3, 36.8, 31.3, 27.0; LRMS (ESI+) calcd. for $C_{10}H_{15}O_4$ (M+H) 199. Found 199.

APPENDIX B

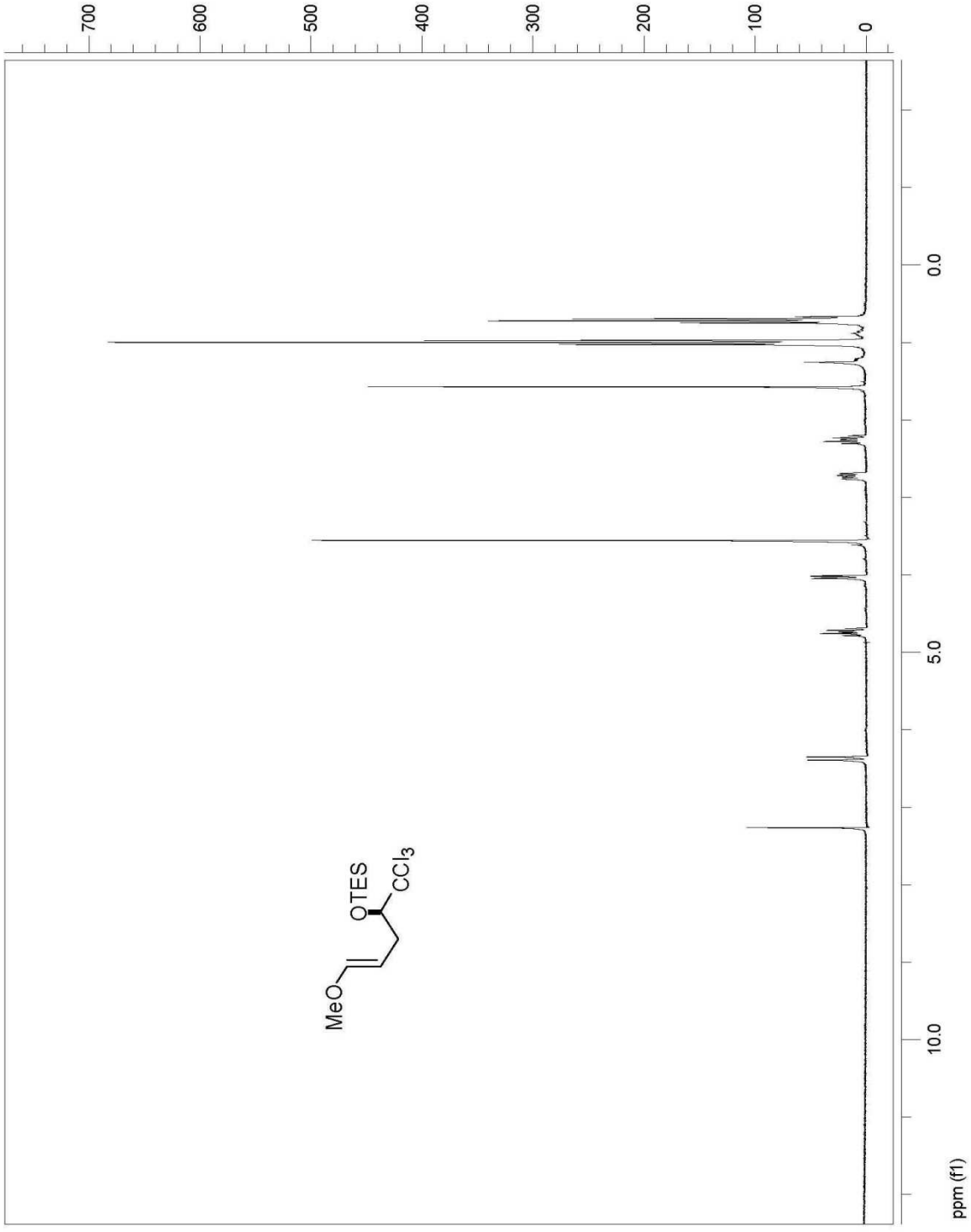
SELECTED SPECTRA DATA



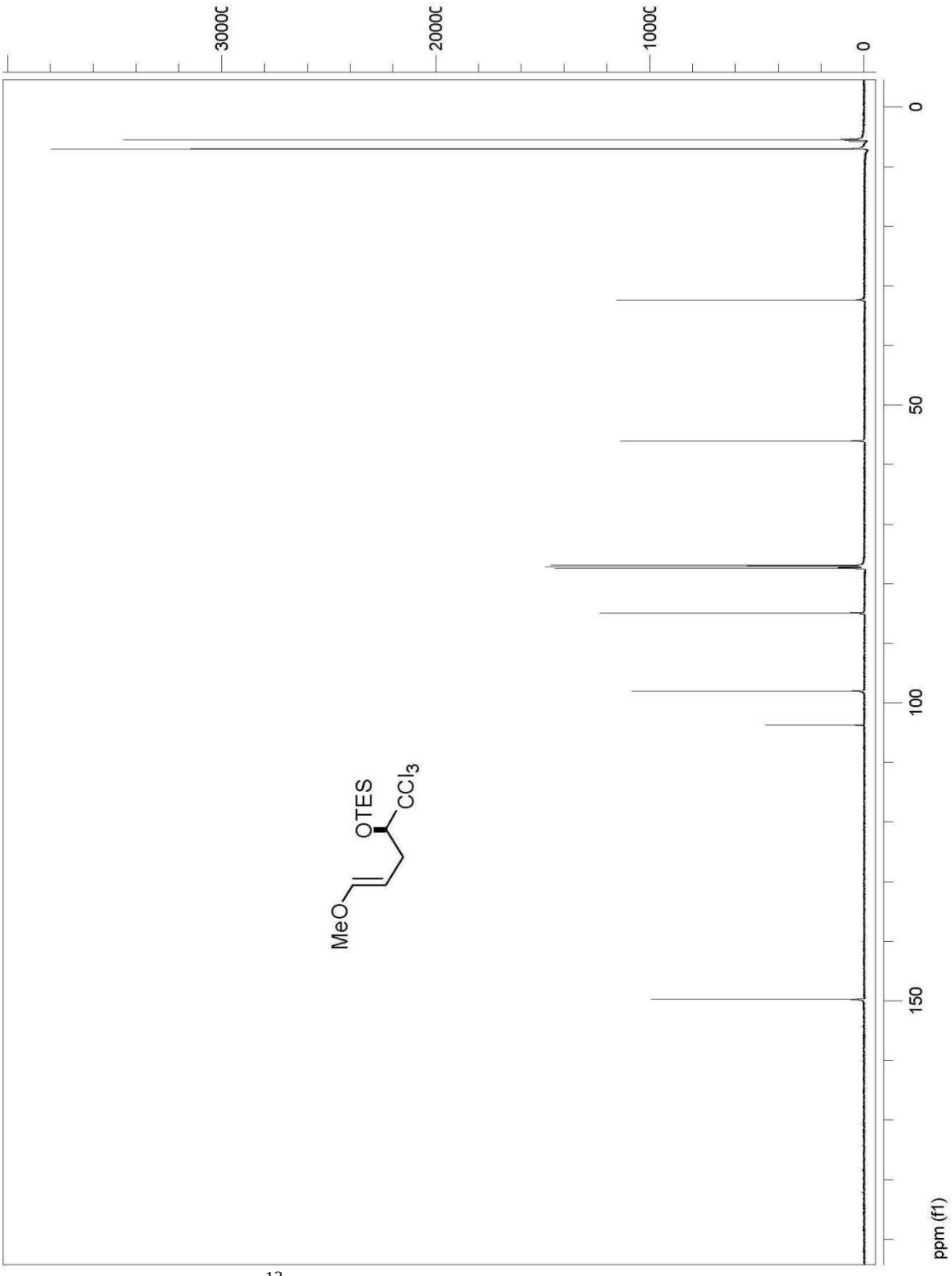
^{1}H NMR (500 MHz) of **2.8Z** in $CDCl_3$



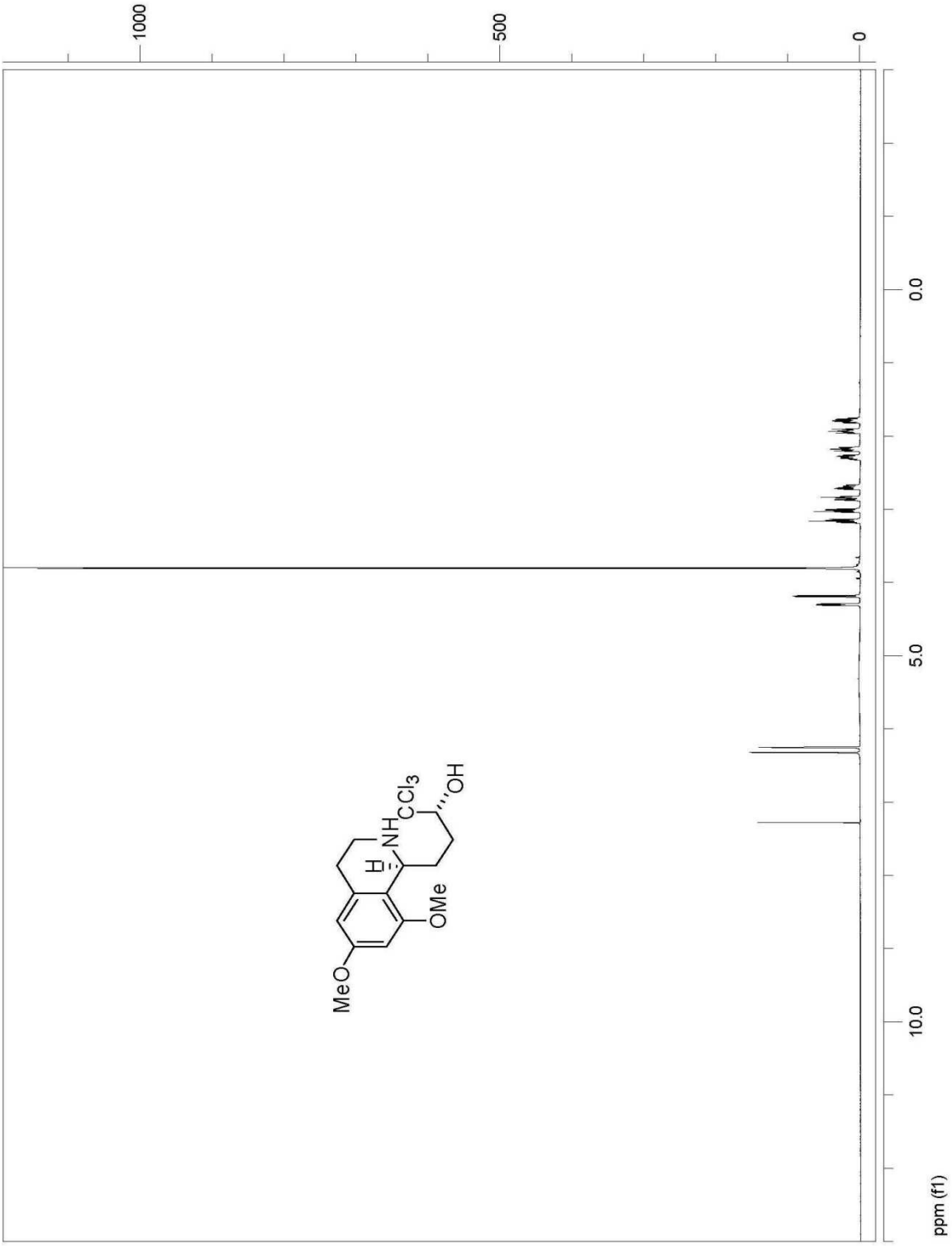
^{13}C NMR (500 MHz) of **2.8Z** in $CDCl_3$



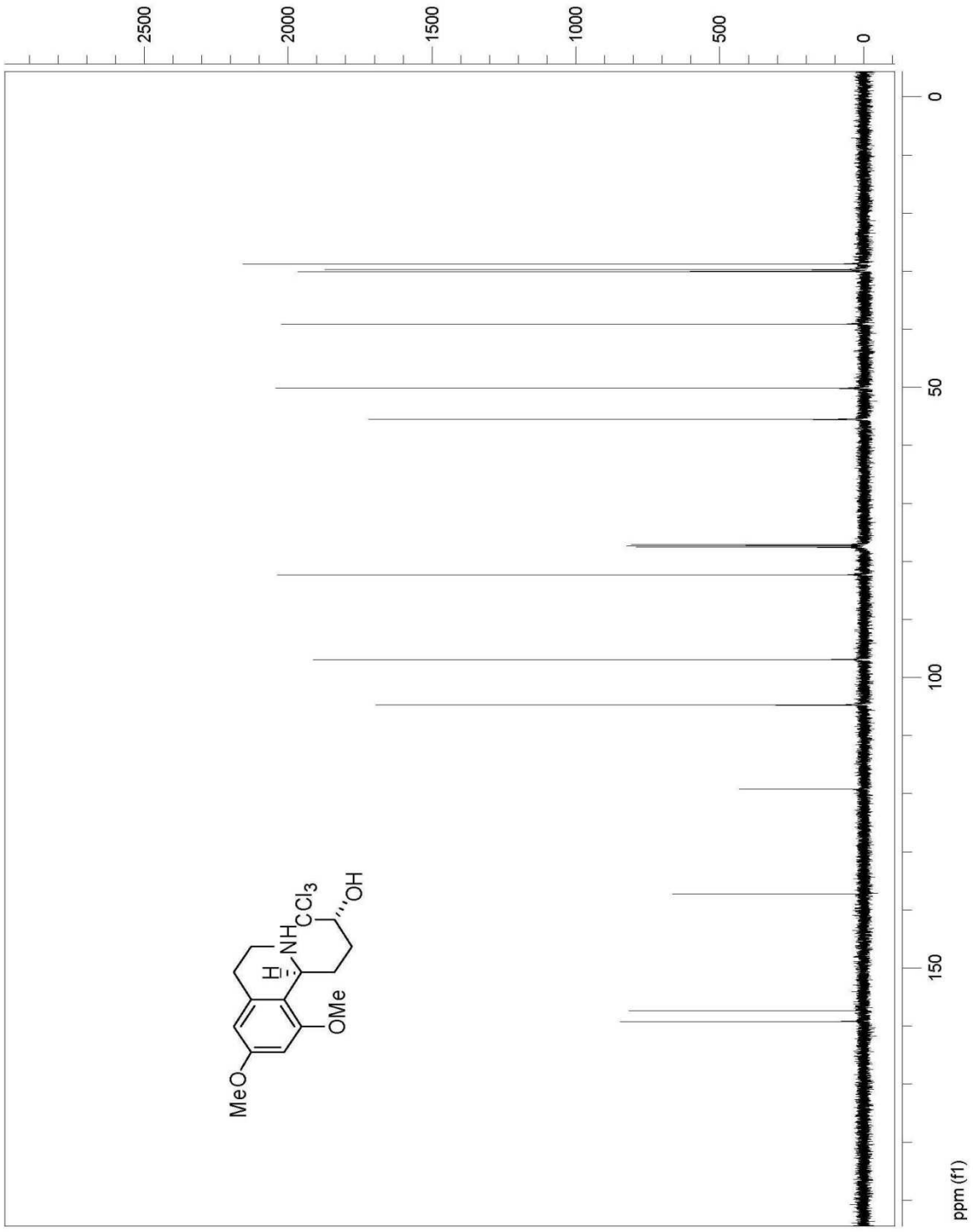
^{1}H NMR (500 MHz) of **2.8E** in $CDCl_3$



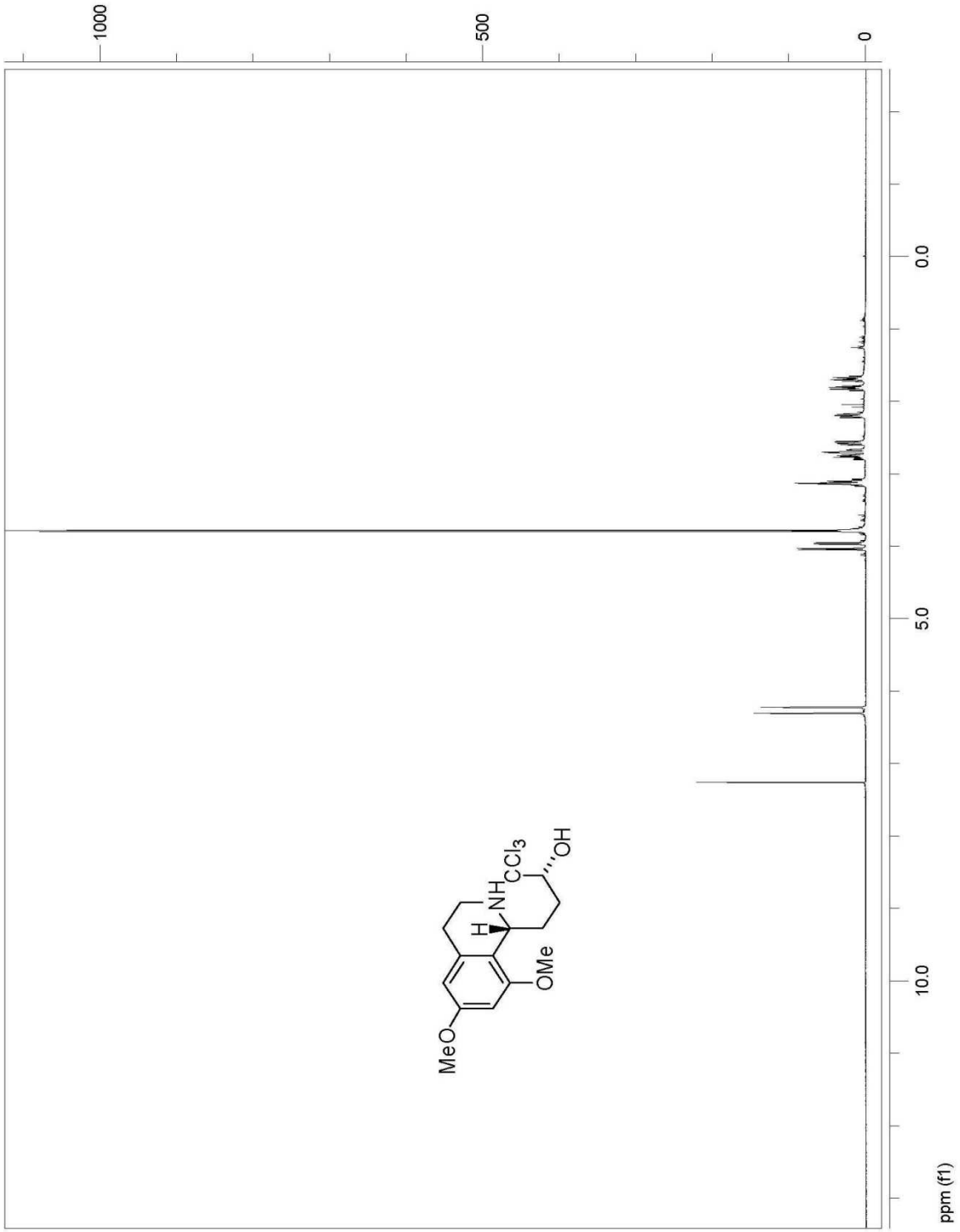
^{13}C NMR (500 MHz) of **2.8E** in $CDCl_3$



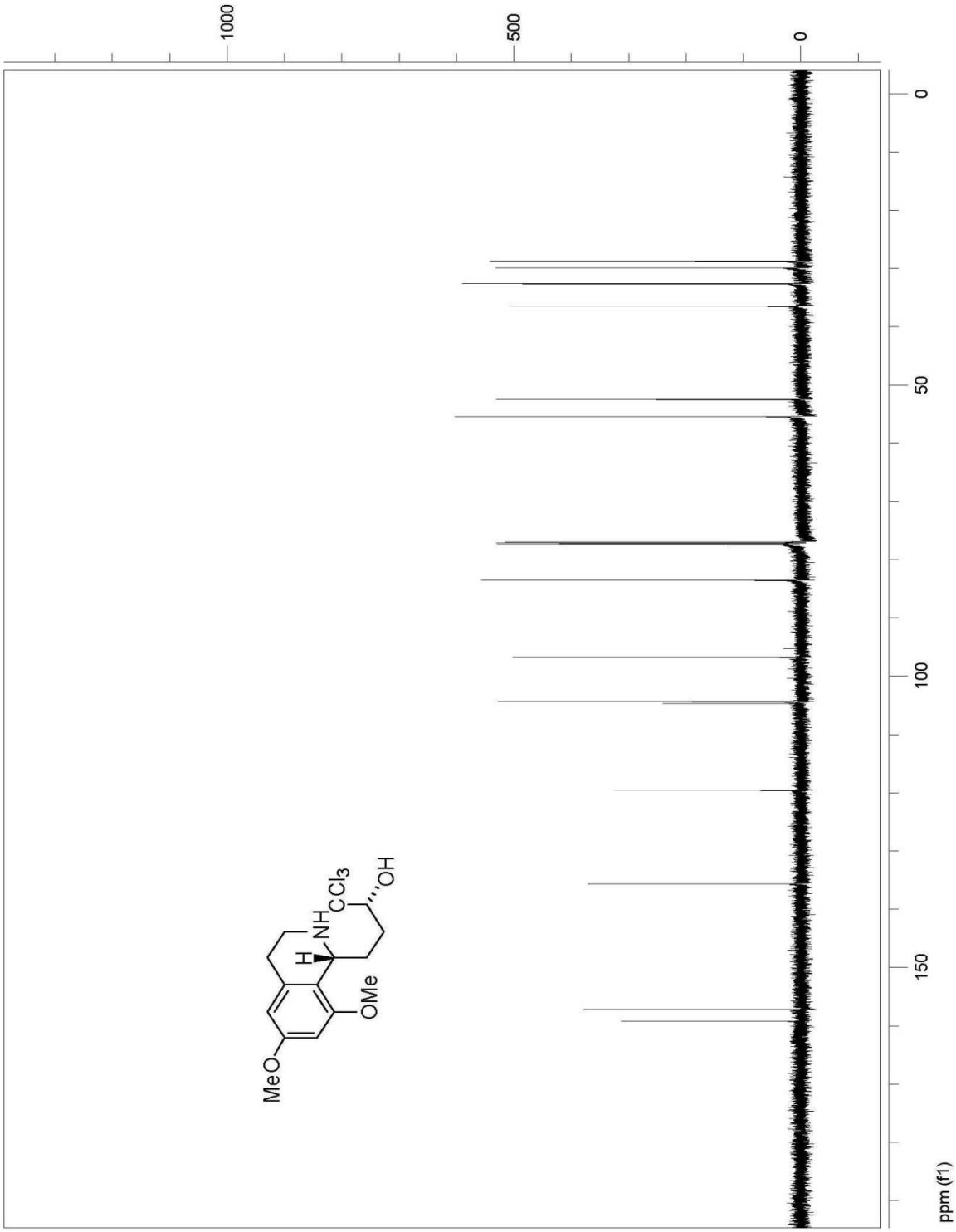
^{1}H NMR (500 MHz) of **2.28a** in $CDCl_3$



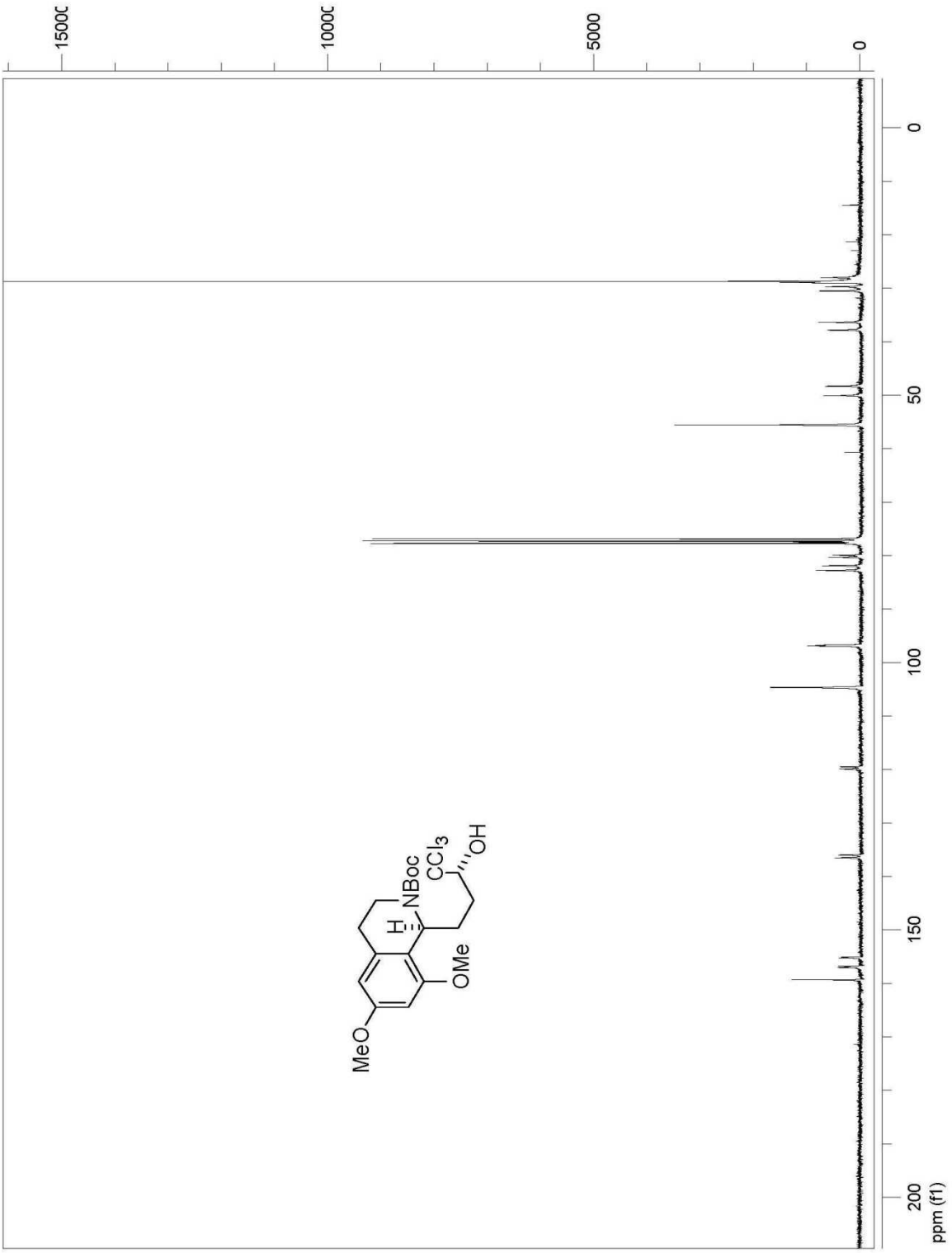
^{13}C NMR (500 MHz) of **2.28a** in $CDCl_3$



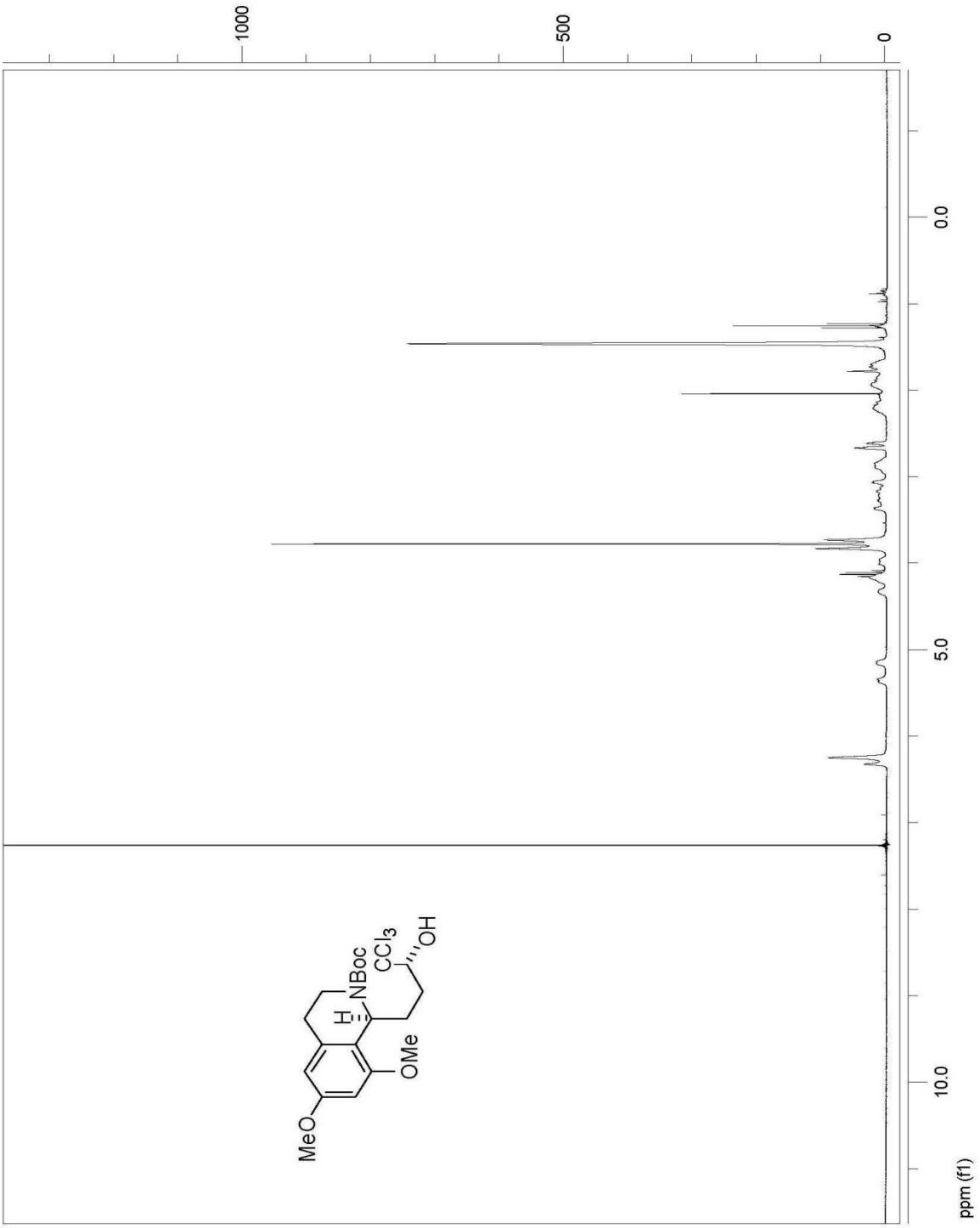
^{1}H NMR (500 MHz) of **2.28b** in $CDCl_3$



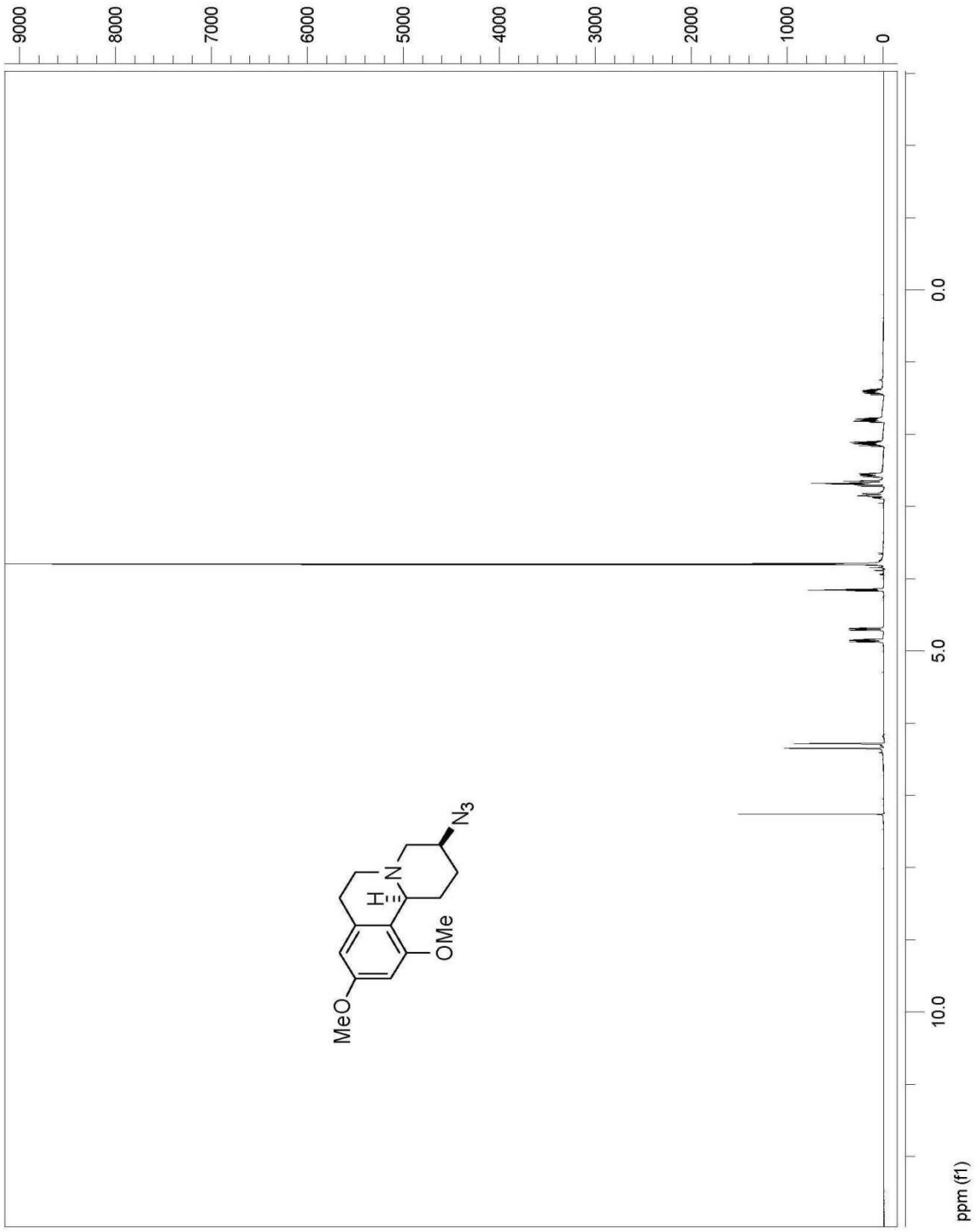
^{13}C NMR (500 MHz) of **2.28b** in $CDCl_3$



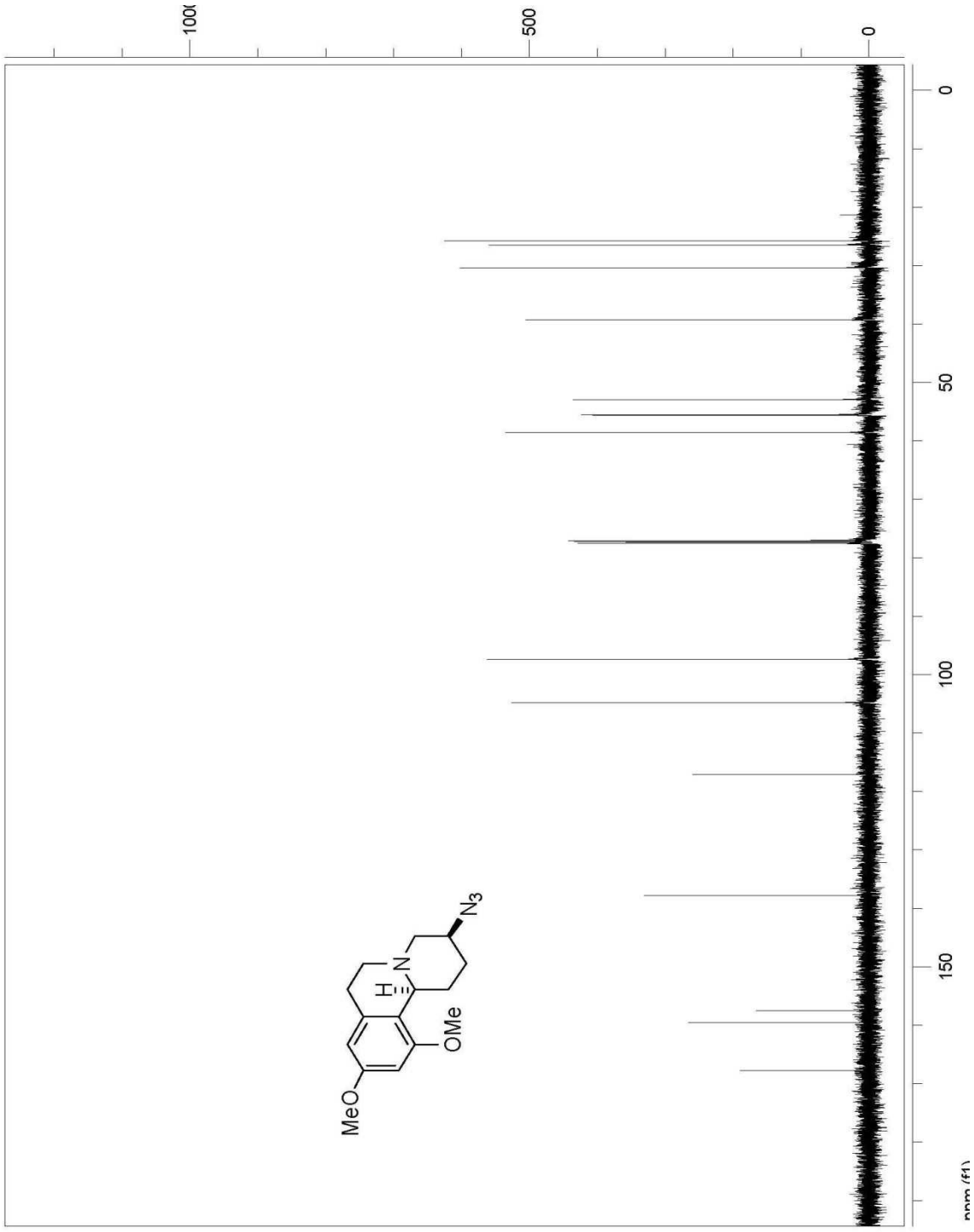
^{1}H NMR (500 MHz) of **2.36a** in $CDCl_3$



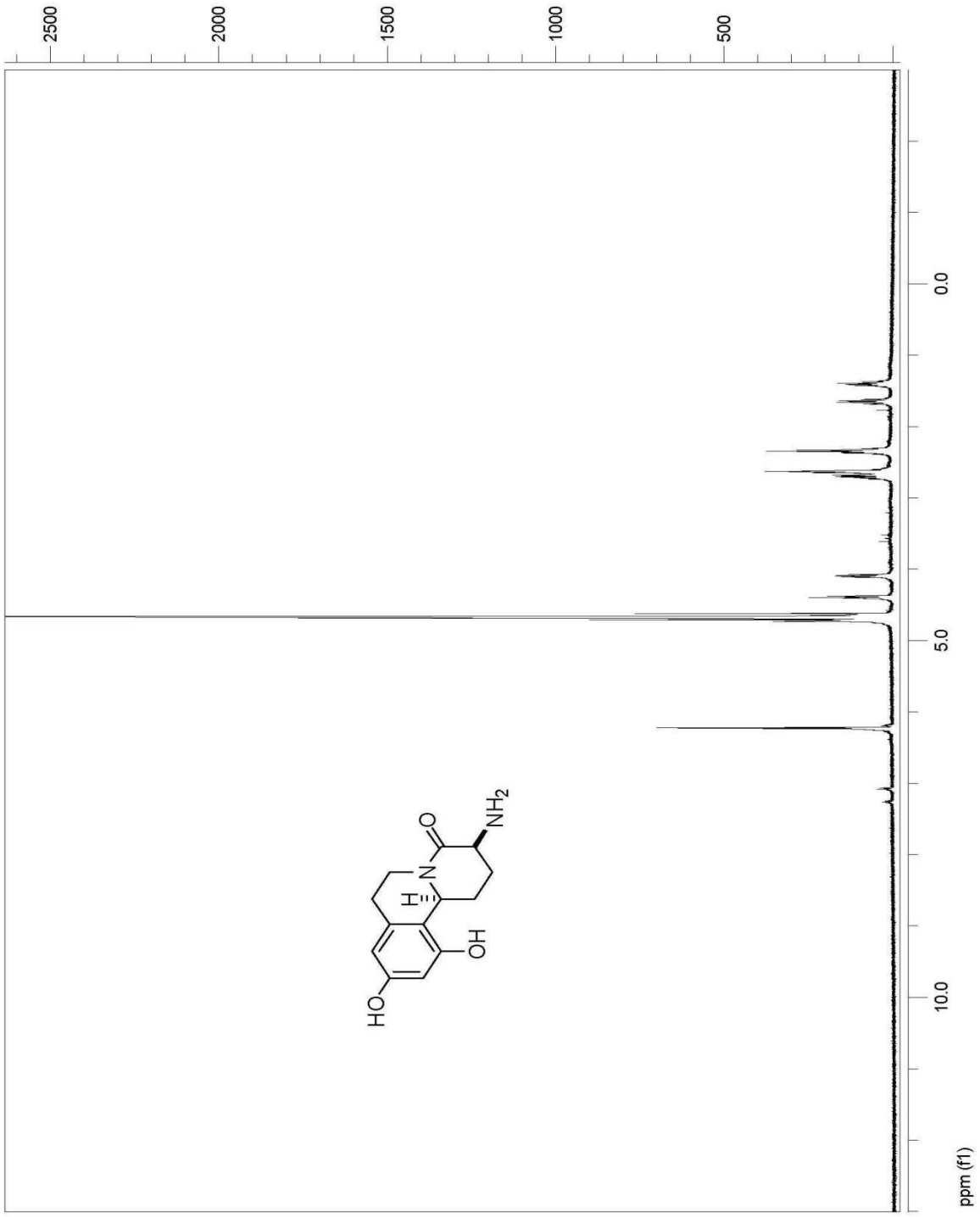
^{13}C NMR (500 MHz) of **2.36a** in $CDCl_3$



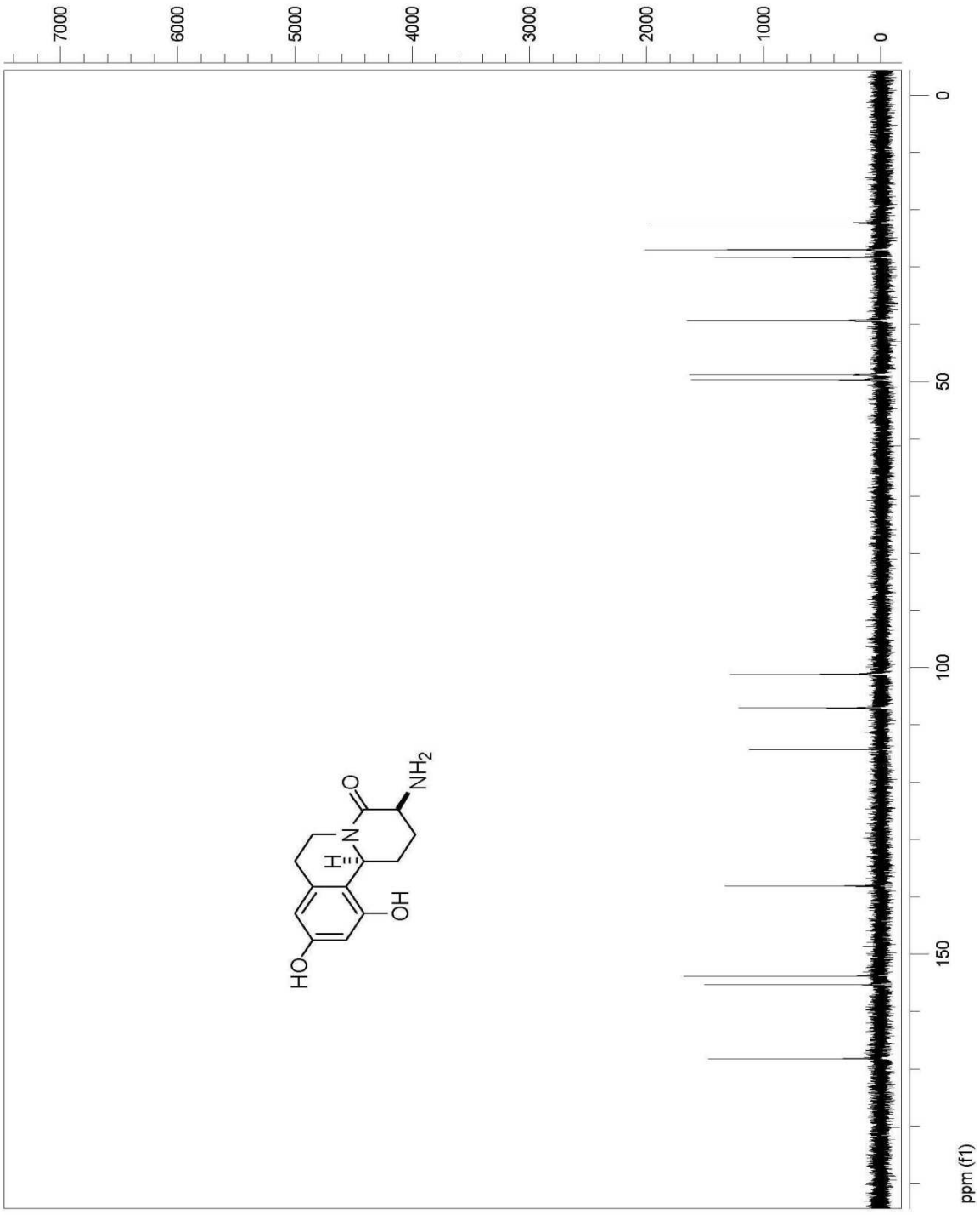
^{1}H NMR (500 MHz) of **2.39a** in $CDCl_3$



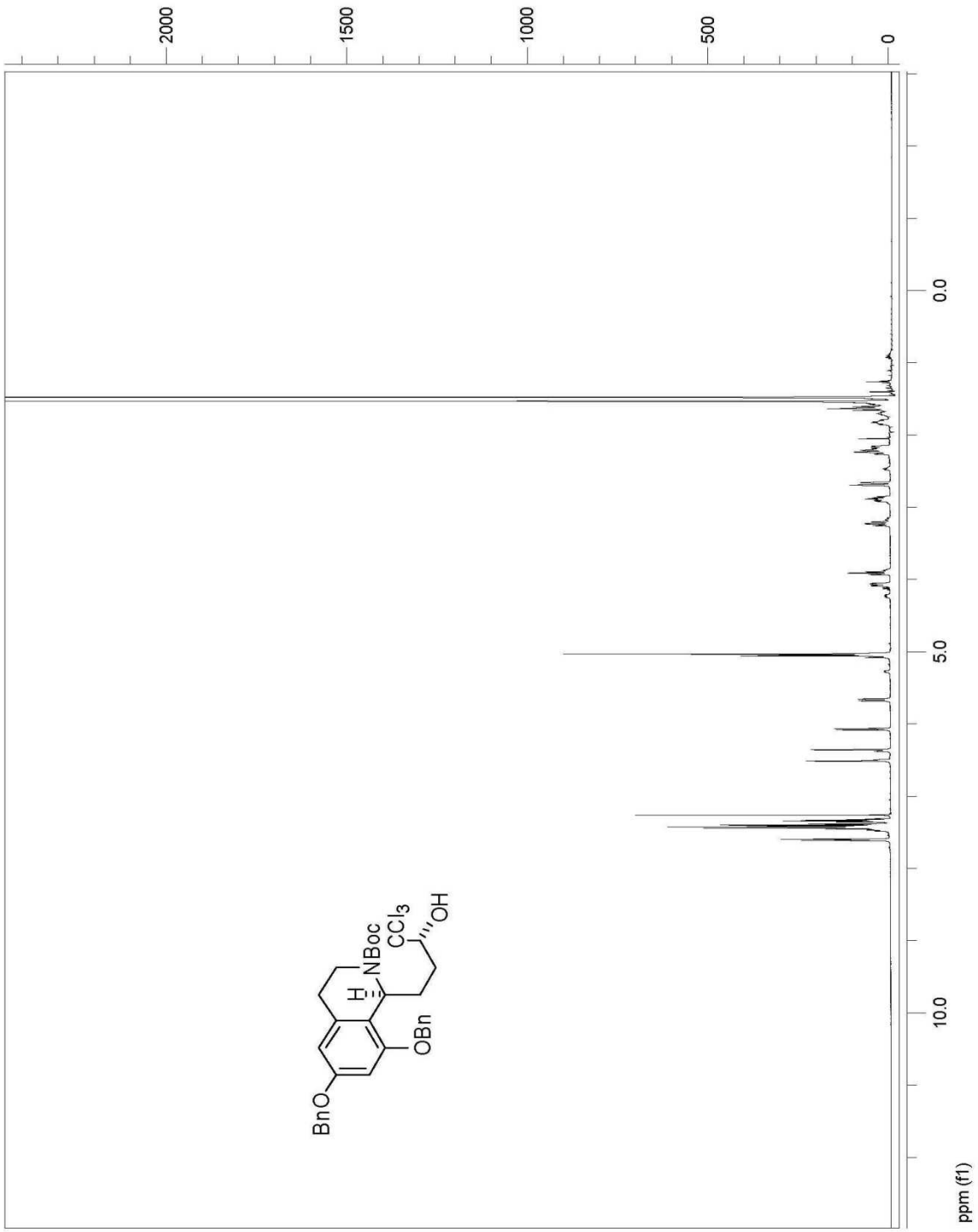
^{13}C NMR (500 MHz) of **2.39a** in $CDCl_3$



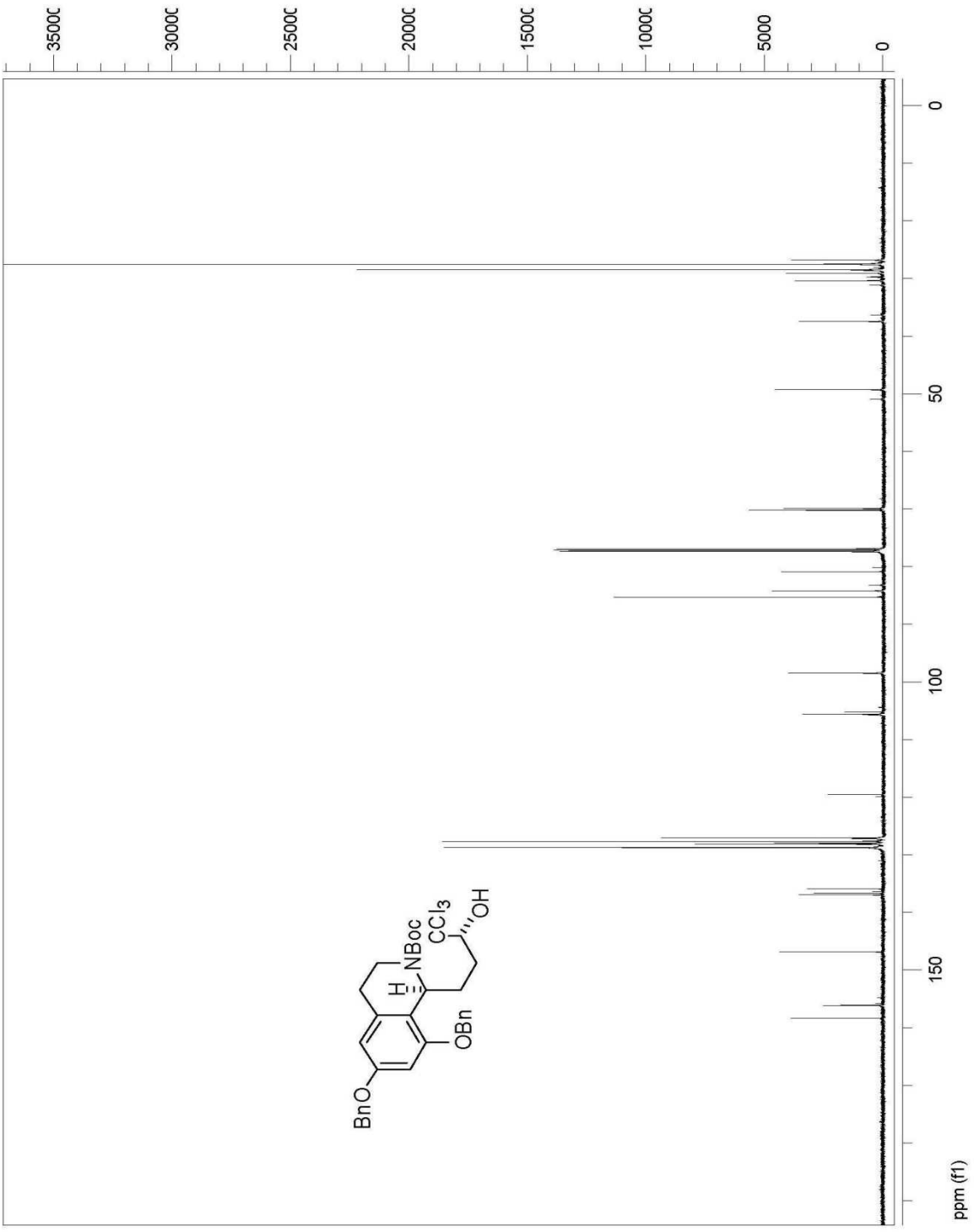
^{1}H NMR (500 MHz) of **2.41a** in $CDCl_3$



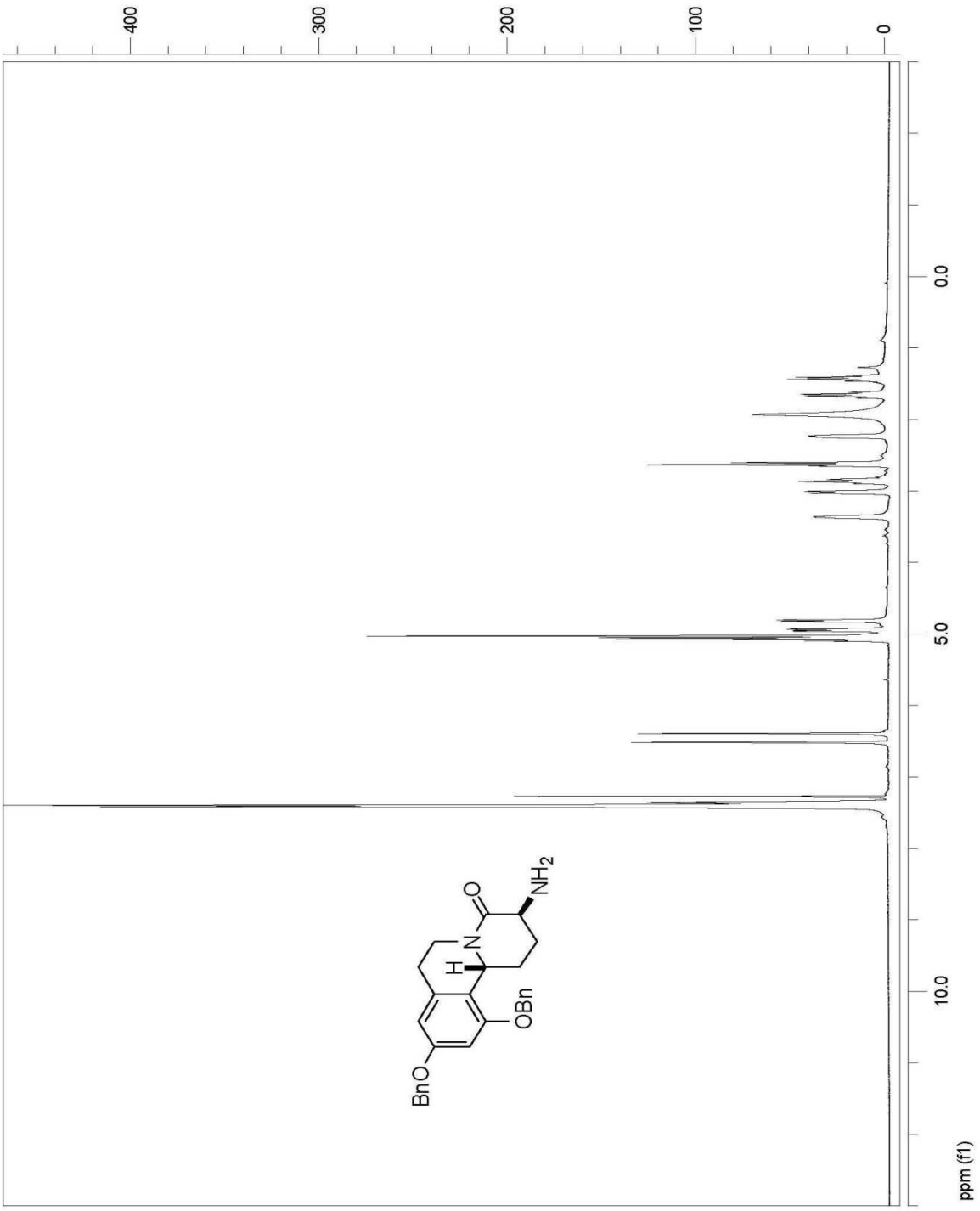
^{13}C NMR (500 MHz) of **2.41a** in $CDCl_3$



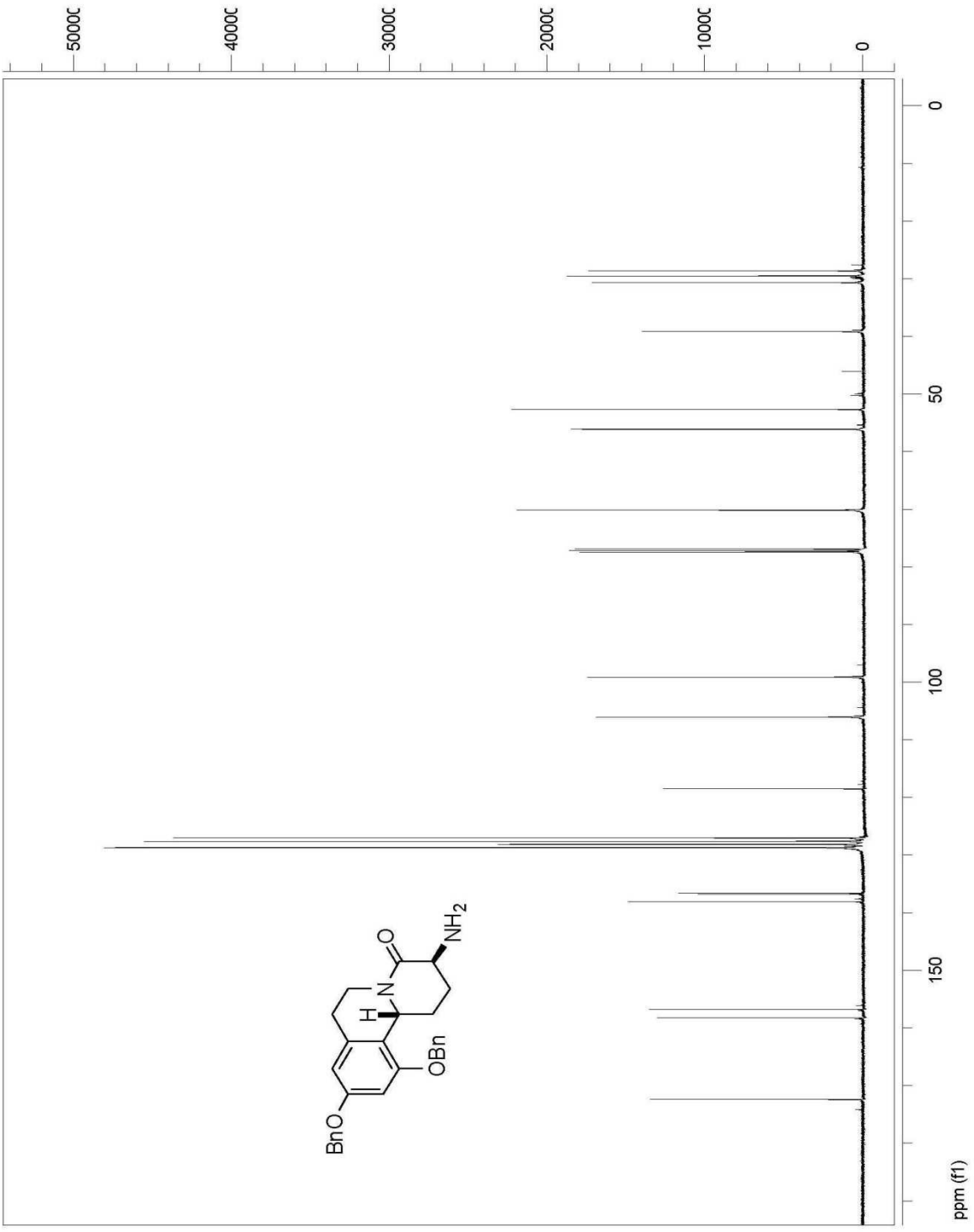
^{1}H NMR (500 MHz) of **2.45a** in $CDCl_3$



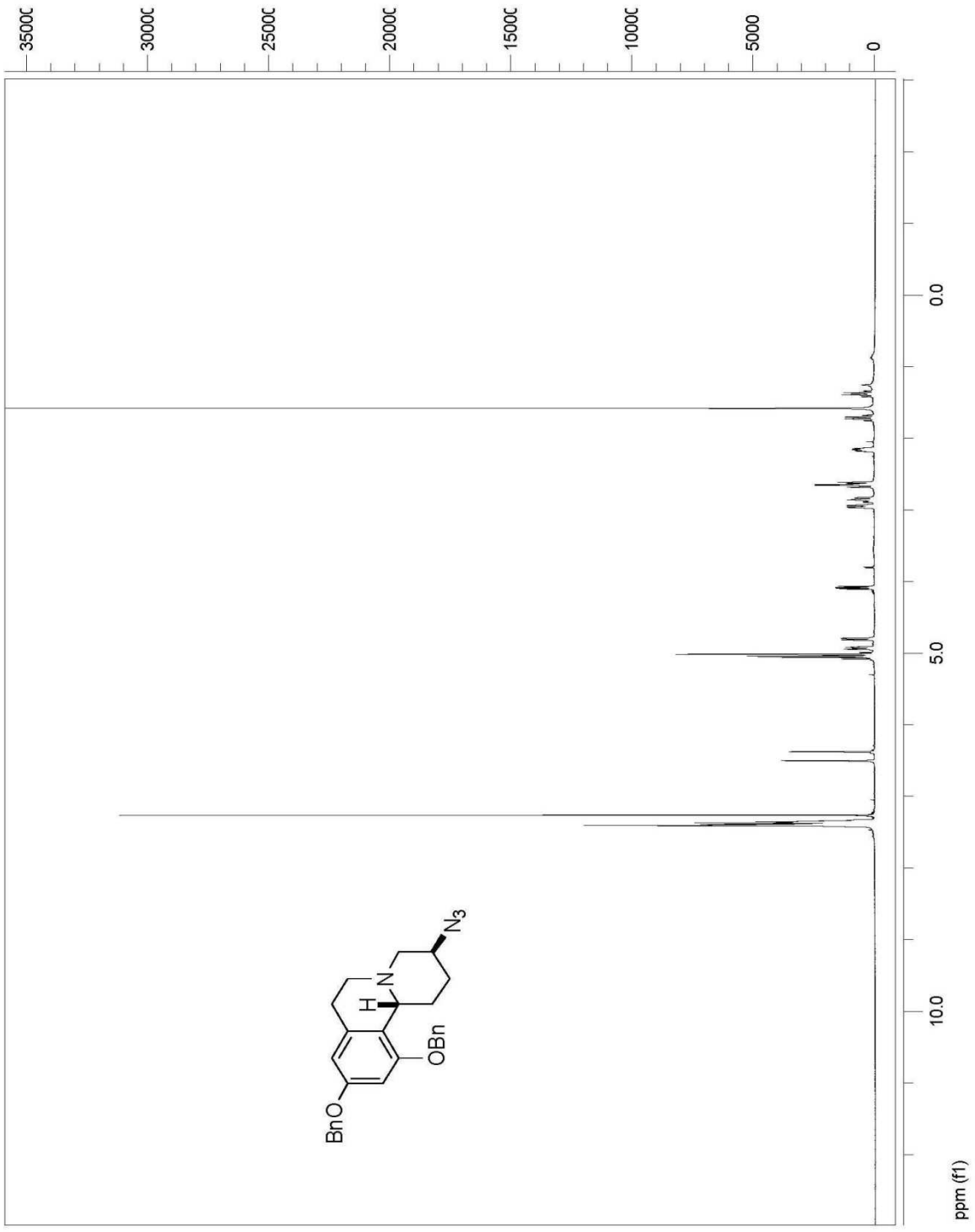
^{13}C NMR (500 MHz) of **2.45a** in $CDCl_3$



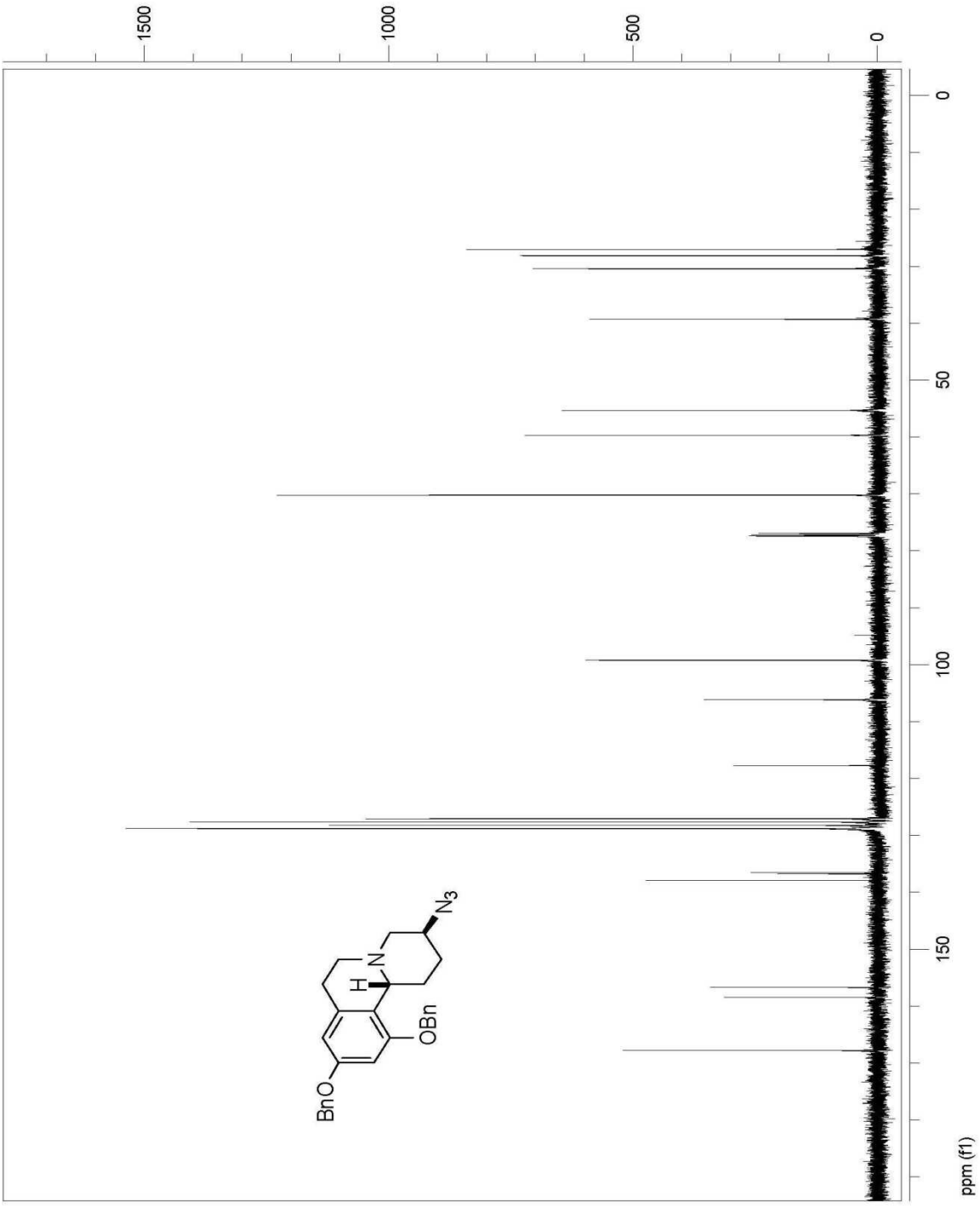
^{1}H NMR (500 MHz) of **2.49b** in $CDCl_3$



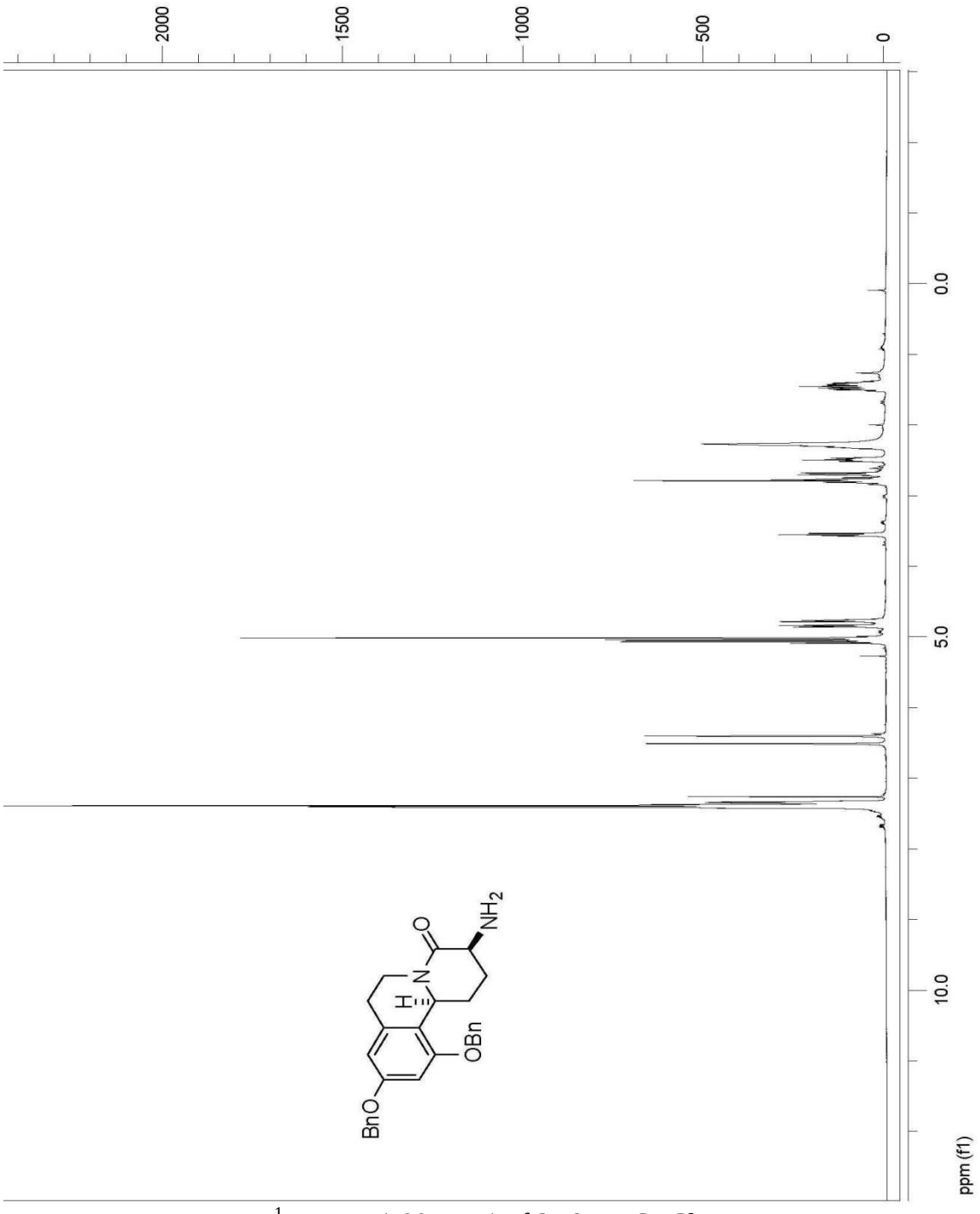
^{13}C NMR (500 MHz) of **2.49b** in $CDCl_3$



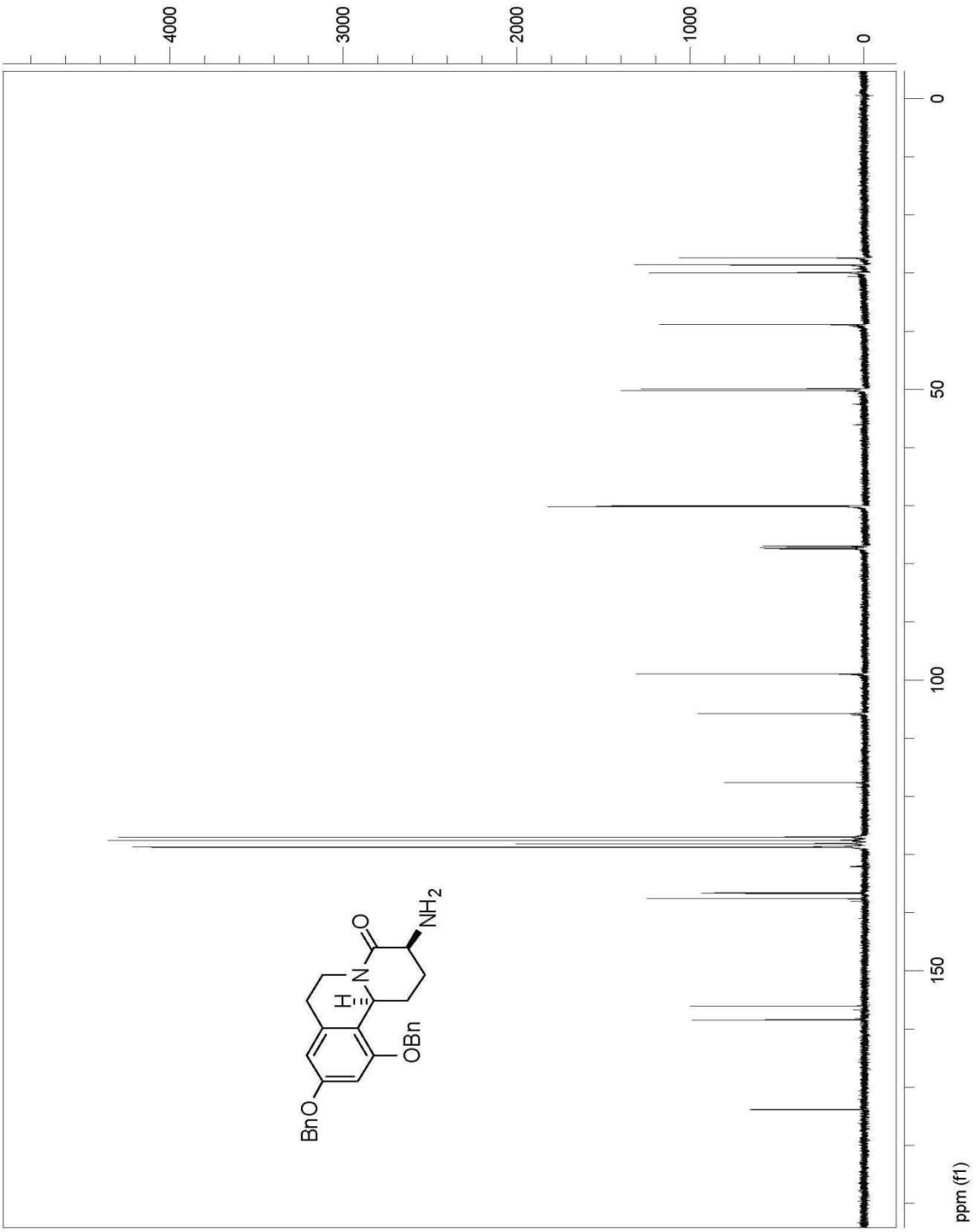
^{1}H NMR (500 MHz) of **2.48b** in $CDCl_3$



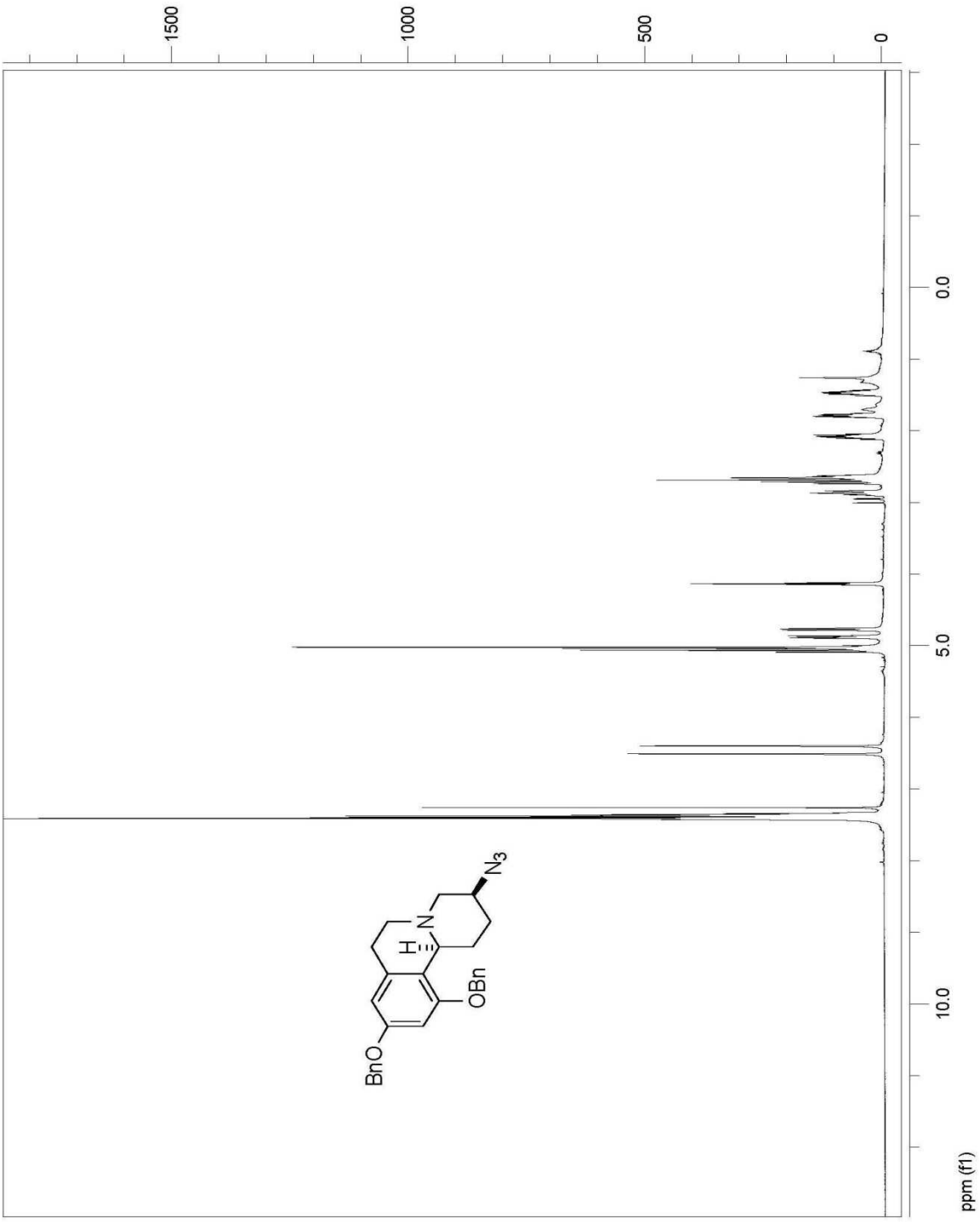
^{13}C NMR (500 MHz) of **2.48b** in $CDCl_3$



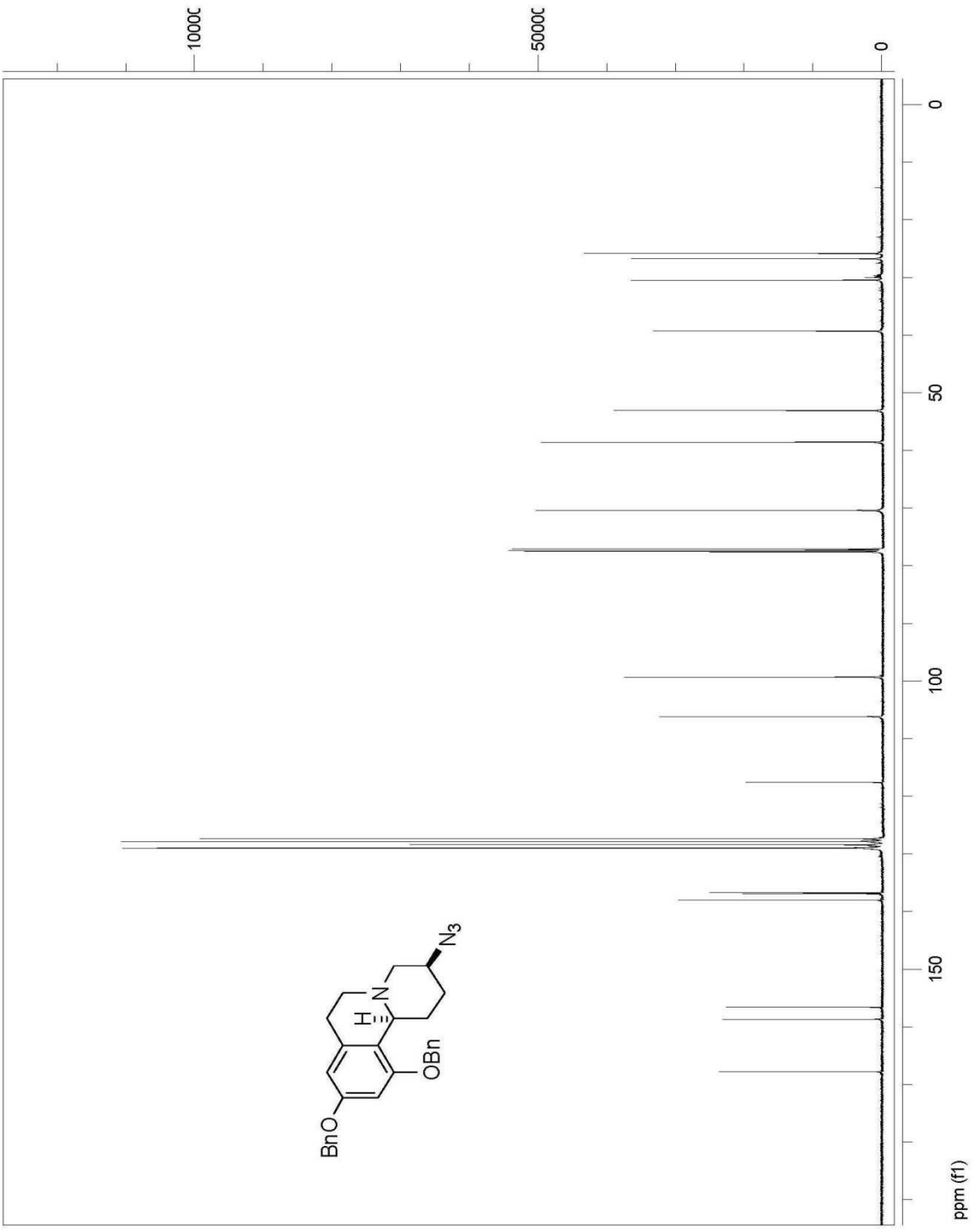
^{1}H NMR (500 MHz) of **2.49a** in $CDCl_3$



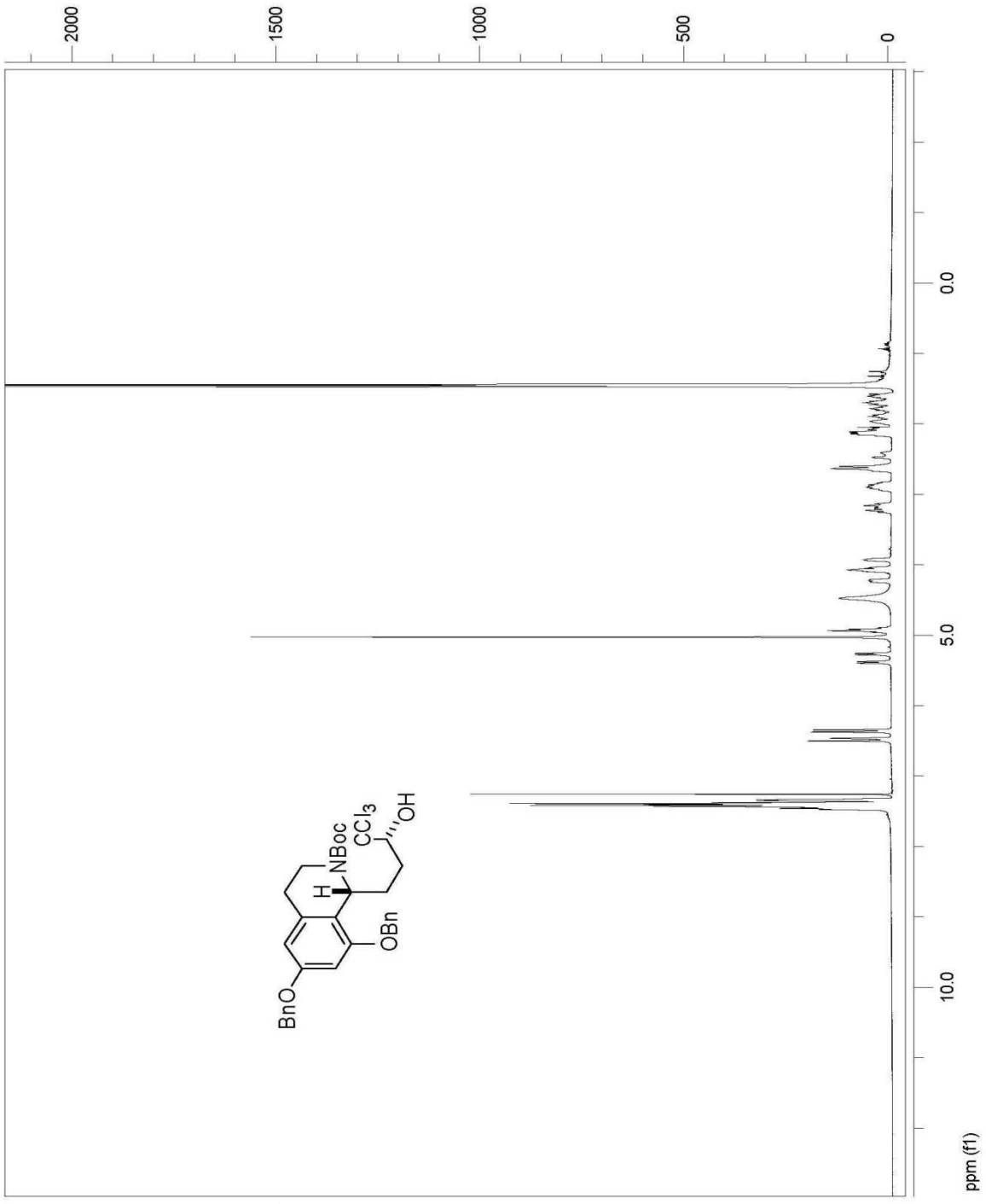
^{13}C NMR (500 MHz) of **2.49a** in $CDCl_3$



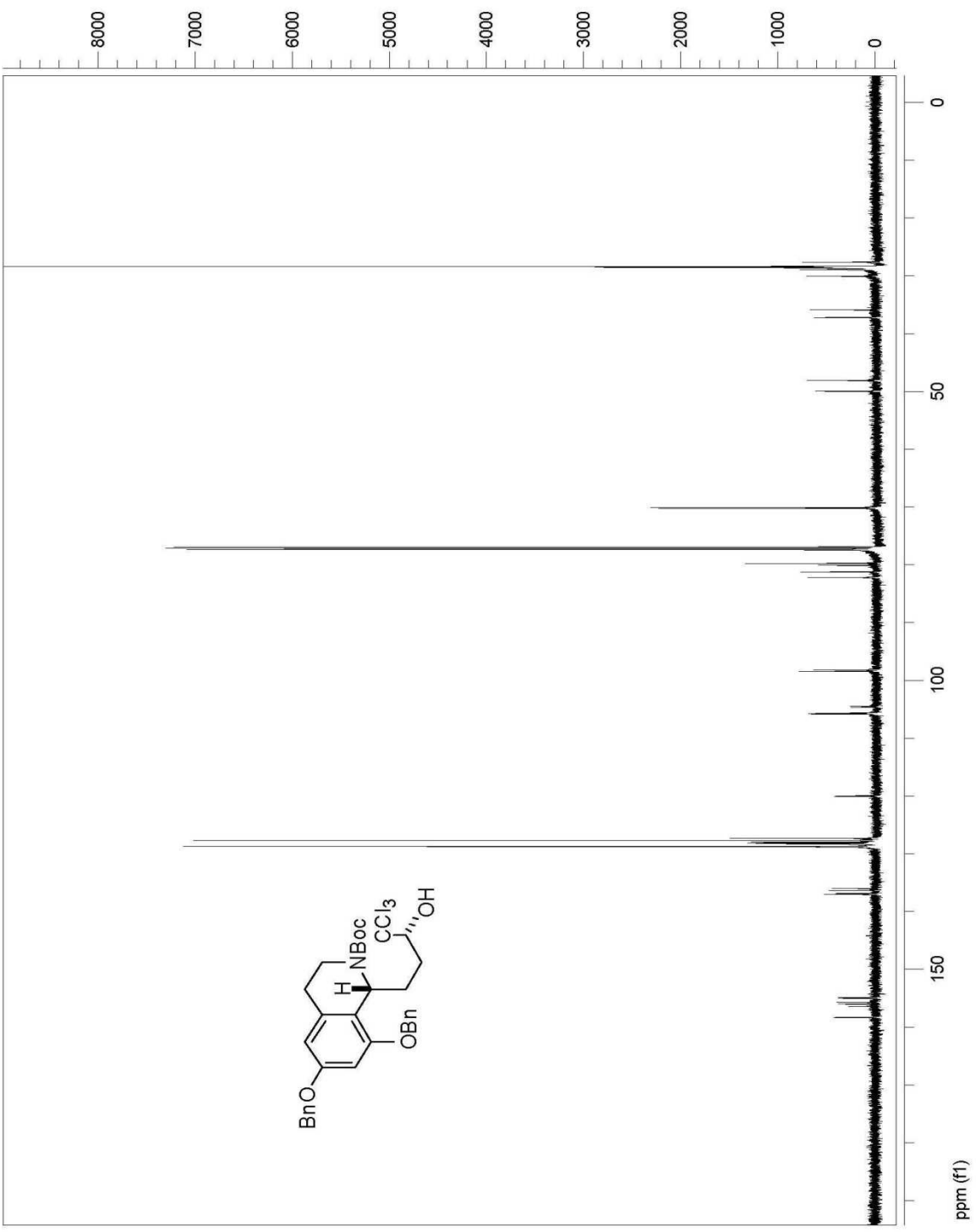
^{1}H NMR (500 MHz) of **2.48a** in $CDCl_3$



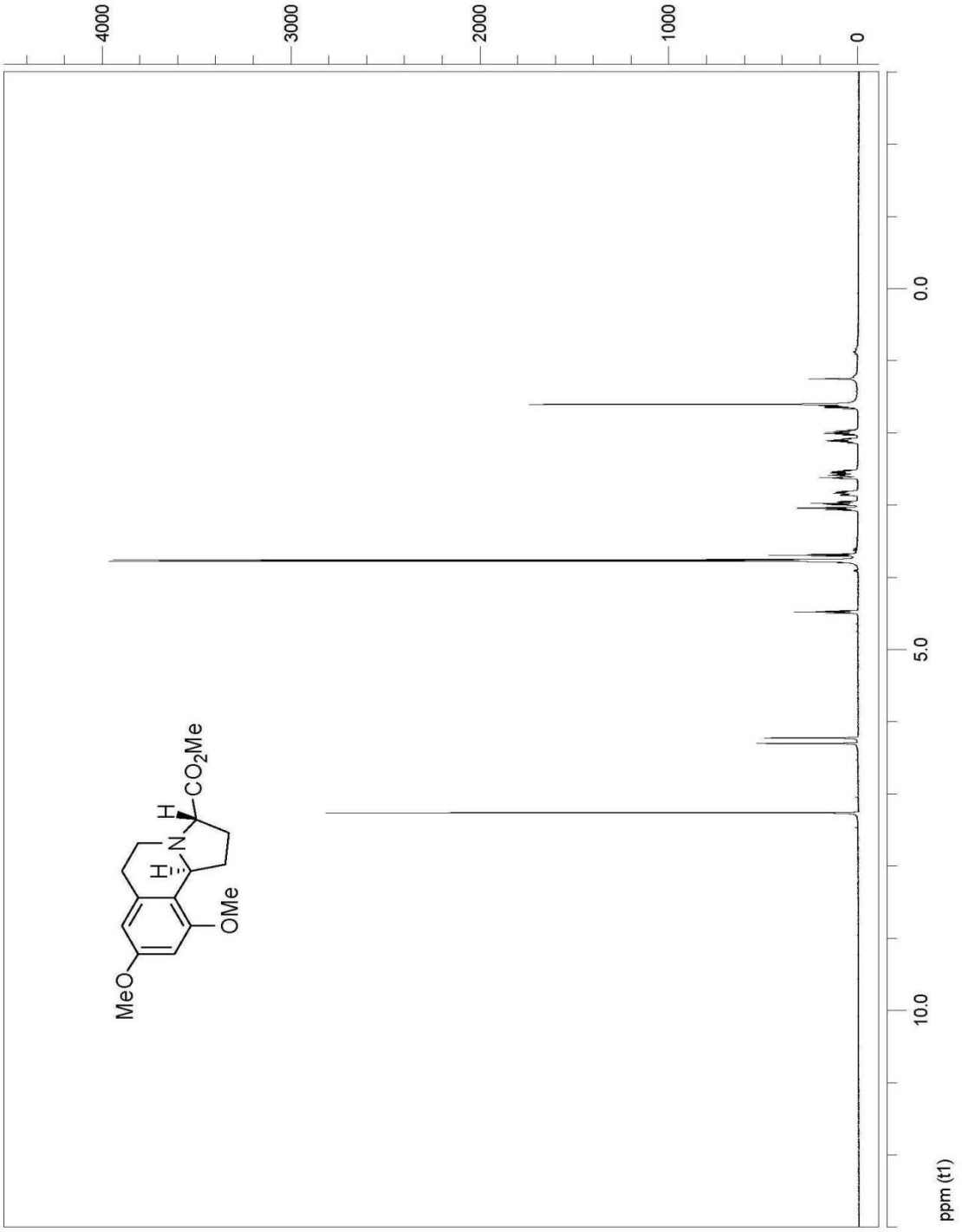
^{13}C NMR (500 MHz) of **2.48a** in $CDCl_3$



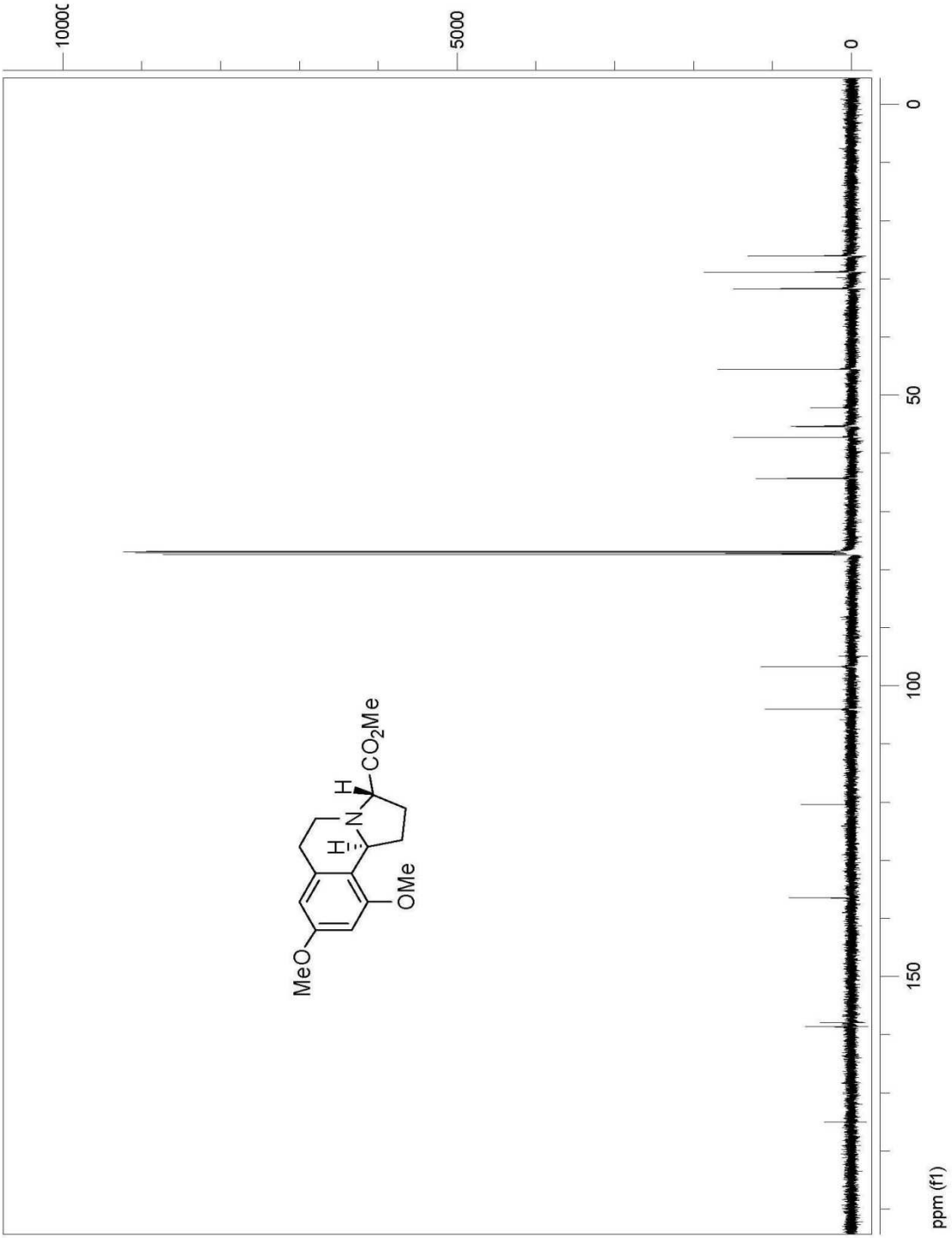
^{1}H NMR (500 MHz) of **2.45b** in $CDCl_3$



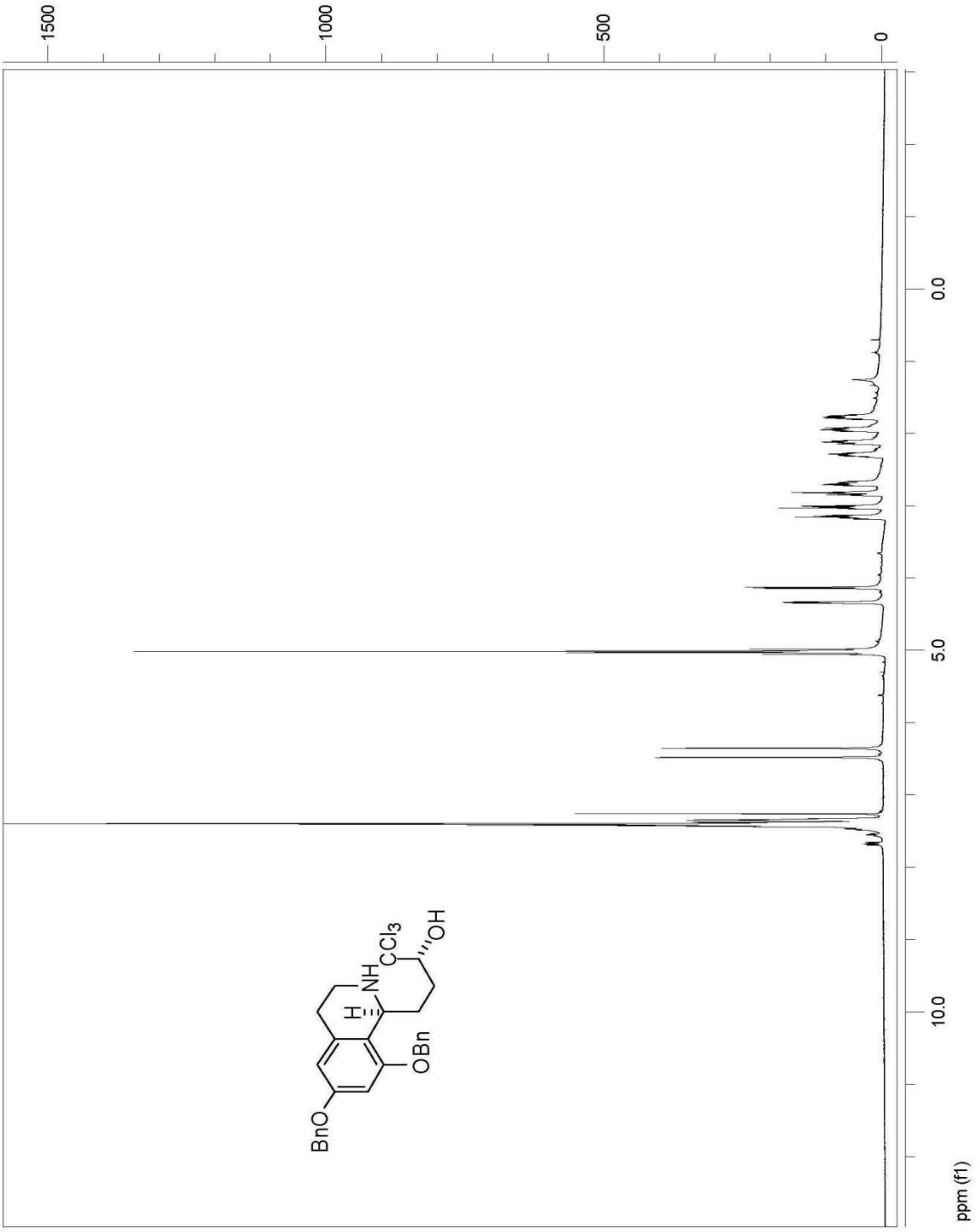
^{13}C NMR (500 MHz) of **2.45b** in $CDCl_3$



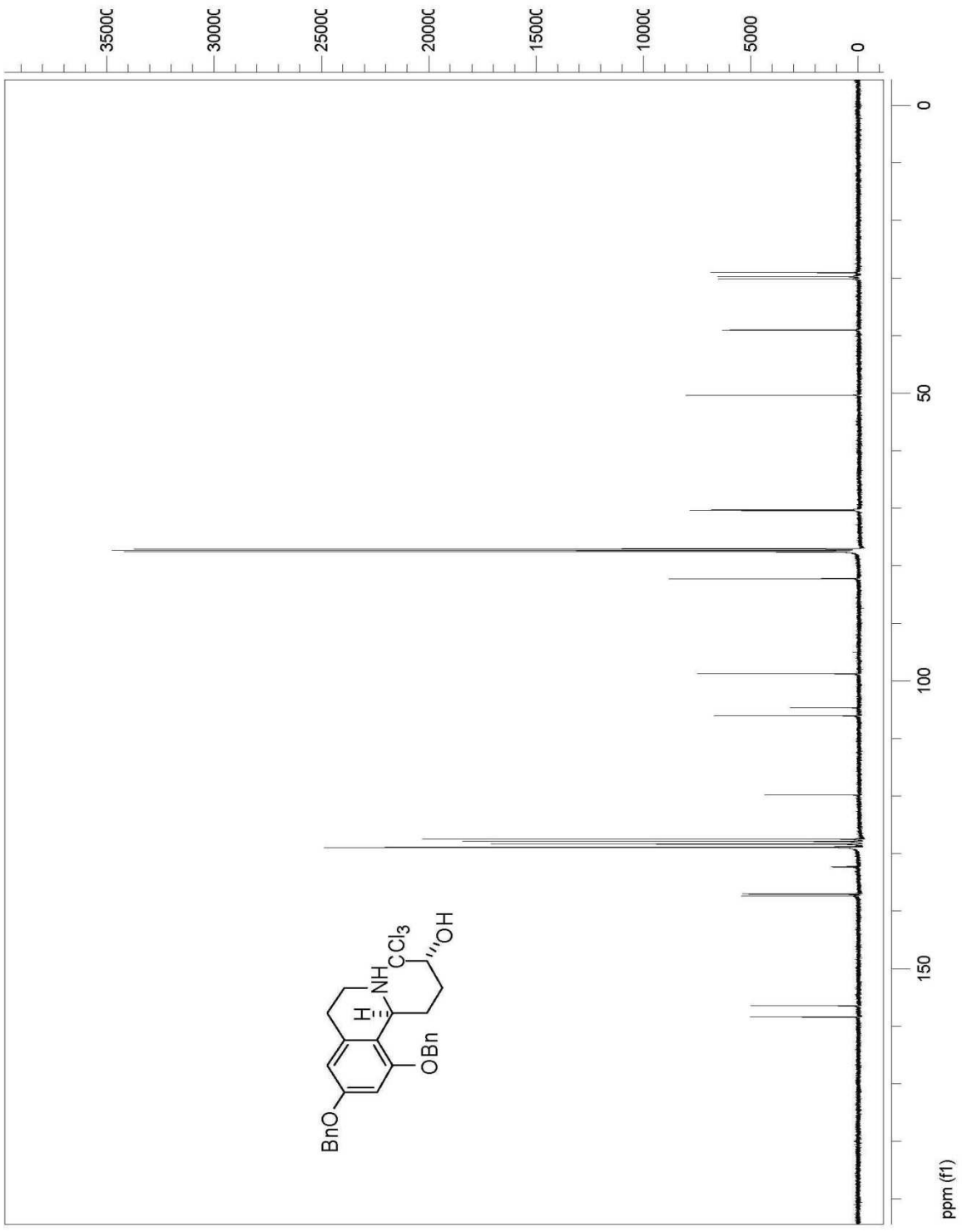
^{1}H NMR (500 MHz) of **2.35** in $CDCl_3$



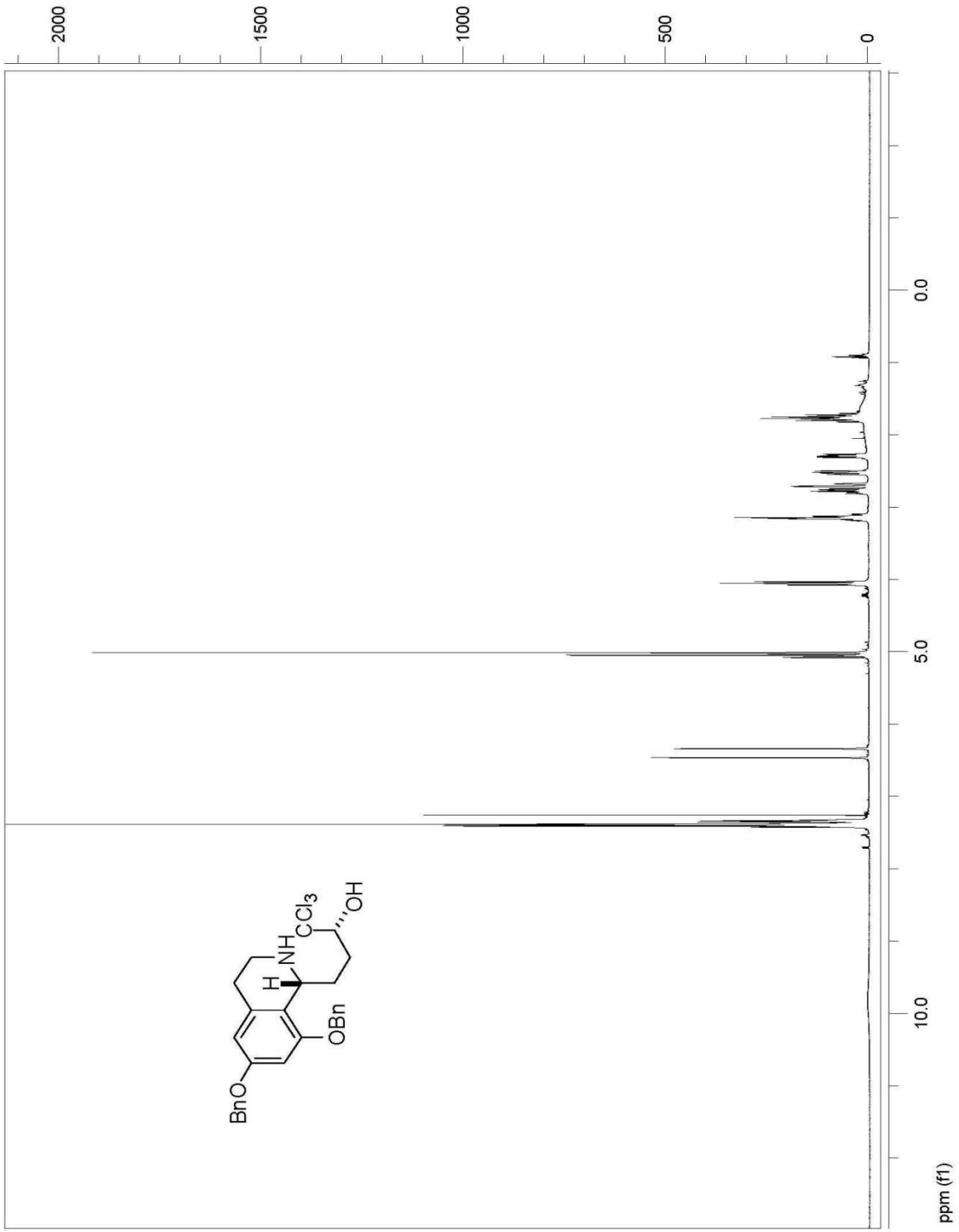
^{13}C NMR (500 MHz) of **2.35** in $CDCl_3$



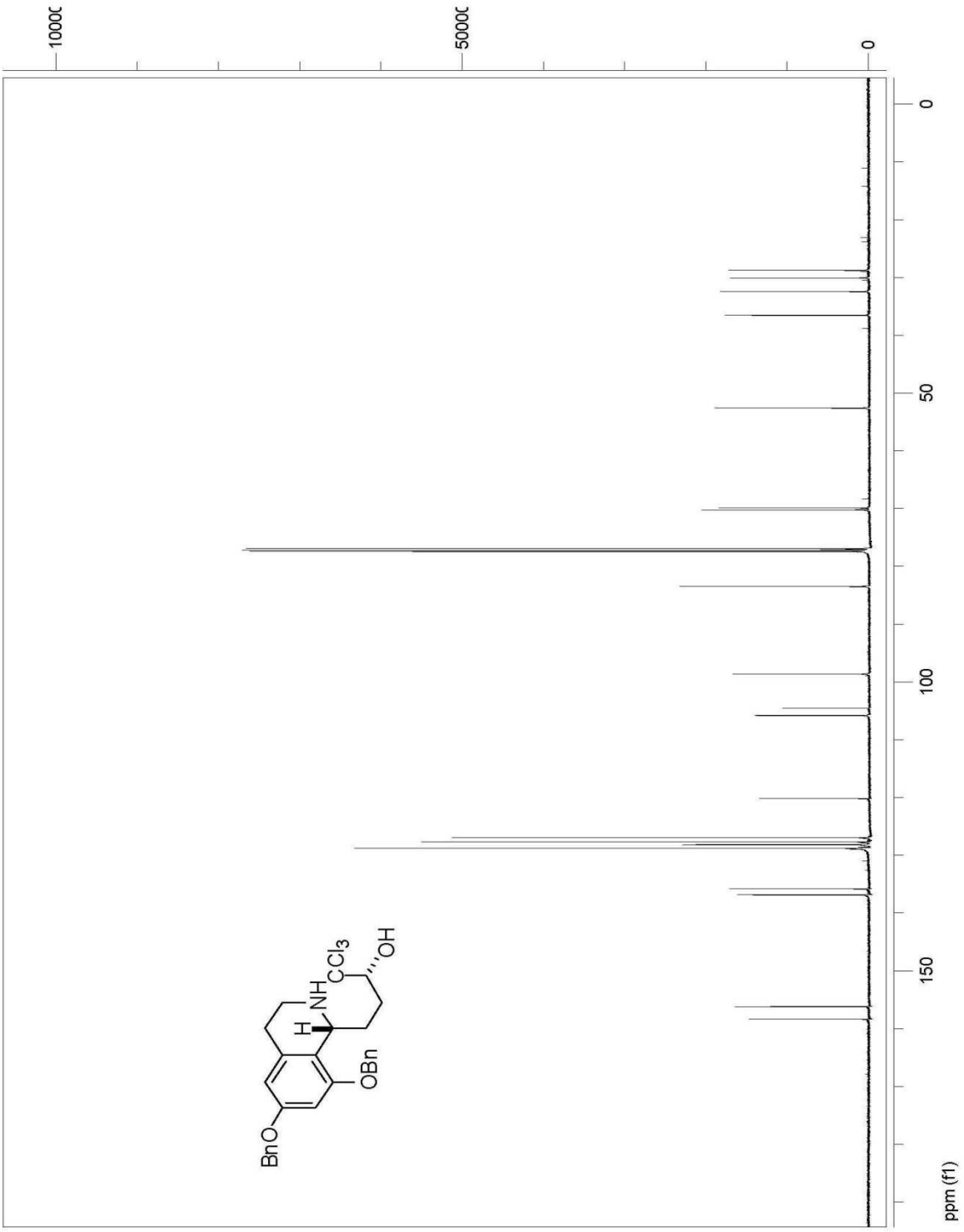
^{1}H NMR (500 MHz) of **2.6a** in $CDCl_3$



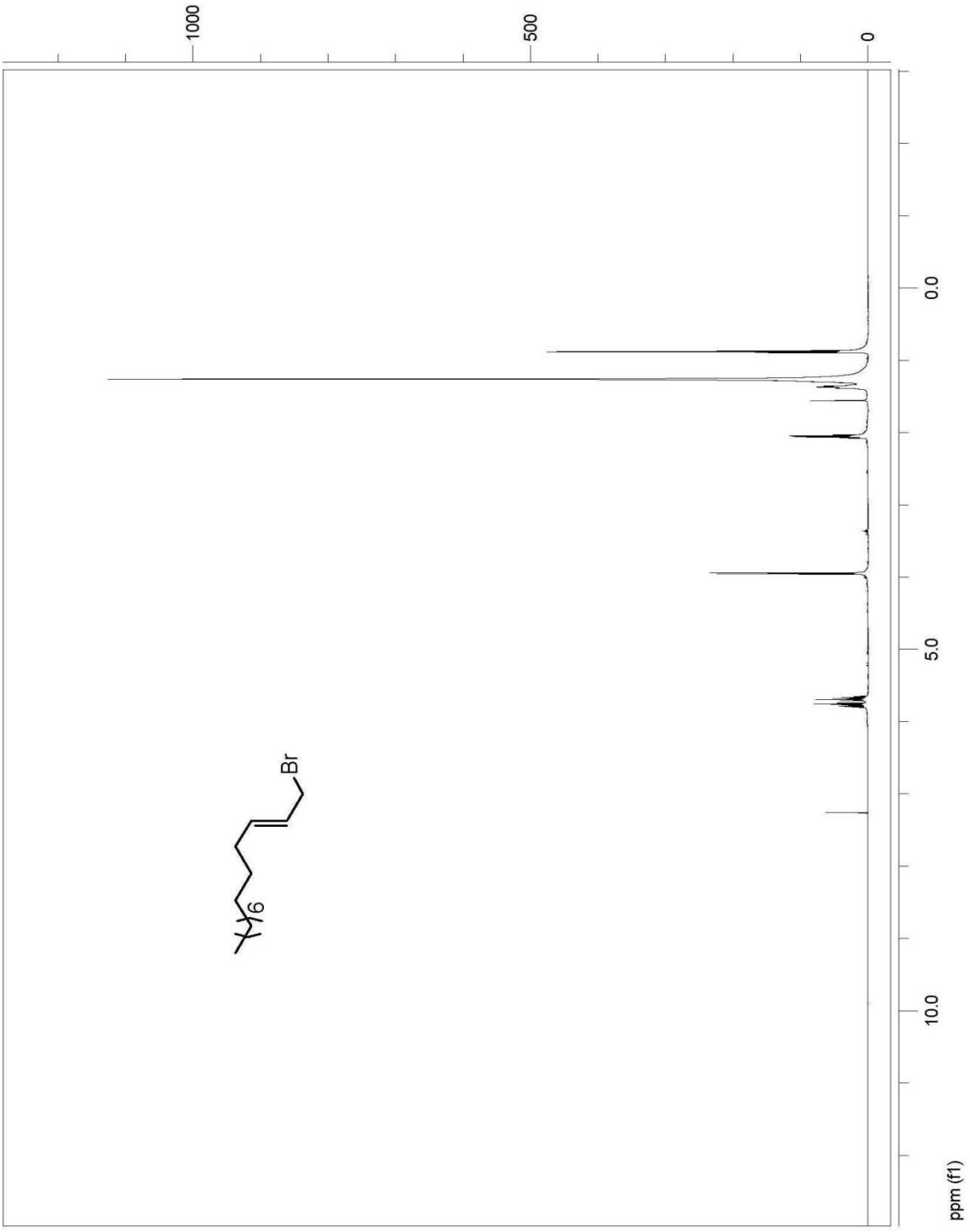
^{13}C NMR (500 MHz) of **2.6a** in $CDCl_3$



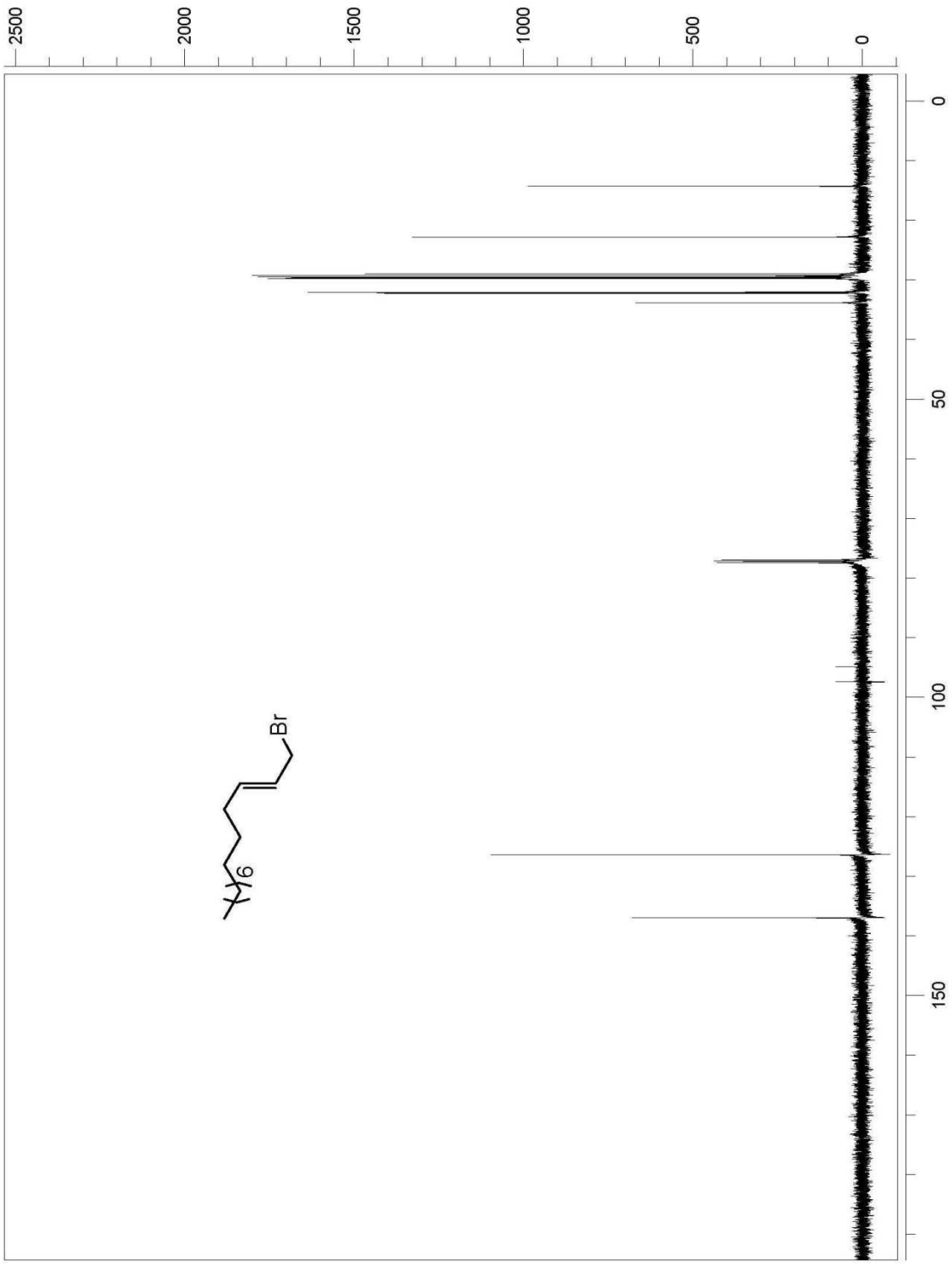
^{1}H NMR (500 MHz) of **2.6b** in $CDCl_3$



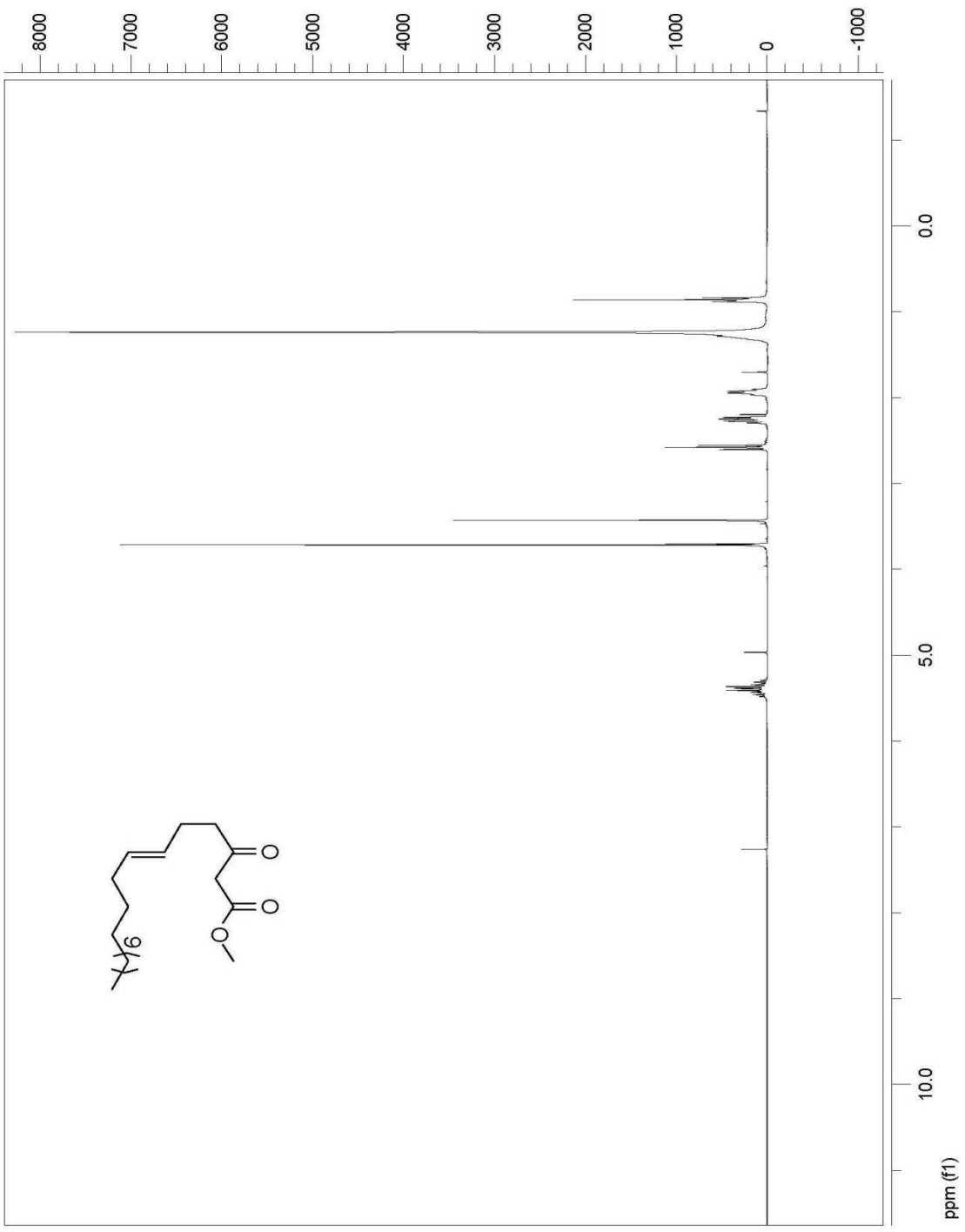
^{13}C NMR (500 MHz) of **2.6b** in $CDCl_3$



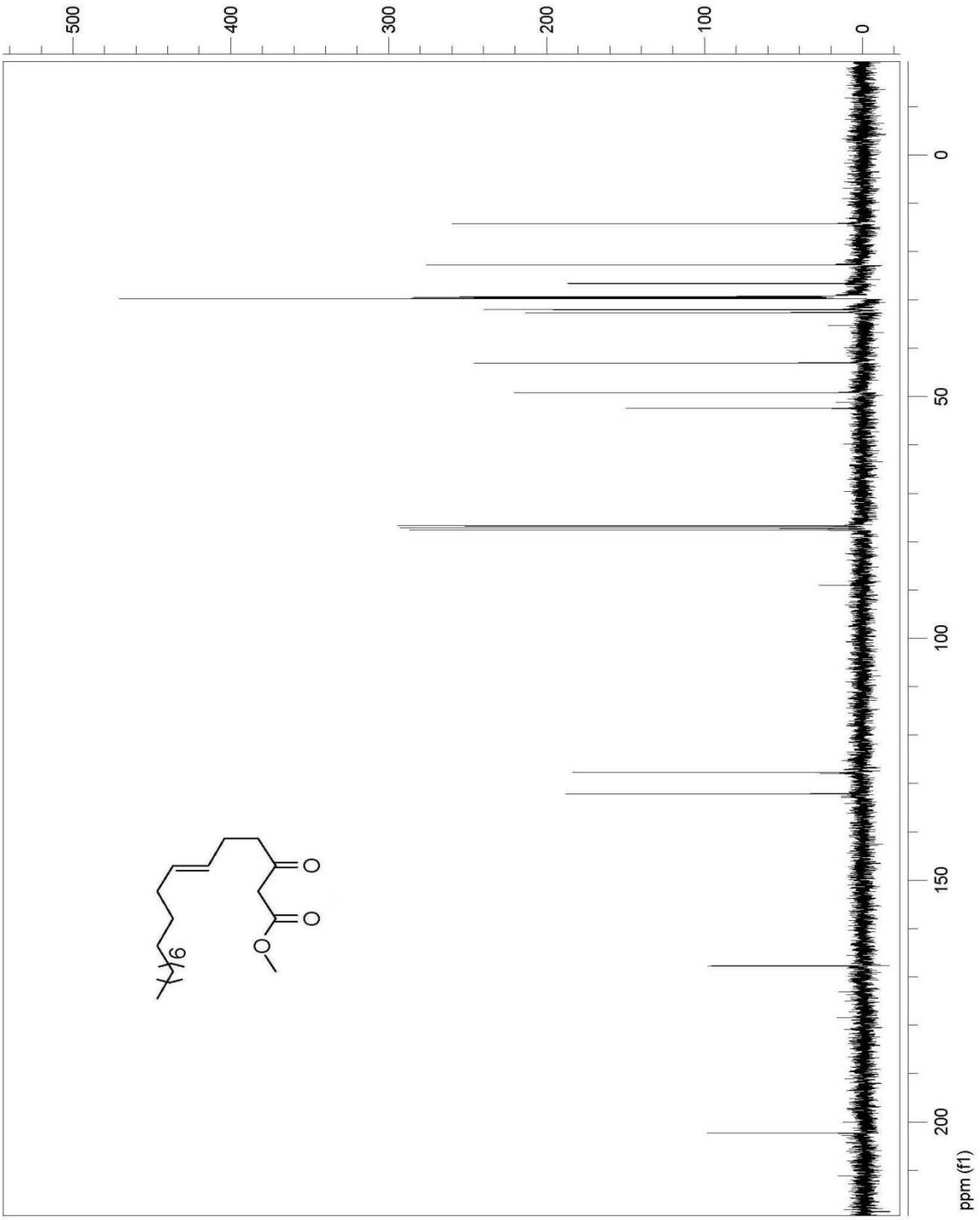
^{1}H NMR (500 MHz) of **2.51** in $CDCl_3$



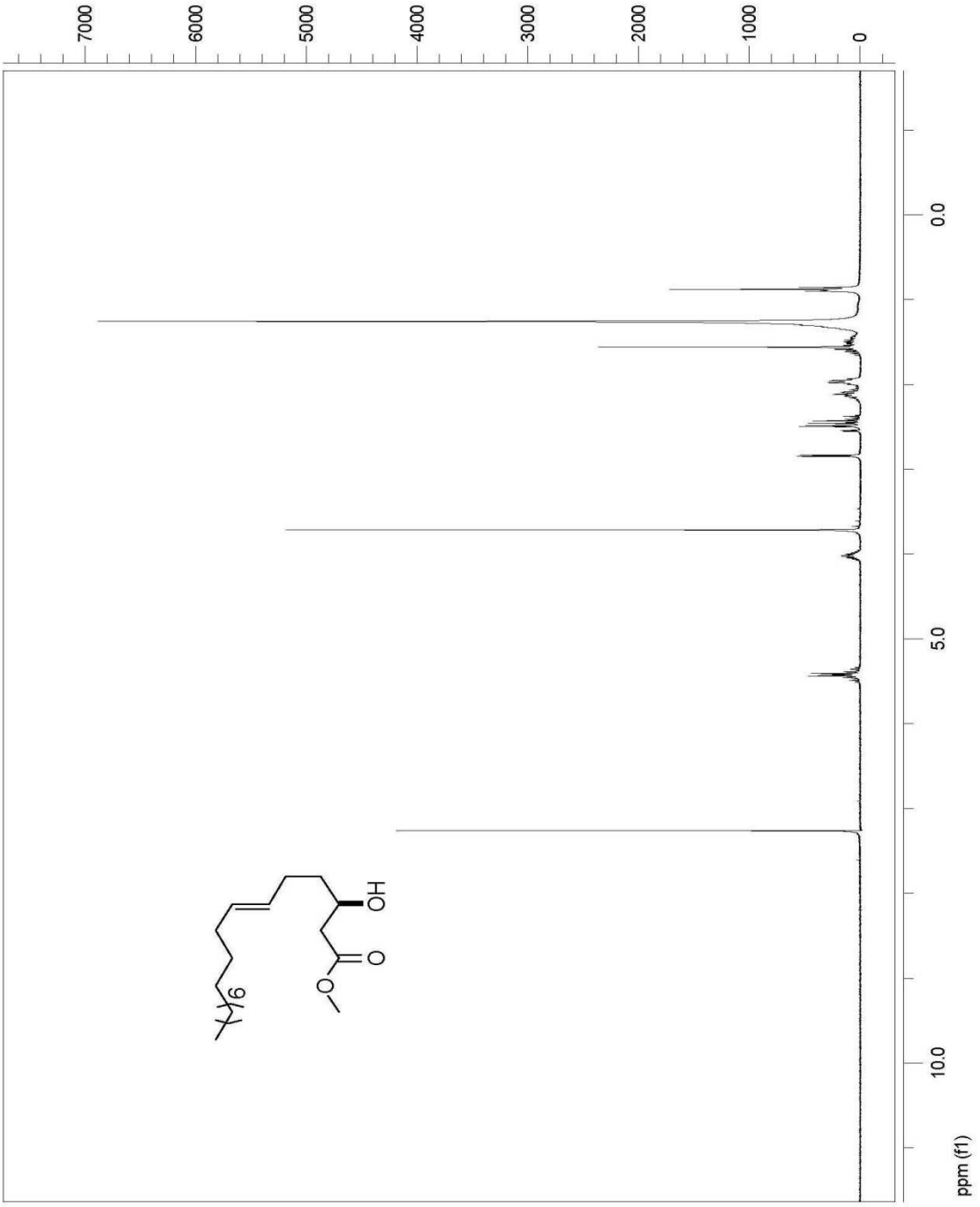
^{13}C NMR (500 MHz) of **2.51** in $CDCl_3$



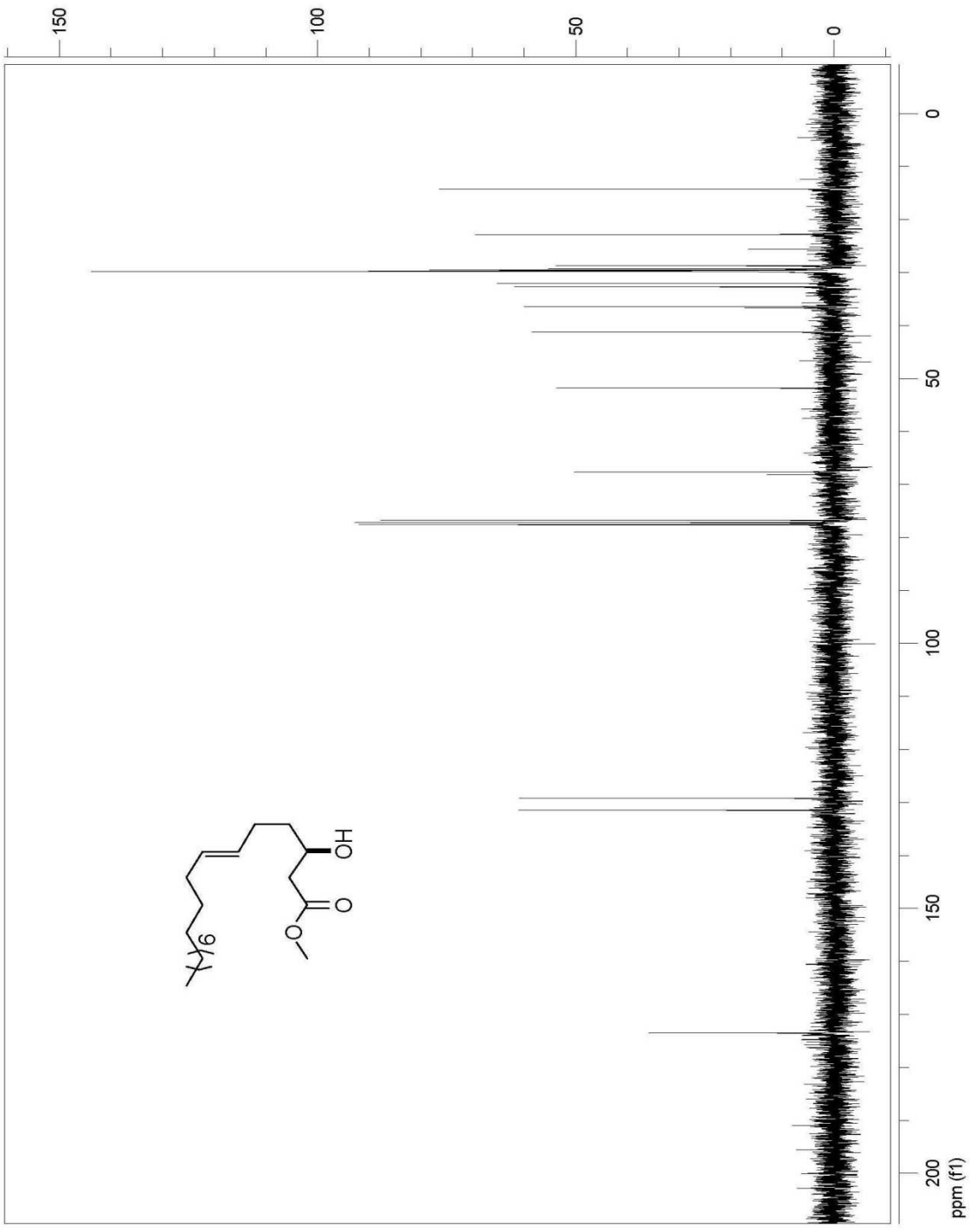
^{1}H NMR (500 MHz) of **2.52** in $CDCl_3$



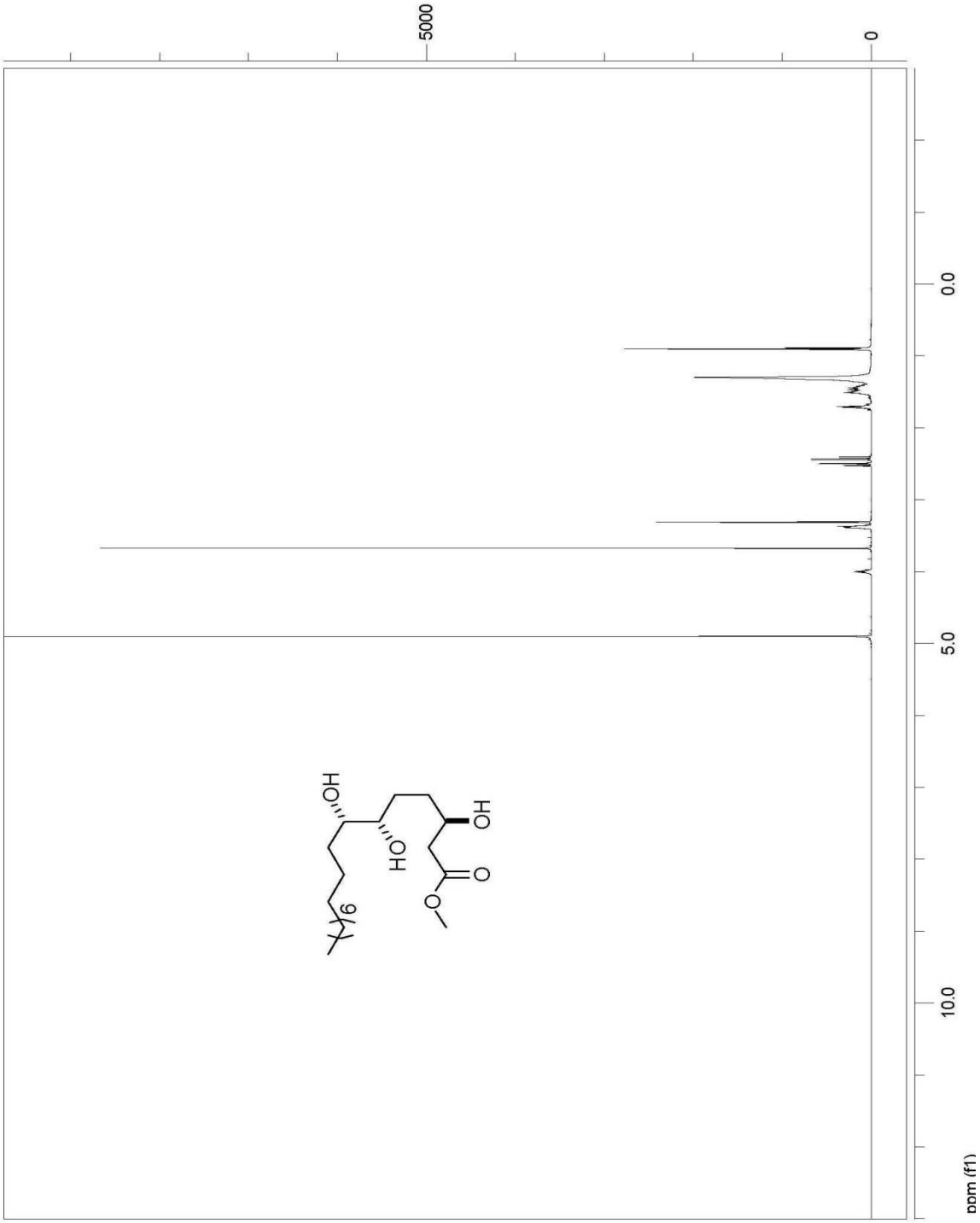
^{13}C NMR (500 MHz) of **2.52** in $CDCl_3$



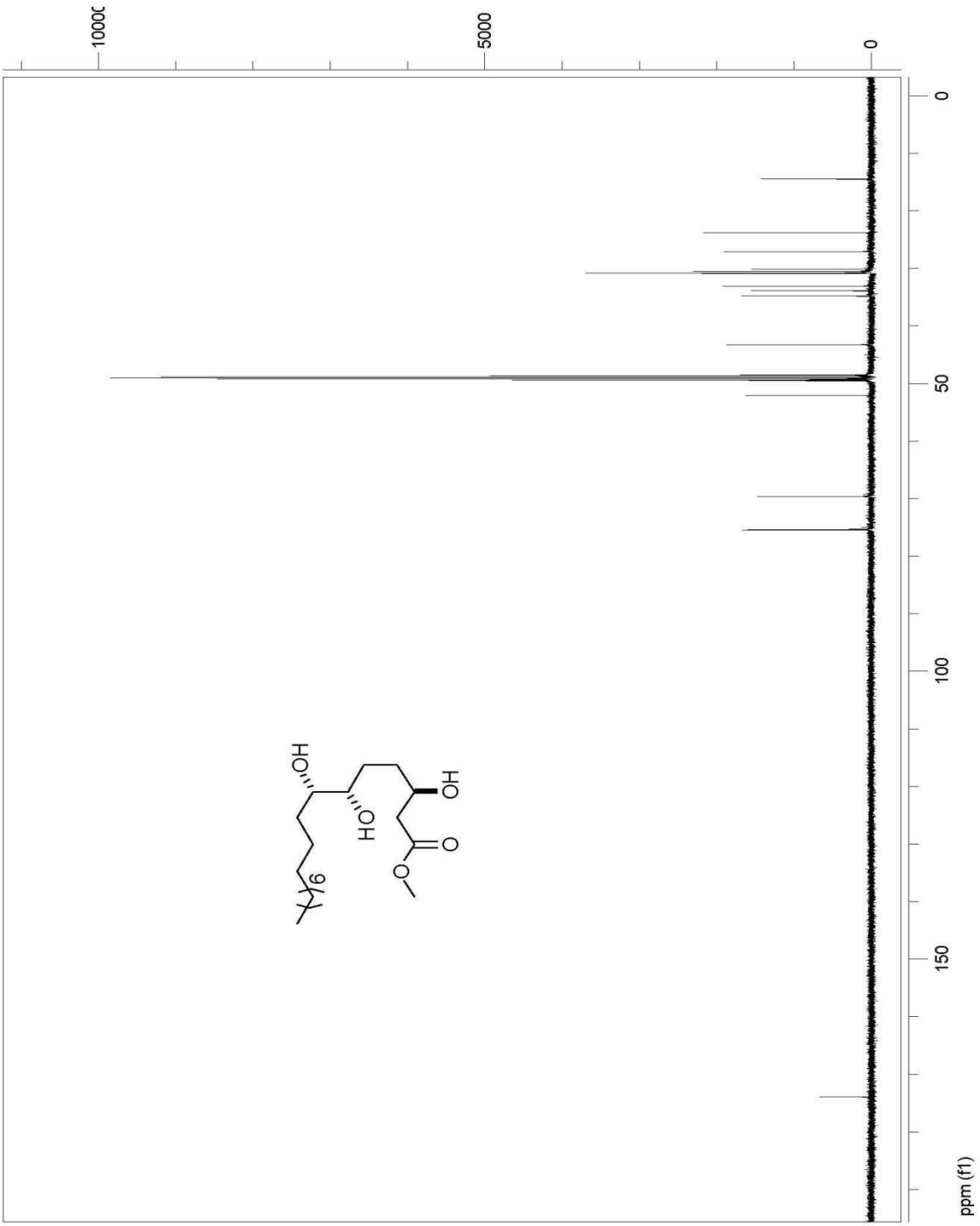
^{1}H NMR (500 MHz) of **2.53** in $CDCl_3$



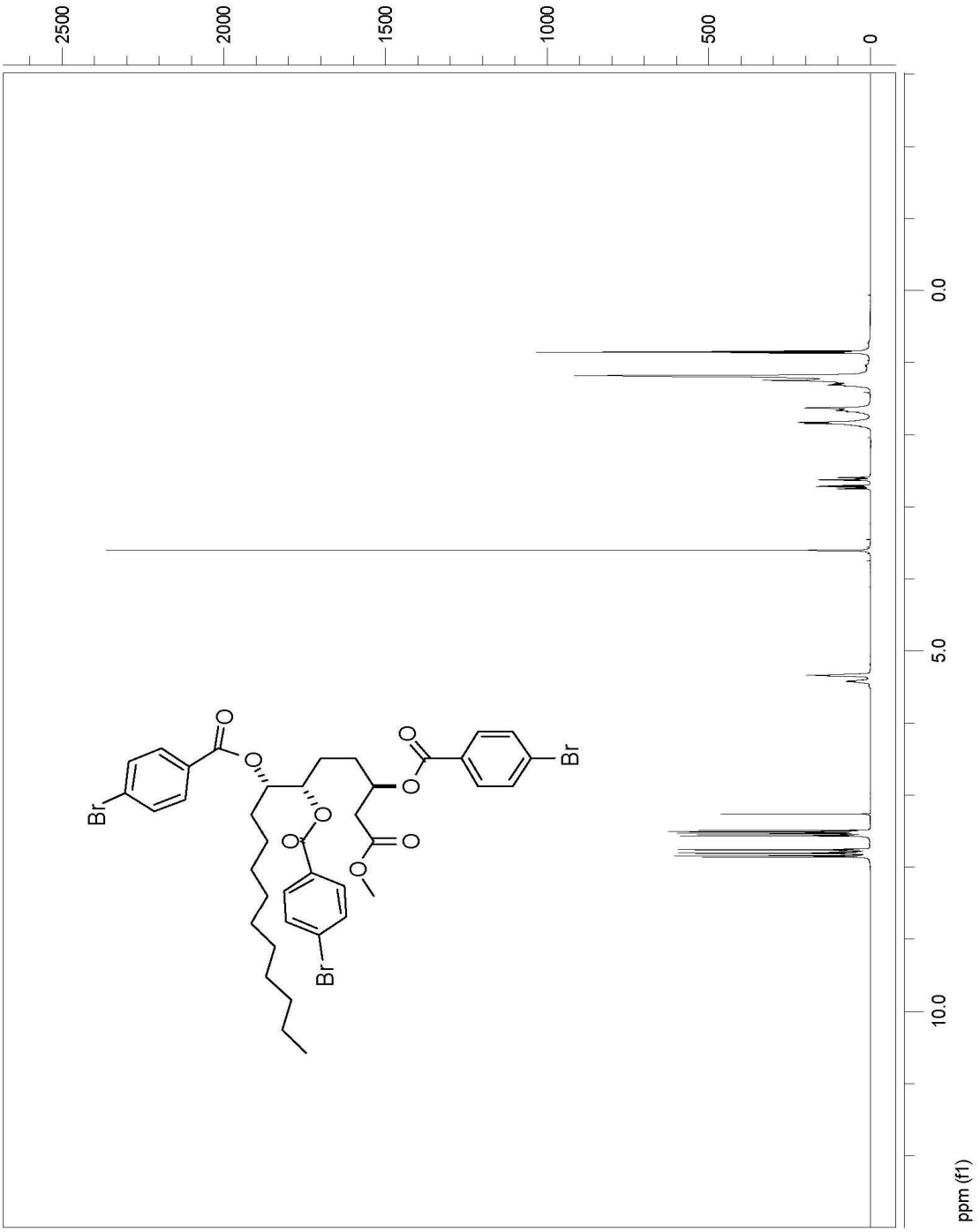
^{13}C NMR (500 MHz) of **2.53** in $CDCl_3$



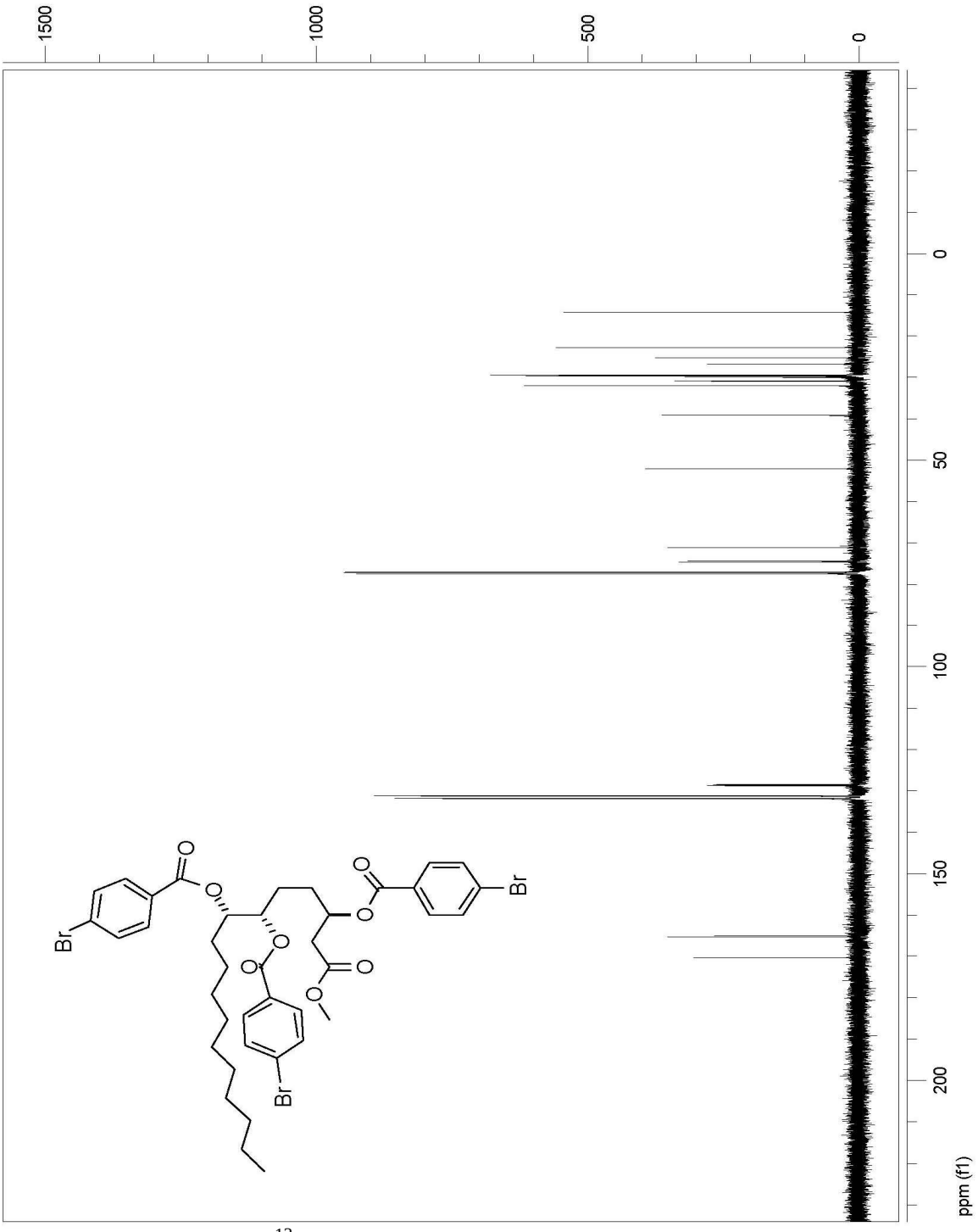
^{1}H NMR (500 MHz) of **2.54** in $CDCl_3$



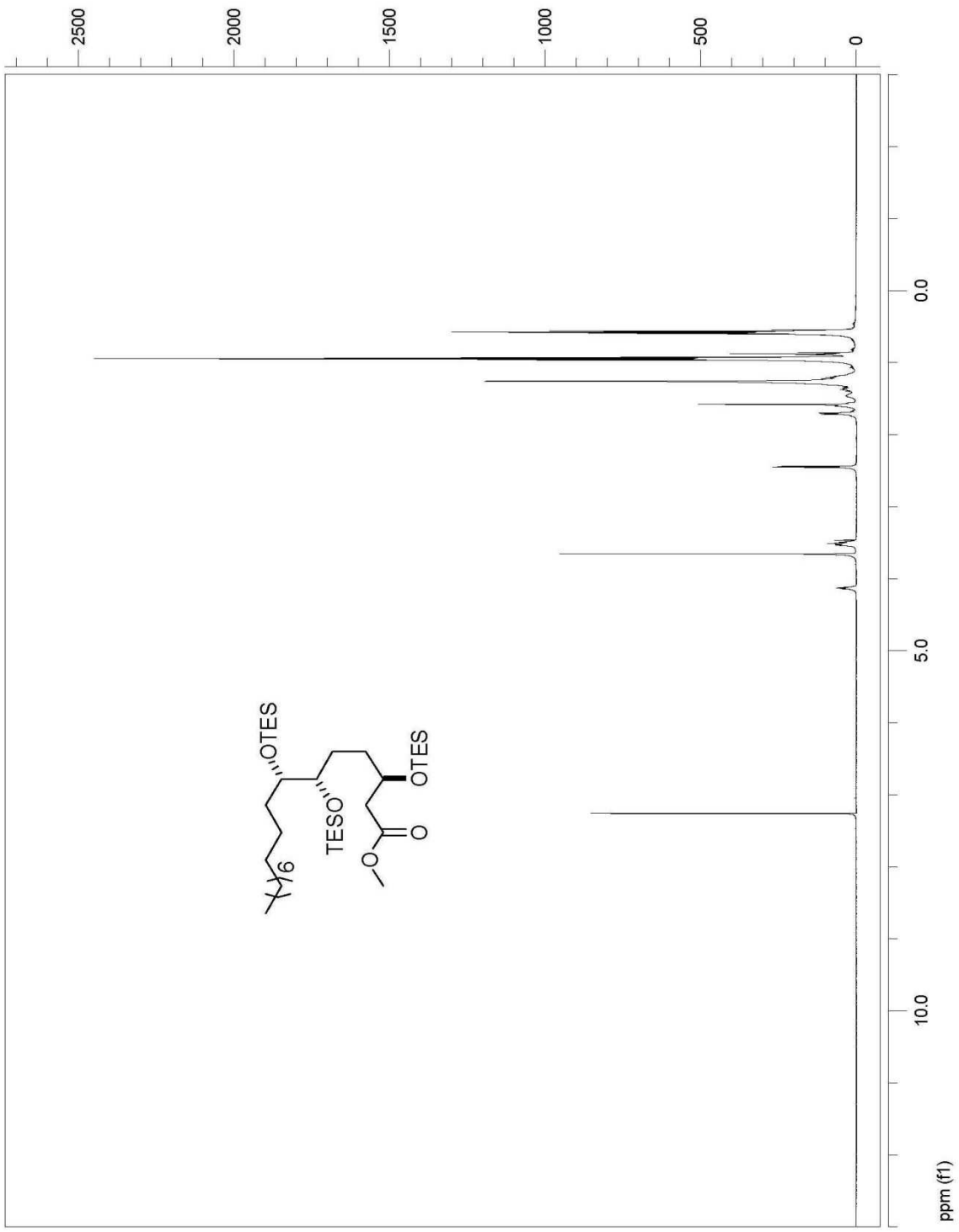
^{13}C NMR (500 MHz) of **2.54** in $CDCl_3$



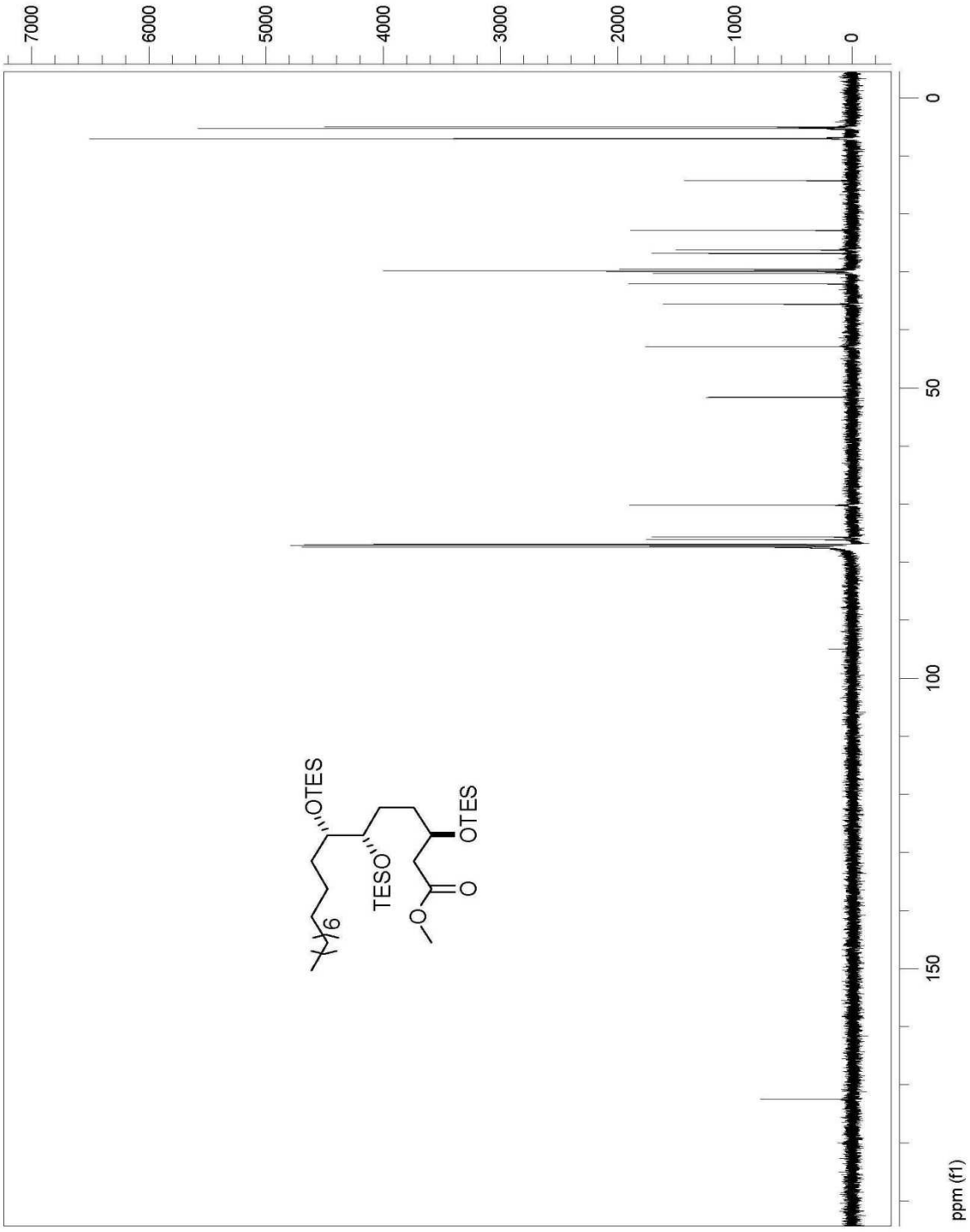
^{1}H NMR (500 MHz) of **2.55** in $CDCl_3$



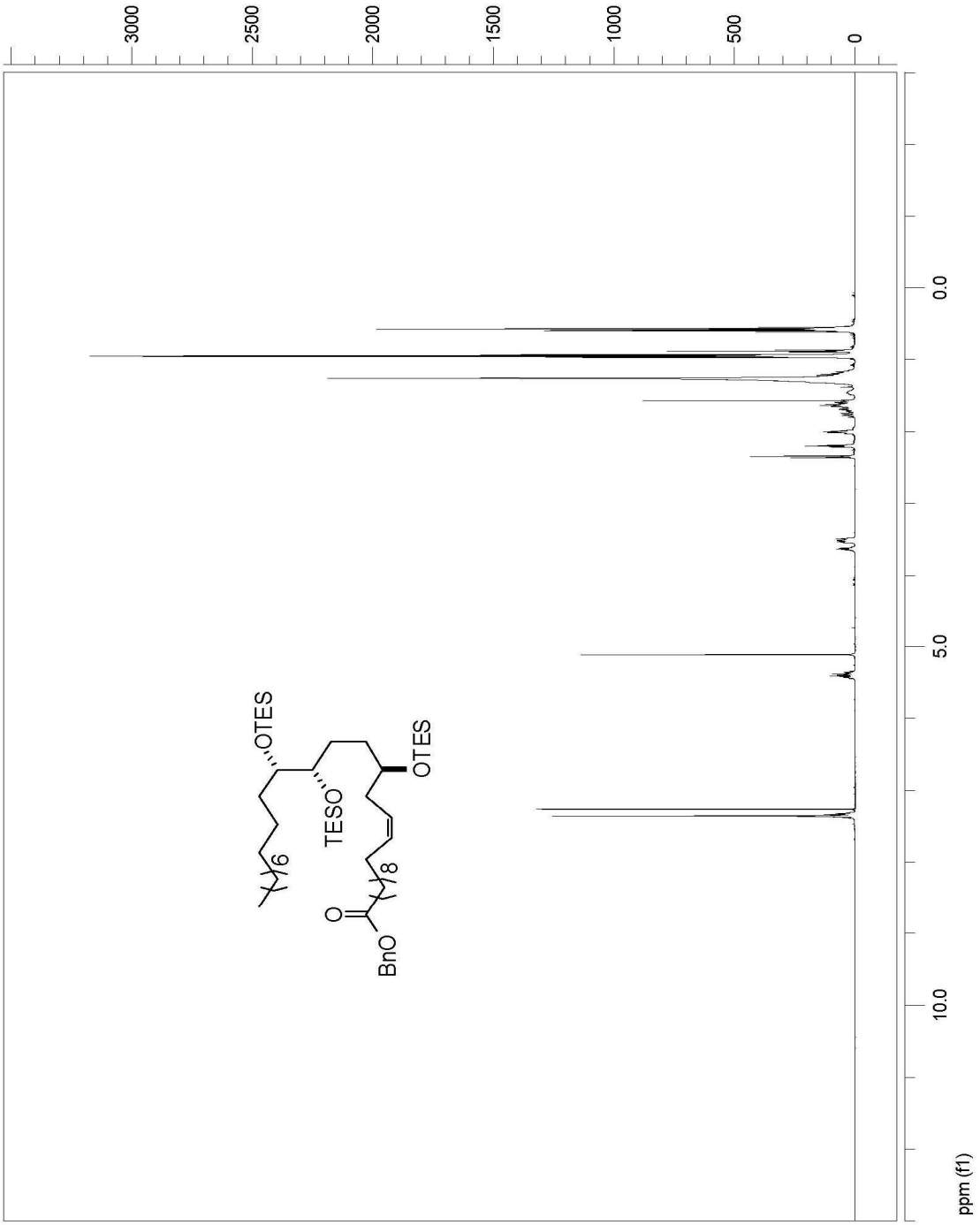
^{13}C NMR (500 MHz) of **2.55** in $CDCl_3$



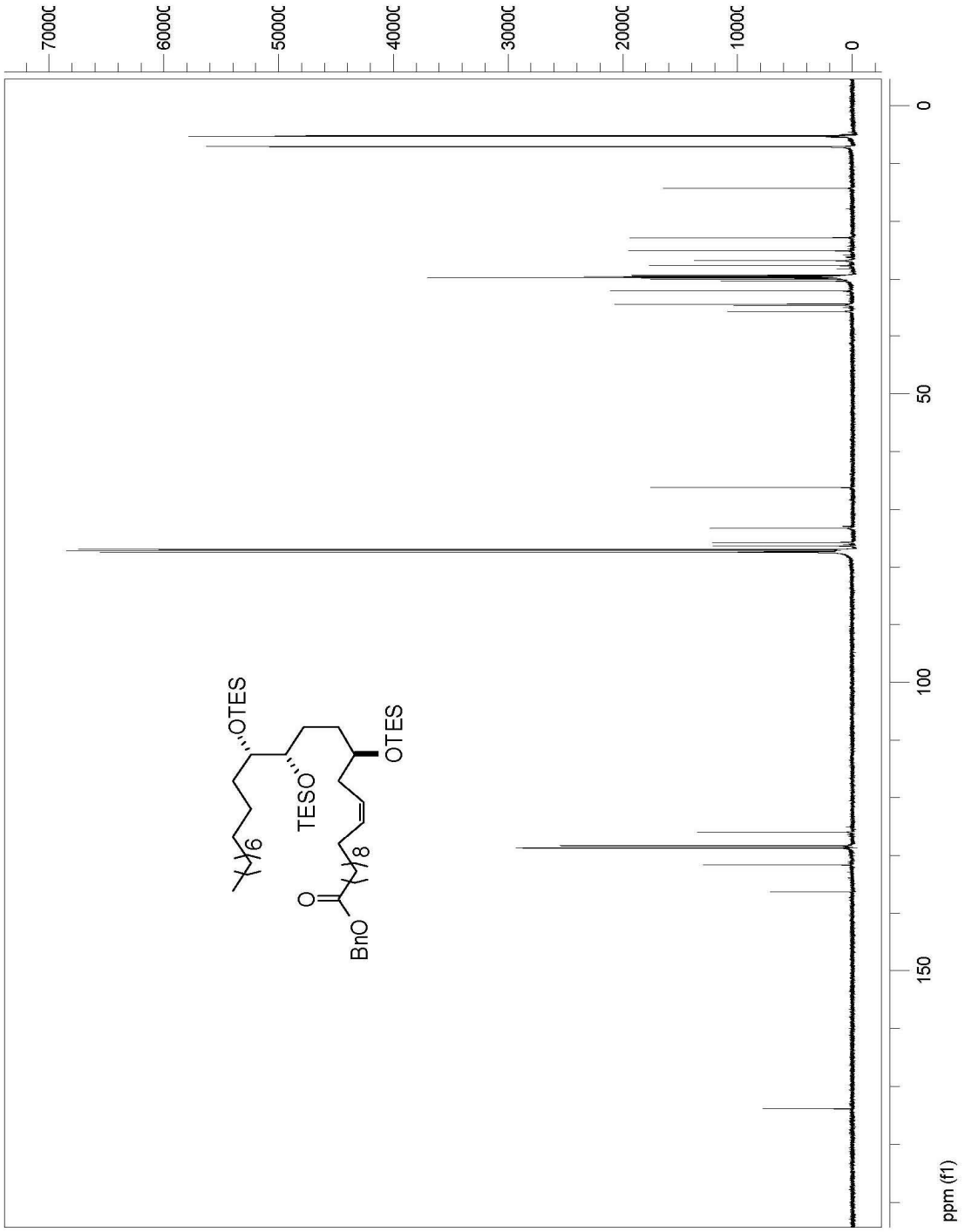
^{1}H NMR (500 MHz) of **2.56** in $CDCl_3$



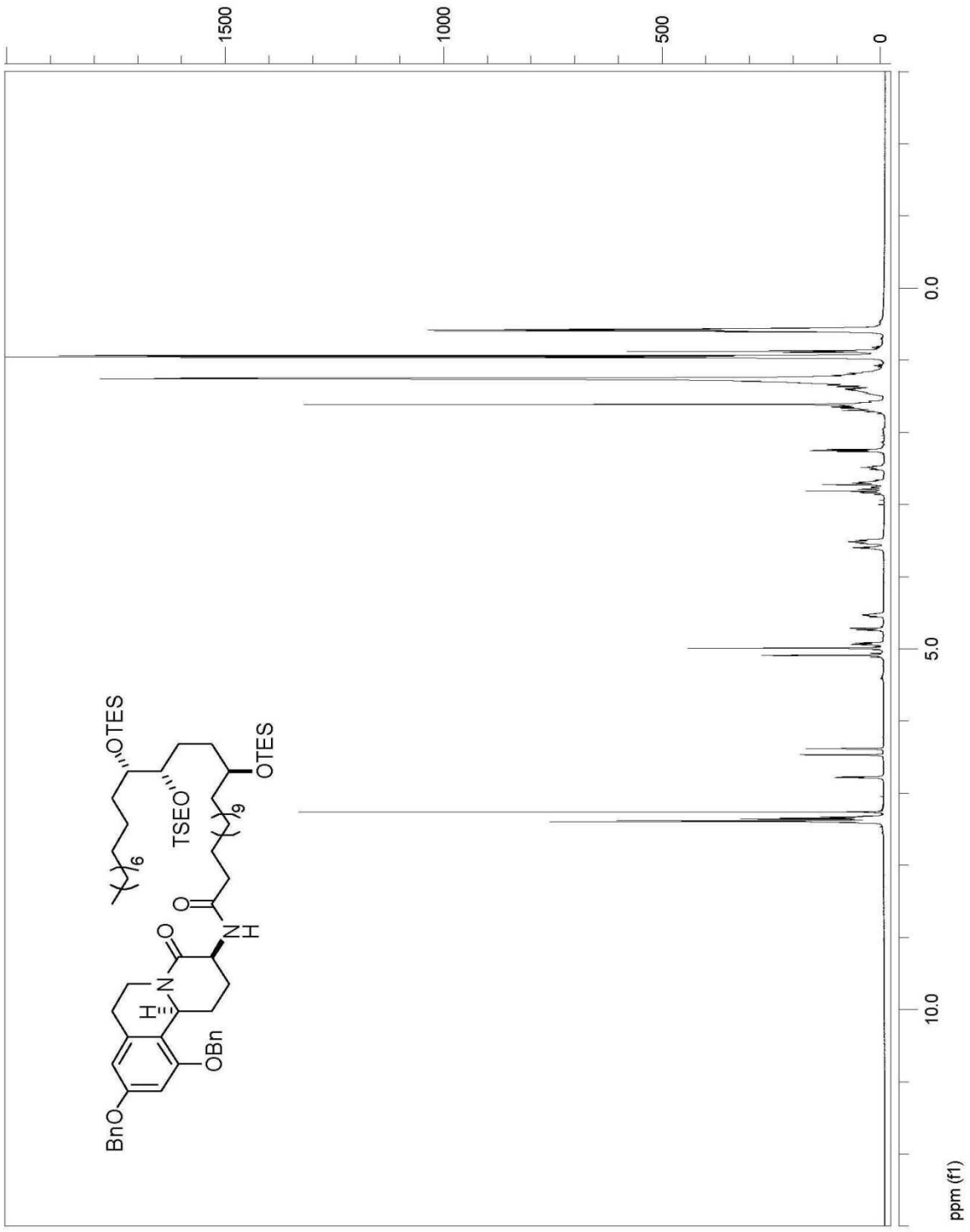
^{13}C NMR (500 MHz) of **2.56** in $CDCl_3$



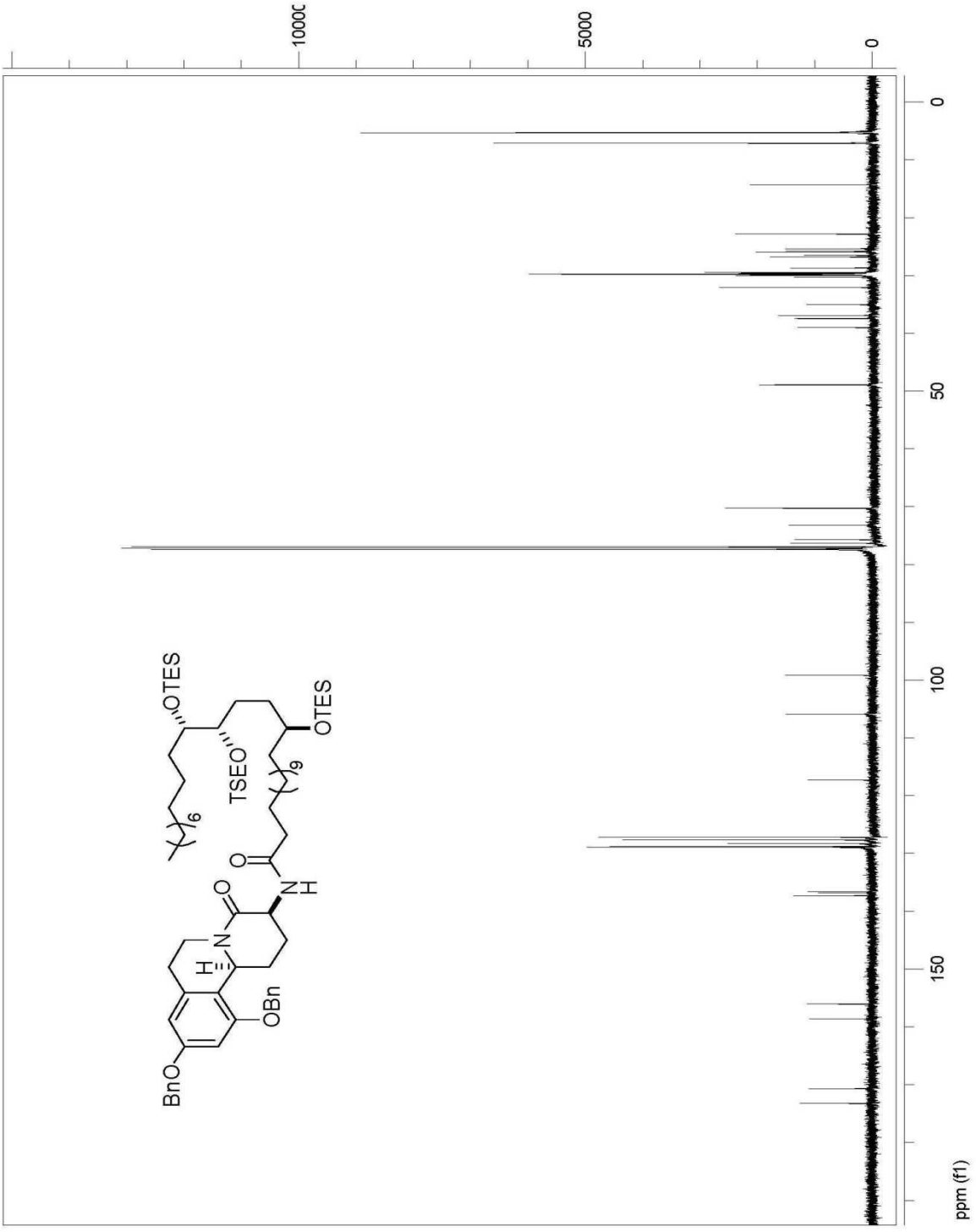
^{1}H NMR (500 MHz) of **2.59** in $CDCl_3$



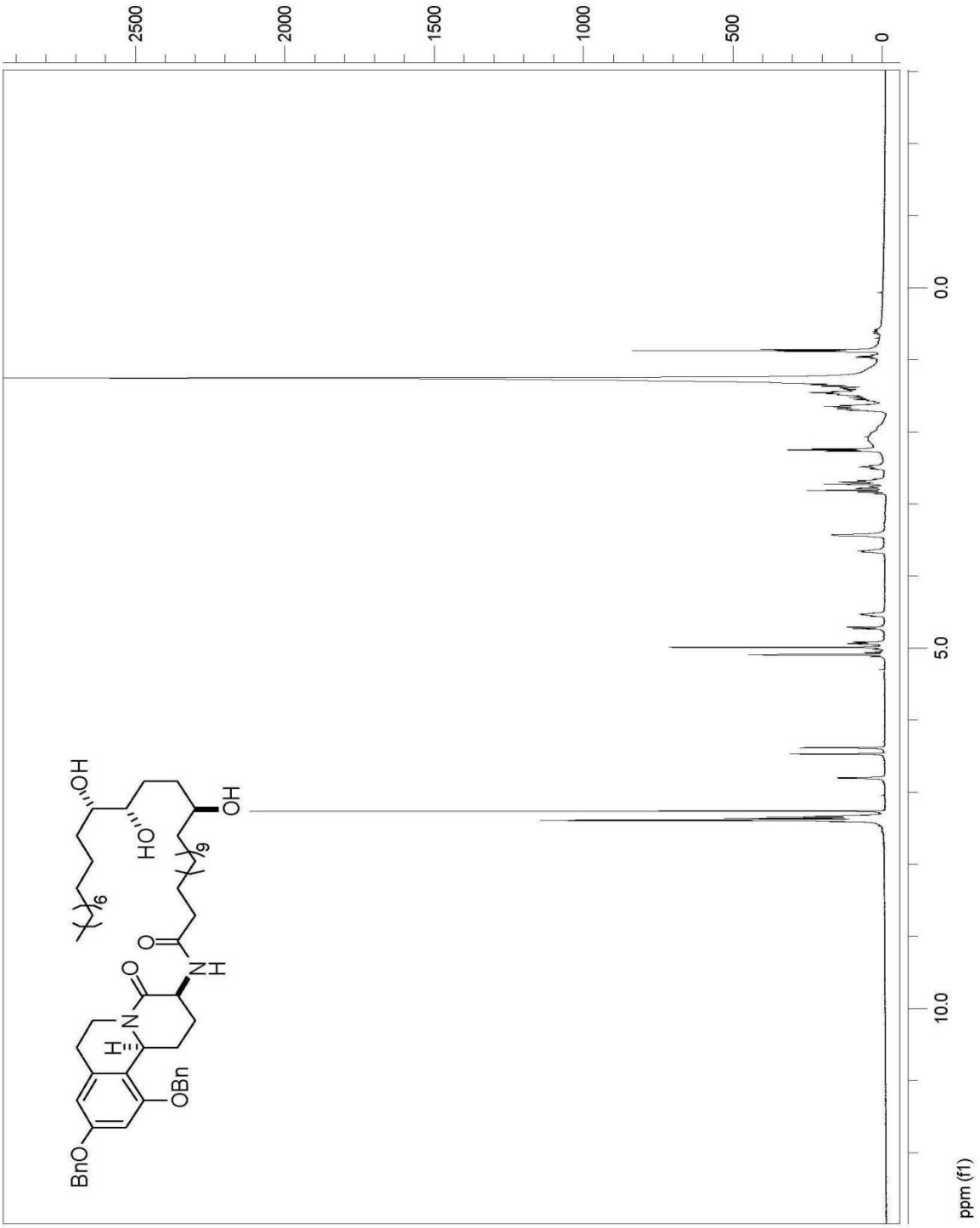
^{13}C NMR (500 MHz) of **2.59** in $CDCl_3$



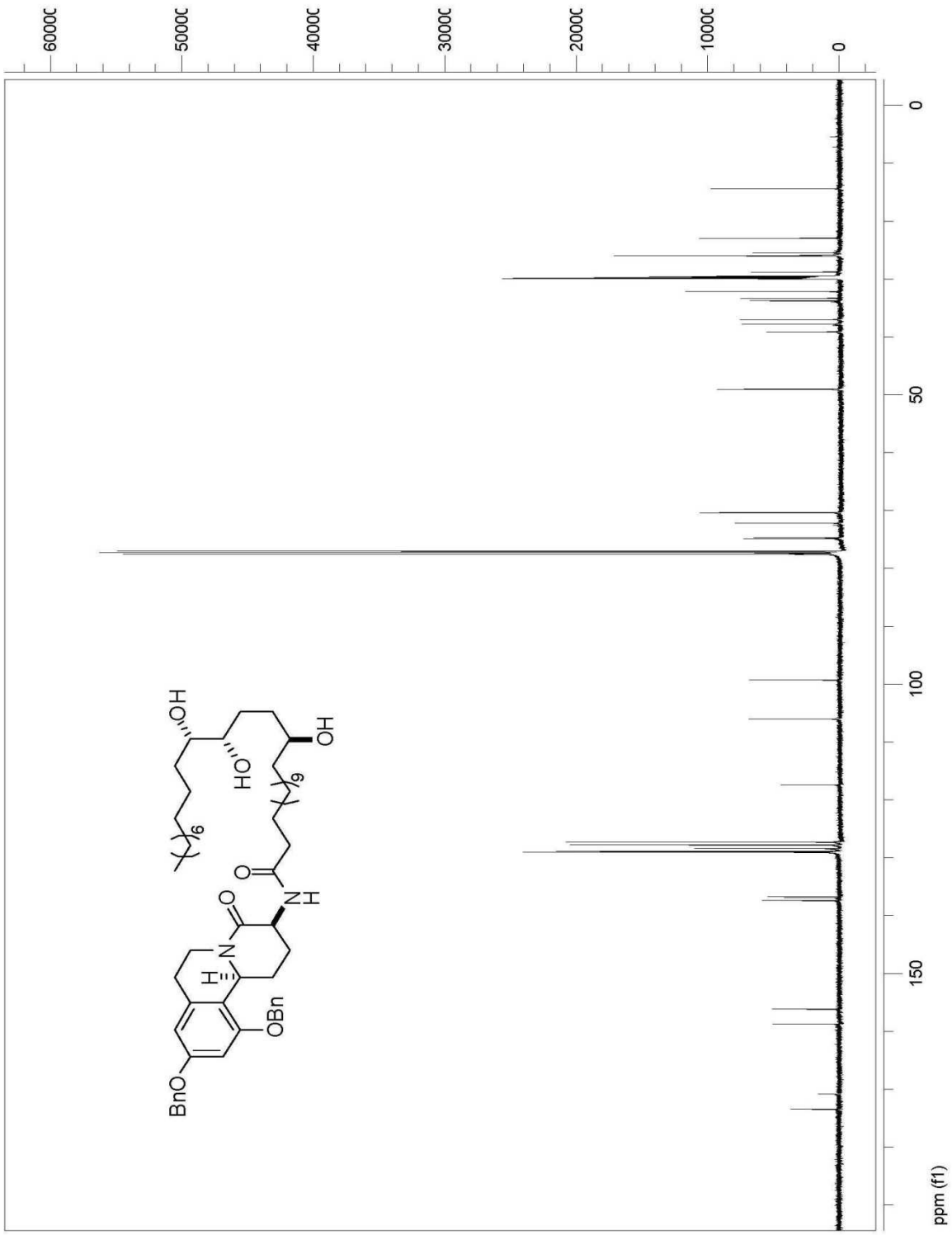
^{1}H NMR (500 MHz) of **2.61a** in $CDCl_3$



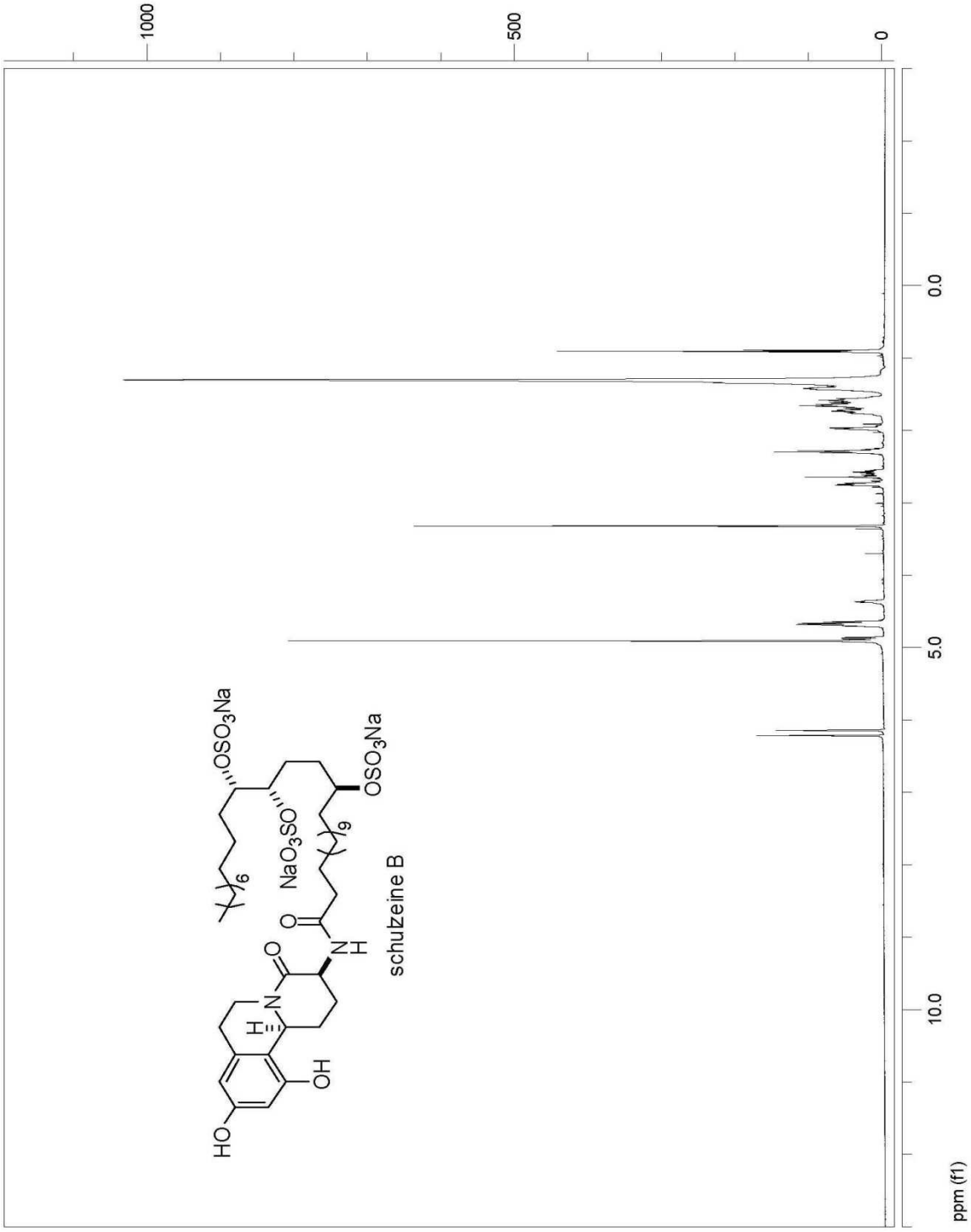
^{13}C NMR (500 MHz) of **2.61a** in $CDCl_3$



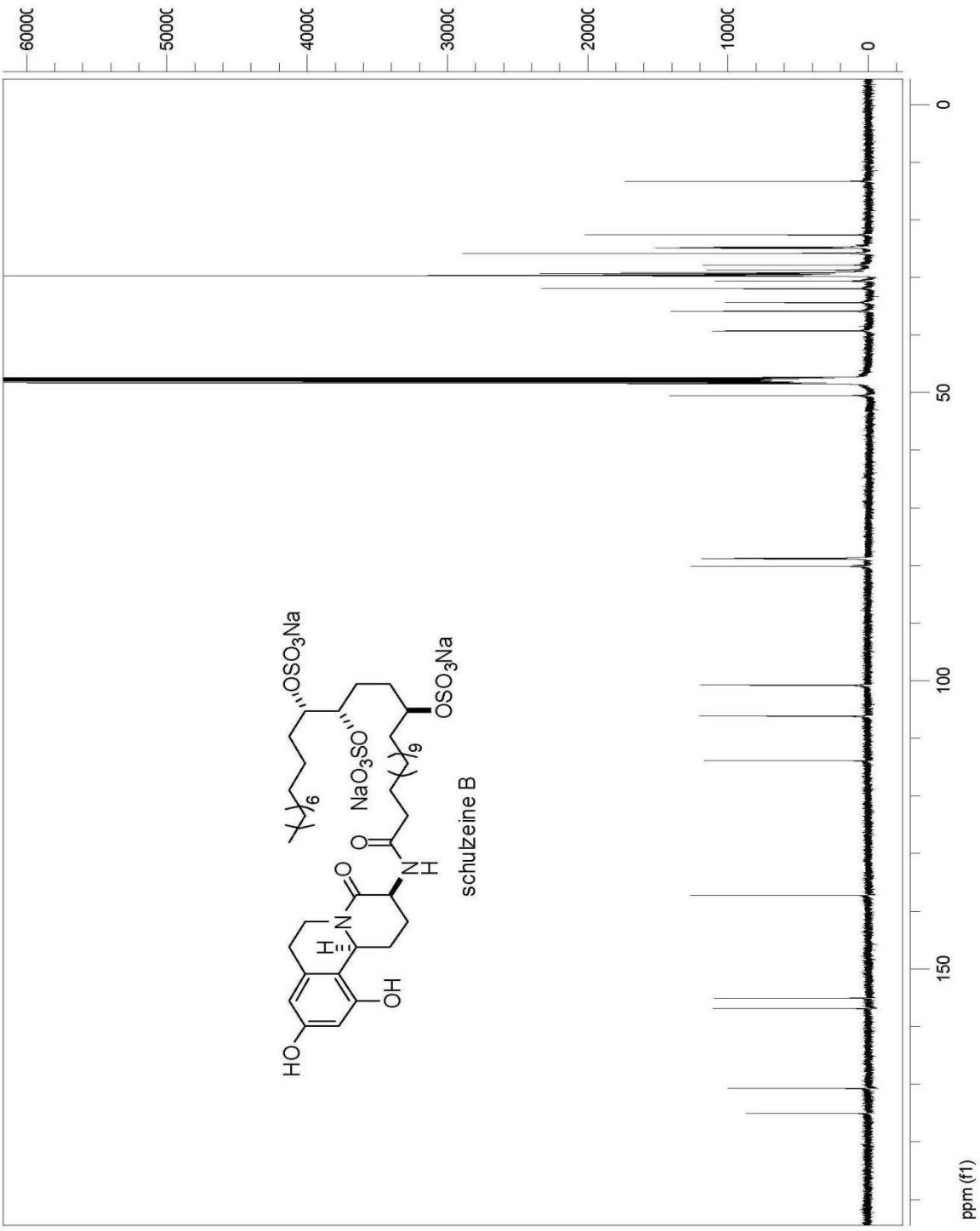
^{1}H NMR (500 MHz) of **2.62a** in $CDCl_3$



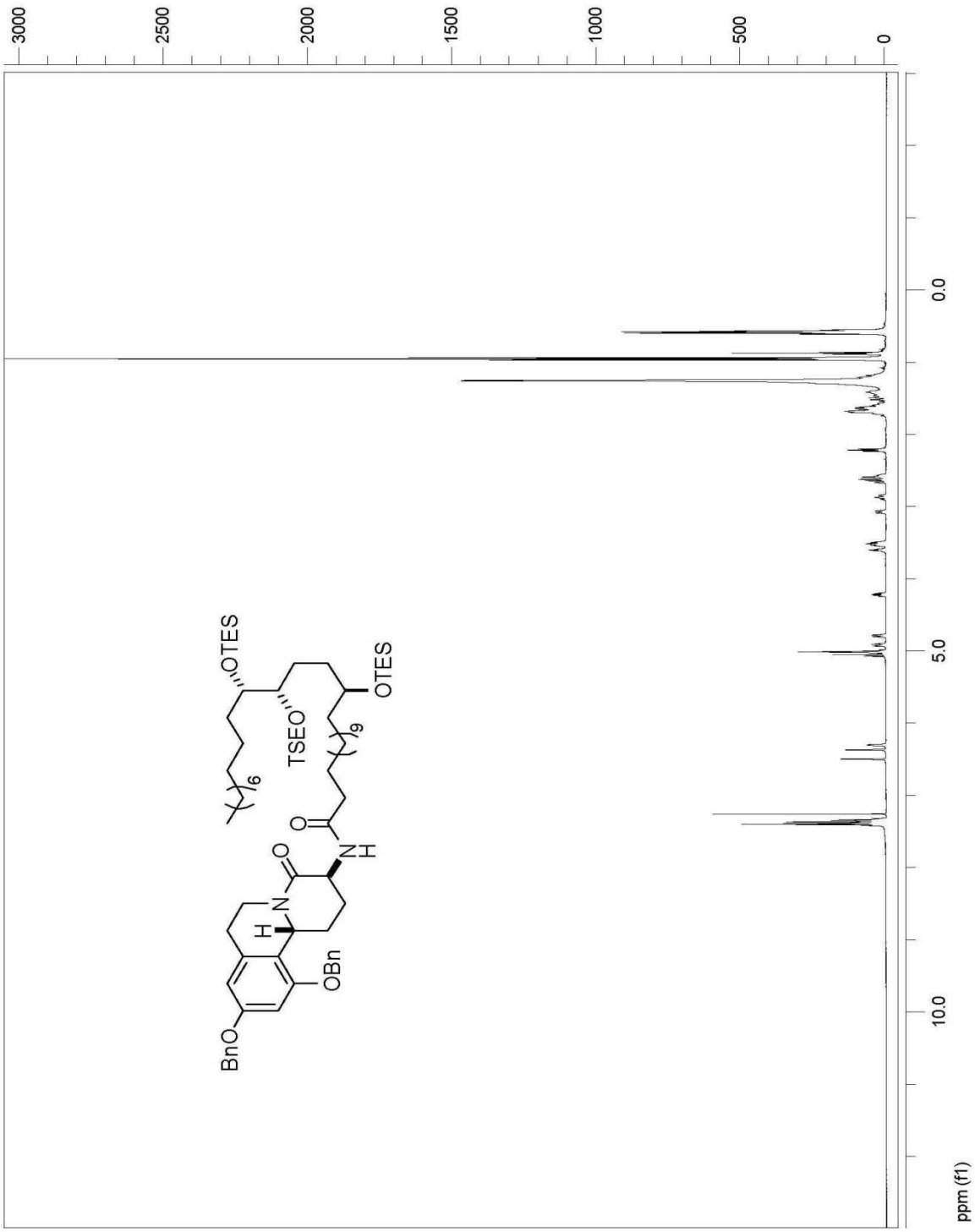
^{13}C NMR (500 MHz) of **2.62a** in $CDCl_3$



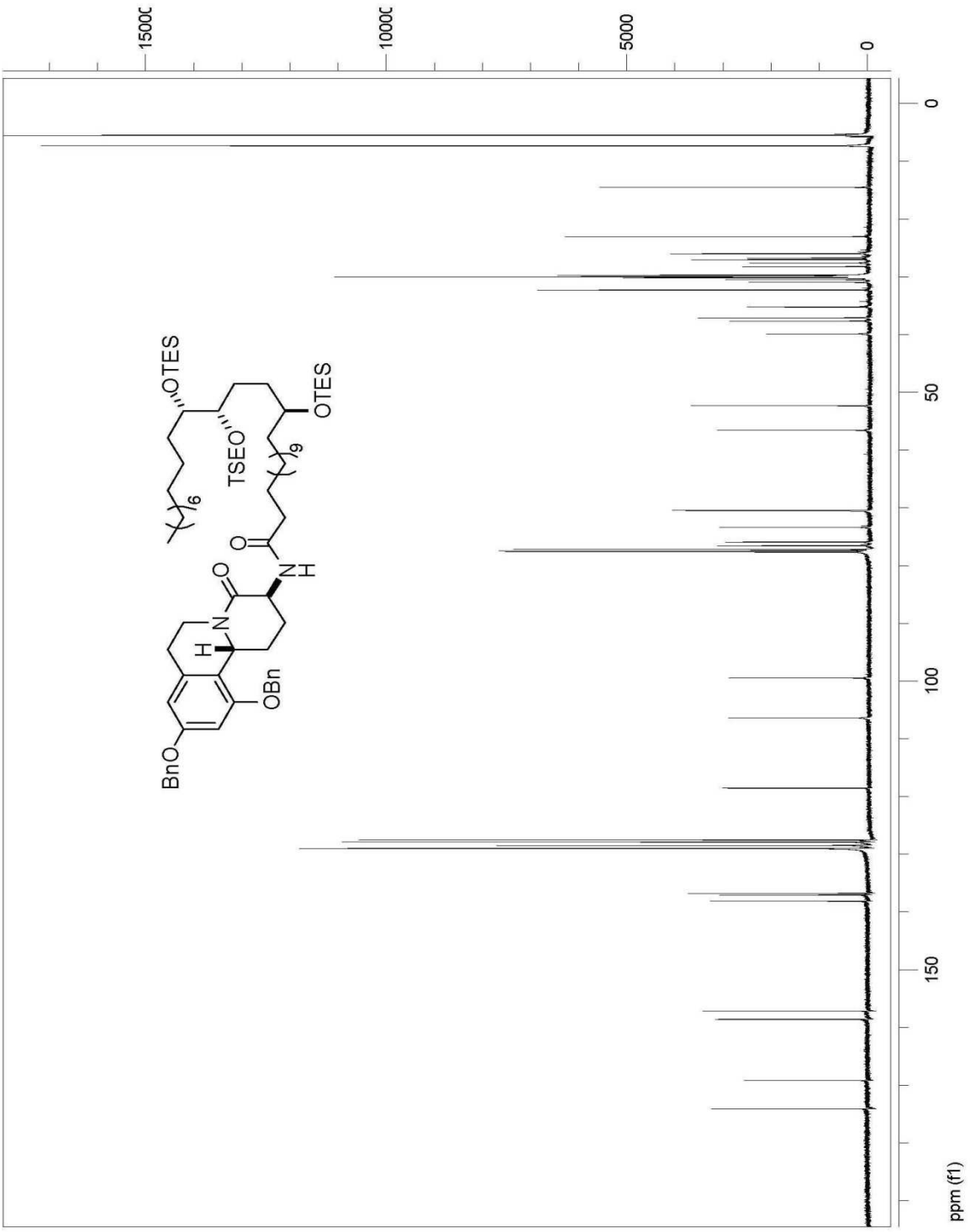
^{1}H NMR (500 MHz) of **Schulzeine B** in CD_3OD



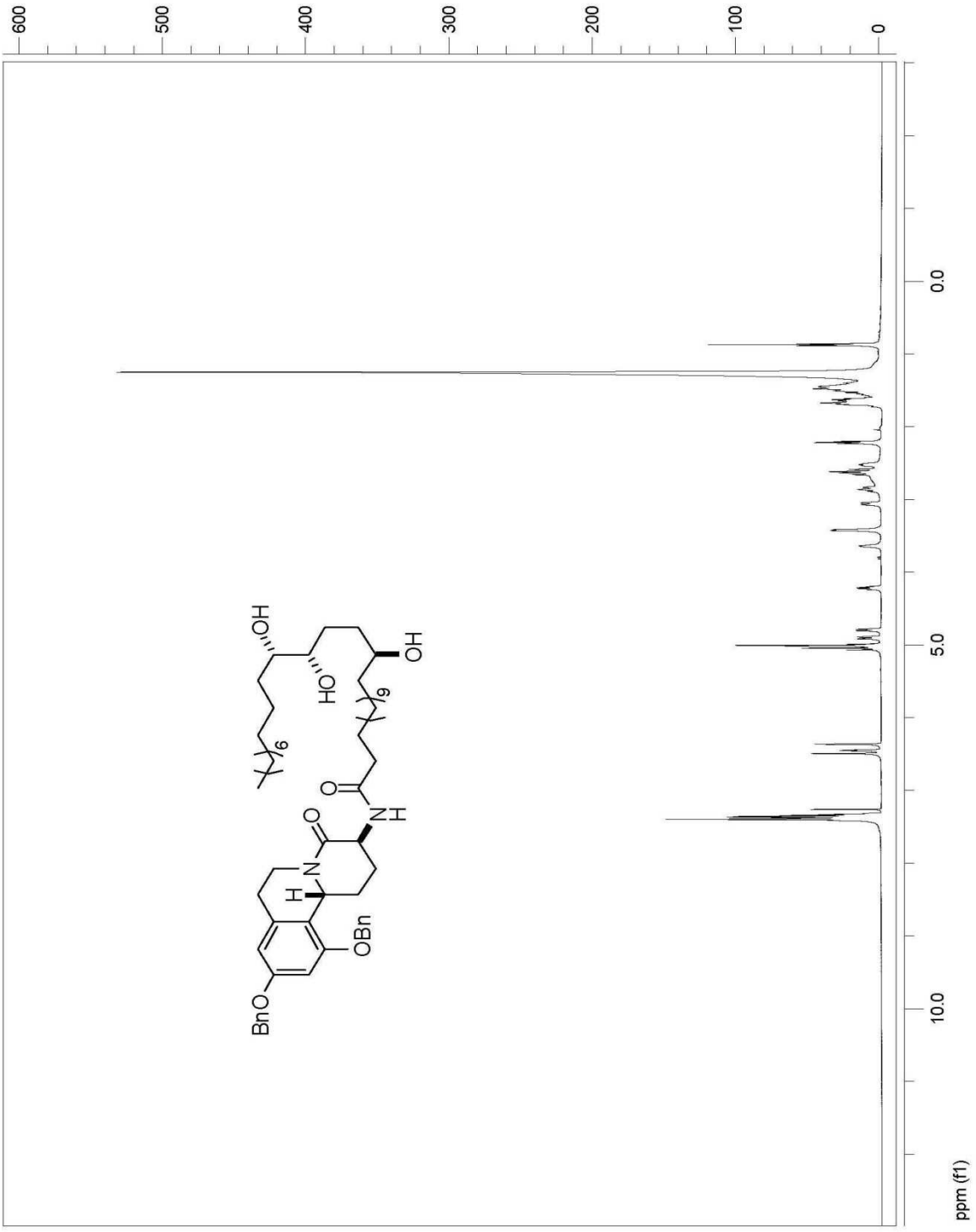
^{13}C NMR (500 MHz) of **Schulzeine B** in CD_3OD



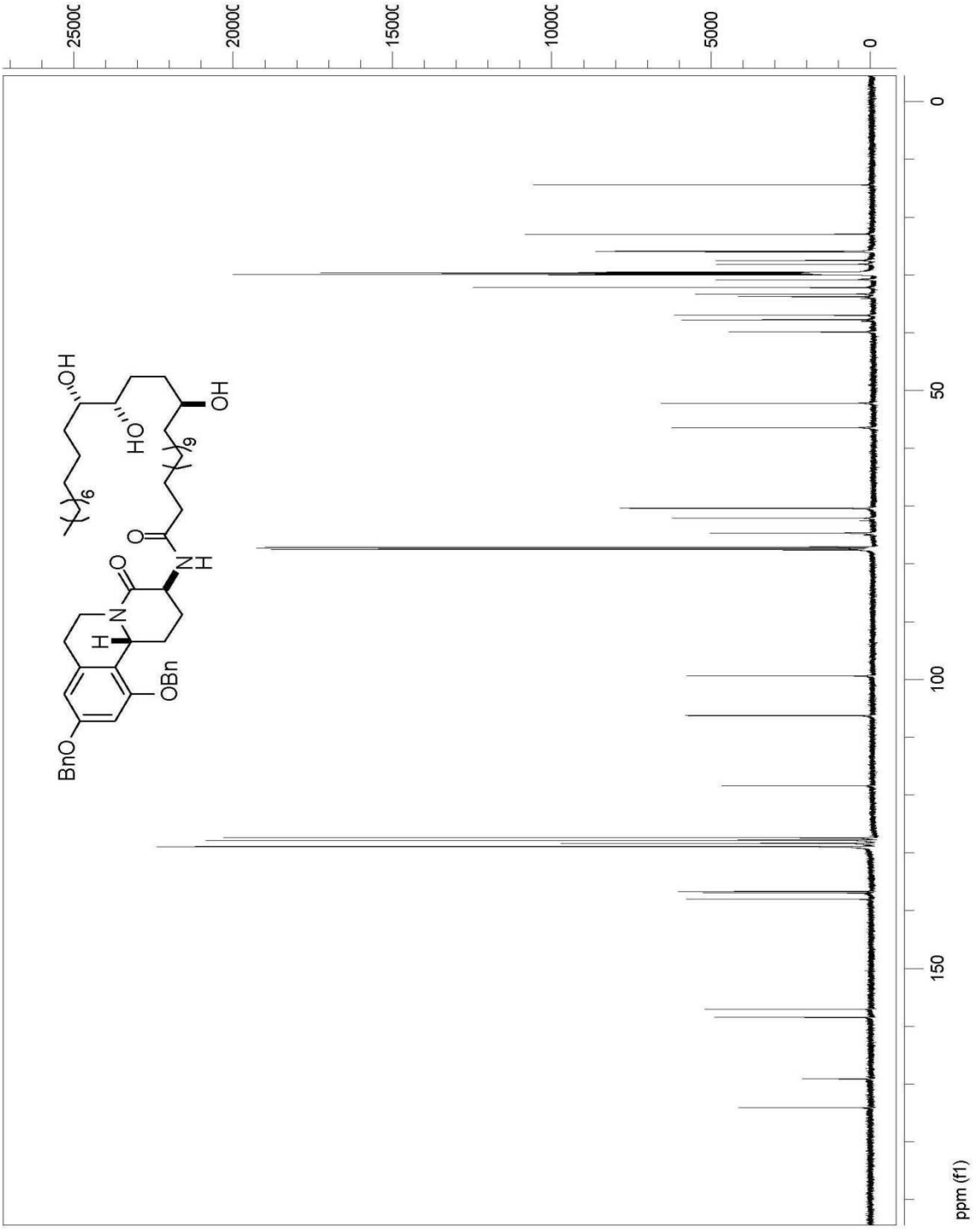
^{1}H NMR (500 MHz) of **2.61b** in $CDCl_3$



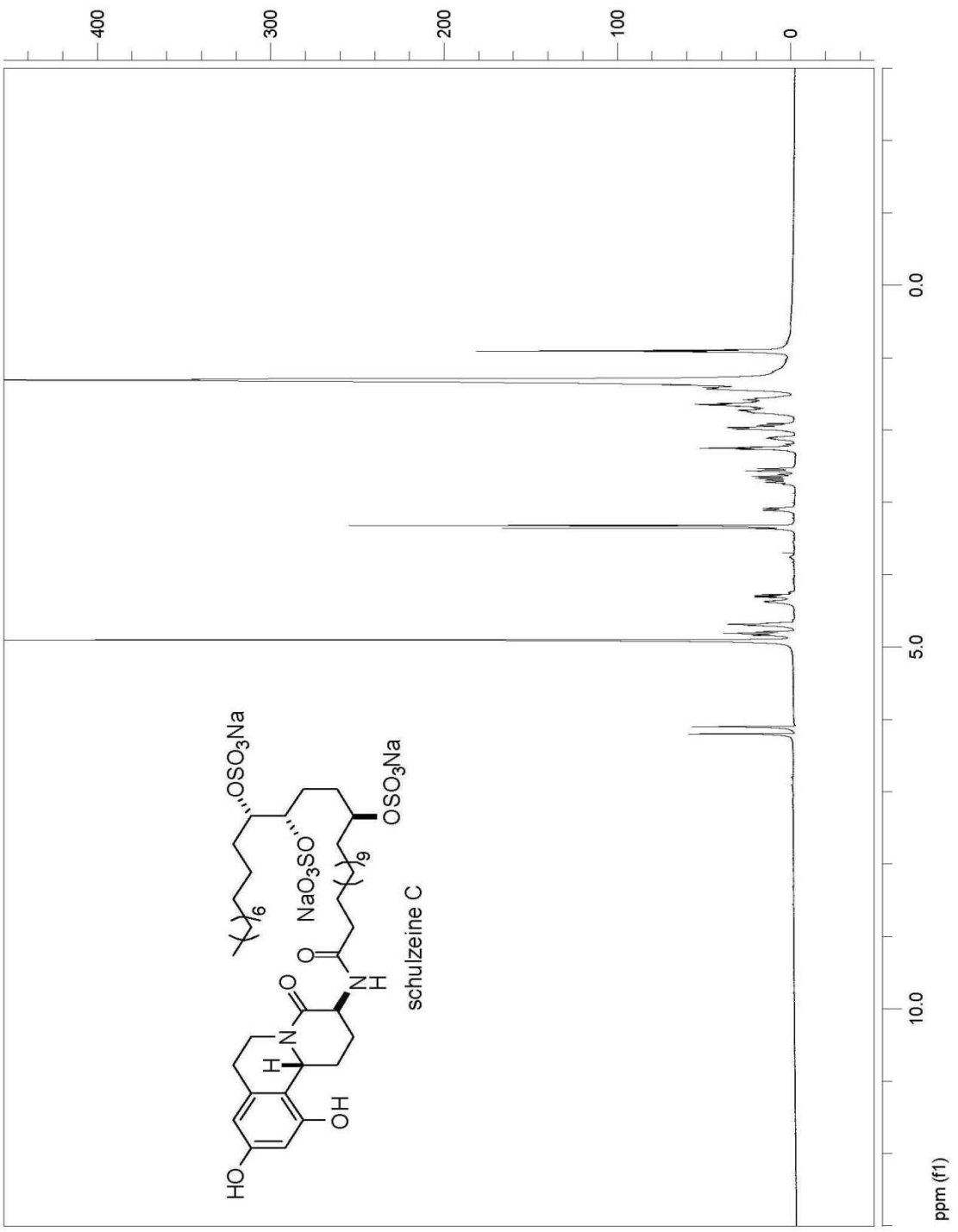
^{13}C NMR (500 MHz) of **2.61b** in $CDCl_3$



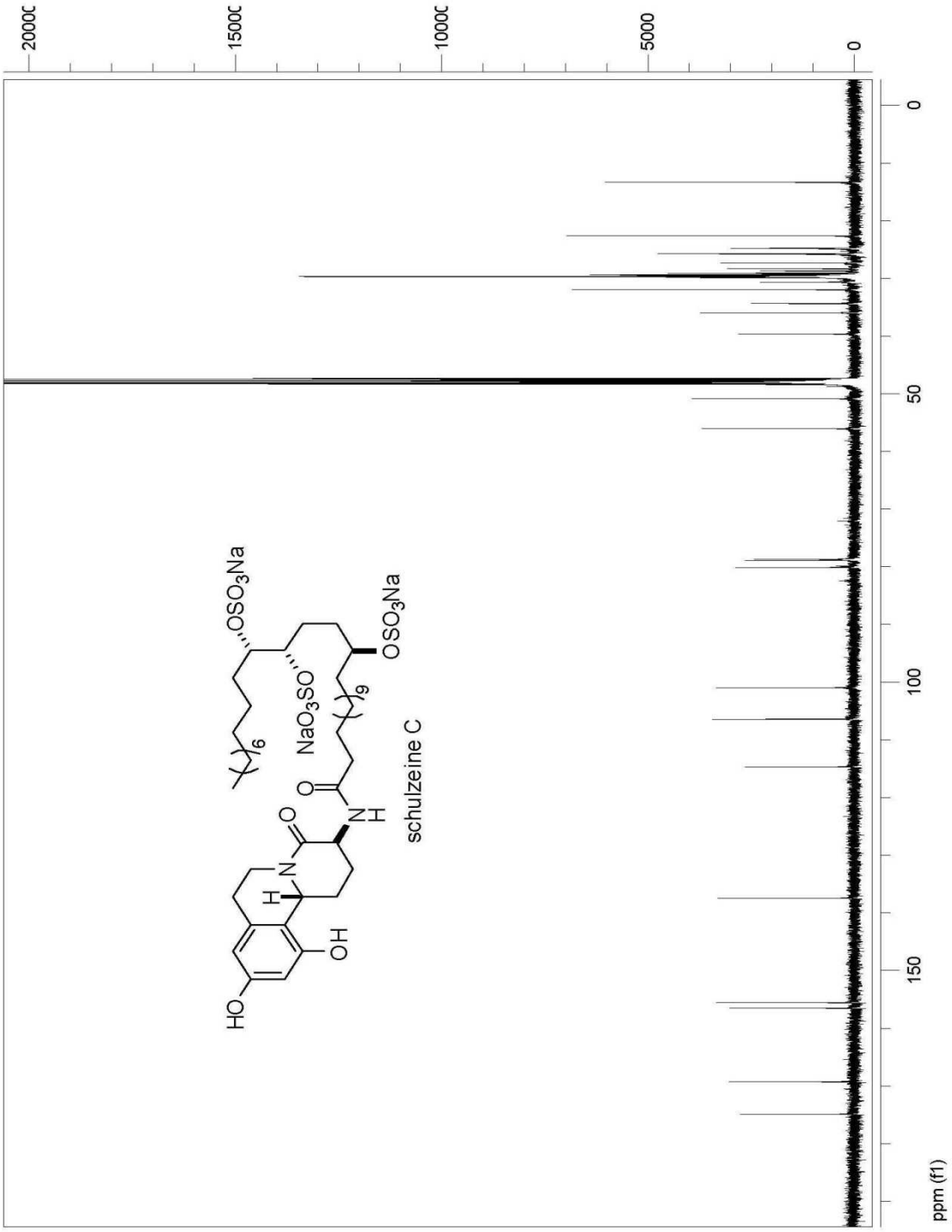
^{1}H NMR (500 MHz) of **2.62b** in $CDCl_3$



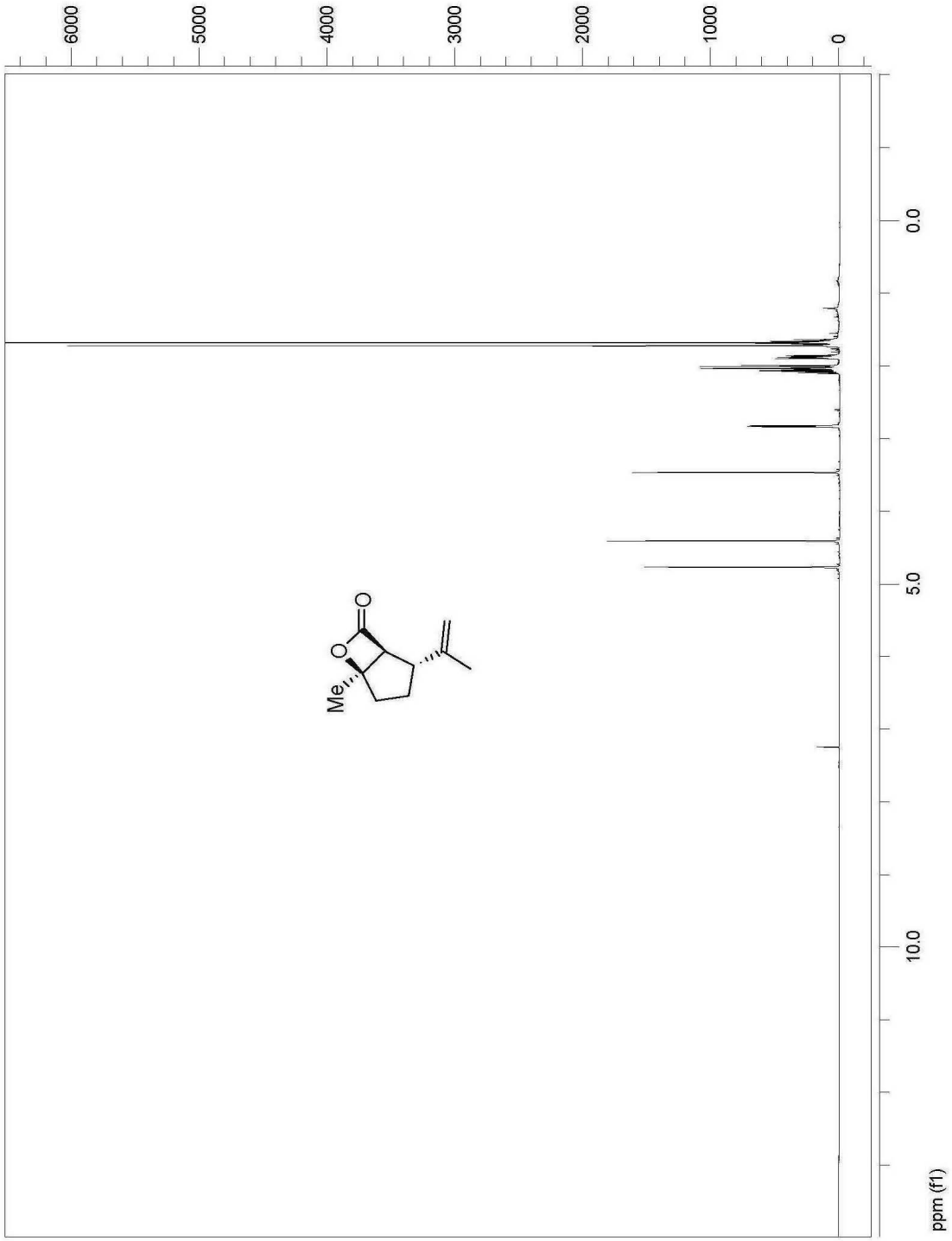
^{13}C NMR (500 MHz) of **2.62b** in $CDCl_3$



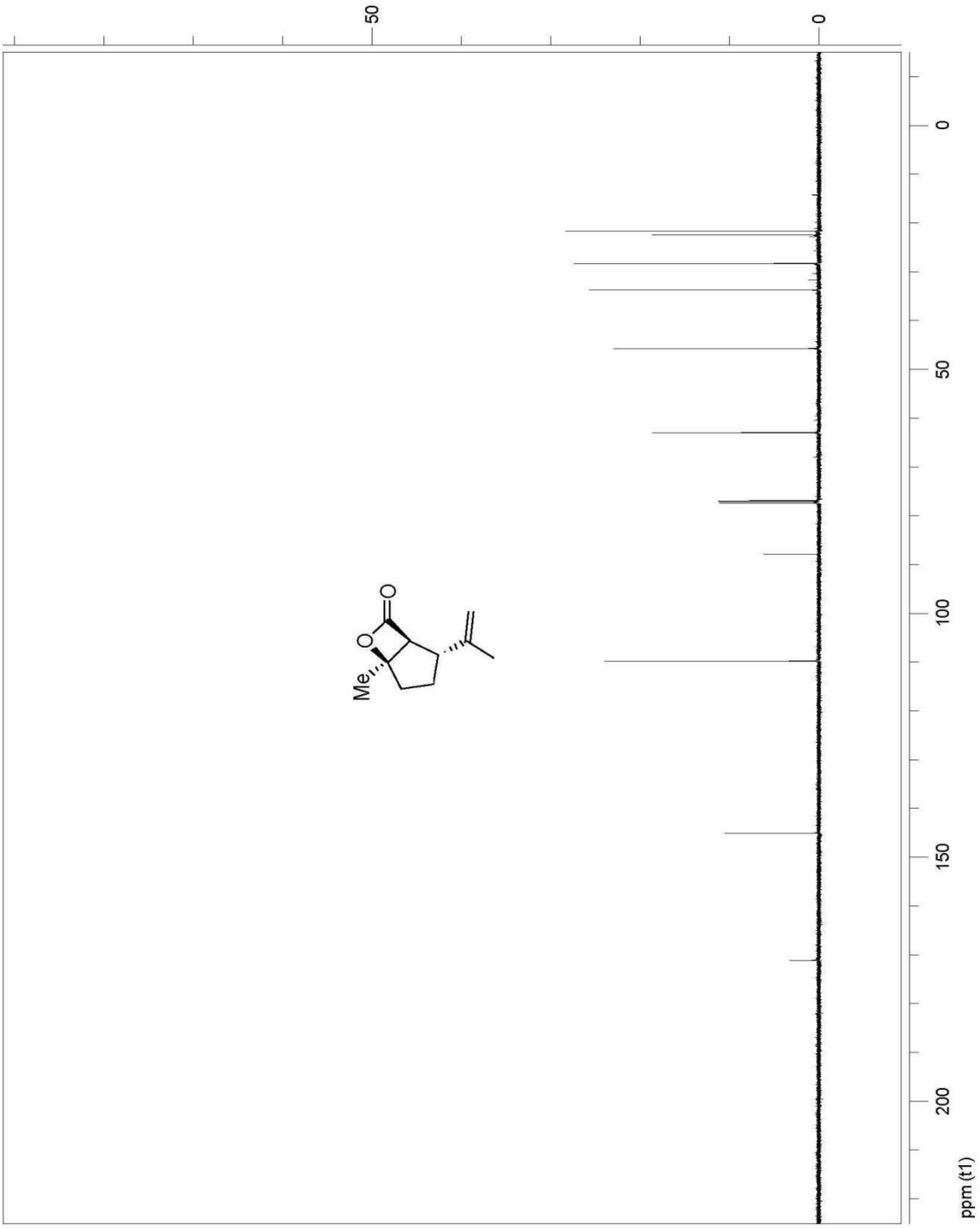
^{1}H NMR (500 MHz) of **Schulzeine C** in CD_3OD



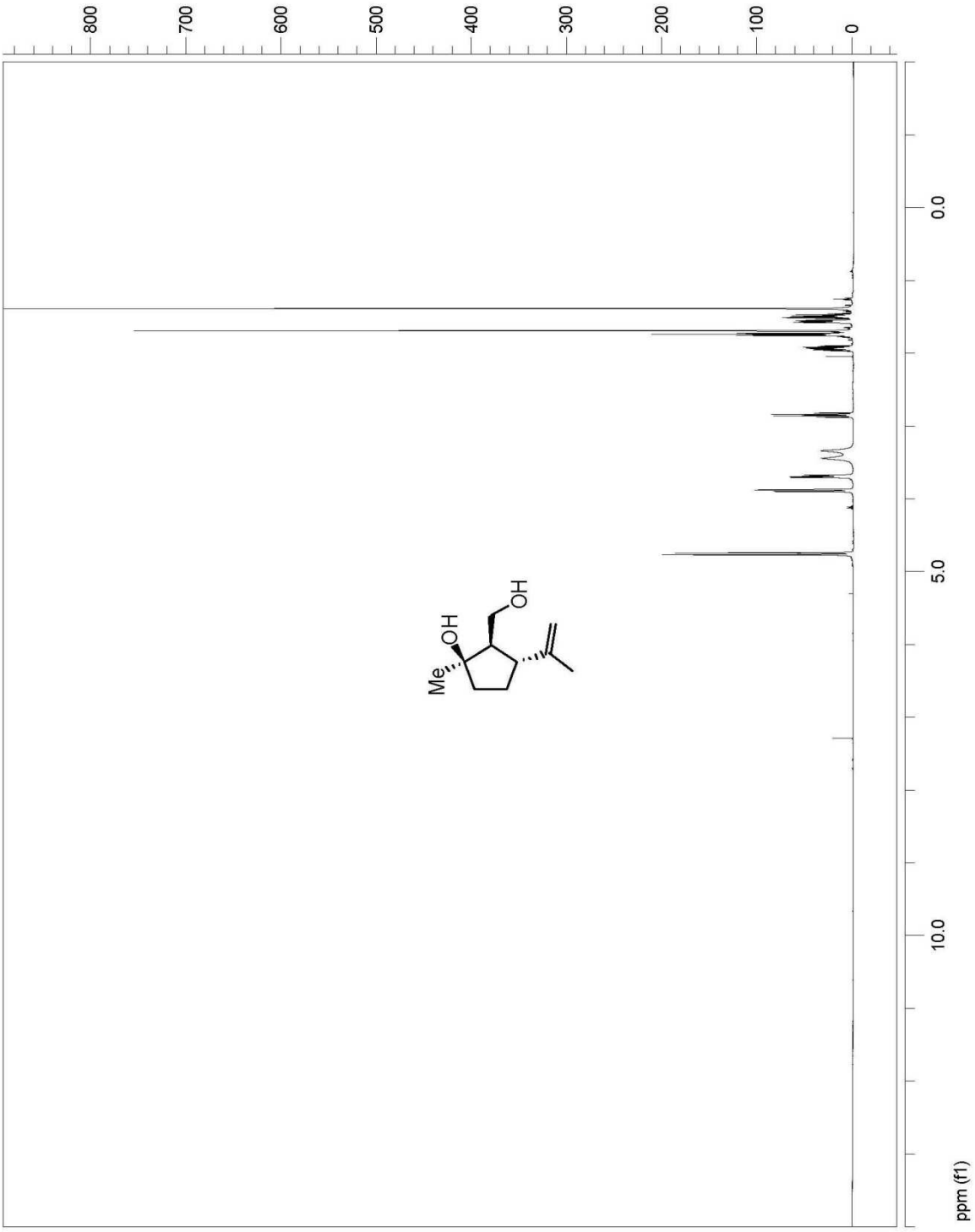
^{13}C NMR (500 MHz) of **Schulzeine C** in CD_3OD



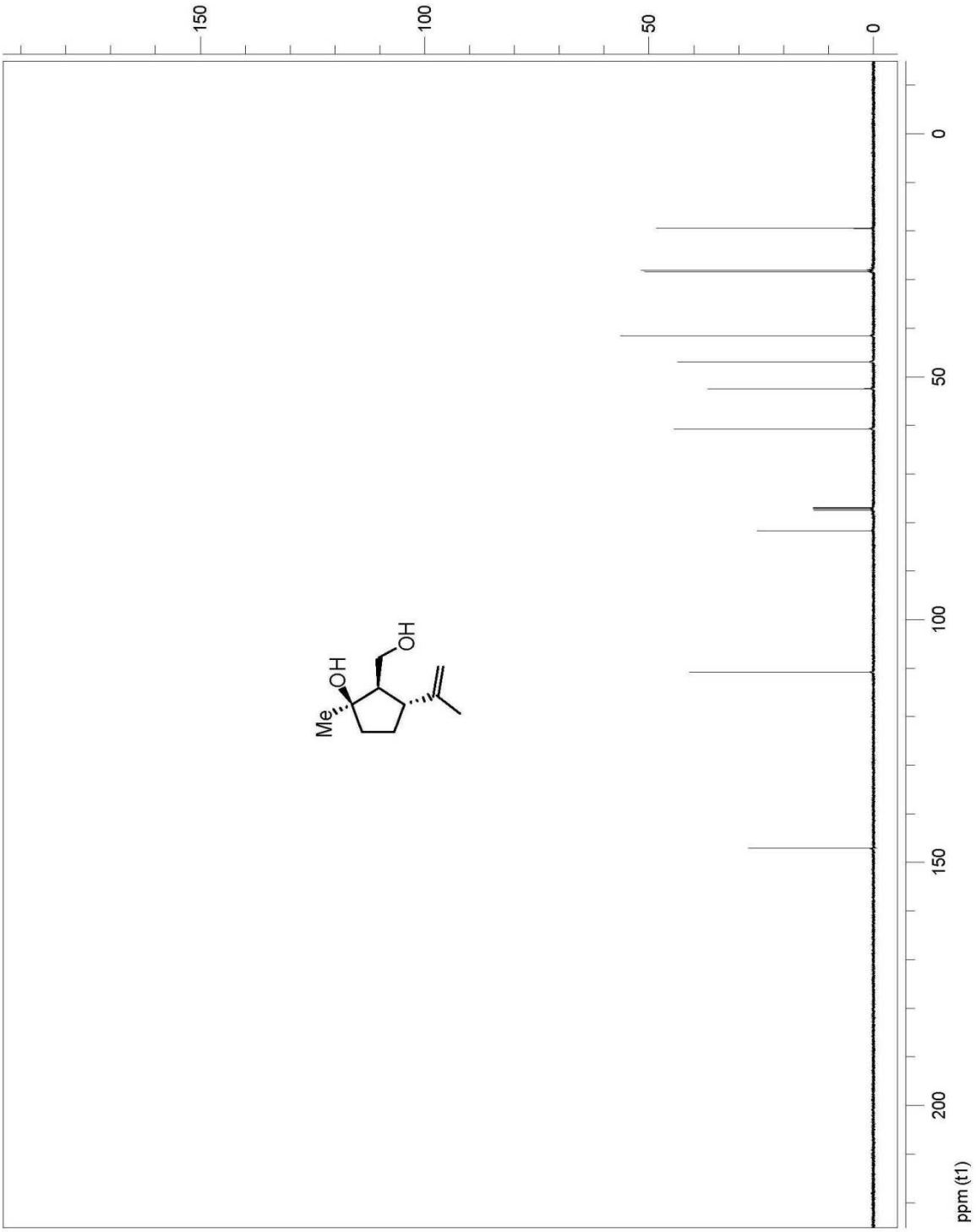
^{1}H NMR (500 MHz) of **3.12** in $CDCl_3$



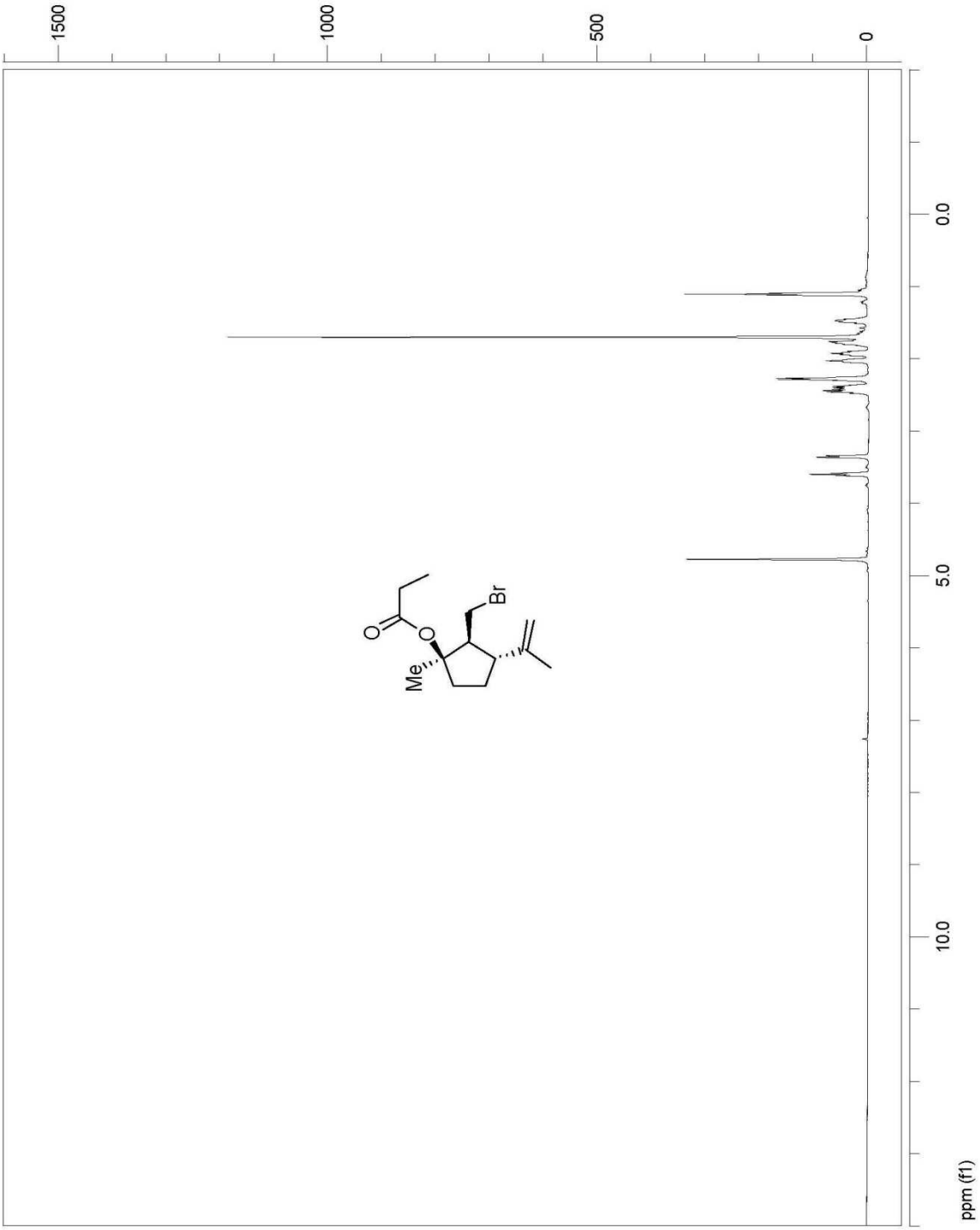
^{13}C NMR (500 MHz) of **3.12** in $CDCl_3$



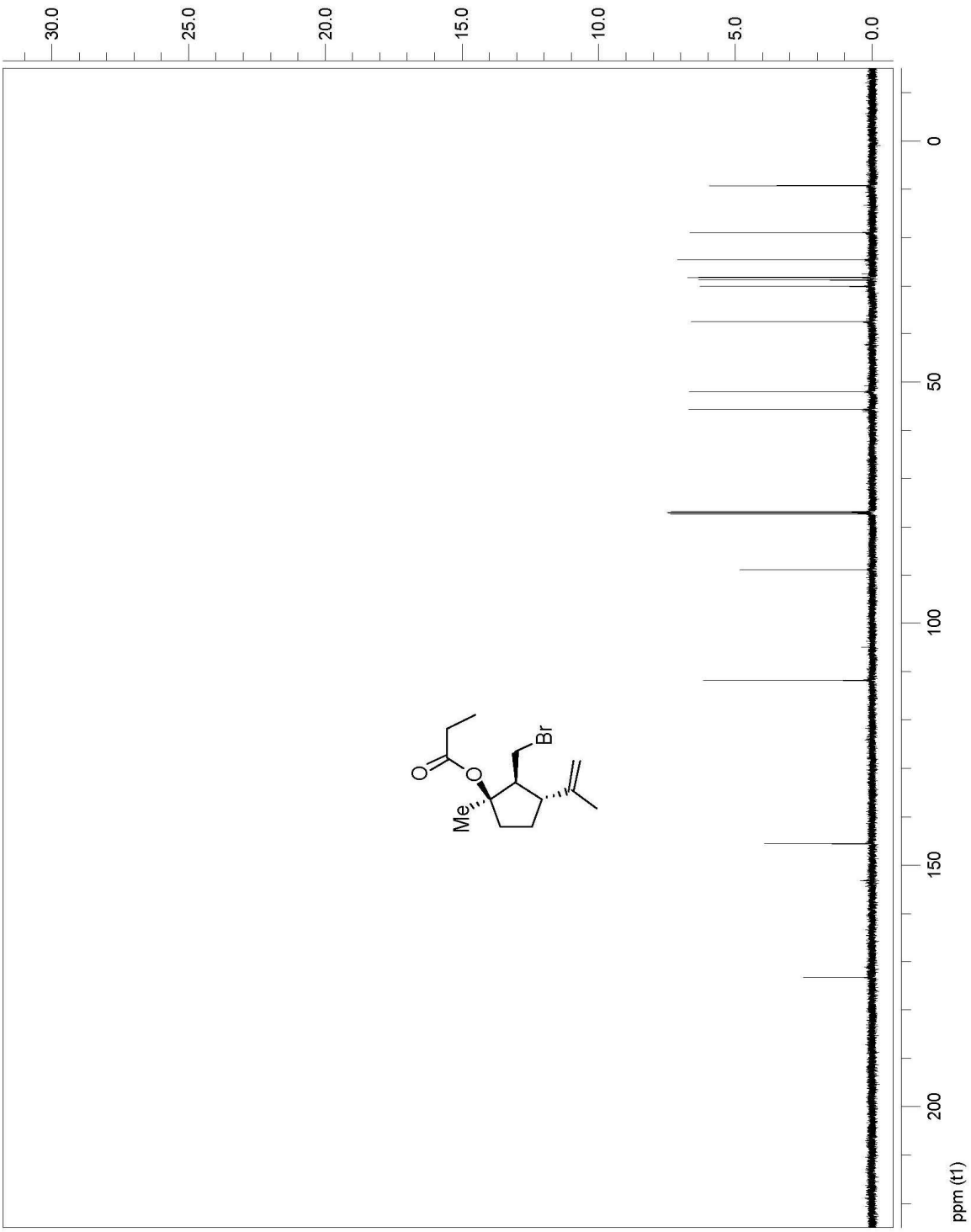
^{1}H NMR (500 MHz) of **3.21** in $CDCl_3$



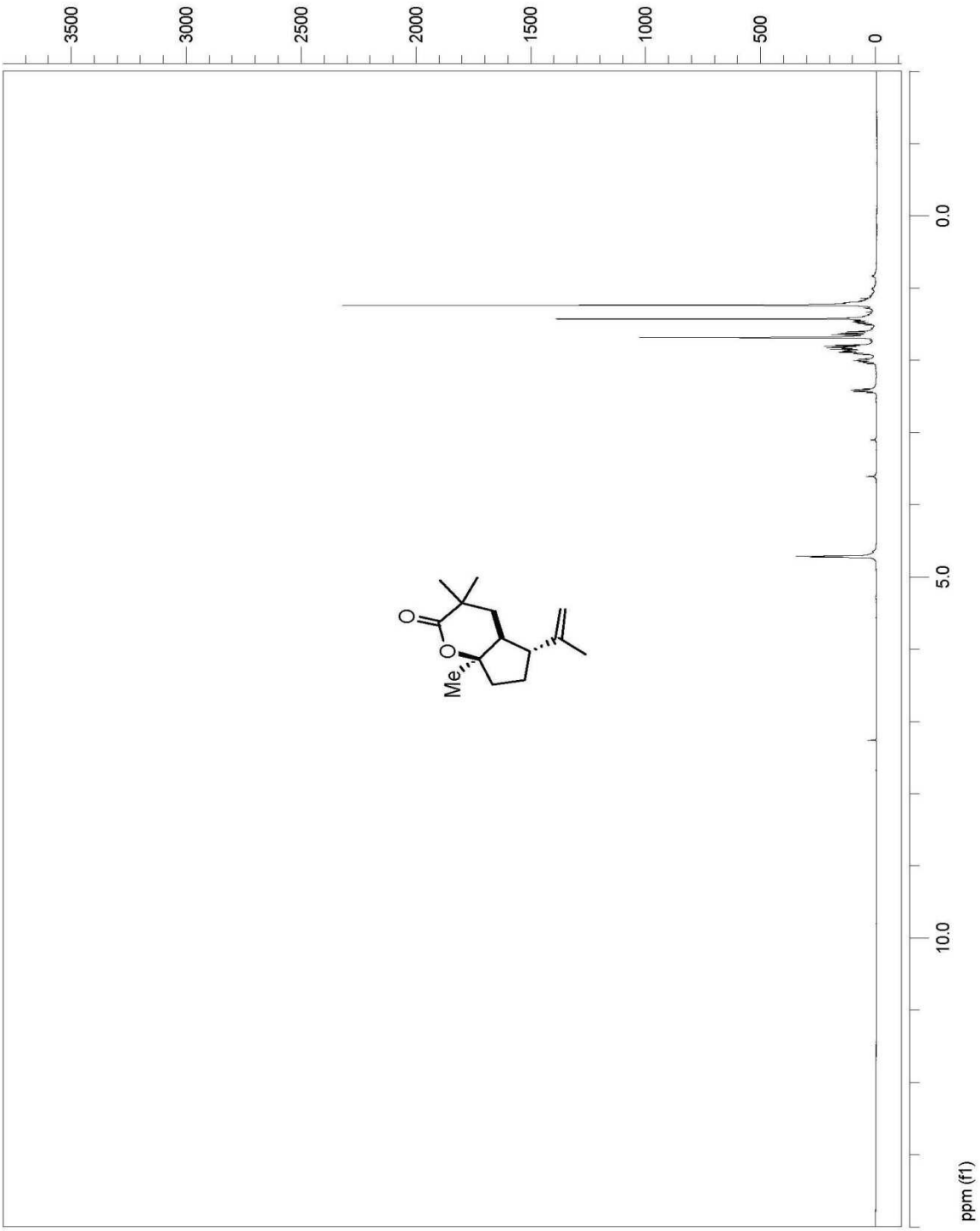
^{13}C NMR (500 MHz) of **3.21** in $CDCl_3$



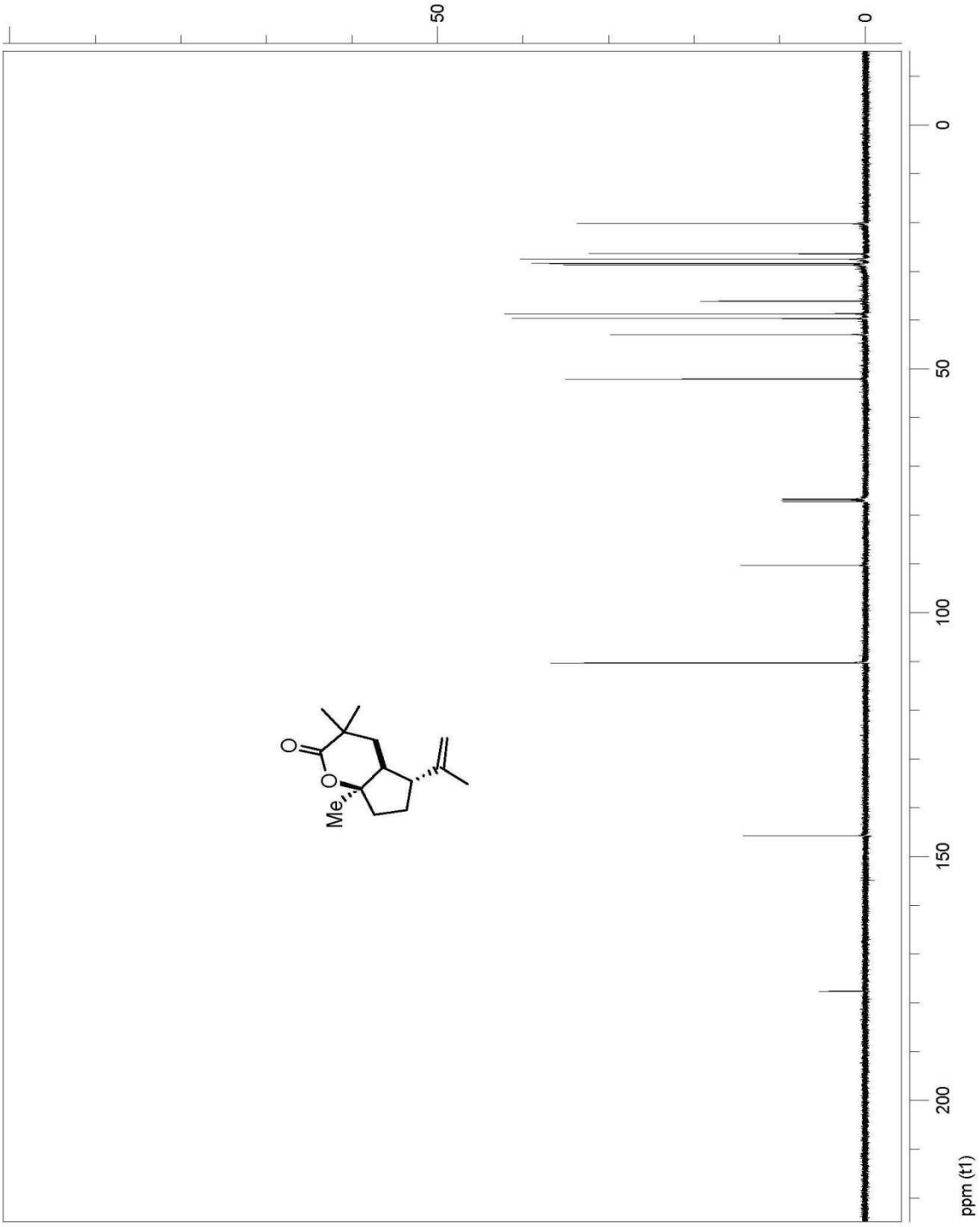
^{1}H NMR (500 MHz) of **3.31** in $CDCl_3$



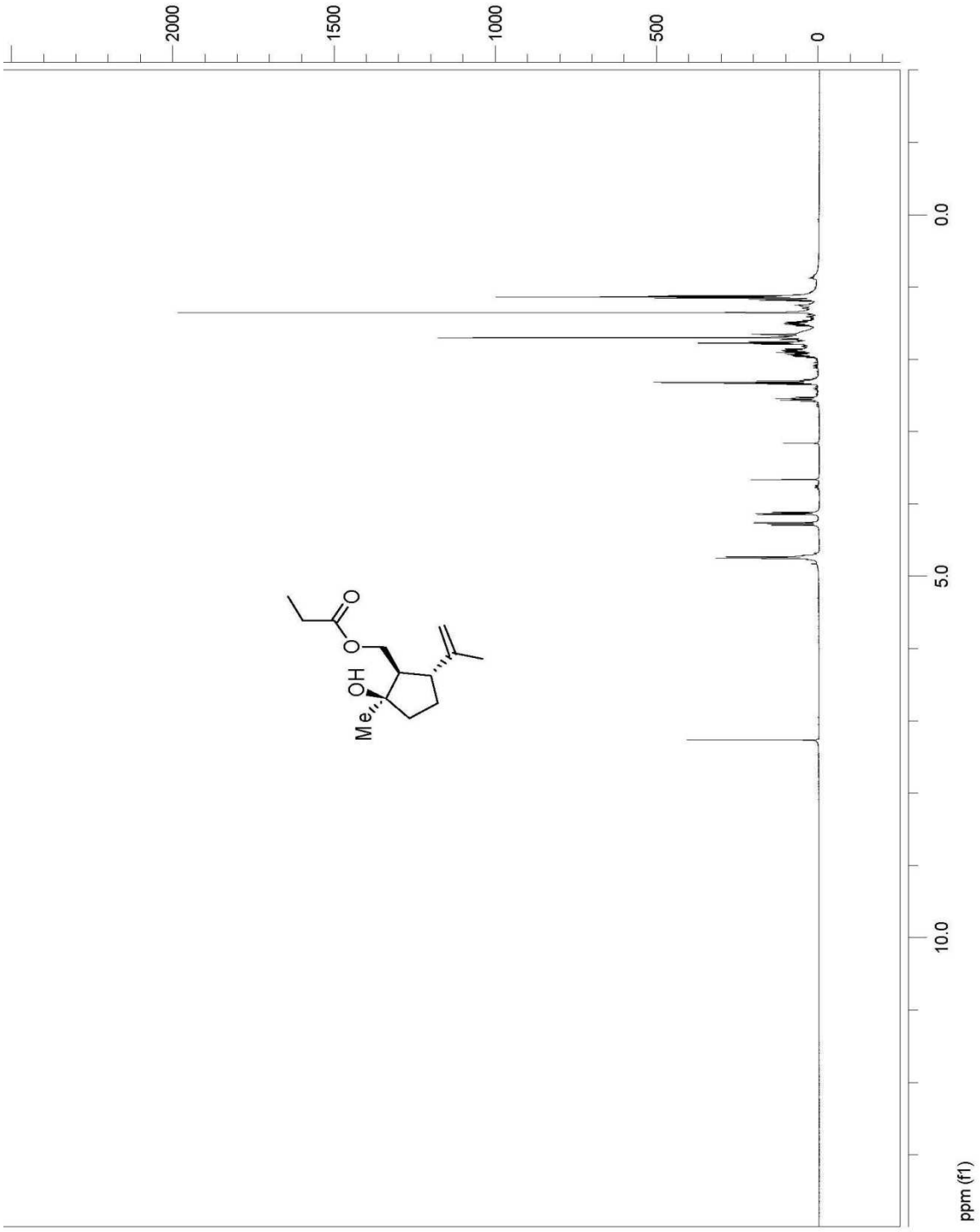
^{13}C NMR (500 MHz) of **3.31** in $CDCl_3$



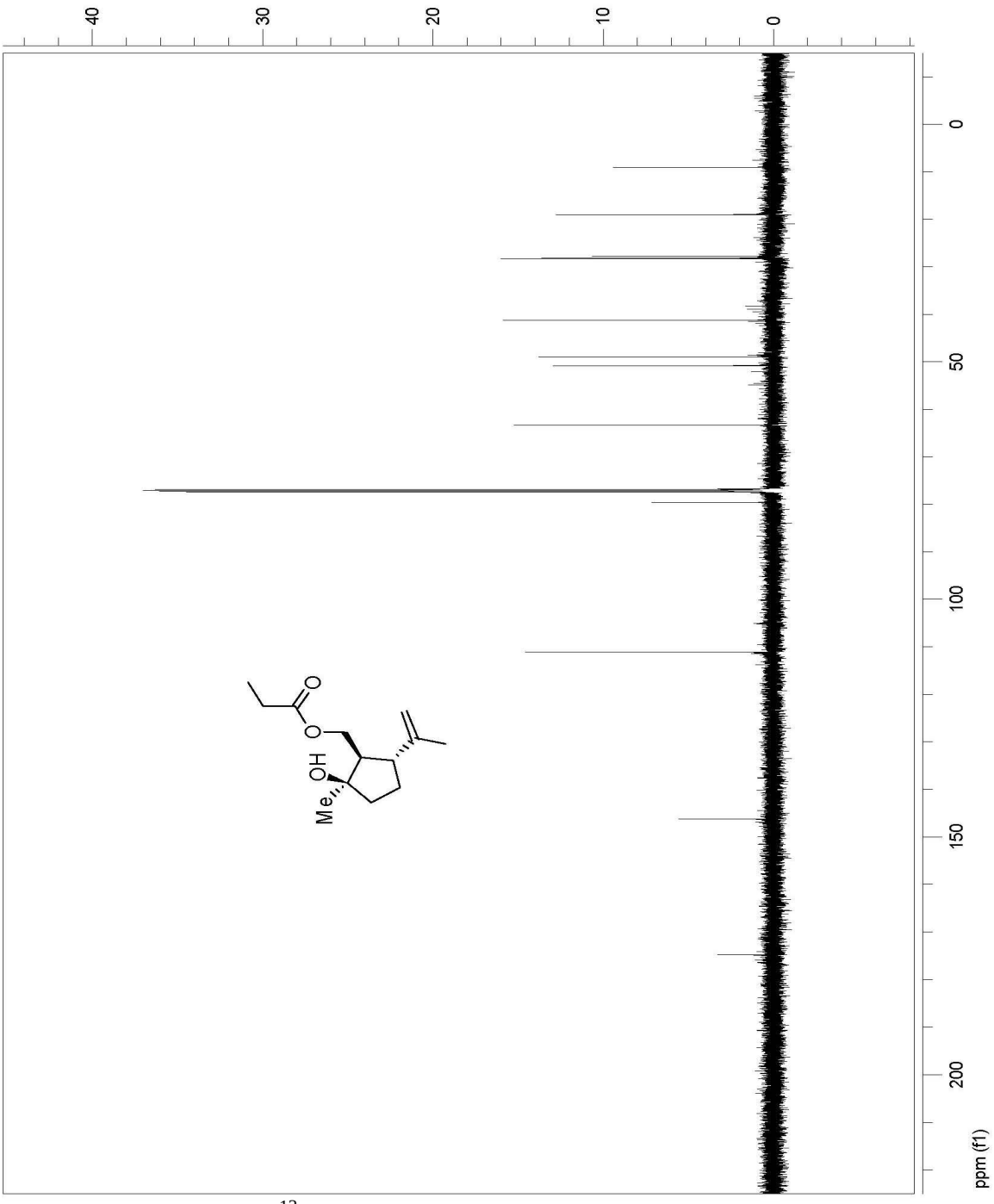
^{1}H NMR (500 MHz) of **3.35** in $CDCl_3$



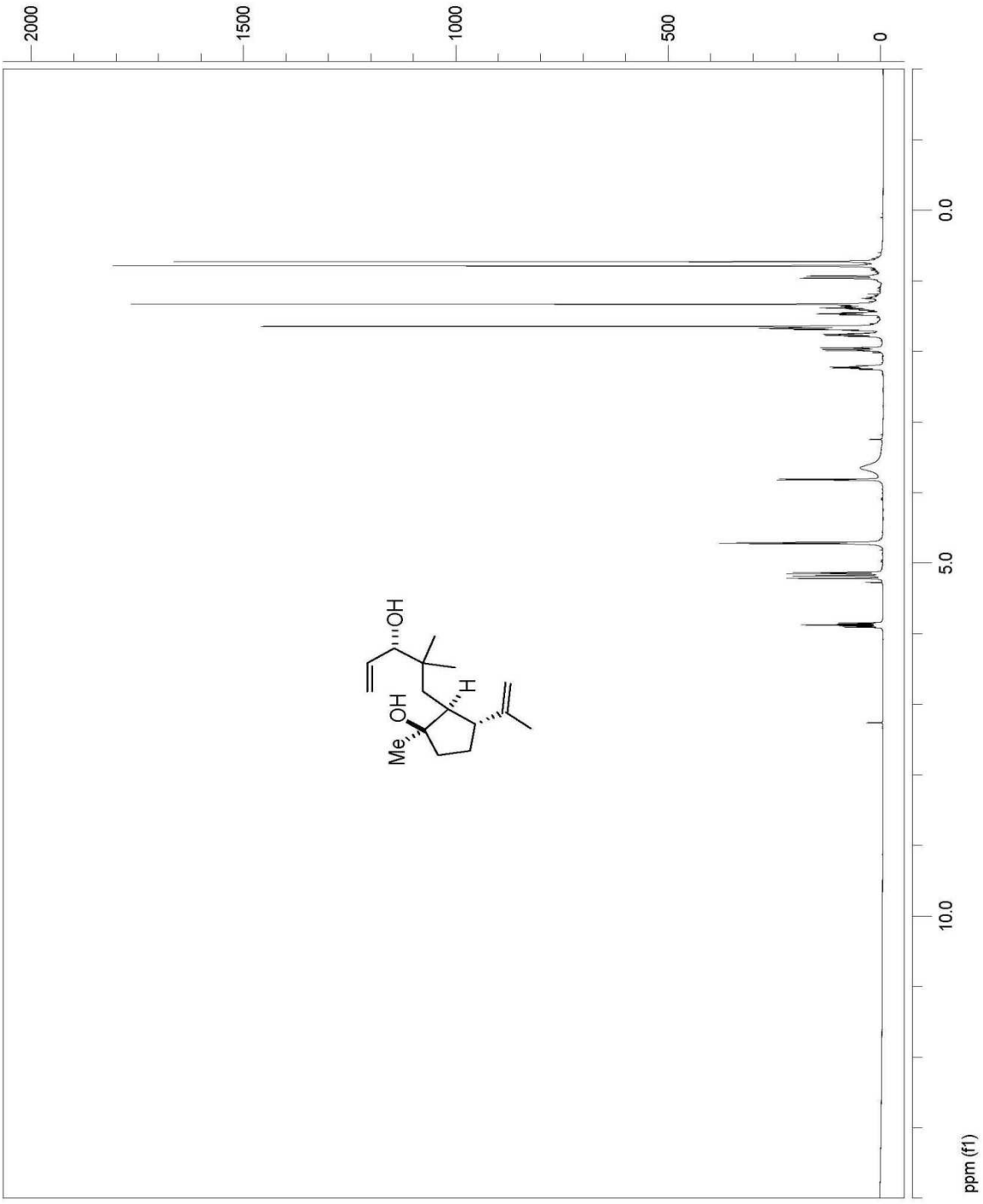
^{13}C NMR (500 MHz) of **3.35** in $CDCl_3$



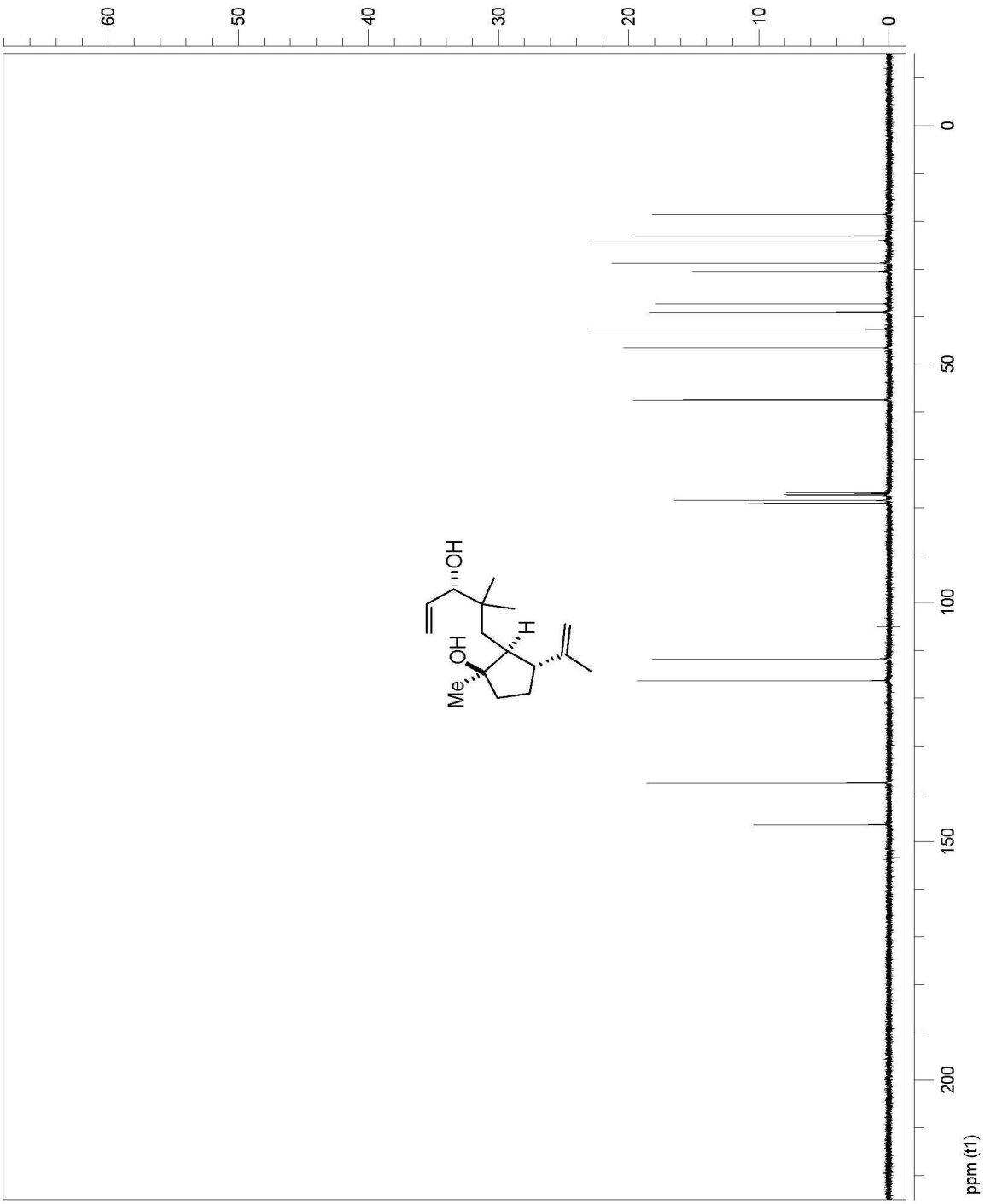
^{1}H NMR (500 MHz) of **3.34** in $CDCl_3$



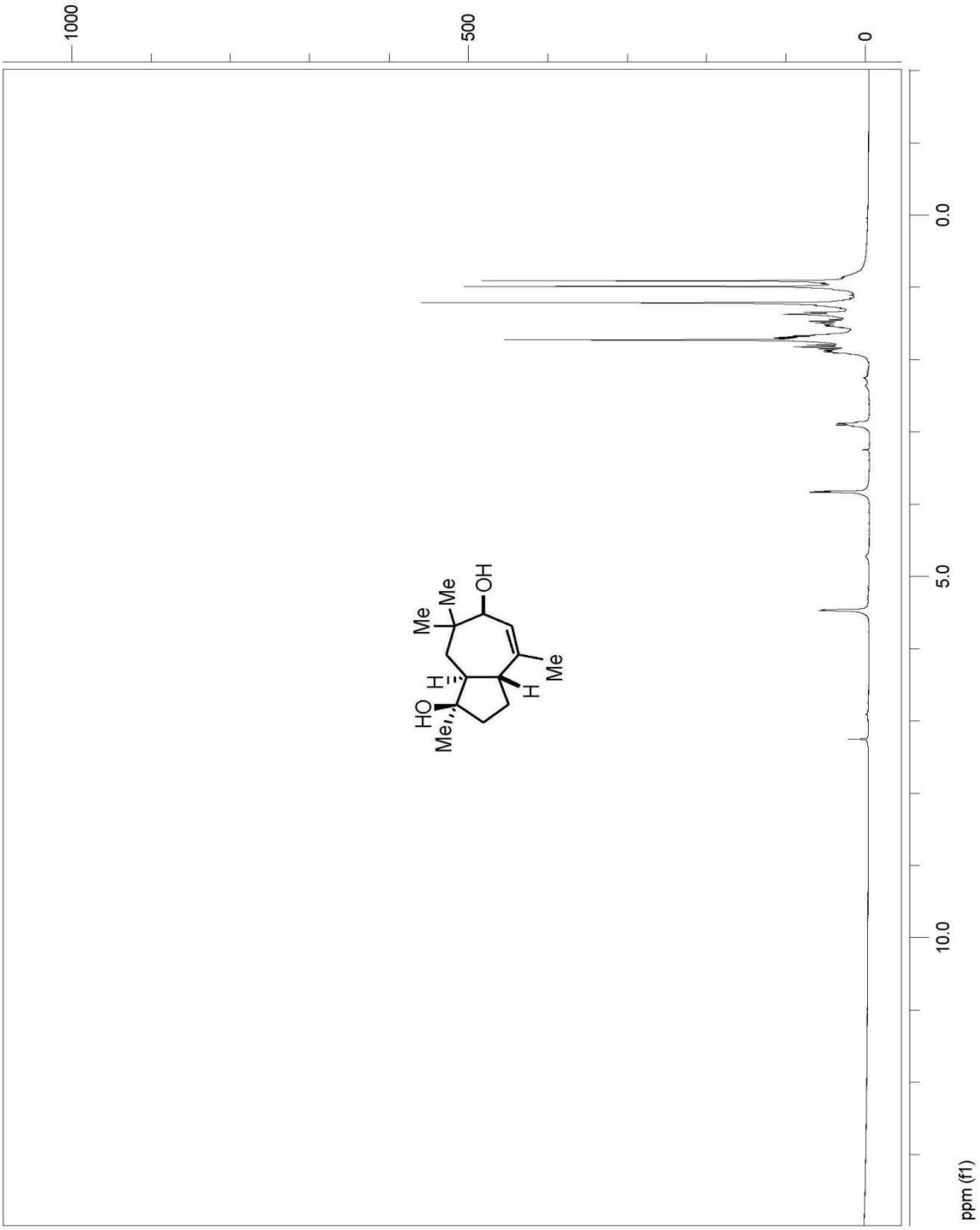
^{13}C NMR (500 MHz) of **3.34** in $CDCl_3$



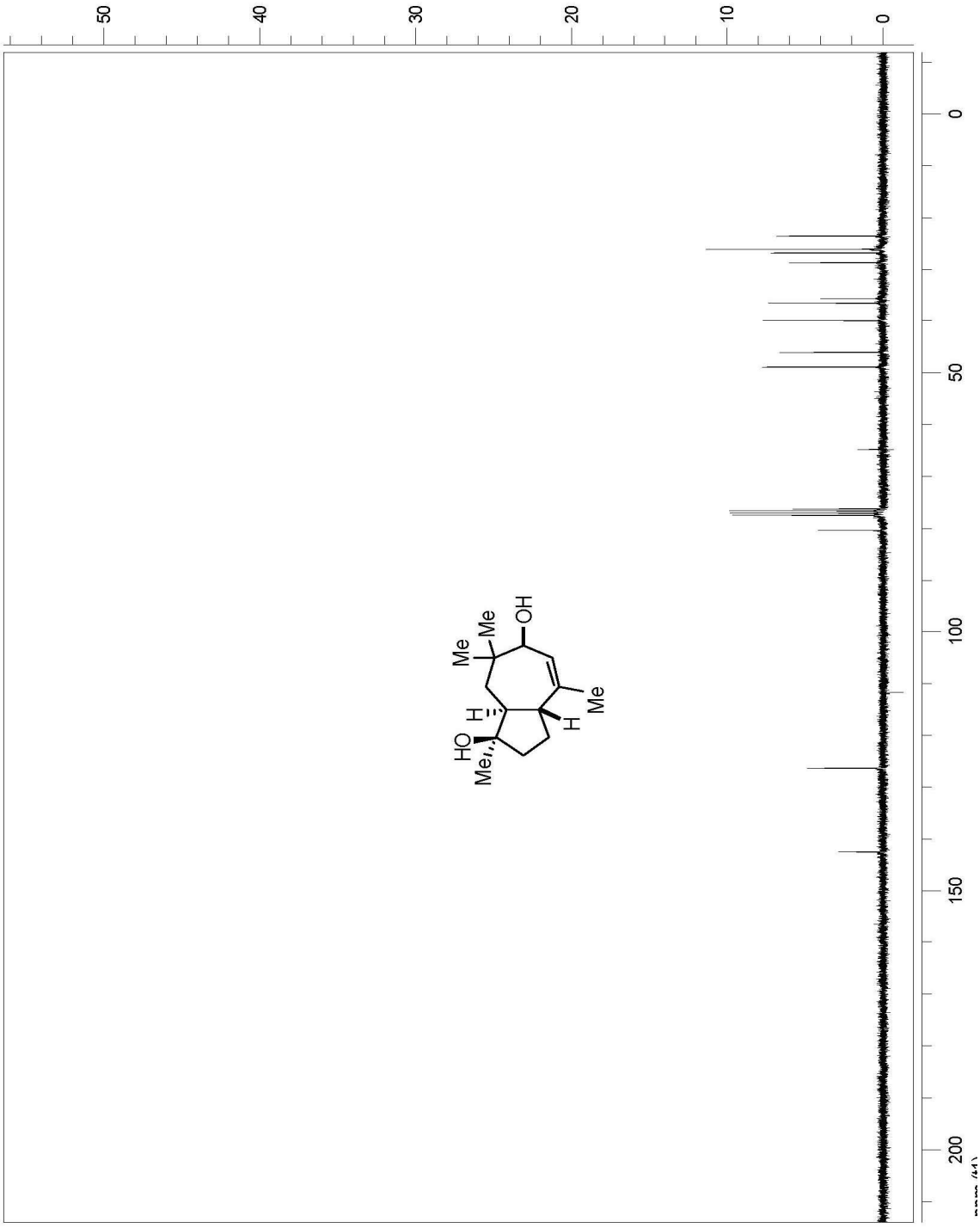
^{1}H NMR (500 MHz) of **3.37** in $CDCl_3$



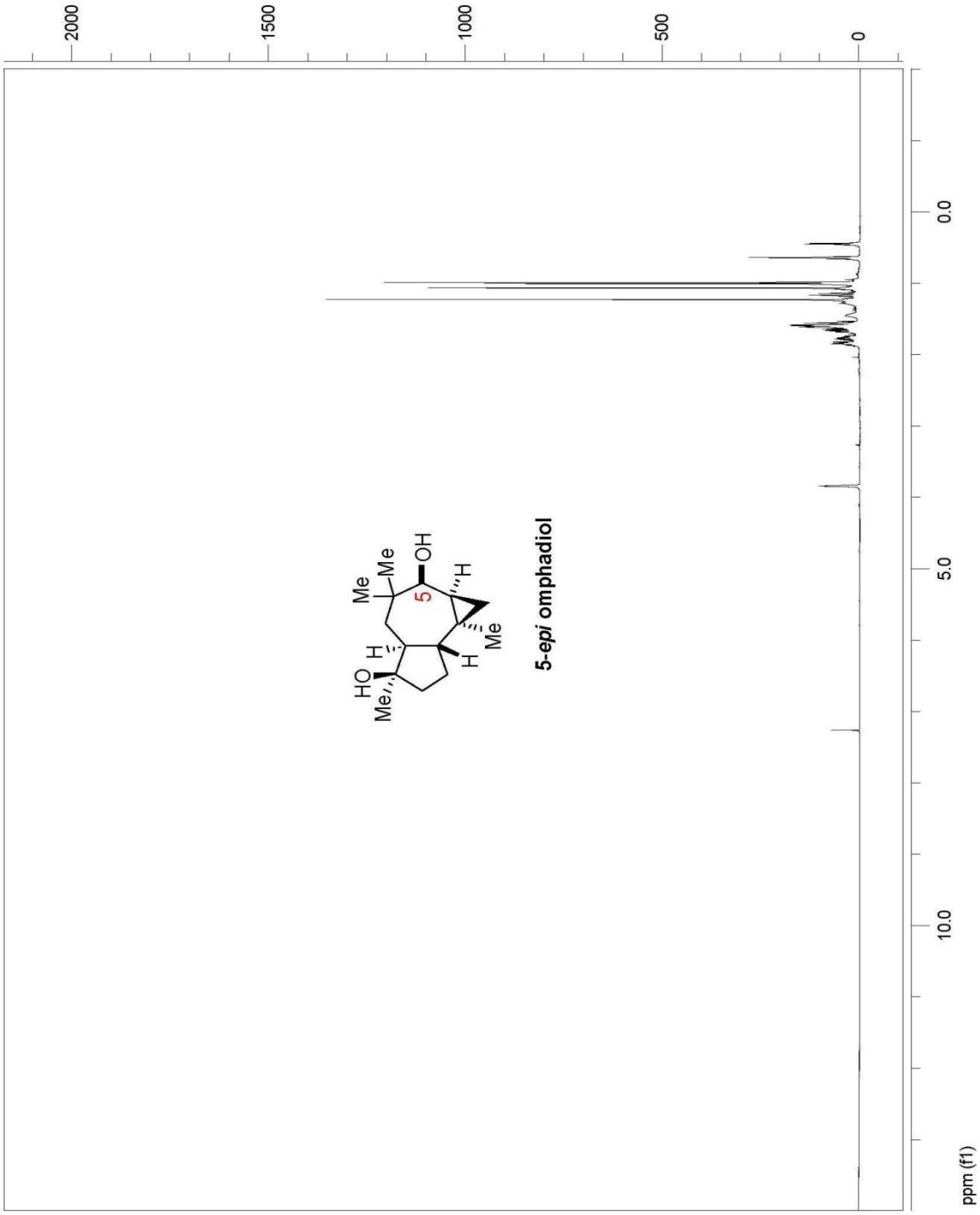
^{13}C NMR (500 MHz) of **3.37** in $CDCl_3$



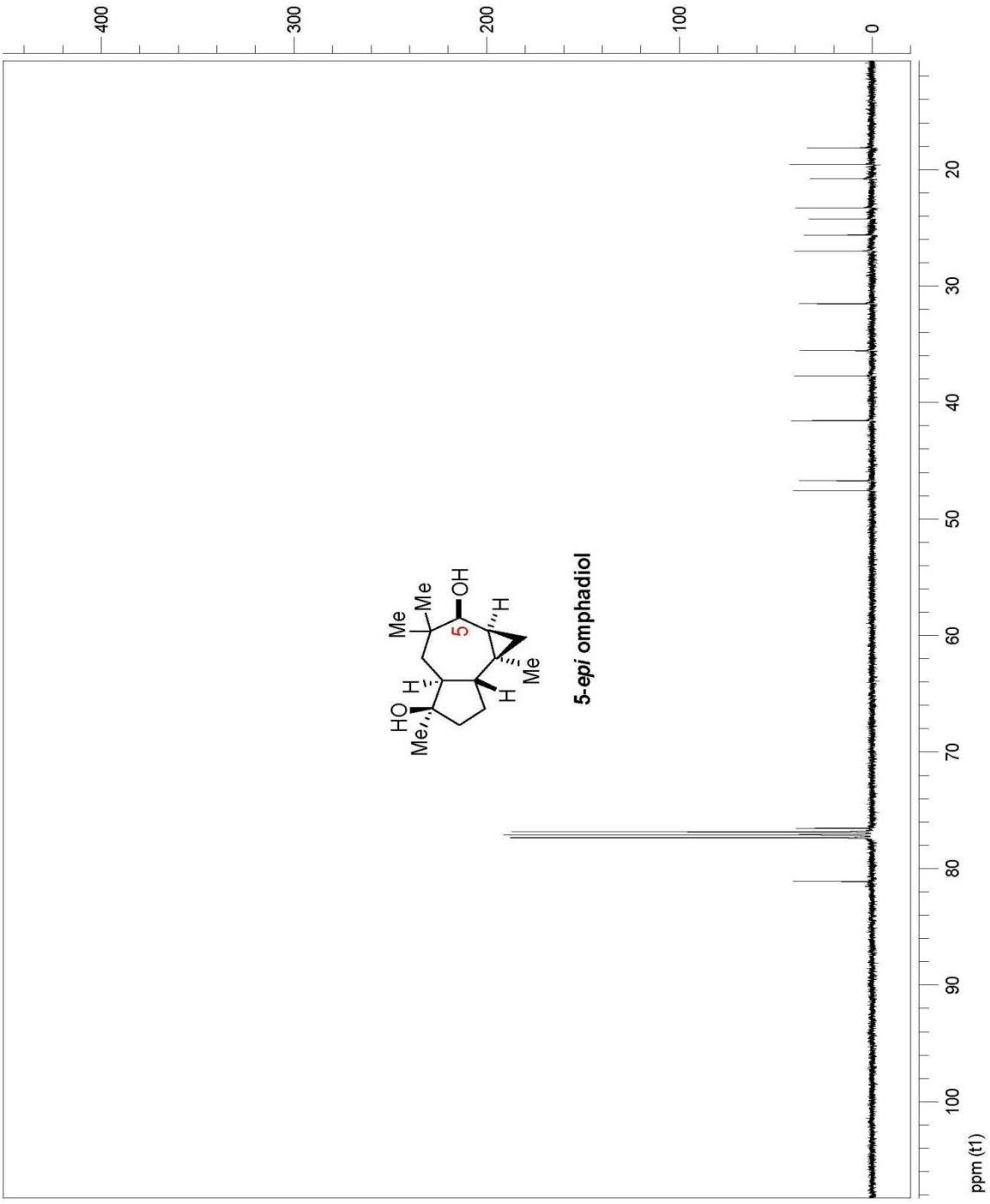
^{1}H NMR (500 MHz) of **3.38** in $CDCl_3$



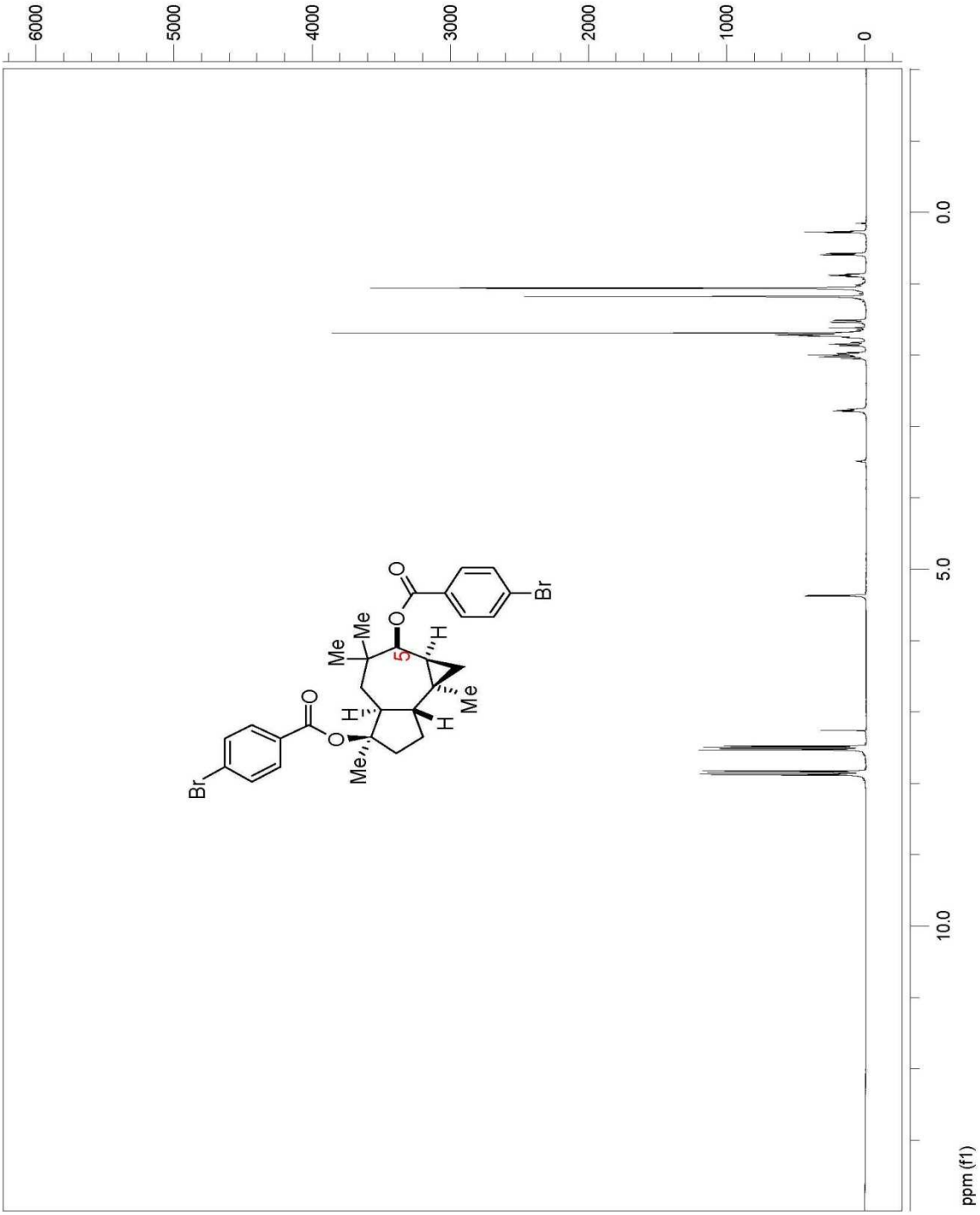
^{13}C NMR (500 MHz) of **3.38** in $CDCl_3$



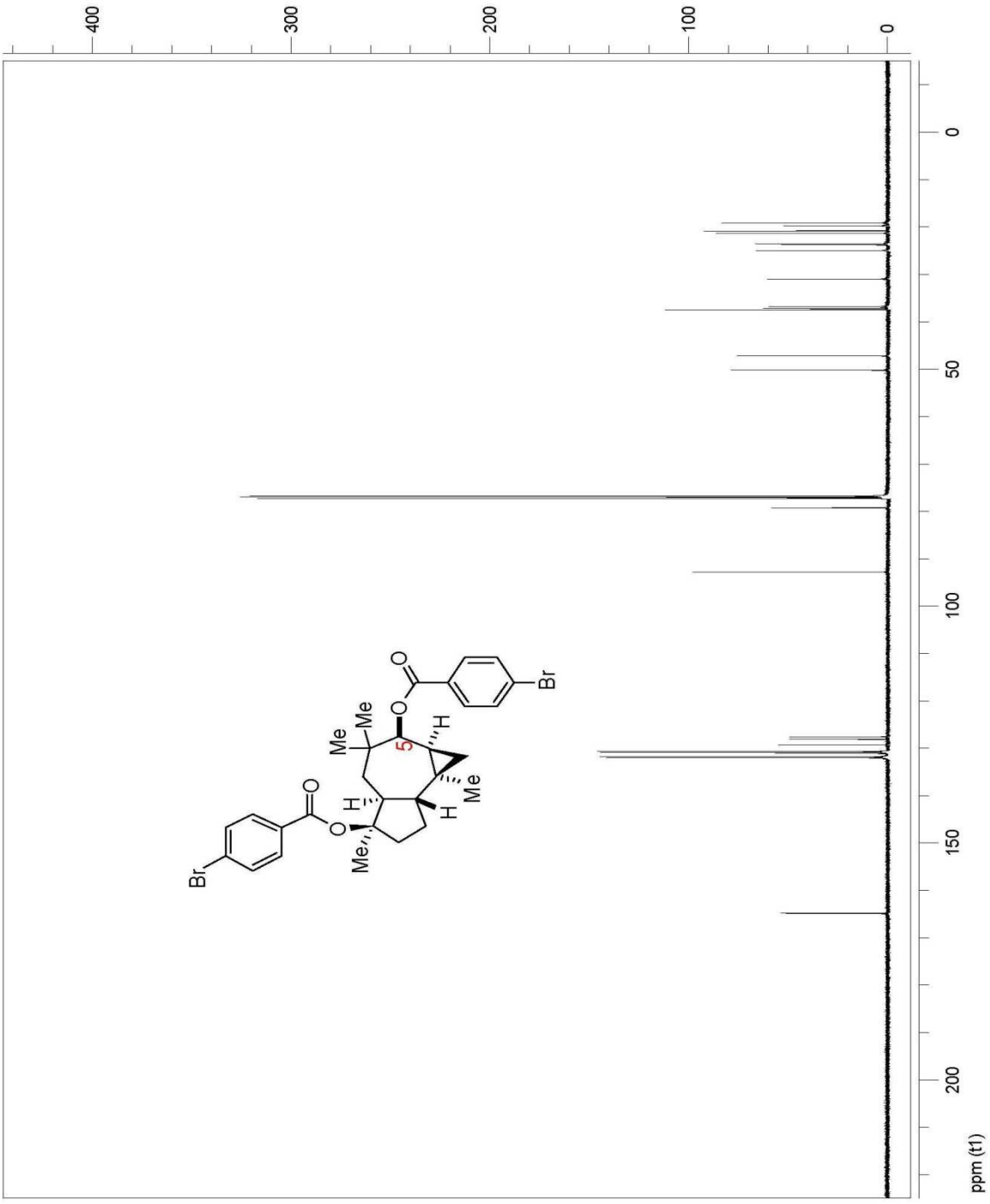
^{1}H NMR (500 MHz) of **3.38** in $CDCl_3$



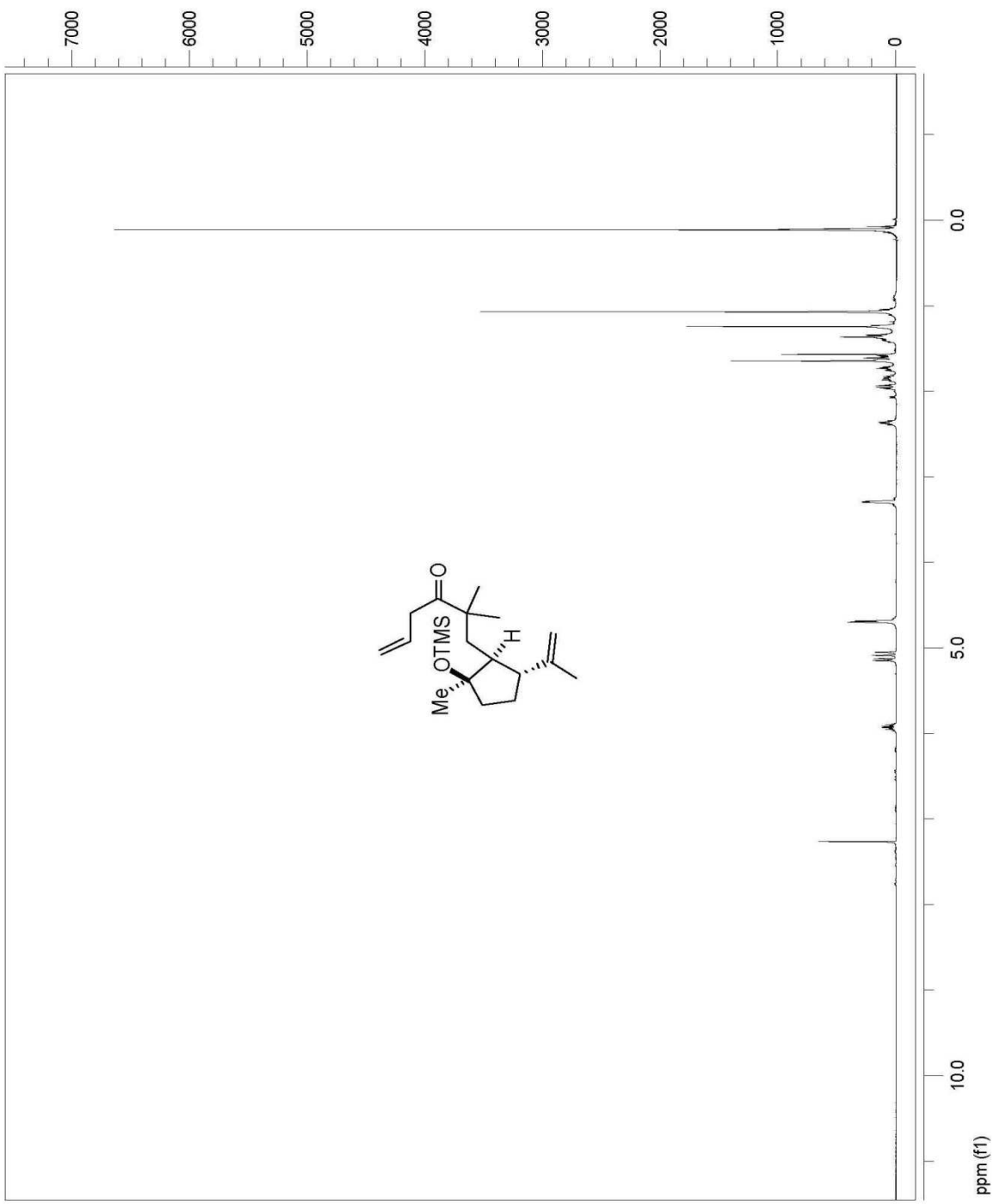
^{13}C NMR (500 MHz) of **3.39** in $CDCl_3$



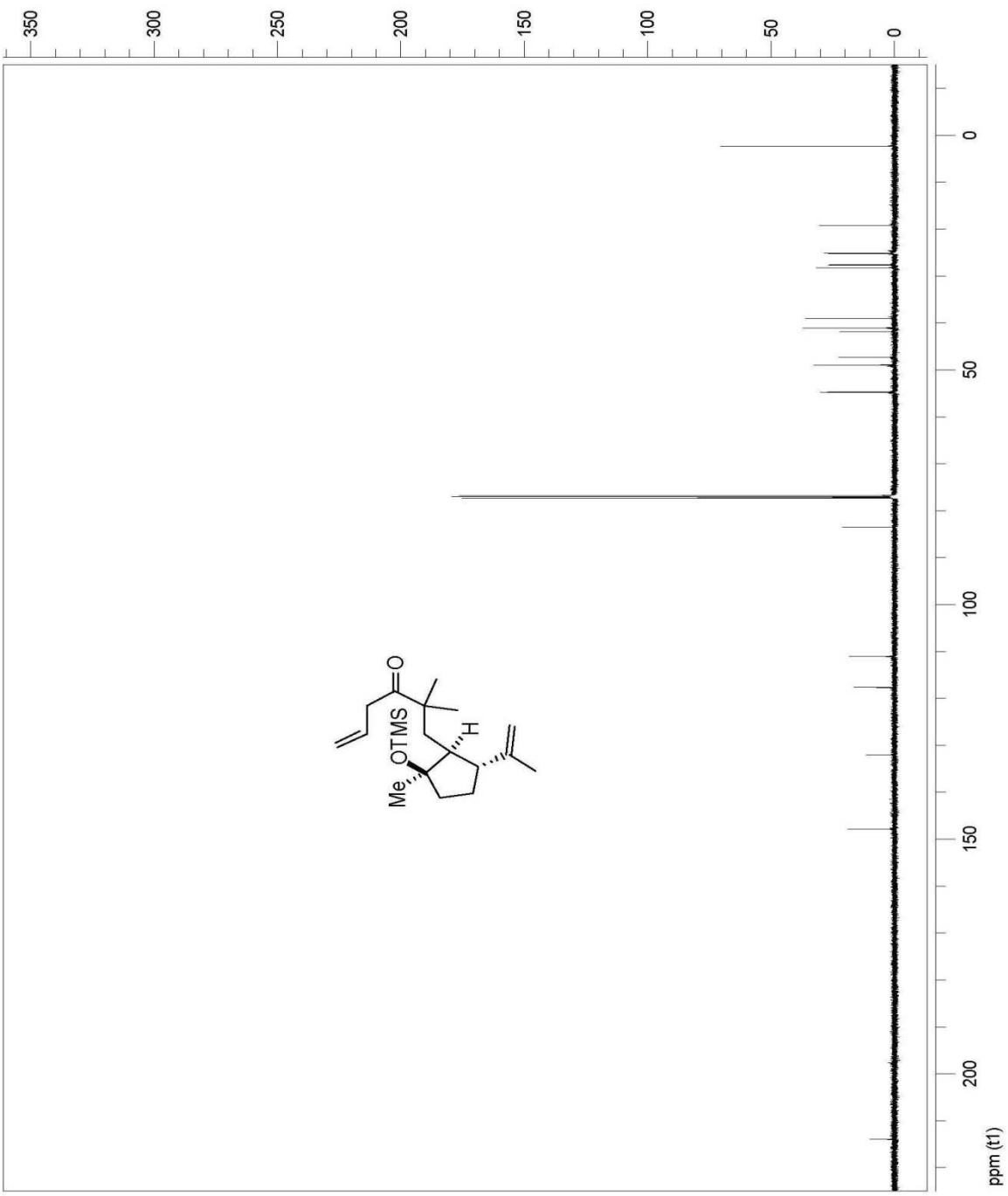
^{1}H NMR (500 MHz) of **3.40** in $CDCl_3$



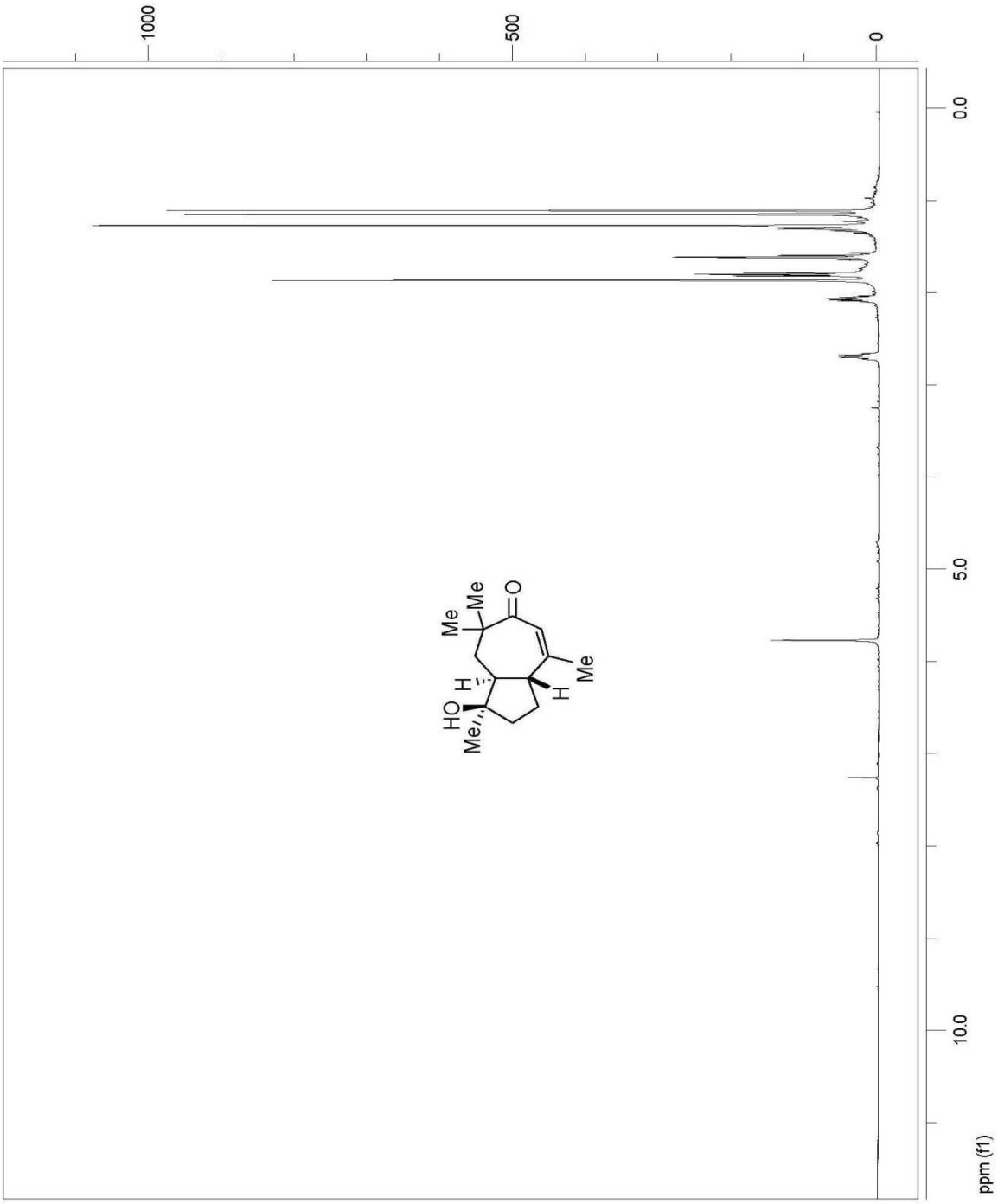
^{13}C NMR (500 MHz) of **3.40** in $CDCl_3$



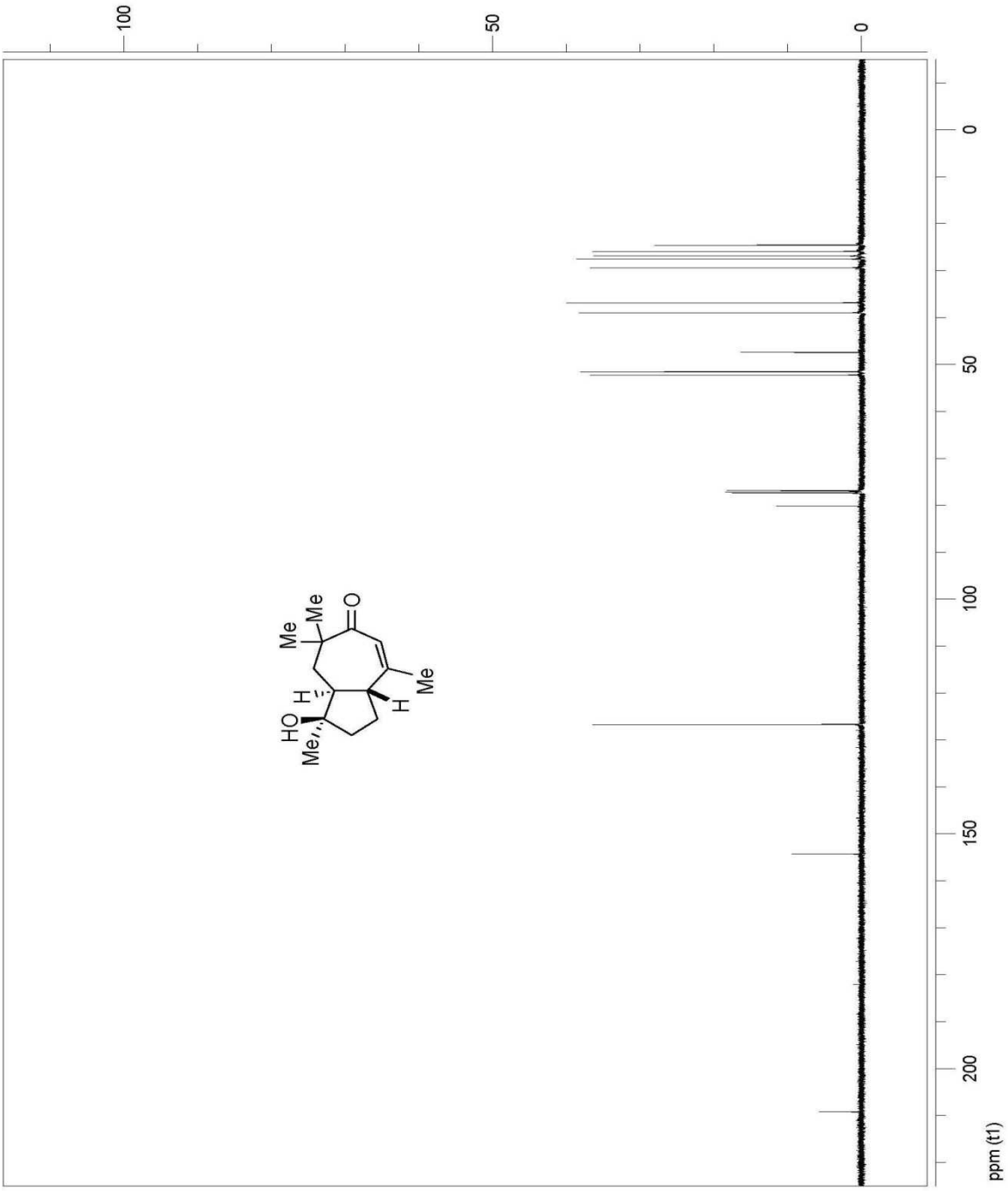
^{1}H NMR (500 MHz) of **S1** in $CDCl_3$



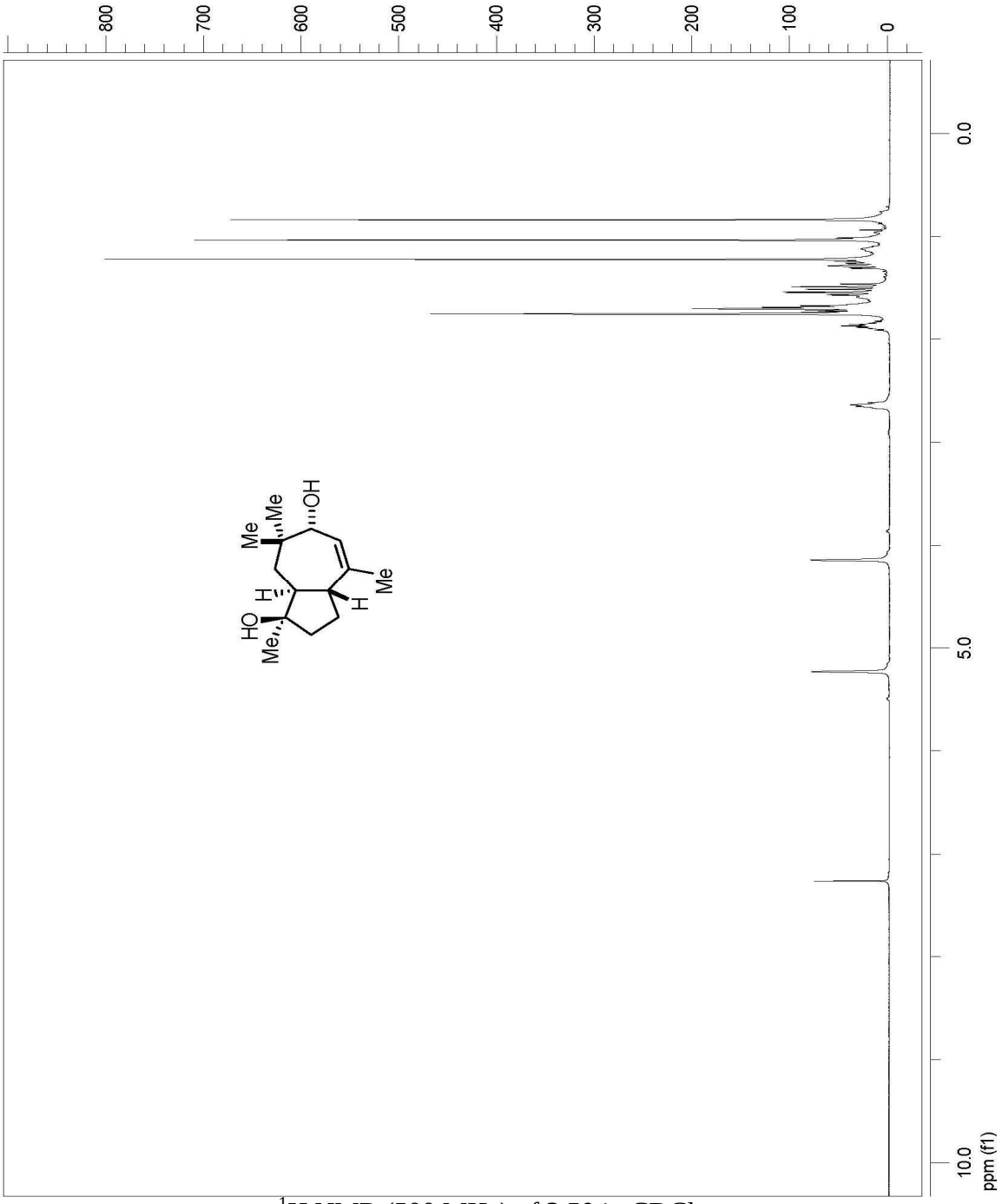
^{13}C NMR (500 MHz) of **S1** in $CDCl_3$



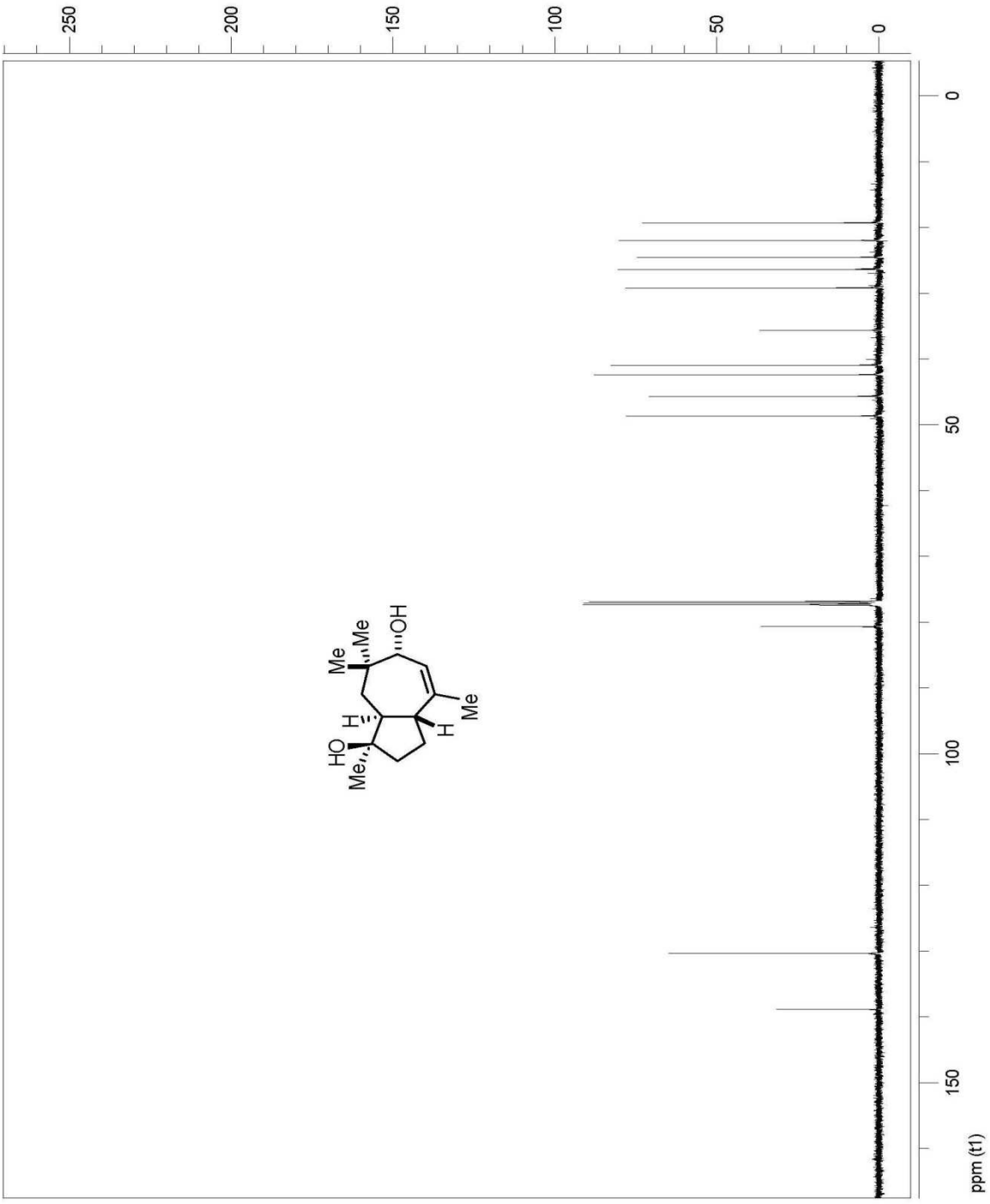
^{1}H NMR (500 MHz) of **3.14** in $CDCl_3$



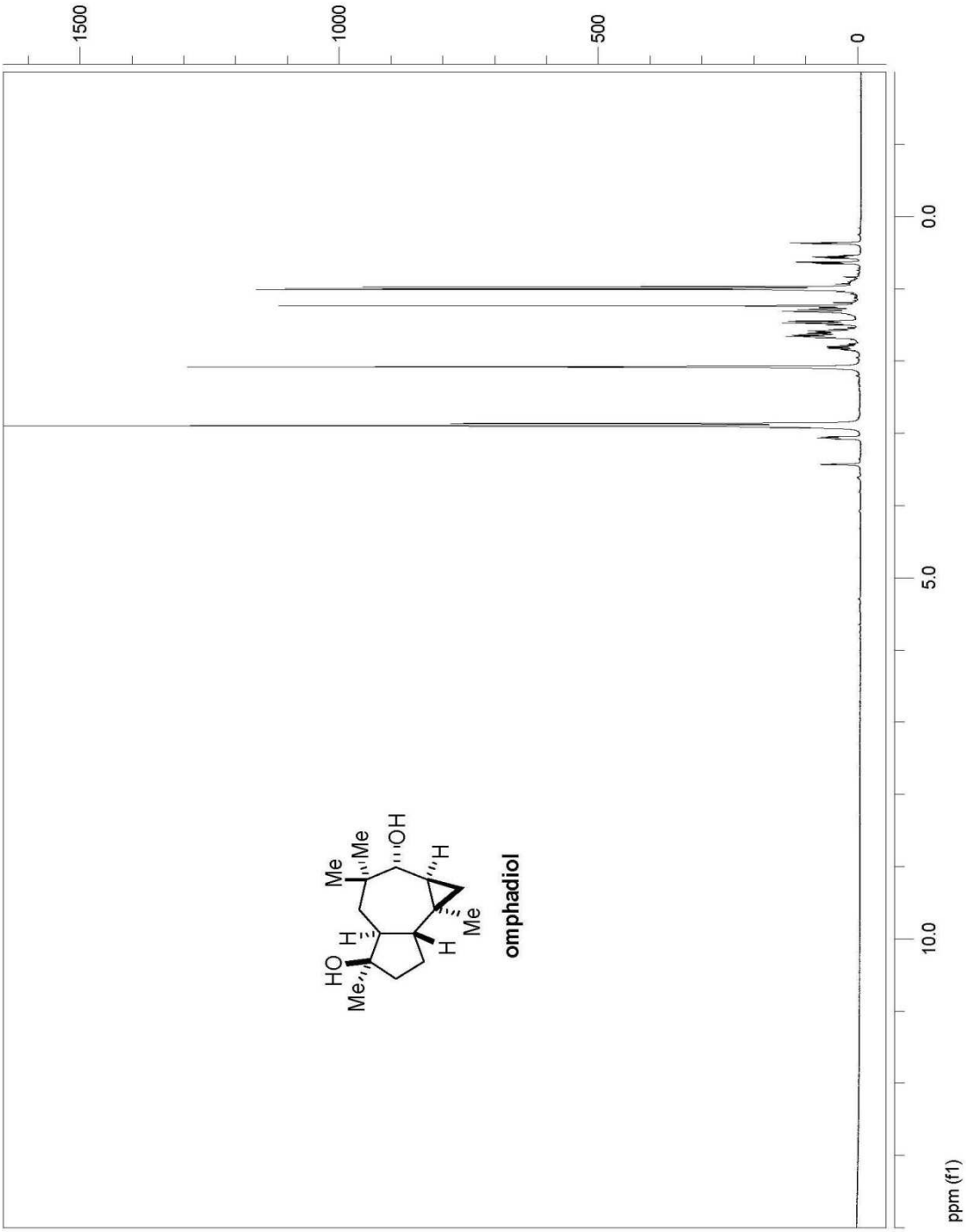
^{13}C NMR (500 MHz) of **3.14** in $CDCl_3$



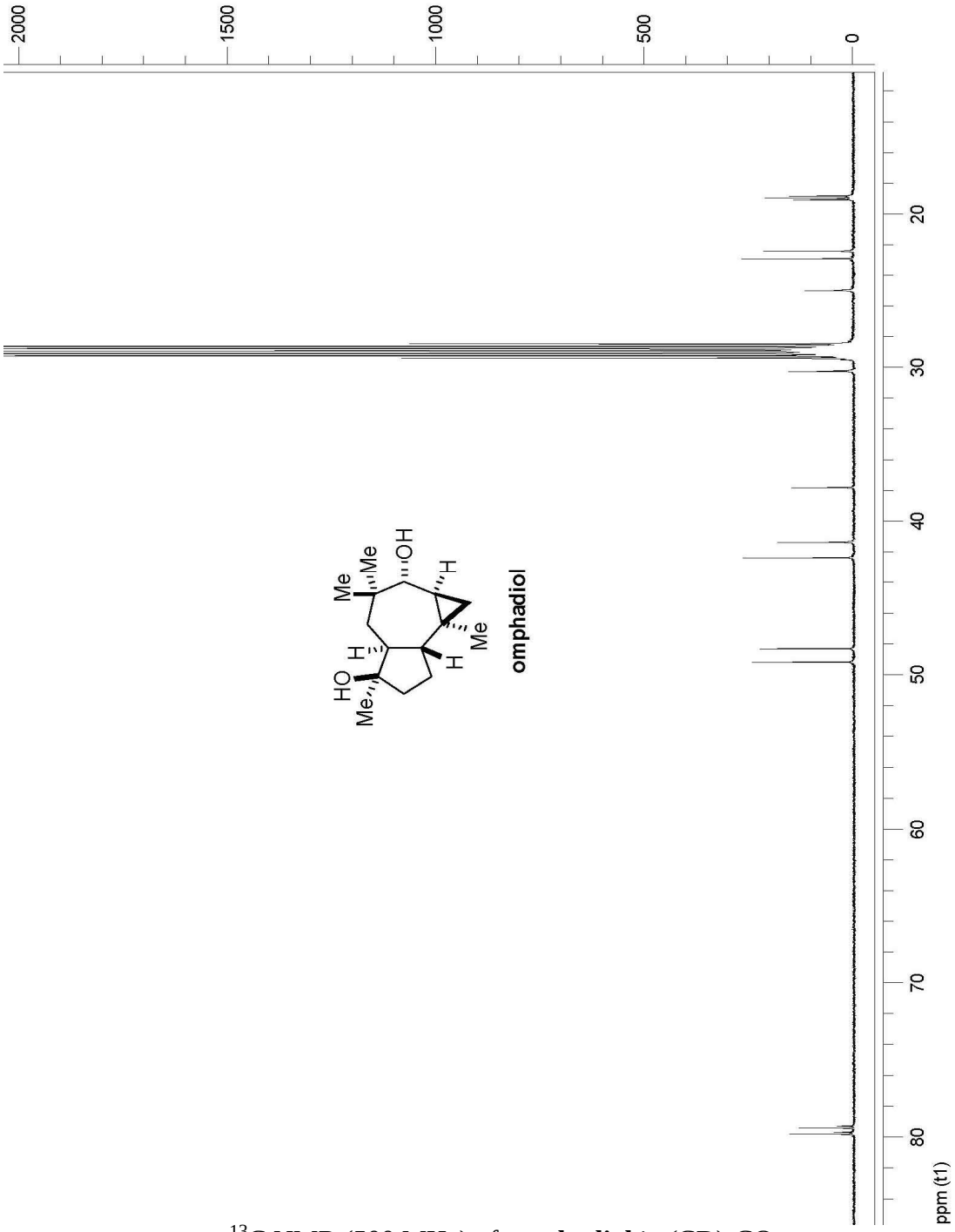
^{1}H NMR (500 MHz) of **3.50** in $CDCl_3$



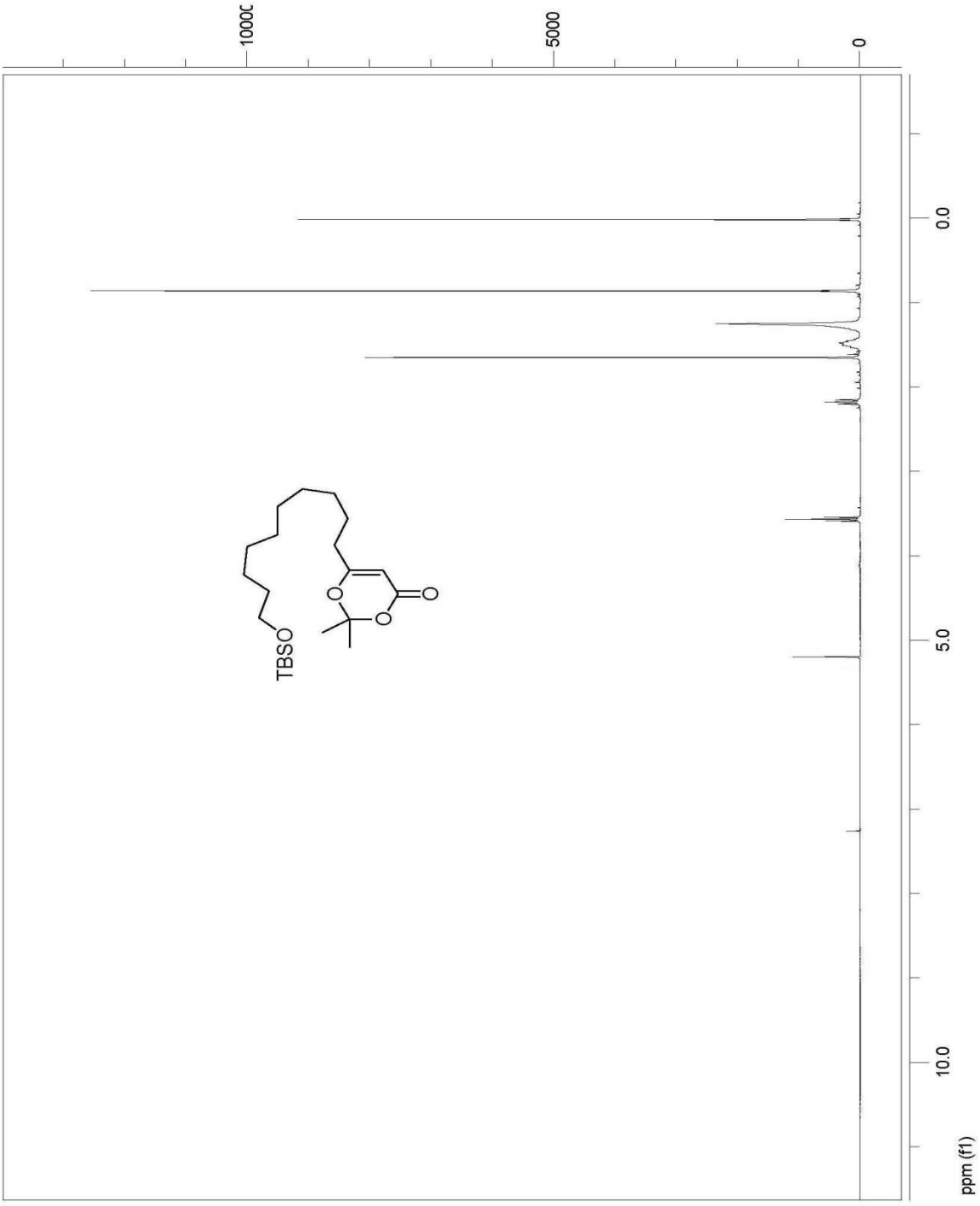
^{13}C NMR (500 MHz) of **3.50** in $CDCl_3$



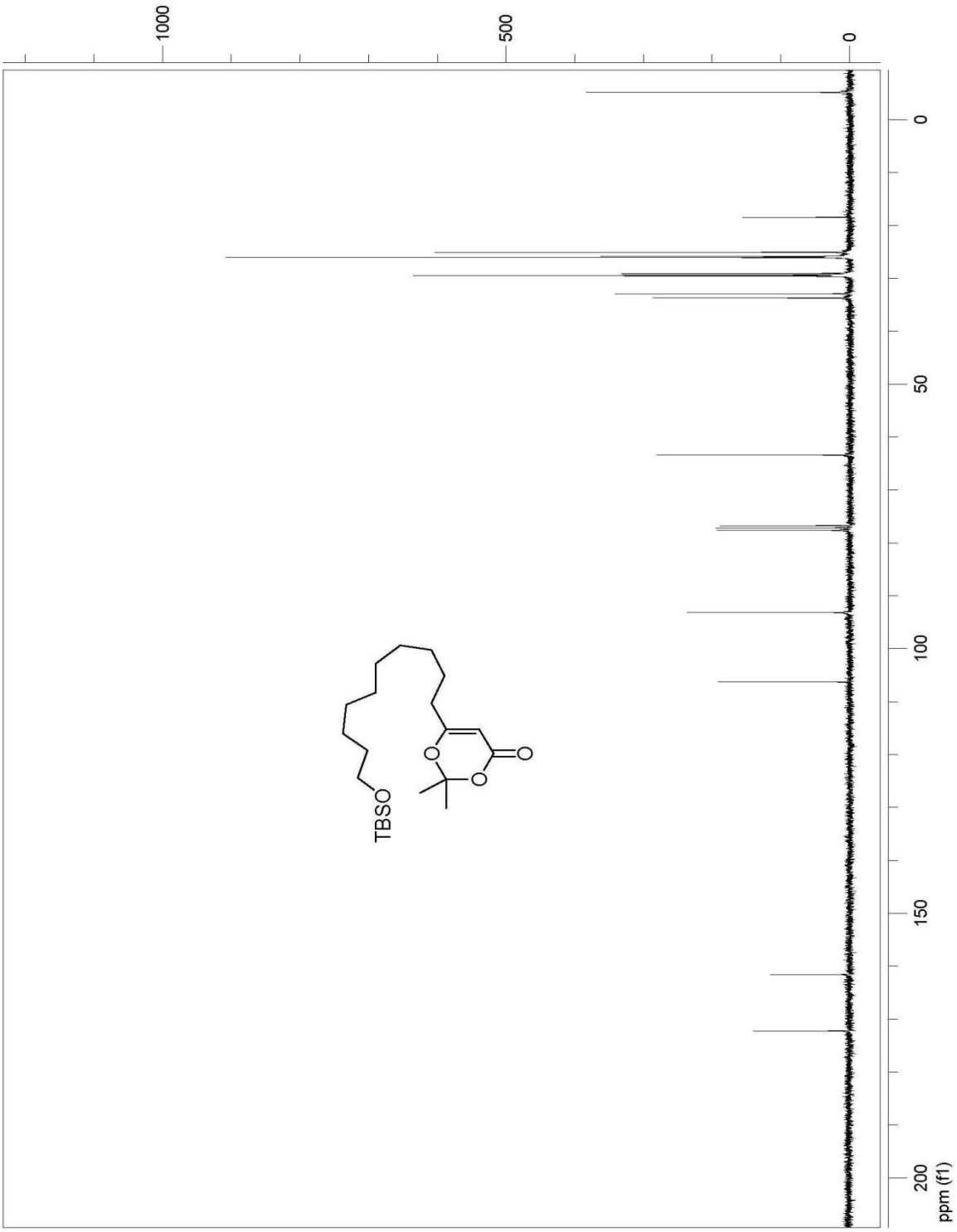
^{1}H NMR (500 MHz) of **omphadiol** in $(CD)_3CO$



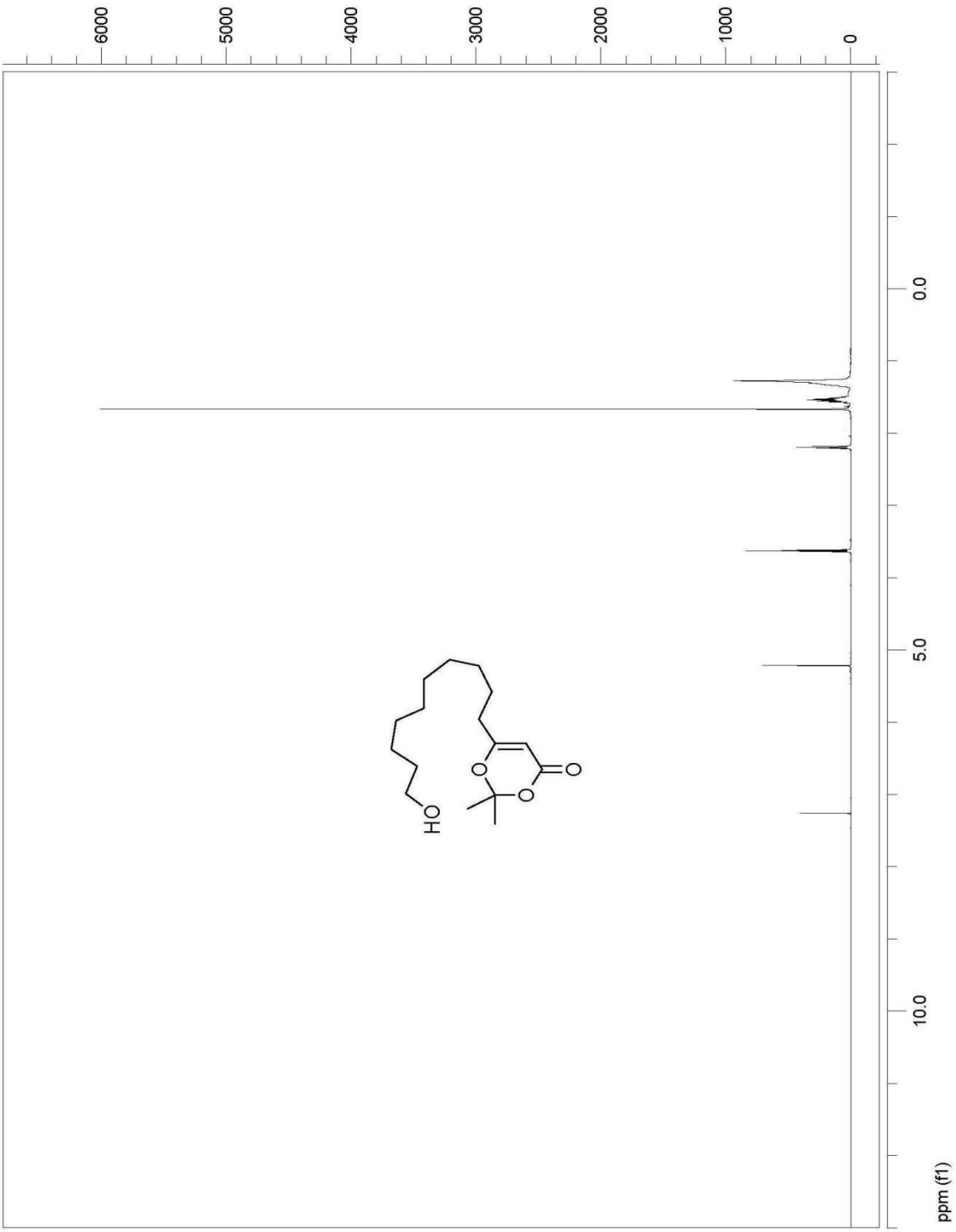
^{13}C NMR (500 MHz) of **omphadiol** in $(CD)_3CO$



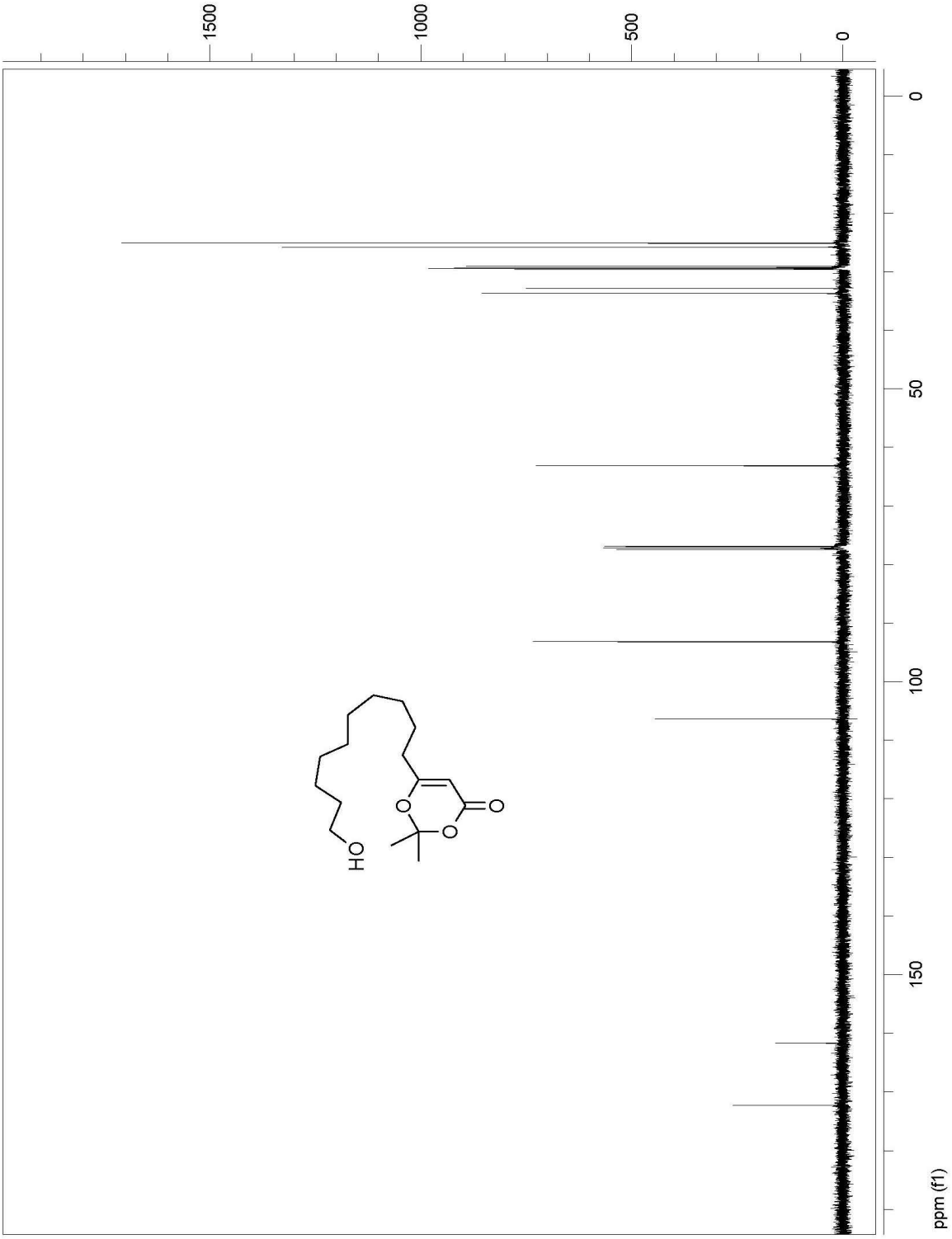
^{1}H NMR (500 MHz) of **4.11** in $CDCl_3$



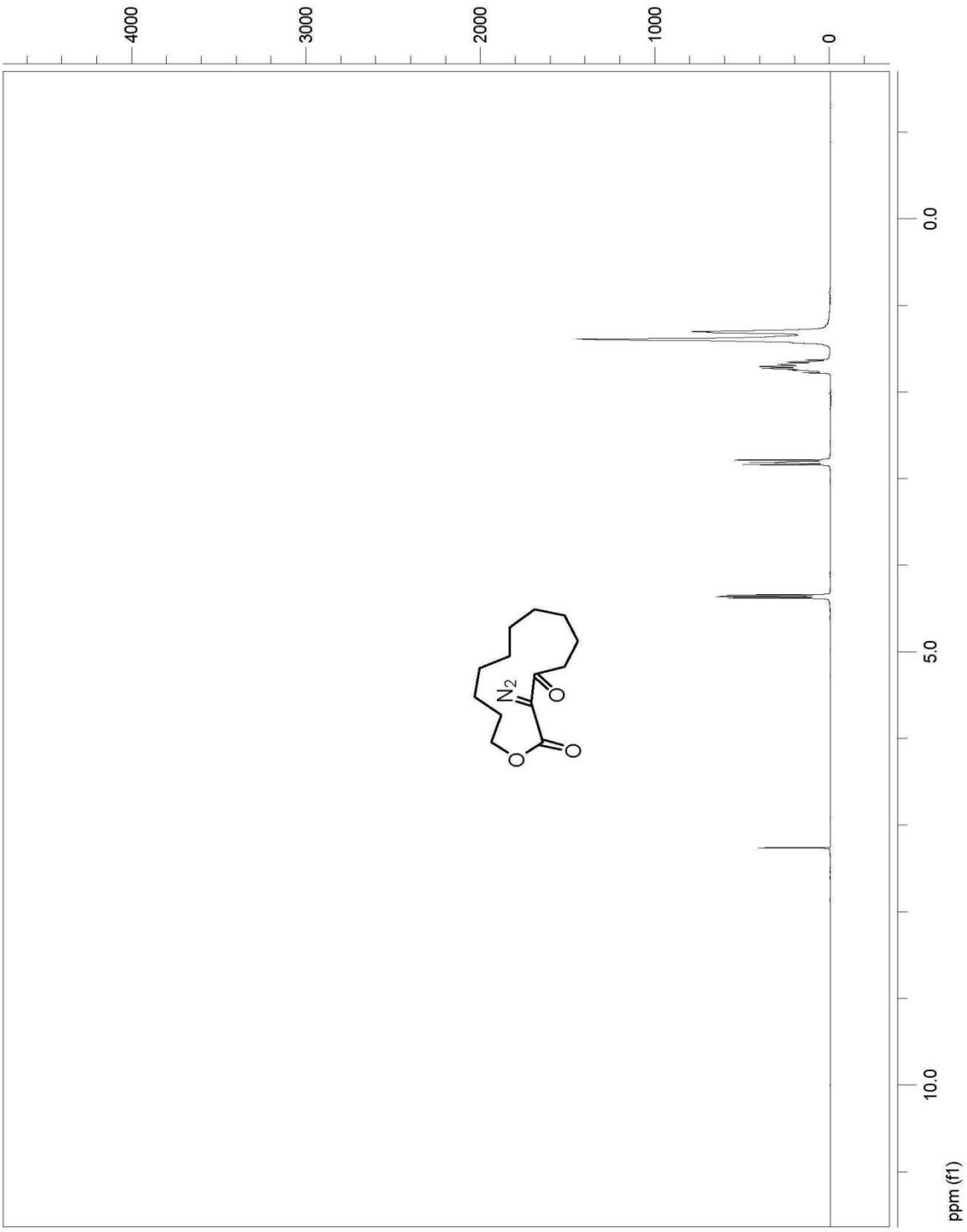
^{13}C NMR (500 MHz) of **4.11** in $CDCl_3$



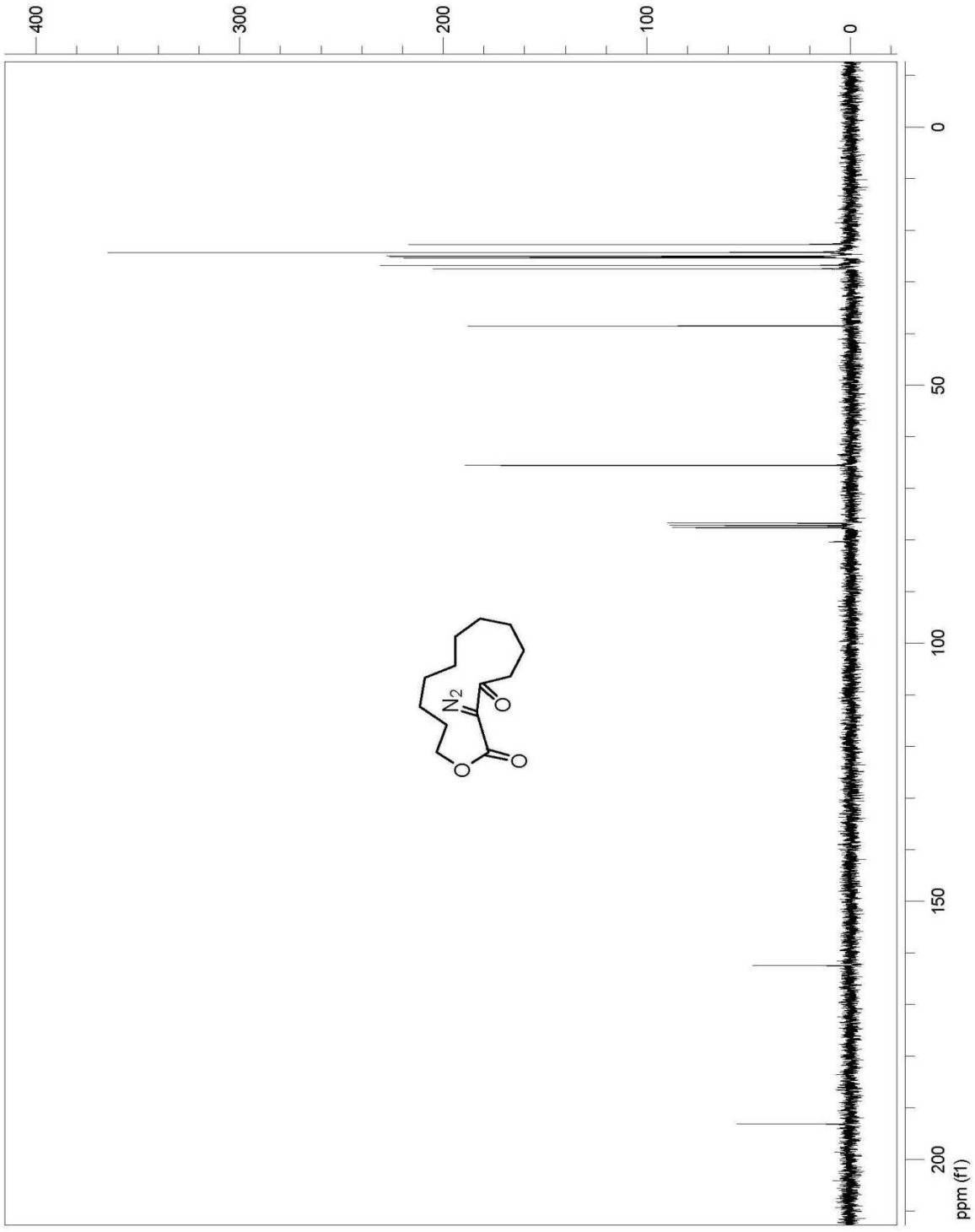
^{1}H NMR (500 MHz) of **4.13** in $CDCl_3$



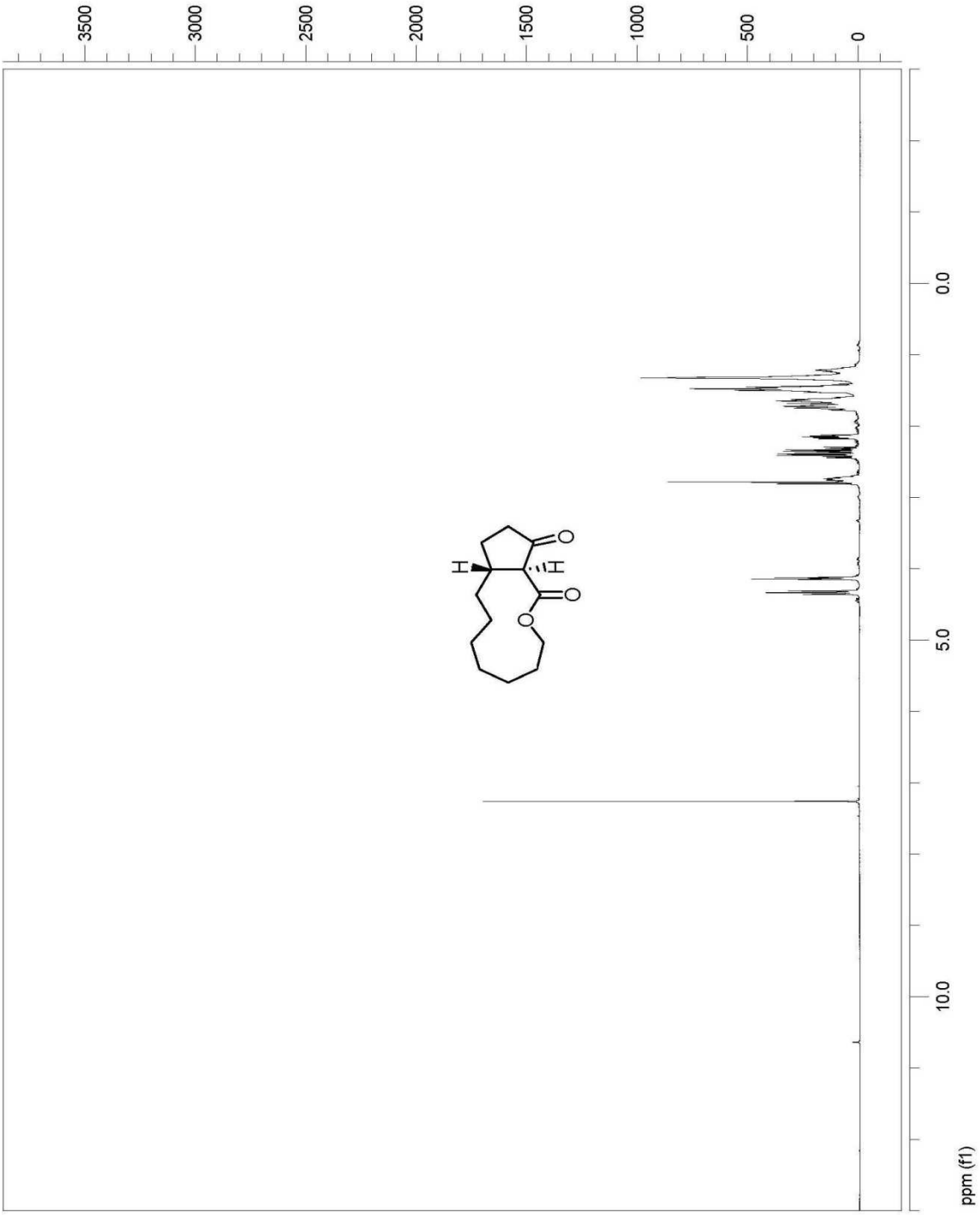
^{13}C NMR (500 MHz) of **4.13** in $CDCl_3$



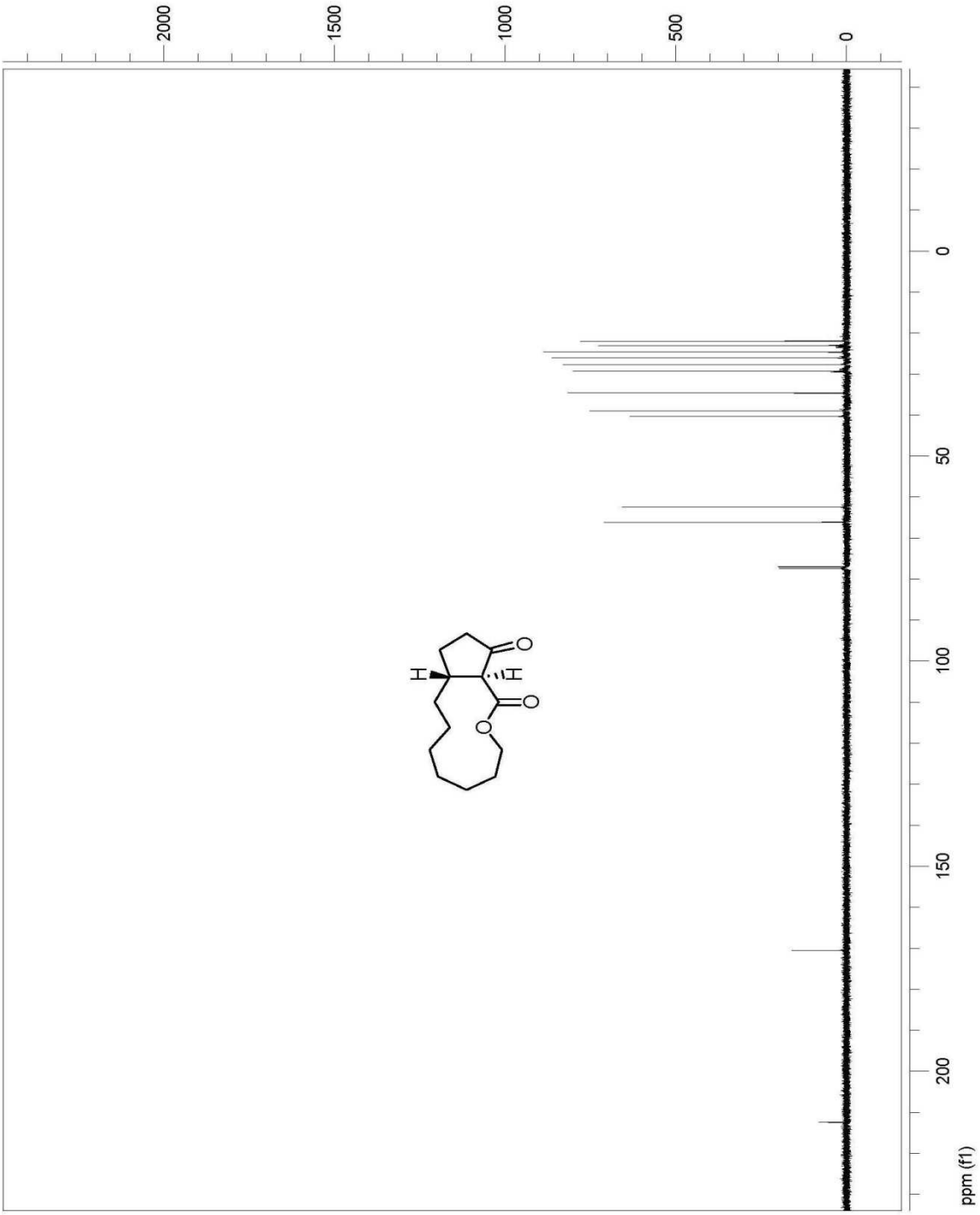
^{1}H NMR (500 MHz) of **4.14** in $CDCl_3$



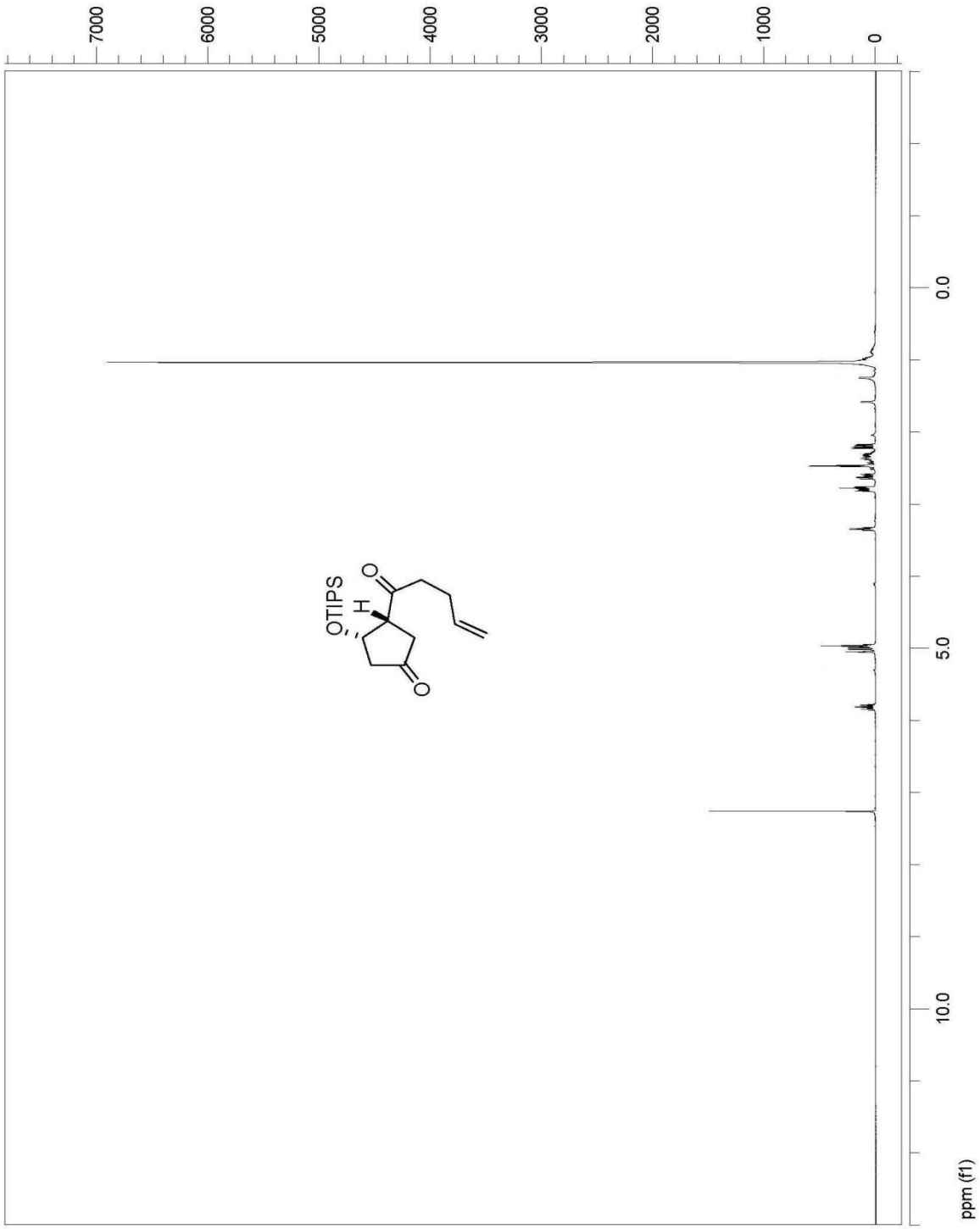
^{13}C NMR (500 MHz) of **4.14** in $CDCl_3$



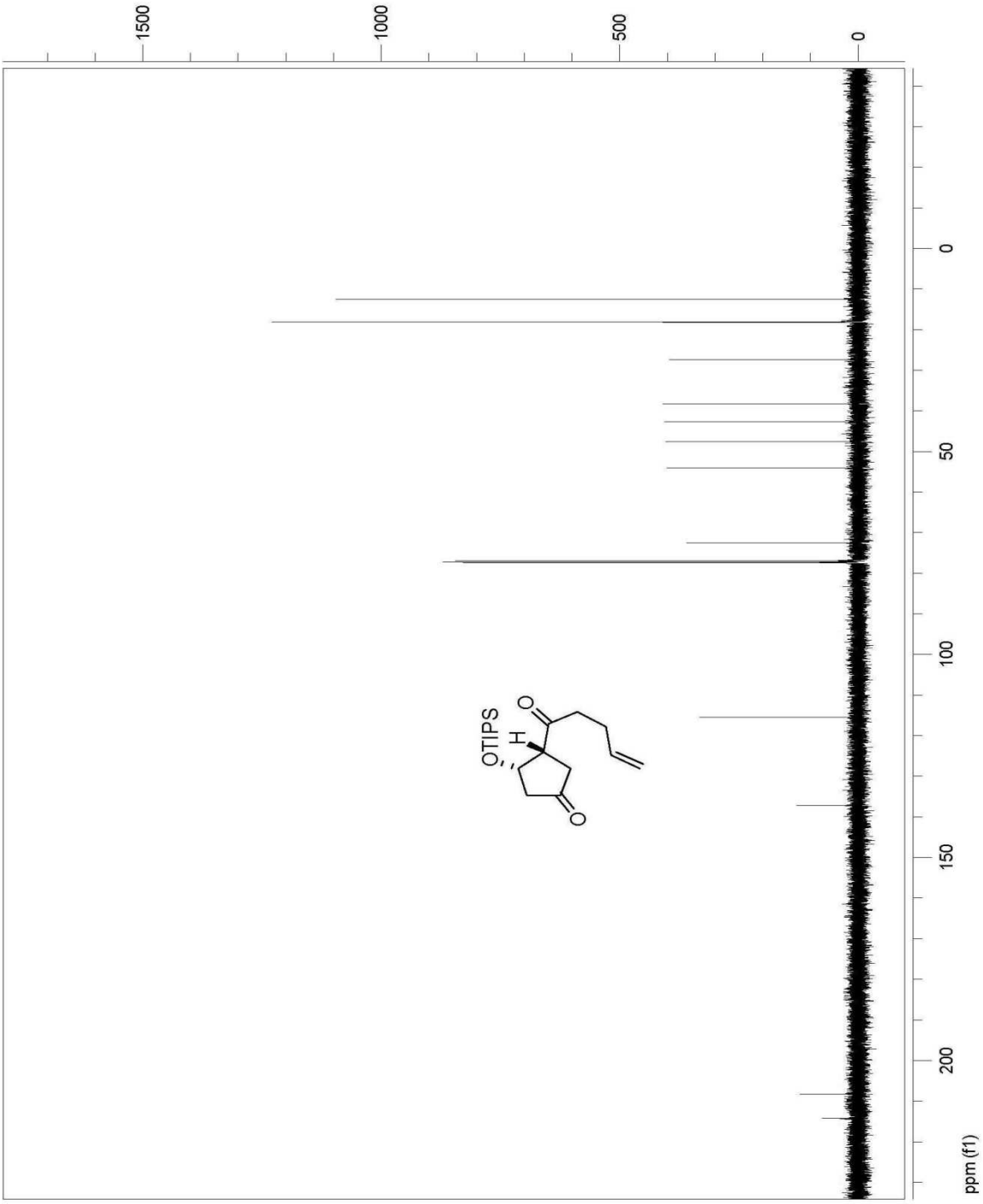
^{1}H NMR (500 MHz) of **4.15** in $CDCl_3$



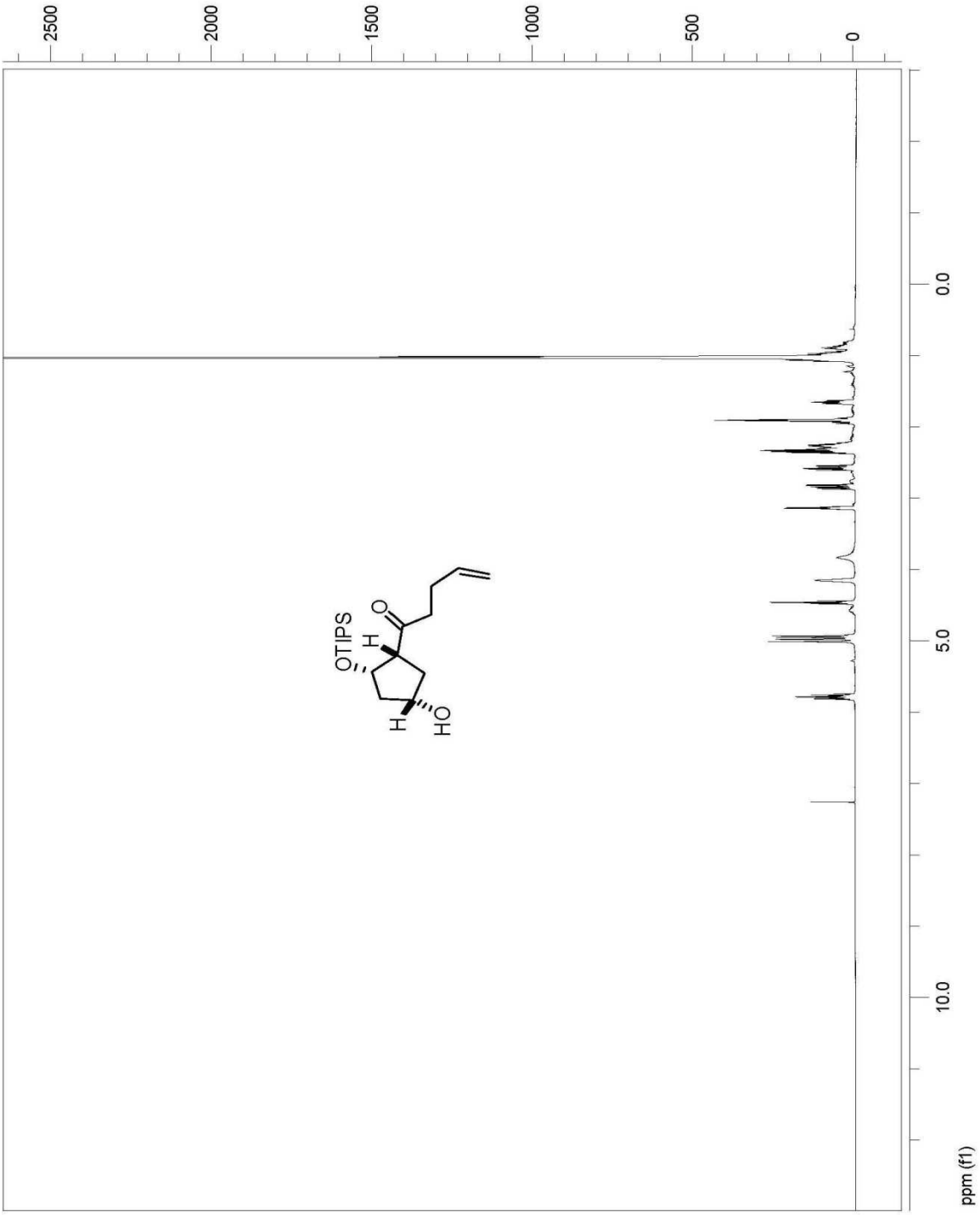
^{13}C NMR (500 MHz) of **4.15** in $CDCl_3$



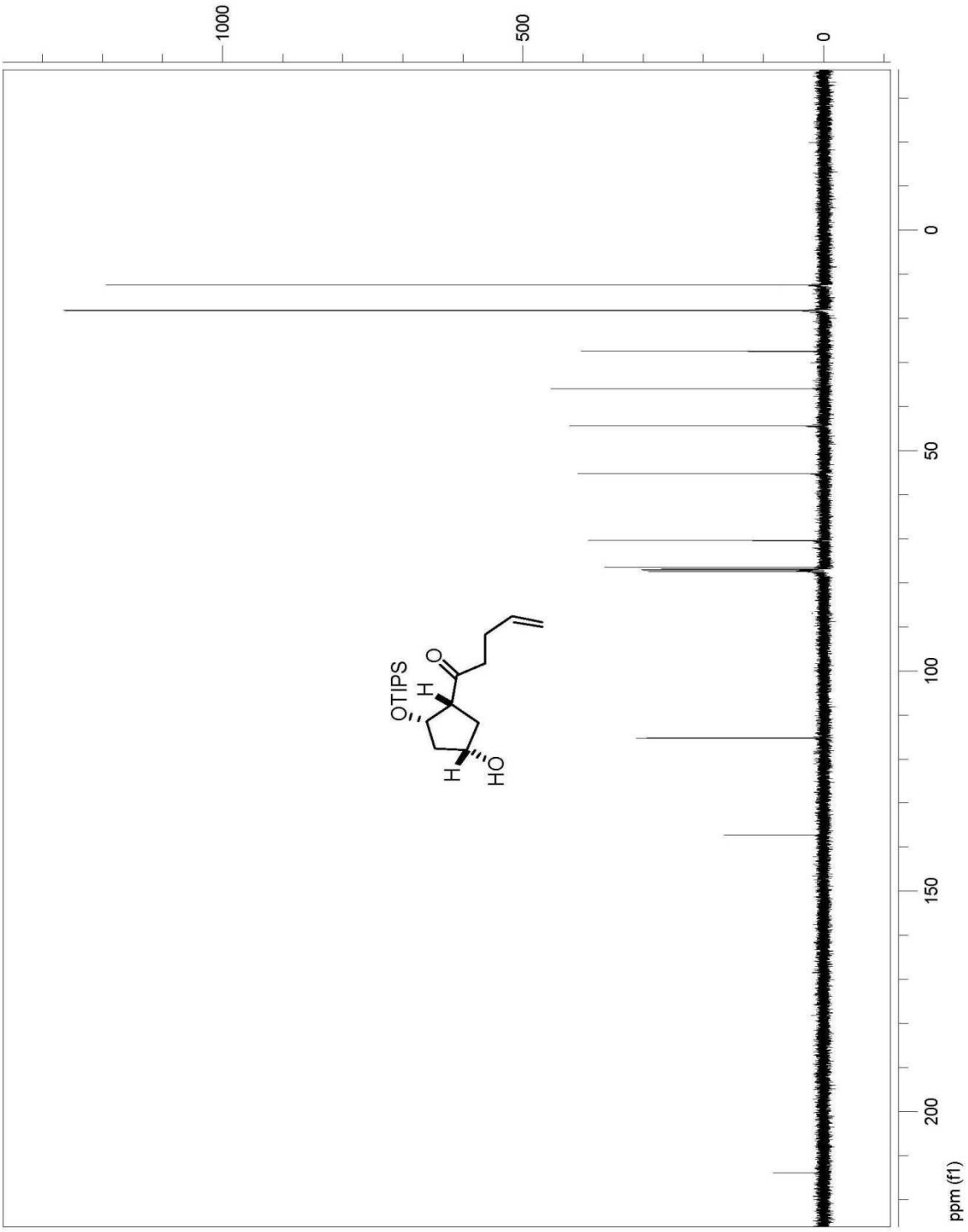
^{1}H NMR (500 MHz) of **4.25** in $CDCl_3$



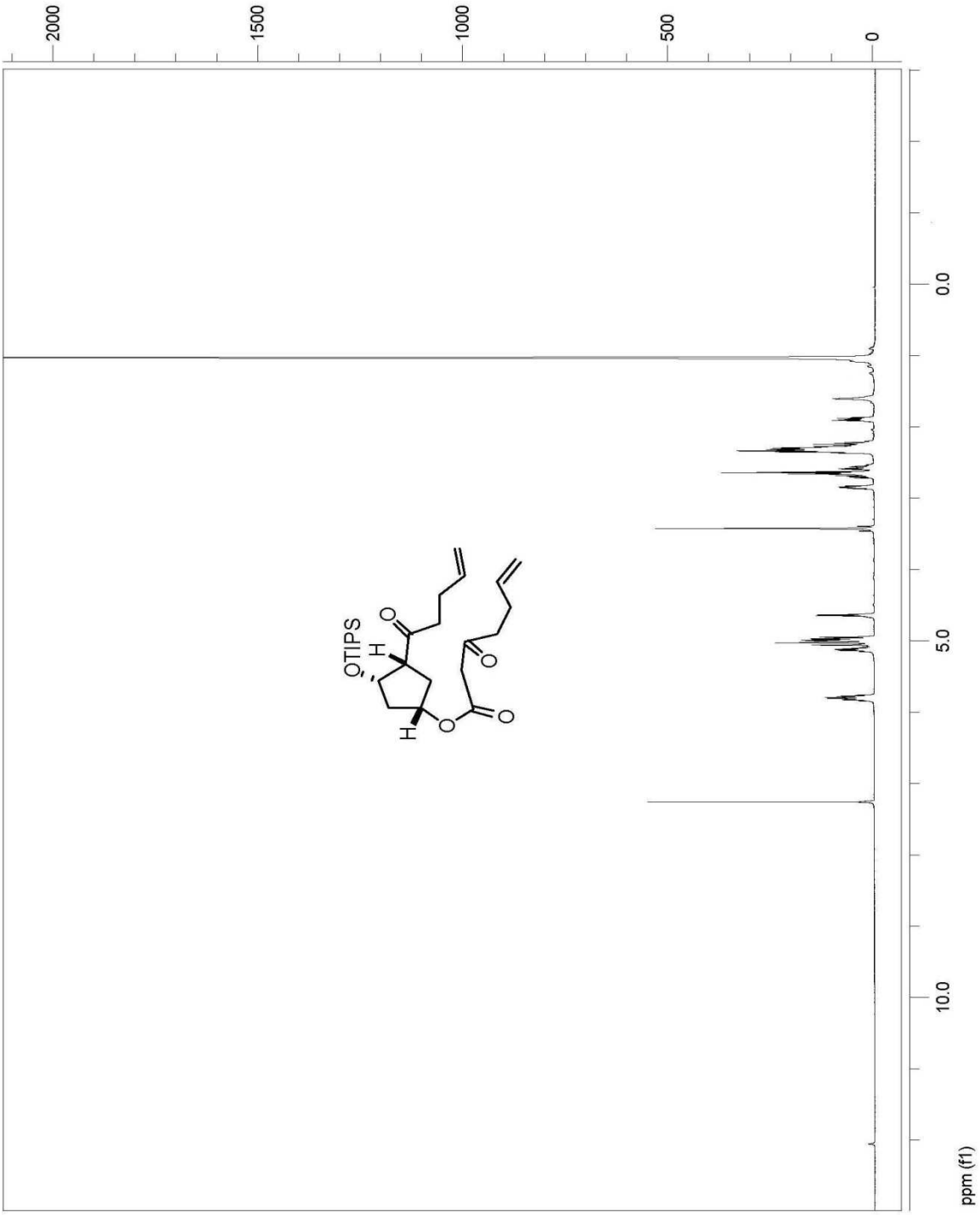
^{13}C NMR (500 MHz) of **4.25** in $CDCl_3$



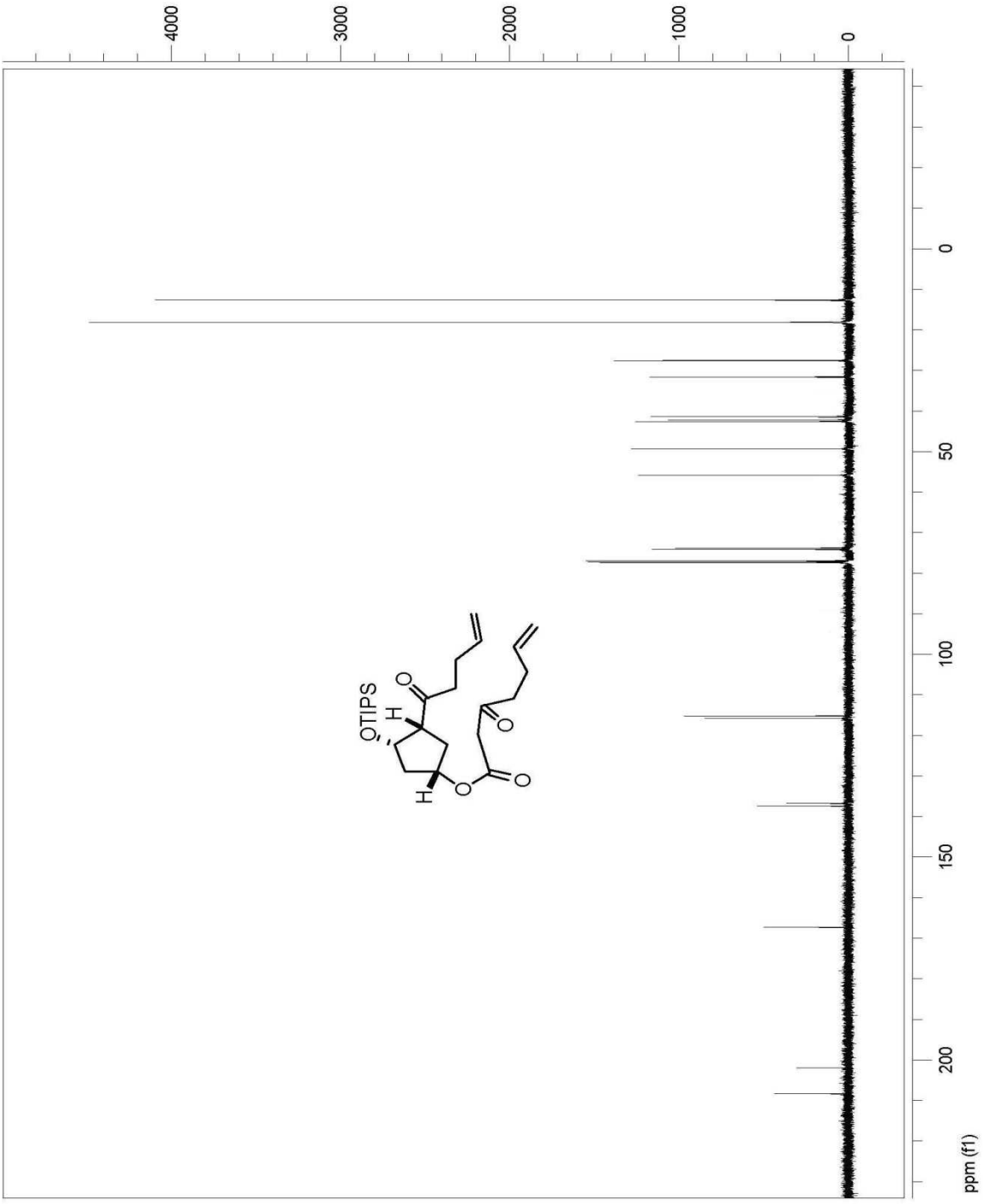
^{1}H NMR (500 MHz) of **4.26** in $CDCl_3$



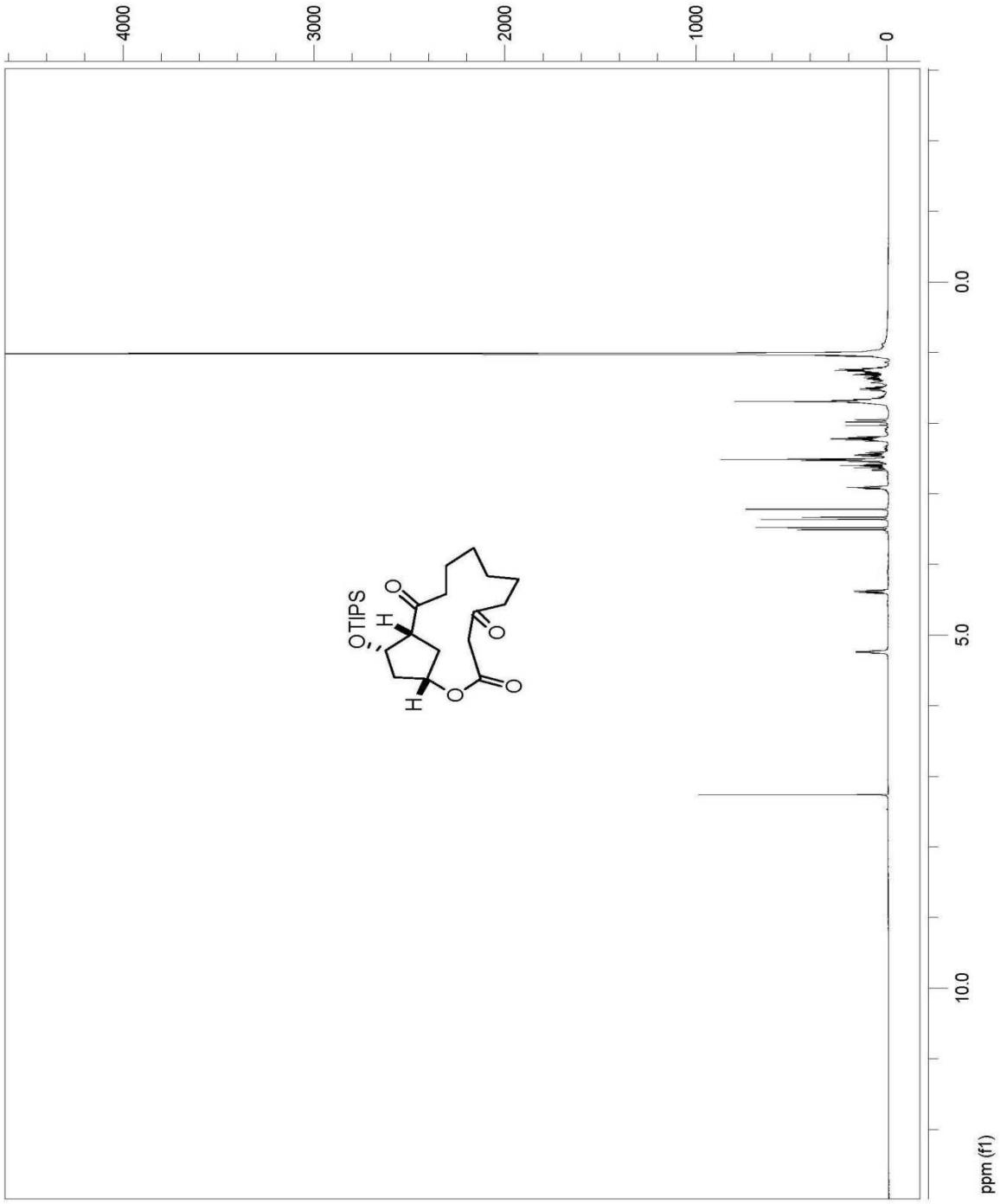
^{13}C NMR (500 MHz) of **4.26** in $CDCl_3$



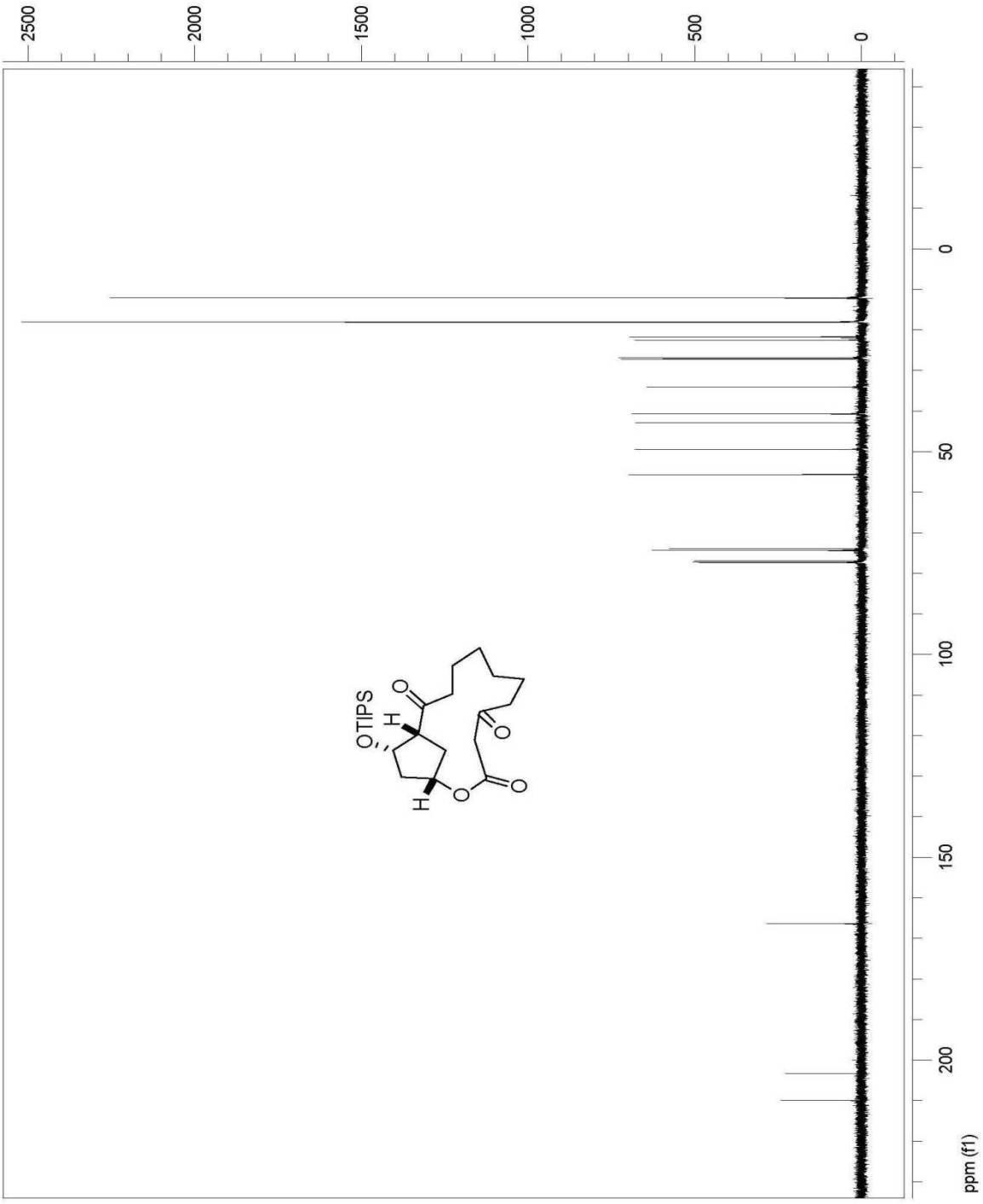
^{1}H NMR (500 MHz) of **4.28** in $CDCl_3$



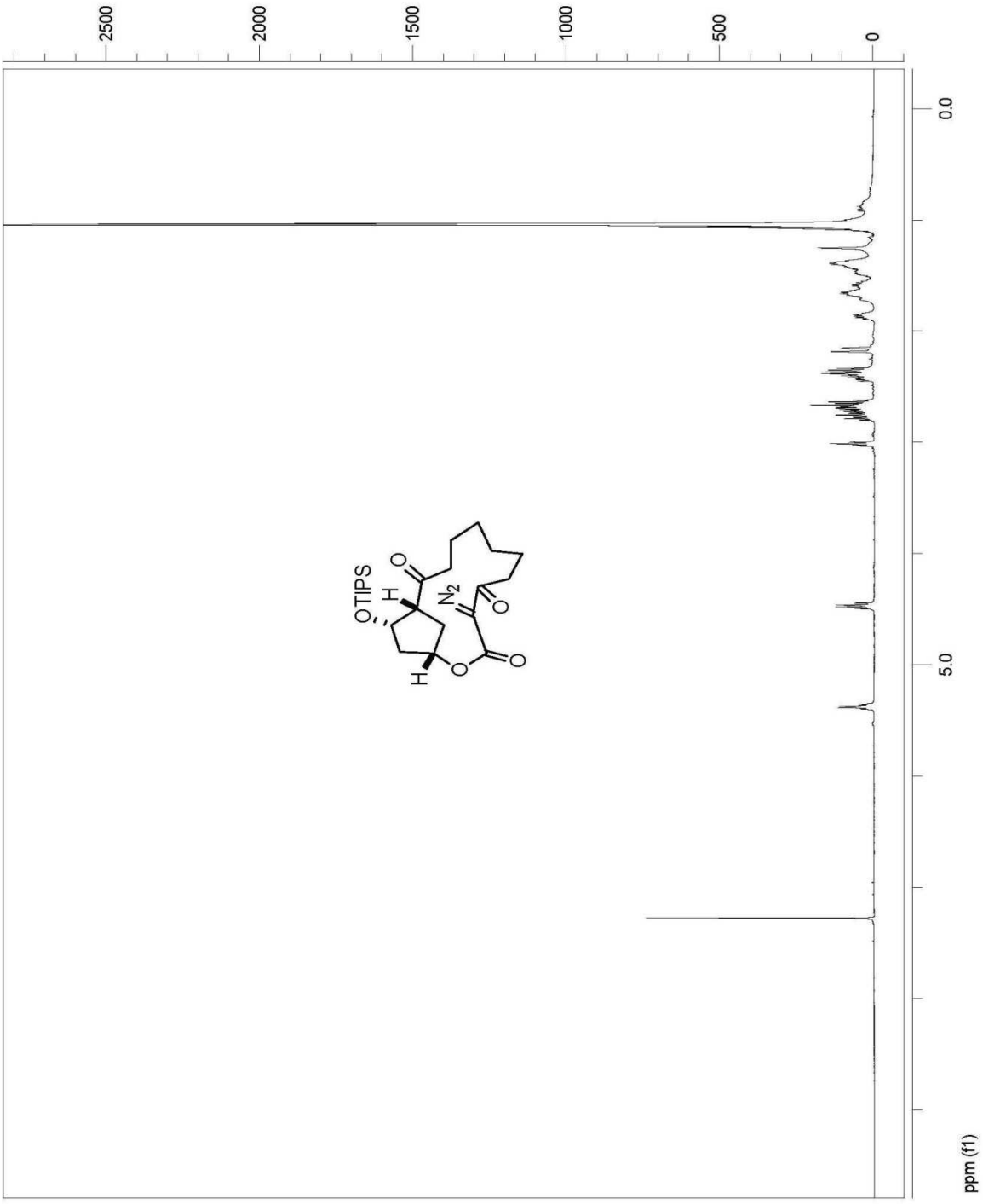
^{13}C NMR (500 MHz) of **4.28** in $CDCl_3$



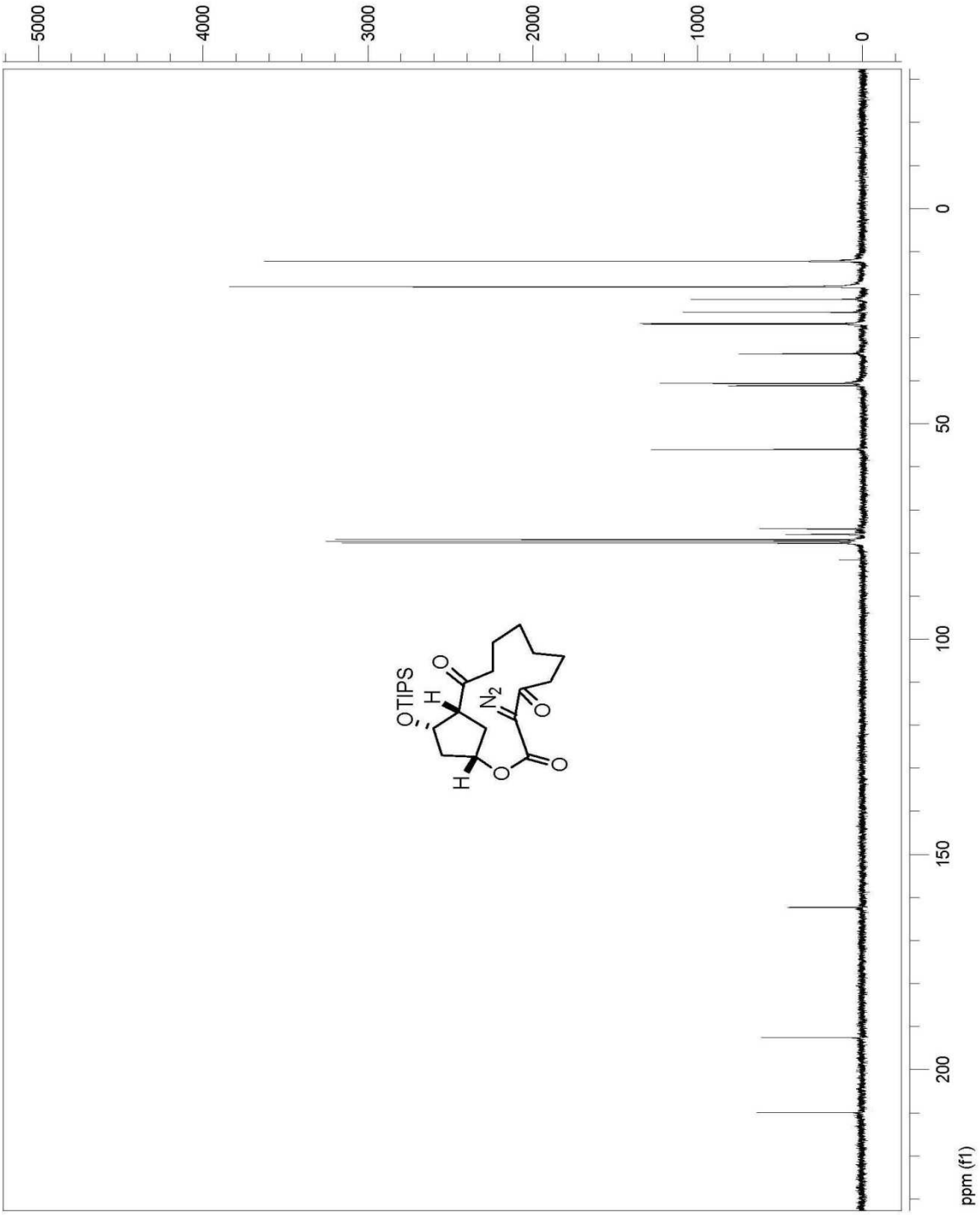
^{1}H NMR (500 MHz) of **4.30** in $CDCl_3$



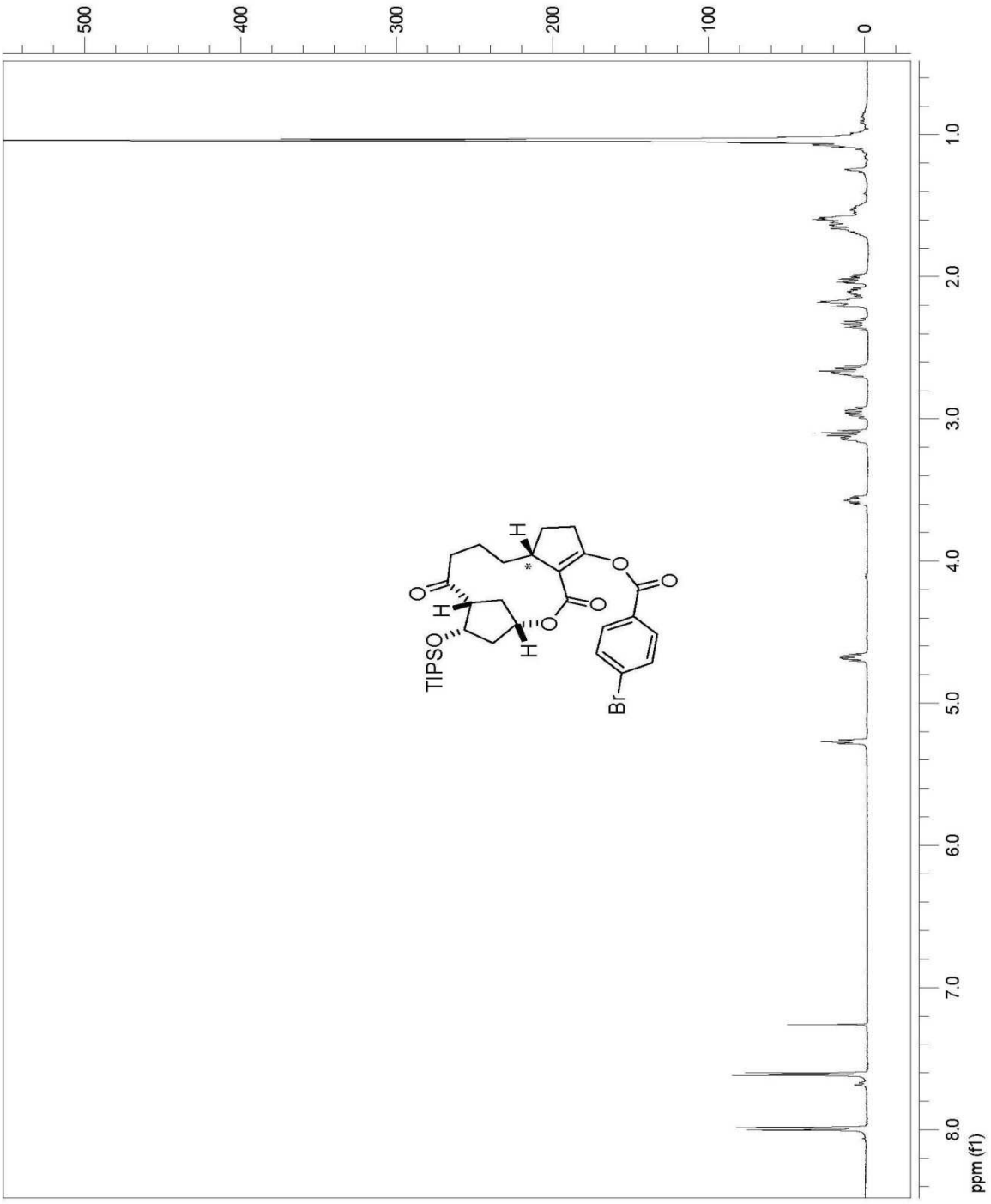
^{13}C NMR (500 MHz) of **4.30** in $CDCl_3$



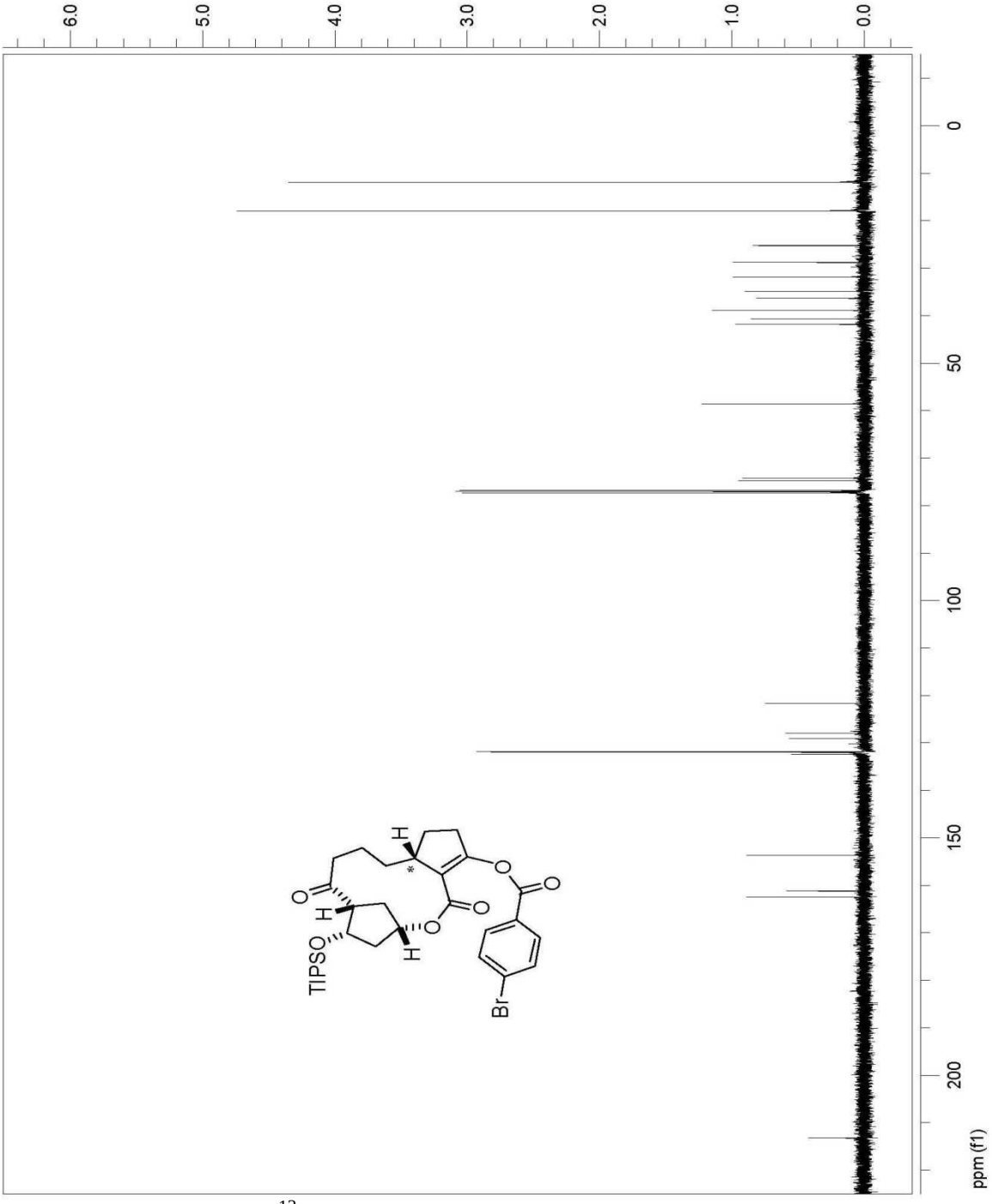
^{1}H NMR (500 MHz) of **4.31** in $CDCl_3$



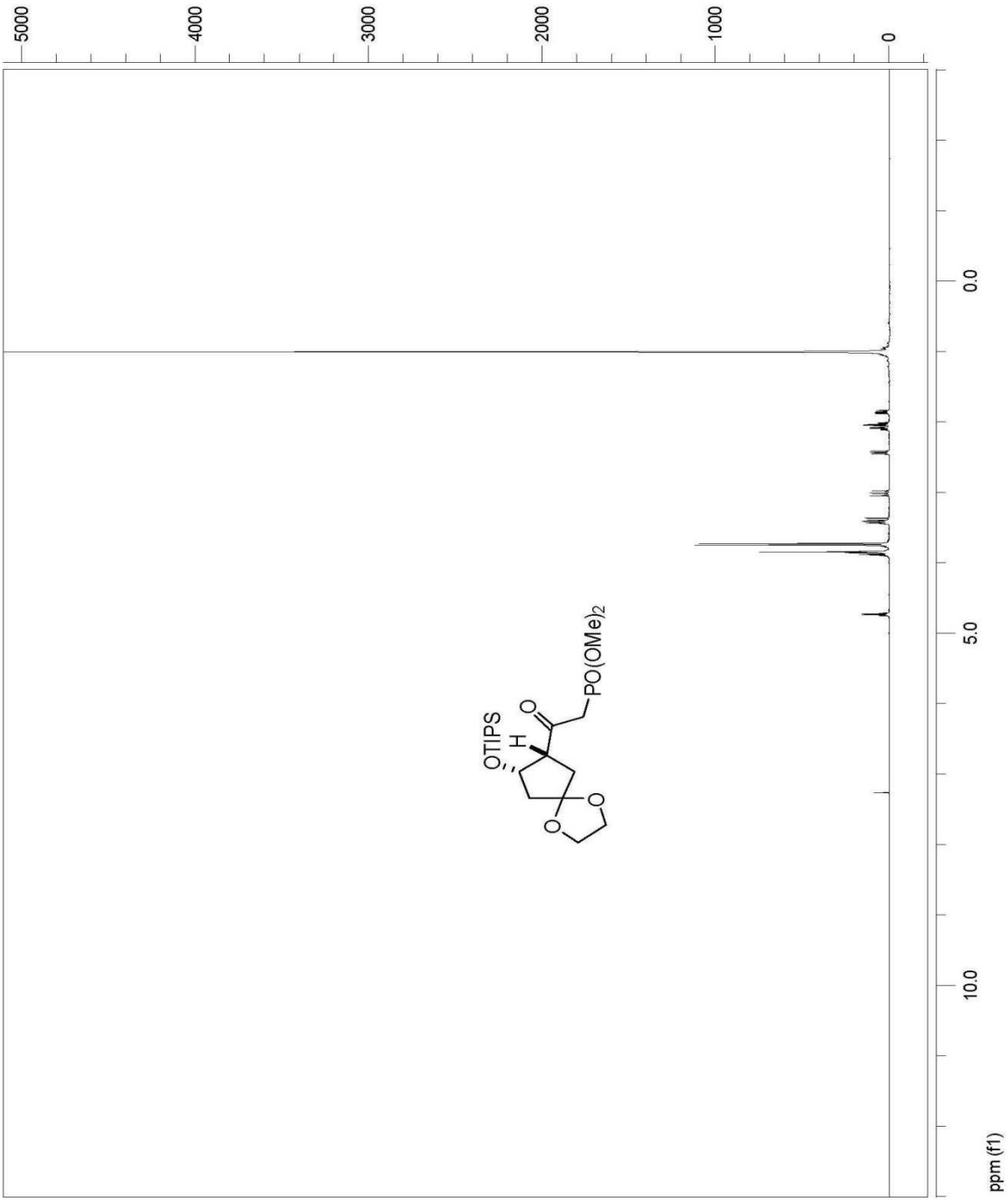
^{13}C NMR (500 MHz) of **4.31** in $CDCl_3$



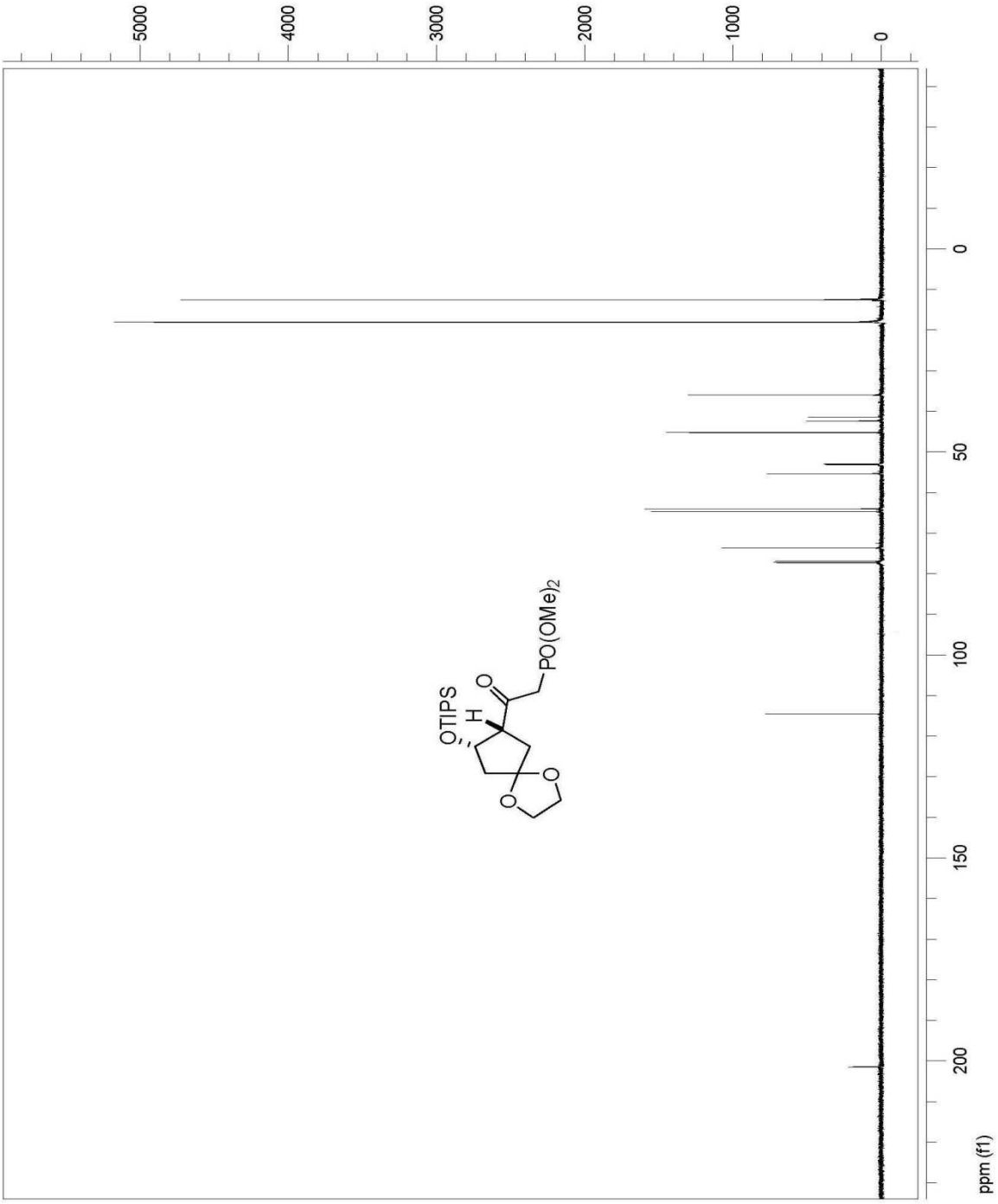
^{1}H NMR (500 MHz) of **4.33** in $CDCl_3$



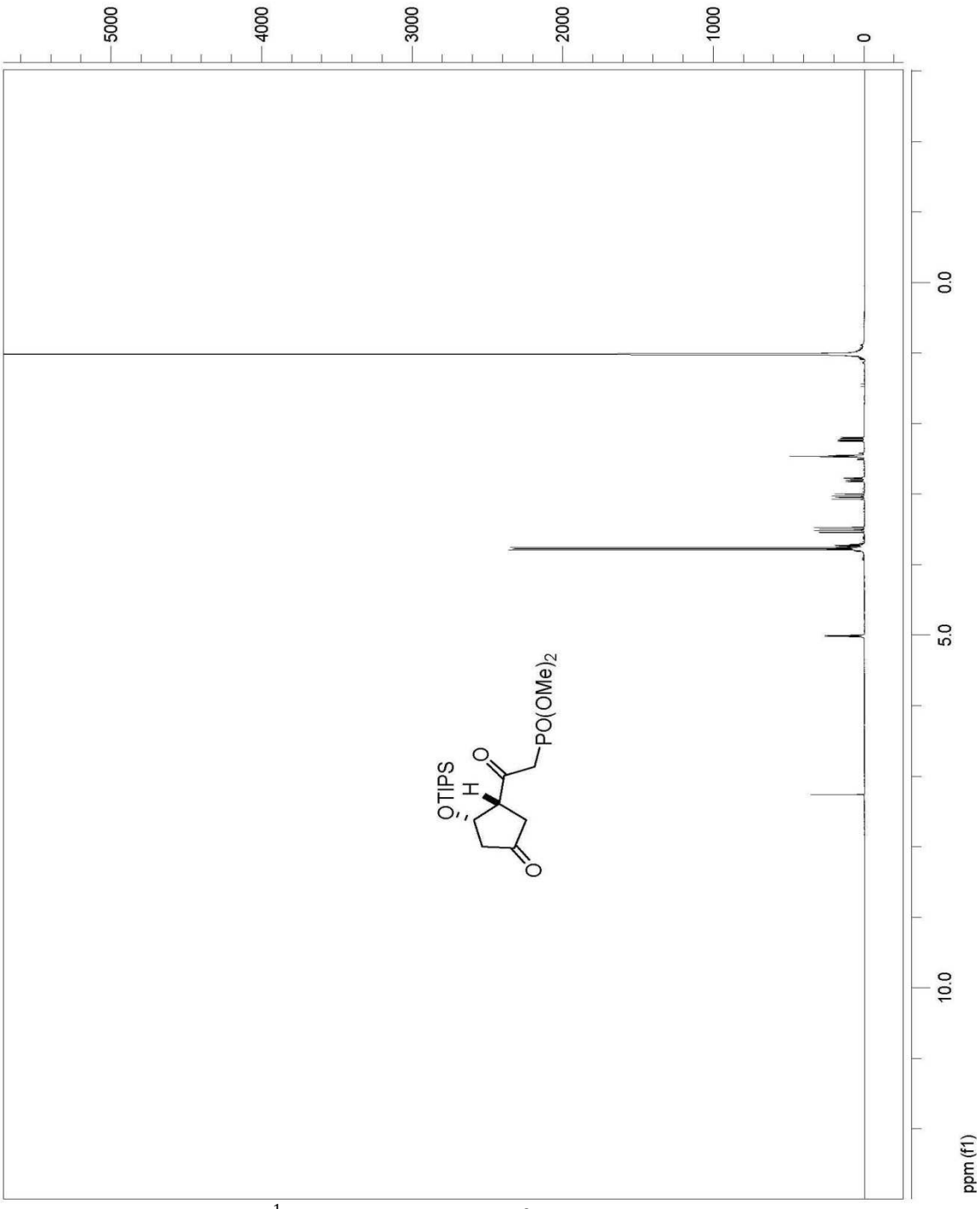
^{13}C NMR (500 MHz) of **4.33** in $CDCl_3$



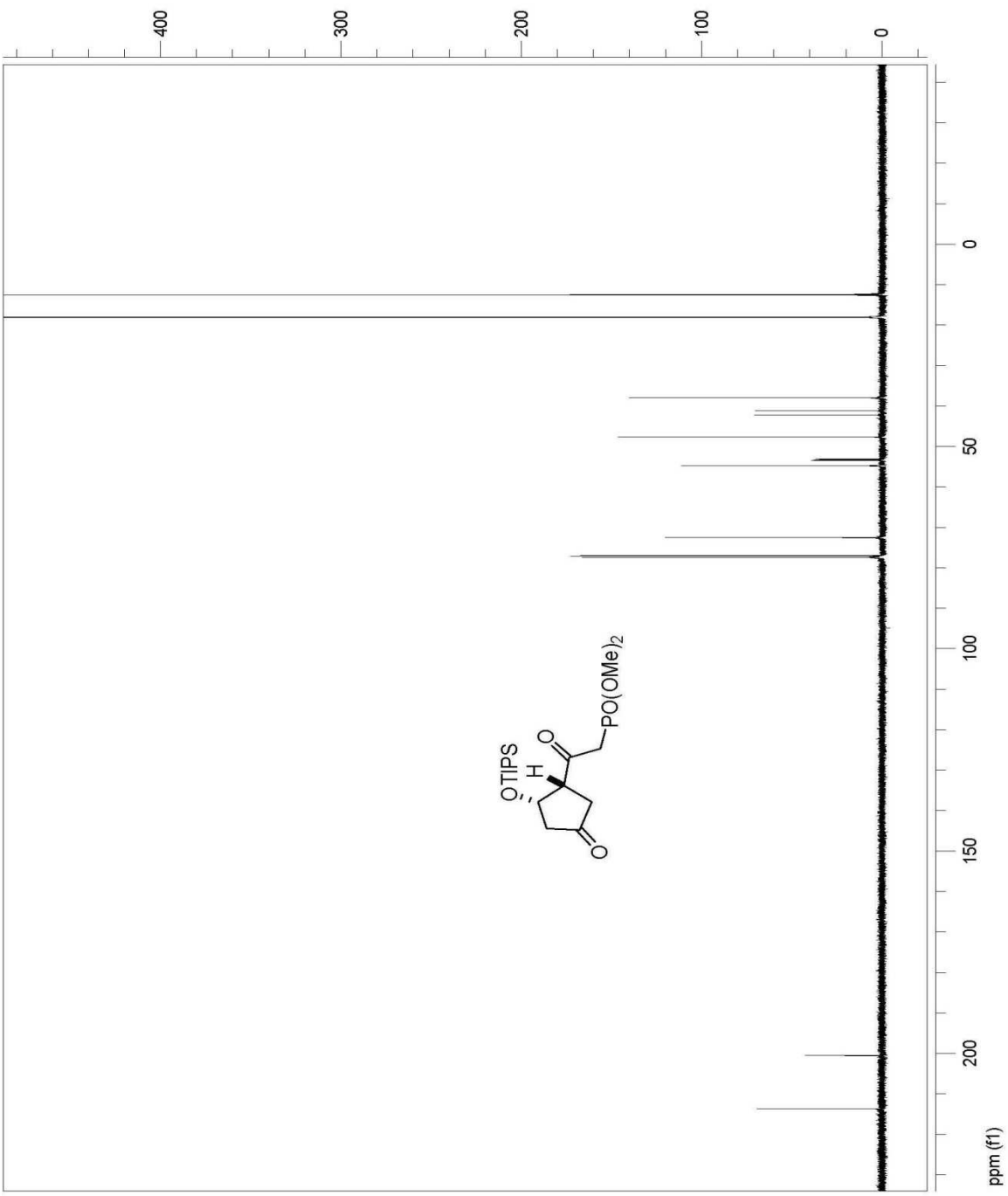
^{1}H NMR (500 MHz) of **4.37** in $CDCl_3$



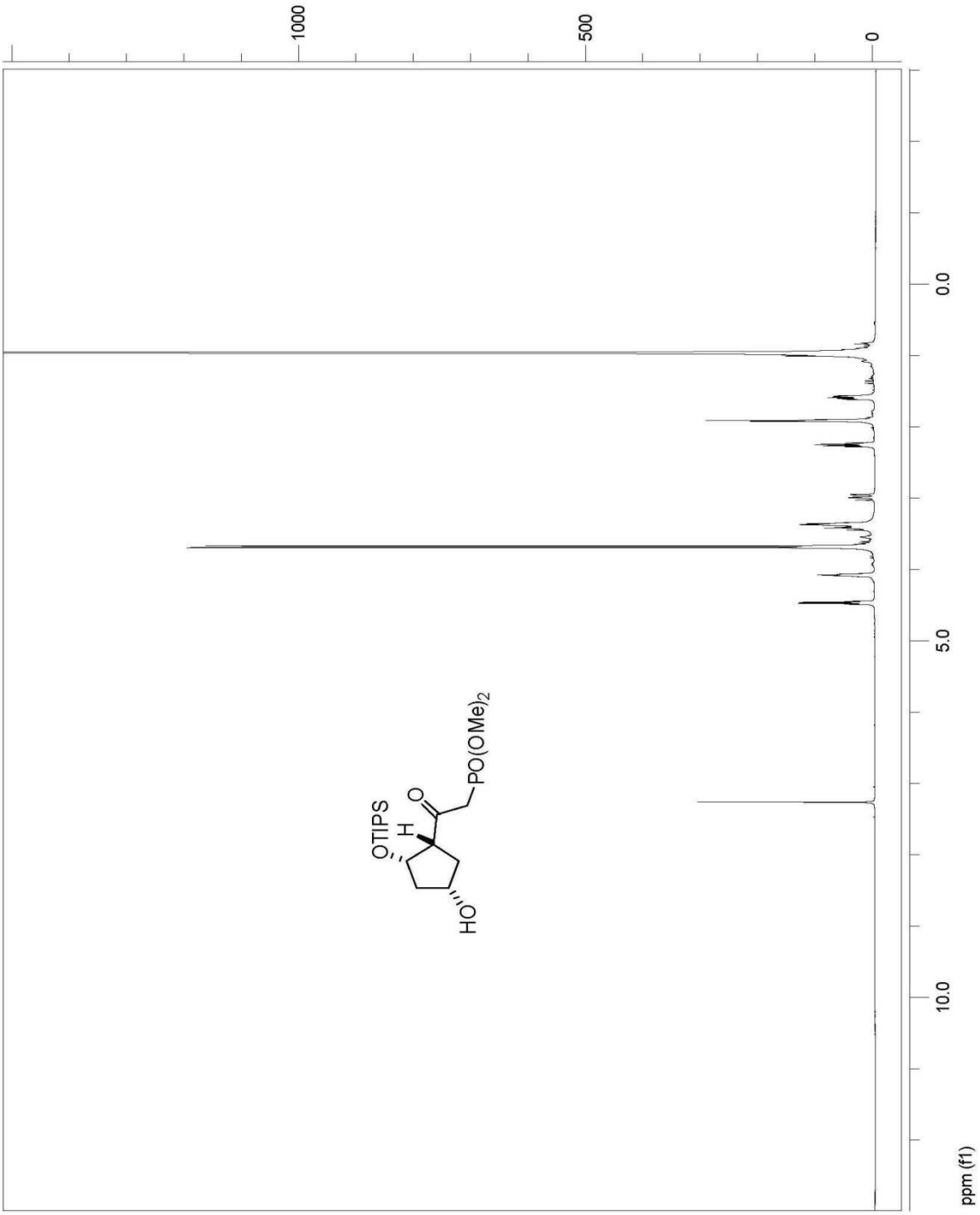
^{13}C NMR (500 MHz) of **4.37** in $CDCl_3$



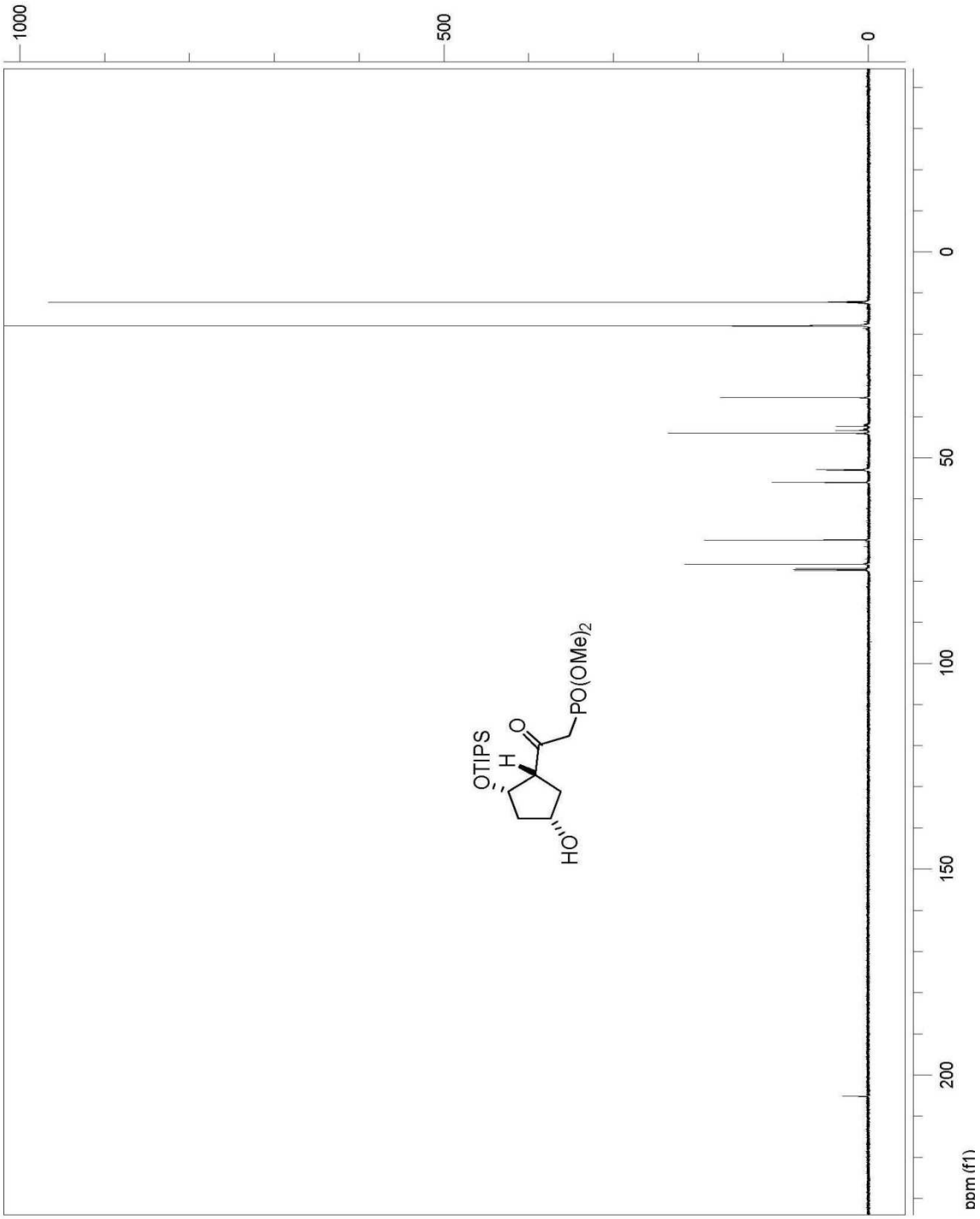
^{1}H NMR (500 MHz) of **4.38** in $CDCl_3$



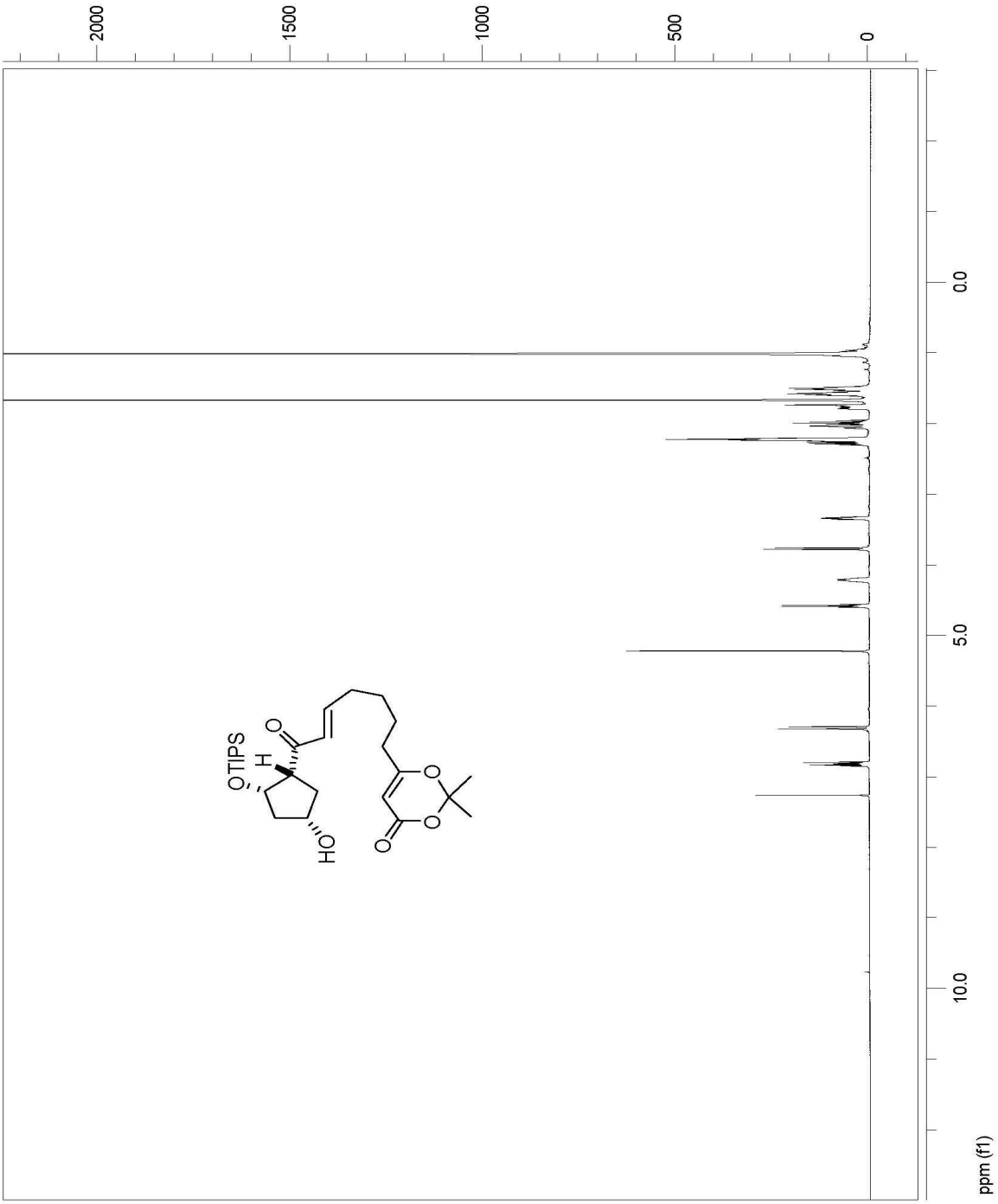
^{13}C NMR (500 MHz) of **4.38** in $CDCl_3$



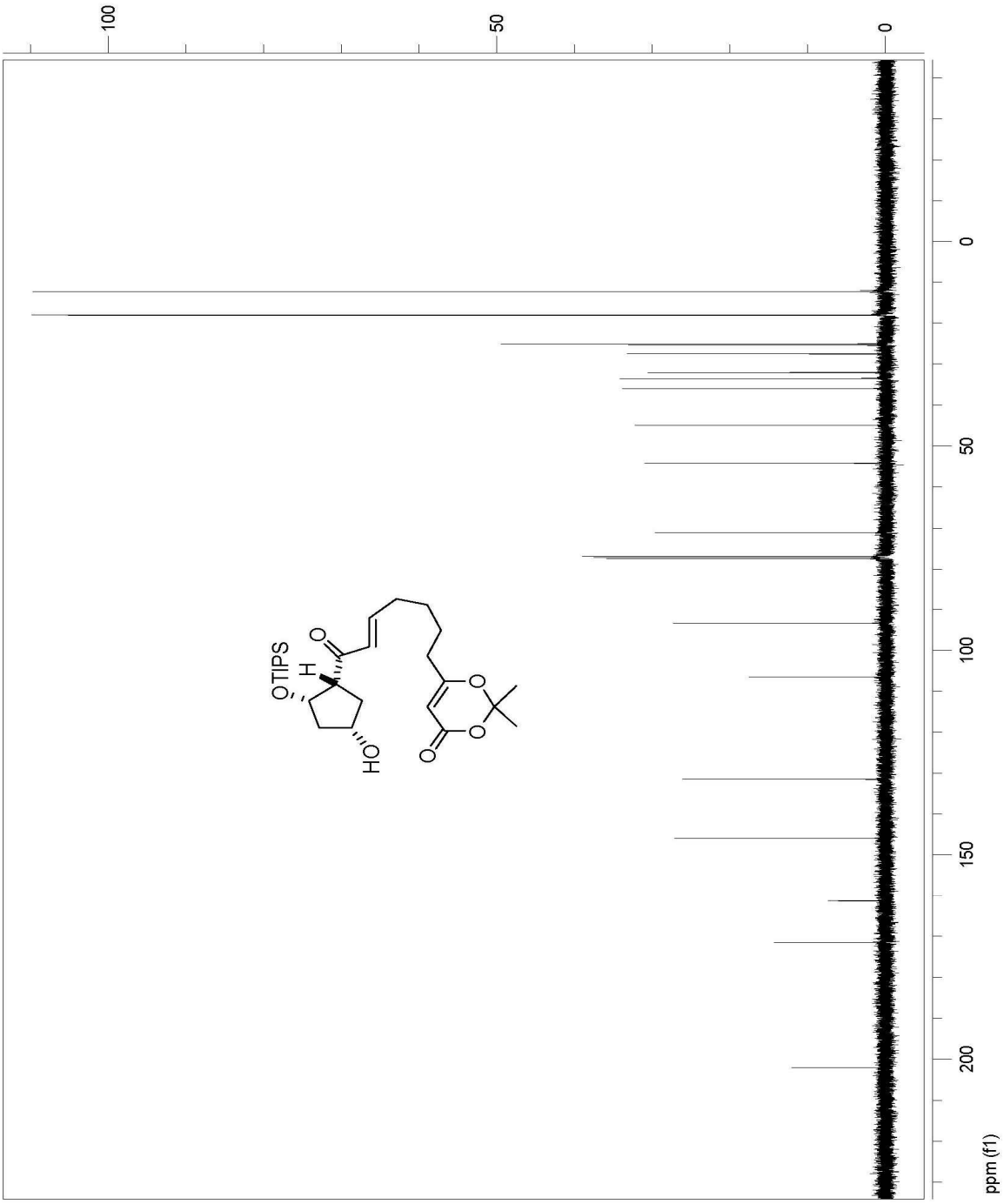
^{1}H NMR (500 MHz) of **4.39** in $CDCl_3$



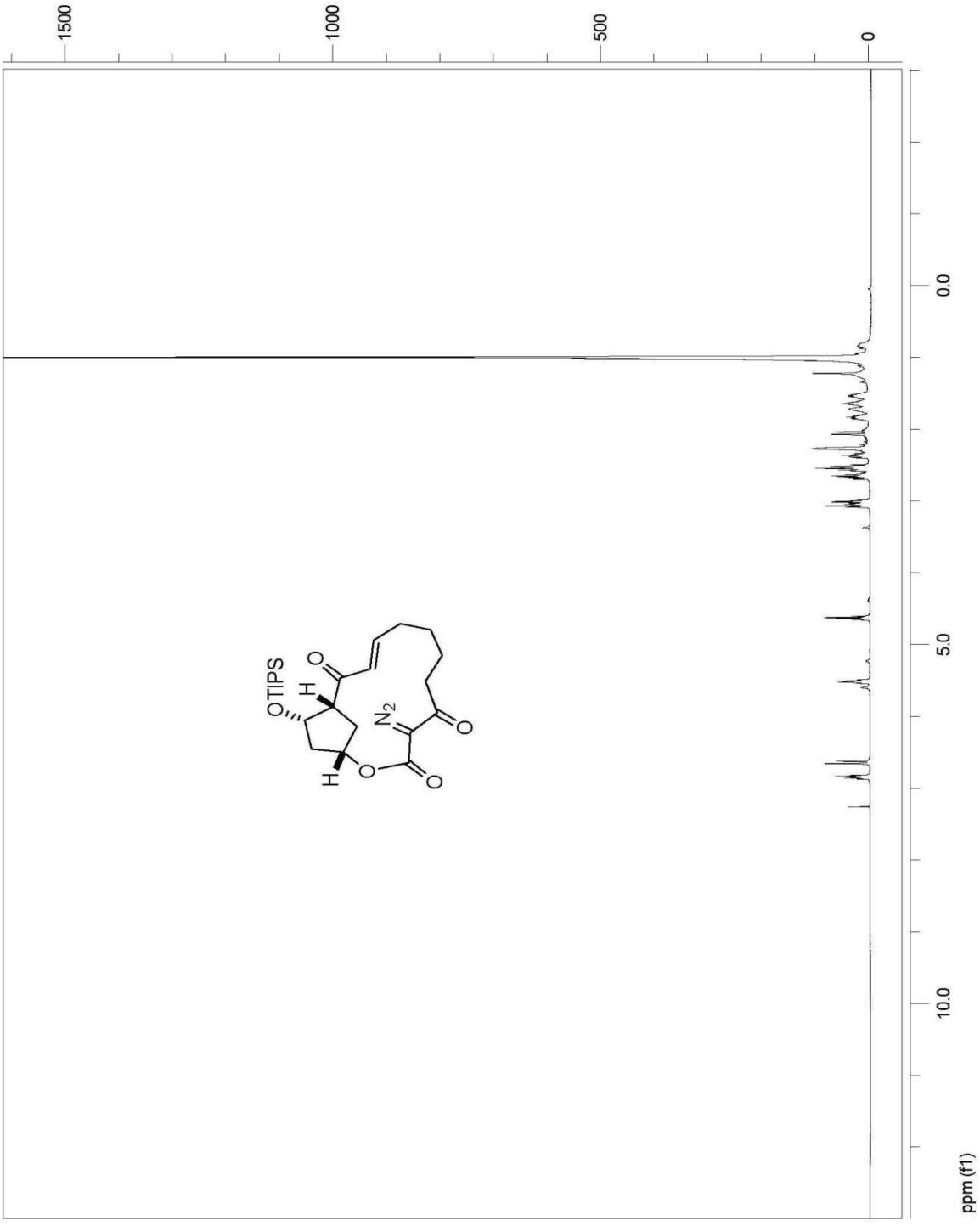
^{13}C NMR (500 MHz) of **4.39** in $CDCl_3$



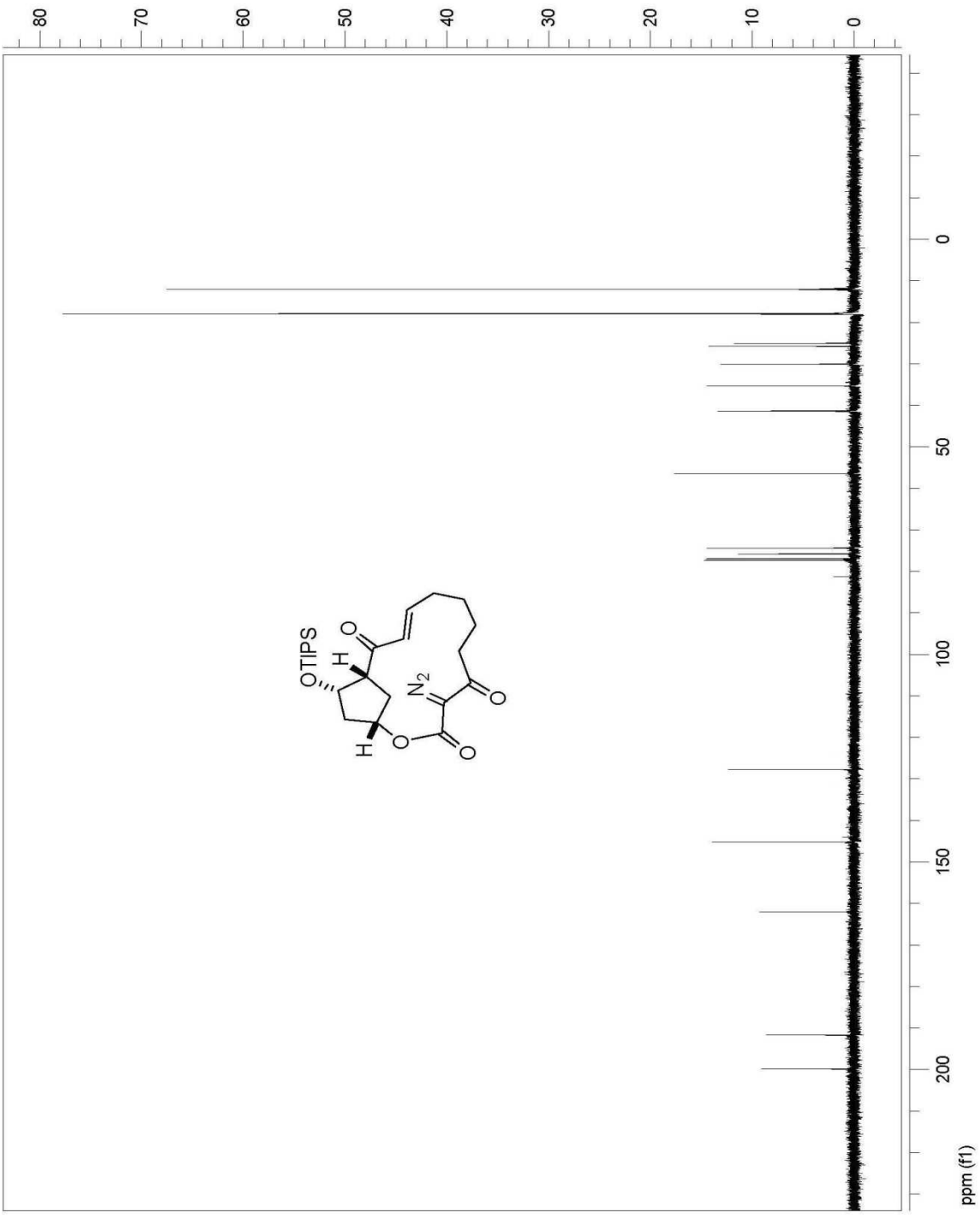
^{1}H NMR (500 MHz) of **4.40** in $CDCl_3$



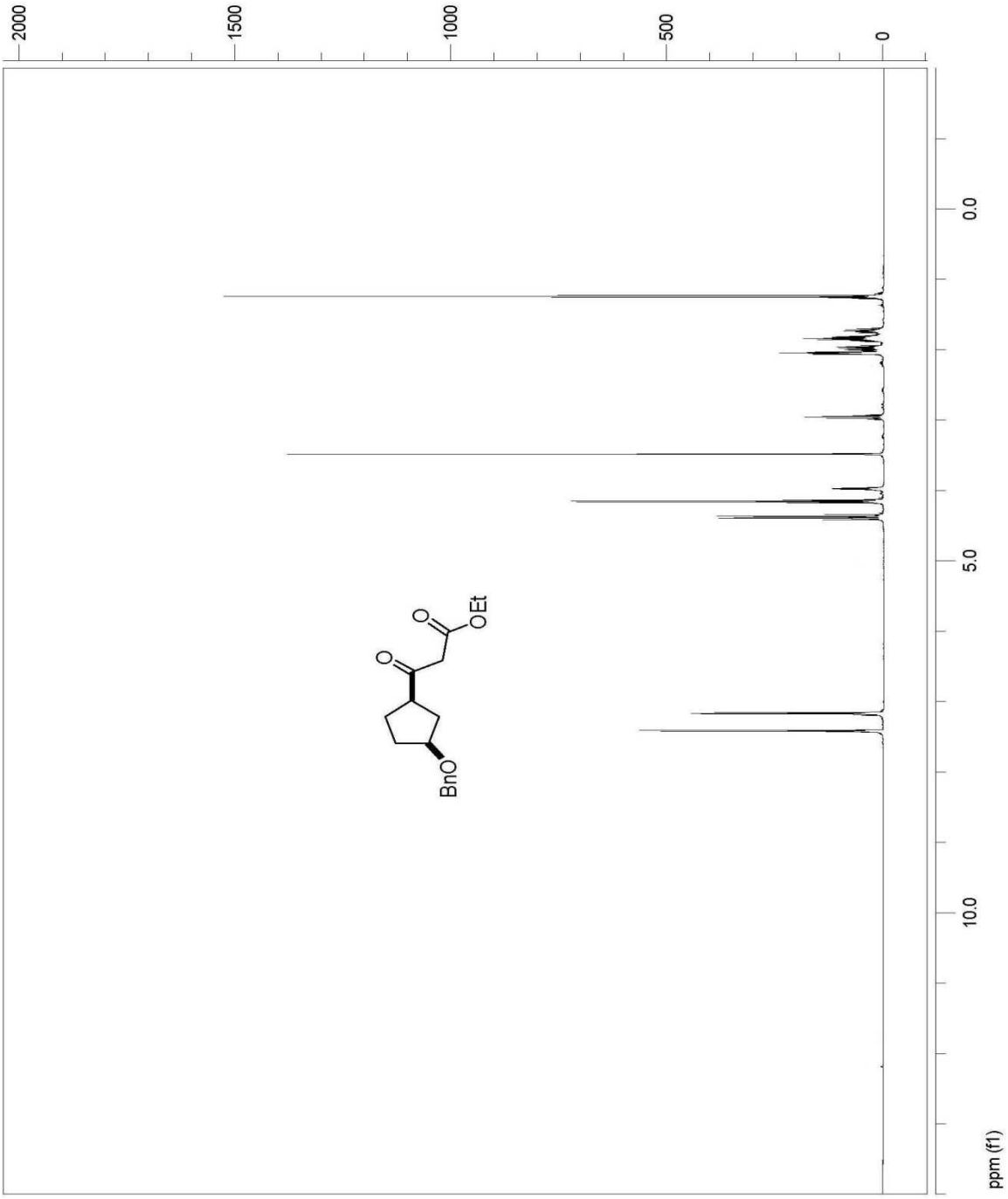
^{13}C NMR (500 MHz) of **4.40** in $CDCl_3$



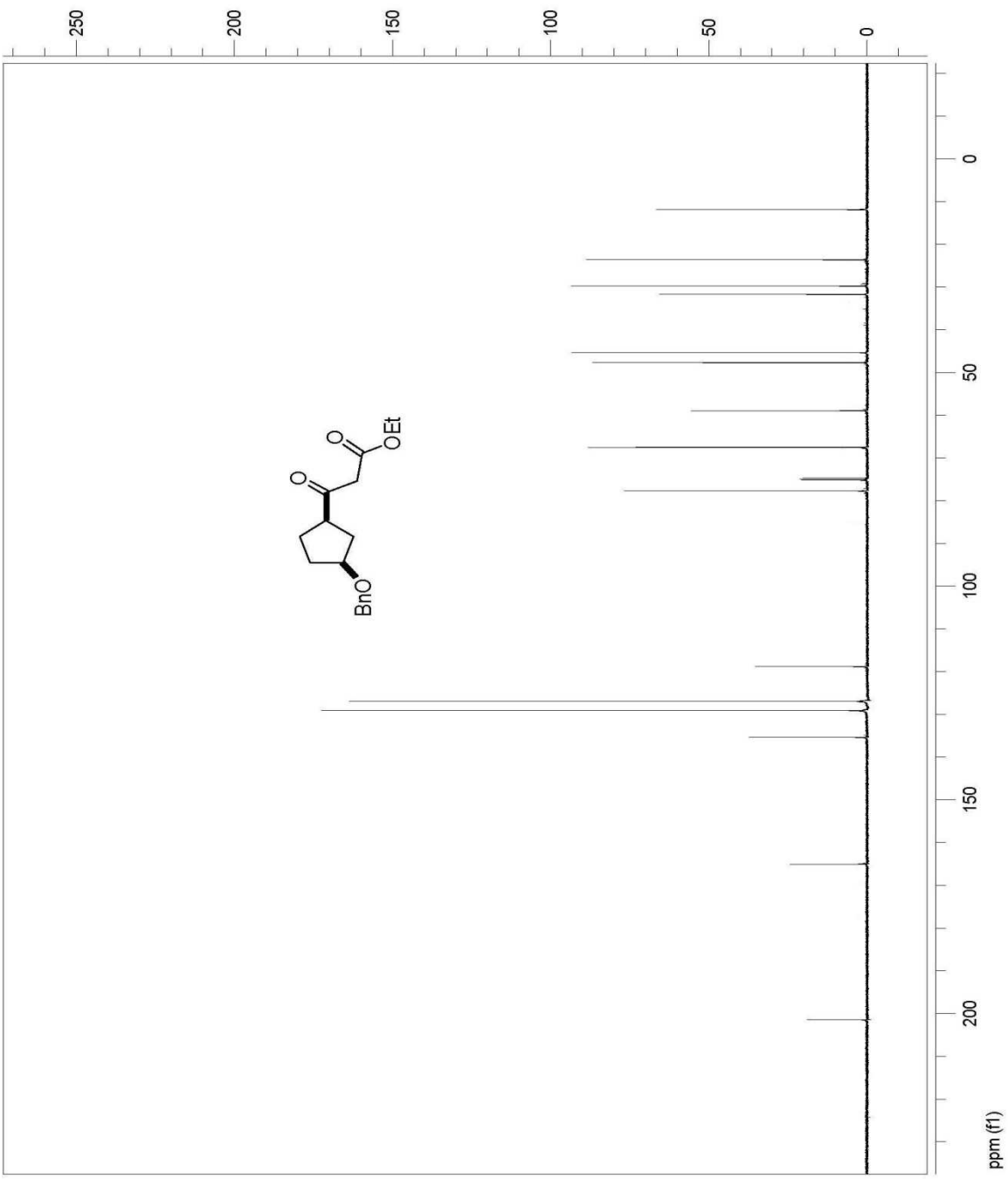
^{1}H NMR (500 MHz) of **4.42** in $CDCl_3$



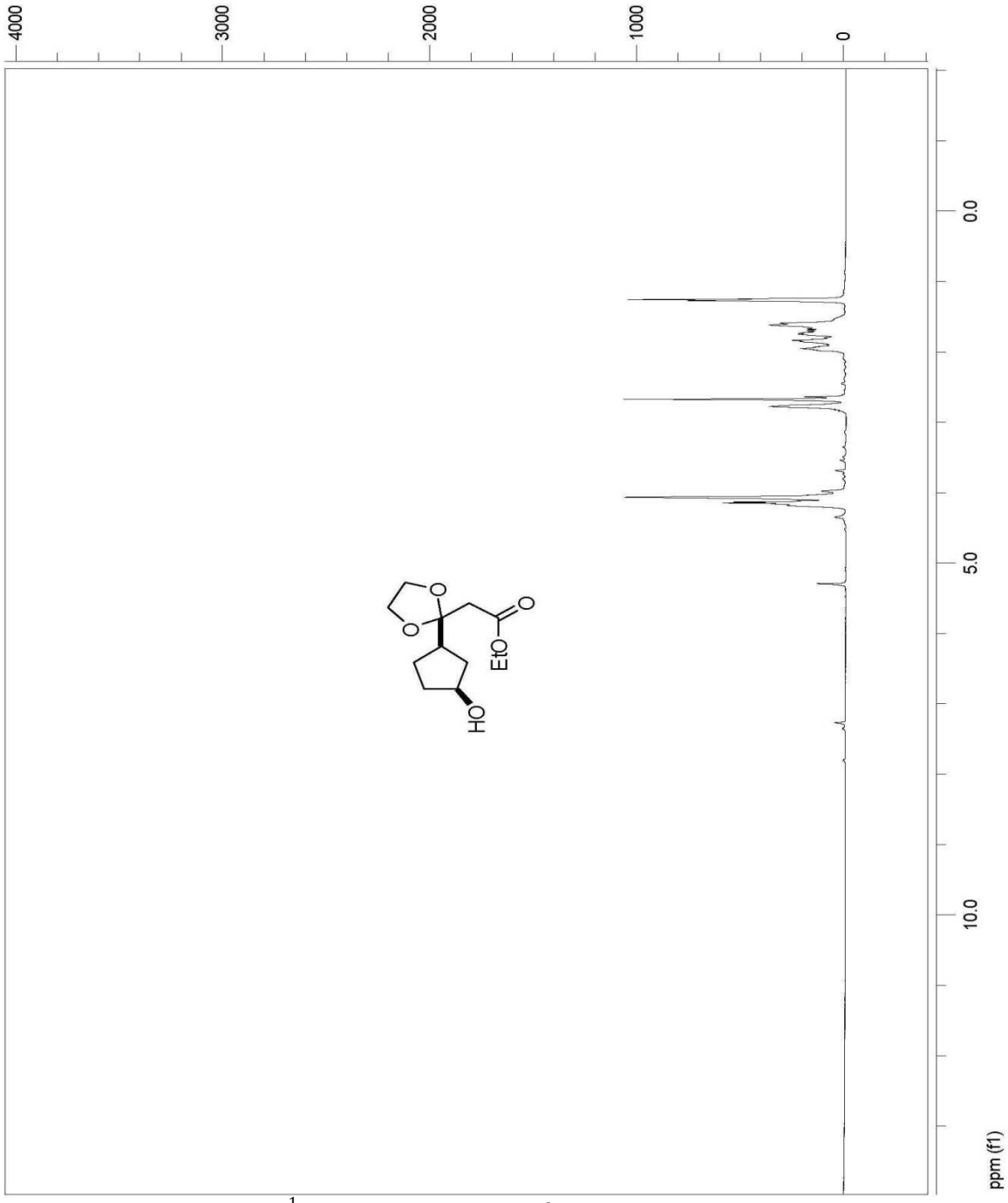
^{13}C NMR (500 MHz) of **4.42** in $CDCl_3$



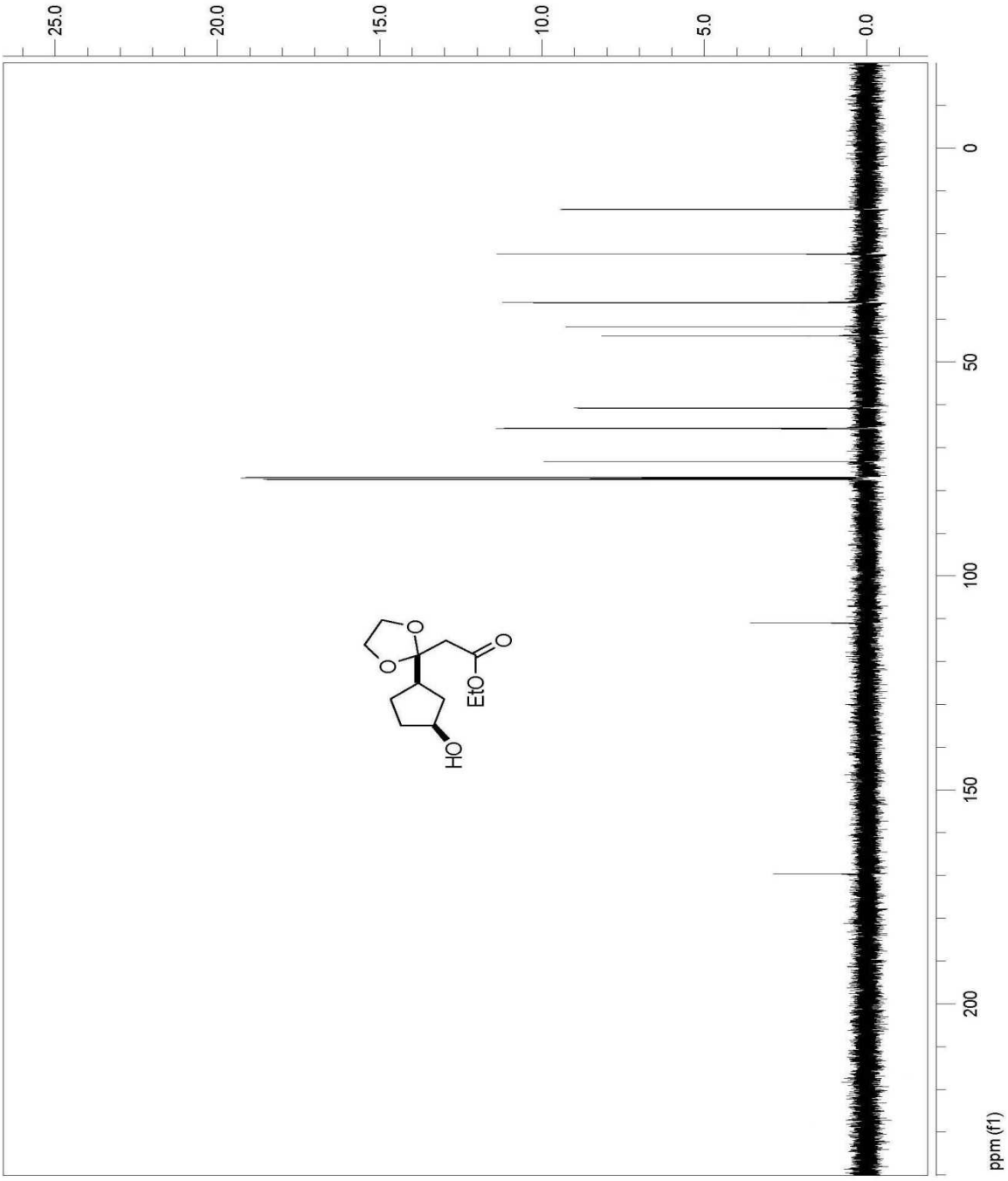
^{1}H NMR (500 MHz) of **4.63** in $CDCl_3$



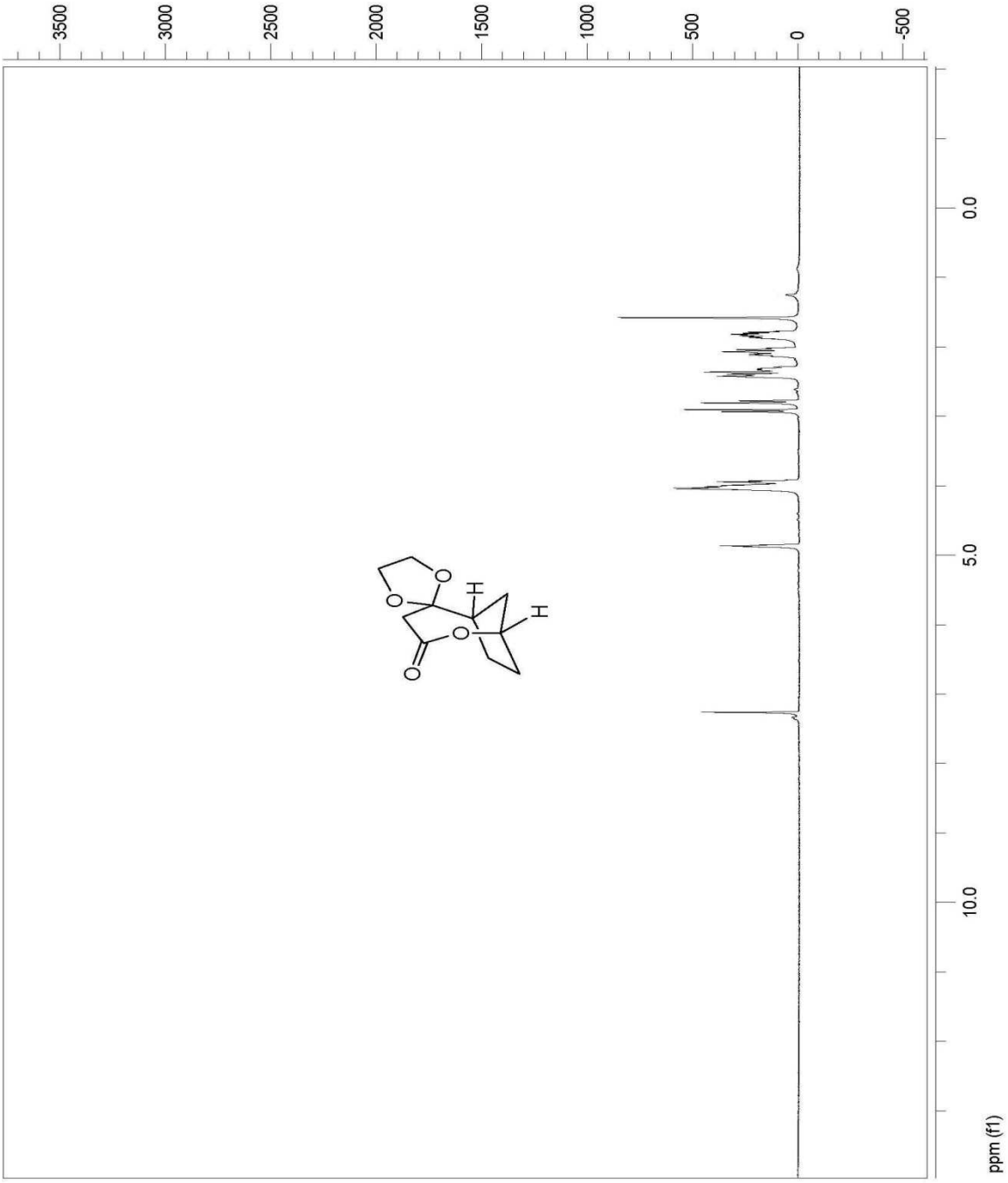
^{13}C NMR (500 MHz) of **4.63** in $CDCl_3$



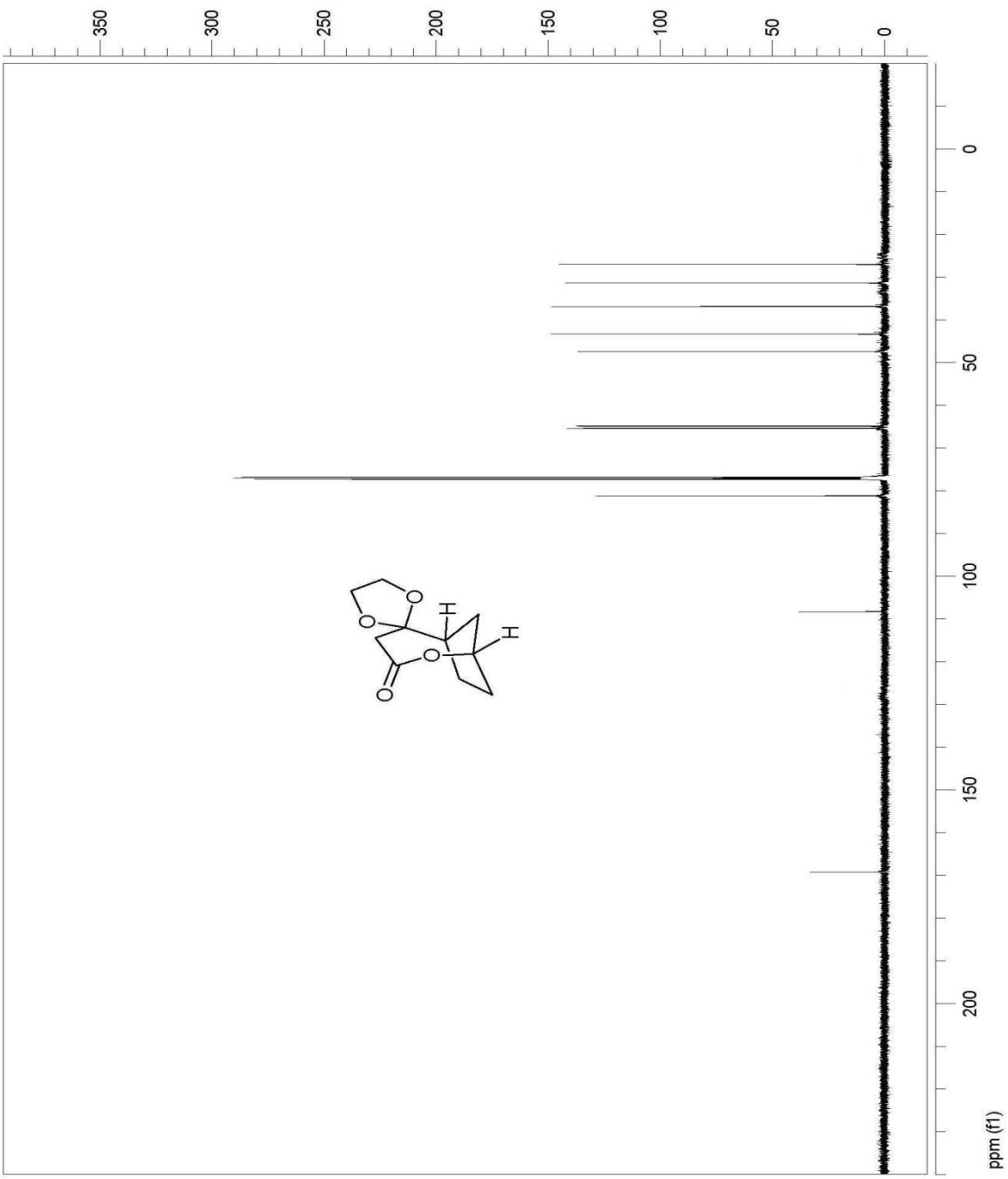
^{1}H NMR (500 MHz) of **4.64** in $CDCl_3$



^{13}C NMR (500 MHz) of **4.64** in $CDCl_3$



^{1}H NMR (500 MHz) of **4.66** in $CDCl_3$



^{13}C NMR (500 MHz) of **4.66** in $CDCl_3$

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