STUDIES TOWARD THE TOTAL SYNTHESIS OF THE MARINE TOXIN, (-)-GYMNODIMINE

A Dissertation

by

KE KONG

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 2007

Major Subject: Chemistry

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Approved by:

Chair of Committee,	Daniel Romo
Committee Members,	David E. Bergbreiter
	Daniel A. Singleton
	Lisa Campbell
Head of Department,	David H. Russell

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ABSTRACT

Studies toward the Total Synthesis of the Marine Toxin, (-)-Gymnodimine.

(December 2007)

Ke Kong, B.S., Tsinghua University, P. R. China;

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Chair of Advisory Committee: Dr. Daniel Romo

(-)-Gymnodimine is a member of a growing family of spirocylic imine containing marine natural products. The construction of the complete skeleton of (-)-gymnodimine has been accomplished in a convergent manner in 23 steps (the longest linear sequence).

A highly diastereo- and enantioselective Diels-Alder reaction employing bis(oxazoline)·Cu(II) catalyst provided the spirolactam core structure of gymnodimine bearing a quaternary carbon stereogenic center. An improved procedure for hydrostannylation of the hindered internal triple bond in **96a** was discovered by slow addition of tributyltin hydride to minimize formation of hydrogenated byproduct.

Fragment coupling featured a Nozaki-Hiyama-Kishi reaction between a vinyl iodide derived from the spirolactam and a tetrahydrofuran moiety. The macrocyclization was realized through a rather unusual intramolecular opening of an activated *N*-tosyllactam by an alkyllithium species generated *in situ*. The butenolide was appended through a vinylogous Mukaiyama aldol addition of silyloxyfuran **155** to the ketone **163**

under meticulously controlled conditions. The generality of this process was explored in some detail. Addition of silyloxyfurans to cyclohexanones proceeds with moderate to good diastereoselectivities. The potential application of this process to the synthesis of butenolide and γ-lactone containing natural products was demonstrated by further transformations of the addition adducts.

Finally, toward our goal of developing an enzyme-linked immunosorbent assay (ELISA) for gymnodimine monitoring a hapten derived from the tetrahydrofuran has been synthesized. Even though the raised antibodies failed to recognize the natural product itself, the results provided some information regarding the essential structural elements of an efficient hapten.

ACKNOWLEDGEMENTS

First, I would like to thank my advisor and the committee chair, Dr. Romo for his guidance and support throughout my graduate career. I would like to thank my committee members, Dr. Bergbreiter, Dr. Singleton and Dr. Campbell for helpful suggestions and valuable instruction. And I would like to thank Dr. Connell for his helpful suggestions and being a substitution for Dr. Bergbreiter for the final defense.

I would like to thank all of the former and current group members for their support and friendship, especially to Andy Mitchell for his friendship throughout my life in the graduate school.

Finally, great thanks to my wife Li for her patience and love. Without her support, the journey would not have been possible. Also, I would like to express appreciation to my parents, my brother, my sister and all of my family members.

TABLE OF CONTENTS

Page

LIST OF FIGURES

FIGURE Page

LIST OF TABLES

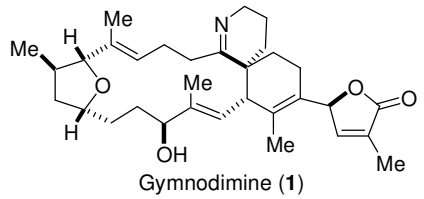
CHAPTER I

INTRODUCTION: GYMNODIMINE AND SPIROCYCLIC IMINE CONTAINING MARINE NATURAL PRODUCTS

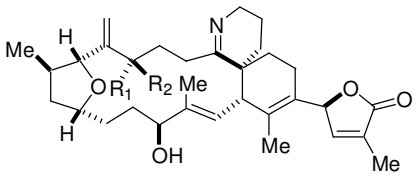
I.1. Isolation and Structure Elucidation of (-)-Gymnodimine

The past several decades have witnessed a growing number of fish and human intoxication incidents as a result of harmful algal blooms leading to massive fish kills and sometimes human death.[1] Early in 1993 a case of neurotoxic shellfish poisoning (NSP) occurred off the coast of New Zealand. This wass believed to be related to the bloom of the dinoflagellate, *Gymnodinium mikimotoi* (later redescribed as *Gymnodinium selliforme* syn. *Karenia selliformis*),[2] after oysters collected from Foveaux Strait off the South Island of New Zealand were later found to be toxic at high levels with concurrent blooms of this dinoflagellate species. Collection of oysters *Tiostrea chilensis* in the same area in 1995 by Yasumoto and coworkers led to the isolation of a new marine toxin, (-)-gymnodimine (Figure 1, **1**).[3] The gross structure was assigned by spectroscopic studies including IR, UV, accurate mass measurements and 2D NMR correlation methods. The structural features of gymnodimine include a trisubstituted tetrahydrofuran within a 16-membered carbocycle, a chiral butenolide, and most interestingly an azaspiro[5.5]undecadiene moiety.

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



Gymnodimine (**1**)

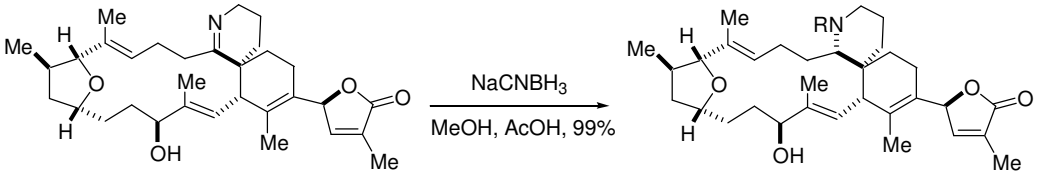


Gymnodimine B (**2**): R_1 = OH, R_2 = H
Gymnodimine C (**3**): R_1= H, R_2 = OH

Figure 1. Structures of gymnodimines.

It was not until 1997 that Munro, Blunt and coworkers established the relative and the absolute configuration of this marine natural product through X-ray crystallographic analysis of a derivative.[4] Thus, a stereoselective reduction of the imine moiety using sodium cyanoborohydride followed by *p*-bromobenzamide formation provided crystalline benzamide **5** suitable for X-ray structural analysis (Scheme 1). More recently, two new analogs were isolated and named gymnodimine B (**2**) and C (**3**), respectively.[5]

Scheme 1



Gymnodimine (**1**)

The presence of a spirocyclic imine[6] in gymnodimines places them into the same family with other marine metabolites that include the pinnatoxins (**6**-**9**),[7] pteriatoxins (**10**,

11),[8] spirolides (**12**-**16**),[9] prorocentrolide (**17**),[10] and spiro-prorocentrimine (**18**)[11] (Figure 2).

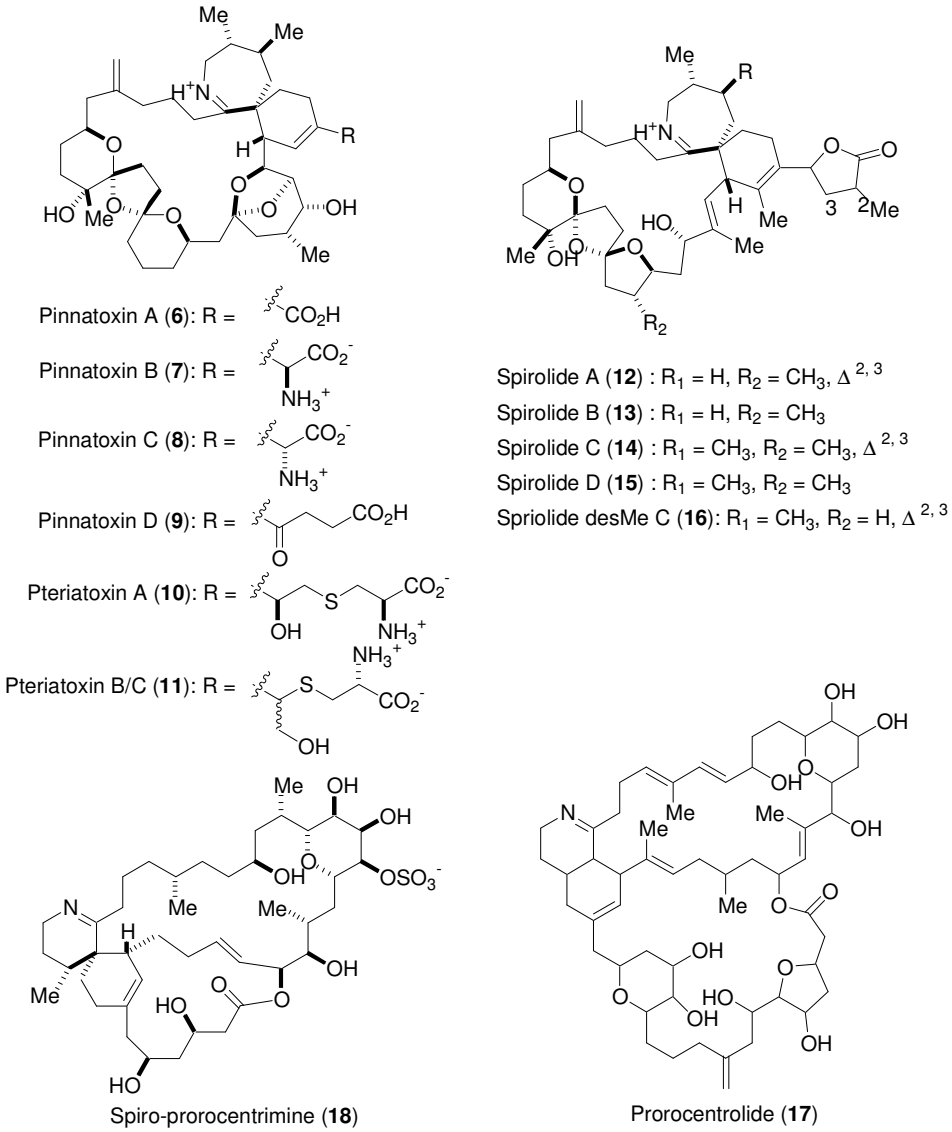


Figure 2. Structures of cyclic imine containing marine natural products.

I.2. Biological Activities

I.2.1 Toxicity of Gymnodimine and Related Marine Toxins

Gymnodimine is believed to be responsible for several neurotoxic shellfish poisoning incidents in New Zealand. Indeed, gymnodimine was found to be highly toxic in a recent assay with LD_{50} of 96 μg/kg by injection and 755 μg/kg by oral administration.[12] However, it showed much lower toxicity when administered with food, and mice did not show any signs of intoxication when voluntarily ingesting food containing gymnodimine at a level sufficient to give a dose of 7500 μg/kg.

Gymnodimine causes a characteristic rapid death in the intraperitoneal mouse assay. The exact mode of action of this "fast-acting toxin" has yet to be understood. However, it might exert its toxic effects via blockage of nicotinic receptors at the neuromuscular junction as pretreatment with physostigmine or neostigmine protected the mice against injected gymnodimine.[10] Preliminary studies showed that gymnodimine and its analogues have variable effects on reducing cell numbers but no effects on the expression of a number of signal transduction proteins.[13] These studies also found gymnodimine sensitizes cells to an apoptosis inducing agent, okadaic acid. Independent studies revealed that gymnodimine affects the neurological system of mice as it appears to cause upper chest paralysis.[14]

The related cyclic imine containing compounds such as pinnatoxins and spirolides have been shown to be more potent neurotoxins. Pinnatoxin A (LD_{50} 2.7 μg/MU (ip.)), pinnatoxin B and C (LD_{50} 0.99 μg/MU) are among the most potent toxins in mouse bioassays, with the latter two as toxic as tetrodotoxin.[15] Pinnatoxin A is

believed to be involved in the activation of Ca^{2+} channels. Spirolides also showed a high level of toxicity against mice (spirolide A: LD_{100} 250 μg/kg).[9a] *In vitro* assays of the spirolides carried out by Wright have shown that they do not interfere with common excitatory amino acid neurotransmitter receptors such as *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) or kainate (KA) receptors. Furthermore, they do not inhibit PP1 and PP2A phosphatases, nor do they activate or block voltage dependent Na^+ channels. However, the spirolides show weak activation of type L Ca^{2+} channels (at 1.7 mM), but this activity does not correlate with the potent toxicity of these compounds.

The toxicity of this family of marine natural products has been attributed, at least partially, to the imine functionality as imine reduction leads to non-toxic derivatives. Wright and coworkers have found that spirolides E and F, in which the imine has been hydrolyzed to a keto amine, are inactive in the mouse lethality assay.[9b] In addition, the imine reduced form of spirolide B failed to elicit any toxic effects even at four times the equivalent of spirolide B dose. Since no significant conformational differences between spirolides B and F were found from molecular modelling studies, the cyclic imine functionality has been postulated to be the pharmacophore for the toxicity of these compounds. This hypothesis was further supported by lack of activity of gymnodiamine (**4**) compared with gymnodimine.[4]

I.2.2. Immunoassays for Detection of Marine Toxins

The increasingly frequent outbreaks of human intoxications due to ingestion of seafood have spurred worldwide surveillance programs for the detection of marine

toxins in the ocean. Currently, there are several methods capable of detecting and quantifying marine toxins such as mouse bioassays, radioimmunoassays (RIA), HPLC, and CE-MS. However antibody-based immunoassays, particularly enzyme-linked immunosorbent assays (ELISA), remain the most desirable method due to their generality, accuracy, sensitivity, and low cost.[16] In the following section, a brief review of development of ELISA for detection of some representative marine toxins as shown in Figure 3 is presented.

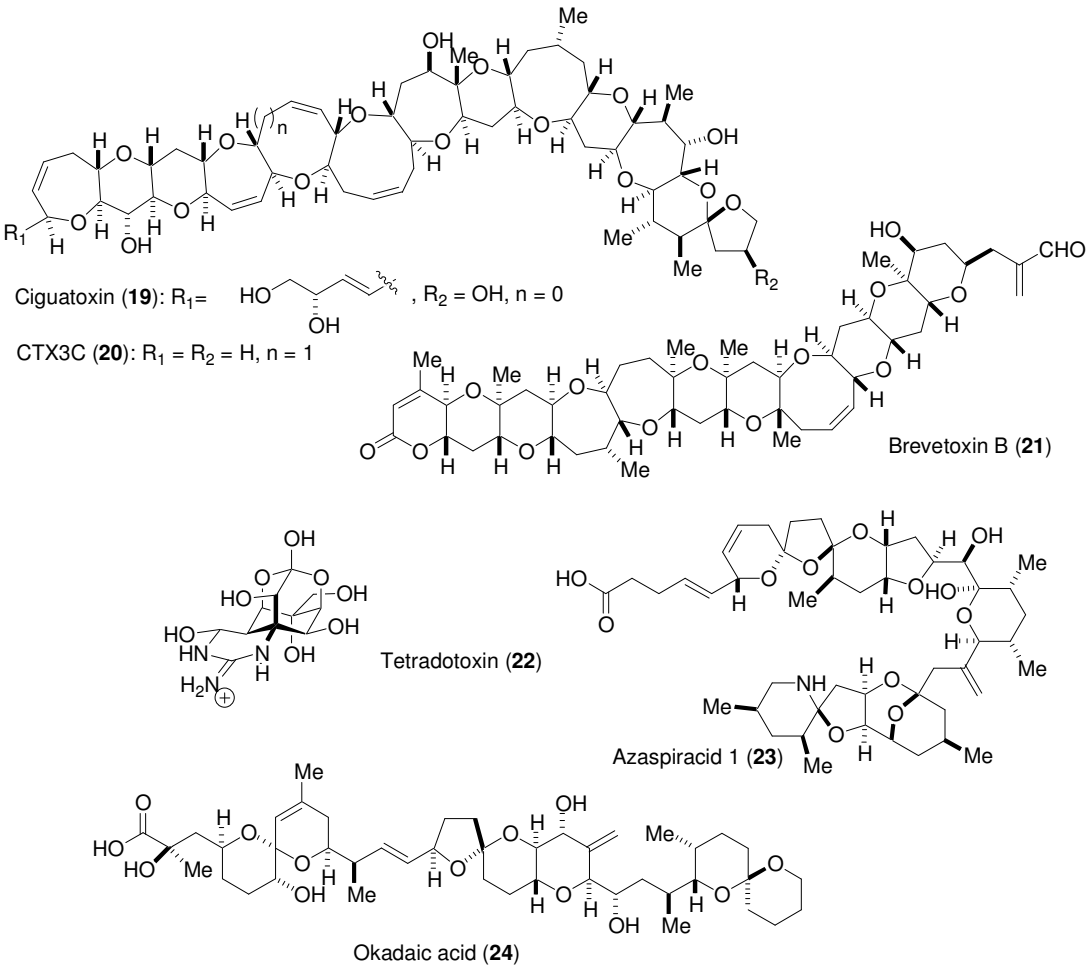


Figure 3. Structures of some potent marine toxins.

In a series of seminal papers, Baden and coworkers developed efficient ELISA-based tools to monitor brevetoxins using antibodies raised against haptens derived from the natural product itself.[17] The isolated antibodies showed high affinity to the natural product. These protocols have been successful for accurate detection of brevetoxins at very low levels (as low as 2.5 μg/100 g shellfish meat) in limited applications.

The major limitation of using natural toxins to raise antibodies lies in the fact that often times extremely low amount of such compounds is available from natural sources, thus severely hampering further development. In this regard, synthetic haptens are more valuable as ease of access to these intermediates is made possible by modern synthetic chemistry. In addition, design of haptens having substructures shared by a whole family of toxic molecules allows detection of different congeners simultaneously, instead of a single compound.

Hirama, Fujii and coworkers have developed a direct sandwich immunoassay for ciguatoxin (CTX) based on this approach.[18] After careful analyses of the hapten structures required for antibody-antigen interactions, two haptens were designed representing the substructures of A-E ring and I-M ring of CTX3C, respectively (Figure 4, **25** and **26**). Immunization of mice with protein conjugates of the synthetic haptens led to preparation of several monoclonal antibodies (mAbs). These antibodies proved to bind specifically to each end of CTX3C with high affinity and a direct sandwich ELISA was established that could detect CTX3C at ppb level.

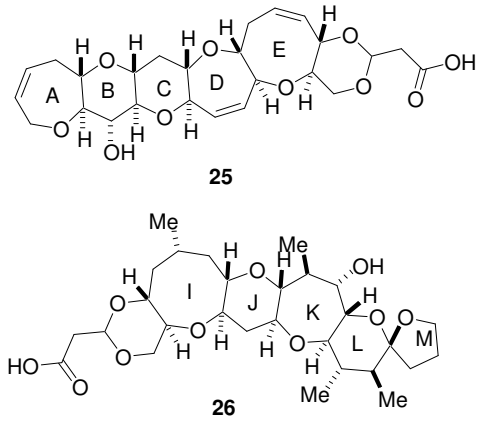


Figure 4. Structures of synthetic haptens for ciguatoxin CTX3C.

The advantages of synthetic haptens-based ELISA are further highlighted in recent studies by Forsyth, Miles, and coworkers for generation of antibodies against azaspiracids (AZA).[19] Their strategy was to utilize a designed hapten **27** representing the invariant C26-C40 domain of azaspiracids (Figure 5). Indeed, antibodies raised against this hapten cross-reacted with AZA 1, AZA 2, AZA 3 and AZA 6 with similar affinity. Furthermore, purified antibody proteins recognized only AZA congeners but not another polyether natural product yessotoxin, while cross-reactivity is often a problem for ELISA assay based on natural product haptens.[20]

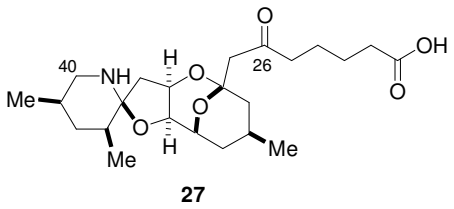


Figure 5. Structure of synthetic hapten for azaspiracids.

I.3. Biosynthetic Origin

It is believed that the biosynthesis of these spirocyclic imine marine natural products follows a polyketide pathway. Uemura first proposed a speculative polyketide biogenetic pathway for pinnatoxins.[15] More recently, compelling evidence has indeed indicated that most carbons from spirolides are polyketide-derived and glycine serves as the source for the imine moiety.[21] Walter and coworkers conducted biosynthetic studies by supplementing cultures of the toxigenic dinoflagellate *Alexandrium ostenfeldii* with stable isotope-labeled precursors [1,2-$^{13}C_2$]acetate, [1-^{13}C] acetate, [2-$^{13}CD_3$]acetate, and [1,2-$^{13}C_2$,^{15}N]glycine and harvasting 13-desmethyl spirolide C. Information garnered from ^{13}C NMR spectroscopic analysis pointed to a biosynthetic pathway starting with a glycine unit followed by unidirectional acetate condensation (Figure 6a).

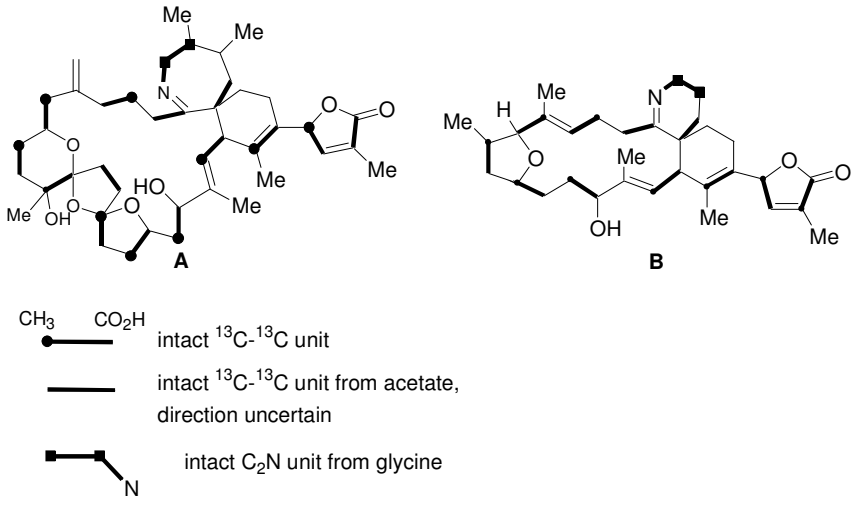


Figure 6. (a) structure of 13-desmethyl spirolide C, showing incorporation of stable isotope labels. (b) structure of gymnodimine with proposal for expected incorporation of isotope labels.

While the biosythetic pathway for gymnodimine has not been studied yet, given its high degree of structural homology with spirolides, it is very likely that the former compound has the same biogenetic origin that is polyketide-derived with glycine as the source of the cyclic imine (Figure 6b).

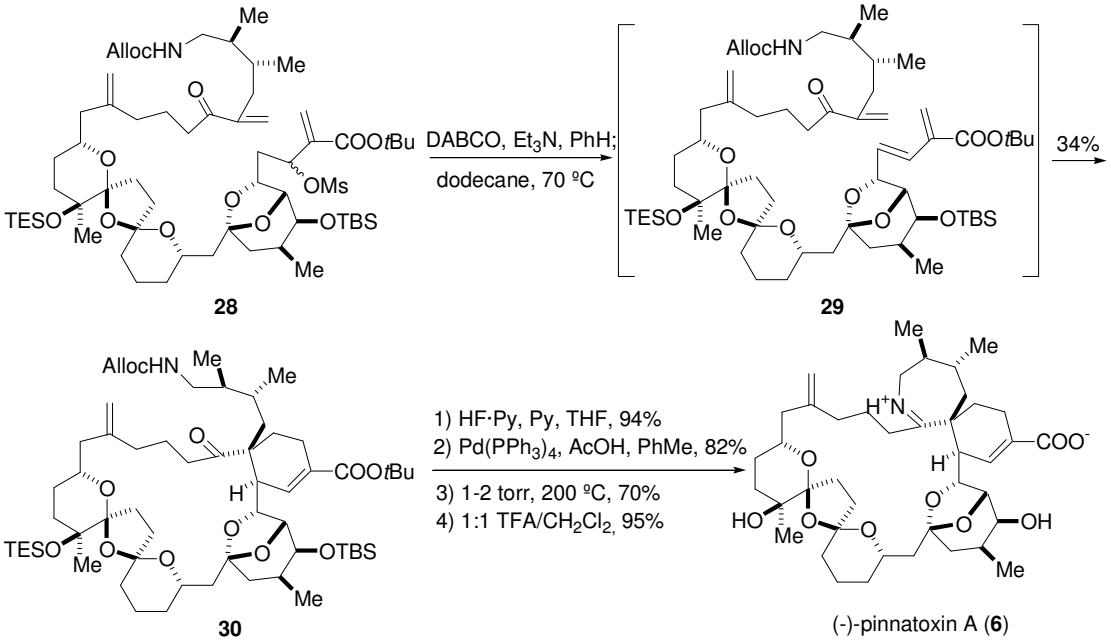
I.4. Synthetic Studies of Spirocyclic Imine Containing Natural Products

I.4.1. Synthetic Studies of Pinnatoxins

Biological activities notwithstanding, the intriguing structures of gymnodimine and related natural products have attracted considerable attention from the synthetic community. Among these, the pinnatoxins have been the most extensively studied, culminating in a total synthesis of pinnatoxin A in 1998 by Kishi [22] and a formal total synthesis in 2004 by Hirama [23].

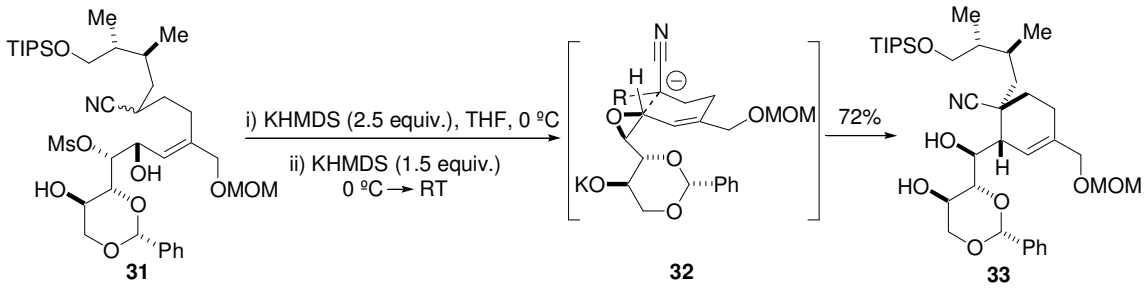
In Kishi's landmark synthesis of (-)-pinnatoxin A leading to the antipode of the natural compound, the defining step was an intramolecular Diels-Alder reaction.[22] This process formed the cyclohexene ring system bearing a quaternary carbon stereogenic center with the simultaneous construction of the macrocycle (Scheme 2). After generation of the advanced intermediate **28**, subsequent treatment of the allylic mesylate with DABCO then triethylamine induced elimination to furnish the requisite diene system. This diene **29** was directly heated at 70 ºC in dodecane to produce the desired *exo* adduct **30** in 34% yield, along with another *exo* product and a minor *endo* congener in a ratio of 1:0.9:0.4, respectively.

Scheme 2



Building on the precedent laid by Kishi, Hirama and coworkers finished a formal synthesis of pinnatoxin A in 2004, wherein the cyclohexene core was constructed via an intramolecular alkylation of an epoxy nitrile (Scheme 3).[23b] Utilizing the strategy developed earlier in the same group,[23a] they treated the mesylate **31** with 2.5 equivalent KHMDS to promote the epoxide formation (see intermediate **32**). In the same pot, addition of excess KHMDS led to opening of the epoxide, giving rise to the desired product **33** as the sole diastereomer in 72% yield. The diastereoselectivity of the cyclization step is consistent with the intermediate structure **32** wherein the large branched carbon chain preferentially occupies the pseudo-equatorial position.

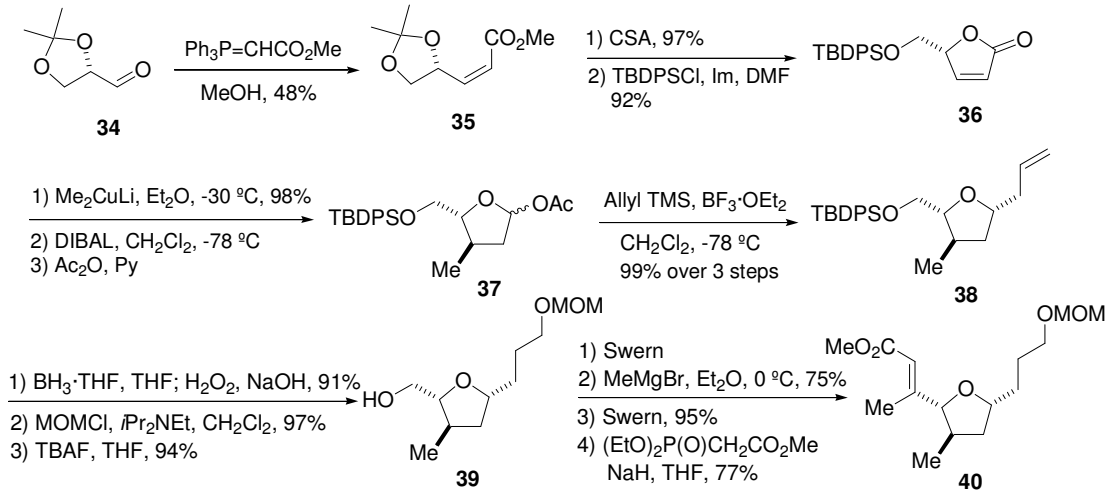
Scheme 3



I.4.2. Synthetic Studies Toward Gymnodimine

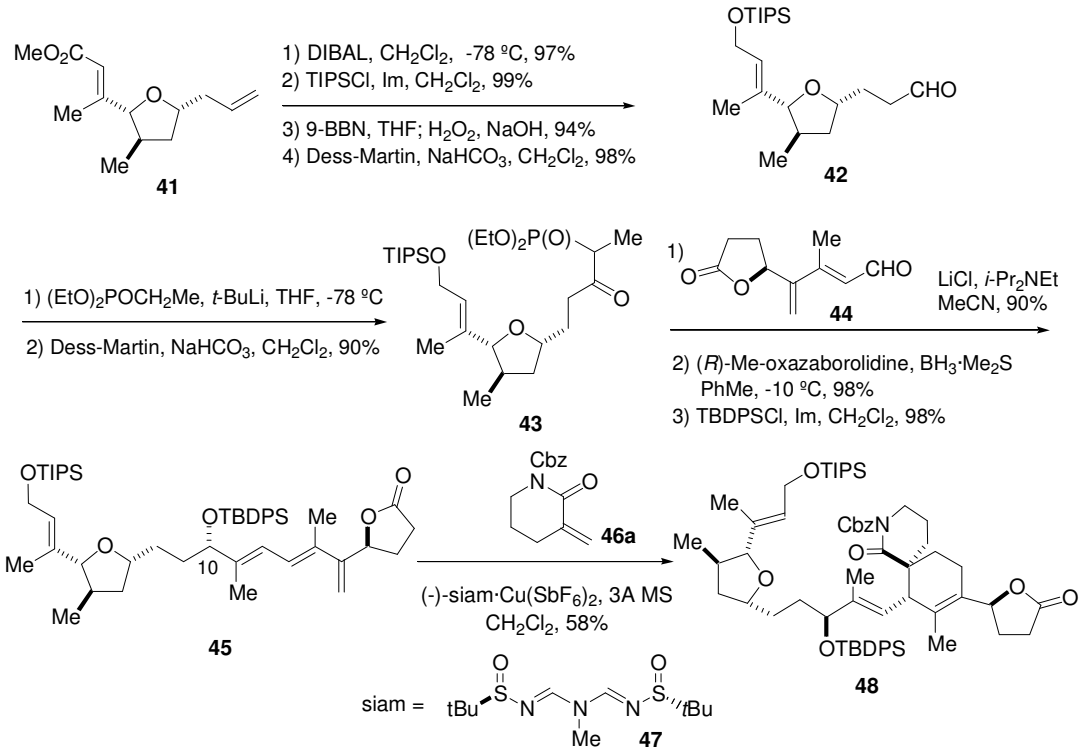
Several groups have disclosed their synthetic studies toward gymnodimine. However, to date a total synthesis of this natural product still remains elusive. Murai and coworkers synthesized the tetrahydrofuran segment of gymnodimine in a highly stereoselective fashion starting from the known α,β-unsaturated ester **35** (Scheme 4).[24] Treatment of this ester with CSA induced lactonization, which then underwent conjugate addition with lithium dimethylcuprate in a highly stereoselective fashion (dr > 20:1). The next key step was a C-glycosylation of acetoxy furanose **37** with allyl trimethylsilane. The allylation proceeded efficiently to give exclusively the α-isomer of tetrahydrofuran **38**. After a few standard transformations, the synthesis of the tetrahydrofuran **40** was accomplished with suitable functionalities for further elaboration.

Scheme 4



In subsequent studies, the Murai group explored a double diastereoselective Diels-Alder reaction to construct the spirocyclic lactam for the gymnodimine synthesis (Scheme 5).[24b] Thus, the tetrahydrofuran **41** was elaborated to the aldehyde **42** in a highly efficient four-step sequence. The derived β-ketone phosphonate **43** was joined with the L-glutamic acid derived aldehyde **44** to furnish a trienenone. A Corey-Bakshi-Shibata reduction was used to introduce the C-10 carbinol center with high diastereoselectivity (dr > 20:1) and the alcohol was then protected to give silyl ether **45**. The key intermolecular Diels-Alder reaction of the triene **45** with α-methylene *N*-Cbz lactam **46a** was conducted in the presence of a full equivalent of Ellman's copper bis(sulfinyl)-imidoamidine (siam) complex.[25] This reaction provided the spirolactam **48** in good yield and remarkably high diastereoselectivity (dr > 20:1).

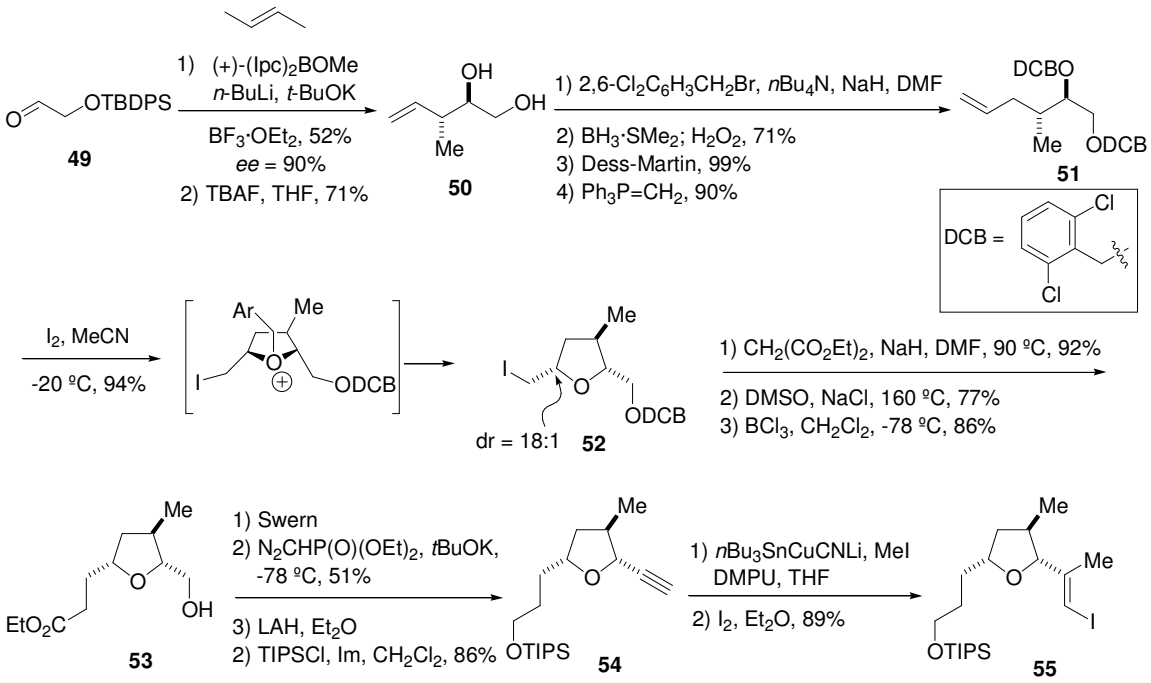
Scheme 5



White's construction of the tetrahydrofuran moiety is depicted in Scheme 6, featuring a highly diastereoselective iodoetherification step.[26a] Asymmetric crotylation of the aldehyde **49** furnished the homoallylic alcohol **50** after cleavage of the silyl group. Reprotection of both hydroxyl groups followed by one carbon homologation gave the olefin **51** for the key iodoetherification. Upon treatment with iodine, the 2,5-*cis*-tetrahydrofuran **52** was formed with highly diastereoselectivity (*dr* = 18:1). The 2,6-dichlorobenzyl substituent was crucial for the high selectivity, promoting a transition state for cyclization that avoids 1,2-steric interactions and permitting facile cleavage of the intermediate oxonium ion. Two-carbon homologation of the resultant iodide **52** to the ester **53** was accomplished by displacement of the iodo substituent with the anion of diethyl malonate, Krapcho decarboxylation of the diester and cleavage of the

dichlorobenzyl ether. A few more transformations led to the iodoalkene **55** through the intermediacy of the alkyne **54**.

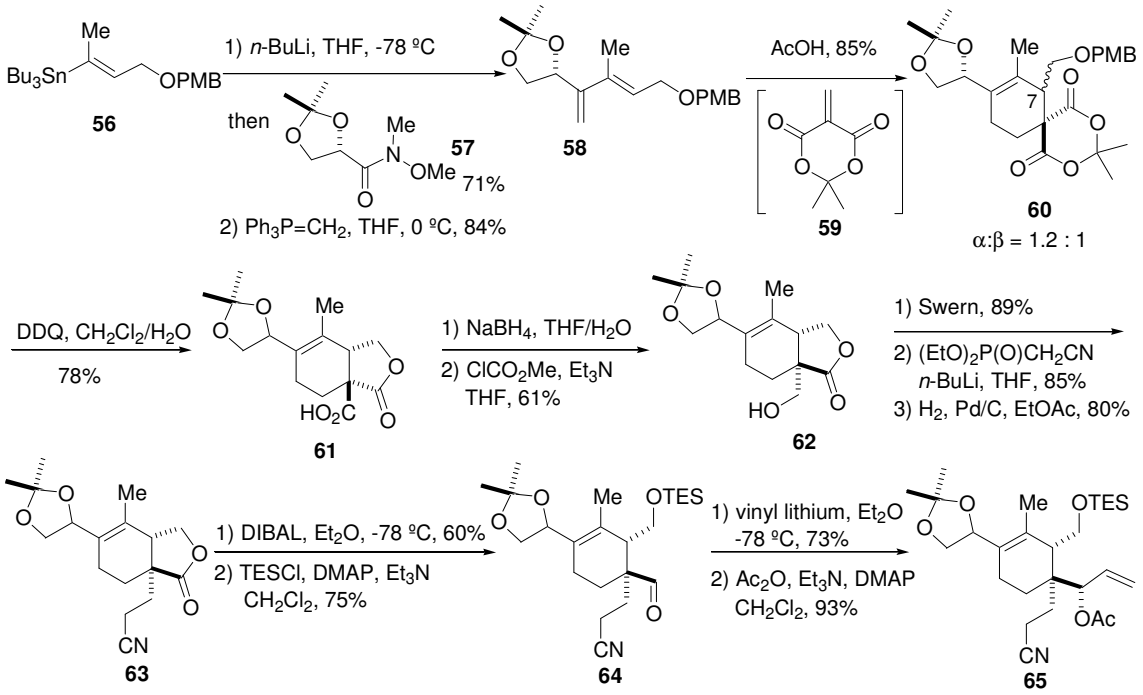
Scheme 6



To access the spirocyclic imine, an intermolecular Diels-Alder reaction of an optically active diene was utilized by White and coworkers (Scheme 7).[26b] Tin-lithium exchange of the vinyl stannane **56** and quenching with the Weinreb amide **57** gave the diene **58** after Wittig methylenation. The Diels-Alder reaction between diene **58** and the *in situ* prepared α-methylene Meldrum's acid **59** afforded **60** in a non-selective fashion (dr = 1.2:1). The C7-α isomer was treated with DDQ to unmask the primary alcohol, which cyclized spontaneously to give lactone **61**. Reduction, mixed anhydride formation followed by treatment with triethylamine provided the *trans*-fused lactone **62**.

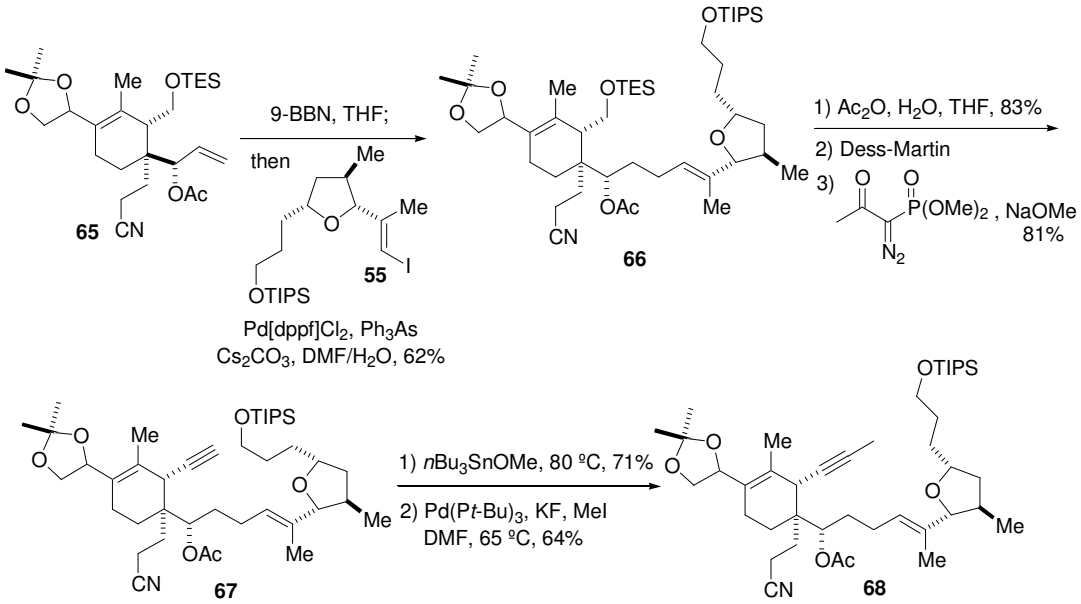
Elaboration to the acetate **65** proceeded smoothly and set the stage for the fragment coupling reaction.

Scheme 7



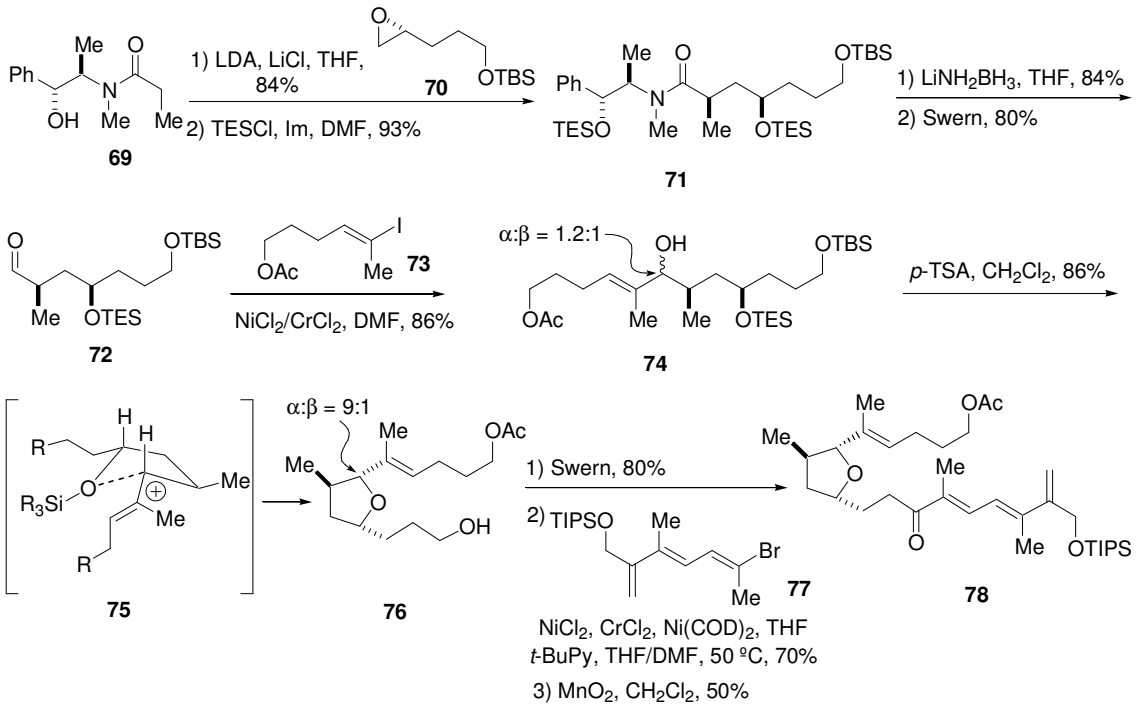
The two fragments were efficiently joined through a B-alkyl Suzuki-Miyaura coupling reaction (Scheme 8).[26c] The acetate **65** was reacted with 9-BBN to give the alkylborane which without isolation was coupled with iodoalkene **55** to produce **66** in 62% yield. The silyl ether **66** was then transformed to the alkyne **67** in good overall yield. A protocol developed by Suzuki [27] was used for the methylation of the alkyne **67**. Unfortunately, all attempts to functionalize the resultant internal alkyne **68** met with failure.

Scheme 8



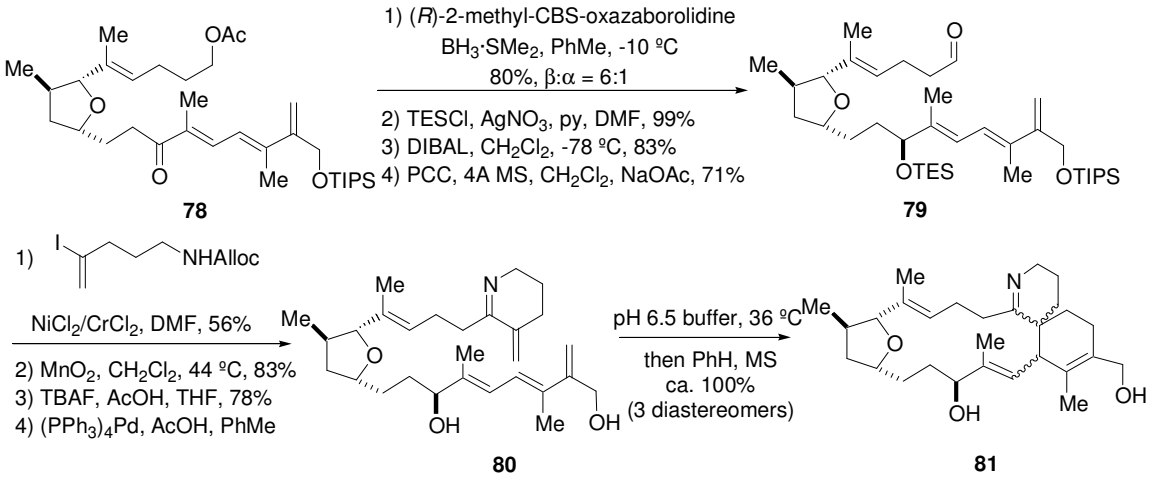
In a manner related to his pinnatoxin studies, Kishi utilized a Diels-Alder/ macrocyclization process for an approach to gymnodimine (Scheme 9).[28] Alkylation of the lithium enolate of the amide **69** with the chiral epoxide **70** yielded the requisite diol as a single diastereomer. Protection of the diol, reductive removal of the chiral auxiliary and oxidation then set the stage for a Ni(II)/Cr(II) mediated coupling, which provided the allylic alcohol **74** as an inconsequential mixture of diastereomers. Upon treatment with *p*-toluenesulfonic acid, a cationic intramolecular cyclization ensued providing the desired tetrahydrofuran **76** with good diastereoselectivity (dr = 9:1). Presumably, minimization of unfavorable steric interactions with pseudo-equatorial placement of the substituents in the intermediate allylic cation **75** accounted for the high selectivity of the cyclization step. Trienone **78** was then readily available from the tetrahydrofuran **76** in a few steps involving another Ni(II)/Cr(II) promoted coupling.

Scheme 9



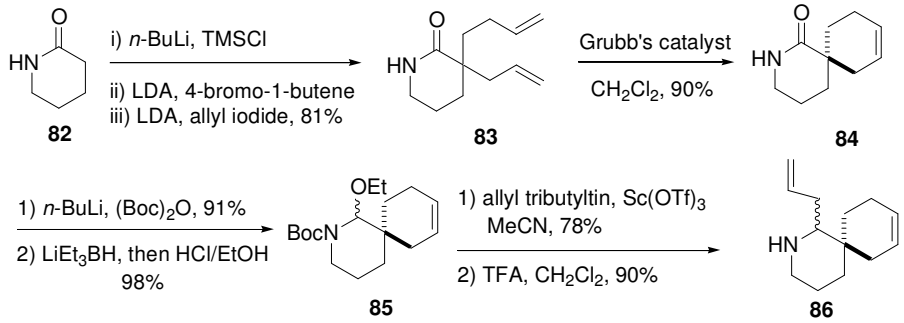
The desired allylic alcohol was then introduced via an asymmetric reduction using the Corey-Bakshi-Shibata protocol with moderate diastereoselectivity (dr = 6:1, Scheme 10). A Ni(II)/Cr(II) promoted coupling reaction paved the way for the synthesis of the α,β-unsaturated imine **80**. Diels-Alder macrocyclization of this imine occurred in water at pH 6.5 under dilute conditions to give the desired product **81** as a mixture of three diastereomers after treatment of the entire reaction mixture with molecular sieves in benzene. The diastereomer corresponding to the natural product could be isolated after reduction of the imine and acylation.

Scheme 10



Brimble and Trzoss developed an alternative approach for synthesis of the spirolactam (Scheme 11).[29] Their method involved double alkylation of the lactam **82** followed by ring closing metathesis of the double alkylated lactam **83**. Even though the spirolactam could be transformed to allylated product **86** through a Lewis acid mediated allylation of a derived acyliminium ion, the potential utility of this methodology for gymnodimine synthesis has not been demonstrated.

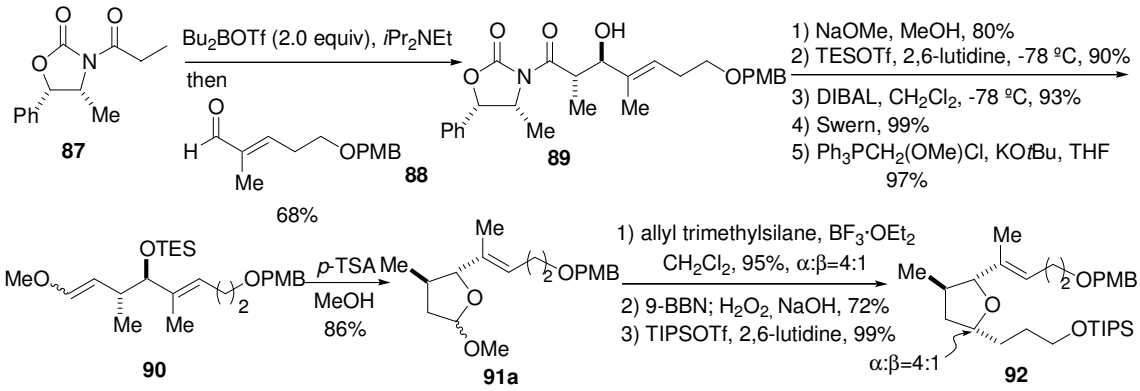
Scheme 11



I.5. Previous Work from Our Laboratory

Previous studies from the Romo group have resulted in concise syntheses of the chiral, non-racemic tetrahydrofuran and the racemic spirolactam moiety.[30] Our synthesis of the tetrahydrofuran commenced with the Heathcock *anti*-aldol reaction between the acyloxazolidinone **87** and the enal **88** (Scheme 12).[30a] Cleavage of the chiral auxiliary through methanolysis and subsequent homologation led to enol ether **90**. Upon treatment with methanolic acid, the unmasked secondary hydroxyl group cyclized onto the enol ether to provide the furanose **91a**. Allylation of the furanose proceeded with modest diastereoselectivity (dr = 4:1) and the product was then transformed to the protected diol **92**.

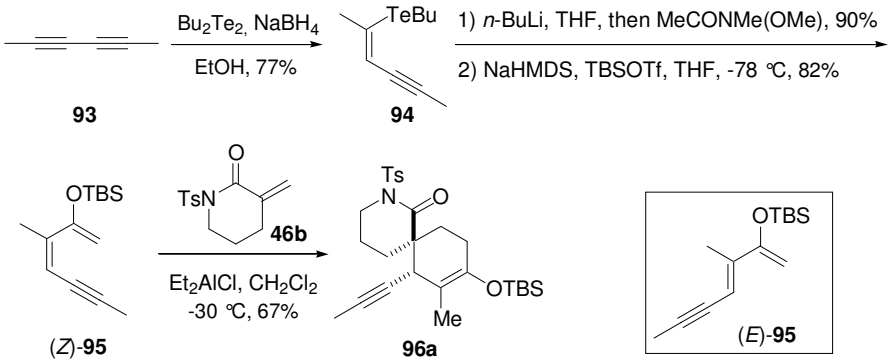
Scheme 12



We also demonstrated the potential of an intermolecular Diels-Alder process between α-methylene lactam **46b** and an oxygenated diene (*Z*)-**95** to rapidly assemble the spirocyclic moiety common to the gymnodimines (Scheme 13).[30a] This [4+2] cycloaddition was promoted by Et_2AlCl and proceeded in good yield and excellent diastereoselectivity. Furthermore, it is of interest to note that the two geometrical

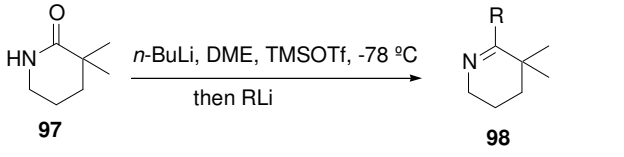
isomers (*Z*)-**95** and (*E*)-**95** behaved similarly in the Diels-Alder reaction both leading to the same diastereomer with high diastereoselectivity which implicated a stepwise mechanism for the [4+2] cycloaddition reaction.

Scheme 13



Subsequent studies also provided a possible solution for the challenging task of coupling the tetrahydrofuran with the spirolactam (Scheme 14).[30b] Based on Hua's protocol for cyclic imine synthesis from silylated lactams,[31] *N*-silylation of the lactam **97** followed by alkyllithium addition led directly to cyclic imines **98** in moderate yields after elimination of silanol.

Scheme 14



R = Me, 58%
R = *n*-Bu, 49%
R = $(CH_2)_3Ph$, 63%

I.6. Design of a Synthetic Strategy Toward Gymnodimine: Plan I

Our initial synthetic plan envisioned a late-stage intramolecular Nozaki-Hiyama-Kishi coupling[32] to close the 16-membered macrocycle following a Hua coupling to generate the imine (Figure 7). It is not unlikely that minimization of transannular or eclipsing interactions of the intermediate vinyl chromium species could lead to preferential formation of one stereoisomer.[33] However, it is rather difficult to predict, *a priori*, the stereochemical outcome of this macrocyclization reaction. In the worst scenario, a Mitsunobu inversion [34] could be used to correct the stereochemistry of the newly generated carbinol center at C-10 if the wrong stereoisomer were obtained.

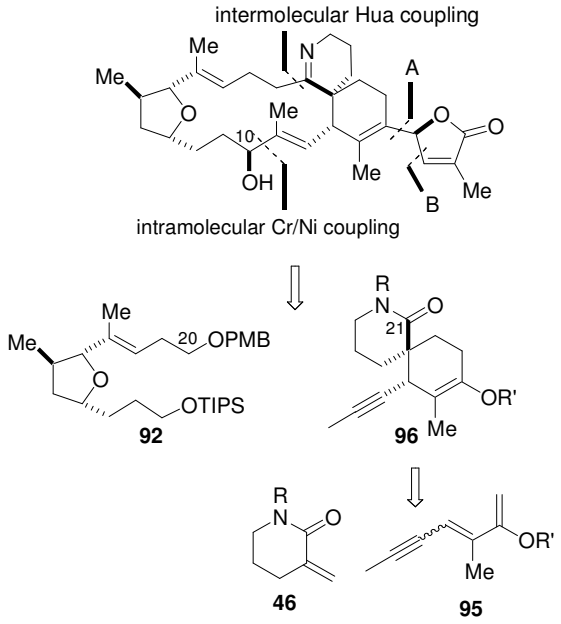


Figure 7. Initial synthetic plan toward gymnodimine (Plan I).

Preliminary studies on more advanced model systems indicated that the modified Hua imine synthesis would not be suitable for fragment coupling. One possible solution to this difficult problem is a cross-coupling reaction between a lactam derived iminoyl

triflate and a suitable organometallic species derived from the tetrahydrofuran **92**. Alternatively, use of an *intra*molecular instead of an *inter*molecular process for the C20-C21 bond formation could overcome the lack of reactivity from a kinetic standpoint. The Eschenmoser sulfide contraction protocol stands out as a viable candidate in this regard.[35]

To achieve maximum convergence and to avoid awkward adjustment of oxidation state, appending the butenolide fragment would ideally happen at a late stage in the synthesis. This would also avoid any potential instability issues known to be problematic with this moiety.[36] A few possibilities were considered initially including a Heck or related coupling reaction between a vinyl triflate and a dihydrofuran (Disconnection A, Figure 7), and nucleophilic addition to an aldehyde derived from **96** after one carbon homologation (Disconnection B, Figure 7).

Building on our success in the racemic Diels-Alder reaction, we envisioned an enantioselective [4+2] cycloaddition reaction[37] between α-methylene lactam **46** and diene **95** to access the optically active spirocylic lactam **96**. Furthermore, we had hoped to accomplish this in a catalytic fashion which would provide another example of catalytic asymmetric Diels-Alder reactions for the construction of stereochemically defined quaternary carbon centers.[38]

Finally, the potential for human consumption of shellfish carrying toxic concentrations of gymnodimines prompted efforts to develop a suitable antibody assay to monitor these marine toxins. By utilizing some of the intermediates during our

synthesis, we planned to synthesize several haptens for protein conjugation to ultimately develop an ELISA to monitor and quantify gymnodimine and congeners.

CHAPTER II

ASYMMETRIC SYNTHESIS OF THE SPIROLACTAM AND FURTHER FUNCTIONALIZATION*

II.1. Diels-Alder Reaction of a (*Z*)-Diene

Since the pioneering work by Koga on menthol-aluminum complex catalyzed Diels-Alder reactions,[39] great efforts have been devoted to the development of the catalytic, asymmetric Diels-Alder reactions to further exploit this already powerful transformation. Excellent, sometimes near perfect, control over both diastereo- and enantioselectivity has been achieved in some catalytic systems. Elegant work from Evans[40] and Corey,[41] among others, has demonstrated the power of these protocols in the synthesis of complex molecules. However, the vast majority of these protocols have only dealt with simple substrates like cyclopentadiene and acrolein derivatives. Therefore, seeking more general catalytic systems is still an active field of research.

We were attracted to the possibility of using bis(oxazoline) (box) copper complexes for the construction of the spirolactam moiety in optically active form. First reported by the Evans group,[42] the copper(II)-bis(oxazoline) complexes are among the most extensively studied catalytic systems for the Diels-Alder reaction. These catalysts benefit from their well-defined catalyst-substrate structures and thus provide high and predictable enantioselectivity across a wide range of substrates. The operational

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simplicity for the preparation of the catalysts is an additional merit. Even though the requirement for two-point catalyst-dienophile binding sometimes represents a limitation, we reasoned that chelation could potentially be achieved by choosing an appropriate protecting group on the nitrogen of the dienophile that provides the second binding point (Figure 8).

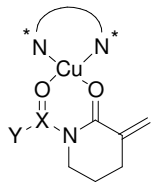
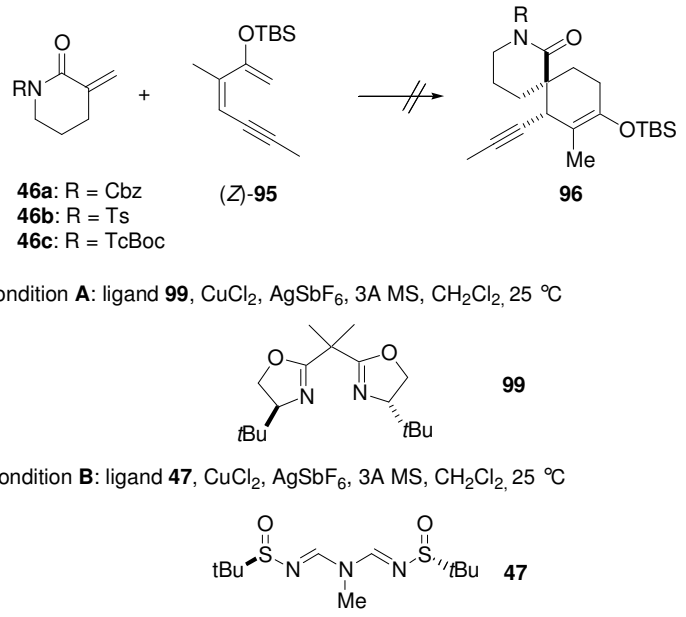


Figure 8. Design of an *exo*-methylene lactam substrate suitable for chelation with Cu(II) center.

Not surprisingly, results employing the *N*-tosyl lactam **46b**, which would not be expected to chelate, with Cu(*t*-Bu-box)$(SbF_6)_2$ complex as catalyst were not encouraging (Scheme 15). Exposure of the mixture of tosyl lactam **46b** and diene (*Z*)-**95** to a solution of Cu(*t*-Bu-Box)$(SbF_6)_2$ catalyst (condition A) only led to desilylation of the diene. To achieve better catalyst-dienophile interactions, the alkoxycarbonyl protected dienophiles **46a** and **46c** were used for the reaction but proved fruitless. Switching to the Cu(II)·bis(sulfinyl)-imidoamidine complex (condition B),[25] which had been successfully applied to the synthesis of the spirolactam core in Murai's approach,[24b] did not provide the desired cycloaddition adduct in any detectable amount.

Scheme 15



II.2. Diels-Alder Reaction of a Homologated Diene

In the attempted Diels-Alder reactions of diene (Z)-**95** with lactam **46**, the majority of the acid-labile diene simply underwent an unproductive desilylation in the presence of the copper catalysts. On the other hand, our preliminary results indicated that generation of a vinyl triflate from the silylenol ether **96** was not viable (*cf.* Chapter V, Eq. 8). Thus, a modified Diels-Alder approach to the spirolactam employing the homologated diene (*cf.* **101,** Figure 9) was deemed more convergent. While the stability of the diene was enhanced, the obvious drawback of this plan was the sacrificed reactivity of the diene. The consequence of this alteration to the planned Diels-Alder reaction had to be determined experimentally.

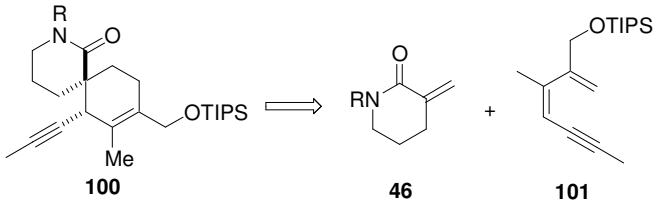
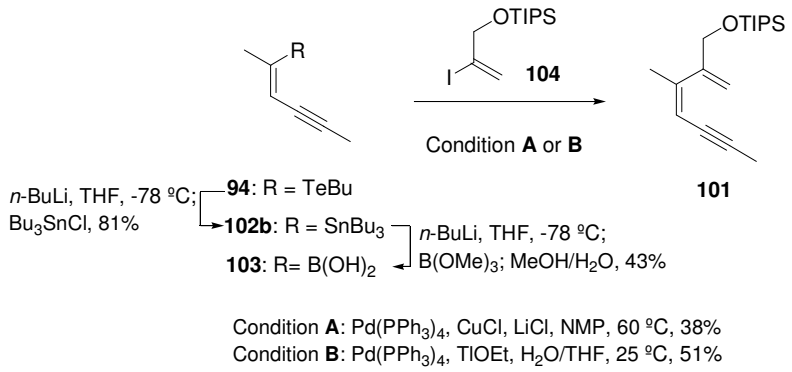


Figure 9. Design of a homologated diene **101** in the Diels-Alder reaction.

For the synthesis of dienyne **101**, we considered a Stille coupling[43] between vinyl stannane **102b** and the readily available vinyl iodide **104** (Scheme 16).[44] Extensive screening of the Stille coupling conditions between vinyl iodide **104** and **102b,** derived from the know vinyl telluride **94**, identified Corey's conditions[45] as optimal which provided the dieneyne **101** in moderate yield (Condition A). Presumably the well-known cine substitution of hindered vinyl stannanes during the Stille coupling accounted for the low yield of this step.[46] The Suzuki coupling using vinyl boronic acid **103** under Roush's modified conditions gave the same product in a slightly improved yield (Condition B).[47]

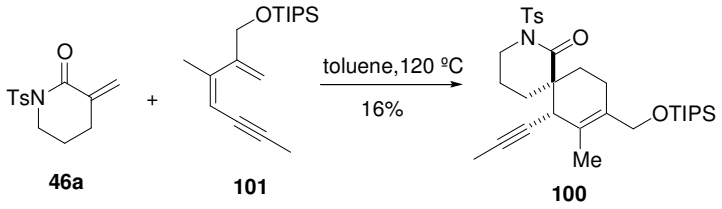
Scheme 16



Not surprisingly, the dienyne **101** only reluctantly participated in the Diels-Alder reaction with *N*-tosyl lactam **46a** (Scheme 17). The cycloaddition reaction did not proceed in the presence of Lewis acid, while thermal conditions provided the desired

adduct **100** in an unsatisfactory yield, and the regio- and diastereoselectivity were temporarily assigned based on previous results.

Scheme 17



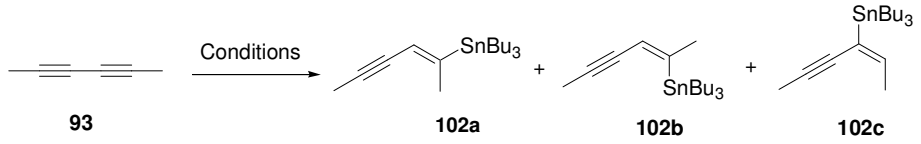
II.3. Diels-Alder Reaction of (*E*)-Diene: Effect of Geometry of the Diene

After these unsuccessful attempts, we began to realize that the lack of reactivity of the diene may be due to the olefin geometry despite the fact that our racemic series indicated that the Diels-Alder process was stereoconvergent with respect to *E*/*Z* isomers. It is generally recognized that (*Z*)-dienes are poor reactants in Diels-Alder reactions, even though some notable exceptions could be found in the literature.[48] Therefore we decided to pursue the synthesis of diene *(E)*-**95**.

Synthesis of this diene commenced with stannylcupration of the readily available 2,4-hexadiyne **93**. The pioneering work by Piers, Oeschlager, Cummins and Pancrazi had demonstrated that highly selective *cis*-addition to the triple bond could be achieved by addition of an external proton source, presumably by trapping the intermediate vinyl cuprate and insuring the formation of the kinetic stannane in an irreversible manner.[49] Indeed, stannylcupration in the presence of methanol afforded a mixture of regio- and stereoisomers with (*E*)-vinyl stannane **102a** being the major (Table 1, entry 1). While radical and metal-catalyzed hydrostannylations gave higher yields, the regio- or

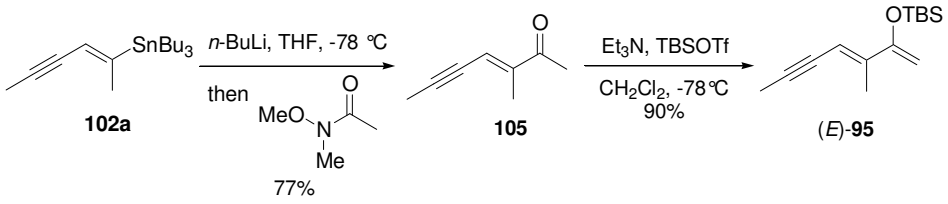
diastereoselectivities were less satisfactory. Radical hydrostannlyation gave comparable amounts of (*E*) and (*Z*) vinyl stannane (entry 2), whereas Pd-catalyzed hydrostannylation[50] gave the undesired regioisomer as the sole product (entry 3). Surprisingly, leaving out the proton source actually led to the desired regioisomer in higher ratio (entry 4), even though the exact reason still remains unclear. Tin-lithium exchange of stannane **102a** followed by reaction with *N*-methoxy-*N*-methyl acetamide gave the corresponding ketone **105** (Scheme 18). Subsequent formation of silylenol ether occurred without incident leading to the diene (*E*)-**95**.

Table 1. Synthesis of Vinyl Stannane **102** from 2, 4-Hexadiyne



entry	condition	yield (%)	ratio (**a**:**b**:**c**)
1	$(Bu_3Sn)_2CuCNLi_2$, MeOH, THF, -78 ºC	86	5:2:1
2	Bu_3SnH, AIBN, PhMe, 80 ºC	90	1:1.4:0
3	Bu_3SnH, $PdCl_2(PPh_3)_2$, THF, 25 ºC	90	0:0:1
4	$(Bu_3Sn)_2CuCNLi_2$, THF, -78 ºC	67	7:0:1

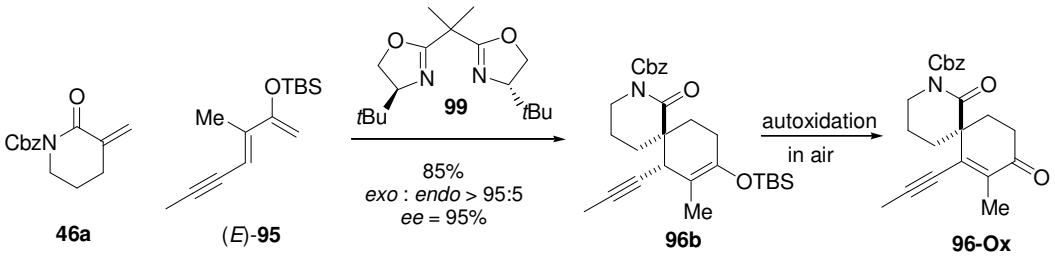
Scheme 18



We were pleased to find that Evans' copper-bis(oxazoline) hexafluoroantimony complex indeed promoted the Diels-Alder reaction of lactam **46a** and diene (*E*)-**95** to afford spirolactam **96b** as a single diastereomer in 85% yield (Scheme 19).[51] The Diels-Alder adduct proved to be rather unstable, as it undergoes spontaneous autoxidation in air at ambient temperature, leading to the formation of the α,β-unsaturated ketone **96-Ox**. Therefore, the subsequent step must be carried out immediately after purification of the Diels-Alder adduct.

After initial disclosure of this asymmetric Diels-Alder reaction,[52] we found that to ensure reproducibility it was best to use the modified procedure (Method B, Scheme 19) for catalyst preparation,[53] especially on larger scale. In addition, molecular sieves appear to slow down the reaction and even erode the enantioselectivity,[54] possibly by preventing the hydrophobic effect exerted by a small amount of adventitious moisture.[55]

Scheme 19

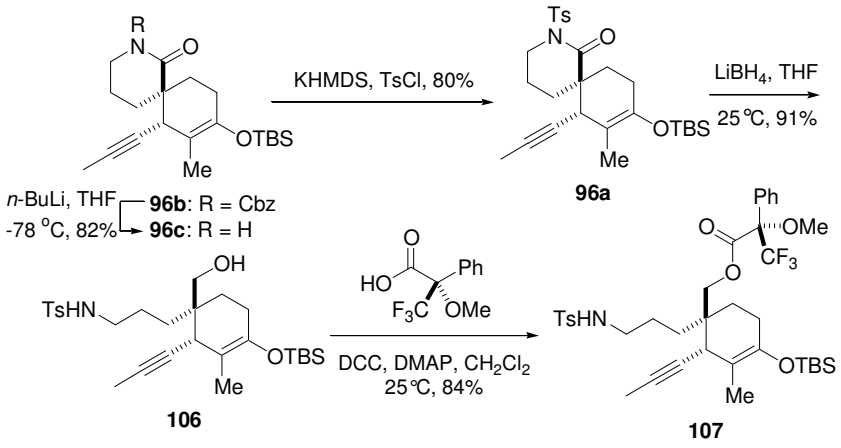


Method **A**: $CuCl_2$, **99** (10 mol%), $AgSbF_6$, CH_2Cl_2, 3A MS, 9 h
Method **B**: $CuCl_2$, **99** (10 mol%), CH_2Cl_2, 2 h; then $AgSbF_6$, 3.5 h

Determination of the enantiomeric excess of the process initially met with some difficulty by attempted use of chiral GC or HPLC. After considerable experimentation, the chiral shift reagent ($Eu(hfc)_3$) provided a good estimate of the enantiomeric excess upon mixing with the lactam **96c**. A more accurate method was finally found through

Mosher ester analysis of a derived alcohol (Scheme 20).[56] In related studies, we found that addition of *n*-BuLi to *N*-Cbz lactams such as **96b** led to exclusive Cbz deprotection.[57] This allowed a chemoselective deprotection and conversion to the *N*-tosyl lactam **96a**. Reduction of lactam to alcohol **106** with $LiBH_4$ proceeded smoothly and the alcohol was converted to Mosher ester **107** via a DCC mediated coupling. Analysis of the crude mixture by ^{19}F NMR (in comparison to the diastereomeric mixture obtained from the racemic adduct) indicated that the Diels-Alder reaction leading to spirolactam **96b** had proceeded with high enantioselectivity (95% ee). The absolute stereochemistry was established by X-ray crystallographic analaysis of lactam **96a** by anamolous dispersion (Figure 10).

Scheme 20



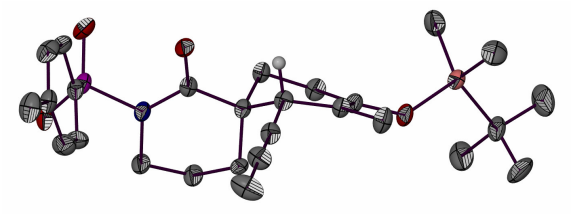


Figure 10. ORTEP representation of X-ray crystal structure of *N*-tosyl lactam **96a** (some hydrogen atoms omitted for clarity).

The Diels-Alder reaction leading to spirolactam **96b** which proceeds with both high diastereo- and enantioselectivity has a few features worthy of comment. An interesting observation is the complete unreactivity of diene *(Z)*-**95**. In contrast, we previously determined that both geometric isomers of diene **95** could be used to provide the *same diastereomer* in high yield using Et_2AlCl as promoter.[30a] These results suggest either different mechanisms for these Diels-Alder reactions (~synchronous vs completely stepwise) or the potential for olefin isomerization with the stronger Lewis acid Et_2AlCl but not with the weakly Lewis acidic chiral catalyst. Calculations suggest that the energy difference between *s-cis* and *s-trans* conformers is not sufficient to rationalize the unreactivity of diene (Z)-**95** due to the low steric requirement of the alkyne (Figure 11).[58] In fact, the *s-cis* conformation of diene (Z)-**95** is lower in energy than *s-trans*. As expected, the *s-trans* conformer of diene (*E*)-**95** is more stable than the *s-cis* conformer but the latter conformer is accessible at room temperature. Taken together, these data suggest that the unreactivity of diene (*Z*)-**95** in the asymmetric reaction is due to steric interactions with the catalyst-ligand complex proceeding through a more or less synchronous process and not the inaccessibility of the reactive *s-cis* conformer (*vide infra*).

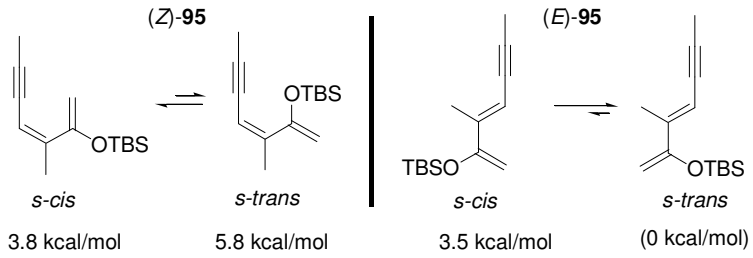


Figure 11. Calculated relative energies for dienes (*Z*)-**95** and (*E*)-**95**.

Another noteworthy feature is the high diastereoselectivity resulting from an *exo*-selective reaction. This selectivity is not unusual for this type of conformationally restricted (*s-cis*) dienophile and has been attributed to favorable dipole cancellation in the *exo*-transition state by Roush and Brown.[59] In the present enantioselective process, the preference for *exo* selectivity would be more pronounced due to interactions of the 2-silyloxy substituent of diene **95** with the chiral ligand in the *endo* transition state as previously observed by Evans in reactions of 3-methyl-1-acetoxy buadienes.[42b] The stereochemistry of adduct **96b** thus results from an *exo* trajectory of the diene (*E*)-**95** from the most accessible face opposite the *t*-butyl substituent (sphere) of the Cu(box)-dienophile complex (Figure 12A). The severe steric interaction of diene (*Z*)-**95** with the catalyst-ligand complex readily explains its low reactivity in the enantioselective Diels-Alder reaction (Figure 12B).

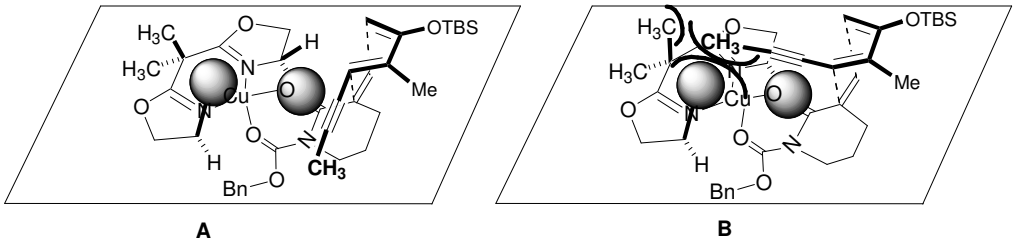


Figure 12. Favored and unfavored transition state arrangements that rationalize the differential reactivity of dienes (*E*) and (*Z*)-**95**.

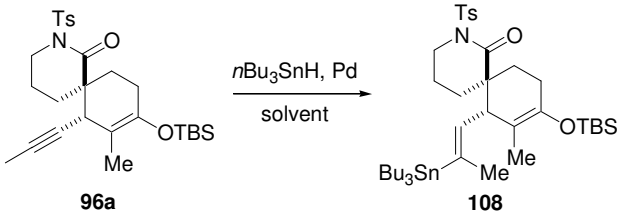
II.4. Functionalization of the Internal Acetylene

Ultimately, it would be necessary to functionalize the internal alkyne to enable assembly of the macrocycle, therefore we sought to ascertain whether such a transformation might be achieved. Spirolactam **96a** thus served as an ideal model for the requisite alkyne functionalization. A close inspection of the substrate revealed that the proximity of the internal triple bond to a trisubstituted and a fully substituted carbon might pose a considerable challenge to this otherwise routine transformation due to steric considerations.

Not unexpectedly, extensive screening of hydrometallation protocols,[60] such as hydrozirconation,[61] hydroboration [62] and hydroalumination,[63] identified the palladium catalyzed hydrostannylation[50] as the only viable way to functionalize the triple bond, albeit in low conversion.

Attempted optimization of the reaction variables, involving the temperature and the catalyst source, did not result in any improvement of the conversion (Table 2). The reaction temperature did not have a notable effect on the conversion (entries 1 and 2). Among the solvents screened, THF remained optimal (entries 1, 3-6). In agreement with Guibé's findings,[50a] the best palladium source was $PdCl_2(PPh_3)_2$ (entries 1, 7, and 8). Employing $PdCl_2(o\text{-}Tol_3P)_2$ catalyst which proved to be particularly useful in a recent hydrostannylation of a hindered internal alkyne[64] did not provide any desired product (entry 9). Finally, use of a mixed solvent of THF/hexanes as recently described by Semmelhack and Lee[65] led to a significant improvement in conversion (entry 10).

Table 2. Optimization of the Hydrostannylation of Spirolactam **96a**

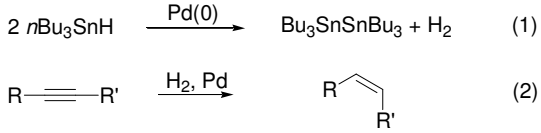


96a **108**

entry	Pd source	conditions	yield (%)
1	$PdCl_2(PPh_3)_2$	THF, 25 ºC	25
2	$PdCl_2(PPh_3)_2$	THF, 70 ºC	23
3	$PdCl_2(PPh_3)_2$	PhMe, 100ºC	<10%
4	$PdCl_2(PPh_3)_2$	NMP, 25 ºC	<5
5	$PdCl_2(PPh_3)_2$	DMF, 25 ºC	<5
6	$PdCl_2(PPh_3)_2$	CH_2Cl_2, 25 ºC	<5
7	$Pd(PPh_3)_4$	THF, 25 ºC	11
8	$Pd_2(dba)_3{\cdot}CHCl_3$, Ph_3As	THF, 25 ºC	NR
9	$PdCl_2(P(o\text{-}tol)_3)_2$	THF, 25 ºC	NR
10	$PdCl_2(PPh_3)_2$	THF/hexanes, 25 ºC	60

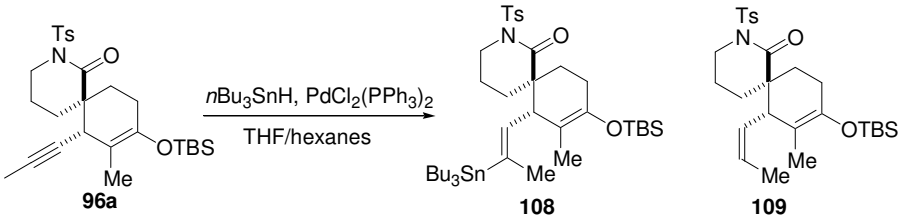
Careful analysis of the reaction mixture identified a significant amount of the alkene **109**, which was not derived from protodestannylation during the reaction or purification (Scheme 21, condition A).[66] The same phenomena were previously observed by Pancrazi and coworkers during hydrostannylation of some hindered substrates, even though possible reasons were not suggested in that report (Scheme 22).[67] It is well recognized that the addition of tin hydride to triple bonds competes with dimerization of tributyltin hydride itself.[50] Therefore it is very likely that molecular hydrogen, the byproduct from the dimerization process (Eq 1), would hydrogenate triple bonds in the presence of Pd leading to the formation of reduction products such as **109** (Eq. 2). This

is particularly true in the case of the hindered internal alkyne substrates when the hydrostannylation step is sufficiently slow. A good control reaction would make use of Bu_3SnD leading to the bis-deuterated alkene however this was not performed.



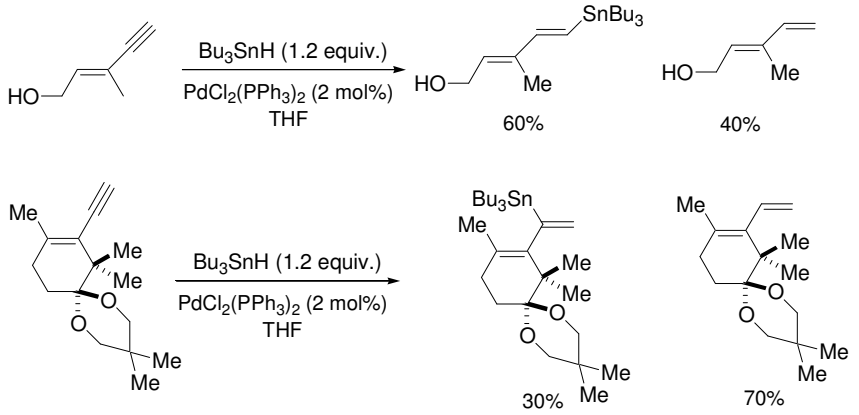
Based on this hypothesis, we speculated that by keeping the concentration of nBu$_3$SnH low throughout the reaction, the competing hydrogenation pathway would be suppressed. Indeed, when tributyltin hydride was added to the reaction over a period of 12 h via syringe pump, the vinyl stannane **108** could be isolated in good yield, along with only a small amount of the hydrogenated product (Scheme 21, condition B).

Scheme 21



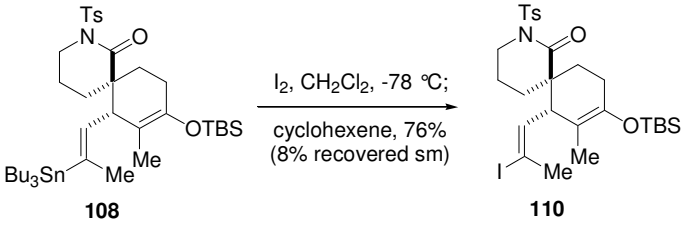
	108	**109**
Condition **A**: normal addition of nBu$_3$SnH	60%	15%
Condition **B**: syringe pump addition of nBu$_3$SnH	85%	< 5%

Scheme 22



The subsequent conversion of the stannane **108** to the corresponding iodide required for the Nozaki-Hiyama-Kishi coupling also took a considerable amount of optimization (Scheme 23). One competing process during this reaction is the α-iodination of the reactive silylenol ether moiety. By keeping the reaction temperature low and controlling the amount of iodine added, a relatively clean reaction resulted. However the product **110** proved to be rather sensitive to standard workup conditions such as sodium thiosulfate as it led to significant amounts of desilylated product. Thus a neutral workup by addition of cyclohexene as the scavenger provided the desired vinyl iodide **110** in good yield.

Scheme 23



108 **110**

CHAPTER III

SYNTHESIS OF THE TETRAHYDROFURAN MOIETY

III.1. Improvement of the Stereoselective Allylation of the Furanose

As described above, previous work from this laboratory had provided a concise route to the tetrahydrofuran moiety of gymnodimine in non-racemic form.[3030a] In addition, previous assignment of stereochemistry of *anti*-aldol adduct **89** based on NMR studies was firmly secured through X-ray crystallographic analysis (Figure 13). However, the modest diastereoselectivity during the allylation of the furanose **91a** left room for further improvement especially given that the diastereomers were inseparable (Scheme 24). Thus optimization studies of the tetrahydrofuran fragment were focused on this pivotal step.

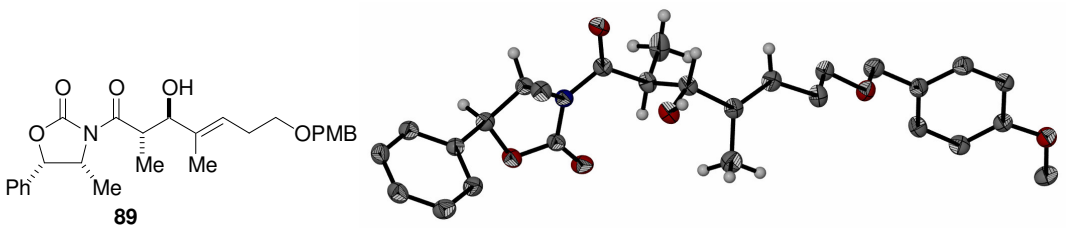
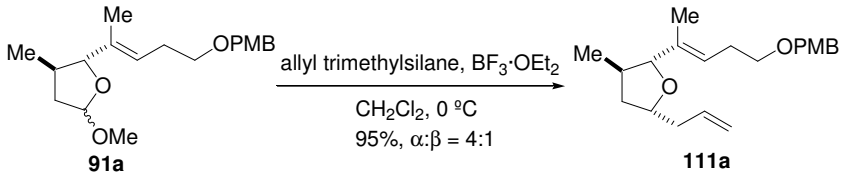


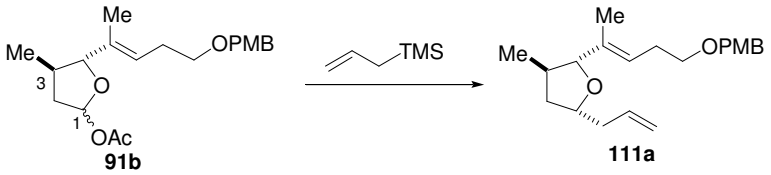
Figure 13. ORTEP representation of X-ray crystal structure of **89** (some hydrogen atoms omitted for clarity).

Scheme 24



The more reactive acetoxyfuranose **91b** was chosen for the optimization in the hope of enhancing the selectivity by lowering the reaction temperature. However, the reaction temperature did not have a notable effect on the stereoselectivity (Scheme 25). Screening of Lewis acids including but not limited to $BF_3{\cdot}OEt_2$, $AlCl_3$, Et_2AlCl, TMSOTf and $TiCl_4$ indicated that the stereochemical outcome depends on Lewis acid only to a minor extent. On the other hand, solvent affected the reaction more pronouncedly and toluene provided the best diastereoselectivity (α:β = 4:1) with excellent reproducibility. Convincing evidence from the Woerpel group has indicated that allylation of five-membered-ring oxocarbenium ions proceeds through a stereoelectronically controlled "inside attack" mode with high 1,3-*anti* stereoselectivity when the C-3 position is occupied by a methyl group.[68] Thus, the discrepancies between our result and those of Woerpel and Murai's[24a] reflect the subtle structural differences in substrates which in turn affect the stereochemical outcome of the allylation reaction.

Scheme 25

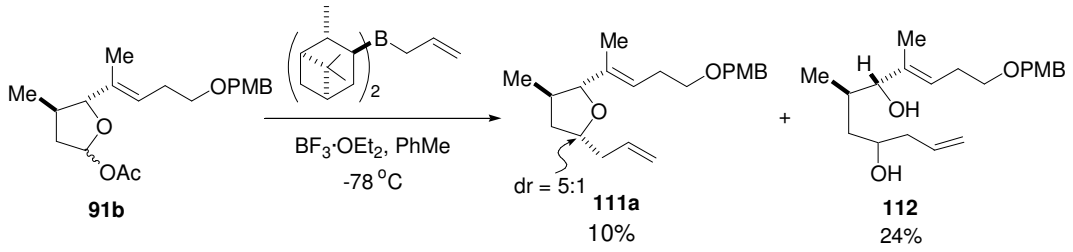


Conditions	Results
$BF_3{\cdot}OEt_2$, CH_2Cl_2, -78 ºC	89%, dr = 3:1
$BF_3{\cdot}OEt_2$, CH_2Cl_2, -95 ºC	65%, dr = 3:1
$BF_3{\cdot}OEt_2$, PhMe, -78 ºC	71%, dr = 4:1

A potentially useful route for the diastereoselective allylation of the oxocarbenium intermediate was use of a chiral allylation reagent in a double diastereoselective process to enhance the modest inherent selectivity through a synergetic effect of the substrate and the reagent. Indeed, preliminary results showed that

allylation using Brown's Ipc_2BAll reagent[69] in the presence of exogenous Lewis acid $BF_3{\cdot}OEt_2$ led to slightly improved diastereoselectivity but in poor yield (Scheme 26, α:β = 5:1). Interestingly, the major byproduct in this transformation was the alcohol **112** possibly derived from the addition of the allyl group to an isomeric oxocarbenium intermediate. Even though the yield of this reaction is still low, this unexplored strategy for the allylation of chiral oxocarbenium ions using chiral allylation reagents holds great potential and deserves further studies.

Scheme 26

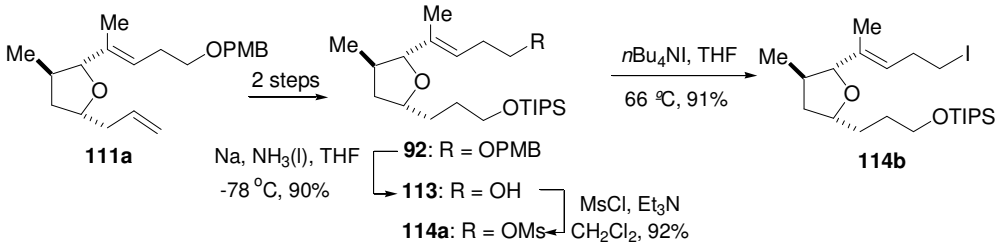


III.2. Synthesis of an Alkyl Iodide Suitable for Fragment Coupling

To construct the macrocycle of gymnodimine, our initial plan was to join the tetrahydrofuran with the spirolactam fragment through the C20-C21 bond formation followed by an intramolecular Nozaki-Hiyama-Kishi coupling (*cf.* Figure 7, Chapter I). Thus, the alkene **111a** had to be functionalized in suitable form for the fragment coupling. Following the established sequence from this laboratory,[30a] the olefin was converted to the protected alcohol **92** in two steps (Scheme 27). While the oxidative cleavage of the PMB ether **92** using standard protocol (DDQ, CH_2Cl_2/H_2O,[70] with or without $NaHCO_3$) was marginally successful, dissolving metal conditions proved to be

more satisfactory, affording the alcohol **113** in good yield. The primary alcohol **113** was then transformed to the alkyl iodide **114b**, which was used in our first generation coupling strategy with great success (*vide infra*).

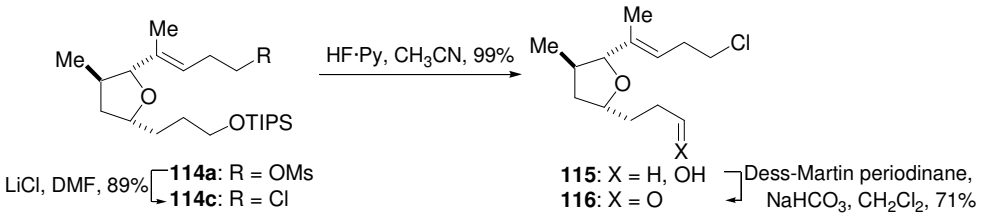
Scheme 27



III.3. Synthesis of an Aldehyde Suitable for Fragment Coupling

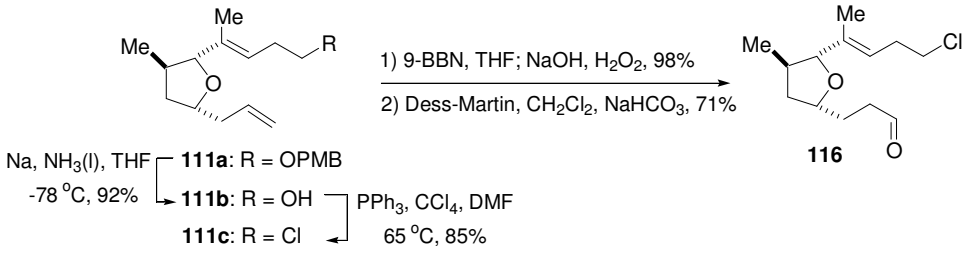
Our original plan of using an intramolecular Nozaki-Hiyama-Kishi reaction for a macrocyclization did not return any fruitful results (*vide infra*) and the modified strategy necessitated a different form of the tetrahydrofuran, such as aldehyde **116** (Scheme 28), for fragment coupling. Along these lines, the mesylate **114a** was converted to the alkyl chloride **114c** upon treatment with LiCl. The silyl group was removed through the action of HF·pyridine and the alcohol **115** was then oxidized to the aldehyde **116** by Dess-Martin periodinane.[71] In order to achieve an efficient coupling with the spirolactam, it was necessary to prepare the aldehyde **116** immediately prior to use. Thus, it was convenient to store the tetrahydrofuran at the alcohol stage.

Scheme 28



While this route did provide the aldehyde in a relatively concise fashion, we reasoned that a more direct way by avoiding the superfluous protection/deprotection steps would allow greater material throughput. The new route commenced with the reductive cleavage of the PMB ether **111a**, again under dissolving metal conditions (Scheme 29). The newly revealed alcohol **111b** was then transformed to the alkyl chloride **111c** in one step, which was hydroborated and oxidized to the aldehyde **116** according to the aforementioned sequence. This new sequence proceeds remarkably well and is more efficient than the previous one (4 steps vs. 7 steps, starting from the alkene **111a**).

Scheme 29



CHAPTER IV

FRAGMENT COUPLING AND MACROCYCLIZATION*

IV.1. Fragment Coupling: Model Studies

After successful construction of the tetrahydrofuran and spirolactam moieties respectively in chiral, non-racemic form our next goal was to find a mild and efficient coupling protocol for their union. The previously developed single-pot Hua reaction[30b] was unfortunately not applicable to the real system. Model studies were then conducted to evaluate various coupling strategies.

One possibility was the cross-coupling reaction between an iminoyl triflate derived from the model lactam **97** and organometallic nucleophiles (Scheme 30). Modern variants of the cross-coupling reactions have allowed some of the most complex molecules to be synthesized under sufficiently mild conditions.[72] However, there are only few reports employing lactam-derived iminoyl triflates in cross-coupling reactions.[73] Our exploration of this reaction between the triflate **117** and various organometallic species involving Sonogashira, Suzuki and Negishi couplings invariably failed. Lack of reactivity of the iminoyl triflate in the cross-coupling reactions promoted us to seek a different method.

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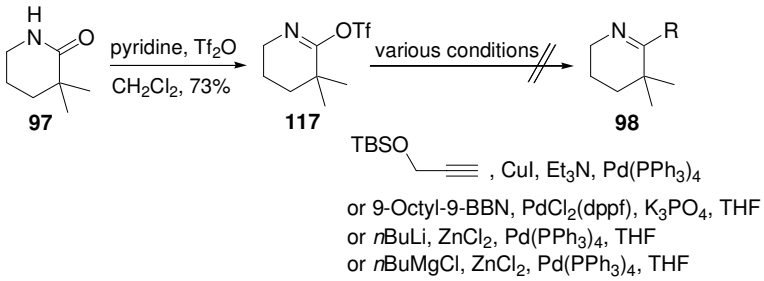
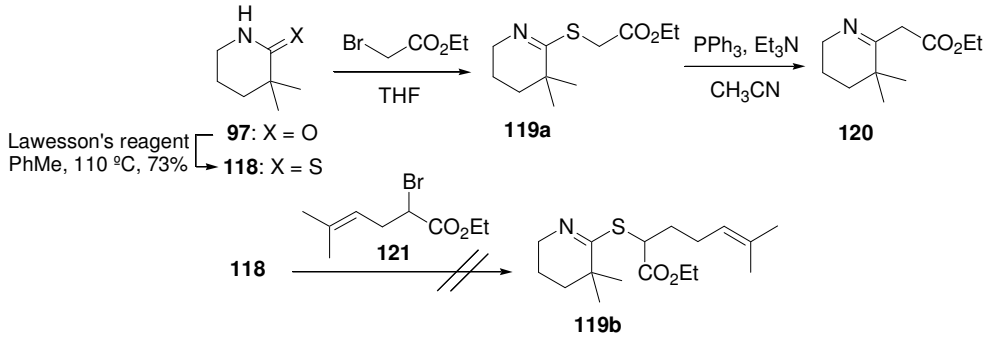
Scheme 30

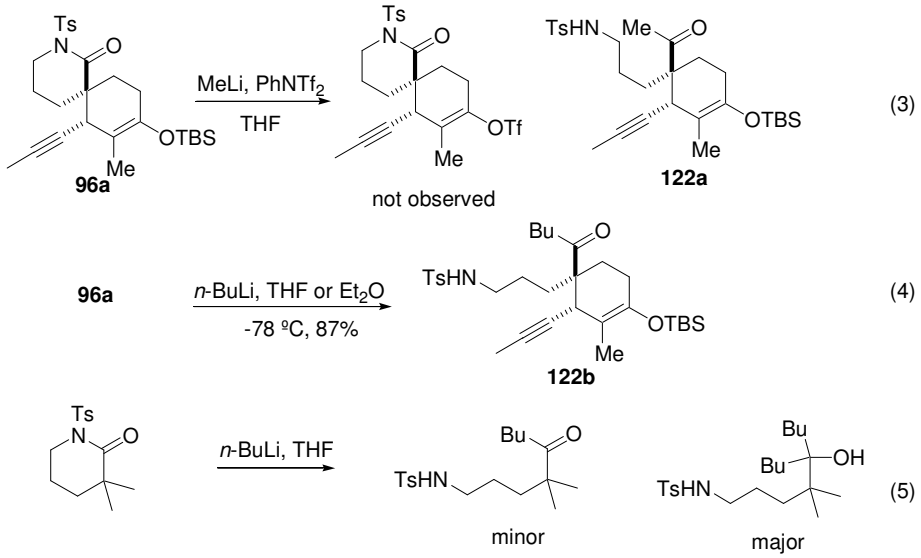


The low reactivity of the iminoyl triflate **117** at least partially stems from the steric nature of the α,α'-disubstituted lactam, implying that an intramolecular process could be used for this bond formation. The Eschenmoser sulfide contraction stood out as a viable candidate to achieve an intramolecular reaction at the hindered carbonyl site. In the event, lactam **97** was converted to the thiolactam **118** through the action of Lawesson's reagent,[74] which was then alkylated on sulfur to afford the thioiminoester **119a** (Scheme 31). Upon treatment with PPh_3 in the presence of a base according to Eschenmoser's protocol, the putative intermediate episulfide collapsed to give the imine **120** after extrusion of triphenylphosphine sulfide. Disappointingly, the method was not applicable to the more advanced model substrate **121**.[75] This α,α'-disubstituted ester failed to undergo the desired nucleophilic displacement with the thiolactam **118** under a variety of conditions.

Scheme 31

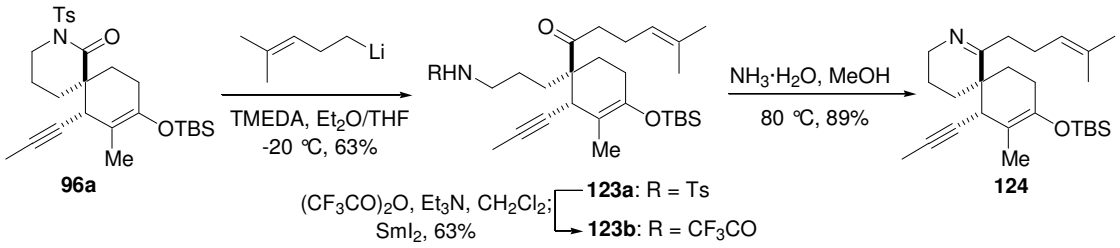


Eventually, it was a serendipitous finding that led to the discovery of the successful coupling strategy. Our initial attempts to transform the silylenol ether **96a** to the corresponding triflate by treatment with methyllithium and $PhNTf_2$ led to isolation of a single product in high yield, which was identified as the amino ketone **122a** instead of the expected vinyl triflate (Eq. 3). Not surprisingly, in retrospect, the hindered, but activated lactam **96a** is already set up for a direct coupling with an alkyllithium species. Further experimentation revealed that *n*-BuLi also opened the lactam in high yield at low temperature (Eq. 4), while *n*-BuMgBr only reacted reluctantly at room temperature. Somewhat unexpected was the dominance of the monoalkylated adducts even when large excess of the alkyllithium species was used, while addition of alkyllithiums to simple α,α'-dimethyl-*N*-tosyl lactams is known to give predominantly alcohols[57] resulting from double alkylation even when one equivalent of alkylithium was employed (Eq. 5).



Capitalizing on this fortunate finding,[76] we started to examine the scope of this reaction for the eventual application to the real system. It was found that this process could be readily extended to other alkyllithiums. Thus, treatment of lactam **96a** with (4-methyl-3-pentenyl)lithium [77] in the presence of TMEDA afforded the desired amino ketone **123a** in good yield. The tosyl group was resistant to cleavage under a variety of conditions. Utilizing a mild, single-pot sequence developed in this laboratory,[78] we were able to convert the *N*-tosyl amine **123a** to trifluoroacetyl amide **123b** by sequential treatment with base, trifluoroacetic anhydride and samarium diiodide. Cleavage of the trifluoroacetamide with warm ammonium hydroxide led to concomitant cyclization to provide imine **124** in good overall yield, which represents the spirocyclic imine portion of gymnodimine.

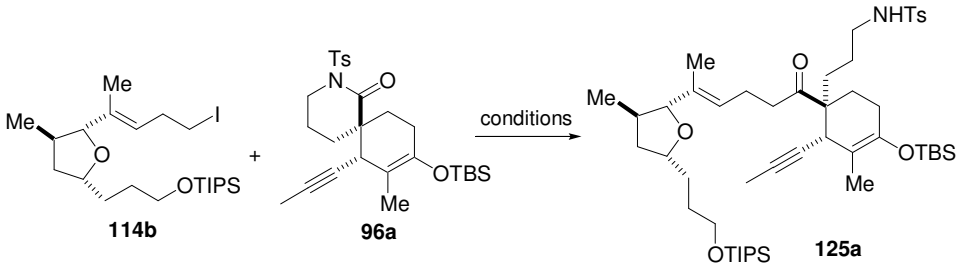
Scheme 32



IV.2. Fragment Coupling and Nozaki-Hiyama-Kishi Macrocyclization

With the success of the model studies, we embarked on further extension of the process to the tetrahydrofuran **114b**. Initial experimentation under the aforementioned conditions by treatment of the alkyllithium species derived from the alkyl iodide **114b** with *N*-tosyllactam **96a** provided the desired amino ketone **125a**, albeit in very low yield (Scheme 33, condition A). Pleasingly, simple inversion of the order of addition by adding *t*-BuLi to a mixture of the reactants at low temperature (condition B) substantially improved the yield of this intermolecular Barbier-type transformation.[79] This of course benefits from the well-known high rate of lithium-iodine exchange preventing any side reactions such as opening of the *N*-tosyl lactam by *t*-BuLi.[80]

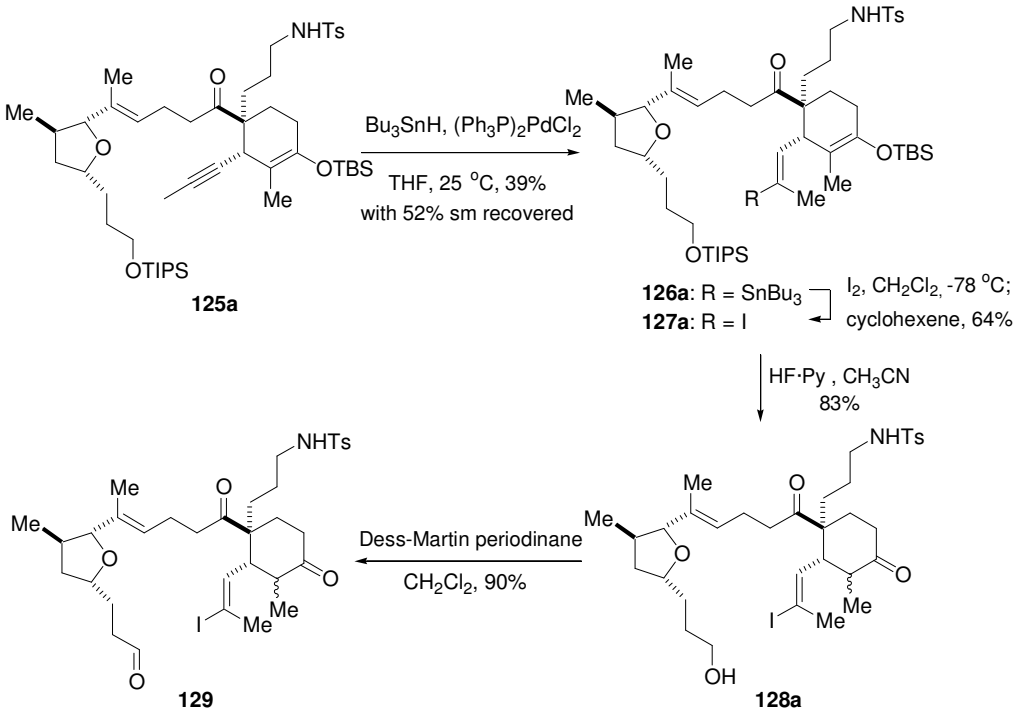
Scheme 33



Condition **A**: **114b**, *t*-BuLi, Et_2O, -78 °C; then **96a** 17%
Condition **B**: **114b**, **96a**, then *t*-BuLi, Et_2O, -78 °C 92%

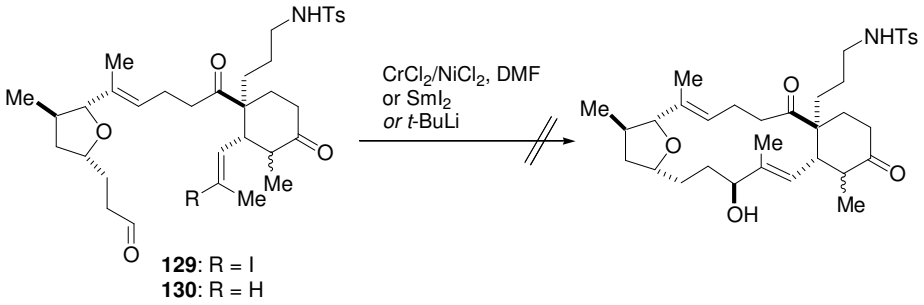
The acetylene **125a** was then hydrostannylated in the presence of the palladium catalyst according to the conditions developed on model substrates (*cf.* Scheme 21, Chapter II), leading to the formation of the vinyl stannane **126a** (Scheme 34). Following tin-iodine exchange, the two silyl groups of **127a** were removed upon treatment with HF·pyridine. The primary alcohol **128a** was finally oxidized to the aldehyde **129** by Dess-Martin periodinane.[71]

Scheme 34



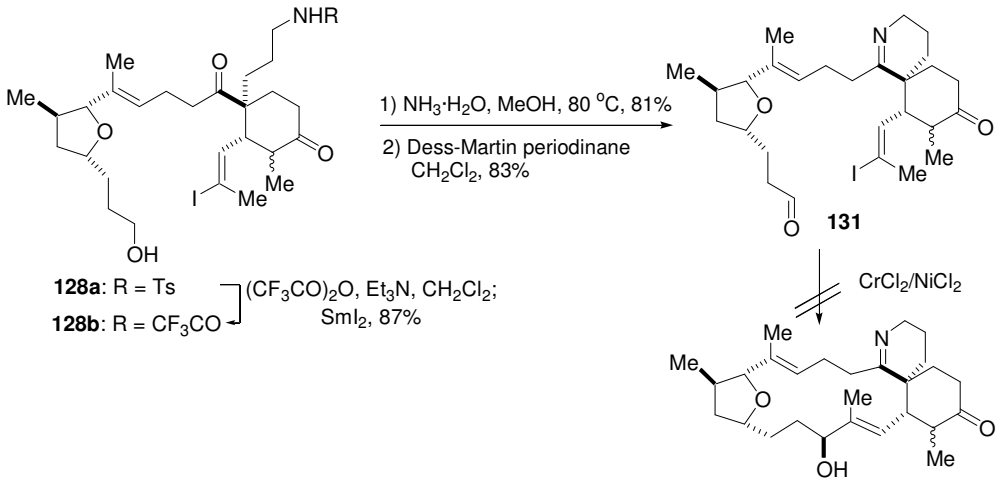
The synthesis of the aldehyde **129** set the stage for the key intramolecular Nozaki-Hiyama-Kishi macrocyclization. Much to our disappointment, this substrate did not undergo the planned cyclization under a variety of conditions (Scheme 35). The sole product isolated from these reactions was in all instances the deiodinated compound **130**. Obviously, during the reaction the intermediate vinyl chromium species resulting from the oxidative addition/transmetallation was not reactive enough to overcome the high enthalpy barrier for the formation of this macrocycle and thus underwent simple hydrolysis during workup to give the olefin **130**. Attempted cyclization under other conditions such as SmI_2 or *t*-BuLi only led to reduction of the aldehyde and deiodination, respectively.

Scheme 35



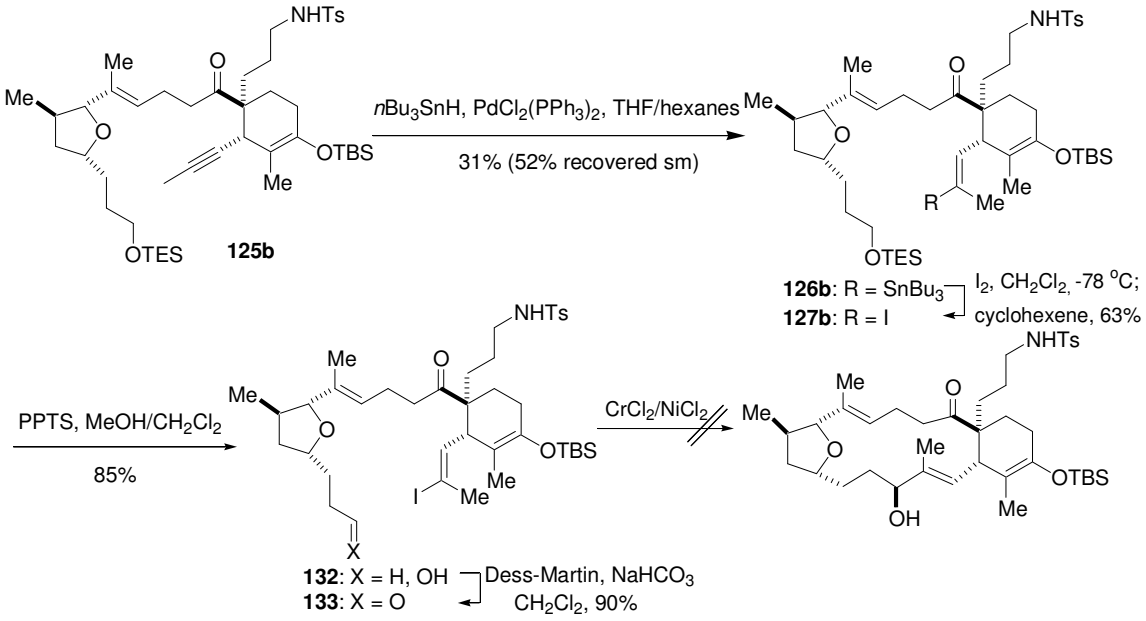
Reasoning that formation of the spiroimine could possibly change the solution conformation of the substrate and assist the macrocyclization by bringing the reactive centers into proximity, the *N*-tosylamine **128a** was converted to trifluoroacetamide **128b** in good yield (Scheme 36). Interestingly, this mild transformation could be performed with the free alcohol presumably because of facile hydrolysis of the intermediate trifluoroacetate. The amide **128b** was then converted to the required aldehyde **131** in two steps following the previously described sequence. Once again, this aldehyde did not undergo the desired macrocyclization under a number of Cr/Ni mediated coupling conditions.

Scheme 36



Our final attempt of the intramolecular Nozaki-Hiyama-Kishi coupling was conducted on substrate **133**. Even though ample precedents have demonstrated the chemoselective reactions of vinyl chromium species with aldehydes, we nevertheless suspected that an electrophilic ketone might interfere with this process. Thus, the triethylsilyl ether **125b** was synthesized in similar fashion as for the preparation of **125a**, allowing a selective removal of the triethylsilyl group (PPTS, $MeOH/CH_2Cl_2$) after completion of the acetylene functionalization (Scheme 37). Dess-Martin oxidation furnished the aldehyde **133** with the silylenol ether moiety remaining intact. Our final efforts were not rewarding, as this substrate also proved to be unsuitable for the macrocyclization under the Nozaki-Hiyama-Kishi protocol.

Scheme 37



IV.3. Intermolcular NHK Coupling and Barbier Macrocyclization

At this stage, convinced that an intramolecular Nozaki-Hiyama-Kishi reaction was not a viable option to close the 16-membered macrocycle, the decision was made to pursue a different route. An alternative was to first conduct an *inter*molecular Nozaki-Hiyama-Kishi coupling followed by an *intra*molecular Barbier-type cyclization (Figure 14). Unlike the intramolecular macrocyclization, the possibility of achieving a diastereoselective intermolecular Cr/Ni-mediated coupling was slim in the absence of any nearby stereocontrol elements. While this difficulty could be overcome either through an oxidation/reduction sequence or a Mitsunobu inversion, the second hurdle was more serious as the lithium-halogen exchange initiated intramolecular Barbier-type cyclization would have to be conducted on a very advanced intermediate.[81] However, the

success of this protocol in an intermolecular setting provided some confidence to pursue this route.

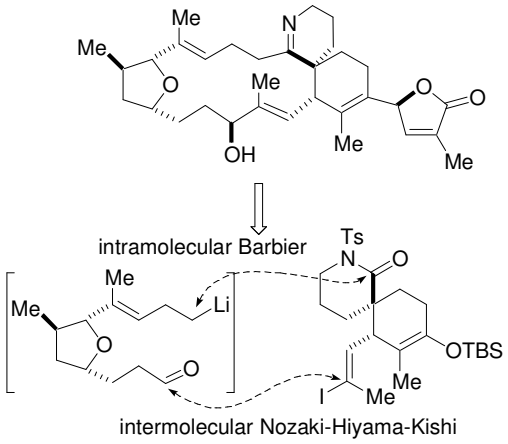
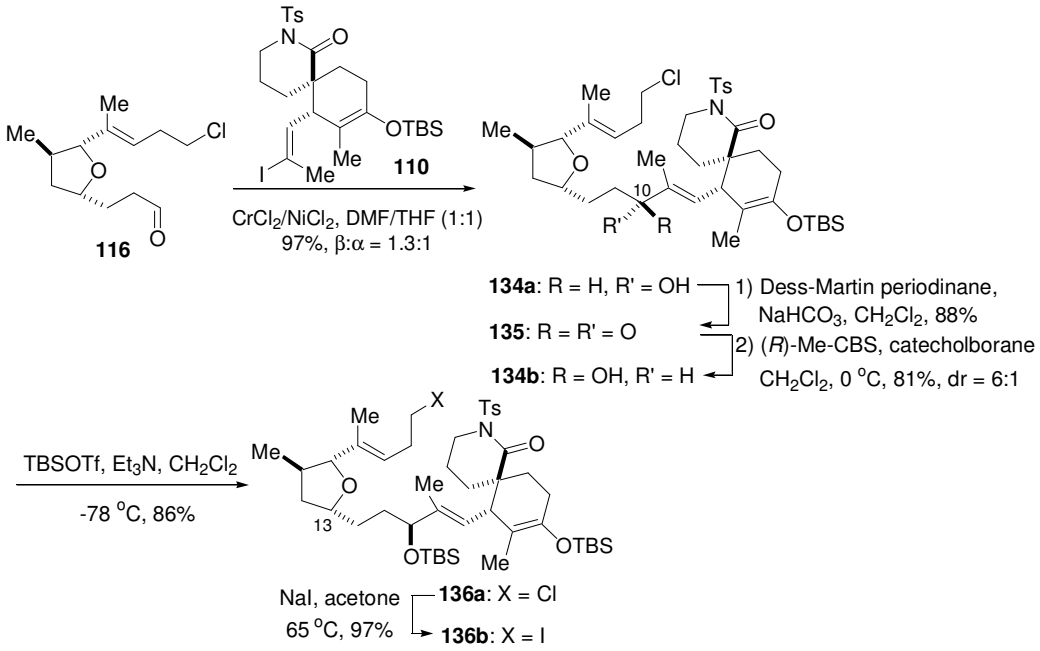


Figure 14. Revised plan for the macrocyclization (Plan II).

Pleasingly, it did not require much effort to find optimal conditions for the intermolecular Nozaki-Hiyama-Kishi coupling (Scheme 38). The smooth intermolecular coupling between vinyl iodide **110** and the aldehyde **116** provided the allylic alcohols **134** in excellent yield as a 1.3:1 mixture of epimers. Although modified Mosher ester analyses [82] did not provide unambiguous evidence for the assignment of the stereochemistry of either diastereomer, X-ray crystallographic analysis of a subsequent intermediate confirmed that the major epimer was the desired one having the β-OH configuration. Thus, the minor epimer **134a** was smoothly converted to the desired one through an oxidation/asymmetric reduction sequence using the Corey-Itsuno protocol.[83] The allylic alcohol **134b** was then protected as silyl ether and the C-13 epimer (derived from minor diastereomer from the allylation of the furanose **91b**, *cf.* Chapter III) could

be separated at this stage from the major diastereomer. Subsequent Finkelstein reaction set the stage for the crucial Barbier-type macrocyclization reaction.

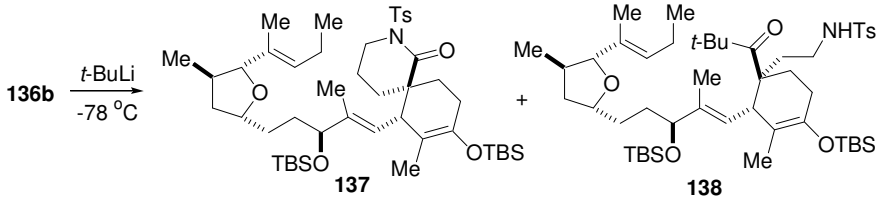
Scheme 38



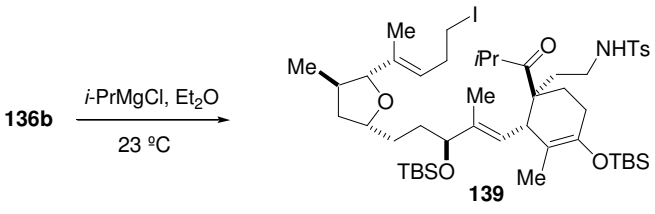
Our optimism quickly gave away to disappointment as attempted macrocyclization of the iodide **136b** under the conditions successful for the intermolecular process only led to minimal amounts of the desired product (Scheme 39). At least two competitive reaction pathways could be discerned after analysis of the reaction mixture. One was the unproductive quenching of the formed alkyllithium species either during the reaction or after workup. The other involved the opening of the *N*-tosyl lactam by the second molecule of *t*-BuLi leading to the formation of **138** after aqueous workup. Thus the intramolecular cyclization appears unable to compete with the intermolecular ring opening by *t*-BuLi under these reaction conditions. Screening of

solvents (Et_2O, THF and Trapp solvent) and additives (TMEDA, HMPA) all gave similar results.

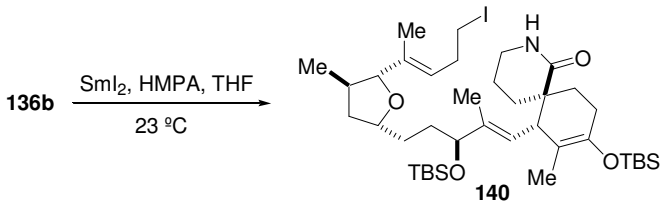
Scheme 39



We briefly considered the possibility of using a different metallating reagent for halogen-metal exchange for this Barbier-type process. Planned formation of a Grignard reagent upon treatment of the substrate **136b** with *i*-PrMgCl only led to the ring opening product **139** (Eq. 6),[84] whereas treatment with SmI_2 simply removed the *N*-tosyl group from lactam (Eq. 7).[85]



(6)

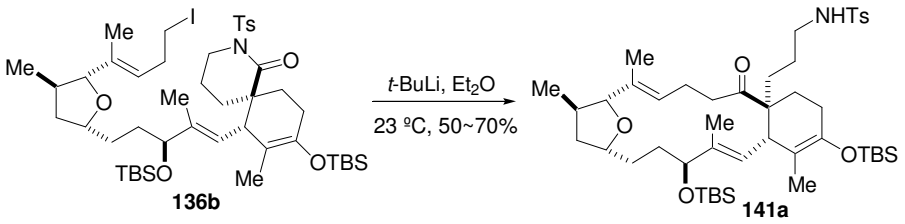


(7)

Thus, the narrow reactivity spectrum of the alkyl iodide **136b** towards nucleophiles, due to the presence of more than one electrophilic/reducible site, promoted us to reinvestigate the *t*-BuLi promoted Barbier cyclization (Scheme 40). One major breakthrough came when it was observed that the desired product **141a** became the major product simply by conducting the reaction at 0 ºC rather than -78 ºC. Further

increasing the reaction temperature to ambient temperature provided the desired product in an impressive 50-70% yield! It seems that the *intramolecular* cyclization of the alkyllithium species dominates at higher temperature (23 ºC) while the *intermolecular* addition of the second equivalent of *t*-BuLi is faster at lower temperature (-78 ºC).

Scheme 40



The exact reason for this dramatic effect of the temperature on the outcome of this reaction is currently not clear and must await further mechanistic studies. What is clear is that assuming the iodine-lithium exchange (Step A, Figure 15) is the fastest step, the *intramolecular* cyclization of the alkyllithium species (Step C) and *intermolecular* addition of the second equivalent of *t*-BuLi (Step B) have different temperature profiles, enabling preferential formation of one product by controlling reaction temperature. In addition, the critical role that the subtle conformation of the substrate played in facilitating the macrocyclization should not be overlooked as a closely related compound **142** did not undergo cyclization under identical conditions (Eq. 8).

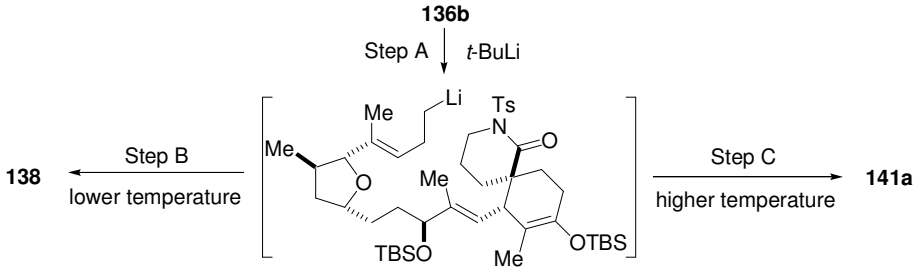
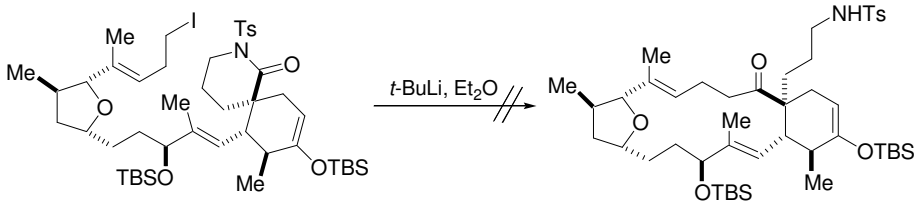


Figure 15. Competing reaction pathways during the Barbier cyclization of **136b**.



142 *iso*-**141a** (8)

CHAPTER V

BUTENOLIDE ANNULATION AND END GAME STRATEGY*

V.1. Butenolide Annulation: the Heck Route

A Heck reaction[86] was originally proposed for the annulation of butenolide (Figure 16). Thus, the Heck reaction would join the dihydrofuran **143** with the presumed intermediate vinyl triflate through the C4-C5 bond formation, while the methyl-bearing stereogenic center residing in dihydrofuran could serve as a stereocontrol element. Moreover, recent developments in asymmetric Heck reactions, such as those by Pfaltz,[87] Ozawa and Hiyashi, [88] provided some confidence in executing a double diastereoselective transformation if the inherent selectivity turned out to be low.

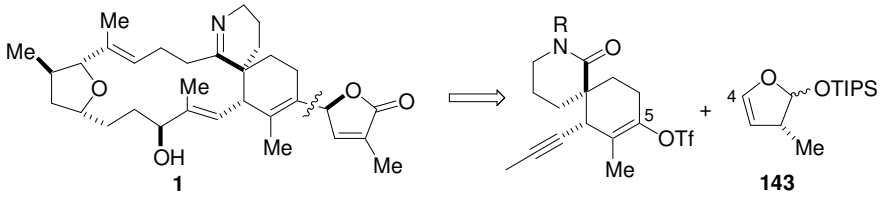


Figure 16. Planned Heck reaction for the butenolide annulation.

The synthesis of the enantiomer of dihydrofuran **143** was pursued starting with the known lactone **144**,[89] readily available in a few steps from (L)-malic acid (Scheme 41). Tosylation of the alcohol **144** was accompanied by the facile β-elimination, which accounted for the low yield of this transformation. DIBAL reduction of the tosylate

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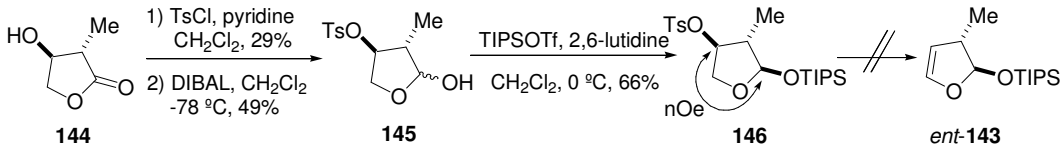
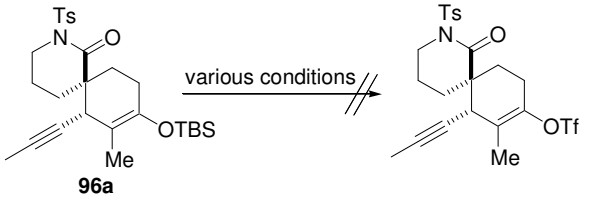
* Reproduced in part with permission from Diastereoselective, Vinylogous Mukaiyama Aldol Addition of Silyloxy Furans to Cyclic Ketones: Annulation of Butenolides and γ-Lactones. Kong, K.; Romo, D. *Org. Lett*. **2006**, *8*, 2909-2912. Copyright [2006] American Chemical Society.

provided a mixture of anomeric lactols **145** in *ca*. 2:1 ratio and the major β-epimer **146** was separated from the minor one after silyl protection. However, planned elimination of **146** under a variety of conditions did not lead to the desired product *ent*-**143** in any detectable amount. Oxidation[90] of a phenylselenide derived from the tosylate **146** (PhSeSePh, $NaBH_4$, EtOH, 31% yield) was also unsuccessful, leading to a mixture of unidentified polar products.

Scheme 41



Due to the difficulties encountered in the synthesis of the dihydrofuran **143**, and more seriously, our incapability to transform the silylenol ether **96a** to the vinyl triflate or any other derivatives suitable for the Heck coupling (Eq. 9), this route was eventually abandoned and a more productive strategy was pursued.



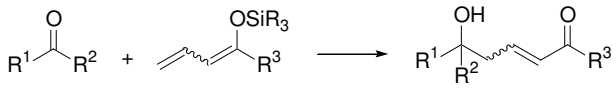
(9)

V.2. The Vinylogous Mukaiyama Aldol Addition to Ketones

After pursuing several unsuccessful strategies, it came to our attention that a vinylogous Mukaiyama aldol addition of a silyloxy furan to a ketone might be used for appending a butenolide. The Mukaiyama aldol reaction is arguably one of the most important carbon-carbon bond forming processes in an organic chemist's repertoire. The

vinylogous version of this process is an important extension and allows concise access to the δ-hydroxy-α,β-unsaturated carbonyl motif (Scheme 42).

Scheme 42



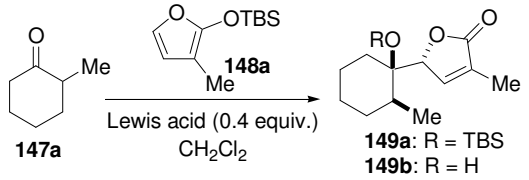
Addition of dienolsilanes to carbonyls or imines has been extensively used in organic synthesis.[91] Considering the significance of this process, it is surprising that there are only scant reports of dienolsilane additions to non-symmetric ketones.[92] This is in sharp contrast with aldehydes which have been extensively explored as substrates for the vinylogous Mukaiyama aldol addition. Presumably low reactivity and low diastereoselectivity have hampered the use of ketones as electrophiles.[93] Since ketones are less reactive than aldehydes towards nucleophilic addition, highly electrophilic ketones,[92b-9292d] such as pyruvate esters, have been used in the vinylogous Mukaiyama aldol reactions. Due to the greater difficulty of differentiating diastereotopic faces of ketones compared to aldehydes, the addition of silyloxyfurans to aliphatic ketones proceeded with only moderate diastereoselectivity in the absence of external chiral ligands.[92a] One solution to this difficulty was the use of tetronic acid derived dianions.[94] In this case, a chelation controlled process allowed the addition to proceed with good diastereoselectivity.

For the problem at hand, the direct attachment of the butenolide to a cyclohexanone substrate by a vinylogous Mukaiyama aldol reaction is very attractive. Furthermore, control of diastereoselectivity might be possible with cyclic ketones due to the conformational rigidity of such substrates, which would lead to better facial

differentiation with the dienolsilane nucleophiles. In addition to providing a concise and convergent route to the gymnodimine problem, if successful, this process could find a broader application for appending butenolides and γ-lactones in natural products possessing such arrays, such as the spirolides (*cf*. Figure 2, **12**-**16**, Chapter I).

Guided by the structure of gymnodimine, 2-methylcyclohexanone (**147a**) and 3-methyl-2-(*tert*-butyldimethyl)silyloxy furan **148a**[95] were chosen as model substrates. We were pleased to find that the Mukaiyama aldol addition afforded the δ-hydroxy butenolide **149a/149b** in good yield in the presence of a variety of Lewis acids (Table 3). The product was obtained as a mixture of the tertiary alcohol **149b** and the corresponding TBS silylether **149a**. The presence of alcohol product **149b** after the reaction has reached completion has important mechanistic implication. It indicates that silylation, whether being an inter or intramolecular silyl transfer, of the aldolate intermediate is a slow step. Thus the silicon-species generated might compete and become the actual catalyst in the reaction (entries 1-3). [96] In most cases, the diastereoselectivity was good, with only two adducts obtained out of four possible stereoisomers for all the Lewis acids screened, with the exception of $ZnBr_2$ which led to poor diastereoselectivity (entry 4). The relative stereochemistry of the major diastereomer **149b** and minor diastereomer *epi*-**149b** was unambiguously established by X-ray crystallographic analysis (Figure 17).

Table 3. Vinylogous Mukaiyama Aldol Reaction of Cyclohexanone **147a** with Silyloxy Furan **148a**: Effect of Lewis Acids



entry	condition	% yield **149a**	dr[b]
1	$BF_3{\cdot}OEt_2$, -78 ºC	67 (17)	10 : 1
2	$TiCl_4$, -78 ºC	70 (9)	9 : 1
3	$SnCl_4$, -78 ºC	58 (13)	9 : 1
4	$ZnBr_2$, -20 ºC[c]	(~20)	2 : 2 : 1 : 1
5	TMSOTf, -78 ºC	16 (69)	11 : 1

[a] Refers to isolated, purified yield. [b] Determined on crude reaction mixture by ^{1}H NMR integration. [c] 1.0 equiv of Lewis acid was employed.

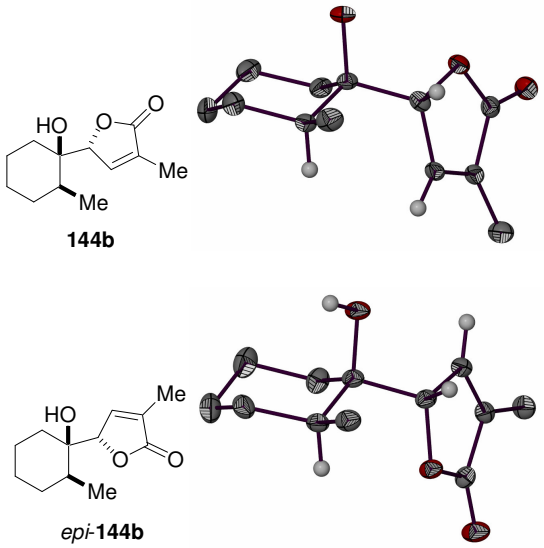


Figure 17. ORTEP representations of X-ray crystal structures of **149b** and *epi*-**149b** (some hydrogen atoms omitted for clarity).

Apparently, during this reaction the silyloxyfuran **148a** approaches the cyclic ketone **147a** in a facially selective manner to avoid 1, 3-diaxial interactions. Consistent with the Jefford and Brown model,[97] a Diels-Alder reaction-like arrangement between the silyloxy furan and the ketone (*si*/*si* face, A, Figure 18) leads to the syn adducts **149a/149b**, while *si*/*re* face approach (B) is less desirable due to the unfavorable interaction of the α-methyl substituent of the ketone **147a** with the C4 hydrogen of the silyloxy furan **148a**.

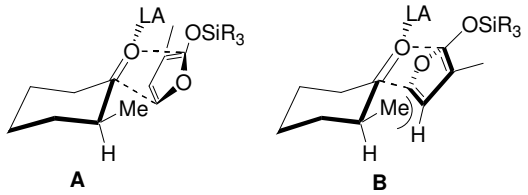
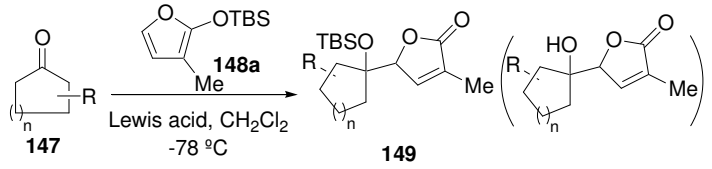


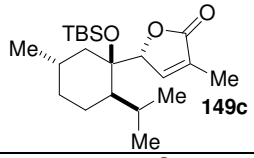
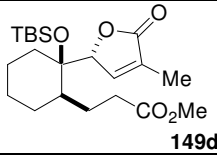
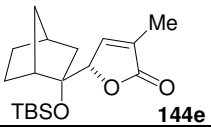
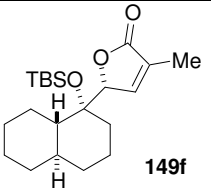
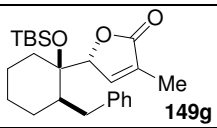
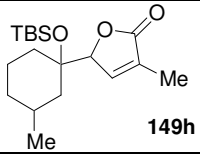
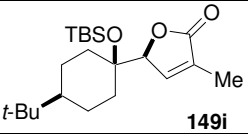
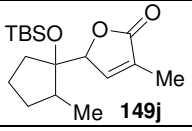
Figure 18. Stereochemical models for the Mukaiyama aldol addition between 2-methylcyclohexanone (**147a**) and silyloxy furan **148a**.

The scope of the reaction was explored further by use of other ketone substrates. While TMSOTf gave the best yield and diastereoselectivity on the model substrate, further experiments indicated that $TiCl_4$ had greater substrate generality and promoted the addition reaction even at -78 ºC. Moreover, Ti(IV) complexes constitute a well-studied platform for asymmetric processes, thus providing impetus for further study. The Mukaiyama aldol addition proceeded with various α-substituted cyclohexanones in good

yields with moderate to high diastereoselectivity (entries 1-5, Table 4). A pendant ester was tolerated (entry 2) and bicyclic ketones, such as norcamphor and *trans*-decalone, also provided good diastereoselectivities as expected (entries 3, 4). However, the addition reaction was susceptible to steric factors, as evidenced by the finding that while norcamphor reacted efficiently (entry 3), camphor was totally inert even at elevated temperatures for extended times (not shown). From these examples, it appears that the α-substituent was responsible for high diastereoselectivity, since 3-methyl cyclohexanone and 4-*tert*-butyl cyclohexanone provided good yields but poor diastereoselectivity (entries 6, 7). This could be easily understood since the lack of the unfavorable interaction (*cf.* B in Figure 18) would reduce the energy difference of these two arrangements when an α-substituent is absent (Figure 18, A and B). The conformational flexibility and the absence of prominent 1,3-diaxial interactions probably account for the poor diastereoselectivity when 2-methyl cyclopentanone was used as a substrate (entry 8).

Table 4. Substrate Scope of the Mukaiyama Aldol Addition



entry	Lewis acid	product	yield (%)[d]	dr[e]
1[a]	$TiCl_4$ (3 equiv.)	 **149c**	14 (63)	10 : 1
2[a]	$TiCl_4$ (3 equiv.)	 **149d**	48(28)	13 : 1
3[b]	$TiCl_4$ (3 equiv)	 **144e**	56(34)	5 : 1
4[b]	$TiCl_4$ (3 equiv.)	 **149f**	50(31)	9 : 1
5[a]	$TiCl_4$ (3 equiv.)	 **149g**	34(42)	10 : 1
6[c]	TMSOTf (0.4 equiv.)	 **149h**	33 (66)	1.5 : 1.5 : 1 : 1
7[b]	TMSOTf (0.4 equiv.)	 **149i**	19 (70)	1.7 : 1
8[c]	$TiCl_4$ (0.4 equiv.)	 **149j**	47 (7)	3.6 : 2.3 : 1

[a] The relative stereochemistry of the product was predicted by the Jefford and Brown model analogous to **149a**. [b] The relative stereochemistry of the major product was established by X-ray crystallographic analysis (Figure 19). [c] Stereochemistry not known. [d] Refers to isolated, purified yield. Yield in parenthesis refers to the non-silylated adduct. [e] Determined on crude reaction mixture by integration of ^{1}H NMR.

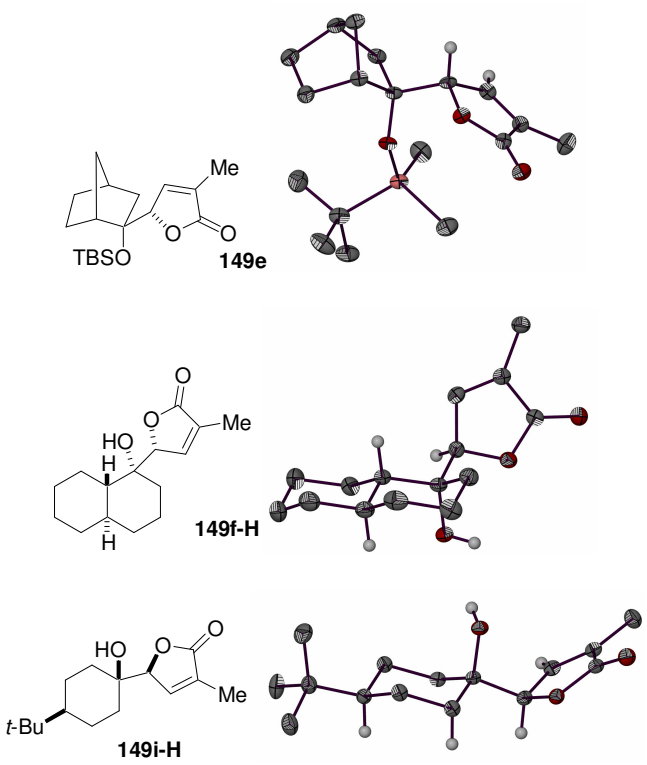
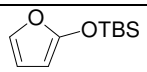
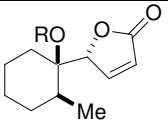
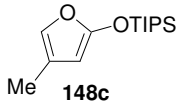
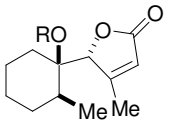
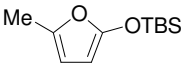
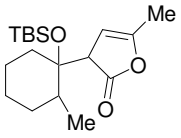


Figure 19. ORTEP representations of X-ray crystal structures of **149e**, **149f**, and **149i** (some hydrogen atoms omitted for clarity).

The silyloxyfuran partner could also be varied (Table 5). Unsubstituted silyloxy furan **148b** and 4-methyl silyloxy furan **148c** both reacted to give the addition adducts in good yield and diastereoselectivity (entries 1 and 2). The fact that the reaction of 4-methyl silyloxy furan **148c** provided only one detectable diastereomer further validated

the rationale in Figure 18. In this case, unfavored interactions as in B (Figure 18) would be more prominent when a vinylic hydrogen is substituted by a methyl group. Intriguingly, the addition of 5-methylsilyloxy furan **148d** to ketone **147a** occured at the α-position (entry 3). Since with silyloxyfuran substrates, γ-addition is favored electronically in Lewis acid promoted vinylogous Mukaiyama aldol additions,[91b] steric reasons must be responsible for the reversal in regioselectivity.[98]

Table 5. Scope of the Mukaiyama Aldol Addition: Reaction of Various Silyloxyfurans with 2-Methylcyclohexanone (**147a**)

entry[a]	silyloxyfuran	product and yield (%)[a]	dr[b]
1	 **148b**	 **149k**: R = TBS, 64 % R = H, 6 %	10 : 1
2	 **148c**	 **149l**: R = TIPS, 66 % R = H, 30 %	>20 : 1
3	 **148d**	 **149m**: 53 %	2 : 1

[a] Reaction conditions: $TiCl_4$ (0.4 equiv.), CH_2Cl_2, -78 ºC. [b] Determined on crude reaction mixture by ^1H NMR integration. The relative stereochemistry of the major product was established by X-ray crystallographic analysis (Figure 20).

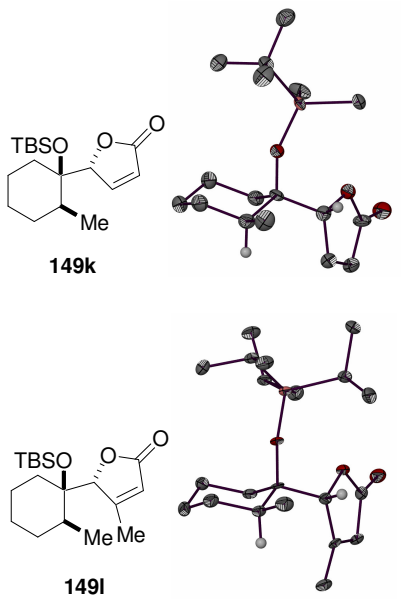
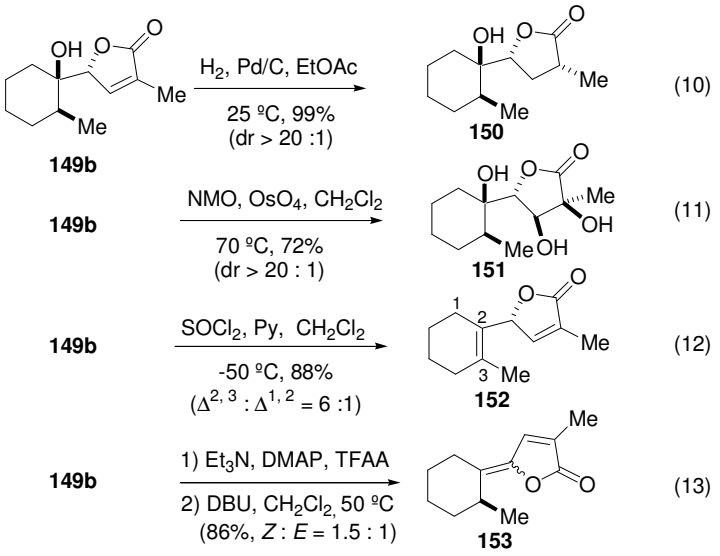


Figure 20. ORTEP representations of X-ray crystal structures of **149k** and **149l** (some hydrogen atoms omitted for clarity).

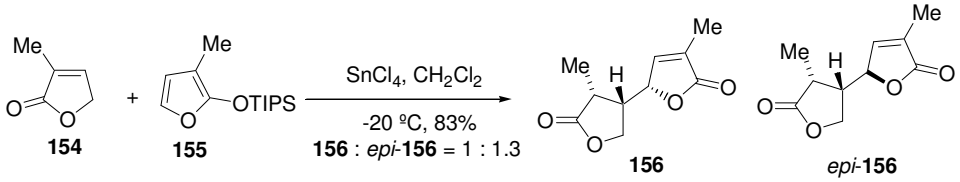
The δ-hydroxy butenolide adducts **149a**-**149m** allow for further functionalization to access various motifs found in natural products. Thus, hydrogenation of butenolide **149b** afforded the γ-lactone **150** in excellent yield as a single diastereomer (Eq. 10). Dihydroxylation was conducted to give triol **151** in excellent diastereoselectivity (Eq. 11). Dehydration under thionyl chloride/pyridine conditions[99] led to cyclohexene **152** with moderate regioselectivity (Eq. 12), the major isomer being a substructure of gymnodimine and the spirolides. Alternatively treatment of trifluoroacetate derived from **149b** led to exocylic elimination adduct **153** as a mixture of *E*/*Z* isomers (Eq. 13). The butenolide was inert towards conjugate addition using methyl cuprate and deoxygenation of the tertiary alcohol proved to be fruitless.



V.3. Silyloxyfuran Dimerization: Some Serendipitous Findings

During the course of optimizing the vinylogous Mukaiyama aldol addition reactions, we observed some dimerization products derived from the silyloxyfurans. Indeed in a separate experiment it was found that the silyloxyfuran **155** undergoes a Mukaiyama-Michael addition by treatment of a mixture of furanone **154** and the silyloxyfuran **155** with $SnCl_4$ (Scheme 43). This led to the isolation of dimers **156** and *epi*-**156** as a 1 : 1.3 mixture of diastereomers in good yield. The relative stereochemistry of the major diastereomer *epi*-**156** was confirmed through single crystal X-ray analysis (Figure 21).

Scheme 43



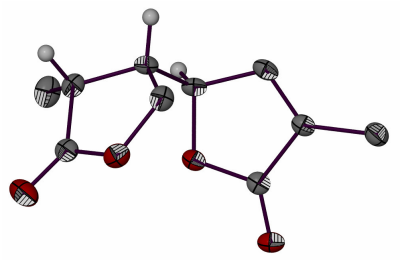
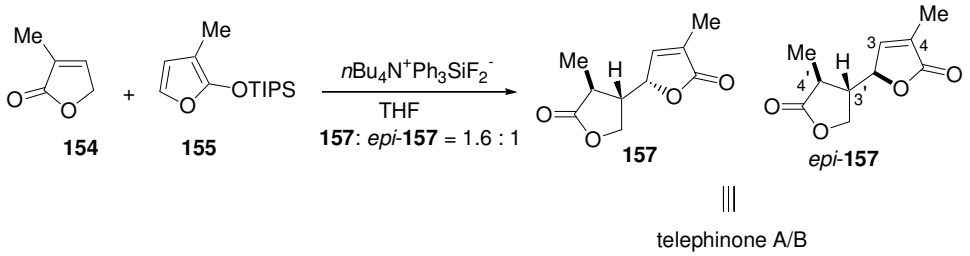
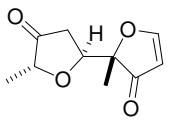


Figure 21. ORTEP representation of X-ray crystal structure of *epi*-**156** (some hydrogen atoms omitted for clarity).

More intriguingly, the fluoride promoted dimerization gave an inseparable mixture of *trans*-substituted γ-lactones **157** and *epi*-**157** instead (Scheme 44). These dimers are epimeric with **156** and *epi*-**156** at C-4' center, respectively. Literature searching revealed that they are actually plant-derived natural products telephinone A and B isolated in 1990 by Fung and coworkers![100] This unexpected yet not surprising finding along with the fact that the natural products were also isolated as racemates leads us to speculate the biosynthetic origin of these second metabolites. Furthermore, the dimerization process also implicates its application in synthesis of other natural occuring dimers such as chilenone A (Figure 22).[101]

Scheme 44





chilenone A

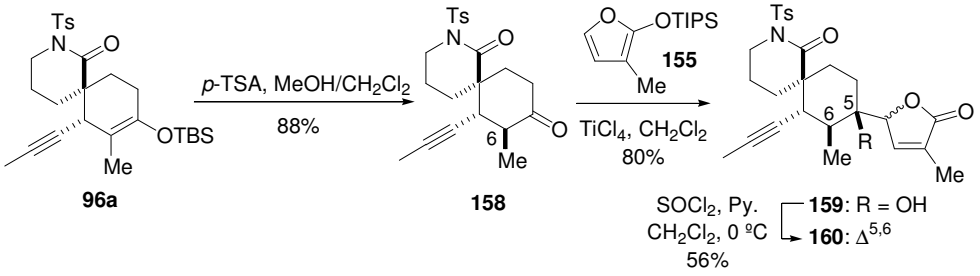
Figure 22. Structure of chilenone A.

V.4. Butenolide Annulation and Further Manipulations

After successfully developing a protocol for appending a butenolide to cyclic ketones, we thought it would be prudent to test the applicability of this reaction on more advanced models before application to gymnodimine synthesis. Thus, two substrates were chosen for this purpose, the first was spirolactam ketone **158** (Scheme 45) and the other was hydroxyl ketones **161** (Scheme 46). It was shown later that the results garnered from these model studies were indispensable for the final realization of this strategy in the synthesis of gymnodimine.

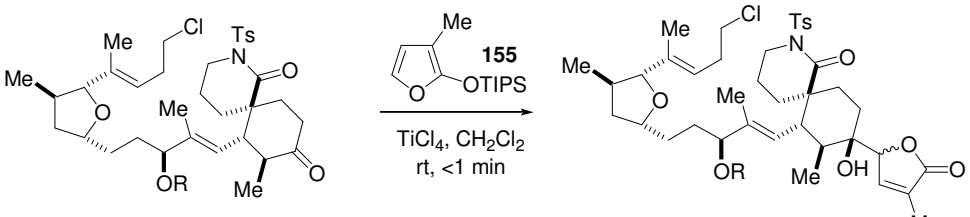
The first model ketone **158** was derived from the racemic silylenol ether **96a** after acid hydrolysis (Scheme 45). The low reactivity of the ketone **158** towards aldol addition dictated use of higher reaction temperatures (-20 ºC or higher) and the more stable triisopropylsilyloxyfuran **155**[102] as utilization of the TBS-counterpart **148a** in the reaction only led to silyloxyfuran hydrolysis. As a result this led to diminished diastereoselectivity and all four possible diastereomers were isolated. Some efforts were devoted to improve the diastereoselectivity by using external chiral sources, such as Carreira's BINAP·CuF_2 system[103] and BINOL·Ti(IV) system,[104] without much success. The alcohols **159** could be dehydrated as described previously providing the desired olefins **160** along with its regioisomers.

Scheme 45



Initial experiments with the more advanced model ketone **161a** were rather disappointing. No desired product could be detected, the major reaction pathways being cleavage of the silyl group and elimination of the allylic alcohol to form a diene (Scheme 46). Switching to a more stable substrate **161b** did not alter the reaction outcome. The tendency of the silyl ether **161a** and **161b** to undergo elimination called for the use of a ketone with a free hydroxyl group. Indeed, when the ketone **161c** and the silyloxyfuran **155** were treated with $TiCl_4$, a small amount of the desired product **162c** was isolated. Further studies revealed that the aldol addition of silyloxyfuran to the ketone **161c** is a fast process followed by slower decomposition of the addition adduct after a few minutes. Addition of a hindered base such as 2,6-di-*tert*-butyl-4-methylpyridine to scavenge adventitious hydrochloric acid did not lead to any notable improvement of yield. Taken together, the optimal protocol consisted of slow addition of $TiCl_4$ to the ketone **161c** in the presence of large excess of silyloxyfuran **155** followed by a fast quenching of the reaction. In this way the desired product **162c** was obtained in greater than 50% yield.

Scheme 46

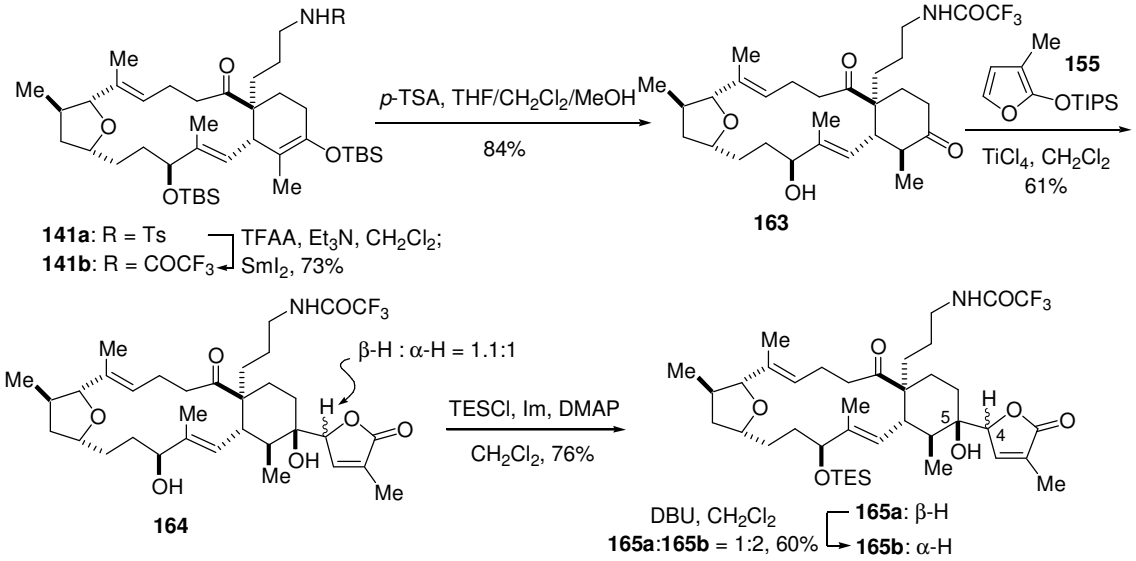


161a: R = TBS
161b: R = TIPS
161c: R = H

162a: R = TBS, 0%
162b: R = TIPS, 0%
162c: R = H, >50%

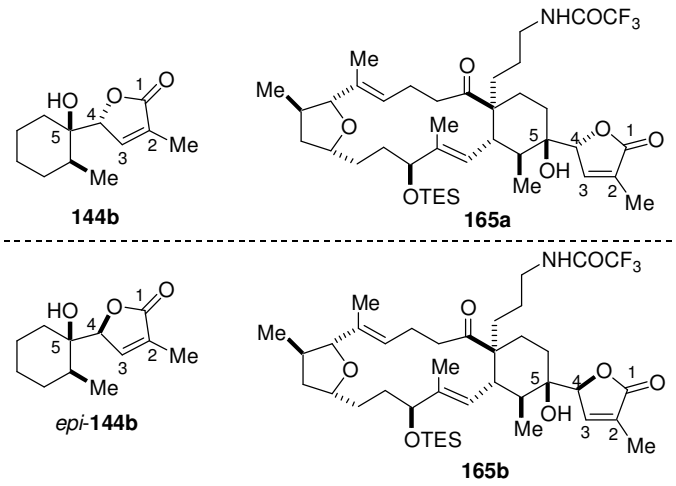
Armed with the valuable information gained from these model studies, we then embarked on the task of completing the synthesis of gymnodimine. Before moving to the key Mukaiyama aldol addition step, it was necessary to switch the robust tosyl group to a more labile trifluoroacetamide as described before (Scheme 47). Both silyl groups in **141b** were then removed under acidic conditions furnishing the hydroxyl ketone **163**, whose structure was firmly established through X-ray analysis (Figure 23). Brief exposure of the mixture of the ketone **163** and silyloxyfuran **155** to $TiCl_4$ provided the γ-hydroxy-α,β-unsaturated lactones **164** (dr = 1.1:1) in excellent yield. The two epimeric tertiary alcohols **164** were readily separated after silyl protection. It was found that the undesired silyl ether **165a** could be epimerized to 2:1 mixture of **165b/165a** upon treatment with DBU at ambient temperature. Thus it allows virtually complete utilization of the epimeric lactones **165**.

Scheme 47



The stereochemistry of the butenolides **165a/165b** was assigned based on the following arguments. The fact that the two compounds are interconvertable under basic conditions implies that they are epimeric at C-4 position. Furthermore, the observation that alcohol **165b** underwent dehydration to give predominantly $\Delta^{5,6}$ olefin (*cf*. Scheme 48) suggests the stereochemistry of the tertiary alcohol center C5 is as depicted in Scheme 47 as *anti*-elimination is preferential under $SOCl_2$/base conditions[105]. Finally, comparison of ^{13}C NMRs of **165a** and **165b** with simpler compounds **144b**/*epi*-**144b,** whose relative stereochemistry has been firmed established through X-ray crystallographic analysis, enabled the assignment of C5 stereochemistry of **165a/165b** with much confidence (Table 6).

Table 6. Comparison of ^{13}C NMR between Butenolides **165a/165b** with Model Compounds **144b**/*epi*-**144b**



	^{13}C NMR ($CDCl_3$) Chemical Shift (ppm)					
	144b	**165a**	$\Delta_1 = \delta_{\mathbf{165a}} - \delta_{\mathbf{144b}}$	*epi*-**144b**	**165b**	$\Delta_2 = \delta_{\mathbf{165b}} - \delta_{\textit{epi}\text{-}\mathbf{144b}}$
C1	174.1	173.5	-0.6	174.3	173.9	-0.4
C2	131.1	132.1	+1.0	130.6	131.1	+0.5
C3	145.1	144.0	-1.1	147.8	147.0	-0.8
C4	86.3	86.1	-0.2	83.1	83.0	-0.1
C5	74.5	73.9	-0.6	74.4	73.8	-0.6

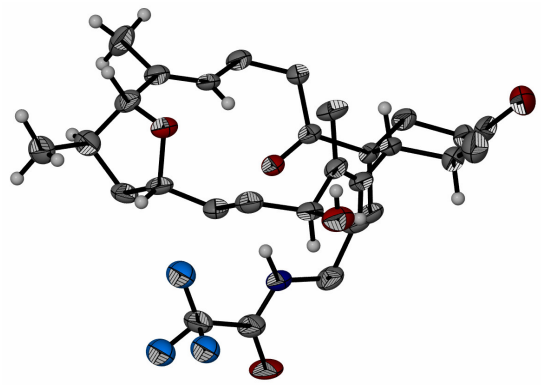


Figure 23. ORTEP representation of X-ray crystal structure of **163** (some hydrogen atoms omitted for clarity).

While dehydration of the tertiary alcohol **165b** under previously described conditions (pyridine, $SOCl_2$) required higher temperature and was capricious, use of a stronger base Et_3N was more reliable and afforded the desired olefin **166a** along with its $\Delta^{5,24}$ regioisomer (Scheme 48). Interestingly, dehydration of **165a** under identical conditions led to the undesired regioisomer as the major product. The ^{13}C NMR of **166b** is in good agreement with that of gymnodimine (Table 7).

Scheme 48

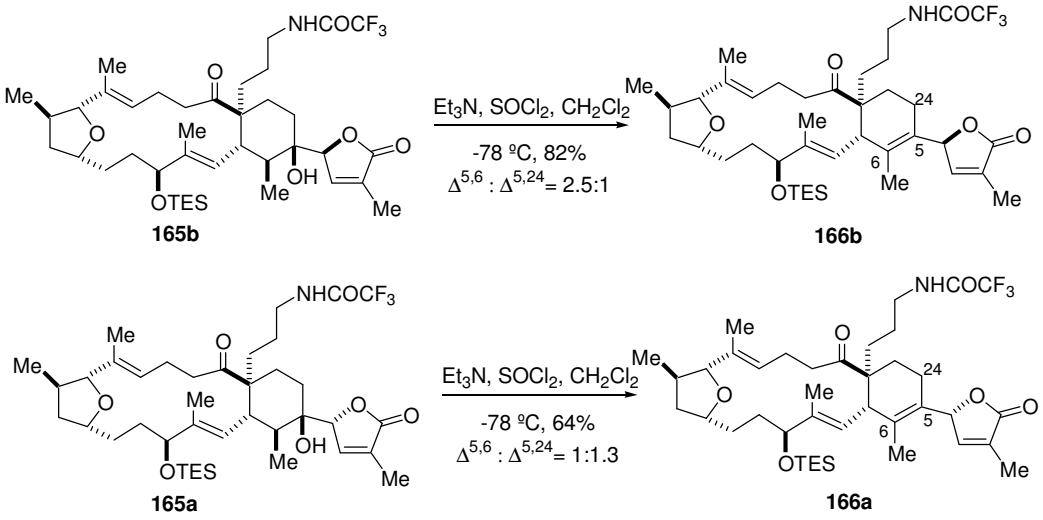
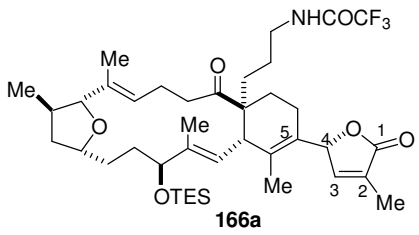
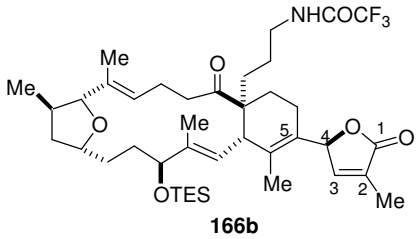


Table 7. Comparison of ^{13}C NMR between Gymnodimine, **166a** and **166b**



166a



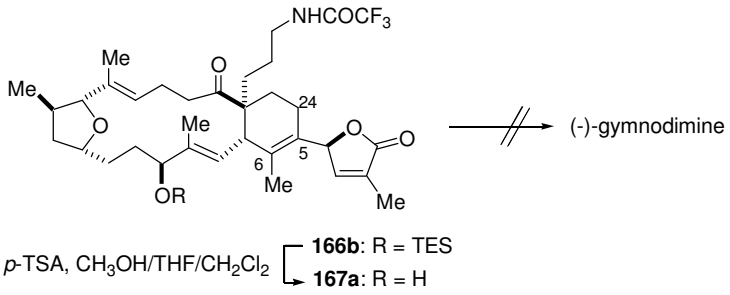
166b

^{13}C NMR ($CDCl_3$) Chemical Shift (ppm)					
	Gymnodimine	**166a**	**166b**	$\Delta_1 = \delta_{166a} - \delta_{gymno}$	$\Delta_2 = \delta_{166b} - \delta_{gymno}$
C1	174.5	174.4	174.6	-0.1	+0.1
C2	130.2	131.1	130.4	+0.9	+0.2
C3	146.8	147.2	146.6	+0.4	-0.2
C4	80.4	79.5	80.3	-0.9	-0.1
C5	124.7	122.3	122.3	-2.4	-2.4
C6	132.5	135.5	132.6	+3.0	+0.1
C7	46.1	46.9	46.7	+0.8	+0.6
C8	126.7	124.8	125.2	-1.9	-1.5
C9	139.6	142.6	142.6	+3.0	+3.0
C10	79.2	79.3	79.2	+0.1	0.0
C13	77.8	78.0	78.1	+0.2	+0.3
C16	89.5	89.1	89.1	-0.4	-0.4
C17	134.9	135.8	135.9	+0.9	+1.0
C18	123.6	122.4	122.3	-1.2	-1.3
C22	41.6	40.4	40.4	-1.2	-1.2
Average				1.16	0.83

The silyl ether was removed under mild acidic conditions to provide the penultimate alcohol **167a** (Scheme 49). Unfortunately, application of previously described basic conditions to hydrolyze the trifluoroacetamide **167a** was detrimental to

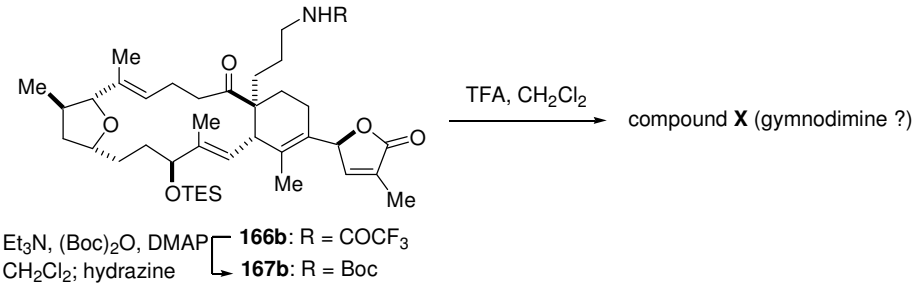
this substrate. A variety of basic conditions such as K_2CO_3/MeOH, $NH_3 \cdot H_2O$/MeOH, LiOH/THF/H_2O, $NaHCO_3$/MeOH were screened and all led to decomposition of this sensitive substrate, in good agreement with Miles' finding that gymnodimine is instable under neutral and alkaline pH values.[36] Attempted acid hydrolysis (2M HCl/MeOH, 44 ºC)[106] also proved too harsh for this highly functionalized substrate.

Scheme 49



Faced with these setbacks, the decision was made to change the trifluoroacetamide group to a more acid labile group such as *t*-butoxycarbonyl group (Scheme 50). Hence, treatment of the trifluoroacetamide **166a** with $(Boc)_2O$ followed by brief exposure to hydrazine provided the *N*-Boc amine **167b**.[107] Acid hydrolysis of the Boc amine **167b** under standard conditions was accompanied by removal of the silyl group providing an unidentified compound **X** after basic workup. Mass spectrum of this compound **X** matched with the natural product, as well as R_f value (5% MeOH/CH_2Cl_2). However, ^{1}H NMR of this compound did not completely correlate with the reported data. Lack of access to an authentic sample made direct comparison impossible and thus a total synthesis of gymnodimine can not be claimed at this time.

Scheme 50


NHR
Me
O
Me
O
Me
O
O
OTES
Me
Me
TFA, CH2Cl2
compound X (gymnodimine ?)
Et3N, (Boc)2O, DMAP
CH2Cl2; hydrazine
166b: R = COCF3
167b: R = Boc

CHAPTER VI

SYNTHESIS OF A GYMNODIMINE IMMUNOGEN SUITABLE FOR ANTIBODY PRODUCTION

VI.1. Strategy for Immunogen Synthesis

When confronted with the invasion of foreign substances, a vertebrate is capable of eliciting an immune response to destroy these entities, which are called “antigens” or “immunogens”. However, small molecules (so called “haptens”) in general cannot cause an immune response on their own, rather they can be made immunogenic by coupling to a suitable carrier molecule. The proteins at the heart of the humoral immune response are antibodies produced by B cells, which could specifically bind to these antigens and eventually lead to their phagocytosis.[108]

The specific interaction between antibody-antigen is the basis for a variety of important analytical procedures, such as enzyme-linked immunosorbent assay (ELISA). In a typical direct ELISA, an antigen is added to a solid surface and absorbs passively on incubation, to which antibodies specific for the antigen and labeled with an enzyme are added. The enzyme would then catalyze a reaction that forms a colored product, which serves as an in-situ readout of the concentration of the antigen both qualitatively and quantitatively. As the first step towards development of an efficient ELISA to monitor gymnodimines, we needed to synthesis suitable haptens and attach them through a linker to a carrier protein (Figure 24).

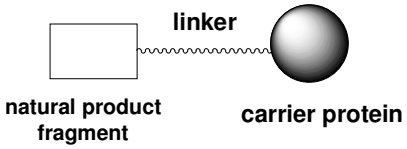


Figure 24. The generic structure of an immunogen.

An efficient hapten should at least mimic some of the structural elements of gymnodimine in order to elicit positive immune responses. Because of the likelihood of the cyclic imine functioning as the pharmacophore of gymnodimines and the instability of the butenolide at neutral and alkaline pH values, the spirocyclic imine hapten **S** was designed (Figure 25). It conserves the important substructure for biological activities and eliminates the unstable elements. In addition, it does not incorporate the variable portion of gymnodimines (*cf.* gymnodimines B and C, Figure 1) and thus the antibodies raised against this hapten should be able to recognize all gymnodimine congeners.

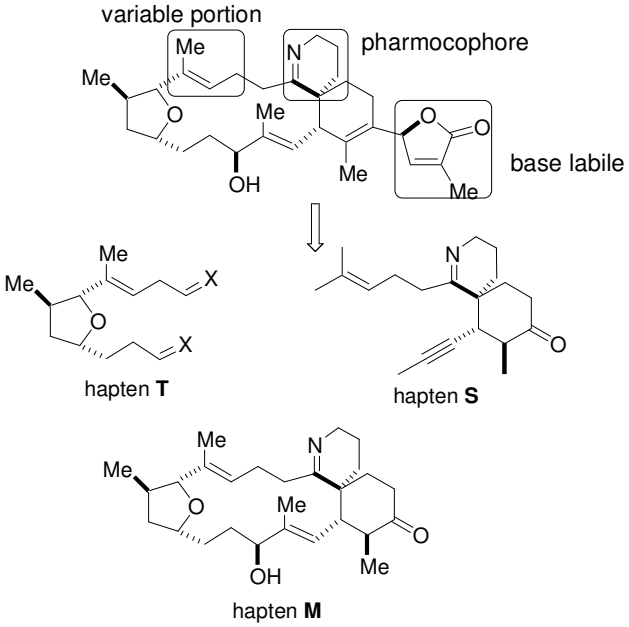


Figure 25. Designed haptens based on structures of gymnodimines.

Even though hapten **T** derived from the tetrahydrofuran does not seem ideal as it lacks the key imine portion, it is structurally complementary to hapten **S** and was proposed to produce antibodies against the tetrahydrofuran portion of gymnodimine. Furthermore, this hapten could provide some insight into the structure-activity relationship of the toxicity of gymnodimine.

The hapten **M** retains most structural and stereochemical information of the natural product. The relatively rigid skeleton of this hapten should mimic the structure of gymnodimine well and the chance of getting positive immune responses is high. However, it would not be expected to lead to a congener-independent immunoassay as it incorporates the variable region.

The design of a suitable linker is not trivial.[109] It should be water-soluble, readily available, stable at physiological pH, and finally of a sufficient length to allow appropriate presentation of all the important recognition elements of the hapten. Based on these principles the amide linker **L** was designed, which would be attached to haptens through an oxime ether from the *N*-terminus (Figure 26).[110] The *C*-terminus would be conjugated to a carrier protein through amide bond formation.

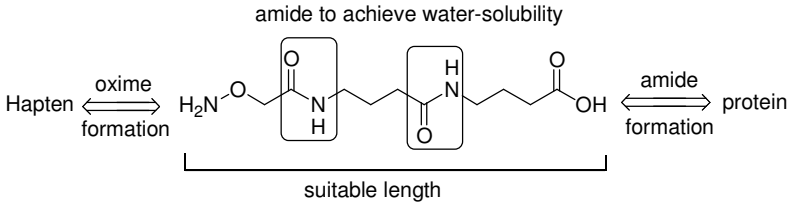


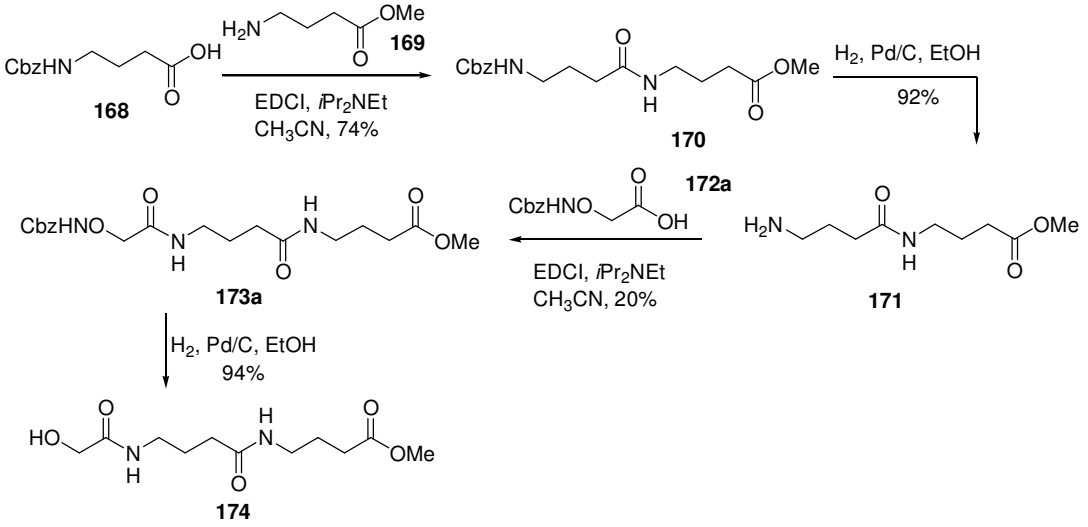
Figure 26. Designed linker **L**.

VI.2. Synthesis of the Linker and a Tetrahydrofuran Hapten

VI.2.1. Synthesis of the Linker

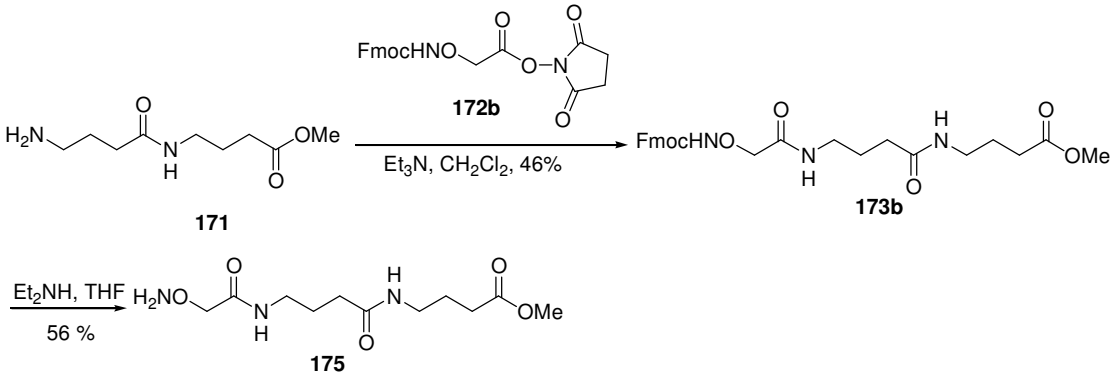
The synthesis of the linker commenced with the amide coupling between the commercially available methyl 4-aminobutyrate (**169**) and *N*-Cbz γ-amino butyric acid **168** (Scheme 51).[111] The dipeptide **170** was then deprotected through hydrogenolysis. The following amide bond formation was complicated by insolubility of the amine **171** in common polar solvents (THF, DMF, and EtOH) in pure form. Thus, it is more convenient to use **171** as a THF/EtOH solution. The coupling between this amine and Cbz-aminooxyacetic acid **172a** provided alkoxyamine **173a**. However, hydrogenolysis of this compound led to cleavage of the N-O bond and provided the alcohol **174** only.

Scheme 51



Hence, a base labile Fmoc group was used for the protection of the *N*-terminus (Scheme 52). Coupling between the activated acid **172b** and the primary amine **171** provided the alkoxyamine **173b**. Upon treatment with Et_2NH, essentially pure hydroxylamine **175** was obtained after washing the crude reaction mixture with EtOAc.

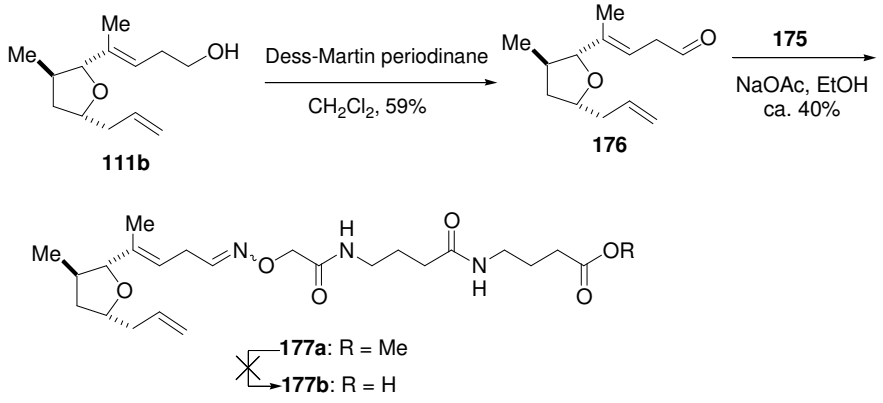
Scheme 52



VI.2.2. Synthesis of a THF Hapten

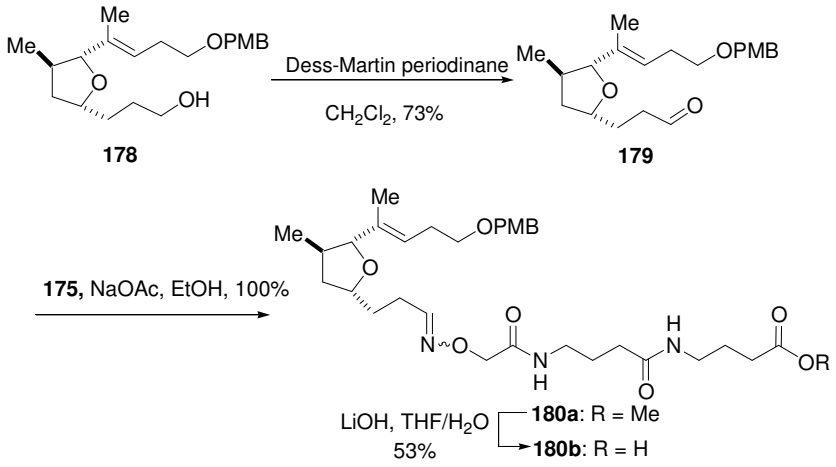
The synthesis of the hapten **T** derived from the tetrahydrofuran was attempted first due to its ease of access (Scheme 53). The previously synthesized alcohol **111b** (*cf.* Chapter III) was oxidized to provide the aldehyde **176** which proved to be rather sensitive towards common manipulations, presumably due to the tendency of the internal double bond to isomerize. The oxime ether formation between this aldehyde and the amine **175** provided the ester **177a** in moderate yield. However, the subsequent basic hydrolysis of **177a** provided the acid **177b** at best in a semipure form which underwent decomposition upon attempted further purification.

Scheme 53



To avoid the problematic double bond isomerization, we decided to attach the linker to the lower arm of the tetrahydrofuran. The synthetic intermediate alcohol **178** was oxidized and treated with the amine **175** in the presence of sodium acetate, leading to the oxime **180a** as a mixture of geometric isomers (Scheme 54). Basic hydrolysis led to the carboxylic acid **180b** in good yield. This hapten has been attached to a carrier protein in our collaborator's laboratory (Prof. Chris Elliott, Queen's College at Belfast, Ireland). Immunization with this antigen led to the production of antibodies (pAbs). However disappointingly, the derived antibodies do not bind to gymnodimine itself. Therefore, further experiments are required to find a suitable hapten that leads to antibodies capable of recognizing gymnodimine.

Scheme 54



CHAPTER VII

CONCLUSIONS

In summary, construction of the complete carbon skeleton of the marine toxin (-)-gymnodimine has been accomplished in a convergent manner in 23 steps (the longest linear sequence, Scheme 55). Key features of the synthesis include a catalytic, asymmetric Diels-Alder reaction to construct the spirolactam core, an intermolecular Nozaki-Hiyama-Kishi coupling for fragment coupling, a Barbier-type reaction for the macrocyclization and finally, a vinylogous Mukaiyama aldol addition to attach the appendant butenolide.

The bis(oxazoline)·Cu(II) complex catalyzed asymmetric Diels-Alder reaction provided the spirolactam core **96b** with high diastereo- and enantioselectivity. An improved procedure for hydrostannylation of the hindered internal triple bond in **96a** was discovered by slow addition of tributyltin hydride to minimize formation of hydrogenated byproduct.

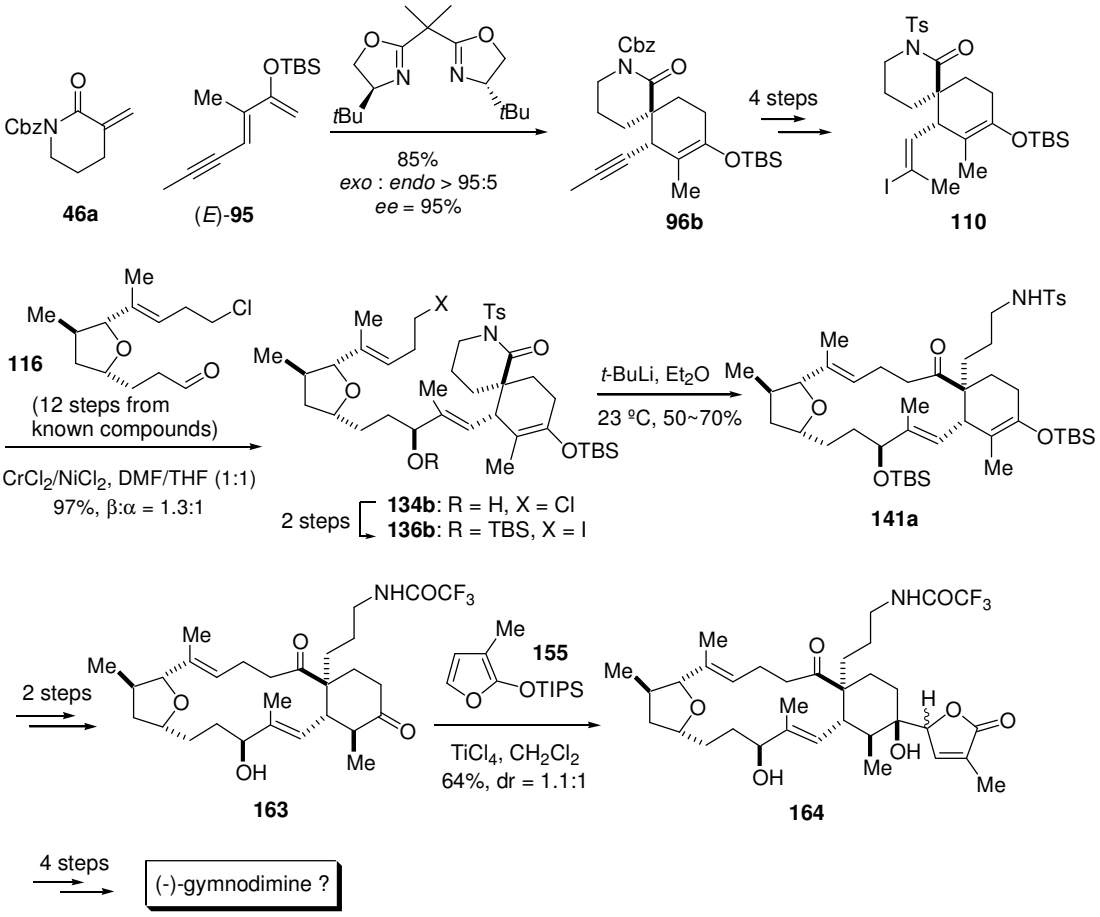
The first approach for fragment coupling employed an intermolecular Barbier-type process providing the coupling adduct **125a** in excellent yield. This route was eventually abandoned due to the failure of the Nozaki-Hiyama-Kishi macrocyclization reaction. The second route proved more successful featuring an intermolecular Cr/Ni mediated coupling followed by an intramolecular Barbier cyclization process. The outcome of this Barbier reaction is critically dependent on reaction temperature and conducting the reaction at ambient temperature allowed macrocyclization in good yield.

The butenolide was appended through a vinylogous Mukaiyama aldol addition of silyloxyfuran **155** to the ketone **163**. Under meticulously controlled conditions, this process provided the γ-hydroxy-α,β-unsaturated lactone **164** in good yield. The generality of this process was explored in some detail. Addition of silyloxyfurans to cyclohexanones proceeds with moderate to good diastereoselectivities. The potential application of this process to the synthesis of butenolide and γ-lactone containing natural products was demonstrated by further transformations of the addition adducts.

A compound closely related to (-)-gymnodimine was synthesized from the Mukaiyama addition adduct **164** in a few steps including switching of *N*-protecting group due to the instability of the natural product under basic conditions.

Finally, a hapten derived from the tetrahydrofuran has been synthesized. Even though the raised antibodies failed to recognize the natural product itself, the results provided some information regarding the essential structural elements of an efficient hapten.

Scheme 55


46a
(E)-95
85%
exo : endo > 95:5
ee = 95%
96b
4 steps
110
116
(12 steps from
known compounds)
CrCl2/NiCl2, DMF/THF (1:1)
97%, β:α = 1.3:1
2 steps
134b: R = H, X = Cl
136b: R = TBS, X = I
t-BuLi, Et2O
23 ºC, 50~70%
141a
2 steps
163
155
TiCl4, CH2Cl2
64%, dr = 1.1:1
164
4 steps
(-)-gymnodimine ?

CHAPTER VIII

EXPERIMENTAL PROCEDURES

VIII.1. General

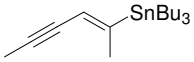
All non aqueous reactions were carried out under nitrogen atmosphere in oven-dried (120 ºC) glassware. Acetonitrile, dichloromethane, tetrahydrofuran, diethyl ether, *N*,*N*-dimethylformamide, toluene were purified by Mbraun solvent purification system. Methanol was distilled from magnesium prior to use. Triethyl amine was distilled from calcium hydride prior to use. The molarities indicated for organolithium reagents were established according to literature procedure.[112] All other commercially obtained reagents were used as received.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity-500, VXR-300 spectrometer. ^{1}H NMR chemical shifts are reported as δ values in ppm relative to tetramethylsilane (TMS, 0.00 ppm). ^{1}H NMR coupling constants (J) are reported in Hertz (Hz) and multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), sep (septet), m (multiplet), br s (broad singlet), dd (doublet of doublet), dt (doublet of triplet), tt (triplet of triplet). Unless indicated otherwise, deuterochloroform ($CDCl_3$) served as an internal standard (77.0 ppm) for all ^{13}C spectra. Trichlorofluoromethane ($CFCl_3$) served as an internal standard (0.0 ppm) for ^{19}F spectra. Flash column chromatography was performed using 60Å Silica Gel (Baker, 230-400 mesh) as a stationary phase. Sometimes basic Al_2O_3 (Brochmann, 150 mesh) was used for purification of acid labile compounds. Mass spectra were obtained on a VG

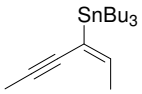
analytical 70S high resolution, double focusing, sectored (EB) mass spectrometer at the center for Chemical Characterization and Analysis. Thin layer chromatography (TLC) was performed using glass-backed silica gel 60F254 (Merck, 250 μm thickness). Infrared spectra were recorded with a Nicolet Impact 410 FTIR spectromer.

Calculations were performed using the unrestricted Harfree-Fock approach to *ab initio* theory as implemented using Gaussian 03 program package* which is available on the supercomputer at Texas A&M University. The standard 3-21G basis set has been used to perform the full geometry optimization. The vibrational frequencies were determined to characterize stationary points and zero-point energies (ZPE), and have been calculated at this level of theory applying the coordinates generated from the full optimization. (*Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A. Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian 98, Revision C.02. Gaussian, Inc., Wallingford CT, 2004.)

VIII.2. Procedure

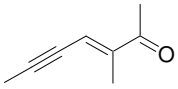


Vinyl stannane **102a:** To a slurry of CuCN (6.9 g, 76.8 mmol) in THF (300 ml) at -35 ºC was added *n*-BuLi (2.3 M in hexanes, 67 ml, 154 mmol). The resulting yellow homogenous solution was stirred at -35 ºC for 30 min, cooled to -78 ºC and nBu$_3$SnH (41 ml, 154 mmol) was added. The yellow-greenish solution was stirred at -78 ºC for 30 min and a solution of 2,4-hexadiyne (3 g, 38.4 mmol) in THF (20 ml) was added down the side of the flask. The reaction mixture was at -78 ºC stirred for 3 h, quenched by slow addition of MeOH (45 ml) followed by saturated NH_4Cl solution (45 ml). The mixture was warmed to room temperature, extracted with Et_2O, washed with brine, dried ($MgSO_4$), concentrated *in vacuo*, and purified by flash chromatography (hexanes) to afford 9.5 g (67%) of colorless oil as mixture of isomers (7:1). Major isomer: R_f = 0.65 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61 (m, 1H), 2.09 (d, J = 2.0 Hz, 3H), 2.02 (d, J = 2.0 Hz, 3H), 1.49 (m, 6H), 1.31 (qt, J = 7.5 Hz, 7.5 Hz, 6H), 0.91 (q, J = 8.0 Hz, 6H), 0.89 (q, J = 7.5 Hz, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 118.7 (d, J = 15 Hz), 89.7, 77.2, 29.3, 27.6, 22.9, 13.9, 9.5, 4.6; HRMS calcd for for $C_{18}H_{34}SnLi$ [M+Li]: 377.1843. Found: 377.1859.

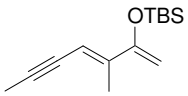


Vinyl stannane **102c**: To a solution of 2,4-hexadiyne (52 mg, 0.666 mmol) in THF (2 ml) was added $PdCl_2(PPh_3)_2$ (23 mg, 0.0333 mmol). *n*-BuSnH (200 µl, 0.732 mmol) was then added over a period of 30 min. The reaction mixture was stirred at room

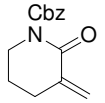
temperature for 30 min, concentrated *in vacuo*, and purified by flash chromatography (pentane) to afford 220 mg (90%) of the desired product as a slightly yellow oil. R_f = 0.68 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (q, *J* = 6.5 Hz, 1H), 2.04 (s, 3H), 1.95 (d, *J* = 6.5 Hz, 3H), 1.53 (m, 6H), 1.33 (qt, *J* = 7.5, 7.5 Hz, 6H), 0.95 (t, *J* = 8.0 Hz, 6H), 0.90 (t, *J* = 7.5 Hz, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.7, 124.9, 94.5, 81.1, 29.2, 27.6, 18.7, 13.7, 10.2, 5.1; LRMS calcd for $C_{18}H_{34}SnLi$ [M+Li]: 377. Found: 377.



Ketone **105:** To a solution of vinyl stannane **102a** (7.08 g, 19.2 mmol) in THF (150 ml) at -78 ºC was added *n*-BuLi (2.0 M in hexanes, 12.0 ml, 24.0 mmol). After stirring at -78 ºC for 20 min, *N*-methoxy-*N*-methyl acetamide (2.4 g, 23.0 mmol) in THF (15 ml) was added dropwise. The resulting light yellow solution was stirred at -78 ºC for 1 h, warmed to room temperature and was quenched by 1 N HCl solution (about 40 ml) until the mixture was slightly acidic. The aqueous layer was extracted with Et_2O and the combined organic layers were dried (Mg_2SO_4), concentrated *in vacuo* and purified by flash chromatography (5% Et_2O/pentane →10% Et_2O/pentane) to afford 1.8 g (77%) of product as a yellow oil. R_f = 0.43 (5% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.47 (m, 1H), 2.31 (d, *J* = 1.0 Hz, 3H), 2.10 (dq, *J* = 2.5 Hz, 0.5 Hz, 3H), 1.97 (q, *J* = 0.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 146.3, 121.0, 101.3, 76.7, 25.5, 14.1, 4.9; IR (thin film): 2220, 1668 cm^{-1}; LRMS Calcd. for $C_8H_{11}O$ [M+H]: 123. Found: 123.

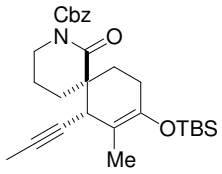


Silyl enol ether (*E*)-**95**: To a solution of ketone **105** (643 mg, 5.25 mmol) in CH_2Cl_2 (30 ml) at -78 ºC was added Et_3N (1.47 ml, 10.5 mmol) and TBSOTf (1.31 ml, 5.79 mmol). The reaction mixture was stirred at -78 ºC for 10 min and quenched by pH 7 buffer. The aqueous layer was extracted with CH_2Cl_2 and combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography on basic Al_2O_3 (pentane) to afford 1.12 g (90%) of product as a colorless oil. R_f = 0.57 (hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (m, 1H), 4.54 (d, *J* = 1.5 Hz, 1H), 4.36 (br s, 1H), 2.05 (d, *J* = 2.4 Hz, 3H), 2.01 (s, 3H), 0.97 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 142.6, 107.7, 93.5, 93.3, 78.1, 25.8, 18.2, 15.8, 4.7, -4.7; IR (thin film): 2220 cm^{-1}; LRMS (ESI) Calcd. for $C_{14}H_{25}OSi$ [M+H]: 237. Found: 237.



N-Cbz lactam **46a**: To a solution of α-methylene δ-lactam (400 mg, 3.60 mmol) in THF (36 ml) at -78 ºC was added LiHMDS (1.0 M in THF, 4.32 mmol). After stirring at -78 ºC for 20 min, benzyl chloroformate (617 µl, 4.32 mmol) was added. The reaction mixture was stirred at -78 ºC for 30 min and quenched by pH 7 buffer. The aqueous layer was extracted with Et_2O and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (10% → 30% → 50% Et_2O/hexanes) to afford 523 mg (59%) of the desired product as a slightly

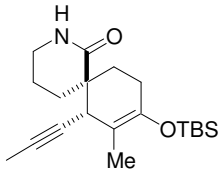
yellowish oil which solidifies upon standing in refrigerator overnight. . m.p.51-53 ºC; R_f = 0.45 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.31 (m, 5H), 6.36 (dd, *J* = 0.9 Hz, 0.9 Hz, 1H), 5.45 (dd, *J* = 0.9, 0.9 Hz, 1H), 5.31 (s, 2H), 3.81 (app q, *J* = 3.9 Hz, 2H), 2.60 (tt, *J* = 0.9 Hz, 3.9 Hz, 2H), 1.90 (tt, *J* = 3.9 Hz, 3.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5, 154.4, 138.2, 135.4, 128.5, 128.2, 128.0, 125.6, 68.5, 47.0, 29.1, 22.4; IR (thin film): 1697 cm^{-1}; HRMS (ESI) Calcd. for $C_{14}H_{16}NO_3$ [M+H]: 246.1130. Found: 246.1199.



N-Cbz spirolactam **96b**: A flask wrapped with aluminum foil was charged with $CuCl_2$ (69.4 mg, 0.516 mmo) and (*S*, *S*)-*tert*-butyl-bis(oxazoline) (167 mg, 0.568 mmol) in a glove box. The flask was removed from the glove box and CH_2Cl_2 (3 ml) was added. The greenish homogeneous solution was stirred at room temperature in dark for 3.5 h, then a solution of $AgSbF_6$ (354.7 mg, 1.03 mmol, weighed in a glove box) in CH_2Cl_2 (3 ml) was added. White precipitate formed immediately. After stirring at room temperature for 2 h, the dark green mixture was filtered through a pad of oven-dried Celite, rinsed with CH_2Cl_2 (3 ml) and the resulting blue catalyst solution was used in the reaction.

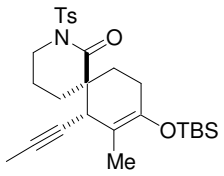
To this catalyst solution was added a solution of Cbz lactam **46a** (1.27 g, 5.16 mmol) in CH_2Cl_2 (6 ml) followed by a solution of TBS enol ether (*E*)-**95** (1.83 g, 7.74 mmol) in CH_2Cl_2 (3 ml). The reaction mixture was stirred at room temperature in dark

for 11 h, concentrated *in vacuo* and purified by flash chromatography (5%→7.5%→10% → 20% EtOAc/hexanes) to afford 2.1 g (84%) of the desired product as a slightly yellow oil. R_f = 0.48 (20% EtOAc/hexanes); $[\alpha]_D^{21}$ + 87.1 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.45-7.32 (m, 5H), 5.27 (dd, AB system, *J* =12.0 Hz, 12.0 Hz, 1H), 3.82 (m, 1H), 3.77 (m, 1H), 3.69 (m, 1H), 2.14-2.07 (m, 3H), 1.98-1.91 (m, 2H), 1.85-1.78 (m, 3H), 1.75 (d, *J* = 2.5 Hz, 3H), 1.71 (q, *J* = 1.5 Hz, 3H), 0.94 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 154.9, 141.8, 135.7, 128.5, 128.1, 128.0, 110.2, 79.3, 77.7, 68.3, 48.0, 47.6, 40.8, 30.3, 21.2, 26.7, 25.8, 20.1, 18.1, 14.8, 3.6, -3.9; IR (thin film): 1772, 1721 cm^{-1}; HRMS calcd for $C_{28}H_{40}NO_4Si$ [M+H]: 482.2727. Found: 482.2748. CAUTION: The product is readily oxidized to α,β-unsaturated ketone when exposed to air and should be immediately (within one hour) used in the following deprotection step after purification.

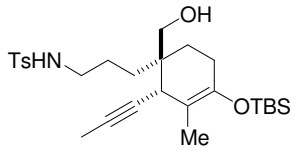


Spirolactam **96c**: To a solution of the lactam **96b** (500 mg, 1.04 mmol) in THF (30 ml, degassed through freeze-thaw processes) at -78 ºC was added *n*-BuLi (2.0 M in hexanes, 675 µl, 1.35 mmol). After stirring for 15 min, another 600 µl of *n*-BuLi (2.0 M in hexanes) was added. The reaction mixture was stirred for 15 min and was quenched by pH 7 buffer. The aqueous layer was extracted with Et_2O, and the combined organic layers were dried (Na_2SO_4), concentrated *in vacuo*, and purified by flash chromatography (50% → 70% EtOAc/hexanes) to afford 296 mg (82%) of the desired

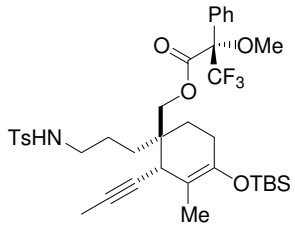
lactam as a white powder. R_f = 0.40 (50% EtOAc/hexanes); $[\alpha]_D^{21}$ +105.6 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.11 (br s, 1H, NH), 3.97 (br s, 1H), 3.40-3.24 (m, 2H), 2.18-1.88 (m, 8H), 1.79 (d, *J* = 2.5 Hz, 3H), 1.71 (app d, *J* = 1.5 Hz, 3H), 0.94 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.7, 141.5, 109.9, 79.1, 78.1, 44.3, 42.4, 39.6, 30.1, 26.3, 25.8, 24.6, 19.6, 18.1, 14.7, 3.6, -3.8, -3.9; IR (thin film): 3192, 1655 cm^{-1}; LRMS calcd for $C_{20}H_{34}NO_2Si$ [M+H]: 348. Found: 348. A mixture of spiro lactam **96c** (3 mg, 0.00863 mmol) and (+)-Eu(hfc)$_3$ (10 mg, 0.00863 mmol) was dissolved in $CDCl_3$. ^1H NMR showed separated peaks for two enantiomers and integration gave 83% ee.



N-Tosyl spirolactam **96a**: To a solution of the lactam **96c** (270 mg, 0.777 mmol) in THF (20 ml) at -78 ºC was added KHMDS (0.5 M in toluene, 2.33 ml, 1.17 mmol). After stirring at -78 ºC for 20 min, TsCl (recrystallized from ether, 250 mg, 1.17 mmol) was added. The reaction mixture was stirred at -78 ºC for 1 h, warmed to room temperature over a period of 1 h, and quenched by pH 7 buffer. The aqueous layer was extracted with Et_2O and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (10%→20% Et_2O/hexanes) to afford 311 mg (80%) of product as a white solid. NMR matched with previously reported. $[\alpha]_D^{21}$ +125.7 (*c* 1.0, $CHCl_3$). Recrystallization from heptane provided white crystals suitable for X-ray analysis.

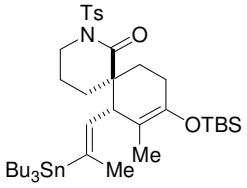


Amino alcohol **106**: To a solution of tosyl lactam **96a** (7.0 mg, 0.0140 mmol) in THF (1 ml) at 0 ºC was added $LiBH_4$ (2M in THF, 70 µl, 0.140 mmol). The reaction mixture was stirred at 25 ºC for 4 h and then quenched by pH 7 buffer. The aqueous layer was extracted with Et_2O, and the combined organic layers were dried (Na_2SO_4), concentrated and purified by flash chromatography (60% EtOAc/Hexanes) to afford 6.4 mg (91%) of the product **106** as a white foam. R_f = 0.15 (30% EtOAc/hexanes); $[\alpha]_D^{21}$ +42.4 (*c* 0.42, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 4.54 (t, *J* = 5.5 Hz, 1 H), 3.49 (d, *J* = 11.0 Hz, 1H), 3.36 (d, *J* = 11.0 Hz, 1H), 2.96 (dt, *J* = 6.0 Hz, 5.5 Hz, 2H), 2.64 (br s, 1H), 2.43 (s, 3H), 1.98 (m, 2H), 1.81 (d, *J* = 2.5 Hz, 3H), 1.66 (app q, *J* = 1.5 Hz, 3H), 1.56 (m, 3H), 1.48 (m, 3H), 0.94 (s, 9H), 0.12 (3H, s), 0.09 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3, 143.1, 136.9, 130.0, 127.2, 110.3, 78.7, 78.5, 64.8, 43.9, 39.2, 39.0, 30.1, 27.1, 27.0, 25.8, 23.2, 21.5, 18.2, 15.4, 3.6, -3.6, -3.9; IR (thin film): 3478, 3278 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{43}NO_4SSiLi$ [M+Li]: 512.2842. Found: 512.2844.



Mosher ester **107**: To a solution of (*S*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (5 mg, 0.0198 mmol) in CH_2Cl_2 (1ml) was added

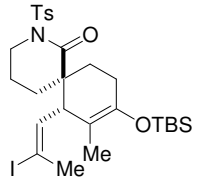
DCC (3 mg, 0.0149 mmol), a solution of amino alcohol **106** (5 mg, 0.00990 mmol) in CH_2Cl_2 (1 ml) and a crystal of DMAP successively. The reaction mixture was stirred at room temperature for 12 h, concentrated *in vacuo*. ^{19}F NMR integration of the crude reaction mixture showed ratio of 97.6:2.4 of the two diastereomers corresponding to 95% ee. The crude mixture was purified by flash chromatography (30% EtOAc/hexanes) to afford 6 mg (84%) of product **107** as a colorless oil. ^{19}F NMR integration of the pure product gave the same ee. R_f = 0.50 (30% EtOAc/hexanes); $[\alpha]_D^{21}$ +26.0 (*c* 0.63, $CHCl_3$); ^{19}F NMR (300 MHz, $CFCl_3$) δ -71.25 (minor diastereomer), -71.29 (major diastereomer); ^1H NMR (500 MHz, C_6D_6) δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.09 (m, 2H), 7.04 (m, 1H), 6.79 (d, *J* = 8.0 Hz, 2H), 4.04 (s, 2H), 3.93 (t, *J* = 6.0 Hz, 1H), 3.38 (s, 3H), 2.64 (dt, *J* = 6.5 Hz, 6.5 Hz, 2H), 2.54 (br s, 1H), 1.98 (m, 2H), 1.89 (s, 3H), 1.83 (s, 3H), 1.63 (m, 1H), 1.54 (d, *J* = 2.5 Hz, 3H), 1.40 (m, 1H), 1.34 (m, 1H), 1.25 (m, 1H), 1.10 (m, 2H), 0.95 (s, 9H), 0.074 (s, 3H), 0.068 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 166.5, 143.5, 142.7, 138.6, 132.9, 130.0, 129.6, 128.7, 128.3, 127.7, 127.5, 125.4 (q, CF_3, *J* = 287 Hz), 123.1, 110.5, 85.2, 78.9, 78.1, 67.0, 55.4, 43.8, 38.6, 38.2, 32.3, 27.5, 27.4, 25.9, 23.7, 21.1, 18.3, 15.9, 3.3, -3.6, -3.7; IR (thin film): 3283, 1752 cm^{-1}; HRMS (ESI) calcd for $C_{37}H_{50}F_3NO_6SSiLi$ [M+Li]: 728.3240. Found: 728.3222.



Vinyl stannane **108**: To a solution of alkyne **96a** (231 mg, 0.461 mmol) in a mixed solvent of THF/hexanes (1:7, total 10.4 ml, hexanes were dried over powdered 4Å molecular sieves) containing $PdCl_2(PPh_3)_2$ (16 mg, 0.0231 mmol) at room temperature was added a solution of tributyltin hydride (124 μl, 0.461 mmol) in hexanes (1 ml) over 12 h via a syringe pump. After finishing the addition, another 16 mg of $PdCl_2(PPh_3)_2$ was added followed by syringe pump addition of a solution of tributyltin hydride (124 μl) in hexanes (1 ml) over 12 h. The dark reaction mixture was concentrated *in vacuo* and purified by flash chromatography (hexanes→5%→10% EtOAc/hexanes) to afford 310 mg (85%) of the desired product **108** as a colorless oil, 5 mg (2%)of hydrogenated product **109** as a white solid and 14 mg (6%) of the recovered starting material.

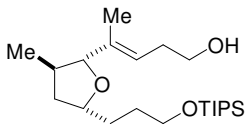
Desired product **108**: R_f = 0.72 (20% EtOAc/hexanes); $[\alpha]_D^{21}$ +128.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.16 (dq, *J* = 10.5 Hz, 1.5 Hz, 1H), 3.92 (ddd, *J* = 6.0 Hz, 6.0 Hz, 12.0 Hz, 1H), 3.82 (ddd, *J* = 6.0 Hz, 6.0 Hz, 12.0 Hz, 1H), 3.64 (d, *J* = 10.5 Hz, 1H), 2.43 (s, 3H), 2.24 (m, 2H), 1.96-1.84 (m, 4H), 1.68-1.60 (m, 2H), 1.57 (d, *J* = 1.5 Hz, 3H), 1.45 (m, 6H), 1.40 (s, 3H), 1.30 (m, 6H), 0.93 (s, 9H), 0.89 (t, *J* = 7.0 Hz, 9H), 0.83 (t, *J* = 8.0 Hz, 6H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 144.1, 142.3, 141.0, 139.1, 136.5, 129.1, 128.6, 112.0, 47.2, 46.6, 43.3, 31.4, 29.2, 28.2, 27.4, 26.9, 25.8, 21.6, 20.6, 19.2, 18.1, 14.4, 13.7, 9.1, -3.9, -4.1; IR (thin film): 1688 cm^{-1}; HRMS (ESI) Calcd. for $C_{39}H_{67}NO_4SSiSnLi$ [M+Li]: 800.3742. Found: 800.3673.

Hydrogenated product **109**: m.p.122-126 ºC; R_f = 0.57 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.5 Hz, 2H), 7.29 (d, *J* = 7.5 Hz, 2H), 5.42 (dq, *J* = 11.0 Hz, 7.0 Hz, 1H), 5.06 (ddq, *J* = 11.0 Hz, 11.0 Hz, 1.5 Hz, 1H), 3.95 (ddd, *J* = 6.0 Hz, 6.0 Hz, 12.0 Hz, 1H), 3.83 (m, 1H), 3.60 (d, *J* = 11.0 Hz, 1H), 2.44 (s, 3H), 2.04 (m, 2H), 1.96-1.88 (m, 3H), 1.86-1.80 (m, 1H), 1.70 (ddd, *J* = 5.0 Hz, 5.0 Hz, 13.0 Hz, 1H), 1.67-1.61 (m, 1H), 1.41 (s, 3H), 1.28 (dd, *J* = 7.0 Hz, 1.5 Hz, 3H), 0.94 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 144.2, 142.1, 136.6, 129.1, 128.9, 128.5, 127.0, 111.9, 47.3, 46.9, 42.8, 31.5, 26.9, 26.8, 25.8, 21.6, 20.7, 18.1, 14.1, 12.7, -3.9, -4.0; IR (thin film): 1686 cm^{-1}; HRMS (ESI) Calcd. for $C_{27}H_{41}NO_4SSiLi$ [M+Li]: 510.2686. Found: 510.2727.



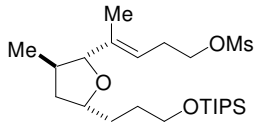
Vinyl iodide **110**: To a solution of the vinyl stannane **108** (268 mg, 0.338 mmol) in CH_2Cl_2 (15 ml) at -78 ºC was added a solution of iodine (79 mg, 0.321 mmol) in CH_2Cl_2 (5 ml). The reaction mixture was stirred at -78 ºC for 10 min and quenched by cyclohexene (1 ml). The yellowish mixture was warmed to room temperature and stirred until the solution turned to colorless (*ca*. 1 h). The solvent was evaporated and the residue was purified by flash chromatography (hexanes→5%→10% EtOAc/hexanes) to afford 161 mg (76%) of the desired product as a white solid and 21 mg (8%) of the recovered starting material. m.p.180-183 ºC; R_f = 0.52 (20% EtOAc/hexanes); $[\alpha]_D^{21}$ +126.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J*

= 8.0 Hz, 2H), 5.82 (dq, *J* = 11.5, 1.5 Hz, 1H), 3.96 (m, 1H), 3.89 (m, 1H), 3.53 (d, *J* = 11.5 Hz, 1H), 2.45 (s, 3H), 2.12-2.00 (m, 2H), 1.98-1.88 (m, 3H), 1.87 (d, *J* = 1.5 Hz, 3H), 1.83-1.77 (m, 1H), 1.75-1.70 (m, 1H), 1.69-1.64 (m, 1H), 1.41 (app d, *J* = 1.5 Hz, 3H), 0.93 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 144.4, 142.7, 140.1, 136.6, 129.4, 128.4, 110.4, 97.6, 47.4, 46.9, 46.8, 31.9, 27.5, 26.5, 26.3, 25.8, 21.6, 20.8, 18.1, 14.1, -3.87, -3.91; IR (thin film): 1675 cm^{-1}; HRMS (ESI) Calcd. for $C_{27}H_{40}INO_4SSiLi$ [M+Li]: 636.1652. Found: 636.1602.

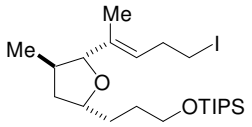


Alcohol **113**: To a three-necked flask immersed in acetone/dry ice bath (-78 ºC) equipped with a cold finger was condensed about 40 ml of liquid ammonia. Sodium (376 mg, 16.4 mmol, cut in small pieces) was added and the resulting blue mixture was stirred for 10 min. Then a solution of PMB ether **92** (826 mg, 1.64 mmol) in THF (25 ml) was added. The reaction mixture was stirred at -78 ºC for 45 min and quenched by slow addition of MeOH (10 ml). The solution was warmed to room temperature, stirred in open air for 1 h and then water (10 ml) and Et_2O (10 ml) were added. The aqueous layer was extracted with Et_2O and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (30% EtOAc/hexanes) to afford 566 mg (90%) of the desired product as a colorless oil as a mixture of two diastereomers (4:1). Major diastereomer: R_f = 0.37 (30% EtOAc/hexanes); $[\alpha]_D^{21}$ -17.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 (t, *J* = 7.0 Hz, 1H), 3.99 (m, 1H), 3.71 (m, 2H), 3.69 (d, *J* = 8.0 Hz, 1H), 3.65 (t, *J* = 6.5 Hz,

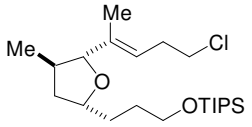
2H), 2.35 (m, 2H), 2.01 (m, 1H), 1.78 (ddd, *J* = 5.5 Hz, 8.5 Hz, 12.5 Hz, 1H), 1.68 (m, 2H), 1.65 (s, 3H), 1.55 (m, 3H), 1.06 (m, 21H), 0.96 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 123.2, 92.2, 77.8, 63.4, 62.3, 39.8, 36.1, 32.8, 31.4, 29.5, 18.0, 17.1, 11.9, 11.4.; IR (thin film): 3401 cm^{-1}; HRMS (ESI) Calcd. for $C_{22}H_{44}O_3SiLi$ [M+Li]:391.3220. Found: 391.3219.



Mesylate **114a**: To a solution of the alcohol **113** (450 mg, 1.17 mmol) in CH_2Cl_2 (20 ml) at -78 ºC was added Et_3N (815 µl, 5.85 mmol) and methanesulfonyl chloride (136 µl, 1.75 mmol). The reaction mixture was stirred at -78 ºC for 10 min and quenched by pH = 7 buffer. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography on Et_3N deactivated SiO_2 (30% EtOAc/hexanes) to afford 498 mg (92%) of the desired product as a colorless oil as a mixture of diastereomers (4:1). Major diastereomer: R_f = 0.47 (30% EtOAc/hexanes); $[\alpha]_D^{21}$ -12.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.40 (t, *J* = 7.0 Hz, 1H), 4.22 (dt, *J* = 2.5 Hz, 6.5 Hz, 2H), 4.00 (m, 1H), 3.71 (t, *J* = 6.0 Hz, 2H), 3.68 (d, *J* = 8.0 Hz, 1H), 3.01 (s, 3H), 2.53 (dt, *J* = 7.0 Hz, 7.0 Hz, 2H), 2.00 (m, 1H), 1.78 (ddd, *J* = 5.5 Hz, 8.5 Hz, 12.5 Hz, 1H), 1.68-1.52 (m, 5H), 1.65 (s, 3H), 1.05 (m, 21H), 0.96 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 120.5, 91.8, 77.9, 69.1, 63.3, 39.7, 37.5, 36.3, 32.7, 29.5, 27.8, 18.0, 17.1, 12.0, 11.6; HRMS (ESI) Calcd. for $C_{23}H_{46}O_5SSiLi$ [M+Li]: 469.2995. Found: 469.3002.

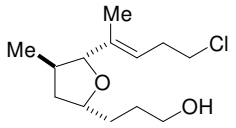


Alkyl iodide **114b**: To a solution of mesylate **114a** (180 mg, 0.389 mmol) in THF (10 ml) was added tetrabutylammonium iodide (287 mg, 0.778 mmol). The mixture was refluxed for 4 h, concentrated *in vacuo* and purified by flash chromatography (5% EtOAc/hexanes) to afford 176 mg (91%) of the desired product as a colorless oil as a mixture of two diastereomers (4:1). Major diastereomer: R_f = 0.53 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (t, *J* = 7.0 Hz, 1H), 4.01 (m, 1H), 3.71 (t, *J* = 5.5 Hz, 2H), 3.68 (d, *J* = 8.0 Hz, 1H), 3.13 (dt, *J* = 2.0 Hz, 7.5 Hz, 2H), 2.69-2.61 (m, 2H), 2.05-1.98 (m, 1H), 1.79 (ddd, *J* = 5.5 Hz, 8.5 Hz, 12.5 Hz, 1H), 1.62 (s, 3H), 1.70-1.52 (m, 5H), 1.06 (m, 21H), 0.94 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.0, 125.9, 91.9, 77.9, 63.3, 39.7, 36.2, 32.8, 32.0, 29.5, 18.0, 17.1, 12.0, 11.6, 5.4; IR (thin film): 2945, 2868, 1107 cm^{-1}; HRMS (ESI) Calcd. for $C_{22}H_{43}IO_2SiLi$ [M+Li]: 501.2237. Found: 501.2234.



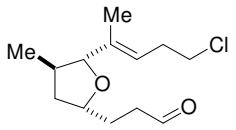
Alkyl chloride **114c**: A solution of the mesylate **114a** (498 mg, 1.08 mmol) in DMF (15 ml) containing anhydrous LiCl (500 mg, 11.8 mmol) was stirred at room temperature for 36 h and was quenched by water (7 ml). The mixture was extracted with Et_2O and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (10% EtOAc/hexanes) to afford 387 mg (89%) of the desired product as a colorless oil as a

mixture of diastereomers (4:1). Major diastereomer: R_f = 0.53 (10% EtOAc/hexanes); $[\alpha]_D^{21}$ -15.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 (t, *J* = 7.0 Hz, 1H), 3.99 (m, 1H), 3.71 (t, *J* = 6.0 Hz, 2H), 3.68 (d, *J* = 8.0 Hz, 1H), 3.51 (m, 2H), 2.52 (m, 2H), 2.00 (m, 1H), 1.78 (ddd, *J* = 5.5 Hz, 8.5 Hz, 12.5 Hz, 1H), 1.67 (m, 2H), 1.63 (s, 3H), 1.55 (m, 3H), 1.05 (m, 21H), 0.96 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5, 122.9, 91.9, 77.8, 63.4, 44.0, 39.7, 36.2, 32.8, 31.2, 29.5, 18.0, 17.1, 12.0, 11.5; LRMS (APCI) Calcd. for $C_{22}H_{44}ClO_2Si$ [M+H]: 403. Found: 403.



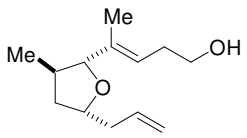
Alcohol **115:** To a solution of TIPS ether **114c** (400 mg, 0.993 mmol) in CH_3CN (15 ml) in a plastic bottle at 0 ºC was added HF·Py (~70 wt% of HF in pyridine, 0.2 ml). The reaction mixture was stirred at room temperature for 20 h and quenched by saturated $NaHCO_3$ solution (10 ml). The aqueous layer was extracted with Et_2O and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (40% EtOAc/hexanes) to afford 243 mg (99%) of the desired product as a colorless oil as a mixture of two diastereomers (4:1). Major diastereomer: R_f = 0.19 (30% EtOAc/hexanes); $[\alpha]_D^{21}$ -16.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 (t, *J* = 7.0 Hz, 1H), 4.00 (m, 1H), 3.71 (d, *J* = 8.0 Hz, 1H), 3.66 (m, 2H), 3.52 (m, 2H), 2.52 (m, 2H), 2.44 (brs, 1H, -OH), 2.02 (m, 1H), 1.78 (ddd, *J* = 5.5 Hz, 8.5 Hz, 12.5 Hz, 1H), 1.68 (m, 5H), 1.63 (s, 3H), 0.97 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.4, 123.2, 92.1, 77.9, 62.9, 44.0, 39.9, 36.2, 33.4, 31.1, 29.8, 17.1, 11.6; IR (thin film): 3378 cm^{-1}; LRMS (APCI) Calcd. for $C_{13}H_{24}ClO_2$ [M+H]: 247. Found: 247.

Alternatively, to a solution of the alkene **111c** (745 mg, 3.26 mmol) in THF (35 ml) at 0 ºC was added 9-BBN (0.5 M in THF, 9.1 ml, 4.56 mmol). The reaction mixture was stirred at room temperature for 12 h, cooled to 0 ºC and quenched by addition of 2 N NaOH solution (10 ml) and H_2O_2 solution (35 wt% in H_2O, 10 ml). The mixture was stirred at 0 ºC for 30 min. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (20% → 40 % EtOAc/hexanes) to afford 791 mg (98%) of the same product.

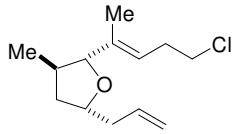


Aldehyde **116:** To a solution of the alcohol **115** (161 mg, 0.652 mmol) in CH_2Cl_2 (10 ml) containing anhydrous $NaHCO_3$ powder (329 mg, 3.91 mmol) at 0 ºC was added Dess-Martin periodinane (553 mg, 1.30 mmol). The reaction mixture was stirred at room temperature for 80 min, diluted with Et_2O and filtered through a pad of Celite. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography (10%→20%→30% EtOAc/hexanes) to afford 113 mg (71%) of the desired product as a colorless oil. Major diastereomer: R_f = 0.52 (30% EtOAc/hexanes); $[\alpha]^{20}_D$ -16.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.5 Hz, 1H), 5.43 (t, *J* = 7.0 Hz, 1H), 4.00 (m, 1H), 3.69 (d, *J* = 8.0 Hz, 1H), 3.53 (m, 2H), 2.54 (m, 4H), 2.01 (m, 1H), 1.90-1.75 (m, 3H), 1.69 (ddd, *J* = 8.0 Hz, 8.0 Hz, 12.0 Hz, 1H), 1.62 (s, 3H), 0.97 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.3, 137.0, 123.3, 92.1, 76.7, 44.0, 40.6,

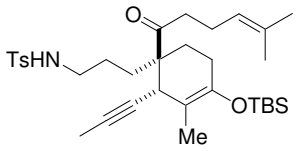
40.0, 36.1, 31.1, 28.6, 16.8, 11.5; IR (thin film): 1724 cm^{-1}; HRMS (ESI) Calcd. for $C_{13}H_{21}ClO_2Li$ [M+Li]: 251.1390. Found: 251.1369.



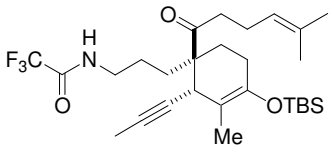
Alcohol **111b**: In a three-necked flask immersed in acetone/dry ice bath (-78 ºC) equipped with a cold finger was condensed about 40 ml of liquid ammonia. Sodium (1.04 g, 45.0 mmol, cut in small pieces) was added and the resulting blue mixture was stirred at -78 ºC for 10 min. Then a solution of the PMB ether **111a** (1.86 g, 5.63 mmol) in THF (30 ml) was added. The reaction mixture was stirred at -78 ºC for 30 min and quenched by slow addition of MeOH (15 ml). The solution was warmed to room temperature, stirred in open air for 1 h and saturated NH_4Cl solution (20 ml) was added. The mixture was extracted with Et_2O and the combined organic layers were washed with brine and concentrated *in vacuo*. The residue was purified by flash chromatography (40% EtOAc/hexanes) to afford 1.09 g (92%) of the desired product as a colorless oil. R_f = 0.27 (30% EtOAc/hexanes); $[\alpha]_D^{21}$ -26.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (m, 1H), 5.41 (t, *J* = 7.5 Hz, 1H), 5.05 (m, 2H), 4.02 (m, 1H), 3.66 (d, *J* = 8.0 Hz, 1H), 3.61 (t, *J* = 7.0 Hz, 2H), 2.33 (m, 2H), 2.28 (m, 1H), 2.24 (m, 1H), 1.99 (m, 1H), 1.81 (ddd, *J* = 5.5 Hz, 8.5 Hz, 12.5 Hz, 1H), 1.62 (s, 3H), 1.60 (m, 1H), 0.93 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 134.9, 123.7, 116.8, 92.3, 77.2, 62.1, 40.7, 39.0, 35.9, 31.3, 16.9, 11.4; IR (thin film): 3395 cm^{-1}; HRMS (ESI) Calcd. for $C_{13}H_{22}O_2Li$ [M+Li]: 217.1780. Found: 217.1777.



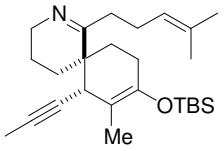
Chloride **111c**: To a solution of the alcohol **111b** (500 mg, 2.38 mmol) in DMF (20 ml) at room temperature were added carbon tetrachloride (1.38 ml, 14.3 mmol) and triphenylphosphine (1.87 g, 7.13 mmol). The reaction mixture was stirred at 65 ºC for 1 h, cooled to room temperature, and quenched by water. The mixture was extracted with Et_2O and the combined organic layers were washed with water, brine, and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes→5% EtOAc/hexanes) to afford 461 mg (85%) of the desired product as a colorless oil. R_f = 0.34 (5% EtOAc/hexanes); $[\alpha]_D^{21}$ -24.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (m, 1H), 5.43 (t, *J* = 7.5 Hz, 1H), 5.06 (m, 2H), 4.04 (m, 1H), 3.69 (d, *J* = 8.5 Hz, 1H), 3.50 (m, 2H), 2.53 (m, 2H), 2.36 (m, 1H), 2.25 (m, 1H), 1.99 (m, 1H), 1.83 (ddd, *J* = 5.5Hz, 8.5Hz, 12.5 Hz, 1H), 1.64 (m, 1H), 1.63 (s, 3H), 0.96 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 134.9, 123.1, 116.8, 92.0, 77.1, 44.0, 40.7, 38.9, 36.1, 31.2, 16.9, 11.5; IR (thin film): 1641 cm^{-1}; HRMS (ESI) Calcd. for $C_{13}H_{22}ClO$ [M+H]: 229.1359. Found: 229.1365.



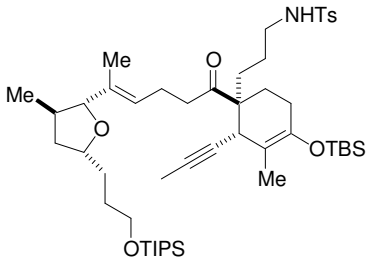
Amino ketone **123a**: To a solution of 5-bromo-2-methyl-2-pentene (9.3 mg, 0.0571 mmol) in Et_2O (1 ml) at -78 ºC was added *t*-BuLi (1.2 M in pentane, 0.095 ml, 0.114 mmol) dropwise. After stirring for 5 min, freshly distilled TMEDA (0.034 ml, 0.228 mmol) was added followed by a solution of **96a** (26 mg, 0.0519 mmol) in THF (1 ml). The reaction mixture was stirred at -20 ºC for 4 h, warmed to room temperature and stirred for 10 h. The reaction was quenched by pH 7 buffer. The aqueous layer was extracted with Et_2O, and the combined organic layers were dried (Na_2SO_4), concentrated *in vacuo* and purified by flash chromatography (10% → 20% EtOAc/Hexanes) to afford 19 mg (63%) of the desired product **123a** as a colorless oil. R_f = 0.67 (30% EtOAc/hexanes); $[\alpha]^{20}_D$ + 65.6 (*c* 0.86, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 5.03 (t and septet, *J* = 7.5 Hz, 1.5 Hz, 1H), 4.27 (t, *J* = 6.5 Hz, 1H), 3.24 (br s, 1H), 2.90 (dt, *J* = 6.5 Hz, 6.5 Hz, 2H), 2.44 (s, 3H), 2.38 (t, *J* = 7.5 Hz, 2H), 2.18 (dt, *J* = 7.5 Hz, 7.5 Hz, 2H), 2.00-1.85 (m, 4H), 1.83 (d, *J* = 2.5 Hz, 3H), 1.70 (br s, 3H), 1.66 (s, 3H), 1.60 (s, 3H), 1.73 (m, 1H), 1.53 (m, 1H), 1.30 (m, 1H), 1.16 (m, 1H), 0.90 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.5, 143.7, 143.5, 137.1, 133.0, 130.0, 127.4, 123.3, 112.8, 78.9, 78.7, 53.6, 43.6, 37.2, 37.0, 34.5, 28.3, 28.2, 26.03, 25.96, 24.1, 22.5, 21.8, 18.4, 17.9, 16.0, 3.9, -3.5, -3.7; IR (thin film): 3283, 1701 cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{51}NO_4SSiLi$ [M+Li]:592.3468. Found: 592.3478.



Amino ketone **123b**: To a solution of **123a** (21 mg, 0.0358 mmol) in THF (2 ml) at room temperature was added triethylamine (0.060 ml, 0.430 mmol) and trifluoroacetic anhydride (0.035 ml, 0.251 mmol). After stirring for 15 min, samarium iodide (0.1 M in THF) was added until the mixture stayed blue (totally about 5 ml, 0.5 mmol). The mixture was stirred for 30 min, diluted with CH_2Cl_2, and quenched with 10% sodium thiosulfate solution. The aqueous layer was extracted with Et_2O, and the combined organic layers were dried (Na_2SO_4), concentrated *in vacuo* and purified by flash chromatography (10% → 20% EtOAc/Hexanes) to afford 12 mg (63%) of the desired product as a slightly yellow oil. R_f = 0.48 (20% EtOAc/hexanes); $[\alpha]^{20}_D$ + 194 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (br s, 1H), 5.05 (t and septet, *J* = 7.0 Hz, 1.5 Hz, 1H), 3.32 (br s, 1H), 3.30 (m, 2H), 2.44 (t, *J* = 7.0 Hz, 2H), 2.21 (m, 2H), 2.02-1.89 (m, 4H), 1.80 (m, 1H), 1.58 (m, 1H), 1.79 (d, *J* = 2.5 Hz, 3H), 1.71 (s, 3H), 1.67(d, *J* = 1.5 Hz, 3H), 1.61 (s, 3H), 1.48 (m, 1H), 1.28 (m, 1H), 0.91 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.6, 157.2 (q, *J* = 36 Hz), 143.4, 133.1, 123.1, 114.6 (q, *J* = 287 Hz), 112.9, 78.8, 78.4, 53.6, 40.2, 37.3, 36.9, 34.4, 28.3, 28.1, 26.0, 25.9, 23.8, 22.5, 18.4, 17.9, 16.0, 3.7, -3.5, -3.9; IR (thin film): 3343, 1706 cm^{-1}; HRMS calcd for $C_{28}H_{44}F_3NO_3SiLi$ [M+Li]: 534.3203. Found: 534.3155.

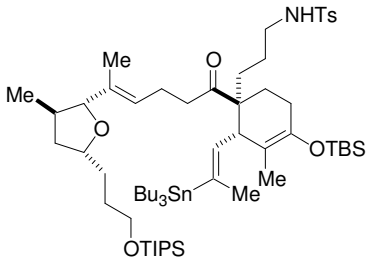


Spirocyclic imine **124**: To a solution of amino ketone **123b** (4.0 mg) in MeOH was added 28% ammonia hydroxide in water (0.2 ml). The mixture was stirred at 80 ºC for 2 h, concentrated and purified by flash chromatography (40% → 60% EtOAc/Hexanes) to afford 2.8 mg (89%) of the desired product as a colorless oil. R_f = 0.49 (60% EtOAc/hexanes); $[\alpha]^{20}_D$ + 77.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.16 (t and septet, *J* = 7.0 Hz, 1.5 Hz, 1H), 3.68 (m, 1H), 3.64 (br s, 1H), 3.56 (m, 1H), 2.35 (m, 2H), 2.22 (m, 2H), 2.12 (m, 1H), 2.00-1.90 (m, 2H), 1.80 (m, 2H), 1.79 (d, *J* = 2.5 Hz, 3H), 1.72 (s, 3H), 1.69 (br s, 3H), 1.63 (br s, 3H), 1.62-1.56 (m, 3H), 0.96 (s, 9H), 0.12 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 142.0, 131.7, 124.4, 109.6, 79.3, 78.0, 49.6, 42.3, 39.5, 33.6, 29.4, 26.4, 25.9, 25.8, 25.7, 24.4, 19.6, 18.2, 17.7, 14.9, 3.5, -3.6, -3.9; IR (thin film): 1685, 1650 cm^{-1}; HRMS calcd for $C_{26}H_{43}NOSiLi$ [M+Li]: 414.3192. Found: 414.3191.



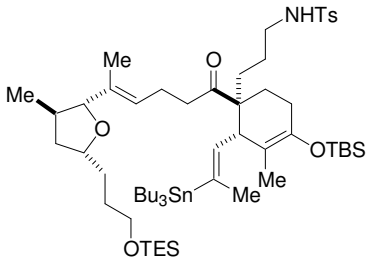
Amino ketone **125a**: Alkyl idodide **114b** (83 mg, 0.168 mmol) and tosylspirolactam **96a** (67 mg, 0.134 mmol) were placed in a flask and azeotropically dried with toluene. The mixture was dissolved in Et_2O (15 ml) and the resulting solution was cooled to -78 ºC. *t*-BuLi (1.5 M in pentane, 246 µl, 0.369 mmol) was then added

dropwise. The reaction mixture was stirred at -78 ºC for 2 h and quenched by pH 7 buffer. The aqueous layer was extracted with Et_2O and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (5%→10%→15% EtOAc/hexanes) to afford 107 mg (92%) of the desired product as a colorless oil. R_f = 0.50 (20% EtOAc/hexanes); $[\alpha]^{20}_D$ +62.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 5.51 (t, *J* = 6.0 Hz, 1H, -NH), 5.31 (t, *J* = 7.0 Hz, 1H), 4.03 (m, 1H), 3.67 (m, 2H), 3.62 (d, *J* = 8.0 Hz, 1H), 3.17 (br s, 1H), 2.85 (m, 2H), 2.47 (m, 1H), 2.43 (s, 3H), 2.38-2.32 (m, 2H), 2.15 (m, 1H), 2.04-1.90 (m, 5H), 1.80 (d, *J* = 2.5 Hz, 3H), 1.78 (m, 2H), 1.68 (s, 3H), 1.65 (m, 1H), 1.62 (s, 3H), 1.62-1.45 (m, 7H), 1.05 (m, 21H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.90 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.7, 143.6, 142.9, 137.6, 135.3, 129.5, 126.9, 126.4, 112.4, 92.1, 78.4, 78.2, 77.9, 63.3, 53.3, 43.4, 39.5, 37.2, 36.1, 35.9, 34.0, 32.7, 29.4, 27.8, 26.8, 25.7, 23.9, 21.5, 21.4, 18.04, 17.96, 16.9, 15.7, 11.9, 11.1, 3.6, -3.8, -4.2; IR (thin film): 3437, 3298, 1701 cm^{-1}; HRMS (ESI) Calcd. for $C_{49}H_{83}NO_6SSi_2Li$ [M+Li]: 876.5640. Found: 876.5641.



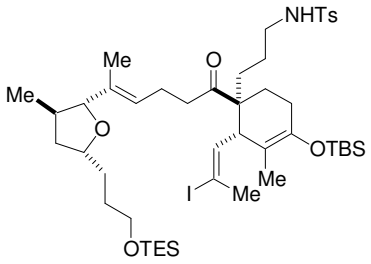
Vinyl stannane **126a**: To a solution of the alkyne **125a** (235 mg, 0.270 mmol) in THF/hexanes (1:7, 8 ml) at room temperature was added $PdCl_2(PPh_3)_2$ (45 mg, 0.0641 mmol) and tributyltin hydride (545 µl, 2.03 mmol) in five portions, with 12 h between

every portion. The resulting dark reaction mixture was concentrated *in vacuo* and purified by flash chromatography (5%→10%→15% EtOAc/hexanes) to afford 122 mg (39%) of the desired product as a colorless oil and 122 mg (52%) of the recovered starting material. R_f = 0.63 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 5.82 (t, *J* = 6.5 Hz, 1H, -NH), 5.31 (t, *J* = 7.5 Hz, 1H), 5.18 (dq, *J* = 9.5 Hz, 2.0 Hz, 1H), 4.07 (m, 1H), 3.67 (m, 2H), 3.63 (d, *J* = 8.0 Hz, 1H), 3.46 (d, *J* = 9.5 Hz, 1H), 2.78-2.46 (m, 4H), 2.41 (s, 3H), 2.37 (m, 1H), 2.20-1.94 (m, 5H), 1.92 (d, *J* = 2.0 Hz, 3H), 1.79 (m, 1H), 1.65 (s, 3H), 1.62-1.56 (m, 3H), 1.49 (m, 12H), 1.30 (m, 8H), 1.08 (m, 2H), 1.04 (m, 21H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.88 (m, 24H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.8, 143.7, 142.7, 140.1, 139.5, 137.9, 135.2, 129.4, 126.89, 126.85, 113.9, 92.3, 78.0, 63.3, 53.2, 43.5, 42.2, 39.5, 36.0, 35.9, 33.4, 32.8, 29.4, 29.2, 27.7, 27.3, 25.9, 25.0, 24.1, 21.5, 21.4, 19.8, 18.2, 18.0, 16.9, 15.3, 13.7, 12.0, 11.2, 9.2, -3.9, -4.2; IR (thin film): 3280, 3186, 1703 cm^{-1}.



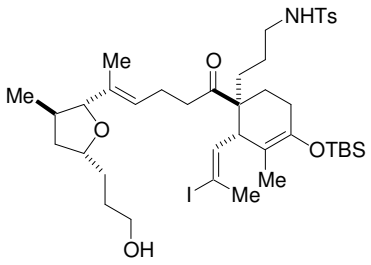
Vinyl stannanne **126b**: To a solution of the alkyne **125b** (62 mg, 0.0748 mmol) in THF/hexanes (1:7, 4 ml) at room temperature was added $PdCl_2(PPh_3)_2$ (3 mg, 0.00374 mmol) followed by a solution of tributyltin hydride (20 μl, 0.0748 mmol) in hexanes (0.5 ml) over 10 h via a syringe pump. The same addition procedure was repeated for

four times. The resulting dark reaction mixture was concentrated *in vacuo* and purified by flash chromatography (hexanes→10%→15% EtOAc/hexanes) to afford 26 mg (31%) of the vinyl stannane intermediate as a colorless oil and 32 mg (52%) of the recovered starting material. R_f = 0.63 (20% EtOAc/hexanes); $[\alpha]^{20}_D$ + 116.0 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 5.86 (t, *J* = 6.5 Hz, 1H, -NH), 5.30 (t, *J* = 7.5 Hz, 1H), 5.17 (dq, *J* = 9.5 Hz, 1.5 Hz, 1H), 4.07 (m, 1H), 3.62 (m, 3H), 3.45 (d, *J* = 9.5 Hz, 1H), 2.78-2.52 (m, 4H), 2.41 (s, 3H), 2.34 (m, 1H), 2.18-1.94 (m, 5H), 1.91 (d, *J* = 1.5 Hz, 3H), 1.79 (m, 1H), 1.64 (s, 3H), 1.62-1.54 (m, 3H), 1.48 (m, 12H), 1.29 (m, 8H), 1.10 (m, 2H), 0.98-0.84 (m, 36H), 0.58 (q, *J* = 8.0 Hz, 6H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.8, 143.7, 142.8, 140.1, 139.4, 137.8, 135.2, 129.4, 126.9, 126.8, 113.9, 92.3, 77.9, 62.8, 53.2, 43.5, 42.2, 39.4, 35.9, 35.8, 33.3, 32.8, 29.24, 29.17, 27.6, 27.3, 25.8, 24.9, 24.1, 21.5, 21.4, 19.8, 18.2, 16.9, 15.3, 13.7, 11.1, 9.1, 6.8, 4.3, -3.9, -4.2; IR (thin film): 3280, 3185, 1701, 1684 cm^{-1}; HRMS (MALDI) Calcd. for $C_{58}H_{106}INO_6SSi_2Sn$ [M+H]: 1120.6301. Found: 1120.7857.

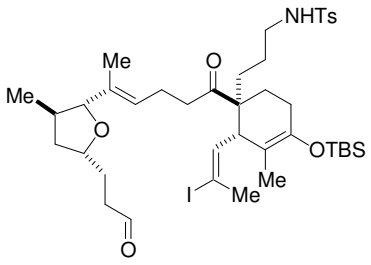


Vinyl iodide **127b**: To a solution of the vinyl stannanne **126b** (24 mg, 0.0223 mmol) in CH_2Cl_2 (2 ml) at -78 ºC was added a solution of iodine (10 mg) in CH_2Cl_2 (1 ml) until the reaction went to *ca*. 90% completion as monitored by TLC (*ca*. 0.5 ml of

the iodine solution was added). The reaction mixture was quenched by cyclohexene (100 μl), warmed to room temperature and stirred for 30 min. The mixture was concentrated *in vacuo* and then purified by flash chromatography (5%→10%→15% EtOAc/hexanes) to afford 13 mg (63%) of the desired product as a colorless oil and 2 mg (8%) of the recovered starting material. R_f = 0.47 (20% EtOAc/hexanes); $[\alpha]^{20}_D$ + 120.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 5.87 (dq, *J* = 11.0 Hz, 1.5 Hz, 1H), 5.79 (t, *J* = 6.0 Hz, 1H, -NH), 5.33 (t, *J* = 7.0 Hz, 1H), 4.04 (m, 1H), 3.64 (d, *J* = 8.0 Hz, 1H), 3.59 (m, 2H), 3.21 (d, *J* = 11.0 Hz, 1H), 2.75 (m, 2H), 2.56 (m, 1H), 2.51 (m, 1H), 2.47 (d, *J* = 1.5 Hz, 3H), 2.43 (s, 3H), 2.37 (m, 1H), 2.14 (m, 1H), 2.01 (m, 4H), 1.78 (m, 1H), 1.68 (m, 1H), 1.65 (s, 3H), 1.58 (m, 2H), 1.52 (s, 3H), 1.48 (m, 3H), 1.33 (m, 2H), 1.12 (m, 1H), 1.01 (m, 1H), 0.95 (m, 12H), 0.90 (s, 9H), 0.59 (q, *J* = 8.0 Hz, 6H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.7, 144.3, 142.9, 140.3, 137.7, 135.3, 129.6, 126.9, 126.6, 112.3, 95.0, 92.2, 77.9, 62.8, 53.1, 45.5, 43.3, 39.4, 35.91, 35.86, 33.4, 32.7, 29.3, 28.1, 27.5, 25.8, 25.3, 24.1, 21.5, 21.4, 18.1, 16.9, 15.2, 11.2, 6.8, 4.4, -3.8, -4.2; IR (thin film): 3280, 3181, 1703, 1684 cm^{-1}; HRMS (ESI) Calcd. for $C_{46}H_{79}INO_6SSi_2$ [M+H]: 956.4211. Found: 956.4056.

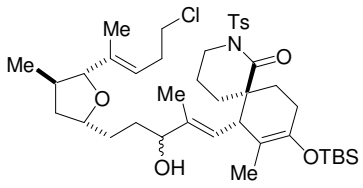


Alcohol **132**: To a solution of the silyl ether **127b** (16 mg, 0.0167 mmol) in CH_2Cl_2/MeOH (1:1, 2 ml) at 0 ºC was added pyridinium *p*-toluenesulfonate (4 mg, 0.0167 mmol). After stirring at 0 ºC for 20 min, the reaction mixture was quenched by sat. $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (5%→10%→15% EtOAc/hexanes) to afford 12 mg (85%) of the desired alcohol as a colorless oil. R_f = 0.13 (30% EtOAc/hexanes); $[\alpha]^{20}_D$ + 118.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.01 ((t, *J* = 6.0 Hz, 1H, -NH), 5.86 (dq, *J* = 11.0 Hz, 1.5 Hz, 1H), 5.35 (t, *J* = 7.0 Hz, 1H), 4.07 (m, 1H), 3.65 (d, *J* = 8.0 Hz, 1H), 3.62 (m, 2H), 3.21 (d, *J* = 11.0 Hz, 1H), 2.75 (m, 2H), 2.61-2.53 (m, 2H including -OH), 2.48 (m, 1H), 2.45 (d, *J* = 1.5 Hz, 3H), 2.43 (s, 3H), 2.38 (m, 1H), 2.14 (m, 1H), 2.06-1.92 (m, 5H), 1.78 (m, 1H), 1.68 (m, 5H), 1.64 (s, 3H), 1.51 (s, 3H), 1.30 (m, 2H), 1.10 (m, 1H), 1.01 (m, 1H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.90 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.7, 144.3, 143.0, 140.3, 137.5, 135.1, 129.6, 127.0, 126.7, 112.3, 94.9, 92.4, 78.0, 62.7, 53.0, 45.4, 43.4, 39.7, 36.03, 35.98, 33.7, 33.2, 29.6, 28.1, 27.5, 25.8, 25.5, 24.0, 21.5, 21.3, 18.1, 17.1, 15.2, 11.3, -3.8, -4.1; IR (thin film): 3498, 3292, 3168, 1701, 1686 cm^{-1}; HRMS (ESI) Calcd. for $C_{40}H_{65}INO_6SSi_2$ [M+H]: 842.3347. Found: 842.3361.



Aldehyde **133**: A solution of the alcohol **132** (3.0 mg, 0.00356 mmol, azeotropically dried with toluene) in CH_2Cl_2 (1 ml) containing anhydrous $NaHCO_3$ powder (4 mg) at 0 ºC was treated with Dess-Martin periodinane (3 mg, 0.00713 mmol). The reaction mixture was stirred at room temperature for 1.5 h, diluted with Et_2O and filtered through a pad of Celite. The solution was concentrated *in vacuo* and the residue was purified by flash chromatography (20%→30% EtOAc/hexanes) to afford 2.7 mg (90%) of the desired product as a colorless oil. R_f = 0.45 (30% EtOAc/hexanes); $[\alpha]^{20}_D$ + 154.4 (*c* 0.73, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (t, *J* = 1.5 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 5.87 (dq, *J* = 10.5 Hz, 1.5 Hz, 1H), 5.66 (t, *J* = 6.5 Hz, 1H, -NH), 5.32 (t, *J* = 7.5 Hz, 1H), 4.12 (m, 1H), 3.64 (d, *J* = 8.5 Hz, 1H), 3.21 (d, *J* = 10.5 Hz, 1H), 2.79 (m, 1H), 2.70 (m, 1H), 2.61-2.49 (m, 4H), 2.46 (d, *J* = 1.5 Hz, 3H), 2.44 (s, 3H), 2.38 (m, 1H), 2.13 (m, 1H), 2.06-1.92 (m, 4H), 1.81 (m, 3H), 1.71 (m, 1H), 1.63 (s, 3H), 1.51 (s, 3H), 1.48 (m, 1H), 1.30 (m, 2H), 1.14 (m, 1H), 1.00 (m, 1H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.90 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.7, 202.3, 144.4, 143.1, 140.3, 137.4, 135.0, 129.7, 127.06, 126.96, 112.2, 95.0, 92.6, 77.2, 53.0, 45.5, 43.4, 40.5, 39.5, 35.9, 35.8, 33.5, 28.7, 28.1, 27.5, 25.8, 25.3, 24.1, 21.51, 21.45, 18.1, 16.7, 15.2, 11.2, -3.8, -4.1; IR (thin film): 3274, 3192,

1723, 1703, 1689 cm^{-1}; HRMS (ESI) Calcd. for $C_{40}H_{63}INO_6SSi_2$ [M+H]: 840.3190. Found: 840.3301.

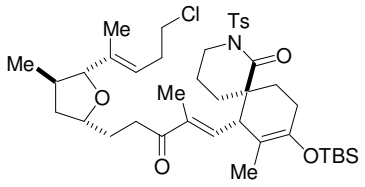


Alcohol **134a/134b**: Anhydrous DMF used in this experiment was degassed through freeze-thaw processes (three times) and further dried over activated powdered 4Å molecular sieves. THF was degassed through freeze-thaw processes (three times).

In a glove box, anhydrous $CrCl_2$ (5 g, 40.7 mmol) and anhydrous $NiCl_2$ (26 mg, 0.201 mmol) were thoroughly mixed. A flask was charged with 995 mg (8.10 mmol) of this mixture. The flask was taken out of the glove box and DMF (4 ml) was added. The resulting green mixture was stirred at room temperature for 30 min. In a separate flask the aldehyde **116** (198 mg, 0.810 mmol) and the vinyl iodide **110** (1.02 g, 1.62 mmol) were azeotropically dried with toluene (2 ml × 2) and dissolved in THF (4 ml). The substrate solution was added to the $NiCl_2/CrCl_2$ solution plus 8 ml of THF/DMF (1:1) rinse. The reaction mixture was stirred at room temperature for 18 h and quenched by water (10 ml). The solution was extracted with Et_2O (20 ml × 3), the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (20%→30%→40% EtOAc/hexanes) to afford 327 mg (54%) of the desired diastereomer **134b** as a white foam and 260 mg (43%) of the epimeric diastereomer **134a** as a white foam.

Major diastereomer **134b**: R_f = 0.42 (40% EtOAc/hexanes); $[\alpha]_D^{21}$ +83.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 5.43 (t, *J* = 7.0 Hz, 1H), 5.14 (d, *J* = 11.5 Hz, 1H), 3.97-3.85 (m, 3H), 3.81 (m, 1H), 3.69 (d, *J* = 8.0 Hz, 1H), 3.53 (m, 3H), 2.52 (m, 3H), 2.42 (s, 3H), 2.00 (m, 4H), 1.94-1.84 (m, 3H), 1.80-1.66 (m, 2H), 1.62 (s, 3H), 1.60-1.46 (m, 6H), 1.38 (s, 3H), 1.33 (s, 3H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.92 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 144.1, 142.1, 140.1, 137.1, 136.5, 129.1, 128.6, 123.8, 123.2, 111.9, 92.0, 77.8, 76.7, 47.2, 47.0, 44.0, 43.6, 39.8, 36.2, 32.1, 31.8, 31.4, 31.1, 27.0, 26.7, 25.8, 21.6, 20.7, 18.1, 17.1, 14.3, 12.5, 11.5, -3.9, -4.0; IR (thin film): 3538, 3426, 1682 cm^{-1}; HRMS (ESI) Calcd. for $C_{40}H_{63}ClNO_6SSi$ [M+H]: 748.3834. Found: 748.3784.

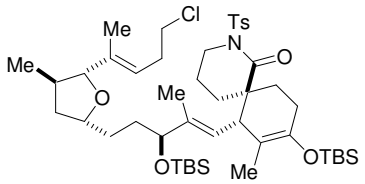
Minor diastereomer **134a**: R_f = 0.27 (40% EtOAc/hexanes); $[\alpha]_D^{21}$ + 93.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 5.43 (t, *J* = 6.5 Hz, 1H), 5.17 (d, *J* = 11.0 Hz, 1H), 4.01-3.88 (m, 3H), 3.81 (m, 1H), 3.70 (d, *J* = 8.0 Hz, 1H), 3.53 (m, 3H), 2.53 (dt, *J* = 6.5 Hz, 6.5 Hz, 2H), 2.43 (s, 3H), 2.40 (br s, OH, 1H), 1.62 (s, 3H),1.46 (s, 3H), 1.39 (s, 3H), 2.06-1.64 (m, 11H), 1.59-1.48 (m, 4H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.93 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 144.4, 142.1, 140.5, 137.2, 136.5, 129.2, 128.6, 124.4, 123.1, 111.9, 92.1, 78.2, 78.0, 47.4, 47.2, 40.03, 40.01, 39.8, 36.3, 33.0, 32.0, 31.1, 31.0, 26.83, 26.76, 25.8, 21.6, 20.7, 18.1, 17.1, 14.4, 11.7, 11.5, -3.88, -3.94; IR (thin film): 3537, 3424, 1682 cm^{-1}.



Ketone **135**: To a solution of the alcohol **134a** (178 mg, 0.238 mmol) in CH_2Cl_2 (10 ml) containing anhydrous $NaHCO_3$ powder (200 mg, 2.38 mmol) at 0 ºC was added Dess-Martin periodinane (202 mg, 0.476 mmol). The reaction mixture was stirred at room temperature for 80 min, diluted with Et_2O and filtered through a pad of Celite. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography (20%→30% EtOAc/hexanes) to afford 156 mg (88%) of the desired ketone as a colorless oil. R_f = 0.59 (30% EtOAc/hexanes); $[\alpha]^{20}_D$ + 103.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.28 (d, *J* = 11.5 Hz, 1H), 5.44 (t, *J* = 7.0 Hz, 1H), 3.97 (m, 2H), 3.77 (m, 1H), 3.69 (d, *J* = 8.5 Hz, 1H), 3.65 (d, *J* = 11.5 Hz, 1H), 3.52 (m, 2H), 2.76 (ddd, *J* = 5.5 Hz, 9.5 Hz, 16.5 Hz, 1H), 2.63 (m, 1H), 2.54 (m, 2H), 2.44 (s, 3H), 2.06 (m, 2H), 2.02-1.92 (m, 3H), 1.87-1.68 (m, 8H), 1.62 (s, 3H), 1.45 (s, 3H), 1.35 (s, 3H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.93 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3, 174.6, 144.6, 143.2, 139.9, 138.7, 137.1, 136.1, 129.2, 128.4, 123.5, 110.2, 92.2, 77.2, 47.1, 46.8, 45.0, 44.0, 40.0, 36.1, 34.3, 31.3, 31.2, 31.1, 27.5, 26.8, 25.8, 21.6, 20.6, 18.1, 16.8, 14.2, 11.6, 11.4, -3.8, -3.9; IR (thin film): 1672 cm^{-1}; LRMS (ESI) Calcd. for $C_{40}H_{61}ClNO_6SSiLi$ [M+H]: 746. Found: 746.

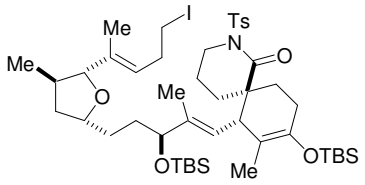
Ketone **135** (250 mg, 0.335 mmol) was azeotropically dried with toluene (2 ml), dissolved in CH_2Cl_2 (20 ml) and cooled to 0 ºC. A solution of (R)-Me-CBS

oxazaborolidine (1.0 M in PhMe, 335 μl, 0.335 mmol) was added followed by catecholborane (107 μl, 1.00 mmol). The mixture was stirred at 0 ºC for 3 h and then quenched by water (2 ml). 2N NaOH solution (8 ml) was added and the black mixture was vigorously stirred at room temperature for 20 min. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine, and concentrated *in vacuo*. The residue was purified by flash chromatography (10%→20%→30%→40% EtOAc/hexanes) to afford 173 mg (69%) of the desired product **134b** and 29 mg (12%) of the epimer **134a**.



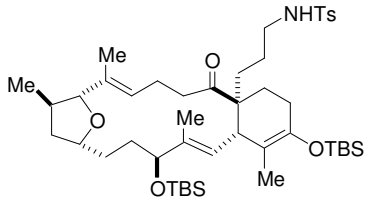
TBS alcohol **136a**: To a solution of the alcohol **134b** (237 mg, 0.317 mmol) in CH_2Cl_2 (20 ml) at -78 ºC were added Et_3N (220 μl, 1.58 mmol) and TBSOTf (179 μl, 0.792 mmol). The reaction mixture was stirred at -78 ºC for 10 min and quenched by pH 7 buffer. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (5%→10%→15% EtOAc/hexanes) to afford 236 mg (86%) of the desired product as a white foam. The undesired C-13 epimer was easily separated at this stage. R_f = 0.15 (10% EtOAc/hexanes); $[\alpha]^{20}_D$ = +74.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 5.43 (t, *J* = 7.0 Hz, 1H), 5.00 (d, *J* = 11.5 Hz, 1H), 3.93 (m, 3H), 3.76 (m, 1H), 3.67 (d, *J* = 8.5 Hz, 1H), 3.51 (m, 3H), 2.53 (m, 2H), 2.42 (s, 3H), 2.02 (m, 3H), 1.86 (m, 3H), 1.74 (m, 3H), 1.66

(m, 4H), 1.62 (s, 3H), 1.52 (m, 2H), 1.40 (s, 3H), 1.35 (s, 3H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.92 (s, 9H), 0.86 (s, 9H), 0.081 (s, 3H), 0.076 (s, 3H), 0.009 (s, 3H), -0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 144.1, 142.0, 140.2, 137.4, 136.4, 129.1, 128.7, 123.9, 122.9, 112.3, 91.8, 77.91, 77.90, 47.1, 47.0, 44.0, 43.3, 39.6, 36.2, 32.8, 32.3, 31.5, 31.2, 27.5, 26.8, 25.82, 25.76, 21.6, 20.4, 18.11, 18.07, 17.0, 14.7, 11.8, 11.5, -3.9, -4.0, -4.7, -4.9; IR (thin film): 1684 cm^{-1}; HRMS (ESI) Calcd. for $C_{46}H_{77}ClNO_6SSi_2$ [M+H]: 862.4699. Found: 862.4665.



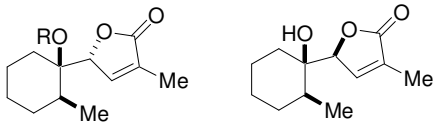
Iodide **136b**: A solution of the alkyl chloride **136a** (236 mg, 0.274 mmol) in acetone (20 ml) containing NaI (410 mg, 2.74 mmol) was heated at 65 ºC for 5 d. The reaction mixture was directly concentrated *in vacuo* and purified by flash chromatography (5%→10% EtOAc/hexanes) to afford 262 mg (99%) of the desired product as a slightly yellow oil. R_f = 0.15 (10% EtOAc/hexanes); $[\alpha]^{20}_D$ = + 67.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 5.37 (t, *J* = 6.5 Hz, 1H), 5.01 (d, *J* = 11.5 Hz, 1H), 3.92 (m, 3H), 3.75 (m, 1H), 3.67 (d, *J* = 8.5 Hz, 1H), 3.49 (d, *J* = 11.5 Hz, 1H), 3.15 (m, 2H), 2.65 (m, 2H), 2.43 (s, 3H), 2.01 (m, 3H), 1.86 (m, 3H), 1.74 (m, 3H), 1.64 (m, 4H), 1.60 (s, 3H), 1.52 (m, 2H), 1.40 (s, 3H), 1.35 (s, 3H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.93 (s, 9H), 0.86 (s, 9H), 0.082 (s, 3H), 0.077 (s, 3H), 0.01 (s, 3H), -0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 144.1, 142.0, 140.2, 136.9, 136.4, 129.1, 128.7, 125.8, 123.9, 112.3, 91.8, 77.96, 77.92, 47.1,

47.0, 43.3, 39.6, 36.2, 32.8, 32.3, 31.9, 31.2, 27.5, 26.8, 25.83, 25.77, 21.6, 20.4, 18.12, 18.08, 17.0, 14.7, 11.8, 11.5, 5.4, -3.9, -4.0, -4.6, -4.9; IR (thin film): 1686 cm^{-1}; HRMS (ESI) Calcd. for $C_{46}H_{77}INO_6SSi_2$ [M+H]: 954.4055. Found: 954.4212.



N-Tosyl amine **141a**: The alkyl iodide **136b** (96 mg, 0.101 mmol) was azeotropically dried with PhMe (1 ml) and dissolved in Et_2O (15 ml). *t*-BuLi (1.6 M in pentane, 140 μl) was then added dropwise at room temperature. The resulting slightly yellow solution was stirred at room temperature for 15 min and quenched by pH 7 buffer (5 ml). The aqueous layer was extracted with Et_2O and the combined organic layers were concentrated *in vacuo*. The residue was purified by flash chromatography (5%→10%→15%→20% EtOAc/hexanes) to afford 47 mg (56%) of the desired product as a white foam. R_f = 0.30 (20% EtOAc/hexanes); $[\alpha]^{20}_D$ + 20.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 5.01 (br t, *J* = 5.0 Hz, 1H), 4.94 (dd, *J* = 11.5 Hz, 1.5 Hz, 1H), 4.86 (t, *J* = 5.5 Hz, 1H, NH), 4.09 (m, 1H), 3.99 (br s, 1H), 3.84 (dd, *J* = 3.5 Hz, 11.5 Hz, 1H), 3.68 (d, *J* = 11.5 Hz, 1H), 2.94 (m, 2H), 2.74 (ddd, *J* = 3.0 Hz, 12.5 Hz, 19.0 Hz, 1H), 2.61 (ddd, *J* = 3.0 Hz, 3.0 Hz, 19.0 Hz, 1H), 2.44 (s, 3H), 2.21 (m, 2H), 2.10-1.96 (m, 5H), 1.82 (m, 1H), 1.73 (m, 2H), 1.69 (d, *J* = 1.5 Hz, 3H), 1.66-1.56 (m, 2H), 1.53 (s, 3H), 1.50 (m, 3H), 1.46 (s, 3H), 1.41 (m, 2H), 1.11 (d, *J* = 7.0 Hz, 3H), 0.96 (s, 9H), 0.86 (s, 9H), 0.142 (s, 3H), 0.135 (s, 3H), 0.05 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.1, 143.1, 143.0, 140.5,

136.8, 135.5, 129.5, 127.2, 123.8, 122.6, 111.9, 89.1, 79.4, 78.1, 53.3, 45.4, 43.7, 37.6, 36.9, 34.6, 32.9, 32.1, 28.8, 27.3, 25.8, 25.6, 24.6, 23.4, 21.5, 20.6, 20.0, 18.1, 18.0, 14.2, 13.8, 10.7, -3.6, -3.8, -4.76, -4.82; IR (thin film): 3281, 1701, 1683 cm^{-1}; HRMS Calcd. for $C_{46}H_{77}NO_6SSi_2Li$ [M+Li]: 834.5170. Found: 834.5163.



149a: R = TBS
149b: R = H

epi-**149b**

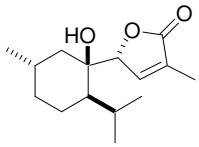
Representative procedure (**procedure A**) for the vinylogous Mukaiyama aldol as described for addition of 3-methyl-2-(*tert*-butyldimethyl)silyloxy furan to 2-methylcyclohexanone (Table 3, entry 5): To a solution of 2-methylcyclohexanone (52 mg, 0.464 mmol) in CH_2Cl_2 (5 ml) at -78 ºC was added TMSOTf (34 µl, 0.185 mmol). After stirring for 15 min, 3-methyl-2-(*tert*-butyldimethyl)silyloxy furan **148a** (128 mg, 0.603 mmol) was added dropwise. The reaction mixture was stirred at -78 ºC for 2 h, quenched by saturated $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O, and the combined organic layers were dried ($MgSO_4$), concentrated and purified by flash chromatography (10→30 % EtOAc/hexanes) to afford 24 mg (16 %) silylated product **149a** as a colorless solid and 67 mg (69 %) non-silylated product as a colorless solid. For characterization purpose, purification of non-silylated product by flash chromatography (low flow rate, 20→30 % EtOAc/hexanes) gave pure **149b** and small amount of *epi*-**149b**.

Silylated butenolide **149a**: m.p.68-80 ºC; R_f = 0.76 (30 % EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 6.98 (dq, *J* = 1.5, 1.5 Hz, 1H), 5.03 (dq, *J* = 1.5, 1.5 Hz, 1H),

1.94 (dd, *J* = 1.5, 1.5 Hz, 3H), 1.72-1.52 (m, 4H), 1.46-1.38 (m, 2H), 1.36-1.31 (m, 1H), 1.20-1.08 (m, 1H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.95 (s, 9H), 0.84 (dt, *J* = 4.5, 13.0 Hz, 1H), 0.23 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 145.2, 131.3, 86.4, 78.2, 39.8, 30.2, 29.4, 26.3, 25.7, 20.4, 19.2, 15.2, 10.8, -2.7, -3.0; IR (thin film): 1753 cm^{-1}; LRMS (ESI) Calcd. for $C_{18}H_{32}O_3SiLi$ [M+Li]: 331. Found: 331.

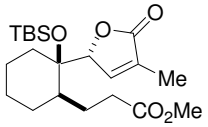
Hydroxy butenolide **149b**: Recrystallization from heptane provided crystals suitable for X-ray analysis. m.p.77-85 ºC; R_f = 0.30 (30 % EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (dq, *J* = 1.5, 1.5 Hz, 1H), 5.10 (dq, *J* = 1.5, 1.5 Hz, 1H), 1.95 (dd, *J* = 1.5, 1.5 Hz, 3H), 1.79 (br s, 1H, OH), 1.68 (m, 1H), 1.61-1.44 (m, 7H), 1.20 (m, 1H), 1.04 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 145.1, 131.1, 86.3, 74.5, 37.4, 31.0, 30.2, 25.4, 20.6, 15.4, 10.8; IR (thin film): 3431, 1738 cm^{-1}; LRMS (ESI) Calcd. for $C_{12}H_{18}O_3Li$ [M+Li]: 217. Found: 217.

Hydroxy butenolide *epi*-**149b**: Recrystallization from heptane provided crystals suitable for X-ray analysis. m.p.77-85 ºC; R_f = 0.22 (30 % EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (dq, *J* = 1.5, 1.5 Hz, 1H), 4.96 (dq, *J* = 2.0, 2.0 Hz, 1H), 1.94 (dd, *J* = 1.5, 2.0 Hz, 3H), 1.87 (m, 1H), 1.71 (br s, 1H, OH), 1.64 (m, 1H), 1.55 (m, 2H), 1.45 (m, 1H), 1.34-1.20 (m, 4H), 0.99 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 147.8, 130.6, 83.1, 74.4, 36.2, 30.8, 30.3, 25.2, 20.9, 14.9, 10.7; IR (thin film): 3495, 1732 cm^{-1}.

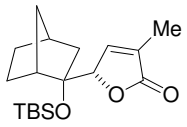


Representative procedure (**procedure B**) for vinylogous Mukaiyama aldol addition of 3-methyl-2-(*tert*-butyldimethyl)silyloxy furan to ketones as described for menthone (Table 4, entry 1): To a solution of menthone (86 mg, 0.558 mmol) in CH_2Cl_2 (5 ml) at -78 ºC was added $TiCl_4$ (1.0 M in CH_2Cl_2, 1.67 ml, 1.67 mmol). After stirring for 15 min, 3-methyl-2-(*tert*-butyldimethyl)silyloxy furan **148a** (237 mg, 1.12 mmol) in CH_2Cl_2 (3 ml) was added over 7 h via a syringe pump. The reaction mixture was quenched by saturated NH_4Cl solution. The aqueous layer was extracted with Et_2O, and the combined organic layers were dried ($MgSO_4$), concentrated and purified by flash chromatography (10→30 % EtOAc/hexanes) to afford 29 mg (14 %) silylated product **149c-TBS** as a colorless solid and 88 mg (63 %) non-silylated product **149c-H** as a colorless solid.

Butenolide **149c-H**, major diastereomer (Table 4, entry 1): m.p.121-126 ºC; R_f = 0.57 (30 % EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (dq, *J* = 1.5, 1.5 Hz, 1H), 5.26 (dq, *J* = 1.5, 1.5 Hz, 1H), 2.12 (dhept, *J* = 2.0, 7.0 Hz, 1H), 1.96 (dd, *J* = 1.5, 1.5 Hz, 3H), 1.81 (d, *J* = 1.0 Hz, 1H, OH), 1.80-1.72 (m, 2H), 1.66-1.47 (m, 3H), 1.21 (m, 1H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.83 (d, *J* = 6.0 Hz, 3H), 0.80 (dq, *J* = 3.5, 13.5 Hz, 1H), 0.61 (q, *J* = 13.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 144.9, 131.4, 86.6, 76.5, 48.1, 40.4, 34.9, 27.1, 26.6, 23.4, 22.2, 20.1, 17.7, 10.8; IR (thin film): 3499, 1739 cm^{-1}; LRMS (ESI) Calcd. for $C_{15}H_{24}O_3Li$ [M+Li]: 259. Found: 259.

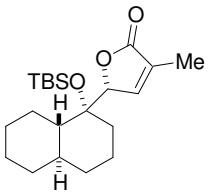


Butenolide **149d** (Table 4, entry 2): The butenolide **149d** was prepared according to general procedure **B** from methyl 3-(2-oxocyclohexyl)propanoate (106 mg, 0.576 mmol). Purification by flash chromatography (20→30→50 % EtOAc/hexanes) afforded 110 mg (48 %) of silylated product **149d**-**TBS** as a colorless oil and 45 mg (28 %) of non-silylated product **149d**-**H** as a colorless oil. Silylated product **149d-TBS**, major diastereomer: R_f = 0.53 (30 % EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (dq, *J* = 2.0, 2.0 Hz, 1H), 5.17 (dq, *J* = 2.0, 2.0 Hz, 1H), 3.70 (s, 3H), 2.45 (ddd, *J* = 6.0, 6.0, 17.0 Hz, 1H), 2.36 (ddd, *J* = 6.0, 10.5, 17.0 Hz, 1H), 1.95 (dd, *J* = 2.0, 2.0 Hz, 3H), 1.72 (m, 2H), 1.55 (m, 4H), 1.40 (m, 3H), 1.08 (m, 1H), 0.93 (s, 9H), 0.83 (dt, *J* = 4.5, 13.0 Hz, 1H), 0.23 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 174.1, 145.7, 131.2, 86.3, 78.4, 51.6, 43.6, 30.4, 29.2, 26.3, 25.5, 25.4, 23.8, 20.3, 19.1, 10.8, -2.7, -3.0; IR (thin film): 1771, 1734 cm^{-1}; LRMS (ESI) Calcd. for $C_{21}H_{36}O_5SiLi$ [M+Li]: 403. Found: 403.

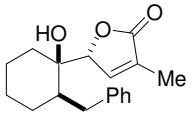


Butenolide **149e** (Table 4, entry 3): The butenolide **149e** was prepared according to general procedure **B** from norcamphor (23 mg, 0.209 mmol). Purification by flash chromatography (10→30 % EtOAc/hexanes) afforded 38 mg (56 %) of silylated product 149**e**-**TBS** as a colorless solid and 15 mg (34 %) of non-silylated product **149e**-**H** as a colorless solid. Silylated product **149e-TBS**, major diastereomer: Recrystallization from

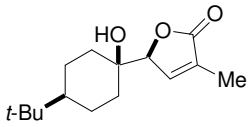
heptane provided crystals suitable for X-ray analysis. m.p.51-68 ºC; R_f = 0.67 (30 % EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (dq, *J* = 1.5, 1.5 Hz, 1H), 4.79 (br s, 1H), 2.26 (m, 2H), 1.94 (dd, *J* = 1.5, 1.5 Hz, 3H), 1.91 (m, 1H), 1.78 (ddd, *J* = 3.0, 4.5, 13.0 Hz, 1H), 1.53 (m, 2H), 1.32 (m, 3H), 1.22 (m, 1H), 0.87 (s, 9H), 0.17 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 146.5, 131.2, 85.9, 82.1, 44.9, 40.5, 37.5, 36.9, 28.0, 25.9, 22.3, 18.4, 10.8, -2.1, -2.4; IR (thin film): 1750, 1738 cm^{-1}; LRMS (ESI) Calcd. for $C_{18}H_{30}O_3SiLi$ [M+Li]: 329. Found: 329.



Butenolide **149f** (Table 4, entry 4): The butenolide **149f** was prepared according to general procedure **B** from *trans*-decalone (100 mg, 0.657 mmol). Purification by flash chromatography (5→20 % EtOAc/hexanes) afforded 119 mg (50 %) of silylated product **149f-TBS** as a colorless solid and 51 mg (31 %) of non-silylated product **149f-H** as a colorless solid. Silylated product **149f-TBS**, major diastereomer: Recrystallization from heptane provided crystals suitable for X-ray analysis. m.p.104-115 ºC; R_f = 0.78 (30 % EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (dq, *J* = 1.5, 1.5 Hz, 1H), 5.06 (dq, *J* = 2.0, 2.0 Hz, 1H), 1.94 (dd, *J* = 2.0, 2.0 Hz, 3H), 1.80 (m, 1H), 1.74-1.54 (m, 8H), 1.44 (m, 2H), 1.22 (m, 2H), 0.95 (s, 9H), 0.84 (m, 3H), 0.23 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 145.1, 131.3, 86.2, 78.1, 50.4, 36.0, 34.4, 33.9, 29.6, 26.39, 26.36, 25.9, 25.0, 20.1, 19.2, 10.8, -2.7, -3.0; IR (thin film): 1757, 1749 cm^{-1}; LRMS (ESI) Calcd. for $C_{21}H_{36}O_3SiLi$ [M+Li]: 371. Found: 371.

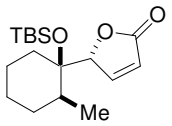


Butenolide **149g** (Table 4, entry 5): The butenolide **149g** was prepared according to general procedure **B** from 2-benzylcyclohexanone (108 mg, 0.574 mmol). Purification by flash chromatography (5→20 % EtOAc/hexanes) afforded 79 mg (34 %) of silylated product **149g-TBS** as a colorless solid and 69 mg (42 %) of non-silylated product **149g-H** as a colorless solid. Non-silylated product **149g-H**, major diastereomer: m.p.115-118 ºC; R_f = 0.33 (30 % EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (m, 2H), 7.24 (dq, *J* = 1.5, 1.5 Hz, 1H), 7.20 (m, 3H), 5.22 (dq, *J* = 1.5, 1.5 Hz, 1H), 3.16 (dd, *J* = 3.5, 13.0 Hz, 1H), 2.35 (dd, *J* = 11.0, 13.5 Hz, 1H), 2.04 (dddd, *J* = 3.5, 3.5, 11.0, 11.0 Hz, 1H), 1.98 (dd, *J* = 1.5, 1.5 Hz, 3H), 1.79 (s, 1H, OH), 1.58 (m, 2H), 1.45 (m, 2H), 1.35 (m, 2H), 1.22 (m, 1H), 1.08 (tq, *J* = 3.5, 13.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 144.8, 140.7, 131.5, 129.1, 128.5, 126.1, 85.9, 75.0, 44.3, 35.9, 31.1, 26.8, 25.1, 20.6, 10.8; IR (thin film): 3449, 1742 cm^{-1}; LRMS (ESI) Calcd. for $C_{18}H_{22}O_3Li$ [M+Li]: 293. Found: 293.

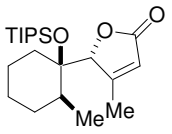


Butenolide **149i** (Table 4, entry 7): The butenolide **149i** was prepared according to general procedure **A** from 4-*tert*-butylcyclohexanone (66 mg, 0.428 mmol). Purification by flash chromatography (10→30 % EtOAc/hexanes) afforded 30 mg (19 %) of silylated product **149i-TBS** as a colorless solid and 76 mg (70 %) of non-silylated product **149i-H** as a colorless solid. Non-silylated product **149i-H**, major

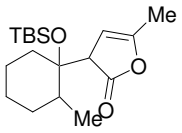
diastereomer: Recrystallization from heptane provided crystals suitable for X-ray analysis. m.p.101-110 ºC; R_f = 0.30 (30 % EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (dq, *J* = 2.0, 2.0 Hz, 1H), 4.67 (dq, *J* = 2.0, 2.0 Hz, 1H), 1.94 (dd, *J* = 2.0, 2.0 Hz, 3H), 1.78 (m, 1H), 1.71-1.61 (m, 3H), 1.50-1.31 (m, 4H), 0.96 (m, 1H) 0.86 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 145.8, 131.1, 87.5, 72.1, 47.6, 33.7, 33.5, 32.3, 29.7, 27.4, 21.7, 10.7; IR (thin film): 3547, 1745 cm^{-1}; LRMS (ESI) Calcd. for $C_{15}H_{24}O_3Li$ [M+Li]: 259. Found: 259.



Butenolide **149k** (Table 5, entry 1): The butenolide **149k** was prepared according to general procedure **A** from 2-methylcyclohexanone (135 mg, 1.20 mmol) and 2-(*tert*-butyldimethyl)silyloxy furan **148b** (310 mg, 1.56 mmol). Purification by flash chromatography (10→30 % EtOAc/hexanes) afforded 240 mg (64 %) of silylated product **149k-TBS** as a colorless solid and 15 mg (6 %) of non-silylated product **149k-H** as a colorless solid. Silylated product **149k-TBS**, major diastereomer: m.p.64-72 ºC; R_f = 0.58 (30% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 1.5, 6.0 Hz, 1H), 6.16 (dd, *J* = 2.0, 6.0 Hz, 1H), 5.20 (dd, *J* = 2.0, 2.0 Hz, 1H), 1.76 (m, 1H), 1.67 (m, 1H), 1.63-1.52 (m, 2H), 1.47-1.39 (m, 2H), 1.38-1.33 (m, 1H), 1.14 (tq, *J* = 4.0, 13.0 Hz, 1H), 0.99 (d, *J* = 6.5 Hz, 3H), 0.95 (s, 9H), 0.85 (dt, *J* = 4.0, 13.5 Hz, 1H), 0.24 (s, 3H), 0.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 152.9, 122.7, 88.7, 78.1, 39.8, 30.1, 29.4, 26.2, 25.6, 20.3, 19.2, 15.2, -2.8, -3.1; IR (thin film): 1759 cm^{-1}; LRMS (ESI) Calcd. for $C_{17}H_{30}O_3SiLi$ [M+Li]: 317. Found: 317.

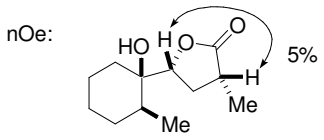


Butenolide **149l** (Table 5, entry 2): The butenolide **149l** was prepared according to general procedure **A** from 2-methylcyclohexanone (47 mg, 0.419 mmol) and 4-methyl-2-(triisopropyl)silyloxy furan **148c** (139 mg, 0.545 mmol). Purification by flash chromatography (10→30 % EtOAc/hexanes) afforded 101 mg (66 %) of silylated product **149l-TIPS** as a colorless solid and 26 mg (30 %) of non-silylated product **149l-H** as a colorless solid. Silylated product **149l-H**, major diastereomer: m.p.35-55 ºC; R_f = 0.55 (30 % EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (dq, *J* = 1.0, 1.0 Hz, 1H), 5.14 (br s, 1H), 2.20 (dd, *J* = 1.0, 1.0 Hz, 3H), 1.77-1.60 (m, 4H), 1.48 (m, 1H), 1.38 (m, 1H), 1.28 (m, 2H), 1.14 (m, 21H), 1.08 (d, *J* = 7.0 Hz, 3H), 0.85 (dt, *J* = 4.0, 13.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 165.4, 120.3, 88.8, 78.6, 38.4, 30.5, 30.2, 25.8, 21.0, 18.99, 18.96, 16.4, 16.2, 14.1; IR (thin film): 1761 cm^{-1}; LRMS (ESI) Calcd. for $C_{21}H_{38}O_3SiLi$ [M+Li]: 373. Found: 373.

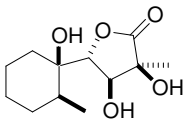


Butenolide **149m** (Table 5, entry 3): The butenolide **149m** was prepared according to general procedure **A** from 2-methylcyclohexanone (39 mg, 0.348 mmol) and 5-methyl-2-(*tert*-butyldimethyl)silyloxy furan **148d** (96 mg, 0.452 mmol). Purification by flash chromatography (5→20 % EtOAc/hexanes) afforded 60 mg (53 %) of **149m** as an inseparable mixture of two diastereomers (2 : 1) as a colorless oil. Major diastereomer: R_f = 0.76 (30 % EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.12 (dq,

J = 2.5, 1.5 Hz, 1H), 3.56 (dq, *J* = 2.5, 2.5 Hz, 1H), 1.99 (dd, *J* = 1.5, 2.5 Hz, 3H), 1.78-1.70 (m, 1H), 1.68-1.54 (m, 2H), 1.52-1.38 (m, 4H), 1.28 (m, 2H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.90 (s, 9H), 0.19 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 152.3, 102.1, 97.4, 52.9, 37.0, 32.6, 30.3, 26.2, 22.1, 22.0, 19.2, 15.5, 14.1, -1.8, -2.0; IR (thin film): 1789 cm^{-1}; LRMS (ESI) Calcd. for $C_{18}H_{32}O_3SiLi$ [M+Li]: 331. Found: 331.

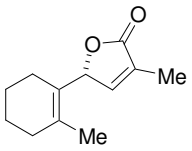


δ-Hydroxy γ-lactone **150**: A mixture of butenolide **149b** (13 mg, 0.0618 mmol) and 5 wt % palladium on carbon (5 mg) in EtOAc (1.5 ml) was bubbled with H_2. The reaction mixture was stirred at 25 ºC for 1 h, filtered through a pad of Celite, concentrated and purified by flash chromatography (30 % EtOAc/hexanes) to afford 13 mg (98 %) of the product **150** as a colorless solid. m.p.55-62 ºC; R_f = 0.49 (40 % EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.51 (dd, *J* = 6.0, 11.0 Hz, 1H), 2.70 (ddq, *J* = 7.0, 8.5, 12.0 Hz, 1H), 2.32 (ddd, *J* = 6.0, 8.5, 12.5 Hz, 1H), 1.78-1.42 (m, 9H), 1.71 (s, 1H, OH), 1.28 (d, *J* = 7.0 Hz, 3H), 1.24 (m, 1H), 0.97 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0, 83.2, 73.3, 36.8, 35.7, 31.7, 30.2, 29.9, 24.8, 20.9, 15.4, 14.9; IR (thin film): 3537, 1750 cm^{-1}; LRMS (ESI) Calcd. for $C_{12}H_{20}O_3Li$ [M+Li]: 219. Found: 219. The stereochemistry was assigned by nOe analysis as shown above.



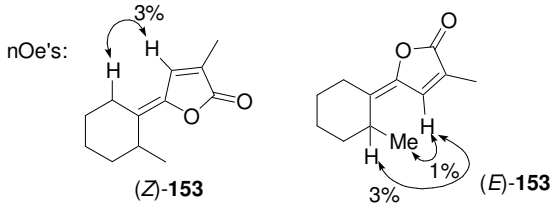
Triol **151**: To a solution of alcohol **149b** (18 mg, 0.0856 mmol) in 5 : 1 THF/H_2O mixture (1 ml) was added *N*-methyl morphiline *N*-oxide hydrate (23 mg, 0.171 mmol)

and osmium tetraoxide (2 mg). The reaction mixture was stirred at 70 ºC for 10 h. The resulting black mixture was quenched by saturated sodium sulfite solution and stirred at room tempreture for 1 h. The aqueous layer was extracted with EtOAc and the combined organic layers were dried ($MgSO_4$), concentrated and purified by flash chromatography (80 % EtOAc/hexanes) to afforded 15 mg (72 %) of product **151** as a colorless oil. R_f = 0.29 (60 % EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.46 (d, *J* = 7.5 Hz, 1H), 4.03 (dd, *J* = 7.5, 9.5 Hz, 1H), 3.50 (s, 1H, OH), 3.02 (d, *J* = 9.5 Hz, 1H, OH), 1.90 (br s, 1H, OH), 1.81 (m, 1H), 1.73 (m, 1H), 1.66-1.50 (m, 5H), 1.49 (s, 3H), 1.46 (m, 1H), 1.30 (m, 1H), 1.02 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 86.8, 73.1, 72.9, 72.3, 36.7, 30.4, 30.3, 23.7, 21.2, 21.1, 15.5. IR (thin film): 3433, 1775 cm^{-1}; LRMS (ESI) Calcd. for $C_{12}H_{20}O_5Li$ [M+Li]: 251. Found: 251.



Cyclohexene **152**: To a solution of alcohol **149b** (17 mg, 0.0809 mmol) in CH_2Cl_2 (1.5 ml) at -50 ºC was added pyridine (131 µl, 1.62 mmol) and thionyl chloride (30 µl, 0.405 mmol). The reaction mixture was stirred at -50 ºC for 2 h, quenched by saturated $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O, and the combined organic layers were dried ($MgSO_4$), concentrated and purified by flash chromatography (10 % EtOAc/hexanes) to afford 13 mg (88 %) of product **152** as a colorless oil (6:1 mixture of regioisomers). Major isomer: R_f = 0.50 (30 % EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (dq, *J* = 1.5, 1.5 Hz, 1H), 5.84 (dq, *J* = 1.5, 1.5 Hz, 1H), 2.02 (m, 2H), 1.94 (dd, *J* = 2.0, 2.0 Hz, 3H), 1.78 (s, 3H), 1.62 (m,

1H), 1.53 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 147.9, 134.5, 130.3, 124.2, 80.0, 32.4, 22.55, 22.51, 22.4, 19.0, 10.6; IR (thin film): 1758 cm^{-1}; LRMS (ESI) Calcd. for $C_{12}H_{16}O_2Li$ [M+Li]: 199. Found: 199. Note: Minor regioisomer is readily distinguished by the presence of additional vinyl proton.



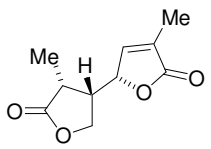
(*E*, *Z*)-Diene 153: To a solution of alcohol **149b** (21 mg, 0.0999 mmol) in CH_2Cl_2 (2 ml) at 25 ºC were sequentially added triethyl amine (70 µl, 0.499 mmol), DMAP (4 mg, 0.0300 mmol) and trifluoroacetic anhydride (71 µl, 0.499 mmol). The reaction mixture was stirred at 25 ºC for 15 min, concentrated and purified by flash chromatography (30 % EtOAc/hexanes) to afford 30 mg (98 %) of trifluoroacetate intermediate as a colorless oil. R_f = 0.34 (30 % EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (dq, *J* = 1.5, 1.5 Hz, 1H), 5.65 (dq, *J* = 2.0, 2.0 Hz, 1H), 2.60 (m, 1H), 1.95 (dd, *J* = 1.5, 2.0 Hz, 3H), 1.91 (m, 1H), 1.73-1.63 (m, 2H), 1.60-1.54 (m, 1H), 1.52-1.44 (m, 2H), 1.42-1.28 (m, 2H), 0.99 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 156.2, 155.9, 155.6, 155.3 (*CO*CF_3, *J* = 42 Hz), 144.5, 131.9, 117.9, 115.6, 113.3, 111.0 (CF_3, *J* = 288 Hz), 91.5, 82.4, 37.2, 30.6, 29.9, 24.3, 21.0, 16.2, 10.8; IR (thin film): 1784, 1775 cm^{-1}; LRMS (ESI) Calcd. for $C_{14}H_{17}F_3O_4Li$ [M+Li]: 313. Found: 313.

To a solution of trifluoroacetate (30 mg, 0.0979 mmol) in CH_2Cl_2 (2 ml) was added DBU (29 µl, 0.196 mmol). The reaction mixture was stirred at 60 ºC for 15 min,

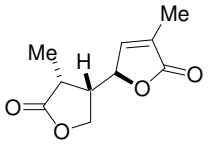
concentrated and purified by flash chromatography (20 % EtOAc/hexanes) to afford 17 mg (88 %) of olefin **153** as a colorless oil (*Z*: *E* = 1.5 : 1, inseperable mixture). R_f = 0.66 (30 % EtOAc/hexanes); IR (thin film): 1756 cm^{-1}; LRMS (ESI) Calcd. for $C_{12}H_{17}O_2$ [M+H]: 193. Found: 193. The stereochemistry of each isomer was assigned by nOe analysis as shown above.

(*Z*)-**153**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (q, *J* = 1.5 Hz, 1H), 2.88 (m, 2H), 2.13 (ddd, *J* = 5.0, 14.0, 14.0 Hz, 1H), 1.99 (s, 3H), 1.88 (m, 1H), 1.72-1.52 (m, 4H), 1.32 (m, 1H), 1.19 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 141.7, 134.3, 132.0, 127.8, 32.7, 30.0, 27.9, 24.7, 20.5, 18.0, 10.6.

(*E*)-**153**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (q, *J* = 1.5 Hz, 1H), 3.33 (m, 1H), 2.38 (m, 1H), 2.24 (ddd, *J* = 4.5, 13.5, 13.5 Hz, 1H), 1.99 (s, 3H), 1.88 (m, 1H), 1.72-1.52 (m, 4H), 1.31 (m, 1H), 1.15 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 142.0, 133.8, 132.1, 127.9, 33.5, 31.1, 27.2, 24.0, 20.5, 19.2, 10.6.



156



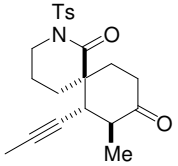
epi-**156**

Furan dimer **156** and *epi*-**156**: To a solution of the silyloxyfuran **155** (33 mg, 0.130 mmol) and 2-methyl-2(5H)-furanone **154** (13 mg, 0.130 mmol) at -78 ºC was added $SnCl_4$ (1.0 M in CH_2Cl_2, 13 µl, 0.0130 mmol). The reaction mixture was stirred at -78 ºC for 2 h, warmed to -20 ºC and stirred for 2 h. The reaction was then quenched by saturated NH_4Cl solution, extracted with CH_2Cl_2 and concentrated *in vacuo*. The residue

was purified by flash chromatography (30%→60%→ 90 % EtOAc/hexanes) to afforded 9 mg (35%) of product **156** as a white solid and 12 mg (48%) of *epi*-**156** as a white solid.

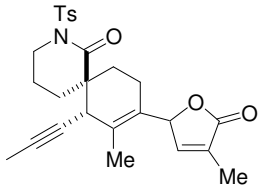
156: R_f = 0.30 (60 % EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (dq, *J* = 2.0 Hz, 1.5 Hz, 1H), 5.05 (ddq, *J* = 5.5 Hz, 2.0 Hz, 2.0 Hz, 1H), 4.20 (dd, *J* = 6.0 Hz, 10.0 Hz, 1H), 3.91 (dd, *J* = 2.5 Hz, 10.0 Hz, 1H), 3.02 (m, 1H), 2.97 (dq, *J* = 7.5 Hz, 7.0 Hz, 1H), 1.98 (dd, *J* = 1.5 Hz, 2.0 Hz, 3H), 1.40 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0, 172.8, 143.9, 133.1, 77.9, 65.1, 41.8, 36.2, 10.9, 10.3; IR (thin film): 1758 cm^{-1}; HRMS (ESI) Calcd. for $C_{10}H_{12}O_4Li$ [M+Li]: 203.0896. Found: 203.0932.

epi-**156**: R_f = 0.10 (60 % EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (m, 1H), 5.01 (ddq, *J* = 5.5 Hz, 1.5 Hz, 1.5 Hz, 1H), 4.28 (dd, *J* = 7.5 Hz, 10.0 Hz, 1H), 4.10 (dd, *J* = 4.0 Hz, 10.0 Hz, 1H), 2.90 (dq, *J* = 7.5 Hz, 7.5 Hz, 1H), 2.73 (m, 1H), 1.98 (dd, *J* = 1.5 Hz, 1.5 Hz, 3H), 1.42 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 172.8, 145.6, 132.6, 78.4, 66.1, 41.3, 36.2, 10.82, 10.76; IR (thin film): 1758 cm^{-1}; HRMS (ESI) Calcd. for $C_{10}H_{12}O_4Li$ [M+Li]: 203.0896. Found: 203.0932. Recrystallization from heptane provided crystals suitable for X-ray analysis.



Ketone **158**: To a solution of the *N*-tosyl lactam **96a** (140 mg, 0.279 mmol) in CH_2Cl_2/MeOH (1:1, 10 ml) at 0 ºC was added *p*-TSA·H_2O (200 mg). The reaction was stirred at room temperature for 12 h and quenched by saturated $NaHCO_3$ solution. The

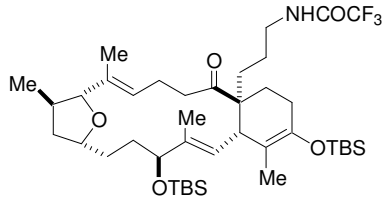
aqueous layer was extracted with Et_2O and the organic layers were dried with $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (30% → 50% EtOAc/Hexanes) to afford 95 mg (88%) of the desired product **158** as a white solid power. R_f = 0.12 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.25 (m, 1H), 3.68 (ddt, *J* = 3.5 Hz, 12.0 Hz, 12.0 Hz, 1H), 2.97 (dq, *J* = 2.5 Hz, 13.0 Hz, 1H), 2.42 (s, 3H), 2.35 (m, 2H), 2.25 (dq, *J* = 6.5 Hz, 13.0 Hz, 1H), 2.14 (m, 2H), 2.04-1.88 (m, 4H), 1.65 (d, *J* = 2.5 Hz, 3H), 1.09 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 144.5, 135.8, 129.0, 128.4, 126.3, 80.8, 76.7, 48.8, 46.7, 45.0, 44.3, 35.9, 32.2, 24.6, 21.5, 20.5, 12.3, 3.3; IR (thin film): 1703, 1676 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{25}NO_4SLi$ [M+Li]: 394.1664. Found: 394.1721. About 10% of the C-6 epimer was also obtained from this reaction, whose structure was confirmed by X-ray analysis after recrystallization from heptane/toluene (3:1).



Butenolide **160**: The ketone **158** (3.6 mg, 0.00929 mmol) was azeotropically dried with PhMe and dissolved in CH_2Cl_2 (1ml). $TiCl_4$ (1.0 M in CH_2Cl_2, 37 μl) was then added and the yellowish cloudy mixture was stirred at room temperature for 10 min. Then silyloxyfuran **155** (9.5 mg, 0.00372 mmol) was added. After stirring at room temperature for 10 min, the reaction was quenched by saturated $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography

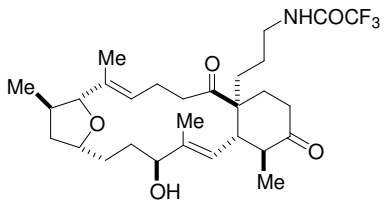
(30%→40%→50%→60% EtOAc/hexanes) to give two fractions, each composed of two diastereomers. Less polar fraction (2.0 mg, 44% yield): R_f = 0.38 (60% EtOAc/hexanes); More polar fraction (1.6 mg, 35% yield): R_f = 0.20 (60% EtOAc/hexanes). No further attempts were made to separate each diastereomer.

To a solution of the less polar fraction (5.0 mg, 0.0103 mmol) in CH_2Cl_2 (1 ml) at room temperature was added pyridine (two drops) and thionyl chloride (4 μl, 0.0515 mmol). The reaction mixture was stirred at room temperature for 1 h and quenched by saturated $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O and the combined organic layers were concentrated. The residue was purified by flash chromatography (40% EtOAc/hexanes) to afford a mixture of regio- and diastereoisomers (2.7 mg, 56% combined yield). For characterization purpose further purification of this mixture (10%→30%EtOAc/hexanes, low flow rate) gave 1.2 mg (25%) of the butenolide **160**. The stereochemistry at the butenolide center was not established. R_f = 0.64 (60% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.83 (dq, *J* = 1.5 Hz, 1.5 Hz, 1H), 5.76 (br s, 1H), 4.12 (m, 1H), 3.73 (ddd, *J* = 4.0 Hz, 10.0 Hz, 12.0 Hz, 1H), 3.59 (br s, 1H), 2.43 (s, 3H), 2.00 (m, 2H), 1.94 (dd, *J* = 1.5 Hz, 2.0 Hz, 3H), 1.90 (m, 1H), 1.87 (d, *J* = 1.0 Hz, 3H), 1.75 (m, 2H), 1.69 (d, *J* = 2.5 Hz, 3H), 1.64 (m, 2H), 1.50 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 174.6, 147.1, 144.4, 136.2, 131.3, 130.3, 129.2, 128.4, 123.5, 80.6, 79.8, 76.2, 47.4, 47.2, 41.5, 29.1, 25.9, 21.7, 20.1, 18.9, 17.3, 10.6, 3.5; IR (thin film): 1757, 1682 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{29}NO_5SLi$ [M+Li]: 468.1845. Found: 468.1987.



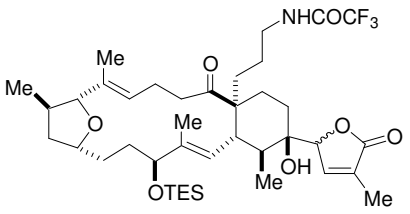
Trifluoroacetamide **141b**: To a solution of the tosylamine **141a** (37 mg, 0.447 mmol) in CH_2Cl_2 (4 ml) at 0 ºC was added triethylamine (62 µl, 0.447 mmol) and trifluoroacetic anhydride (38 µl, 0.268 mml). After stirring at 0 ºC for 15 min, SmI_2 (0.1 M in THF) was added until the intermediate disappeared as monitored by TLC (*ca*. 0.5 ml of SmI_2 solution was added). The reaction mixture was stirred for additional 10 min and quenched by half saturated $Na_2S_2O_3$ solution (2 ml). The aqueous layer was extracted with Et_2O and the organic layers were concentrated *in vacuo* and purified by flash chromatography (5%→10%→15% EtOAc/hexanes) to afford 25 mg (73%) of the desired product as a white foam. R_f = 0.65 (20% EtOAc/hexanes); $[\alpha]^{20}_D$ + 1.26 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (br s, 1H), 5.00 (br t, *J* = 5.0 Hz, 1H), 4.96 (d, *J* = 11.5 Hz, 1H), 4.06 (m, 1H), 3.97 (br s, 1H), 3.81 (dd, *J* = 3.5 Hz, 11.5 Hz, 1H), 3.73 (d, *J* = 11.5 Hz, 1H), 3.35 (m, 2H), 2.81 (m, 1H), 2.65 (m, 1H), 2.28 (m, 1H), 2.18 (m, 1H), 2.09 (m, 4H), 1.98 (m, 1H), 1.86 (m, 1H), 1.77 (m, 1H), 1.69 (s, 3H), 1.64 (m, 2H), 1.56 (m, 1H), 1.49 (s, 3H), 1.47 (s, 3H), 1.43 (m, 3H), 1.38-1.28 (m, 2H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.96 (s, 9H), 0.86 (s, 9H), 0.142 (s, 3H), 0.135 (s, 3H), 0.06 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.3, 157.6 (*C*OCF_3, q, *J* = 37 Hz), 143.2, 140.8, 135.7, 123.6, 122.4, 115.9 (CF_3, q, *J* = 286 Hz), 112.0, 89.1, 79.4, 78.1, 53.8, 45.5, 40.6, 37.6, 36.6, 34.7, 32.9, 31.9, 28.8, 27.6, 25.8, 25.7, 23.4, 23.2, 20.5, 19.9,

18.2, 18.0, 14.2, 13.9, 10.8, -3.6, -3.8, -4.77, -4.85; IR (thin film): 3319, 1722, 1709 cm^{-1}; HRMS (ESI) Calcd. for $C_{41}H_{70}F_3NO_5Si_2Na$ [M+Na]: 792.4642. Found: 792.4852.



Ketone **163**: To a solution of the silyl ether **141b** (17 mg, 0.0221 mmol) in THF/CH_2Cl_2/MeOH (1:1:1, 1.8 ml) at room temperature was added *p*-toluenesulfonic acid monohydrate (17 mg, 0.0883 mml). The reaction mixture was stirred at room temperature for 2.5 h and quenched by saturated $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O and the combined organic layers were concentrated *in vacuo*. The residue was purified by flash chromatography (40%→70%→100% EtOAc/hexanes) to afford 10 mg (84%) of the desired product as a white foam. R_f = 0.42 (70% EtOAc/hexanes); $[\alpha]^{20}_D$ –84.4 (*c* 0.473, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.16 (d, *J* = 11.0 Hz, 1H), 4.97 (br t, *J* = 5.0 Hz, 1H), 4.09 (m, 1H), 3.98 (br s, 1H), 3.91 (dd, *J* = 11.5 Hz, 2.5 Hz, 1H), 3.43 (m, 2H), 3.00 (dd, *J* = 11.5 Hz, 11.5 Hz, 1H), 2.69 (m, 2H), 2.52 (m, 1H), 2.46-2.38 (m, 2H), 2.29 (m, 1H), 2.24-2.14 (m, 3H), 2.12-1.96 (m, 4H), 1.85 (m, 1H), 1.72-1.62 (m, 3H), 1.69 (s, 3H), 1.52 (s, 3H), 1.47 (m, 1H), 1.36 (m, 1H), 1.11 (d, *J* = 7.0 Hz, 3H), 1.06 (m, 1H), 1.03 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.4, 209.6, 157.6 (*C*OCF_3, q, *J* =36 Hz), 140.7, 136.1, 124.6, 121.8, 98.2, 78.8, 78.0, 115.9 (CF_3, q, *J* = 286 Hz), 55.0, 50.5, 45.9, 40.2, 37.7, 37.5, 36.7, 34.8, 31.9, 31.3, 31.1, 23.3, 22.8, 20.5, 19.9, 14.2, 11.9, 11.2; IR (thin film): 3483, 3320, 1706, 1558

cm^{-1}; HRMS (ESI) Calcd. for $C_{29}H_{42}F_3NO_5Na$ [M+Na]: 564.2913. Found: 564.2983. Recrystallization from EtOAc provided colorless crystals suitable for X-ray analysis.



Alcohols **165a/165b**: A mixture of the ketone **163** (8.4 mg, 0.0155 mmol) and silyloxyfuran **155** (39 mg, 0.155 mmol) was azeotropically dried with PhMe and dissolved in CH_2Cl_2 (0.8 ml). At room temperature to this vigorously stirred solution was added $TiCl_4$ (1.0 M in CH_2Cl_2, 39 μl) dropwise over 30 s. The cloudy yellow reaction mixture was stirred at room temperature for 30 s and quenched by saturated NH_4Cl solution. The mixture was extracted with Et_2O and the combined organic layers were concentrated *in vacuo*. The residue was purified by flash chromatography (40%→70%→100% EtOAc/hexanes) to afford 6.1 mg (61%) of the addition product **164** as a white solid as a mixture of two diastereomers (dr = 1.1:1). R_f = 0.16 (70% EtOAc/hexanes).

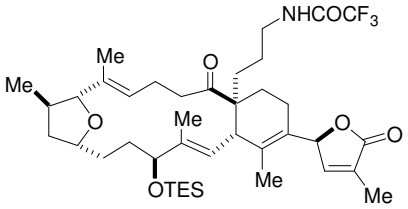
A mixture of **164** (10.0 mg, 0.0156 mmol, used as a mixture of two diastereomers), imidazole (21 mg, 0.313 mmol) and one crystal of DMAP was azeotropically dried with PhMe. The mixture was dissolved in CH_2Cl_2 (1 ml) and at room temperature was treated with TESCl (26 μl, 0.156 mmol). White precipitate formed immediately. The reaction mixture was stirred at room temperature for 5 min and quenched by saturated $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O and the combined organic layers were concentrated and purified by flash

chromatography (30%→40%→50% EtOAc/hexanes) to afford 4.1 mg (34%) of the desired product **165b** and 5.0 mg (42%) the C-4 epimer **165a**, respectively.

165a: R_f = 0.81 (70% EtOAc/hexanes); $[\alpha]^{20}_D$ –14.1 (*c* 0.778, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (br s, 1H, -NH), 7.05 (dq, *J* = 1.5 Hz, 1.5 Hz, 1H), 5.15 (dq, *J* = 1.5 Hz, 1.5 Hz, 1H), 5.00 (br s, 1H), 4.83 (d, *J* = 11.0 Hz, 1H), 4.06 (m, 1H), 3.97 (br s, 1H), 3.77 (dd, *J* = 3.5 Hz, 11.5 Hz, 1H), 3.35 (m, 2H), 3.12 (dd, *J* = 11.0 Hz, 11.0 Hz, 1H), 2.79 (m, 2H), 2.23 (m, 3H), 2.03 (m, 4H), 1.99 (dd, *J* = 1.5 Hz, 1.5 Hz, 3H), 1.87 (m, 2H), 1.69 (s, 3H), 1.62 (m, 3H), 1.51 (s, 3H), 1.46 (m, 4H), 1.30 (m, 2H), 1.10 (d, *J* = 7.0 Hz, 3H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 8.0 Hz, 9H), 0.55 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.1, 173.5, 157.8 (*C*OCF_3, q, *J* = 36 Hz), 144.0, 141.9, 135.6, 132.1, 123.3, 122.5, 117.1 (CF_3, q, *J* = 286 Hz), 89.1, 86.1, 79.7, 78.0, 73.9, 54.7, 42.8, 40.3, 37.6, 37.5, 36.8, 34.7, 32.9, 32.3, 26.8, 25.1, 23.1, 22.5, 20.6, 20.0, 14.2, 11.4, 11.3, 11.0, 6.9, 4.9; IR (thin film): 3447, 3328, 1757, 1716 cm^{-1}.

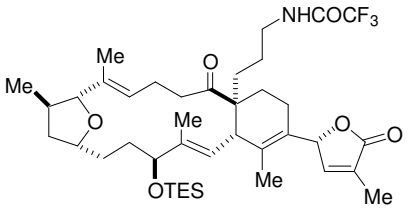
165b: R_f = 0.65 (70% EtOAc/hexanes); $[\alpha]^{20}_D$ –48.8 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (br s, 1H, -NH), 7.22 (dq, *J* = 1.5 Hz, 1.5 Hz, 1H), 5.00 (br s, 1H), 4.97 (dq, *J* = 1.5 Hz, 1.5 Hz, 1H), 4.89 (d, *J* = 11.0 Hz, 1H), 4.07 (m, 1H), 3.97 (br s, 1H), 3.78 (dd, *J* = 3.0 Hz, 11.5 Hz, 1H), 3.34 (m, 2H), 2.96 (dd, *J* = 11.0 Hz, 11.0 Hz, 1H), 2.76 (m, 2H), 2.21 (m, 3H), 2.02 (m, 5H), 1.97 (dd, *J* = 1.5 Hz, 1.5 Hz, 3H), 1.85 (m, 2H), 1.68 (s, 3H), 1.62 (m, 3H), 1.51 (s, 3H), 1.48 (m, 3H), 1.33 (m, 2H), 1.11 (d, *J* = 7.0 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.93 (t, *J* = 8.0 Hz, 9H), 0.55 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.9, 173.9, 157.5 (*C*OCF_3, q, *J* = 36 Hz), 147.0, 141.2, 135.8, 131.1, 123.7, 122.4, 115.9 (CF_3, q, *J* = 286 Hz), 89.1, 83.0, 79.6, 78.0, 73.8, 54.9, 43.3,

40.4, 37.5, 36.73, 36.68, 34.7, 32.9, 32.3, 26.4, 25.2, 22.9, 22.4, 20.6, 19.9, 14.2, 11.3, 10.9, 10.8, 6.9, 4.9; IR (thin film): 3468, 3326, 1754, 1721, 1711 cm^{-1}; HRMS (ESI) Calcd. for $C_{40}H_{62}F_3NO_7Li$ [M+Li]: 760.4408. Found: 760.4666.

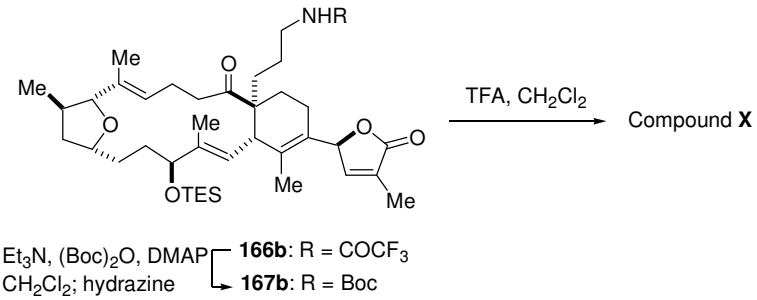


Olefin **166b**: To a solution of the alcohol **165b** (2 mg, 0.00265 mmol, azeotropically dried with PhMe) in CH_2Cl_2 (1 ml) at -78 ºC was added Et_3N (three drops) and 48 µl of a solution of $SOCl_2$ (20 µl) in CH_2Cl_2 (1 ml). The reaction mixture was stirred at -78 ºC for 1 h and quenched by saturated $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O and the combined organic layers were concentrated *in vacuo*. The residue was purified by flash chromatography (40% EtOAc/hexanes) to afford 1.6 mg (82%) of the desired olefin **166a** and its regioisomer ($\Delta^{5,6}$: $\Delta^{5,24}$ = 3:1). R_f = 0.58 (40% EtOAc/hexanes); $[\alpha]^{20}_D$ –67.7 (*c* 0.268, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (br s, 1H, -NH), 6.92 (br s, 1H), 5.84 (br s, 1H), 4.97 (m, 2H), 4.07 (m, 1H), 3.98 (br s, 1H), 3.85 (dd, *J* = 3.0 Hz, 11.5 Hz, 1H), 3.63 (d, *J* = 11.5 Hz, 1H), 3.33 (m, 2H), 2.70 (m, 3H), 2.28 (m, 1H), 2.18 (m, 1H), 2.13 (m, 2H), 1.98 (s, 3H), 1.92 (m, 2H), 1.83 (m, 4H), 1.73 (s, 3H), 1.68 (s, 3H), 1.64 (m, 2H), 1.52 (s, 3H), 1.45 (m, 2H), 1.32 (m, 2H), 1.11 (d, *J* = 7.0 Hz, 3H), 0.93 (t, *J* = 8.0 Hz, 9H), 0.56 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.6, 174.6, 157.6 (*C*OCF_3, q, *J* = 36 Hz), 146.6, 142.6, 135.9, 132.6, 130.4, 125.2, 122.31, 122.28, 116.0 (CF_3, q, *J* = 286 Hz), 89.1, 80.3, 79.2, 78.1, 53.6, 46.7, 40.4, 37.6, 36.5, 34.6, 32.9, 31.9, 28.2, 23.3, 23.0, 20.5, 19.9, 19.6, 16.3,

14.2, 11.0, 10.7, 6.9, 4.9; IR (thin film): 3502, 3328, 1761, 1721, 1707 cm^{-1}; HRMS (MALDI) Calcd. for $C_{40}H_{60}F_3NO_6Na$ [M+Na]: 758.4040. Found: 758.4523.



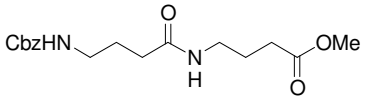
Olefin **166a**: To a solution of the alcohol **165a** (4 mg, 0.00265 mmol, azeotropically dried with PhMe) in CH_2Cl_2 (1 ml) at -78 ºC was added Et_3N (20 µl) and 100 µl of a solution of $SOCl_2$ (20 µl) in CH_2Cl_2 (1 ml). The reaction mixture was stirred at -78 ºC for 25 min and quenched by saturated $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O and the combined organic layers were concentrated *in vacuo*. The residue was purified by flash chromatography (50%→60%→70%→80% Et_2O/hexanes) to afford 1.1 mg (28%) of the desired olefin **166a** and 1.4 mg (36%) of the undesired regioisomer ($\Delta^{5,6}$: $\Delta^{5,24}$ = 1:1.3). R_f = 0.58 (40% EtOAc/hexanes); $[\alpha]^{20}_D$ +26.3 (*c* 0.262, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (t, *J* = 1.5 Hz, 1H), 5.88 (br t, 1H), 4.98 (m, 2H), 4.08 (m, 1H), 3.98 (br s, 1H), 3.84 (dd, *J* = 3.5 Hz, 11.5 Hz, 1H), 3.69 (d, *J* = 10.0 Hz, 1H), 3.53 (m, 2H), 2.71 (m, 3H), 2.28 (m, 1H), 2.18 (m, 1H), 2.08 (m, 2H), 1.98 (s, 3H), 1.96 (m, 2H), 1.83 (m, 4H), 1.75 (s, 3H), 1.74 (s, 3H), 1.64 (m, 2H), 1.52 (s, 3H), 1.49 (m, 2H), 1.32 (m, 2H), 1.11 (d, *J* = 7.0 Hz, 3H), 0.93 (t, *J* = 8.0 Hz, 9H), 0.53 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.7, 174.4, (*C*OCF_3 missing), 147.2, 142.6, 135.8, 135.5, 131.1, 124.8, 122.4, 122.3, (CF_3 missing), 89.1, 79.5, 79.3, 78.0, 53.3, 46.9, 40.4, 37.6, 36.6, 34.6, 32.9, 31.9, 28.0, 23.4, 23.1, 20.5, 20.4, 19.9, 16.8, 14.2, 11.0, 10.8, 6.9, 4.9.



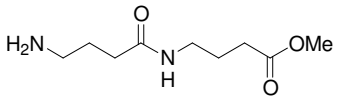
Compound **X**: To a solution of the trifluoroacetamide **166b** (3.0 mg, 0.00408 mmol, azeotropically dried with PhMe, R_f = 0.39 in 30% EtOAc/hexanes) in CH_2Cl_2 (0.5 ml) at room temperature was added Et_3N (20 µl), DMAP (5 mg) and a solution of $(Boc)_2O$ (9 mg, azeotropically dried with PhMe) in CH_2Cl_2 (0.5 ml). The reaction mixture was stirred at room temperature for 30 min and TLC indicated the starting material was completely converted to a new intermediate (R_f = 0.61, 30% EtOAc/hexanes). Hydrazine hydrate (10 µl) was added and the cloudy reaction mixture was stirred at room temperature for 5 min (TLC indicated the complete hydrolysis of this intermediate). The mixture was then quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O, the combined organic layers were concentrated *in vacuo* and passed through a pad of silica gel (eluted with 25% EtOAc/hexanes) to give 1.9 mg of the crude **167b**. R_f = 0.39 (30% EtOAc/hexanes); HRMS (ESI) Calcd. for $C_{43}H_{70}NO_7Si$ [M+H]: 740.4922. Found: 740.5005.

The crude **167b** was dissolved in CH_2Cl_2 (0.2 ml) and treated with trifluoroacetic acid (20 µl). The reaction mixture was stirred at room temperature for 4 h and was quenched by solid $NaHCO_3$. The mixture was stirred at room temperature for 10 min, filtered through a pad of cotton and rinsed with CH_2Cl_2 (1 ml). The filtrate was

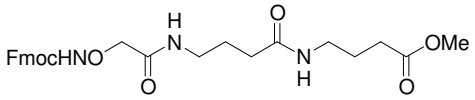
concentrated *in vacuo* and the residue was purified by flash chromatography (50% EtOAc/hexanes→5%→10% MeOH/CH_2Cl_2) to afford 0.4 mg of the compound **X**. R_f = 0.33 (5% MeOH/CH_2Cl_2); HRMS (ESI) Calcd. for $C_{32}H_{46}NO_4$ [M+H]: 508.3427. Found: 508.3430.



Dipeptide **170**: To a solution of methyl 4-aminobutyrate hydrochloride **169** (1.26g, 8.21 mmol) in CH_3CN (45 ml) at 0 ºC were successively added *i*Pr_2NEt (1.43 ml, 8.21 mmol), *N*-Cbz γ-amino butyric acid **168** (1.77g, 7.46 mmol) and EDCI (1.57 g, 8.21 mmol). The reaction mixture was stirred at room temperature overnight, concentrated *in vacuo* and the residue was redissolved in EtOAc (150 ml). The solution was washed with 2 M $NaHSO_4$ (2×20 ml), saturated $NaHCO_3$ solution (2×20 ml), brine, dried ($MgSO_4$) and concentrated to afford 1.85 g (74%) of the desired product as a white solid, which was used in the next step without further purification. m.p.68-73 ºC; R_f = 0.65 (10% MeOH/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (s, 5H), 6.18 (br s, 1H, -NH), 5.07 (s, 2H), 3.61 (s, 3H), 3.30 (t, *J* = 6.3 Hz, 2H), 3.24 (t, *J* = 6.3 Hz, 2H), 2.37 (t, *J* = 7.2 Hz, 2H), 2.21 (t, *J* = 6.9 Hz, 2H), 1.84 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 172.7, 156.8, 136.4, 128.4, 127.94, 127.88, 66.5, 51.6, 40.2, 38.7, 33.4, 31.3, 25.9, 24.5; IR (thin film): 3337, 3299, 1729, 1682, 1635, 1535 cm^{-1}; HRMS (ESI) Calcd. for $C_{17}H_{25}N_2O_5$ [M+H]: 337.1763. Found: 377.1639.

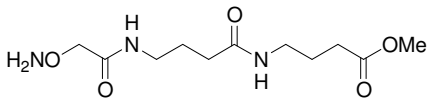


Amine **171**: A solution of dipeptide **170** (1.85 g, 5.51 mmol) in EtOH (30 ml) containing 10% Pd/C (290 mg, 0.275 mmol) was bubbled with H_2 using a balloon. The reaction mixture was stirred at room temperature for 1.5 h, filtered through a pad of Celite and concentrated to afford 1.12 g (92%) of the desired product as a white solid, which was used directly in the next step without further purification. m.p.146-153 ºC (decomposed); R_f = 0.41 (MeOH containing 1% AcOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.52 (br s, 1H, -NH), 3.63 (s, 3H), 3.23 (dt, *J* = 6.0 Hz, 6.6 Hz, 2H), 2.70 (t, *J* = 6.9, 2H), 2.33 (t, *J* = 7.2 Hz, 2H), 2.21 (t, *J* = 7.2 Hz, 2H), 1.81 (m, 2H), 1.74 (m, 2H), 1.68 (br s, 2H, $-NH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 172.9, 51.6, 41.4, 38.7, 33.9, 31.4, 28.9, 24.5; IR (thin film): 3310, 1737, 1647, 1637, 1546 cm^{-1}; HRMS (ESI) Calcd. for $C_9H_{19}N_2O_3$ [M+H]: 203.1396. Found: 203.1391. IMPORTANT: The pure form of the amine **171** as a solid is barely soluble in ALL solvents tested. Therefore, for the success of the following step, it is crucial to store the amine with small amount of EtOH and use as such in the following step.

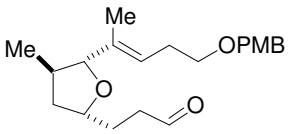


Fmoc alkoxyamine **173b**: To a solution of the amine **171** (2.0g, 4.09 mmol, containing small amount of ethanol) in CH_2Cl_2 (35 ml) at room temperature were added *i*Pr_2NEt (0.855 ml, 4.91 mmol) and Fmoc-aminooxyacetic acid **172b** (2g, 4.91 mmol). The reaction mixture was stirred at room temperature for 2h, concentrated *in vacuo* and purified by flash chromatography (EtOAc→5%→10% MeOH/EtOAc) to afford 920 mg

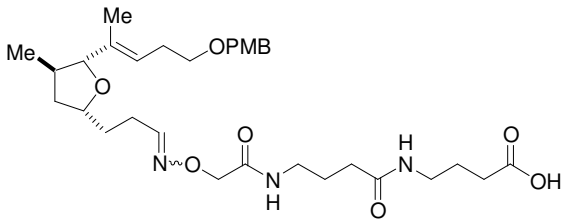
(46%) of the desired product as a white solid. m.p.94-98 ºC; R_f = 0.44 (10% MeOH/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86 (br s, 1H, -NH), 8.00 (br s, 1H, -NH), 7.75 (d, *J* = 7.2 Hz, 2H), 7.56 (d, *J* = 7.2 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 2H), 6.59 (app t, 1H, -NH), 4.48 (d, *J* = 6.9 Hz, 2H), 4.33 (s, 2H), 4.22 (t, *J* = 6.9 Hz, 1H), 3.62 (s, 3H), 3.33 (dt, *J* = 6.0 Hz, 6.0 Hz, 2H), 3.24 (dt, *J* = 6.6 Hz, 6.0 Hz, 2H), 2.32 (t, *J* = 7.2 Hz, 2H), 2.21 (t, *J* = 6.6 Hz, 2H), 1.83 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 173.0, 169.1, 158.3, 143.1, 141.2, 127.9, 127.1, 124.9, 120.1, 76.1, 67.9, 51.7, 46.8, 39.0, 38.4, 33.8, 31.4, 25.3, 24.5; IR (thin film): 3306, 1725, 1634 cm^{-1}; HRMS (ESI) Calcd. for $C_{26}H_{32}N_3O_7$ [M+H]: 498.2240. Found: 498.2254.



Alkoxyamine **175**: To a solution of the Fmoc alkoxyamine **173b** (2.6g, 5.23 mmol) in THF (60 ml) at room temperature was added diethylamine (2.7 ml, 26.1 mmol). The reaction mixture was stirred at room temperature for 20 h and concentrated *in vacuo*. The residue was loaded on filter paper and washed with EtOAc (20 ml). The solid collected from filter paper was dried under high vacuum to give 800 mg (56%) of the desired product as a white powder. R_f = 0.35 (MeOH containing 1% AcOH); ^{1}H NMR (300 MHz, CD_3OD) δ 4.08 (s, 2H), 3.66 (s, 3H), 3.28 (t, *J* = 6.9 Hz, 2H), 3.20 (t, *J* = 6.9 Hz, 2H), 2.36 (t, *J* = 7.5 Hz, 2H), 2.23 (t, *J* = 7.5 Hz, 2H), 1.81 (m, 4H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.8, 175.5, 173.4, 75.7, 52.3, 39.9, 39.6, 34.6, 32.3, 27.0, 26.0; IR (thin film): 3312, 1732, 1634, 1538 cm^{-1}; HRMS (ESI) Calcd. for $C_{11}H_{22}N_3O_5$ [M+H]: 276.1559. Found: 276.1545.



Aldehyde **179:** To a solution of the alcohol **178** (62 mg, 0.178 mmol) in CH_2Cl_2 (5 ml) at 0 ºC was added Dess-Martin periodinane (133 mg, 0.314 mmol). The reaction mixture was stirred at room temperature for 2 h and was quenched by saturated $NaHCO_3$ solution (2 ml) and saturated $Na_2S_2O_3$ solution (2 ml). The aqueous layer was extracted with Et_2O and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (10%→20% EtOAc/hexanes) to afford 45 mg (73%) of the desired product as a colorless oil. R_f = 0.40 (30% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.5 Hz, 1H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.43 (t, *J* = 7.0 Hz, 1H), 4.44 (s, 2H), 3.97 (m, 1H), 3.80 (s, 3H), 3.66 (d, *J* = 8.5 Hz, 1H), 3.45 (dt, *J* = 3.0 Hz, 7.0 Hz, 2H), 2.57 (m, 2H), 2.37 (m, 2H), 1.99 (m, 1H), 1.87-1.74 (m, 3H), 1.69 (ddd, *J* = 8.0 Hz, 8.0 Hz, 12.0 Hz, 1H), 1.59 (s, 3H), 0.94 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.3, 159.0, 135.3, 130.5, 129.1, 124.2, 113.7, 92.4, 76.5, 72.4, 69.4, 55.2, 40.5, 39.6, 35.9, 28.6, 28.4, 16.8, 11.2; IR (thin film): 1722 cm^{-1}; HRMS (ESI) Calcd. for $C_{21}H_{31}O_4$ [M+H]: 347.2222. Found: 347.2168.



Oxime ether **180b:** To a solution of the aldehyde **179** (43 mg, 0.124 mmol) in EtOH (3 ml) at room temperature was added the amine **175** (81 mg, 0.296 mmol) and NaOAc (29 mg, 0.355 mmol). The reaction mixture was stirred at room temperature for 13 h, concentrated and purified by flash chromatography (50%→100% EtOAc→10% MeOH/EtOAc) to afford 74 mg (100%) of the desired product **180a** as a colorless oil. R_f = 0.62 (10% MeOH/EtOAc).

To a solution of the methyl ester **180a** (74 mg, 0.123 mmol) in THF/H_2O (4 ml, 4:1) was added LiOH (26 mg, 0.613 mmol). The reaction mixture was stirred at room temperature for 4 h, concentrated *in vacuo* and purified by flash chromatography (10% →20%→30% MeOH/EtOAc) to afford 38 mg (53%) of the oxime ether **180b** as an inseparable mixture of E/Z isomers (*E*:*Z* ≈ 2.3:1) as a colorless oil.

Major isomer: R_f = 0.43 (10% MeOH/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (t, *J* = 5.5 Hz, 1H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.96 (m, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.74 (t, *J* = 5.5 Hz, 1H), 5.42 (t, *J* = 6.5 Hz, 1H), 4.46 (s, 2H), 4.44 (s, 2H), 3.99 (m, 1H), 3.79 (s, 3H), 3.66 (d, *J* = 8.5 Hz, 1H), 3.45 (t, *J* = 7.0 Hz, 2H), 3.29 (m, 4H), 2.36 (m, 6H), 2.20 (m, 2H), 1.98 (m, 1H), 1.80 (m, 8H), 1.60 (s, 3H), 0.94 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 173.2, 170.9, 159.1, 153.5, 135.3, 130.5, 129.2, 124.3, 113.7, 92.4, 76.70, 76.66, 72.5, 69.4, 55.2, 39.8, 39.6, 39.0, 38.4, 35.9, 33.4, 33.0,

28.4, 26.2, 25.6, 24.7, 16.8, 11.3; IR (thin film): 3308, 1654, 1615, 1546, 1514 cm^{-1}; HRMS (ESI) Calcd. for $C_{31}H_{48}N_3O_8$ [M+H]: 596.3523. Found: 596.3511.

REFERENCES

(1) (a) Anderson, D. M. *Sci. Am.* **1994**, *271*, 62-68. (b) Van Dolah, F. M. *Environ. Health Perspect. Suppl.* **2000**, *108*, 133-141.

(2) Haywood, A. J.; Steidinger, K. A.; Truby, E. W.; Bergquist, P. R.; Bergquist, P. L.; Adamson, J.; MacKenzie, L. *J. Phycol.* **2004**, *40*, 165-179.

(3) Seki, T.; Satake, M.; Mackenzie, L.; Kaspar, H.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 7093-7096.

(4) Stewart, M.; Blunt, J. W.; Munro, M. H. G.; Robinson, W.T.; Hannah, D. J. *Tetrahedron Lett.* **1997**, *38*, 4889-4890.

(5) (a) Miles, C. O.; Wilkins, A. L.; Stirling, D. J.; MacKenzie, A. L. *J. Agric. Food Chem.* **2000**, 48, 1373-1376. (b) Miles, C. O.; Wilkins, A. L.; Stirling, D. J.; MacKenzie, A. L. *J. Agric. Food Chem.* **2003**, 51, 4838-4840.

(6) (a) For a review on imine-containing natural products, see: Kita, M.; Uemura, D. *Chem. Lett.* **2005**, *34*, 454-459. (b) For a review on synthesis of spiroimine-containing natural products, see: O'Connor, P. D.; Brimble, M. A. *Nat. Prod. Rep.* **2007**, *24*, 869-885.

(7) (a) Uemura, D.; Chou, T.; Haino, T.; Nagatsu, A.; Fukuzawa, S.; Zheng, S.; Chen, H. *J. Am. Chem. Soc.* **1995**, *117*, 1155-1156. (b) Chou, T.; Kamo, O.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 4023-4026. (c) Chou, T.; Haino, T.; Kuramoto, M.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 4027-4030. (d) Takada, N.; Umemura, N.; Suenaga, K.; Chou, T.; Nagatsu, A.; Haino, T.; Yamada, K.; Uemura, D. *Tetrahedron Lett.* **2001**, *42*, 3491-3494.

(8) Takada, N.; Umemura, N.; Suenaga, K.; Uemura. D. *Tetrahedron Lett.* **2001**, *42*, 3495-3497.

(9) (a) Hu, T.; Curtis, J.; Oshima, Y.; Quilliain, M.; Walter, J.; Wright, W.; Wright, J. *J. Chem. Soc., Chem. Comm.* **1995**, 2159-2161. (b) Hu, T.; Curtis, J. M.; Walter, J.; Wright, J. L. C. *Tetrahedron Lett.* 1996, *37*, 7671-7674. (c) Hu, T.; Burton, I. W.; Cembella, A. D.; Curtis, J. M.; Quilliam, M. A.; Walter, J. A.; Wright, J. L. C. *J. Nat. Prod.* **2001**, *64*, 308-312. (d) Falk, M.; Burton, I. W.; Hu, T.; Walter, J. A.; Wright, J. L. C. *Tetrahedron* **2001**, *57*, 8659-8665.

(10) Torigoe, K.; Murata, M.; Yasumoto, T.; Iwashita, T. *J. Am. Chem. Soc.* **1988**, *110*, 7876-7877.

(11) Lu, C.-K.; Lee, G.-H; Huang, R.; Chou, H.-N. *Tetrahedron Lett.* **2001**, *42*, 1713-1716.

(12) Munday, R.; Towers, N. R.; Mackenzie, L.; Beuzenberg, V.; Holland, P. T.; Miles, C. O. *Toxicon*, **2004**, *44*, 173-178.

(13) Dragunow, M.; Trzoss, M.; Brimble, M. A.; Cameron, R.; Beuzenberg, V.; Holland, P.; Mountfort, D. *Environ. Toxicol. Pharmacol.* **2005**, *20*, 305-312.

(14) Private communication from Dr. Jeffrey L. Wright, Institute for Marine Biosciences, National Research Council of Canada, Halifax, NS, Canada.

(15) Kuramoto, M.; Arimoto, H.; Uemura, D. *Mar. Drugs* **2004**, *2*, 39-54.

(16) (1) For a review of comparison of different analytic methods for natural toxins, see: Pravda, M.; Kreuzer, M. P.; Guilbault, G. G. *Anal. Lett.* **2002**, *35*, 1-15. (2) *Immunoassays for Residue Analysis*, Beiber, R. C.; Stanker, L. H., Eds.; ACS Symposium Series 621; American Chemical Soicety: Washington, D. C., **1996**.

(17) (a) Baden, D. G.; Mende, T. J.; Walling, J.; Schultz, D. R. *Toxicon* **1984**, *22*, 783-789. (b) Trainer, V. L.; Baden, D. G. *Toxicon* **1991**, *29*, 1387-1394. (c) Baden, D. G.; Melinek, R.; Sechet, V.; Trainer, V. L.; Schultz, D. R.; Rein, K. S.; Tomas, C. R.; Delgado, J.; Hale, L. *J. AOAC Int.* **1995**, *78*, 499-508. (d) Naar, J.; Bourdelais, A.; Tomas, C.; Kubanek, J.; Whitney, P. L.; Flewelling, L.; Steidinger, K.; Lancaster, J.; Baden, D. G. *Environ. Health Persp.* **2002**, *110*, 179-185.

(18) Oguri, H.; Hirama, M.; Tsumuraya, T.; Fujii, I.; Maruyama, M.; Uehara, H.; Nagumo, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7608-7612 and referentes therein.

(19) Forsyth, C. J.; Xu, J.; Nguyen, S. T.; Samdal, I. A.; Briggs, L. R.; Rundberget, T.; Sandvik, M.; Miles, C. O. *J. Am. Chem. Soc.* **2006**, *128*, 15114-15116.

(20) Hokama, Y.; Hong, T. W. P.; Isobe, M.; Ichikawa, Y.; Yasumoto, T. *J. Clin. Lab. Anal.* **1992**, *6*, 54-58.

(21) MacKinnon, S. L.; Cembella, A. D.; Burton, I. W.; Lewis, N.; LeBlanc, P.; Walter, J. A. *J. Org. Chem.* **2006**, *71*, 8724-8731.

(22) McCauley, J. A.; Nagasawa, K.; Lander, P. A.; Mischke, S. G.; Semones, M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 7647-7648.

(23) (a) Wang, J.; Sakamoto, S.; Kamada, K.; Nitta, A.; Noda, T.; Oguri, H.; Hirama, M. *Synlett* **2003**, 891-893. (b) Sakamoto, S.; Sakazaki, H.; Hagiwara, K.; Kamada, K.; Ishii, K.; Noda, T.; Inoue, M.; Hirama, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 6505-6510.

(24) (a) Ishihara, J.; Miyakawa, J.; Tsujimoto, T.; Murai, A. *Synlett* **1997**, 1417-1419. (b) Tsujimoto, T.; Ishihara, J.; Horie, M.; Murai, A. *Synlett* **2002**, 399-402.

(25) (a) Owens, T. D.; Hollander, F. J.; Oliver, A. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 1539-1540. (b) Owens, T. D.; Souers, A. J.; Ellman, J. A. *J. Org. Chem.* **2003**, *68*, 3-10.

(26) (a) White, J. D.; Wang, G.; Quaranta, L. *Org. Lett.* **2003**, 5, 4109-4112. (b) White, J. D.; Wang, G.; Quaranta, L. *Org. Lett.* **2003**, *5*, 4983-4986. (c) White, J. D.; Quaranta, L.; Wang, G. *J. Org. Chem.* **2007**, *72*, 1717-1728.

(27) Hosoya, T.; Wakao, M.; Kondo, Y.; Doi, H.; Suzuki, M. *Org. Biomol. Chem.* **2004**, *2*, 24-27.

(28) (a) Johannes, J. W.; Wenglowsky, S.; Kishi, Y. *Org. Lett.* **2005**, *7*, 3997-4000. (b) Johannes, J. W. Ph. D. Dissertation, Harvard University, Cambridge, MA, 2005.

(29) (a) Trzoss, M.; Brimble, M. A. *Synlett* **2003**, 2042-2046. (b) Trzoss, M.; Brimble, M. A. *Tetrahedron* **2004**, *60*, 5613-5622.

(30) (a) Yang, J.; Cohn, S. T. Romo, D. *Org. Lett.* **2000**, *2*, 763-766. (b) Ahn, Y.; Cardenas, G. I.; Yang, J.; Romo, D. *Org. Lett.* **2001**, *3*, 751-754.

(31) Hua, D. H.; Miao, S. W.; Bharathi, S. N.; Katsuhira, T.; Bravo, A. A. *J. Org. Chem.* **1990**, *55*, 3682-3684.

(32) (a) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048-6049. (b) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644-5645. (c) For an excellent review, see: Fürstner, A. *Chem. Rev.* **1999**, *99*. 991-1045.

(33) For one such example from recent literature, see: Macmillan, D. W. C.; Overman, L. E.; Pennington, L. D. *J. Am Chem. Soc.* **2001**, *123*, 9033-9044.

(34) Mitsunobu, O. *Synthesis* **1981**, 1-28.

(35) Roth, M.; Dubs, P.; Gotschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710-734.

(36) Miles, C. O.; Hawkes, A. D.; MacKenzie, A. L.; Munday, R.; Towers, N. R.; Prinsep, M. R. Marine Biotoxin Science Workshop, New Zealand, **1999**, p94-98.

(37) For a review of catalytic, asymmetric Diels-Alder reactions: Dias, L. C. *J. Braz. Chem. Soc.* **1997**, *8*, 289-332 and references therein.

(38) Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 388-401.

(39) Hashimoto, S.; Komeshima, N.; Koga, K. *J. Chem. Soc., Chem. Comm.* **1979**, 437-438.

(40) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325-335.

(41) Corey, E. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1650-1667.

(42) (a) Evans, D. A.; Miller, S. J.; Lectka, T.; Matt, P. V. *J. Am. Chem. Soc.* **1999**, *121*, 7559-7573. (b) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; Matt, P. V.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582-7594.

(43) Stille, J. K. *Angew. Chem. Int. Ed.* **1986**, *25*, 508-524.

(44) Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett*, **1990**, 675-676.

(45) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600-7605.

(46) Flohr, A. *Tetrahedron Lett.* **1998**, *39*, 5177-5180 and references therein.

(47) Frank. S. A.; Chen, H.; Kunz, R. K.; Schnaderbeck, M. J.; Roush, W. R. *Org. Lett.* **2000**, *2*, 2691-2694.

(48) Roush, W. J.; Barda, D. A. *J. Am. Chem. Soc.* **1997**, *119*, 7402-7403.

(49) (a) Piers, E.; Morton, H. E. *J. Org. Chem.* **1980**, *45*, 4263-4264. (b) Singer, R. D.; Hutzinger, M. W.; Oeschlager, A. C. *J. Org. Chem.* **1991**, *56*, 4933-4938. (c) Cummins, C. H.; Gordon, E. J. *Tetrahedron Lett.* **1994**, *35*, 8133-8136. (d) Betzer, J-F.; Ardisson, J., Lallemand, J-Y.; Pancrazi, A. *Tetrahedron Lett.* **1997**, *38*, 13, 2279-2282.

(50) (a) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857-1867. (b) For a review, see: Smith, N. D.; Mancuso, J.; Lautens, M. *Chem. Rev.* **2000**, *100*, 3257-3282.

(51) For use of the triflate salt in related Diels-Alder reactions, see: Ishihara, J.; Horie, M.; Shimada, Y.; Tojo, S.; Murai, A. *Synlett* **2002**, 404-406.

(52) Kong, K.; Moussa, Z.; Romo, D. *Org. Lett.* **2005**, *7*, 5127-5130.

(53) Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541-4544. Prof. Brian Connell is greatly acknowledged (Texas A&M) for bringing this procedure to our attention.

(54) For a similar observation, see ref. 42a.

(55) For a review, see: Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159-164.

(56) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512-519.

(57) Conducted by Dr. Ziad Moussa. Current address: Chemistry Department, Faculty of Science, Taihah University, Almadinah Almunawarah**,** P O Box 344, Saudi Arabia.

(58) DFT calculations were performed using the Gaussian 03 program package (B3LYP/6-31G* basis set + zpe). See supporting information for further details.

(59) Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1992**, *57*, 3380-3387.

(60) Trost, B. M.; Ball, Z. T. *Synthesis* **2005**, 853-887.

(61) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679-680.

(62) (a) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370-4371. (b) Brown, H. C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc.* **1973**, *95*, 5786-5788.

(63) Zweifel, G.; Whitney. C. C. *J. Am. Chem. Soc.* **1967**, *89*, 2753-2754.

(64) Durham, T. B.; Blanchard, N.; Savall, B. M.; Powell, N. A.; Roush, W. R. *J. Am. Chem. Soc.* **2004**, *126*, 9307-9317.

(65) (a) Semmelhack, M. F.; Hooley, R. J. *Tetrahedron Lett.* **2003**, *44*, 5737-5739. (b) Yuan, Y.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 14720-14721.

(66) This was confirmed by conducting the reaction in the presence of *i*Pr_2NEt and by purification of the reaction mixture by Et_3N-deactivated silica gel or basic alumina.

(67) Betzer, J-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768-7780.

(68) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208-12209.

(69) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432-439.

(70) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021-3028.

(71) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155-4156.

(72) *Metal Catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; WILEY-VCH: New York, 1998.

(73) (a) Sonogashira coupling of iminoyl triflates, excluding pyridine derivatives: Jacobi, P. A.; Liu, H. *J. Am. Chem. Soc.* **1999**, *121*, 1958-1959. (b) Heck reaction: Na, Y.; Park, S.; Han, S. B.; Han, H.; Ko, S.; Chang, S. *J. Am. Chem. Soc.* **2004**, *126*, 250-258. (c) Palladium catalyzed cross-coupling reactions of lactam derived vinyl triflates abound in literature. For leading references, see: Occhiato, E. G.; Trabocchi, A.; Guarna, A. *J. Org. Chem.* **2000**, *66*, 2459-2465 and references therein.

(74) Thomsen, I.; Clausen, K.; Scheibye, S.; Lawesson, S.-O. *Org. Synth.* **1984**, *62*, 158-161.

(75) Mignani, G.; Morel, D.; Grass, F. *Tetrahedron Lett.* **1987**, 28, 5505-5508.

(76) (a) For a related example from recent literature of nucleophilic opening of tosyllactam, see: Li, C.; Chan, C.; Heimann, A. C.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 1448-1450. (b) For related transformations of nucleophilic opening of activated lactams, see: Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424-2426. (c) Giovannini, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1989**, *54*, 228-234.

(77) Hudlicky, T.; Govindan, S. V.; Frazier, J. *J. Org. Chem.* **1985**, *50*, 4166-4170.

(78) Moussa, Z.; Romo, D. *Synlett* **2006**, 3294-3298.

(79) This condition was inspired by literature precedents, for selected examples, see: (a) Crimmins, M. T.; King, B. W. *J. Am. Chem. Soc.* **1998**, *120*, 9084-9085. (b) Charest, M. G.; Lerner, C. D.; Brubaker, J. D.; Siege, D. R.; Myers, A. G. *Science* **2005**, *308*, 395-398.

(80) (a) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404-5406. (b) Negishi, E.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406-5409. (c) Iodine-lithium exchange is known to be an extremely fast process that it could even proceed in the presence of MeOH in some cases, see: Bailey, W. F.; Patricia, J. J.; Nurmi, T. T.; Wang, W. *Tetrahedron Lett.* **1986**, *27*, 1861-1864. (d) *Organolithiums*: *Selectivity for Synthesis*; Clayden, J. Pergamon: 2002.

(81) For some examples in early literature for such a transformation in simple substrates, see: (a) Cooke Jr, M. P.; Houpis, I. N. *Tetrahedron Lett.* **1985**, *26*, 4987-4990. (b) Souchet, M.; Clark, R. D. *Synlett* **1990**, 151-152.

(82) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092-4096.

(83) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986-2012.

(84) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 4302-4320.

(85) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745-777.

(86) de Meijere, A.; Meyer, F. E. *Angew. Chem. Int. Ed.* **1994**, *33*, 2379-2411.

(87) Loiseleur, O.; Meier, P.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1996**, *35*, 200-202.

(88) (a) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417-1419. (b) Ozawa, F.; Kobatake, Y.; Hayashi, T. *Tetrahedron Lett.* **1993**, *34*, 2505-2508.

(89) Larcheveque, M.; Henrot, S. *Tetrahedron*, **1987**, *43*, 2303-2310.

(90) Sharpless, K. B.; Lauser, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697-2699.

(91) For reviews, see: (a) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929-1972. (b) Denmark, S. E.; Heemstra, J. R.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 4682-4698. (c) Kalesse, M. *Top. Curr. Chem.* **2005**, *244*, 43-76.

(92) (a) Jefford, C. W.; Jaggi, D.; Bernardinelli, G.; Boukouvalas, J. *Tetrahedron Lett.* **1987**, *28*, 4041-4044. (b) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686-699. (c) Naito, S.; Escobar, M.; Kym, P. R.; Liars, S.; Martin, S. F. *J. Org. Chem.* **2002**, *67*, 4200-4208. (d) Le, J. C.-D.; Pagenkopf, B. L. *Org. Lett.* **2004**, *6*, 4097-4099.

(93) (a) For a brief explanation on low reactivity of ketones as electrophiles, see: Betancort, J. M.; Garcia, C.; Walsh, P. J. *Synlett* **2004**, 749-760. (b) In a recent review of allylic metal addition to carbonyl compounds (Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763-2794), only two pages were dedicated to ketones.

(94) Honda, T.; Kondoh, H.; Okuyama, A.; Hayakawa, T.; Tsubuki, M.; Nagase, H. *Heterocycles* **1992**, *33*, 67-72

(95) Jefford, C. W.; Sledeski, A. W.; Rossier, J.-C.; Boukouvalas, J. *Tetrahedron Lett.* **1990**, *31*, 5741-5744.

(96) (a) Carreira, E. M.; Singer, R. A. *Tetrahedron Lett.* **1994**, *35*, 4323-4326. (b) Denmark, S. E.; Chen, C.-T. *Tetrahedron Lett.* **1994**, *35*, 4327-4330. (c) Hollis, T. K.; Bosnich, B. *J. Am. Chem. Soc.* **1995**, *117*, 4570-4581.

(97) (a) Brown, D. W.; Campbell, M. M.; Taylor, A. P.; Zhang, X. *Tetrahedron Lett.* **1987**, *28*, 985-988. (b) Jefford, C. W.; Jaggi, D.; Boukouvalas, J. *Tetrahedron Lett.* **1987**, *35*, 4037-4040.

(98) For similar findings, see: Redero, E.; Sandoval, C.; Bermejo, F. *Tetrahedron* **2001**, *57*, 9597-9605.

(99) For a related example, see: Kido, F.; Fujishita, T.; Tsutsumi, K.; Yoshikoshi, A. *J. Chem. Soc., Chem. Comm.* **1975**, 337-338.

(100) (a) Fung, S. Y.; Schripsema, J.; Verpoorte, R. *Phytochemistry* **1990**, *29*, 517-519. (b) A direct comparison between the natural and synthetic products is not possible due to the unavailability of the natural products, personal communications with S. Y. Fung and Prof R. Verpoorte (Netherlands).

(101) San Martin, A.; Rovirosa, J.; Muñoz, O.; Chen, M. H. M.; Guneratne, R. D.; Clardy, J. *Tetrahedron Lett.* **1983**, *24*, 4063-4066.

(102) Martin, S. F.; Barr, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 3299-3300.

(103) Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837-838.

(104) Szlosek, M.; Franck, X.; Figadère, B.; Cavé, A. *J. Org. Chem.* **1998**, *63*, 5169-5172.

(105) For a recent example, see: Ozawa, T.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **2001**, *66*, 3338-3347.

(106) King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1994**, *116*, 562-570.

(107) Burk, M. J.; Allen, J. G. *J. Org. Chem.* **1997**, *62*, 7054-7057.

(108) For general reading, see: *The ELISA Guidebook*; Crowther, J. R., Ed.; Humana Press: Totowa, NJ, 2000.

(109) For a discussion of the design of linker, see: Isomura, S.; Wirsching, P.; Janda, K. D. *J. Org. Chem.* **2001**, *66*, 4115-4121.

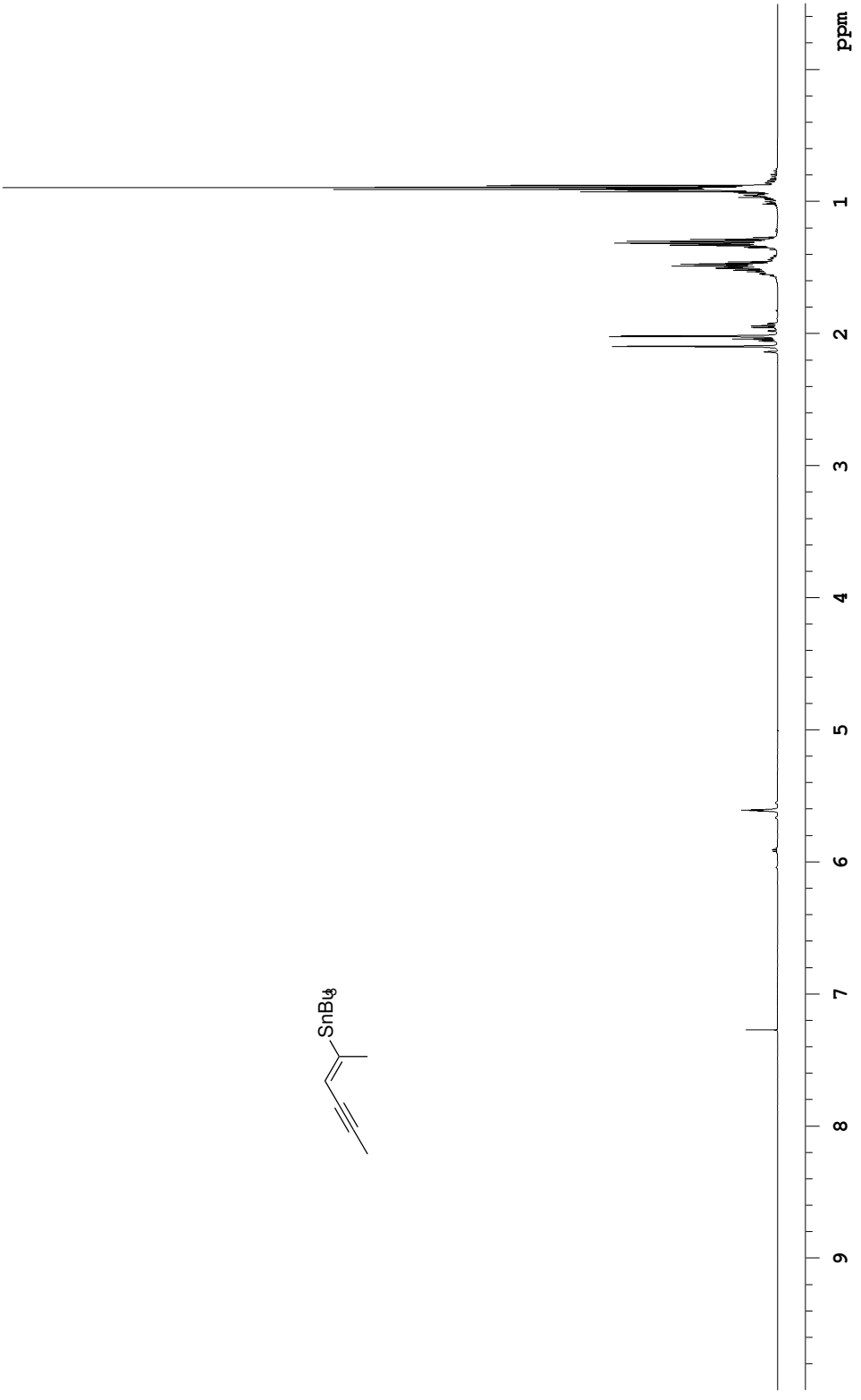
(110) Lei, X.; Zaarur, N.; Sherman, M. Y.; Porco, J. A., Jr. *J. Org. Chem.* **2005**, *70,* 6474-6483 and references therein.

(111) Blankespoor, R. L.; Lau, A. N. K.; Miller, L. L. *J. Org. Chem.* **1984**, *49*, 4441-4446.

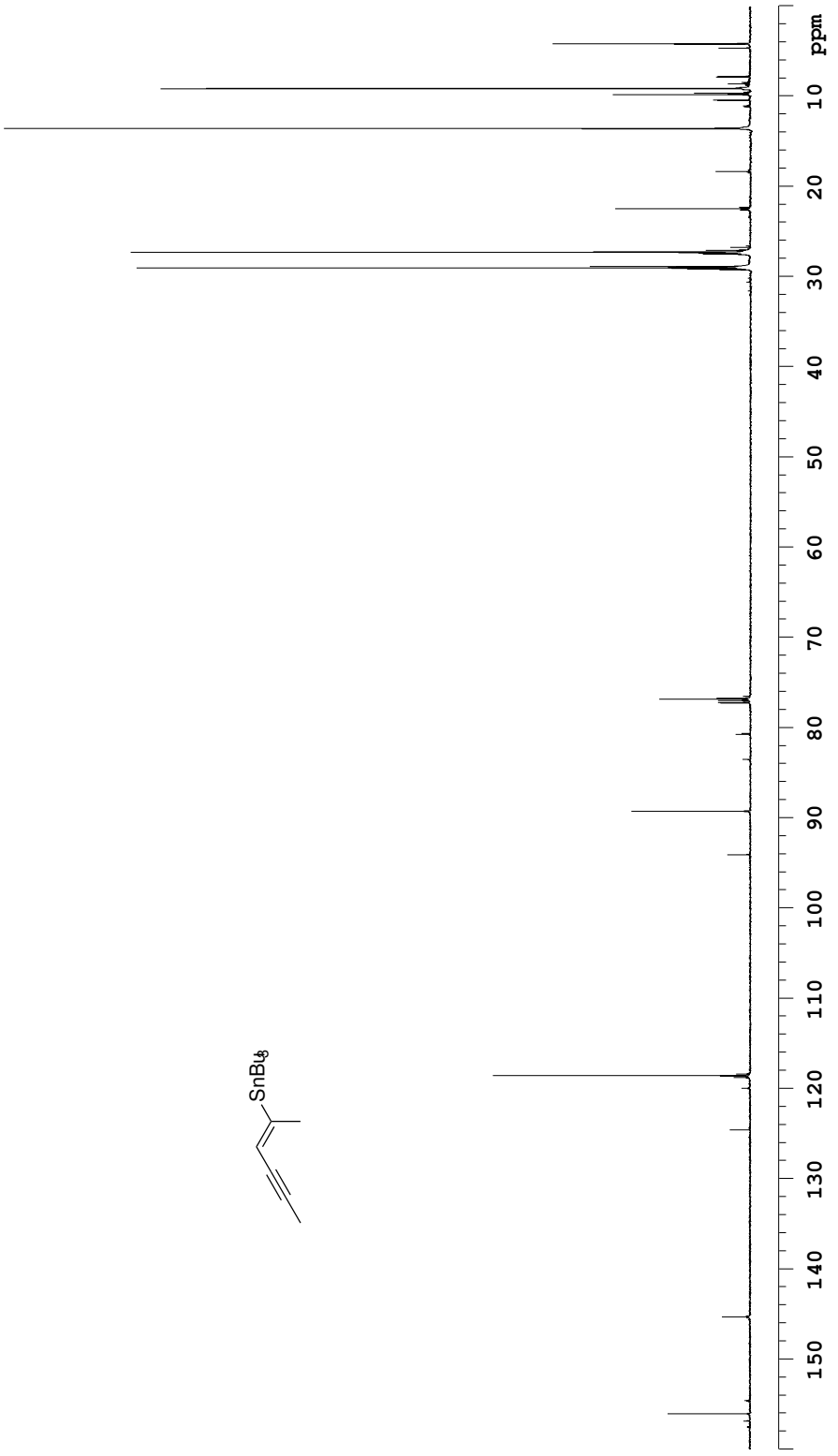
(112) Suffert, J. *J. Org. Chem.* **1989**, *54*, 509-510.

APPENDIX A

SELECTED SPECTRAL DATA



^{1}H NMR spectrum of vinyl stannane **102a**



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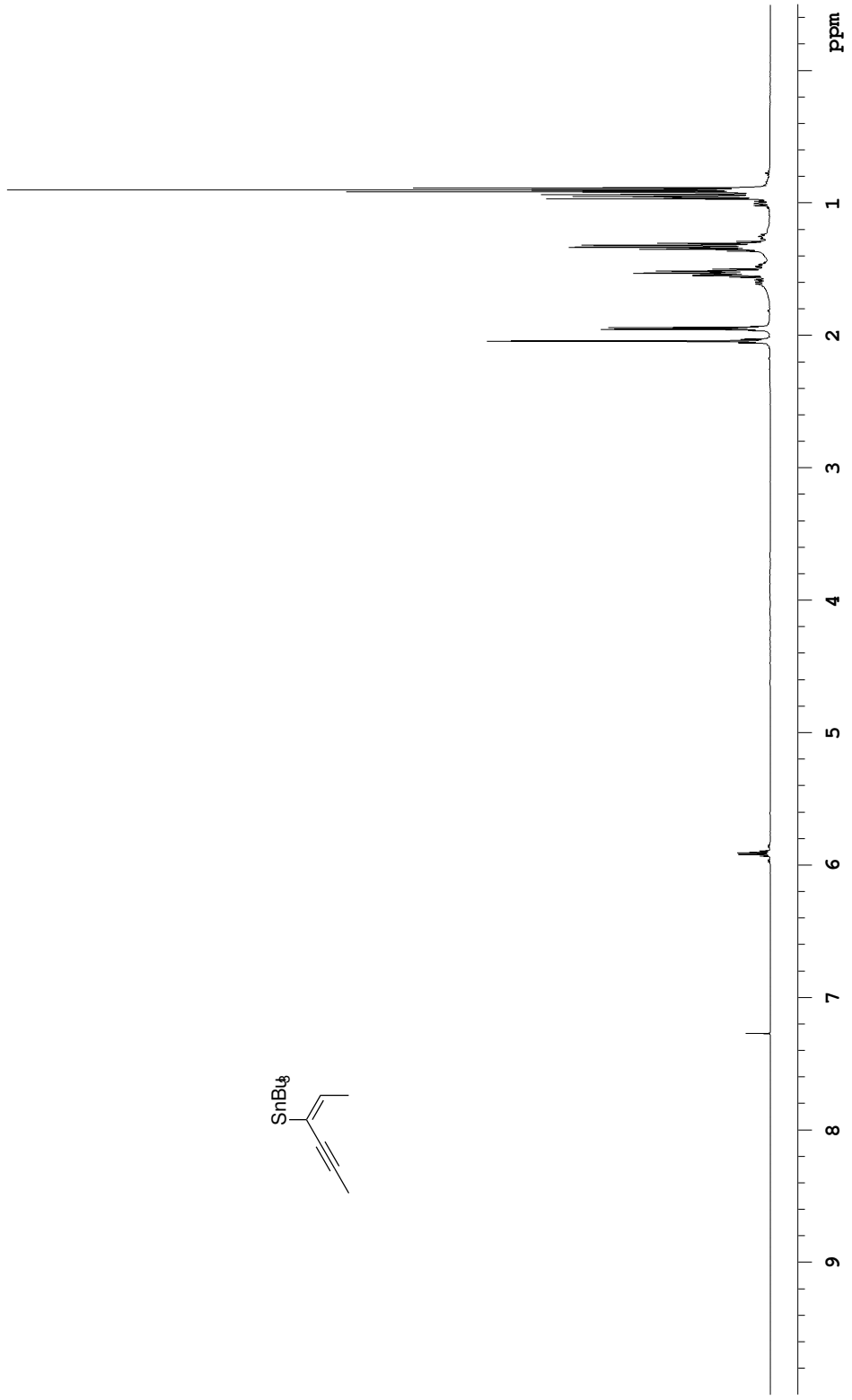

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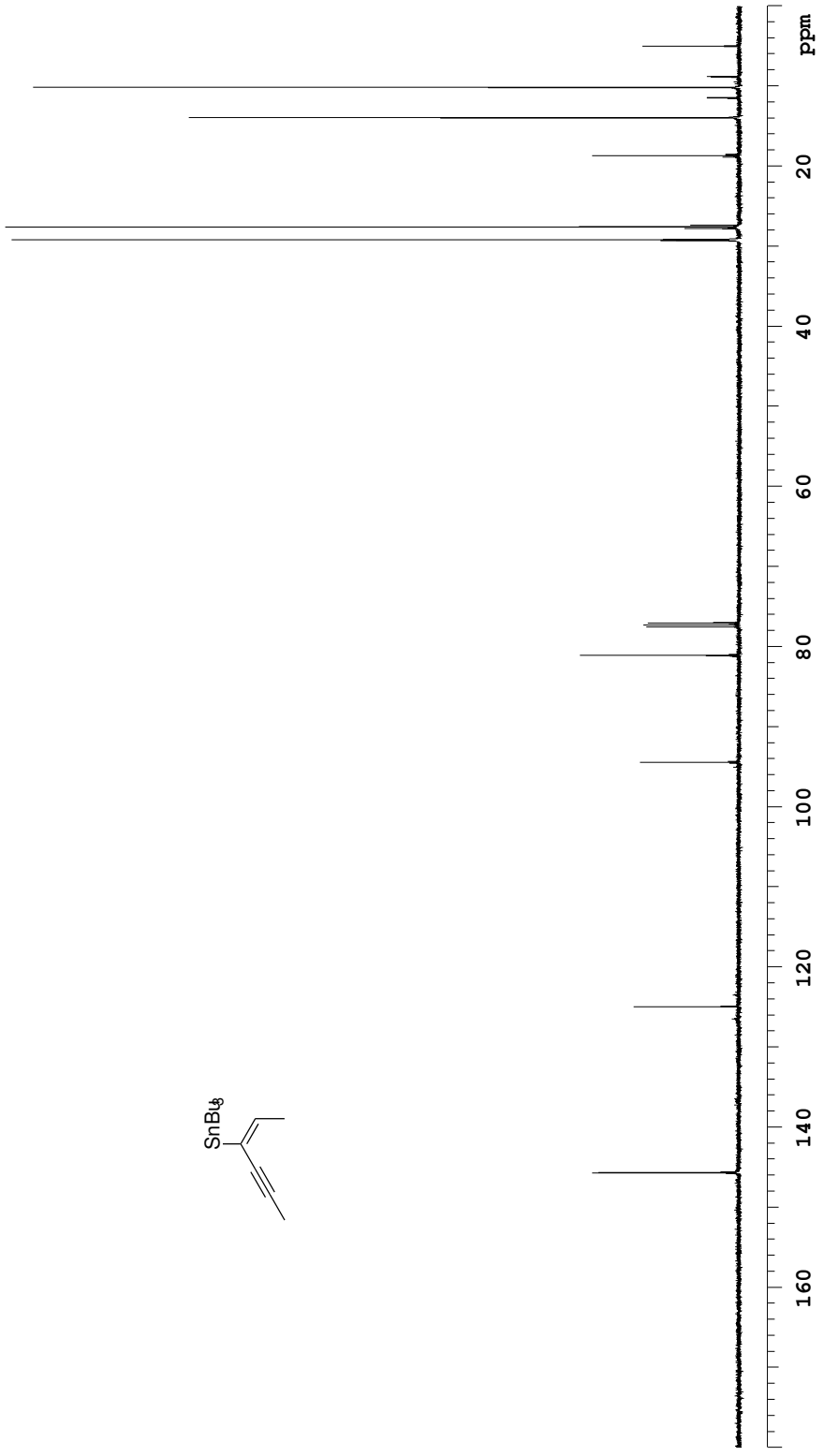

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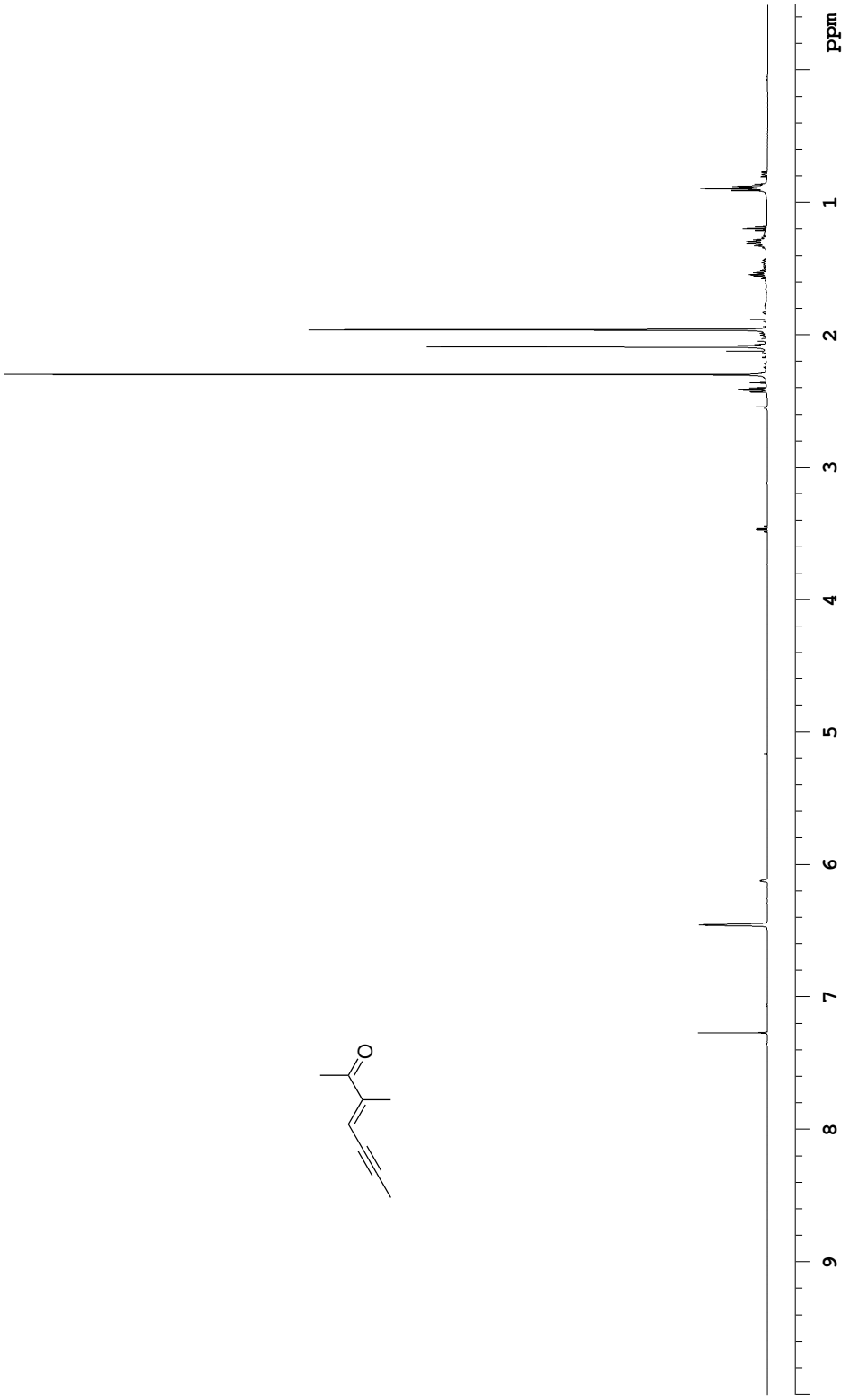

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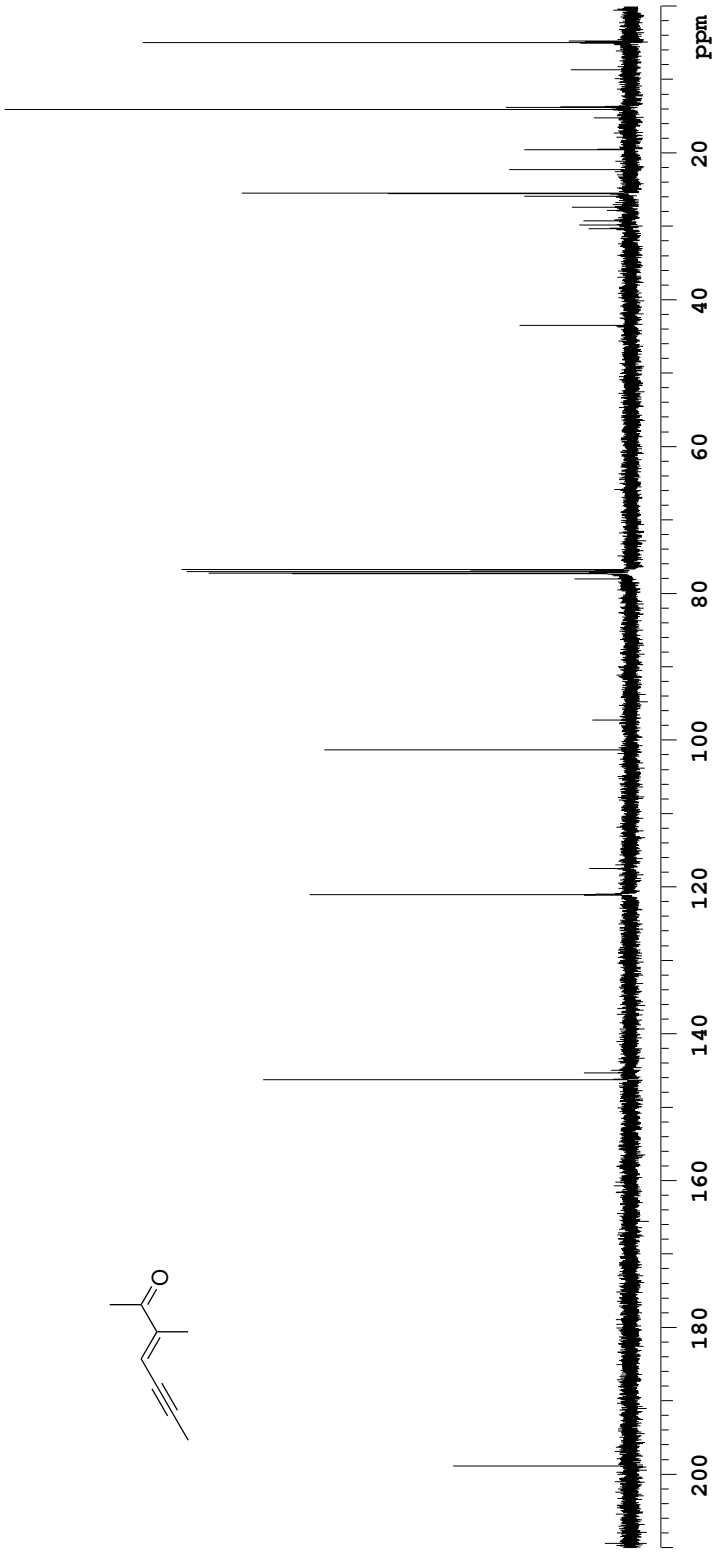

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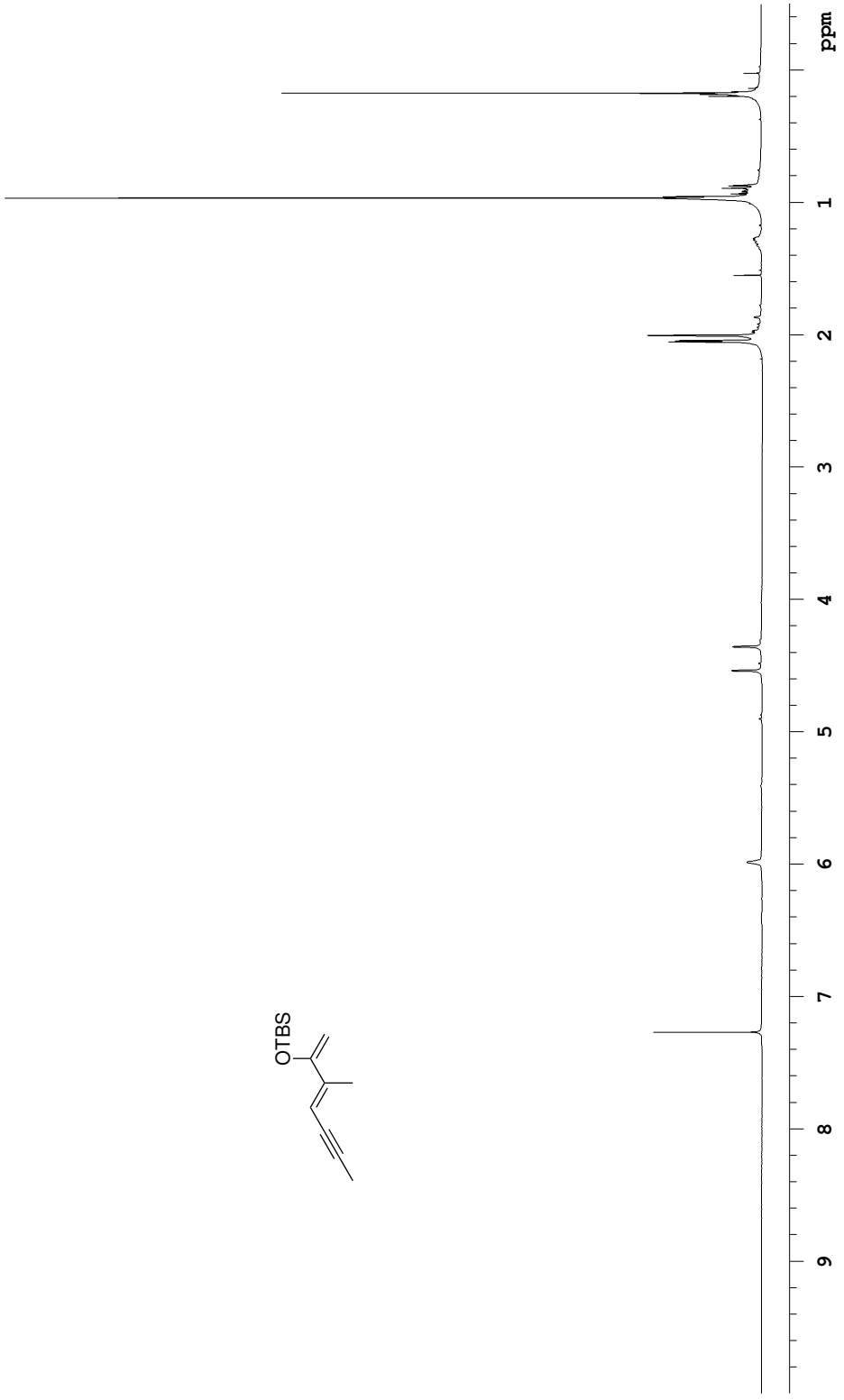

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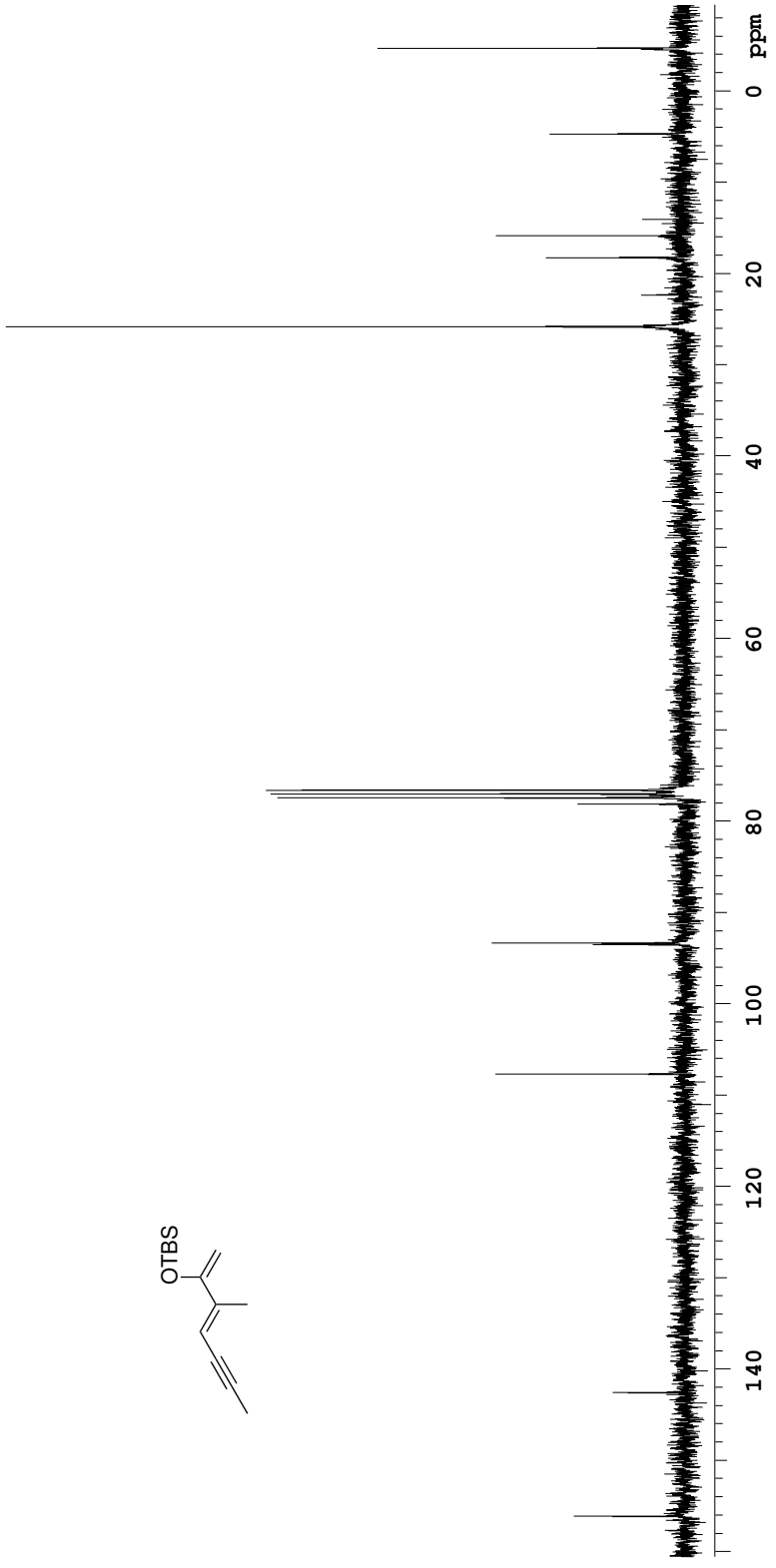

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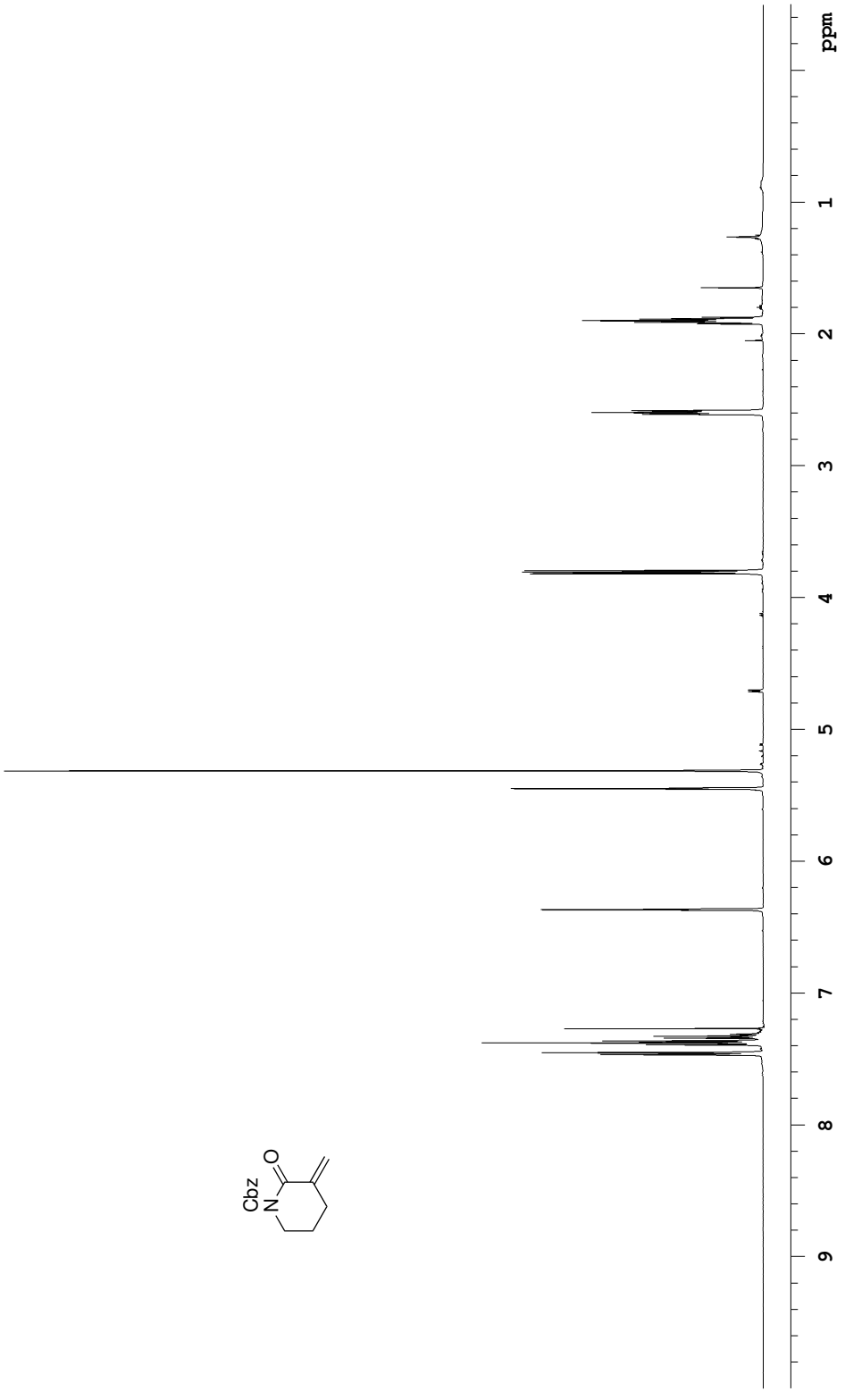

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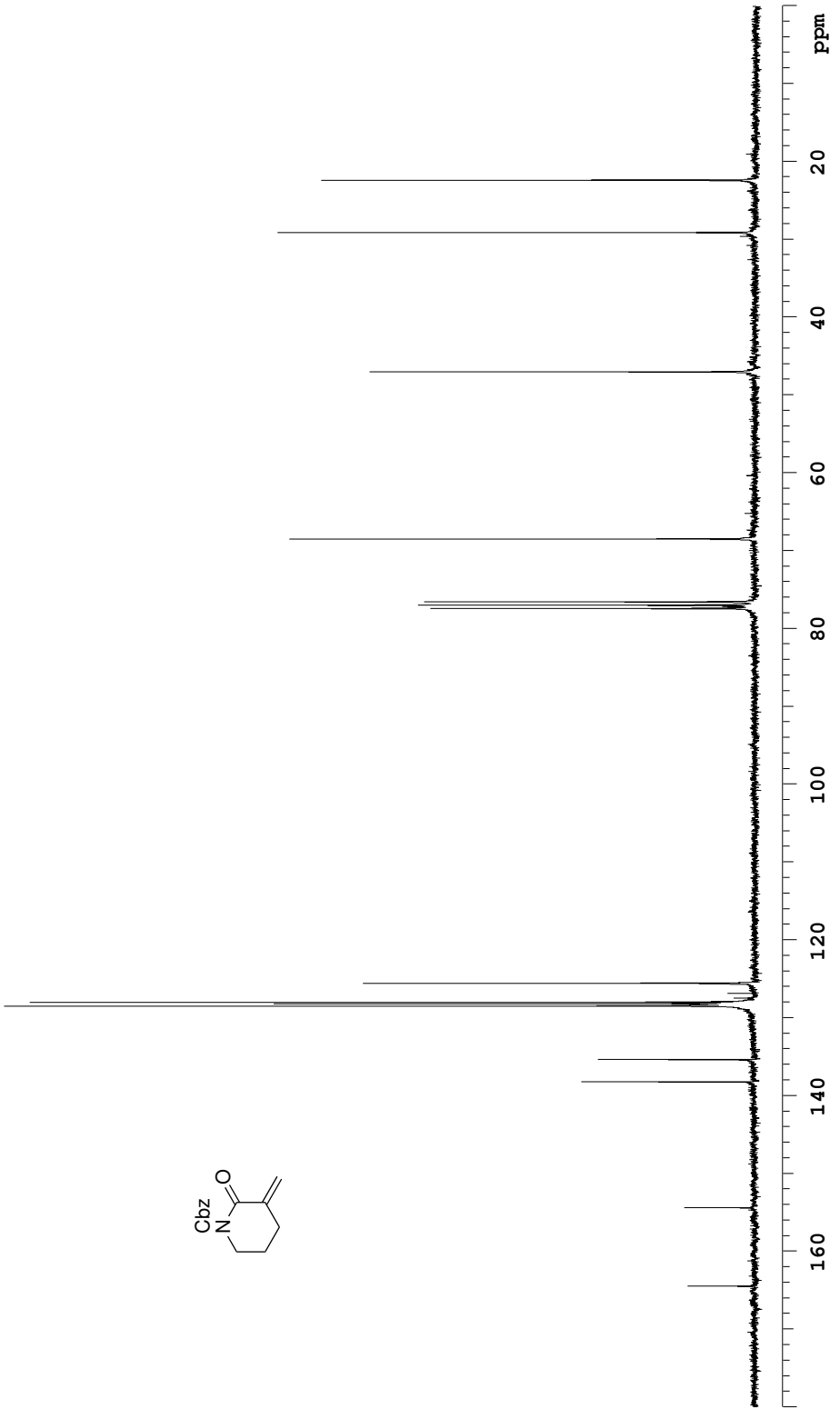
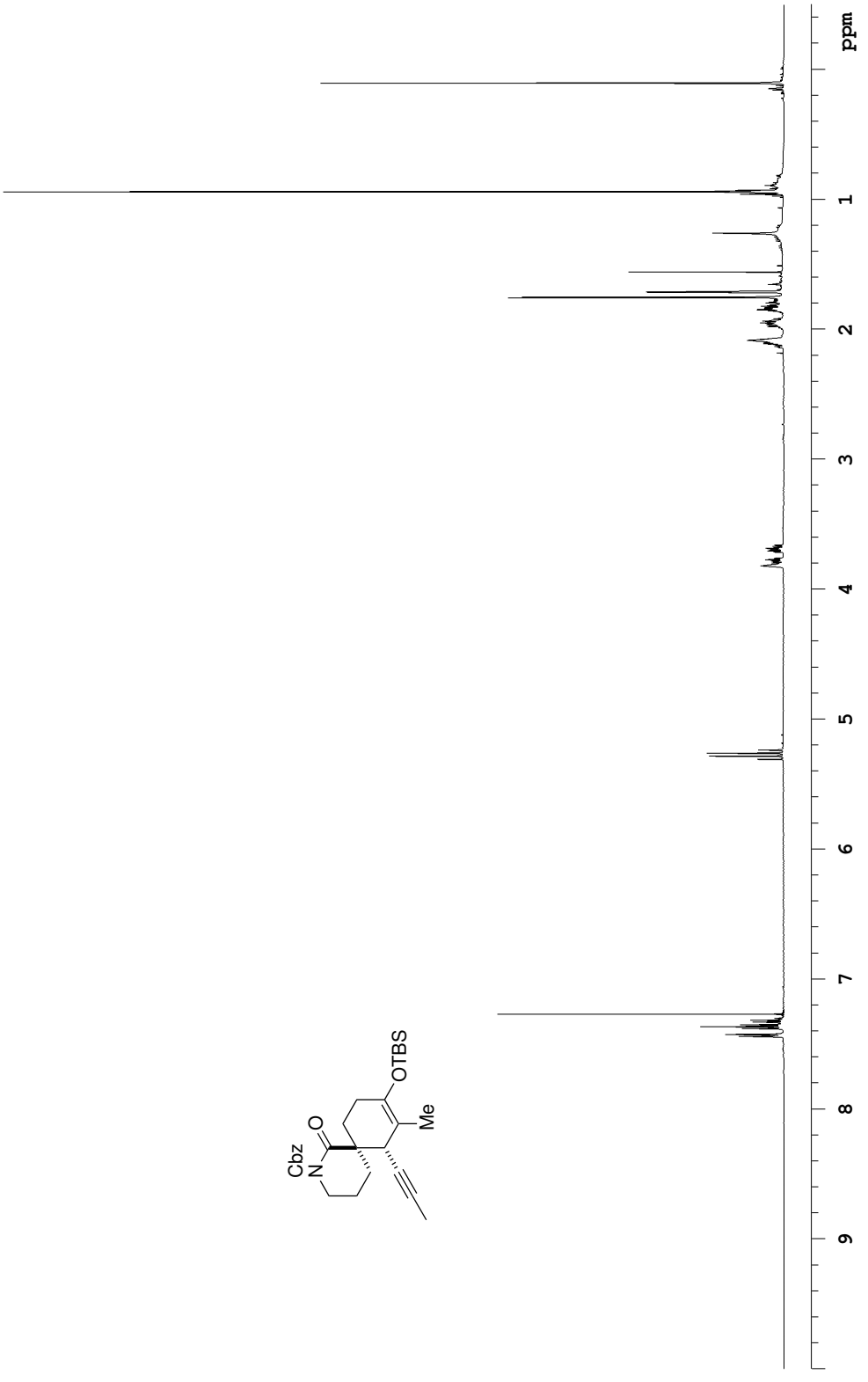
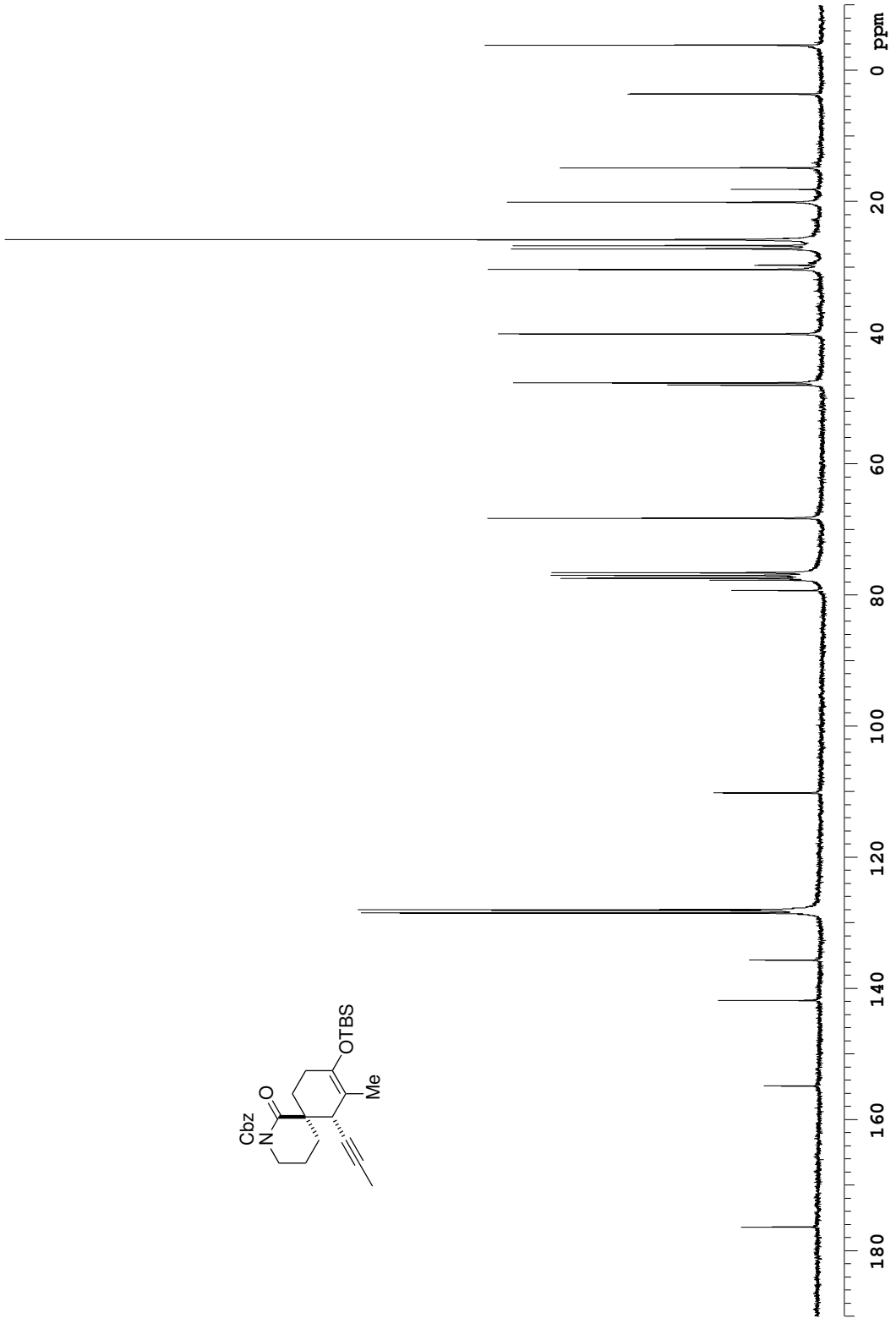


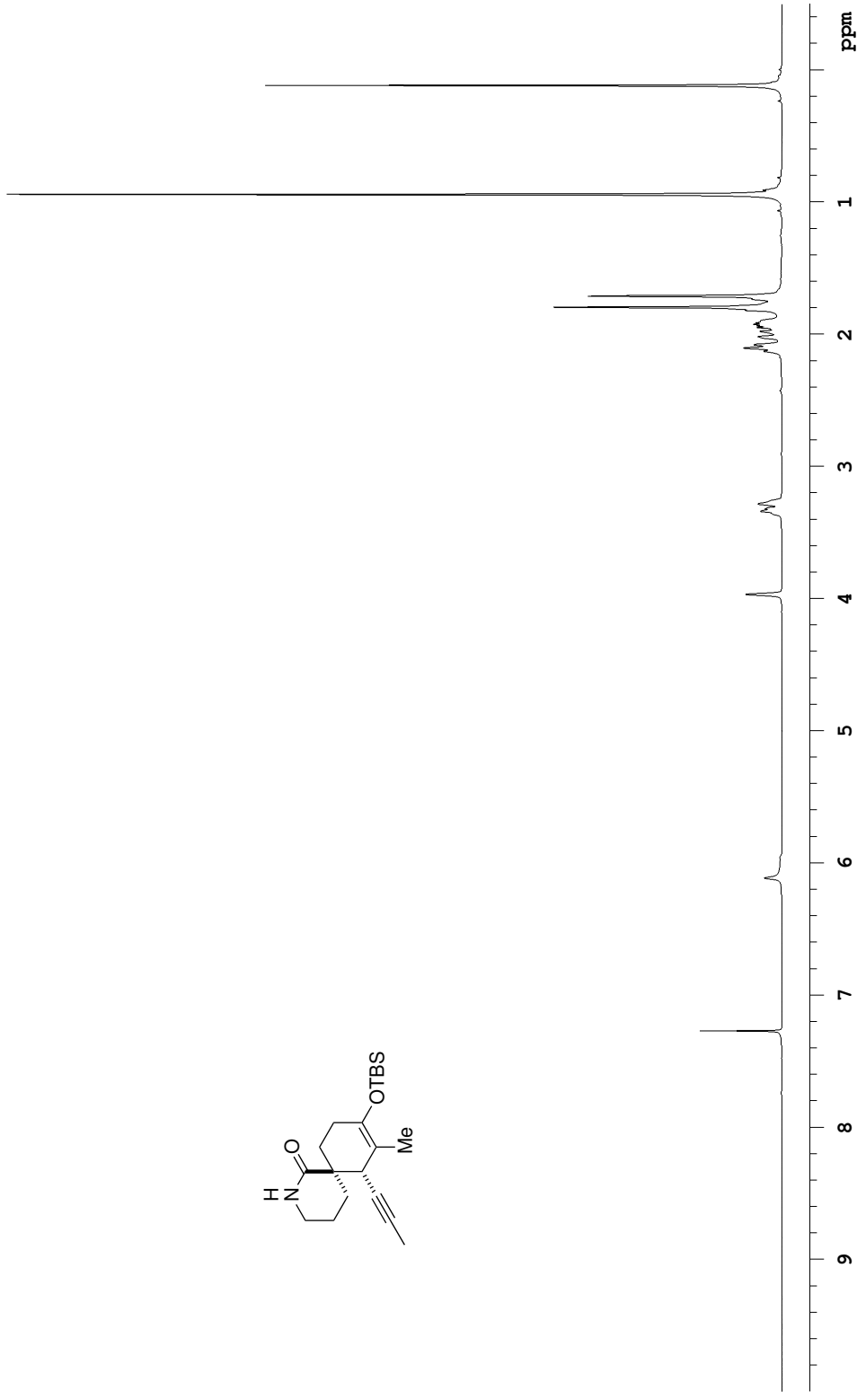
^{13}C NMR spectrum of *N*-Cbz lactam **46a**



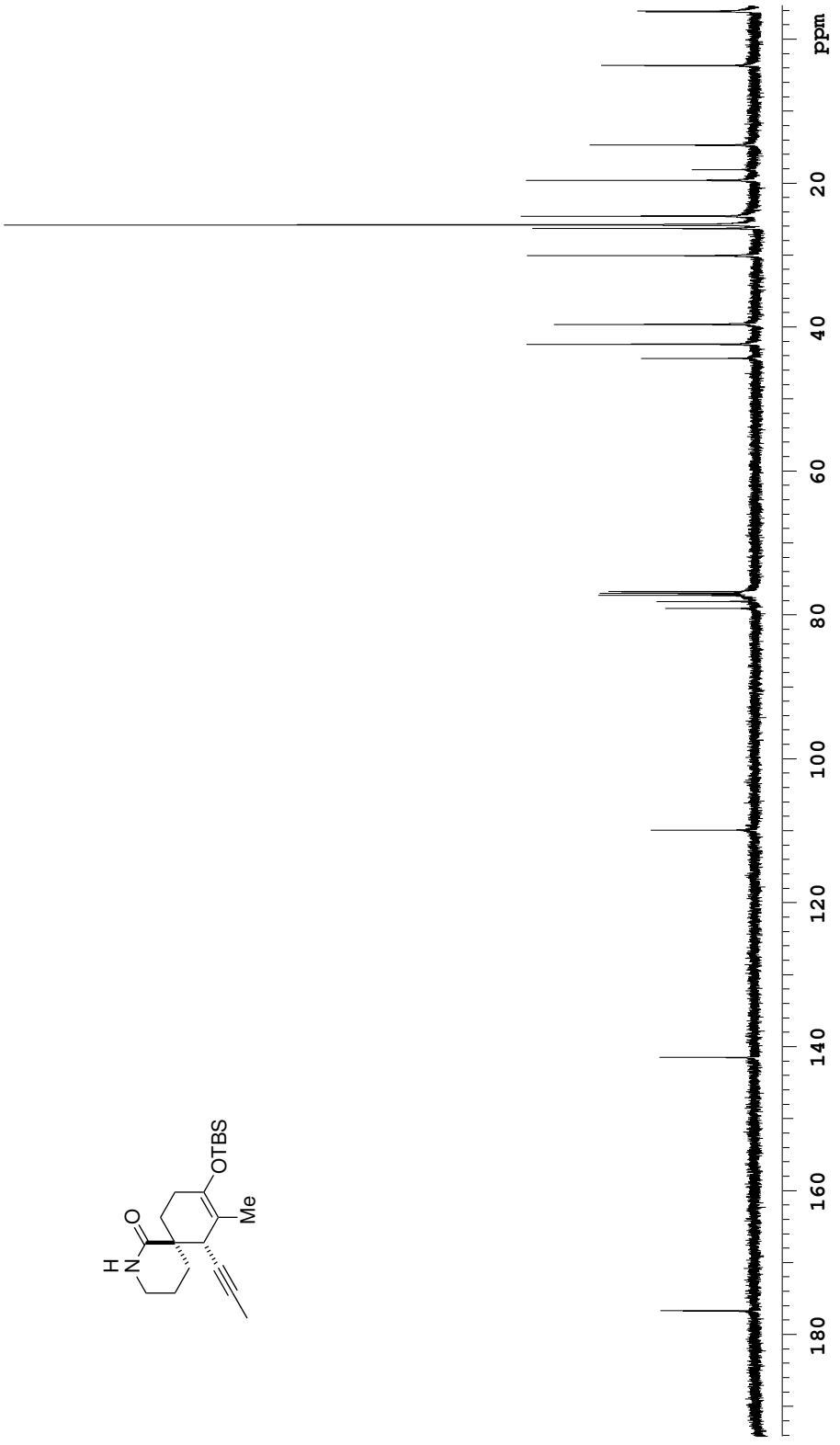
^{1}H NMR spectrum of *N*-Cbz spirolactam **96b**



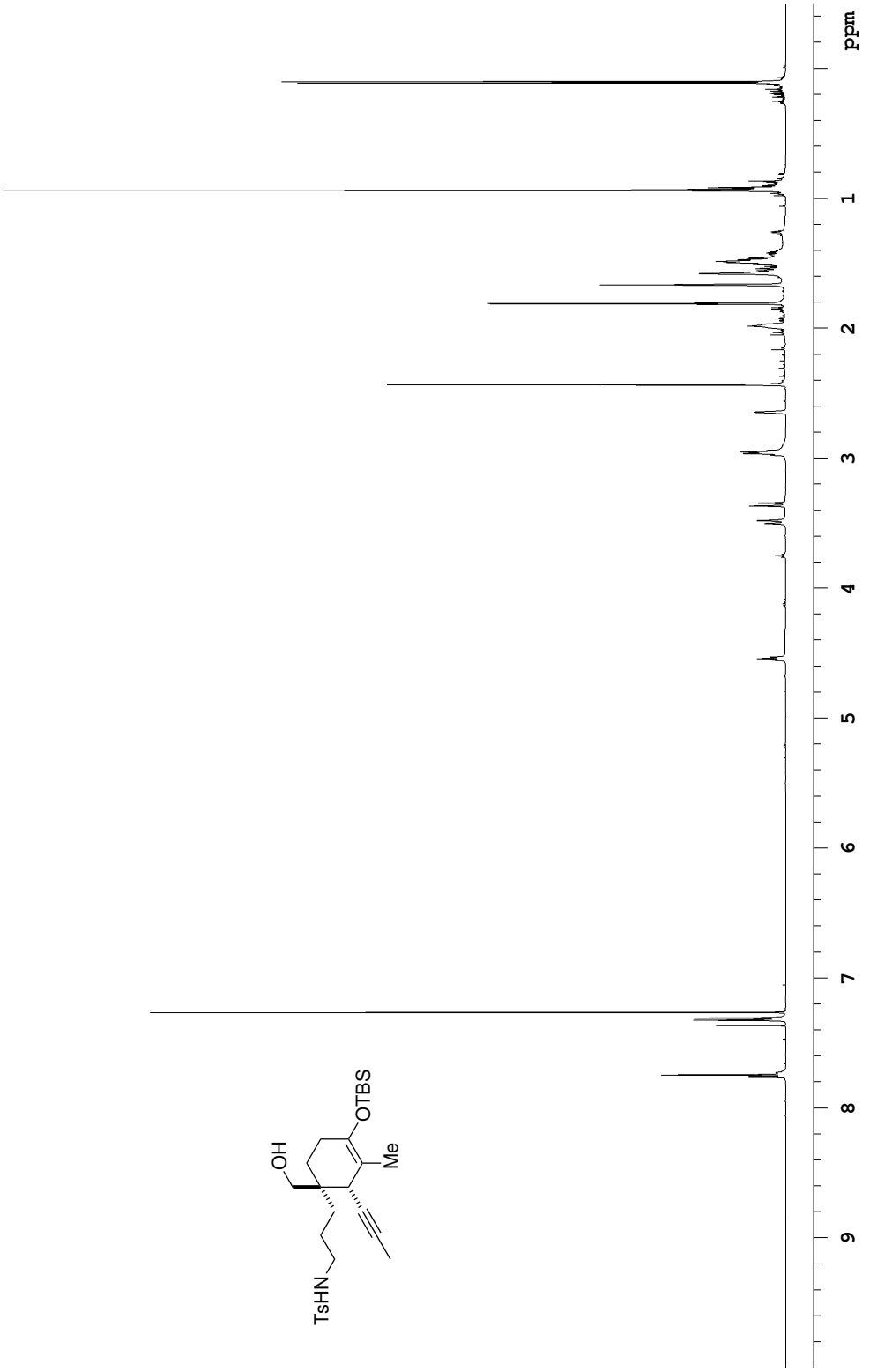
^{13}C NMR spectrum of *N*-Cbz spirolactam **96b**



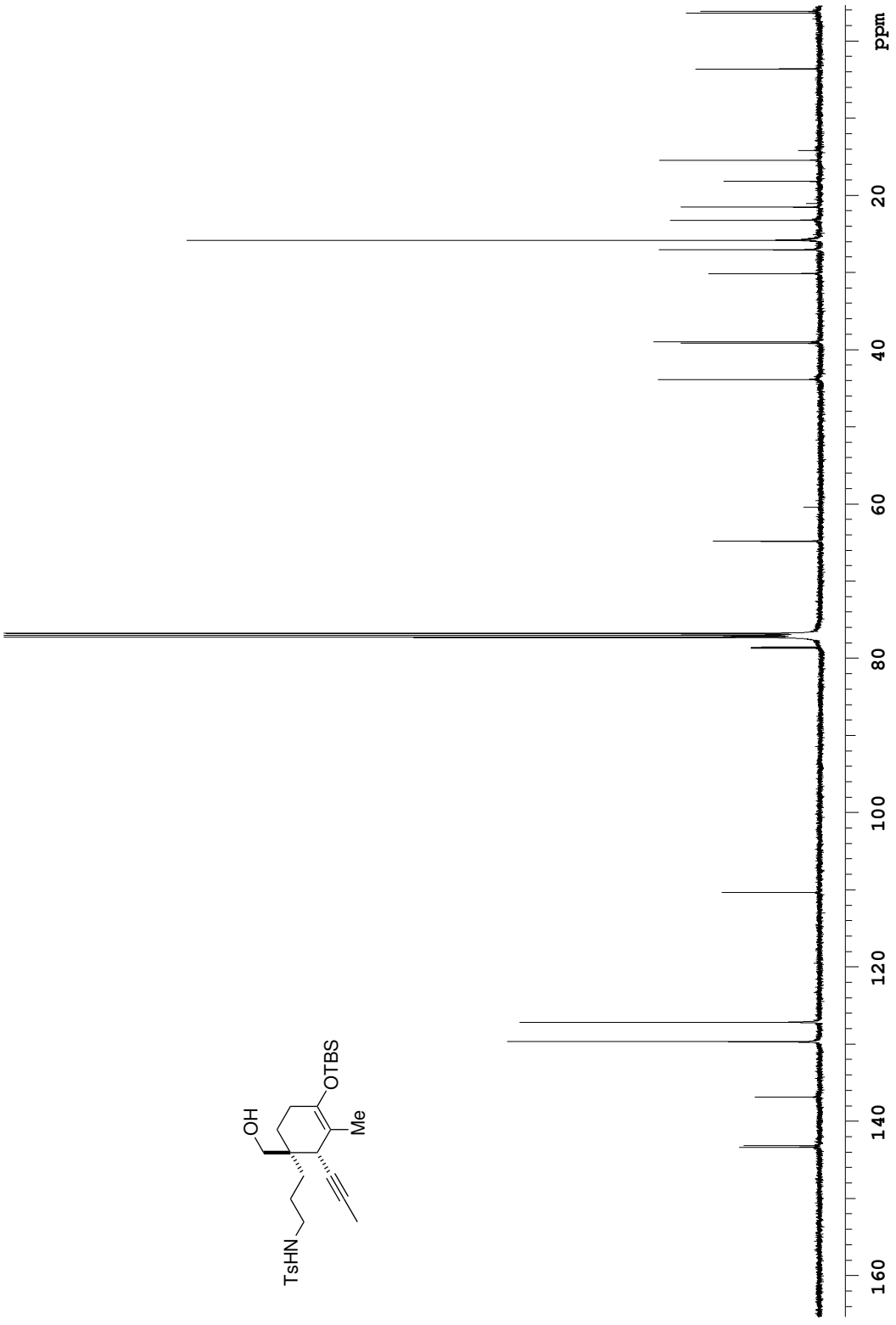
^{1}H NMR spectrum of spirolactam **96c**



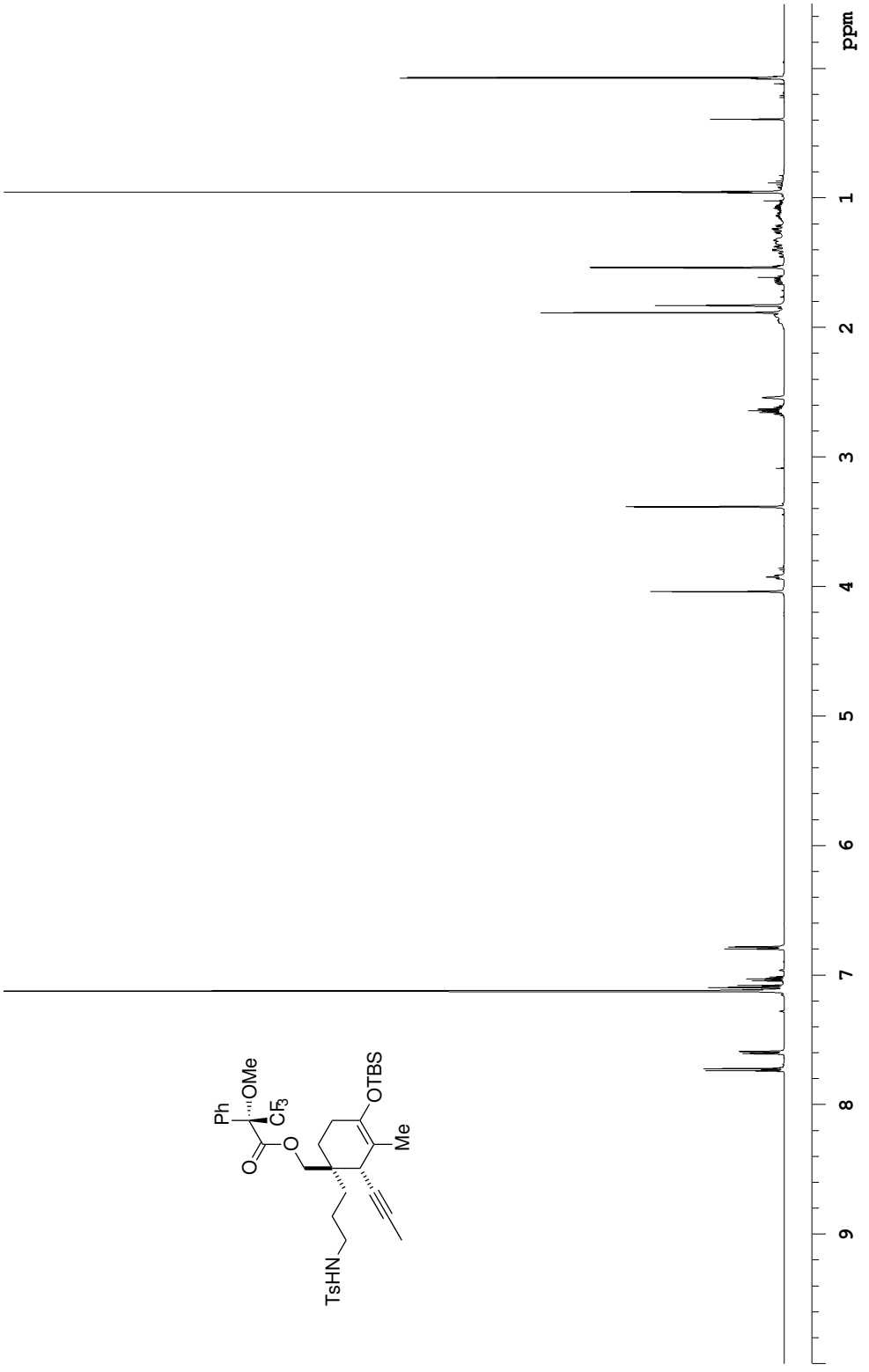
^{13}C NMR spectrum of spirolactam **96c**



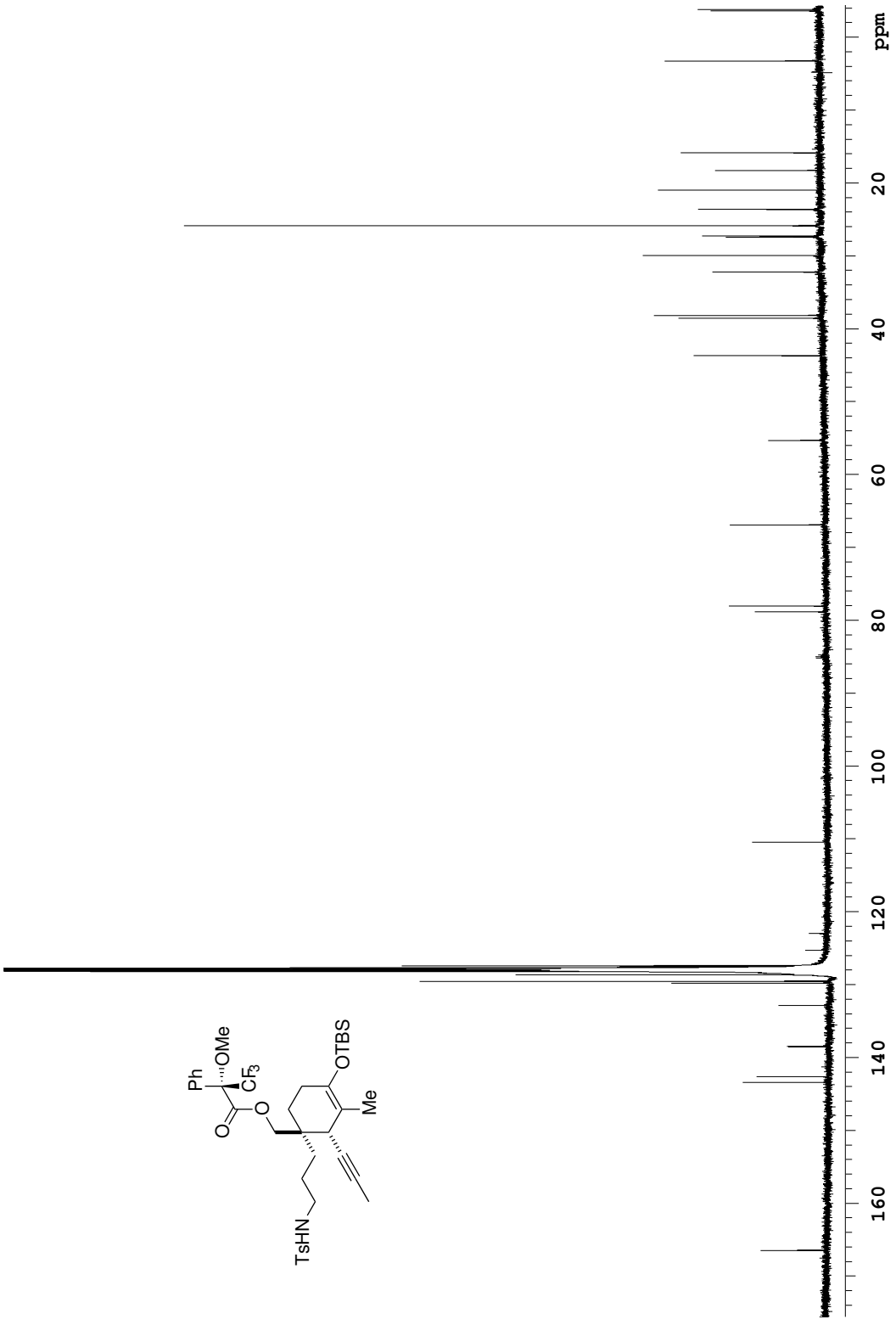
^{1}H NMR spectrum of amino alcohol **106**



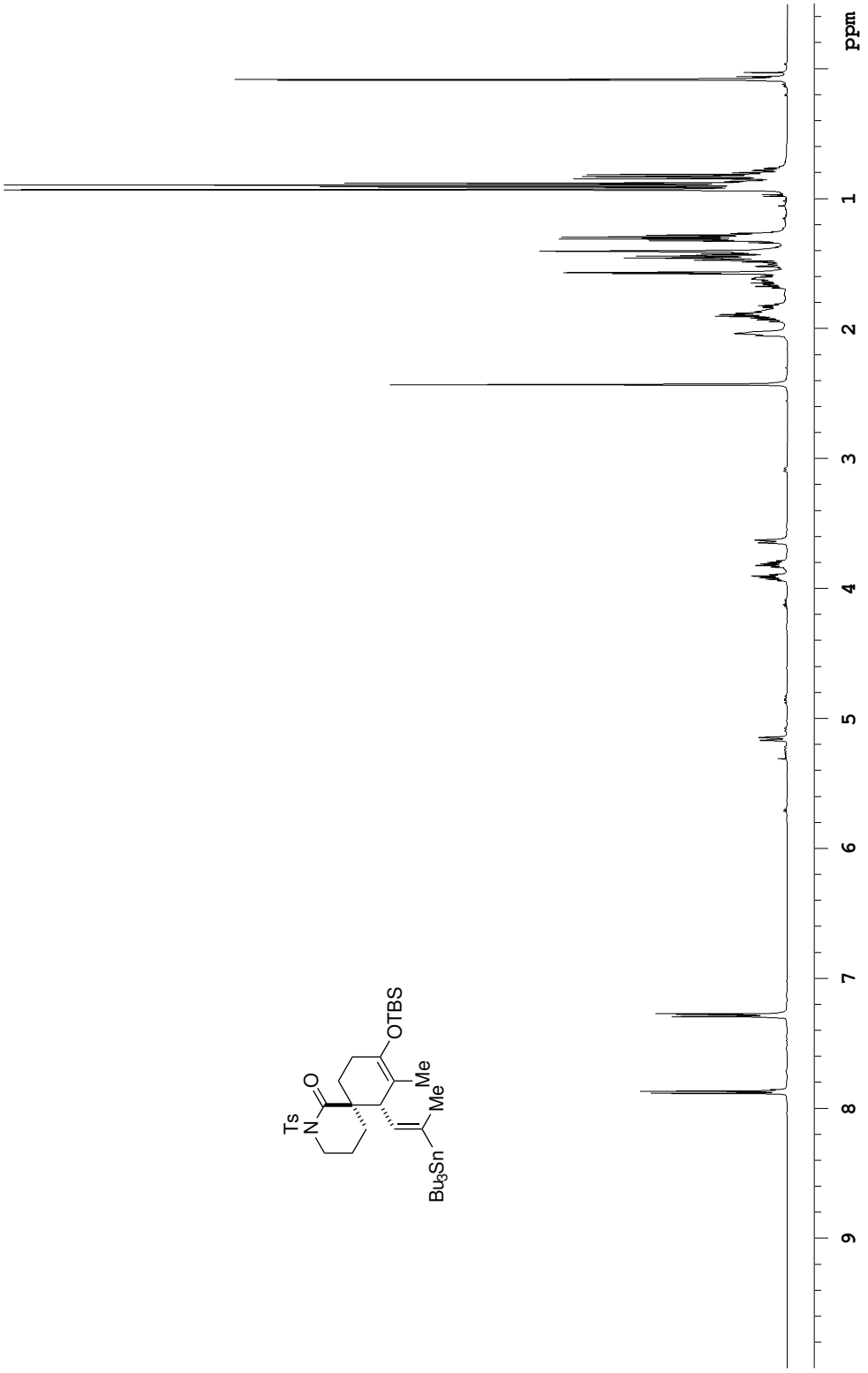
^{13}C NMR spectrum of amino alcohol **106**



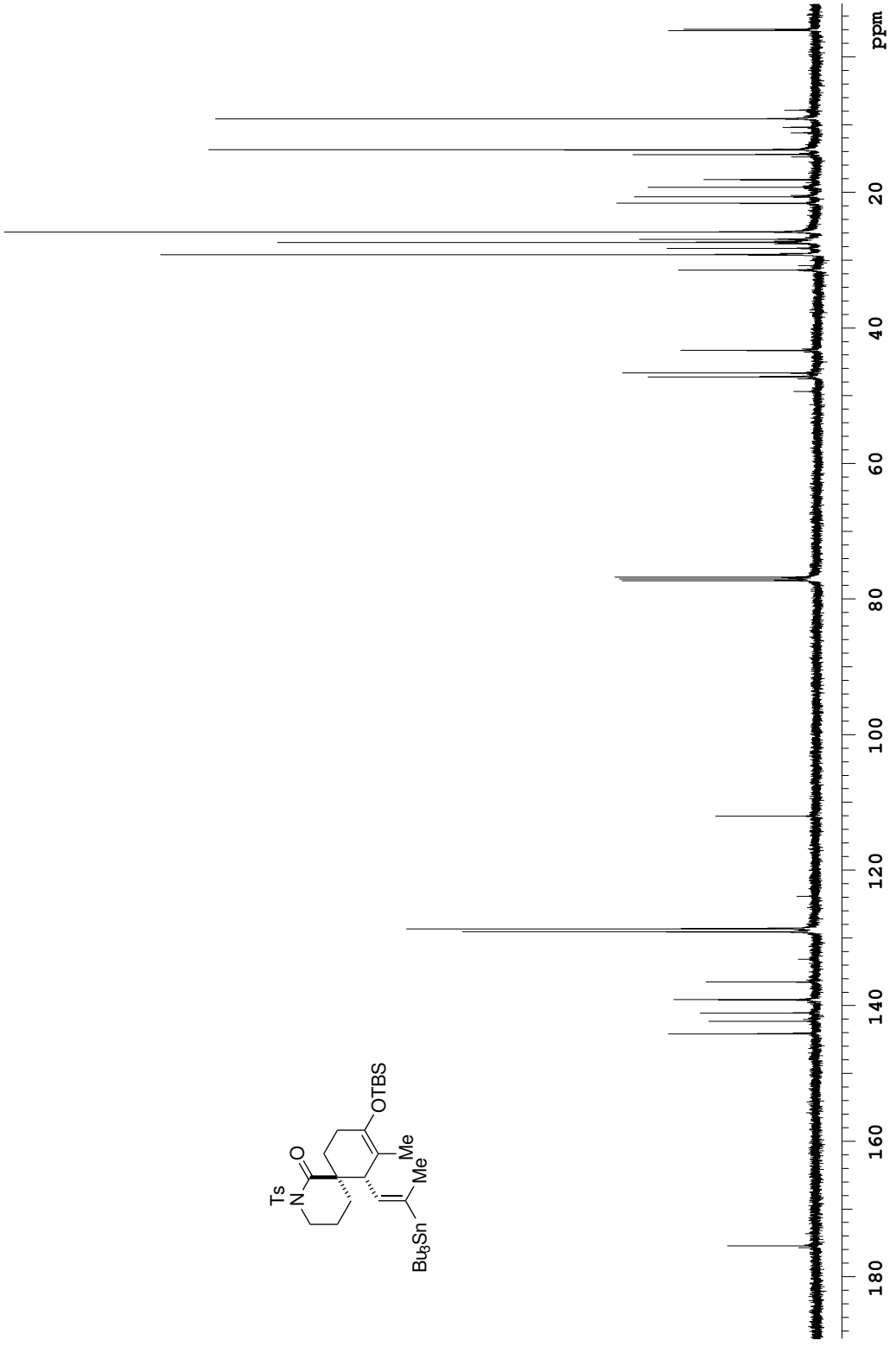
^{1}H NMR spectrum of Mosher ester **107**



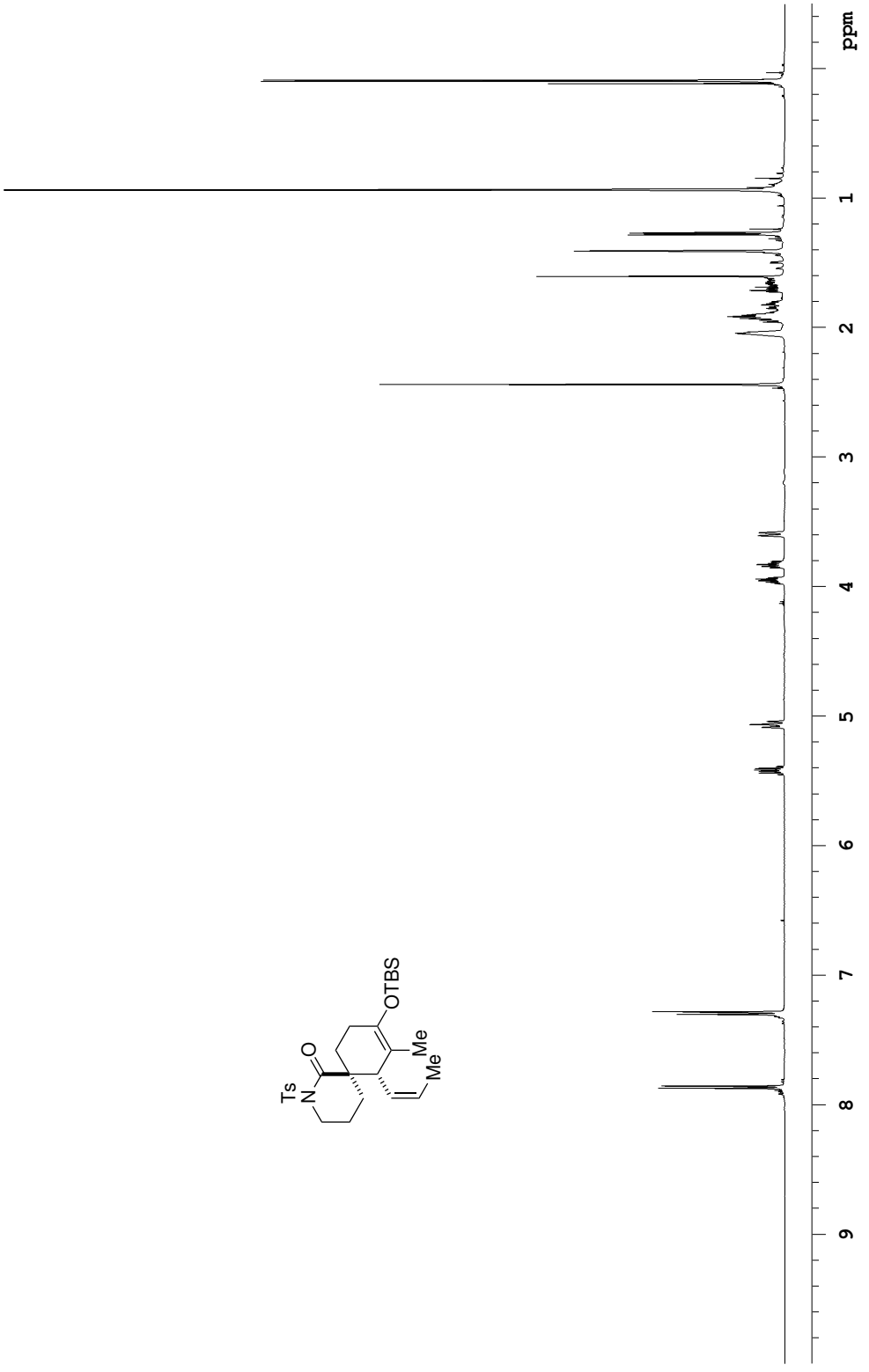
^{13}C NMR spectrum of Mosher ester **107**



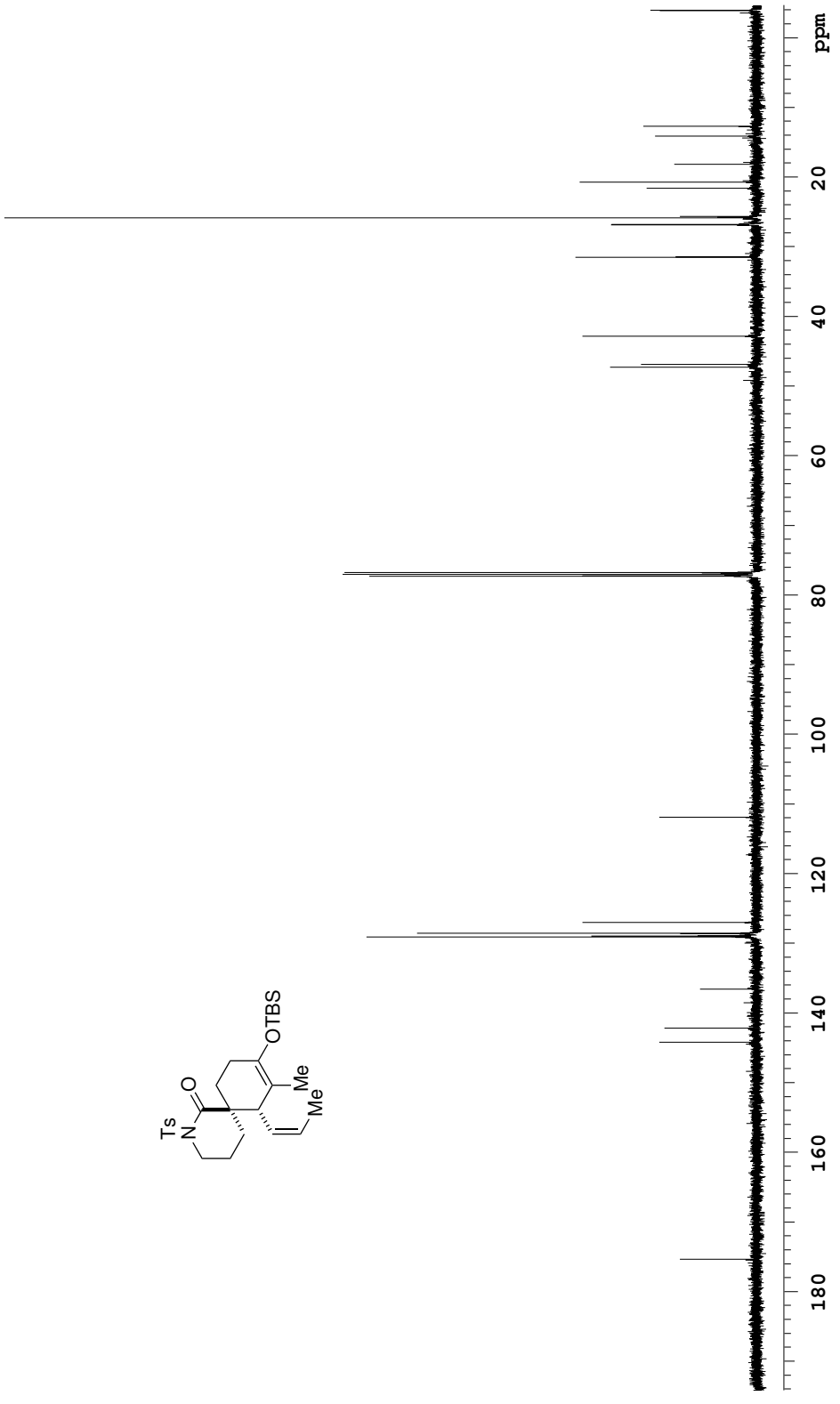
^{1}H NMR spectrum of vinyl stannane **108**



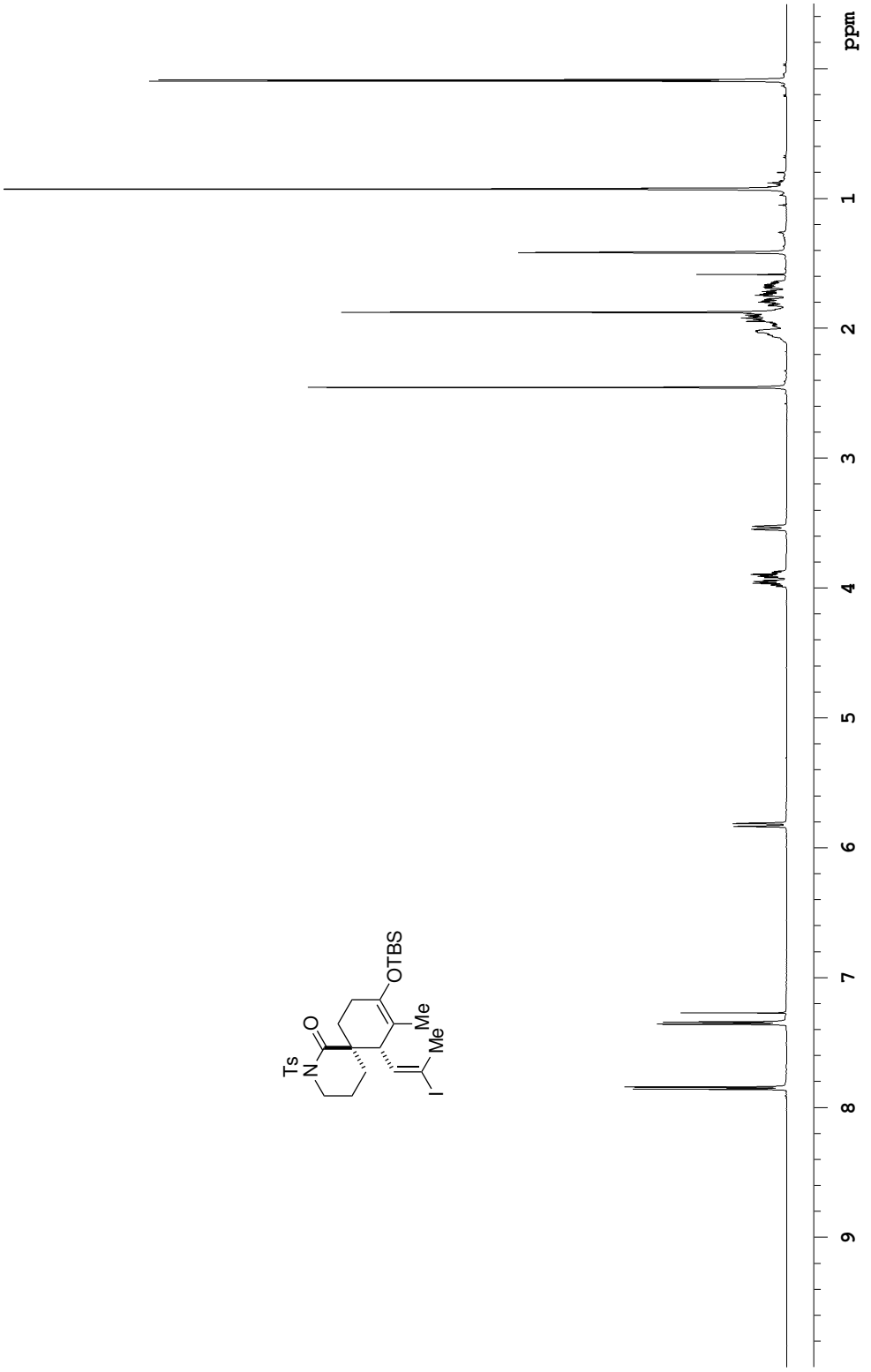
^{13}C NMR spectrum of vinyl stannane **108**



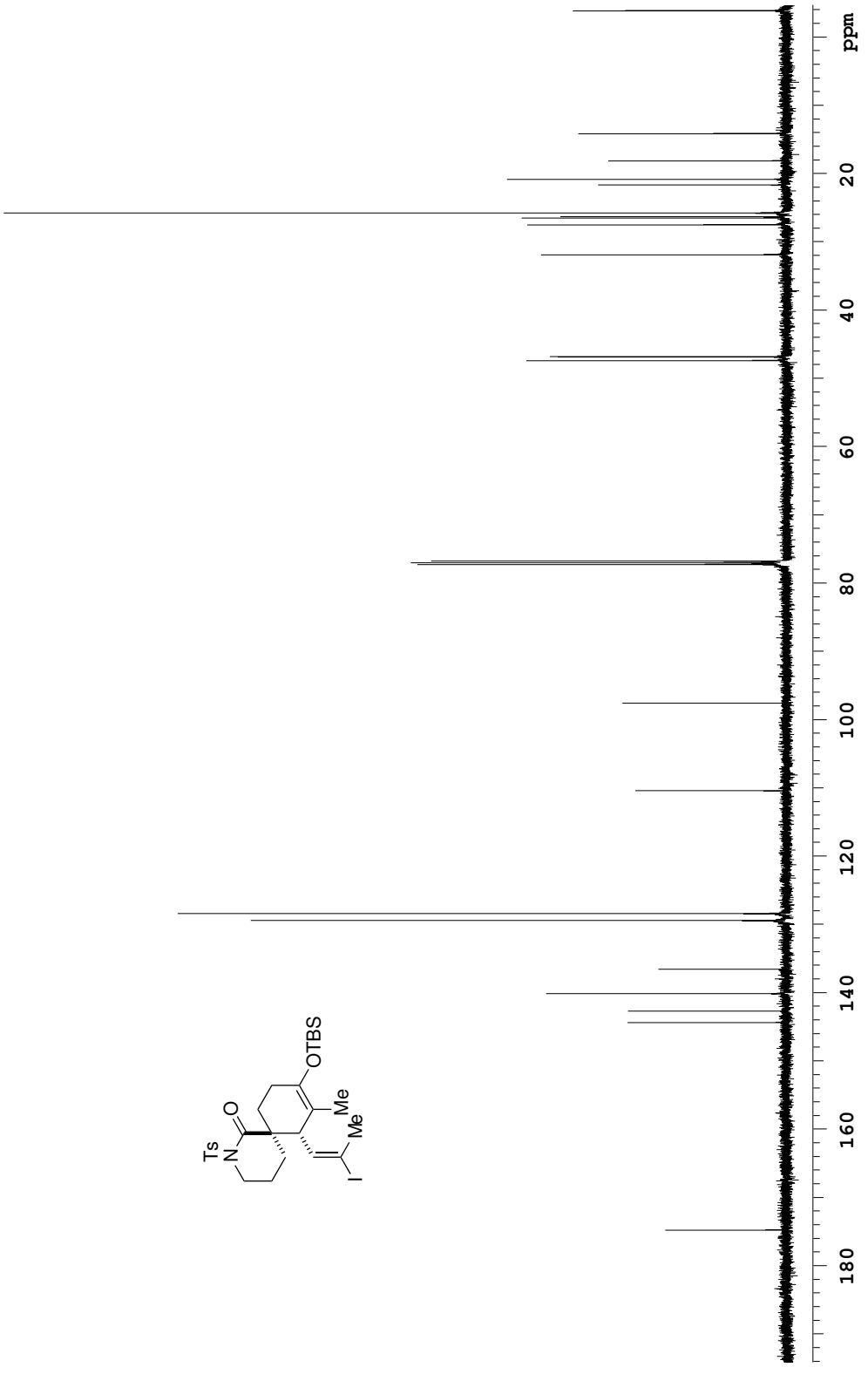
^{1}H NMR spectrum of hydrogenated product **109**



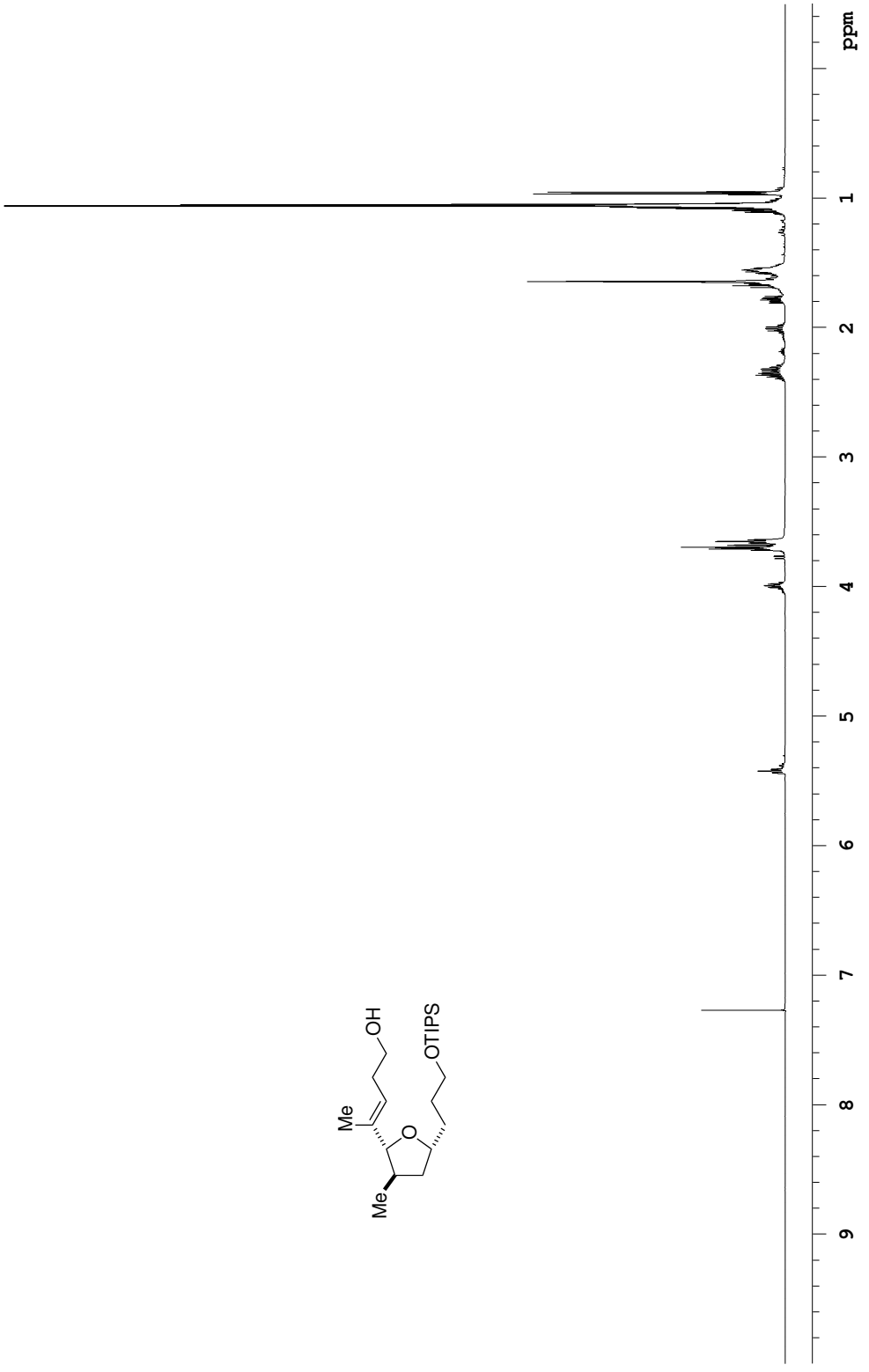
^{13}C NMR spectrum of hydrogenated product **109**



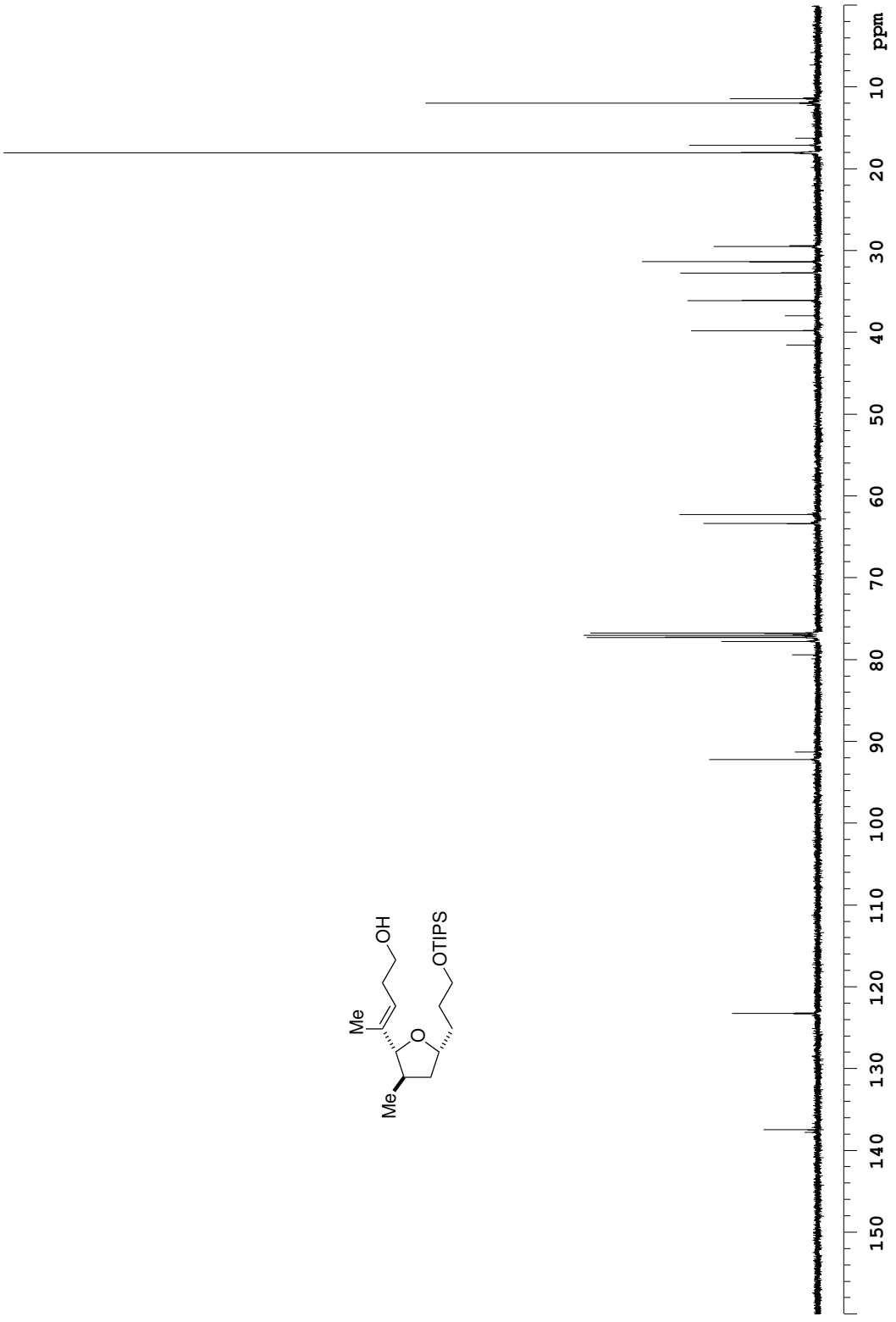
^{1}H NMR spectrum of vinyl iodide **110**



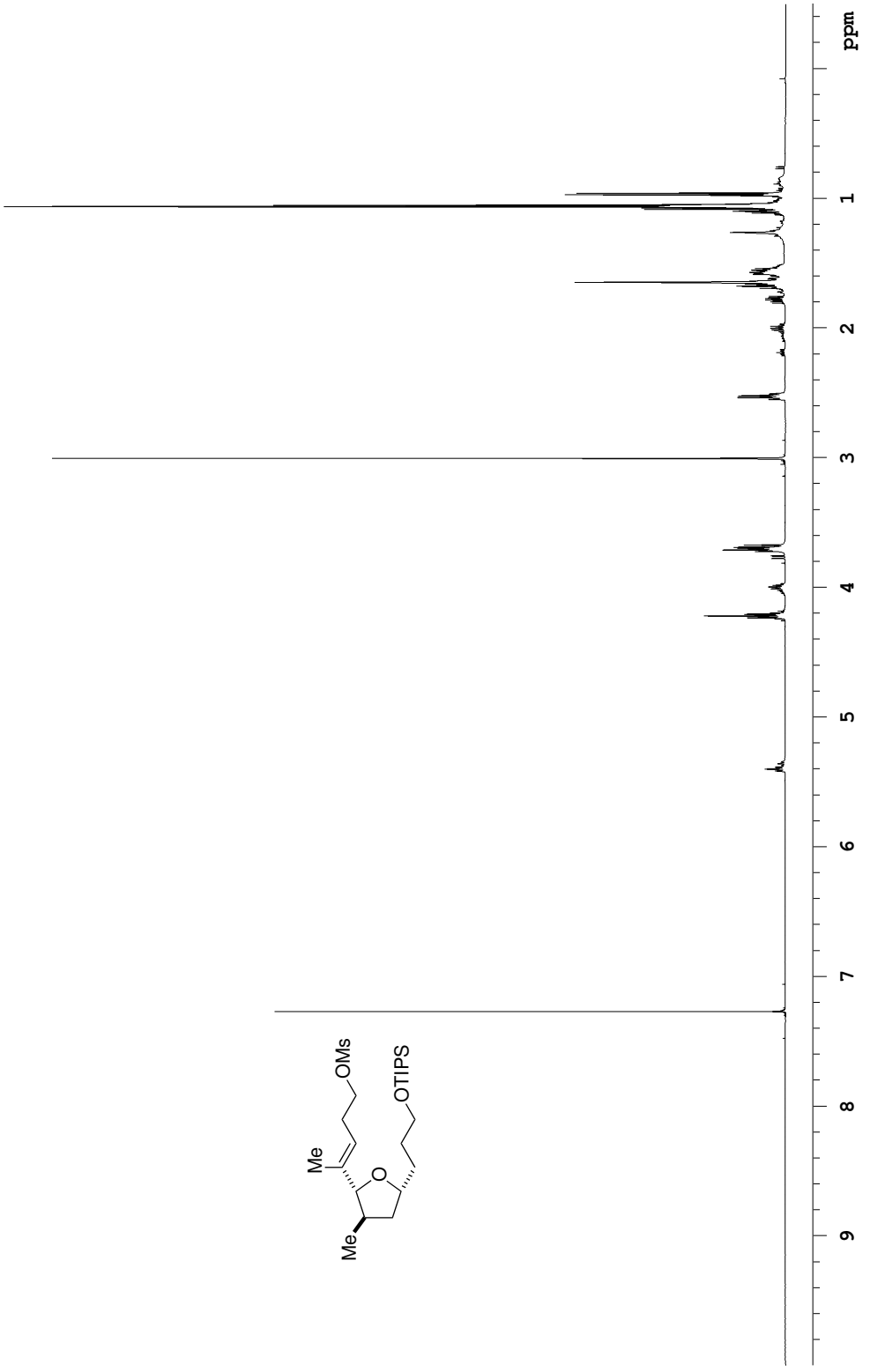
^{13}C NMR spectrum of vinyl iodide **110**



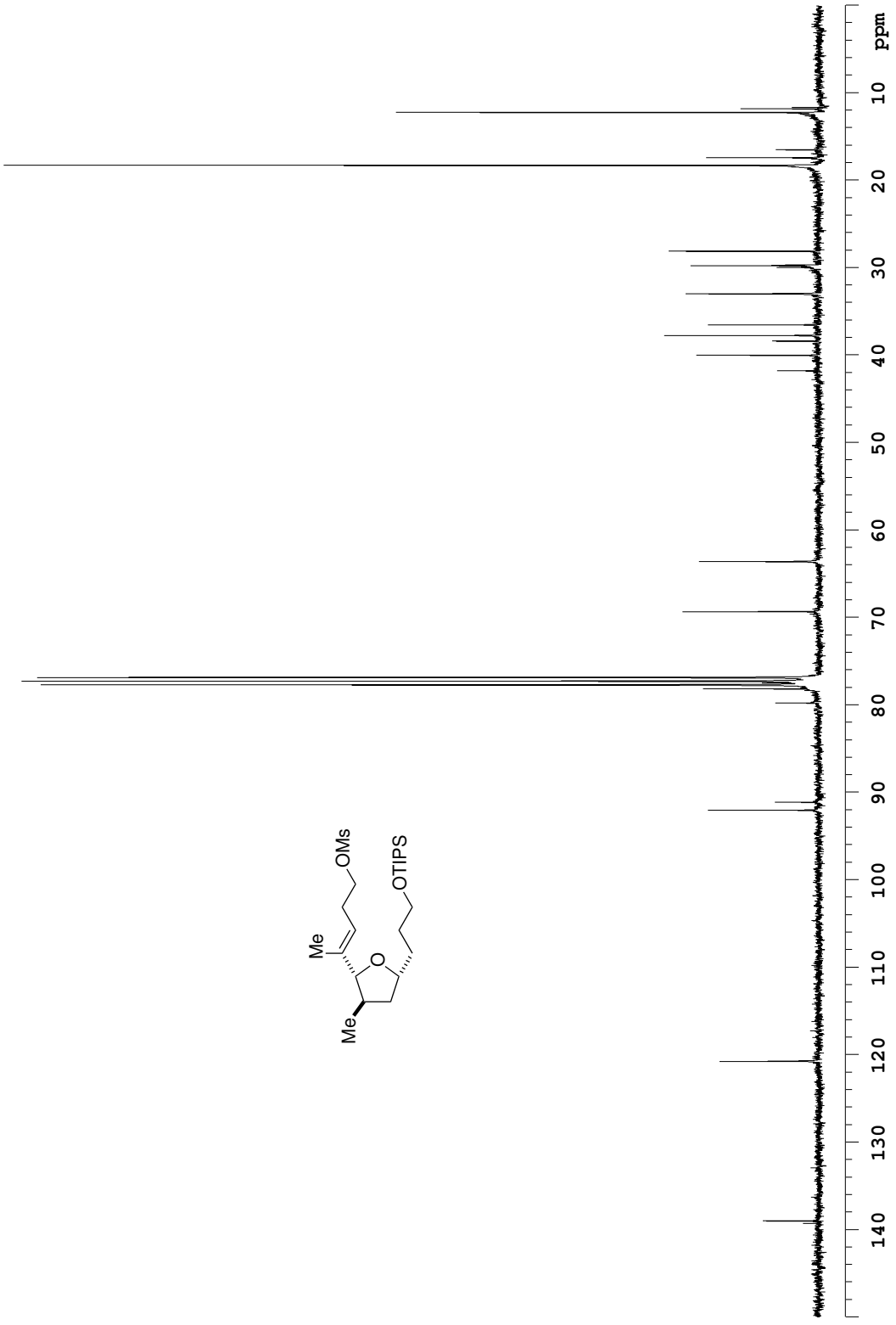
^{1}H NMR spectrum of alcohol **113**



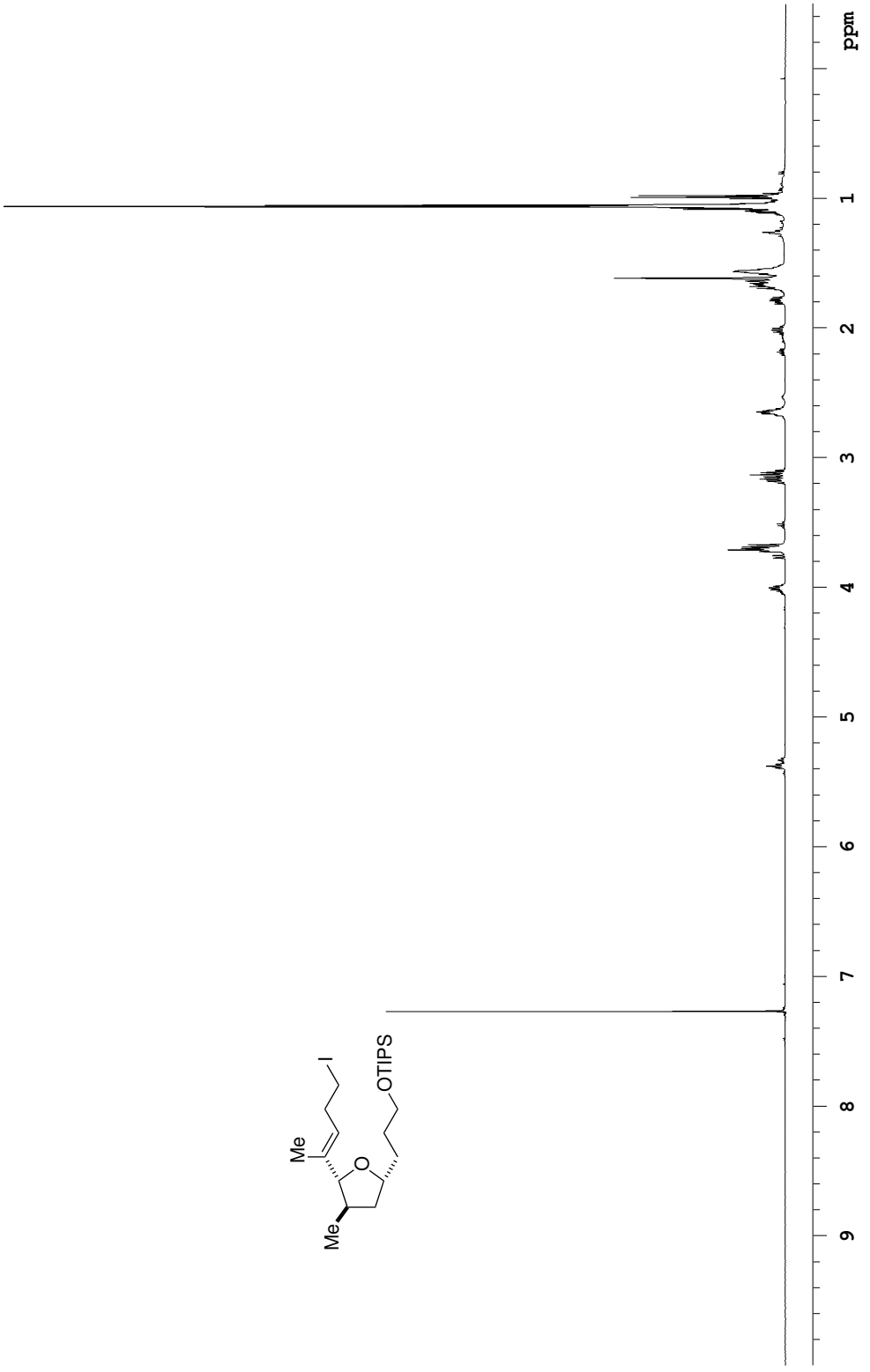
^{13}C NMR spectrum of alcohol **113**



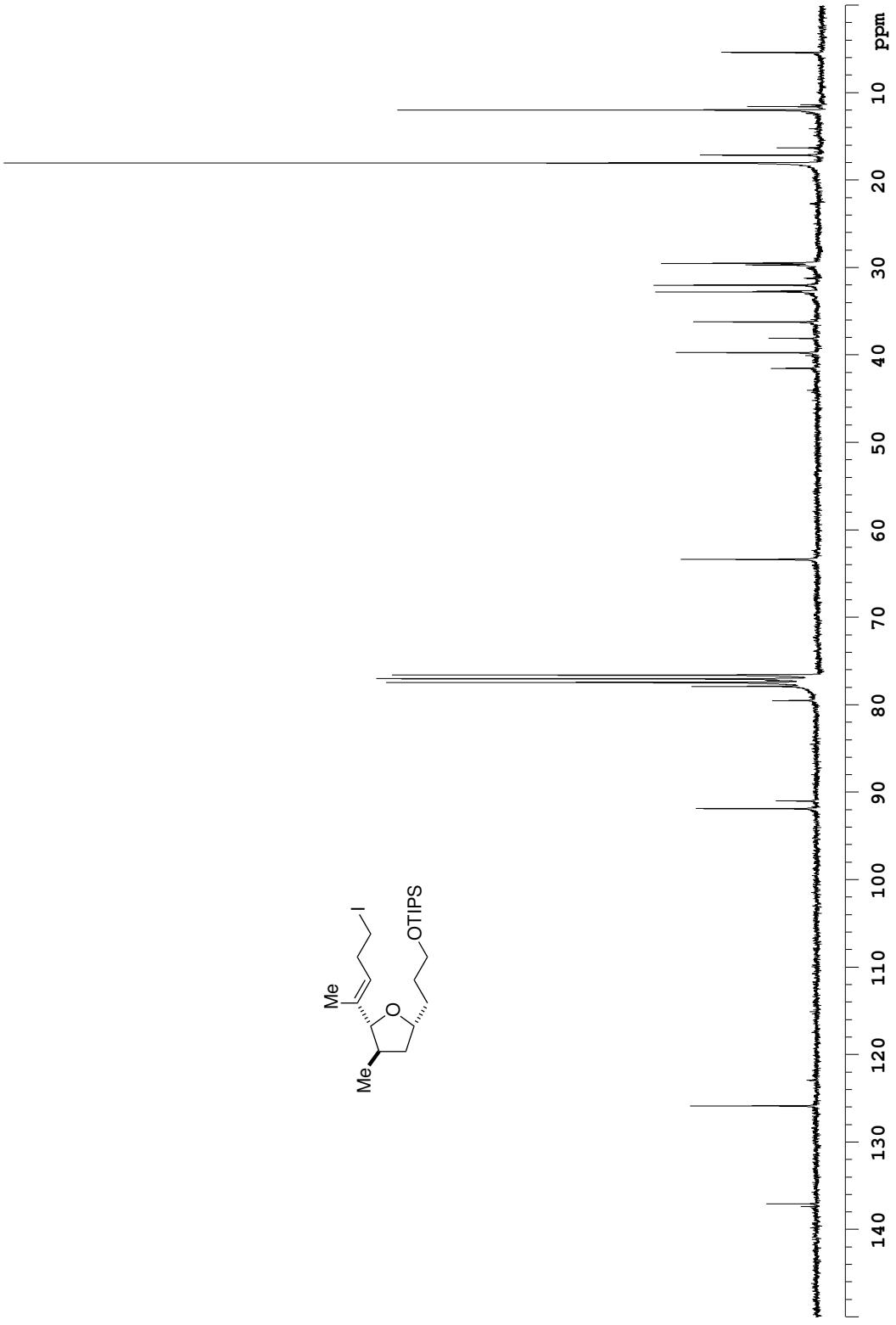
^{1}H NMR spectrum of mesylate **114a**



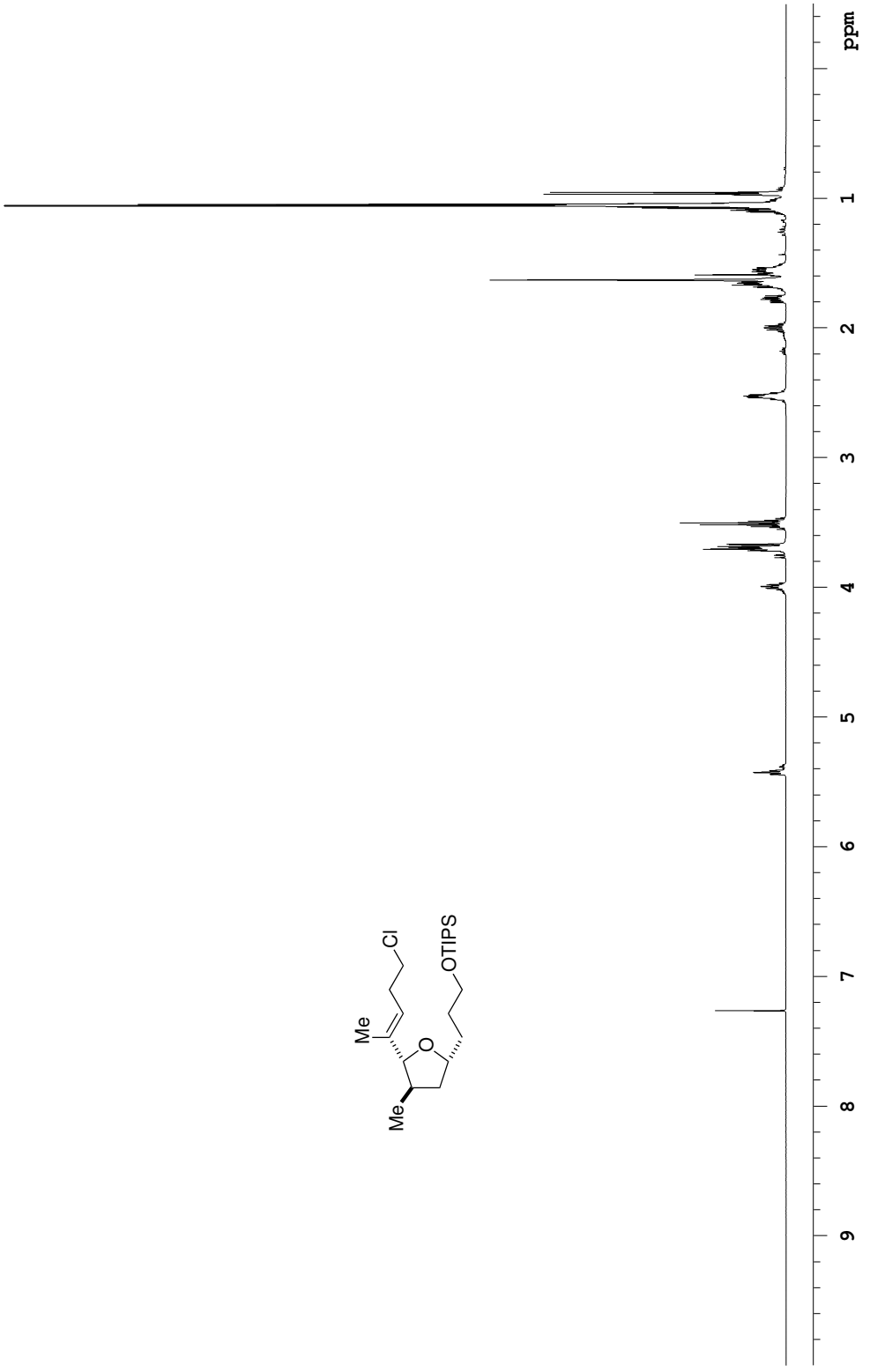
^{13}C NMR spectrum of mesylate **114a**



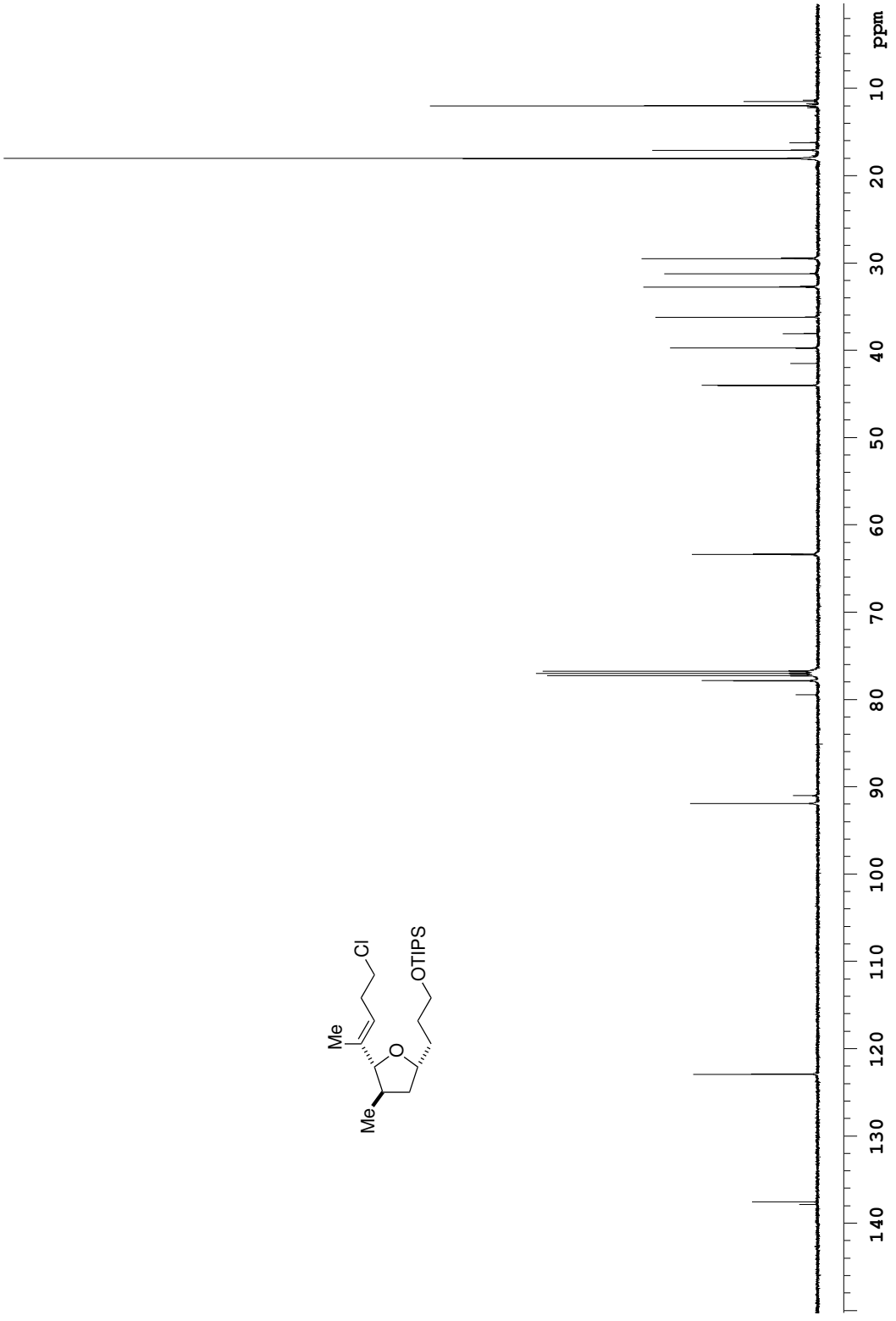
^{1}H NMR spectrum of alkyl iodide **114b**



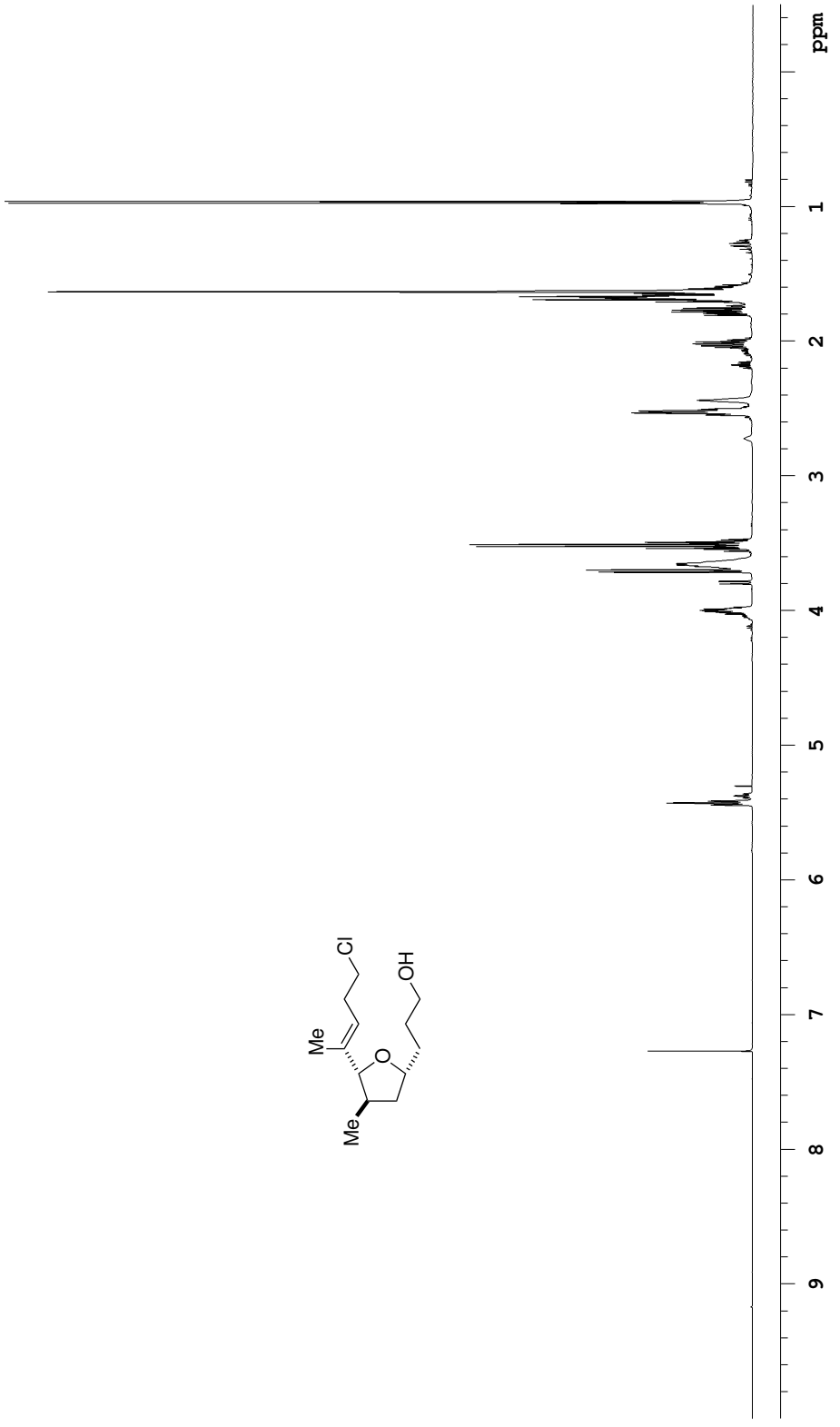
^{13}C NMR spectrum of alkyl iodide **114b**



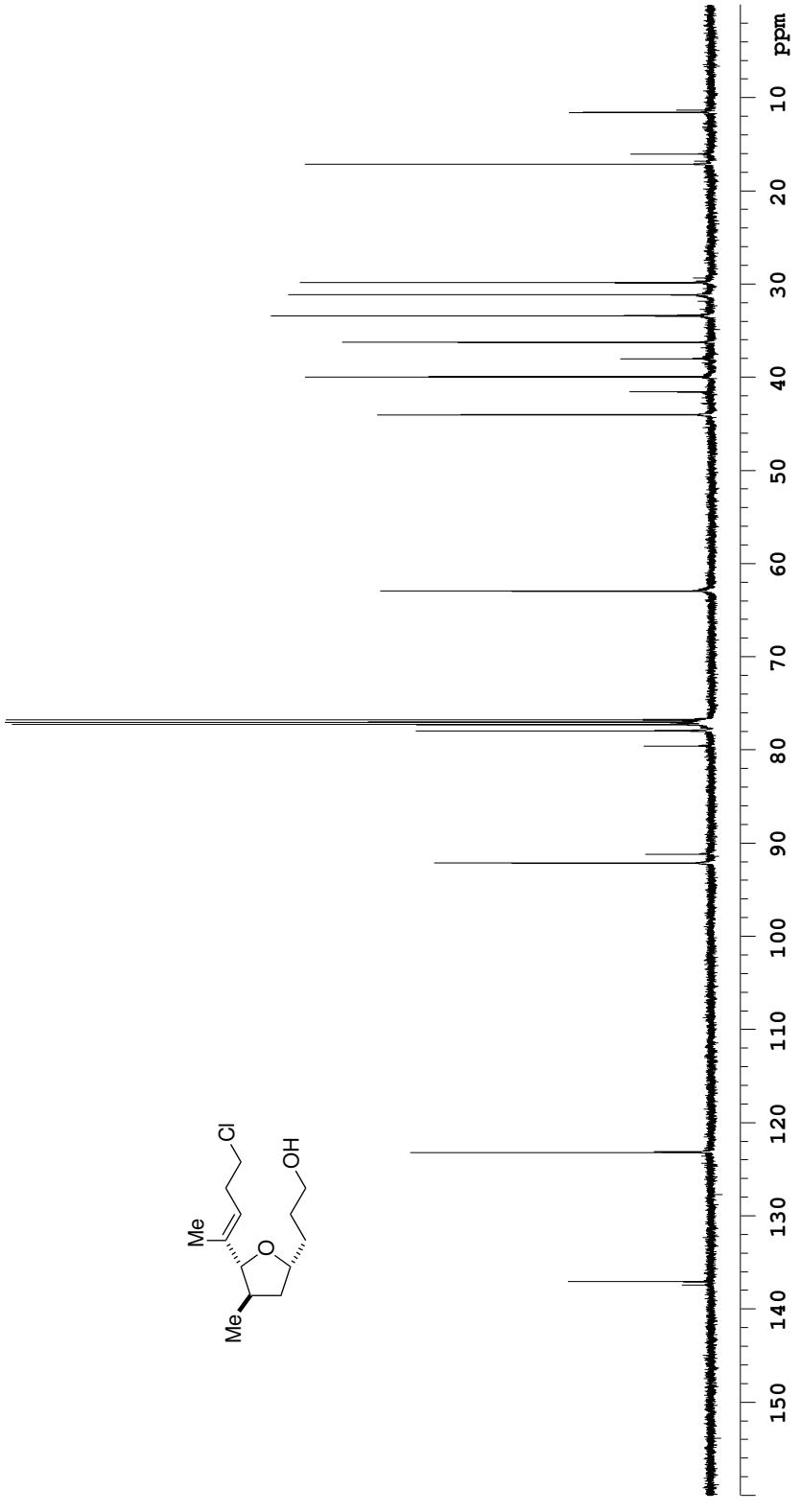
^{1}H NMR spectrum of alkyl chloride **114c**



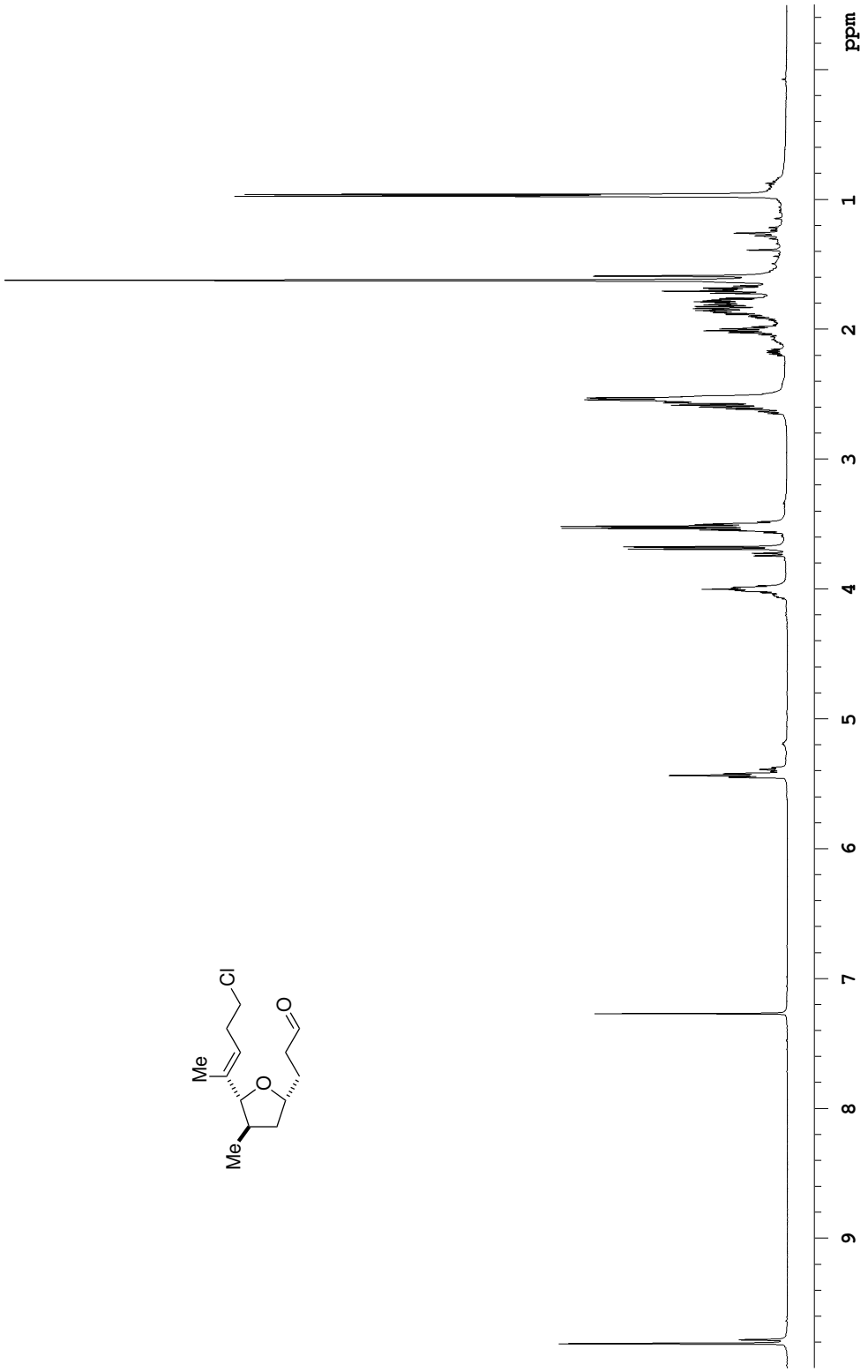
^{13}C NMR spectrum of alkyl chloride **114c**



^{1}H NMR spectrum of alcohol **115**

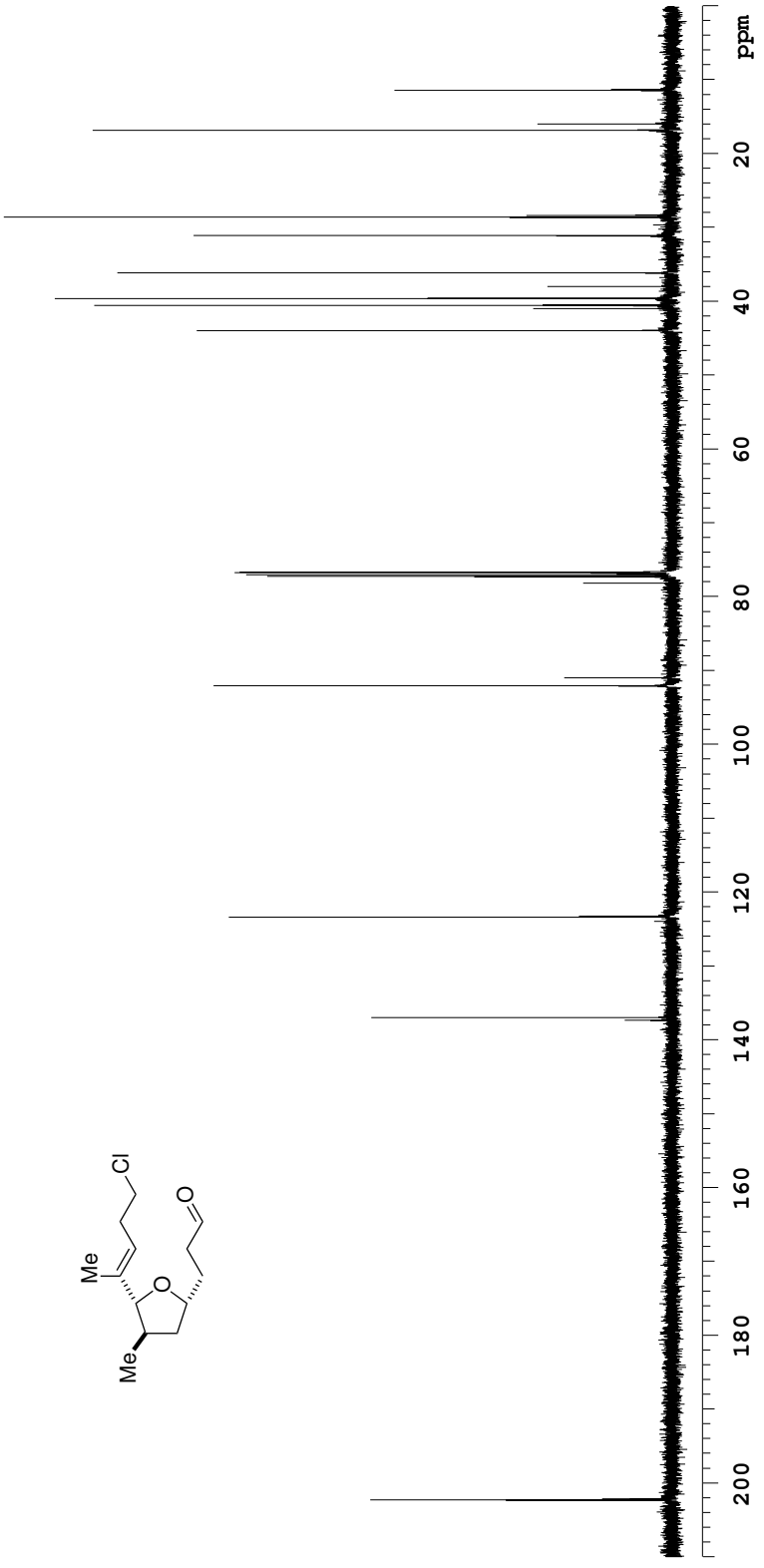


^{13}C NMR spectrum of alcohol **115**

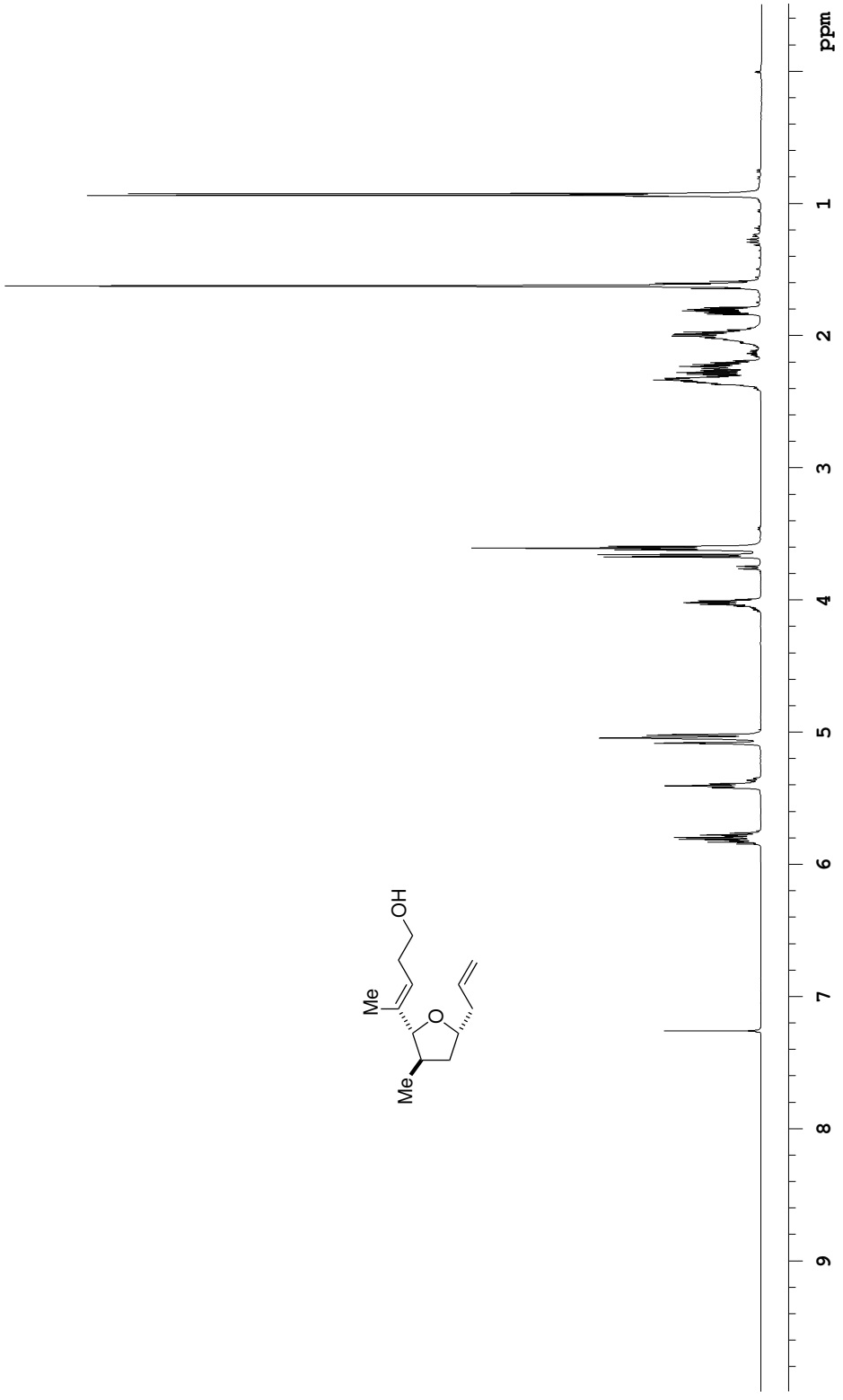


^{1}H

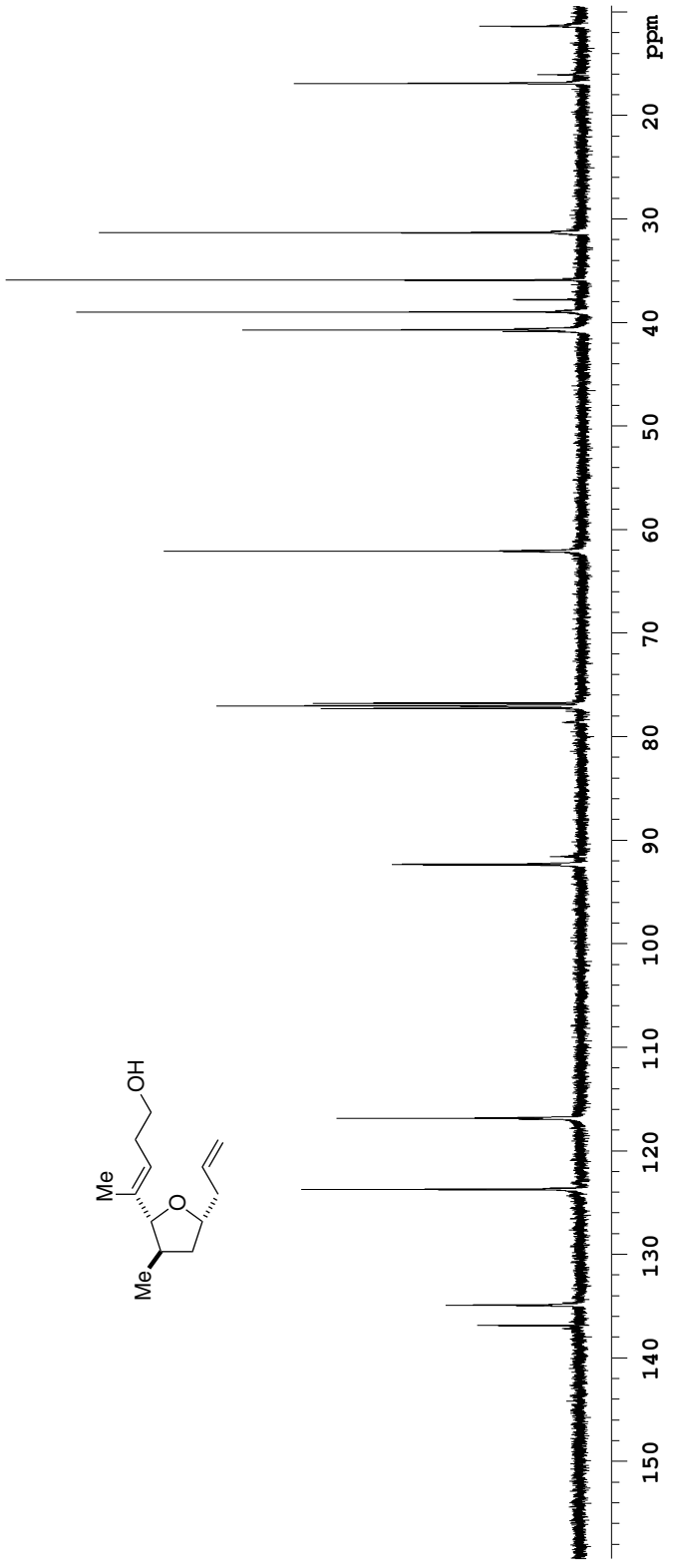
NMR spectrum of aldehyde **116**



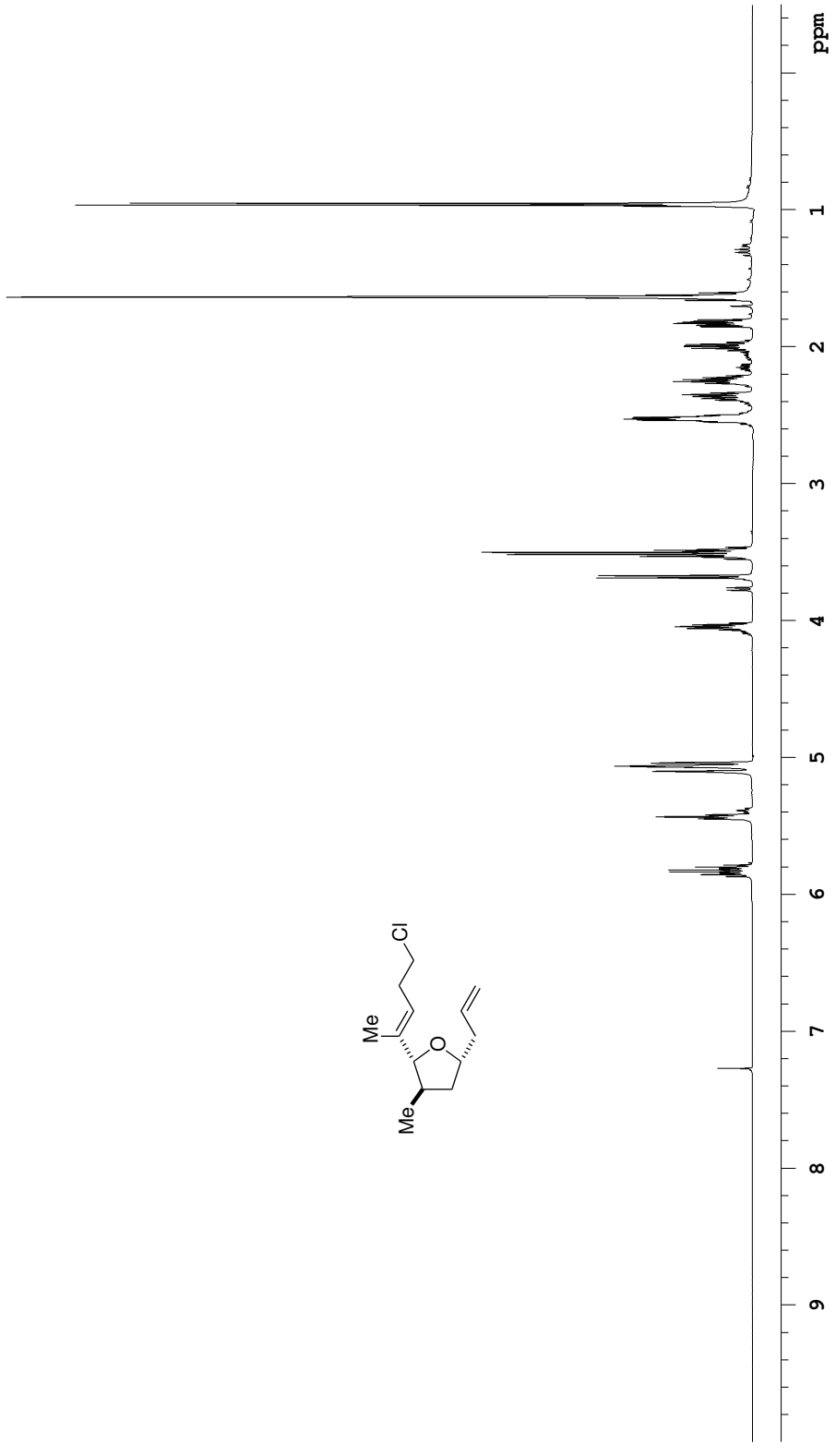
^{13}C NMR spectrum of aldehyde **116**



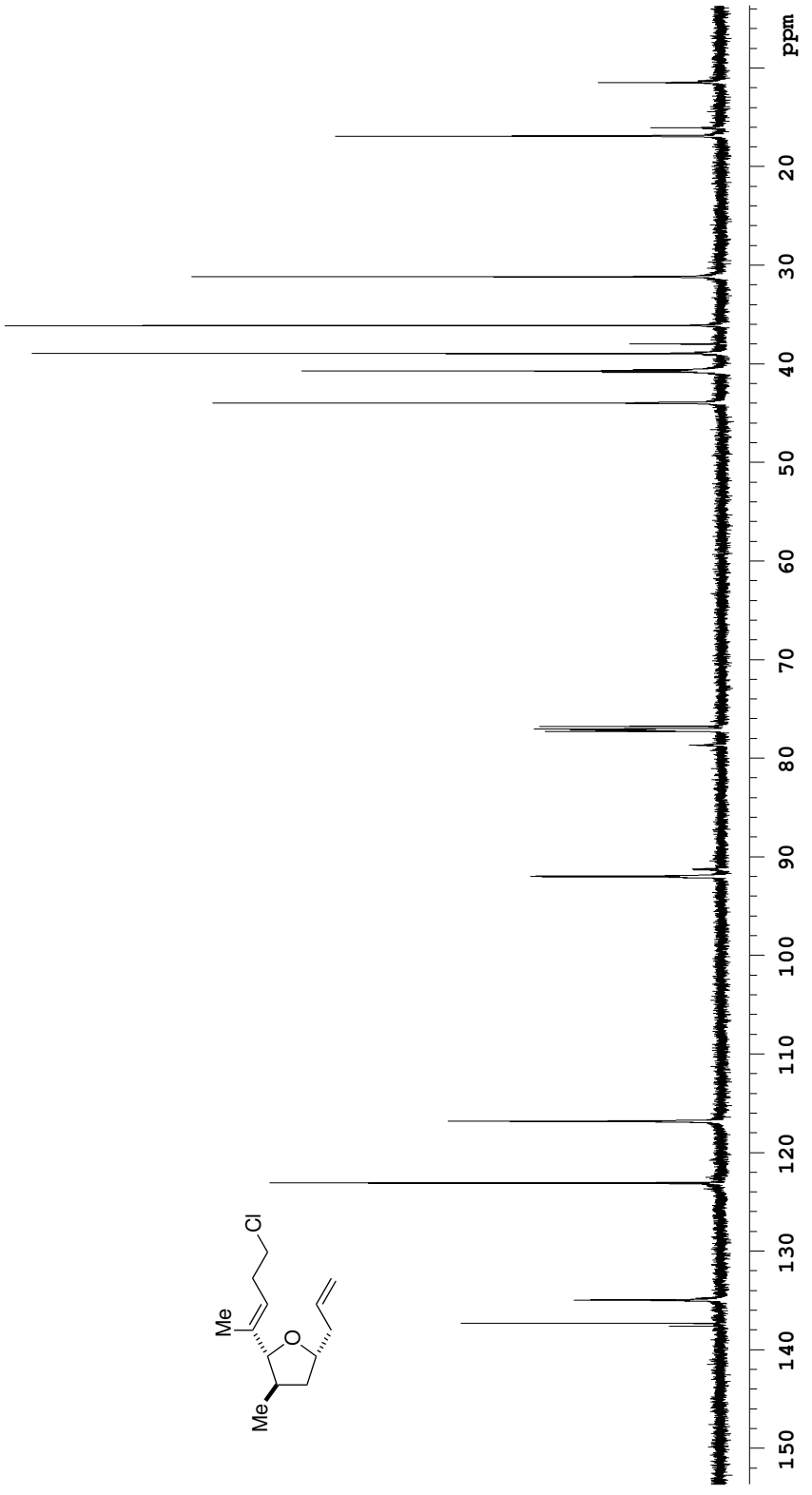
^{1}H NMR spectrum of alcohol **111b**



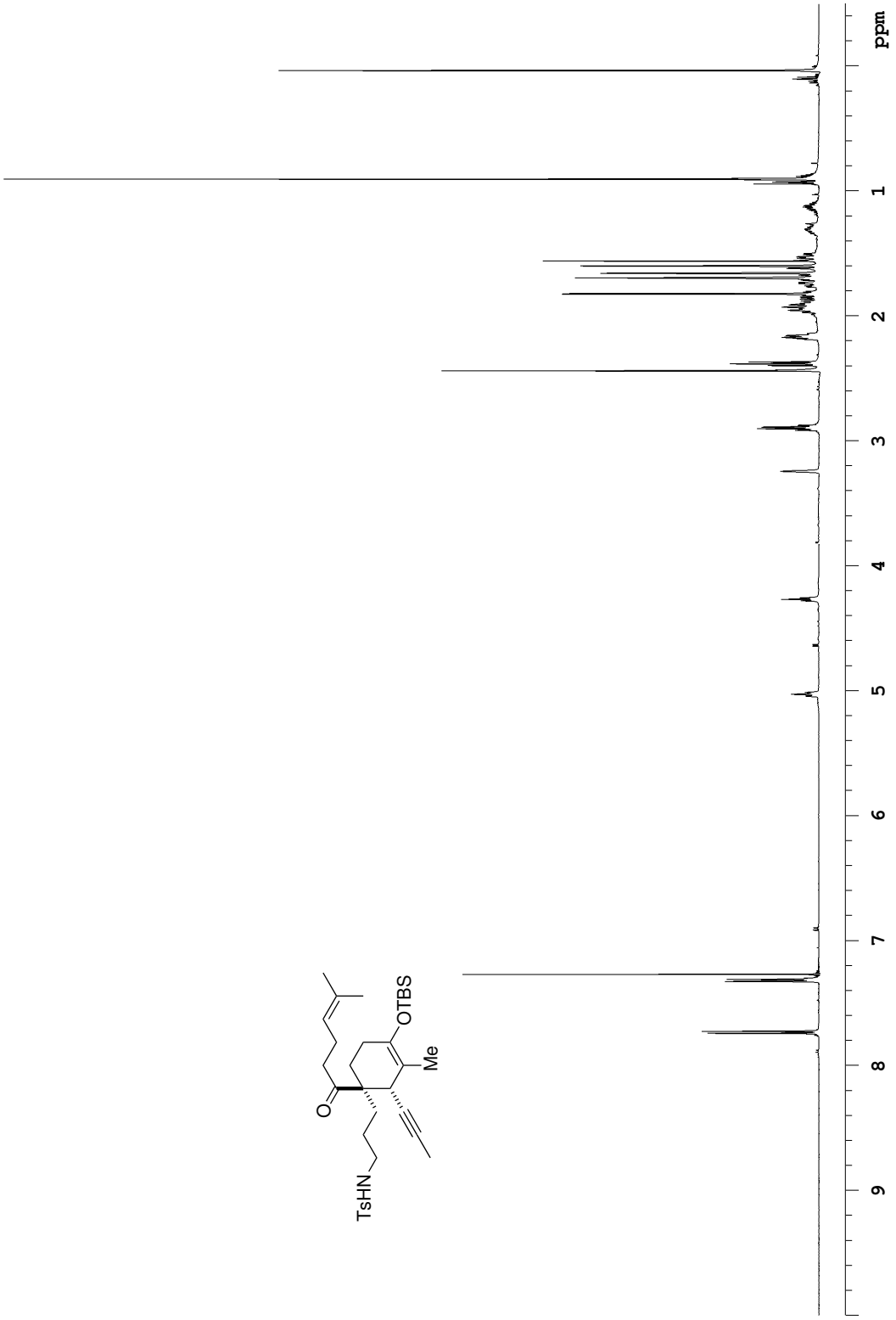
^{13}C NMR spectrum of alcohol **111b**



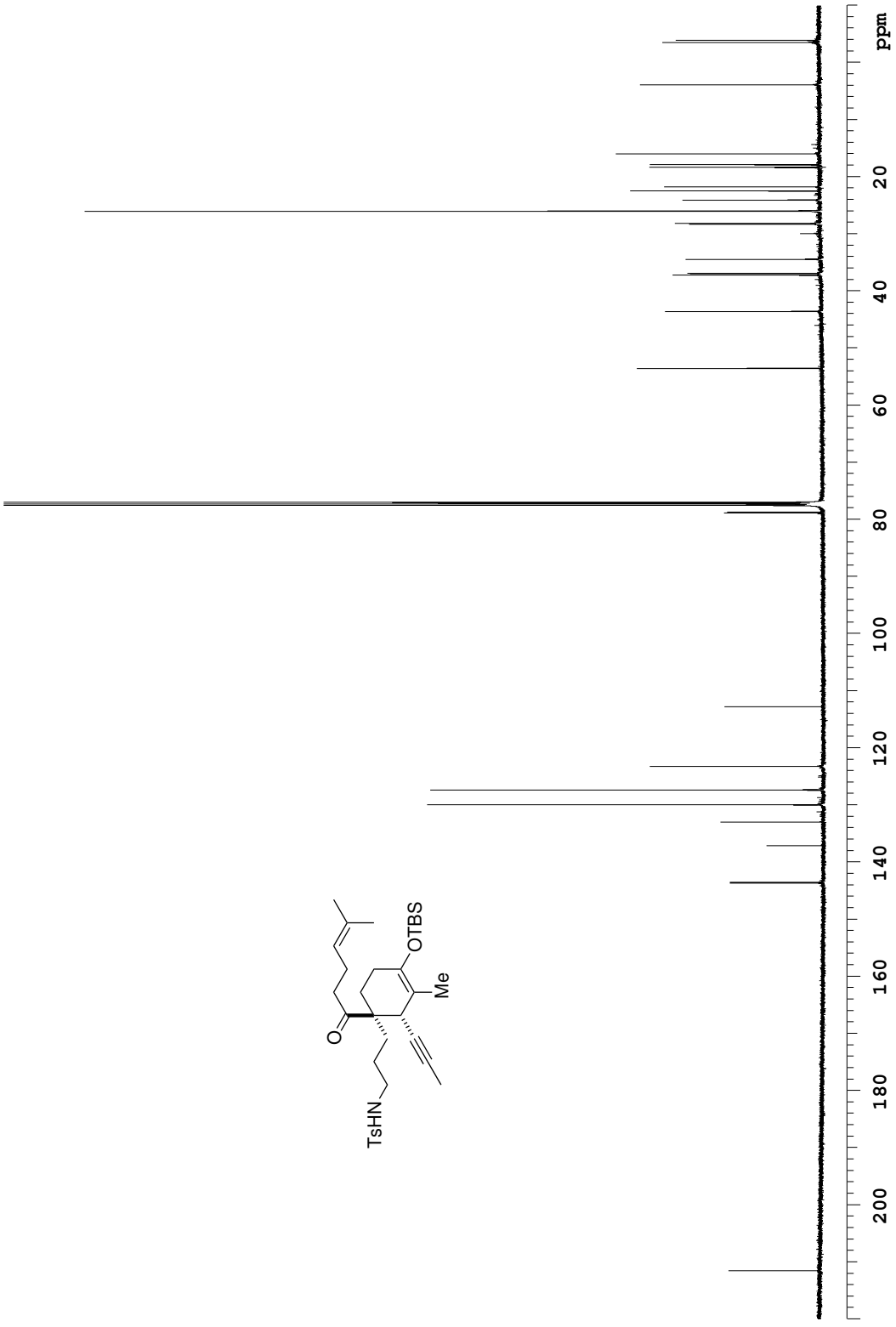
^{1}H NMR spectrum of chloride **111c**



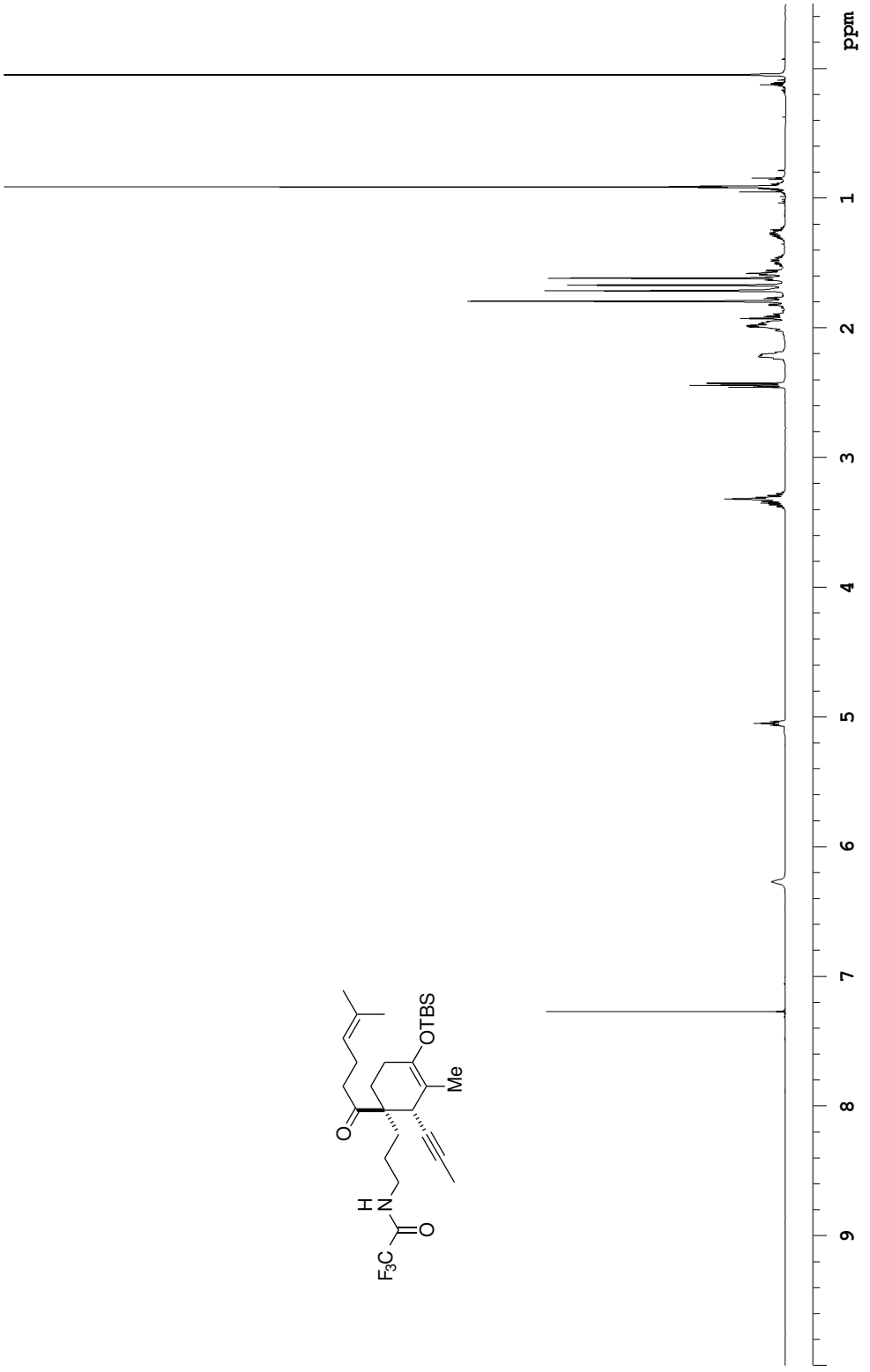
^{13}C NMR spectrum of chloride **111c**



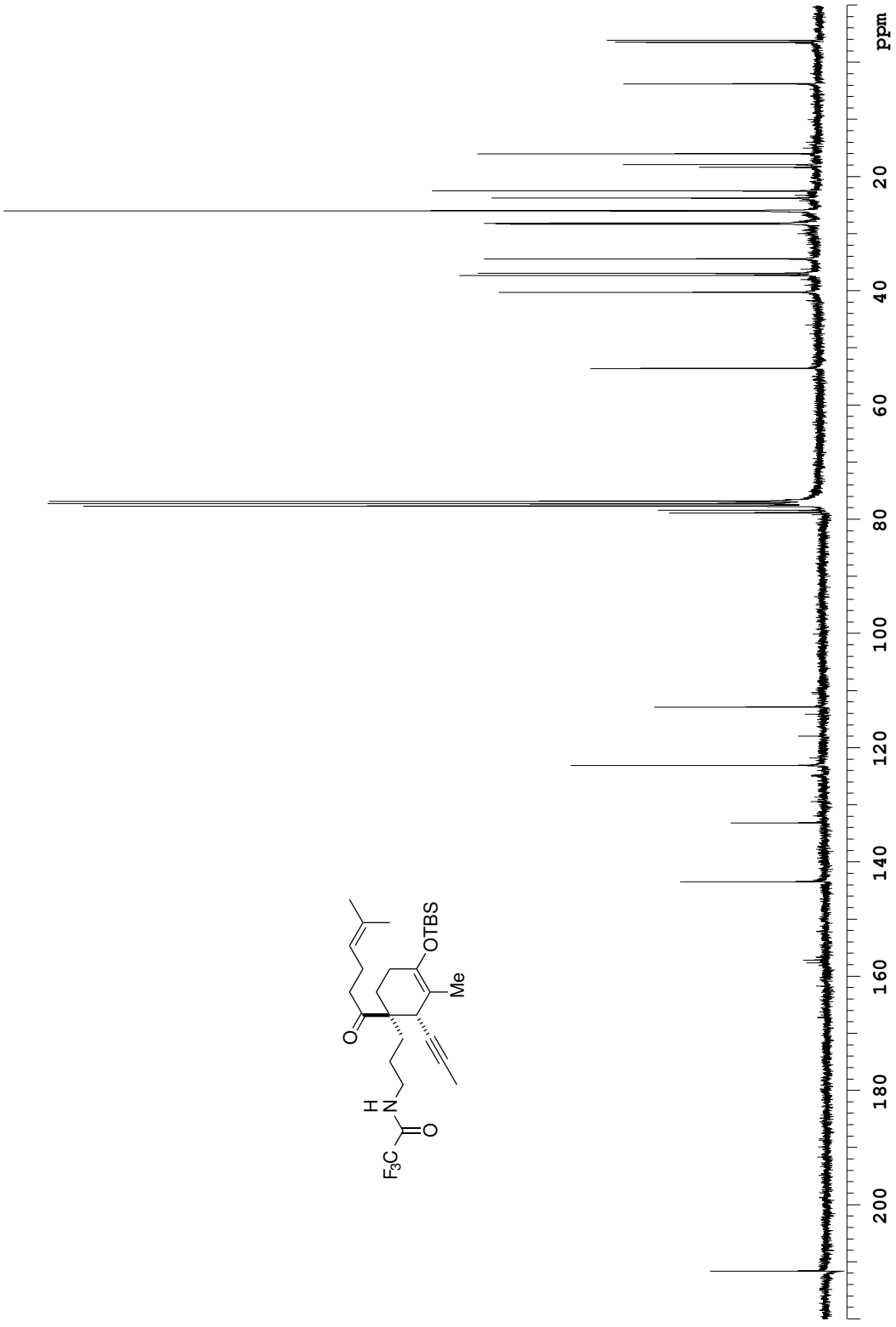
^{1}H NMR spectrum of amino ketone **123a**



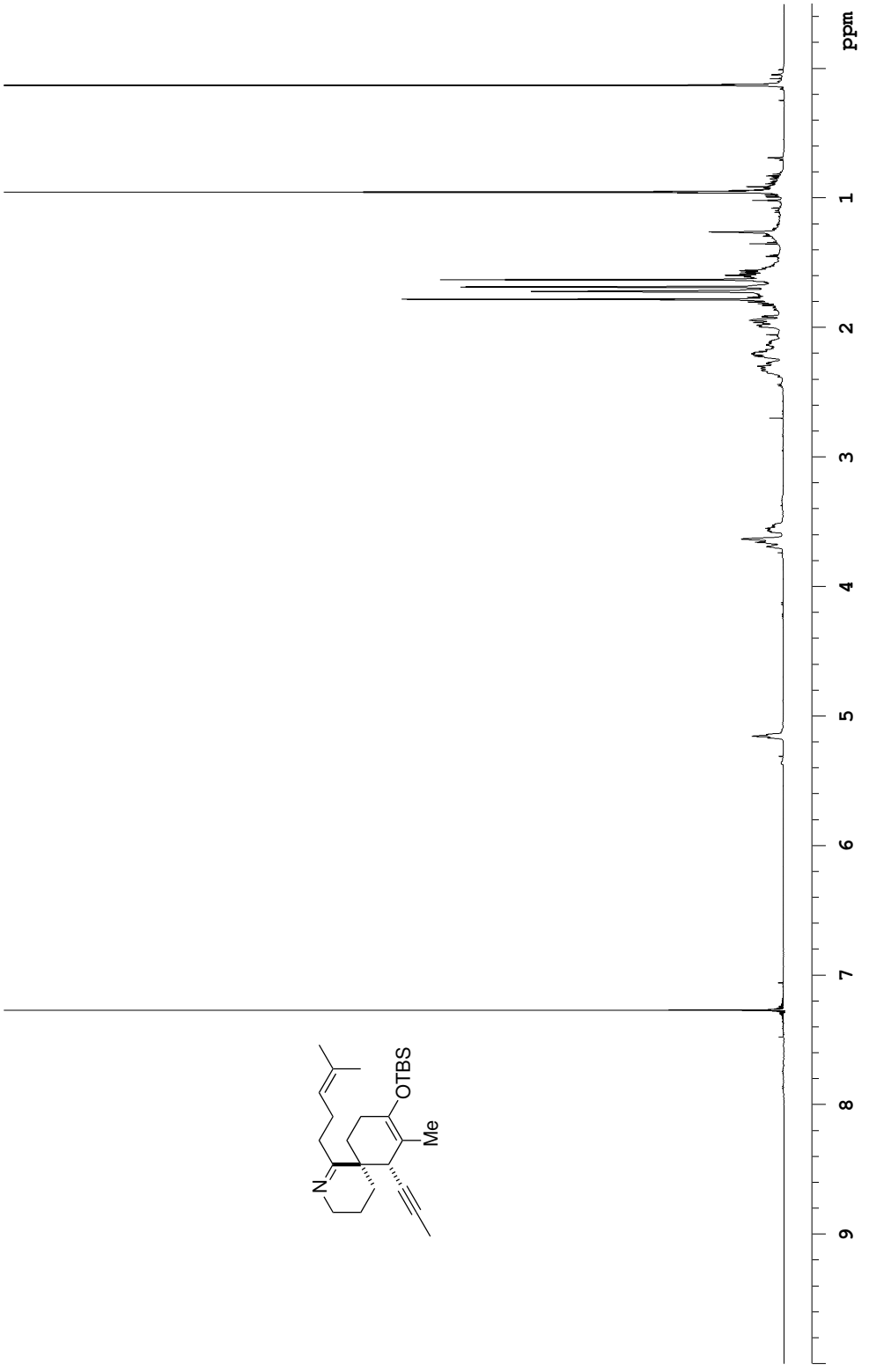
^{13}C NMR spectrum of amino ketone **123a**



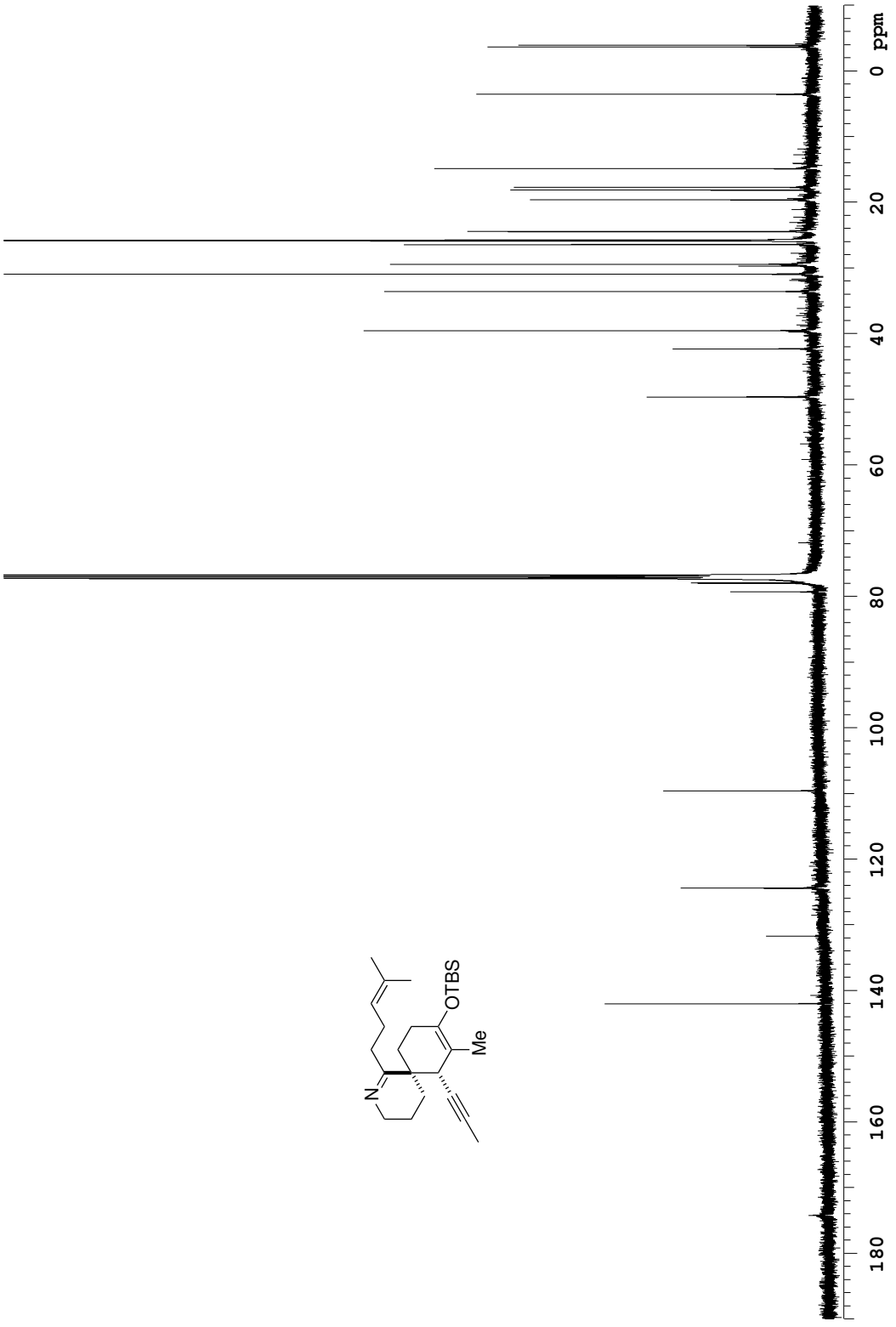
^{1}H NMR spectrum of amino ketone **123b**



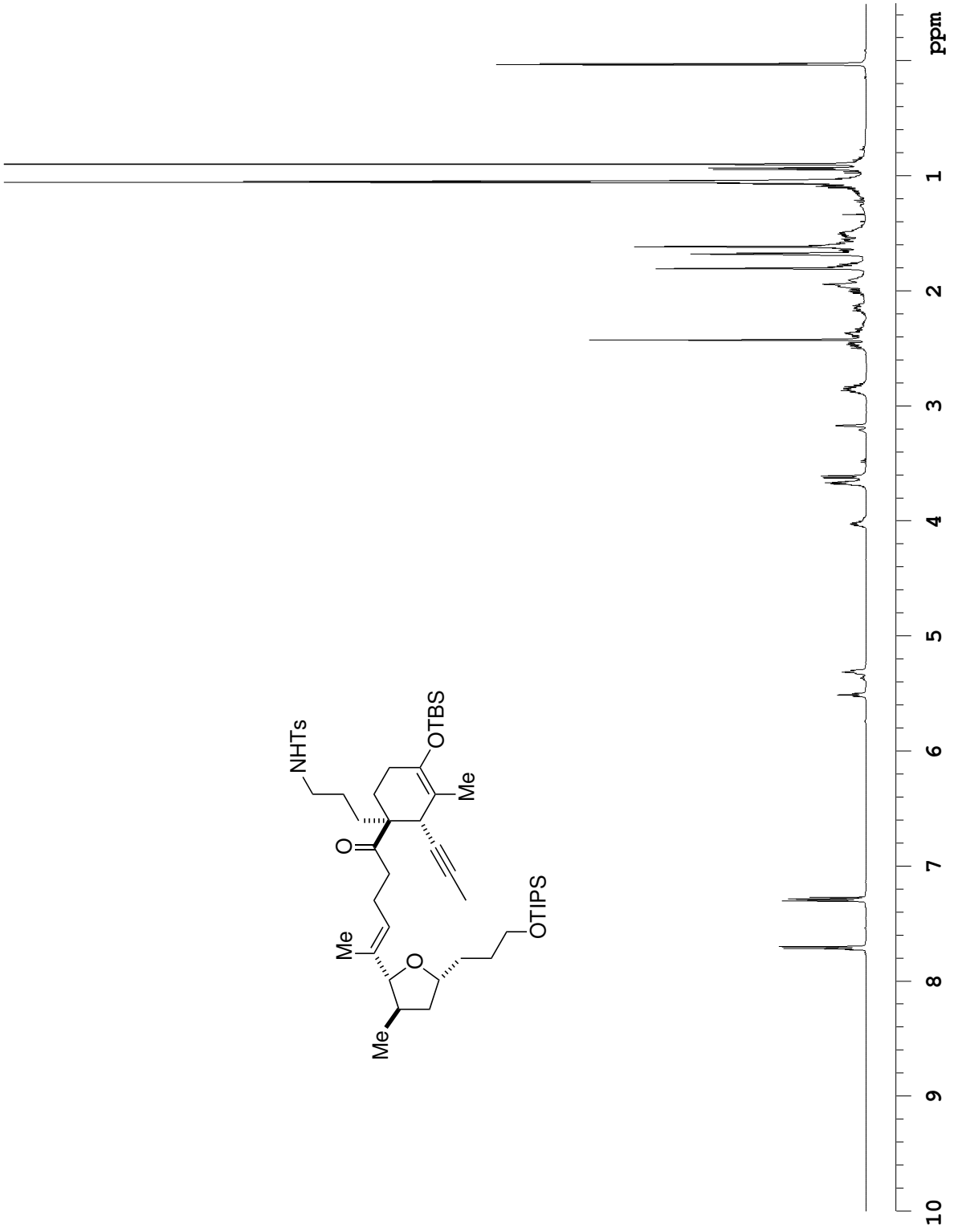
^{13}C NMR spectrum of amino ketone **123b**



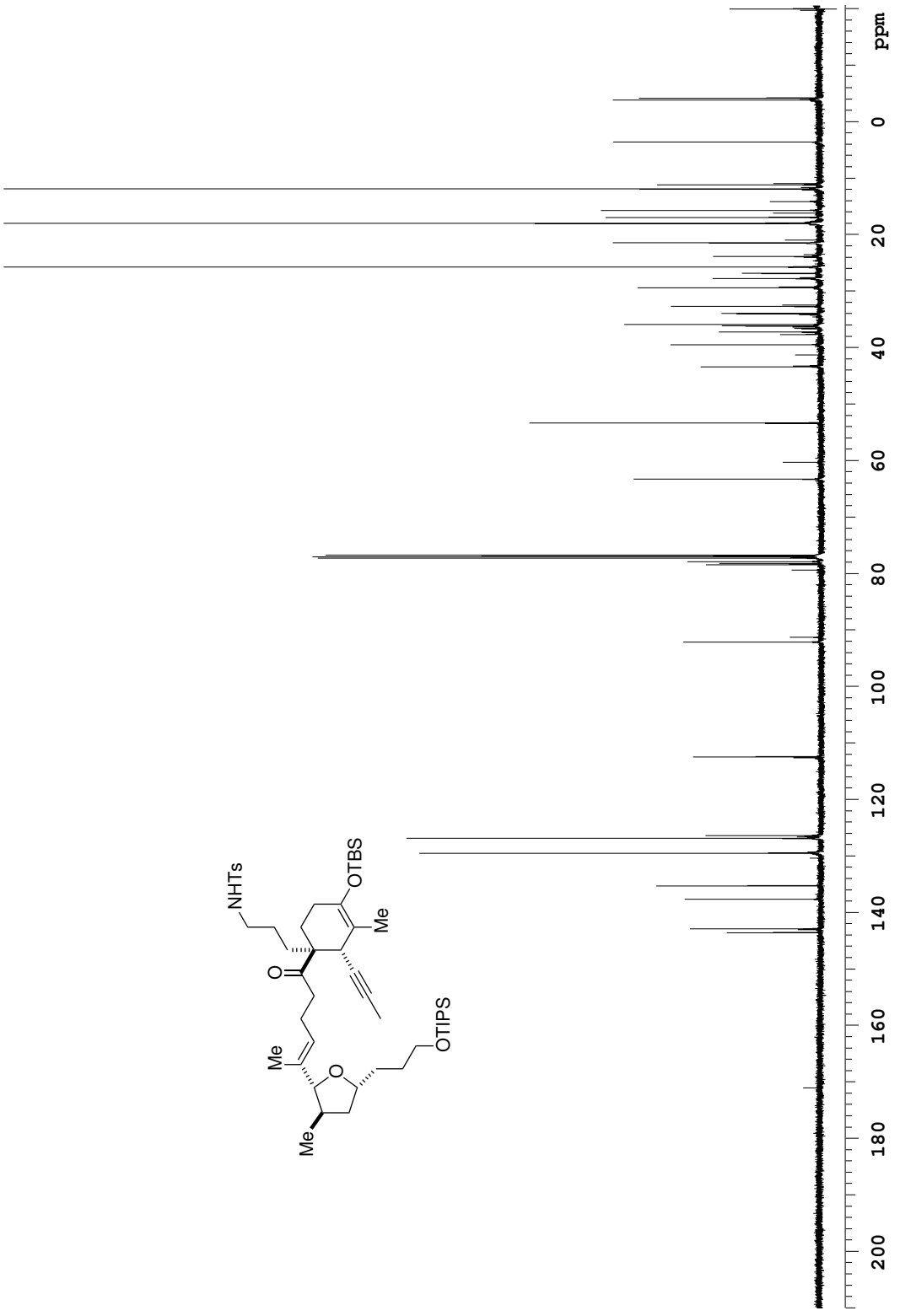
^{1}H NMR spectrum of spirocyclic imine **124**



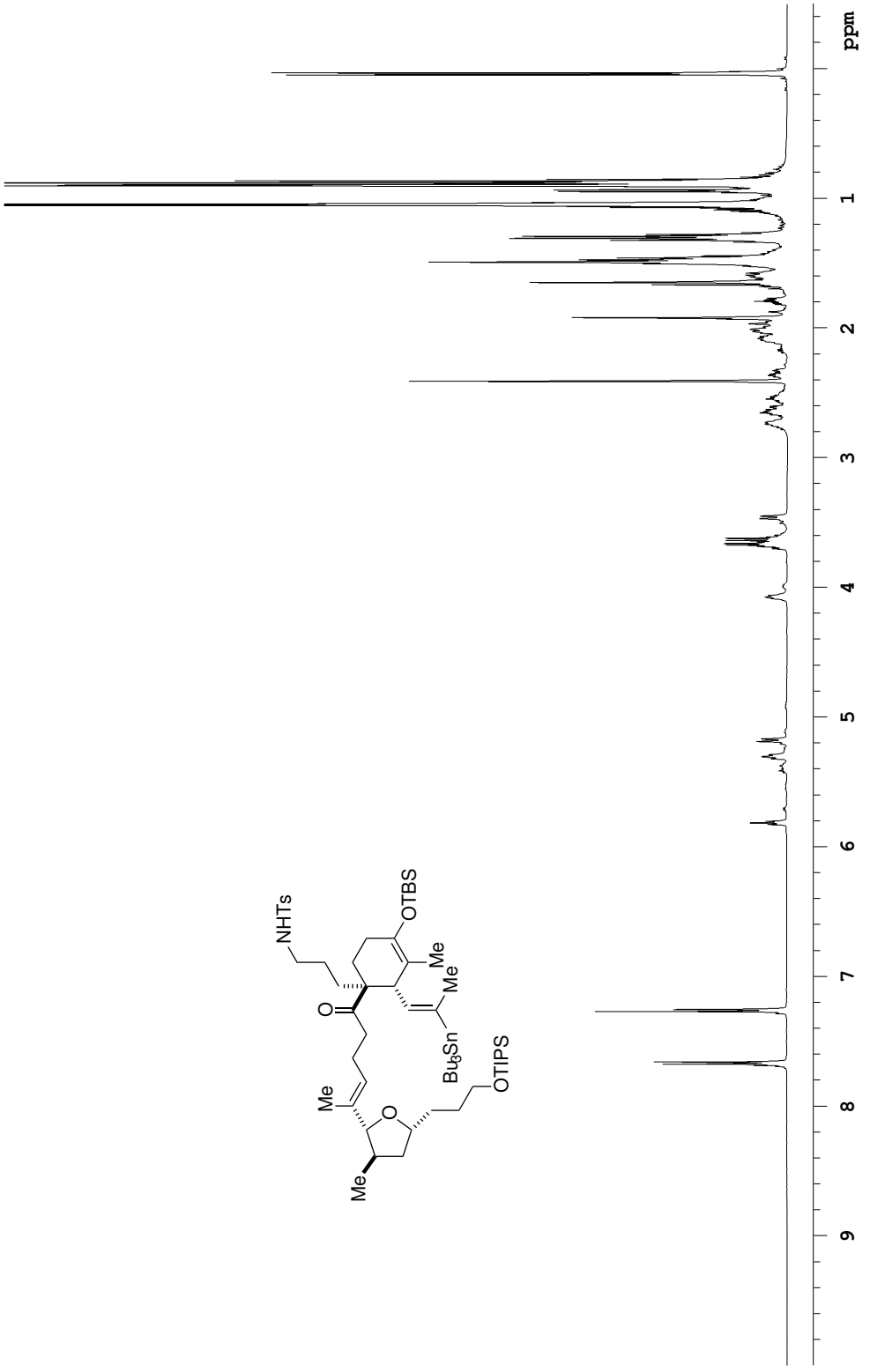
^{13}C NMR spectrum of spirocyclic imine **124**



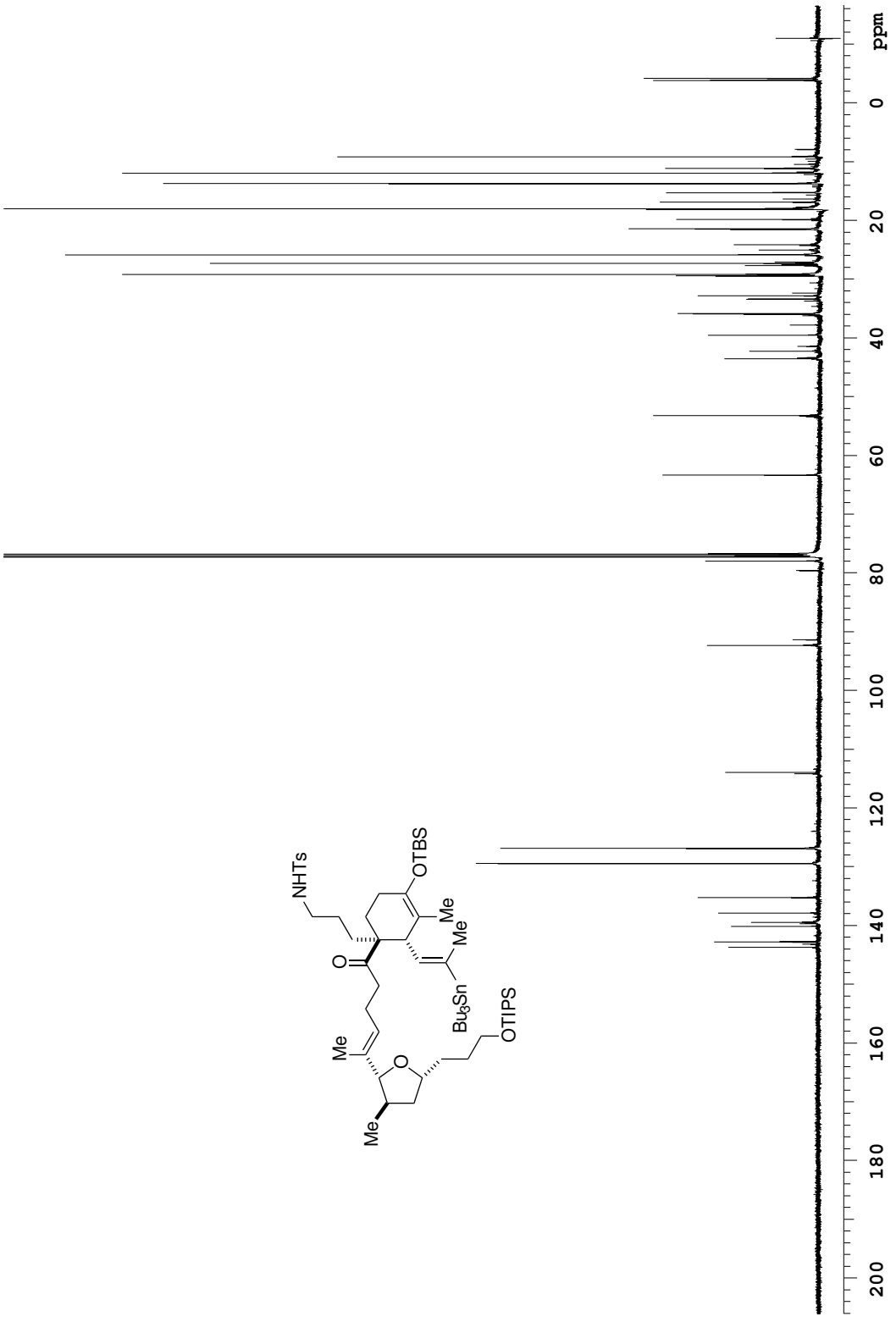
^{1}H NMR spectrum of amino ketone **125a**



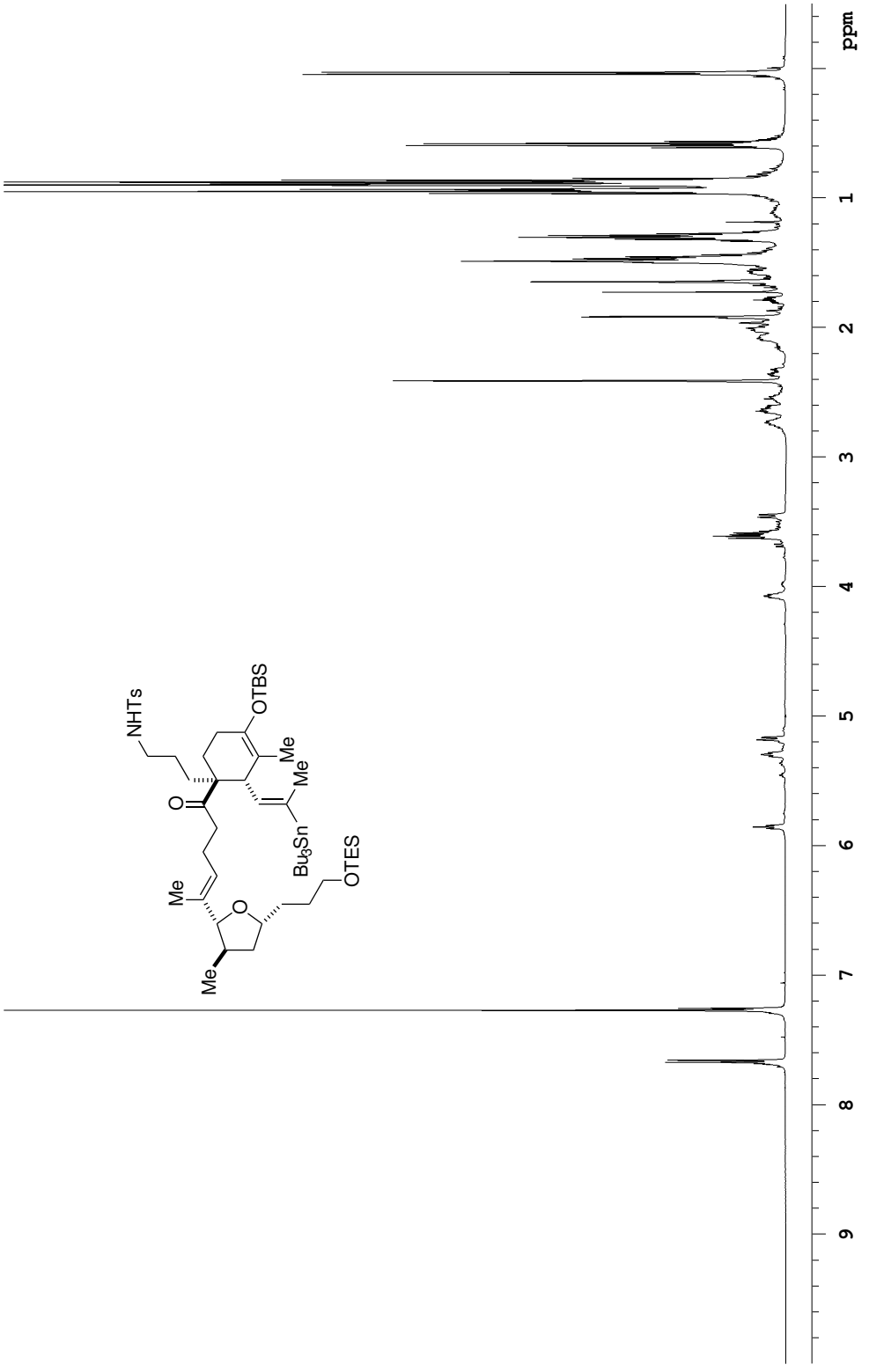
^{13}C NMR spectrum of amino ketone **125a**



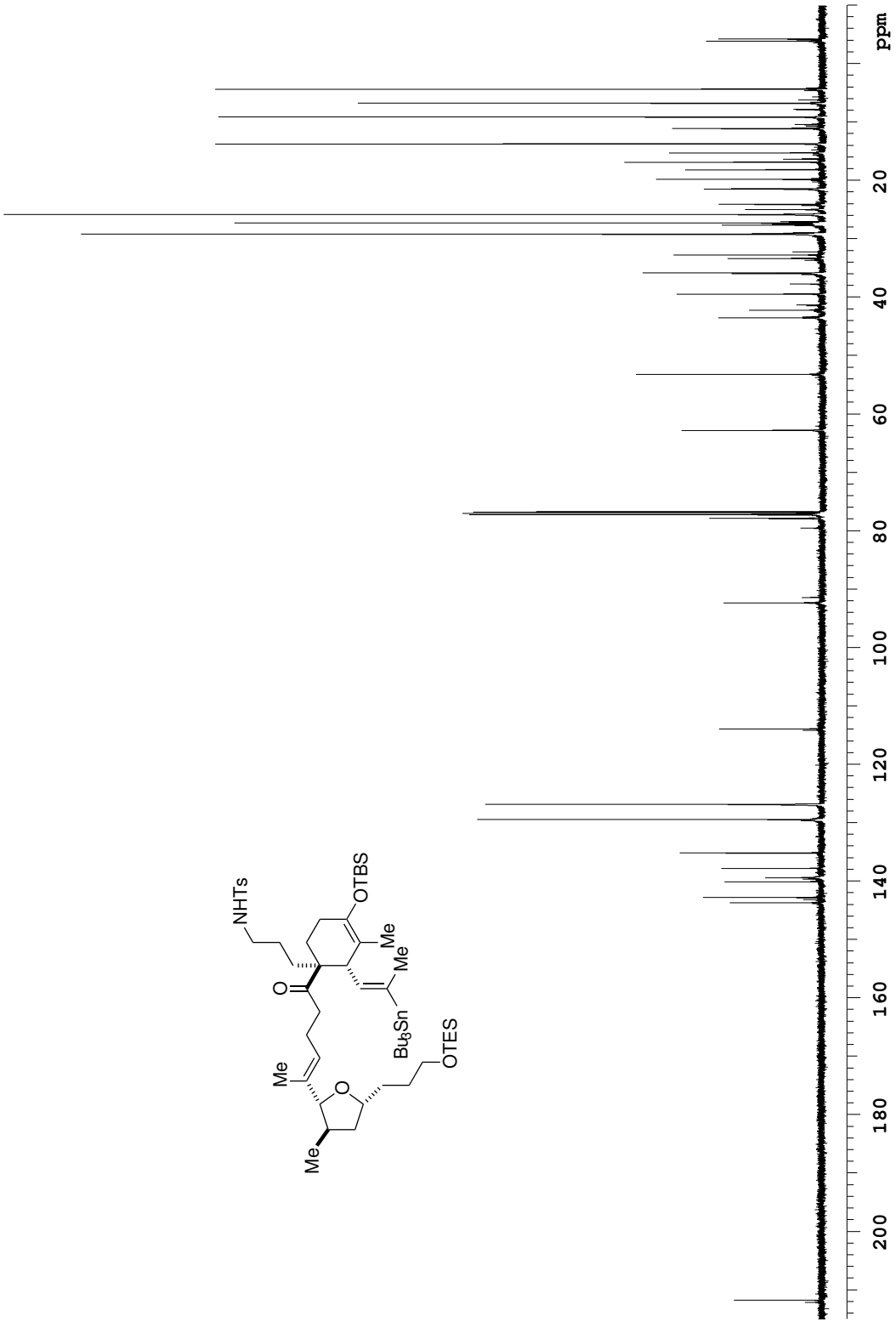
^{1}H NMR spectrum of vinyl stannane **126a**



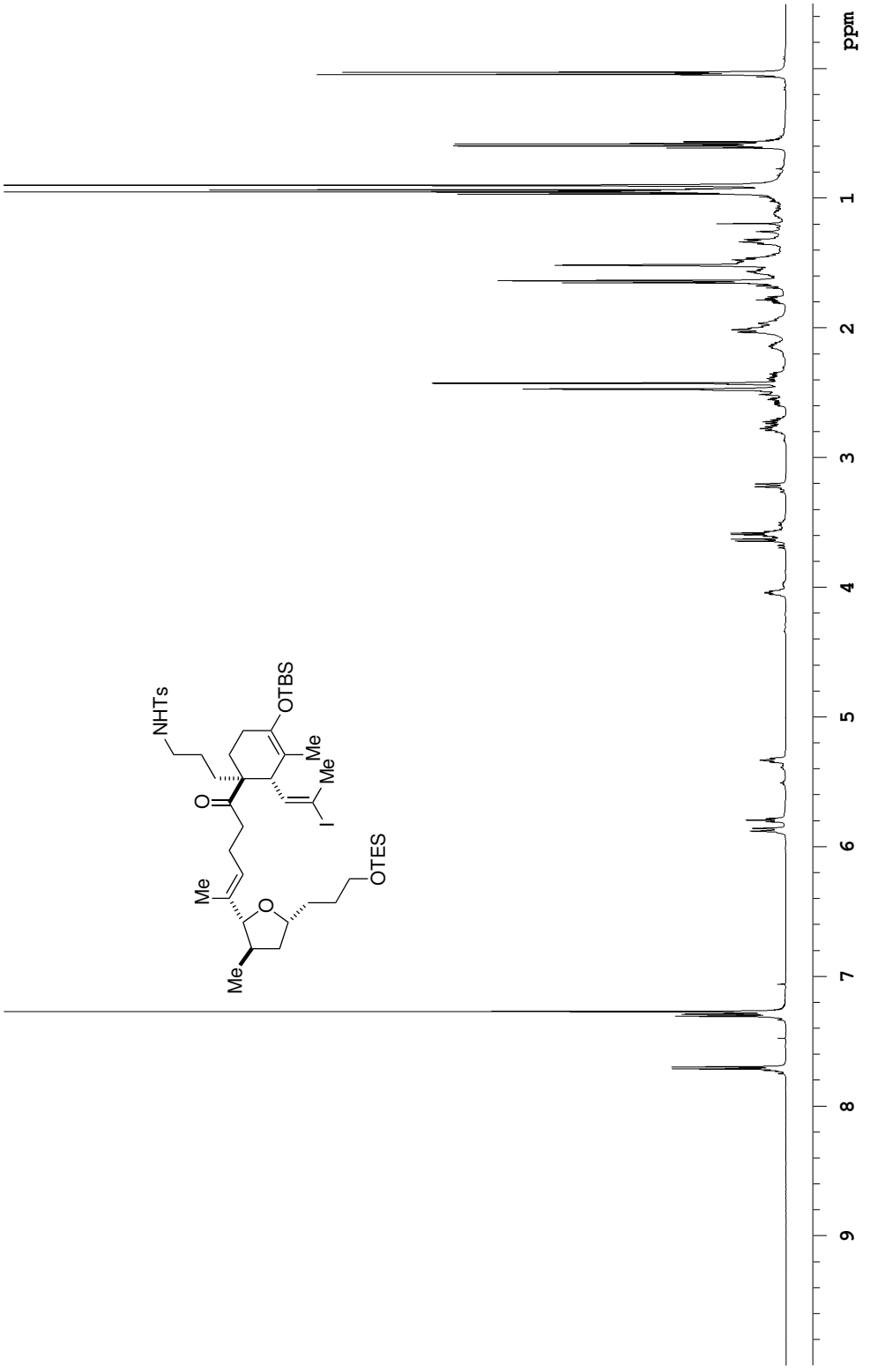
^{13}C NMR spectrum of vinyl stannane **126a**



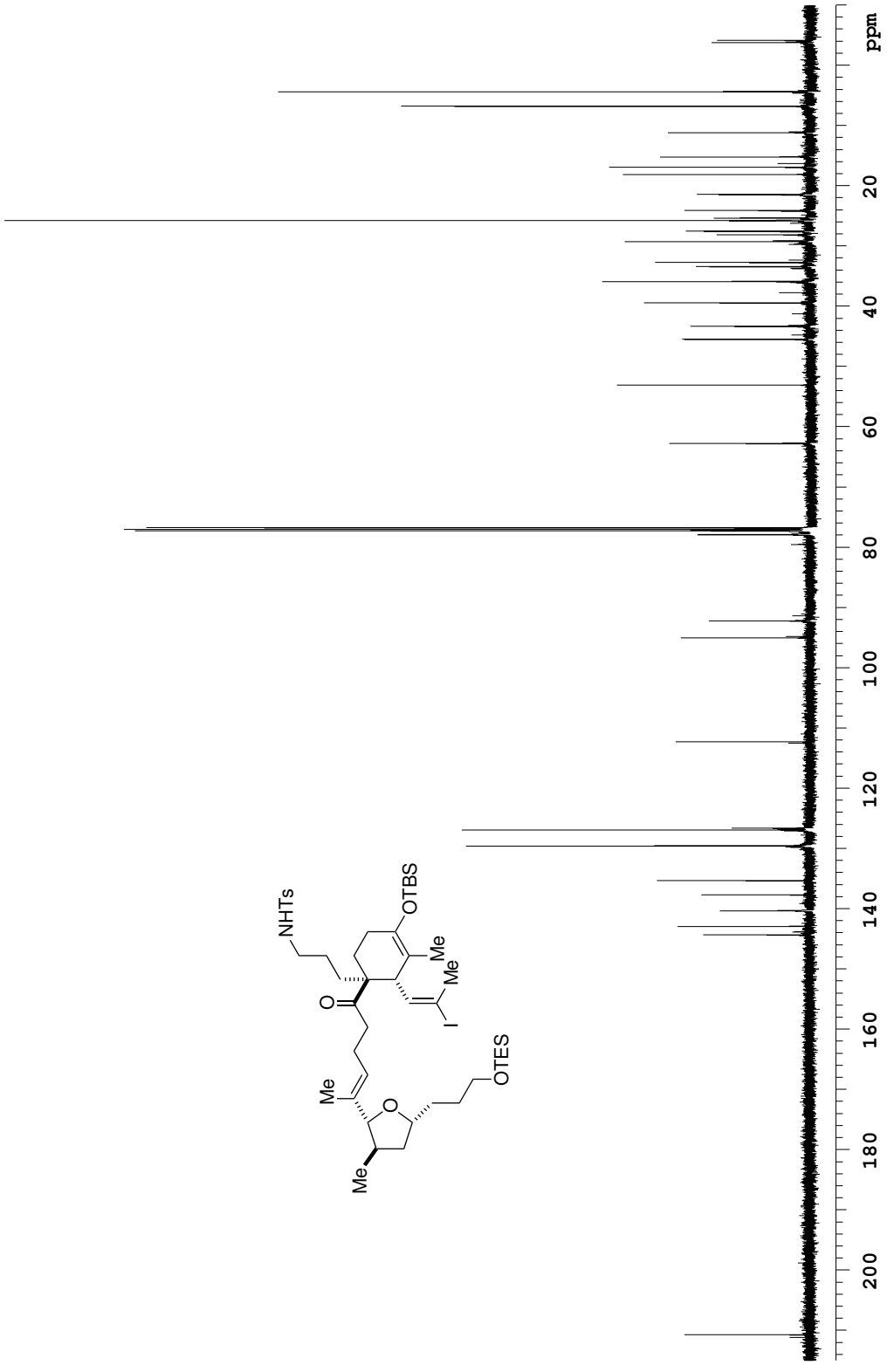
^{1}H NMR spectrum of vinyl stannanne **126b**



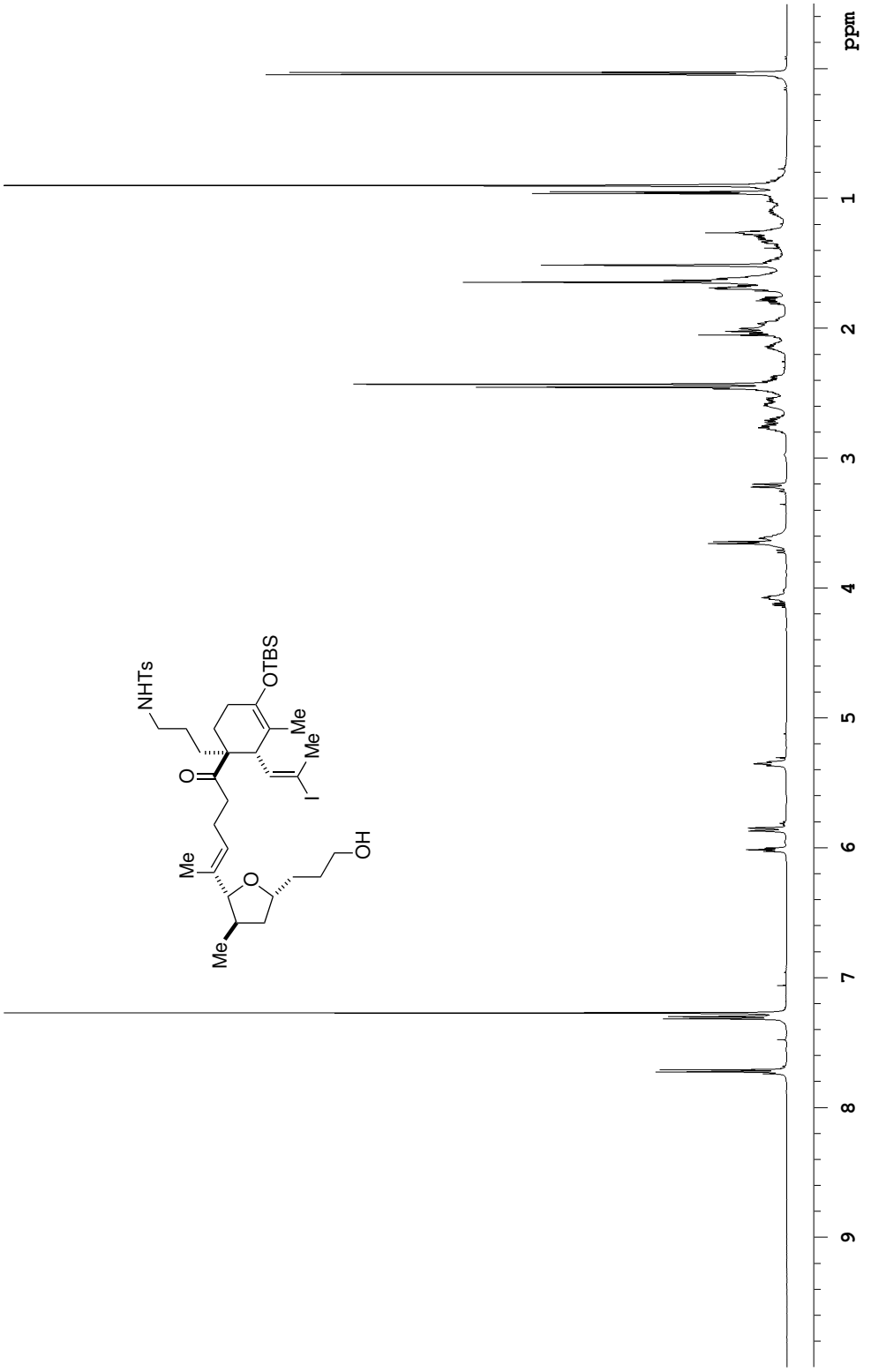
^{13}C NMR spectrum of vinyl stannane **126b**



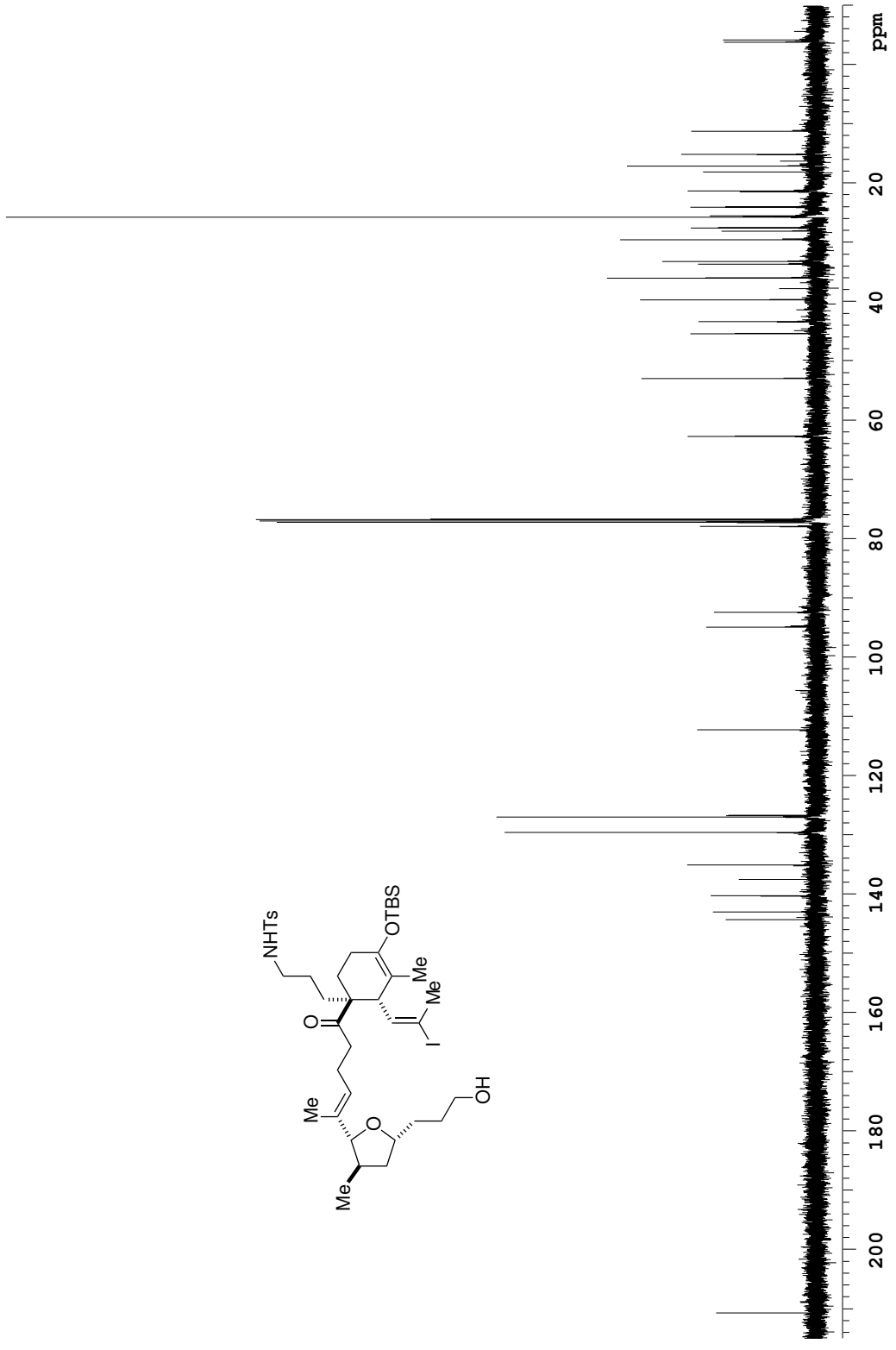
^{1}H NMR spectrum of vinyl iodide **127b**



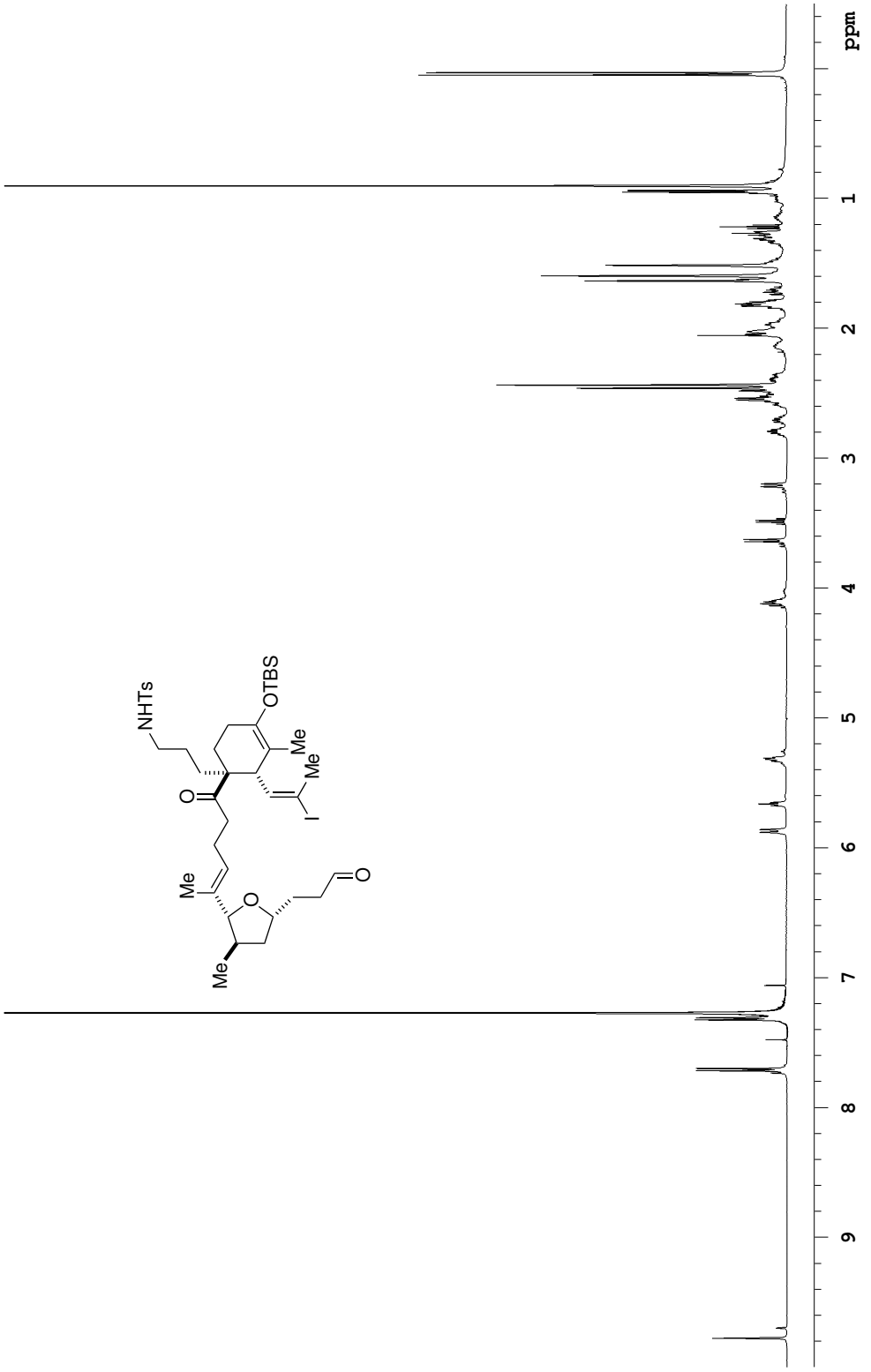
^{13}C NMR spectrum of vinyl iodide **127b**



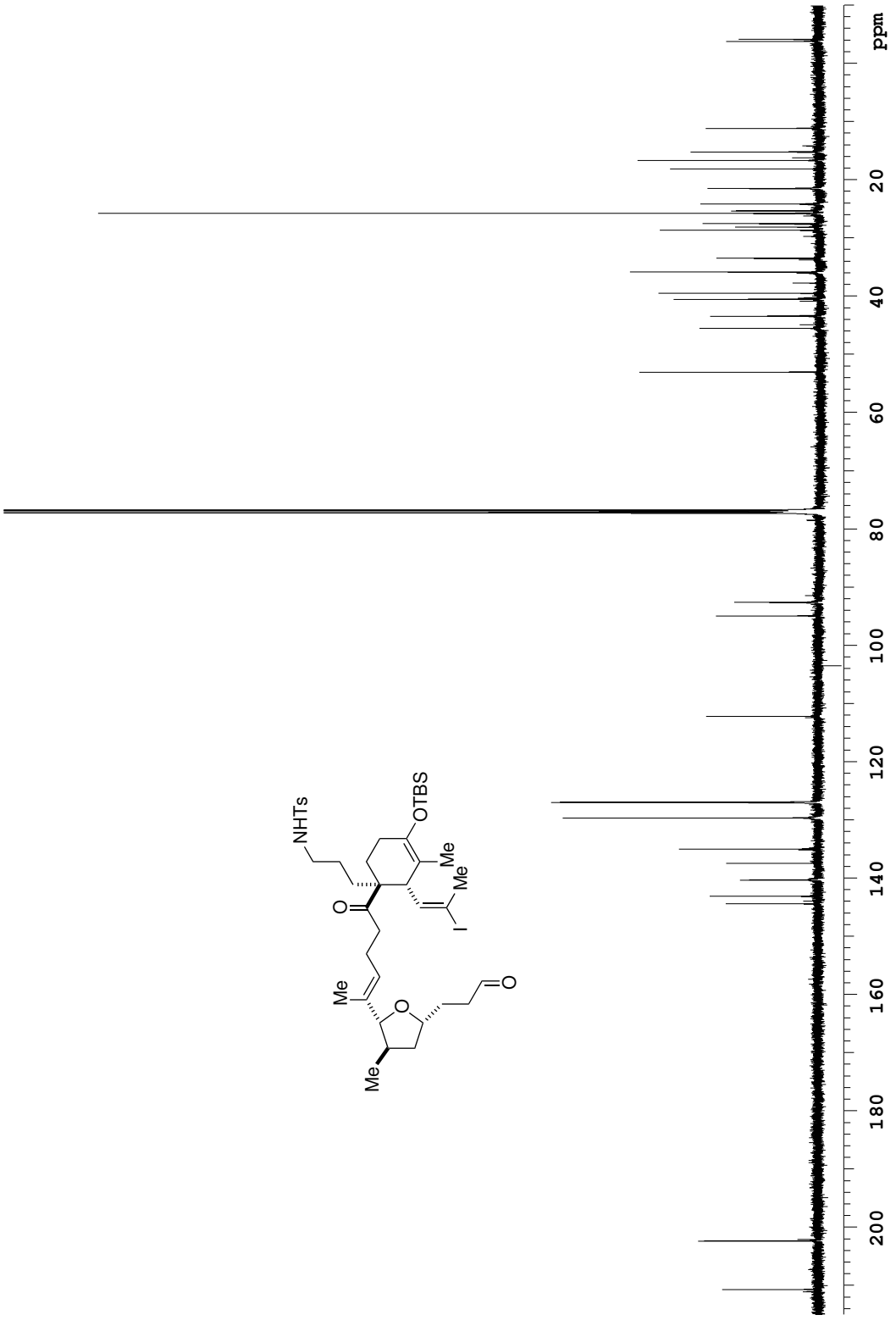
^{1}H NMR spectrum of alcohol **132**



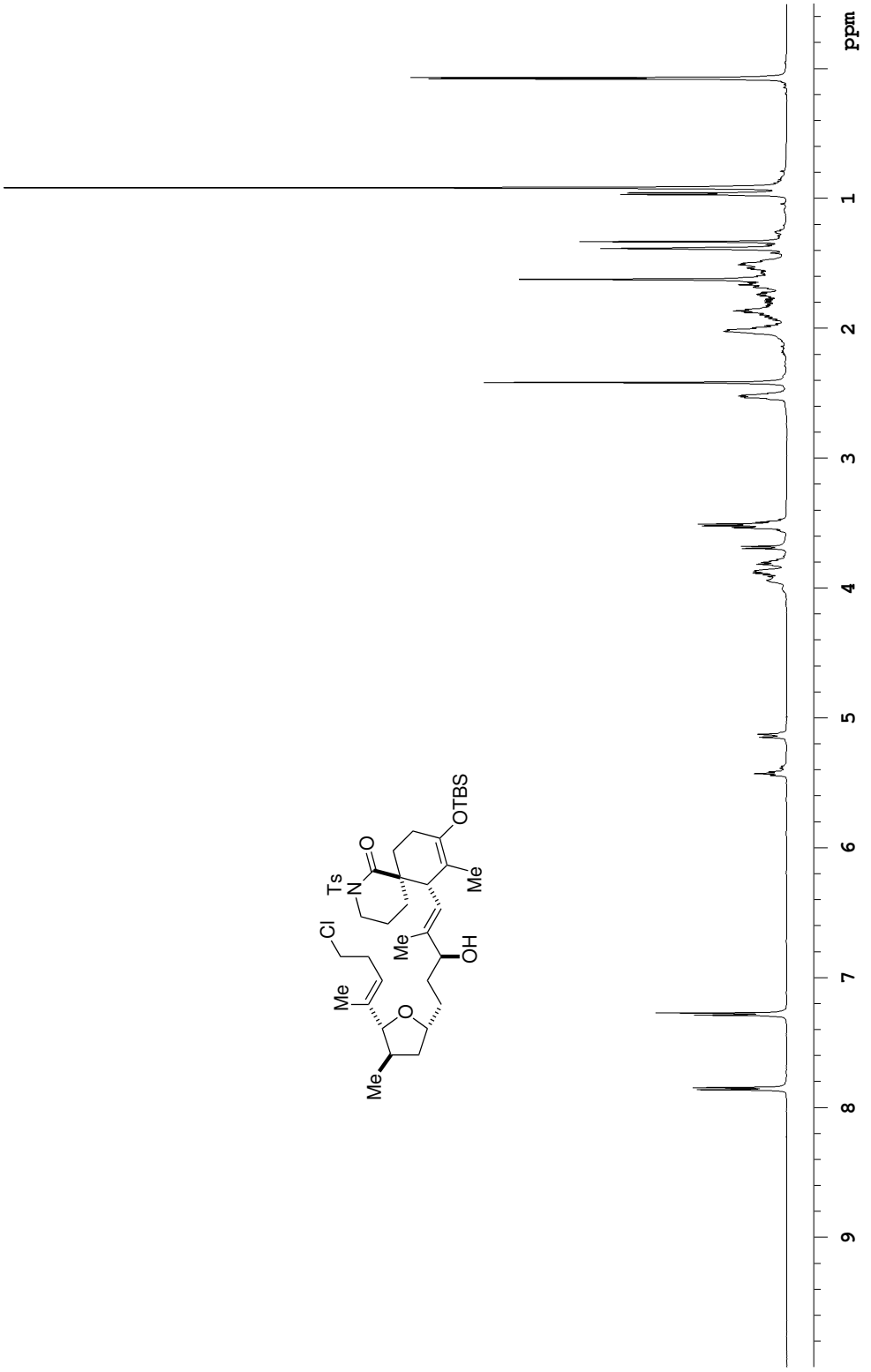
^{13}C NMR spectrum of alcohol **132**



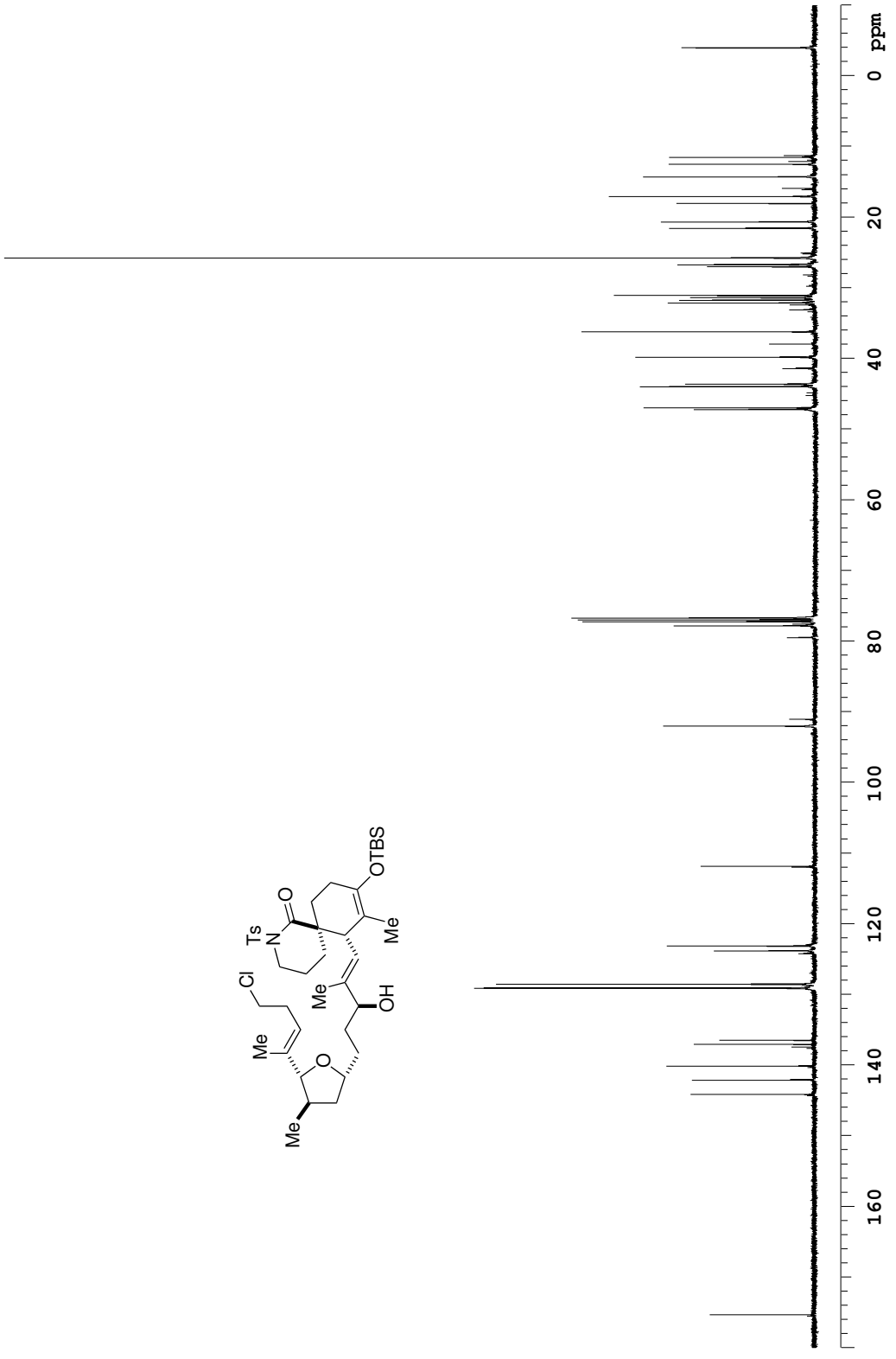
^{1}H NMR spectrum of aldehyde **133**



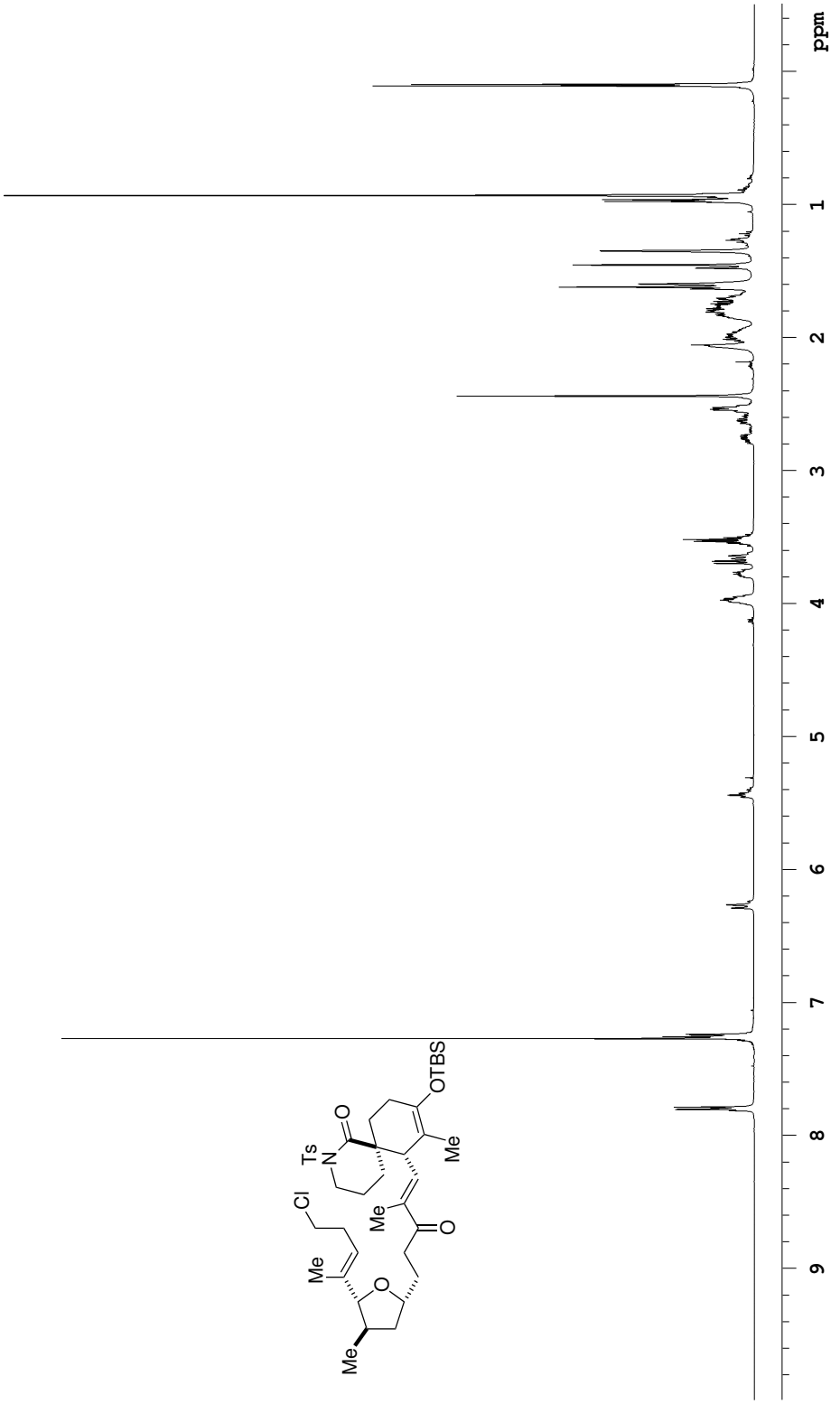
^{13}C NMR spectrum of aldehyde **133**



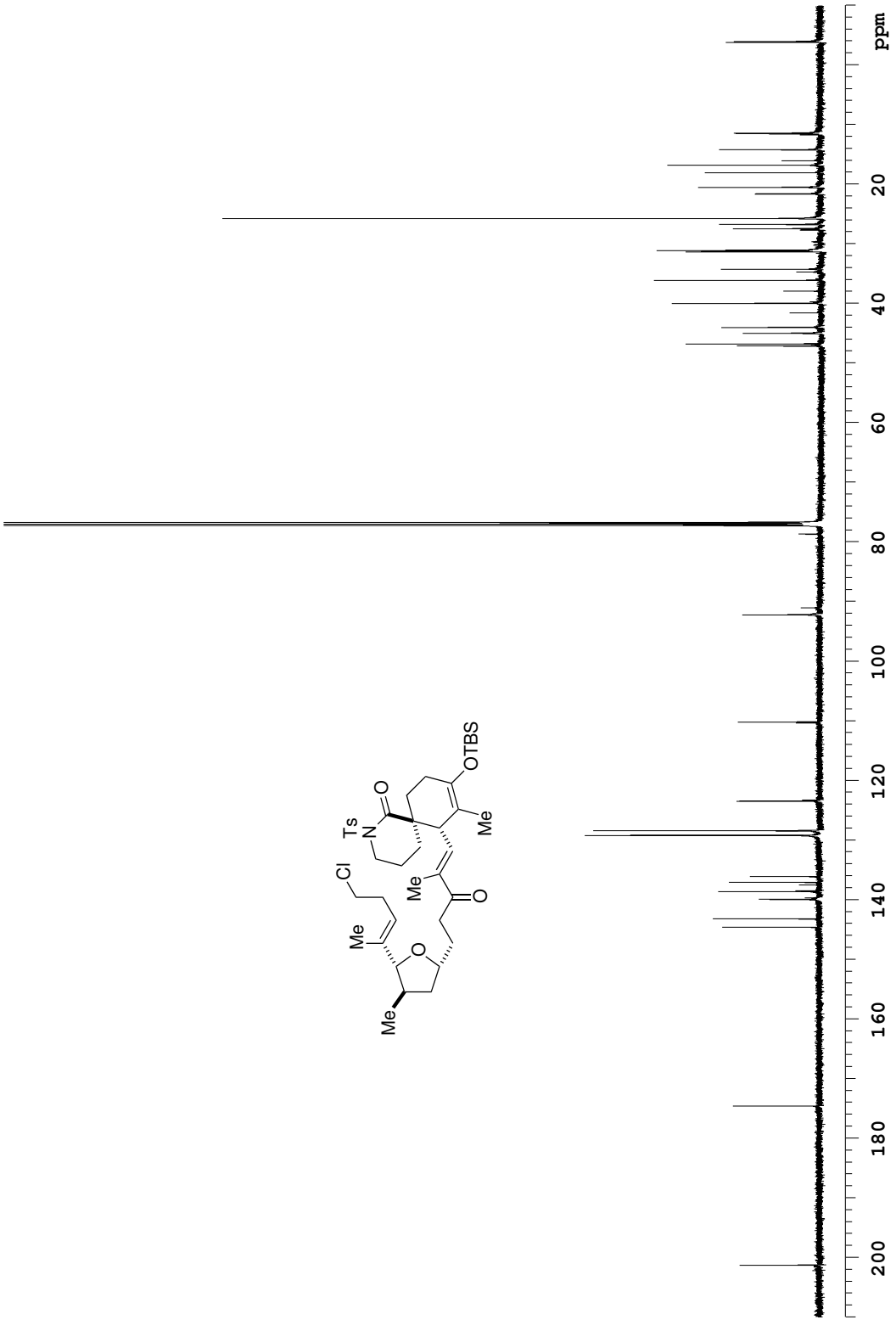
^{1}H NMR spectrum of alcohol **134b**



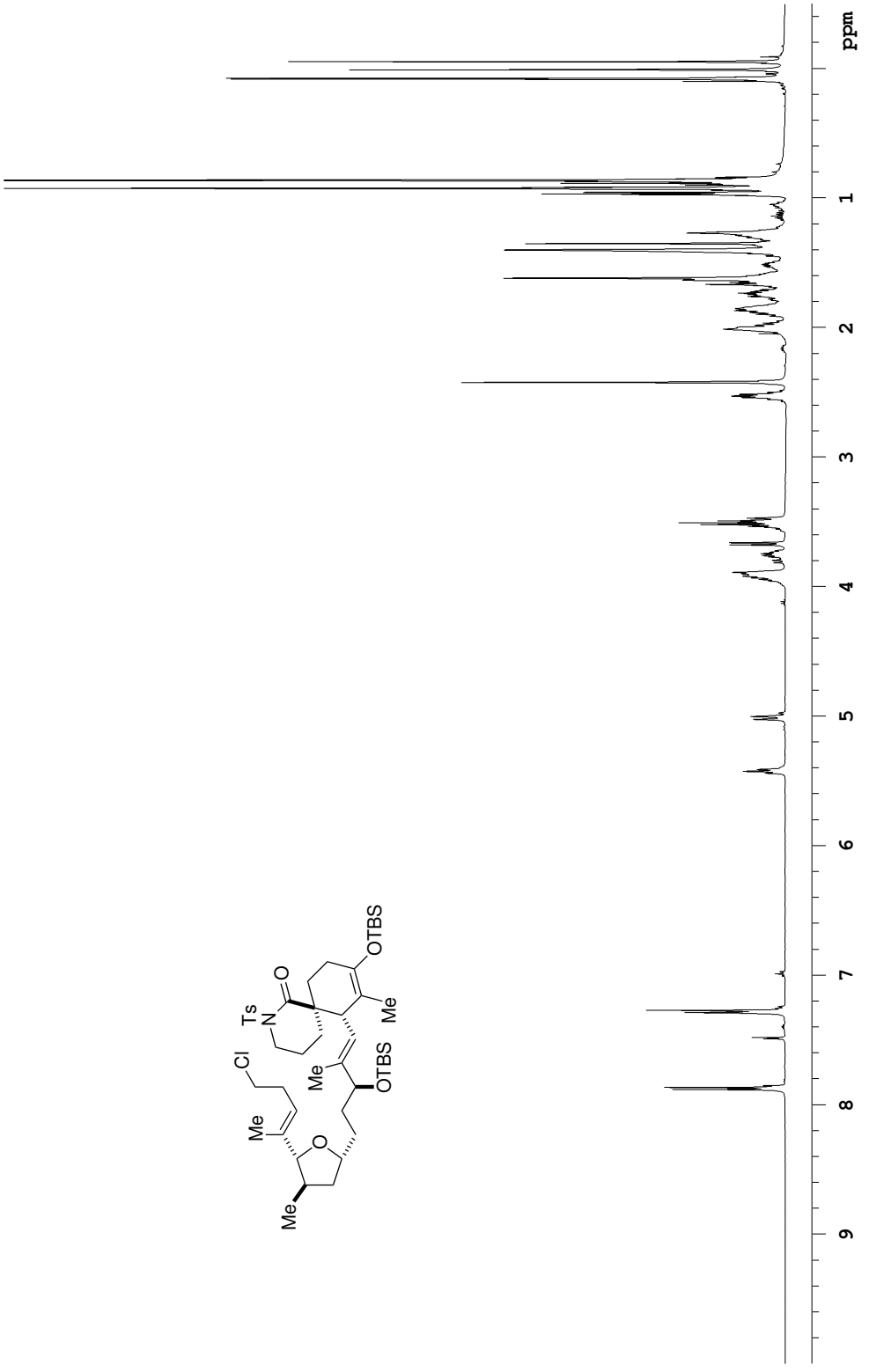
^{13}C NMR spectrum of alcohol **134b**



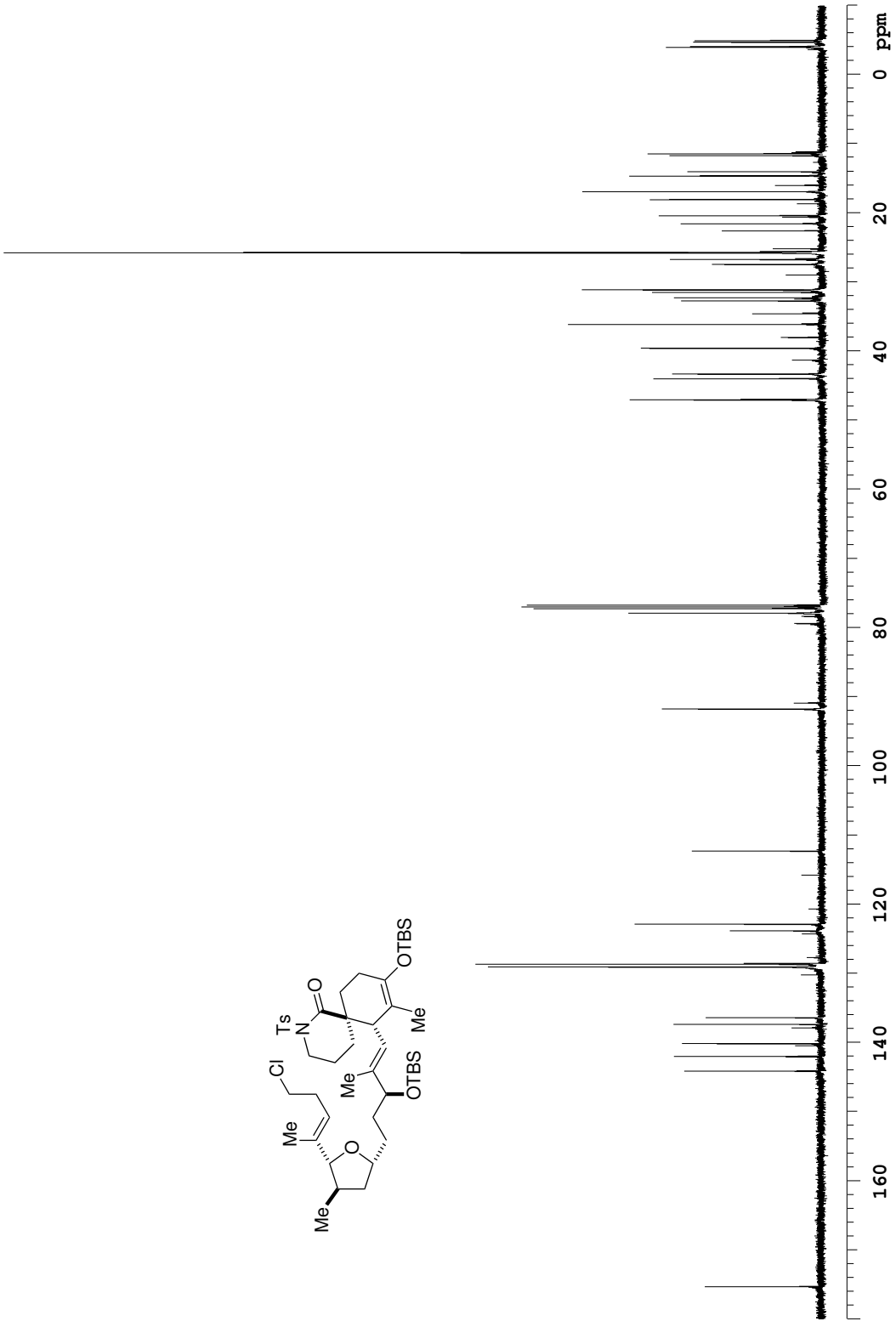
^{1}H NMR spectrum of ketone **135**



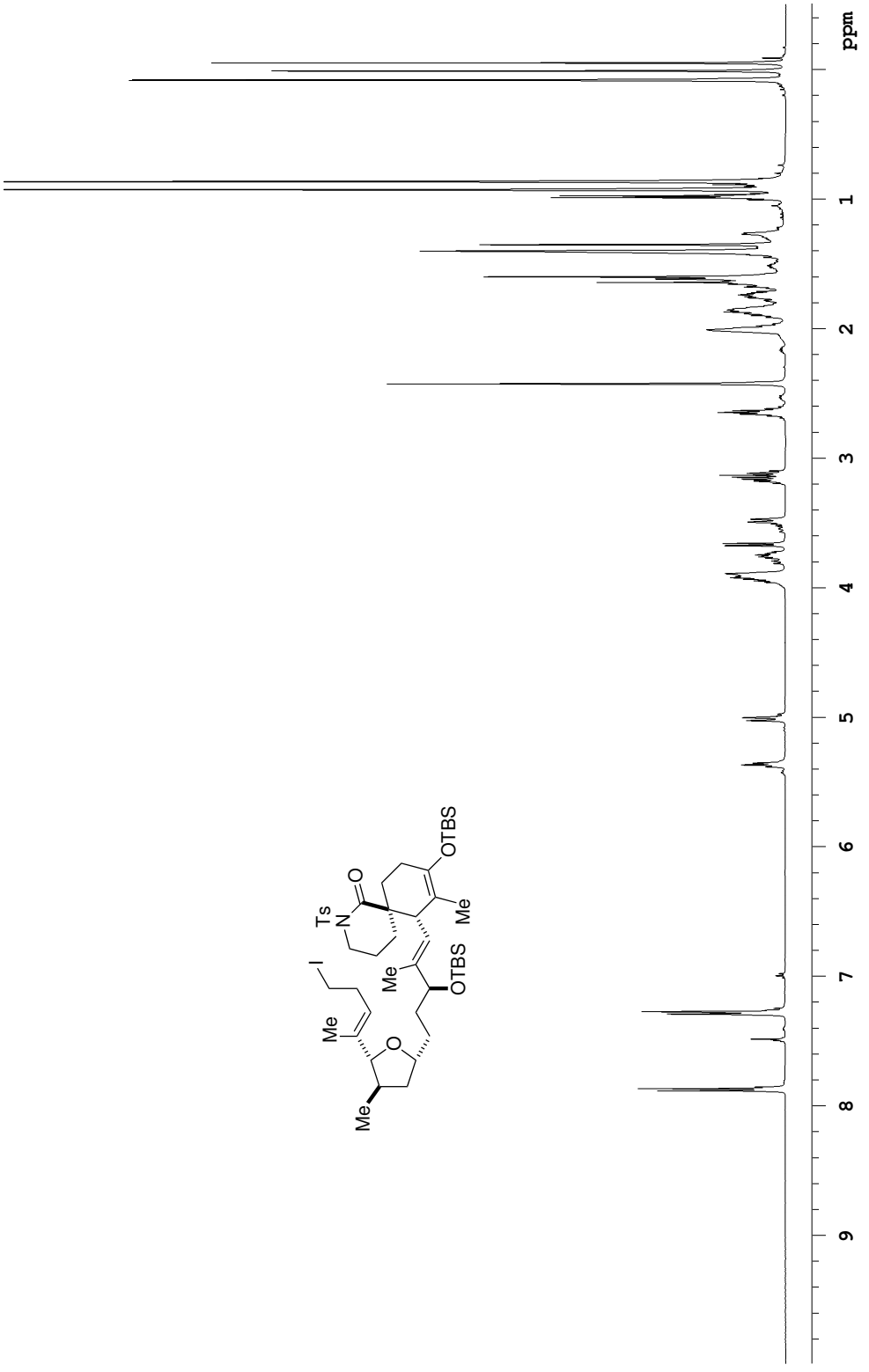
^{13}C NMR spectrum of ketone **135**



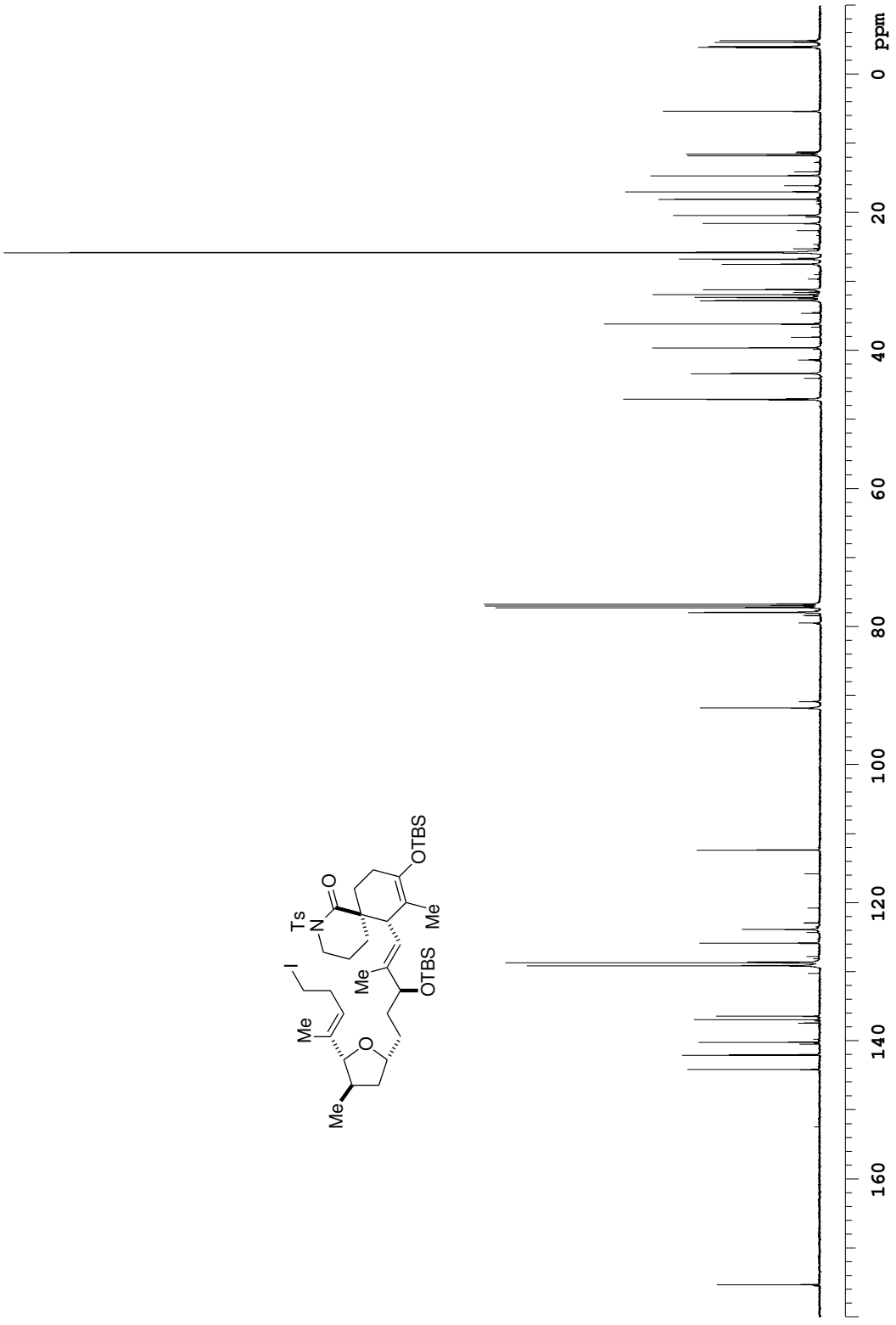
^{1}H NMR spectrum of *t*-butyldimethylsilyl ether **136a**



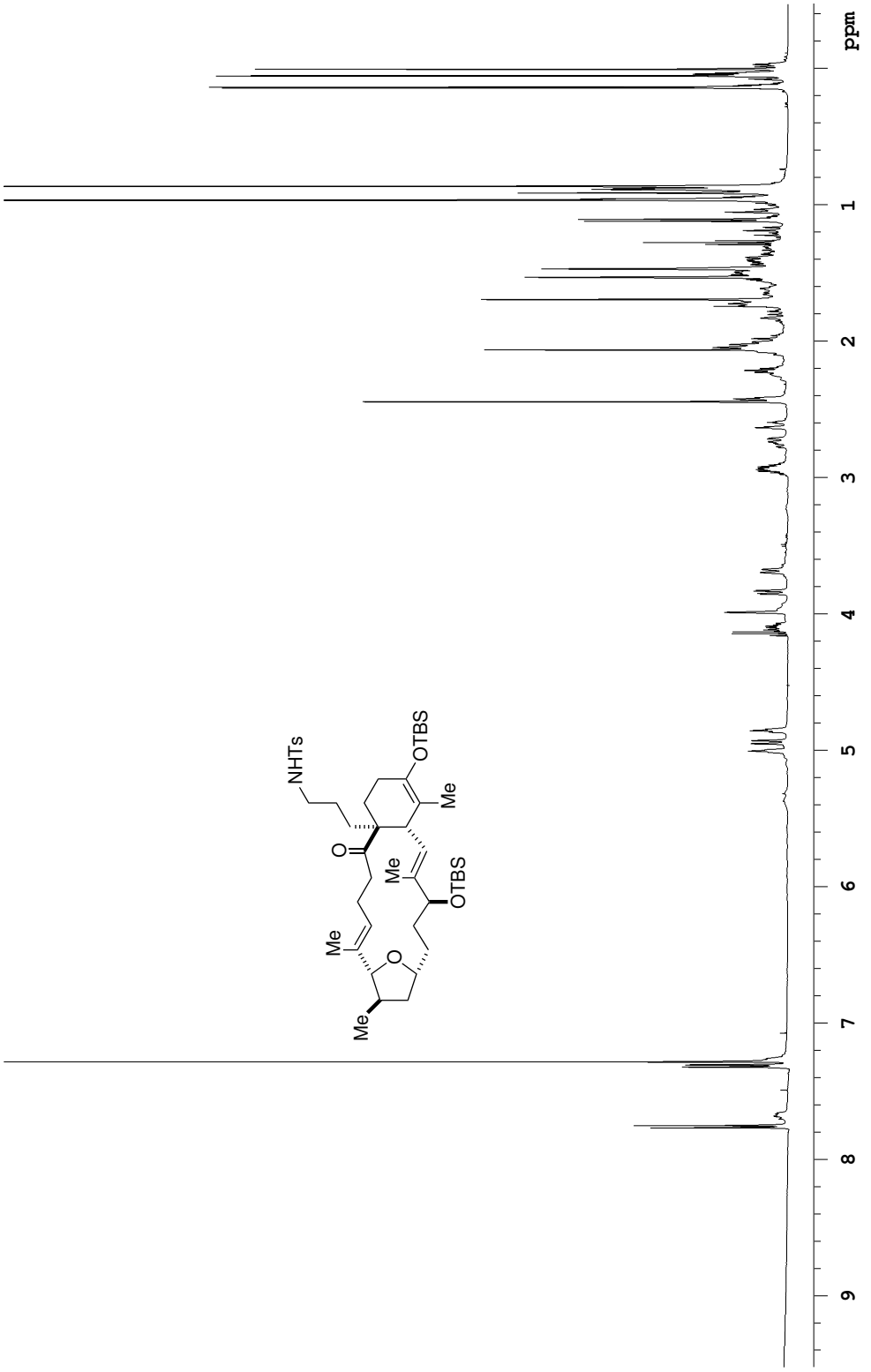
^{13}C NMR spectrum of *t*-butyldimethylsilyl ether **136a**



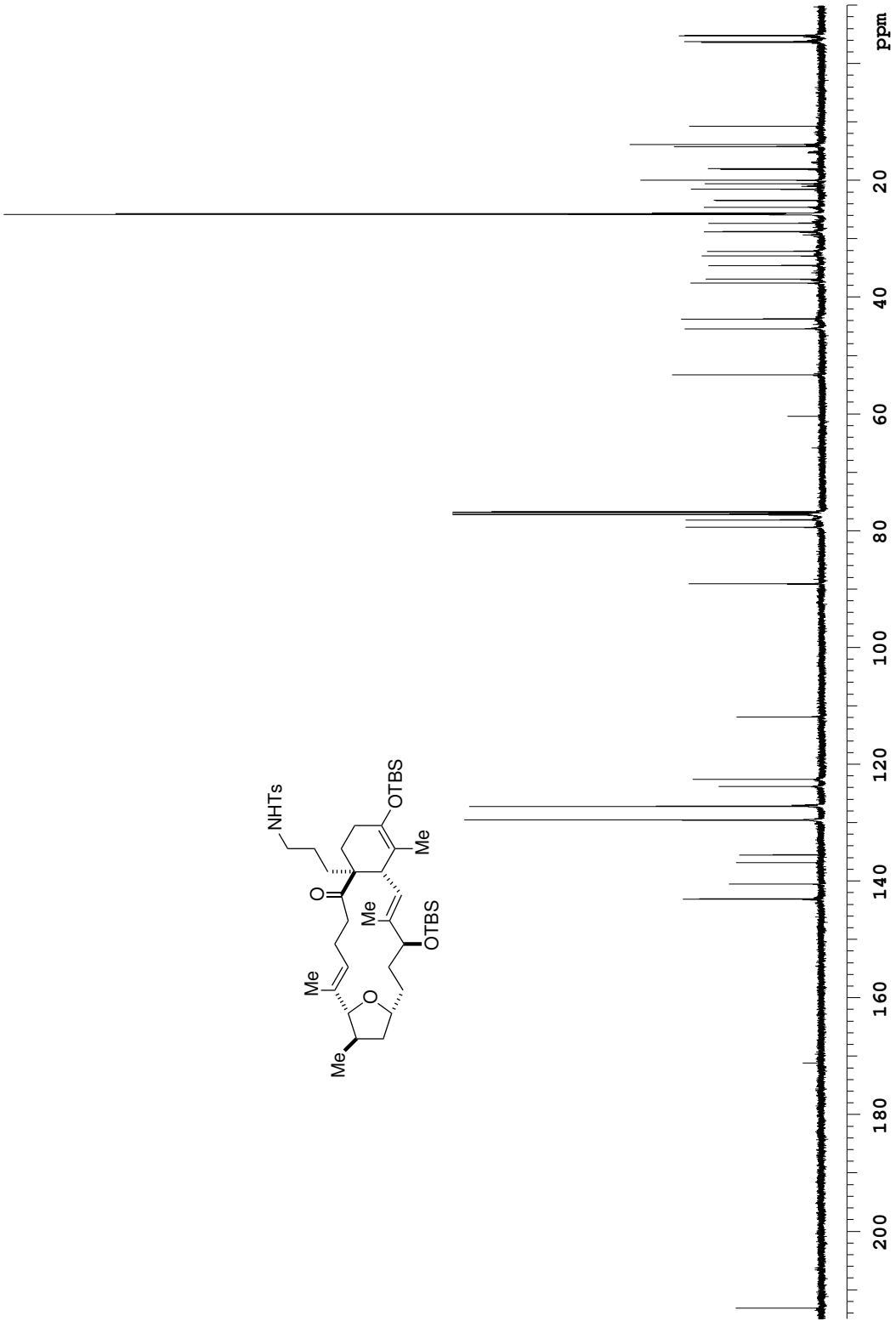
^{1}H NMR spectrum of iodide **136b**



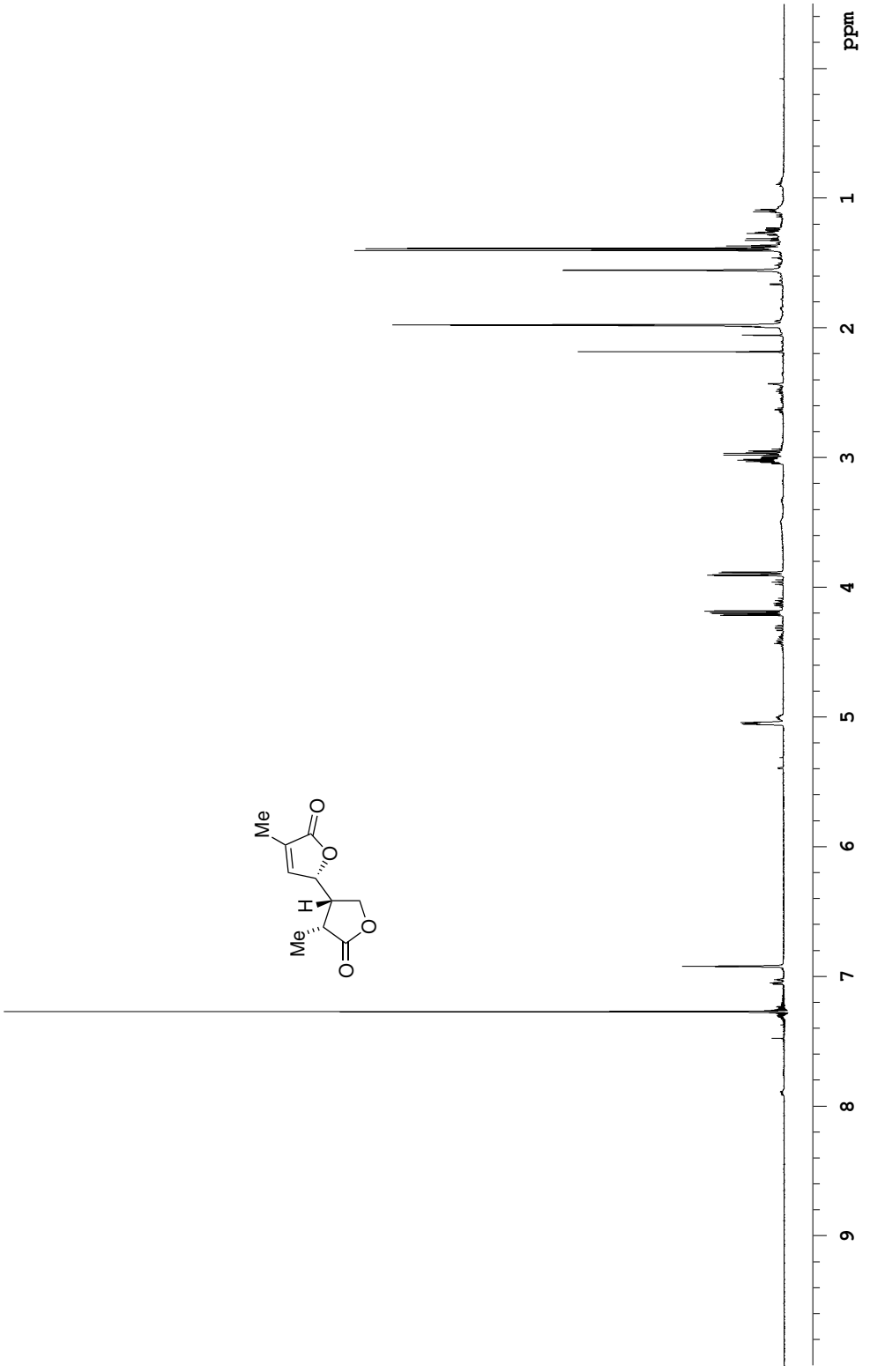
^{13}C NMR spectrum of iodide **136b**



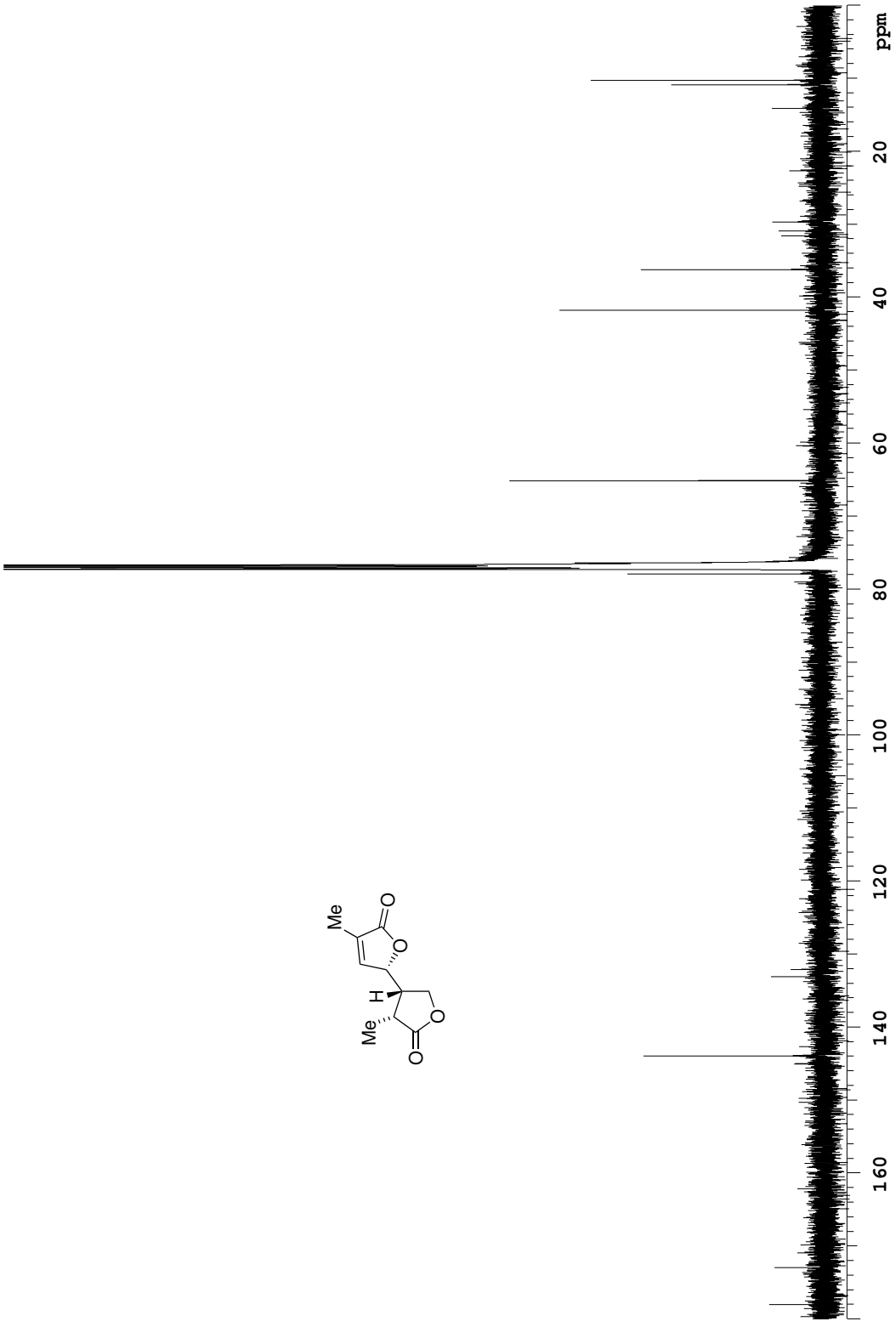
^{1}H NMR spectrum of *N*-tosyl amine **141a**



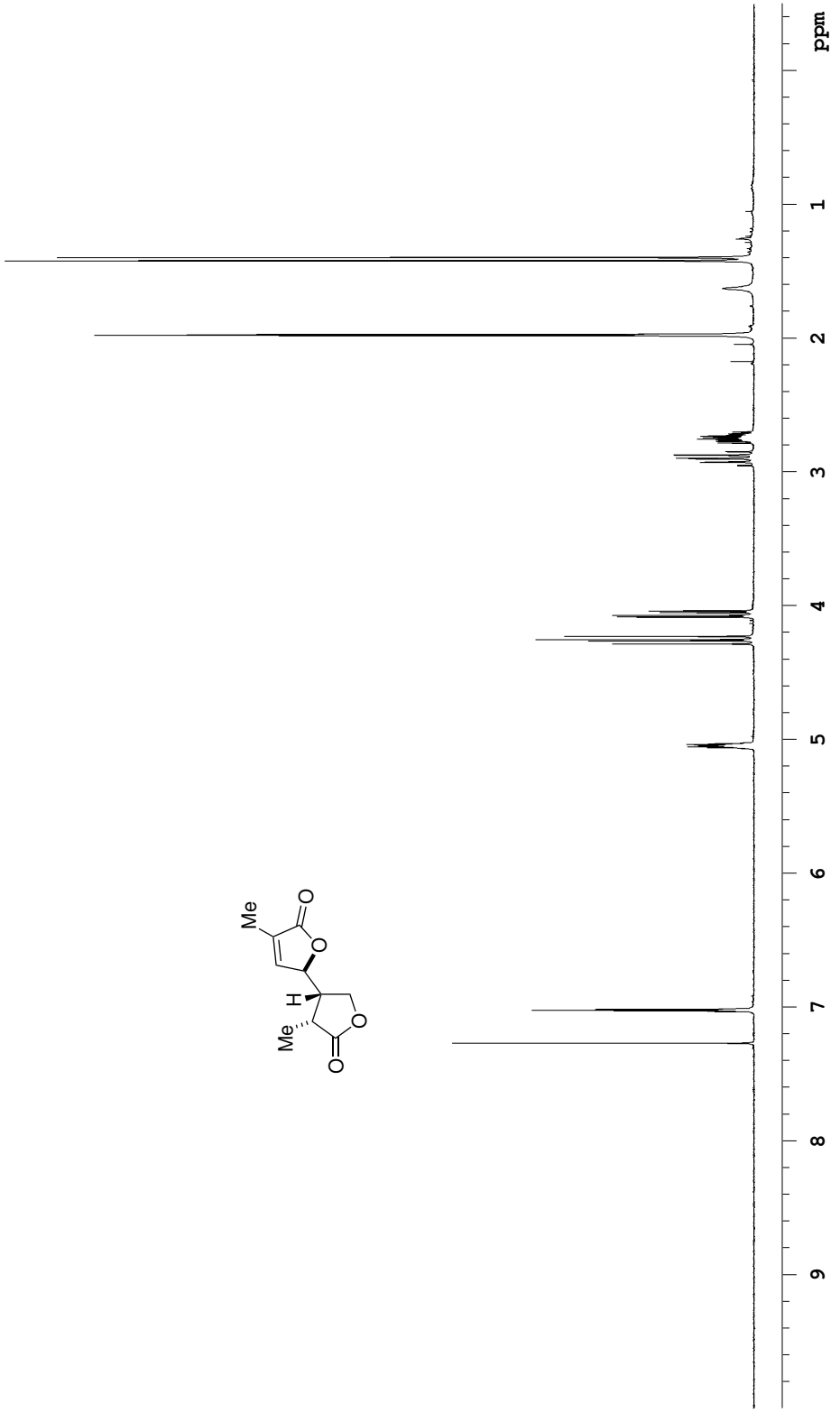
^{13}C NMR spectrum of *N*-tosyl amine **141a**



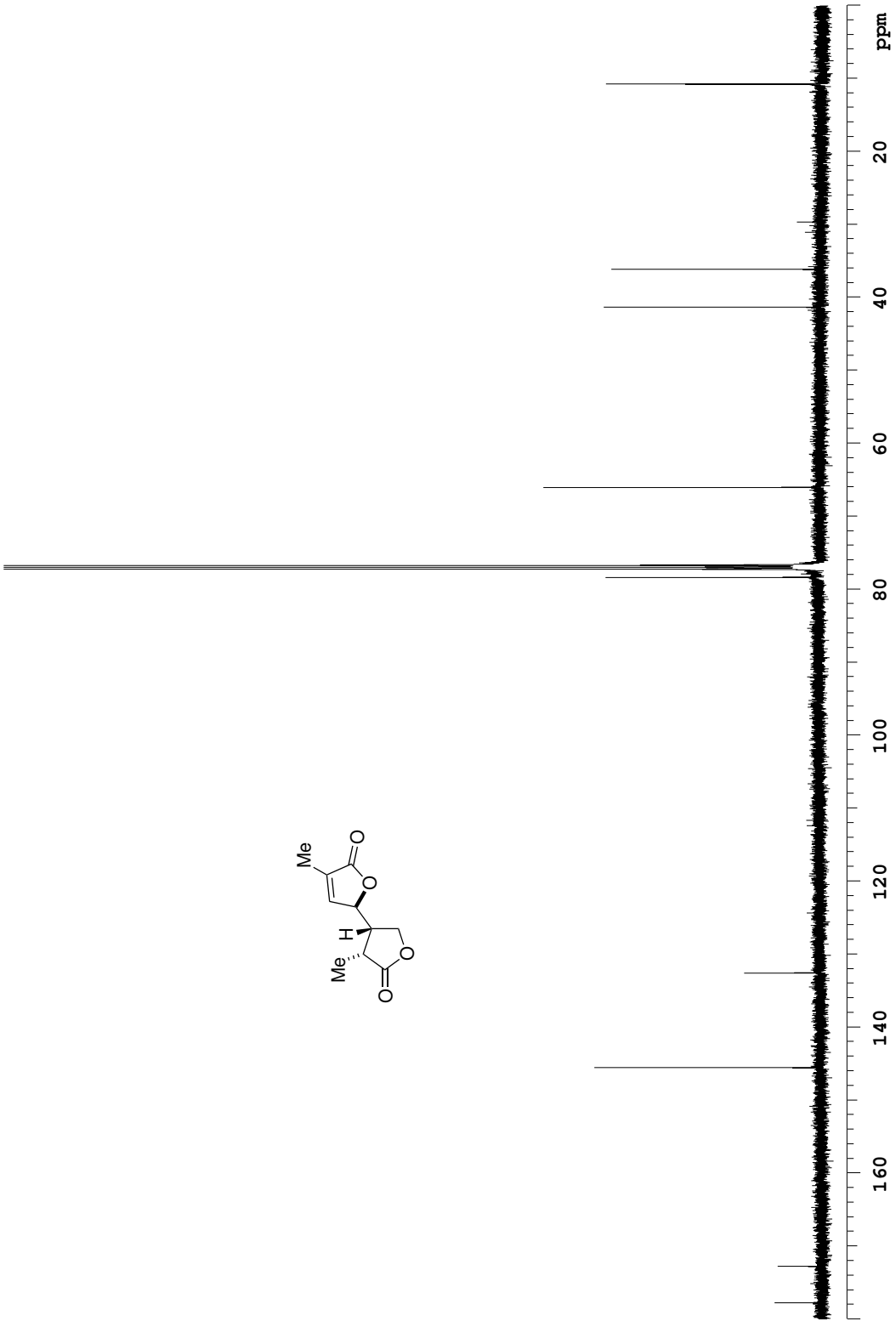
^{1}H NMR spectrum of dimer **156**



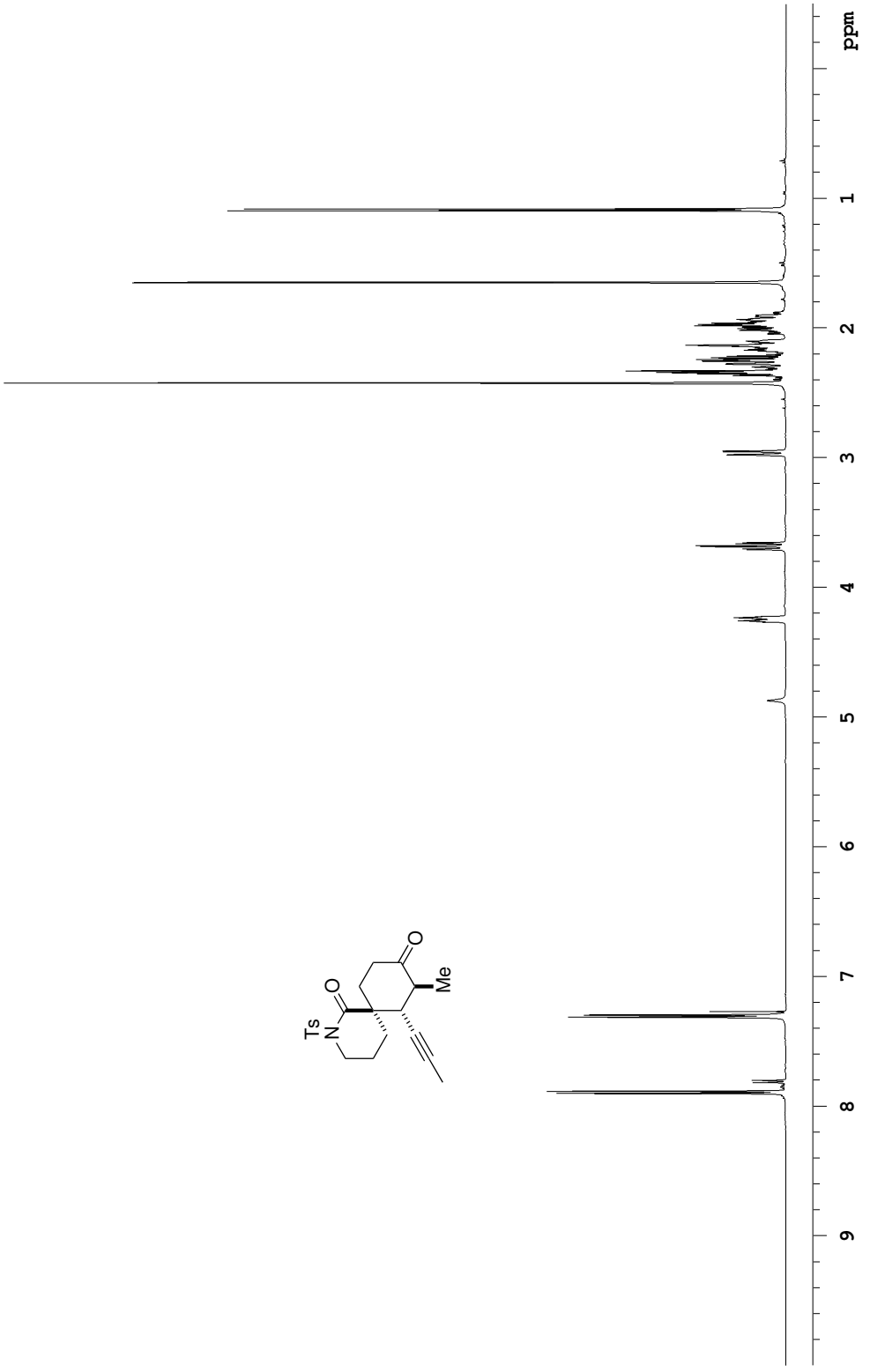
^{13}C NMR spectrum of dimer **156**



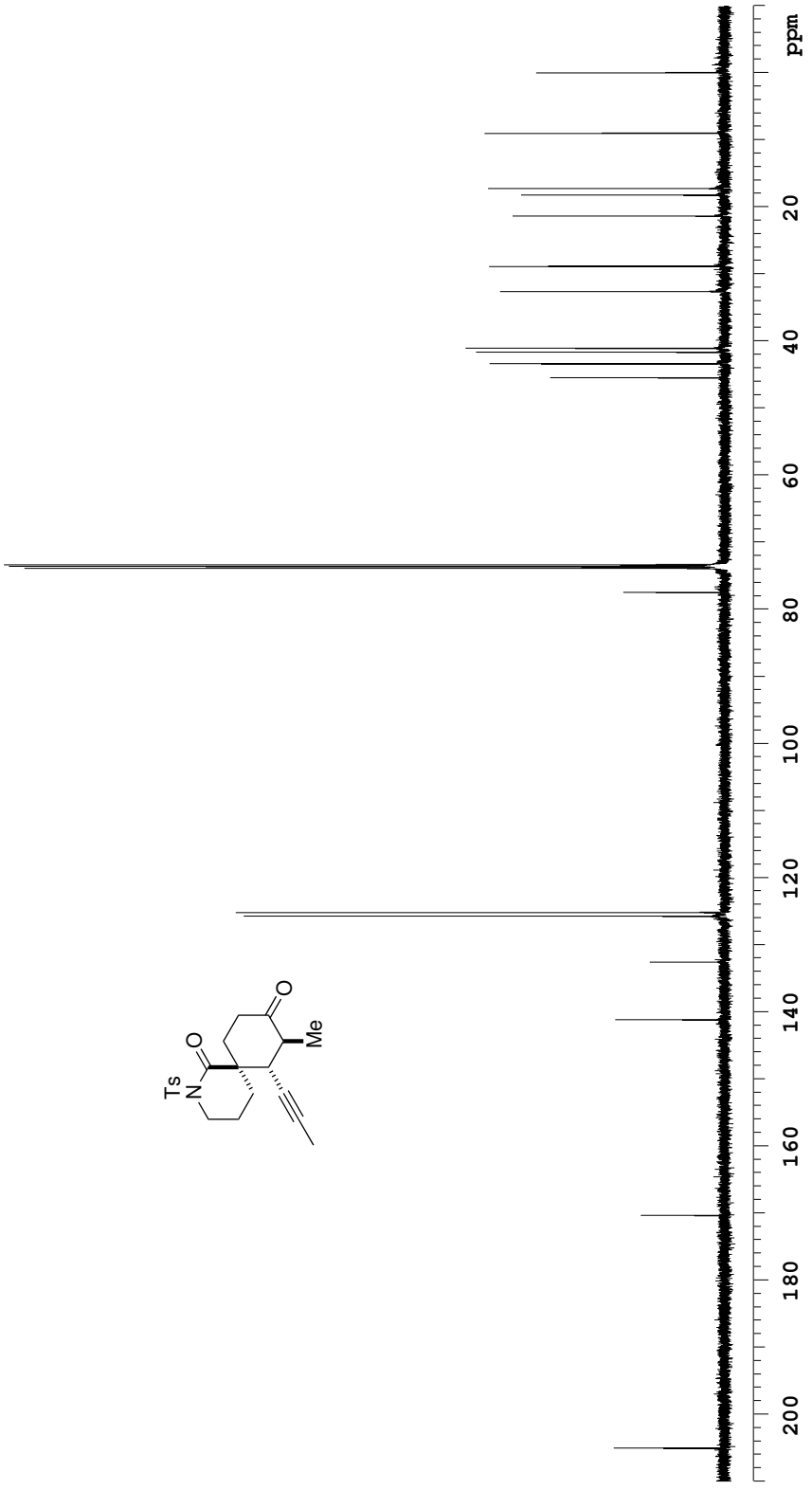
^{1}H NMR spectrum of dimer *epi*-**156**



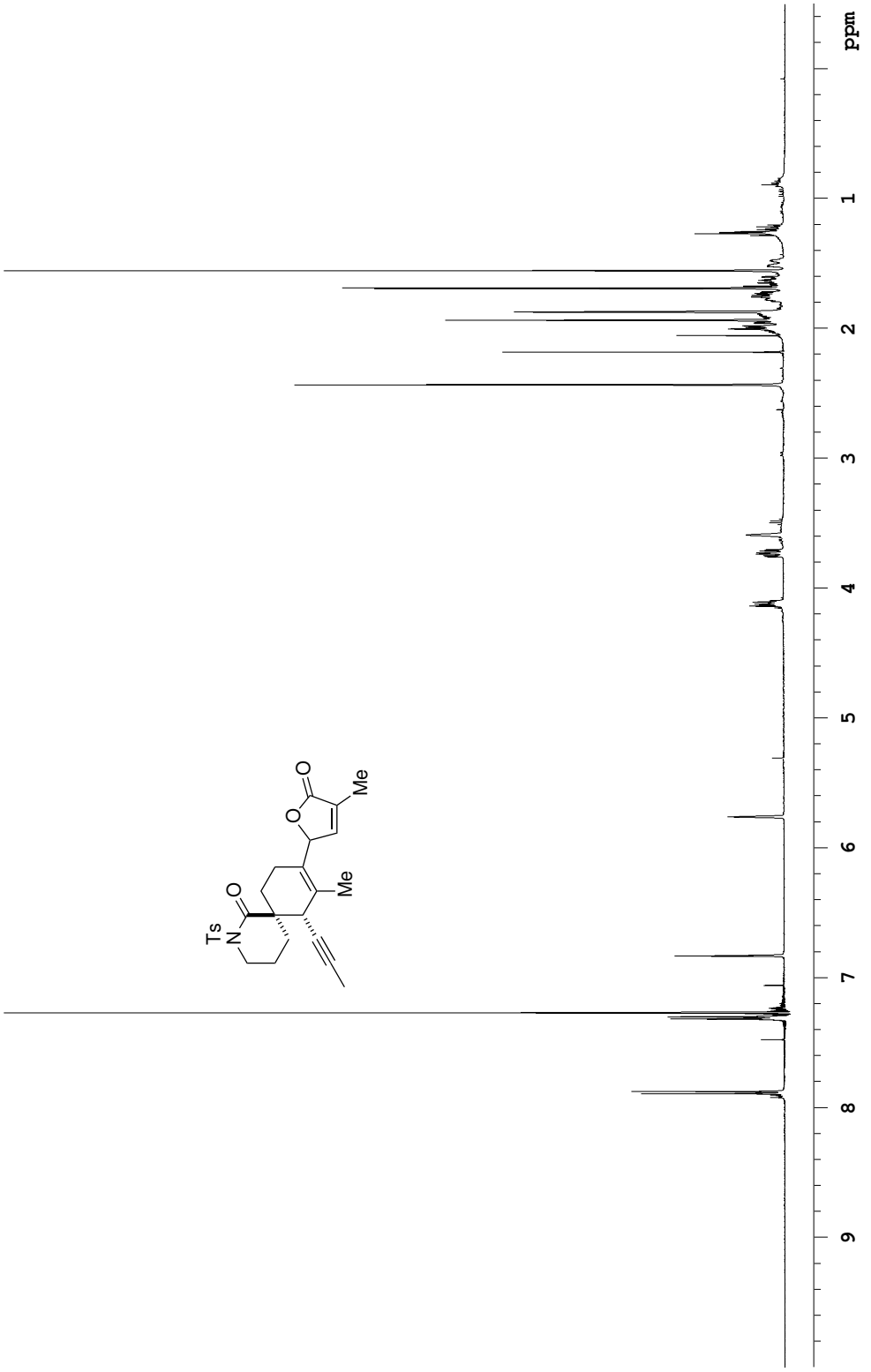
^{13}C NMR spectrum of dimer *epi*-**156**



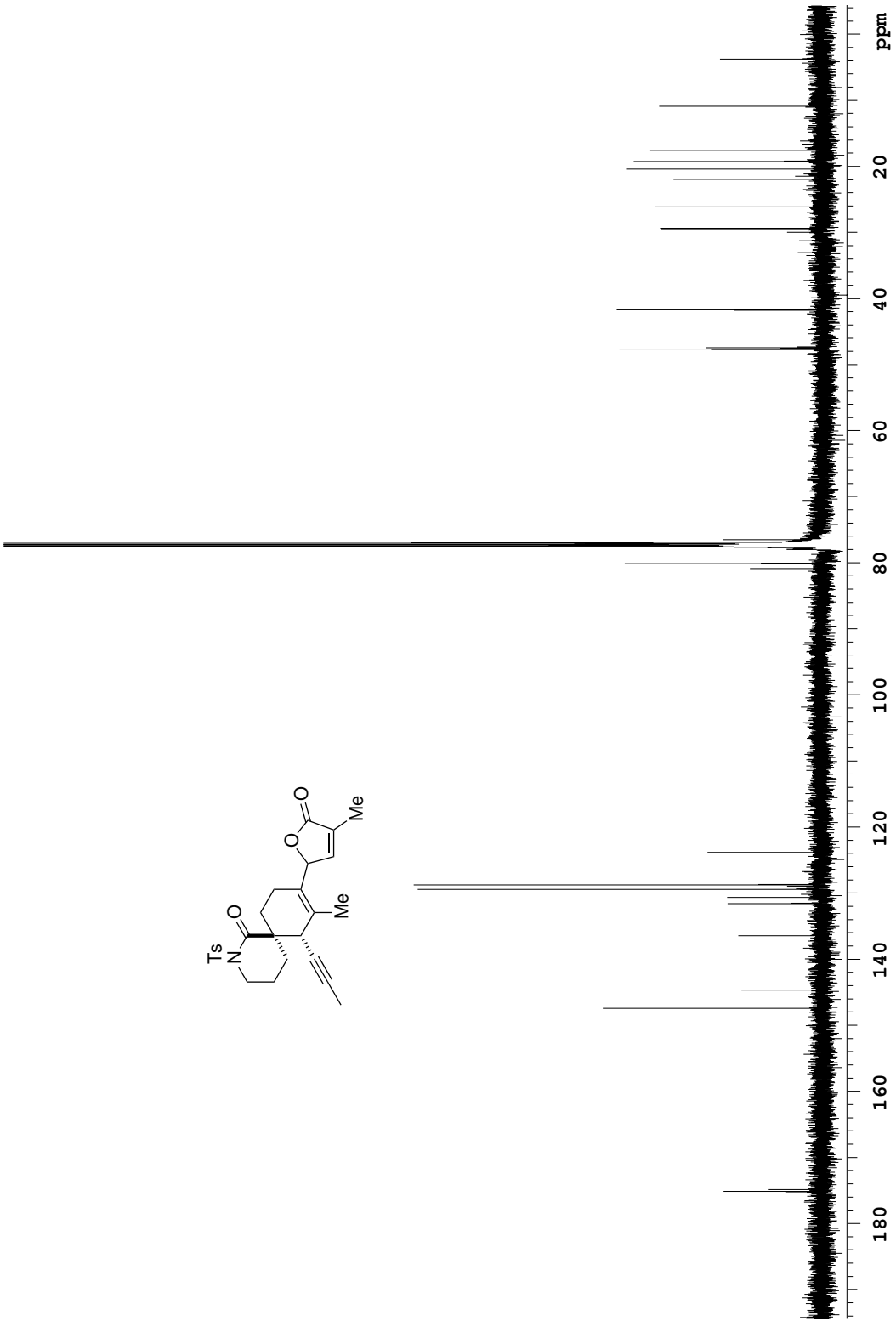
^{1}H NMR spectrum of ketone **158**



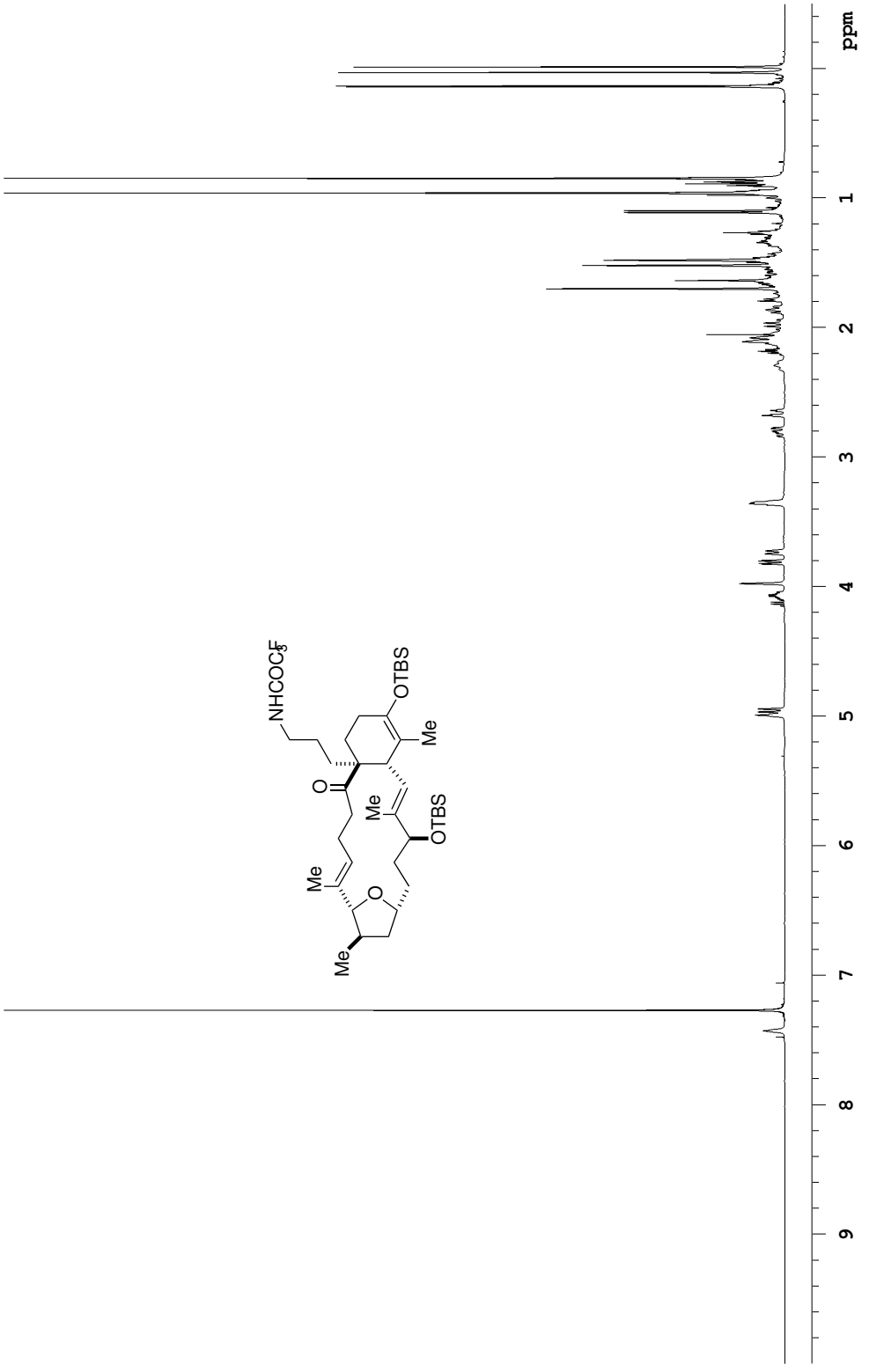
^{13}C NMR spectrum of ketone **158**



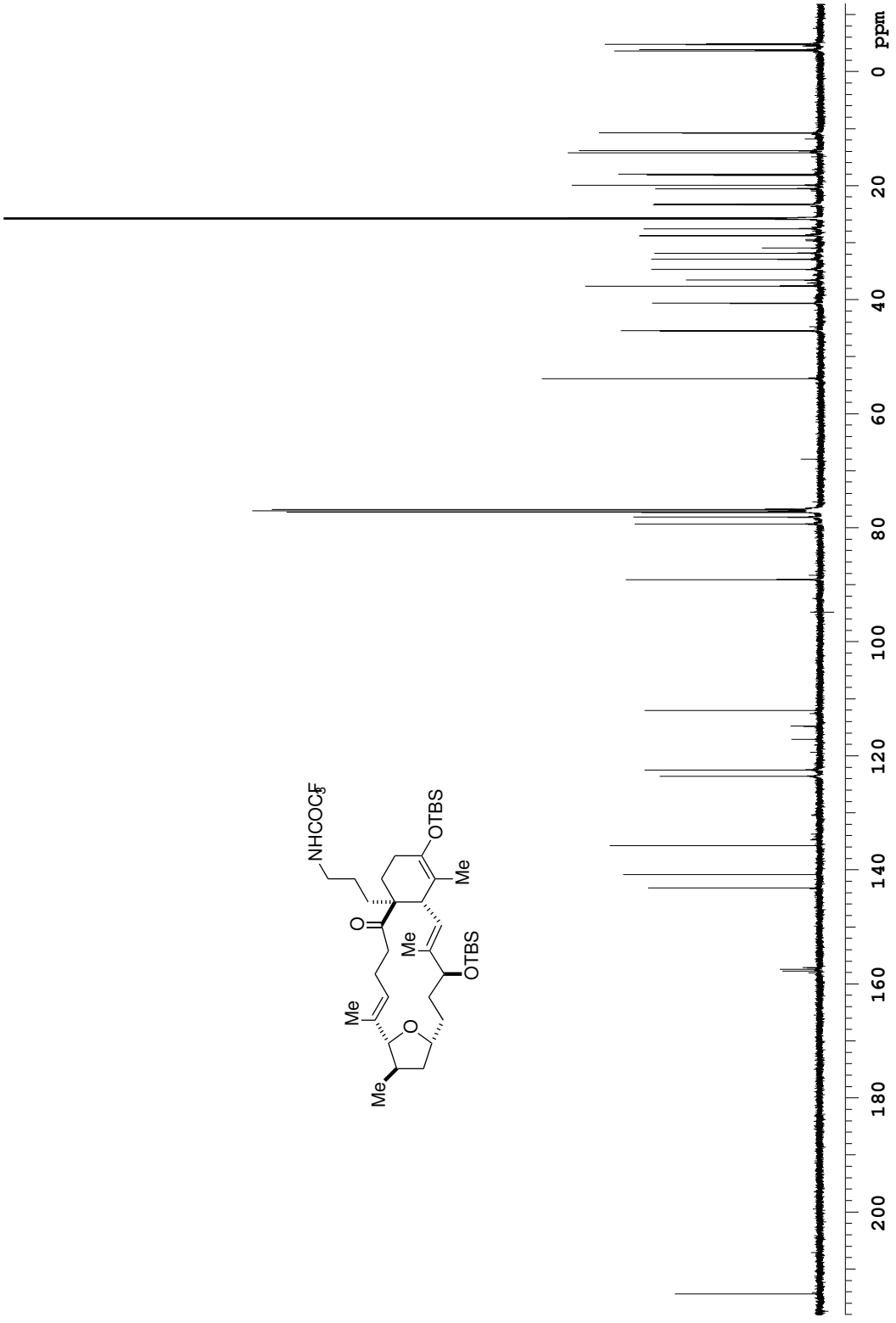
^{1}H NMR spectrum of butenolide **160**



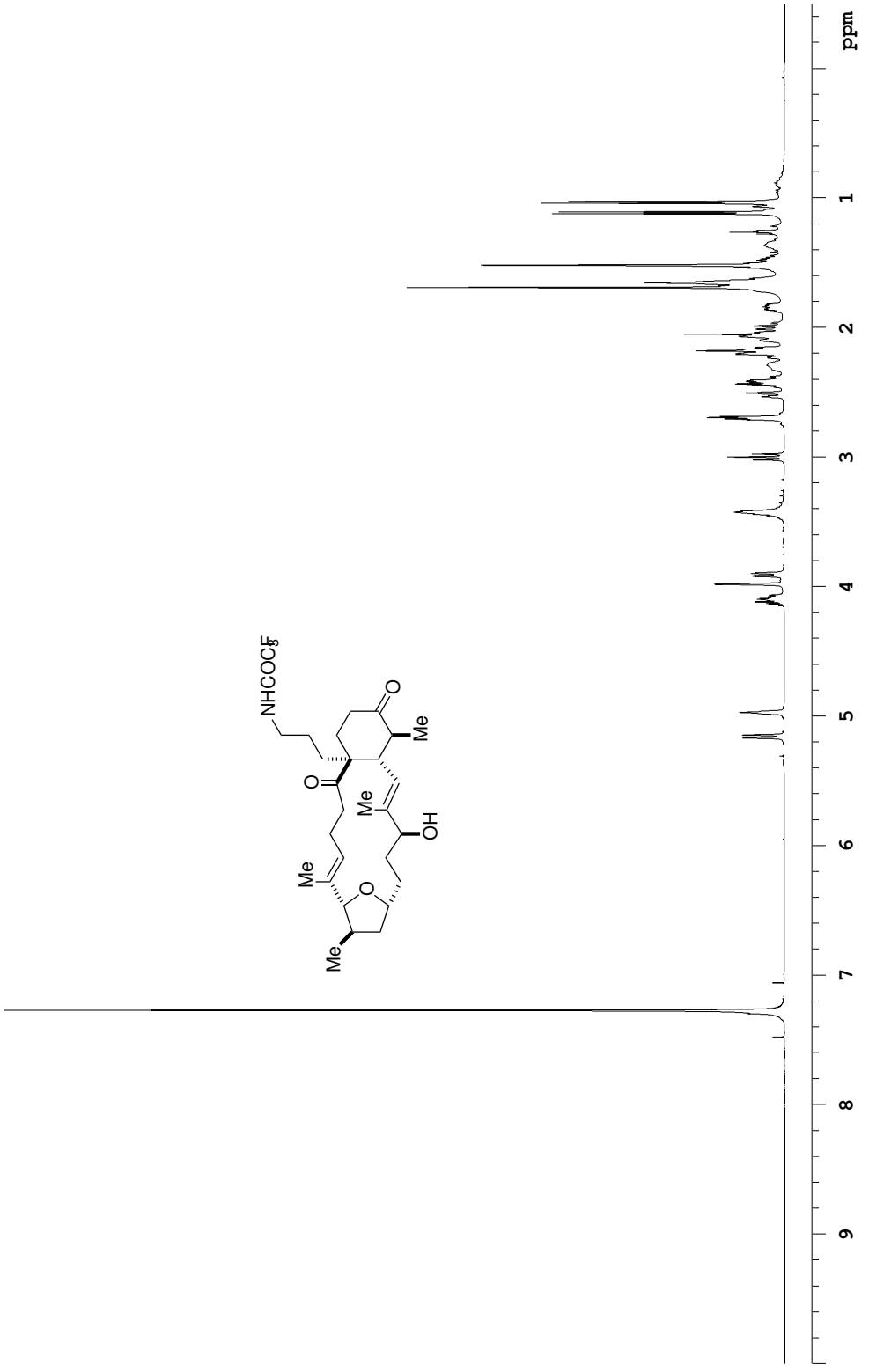
^{13}C NMR spectrum of butenolide **160**



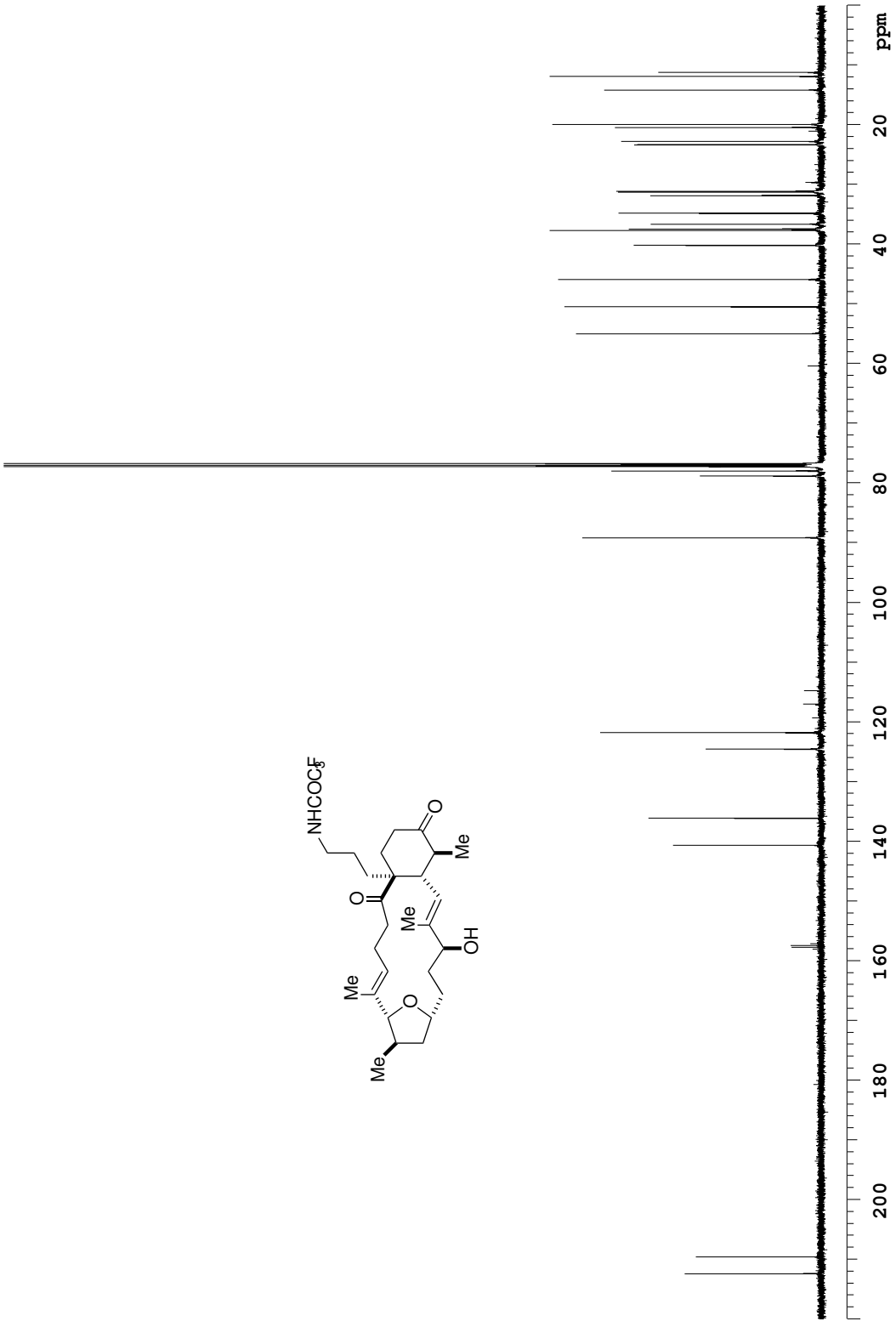
^{1}H NMR spectrum of trifluoroacetamide **141b**



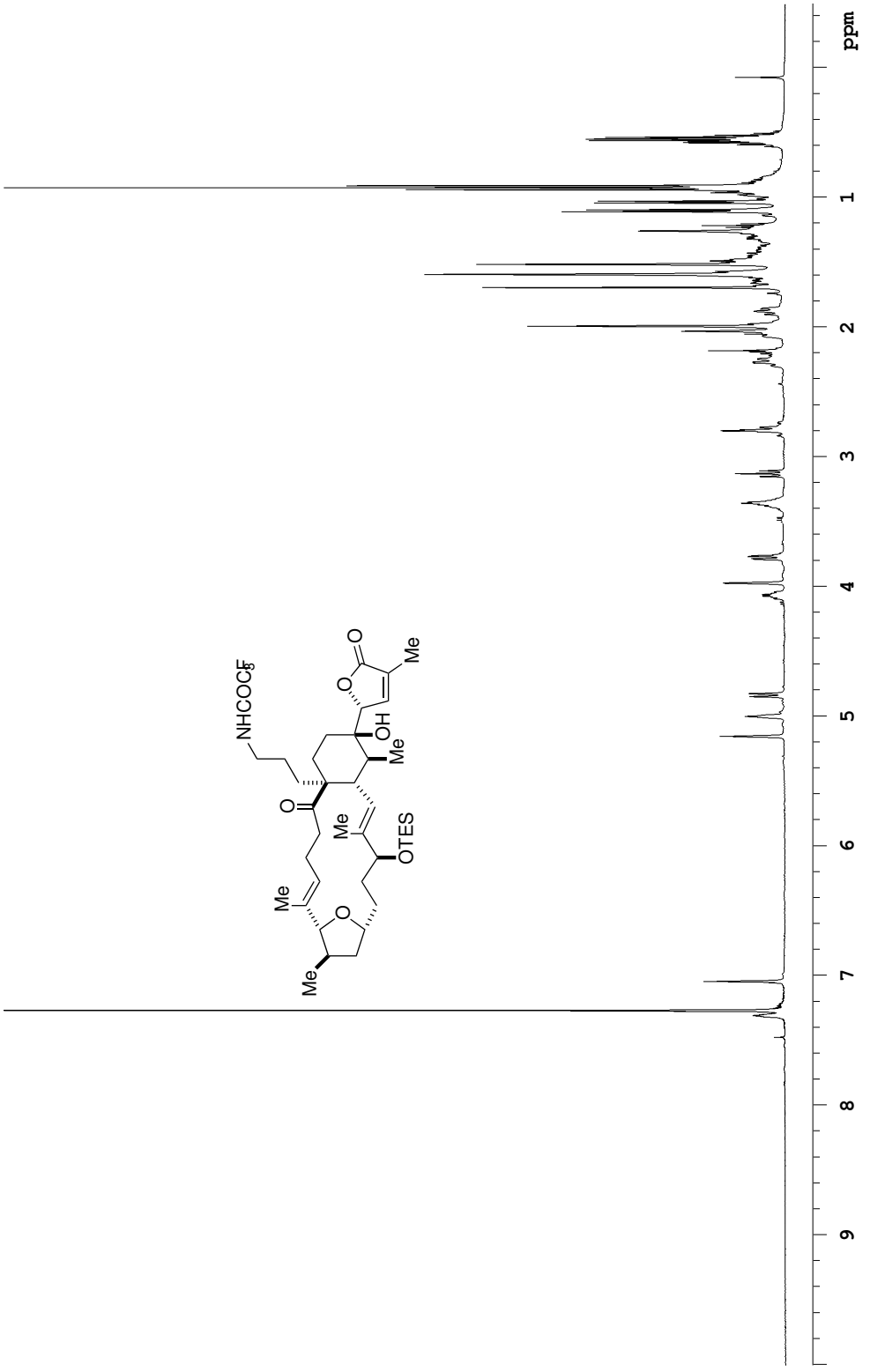
^{13}C NMR spectrum of trifluoroacetamide **141b**



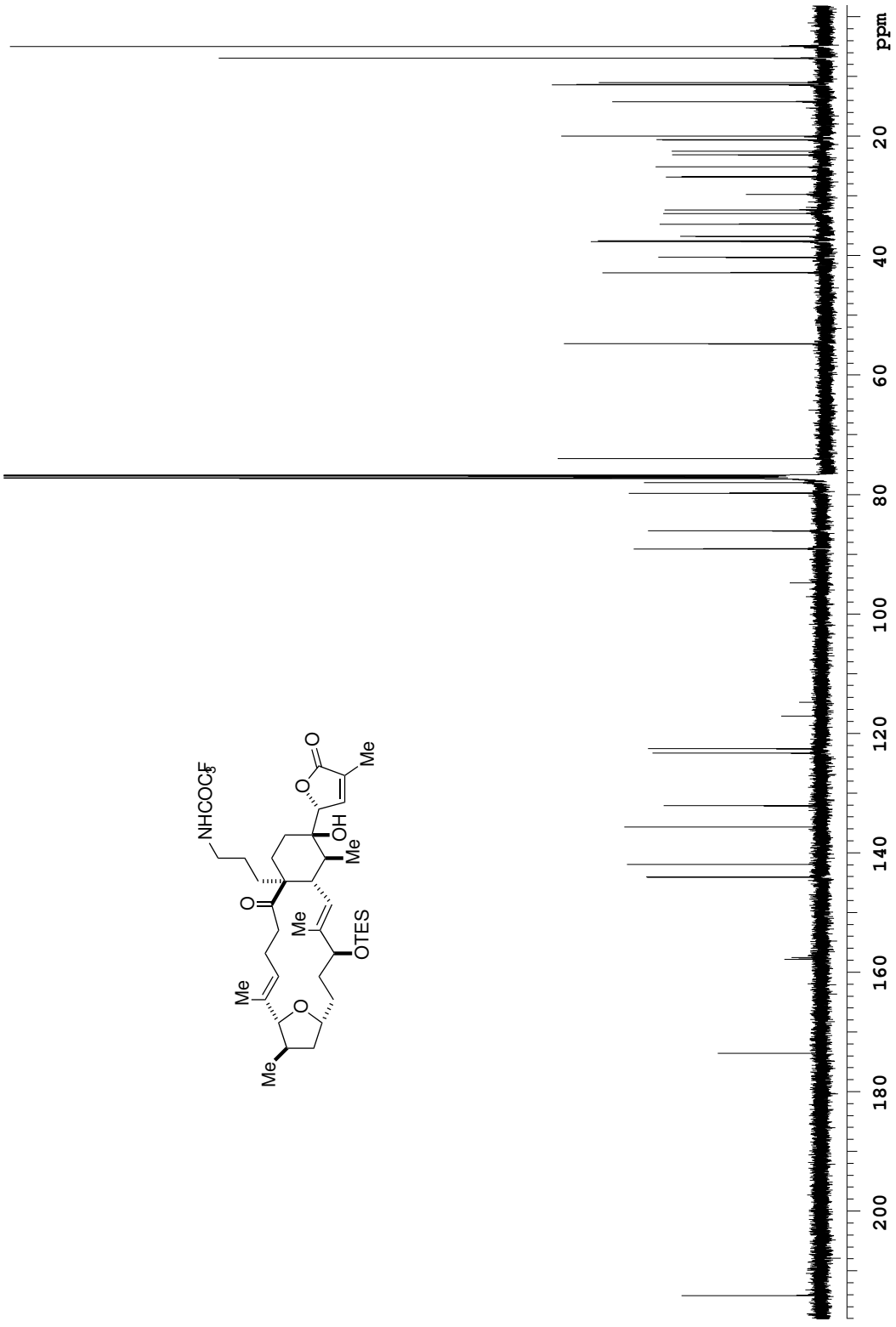
^{1}H NMR spectrum of ketone **163**



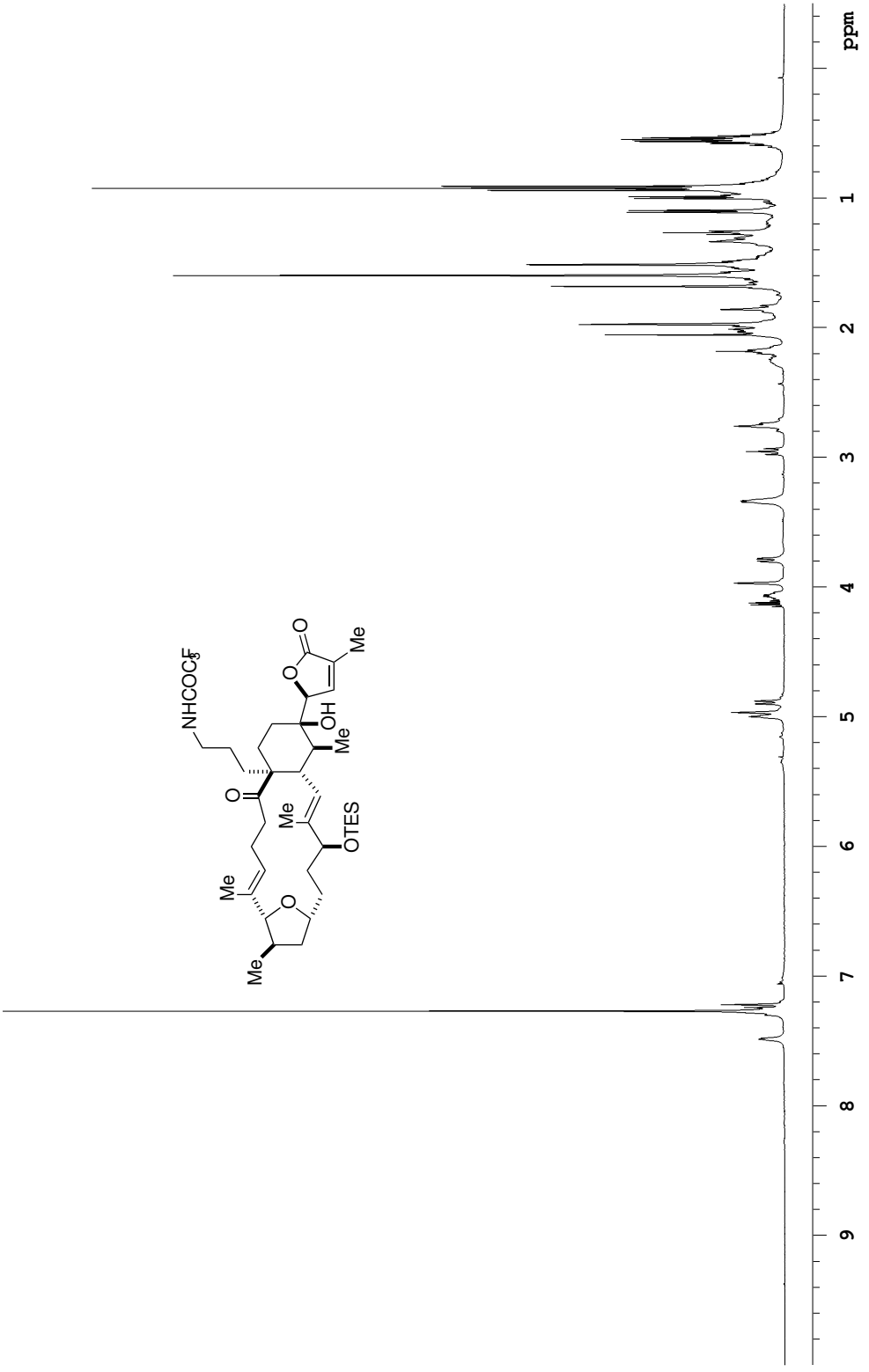
^{13}C NMR spectrum of ketone **163**



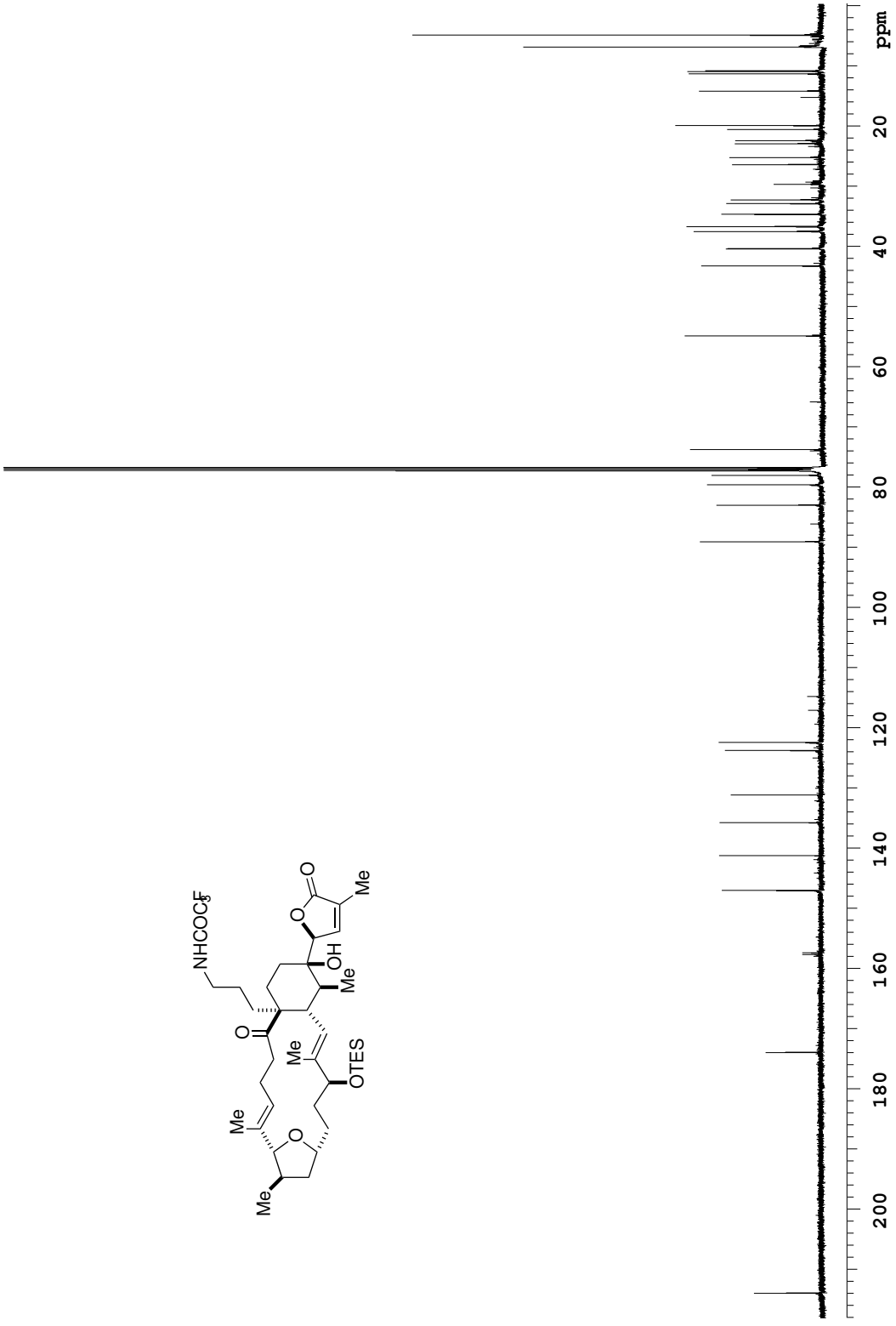
^{1}H NMR spectrum of alcohol **165a**



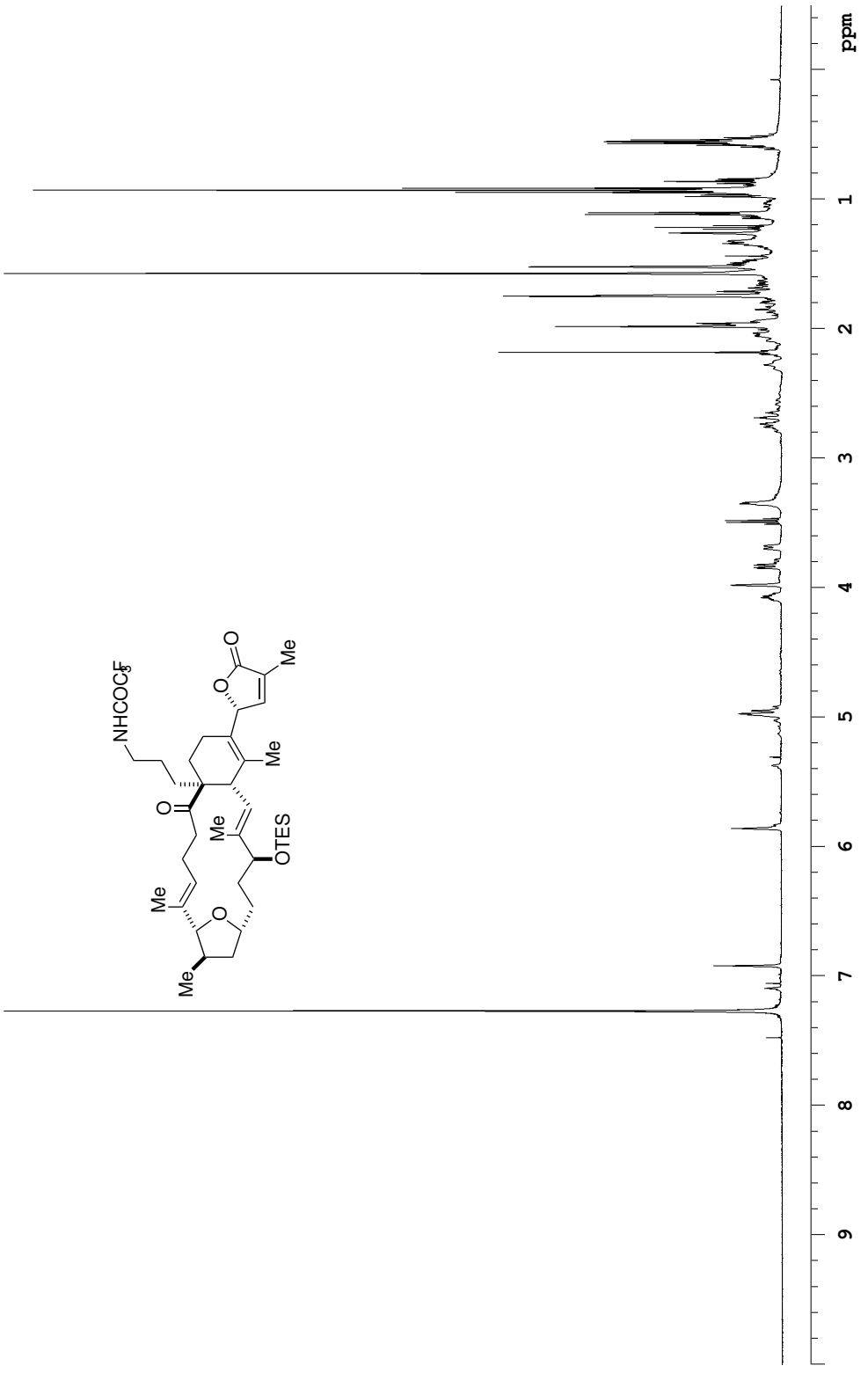
^{13}C NMR spectrum of alcohol **165a**



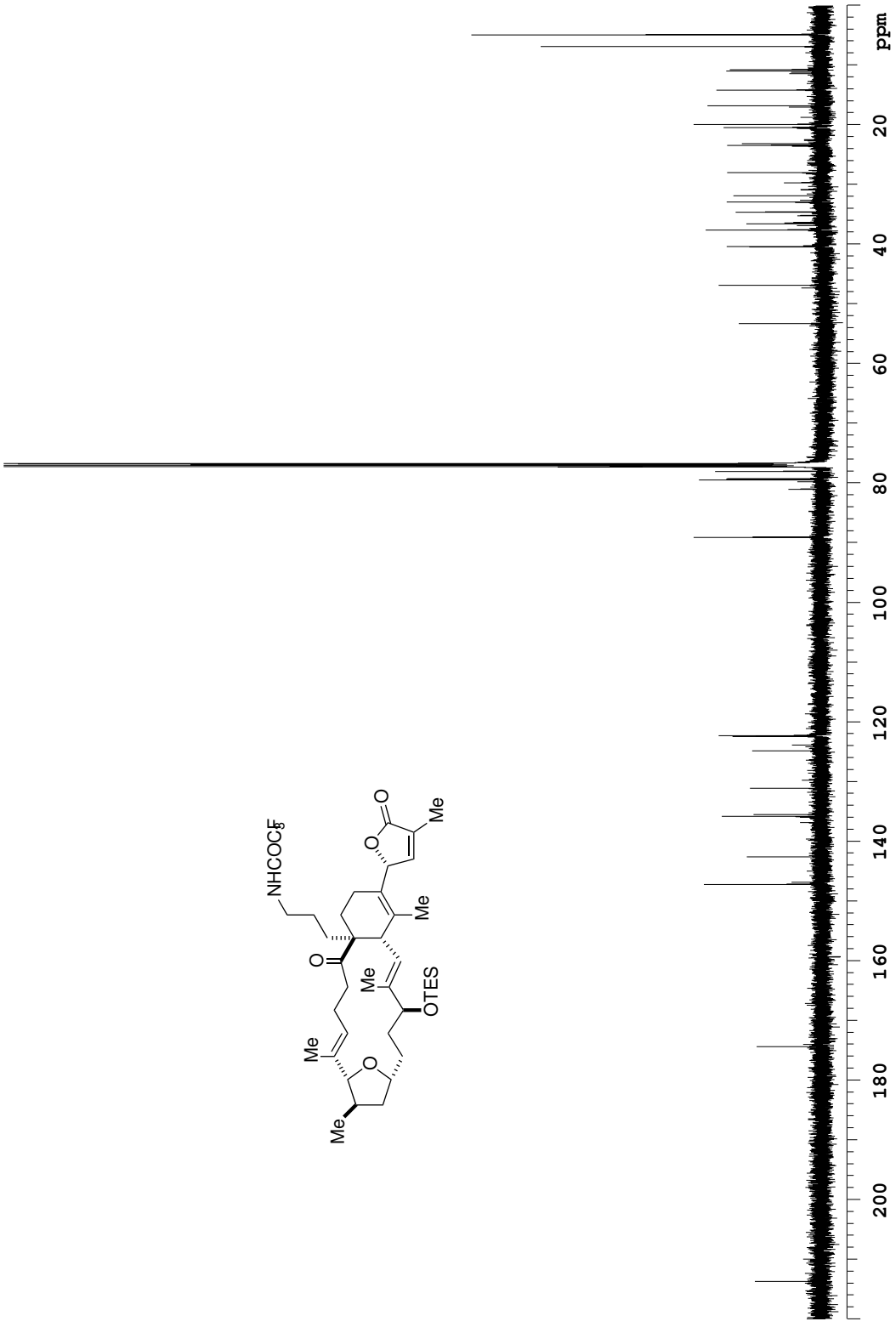
^{1}H NMR spectrum of alcohol **165b**



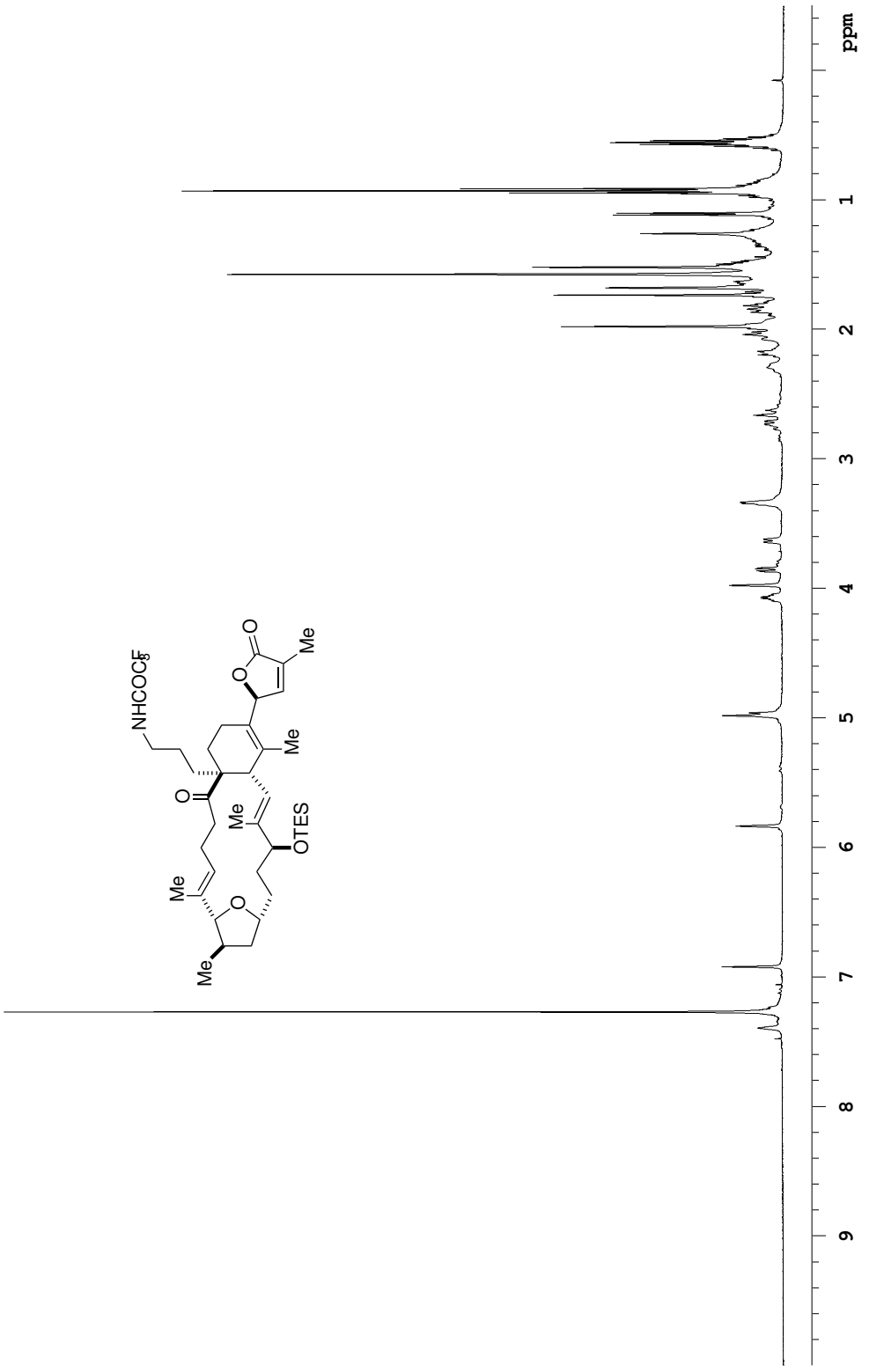
^{13}C NMR spectrum of alcohol **165b**



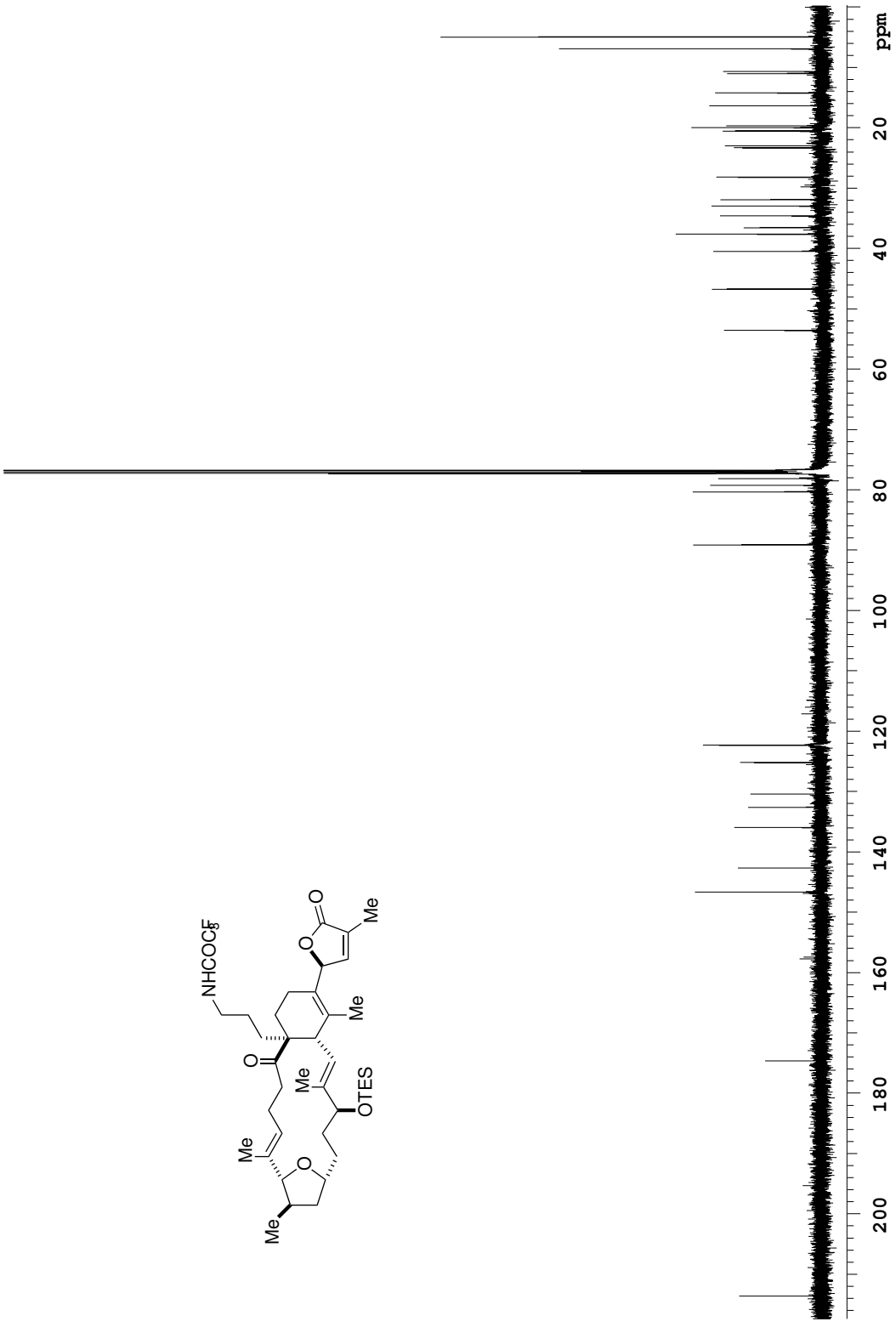
^{1}H NMR spectrum of olefin **166a**



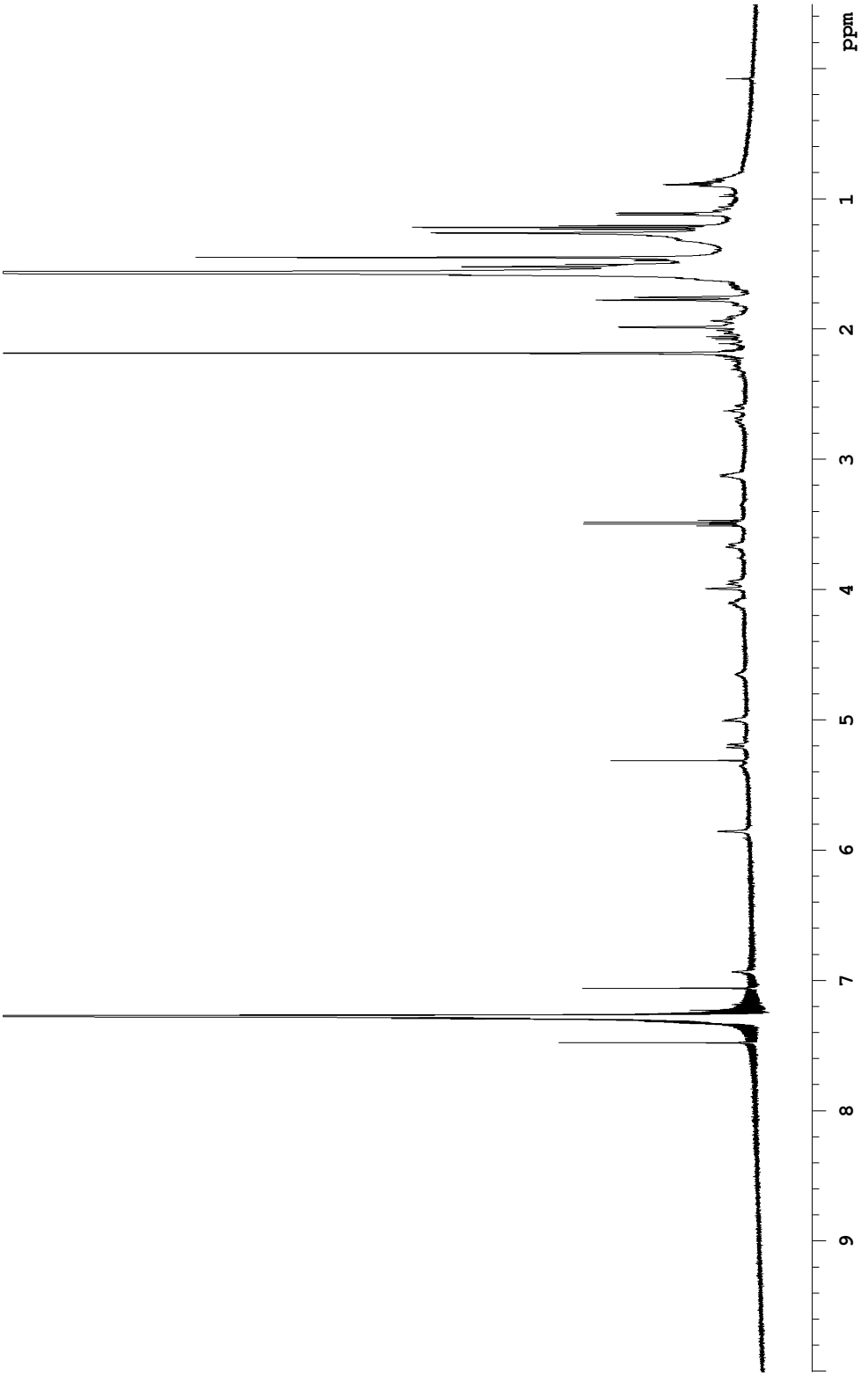
^{13}C NMR spectrum of olefin **166a**



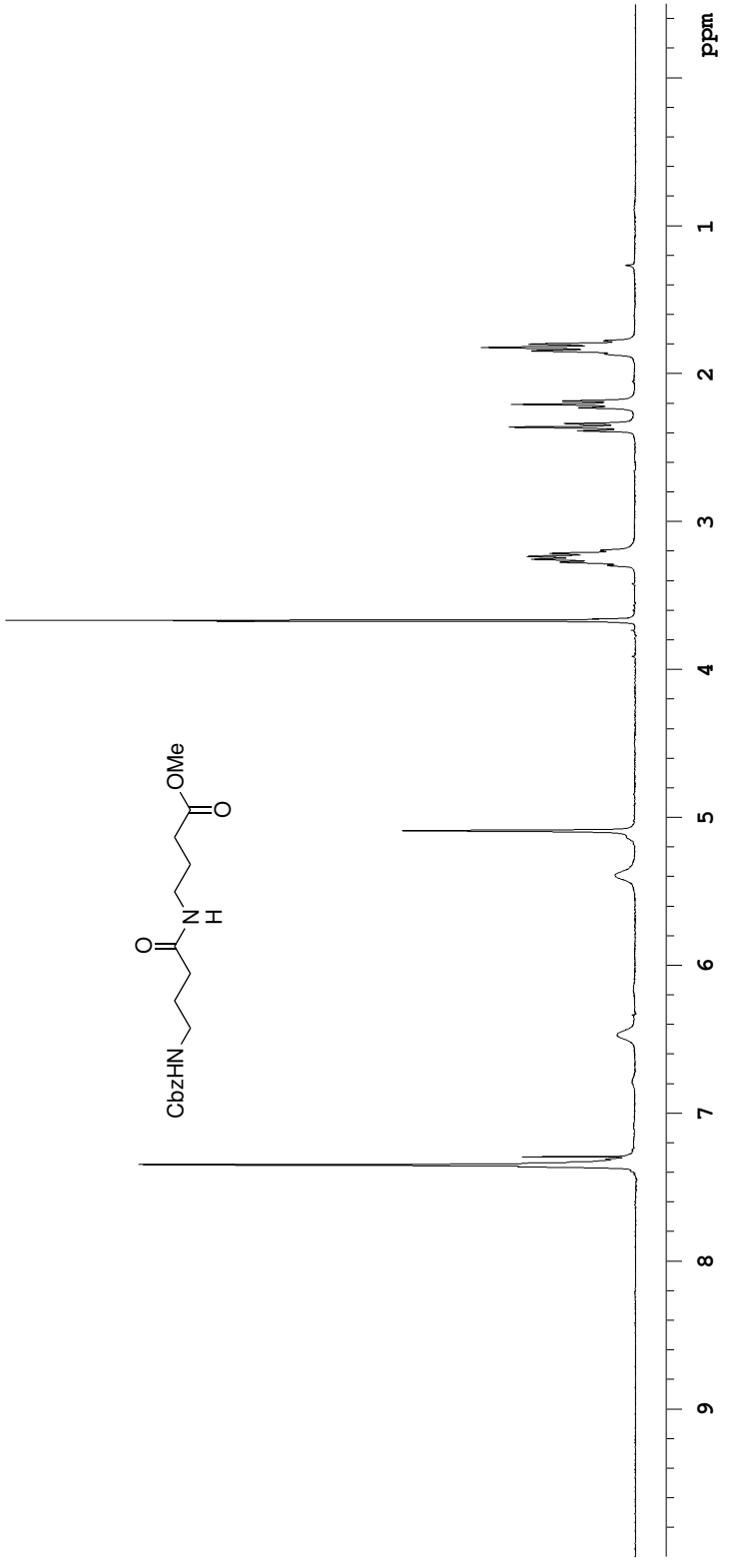
^{1}H NMR spectrum of olefin **166b**



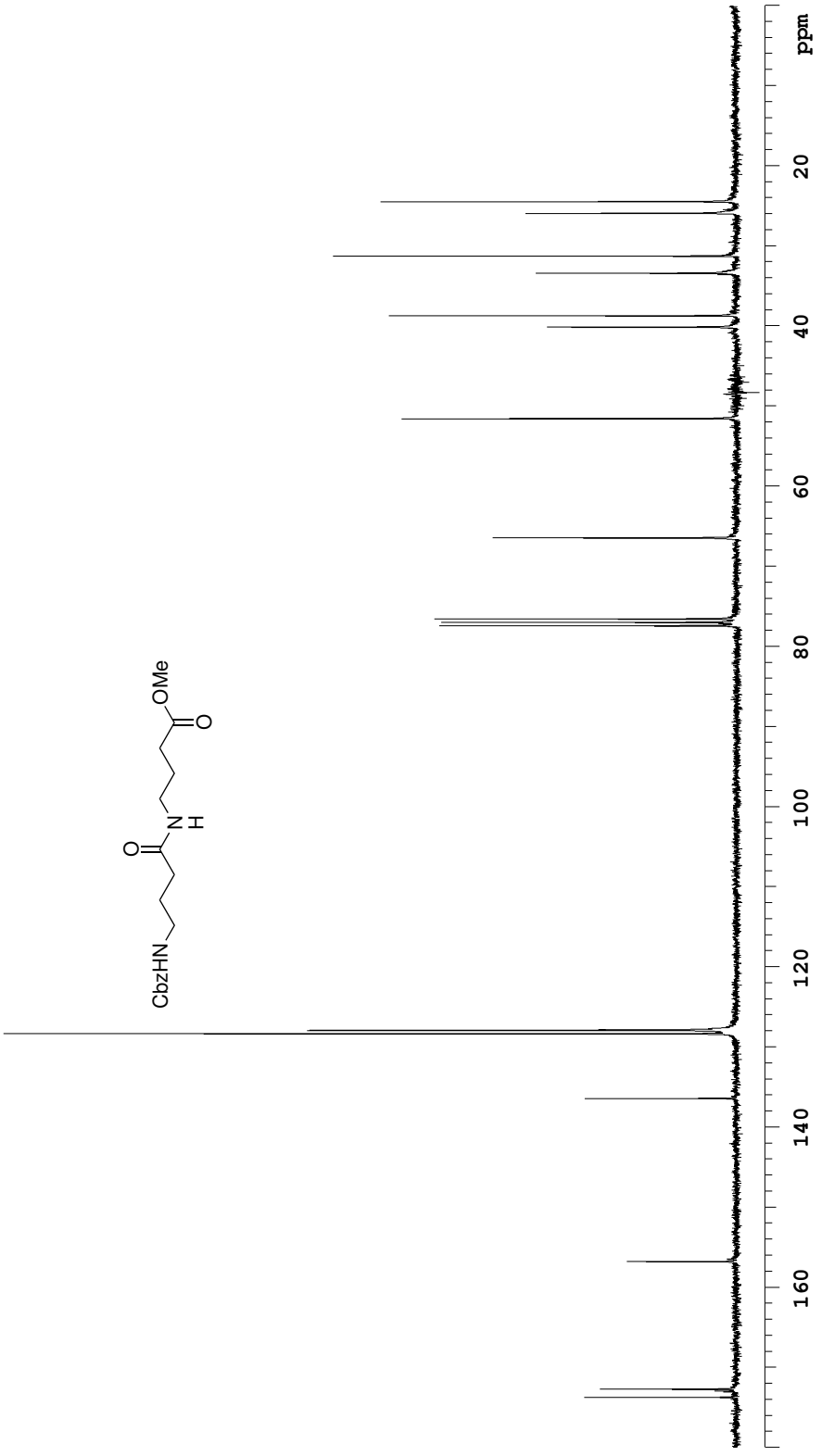
^{13}C NMR spectrum of olefin **166b**



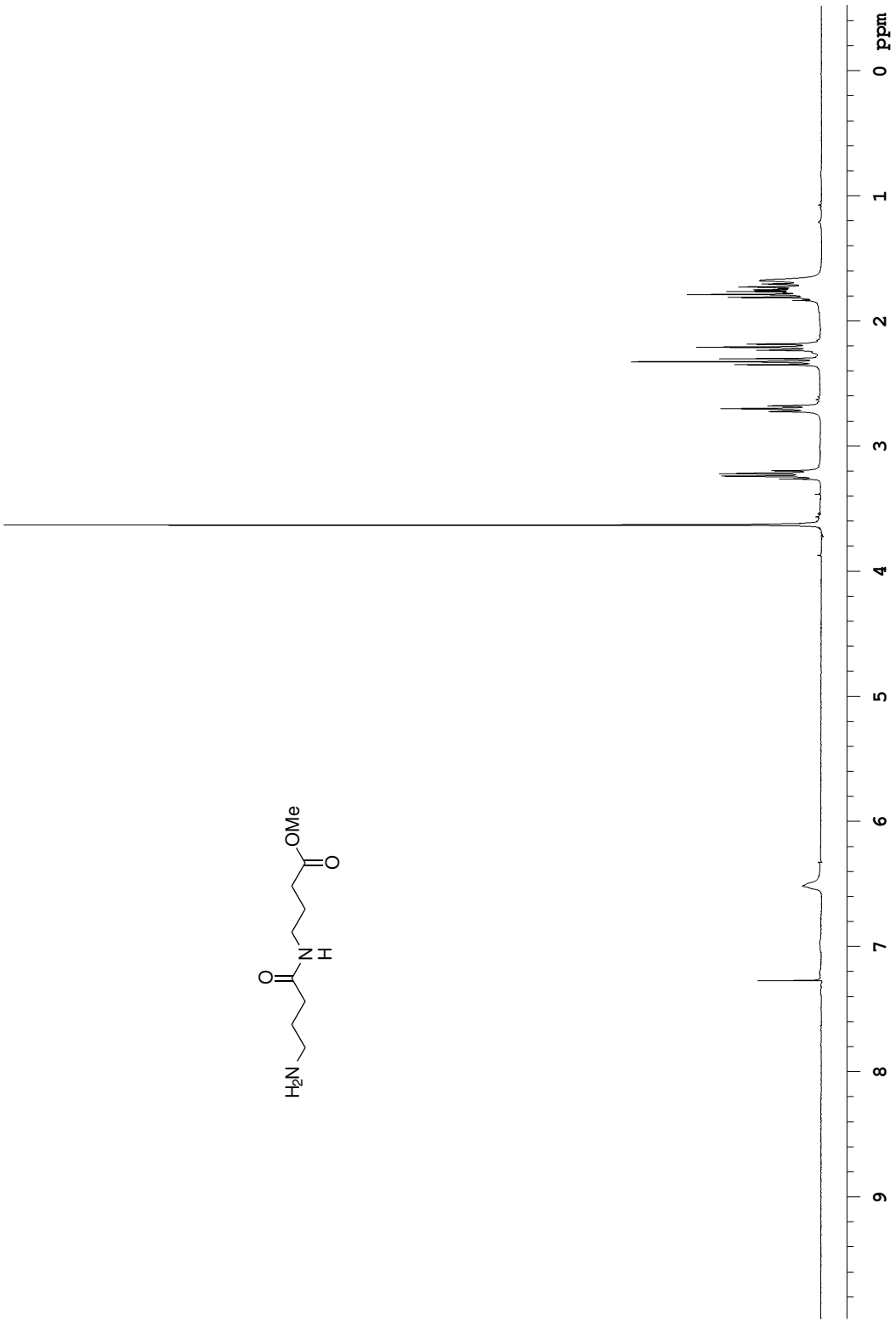
^{1}H NMR spectrum of compound **X**



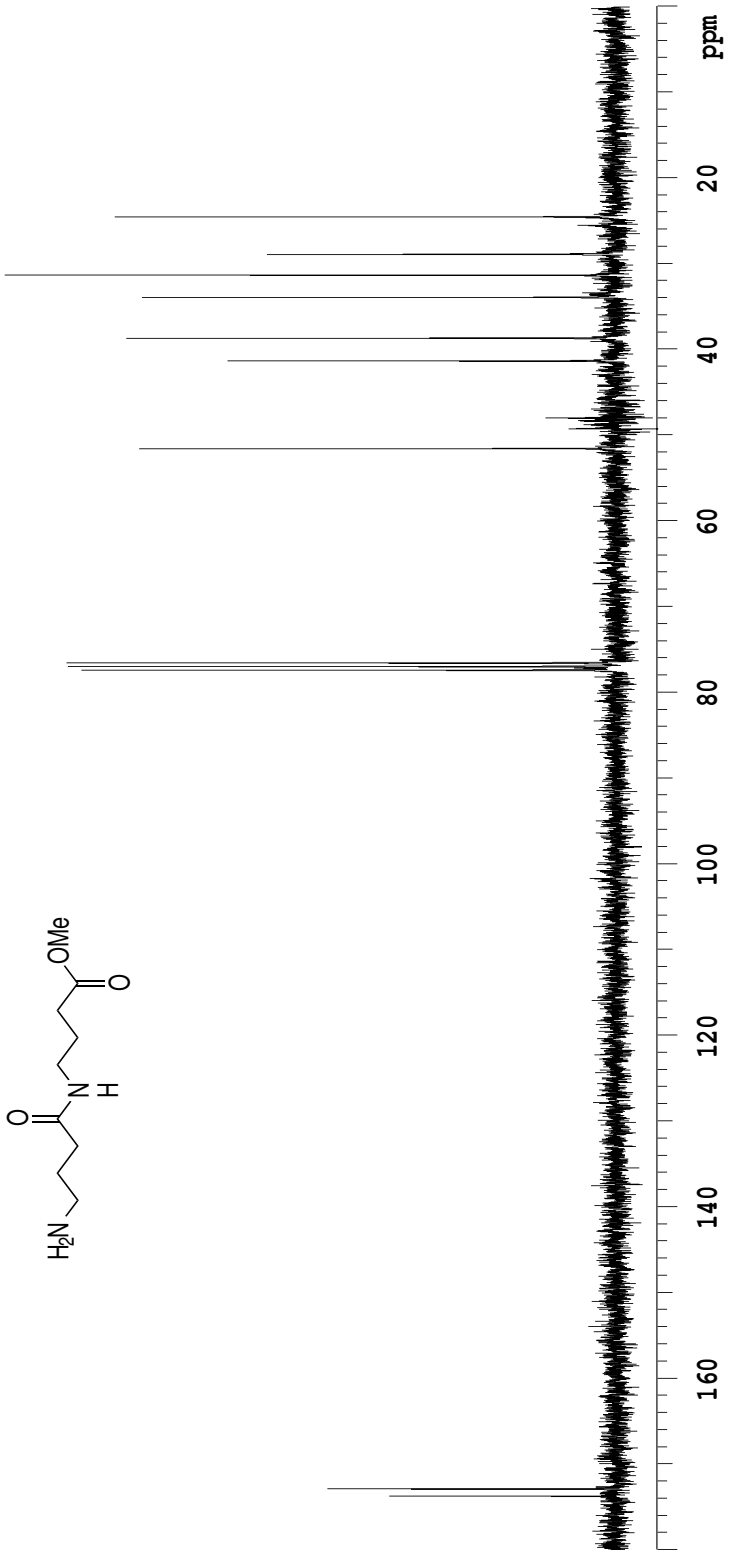
^{1}H NMR spectrum of dipeptide **170**



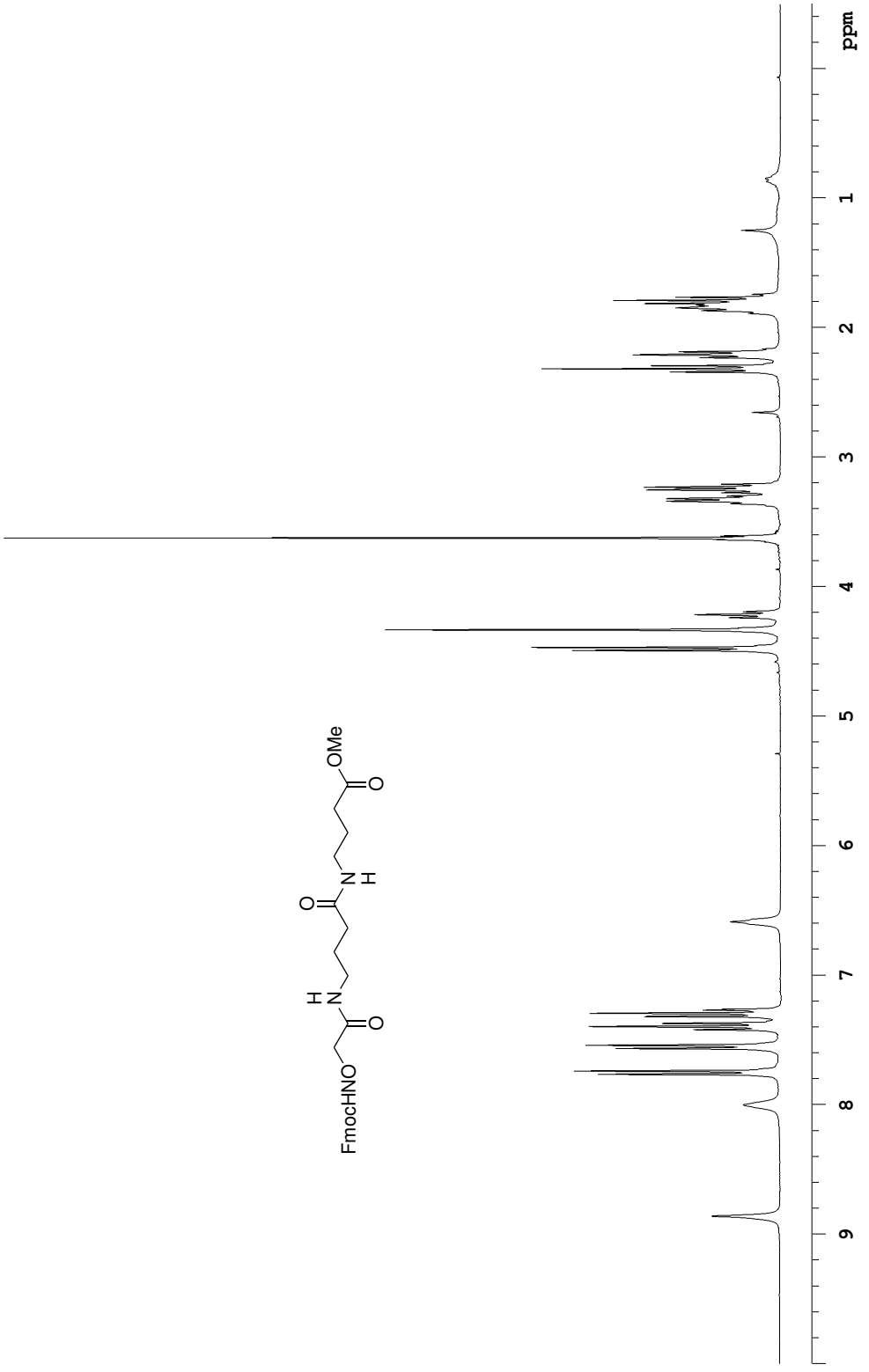
^{13}C NMR spectrum of dipeptide **170**



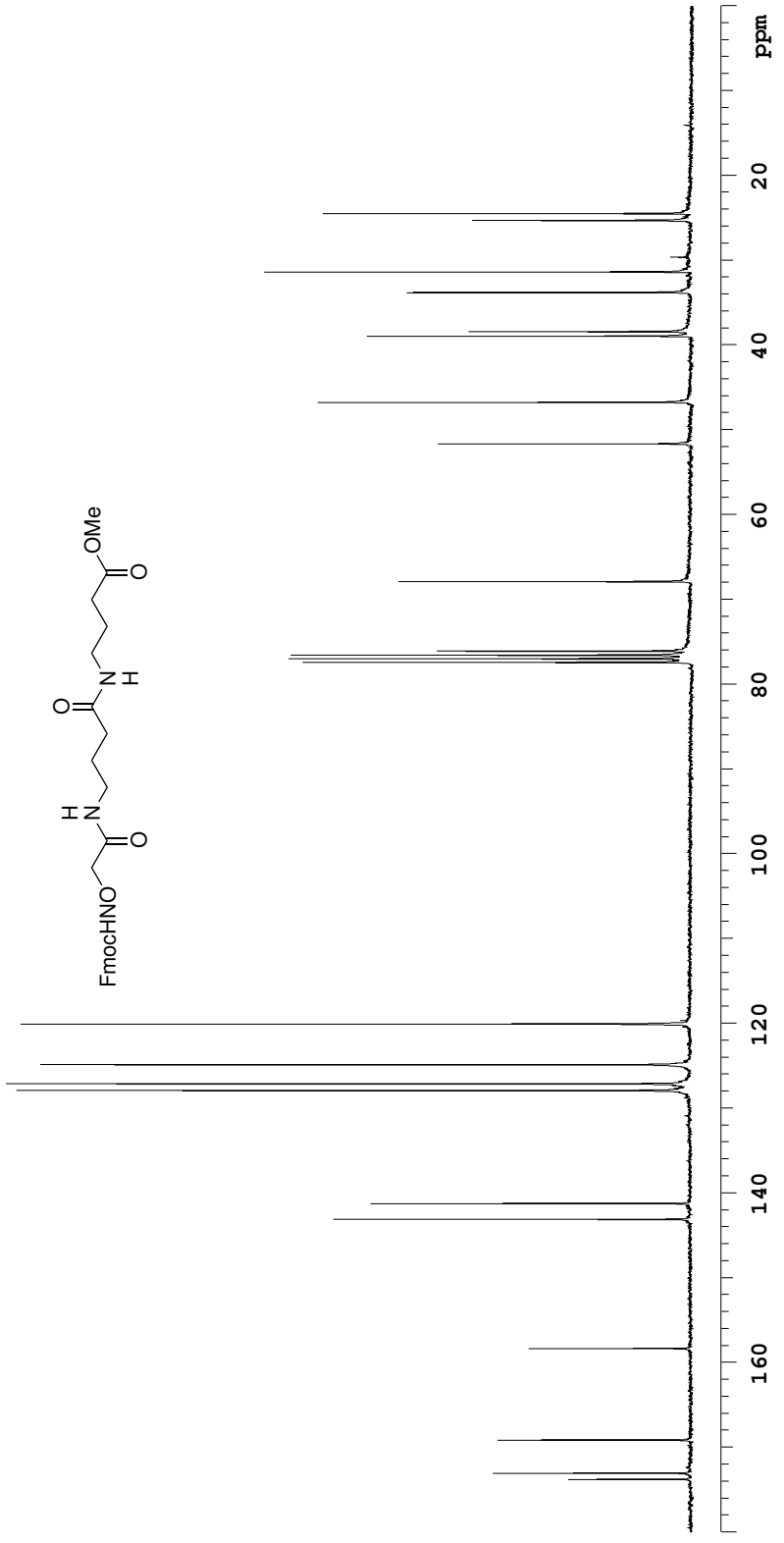
^{1}H NMR spectrum of amine **171**



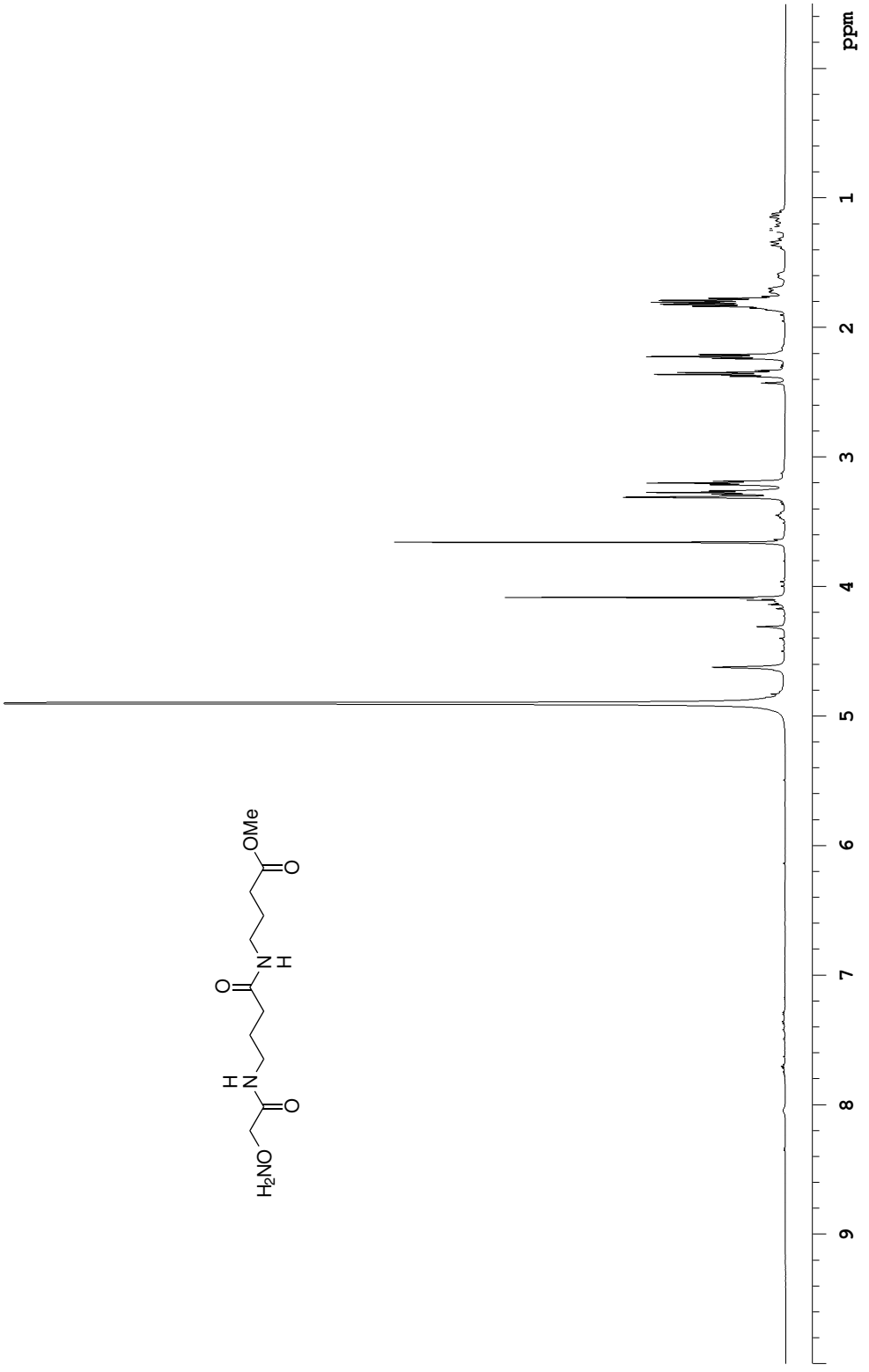
^{13}C NMR spectrum of amine **171**



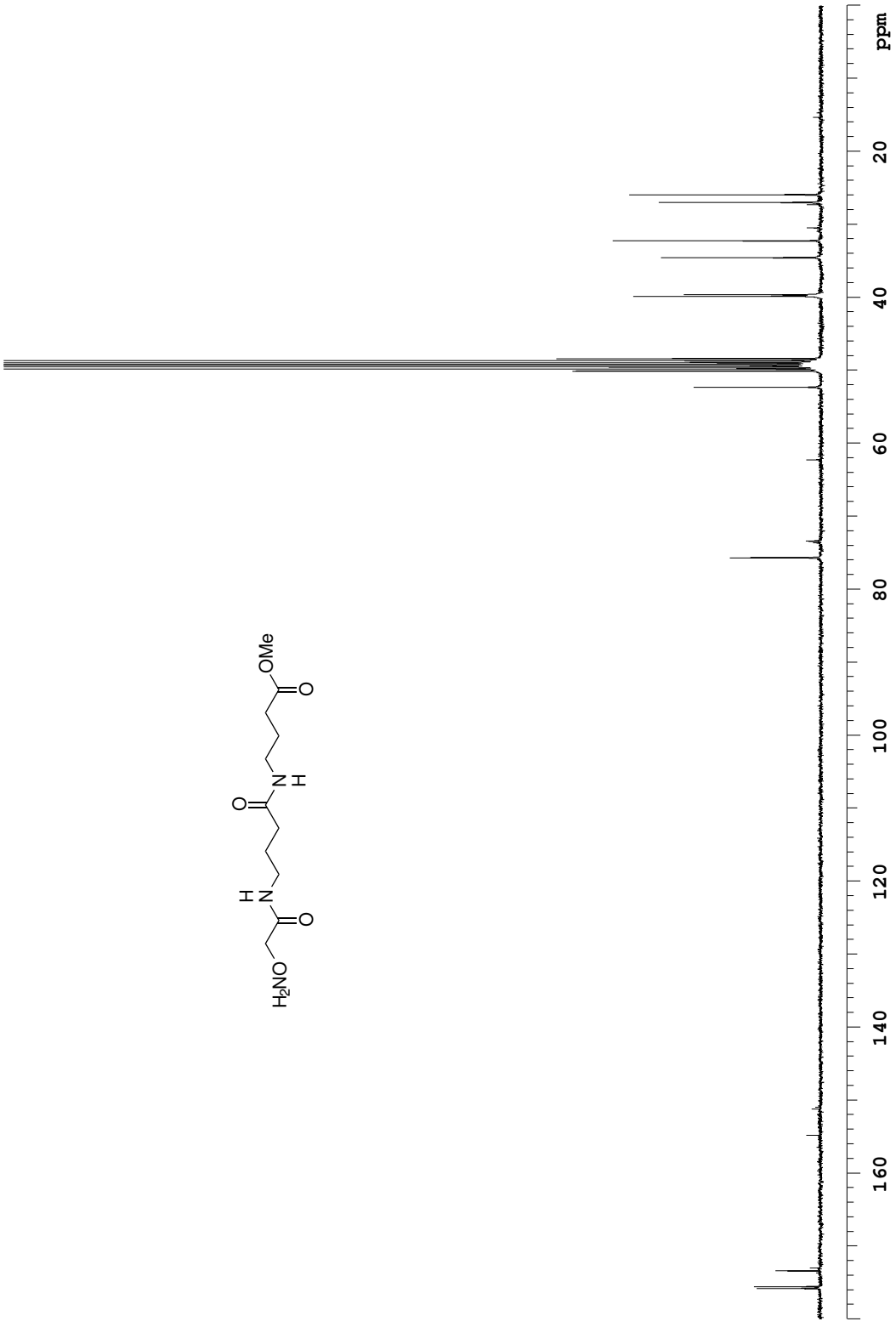
^{1}H NMR spectrum of Fmoc alkoxyamine **173b**



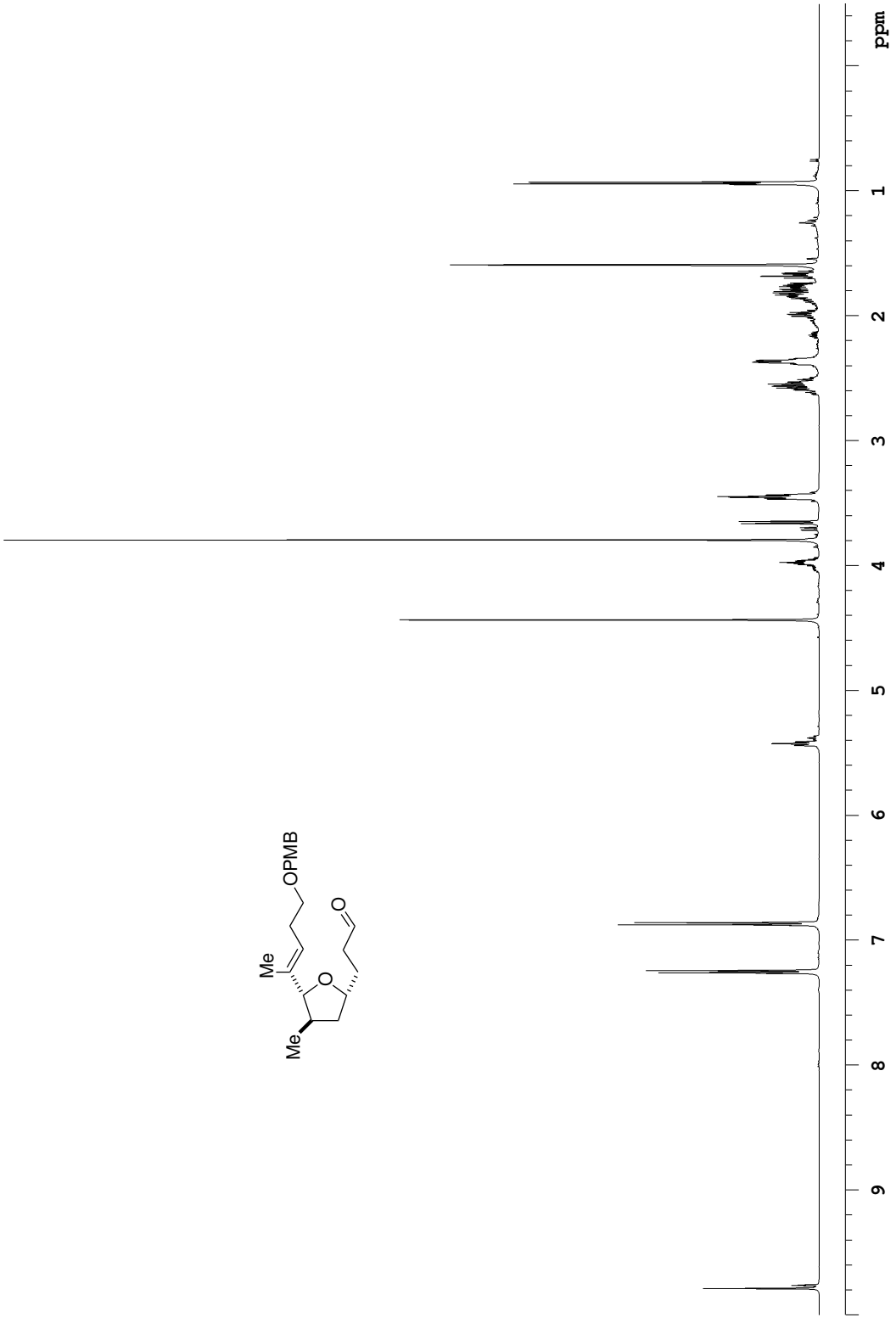
^{13}C NMR spectrum of Fmoc alkoxyamine **173b**



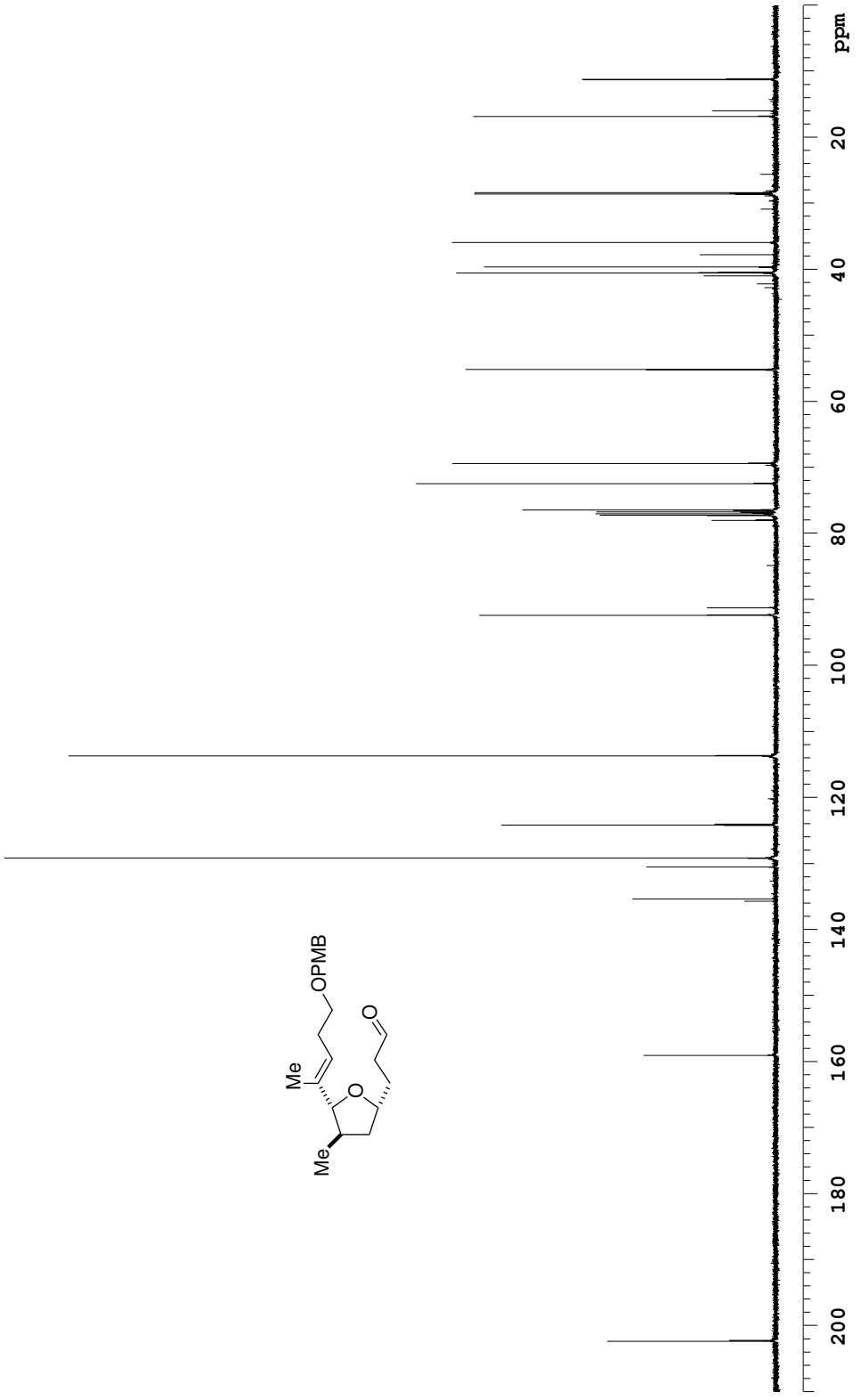
^{1}H NMR spectrum of alkoxyamine **175**



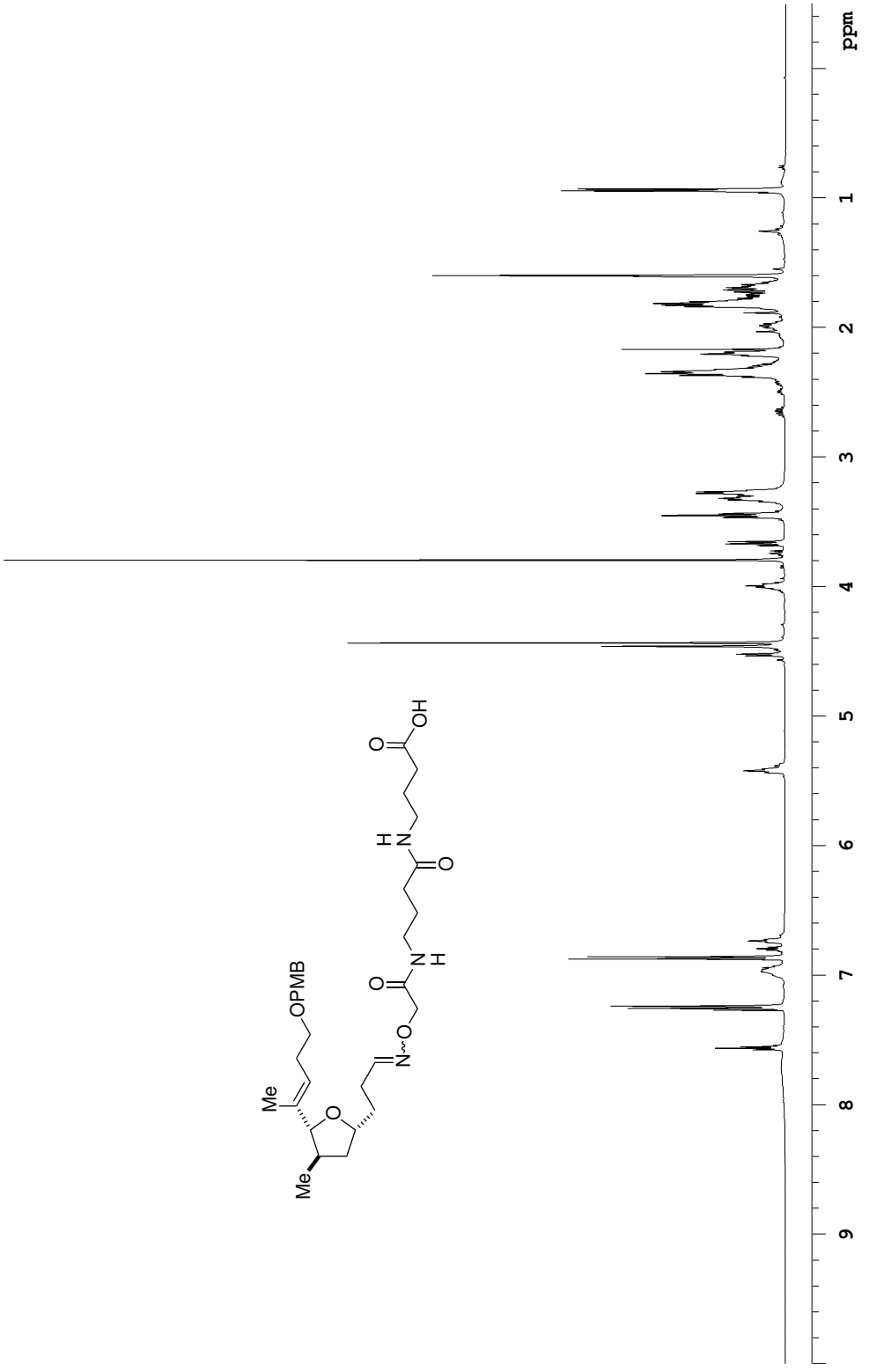
^{13}C NMR spectrum of alkoxyamine **175**



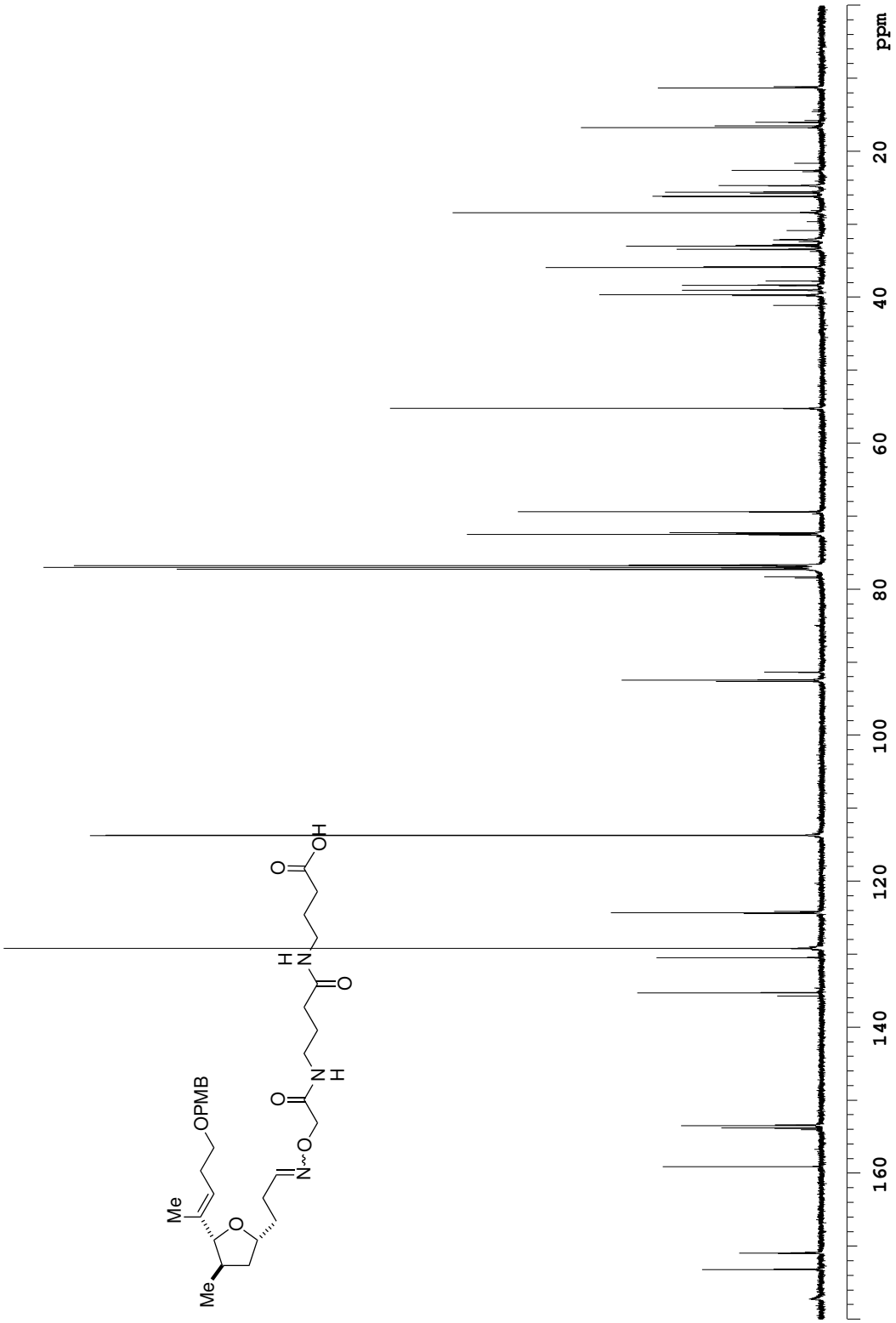
^{1}H NMR spectrum of aldehyde **179**



^{13}C NMR spectrum of aldehyde **179**



^{1}H NMR spectrum of oxime ether **180b**



^{13}C NMR spectrum of oxime ether **180b**

APPENDIX B

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	(b) Kong, K.; Moussa, Z.; Romo, D. Studies toward a Marine Toxin Immunogen: Enantioselective Synthesis of the Spirocyclic Imine of (–)-Gymnodimine. *Org. Lett*. **2005**, *7*, 5127-5130.