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INTRAMOLECULAR ANODIC OLEFIN COUPLING REACTIONS: SYNTHESIS OF NITROGEN- AND OXYGEN-HETEROCYCLES

By

Haichao Xu

A dissertation presented to the

Graduate School of Arts and Sciences

of Washington University in

partial fulfillment of the

requirements for the degree

of Doctor of Philosophy

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ABSTRACT

INTRAMOLECULAR ANODIC OLEFIN COUPLING REACTIONS: SYNTHESIS OF NITROGEN- AND OXYGEN-HETEROCYCLES

By

Haichao Xu

Doctor of Philosophy in Chemistry

Washington University in St. Louis, 2010

Professor Kevin D. Moeller, Chairperson

Anodic oxidation has been shown to be a powerful method for initiating umpolung reactions that allow the coupling of two nucleophilic functional groups. Most of the work in this area concentrates on making carbon-carbon bond. Hence, the reactions are usually terminated with olefin nucleophiles. The use of heteroatom-based coupling partners to form carbon-heteroatom bond is less explored despite the wide occurrence of heterocyclic compounds as natural products, pharmaceuticals, and synthetic building blocks. Therefore, this thesis focuses on the application of heteroatom-based coupling partners in intramolecular anodic olefin coupling reactions for the synthesis of N- and O-heterocyclic compounds.

First, a synthesis of (-)-crobarbatic acid was accomplished in 10 steps by employing as the key step anodic coupling of an alcohol and a ketene dithioacetal. The key to the

success of the oxidative cyclization reaction is the use of lithium methoxide as a base instead of the commonly used weak base, 2,6-lutidine. The synthesis demonstrates that a vinyl substituted ketene dithioacetal is compatible with anodic cyclizations and that it is possible to reverse the stereochemistry of the newly formed stereogenenic center in the electrolysis product.

Next, the anodic coupling of sulfonamides and electron-rich olefins was developed in order to build cyclic amino acid derivatives. Low yields were obtained under reaction conditions employing 2,6-lutidine as a base. However, with the use of a stronger base, LiOMe, a variety of electron-rich olefins such as enol ethers, vinyl sulfides, ketene dithioacetals, and allylsilanes, are compatible with the cyclizations affording proline and pipecolic acid derivatives in good to excellent yields and diastereoselectivity. The mechanism of the reactions under the basic reaction conditions was investigated using competition studies.

The harsh reaction conditions associated with the removal of the tosyl group from the electrolysis products prompted us to study the use of primary amines as coupling partners. The oxidative coupling of unprotected amines with ketene dithioacetals afforded proline and pipecolic acid derivatives with α-tetrasubstituted carbon atoms despite the oxidation potential of the product being significantly lower than either functional group in the substrate. The competing oxidation of the product was avoided because the oxidation potential of the substrate is lowered by a fast cyclization.

One of the limitations of the oxidative cyclization reactions is the failure to afford cyclic amino acids that do not have α-tetrasubstituted carbon atoms. Hence, a

complementary method, base induced intramolecular hydroamination of ketene dithioacetals, was developed to address this issue. The catalytic cyclizations afforded both five and six-membered ring products with an aldehyde equivalent at C2 in excellent yield and diastereoselectivity.

Amides such as O-benzyl hydroxamate and N-phenyl amides were employed successfully in intramolecular anodic olefin coupling reactions to provide lactams. This study demonstrates that amidyl radicals can be generated easily from N-H amides using anodic oxidation. Compared with established methods for the generation of amidyl radicals, which usually involve the fragmentation of amide derivatives under relative high temperatures, the electrochemical oxidation method generates amidyl radicals at room temperature and avoids the preparation of amide derivatives, which are usually unstable and hard to prepare.

In addition to the synthesis of N-heterocycles, carboxylic acids were used as nucleophiles in anodic coupling reactions to provide lactones with a carbonyl equivalent at the C2 position. Such structures can be found in many natural products. The cyclizations afforded both γ-butyro- and δ-valerolactones in good to excellent yields and diastereoselectivity.

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ABBREVIATIONS AND SYMBOLS

br	broad (NMR)
Bu	butyl
Boc	*tert*-butoxycarbonyl
cm^{-1}	wave number (IR)
CV	cyclic voltammetry
δ	chemical shift in ppm
d	doublet
DIPEA	diisopropylethylamine
DMAP	dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
ESI	electrospray ionization
Et	ethyl
equiv	equivalent
F	faraday
g	gram

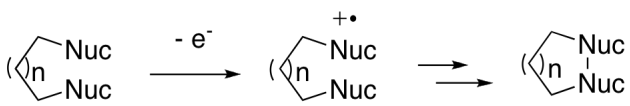
Hz	Hertz
IR	Infrared Spectroscopy
J	scalar coupling constant
LAH	lithium aluminum hydride
LDA	Lithium diisopropylamide
m	multiple (NMR)
mA	milliamperes
Ms	mesylate
m/z	mass to charge ratio
NCS	N-chlorosuccinimide
PCC	pyridinium chlorochromate
q	quartet (NMR)
t	triplet (NMR)
TBS	tert-butyldimethylsilyl
TLC	thin layer chromatography
V	volt

Chapter 1 Introduction

Electrochemical oxidation is a powerful tool for removing electrons from organic molecules and triggering interesting umpolung reactions.[1,2] By controlling the applied potential or current, electrons can be removed from desired reaction site in a highly selective fashion under relatively mild conditions (e.g., room temperature, normal pressure, neutral pH etc.). Because of the adjustable feature of the current, the concentration of the transient species (proportional to current density) such as radicals or radical ions can be generated in a controlled rate. Also by adjusting the electrode potential, a large range of functional groups can be oxidized at the same electrode. Anodic oxidation avoids the use of stoichiometric chemical oxidants that are usually toxic and/or expensive and produce a stoichiometric amount of waste. Thus, electrochemistry has potential environmental and economic benefits.

The removal of electrons from organic molecules generates reactive intermediates such as radicals or radical cations.[1] These species can fragment, be used as reagents, or couple with another nucleophilic functional group.[1] Research described in this thesis falls into the last category and focuses on intramolecular trapping of the anode-generated radicals and radical cations by electron-rich olefins.[1e] These reactions result in the net coupling of two nucleophilic groups to form a cyclic compound that would otherwise require multiple steps to synthesize (Scheme 1-1).

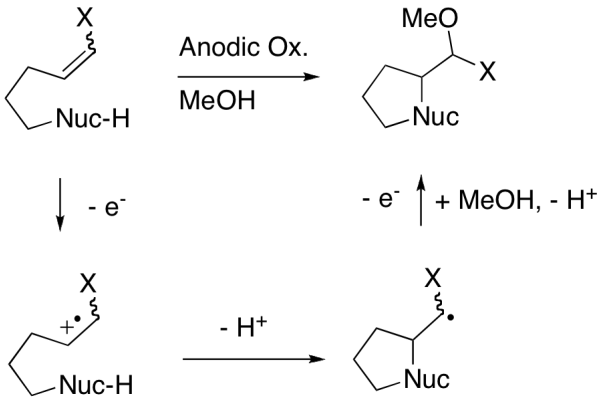
Scheme 1-1 Anodic Induced Umpolung



1.1 Intramolecular Anodic Olefin Coupling Reactions

A general intramolecular anodic olefin coupling reaction of interest is depicted in Scheme 1-2.[1e] In the substrate, an electron-rich olefin is tethered to a nucleophilic functional group, which could be another electron-rich olefin (or aromatic ring) or a heteroatom-based nucleophile. Removal of an electron from the electron-rich olefin at the anode produces a radical cation. Subsequent trapping of the electron-deficient intermediate by the internal nucleophile followed by losing an proton leads to a cyclized radical. Further oxidation of the radical and reaction with methanol solvent furnishes the final product. Of course, the reaction can also be initiated by the oxidation of the nucleophile instead of the olefin.[3] Both cyclizations lead to the same product.

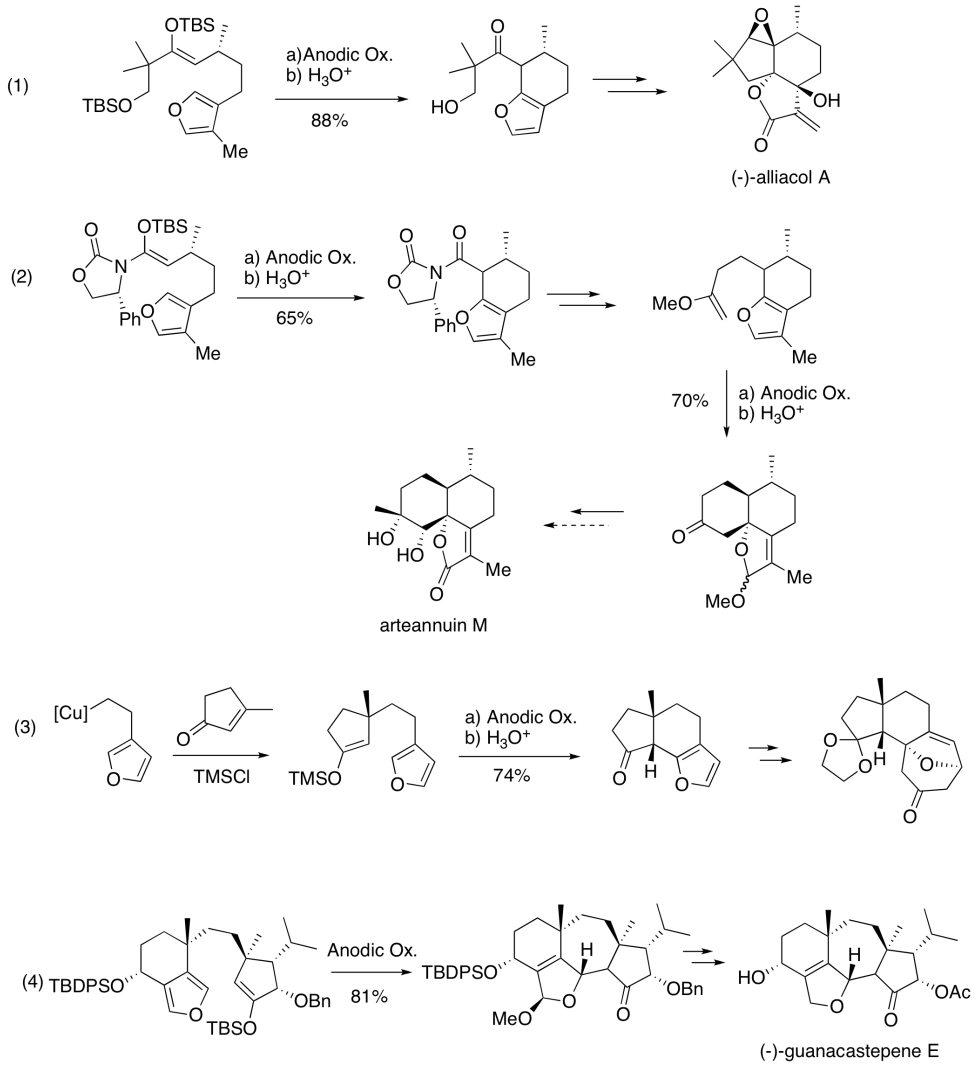
Scheme 1-2 Intramolecular Anodic Olefin Coupling Reaction



In these reactions (Scheme 1-2), new bonds and ring skeletons are generated and the functional groups used to initiate the reactions are preserved and available for further manipulations. For example, the electron-rich olefin, an aldehyde equivalent, leads to an acetal in the product (Scheme 1-2). These features of anodic olefin coupling reactions indicate great potential for application in synthesis of complex molecules.

The Moeller group has systematically studied the intramolecular anodic coupling reactions.[1e] They have shown that the cyclizations can be initiated by the oxidation of a

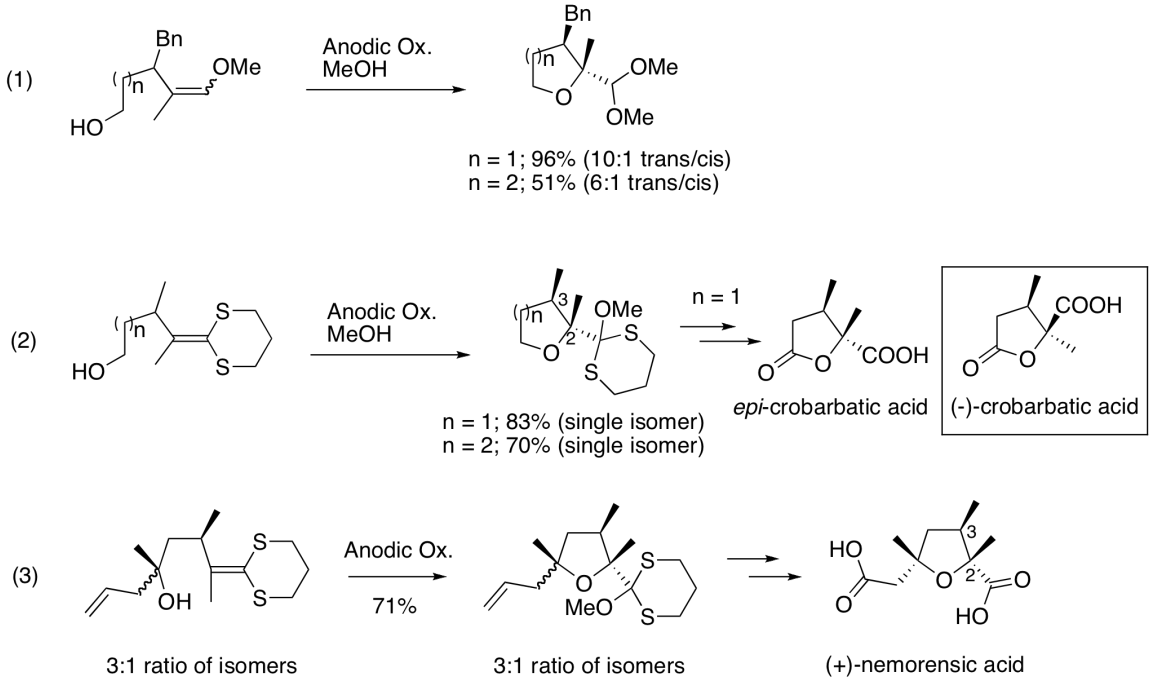
Scheme 1-3 Application of Anodic Coupling Reactions in Synthesis



host of electron-rich functionalities such as electron-rich phenyl rings,[4] furans,[4] enol ethers,[5] ketene acetals,[6] and allylsilanes.[7] Trapping of the radical cation produced at the anode by carbon-based nucleophiles such as electron-rich aromatics, enol ethers, allyl- and vinylsilanes has been studied by the Moeller group to make new ring skeletons.[4-7,8]

The mild and selective nature of the electrochemical protocol was captured both by the Moeller group and others and implemented in the synthesis of alliacol A,[9] arteannuin M[6h], the cyathin-core ring skeleton,[10] and guanacastepene[11] (Scheme 1-3). The synthesis in reaction (4) (Scheme 1-3) is remarkable because it demonstrates that anodic olefin coupling reactions can be employed not only in an early stage of a synthesis but also at a very late stage with complicated substrates.

Scheme 1-4 The Use of Alcohol Trapping Groups in Anodic Coupling Reactions



While the formation of C-C bonds using electrochemical protocols have been extensively studied, the use of heteroatom-based coupling partners to afford heterocyclic compounds is less explored. Nonetheless, alcohols have been shown by the Moeller group to be effective trapping groups for enol ether[12] and dithioketene acetal[12] derived radical cations (Scheme 1-4). These reactions afford cyclic ethers with a carbonyl derivative at the C-2 position in high yield and diastereoselectivity. With the use of

dithioketene acetal as the electron-rich olefin, the products were obtained as a single diastereomer with the dithio orthoester *trans* to the methyl at C3 position.[13] The stereochemistry was controlled by steric interactions between the allylic methyl and the dithiane group. The Moeller group implemented this reaction as a key step in their synthesis of (+)-nemorensic acid (equation 3, Scheme 1-4).[13]

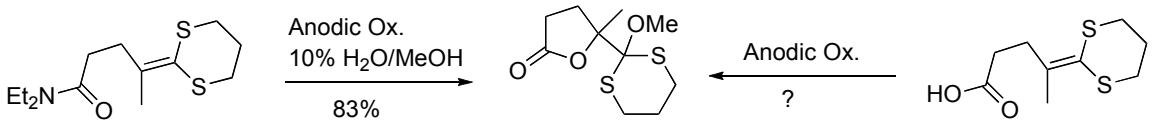
While the reactions described above are ideal for the synthesis of structures like (+)-nemorensic acid, they would give the wrong stereochemistry for compounds like (-)-crobarbatic acid[14] as demonstrated by Moeller and Brandt[15] (equation 2, Scheme 1-4). In this case, the obtained structure has the C2-stereochemistry opposite to that of (-)-crobarbatic acid. Hence, it calls for another strategy to access stereochemistry presented in (-)-crobarbatic acid. Chapter 2 of this thesis is devoted to solving this problem and expanding the scope of the electrolysis reactions in the context of the synthesis of (-)-crobarbatic acid.

The success of including alcohols as trapping groups for radical cations raised the question if nitrogen-based nucleophiles could be employed as coupling partners.[16] If successful, these reactions would provide versatile routes to cyclic amino acid derivatives and peptidomimitics.[17-19] The quest to answer this question is described in Chapters 3, 4, 5, 6 and 8.

In 2002, the Moeller group reported the use of a dialkylamide as nucleophile in intramolecular anodic coupling reactions for the synthesis of lactones with a carbonyl equivalent at C2,[13] the skeleton of which is found in many natural products.[20] The reactions take advantage of the nucleophilic nature of the carbonyl oxygen atom of the

amide group. The iminolactone formed was hydrolyzed to the lactone *in situ* by addition of water to the reaction mixture (Scheme 1-5).[6d] Another possible approach to such structures would be the use of a carboxylic acid as the coupling partner (Scheme 1-5, reaction on right). The results of this method were discussed in Chapter 9.

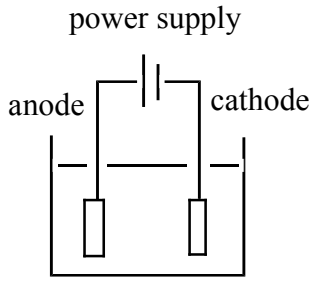
Scheme 1-5 Synthesis of Lactones



1.2 Practical Aspects of Preparative Electrolysis

A typical experimental setup for electrolysis consists of an electrolysis cell and a DC power supply (Figure 1-1).[1] The cell contains the electroactive species, solvent, electrolyte, and at least two electrodes (an anode and a cathode). Two types of cells are usually used

Figure 1-1 Electrolysis Setup



in electrolysis reactions. One is a divided cell, which contains two chambers separated by a semi-permeable membrane. This type of cell is used when products produced at the counter-electrode interfere with the reaction at the electrode of interest. The most

frequently used electrolysis cell in the Moeller group is an undivided cell, which can be as simple as a beaker or a round bottom flask. The power supply is used to provide and regulate current.

All sorts of conducting materials can be used as electrodes.[1a,b] For an anode, high resistance to corrosion is generally required. Hence, materials such as carbon and platinum are generally used. Electrolysis reactions in this thesis are all conducted with a reticulated vitreous carbon (RVC) anode. RVC is sponge-like glassy carbon with high surface area. Since it is chemical resistance, RVC is a frequently used electrode. The cathode reaction in the olefin coupling reactions generally involves the reduction of alcoholic solvents to produce hydrogen gas and alkoxide. Hence, materials with low hydrogen overvoltage such as platinum are generally preferred.

A wide range of solvents, such as methanol, isopropanol, tetrahydrofuran, dichloromethane, and acetonitrile can be used for electrolysis reactions.[1a,b] Most anodic coupling reactions use either methanol or methanol in combination with other non-protic solvents such as tetrahydrofuran and dichloromethane. Methanol is included both to serve as a reactant in the electrolysis reaction and to produce methoxide at the cathode to neutralize the acid generated at anode.

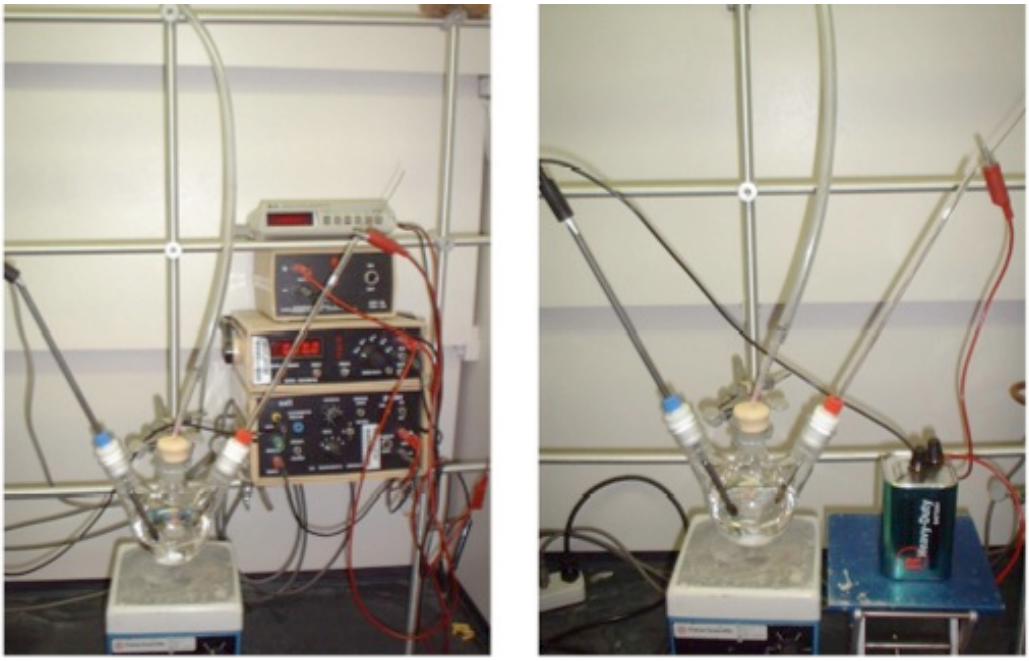
Electrolytes are usually employed in electrolyses to increase the conductance of the solution. Two of the most frequently used electrolytes in the Moeller group are tetraethylammonium tosylate and lithium perchlorate. These two electrolytes have high solubility in the organic solvents commonly used for electrolysis, are electrochemically stable over a wide range of potentials, and are easy to remove with an aqueous workup.

There are two major methods to regulate the current flow through the cell. One is controlled potential electrolysis; the other is a controlled current electrolysis. For the former, the potential of the working electrode is held constant relative to a reference electrode throughout the electrolysis. By careful control of the potential, selective oxidation of one functional group in the presence of many electroacitve sites can be realized. This method usually offers better selectivity over the alternative, controlled current electrolysis. However, as the substrate is consumed, the resistant across the cell increases and the current drops. As the current decreases, it takes a longer time to oxidize (in our case) the substrate. Hence, the time required for complete consumption of the substrate in a constant potential electrolysis is usually much longer than that for a controlled current electrolysis. All the anodic coupling reactions studied in this thesis employed the later method, the constant current electrolysis. In such experiments, the current passing through the cell is held constant. The electrode potential increases until it reaches the potential of the first electroactive species. The potential then stays relatively constant until the consumption of this substrate. Once the first substrate is consumed, the electrode potential climbs until a second electroactive species or solvent can be oxidized. For most of the electrolyses we investigated, the electrolysis products are either electrochemical inactive or have potentials much higher than that of the starting material. Hence, selectivity was not an issue and the constant current method employed due to its ease of operation and the relative short time it requires to finish the reaction.

A typical electrolysis setup for controlled current electrolysis in the Moeller group is shown on the left side of Figure 1-2. In this case, a three-neck flask was used as the electrolysis cell. The power supply consists from top to bottom of an ammeter, an AC/DC

converter, a coulometer and a potentiostat. The ammeter reads the current passing through the cell and the coulometer counts the charge that has been passed. Although most of the electrolysis reactions in this thesis are operated using this setup, simpler power supplies such as a 6V-lantern battery can also be used (right picture, Figure 1-2).[21]

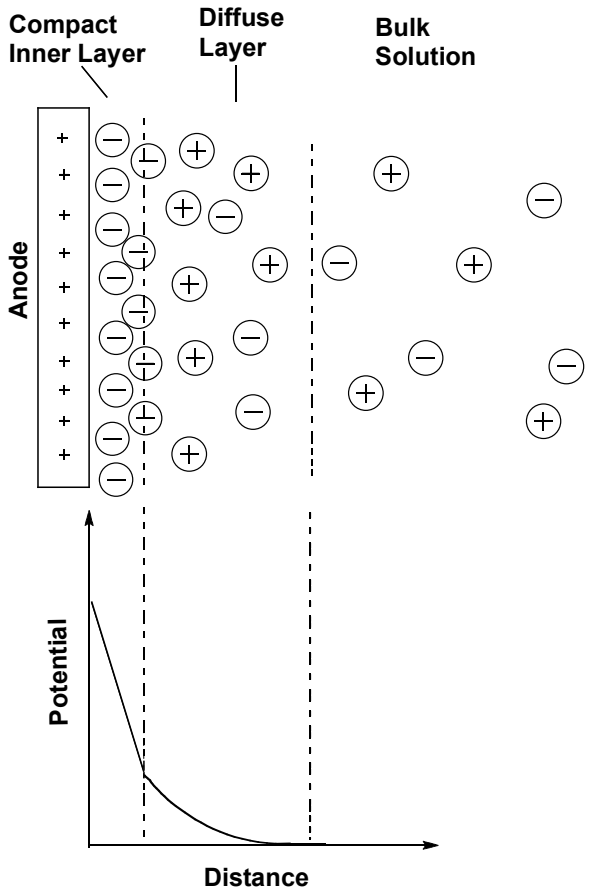
Figure 1-2 Electrolysis Setup Used in This Thesis



For the reaction described in Scheme 1-2, two electrons are required for conversion of the substrate to product. The theoretical amount of charges needed for a two-electron oxidation reaction equals $2nF$ (coulomb), where n is the mole of substrate and F is Faraday constant and equals 96455 C mol^{-1}. If the current is held constant and assuming 100% current efficiency, the time needed to complete the electrolysis can be calculated from $t = 2nF/3600I$ (h), where I is the current in ampere (A).

When potential is applied, the anode becomes positively charged (Figure 1-3). To balance the charges, negative ions would be attracted from the solution to form a tight negatively charged layer, which in turn attracts cations to form a second layer of ions. The electron density in the second layer is significantly reduced compared with the inner layer because the positively charged anode compensates most of the charges. As a result, the ions in the second layer tend to diffuse away into the bulk solution. Hence, this layer is usually referred to as the diffuse layer. The compact inner layer and the diffuse layer constitute the electrochemical double layer, the thickness of which can be anywhere from

Figure 1-3 Electrochemical Double Layer



a few tens to hundreds of Ångstroms.[1c] The potential drops from the electrode first linearly in the inner layer and then exponentially in the diffuse layer and reaches that of the bulk solution at the outermost boundary of the diffuse layer. The oxidations we investigated occur in the double layer. The cyclizations are usually kinetically faster than diffusion of the oxidized species away from the electrode into the bulk solution. In the double layer, solvent concentration is reduced. Hence, the double layer serves to protect highly reactive species, such as radical cations, from nucleophilic solvents (methanol in our case). This "buys" more time for the intramolecular cyclizations. As a result, special attention should be paid to the parameters that affect the double layer structure if optimization of reaction conditions is required.

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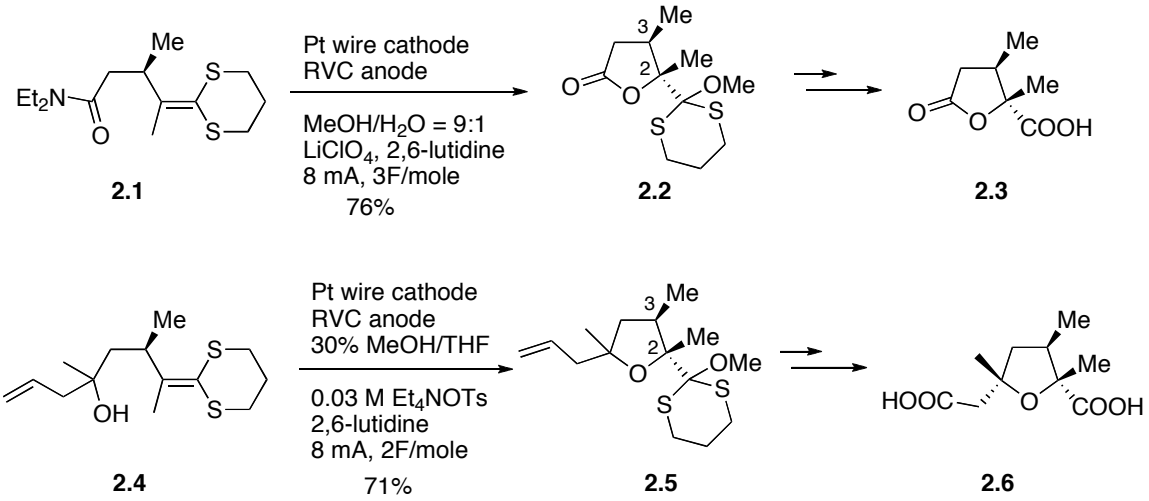
Chapter 2 Expanding the Scope of Anodic Coupling Reactions and the Synthesis of (-)-Crobarbatic Acid[1]

2.1. Introduction

Anodic oxidation of electron-rich olefins readily produces highly reactive radical cation intermediates.[2-3] Because of the high reactivity of these species, intramolecular anodic olefin coupling reactions were used to generate a variety of quaternary and tetrasubstituted carbons.[4] For instance, the anodic coupling reaction between a diethylamide and a ketene dithioactal was used in the synthesis of 2-*epi*-crobarbatic acid (**2.3**).[5] In another example, (+)-nemorensic acid (**2.6**) was synthesized by employing an anodic coupling of a hydroxyl group and a ketene dithioacetal as the key step.[4d]

Scheme 2-1 Stereoselectivity of Anodic Coupling Reactions

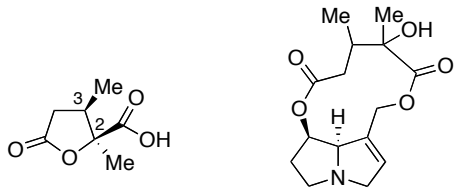


RVC = Reticulated Vitreous Carbon

In both of the anodic coupling reactions shown and many presented in the following chapters of this thesis, the stereochemistry of the newly formed tetrasubstituted-carbon

atom (C2) was controlled by sterics with the large dithioorthoester winding up *trans* to the methyl group at C_3. The natural propensity of the electrolysis reactions to put the two methyl groups *cis* to each other calls for a strategy to address the stereochemistry of structures like (-)-crobarbatic acid that has two *trans* methyl groups.[6]

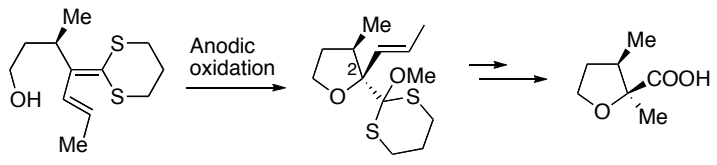
Figure 2-1 Structure of (-)-crobarbatic acid and crobarbatine



2.7 (-)-Crobarbatic Acid **2.8** Crobarbatine

Hence, (-)-crobarbatic acid was chosen as a platform for us to develop new chemistry that will overcome the stereochemical limitations of the electrolysis reaction. Crobarbatic acid (**2.7**, Figure 2-1) is the hydrolysis product of the pyrrolizidine alkaloid crobarbatine (**2.8**, Figure 2-1).[7] While the relative stereochemistry of crobarbatic acid has been shown to bear two *trans* methyl groups, its absolute stereochemistry is still unknown.[6] The interesting biological properties of pyrrolizidine alkaloids such as hepatotoxic and carcinogenic activities have ensured continuous efforts in the synthesis of such compounds.[8]

Scheme 2-2 Proposed Strategy for Reversing Stereochemistry of C2



2.9 **2.10** **2.11**

One method for solving the stereochemistry problem that posed by crobarbatic acid

would be to incorporate functional groups into the electrolysis substrate that would allow for manipulation of product stereochemistry after the cyclization. For instance, if a vinyl substituted ketene dithioacetal such as **2.9** were used for the electrolysis, product **2.10** would be obtained. Oxidation of the olefin in **2.10** to a carboxylic acid and reduction of the dithioorther ester to a methyl group would furnish compound **2.11** that has two *trans* methyl groups needed for the synthesis of crobarbatic acid.

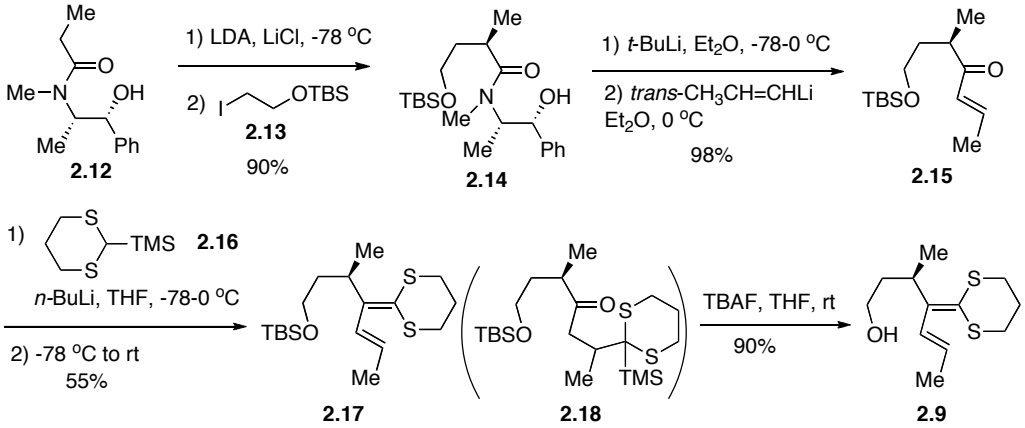
The use of a vinyl-substituted ketene dithioacetal was attactive in several aspects. First, the vinyl substituent would lower the oxidation potential of the electron-rich olefin and help the anodic oxidation. Furthermore, the oxidation of the vinyl group to carboxylic acid and the tetrahydrofuran ring to a lactone might be conducted in one step. In addition, we wanted to know the reactivity of a vinyl-substituted radical cation, which had not been investigated. Earlier work from the Moeller group had shown that the reactivity of a radical cation can be changed significantly by its substituents.[4a]

2.2 Synthesis of the Electrolysis Substrate

Our study commenced with the preparation of the electrolysis substrate **2.9** as shown in Scheme 2-3. Alkylation of the commercially available pseudoephedrine propionamide (**2.12**) with iodide **2.13** afforded compound **2.14** in 90% yield.[9] Deprotonation of the hydroxyl group with one equivalent of *tert*-butyllithium at -78 ºC followed by reaction with two equivalents of 1-lithium-1-propene yielded ketone **2.15** (98%). Initially three equivalents of *trans*-1-lithium-1-propene were used for both deprotonation and reaction with the amide. However, because of the high cost of the vinyllithium reagent, one equivalent of *tert*-butyllithium was used to replace an equal amount of the vinyllithium for deprotonation. Further decrease of the amount of the vinyllithium reagent resulted in

incomplete reaction. The ketone **2.15** was treated with 0.8 equivalent of the lithium reagent derived from 2-trimethylsilyl-1,3-dithiane to furnish dithioacetal **2.17** in 55% yield.[10] In addition to the desired product, a 1,4-addition product **2.18** was also isolated in 31% yield. Using 1.2 equiv of lithium reagent resulted in a messier reaction with lower yields (40% for **2.17** and 20% for **2.18**). Finally, removal of the silyl protecting group with tetrabutylammonium fluoride (TBAF) afforded the desired electrolysis substrate **2.9** in 90% yield.

Scheme 2-3 Synthesis of Electrolysis Substrate 2.9

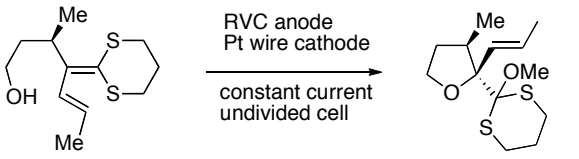


2.3 Electrolysis Reaction

With compound **2.9** in hand, its oxidation was investigated. The reaction was first conducted using the reaction conditions similar to those used for oxidizing **2.6** (Table 2-1).[4d] The electrolysis was carried out at rt in an undivided cell with constant current (8 mA) until the disappearance of the substrate. A Pt wire cathode and a reticulated vitreous carbon (RVC) anode were used as electrodes. The reaction used tetraethylammonium tosylate (Et_4NOTs, 0.1 M) as electrolyte, 30% MeOH/THF as solvent, and six-equivalents of 2,6-lutidine as an acid scavenger to protect the acid labile substrate (Table 2-1, entry 1). Under these reaction conditions, the desired product **2.10** was isolated in

57% yield as a 5:1 ratio of inseparable mixture of diastereoisomers (only the major isomer was shown). Attempts to optimize the reaction by cutting down the methanol concentration and by using dichloromethane as a cosolvent (entry 2) resulted in only diminished yield (20%). Conducting the reaction in a divided cell (entry 3) also failed to increase the yield. In this case, the yield dropped to 15%.

Table 2-1 Optimization of Electrolysis Conditions



2.9 **2.10** (dr = 5:1)

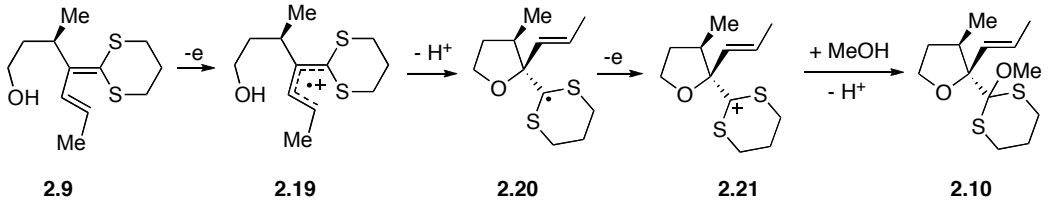
Entry	Conditions	Yield	Entry	Conditions	Yield
1	30% MeOH/THF 0.1 M Et_4NOTs 2,6-lutidine 8 mA, 1.8 F/mole	57%	4	30% MeOH/THF 0.1 M Et_4NOTs 0.5 equiv LiOMe 6 mA, 2 F/mole	72%
2	20% MeOH/CH_2Cl_2 0.1 M Et_4NOTs 2,6-lutidine 8 mA, 1.8 F/mole	20%	5	30% MeOH/THF 0.1 M Et_4NOTs 0.25 equiv LiOMe 6 mA, 2 F/mole	60%
3	divided cell 30% MeOH/THF 0.1 M Et_4NOTs 2,6-lutidine 6 mA, 1.8 F/mole	15%	6	30% MeOH/THF 0.1 M Et_4NOTs 1.0 equiv LiOMe 6 mA, 2 F/mole	61%

Fortunately, the yield of the reaction could be improved by switching the base from 2,6-lutidine to lithium methoxide. With everything else the same but replacing 2.6-lutdine with 0.5 equivalent of LiOMe as the base led to a 72% yield of product (entry 4). It seems that 0.5 equiv of LiOMe was an optimum amount for the reaction. Either lower or higher concentration of LiOMe led to diminished yield (entry 5 and 6).

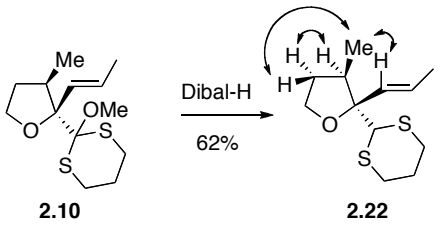
A proposed mechanism of the electrolysis reaction is depicted in Scheme 2-4. Removal of one electron at the anode from ketene dithioacetal afforded radical cation **2.19**, which then cyclized to give radical **2.20**. Further oxidation and reaction with

methanol furnished the final product. Efficient trapping of the radical cation **2.19** by the hydroxyl group before undesirable pathways taking place such as elimination and solvent trapping is critical for obtaining a good yield of the desired product. Also important is the prompt trapping of the cation **2.21** produced after the cyclization with methanol solvent. While the addition of LiOMe increases the competing ability of the solvent for the radical cation and might be detrimental for the reaction, its presence should also enhance the trapping ability of the solvent for the cation **2.21**. The observation that the best yield was obtained with a medium concentration of LiOMe suggested that these conditions reached a balance between the two pathways.

Scheme 2-4 Proposed Mechanism of Oxidation of 2.9



Scheme 2-5 Reduction of 2.10 and Key NOE Interactions in Compound 2.22

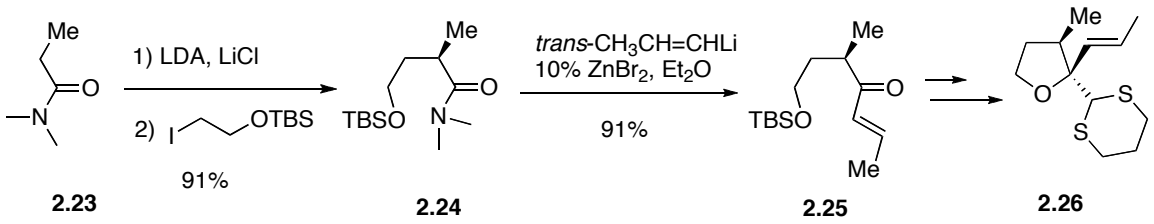


In analogy to earlier cyclization reactions, the major stereoisomer obtained from the anodic cyclization had the large dithioorthoester group *trans* to the methyl at C_3.[4d] This stereochemical assignment was made using nuclear Overhauser effect spectroscopy (NOESY) on compound **2.22**, which was prepared by the reduction of the electrolysis product **2.10** with Dibal-H (Scheme 2-5).[11] The conversion of **2.10** to **2.22** simplified the separation of the two diastereoisomers. It is worth noting that the reduction of **2.10** using

a combination of BF_3 and Et_3SiH afforded **2.22** in less than 40% yield.[12]

In addition to assigning the relative stereochemistry, the entiomeric excess (ee) of **2.22** was measured to check if the stereogenic center at C_3 was epimerized during either the reaction to form the ketene dithioacetal **2.17** or the electrolysis reaction. Racemic material **2.26** was independently synthesized for comparison (Scheme 2-6). HPLC analysis using a chiral stationary phase (CHIRALPAK®ADH) showed **2.22** to have a 97% ee, a value consistent with the alkylation reaction to form **2.14** as reported in the literature.[9]

Scheme 2-6 Synthesis of Racemic 2.26

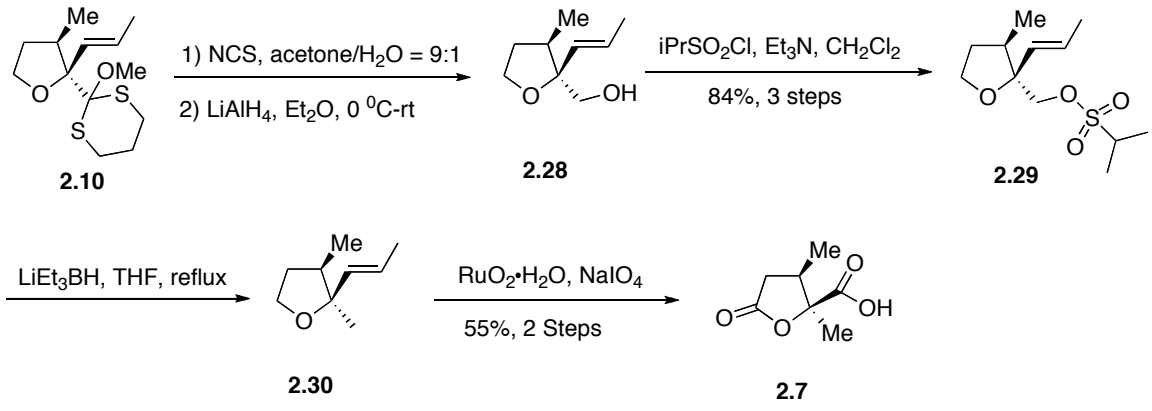


The synthesis of racemic **2.26** is shown in Scheme 2-6. Alkylation of N,N-dimethylpropionamide (**2.23**) followed by reaction with *trans*-1-lithium-1-propene in the presence of 10% Lewis acid catalyst $ZnBr_2$ afforded **2.25** in high yield. The addition of Lewis acid to activate the amide was crucial for the ketone formation reaction. Without the additive $ZnBr_2$, no reaction occurred and the starting dimethylamide was recovered. Under these conditions, dialkylamides react readily with both alkyl- and vinyllithium reagents to afford ketones in excellent yields. Many ketones used in my later studies were prepared using this useful reaction. Conversion of **2.25** to **2.26** was accomplished by following the procedure in Scheme 2-3.

2.4 Finishing the Synthesis

While it was clear that the vinyl substituent is compatible with the cyclization, the question remained as to whether its use would enable the synthesis of a product having the relative stereochemistry found in crobarbatic acid. We initially focused on selective reduction of the dithioacetal in **2.22** to a methyl group in the presence of a disubstituted olefin.[13] A subsquent oxidative cleavage of the olefin to a carboxylic acid would give a product with the correct C2 stereochemistry for crobarbatic acid. However, all attempts to selective remove the dithiane failed. Desulfurization with Raney-Ni in ethanol led to reduction of both the dithioacetal and the olefin. While it was reported that trisubstituted olefins were stable under such conditions,[13] it was clear that the disubstituted double bond in compound **2.22** was not. Nickel-complexed reducing agents (NiCRAs),[14] prepared by the reaction of *t*-$C_5H_{11}OH$ with a mixture of sodium hydride and nickel acetate in THF, were reported to be chemoseletive for desulfurization in the presence of olefins. However, with substrate **2.22**, the reagents led to the decomposition of the starting material and nonoe of desired product.

Scheme 2-7 Synthesis of (-)-Crobarbatic Acid



Hence, a different tact was taken to convert the dithioorthoester to a methyl group (Scheme 2-7). N-chlorosuccinimide-assisted hydrolysis[5] of the dithiane moiety in **2.10**

led to the formation of a methyl ester that was subsequently reduced with $LiAlH_4$ and converted to isopropylsulfonyl ether **2.29** (84% yield over three steps). Reduction of **2.29** with superhydride ($LiEt_3BH$) in refluxing THF afforded the desired methyl substituent on C2. The isopropylsulfonyl group was used in this sequence instead of a mesylate because reduction of the mesylate led to only a small amount of **2.30** along with recovered alcohol **2.28** arising from reduction at the sulfur center.[15] No such problem occurred with the isopropyl sulfonyl ether, apparently because the reduction was channeled to the C-O bond by the increased steric hindrance around the sulfur atom.

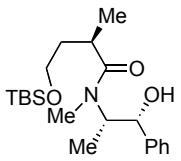
Oxidation of compound **2.30** with catalytic amount of ruthenium (IV) oxide hydrate and a cooxidant ($NaIO_4$), furnished (-)-crobarbatic acid (**2.7**) in 55% yield over two steps. The final oxidation step was very satisfying in that it did allow for both the cleavage of the olefin to the acid and the oxidation of the tetrahydrofuran ring in a single step. The absolute stereochemistry of **2.7** was established by comparing its optical rotation ($[\alpha]_D$ = -2.8° (*c* = 1.4, H_2O)) to the literature values ((-)-**2.7**[7b]: $[\alpha]_D$ = -3.7° (*c* = 1.4, H_2O); (+)-**2.7**[7e]: $[\alpha]_D$ = +3.56° (*c* = 1.4, H_2O)).

2.5 Conclusion

In conclusion, a vinyl-substituted ketene dithioacetal was employed successfully as a coupling partner in anodic coupling reactions. The electrolysis product was converted to (-)-crobarbatic acid. The synthesis illustrated a strategy for synthesizing products having relative stereochemistry opposite to that originally afforded by the cyclization. Although the presence of a vinyl substitute did alter the cyclization, the reaction was optimized using LiOMe as a base. During the synthesis, we developed a flexible and stereoselective route to functionalized anodic cyclization substrates. The stream-lined

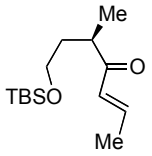
route to the electrolysis substrates was used frequently in my later studies and allowed us to probe the generality of anodic cyclization reactions for assembling a variety of functionalized molecules containing highly hindered tetrasubstituted carbon atoms. *More importantly, the basic reaction conditions developed here are the key to the success of many reactions described in the following chapters.*

2.6 Experimental Section:



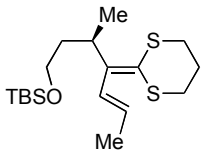
(*R*)-4-(*tert*-butyldimethylsilyloxy)-*N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethylbutanamide (2.14)

To a solution of diisopropylamine (14.7 mL, 105 mmol) in THF (56 mL) containing a suspension of LiCl (11.8, 42.4 mmol) was added n-butyllithium (1.6 M in hexanes, 61.0 mL, 97.6 mmol) at -78 °C under argon atmosphere. Upon complete addition, the reaction was warmed to 0 °C for 15 minutes and cooled back to -78 °C prior to the addition of **2.12** in THF (140 mL) *via* cannula. After stirring at -78 °C for 1 h, 0 °C for 15 minutes, and room temperature for 5 min, the reaction was cooled to 0 °C and treated with 2-(*tert*-butyldimethylsilyloxy) ethyl iodide (**2.13**). After being kept at 0 °C for 5 h, the reaction was quenched with saturated NH_4Cl solution (150 mL) and extracted with ether (3x 150 mL). The combined organic solution was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, ether/hexanes, 7:3) to afford compound **2.14** as a colorless oil (17.3 g, 98%). All the spectra data matched the data reported in the literature.



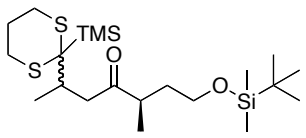
(*R*, *E*)-7-(*tert*-butyldimethylsilyloxy)-5-methylhept-2-en-4-one (2.15)

A solution of **2.14** (6.38g, 16.8 mmol) in ether (120 mL) was cooled to -78 °C and treated with *tert*-butyllithium (1.7 M solution in pentane, 9.9 mL, 16.8 mmol) followed by a solution of *trans*-1-lithium-1-propene, which was prepared by reacting (*E*)-1-propenyl bromide (2.9 mL, 33.7 mmol) in ether (15 mL) with *tert*-butyllithium (1.7 M solution in pentane, 39.7 mL, 67.5 mmol) at -78 °C for 30 minutes and 0 °C for 45 minutes. The reaction was warmed to 0 °C, stirred for 2.5 h, and poured into a mixture of 5% $NaHCO_3$ solution (200 mL) and ether (200 mL). The separated aqueous phase was extracted with ether (2 x 200 mL). The combined organic solution was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluted with 5% ethyl acetate in hexanes) to furnish the title compound as a light yellow oil (4.31 g, 98%); IR (neat, cm^{-1}) 3035, 1697, 1672, 1632, 1098; ^1H NMR (300 MHz, $CDCl_3$) δ 6.97-6.85 (m, 1H), 6.21-6.14 (m, 1H), 3.66-3.54 (m, 2H), 3.05-2.93(m, 1H), 1.99-1.88 (m, 4H), 1.56-1.45(m, 1H), 1.09 (d, J = 6.9, 3H), 0.89 (s, 9H), 0.035 (s, 3H), 0.028 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.9, 142.6, 131.0, 60.8, 39.9, 36.2, 26.1 (3C), 18.4 (2C), 16.8, -5.2 (2C); ESI HRMS m/z $(M+Na)^+$ calcd 279.1756, obsd 279.1748.



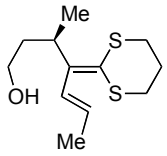
(*R*,*E*)-(4-(1,3-dithian-2-ylidene)-3-methylhept-5-enyloxy)(*tert*-butyl)dimethylsilane (2.17)

Butyllithium (1.6 M in hexanes, 9.83 mL, 15.7 mmol) was added to a solution of 2-trimethylsilyl-1,3-dithiane (2.64 mL, 14.3 mmol) in THF (33 mL) under argon atmosphere at -78°C. The resulting solution was allowed to warm to 5 °C in 5 hours and then cooled back down to -78°C prior to the addition of **2.15** (4.40 g, 17.2 mmol). The reaction mixture was stirred overnight and warmed to room temperature gradually, poured into water (50 mL), and then extracted with ether (3 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Chromatography of the crude product through silica gel (elution with 20:1 hexanes/ether) afforded 3.39 g (55%) of **2.17** along with 2.00 g of the 1,4-addition product **2.18** (31%). IR (neat, cm^{-1}) 3014, 1471, 1254, 1097, 853; ^1H NMR (300 MHz, $CDCl_3$) δ 6.20-6.14 (m, 1H), 5.77-5.65 (m, 1H), 3.54 (t, J = 7.2, 2H), 3.34-3.22 (m, 1H), 2.93-2.85 (m, 4H), 2.14-2.05 (m, 2H), 1.81-1.56 (series of m, 5H), 1.07 (d, J = 6.9, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5, 129.2, 126.9, 124.7, 61.9, 38.5, 33.7, 30.0, 29.9, 26.2 (3C), 24.8, 19.4, 19.1, 18.5, -5.0, -5.1; ESI HRMS m/z $(M+Na)^+$ calcd 381.1718, obsd 381.1708.



(*R*)-1-(*tert*-butyldimethylsilyloxy)-3-methyl-6-(2-(trimethylsilyl)-1,3-dithian-2-yl)heptan-4-one (2.18)

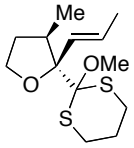
IR (neat, cm^{-1}) 1709, 1472, 1462, 1250, 1101, 840, 756; ^1H NMR (300 MHz, $CDCl_3$, two diastereoisomers) δ 3.64-3.58 (m, 2H), 3.31-2.96 (series of m, 4H), 2.82-2.69 (m, 1H), 2.51-2.29 (series of m, 3H), 2.05-1.79 (series of m, 3H), 1.56-1.41 (m, 1H), 1.20-1.16 (m, 3H), 1.10-1.08 (m, 3H), 0.89-0.88 (m, 9H), 0.25-0.24 (m, 9H), 0.04-0.03 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.9, 60.8 (d), 47.5, 47.3, 44.6, 44.5, 43.4 (d), 36.0, 35.6, 34.6, 26.1, 24.8, 23.6, 23.5, 23.4, 19.4, 19.2, 18.5, 16.5, 16.3; ESI HRMS *m/z* $(M+Na)^+$ calcd 471.2219, obsd 471.2210.



(*R*, *E*)-4-(1,3-dithian-2-ylidene)-3-methylhept-5-en-1-ol (2.9)

To a solution of **2.17** (1.61g, 4.49 mmol) in THF (30 mL) was added tetrabutylammonium floride (1.0 M solution in THF, 6.73 mL, 6.73 mmol) under argon atmosphere at rt. After stirring for 4 h, the reaction was cooled to 0°C and quenched with saturated ammonium chloride solution (15 mL). The organic phase was separated and aqueous layer extracted with Et_2O/CH_2Cl_2 (2:1, 3 x 20 mL). The combined organic solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by flash chromatography (silica gel, ether/hexanes 1:1) afforded 1.02 g of **2.9** as a colorless oil (93%). IR (neat, cm^{-1}) 3368, 3014, 1650, 1447, 1048, 963; ^1H NMR (300 MHz, $CDCl_3$) δ 6.18-6.11 (m, 1H), 5.78-5.66 (m, 1H), 3.59-3.49 (m, 2H), 3.37-3.25 (m, 1H), 3.03-2.80 (m, 4H), 2.15-2.06 (m, 2H), 1.81-1.61 (m, 5H), 1.11 (d, J = 6.9, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.4, 129.5, 126.4, 125.0, 61.2,

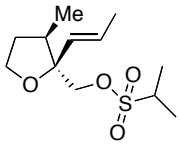
38.1, 33.5, 29.8, 29.7, 24.4, 19.5, 19.0; ESI HRMS *m/z* $(M+Na)^+$ 267.0853, obsd 267.0850.



(2*S*,3*R*)-2-(2-methoxy-1,3-dithian-2-yl)-3-methyl-2-((*E*)-prop-1-enyl)tetrahydro-furan (2.10)

A solution of **2.9** (122 mg, 0.499 mmol) in 30% MeOH/THF (17 mL) was placed in a flame-dried three-neck round bottom flask containing tetraethylammonium *p*-toluene-sulfonate (0.500g, 1.66 mmol) and 2,6-lutidine (0.35 mL, 3.0 mmol) under a argon atmosphere. BuLi (1.6 M solution in hexanes, 0.16 mL, 0.25 mmol) was added. Two of the three septa were replaced by a reticulated vitreous carbon anode (100 PPI) and platinum wire cathode. After sonicating for 10 minutes, the electrolysis reaction was carried out at constant current of 6.0 mA until 2 F/mol of electricity had been passed. The solution was freed of solvent under reduced pressure. The residue was diluted with ether, the electrolyte removed by filtration, and the resulting solution concentrated *in vacuo*. The crude product was chromatograghed through a silica gel column (slurry packed using a 2% triethylamine in hexane solution and eluted with 5% ether in hexanes) to give **2.10** as 5:1 ratio of inseparable diastereoisomers (99 mg, 72%); IR (neat, cm^{-1}) 3033, 1667, 1446, 1079; ^1H NMR (300 MHz, $CDCl_3$, * denotes minor isomer) δ 5.84-5.61 (m, 2H), 3.98-3.82 (m, 2H), 3.50 (s, 2.5H), *3.53 (s, 0.5H), 3.26-2.69 (series of m, 5H), 2.02-1.81 (m, 3H), 1.76 (dd, *J* = 6.3, 1.5, 2.5H), *1.73 (dd, *J* = 6.0, 0.9, 0.5H), 1.61-1.46 (m, 1H), *1.32 (d, *J* = 7.2, 0.5H), 1.03 (d, *J* = 6.6, 2.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ *133.4,

129.2, 126.9, *124.2, 103.9, 92.9, 68.0, *67.3, *52.8, 52.7, *43.5, 40.0, 34.8, *34.0, *29.9, *27.7 (2C), 27.6 (2C), *23.5, 23.2, 18.0, *17.8, 17.0, *16.7; ESI HRMS *m/z* $(M+Na)^+$ calcd 297.0959, obsd 297.0944.



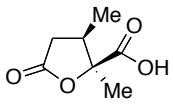
((2S,3R)-3-methyl-2-((E)-prop-1-enyl)tetrahydrofuran-2-yl)methyl propane-2-sulfonate (2.29)

To a solution of **2.10** (1.14g, 4.15 mmol) in acetone (16 mL) and water (1.8 mL) was added NCS (1.16 mg, 8.72 mmol) in acetone (83 mL) and water (9.2 mL) at room temperature under an argon atmosphere. The resulting solution was stirred at room temperature for 3 h, poured into a saturated aqueous ammonium chloride solution (100 mL), and extracted with ether (3x100 mL). The combined organic solution was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure.

The residue was dissolved in tetrahydrofuran (40 mL) and treated with $LiAlH_4$ (1.0 M in ether, 21 mL, 21 mmol) at 0°C under argon atmosphere. The reaction was stirred at 0°C for 1h and room temperature for 3h. After diluting with CH_2Cl_2 (20 mL), the reaction was quenched with 0.1 N HCl. The organic layer was separated and aqueous phase extracted with CH_2Cl_2 (3 x 60 mL). The combined organic extractions were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a colorless oil.

The oil obtained was dissolved in tetrahydrofuran (25 mL). Triethylamine (4.70 mL, 33.8 mmol) was added at room temperature under argon atmosphere, followed by

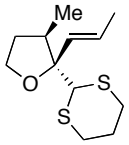
isopropylsulfonylchloride (1.85 mL, 16.9 mmol). The reaction mixture was stirred overnight, diluted with CH_2Cl_2, and quenched with saturated $NaHCO_3$ solution (30 mL). The organic phase was separated and aqueous layer extracted with CH_2Cl_2 (3 x 40 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, ether/hexanes =1:1) to give **2.29** (918 mg, 84%) as a colorless oil; IR (neat, cm^{-1}) 3030, 1349, 1179, 1157, 978, 821; ^1H NMR (300 MHz, $CDCl_3$, *denotes minor isomer) δ 5.85-5.74 (m, 1H), 5.51-5.46 (m, 0.17H), 5.35-5.28 (m, 0.83H), 4.11 (s, 2H), 3.97-3.76 (series of m, 2H), 3.30-3.44 (m, 1H), 2.29-1.98 (series of m, 2H), 1.73 (dd, *J* = 6.6, 1.8, 3H), 1.65-1.54 (m, 1H), 1.42 (dd, *J* = 6.9, 1.5, 6H), 1.10 (d, *J* = 7.2, 0.5H), 1.00 (d, *J* = 6.9, 2.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ *131.6, 128.1, 127.8, *126.0, 84.8, *84.0, 72.1, *71.2, 67.0, 52.4, 52.3, *42.2, 38.5, *34.2, 33.5, *27.5, *18.2, *18.1, 16.8 (2C), 14.8, *13.9; ESI HRMS *m/z* $(M+Na)^+$ calcd 285.1136, obsd 285.1125.



(-)-Crobarbatic acid (2.7)

Compound **2.29** (918 mg, 3.50 mmol) was placed in a 25 mL round-bottom flask equipped with a condenser. $LiBEt_3H$ solution (1.0 M solution in THF, 14.0 mL, 14.0 mmol) was added under argon atmosphere. The resulting solution was heated to reflux for 3 h, cooled to 0 °C, quenched with brine (20 mL), and extracted with ether (3 x 20 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was filtered through a short silica gel column

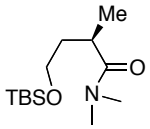
(eluted with CH_2Cl_2). The elution was concentrated under reduced pressure to about 0.5 mL, to which was added carbon tetrachloride (20 mL), acetonitrile (20 mL), 0.1 M $KHSO_4$ solution (30 mL), sodium periodate (15.0 g, mmol), and $RuO_2 \cdot xH_2O$ (250 mg). The resulting mixture was stirred vigorously for 24 h before the addition of water (40 mL) and extraction with CH_2Cl_2 (5 x 100 mL). The combined organic solutions were dried with Na_2SO_4 and concentrated under reduced pressure. The residue was diluted with ether and stored at room temperature for several hours to precipitate ruthenium species prior to being filtered through a pad of celite. The elution was concentrated *in vacuo* and the residue chromatographed on silica gel (eluted with ether/hexane = 1:1, and ether) to give **2.7** as a white crystal (304 mg, 55%); $[a]_D$ -2.8° (*c* = 1.4, H_2O); ^1H NMR (600 MHz, D_2O) δ 2.86-2.78 (dd, *J* = 17, 8.2, 1H), 2.70-2.57 (m 1H), 2.47-2.38 (dd, *J* = 17, 9.7, 1H), 1.61 (s, 3H), 1.06 (d, *J* = 6.9, 3H); ^{13}C NMR (150 MHz, D_2O) δ 180.2, 174.4, 89.5, 39.8, 35.8, 21.4, 14.0; ESI HRMS *m/z* $(M+Na)^+$ calcd 181.0477, obsd 181.0470.



(2S,3R)-2-(1,3-dithian-2-yl)-3-methyl-2-((E)-prop-1-enyl)tetrahydrofuran (2.22)

To a solution of **2.10** (205mg, 0.747 mmol) in ether (7.0 mL) was added Dibal-H (1 M soution in toluene, 2.24 mL, 2.24 mmol) at 0 °C under argon atmosphere. After stirred at 0 °C for 10 minutes and room temperature for 2.5 h, the reaction was quenched with saturated NH_4Cl solution at 0 °C. 10% aqueous $KHSO_4$ solution was added until a clear aqueous phase. The organic layer was separated and aqueous phase extracted with ether (3 x 15 mL). The combined organic solution was dried over $MgSO_4$, and concentrated *in*

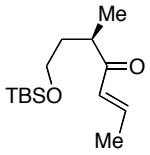
vacuo. Chromatography (silica gel, ether/hexanes = 1:1) of the residue furnished **2.22** as a colorless oil (113 mg, 62%). IR (neat, cm^{-1}) 3032, 1670, 1449, 1421, 1075, 973, 780; ^1H NMR (500 MHz, $CDCl_3$) δ 5.81-5.74 (m, 1H), 5.49-5.46 (m, 1H), 4.24 (s, 1H), 3.95-3.80 (m, 2H), 2.89-2.85 (m, 4H), 2.65-2.57 (m, 1H), 2.10-1.83 (m, 3H), 1.76 (dd, *J* = 6.5, 1.2, 3H), 1.61-1.53 (m, 1H), 1.04 (d, *J* = 7.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 129.1, 87.4, 67.3, 57.9, 40.5, 34.0, 31.2, 30.7, 26.1, 17.8, 15.8; ESI HRMS *m/z* $(M+Na)^+$ calcd 267.0853, obsd 267.0846.



(*R*)-4-(*tert*-butyldimethylsilyloxy)-*N*,*N*,2-trimethylbutanamide (2.24)

To a 250 mL round-bottom flask containing LiCl (7.70 g, 181 mmol), diisopropyl-amine (4.80 mL, 34.1 mmol), and THF (40 mL) was added *n*-butyllithium (1.6 *M* solution in hexanes, 20.0 mL, 32.0 mmol) at -78 °C under argon atmosphere. Upon complete addition, the reaction was warmed to 0°C and stirred for 15 min. After recooling the reaction to -78 °C, *N*,*N*-dimethylpropanamide (3.06 g, 30.3 mmol) in THF (40 mL) was added. The reaction was stirred at -78 °C for 1 hour, 0 °C for 15 minutes, rt for 5 minutes, and then cooled to 0°C. To this solution was added 2-(*tert*-butyldimethyl-silyloxy) ethyl iodide in a drop-wise fashion. After stirring at 0 °C for 3.5 h, the reaction was quenched by adding saturated NH_4Cl solution. The layers were separated and the aqueous phase extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed through silica gel (eluting with ethyl acetate/ hexanes 1:1) to afford **2.24** (7.14 g, 91%) as a faint yellow oil. IR (neat, cm^{-1}) 1650, 1472, 1255, 1100, 835, 776; ^1H NMR (300 MHz,

$CDCl_3$) δ 3.67-3.52 (m, 2H), 3.06 (s, 3H), 3.06-2.95 (m, 1H), 2.95 (s, 3H), 1.94-1.84 (m, 1H), 1.58-1.49 (m, 1H), 1.10 (d, J = 6.9 Hz, 3H), 0.88 (s, 9H), -0.02 (two s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.6, 60.8, 37.3, 37.2, 35.7, 31.6, 26.1, 18.4, 17.3, -5.2; ESI HRMS *m/z* $(M+Na)^+$ calcd 282.1860, obsd 282.1859.



(±)-7-(*tert*-butyldimethylsilyloxy)-5-methylhept-2-en-4-one (2.25)

To a solution of **2.24** (2.87 g, 11.0 mmol) and $ZnBr_2$ (248 mg, 1.1 mmol) in ether (80 mL) at -10 ºC was added a solution of *trans*-1-lithium-1-propene, which was prepared by reacting (*E*)-1-propenyl bromide (1.90 mL, 22.1 mmol) in ether (10 mL) with *tert*-butyllithium (1.7 M solution in pentane, 26.0 mL, 44.2 mmol) at -78 °C for 30 min and 0 °C for 45 min. The reaction was warmed to 0 °C, stirred for 2.5 h, and poured into a mixture of 5% $NaHCO_3$ solution (100 mL) and ether (100 mL). The separated aqueous phase was extracted with ether (2 x 100 mL). The combined organic solution was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed through silica gel (eluted with 5% ethyl acetate in hexanes) to furnish the title compound as a light yellow oil (2.26 g, 91%).

2.7 Spectra: see Appendix A

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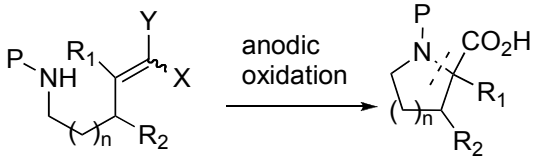
Chapter 3 The Use of a Nitrogen-Based Nucleophile in Intramolecular Anodic Coupling Reactions (Part I): Building Proline Derivatives

3.1 Introduction

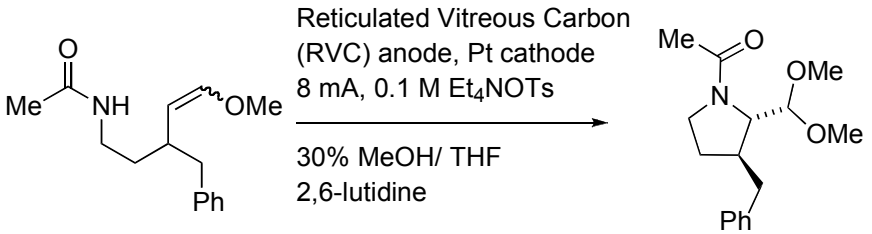
Anodic oxidation is a powerful method for triggering interesting umpolung reactions.[1] Typically, oxidations result in the coupling of two groups normally thought to be nucleophiles. They can be used to trigger a variety of cyclizations involving the formation of either carbon-carbon or carbon-oxygen bonds.[2] With this in mind, we hoped to expand the reactions to include cyclizations forming carbon-nitrogen bonds (Scheme 3-1). In principle, anodic cyclization reactions of this type would be useful for the synthesis of cyclic amino acid derivatives and a variety of peptidomimetics.[3-7]

Scheme 3-1 Proposed Synthesis of Cyclic Amino Acid Derivatives



3.1 **3.2**

Scheme 3-2 Initial Efforts from the Moeller Group



3.3 **3.4** 37%

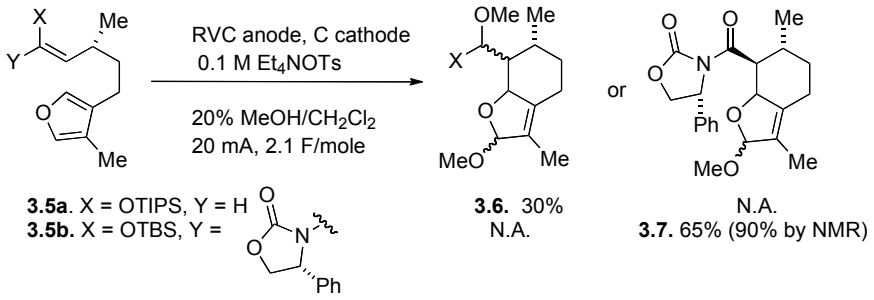
Initial attempts within the Moeller group were not encouraging.[8] A number of

substituent patterns were tried for the reactions. Oxidation of substrates with an amine or methoxy amine tethered to an enol ether in the hope to make proline derivatives resulted in the decomposition of the enol ether and no desired product.[9-10] When an acylated amine was used, the cyclized product was obtained although in low yield (scheme 3-2).

Recent work by Dr. Feili Tang from the Moeller group demonstrated that the nature of the substituent on a radical cation intermediate can have a profound influence on its ability to react with various trapping groups.[11] More polarized radical cations tend to favor carbon-carbon bond forming reactions while less polarized radical cations favor reactions with methanol solvent. This observation was used to optimize a coupling reaction between an electron-rich olefin and an electron-rich furan ring in Wu and Moeller's synthesis of the arteannuin ring system (Scheme 3-3).[12] In this case, the use of a more polarized ketene acetal derived radical cation dramatically improved the yield of the cyclization relative to the use of an enol ether derived radical cation.

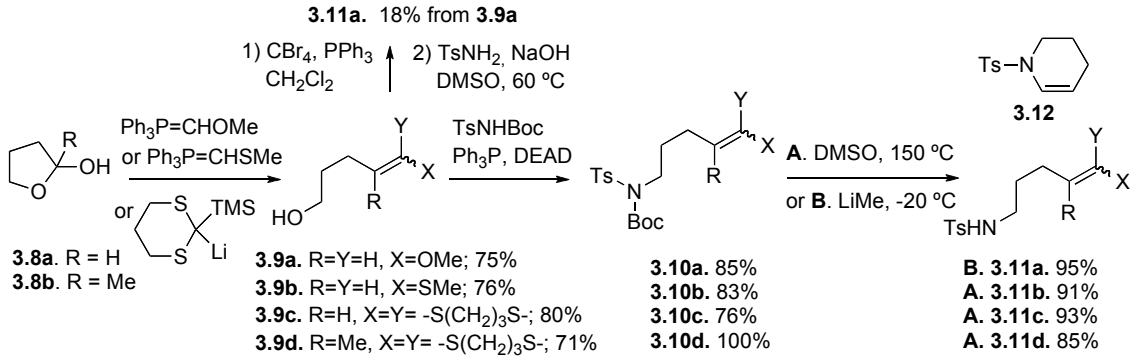
Having used a more polarized radical cation to improve the cyclization highlighted in Scheme 3-3, we wondered if the use of a less polarized radical cation might improve the cyclizations highlighted in Scheme 3-2.

Scheme 3-3 Anodic Coupling of a Furan and a Ketene Acetal



3.2 Initial Studies

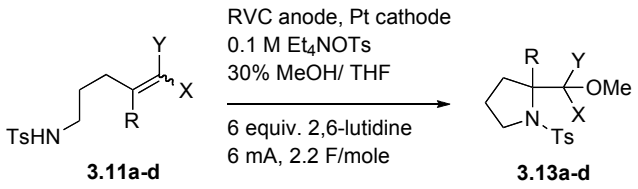
Scheme 3-4 Synthesis of Substrates



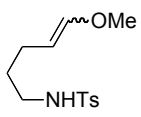
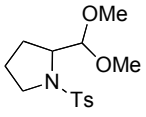
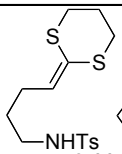
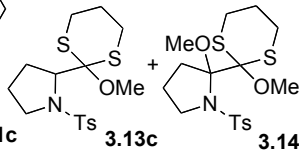
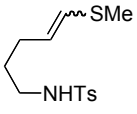
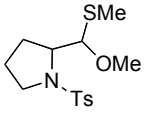
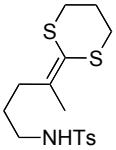
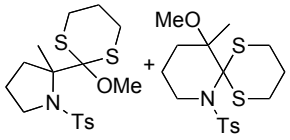
Our study commenced with the synthesis of four substrates, one containing enol ether, one vinyl sulfide, and two ketene dithioacteals as shown in scheme 3-4. Sulfonamides were chosen as coupling partners because of their known reactivity as nucleophiles.[13] The substrates were synthesized starting either from 2-hydroxyltetrahydrofuran (**3.8a**) or 3-acetyl-1-propanol (**3.8b**) in three steps (Scheme 3-4). First, **3.8a** and **3.8b** were transformed into alcohols **3.9a-d** with either a Wittig reaction or a Peterson olefination reaction. The alcohols were converted to the sulfonamides **3.11a-d** by taking advantage of the two-step protocol developed by Weinreb and coworkers.[14] A Mitsunobu reaction was used to transform the alcohols **3.9a-d** into **3.10a-d** followed by removal of the *t*-Boc group. Deprotection of the *t*-Boc group was conducted by heating in DMSO at 150 ºC for 50 min. While compounds **3.11c-d** were obtained in excellent yields, none of **3.11a** was observed and **3.12** was isolated in 75% yield instead. It appears that the initially formed **3.11a** was not stable under the reaction conditions and cyclized to give **3.12**. Hence, another route was taken to prepare substrate **3.11a**. The alcohol **3.9a** was reacted with Ph_3P and CBr_4 and then *p*-toluene sulfonamide to furnish **3.11a** in 16%

yield over two steps. Later, we found *t*-Boc group could be easily removed by reaction with LiMe in ether at -20 ºC for 15 minutes. Under these conditions, **3.11a** was obtained in 95% yield from **3.10a**.

Table 3-1 Initial Studies



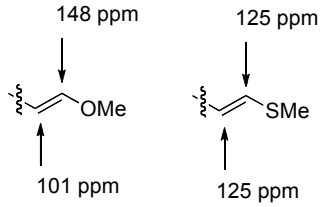
3.11a-d **3.13a-d**

entry	substrate	product(s)	yield(s)	entry	substrate	product(s)	yield(s)
1	 **3.11a**	 **3.13a**	20%	3	 **3.11c**	 **3.13c** **3.14**	14% + 4%
2	 **3.11b**	 **3.13b**	54%	4	 **3.11d**	 **3.13d** **3.15**	19% + 24%

With the substrates in hand, we set out to investigate the electrolysis reactions (Table 3-1). The substrates were oxidized (constant current, 6 mA) in an undivided cell equipped with reticulated vitreous carbon anode (RVC) and platinum wire cathode until 2.2 F/mol of charge had been passed. The reactions were conducted with 0.1 M Et_4NOTs in 30% MeOH/THF electrolyte solution and 2,6-lutidine as base. Under these conditions, the oxidation of the enol ether substrate **3.11a** afforded the cyclized product **3.13a** in 20% yield. The yield was increased to 54% when the vinyl sulfide substrate **3.11b** was oxidized under the same conditions. This was consistent with early findings from the Moeller group that less polar radical cations favored carbon hetereoatom bond

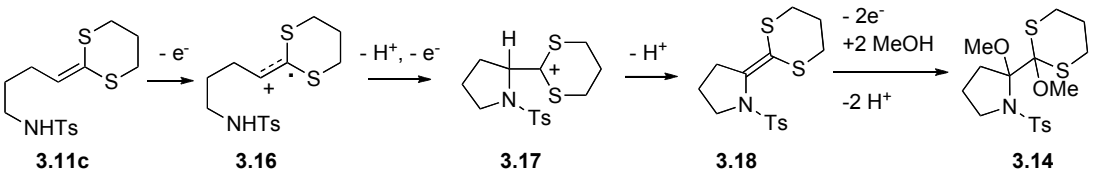
formation.[11] The radical cation derived from vinyl sulfide showed less polar than that from enol ether as suggested by ^{13}C-NMR (Figure 3-1). In the starting olefin, the oxygen clearly donates electron density into the π system of the enol ether double bond to a greater extent than does the sulfide group to the π–system of the vinyl sulfide. In fact, the vinyl sulfide π–system is not polarized at all.

Figure 3-1 Polarity of an Enol Ether and an Vinyl Sulfide



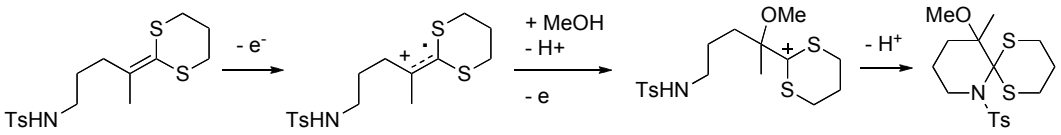
The oxidation of ketene dithioacetal **3.11c** under the same conditions described above afforded the desired product **3.13c** in 14% yield along with 4% of the over-oxidized product **3.14** (Table 3-1, entry 3). A possible mechanism for the formation of **3.14** was depicted in Scheme 3-5. **3.11c** was oxidized at the anode to give a radical cation **3.16** that was then cyclized and further oxidized to give the cation **3.17**. Elimination of a proton from **3.17** would afford **3.18**, which was oxidized in the presence of methanol to give **3.14**. It seems that the elimination from cation **3.17** is competing with the methanol trapping to afford **3.13c**.

Scheme 3-5 Proposed Mechanism for the Formation of Compound 3.14



Replacing the vinyl proton with a methyl group avoided the elimination. However, the expected product was isolated in only 19% yield along with a six-membered ring product **3.15** in 24% yield (entry 4). Compound **3.15** was probably arose from competitive trapping of the radical cation **3.19** by methanol solvent (Scheme 3-6). The resulting radical was oxidized and trapped intramolecularly by the toluene sulfonamide to afford **3.15**.

Scheme 3-6 Proposed Mechanism for the Formation of Compound 3.15



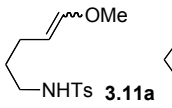
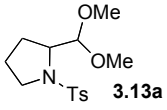
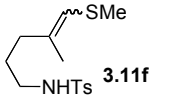
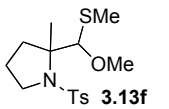
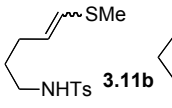
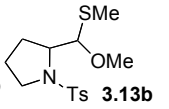
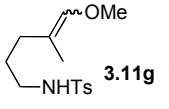
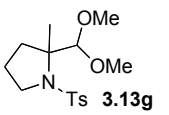
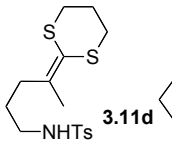
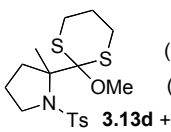
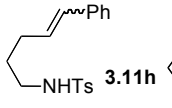
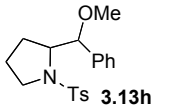
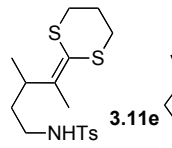
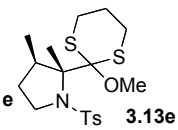
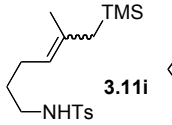
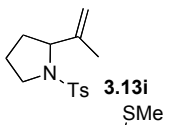
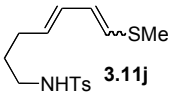
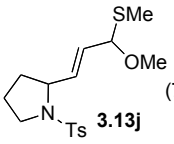
3.11d **3.19** **3.20** **3.15**

3.3 Reactions Using More Basic Conditions

The formation of the six-membered ring product **3.15** suggested that the trapping of the radical cation by the nitrogen-based nucleophile was not fast enough to compete with solvent trapping (reaction with methanol). One possible solution would be to enhance the reactivity of the sulfonamide by conducting the oxidation under more basic conditions. The idea was to take advantage of the acidity of the sulfonamide (p*K*a = 10) relative to that of the methanol solvent (p*K*a = 16). In order to make a more basic reaction medium, 2,6-lutidine, typically used as a bse in the reactions, was replaced by 0.5 equivalent of lithium methoxide as used previously for the oxidation of **2.9**.[15] For an electrolysis reaction in an undivided cell, acid is produced at the anode and equal amount of base is produced at the cathode by the reduction of methanol. The overall electrolysis reaction is neutral, thereby maintaining the initial pH of the reaction. The addition of sub-

stoichiometric amount of lithium methoxide is sufficient to keep a basic reaction medium through out the electrolysis reaction. Under these conditions, the toluene sulfonamde is deprotonated. The resulting sulfonamide anion should be more nucleophilic than the initial nucleophile. The lithium methoxide was either produced *in situ* by adding *n*-BuLi to the methanol-based solvent mixture or introduced more conveniently as a methanol solution (available from Aldrich).

Table 3-2 Scope

entry	substrate	product(s)	yield(s)	entry	substrate	product(s)	yield(s)
1	 **3.11a**	 **3.13a**	(70%)[a] (82%)[b]	5	 **3.11f**	 **3.13f**	(89%)[b]
2	 **3.11b**	 **3.13b**	(85%)[a] (90%)[b] (91%)[c]	6	 **3.11g**	 **3.13g**	(77%)[b]
3	 **3.11d**	 **3.13d** + **3.15**	(72% + 0%)[a] (73% + 7%)[b]	7	 **3.11h**	 **3.13h**	(88%)[b]
4	 **3.11e**	 **3.13e**	(28%)[a] (83%)[b]	8	 **3.11i**	 **3.13i**	(90%)[b]
				9	 **3.11j**	 **3.13j**	(70%)[c]

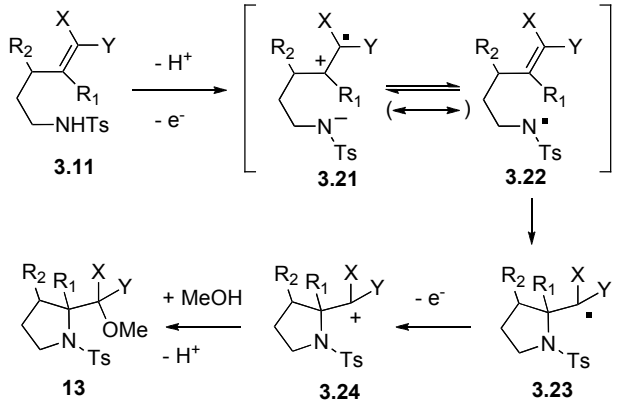
a. reaction conditions: RVC anode, Pt wire cathode, 0.5 equiv. LiOMe, 30% MeOH-THF, 0.1 M Et_4NOTs, 6 mA, 2.0-2.4 F/mole; b. MeOH as solvent; c. 0.7 equiv. LiOMe (No additional electrolyte was used), MeOH.

The more basic reaction conditions had a dramatic influence on the reactions (Table 3-2). For example, the oxidation of the enol ether substrate **3.11a** (entry 1) led to the formation of cyclic product **3.13a** in 70% isolated yield when 30% MeOH/THF was used as the solvent for the reaction. When methanol was used as solvent, the isolated yield of **13a** increased to 82%. The reaction utilizing the thioenol ether (**3.13b**) led to 85% yield

of desired product when 30% MeOH/THF was used as solvent and 90% yield when methanol was used.

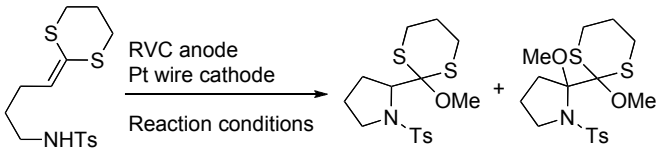
The role of LiOMe in these reactions is thought to be the deprotonation of the toluene sulfonamide in order to make a better coupling partner for the reaction. This can occur either by the sulfonamide anion serving as a better nucleophile for the radical cation (**3.21**) or by the formation of a nitrogen radical type intermediate (**3.22**)[16] that then adds to the olefin (Scheme 3-7). Later mechanistic studies (see Chapter 5) using cyclic voltammetry and competition methods show that the mechanism is probably dependent on the electron-rich olefin used. For reactions that involve ketene dithioacetal and enol ether, the cyclizations appear to proceed through a radical cation type transition state (**3.21)** while the oxidation of vinyl sulfide substrates appears more consistent with a reaction going through a nitrogen-centered radical type transition state (**3.22**). It is thought that the reactions benefit from the use of pure methanol as solvent because of a need to effectively trap cation **3.24**.

Scheme 3-7 Possible Mechanism of Anodic Oxidation of Unsaturated Tosylamides



Even with the more basic reaction conditions, the oxidation of **3.11c** remained problematic (Table 3-3). Under all reaction conditions attempted, the ratio of **3.13c** to **3.14** remained constant at about 3:1. While increasing the methanol concentration from 30% MeOH/THF to 60% MeOH/THF to pure methanol in order to accelerate trapping of the cation **3.17** had little effect on the yields of the cyclic products (entries 1-3), reducing the electrolyte concentration from 0.1 M to 0.03 M resulted in an increase of the total yield of **3.13c** and **3.14** to 66% (entry 4). Further reducing the electrolyte concentration caused a drop in the combined yield of the products (entry 5). Replacing the electrolyte tetraethylammonium tosylate (Et_4NOTs) with $LiClO_4$ had no beneficial effect on the reaction and **3.13c** and **3.14** were isolated in only 10% yield (entry 6).

Table 3-3 Anodic Oxidation of Substrate 3.11c



3.11c **3.13c** 3:1 **3.14**

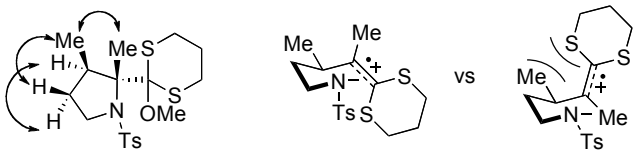
entry	Reaction conditions	yields	entry	Reaction conditions	yields
1	0.5 equiv. *n*-BuLi 30% MeOH/THF, 0.1 M Et_4NOTs, 6 mA, 2.4 F/mol	34%	4	0.5 equiv. *n*-BuLi MeOH, 0.03 M Et_4NOTs, 6 mA, 3.3 F/mol	66%
2	0.5 equiv. *n*-BuLi 60% MeOH-THF, 0.1 M Et_4NOTs 6 mA, 2.4 F/mol	33%	5	0.5 equiv. *n*-BuLi MeOH, 0.003 M Et_4NOTs, 6 mA, 3.8F/mol	47%
3	0.5 equiv. *n*-BuLi MeOH, 0.1 M Et_4NOTs, 6 mA, 9.4 F/mol	39%	6	0.5 equiv. *n*-BuLi MeOH, 0.03 M $LiClO_4$, 6 mA, 4 F/mol	10%

The use of the more basic reaction conditions did solve the problem initially encountered with substrate **3.11d** (Table 3-2, entry 3). In this case, the reaction utilizing the 30% MeOH/THF conditions afforded the desired cyclization product in a 72% isolated yield without observation of any of the methanol-trapping product. The use of

MeOH as the solvent did lead to some of the MeOH trapping product but did not lower the yield of the desired five-membered ring product obtained. Evidently, the loss of product through trapping of the radical cation with methanol solvent was counteracted by the improved yield of the cyclic product by methanol trapping of cation **3.24**.

The need for having sufficient methanol present to trap the cyclic cation **3.24** was acutely observed when substrate **3.11e** was oxidized (Table 3-2, entry 4). The oxidation of **3.11e** in 30% MeOH/THF led to only a 28% yield of the desired product. The yield was raised to 80% by using pure methanol as solvent. The product was formed as a single diastereomer that was assigned with the use of an NOESY experiment (Figure 3-2). The stereochemistry can be rationalized by the preference of the transition state in which dithiane group was placed *trans* to the neighboring methyl group to avoid unfavorable $A^{1,3}$ interaction (Figure 3-2). The stereochemistry of the reaction is consistent with earlier cyclizations using oxygen nucleophiles.[15]

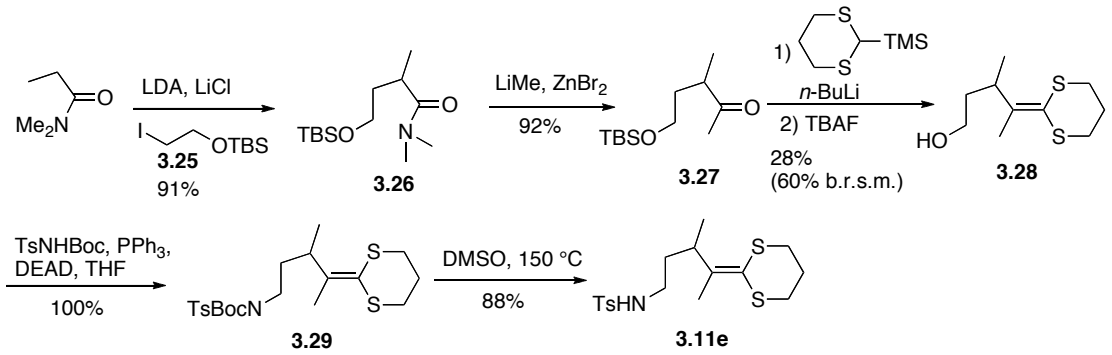
Figure 3-2 Key NOE Interactions in Compound 3.13e and Origin of Stereoselectivity in Oxidation of 3.11e



The synthesis of the substrate **3.11e** was depicted in scheme 3-8. N,N-dimethylpropionamide was alkylated with iodide **3.25** and treated with LiMe in the presence of catalytic amount of Lewis acid $ZnBr_2$ to furnish ketone **3.27**. Introducing the ketene dithioacetal functionality using a Peterson olefination reaction resulted in low

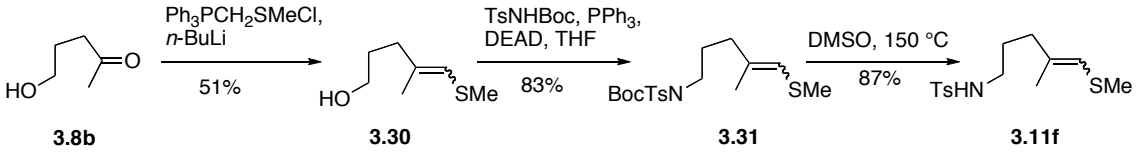
conversion because of the steric hindrance of the ketone. Desilylation with tetrabutylammonium fluoride afforded alcohol **3.28** in a 28% yield for two steps (60% based on recovered starting material **3.27**). Compound **3.28** was converted the toluene sulfonamide **3.11e** in excellent yield by following standard protocols.

Scheme 3-8 Synthesis of Substrate 3.11e

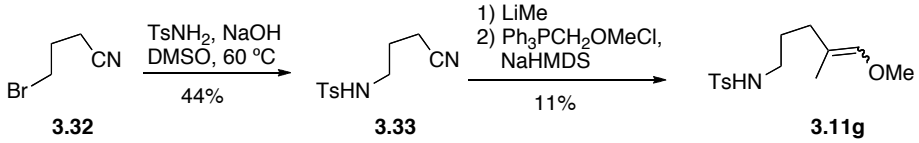


The vinyl sulfide (Table 3-2, entry 5) and enol ether substrates (Table 3-2, entry 6) were also compatible with the generation of tetrasubstituted carbons.[18] Both oxidation of the vinyl sulfide **3.11f** and enol ether **3.11g** afforded the desired cyclized product in good yields.

Scheme 3-9 Synthesis of Substrate 3.11f

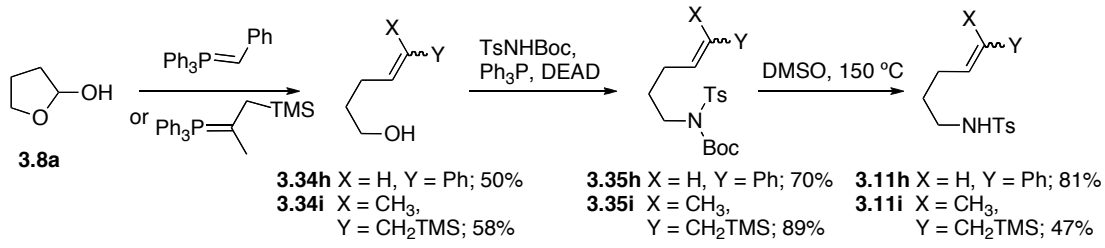


Scheme 3-10 Synthesis of Substrate 3.11g



The synthesis of substrate **3.11f** followed the protocol used for the synthesis of **3.11a-d** as shown in Scheme 3-4 and started from 3-acyl-1-propanol **3.8b** (Scheme 3-9). Another strategy was taken to prepare the enol ether substrate **3.11g** because of its incompatibility with last thermal deprotection protocol (Scheme 3-10). The synthesis started from the commercially available 4-bromo-butyrnitrile (**3.32**). An excess of *p*-toluene sulfonamide (2.2 equiv) and compound **3.32** were heated in DMSO at 60 ºC in the presence of NaOH in order to afford **3.33** in 44% yield. The moderate yield was caused mostly by over-akylation of the product **3.33** with bromide **3.32**. Compound **3.33** was treated with methyllithium followed by acid hydrolysis to give an inseparable mixture of the desired methyl ketone and starting material in a ratio of 2:3. The low conversion was probably due to the tosylamide anion adding to the nitrile and making it unreactive toward the addition of methyllithium. No attempts were made to optimize the reaction and the mixture obtained was treated with methoxymethylenetriphenyl-phosphorane to afford **3.11g**. With the new procedure to remove the *t*-Boc group (LiMe, -20 ºC), substrate like **3.11g** should be able to be prepared using the sequence described in Scheme 3-4.

Scheme 3-11 Synthesis of Substrate 3.11h and 3.11i

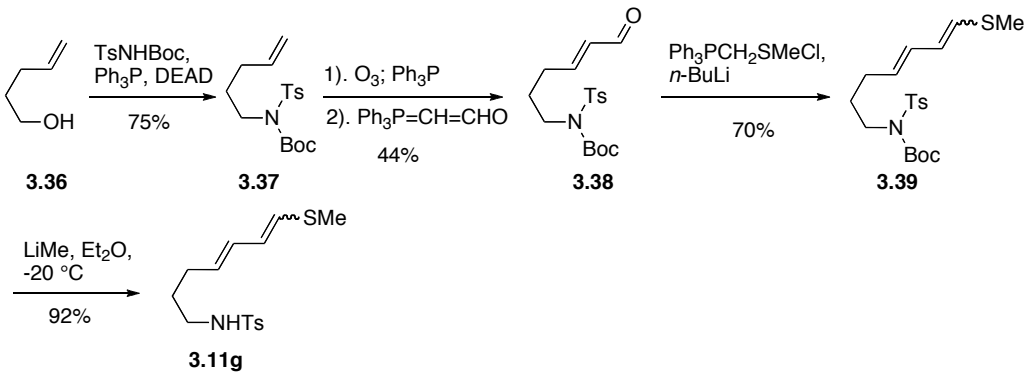


The success of the reactions under the more basic conditions with both polar and non-polar olefins prompted us to investigate other electron-rich olefins. Thus a styrene

derivative **3.11h** and an allylsilane substrate **3.11i** were synthesized from 2-hydroxyl tetrahydrofuran in three steps (Scheme 3-11).[17b] In both cases, anodic oxidation of the substrate led smoothly to the cyclized product in excellent yield. In the case of a styrene-based substrate **3.11h** (Table 3-2, entry 7) an 88% isolated yield of product was obtained, while oxidation of an allylsilane-based substrate **3.11i** (Table 3-2, entry 8) led to a 90% isolated yield of product.

The use of a diene as coupling partner was also investigated. The synthesis of the substrate started with the conversiton of alcohol **3.36** to protected sulfonamide **3.37** in 75% yield. Ozonolytic scission of the monosubstituted olefin followed by a Wittig reaction[18] furnished enone **3.38** which was converted to the vinyl sulfide **3.39** using another Wittig reaction. Removal of the *t*-Boc group with LiMe in ether afforded the substrate **3.11j** in 92% yield.

Scheme 3-12 Synthesis of Substrate 3.11g



The oxidation of **3.11j** was conducted with 0.7 equivalent of LiOMe in methanol without additional electrolyte. The reaction led to a 70% isolated yield of the desired five-membered ring product **3.13j** (entry 9, Table 3-2). To explore the generality of the

"electrolyte-free" electrolysis conditions, the oxidation of **3.11b** was repeated under the same conditions to afford a 91% yield of the desired product (entry 2, Table 3-2). It appears the LiOMe used in the reactions can fulfill the role of both base and electrolyte, which makes the reactions more environmentally benign and experimentally convenient.

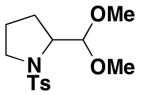
3.4 Conclusion

In summary, toluene sulfonamides were successfully used in intramolecular anodic coupling reactions to build proline derivatives. The reactions benefited greatly from the use of basic reaction conditions, and are compatible with a variety of electron-rich olefins such as an enol ether, vinylsulfide, ketene dithioacetal, allylsilane, styrene, and diene. Expanding the reactions to make pipecolic acid derivatives will be discussed in the following chapter of this thesis.

3.5 Experimental Section

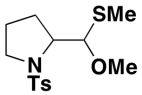
General procedure for electrolysis reactions: LiOMe (1.0 *M* in MeOH, 0.5 equiv) was added to either a methanol or 30% MeOH/THF solution of the substrate (0.03 *M*, 1 equiv) and the electrolyte tetraethylammonium *p*-toluenesulfonate in a three-neck round bottom flask at rt under argon atmosphere. Two of the three septa were replaced by a reticulated vitreous carbon anode (100 PPI) and platinum wire cathode. The solution was sonicated for 10 min. The electrolysis reaction was carried out at constant current of 6.0 mA until complete consumption of the starting material (the progress of the reaction was monitored by ^{1}H-NMR). When complete, the reaction was concentrated under reduced pressure and then the residue chromatographed through a silica gel column (slurry packed using 1% triethylamine in hexane solution) to give the desired product.

Spectra of Electrolysis Products:



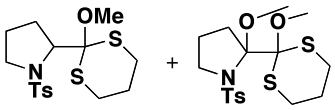
2-(dimethoxymethyl)-1-tosylpyrrolidine (3.13a)

IR (neat, cm^{-1}) 1344, 1160, 1093, 663, 591; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 4.63 (d, J = 2.7 Hz, 1H), 3.69-3.65 (m, 1H), 3.58 (s, 3H), 3.46 (s, 3H), 3.58-3.83 (m, 1H), 3.22-3.14 (m, 1H), 2.43 (s, 3H), 2.08-1.81 (m, 2H), 1.53-1.36 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 134.6, 129.9, 127.8, 108.0, 62.0, 58.9, 56.3, 49.8, 25.4, 25.1, 21.7; ESI HRMS m/z $(M+H)^+$ calcd 300.1264, obsv 300.1270.



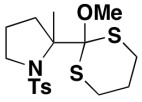
2-(methoxy(methylthio)methyl)-1-tosylpyrrolidine (3.13b)

IR (neat, cm^{-1}) 1342, 1158, 1092, 663, 588, 546; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 4.76 (d, J = 2.1 Hz, 1H), 3.97-3.91 (m, 0.2H), 3.89-3.84 (m, 0.8H), 3.51 (s, 2.4H), 3.47 (s, 0.6H), 3.46-3.37 (m, 1H), 3.27-3.18 (m, 1H), 2.43 (s, 3H), 2.27 (s, 0.6H), 2.21 (s, 2.4H), 2.06-1.82 (m, 2H), 1.67-1.55 (m, 1H), 1.46-1.38 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, * denotes minor isomer) δ 143.7, 134.9, 129.9, 127.7, 95.1*, 92.4, 64.6, 63.1*, 58.7, 57.0*, 49.9, 27.8*, 26.7, 25.1, 25.0*, 21.7, 14.3; ESI HRMS m/z $(M+H)^+$ calcd 316.1036, obsv 316.1043.



2-methoxy-2-(1-tosylpyrrolidin-2-yl)-1,3-dithian-4-ylium (3.13c) and 2-methoxy-2-(2-methoxy-1,3-dithian-2-yl)-1-tosylpyrrolidine (3.14)

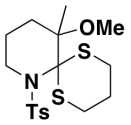
An inseparable mixture of **3.13c** and **3.14** was obtained. IR (neat, cm^{-1}) 1347, 1160, 1091, 668, 589, 547; ^{1}H NMR (300 MHz, $CDCl_3$, *denotes **3.13c**) δ 7.88* (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.21* (d, *J* = 8.4 Hz, 2H), 4.55 (dd, *J* = 9.0 Hz, 3.6 Hz, 1H), 4.13-4.07* (m, 1H), 3.64* (s, 3H), 3.60-3.52 (m, 1H), 3.49 (s, 3H), 3.45* (s, 3H), 3.33-3.21 (m, 1H), 3.05-2.88 (m, 2H), 2.87-2.72 (m, 2H), 2.67-2.51* (m, 2H), 2.41 (s, 3H), 2.39* (s, 3H), 2.22-2.10 (m, 1H), 2.04-1.65 (m, 4H), 1.44-1.31 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 142.5, 137.0, 129.8, 128.6, 128.4, 127.9, 107.0, 100.9, 99.8, 66.6, 55.4, 52.7, 52.6, 50.8, 50.3, 36.4, 27.7 (d), 27.5, 27.4, 27.4, 25.4, 24.5, 23.7, 23.1, 21.8; ESI HRMS *m/z* $(M+Na)^+$ calcd for **3.13c** 396.0732, obsv 396.0741, *m/z* $(M+Na)^+$ calcd for **3.14** 426.0838, obsv 426.0846.



2-(2-methoxy-1,3-dithian-2-yl)-2-methyl-1-tosylpyrrolidine (3.13d)

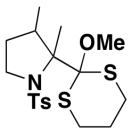
IR (neat, cm^{-1}) 1335, 1156, 1090, 665, 583, 549; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 3.73-3.67 (m, 1H), 3.56 (s, 3H), 3.40-3.32 (m, 1H), 3.02-2.68 (m, 5H), 2.41 (s, 3H), 2.03-1.93 (m, 1H), 1.91-1.75 (m, 3H), 1.86 (s, 3H), 1.64-1.56 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 139.2, 129.4, 128.0, 103.6,

78.9, 53.4, 53.3, 40.6, 28.4 (d), 23.8, 23.7, 22.8, 21.8; ESI HRMS *m/z* $(M+Na)^+$ calcd 410.0889, obsv 410.0883.



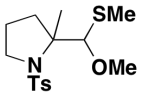
11-methoxy-11-methyl-7-tosyl-1,5-dithia-7-azaspiro[5.5]undecane (3.15)

IR (neat, cm^{-1}) 1331, 1158, 1095, 659, 542; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 4.35 (dt, *J* = 14.7, 3.9 Hz, 1H), 4.00-3.90 (m, 1H), 3.58-3.48 (m, 1H), 3.07-2.98 (m, 1H), 2.76 (s, 3H), 2.72-2.61 (m, 2H), 2.40 (s, 3H), 2.07-2.00 (m, 1H), 1.90-1.76 (m, 3H), 1.68-1.54 (m, 1H), 1.44 (s, 3H), 1.44-1.34 (m, 1H); ^{13}C NMR; (75 MHz, $CDCl_3$) δ 142.2, 141.2, 128.7, 128.3, 81.8, 81.2, 48.8, 45.4, 29.6, 28.8, 26.3, 23.8, 21.8, 21.5, 21.2; ESI HRMS *m/z* $(M+H)^+$ calcd 410.0889, obsv 410.0885.



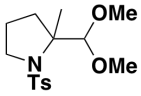
2-(2-methoxy-1,3-dithian-2-yl)-2,3-dimethyl-1-tosylpyrrolidine (3.13e)

IR (neat, cm^{-1}) 1335, 1156, 1087, 660, 546; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 3,65-3.58 (m, 1H), 3.56 (s, 3H), 3.38-3.29 (m, 1H), 3.02-2.78 (m, 5H), 2.40 (s, 3H), 2.01-1.83 (m, 3H), 1.71 (s, 3H), 1.23-1.10 (m, 1H), 0.99 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 139.2, 129.3, 127.9, 105.0, 80.1, 53.0, 50.9, 42.0, 33.2, 28.4(d), 22.6, 21.7, 18.3, 18.1; ESI HRMS *m/z* $(M+H)^+$ calcd 402.1225, obsv 402.1220.



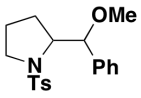
2-(methoxy(methylthio)methyl)-2-methyl-1-tosylpyrrolidine (3.13f)

IR (neat, cm^{-1}) 1334, 1154, 1092, 663, 589, 550; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 4.93 (s, 1H), 3.53 (s, 3H), 3.46-3.35 (m, 2H), 2.46 (s, 3H), 2.41-2.29 (m, 1H), 2.28 (s, 3H), 1.97-1.84 (m, 1H), 1.80-1.68 (m, 2H), 1.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0, 139.0, 129.7, 127.3, 96.9, 72.6, 57.7, 50.5, 36.2, 25.0, 23.3, 21.8, 16.3; ESI HRMS *m/z* $(M+Na)^+$ calcd 352.1012, obsv 352.1020.



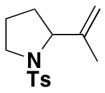
2-(dimethoxymethyl)-2-methyl-1-tosylpyrrolidine (3.13g)

IR (neat, cm^{-1}) 1333, 1156, 1109, 1093, 1077, 663; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 4.76 (s, 1H), 3.65 (s, 3H), 3.53 (s, 3H), 3.53-3.42 (m, 1H), 3.34-3.25 (m, 1H), 2.46-2.37 (m, 1H), 2.43 (s, 3H), 2.00-1.89 (m, 1H), 1.72-1.59 (m, 1H), 1.52-1.43 (m, 1H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 138.9, 129.6, 127.4, 110.6, 70.2, 59.2, 58.1, 50.4, 34.9, 23.5, 23.3, 21.7; ESI HRMS *m/z* $(M+Na)^+$ calcd 336.1240, obsv 336.1232.



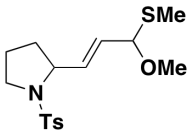
2-(methoxy(phenyl)methyl)-1-tosylpyrrolidine (3.11h)

IR (neat, cm^{-1}) 3063, 3027, 1344, 1159, 663, 589; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.1 Hz, 2H), 7.36-7.27 (m, 7H), 4.81 (d, *J* = 2.1 Hz, 0.9H), 4.77 (d, *J* = 2.4 Hz, 0.1H), 4.02-3.96 (m, 0.1H), 3.74-3.69 (m, 0.9 H), 3.53-3.44 (m, 1H), 3.36 and 3.35 (2s, 3H), 3.32-3.24 (m, 1H), 2.43 and 2.40 (2s, 3H), 2.05-1.88 (m, 2H), 1.38-1.19 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 140.0, 135.4, 129.9, 128.7, 127.7, 126.5, 85.7, 66.0, 58.3, 50.1, 25.1(d), 21.7; ESI HRMS *m/z* $(M+H)^+$ calcd 346.1471, obsv 346.1464.



2-(prop-1-en-2-yl)-1-tosylpyrrolidine (3.13i)

IR (neat, cm^{-1}) 1345, 1159, 666, 588, 549; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 2H), 5.00 (s, 1H), 4.87 (s, 1H), 4.04 (t, *J* = 6.3 Hz, 1H), 3.50-3.43 (m, 1H), 3.32-3.24 (m, 1H), 2.43 (s, 3H), 1.84-1.63 (m, 6H), 1.60-1.51 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3, 143.5, 135.2, 129.8, 127.8, 112.0, 65.2, 49.5, 31.7, 24.3, 21.8, 18.9; ESI HRMS *m/z* $(M+H)^+$ calcd 266.1209, obsv 266.1211.



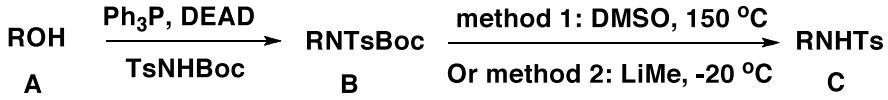
(E)-2-(3-methoxy-3-(methylthio)prop-1-enyl)-1-tosylpyrrolidine (3.13j)

IR (neat, cm^{-1}) 1345, 1159, 666, 586, 550; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 5.76-5.71 (m, 2H), 4.86 (d, *J* = 2.7 Hz, 1H), 4.22-4.14 (m, 1H), 3.49-3.37 (m, 1H), 3.37 (s, 3H), 3.32-3.15 (m, 1H), 2.42 (s, 3H), 1.96, 1.93 (2s, 3H), 1.86-1.57 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 143.5, 135.5, 135.2,

132.3, 132.2, 129.8, 129.8, 129.0, 129.0, 127.7, 127.7, 84.6, 61.0, 55.8, 49.1, 48.9, 33.0, 32.9, 24.1, 21.7, 9.54; ESI HRMS *m/z* $(M+Na)^+$ calcd 364.1022, obsv 364.1012.

Synthesis of Electrolysis Substrates:

General procedure for synthesis of *p*-toluene sulfonamides from alcohols:



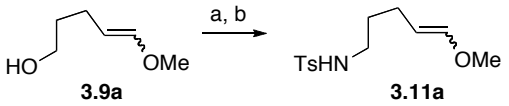
Synthesis of B: A diethyl azodicarboxylate (DEAD) solution (40 wt% solution in toluene, 2.5 equiv) was added dropwise to a solution of the alcohol **A** (1 equiv), *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (1.5 equiv), and triphenylphosphine (3 equiv) in THF at rt. When the reaction was complete, the solvent was removed and the residue chromatographed through silica gel to afford **B**.

Deprotection of *t*-Boc group:

Method 1: B was dissolved in DMSO and the solution heated to 150 ^oC for 50 min. The mixture was cooled to rt and water and ether added. The layers were separated. The aqueous layer was extracted with ether twice. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed through silica gel (slurry packed with 1% Et_3N) to give the desired product **C.**

Method 2: B was dissolved in anhydrous diethyl ether and treated with LiMe (1.6 M in Et_2O, 6 equiv) at -20 °C. After 15 min at the same temperature, the reaction was quenched with water and brought to rt. The layers were separated and the aqueous layer extracted with ether. The organic phase was dried and concentrated. The residue was

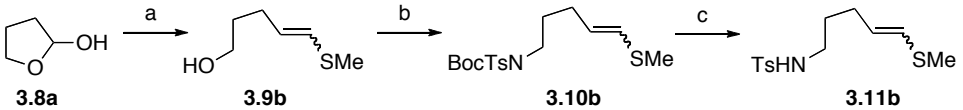
chromatographed through silica gel (slurry packed with 1% Et_3N) to give the desired product **C**.



3.9a **3.11a**

Reaction conditions: a. TsNHBoc, Ph_3P, DEAD, THF; b. LiMe, -20 °C, 72% (2 steps).

Synthesis of 3.11a: **3.11a** was synthesized from the known compound **3.9a** by following the general procedure described above for the synthesis of sulfonamides. IR (neat, cm^{-1}) 3287, 1331, 1159, 934, 665, 550; ^1H NMR (300 MHz, $CDCl_3$, 3:1 mixture of isomers) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 6.22 (d, *J* = 12.6 Hz, 0.75H), 5.88 (dt, *J* = 6.0, 1.2 Hz, 0.25H), 4.73 (br, 0.25), 4.63-4.54 (m, 0.75H), 4.32 (br, 0.75H), 4.27-4.20 (m, 0.25H), 3.57 (s, 0.75H), 3.47 (s, 2.25H), 2.94 (m, 2H), 2.43 (s, 3H), 2.08-2.00 (m, 0.5H), 1.96-1.88 (m, 1.5H), 1.56-1.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, only the major isomer was shown) δ 148.0, 143.4, 137.3, 129.8, 127.3, 101.6, 56.1, 42.6, 30.6, 24.8, 21.7; ESI HRMS *m/z* $(M+H)^+$ calcd 270.1158, obsv 270.1155.



3.8a **3.9b** **3.10b** **3.11b**

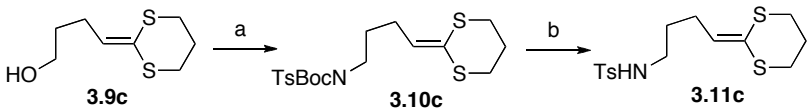
Reaction conditions: a. Ph_3PCH_2SMeCl, *n*-BuLi, THF, 76%; b. TsNHBoc, Ph_3P, DEAD, THF, 83%; c. DMSO, 150 °C, 91%.

Synthesis of 3.9b: To a suspension of (methylthiomethyl)triphenylphosphonium chloride (12.5 g, 35.0 mmol) in THF (100 mL) was added an *n*-butyllithium solution (2.5 M in hexanes, 13.6 mL, 34.0 mmol) at 0 °C under argon atmosphere. After the addition

was complete, the clear solution was stirred at 0 °C for 30 min and then treated with 2-hydroxytetrahydrofuran. The reaction was warmed to room temperature and then stirred overnight. The reaction was cooled to 0 ^{o}C and brine and ether added. The organic phase was separated and the aqueous layer extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated. Chromatography on silica gel gave **3.9b** as a colorless oil (1.0 g, 76%, 4:1 mixture of isomers). IR (neat, cm^{-1}) 3350, 1437, 1057, 938; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (dt, *J* = 20.7 Hz, 1.2, 0.8H), 5.93 (d, *J* = 8.7, 0.2H), 3.66 (m, 2H), 2.28 (m, 0.6 H), 2.23-2.15 (m, 4.4 H), 1.72-1.61 (m, 2H), 1.53 (t, *J* = 6.0 Hz, 0.2H), 1.28 (t, *J* = 5.4 Hz, 0.8 H); ^{13}C NMR (75 MHz, $CDCl_3$, * denotes the minor isomer) 128.2*, 127.6*, 126.8, 124.5, 62.2, 32.6, 31.9*, 29.6, 25.5*, 17.2*, 15.3; ESI HRMS *m/z* $(M+H)^+$ calcd 133.0681, obsv 133.0680.

Synthesis of 3.10b: Diethyl azodicarboxylate solution (40 wt% solution in toluene, 5.70 mL, 12.5 mmol) was added dropwise to a solution of S-2 (0.66 g, 5.0 mmol), *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (2.00 g, 7.5 mmol) and triphenylphosphine (3.90 g, 15.0 mmol) in THF (60 mL) at rt. After stirring overnight, the solvent was removed and the residue chromatographed to give **3.10b** as a white solid (1.59 g, 83%). IR (neat, cm^{-1}) 1726, 1354, 1155, 674, 581, 545; ^{1}H NMR (300 MHz, $CDCl_3$, a 4:1 mixture of isomers was obtained. Only the data for the major isomer is reported) δ 7.79 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.7 Hz, 2H), 6.06 (d, *J* = 15.0 Hz, 1H), 5.51-5.42 (m, 1H), 3.83 (t, *J* = 7.8 Hz, 2H), 2.46 (s, 3H), 2.26 (s, 3 H), 2.24-2.17 (m, 2H), 1.94-1.83 (m, 2H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 144.3, 137.7, 129.5, 128.1, 125.9, 125.0, 84.0, 46.9, 30.6, 30.1, 28.1, 21.9, 15.2; ESI HRMS *m/z* $(M+Na)^+$ calcd 408.1274, obsv 408.1272.

Synthesis of 3.11b: A solution of **3.10b** (1.45 g, 3.76 mmol) in anhydrous DMSO (12 mL) was heated at 150 °C for 50 min. The reaction was cooled to rt, poured into water (120 mL), and then extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product purified by flash chromatography on silica gel (slurry packed with 1% triethylamin and eluted with ether/hexane, 1:1) to give **3.11b** as a white solid (0.98 g, 91%, 4:1 mixture of isomers). IR (neat, cm^{-1}) 3281, 1435, 1324, 1158, 1093, 814, 663, 551; ^1H NMR (600 MHz, $CDCl_3$) d 7.75 (d, J = 7.8 Hz, 2H), 7.31 (d, J = 7.8 Hz, 2H), 5.93 (d, J = 15.6 Hz, 0.8H), 5.90 (d, J = 9.6 Hz, 0.2H), 5.43-5.39 (m, 0.2H), 5.32-5.27 (m, 0.8H), 4.69 (t, J = 6.0 Hz, 0.2H), 4.57 (t, J = 6.0 Hz, 0.8 H), 2.96-2.92 (m, 2H), 2.43 (s, 3H), 2.25 (s, 0.6H), 2.20 (s, 2.4H), 2.11-2.07 (m, 2H), 1.57-1.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, * denotes minor isomer) δ 143.4, 136.9, 129.7, 128.2*, 127.1, 126.8*, 125.2, 125.1, 42.5*, 42.4, 29.9, 29.3, 28.5*, 25.9*, 21.5, 16.9*, 14.9; ESI HRMS *m/z* $(M+Na)^+$ calcd 308.0749, obsv 308.0745.



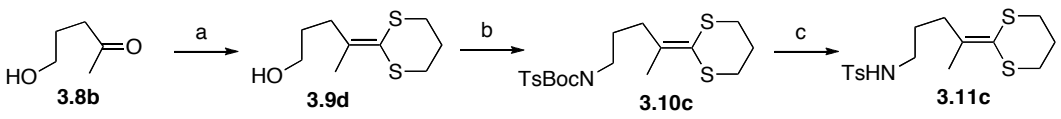
Reaction conditions: a. TsNHBoc, PPh_3, DEAD, THF, 76%; b. DMSO, 150 °C, 93%.

Synthesis of 3.11c: Starting from the known compound **3.9c**, **3.10c** was prepared by following the general procedure.

Spectral data for 3.10c: IR (neat, cm^{-1}) 1726, 1354, 1155, 673, 575, 545; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 5.96 (t, J = 6.9 Hz, 1H), 3.82 (t, 7.8, 2H), 2.87 (t, 6.3, 4H), 2.44 (s, 3H), 2.87 (q, J = 7.5 Hz, 2H), 2.20-2.14

(m, 2H), 1.89-1.80 (m, 2H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 144.2, 137.7, 132.7, 129.4, 128.1, 127.2, 84.3, 46.9, 30.5, 29.8, 29.6, 28.1, 26.9, 25.4, 21.8; ESI HRMS *m/z* $(M+Na)^+$ calcd 466.1151, obsv 466.1170.

Spectral data for 3.11c: IR (neat, cm^{-1}) 3279, 1597, 1422, 1325, 1158, 1093, 814, 663, 551; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 5.79 (t, *J* = 7.5 Hz, 1H), 4.56 (t, *J* = 6.3 Hz, 1H), 2.95 (q, *J* = 6.6 Hz, 2H), 2.83 (m, 4H), 2.42 (s, 3H), 2.22-2.10 (m, 4H), 1.58-1.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 137.3, 132.3, 130.0, 127.6, 127.4, 42.7, 30.5, 29.8, 28.9, 26.4, 25.3, 21.8; ESI HRMS *m/z* $(M+H)^+$ calcd 344.0807, obsv 344.0803.



Reaction conditions: a. 2-trimethylsilyl-1,3-dithiane, *n*-BuLi, THF, 71%; b. TsNHBoc, PPh_3, DEAD, THF, 100%; c. DMSO, 150 °C, 85%.

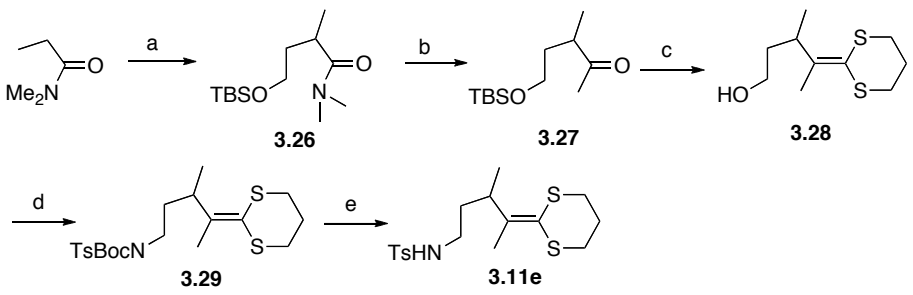
Synthesis of 3.9d: *n*-BuLi (1.6 *M* in hexanes, 9.50 mL, 15.2 mmol) was added to a -78 °C solution of 2-trimethylsilyl-1,3-dithiane in THF (30 mL). The reaction was stirred at -78 °C for 0.5 h and 0 °C for an additional 0.5 h. The reaction was cooled to -78 °C and the resulting mixture treated with 3-acetyl-1-propanol (0.77 g, 7.6 mmol). The reaction was allowed to gradually warm too room temperature and stirred overnight. Ether and brine was added. The layers were separated and the aqueous phase extracted with ether. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by flash chromatography to afford **3.9d** as a colorless oil (1.10g, 71%). IR (neat, cm^{-1}) 3367, 1421, 1275, 1060, 1005, 911; ^{1}H NMR

(300 MHz, $CDCl_3$) δ 3.60 (t, *J* = 6.3 Hz, 2H), 2.88-2.83 (m, 4H), 2.42 (t, *J* = 7.5 Hz, 2H) 2.26 (s, 1H), 2.15-2.09 (m, 2H), 1.90 (s, 3H), 1.70-1.61 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 119.7, 62.0, 32.0, 30.6, 30.5, 30.3, 25.0, 20.3; ESI HRMS *m/z* $(M+Na)^+$ calcd 227.0535, obsv 227.0540.

Synthesis of 3.11d: The general procedure was employed to make **3.11d** as shown above.

Spectral data for 3.10d: IR (neat, cm^{-1}) 1726, 1354, 1285, 1155, 1087, 720, 674, 574; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 3.78 (t, *J* = 7.8 Hz, 2H), 2.88-2.82 (m, 4H), 2.44-2.39 (m, 5H), 2.15-2.07 (m, 2H), 1.93 (s, 3H), 1.89-1.79 (m, 2H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 151.1, 144.2, 139.1, 137.7, 129.4, 128.1, 120.4, 84.2, 47.0, 33.2, 30.5, 30.3, 28.5, 28.1, 25.1, 21.8, 20.3; ESI HRMS *m/z* $(M+Na)^+$ calcd 480.1307, obsv 480.1312.

Spectral data for 3.11d: IR (neat, cm^{-1}) 3277, 1421, 1324, 1158, 1092, 814, 662, 550; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 2H), 4.76 (t, *J* = 6.0 Hz, 1H), 2.96-2.92(m, 2H), 2.86-2.81 (m, 4H), 2.43 (s, 3H), 2.31 (t, *J* = 7.2 Hz, 2H), 2.12-2.09 (m, 2H), 1.81 (s, 3H), 2.56-1.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3, 138.2, 137.2, 129.7, 127.1, 120.8, 42.4, 32.4, 30.2, 30.0, 27.4, 24.7, 21.5, 19.9; ESI HRMS *m/z* $(M+H)^+$ calcd 358.0964, obsv 358.0959.



Reaction conditions: a. LDA, ICH_2CH_2OTBS, LiCl, THF, 91%; b. MeLi, $ZnBr_2$, Et_2O, 92%; c. 1. 2-trimethylsilyl-1,3-dithiane, *n*-BuLi, THF; 2. TBAF, THF, 28 %; d. TsNHBoc, PPh_3, DEAD, THF, 100%; e. DMSO, 150 °C, 88%.

Synthesis of 3.26: To a 250 mL round-bottom flask containing LiCl (7.70 g, 181 mmol), diisopropylamine (4.80 mL, 34.1 mmol), and THF (40 mL) was added butyllithium (1.6 *M* solution in hexanes, 20.0 mL, 32 mmol) at -78 °C under argon atmosphere. Upon complete addition, the reaction was warmed to 0°C and stirred for 15 min. After recooling the reaction to -78 °C, *N*,*N*-dimethylpropanamide (3.06 g, 30.3 mmol) in THF (40 mL) was added. The reaction was stirred at -78 °C for 1 h, 0 °C for 15 min, rt for 5 min, and then cooled to 0°C. To this solution was added 2-(*tert*-butyldimethylsilyloxy) ethyl iodide in a dropwise fashion. Afer stirring at 0°C for 3.5 h, the reaction was quenched by adding saturated NH_4Cl solution. The layers were separated and the aqueous phase extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed through silica gel (eluting with ethyl acetate/ hexanes 1:1) to afford **3.26** (7.14 g, 91%) as a faint yellow oil. IR (neat, cm^{-1}) 1650, 1472, 1255, 1100, 835, 776; ^1H NMR (300 MHz, $CDCl_3$) δ 3.67-3.52 (m, 2H), 3.06 (s, 3H), 3.06-2.95 (m, 1H), 2.95 (s, 3H), 1.94-1.84 (m, 1H), 1.58-1.49 (m, 1H), 1.10 (d, J = 6.9 Hz, 3H), 0.88 (s, 9H),

-0.02 (two s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.6, 60.8, 37.3, 37.2, 35.7, 31.6, 26.1, 18.4, 17.3, -5.2; ESI HRMS *m/z* $(M+Na)^+$ calcd 282.1860, obsv 282.1859.

Synthesis of 3.27: Methyllithium was added dropwise to a solution of **3.26** (5.92 g, 22.8 mmol) and zinc bromide (513 mg, 2.28 mmol) in diethyl ether at -10 °C under an argon atmosphere. The mixture was stirred for 3 h during which time the temperature was allowed to warm to rt. After cooling the reaction back down to 0 °C, it was quenched by 5% $NaHCO_3$ solution and extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography (silica gel, eluting with 5% ether/hexane) afforded **3.27** as a colorless oil (4.84g, 92%). IR (neat, cm^{-1}) 1715, 1255, 1099, 835, 776; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.61 (t, *J* = 6.0 Hz, 2H), 2.75-2.64 (m, 1H), 2.14 (s, 3H), 1.98-1.85 (m, 2H), 1.46-1.57 (m, 2H), 1.09 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.029 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.5, 60.8, 43.8, 35.8, 28.4, 26.0, 18.4, 16.3, -5.3; ESI HRMS *m/z* $(M+Na)^+$ calcd 253.1594, obsv 253.1604.

Synthesis of 3.28: To a -78 °C solution of 2-trimethylsilyl-1,3-dithiane (3.0 mL, 16 mmol) in THF 35 mL was added dropwise butyllitium solution (1.6 M in hexanes, 6.4 mL, 16 mmol). The resulting mixture was stirred at -78 °C for half an hour and 0 °C for an additional half an hour and then cooled back to -78 °C. **3.27** (3.73 g, 16.2 mmol) was added dropwise. Upon complete addition, the reaction was allowed to warm to room temperature slowly and stirred overnight. The reaction mixture was poured into water (50 mL) and extracted with ether. The combined extractions were dried over $MgSO_4$ and evaporated. The starting material (1.64g, 44%) and product were separated out of the residue by flash chromatography. The product was contaminated by 2-trimethylsilyl-1,3-

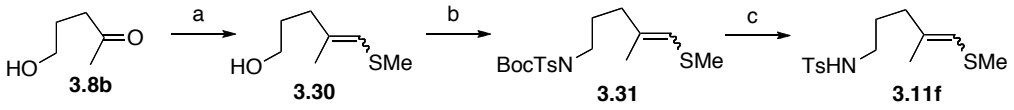
dithiane but was still used without further purification by dissolving it in THF (45 mL) and treating it with a tetrabutylammonium floride solution (1.0 M in THF, 15 mL, 15 mmol) at room temperature under argon atmosphere. After stirring at rt for 3 h, the reaction was quenched with saturated aqueous sodium bicarbonate solution (50 mL) and extracted with ether. The organic layers were combined, dried over $MgSO_4$, and concentrated. The crude product was purified on a silica gel column to give **3.28** as a colorless oil (1.00 g, 28%). IR (neat, cm^{-1}) 3367, 1456, 1421, 1275, 1049, 997, 911; ^1H NMR (300 MHz, $CDCl_3$) δ 3.54-3.49 (m, 2H), 3.38-3.31 (m, 1H), 2.90-2.86 (m, 4H), 2.43 (s, 1H), 2.17-2.08 (m, 2H), 1.78 (s, 3H), 1.66-1.52 (m, 2H), 1.01 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 119.8, 61.2, 37.6, 34.0, 30.6, 30.2, 25.2, 19.1, 14.8; ESI HRMS *m/z* $(M+Na)^+$ calcd 219.0872, obsv 219.0866.

Synthesis of 3.11e: 3.11e was synthesized from **3.28** by following the general procedure.

Spectral data for 3.29: IR (neat, cm^{-1}) 1726, 1354, 1288, 1156, 675, 572, 545; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 7.8 Hz, 2H), 3.84-3.74 (m, 1H), 3.70-3.60 (m, 1H), 3.42-3.31 (m, 1H), 2.95-2.88 (m, 4H), 2.47 (s, 3H), 2.20-2.10 (m, 2H), 1.96-1.77 (m, 5H), 1.36 (s, 9H), 1.06 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 144.2, 142.4, 137.8, 129.5, 128.0, 120.4, 84.3, 46.1, 35.6, 35.4, 30.6, 30.3, 28.2, 25.4, 21.9, 19.1, 14.7; ESI HRMS *m/z* $(M+H)^+$ calcd 472.1644, obsv 472.1636.

Spectral data for 3.11e: IR (neat, cm^{-1}) 3278, 1420, 1325, 1158,1092, 814, 662, 551; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 4.89-

4.85 (m, 1H), 3.22-3.11 (m, 1H), 3.18-2.91 (m, 1H), 2.88-2.73, (m, 5H), 2.43 (s, 3H), 2.15-2.07 (m, 2H), 1.68 (s, 3H), 1.47-1.43 (m, 2H), 0.90 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 141.3, 137.6, 129.9, 127.3, 120.7, 41.7, 34.6, 34.3, 30.4, 30.1, 25.0, 21.8, 18.9, 14.6; ESI HRMS *m/z* $(M+H)^+$ calcd 372.1120, obsv 372.1117.



Reaction conditions: a. Ph_3PCH_2SMeCl, *n*-BuLi, THF, 51%; b. TsNHBoc, PPh_3, DEAD, THF, 83%; c. DMSO, 150 °C, 87%.

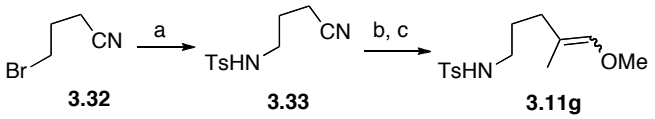
Synthesis of 3.11f: **3.11f** was synthesized in the same fashion as **3.11b**.

Spectral data for 3.30 (4:1 mixture of isomers): IR (neat, cm^{-1}) 3367, 1624, 1437, 1062; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63 (s, 1H), 3.62 (t, J = 6.0 Hz, 2H), 2.25 and 2.24 (two s, 3H), 2.26-2.21 (m, 0.4 H), 2.14 (m, 1.6H), 1.76-1.63 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, * denotes minor isomer) δ 136.5*, 135.8, 121.0*, 120.8, 62.5, 62.1*, 35.6, 30.9, 30.0*, 29.7*, 22.9*, 17.9, 17.4*, 17.4; ESI HRMS *m/z* $(M+H)^+$ calcd 147.0838, obsv 147.0842.

Spectral data for 3.31 (4:1 mixture of isomers): IR (neat, cm^{-1}) 1726, 1354, 1155, 674, 583, 545; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 5.67 (s, 0.8H), 5.66 (s, 0.2H), 3.78 (t, J = 7.5 Hz, 2H), 2.44 (s, 3H), 2.26 (s, 2.4H), 2.23 (s, 0.6H), 2.13 (t, J = 7.5 Hz, 2H), 1.94-1.86 (m, 2H), 1.80 (s, 0.6 H), 1.75 (s, 2.4H), 1.34 and 1.33 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, only the major isomer is

shown) δ 151.1, 144.3, 137.8, 134.9, 129.4, 128.0, 121.2, 84.3, 47.0, 36.4, 28.4, 28.1, 21.8, 17.9, 17.4; ESI HRMS *m/z* $(M+Na)^+$ calcd 422.1430, obsv 422.1447.

Spectral data for 3.11f (4:1 mixture of isomers): IR (neat, cm^{-1}) 3282, 1431, 1323, 1158, 1093, 814, 662, 550; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 5.56 (s, 0.2H), 5.55 (s, 0.8H), 5.12-5.07 (m, 0.2H), 5.02-4.97 (m, 0.8H), 2.93-2.86 (m, 2H), 2.42 (s, 3H), 2.21 (s, 2.4H), 2.20 (s, 0.6H), 2.10 (t, *J* = 7.2 Hz, 0.4H), 2.02 (t, *J* = 7.2 Hz, 1.6H), 1.66-1.54 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, * denotes minor isomer) δ 143.6, 143.5*, 137.5*, 137.2, 135.5*, 134.6, 129.9, 127.3, 121.7*, 121.6, 42.8, 42.7*, 36.1, 30.4*, 27.9, 27.0*, 22.7*, 21.7, 17.8, 17.4*, 17.3; ESI HRMS *m/z* $(M+Na)^+$ calcd 322.0906, obsv 322.0910.



3.32 **3.33** **3.11g**

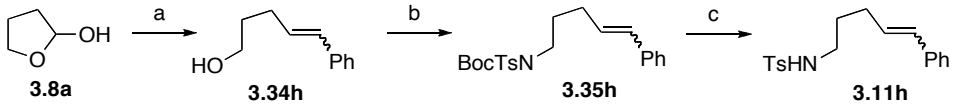
Reaction conditions: a. $TsNH_2$, NaOH, DMSO, 60 °C; b. MeLi, THF; c. Ph_3PCH_2OMeCl, NaHMDS, THF.

Synthesis of 3.33: *p*-toluenesulfonamide (6.60 g, 38.6 mmol) and NaOH (0.77 g, 19 mmol) were placed in a 100 mL RB flask and DMSO (34 mL) was added. The resulting suspension was heated at 60 °C for half an hour and then treated with 4-bromobutanitrile (2.60 g, 17.6 mmol). The reaction was stirred at 60 °C for 2 h, poured into water (300 mL), and extracted with CH_2Cl_2. The combined layers were concentrated, diluted with ethyl acetate (150 mL), washed with water (2 x 50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed through silica gel in order to afford **3.33** (1.84 g, 44%) as a white solid. IR (neat, cm^{-1}) 3274, 2249, 1425, 1158, 1093,

815, 662, 550; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 5.48 (t, *J* = 6.3 Hz, 1H), 3.75 (t, *J* = 7.8 Hz, 2H), 3.02 (q, *J* = 6.6 Hz, 2H), 2.44 (t, *J* = 7.2 Hz, 5H), 1.89-1.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 136.7, 130.2, 127.3, 119.5, 41.8, 25.9, 21.8, 14.6; ESI HRMS *m/z* $(M+H)^+$ calcd 239.0848, obsv 239.0844.

Synthesis of 3.11g: Methyllithium (1.6 *M* in ether, 25 mL, 40 mmol) was added to a solution of **3.33** (1.90 g, 7.98 mmol) in THF (40 mL) at 0 °C under argon atmosphere. The reaction was allowed to warm to room temperature gradually and stirred overnight. Saturated NH_4Cl (40 mL) was added at 0 °C and the reaction stirred at rt for 30 min and extracted with ether. The combined organic layers were dried with $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed through a silica gel column to afford a 2:3 mixture of desired product and **3.33** (0.73 g). To a suspension of methoxymethyltriphenylphosphonium chloride (2.80 g, 18.7 mmol) in THF (17 mL) was added NaHMDS (1.0 M in THF, 8.20 mL, 8.20 mmol) at 0 °C. The dark red solution was stirred at the same temperature for half an hour and then treated with the mixture (dissolved in 5 mL of THF) made above. The reaction was allowed to warm to room temperature slowly and stirred overnight. Brine was added, followed by ether. The organic layer was separated and aqueous layer extracted twice with ether. The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. Chromatography through silica gel gave **3.11g** as a 2:3 mixture of isomers (0.25 g, 11%). IR (neat, cm^{-1}) 3281, 1450, 1326, 1159, 1133, 1094, 815, 662, 550; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.84 (m, 2H), 7.33-7.29 (m, 2H), 5.75-5.72 (m, 1H), 5.26 (t, *J* = 6.3 Hz, 0.4 H), 4.98 (t, *J* = 6.33 Hz, 0.6H), 3.51 (s, 3H), 2.90 (q, *J* = 6.6 Hz, 2H), 2.43 (s, 3H), 2.05 (t, *J* = 7.2 Hz,

0.8 H), 1.86 (t, J = 7.2 Hz, 1.2H), 1.58-1.43 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) 143.5, 143.3, 142.7, 142.5, 137.7, 137.3, 129.9, 127.3, 127.2, 112.5, 112.3, 59.4, 42.8, 42.1, 30.9, 27.9, 26.2, 25.3, 21.7, 17.1, 12.7; ESI HRMS *m/z* $(M+Na)^+$ calcd 306.1134, obsv 306.1139.



3.8a **3.34h** **3.35h** **3.11h**

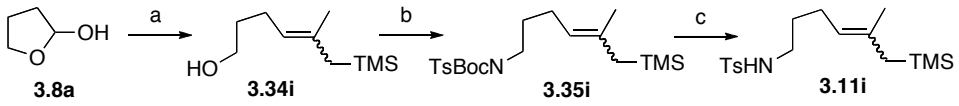
Reaction Conditions: a. $Ph_3PCHPhBr$, NaHMDS, THF, 50%, b. TsNHBoc, PPh_3, DEAD, THF, 70%; c. DMSO, 150 °C, 81%.

Synthesis of 3.34h: To a suspension of benzyltriphenylphosphorane bromide (4.77 g, 11 mmol) in THF (20 mL) was added NaHMDS (1.0 *M* in THF, 11 mL, 11 mmol) at 0 °C. The resulting red mixture was stirred at rt for 1 h, cooled to -78 °C, and treated with 2-hydroxytetrahydrofuran (dissolved in 20 mL of THF). The reaction was allowed to slowly warm to rt and stirred overnight. Water and ether were added to quench the reaction. The layers were separated and the aqueous layer extracted with ether. The combined organic layers were dried with $MgSO_4$, concentrated, and chromatographed to give **3.34** as a 9:1 mixture of isomers. The spectral data were consistent with the reported ones.

Synthesis of 3.11h: **3.34h** was converted to **3.11h** by following the general procedure. **3.11h** was obtained as a 9:1 mixture of isomers and the spectra were consistent with the ones in the literature.

Spectral data for 3.35h (9:1 mixture of isomers): IR (neat, cm^{-1}) 3032, 1725, 1354, 1154, 673; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 8.4 Hz, 2H), 7.37-7.17 (m, 7H),

6.44 (d, J = 15.9 Hz, 1H), 6.28-6.19 (m, 0.9 H), 5.74-5.65 (m, 0.1H), 3.91-3.80 (m, 2H), 2.43 (s, 3H), 2.33-2.26 (m, 2H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 144.3, 137.8 (d), 130.8, 129.6, 129.5, 128.7, 128.0, 127.2, 126.2, 84.4, 47.0, 30.4, 30.0, 28.1, 21.8; ESI HRMS *m/z* $(M+Na)^+$ calcd 438.1710, obsv 438.1723.



3.8a **3.34i** **3.35i** **3.11i**

Reaction Conditions: a. $Ph_3PCH_2CH_3Br$, ICH_2TMS, *n*-BuLi, 58%; b. TsNHBoc, PPh_3, DEAD, THF, 89%; c. DMSO, 150 °C, 47%.

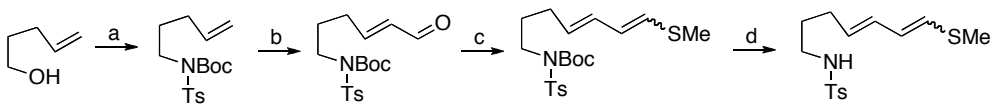
Synthesis of 3.34i: To a suspension of ethyltriphenylphosphonium bromide (18.5 g, 49.5 mmol) in THF (150 mL) was added dropwise *n*-butyllithium solution (1.6 M in hexanes, 31 mL, 50 mmol) at -78 °C under argon atomosphere. The reaction was allowed to warm to rt, stirred for 1 h, and cooled back to -78 °C. Trimethylsilanylmethyliodide (7.2 mL, 48 mmol) was added dropwise. Upon complete addition the reaction was stirred at rt for 3 h. After being cooled down to -78 °C, the reaction mixture was treated with *n*-butyllithium (1.6 *M* in hexanes, 31 mL, 49.6 mmol). The cold bath was removed and the mixture stirred at rt in 1.5 h. 2-Hydroxytetrahydrofuran (1.76 g, 20 mmol) was added at -78 °C and the reaction allowed to warm to rt and stirred overnight. Brine (100 mL) was added at 0 °C. The layers were separated and the aqueous phase extracted with ether (2 x 100 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was chromatographed through silica gel (gradiant elution with ether/hexanes, 5% to 50%) to give **3.34i** (2.5 g, 58%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.99-4.89 (m, 1H), 3.60 (t, J = 6.6 Hz, 2H), 2.06-1.92 (m, 2H),

1.63-1.43 (m, 7H), -0.01 and -0.04 (two s, 9H); ESI HRMS *m/z* $(M+H)^+$ calcd 187.1513, obsv 187.1508. This compound was used without further characterization.

Synthesis of 3.11i: **3.34i** was converted to **3.11i** by following the general procedure.

Spectral data for 3.35i (7:3 mixture of isomers): IR (neat, cm^{-1}) 1727, 1357, 1156, 849, 673; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 5.00-4.92 (m, 1H), 3.79 (t, *J* = 7.5 Hz, 2H), 2.42 (s, 3H), 2.07-1.92 (m, 2H), 1.82-1.72 (m, 2H), 1.66 (d, *J* = 1.2 Hz, 0.9H), 1.58 (d, *J* = 0.6 Hz, 2.1H), 1.50 (s, 0.6H), 1.46 (s, 1.4H), 1.32 (s, 9H), 0.017 and -0.001 (two s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 151.2, 144.1, 137.9, 134.1, 133.9, 129.4, 128.0, 121.3, 121.0, 84.1, 47.2 (d), 30.7, 30.5, 30.1, 28.1, 26.4, 26.0, 25.7, 23.5, 21.8, 18.9, -0.5, -1.0; ESI HRMS *m/z* $(M+H)^+$ calcd 440.2285, obsv 440.2290.

Spectral data for 3.11i (3:2 mixture of isomers): IR (neat, cm^{-1}) 3282, 1422, 1247, 1160, 1094, 842, 663, 551; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 4.87-4.71 (m, 2H), 2.95-2.88 (m, 2H), 2.42 (s, 3H), 1.97-1.82(m, 2H), 1.62 (d, *J* = 0.6 Hz, 1.2H), 1.51-1.41 (m, 5.8H), -0.016 and -0.047 (two s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 137.3, 134.6, 134.4, 129.9, 127.3, 121.0, 120.7, 43.3, 43.1, 30.1, 29.9, 26.4, 25.8, 25.4, 23.5, 21.7, 18.8, -0.5, -1.0; ESI HRMS *m/z* $(M+H)^+$ calcd 340.1761, obsv 340.1767.



3.36 **3.37** **3.38** **3.39** **3.11j**

Reaction conditions: a. TsNHBoc, Ph_3P, DEAD, THF, 75%; b. 1. O_3, Ph_3P, CH_2Cl_2, 2. Ph_3P=CH=CHO, 44%; c. Ph_3PCH_2SMeCl, *n*-BuLi, THF, 70%; d. LiMe, Et_2O, -20 °C, 10 min, 92%.

Synthesis of 3.37: Diethyl azodicarboxylate solution (40 wt% solution in toluene, 15 mL, 33 mmol) was added dropwise to a solution of 4-penten-1ol (2.86 g, 33.2 mmol), *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (9.00 g, 33.2 mmol), and triphenylphosphine (8.70 g, 33.2 mmol) in THF (120 mL) at rt. After stirring the reaction overnight, the solvent was removed and the residue chromatographed through silica gel to give the desired product **3.37** as a white solid (8.51 g, 75%). IR (neat, cm^{-1}) 3074, 1725, 1355, 1156, 673; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 5,91-5.77 (m, 1H), 5.11-4.96 (m, 2H), 3.82 (t, *J* = 7.5 Hz, 2H), 2.43 (s, 3H), 2.17-2.09 (m, 2H), 1.92-1.82 (m, 2H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 144.2, 137.6, 129.4, 127.9, 115.3, 84.2, 46.9, 31.0, 29.3, 28.0, 21.7; ESI HRMS *m/z* $(M+Na)^+$ calcd 340.1577, obsv 340.1575.

Synthesis of 3.38: Ozone was passed through a solution of **3.37** (1.56g, 4.59 mmol) in CH_2Cl_2 (40 mL) at -78 °C until the solution turned light blue. PPh_3 (3.61 g, 13.8 mmol) was added and the dry ice-acetone bath was removed. Anhydrous $MgSO_4$ was added and the reaction was stirred at rt for about 2 h. The solvent was removed and residue dissolved in benzene (30 mL). (Triphenylphosporanylidene)acetaldehyde (4.20 g, 13.8 mmol) was added and the reaction was refluxed for 10 h. Solvent was removed under reduced pressure and the residue chromatographed through silica gel (ether/hexanes, 1:1) to give the desired product **3.38** (0.74 g, 44%). IR (neat, cm^{-1}) 1726, 1689, 1353, 1156, 674; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.50 (d, *J* = 7.5, 1H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.28

(d, *J* = 8.1 Hz, 2H), 6.87 (dt, *J* = 15.6, 6.6, 1H), 6.15 (dd, *J* = 15.6, 7.5, 1H), 3.85 (t, *J* = 7.5, 2H), 2.42 (s, 3H), 2.46-2.38 (m, 2H), 2.02-1.92 (m, 2H), 1.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.1, 157.2, 151.1, 144.5, 137.5, 133.6, 129.5, 127.9, 84.7, 46.6, 30.0, 28.5, 28.1, 21.8; ESI HRMS *m/z* $(M+Na)^+$ calcd 390.1346, obsv 390.1347.

Synthesis of 3.39: To a suspension of (methylthiomethyl)triphenylphosphonium chloride (1.91 g, 5.31 mmol) in THF (10 mL) was added *n*-butyllithium (1.6 M in hexanes, 3.1 mL, 5.0 mmol) at 0 °C under argon atmosphere. After the addition was complete, the solution was stirred at 0 °C for 0.5 h. **3.38** (0.65 g, 1.8 mmol) in THF (2 ml) was added dropwise. The reaction was stirred overnight and allowed to warm to rt. The reaction was quenched with water at 0 °C, ether added, and the organic phase separated. The aqueous layer was extracted with 2X with ether. The combined organic solution was dried over anhydrous $MgSO_4$, concentrated, and purified by chromatography through a silica gel column (ether/hexanes, 1:5) to afford the desired product **3.39** (0.51 g, 70%). IR (neat, cm^{-1}) 1726, 1355, 1156, 674; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82-7.78 (m, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 6.41-5.55 (m, 4H), 3.88-3.82 (m, 2H), 2.47 (s, 3H), 2.34, 2.31 (2s's, 3H), 2.26-2.14 (m, 2H), 1.95-1.83 (m, 2H), 1.36 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 144.3, 137.7, 134.2, 130.4, 130.0, 129.5, 128.1, 128.0, 127.0 (t), 126.7, 126.0, 84.4, 47.0, 30.4, 30.0 (t), 28.1, 21.9, 17.6, 15.1; ESI HRMS *m/z* $(M+Na)^+$ calcd 410.0889, obsv 410.0883

Synthesis of 3.11j: To a solution of **3.39** (0.50 g, 1.2 mmol) in ether (12 mL) was added MeLi (1.6 *M* in ether, 2.5 mL, 4.0 mmol) at -20 °C under argon atmosphere. After stirring at the same temperature for 10 min, the reaction was quenched with water. The organic phase was separated and aqueous layer extracted with ether. The extractions were

dried over anhydrous $MgSO_4$ and concentrated. Purification of the crude product by chromatography (silica gel, ether/hexanes =1:1) gave **3.11j** (0.35 g, 92%). IR (neat, cm^{-1}) 3281, 1325, 1159, 1093, 815, 663, 550; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 6.22-5.74 (m, 3H), 5.56-5.25 (m, 2H), 2.98-2.83 (m, 2H), 2.36 (s, 3H), 2.23, 2.20 (2s, 3H), 2.06-1.95 (m, 2H), 1.55-1.47 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 137.2, 133.9, 130.5, 130.0, 129.7, 127.0, 126.9, 126.8, 126.7, 125.9, 42.9, 42.7, 30.0, 29.6, 29.3, 21.7, 17.5, 15.0; ESI HRMS m/z $(M+Na)^+$ calcd 434.1439, obsv 434.1430.

3.6 Spectra: see Appendix B

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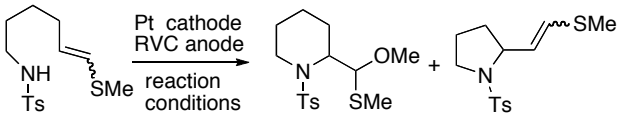
Chapter 4 Chapter 4 The Use of a Nitrogen-Based Nucleophile in Intramolecular Anodic Coupling Reactions (Part II): Building Pipecolic Acid Derivatives[1]

4.1 Problems with the six-membered ring cyclizations

In Chapter 3 of this thesis we described the oxidative coupling of sulfonamides and electron-rich olefins to form proline derivatives. With the success of the cyclizations leading to five-membered rings, attention was turned toward the more difficult to generate six-membered ring products. Initially, a thioenol ether substrate (Table 4-1, entry 1), synthesized in three steps from 2-hydroxyl-tetrahydropyran (Scheme 4-1), was

Table 4-1 Anodic Oxidation of Substrate 4.1



4.1 **4.2** **4.3**

entry	reaction conditions	**4.2**	**4.3**
1	0.5 equiv. *n*-BuLi, MeOH 0.1 M Et_4NOTs, 6 mA, 2.3 F/mol	20%	9%
2	0.5 equiv. *n*-BuLi, 30% MeOH/THF 0.1 M Et_4NOTs, 6 mA, 2.3 F/mol	27%	8%
3	c = 0.006 *M*, 0.5 equiv. *n*-BuLi, MeOH, 0.1 M E_4NOTs, 6 mA, 14 F/mole	17%	5%

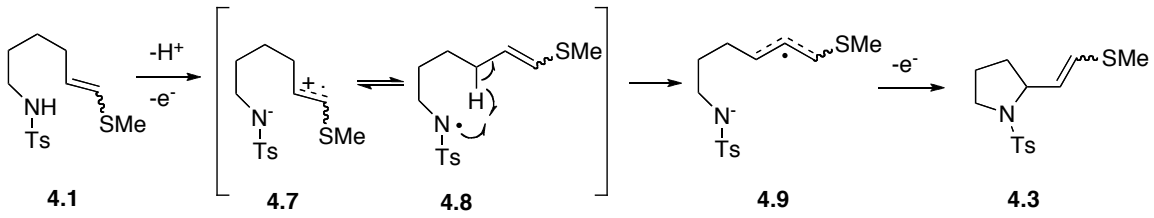
oxidized under the optimized conditions previously used for the five-membered ring cyclizations (Chapter 3, Table 3-2). The vinyl sulfide was one of the best coupling partners for the sulfonamides to make five-membered rings (Chapter 3). However, in this case the reaction led to only a 20% yield of the desired product **4.2** (Table 4-1, entry 1). In addition, a five-membered ring product (**4.3**) was isolated in 20% yield. Attempts to

optimize the reaction by reducing the methanol concentration (entry 2) or the substrate concentration (entry 3) failed.

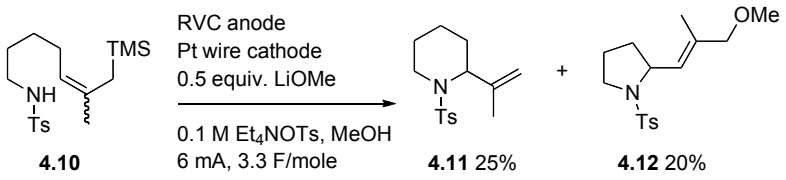
Compound **4.3** arose from either an elimination reaction involving a radical cation intermediate (**4.7**, Scheme 4-2) or a hydrogen atom abstraction (**4.8**). The later was more consistent with our mechanistic studies (Chapter 5).[2] In addition, intramolecular hydrogen atom abstraction by tosylamide and acylamide radicals from δ-positions has been reported in the literature.[3]

Scheme 4-1 Synthesis of Substrate 4.1

Scheme 4-2 Proposed Mechanism for the Formation of Compound 4.3



Scheme 4-3 Oxidation of Substrate 4.10

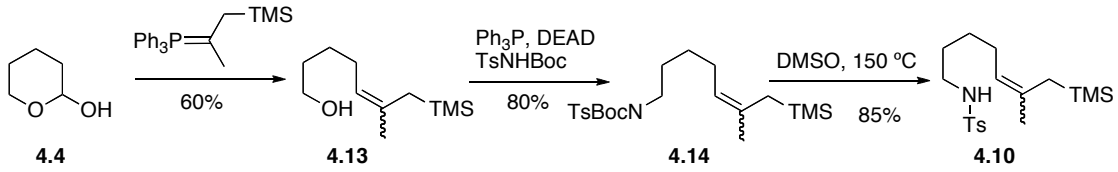


A similar problem was encountered when an allylsilane-based substrate (**4.10**) was used (Scheme 4-3). While excellent yields were obtained for the oxidation of **3.11i** to

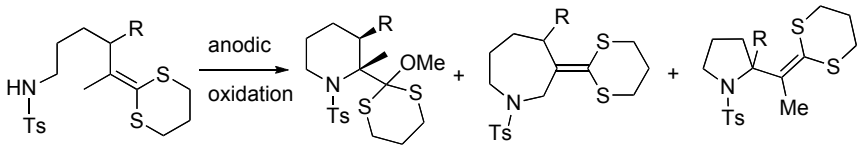
make a five-membered ring, the oxidation of the six-membered ring counterpart (**4.10**) led to only 25% yield of the desired product (**4.11**) along with 20% of a five-membered ring product (**4.12**).

The synthesis of **4.10** was depicted in Scheme 4-4. The allylsilane functionality was introduced by a Wittig reaction. The resulting alcohol **4.13** was transformed into the tosylamide **4.10** by standard procedures.

Scheme 4-4 Synthesis of Substrate 4.10



Scheme 4-5 Oxidation of Susbtrate 4.15a and 4.15b

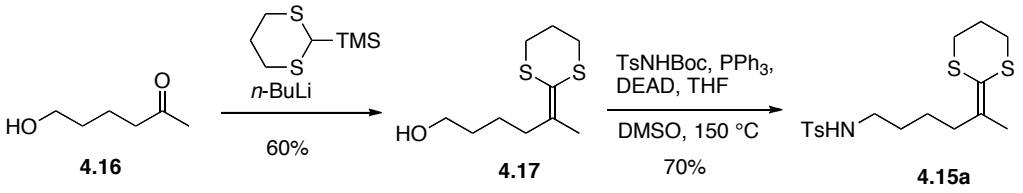


Reaction Conditions: a. RVC anode, 0.5 eq. LiOMe, 0.1 M Et_4NOTs, MeOH, 6 mA, 2.4 F/mole; b. RVC anode, 0.5 eq. LiOMe, 0.1 M $LiClO_4$, MeOH, 6 mA, 2.4 F/mole.

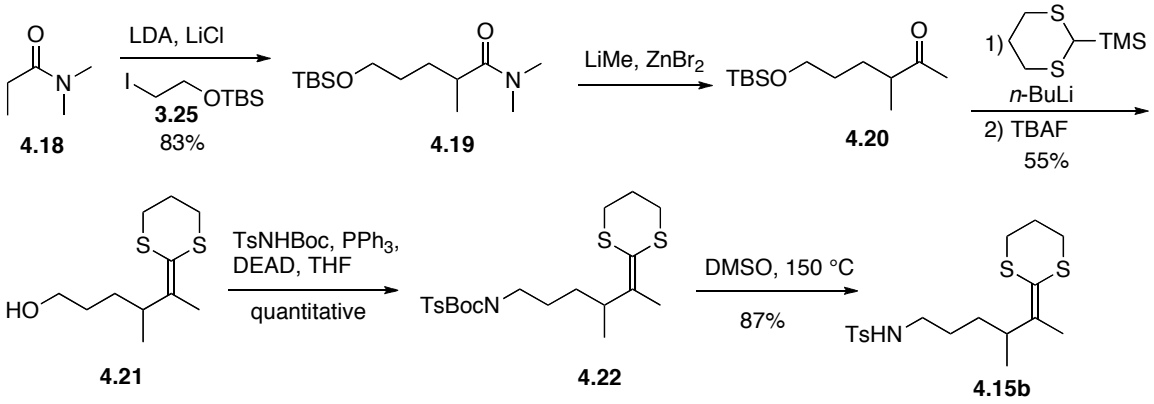
The oxidation of ketene dithioacetals **4.15a** and **4.15b** were also investigated (Scheme 4-5). The synthesis of **4.15a** and **4.15b** followed the same protocols used for the synthesis of their five-membered ring counterparts (Scheme 4-6 and Scheme 4-7). The oxidation of both substrates led to a low yield of the desired product **4.23** along with products derived from eliminations. For the oxidation of **4.15a**, the elimination occurred

from both allylic positions leading to both seven- and five-membered ring products. The oxidation of **4.15b** under the same conditions afforded 40% of the desired six membered-ring product along with trace amount of **4.24b**. Switching the electrolyte from Et_4NOTs to $LiClO_4$ resulted in increased yields for both **4.23b** and **4.24b**. In this case, a 51% of **4.23a** was isolated along with **4.24b** in 10% yield.

Scheme 4-6 Synthesis of Substrate 4.15a



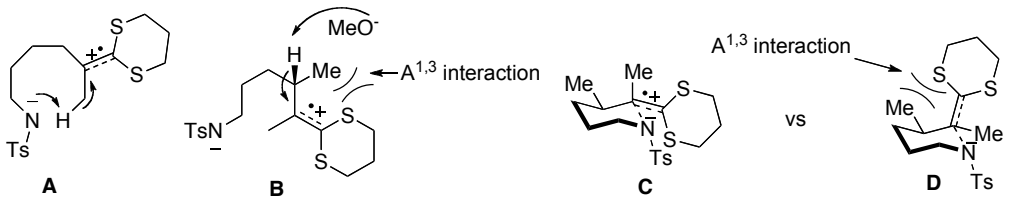
Scheme 4-7 Synthesis of Substrate 4.15b



The side products in the above two cases most likely arose from intermolecular deprotonation of the ketene dithioacetal-derived radical cations generated at the anode.[4] Later studies (Chapter 5) showed that the anodic cyclization of a tosylamide onto a ketene dithioacetal occurred through radical cation type intermediate rather than nitrogen-based radical. Intramolecular deprotonation or hydrogen atom abstraction would have to go through an eight-membered ring transition state (Figure 4-1, **A**) to account for the

formation of the seven-membered ring product. The elimination from the tertiary allylic position to form **4.25b** was hindered by $A^{1,3}$ interaction (Figure 4-1, **B**).[5]

Figure 4-1 Origin of Stereoselectivity in the Oxidation of Substrate 4.15b

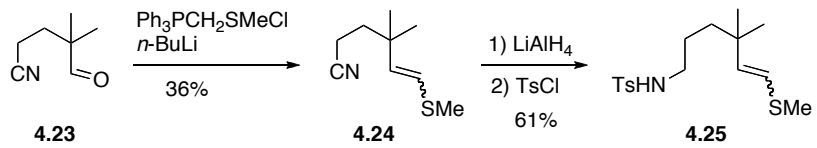


The oxidation of **4.15b** afforded the six-membered ring product as a single diastereomer with the dithioorthoester *trans* to the neighboring methyl group. This stereochemical outcome could be rationalized by the preference of the transition state to minimize $A^{1,3}$ interaction by placing the dithioacetal *trans* to the allylic methyl (Figure 4-1, **C** vs **D**).[5]

4.2 Efforts to improve the cyclizations

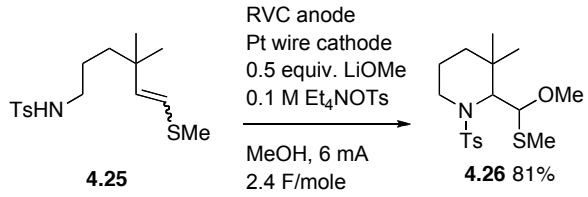
It was clear that hydrogen atom abstraction or elimination from the radical cation were competing with the relatively slow six-membered ring cyclizations. In order to elucidate the success of six-membered ring formation in the absence of the elimination reactions, substrates **4.25** was synthesized (Scheme 4-8).

Scheme 4-8 Synthesis of Substrate 4.25

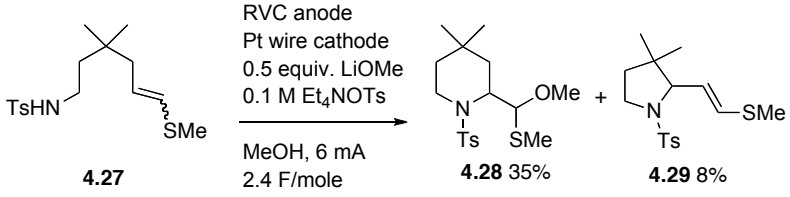


Two methyl groups were introduced at the allylic position to avoid side reactions at this position. The synthesis of compound **4.25** commenced with conversion of aldehyde **4.23** to vinyl sulfide **4.24** in 36% yield using a Wittig reaction, followed by $LiAlH_4$ reduction and installation of the tosyl group to yield the substrate **4.25** (61% yield over two steps.) The oxidation of **4.25** led to an 81% isolated yield of desired product **4.26** (Scheme 4-9).

Scheme 4-9 Anodic Oxidation of Substrate 4.25



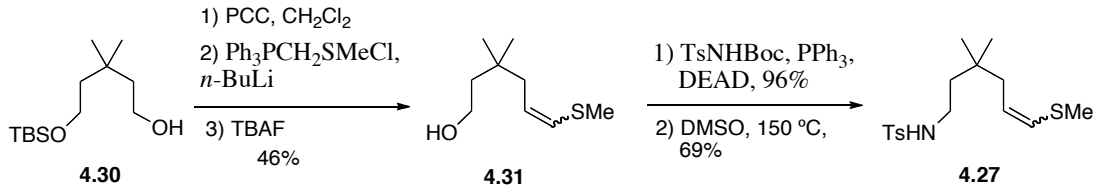
Scheme 4-10 Anodic Oxidation of Substrate 4.27



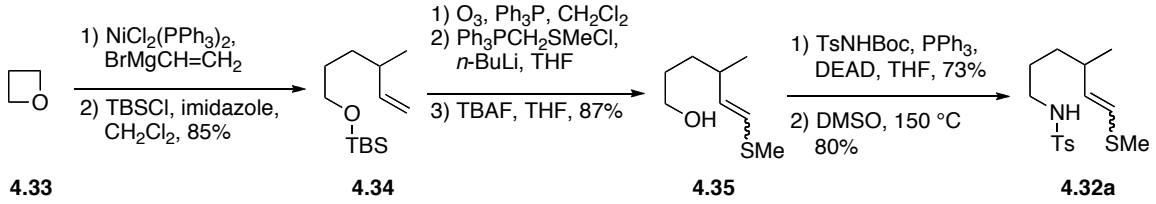
The oxidation of **4.27** was employed to provide a control experiment to determine whether the success of the cyclization resulting from **4.25** was really due to the *gem*-dimethyl groups stopping the hydrogen atom abstraction or if it was the result of a faster cyclization due to the *gem*-dialkyl effect.[6] While the presence of the *gem* methyl groups in **4.27** improved the cyclization relative to reaction originating from **4.1** (Table 4-1 vs Scheme 4-10), it was clear that the 81% yield of product **4.26** was mainly due to the *gem*-

dimethyl group in **4.25** preventing the hydrogen atom abstraction. Compound **4.27** was synthesized from known alcohol **4.30** by standard transformations (Scheme 4-11).

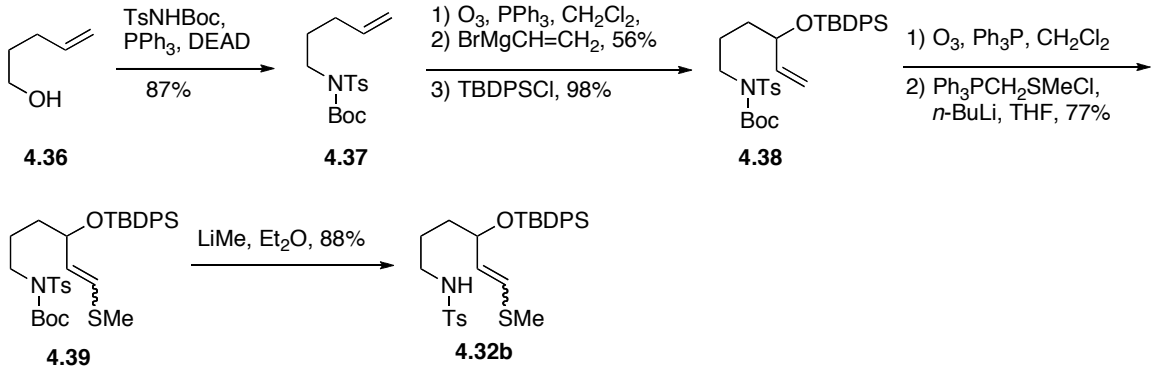
Scheme 4-11 Synthesis of Substrate 4.27



Scheme 4-12 Synthesis of Substrate 4.32a



Scheme 4-13 Synthesis of Substrate 4.32b



With the knowledge that the six-membered ring cyclizations can be successful, attention was turned toward developing a strategy for the synthesis of 3-substituted pipecolic acid derivatives. The plan was to take advantage of sterics to slow down the elimination reaction or hydrogen abstraction and increase the time available for the

cyclization. It was hoped that a single substituent on the allylic carbon of the substrate would accomplish this task. Since substrates like **4.32a** (Scheme 4-12) and **4.32b** (Scheme 4-13) can be synthesized in an asymmetric fashion, a successful cyclization would allow access to the chiral amino acid derivatives.[7]

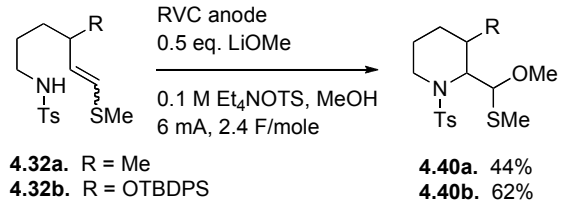
In practice, compounds **4.32a** and **4.32b** were synthesized as racemic mixtures as shown in Scheme 4-12 and 4-13, respectively. The synthesis of **4.32a** started with the ring opening of trimethyleneoxide with a Grignard reagent generated *in situ* using nickel-catalyzed dimerization of vinylmagnesium bromide to afford an alcohol,[8] which was protected to afford silylether **4.34** in 85% yield over two steps. Ozonolytic scission, Wittig olefination, and removal of the silyl protecting group led to alcohol **4.35**, which was converted into substrate **4.32a** by the two-step standard procedures for the installation of tosyl amides.

On the other hand, compound **4.32b** was synthesized from commercially available alcohol, 4-penten-1-ol (**4.36**). A Mistunobu reaction afforded the protected tosylamide (**4.37**) in 87% yield. Ozonolysis and reaction with vinylmagnesium bromide led to an allylic alcohol (56% over two steps), which was protected as a silylether **4.38** in 98% yield. The olefin in **4.38** was cleaved and the resulting aldehyde converted to vinyl sulfide (**4.39**) using a Wittig reaction (77% over two steps). Finally, the *t*-Boc group was excised by brief exposure to methyllithium to furnish **4.32b** in 88% yield.

With the substrates in hand, the cyclizations were examined (Scheme 4-14). When a methyl group was placed on the allylic carbon of the substrate the yield of cyclized product improved to 44% (20% without the methyl). The yield could be raised to 62% by

placing a larger *t*-butyldiphenylsiloxy group on the allylic carbon of the substrate. In both cases, a mixture of diastereomers were obtained.

Scheme 4-14 Anodic Oxidation of Substrates 4.32a and 4.32b

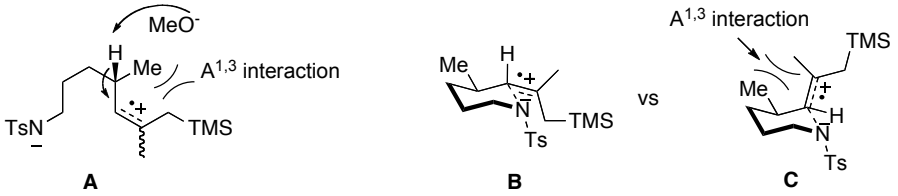


4.32a. R = Me
4.32b. R = OTBDPS

4.40a. 44%
4.40b. 62%

While the oxidation of **4.32b** was moderately successful, the need for a large group at the allylic position limited the types of pipecolic acid derivatives that could be made with the cyclizations. In addition, the oxidations of 4.32a and 4.32b afforded no stereochemical control. Insights to further improve the cyclization came from the observation made during the oxidation of substrate **4.15b**. In that case, elimination from one of the allylic positions was effectively blocked because of the presence of $A^{1,3}$ interaction between the dithane and the allylic substituent (Figure 4-1, **B**). Hence, we

Figure 4-2 Role of $A^{1,3}$ Interaction in the Oxidation of 4.42

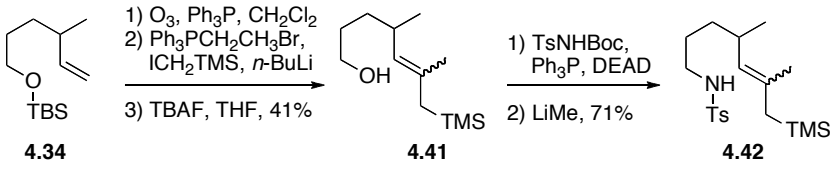


reasoned that a substrate like **4.42** (Scheme 4-15) employing a trisubstituted allylsilane as electron-rich olefin might lead to a successful cyclization. For the elimination to occur, the allylic proton needs to be perpendicular to the radical cation (Figure 4-2, **A**). However, the presence of $A^{1,3}$ interaction disfavors such a conformation. The poor

overlap between the allylic proton and the radical cation would be expected to lead to a slow elimination reaction and buy more time for the cyclization.

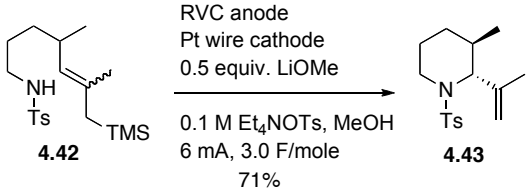
Substrate **4.42** was synthesized by standard procedures from silyl ether **4.34**, an intermediate used in the synthesis of substrate **4.32a**. The oxidation of compound **4.42** afforded a 71% isolated yield of the cyclized product as a single diastereomer. Clearly, the introduce of $A^{1,3}$ interaction not only hindered effectively the elimination (Figure 4-2, **A**) but also served to control the diastereoselectivity of the product. The two substituents were placed *trans* to each other in the transition state to avoid unfavorable $A^{1,3}$ interaction (Figure 4-2, **B** vs **C**). Since substrate like **4.42** can be synthesized asymmetrically, the oxidative cylization affords a potential powerful route to 3-substituted pipecolic acid derivatives.

Scheme 4-15 Synthesis of Substrate 4.42



4.34 **4.41** **4.42**

Scheme 4-16 Anodic Oxidation of Substrate 4.42



4.42 **4.43**

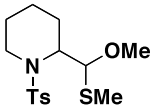
4.3 Conclusions

Intramolecular anodic olefin coupling reactions were used successfully to generate carbon-nitrogen bonds and synthesize substituted proline and pipecolic acid derivatives. The cyclization reactions benefit from the use of LiOMe as a base and methanol solvent. For the synthesis of five-membered ring products, the cyclizations proceed well with a variety of electron-rich olefins. Coupling reactions leading to six-membered rings are more difficult because of the competing elimination from the allylic position. This problem can be minimized by manipulating the sterics of the reactions, an observation that suggests the use of a trisubstituted allylsilane as an optimized olefin coupling partner for the reactions.

4.4 Experimental Section

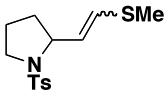
General procedure for electrolysis reactions: LiOMe (1.0 *M* in MeOH, 0.5 equiv) was added to either a methanol or 30% MeOH/THF solution of the substrate (0.03 *M*, 1 equiv) and the electrolyte tetraethylammonium *p*-toluenesulfonate in a three-neck round bottom flask at rt under argon atmosphere. Two of the three septa were replaced by a reticulated vitreous carbon anode (100 PPI) and platinum wire cathode. The solution was sonicated for 10 min. The electrolysis reaction was carried out at constant current of 6.0 mA until complete consumption of the starting material (the progress of the reaction was monitored by ^{1}H-NMR). When complete, the reaction was concentrated under reduced pressure and then the residue chromatographed through a silica gel column (slurry packed using 1% triethylamine in hexane solution) to give the desired product.

Spectra data for electrolysis products:



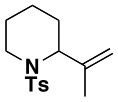
2-(methoxy(methylthio)methyl)-1-tosylpiperidine (4.2)

IR (neat, cm^{-1}) 1337, 1156, 1091, 734, 654, 549; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 4.60 (d, *J* = 7.5 Hz, 1H), 4.19-4.15 (m, 1H), 3.70 (dd, *J* = 14.7, 4.5 Hz, 1H), 3.39 (s, 3H), 3.12-3.02 (m, 1H), 2.41 (s, 3H), 2.07 (s, 3H), 2.00-1.95 (m, 1H), 1.53-1.36 (m, 4H), 1.24-1.15 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 138.8, 129.8, 127.4, 89.0, 56.6, 54.6, 42.4, 24.2, 23.9, 21.7, 19.4, 11.2; ESI HRMS *m/z* $(M+H)^+$ calcd 330.1192, obsv 330.1185.



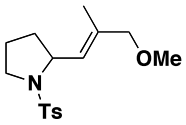
2-(2-(methylthio)vinyl)-1-tosylpyrrolidine (4.3)

IR (neat, cm^{-1}) 1344, 1158, 1092, 665, 587; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 6.29 (dd, *J* = 15.0, 1.2 Hz, 0.9H), 5.98 (d, *J* = 9.9 Hz, 0.1H), 5.71 (dd, *J* = 9.9, 8.1Hz, 0.1H), 5.17 (dd, *J* = 15.0, 6.6 Hz, 0.9H), 4.29-4.26 (m, 1H), 3.46-3.38 (m, 1H), 3.34-3.26 (m, 1H), 2.43 (s, 3H), 2.17 (s, 2.7H), 2.01 (s, 0.3H), 1.86-1.61 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 136.0, 129.8, 127.8, 127.2, 125.2, 62.0, 48.7, 33.1, 24.1, 21.8, 14.8; ESI HRMS *m/z* $(M+Na)^+$ calcd 320.0749, obsv 320.0747.



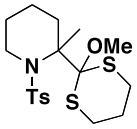
2-(prop-1-en-2-yl)-1-tosylpiperidine (4.11)

IR (neat, cm^{-1}) 1337, 1155, 660, 551; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 5.06-5.05 (m, 1H), 4.93-4.92 (m, 1H), 4.54 (s, 1H), 3.79-3.73 (m, 1H), 3.10-3.00 (m, 1H), 2.46 (s, 3H), 1.96-1.90 (m, 1H), 1.75 (s, 3H), 1.51-1.39 (m, 4H), 1.28-1.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 142.2, 139.0, 129.9, 127.3, 113.7, 57.2, 42.1, 26.1, 24.6, 21.8, 21.4, 19.5; ESI HRMS *m/z* $(M+H)^+$ calcd 280.1366, obsv 280.1365.



(E)-2-(3-methoxy-2-methylprop-1-enyl)-1-tosylpyrrolidine (4.12)

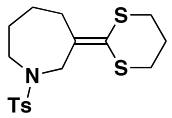
IR (neat, cm^{-1}) 1344, 1159, 1093, 665, 587, 550; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 5.46-5.42 (m, 1H), 4.39-4.32 (m, 1H), 3.79-3.78 (m, 2H), 3.50-3.33 (m, 2H), 3.30 (s, 3H), 2.45 (s, 3H), 1.94-1.80 (m, 2H), 1.75 (d, *J* = 1.5 Hz, 3H), 1.68-1.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 135.6, 133.1, 129.6, 128.7, 127.6, 57.7, 57.6, 48.9, 33.5, 24.4, 21.7, 14.1; ESI HRMS *m/z* $(M+Na)^+$ calcd 332.1291, obsv 332.1290.



2-(2-methoxy-1,3-dithian-2-yl)-2-methyl-1-tosylpiperidine (4.23a)

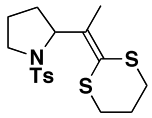
IR (neat, cm^{-1}) 1331, 1086, 656, 547; ^1H NMR (600 MHz, $CDCl_3$, contaminated with unknown compound) δ 7.82 (d, *J* = 7.8 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 2H), 3.75-3.70 (m, 1H), 3.60-3.58 (m, 1H), 3.55 (s, 3H), 2.95-2.87 (m, 4H), 2.41 (s, 3H), 2.39-2.35 (m, 1H),

1.98 (s, 3H), 1.98-1.87 (m, 2H), 1.72-1.70 (m, 1H), 1.59-1.55 (m, 1H), 1.55 (s, 3H), 1.34-1.31 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.3, 140.1, 106.1, 72.7, 51.8, 44.6, 33.6, 29.7, 28.3, 28.0, 22.1, 21.7, 17.9; ESI HRMS *m/z* $(M+Na)^+$ calcd 424.1045, obsv 424.1051.



3-(1,3-dithian-2-ylidene)-1-tosylazepane (4.24a)

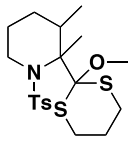
IR (neat, cm^{-1}) 1333, 737, 667, 549; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 4.10 (s, 2H), 3.12 (t, *J* = 5.4 Hz, 2H), 2.91 (t, *J* = 6.6 Hz, 2H), 2.86 (t, *J* = 6.6 Hz, 2H), 2.53 (t, *J* = 3.0 Hz, 2H), 2.13-2.09 (m, 2H), 1.71-1.68 (m, 2H), 1.57-1.54 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.0, 136.8, 136.6, 129.7, 127.0, 124.7, 51.9, 48.8, 31.5, 30.0, 29.5, 29.3, 27.1, 24.6, 21.5; ESI HRMS *m/z* $(M+Na)^+$ calcd 392.0783, obsv 392.0788.



2-(1-(1,3-dithian-2-ylidene)ethyl)-1-tosylpyrrolidine (4.25a)

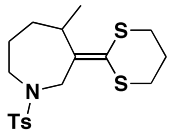
IR (neat, cm^{-1}) 1344, 1091, 659, 586, 548; ^{1}H NMR (600 MHz, $CDCl_3$, contaminated with unknown compound) δ 7.77 (d, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 2H), 4.97 (t, *J* = 7.8 Hz, 1H), 3.45-3.38 (m, 2H), 3.13-3.08 (m, 1H), 2.99-2.95 (m, 1H), 2.93-2.89 (m, 2H), 2.79 (m, 1H), 2.43 (s, 3H), 2.18-2.14 (m, 1H), 1.92-1.84 (m, 1H), 1.88 (s, 1H), 1.78-1.73 (m, 1H), 1.58-1.52 (m, 1H), 1.40-1.33 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.2,

139.8, 134.5, 129.5, 127.9, 122.3, 61.5, 50.1, 31.7, 30.3, 29.8, 25.1, 24.7, 21.6, 15.4; ESI HRMS *m/z* $(M+Na)^+$ calcd 392.0783, obsv 392.0786.



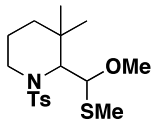
2-(2-methoxy-1,3-dithian-2-yl)-2,3-dimethyl-1-tosylpiperidine (4.23b)

IR (neat, cm^{-1}) 1334, 1160, 1090, 547; ^1H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 3.90-3.80 (m, 1H), 3.74-3.66 (m, 1H), 3.53 (s, 3H), 2.97-2.76 (m, 4H), 2.48-2.45 (m, 1H), 2.40 (s, 3H), 1.97-1.81 (m, 3H), 1.91 (s, 3H), 1.30-1.19 (m, 2H), 1.12-1.01 (m, 1H), 0.88 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.4, 140.2, 129.2, 127.3, 108.2, 76.3, 51.0, 44.6, 33.4, 28.6, 28.5, 28.3, 21.5, 21.4, 21.2, 19.9, 19.2; ESI HRMS *m/z* $(M+H)^+$ calcd 416.1382, obsv 416.1367



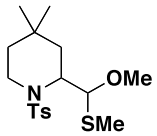
3-(1,3-dithian-2-ylidene)-4-methyl-1-tosylazepane (4.24b)

IR (neat, cm^{-1}); ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 4.30 (d, *J* = 13.5 Hz, 1H), 3.83 (d, *J* = 13.5 Hz, 1H), 3.34-3.22 (m, 2H), 2.99-2.81 (m, 5H), 2.42 (s, 3H), 2.13-2.05 (m, 2H), 1.91-1.80 (m, 1H), 1.64-1.47 (m, 3H), 1.09 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 137.7, 136.0, 129.9, 128.9, 127.5, 48.7, 48.6, 36.9, 33.2, 29.6, 29.4, 26.5, 24.6, 21.8, 18.0; ESI HRMS *m/z* $(M+H)^+$ calcd 384.1120, obsv 384.1109.



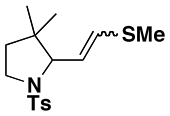
2-(methoxy(methylthio)methyl)-3,3-dimethyl-1-tosylpiperidine (4.26)

IR (neat, cm^{-1}) 1335, 1156, 1092, 656, 584; ^1H NMR (300 MHz, $CDCl_3$, only the major isomer is shown) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 4.62 (d, *J* = 3.9 Hz, 1H), 3.99 (d, *J* = 3.9 Hz, 1H), 3.73-3.68 (m, 1H), 3.37 (s, 3H), 3.15 (td, *J* = 13.2, 3.3 Hz, 1H), 2.44 (s, 3H), 2.16 (s, 3H), 1.86 (td, *J* = 13.5, 4.2 Hz, 1H), 1.68-1.52 (m, 1H), 1.46-1.40 (m, 1H), 1.18-1.11 (m, 1H), 1.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 138.8, 129.7, 127.4, 94.9, 64.8, 55.6, 42.4, 34.0, 33.8, 28.4, 28.2, 21.8, 21.5, 16.4; ESI *m/z* $(M+H)^+$ calcd 380.1325, obsv 380.1325.



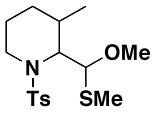
2-(methoxy(methylthio)methyl)-4,4-dimethyl-1-tosylpiperidine (4.28)

IR (neat, cm^{-1}) 1156, 1093, 731, 658, 550; ^1H NMR (300 MHz, $CDCl_3$, only the major isomer is shown) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 4.59 (d, *J* = 7.5 Hz, 1H), 4.21-4.15 (m, 1H), 3.60-3.53 (m, 1H), 3.38 (s, 3H), 3.18-3.06 (m, 1H), 2.42 (s, 3H), 2.05 (s, 3H), 1.85 (dd, *J* = 14.1, 4.5, Hz, 1H), 1.37 (dd, *J* = 14.1, 6.3 Hz, 1H), 1.26-1.14 (m, 2H), 0.95 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 138.5, 129.8, 127.7, 88.6, 56.4, 54.8, 40.0, 36.2, 35.7, 32.7, 28.2, 28.0, 21.8, 10.8; ESI HRMS *m/z* $(M+Na)^+$ calcd 380.1325, obsv 380.1322.



3,3-dimethyl-2-(2-(methylthio)vinyl)-1-tosylpyrrolidine (4.29)

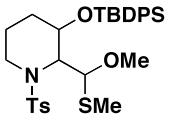
IR (neat, cm^{-1}) 1345, 1161, 1095, 663; ^{1}H NMR (300 MHz, $CDCl_3$, ~ 85:15 mixture of isomers and * denotes the minor one) δ 7.76 (d, *J* = 8.1 Hz, 0.3H), 7.68 (d, *J* = 8.1 Hz, 1.7H), 7.29 (d, *J* = 8.1 Hz, 2H), 6.16 (d, *J* = 15.0 Hz, 1H), 5.58 (dd, *J* = 9.6, 9.3 Hz, 0.15H), 5.07 (dd, *J* = 15.0, 8.1 Hz, 0.85H), 3.81 (d, *J* = 9.3 Hz, 0.15H), 3.60 (d, *J* = 8.1 Hz, 0.85H), 2.44*, 2.42 (2s, 3H), 2.32* (s, 0.45H), 2.16 (s, 2.55H), 1.72-1.57 (m, 1H), 1.50-1.42 (m, 1H), 0.93 (s, 0.45H), 0.89 (s, 2.55H), 0.77 (s, 2.55H), 0.75 (s, 0.45H); ^{13}C NMR (75 MHz, $CDCl_3$, only the major isomer is shown) δ 143.3, 136.0, 129.6, 127.8, 127.7, 122.9, 71.8, 46.5, 42.7, 37.6, 26.4, 23.3, 21.8, 14.7; ESI HRMS *m/z* $(M+Na)^+$ calcd 348.1062, obsv 348.1060.



2-(methoxy(methylthio)methyl)-3-methyl-1-tosylpiperidine (4.40a)

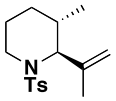
Only one of the isomers is shown here. IR (neat, cm^{-1}) 1337, 1160, 1091, 661, 549; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 4.62 (d, *J* = 6.3 Hz, 1H), 3.93 (d, *J* = 6.3 Hz, 1H), 3.66-3.60 (m, 1H), 3.40 (s, 3H), 2.89-2.74 (m, 1H), 2.45 (s, 3H), 2.32-2.36 (m, 1H), 2.13 (s, 3H), 1.89-1.79 (m, 1H), 1.72-1.55 (m, 1H), 1.41-1.30 (m, 2H), 1.05 (d, *J* = 7.2 Hz, 0.9 H), 1.01 (d, *J* = 7.5 Hz, 2.1H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 143.1, 138.6, 90.9, 60.4, 56.7, 42.5, 26.8, 25.9, 21.8, 19.4, 19.2, 12.4; ESI HRMS *m/z* $(M+Na)^+$ calcd 366.1165, obsv 366.1168.



3-(*tert*-butyldiphenylsilyloxy)-2-(methoxy(methylthio)methyl)-1-tosylpiperidine (4.40b)

IR (neat, cm^{-1}) 3069, 1427, 1158, 1111, 703; ^1H NMR (600 MHz, $CDCl_3$, only one isomer was shown) δ 7.89 (d, *J* = 7.8 Hz, 2H), 7.76 (d, *J* = 6.6 Hz, 2H), 7.72 (d, *J* = 6.6 Hz, 2H), 7.43-7.37 (m, 6H), 7.20 (d, *J* = 8.4 Hz, 2H), 4.54-4.12 (m, 2H), 4.15 (d, *J* = 10.2 Hz, 1H), 3.45-3.43 (m, 1H), 3.18 (s, 3H), 2.79-2.74 (m, 1H), 2.40 (s, 3H), 2.08-2.03 (m, 1H), 1.71 (s, 3H), 1.49 (d, *J* = 13.2 Hz, 1H), 1.33-1.26 (m, 2H), 1.16 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.3, 138.8, 136.2, 136.0, 134.0, 133.6, 127.7, 127.7, 129.0, 127.9, 127.6, 82.7, 65.6, 60.8, 55.6, 40.7, 27.1, 26.8, 21.5, 19.3, 18.7, 8.3; ESI HRMS *m/z* $(M+Na)^+$ calcd 606.2138, obsv 606.2136.



(2S,3S)-3-methyl-2-(prop-1-en-2-yl)-1-tosylpiperidine (4.43)

IR (neat, cm^{-1}) 1452, 1337, 1163, 1094, 665, 546; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 4.94 (m, 1H), 4.75 (s, 1H), 4.0 (s, 1H), 3.49-3.42 (m, 1H), 3.20-3.11 (m, 1H), 2.42 (s, 3H), 2.13-2.06 (m, 1H), 1.70 (s, 3H), 1.68-1.56 (m, 2H), 1.40-1.18 (m, 2H), 0.95 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

143.0, 142.8, 138.1, 129.6, 127.5, 114.1, 65.1, 42.8, 29.2, 26.3, 21.8, 21.0, 20.5, 18.8; ESI HRMS *m/z* $(M+H)^+$ calcd 294.1530, obsv 294.1522.

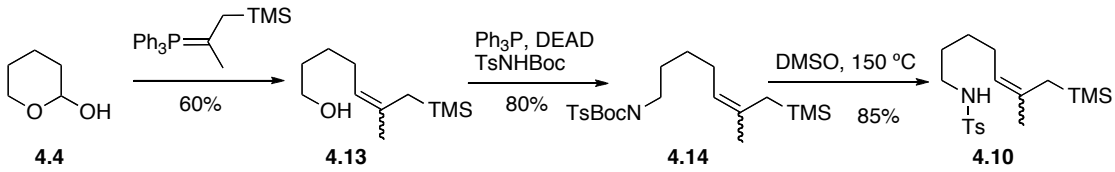
Synthesis of Electrolysis Substrates:

Synthesis of 4.6: *n*-BuLi (1.6 *M* in hexanes, 25 mL, 40 mmol) was added to a suspension of (methylthiomethyl)triphenylphosphonium chloride (14.3 g, 40 mmol) in THF (110 mL) at 0 °C under argon atmosphere. Upon complete addition, the solution was stirred at the same temperature for 0.5 h and then 2-hydroxytetrahydropyran was added dropwise. The reaction was stirred overnight and allowed to warm to rt. Brine and ether were added at 0 °C. The organic layer was separated and aqueous phase extracted with ether. The combined organic solution was dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was chromatographed through silica gel to give a mixture of 2-hydroxytetrahydropyran and the desired product **4.5**.

Without further purification, the mixture was dissolved in THF (70 mL) under argon atmosphere. *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (2.6 g, 9.6 mmol), triphenylphosphine (5.0 g, 19 mmol), and diethyl azodicarboxylate solution (40 wt% solution in toluene, 7.1 mL, 16 mmol) were added sequentially at rt. The resulting yellow solution was stirred overnight. Solvent was removed and the residue chromatographed (silica gel, ether/hexane, 1:10, 1:5) to gave **4.6** (1.7 g, 43%). IR (neat, cm^{-1}) 1726, 1355, 1257, 1155, 674, 581; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* =

8.4 Hz, 2H), 6.00 (d, *J* = 15.0 Hz, 0.75H), 5.90 (d, *J* = 9.3 Hz, 0.25H), 5.55-5.39 (m, 1H), 3.82 (t, *J* = 7.5 Hz, 2H), 2.44 (s, 3H), 2.27, 2.24 (2s, 3H), 2.24-2.12 (m, 2H), 1.84-1.71 (m, 2H), 1.54-1.37 (m, 2H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 144.2, 144.2, 137.8, 129.4, 128.4, 128.0, 127.5, 127.0, 124.5, 84.2, 84.2, 47.2, 32.8, 30.0, 29.7, 28.8, 28.1, 26.7, 26.2, 21.8, 17.2, 15.3; ESI HRMS *m/z* $(M+Na)^+$ calcd 422.1430, obsv 422.1428

Synthesis of 4.1: 4.1 was synthesized from **4.6** by **method 1** described in the general procedure of Chapter 3. IR (neat, cm^{-1}) 3281, 1323, 1158, 1093, 814, 663, 551; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 5.91 (d, *J* = 14.7 Hz, 0.75H), 5.85 (d, *J* = 9.6 Hz, 0.25H), 5.43-5.27 (m, 1H), 5.14, 5.09 (2t, *J* = 6.0, 6.0 Hz, 1H), 2.97-2.87 (m, 2H), 2.42 (s, 3H), 2.23, 2.19 (2s, 3H), 2.05-1.98 (m, 2H), 1.50-1.31 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 143.5, 137.2, 129.9, 128.2, 127.5, 127.3, 126.8, 124.5, 43.2, 43.2, 38.4, 32.6, 29.2, 29.0, 28.6, 26.5, 26.0, 21.7, 17.2, 15.2; ESI HRMS *m/z* $(M+H)^+$ calcd 300.1086, obsv 300.1087.



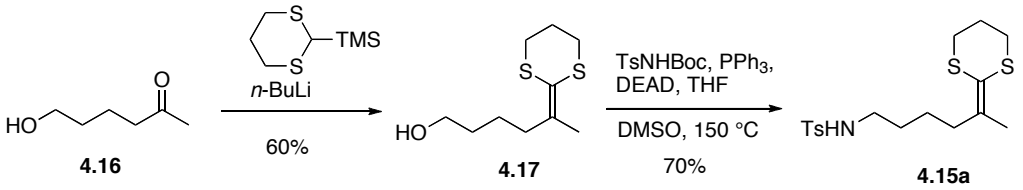
Synthesis of 4.10: **4.10** was synthesized in the same fashion as **3.11i**.

Spectra data for 4.13: IR (neat, cm^{-1}) 3329, 1247, 855; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.99-4.90 (m, 1H), 3.61 (t, *J* = 6.6, 2H), 2.20-1.88 (m, 2H), 1.65-1.31 (m, 9H), 0.01, -0.02 (2s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.4, 133.2, 122.4, 122.2, 63.1, 32.7, 32.6,

30.1, 28.4, 28.1, 26.5, 26.4, 26.3, 23.4, 18.8, -0.5, -1.0; ESI HRMS *m/z* $(M+H)^+$ calcd 201.1669, obsv 201.1663.

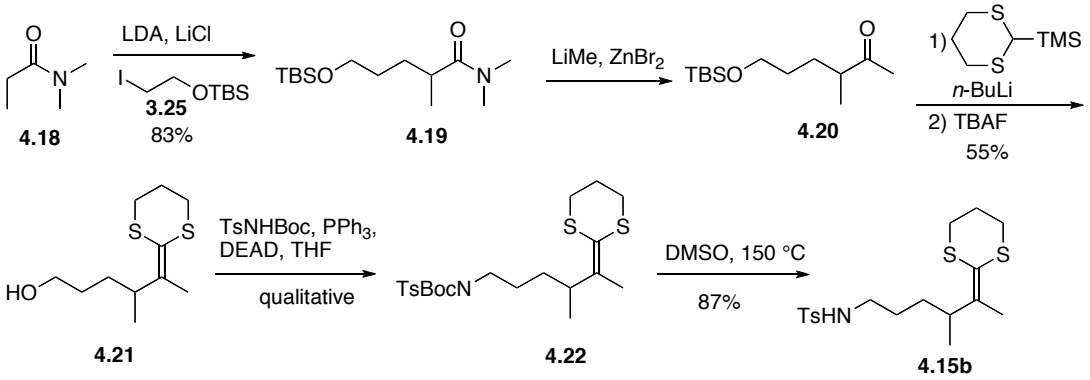
Spectra data for 4.14: IR (neat, cm^{-1}) 1727, 1357, 1156, 851, 674; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 4.99-4.90 (m, 1H), 3,82-3.77 (m, 2H), 2.41 (s, 3H), 2.05-1.90 (m, 2H), 1.79-1.69 (m, 2H), 1.65 (d, *J* = 1.2 Hz, 1.6H), 1.57 (s, 1.4H), 1.49, 1.44 (2s, 2H), 1.40-1.27 (m, 2H), 1.30, 1.31 (2s, 9H), 0.01, -0.02 (2s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 144.1, 137.9, 137.9, 133.5, 133.3, 129.4, 128.0, 128.0, 122.3, 122.0, 84.1, 47.4, 30.2, 30.1, 30.1, 28.3, 28.1, 28.0, 27.5, 27.3, 26.5, 23.5, 21.8, 18.9, -0.45, -0.99; ESI HRMS *m/z* $(M+H)^+$ calcd 454.2442, obsv 454.2431.

Spectra data for 4.10: IR (neat, cm^{-1}) 3280, 1326, 1160, 1094, 856, 664, 551; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 5.07-5.02 (m, 1H), 4.88-4.79 (m, 1H), 2.91-2.85 (m, 2H), 2.40 (s, 3H), 1.91-1.76 (m, 2H), 1.61, 1.50 (2s, 3H), 1.48-1.40 (m, 4H), 1.30-1.20 (m, 2H), -0.02, -0.05 (2s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 137.3, 133.6, 133.4, 129.9, 127.3, 122.1, 121.7, 43.4, 43.4, 30.1, 29.4, 29.3, 28.1, 27.7, 27.2, 27.0, 26.4, 23.4, 21.7, 18.8, -0.48, -1.0; ESI HRMS *m/z* $(M+H)^+$ calcd 354.1918, obsv 354.1910.



Synthesis of 4.15a: **4.15a** was synthesized in the same fashion as **3.11d**. The spectra data of **4.17** was consistent the literature.[2] Spectra data for **4.15a**: IR (neat, cm^{-1}) 3280, 1324, 1158, 662, 551; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4

Hz, 2H), 5.02 (t, *J* = 6.0 Hz, 1H), 2.98-2.94 (m, 2H), 2.91-2.80 (m, 4H), 2.44 (s, 3H), 2.28 (t, *J* = 6.9 Hz, 2H), 2.14-2.06 (m, 2H), 1.84 (s, 3H), 1.48-1.34 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 140.1, 137.2, 130.0, 127.4, 120.9, 43.3, 35.3, 30.5, 30.3, 29.2, 25.2, 25.0, 21.8, 20.3; ESI HRMS *m/z* $(M+H)^+$ calcd 394.0940, obsv 394.0941.



Synthesis of 4.15: **4.15** was synthesized in the same fashion as **3.11e**.

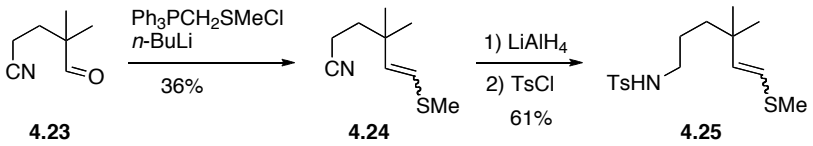
Spectra data for 4.19: IR (neat, cm^{-1}) 1649, 1255, 1098, 836, 776; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.60 (t, *J* = 6.6 Hz, 2H), 3.05 (s, 3H), 2.95 (s, 3H), 2.77-2.70 (m, 1H), 1.73-1.64 (m, 1H), 1.55-1.39 (m, 3H), 1.10 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 63.3, 37.4, 35.8, 35.5, 30.8, 30.5, 26.2, 18.6, 17.6, -5.1; ESI HRMS *m/z* $(M+H)^+$ calcd 274.2197, obsv 274.2193.

Spectra data for 4.20: IR (neat, cm^{-1}) 1715, 1255, 1100, 836, 776; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.60 (t, *J* = 6.3 Hz, 2H), 2.57-2.50 (m, 1H), 2.14 (s, 3H), 1.77-1.65 (m, 1H), 1.54-1.37 (m, 3H), 1.09 (d, *J* = 7.2 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.9, 63.1, 47.1, 30.5, 29.3, 28.1, 26.2, 18.5, 16.4, -5.1; ESI HRMS *m/z* $(M+H)^+$ calcd 245.1931, obsv 245.1925.

Spectra data for 4.21: IR (neat, cm^{-1}) 3349 (br), 1421, 1057, 910; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.61 (t, *J* = 6.3 Hz, 2H), 3.27-3.20 (m, 1H), 2.88-2.81 (m, 4H), 2.14-2.06 (m, 2H), 1.76 (s, 3H), 1.51-1.34 (m, 5H), 0.95 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 119.6, 63.2, 37.2, 31.1, 31.0, 30.6, 30.3, 25.4, 19.0, 14.6; ESI HRMS *m/z* $(M+H)^+$ calcd 233.1028, obsv 233.1026.

Spectra data for 4.22: IR (neat, cm^{-1}) 1727, 1355, 1156, 673, 574, 545; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 3.78 (t, *J* = 7.5 Hz, 2H), 3.30-3.22 (m, 1H), 2.92-2.77 (m, 4H), 2.41 (s, 3H), 2.14-2.75 (m, 2H), 1.75 (s, 3H), 1.74-1.52 (m, 2H), 1.39-1.25 (m, 2H), 1.31 (s, 9H), 0.95 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 144.2, 143.3, 137.8, 119.9, 84.2, 47.4, 37.1, 32.0, 30.5, 30.3, 28.4, 28.1, 25.4, 21.8, 19.0, 14.6; ESI HRMS *m/z* $(M+H)^+$ calcd 486.1801, obsv 486.1797.

Spectra data for 4.15b: IR (neat, cm^{-1}) 3279, 1325, 1159, 1093, 814, 663, 551; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 4.65 (t, *J* = 6.0 Hz, 1H), 3.15-3.08 (m, 1H), 2.94-2.77 (m, 6H), 2.41 (s, 3H), 2.11-2.03 (m, 2H), 1.67 (s, 3H), 1.36-1.20 (m, 4H), 0.87 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 142.8, 137.3, 129.9, 127.3, 120.1, 43.5, 36.8, 31.9, 30.5, 30.2, 27.7, 25.3, 21.7, 18.9, 14.5; ESI HRMS *m/z* $(M+H)^+$ calcd 386.1277, obsv 386.1272.

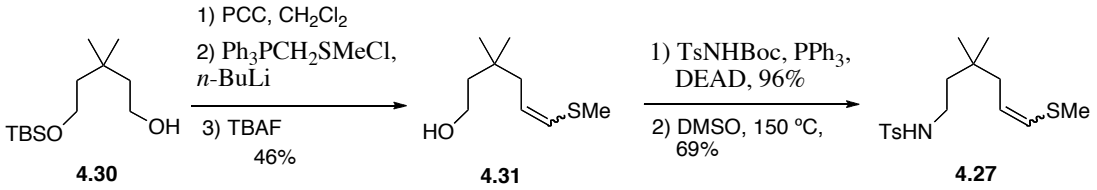


4.23 **4.24** **4.25**

Synthesis of 4.24: *n*-BuLi (1.6 M in hexanes, 18.7 mL, 30 mmol) was added dropwise to a supension of (methylthiomethyl)triphenylphosphonium chloride (10.7 g, 30.0 mmol) in THF (75 mL) at 0 °C under argon atmosphere. 2,2-Dimethyl-4-cyanobutyraldehyde was added dropwise in 10 min and the reaction stirred overnight. Water and ether were then added at 0 °C. The organic phase was separated and aqueous phase extracted with ether. The combined organic solution was dried with $MgSO_4$, concentrated, and the residue chromatographed through silica gel to give the desired product (0.69 g, 36%). IR (neat, cm^{-1}) 2245, 1590, 1471, 695; ^1H NMR (300 MHz, $CDCl_3$) δ 5.98 (d, *J* = 16.2 Hz, 0.2H), 5.89 (d, *J* = 11.1 Hz, 0.8H), 5.26 (d, *J* = 11.1 Hz, 0.8 H), 5.24 (d, J = 16.2 Hz, 0.2H), 2.35-2.22 (m, 5H), 1.93-1.88 (m, 1.6H), 1.75-1.66 (m, 0.4H), 1.17 (s, 4.8H), 1.08 (s, 1.2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.2, 133.0, 128.1, 123.6, 120.9, 38.6, 37.2, 36.7, 27.7, 27.0, 26.4, 18.7, 15.0, 13.3, 13.1; ESI HRMS *m/z* $(M+Na)^+$ calcd 192.0817, obsv 192.0817.

Synthesis of 4.25: $LAlH_4$ (1.0 *M* in ether, 4.2 mL, 4.2 mmol) was added to a solution of **4.25** (0.60 g, 3.5 mmol) in THF (8 mL) at 0 °C under argon atmosphere. Upon complete addition, the reaction was kept at rt for 5 h and then cooled to 0 °C. 10% NaOH solution was added and the resulting solution was extracted with ether. The ether extractions were combined and dried over $MgSO_4$. The solvent was removed and the residue dissolved in THF (30 mL). Triethylamine (2.9 mL, 21 mmol) and *p*-toluenesulfonylchloride (1.33g, 7.0 mmol) were added at 0 °C. The reaction was allowed to warm to rt, stirred overnight, and poured into a mixture of water (50 mL) and ethyl acetate (100 mL). The aqueous layer was separated and organic phase washed with water (40 mL), dried over $MgSO_4$, and concentrated. The residue was purified on a silica gel column to give **4.25** (0.70 g,

61%, 2 steps). IR (neat, cm^{-1}) 3310, 1329, 1162, 1108, 819, 675, 554; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 5.77 (d, *J* = 15.6, 0.2H), 5.66 (d, *J* = 10.8 Hz, 0.8H), 5.23 (d, *J* = 15.6 Hz, 0.2H), 5.19 (d, *J* = 10.8 Hz, 0.8H), 5.09-5.02 (m, 1H), 2.90-2.80 (m, 2H), 2.38 (s, 3H), 2.18, 2.15 (2s, 3H), 1.42-1.29 (m, 4H), 1.00 (s, 4.8H), 0.89 (s, 1.2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 143.4, 137.3, 136.3, 135.5, 129.9, 127.4, 127.3, 126.0, 121.2, 44.1, 40.1, 39.1, 36.8, 36.5, 27.8, 27.4, 25.2, 25.1, 21.7, 18.7, 15.2; ESI HRMS *m/z* $(M+H)^+$ calcd 328.1399, obsv 328.1399.



4.30 **4.31** **4.27**

Synthesis of 4.31: To a suspension of PCC (3.2 g, 15 mmol) in CH_2Cl_2 (30 mL) was added the known compound **4.30** (2.46 g, 10 mmol) in CH_2Cl_2 (10 mL). Diethyl ether (200 mL) was added after 2h and the resulting mixture was passed through a pad of silica gel and concentrated to give an aldehyde.

n-BuLi (1.6 M in hexanes, 18.7 mL, 30 mmol) was added dropwise to a supension of (methylthiomethyl)triphenylphosphonium chloride (10.7 g, 30 mmol) in THF (75 mL) at 0 °C under argon atompshophere. After the reaction was stirred for 20 min at the same temperature, the crude aldehyde made above was dissolved in THF (6 mL) and added. The reaction was allowed to warm to rt and stirred for 6 h. Water and ether were then added at 0 °C. The organic phase was separated and aqueous layer extracted with ether twice. The combined organic solution was dried with $MgSO_4$, concentrated, and

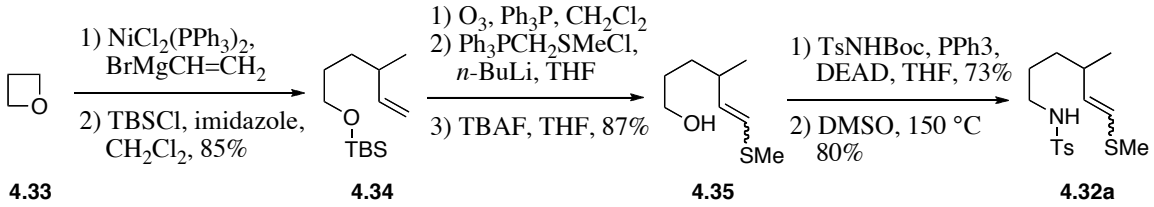
chromatographed through silica gel to give the desired vinyl sulfide contaminated with triphenylphosphine.

Without further purification, the above mixture was dissolved in THF (30 mL) and treated with TBAF (1.0 *M* in THF, 8.0 mL, 8.0 mmol) at rt. The reaction was stirred at rt for 2 h and then quenched with the addition of saturated sodium bicarbonate solution (30 mL) and ether. The organic layer was separated and aqueous phase extracted with ether. The combined organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude alcohol was purified by flash chromatography to give **4.31** (0.80 g, 46%). IR (neat, cm^{-1}) 3337, 1468, 1365, 1029; ^1H NMR (300 MHz, $CDCl_3$) δ 6.00-5.94 (m, 1H), 5.63-5.40 (m, 1H), 3.70 (t, *J* = 7.5 Hz, 2H), 2.27 (s, 1.8), 2.24 (s, 1.2H), 2.06-1.99 (m, 1H), 1.57-1.46 (m, 3H), 0.93 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.8, 126.3, 125.6, 124.0, 60.0, 59.9, 46.4, 44.4, 41.8, 33.6, 33.2, 27.6, 27.4, 17.3, 15.4; ESI HRMS *m/z* $(M+Na)^+$ calcd 197.0971, obsv 197.0980.

Synthesis of 4.27: **4.27** was synthesized from **4.31** by employing the general procedure.

Spectra data for the intermediate before deprotection: IR (neat, cm^{-1}) 1726, 1355, 1156, 675, 579, 545; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84-7.79 (m, 2H), 7.34-7.30 (m, 2H), 6.09-6.02 (m, 1H), 5.71-5.49 (m, 1H), 3.94-3.84 (m, 2H), 2.46 (s, 3H), 2.30, 2.29 (2s, -SCH_3, 3H), 2.12-2.06 (m, 2H), 1.75-1.66 (m, 2H), 1.01 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 144.3, 144.2, 137.8, 129.5, 129.1, 128.1, 126.3, 125.3, 123.4, 84.3, 84.2, 45.7, 44.1, 44.0, 41.5, 41.3, 33.9, 33.5, 28.2, 27.0, 21.9, 17.3, 15.3; ESI HRMS *m/z* $(M+Na)^+$ calcd 450.1743, obsv 450.1747.

Spectra data for 4.27: IR (neat, cm^{-1}) 3280, 1325, 1159, 662, 551; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.36-7.30 (m, 2H), 5.97-5.88 (m, 1H), 5.53-5.29 (m, 1H), 4.69-4.65 (m, 1H), 3.00-2.91 (m, 2H), 2.46 (s, 3H), 2.25, 2.23 (2s, -SCH_3, 3H), 1.94 (t, *J* = 7.5 Hz, 2H), 1.43-1.35 (m, 2H), 0.86 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 143.6, 137.1, 137.1, 130.0, 130.0, 129.2, 127.4, 127.4, 126.7, 125.0, 123.2, 45.9, 41.3, 41.2, 39.9, 39.7, 33.7, 33.3, 27.3, 27.0, 21.8, 17.3, 15.3; ESI HRMS *m/z* $(M+H)^+$ calcd 328.1399, obsv 328.1398.



4.33 **4.34** **4.35** **4.32a**

Synthesis of 4.34: $NiCl_2(PPh_3)_2$ (0.62g, 0.95 mmol), trimethyleneoxide (1.84 g, 31.8 mmol), and THF (10 mL) were placed in a round-bottom flask and cooled to -45 °C. Vinylmagnesium bromide (1.0 *M* in THF, 70 mL, 70 mmol) was added and the resulting reaction mixture was stirred overnight. 1 *M* HCl was added at 0 °C, followed by ether. The organic phase was separated and organic layer extracted with ether. The combined organic solution was dried with $MgSO_4$ and stripped of solvent *in vacuo*. To the residue was added imidazole (4.31 g, 63 mmol) and CH_2Cl_2 (18 ml). *tert*-Butyldimethylsilyl chloride (6.02 g, 40 mmol) in THF (8 mL) was added at 0 °C. After kept at 0 °C for 3 h, the reaction mixture was poured into water (100 mL). Ether was added and the layers were separated. The aqueous phase was extracted with ether. The combined organic solution was dried over anhydrous $MgSO_4$, concentrated, and chromatographed (silica gel, ether/hexane, 1:20) to give **4.34** (6.21 g, 85%, 2 steps). IR (neat, cm^{-1}) 3076, 1255,

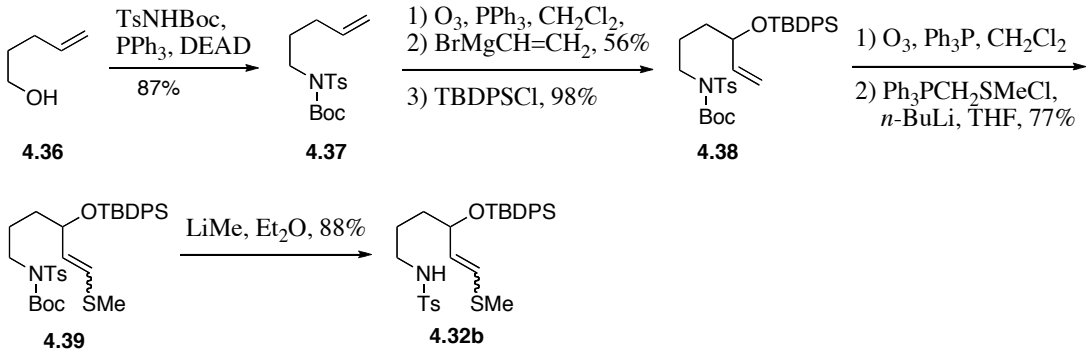
1101, 836, 774; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75-5.63 (m, 1H), 4.99-4.89 (m, 2H), 3.60 (t, *J* = 6.6 Hz, 2H), 2.17-2.08 (m, 1H), 1.57-1.44 (m, 2H), 1.36-1.27 (m, 2H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.91 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 112.7, 63.5, 37.8, 33.0, 30.8, 26.2, 20.4, 18.6, -5.1; ESI HRMS *m/z* $(M+H)^+$ calcd 229.1982, obsv 229.1985.

Spectra data of 4.35: IR (neat, cm^{-1}) 3337, 1454, 1057, 939; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (dd, *J* = 15.0, 0.9 Hz, 0.7H), 5.83 (d, *J* = 9.3 Hz, 0.3H), 5.34-5.27 (m, 1H), 3.62-3.57 (m, 2H), 2.54-2.17 (m, 5H), 1.62-1.23 (m, 4H), 1.01 (d, *J* = 6.6 Hz, 2.1H), 0.98 (d, *J* = 6.9 Hz, 0.9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.9, 133.2, 125.9, 122.7, 63.0, 63.0, 37.6, 33.9, 33.4, 30.7, 30.7, 20.9, 20.6, 17.3, 15.3; ESI HRMS *m/z* $(M+Na)^+$ calcd 183.0810, obsv 183.0814.

Synthesis of 4.32a: **4.32a** was synthesized from **4.35** by applying the general procedure.

Spectra data for the intermediate before removal of t-Boc group: IR (neat, cm^{-1}) 1726, 1355, 1156, 673; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80-7.76 (m, 2H), 7.32-7.28 (m, 2H), 5.98 (d, *J* = 15.0 Hz, 0.7H), 5.85 (d, *J* = 9.3 Hz, 0.3H), 5.36-5.27 (m, 1H), 3.80 (t, *J* = 7.5 Hz, 2Hz), 2.59-2.51 (m, 0.3H), 2.43 (s, 3H), 2.31-2.22 (m, 0.7H), 2.26, 2.23 (2s, 3H), 1.78-1.70 (m, 2H), 1.38-1.30 (m, 3H), 1.02 (d, *J* = 6.9 Hz, 2.1H), 1.00 (d, *J* = 6.6 Hz, 0.9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 144.2, 144.1, 137.8, 137.8, 134.7, 132.8, 129.4, 129.4, 128.0, 128.0, 126.2, 123.1, 84.2, 84.1, 47.4, 47.3, 37.4, 34.2, 33.9, 28.2, 28.1, 21.8, 20.9, 20.5, 17.3, 15.3; ESI HRMS *m/z* $(M+Na)^+$ calcd 436.1587, obsv 436.1571.

Spectra data for 4.32a: IR (neat, cm^{-1}) 3281, 1325, 1160, 1094, 814, 663, 551; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 5.87 (d, *J* = 15.0 Hz, 0.7H), 5.78 (d, *J* = 9.6 Hz, 0.3H), 5.24-5.15 (m, 1.7H), 5.08 (t, *J* = 6.0 Hz, 0.3 H), 2.94-2.85 (m, 2H), 2.42 (s, 3H), 2.42-2.32 (m, 0.3H) 2.21, 2.18 (2s, 3H), 2.14-2.05 (m, 0.7H), 1.48-1.16 (m, 4H), 0.92 (d, *J* = 6.9 Hz, 2.1H), 0.89 (d, *J* = 7.5 Hz, 0.9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 143.4, 137.3, 134.4, 132.6, 129.9, 127.3, 126.2, 123.0, 43.4, 37.3, 34.0, 33.7, 27.5, 21.7, 20.9, 20.5, 17.3, 15.2; ESI HRMS *m/z* $(M+H)^+$ calcd 314.1236, obsv 314.1243.



Synthesis of 4.37: To a solution of 4-penten-1-ol (1.29 g, 15 mmol), *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (4.06 g, 15 mmol), and triphenylphosphine (3.93 g, 15 mmol) in THF (60 mL) was added a diethyl azodicarboxylate solution (40 wt% in toluene, 6.58 mL, 15 mmol) at rt under an argon atmosphere. The reaction was stirred overnight. The solvent was removed and the residue chromatographed (silica gel, ether/hexanes, 1:20, 1:10) to afford **4.37** as a white solid (4.43 g, 87%). IR (neat, cm^{-1}) 1726, 1355, 1156, 673; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 5.91-5.77 (m, 1H), 5.11-4.98 (m, 2H), 3.82 (t, *J* = 7.5 Hz, 2H), 2.43 (s, 3H), 2.17-2.09 (m, 2H), 1.92-1.82 (m, 2H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

151.1, 144.2, 137.6, 129.4, 127.9, 115.3, 84.2, 46.9, 31.0, 29.3, 28.0, 21.7; ESI HRMS *m/z* $(M+H)^+$ calcd 340.1577, obsv 340.1575.

Synthesis of the allyl alcohol: Ozone was passed through a solution of **4.37** (3.64 g, 10.7 mmol) in CH_2Cl_2 (40 mL) at -78 °C until a light blue color persisted. PPh_3 (8.4 g, 32.1 mmol) was added and the cooling bath was removed. After 2 h, the solvent was removed and ether and anhydrous $MgSO_4$ added. After filtration and evaporation of the solvent, the crude aldehyde was dissolved in THF (100 mL) and cooled to -78 °C. Vinyl magnesium bromide (1.0 M in ether, 26 mL, 26 mmol) was added and the reaction was kept at the same temperature for 3h. Water was added and then the cooling bath removed. Ether and saturated NH_4Cl solution was then added. The layers were separated and the aqueous layer extracted with diethyl ether. After the combined organic layers were concentrated, dried over $MgSO_4$, and chromatographed through a silica gel column (ether/hexanes, 1:2, 2:1) furnished the desired alcohol (2.23 g, 56%). IR (neat, cm^{-1}) 3536, 1727, 1354, 1155, 674, 577, 546; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 5.94-5.83 (m, 1H), 5.26 (d, *J* = 17.1 Hz, 1H), 5.14 (d, *J* = 10.5 Hz, 1H), 4.22-4.14 (m, 1H), 3.87 (t, *J* = 7.5 Hz, 2H), 2.44 (s, 3H), 1.93-1.80 (m, 2H), 1.66-1.54 (m, 2H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.3, 144.3, 141.1, 137.7, 129.4, 128.0, 115.1, 84.4, 72.8, 47.1, 34.0, 28.1, 26.3, 21.8; ESI HRMS *m/z* $(M+Na)^+$ calcd 392.1502, obsv 392.1490.

Synthesis of 4.38: To a solution of allyl alcohol made above (2.20 g, 5.96 mmol) and imidazole (1.21 g, 17.9 mmol) in CH_2Cl_2 was added tert-butyldiphenylsilyl chloride (1.80 g, 6.66 mmol) in CH_2Cl_2 (5 mL) at 0 °C under argon atmosphere. The reaction was stirred at rt for 1 h, poured into water, and extracted with ether. The combined organic

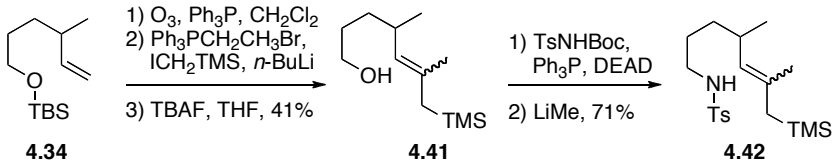
layers were dried over $MgSO_4$, concentrated, and chromatographed through silica gel (ether/hexanes, 1:3) to afford the product (3.60 g, 99%). IR (neat, cm^{-1}) 1727, 1358, 1154, 703; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78-7.67 (m, 6H), 7.47-7.34 (m, 6H), 7.28 (d, *J* = 8.1 Hz, 2H), 5.88-5.76 (m, 1H), 5.07-4.99 (m, 2H), 4.26-4.21 (m, 1H), 3.75-3.69 (m, 2H), 2.43 (s, 3H), 1.77-1.70 (m, 2H), 1.57-1.50 (m, 2H), 1.33 (s, 9H), 1.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 144.2, 140.6, 137.9, 136.2, 136.2, 135.0, 134.5, 134.4, 129.9, 129.7, 129.4, 128.1, 127.9, 127.8, 127.6, 115.1, 84.1, 74.3, 47.3, 34.8, 28.1, 27.3, 26.8, 25.4, 21.8, 19.6; ESI HRMS *m/z* $(M+H)^+$ calcd 630.2666, obsv 630.2680.

Synthesis of 4.39: Ozone was passed through a solution of **4.38** (3.58 g, 5.89 mmol) in CH_2Cl_2 (20 mL) at -78 °C until a light blue color persisted. PPh_3 (4.63g, 17.7 mmol) was added and the cooling bath was removed. Solvent was removed after 2 h. Ether and anhydrous $MgSO_4$ was added. After filtration and evaporation of the solvent, the crude aldehyde was obtained and used without purification.

n-BuLi (1.6 *M* in hexanes, 11.0 mL, 17.6 mmol) was added dropwise to a supension of (methylthiomethyl)triphenylphosphonium chloride (6.30 g, 17.7 mmol) in THF (30 mL) at 0 °C under argon atmosphere. After the reaction was stirred for 20 min at the same temperature, the crude aldehyde made above (dissolved in 10 mL of THF) was added. The reaction was allowed to warm to rt and stirred for 2 h. Water and ether were then added at 0 °C. The organic phase was separated and the aqueous layer extracted with ether. The combined organic solution was dried with $MgSO_4$, concentrated, and chromatographed through silica gel to give **4.39** (3.00 g, 77%). IR (neat, cm^{-1}) 1727, 1357, 1155, 703; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80-7.66 (m, 6H), 7.47-7.25 (m, 8H), 5.84 (d, *J* = 15.0 Hz, 0.6H), 5.76 (d, *J* = 9.6 Hz, 0.4H), 5.62 (dd, *J* = 9.6, 8.1 Hz, 0.4H),

5.30 (dd, *J* = 15.0, 7.5 Hz, 0.6H), 4.66-4.60 (m, 0.4H), 4.28-4.22 (m, 0.6H), 3.81-3.73 (m, 2H), 2.43 (s, 3H), 2.06 (s, 3H), 1.83-1.70 (m, 2H), 1.66-1.48 (m, 2H), 1.33 (s, 9H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 144.2, 144.1, 137.8, 136.2, 136.2, 136.1, 135.0, 134.7, 134.5, 134.5, 134.4, 131.9, 129.8, 129.7, 129.6, 129.4, 129.4, 128.1, 128.1, 127.9, 129.8, 127.7, 127.6, 127.5, 127.1, 126.7, 84.2, 84.1, 74.5, 70.9, 47.3, 47.2, 35.4, 35.0, 28.1, 27.3, 26.8, 25.8, 21.8, 19.6, 17.8, 14.6; ESI HRMS *m/z* $(M+Na)^+$ calcd 676.2557, obsv 676.2564.

Synthesis of 4.32b: **32b** was synthesized from **4.39** by following the general procedure. IR (neat, cm^{-1}) 3278, 1427, 1326, 1160, 1110, 702; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73-7.60 (m, 6H), 7.45-7.26 (m, 8H), 5.77 (d, *J* = 15.0 Hz, 0.6H), 5.72 (d, *J* = 9.9 Hz, 0.4H), 5.52 (dd, *J* = 9.9, 7.8 Hz, 0.4H), 5.18 (dd, *J* = 15.0, 7.5 Hz, 0.6H), 4.60-4.56 (t, *J* = 6.0 Hz, 0.4H), 4.51-4.45 (m, 1H), 4.17-4.14 (m, 0.6H), 2.84-2.78 (m, 2H), 2.42 (s, 3H), 2.04, 2.04 (2s, 3H), 1.50-1.39 (m, 4H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 143.4, 137.4, 137.3, 136.2, 136.1, 136.1, 134.4, 134.4, 134.2, 131.7, 129.9, 129.9, 129.9, 129.8, 129.7, 127.8, 127.8, 127.7, 127.6, 127.3, 127.2, 126.7, 74.2, 70.4, 43.4, 35.1, 34.7, 27.3, 27.2, 25.1, 25.1, 21.8, 19.5, 17.6, 14.6; ESI HRMS *m/z* $(M+Na)^+$ calcd 576.2033, obsv 576.2034.



4.34 **4.41** **4.42**

Synthesis 4.41: **4.34** (3.40g, 14.9 mmol) was dissolved in CH_2Cl_2 (50 mL) and cooled to -78 °C. Ozone was passed through the solution until it turned light blue. PPh_3 (11.7g,

44.7 mmol) was added before the cooling bath was removed. The solvent was removed after the reaction reached rt. The residue was dissolved in ether and dried over anhydrous $MgSO_4$. The solvent was removed and the aldehyde obtained used in the following reaction without purification.

To a suspension of ethyltriphenylphosphonium bromide (11.1, 30.0 mmol) in THF (60 mL) was added dropwise *sec*-butyllithium solution (1.4 *M* in hexanes, 21.4 mL, 30.0 mmol) at -78 °C under argon atmosphere. The reaction was stirred at -78 °C for 0.5 h and rt for another 0.5 h. Trimethylsilanylmethyliodide (7.2 mL, 48.4 mmol) was added dropwise after the solution was cooled to -78 °C. Upon complete addition, the reaction was allowed to gradually warm to rt over a period of 3 h. After cooling the reaction to -15 °C, it was treated with a *n*-butyllithium solution (1.6 *M* in hexanes, 18.7 mL, 29.9 mmol). Upon complete addition, the reaction was warmed to 0 °C and stirred for 0.5 h. The aldehyde obtained above was dissolved in THF (5 mL) and then added to the ylide at -78 °C. The reaction was allowed to warm to rt and stirred overnight. The reaction was then cooled to 0 °C and quenched with 100 mL of brine. The organic layer was separated and the aqueous phase extracted with ether (2 x 100 mL). The combined organic solution was dried over $MgSO_4$ and concentrated under reduced pressure to give a crude allylsilane compound that was used without purification.

The allylsilane compound made above was dissolved in THF (90 mL) and treated with TBAF (1.0 *M* in THF, 20 mL, 20 mmol) at 0 °C under an argon atmosphere. The reaction was allowed to warm to rt and stirred for 5 h. Brine and ether was added. The organic layer was separated and aqueous phase extracted with ether. The combined organic solution was dried with anhydrous $MgSO_4$, concentrated, and chromatographed through

silica gel to give the desired product **4.41** (1.30 g, 41% over 3 steps). IR (neat, cm^{-1}) 3337, 1248, 858, 837; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.76 (d, *J* = 9.6 Hz, 0.7H), 4.69 (d, *J* = 9.3 Hz, 0.3H), 3.63-3.57 (m, 2H), 2.36-2.15 (m, 1H), 1.64-1.10 (m, 9H), 0.90, 0.91 (2d, *J* = 5.4, 6.6 Hz, 3H), -0.02, -0.01 (2s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.9, 131.7, 129.4, 129.0, 63.5, 63.6, 58.7, 34.2, 34.1, 32.7, 32.5, 31.2, 31.0, 30.0, 26.5, 25.9, 23.4, 21.9, 21.4, 19.1, -0.42, -0.98; ESI HRMS *m/z* $(M+Na)^+$ calcd 215.1826, obsv 215.1826.

Synthesis of 4.42: A diethyl azodicarboxylate solution (40 wt% soluion in toluene, 2.70 mL, 6.3 mmol) was added dropwise to a solution of **4.41** (0.90 g, 4.2 mmol), *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (1.71 g, 6.3 mmol) and triphenylphosphine (1.65 g, 6.3 mmol) in THF (35 mL) at rt. After stirring the reaction overnight, the solvent was removed and the residue passed through a pad of silica gel (washed with ether) to give a mixture of desired product and PPh_3. Without further purification, the mixture was dissolved in ether (40 mL) under argon atmosphere and treated with LiMe (1.6 *M* in ether, 8.0 mL, 12.8 mmol) at -20 °C. After stirring at the same temperature for 10 min, the reaction was quenched with water and saturated NH_4Cl. The ether layer was separated and the aqueous phase extracted with ether. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed through silica gel (ether/hexanes, 1:1) to furnish **4.42** (1.10 g, 71%). IR (neat, cm^{-1}) 3280, 1418, 1326, 1160, 1094, 859, 665, 551; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 4.70 (d, *J* = 10.2 Hz, 0.6H), 4.63 (d, *J* = 10.2 Hz, 0.4H), 4.38 (br, 1H), 2.99-2.95 (m, 2H), 2.46 (s, 3H), 2.25-2.09 (m, 1H), 1.65-1.05 (m, 9H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.04, 0.01 (2s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 137.3, 132.0,

129.8, 129.0, 127.3, 43.8, 43.6, 34.9, 32.4, 32.3, 30.0, 27.8, 27.7, 26.4, 23.4, 21.8, 21.7,

21.3, 19.0, -0.43, -0.97; ESI HRMS *m/z* $(M+H)^+$ calcd 368.2074, obsv 368.2064.

4.5 Spectra: see Appendix C

References and Notes

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2. See Chapter 5 of this thesis for details and Xu, H.-C.; Moeller, K. D. *Org. Lett*. **2010**, *12*, 1720.
3. (a) Shono, T.; Matsumura, Y.; Katoh, S.; Takeuchi, K.; Sasaki, K.; Kamada, T.; Shimizu, R. *J. Am. Chem. Soc*. **1990**, *112*, 2368. (b) Horner, J. H.; Musa, O. M.; Bouvier A.; Newcomb, M. *J. Am. Chem. Soc*. **1998**, *120*, 7738.
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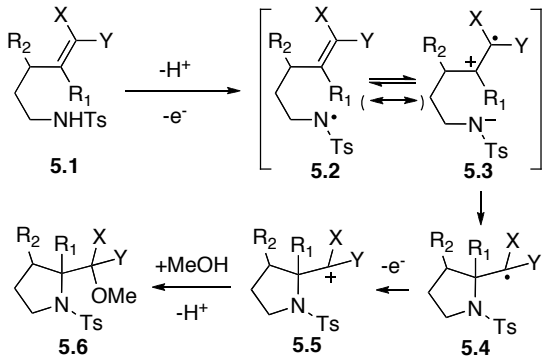
Chapter 5 Using Competition Studies to Probe The Mechanism of Oxidative Cyclization Reactions[1]

5.1 Introduction

While the anodic olefin coupling reaction has proven to be a valuable synthetic tool for constructing new bonds and generating new ring systems, many mechanistic aspects of the reactions remain a mystery.[2] A deeper understanding of the reaction mechanism would help us further expand the scope of the reaction and increase its synthetic utility. For example, consider the anodic coupling of electron-rich olefins and toluene sulfonamides recently used to generate functionalized-proline and pipecolic acid derivatives (Scheme 5-1).[3,4] The reactions benefit greatly from

Scheme 5-1 Possible Mechanism for the Oxidative Coupling of Tosylamides and Electron-Rich Olefins



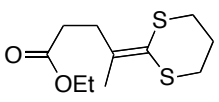
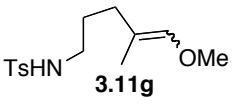
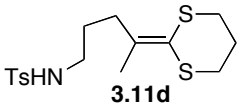
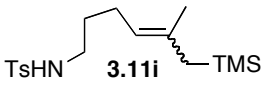
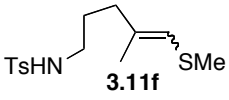
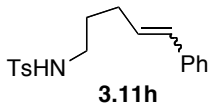
the use of basic reaction conditions, an observation that can be explained in one of two ways. Both would start with an initial deprotonation of the sulfonamide followed by an oxidation to generate a rapid equilibrium between intermediates **5.2** and **5.3**. The reaction would then proceed through either a transition state having a nitrogen anion adding to a radical cation or a transition state having a nitrogen radical adding to an electron-rich

olefin.[5] In this chapter, we want to discuss our efforts to distinguish these two pathways. Of course, **5.2** and **5.3** can also be viewed as resonance structures. Then the question would be which one dominates in the transition state leading to radical **5.4**. Both considerations would lead to similar conclusions from the following studies. Hence, for the ease of discussion, we assume that **5.2** and **5.3** are in a fast equilibrium.

5.2 Cyclic Voltammetry Studies

One of the most useful techniques for the study of electrochemical reactions is cyclic voltammetry, which provides insights into the reaction mechanism. Oxidation potentials for some of substrates used in the oxidative cyclizations were measured by cyclic voltammetry (Table 5-1). The voltammograms were recorded in a methanol solution with a carbon anode, a Ag/AgCl reference electrode, and a platinum wire cathode. The voltammegrams were recorded either with (condition B) or without a base (condition A).

Table 5-1 Oxidation Potentials of Some Substrates Used in Chapters 3 and 4

entry	substrate	conditions[a]	$E_{p/2}$ (V)	entry	substrate	conditions	$E_{p/2}$ (V)
1		A	1.06	4	 **3.11g**	A B	1.18 0.78
2	 **3.11d**	A B	0.98 0.69	5	 **3.11i**	A B	1.23 0.76
3	 **3.11f**	A B	1.08 0.77	6	 **3.11h**	A B	1.36 0.77

[a] A: Carbon anode, Pt cathode, Ag/AgCl reference electrode, scan rate 50 mV/s, 0.1 M Et_4NOTs, MeOH, 0.025 M of substrate; B: 0.6 equiv LiOMe (1.0 M in MeOH) was added.

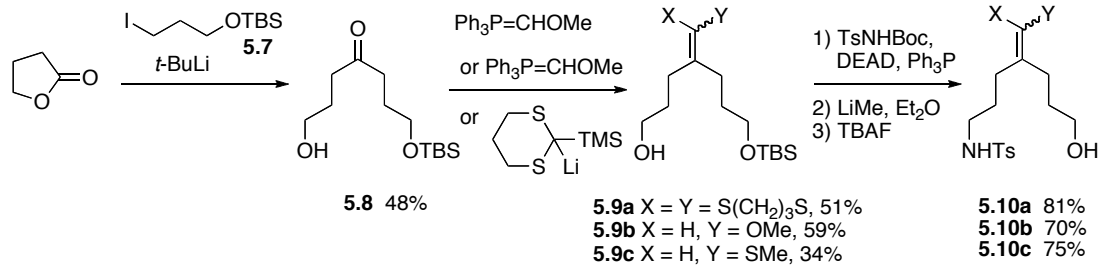
Under the neutral conditions (condition A), the tosylamide is oxidized at a potential higher than the decomposition potential of methanol solvent (> 1.8 V vs. Ag/AgCl).[6] However, with the addition of 0.6 equivalent of lithium methoxide, the oxidation potential of the tosylamide is reduced to $E_{p/2}$ = 0.90 V vs. Ag/AgCl, a potential lower than those of the electron-rich olefins studied. Under these conditions, the tosylamide exists as an amide anion and the potential measured is that of the amide anion. A ketene dithioacetal, the electron-rich olefin that has the lowest potential, is oxidized at $E_{p/2}$ = 1.06 V vs. Ag/AgCl (entry 1, Table 5-1). Hence, under the basic conditions, the electrolysis reactions probably start with the removal of an electron from the tosylamide anion to give an amidyl radical like **5.2**. This is consistent with the observation that the substrates are oxidized at similar potentials despite the potentials of the olefins ranging from 1.06 V of the ketene dithioacetal to 1.56 V of the styrene in **3.11h**. Without the addition of any base, the potentials of the substrates reflect those of the electron-rich olefins. Cyclization of the nitrogen-centered radical onto the electron-rich olefin would afford the cyclized radical **5.4**. However, intramolecular electron transfer between close functional groups could be very fast.[7] Hence, the cyclization could also go through a radical cation type transition state like **5.3** (Scheme 5-1). Although the voltammetry studies do provide us with useful information about which group is initially oxidized, the actual reaction pathway could not be derived by simply looking at the potentials obtained in those studies.

5.3 Competition Studies

A reaction that proceeds through a transition state resembling **5.3** would involve a large change in polarity moving from the zwitterionic starting material to the neutral

product. The transition state for the cyclization would be less polar than the starting material, and the reaction would be favored by the use of less polar solvents.[8] A reaction that proceeds through a nitrogen-based radical (**5.2**) would involve a neutral starting material, transition state, and product. Such a reaction would not be sensitive to changes in solvent polarity.[8] Therefore, by varying the solvent polarity for the reaction it should be possible to determine which of the two pathways dominates the reaction mechanism.[9] However, such a strategy for answering mechanistic questions about the reactions requires a method for determining if and how different electrolysis conditions alter the rate of the cyclization.

Scheme 5-2 Synthesis of Substrates for Competition Studies



5.8 48%

5.9a X = Y = $S(CH_2)_3S$, 51%
5.9b X = H, Y = OMe, 59%
5.9c X = H, Y = SMe, 34%

5.10a 81%
5.10b 70%
5.10c 75%

Our work began with examining the oxidative-coupling of sulfonamides with a ketene dithioacetal group. To this end, substrate **5.10a** was synthesized (Scheme 5-2). Ring opening of γ-butyrolactone with one equivalent of alkyllithium regent derived from iodide **5.7** led to ketone **5.8** (48% yield), which was converted to ketene dithioacetal **5.9a** in 51% yield using a Peterson olefination. Installation of the tosyl amide by standard methods (Chapter 3 and 4) followed by desilylation afforded the desired product **5.10a** in 81% yield over three steps.

Since the trapping of a radical cation by an alcohol[10] affords a second, cyclic radical cation (Figure 5-1), the reaction leads to no net change in the charge of the transition state for the reaction relative to the starting material. Hence, the rate of the alcohol-derived

Figure 5-1 Trapping of a Ketene Dithioacetal-Derived Radical Cation with an Alcohol

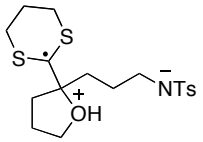
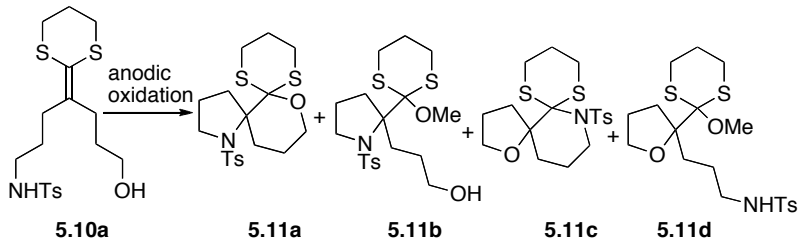


Table 5-2 Anodic Oxidation of 5.10a



Entry	Reaction Conditions	**5.11a+5.11b** (%)	**5.11a,b/5.11c,d**	**5.11c** (%)	**5.11d** (%)
1	MeOH 0.5 LiOMe, Et_4NOTs	58 (4.8/1)[a]	2.9/1	20	ND[b]
2	60% MeOH/THF 0.5 LiOMe, Et_4NOTs	76 (5.3/1)	12.7/1	6	ND
3	30% MeOH/ THF 0.5 LiOMe, Et_4NOTs	87 (4.1/1)	--	ND	ND
4	MeOH 0.5 LiOMe, $LiClO_4$	50 (4.0/1)	1.8/1	27	ND
5	60% MeOH/THF 0.5 LiOMe, $LiClO_4$	75 (4.8/1)	4.7/1	16	ND
6	30% MeOH/ THF 0.5 LiOMe, $LiClO_4$	83 (5.9/1)	27.7/1	3	ND
7	30% MeOH/ THF lutidine, Et_4NOTs	ND	ND	39	17
8	30% MeOH/ THF lutidine, $LiClO_4$	ND	ND	72	15

[a] The numbers in the parentheses indicate the ration of 5.11a/5.11b. [b] Not Detected.

cyclization should not be very sensitive to changes in solvent polarity, and thus should provide an effective "internal-standard" for probing how varying the reaction conditions for the electrolysis alters the rate of the nitrogen-based cyclization.

All of the anodic oxidation reactions utilizing substrate **5.10a** were conducted using an RVC (reticulated vitreous carbon) anode, a Pt-cathode, an undivided cell, and a constant current of 6 mA until 2.2 F/mole of charge was passed. In the first three oxidations (Table 5-2, entries 1-3), lithium methoxide was employed as a base and tetraethylammonium tosylate was used as the electrolyte. The three entries differed only in the solvent used for the reaction with the first using pure methanol, the second 60% MeOH/THF, and the third 30% MeOH/THF. When methanol was used as the solvent (entry 1), three products were generated. Two (**5.11a** and **5.11b**) were derived from a cyclization involving the toluene sulfonamide group. The third product (**5.11c**) was derived from alcohol trapping of the radical cation. The ratio of nitrogen trapping to oxygen trapping was 2.9:1. The oxidative cyclization was then repeated with increasing amounts of THF cosolvent in order to reduce the polarity of the reaction medium. When 60% MeOH/ THF was used, the ratio of nitrogen to oxygen trapping climbed to 12.7:1, and the yield of nitrogen trapping derived product climbed to 76%. With 30% MeOH/ THF, none of the alcohol trapping product was observed, and an 87% isolated yield of nitrogen trapping product was obtained. Clearly, nitrogen trapping was favored by less polar solvents supporting a radical cation (**5.2**) type mechanism.

The same trend was observed when lithium perchlorate was used as the electrolyte (Table 5-2, entries 4-6). The less polar the medium, the more nitrogen trapping product observed. All of the reactions using lithium perchlorate as the electrolyte were less

selective for nitrogen trapping than the corresponding reactions using tetraethylammonium tosylate as the electrolyte. This observation is consistent with the fact that the use of lithium perchlorate leads to a more polar reaction medium.

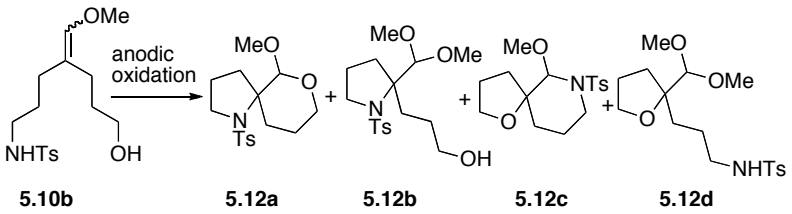
The competition study was also used to probe our initial premise that the yield of the nitrogen-based cyclizations improved when LiOMe was used as the base because it accelerates trapping of the radical cation by the sulfonamide relative to competitive solvent (methanol) trapping. When 2,6-lutidine was used in place of LiOMe as the base for the cyclization (Table 5-2, entries 7 and 8), only products from oxygen trapping of the radical cation were obtained. Clearly, the use of LiOMe accelerates the nitrogen-trapping reaction.

With the success of the competition study for probing reactions using the ketene dithioacetal moiety, attention was turned toward probing similar reactions involving enol ether and vinylsulfide groups. For these efforts, substrates **5.10b** and **5.10c** were synthesized (Scheme 5-2). In both cases, the oxidations were more selective for cyclizations involving the tosylamide trapping group than was the reaction triggered by the oxidation of **5.10a**. This result is consistent with earlier findings that ketene dithioacetal derived radical cations undergo very efficient trapping reactions with alcohol nucleophiles.[10]

With both the oxidation of **5.10b** and **5.10c**, no evidence of alcohol trapping could be observed when the less polar reaction conditions using tetraethylamomium tosylate as the electrolyte were utilized. Even when the more polar reaction conditions using lithium perchlorate were employed, alcohol trapping was only observed when the most polar

solvent was chosen (Tables 5-3 and 5-4, entry 4). In the case of enol ether substrate **5.10b**, the oxidation using the most polar set of conditions led to a 10% isolated yield of

Table 5-3 Anodic Oxidation of 5.10b



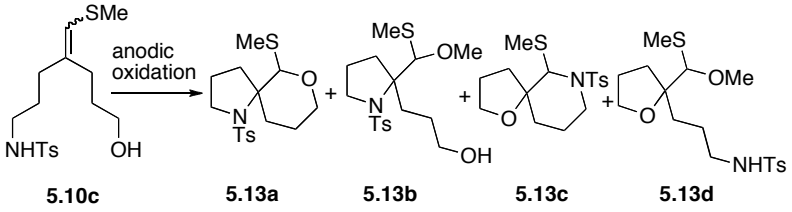
Entry	Reaction Conditions	**5.12a + 5.12b** (%)	**5.12c** (%)	**5.12d** (%)
1	MeOH 0.5 LiOMe, Et_4NOTs	83 (9.4/1)[a]	ND[b]	ND
2	60% MeOH/THF 0.5 LiOMe, Et_4NOTs	82 (4.1/1)	ND	ND
3	30% MeOH/THF 0.5 LiOMe, Et_4NOTs	91 (3.6/1)	ND	ND
4	MeOH 0.5 LiOMe, $LiClO_4$	48 (3.1/1)	ND	10
5	60% MeOH/THF 0.5 LiOMe, $LiClO_4$	85 (3.5/1)	ND	ND
6	30% MeOH/ THF 0.5 LiOMe, $LiClO_4$	79 (3.6/1)	ND	ND
7	30% MeOH/ THF 2,6-lutidine, Et_4NOTs	ND	ND	27
8	30% MeOH/ THF 2,6-lutidine, $LiClO_4$	ND	ND	20

[a] The numbers in the parentheses indicate the ratio of 5.12a/5.12b. [b] Not Detected.

the alcohol trapping product along with a decreased amount of the nitrogen-trapping product. The use of a less polar solvent combination led to the disappearance of alcohol-trapping along with a corresponding increase in the yield of product derived from nitrogen-trapping (Table 5-3, entries 5 and 6). As with the ketene dithioacetal, this observation was consistent with the rate of nitrogen-trapping being favored by less polar

solvents and therefore a mechanism that proceeded through radical cation **5.2**. The low mass balance in the case of entry 4 appears to stem from a low yield of the oxygen trapping product once the pathway to that product becomes engaged. Evidence for this statement can be gathered from entries 7 and 8. In these experiments, the cyclizations were channeled toward alcohol trapping by removing the lithium methoxide and using 2,6-lutidine as the base. As in the earlier oxidation of the ketene dithioacetal and the oxidation of the vinylsulfide below, no product from nitrogen-trapping was observed in

Table 5-4 Anodic Oxidation of 5.10c



5.10c **5.13a** **5.13b** **5.13c** **5.13d**

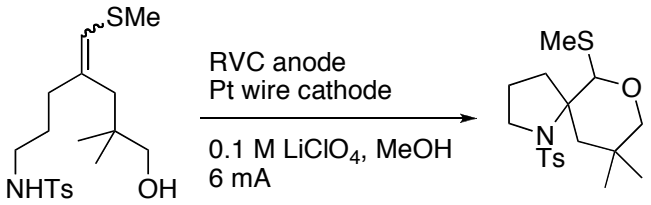
Entry	Reaction Conditions	**5.13a** + **5.13b** (%)	**5.13c** (%)	**5.13d** (%)
1	MeOH 0.5 LiOMe, Et_4NOTs	88 (1/1.4)[a]	ND[b]	ND
2	60% MeOH/THF 0.5 LiOMe, Et_4NOTs	85 (1/1.6)	ND	ND
3	30% MeOH/ THF 0.5 LiOMe, Et_4NOTs	84 (1/2.1)	ND	ND
4	MeOH 0.5 LiOMe, $LiClO_4$	82 (1/1.7)	ND	1-3
5	60% MeOH/THF 0.5 LiOMe, $LiClO_4$	89 (1/2.8)	ND	ND
6	30% MeOH/ THF 0.5 LiOMe, $LiClO_4$	92 (1/4.3)	ND	ND
7	30% MeOH/ THF 2,6-lutidine, Et_4NOTs	ND	10	74
8	30% MeOH/ THF 2,6-lutidine, $LiClO_4$	ND	19	43

[a] The numbers in the parentheses indicate the ratio of **5.13a/5.13b**. [b] Not Detected.

these experiments. However, unlike the other examples (entries 7 and 8 in Tables 5-2 and 5-4) the reactions could not be optimized to obtain an acceptable yield of alcohol trapping product. The same should be true for the reaction run in entry 4.

The oxidation of **5.10c** showed little dependence on the polarity of the solvent used. While a tiny amount of alcohol-trapping was seen when the most polar reaction conditions were employed (Table 5-4, entry 4), the yield of toluene sulfonamide coupling was consistently high for each of the reaction conditions attempted. To increase the oxygen cyclization rate, we resort to *gem*-diakly effect, which has been shown to dramatically accelerate oxidative cyclizations.[11] Hence, substrate **5.10d** was synthesized by Mr. John Campbell and oxidized under the most polar reaction conditions (Scheme 5-3). However, he found that even with the *gem*-dimethyl groups to help the oxygen cyclization, only nitrogen-cyclization products were observed. These observations are more consistent with the vinylsulfide-derived cyclization proceeding through a nitrogen radical like **5.3** rather than nitrogen anion trapping of a radical cation.

Scheme 5-3 Oxidation of 5.10d

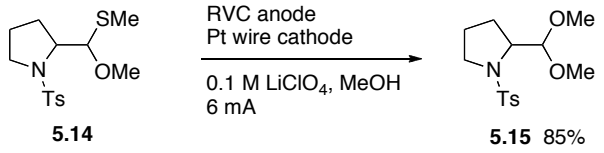


5.10d 70%

As in the earlier oxidation of **5.10a**, the selective formation the tetrahydrofuran derivatives from the oxidation of **5.10c** could be realized in good yield by switching the base from LiOMe to 2,6-lutidine (Table 5-4, entries 7 and 8). In this case, the yield

product from alcohol-trapping could be raised to 84% when tetraethylammonium tosylate was used as the electrolyte for the reaction. For the oxidation of **5.10c**, the expected products were obtained along with a small amount of **5.12c** (~1%) and **5.12d** (~3-4%)

Scheme 5-4 Oxidative Methanolysis of 5.14



using either electrolyte. These products were formed most probably by the oxidative methanolysis of **5.13c** and **5.13d**. In another experiment, S,O-acetal (**5.14**) was converted to dimethoxyacetal (**5.15**) in good yields using the electrolysis conditions (Scheme 5-4).[12]

5.4 Conclusion

In conclusion, the competition studies provide a valuable tool for probing the nature of oxidative cyclizations between electron-rich olefins and tosylamide nucleophiles. The studies show that when a dithioketene acetal olefin is used in the reactions, the use of LiOMe as a base leads to a mechanism that can best be described as proceeding *via* the trapping of a radical cation intermediate by a sulfonamide anion. A similar result was obtained for an enol ether derived reaction, but the data obtained for a vinylsulfide-derived reaction suggested a cyclization involving a nitrogen radical addition to an electron-rich olefin.

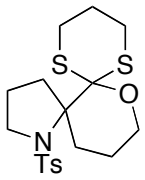
The competition studies are currently being carried on by Mr. John Campbell to systematically study the trapping abilities of differently nuceleophiles.

5.5 Experimental section

General procedure for electrolysis reactions:

LiOMe (1.0 *M* in MeOH, 0.5 equiv) was added to a methanol solution of the substrate (0.03 *M*, 1 equiv) and the electrolyte Et_4NOTs (0.1 M) in a three-neck round bottom flask at rt under argon atmosphere. Two of the three septa were replaced by a reticulated vitreous carbon anode (100 PPI) and platinum wire cathode. The solution was sonicated for 10 min. The electrolysis reaction was carried out at constant current of 6.0 mA until complete consumption of the starting material (the progress of the reaction was monitored by ^{1}H-NMR). When complete, the reaction was concentrated under reduced pressure if Et_4NOTs was used as electrolyte. And then the residue was chromatographed through a silica gel column (slurry packed using 1% triethylamine in hexane solution) to give the desired product. In the case in which $LiClO_4$ was used as electrolyte, water and ether were added. The ether layer was separated and aqueous layer extracted with ether. The combined organic solution was dried and concentrated. The residue was chromatographed in a way described above to afford the desired product.

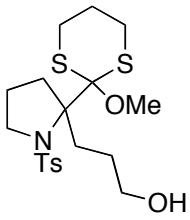
Spectra Data:



5.11a

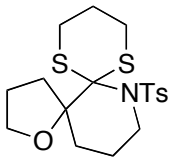
IR (neat, cm^{-1}) 1355, 1100, 836, 754; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 4.11 (td, *J* = 11.4, 3.6 Hz, 1H), 3.76 (dd, *J* = 5.1 Hz, 1H), 3.56-3.26 (m, 4H), 2.96-2.83 (m, 2H), 2.70-2.59 (m, 2H), 2.38 (s, 3H), 2.10-1.68 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 138.9, 129.6, 128.1, 98.9, 74.9, 62.8, 52.4,

37.4, 31.0, 27.5, 26.5, 25.1, 24.6, 23.5, 21.7; ESI HRMS *m/z* $(M+Na)^+$ calcd 422.0899, obsd 422.0887.



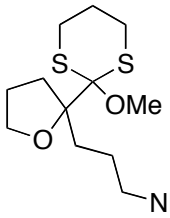
5.11b

IR (neat, cm^{-1}) 3647, 1154, 670, 589; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 4.11-4.03 (m, 1H), 3.74 (t, *J* = 5.7 Hz, 2H), 3.55-3.46 (m, 1H), 3.35 (s, 3H), 2.88-2.64 (m, 6H), 2.12-1.71 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2, 140.2, 128.8, 127.7, 102.2, 83.1, 63.3, 54.2, 52.7, 38.2, 31.1, 28.7, 28.1, 24.2, 22.3, 21.8; ESI HRMS *m/z* $(M+Na)^+$ calcd 454.1151, obsd 454.1144.



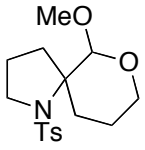
5.11c

IR (neat, cm^{-1}) 1330, 1050, 657, 572; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 4.22-4.17 (m, 1H), 4.04-3.98 (m, 1H), 3.76-3.62 (m, 2H), 3.08-3.04 (m, 1H), 3.00-2.91 (m, 1H), 2.79-2.62 (m, 2H), 2.58-2.51 (m, 1H), 2.39 (s, 3H), 2.01-1.90 (m, 2H), 1.88-1.71 (m, 5H), 1.69-1.60 (m, 1H), 1.57-1.50 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4, 141.3, 128.8, 127.9, 89.5, 69.8, 45.2, 35.7, 33.7, 27.9, 26.9, 26.98, 23.6, 22.8, 21.8; ESI HRMS *m/z* $(M+Na)^+$ calcd 422.0899, obsd 422.0882.



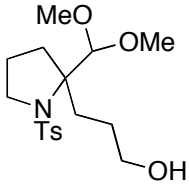
5.11d

IR (neat, cm^{-1}) 3283, 1193, 1159, 1058; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 4.54 (t, *J* = 6.3 Hz, 1H), 3.94-3.90 (m, 2H), 3.50 (s, 3H), 3.03-2.87 (m, 4H), 2.83-2.70 (m, 2H), 2.42 (s, 3H), 2.03-1.46 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 137.3, 129.7, 127.4, 102.6, 92.8, 71.2, 53.6, 41.1, 33.7, 33.0, 27.6, 27.2, 27.1, 24.6, 24.0, 21.8; ESI HRMS *m/z* $(M+Na)^+$ calcd 454.1151, obsd 454.1173.



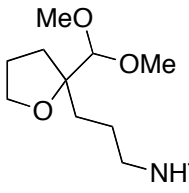
5.12a

IR (neat, cm^{-1}) 1102, 670, 587, 545; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 4.82 (s, 1H), 3.96-3.90 (m, 1H), 3.50 (td, *J* = 11.4, 3.6 Hz, 1H), 3.41-3.30 (m, 5H), 2.48-2.43 (m, 1H), 2.41 (s, 3H), 1.95-1.87 (m, 1H), 1.71-1.53 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0, 139.0, 129.7, 127.3, 105.2, 69.7, 66.4, 56.7, 50.4, 34.7, 32.3, 25.2, 23.3, 21.7; ESI HRMS *m/z* $(M+Na)^+$ calcd 348.1240, obsd 348.1251.



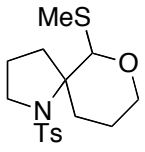
5.12b

IR (neat, cm^{-1}) 3495, 1328, 669, 592; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 4.66 (s, 1H), 3.61-3.56 (m, 2H), 3.52 (s, 3H), 3.41-3.28 (m, 5H), 2.40 (s, 3H), 2.35-2.28 (m, 1H), 2.12-2.03 (m, 1H), 1.81-1.41 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0, 138.9, 129.6, 127.2, 110.5, 73.9, 63.3, 59.3, 57.5, 50.9, 32.2, 31.7, 27.4, 23.7, 21.7; ESI HRMS *m/z* $(M+Na)^+$ calcd 380.1502, obsd 380.1498.



5.12d

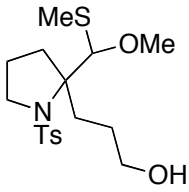
IR (neat, cm^{-1}) 3276, 1080, 815, 662, 550; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 7.29 (d, *J* = 8.4 Hz, 2H), 4.90 (t, *J* = 6.0 Hz, 1H), 4.00 (s, 1H), 3.80-3.75 (m, 2H), 3.48 (s, 3H), 3.41 (s, 3H), 2.95-2.87 (m, 2H), 2.41 (s, 3H), 2.06-1.73 (m, 3H), 1.56-1.45 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 137.3, 129.8, 127.3, 110.0, 86.6, 69.2, 58.6, 57.1, 44.0, 33.4, 30.9, 26.9, 23.8, 21.7; ESI HRMS *m/z* $(M+Na)^+$ calcd 380.1502, obsd 380.1494.



5.13a

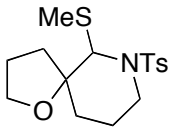
Two isomers were obtained. Isomer 1: IR (neat, cm^{-1}) 1329, 1005, 662, 591, 574; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 5.18 (s, 1H), 4.03-3.98 (m, 1H), 3.53 (td, *J* = 11.1, 3.0 Hz, 1H), 3.37-3.27 (m, 2H), 2.65-2.58 (m, 1H), 2.43-2.35 (m, 4H), 2.24 (s, 3H), 1.96-1.62 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 138.5, 129.6, 127.5, 92.4, 69.7, 69.3, 49.9, 35.4, 33.9, 25.3, 23.5, 21.7, 14.6; ESI

HRMS *m/z* $(M+Na)^+$ calcd 364.1012, obsd 364.1033. Isomer 2: IR (neat, cm^{-1}) 1338, 1068, 660, 592, 546; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.1 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 4.79 (s, 1H), 4.15 (td, *J* = 11.7, 3.9 Hz, 1H), 3.54-3.48 (m, 1H), 3.38-3.28 (m, 2H), 3.18 (td, *J* = 12.9, 5.4 Hz, 1H), 2.68 (ddd, *J* = 12.6, 6.0, 2.1 Hz), 2.40 (s, 3H), 2.04 (s, 3H), 1.90-1.57 (m, 5H), 1.48 (td, *J* = 12.0, 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 138.3, 129.6, 128.0, 88.8, 70.2, 58.5, 50.2, 38.2, 29.0, 24.6, 21.7, 21.5, 13.7; ESI HRMS *m/z* $(M+Na)^+$ calcd 364.1012, obsd 364.1022.



5.13b

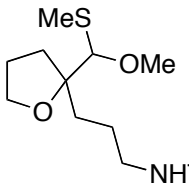
IR (neat, cm^{-1}) 3512, 1322, 667, 590; ^1H NMR (300 MHz, $CDCl_3$, 1:4 mixture of isomers) δ 7.90 (d, *J* = 8.1 Hz, 0.4H), 7.74 (d, *J* = 8.1 Hz, 1.6H), 7.27 (d, *J* = 8.1 Hz, 2H), 4.98 (s, 0.2 H), 4.69 (s, 0.8H), 3.64-3.63 (m, 1.6H), 3.49-3.43 (m, 2.2H), 3.43-3.27 (m, 0.8H), 3.17 (s, 2.4H), 2.40 (s, 3H), 2.33 (s, 0.6H), 2.21-2.12 (m, 5H), 1.88-1.54 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 138.9, 129.6, 127.2, 97.6, 76.0, 63.2, 56.0, 51.2, 33.7, 33.4, 27.7, 23.8, 21.7, 16.9; ESI HRMS *m/z* $(M+Na)^+$ calcd 396.1274, obsd 396.1266.



5.13c

IR (neat, cm^{-1}) 1336, 1161, 1091, 655, 574; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 5.00 (s, 1H), 3.89 (t, *J* = 6.6 Hz, 2H), 3.56-3.50 (m,

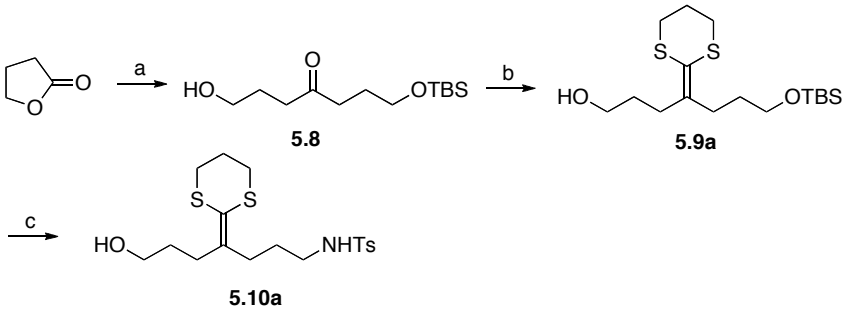
1H), 3.01 (td, J = 12.6, 3.3 Hz, 1H), 2.42 (s, 3H), 2.14-1.91 (m, 7H), 1.74-1.62 (m, 2H), 1.51-1.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 137.4, 129.8, 127.7, 84.0, 71.2, 68.1, 40.6, 35.1, 31.5, 25.9, 23.8, 21.8, 16.0; ESI HRMS m/z $(M+Na)^+$ calcd 364.1012, obsd 364.1026.



5.13d

IR (neat, cm^{-1}) 3267, 1326, 1093, 662, 550; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 5.07-5.02 (m, 1H), 4.14 (s, 1H), 3.89-3.79 (m, 2H), 3.45, 3.44 (2s, 3H), 2.95-2.90 (m, 2H), 2.42 (s, 3H), 2.17, 2.12 (2s, 3H), 2.07-1.49 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 137.3, 129.9, 127.3, 96.5, 95.2, 88.2, 87.9, 69.5, 69.3, 58.0, 57.6, 43.9 (d), 34.5, 34.4, 33.2, 32.4, 26.9 (d), 24.1, 21.7, 15.7, 14.5; ESI HRMS m/z $(M+Na)^+$ calcd 396.1274, obsd 396.1269.

Synthesis of the Substrates:



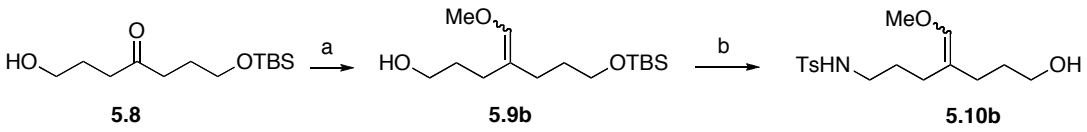
Reaction conditions: a. $ICH_2CH_2CH_2OTBS$, t-BuLi, Et_2O, -78 °C, 48%; b. 2-trimethylsilyl-1,3-dithane, n-BuLi, 52%; c. 1. TsNHBoc, Ph_3P, DEAD, THF, rt, 2. LiMe, -20 °C, Et_2O, 3. TBAF, THF, rt, 81%.

Synthesis of 5.8: To a solution of *tert*-butyl(3-iodopropoxy)dimethylsilane (6.0 g, 20 mmol) was added *t*-BuLi solution (1.7 M in pentane, 23.5 mL, 40 mmol) at -78 °C under argon atmosphere. The resulting mixture was stirred at -78 °C for 0.5 h and then rt for 1 h. In another flask, a solution of butyrolactone (1.7 g, 20 mmol) in Et_2O was cooled to -78 °C and treated with the above lithium reagent. Water was added after 15 min and the cold bath was removed. Ether layer was separated and the aqueous phase extracted with ether. The combined organic solution was dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed through silica gel (eluted with acetone/hexane, 1:4) to give **5.8** (2.5 g, 48%) and. IR (neat, cm^{-1}) 3411, 1713, 1255, 1100, 836; ^1H NMR (300 MHz, $CDCl_3$) δ 3.63-3.56 (m, 4H), 2.57-2.47 (m, 4H), 1.83-1.74 (m, 4H), 0.86 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.8, 62.4, 62.3, 39.8, 39.4, 27.0, 26.7, 26.1, 18.5, -5.2; ESI HRMS *m/z* $(M+Na)^+$ calcd 283.1700, obsd 283.1689.

Synthesis of 5.9a: *n*-BuLi (1.6 M in hexanes, 13.2 mL, 21.2 mmol) was added drop-wise to a solution of 2-trimethylsilyl-1,3-dithiane (3.93 mL, 21.2 mmol) in THF (40 mL). The resulting mixture was stirred at -78 °C for 0.5 h and then 0 °C for an additional 0.5 h. The reaction was then cooled to -78 °C and treated with **5.8** (1.84 g, 7.07 mmol). Upon complete addition, the reaction was allowed to warm to rt slowly and stirred overnight. The reaction mixture was poured into water (50 mL) and extracted with ether. The combined extractions were dried over $MgSO_4$ and evaporated. Chromatography through silica gel afforded **5.8** (0.50 g, 27%) and **5.9a** (1.34g, 52%). IR (neat, cm^{-1}) 3868, 1254, 1102, 835, 775; ^1H NMR (300 MHz, $CDCl_3$) δ 3.59-3.55 (m, 4H), 2.85-2.79 (m, 4H), 2.40-2.29 (m, 4H), 2.14-2.04 (m, 3H), 1.65-1.54 (m, 4H), 0.85 (s, 9H), 0.02 (s, 6H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 144.3, 120.9, 63.1, 62.1, 31.7, 30.9, 30.6, 30.5, 30.4, 29.9, 26.2, 25.2, 18.5; ESI HRMS *m/z* $(M+Na)^+$ calcd 385.1662, obsd 385.1651.

Synthesis of 5.10a: Diethyl azodicarboxylate solution (40 wt% soluion in toluene, 3.40 mL, 7.50 mmol) was added drop-wise to a solution of **5.9a** (1.06 g, 2.92 mmol), *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (1.22 g, 4.50 mmol) and triphenylphosphine (2.36 g, 9.00 mmol) in THF (40 mL) at rt. After stirred overnight, the solvent was removed and the residue filtered through a pad of silica gel to give a mixture of the desired product and Ph_3P. The mixture was then dissolved in Et_2O (24 mL) and treated with LiMe (9.10 mL, 14.5 mmol) at -20 °C. Water was added slowly after 15 min and the cold bath was then removed. The organic layer was separated and aqueous phase extracted with ether. The combined organic solution was dried with $MgSO_4$, filtered and concentrated. The residue was dissolved in THF (15 mL) and treated with TBAF (4.80 mL, 4.80 mmol) at rt. The reaction was kept at rt for 2 h and then poured into water (40 mL). Ether was added and organic layer separated. The water layer was extracted with ether. The organic solutions were combined, dried with $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed (silica gel, ether) to give **7** (0.95 g, 81%). IR (neat, cm^{-1}) 3499, 3278, 1323, 814, 662, 550; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 4.81 (t, *J* = 6.0 Hz, 1H), 3.61-3.55 (m, 2H), 2.97-2.91 (m, 2H), 2.86-2.81 (m, 4H), 2.42 (s, 3H), 2.34-2.26 (m, 4H), 2.14-2.06 (m, 2H), 1.79 (t, *J* = 5.7 Hz, 1H), 1.66-1.50 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 142.8, 137.3, 130.0, 127.4, 122.0, 62.2, 43.0, 31.0, 30.6, 30.5, 29.8, 28.0, 25.0, 21.8; ESI HRMS *m/z* $(M+Na)^+$ calcd 424.1045, obsd 424.1043.



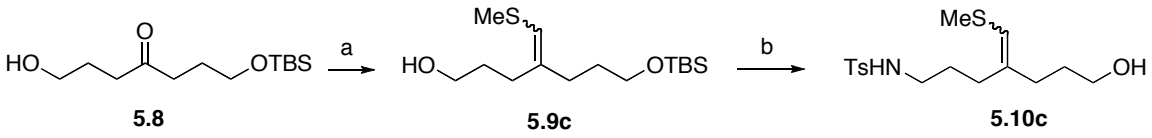
5.8 **5.9b** **5.10b**

Reaction conditions: a. Ph_3PCH_2OMeCl, NaHMDS, THF, 59%; b. 1. TsNHBoc, Ph_3P, DEAD, THF, rt, 2. LiMe, -20 °C, Et_2O, 3. TBAF, THF, rt, 70%.

Synthesis of 5.9b: To a suspension of methoxymethyltriphenylphosphonium chloride (27.4 g, 80.0 mmol) in THF (160 mL) was added NaHMDS solution (1.0 M in THF, 80.0 mL, 80.0 mmol) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 0.5 h and then treated with **5.8** (5.2 g, 20.0 mmol). The reaction was stirred overnight and warmed to rt. Water was added, followed by ether. The organic layer was separated and aqueous layer extracted twice with ether. The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. Chromatography through silica gel gave **S-3** as a 2:3 mixture of isomers (3.40 g, 59%). IR (neat, cm^{-1}) 3363, 1255, 1100, 836; ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (s, 0.4H), 5.73 (s, 0.6H), 3.56-3.52 (m, 4H), 3.49 (s, 1.2H), 3.46 (s, 1.8H), 2.10 (t, J = 7.2 Hz, 1.2H), 2.02, (t, J = 7.8 Hz, 1.8H), 1.92-1.83 (m, 2H), 1.59-1.50 (m, 4H), 0.84 (s, 9H), -0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 142.6, 117.4, 116.9, 63.4, 62.8, 62.5, 61.5, 59.5, 59.3, 31.4, 31.3, 31.2, 29.9, 28.0, 27.7, 26.1, 23.3, 22.6, 18.5, -5.1; ESI HRMS *m/z* $(M+Na)^+$ calcd 311.2013, obsd 311.2006.

Synthesis of 5.10b: Compound **5.10b** was synthesized from **5.9b** by following the same procedure described for the synthesis of **5.10a**. IR (neat, cm^{-1}) 3499, 3280, 1323, 1128, 662, 550; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70, 7.68 (2d, J = 8.1, 8.4 Hz, 2H), 7.25 (d, J = 7.8 Hz, 2H), 5.72 (s, 1H), 5.44-5.36 (m, 1H), 3.54-3.43 (m, 5H), 2.82 (q, J = 8.1 Hz, 2H), 2.68 (t, J = 6.3 Hz, 0.6H), 2.37 (s, 3.4H), 2.03-1.96 (m, 2H), 1.79 (t, 7.5 Hz, 2H), 1.55-

1.41 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 143.4, 143.2, 137.5, 137.2, 129.9, 129.8, 127.3, 127.2, 116.1, 115.8, 62.4, 61.6, 59.6, 42.8, 42.4, 31.1, 29.9, 28.4, 28.0, 27.5, 26.9, 23.4, 22.4, 21.9; ESI HRMS *m/z* $(M+Na)^+$ calcd 350.1397, obsd 350.1406.



5.8 **5.9c** **5.10c**

Reaction conditions: a. Ph_3PCH_2SMeCl, *n*-BuLi, THF, 34%; b. 1. TsNHBoc, Ph_3P, DEAD, THF, rt, 2. LiMe, -20 °C, Et_2O, 3. TBAF, THF, rt, 75%.

Synthesis of S-5.9c: To a suspension of (methylthiomethyl)triphenylphosphonium chloride (21.5 g, 60.0 mmol) in THF (150 mL) was added drop-wise *n*-BuLi solution (1.6 M in hexanes, 37.5 mL, 60.0 mmol) at 0 °C under argon atmosphere. After complete addition, solution was stirred at 0 °C for 0.5 h and then treated with **S-1** (5.2 g, 20 mmol). The reaction was stirred at rt for 4 days. Brine and ether were added at 0 °C. The organic phase was separated and aqueous layer extracted with ether. The organic solutions were combined, dried over $MgSO_4$, and concentrated. Chromatography on silica gel afforded **5.8** (1.00 g, 19%) and **5.9c** (2.10 g, 34%). IR (neat, cm^{-1}) 3350, 1255, 1102, 836; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.58 (s, 1H), 3.56 (t, J = 6.6 Hz, 4H), 2.25 (br, 1H), 2.18 (s, 3H), 2.15-2.06 (m, 4H), 1.67-1.54 (m, 4H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6, 121.2, 63.3, 62.5, 33.0, 31.0, 30.9, 8.6, 26.1, 18.5, 17.4, -5.0; ESI HRMS *m/z* $(M+Na)^+$ calcd 327.1784, obsd 327.1790.

Synthesis of 5.10c: Compound **5.10c** was synthesized from **5.9c** by following the same procedure described for the synthesis of **5.10a**. IR (neat, cm^{-1}) 3494, 3280, 1321, 1157, 661, 550; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 8.1 Hz,

2H), 5.54 (s, 1H), 5.40 (t, J = 6.0 Hz, 1H), 3.56-3.50 (q, J = 5.7 Hz, 2H), 2.89-2.82 (q, J = 6.6 Hz, 2H), 2.38-2.34 (m, 4H), 2.17 (s, 3H), 2.09 (t, J = 6.9 Hz, 2H), 2.00 (t, J = 8.1 Hz, 2H), 1.61-1.50 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 138.3, 137.2, 129.9, 127.3, 122.1, 62.2, 42.9, 33.3, 30.3, 28.0, 21.7, 17.4; ESI HRMS *m/z* $(M+Na)^+$ calcd 366.1168, obsd 366.1162.

5.6 Spectra: see Appendix D

References and Notes

1. Xu, H.-C.; Moeller, K. D. *Org. Lett.* **2010**, *12*, 1720.
2. For a review see Moeller, K. D. *Synlett.* **2009**, *8*, 1208.
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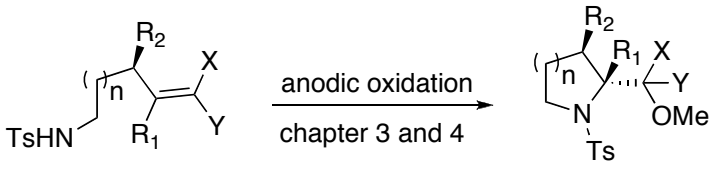
Chapter 6 Intramolecular Anodic Coupling Reactions: Use of Reaction Rate to Control Substrate/Product Selectivity[1]

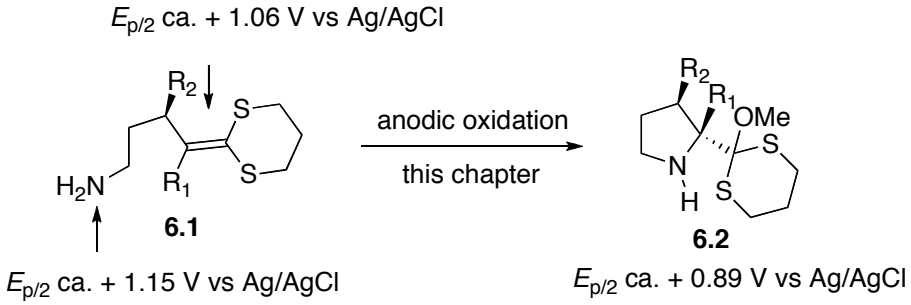
6.1 Introduction

We have demonstrated that the intramolecular anodic coupling of tosylamides with electron-rich olefins provide easy access to functionalized cyclic amino acid derivatives (Scheme 6-1).[2,3] While the tosyl group was introduced easily and served as an effective protecting group for the nitrogen, its removal usually requires drastic conditions such as concentrated acids and strong reducing regents.[4]

Scheme 6-1 Anodic Coupling of Electron-Rich Olefins and Sulfonamides



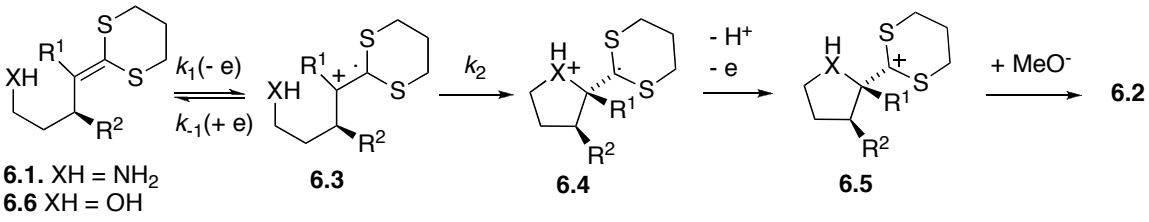
Scheme 6-2 Proposed Anodic Coupling of Primary Amines and Dithioketene Acetals



Instead of looking for alternative protecting groups that can be removed more easily, we decided to take a more intriguing approach including the use of an unprotected amine as coupling partner (Scheme 6-2). A concern for such a method is that the secondary

amine product might be oxidized during the electrolysis. An examination of the oxidation potentials[5] shows that the individual coupling partners, the amine ($E_{p/2}$ = + 1.15 V vs. Ag/AgCl) and the dithioketene acetal ($E_{p/2}$ = + 1.06 V vs. Ag/AgCl), are oxidized at lower potentials than that of the product ($E_{p/2}$ = + 0.89 V vs. Ag/AgCl), a scenario that suggests overoxidation. However, such an analysis ignores the cyclization reaction and its affect on the oxidation potential of the substrate.[6] For example, the alcohol substrate **6.6** (XH = OH, R_1 = R_2 = Me, Figure 6-1) has an oxidation potential of $E_{p/2}$ = + 0.95 V vs. Ag/AgCl, a 110 mV drop in potential from that of the isolated dithioketene acetal ($E_{p/2}$ = + 1.06 V vs. Ag/AgCl).

Figure 6-1 The Relationship of Observed Potential and Cyclization Rates.



$$E_{obsv} = E^{o} - (RT/(nF)) \ln \left(\frac{[\textbf{6.1 or 6.6}]}{[\textbf{6.3}]} \right) \quad (\textbf{1})$$

If "steady-state", then....

$$[\textbf{6.3}] = \frac{k_1[\textbf{6.1 or 6.6}]}{(k_{-1} + k_2)} \quad (\textbf{2})$$

the Nernst Equation becomes:

$$E_{obsv} = E^{o} - (RT/(nF)) \ln \left(\frac{(k_{-1} + k_2)}{k_1} \right) \quad (\textbf{3})$$

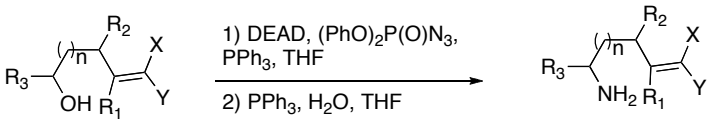
The drop in substrate potential caused by the subsequent cyclization of the radical cation can be explained using Nerst equation and steady state kinetics. As shown in Figure 6-1, the potential of substrate is given by Nerst equation (**1**). The concentration of

the radical cation **6.3** can be derived using steady state kinetics leading to equation (**2**). Substitution of equation (**2**) into (**1**) affords equation (**3**), which describes the relationship between observed potential and the rate of cyclization. In equation (**3**), E^{o} is positive and RT/nF is positive and constant. Hence, as k_2 gets larger and the reaction gets faster, E_{obsv} decreases. With a stronger amine nucleophile we expect that the cyclization would proceed even faster than a reaction using an alcohol substrate leading to an even lower potential for the amine substrate. But would the potential be lowed to a point where competitive oxidation of the product could be avoided?

6.2 Results and Discussion

Our studies commenced by examining ketene dithioacetal **6.1a**. Ketene dithioactals have been shown to be excellent coupling partners for heteroatom-based nucleophiles such as alcohols and sulfonamides and have relative low oxidation potentials. The amine substrates were prepared from the corresponding alcohols that were either used in

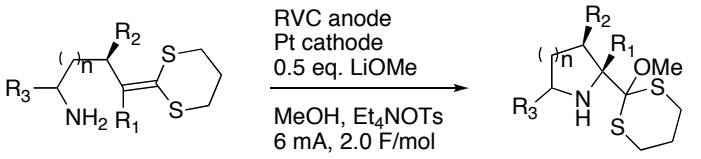
Scheme 6-3 Synthesis of Amine Substrates 6.1a-j

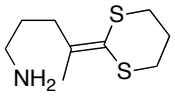
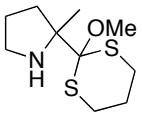
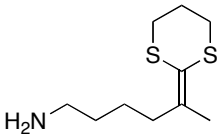
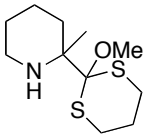
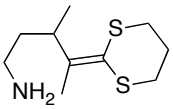
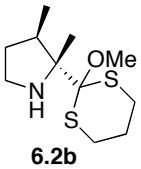
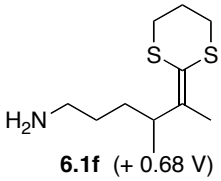
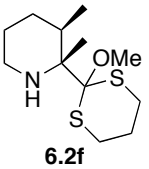
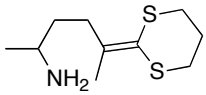
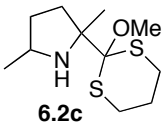
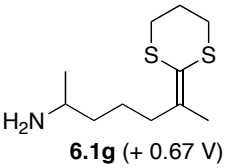
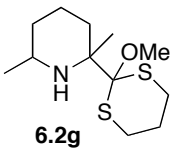
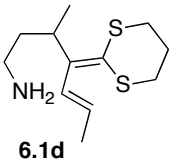
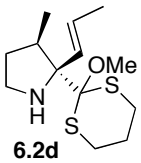
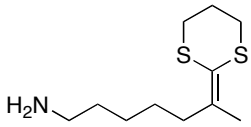
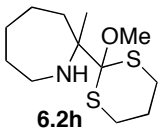


6.7a n = 1, $R_2 = R_3 = H$, R_1 = Me, X = Y = $S(CH_2)_3S$	**6.1a** 57%
6.7b n = 1, $R_1 = R_2$ = Me, $R_3 = H$, X = Y = $S(CH_2)_3S$	**6.1b** 55%
6.7c n = 1, $R_2 = H$, $R_1 = R_3$ = Me, X = Y = $S(CH_2)_3S$	**6.1c** 58%
6.7d n = 1, R_2 = Me, R_1 = CH=CHMe, X = Y = $S(CH_2)_3S$	**6.1d** 60%
6.7e n = 2, $R_2 = R_3 = H$, R_1 = Me, X = Y = $S(CH_2)_3S$	**6.1e** 53%
6.7f n = 2, $R_1 = R_2$ = Me, $R_3 = H$, X = Y = $S(CH_2)_3S$	**6.1f** 66%
6.7g n = 2, $R_2 = H$, $R_1 = R_3$ = Me, X = Y = $S(CH_2)_3S$	**6.1g** 75%
6.7h n = 3, $R_2 = R_3 = H$, R_1 = Me, X = Y = $S(CH_2)_3S$	**6.1h** 58%
6.7i n = 1, $R_2 = R_3 = H$, R_1 = Me, X =H, Y = SMe	**6.1i** 40%
6.7j n = 1, $R_1 = R_2 = R_3 = H$, X = Y = $S(CH_2)_3S$	**6.1j** 46%

previous studies (**6.7a-b**, **6.7d-f**, **6.7i-j**, Chapters 2, 3 and 4) or synthesized by following literature procedures (**6.7c**, **6.7g-h**, Scheme 6-3).[2,7] Functional group interconversion through azide formation using a Mitsunobu reaction and subsequent reduction with triphenylphosphine in wet THF under refluxing conditions converted the alcohols to primary amines.

Table 6-1 Anodic Coupling of Unprotected Amines and Dithioketene Acetals



entry	substrate	product	yield (%)	entry	substrate	product	yield (%)
1	 **6.1a** (+ 0.60 V)[a]	 **6.2a** (+ 0.89 V)	84	5	 **6.1e** (+ 0.65 V)	 **6.2e** (+ 0.95 V)	72
2	 **6.1b** (+ 0.62 V)	 **6.2b**	81 > 20:1 dr	6	 **6.1f** (+ 0.68 V)	 **6.2f**	83[c] > 20:1 dr
3	 **6.1c** (+ 0.58 V)	 **6.2c**	92 (40)[b] 3:2 dr	7	 **6.1g** (+ 0.67 V)	 **6.2g**	64[d]
4	 **6.1d**	 **6.2d**	90 10:1 dr	8	 **6.1h** (+ 0.70 V)	 **6.2h**	0

[a] Oxidation potential measure by cyclic voltammetry on a carbon anode vs. Ag/AgCl reference elelctrode. [b] NMR yield, 6 equiv 2,6-lutidine as base. [c] 2.3 F/mol. [d] 2.4F/mol

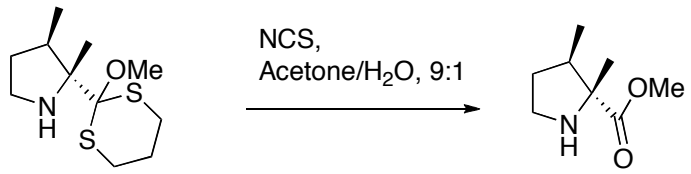
The preparative electrolysis reactions were conducted in an undivided cell with constant current of 6 mA until 2.0 F/mol of current (theoretical amount for a two-electron

oxidation) had been passed. The reactions used 0.5 equiv of LiOMe as base and 0.1 M Et_4NOTs in methanol electrolyte solution. These conditions were optimized previously for the oxidative coupling of sulfonamides with electron-rich olefins.[2] To our delight, substrate **6.1a** cyclized to afford the desired product **6.2a** in 84% yield (Table 6-1, entry 1). The success of the cyclization was consistent with an examination of the oxidation potential for the substrate. The potential of **6.1a** was measured by cyclic voltammetry to be $E_{p/2}$ = + 0.60 V vs. Ag/AgCl, which is much lower than that of the individual coupling partners and the cyclized product ($E_{p/2}$ = + 0.89 V vs. Ag/AgCl). A potential drop of 460 mV from the dithioketene acetal is the biggest we observed to date and suggests a very fast cyclization. The cyclization of **6.1a** proceeds much faster than that of **6.6** because of the enhanced nucleophilicity of the amine compared with the alcohol. Competitive oxidation of the product in this case was avoided because of the dramatic drop in substrate potential.

Substitutents were introduced at R_2 and R_3 positions to probe the stereoselectivity of the cyclization. With a methyl group at the allylic position, the electrolysis of **6.1b** furnished **6.2b** in 81% yield as a single diastereoisomer (Table 6-1, entry 2). The stereochemistry was assigned as shown in analogy to previous observations. Presumably, it is controlled by the steric interaction between the allylic methyl and the dithiane group.[2] Moving the methyl group to position R_3 thus away from the dithioacetal resulted in diminished stereoselectivity. Under the same reaction conditions, the cyclization of **6.1c** afforded the desired product in 92% yield but as a mixture of diastereomers in a ratio of 3:2 (Table 6-1, entry 3).

The orthoester in **6.2b** can be hydrolyzed to a methyl ester (**6.8)** with the use of N-chlorosuccinimide (NCS) in a mixture of water and acetone (Scheme 6-4).[8]

Scheme 6-4 Hydrolysis of the Electrolysis Product 6.2b



6.2b **6.8** 73%

The need for LiOMe in the electrolysis was probed with substrate **6.2c**. Switching the base from lithium methoxide to a weaker base, 2,6-lutidine, resulted in dramatic decrease in yield (Table 6-1, entry 3). In this case, only 40% of the desired product **6.2c** was formed. The yield was determined using a ^{1}H-NMR spectrum of the crude reaction mixure with coumarin as an internal standard. The reaction gave a mixture of products and the desired product could not be isolated in a pure form. The decrease in yield can be explained in several ways. First, it is possible that the nucleophilicity of the primary amine was reduced as a result of protonation by the acid produced at the anode. During the electrolysis, acid is produced at the anode and equal amount of base (methoxide) is produced at the cathode as a result of the reduction of methanol. While the overall electrolysis reaction is neutral, regions around the anode are acidic. When approaching the anode, the more basic primary amine might be protonated instead of the added "acid scavenger" 2,6-lutidine. Hence, passivation of the amine nucleophile by anode-produced acid is expected. Secondly, LiOMe might serve as a better base to deprotonate intermediate **6.4** (Figure 6-1) and thus help the cyclization by reducing the rate of reverse reaction. Lastly, it is possible that the use of LiOMe accelerates the trapping of the cation

6.5 (Figure 6-1) thereby reducing the chance for its involvement in unproductive pathways. The importance of the trapping of this cation for the electrolysis reaction has been demonstrated in previous studies.[3,9]

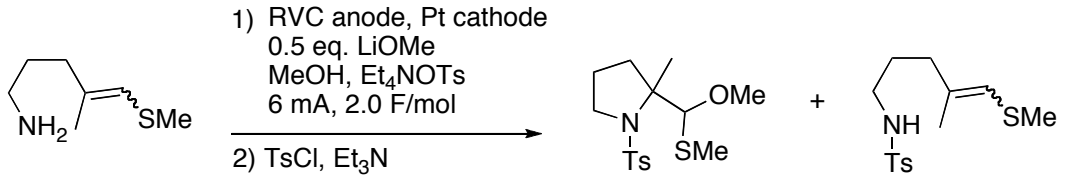
A vinyl-substituted ketene dithioacetal **6.1d**, prepared from the alcohol **6.1g** used in the synthesis of crobarbatic acid (Chapter 2), was also cyclized nicely to afford the desired product in 90% yield with good diastereoselectivity (10:1 dr, Table 6-1, entry 4). The success of using a vinyl-substituted olefin meant that the reversing of the stereochemistry at the tretrasubstituent carbon after the cyclization was possible (Scheme 2-7 for example), thereby making both stereochemistries of the tetrasubstituted carbon available from the same cyclization.[8]

Reactions leading to six-membered ring products were also studied. The electrolyses were carried out under the same conditions described above and preceded much better than those using sulfonamides as coupling partners. For example, oxidation of **6.1e** afforded the pipecolic acid derivative **6.2e** in 72% yield (Table 6-1, entry 5), while the corresponding sulfonamide counterpart only afforded the desired product in 20% yield.[2b] With an allylic methyl to induce stereoselectivity, the cyclization formed the expected product **6.2f** in 82% yield as a single diastereomer (Table 6-1, entry 6). The two methyls were assigned to be *cis* in analogy to early cyclization employing sulfonamide as a coupling partner (Chapter 4).[2b] Since a substrate like this can be prepared enantioselectively,[8] the oxidative cyclization would afford a great way to build stereochemistry defined 3-substituted pipecolic acid derivatives. Once again, with a methyl group at R_3 instead of R_2, the cyclization afforded the product in low stereoselectivity (entry 7). In this case, a moderate yield of **6.2g** was obtained as a

mixture of diastereoisomers (2:1 dr). The stereochemical mixture observed in this example suggests that the cyclizations are under kinetic control with an early transition state (no clearly defined equatorial and axial positions). This suggestion is consistent with the very fast cyclzation rate as indicated by the large potential drops. The potentials of the substrates **6.1a-c** are lower than that of the cyclized product ($E_{p/2}$ = 0.95 V vs. Ag/AgCl) but not as low as those for substrates **6.1e-g**. This is consistent with the fact that six-membered ring cyclizations are slower than those of five.

Attempt to synthesize a seven-membered ring product by employing substrate **6.1h** failed (Table 6-1, entry 8). The reaction afforded a complex mixture of products and none of the desired product was observed. The potential of **6.1h** was measured to be $E_{p/2}$ = + 0.70 V vs. Ag/AgCl, a 360 mV drop from the dithioketene acetal suggesting that the cyclization is still very fast. In addition, solvent trapping products that usually observed in a failed cyclization reaction were not observed. Hence, it appeared that the substrate did cyclize. In theis case, either the cyclized intermediates failed to lead to the final product or it is possible the product was not stable under the reaction conditions.

Scheme 6-5 Anodic Coupling of an Amine and a Vinyl Sulfide

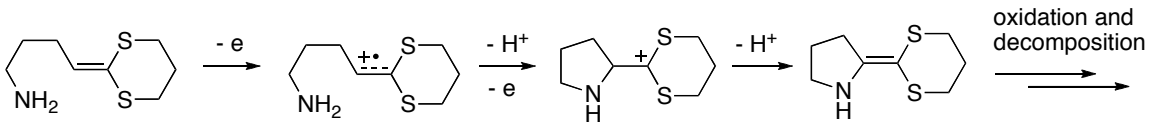


6.1j **6.9** 20% **6.10** 17%

The success of the reactions using dithioketene acetals and the large potential drops observed in these cyclizations prompted us to investigate the possibility of employing

electron rich olefins with higher oxidation potentials. Hence, vinyl sulfide **6.1i** was synthesized by the general procedure and oxidized. Under the same reaction conditions and with the use of 2.0 F/mol of current, oxidation of **6.1i** formed the cyclized product along with some leftover starting material, both of which were converted to the tosylamides to facilitate separation. In this way, compound **6.9** was isolated in 20% yield along with 17% of **6.10** derived from unreacted starting material **6.1i**. Passing more current to consume the starting material caused decomposition of the product. For example, the substrate **6.1i** disappeared along with the product after 2.7 F/mol of current had been passed through the electrolysis cell. In this case, the vinyl sulfide has an oxidation potential of $E_{p/2}$ = + 1.22 V vs. Ag/AgCl and is oxidized slightly more positively than the amine. However, because of potentially fast electron transfer between the two functional groups, it wouldn't matter where the initial oxidation occurred.[10] A substantial potential drop for the substrate was once again observed in this case (370 mV from the amine to $E_{p/2}$ = + 0.78 V vs. Ag/AgCl) suggesting a fast cyclization. However, the decreased potential gap between the substrate and the product might have caused competitive oxidation of the product during the electrolysis.

Scheme 6-6 Proposed Explanation for the Failure of the Cyclization of 6.1j



6.1j **6.11** **6.12** **6.13**

Lastly, the use of a trisubstituted dithioketene acetal in the cyclization was explored. However, the oxidation of **6.1j** afforded no desired product (Scheme 6-6). As measured

by cyclic voltammetry, the dithioketene acetal used in this case and the substrate **6.1j** have oxidation potentials of + 1.11 V and + 0.55 V ($E_{p/2}$ vs. Ag/AgCl), respectively. The large potential drop (560 mV) excludes the cyclization step being the problem. The failure of this substrate was probably caused by elimination of a proton from the cyclized cation intermediate **6.12** competing with methanol trapping to give the desired product.[2] The elimination would give a very electron-rich nitrogen substituted dithioketene acetal **6.13**, which would be rapidly oxidized under the reaction conditions (Scheme 6-6). Similar problem was encountered previously in the anodic coupling of the same ketene dithioacetal with a sulfonamide (Chapter 3).[2] The even more dramatic potential drop of **6.1j** than that of **6.1a** (560 mV vs. 460 mV) is consistent with a faster cyclization of **6.1j** because the reaction does not need to form a hindered tetrasubstituted carbon atom.

6.3 Conclusion

Unprotected amines were used successfully in intramolecular anodic coupling reactions to build proline and pipecolic acid derivatives with tetrasubstituted α-carbons. The reactions initially appear problematic because the product is oxidized at lower potential than either group in the substrate. However, a fast cyclization lowers the oxidation potential of the substrate significantly below that of the product and thus competitive oxidation of the product is avoided. Compared with the reactions that use sulfonamides as coupling partners, this method uses no protecting group for the nitrogen and therefore is synthetically more attractive.

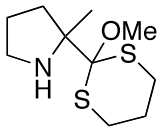
One limitation of these reactions is the failure to use trisubstituted dithioketene acetals in the cyclizations. In order to address such an issue we investigated the catalytic hydroamination of ketene dithioacetals. The results are discussed in the next chapter.

6.4 Experimental Section

General procedure for electrolysis reactions:

LiOMe (1.0 M in MeOH, 0.15 ml, 0.15 mmol) was added to a methanol (10 mL) solution of the substrate (0.30 mmol, 1 equiv) and the electrolyte Et_4NOTs (1.0 mmol) in a three-neck round bottom flask at rt under argon atmosphere. Two of the three septa were replaced by a reticulated vitreous carbon anode (RVC, 100 PPI) and platinum wire cathode. The solution was sonicated for 1 min. The electrolysis reaction was carried out at constant current of 6.0 mA until complete consumption of the starting material. When complete, the reaction was concentrated under reduced pressure. The residue was then chromatographed through a silica gel column (slurry packed using 1% triethylamine in ether solution, eluting with 20% MeOH/ether, Rf = 0.1) to give the desired product.

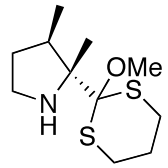
Electrolysis products:



2-(2-methoxy-1,3-dithian-2-yl)-2-methylpyrrolidine (6.2a)

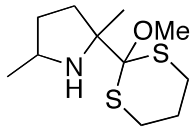
2.0 F/mol of charge was used, 84% yield. IR (neat, cm^{-1}) 3338, 1681, 1443, 1087; ^1H NMR (300 MHz, $CDCl_3$) δ 3.52 (s, 3H), 3.03-2.88 (m, 4H), 2.82-2.68 (m, 2H), 2.29-2.19 (m, 1H), 2.03-1.94 (m, 1H), 1.89-1.51 (m, 5H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$)

δ 102.3, 71.6, 53.6, 47.6, 36.6, 27.8, 27.6, 26.4, 24.6, 24.1; ESI HRMS *m/z* $(M+H)^+$ calcd 234.0981, obsd 234.0981.



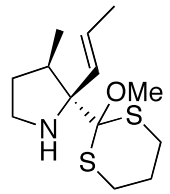
(2*R*,3*R*)-2-(2-methoxy-1,3-dithian-2-yl)-2,3-dimethylpyrrolidine (6.2b)

2.0 F/mol of charge was used, 81% yield. IR (neat, cm^{-1}) 3368, 1194, 1057; ^1H NMR (300 MHz, $CDCl_3$) δ 3.03-2.77 (m, 5H), 2.68-2.60 (m, 1H), 2.04-1.79 (m, 3H), 1.71 (s, 1H), 1.43-1.28 (m, 1H), 1.19 (s, 3H), 1.10 (d, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.5, 72.7, 53.2, 45.5, 39.1, 36.3, 28.1, 27.9, 23.5, 20.1, 17.3; ESI HRMS *m/z* $(M+H)^+$ calcd 248.1137, obsd 248.1137.



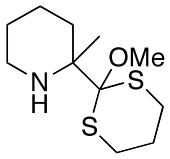
2-(2-methoxy-1,3-dithian-2-yl)-2,5-dimethylpyrrolidine (6.2c)

2.0 F/mol of charge was used. The title compound was obtained as a mixture of diastereomers (dr = 3:2) in 92% yield. IR (neat, cm^{-1}) 3338, 1446, 1087; ^1H NMR (300 MHz, $CDCl_3$) δ 3.58, 3.57 (2s, 3H), 3.38-3.26 (m, 1H), 3.06-2.72 (m, 4H), 2.42-2.32 (m, 1H), 2.08-1.80 (m, 3H), 1.71-1.51 (m, 1H), 1.44-1.23 (m, 1H), 1.39, 1.37 (2s, 3H), 1.17, 1.16 (2d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.8, 126.3, 102.6, 101.4, 73.1, 72.3, 56.6, 53.7, 53.5, 56.6, 53.7, 53.5, 37.5, 36.2, 34.8, 34.1, 28.2, 27.9, 27.8, 27.6, 26.2, 24.4, 24.0, 23.5, 21.7, 21.2; ESI HRMS *m/z* $(M+H)^+$ calcd 248.1137, obsd 248.1138.



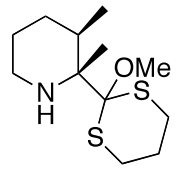
(2*S*,3*R*)-2-(2-methoxy-1,3-dithian-2-yl)-3-methyl-2-((*E*)-prop-1-enyl)pyrrolidine (6.2d)

2.0 F/mol of charge was used. dr = 10:1, yield = 90%. IR (neat, cm^{-1}) 3384, 3033, 1091, 980; ^{1}H NMR (300 MHz, $CDCl_3$, 10:1 ratio of isomers – data is for the major isomer) δ 5.81 (dq, *J* = 15.9, 1.5 Hz), 5.62 (dq, *J* = 15.9, 6.3 Hz), 3.53 (s, 3H), 3.06-2.60 (m, 7H), 2.02-1.83 (m, 4H), 1.79 (dd, *J* = 6.3, 1.5 Hz, 3H), 1.40-1.26 (m, 1H), 1.00 (d, *J* = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.2, 125.1, 104.6, 76.3, 53.0, 45.1, 40.1, 35.0, 28.6, 28.2, 23.4, 18.1, 17.6; ESI HRMS *m/z* $(M+H)^+$ calcd 274.1294, obsd 274.1292.



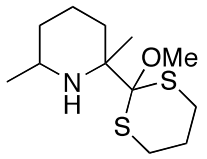
2-(2-methoxy-1,3-dithian-2-yl)-2-methylpiperidine (6.2e)

2.0 F/mol of charge was used, 72% yield. IR (neat, cm^{-1}) 3334, 1443, 1084; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.55 (s, 3H), 2.97-2.73 (m, 6H), 1.97-1.75 (m, 4H), 1.67-1.46 (m, 4H), 1.40-1.28 (m, 1H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 105.0, 64.6, 52.8, 41.7, 31.4, 28.2, 28.0, 26.5, 22.4, 17.3; ESI HRMS *m/z* $(M+H)^+$ calcd 248.1137, obsd 248.1136.



(2*R*,3*R*)-2-(2-methoxy-1,3-dithian-2-yl)-2,3-dimethylpiperidine (6.2f)

2.3 F/mol of charge was used. dr = 10:1, yield = 83%. IR (neat, cm^{-1}) 1457, 1194, 1089, 731; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.56 (s, 3H), 3.09-2.72 (m, 6H), 2.14-1.76 (m, 4H), 1.56-1.25 (m, 4H), 1.22 (3H), 0.93 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 106.8, 67.7, 52.0, 41.4, 36.0, 31.7, 28.8, 27.9, 27.3, 22.0, 19.9, 12.4; ESI HRMS *m/z* $(M+H)^+$ calcd 262.1294, obsd 262.1293.



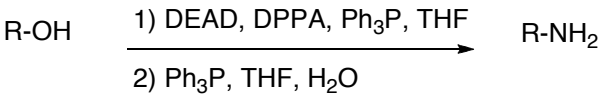
2-(2-methoxy-1,3-dithian-2-yl)-2,6-dimethylpiperidine (6.2g)

2.4 F/mol of charge was used. dr = 2:1, yield = 64%. IR (neat, cm^{-1}) 3400, 1194, 1083, 1058; ^{1}H NMR (300 MHz, $CDCl_3$, dr = 2:1) δ 3.58 (s, 2H), 3.53 (s, 1H), 3.03-2.73 (m, 5H), 2.03-1.75 (m, 4H), 1.67-1.48 (m, 5H), 1.35 (s, 1H), 1.32 (s, 2H), 0.99 (d, J = 6.0 Hz, 2H), 0.97 (d, J = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, major isomer) δ 105.1, 65.2, 53.1, 46.9, 34.6, 31.2, 28.0, 28.3, 24.0, 22.3, 21.7, 18.2; ESI HRMS *m/z* $(M+H)^+$ calcd 262.1294, obsd 262.1294.

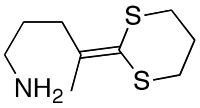
Synthesis of the Electrolysis Substrates:

The amines were synthesized from the corresponding alcohols according to the following

two-step process:

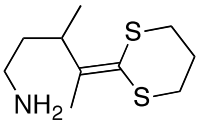


Typical procedure: Diethyl azodicarboxylate (DEAD, 5.5 mmol) was added to a solution of the alcohol (5.0 mmol) and triphenylphosphine (5.5 mmol) in THF (50 mL) at rt, followed by the addition of diphenylphosphoryl azide (DPPA, 5.5 mmol).[11] The reaction was stirred overnight and then the solvent removed. The residue was chromatographed through a silica gel column (eluting with ether:hexane = 1:10) to give an azide (3.0 mmol). The azide obtained was dissolved in THF (20 mL). Triphenylphosphine (7.5 mmol) and water (15 mmol) were added. The resulting reaction mixture was heated to reflux for 5 h, concentrated, and chromatographed through silica gel (eluting with MeOH:CH_2Cl_2:Et_3N = 4:1:0.1, Rf = 0.3) to give the desired amine.



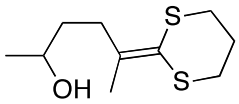
4-(1,3-dithian-2-ylidene)pentan-1-amine (6.1a)

Yield = 57%. IR (neat, cm^{-1}) 3299, 1575, 1488, 1300; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.88-2.83 (m, 4H), 2.68 (t, J = 7.2 Hz, 2H), 2.40 (t, J =7.5 Hz, 2H), 2.15-2.07 (m, 2H), 1.90 (s, 3H), 1.59-1.50 (m, 2H), 1.25 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.1, 119.6, 41.8, 33.2, 31.9, 30.5, 30.3, 25.1, 20.3; ESI HRMS m/z $(M+H)^+$ calcd 204.0875, obsd 204.0877.



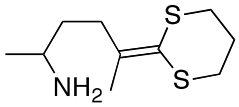
4-(1,3-dithian-2-ylidene)-3-methylpentan-1-amine (6.2b)

Yield = 55%. IR (neat, cm^{-1}) 3359, 3289, 1580, 1469; ^1H NMR (300 MHz, $CDCl_3$) δ 3.41-3.29 (m, 1H), 2.90-2.84 (m, 4H), 2.61-2.56 (m, 2H), 2.16-2.08 (m, 2H), 1.77 (s, 3H), 1.58-1.38 (m, 2H), 1.25 (s, 2H), 0.98 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 119.6, 40.5, 39.0, 34.8, 30.6, 30.2, 25.3, 19.1, 14.7; ESI HRMS m/z $(M+H)^+$ calcd 218.1032, obsd 218.1031.



5-(1,3-dithian-2-ylidene)hexan-2-ol (6.S1)

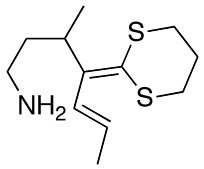
The title compound was prepared in 65% yield from 5-hydroxy-2-hexanone and 2-trimethylsilyl-1,3-dithiane according to published procedures.[1a] IR (neat, cm^{-1}) 3367, 1275, 1127; ^1H NMR (300 MHz, $CDCl_3$) δ 3.79-3.73 (m, 1H), 2.89-2.84 (m, 4H), 2.57-2.47 (m, 1H), 2.39-2.30 (m, 1H), 2.21 (s, 2H), 2.16-2.09 (m, 2H), 1.91 (s, 3H), 1.57-1.50 (m, 2H), 1.20 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.1, 119.6, 67.4, 37.1, 32.2, 30.5, 30.3, 25.1, 23.4, 20.3; ESI HRMS m/z $(M+Na)^+$ calcd 241.0691, obsd 241.0697.



5-(1,3-dithian-2-ylidene)hexan-2-amine (6.1c)

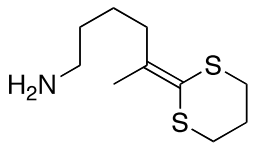
Yield = 58%. IR (neat, cm^{-1}) 3358, 3279, 1578, 1370; ^1H NMR (300 MHz, $CDCl_3$) δ 2.88-2.81 (m, 5H), 2.48-2.30 (m, 2H), 2.15-2.07 (m, 2H), 1.90 (s, 3H), 1.49-1.31 (m,

2H), 1.31 (s, 2H), 1.07 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.4, 119.4, 46.8, 38.2, 33.0, 30.5, 30.3, 25.2, 24.0, 20.3; ESI HRMS m/z $(M+H)^+$ calcd 218.1032, obsd 218.1034.



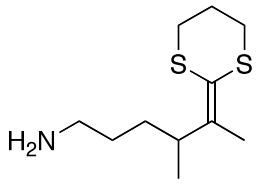
(*E*)-4-(1,3-dithian-2-ylidene)-3-methylhept-5-en-1-amine (6.1d)

Yield = 60%. IR (neat, cm^{-1}) 3363, 3288, 1581, 964; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.07 (dq, J = 15.9, 1.5 Hz, 1H), 5.64 (dq, J = 15.9, 6.6 Hz, 1H), 3.25-3.17 (m, 1H), 2.88-2.73 (m, 4H), 2.53 (t, J = 6.9 Hz, 2H), 2.07-1.99 (m, 2H), 1,72 (dd, J = 6.6, 1.5 Hz, 3H), 1.68-1.49 (m, 1H), 1.47-1.35 (m, 1H), 1.40 (s, 2H), 1.01 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2, 129.4, 126.6, 124.8, 40.6, 39.5, 34.6, 30.0, 24.7, 19.6, 19.1; ESI HRMS m/z $(M+H)^+$ calcd 244.1188, obsd 244.1188.



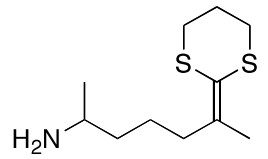
5-(1,3-dithian-2-ylidene)hexan-1-amine (6.1e)

Yield = 53%. IR (neat, cm^{-1}) 3301, 1578, 1468; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.88-2.82 (m, 4H), 2.70 (t, J = 6.6 Hz, 2H), 2.36 (t, J = 7.5 Hz, 2H), 2.16-2.08 (m, 2H), 1.91 (s, 3H), 1.46-1.41 (m, 4H), 1.32 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5, 119.5, 41.7, 35.7, 32.6, 30.4, 30.3, 25.3, 25.2, 20.3; ESI HRMS m/z $(M+H)^+$ calcd 218.1032, obsd 218.1033.



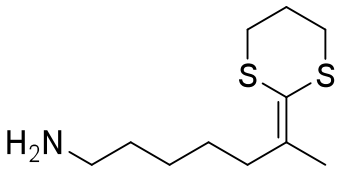
5-(1,3-dithian-2-ylidene)-4-methylhexan-1-amine (6.1f)

Yield = 66%. IR (neat, cm^{-1}) 3352, 3291, 1578, 1458; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.27-3.20 (m, 1H), 2.90-2.83 (m, 4H), 2.71-2.61 (m, 2H), 2.16-2.08 (m, 2H), 1.77 (s, 3H), 1.42-1.32 (m, 4H), 1.23 (s, 2H), 0.96 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 119.6, 40.5, 39.0, 34.8, 30.6, 30.2, 25.3, 19.1, 14.7; ESI HRMS *m/z* $(M+H)^+$ calcd 232.1188, obsd 232.1188.



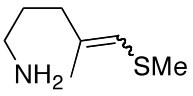
6-(1,3-dithian-2-ylidene)heptan-2-amine (6.1g)

Yield = 75%. IR (neat, cm^{-1}) 3357, 3291, 1578, 1370; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.76-2.65 (m, 5H), 2.22-2.15 (m, 2H), 1.98-1.90 (m, 2H), 1.74 (s, 3H), 1.30-1.10 (m, 4H), 1.00 (s, 2H), 0.89 (d, J = 6.3Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5, 119.4, 46.8, 39.9, 35.9, 30.4, 30.3, 25.1, 24.8, 24.2, 20.3; ESI HRMS *m/z* $(M+H)^+$ calcd 232.1188, obsd 232.1188.



6-(1,3-dithian-2-ylidene)heptan-1-amine (6.1h)

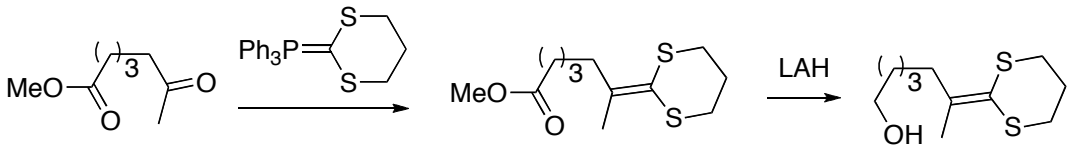
Yield = 58%. IR (neat, cm^{-1}) 3361, 1584, 1275, 991; ^1H NMR (300 MHz, $CDCl_3$) δ 2.80-2.74 (m, 4H), 2.60 (t, *J* = 7.2 Hz, 2H), 2.72 (t, *J* = 7.2 Hz, 2H), 2.07-1.82 (m, 2H), 1.82 (s, 3H), 1.40-1.20 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.9, 119.2, 42.4, 36.0, 33.9, 30.5, 30.3, 27.9, 26.8, 25.2, 20.4; ESI HRMS *m/z* $(M+H)^+$ calcd 232.1194, obsd 232.1188.



4-methyl-5-(methylthio)pent-4-en-1-amine (6.1i)

Compound **6.1i** was synthesized from the corresponding alcohol in 45% yield by following the general procedure. IR (neat, cm^{-1}) 3337, 1560, 1308; ^1H NMR (300 MHz, $CDCl_3$) δ 5.61 (s, with fine couplings, 1H), 2.68 (t, *J* = 7.2 Hz, 2H), 2.24 (s, 3H), 2.09 (t, *J* = 7.8 Hz, 2H), 1.72 (s, with fine couplings, 3H), 1.61-1.52 (m, 2H), 1.50 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.1, 120.5, 41.9, 36.7, 32.0, 18.0, 17.4; ESI *m/z* $(M+H)^+$ calcd 146.0998, obsd 146.1002.

Synthesis of 6.1h:



6.S2 **6.S3** **6.6h**

Methyl 6-(1,3-dithian-2-ylidene)heptanoate (6.S2): **6.S2** was synthesized according to literature procedure.[1c] Hence, starting with **6.S1** (6.5g, 41 mmol), **6.S2** was obtained in

66% yield. IR (neat, cm^{-1}) 1738, 1239, 1086; ^1H NMR (300 MHz, $CDCl_3$) δ 3.60 (s, 3H), 2.82-2.76 (m, 4H), 2.32-2.25 (m, 4H), 2.09-2.01 (m, 2H), 1.83 (s, 3H), 1.62-1.51 (m, 2H), 1.41-1.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 140.2, 119.8, 51.6, 35.5, 34.1, 30.4, 30.3, 27.5, 25.2, 24.7, 20.3; ESI HRMS *m/z* $(M+H)^+$ calcd 261.0983, obsd 261.0990.

6-(1,3-dithian-2-ylidene)heptan-1-ol (6.6h): To a solution of **6.S2** (3.10 g, 11.9 mmol) in THF (70 mL) was added $LiAlH_4$ (1.0 M in THF, 17 mL, 17 mmol) at 0 °C under argon atmosphere. Upon complete addition, the reaction was stirred at rt for 3 h and then cooled to 0 °C. Water (0.65 mL), 10% NaOH in water (1.3 mL), and water (1.9 mL) were added sequentially. The suspension was filtered and washed with ether. The organic solution was concentrated under reduced pressure to give **6.6h** (2.60 g, 94%). IR (neat, cm^{-1}) 3350, 1275, 1050, 912; ^1H NMR (300 MHz, $CDCl_3$) δ 3.62 (t, *J* = 6.6 Hz, 2H), 2.88-2.82 (m, 4H), 2.36 (t, *J* = 7.5 Hz, 2H), 2.15-2.07 (m, 3H), 1.89 (s, 3H), 1.63-1.53 (m, 2H), 1.47-1.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.9, 119.2, 63.0, 36.0, 32.8, 30.5, 30.4, 27.9, 25.7, 25.2, 20.4; ESI HRMS *m/z* $(M+H)^+$ calcd 233.1034, obsd 233.1029.

Hydrolysis of 6.2b: To a solution of **6.2b** (24.0 mg, 0.0976 mmol) in acetone/water (9:1, 1 mL) was added slowly at -20 °C a solution of N-chlorosuccinimide (33.0 mg, 0.247 mmol) in acetone/water (9:1, 2 mL). Upon complete addition, the mixture was stirred at the same temperature for 5 min and then the solvent removed in vacuum. The residue was purified by preparative TLC (CH_2Cl_2/MeOH = 4:1, Rf = 0.3) to give compound **6.8** (11.2 mg, 73%). IR (neat, cm^{-1}) 3409, 1739, 1292, 1120; ^1H NMR (300 MHz, $CDCl_3$) δ 3.84 (s, 3H), 3.60-3.46 (m, 2H), 2.58-2.51 (m, 1H), 2.24-2.13 (m, 1H), 1.86-1.74 (m, 1H), 1.66

(s, 3H), 1.25 (s, 1H), 1.17 (d, J = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.7, 70.3, 53.6, 43.3, 40.3, 30.8, 16.5, 14.1; ESI HRMS m/z $(M+H)^+$ calcd 158.1181, obsd 158.1180.

6.5 Spectra: see Appendix E

References and Notes

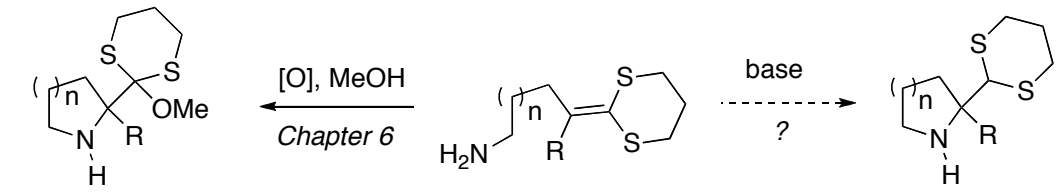
1. Published work: Xu, H.–C.; Moeller, K. D. *Angew. Chem. Intl. Ed.* **2010**, 49, 8004.
2. (a) Xu, H.–C.; Moeller, K. D. *J. Am. Chem. Soc.* **2008**, *130*, 13542. (b) Xu, H.–C.; Moeller, K. D. *J. Am. Chem. Soc.* **2010**, *132*, 2839.
3. (a) For a review of cyclic amino acid derivatives see: Park, K. –H.; Kurth, M. J. *Tetrahedron* **2002**, *58*, 8629-8659. (b) For recent references please see the Chapter 3 of this thesis.
4. P. G. M. Wuts, T. W. Greene, "*Protective Groups in Organic Synthesis*", 4th Ed., John Wiley & Sons, New York, **2007**, pp. 855-859.
5. All potentials were measured by cyclic voltammetry using a BAS 100B Electrochemical Analyzer, a C working electrode, a Pt auxiliary electrode, a Ag/AgCl reference electrode, a 0.1 M Et_4NOTs in acetonitrile electrolyte solution, a substrate concentration of 0.025 M, and a sweep rate of 25 mV/sec.
6. For other examples see: a) K. D. Moeller, L. V. Tinao, *J. Am. Chem. Soc.* **1992**, *114,* 1033; b) S. H. K. Reddy, K. Chiba, Y. Sun, K. D. Moeller, *Tetrahedron* **2001**, *57*, 5183; c) Y. Huang, K. D. Moeller, *Tetrahedron* **2006**, *62*, 6536.
7. Liu, B.; Duan, S.; Sutterer, A. C.; Moeller, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 10101.
8. Xu, H.-C.; Brandt, J. D.; Moeller, K. D. *Tetrahedron Lett.* **2008**, *49*, 3868.
9. Brandt, J. D.; Moeller, K. D. *Org. Lett.* **2005**, *7*, 3553.
10. S. Duan, K. D. Moeller, *J. Am. Chem. Soc.* **2002**, *124*, 9368.
11. Lal, B.; Pramanik, B.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, *18*, 1977.

Chapter 7 Catalytic Hydroamination of Dithioketene Acetals[1]

7.1 Introduction

In Chapter 6 of this thesis, we reported the preparation of cyclic amino acid derivatives by anodic coupling of dithioketene acetals and primary amines. These reactions provide a versatile route to both proline and pipecolic acid derivatives in good to excellent yields (Scheme 7-1). The limitation of these reactions lies in the failure to employ trisubstitued ketene dithioacetals as coupling partners. With our continuing interests in making functionalized cyclic amines, we wondered if a base-promoted hydroamination reaction using the amine substrates might prove useful for builing *N*-heterocycles (Scheme 7-1).

Scheme 7-1 Strategies for the Synthesis of Cyclic Amino Acid Derivatives



R ≠ H good to excellent yield

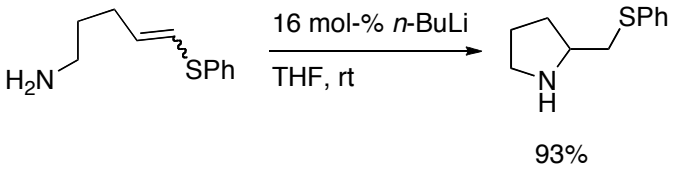
R = H 0%

n = 1, 2

Dithioketene acetals are reactive at the non-sulfur substituted carbon toward both electrophiles and nucleophiles due to the ability of the sulfur atoms to stabilize neighboring positive as well as negative charges.[2] Syntheses capitalize on the electrophilic nature of these systems are well documented. However, direct addition of nucleophiles to ketene dithioacetals is less studied.[2] In isolated cases, the addition of Grinard and alkyl or allyllithium reagents to certain ketene dithioacetals has been

reported.[2,3] Encouraged by the work of Markó *at. al.* showing that intramolecular hydroamination of vinylsulfides proceeds readily with catalytic amount of *n*-BuLi (Scheme 7-2),[4] we set out to investigate the feasibility of intramolecular hydroamination of ketene dithioacetals to provide cyclic amino acid derivatives.

Scheme 7-2 Hydroamination of Vinyl Sulfide

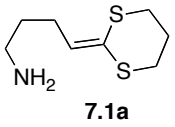
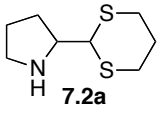
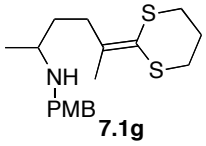
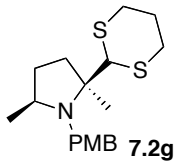
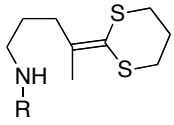
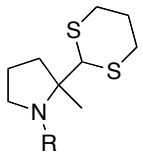
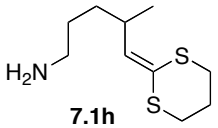
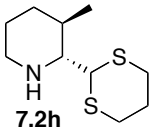
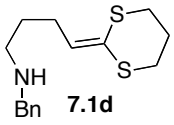
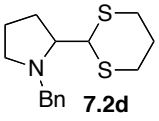
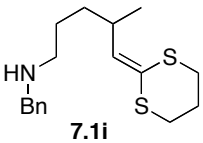
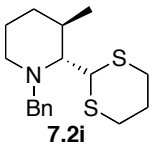
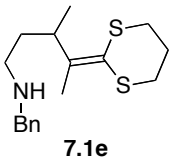
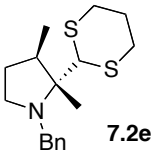
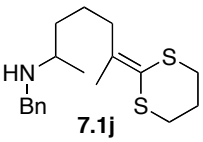
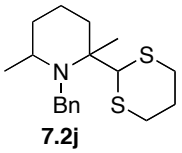
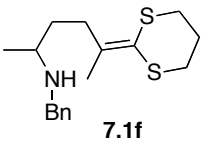
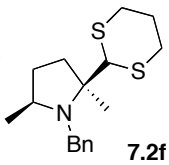
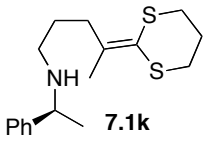
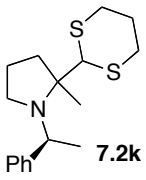


7.2 Results and Discussions

Our study commenced with the examination of substrates **8.1a** and **8.1b**, which were used previously in the oxidative cyclizations (Chapter 6). With the use of 16% of *n*-BuLi as precatalyst in THF at rt, **7.1a** cyclized to afford the desired product **7.2a** in 92% yield within 30 min (Table 7-1, entry 1). However, none of the product **7.2b** was observed when substrate **7.1b** was used under the same reaction conditions (entry 2). The starting material was recovered along with the isolation of a small amount of 1,3-dithiane, which was probably arisen from the decomposition of the cyclized product (Scheme 7-3). The reaction is probably driven by strain around the tetrasubstituted carbon and the higher acidity of 1,3-dithiane than the secondary amine in **7.2b** (Scheme 7-3). If this is the case, We hypothesized that the problem might be avoided by switching to a secondary amine. With such a substrate, there would be after the cyclization no proton left on the nitrogen available for elimination. For this purpose, benzyl amine **7.1c** was synthesized. The

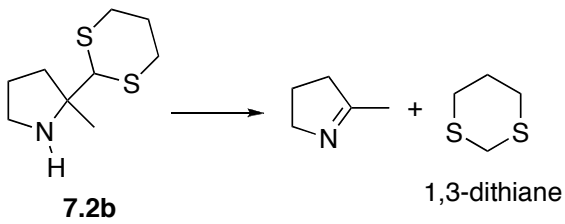
secondary amine substrates were synthesized in two steps from the corresponding alcohols that were used either in previous studies or synthesized by standard procedures.[5]

Table 7-1 Hydroamination of Ketene Dithioacetals

entry	substrate	product	yield (%)[a,b]	entry	substrate	product	yield (%)
1	 **7.1a**	 **7.2a**	92	6	 **7.1g**	 **7.2g**	98 10:1 dr
2	 **7.1b** R = H **7.1c** R = Bn	 **7.2b** **7.2c**	0 98	7	 **7.1h**	 **7.2h**	95[c] >20:1 dr
3	 **7.1d**	 **7.2d**	97	8	 **7.1i**	 **7.2i**	99 >20:1 dr
4	 **7.1e**	 **7.2e**	98 >20:1 dr	9	 **7.1j**	 **7.2j**	0
5	 **7.1f**	 **7.2f**	95 10:1 dr	10	 **7.1k**	 **7.2k**	0

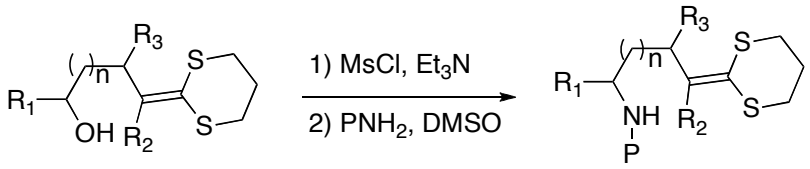
[a] Isolated yield. [b] Reaction conditions: 16% *n*-BuLi, THF, rt. [c] 30% *n*-BuLi was used.

Scheme 7-3 Decomposition of Compound 7.2b



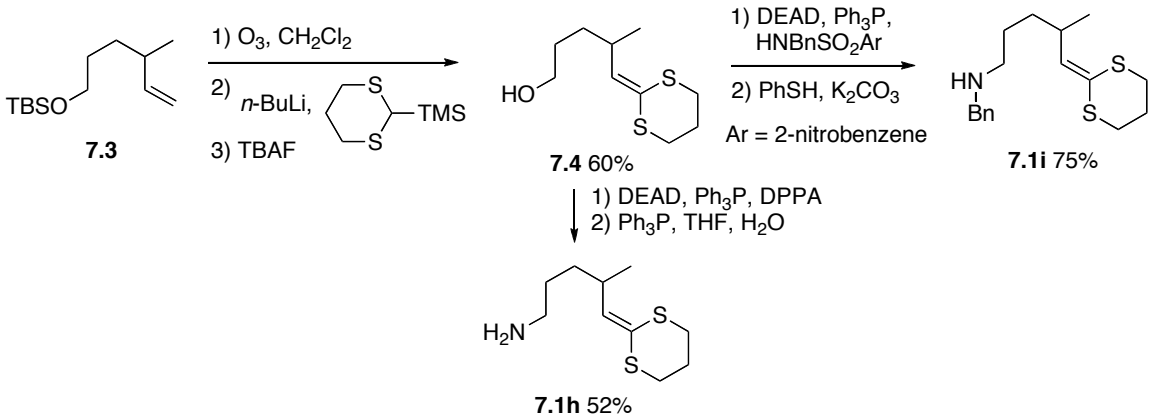
The alcohols were first converted to mesylates followed by replacement with appropriate amines to provide the substrates for cyclizations (Scheme 7-4). The cyclization of **7.1c** promoted with catalytic amount of *n*-BuLi proceeded smoothly to deliver the expected product **7.2c** in 95% yield. The benzyl amine **7.1d** was also synthesized and cyclized. The cyclization was faster than the primary amine counterpart **7.1a** and afforded the desired product in high yield in 10 min.

Scheme 7-4 Synthesis of Substrates 7.1c-k



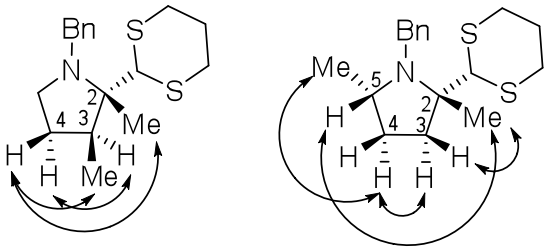
7.1c n = 1, R_1 = R_3 = H, R_2 = Me, P = Bn; 65%
7.1d n = 1, R_1 = R_2 = R_3 = H, P = Bn; 37%
7.1e n = 1, R_1 = H, R_2 = R_3 = Me, P = Bn; 70%
7.1f n = 1, R_1 = R_2 = Me, R_3 = H, P = Bn; 62%
7.1g n = 1, R_1 = R_2 = Me, R_3 = H, P = PMB; 57%
7.1j n = 2, R_1 = R_2 = Me, R_3 = H, P = Bn; 72%
7.1k n = 1, R_1 = R_3 = Me, R_3 = H, P = 1-Phenylethyl; 67%

Scheme 7-5 Synthesis of Substrates 7.1i and 7.1h



The cyclizations are compatible with substituents at α- and γ-positions. For example, with an allylic methyl, the reaction afforded a 98% yield of **7.2e** as a single diastereoisomer. The two methyl groups were assigned to be trans by nuclear Overhauser effect spectroscopy (NOESY) experiment (Figure 7-1). The stereochemistry in this case is consistent with those observed in the oxidative cyclizations.[6] Excellent yield (95%) and diastereoselectivity (10:1) were also obtained with the γ-sustistuented benzyl amine **7.2f**. Once again, the major isomer was shown to have two *trans* methyl groups by nuclear Overhauser effect spectroscopy (NOESY) experiment (Figure 7-1). The use of a *p*-methoxybenzyl amine in the cyclization was also successful (entry 6). Compatible yield and diastereoselectivity were observed with those from benzyl amine **7.1f**.

Figure 7-1 Key NOE Interactions in Compounds 7.2e and 7.2f



The success of the five-membered ring cyclizations prompted us to investigate the formation of six-membered rings. Hence, substrate **7.1f** and **7.1g** were synthesized from alkene **7.3** (Scheme 7-5).[7] Ozonolysis followed by Peterson olefination and deprotection of the silyl group afforded the alcohol **7.4** in 60% yield over three steps. Conversion of the alcohol to a sulfonyl and benzyl bis-protected amine using a Mistunobu reaction and subsequent removal of the sulfonyl group readily formed the benzyl amine **7.1i** in 75% yield over two steps.[8] On the other hand, the alcohol was transformed easily into amine

7.1h through azide formation and then reduction with triphenylphosphine in wet refluxing THF.[9] In both cases, base-induced cyclization provided excellent yield of the desired product as a single diastereomer (Table 7-1, entry 7, 8). The *trans* stereochemistry was assigned in analogy to the five-membered ring cyclizations and earlier observations.[6] Attempts to build a piperidine ring with the concomitant formation of a tetrasubstituted carbon failed (entry 9). No reaction took place even at 50 ºC and the starting material was recovered.[4] The same situation was encountered when a chiral benzyl amine was used in order to effect asymmetric induction (entry 10). The cylizations were probably hampered by the increased steric hindrance of the olefin in the case of **7.1j** and the amine in the case of **7.1k**.

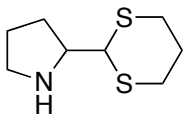
7.3 Conclusion

In summary, a base promoted intramolecular hydroamination of ketene dithoacetals was developed. The cyclizations use easily accessed alkaline metal base as precatalyst and afford functionalized cyclic amines in excellent yield and diastereoselectivity. The method developed here is complementary to the oxidative coupling reactions described in the previous chapter. While the oxidative cyclizations give carboxylic acid derivatives, the reactions in this account afford aldehyde equivalents at the C terminus. The ketene dithioacetals with a vinyl proton that failed to afford any desired products previously under the oxidative conditions were employed successfully. On the other hand, the anodic coupling reactions are superior in the formation of piperidine rings with a tetrasubstituted carbon atom. Hence, the combination of these two approaches provide easy access to a variety of cyclic amino acid derivatives, peptidomimetics, and other nitrogen-heterocycles.

7.4 Experimental Section

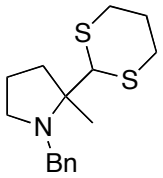
General procedure for hydroamination reactions:

To a solution of the amine (0.3 mmol, 1 equiv) in THF was added *n*-BuLi (0.16 equiv, 1.6 M in hexanes) at rt under argon atmosphere. The progress of the reaction was monitored by ^{1}H-NMR. Once the reaction is complete, one drop of water was added to quench the reaction and the solvent was removed. The residue was passed through a short silica gel pad and washed with ether to give the desired product.



2-(1,3-dithian-2-yl)pyrrolidine (7.2a)

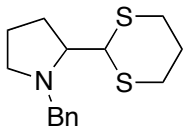
IR (neat, cm^{-1}) 3324, 1420, 1275; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (d, J = 7.5 Hz, 1H), 3.34-3.27 (m, 1H), 3.00-2.93 (m, 1H), 2.89-2.73 (m, 5H), 2.11-2.01 (m, 1H), 1.93-1.63 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.4, 53.8, 47.0, 30.1, 29.9, 29.7, 26.3, 25.8; ESI HRMS *m/z* $(M+H)^+$ calcd 190.0719, obsd 190.0721.



1-benzyl-2-(1,3-dithian-2-yl)-2-methylpyrrolidine (7.2c)

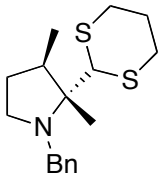
IR (neat, cm^{-1}) 3083, 3059, 3023, 736, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, J = 7.5 Hz, 2H), 7.32-7.20 (m, 3H), 4.42 (s, 1H), 4.02 (d, J = 13.2 Hz, 1H), 3.22 (d, J = 13.2 Hz,

1H), 2.92-2.84 (m, 4H), 2.39-2.30 (m, 2H), 2.14-2.07 (m, 1H), 1.95-1.59 (m, 5H), 1.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.6, 128.9, 128.3, 126.8, 65.5, 59.1, 53.0, 50.9, 35.8, 31.5, 31.1, 26.7, 21.4, 17.9; ESI HRMS *m/z* $(M+H)^+$ calcd 294.1345, obsd 294.1352.



1-benzyl-2-(1,3-dithian-2-yl)pyrrolidine (7.2d)

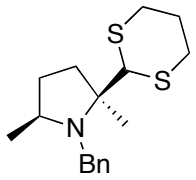
IR (neat, cm^{-1}) 3082, 3059, 3022, 738, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.21 (m, 5H), 4.32 (d, *J* = 4.2 Hz, 1H), 4.13 (d, *J* = 12.9 Hz, 1H), 3.34 (d, *J* = 12.9 Hz, 1H), 2.98-2.91 (m, 1H), 2.88-2.80 (m, 5H), 2.24-1.63 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8, 129.1, 128.4, 127.1, 66.7, 59.3, 54.4, 53.6, 31.3, 30.8, 28.7, 27.0, 23.4; ESI HRMS *m/z* $(M+H)^+$ calcd 280.1188, obsd 280.1186.



(2*R*,3*R*)-1-benzyl-2-(1,3-dithian-2-yl)-2,3-dimethylpyrrolidine (7.2e)

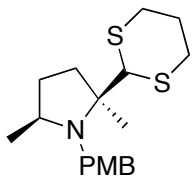
IR (neat, cm^{-1}) 3082, 3059, 3024, 1163, 734; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.5 Hz, 2H), 7.33-7.16 (m, 3H), 4.40 (s, 1H), 4.33 (d, *J* = 12.9 Hz, 1H), 3.25 (d, *J* = 12.9 Hz, 1H), 2.88-2.72 (m, 5 H), 2.30-2.22 (m, 1H), 2.12-2.05 (m, 1H), 1.97-1.70 (m, 2H), 1.36-1.27 (m, 1H), 1.07=8 (s, 3H), 1.00 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$)

δ 140.6, 129.0, 128.2, 126.8, 67.3, 59.9, 54.0, 49.2, 39.4, 32.5, 32.1, 30.4, 26.9, 16.8, 12.4; ESI HRMS *m/z* $(M+H)^+$ calcd 308.1501, obsd 308.1502.



(2*S*,5*S*)-1-benzyl-2-(1,3-dithian-2-yl)-2,5-dimethylpyrrolidine (7.2f)

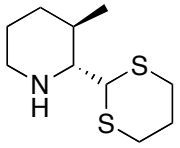
IR (neat, cm^{-1}) 3082, 3059, 3024, 1453, 1150, 727, 698; ^1H NMR (300 MHz, $CDCl_3$, dr = 10:1, only the major one was shown) δ 7.59 (d, *J* = 6.9 Hz, 2H), 7.32-7.18 (m, 3H), 4.11 (s, 1H), 3.98 (d, *J* = 13.8 Hz, 1H), 3.42 (d, *J* = 13.8 Hz, 1H), 2.93-2.68 (m, 5H), 2.40-2.30 (m, 1H), 2.11-2.02 (m, 1H), 1.97-1.71 (m, 2H), 1.57-1.32 (m, 2H), 1.27 (s, 3H), 0.74 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2, 129.3, 127.9, 126.7, 68.0, 60.1, 59.8, 53.1, 34.6, 31.9, 31.5, 31.1, 26.9, 22.6, 20.3; ESI HRMS *m/z* $(M+H)^+$ calcd 308.1501, obsd 308.1506.



(2*S*,5*S*)-2-(1,3-dithian-2-yl)-1-(4-methoxybenzyl)-2,5-dimethylpyrrolidine (7.2g)

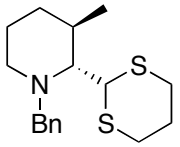
IR (neat, cm^{-1}) 3059, 1500, 1244, 1036; ^1H NMR (300 MHz, $CDCl_3$, dr = 9:1, only the major isomer was shown) δ 7.49 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 4.12 (s, 1H), 3.90 (d, *J* = 13.8 Hz, 1H), 3.79 (s, 3H), 3.36 (d, *J* = 13.8 Hz, 1H), 2.90-2.67 (m, 5H), 2.36-2.27 (m, 1H), 2.10-2.03 (m, 1H), 1.96-1.74 (m, 2H), 1.55-1.31 (m, 2H), 1.25 (s,

3H), 0.71 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 134.1, 130.3, 113.3, 67.9, 59.9, 59.7, 55.5, 52.4, 34.5, 31.8, 31.5, 31.1, 26.7, 22.7, 20.2; ESI HRMS *m/z* $(M+H)^+$ calcd 338.1607, obsd 338.1614.



(2*R*,3*R*)-2-(1,3-dithian-2-yl)-3-methylpiperidine (7.2h)

IR (neat, cm^{-1}) 3314, 1455, 1193; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.47 (d, J = 2.4 Hz, 1H), 3.10-2.95 (m, 2H), 2.90-2.79 (m, 3H), 2.61-2.51 (m, 1H), 2.45-2.42 (m, 1H), 2.14-2.04 (m, 1H), 1.91-1.37 (m, 6H), 1.12-1.00 (m, 1H), 0.89 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 67.6, 52.3, 47.3, 34.1, 33.7, 31.7, 31.0, 26.8, 26.7, 18.5; ESI HRMS *m/z* $(M+H)^+$ calcd 218.1032, obsd 218.1035.



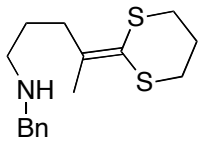
(2*R*,3*R*)-1-benzyl-2-(1,3-dithian-2-yl)-3-methylpiperidine (7.2i)

IR (neat, cm^{-1}) 3082, 3059, 3023, 738, 699; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, J = 7.5 Hz, 2H), 7.34-7.22 (m, 3H), 4.65 (d, J = 13.2 Hz, 1H), 4.63 (d, J = 6.6 Hz, 1H), 3.40 (d, J = 13.2 Hz, 1H), 2.99-2.75 (m, 5H), 2.33 (dd, J = 7.8, 3.3 Hz, 1H), 2.15-1.76 (m, 5H), 1.48-1.40 (m, 2H), 1.20-1.10 (m, 1H), 1.11 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8, 128.9, 128.3, 126.7, 72.5, 59.7, 53.6, 50.9, 32.9, 32.7, 32.1, 32.0, 27.2, 22.6, 20.7; ESI HRMS *m/z* $(M+H)^+$ calcd 308.1501, obsd 308.1507.

General procedure for synthesis of compounds 7.1c-g and 7.1j-k:

Methanesulfonyl chloride (1 equiv) was added dropwise to a solution of the alcohol (1 equiv) and triethylamine (10 equiv) in THF at 0 ºC under argon atmosphere. Upon complete addition, the reaction was stirred at the same temperature for 0.5 h. Water and ether were added. The organic layer separated and aqueous layer extracted with ether twice. The combined organic solution was dried over anhydrous $MgSO_4$, filtered, and concentrated to give the crude mesylate, which was used without purification and characterization.

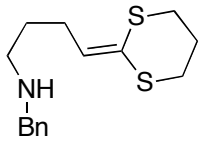
The mesylate (1 equiv) obtained above was dissolved in DMSO and the corresponding amine (10 equiv) was added. The resulting reaction mixture was heated at 60 ºC for 12 hours under argon atmosphere. Water and ether were added. The organic layer was separated and aqueous layer extracted with ether. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluting with MeOH:CH_2Cl_2:Et_3N = 4:1:0.1) to give the desired product.



***N*-benzyl-4-(1,3-dithian-2-ylidene)pentan-1-amine (7.1c)**

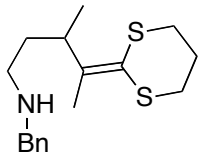
IR (neat, cm^{-1}) 3306, 3082, 3059, 3024, 1452, 735, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.20 (m, 5H), 3.78 (s, 2H), 2.86-2.78 (m, 4H), 2.62 (t, *J* = 6.9 Hz, 2H), 2.40 (t, *J* = 7.5 Hz, 2H), 2.12-2.04 (m, 2H), 1.90 (s, 3H), 1.67-1.57 (m, 2H), 1.52 (br, 1H); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 140.8, 140.3, 128.6, 128.4, 127.1, 119.8, 54.3, 49.2, 33.8, 30.5, 30.4, 28.3, 25.2, 20.4; ESI HRMS *m/z* $(M+H)^+$ calcd 294.1345, obsd 294.1353.



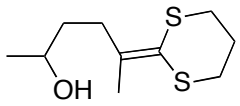
_N_-benzyl-4-(1,3-dithian-2-ylidene)butan-1-amine (7.1d)

IR (neat, cm^{-1}) 3083, 3059, 3024, 1193, 699; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, *J* = 4.8 Hz, 4H), 7.27-7.24 (m, 1H), 5.95 (t, *J* = 7.5 Hz, 1H), 3.78 (s, 2H), 2.87-2.81 (m, 4H), 2.65 (t, *J* = 6.9 Hz, 2H), 2.27 (q, *J* = 7.5 Hz, 2H), 2.19-2.11 (m, 2H), 1.66-1.56 (m, 2H), 1.36 (s, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8, 134.1, 128.6, 128.3, 127.1, 126.3, 54.3, 49.0, 30.6, 29.9, 29.5, 27.4, 25.5; ESI HRMS *m/z* $(M+H)^+$ calcd 280.1188, obsd 280.1193.



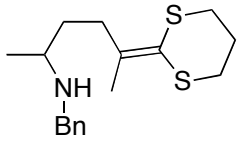
_N_-benzyl-4-(1,3-dithian-2-ylidene)-3-methylpentan-1-amine (7.1e)

IR (neat, cm^{-1}) 3304, 3083, 3060, 3025, 1452, 736; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.20 (m, 5H), 3.76 (s, 2H), 3.36-3.29 (m, 1H), 2.87-2.69 (m, 4H), 2.59-2.50 (m, 2H), 2.12-2.04 (m, 2H), 1.77 (s, 3H), 1.70-1.52, (m, 2H), 1.34 (br, 1H), 0.97 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 140.8, 128.6, 128.3, 127.0, 119.7, 54.4, 47.9, 35.4, 35.2, 30.6, 30.3, 25.3, 19.2, 14.8; ESI HRMS *m/z* $(M+H)^+$ calcd 308.1501, obsd 308.1500.



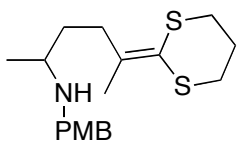
5-(1,3-dithian-2-ylidene)hexan-2-ol (7.5)

This compound was prepared from 5-hydroxyhexan-2-one according to the reported procedures. IR (neat, cm^{-1}) 3369, 1275, 1127; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.81-3.71 (m, 1H), 2.87-2.84 (m, 4H), 2.57-2.47 (m, 1H), 2.39-2.30 (m, 1H), 2.21 (s, 1H), 2.16-2.08 (m, 2H), 1.91 (s, 3H), 1.57-1.48 (m, 2H), 1.20 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.13, 119.6, 67.4, 37.1, 32.2, 30.5, 30.3, 25.1, 23.4, 20.3. ESI HRMS m/z $(M+Na)^+$ calcd 241.0691, obsd 241.0697.



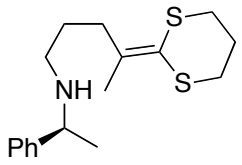
***N*-benzyl-5-(1,3-dithian-2-ylidene)hexan-2-amine (7.1f)**

IR (neat, cm^{-1}) 3307, 3083, 3060, 3024, 1194, 699; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.21 (m, 5H), 3.85-3.73 (m, 2H), 2.88-2.81 (m, 4H), 2.74-2.66 (m, 1H), 2.43-2.37 (m, 2H), 2.15-2.07 (m, 2H), 1.91 (s, 3H), 1.62-1.40 (m, 2H), 1.24 (br, 1H), 1.12 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 140.7, 128.6, 128.4, 127.0, 119.4, 52.5, 51.6, 35.0, 32.6, 30.5, 30.4, 25.2, 20.7, 20.4; ESI HRMS m/z $(M+H)^+$ calcd 308.1501, obsd 358.1506.



5-(1,3-dithian-2-ylidene)-*N*-(4-methoxybenzyl)hexan-2-amine (7.1g)

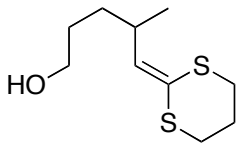
IR (neat, cm^{-1}) 3314, 3099, 3059, 3028, 1500, 1246, 1036; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 3.79 (s, 3H), 3.71 (AB, *J* = 12.6 Hz, 2H), 2.88-2.81 (m, 4H), 2.70-2.64 (m, 1H), 2.41-2.33 (m, 2H), 2.15-2.07 (m, 2H), 1.90 (s, 3H), 1.61-1.37 (m, 2H), 1.17 (br, 1H), 1.10 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 140.7, 133.3, 129.5, 119.3, 114.0, 95.0, 55.5, 52.4, 50.9, 34.9, 32.6, 30.5, 30.3, 25.2, 20.6, 20.4; ESI HRMS *m/z* $(M+H)^+$ calcd 338.1607, obsd 338.1607.



(*S*)-4-(1,3-dithian-2-ylidene)-*N*-(1-phenylethyl)pentan-1-amine (7.1k)

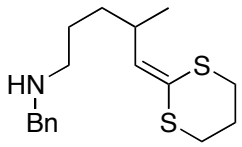
IR (neat, cm^{-1}) 3307, 3081, 3059, 3023, 1194, 700; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.18 (m, 5H), 3.75 (q, *J* = 6.6 Hz, 1H), 2.85-2.77 (m, 4H), 2.53-2.27 (m, 4H), 2.12-2.04 (m, 2H), 1.51-1.51 (m, 2H), 1.34 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.1, 140.4, 128.6, 127.0, 126.8, 119.6, 58.5, 47.5, 33.7, 30.5, 30.4, 28.4, 25.2, 24.6, 20.3; ESI HRMS *m/z* $(M+H)^+$ calcd 308.1501, obsd 308.1506.

Synthesis of substrate 7.1h and 7.1i:



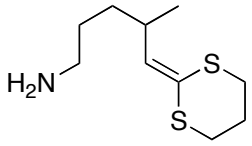
5-(1,3-dithian-2-ylidene)-4-methylpentan-1-ol (7.7)

O_3 was passed through a solution of 8.6 (2.28 g, 10.0 mmol) in CH_2Cl_2 (30 mL) at -78 ºC until the solution turned light blue. PPh_3 (6.5 g, 25 mmol) and anhydrous Na_2SO_4 were added and the cold bath removed. The reaction mixture was stirred at room temperature for 1 h, filtered, and the filtration was concentrated to give an aldehyde. In another flask, n-BuLi (7.20 mL, 11.6 mmol) was added to a solution of 2-trimethylsilyl-1,3-dithiane (2.32 g, 11.6 mmol) in THF (30 mL) at -78 ºC. The reaction was stirred at -78 ºC for 0.5 h, 0 ºC 0.5 h, and then cooled down to -78 ºC. The aldehyde prepared above was added and the reaction was left overnight and raised to room temperature. Water and ether were added. The organic phase was separated and aqueous layer extracted with ether. The combined organic solution was dried over $MgSO_4$, filtered and concentrated. Chromatography on silica gel (eluting with ether:hexane = 1:10) afforded the desired ketene dithioacetal contaminated with 2-trimethylsilyl-1,3-dithane. Without further purification, the mixture was dissolved in THF (20 mL) and treated with tetrabutylammonium floride (1.0 M in THF, 15 mL, 15 mmol) at room temperature for 3 h. Water and ether were added. The organic phase was separated and aqueous layer extracted with ether. The combined organic solution was dried over $MgSO_4$, filtered and concentrated. Chromatography on silica gel (eluting with ether:hexane = 1:1) afforded the desired alcohol **7.7** in 60% yield. IR (neat, cm^{-1}) 3348, 1056, 911; ^{1}H NMR (300 MHz, CD_3OD) δ 5.72 (d, J = 9.9 Hz, 1H), 3.56 (t, J = 6.3 Hz, 2H), 2.90-2.85 (m, 4H), 2.81-2.74 (m, 1H), 2.20-2.12 (m, 2H), 1.59-1.27 (m, 4H), 0.99 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140, 124.8, 63.1, 34.0, 33.3, 30.8, 30.0, 25.5, 20.7; ESI HRMS m/z $(M+H)^+$ calcd 219.0872, obsd 219.0880.



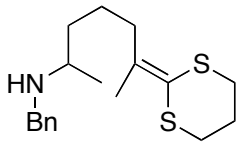
***N*-benzyl-5-(1,3-dithian-2-ylidene)-4-methylpentan-1-amine (7.1i)**

DEAD (40 wt% in toluene, 2.9 mL, 6.3 mmol) was added to a solution of 8.7 (0.55 g, 2.5 mmol), triphenylphosphine (1.98 g, 7.5 mmol), and *N*-benzyl-2-nitrobenzenesulfonamide (1.1 g, 3.8 mmol) in dichloromethane (20 mL) at room temperature under argon atmosphere. The reaction was stirred overnight and concentrated under reduced pressure. The viscous residue was chromatographed on silica gel to afford a bis-protected amide contaminated with unknown compound. Without further purification, the mixture was dissolved in DMF (10 mL) and treated with K_2CO_3 (0.84 g, 20 mmol) and thiophenol (1.0 g, 10 mmol) at room temperature. The reaction mixture was stirred overnight. Water and ether were added. The organic phase was separated and aqueous layer extracted with ether. The combined organic solution was dried over $MgSO_4$, filtered and concentrated. Chromatography on silica gel (eluting with ether:hexane = 1:1) afforded the desired alcohol **7.1i** in 75% yield over two steps. IR (neat, cm^{-1}) 3308, 3083, 3060, 3025, 1452, 734, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.22 (m, 5H), 5.74 (d, J = 9.6 Hz, 1H), 3.78 (s, 2H), 2.87-2.80 (m, 4H), 2.76-2.59 (m, 3H), 2.19-2.11 (m, 2H), 1.54-1.67 (m, 5H), 0.96 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8, 140.8, 128.6, 128.3, 127.0, 124.8, 54.3, 49.8, 34.9, 34.2, 30.7, 30.0, 28.1, 25.6, 20.7; ESI HRMS *m/z* $(M+H)^+$ calcd 308.1501, obsd 308.1504.



5-(1,3-dithian-2-ylidene)-4-methylpentan-1-amine (7.1h)

Substrate **7.1h** was prepared from **7.7** using the chemistry described in Chapter 6. IR (neat, cm^{-1}) 3351, 1571, 1024; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73 (d, J = 9.6 Hz, 1H), 2.86-2.81 (m, 4H), 2.72-2.63 (m, 3H), 2.18-2.10 (m, 2H), 1.46-1.21 (m, 6H), 0.95 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.9, 124.6, 42.5, 34.5, 34.1, 31.7, 30.7, 30.0, 25.6, 20.6; ESI HRMS m/z $(M+H)^+$ calcd 218.1032, obsd 218.1036.



***N*-benzyl-6-(1,3-dithian-2-ylidene)heptan-2-amine (7.1j)**

IR (neat, cm^{-1}) 3315, 3083, 3060, 3024, 1194, 732; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.19 (m, 5H), 3.82 (d, J = 12.9 Hz, 1H), 3.72 (d, J = 12.9 Hz, 1H), 2.86-2.79 (m, 4H), 2.72-2.67 (m, 1H), 2.36-2.31 (m, 2H), 2.12-2.04 (m, 2H), 1.89 (s, 3H), 1.50-1.24 (m, 5H), 1.08 (d, J = 6.3 Hz, 3H); δ 141.1, 140.7, 128.6, 128.4, 127.0, 119.5, 52.5, 51.7, 36.9, 36.2, 30.5, 30.4, 25.2, 24.5, 20.6, 20.5; ESI HRMS m/z $(M+H)^+$ calcd 322.1658, obsd 322.1657.

7.5 Spectra: see Appendix F

References and Notes

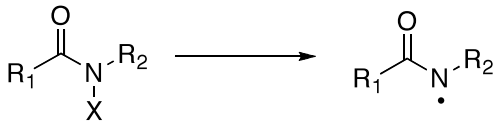
1. Xu, H.-C; Moeller, K. D. *Org. Lett.* **2010**, *12*, 5174.
2. For a review see: Kolb, M. *Synthesis* **1990**, *3*, 171.
3. Herrmann, J. L.; Kieczykowski, G. R.; Romanet, R. F.; Wepplo, P. J.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, *47*, 4711.
4. Quinet, C.; Sampoux, L.; Marko, I. E. *Eur. J. Org. Chem.* **2009**, 1806.
5. For synthetic details please see the experimental sections of Chapter 6 and 7.
6. For similar stereochemistry assignment please see Chapters 2, 3, 4, and 8 of this thesis.
7. For the synthesis of compound **7.3**, please see Chapter 3.
8. Lal, B.; Pramanik, B.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, *18*, 1977.
9. Kurosawa, W.; Kan, T.; Fukuyama, T. *Org. Synth.* **2002**, *79*, 186.

Chapter 8 Anode-Generated Amidyl Radicals and Their Cylizations

8.1 Introduction

Recent years have witnessed a dramatic increase of interest in application of nitrogen-centered radicals in organic synthesis.[1] Cyclization of nitrogen-centered radicals onto C=C bonds provides biologically interesting N-heterocycles.[1] Among various types of N-centered radicals, amidyl radicals are of particular interest and have attracted much attention due to their high reactivity and electrophilic nature.[2e] Methods for the generation of amidyl radicals involve the fragmentation of N-PTOC (PTOC = N-hydroxypyridine-2(1*H*)thione),[2] N-nitroso,[3] N-chloro,[4] and N-(phenylthio) derivatives[5] and others[6] (Scheme 8-1). However, these approaches frequently involve the use of toxic tin compounds and the precursors for such fragmentation reactions are usually not stable and thus hard to prepare. In addition, the eletrophilic nature of the N-halo and N-thiophenyl derivatives might cause undesirable reactions.

Scheme 8-1 Generation of Amidyl Radicals by Fragmentation Reactions

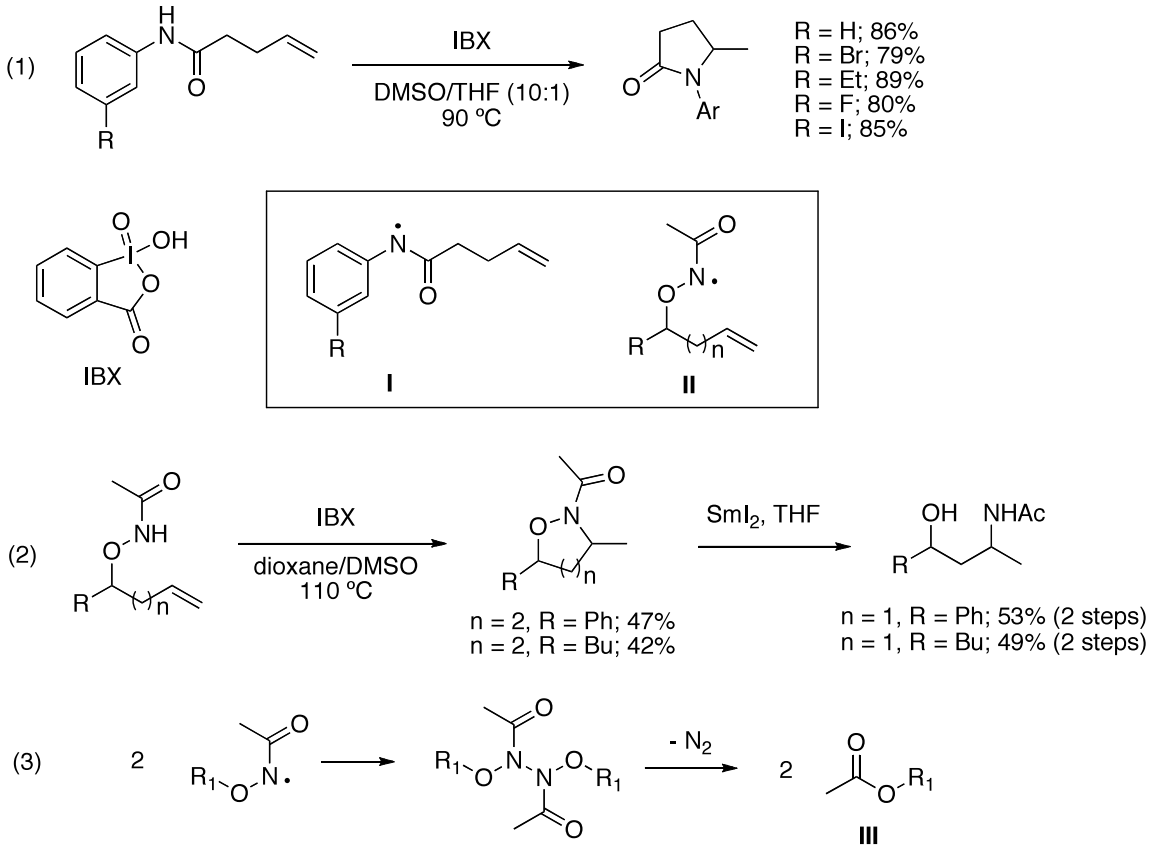


X = PTOC, NO, Cl, SPh

Recently, Nicolaou and coworkers reported IBX (*o*-iodoxybenzoic acid)-mediated 5-*exo* cyclizations of unsaturated N-aryl amides (Scheme 8-2, equation 1). The authors argued that N-centered radicals (**I**) were involved in these cyclizations and generated by single electron transfer from the amide to IBX.[7]

Later, Studer and coworkers adapted this protocol and extended the methodology to the cyclization of unsaturated N-acyl hydroxamines (Scheme 8-2, equation 2).[8] Their initial attempt to make the alkoxyamidyl radicals through fragmentation reactions failed because none of the classic amide derivatives could be synthesized. The 5-*exo* cyclizations of these N-centered radicals (**II**) under high temperature (110 ºC) afforded isoxazolidines, which were reductively cleaved to give N-acylated 1,3-amino alcohols in moderate yields. Six-membered ring products could also be obtained under these conditions although in less efficiency. A major side product observed in these cyclizations is the ester **III**, which was formed by the dimmerization of the alkoxyamidyl

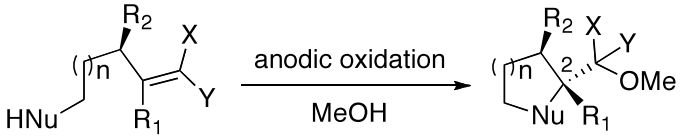
Scheme 8-2 IBX-Mediated Radical Cyclizations of Unsaturated Amides



radical followed by decomposition of the dimer.[9] The difficulty associated with the preparation of the amide derivatives together with the natural propensity of the alkoxyamidyl radicals to dimmerize probably accounts for the fact that, to the best of our knowledge, the radical cyclizations of unsaturated alkoxyamides have only been reported by Studer and coworkers.

The straightforward oxidative approach to the amidyl radicals employs N-H amides directly and avoids the preparation of the amide derivatives and thus has significantly increased the synthetic utilities of the amidyl radical cyclizations. However, the requirement for excess of oxidants and high temperatures imposes limitations on the range of functional groups that are compatible in these reactions.[8,9] Hence, the development of a more general and gentle process for the generation of these transient species is still of significance. In this chapter we describe an electrochemical method for generation of amidyl radicals from N-H amides under mild conditions and their cyclizations to form lactams with a carbonyl at C2.

Scheme 8-3 Oxidative Cylizations to Form Heterocylic Compounds

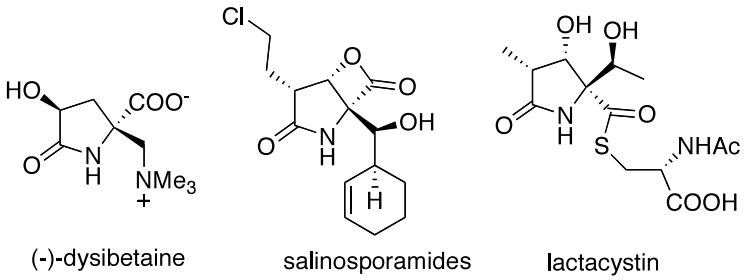


-NuH = -OH, -NHTs, -NH_2, -COOH
X, Y = heteroatoms

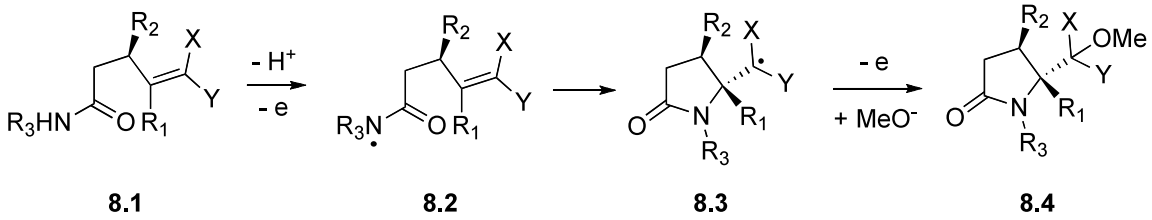
Anodic oxidations have shown to be great methods for generation of radicals and radical cations and triggering interesting new cyclizations.[10,11] In such reactions, stoichiometric amount of oxidants are avoided. We have demonstrated that cyclizations

involving the anode-generated transient species provide versatile route to O- and N-heterocycles with a carbonyl equivalent at the C2 position (Scheme 8-3) in a highly stereoselective fashion.[12] Similar strategies employing an amide as coupling partner might allow access to lactams **8.4** (Scheme 8-4).[13] Lactam ring systems form the core structure of a growing number of natural products such as (−)-dysibetaine,[14] lactacystin,[15] and salinosporamides[16] (Figure 8-1). The interesting biological activities of these compounds have stimulated intense synthetic interests. The synthesis of these interesting targets has been accomplished by many groups.[14-16] However, a general and stereoselective route to the core skeletons of these compounds remains elusive.[17]

Figure 8-1 Examples of Lactam Natural Products



Scheme 8-4 Proposed Anodic Coupling of Amides and Electron-Rich Olefins



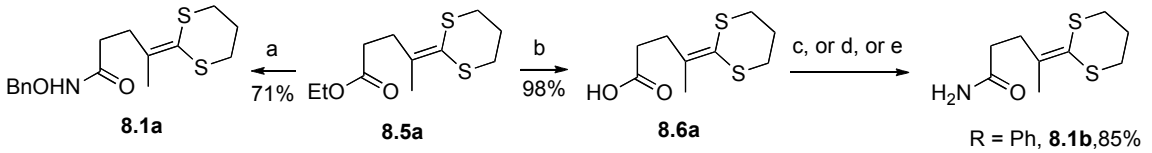
We envisioned that anodic oxidation of the amide to an amidyl radical followed by cyclization would afford radical **8.3** (Scheme 8-4). Further oxidation of the radical to a

cation and reaction with methanol solvent would afford the pyroglutamic acid derivatives.

8.2 Results and Discussion

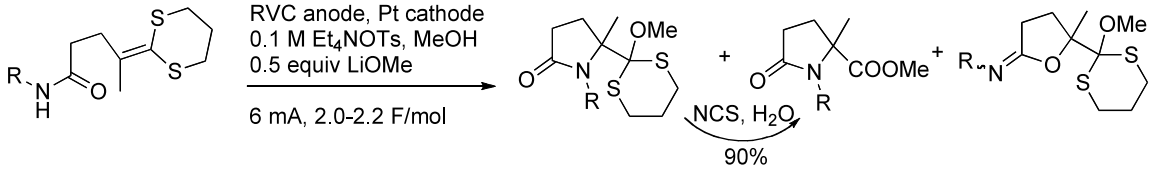
Our study began by identifying suitable amides for the cyclization. Hence, a series of amides **8.1a**-**d** were prepared from known compound **8.5a**[13] as shown in Scheme 8-5.

Scheme 8-5 Synthesis of Substrates 8.1a-d



Reaction conditions: a. $BnONH_2$•HCl, LHMDS, -78 ºC; b. LiOH, THF/H_2O; c. EDC, DMAP, $PhNH_2$; d. ClCOOEt, Et_3N, NH_4OH; e. EDC, Et_3N, DMAP, $MeNH_2$• HCl.

Scheme 8-6 Identification of Suitable Amides for Cyclizations



8.1a, R = OBn
8.1b, R = Ph
8.1c, R = H
8.1d, R = Me

8.4a, 80% (81%)[a]
8.4b, 87%
8.4c, –
8.4d, --

8.7a, 8% (3%)[a]
8.7b, –
8.7c, --
8.7d, –

8.8a, --
8.8b, –
8.8c, --
8.8d, 75%

[a] A 6 V lattern battery was used as power source.

The electrolyses were carried out at room temperature in an undivided cell with a reticulated vitreous carbon (RVC) anode, a platinum wire cathode, a methanol solution with Et_4NOTs as electrolyte, LiOMe as base, and a constant current of 6 mA until the substrate was completely consumed as monitored by ^{1}H-NMR (Scheme 8-6).[12] Pleasingly, the oxidation of the O-benzyl hydroxamate **8.1a** afforded the expected

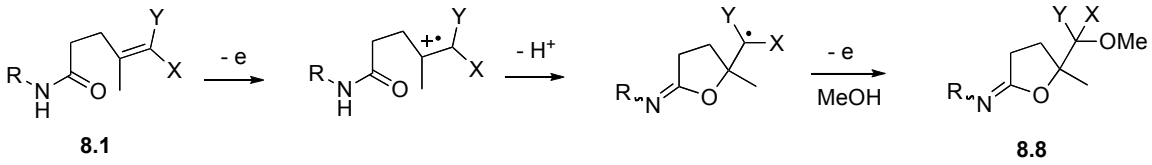
product **8.4a** in 80% yield along with methyl ester **8.7a** in 8% yield. No product arising from the dimerization of the alkoxyamidyl radical was observed, which suggests that the cyclization is much faster than the dimmerization reaction. The methyl ester **8.7a** most likely arose from the hydrolysis of **8.4a** during the reaction and/or purification process. Treating the cyclization product **8.4a** with N-chlorosuccinimide in acetone and water (9:1) led to the formation of **8.7a** in 90% yield (Scheme 8-6).[12e] The proneness of **8.4a** to hydrolysis is probably due to the steric congestion around the tetrasubstituted carbon. The formation of **8.7a** is not an concern since employing **8.4a** for synthesis would involve hydrolysis of the dithioorthoester. Under the same conditions described above, the oxidation of the N-phenyl amide **8.1b** led to the desired product **8.4b** in 87% yield. Oxidation of **8.1c**, on the other hand, afforded a complex mixture of products and the desired lactam **8.4c** was not observed. Switching to the amide **8.1d** resulted in the isolation of iminolactone **8.8d** in 75% yield. Hence N-OBn and N-Ph amides are required for the generation of amidyl radicals using anodic oxidations and synthesis of lactams.

O-Benzyl hydroxmate and N-phenyl amide have pKa's lower than that of methanol.[18] Hence, under the basic reactions conditions, amides **8.1a** and **8.1b** exist as their anions. The oxidation potential of O-Benzyl hydroxmate and N-phenyl amide under the basic reaction conditions were measured by cyclic voltammetry[19] to be 0.52 V and 0.80 V ($E_{p/2}$ vs. Ag/AgCl), respectively, which are lower than that of the ketene dithioacetal ($E_{p/2}$ = 1.06 V vs. Ag/AgCl). The potentials of the **8.1a** and **8.1b** were measured under the same conditions to be 0.40 V and 0.71 V ($E_{p/2}$ vs. Ag/AgCl), respectively. Hence the electrolyses of these amides under basic reaction conditions

probably followed the proposed reaction pathway as shown in Scheme 8-4 to afford the lactams.

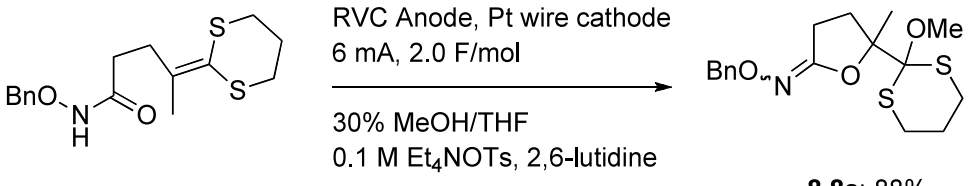
On the other hand, the less acidic amides in **8.1c** and **8.1d** are less acidic than methanol and oxidized at potentials higher than that of ketene dithioacetal. Hence, in the cases of **8.1c** and **8.1d**, the reactions probably started with the oxidation of the electron-rich olefin to a radical cation (Scheme 8-7). For neutral amides, oxygen atom of the amide is usually more nucleophilic than the nitrogen atom.[13] Hence, O-cyclization would afford a cyclized radical, which would eventually lead to the iminolactone **8.8**. For the oxidation of **8.1c**, the final product is probably not stable under the reaction conditions.

Scheme 8-7 Proposed Mechanism for the Formation of Iminolactones



8.1 **8.8**

Scheme 8-8 Oxidation of 8.1a Under Less Basic Reaction Conditions



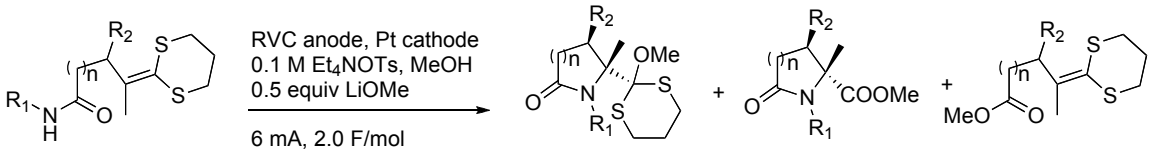
8.1a **8.8a**; 88%

Without deprotonation, the amide in **8.1a** is oxidized at a potential much higher relative to that of the ketene dithioacetal and could not be measured in methanol solution. Hence, replacing LiOMe with a weak base, 2,6-lutidine, resulted in no observation of the lactam formation. Instead, iminolactone **8.8a** was isolated in 88% yield (Scheme 8-8).

Under these reaction conditions, the reaction most likely followed the reaction pathway described in Scheme 8-7.

Although the electrolysis reactions in this work were carried out using the setup depicted in Figure 1-1, Chapter 1, other simpler power supplies can also be used. For example, oxidation of **8.1a** using a 6 V lantern-battery purchased from RadioShack as power source afforded **8.4a** and **8.7a** in 81% and 3% yield, respectively (Scheme 8-6).[20] The initial current passing through the cell in this case was about 25 mA. Hence, even with a higher concentration of the amidyl radical (proportional to the current), the intramolecular cyclization is still favored over the undesired dimmerization reaction.

Scheme 8-9 Oxidation of Amides 8.1e-h



8.1e, n = 1, R_1 = OBn, R_2 = Me
8.1f, n = 2, R_1 = OBn, R_2 = H
8.1g, n = 2, R_1 = Ph , R_2 = H
8.1h, n = 3, R_1 = OBn, R_2 = H

[a] Reaction temperature: 65 ºC

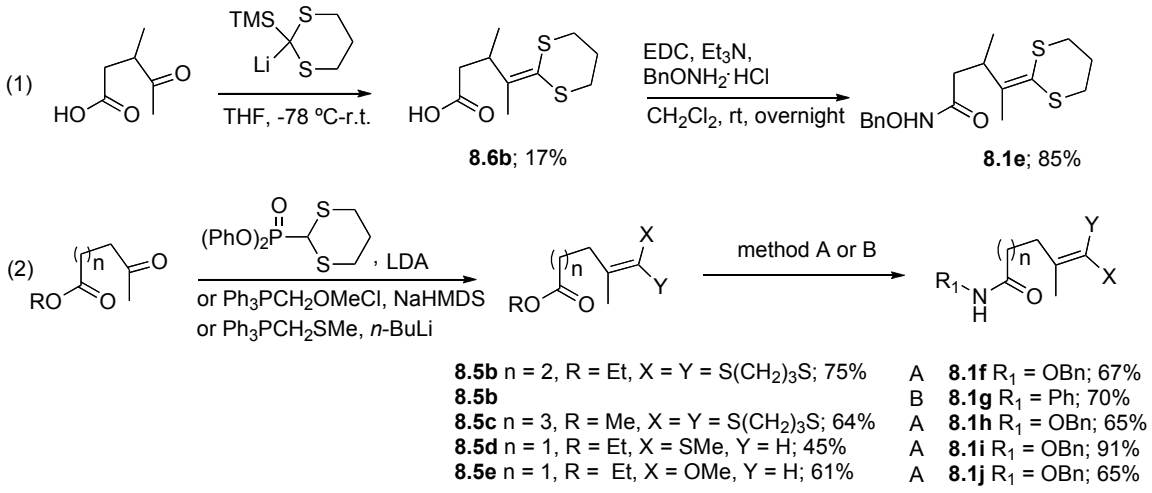
8.4e, 78%	**8.7e**, 8%	--
8.4f, 73%	**8.7f**, 10%	--
8.4g, --	**8.7g**, --	--
8.4h, --	**8.7g**, --	**8.5c**, 74% (85%)[a]

With a methyl at the allylic to induce stereoselectivity, the oxidation of **8.1e** led to 78% of **8.4e**, along with 8% of **8.7e**, both as a single diastereomer (Scheme 8-9). The stereochemistry was assigned in analogy to earlier cyclizations.[12]

Synthesis of the δ-valerolactam was also successful with the use of N-OBn amide. The oxidation **8.1f** provided **8.4f** and **8.7f** in 73% and 10% yield, respectively (Scheme 8-9). No product arising from the dimerization of the amidyl radical was observed. The potential of **8.1f** was measured under the reaction conditons to be 0.41 V ($E_{p/2}$ vs.

Ag/AgCl), similar to that of the five-membered ring substrate **8.1a** ($E_{p/2}$ = 0.40 V vs. Ag/AgCl). It suggests that the six-membered ring cyclization is still very fast.[12d]

Scheme 8-10 Synthesis of Substrates 8.1e-j



Switching to the N-phenyl amide **8.1g**, however, afforded a complex mixture of products and the desired lactam product was not observed (Scheme 8-9).[7] The failure of the cyclization was probably due to a slow cyclization as suggested by the oxidation potential of **8.1g** to be $E_{p/2}$ = 0.80 V vs. Ag/AgCl, the same as that of an isolated N-phenyl amide.[12d]

Attempt to form a seven-membered ring product using substrate **8.1h** failed (Scheme 8-9). Instead, methyl ester **8.5c** was isolated in 74% yield. Running the reaction at higher temperature did not improve the cyclization. In analogy to earlier amide radicals,[8,9] the formation of **8.5c** could be explained by the dimerization of the N-alkoxyamidyl radical **8.2** to give a hydrazide **8.9** (Scheme 8-11), which decomposes under the basic conditions to give the methyl ester **8.5c** and benzyl alcohol. Benzyl alcohol was observed in a ^{1}H

NMR spectrum of the crude reaction mixture. It seems that the seven-membered ring cyclization is too slow to compete with the dimerization reaction. The potential of **8.1h** was measured to be 0.52 V ($E_{p/2}$ vs. Ag/AgCl), the same as that of an isolated N-OBn amide and much higher than those of **8.1a** ($E_{p/2}$ = 0.40 V vs. Ag/AgCl) and **8.1f** ($E_{p/2}$ = 0.41 V vs. Ag/AgCl). The fact that no potential drop is observed for **8.1h** indicates that the seven-membered ring cyclization is much slower than those of the five- and six-membered rings.[12d]

Scheme 8-11 Possible Pathway for the Formation of 8.5c in the Oxidation of 8.1h

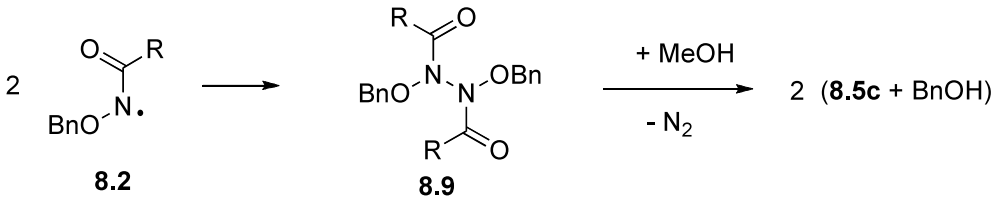
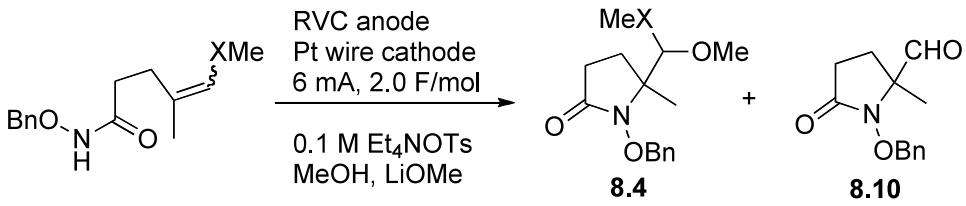


Table 8-1 Oxidative Coupling of Amides with a Vinyl Sulfide and an Enol Ether

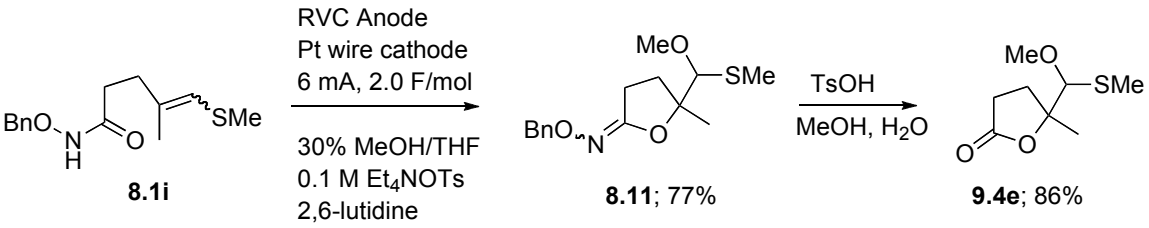


entry	substrate	X	$E_{p/2}$ (V)	*T*	**8.4**%	**8.10**%
1	**8.1i**	S	0.43	r.t.	60	11
2	**8.1i**	S		65 °C	88	–
3	**8.1j**	O	0.46	r.t.	41	trace
4	**8.1j**	O		65 °C	35	–

The use of other electron-rich olefins as coupling partners was also studied (Table 8-1). First, vinyl sulfide **8.1i** was cyclized under the basic reaction conditions to give **8.4i** in 60% yield along with 11% of aldehyde **8.10**, arising probably from the hydrolysis of **8.4i**. The yield of **8.4i** was improved to 88% by carrying out the electrolysis at higher temperature (Table 8-1, entry 2). In this case, no aldehyde was observed. It is possible that the aldehyde formed was not stable under the more harsh conditions and decomposed during the reaction. The temperature effect observed in this case can be understood in that the intramolecular cyclization has smaller entropy of activation than that of the dimerization and thus is favored to a greater extent at higher temperature.[21]

The need to use LiOMe for the lactam formation was also probed with **8.1i** (Scheme 8-12). Hence, with the use of 2,6-lutidine as a base, the reaction led to the formation of only the O-cyclization product **8.11** (77% yield). Hydrolysis of **8.11** in the presence of *p*-toluenesulfonic acid proceeded smoothly to provide lactone **9.4e**, which was independently synthesized as shown in Chapter 9 of this thesis.

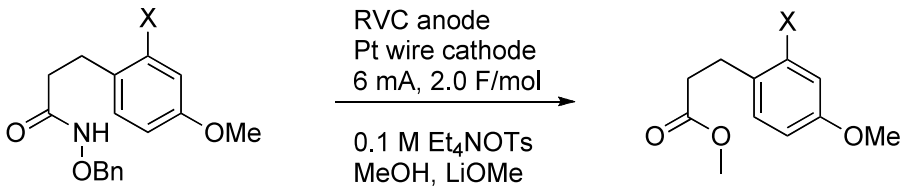
Scheme 8-12 Oxidation of 8.1i Under Less Basic Conditions



The use of the enol ether substrate **8.1j** afforded the expected product **8.4f** in 41% (Table 8-1, entry 3). A small amount of aldehyde and benzyl alcohol was also observed in the ^{1}H-NMR spectrum of the crude product mixture. The formation of benzyl alcohol

suggests that the dimerization reaction is competing with a relatively slow cyclization. This observation is consistent with the relative high potential of the substrate ($E_{p/2}$ = 0.46 V vs Ag/AgCl). Running the reaction at higher temperature did not improve the cyclization (entry 4). The products formed may not stable to the reaction conditions at higher temperature.

Scheme 8-13 Anodic Oxidation of 8.1k and 8.1l



8.1k, X = OMe

8.1l, X = H

8.12, 82%

8.13, 85%

Efforts to utilize electron-rich aromatic rings as coupling partners met with failure (Scheme 8-13). The oxidation of **8.1k**[22] and **8.1l** led to no cyclization products. Instead, methyl esters **8.12** and **8.13** were isolated in 82% and 85% yield, respectively. Hence, cyclization of these amidyl radicals onto electron-rich aromatics is two slow to compete with the dimerization reaction.

8.3 Conclusion and Future Studies

In summary, we have developed a convenient electrochemical oxidation method for the generation of amidyl radicals. Cylization of these anode-generated N-centered radicals onto tethered electron-rich olefins led to five- and six-membered ring lactams with a carbonyl equivalent at C2 position.

The lactam products can be potentially reduced to give cyclic amines like those obtained in previous chapters (Scheme 8-14). One obvious advantage of the lactam products is that functionalization to introduce substitutes at the C2- and C3-positions of the ring is in place following the cyclization (Scheme 8-14)

Scheme 8-14 Proposed Transformation for the Electrolysis Products

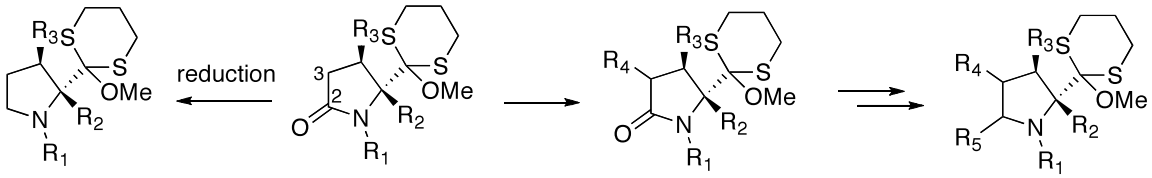
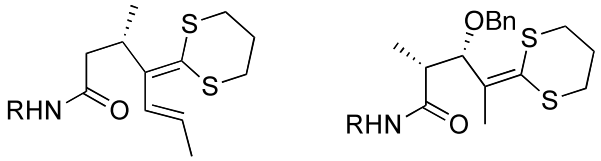


Figure 8-2 Proposed Substrates for Further Studies



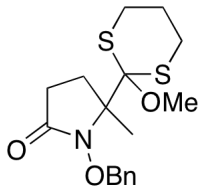
Future studies would (1) further explore the substrate scope and test the compatibility of the cyclization with more complicated substrates (Figure 8-2), (2) expand the method for the generation of other types of N-centered radicals, (3) apply the methodology in the synthesis of biologically active compounds.

8.4 Experimental Section

General procedure for electrolysis reactions: LiOMe (1.0 M in MeOH, 0.5 equiv) was added to a methanol solution of the substrate (0.03 M, 1 equiv) and the electrolyte tetraethylammonium *p*-toluenesulfonate (0.1 M) in a three-neck round bottom flask at rt under argon atmosphere. Two of the three septa were replaced by a reticulated vitreous

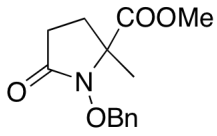
carbon anode (100 PPI) and platinum wire cathode. The solution was sonicated for 10 min. The electrolysis reaction was carried out at constant current of 6.0 mA until complete consumption of the starting material (the progress of the reaction was monitored by ^{1}H-NMR). When complete, the reaction was concentrated under reduced pressure and then the residue chromatographed through a silica gel column (slurry packed using 1% triethylamine in hexane solution) to give the desired product.

Products from Electrolyses:



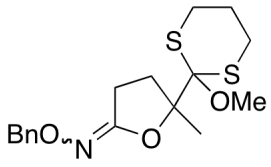
1-(Benzyloxy)-5-(2-methoxy-1,3-dithian-2-yl)-5-methylpyrrolidin-2-one (8.4a)

IR (neat, cm^{-1}) 1713, 1375, 1066, 754, 699; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.26 (m, 5H), 5.21 (A of AB, J = 9.6 Hz, 1H), 5.05 (B of AB, J = 9.6 Hz, 1H), 3.56 (s, 1H), 2.98-2.78 (m, 4H), 2.67-2.59 (m, 1H), 2.54-2.41 (m, 1H), 2.28-2.19 (m, 1H), 1.99-1.74 (m, 3H), 1.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 135.8, 129.4, 128.6, 128.5, 101.4, 77.60, 72.7, 53.1, 28.5, 28.2, 27.1, 22.5, 22.0; ESI HRMS m/z $(M+H)^+$ calcd 354.1192, obsd 154.1189.



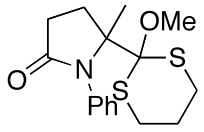
methyl 1-(benzyloxy)-2-methyl-5-oxopyrrolidine-2-carboxylate (8.7a)

IR (neat, cm^{-1}) 1740, 1718, 1454, 756, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48-7.30 (m, 5H), 5.12 (A of AB, *J* = 10.2 Hz, 1H), 5.06 (B of AB, *J* = 10.2 Hz, 1H), 3.77 (s, 3H), 2.58-2.35 (m, 2H), 2.30-2.21 (m, 1H), 2.00-1.89 (m, 1H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ;173.2, 173.0, 135.4, 129.9, 129.0, 128.7, 78.6, 66.0, 53.1, 29.1, 26.7, 21.4; ESI HRMS *m/z* $(M+Na)^+$ calcd 286.1050, obsd 286.1051.



5-(2-Methoxy-1,3-dithian-2-yl)-5-methyldihydrofuran-2(3H)-one O-benzyl oxime (8.8a)

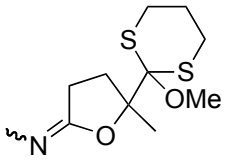
IR (neat, cm^{-1}) 1674, 1453, 1052, 732, 698; ^1H NMR (300 MHz, $CDCl_3$, 4:1 ratio of isomers) δ 7.43-7.22 (m, 5H), 4.97 (s, major, 1.6H), 4.93 (s, minor, 0.4H), 3.54 (s, major, 2.4H), 3.52 (s, minor, 0.6H), 3.02-2.56 (m, 7H), 1.97-1.76 (m, 3H), 1.57 (s, major, 2.4H), 1.50 (s, minor, 0.6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 138.8, 128.5, 128.0, 127.6, 100.6, 96.9, 75.9, 53.1, 31.9, 28.0, 27.7, 26.7, 23.0, 22.9; ESI HRMS *m/z* $(M+H)^+$ calcd 354.1192, obsd 354.1192.



5-(2-Methoxy-1,3-dithian-2-yl)-5-methyl-1-phenylpyrrolidin-2-one (8.4b)

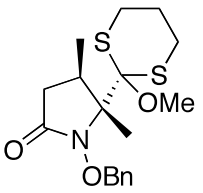
IR (neat, cm^{-1}) 1697, 1362, 1086, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.21 (m, 5H), 3.34 (s, 3H), 3.00-2.68 (m, 6H), 2.50-2.40 (m, 1H), 2.06-1.75 (m, 3H), 1.69 (s, 3H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 176.9, 138.6, 130.6, 128.5, 127.8, 103.0, 52.0, 31.4, 30.7, 29.1, 28.6, 25.1, 21.7; ESI HRMS *m/z* $(M+H)^+$ calcd 324.1186, obsd 324.1100.



_N_-(5-(2-methoxy-1,3-dithian-2-yl)-5-methyldihydrofuran-2(3_H_)-ylidene) methanamine (8.8d)

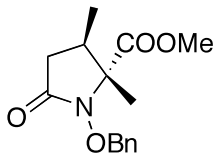
IR (neat, cm^{-1}) 1714, 1126, 1062; ^1H NMR (300 MHz, $CDCl_3$) δ 3.53 (s, 3H), 3.19-2.71 (m, 4H), 2.89 (s, 3H), 2.63-2.50 (m, 3H), 2.02-1.77 (m, 3H), 1.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 100.0, 93.4, 53.7, 34.7, 32.2, 28.8, 27.4, 27.0, 23.8, 22.6; ESI HRMS *m/z* $(M+H)^+$ calcd 262.0930, obsd 262.0936.



(4R,5R)-1-(benzyloxy)-5-(2-methoxy-1,3-dithian-2-yl)-4,5-dimethylpyrrolidin-2-one (8.4e)

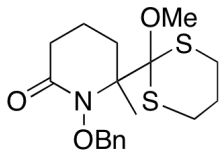
IR (neat, cm^{-1}) 1706, 1376, 1080; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50-7.47 (m, 2H), 7.37-7.33 (m, 3H), 5.25 (A of AB, *J* = 9.6 Hz, 1H), 5.05 (B of AB, *J* = 9.6 Hz, 1H), 3.58 (s, 3H), 2.94-2.71 (m, 6H), 2.01-1.76 (m, 3H), 1.44 (s, 3H), 1.10 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 135.7, 129.4, 128.6, 128.5, 102.7, 77.4, 75.3, 53.0, 36.5,

30.7, 28.4, 28.1, 22.4, 19.3, 16.1; ESI HRMS *m/z* $(M+H)^+$ calcd 368.1349, obsd 368.1344.



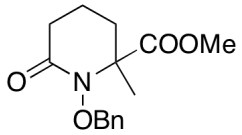
(2R,3R)-methyl 1-(benzyloxy)-2,3-dimethyl-5-oxopyrrolidine-2-carboxylate (8.7e)

IR (neat, cm^{-1}) 1737, 1727, 754, 701; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44-7.33 (m, 5H), 5.17 (A of AB, *J* = 9.9 Hz, 1H), 5.08 (B of AB, *J* = 9.9 Hz, 1H), 3.76 (s, 3H), 2.62 (dd, *J* = 16.8, 8.7 Hz, 1H), 2.50-2.42 (m, 1H), 1.97 (dd, *J* = 16.8, 6.6 Hz, 1H), 1.31 (s, 3H), 1.08 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 172.2, 135.5, 129.7, 128.9, 128.6, 78.4, 69.5, 53.0, 35.1, 32.9, 15.7, 15.0; ESI HRMS *m/z* $(M+H)^+$ calcd 278.1387, obsd 278.1386.



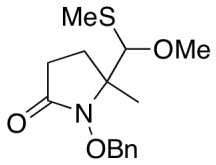
1-(Benzyloxy)-6-(2-methoxy-1,3-dithian-2-yl)-6-methylpiperidin-2-one (8.4f)

IR (neat, cm^{-1}) 1671, 1332, 1085, 734, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49-7.47 (m, 2H), 7.34-7.26 (m, 3H), 5.20 (d, *J* = 9.6 Hz, 1H), 4.83 (d, *J* = 9.6 Hz, 1H), 3.54 (s, 3H), 2.91-2.80 (m, 4H), 2.49-2.40 (m, 3H), 1.96-1.78 (m, 4H), 1.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 136.1, 129.2, 128.4, 128.3, 102.9, 73.7, 53.0, 35.5, 34.2, 28.4, 28.1, 22.4, 22.2, 18.2; ESI HRMS *m/z* $(M+Na)^+$ calcd 3681349, obsd 3681350.



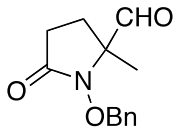
Methyl 1-(benzyloxy)-2-methyl-6-oxopiperidine-2-carboxylate (8.7f)

IR (neat, cm^{-1}) 1739, 1678, 756, 699; ^1H NMR (300 MHz, $CDCl_3$) δ 5.10 (A of AB, *J* = 9.6 Hz, 1H), 4.88 (B of AB, *J* = 9.6 Hz, 1H), 3.74 (s, 3H), 2.57-2.51 (m, 2H), 2.22-2.15 (m, 2H), 1.99-1.89 (m, 1H), 1.79-1.70 (m, 2H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 170.1, 135.6, 129.6, 128.7, 128.6, 69.1, 53.0, 36.2, 33.5, 23.0, 18.3; ESI HRMS *m/z* $(M+Na)^+$ calcd 300.1217, obsd 300.1212.



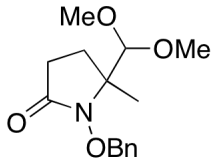
1-(benzyloxy)-5-(methoxy(methylthio)methyl)-5-methylpyrrolidin-2-one (8.4i)

IR (neat, cm^{-1}) 1714, 1453, 1092, 755, 698; ^1H NMR (300 MHz, $CDCl_3$, 5:1 ratio of isomers) δ 5.22 (minor,) and 5.13 (major) (A of AB, *J* = 9.9 Hz, 1H), 4.96 (major) and 4.93 (minor) (B of AB, *J* = 9.9 Hz, 1H), 4.33 (major) and 4.28 (minor) (2s, 1H), 3.45 (minor) and 3.41 (major) (2s, 3H), 2.60-2.33 (m, 1H), 2.27-2.20 (m, 2H), 2.18 (major) and 2.14 (minor) (2s, 3H), 1.71-1.60 (m, 1H), 1.35 (minor) and 1.31 (major) (2s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, only the major isomer is shown) δ 173.1, 135.7, 129.6, 128.9, 128.6, 94.0, 78.4, 67.5, 58.3, 27.3, 25.5, 23.5, 15.5; ESI HRMS *m/z* $(M+Na)^+$ calcd 318.1136, obsd 318.1140.



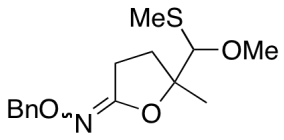
1-(benzyloxy)-2-methyl-5-oxopyrrolidine-2-carbaldehyde (8.10)

IR (neat, cm^{-1}) 1707, 1065, 699; ^1H NMR (300 MHz, $CDCl_3$) δ 9.23 (s, 1H), 7.43-7.34 (m, 5H), 5.00 (s, 2H), 2.41 (t, *J* = 7.8 Hz, 2H), 2.16-2.07 (m, 1H), 1.82-1.72 (m, 1H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 172.7, 135.0, 129.9, 129.3, 128.9, 78.7, 69.4, 26.1, 25.1, 17.3; ESI HRMS *m/z* $(M+H)^+$ calcd 234.1125, obsd 234.1126.



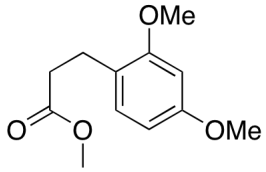
1-(benzyloxy)-5-(dimethoxymethyl)-5-methylpyrrolidin-2-one (8.4j)

IR (neat, cm^{-1}) 1712, 1076, 699; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45-7.35 (m, 5H), 5.19 (d, *J* = 9.9 Hz, 1H), 4.91 (d, *J* = 9.9 Hz, 1H), 4.22 (s, 1H), 4.38 (s, 3H), 4.35 (s, 3H), 3.46-2.17 (m, 3H), 1.58-1.47 (m, 1H), 1.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 135.7, 129.6, 128.9, 128.6, 108.6, 78.5, 65.6, 59.1, 57.6, 27.5, 23.9, 21.9; ESI HRMS *m/z* $(M+Na)^+$ calcd 302.1375, obsd 302.1368.



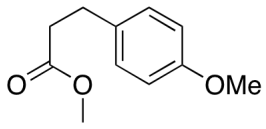
5-(methoxy(methylthio)methyl)-5-methyldihydrofuran-2(3H)-one O-benzyl oxime (8.11)

IR (neat, cm^{-1}) 1671, 1453, 1095, 698; ^1H NMR (300 MHz, $CDCl_3$, four isomers in a ratio of 5:5:1:1, the major two were shown) δ 7.38-7.25 (m, 5H), 4.98, 4.97 (2s, 2H), 4.30, 4.21 (2s, 1H), 3.49, 3.46 (2s, 3H), 2.85-2.55 (m, 2H), 22.40-2.22 (m, 1H), 2.16 (s, 3H), 1.91-1.75 (m, 1H), 1.53, 1.50 (2s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 159.2, 138.9, 138.8, 128.4, 128.1, 127.7, 95.1, 94.7, 93.2, 92.7, 77.7, 77.3, 76.9, 76.0, 58.6, 57.7, 31.5, 30.7, 29.9, 27.4, 27.2, 24.6, 24.3, 14.4, 14.3; ESI HRMS *m/z* $(M+Na)^+$ calcd 318.1133, obsd 318.1140.



Methyl 3-(2,4-dimethoxyphenyl)propanoate (8.12)

IR (neat, cm^{-1}) 1736, 1507, 1209, 834; ^1H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, J = 8.4 Hz, 1H), 6.44-6.38 (m, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.66 (s, 3H), 2.87 (t, J = 8.1 Hz, 2H), 2.57 (t, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 159.8, 158.6, 130.3, 121.4, 104.0, 98.7, 55.6, 55.4, 51.7, 34.5, 25.7; ESI HRMS *m/z* $(M+H)^+$ calcd 225.1121, obsd 225.1121.



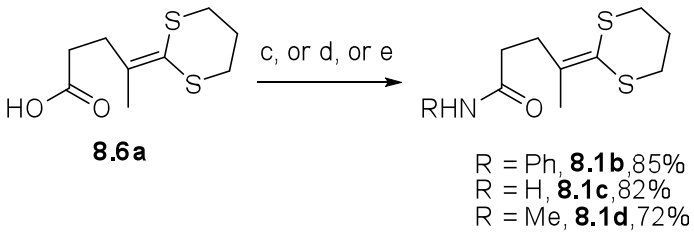
Methyl 3-(4-methoxyphenyl)propanoate (8.13)

IR (neat, cm^{-1}) 1736, 1513, 1247, 828; ^1H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J = 9.0 Hz, 2H), 6.83 (d, J = 9.0 Hz, 2H), 3.78 (s, 3H), 3.67 (s, 3H), 2.90 (t, J = 8.1 Hz, 2H), 2.60 (t,

J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 158.3, 132.8, 129.4, 114.1, 55.5, 51.8, 36.2, 30.3; ESI HRMS m/z $(M+Na)^+$ calcd 217.0832, obsd 217.0841.

N-(benzyloxy)-4-(1,3-dithian-2-ylidene)pentanamide (8.1a)[24]

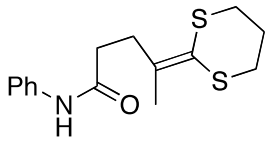
To a suspension of O-benzylhydroxylamine hydrochloride (0.72 g, 4.5 mmol) in THF (15 mL) was added LHMDS (1.0 M in THF, 15 mL, 15 mmol) at – 78 °C. The resulting mixture was stirred at 0 °C until a clear solution. The reaction was cooled down to – 78 °C and compound **8.5a** (0.74 g, 3.0 mmol) in THF (3 mL) was added. The reaction was stirred at the same temperature for 5 h. Water and ether were added. The organic phase separated and the aqueous phase extracted with ether twice. The combined organic solution was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatograph on silica gel (eluting with ether/hexane, 3/1) to provide 0.69 g of the title compound as a colorless solid (71% yield). (IR (neat, cm^{-1}) 3187, 1655, 749, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19, 8.33 (2s, br, 1H), 7.34-7.26 (m, 5H), 4.84 (s, 2H), 2.82-2.75 (m, 4H), 2.60 (t, J = 7.8 Hz, 2H), 2.36-2.00 (m, 4H), 1.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 137.7, 135.7, 129.5, 128.8, 121.6, 78.3, 31.7, 30.3, 30.1, 24.9, 20.3; ESI HRMS m/z $(M+Na)^+$ calcd 346.0905, obsd 346.0911.



8.6a

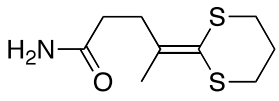
R = Ph, **8.1b**, 85%
R = H, **8.1c**, 82%
R = Me, **8.1d**, 72%

Reaction conditions: c. EDC•HCl, DMAP, $PhNH_2$; d. ClCOOEt, Et_3N, NH_4OH; e. EDC, Et_3N, DMAP, $MeNH_2$•HCl.



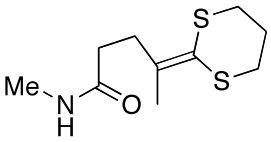
4-(1,3-dithian-2-ylidene)-*N*-phenylpentanamide (8.1b)

To a solution of **8.6a** (0.57 g, 2.6 mmol), aniline (0.48 g, 5.2 mmol) and 4-dimethyaminepydridine (32 mg, 0.26 mmol) in dichloromethane was added EDC•HCl (0.75 g, 3.9 mmol) at rt. The reaction was stirred overnight. Ether and 1 N HCl was added. The organic phase was separated and washed with 1 N HCl twice. The combined aqueous phase was extracted with dichloromethane. The organic extractions were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel to afford **8.1b** as a colorless solid (0.65 g, 85%). IR (neat, cm^{-1}) 3297, 1659, 1599, 1544, 1498, 1442, 755; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (br, 1H), 7.51 (d, J = 8.1 Hz, 2H), 7.30-7.25 (m, 2H), 7.07 (t, J = 7.5 Hz, 1H), 2.87-2.72 (m, 6H), 2.46-2.41 (m, 2H), 2.11-2.03 (m, 2H), 1.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 138.3, 137.7, 129.1, 124.4, 121.7, 120.3, 36.0, 31.9, 30.3, 30.1, 24.9, 20.3; ESI HRMS m/z $(M+H)^+$ calcd 294.0981, obsd 294.0989.



4-(1,3-Dithian-2-ylidene)pentanamide (8.1c)

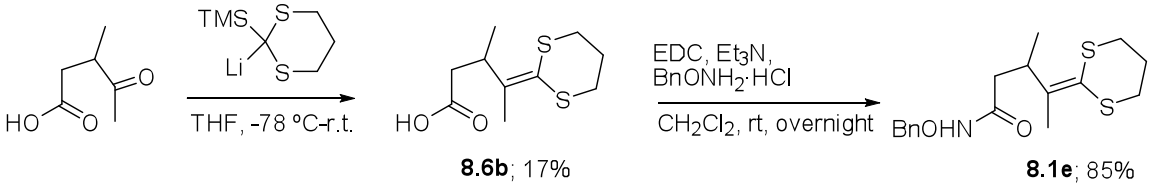
To a solution of **8.6a** (0.44 g, 2.0 mmol) in THF (5 ml) was added triethylamine (0.29 mL, 2.1 mmol). The solution was cooled to 0 °C and ethylchloroformate (0.20 mL, 2.1 mmol) was added. The reaction was stirred at the same temperature for 0.5 h. Ammonium hydroxide (28-30% in water, 2.5 mL) was added. The resulting reaction mixture was stirred overnight. Dichloromethane and water was added. The organic phase was separated and washed with 1 N NaOH, dried over $MgSO_4$, filtered. Removal of the solvent afforded the title compound as a colorless solid (0.35 g, 82%). IR (neat, cm^{-1}) 3345, 3185, 1667, 1643, 909; ^1H NMR (300 MHz, $CDCl_3$) δ ; 6.28 (br, 1H), 5.89 (br, 1H), 2.90-2.85 (m, 4H), 2.67 (t, J = 8.1 Hz, 2H), 2.31 (t, J = 8.1 Hz, 2H), 2.16-2.08 (m, 2H), 1.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 138.0, 121.3, 34.3, 31.9, 30.3, 30.1, 24.9, 20.2; ESI HRMS m/z $(M+H)^+$ calcd 218.0668, obsd 218.0671.



4-(1,3-Dithian-2-ylidene)-*N*-methylpentanamide (8.1d)

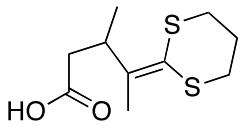
To a solution of **8.6a** (287 mg, 1.32 mmol) in CH_2Cl_2 was added Et_3N (0.20 mL, 1.45 mmol), EDC•HCl (274 mg, 1.45 mmol), DMAP (16 mg, 0.13 mmol), and methylamine hydrochloride (96 mg, 1.4 mmol). The reaction was stirred overnight and quenched with 1 N HCl. The organic phase was separated, dried over $MgSO_4$, and concentrated. Purification of the residue by flash chromatograph (silica gel) afforded the title compound as a colorless solid (219 mg, 72%). IR (neat, cm^{-1}) 3305, 1642, 1557; ^1H NMR (300 MHz, $CDCl_3$) δ 6.01 (br, 1H), 2.90-2.84 (m, 4H), 2.81 (s, 1.5 H), 2.79 (s, 1.5 H), 2.69-2.64 (m, 2H), 2.29-2.24 (m, 2H), 2.16-2.08 (m, 2H), 1.91 (s, 3H); ^{13}C NMR (75

MHz, $CDCl_3$) δ 173.1, 138.3, 121.2, 34.9, 32.2, 30.3, 30.2, 26.6, 24.9, 20.2; ESI HRMS *m/z* $(M+H)^+$ calcd 232.0824, obsd 232.0826.



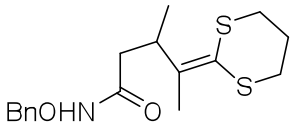
8.6b; 17%

8.1e; 85%



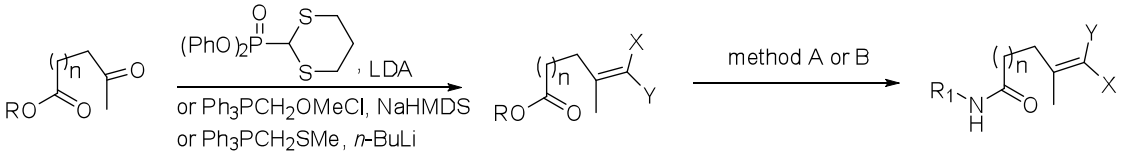
4-(1,3-dithian-2-ylidene)-3-methylpentanoic acid (8.6b)

To a solution of 2-trimethylsilyl-1,3-dithiane (3.84 g, 20 mmol) in THF (40 mL) was added *n*-BuLi (1.6 M in hexanes, 12.5 mL, 20 mmoL) at -78 ºC under argon atmosphere. The solution was stirred at the same temperature for 0.5 h and then 0 ºC for 0.5 h. 3-Methyl-4-oxopentanoic acid (1.30 g, 10 mmol) in THF (5 mL) was added at -78 ºC. The reaction was allowed to warm to rt gradually and stirred overnight. Water and ether were added. The aqueous phase was separated and acidified by 1 N HCl to pH = 2. The solution was exacted with ether twice. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed on silica gel (eluting with ether:hexane = 1:2) to give the desired product **8.6b** (0.40 g, 17%). IR (neat, cm^{-1}) 1705, 1297, 911; ^1H NMR (300 MHz, $CDCl_3$) δ 3.74-3.61 (m, 1H), 2.83-2.77 (m, 4H), 2.37-2.23 (m, 2H), 2.08-2.94 (m, 2H), 1.73 (s, 3H), 0.97 (d, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 140.4, 121.6, 39.5, 34.5, 30.4, 30.1, 25.1, 18.5, 15.1; ESI HRMS *m/z* $(M+H)^+$ calcd 233.0664, obsd 233.0665.



N-(benzyloxy)-4-(1,3-dithian-2-ylidene)-3-methylpentanamide (8.1e)

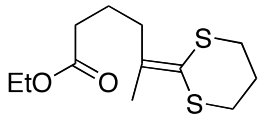
To a solution of **8.6b** (320 mg, 1.38 mmol) in CH_2Cl_2 (3 mL) was added Et_3N (0.20 mL, 1.44 mmol), EDC•HCl (291 mg, 1.52 mmol), and O-benzylhydroxylamine hydrochloride (253 mg, 1.58 mmol) at rt under argon atmosphere. The reaction was stirred overnight. Ether and 1 N HCl were added. The organic phase was separated and aqueous phase extracted with dichloromethane. The combined organic solution was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatograph (silica gel, eluting with ether/hexane, 3/1) to provide the title compound as a colorless oil (395 mg, 85%). IR (neat, cm^{-1}) 3183, 1654, 745, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 8.39 (br, 1H), 7.37-7.35 (m, 5H), 4.93-4.83 (m, 2H), 3.66-3.63 (m, 1H), 2.87-2.76 (m, 4H), 2.13-2.04 (m, 4H), 1.75 (s, 3H), 0.99 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 140.7, 135.7, 129.4, 128.7, 121.4, 78.3, 53.8, 38.6, 34.7, 30.3, 30.0, 25.1, 18.5, 15.1; ESI HRMS m/z $(M+H)^+$ calcd 338.1243, obsd 338.1245.



8.5b n = 2, R = Et, X = Y = $S(CH_2)_3S$; 75%
8.5b
8.5c n = 3, R = Me, X = Y = $S(CH_2)_3S$; 64%
8.5d n = 1, R = Et, X = SMe, Y = H; 45%
8.5e n = 1, R = Et, X = OMe, Y = H; 61%

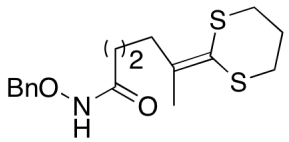
A **8.1f** R_1 = OBn; 67%
B **8.1g** R_1 = Ph; 70%
A **8.1h** R_1 = OBn; 65%
A **8.1i** R_1 = OBn; 91%
A **8.1j** R_1 = OBn; 65%

Method A: $BnONH_2$·HCl, LHMDS, -78 °C.
Method B: 1) LiOH, THF/H_2O; 2) EDC, DMAP, $PhNH_2$, CH_2Cl_2, rt.



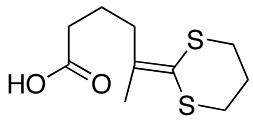
Ethyl 5-(1,3-dithian-2-ylidene)hexanoate (8.5b)

The title compound was prepared from ethyl 5-oxohexanoate by following literature procedure used for the synthesis of **8.5a**.[14] Hence, starting with 6.48 g (41 mmol) of ethyl 5-oxohexanoate, compound **8.5b** was isolated in 75% yield. IR (neat, cm^{-1}) 1732, 1244, 1147; ^1H NMR (300 MHz, $CDCl_3$) δ 4.12 (q, J = 6.9 Hz, 2H), 2.88-2.81 (m, 4H), 2.38 (t, J = 7.5 Hz, 2H), 2.88 (t, J = 7.5 Hz, 2H), 2.14-2.06 (m, 2H), 1.89 (s, 3H), 1.78-1.67 (m, 2H), 1.25 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 139.0, 120.7, 60.3, 31.2, 33.9, 30.4, 30.2, 25.1, 23.2, 20.2, 14.4; ESI HRMS m/z $(M+H)^+$ calcd 261.0977, obsd 261.0978.



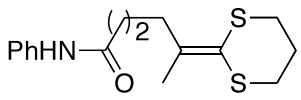
N-(benzyloxy)-5-(1,3-dithian-2-ylidene)hexanamide (8.1f)

Compound was obtained in 67% yield from **8.5b** (0.78 g, 3.0 mmol) by following the procedure employed for the synthesis of **8.1a**. IR (neat, cm^{-1}) 3186, 1655, 748, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.39 (s, 5H), 4.92 (s, 2H), 2.88-2.78 (m, 4H), 2.36 (t, J = 7.5 Hz, 2H), 2.13-2.02 (m, 4H), 1.88 (s, 3H), 1.80-1.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 139.3, 135.7, 129.4, 128.8, 120.5, 78.3, 35.3, 32.8, 30.4, 30.3, 25.0, 23.7, 20.2; ESI HRMS m/z $(M+Na)^+$ calcd 360.1072, obsd 360.1068.



5-(1,3-dithian-2-ylidene)hexanoic acid (S1)

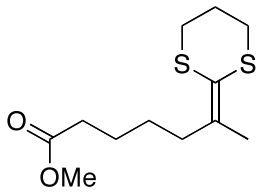
To a solution of **8.5b** (0.47g, 1.8 mmol) in THF (6 mL) and water (2 mL) was added lithium hydroxide monohydrate (0.38 g, 9.0 mmol). The reaction mixture was stirred overnight. 1 N HCl was added to adjust the pH of the aqueous solution to 1. Ether was then added and organic phase separated. The aqueous phase was exacted with ether twice. The organic phase was combined, dried over $MgSO_4$, filtered, and concentrated under vacuum to give the title compound as a white solid, which was used directly for the following reaction.



5-(1,3-dithian-2-ylidene)-N-phenylhexanamide (8.1g)

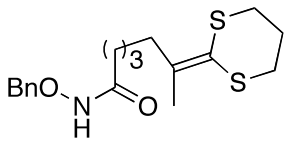
Acid **S1** was dissolved in CH_2Cl_2 (5 mL). Aniline (0.33 g, 3.6 mol), DMAP (22 mg, 0.18 mmol), and EDC•HCl (0.52 g, 2.7 mmol) were added. The resulting mixture was stirred overnight. 1 N HCl was added and the organic phase was separated and washed with 1 N HCl twice. The combined aqueous phase was extracted with dichloromethane. The organic phases were combined, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatograph (silica gel, eluting with ether/hexane, 1:1) to provide the title compound as a solid (0.39 g, 70%). IR (neat, cm^{-1}) 3297, 1659, 1599, 1543, 1498, 1442, 755; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.56 (d, J = 8.1 Hz, 2H), 7.33 (m, 2H), 7.12 (t, J = 7.5 Hz, 1H), 2.91-2.84 (m, 4H), 2.47 (t, J = 7.2 Hz, 2H), 2.37 (t, J = 7.5

Hz, 2H), 2.17-2.07 (m, 2H), 1.94 (s, 3H), 1.92-1.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 139.5, 138.3, 129.1, 124.3, 120.5, 120.2, 37.1, 35.3, 30.5, 30.3, 25.1, 23.8, 20.3; ESI HRMS *m/z* $(M+Na)^+$ calcd 330.0957, obsd 330.0959.



Methyl 6-(1,3-dithian-2-ylidene)heptanoate (8.5c)

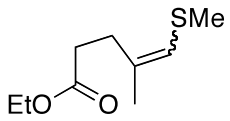
The title compound was prepared from methyl 6-oxoheptanoate by following literature procedure used for the synthesis of **8.5a**.[14] Hence, starting with 6.48 g of 6-oxoheptanoate, the desired product **8.5c** was isolated in 64% yield. IR (neat, cm^{-1}) 1737, 1434, 1192; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.60 (s, 3H), 2.82-2.76 (m, 4H), 2.33-2.25 (m, 4H), 2.09-2.03 (m, 2H), 1.83 (s, 3H), 1.62-1.51 (m, 2H), 1.41-1.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 140.2, 119.8, 51.6, 35.5, 34.1, 30.4, 30.3, 27.5, 25.2, 24.7, 20.3; ESI HRMS *m/z* $(M+Na)^+$ calcd 283.0797, obsd 283.0802.



N-(benzyloxy)-6-(1,3-dithian-2-ylidene)heptanamide (8.1h)

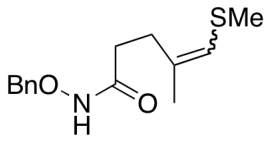
The title compound was prepared from **8.5c** in a similar fashion as that of substrate **8.1a**. Hence, starting with 3.0 mmol of **8.5c**, the desired product was obtained as a colorless oil in 65% yield. IR (neat, cm^{-1}) 3194, 3062, 3029, 1658, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (br, 1H), 7.36 (s, 5H), 4.87 (s, 2H), 2.85-2.77 (m, 4H), 2.32 (t, *J* = 7.8 Hz, 2H), 2.11-

2.03 (m, 4H), 1.86 (s, 3H), 1.61-1.54 (m, 2H), 1.42-1.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 140.3, 135.6, 129.4, 128.8, 119.7, 78.4, 48.7, 35.5, 33.9, 33.3, 30.5, 30.3, 27.4, 25.2, 20.3; ESI HRMS *m/z* $(M+Na)^+$ calcd 374.1221, obsd 374.1224.



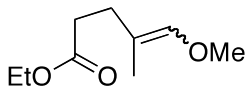
Ethyl 4-methyl-5-(methylthio)pent-4-enoate (8.5d)

To a suspension of (methylthiomethyl)triphenylphosphonium chloride (10.7 g, 30 mmol) in THF (100 mL) was added an *n*-butyllithium solution (1.6 M in hexanes, 18.7 mL, 30 mmol) at 0 °C under argon atmosphere. After the addition was complete, the clear solution was stirred at 0 °C for 30 min and then treated with ethyl levulinate (4.2 mL, 30 mmol). The reaction was warmed to room temperature and then stirred overnight. The reaction was cooled to 0 ^{o}C and brine and ether were added. The organic phase was separated and the aqueous layer extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated. Chromatography on silica gel gave **8.5d** as a colorless oil (2.5 g, 45%). IR (neat, cm^{-1}) 1732, 1372, 1157; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.62 (s, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 2.44-2.32 (m, 4H), 2.21 (s, 3H), 1.69 (m, 3H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 134.1, 121.8, 60.5, 34.4, 33.2, 17.8, 17.3, 14.4; ESI HRMS *m/z* $(M+H)^+$ calcd 189.0944, obsd 189.0944.



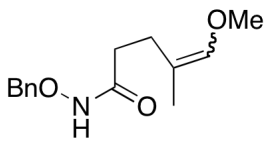
N-(benzyloxy)-4-methyl-5-(methylthio)pent-4-enamide (8.1i)

The title compound was synthesized from **8.5d** in a similar fashion as **8.1a**. Hence, starting with 1.7 mmol of **8.5d**, the title compound was obtained as a colorless oil in 91% yield. IR (neat, cm^{-1}) 3185, 1654, 750, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 9.21, 8.99, 8.25 (3s, br, 1H), 7.34 (s, 5H), 5.61 (s, 1H), 4.84 (s, 2H), 2.42-2.11 (m, 7H), 1.70, 1.66 (2s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 135.6, 133.8, 129.4, 128.8, 122.3, 78.3, 34.7, 31.9, 23.0, 17.8, 17.3; ESI HRMS *m/z* $(M+Na)^+$ calcd 288.1036, obsd 288.1034.



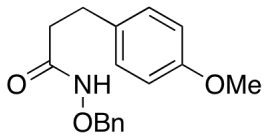
Ethyl 5-methoxy-4-methylpent-4-enoate (8.5e)

To a suspension of methoxymethyltriphenylphosphonium chloride (2.16 g, 15.0 mmol) in THF (50 mL) was added NaHMDS (1.0 M in THF, 15.0 mL, 15.0 mmol) at 0 °C. The dark red solution was stirred at the same temperature for 0.5 h and then treated with ethyl levulinate. The reaction was allowed to warm to room temperature slowly and stirred overnight. Brine was added, followed by ether. The organic layer was separated and aqueous layer extracted twice with ether. The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. Chromatography through silica gel gave **8.5e** as a mixture of isomers (1.60 g, 62%). IR (neat, cm^{-1}) 1735, 1685, 1207, 1129; ^1H NMR (300 MHz, $CDCl_3$ two isomers, 2.7:1) δ 5.81, 5.75 (2s with fine couplings, 1H), 4.11 (q, J = 6.9 Hz, 2H), 3.53, 3.51 (2s, 3H), .39-2.17 (m, 4H), 1.58, 1.53 (2s with fine couplings, 3H), 1.24 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 173.4, 142.8, 142.7, 112.3, 112.1, 60.3, 59.4, 33.6, 32.7, 29.6, 24.8, 17.2, 14.4, 12.6; ESI HRMS *m/z* $(M+Na)^+$ calcd 195.0992, obsd 195.0985.



N-(benzyloxy)-5-methoxy-4-methylpent-4-enamide (8.1j)

The title compound was prepared from **8.5e** by following the procedure employed for the synthesis of **8.1a**. Starting with 3.2 mmol of **8.5e**, the desired product was isolate as a white oil in 65% yield. IR (neat, cm^{-1}) 3187, 1656, 1207, 1129, 750, 698; ^{1}H NMR (300 MHz, $CDCl_3$, 2:1 ratio of isomers) δ 9.13 (major) and 9.08 (minor) (2s, br, 1H), 7.34 (s, 5H), 5.77 (major) and 5.65 (minor) (2s, 1H), 4.84 (s, 2H), 3.47 (major) and 3.38 (minor) (2s, 3H), 2.28-2.12 (m, 4H), 1.53 (major) and 1.47 (minor) (2s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 170.6, 143.1, 142.6, 135.8, 129.4, 129.4, 128.7, 78.3, 59.4, 32.3, 31.9, 29.9, 24.5, 17.2, 12.7; ESI HRMS *m/z* $(M+Na)^+$ calcd 272.1261, obsd 272.1263.



N-(benzyloxy)-3-(4-methoxyphenyl)propanamide (8.1l)

To a solution of 3-(4-methoxyphenyl)propionic acid (0.54 g, 3.0 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (0.40 mL, 3.1 mmol), EDC (0.61g, 3.1 mmol), and O-benzylhydroxylamine hydrochloride (0.50 g, 3.1 mmol). The reaction was stirred at rt overnight and quenched with 1 N HCl. The organic phase was separated and aqueous extracted with dichloromethane twice. The combined organic solution was dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatograph (silica gel, ether/hexane, 3/1) to give the title compound as a white solid (0.68 g, 80%). IR (neat, cm^{-}

[1]) 3191, 1654, 1512, 1247, 698; ^{1}H NMR (300 MHz, $CDCl_3$, a mixture of rotamers in a ratio of 7:1) δ 8.91 (major) and 8.18 (minor) (2s, br, 1H), 7.30-7.26 (m, 5H), 7.07 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 2H), 4.78 (major) and 4.66 (minor, br) (2s, 2H), 2.86 (t, *J* = 7.5 Hz, 2H), 2.61 (minor, br) and 2.29 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 158.3, 135.6, 132.7, 129.6, 129.4, 128.8, 114.2, 78.3, 55.4, 35.4, 30.7; ESI HRMS *m/z* $(M+Na)^+$ calcd 318.1256, obsd 318.1263.

8.5 Spectra: see Appendix G

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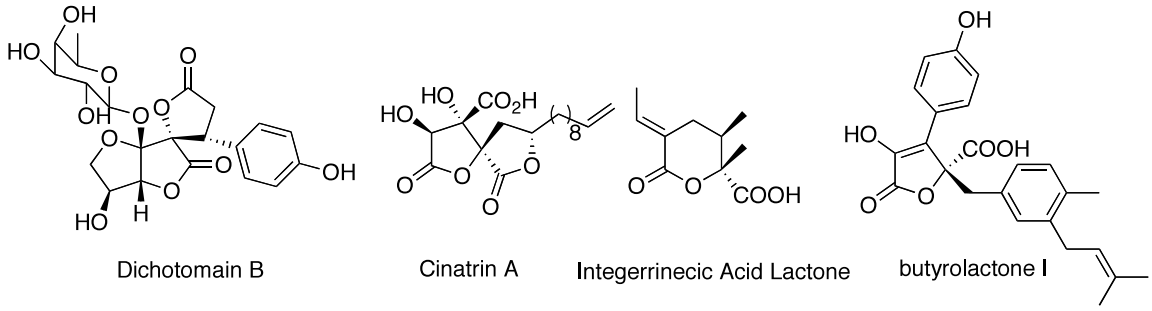
Chapter 9 The Use of Carboxylic Acids as Trapping Groups in Intramolecular Anodic Olefin Coupling Reactions

9.1 Introduction

Structures like **9.1** (Scheme 9-1) can often be found in natural products, some of which are shown in Figure 9-1. Dichotomain B, isolated from fronds of Dicranopteris dichotoma, shows anti-HIV-1 activity.[1] Cinatrin A belongs to a family of phospholipase A_2 inhibitors.[2] (+)-Integerrinecic acid lactone is the necic acid component of integerrimine, a member of the pyrrolizidine alkaloids that exhibit interesting biological properties such as hepatotoxic and carcinogenic activities.[3] Butyrolactone I was found to be a kinase inhibitor.[4]

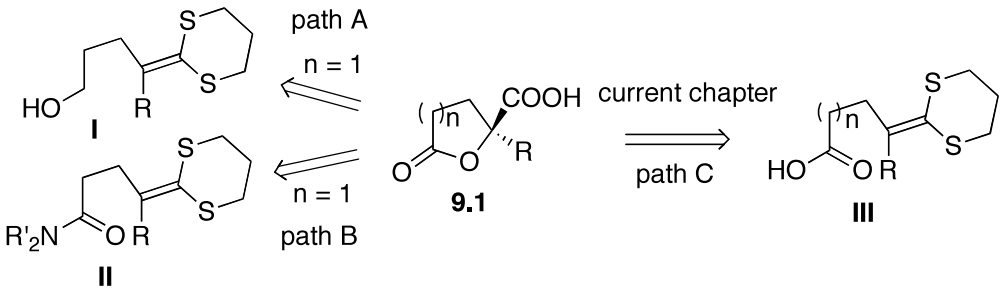
Figure 9-1 Examples of Lactone Natural Products



In Chapter 2 of this thesis we presented a two-step process for the construction of such a skeleton (path A, Scheme 9-1).[5] Intramolecular anodic coupling of an alcohol with a ketene dithioacetal was first used to build a tetrahydrofuran ring, which was oxidized later by ruthenium tetraoxide to afford the lactone needed for the natural product (-)-crobarbatic acid. In another study by Moeller and coworkers, dialkylamides were used as coupling partners in anodic coupling reactions to make γ-butyrolactones (path B, Scheme

9-1).[6] In this case, the first-formed iminolactone was hydrolyzed to a lactone *in situ* by addition of water to the reaction mixture.[6]

Scheme 9-1 Strategies for the Synthesis of Lactone 9.1



Another approach to structures like **9.1** would be the oxidation of acid **III** (path C, Scheme 9-1). An immediate concern of such a methodology would be the fast oxidative decarboxylation reaction, the Kolbe electrolysis (Scheme 9-2).[7] However, from a search of the literature, we found that the use of carboxylic acids as trapping groups in electrochemical oxidation reactions had been reported.

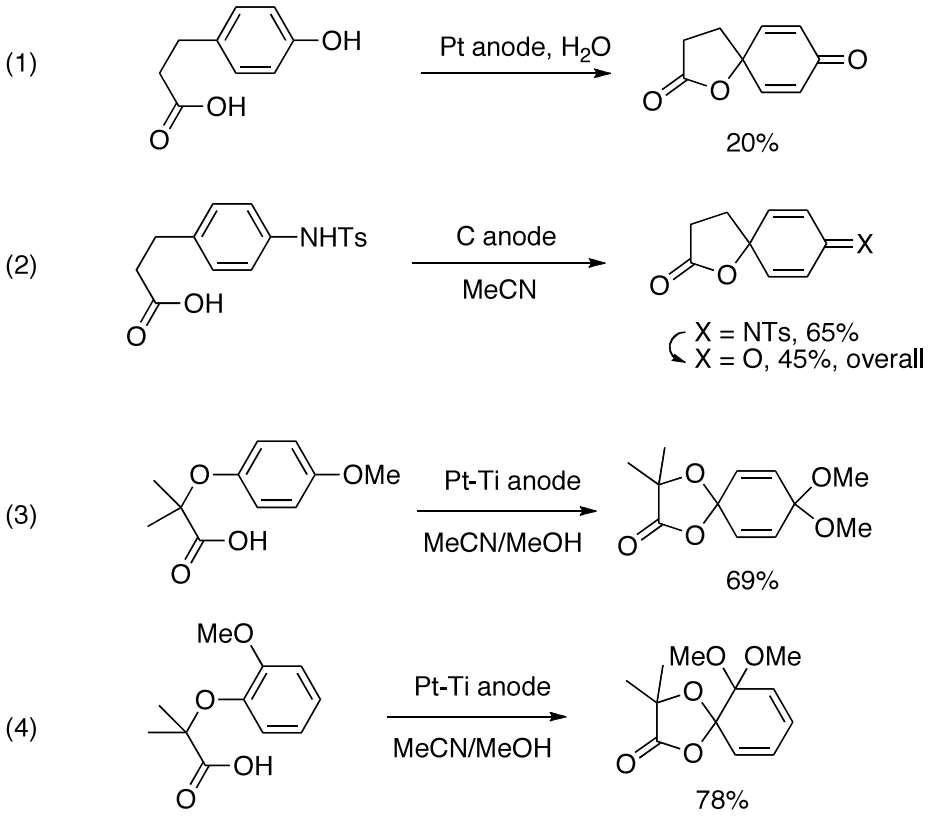
Scheme 9-2 Oxidative Decarboxylation

In 1963, Scott and coworkers reported the electrochemical oxidation of phloretic acid with applied potential of 70 V to afford the dienone in 20% yield (Scheme 9-3, reaction 1).[8] Later, Coutts and coworkers optimized the reactions by using aromatic sulfonamides as phenol equivalent (Scheme 9-3, reaction 2).[9] The oxidations were carried under more gentle conditions (1.4 V vs S.C.E) to give the cyclized products in good

yields. The spirolactones were obtained after passing the sulfonimine through a neutral alumina column.

The anodic oxidation of α-(4-methoxyphenoxy)-alkanoic acid was first studied by Thomas and coworkers.[10] The oxidations afforded the spirolactones in 10-40% yield using graphite electrodes in acetonitrile with excess of triethylamine and a current of 0.5 A. Recently, Quideau and coworkers reinvestigated the electrolyses and extended the scope to the oxidation of α-(2-methoxyphenoxy)-alkanoic acids (Scheme 9-3, reactions 3 and 4).[11] They showed that the cyclized product could be obtained only with the presence of the *gem*-dimethyl groups.

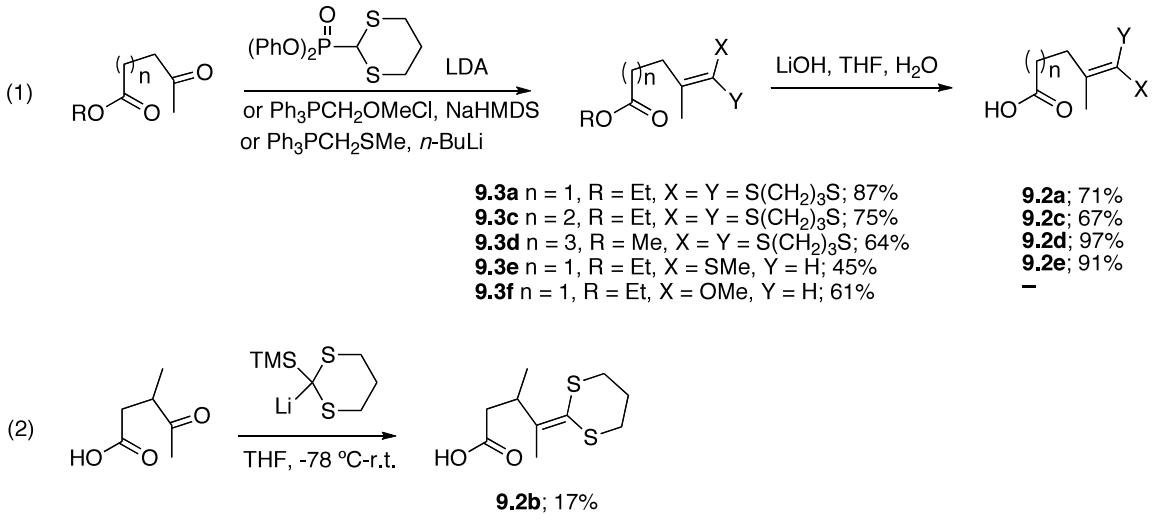
Scheme 9-3 Anodic Coupling of Carboxylic Acids and Phenyl Rings



9.2 Results and Discussions

With this in mind, we began our study by examining the dithioketene acetal **9.2a** (Scheme 9-4), which was synthesized from ethyl levulinate using Peterson olefination reaction to introduce the dithioketene acetal followed by hydrolysis of the ethyl ester to an acid.[12] The oxidation of **9.2a** was conducted in 30% MeOH/THF solution with 0.1 M Et_4NOTs as electrolyte, 2,6-lutidine as base, and constant current of 6 mA until 2.0 F/mol of charge had been passed. To our delight, the reaction afforded the desired lactone **9.4a** in 74% yield (Table 9-1, entry 1). The yield was improved to 87% with the use of LiOMe as base (entry 2). Similar results were obtained when pure methanol was used as solvent (entry 3).

Scheme 9-4 Synthesis of Substrates

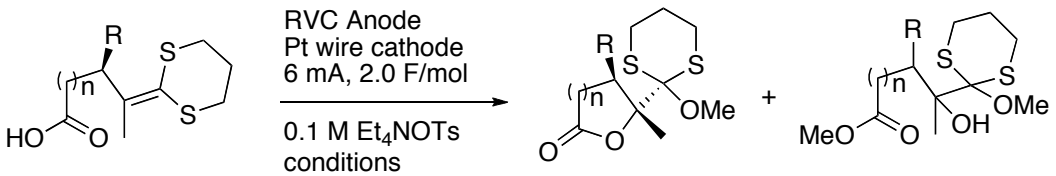


It is obvious that even under the basic reaction conditions the oxidative decarboxylation reaction did not compete with the cyclization. The ketene dithioacetal and the carboxylate are oxidized at potentials ($E_{p/2}$ vs. Ag/AgCl) of 1.06 V[13a] and 1.58 V,

respectively. The oxidation potential of substrate **9.2a** was measured with the addition of 0.6 equiv of LiOMe to be $E_{p/2}$ = +0.68 V vs. Ag/AgCl.[13b] A potential drop of 380 mV from the isolated dithioketene acetal suggested a fast cyclization.[14] The higher potential of the carboxylate than that of the ketene dithioacetal suggested that the reactions start with the oxidation of the electron-rich olefin.

With a methyl at the allylic position to induce diastereoselectivity, the cyclization of **9.2b** afforded the desired product in 93% yield as a single diastereomer (Table 9-1, entry 4). The two methyl groups were assigned to be *trans* in analogy to earlier cyclizations.[14b]

Table 9-1 Anodic Coupling of Dithioketene Acetals and Carboxylic Acids



9.2a-c **9.4a-c** **9.5/9.6**

entry	subs.	n	R	$E_{p/2}$	conditions	product, yield (%)
1	**9.2a**	1	H	0.68	30% MeOH/THF, 2,6-lutidine	**9.4a,** 74
2	**9.2a**				30% MeOH/THF, 0.5 equiv LiOMe	**9.4a**, 87
3	**9.2a**				MeOH, 0.5 equiv LiOMe	**9.4a**, 88
4	**9.2b**	1	Me	--	MeOH, 0.5 equiv LiOMe	**9.4b**, 93[a]
5	**9.2c**	2	H	0.71	30% MeOH/THF, 0.5 equiv LiOMe	**9.5**, 87
6	**9.2c**				30% MeOH/THF, 2,6-lutidine	**9.4c**, 72
7	**9.2d**	3	H	1.06	30% MeOH/THF, 0.5 equiv LiOMe	**9.6**, 30

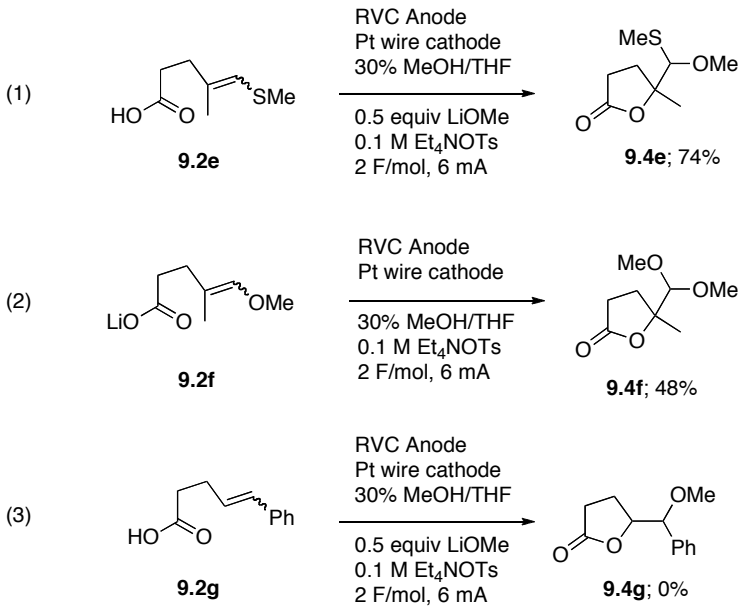
[a] single diastereomer

We next examined the more challenging six-membered ring cyclization. Substrate **9.2c** was prepared in a similar fashion as **9.2a** (Scheme 9-4). Oxidation of **9.2c** in 30%

MeOH/THF and with LiOMe as a base afforded methyl ester **9.5** in 87% yield (entry 5). Replacing the base lithium methoxide with 2,6-lutidine afforded the lactone **9.4c** in 72% yield (entry 6). Under the more basic conditions, compound **9.5** was probably formed through the methanolysis of **9.4c**. A potential drop of 350 mV observed for substrate **9.2c** ($E_{p/2}$ = 0.71 V vs. Ag/AgCl) indicates that the cyclization to form the six-membered ring product is still very fast.[14]

Further increase of the chain length and attempt to form a seven-membered ring resulted in diminished yield (entry 7). The oxidation of **9.2d** under the basic conditions afforded the methyl ester **9.6** in 30% yield. The decrease in yield is probably due to the slow reaction rate as indicated by the fact that no potential drop was observed for substrate **9.2d**.

Scheme 9-5 Anodic Coupling of Carboxylic Acids and Electron-Rich Olefins



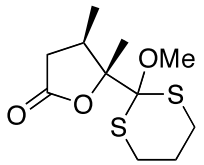
The use of other coupling partners with higher oxidation potentials than that of ketene dithioacetal was also investigated (Scheme 9-5). While the oxidation of the vinyl sulfide **9.2e** furnished the expected product **9.4e** in good yield (74%), further increase of the oxidation potential of the olefin with the use of an enol ether resulted in only moderate yield (48%). In the later case, no base was added and the lithium carboxylate was used directly for the electrolysis instead of the carboxylic acid because of the concern that the acid might not be stable to be isolated. The use of a styrene, an olefin with an even higher potential, led to no expected product (Scheme 9-5, reaction 3), although it has been reported that the electro-oxidation of the sodium carboxylate of **9.2f** with a platinum anode and potential of 100 V provided **9.4g** in high yield.[15] Replacing LiOMe with 2,6-lutidine didn't improve the situation. The vinyl sulfide in substrate **9.2e**, the enol ether in **9.2f**, and the styrene in **9.2g** have oxidation potentials ($E_{p/2}$ vs. Ag/AgCl) of 1.22 V, 1.34 V, 1.56 V, respectively. The diminished yield of the cylization products in the cases of **9.2f** and **9.2g** is probably caused by competitive decarboxylation reaction.

9.3 Conclusion

To sum up, carboxylic acids and electron-rich olefins were coupled successfully to afford γ-butyrolactones and valerolactones with a carbonyl equivalent at C2 position. Oxidative decarboxylation didn't compete with cyclizations even under basic reaction conditions. The reactions afforded the cyclized products in good yield and diastereoselectivity under mild reaction conditions. Future work would be to employ the cyclizations for the synthesis biologically interesting compounds.

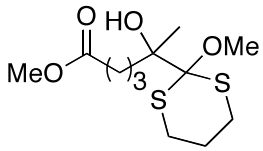
9.4 Experimental Section

General procedure for electrolysis reactions: LiOMe (1.0 M in MeOH, 0.5 equiv) was added to either a methanol or 30% MeOH/THF solution of the substrate (0.03 M, 1 equiv) and the electrolyte tetraethylammonium *p*-toluenesulfonate (0.1 M) in a three-neck round bottom flask at rt under argon atmosphere. Two of the three septa were replaced by a reticulated vitreous carbon anode (100 PPI) and platinum wire cathode. The solution was sonicated for 10 min. The electrolysis reaction was carried out at constant current of 6.0 mA until complete consumption of the starting material (the progress of the reaction was monitored by ^{1}H-NMR). When complete, the reaction was concentrated under reduced pressure and then the residue chromatographed through a silica gel column (slurry packed using 1% triethylamine in hexane solution) to give the desired product.



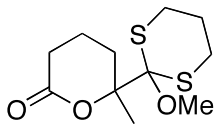
(4*R*,5*R*)-5-(2-methoxy-1,3-dithian-2-yl)-4,5-dimethyldihydrofuran-2(3*H*)-one (9.4b)

IR (neat, cm^{-1}) 1770, 1089, 930; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.54 (s, 3H), 3.16-2.84 (m, 5H), 2.77 (dd, *J* = 17.7, 9.6 Hz, 1H), 2.19 (dd, *J* = 17.7, 9.9 Hz), 2.00-1.84 (m, 2H), 1.48 (s, 3H), 1.14 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 102.4, 94.6, 52.9, 37.2, 34.7, 28.0, 27.7, 22.7, 17.4; ESI HRMS *m/z* $(M+Na)^+$ calcd 285.0590, obsd 285.0580.



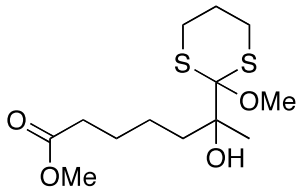
methyl 5-hydroxy-5-(2-methoxy-1,3-dithian-2-yl)hexanoate (9.5)

IR (neat, cm^{-1}) 3499, 1736, 1087; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.64 (s, 3H), 3.54 (s, 3H), 2.96-2.80 (m, 4H), 2.34-2.29 (m, 3H), 1.97-1.70 (m, 6H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 104.2, 81.4, 53.1, 51.7, 35.7, 34.6, 27.9, 27.9, 22.4, 21.6, 19.6; ESI HRMS *m/z* $(M+Na)^+$ calcd 317.0852, obsd 317.0860.



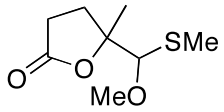
6-(2-methoxy-1,3-dithian-2-yl)-6-methyltetrahydro-2*H*-pyran-2-one (9.4c)

IR (neat, cm^{-1}) 1738, 1255, 1089; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.58 (s, 3H), 3.05-2.84 (m, 4H), 2.63-2.54 (m, 1H), 2.45-2.37 (m, 1H), 2.27-2.16 (m, 1H), 2.00-1.73 (m, 5H), 1.58 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 102.8, 90.9, 53.1, 30.4, 29.4, 27.9, 22.7, 22.6, 17.4; ESI HRMS *m/z* $(M+H)^+$ calcd 263.0770, obsd 263.0771.



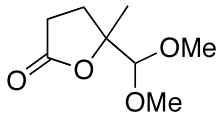
methyl 6-hydroxy-6-(2-methoxy-1,3-dithian-2-yl)heptanoate (9.6)

IR (neat, cm^{-1}) 3480, 1735, 1680, 1173; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.59 (s, 3H), 3.02-2.84 (m, 4H), 2.36 (t, J = 7.5 Hz, 2H), 2.21 (s, 1H), 2.04-1.40 (m, 8H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 104.4, 81.5, 53.1, 51.7, 36.0, 34.4, 28.0, 25.7, 23.6, 22.4, 21.6; ESI HRMS *m/z* $(M+H)^+$ calcd , obsd .



5-(methoxy(methylthio)methyl)-5-methyldihydrofuran-2(3*H*)-one (9.4e)

IR (neat, cm^{-1}) 1772, 1190, 1094; ^1H NMR (300 MHz, $CDCl_3$, 1:1 ratio of isomers) δ 4.21 (s, 0.5 H), 4.12 (s, 0.5 H), 3.47 (s, 1.5 H), 3.45 (s, 1.5 H), 2.78-2.21 (m, 3H), 2.17, 2.13 (2s, 3H), 1.51, 1.50 (2s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 177.1, 95.2, 94.9, 88.9, 88.6, 59.1, 57.5, 30.8, 29.9, 29.7, 29.6, 25.0, 14.7, 14.0; ESI HRMS *m/z* $(M+H)^+$ calcd 191.0731, obsd 191.0736.

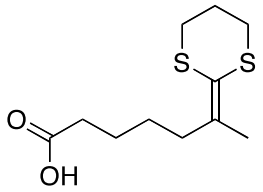


5-(dimethoxymethyl)-5-methyldihydrofuran-2(3*H*)-one (9.5f)

IR (neat, cm^{-1}) 1776, 1104, 1078; ^1H NMR (300 MHz, $CDCl_3$) δ 4.13 (s, 1H), 3.50 (s, 3H), 3.48 (s, 3H), 2.71-2.51 (m, 1H), 2.50-2.38 (m, 2H), 1.82-1.71 (m, 1H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 109.5, 86.9, 58.7, 57.5, 29.7, 28.3, 23.3; ESI HRMS *m/z* $(M+H)^+$ calcd 175.0965, obsd 175.0966.

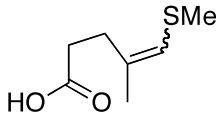
Synthesis of Substrates:

For the synthesis of 9.3a-d, 9.2b and 9.2c, see Chapter 8 of this thesis. For the synthesis of 9.2a, see reference 12.



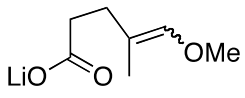
6-(1,3-dithian-2-ylidene)heptanoic acid (9.2d)

The title compound was prepared from **9.3d** by following the procedure used for the synthesis of **9.2c**. IR (neat, cm^{-1}) 1706, 1420, 1276; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.97-2.91 (m, 4H), 2.50-2.44 (m, 4H), 2.24-2.16 (m, 2H), 1.99 (s, 3H), 1.77-1.67 (m, 2H), 1.57-1.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.6, 140.3, 120.0, 35.6, 34.3, 30.6, 30.5, 27.6, 25.3, 24.6, 20.5; ESI HRMS *m/z* $(M+H)^+$ calcd 247.0821, obsd 247.0821.



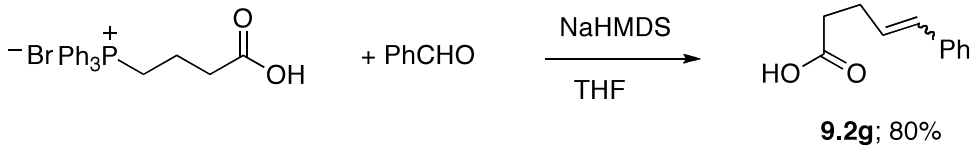
4-methyl-5-(methylthio)pent-4-enoic acid (9.2e)

IR (neat, cm^{-1}) 1710, 1436, 1301; ^{1}H NMR (300 MHz, $CDCl_3$, two isomers in a ratio of 1:1) δ 11.8 (br, 1H), 5.65 (s, with fine couplings, 1H), 2.49-2.34 (m, 4H), 2.22, 2.21 (2s, 3H), 1.75 (d, J = 1.5 Hz, 1.5 H), 1.70 (s, 1.5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.0, 179.9, 134.5, 133.6, 122.5, 122.1, 34.0, 33.0, 32.0, 28.8, 22.9, 17.9, 17.5, 17.3; ESI HRMS *m/z* $(M+H)^+$ calcd 161.0631, obsd 161.0631.



lithium 5-methoxy-4-methylpent-4-enoate (9.2f)

To a solution of **9.3f** (69.0 mg, 0.40 mml) in THF (6 mL) and water (2 mL) was added lithium hydroxide monohydrate (17 mg, 0.40 mmol). The suspension was stirred overnight and the solvent was removed in vacuum to give the title compound, which was used in the electrolysis without further manupilation.



9.2g; 80%

5-phenylpent-4-enoic acid (9.2g)

To a solution of the Wittig reagent (6.4 g, 15 mmol) in THF (30 mL) was added at 0 ºC a solution of NaHMDS (1.0 M in THF, 35 mL, 35 mmol) followed by benzyl aldehyde (2.1 g, 20 mmol). The resulting reaction mixture was stirred at rt for 4 h. Water and ether were added. The aqueous phase was separated, acidified with 1 N HCl to pH = 1, and extracted with ethyl acetate twice. The combined organic phase was dried over MgSO4, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluting with ether:hexane = 3:1) to give 2.1 g of **9.2g** (80%) as a white solid. IR (neat, cm^{-1}) 1706, 1210, 971, 748; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.18 (m, 5H), 6.45 (d, J = 15.6 Hz, 1H), 6.27-6.17 (m, 1H), 2.56-2.53 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.8, 137.5, 131.5, 128.8, 128.2, 127.5, 126.4, 34.1, 28.1; ESI HRMS m/z $(M+H)^+$ calcd 177.0910, obsd 177.0911.

9.5 Spectra: see appendix H

References and Notes

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13. (a) All potentials were measured by cyclic voltammetry with a BAS 100B Electrochemical Analyzer, a carbon working electrode, a Pt auxiliary electrode, a Ag/AgCl reference electrode, an electrolyte solution composed of Et_4NOTs (0.1 M) in methanol, a substrate concentration of 0.025 M, and a sweep rate of 50 mVs^{-1}. (b) Measured in the presence of 0.6 equivalent of LiOMe.
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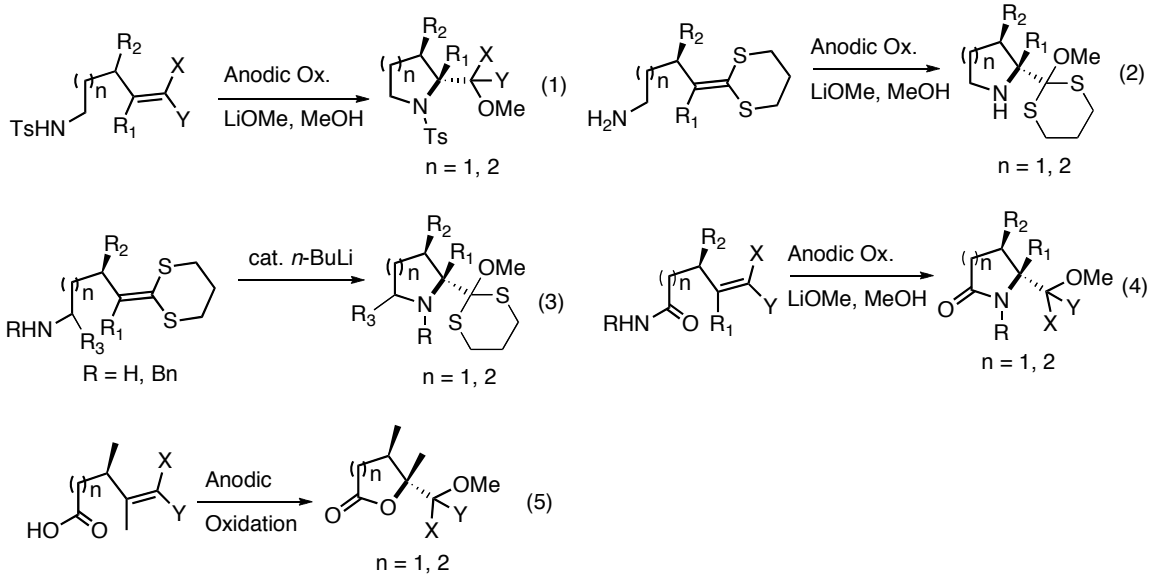
Chapter 10 Conclusion and Future Work

10.1 Conclusion

In this thesis, the development of some new intramolecular anodic olefin coupling reactions for the synthesis nitrogen- and oxygen-hetereocycles was presented (Scheme 10). Nitrogen based coupling partners such as tosylamides (eq 1),[1] primary amines (eq 2),[2] and N-Ph and N-OBn amides (eq 4)[3] were employed successfully in anodic olefin coupling reactions for the synthesis cyclic amino acid derivatives and lactams. A non-electrochemical approach that complements the oxidative cyclizations for the synthesis of cyclic amino acid derivatives has also been developed (eq 3).[4] The use of carboxylic acids as nucleophiles in the anodic olefin coupling reactions afforded lactones (eq 5).[3] The success of most of these oxidative cyclization reactions relies on the use of LiOMe

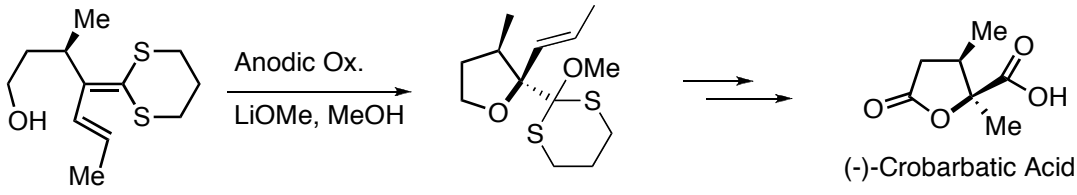
Scheme 10-1 Synthesis of Nitrogen- and Oxygen-Hetereocycles



as a base instead of the commonly used base 2,6-lutidine.[1,2] A competition study was used to investigate the mechanism of the anodic coupling of sulfonamides and electron-rich olefins. [5]

The natural propensity of the electrolysis reactions to put R_1 and R_2 groups *cis* to each other (Scheme 10-1) calls for a strategy to address the stereochemistry of structures like (-)-crobarbatic acid that has two *trans* methyl groups. A useful method to solve the stereochemical limitations was developed and demonstrated in the synthesis of (-)-crobarbatic acid. The strategy involved the use of a vinyl-substituted ketene dithioacetal as the electron-rich olefin in the electrolysis reaction and reversing the stereochemistry of the newly formed stereogenic center after the oxidative cyclization (Scheme 10-2).[6]

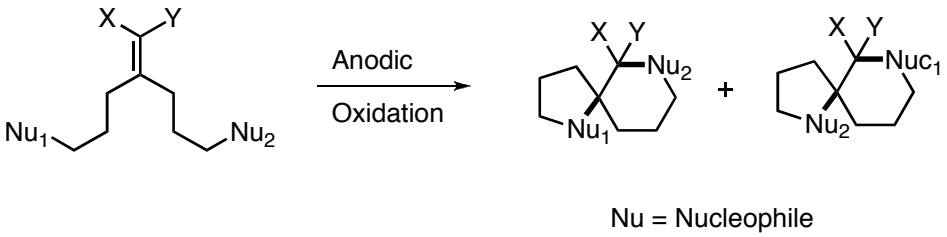
Scheme 10-2 Synthesis of (-)-Crobarbatic Acid



10.2 Future Work

Application of these potentially powerful reactions in the synthesis of biologically important compounds should be the focus of future work. The competition method developed in Chapter 5 of this thesis provides us a useful tool to study the mechanistic aspects of the electrolysis reactions.[5] This project has been carried on by Mr. John Campbell to study the mechanism of other electrolysis reactions and the trapping abilities of different trapping groups toward a variety of radical cations (Scheme 10-3).

Scheme 10-3 Competition Studies

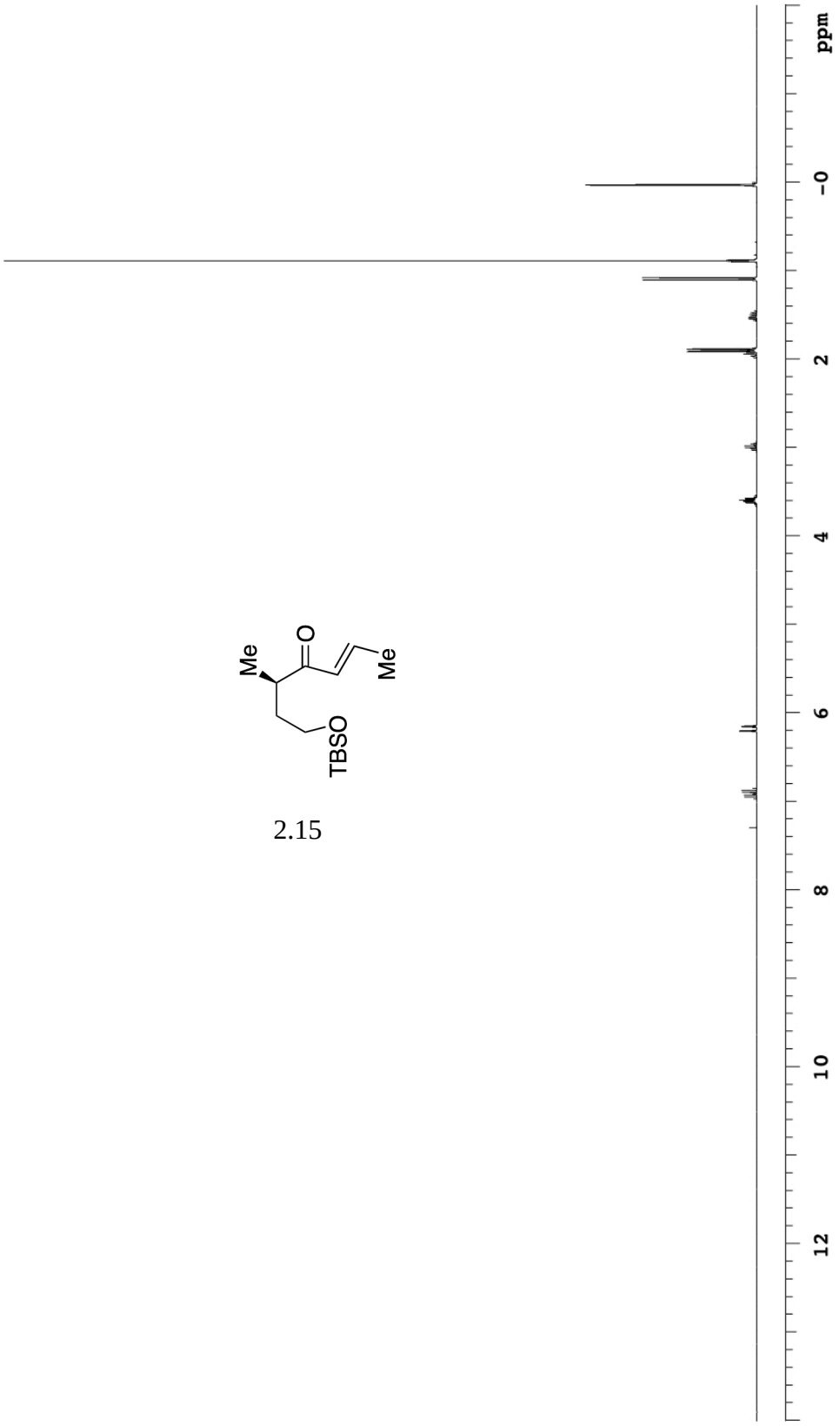


Nu = Nucleophile

The chemistry described in Chapter 8 demonstrates that electrochemical oxidation is a mild and powerful method for the generation of amidyl radicals. Future studies would expand the method for the generation of other types of N-centered radicals.

References

1. (a) Xu, H.-C.; Moeller, K. D. *J. Am. Chem. Soc*. **2010**, *132*, 2839. (b) Xu, H.-C.; Moeller, K. D. *J. Am. Chem. Soc*. **2008**, *130*, 13542.
2. Xu, H.-C.; Moeller, K. D. *Angew. Chem. Intl. Ed*. **2010**, *49*, 8004.
3. Unpublished results.
4. Xu, H.-C.; Moeller, K. D. *J. Am. Chem. Soc*. **2010**, *132*, 2839.
5. Xu, H.-C.; Moeller, K. D. *Org. Lett*. **2010**, *12*, 1720.
6. Xu, H.-C.; Brandt, J. D.; Moeller, K. D. *Tetrahedron Lett*. **2008**, *49*, 3868.



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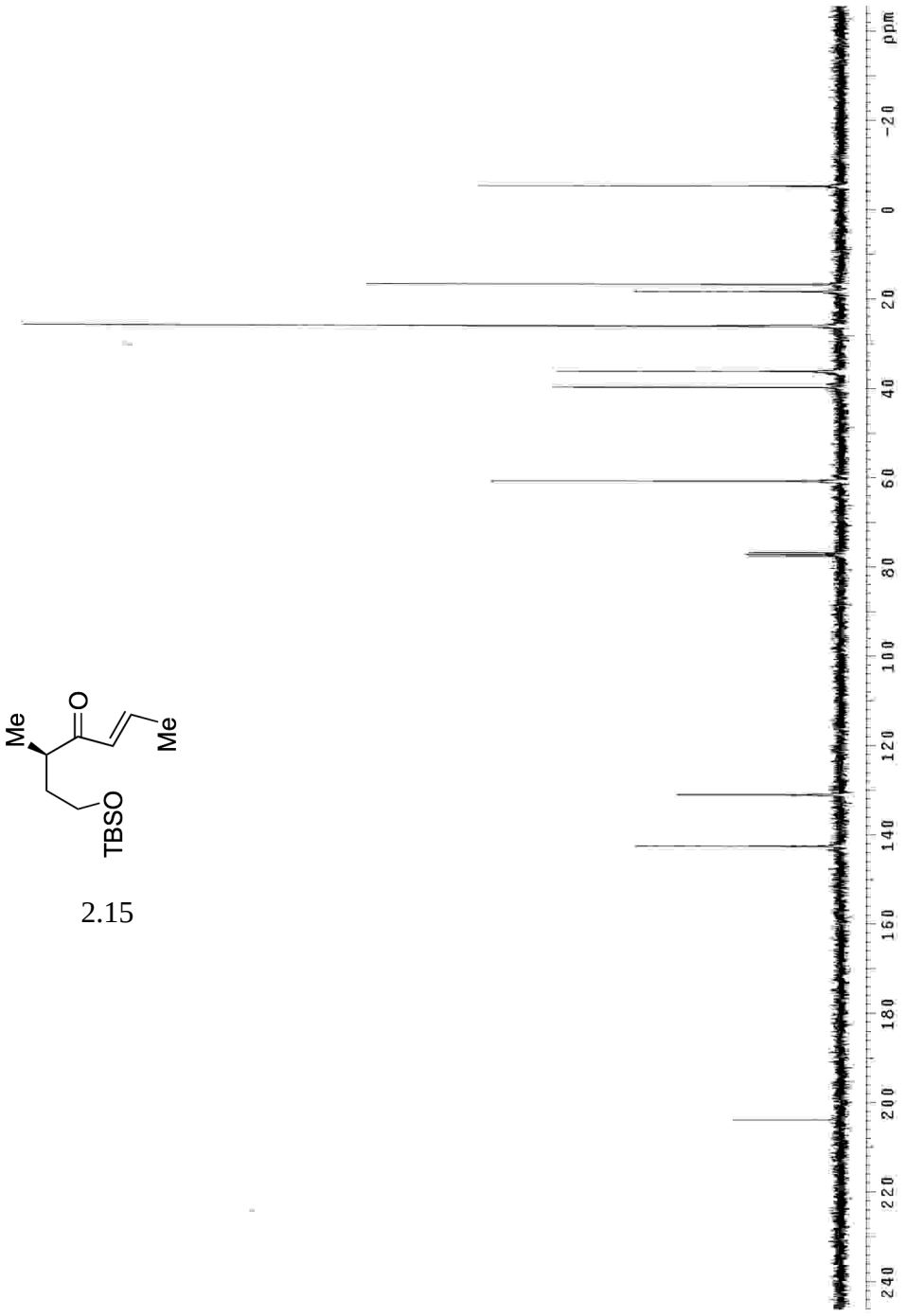

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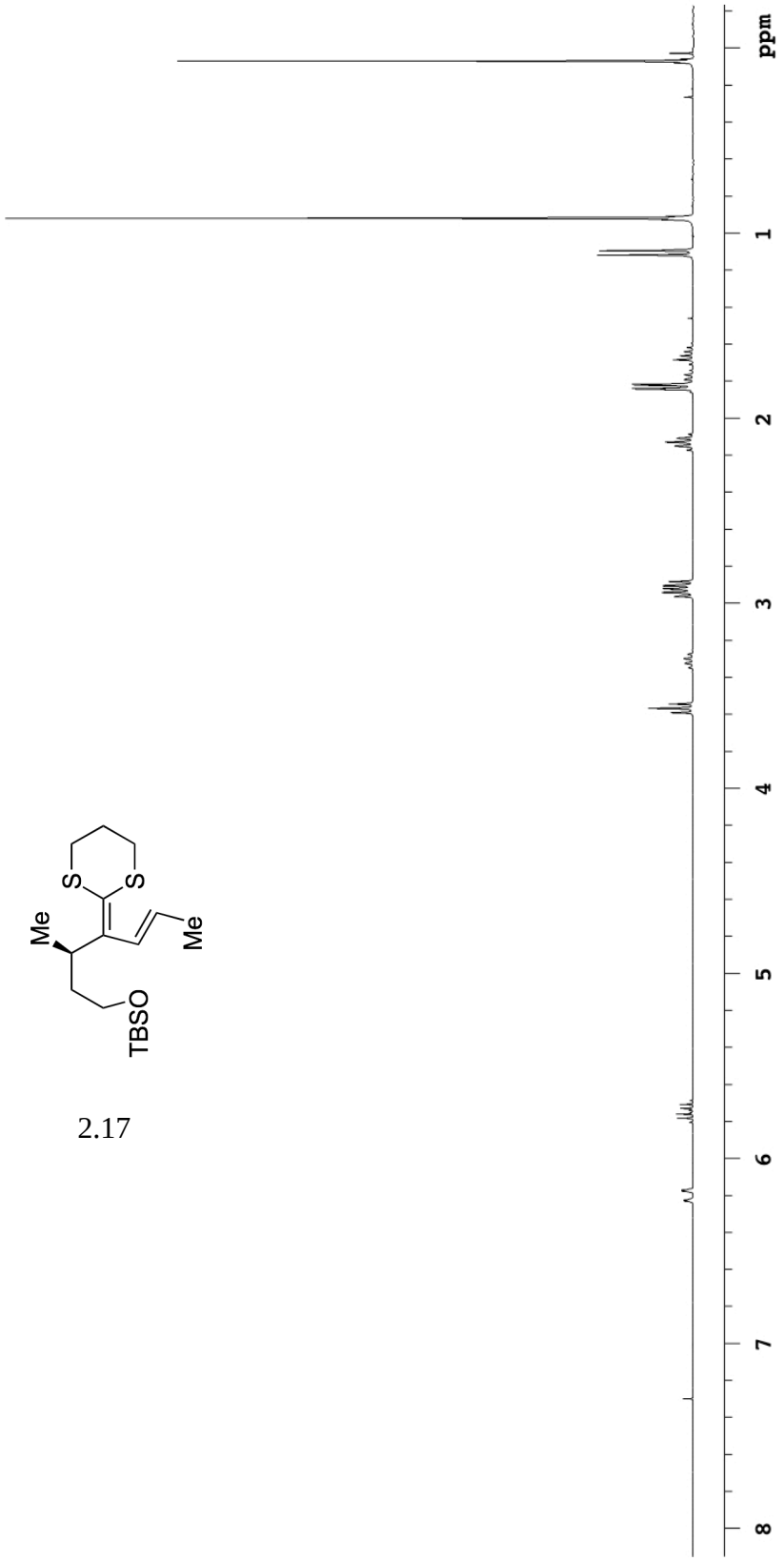

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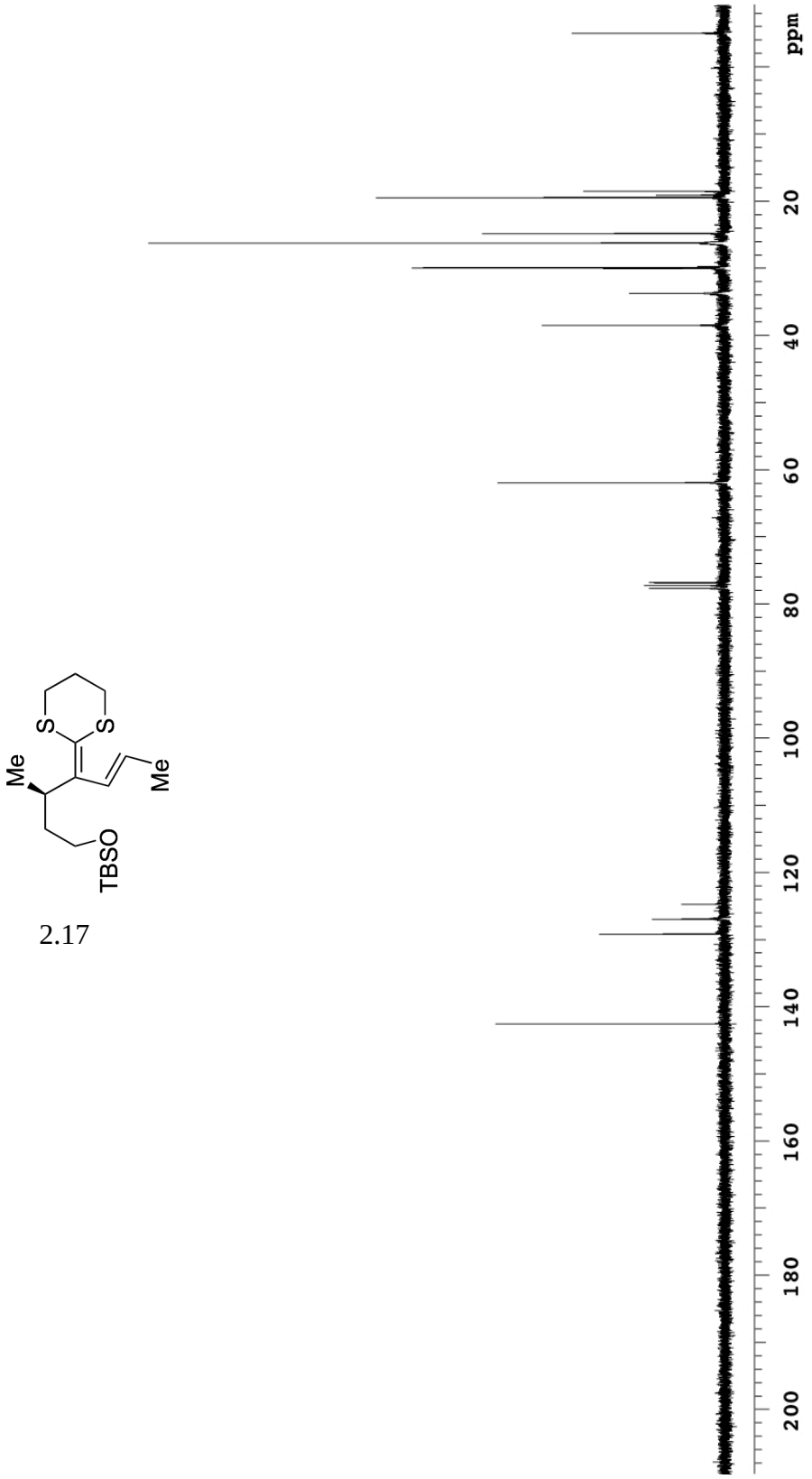

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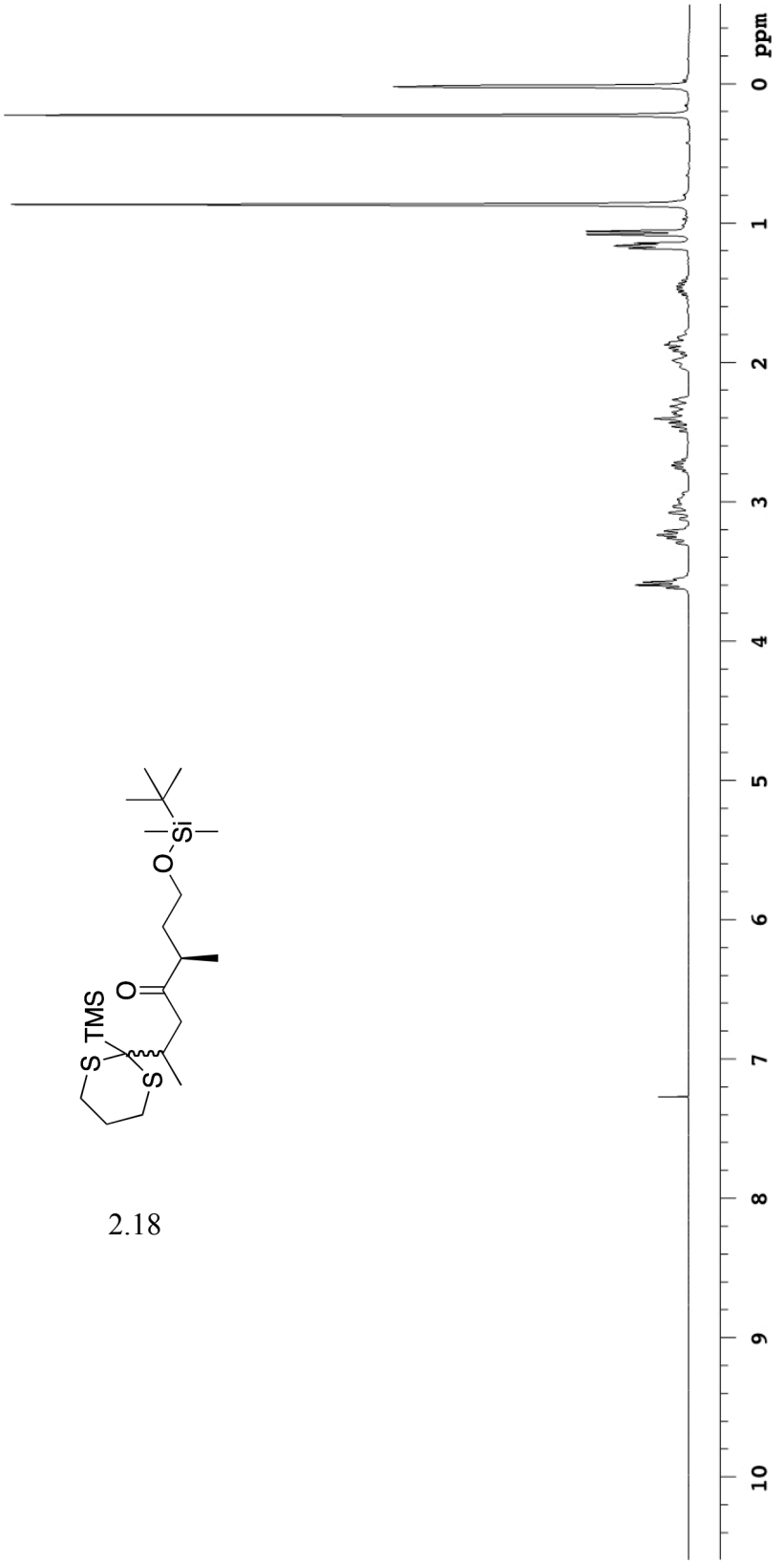

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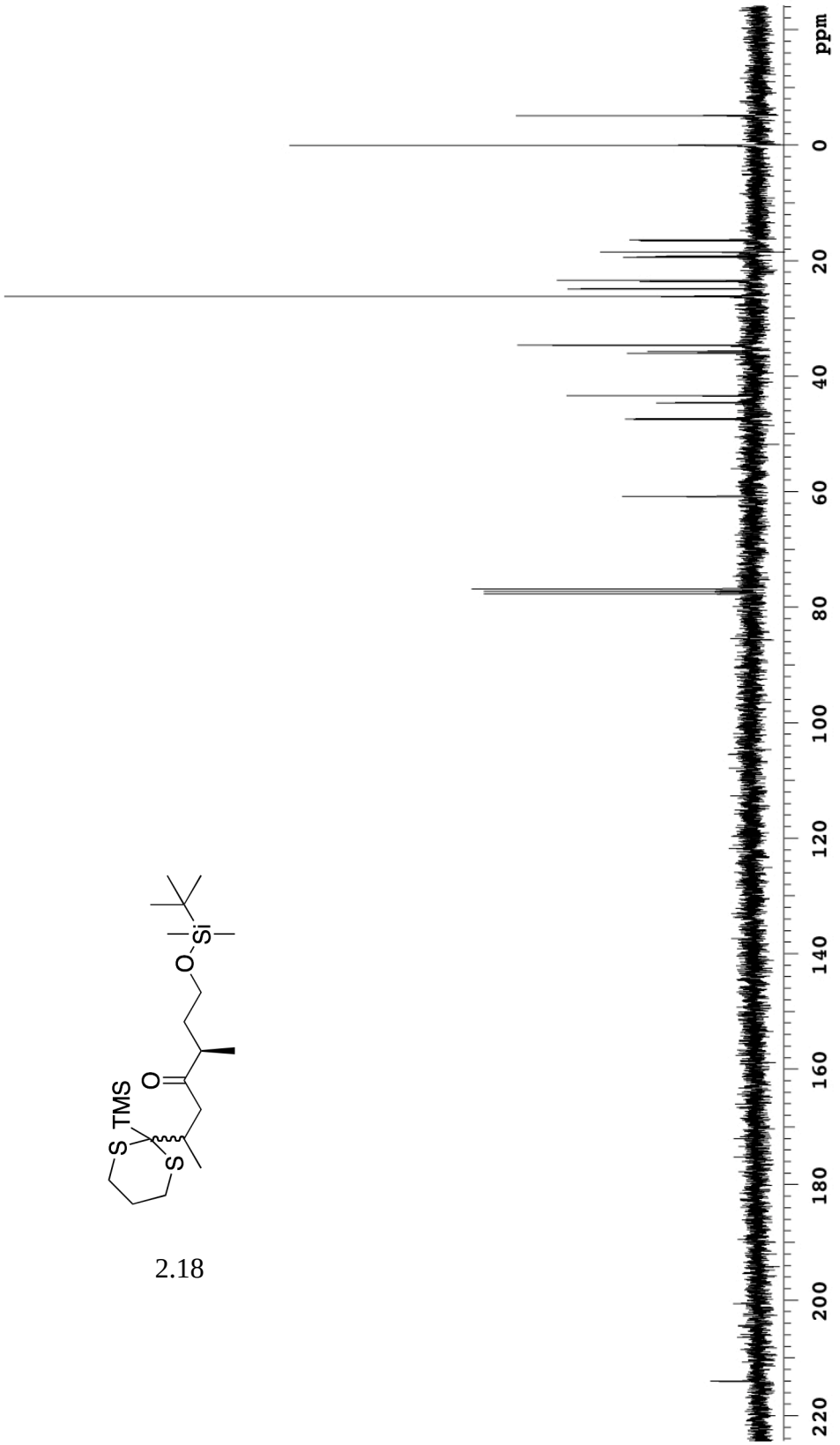

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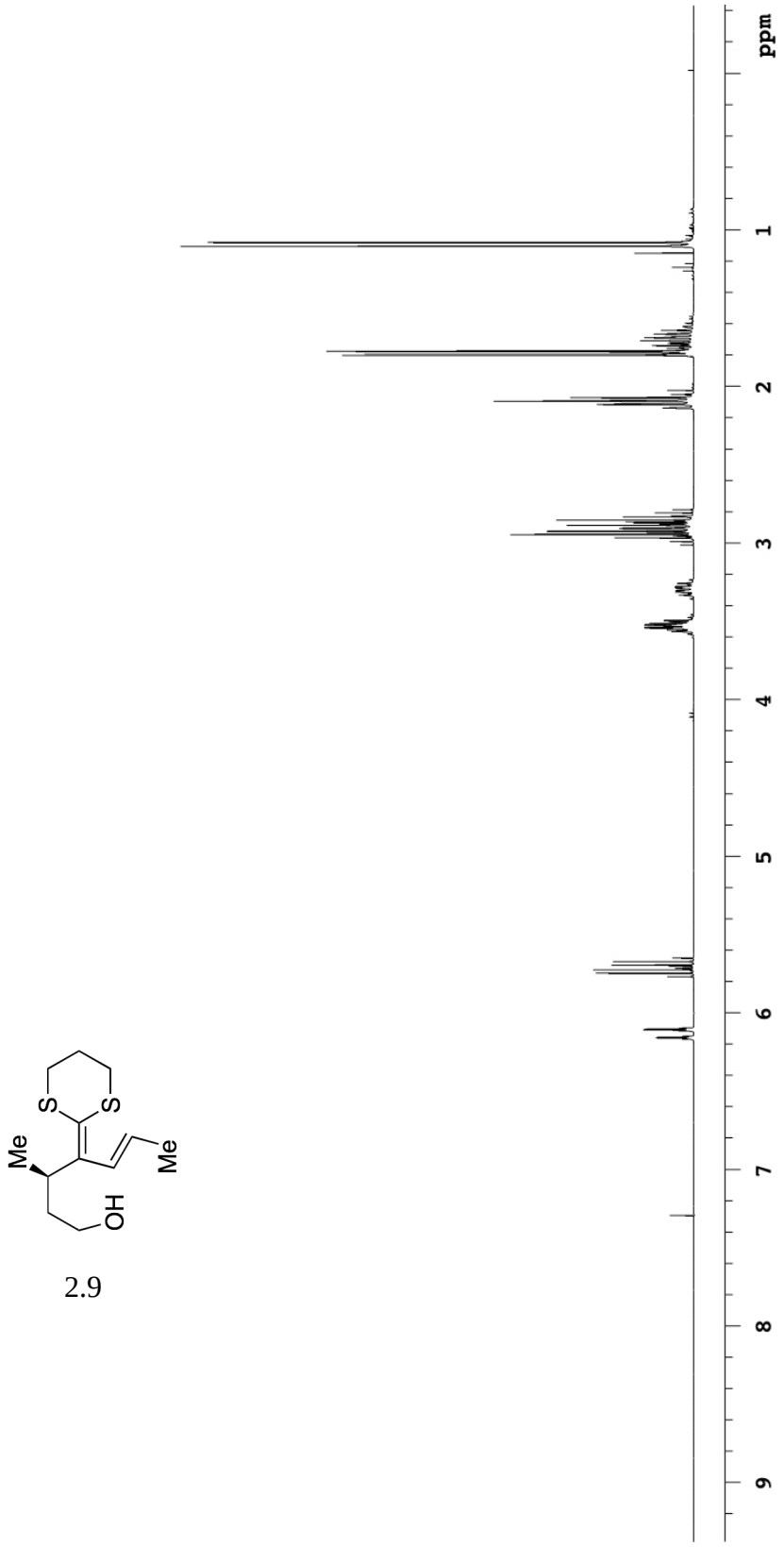

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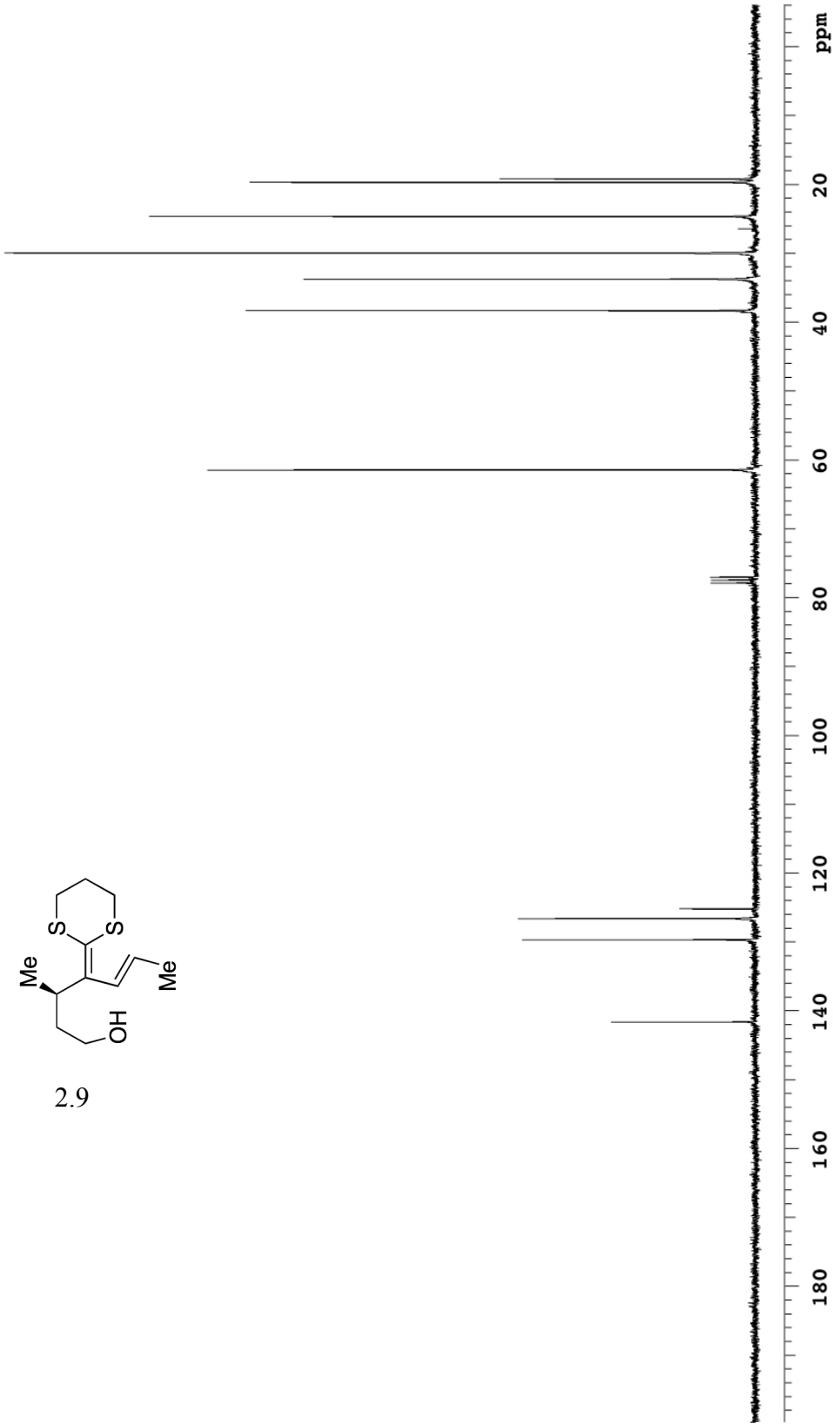

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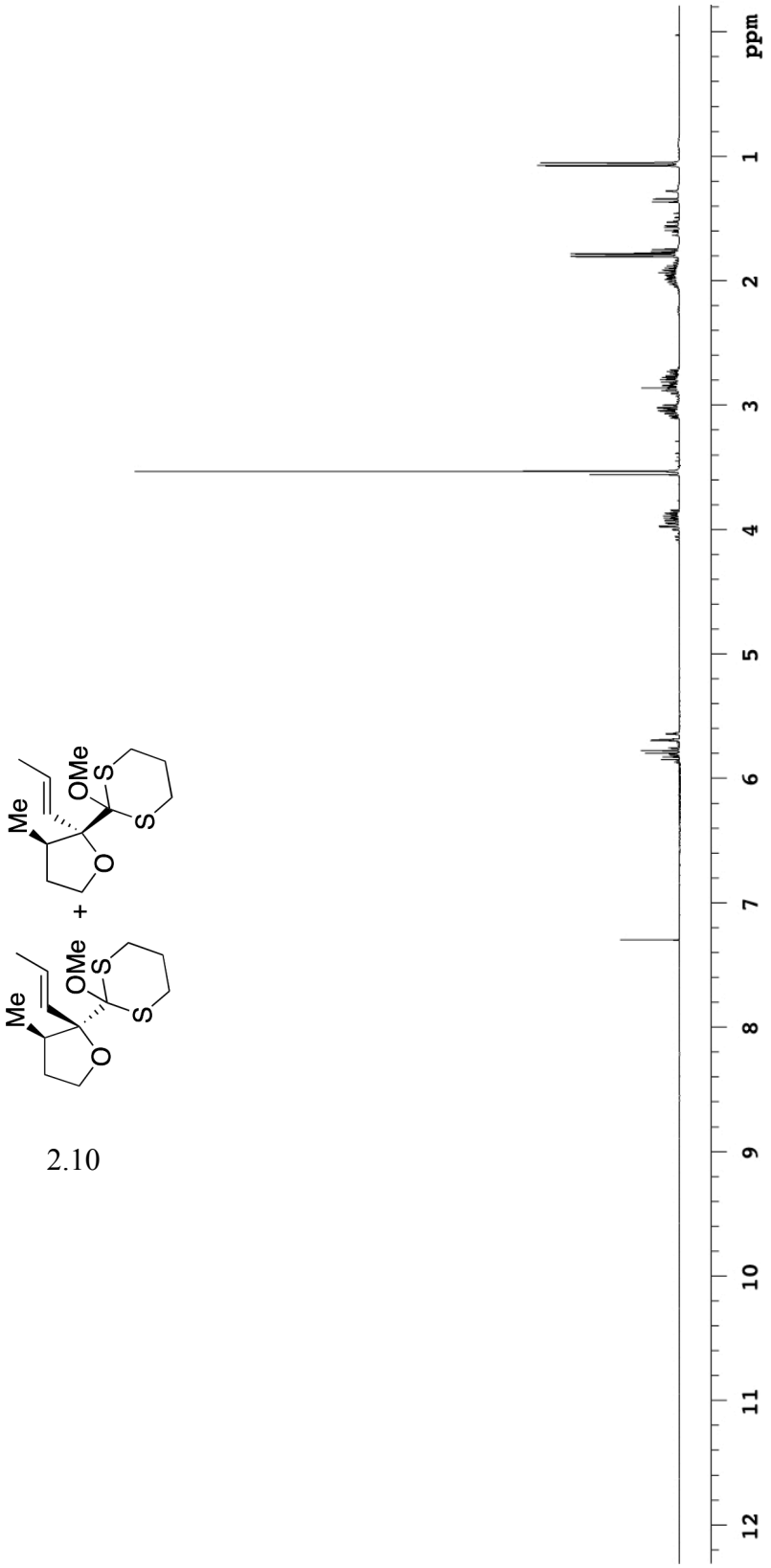

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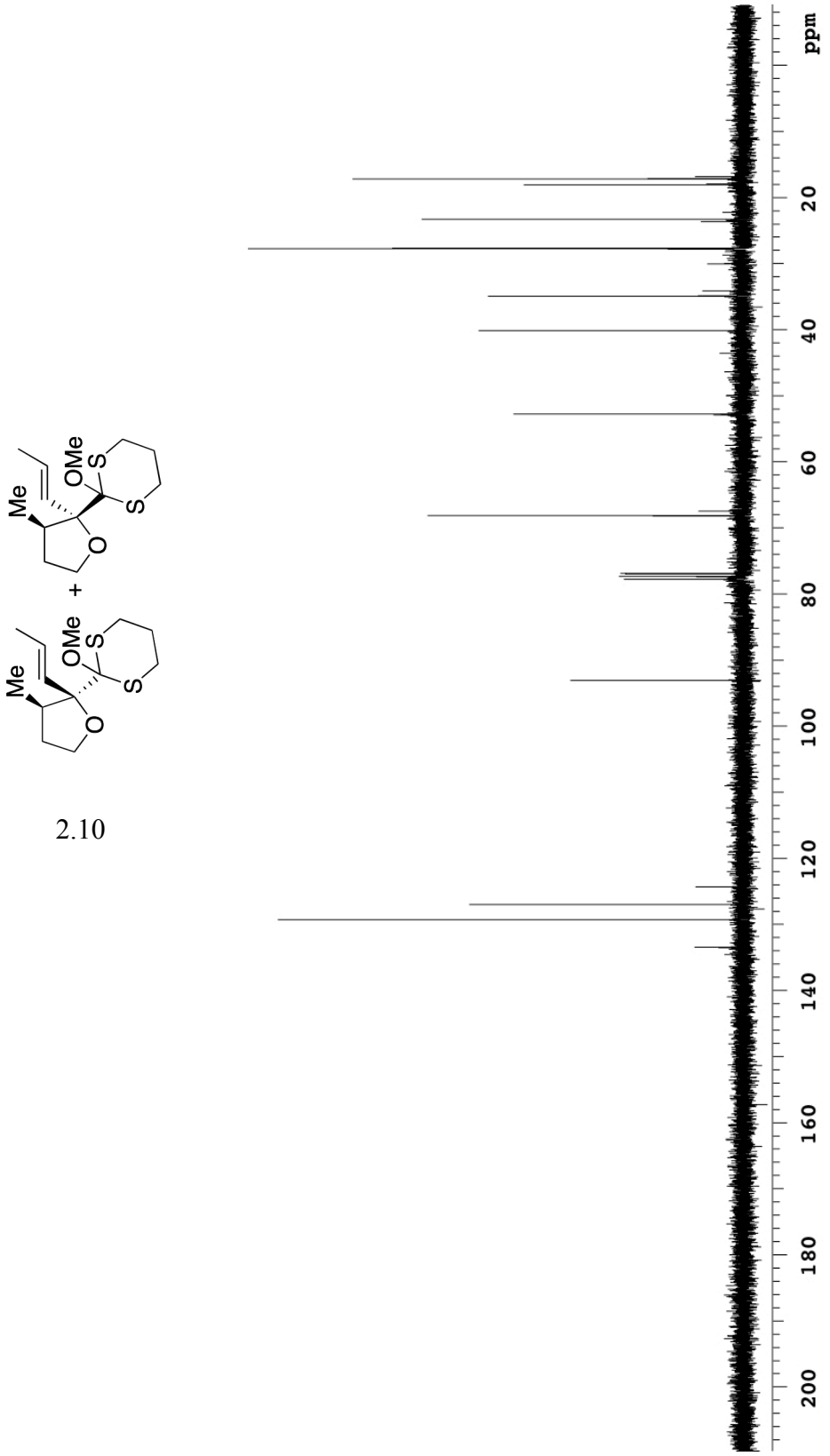

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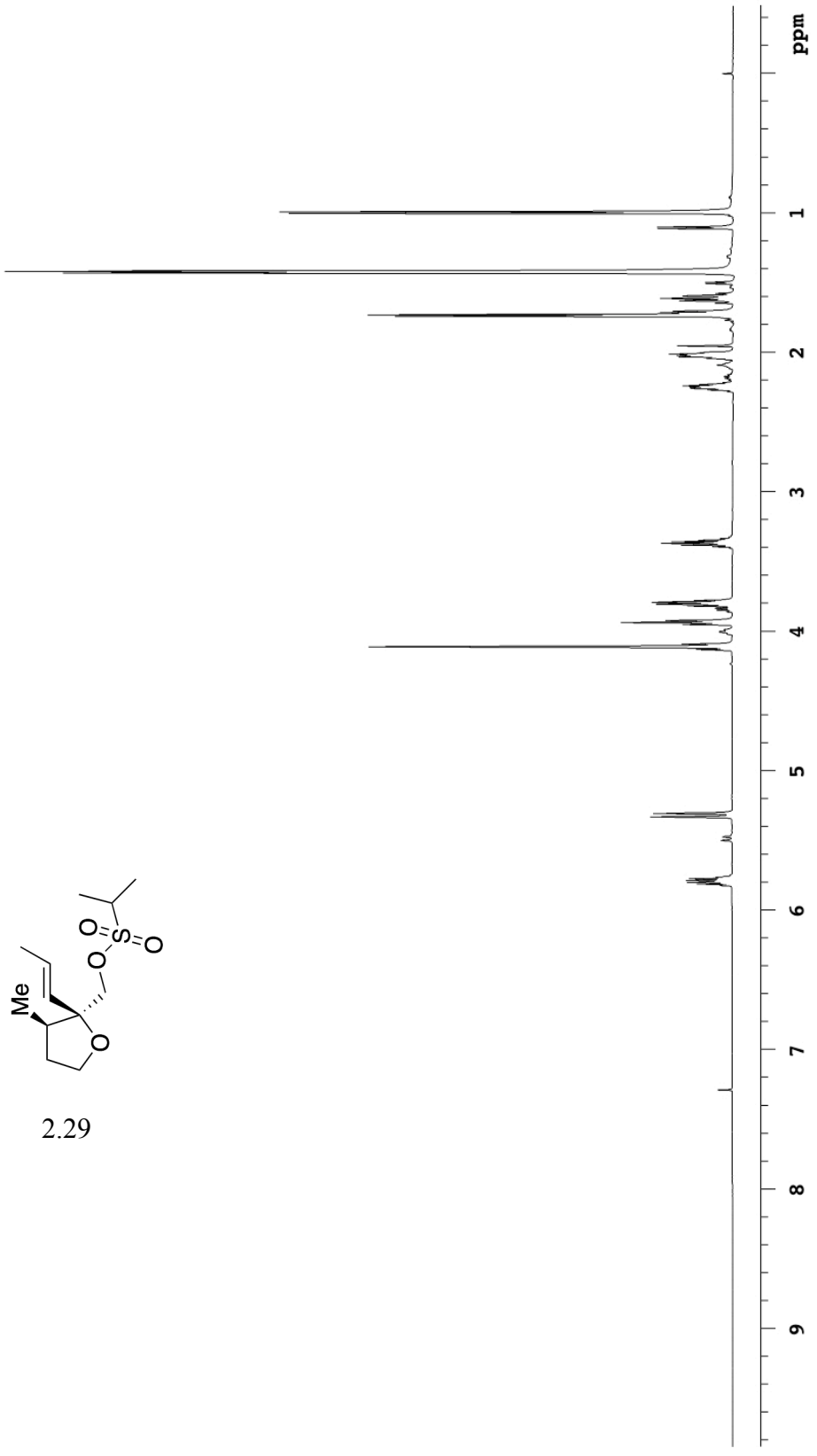

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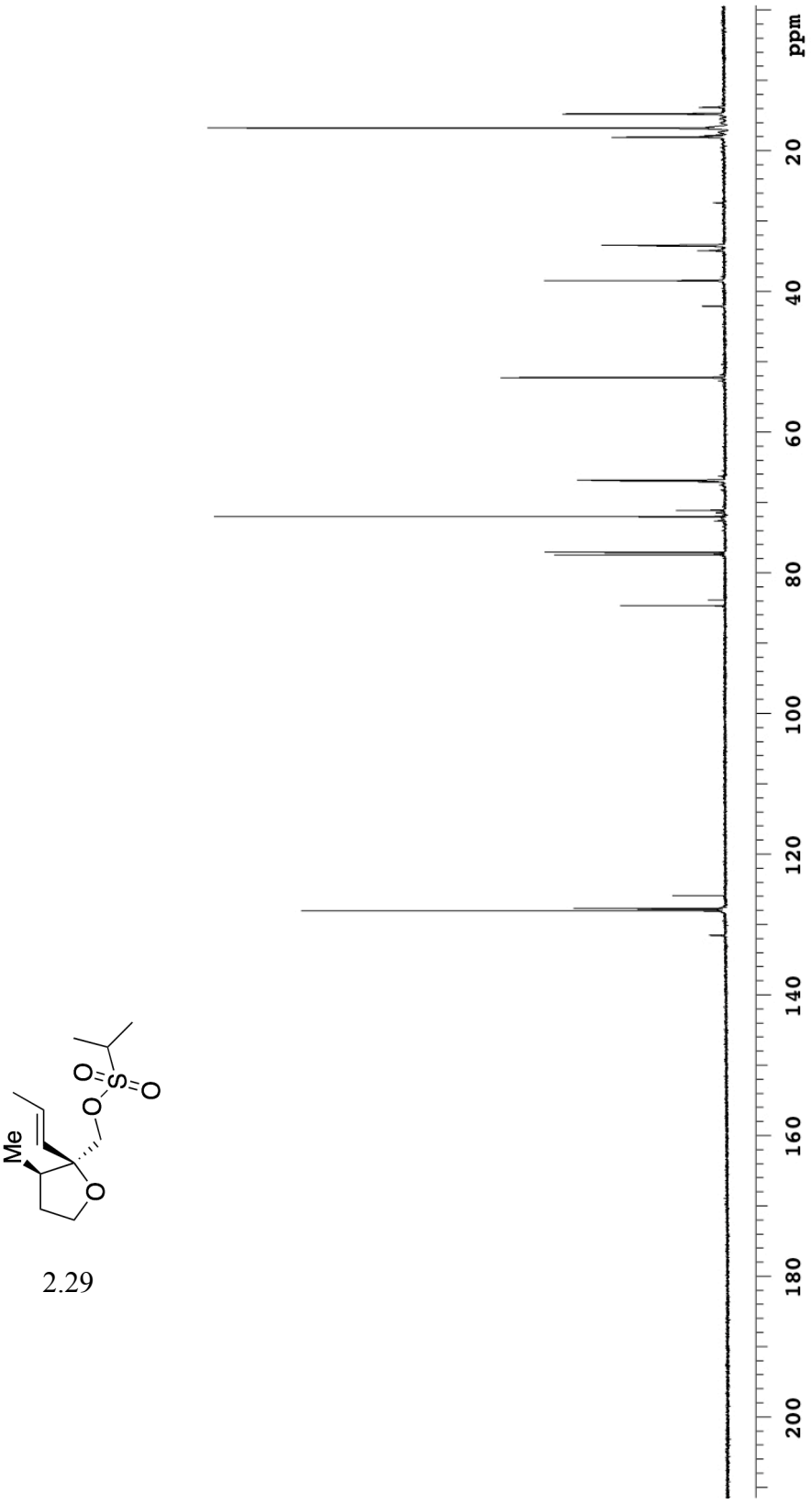

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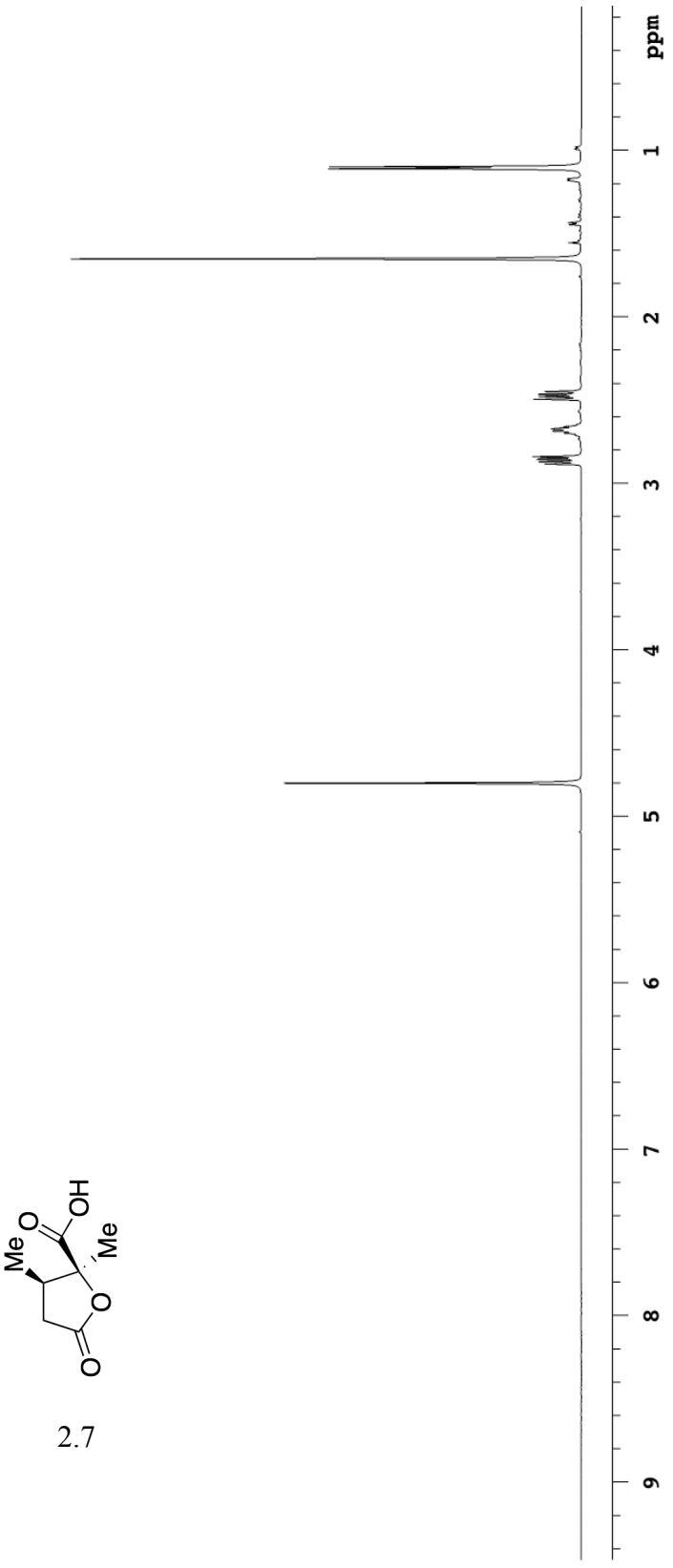

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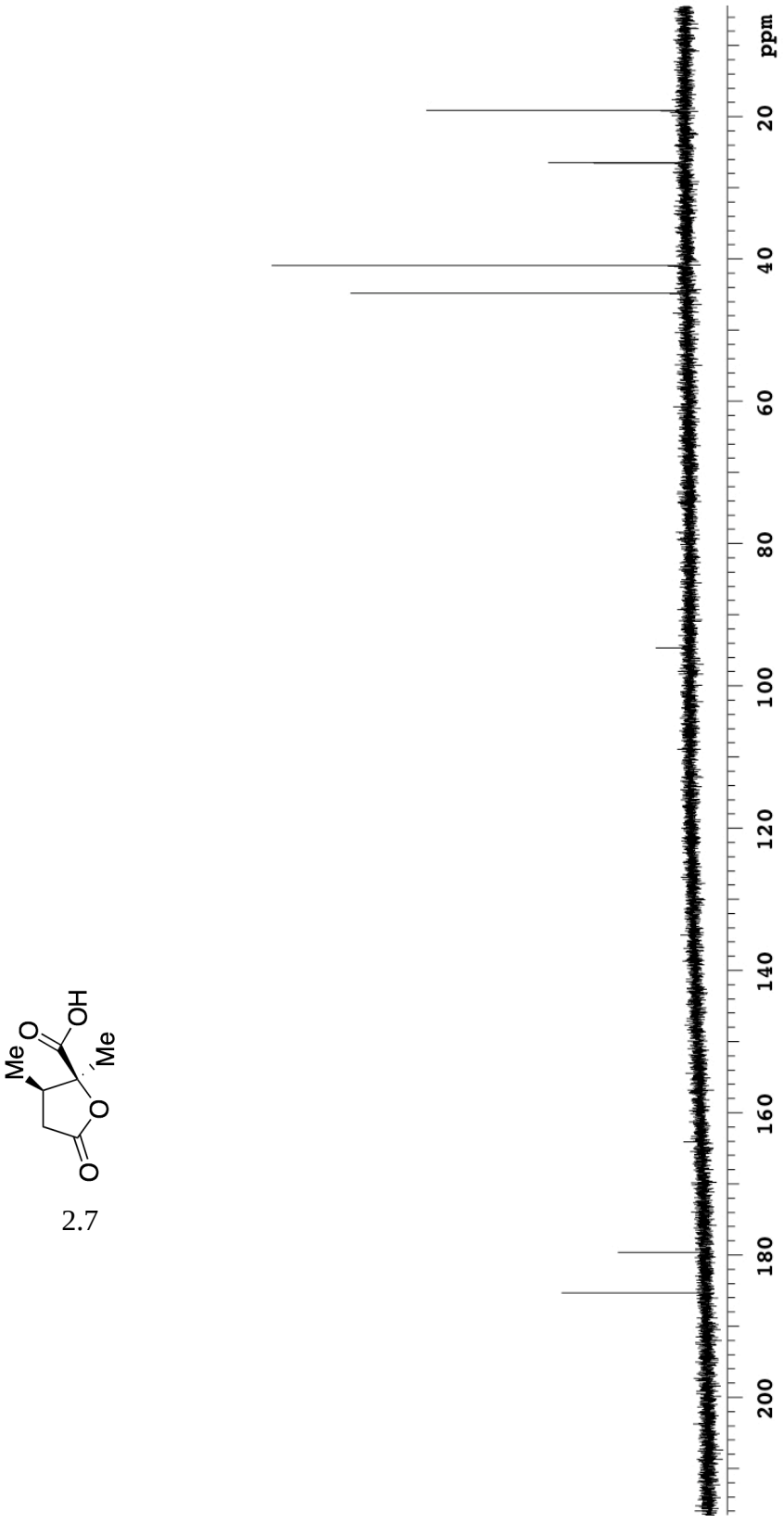

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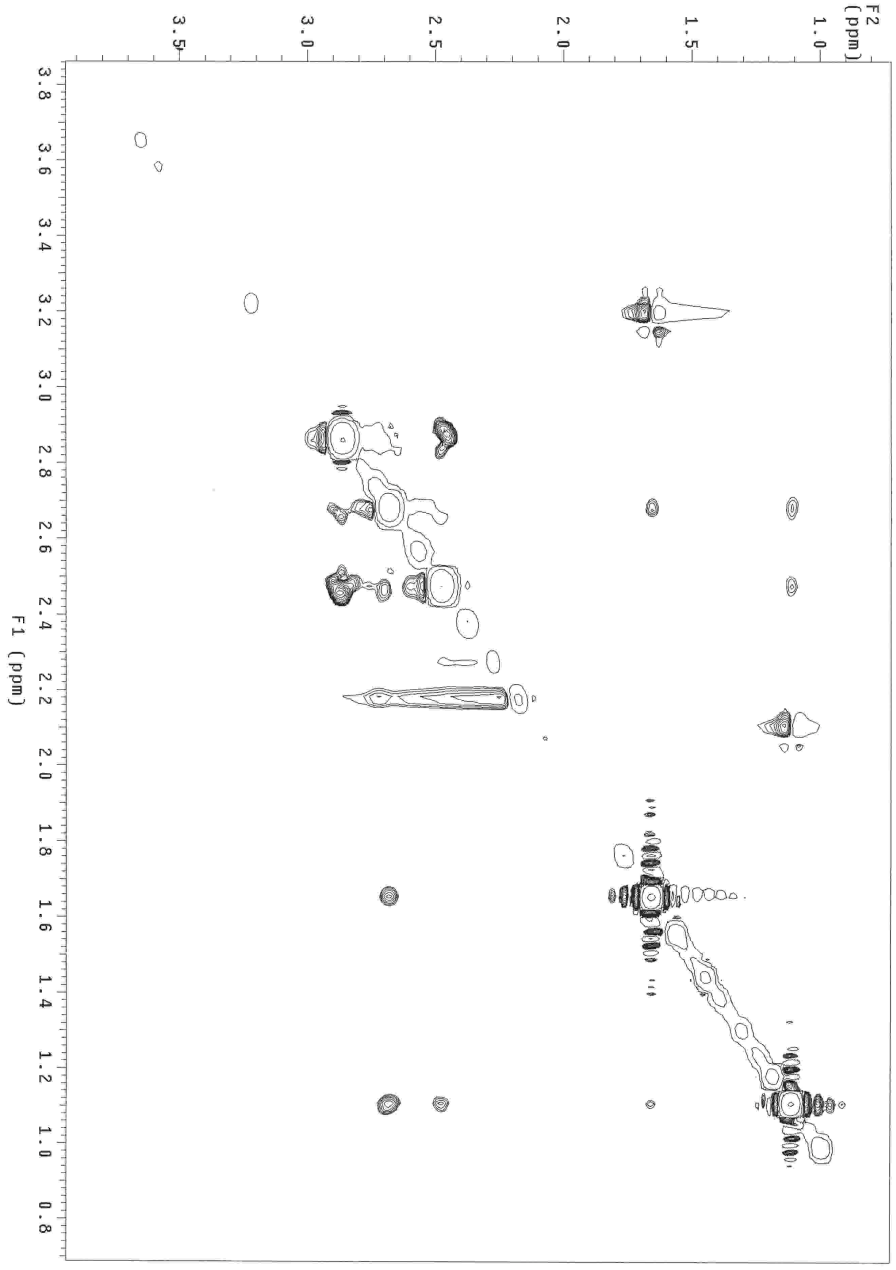

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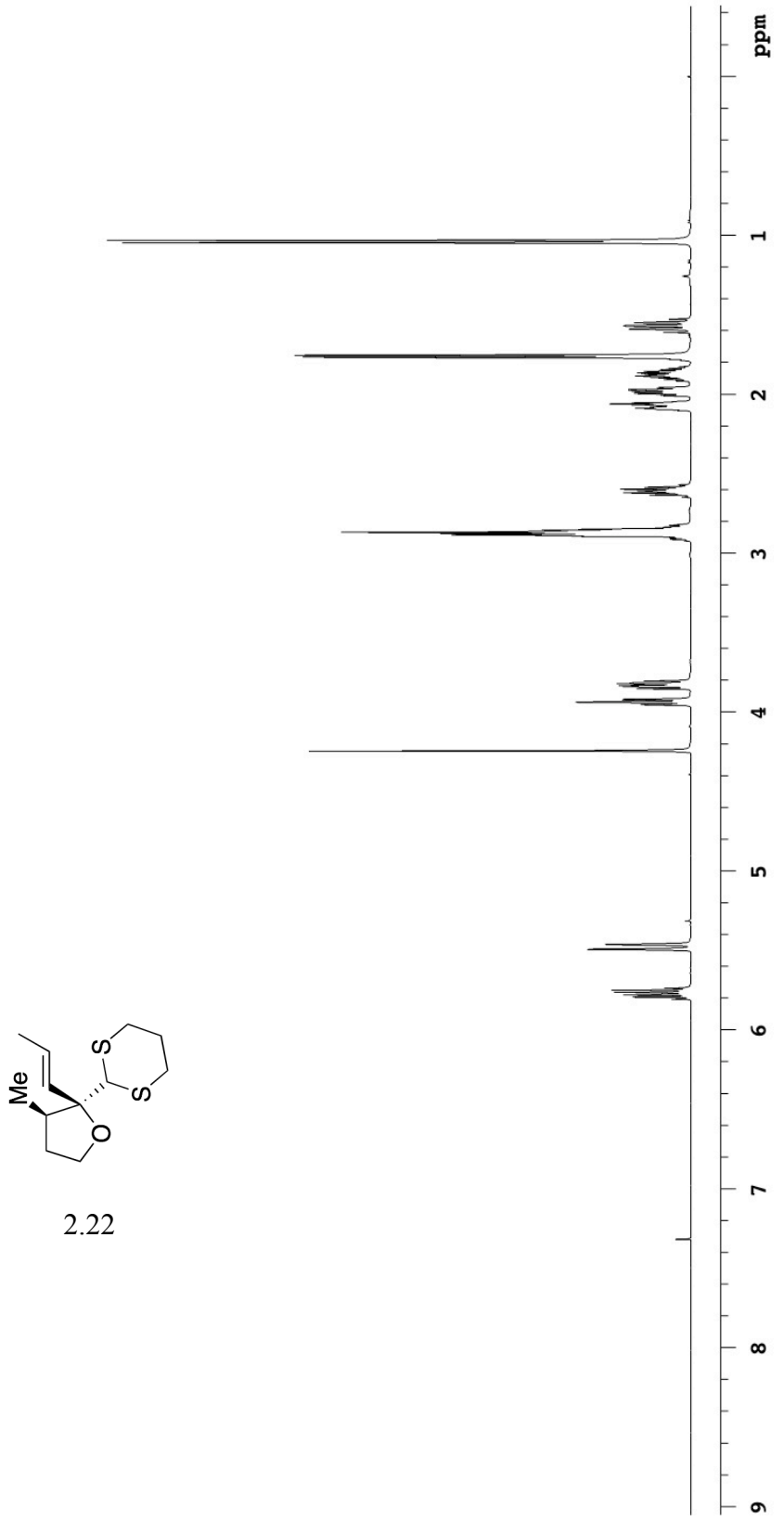

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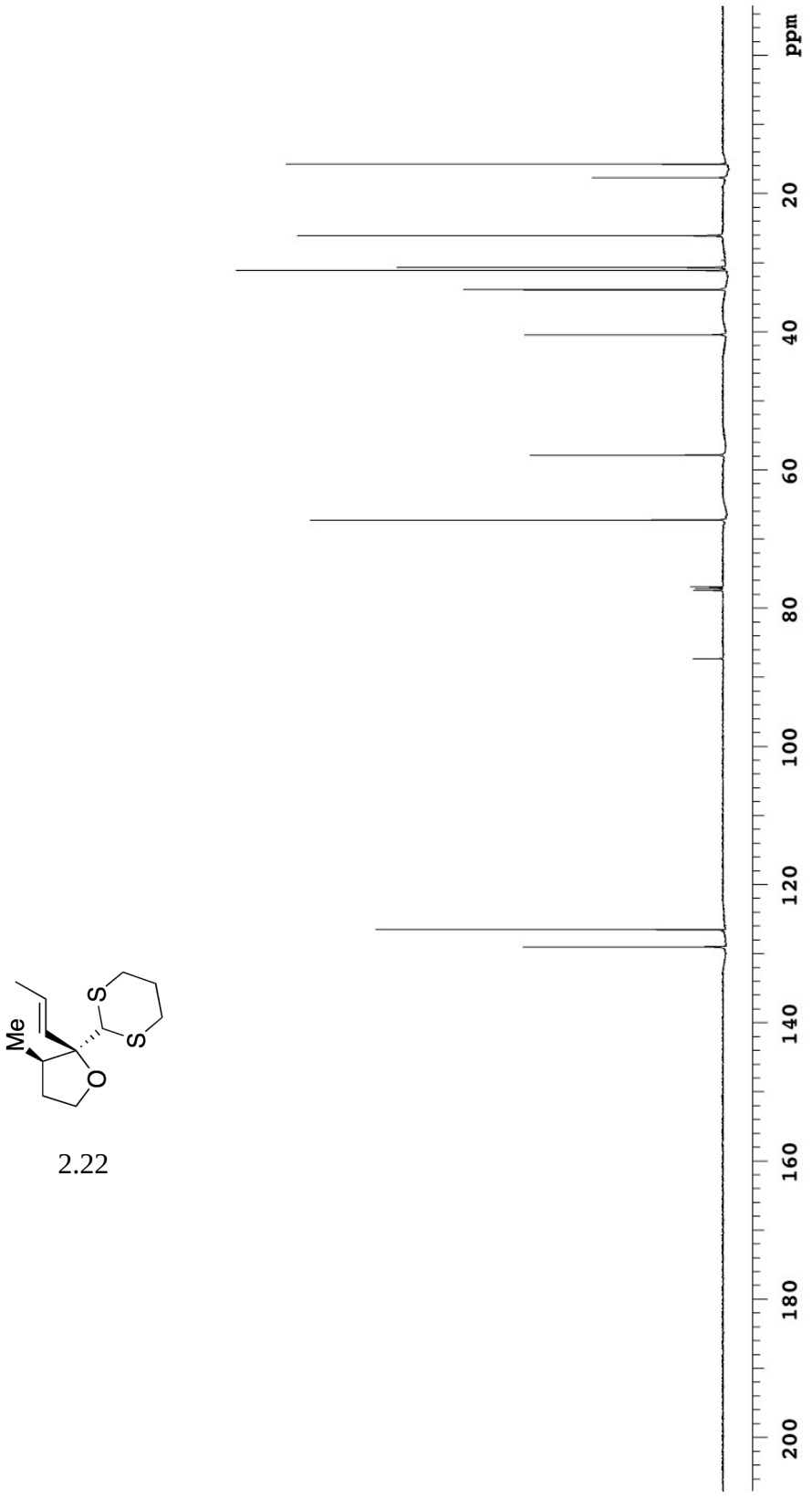

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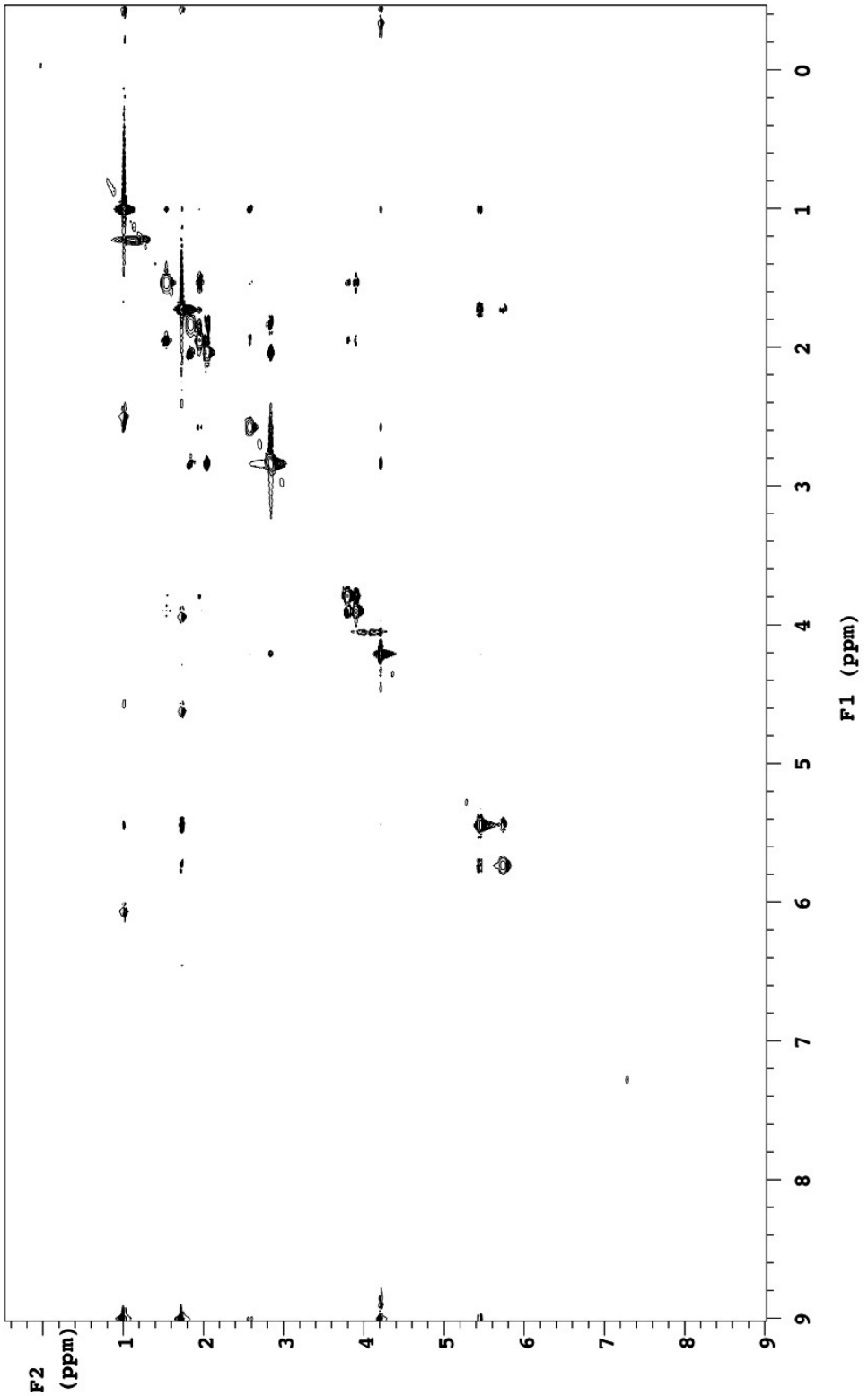

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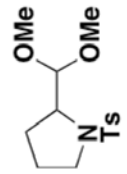

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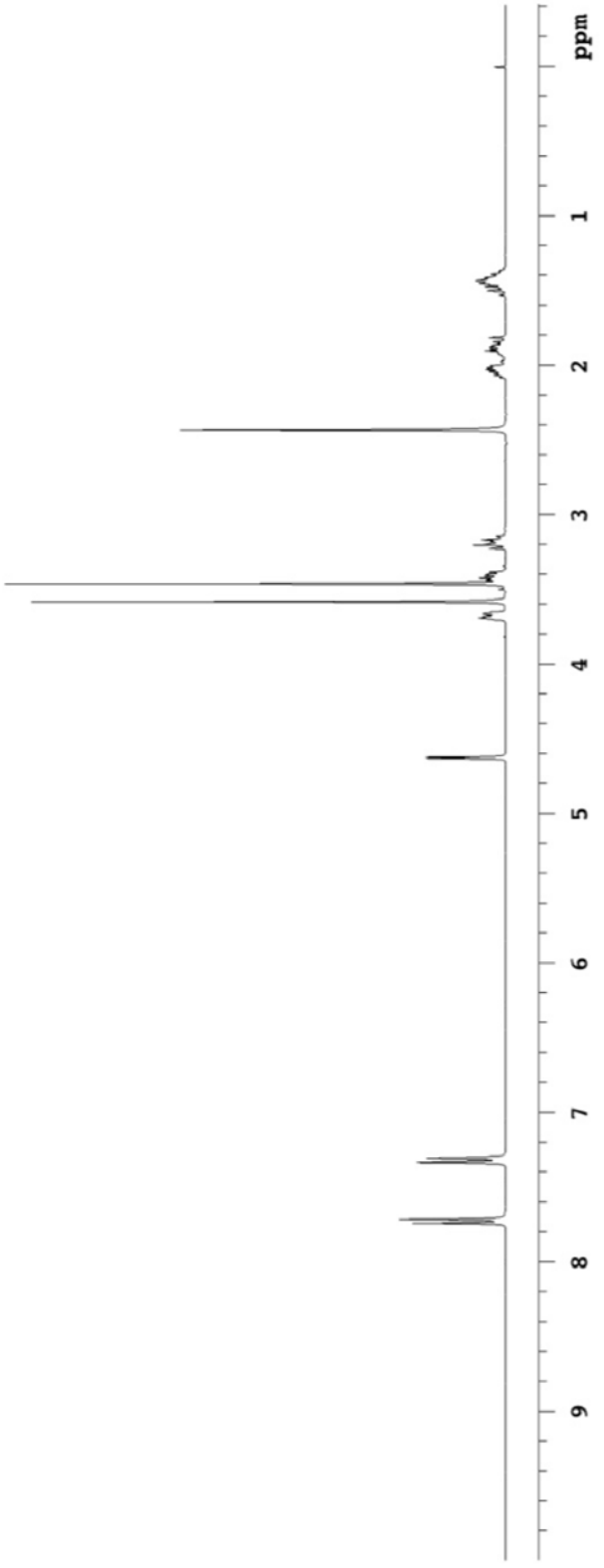

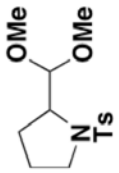

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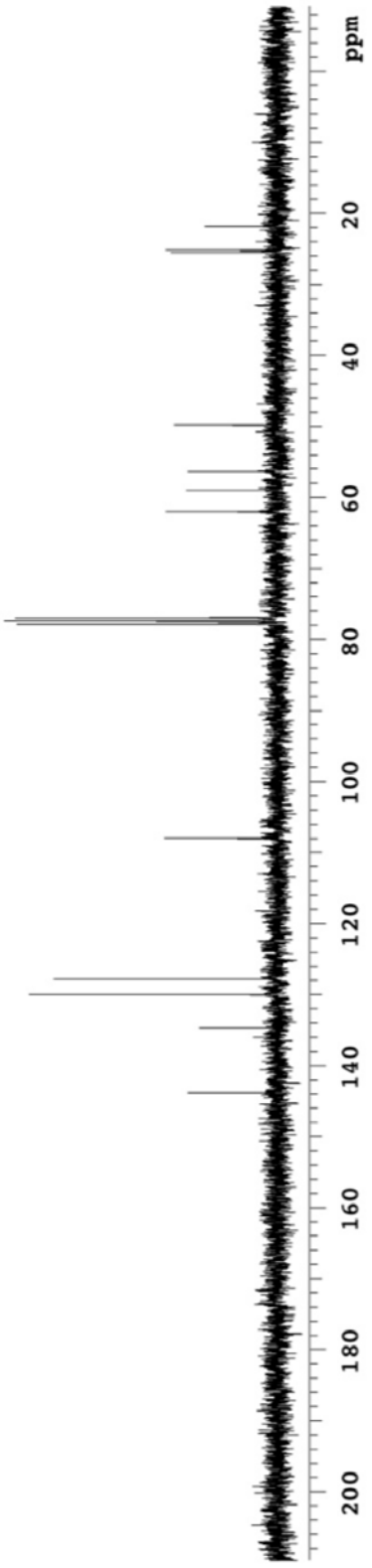

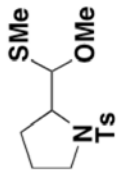

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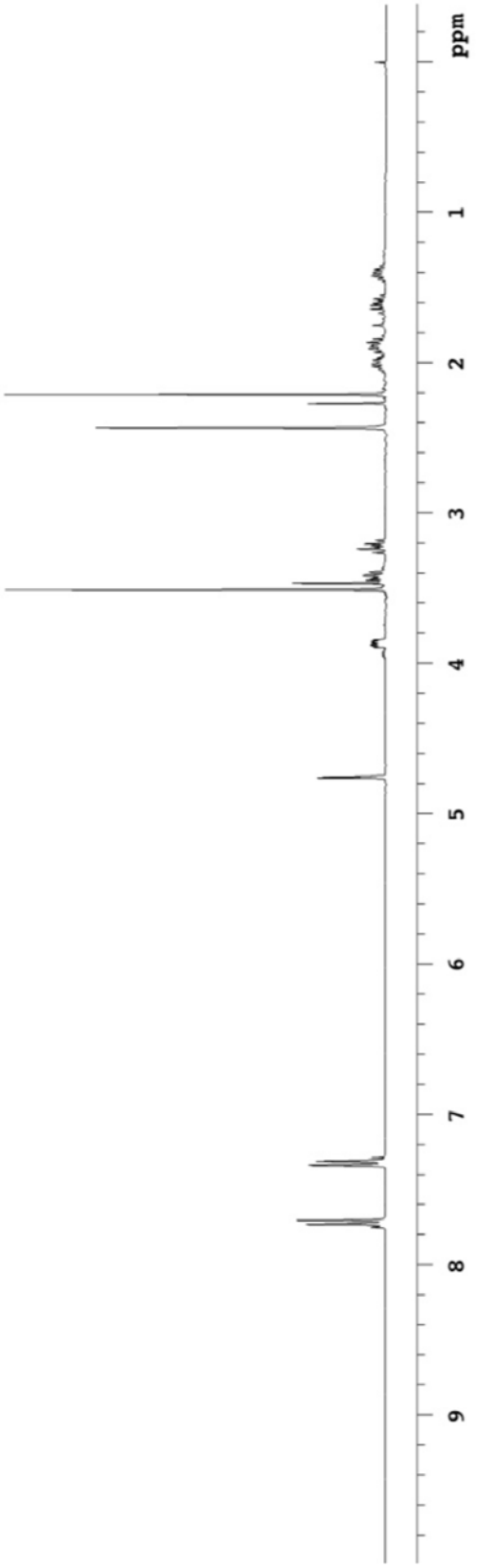

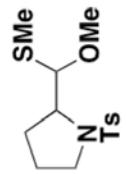

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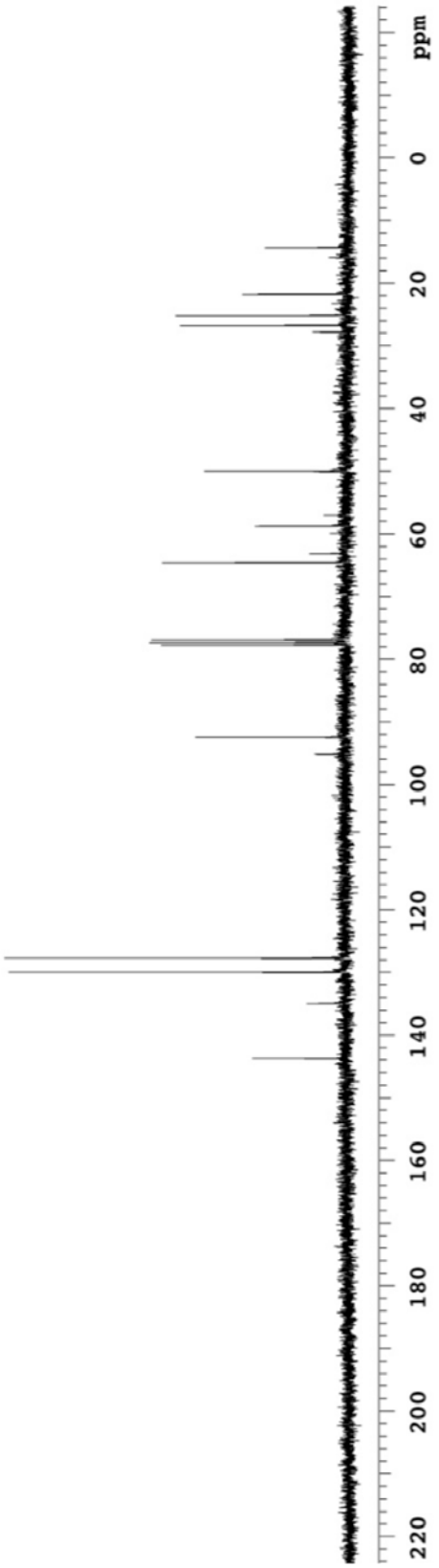

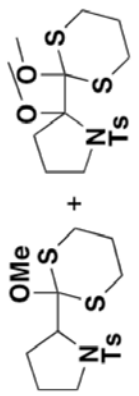

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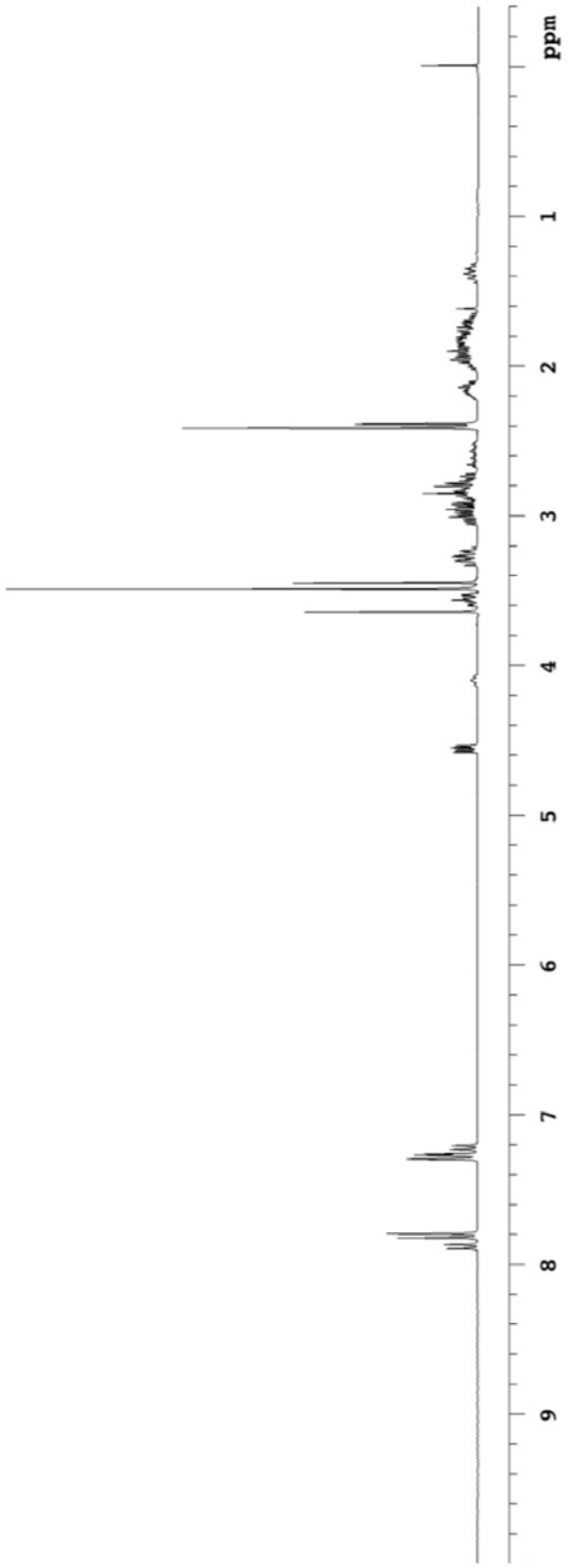

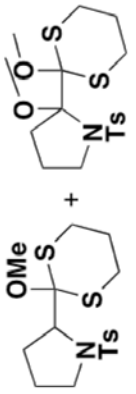

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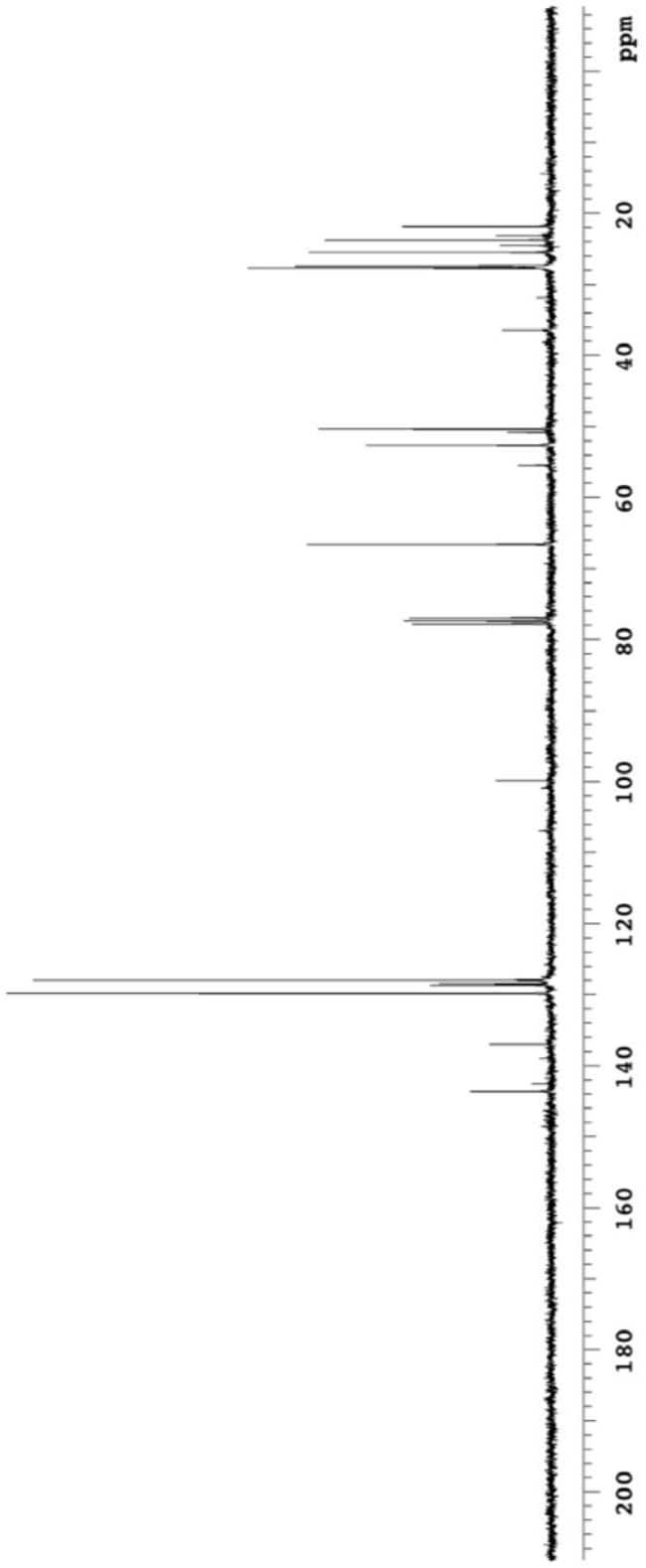

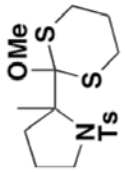

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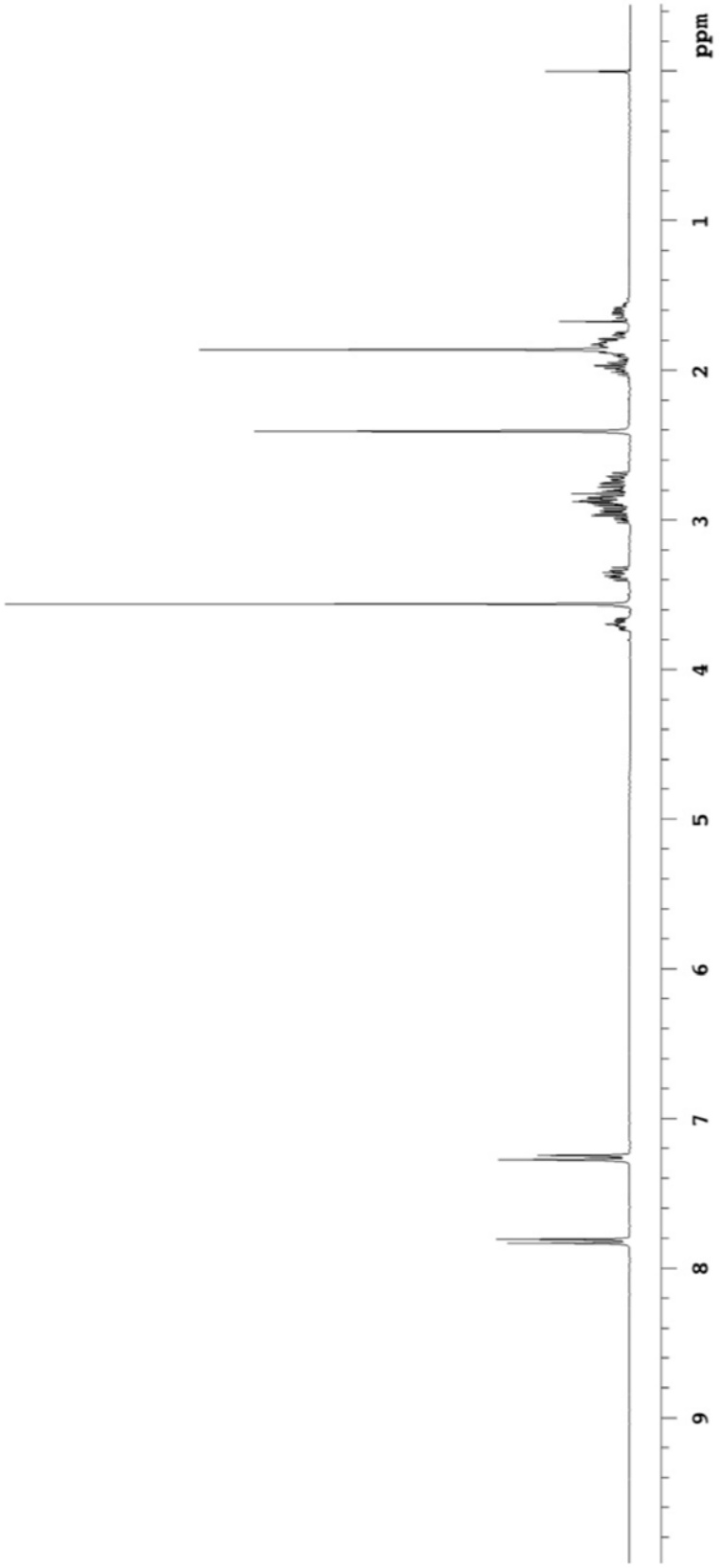

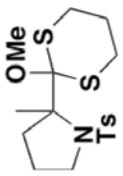

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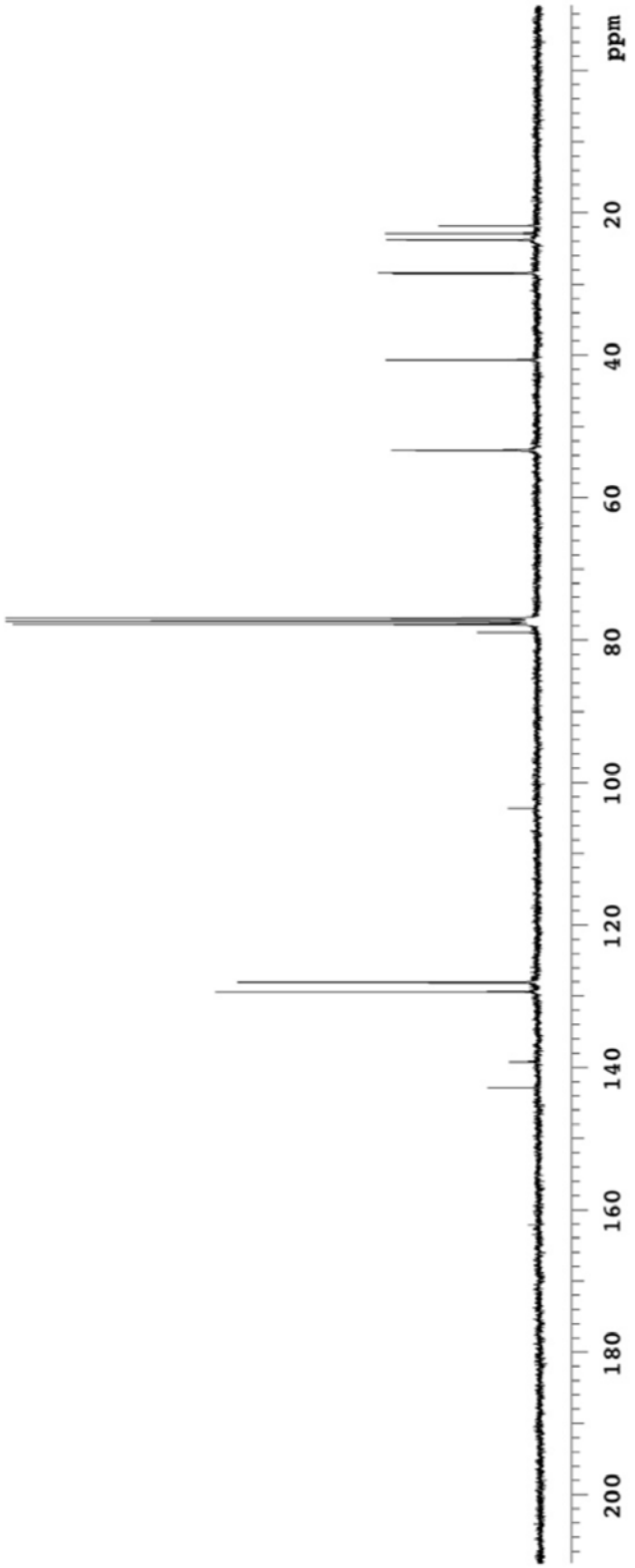

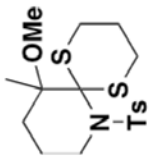

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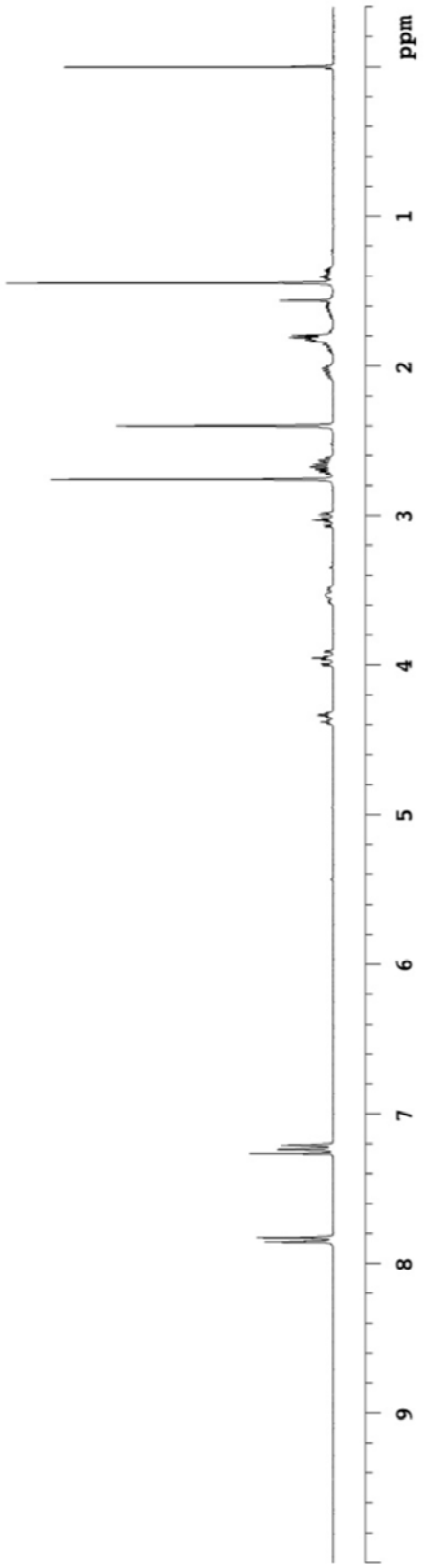

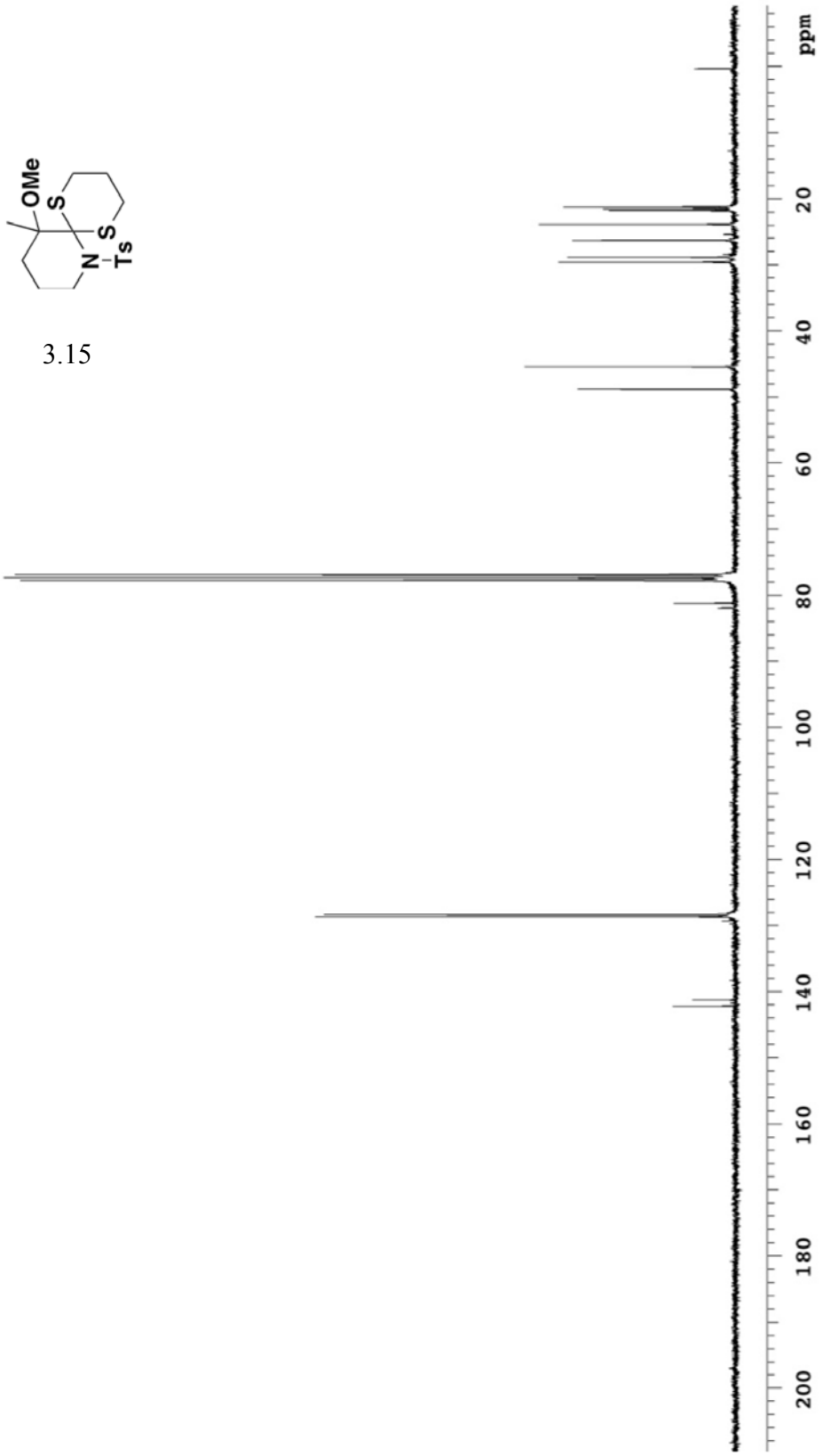

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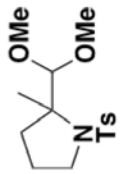

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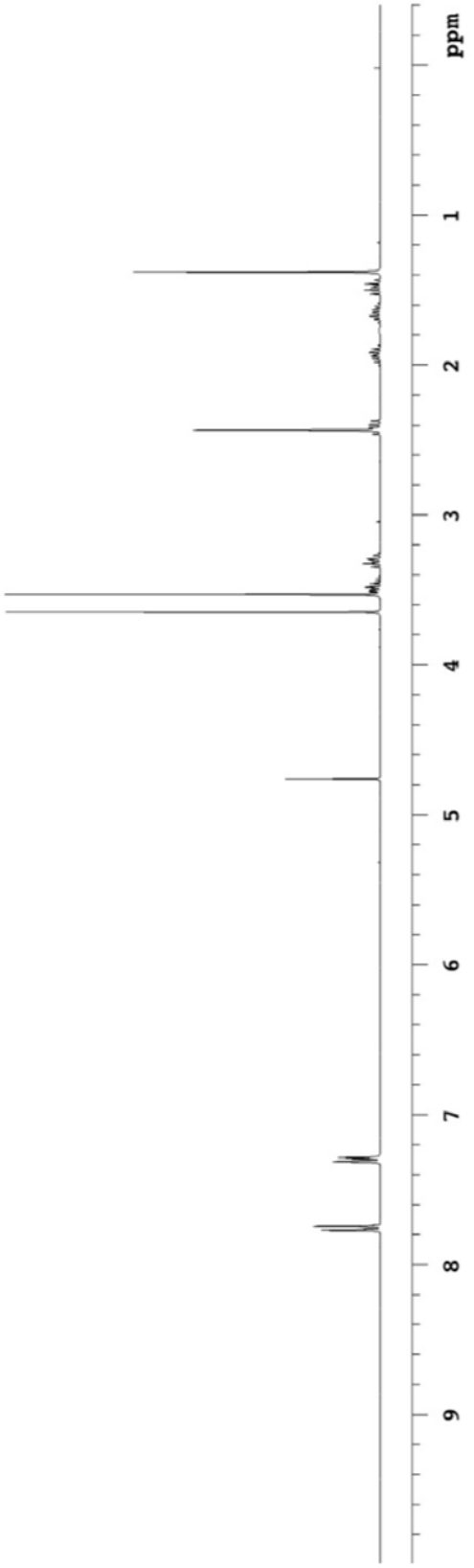

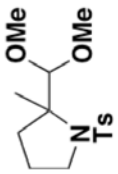

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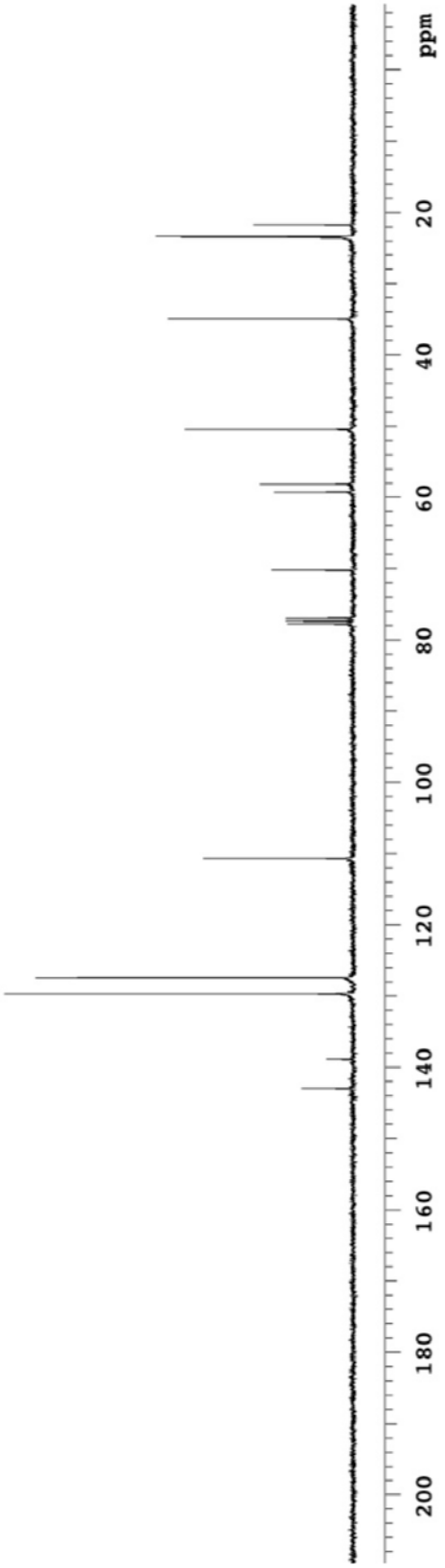

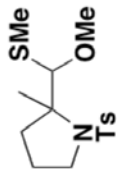

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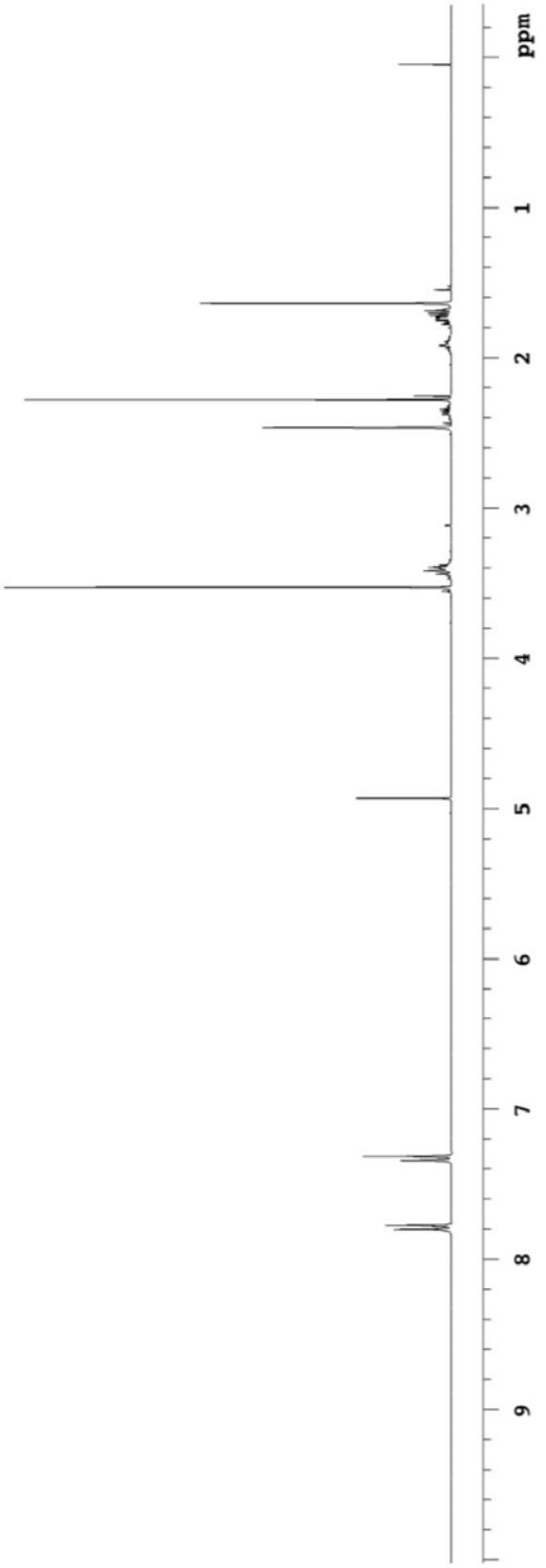

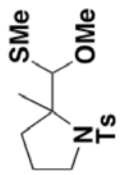

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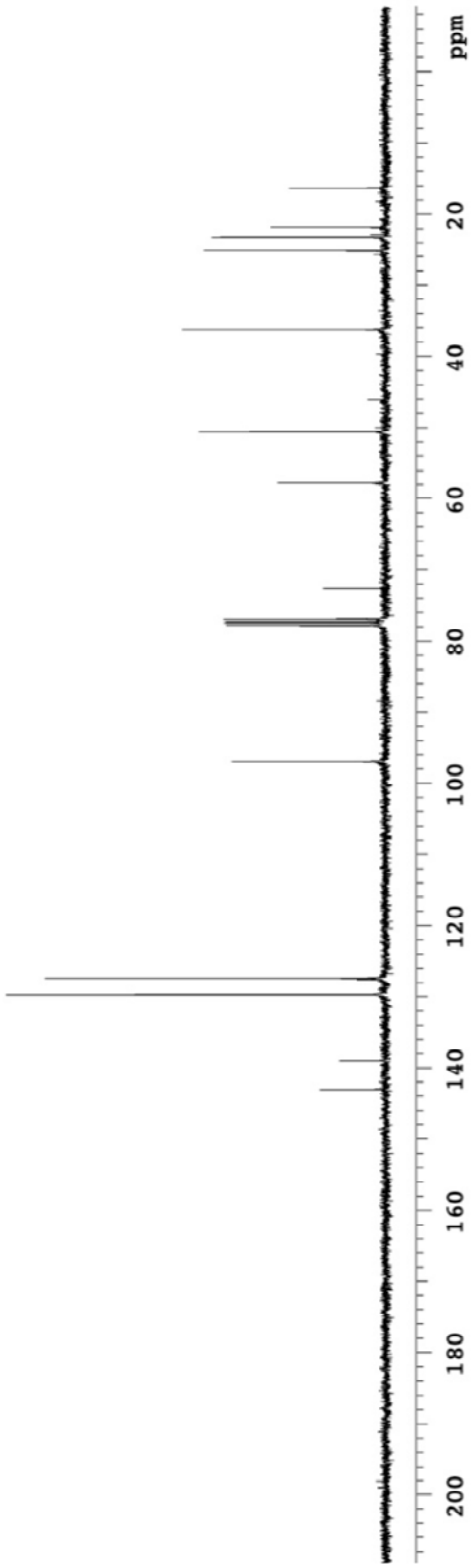

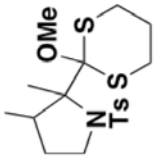

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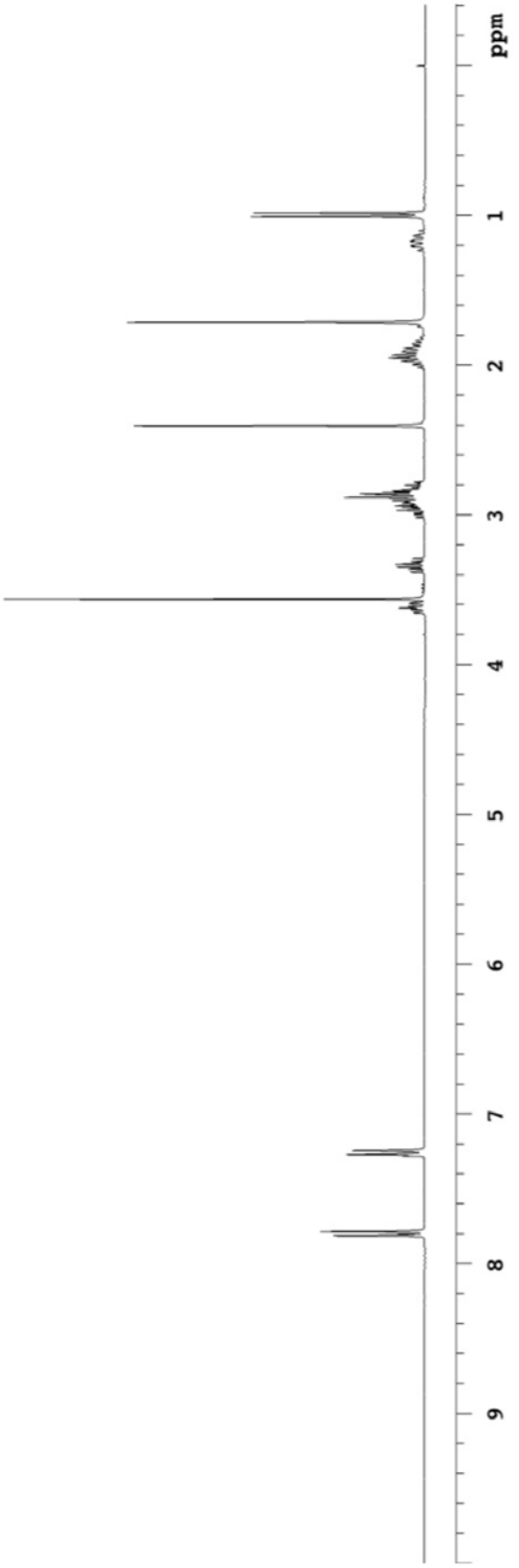

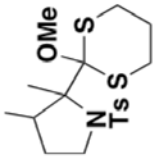

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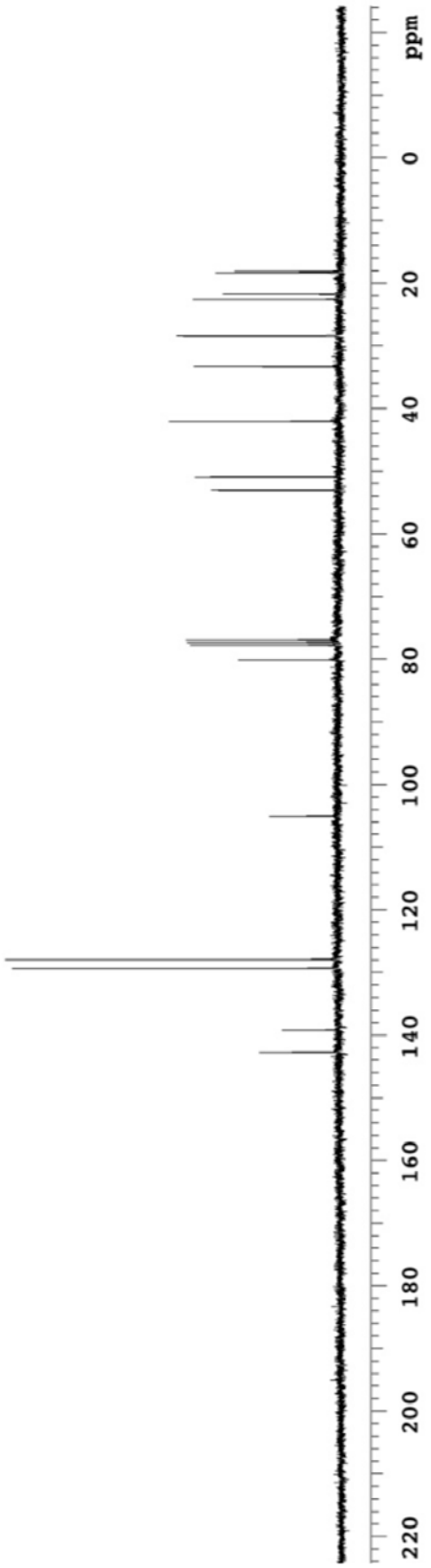

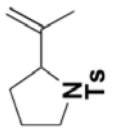

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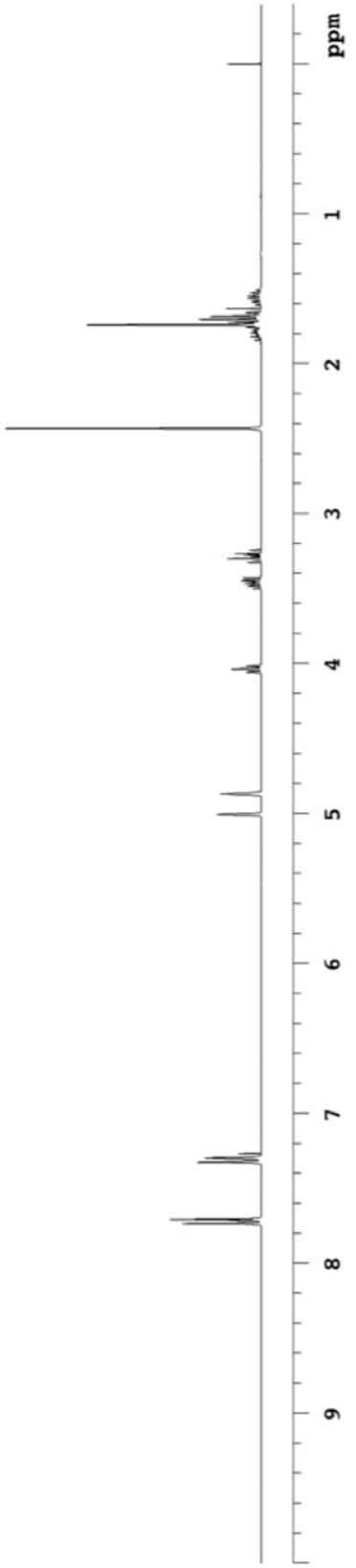

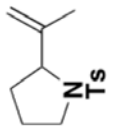

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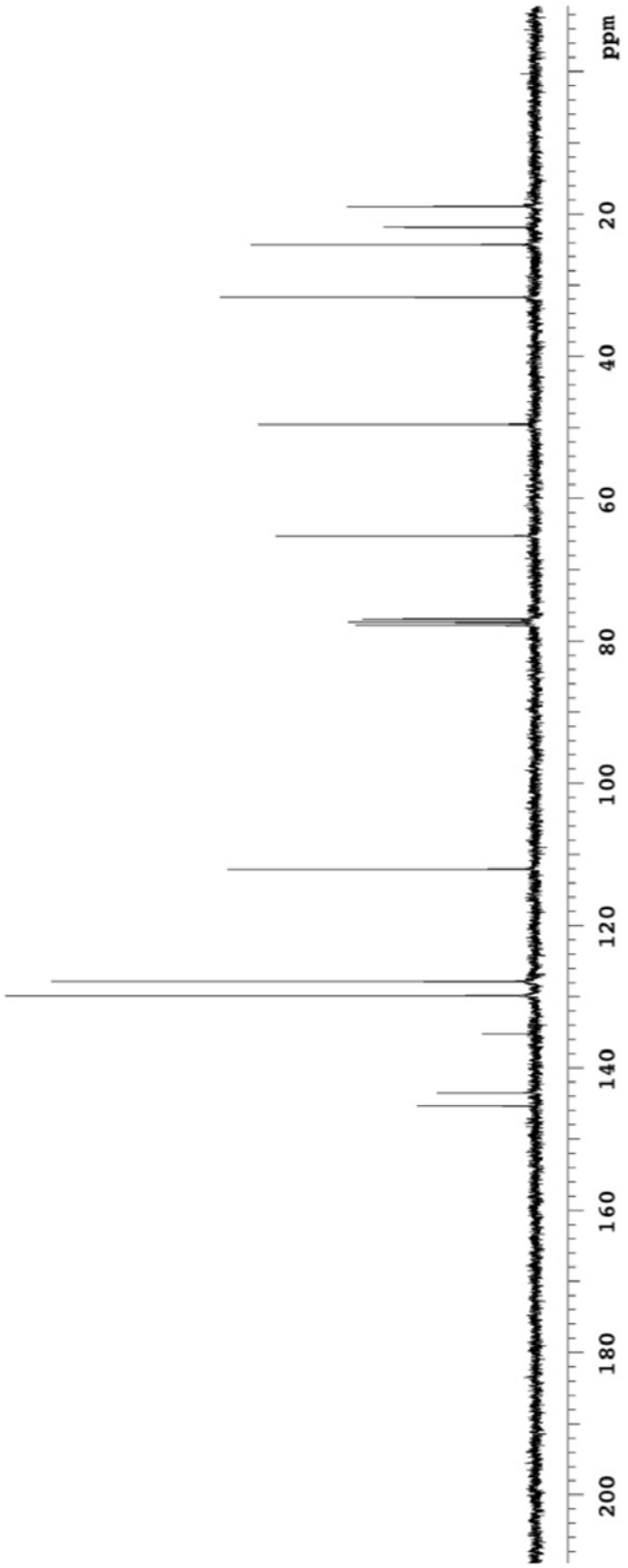

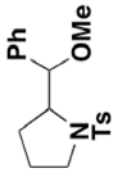

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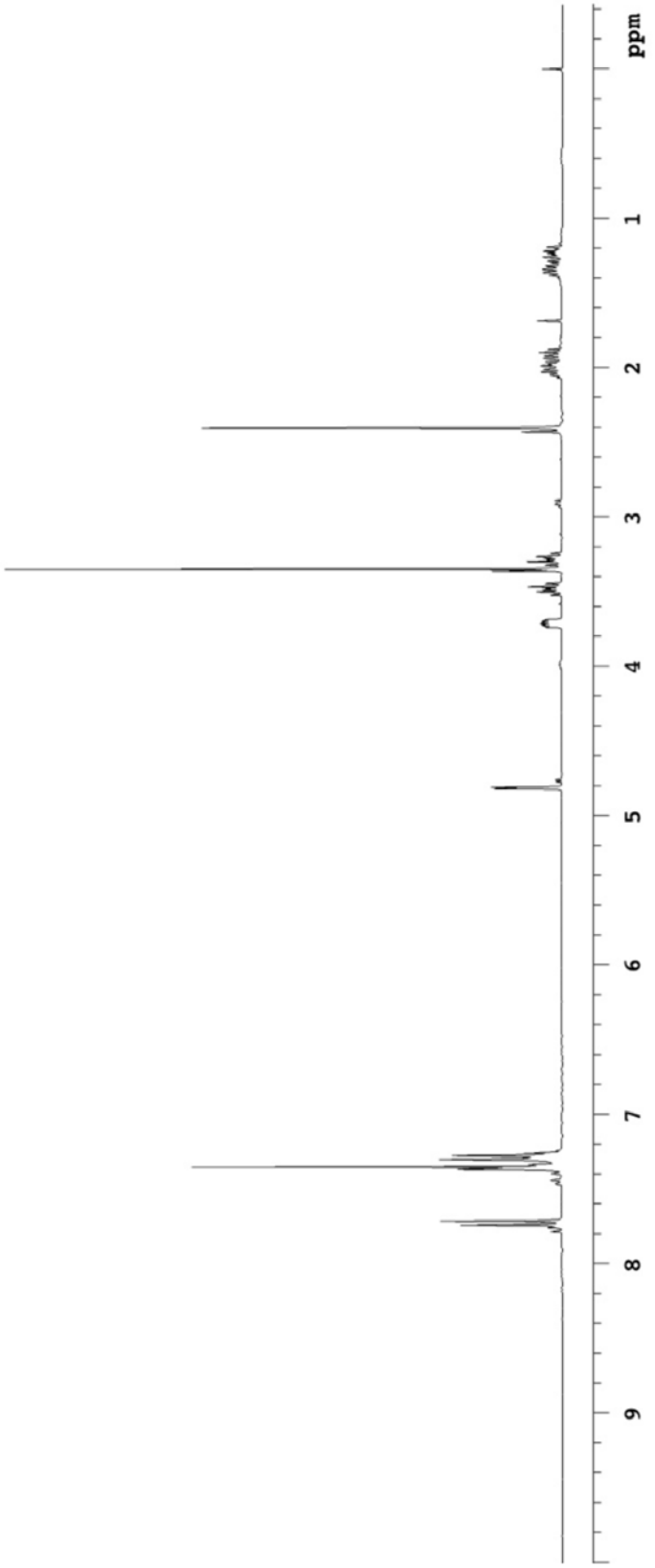

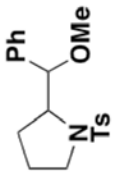

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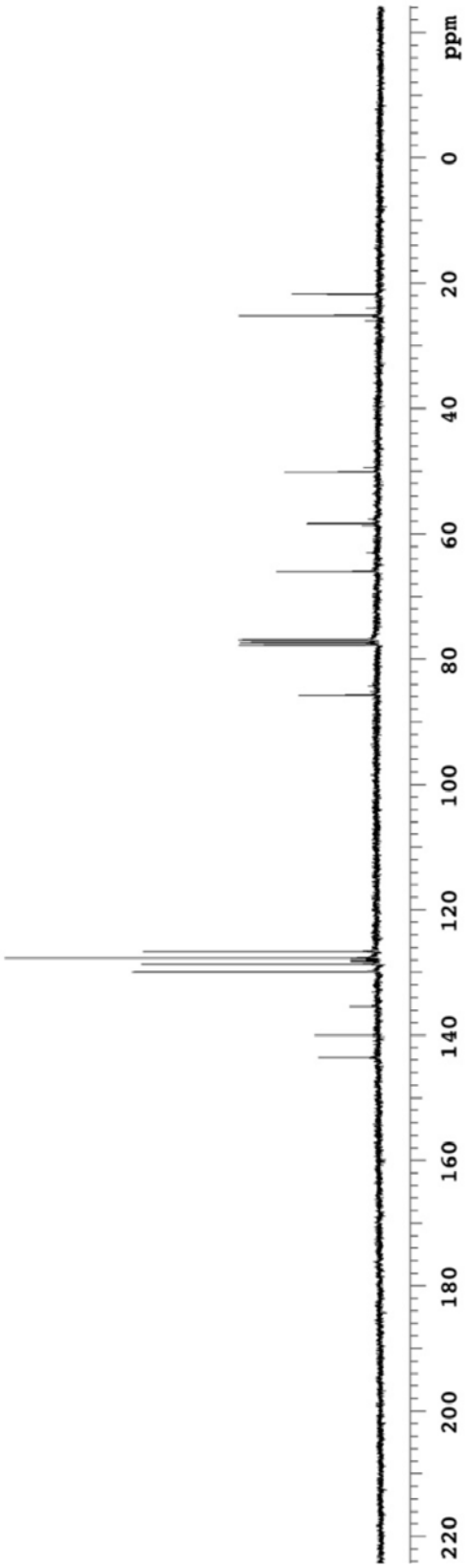

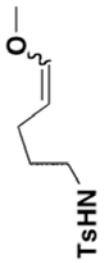

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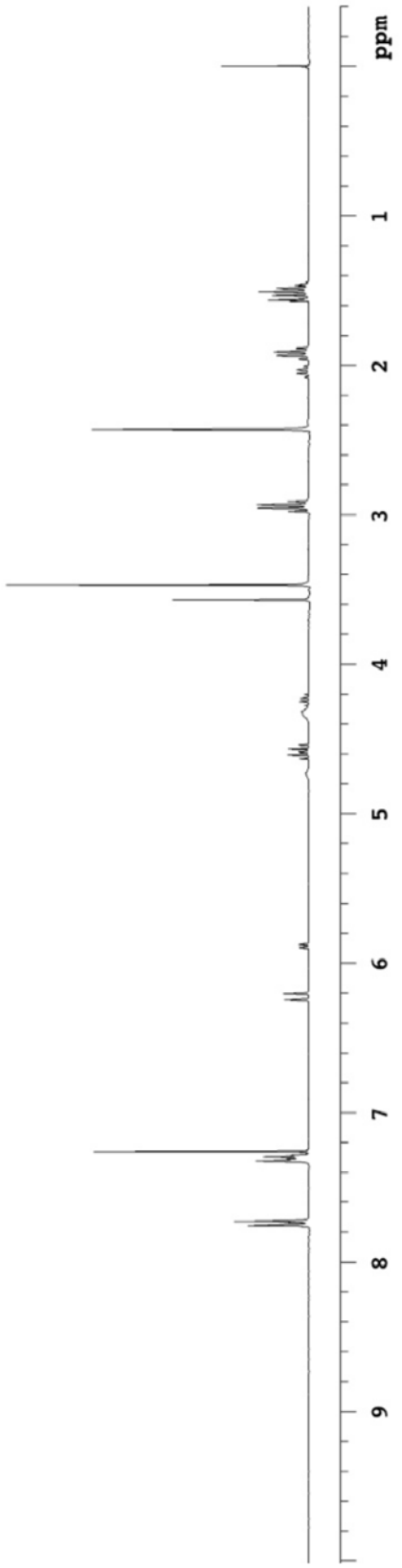

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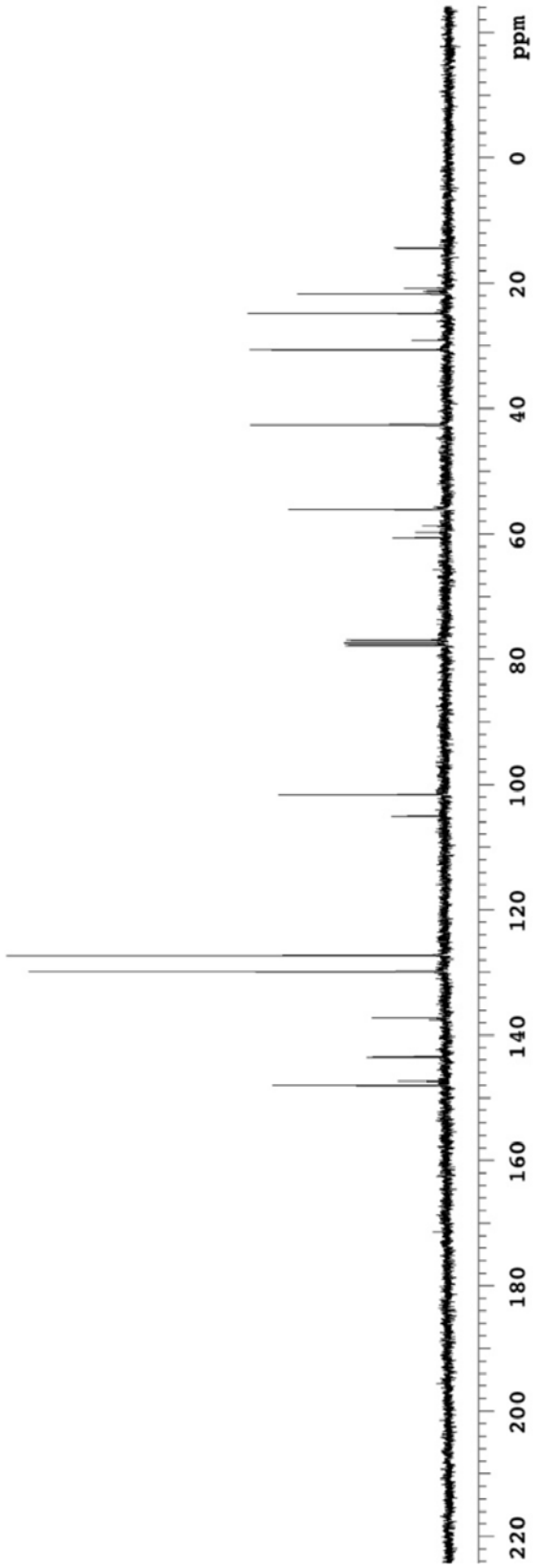

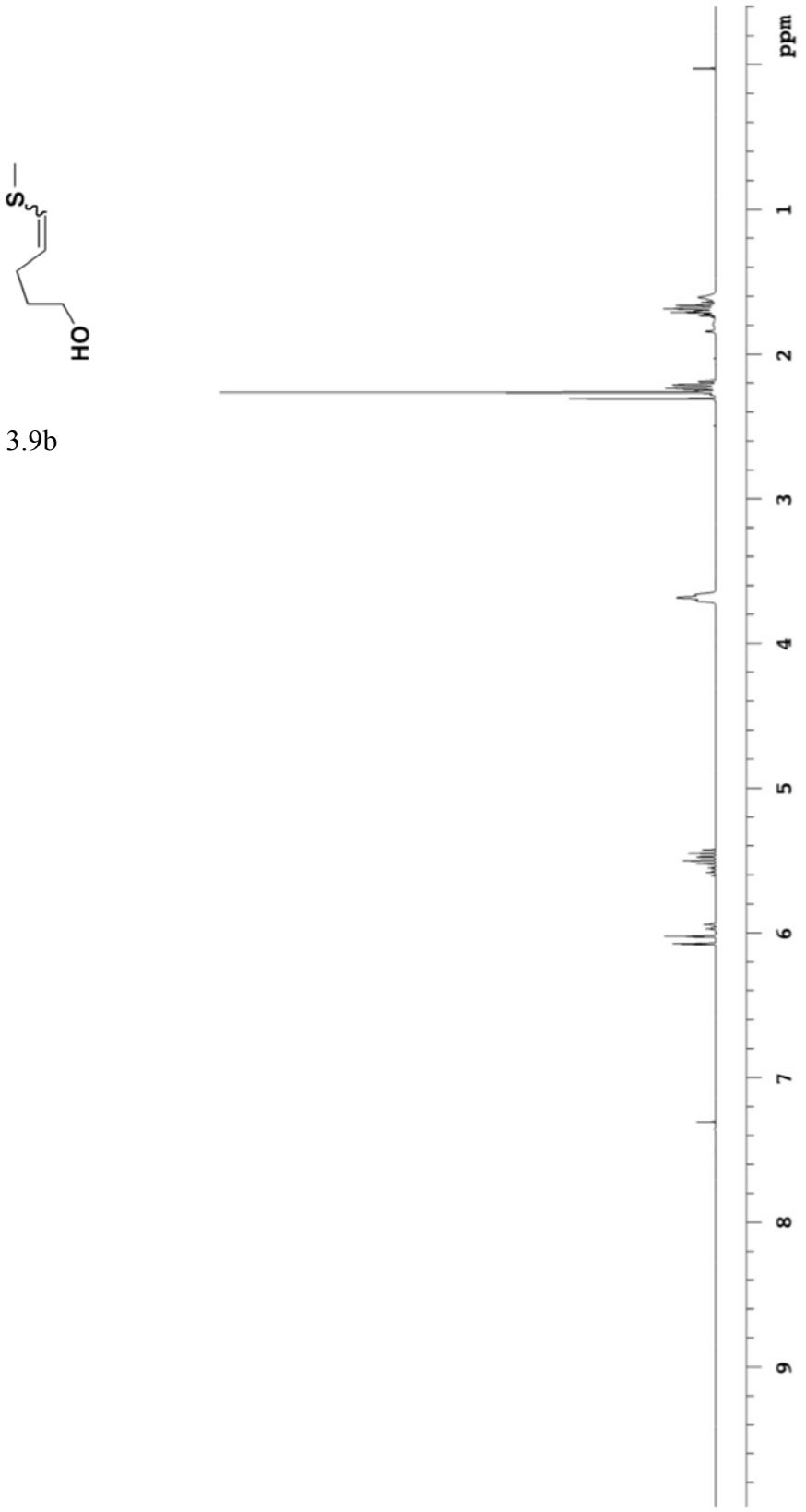

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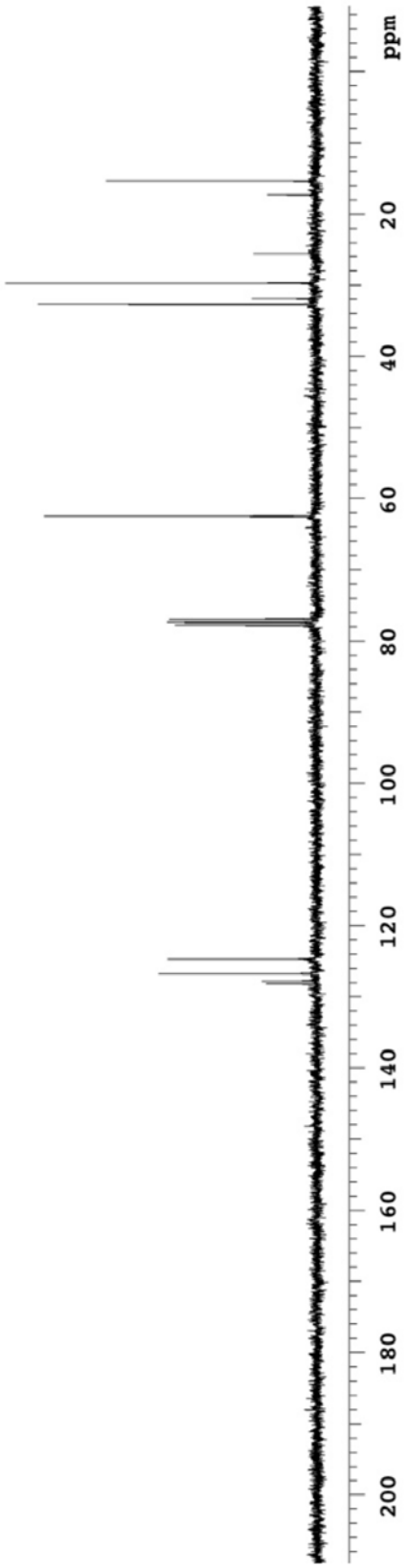
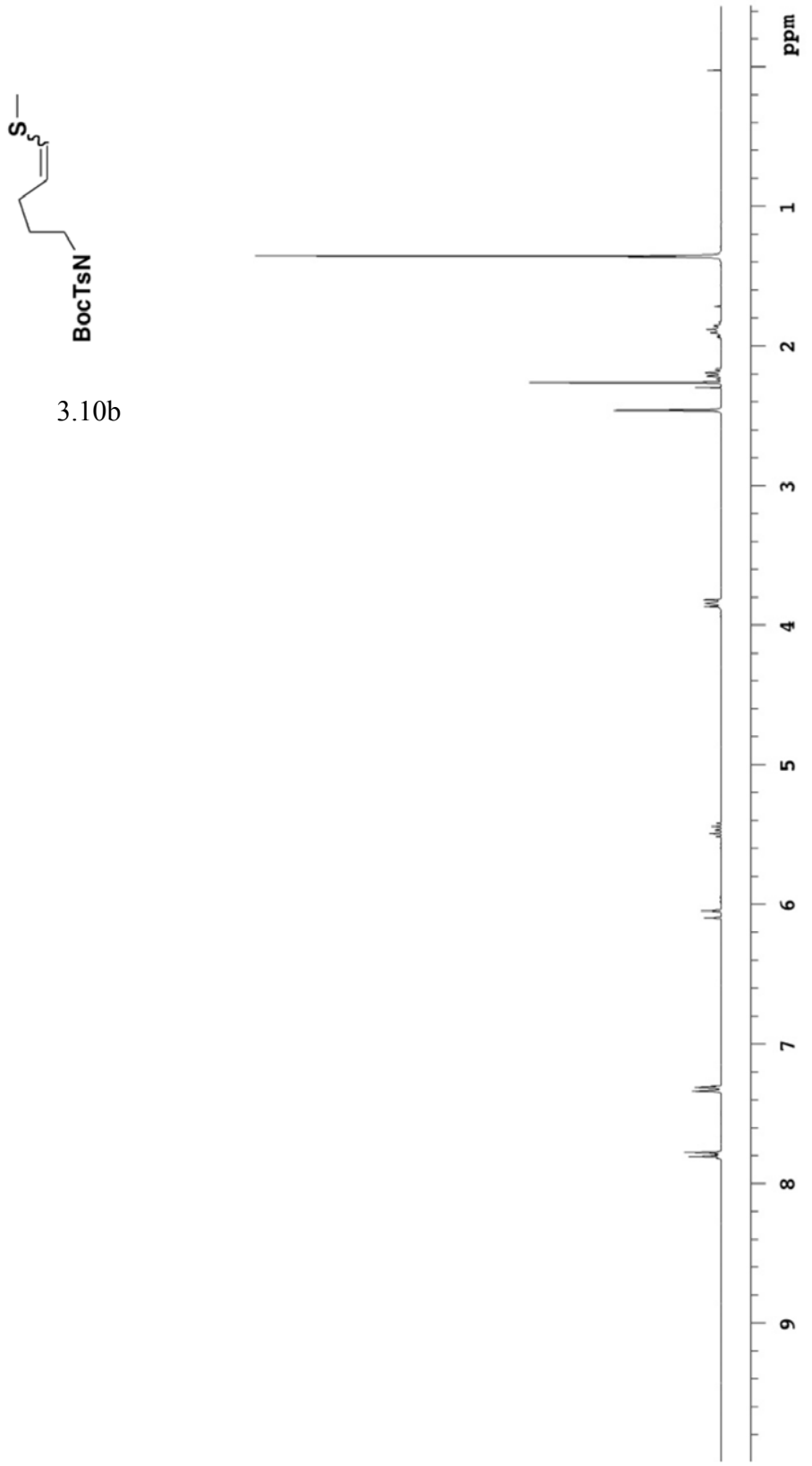
3.9b





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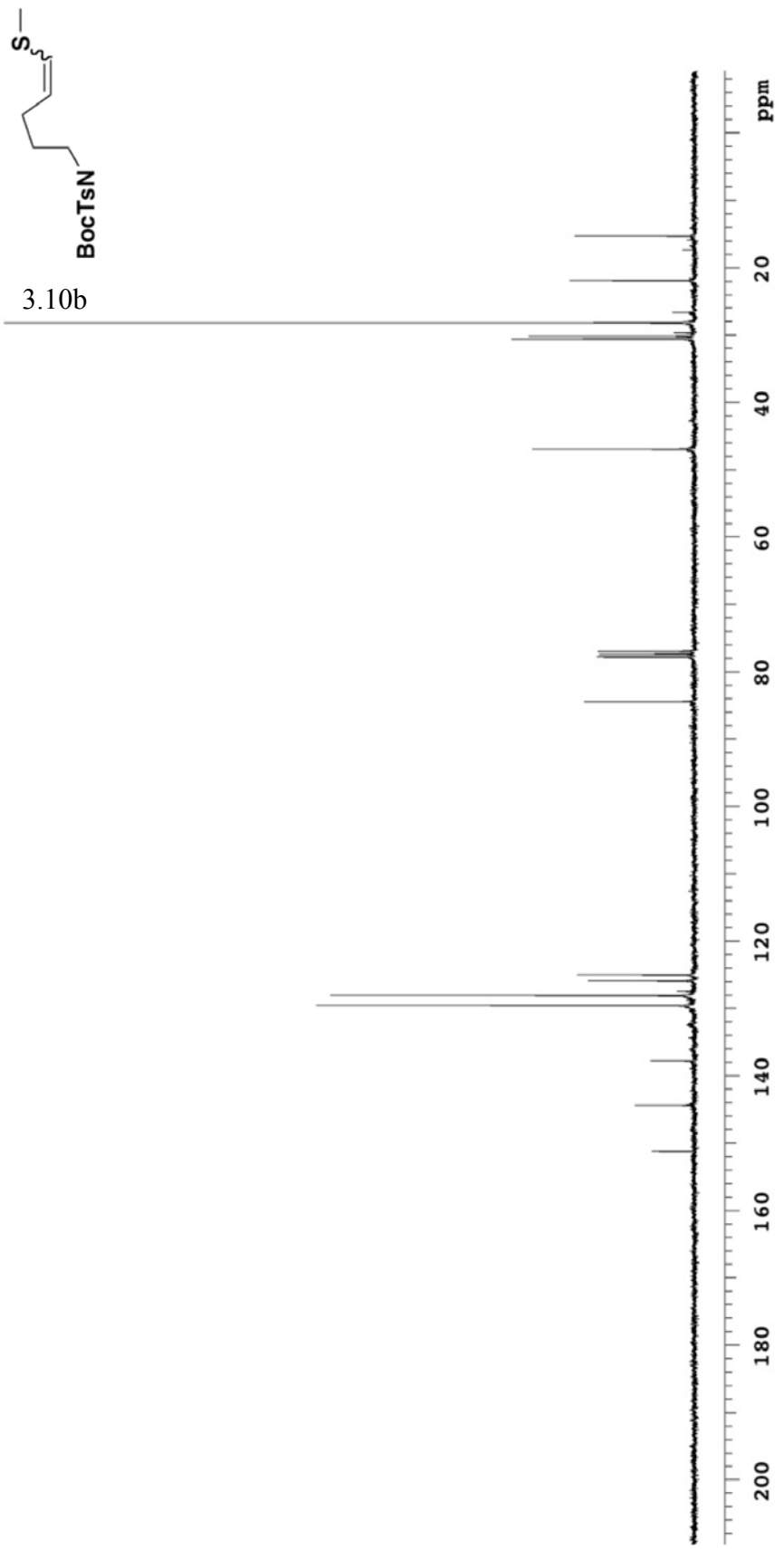
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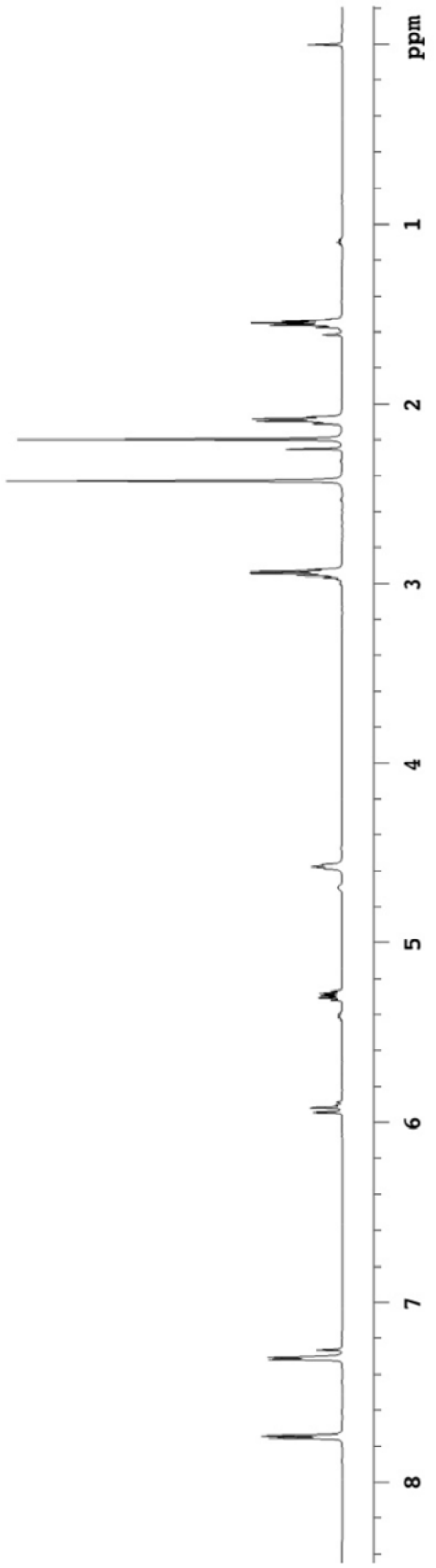

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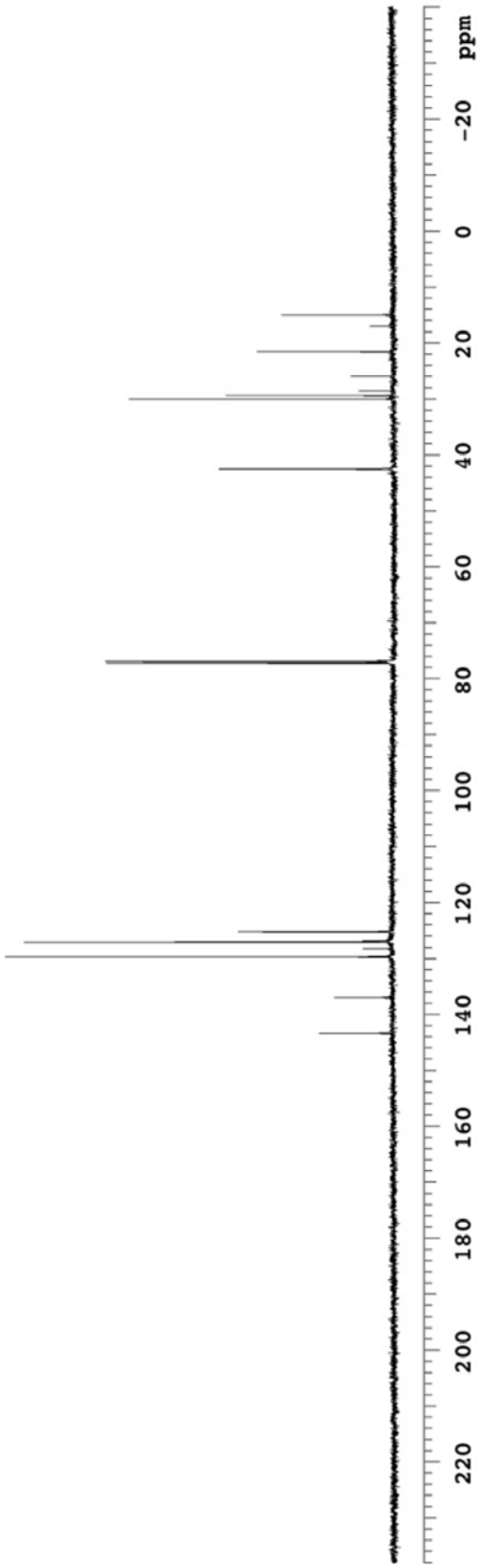

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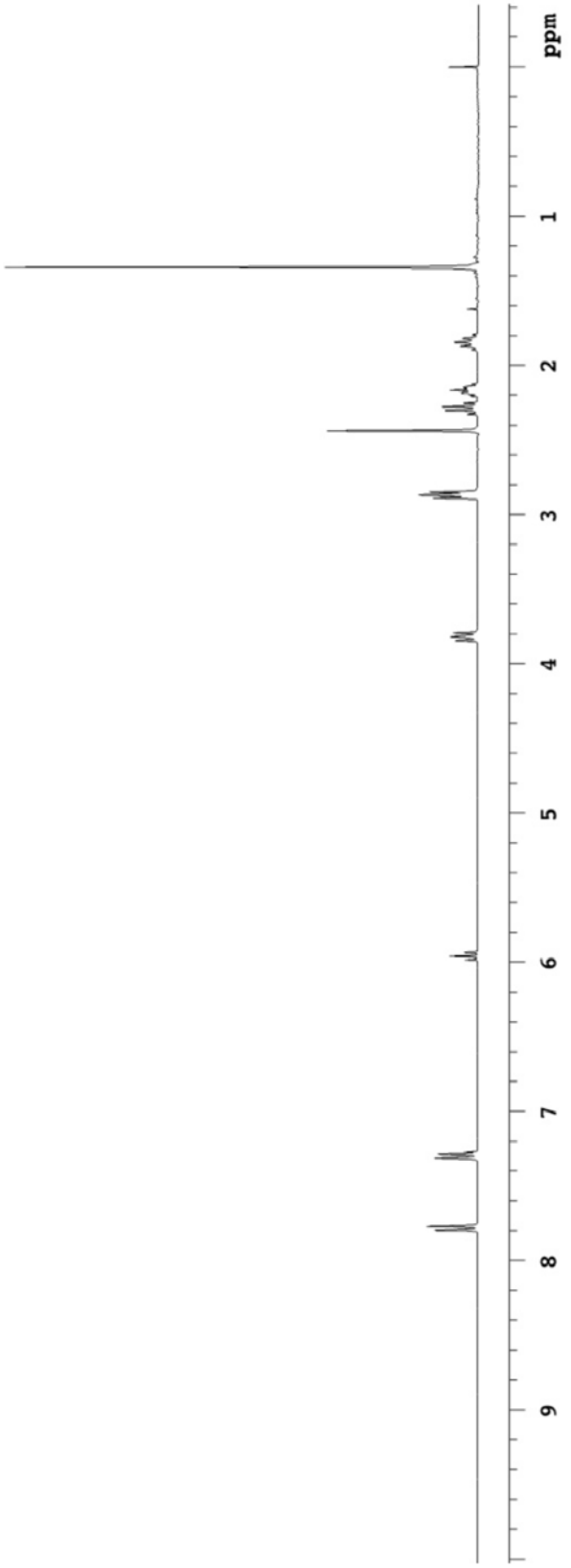

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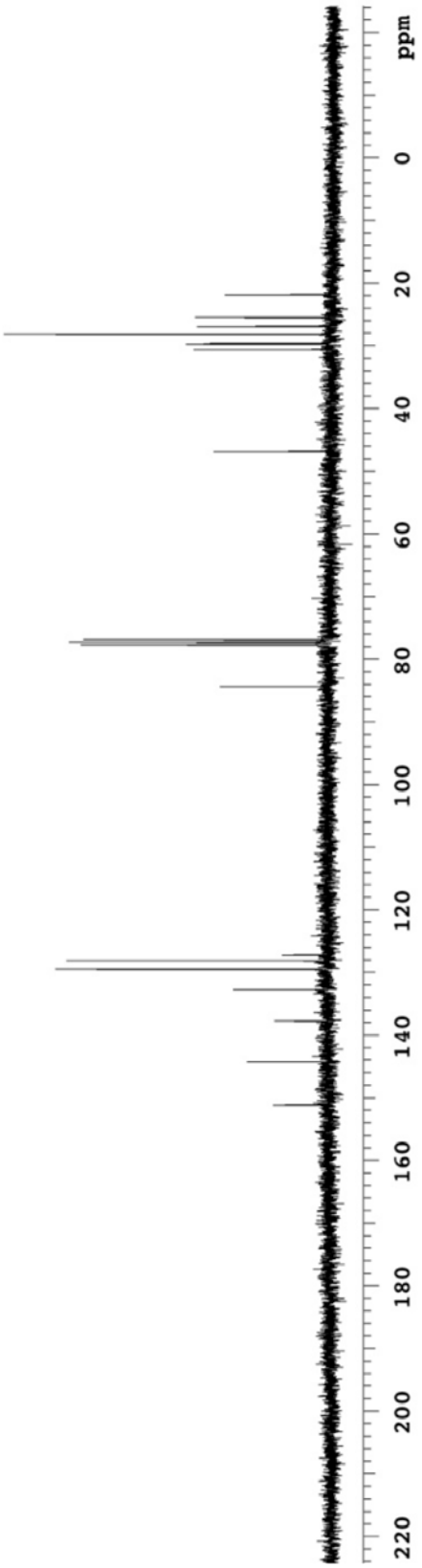

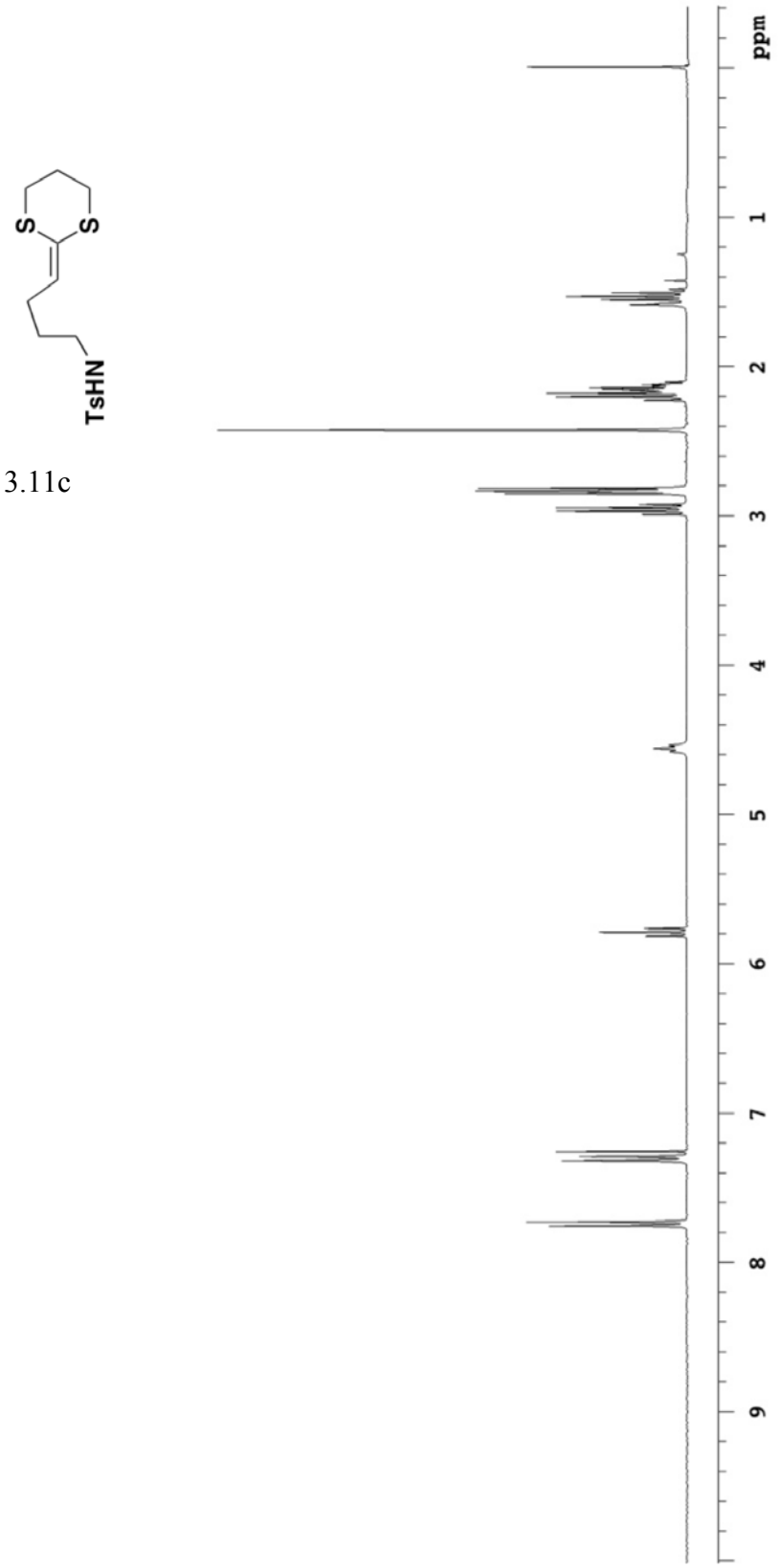

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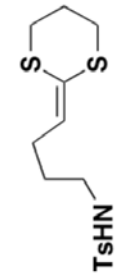

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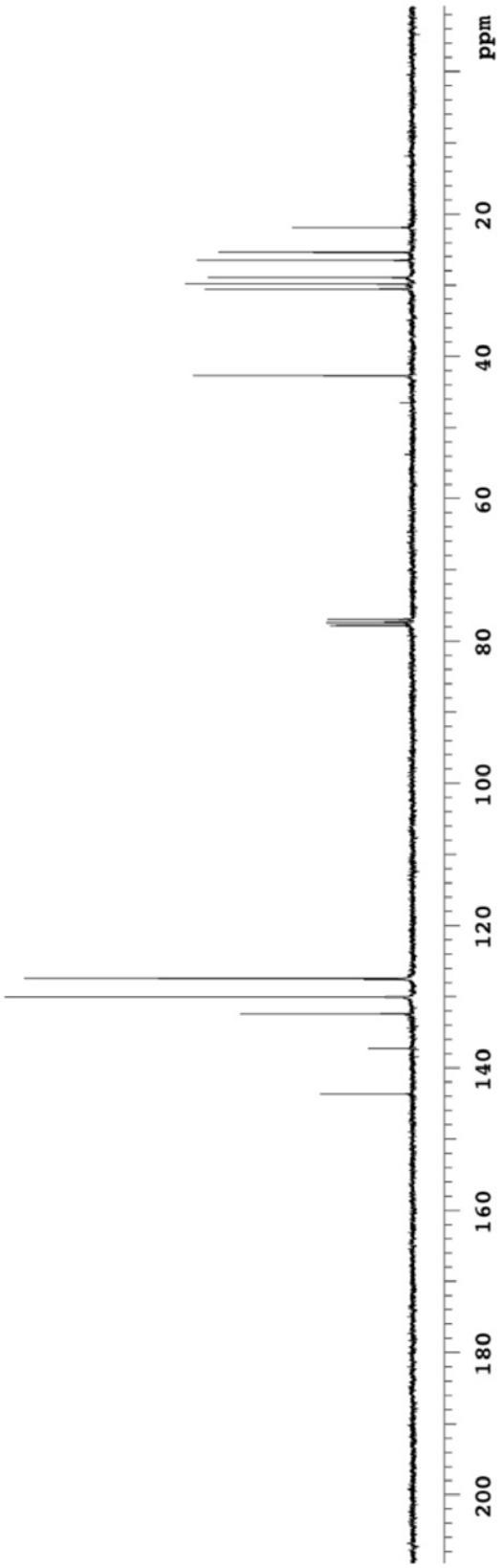

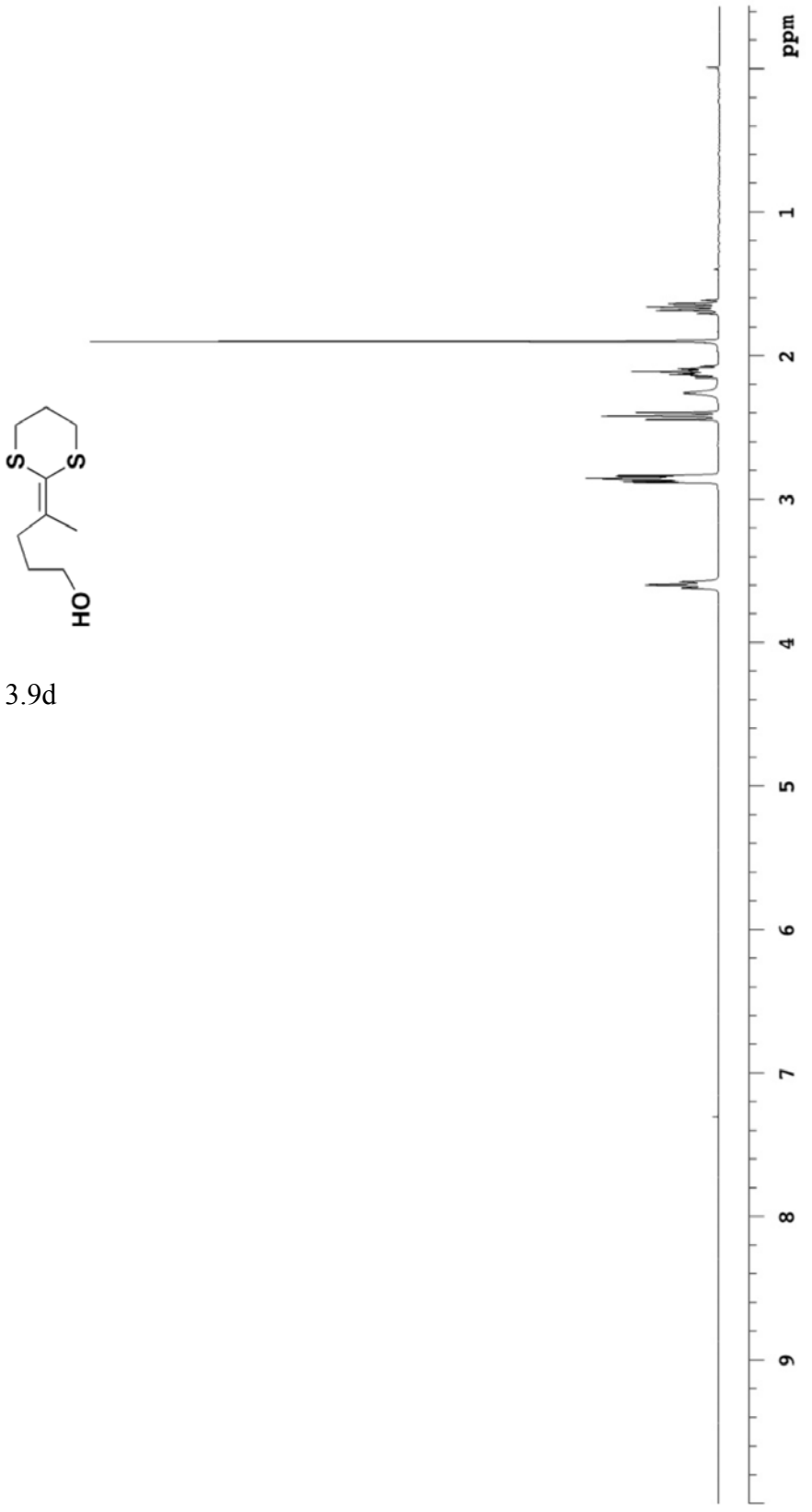

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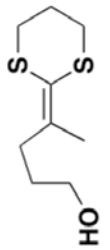

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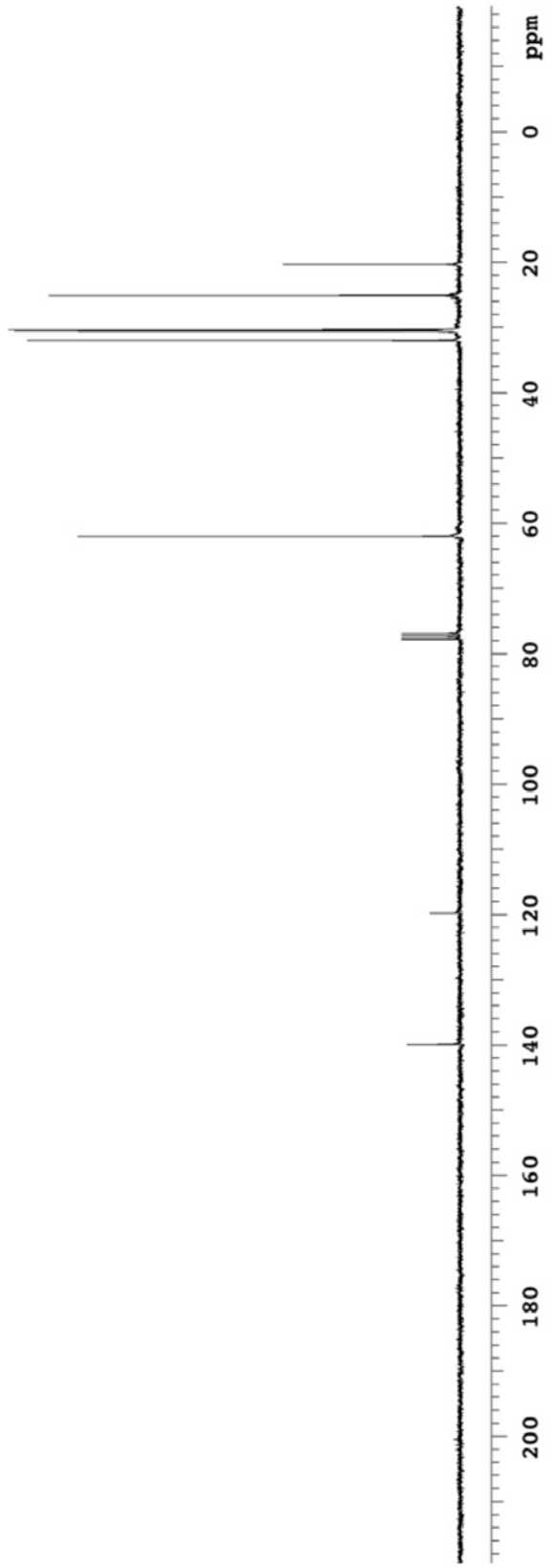

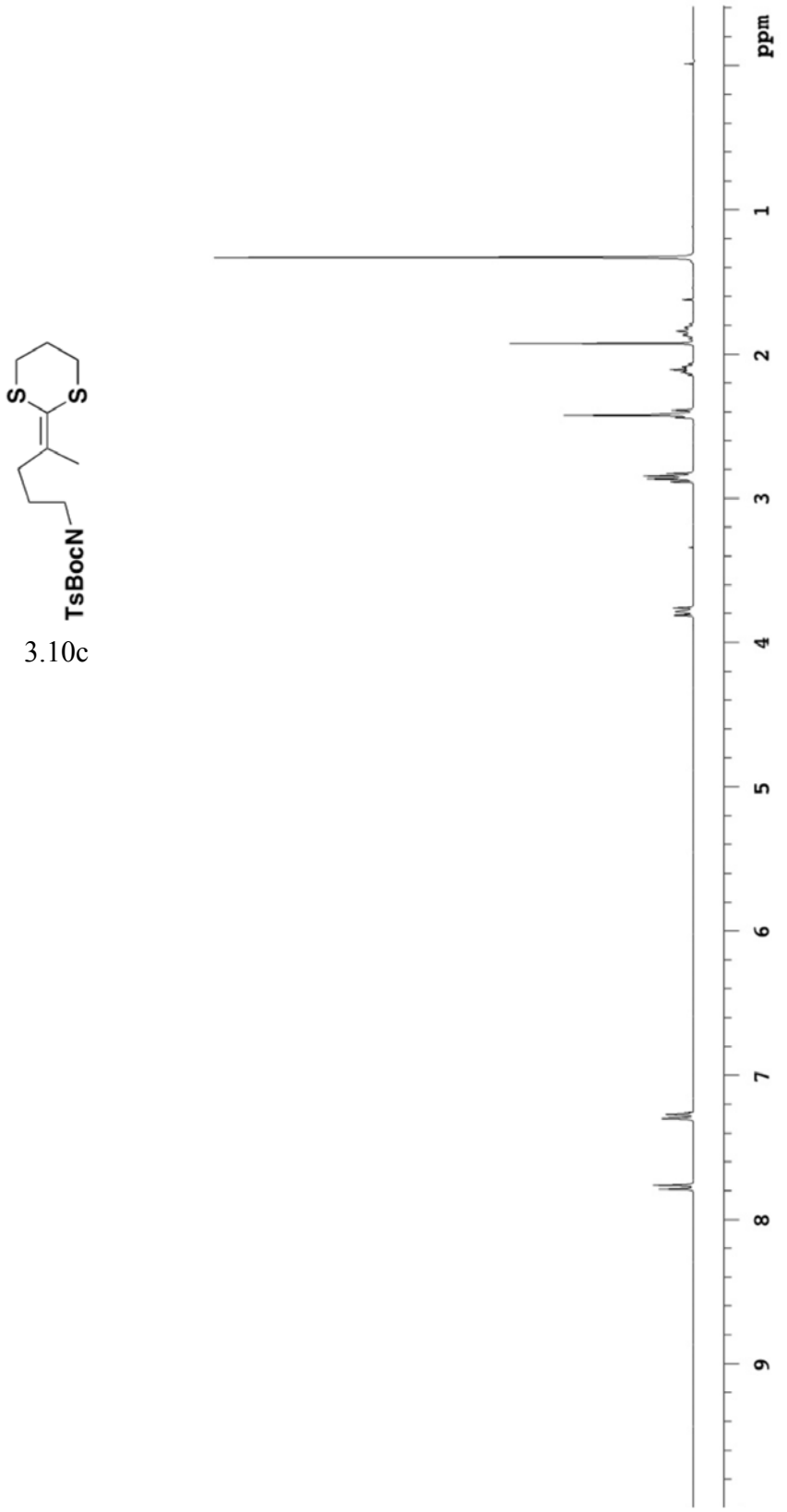

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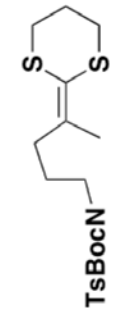

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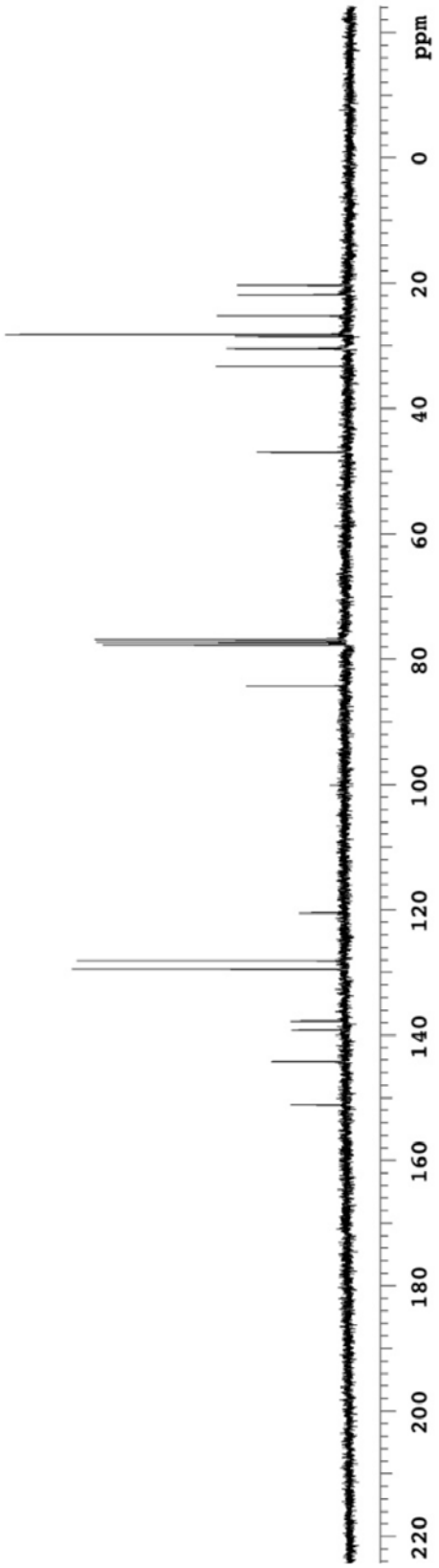

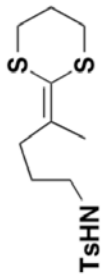

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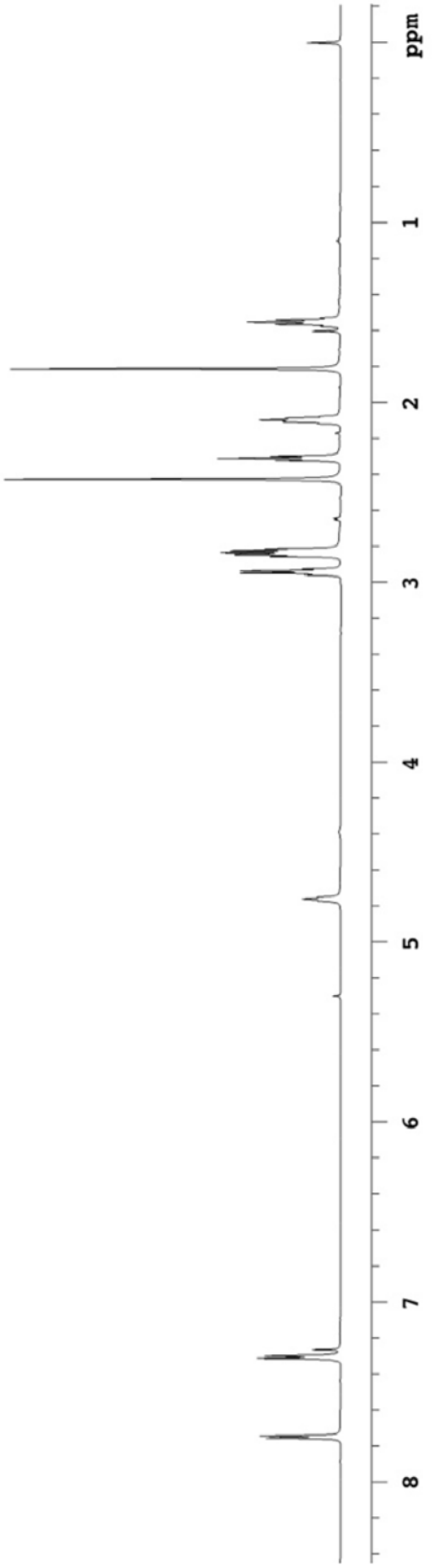

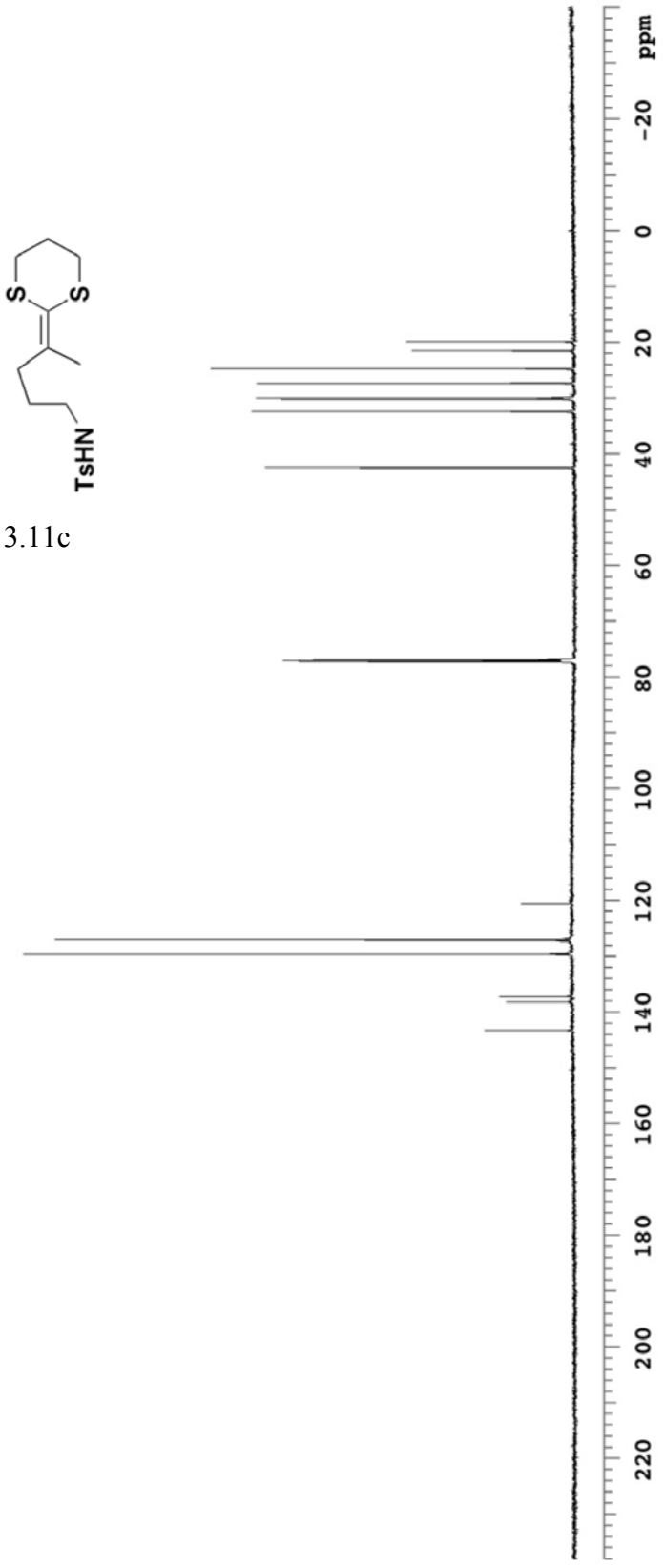

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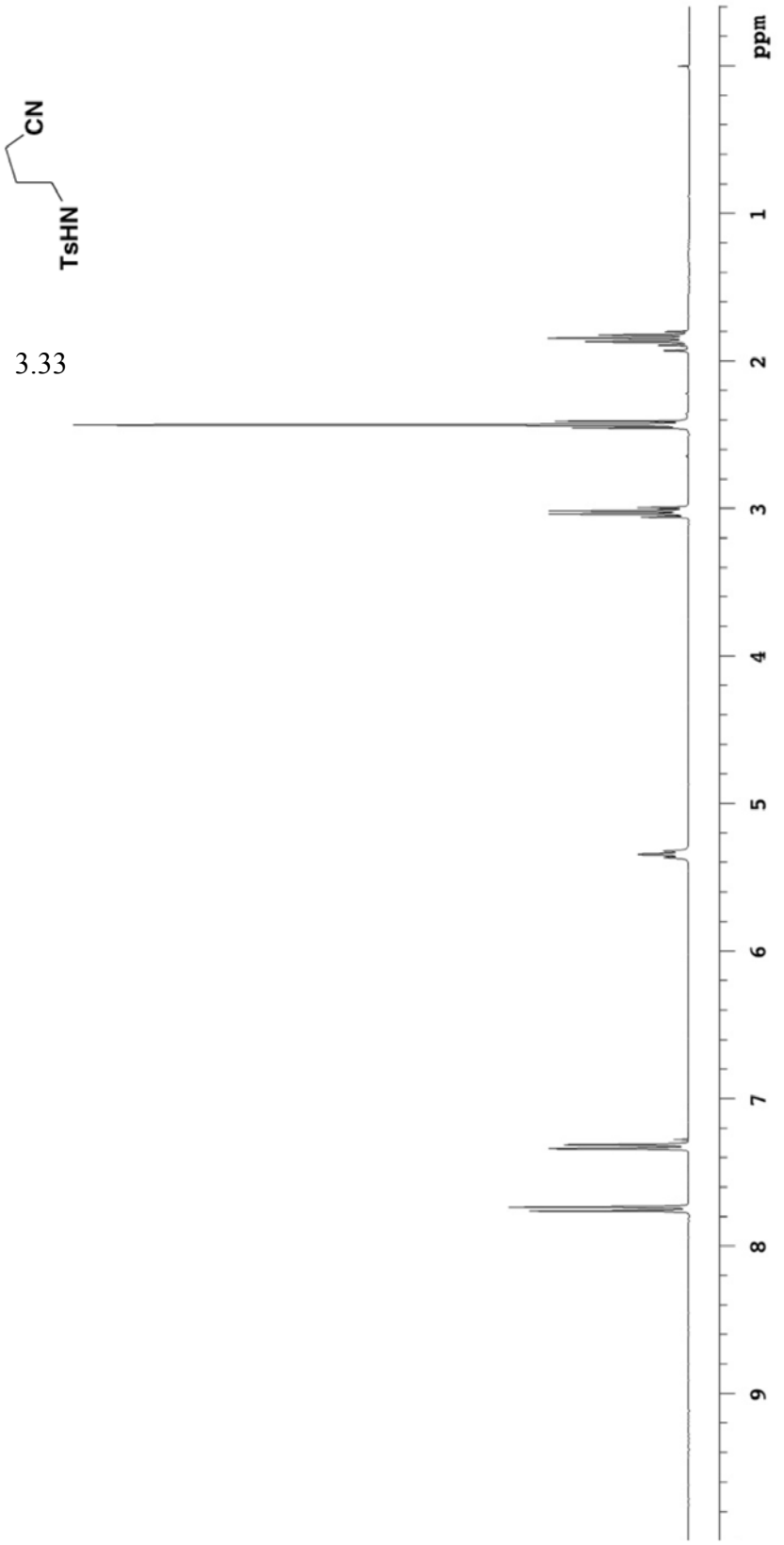
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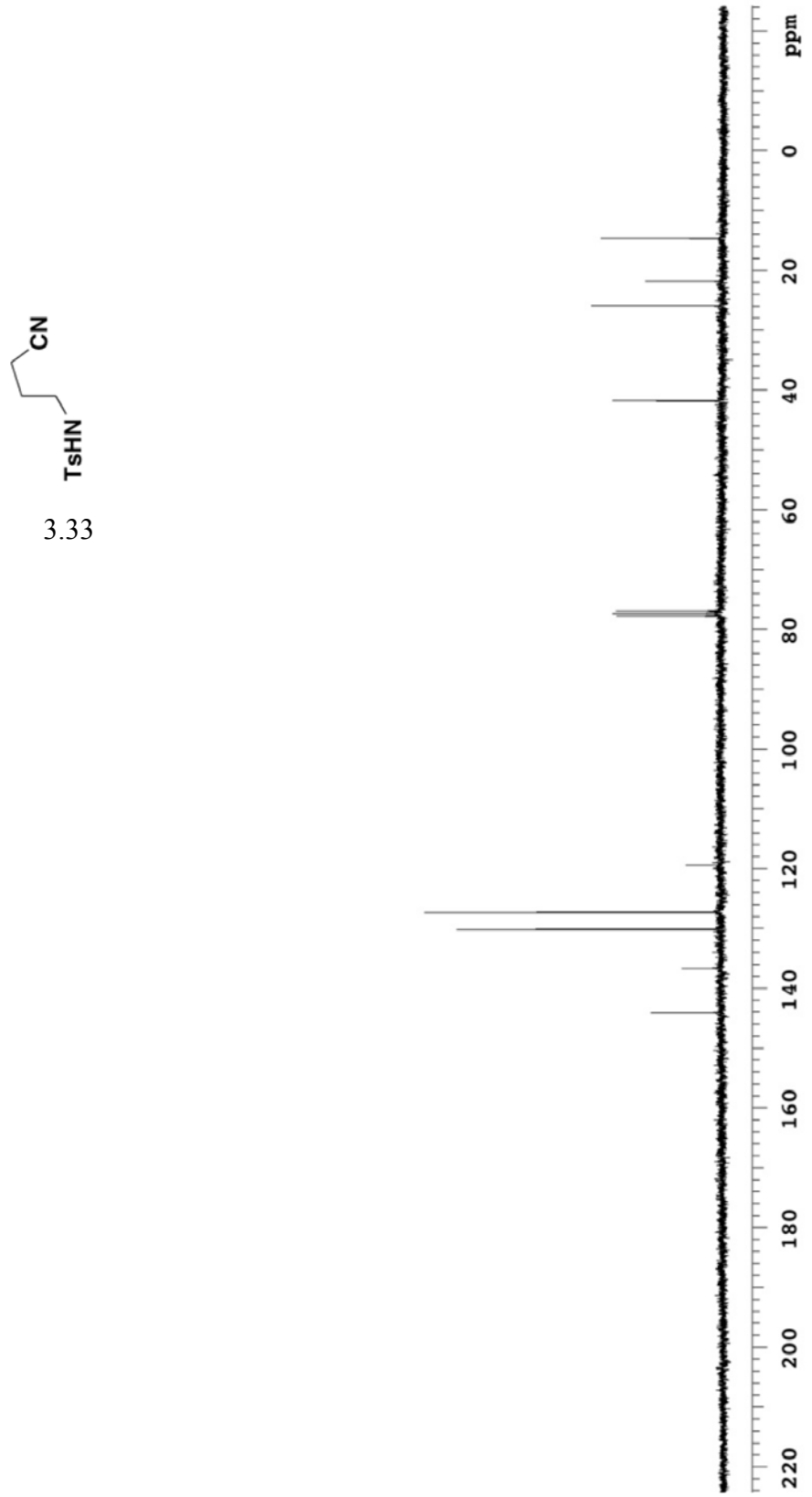

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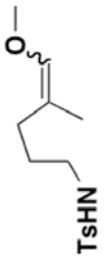

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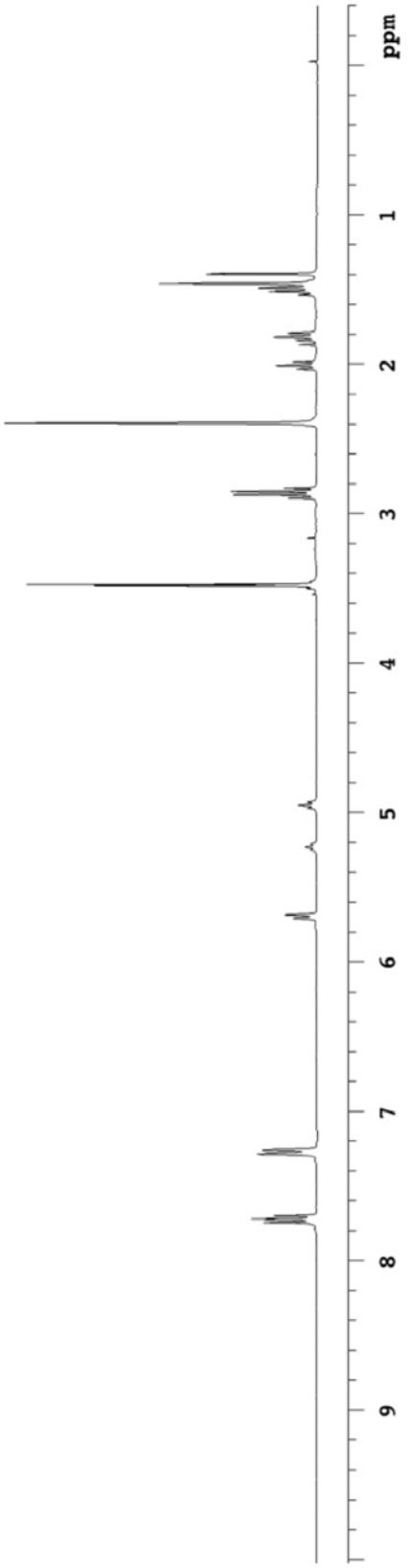

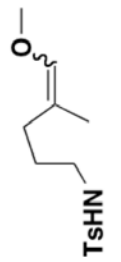

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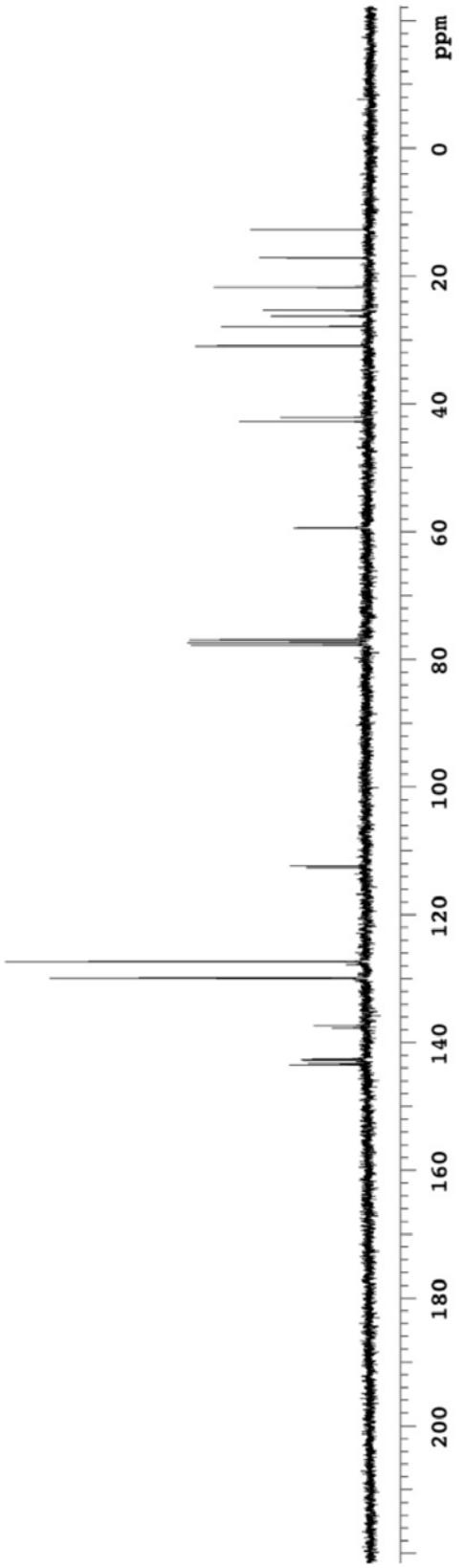

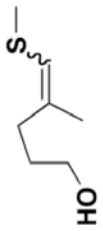

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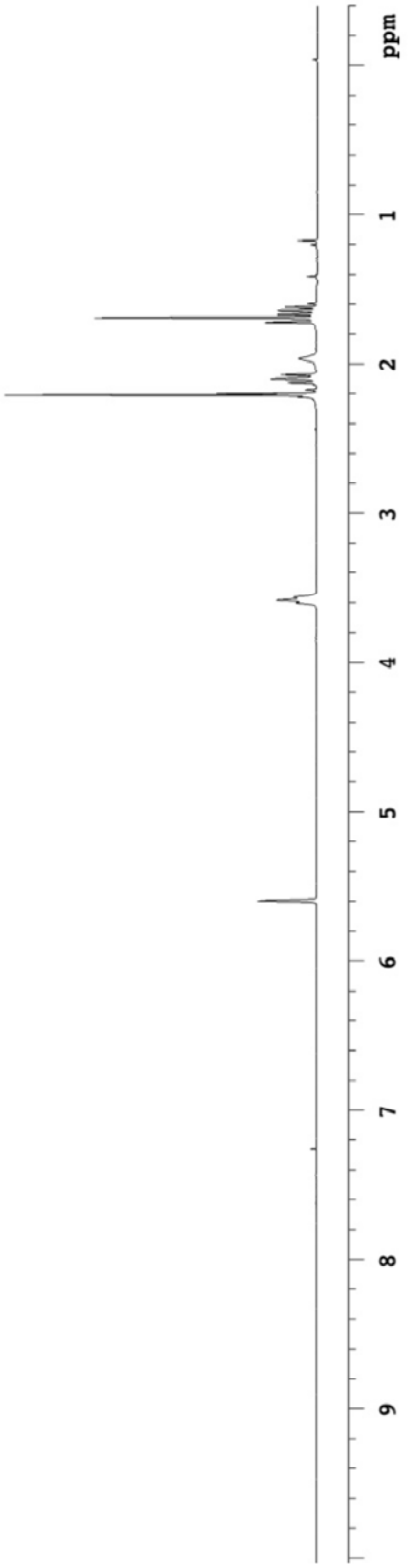

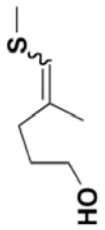

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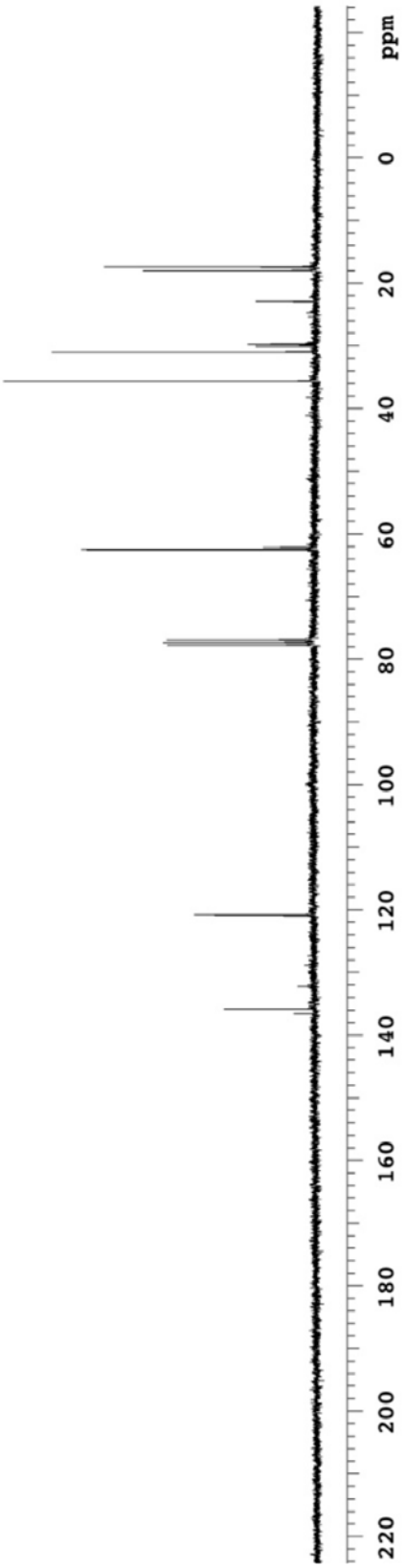

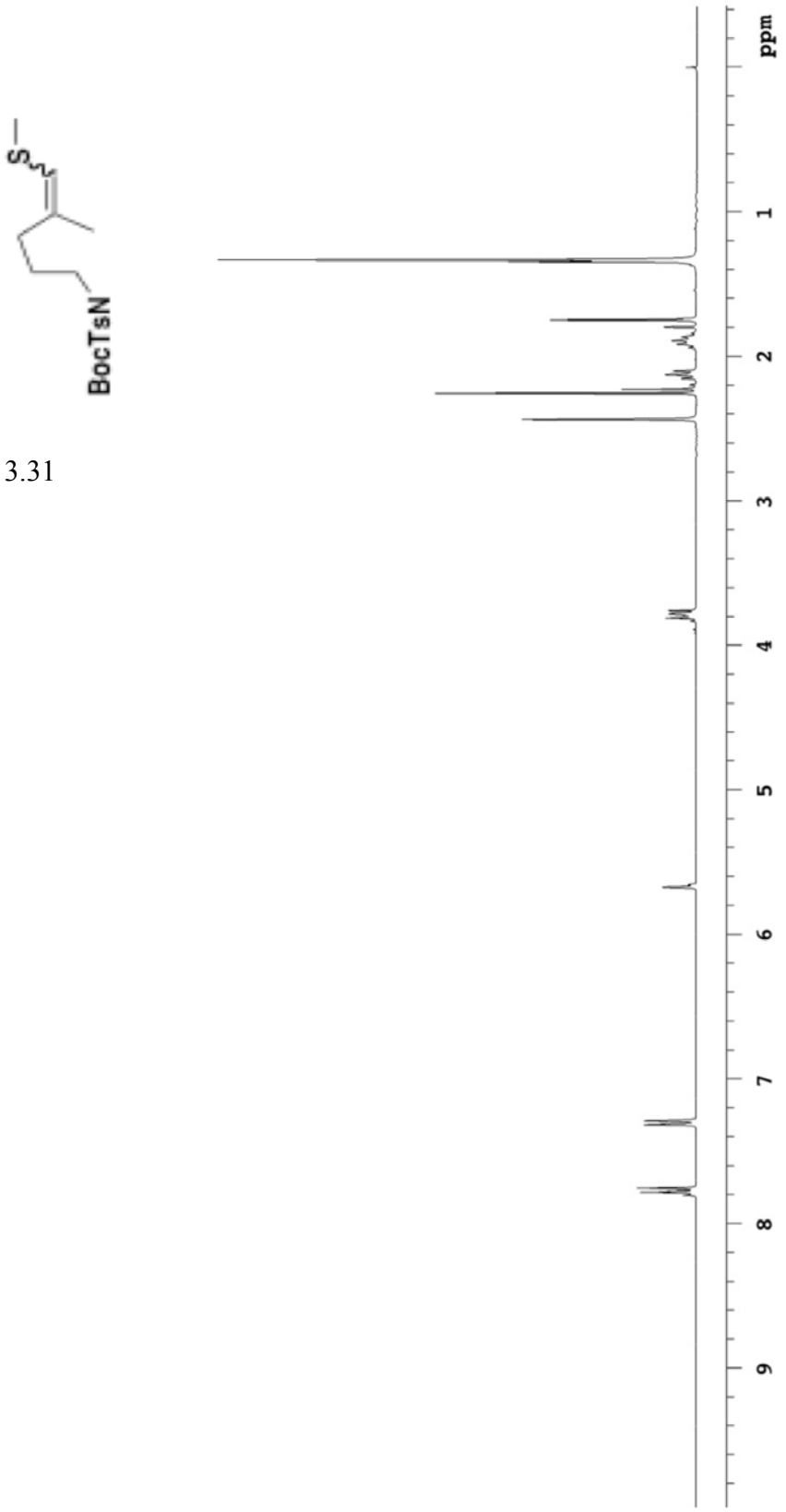

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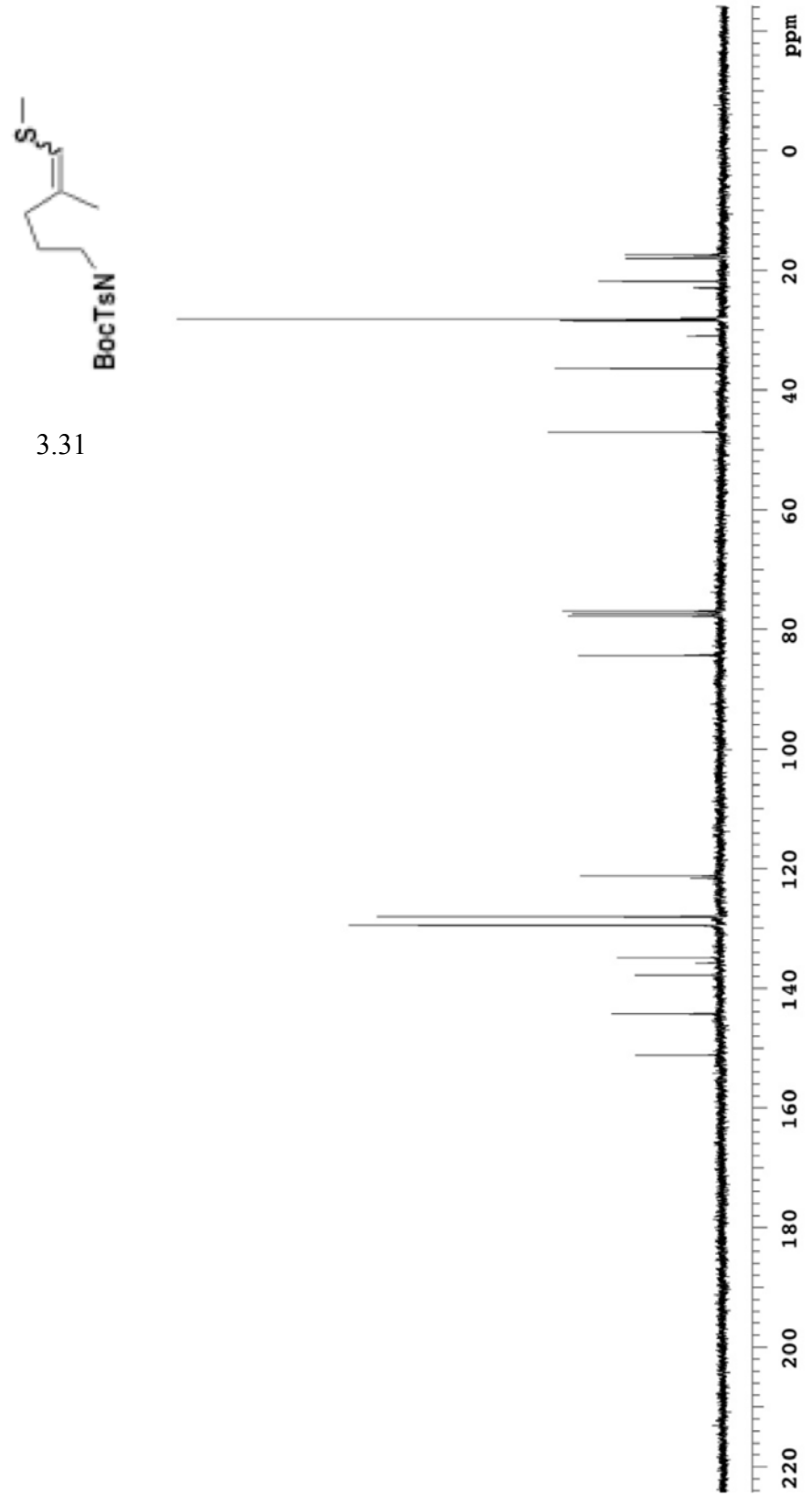

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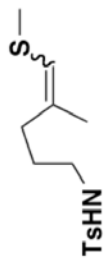

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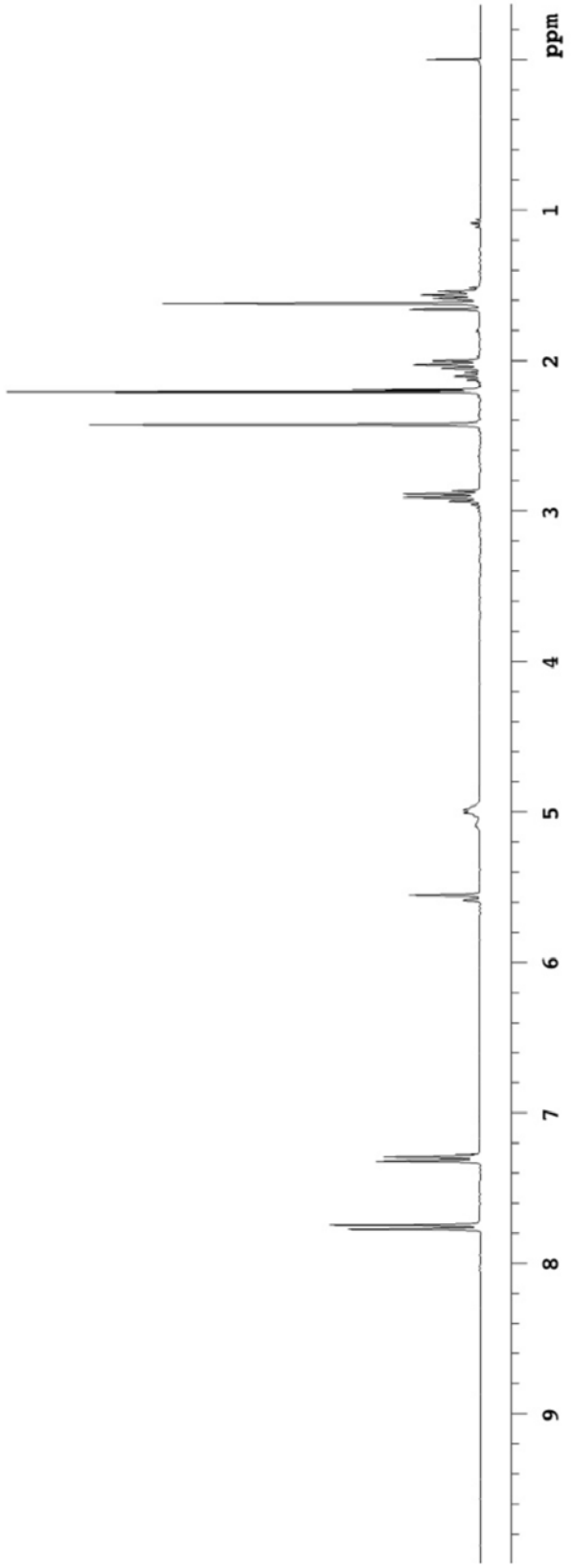

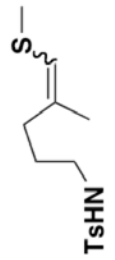

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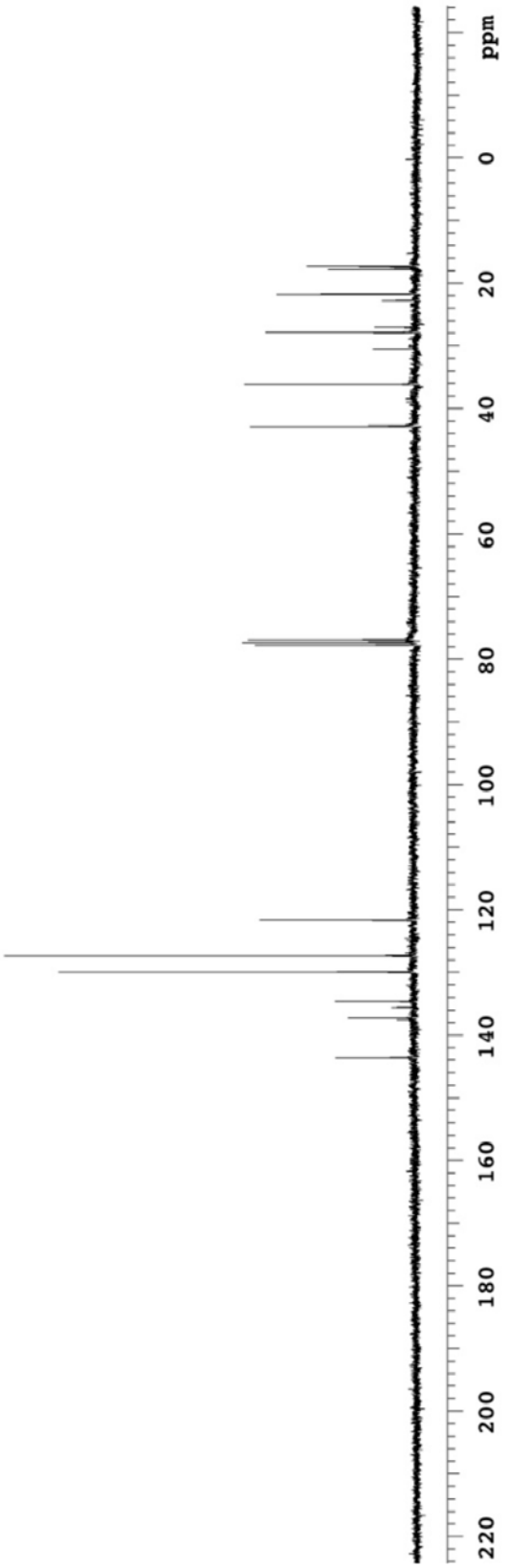

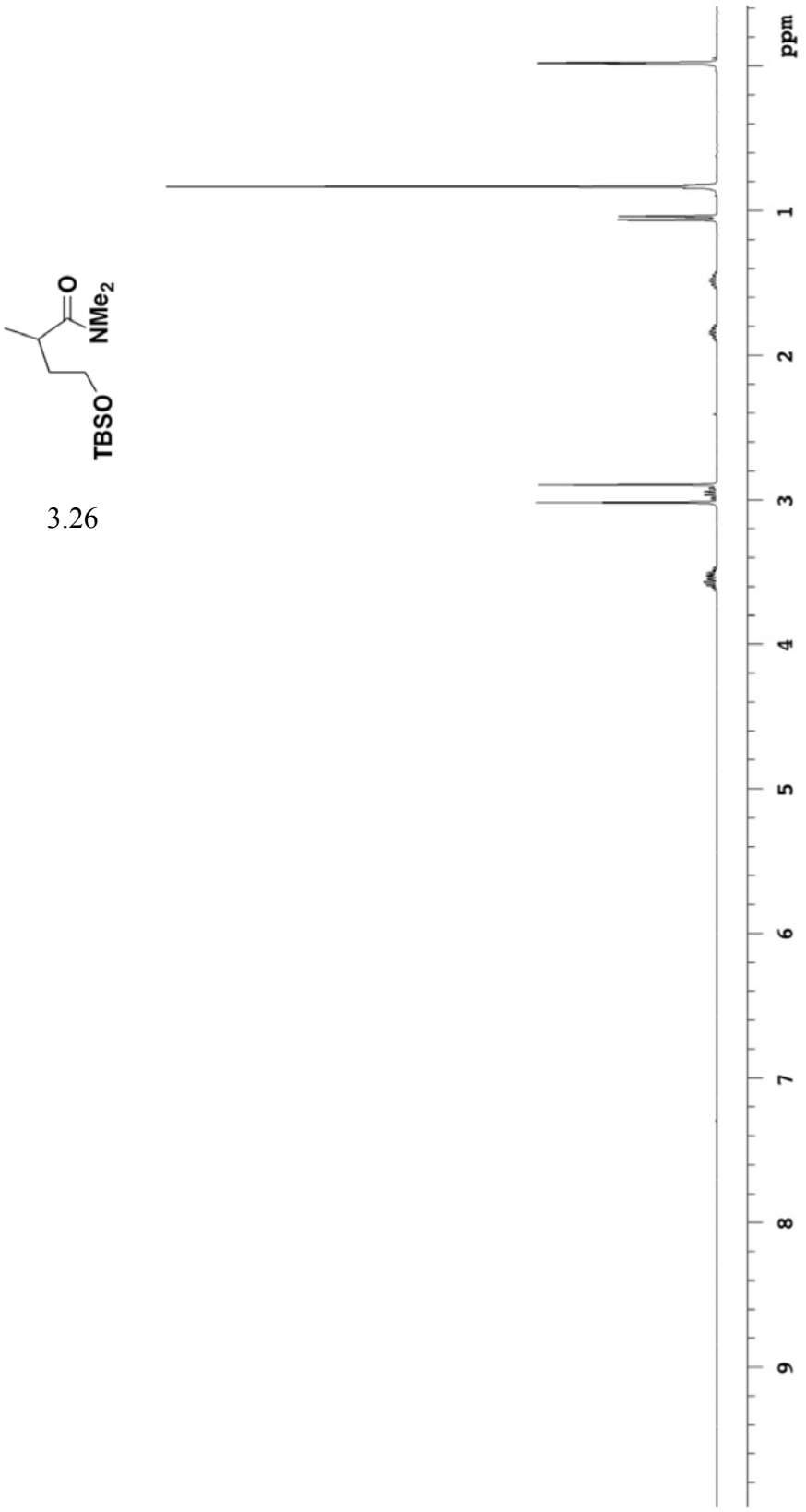

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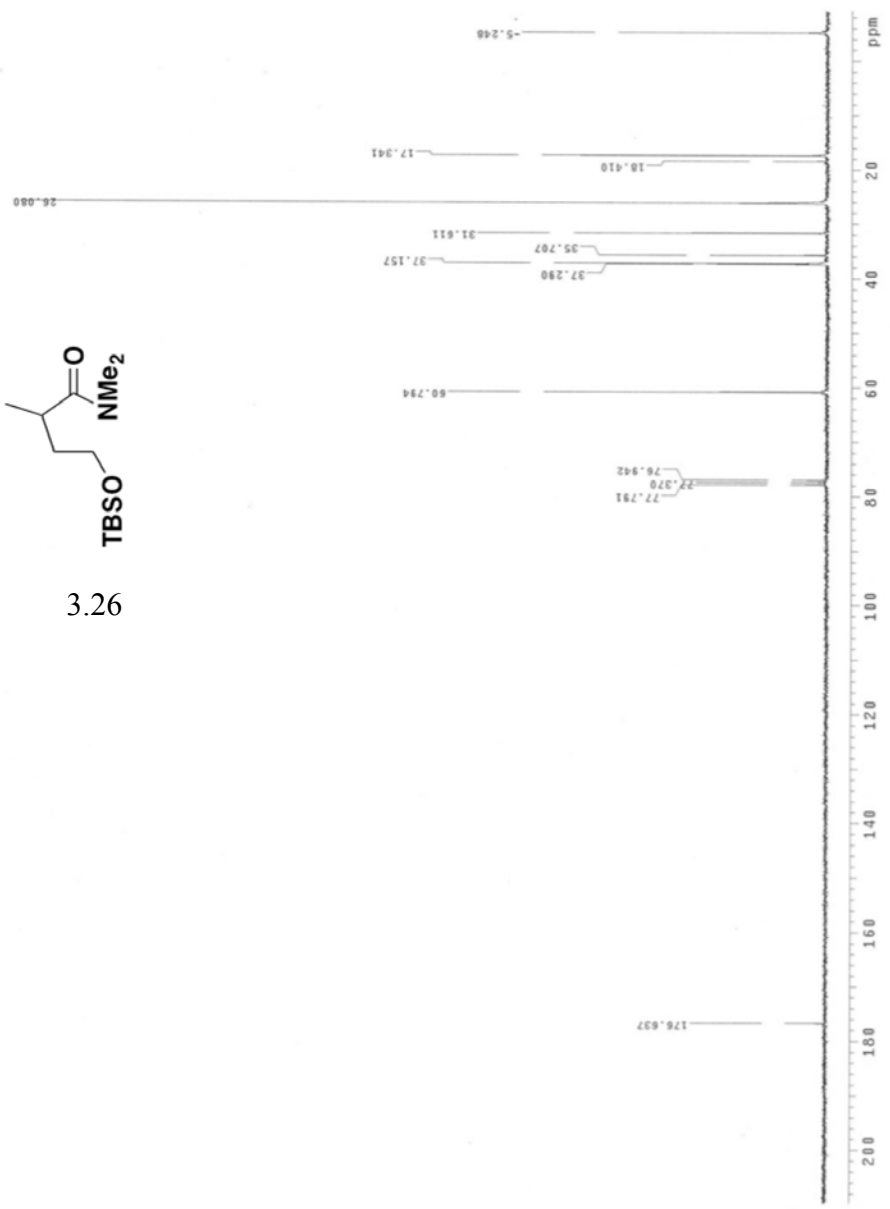
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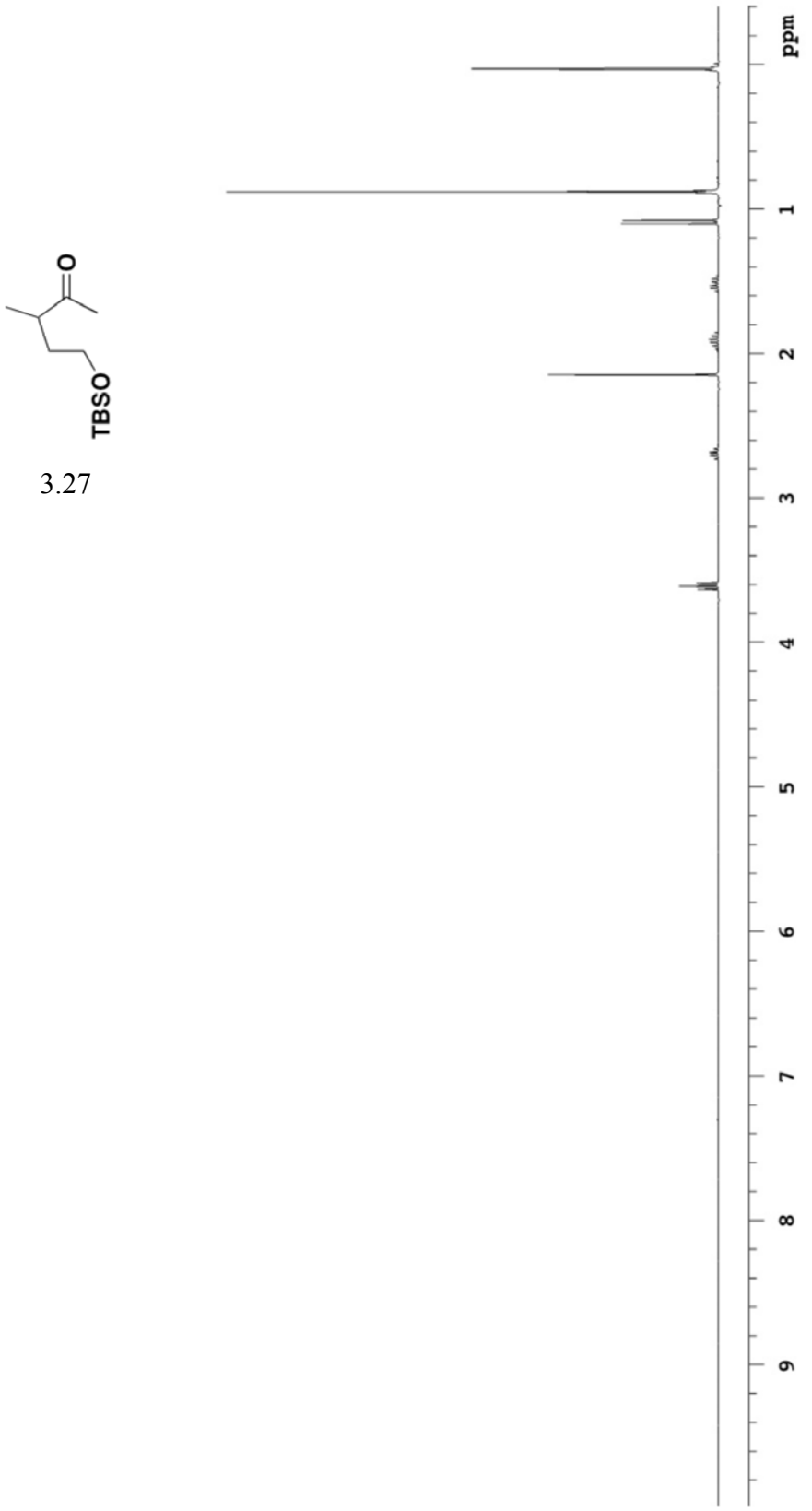

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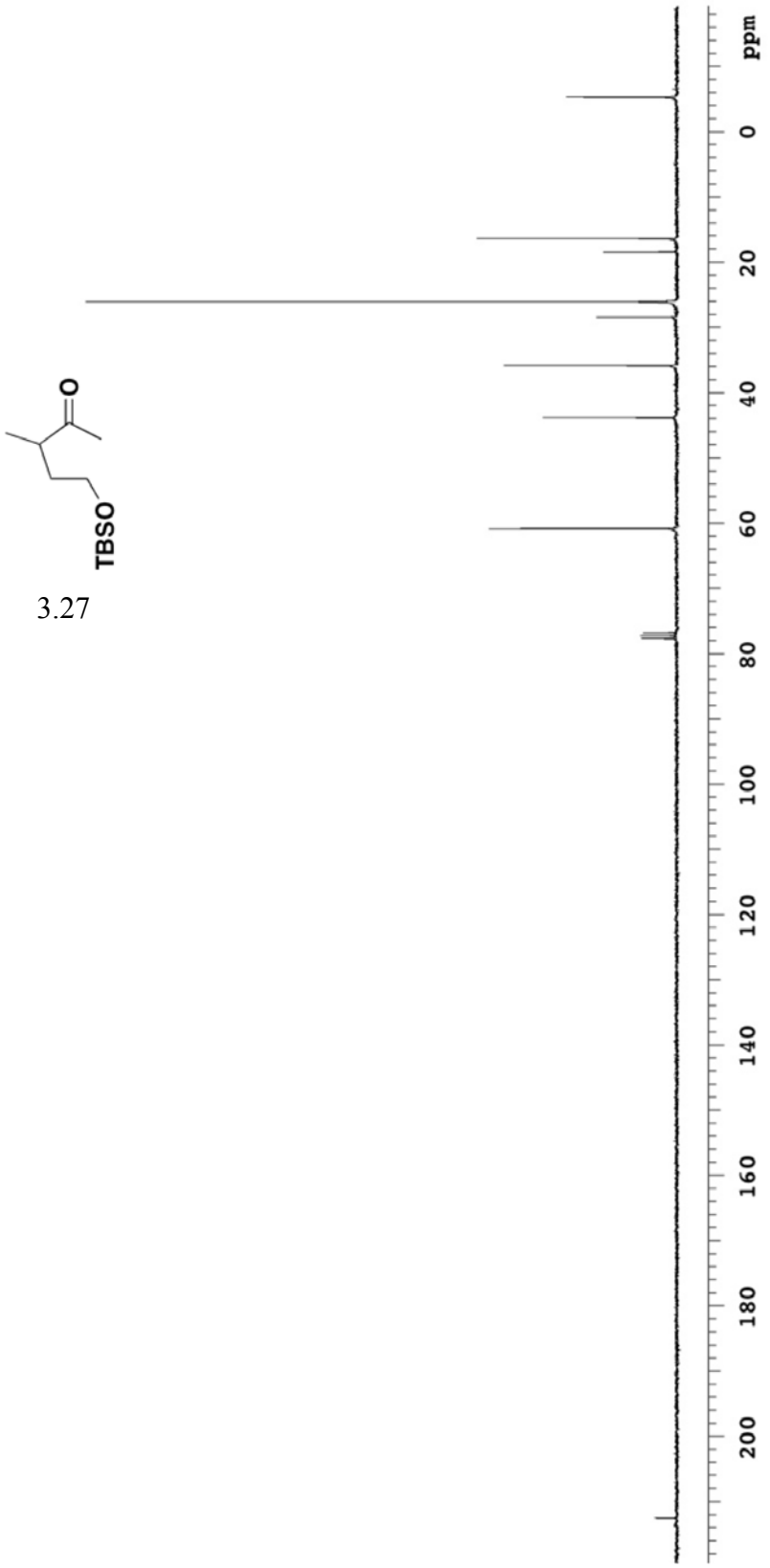

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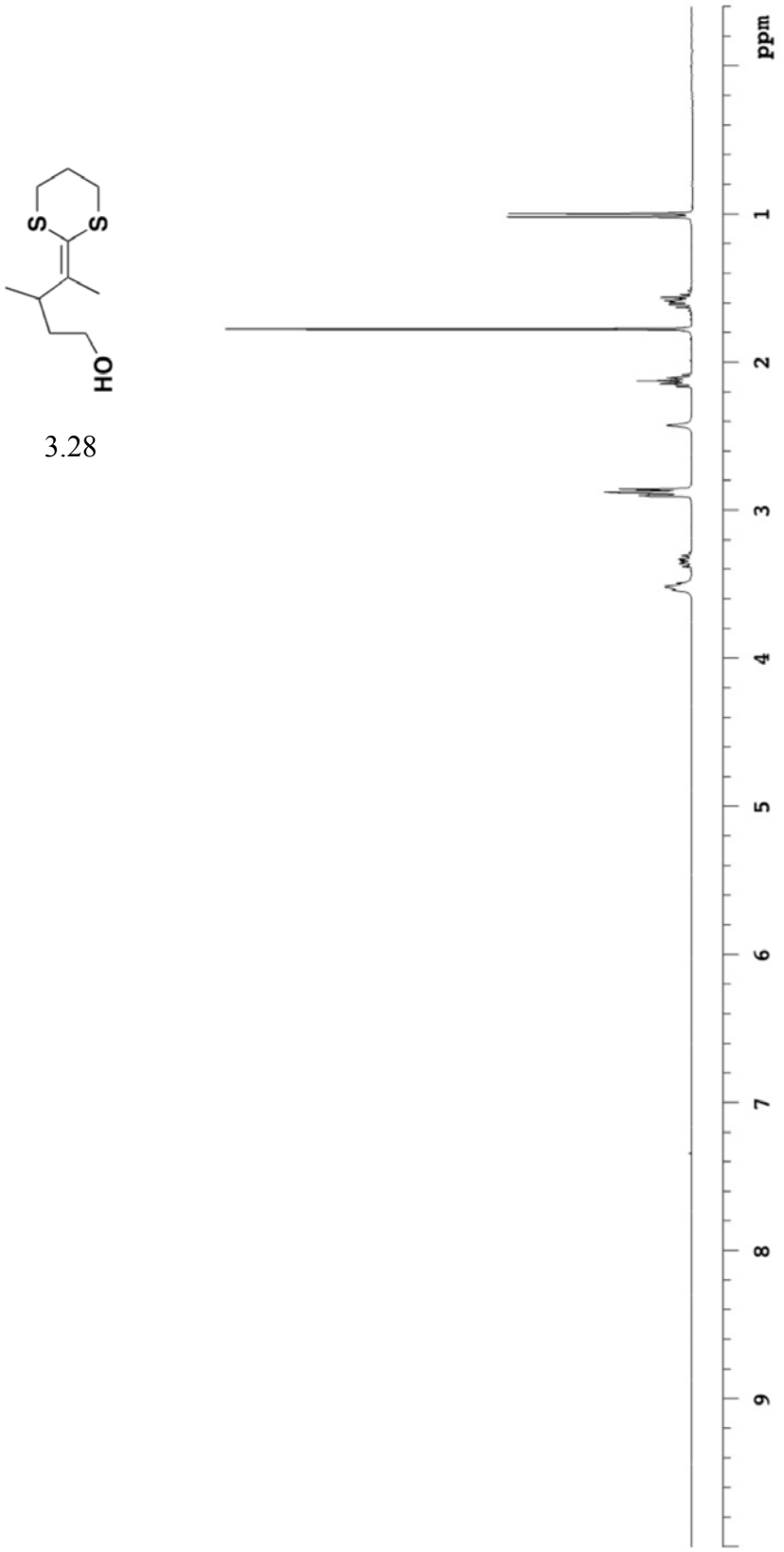

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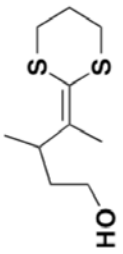

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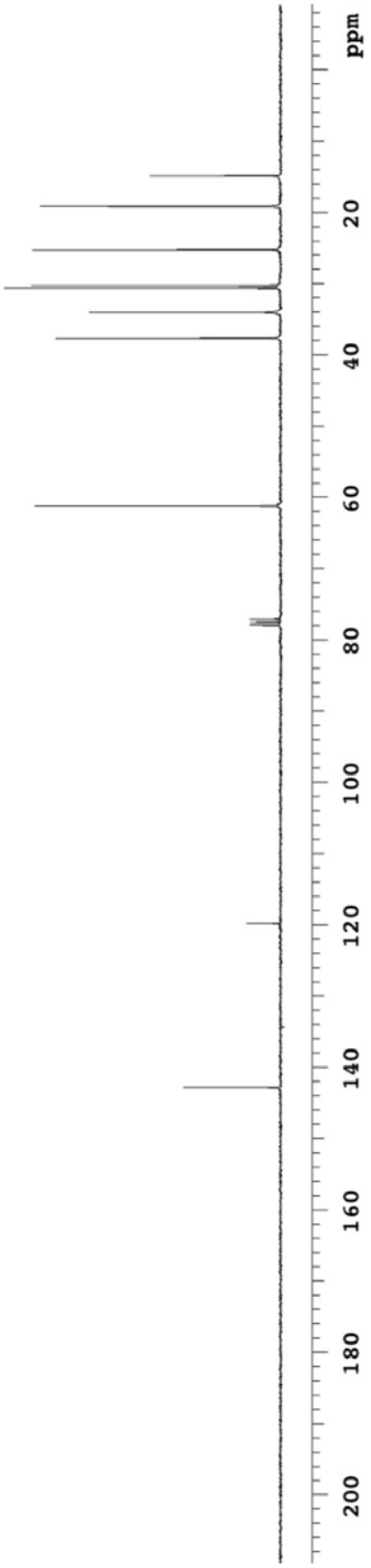

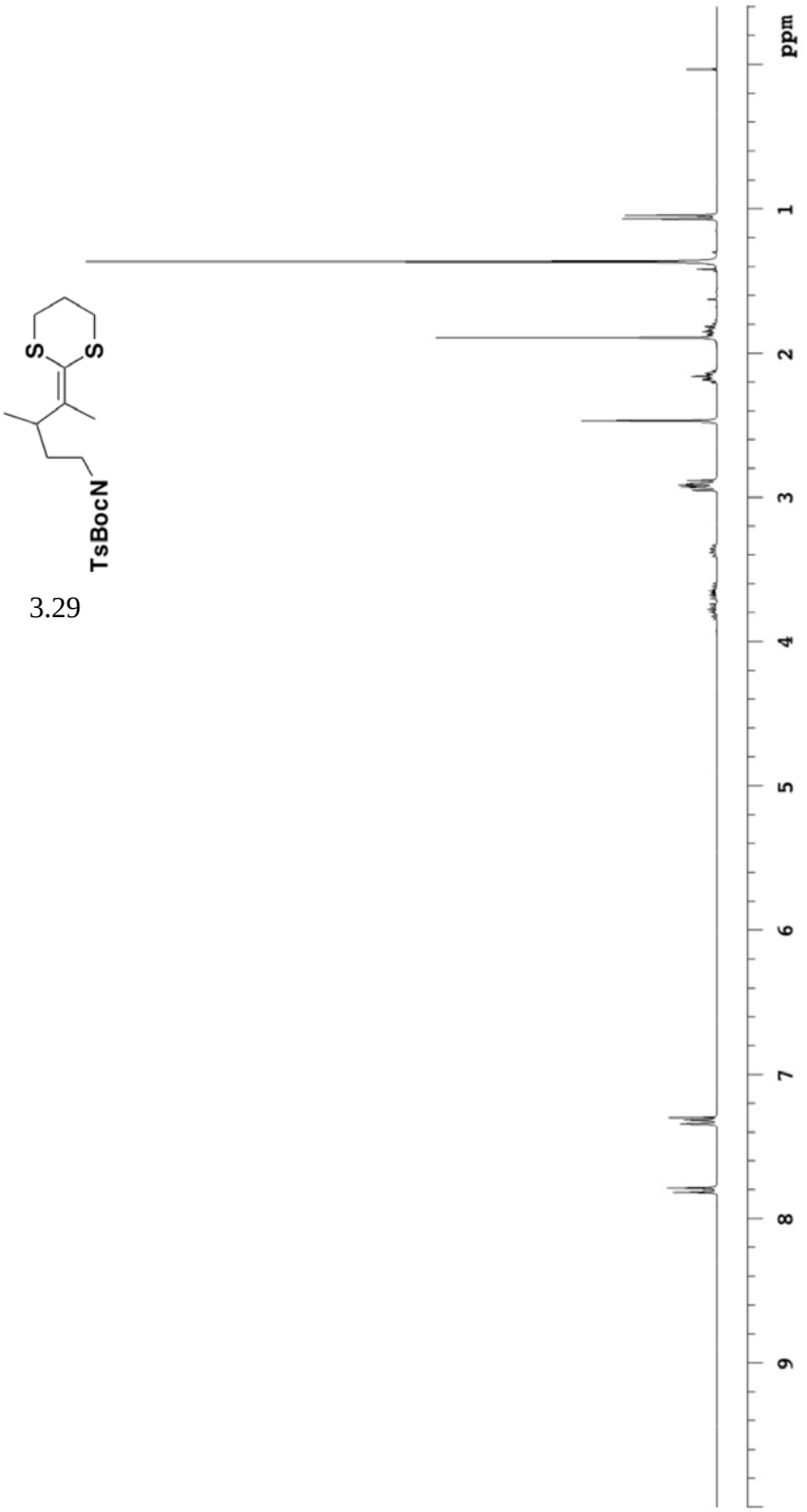

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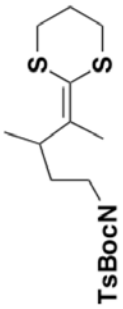

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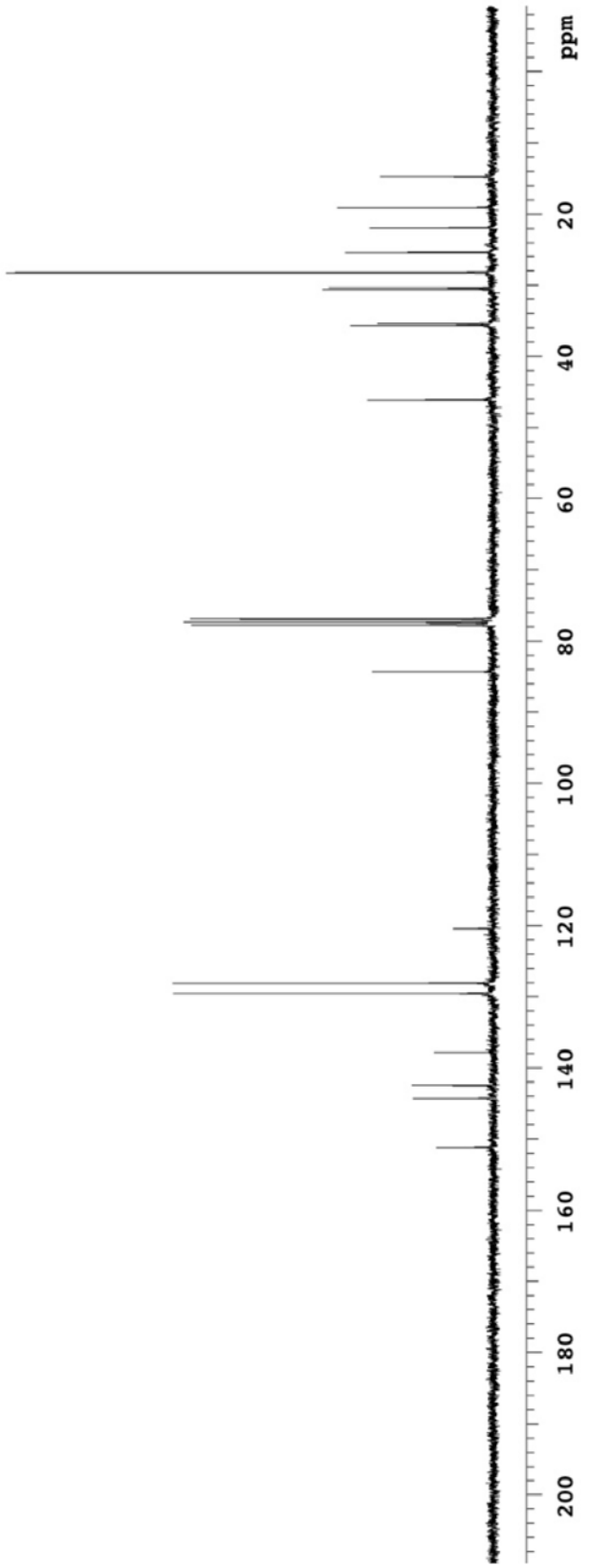

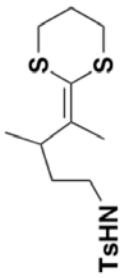

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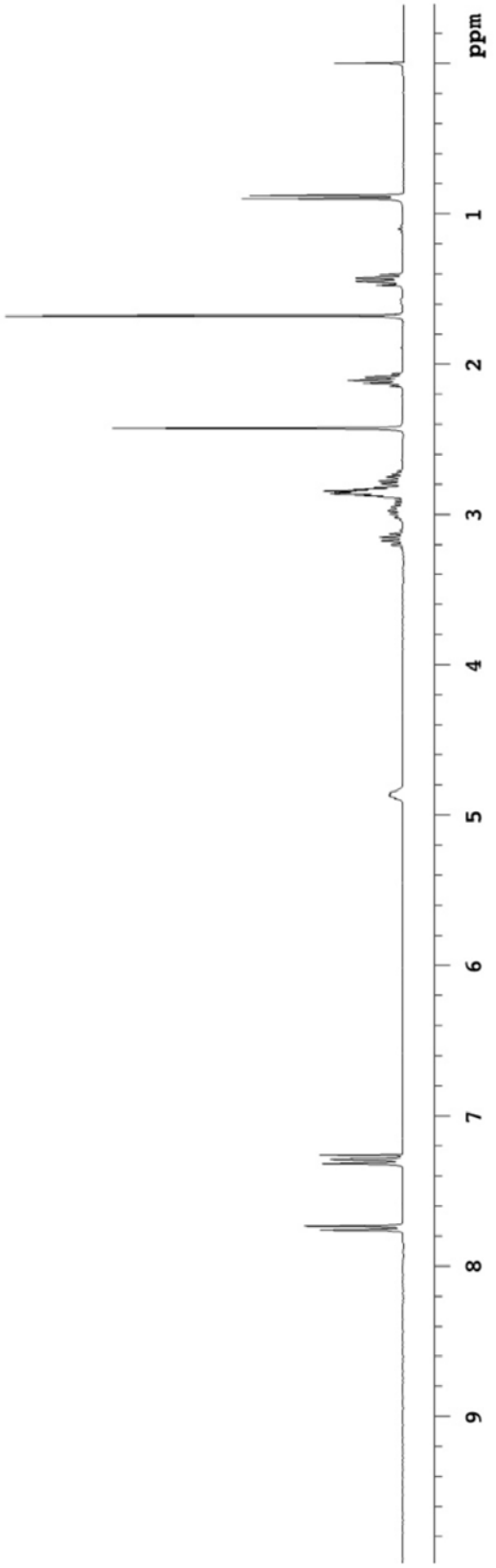

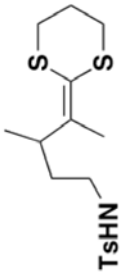

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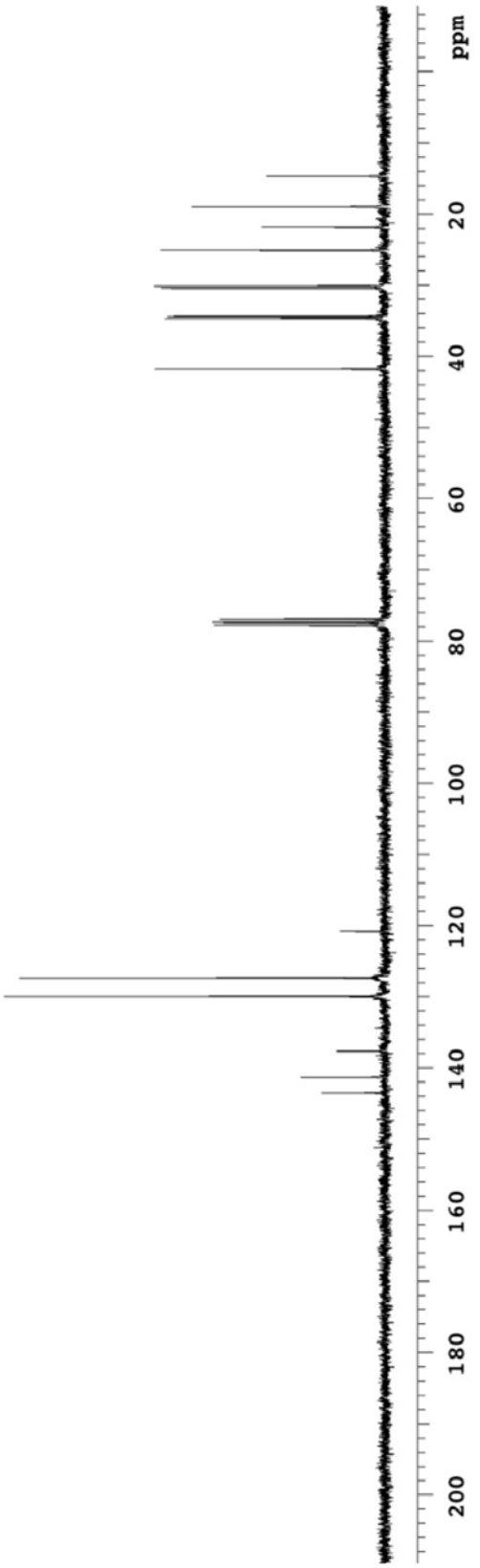

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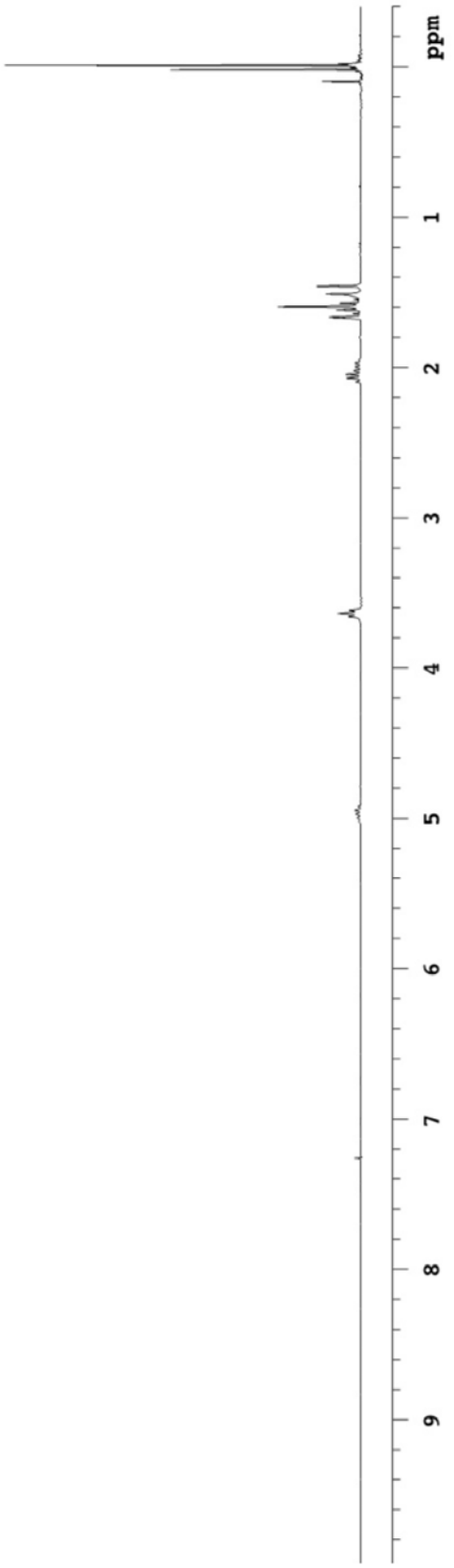

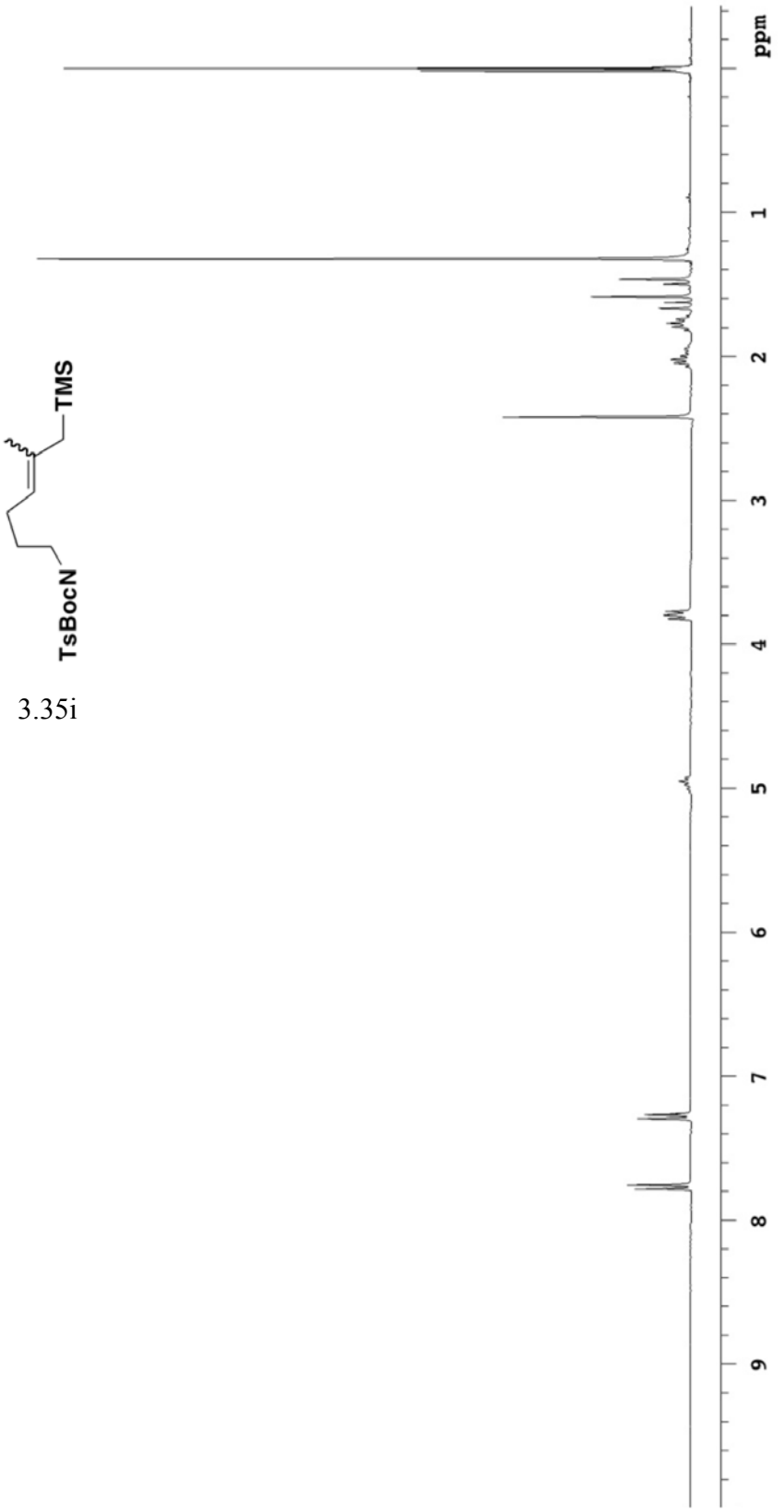

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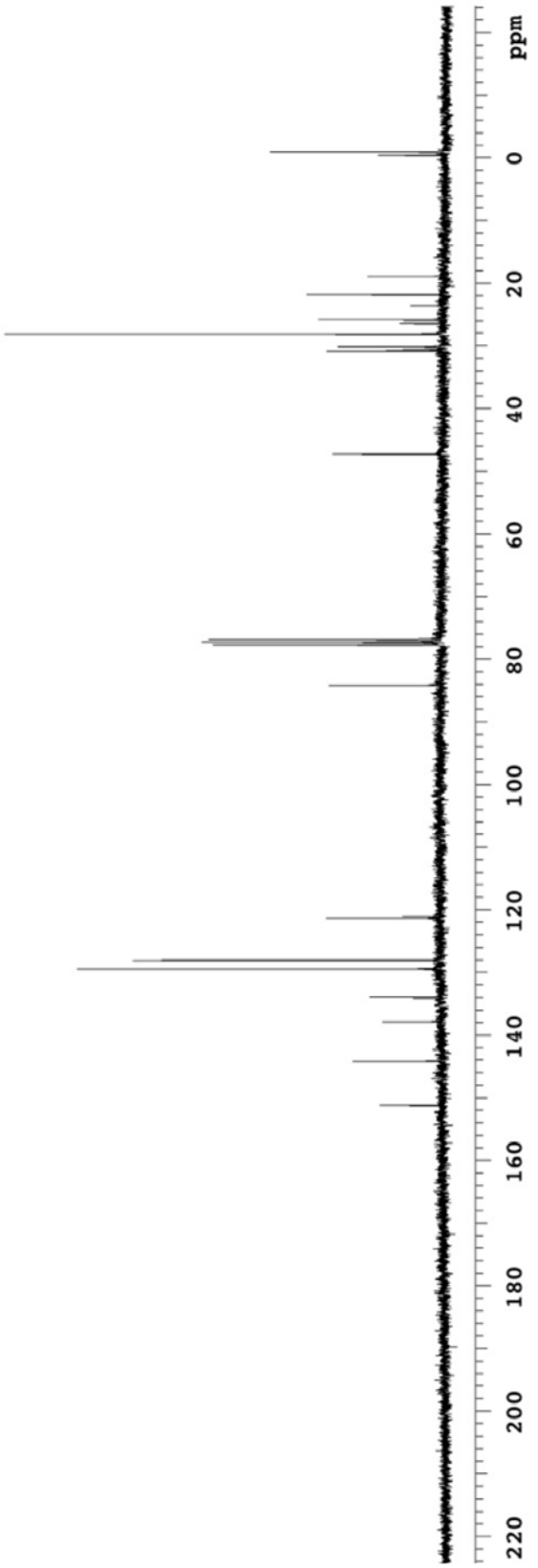
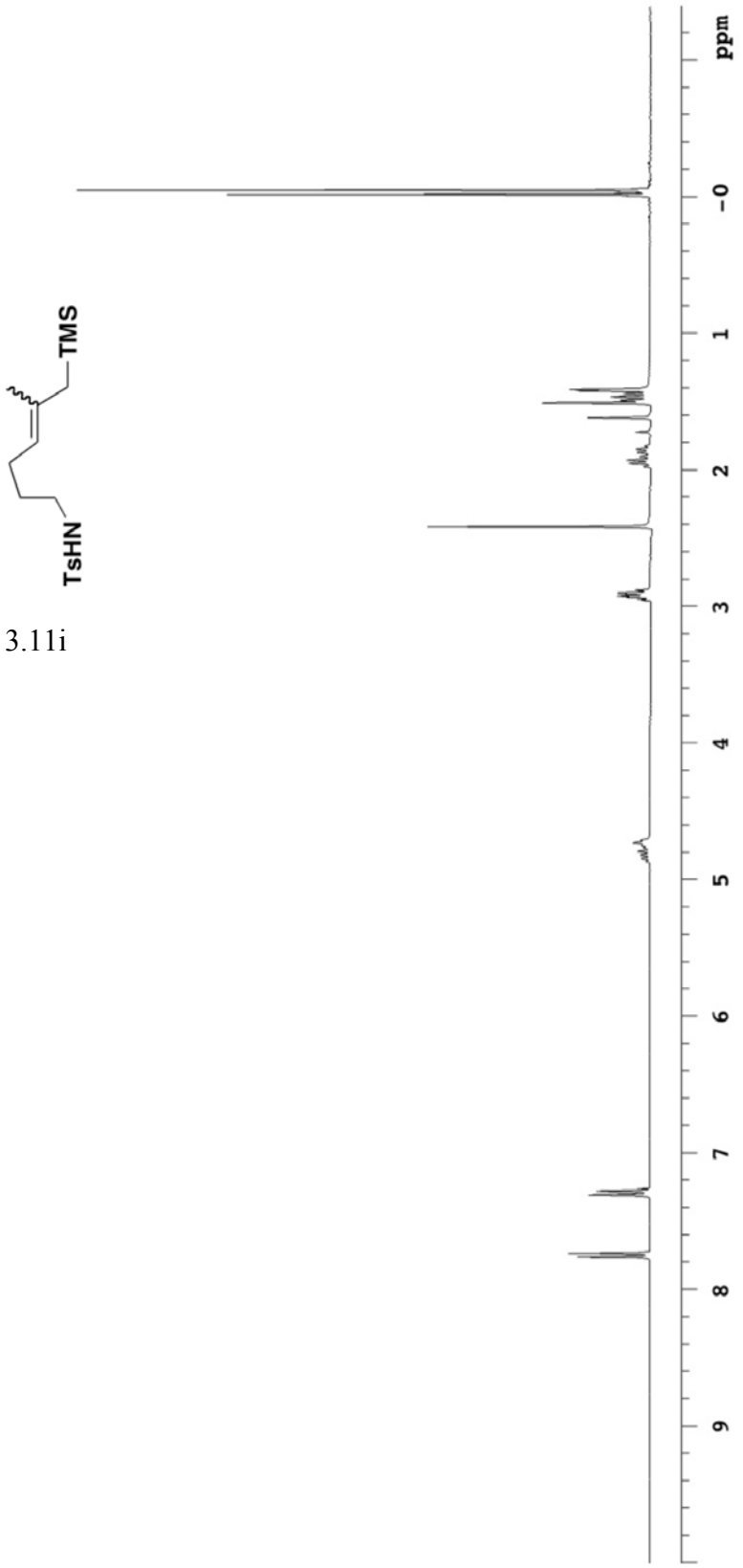
3.35i





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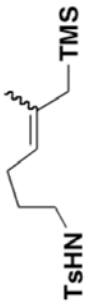

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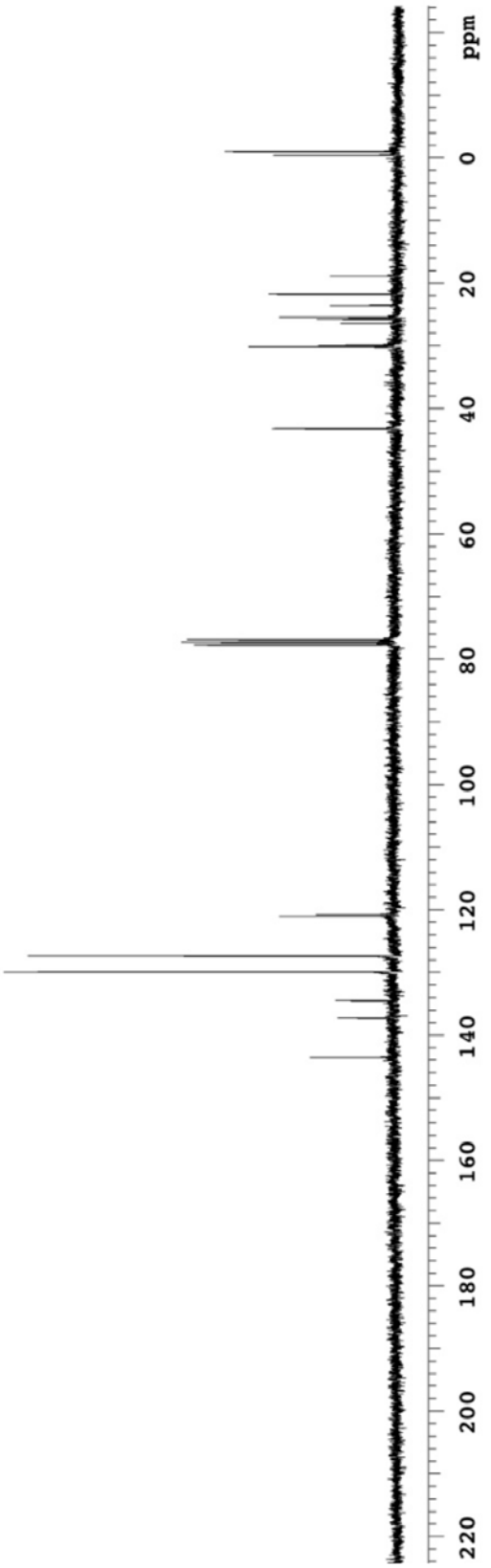

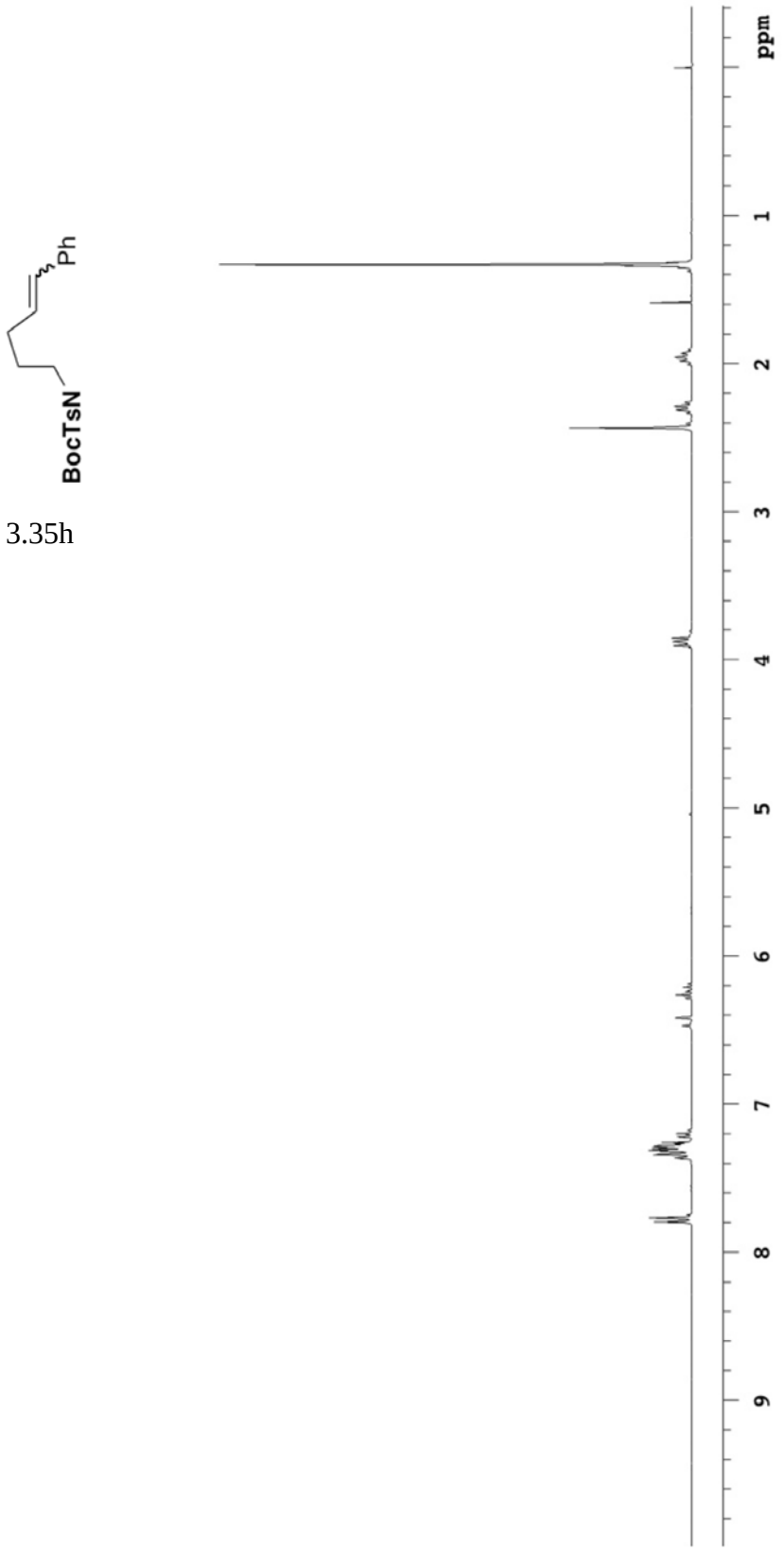

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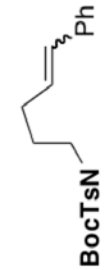

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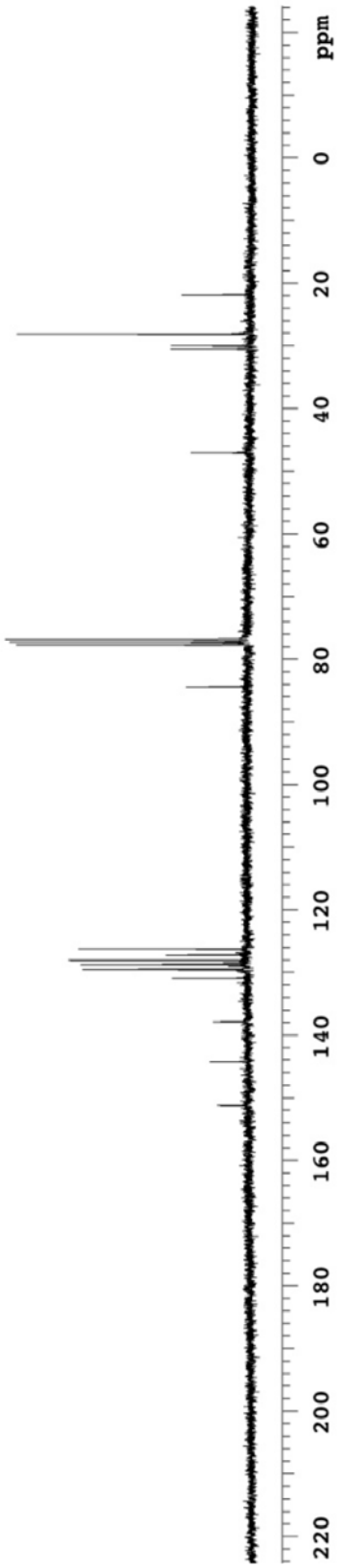

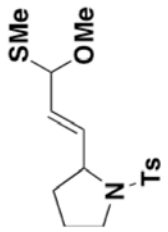

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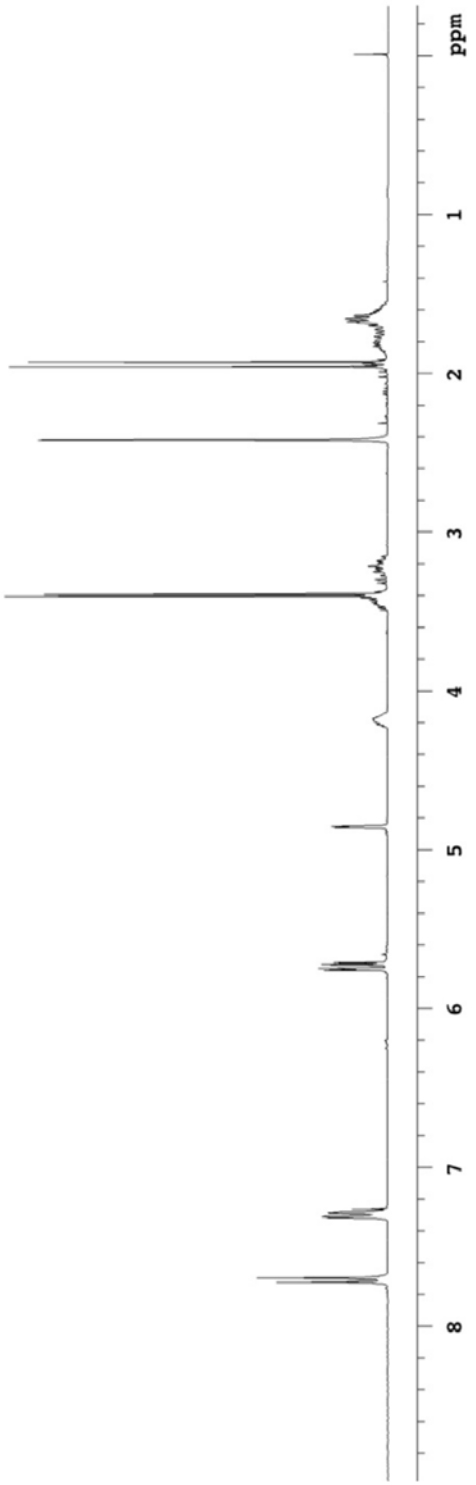

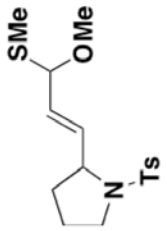

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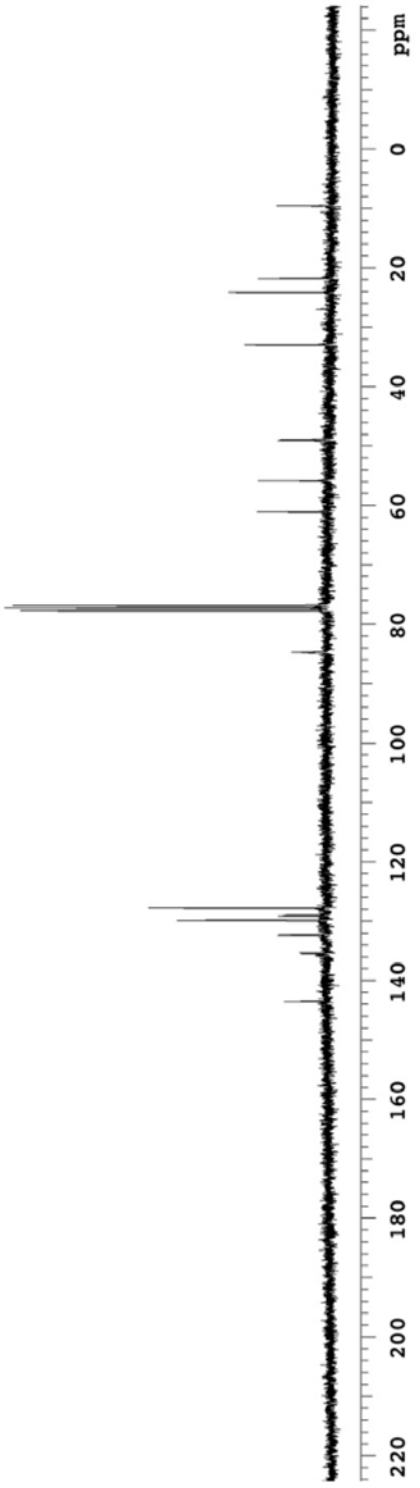

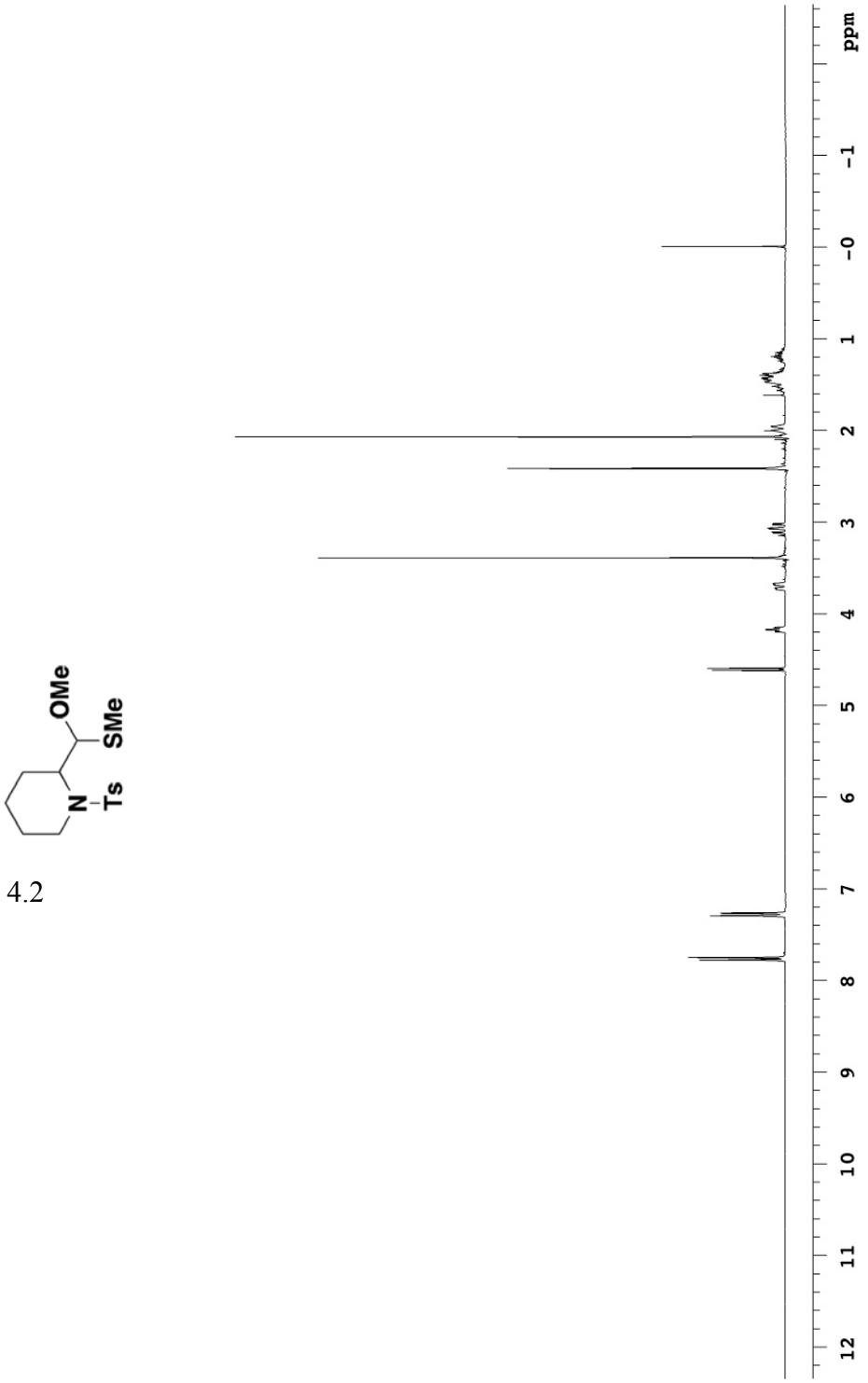

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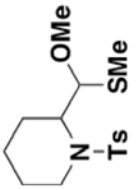

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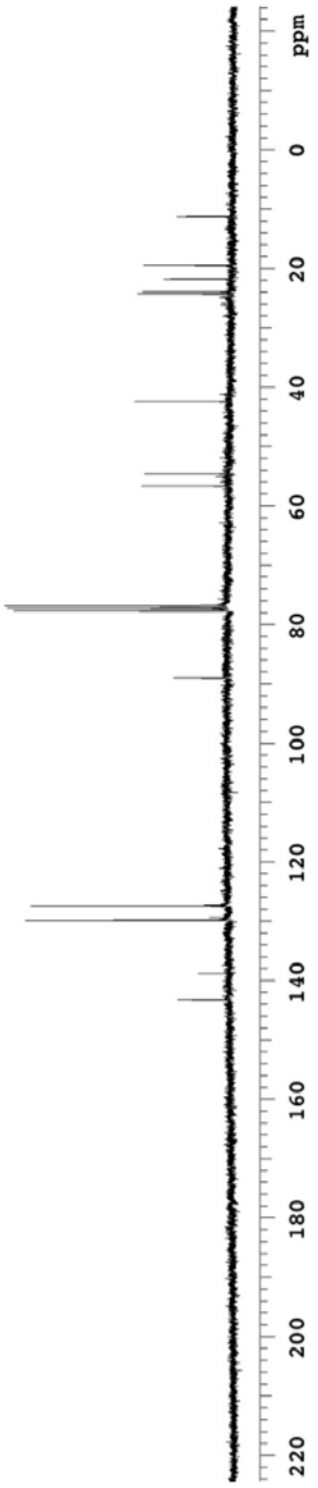

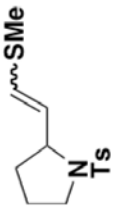

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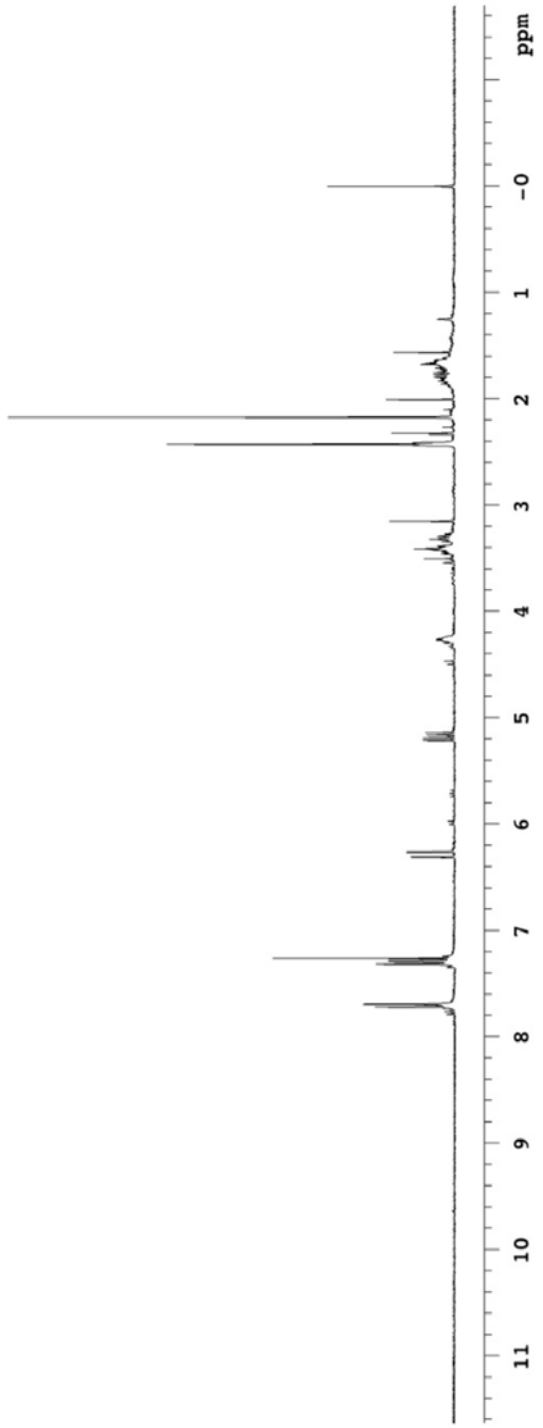

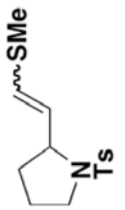

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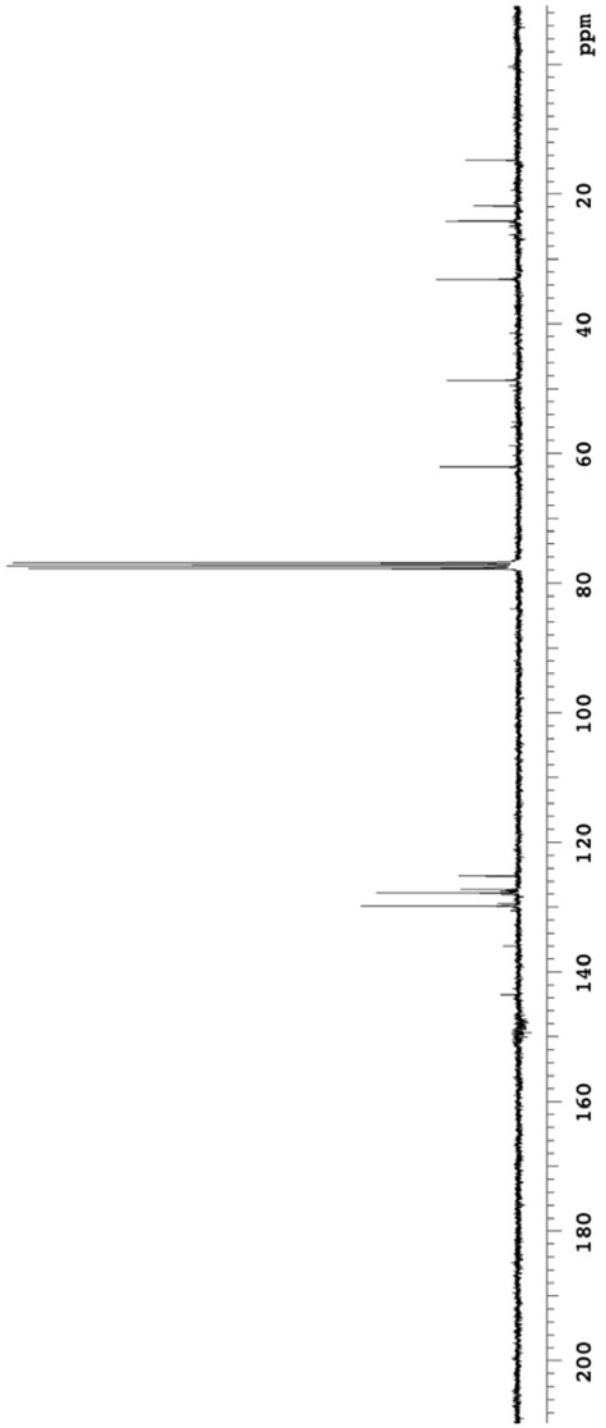

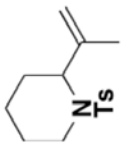

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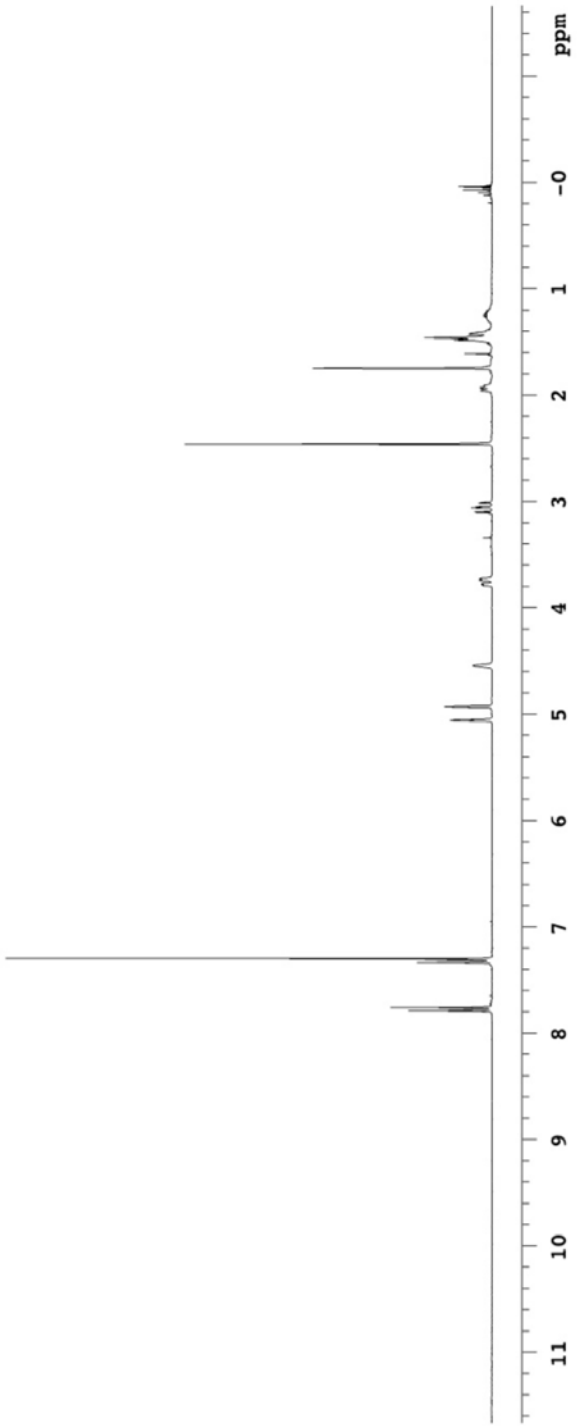

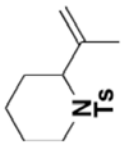

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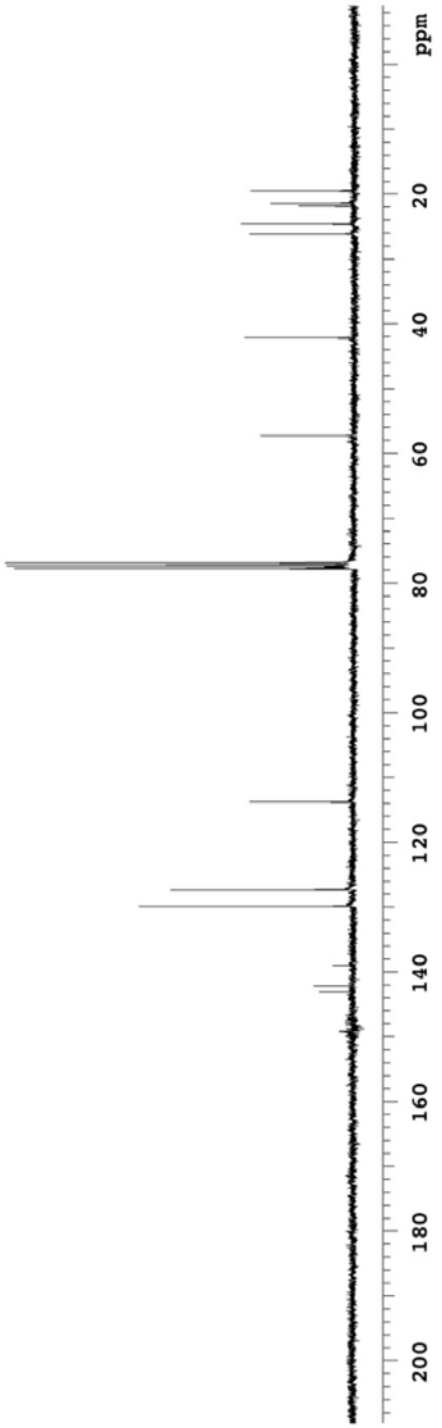

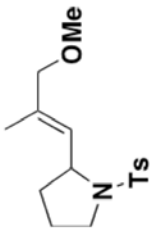

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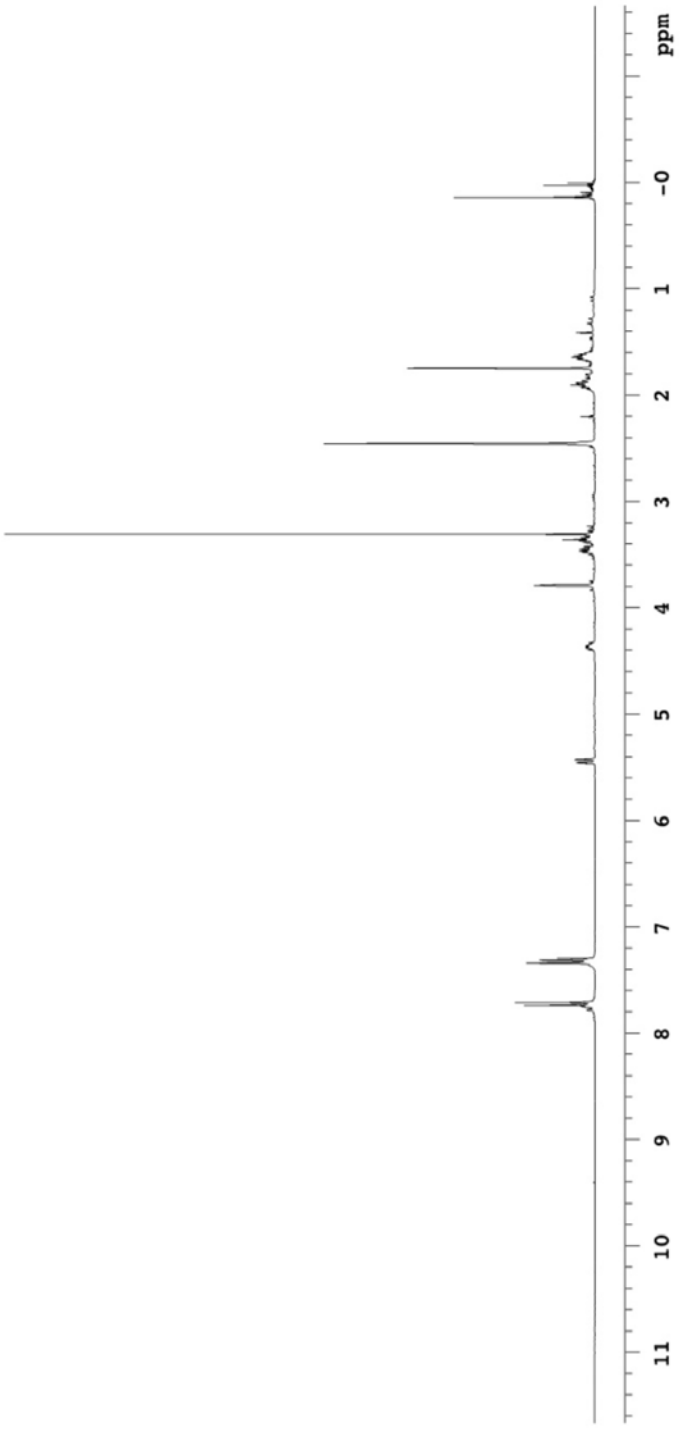

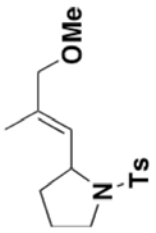

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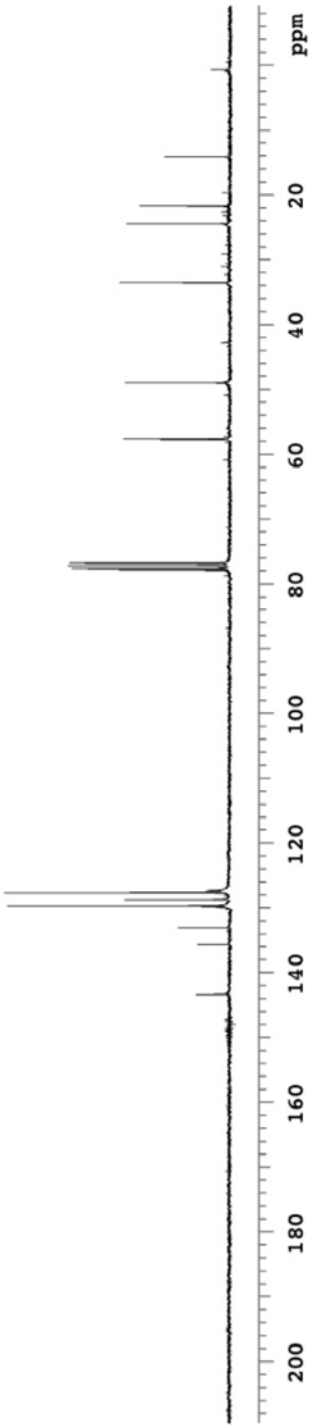

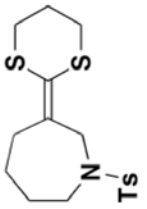

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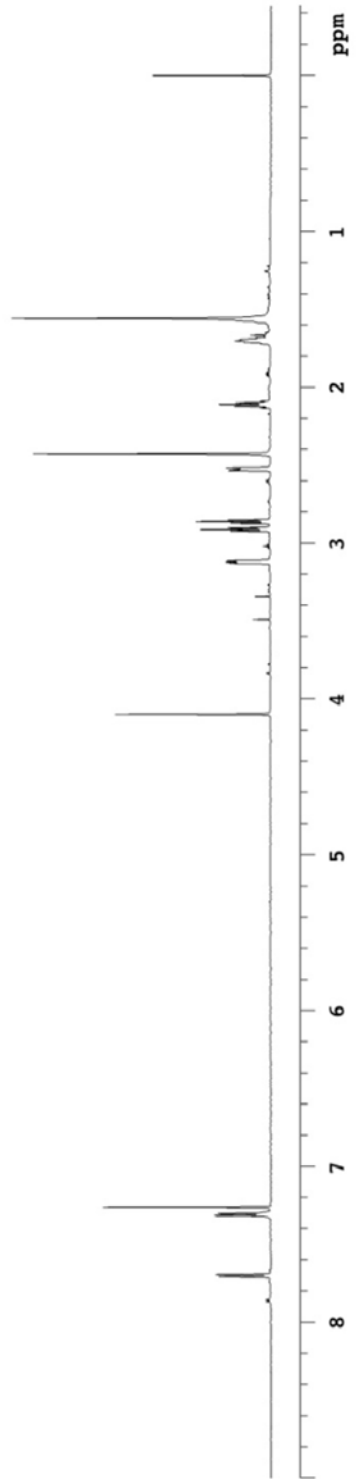

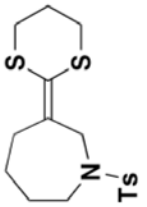

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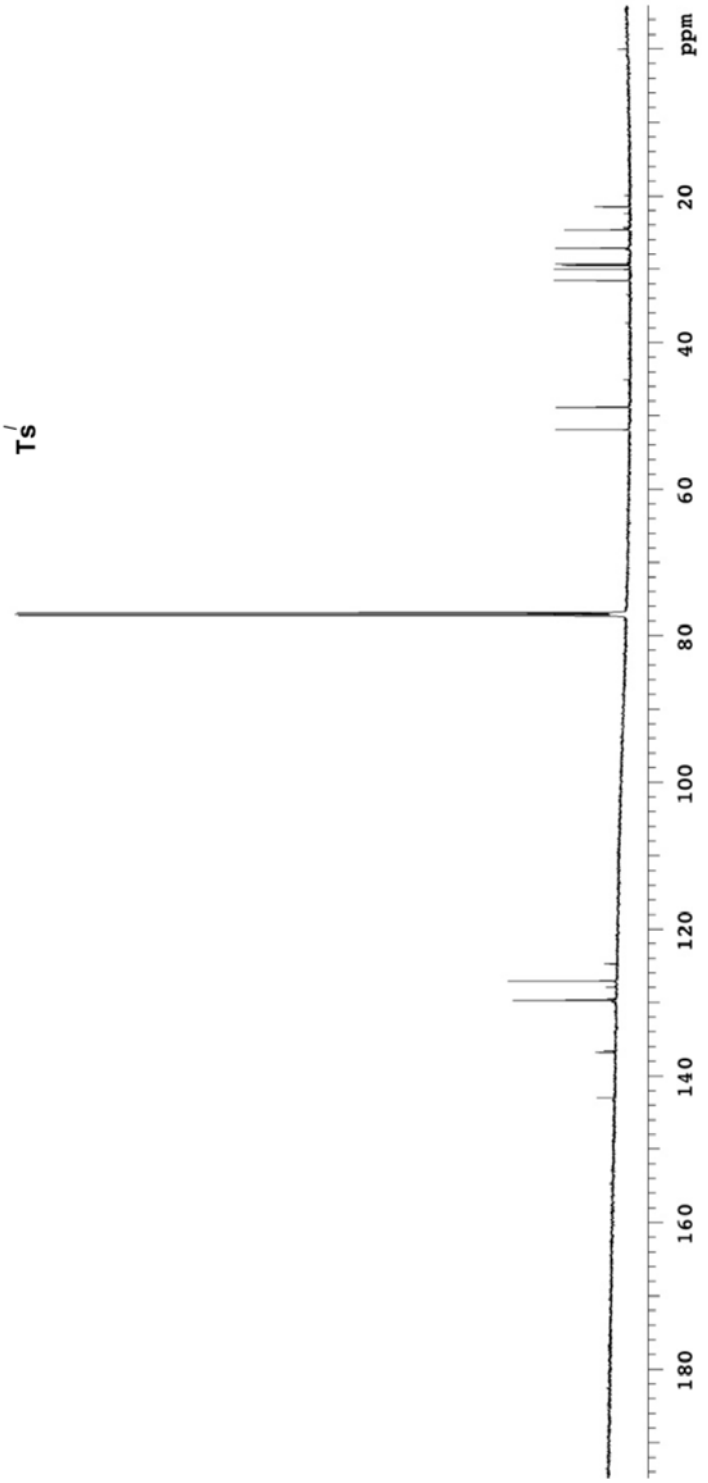

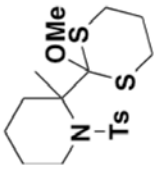

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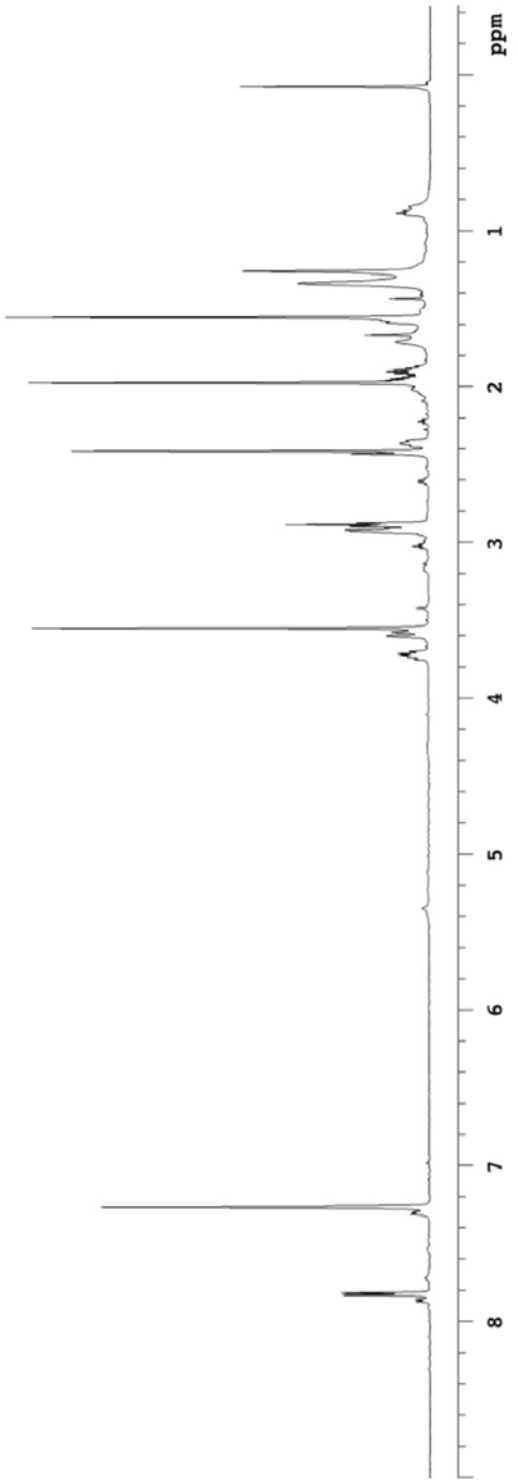

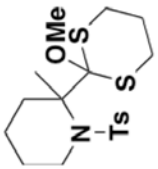

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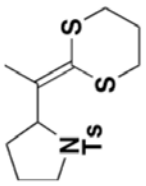

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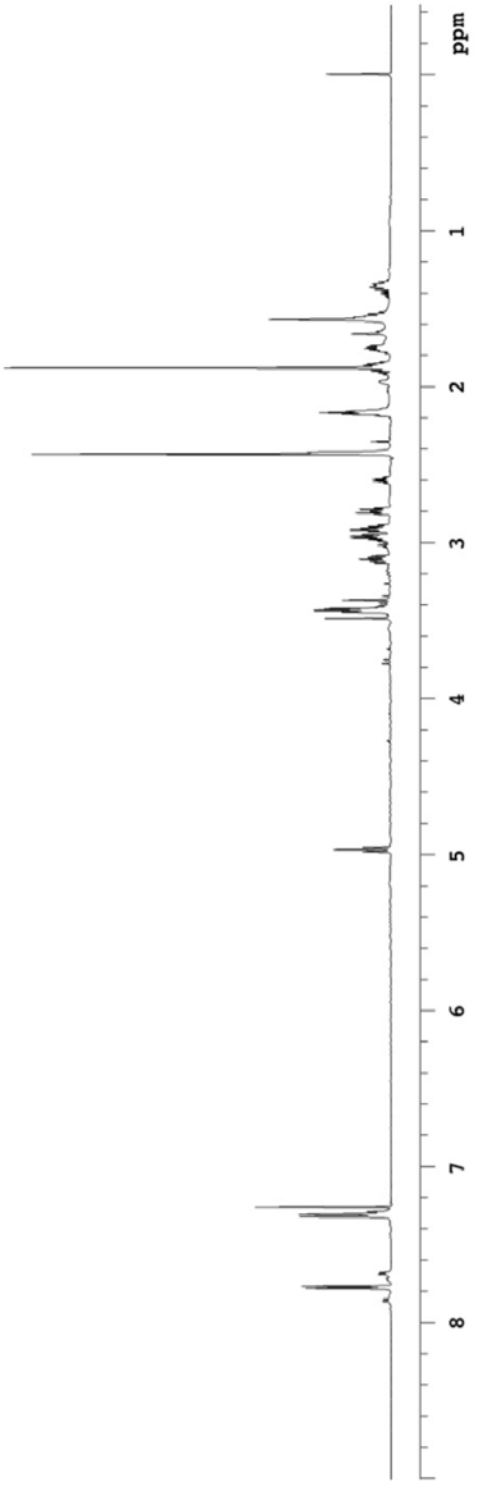

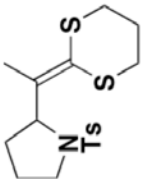

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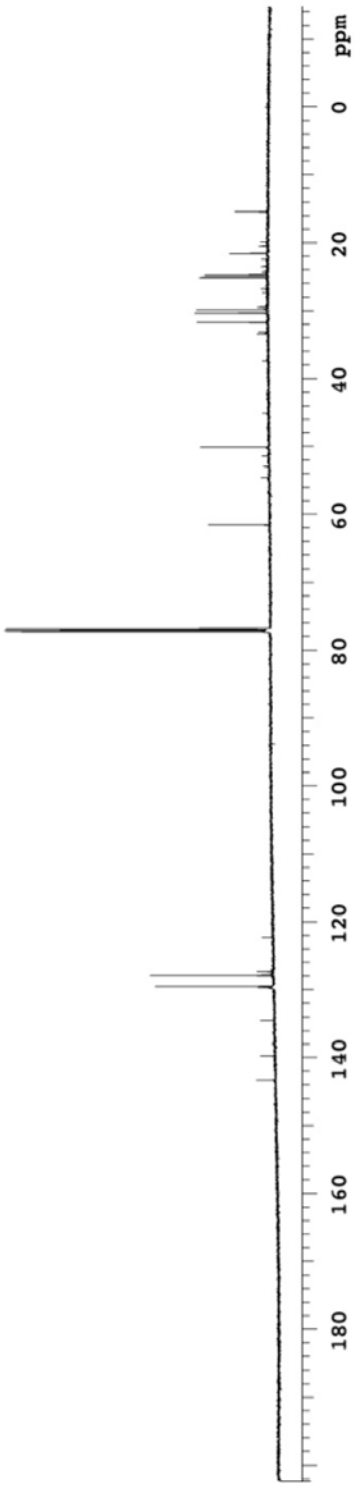

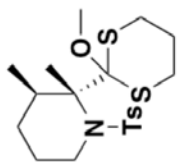

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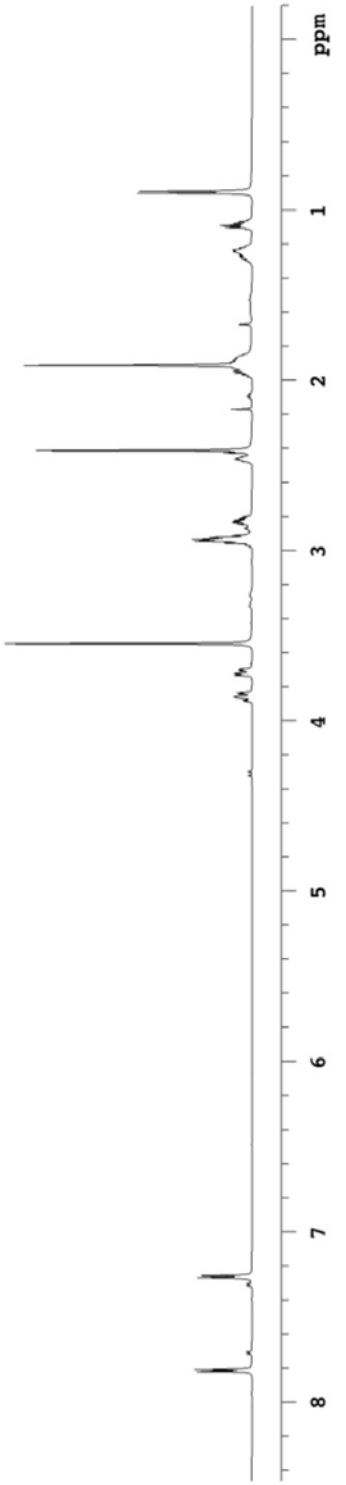

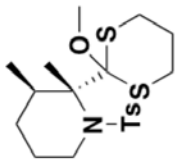

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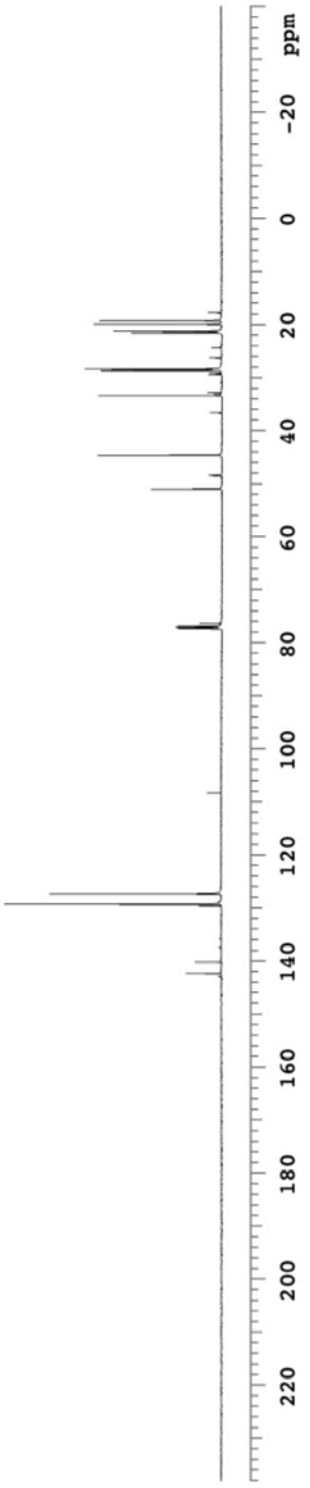

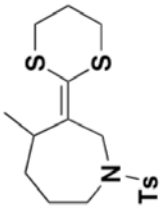

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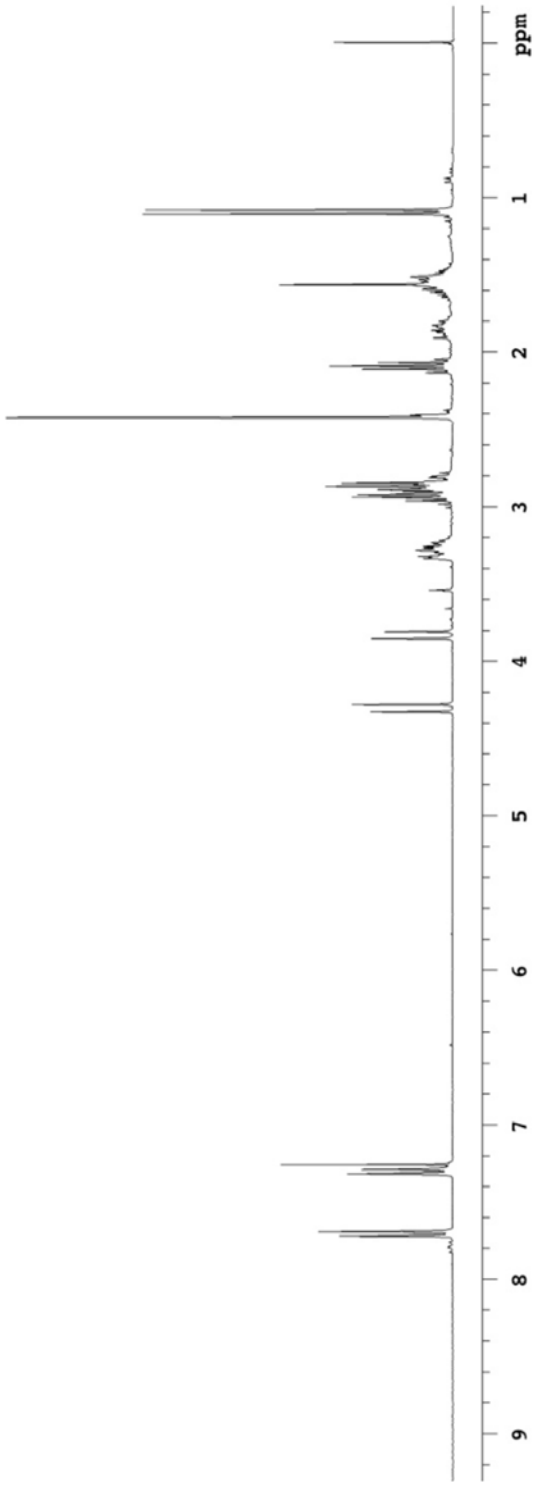

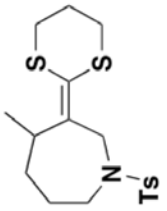

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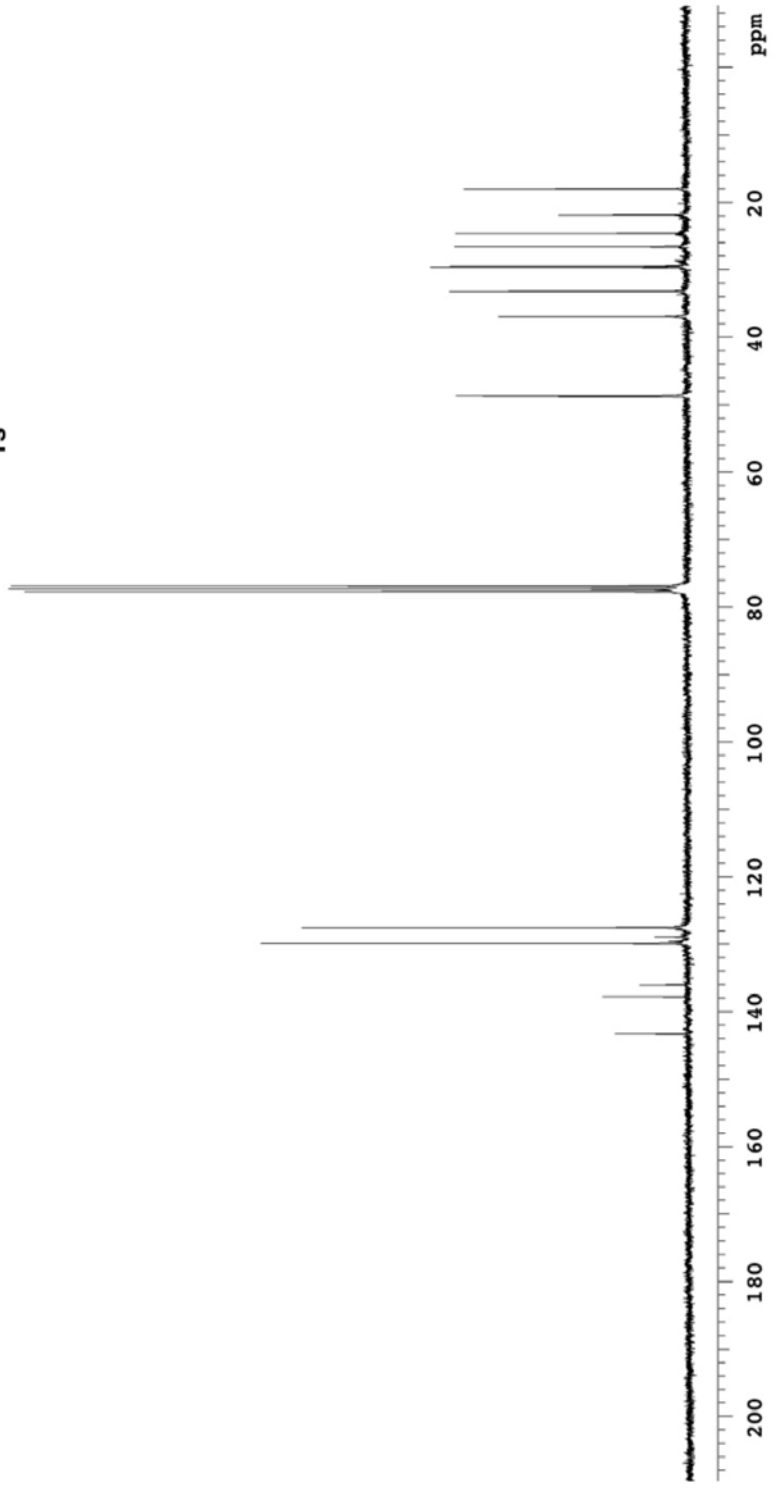

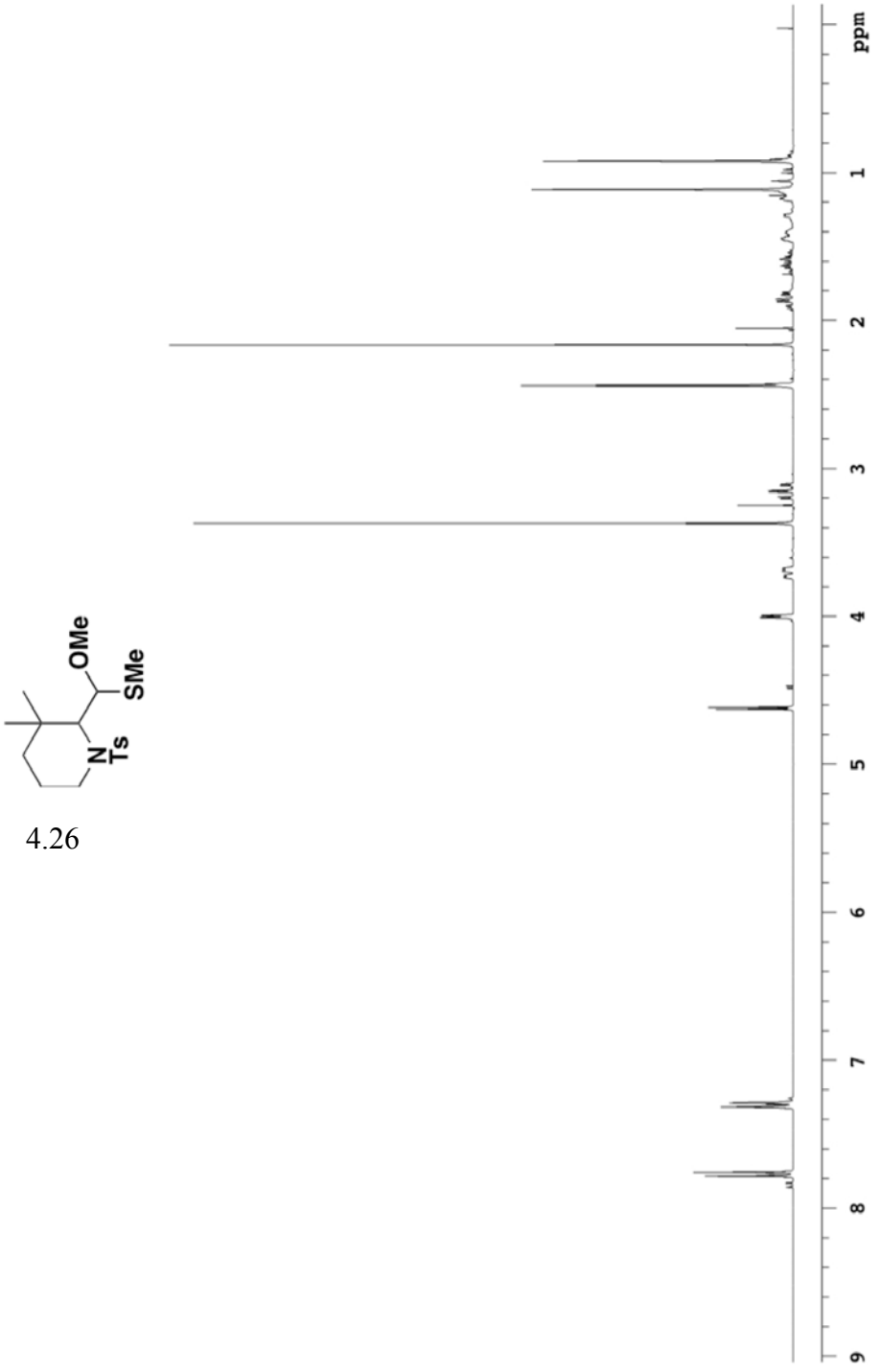

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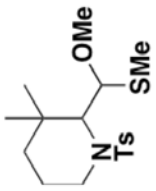

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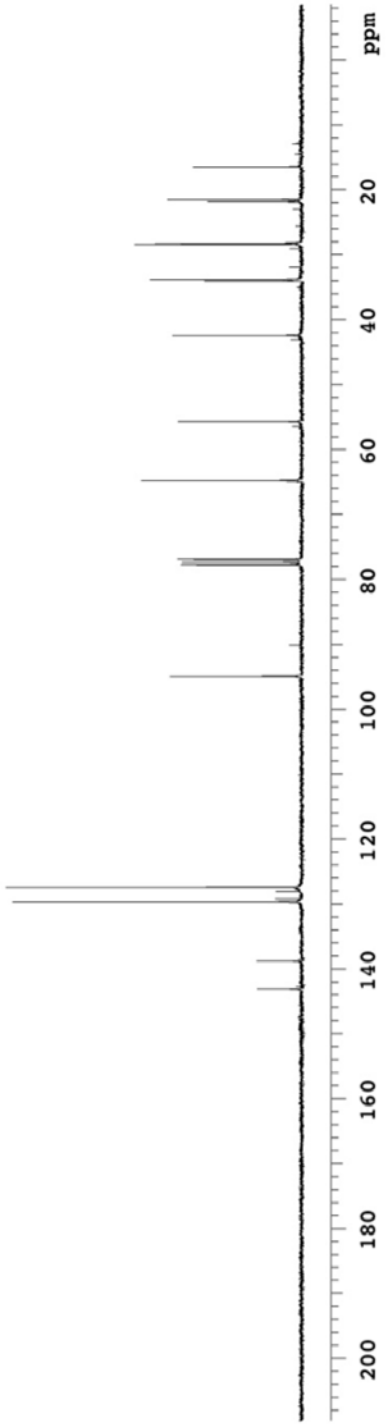

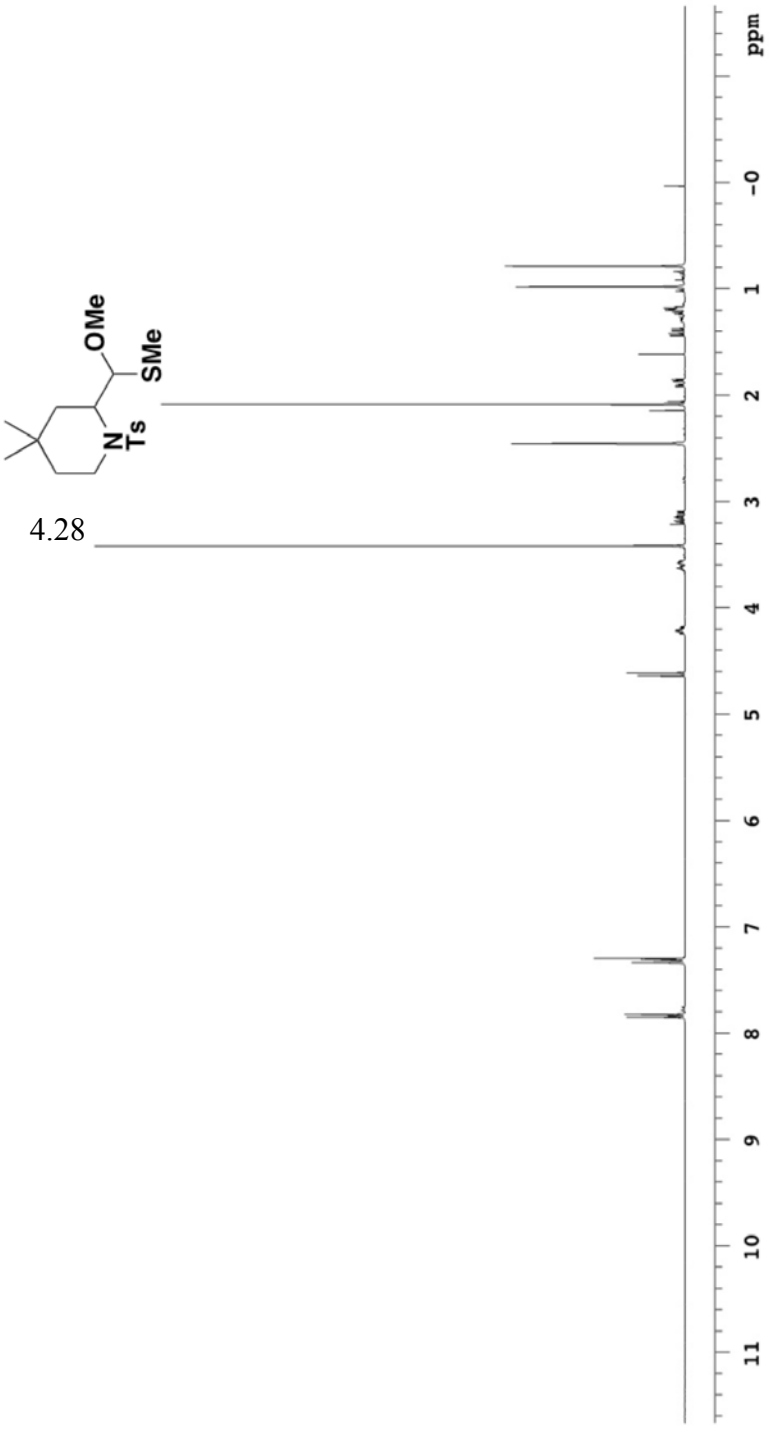
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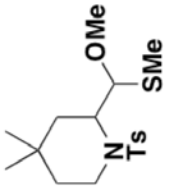

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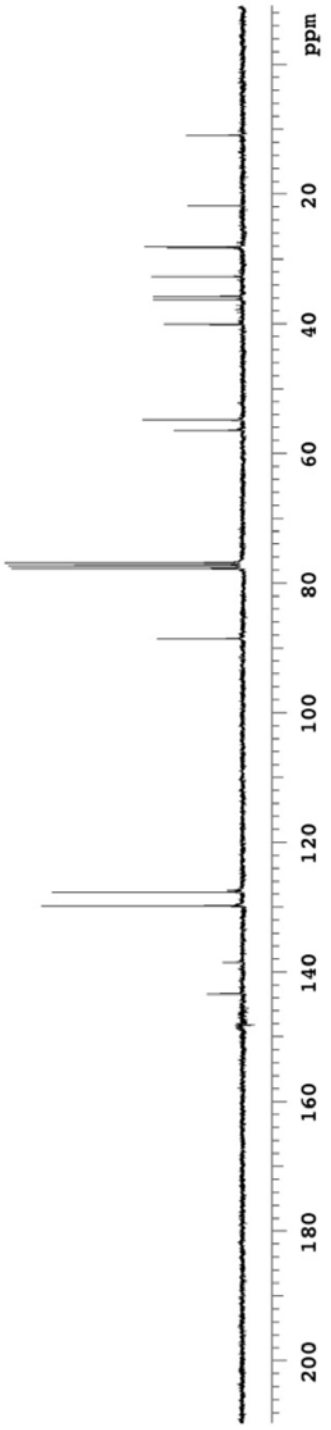

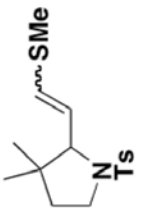

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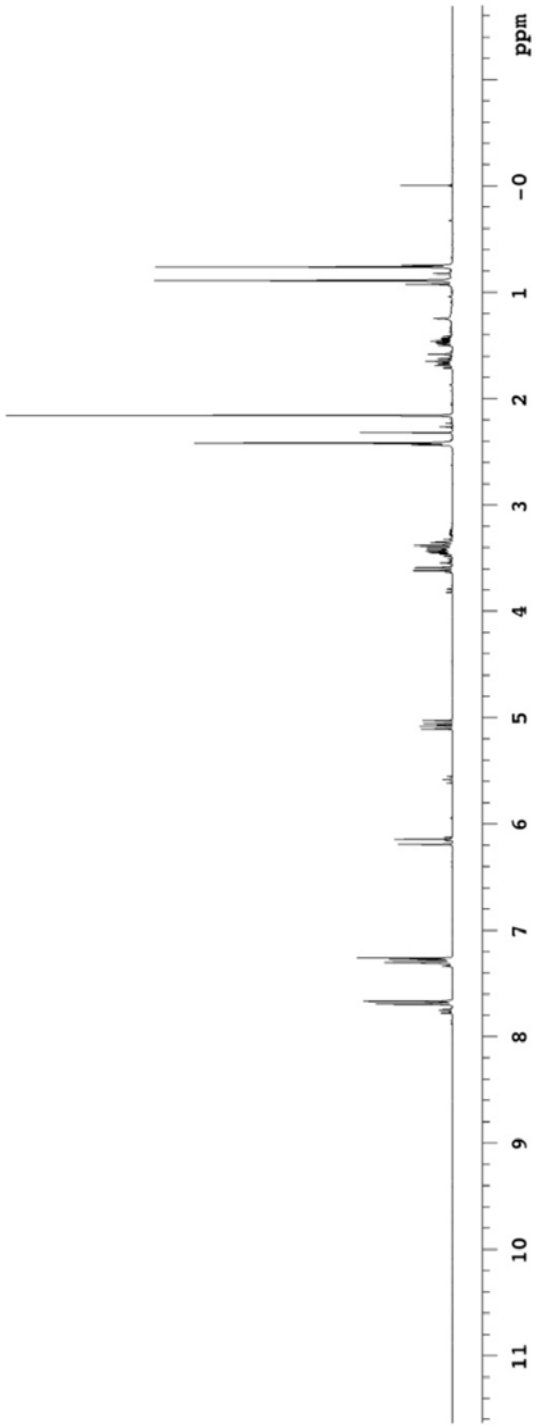

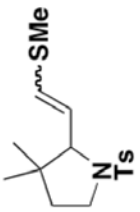

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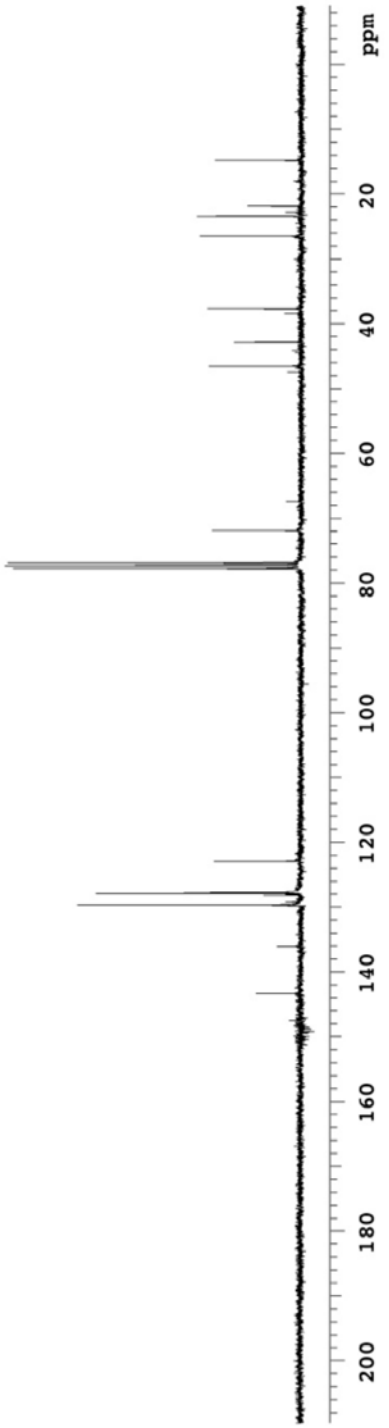

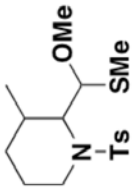

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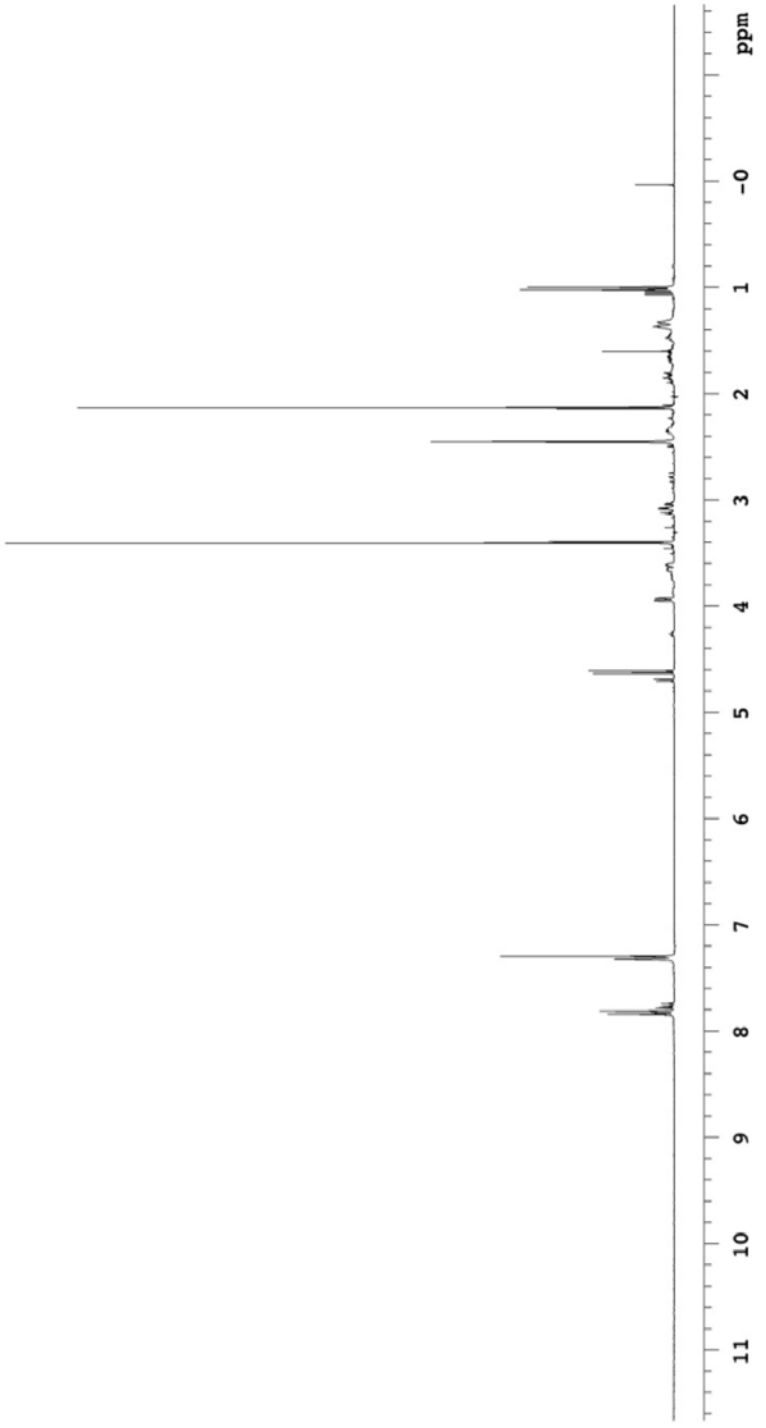

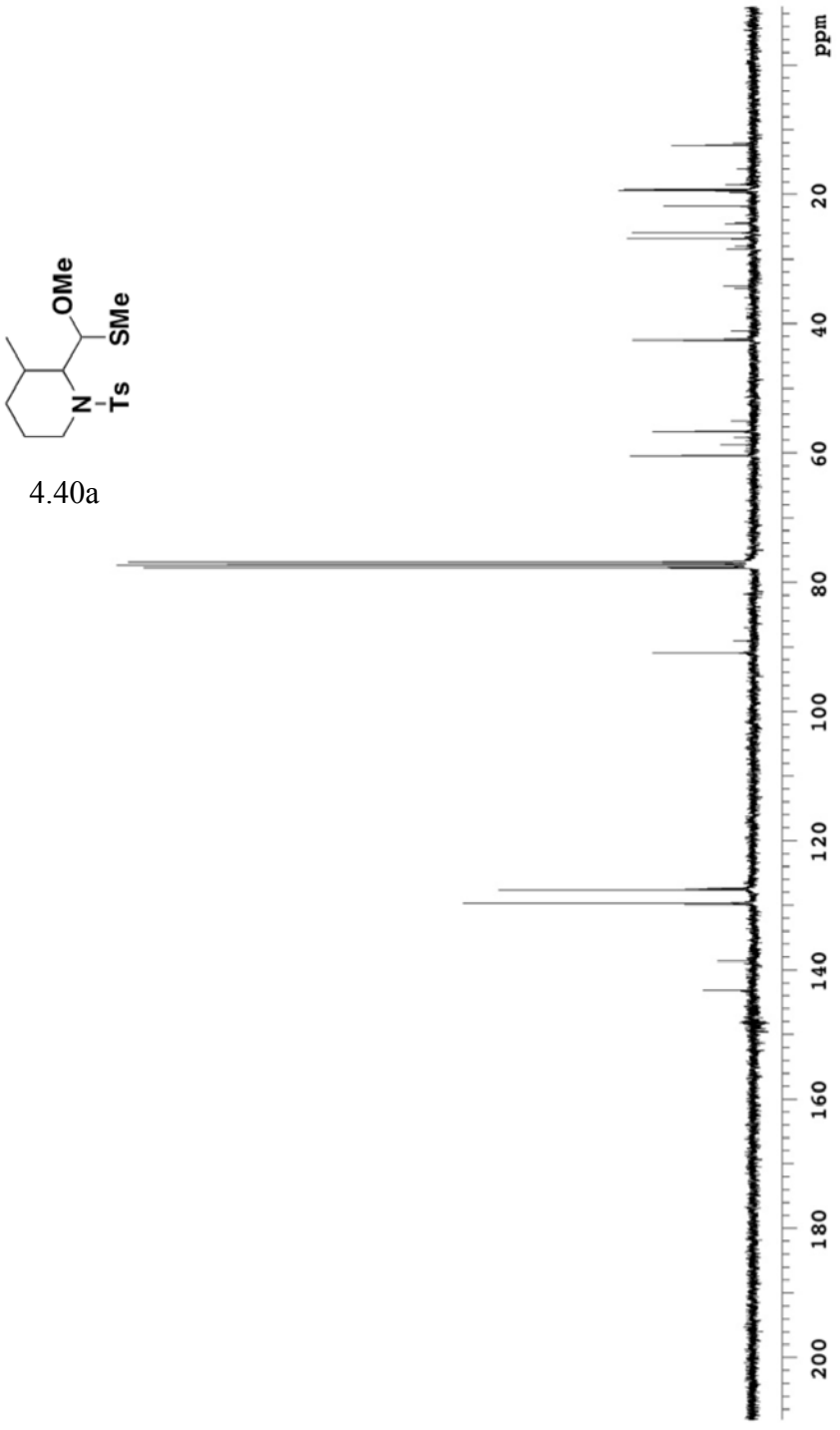

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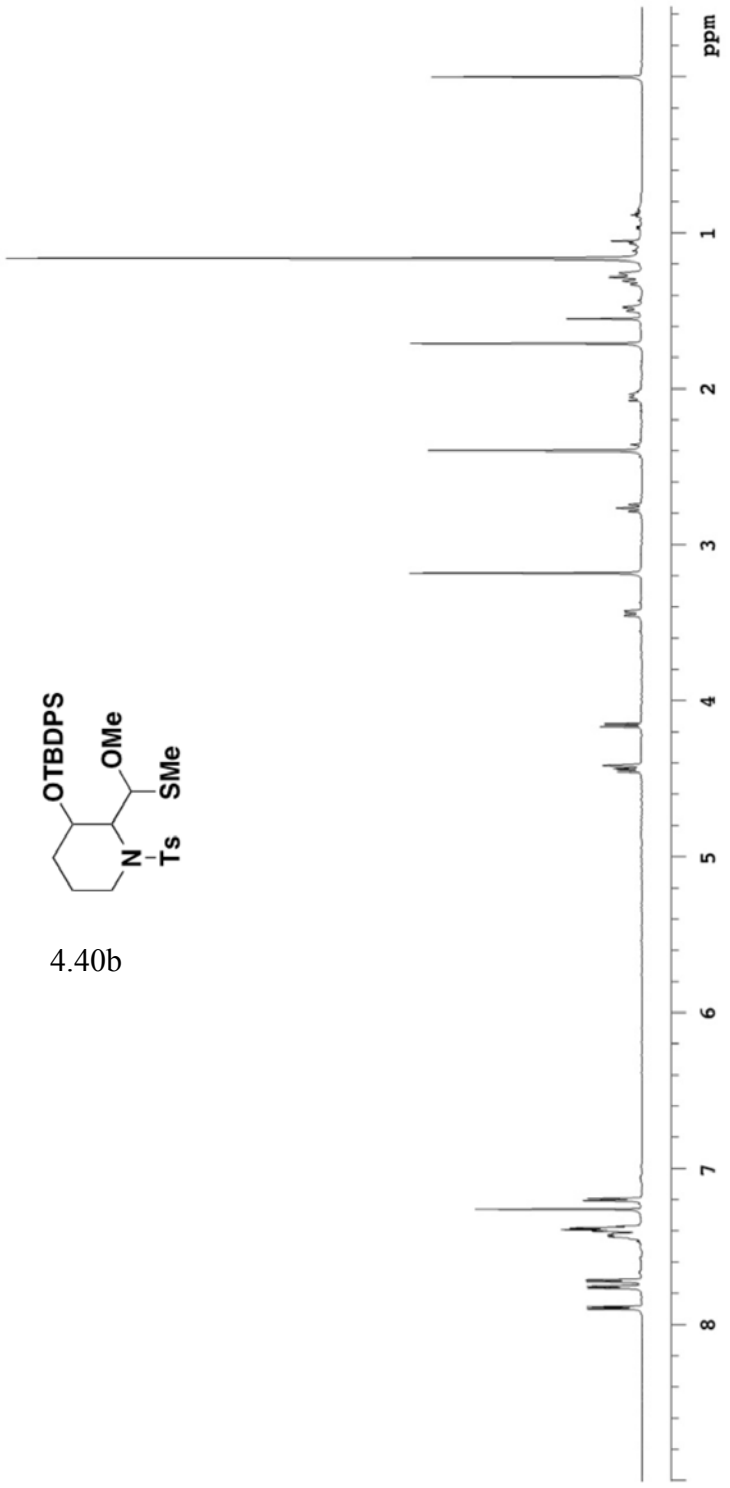

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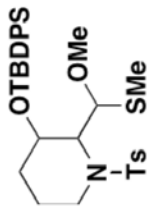

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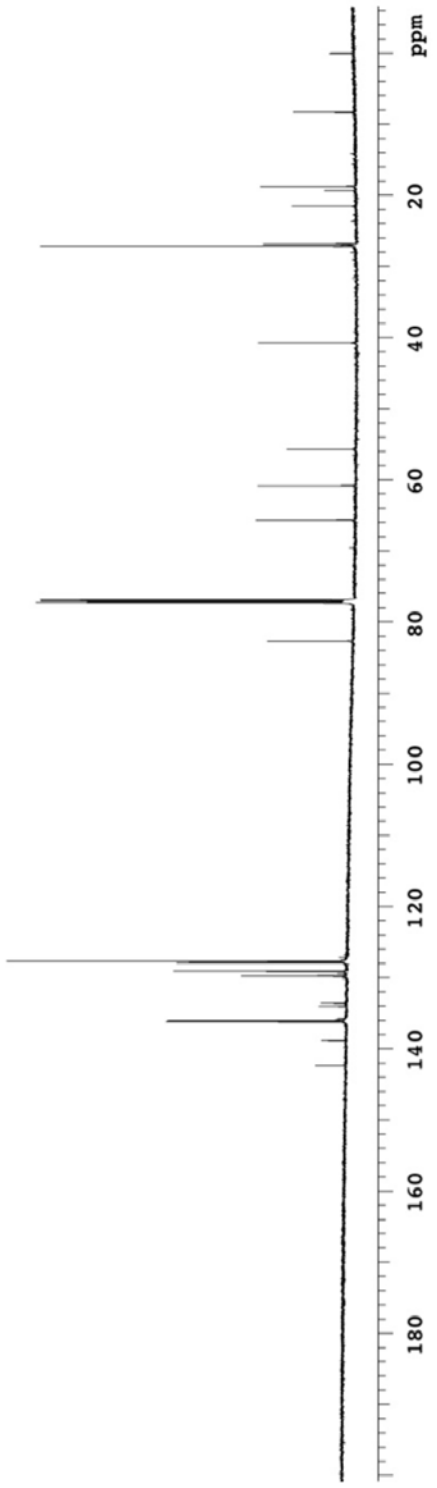

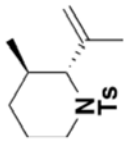

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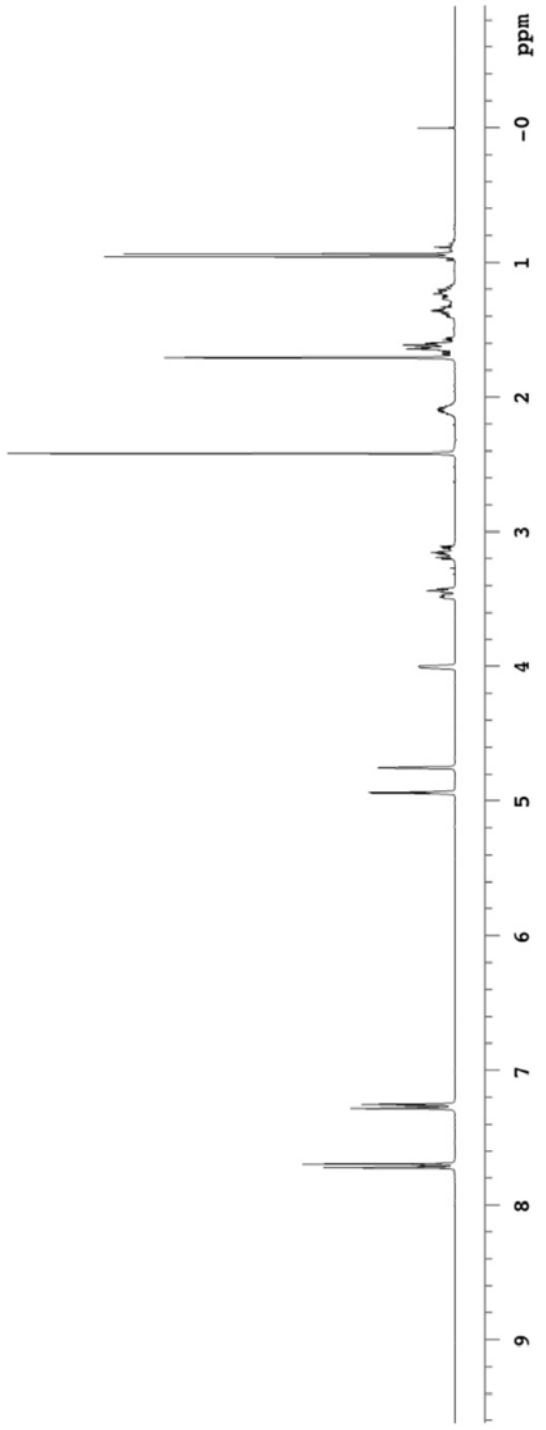

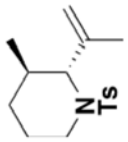

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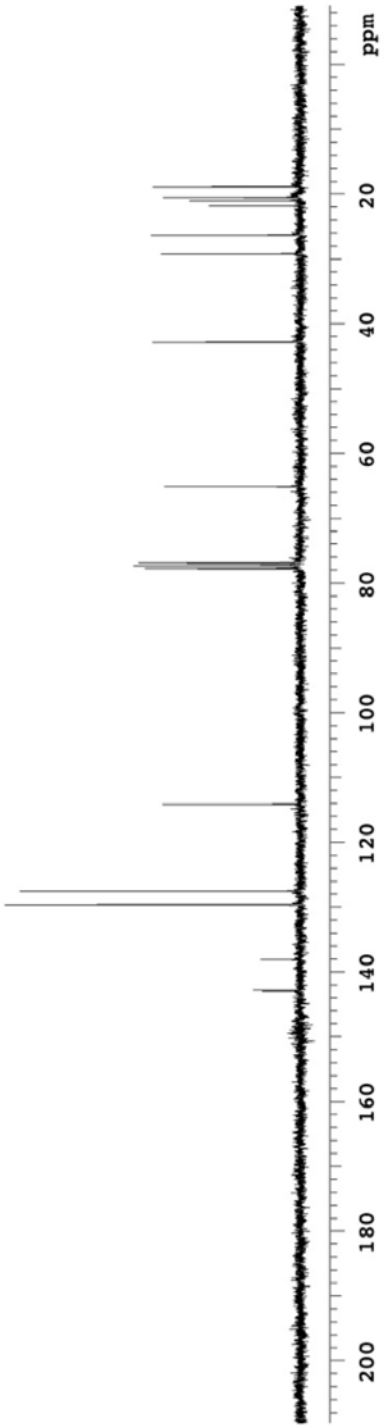

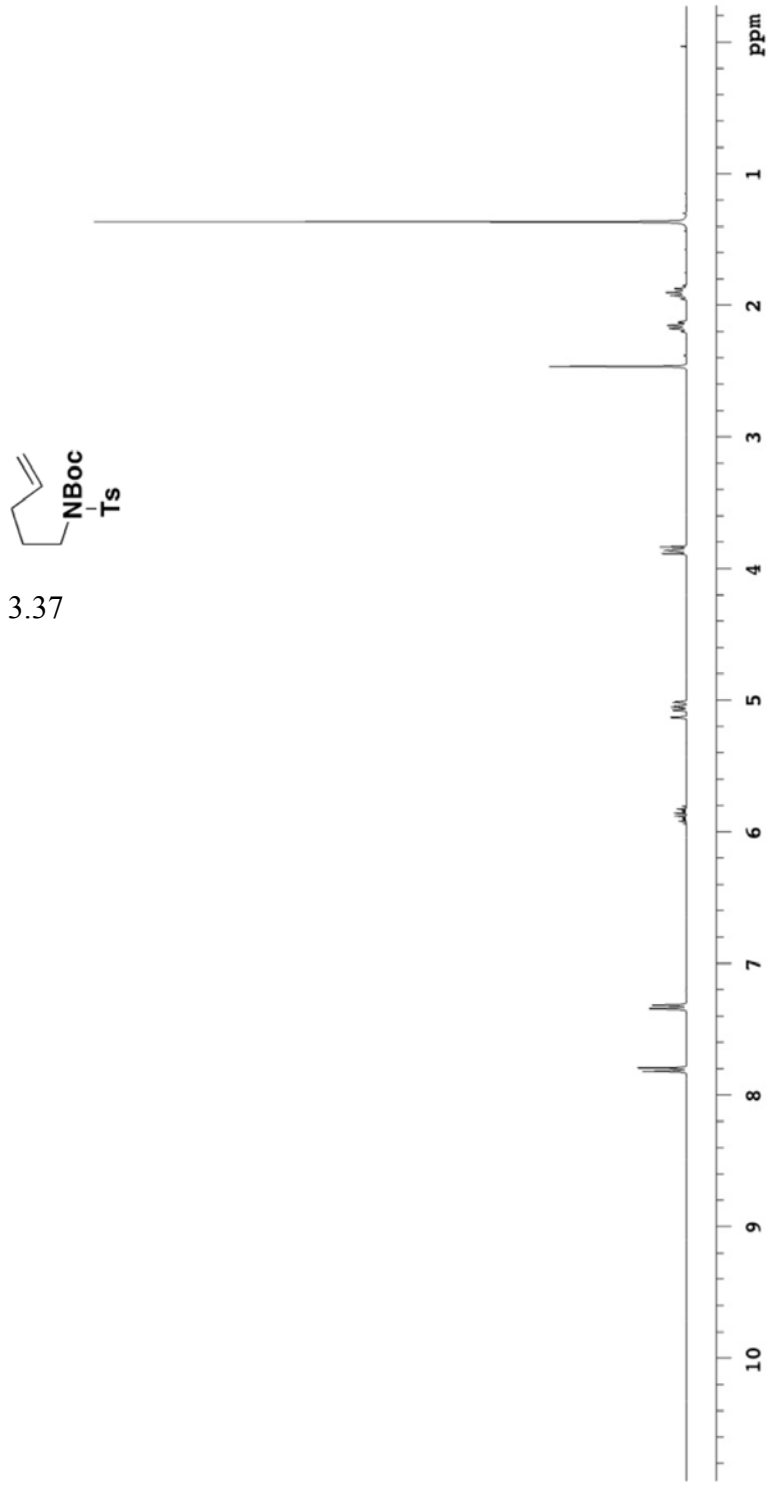

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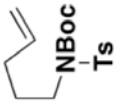

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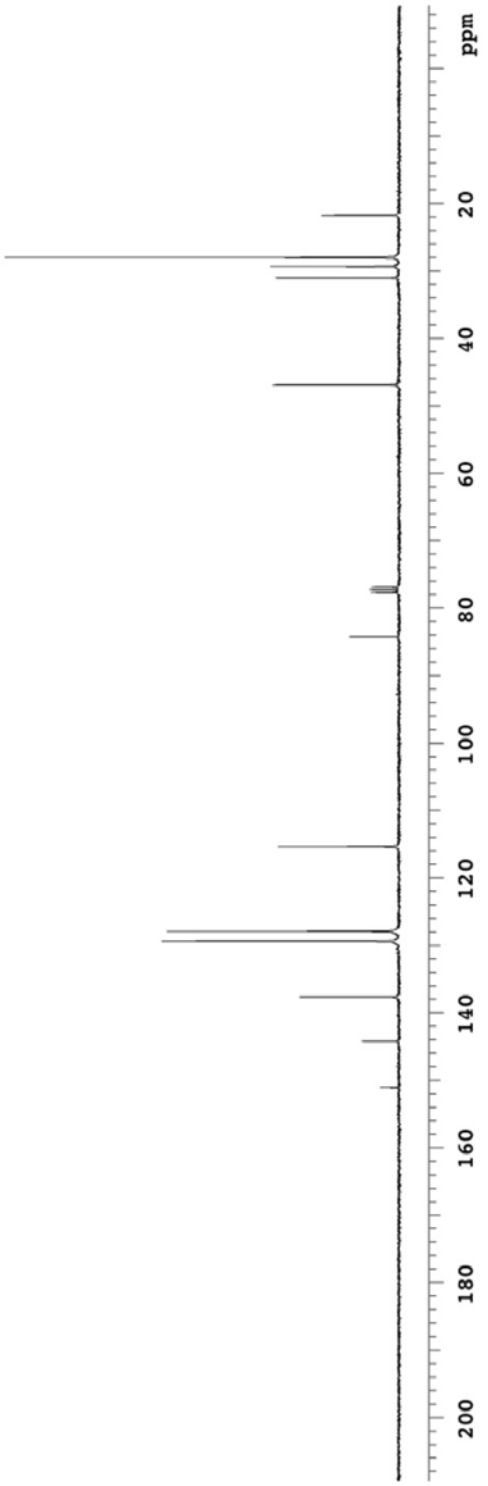

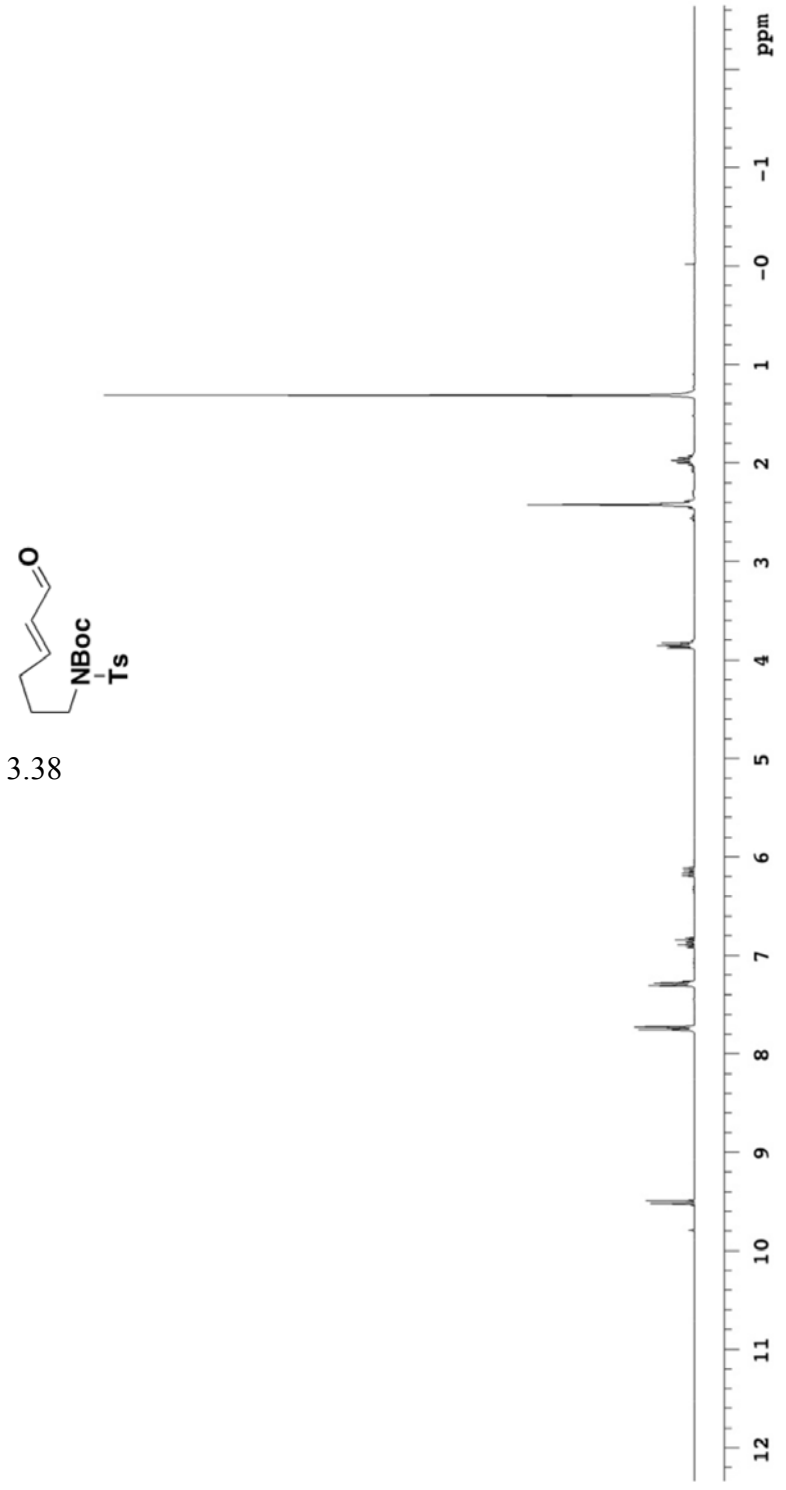

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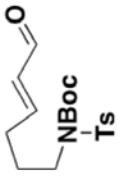

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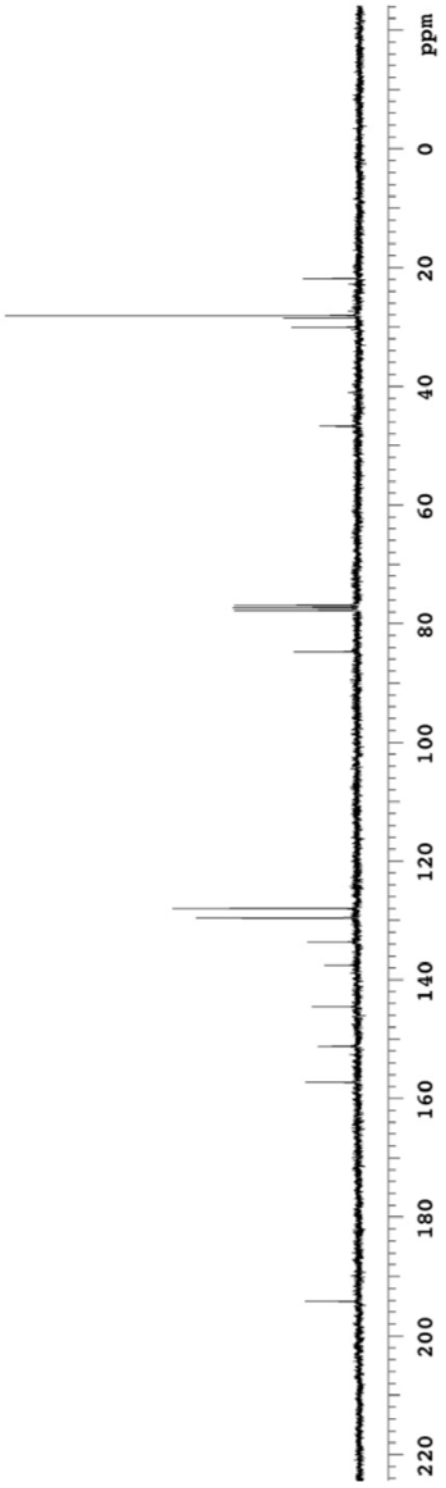

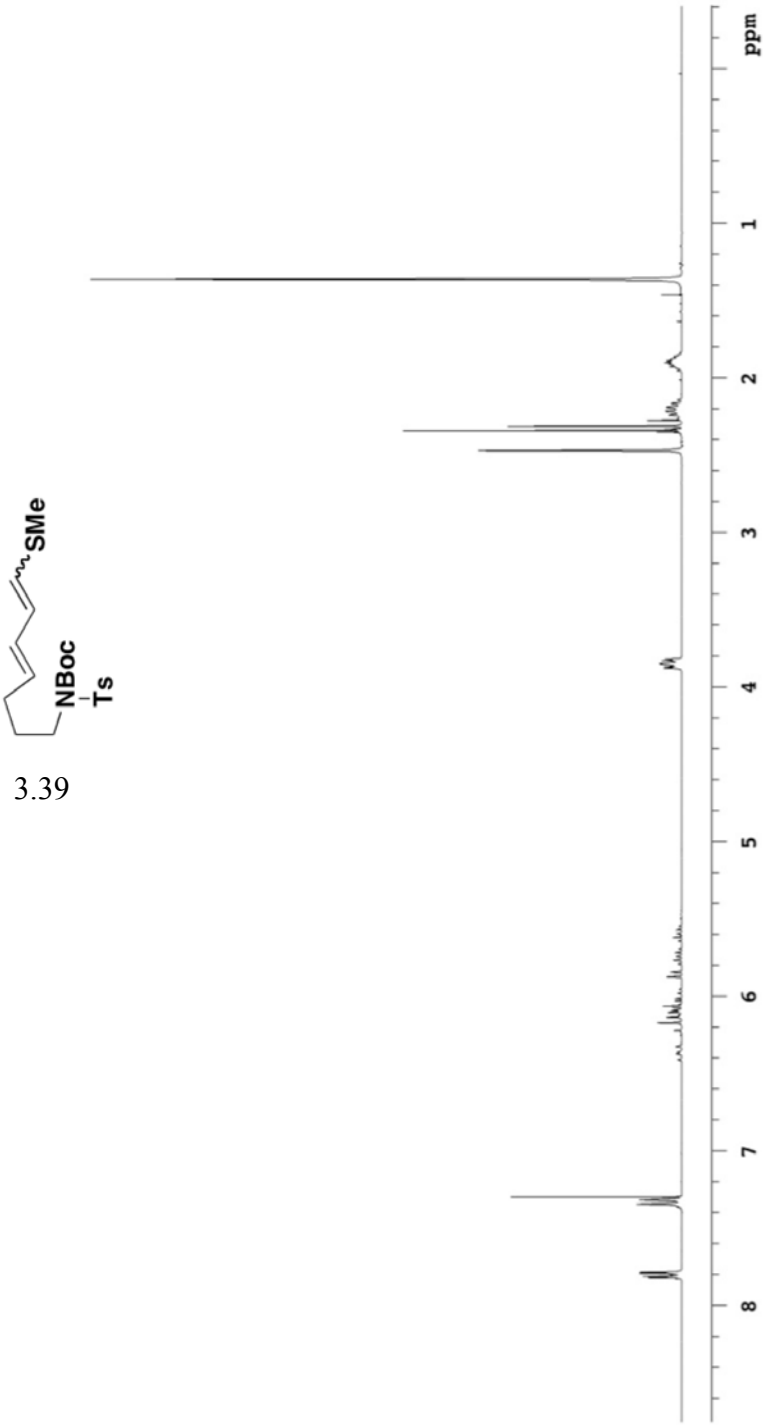

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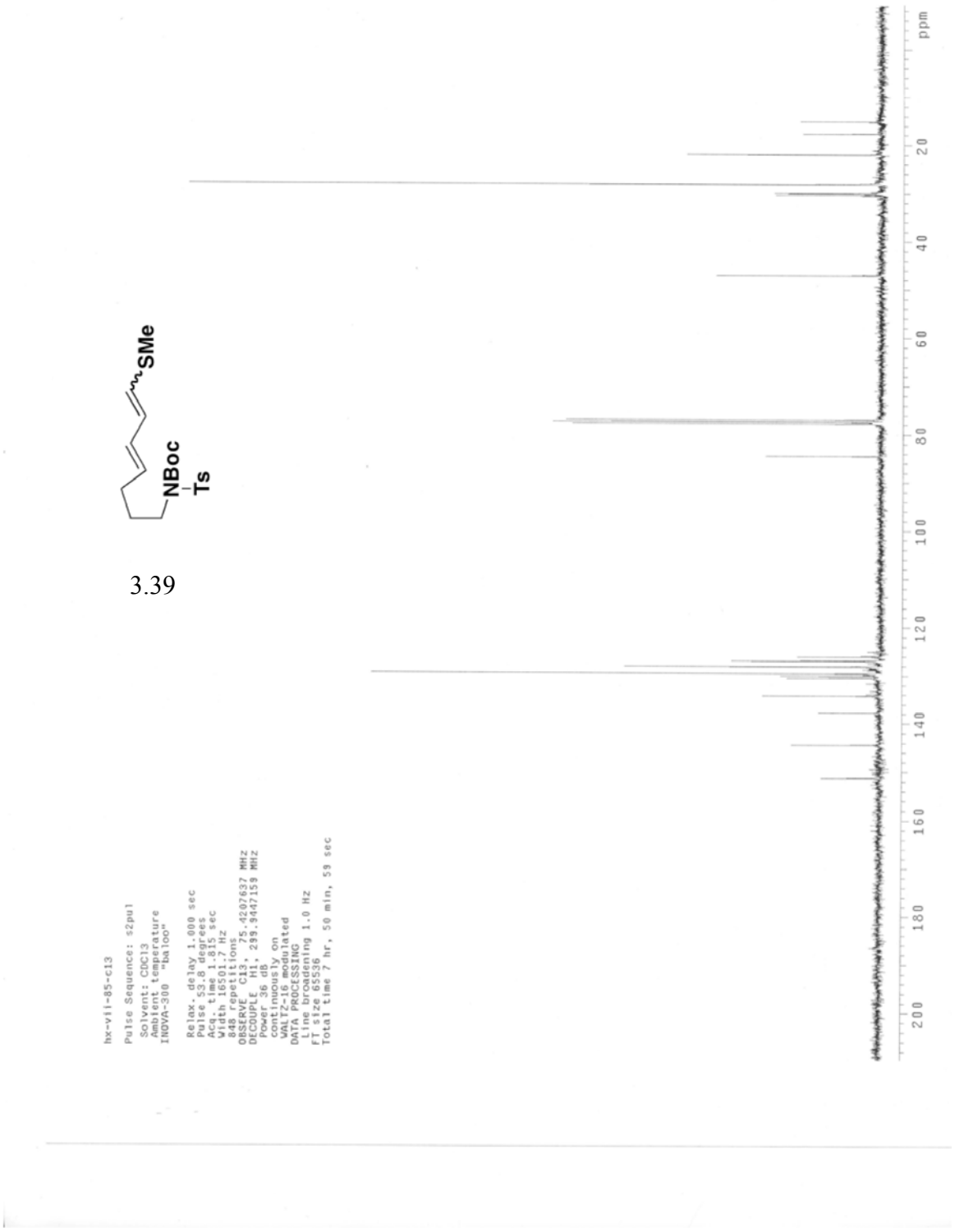
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Solvent: CDCl3
Ambient temperature
INOVA-300 "baloo"
Relax. delay 1.000 sec
Pulse 53.8 degrees
Acq. time 1.815 sec
Width 16501.7 Hz
848 repetitions
OBSERVE C13, 75.4207637 MHz
DECOUPLE H1, 299.9447159 MHz
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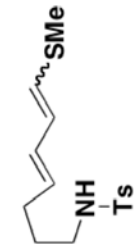
3.39



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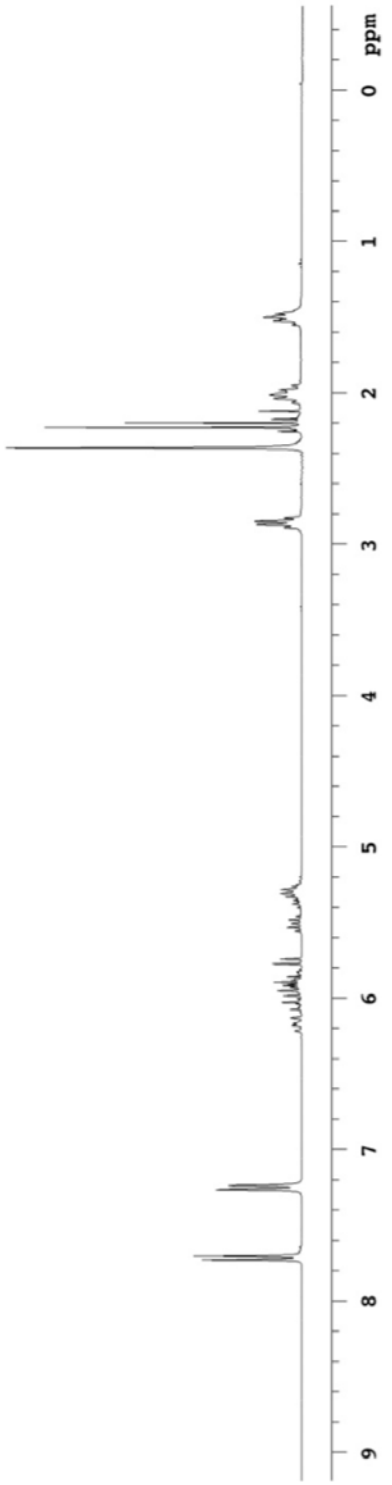

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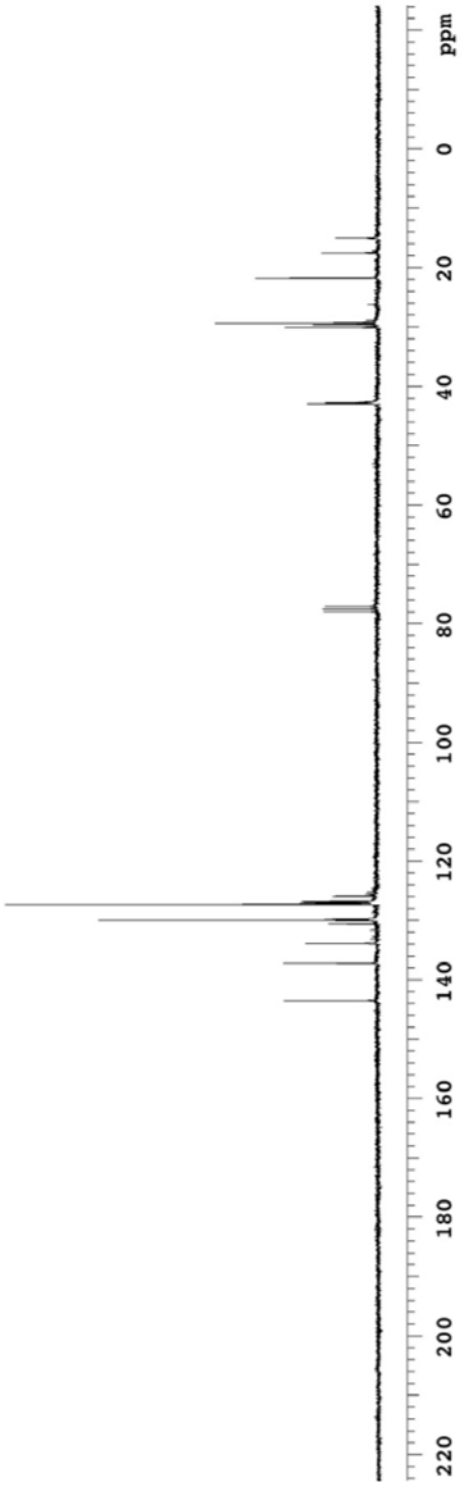

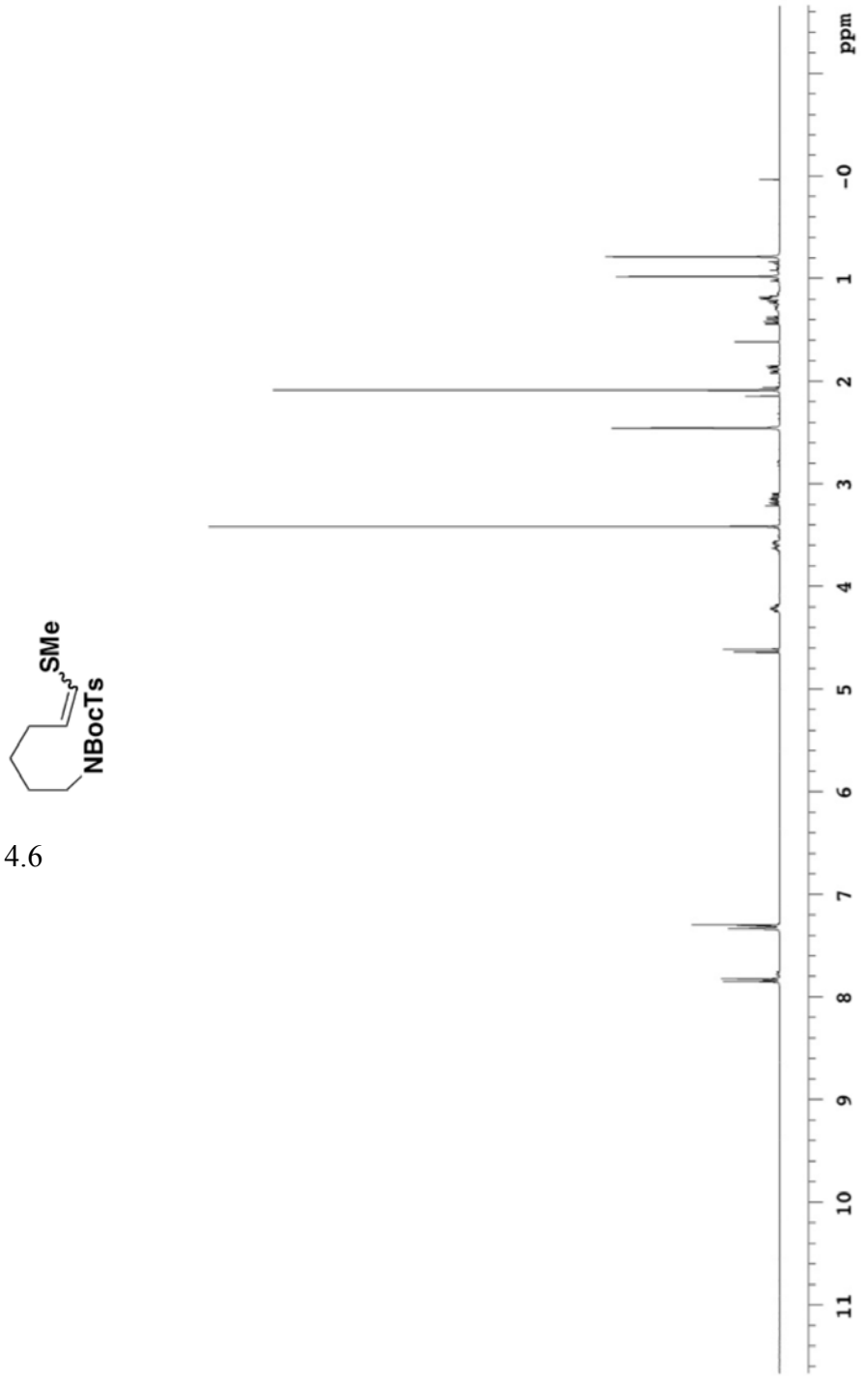

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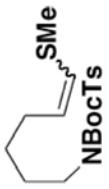

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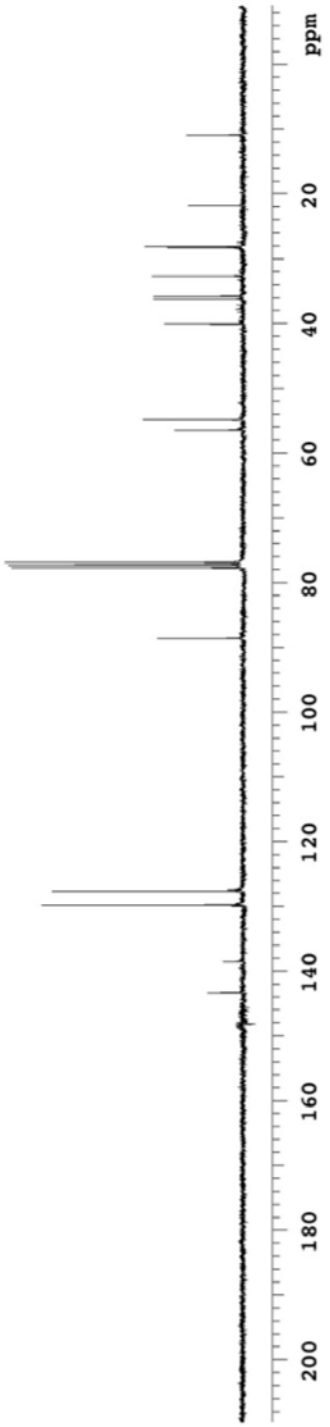

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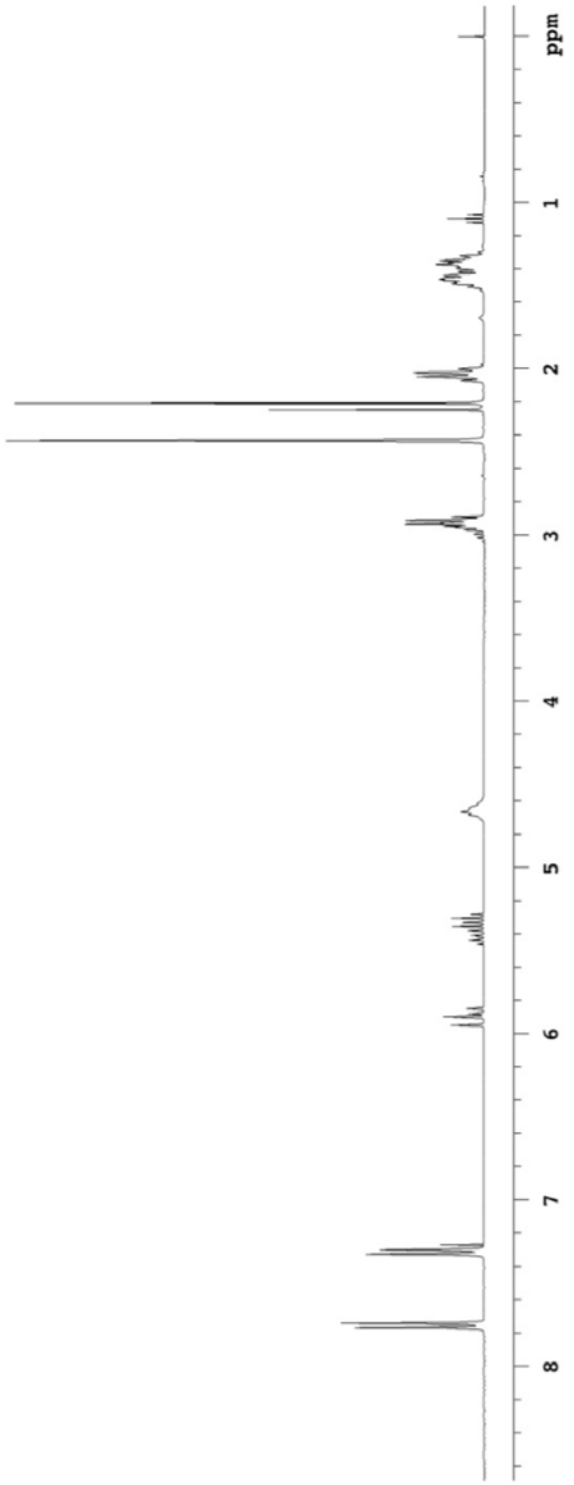

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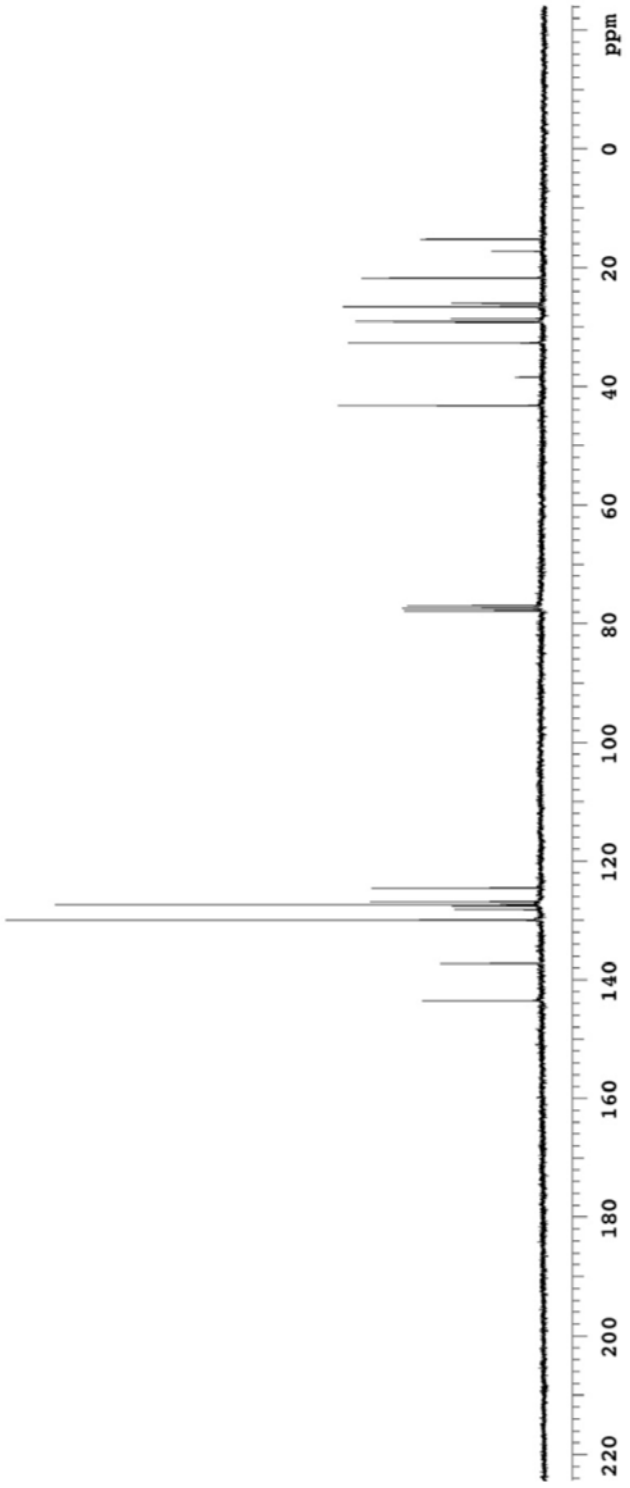

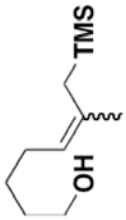

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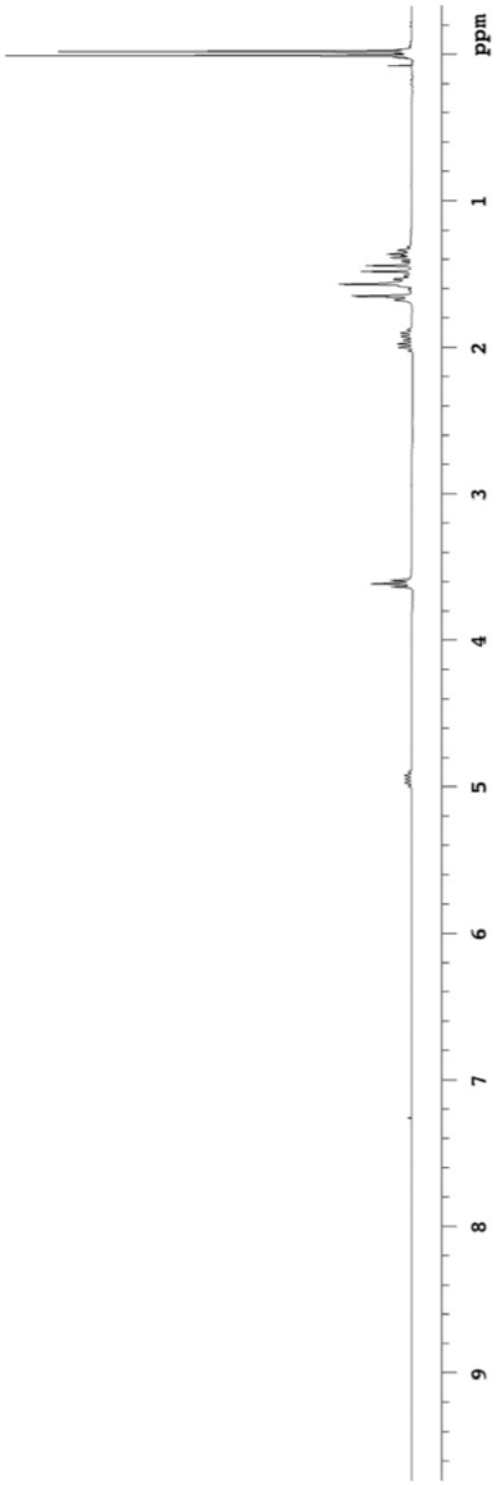

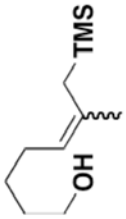

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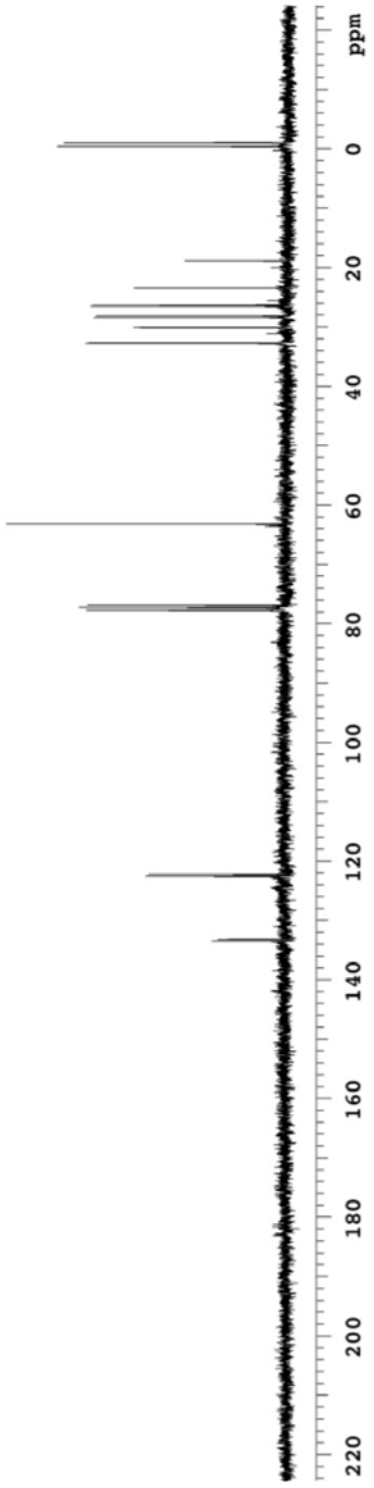

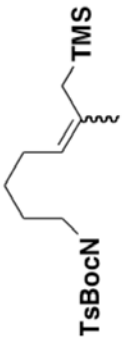

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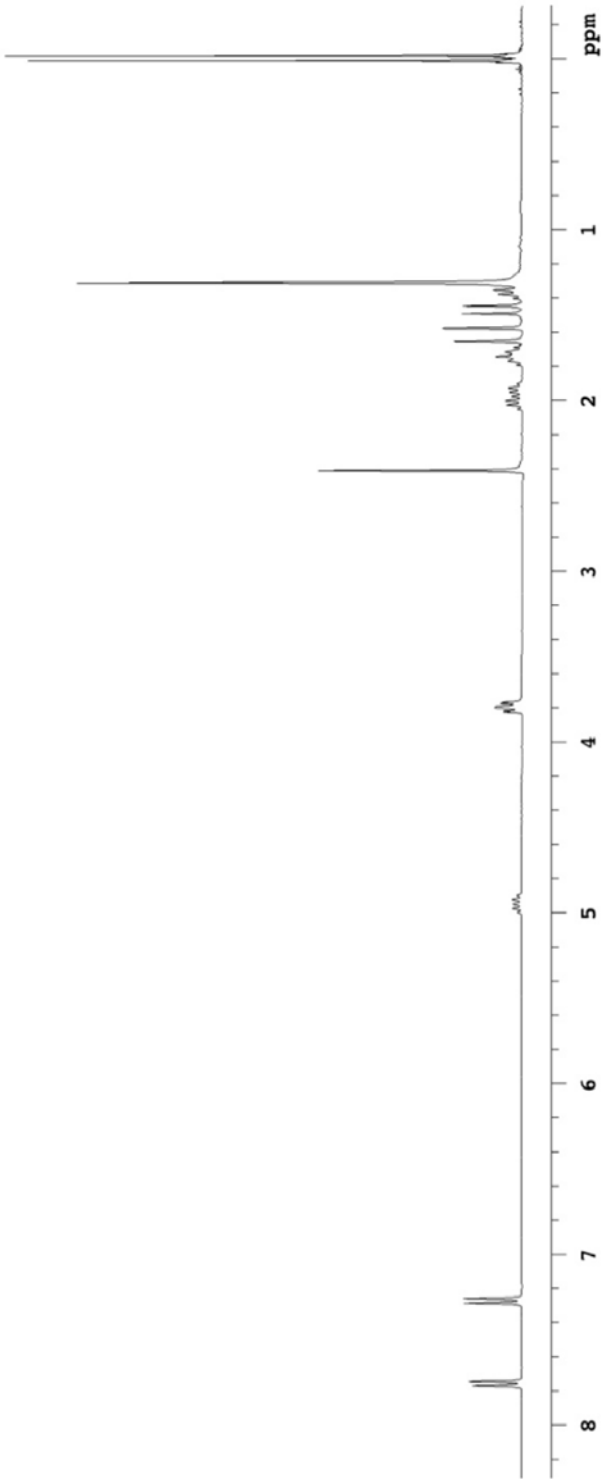

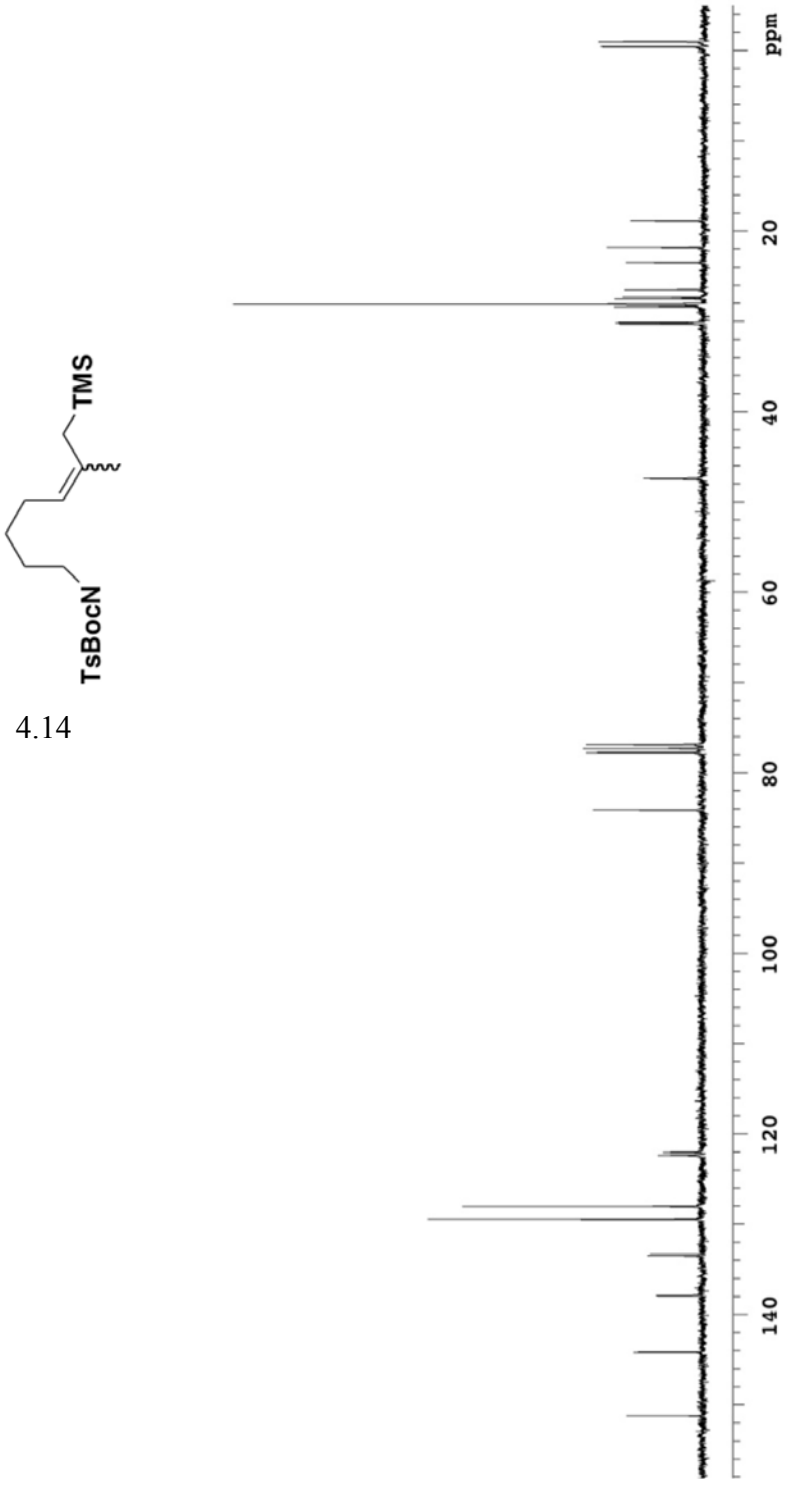

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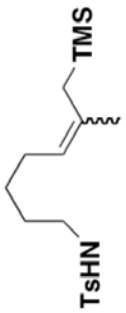

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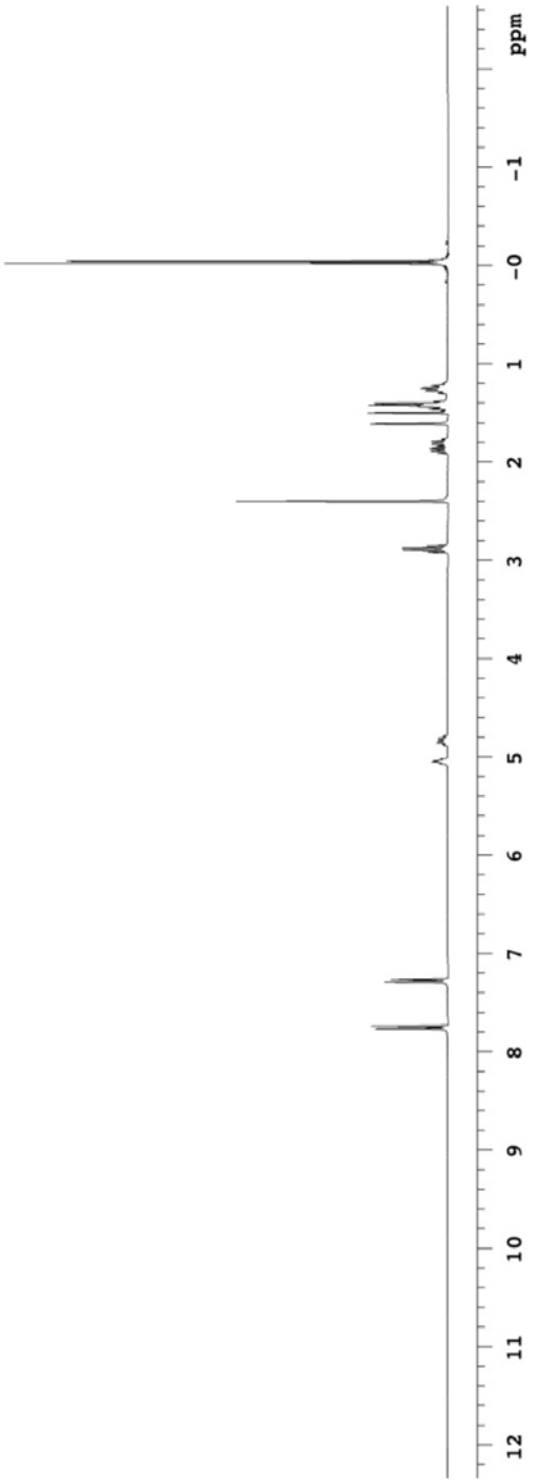

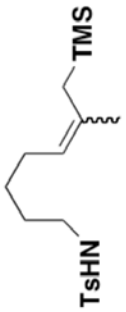

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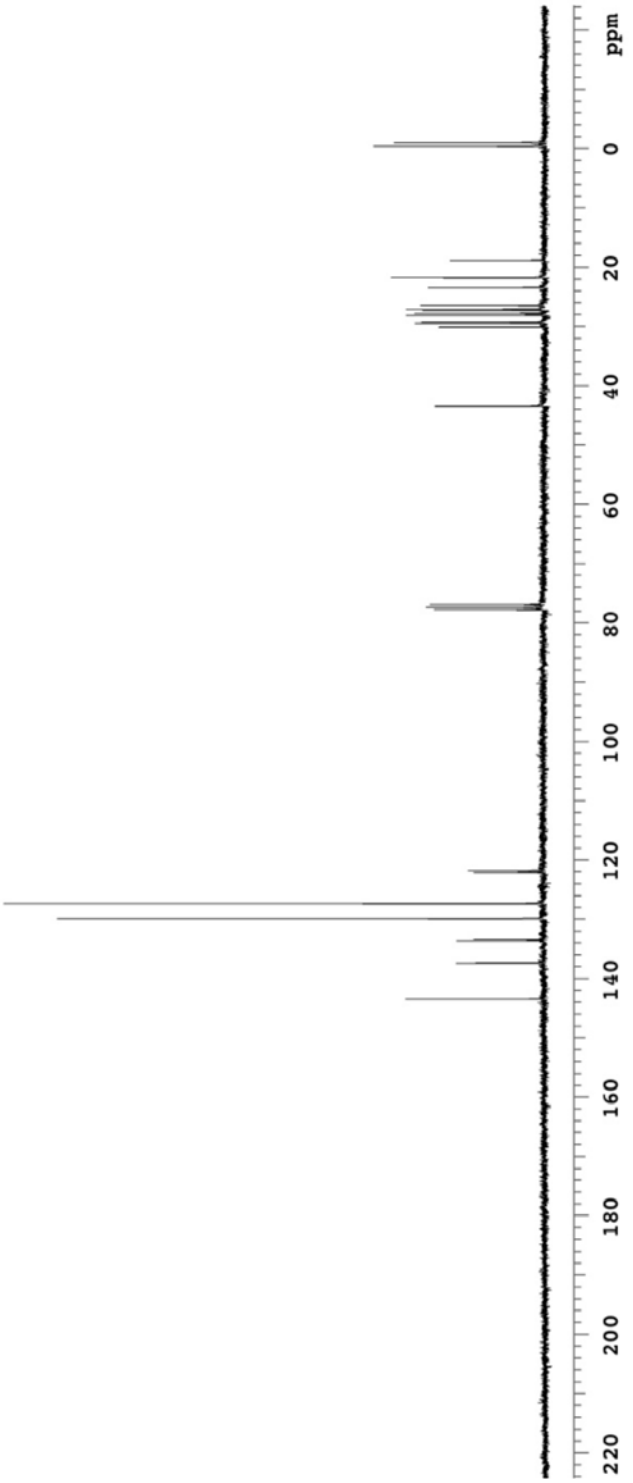

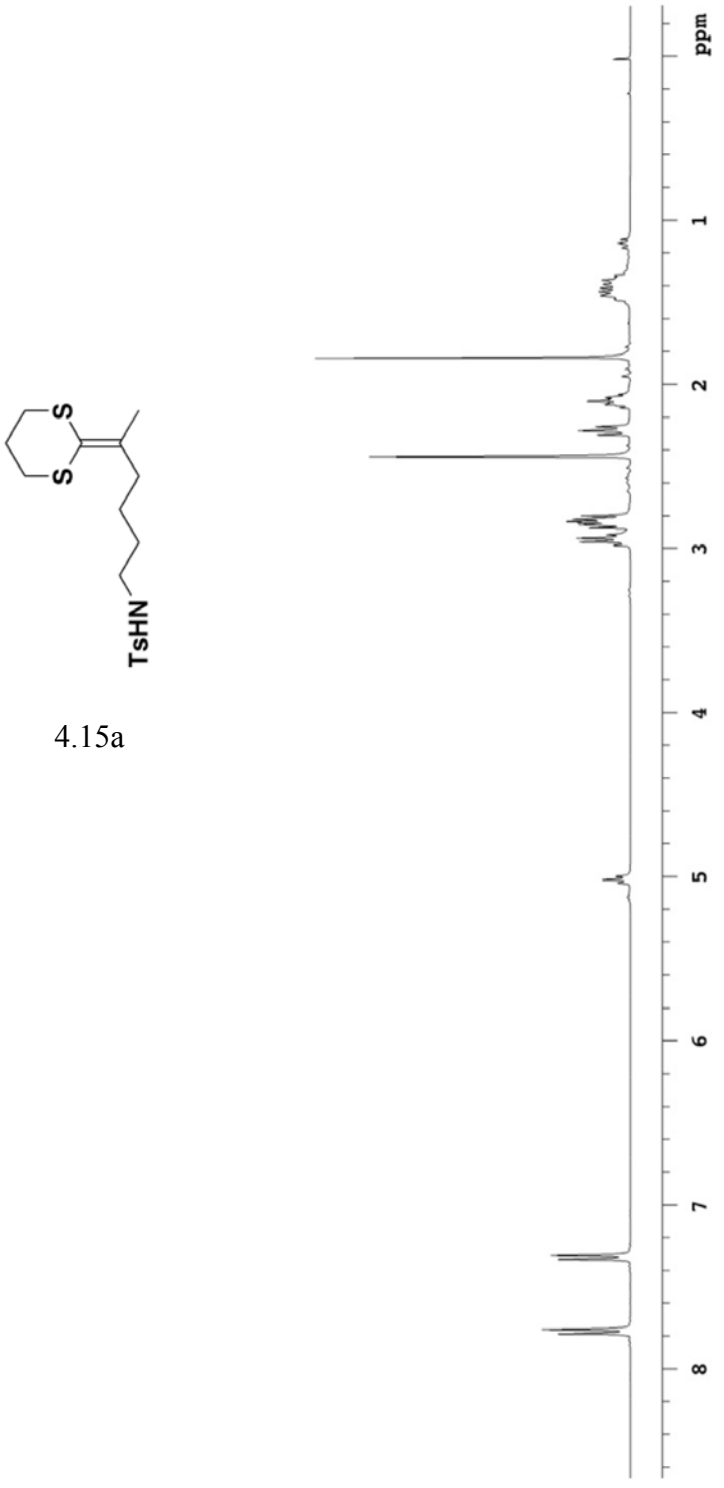

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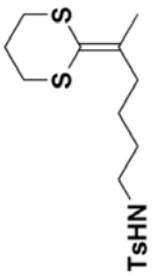

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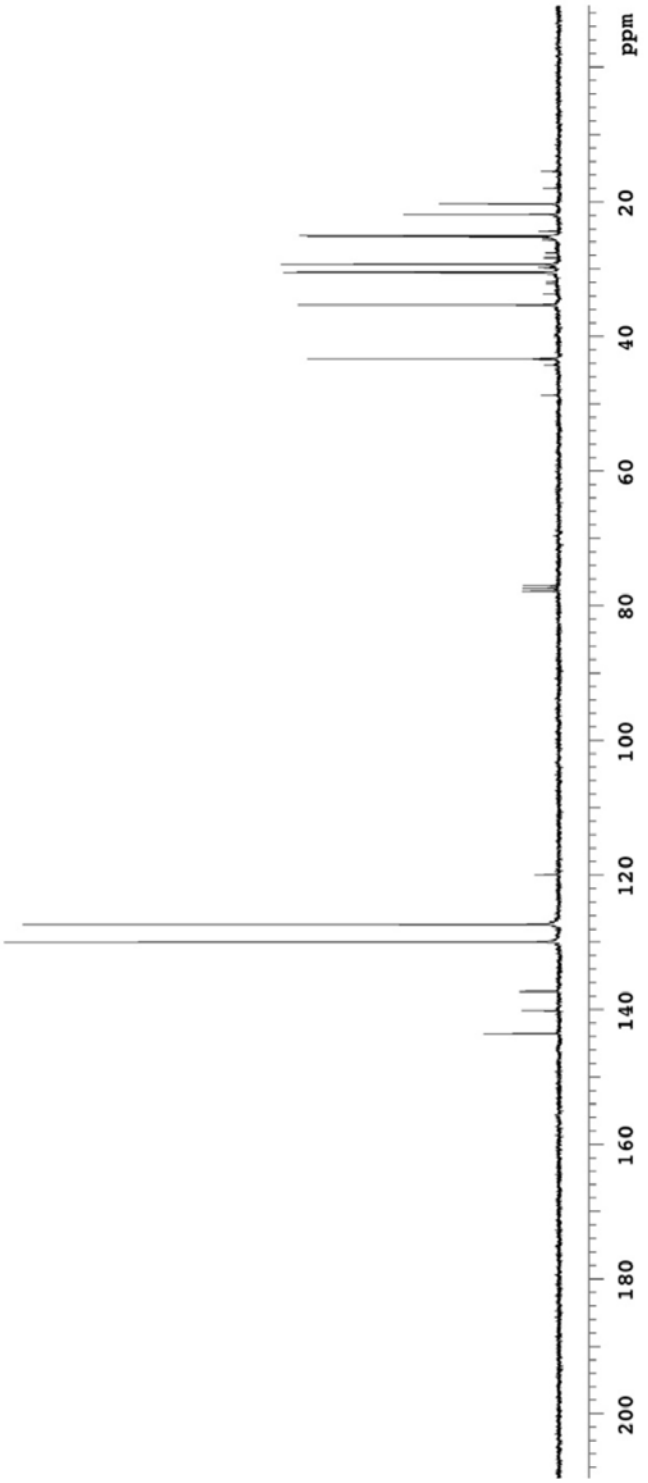

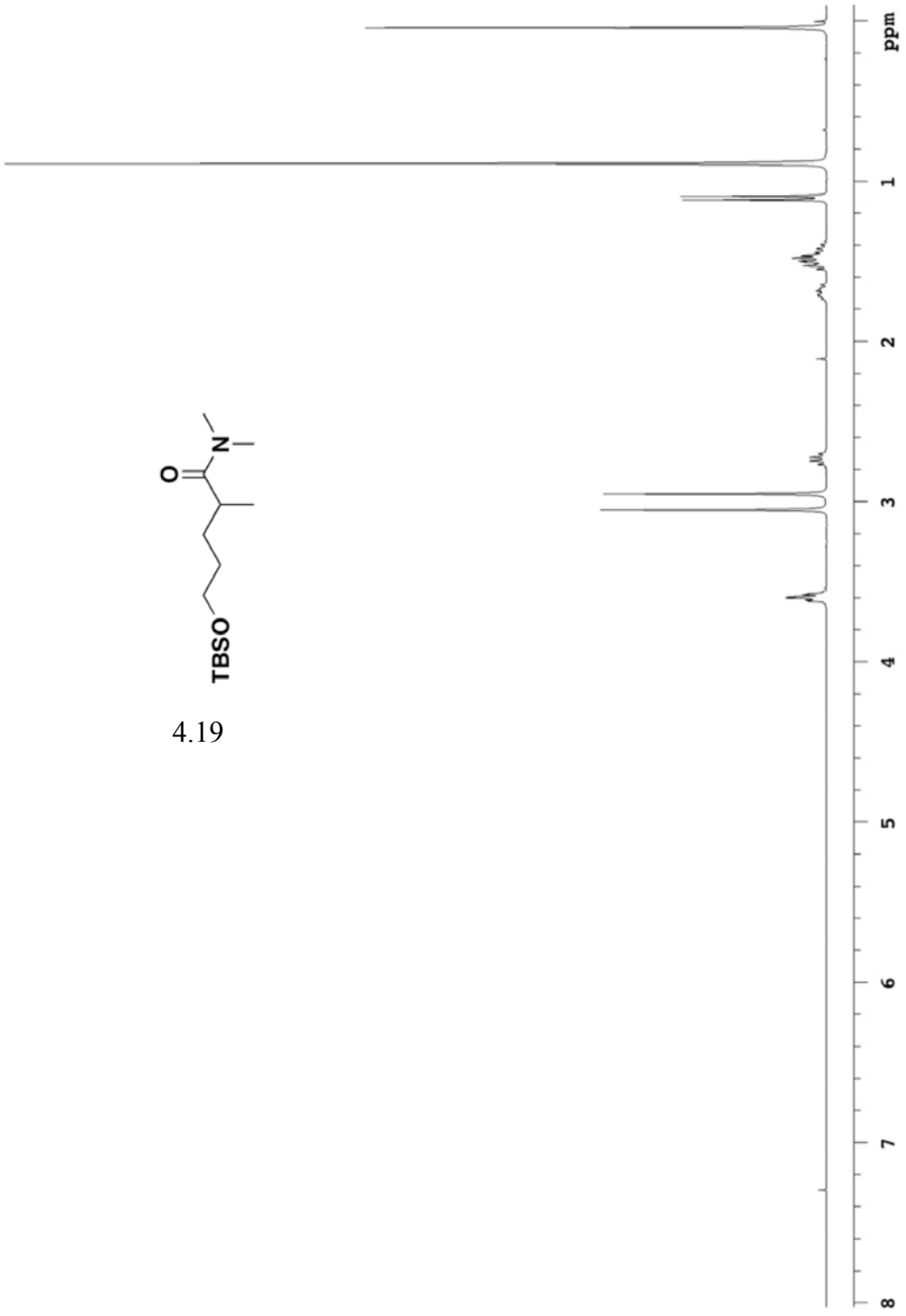

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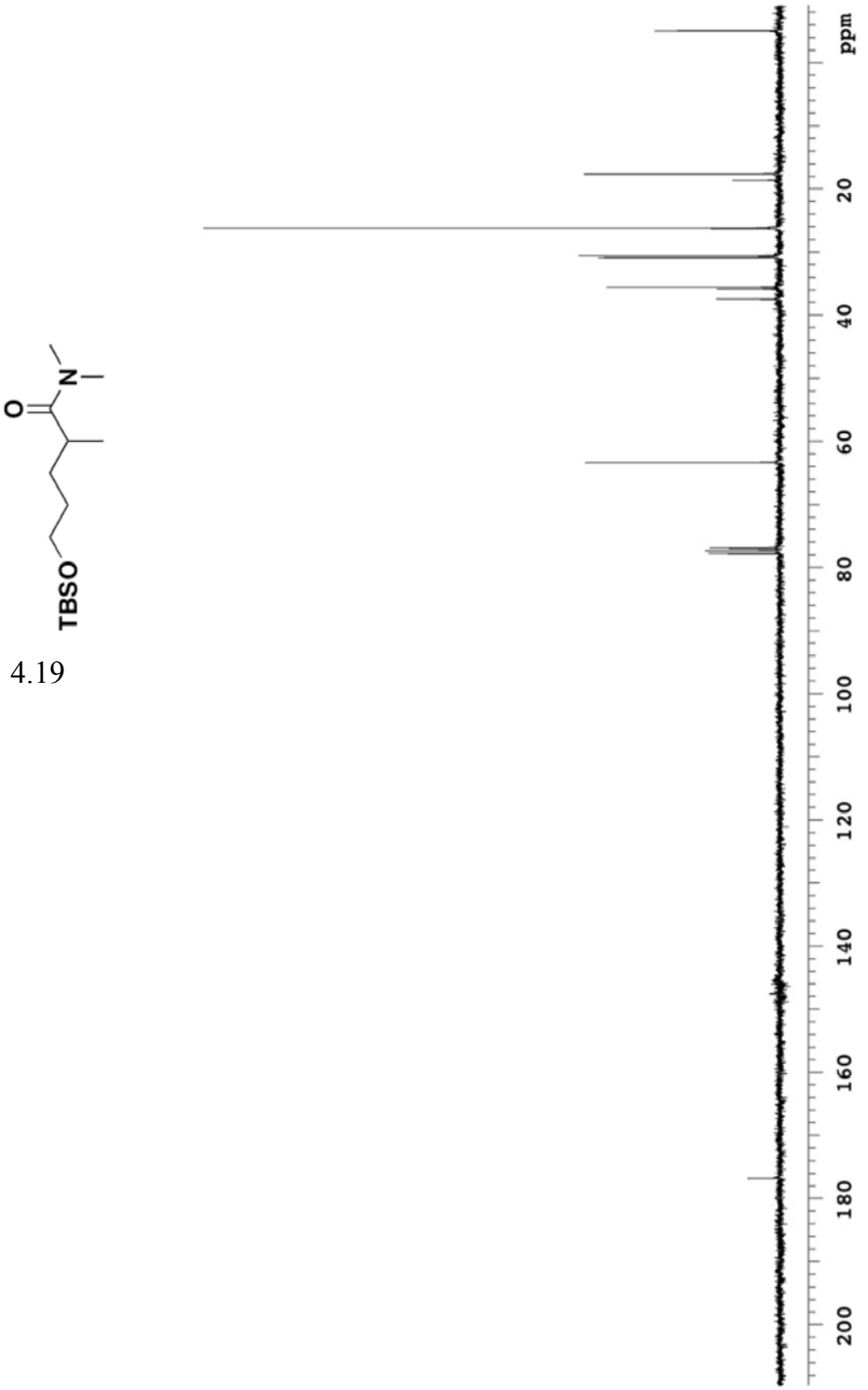

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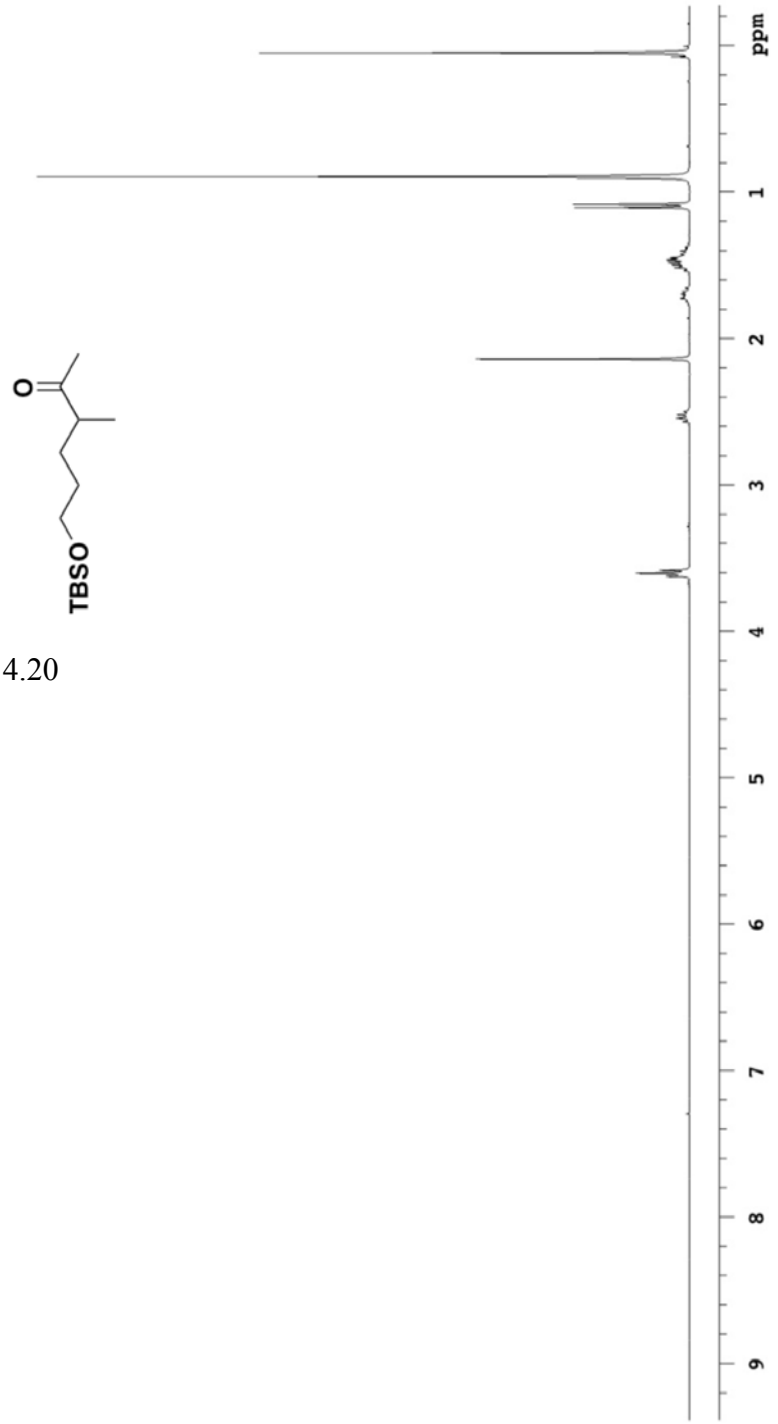

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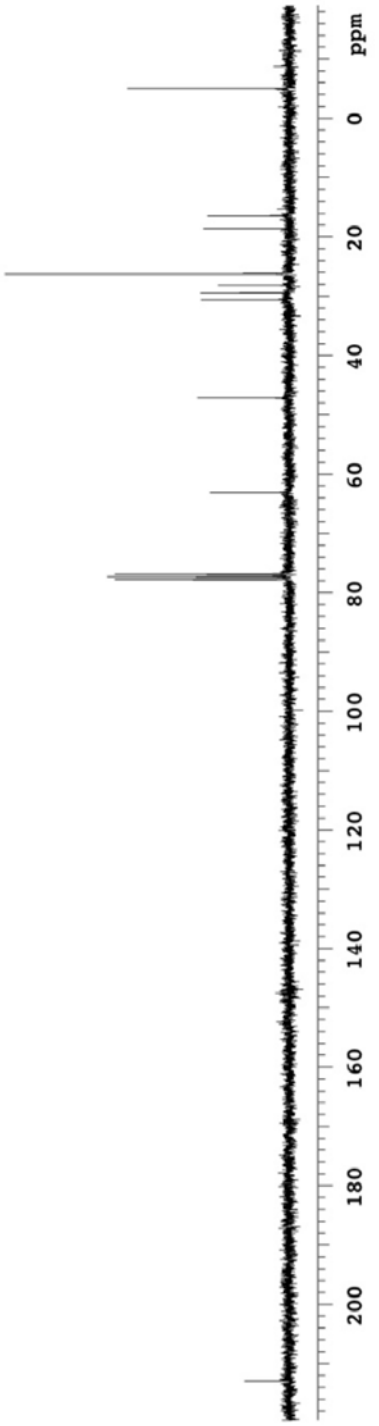

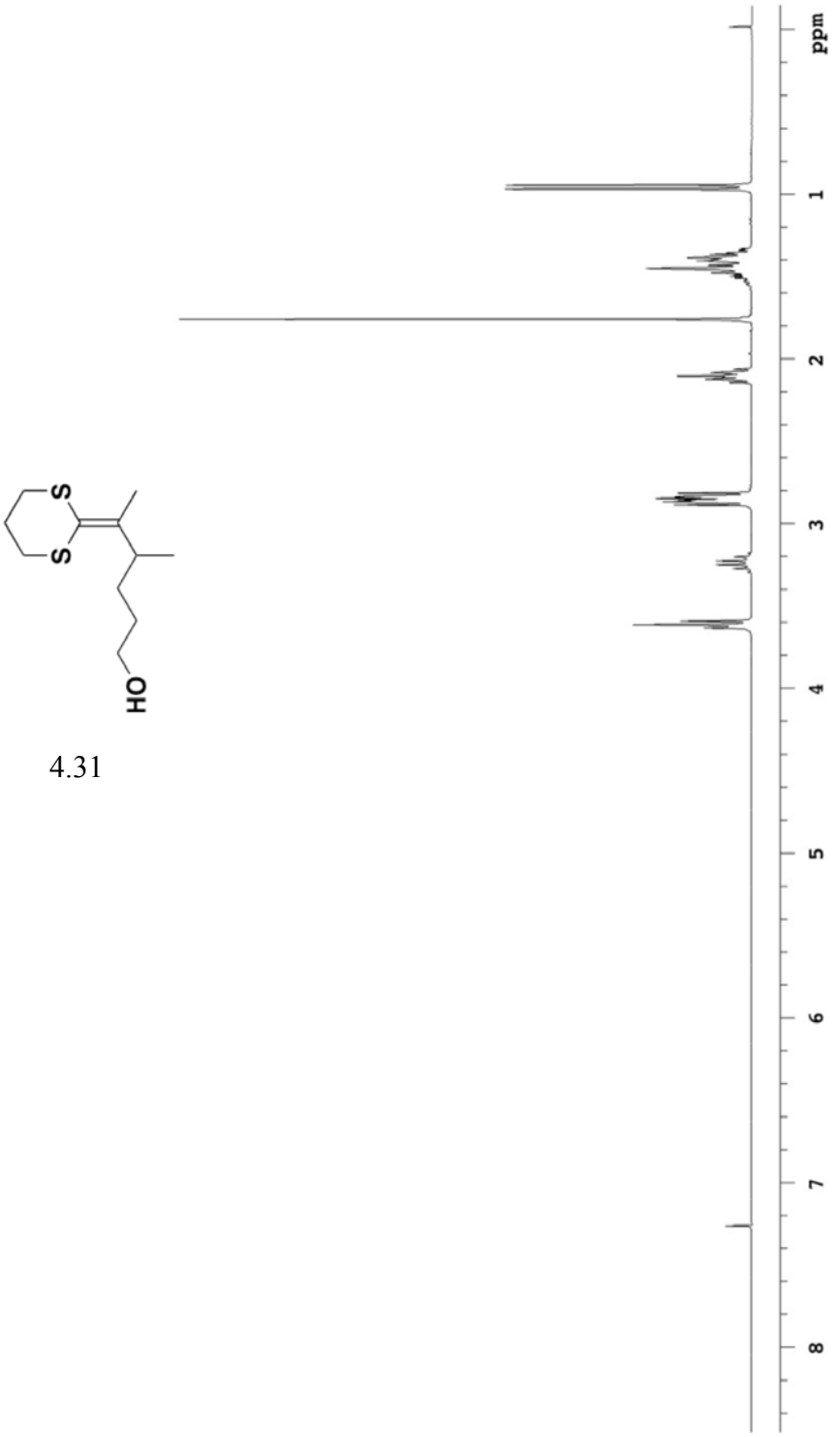

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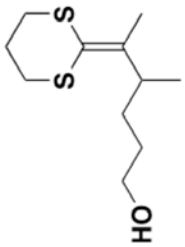

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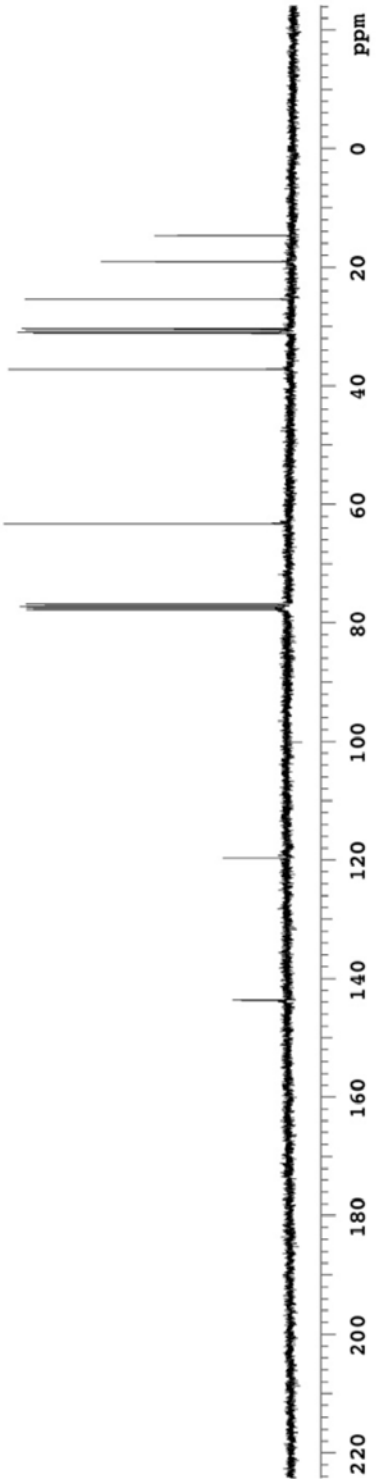

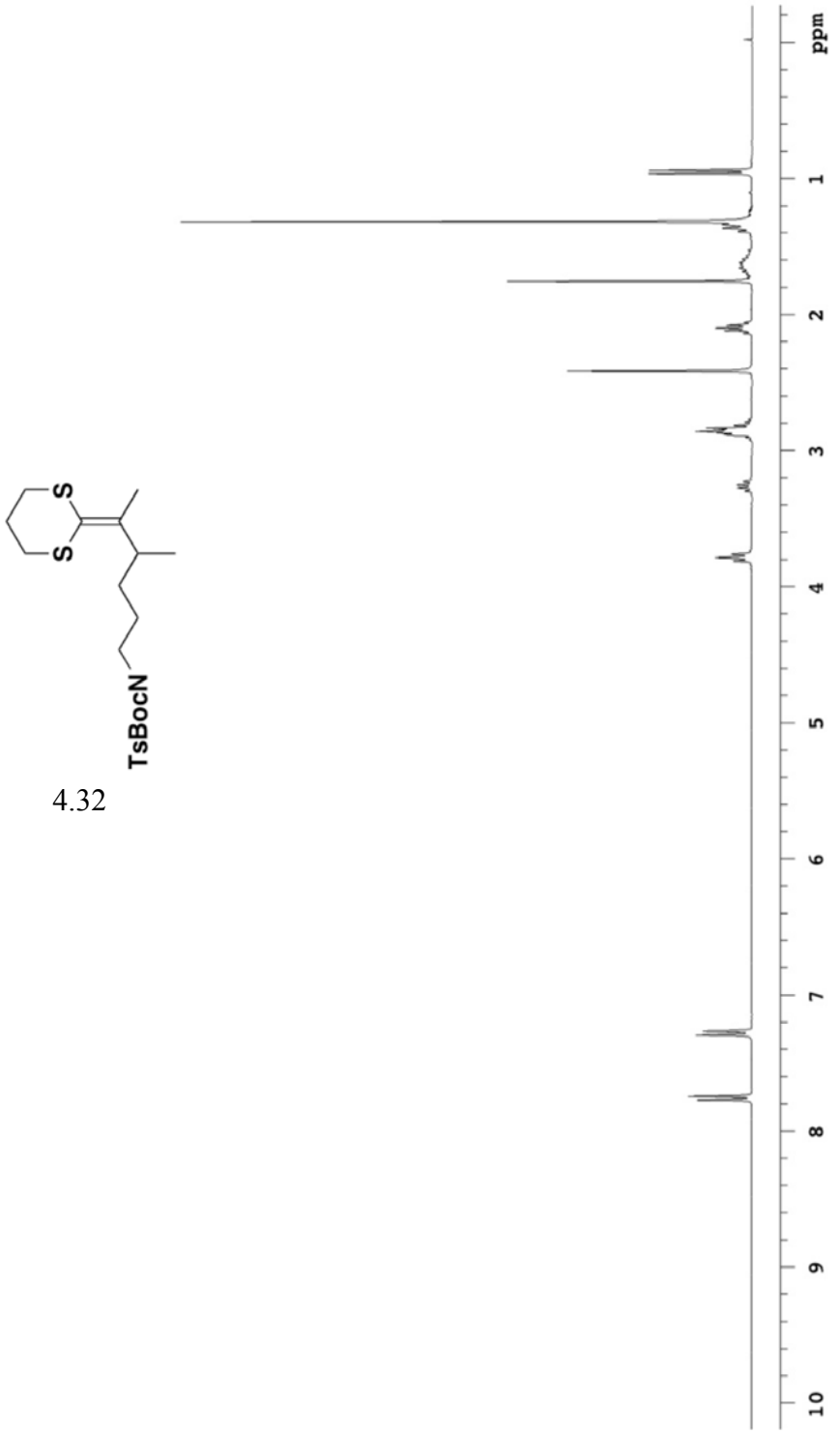

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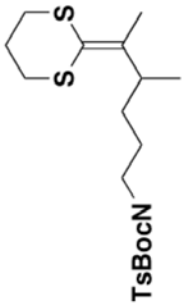

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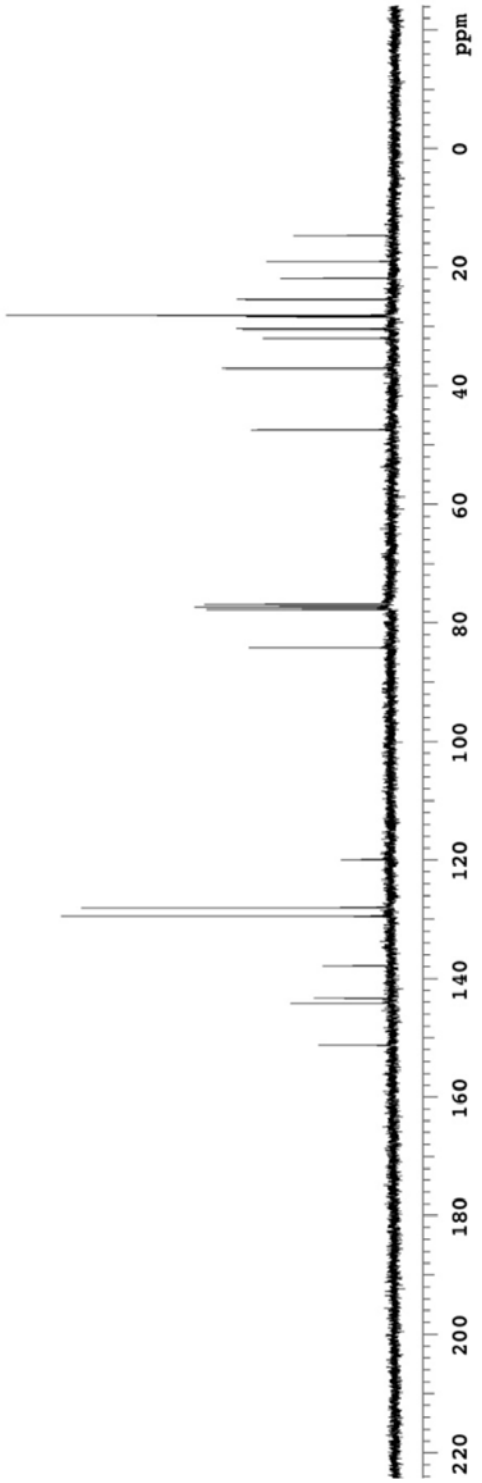

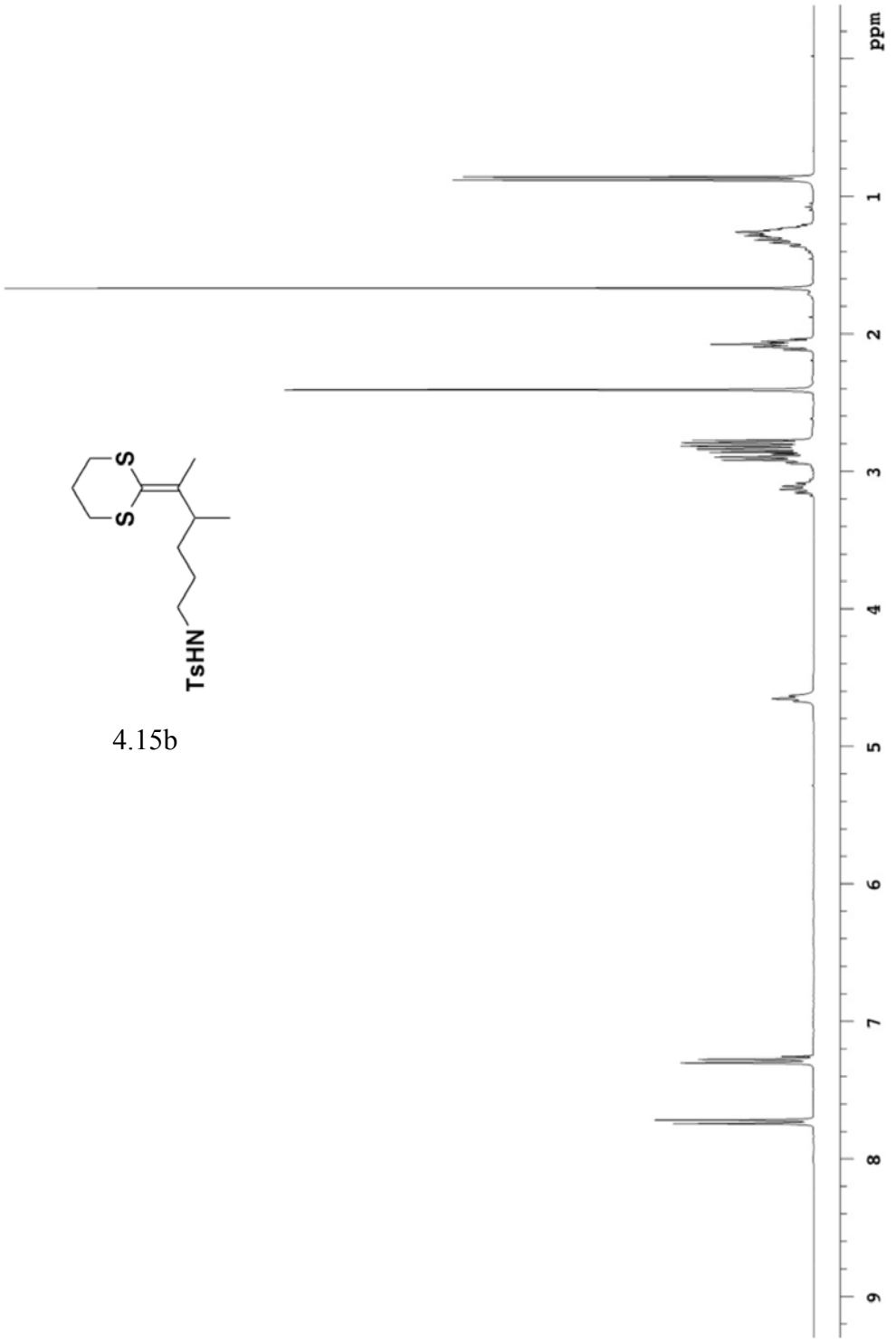

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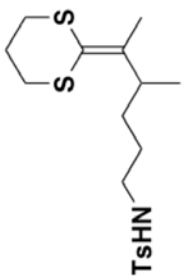

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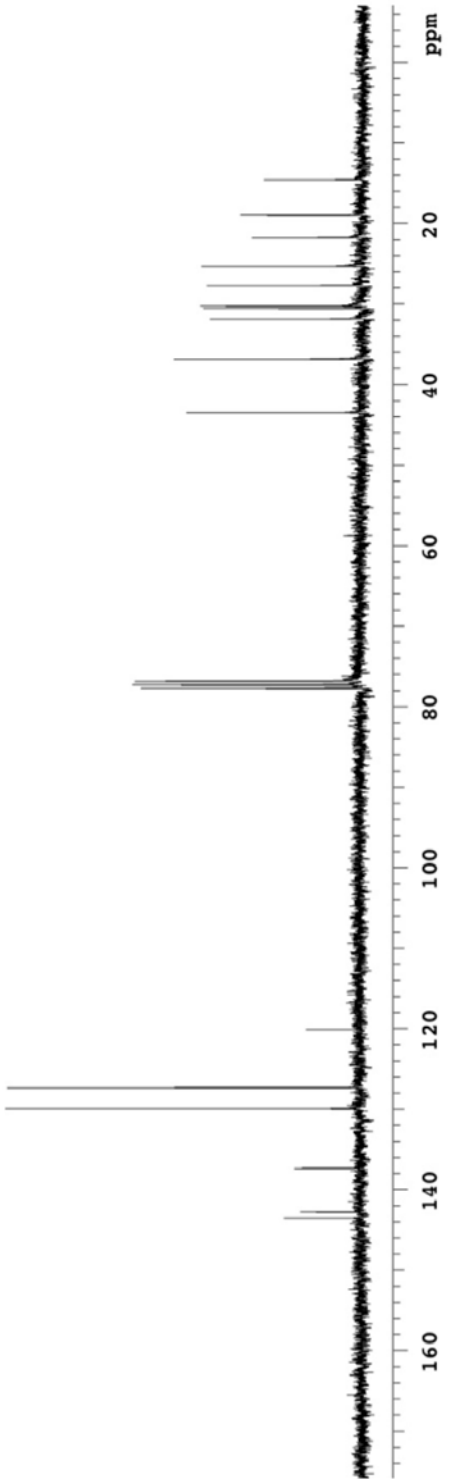

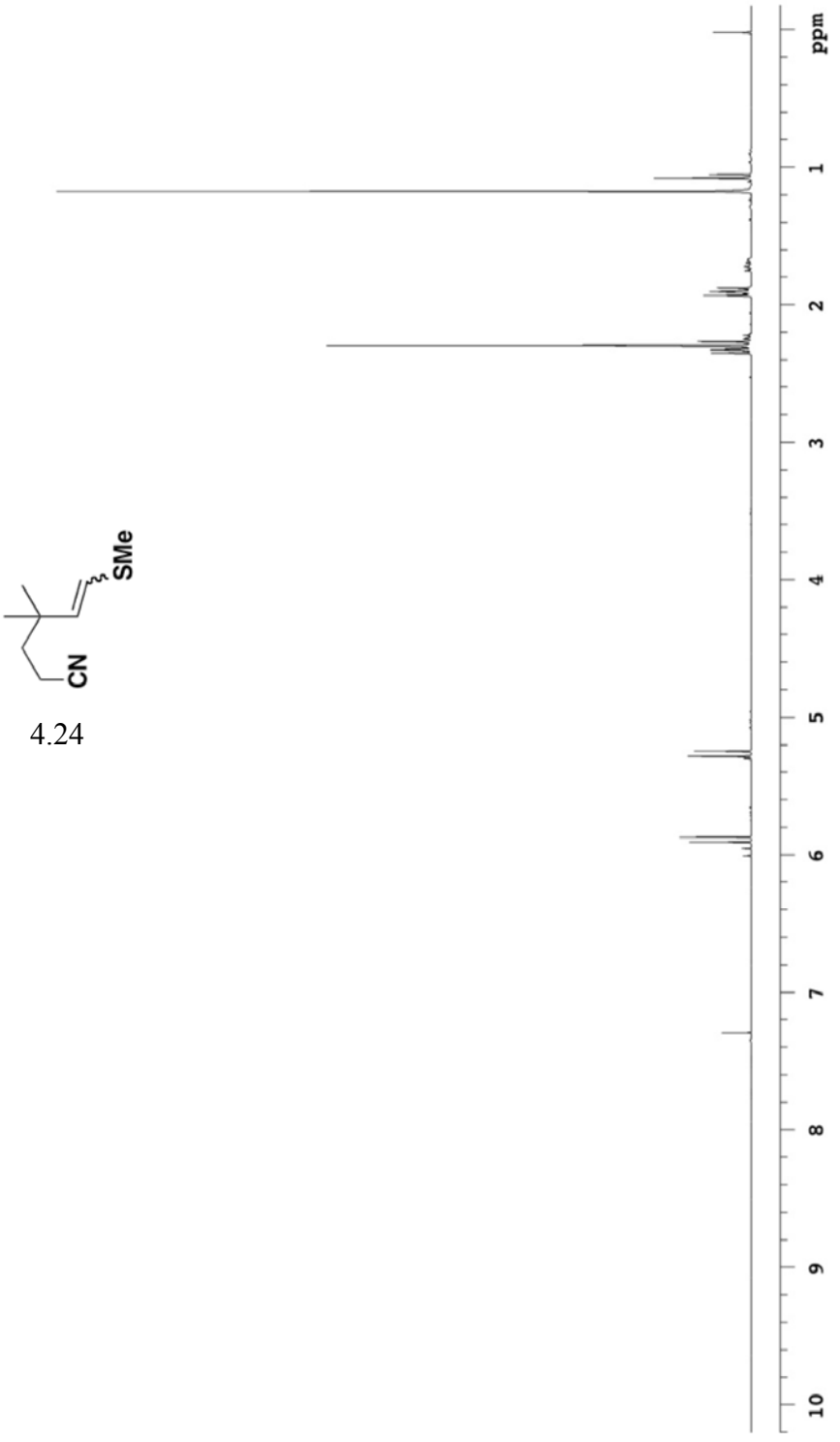

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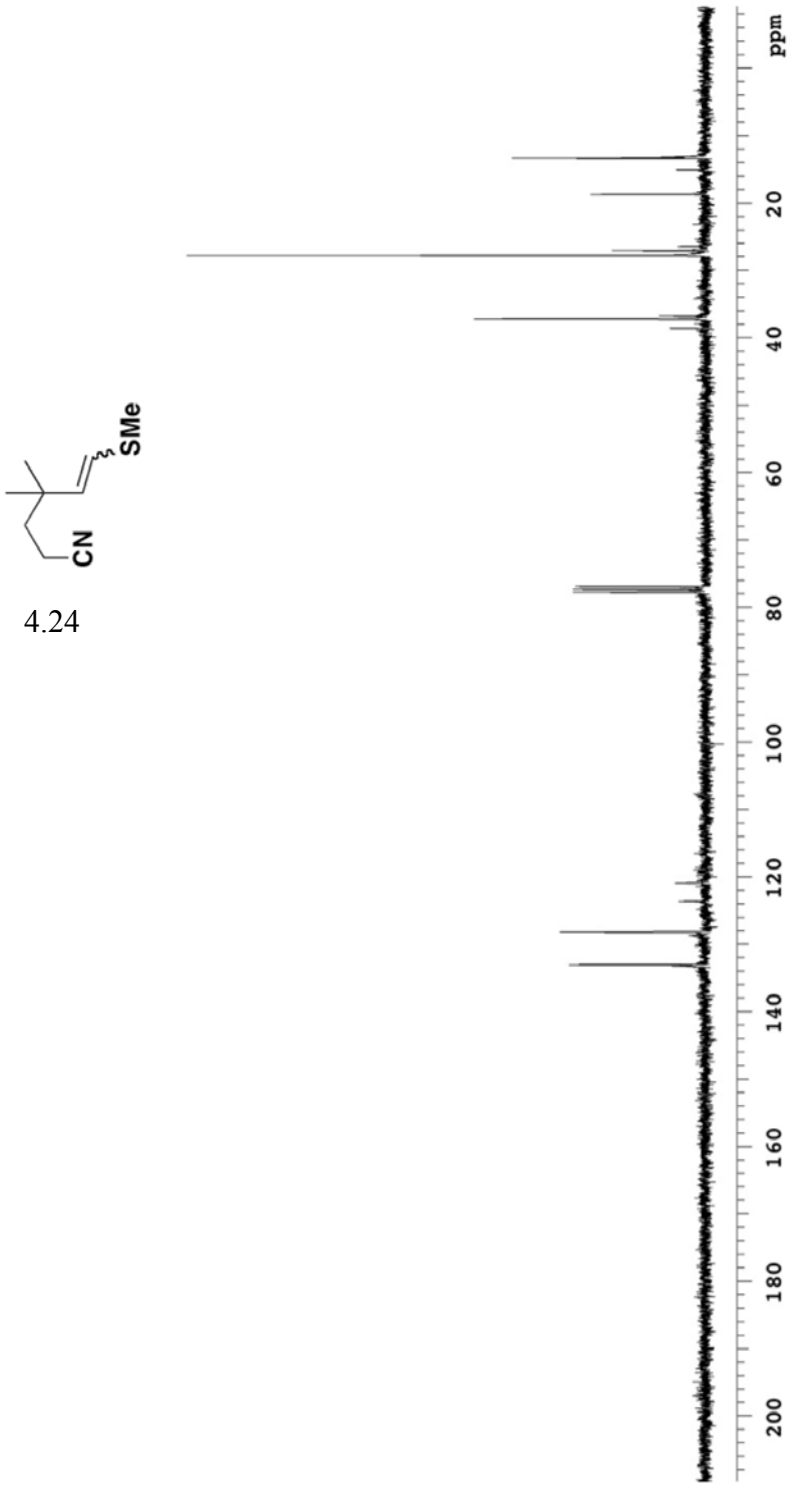

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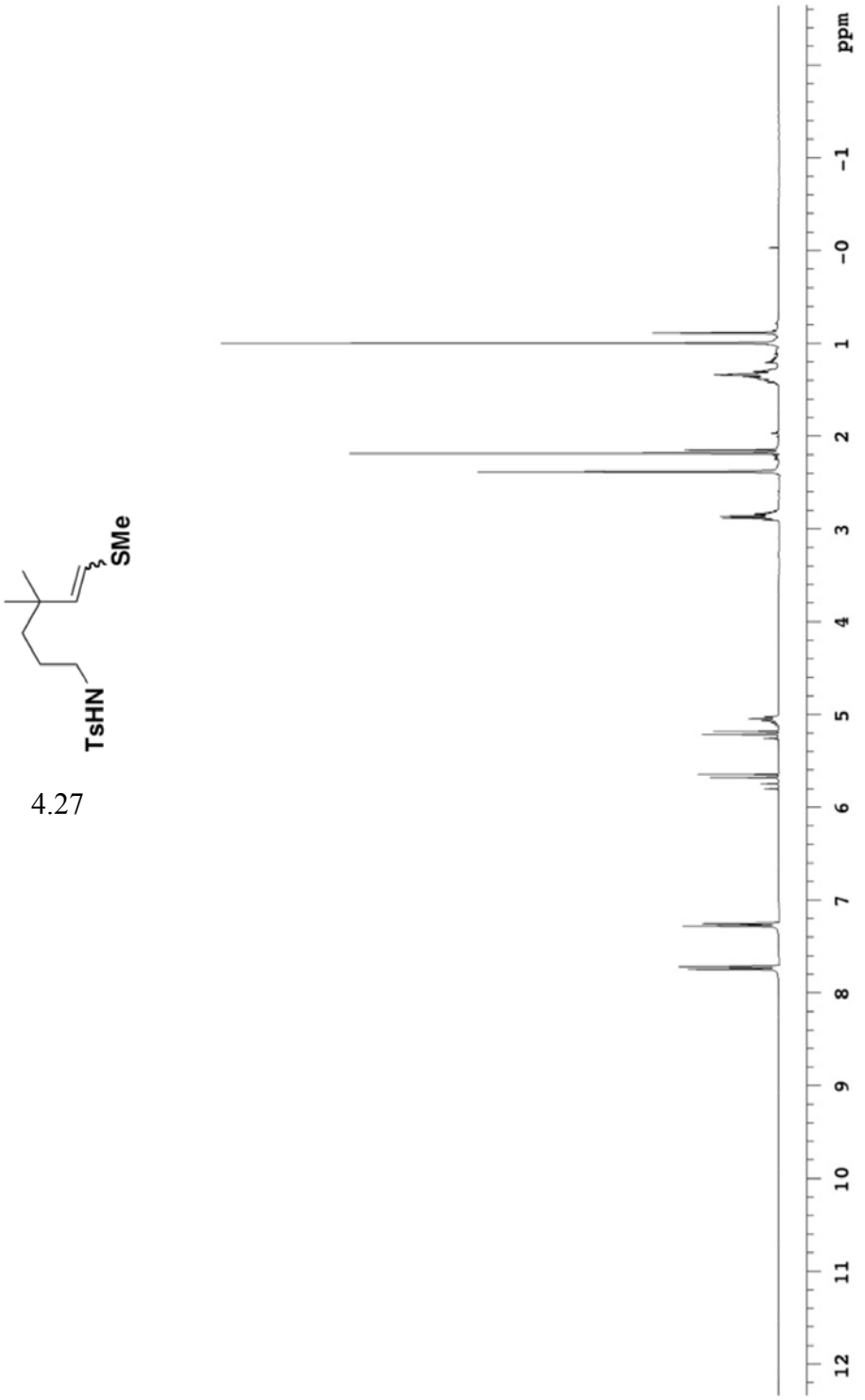

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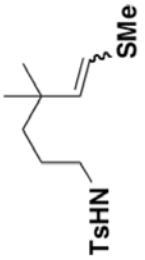

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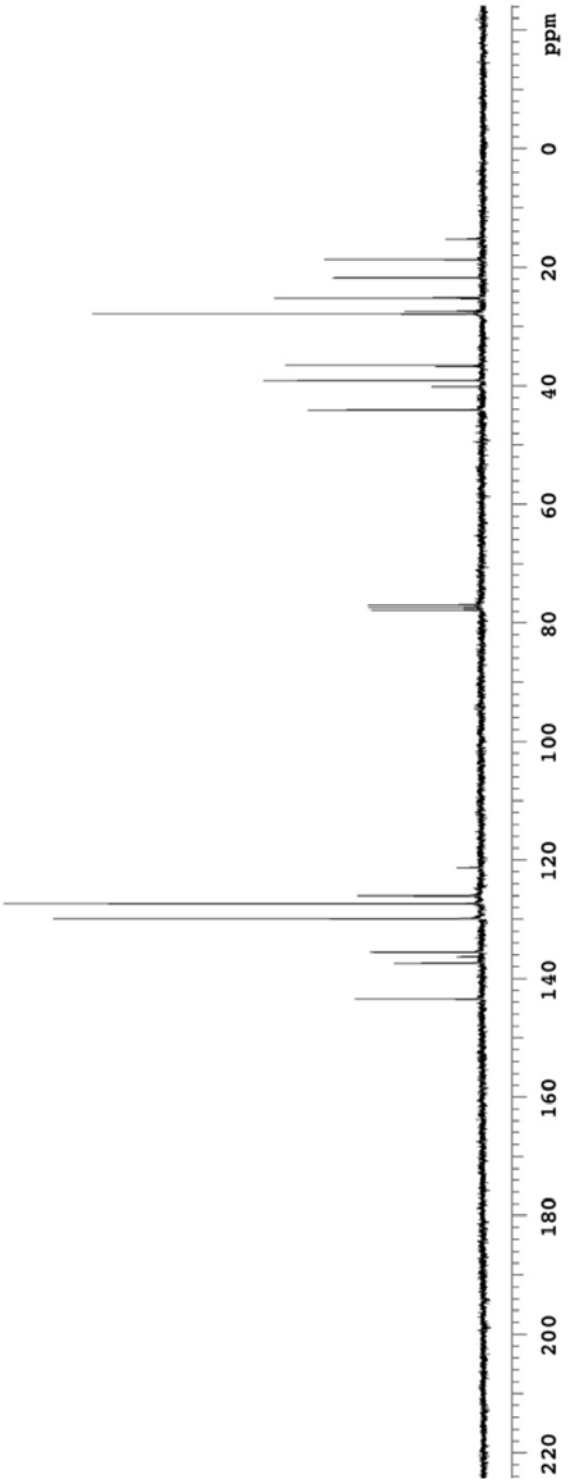

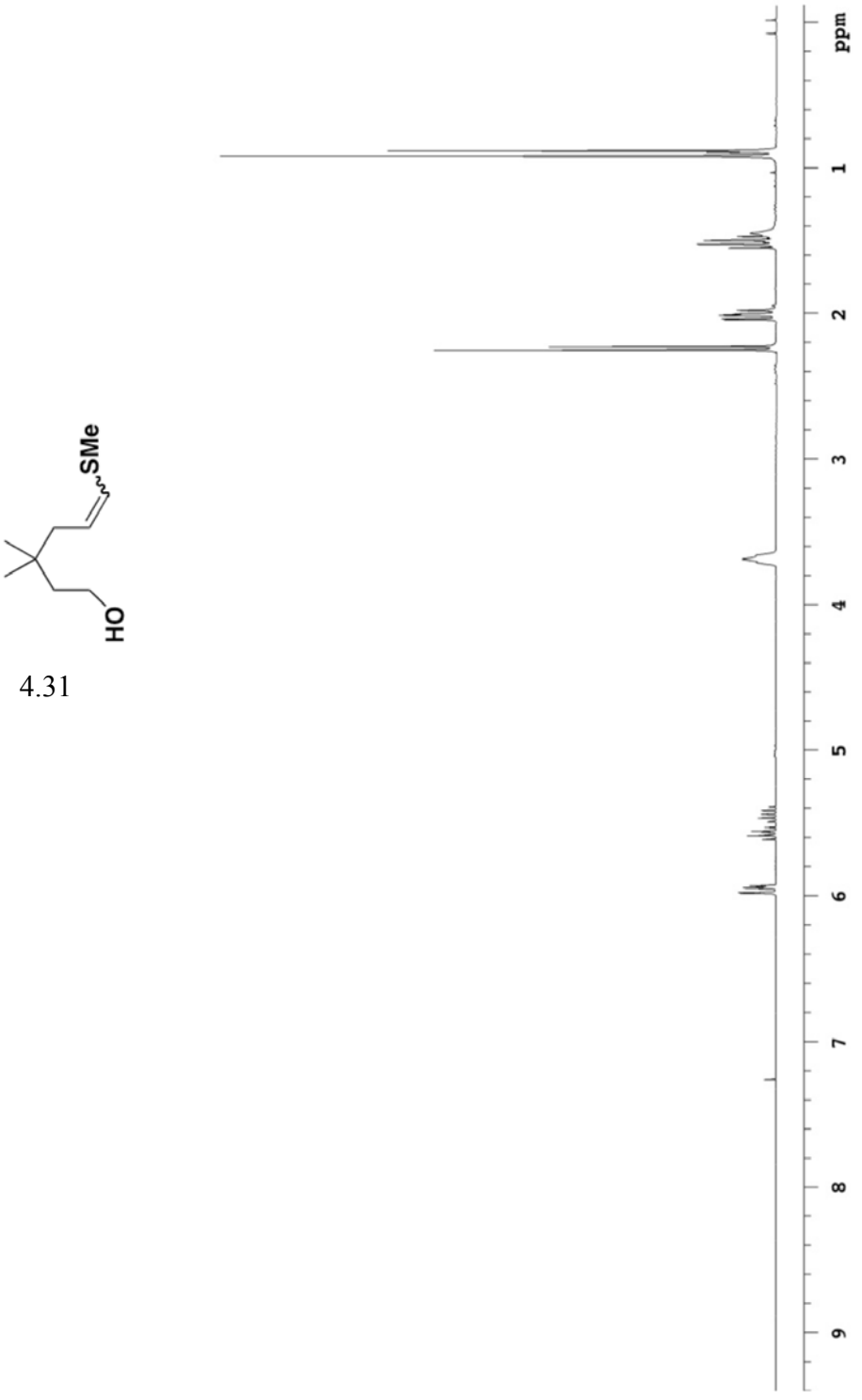

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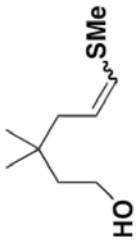

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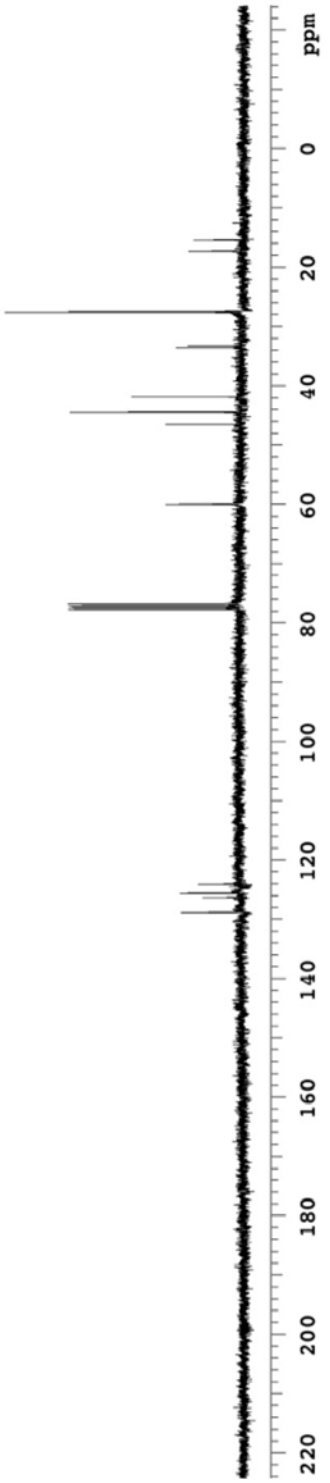

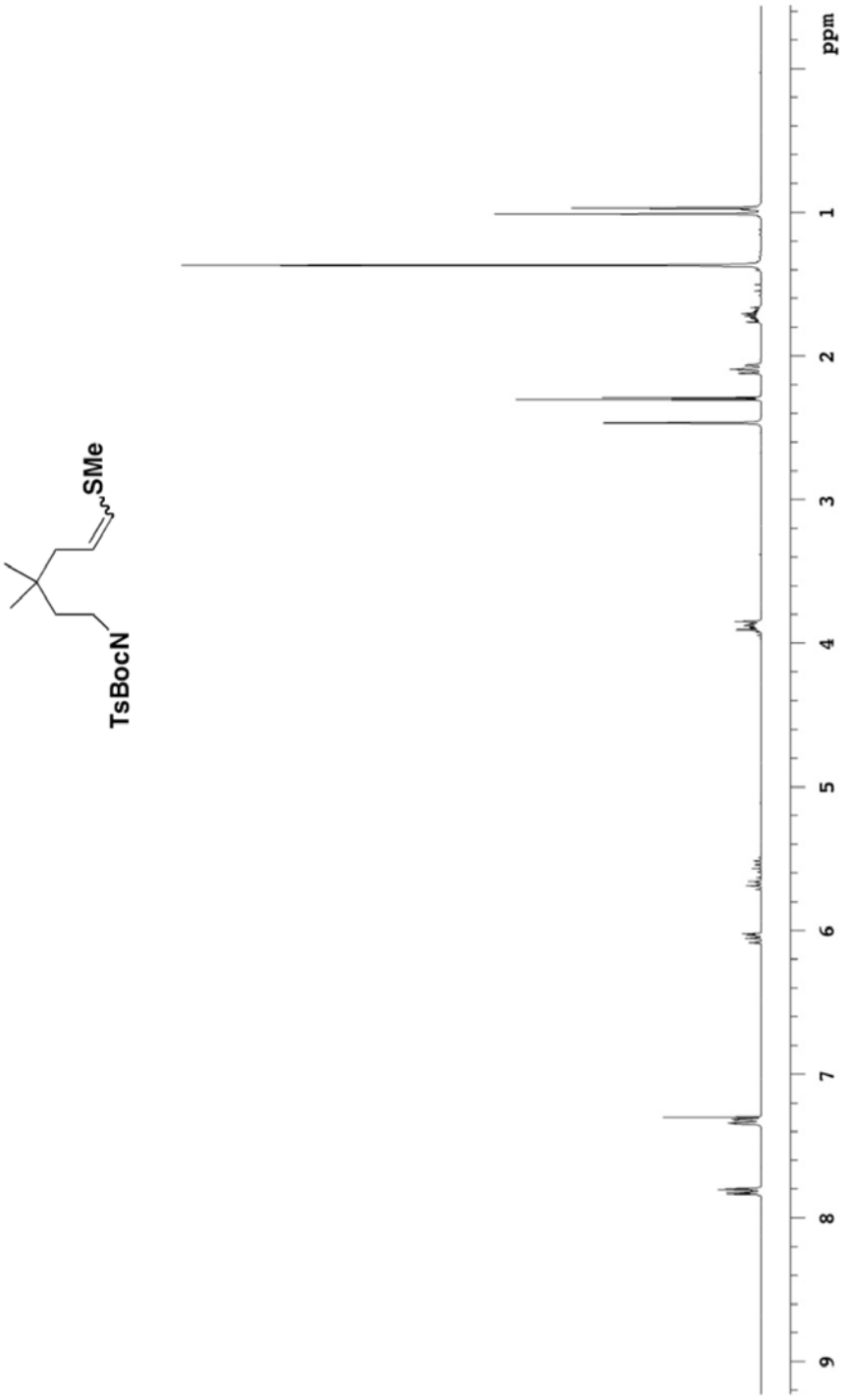
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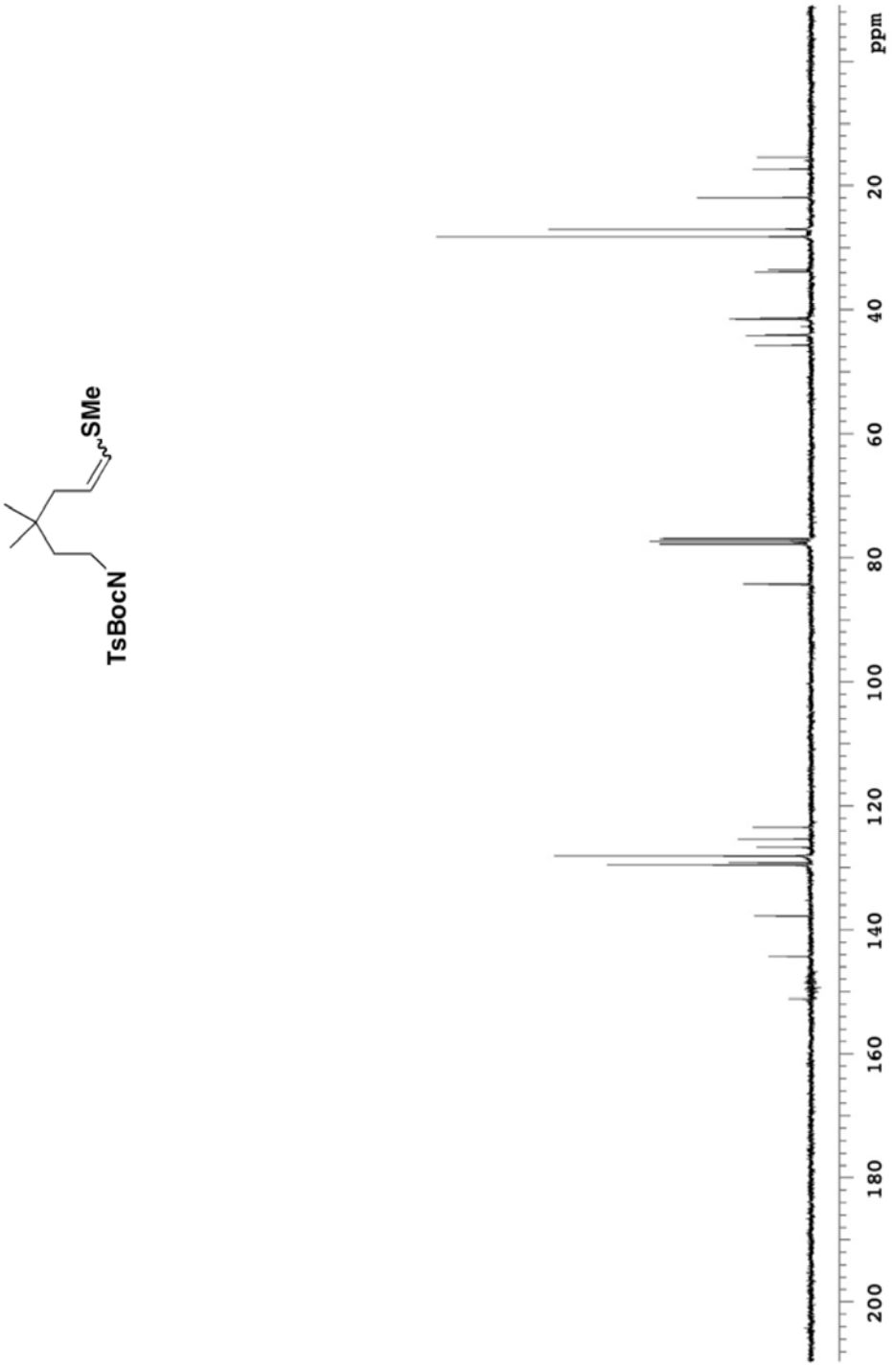
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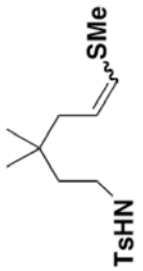

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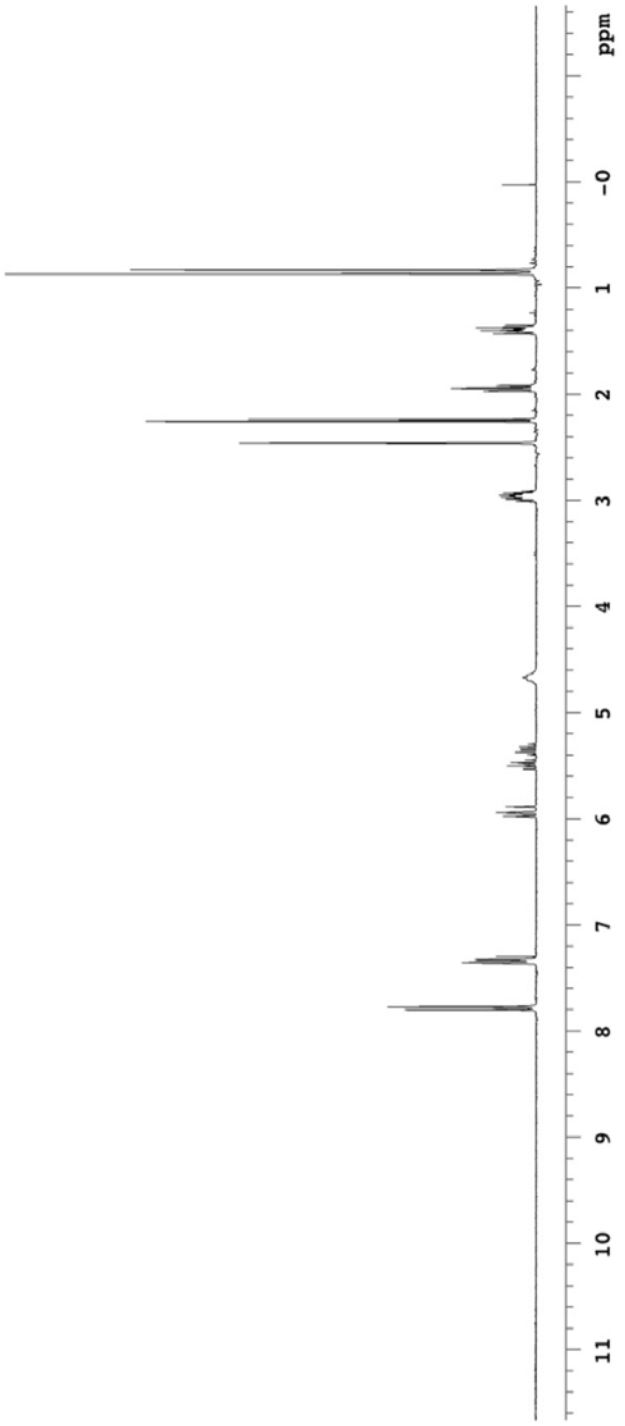

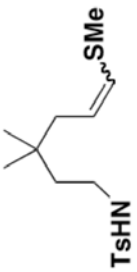

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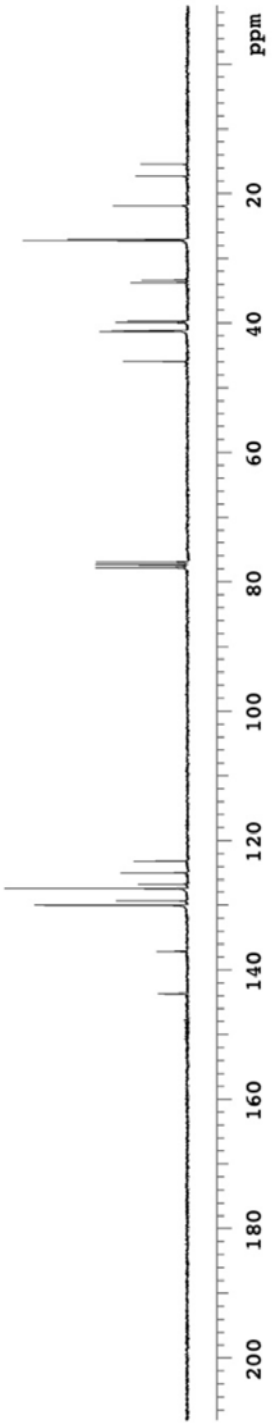

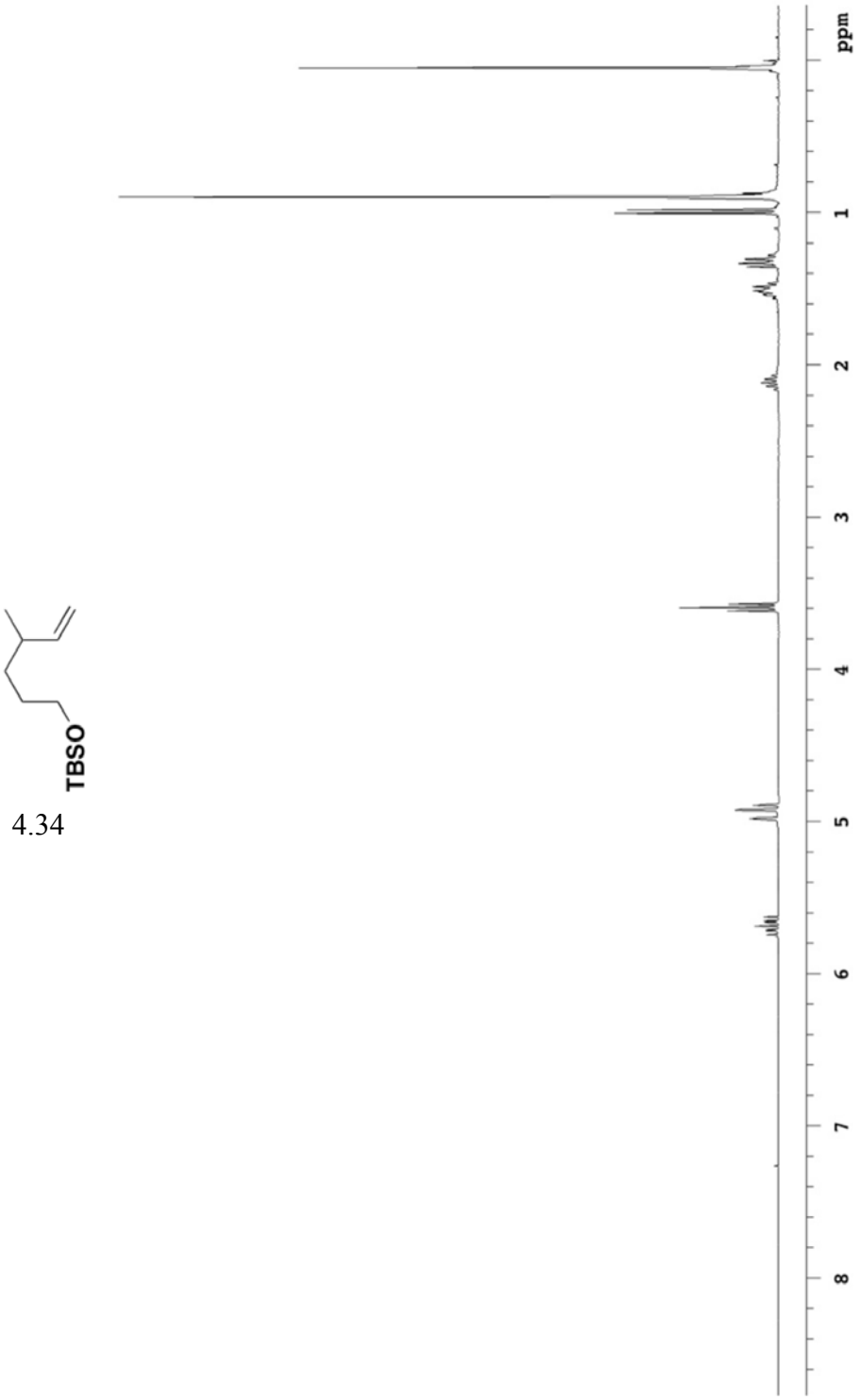

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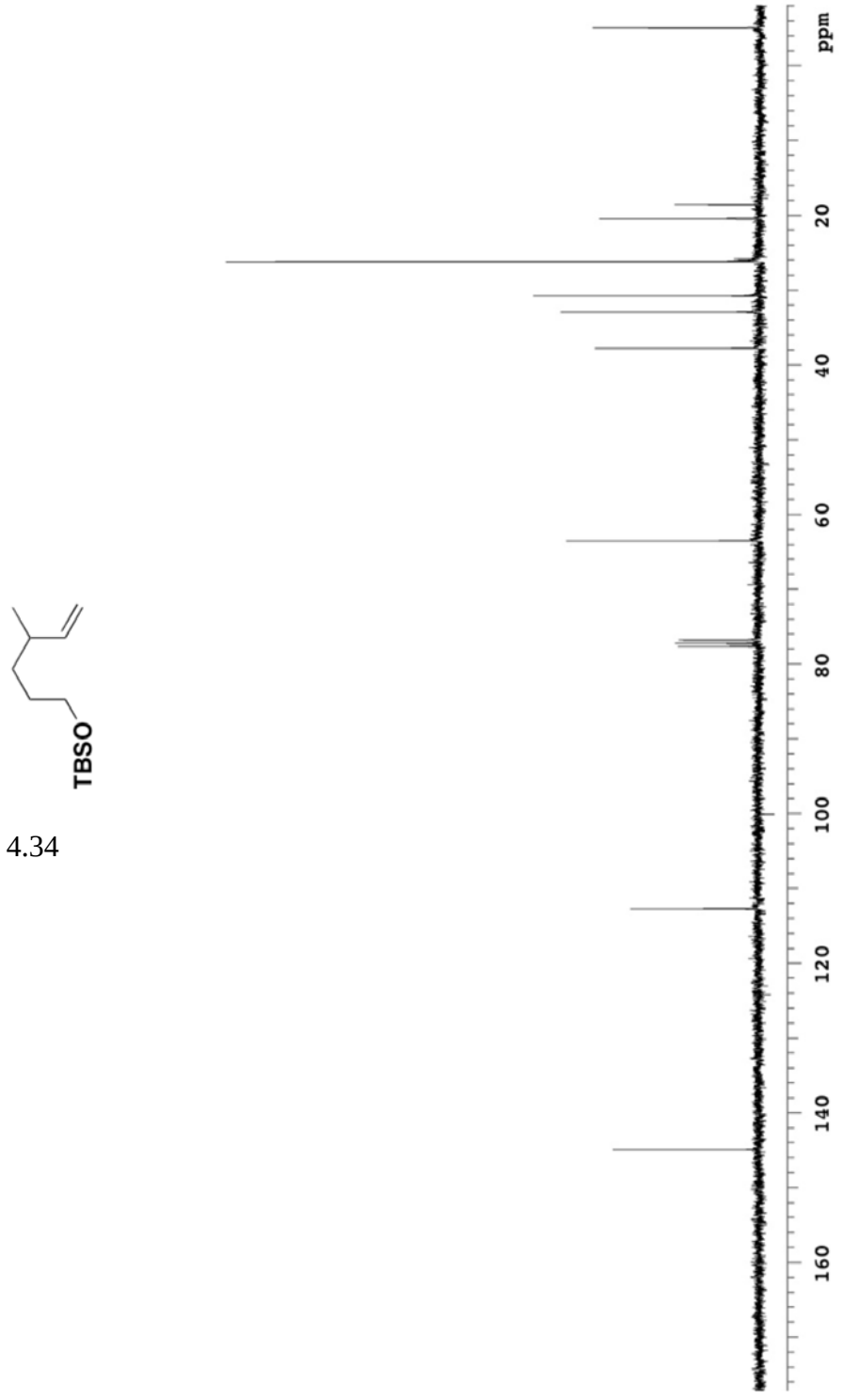

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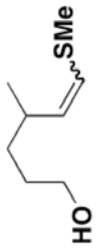

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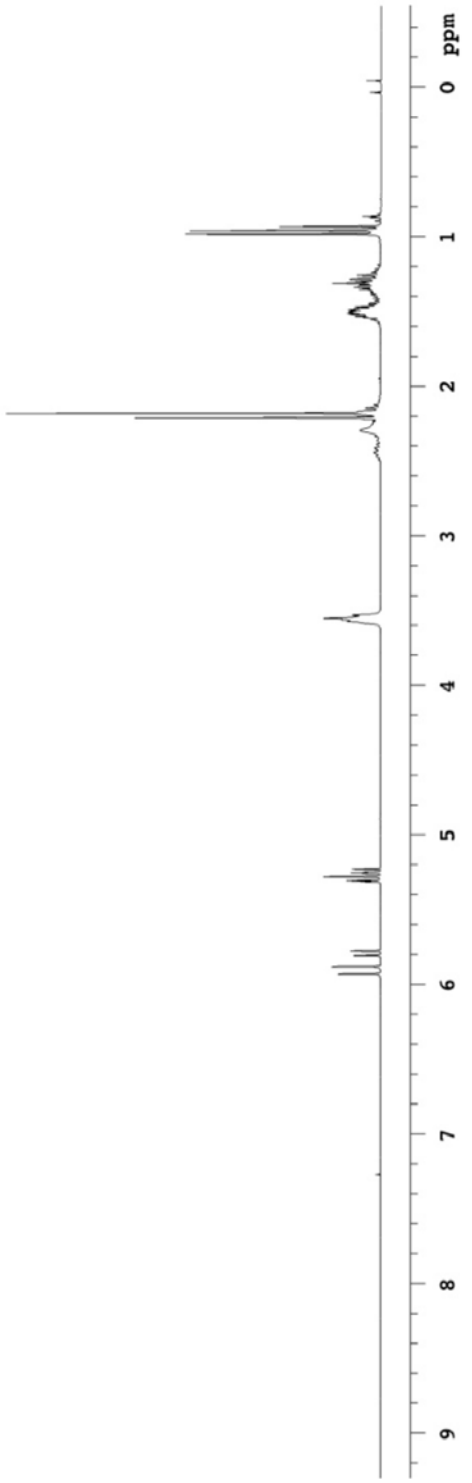

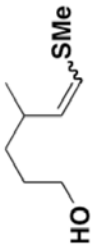

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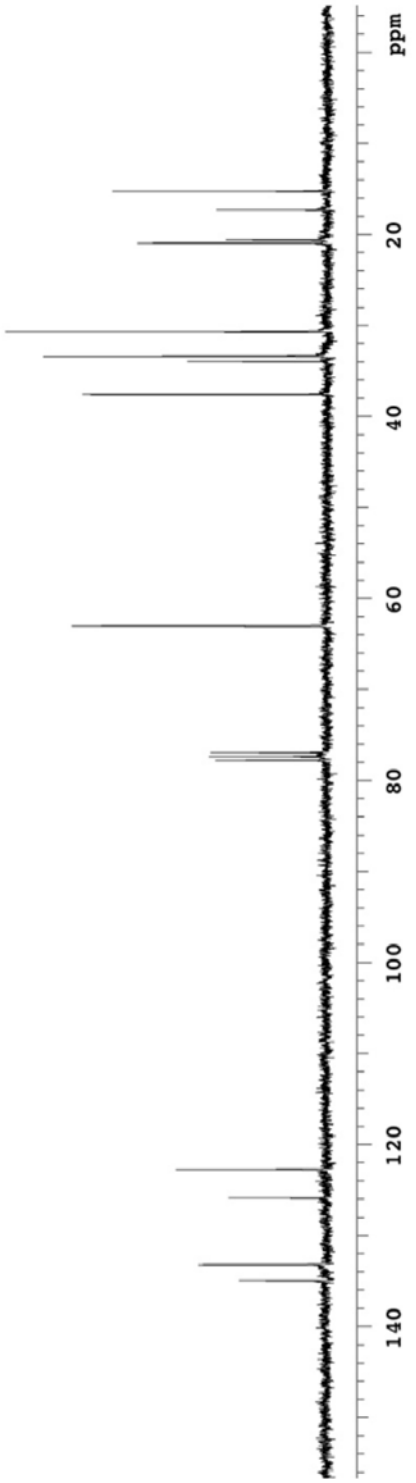

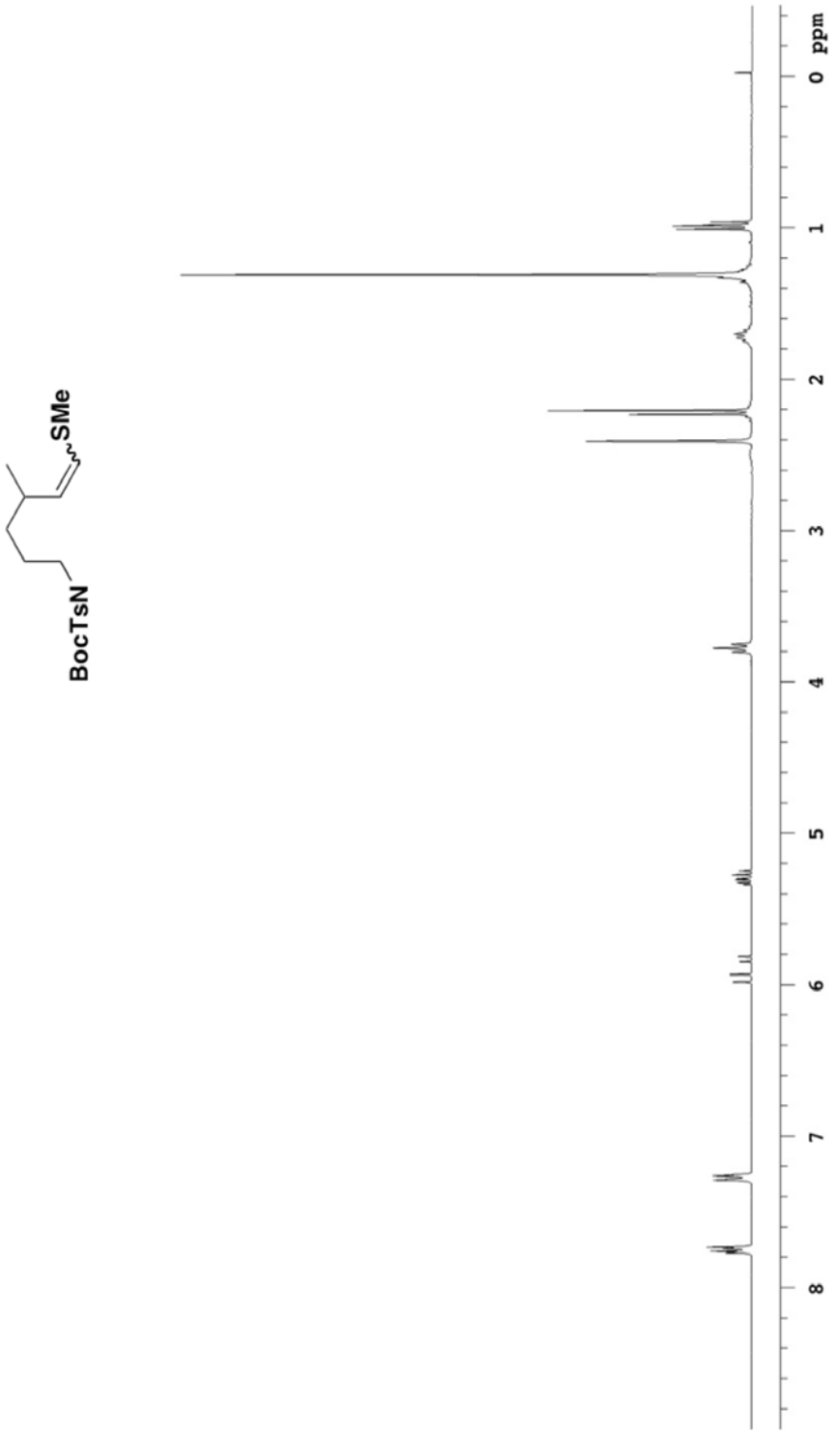
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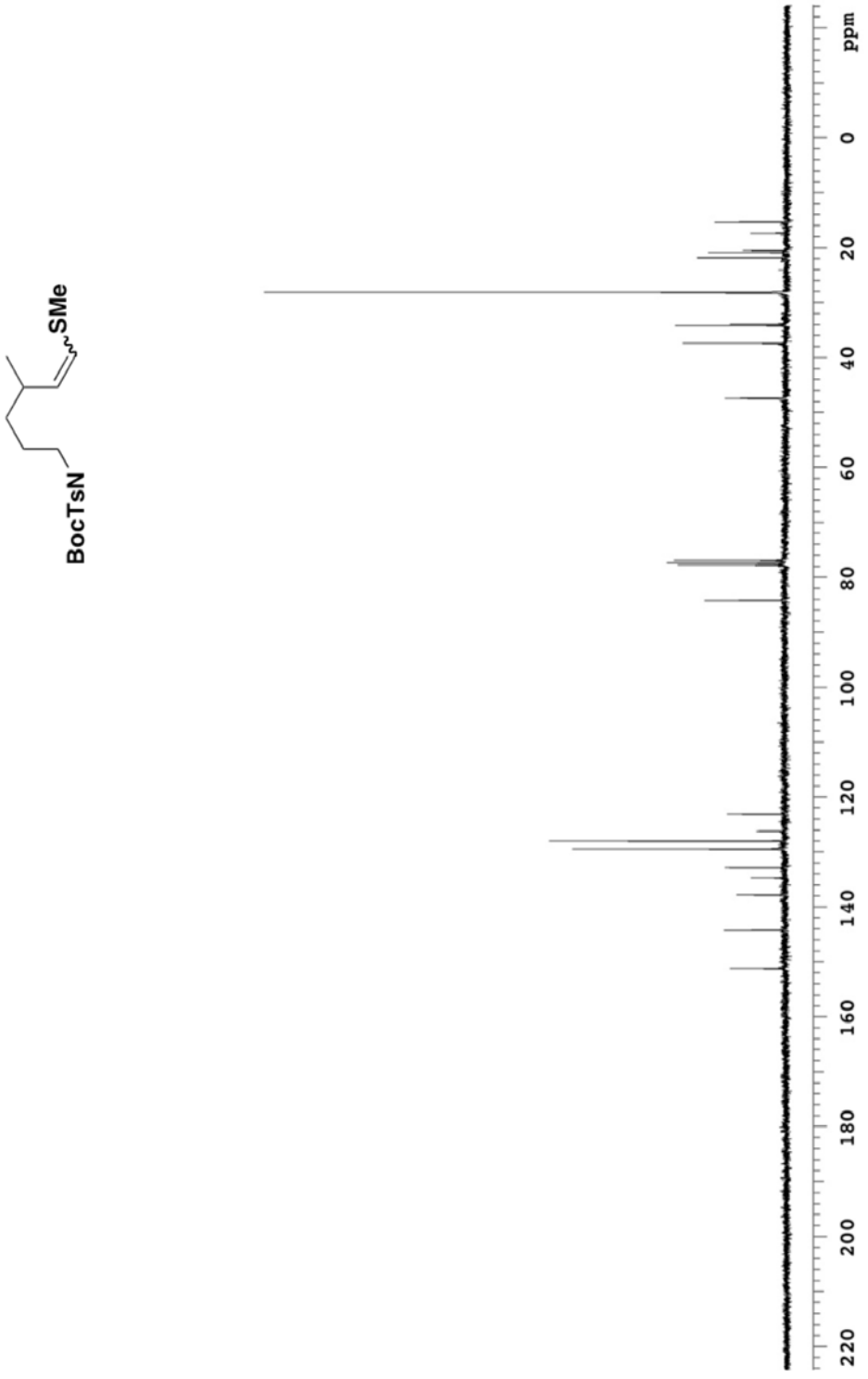
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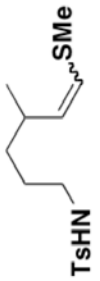

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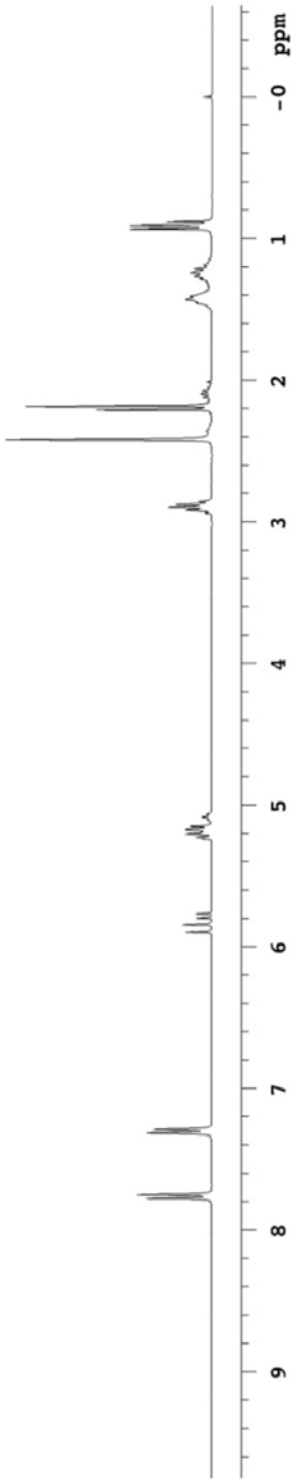

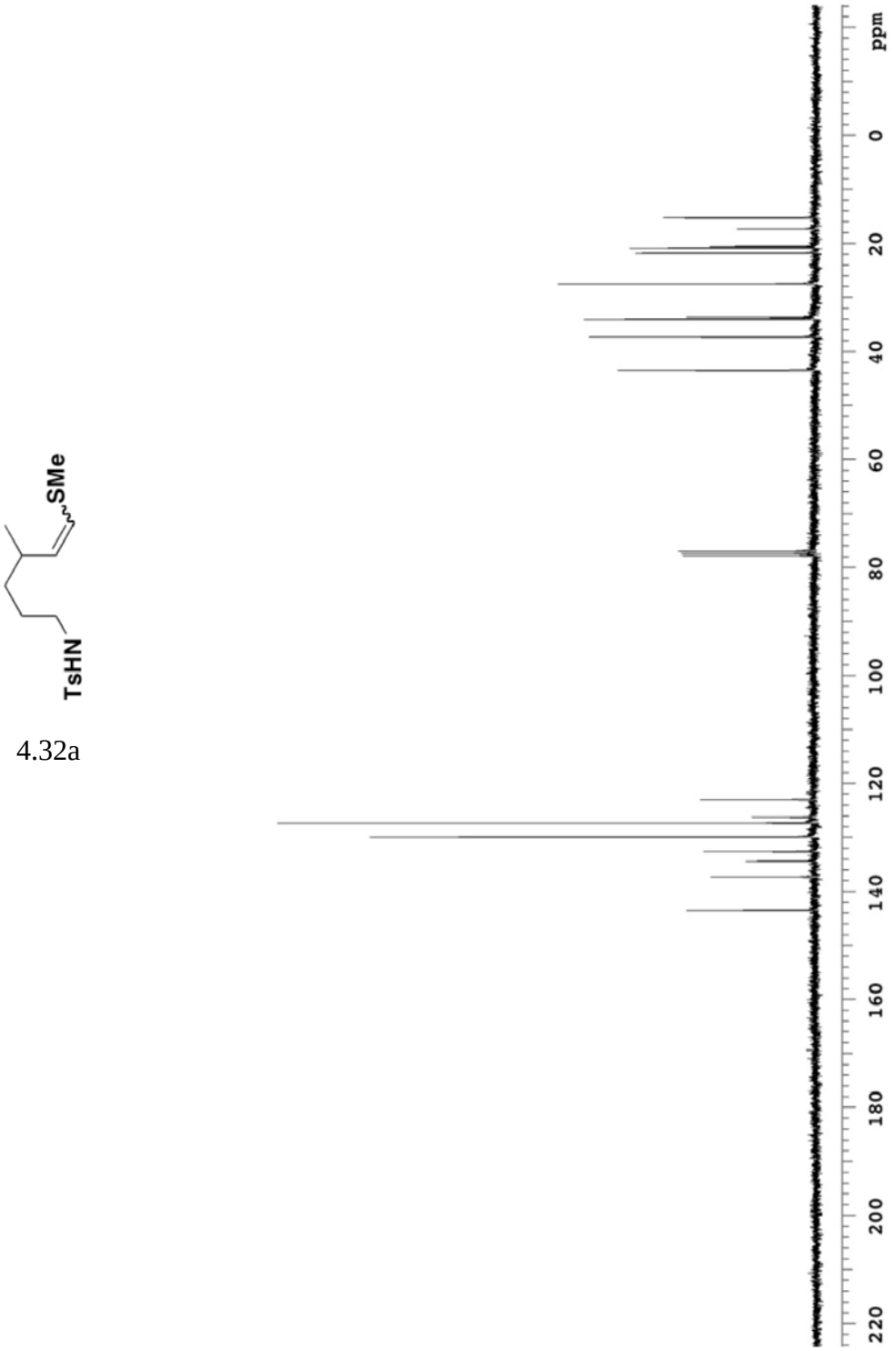

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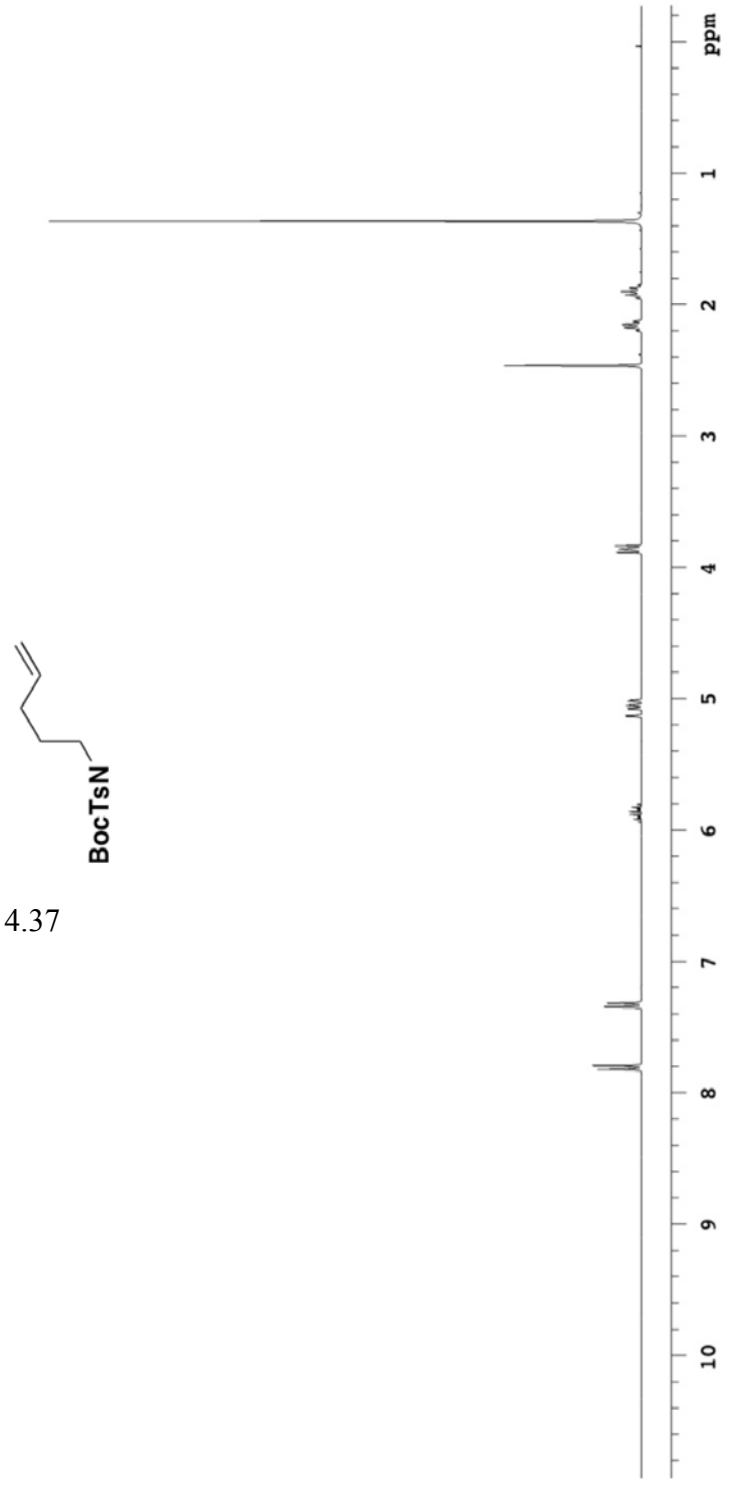

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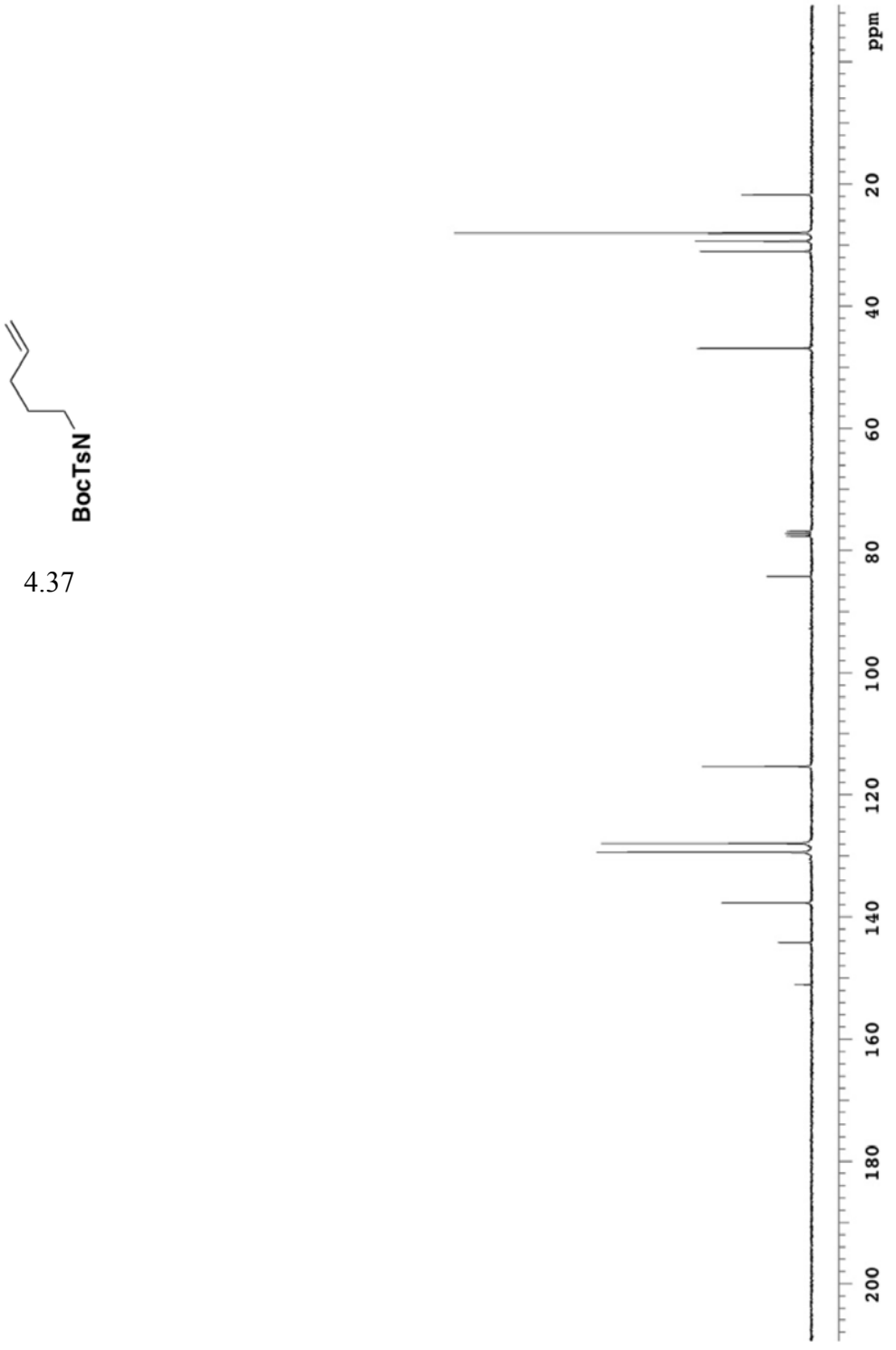

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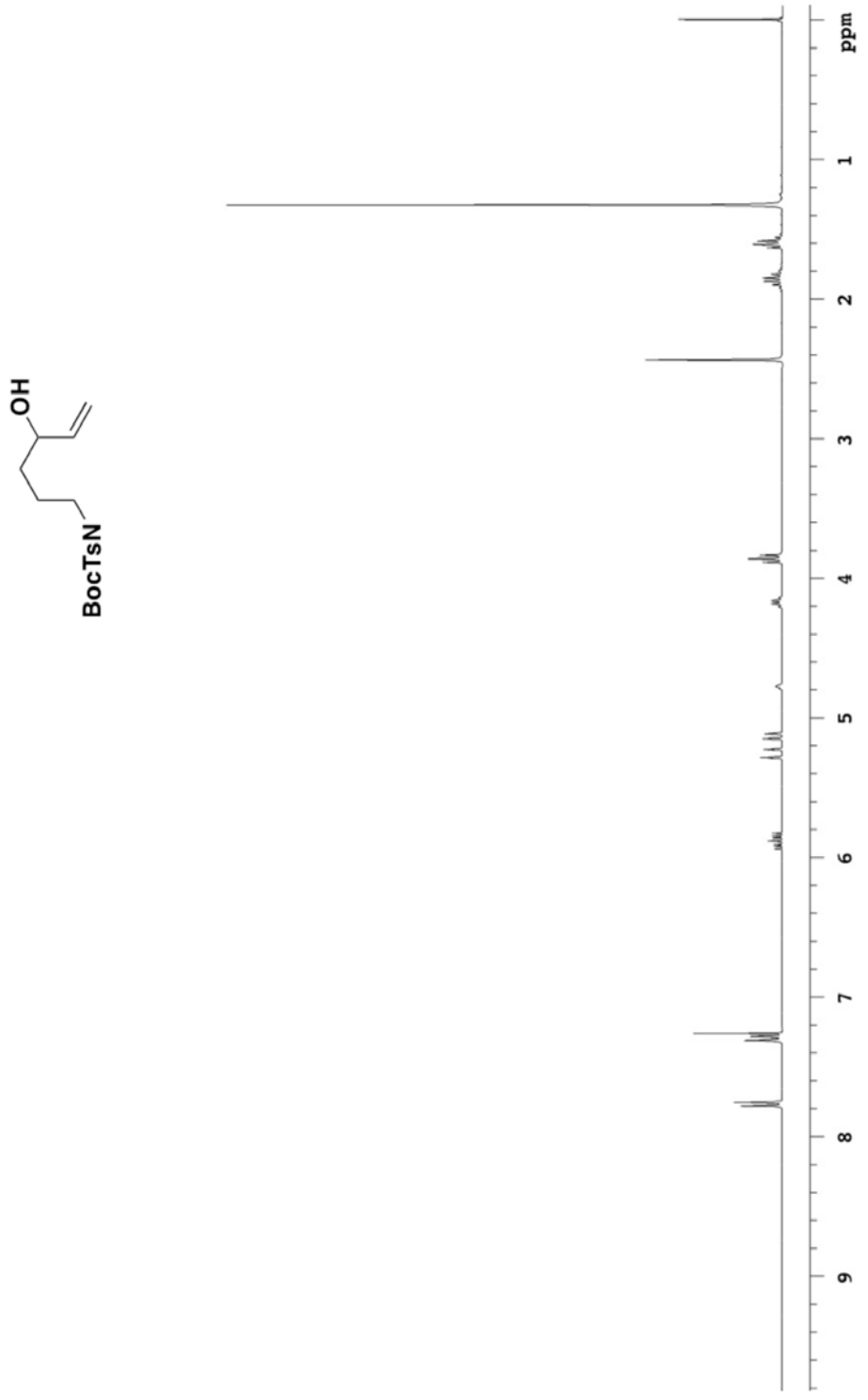
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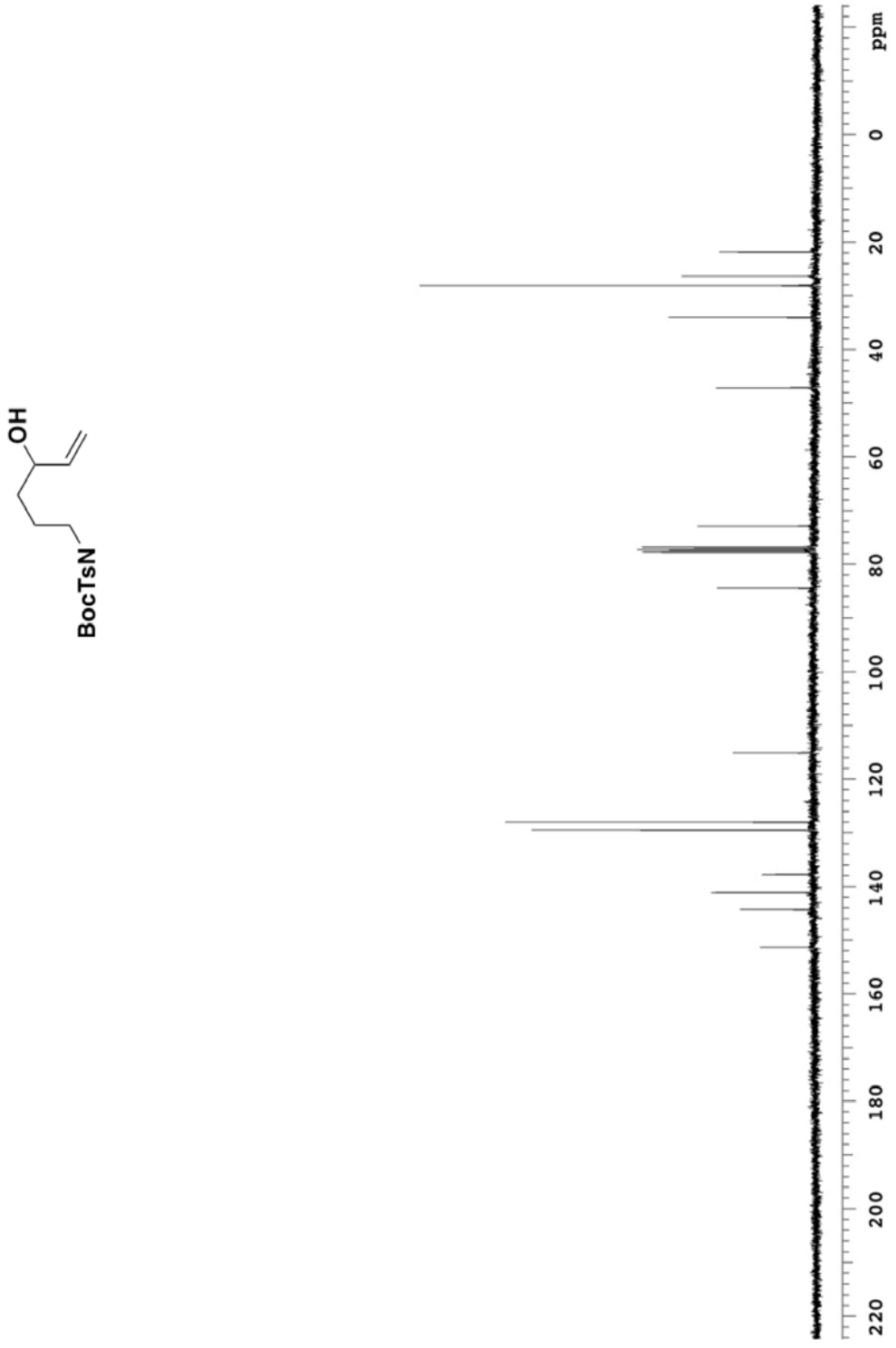
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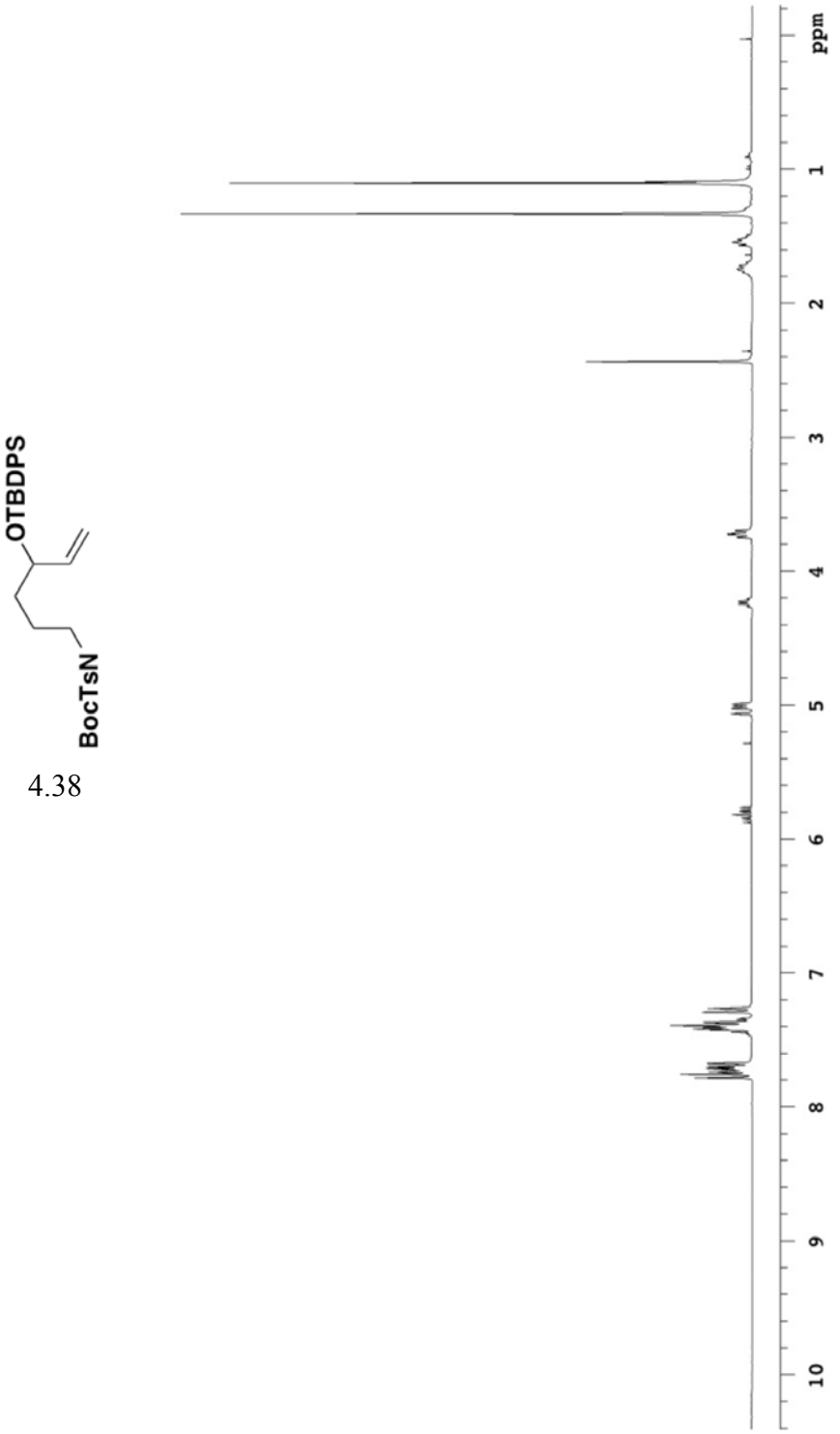

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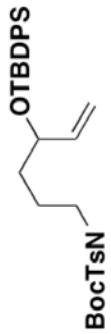

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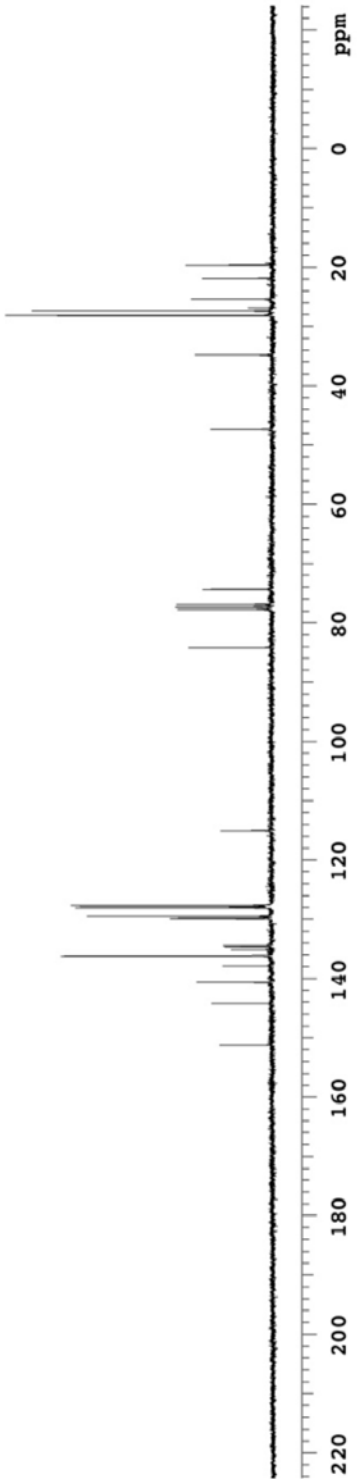

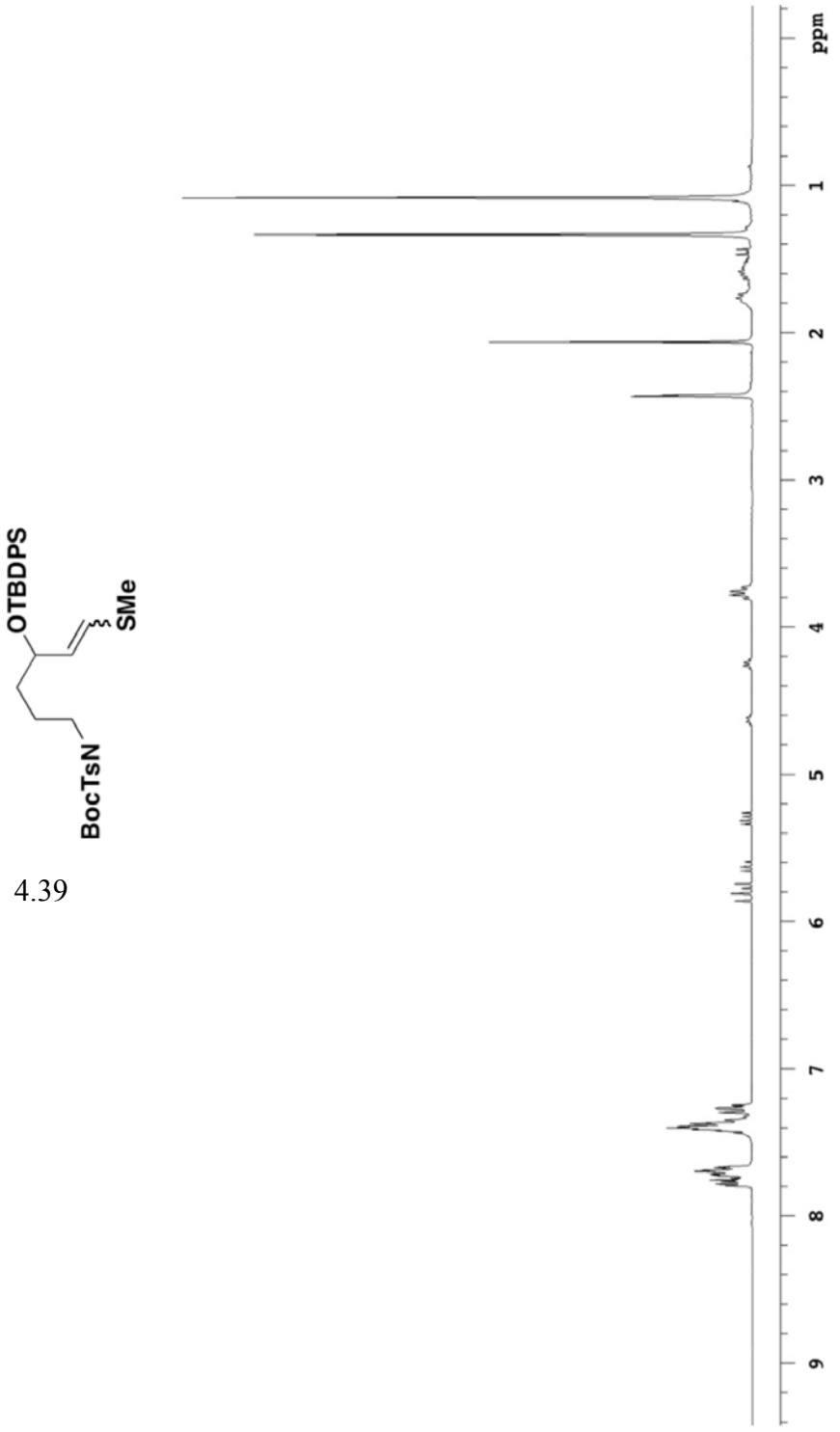

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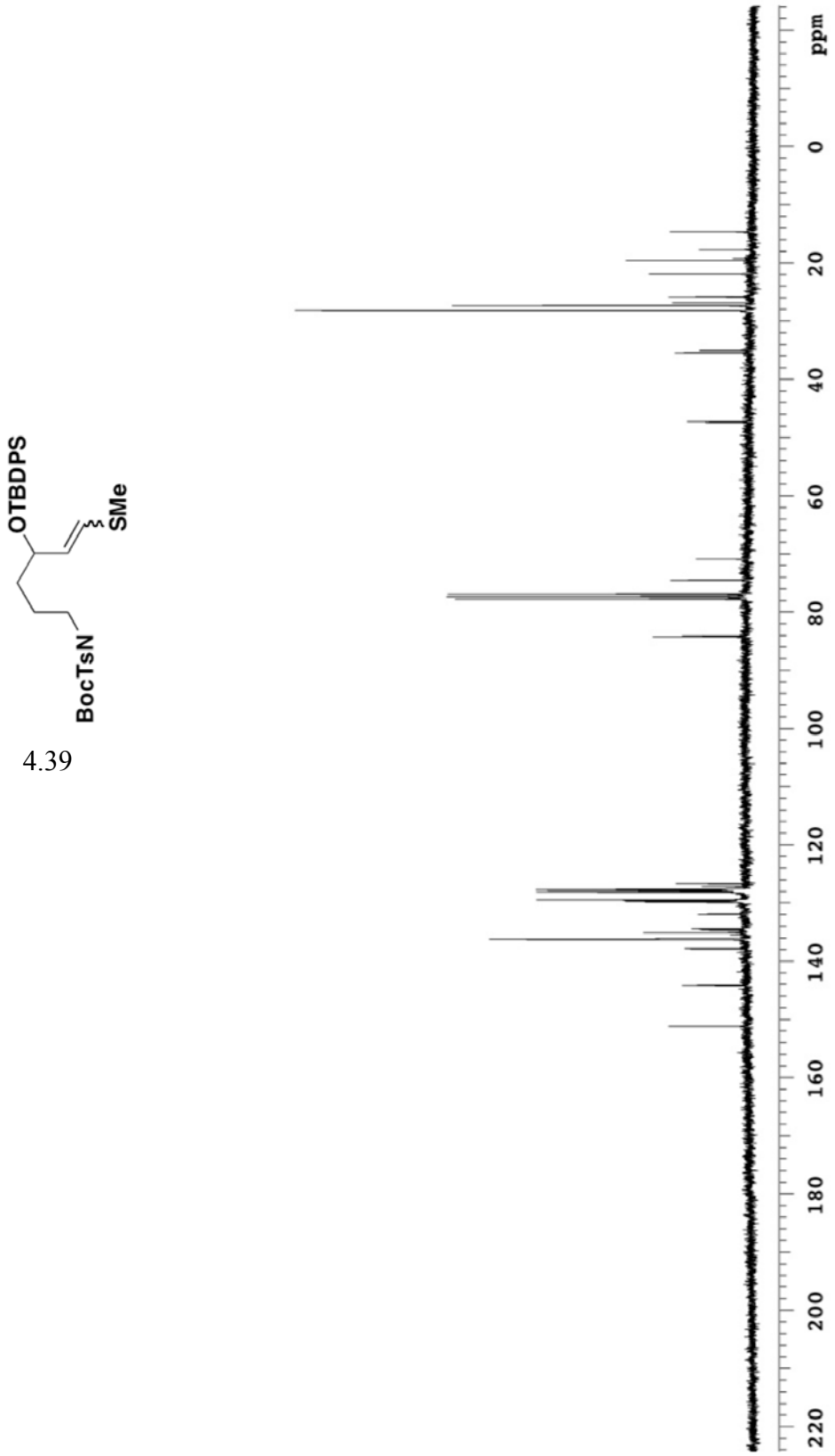

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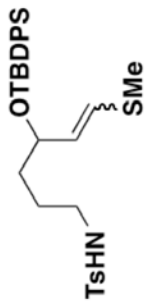

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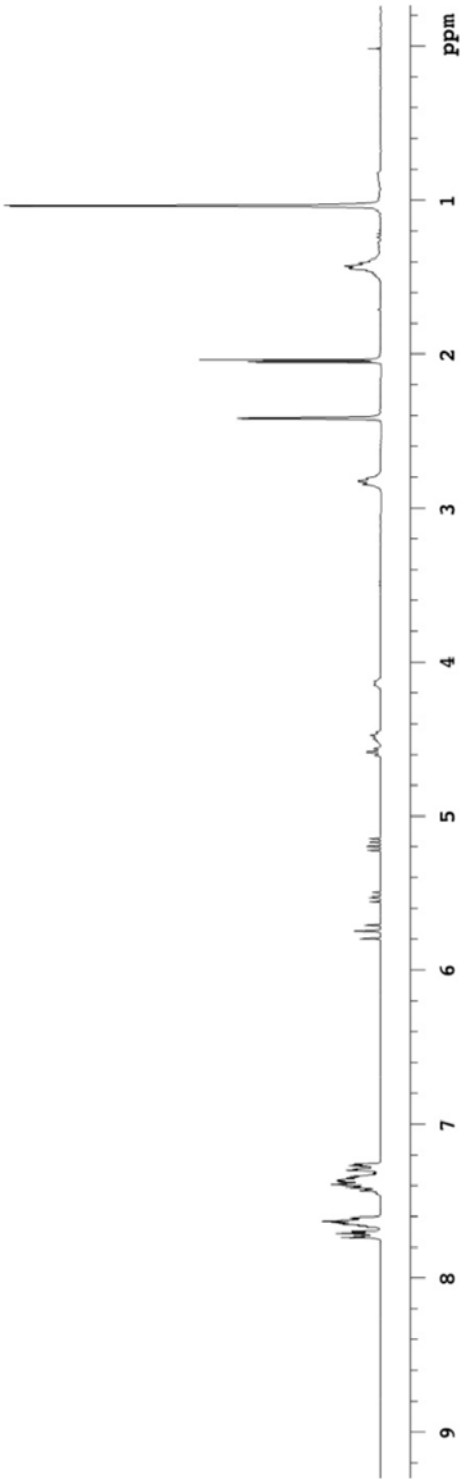

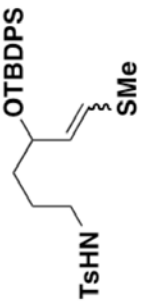

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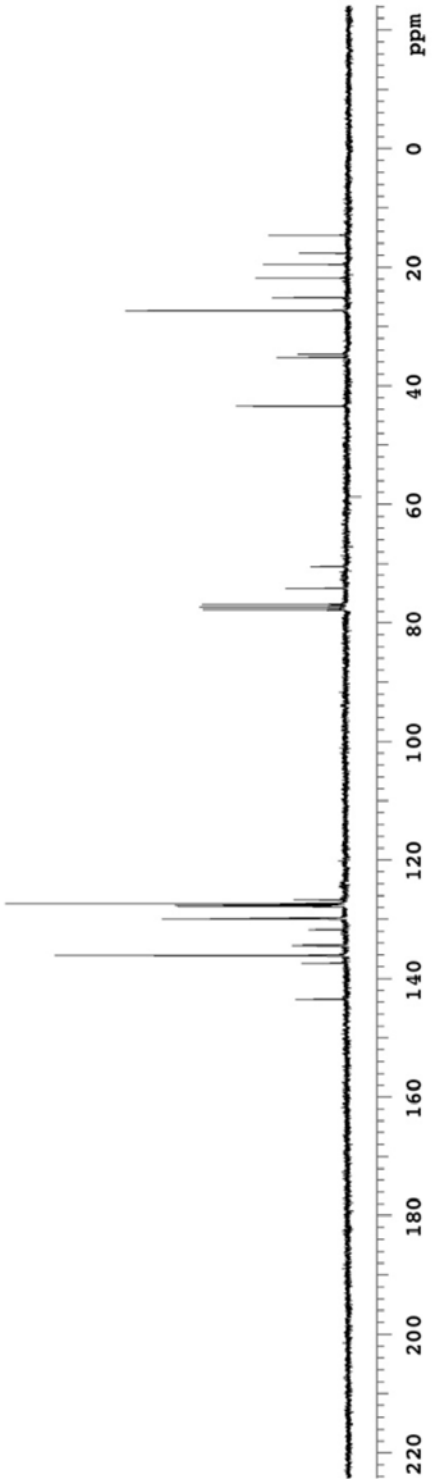

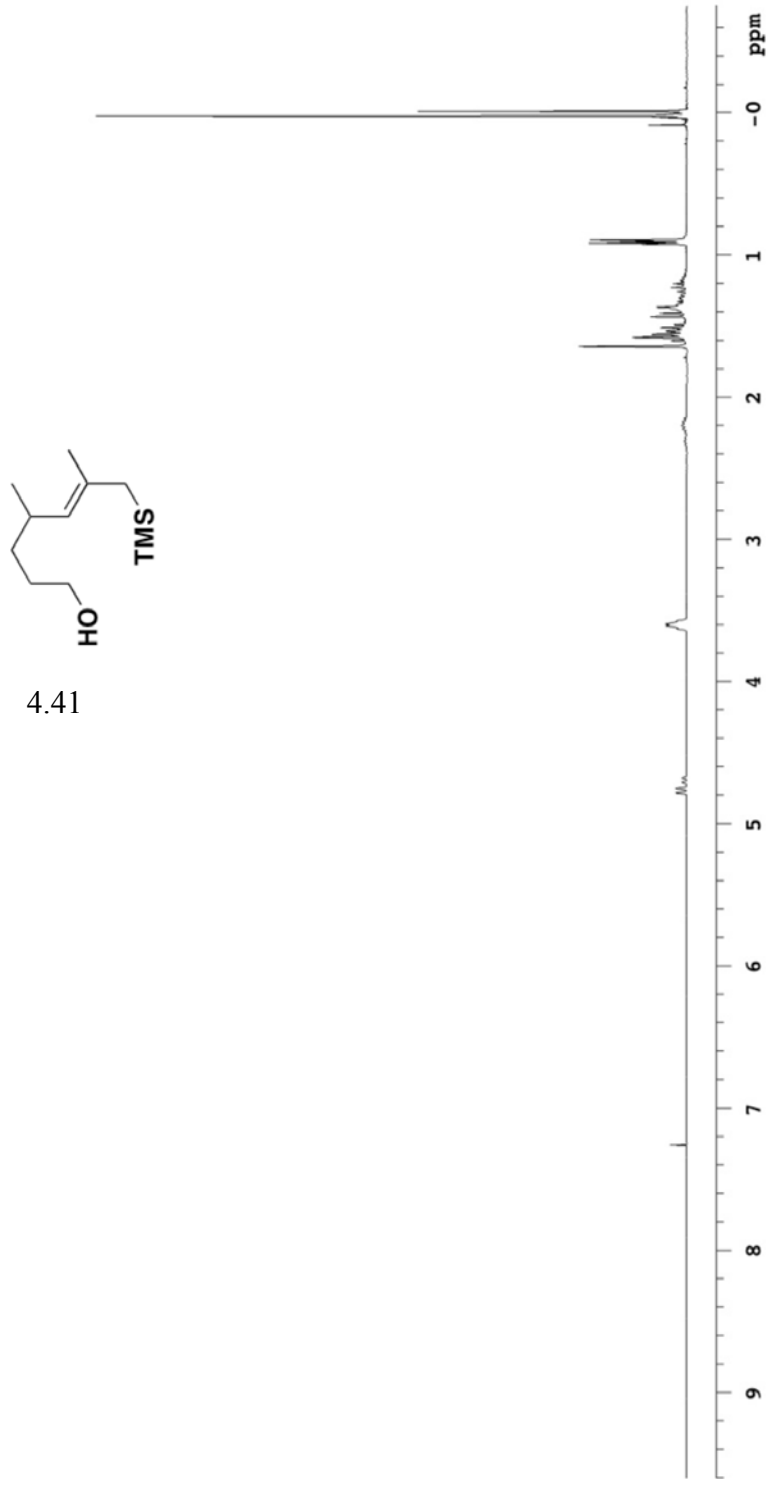

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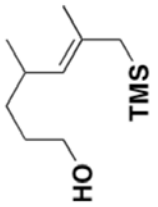

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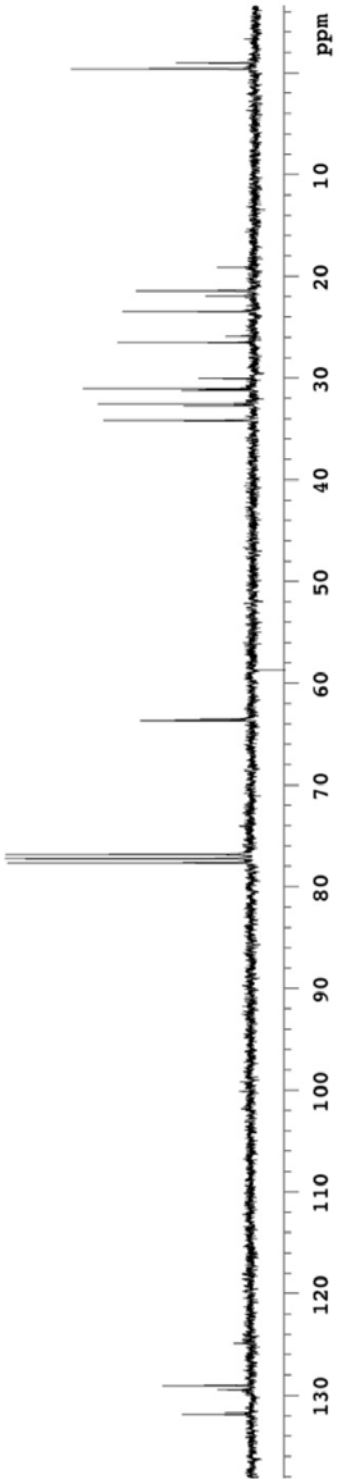

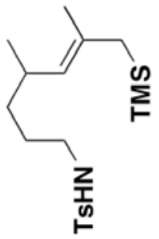

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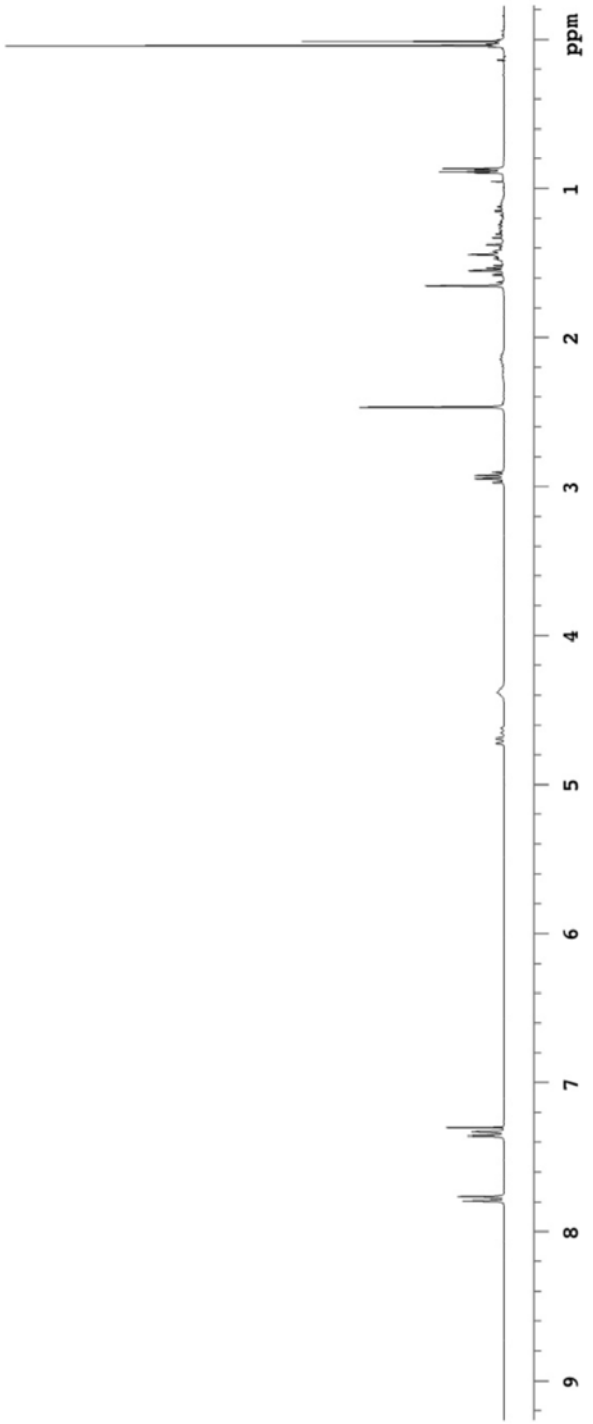

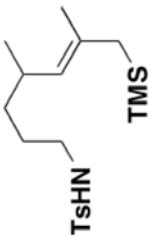

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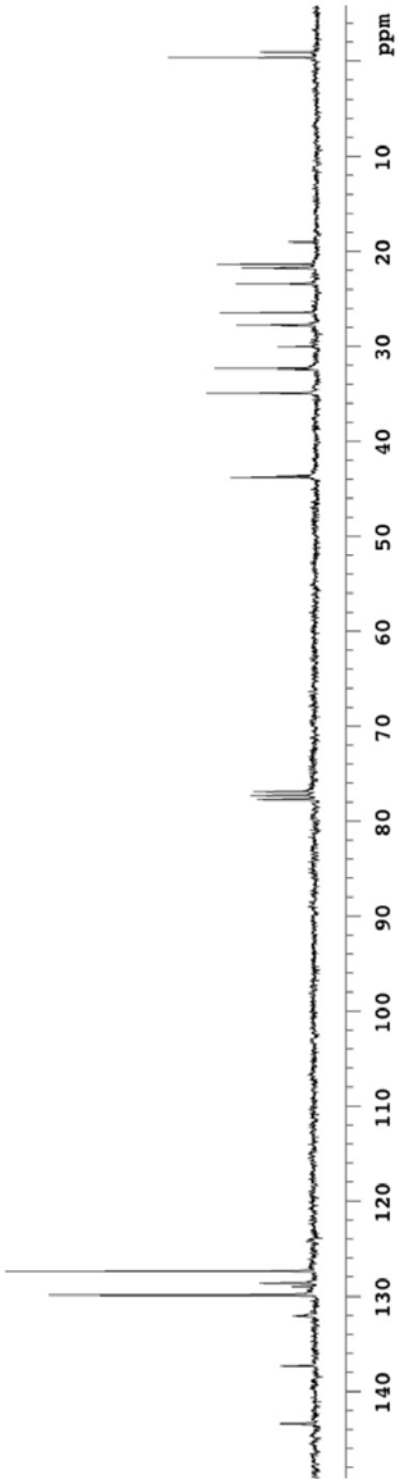

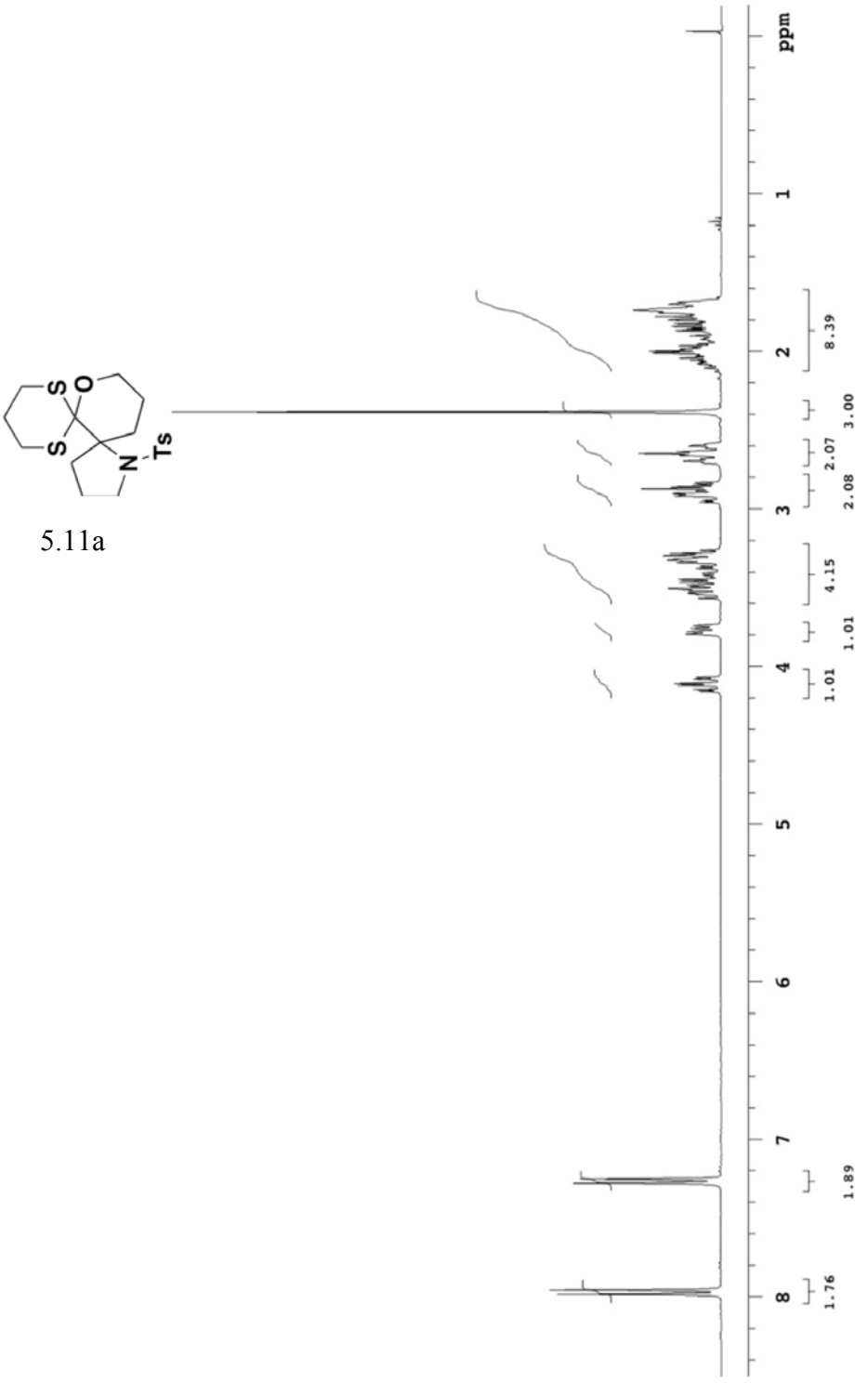

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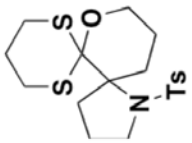

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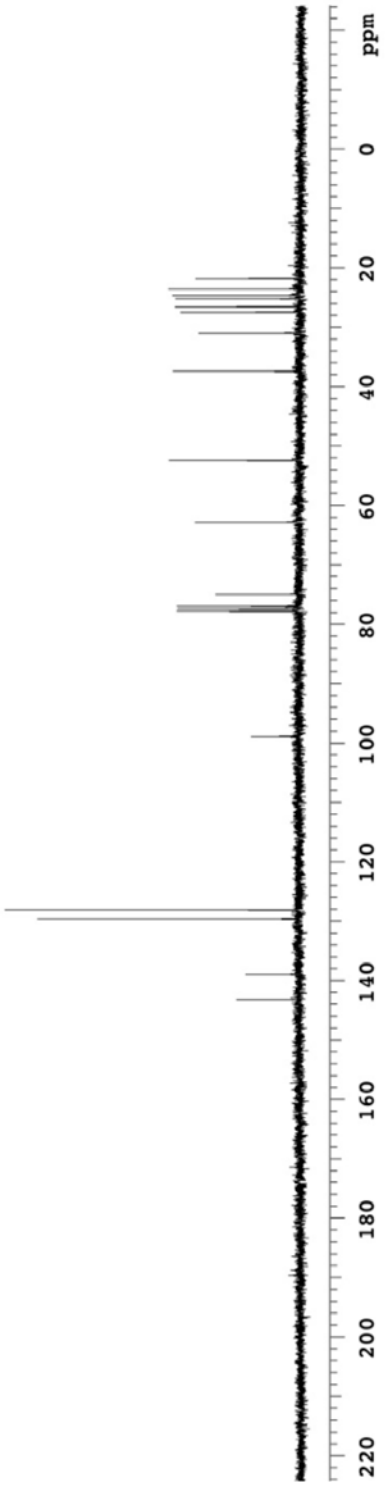

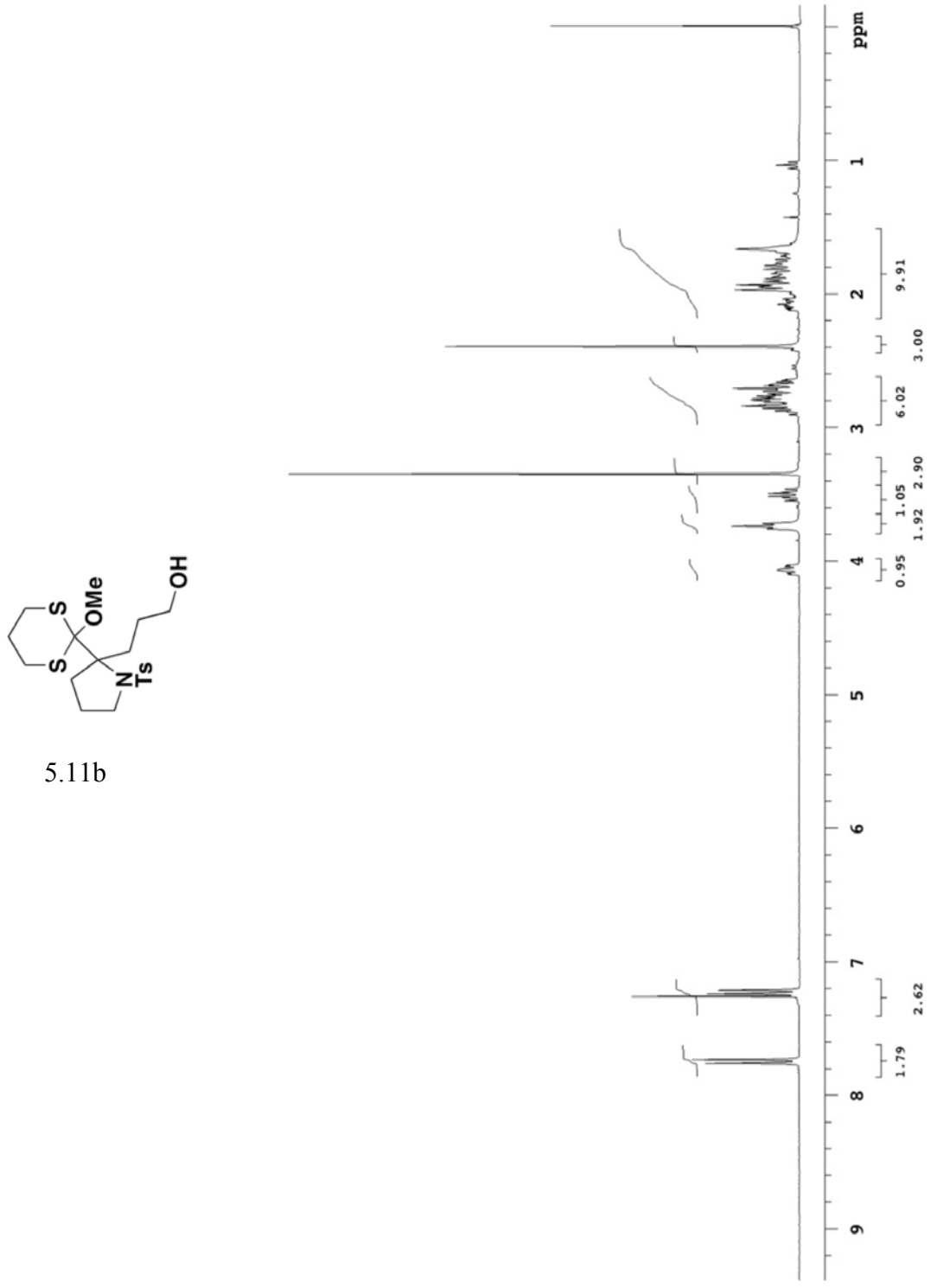

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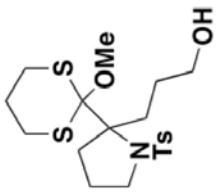

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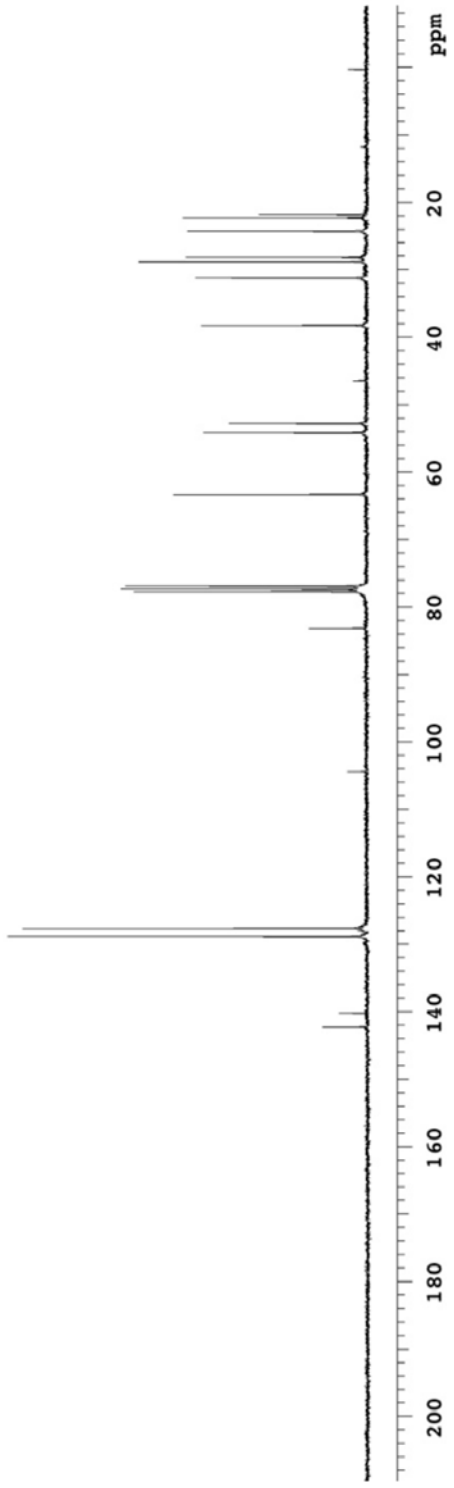

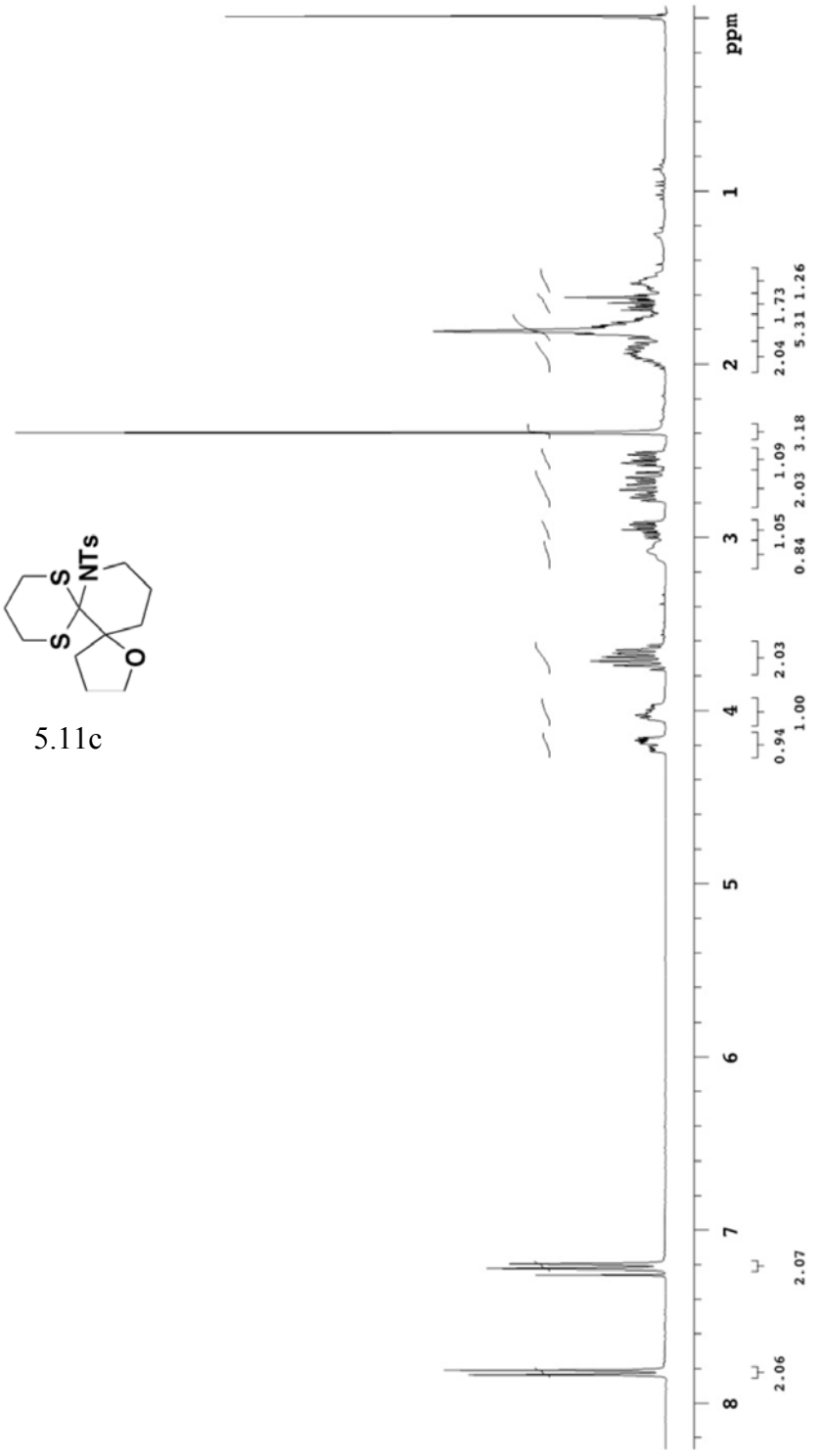
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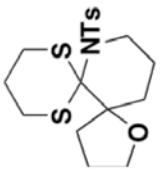
1.00
2.07
2.06

5.11c



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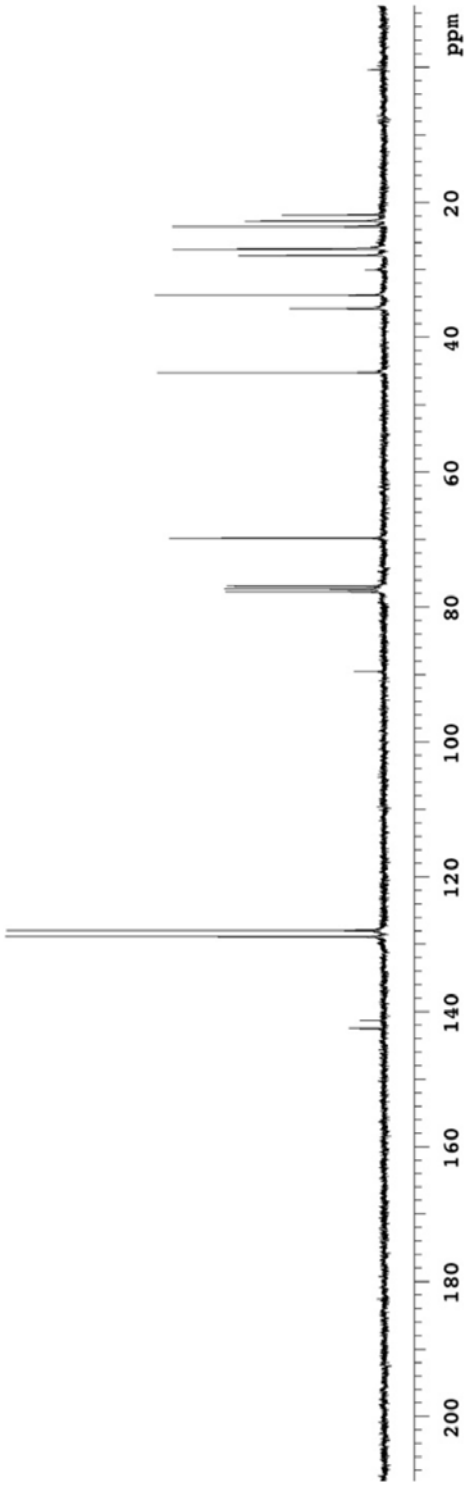
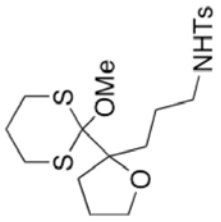
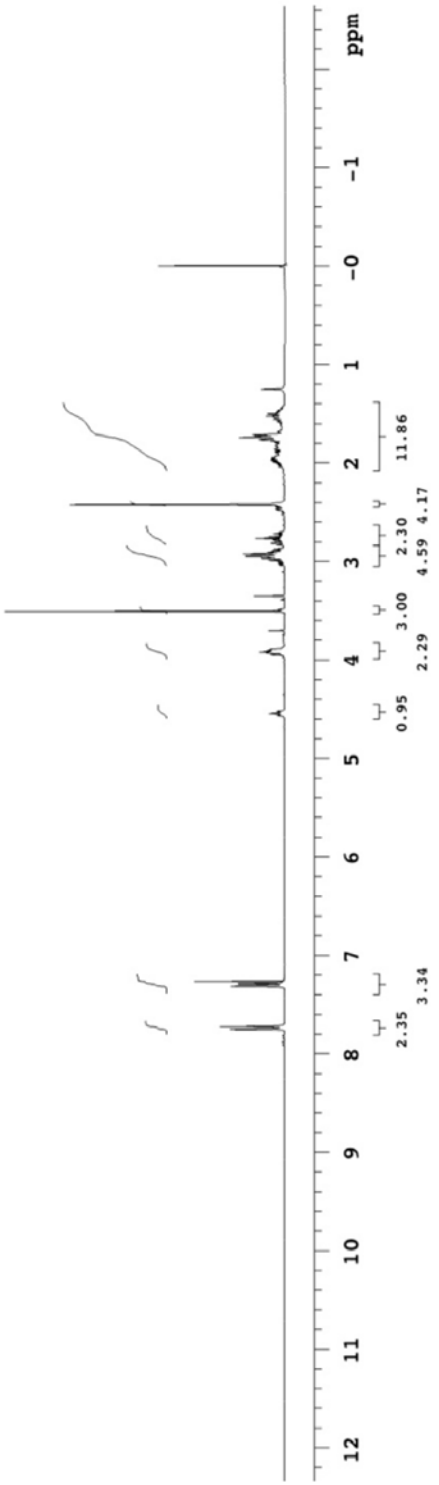



S
S
OMe
O
NHTs

5.11d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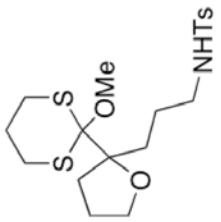

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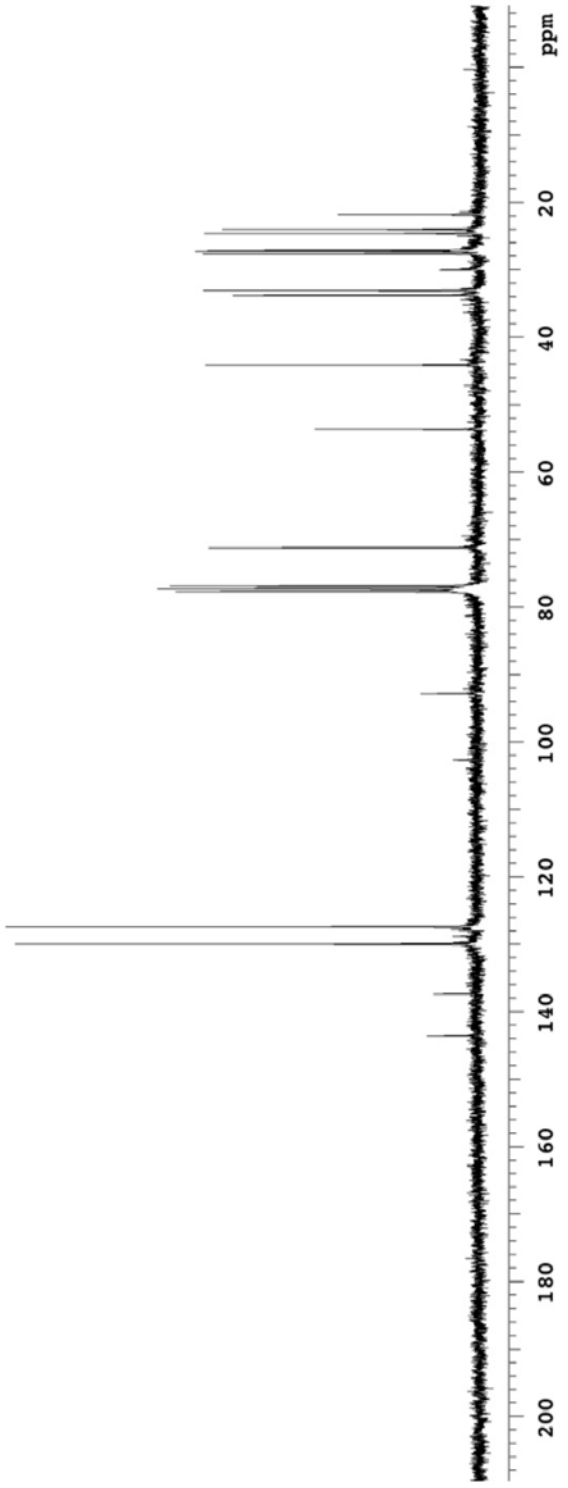

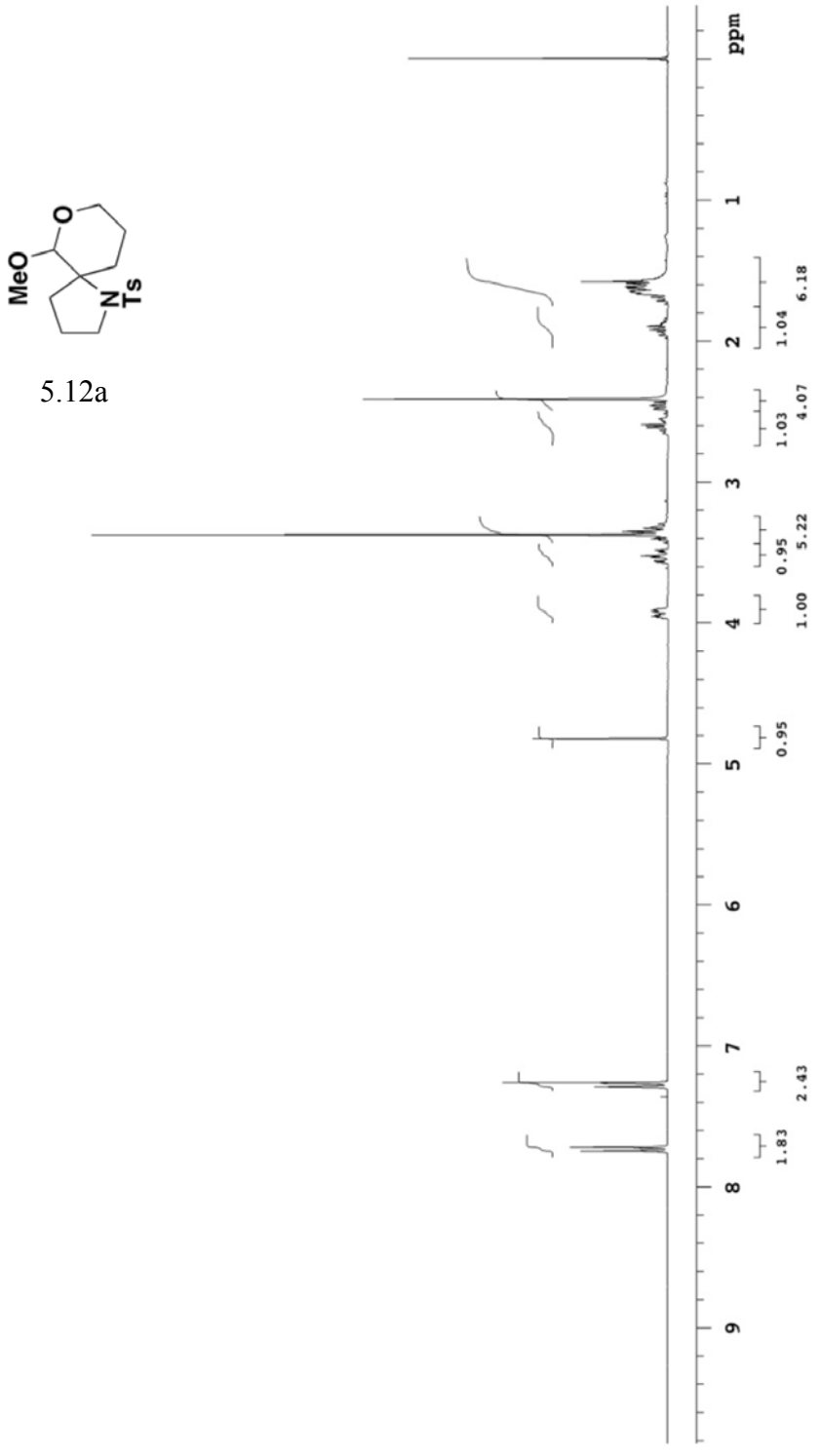

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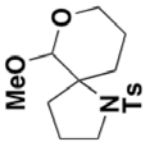

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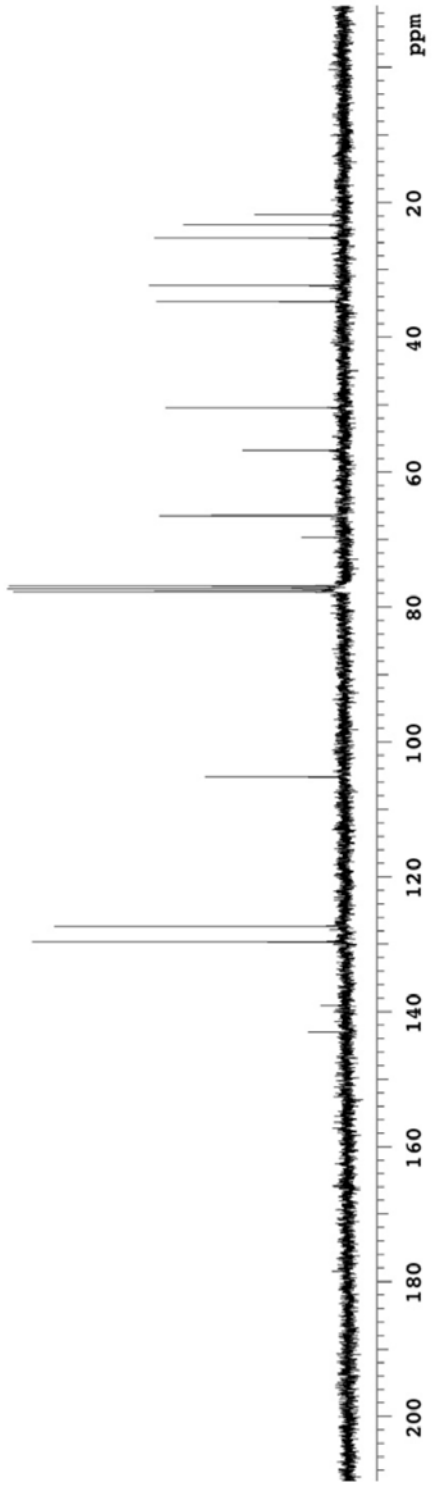

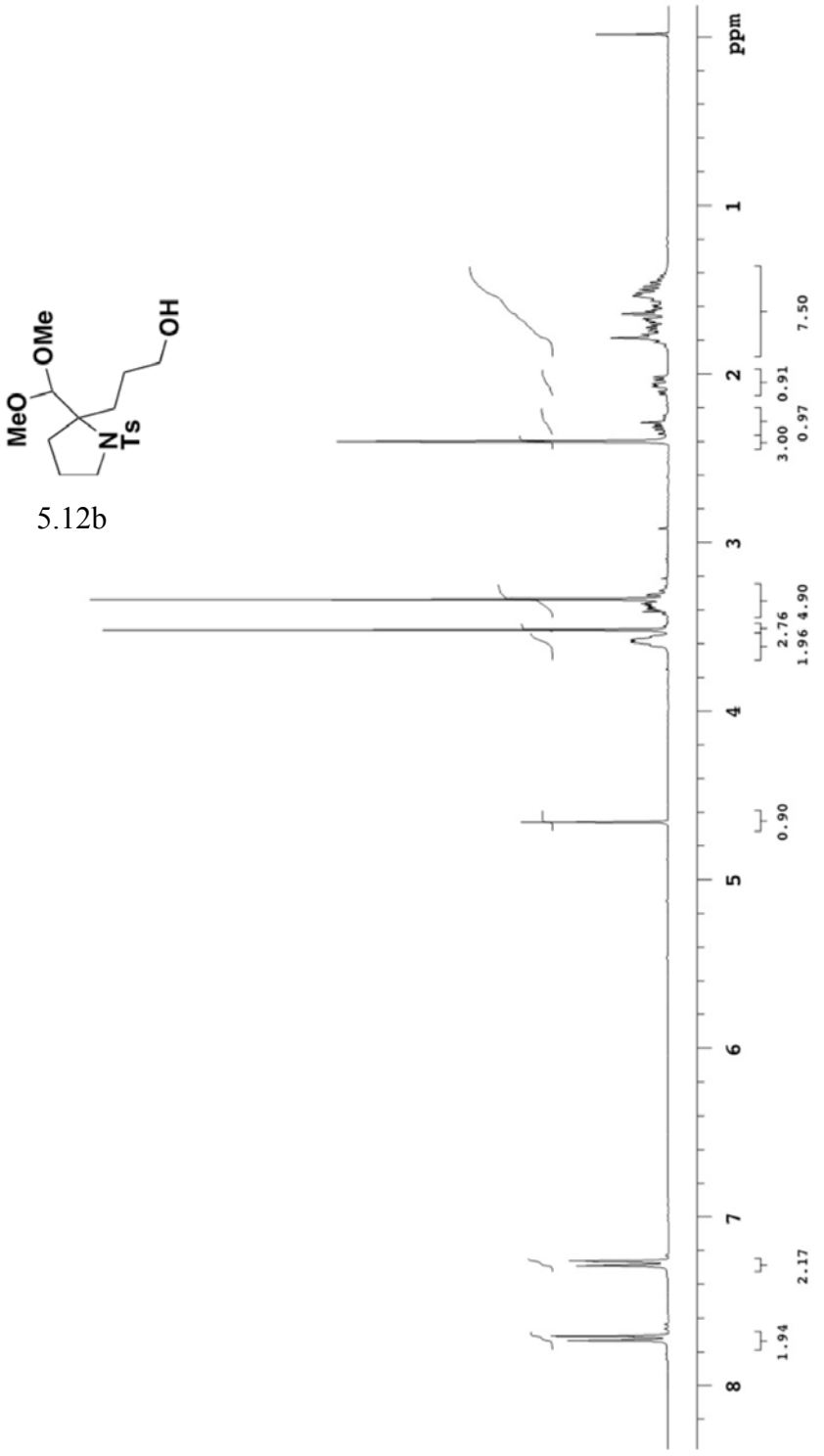
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0.90
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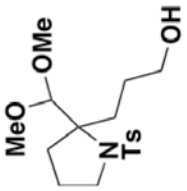
2.17

5.12b



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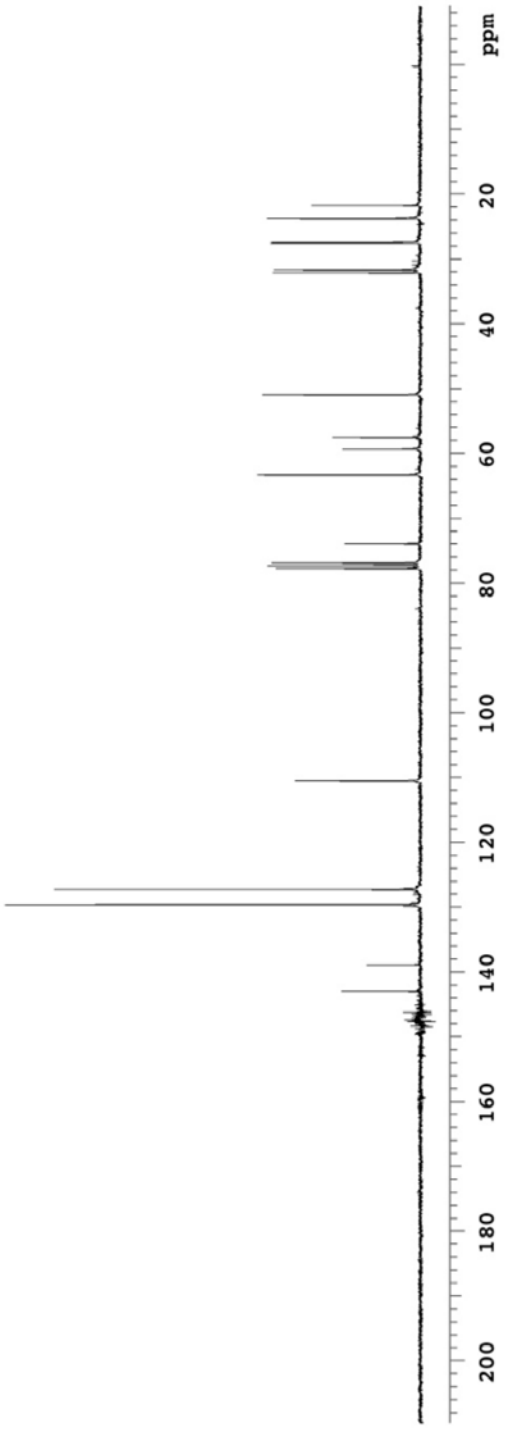

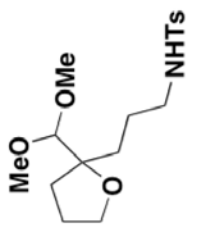
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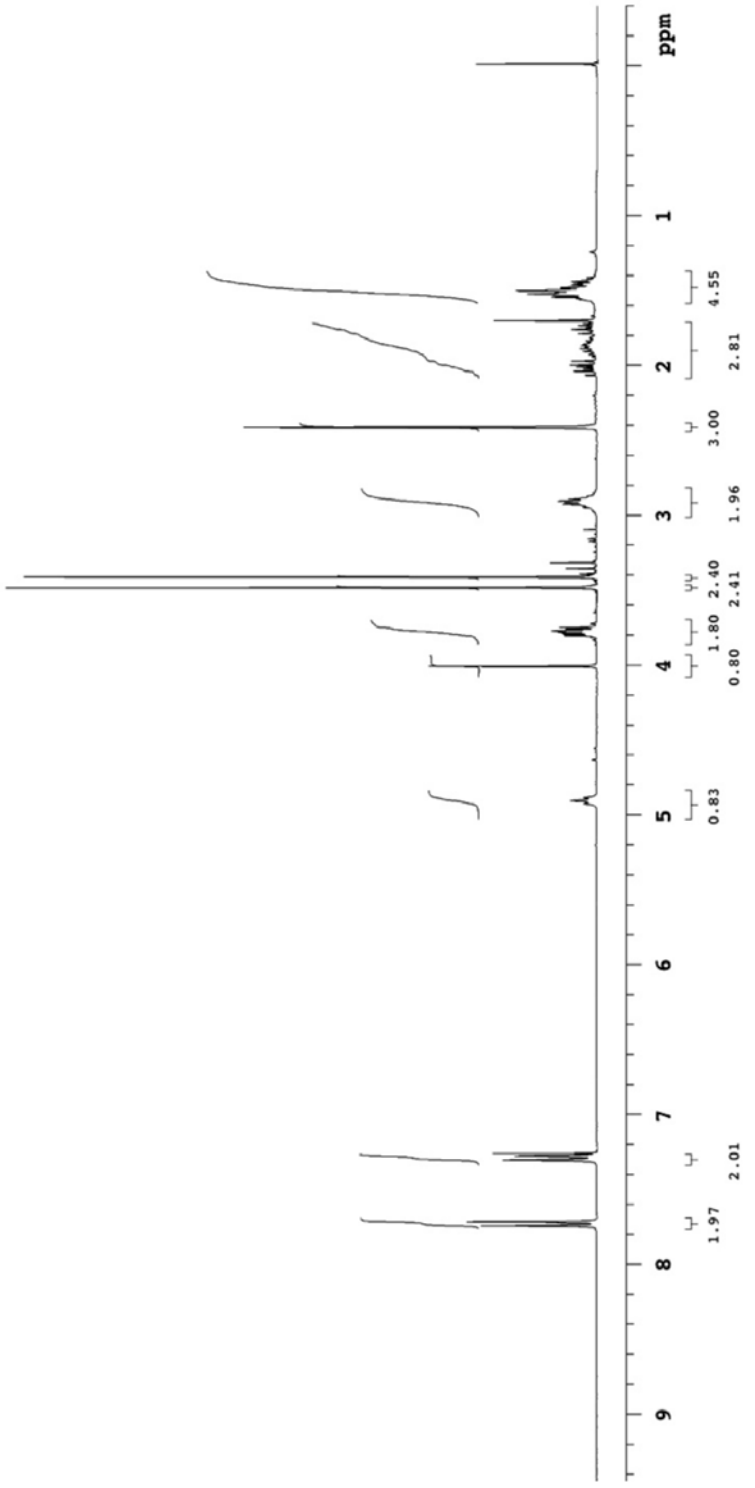
OMe
O
NHTs

5.12d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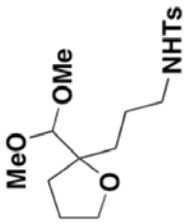
2.01



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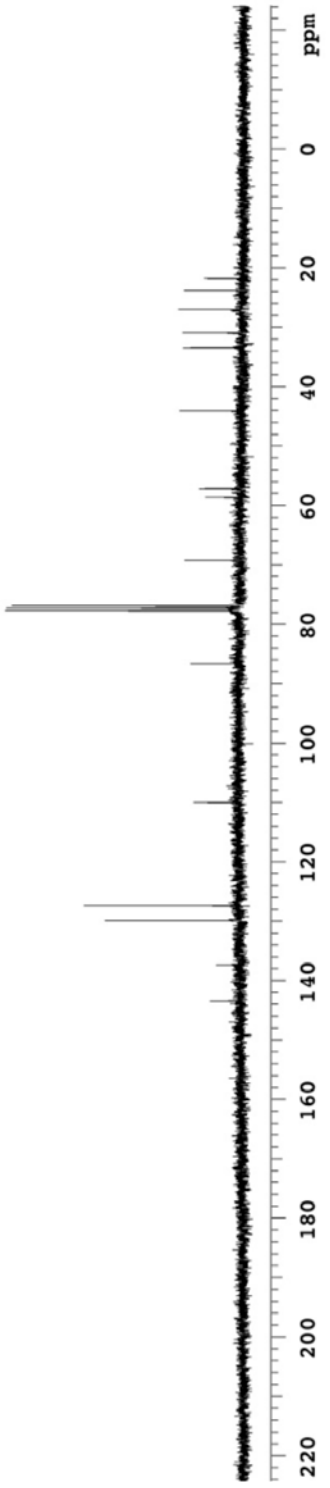

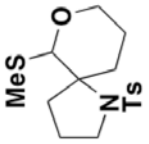

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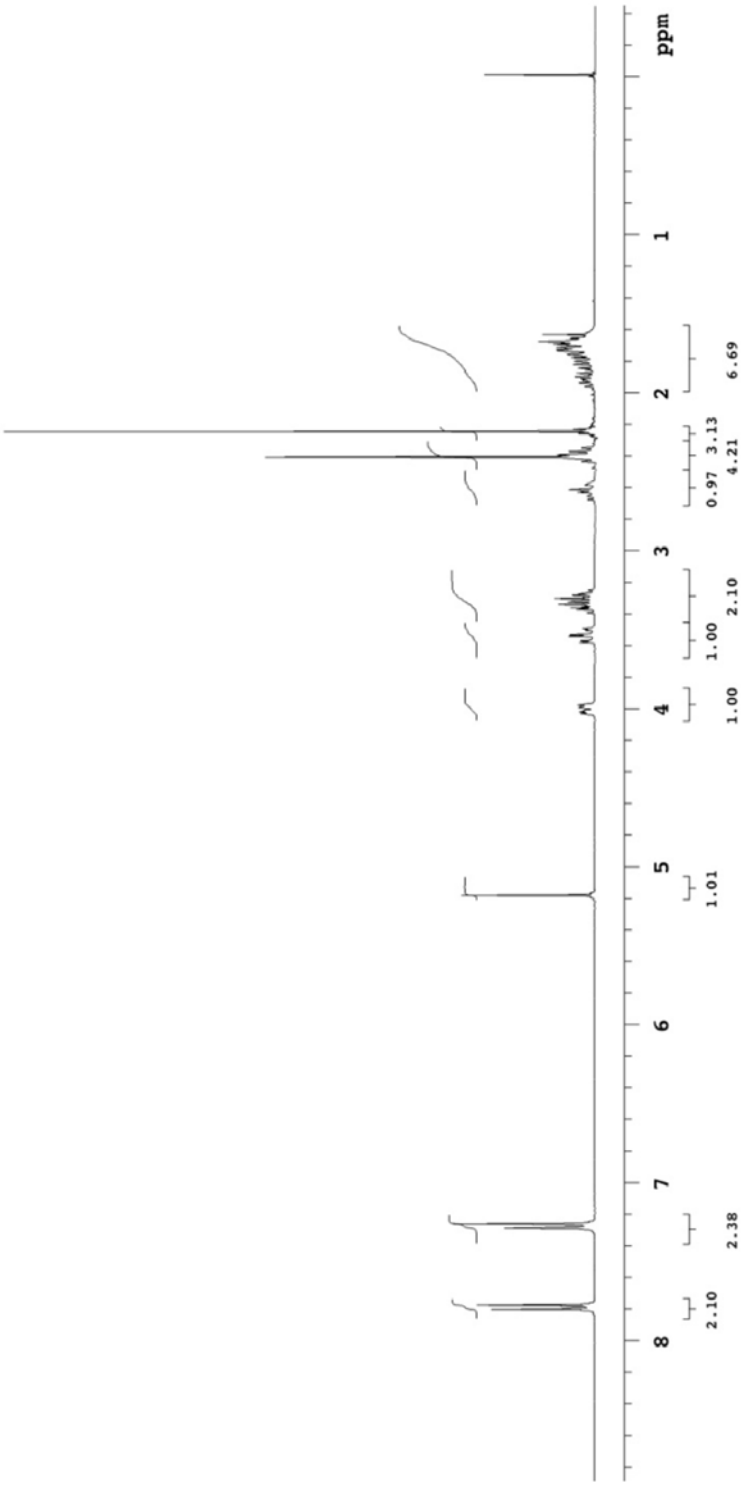
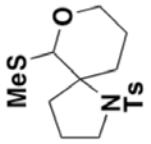
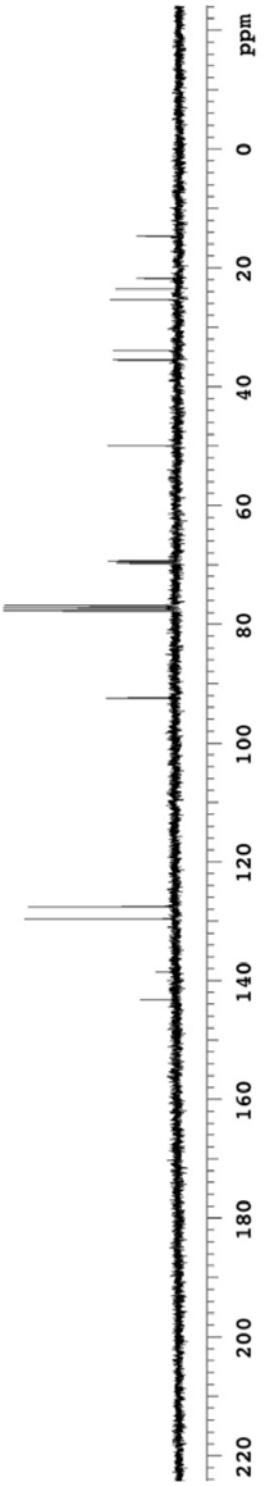
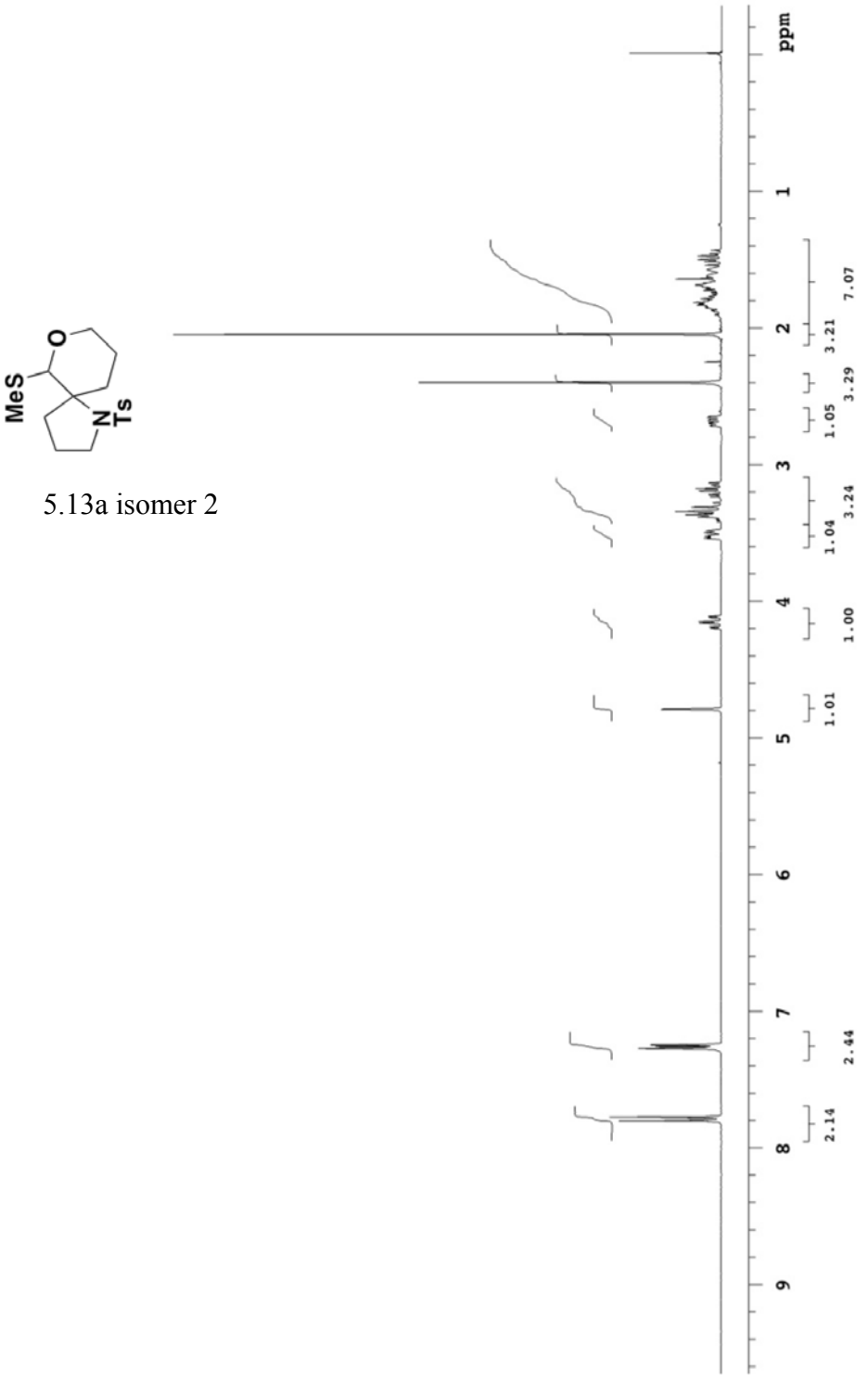




5.13a isomer 1





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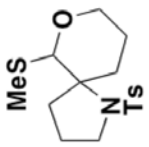
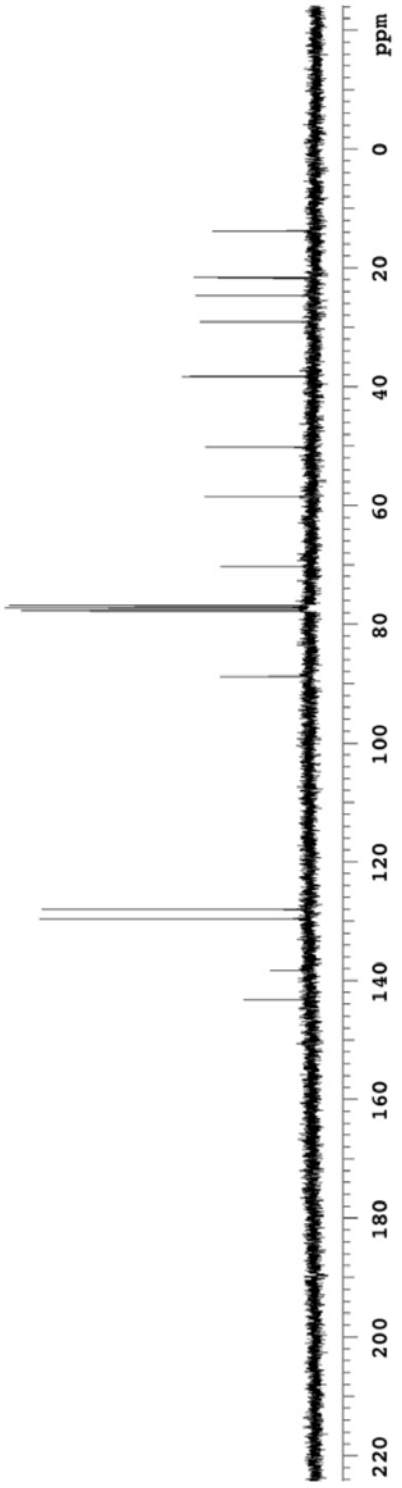
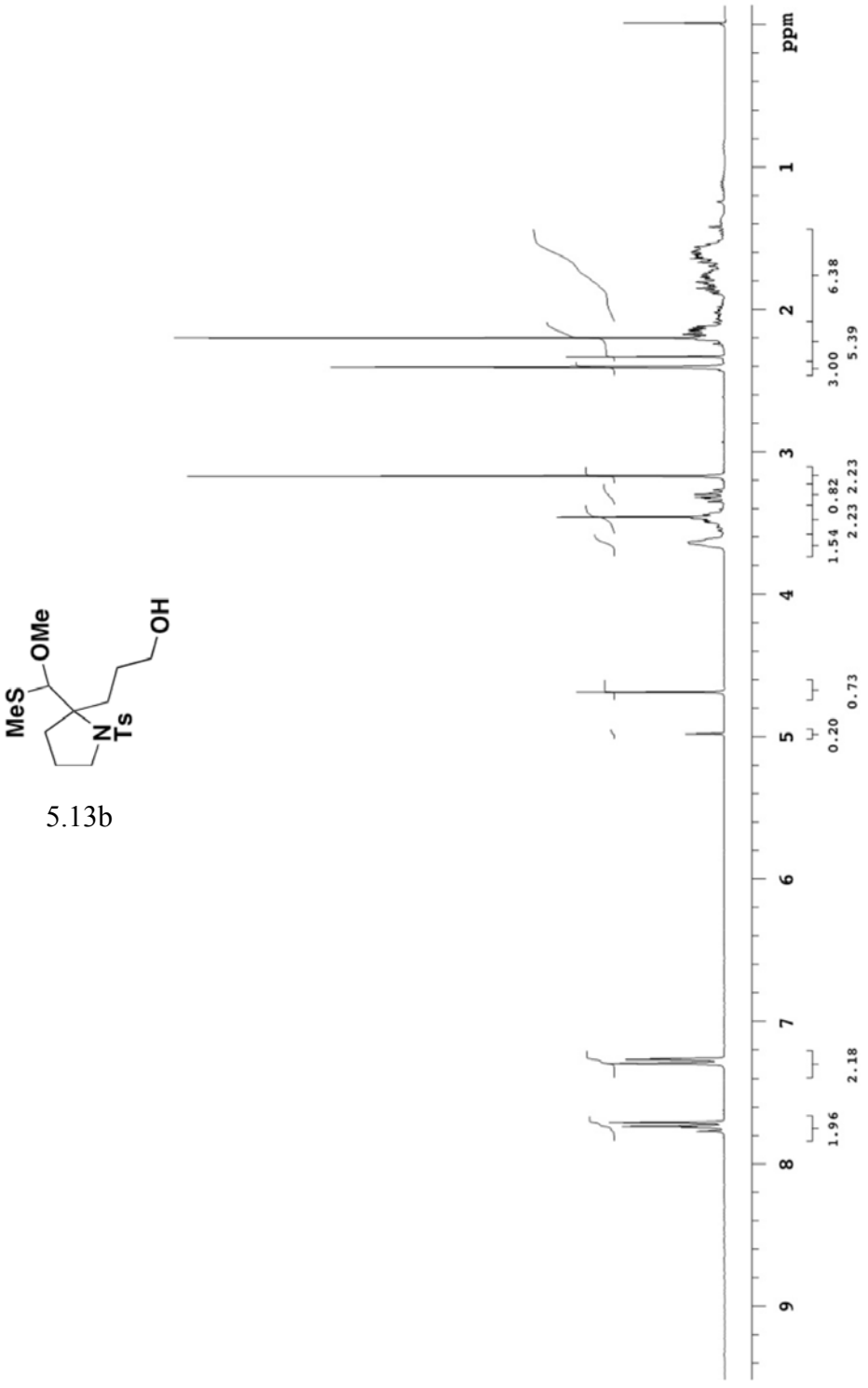


5.13a isomer 2

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OMe
OH
N
Ts
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2.23
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0.20
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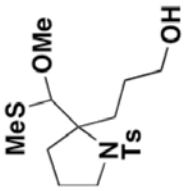
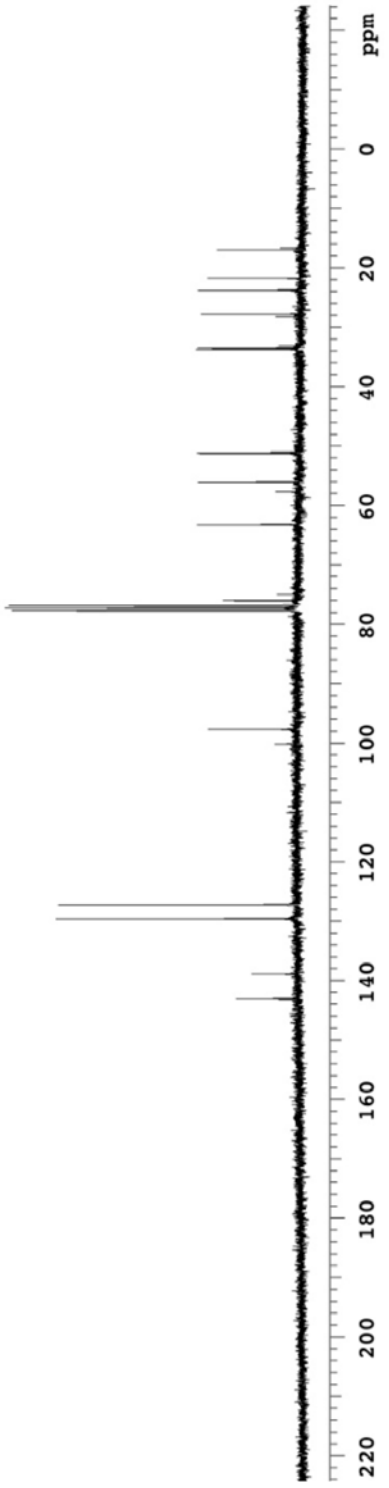
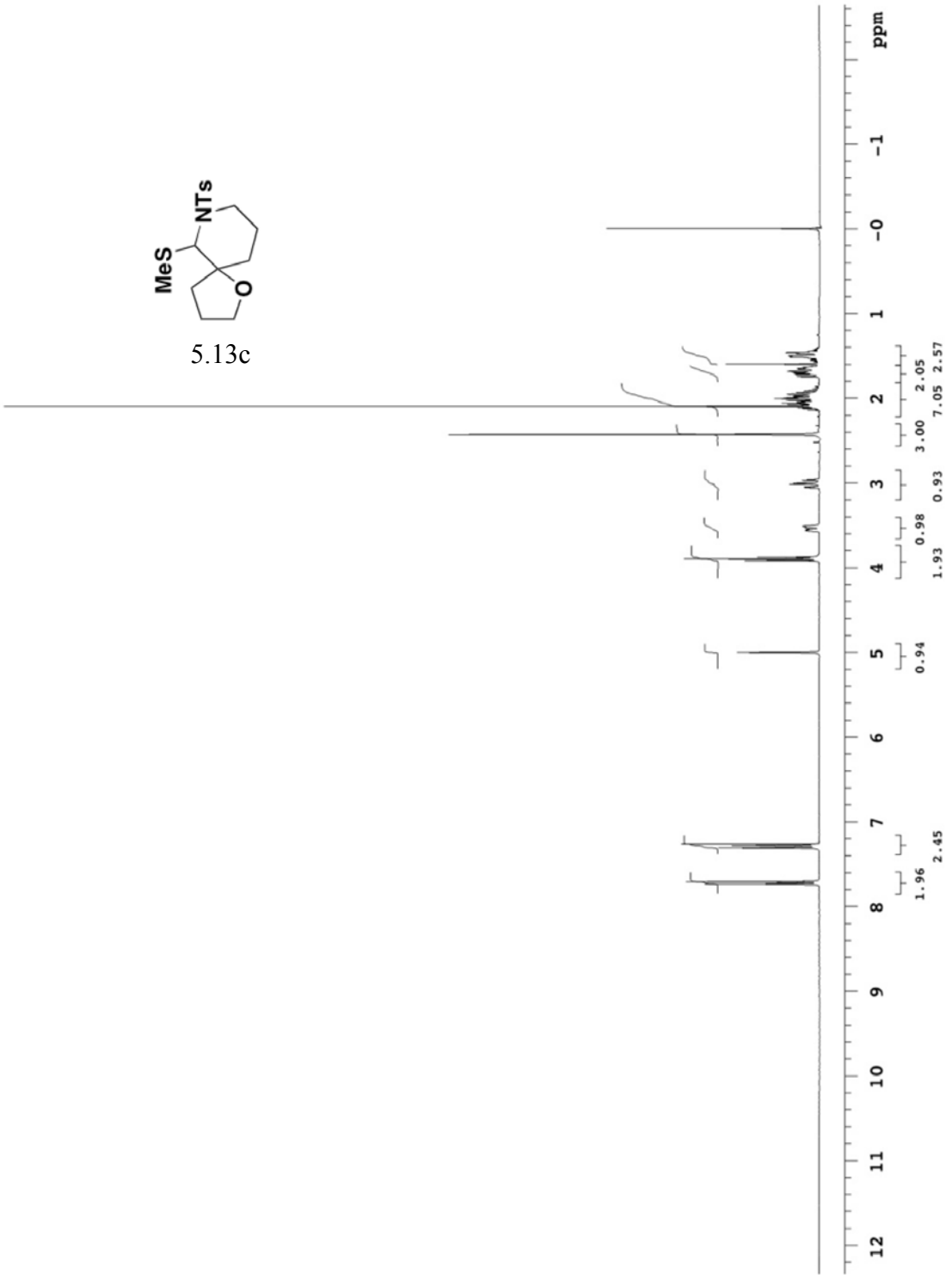
1.96

5.13b



5.13b

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NTs
O
5.13c
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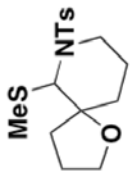

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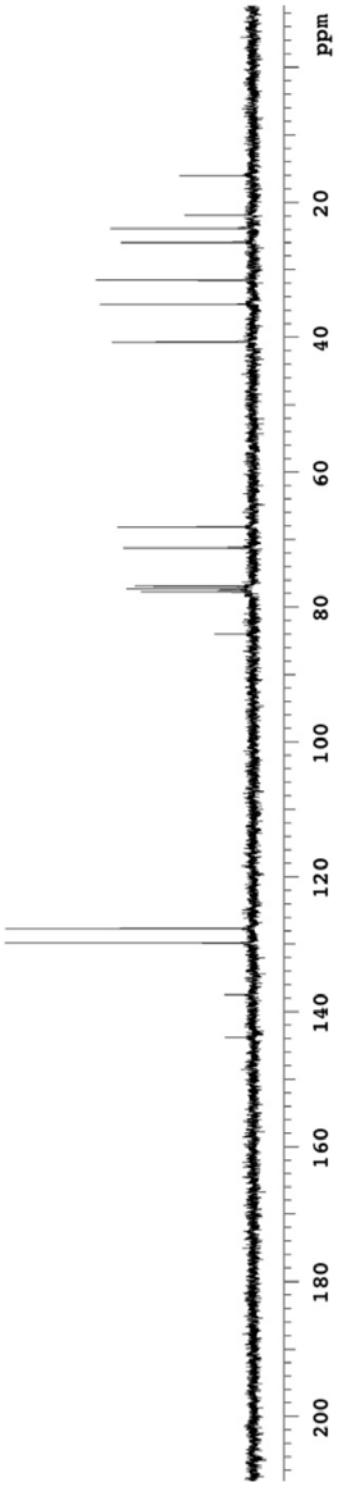
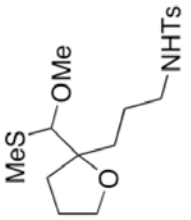
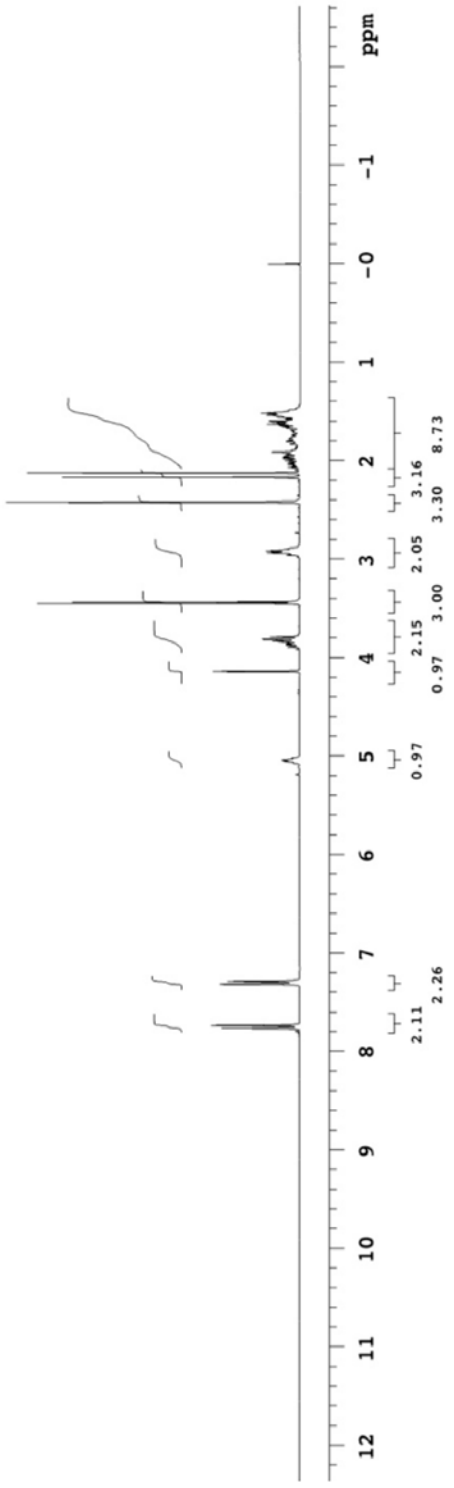



MeS
OMe
NHTs
O

5.13d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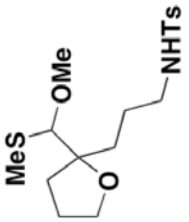
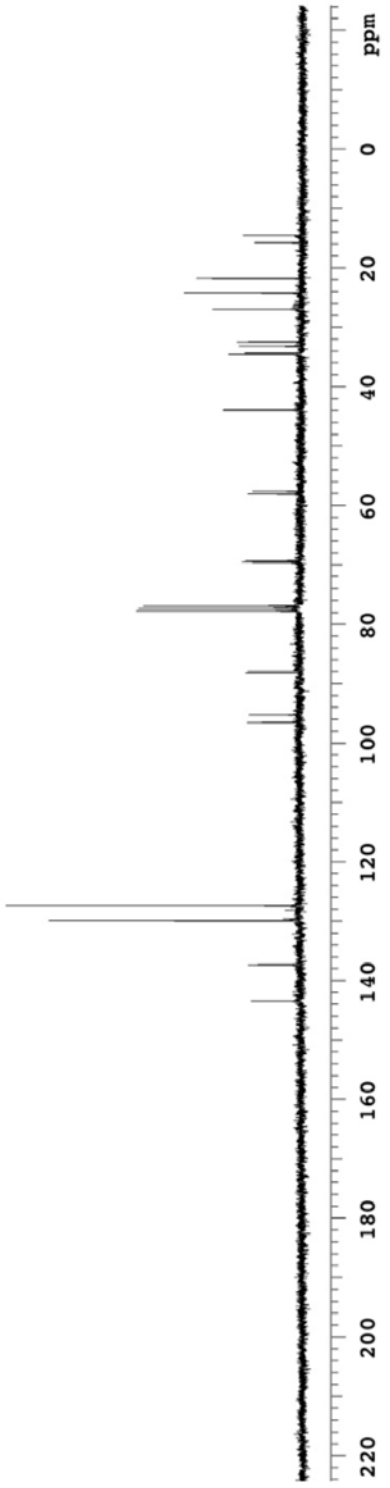
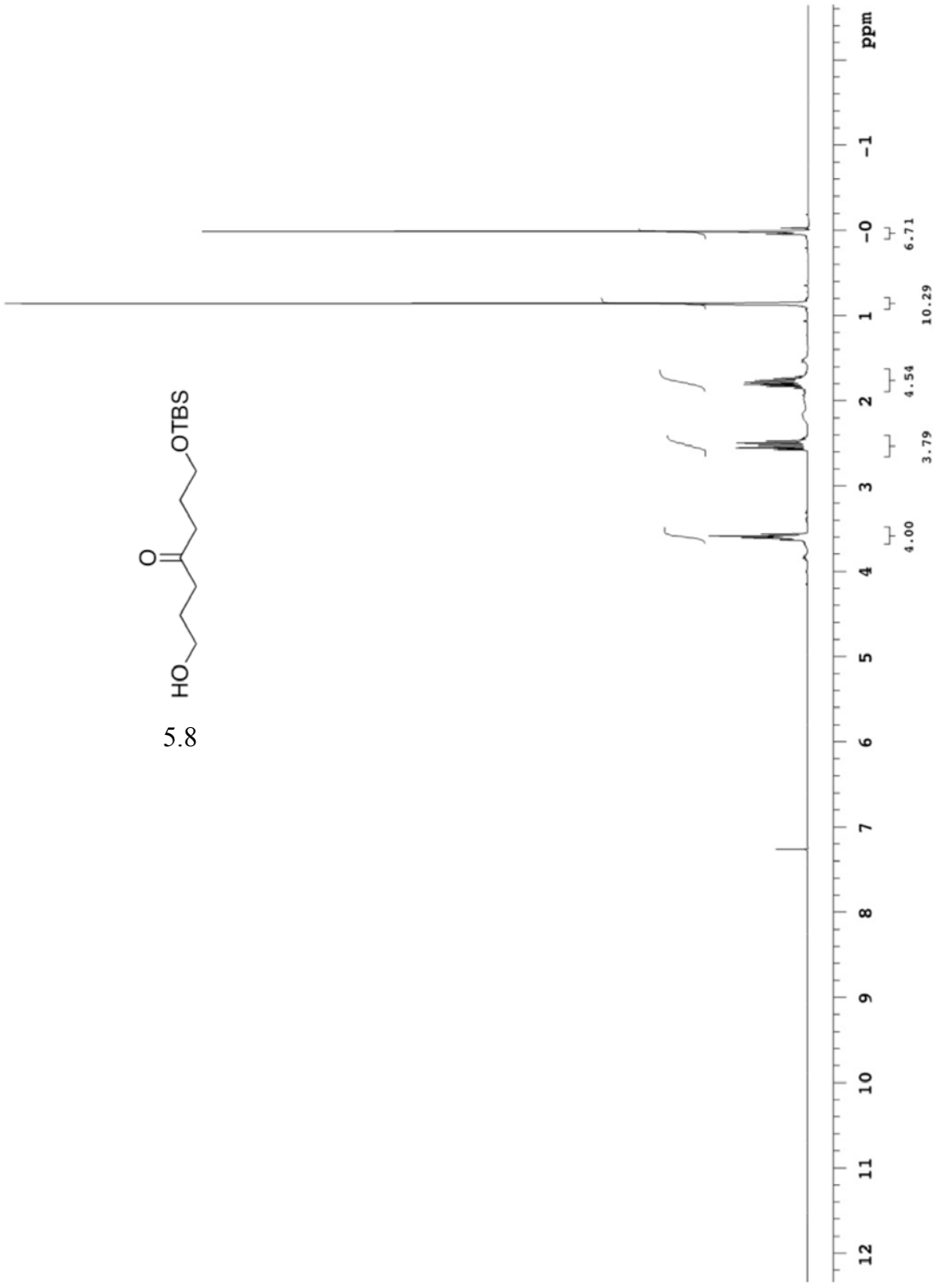


5.13d





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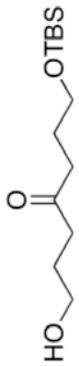

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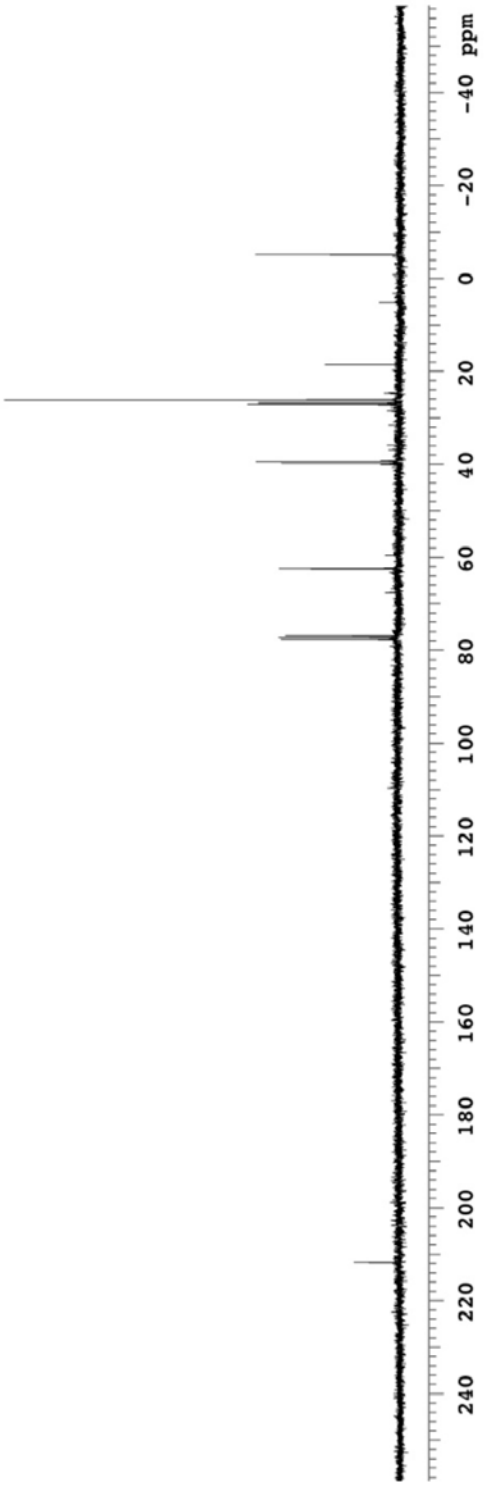

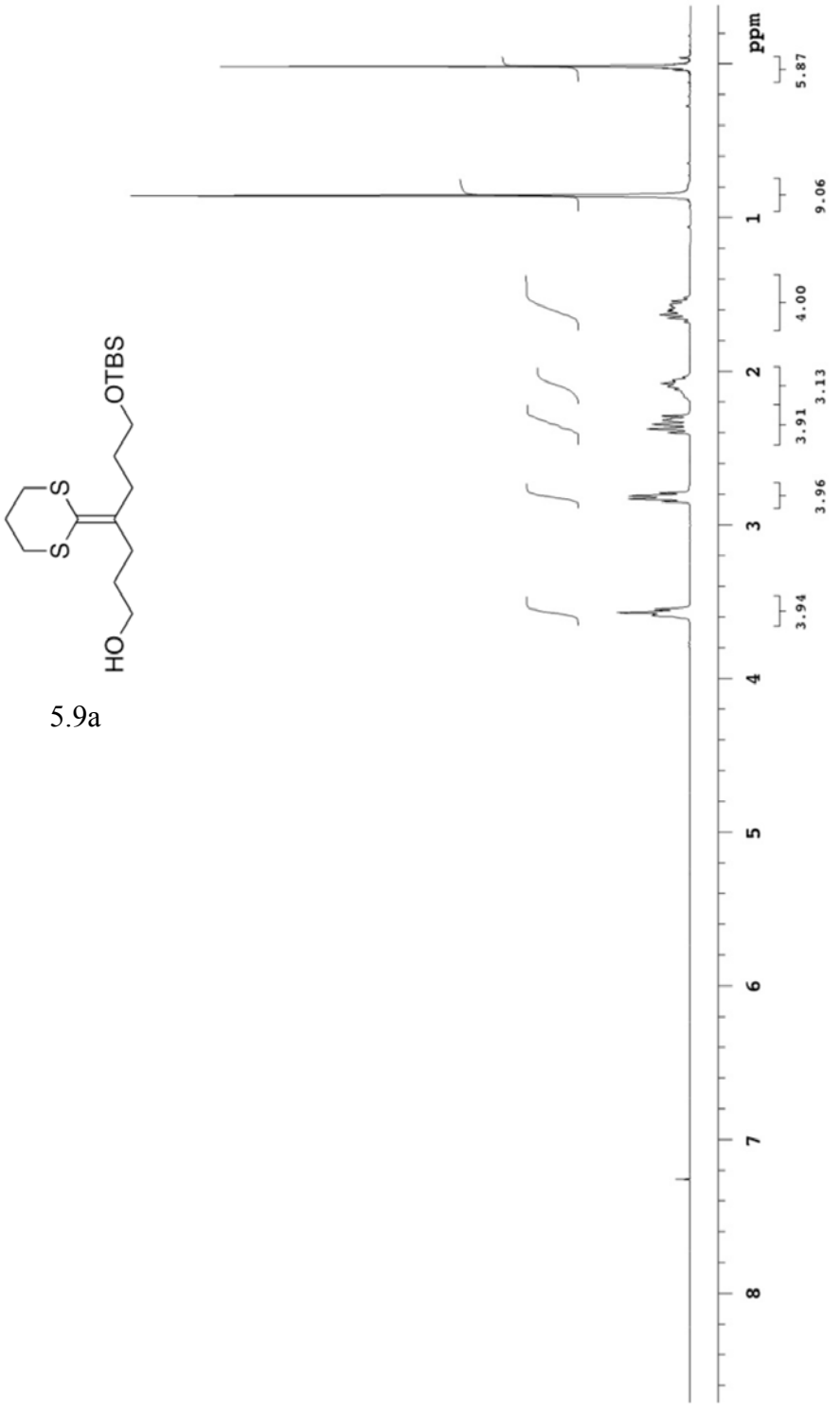

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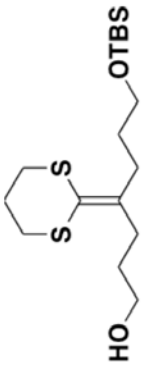
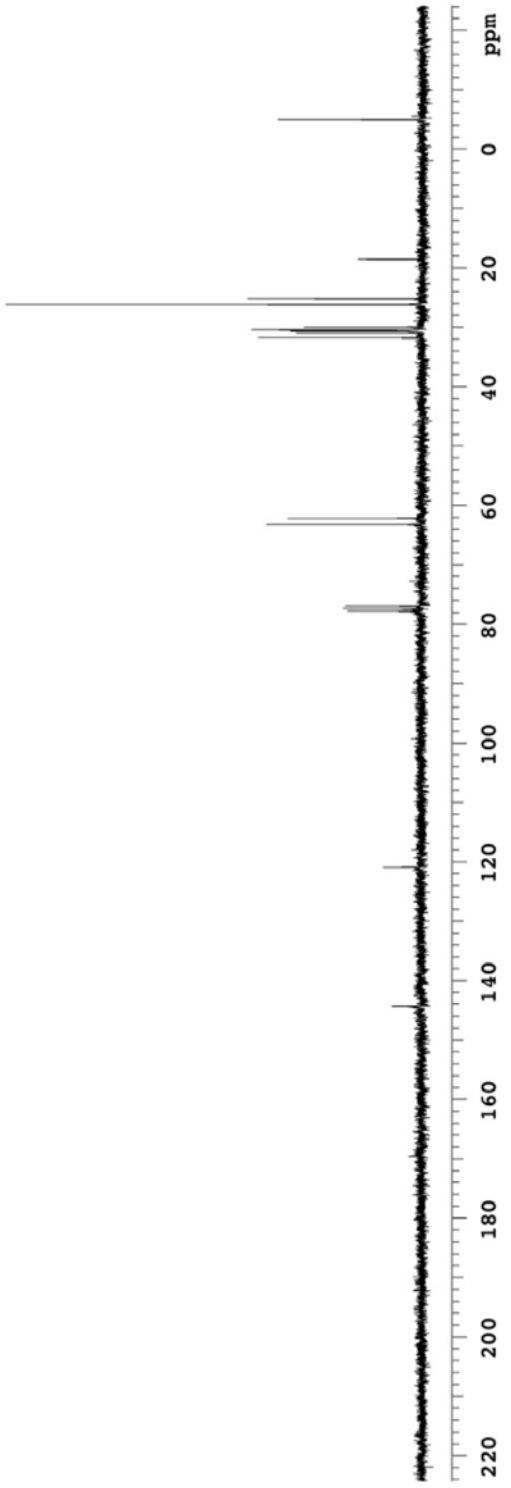
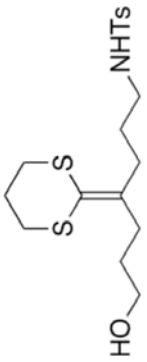


5.9a

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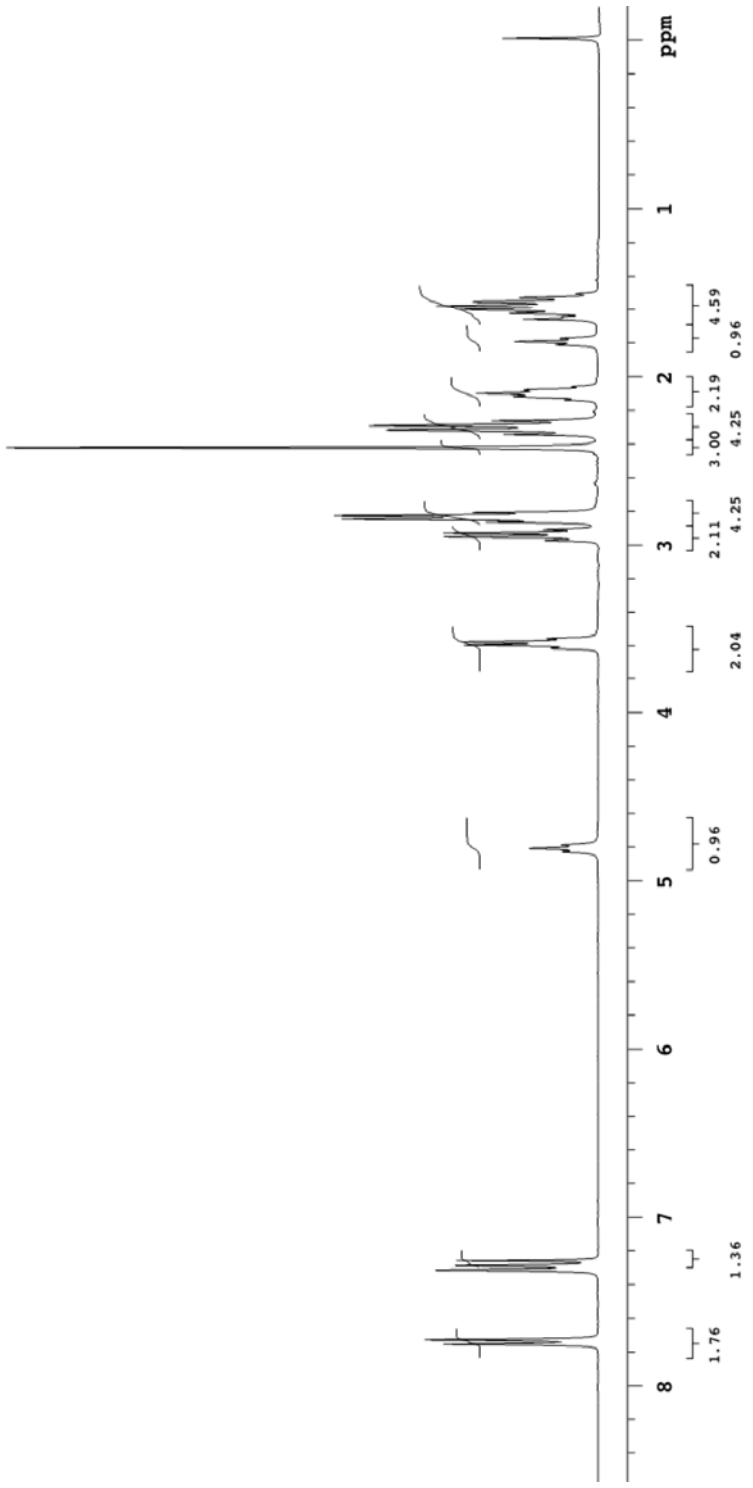
S
S
HO

5.10a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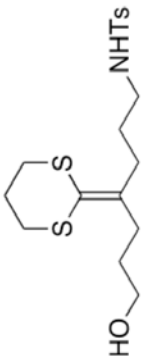

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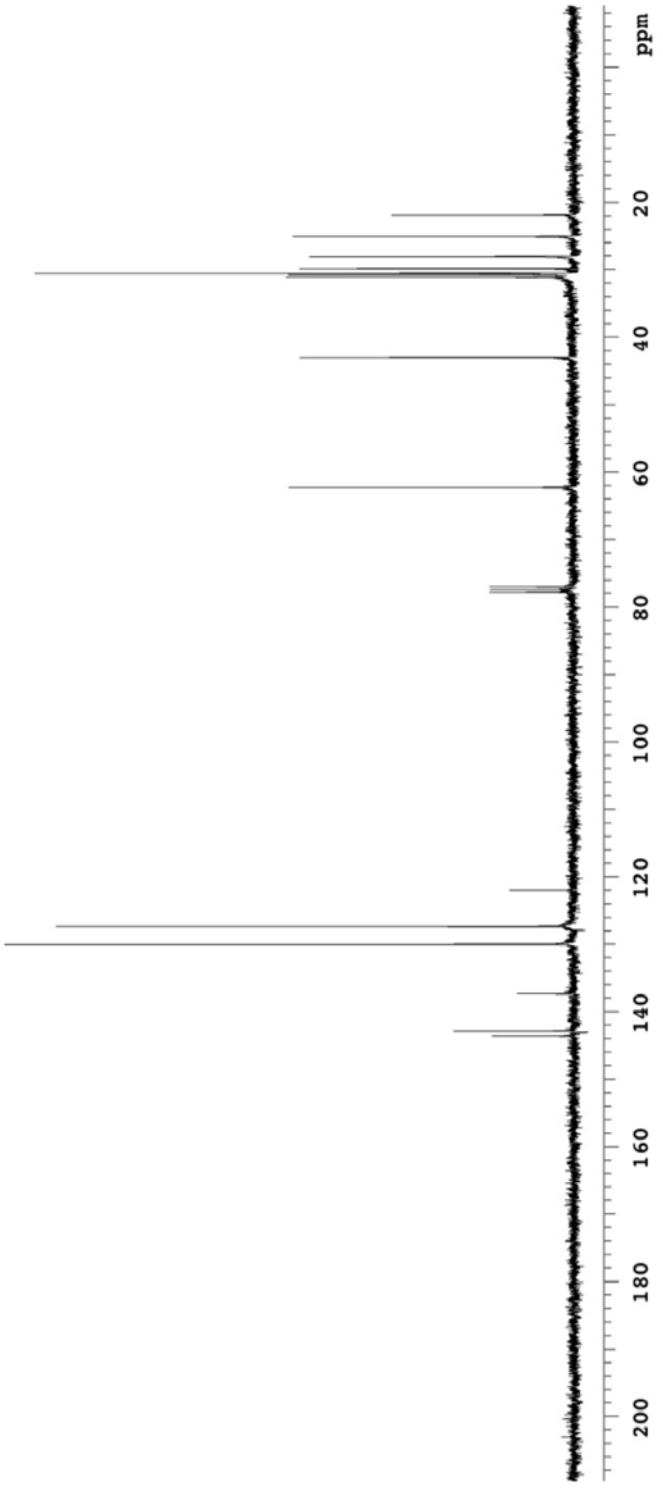

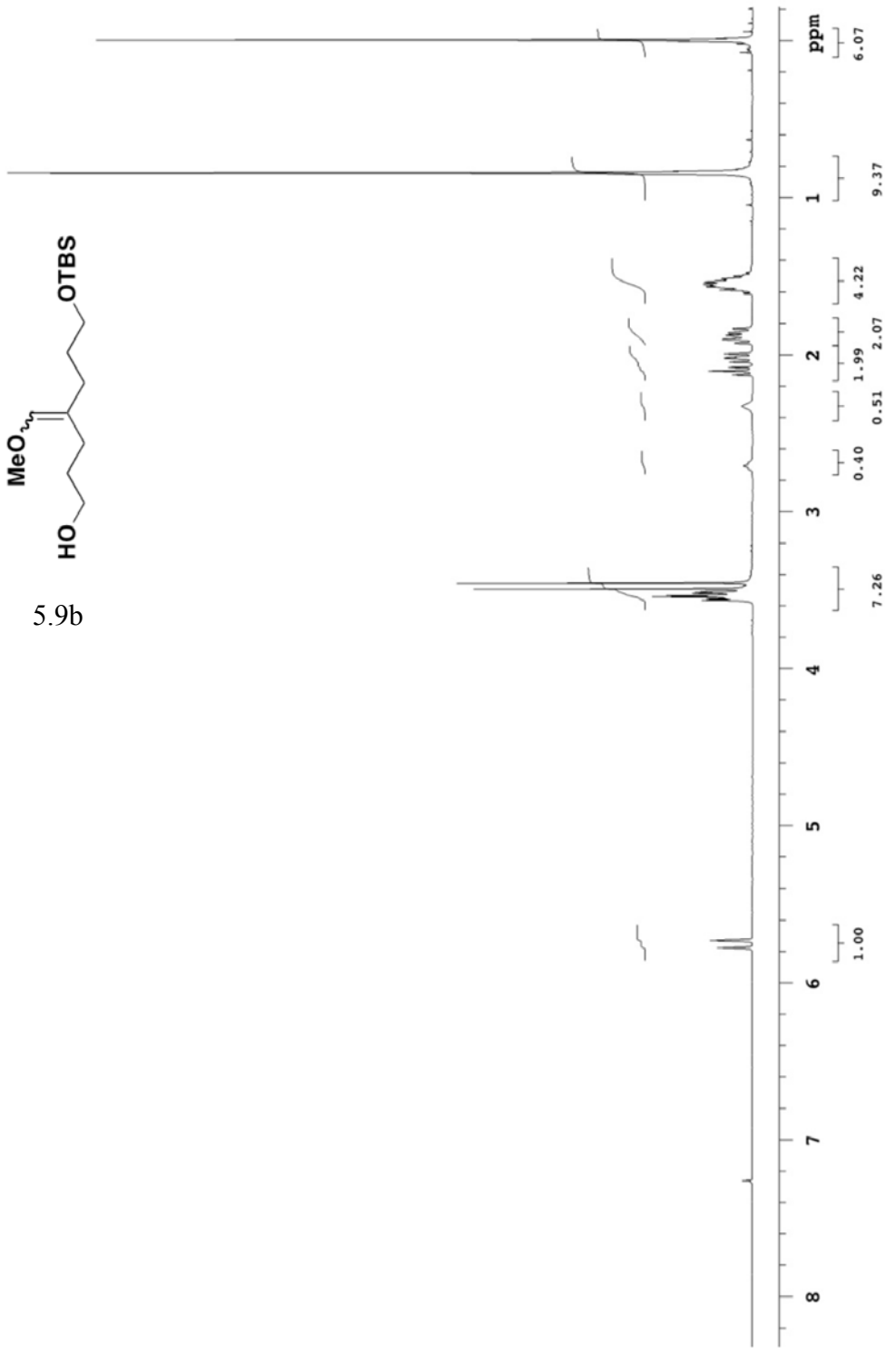

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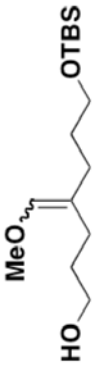

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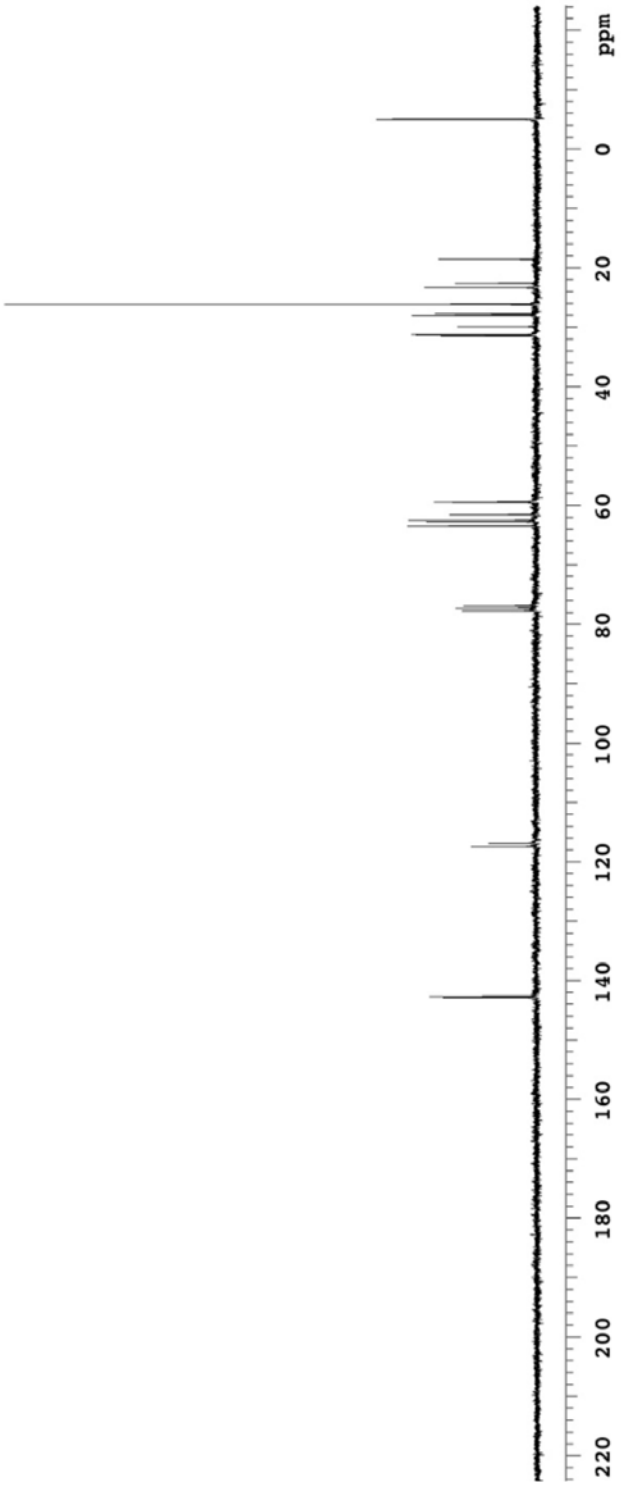

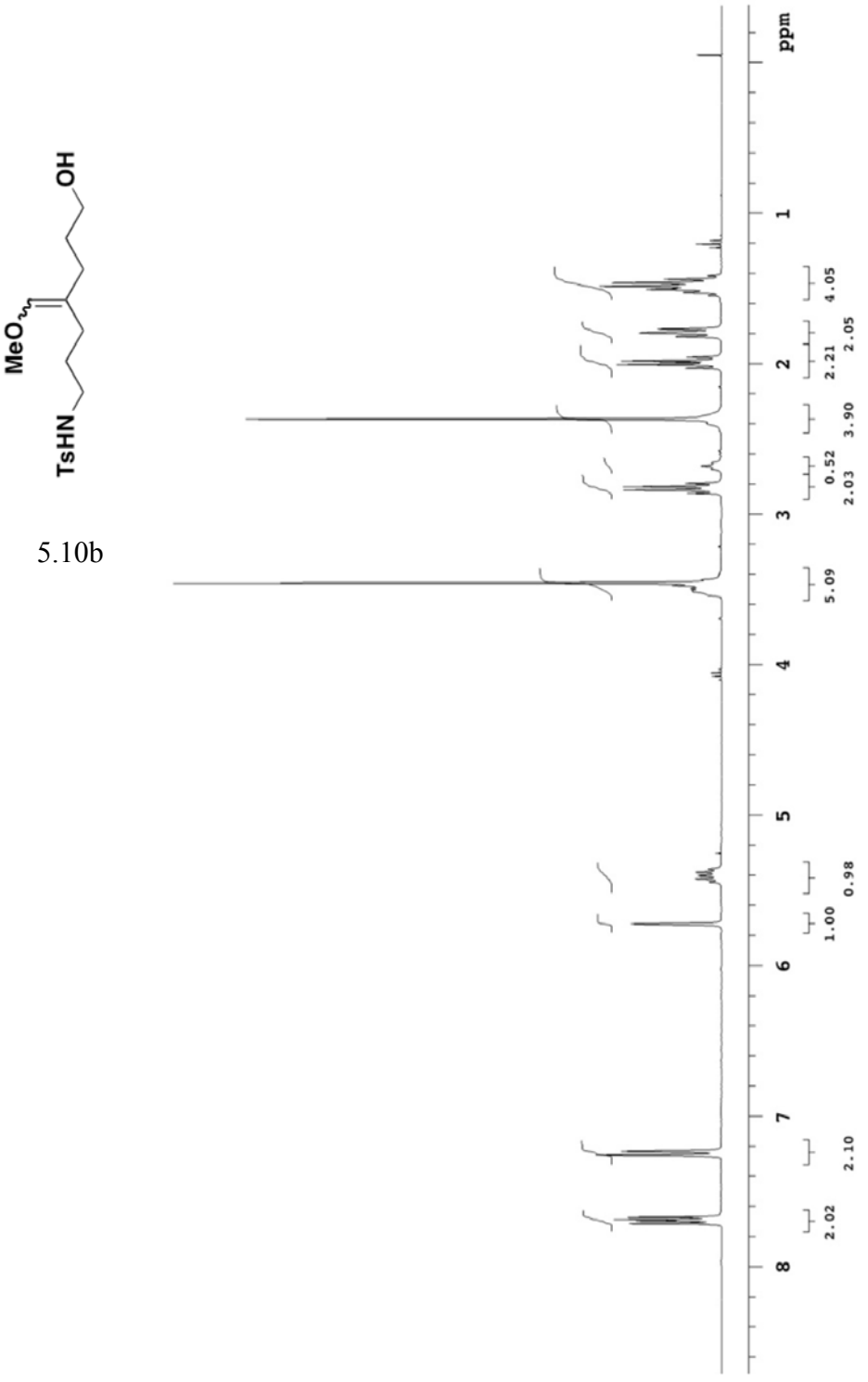
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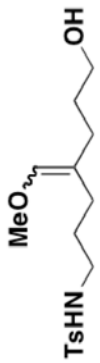
5.10b



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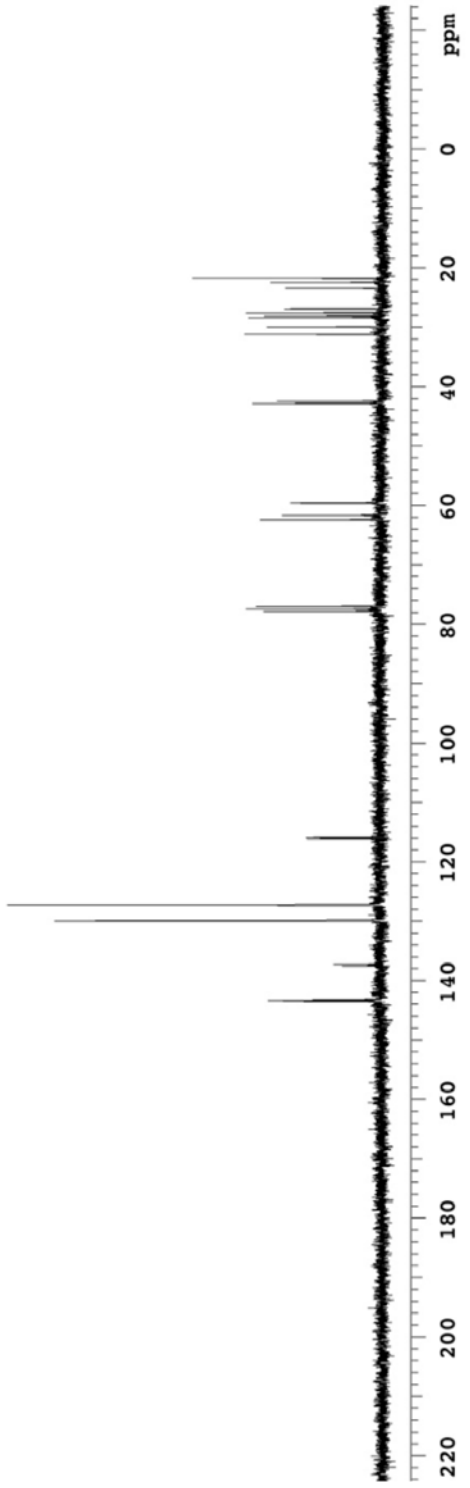

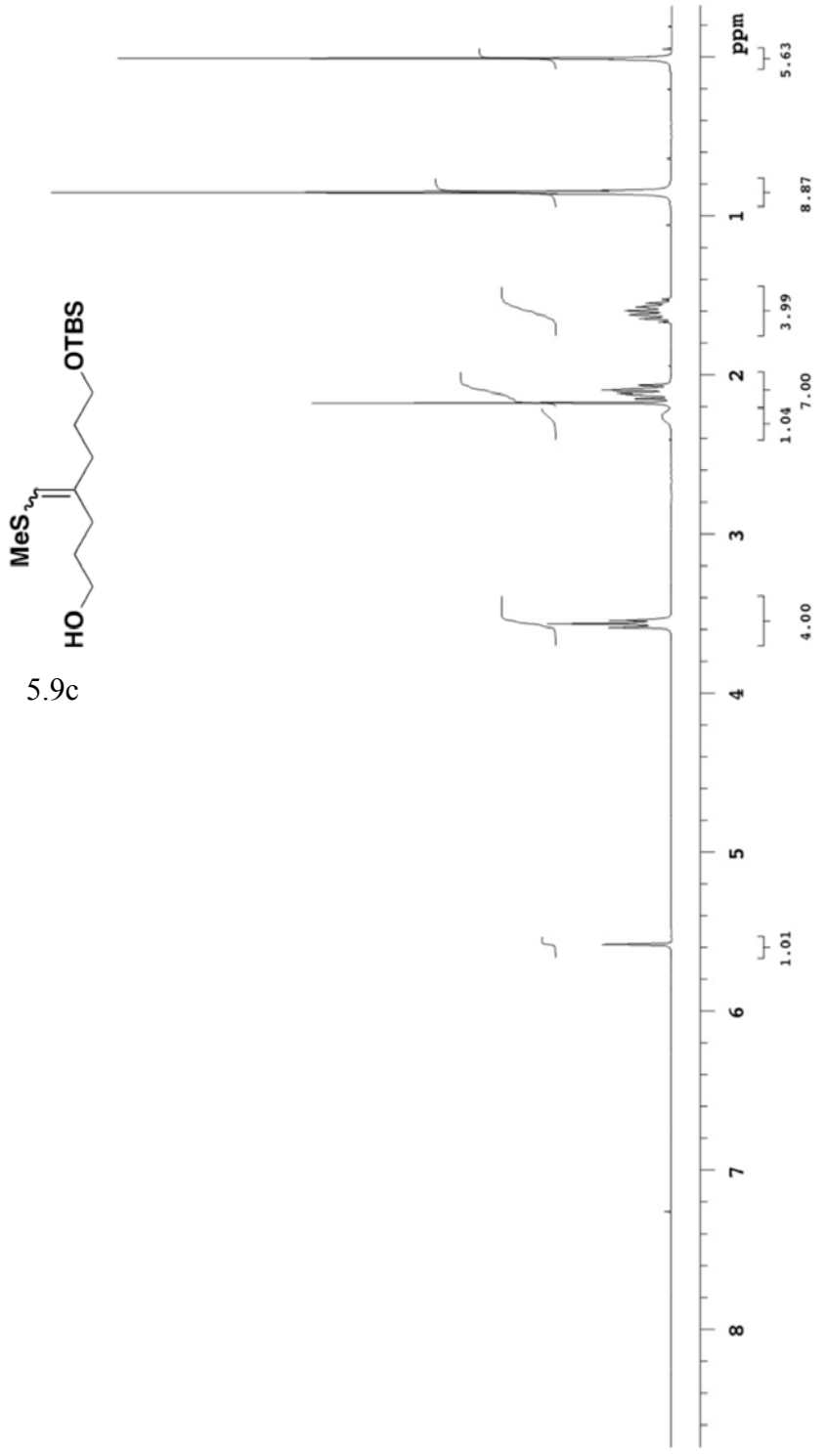

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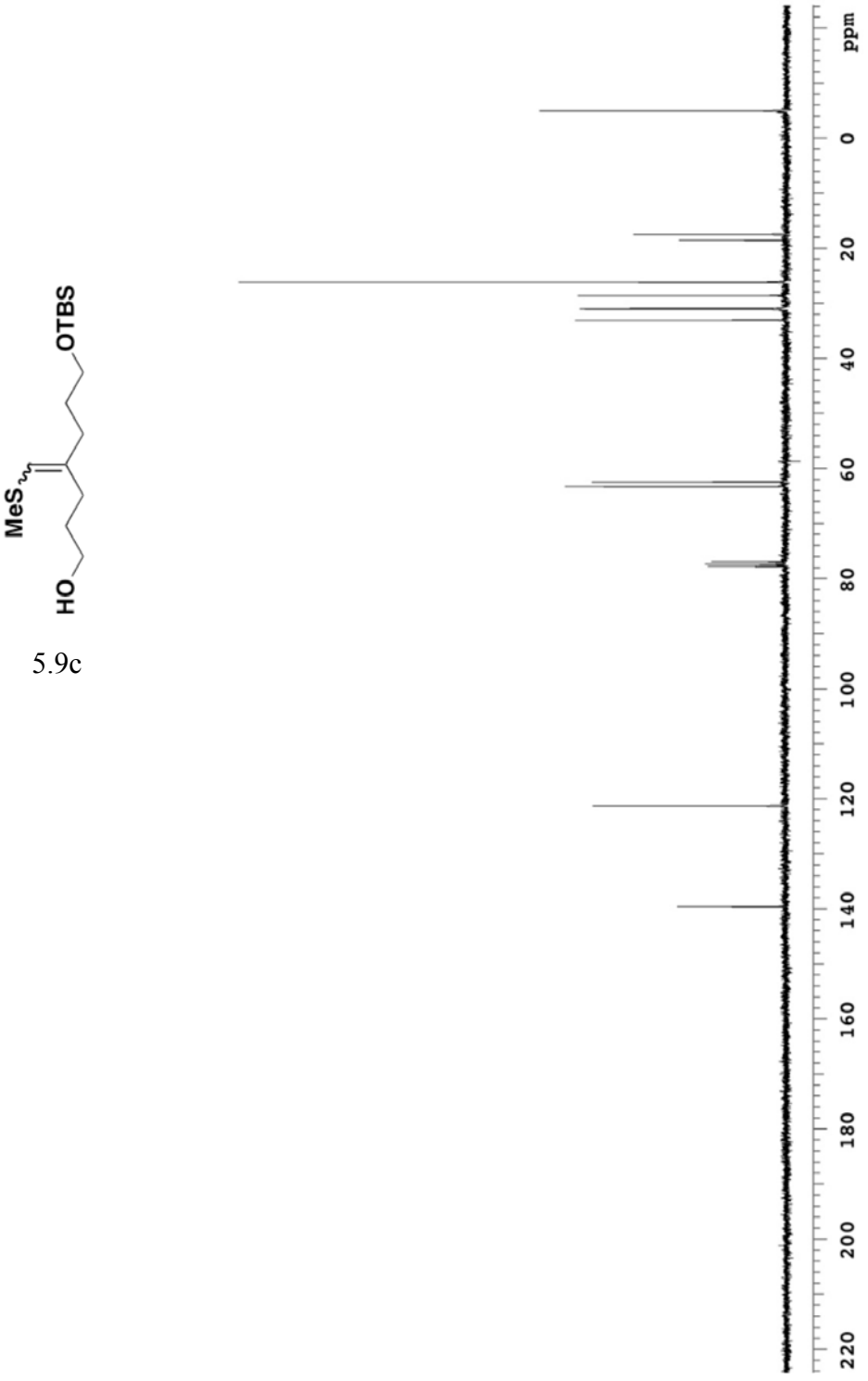

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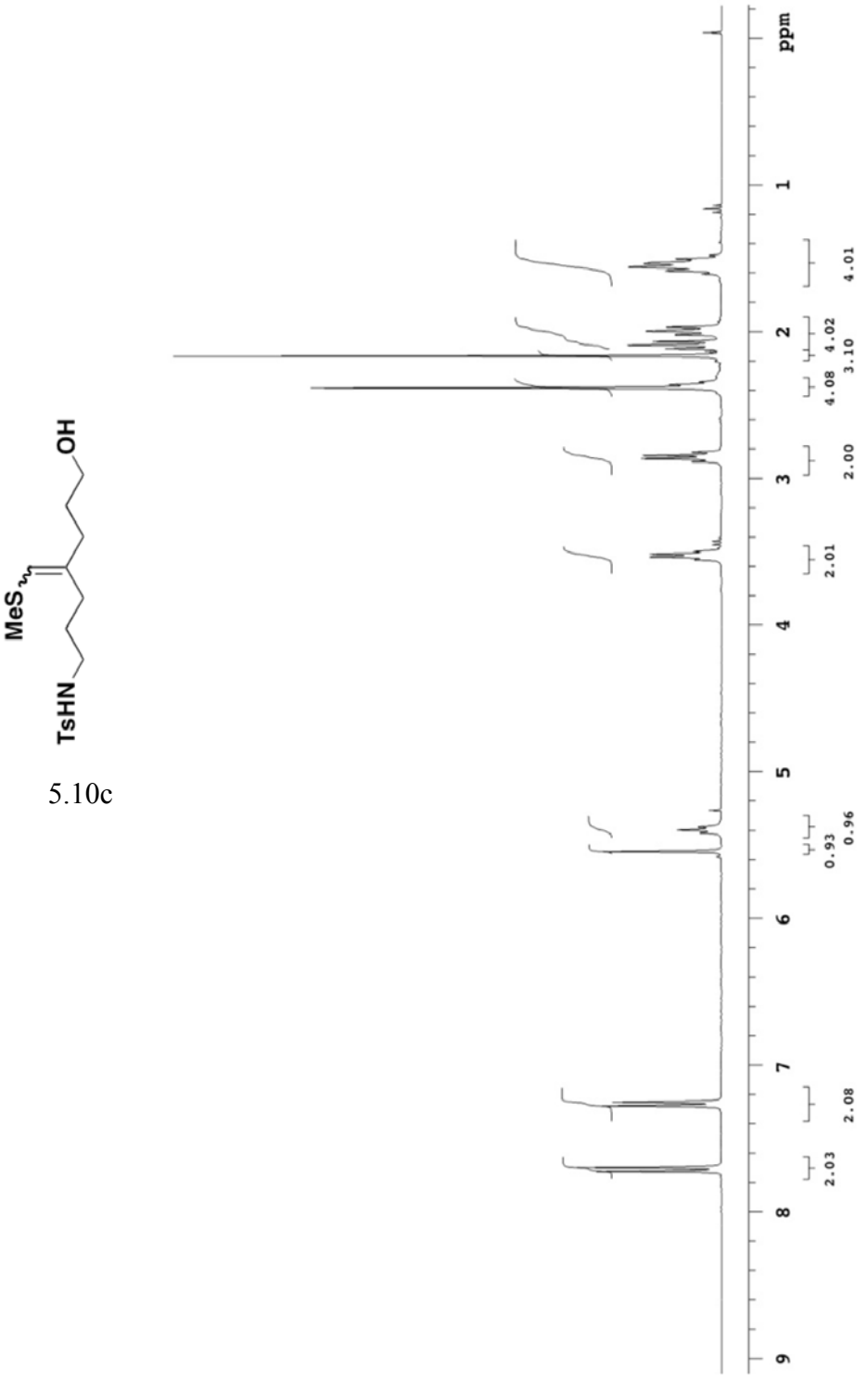
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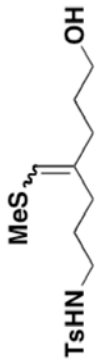
2.08
2.03

5.10c



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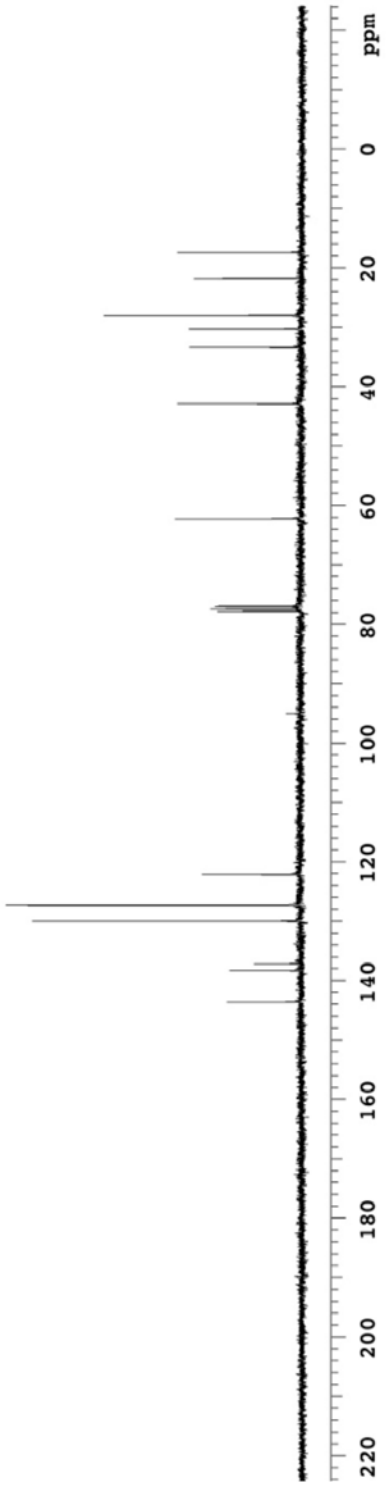
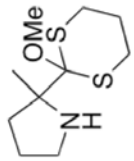
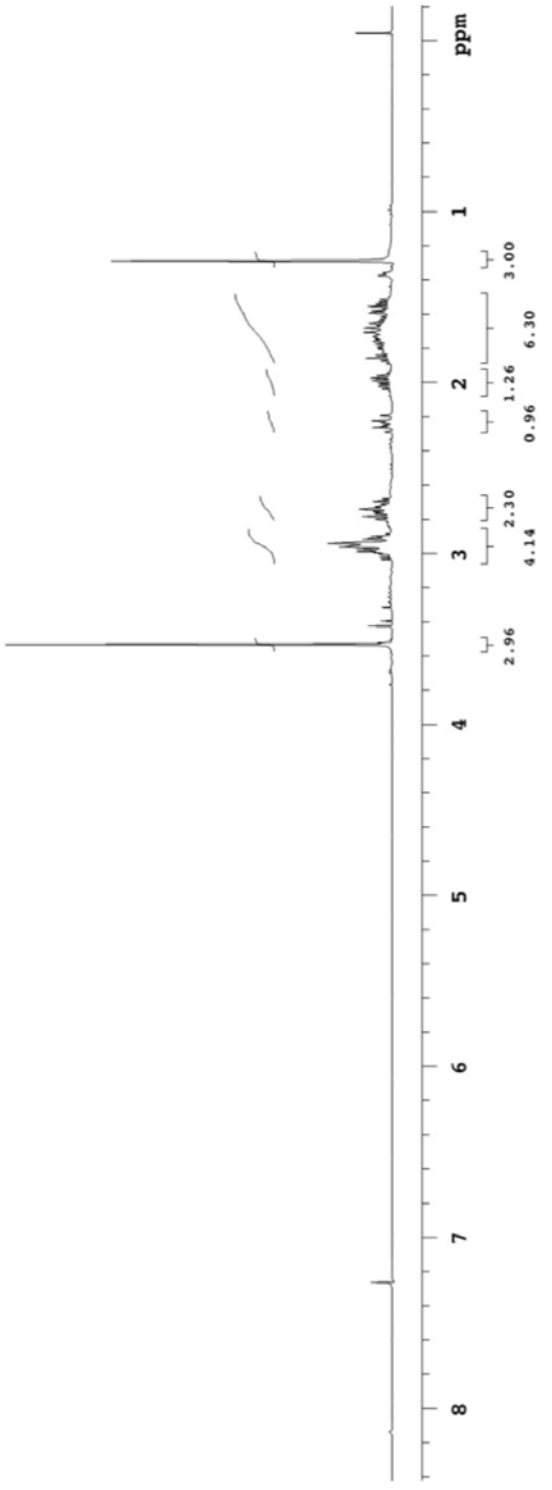
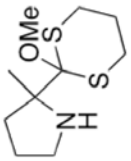




6.2a





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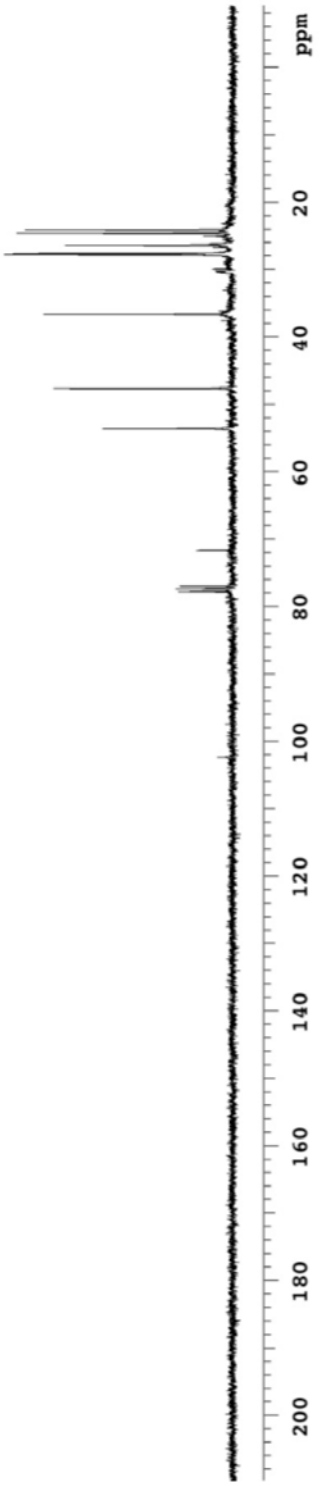

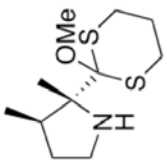

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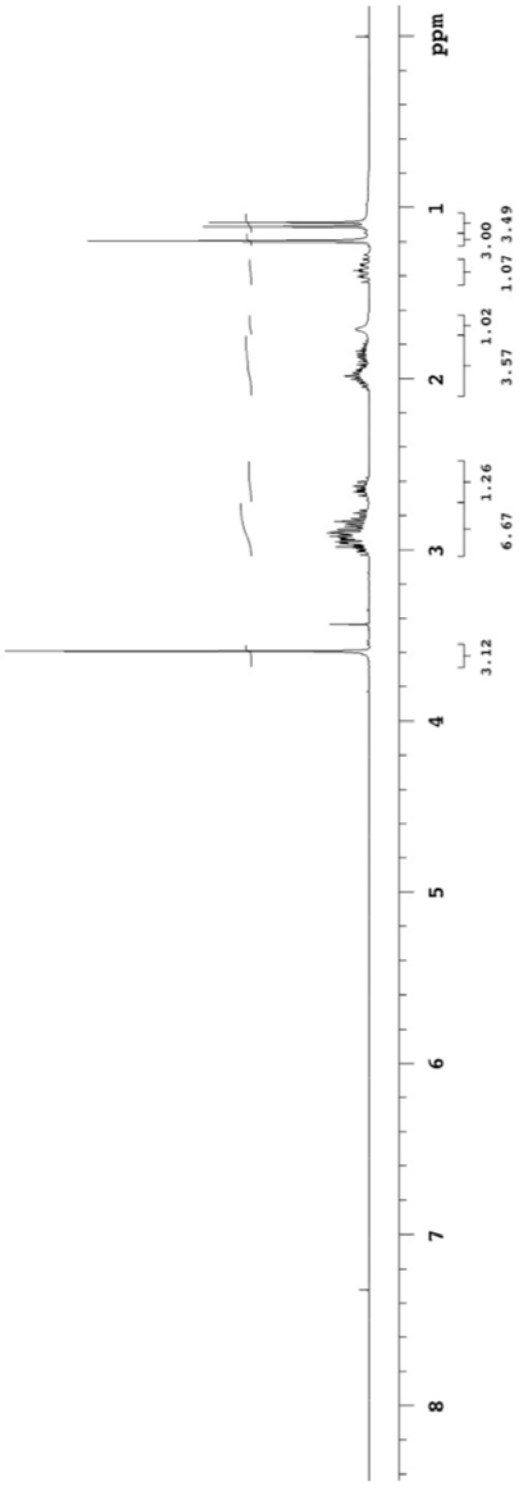
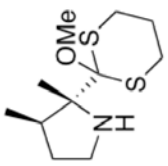
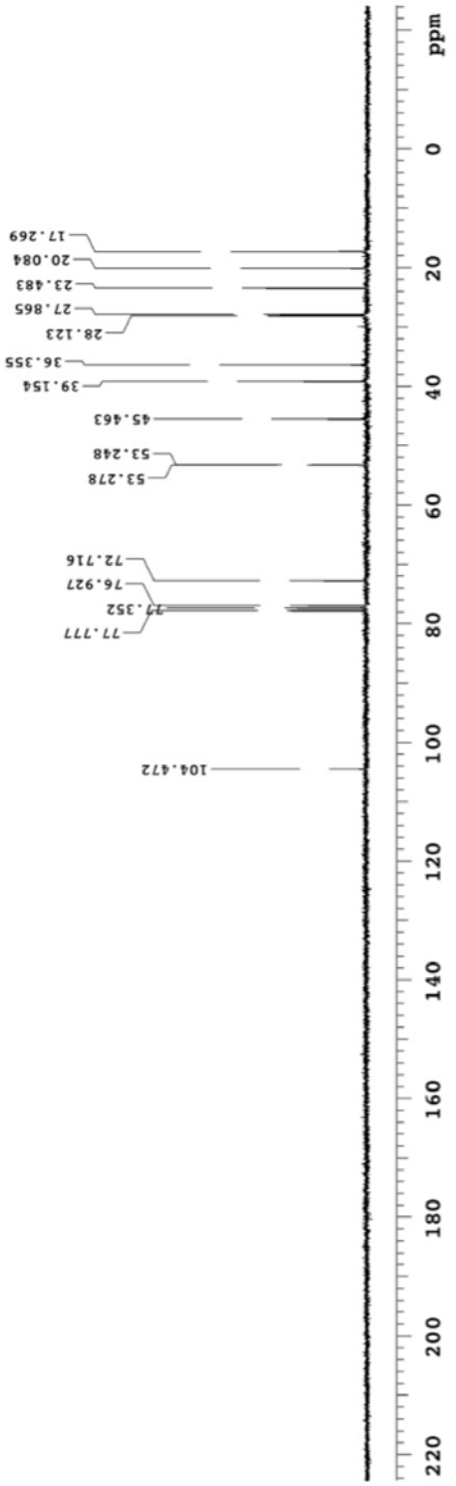



OMe
S
S
NH

6.2b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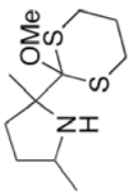
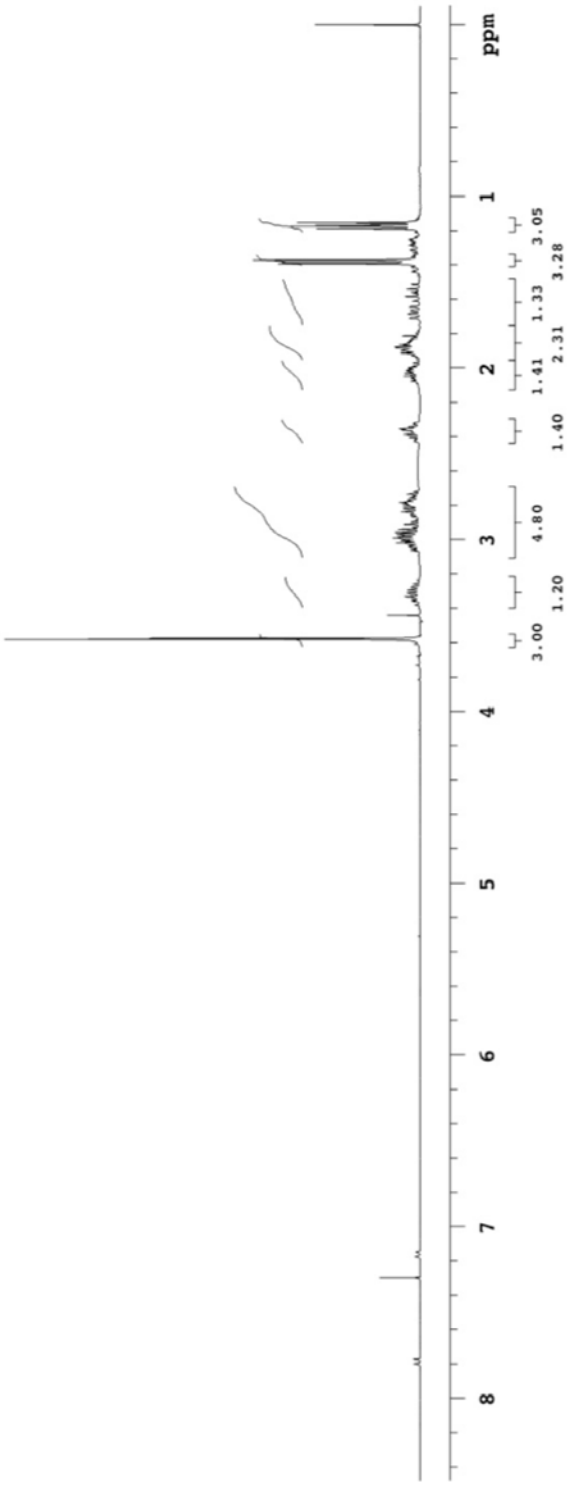
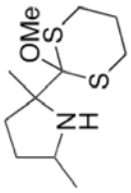
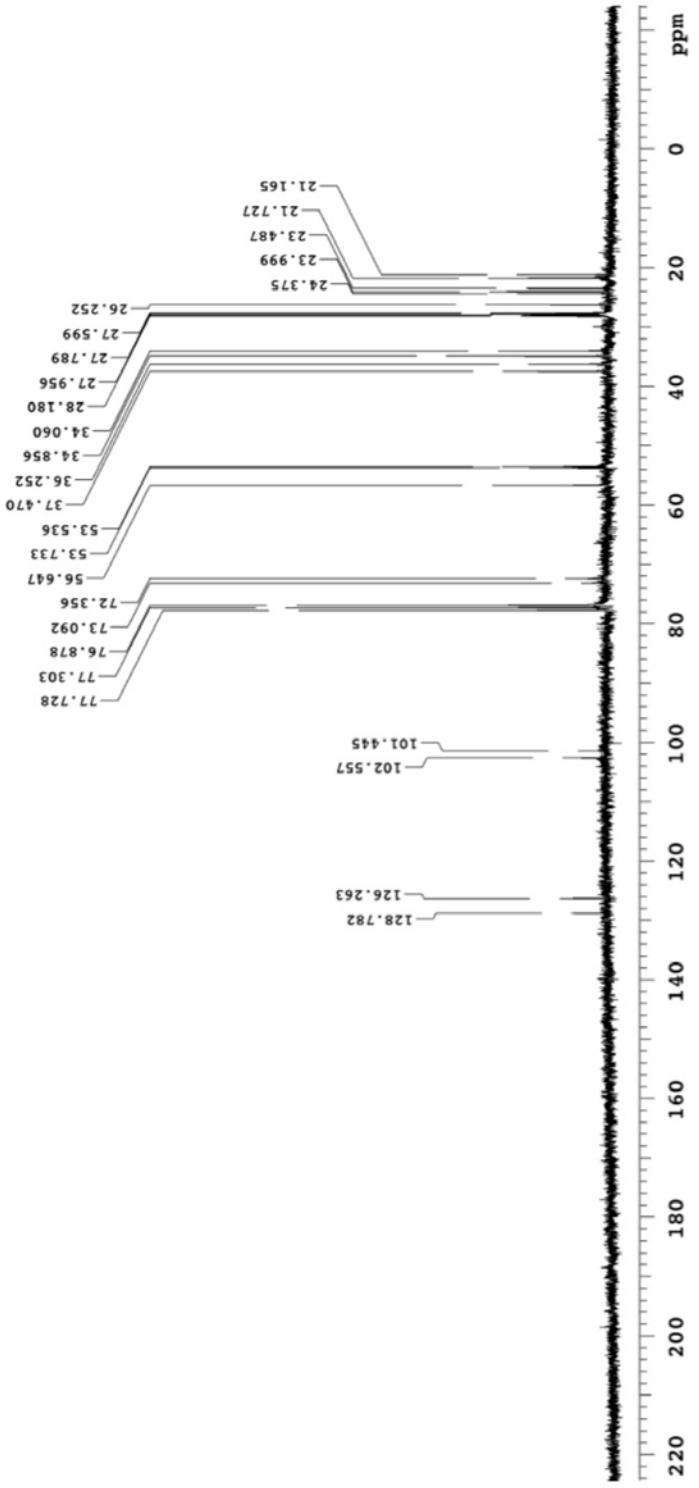


6.2c




OMe
S
S
N
H

6.2c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24.375
26.252
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27.789
27.956
28.180
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34.856
36.252
37.470
53.536
53.733
56.647
72.356
73.092
76.878
77.303
77.728
101.445
102.557
126.263
128.782
ppm
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40
60
80
100
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180
200
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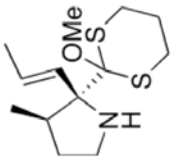
OMe
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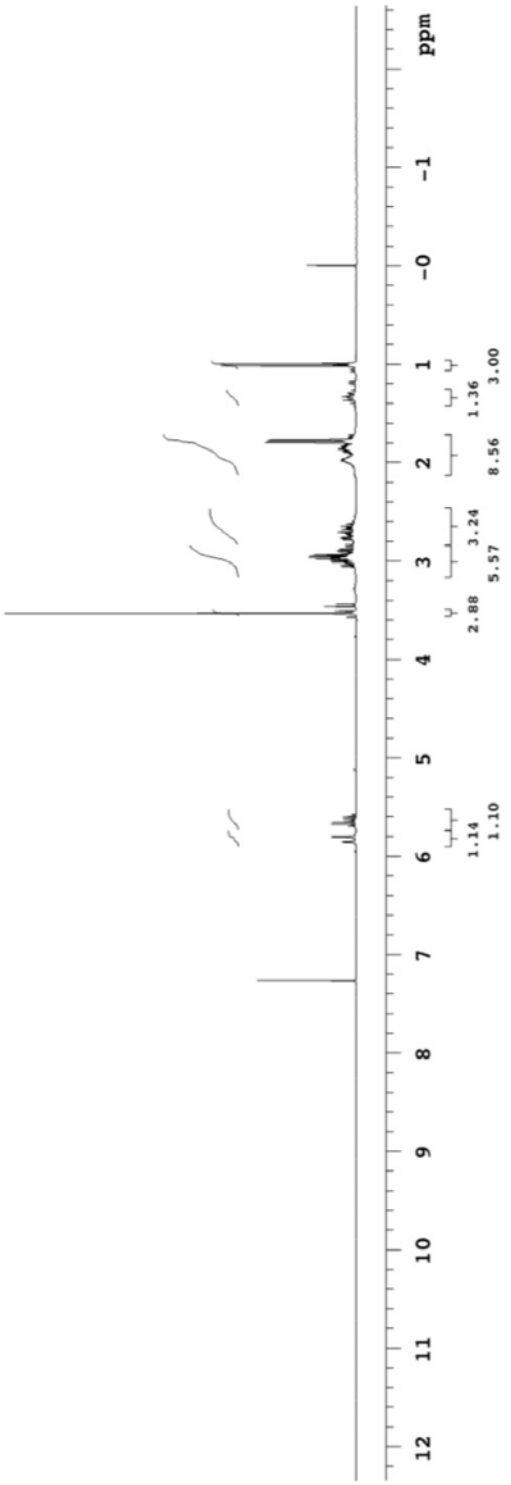
N
H

6.2d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9
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6
5
4
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-1
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1.10
2.88
3.24
5.57
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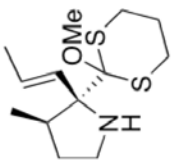
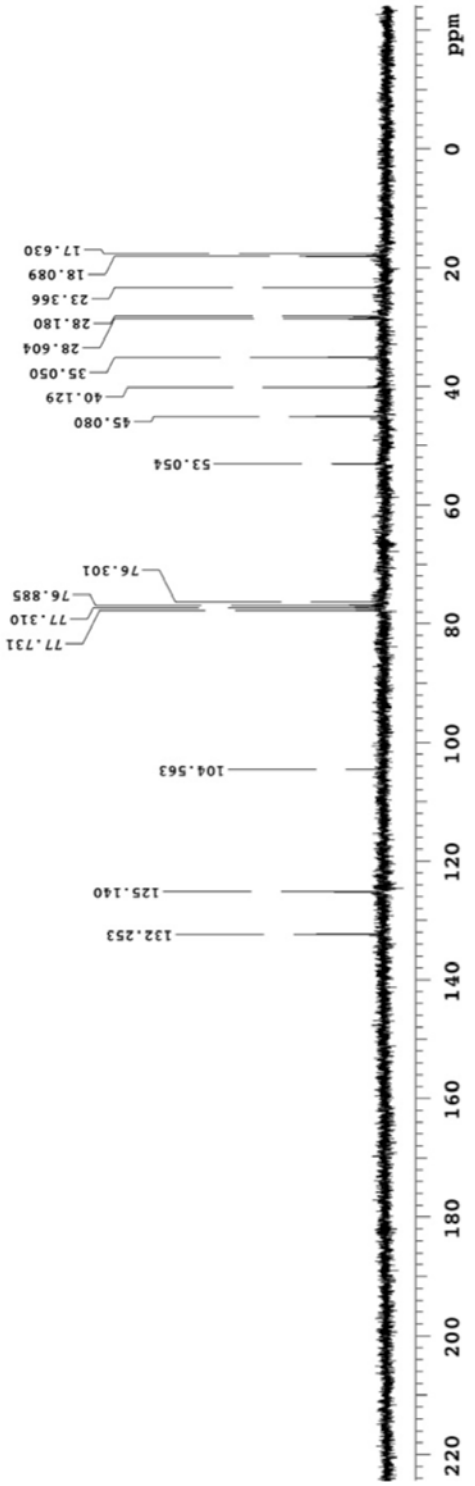
8.56
3.00


OMe
S
S
H
N

6.2d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23.366
28.180
28.604
35.050
40.129
45.080
53.054
76.301
76.885
77.310
77.731
104.563
125.140
132.253
ppm
0
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40
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80
100
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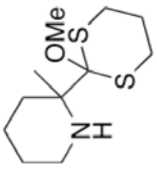
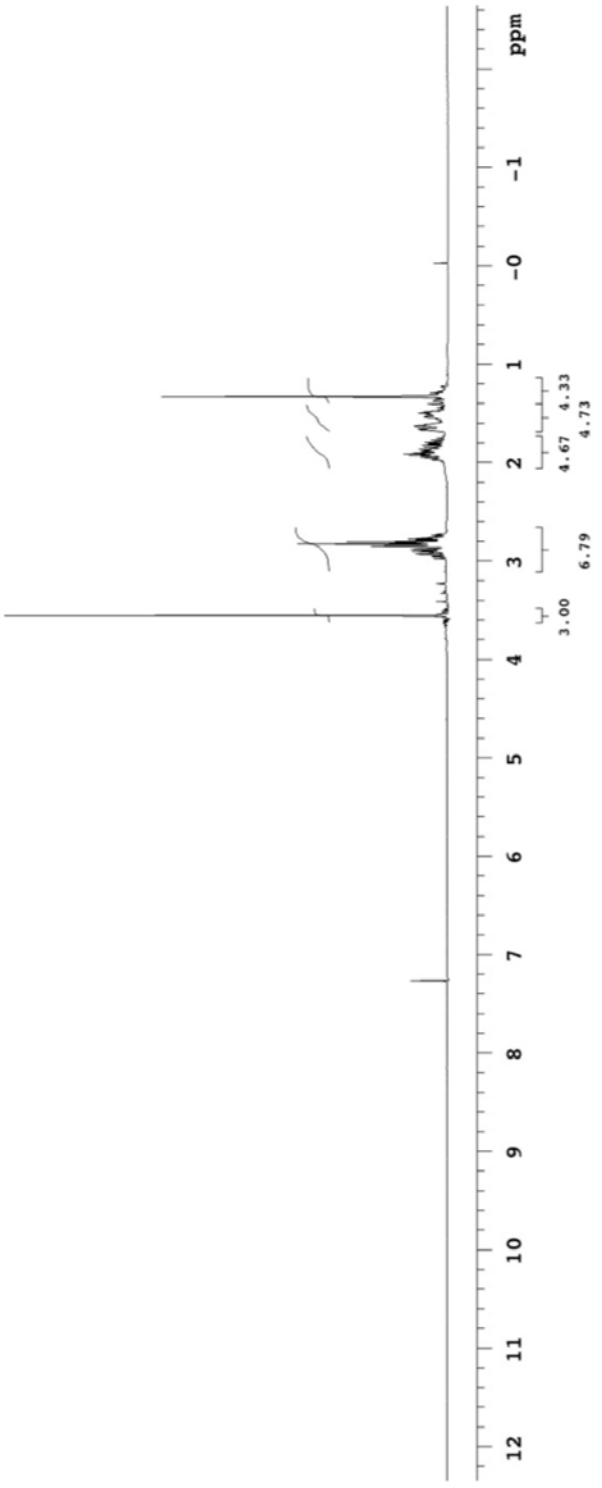
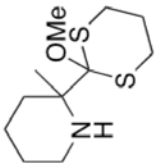
160
180
200
220

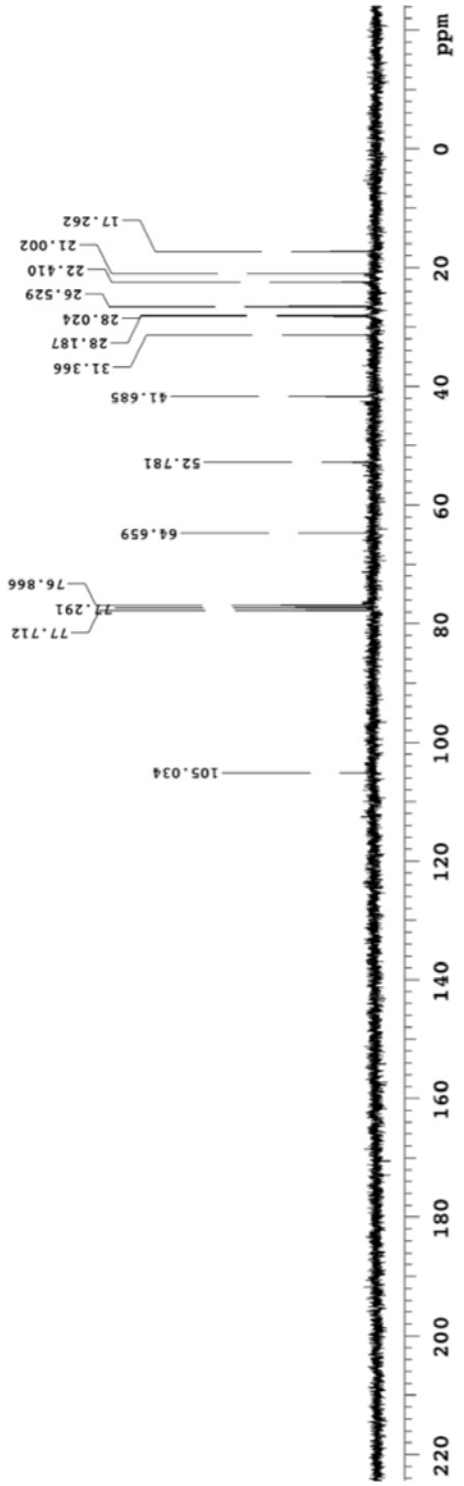


6.2e




OMe
S
S
N
H

6.2e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28.187
31.366
41.685
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64.659
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77.712
105.034
ppm
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200
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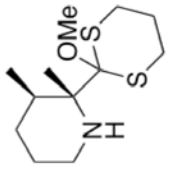
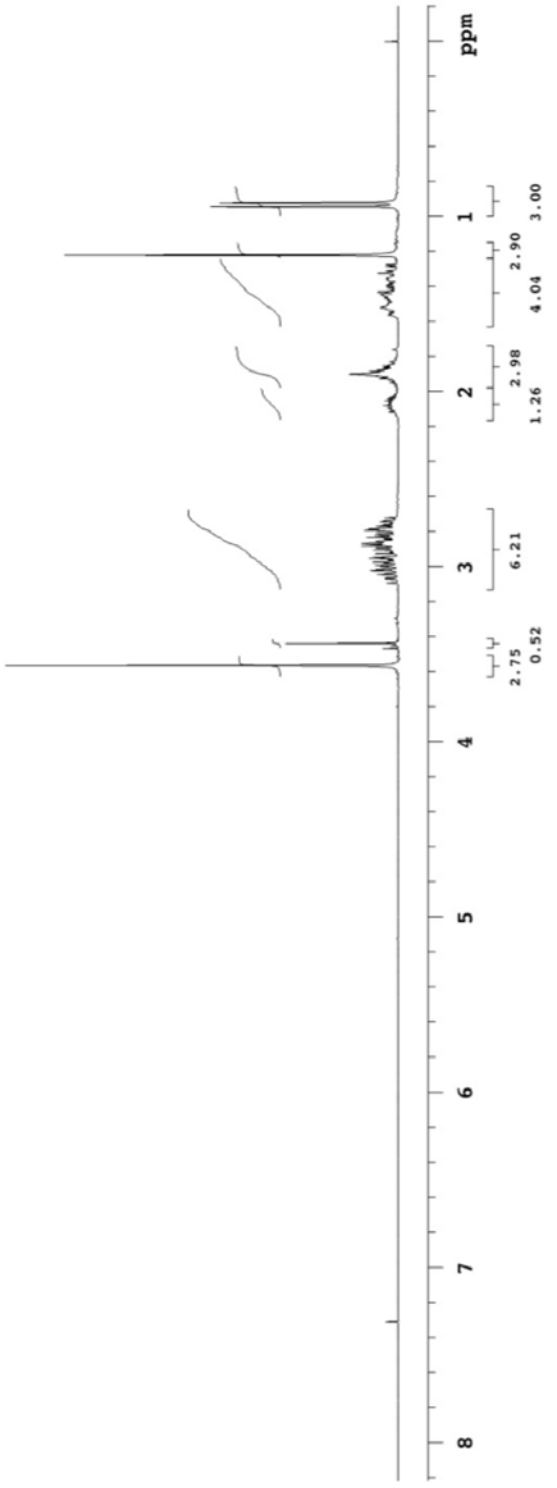
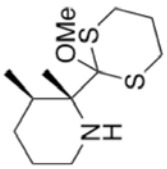
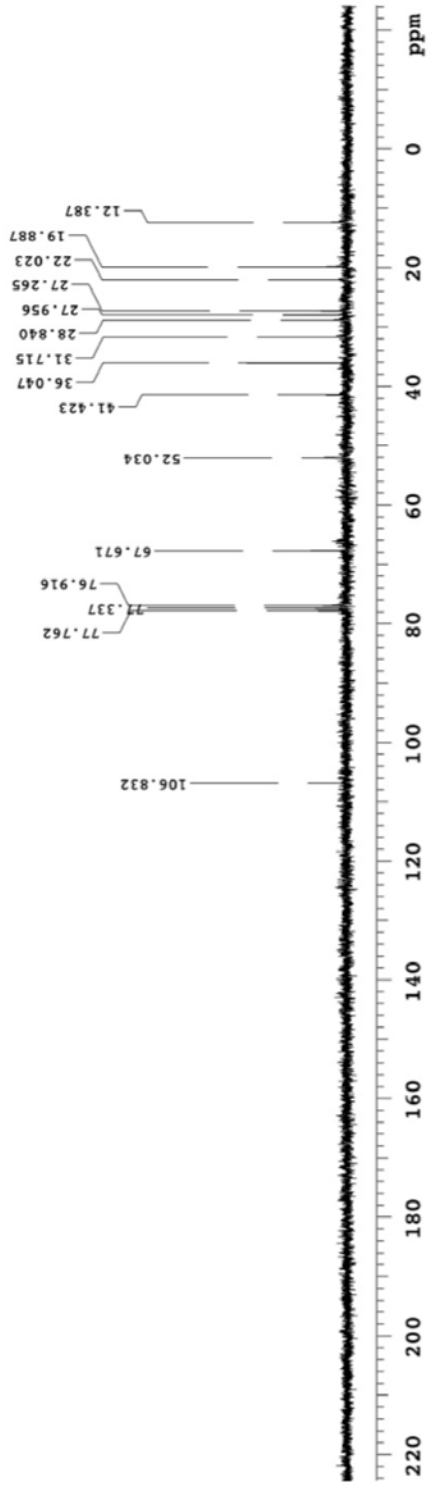


6.2f




OMe
S
S
N
H

6.2f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36.047
41.423
52.034
67.671
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77.762
106.832
ppm
0
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80
100
120
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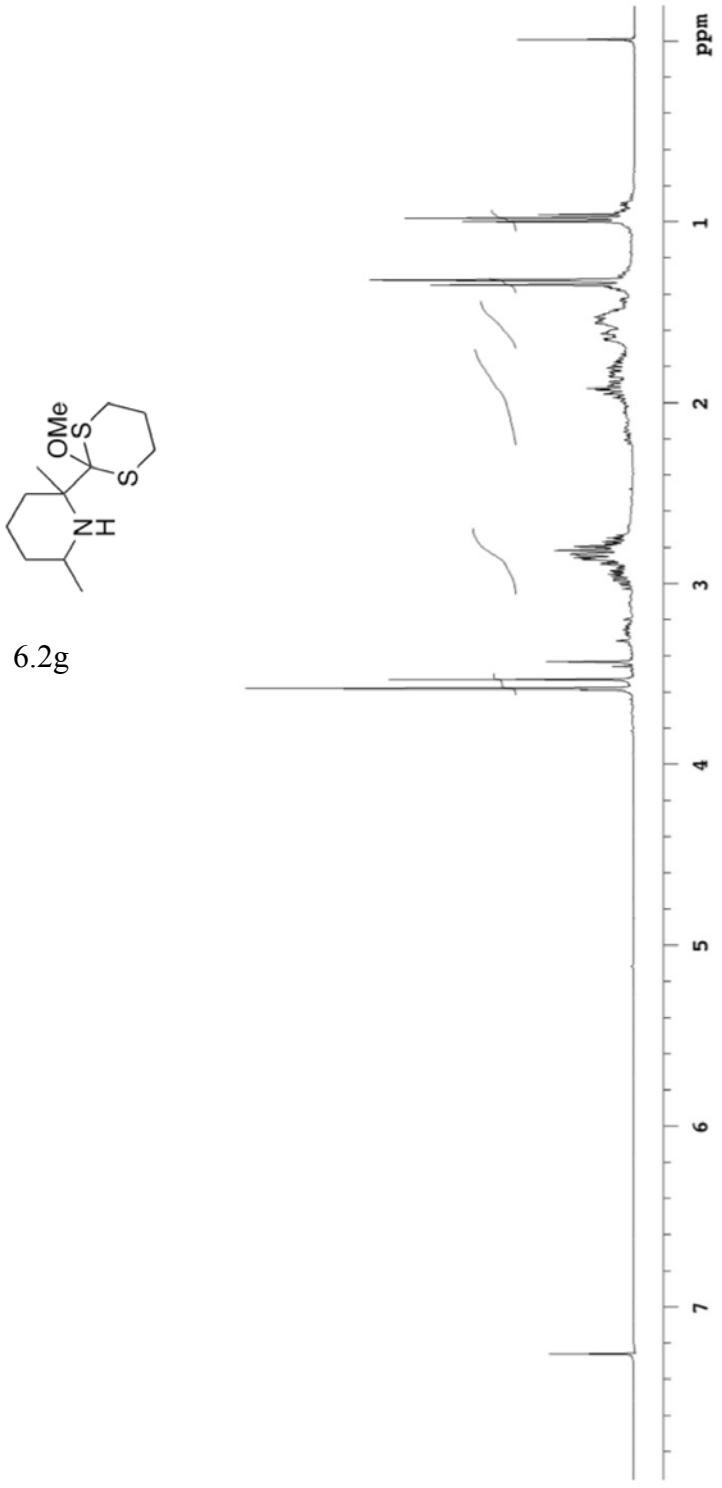
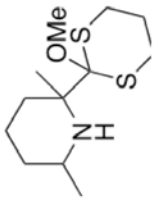
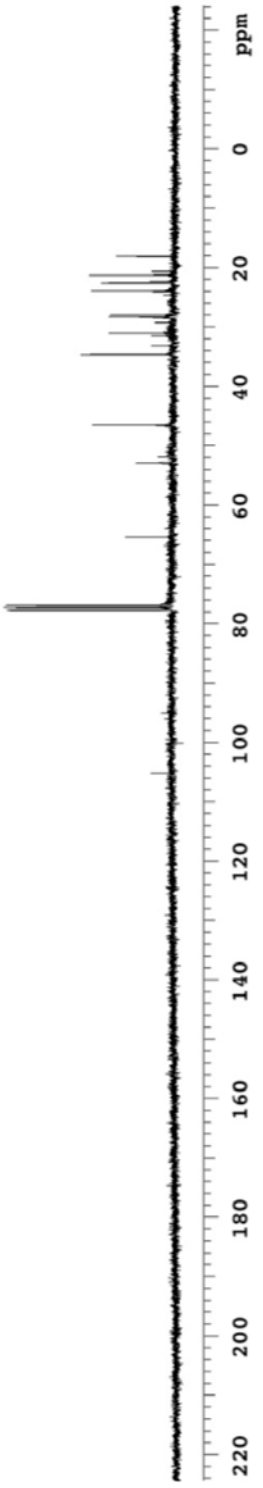
160
180
200
220

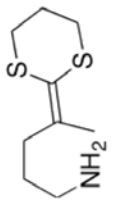


6.2g

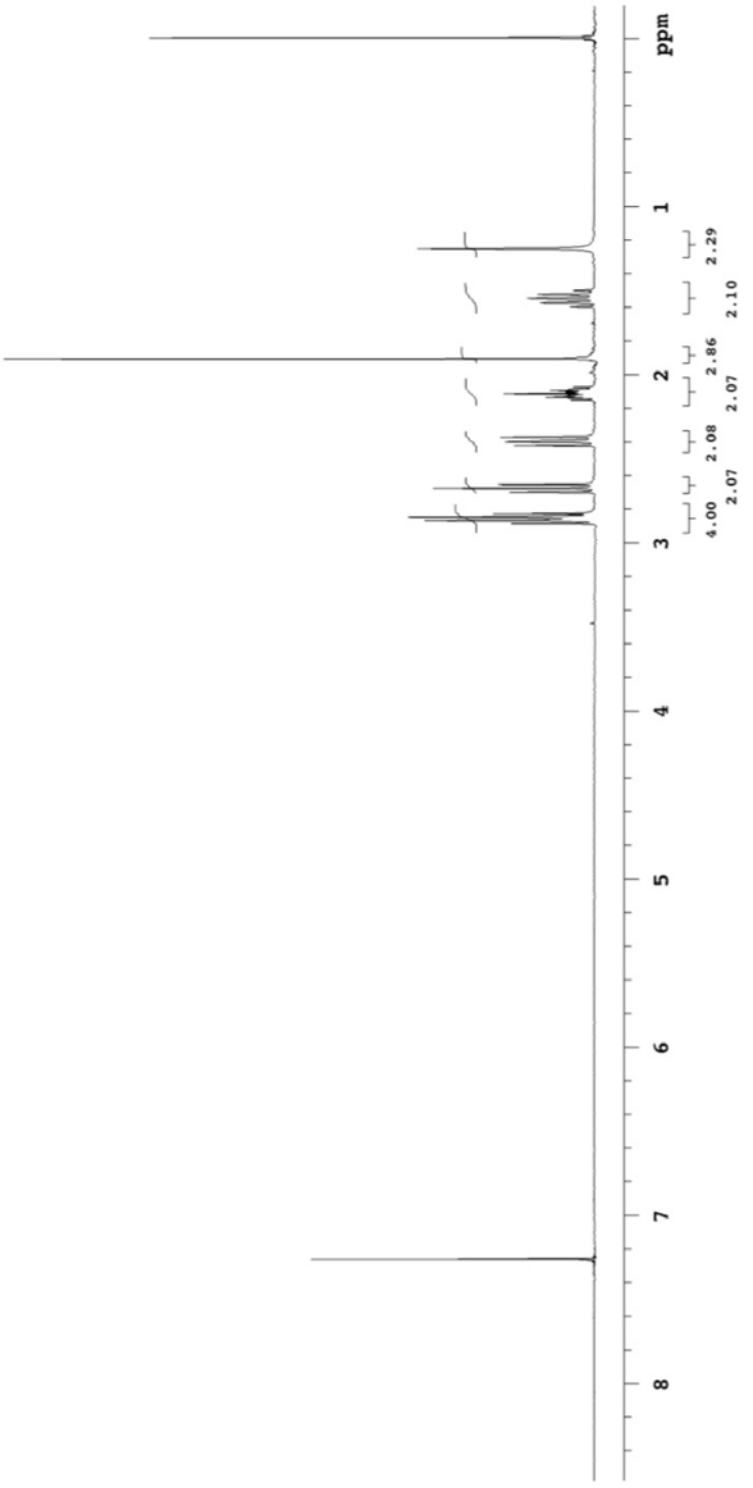


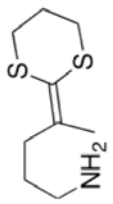
6.2g



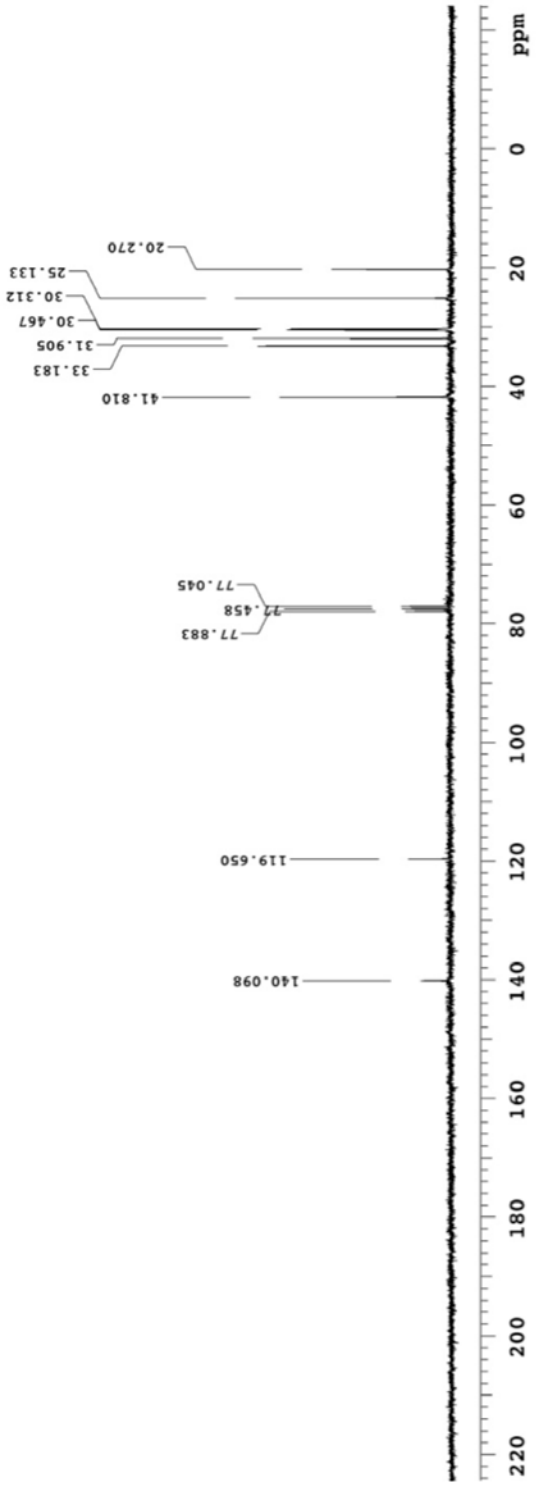


6.1a




S
S
NH2

6.1a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31.905
33.183
41.810
77.045
77.458
77.883
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140.098
ppm
0
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40
60
80
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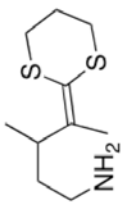
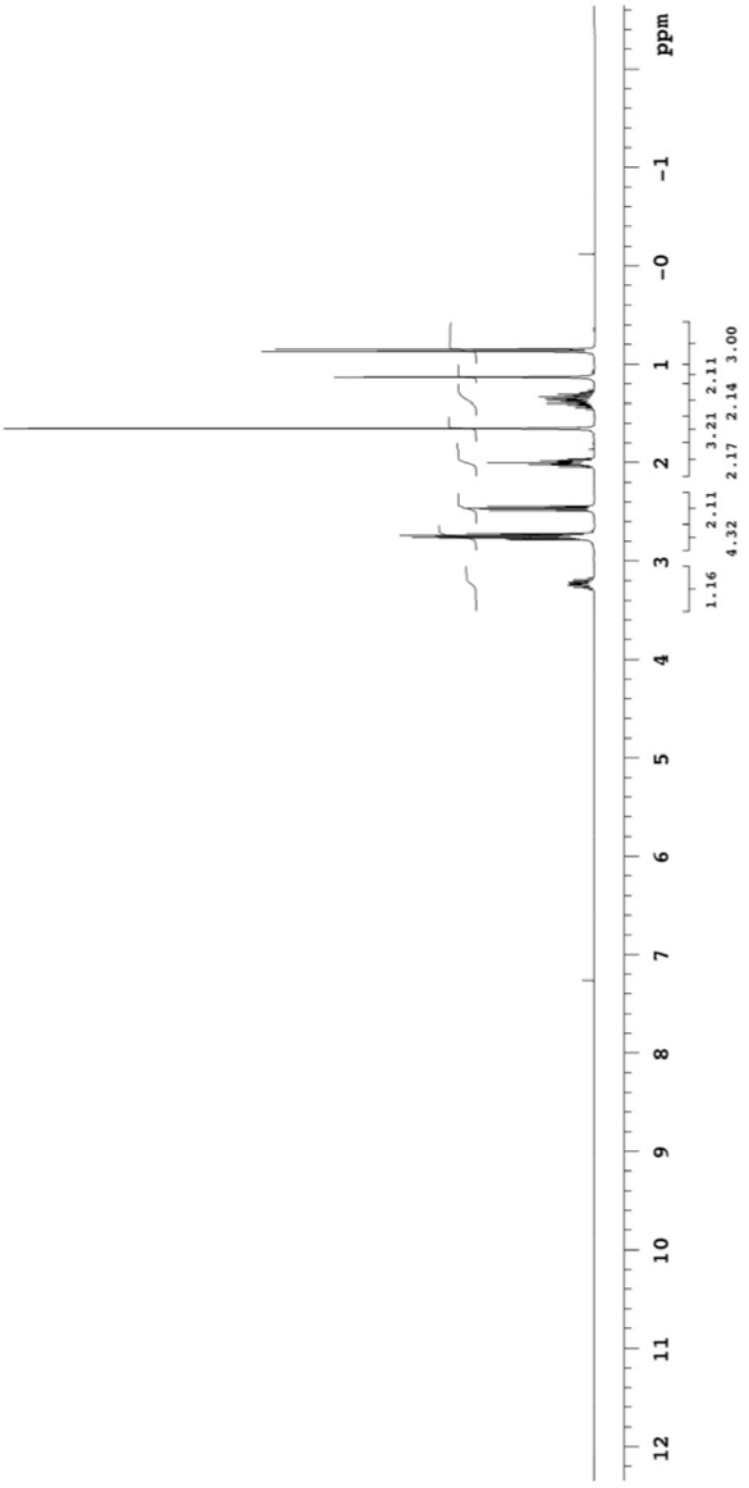
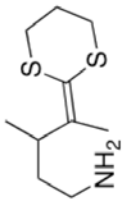
160
180
200
220

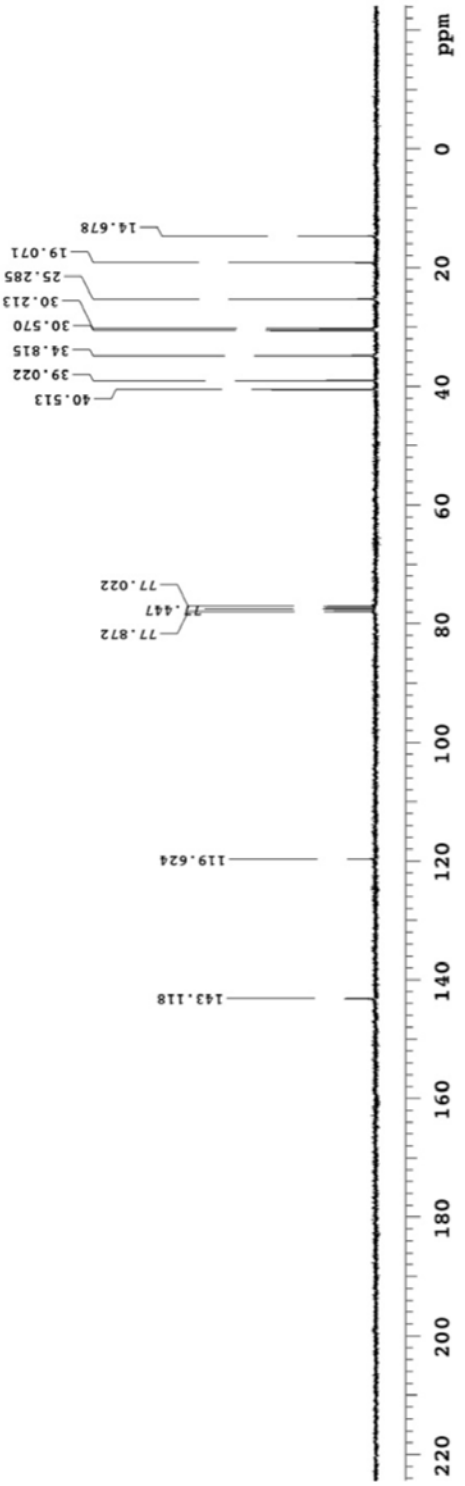


6.2b




S
S
NH2

6.2b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34.815
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40.513
77.022
77.447
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119.624
143.118
ppm
0
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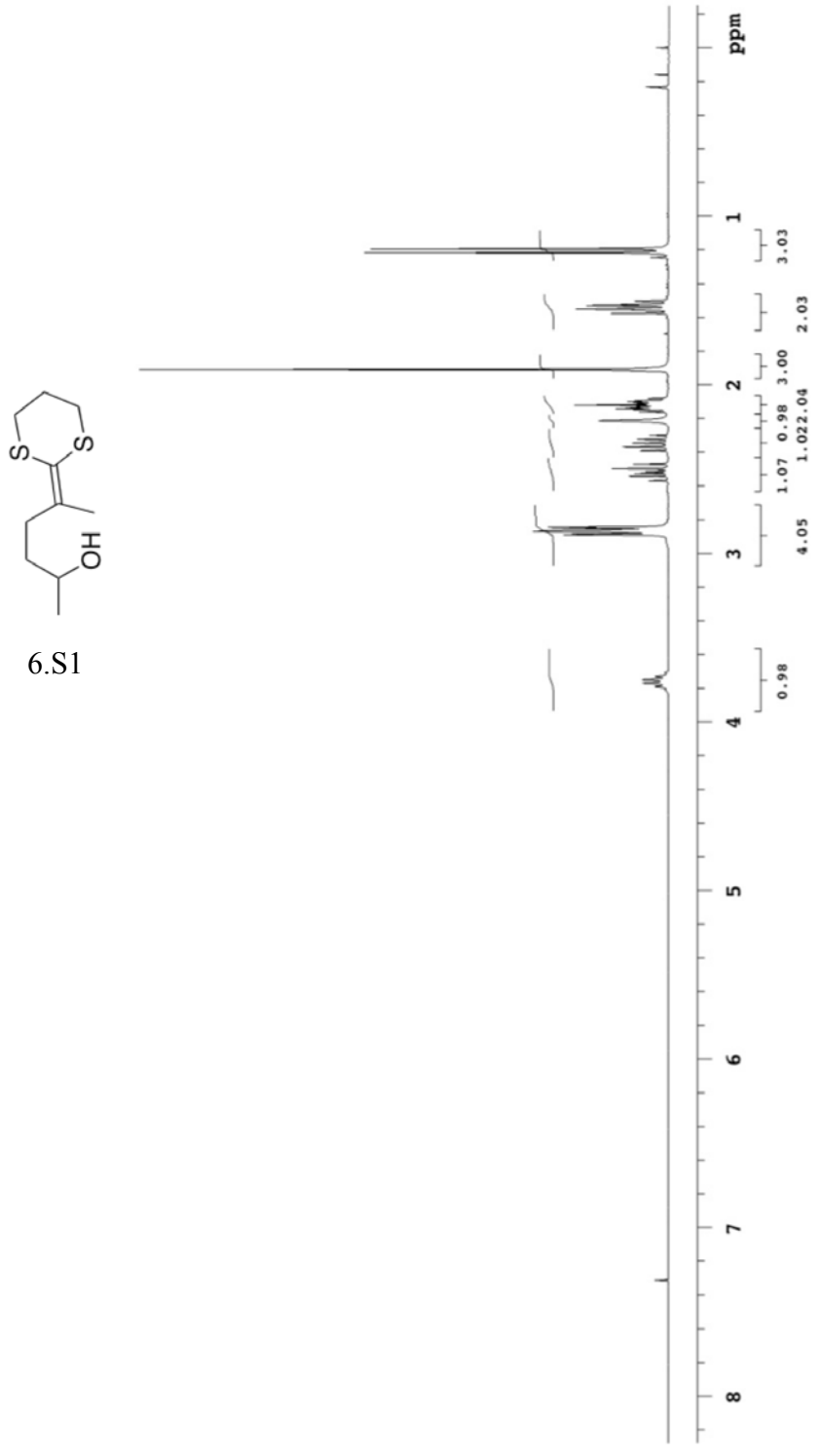
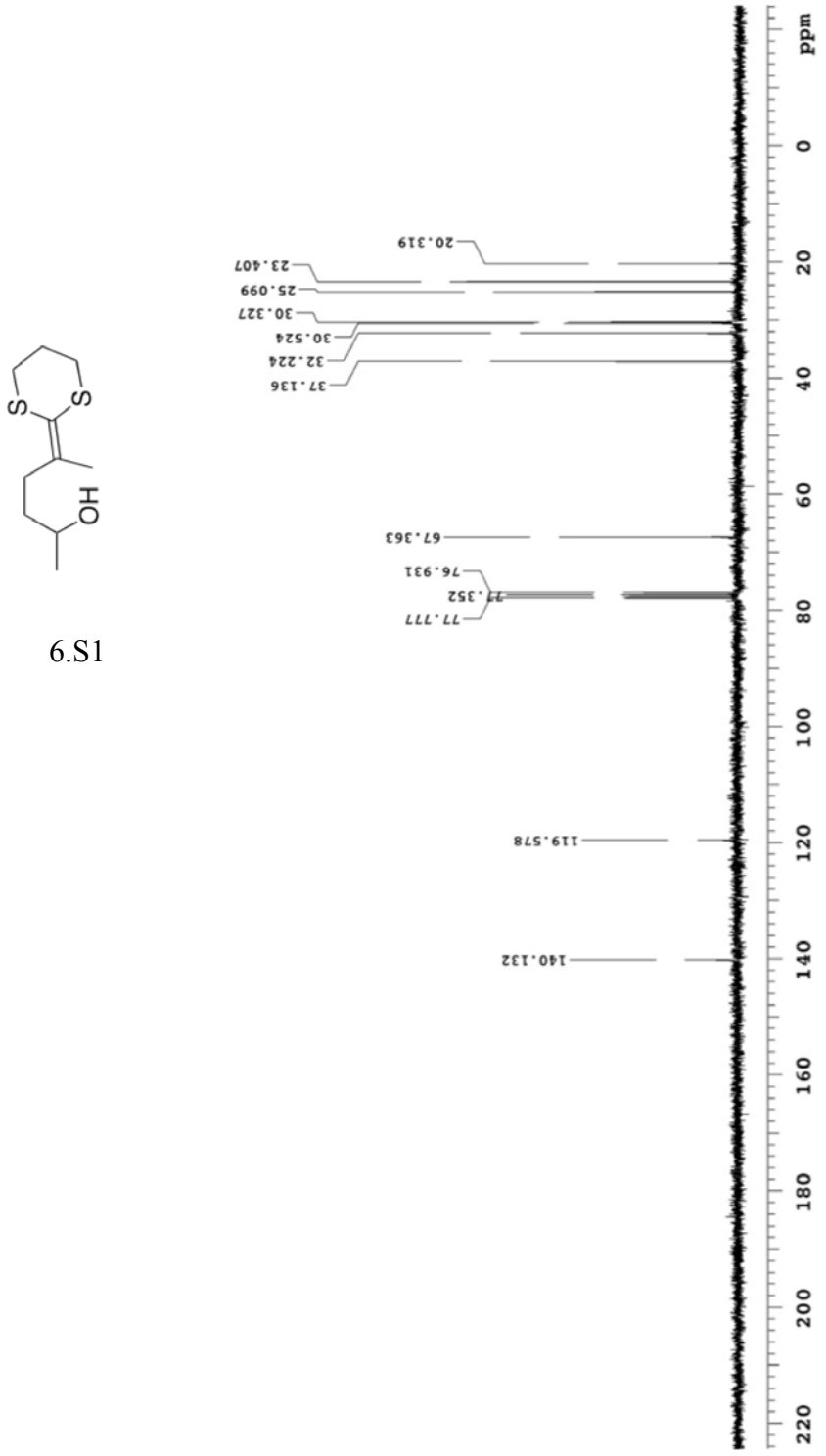
40
60
80
100
120
140
160
180
200
220



6.S1


S
S
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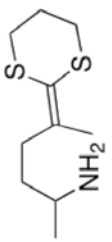
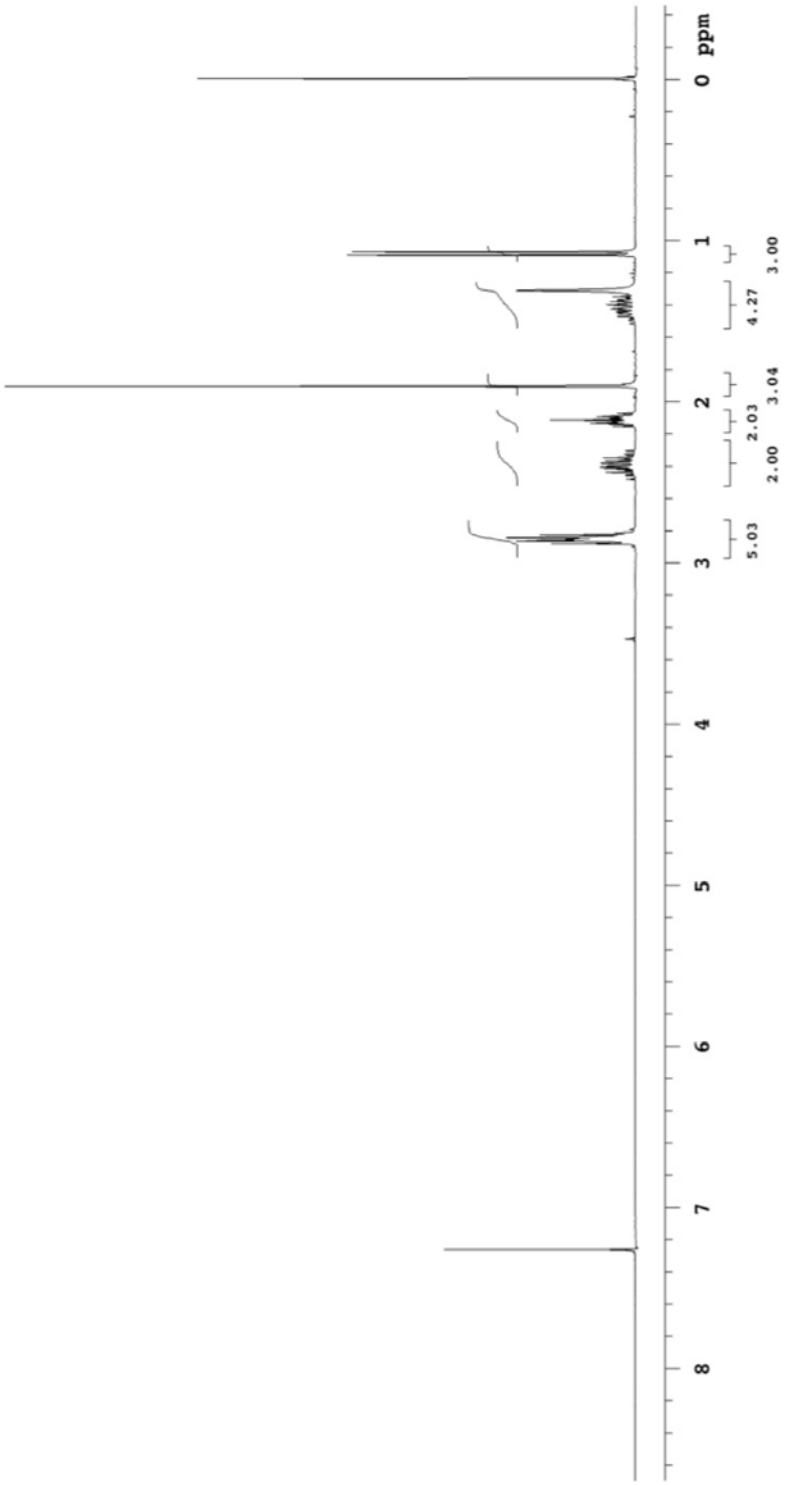
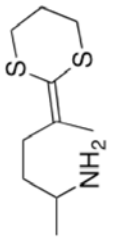
30.327
30.524
32.224
37.136
67.363
76.931
77.352
77.777
119.578
140.132
ppm
0
20
40
60
80
100
120
140
160
180
200
220

6.S1

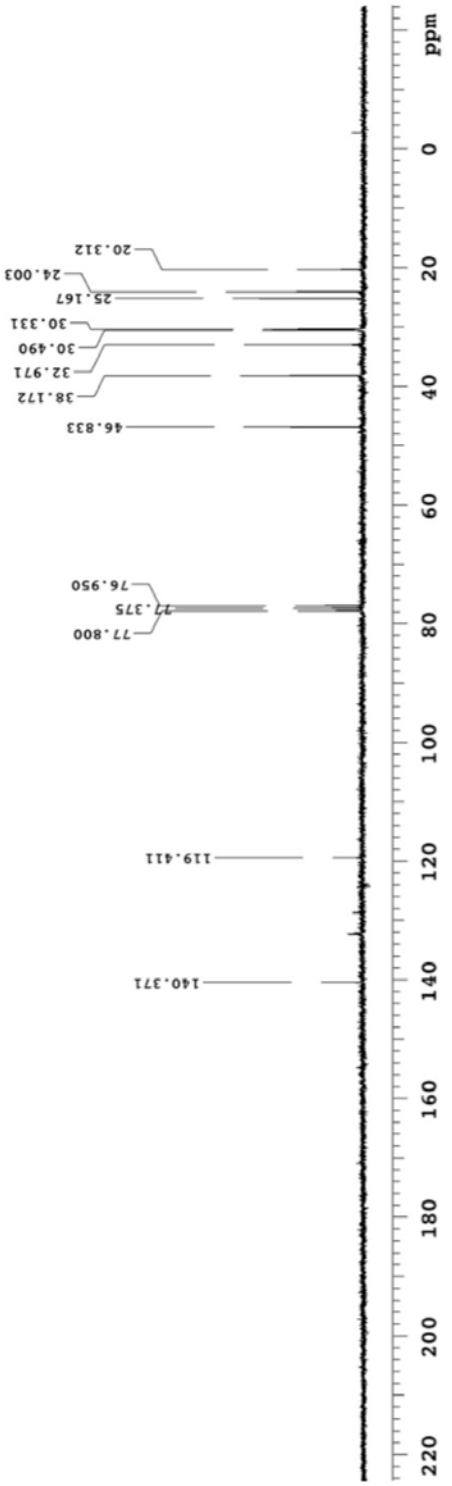


6.1c




S
S
NH2

6.1c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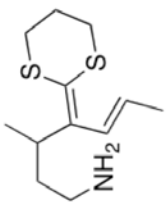
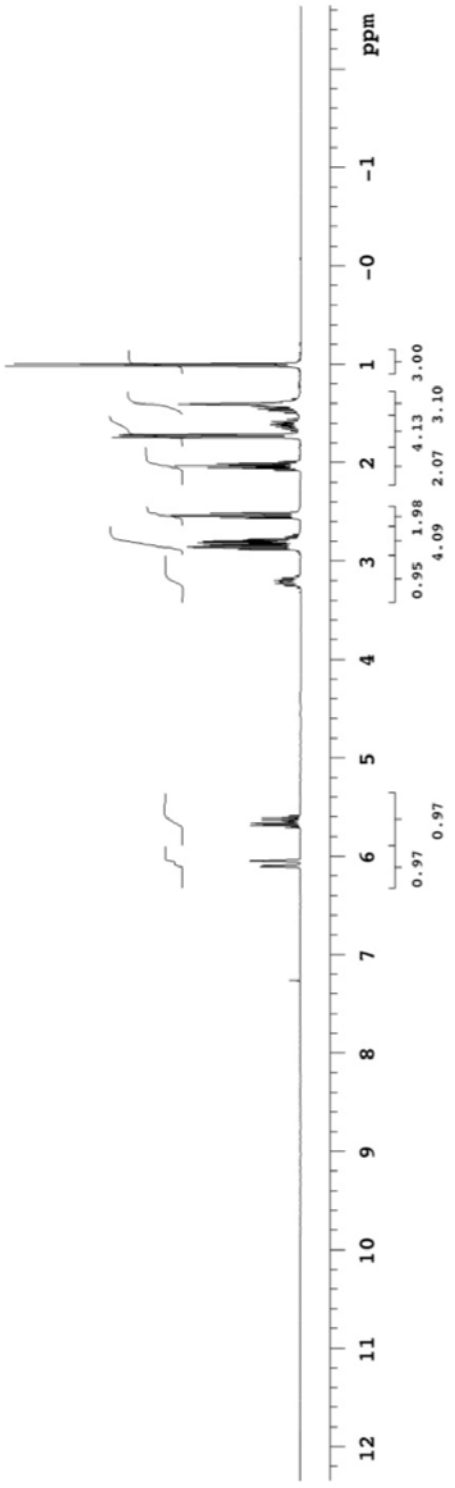
25.167
30.331
30.490
32.971
38.172
46.833
76.950
77.375
77.800
119.411
140.371
ppm
0
20
40
60
80
100
120
140
160
180
200
220


S
S
NH2

6.1d


ppm
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11
10
9
8
7
6
5
4
3
2
1
-0
-1
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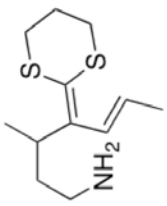
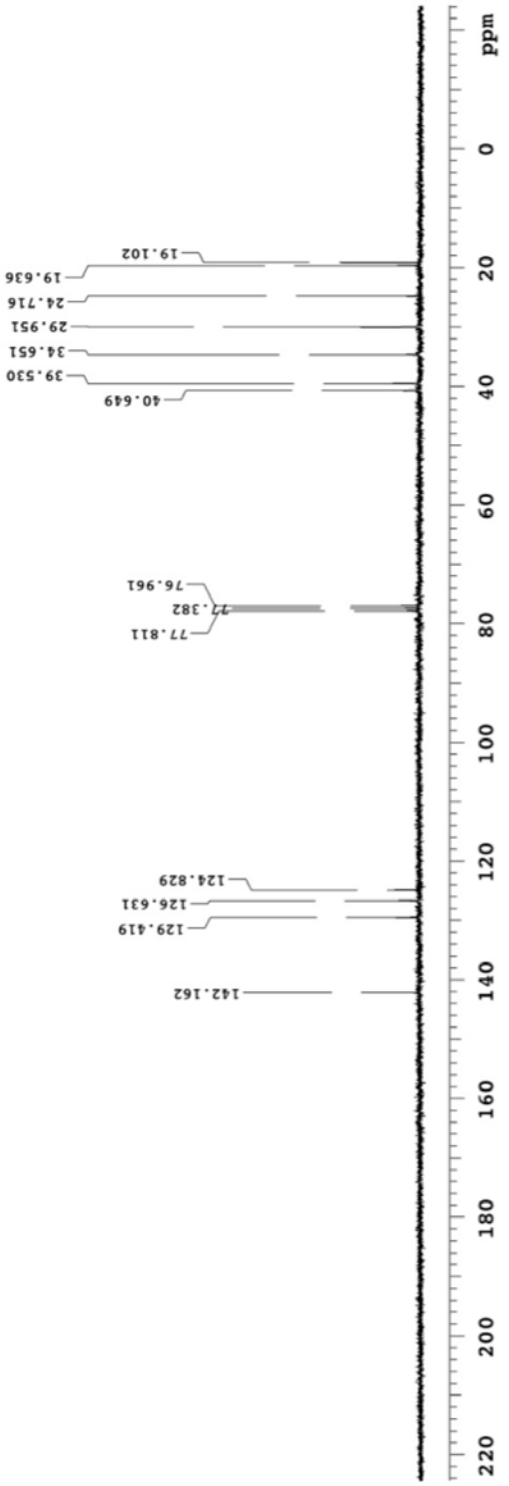
0.95
1.98
4.09
4.13
2.07
3.00
3.10


S
S
NH2

6.1d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19.636
24.716
29.951
34.651
39.530
40.649
76.961
77.382
77.811
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129.419
142.162
ppm
0
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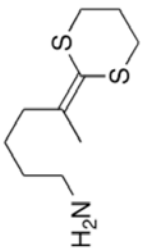
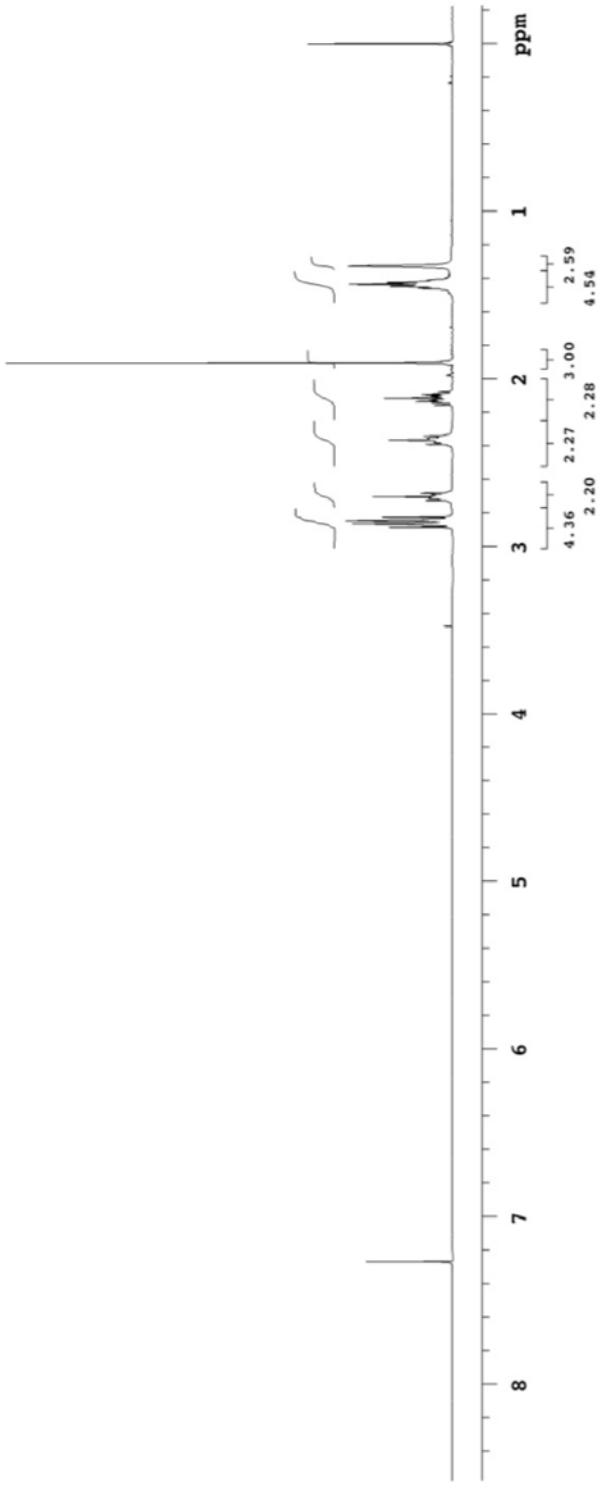
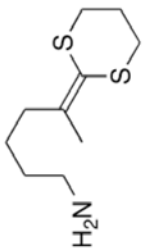
40
60
80
100
120
140
160
180
200
220

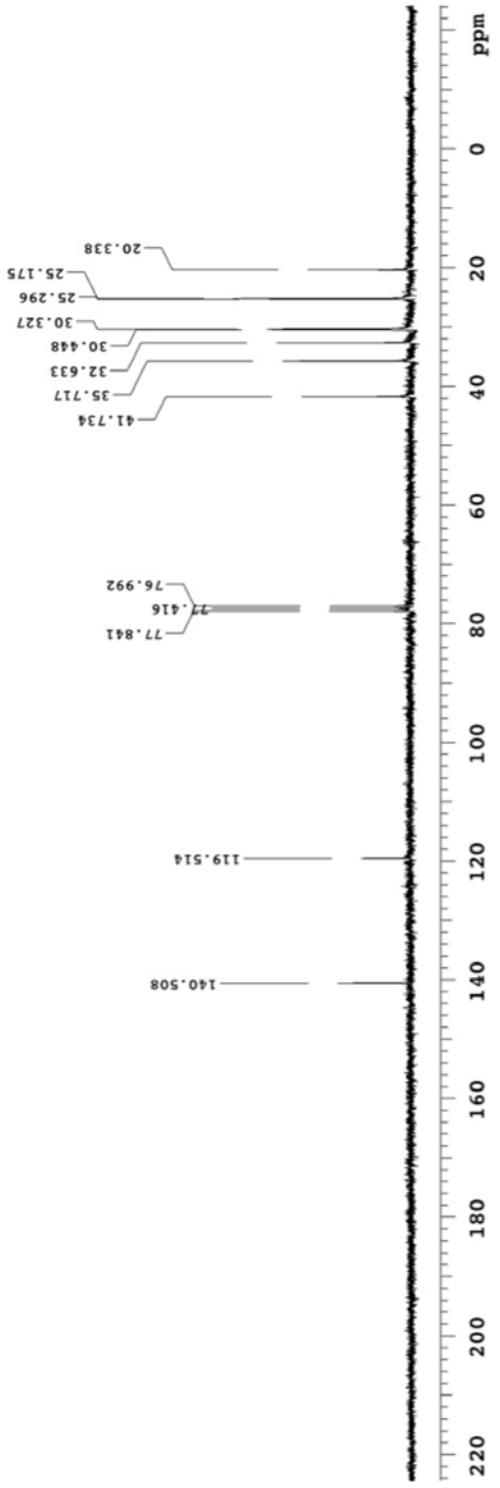


6.1e




S
S
H2N

6.1e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32.633
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119.514
140.508
ppm
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80
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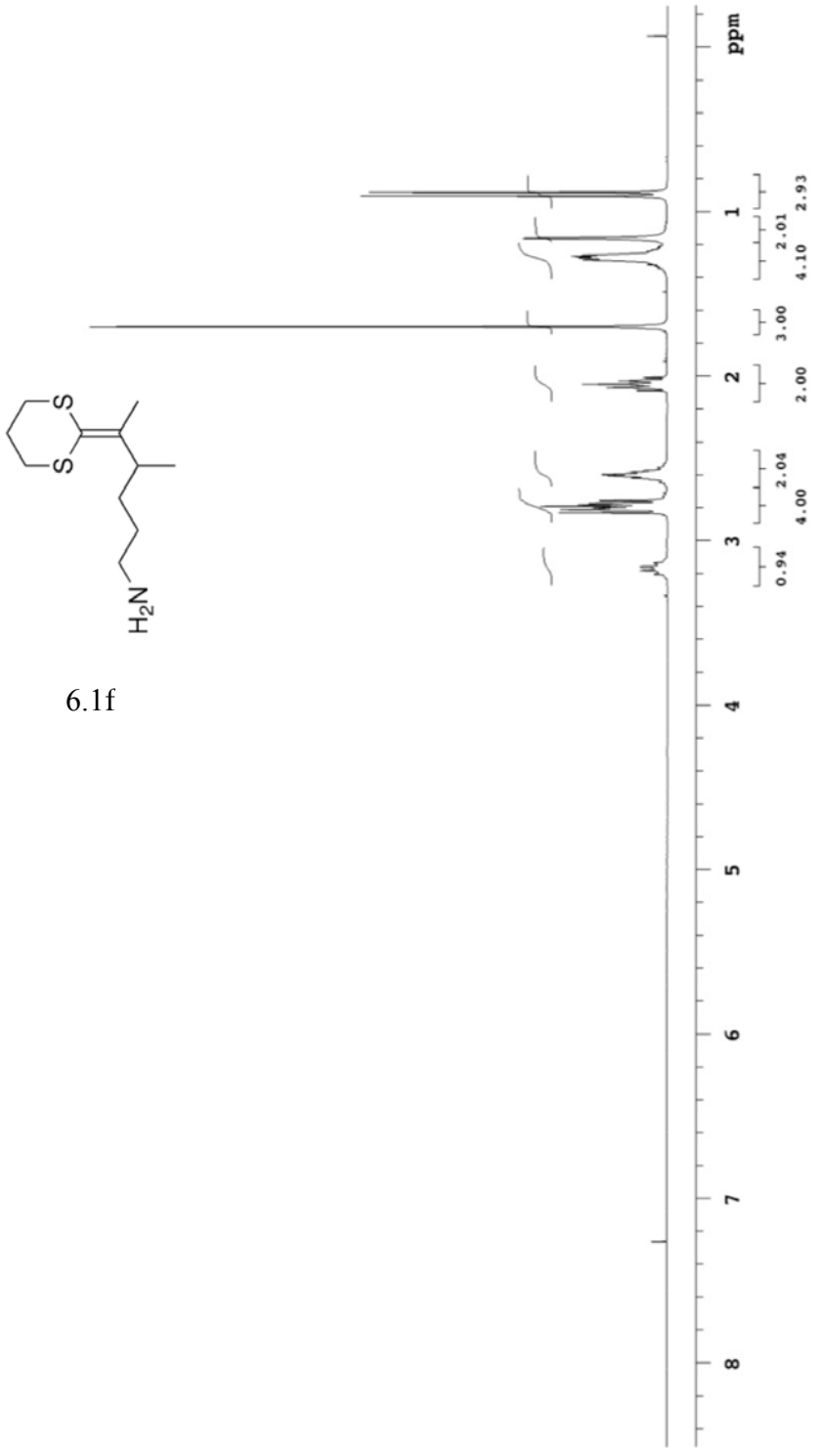
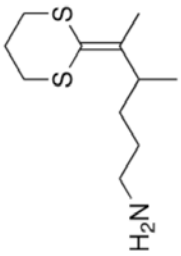
220



6.1f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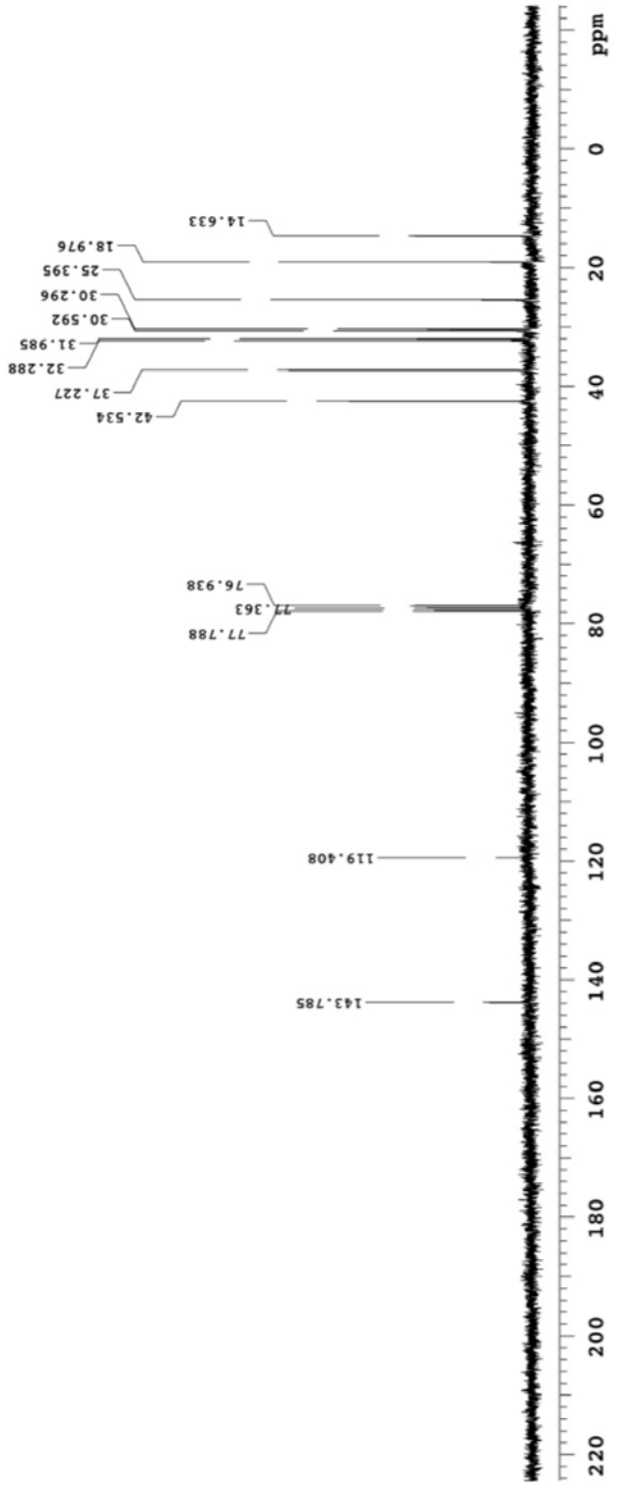
S
H_2N

6.1f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76.938
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119.408
143.785
ppm
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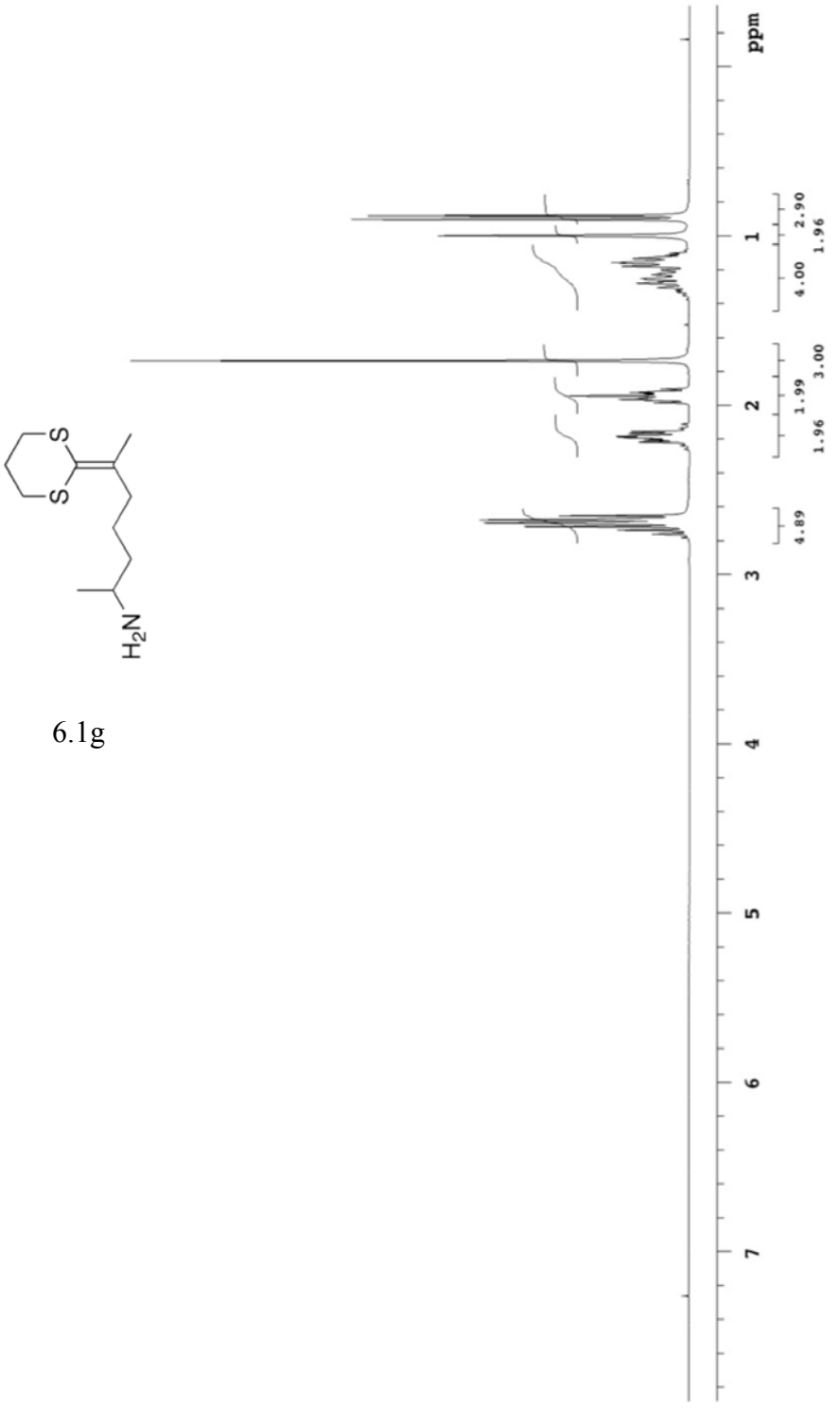
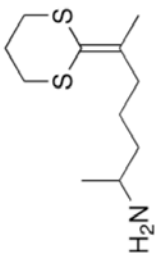


6.1g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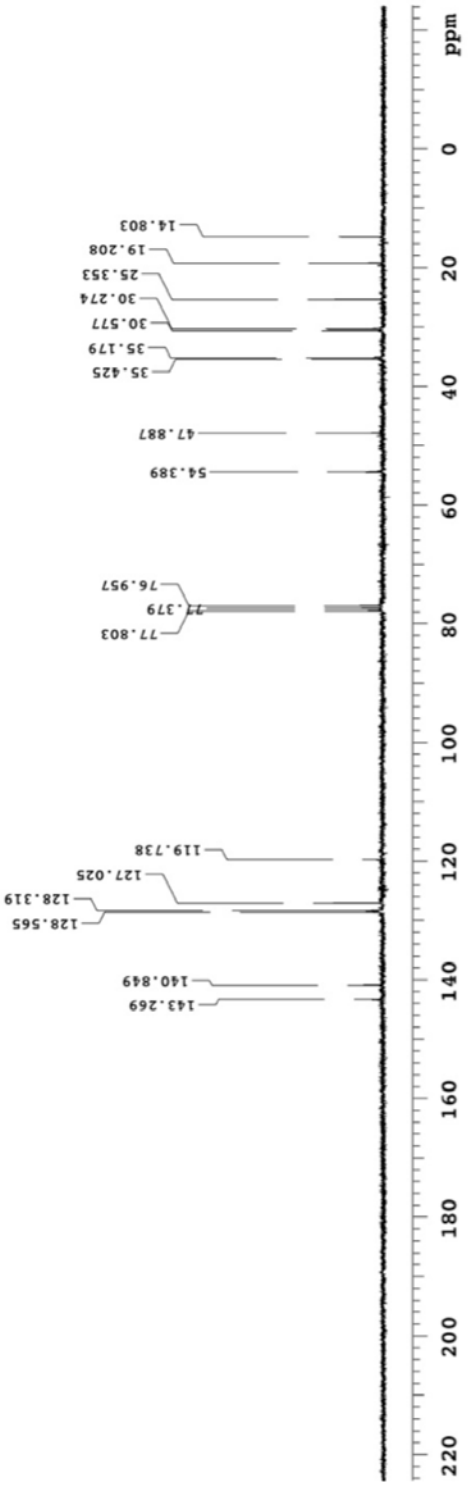
S
H_2N

6.1g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35.179
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47.887
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76.957
77.379
77.803
119.738
127.025
128.319
128.565
140.849
143.269
ppm
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100
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200
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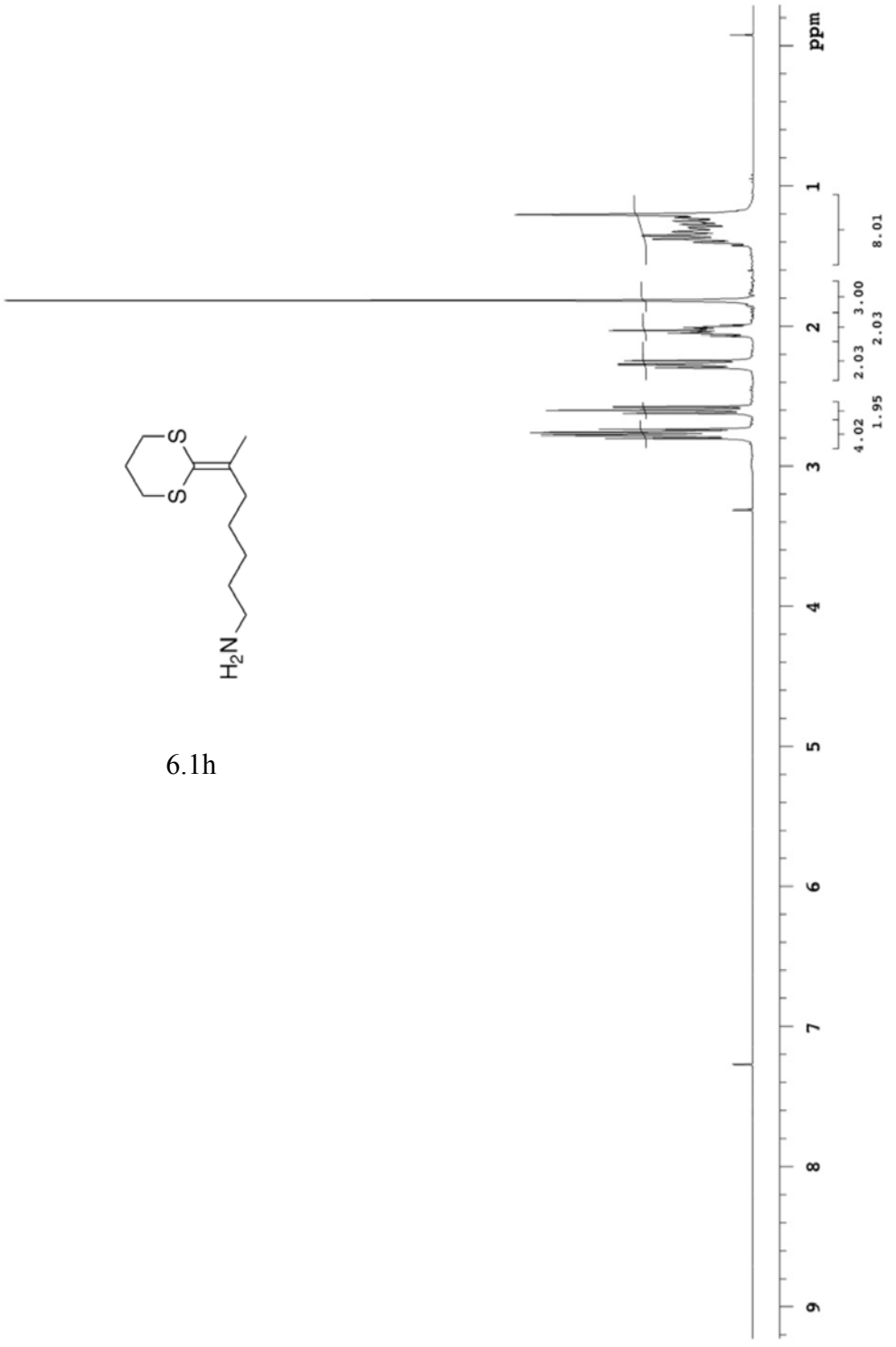
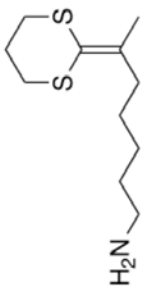


6.1h



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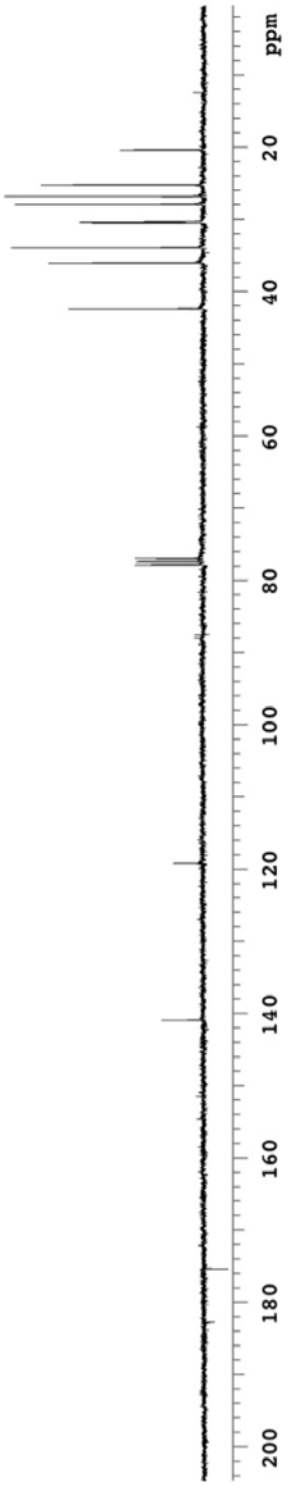

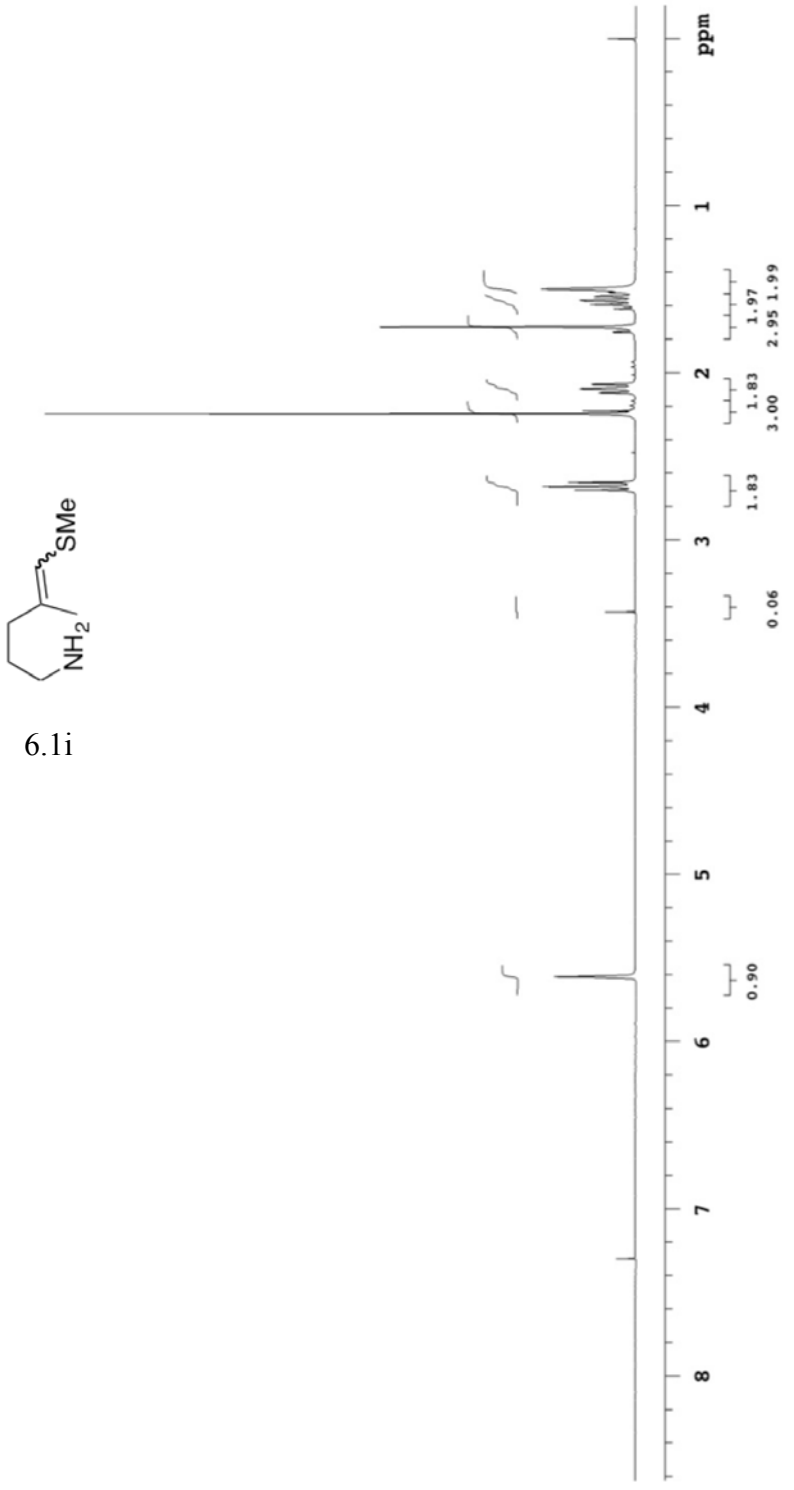

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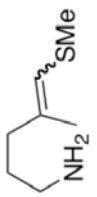
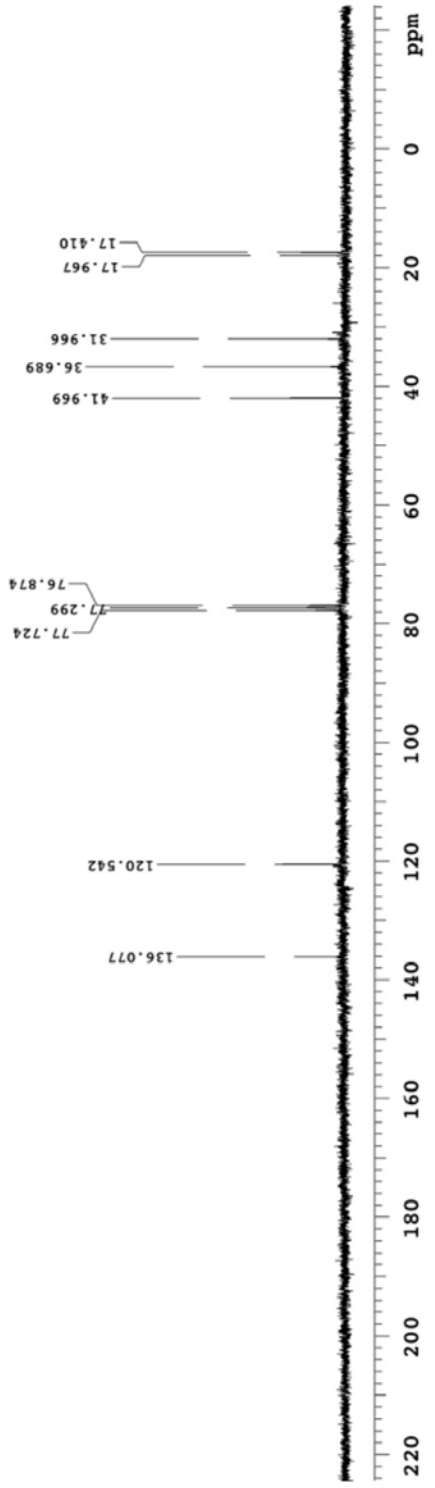

SMe
NH2

6.1i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77.724
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136.077
ppm
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80
100
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200
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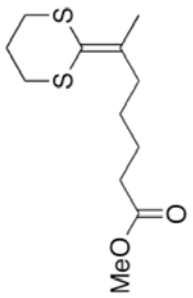

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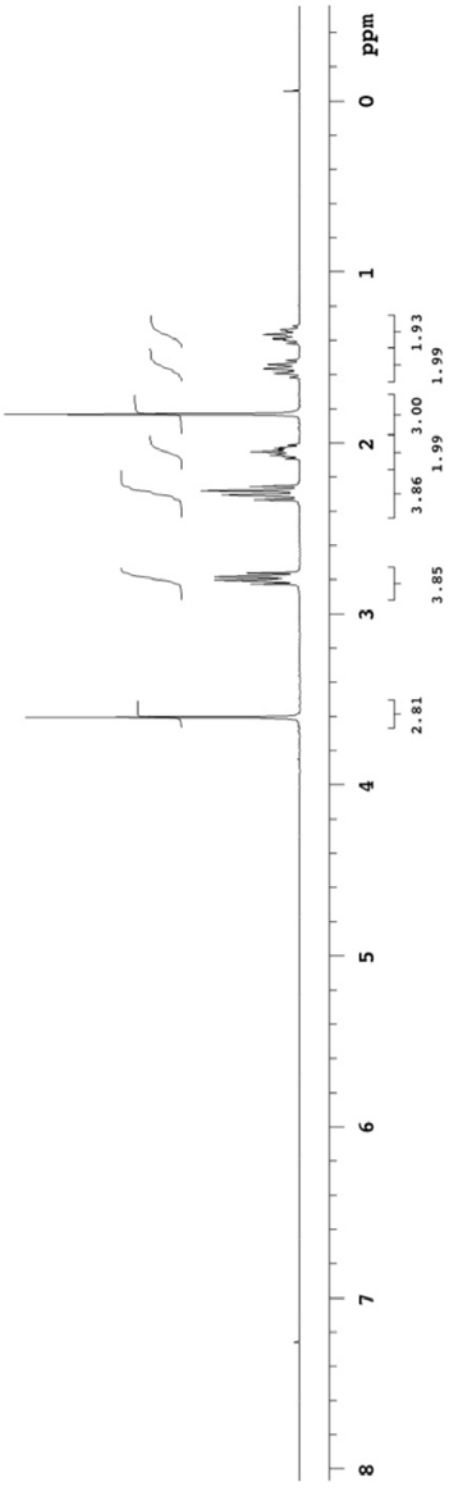

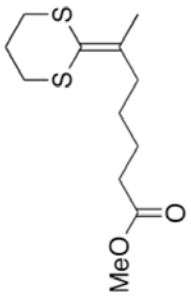

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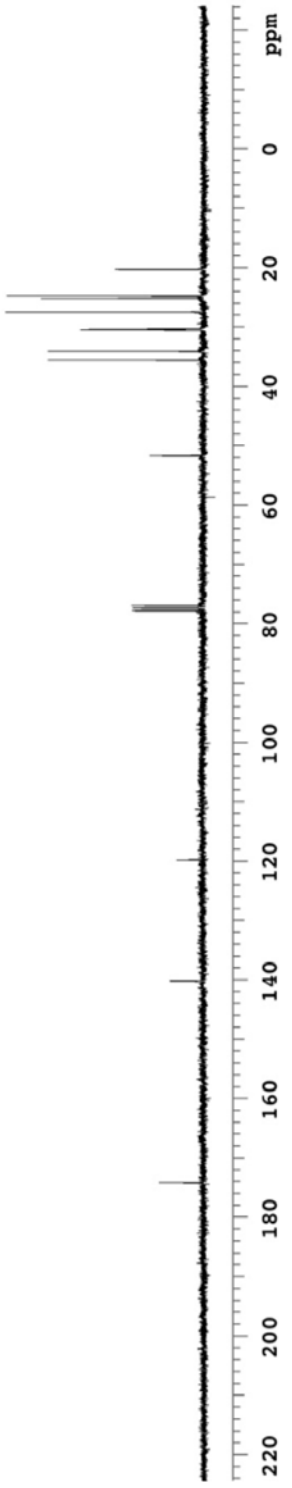
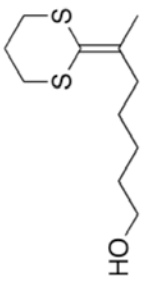
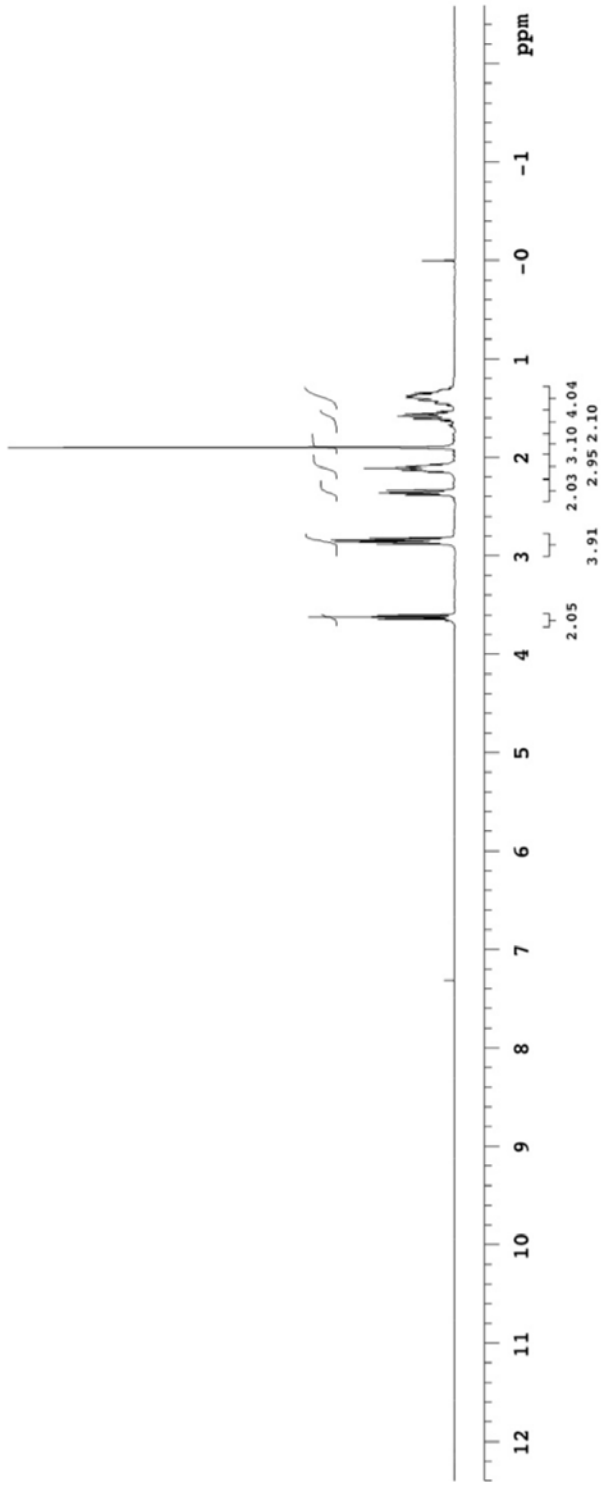
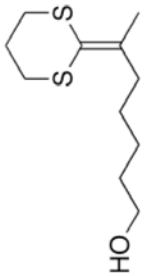




6.6h





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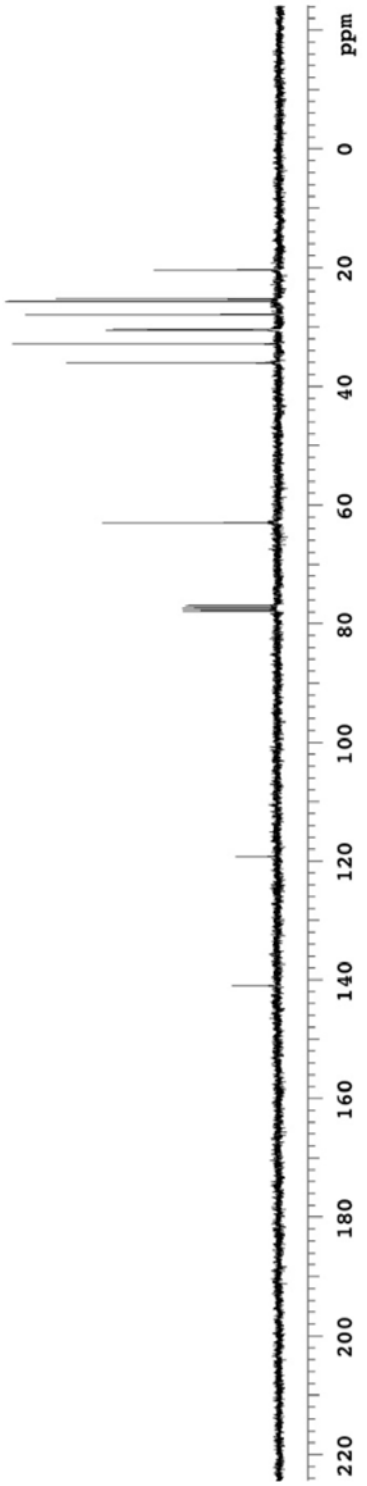

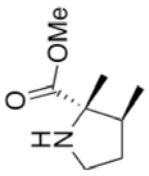

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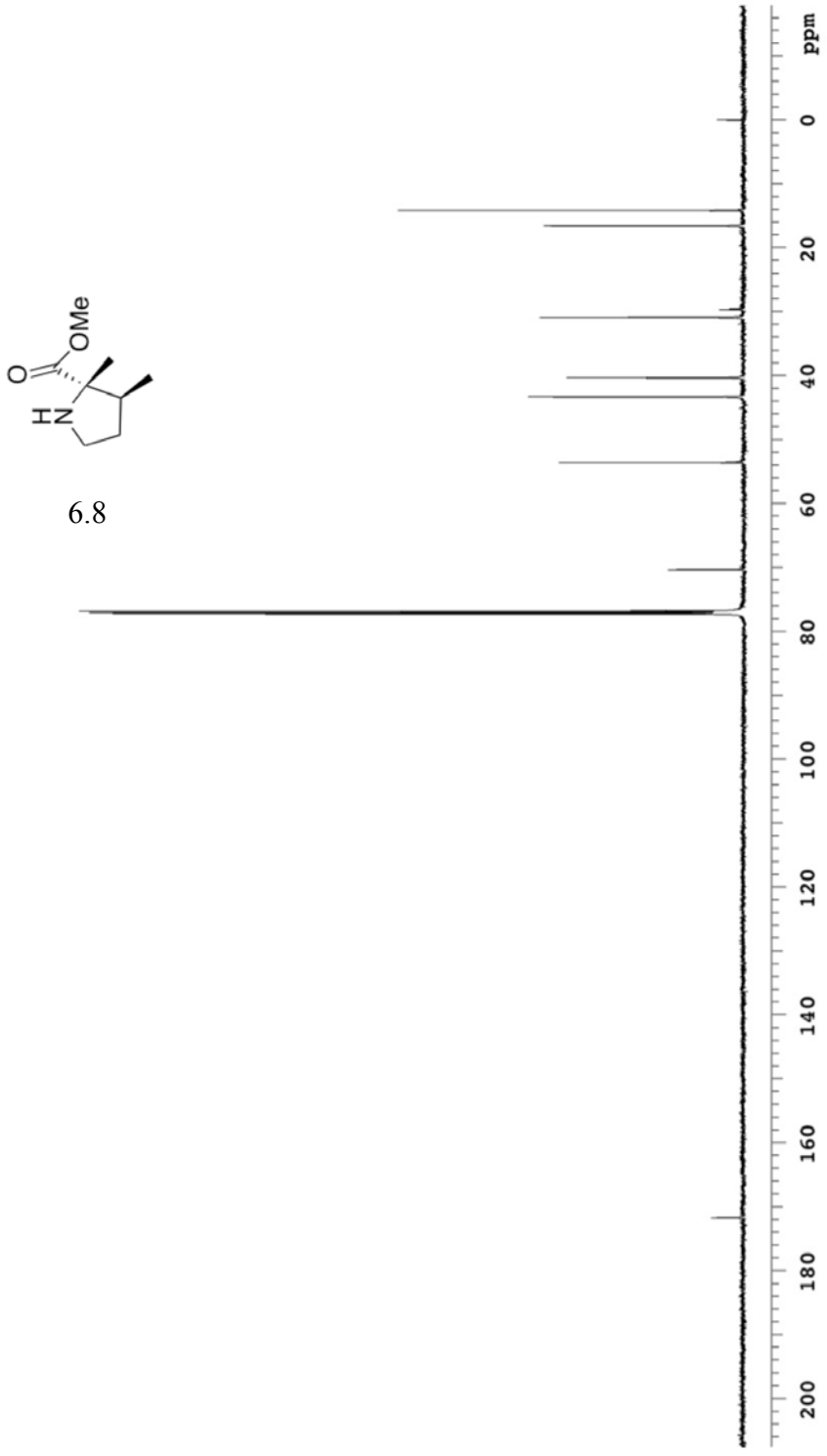

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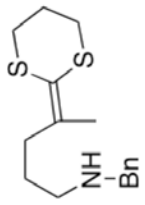
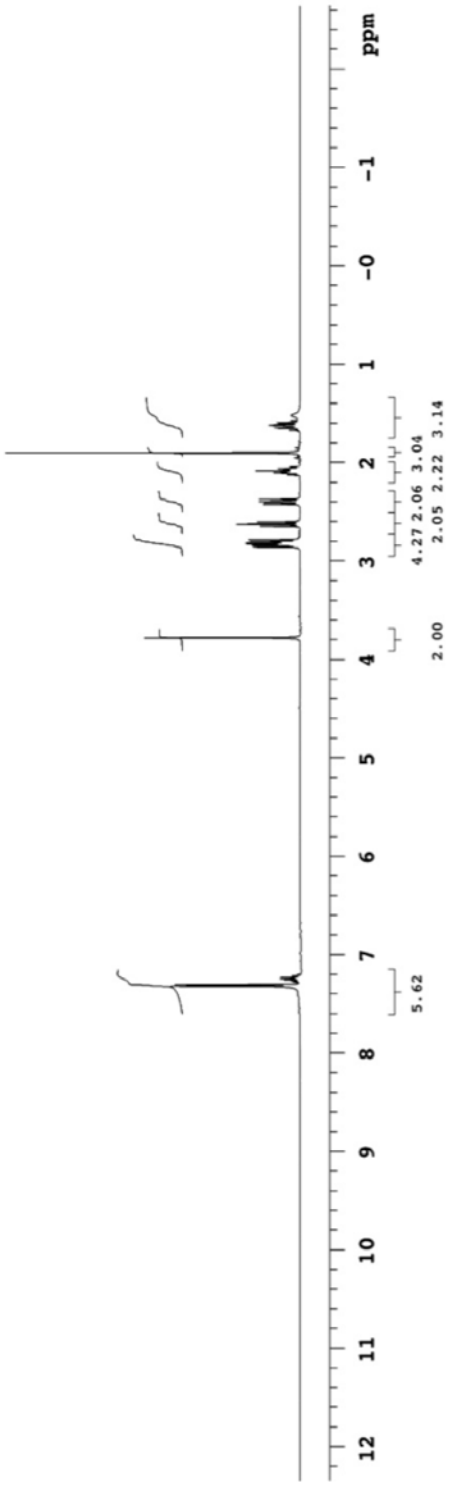

S
S
NH
Bn

7.1c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9
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7
6
5
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1
-0
-1
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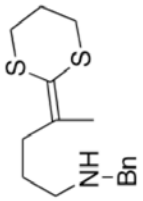
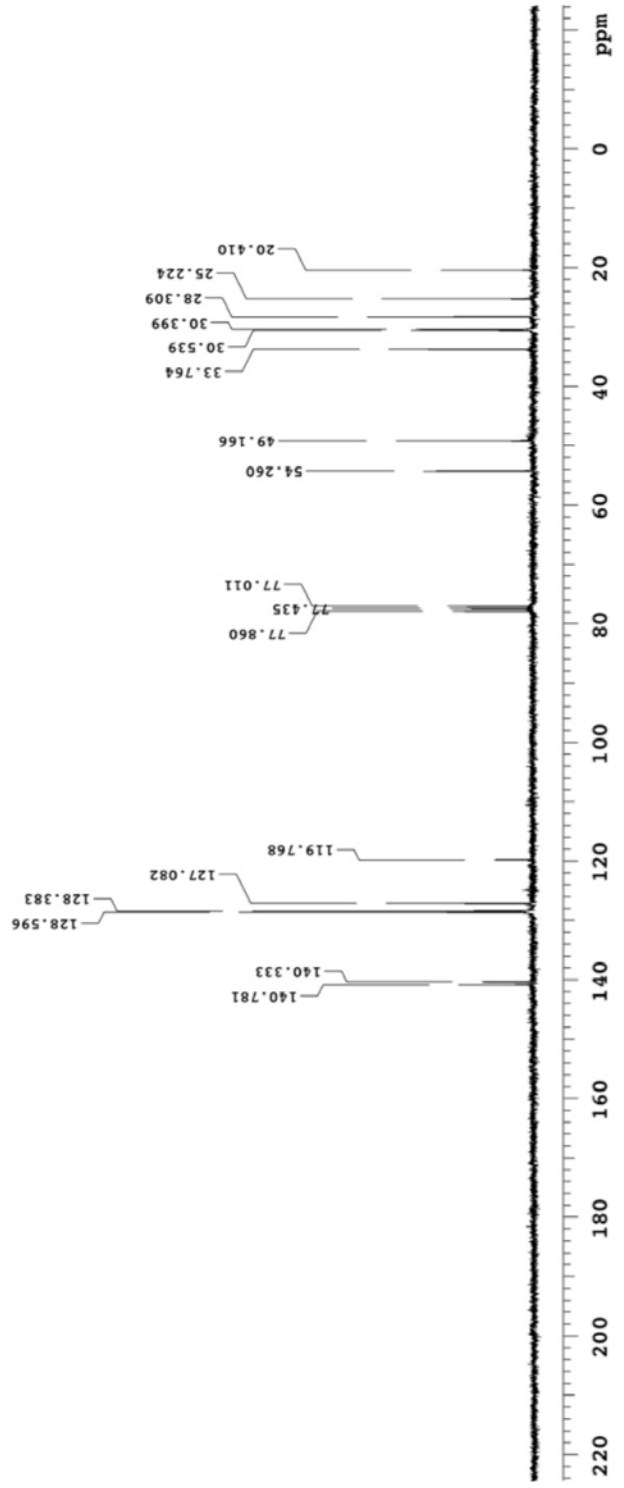
2.00
4.27 2.06 3.04
2.05 2.22 3.14


S
S
NH
Bn

7.1c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127.082
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140.333
140.781
ppm
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200
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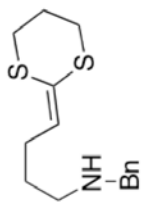

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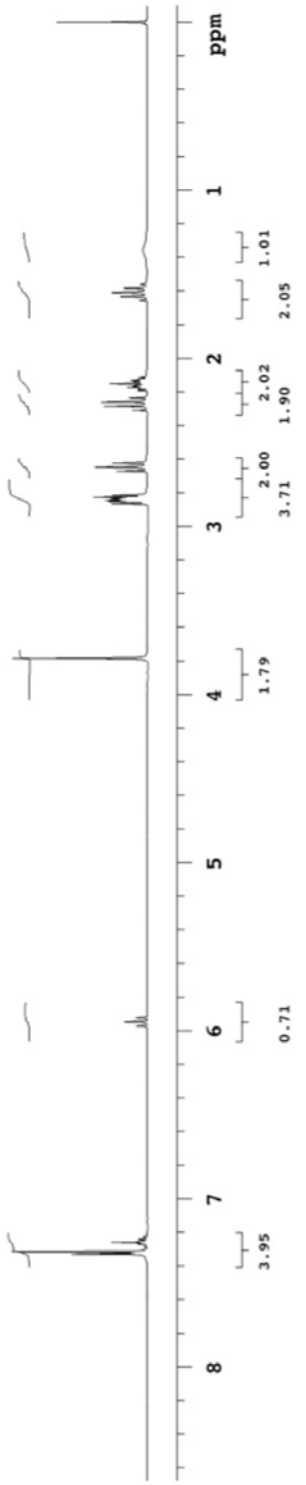
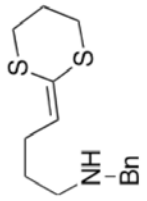
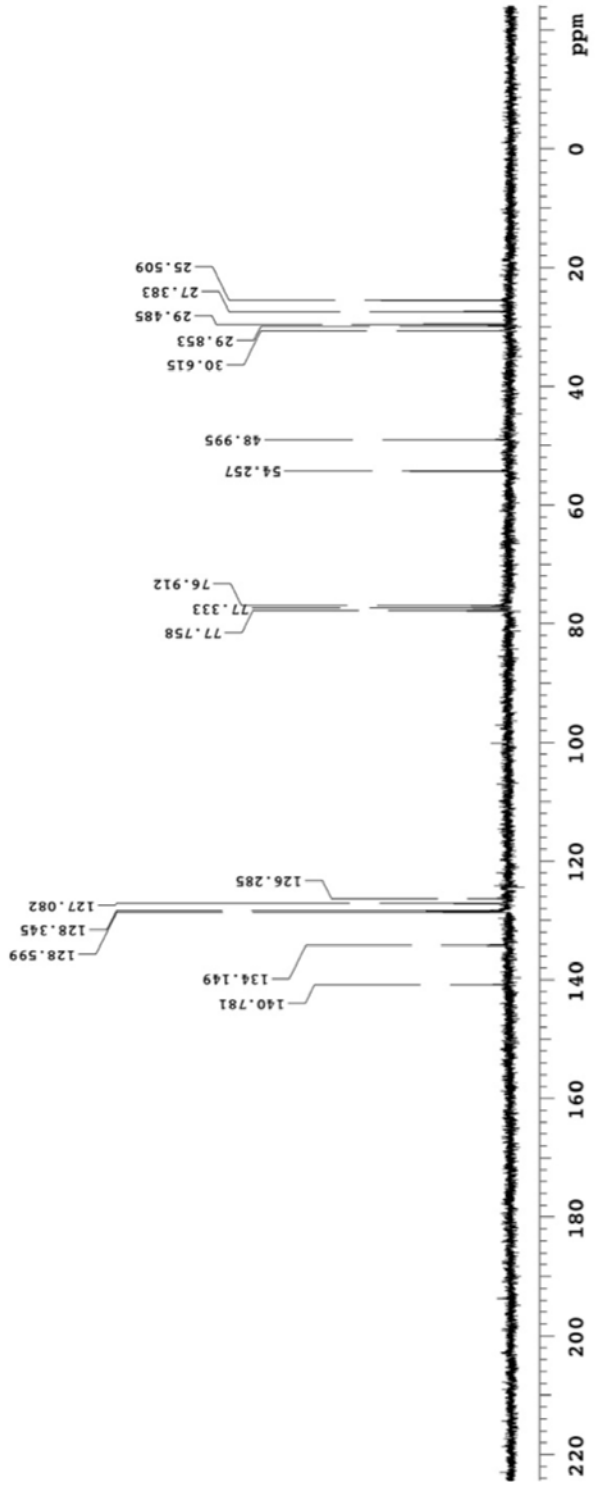



S
S
NH
Bn

7.1d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134.149
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ppm
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200
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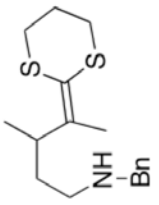

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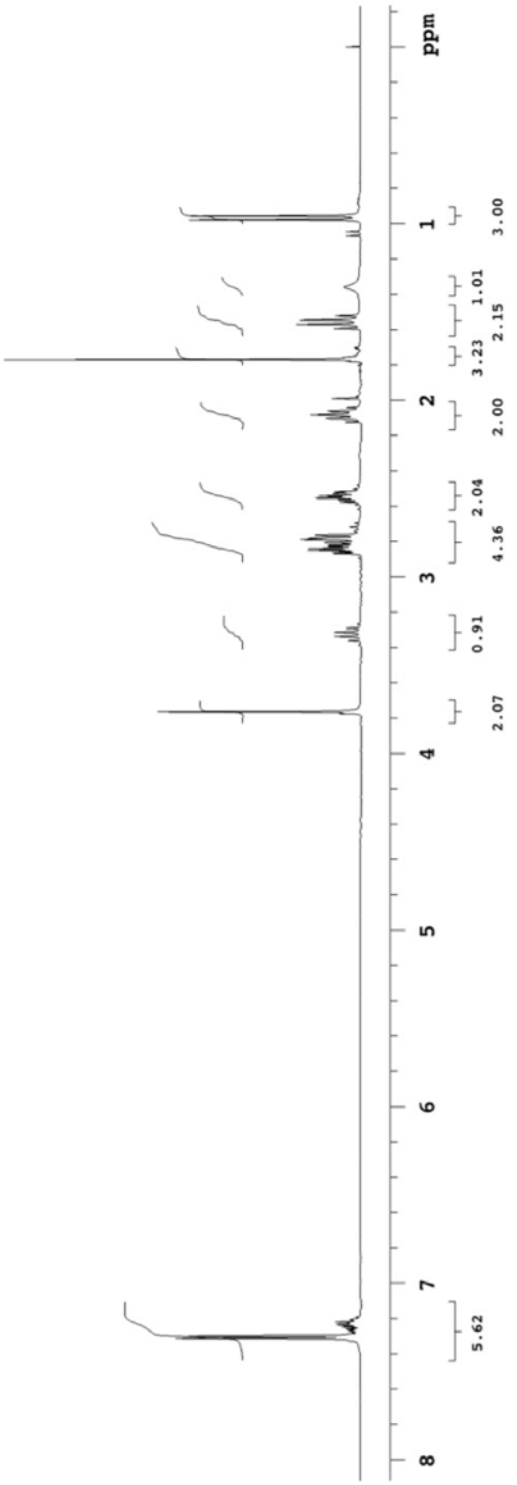

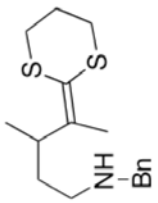
S
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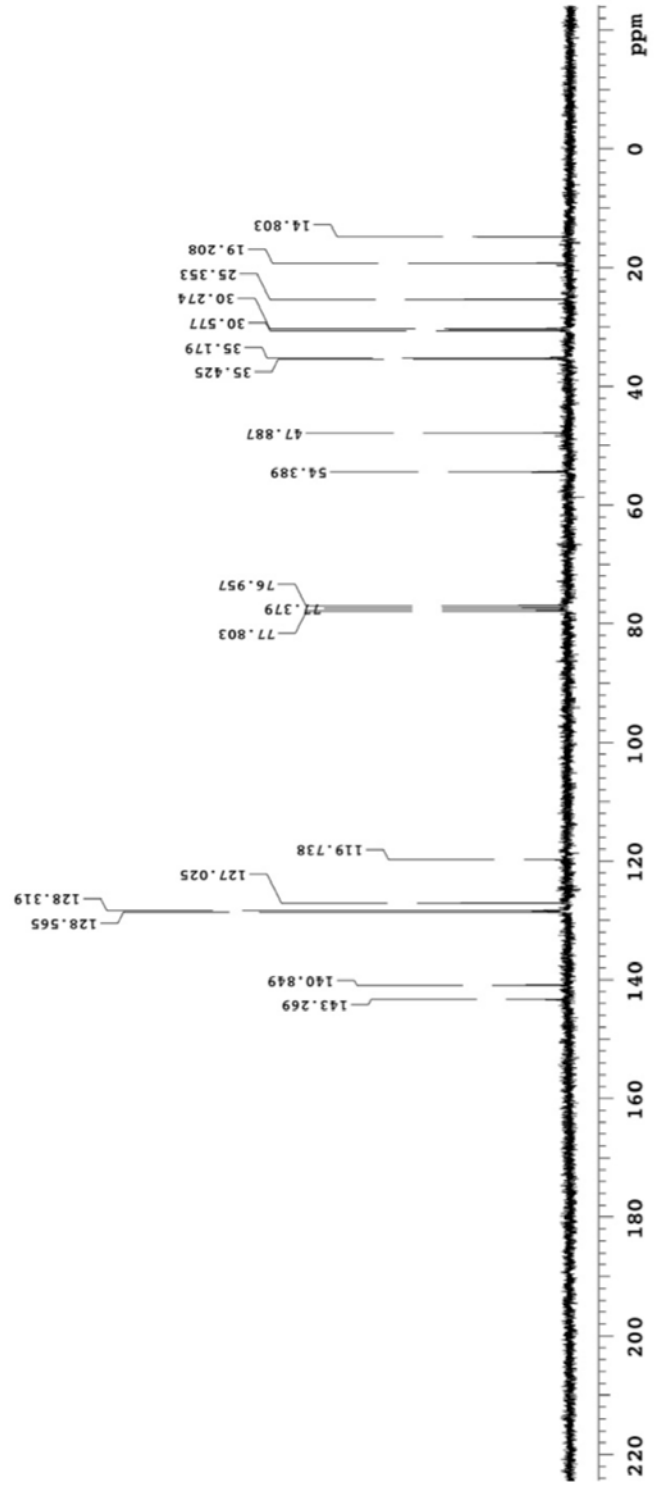
Bn

7.1e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35.425
47.887
54.389
76.957
77.379
77.803
119.738
127.025
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143.269
ppm
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80
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200
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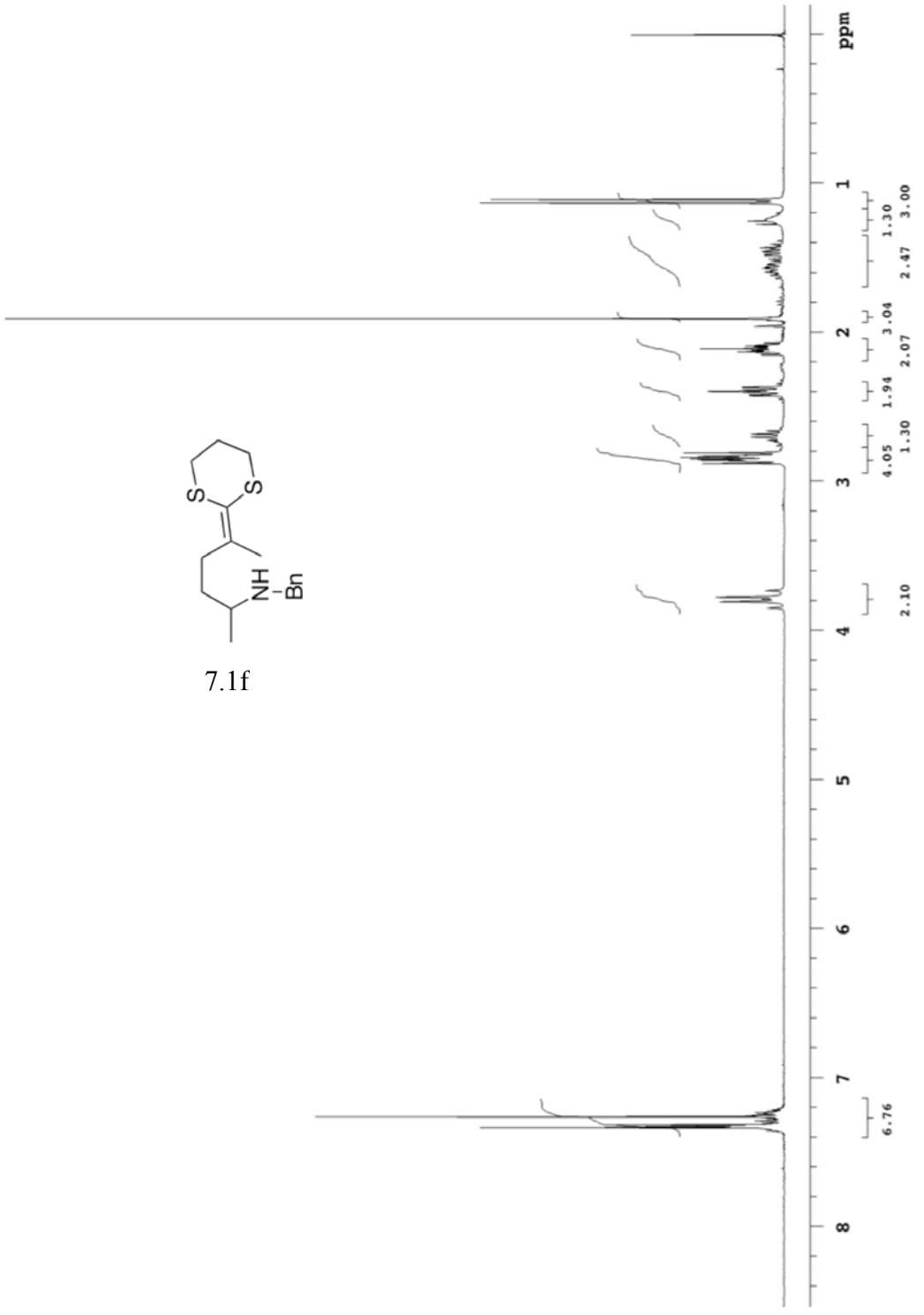
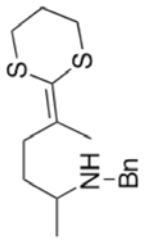
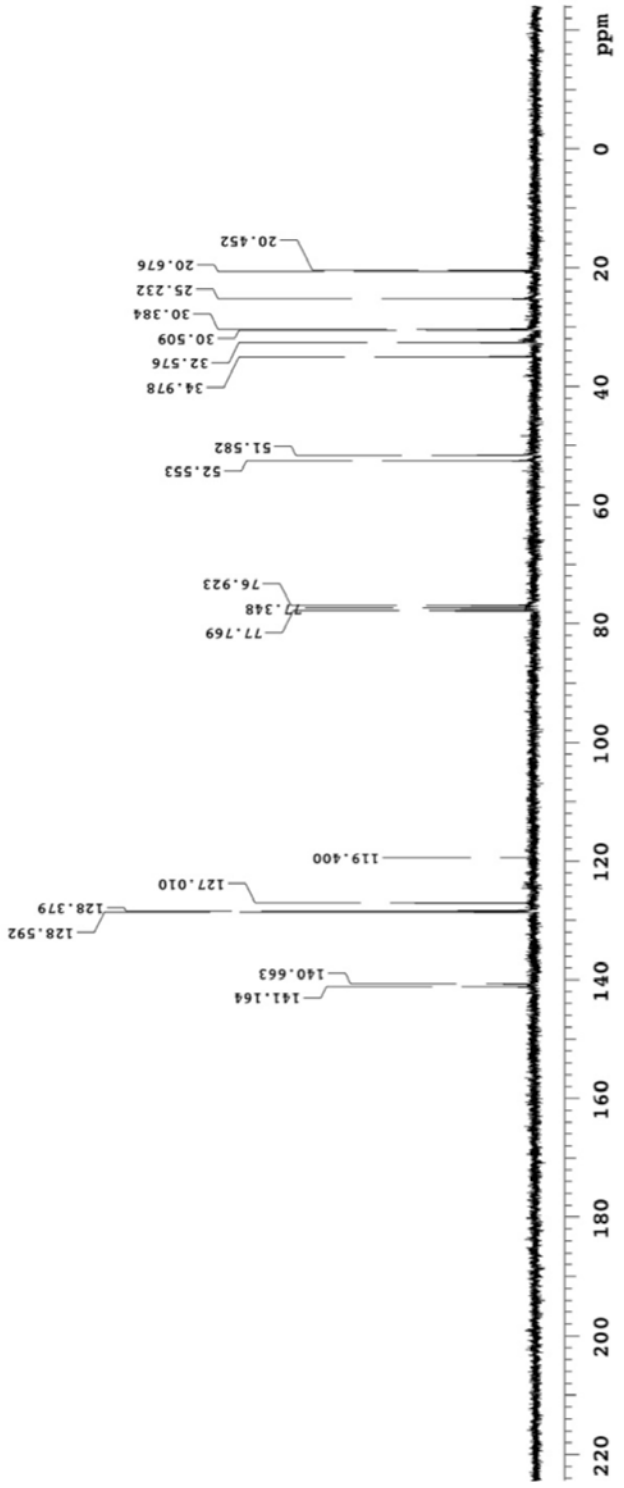


7.1f


S
S
NH
Bn

7.1f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127.010
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140.663
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ppm
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80
100
120
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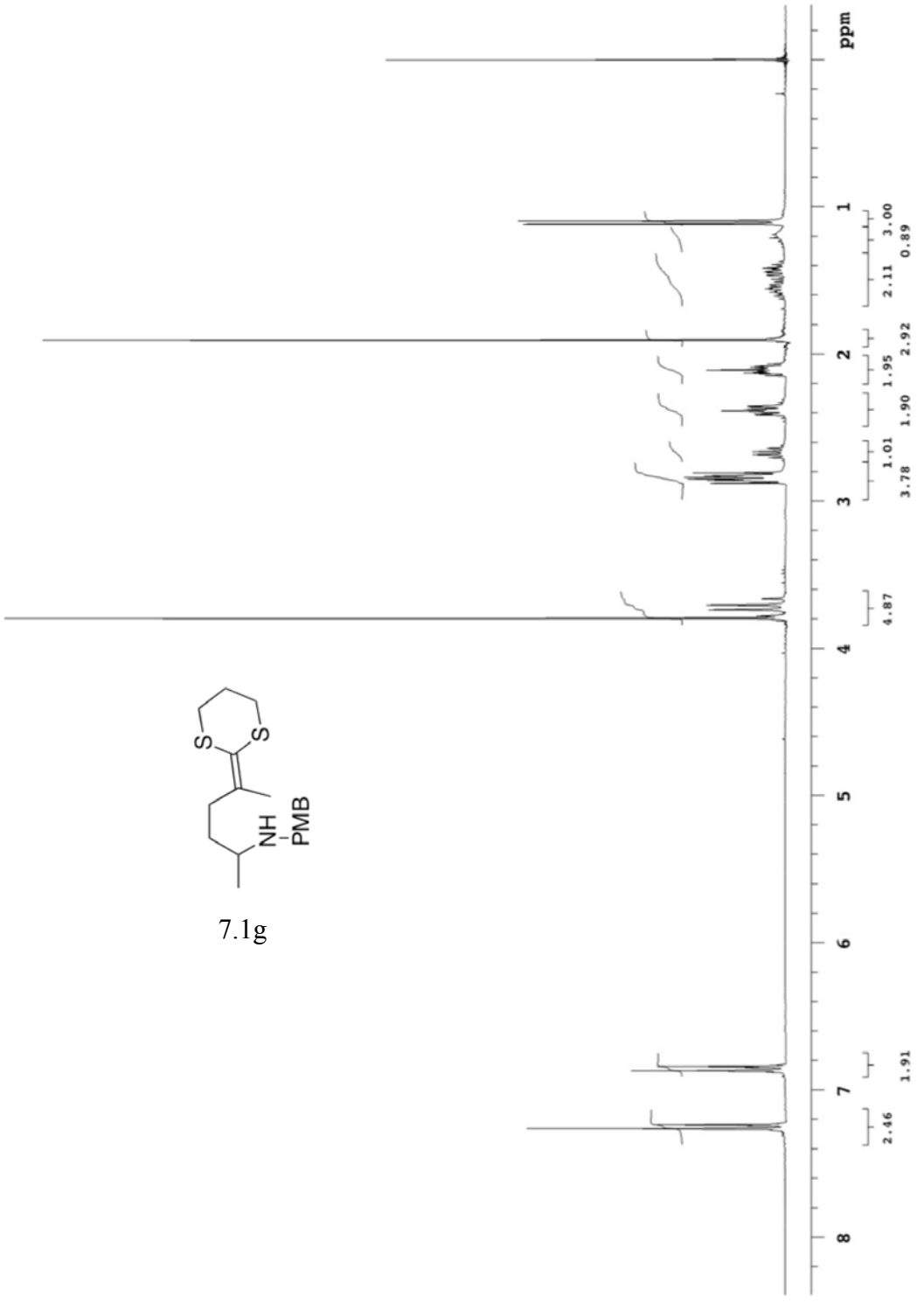
160
180
200
220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S
NH
PMB
ppm
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8
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1.01
3.78
4.87
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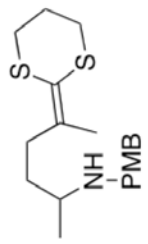
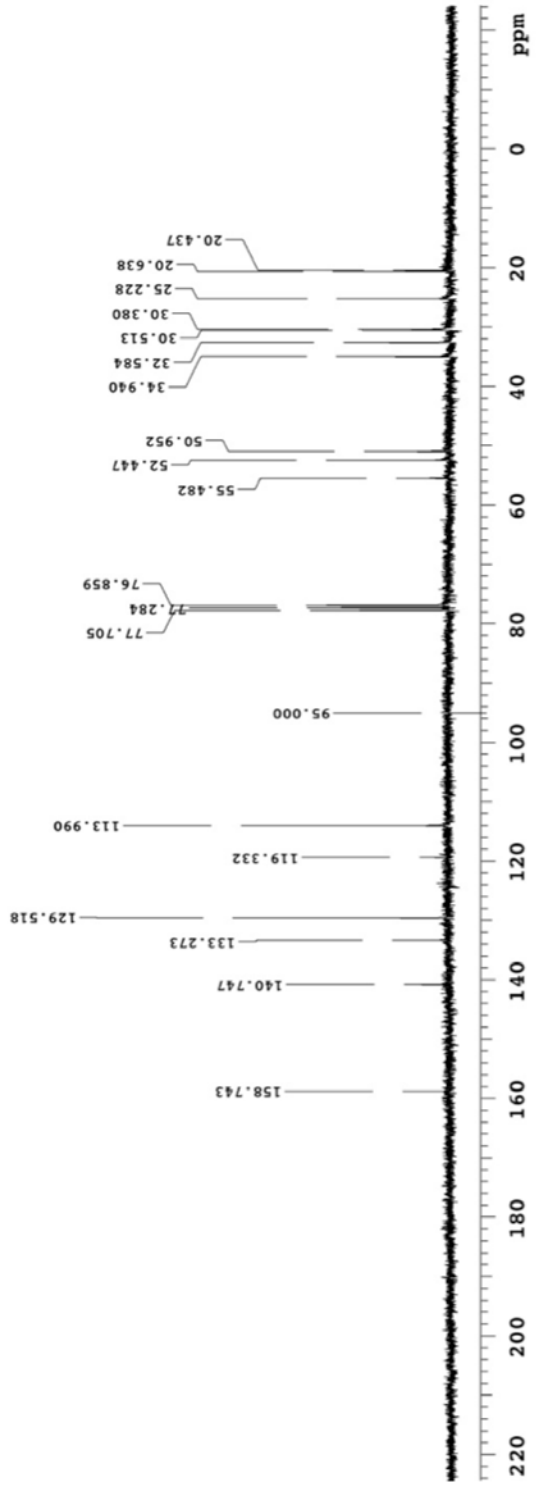
2.46

7.1g


S
S
NH
PMB

7.1g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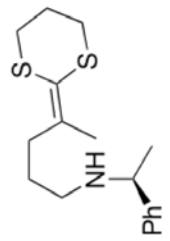

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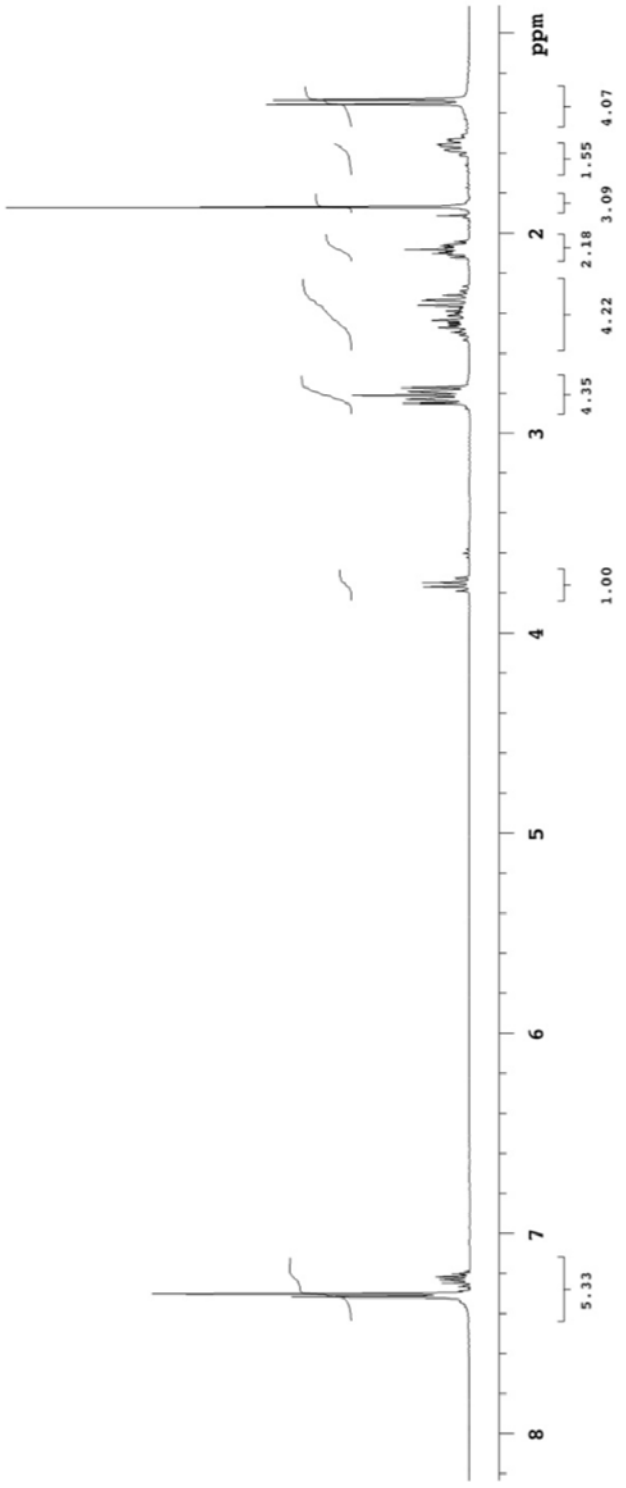
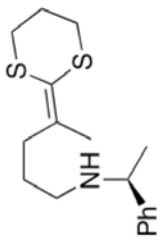
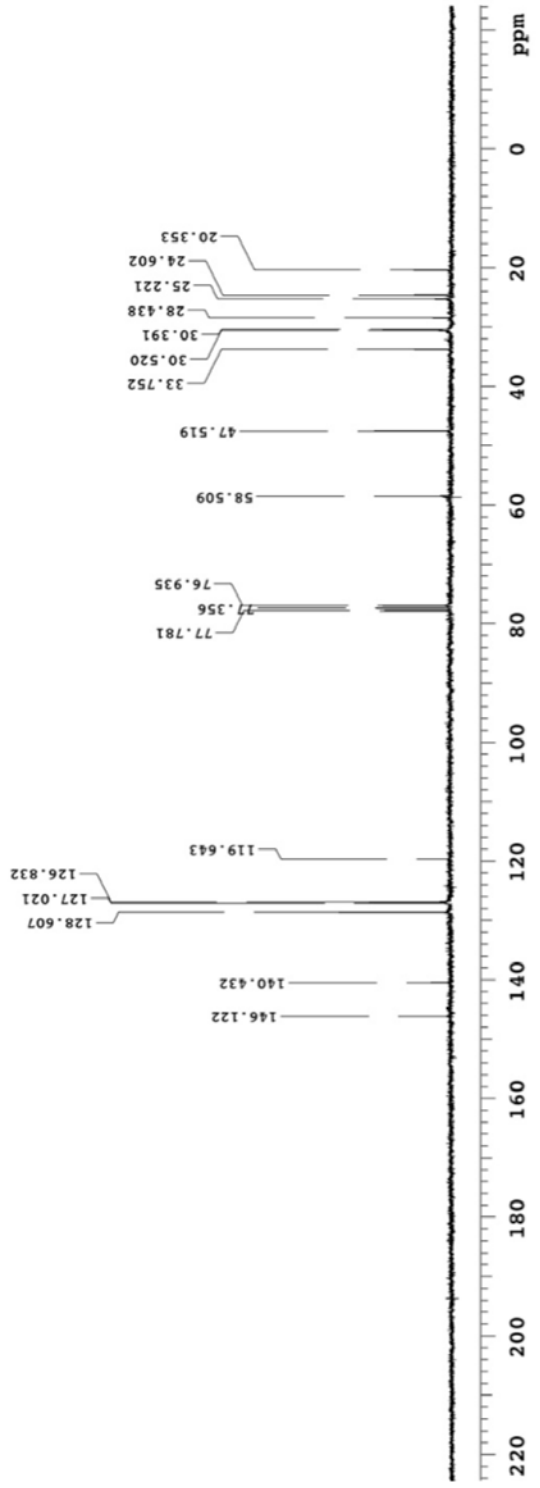



S
S
NH
Ph

7.1k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25.221
28.438
30.391
30.520
33.752
47.519
58.509
76.935
77.356
77.781
119.643
126.832
127.021
128.607
140.432
146.122
ppm
0
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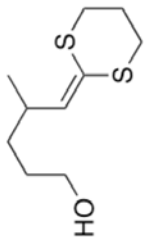
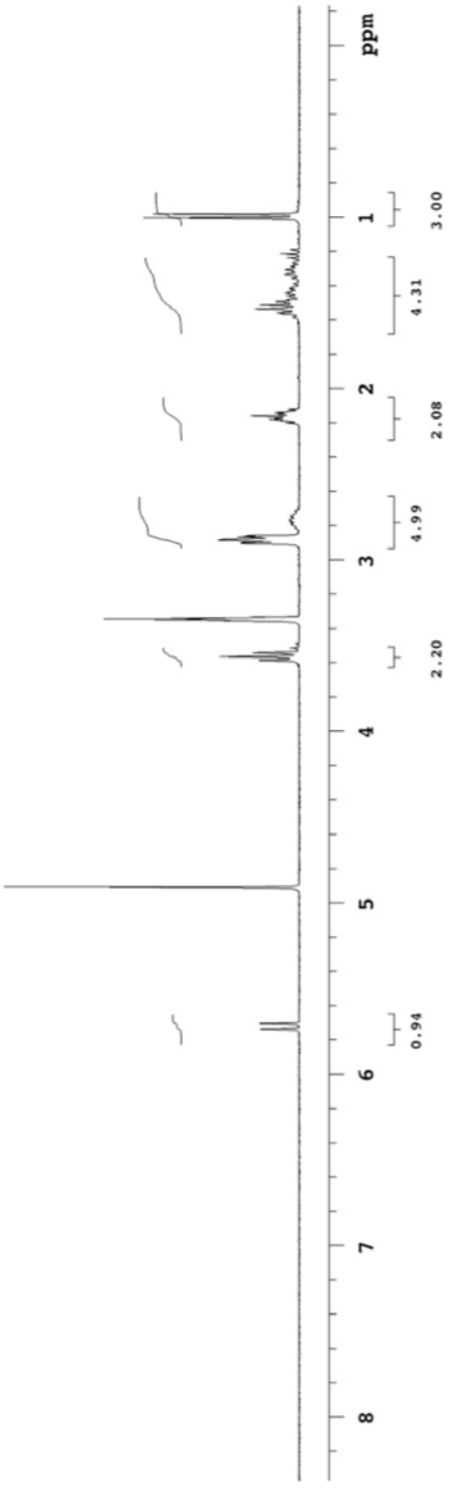
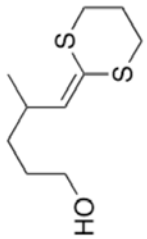
40
60
80
100
120
140
160
180
200
220

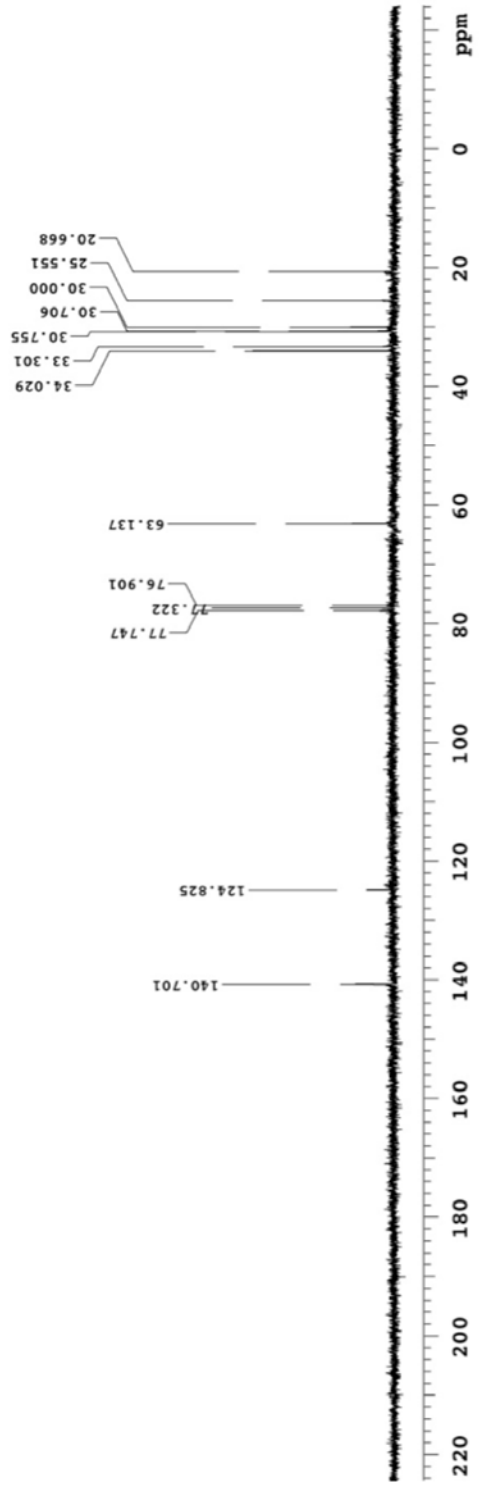


7.7




S
S
HO

7.7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63.137
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77.322
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124.825
140.701
ppm
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80
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200
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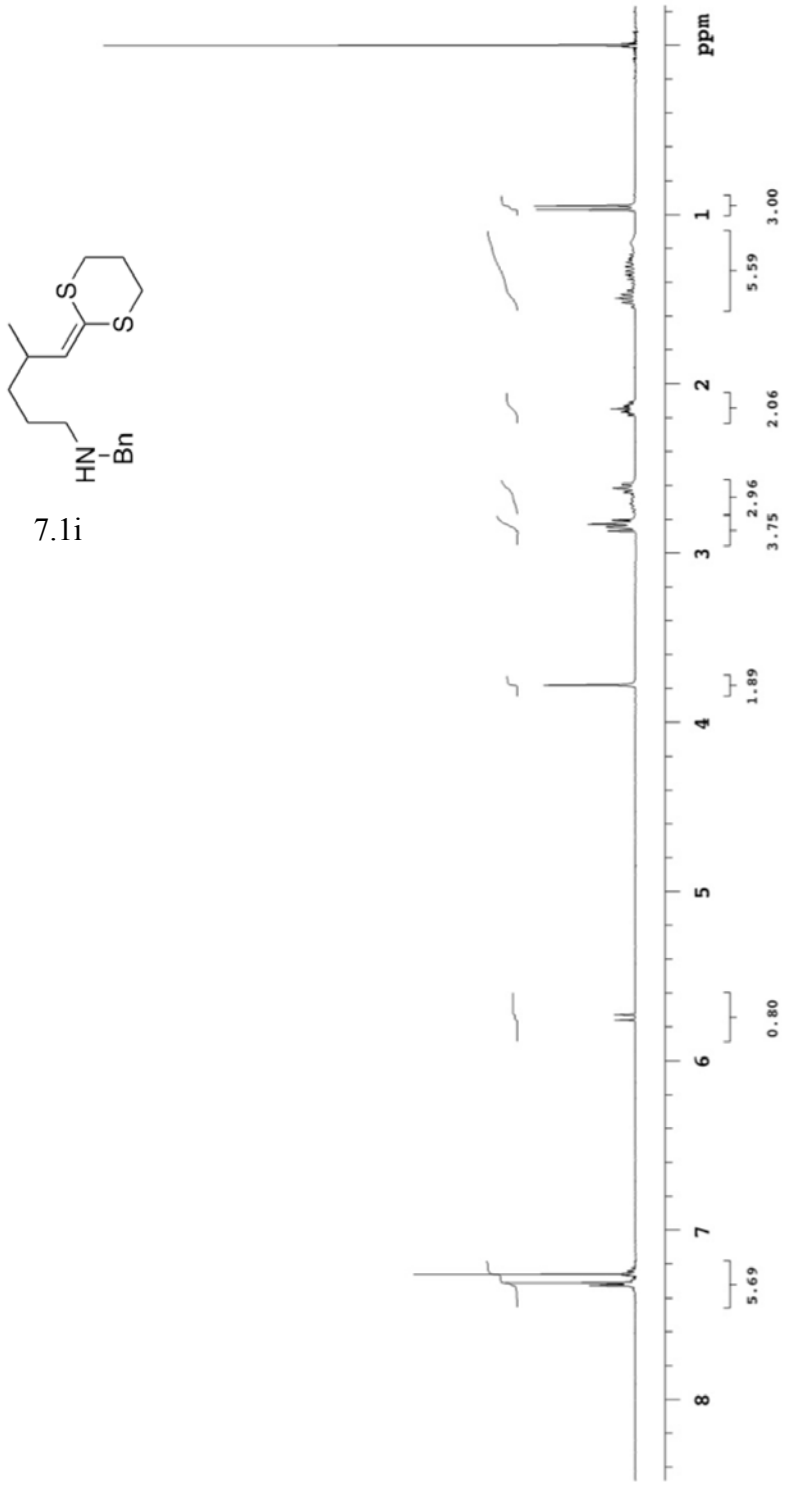
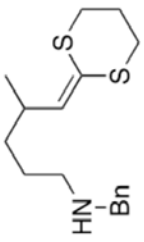
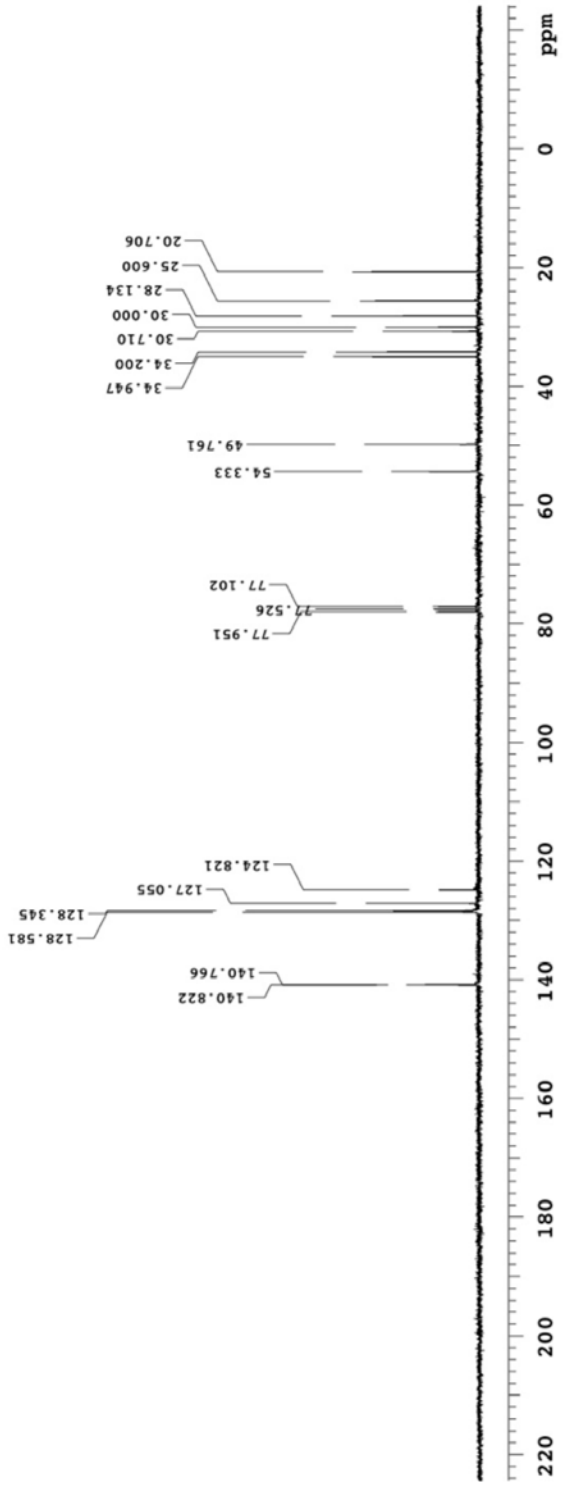


7.1i


S
S
HN
Bn

7.1i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28.134
30.000
30.710
34.200
34.947
49.761
54.333
77.102
77.526
77.951
124.821
127.055
128.345
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140.822
ppm
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80
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160
180
200
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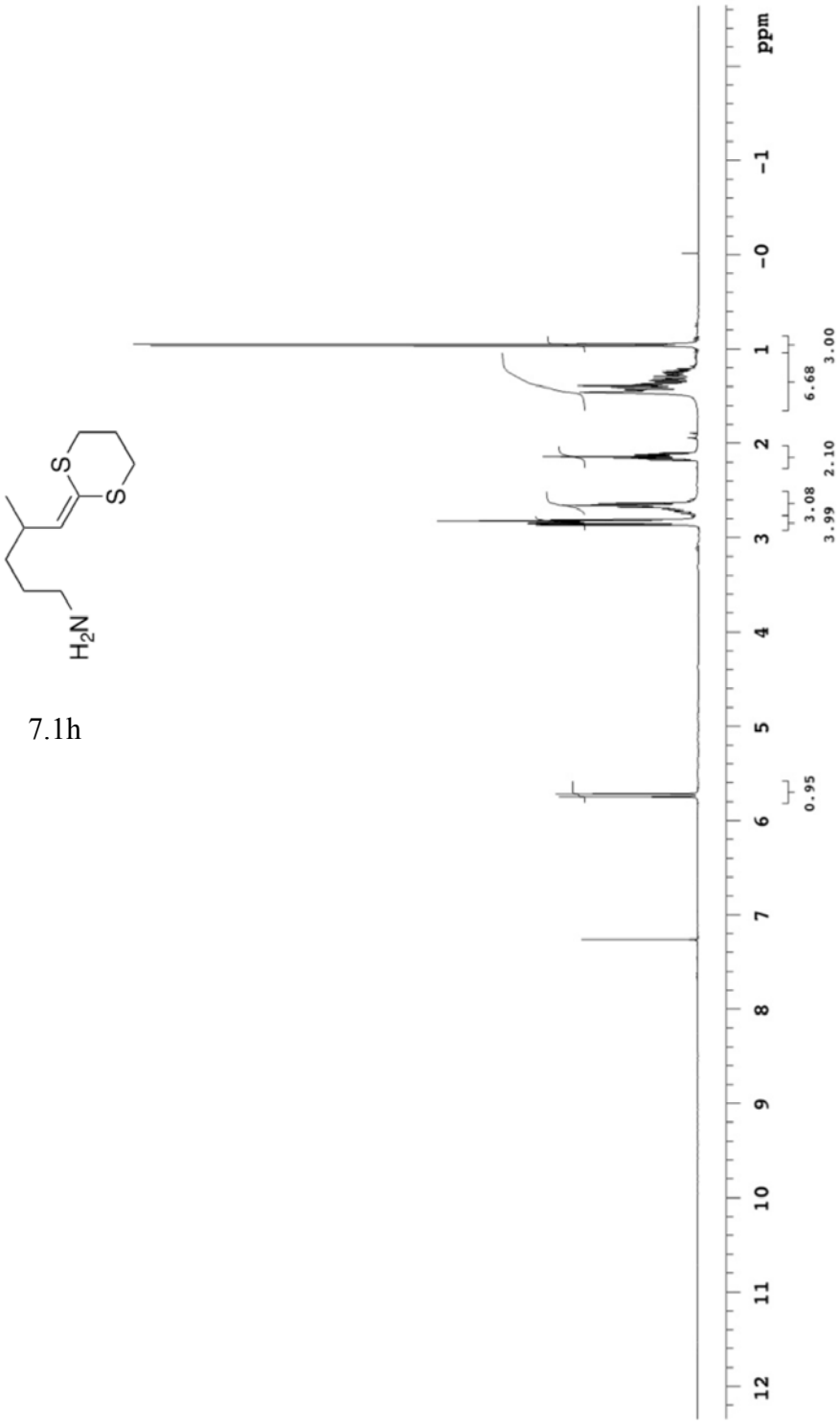
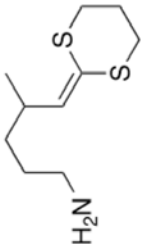
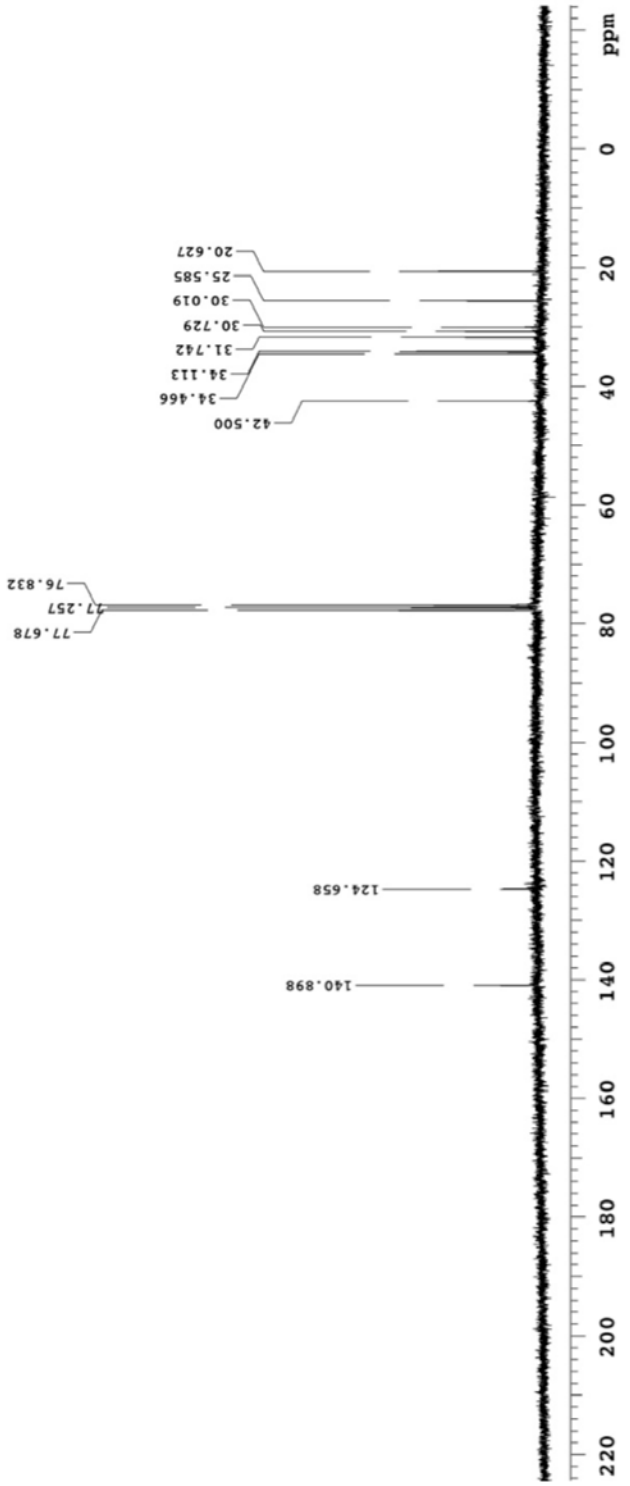


7.1h


S
S
H_2N

7.1h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31.742
34.113
34.466
42.500
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124.658
140.898
ppm
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80
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120
140
160
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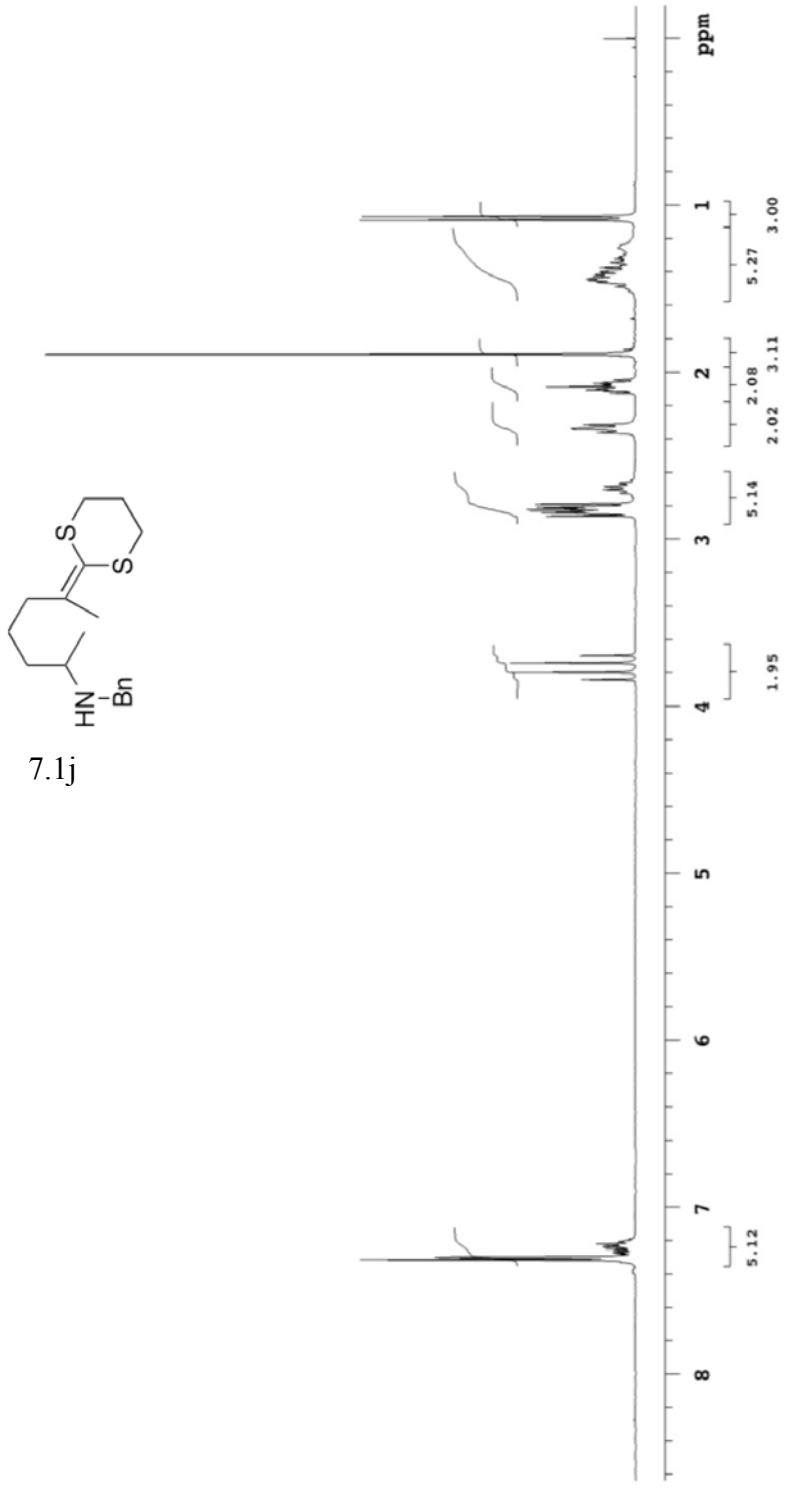
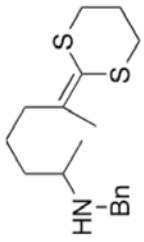
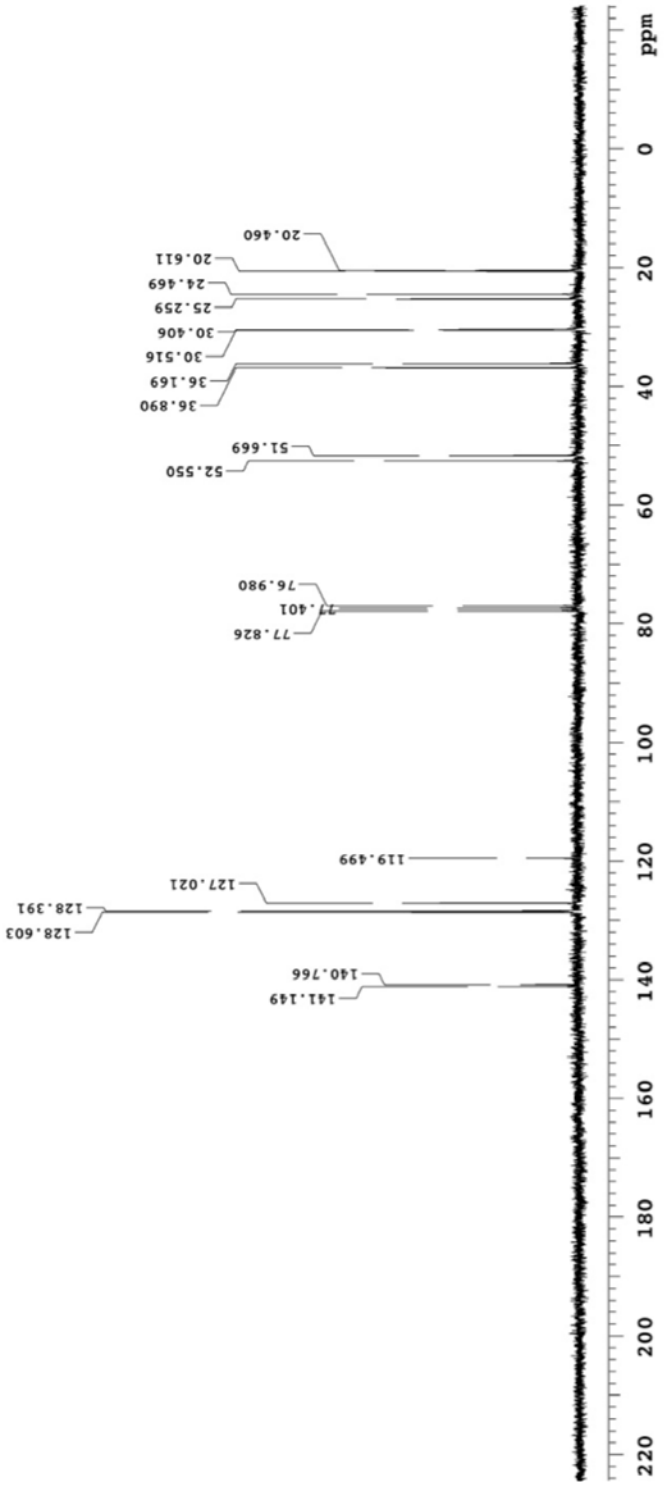
200
220



7.1j


S
S
HN
Bn

7.1j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25.259
30.406
30.516
36.169
36.890
51.669
52.550
76.980
77.401
77.826
119.499
127.021
128.391
128.603
140.766
141.149
ppm
0
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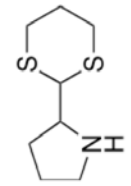
60
80
100
120
140
160
180
200
220



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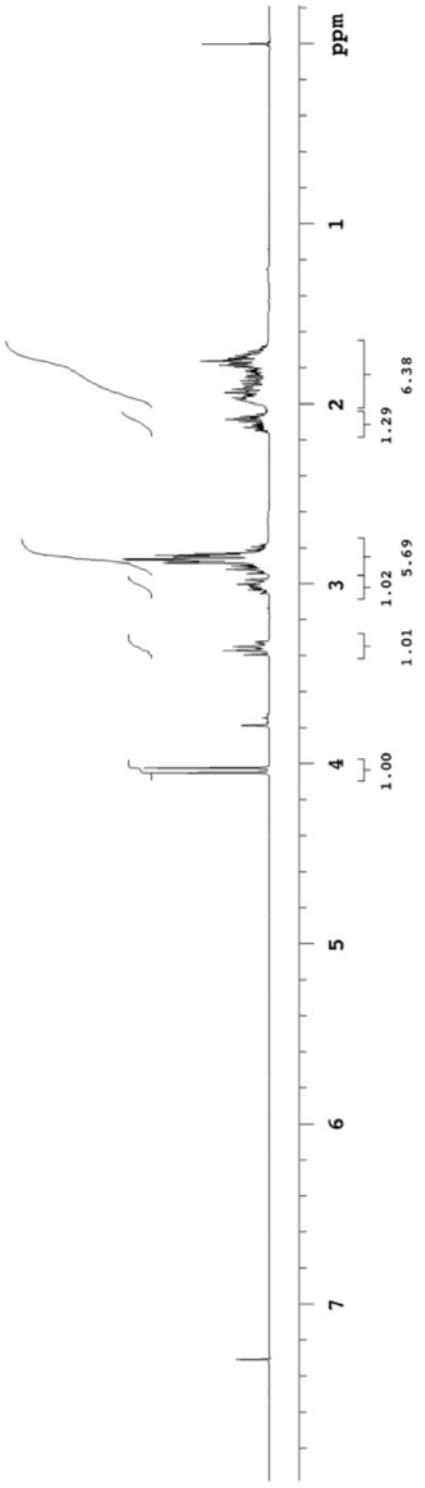
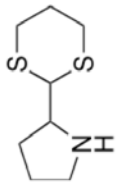
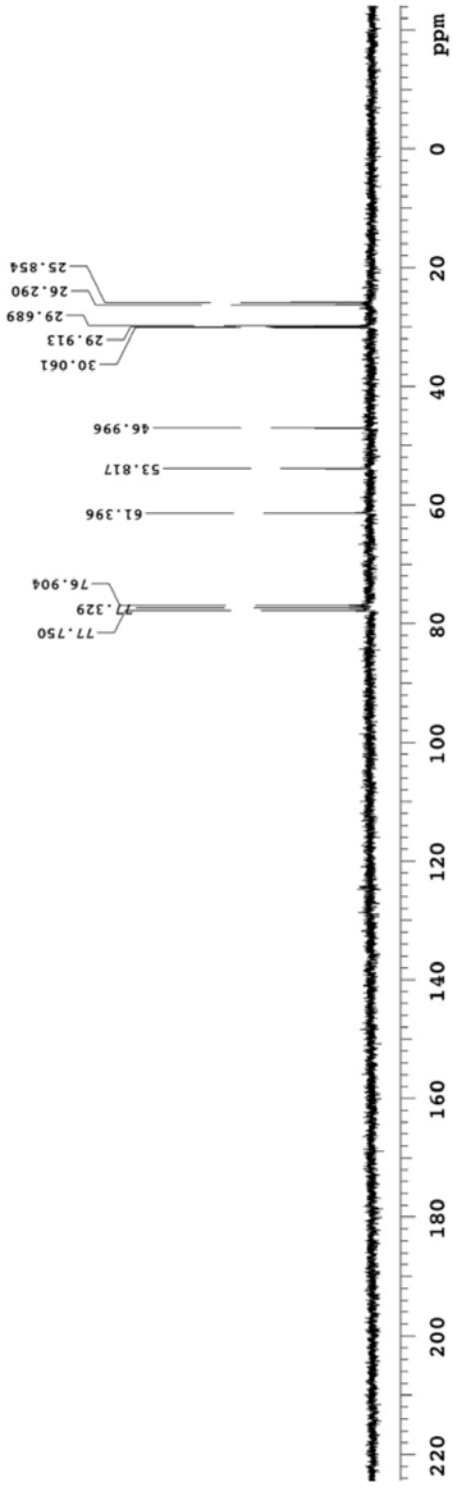



S
S
NH

7.2a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30.061
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53.817
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76.904
77.329
77.750
ppm
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40
60
80
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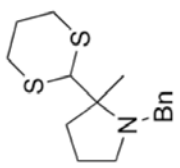
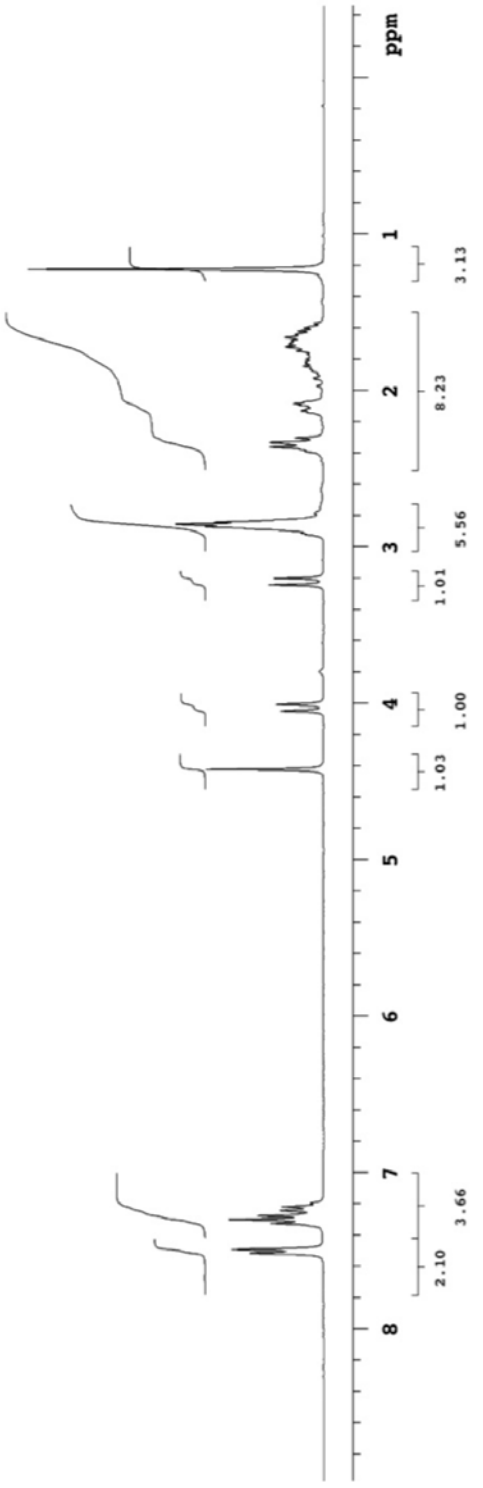
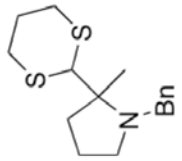
140
160
180
200
220

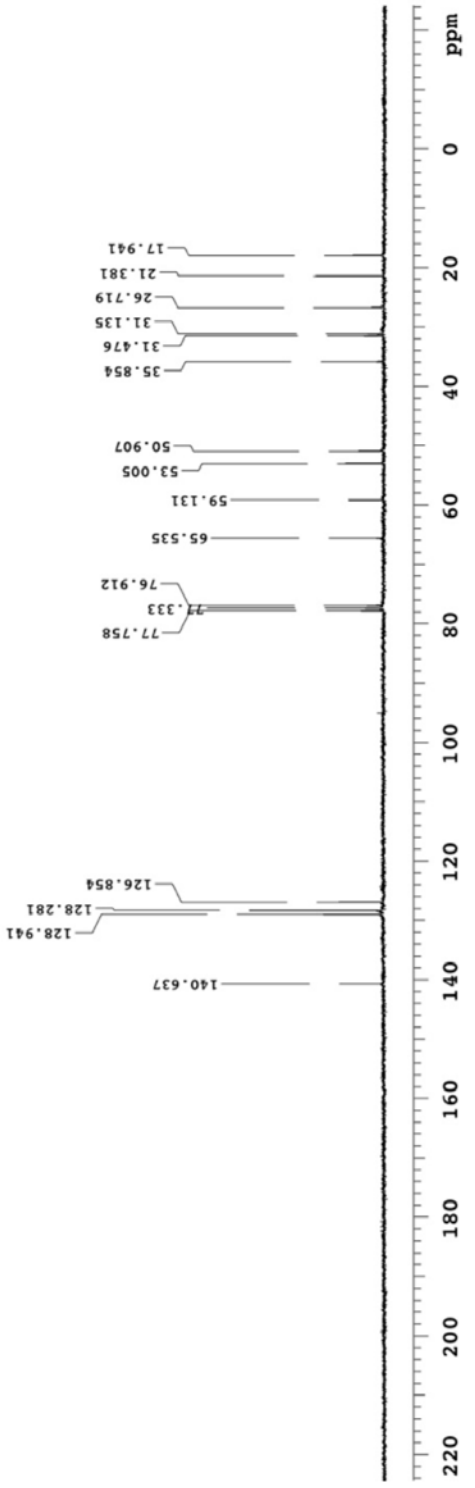


7.2c




S
S
N
Bn

7.2c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31.476
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53.005
59.131
65.535
76.912
77.333
77.758
126.854
128.281
128.941
140.637
ppm
0
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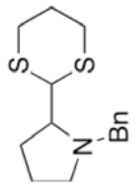
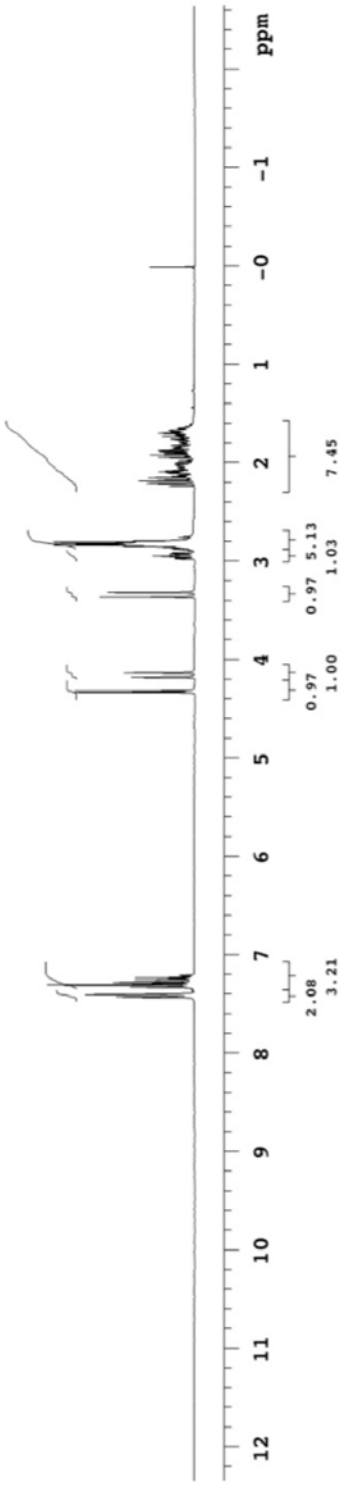
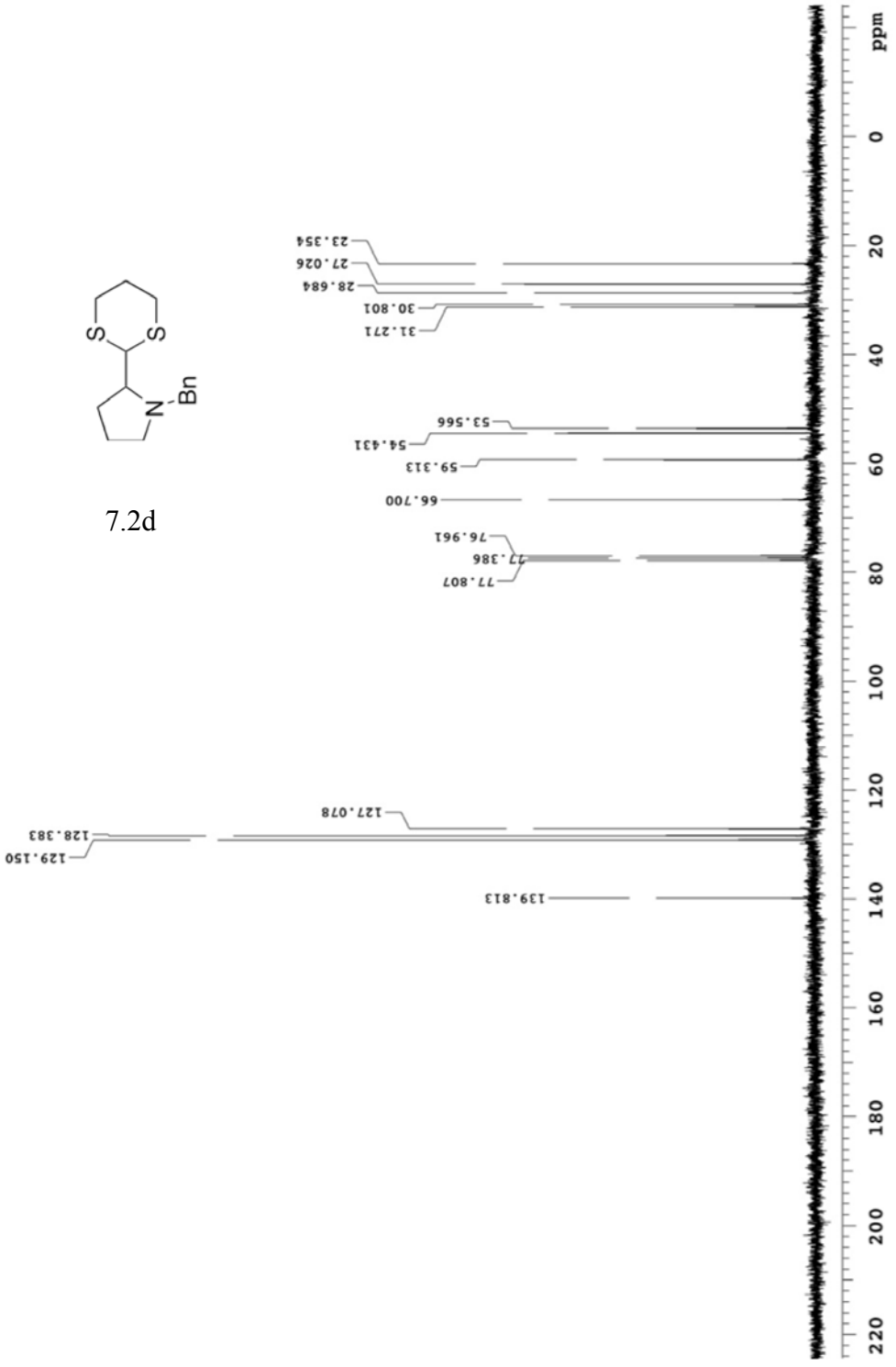
40
60
80
100
120
140
160
180
200
220



7.2d




S
S
N
Bn
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27.026
28.684
30.801
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53.566
54.431
59.313
66.700
76.961
77.386
77.807
127.078
128.383
129.150
139.813
ppm
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40
60
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120
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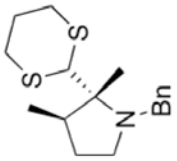
180
200
220

7.2d



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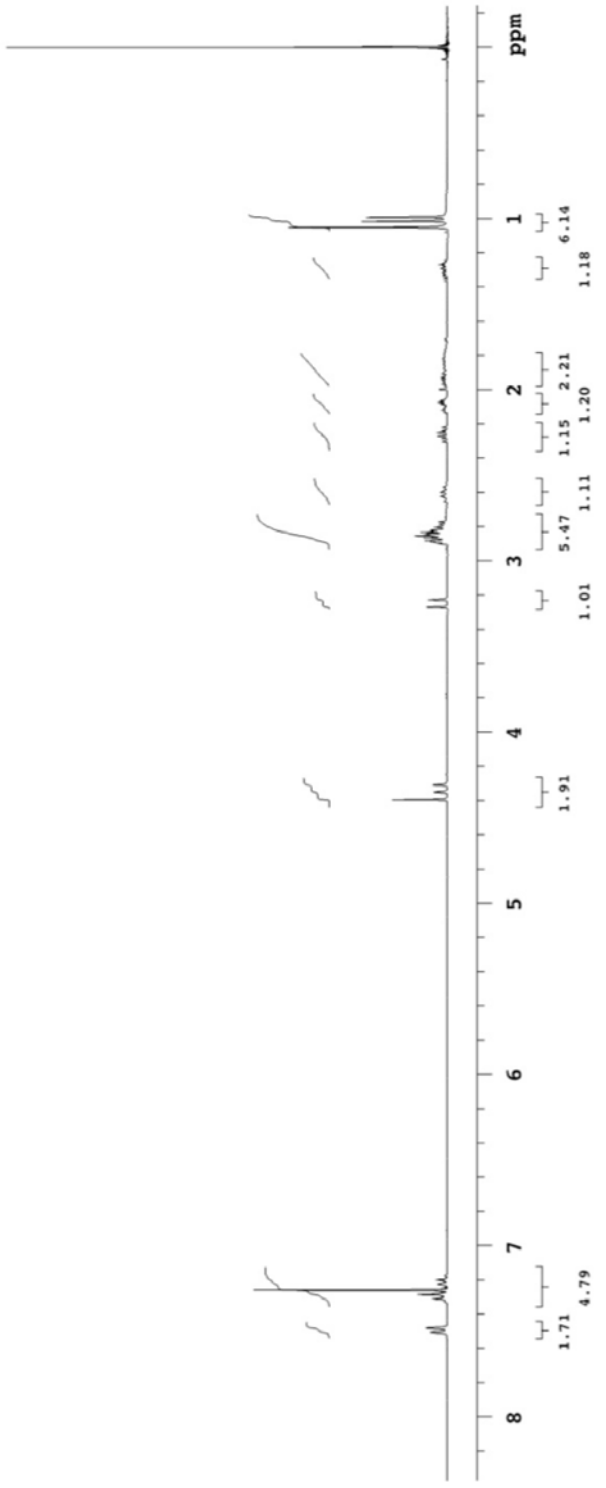
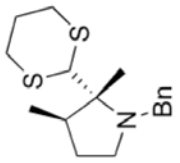
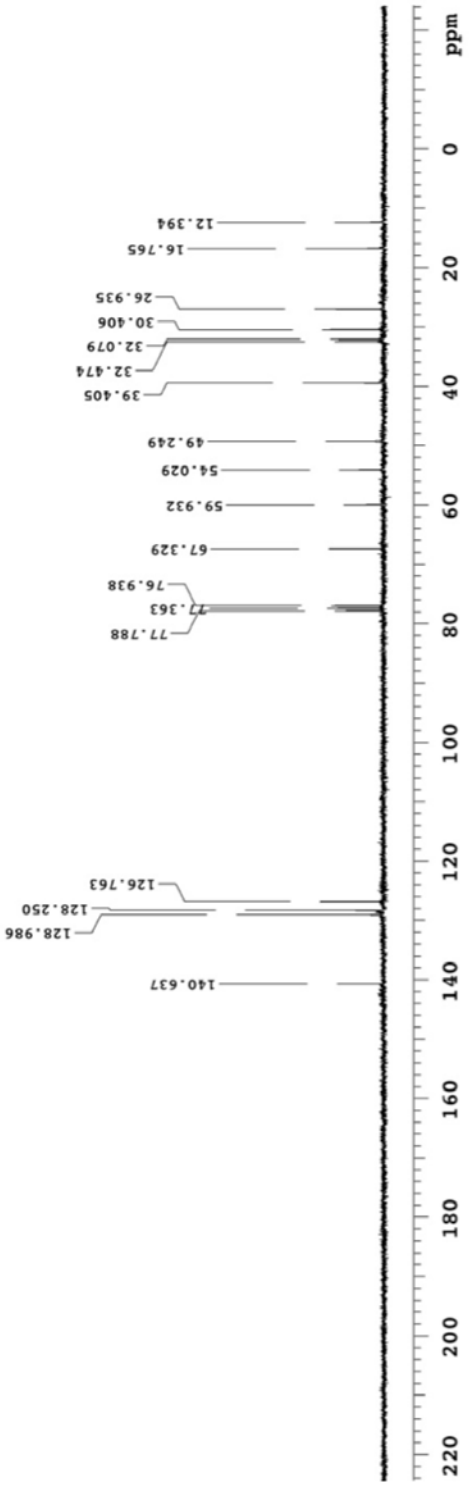



S
S
N
Bn

7.2e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80
100
120
140
160
180
200
220
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30.406
32.079
32.474
39.405
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67.329
76.938
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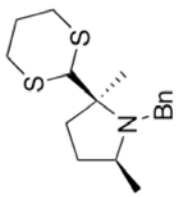
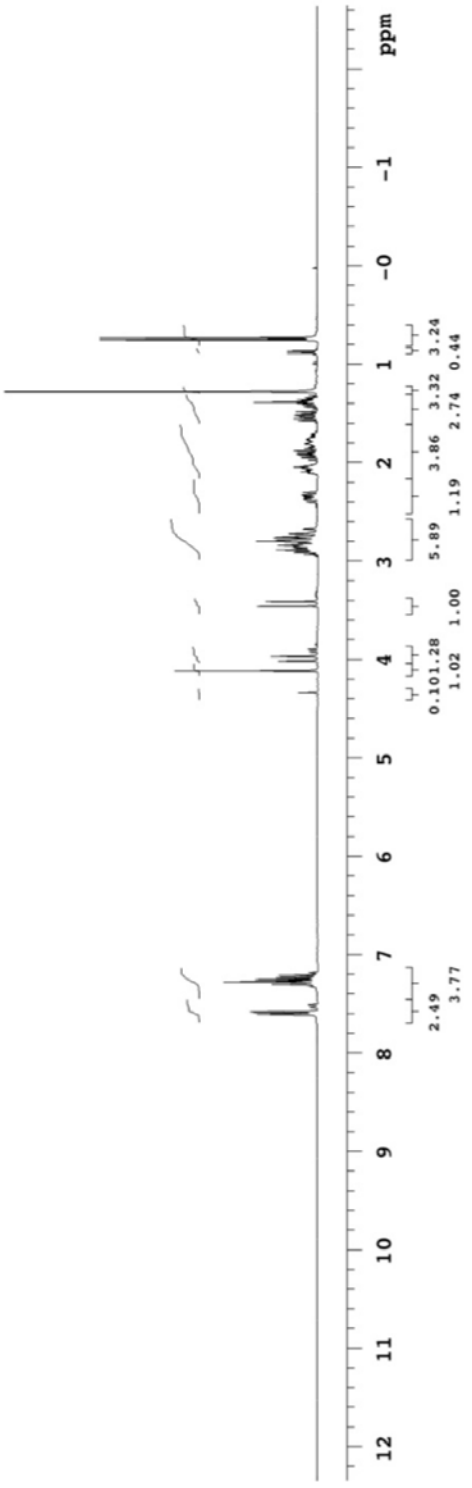
140.637


S
S
N
Bn

7.2f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9
8
7
6
5
4
3
2
1
-0
-1
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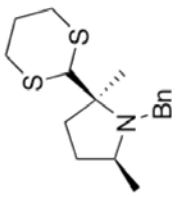
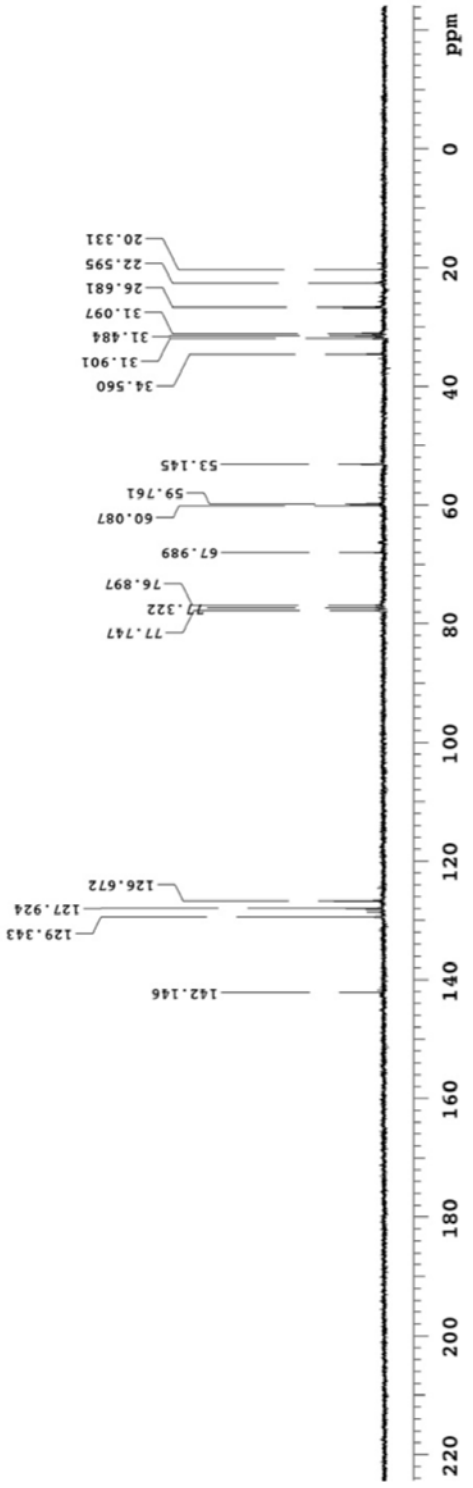
3.77
0.101.28
1.02
1.00
5.89
1.19
3.86
3.32
2.74
3.24
0.44


S
S
N
Bn

7.2f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31.901
34.560
53.145
59.761
60.087
67.989
76.897
77.322
77.747
126.672
127.924
129.343
142.146
ppm
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40
60
80
100
120
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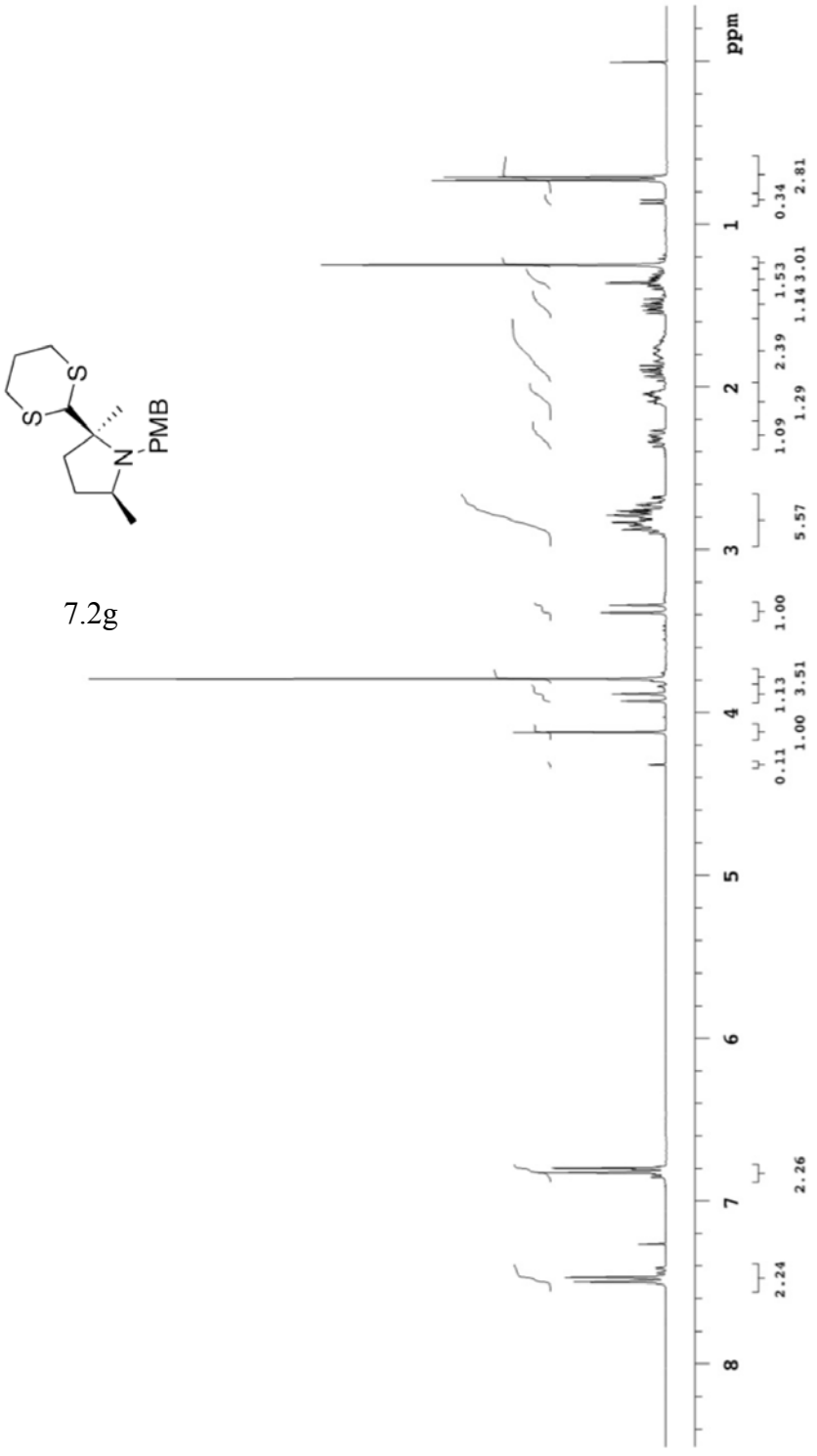
160
180
200
220


S
S
N
PMB
ppm
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2
3
4
5
6
7
8
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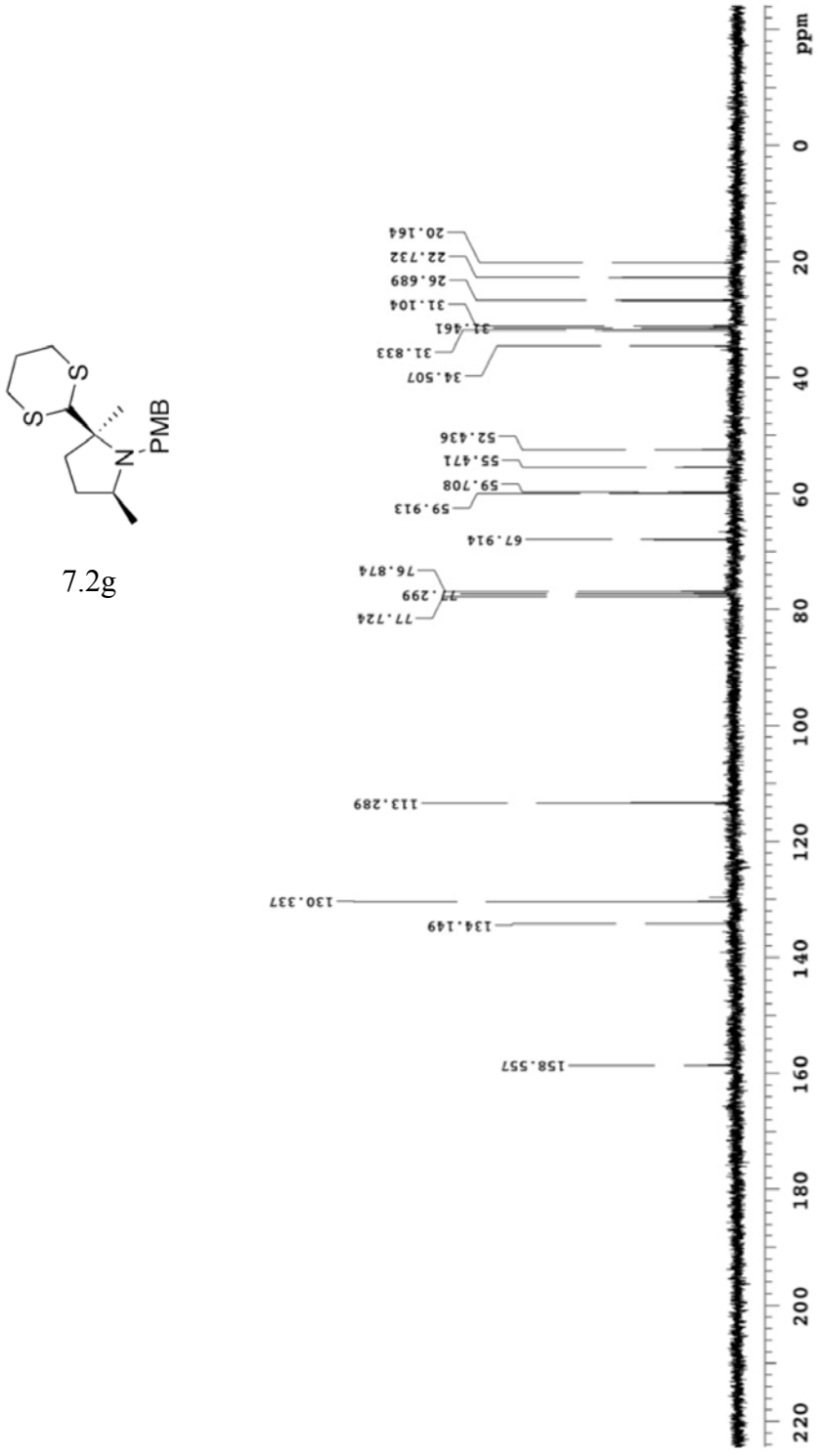
2.81
1.53
3.01
2.39
1.14
1.09
1.29
5.57
1.00
1.13
3.51
0.11
1.00
2.24
2.26

7.2g


S
S
N
PMB
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34.507
52.436
55.471
59.708
59.913
67.914
76.874
77.299
77.724
113.289
130.337
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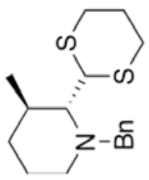
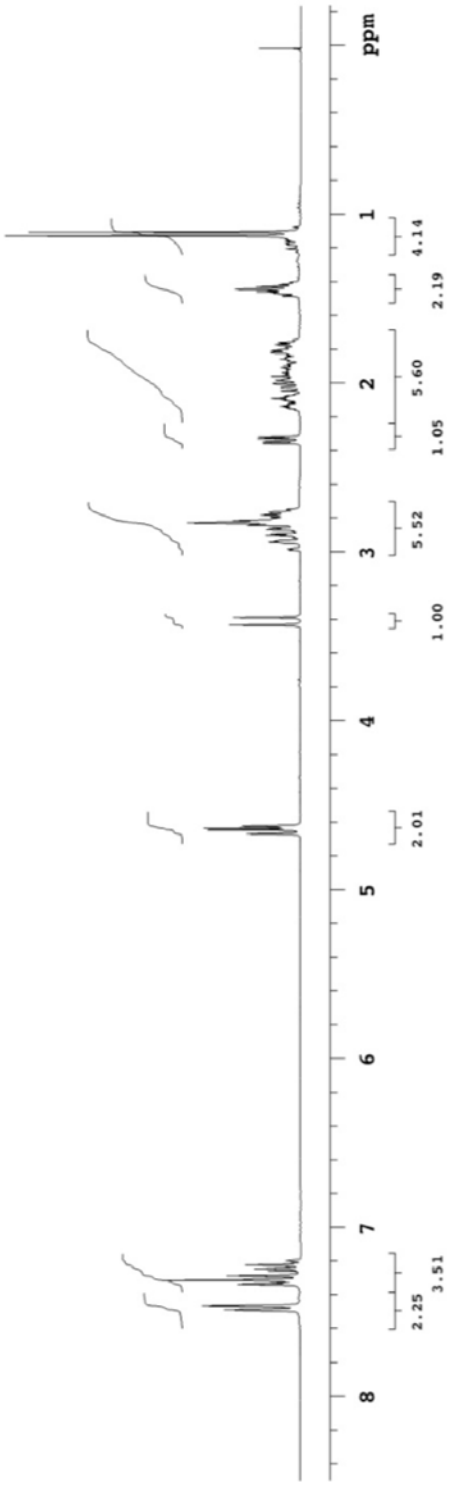
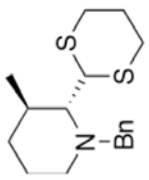
158.557
ppm
0
20
40
60
80
100
120
140
160
180
200
220

7.2g

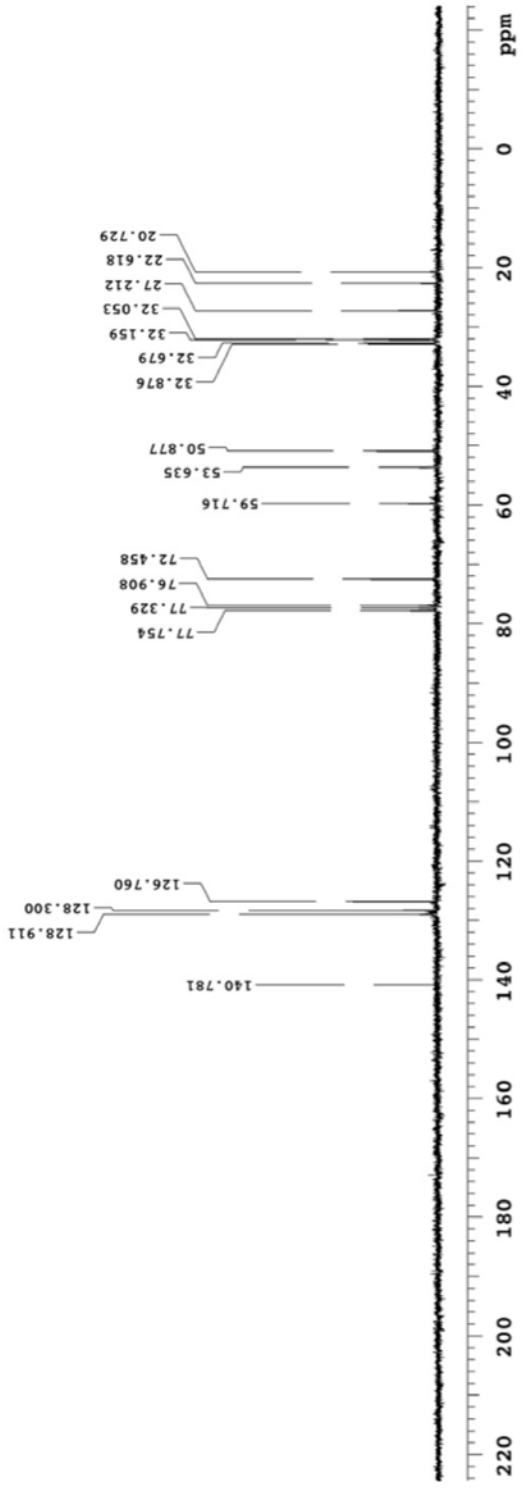


7.2i




S
S
N
Bn

7.2i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27.212
32.053
32.159
32.679
32.876
50.877
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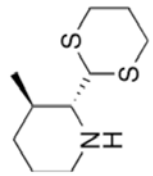
59.716
72.458
76.908
77.329
77.754
126.760
128.300
128.911
140.781
ppm
0
20
40
60
80
100
120
140
160
180
200
220



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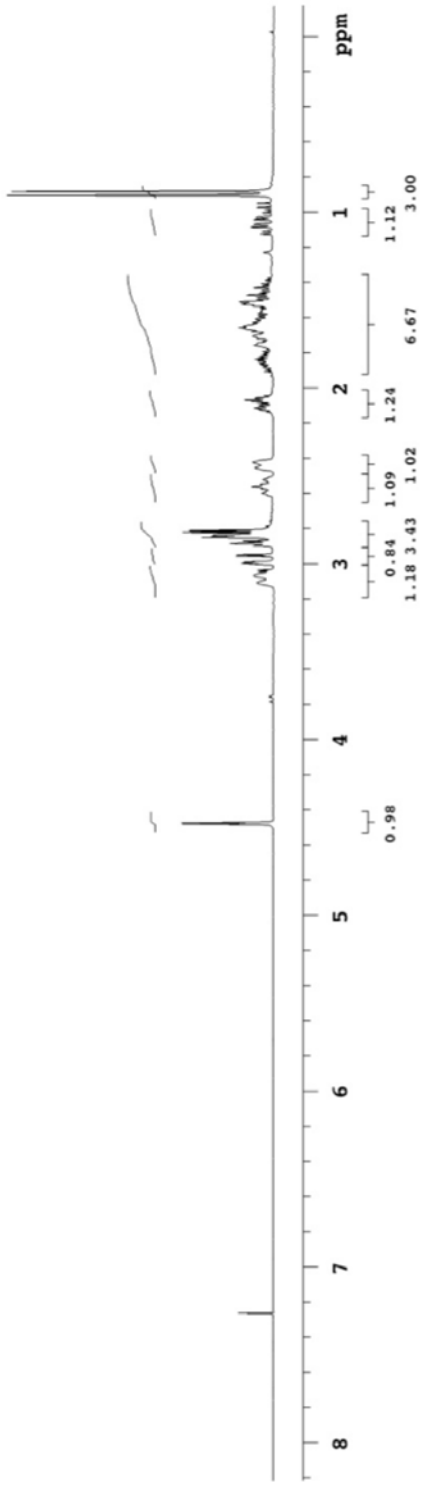

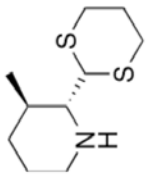
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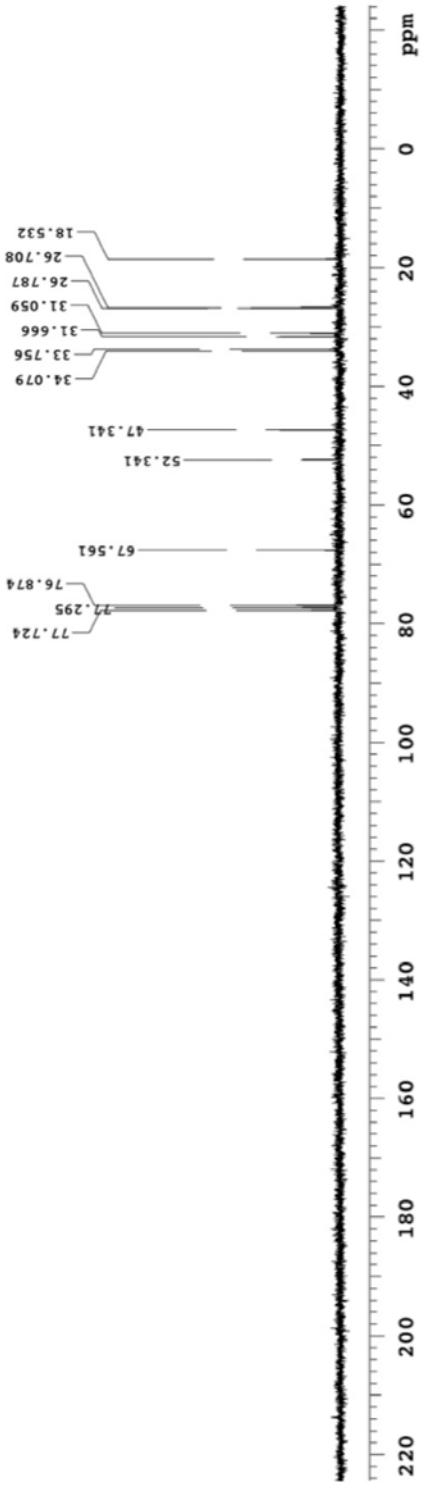
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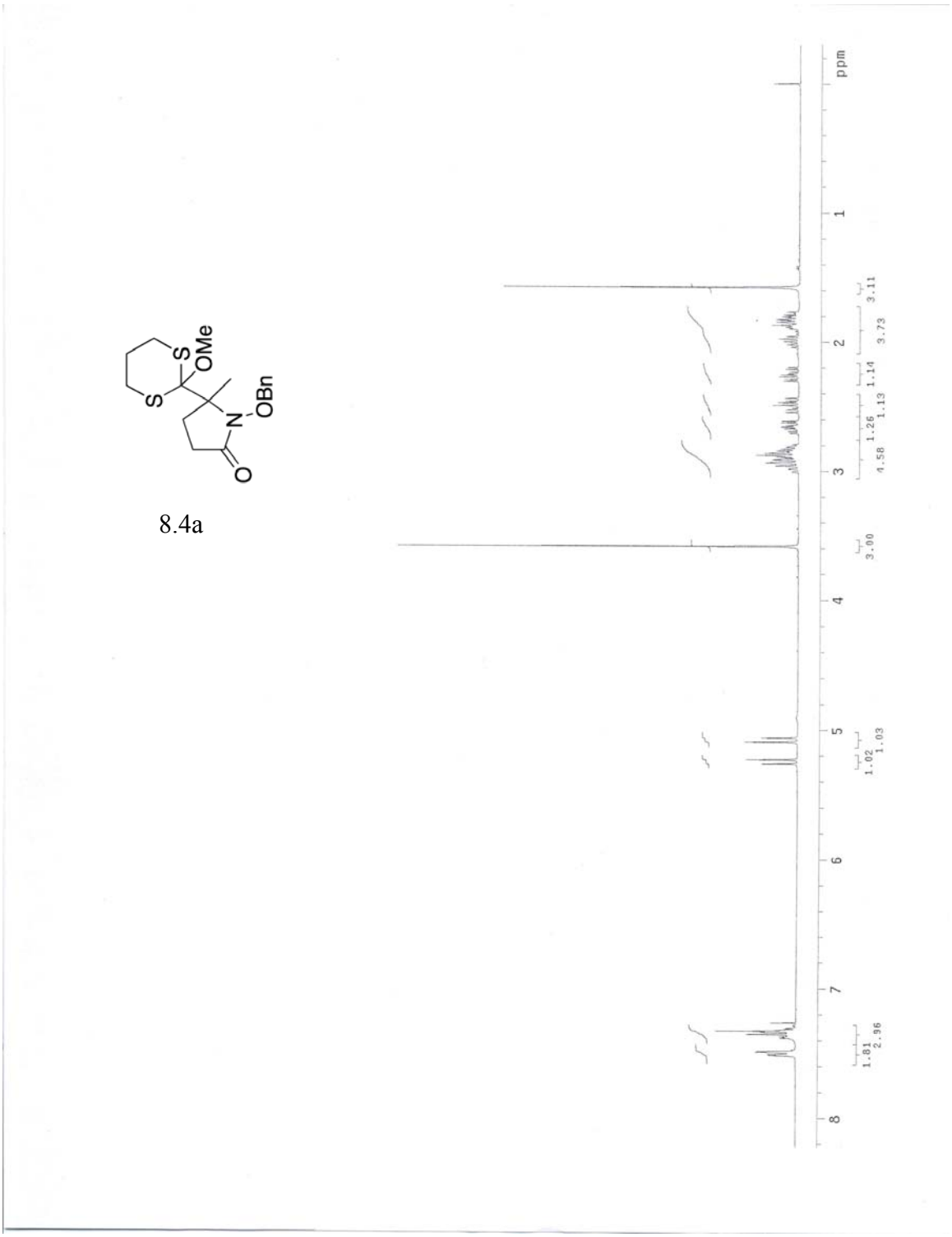
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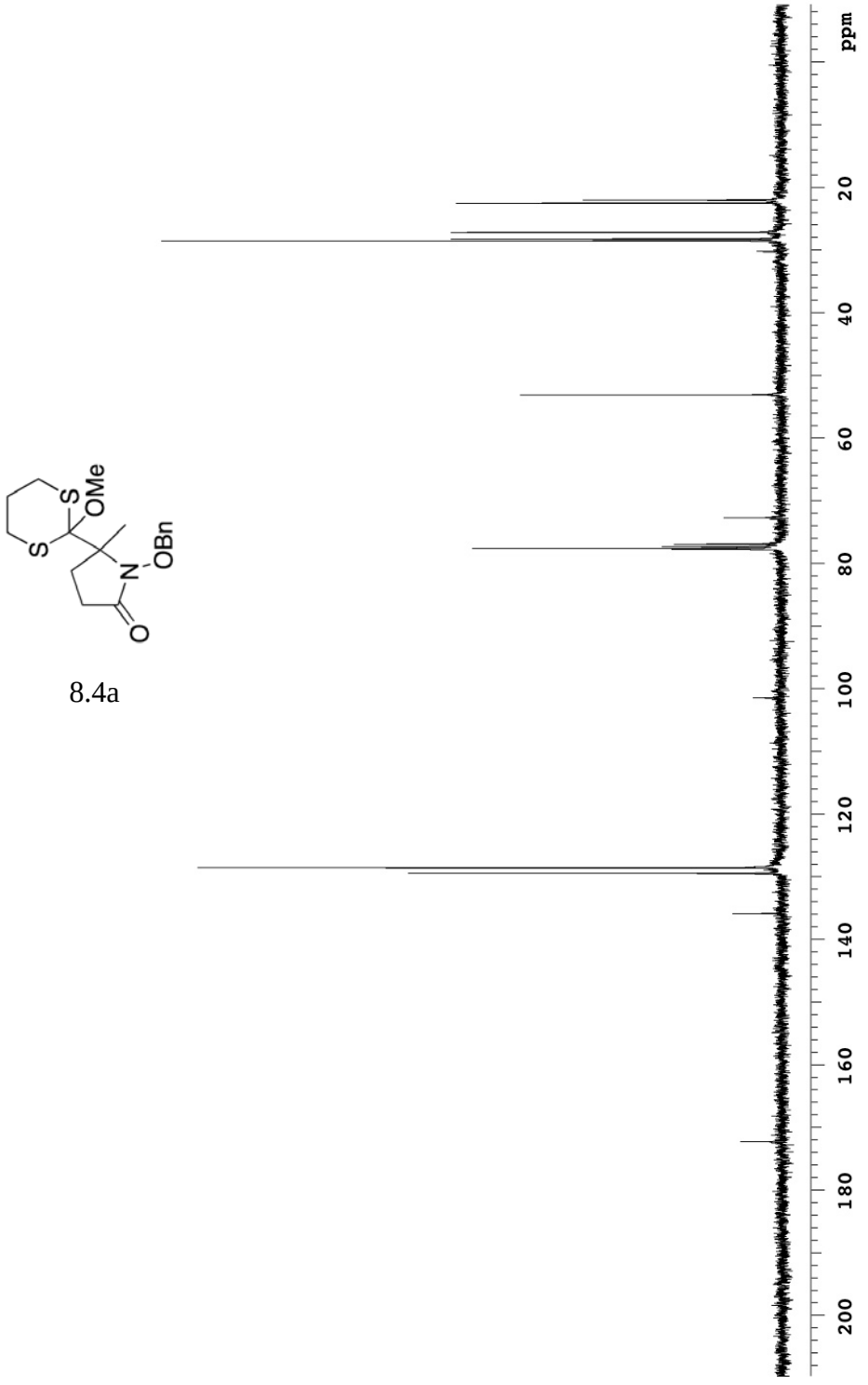

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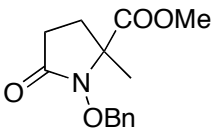

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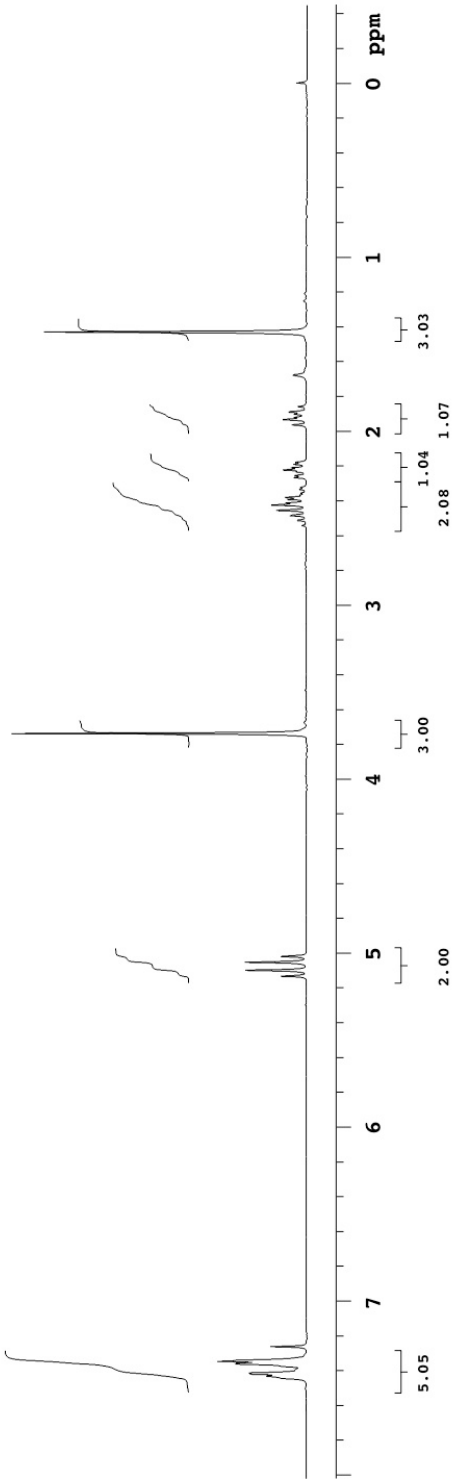

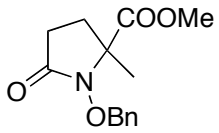

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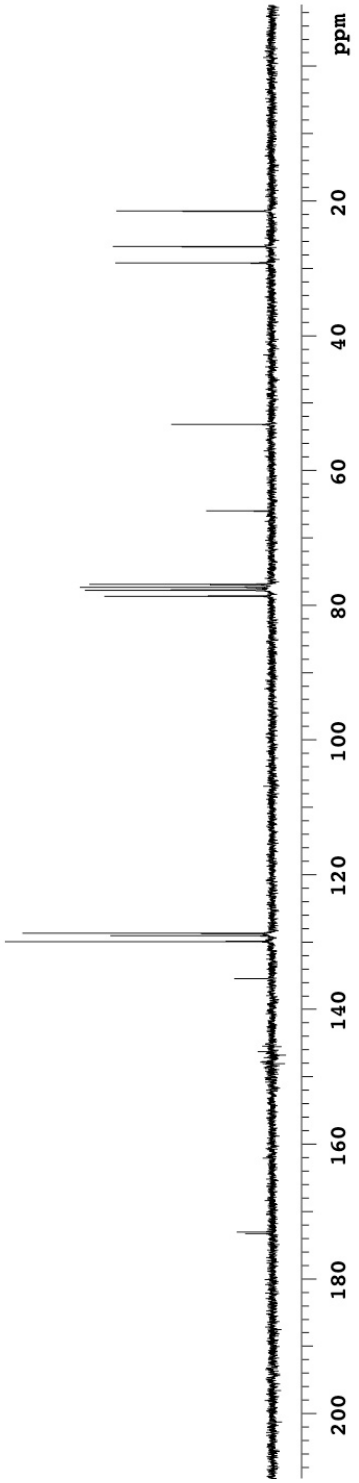

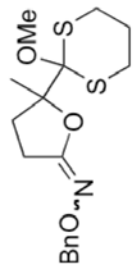

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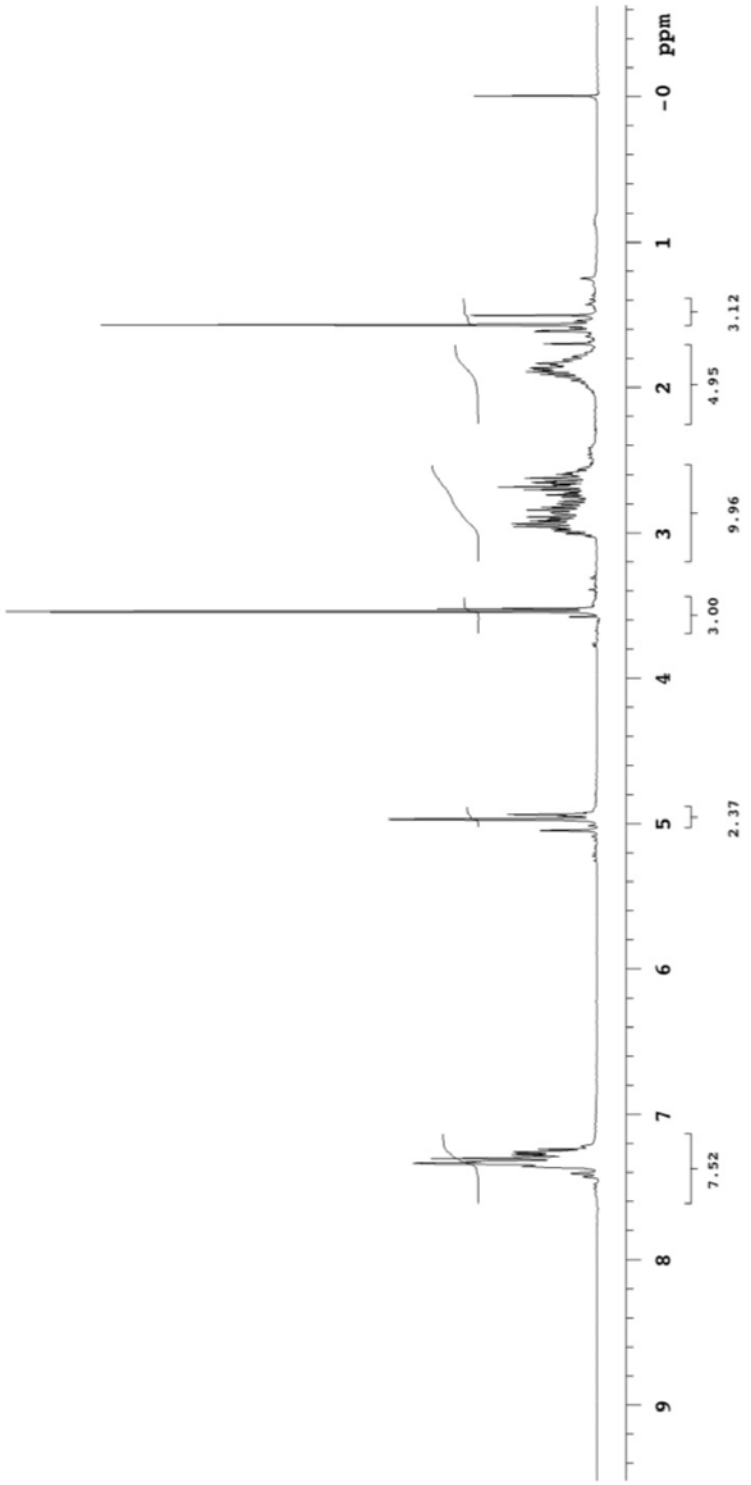

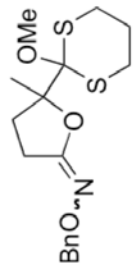

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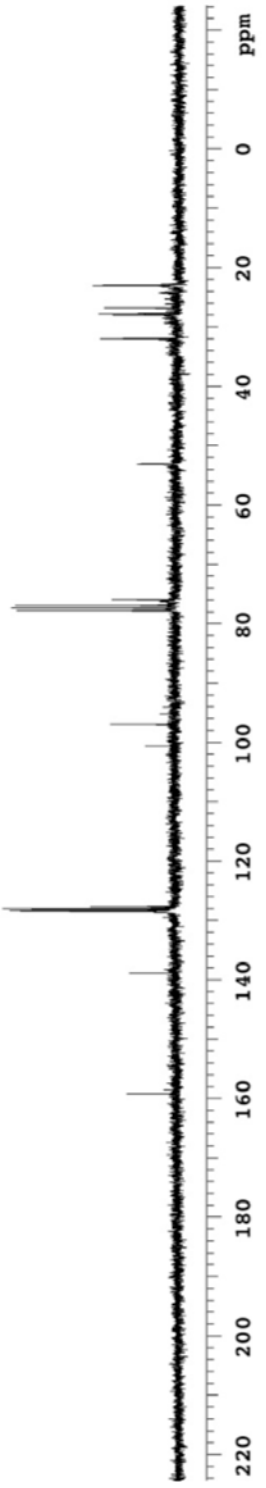

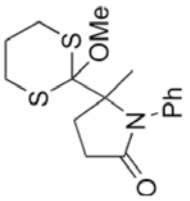

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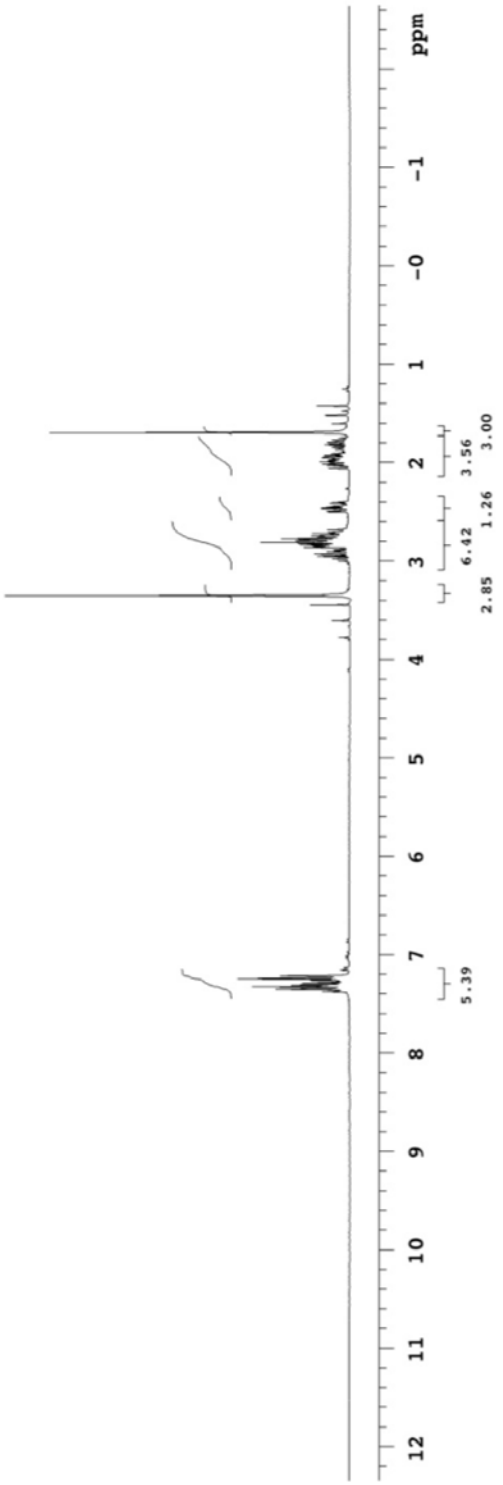

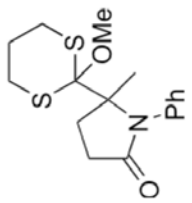

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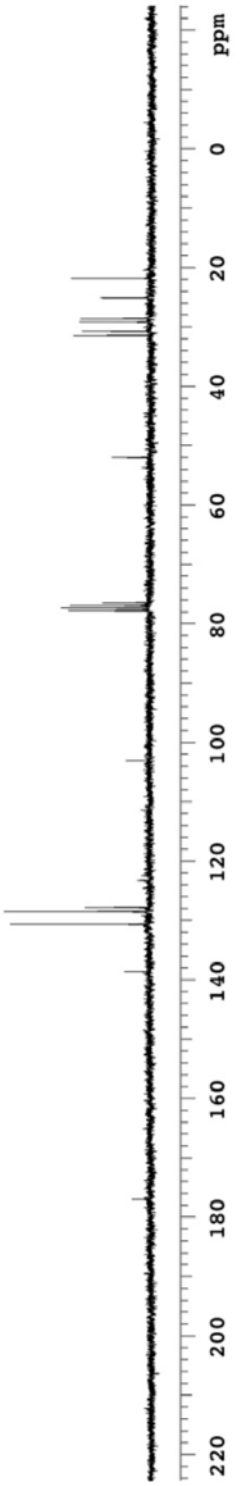

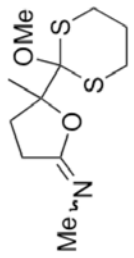

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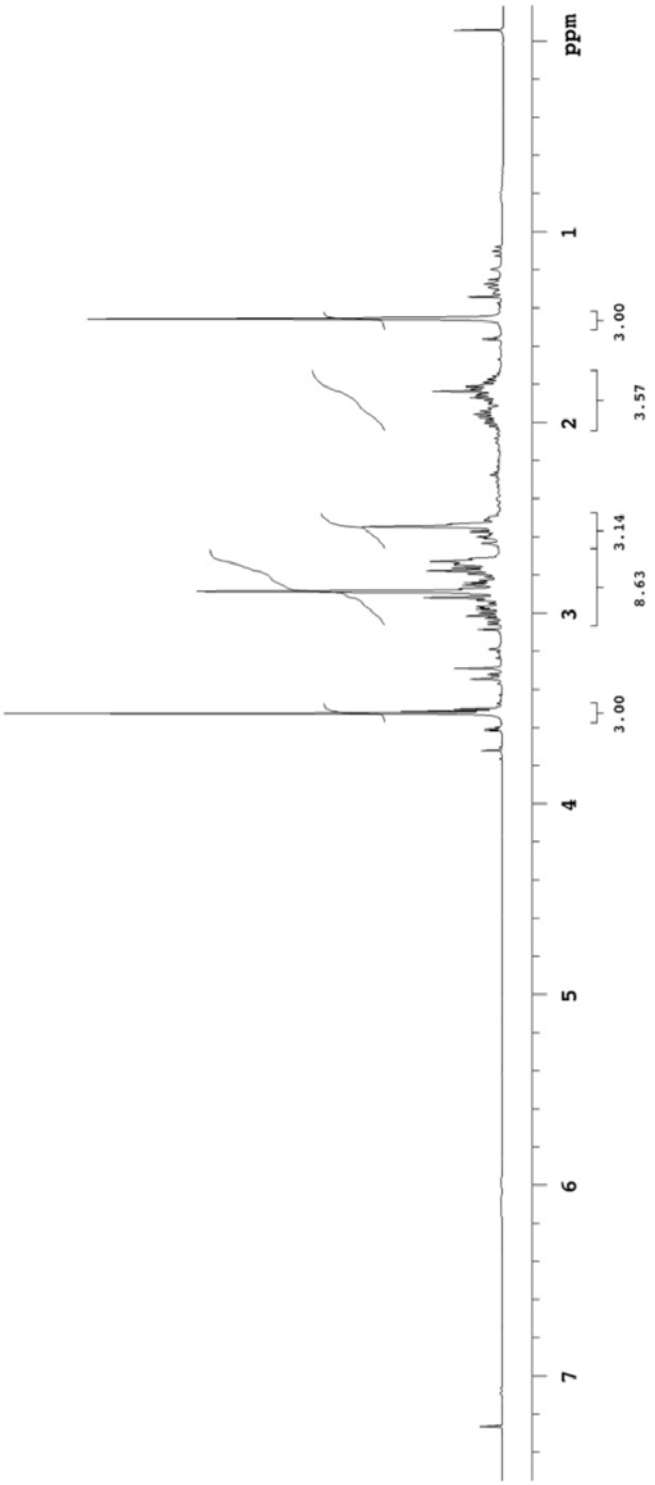

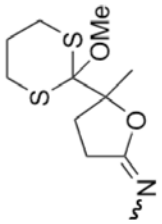

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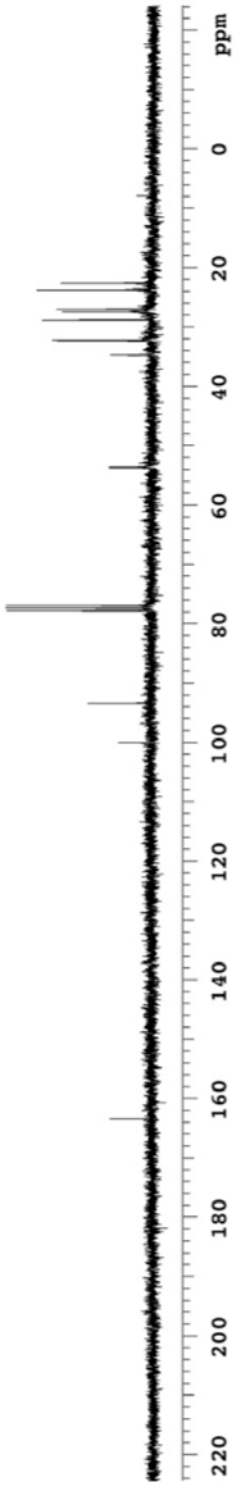

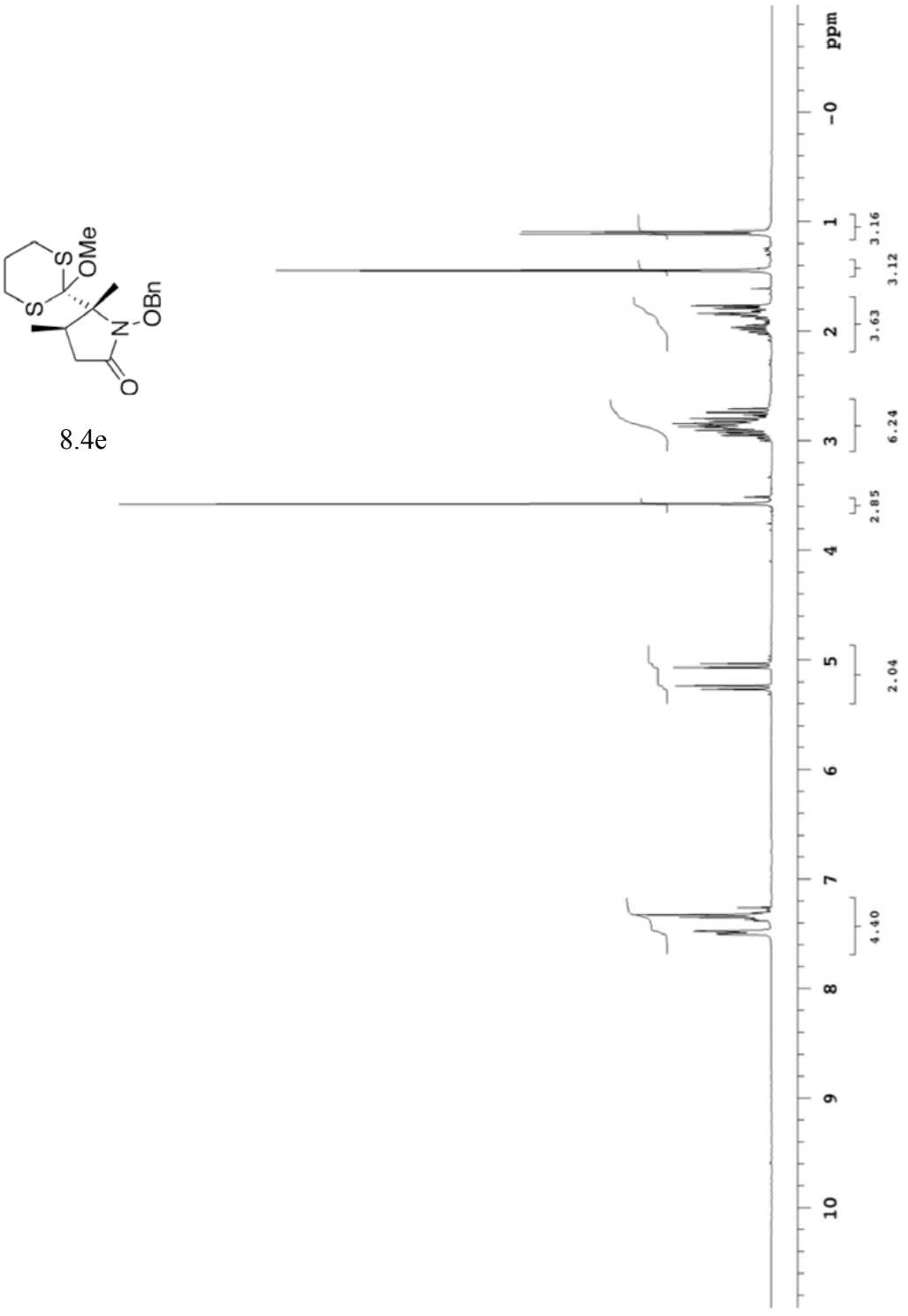

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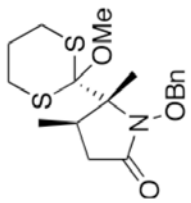

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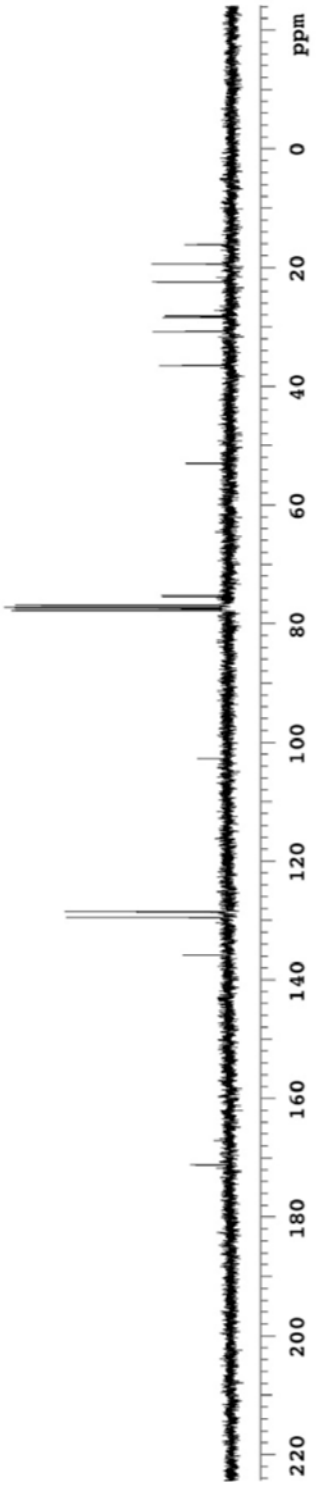

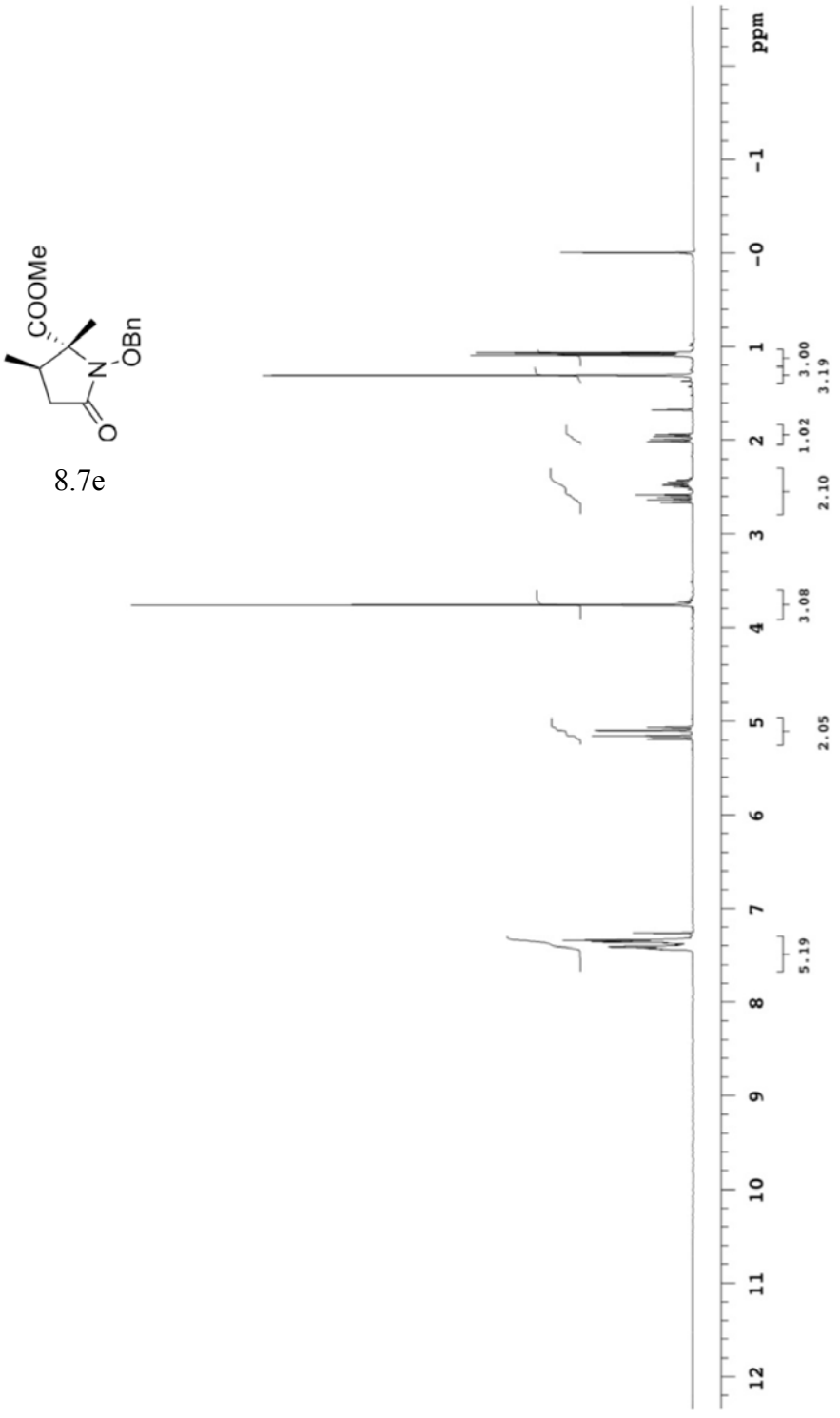
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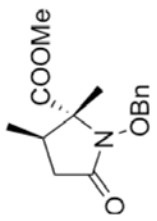

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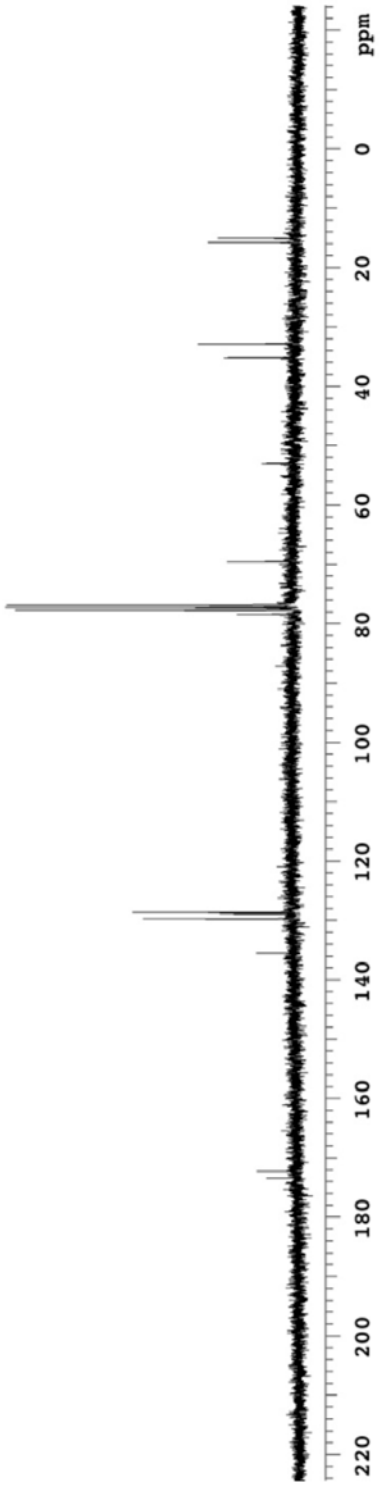

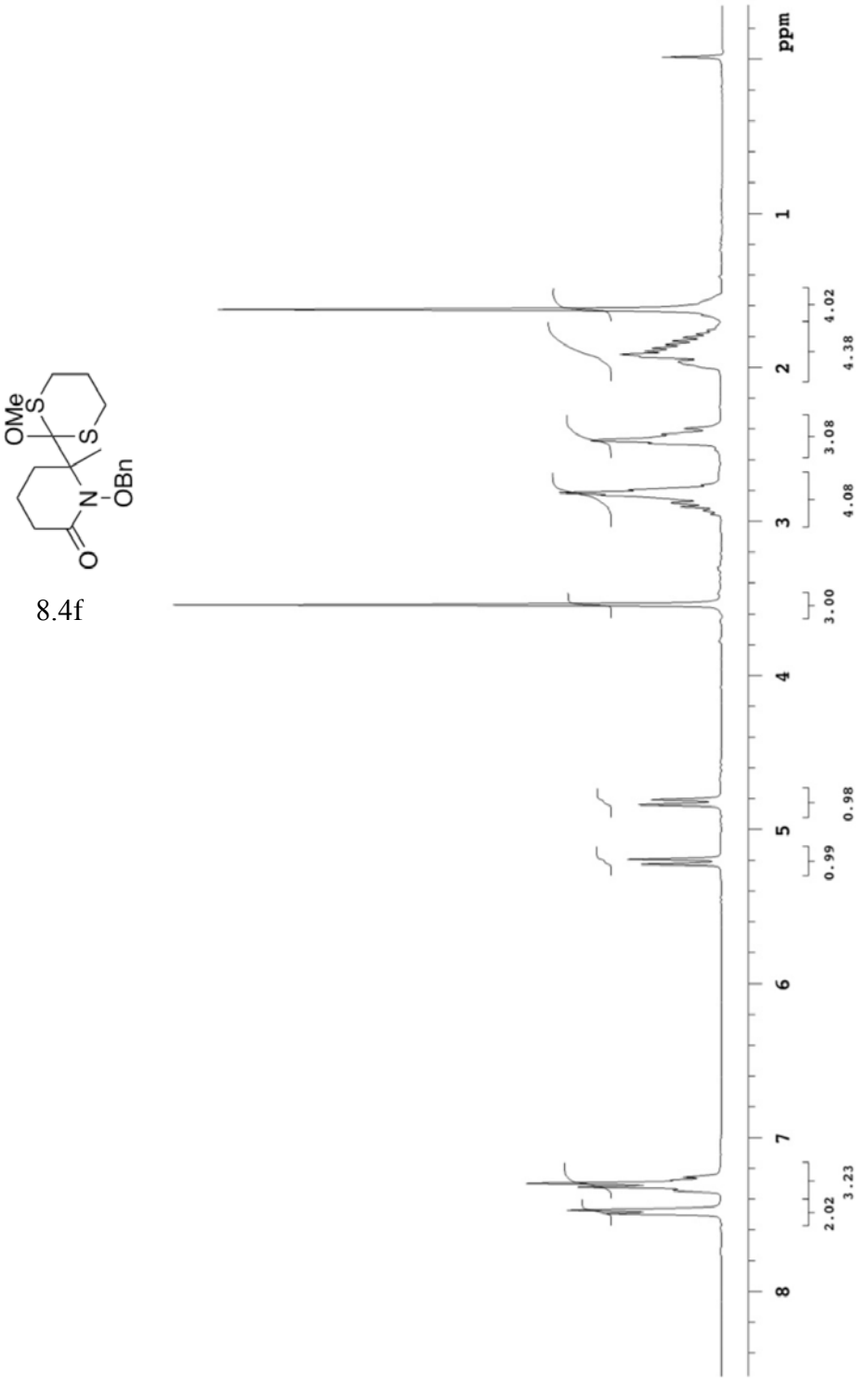

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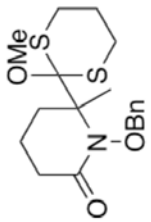

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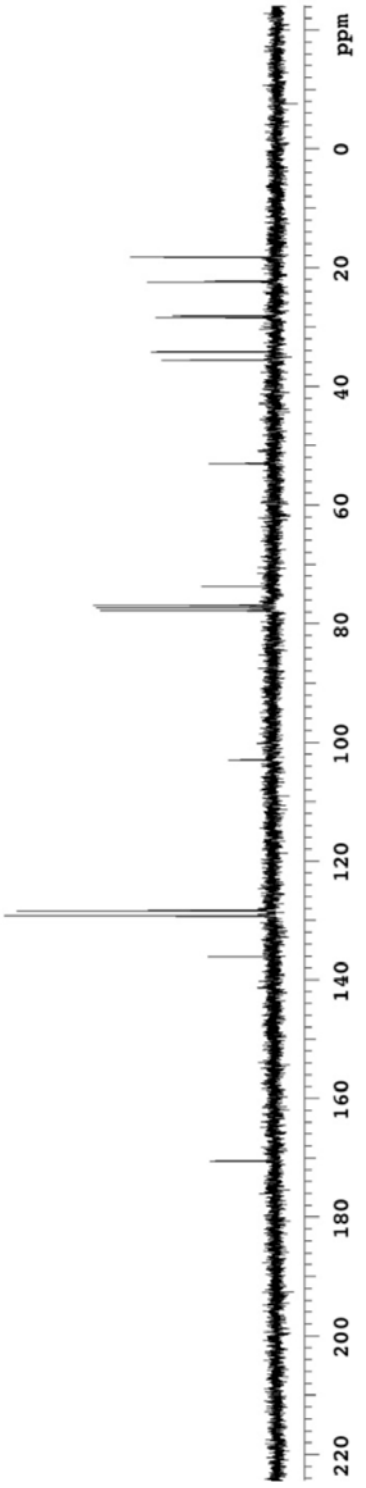

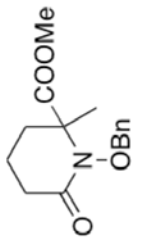

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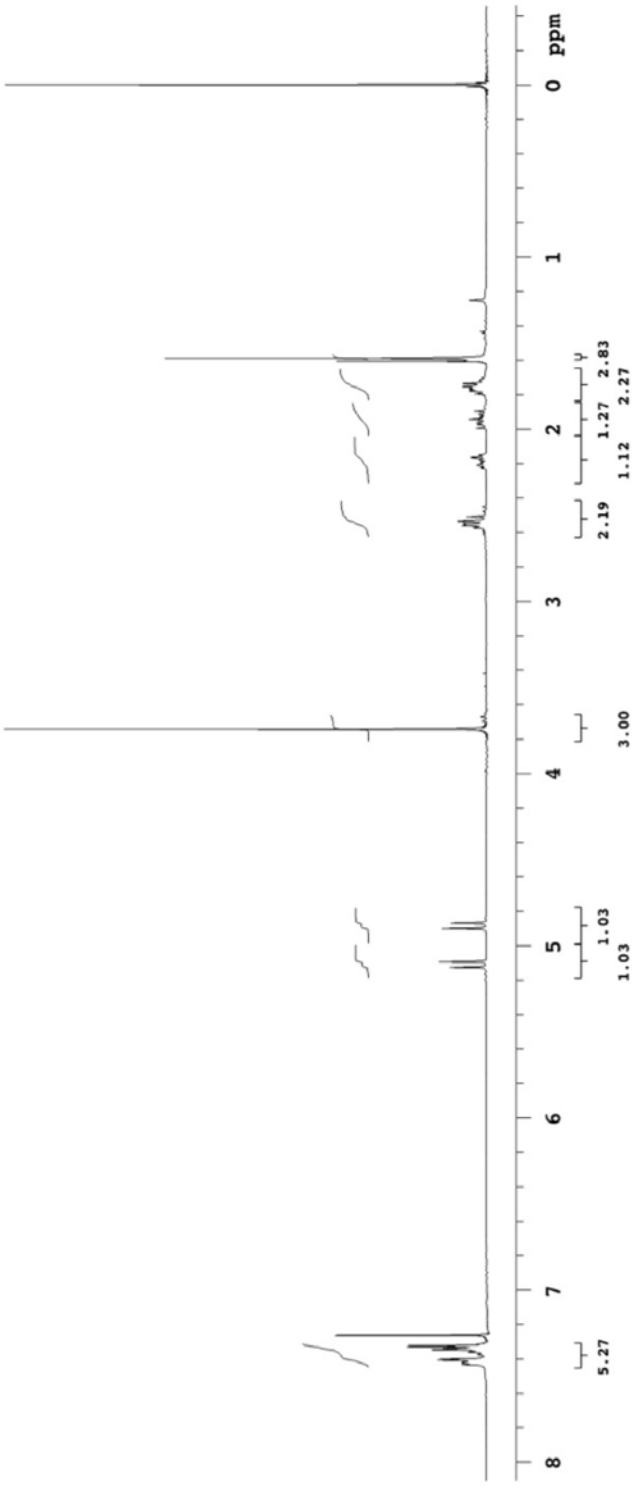

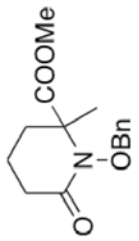

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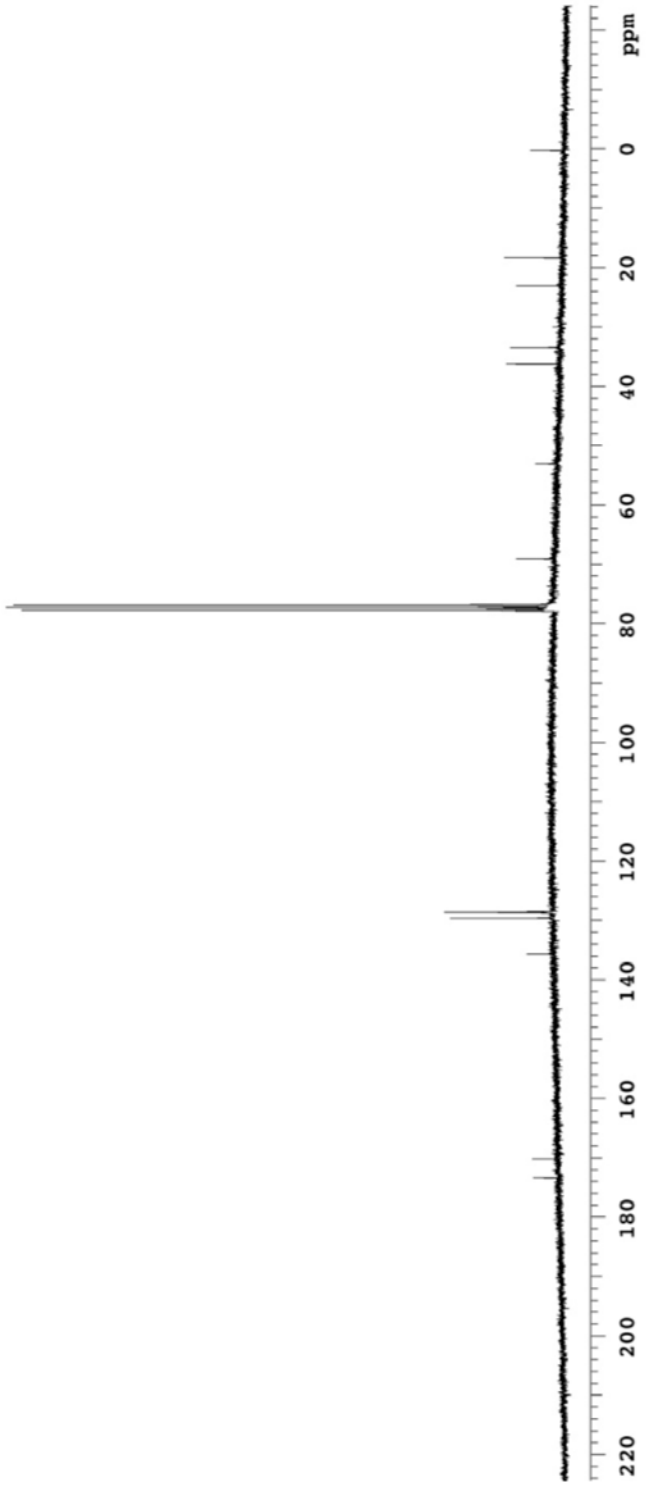

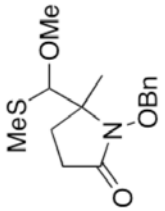

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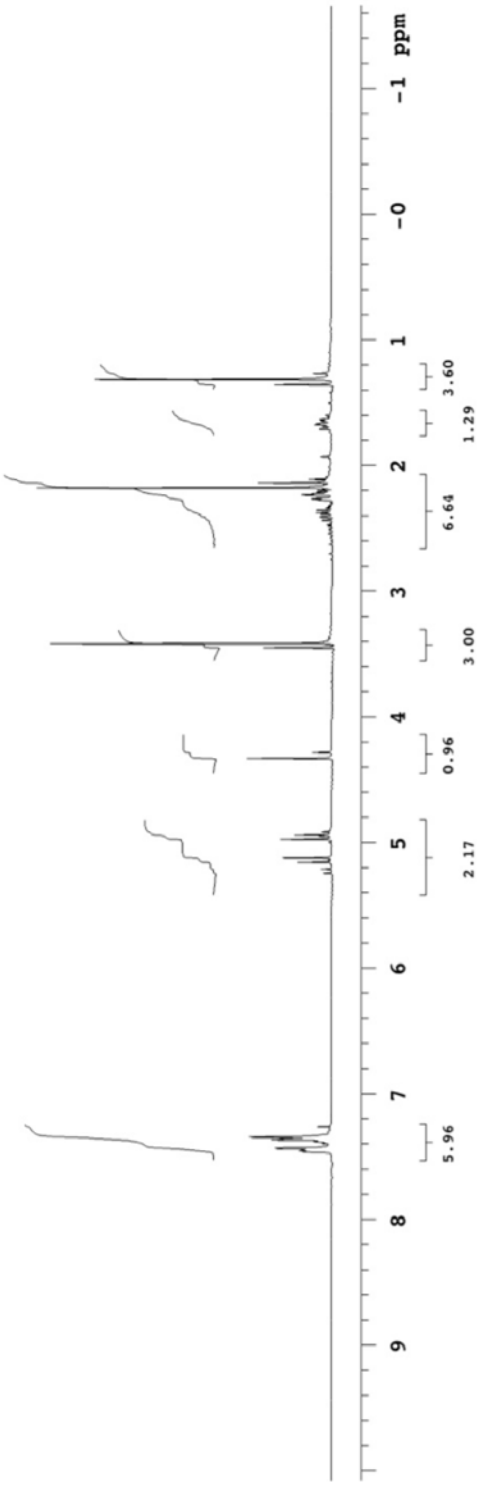

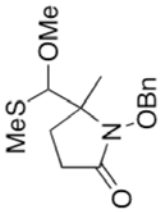

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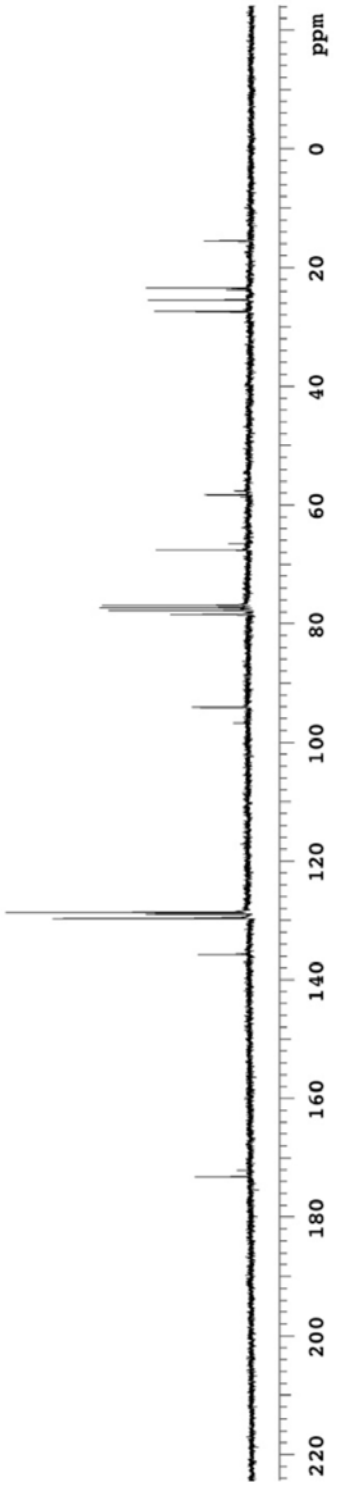

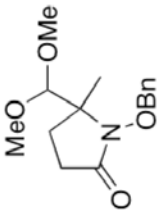
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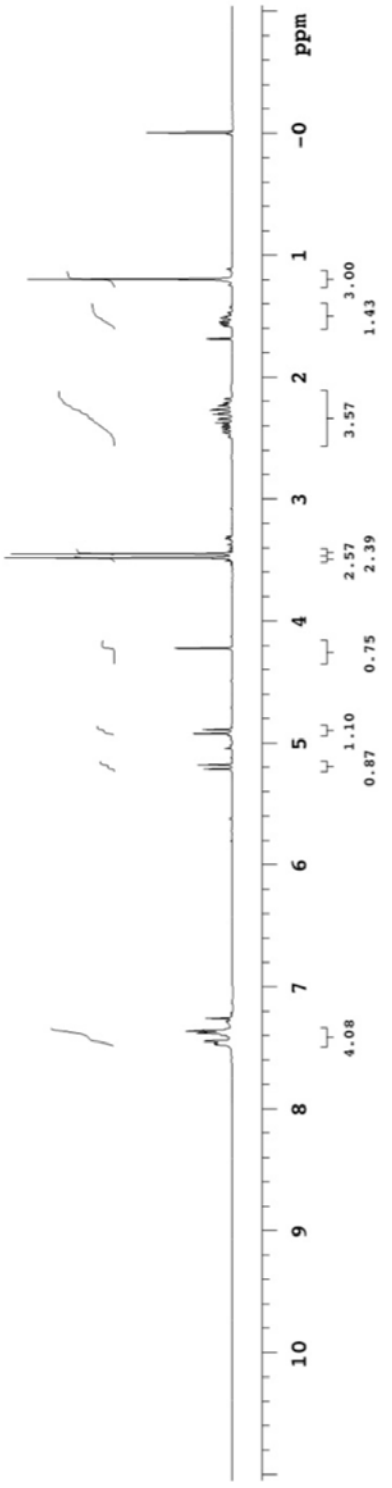
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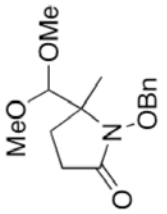

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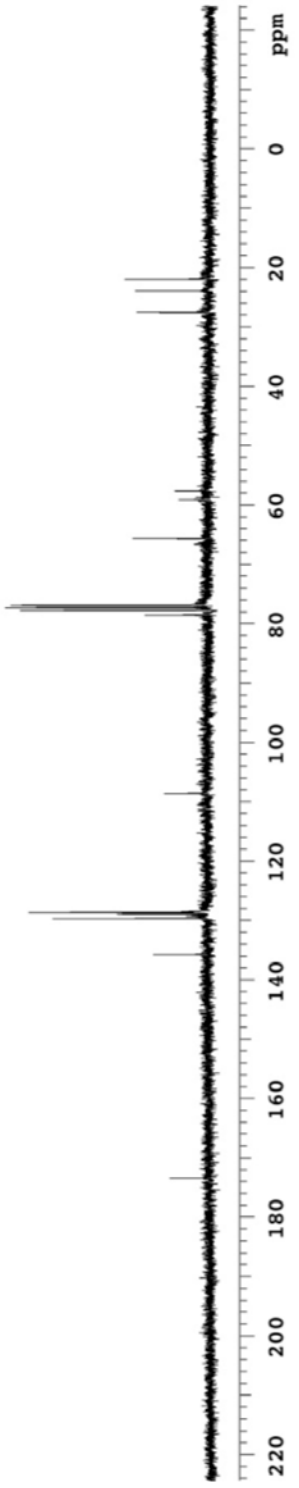

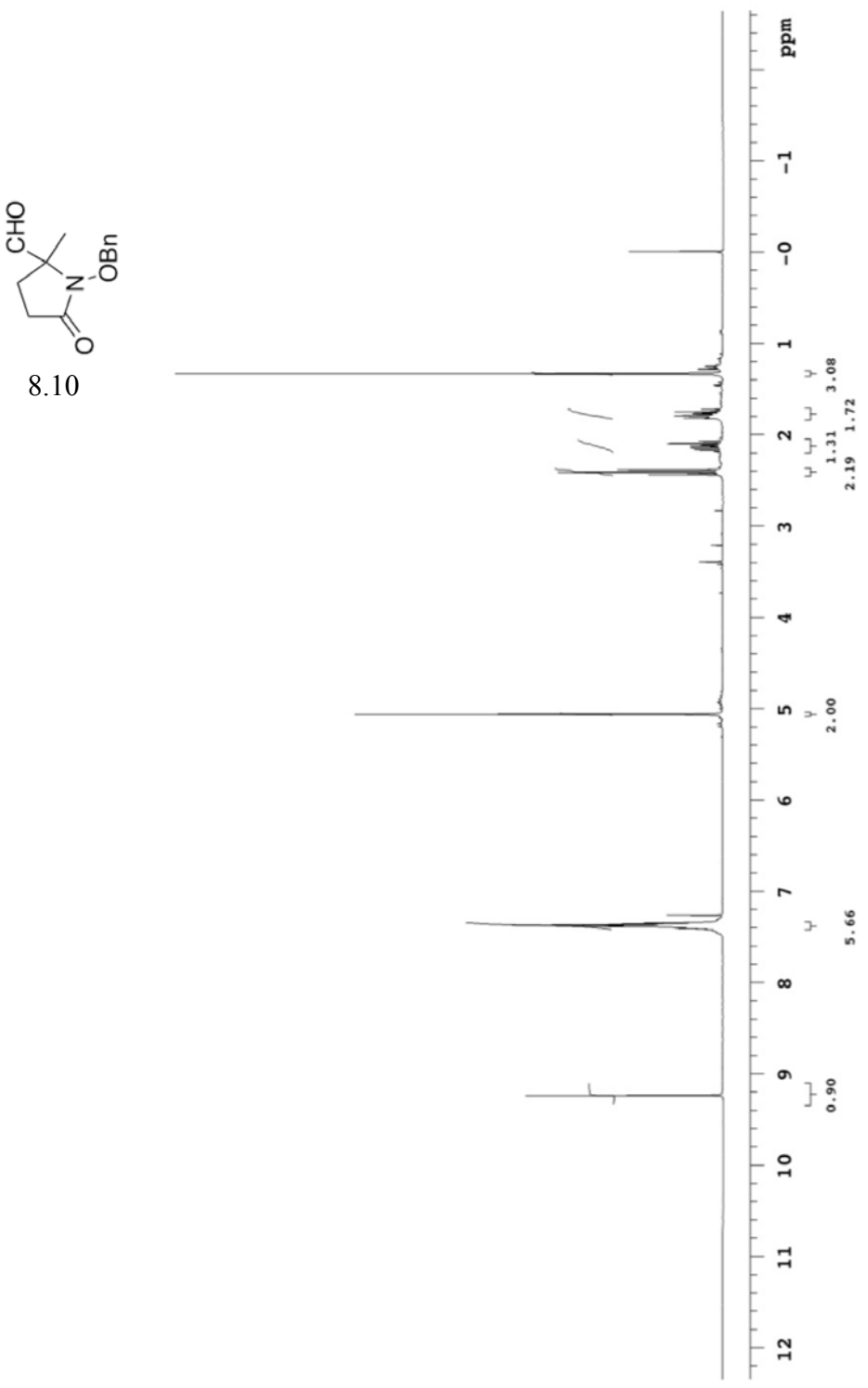
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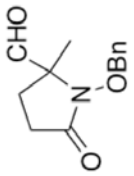

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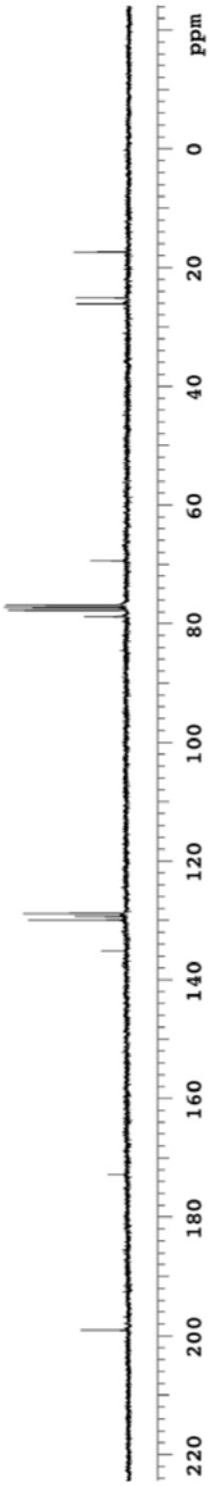

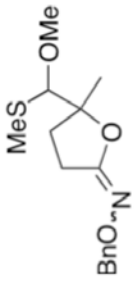

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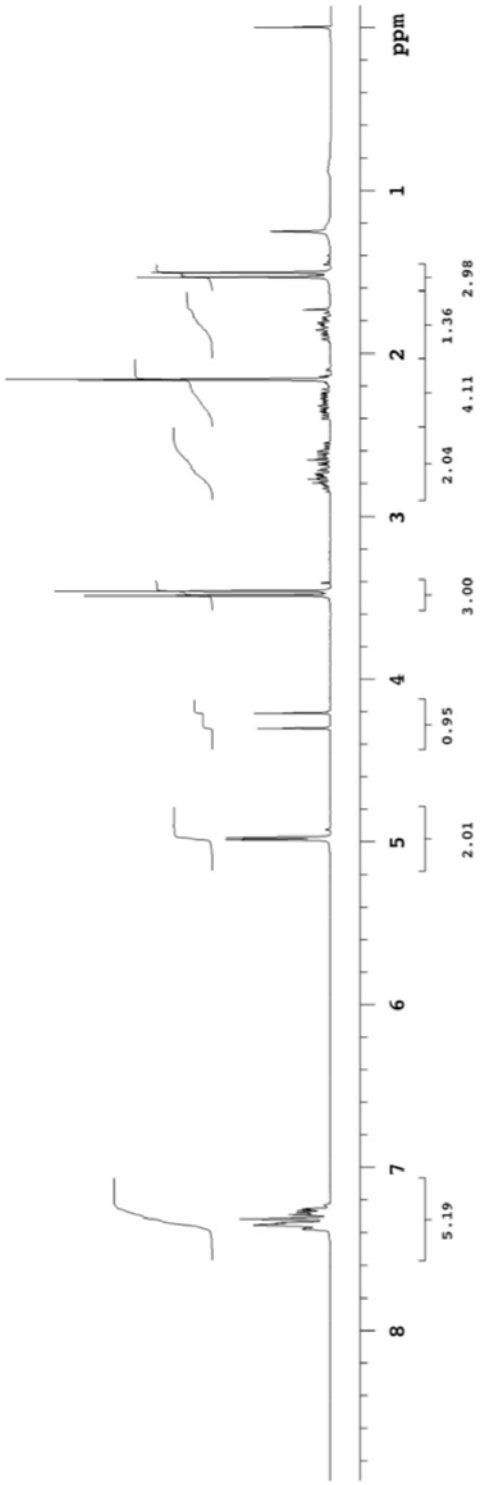

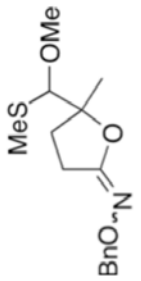

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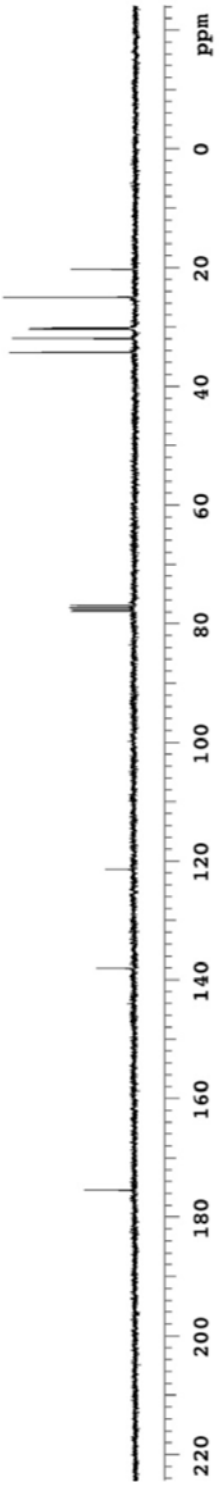

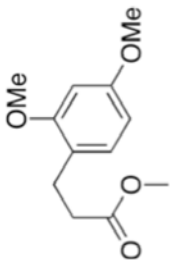

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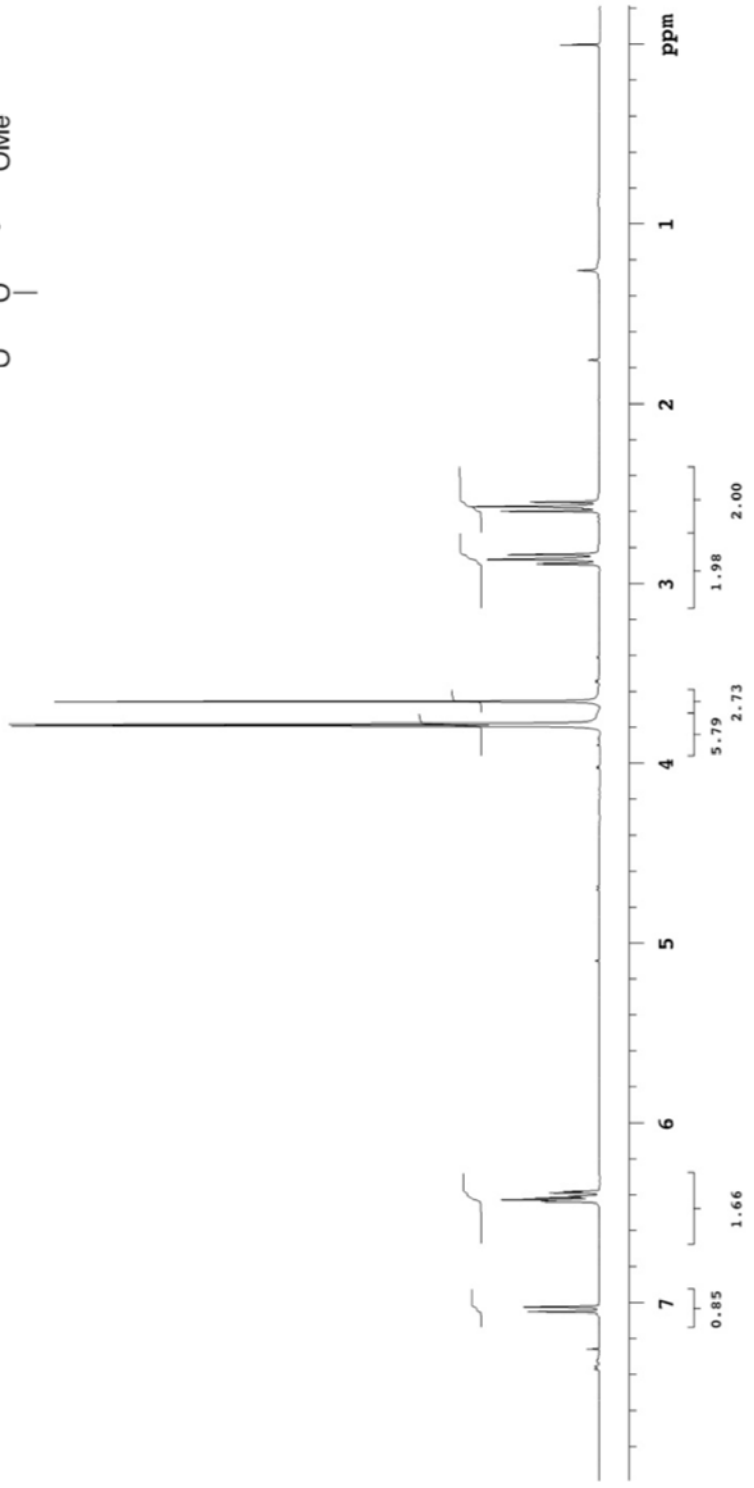

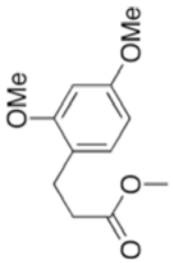

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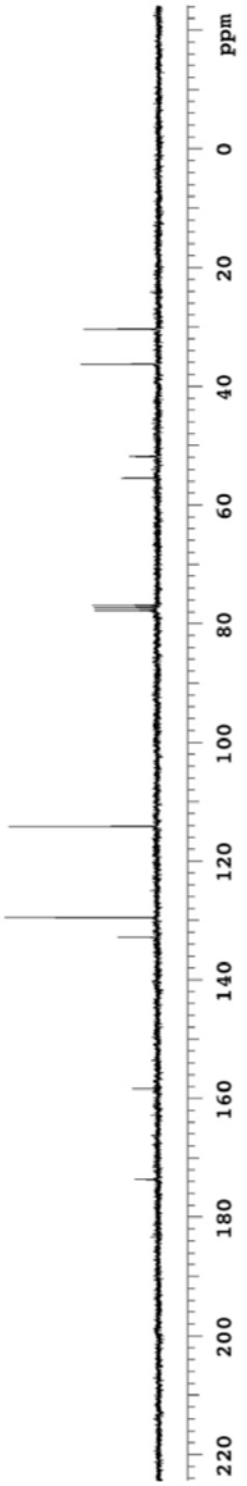

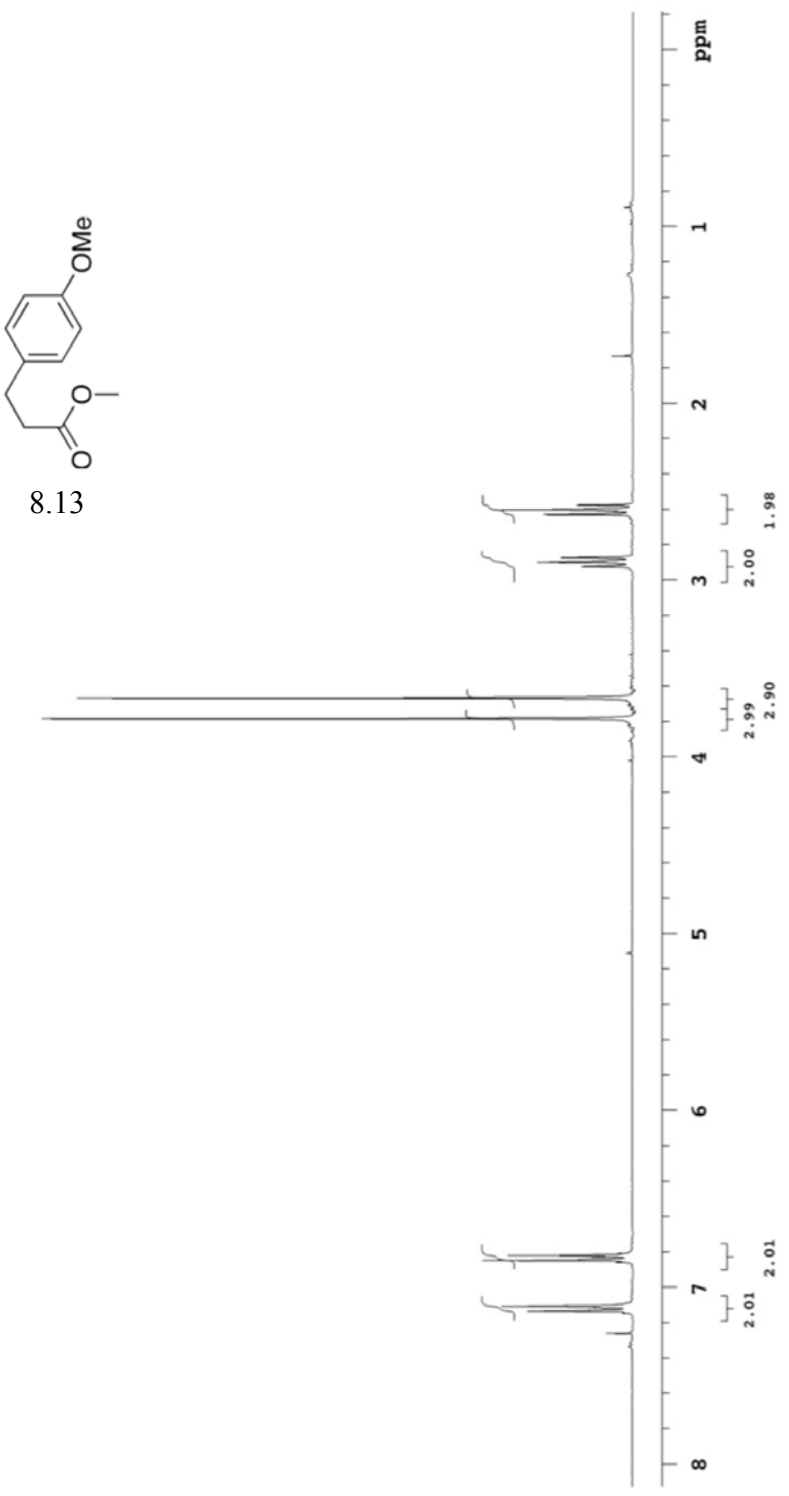

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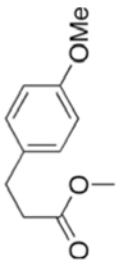

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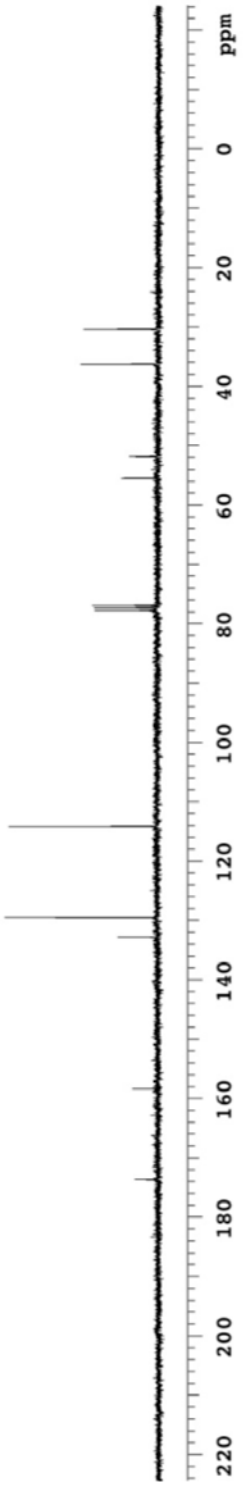

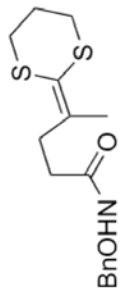
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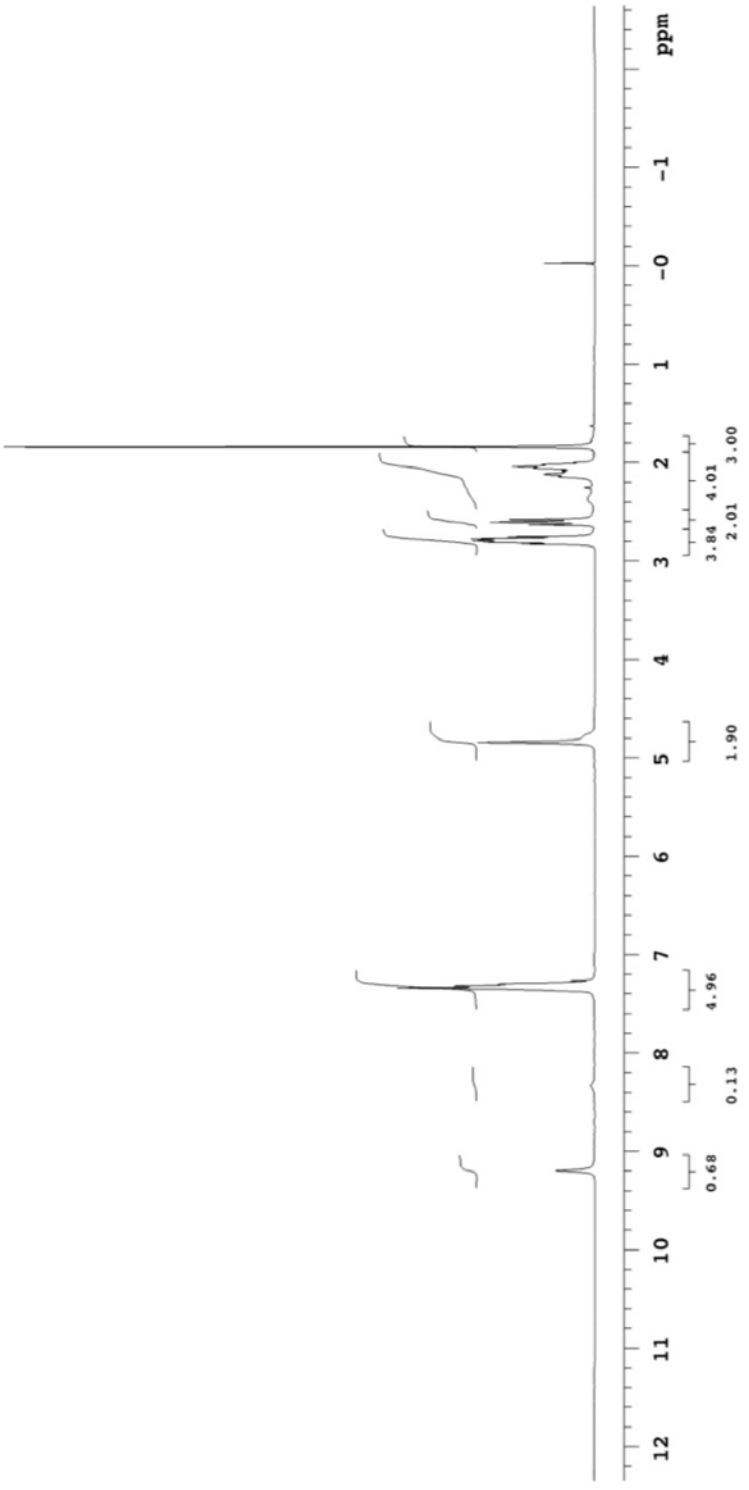
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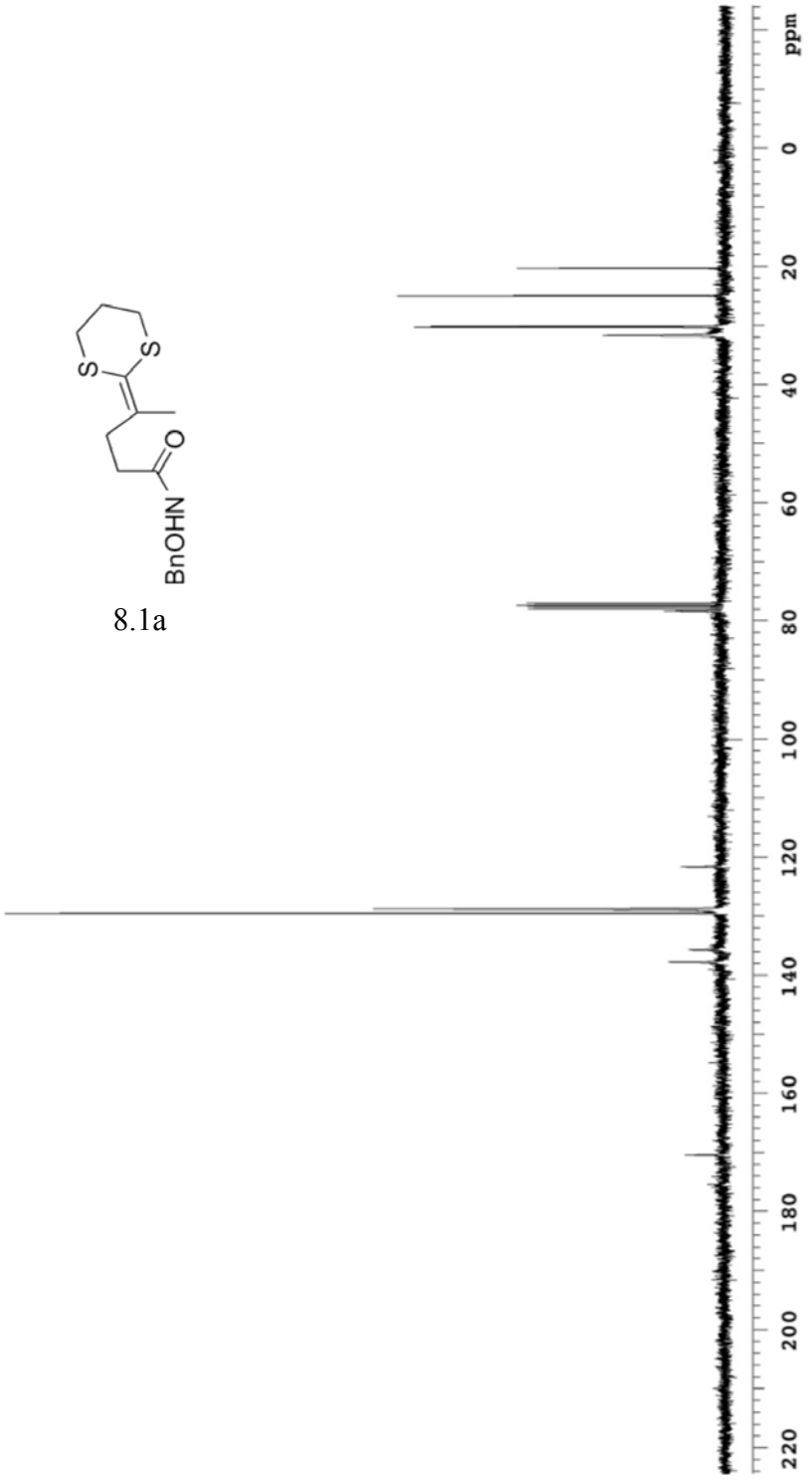

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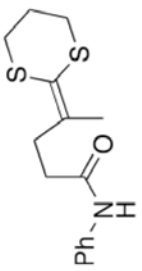

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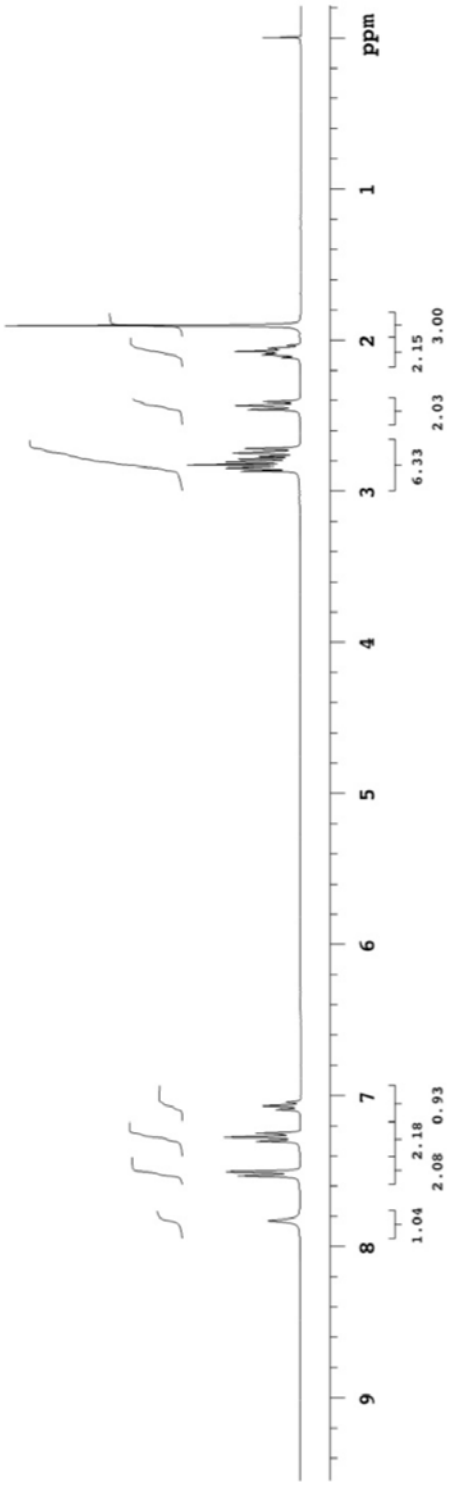

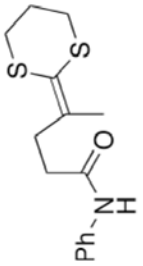

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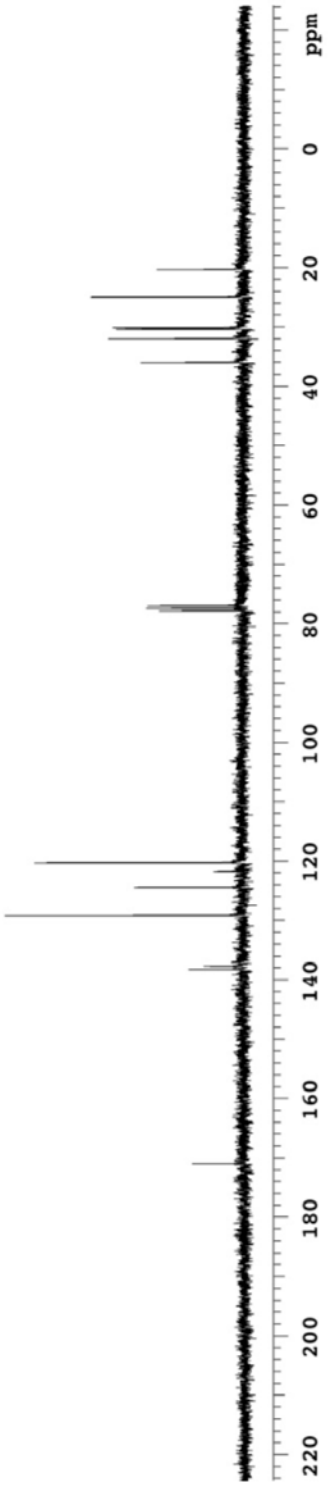

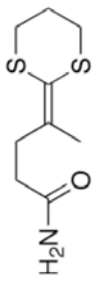

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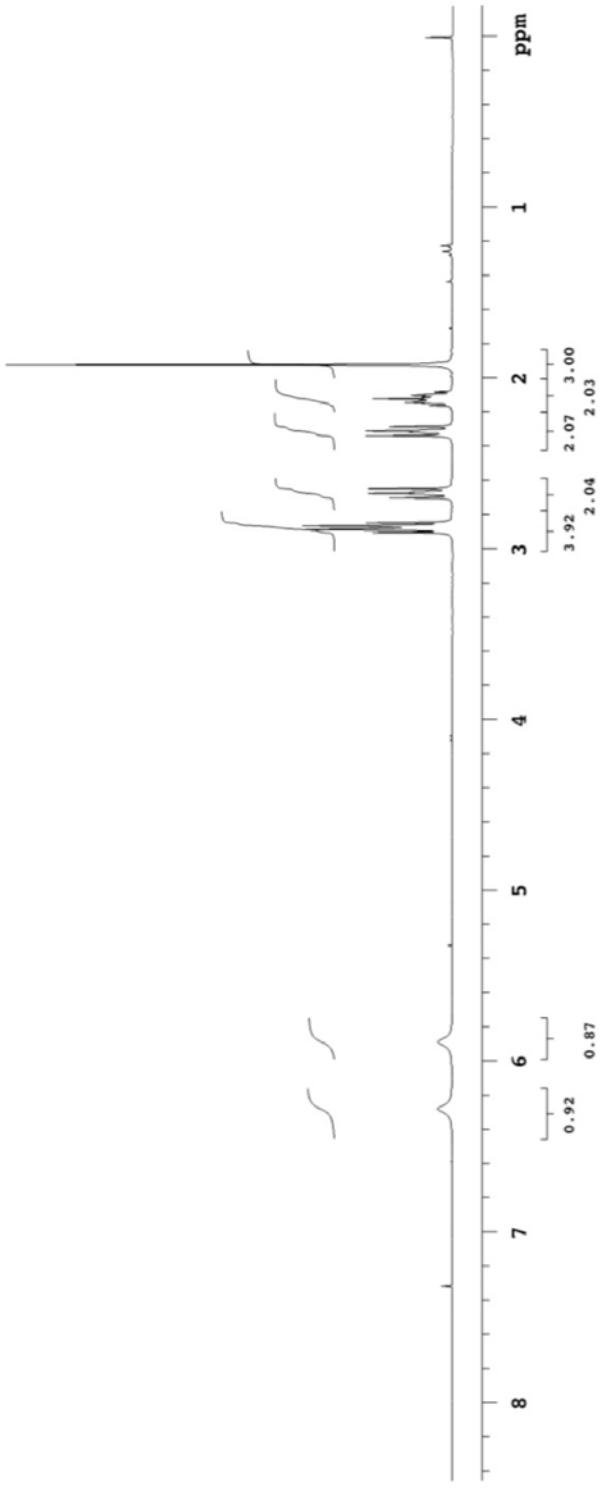

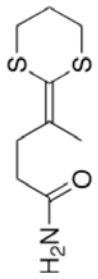

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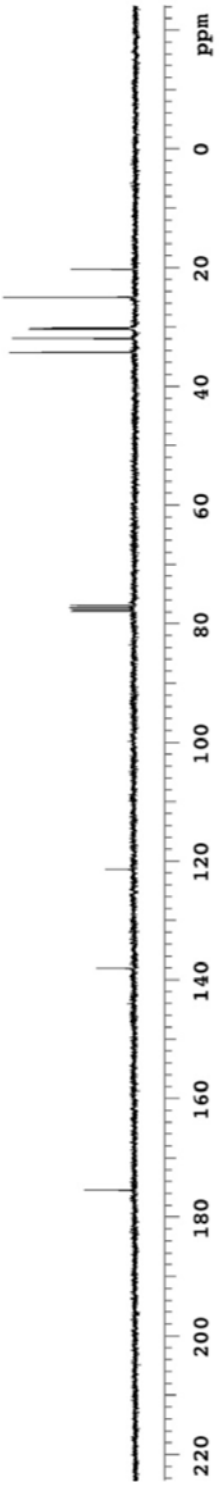

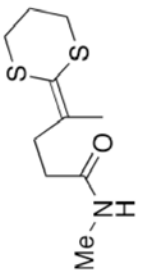

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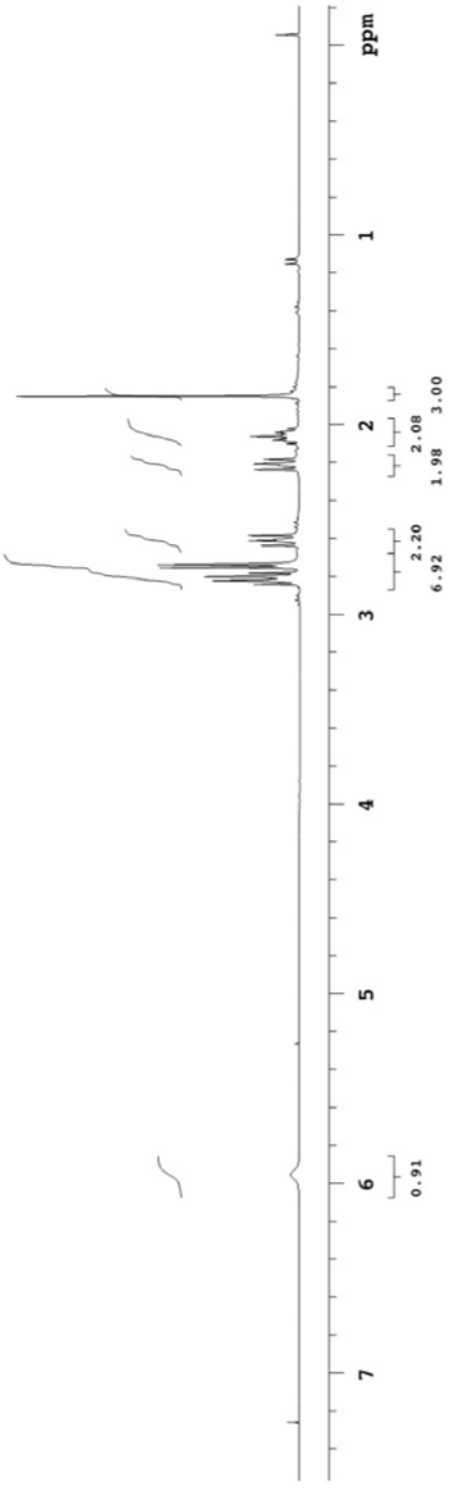

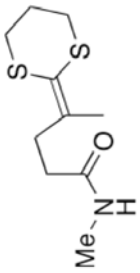

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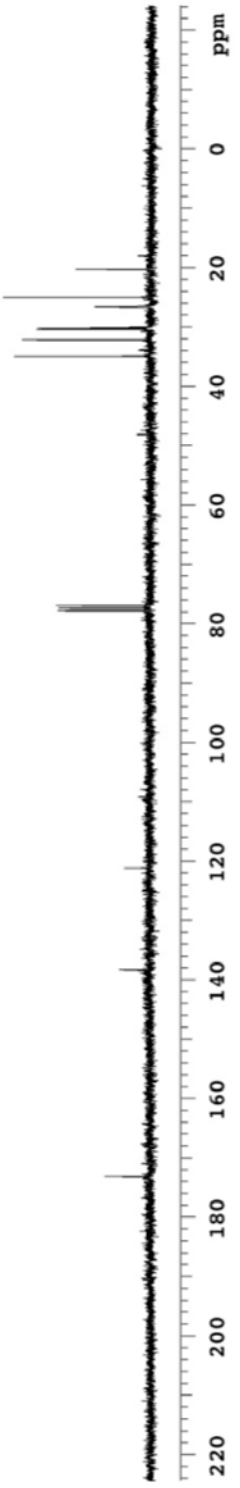

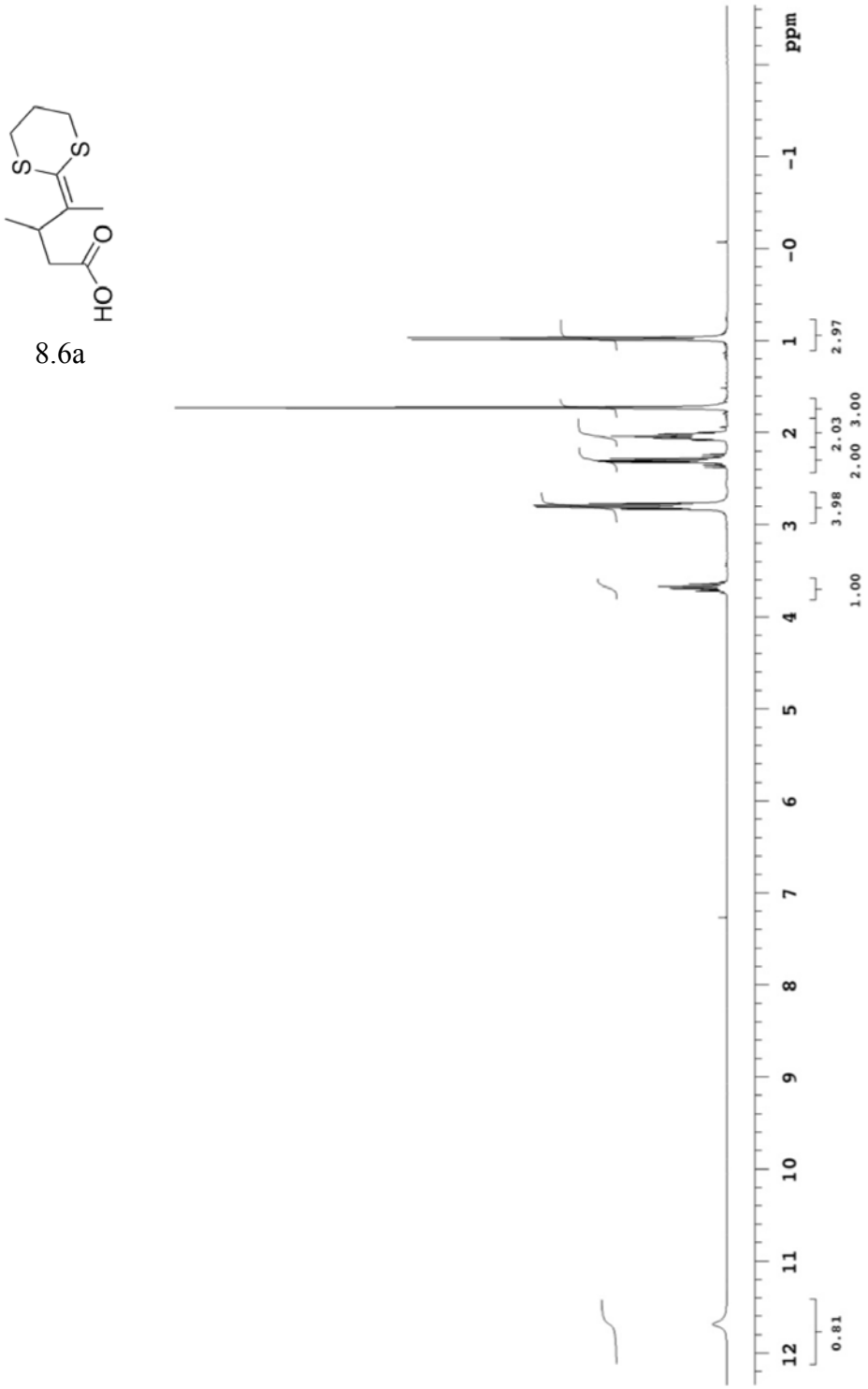

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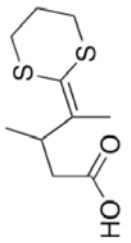

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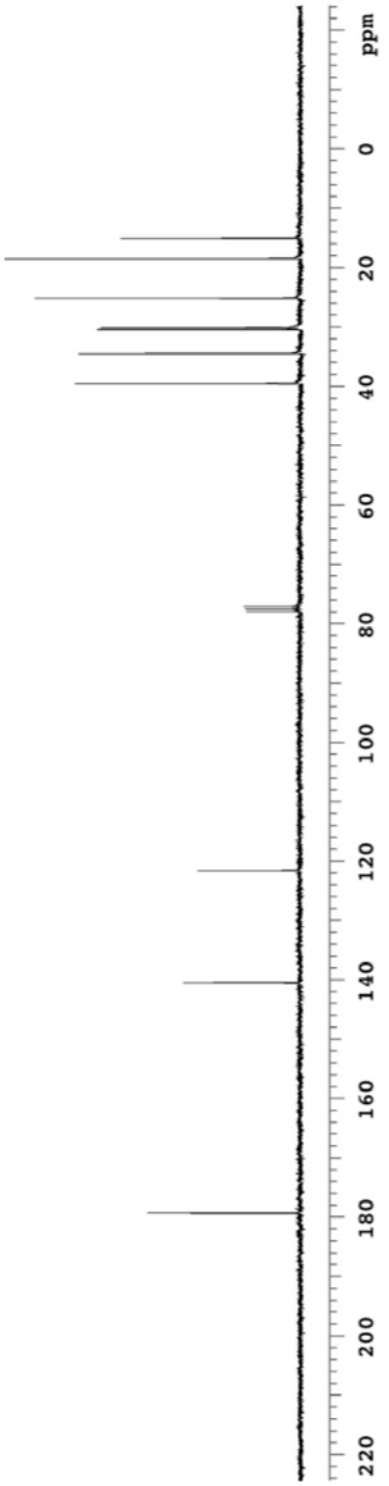

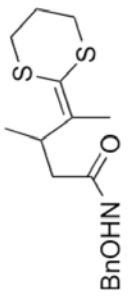
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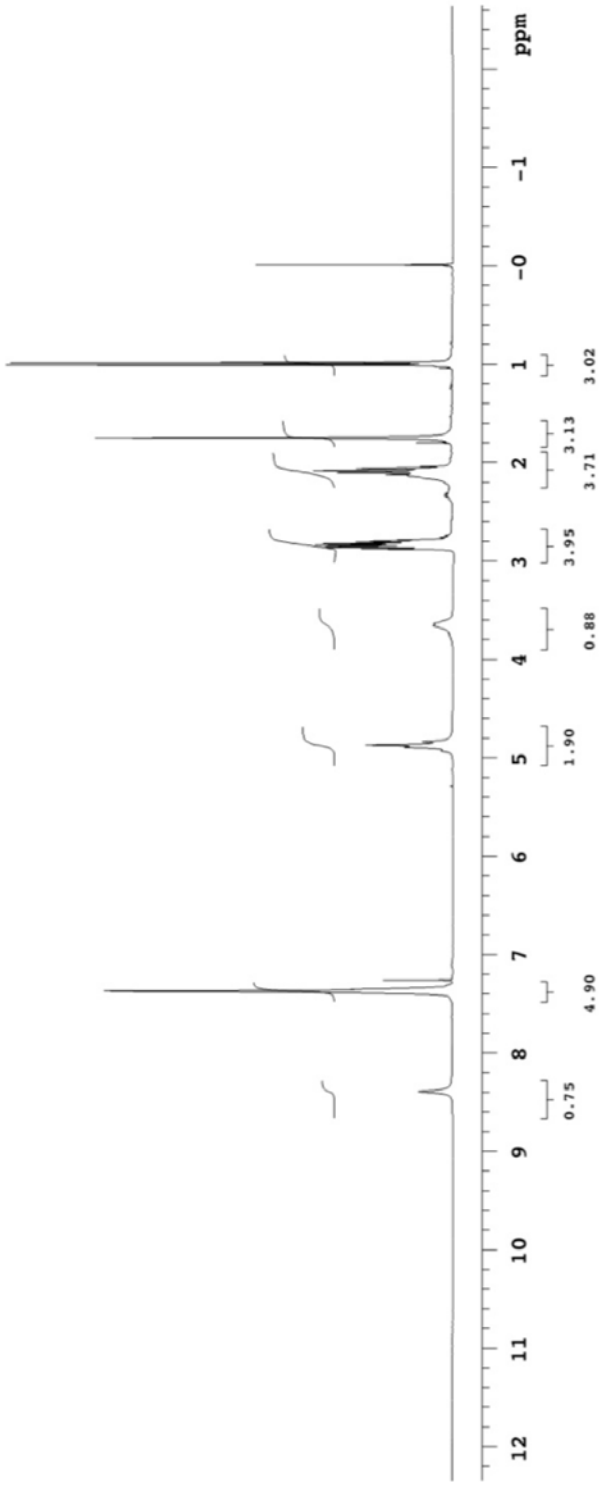
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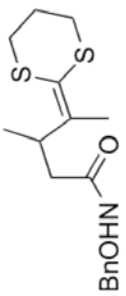

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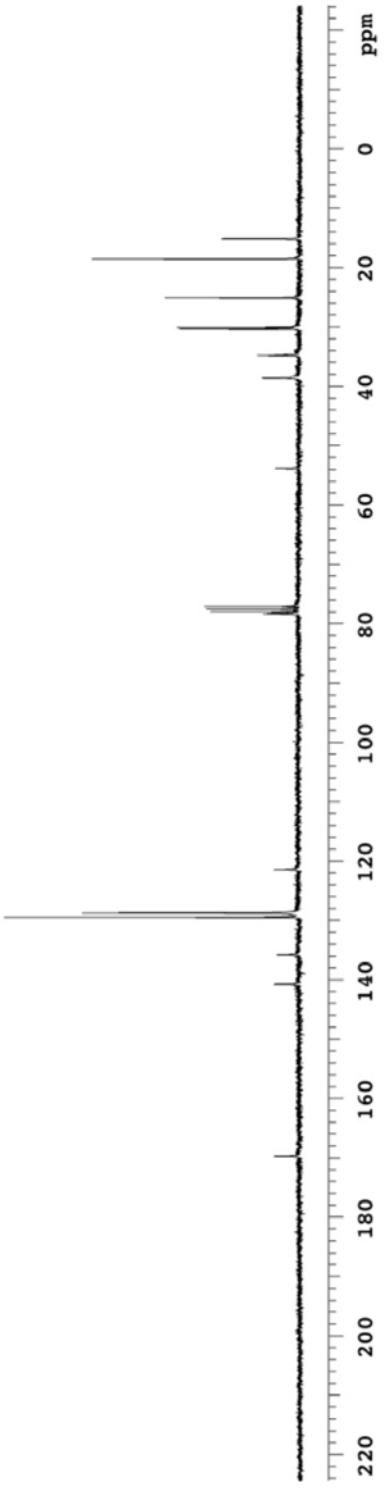

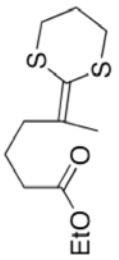

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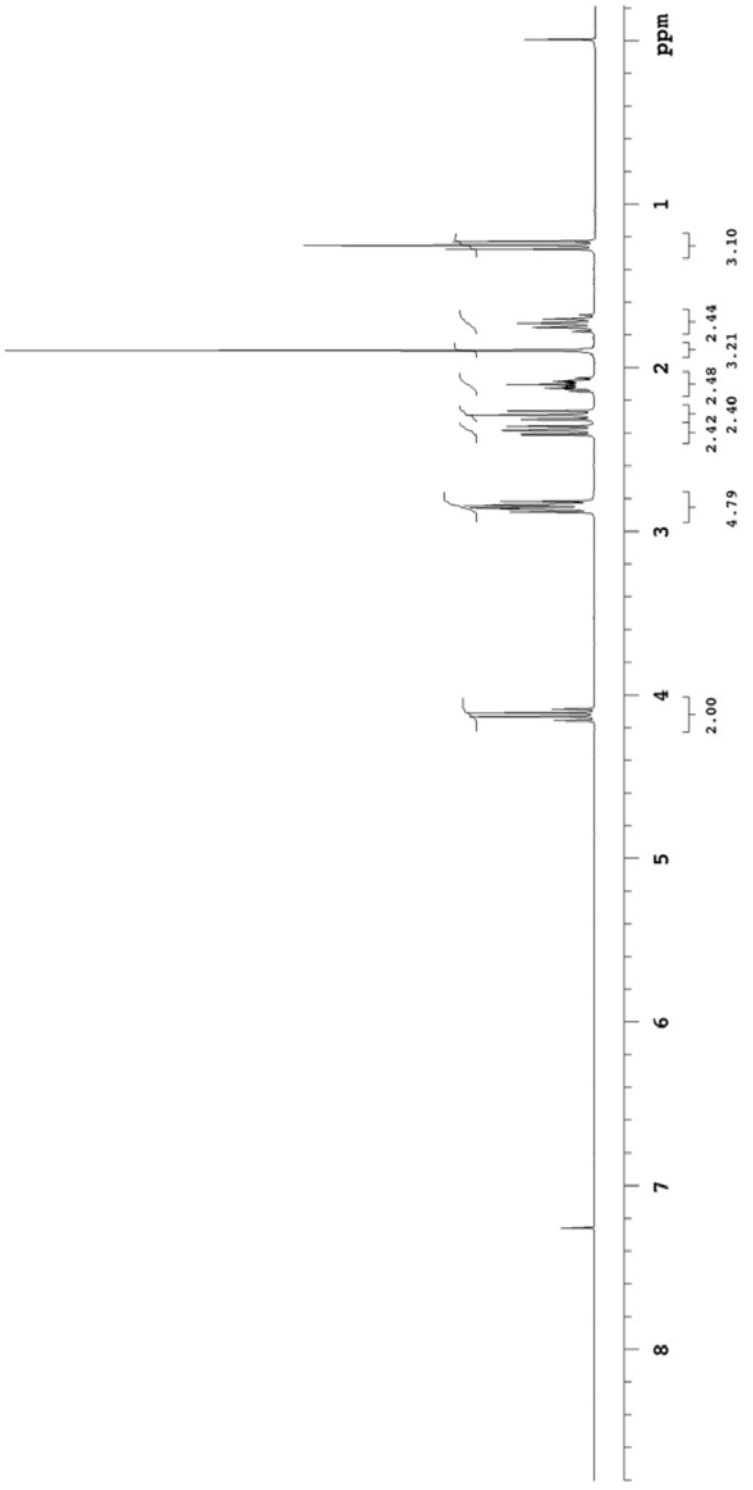

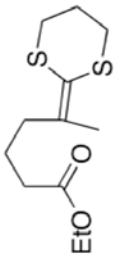

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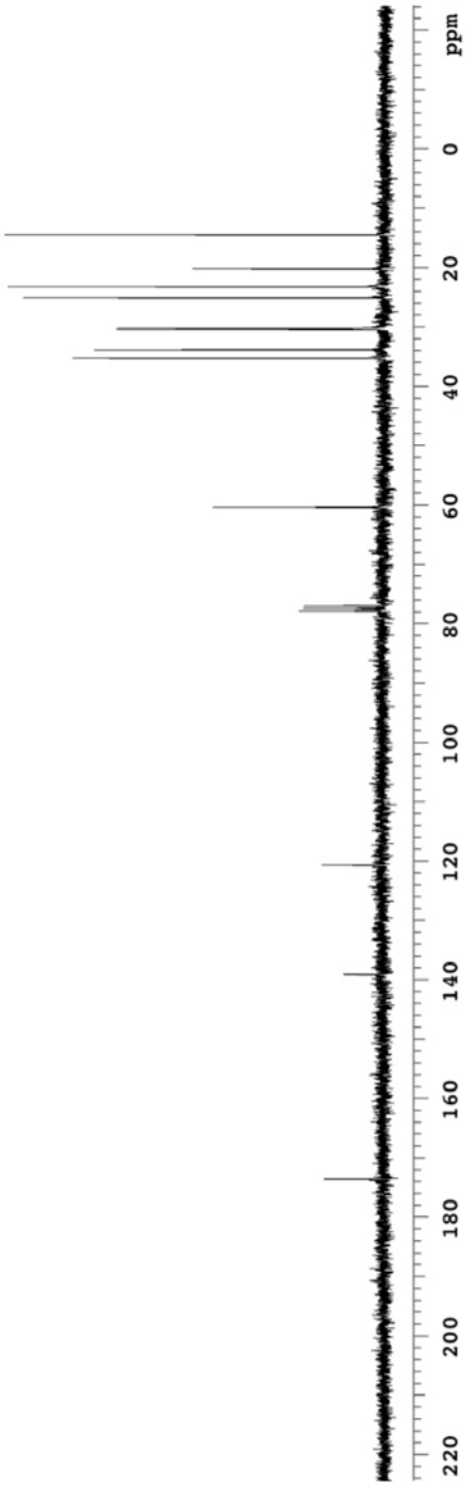

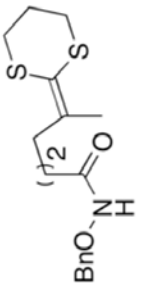

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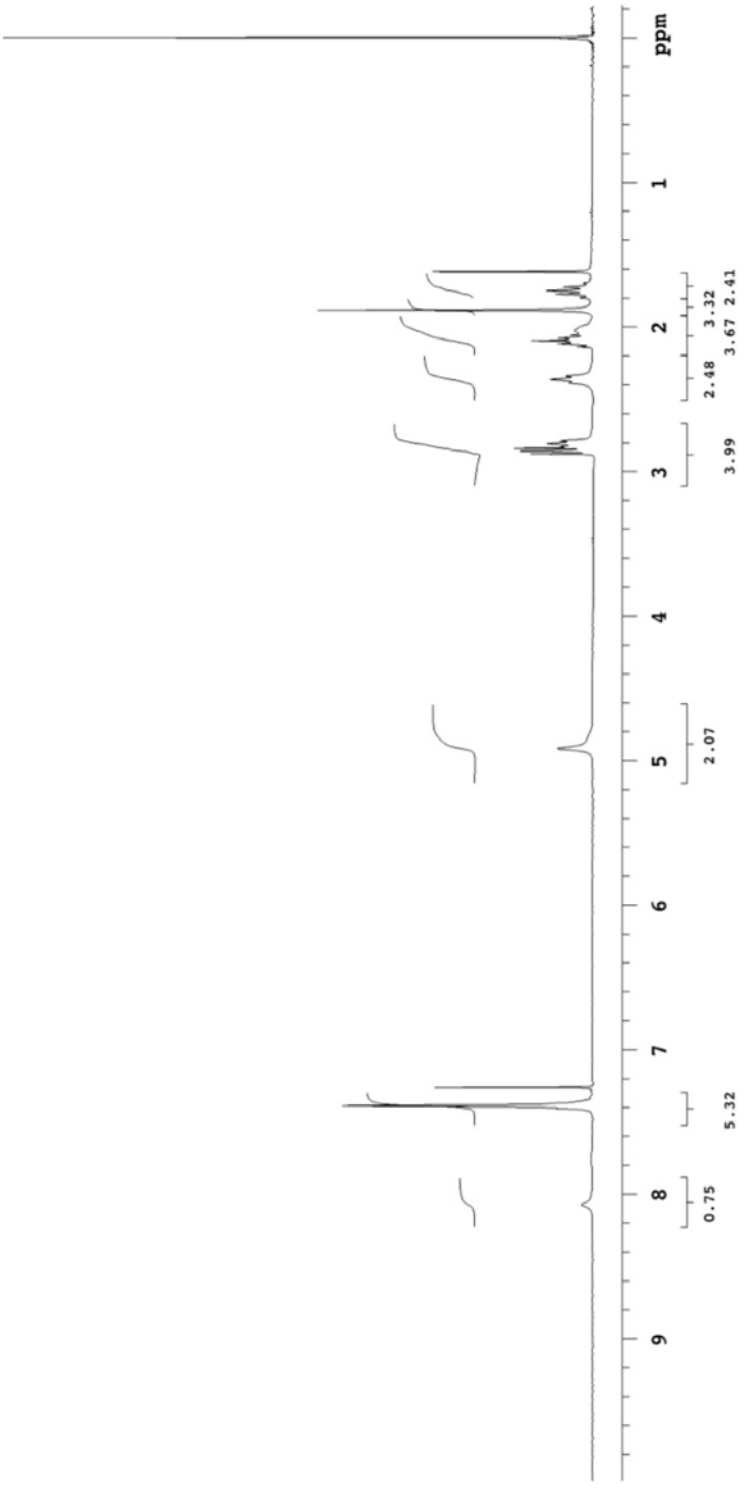

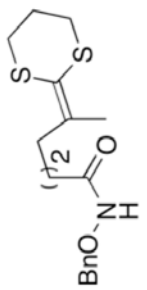

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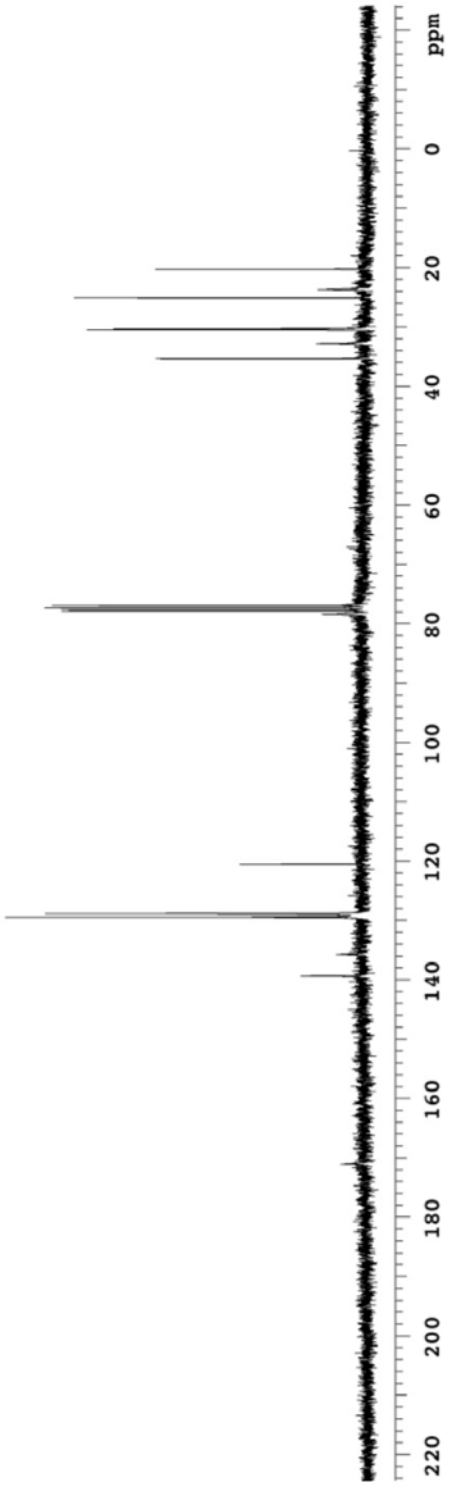

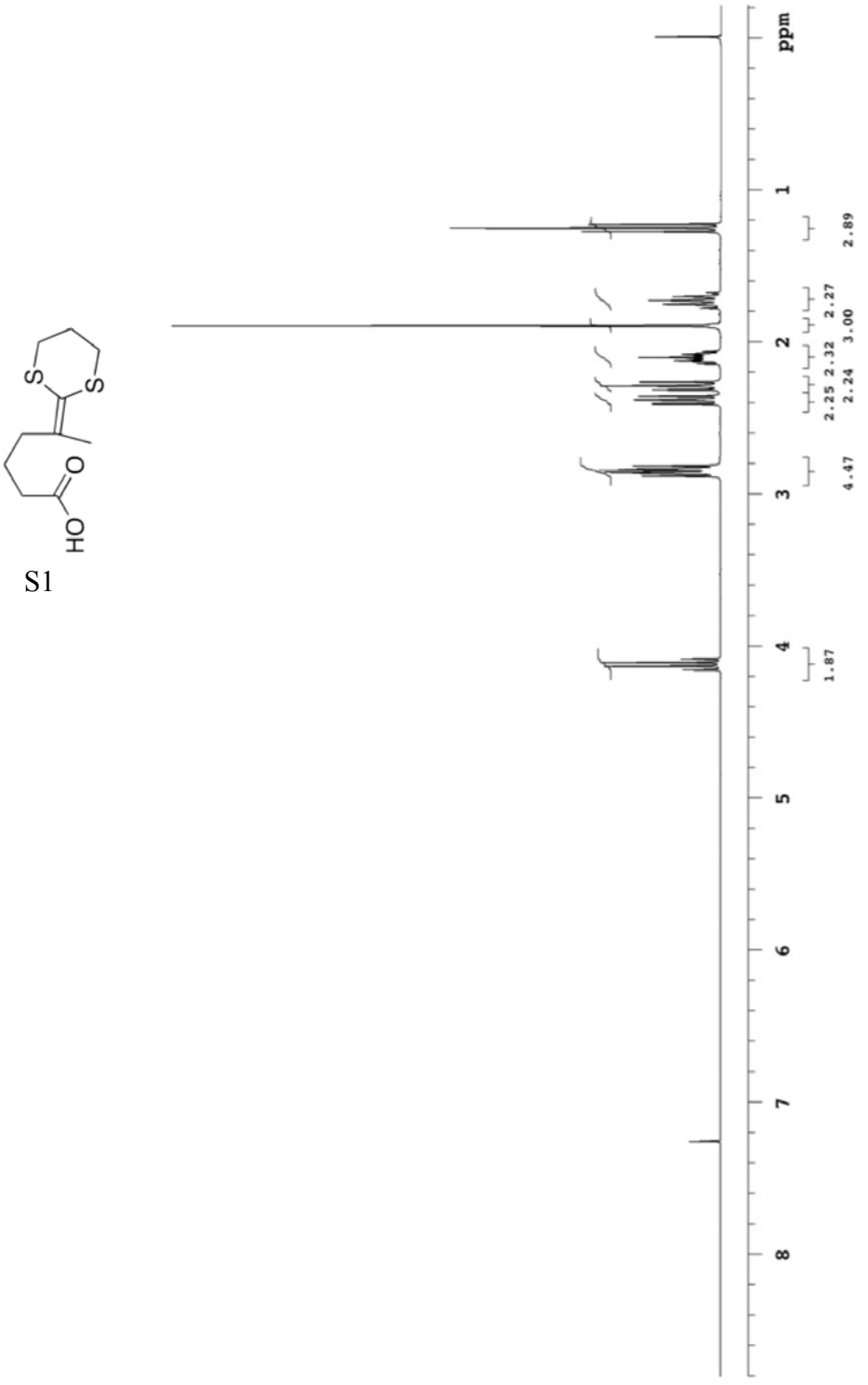

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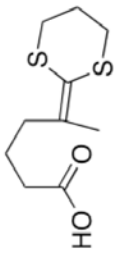

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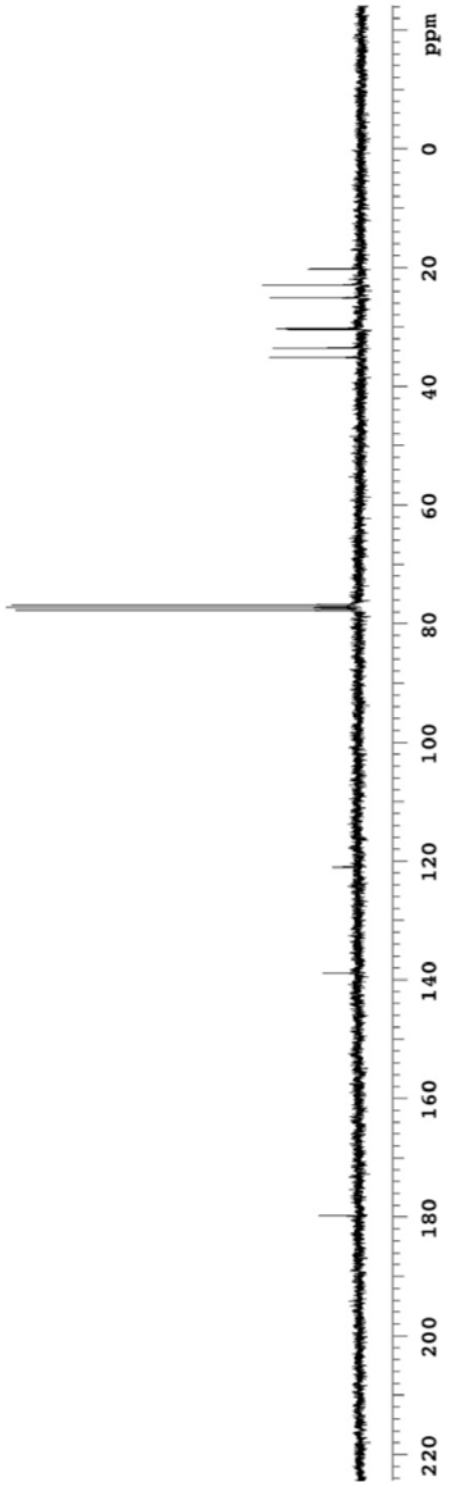

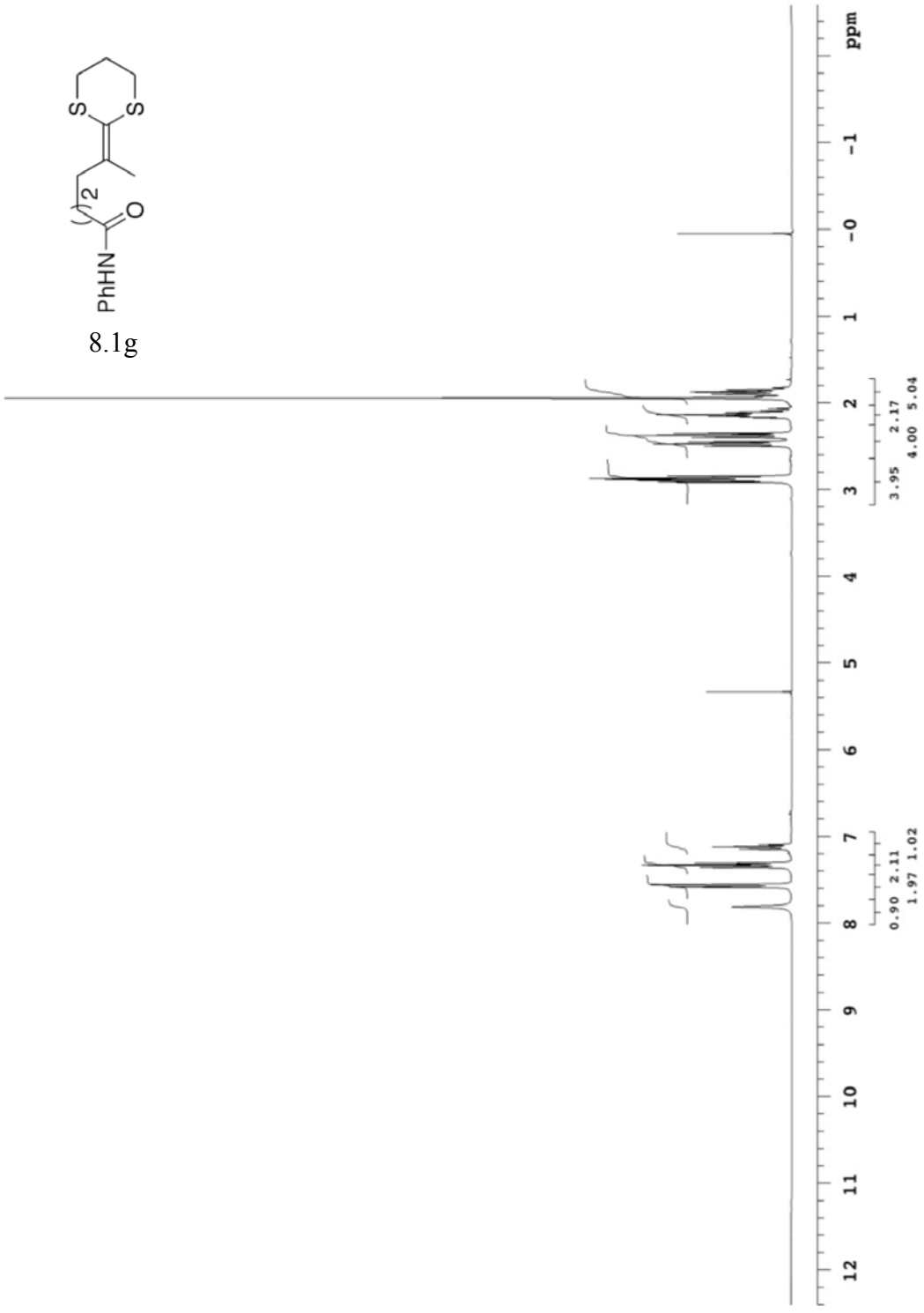
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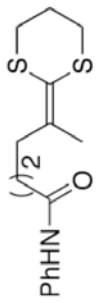

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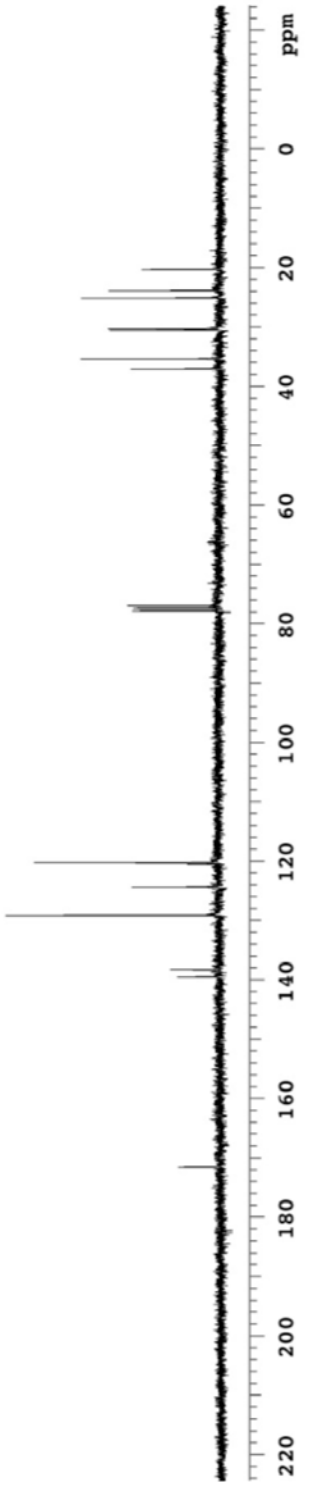

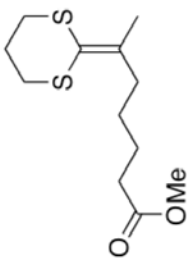

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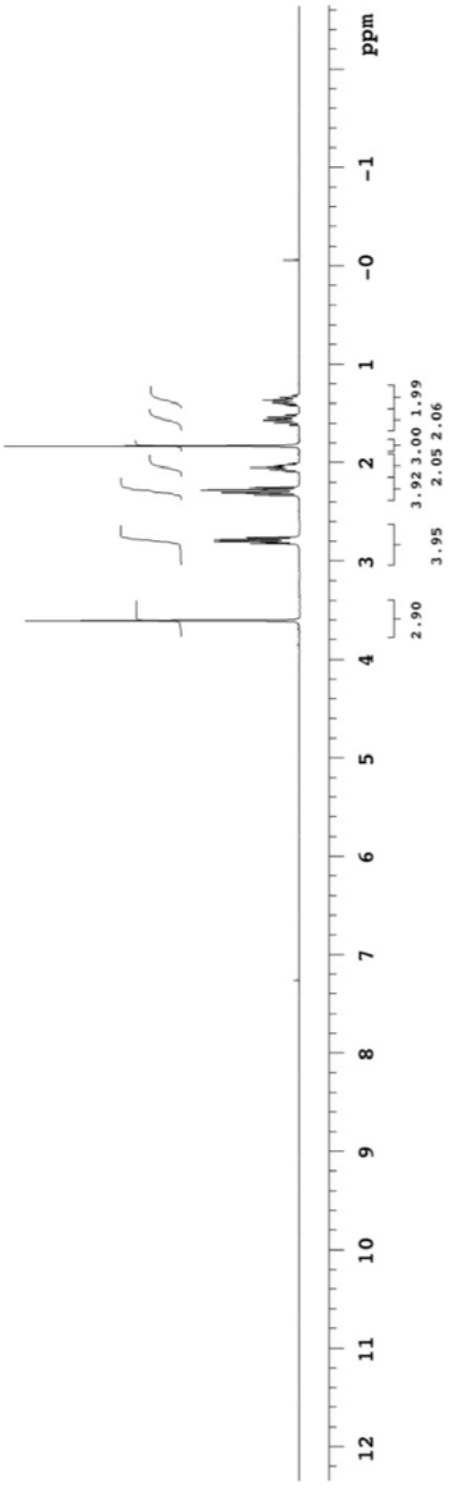

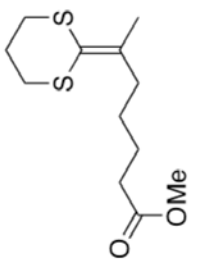

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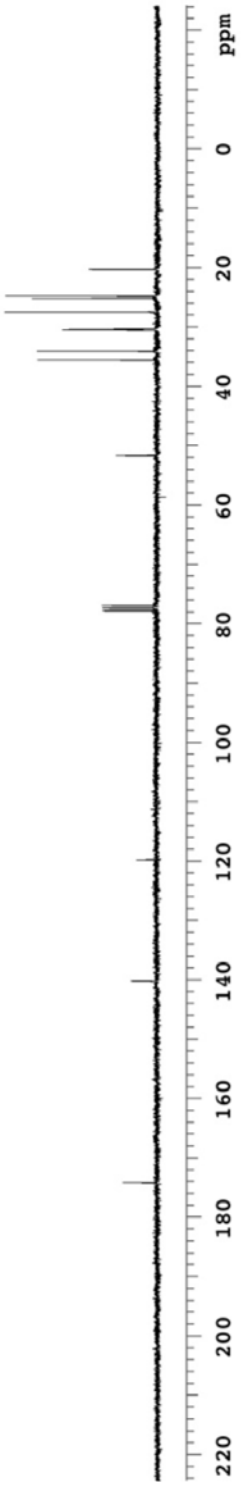

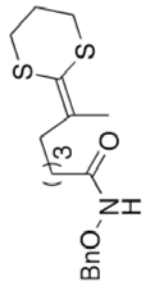
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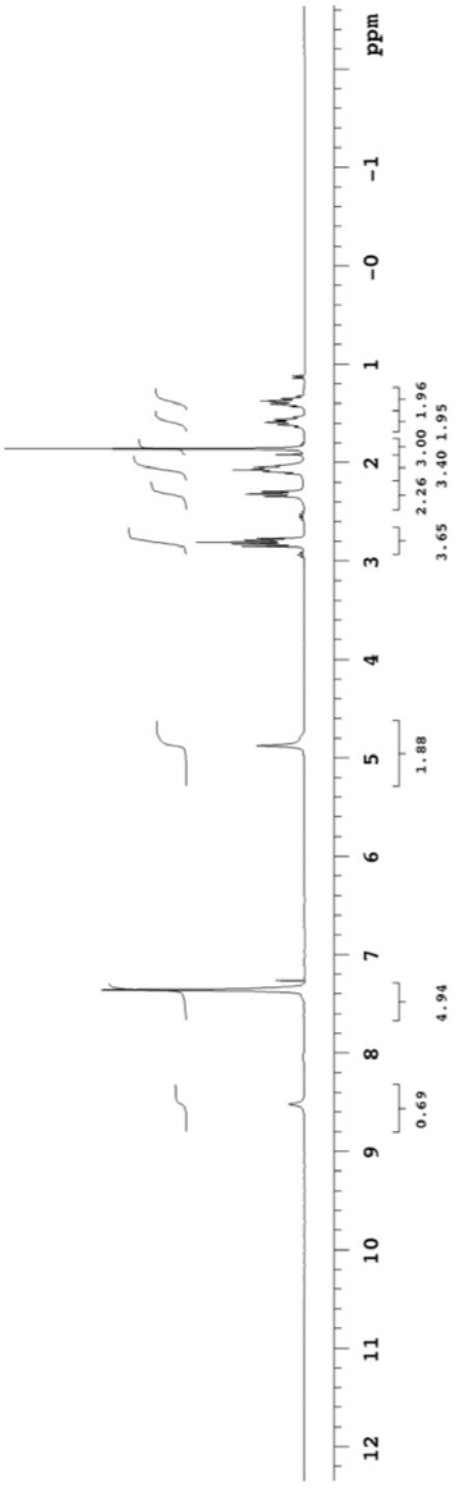
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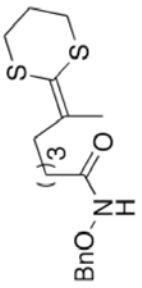

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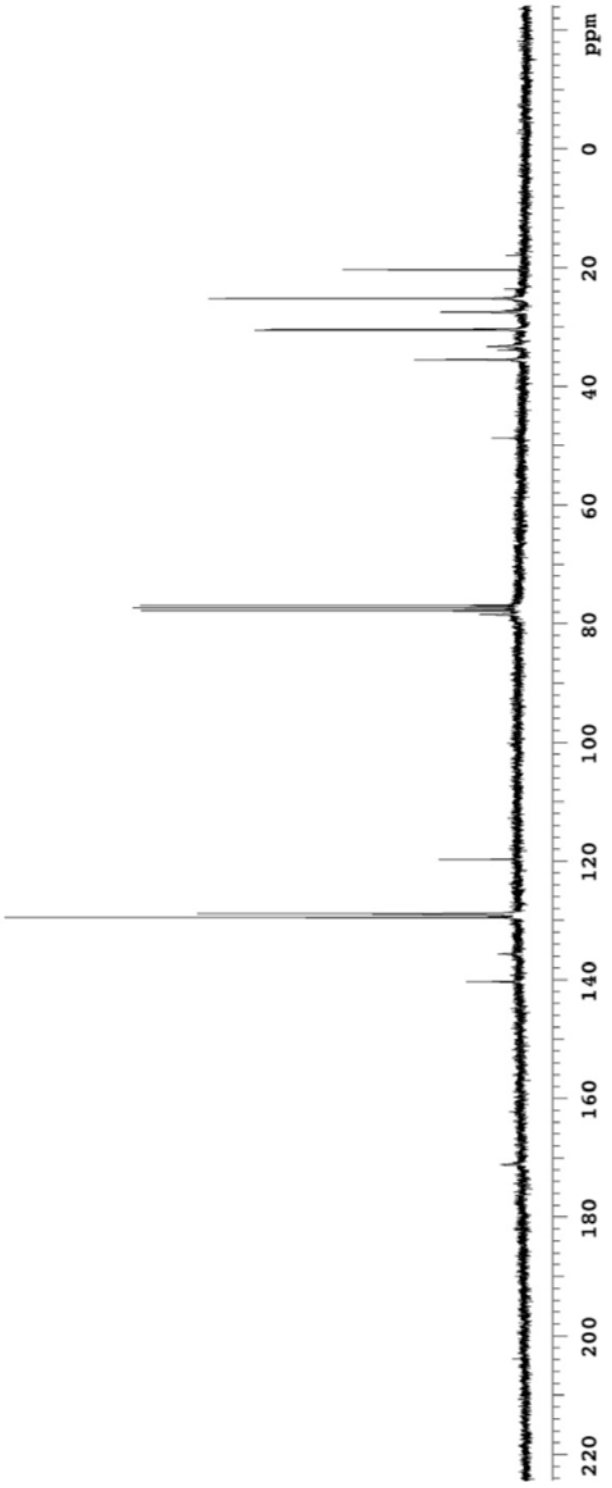

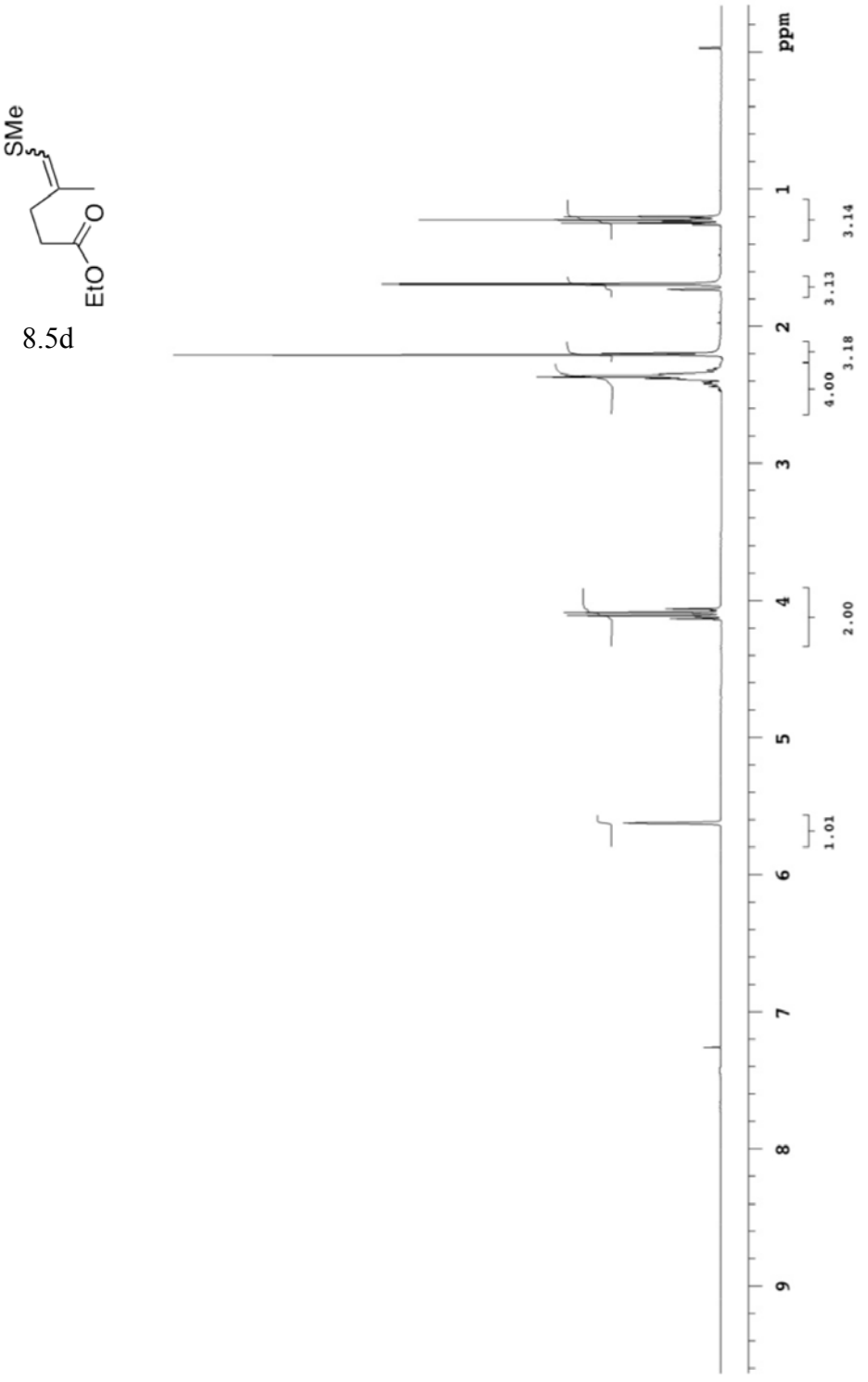

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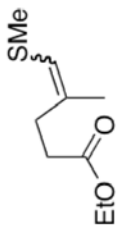

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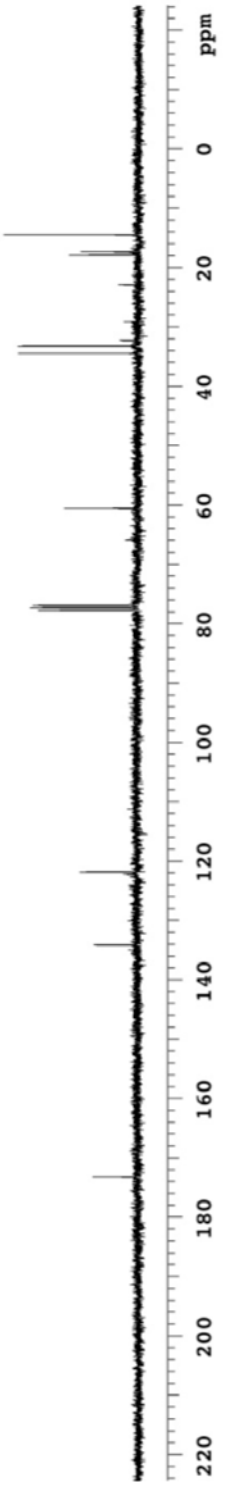

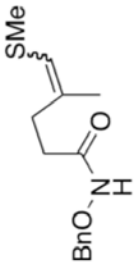
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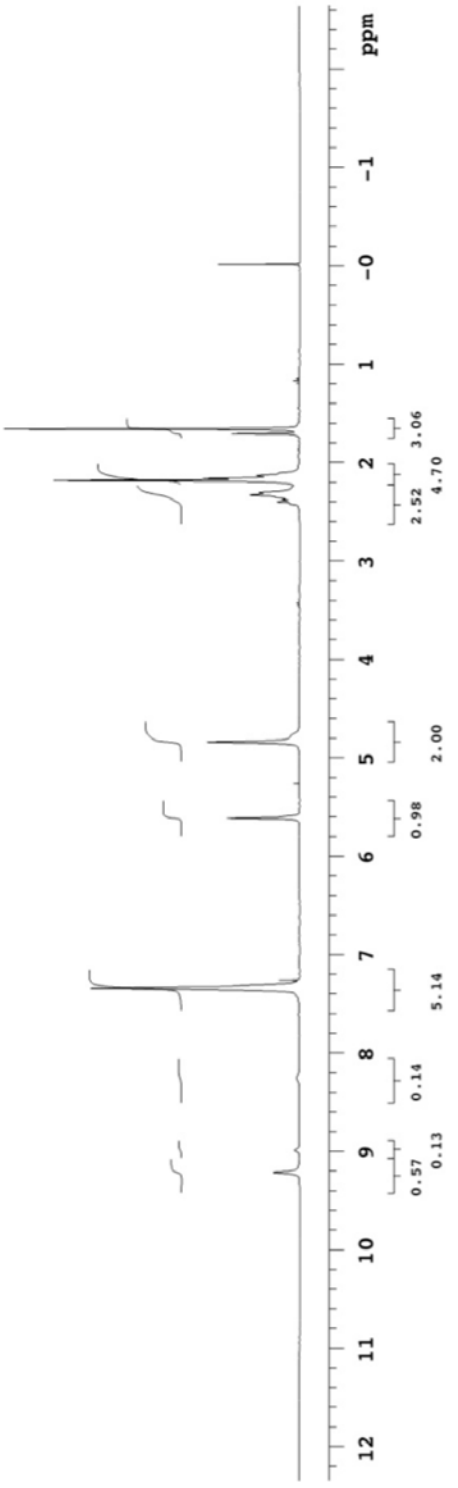
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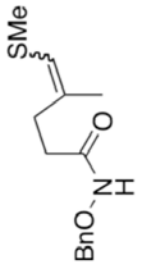

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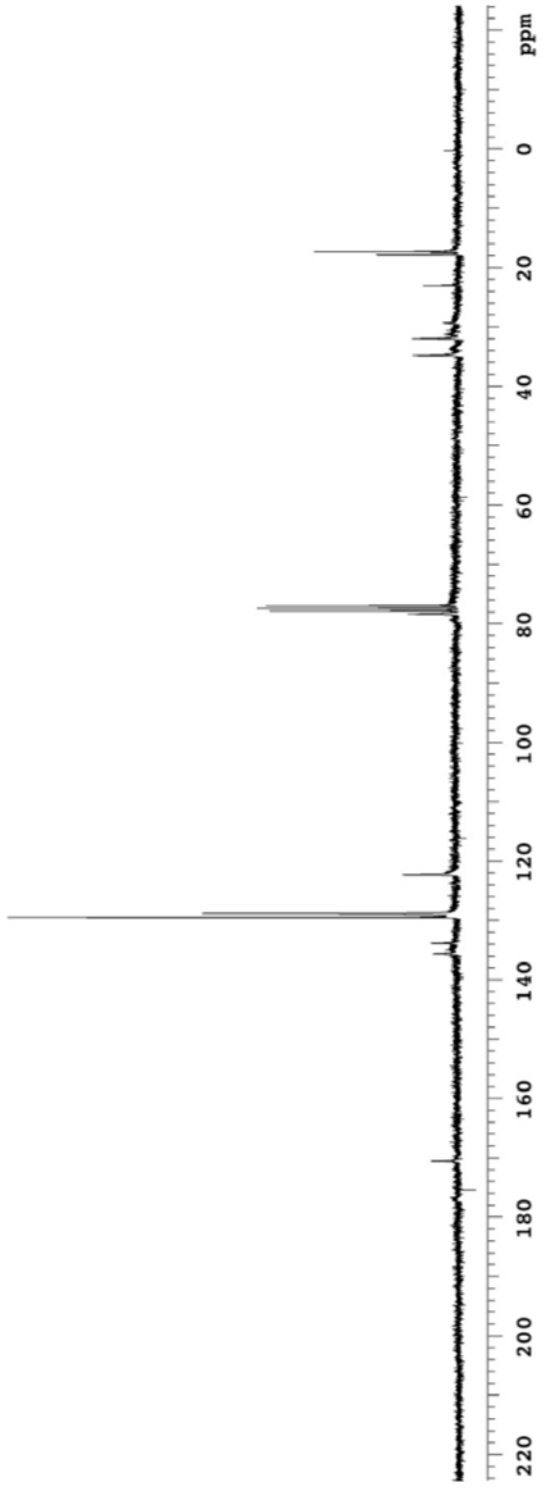

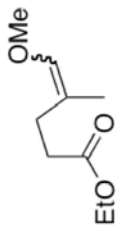

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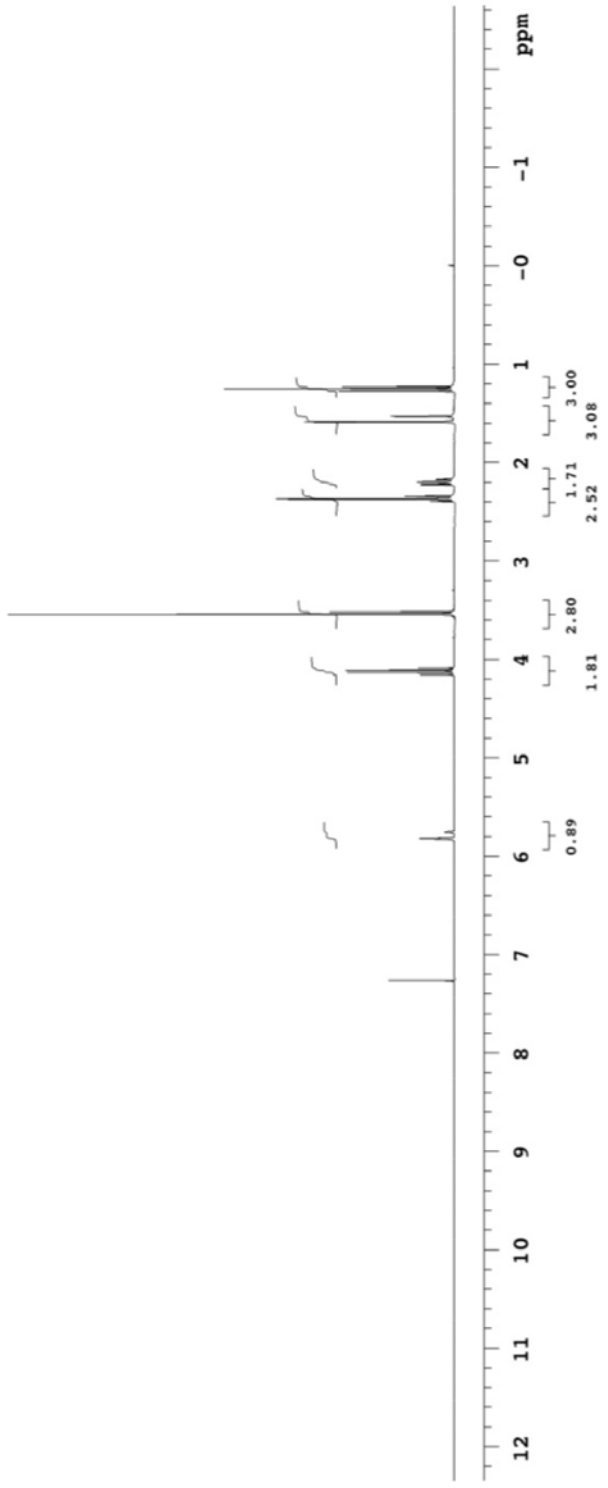

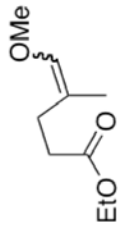

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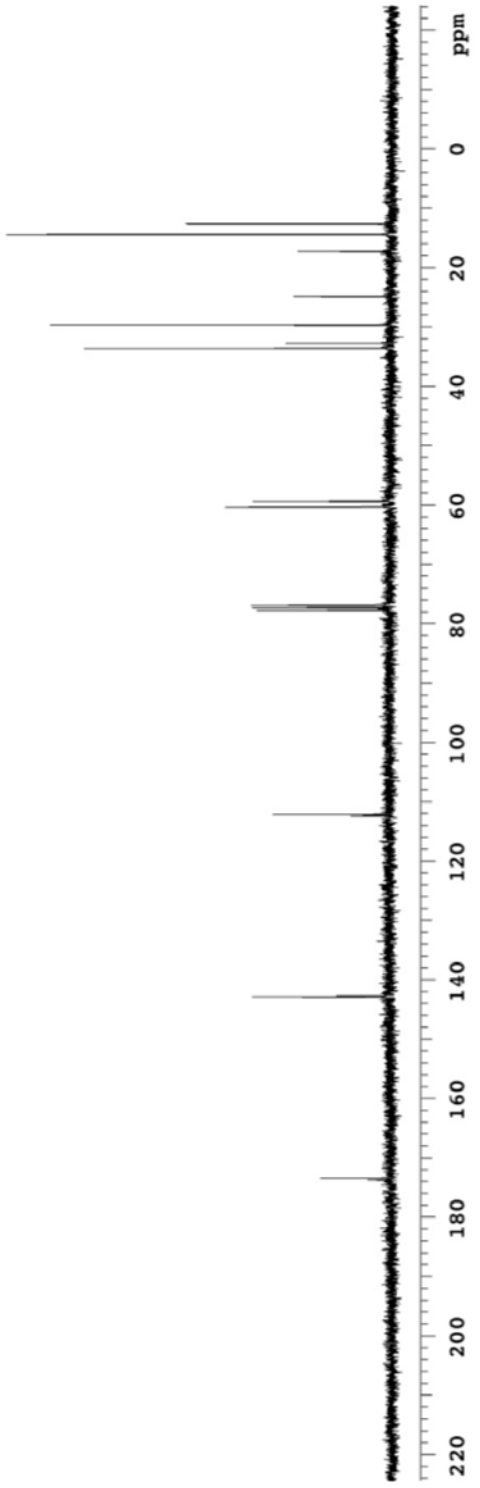

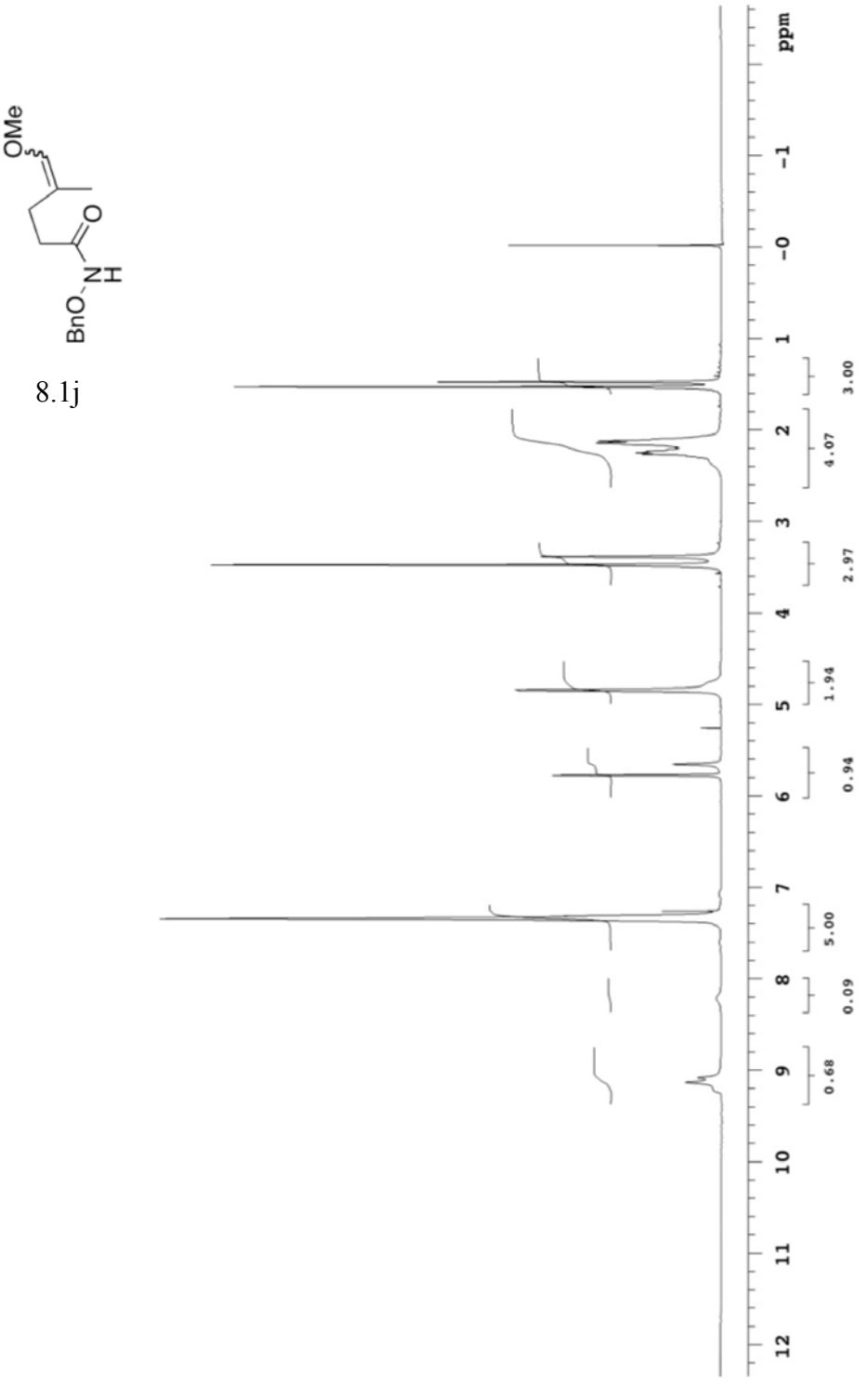
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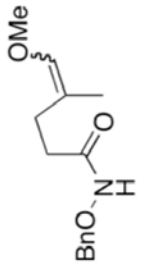
8.1j



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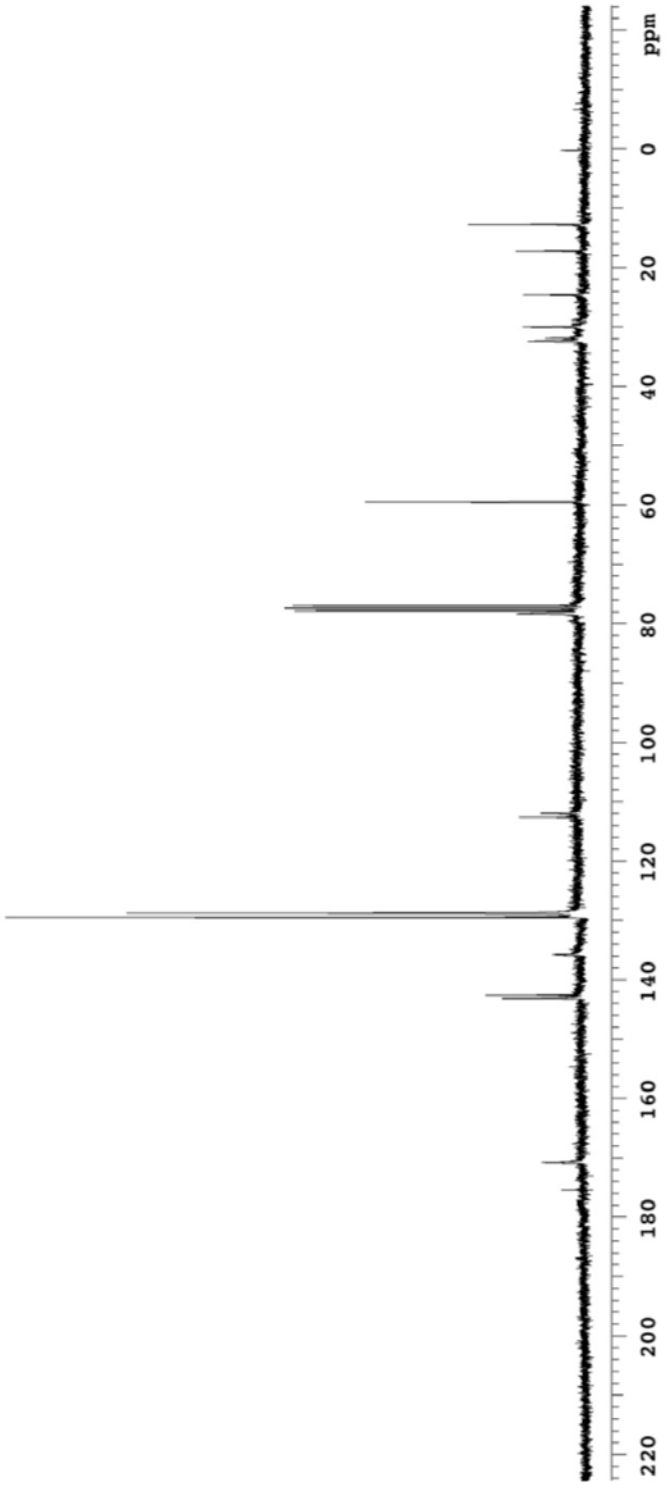

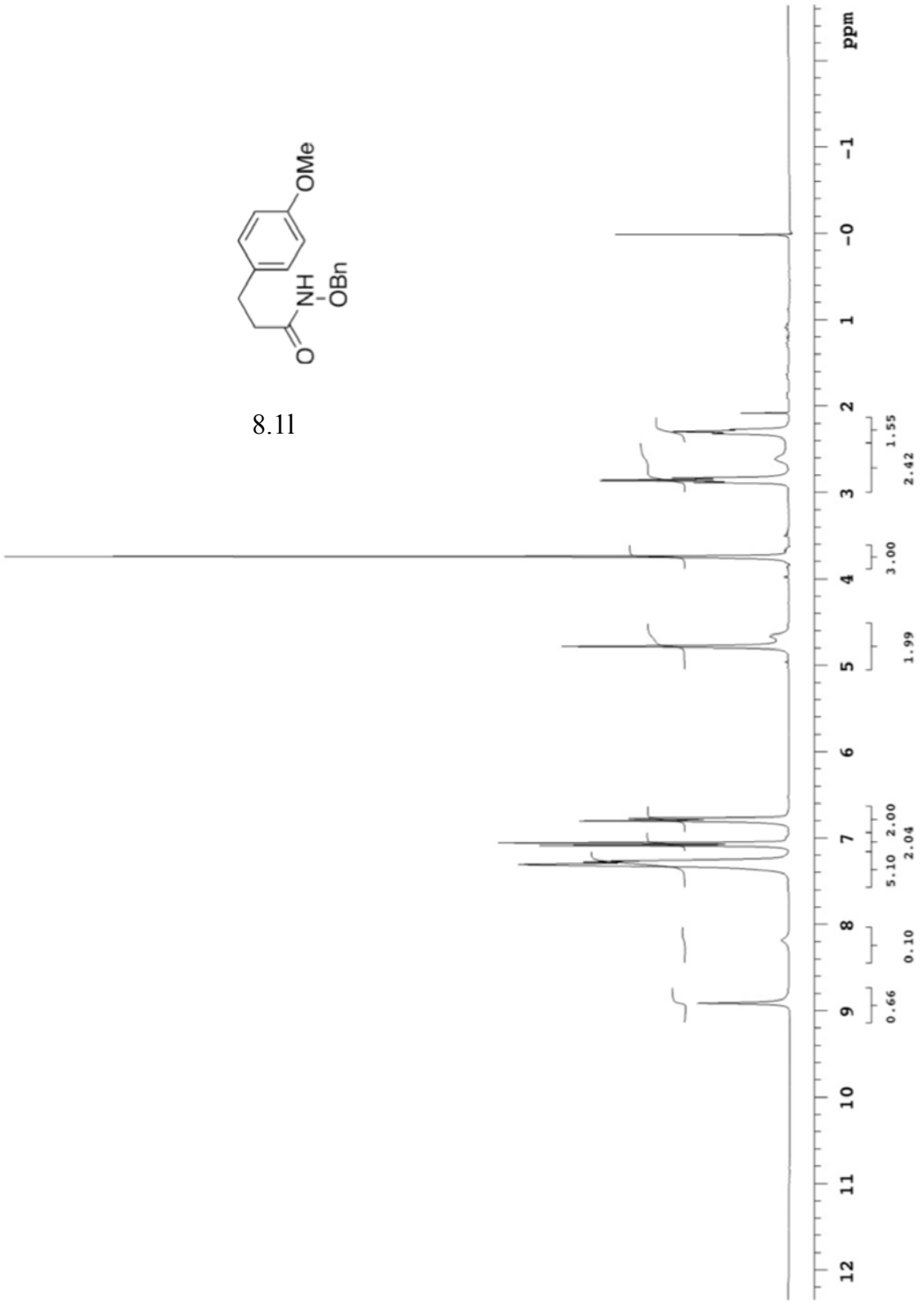
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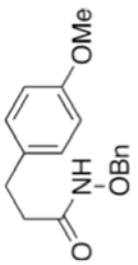

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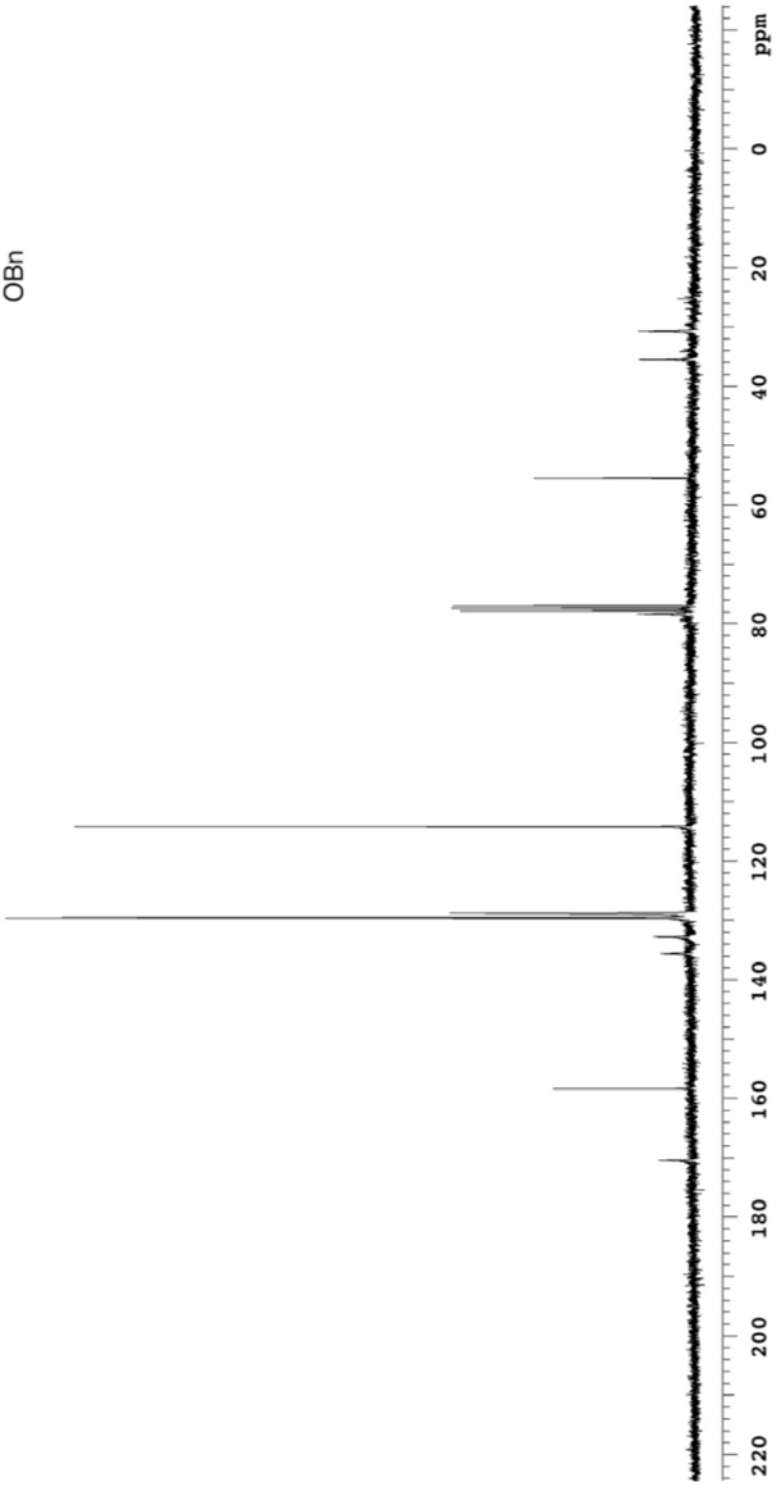

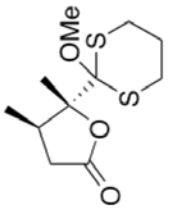

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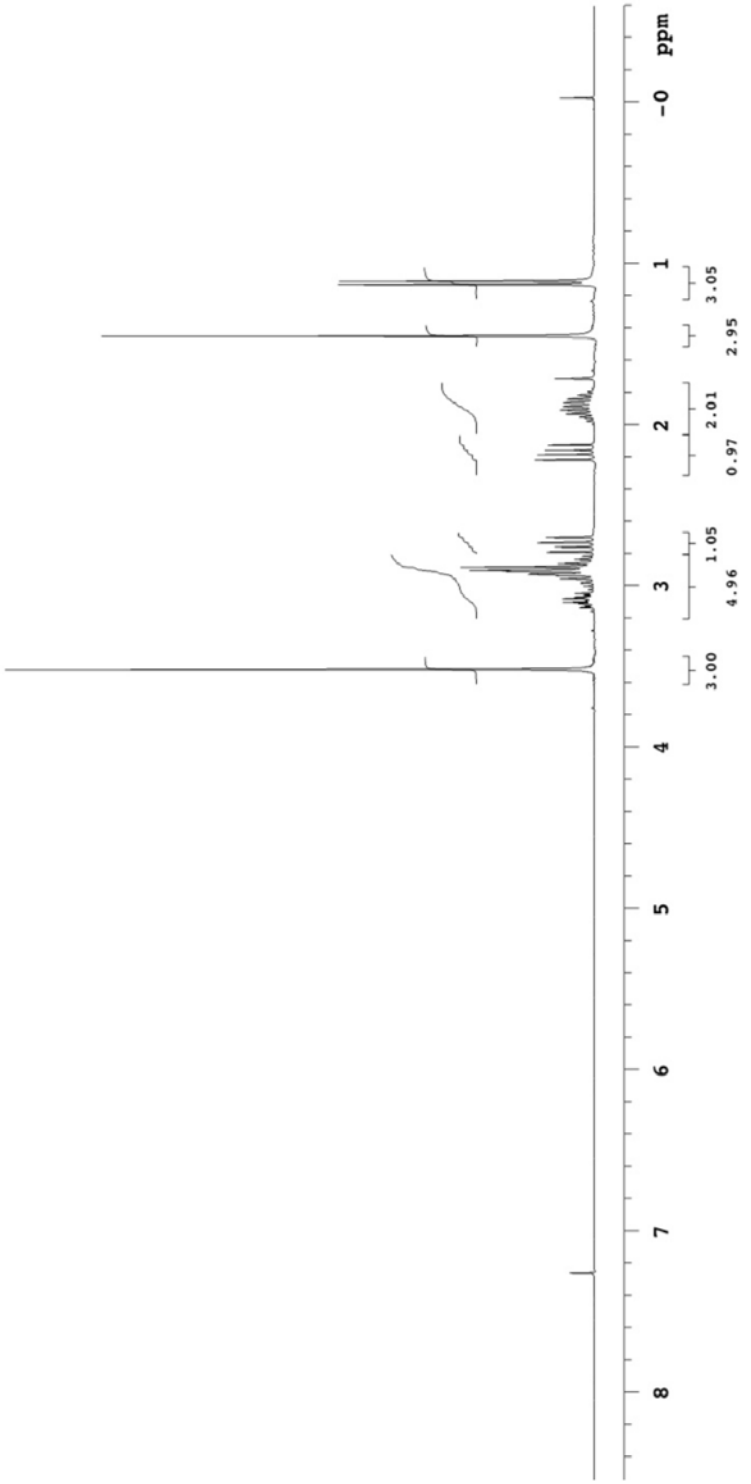

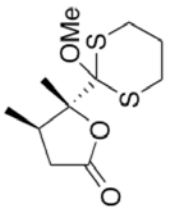

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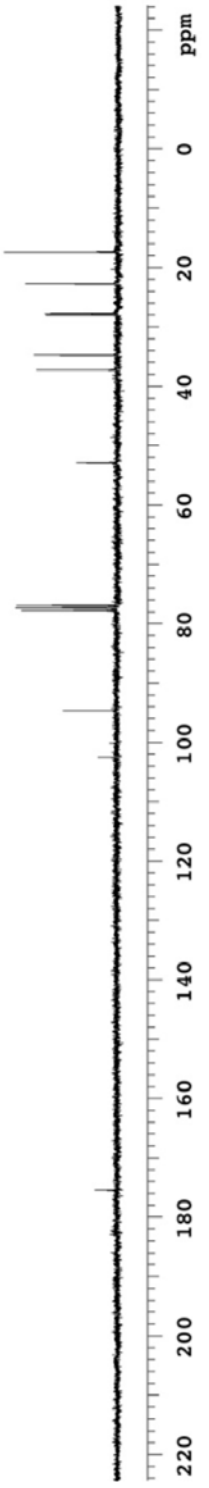

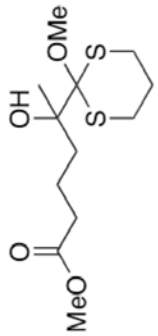

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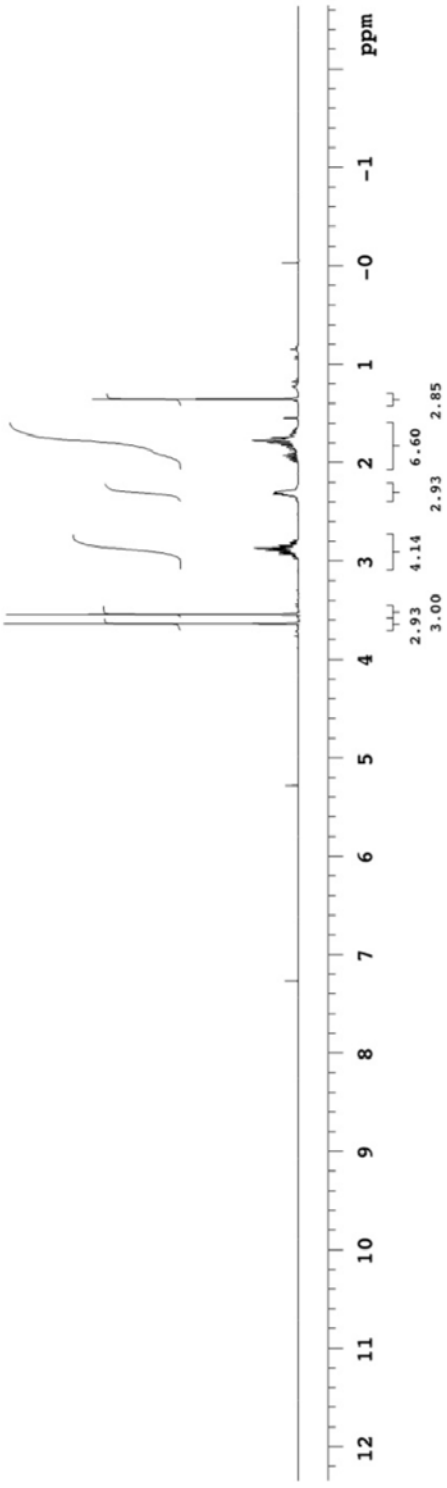

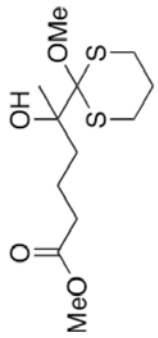

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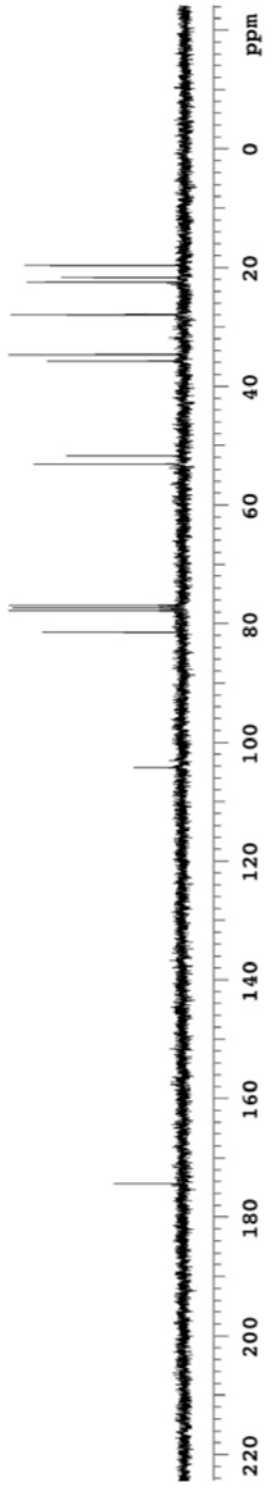

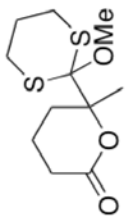

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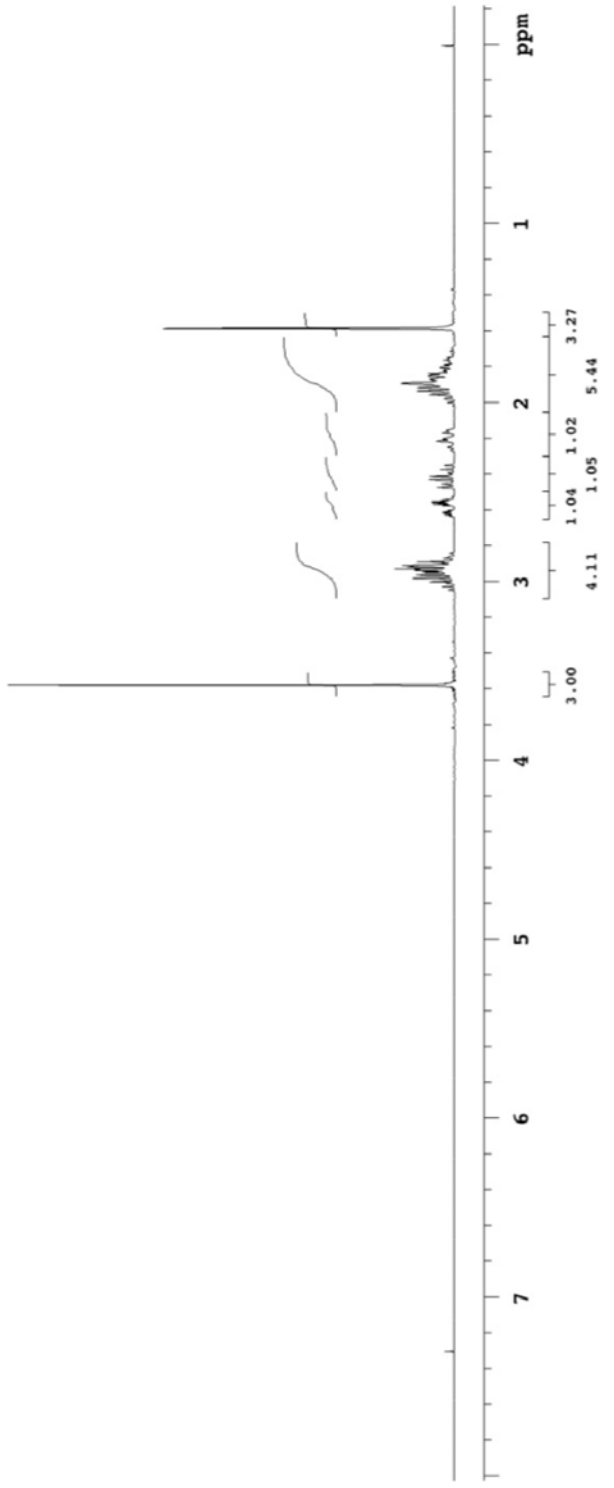

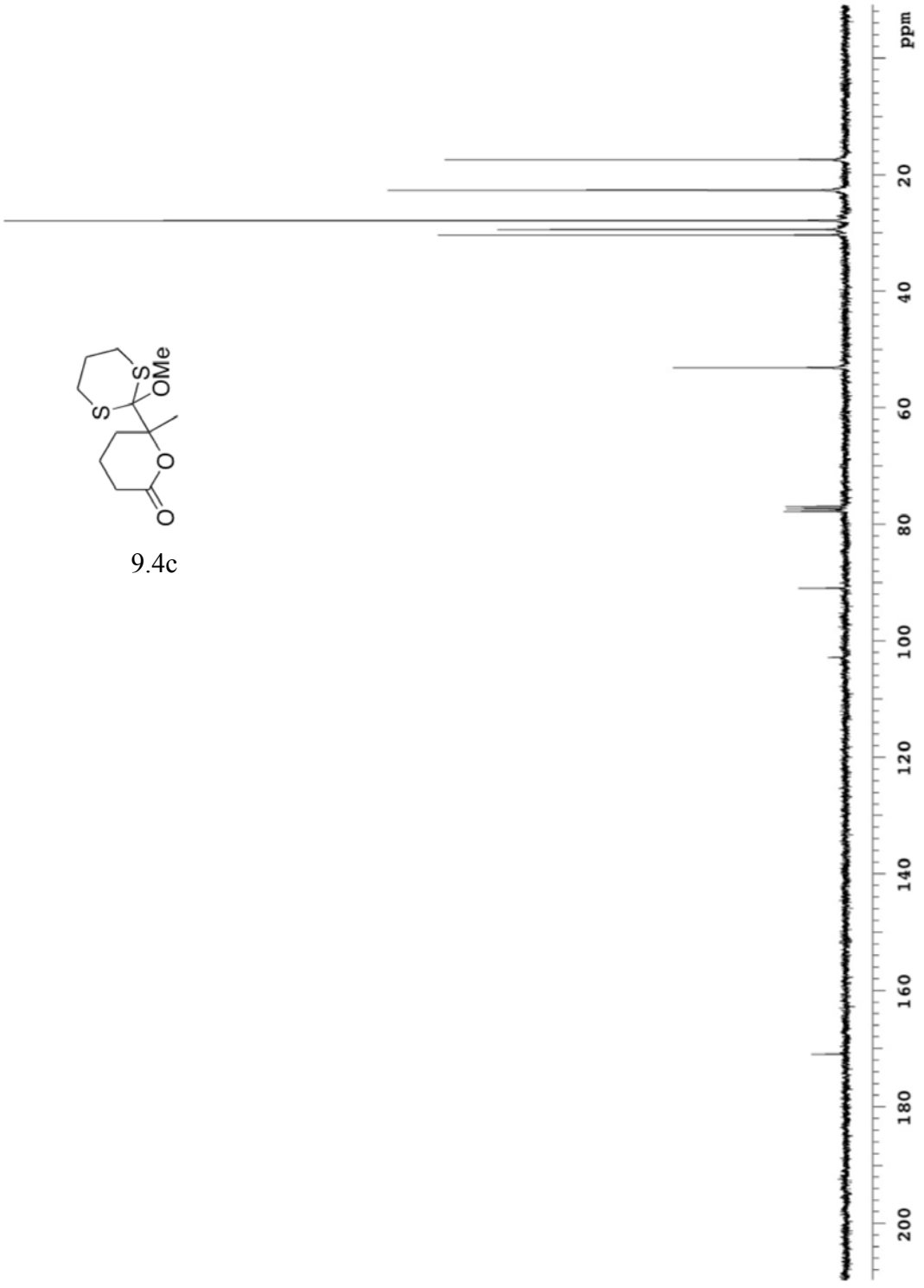

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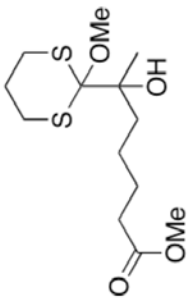

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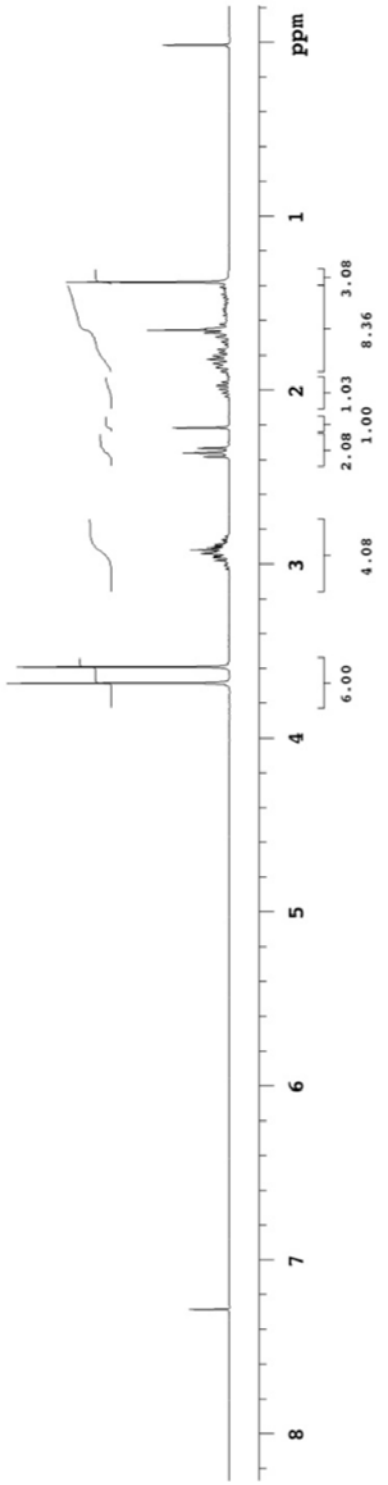

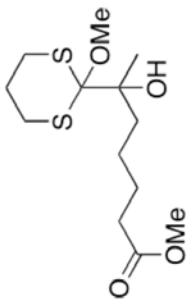

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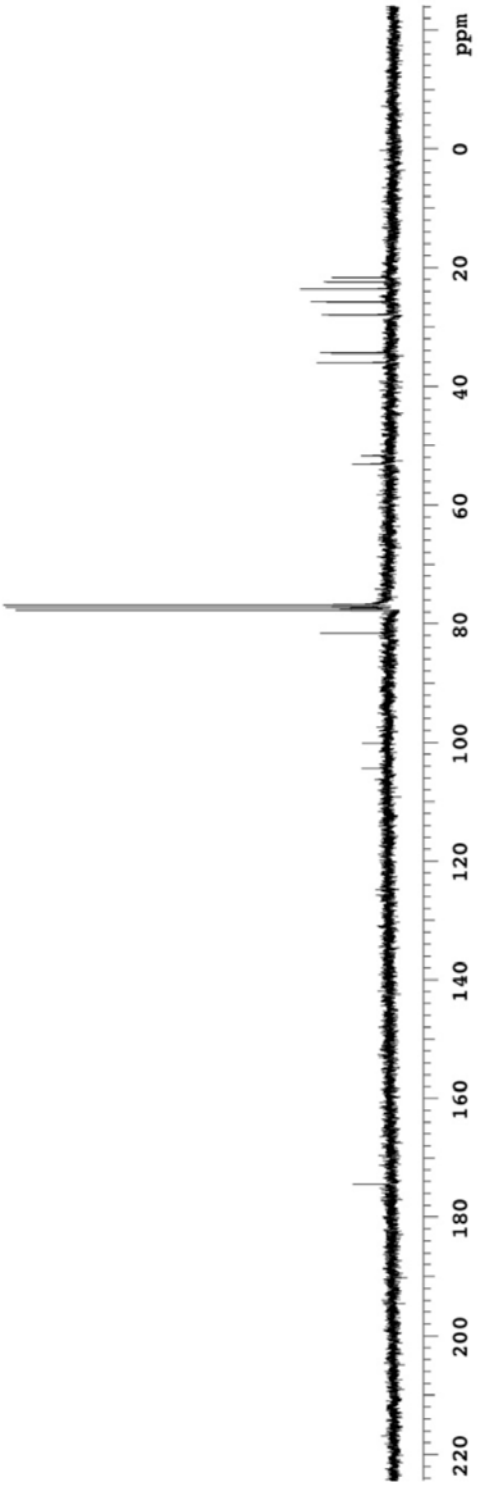

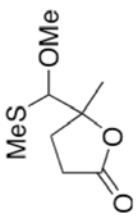

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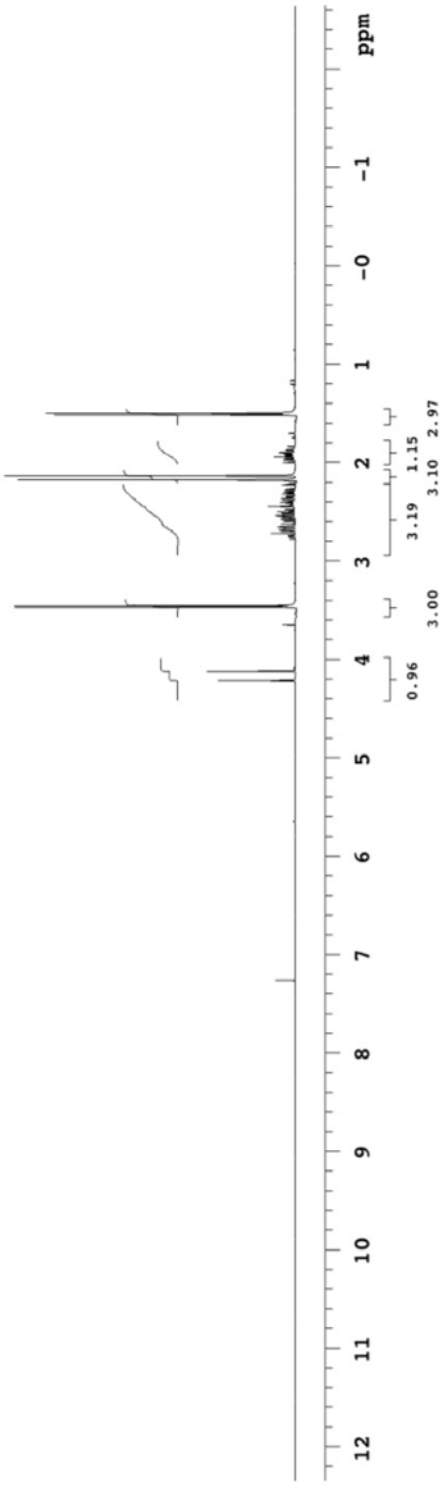

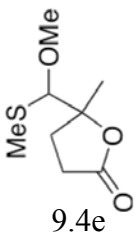

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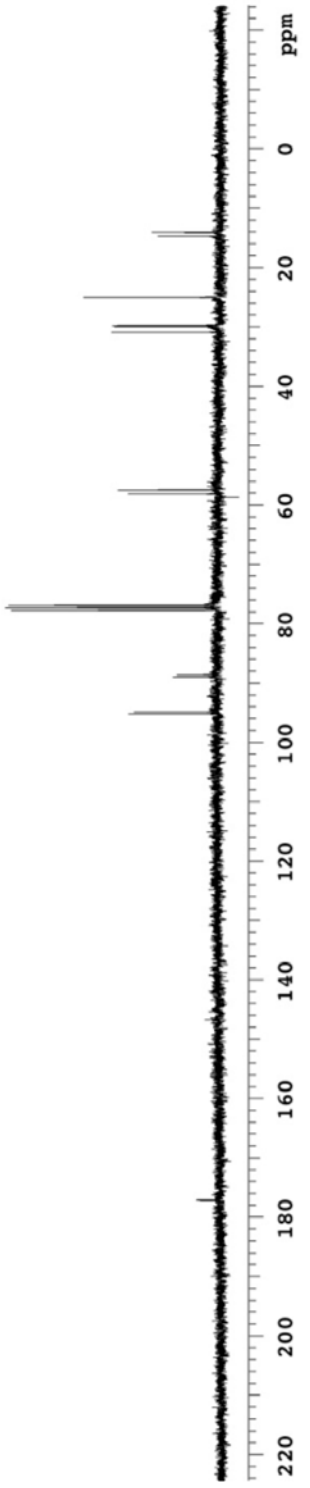

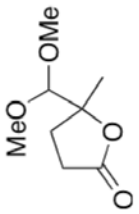

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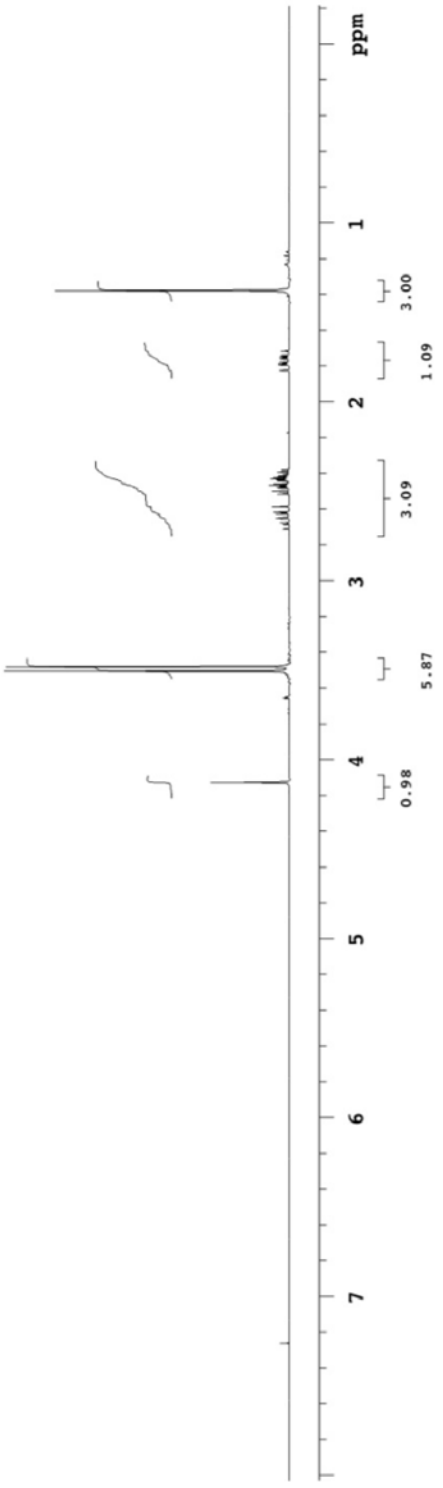

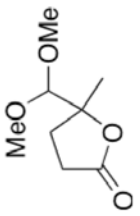

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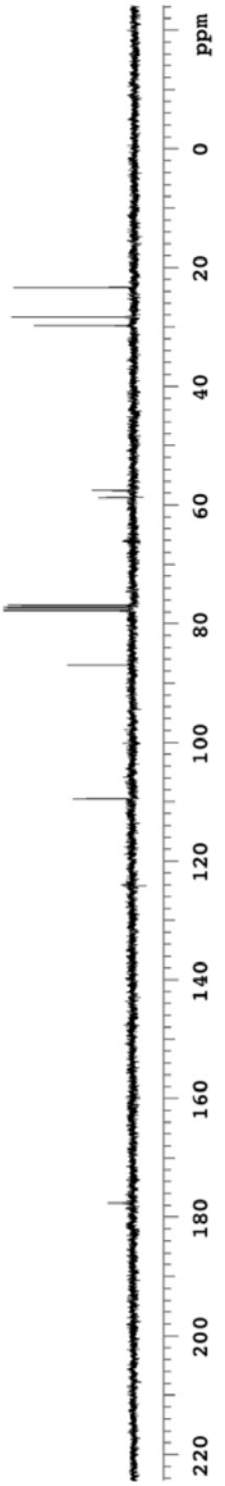

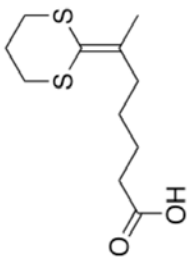

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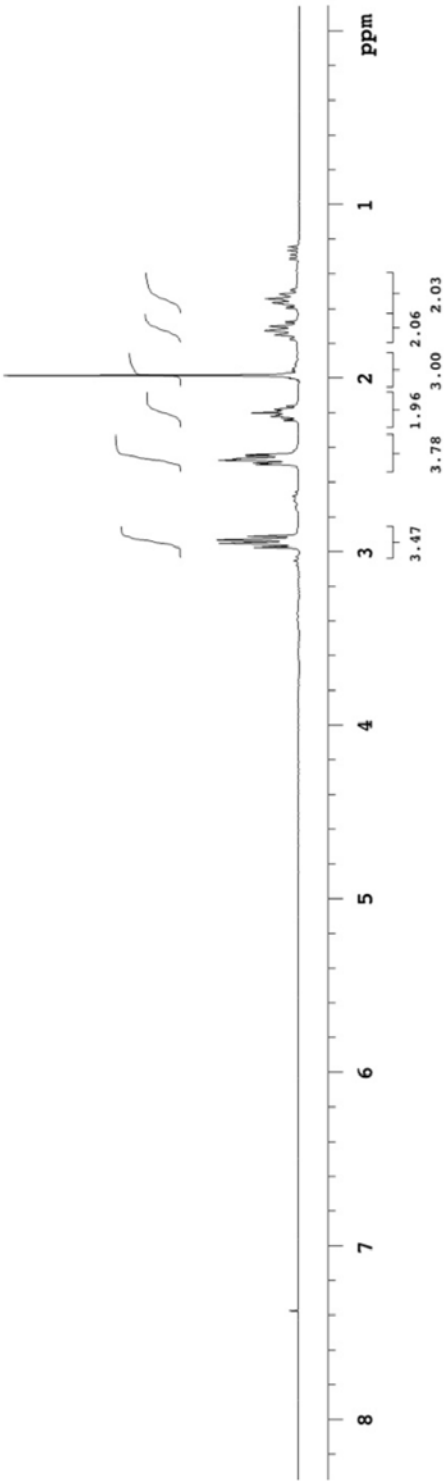

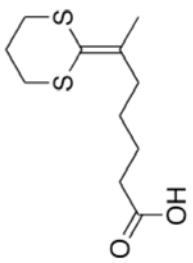

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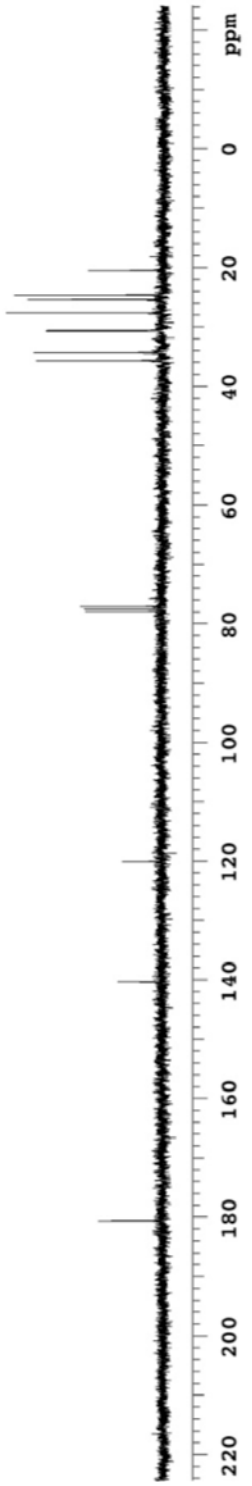

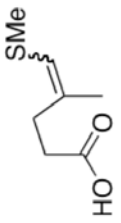

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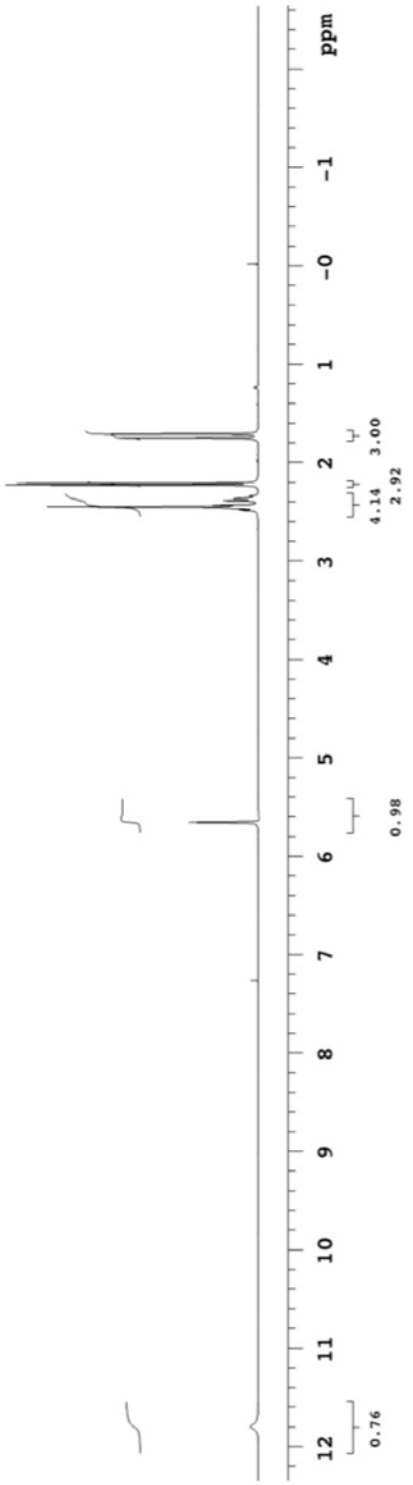

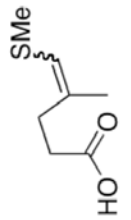

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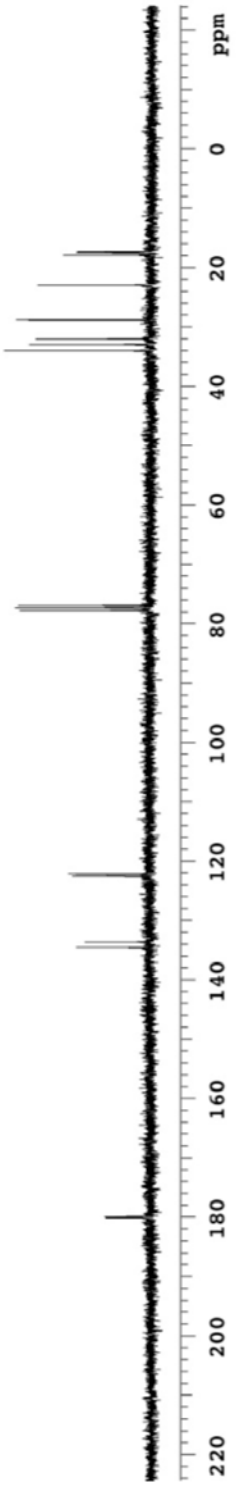

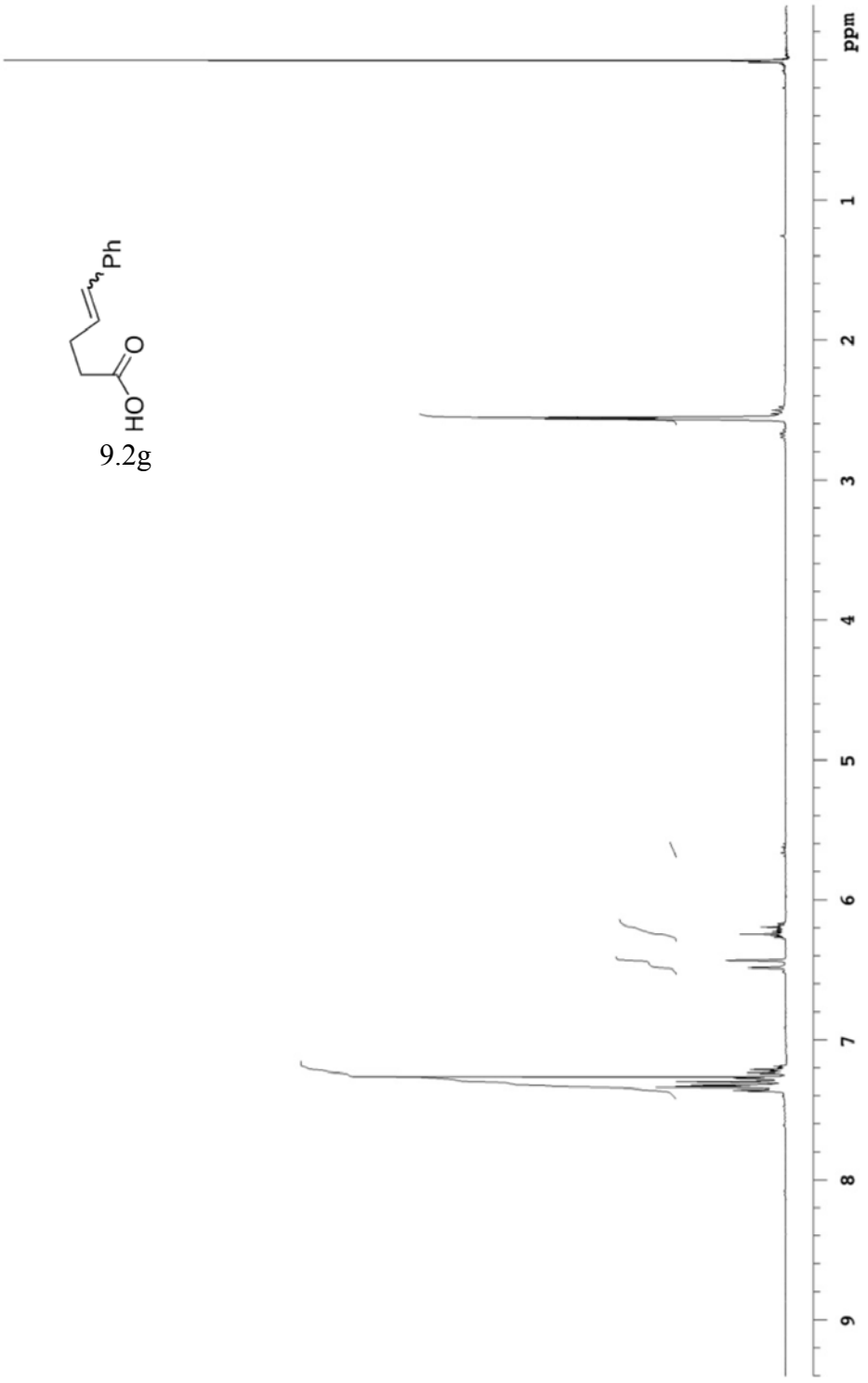

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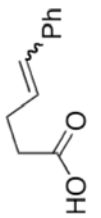

9.2g