CHAPTER I: ELIMINATION REACTIONS USING ARYL ISOTHIOCYANATES

CHAPTER II: INTRAMOLECULAR FRIEDEL–CRAFTS CYCLIZATIONS OF ARYLSILANES

by

STEPHEN BRADFORD THOMPSON

(Under the Direction of George Majetich)

ABSTRACT

Chapter I: The Chugaev elimination is a commonly-employed method for the preparation of alkenes from alcohols possessing a *syn*-β-hydrogen. The introduction of tin and silicon atoms as the *S* substituent of the xanthate instead made it more stable toward pyrolysis, causing it to eliminate at higher temperatures. However, carbonimidothioates, prepared via aryl isothiocyanates, proved to be a viable alternative to the Chugaev elimination, undergoing pyrolysis at the same temperature as *S*-methyl xanthates.

Chapter II: Lewis acid-catalyzed cyclialkylation is an established method for creating tricyclic compounds composed of a central cycloheptane ring. By applying this method to arene-dienone systems with silyl-substituted arenes, we hoped to observe *meta*-directed electrophilic aromatic substitution with retention of the silyl moiety. Preliminary investigations have proven the silyl moiety too labile, and cyclialkylation was accompanied by protodesilylation.

INDEX WORDS: Chugaev elimination, isothiocyanate, Friedel–Crafts cyclialkylation, arylsilane

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LIST OF ABBREVIATIONS

AcOH .....acetic acid

AIBN .....azo-*bis*-isobutyronitrile

DCM .....dichloromethane

DMSO.....dimethyl sulfoxide

DSC .....differential scanning calorimetry

EDG .....electron-donating group

EWG .....electron-withdrawing group

EtOAc .....ethyl acetate

Et_2O .....diethyl ether

HMPA .....hexamethylphosphoramide

LA .....Lewis acid

LDA .....lithium diisopropylamide

m-CPBA .....*meta*-chloroperoxybenzoic

NaOAc .....sodium acetate

NBS .....*N*-bromosuccinimide

n-BuLi..... *n*-butyllithium

$(n\text{-Bu})_3SnCl$ .....*tri*-*n*-butyltin chloride

p-TsOH .....*para*-toluenesulfonic acid

PDC.....pyridinium dichromate

TEA .....triethylamine

TGA .....thermogravimetric analysis

THF .....tetrahydrofuran

TLC .....thin layer chromatography

TMS .....trimethylsilyl

TMSCl .....trimethylsilyl chloride

TsCl .....*para*-toluenesulfonyl chloride

CHAPTER I

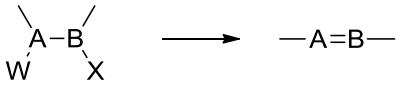
ELIMINATION REACTIONS USING ARYL ISOTHIOCYANATES

ABSTRACT

The Chugaev elimination is a commonly-employed method for the preparation of alkenes from alcohols possessing a *syn*-β-hydrogen. The introduction of tin and silicon atoms as the *S* substituent of the xanthate instead made it more stable toward pyrolysis, causing it to eliminate at higher temperatures. However, carbonimidothioates, prepared via aryl isothiocyanates, proved to be a viable alternative to the Chugaev elimination, undergoing pyrolysis at the same temperature as *S*-methyl xanthates.

1.1 INTRODUCTION TO ELIMINATION REACTIONS

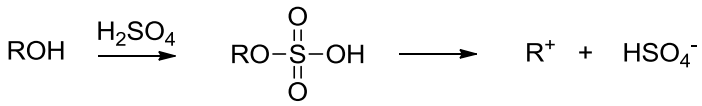
A β-elimination reaction in its simplest form is the removal of two groups from adjacent atoms so that a new double (or triple) bond can be formed (Scheme 1.1.1). There are two types of β-elimination reactions: (1) those that take place in solution and (2) those that take place in the gas phase (pyrolytic elimination or flash vacuum pyrolysis).[1]



Scheme 1.1.1

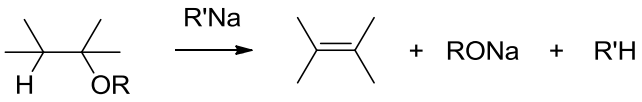
Most elimination reactions involve the loss of water (dehydration) to form olefins. The most general and common method for dehydration is to use an acid, e.g., sulfuric,

phosphoric, or *p*-toluenesulfonic (Scheme 1.1.2). These reactions normally involve the formation of a carbonium ion, which, under normal conditions, can lead to the rearrangement of the carbon skeleton.[2] Eliminations, occurring in solvent, that employ sulfonate esters of alcohols can also lead to the same rearrangement products. These acid–promoted eliminations can be disadvantageous when the alcohol possesses other acid–sensitive functional groups. In these cases, other conditions, e.g., basic, must be used.



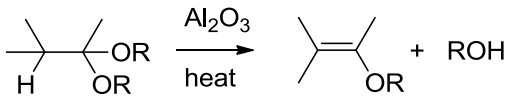
Scheme 1.1.2

Alkenes have been formed through the treatment of ethers with very strong bases, such as alkylsodium (Scheme 1.1.3), alkyllithium reagents or sodium amide, although these reagents produce unfavorable side reactions. This elimination is aided by the introduction of electron-withdrawing groups in the β-position, and some systems can undergo elimination simply upon heating without any base added.[3]



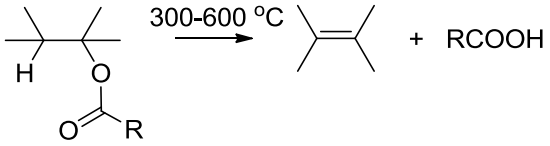
Scheme 1.1.3

Vapor-phase dehydration of alcohols over aluminum oxide (Scheme 1.1.4) or phosphorous oxide is another viable option. It can be a superior method to acid dehydration in the liquid phase, but the high reaction temperatures (300-500 ^{o}C) required for this elimination to occur render it useless for compounds which cannot be vaporized readily or undergo decomposition or rearrangement.[3]



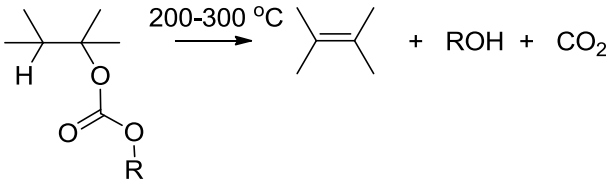
Scheme 1.1.4

Another useful and commonly employed dehydration method is the pyrolysis of esters, commonly the acetates (Scheme 1.1.5). Esters in which the alkyl group has a β-hydrogen can be pyrolyzed, most often in the gas phase, to give the corresponding acid, most often acetic acid, and an alkene. No solvent is required, and few side reactions or rearrangements occur. The reaction is simple, and workup is easy; however, these eliminations also require high temperatures (300-600 ^{o}C), which are disadvantageous for many systems.[5]



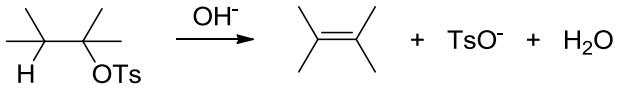
Scheme 1.1.5

Two other functional groups that are not quite as stable to pyrolysis as an ester are a carbonate (Scheme 1.1.6) and a carbamate. Carbonate esters possess the additional advantage that the byproducts produced, carbon dioxide and an alcohol, are neutral and do not react with the newly formed olefin. This method, while relatively mild in its conditions, and yielding neutral byproducts, has not found general use.[6]



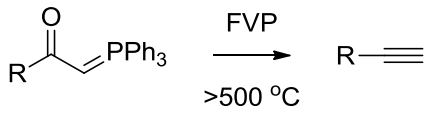
Scheme 1.1.6

Several other esters undergo elimination to create olefins. For example, esters of sulfuric, sulfurous, and other acids undergo elimination in solution, as do tosylates (Scheme 1.1.7) and other esters of sulfonic acids.[7] Aryl sulfonates produce alkenes upon heating without solvent or base. Esters of $PhSO_2OH$ and *p*-TsOH have been cleaved to alkenes when heated in dipolar aprotic solvents such as DMSO or HMPA.[8]



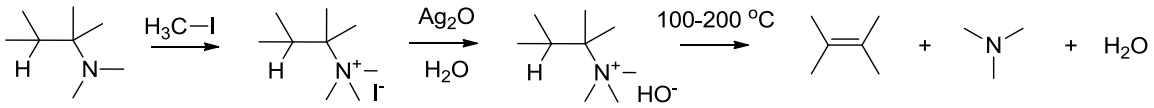
Scheme 1.1.7

Phosphorous ylids are common in organic synthesis, as are keto-phosphorous ylids. Upon heating (flash vacuum pyrolysis, FVP) to temperatures greater than 500 ^oC, alkynes are formed (Scheme 1.1.8). Simple alkynes, keto-alkynes, and en-ynes all can be prepared using this method.[9]



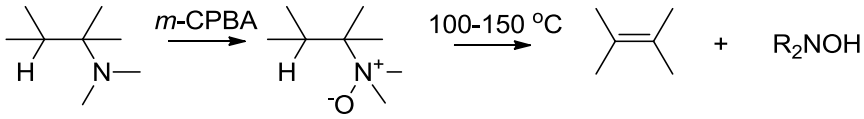
Scheme 1.1.8

In the Hoffman exhaustive methylation, a quaternary ammonium hydroxide, prepared from an amine, undergoes elimination upon heating (Scheme 1.1.9). In the first step, a primary, secondary, or tertiary amine is converted to a quaternary ammonium iodide upon treatment with methyl iodide. In the second step, the quaternary ammonium iodide is converted to the quaternary ammonium hydroxide by treatment with silver oxide. The hydroxide, in aqueous or alcoholic solution, is then distilled, and elimination to the desired alkene occurs between 100 and 200 ^oC.[10]



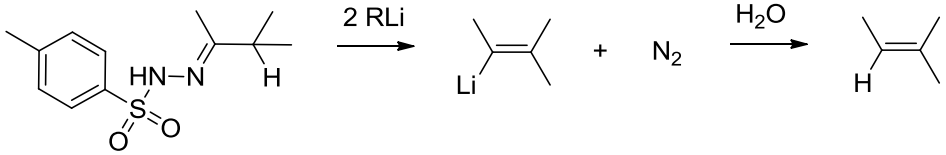
Scheme 1.1.9

The Cope elimination describes the cleavage of an amine oxide to produce an alkene and a hydroxylamine (Scheme 1.1.10). The amine oxide is first prepared via treatment of an amine with an oxidizing agent, usually hydrogen peroxide or *m*-CPBA. The conditions for the elimination are relatively mild (100-150 ^{o}C), and there are few side reactions and alkene rearrangements, making this a useful method for the preparation of alkenes.[11]



Scheme 1.1.10

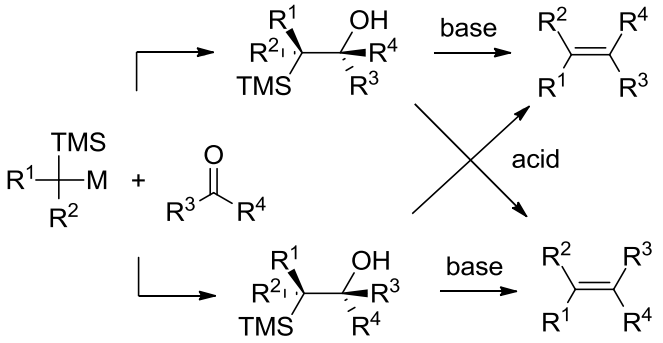
In the Shapiro reaction, a tosylhydrazone undergoes elimination upon treatment with a strong base, usually an alkyllithium reagent (Scheme 1.1.11). The tosylhydrazone is first prepared from an aldehyde or a ketone via treatment with tosylhydrazine. Upon treatment of tosylhydrazone with a strong base, elimination occurs, accompanied by a hydrogen shift, to give the alkene. This procedure has few side reactions and predominantly gives the less highly substituted alkene when a choice is possible.[12]



Scheme 1.1.11

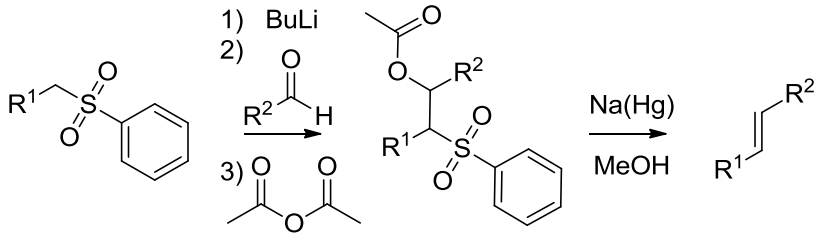
The Peterson reaction describes the preparation of alkenes from α-silylcarbanions (Scheme 1.1.12). The first step involves the addition of the α-silylcarbanion to a carbonyl

compound, producing diastereomeric adducts of the β-hydroxy silane. These diastereomers can be isolated and then treated with either acid or base to produce the desired alkene. Since treatment with acid or base produces different alkene stereoisomers, it is possible to increase the yield of the desired stereoisomer by performing two different eliminations on the diastereomeric β-hydroxy silanes.[13]



Scheme 1.1.12

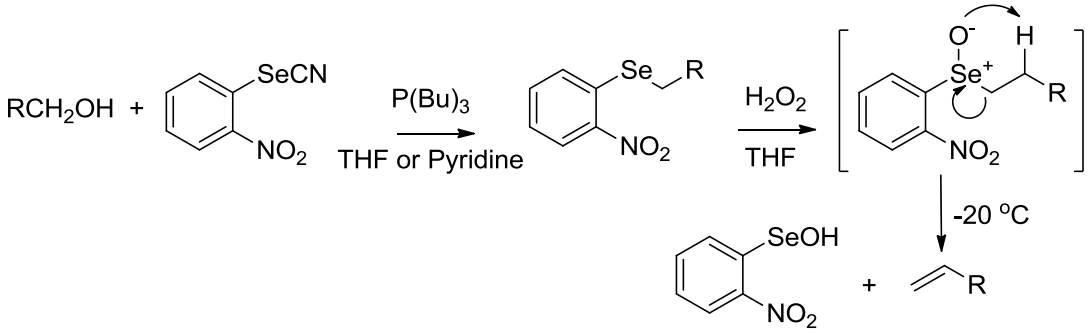
In the Julia olefination, alkenes are prepared from phenyl sulfones (Scheme 1.1.13). The alkoxide of phenyl sulfone is first created and reacted with a carbonyl compound. The resulting anion is trapped with acetic anhydride to form an acetate. Upon treatment with sodium-mercury amalgam or samarium(II) iodide, the alkene is produced via a vinylic radical species. This reaction highly favors the creation of the *trans*-alkene.[14]



Scheme 1.1.13

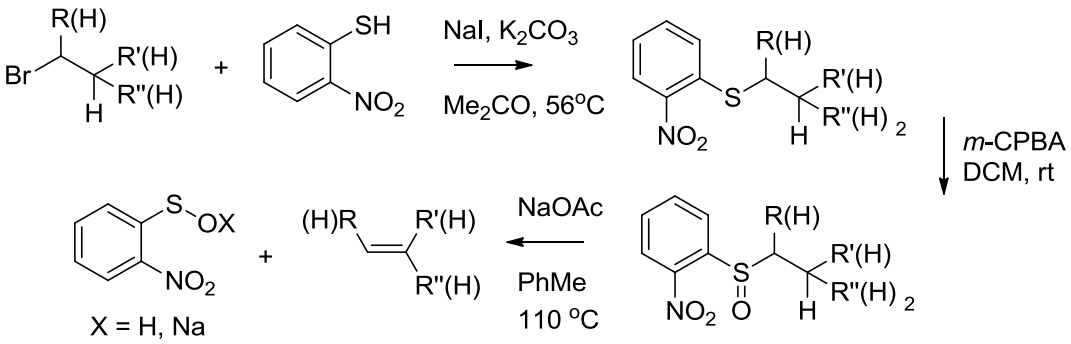
Organoselenium complexes have also been employed in olefin syntheses. The Grieco olefination (Scheme 1.1.14) is a prominent example of an elimination reaction of

a primary alcohol to a terminal alkene via a selenide intermediate. The reactants in the Grieco olefination are *o*-nitrophenylselenocyanate and tri-*n*-butylphosphine which first converts the alcohol to a selenide through a nucleophilic substitution on the electron-deficient selenium. Oxidation of the selenide to a selenoxide with hydrogen peroxide causes for the elimination to occur accompanied by the evolution of phenylselenol. This reaction was made more favorable by the addition of the electron-withdrawing groups on the phenyl ring which allowed for elimination to take place at very low temperatures, e.g., -20 ^{o}C.[15]



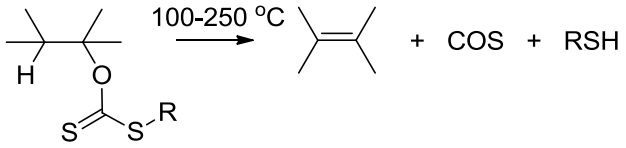
Scheme 1.1.14

Like selenoxides, sulfoxides also undergo olefination. Lu and Long found that *o*-nitrophenyl sulfoxides underwent elimination to produce the desired alkene (Scheme 1.1.15).[16] Reaction of an alkyl halide with *o*-nitrothiophenol created a sulfide which was oxidized with *m*-CPBA to produce an *o*-nitrophenyl sulfoxide. Elimination occurred in toluene and NaOAc to generate substituted and terminal alkenes and the *o*-nitrophenyl sulfenic acid byproduct.



Scheme 1.1.15

A final method of elimination and the basis for this study is the Chugaev elimination (Scheme 1.1.16) which offers the advantages of low temperatures, basic reaction conditions, and no rearrangements.[17] Sometimes the Chugaev reaction experiences difficulties in either the preparation or the purification of the requisite xanthate esters, or in the removal of sulfur-containing impurities from the olefin.



Scheme 1.1.16

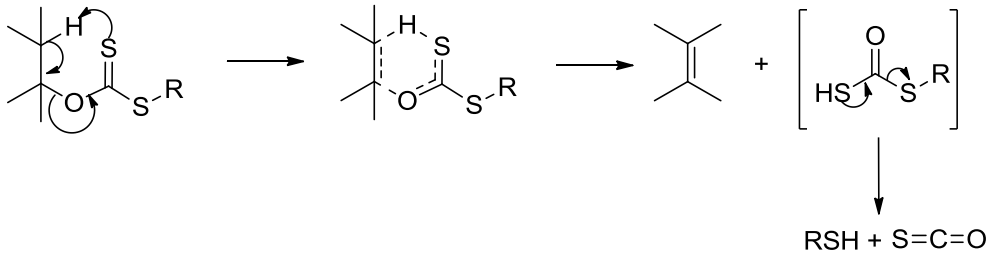
1.2 THE CHUGAEV ELIMINATION

The Chugaev elimination is broadly defined as the thermal decomposition or pyrolysis of a xanthate ester of an alcohol that contains at least one β-hydrogen to produce an olefin, carbon oxysulfide, and a thiol (Scheme 1.1.8). This reaction is similar to the thermal decomposition of acetates, carbamates, and carbonates, to produce olefins.

Chugaev discovered the reaction in 1899[17] in connection with his studies on the optical properties of xanthates.[18] This reaction was employed in his investigation of

terpenes, and he demonstrated its use as an olefin-forming reaction and its usefulness in structure determination.

Examination of the Chugaev elimination has revealed that the reaction proceeds via the formation of a cyclic transition state involving the *syn*-β-hydrogen of the alcohol moiety and the thion (double bond) sulfur atom of the xanthate. An olefin and an unstable dithiocarbonate derivative are. The dithiocarbonate subsequently decomposes to carbon oxysulfide and a thiol (Scheme 1.2.1).



Scheme 1.2.1

Barton[19] and Cram[20] proposed that the reaction was concerted, involving a *syn*-β-hydrogen atom, and involved β-hydrogen abstraction by the less hindered thion sulfur atom rather than the thiol sulfur atom (Scheme 1.2.1). Evidence for this assertion that the thion sulfur atom was involved in the abstraction was reported by Bader and Burns,[21] based on a study of sulfur and carbon isotope effects for the pyrolysis of *trans*-2-methyl-1-indanyl xanthate of natural isotopic abundance (Table 1.2.1).

Table 1.2.1 Isotope effects in the pyrolysis at 80 ^{o}C of *S*-methyl *trans*-2-methyl-1-andayl xanthate.

	Per Cent Isotope Effect, $100(k^L/k^H - 1)$		
	Thiol Sulfur S^{32}/S^{34}	Thion Sulfur S^{32}/S^{34}	Carbonyl Carbon C^{12}/C^{13}
Predicted Thiol Sulfur Thion Sulfur	 ~ 1.2 ~0.0	 ~ 0.0 0.7 – 1.0	 3.0 – 4.0 ~0.0
Found	0.21 ± 0.07	0.86 ± 0.16	0.04 ± 0.06

Barton used the term "molecular mechanism" to describe the mechanism of the Chugaev elimination, acetate pyrolysis, and other olefinations. These eliminations proceed through a cyclic transition state involving neither ions nor radicals, but rather a redistribution of the electrons accompanied by concerted bond making and bond breaking.[19] He also examined the preferred *syn* course of the Chugaev reaction, thereby predicting the configurations of a number of eliminations.

The *S*-methyl xanthates are the most frequently used, but higher *S*-alkyl and *S*-benzyl substituted xantates have also been used to successfully prepare olefins. Xanthates have been prepared and successfully pyrolyzed from primary alcohols, secondary acyclic and alicyclic alcohols, tertiary acyclic and alicyclic alcohols, glycols, and dihaloalkanes. It has been suggested that primary alcohols are more stable to pyrolysis than secondary or tertiary alcohols; however, there is not enough evidence to support this claim.[22]

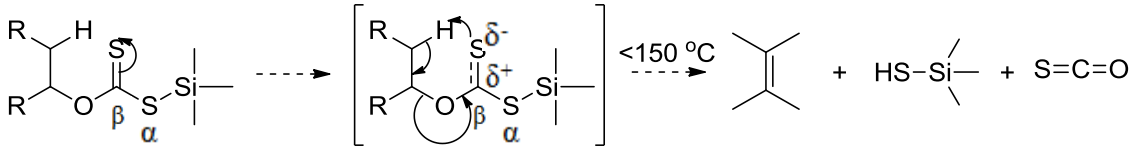
1.3 MODIFYING THE CHUAGEV ELIMINATION

Qualitative studies on the (–)-menthyl xanthates showed that varying the *S*-alkyl group affected the stability of the xanthate toward pyrolysis.[23] The use of an isopropyl group instead of a methyl group increased the stability of the xanthate while a benzyl

group decreased the stability and a *p*-nitrobenzyl group decreased the stability further. This suggests that electronegative groups on the thiol sulfur decrease the activation energy for the Chugaev reaction. The stability of xanthogen amides was also examined and found to require higher temperatures (200-220 ^{o}C) for the formation of the olefin.[24]

By examining these findings and the mechanism of the Chugaev elimination, we hypothesized that the reaction could be improved by changing the sulfur substituent of the xanthate. Previous investigations have examined the effects of changing the *S* alkyl substitutent, but no attention has been directed toward the possible stabilizing effects of an appropriately functionalized *S* substituent.

Silicon has been found to aid in 1,2- and 1,4-eliminations.[25] It, along with tin, has been found to produce a β-effect, which helps stabilize positive charges thereby making the thion (double bond) sulfur atom a better base.[26] While the Chugaev elimination proceeds via a concerted mechanism, the introduction of a silicon or a tin atom could stabilize the partial negative charge build-up on the thion sulfur atom, increasing the nucleophilicity of the thion sulfur atom and thereby lowering the pyrolysis temperature (Scheme 1.3.1).

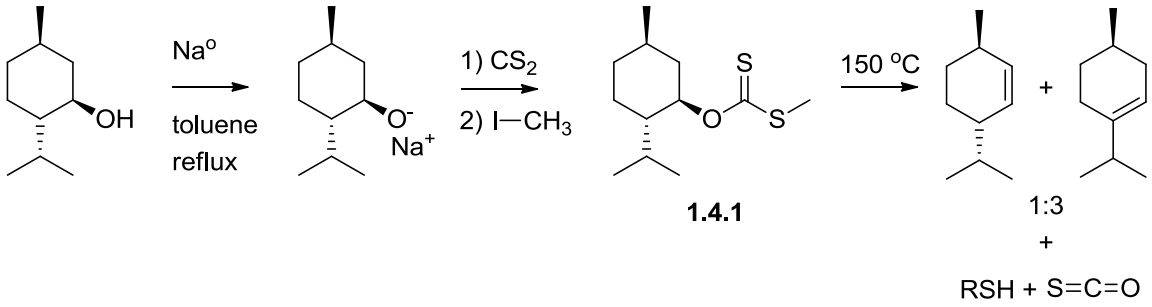


Scheme 1.3.1

1.4 SYN**THESIS OF XANTHATES**

Our investigation of the Chugaev elimination began by first preparing the *S*-methyl xanthate (**1.4.1**) of (–)-menthol under standard conditions[17, 27] by treating the alcohol with sodium metal and carbon disulfide (Scheme 1.4.1). The purification of the

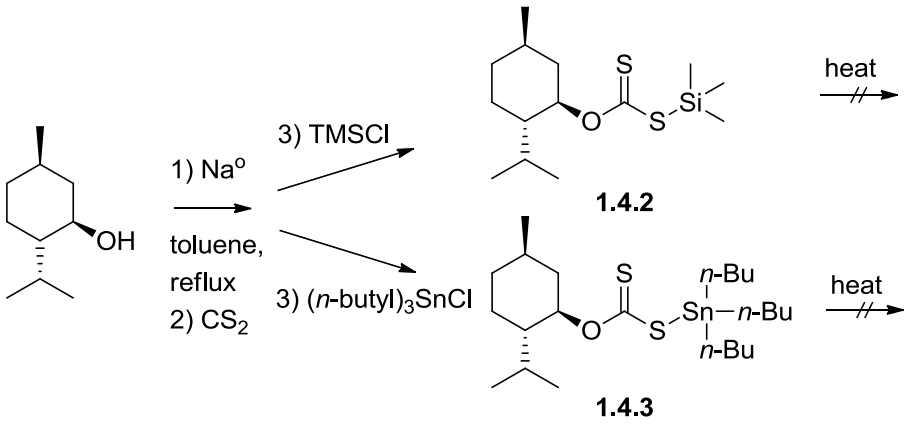
xanthate was accomplished through recrystallization in ethanol and water, but was later done with column chromatography, resulting in a greater yield. The pyrolysis elimination was carried out at 150 ^{o}C by refluxing the xanthate neat (Scheme 1.4.1). This reaction temperature is relatively close to the boiling point of the menthene, which is 165 ^{o}C. A mixture of menthenes was isolated in a relatively low yield, and attempts to separate the olefins proved to be futile.



Scheme 1.4.1

Once the Chugaev elimination had successfully been observed, we tested the hypothesis that the stabilizing effect of silicon and tin atoms would make the corresponding functionalized xanthates less stable to pyrolysis. The xanthates of (–)-menthol were prepared under standard conditions by treating the alcohol with sodium metal and carbon disulfide.[17, 27] The anion was trapped first using trimethylsilyl chloride to produce *O*-((1*R*,2*R*,5*R*) 2-isopropyl-5-methylcyclohexyl) *S*-(trimethylsilyl) carbonodithioate (**1.4.2**) and in another trial, was trapped again with tri-*n*-butyltin chloride to produce *O*-((1*R*,2*R*,5*R*) 2-isopropyl-5-methylcyclohexyl) *S*-(tributylstannyl) carbonodithioate (**1.4.3**). The xanthate synthesized from the reaction with tri-*n*-butyltin chloride was produced in higher yields and higher purity, requiring virtually no purification. However, the xanthate synthesized by adding trimethylsilyl chloride was produced in low yield and low purity and required purification via silica gel

chromatography. These two xanthates were refluxed at 150 ^{o}C neat, producing no elimination and no menthenes! Starting material was recovered in both cases, except xanthate **1.4.3**, which showed some decomposition to an unknown product (Scheme 1.4.2).



Scheme 1.4.2

The acetate of (–)-menthol was prepared by reacting the alkoxide with acetic anhydride. This compound was used as a comparison in the elimination studies of the xanthate derivatives we prepared. The acetate did not undergo elimination at 150 ^{o}C or at temperatures as high as 200 ^{o}C, the highest temperature tested in this study. This observation is consistent with reports that acetates only undergo elimination at 300 ^{o}C or higher.[5]

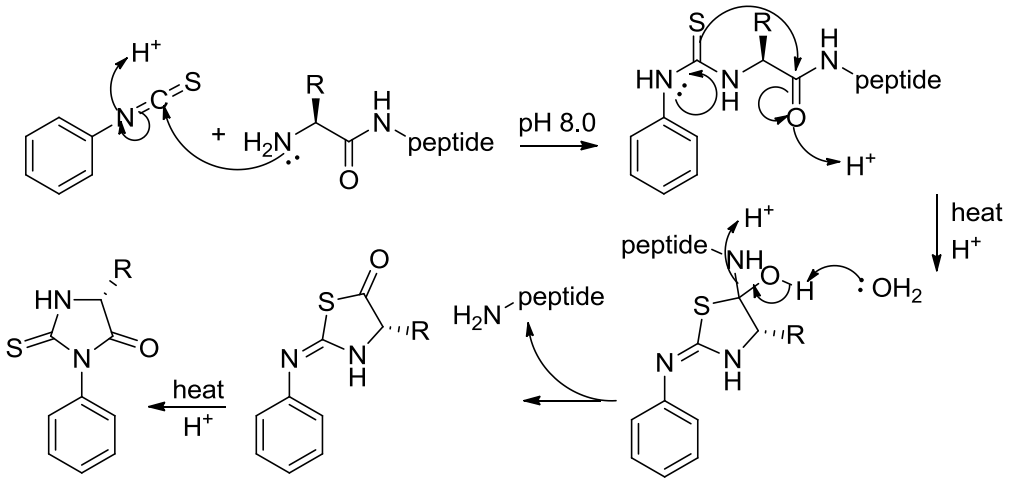
1.5 THE USE OF PHENYL ISOTHIOCYANATE IN ELIMINATION REACTIONS

After it was discovered that the group 14 metals, silicon and tin, made the menthyl xanthate more stable towards elimination, other alternatives were sought to improve the Chugaev elimination. The first alternative tested was tetramethylthiourea.

This compound seemed to possess the necessary electrophilic quality to enable nucleophilic attack by the alkoxide of (–)-menthol. However, the alkoxide of (–)-menthol did not add to the tetramethylthiourea, due perhaps to solubility issues as both reactants were recovered.

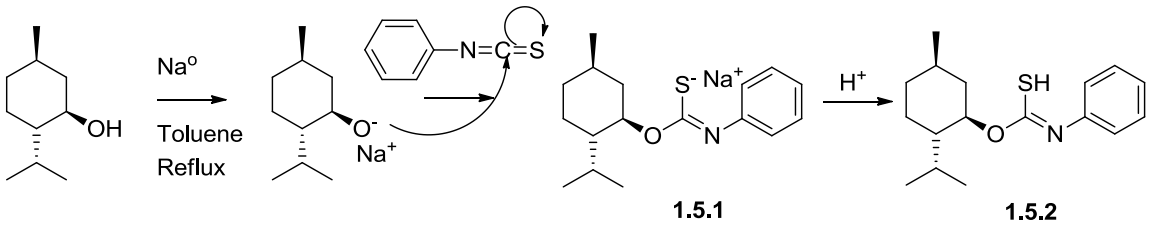
Examination of the structure of tetramethylthiourea revealed that perhaps the electrophilic character of the central carbon could be increased by having a double bond between the carbon and the nitrogen as well as the sulfur; this compound is known as an isothiocyanate, particularly, the readily available phenyl isothiocyanate. The reaction between the phenyl isothiocyanate and the alkoxide of (–)-menthol occurred in high yield at room temperature and required only one equivalent of the phenyl isothiocyanate. The purity of the product was also extremely high as only a short silica gel column was required to remove any solid impurities.

The reaction between the alkoxide of (–)-menthol and the phenyl isothiocyanate was believed to occur along the same mechanism as the Edman degradation.[28] This reaction proceeds via the nucleophilic attack of a terminal amine of a protein on phenyl isothiocyanate. The electrons contained in the double bond between the nitrogen and the central carbon are believed to be displaced by the attack and migrate to the nitrogen, establishing a negative charge on the nitrogen (Scheme 1.5.1).



Scheme 1.5.1

To fully understand the mechanism of the addition of (–)-menthol to the phenyl isothiocyanate, the anion created in the intermediate, **1.5.1**, was trapped with iodomethane. The observed ^{1}H NMR shift at 2.3 ppm of the methyl group established that the mechanism of the Edman degradation did not apply to our system. Instead, the electrons in the double bond between the sulfur and the central carbon are displaced by the nucleophilic attack of the alkoxide. This establishes a negative charge on the sulfur atom. Therefore, the reaction between (–)-menthol and phenyl isothiocyanate resulted in (*Z*)-*O*-((1*R*,2*R*,5*R*)-2-isopropyl-5-methylcyclohexyl) *S*-hydrogen phenylcarbonimidothioate (**1.5.2**, Scheme 1.5.2).

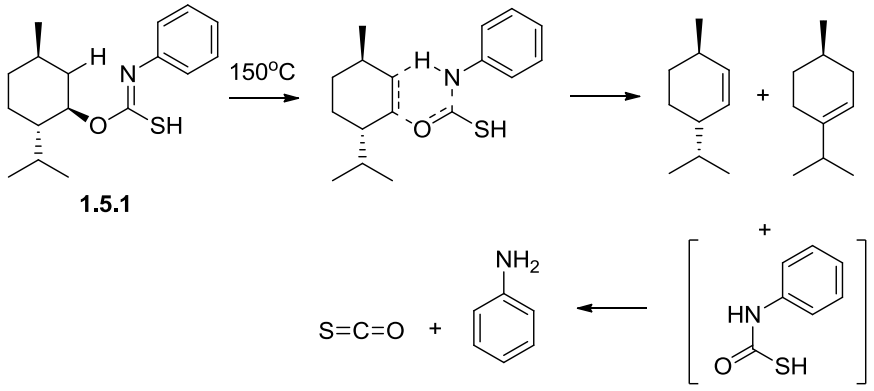


Scheme 1.5.2

Compound **1.5.2** was refluxed at 150 °C to undergo elimination to afford a mixture of menthenes. According to ^{1}H NMR analyses, the conversion of compound

1.5.2 to a mixture of menthenes occurred in the same yield as that observed for the *S*-menthyl xanthate of the general Chugaev elimination.

Unfortunately, no definitive conclusions can be reached about the mechanism of this elimination. We assume that the double-bonded nitrogen is responsible for nucleophilic attack on the *syn*-β-hydrogen, since nitrogen is more nucleophilic, assuming the same mechanism as the Chugaev elimination (Scheme 1.5.3). As with the Chugaev elimination, there are a variety of byproducts that have been difficult to characterize. A minor byproduct was found to be aniline (TLC and ^{1}H NMR spectra). The isolation of aniline suggests that Scheme 1.5.3 is a possible mechanism; however, further studies, including isotope effects, are needed to confirm it.



Scheme 1.5.3

We next investigated the sodium salt, **1.5.1**, in hopes that a differentiation in the temperature of pyrolysis would be observed. This investigation also included the potassium and lithium salts, both of which were created by using the respective metals, postassium and lithium, instead of sodium metal to create the alkoxide.

Because of the high boiling points of these salts, they were not simply refluxed neat. Instead they were refluxed in either toluene (bp 110 ^{o}C) or *o*-xylene (bp 144 ^{o}C). It was found that elimination occurred in the *o*-xylene but not in the toluene. These results

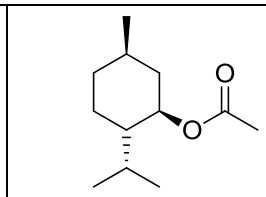
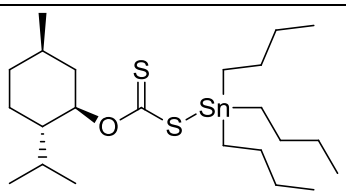
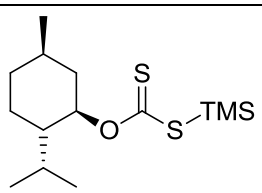
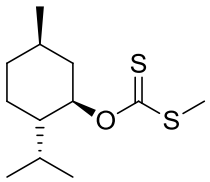
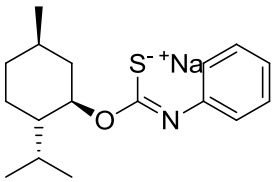
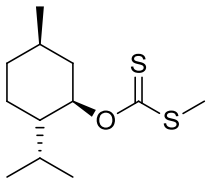
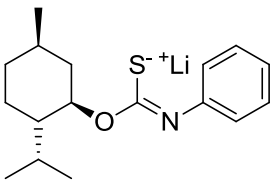
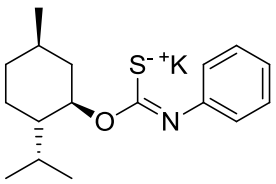
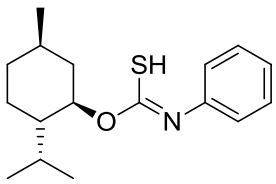
indicate that these salts undergo elimination at roughly the same temperature as a Chugaev xanthate.

We tried to establish for each prepared compound a distinct temperature where upon pyrolysis occurred. Thus, we sought some method in which weight loss could be registered at various temperatures. The analytical method decided upon was thermogravimetric analysis (TGA).[29]

The results of the TGA are summarized in Figure 1.5.1. Table 1.5.1 is a numbering key to Figure 1.5.1. We concluded that the TGA results were not indicating the temperature at which pyrolysis was occurring but rather the boiling point for each of the nine compounds. It was hoped that differential scanning calorimetry (DSC) might be more useful to identify the actual temperature of pyrolysis.[30] Only the first two compounds were tested using DSC as summarized in Figure 1.5.2. The DSC data also proved to be inconclusive, most likely giving the enthalpies of vaporization instead of the heats of pyrolysis. Because both the DSC and TGA analytical methods proved unable to provide insight into the temperature of pyrolysis, a more practical method was developed.

Because pyrolysis occurs in the gas phase and refluxing is required for the formation of the alkenes, sealed ampoules were employed to test the stability toward pyrolysis of each substrate. Five baths were maintained at five different temperatures, spanning the range of 100 to 200 ^{o}C at 25 ^{o}C intervals. Each substrate was heated for six hours at each temperature, and then a ^{1}H NMR spectrum was obtained to deduce the extent of elimination

Table 1.5.1. Reference Table for Numbering Scheme of Figure 1.5.1. Numbers 1 and 2 are the same for Figure 1.5.2.

1		4		7	
2		5		8	
3		6		9	

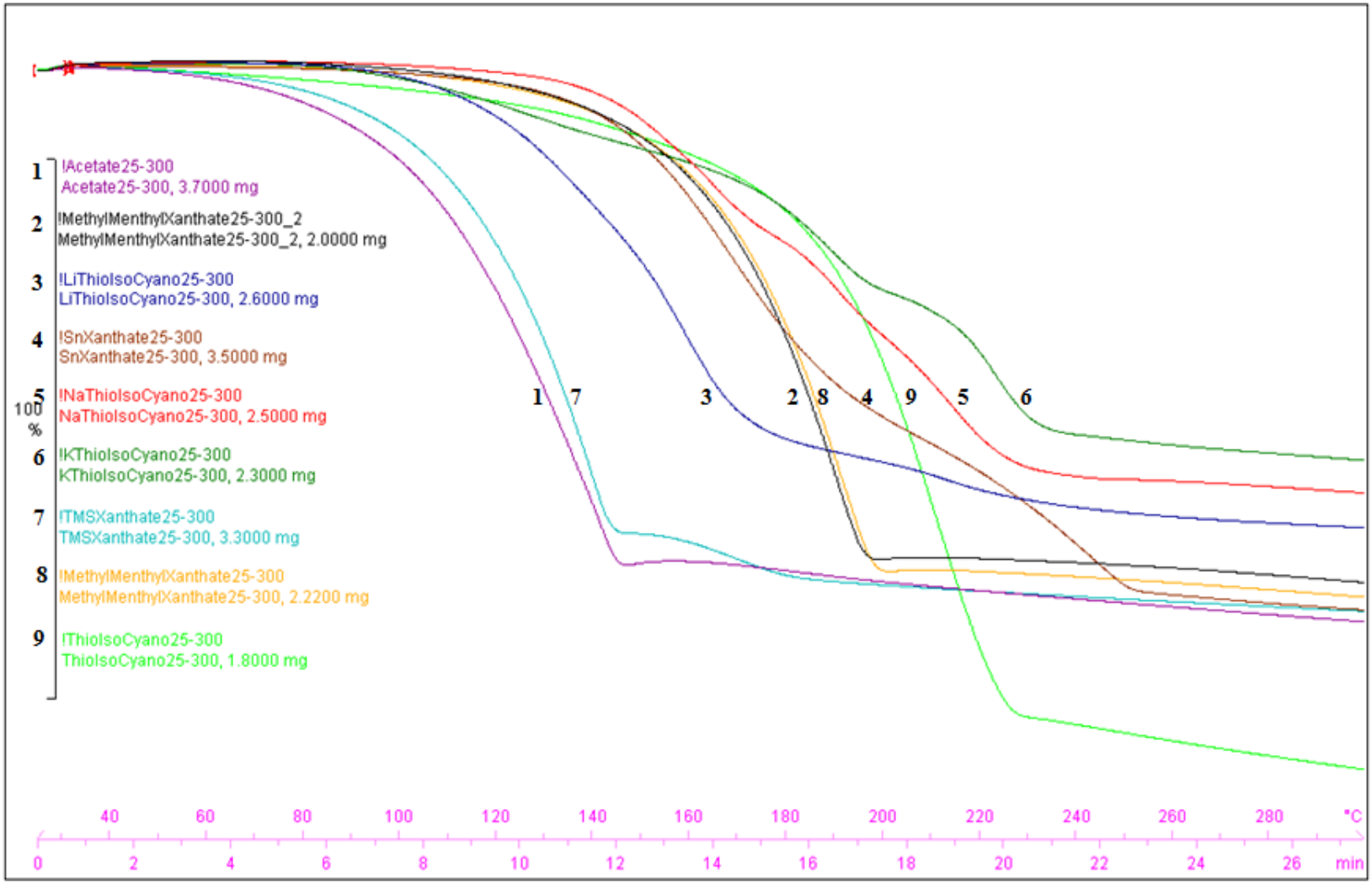


Figure 1.5.1. Results from TGA analysis of select compounds. See the numbering Scheme in the figure or in the text for correlation.

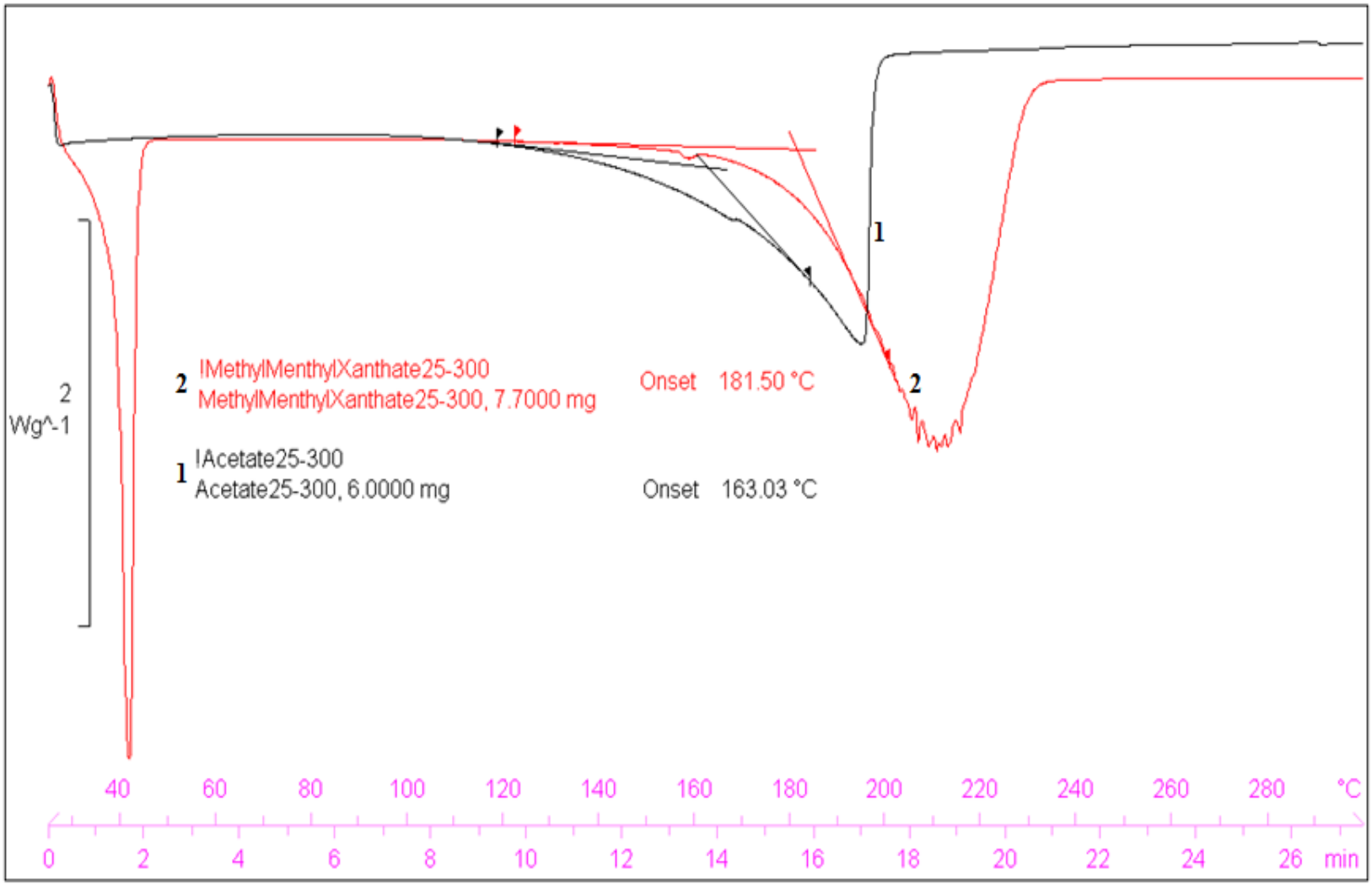


Figure 1.5.2. Results from DSC analysis of select compounds. See the numbering Scheme in the figure or in the text for correlation.

Out of the three xanthates (**1.4.1**, **1.4.2**, and **1.4.3**), only the original Chugaev *S*-methyl xanthate, **1.4.1**, of (–)-menthol eliminated at 150 ^{o}C, as was known.[27] The xanthates formed from TMSCl (**1.4.2**) and tri-*n*-butyltin chloride (**1.4.3**) failed to eliminate even at elevated temperatures. The fact that these xanthate derivatives were stable to heating was attributed to the electro-positive nature of the silicon and tin atoms, which also donate electrons.

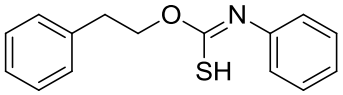
Electronegative groups on the thiol sulfur atom decrease the activation energy for the Chugaev elimination, making the xanthate less stable toward pyrolysis. Electron-donating groups have the opposite effect of stabilizing the xanthate, forcing it to eliminate at higher temperatures.[23]

Compound **1.5.2** produced menthenes beginning at 150 ^{o}C in a yield which is comparable to xanthate **1.4.1**. Both compounds produced maximum conversion to menthenes by 175 ^{o}C. These findings confirmed that phenyl isothiocyanate is a viable alternative to xanthates in pyrolytic elimination reactions. The Na^{+}, Li^{+}, and K^{+} salts of compound **1.5.2** were tested at the five temperatures, and elimination occurred at temperatures greater than 150 ^{o}C.

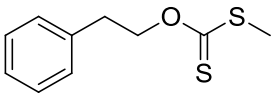
The fact that the alkali metal salts of compound **1.5.2** failed to produce the elimination product at a lower temperature suggests that the sulfur atom is not involved in the elimination mechanism, adding further evidence to the possibility that the nitrogen is really responsible for the nucleophilic attack and subsequent elimination.

The use of phenyl isothiocyanates in the elimination of alcohols via *syn*-β-dehydrogenation elimination was also studied using 2-phenylethanol. The alkoxide of this alcohol was again generated through dissolving sodium metal, but it was found that

refluxing THF decreased the temperature and the time of reaction for the formation of the alkoxide. This was attributed to the different substrate as well as the polarity of the solvent. After the generation of the alkoxide, one equivalent of phenyl isothiocyanate was again added to the solution to generate, (*Z*)-*O*-phenethyl *S*-hydrogen phenylcarbonimidothioate, **1.5.3**. This compound was again tested against the *S*-methyl xanthate of the alcohol, **1.5.4**, to determine the viability of the method. The advantage of this alcohol over (–)-menthol is that only one elimination product can be created, styrene, which is a well-characterized compound.



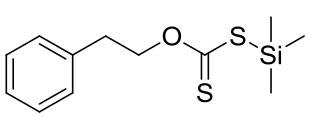
1.5.3



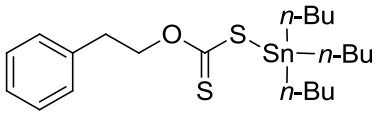
1.5.4

Again, the different salts of compound **1.5.3** were prepared using the three different alkali metals, sodium, lithium, and potassium, to create the alkoxide, and no acid was added in workup to protonate the sulfur. These salts were refluxed in toluene and *o*-xylene; elimination occurred in the *o*-xylene but not in toluene. The salts were tested at the five temperatures cited, and again, elimination occurred at 150 ^{o}C. Like the salts of compound **1.5.2**, these salts also failed to melt at temperatures less than 150 ^{o}C. The protonated compound **1.5.3** underwent elimination at 150 ^{o}C just as compound **1.5.2.** From the ^{1}H NMR spectrum, it appeared that the yield of elimination product for both compounds **1.5.3** and **1.5.4** was less than that observed for (–)-menthol, a conclusion that lends legitimacy to the claim that primary alcohols are more stable toward pyrolysis. However, both compounds **1.5.3** and **1.5.4** underwent elimination at the same temperature in comparable conversion, based on ^{1}H NMR.

To demonstrate the lack of reactivity of the silicon and tin xanthates, those experiments were also repeated on this substrate to yield compounds **1.5.5** and **1.5.6**.



1.5.5



1.5.6

No elimination occurred upon heating either substrate in the temperature range of 100-200 ^{o}C. This observation supports the conclusion that electronegativity plays a large role in the stability of the xanthate toward elimination.

1.6 ARYL ISOTHIOCYANATE DERIVATIVES IN ELIMINATION REACTIONS

After testing phenyl isothiocyanate as a viable alternative to the normal, *S*-methyl Chugaev elimination, it was necessary to examine the effect of adding substituents on the aryl moiety. Upon examination of previous elimination reactions involving substituted aryl systems, e.g., the Grieco olefination, it was decided to test the effect of adding both electron-withdrawing and electron-donating groups to the *para* position of the aryl moiety.

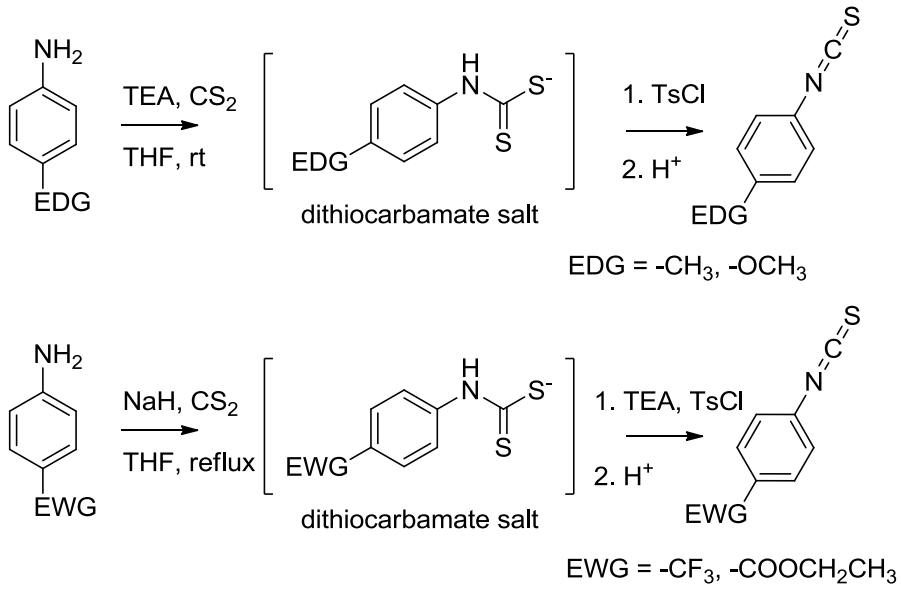
Examination of the Grieco olefination revealed that the addition of a nitro group *ortho* to the Se position on the benzene ring greatly decreased the stability of the system toward elimination, allowing it to proceed at much lower temperatures.[15] The first substrate made was 1-isothiocyanato-4-nitrobenzene. A literature procedure reported the conversion of aniline to phenyl isothiocyanate by first creating an ammonium phenyldithiocarbamate salt with carbon disulfide and aqueous ammonia. This salt was then reacted with lead nitrate to give phenyl isothiocyanate and lead sulfide, a highly

insoluble byproduct.[31] This procedure was repeated on *p*-nitroaniline but no product was obtained.

Another procedure for the synthesis of isothiocyanates involved the creation of dithiocarbamate salt from aniline but used triethylamine and carbon disulfide. The salt was not reacted with lead nitrate as in the previous procedure but was reacted with *p*-toluenesulfonyl chloride followed by an acidic workup.[32] This procedure did not produce the insoluble lead sulfide as a byproduct, making it a much easier synthetic procedure. This route also reported yields for the creation of different aryl isothiocyanates. Unfortunately, it reported a 0% yield for the creation of 1-isothiocyanato-4-nitrobenzene. Therefore, other substrates were focused upon.

Upon examination of the various isothiocyanates that had been synthesized in the literature,[32] four substrates were chosen. The electron-withdrawing groups chosen were a trifluoromethyl group and an ethyl ester. The electron-donating groups chosen were a methyl group and a methyl ether.

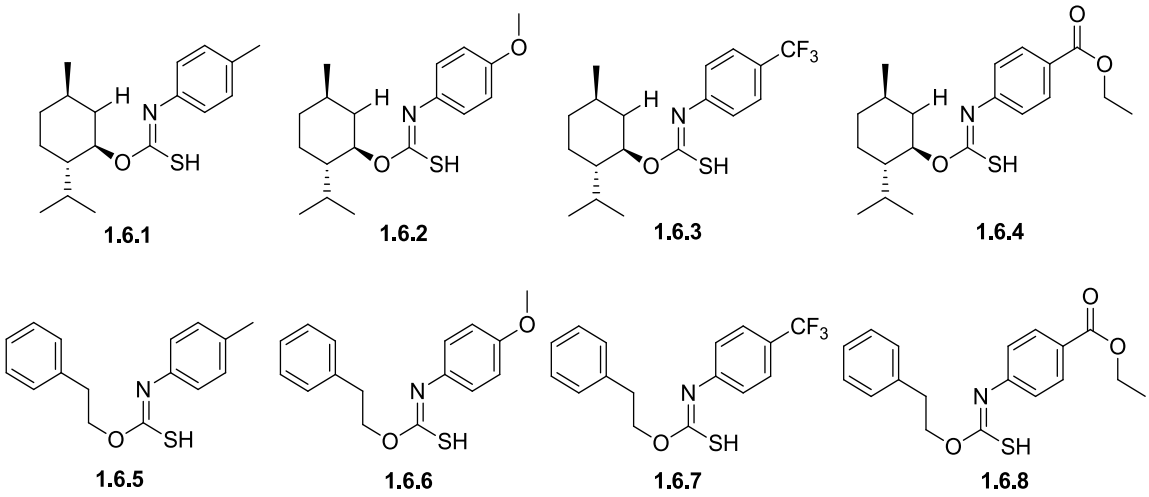
The procedure for the creation of an isothiocyanate from an electron-rich aryl amine system involved the creation of the dithiocarbamate salt using triethylamine and carbon disulfide at room temperature. The salt was then reacted with *p*-toluenesulfonyl chloride followed by acidic workup to create the isothiocyanate. For electron-poor aryl amine systems, the aniline starting material was reacted with sodium hydride and carbon disulfide in refluxing THF to create the dithiocarbamate salt. The salt was then reacted with additional triethylamine, followed by *p*-toluensulfonyl chloride and acidic workup. Both routes are summarized in Scheme 1.6.1.



Scheme 1.6.1

The creation of the aryl isothiocyanate analogues occurred in relatively high yields, with the electron-rich systems having higher yields than the electron-poor systems. While the yields were high, the reactions themselves produced a large number of byproducts that had to be separated via column chromatography. This proved difficult as the desired isothiocyanates had polarities similar to many of the byproducts. Later, we found that simple distillation under reduced pressure produced the desired isothiocyanates in similar yields and high purity.

Once the four aryl isothiocyanates were synthesized, they were reacted with both the menthyl alkoxide and the alkoxide of the 2-phenylethanol in a manner similar to Scheme 1.5.2. This produced compounds **1.6.1**, **1.6.2**, **1.6.3**, **1.6.4**, **1.6.5**, **1.6.6**, **1.6.7**, and **1.6.8**.



The synthesis of these analogues was accomplished with a 1:1 ratio of alcohol to isothiocyanate. It was also found that if the isothiocyanate was properly isolated and pure, the addition of the isothiocyanate to the alcohol required no purification. In most cases, only a short column to remove any residual solids was needed, but no separation was required. Generally, the yields for the production of the various compounds were high. It was found that the compounds produced from electron-poor aryl isothiocyanates had lower yields than those made with electron-rich isothiocyanates.

Upon heating, all compounds, **1.6.1**, **1.6.2**, **1.6.3**, **1.6.4**, **1.6.5**, **1.6.6**, **1.6.7**, and **1.6.8**, underwent elimination at 150 ^{o}C. Although these results confirm the viability of using isothiocyanates as tools in elimination reactions, there was no discernable advantage of the various electron-withdrawing and electron-donating groups on the stability of the compound toward elimination. This is contrary to what has been seen in other situations, e.g., Grieco olefination, and is contrary to what was expected. The electron-withdrawing groups should have decreased the stability of the system toward elimination just as electronegative *S* groups on Chugaev xanathates decreased their stability toward elimination. The mechanism of these reactions is also assumed to be the

same as that outlined in Scheme 1.5.3, clearly further research is required to establish a mechanism for the reaction.

1.7 CONCLUSIONS

It is known that the Chugaev elimination is controlled by the electronegativity of the *S*-xanthate substituent, with greater electronegativity correlating to lower stability toward elimination. During this investigation, tin and silicon were introduced as the *S*-xanthate substituent, both of which are electropositive and electron-donating. However, experimentally, these xanthates were more stable and did not even eliminate at the highest temperature tested, 200 ^{o}C. This finding reinforces the conclusion that the Chuagev is controlled by the electronegativity of the *S*-substituent of the xanthate. The study also focused on finding an alternative method for pyrolitic elimination witnessed in the Chugaev elimination. This alternative was found in reacting the alkoxide of an alcohol with aryl isothiocyanates. The resulting carbonimidothioate eliminated at roughly the same temperature as *S*-methyl xanthates, approximately 150 ^{o}C. Finally, the presence of electron-withdrawing or electron-donating groups on the benzene ring of the isothiocyanate showed no change in stability toward elimination.

1.8 FUTURE STUDIES

Several additional investigations need to be made in order to complete this study of the Chugaev elimination and the use of isothiocyanates in elimination reactions.

The first future study includes the application of the work completed by Lu and Long[16] to alkyl xanthates. The oxidative elimination via the creation of a sulfoxide occurs at low temperatures and will hopefully improve the Chugaev elimination. Preliminary studies into this procedure have not reached any definitive conclusion. When applied to the *S*-methyl xanthate of (–)-menthol, no elimination occurred, but we were unsure what effect the sterics of the cyclohexane ring had on this reaction. Application of this method to other substrates is needed.

A second study involves the use of the various Na, Li, and K salts of phenylcarbonimidothioates created during the course of this study. We believe that by heating these salts in various solvents that promote nucleophilic attack by an anion, e.g., DMSO and HMPA, the temperature of pyrolysis will be lowered.

Additional substrates, such as citronellol, an acyclic alkene with a terminal, primary alcohol, need to be investigated to confirm the conclusions detailed in this investigation.

Finally, alkyl isothiocyanates need to be investigated to determine what, if any, effect the arene ring has on the temperature of pyrolysis. This modification will also determine the effect that the electronegativity of the *N*-substituent has on these elimination reactions.

1.9 EXPERIMENTAL SECTION

General Procedures

All reactions were run under a nitrogen atmosphere and monitored by TLC analysis. Unless otherwise indicated, all extractive workups consisted of the following procedure: the organic reaction solvent was removed under reduced pressure on a rotary evaporator, and the residue was taken up in diethyl ether. The combined extractive extracts were washed with water, brine, and dried over anhydrous magnesium sulfate. Filtration, followed by concentration at reduced pressure on a rotary evaporator and at 4 torr to a constant weight, afforded a crude residue which was purified by flash chromatography using silica gel 60 (230-400 mesh ASTM) and distilled reagent grade petroleum ether (pet ether), diethyl ether, and/or ethyl acetate. ^{1}H NMR spectra were recorded on a Varian Mercury plus 400 MHz in $CDCl_3$ and were calibrated using trace $CHCl_3$ present (δ 7.27) as an internal reference.

General Procedure A (Preparation of Xanthates).

The alcohol was dissolved in either toluene or THF under N_2. Sodium metal (1.12 equivalents) was added to the solution, which was then refluxed until all the sodium metal had dissolved. For (–)-menthol this took 48 hours, but for 2-phenethanol, this deprotonation only required 24 hours. Upon formation of the alkoxide, the solution was cooled to room temperature, and any unreacted sodium was physically removed from the solution with a wire. The solution was then chilled to 0 ^{o}C in an ice bath. To the solution were added carbon disulfide (2 equivalents). After the reaction with the CS_2 had subsided, the resulting anion was trapped with 1.0 equivalent of either iodomethane, freshly distilled trimethylsilyl chloride, or freshly distilled tri-*n*-butyltin chloride. The

solution was stirred for 0.5 hours. The solution was filtered to remove salts and purified with silica gel chromatography, giving:

***O*-[(1*R*,2*R*,5*R*)-2-Isopropyl-5-methylcyclohexyl] *S*-methyl carbonodithioate (1.4.1)**

As a pale yellow solid in 81% yield, homogenous by TLC analysis [R_f (**1.4.1**) = 0.66, hexanes]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58 – 5.42 (td, *J* = 10.9, 4.4 Hz, 1H), 2.57 – 2.47 (s, 3H), 2.25 – 2.15 (m, 1H), 1.93 – 1.78 (dtd, *J* = 14.0, 7.0, 2.7 Hz, 1H), 1.76 – 1.56 (m, 2H), 1.56 – 1.42 (m, 1H), 1.18 – 0.93 (m, 2H), 0.93 – 0.87 (td, *J* = 6.9, 1.4 Hz, 7H), 0.82 – 0.76 (dd, *J* = 7.0, 1.2 Hz, 3H).

***O*-(2-Isopropyl-5-methylcyclohexyl) *S*-(trimethylsilyl) carbonodithioate (1.4.2)**

As a yellow oil in 53% yield, homogenous by TLC analysis [R_f (**1.4.2**) = 0.56, hexanes]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.46 – 3.32 (td, *J* = 10.3, 4.2 Hz, 1H), 2.21 – 2.03 (dtd, *J* = 14.1, 6.9, 2.5 Hz, 1H), 1.90 – 1.80 (m, 1H), 1.68 – 1.55 (m, 2H), 1.45 – 1.31 (dddq, *J* = 12.9, 9.6, 6.6, 3.0 Hz, 1H), 1.21 – 1.08 (m, 1H), 1.06 – 0.93 (m, 2H), 0.93 – 0.86 (m, 7H), 0.76 – 0.70 (m, 3H), 0.14 – 0.09 (m, 9H).

***O*-(2-Isopropyl-5-methylcyclohexyl) *S*-(tributylstannyl) carbonodithioate (1.4.3)**

As a yellow oil in 72% yield, homogenous by TLC analysis [R_f (**1.4.3**) = 0.27, hexanes]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 – 5.20 (td, *J* = 10.9, 4.1 Hz, 1H), 2.22 – 2.12 (dd, *J* = 7.4, 4.6 Hz, 1H), 1.97 – 1.82 (m, 1H), 1.79 – 1.59 (m, 9H), 1.41 – 1.24 (m, 14H), 0.95 – 0.87 (dtd, *J* = 10.3, 5.0, 3.2 Hz, 16H), 0.83 – 0.79 (dd, *J* = 6.8, 1.9 Hz, 3H).

***S*-Methyl *O*-phenethyl carbonodithioate (1.5.3)**

As an orange oil in 90% yield, homogenous by TLC analysis [R_f (**1.5.3**) = 0.76, 10:1, hexanes:EtOAc]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.29 (m, 2H), 7.28 – 7.19 (m, 3H), 4.88 – 4.74 (td, *J* = 7.1, 1.9 Hz, 2H), 3.19 – 3.03 (td, *J* = 7.1, 1.8 Hz, 2H), 2.59 –

2.47 (d, *J* = 1.8 Hz, 3H).

_O_-Phenethyl _S_-(trimethylsilyl) carbonodithioate (1.5.4)

As an orange oil in 71% yield, homogenous by TLC analysis [R_f (**1.5.4**) = 0.63, 10:1, hexanes:EtOAc]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.29 (m, 2H), 7.28 – 7.19 (s, 3H), 4.88 – 4.74 (td, *J* = 7.1, 1.9 Hz, 2H), 3.19 – 3.03 (td, *J* = 7.1, 1.8 Hz, 2H), 0.14 – 0.09 (s, 9H).

_O_-Phenethyl _S_-(tributylstannyl) carbonodithioate (1.5.5)

As an orange oil in 83% yield, homogenous by TLC analysis [R_f (**1.5.5**) = 0.68, 10:1, hexanes:EtOAc]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 2H), 7.28 – 7.20 (m, 3H), 4.75 – 4.52 (t, *J* = 7.5 Hz, 2H), 3.15 – 3.05 (t, *J* = 7.4 Hz, 2H), 1.64 – 1.54 (m, 6H), 1.41 – 1.18 (m, 12H), 0.94 – 0.86 (t, *J* = 7.3 Hz, 9H).

General Procedure B (Preparation of Isothiocyanates from Electron-rich Anilines).

The aniline (0.12 mol) was added to a solution of triethylamine (4.4 equivalents) dissolved in dry THF. To the solution at 0 ^{o}C under N_2 was added carbon disulfide (2 equivalents) over a 1.0-hour period. The resulting solution was warmed to room temperature and stirred overnight. The dithiocarbamate salt formed as a precipitate in solution. *p*-Toluenesulfonyl chloride (1.1 equivalents) was then added to the solution at 0 ^{o}C. The resulting solution was warmed to room temperature and stirred for 1.0 hour followed by the addition of 1.0*M* HCl and diethyl ether (200 mL). The aqueous layer was separated and back extracted (making sure that the aqueous layer was acidic), and the ethereal extracts were combined. Standard extractive workup was followed by drying over anhydrous Na_2SO_4. The ethereal phase was filtered and then concentrated in vacuo,

and the resulting crude oil was purified via silica gel chromatography. Some syntheses were purified via distillation, giving:

1-Isothiocyanato-4-methylbenzene

As a white solid in 82% yield, homogenous by TLC analysis [R_f = 0.85, 10:1, hexanes:EtOAc]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.06 (m, 2H), 2.39 – 2.27 (s, 3H).

1-Isothiocyanato-4-methoxybenzene

As a yellow oil in 89% yield, homogenous by TLC analysis [R_f = 0.61, 10:1, hexanes:EtOAc]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.10 (m, 2H), 6.90 – 6.80 (m, 2H), 3.83 – 3.72 (m, 3H).

General Procedure C (Preparation of Isothiocyanates from Electron-poor Anilines). The aniline (0.12 mol) was added to a solution of sodium hydride (1.5 equivalents) dissolved in dry THF. To the resulting solution at 0 ^{o}C under N_2 was added carbon disulfide (3 equivalents) over a 1.0-hour period. The solution was refluxed for 24 hours. Normally, the dithiocarbamate salt forms as a precipitate in solution. The solution was chilled to 0 ^{o}C, and triethylamine (2.2 equivalents) was added followed by *p*-toluenesulfonyl chloride (1.1 equivalents). The resulting solution was warmed to room temperature and stirred for 1.0 hour followed by the addition of 1.0*M* HCl and diethyl ether (200 mL). The aqueous layer was separated and back extracted (making sure that the aqueous layer was acidic), and the ethereal extracts were combined. Standard extractive workup was followed by drying over anhydrous Na_2SO_4. The ethereal phase was filtered and then concentrated in vacuo, and the resulting crude oil was purified via silica gel chromatography. Some syntheses were purified via distillation, giving:

1-Isothiocyanato-4-(trifluoromethyl)benzene

As a clear oil in 59% yield, homogenous by TLC analysis [R_f = 0.83, 10:1, hexanes:EtOAc]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.49 (t, *J* = 5.9 Hz, 2H), 7.49 – 7.44 (t, *J* = 4.1 Hz, 2H).

Ethyl 4-isothiocyanatobenzoate

As an off-white solid in 85% yield, homogenous by TLC analysis [R_f = 0.56, 10:1, hexanes:EtOAc]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 7.91 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.30 – 7.14 (m, 2H), 4.45 – 4.24 (qd, *J* = 7.2, 1.2 Hz, 2H), 1.48 – 1.31 (m, 3H).

General Procedure D (Preparation of Aryl Carbonimidothioates).

The alcohol was dissolved in either toluene or THF under N_2. Sodium metal (1.12 equivalents) was added to the solution, which was then refluxed until all the sodium had dissolved. For (–)-menthol this took 48 hours, but for 2-phenethanol deprotonation only required 24 hours. Upon formation of the alkoxide, the solution was cooled to room temperature, and any unreacted sodium was physically removed from the solution with a wire. The solution was then chilled to 0 ^{o}C in an ice bath, and the aryl isothiocyanate (1.0 equivalent) was added to the solution. Following completion of the reaction, 1.0*M* HCl was added to the solution followed by diethyl ether (100 mL). The aqueous layer was separated and back extracted (making sure that the aqueous layer was acidic), and the ethereal extracts were combined. Standard extractive workup was followed by drying over anhydrous Na_2SO_4. The ethereal phase was filtered and then concentrated in vacuo, and the product was filtered through a plug of silica gel. Some products required additional purification via silica gel chromatography, giving:

(*Z*)-*O*-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl] *S*-hydrogen phenylcarbonimidothioate (1.5.1)

As a white solid in 95% yield, homogenous by TLC analysis [R_f (**1.5.1**) = 0.57, 10:1, hexanes:EtOAc]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 – 8.13 (s, 1H), 7.49 – 6.97 (m, 5H), 5.51 – 5.21 (m, 1H), 2.35 – 2.22 (d, *J* = 11.5 Hz, 1H), 1.99 – 1.83 (m, 1H), 1.76 – 1.64 (ddd, *J* = 12.7, 5.6, 3.1 Hz, 2H), 1.56 – 1.49 (m, 1H), 1.22 – 0.98 (m, 2H), 0.97 – 0.85 (m, 7H), 0.85 – 0.78 (d, *J* = 6.9 Hz, 3H).

(*Z*)-*O*-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl] *S*-hydrogen *p*-tolylcarbonimidothioate (1.6.1)

As an off-white solid in 92% yield, homogenous by TLC analysis [R_f (**1.6.1**) = 0.55, 10:1, hexanes:EtOAc]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 – 8.45 (s, 1H), 7.22 – 7.00 (m, 4H), 5.44 – 5.21 (m, 1H), 2.39 – 2.18 (s, 4H), 1.99 – 1.81 (dt, *J* = 15.2, 6.5 Hz, 1H), 1.76 – 1.63 (tp, *J* = 7.9, 3.0 Hz, 2H), 1.59 – 1.47 (m, 1H), 1.22 – 0.96 (m, 2H), 0.94 – 0.85 (m, 7H), 0.85 – 0.81 (d, *J* = 7.0 Hz, 3H).

(*Z*)-*O*-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl] *S*-hydrogen (4-methoxyphenyl)carbonimidothioate (1.6.2)

As a light orange, viscous oil in 90% yield, homogenous by TLC analysis [R_f (**1.6.2**) = 0.36, 10:1, hexanes:EtOAc]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 – 8.08 (s, 1H), 7.19 – 7.06 (d, *J* = 8.1 Hz, 2H), 6.96 – 6.74 (d, *J* = 9.0 Hz, 2H), 5.42 – 5.21 (m, 1H), 3.84 – 3.66 (d, *J* = 1.8 Hz, 3H), 2.36 – 2.18 (s, 1H), 1.98 – 1.79 (s, 1H), 1.73 – 1.66 (dd, *J* = 10.3, 2.7 Hz, 2H), 1.55 – 1.45 (s, 1H), 1.22 – 0.96 (m, 2H), 0.95 – 0.87 (m, 7H), 0.85 – 0.78 (m, 3H).

(*Z*)-*O*-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl] *S*-hydrogen (4-(trifluoromethyl)phenyl)carbonimidothioate (1.6.3)

As a white solid in 81% yield, homogenous by TLC analysis [R_f (**1.6.3**) = 0.50, 10:1,

hexanes:EtOAc]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 – 8.31 (s, 1H), 7.79 – 7.19 (m, 4H), 5.42 – 5.29 (td, *J* = 10.9, 4.4 Hz, 1H), 2.42 – 2.19 (d, *J* = 11.4 Hz, 1H), 1.98 – 1.84 (dtd, *J* = 13.8, 6.9, 2.5 Hz, 1H), 1.78 – 1.68 (dp, *J* = 13.8, 3.3 Hz, 2H), 1.62 – 1.46 (m, 1H), 1.19 – 0.99 (m, 2H), 0.99 – 0.88 (dd, *J* = 11.4, 6.7 Hz, 7H), 0.85 – 0.80 (d, *J* = 7.0 Hz, 3H).

Ethyl 4-((*Z*)-[(((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)(mercapto)methylene)amino]benzoate (1.6.4)

As a pale yellow solid in 89% yield, homogenous by TLC analysis [R_f (**1.6.4**) = 0.33, 10:1, hexanes:EtOAc]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 – 8.33 (s, 1H), 8.07 – 7.94 (m, 2H), 7.55 – 7.27 (s, 2H), 5.46 – 5.24 (td, *J* = 10.8, 4.3 Hz, 1H), 4.41 – 4.26 (m, 2H), 2.36 – 2.21 (d, *J* = 11.6 Hz, 1H), 1.99 – 1.83 (m, 1H), 1.77 – 1.64 (m, 2H), 1.64 – 1.45 (m, 1H), 1.43 – 1.32 (m, 3H), 1.18 – 0.98 (m, 2H), 0.99 – 0.84 (m, 7H), 0.84 – 0.74 (m, 3H).

(*Z*)-*O*-Phenethyl *S*-hydrogen phenylcarbonimidothioate (1.5.2)

As a yellow solid in 98% yield, homogenous by TLC analysis [R_f (**1.5.2**) = 0.37, 10:1, hexanes:EtOAc]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 – 8.13 (s, 1H), 7.49 – 6.97 (m, 5H), 5.51 – 5.21 (m, 1H), 2.35 – 2.22 (d, *J* = 11.5 Hz, 1H), 1.99 – 1.83 (m, 1H), 1.76 – 1.64 (ddd, *J* = 12.7, 5.6, 3.1 Hz, 2H), 1.56 – 1.49 (m, 1H), 1.22 – 0.98 (m, 2H), 0.97 – 0.85 (m, 7H), 0.85 – 0.78 (d, *J* = 6.9 Hz, 3H).

(*Z*)-*O*-Phenethyl *S*-hydrogen *p*-tolylcarbonimidothioate (1.6.5)

As a yellow solid in 95% yield, homogenous by TLC analysis [R_f (**1.6.5**) = 0.37, 10:1, hexanes:EtOAc]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 – 8.18 (s, 1H), 7.35 – 6.88 (m, 9H), 4.91 – 4.67 (t, *J* = 7.4 Hz, 2H), 3.13 – 3.00 (t, *J* = 6.9 Hz, 2H), 2.44 – 2.22 (s, 3H).

(*Z*)-*O*-Phenethyl *S*-hydrogen (4-methoxyphenyl)carbonimidothioate (1.6.6)

As a yellow solid in 92% yield, homogenous by TLC analysis [R_f (**1.6.6**) = 0.19, 10:1,

hexanes:EtOAc]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 – 8.13 (s, 1H), 7.44 – 7.01 (m, 5H), 6.95 – 6.84 (d, *J* = 8.4 Hz, 2H), 6.78 – 6.67 (d, *J* = 8.5 Hz, 2H), 4.78 – 4.52 (m, 2H), 3.74 – 3.62 (s, 3H), 3.09 – 2.87 (t, *J* = 6.4 Hz, 2H).

(*Z*)-*O*-Phenethyl *S*-hydrogen [4-(trifluoromethyl)phenyl]carbonimidothioate (1.6.7)

As a yellow solid in 85% yield, homogenous by TLC analysis [R_f (**1.6.7**) = 0.35, 10:1, hexanes:EtOAc]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 – 8.17 (s, 1H), 7.49 – 7.11 (m, 9H), 4.91 – 4.64 (s, 2H), 3.17 – 2.98 (t, *J* = 6.9 Hz, 2H).

(*Z*)-Ethyl 4-[(mercapto(phenethoxy)methylene)amino]benzoate (1.6.8)

As a yellow solid in 91% yield, homogenous by TLC analysis [R_f (**1.6.8**) = 0.19, 10:1, hexanes:EtOAc]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 – 8.20 (s, 1H), 8.01 – 7.84 (m, 2H), 7.37 – 7.13 (m, 7H), 4.91 – 4.65 (m, 2H), 4.40 – 4.33 (qd, *J* = 7.0, 1.6 Hz, 2H), 3.17 – 3.08 (t, *J* = 6.9 Hz, 2H), 1.41 – 1.34 (dt, *J* = 6.9, 3.8 Hz, 3H).

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CHAPTER II

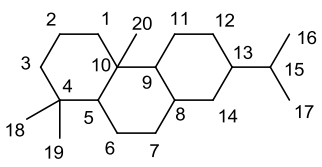
INTRAMOLECULAR FRIEDEL–CRAFTS CYCLIZATION OF ARYLSILANES

ABSTRACT

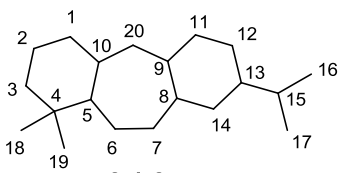
Lewis acid-catalyzed cyclialkylation is an established method for creating tricyclic compounds composed of a central cycloheptane ring. By applying this method to arene-dienone systems with silyl-substituted arenes, we hoped to observe *meta*-directed electrophilic aromatic substitution with retention of the silyl moiety. Preliminary investigations have proven the silyl moiety too labile, and cyclialkylation was accompanied by protodesilylation.

2.1 INTRODUCTION

A variety of natural products have been isolated and synthesized that consist of a tricyclic framework, many from shrubs and plants of the *Salvia* genus. These tryciclic natural products include the diterpenoids that contain the abietane (**2.1.1**) skeleton, which is typified by a 6-6-6 tricyclic carboskeleton. This general framework has been biosynthetically linked to the 6-7-6 skeleton of the icetexanes (**2.1.2**).[1]

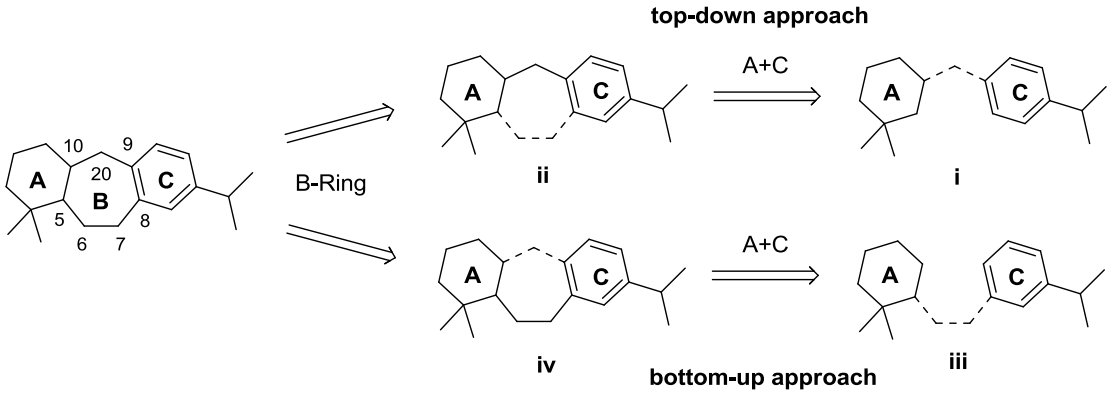


2.1.1
abietanes



2.1.2
icetexanes

The synthesis of these tricyclic compounds has been achieved through an A + C → ABC strategy. One of the most difficult aspects of this strategy is the formation of the seven-membered carbocycles. There are two methods for the formation of the B-ring: a top-down approach and a bottom-up approach. In the top-down approach, the C10-C20-C9 (**i**) bonds are first formed, followed by the formation of the bottom C5-to-C8 (**ii**) bonds. Conversely, a bottom-up approach first creates the bottom portion of the central ring, C5-to-C8 bonds (**iii**), followed by ring closure to create the top C10-C20-C9 (**iv**) bonds (Scheme 2.1.1).[2]

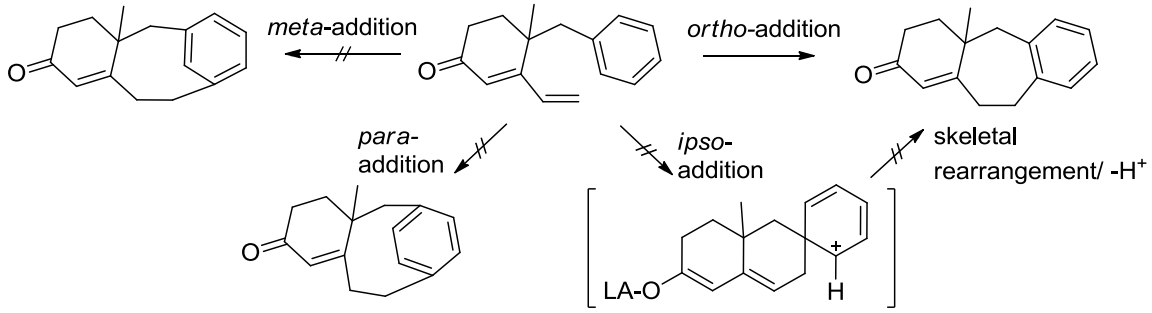


Scheme 2.1.1

Majetich and co-workers utilized the top-down approach by using Lewis acid-catalyzed, intramolecular Friedel–Crafts alkylation, or cyclialkylation, to create tricyclic compounds containing a central cycloheptane ring (Scheme 2.1.2).[3]

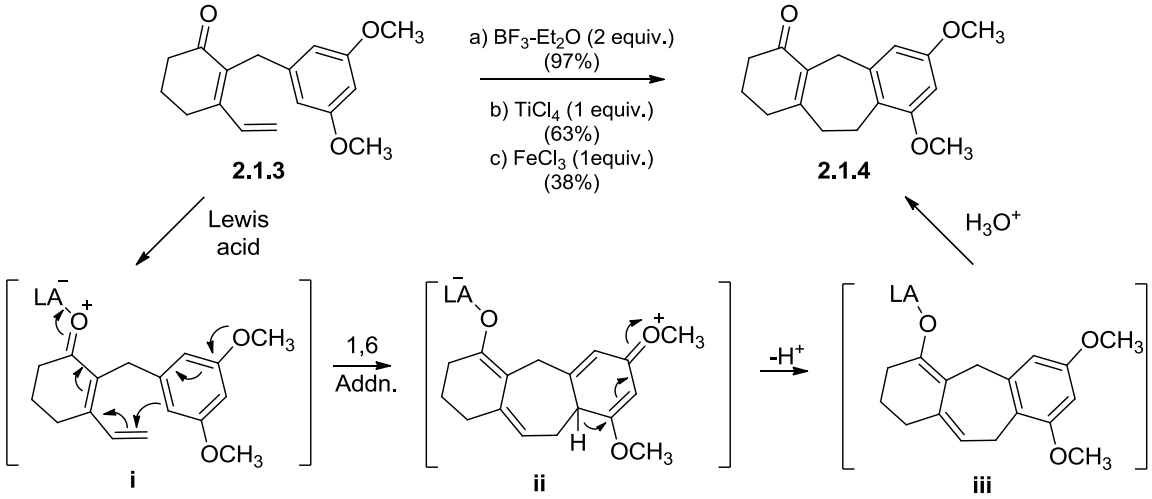
The introduction of activating groups on the arene ring promoted this alkylation and governed the annulations through directing effects. The geometric constraints of the cyclization precursor also strongly influenced the site of the substitution. Majetich and co-workers also found no evidence of skeletal rearrangements which are common to Friedel–Crafts reactions, suggesting the lack of an *ipso*-attack-based mechanism. These

findings are summarized in Scheme 2.1.3, which shows the four possible and the actual routes of electrophilic susbstitution.[3]



Scheme 2.1.3

Mechanistic studies demonstrated that Lewis-acid activation of the dienone motif of **2.1.3** creates intermediate **i**. Electrophilic 1,6-addition of the arene ring to the vinyl moiety establishes the tricyclic intermediate species **ii**. Aromaticity is then re-established (**iii**) through deprotonation, and acidic workup yields the more stable tricyclic enone **2.1.4**.

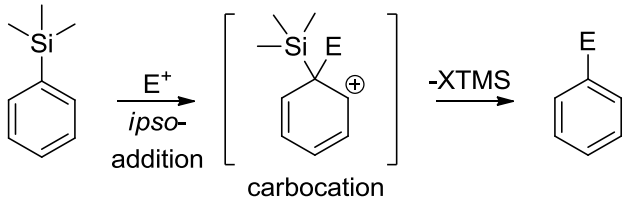


Scheme 2.1.2

2.2 APPLICATION OF CYCLIALKYLATION TO ARYLSILANES

We hoped to apply this cyclialkylation method to arene-dienone systems in which the arene ring is substituted with a trialkylsilyl group. Treatment of this system with a Lewis acid under kinetic control should produce the cycloheptane ring without affecting the silyl substituent on the arene ring. The introduction of the silyl functionality would offer a handle for further synthetic transformations, leading to more diverse structures.

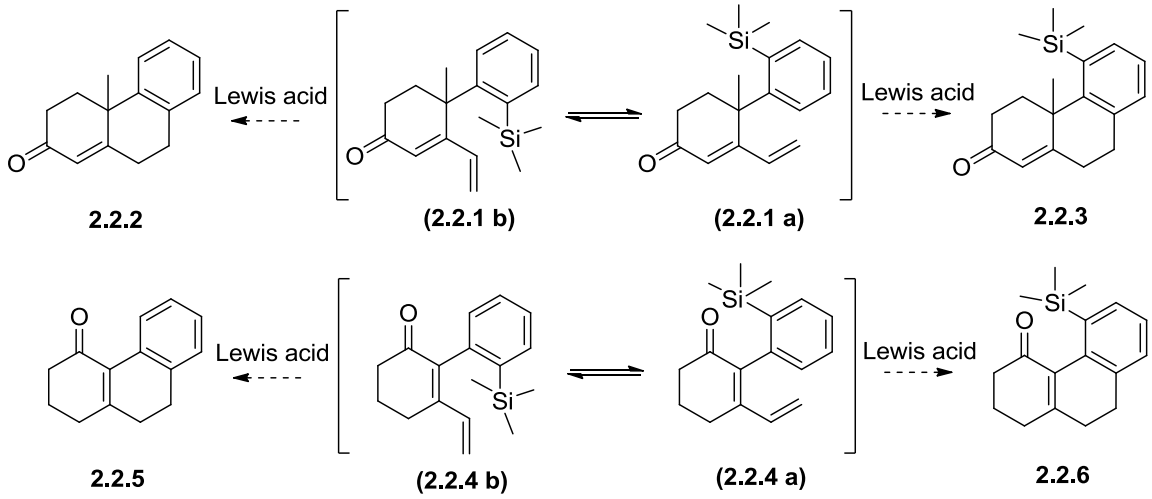
When an electrophile reacts with an arylsilane, it adds to the *ipso* carbon atom bearing the silyl moiety. This addition generates a carbocation, which is stabilized by the well established β-effect of the silicon atom.[4] Loss of the trimethylsilyl moiety results in a product in which the silyl group has been replaced by the electrophile (Scheme 2.2.1).[5] Arylsilanes can be involved in a variety of electrophilic aromatic substitutions, including halogenation,[6] Friedel–Crafts alkylation,[6] Friedel–Crafts acylation,[7] and nitration.[3] Considering the variety of the possible electrophilic aromatic substitutions that are capable of reacting with arylsilanes, it is easy to see why arylsilanes are useful intermediates for the preparation of functionalized arenes.



Scheme 2.2.1

We were curious whether Lewis acid-promoted electrophilic aromatic substitution could be applied to arene-dienone systems containing a silyl-substituted arene to form tricyclic compounds composed of a central cycloheptane ring. We have found that conformational effects[8] highly influence intramolecular Friedel–Crafts cyclizations[9] or

cyclialkylation.[10] Cyclialkylation of substrates **2.2.1** and **2.2.4** would either undergo *ipso* attack to form products **2.2.2** and **2.2.5**, respectively, or would form tricycles **2.2.3** and **2.2.6**, respectively, in which the silyl group is retained due to their steric congestion. Furthermore, the electropositive silicon atom should act as a *meta* director in the Friedel–Crafts reaction, favoring the production of **2.2.3** and **2.2.6**. Lewis acids not only promote cyclization but also promote protodesilylation. Therefore, the desired products **2.2.3** and **2.2.6** could undergo protodesilylation to furnish enones **2.2.2** and **2.2.5** (Scheme 2.2.2).

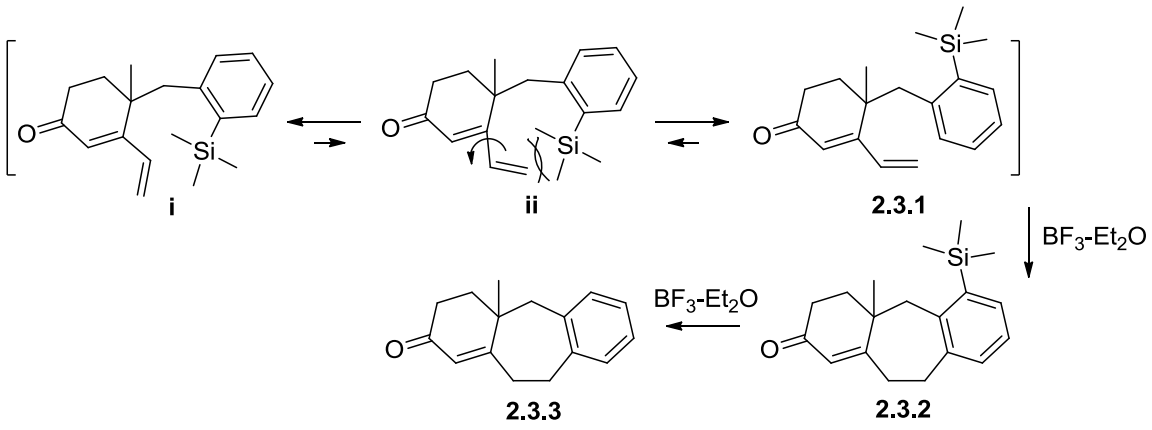


Scheme 2.2.2

2.3 SYNTHESIS OF ARENE-DIENONE AND ITS CYCLIALKYLATION

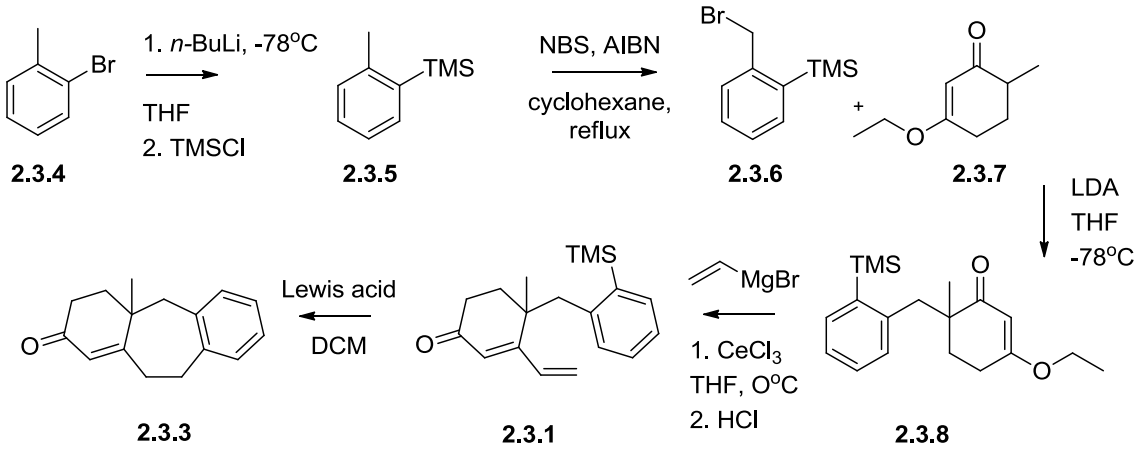
Yong Zhang originally proposed the application of cyclialkylation to arene-dienones with silyl-substituted arene rings to create a 6-7-6 tricyclic system.[3] His preliminary investigation found that the intramolecular cyclization of arylsilanes with a conjugated dienone via BF_3-etherate resulted in ring closure *meta* to the electron-donating trimethylsilyl substituent (Scheme 2.3.1). Cyclialkylation does not proceed via an *ipso*-addition mechanism (congested conformer **ii**) and is precluded in conformer **i**.

Upon treatment with BF_3-etherate, **2.3.1** cyclized to form tricyclic enone **2.3.2**. Re-submission of isolated enone **2.3.2** to BF_3-etherate gave desilylated tricycle **2.3.3** (Scheme 2.3.1



Scheme 2.3.1

Scheme 2.3.2 depicts the synthesis of 4-methyl-4-(2-(trimethylsilyl)benzyl)-3-vinylcyclohex-2-enone (**2.3.1**), the only arene-dienone that has been synthesized and investigated regarding its ability to undergo cyclialkylation. The synthesis is convergent, with the A- and C-rings coupling to form arene-dienone **2.3.1**.



Scheme 2.3.2

The synthesis of the C-ring began with 2-bromotoluene (**2.3.4**) which was transmetalated with *n*-butyllithium and then reacted with trimethylsilyl chloride to give **2.3.5**. The resulting arylsilane underwent radical bromination through treatment with NBS and AIBN to give benzylic bromide **2.3.6**, completing the synthesis of the C-ring.

The A-ring portion, 3-ethoxy-6-methylcyclohex-2-enone (**2.3.7**), was synthesized via the Stork-Danheiser protocol[11] from cyclohexane-1,3-dione. Compound **2.3.8** was synthesized by treating **2.3.7** with LDA, then coupling it to **2.3.5**. We attempted this coupling with varying reaction parameters, but **2.3.8** was synthesized in consistently low yield. Surprisingly, unreacted A-ring was consistently recovered in greater amounts than C-ring; however, varying the ratio of A-ring to C-ring did not afford any change in the yield.

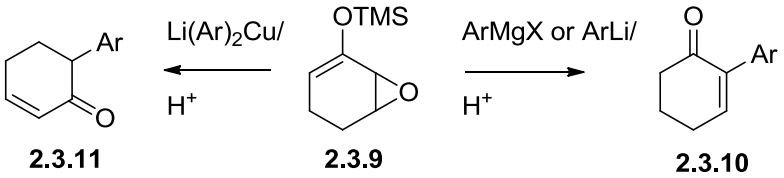
Treatment of the coupled system, **2.3.8**, with vinylmagnesium bromide and cerium chloride catalyst produced the desired arene-dienone, 4-methyl-4-(2-(trimethylsilyl)benzyl)-3-vinylcyclohex-2-enone (**2.3.1**). This reaction was attempted in both dry THF and dry Et_2O, with dry THF affording a greater yield. The addition of the vinyl group was achieved in good yield with vinylmagnesium bromide, while other reagents, e.g., vinyllithium and lithium trimethylsilylacetilide, proved unsuccessful at installing the vinyl moiety.

Arene-dienone **2.3.1** was treated with a variety of Lewis acids to promote cyclialkylation. Titanium(IV) tetrachloride, indium(III) chloride, iron(III) chloride, and zinc(II) bromide all produced the cyclized product **2.3.3**, 4a-methyl-3,4,4a,5,10,11-hexahydro-2*H*-dibenzo[a,d][7]annulen-2-one. These reactions were all performed in DCM, normally with one equivalent of Lewis acid. All of these Lewis acids were deemed

too reactive and thus, caused protodesilylation. The more mild Lewis acid, boron trifluoride etherate, was tested extensively at various temperatures and solvent dilutions, but all cases resulted in protodesilylation.

The next arylsilane, conjugated dienone system to be tested for its ability to undergo cyclialkylation was **2.2.4**. Steric effects should have a greater influence in this system due to the smaller B-ring, which is a cyclohexane ring versuses the previously tested cycloheptane ring. The synthesis is also convergent, with the A- and C-rings coupling to form arene-dienone **2.2.4**. Currently, this is an incomplete synthetic strategy with only the basic components prepared. The A-ring is to be prepared from 2-cyclohexenone.

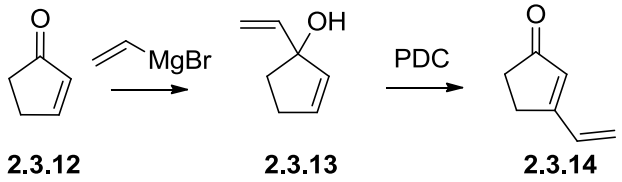
Wender and co-workers found in the 1980's that treatment of an epoxide **xx** with either an organolithium species or a Grignard reagent produced 2-alkyl(or aryl)-2-cyclohexenones (**2.3.10**) in good yield. If dialkyl or diarylcuprates were used instead, an SN_2' reaction took place, and the 6-alkyl(or aryl)-2-cyclohexenones (**2.3.11**) were produced (Scheme 2.3.3).[12]



2.3.11 **2.3.9** **2.3.10**

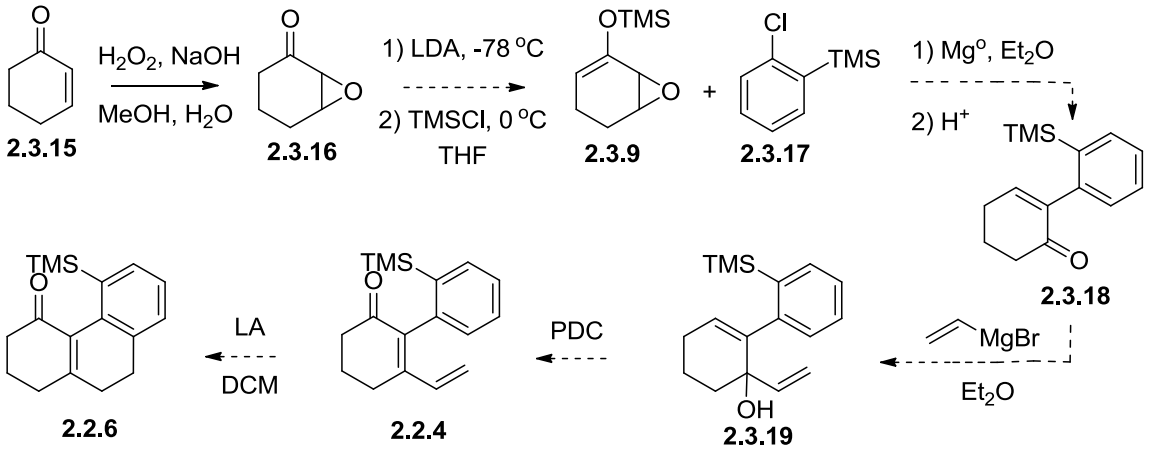
Scheme 2.3.3

Majetich and co-workers found that oxidizing the *bis*-allylic tertiary alcohol (**2.3.13**) of 2-cyclopentenone (**2.3.12**) with PDC produced the corresponding 3-vinyl-2-cyclopentenone (**2.3.14**) via an oxidative rearrangement (Scheme 2.3.4).[13]



Scheme 2.3.4

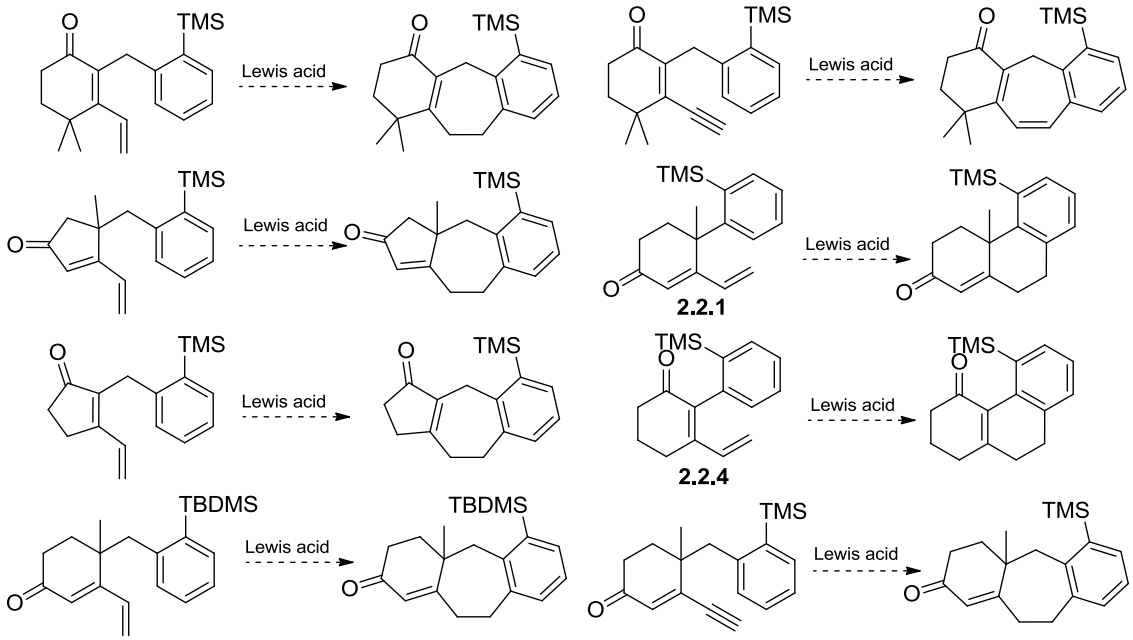
By coupling Wender's and Majetich's procedures, a synthetic route was prepared for the creation of **2.2.4**. The epoxide (**2.3.16**) was created by treating 2-cyclohexenone (**2.3.15**) with hydrogen peroxide. The enolate of **2.3.16** can be prepared through treatment with LDA followed by TMSCl. The arylsilane (**2.3.17**) can be prepared from 1,2-dichlorobenzene via the same transmetallation employed in Scheme 2.3.2. The A-ring (**2.3.9**) can then be coupled to the C-ring (**2.3.17**) via the creation of a Grignard reagent to produce **2.3.18** in accordance with Wender's method (Scheme 2.3.3). Treatment of **2.3.18** with vinylmagnesium bromide should give the *bis*-allylic tertiary alcohol substrate needed for Majetich's method (Scheme 2.3.4). In accordance with Majetich's method, treatment of **2.3.19** with PDC should produce the desired arylsilane, conjugated dienone (**2.2.4**). This substrate (**2.2.4**) can then be tested for cyclialkylation via treatment with various Lewis acids (Scheme 2.3.5).



Scheme 2.3.5

2.4 CONCLUSIONS AND FUTURE STUDIES

The work done in this investigation has a laid the groundwork for future exploration of cyclialkylations involving arylsilanes. Scheme 2.4.1 details the range of possible substrates on which this reaction can be tested. The arene-dienone **2.3.1** already explored does not fully exploit the steric effects of the trimethylsilyl moiety which should be more pronounced in other arene-dienone systems, e.g., **2.2.1** and **2.2.4**. These two systems can be synthesized via the method outlined in Scheme 2.3.5. By employing an diarylcuprate instead of a Grignard reagent to couple the A-ring to the C-ring, **2.2.1** should be produced in accordance with Wender's method. A range of tricyclic systems must be investigated before any conclusion regarding cyclialkylation and arylsilanes can be reached.



Scheme 2.4.1

2.5 EXPERIMENTAL SECTION

General Procedures

All reactions were run under a nitrogen atmosphere and monitored by TLC analysis. Unless otherwise indicated, all extractive workups consisted of the following procedure: the organic reaction solvent was removed under reduced pressure on a rotary evaporator, and the residue was taken up in diethyl ether. The combined extractive extracts were washed with water, brine, and dried over anhydrous magnesium sulfate. Filtration, followed by concentration at reduced pressure on a rotary evaporator and at 4 torr to a constant weight, afforded a crude residue which was purified by flash chromatography using silica gel 60 (230-400 mesh ASTM) and distilled reagent grade petroleum ether (pet ether), diethyl ether, and/or ethyl acetate. ^{1}H NMR spectra were recorded on a Varian Mercury plus 400 MHz in $CDCl_3$ and were calibrated using trace $CHCl_3$ present (δ 7.27) as an internal reference.

Preparation of trimethyl(*o*-tolyl)silane (2.3.5).

A 100 mL flask was charged with 2-bromotoluene, **2.3.4**, (3.49 mL, 30 mmol) in dry THF (40 mL). To this solution, stirring under N_2 at -78 ^{o}C, was added *n*-butyllithium (12.8 mL, 2.5M, 32 mmol), dropwise. The solution was stirred at -78 ^{o}C for 1.0 hour. To the resulting solution at -78 ^{o}C was added freshly distilled TMSCl (4.8 mL, 38 mmol). The solution was warmed to room temperature. Diethyl ether (100 mL) was added to the solution. The aqueous layer was separated and back extracted, and the ethereal extracts were combined. Standard extractive workup was followed by drying over anhydrous Na_2SO_4. The ethereal phase was filtered and then concentrated in vacuo, producing 4.3 g (90%) of trimethyl(*o*-tolyl)silane (**2.3.5**) as a light brown oil, homogenous by TLC

analysis [R_f (**2.3.5**) = 0.61, 2:1, hexanes:EtOAc]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 6.75 (m, 4H), 2.15 – 2.09 (s, 3H), 0.10 – 0.5 (s, 9H).

INSERT SPECTRAL INFORMATION AND RF VALUES

Preparation of (2-(bromomethyl)phenyl)trimethylsilane (2.3.6).

A 250 mL flask was charged with trimethyl(*o*-tolyl)silane, **2.3.5**, (4.4 g, 30 mmol) in cyclohexane (100 mL). To this solution was added NBS (8.01 g, 45 mmol) and AIBN (0.245 g, 1.5 mmol). The resulting solution was refluxed under N_2 for 12 hours. Diethyl ether (100 mL) was added to the solution. The aqueous layer was separated and back extracted, and the ethereal extracts were combined. Standard extractive workup was followed by drying over anhydrous Na_2SO_4. The ethereal phase was filtered and then concentrated in vacuo, and the crude product was purified via silica gel chromatography, producing 6.2 g (95%) of (2-(bromomethyl)phenyl)trimethylsilane (**2.3.6**) as a light brown oil, which was homogeneous by TLC analysis[R_f (**2.3.6**) = 0.83, 10:1, hexanes:EtOAc]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 6.80 (m, 4H), 4.40 – 4.25 (d, *J* = 1.5 Hz, 2H), 0.13 – 0.08 (s, 9H).

Preparation of 6-methyl-6-(2-(trimethylsilyl)benzyl)cyclohex-2-enone (2.3.8).

A 25 mL flask was charged with diisopropylamine (0.54 mL, 3.8 mmol) in dry THF (5 mL). To this solution, stirring under N_2 at -78 ^{o}C, was added *n*-butyllithium (1.48 mL, 2.5M, 3.7 mmol), dropwise. To the resulting solution at -78 ^{o}C was added 3-ethoxy-6-methylcyclohex-2-enone, **2.3.7**, (0.5 g, 3.0 mmol) in dry THF (3 mL). The solution was stirred for 1.0 hour to allow for deprotonation. To the resulting solution at -78 ^{o}C was added (2-(bromomethyl)phenyl)trimethylsilane, **2.3.6**, (0.729 g, 3.0 mmol) in dry THF (3 mL), and the solution was slowly warmed to room and stirred overnight. The reaction

was quenched with the addition of 10 mL of water. Diethyl ether (50 mL) was added to the solution. The aqueous layer was separated and back extracted, and the ethereal extracts were combined. Standard extractive workup was followed by drying over anhydrous Na_2SO_4. The ethereal phase was filtered and then concentrated in vacuo, and the crude product was purified via silica gel chromatography, producing 0.5 g (50%) of 6-methyl-6-(2-(trimethylsilyl)benzyl)cyclohex-2-enone (**2.3.8**) as a yellow oil which was homogeneous by TLC analysis[R_f (**2.3.8**) = 0.24, 10:1, hexanes:EtOAc]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 6.66 (m, 4H), 5.10 – 4.99 (d, *J* = 1.2 Hz, 1H), 3.62 – 3.50 (qd, *J* = 7.1, 2.5 Hz, 2H), 3.33 – 3.21 (d, *J* = 14.6 Hz, 1H), 2.47 – 2.32 (d, *J* = 14.5 Hz, 1H), 2.22 – 2.09 (m, 1H), 1.99 – 1.84 (ddd, *J* = 17.9, 5.4, 4.1 Hz, 1H), 1.55 – 1.42 (ddd, *J* = 13.6, 11.0, 5.5 Hz, 1H), 1.25 – 1.15 (ddd, *J* = 9.5, 5.3, 2.6 Hz, 1H), 1.08 – 0.96 (t, *J* = 7.0 Hz, 3H), 0.83 – 0.78 (s, 3H), 0.06 – 0.00 (s, 9H).

Preparation of 4-methyl-4-(2-(trimethylsilyl)benzyl)-3-vinylcyclohex-2-enone (2.3.1). A 25 mL dry flask was charged with 6-methyl-6-(2-(trimethylsilyl)benzyl)cyclohex-2-enone, **2.3.8**, (252 mg, 0.8 mmol) and $CeCl_2$ (20 mg, 0.08 mmol) in dry THF (2 mL) under N_2 at 0 ^{o}C. To this solution was added vinylmagnesium bromide (3.2 mL, 1.0*M*, 3.2 mmol), dropwise over 5 minutes. The reaction was warmed to room temperature and stirred for 4.0 hours. After the reaction was quenched with ice, the solution was treated with 1.0*M* HCl for 20 minutes. Diethyl ether (50 mL) was added to the solution. The aqueous layer was separated and back extracted (making sure that the aqueous layer was acidic), and the ethereal extracts were combined. Standard extractive workup was followed by drying over anhydrous Na_2SO_4. The ethereal phase was filtered and then concentrated in vacuo, and the product was filtered through a plug of silica, producing

215 mg (90%) of 4-methyl-4-(2-(trimethylsilyl)benzyl)-3-vinylcyclohex-2-enone (**2.3.1**) as a yellow oil which was homogeneous by TLC analysis[R_f (**2.3.1**) = 0.76, 10:1, hexanes:EtOAc]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 – 6.69 (m, 4H), 6.33 – 6.11 (dd, *J* = 17.2, 11.0 Hz, 1H), 5.93 – 5.82 (s, 1H), 5.56 – 5.38 (dt, *J* = 17.0, 1.2 Hz, 1H), 5.14 – 5.03 (dt, *J* = 10.9, 1.3 Hz, 1H), 2.97 – 2.83 (d, *J* = 15.1 Hz, 1H), 2.66 – 2.51 (m, 1H), 2.12 – 1.96 (m, 1H), 1.89 – 1.61 (m, 2H), 1.31 – 1.21 (m, 1H), 1.00 – 0.96 (d, *J* = 1.7 Hz, 3H).

4a-methyl-3,4,4a,5,10,11-hexahydro-2H-dibenzo[a,d][7]annulen-2-one (2.3.3)

As a clear oil, homogenous by TLC analysis [R_f (**2.3.3**) = 0.5, 10:1, hexanes:EtOAc]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 – 6.67 (m, 5H), 5.45 – 5.36 (s, 1H), 2.70 – 2.58 (m, 1H), 2.58 – 2.47 (td, *J* = 11.8, 11.4, 5.4 Hz, 2H), 2.40 – 2.31 (d, *J* = 13.9 Hz, 1H), 2.15 – 1.99 (m, 2H), 1.78 – 1.62 (td, *J* = 13.0, 5.0 Hz, 1H), 1.56 – 1.41 (t, *J* = 4.9 Hz, 1H), 0.71 – 0.67 (s, 3H).

2.5 REFERENCES

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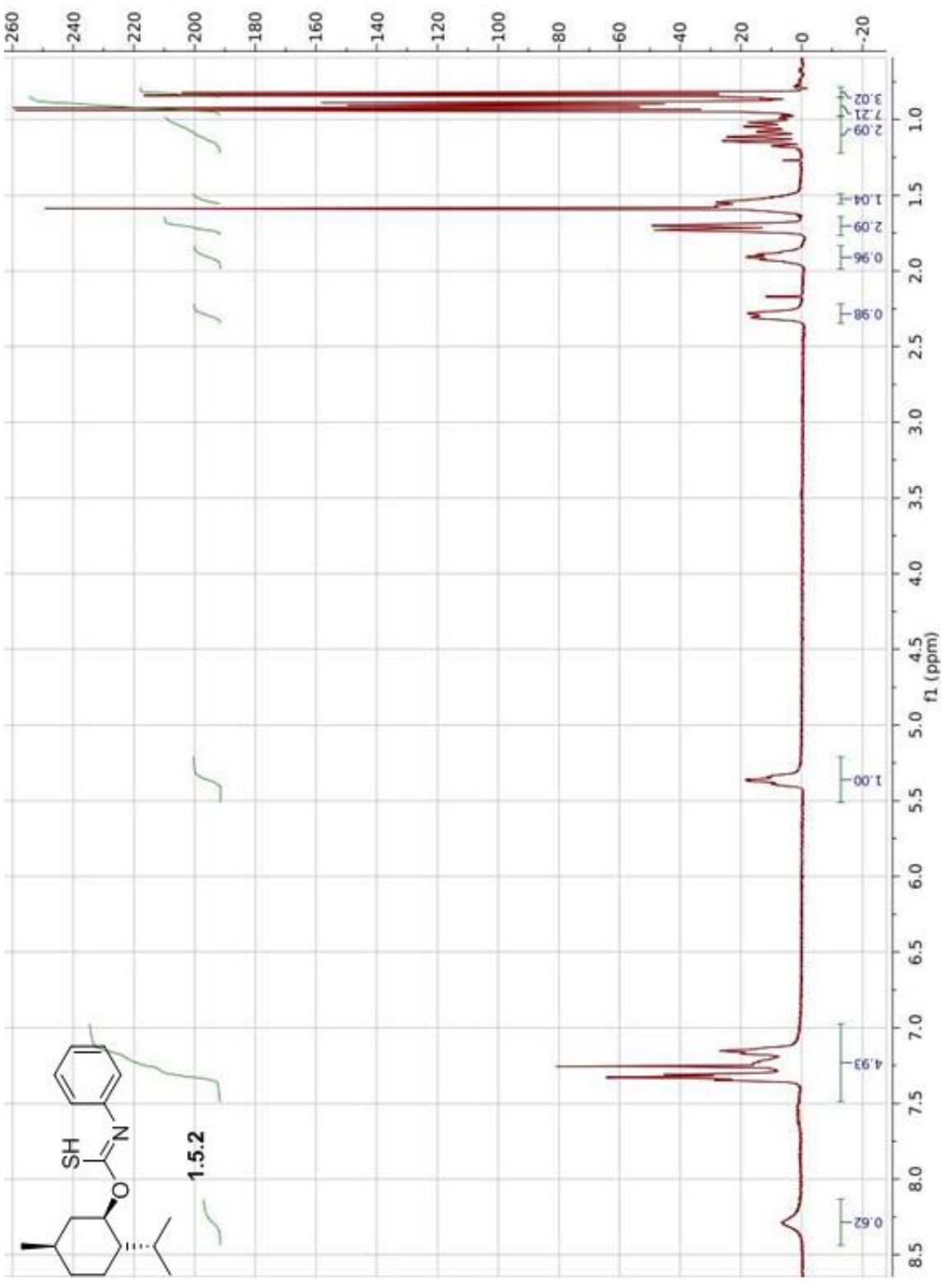
APPENDIX A

^{1}H NMR SPECTRA RELEVANT TO CHAPTER I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0.96
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1.00
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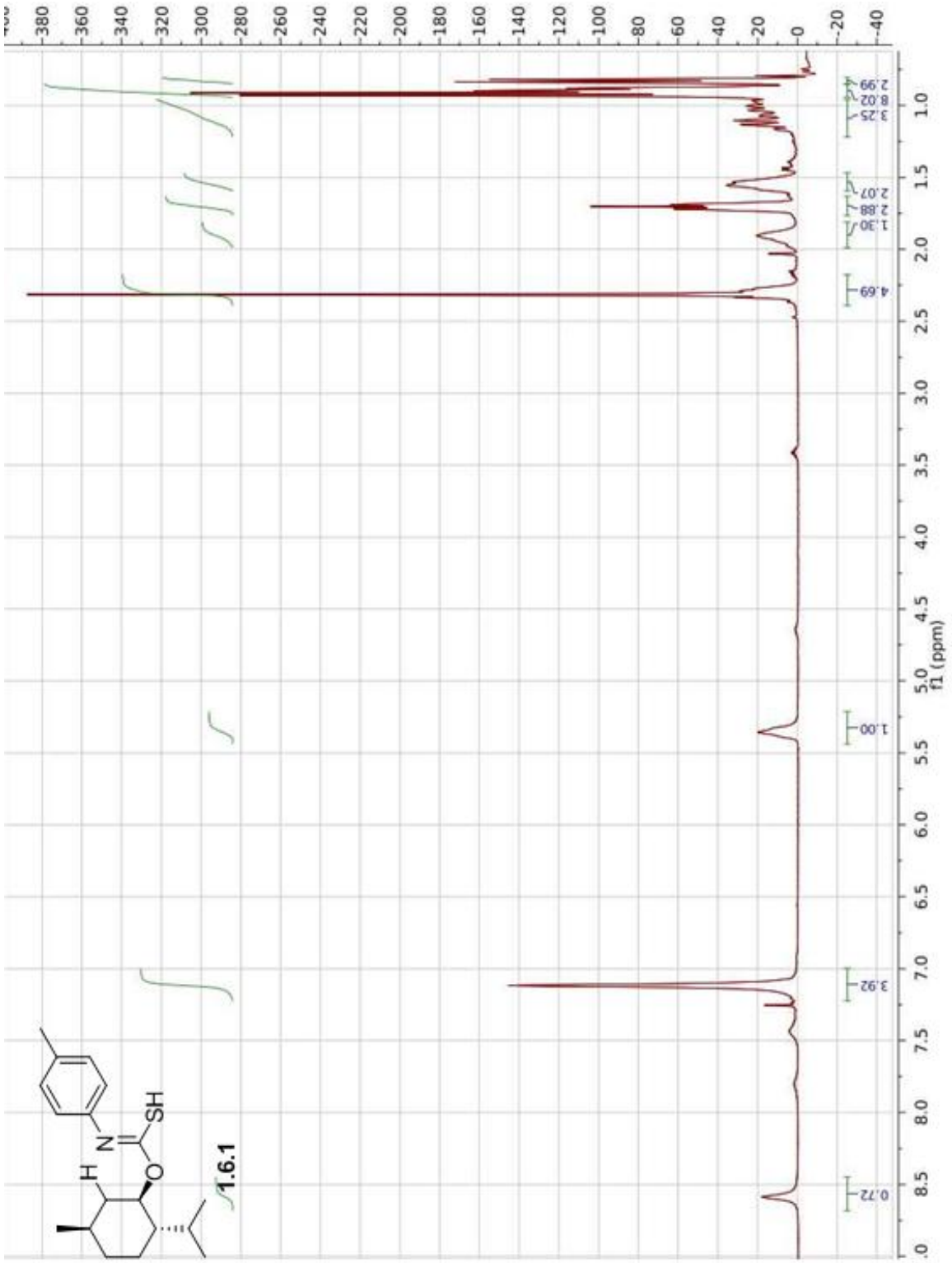
0.62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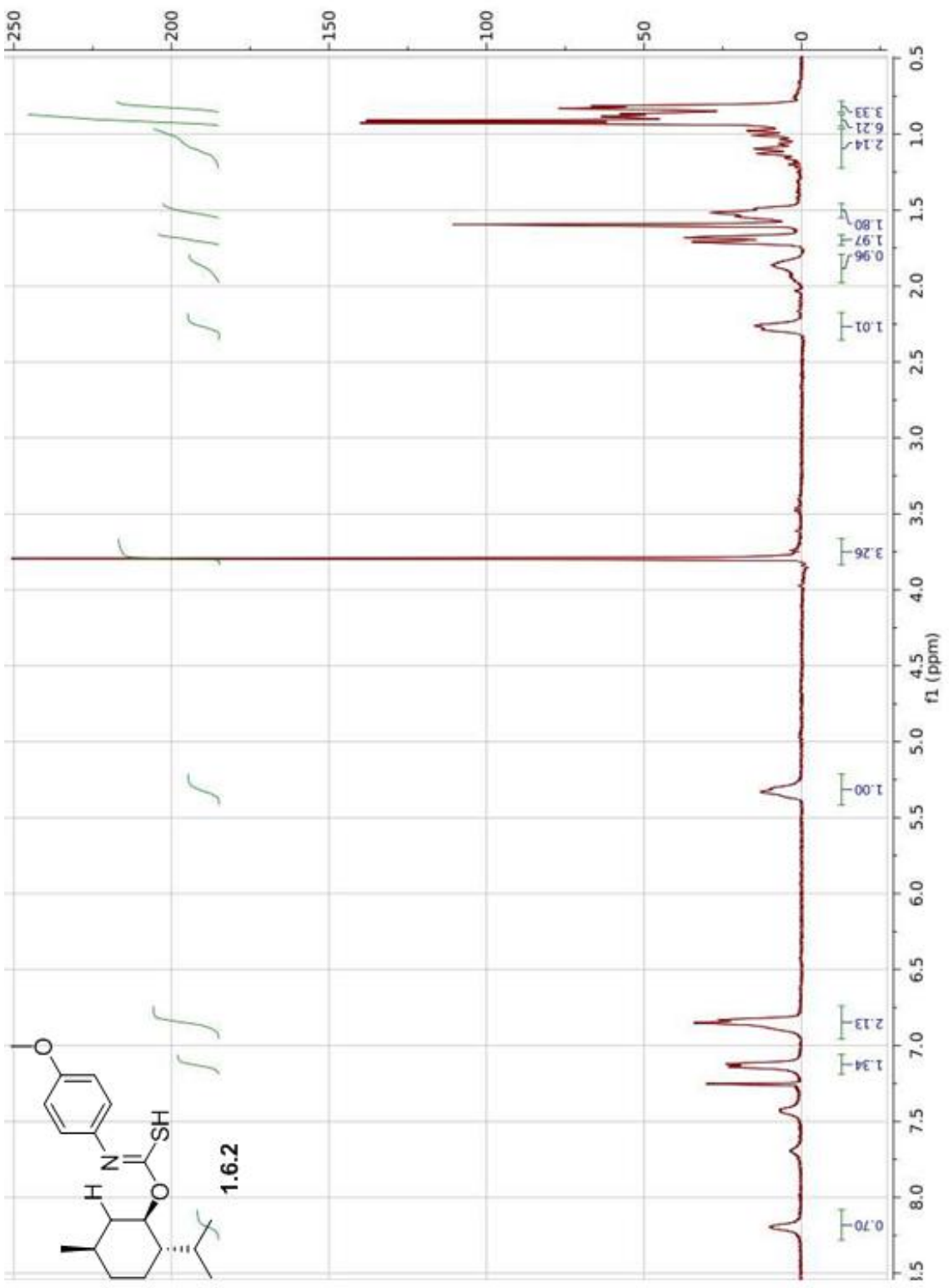
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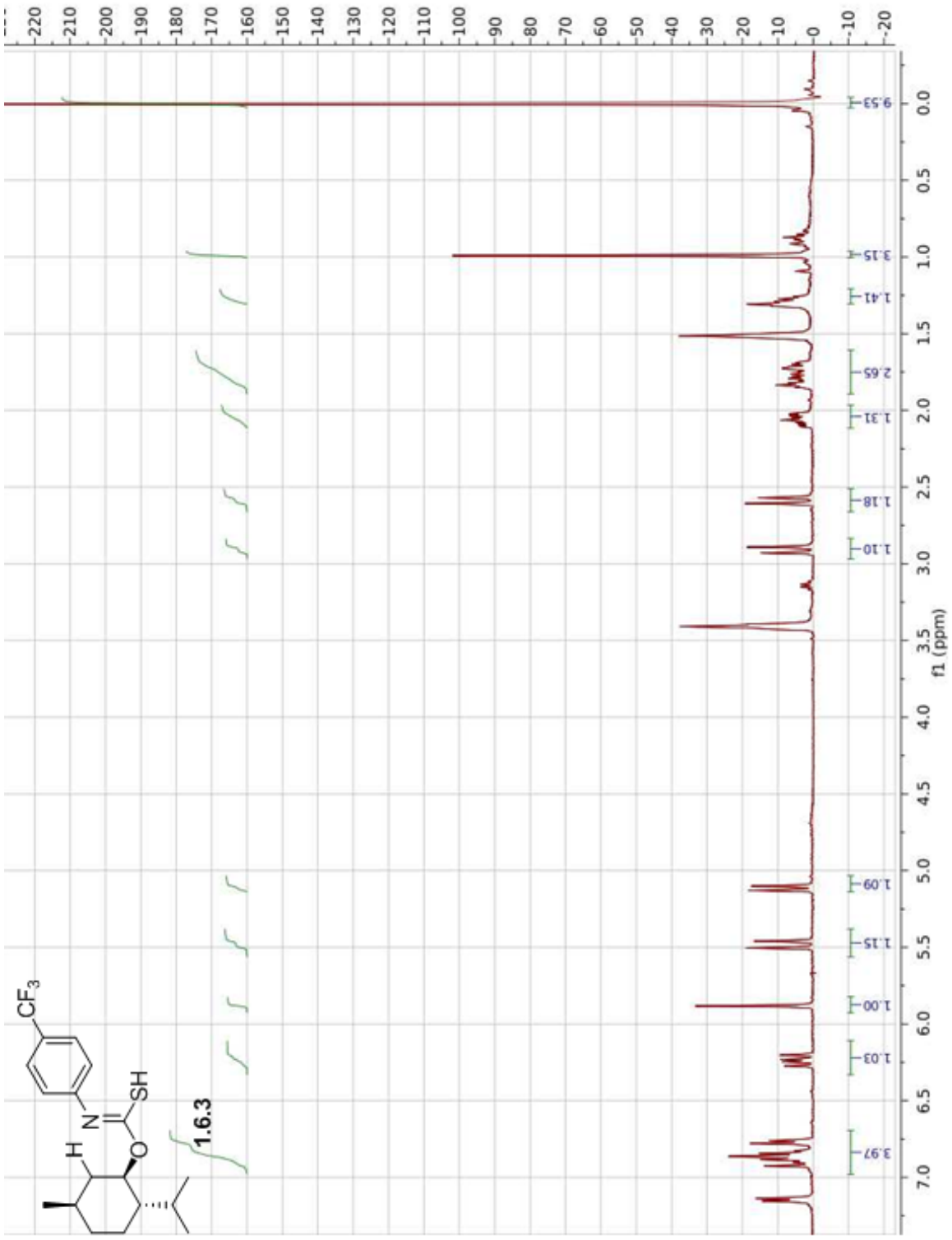
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H
SH
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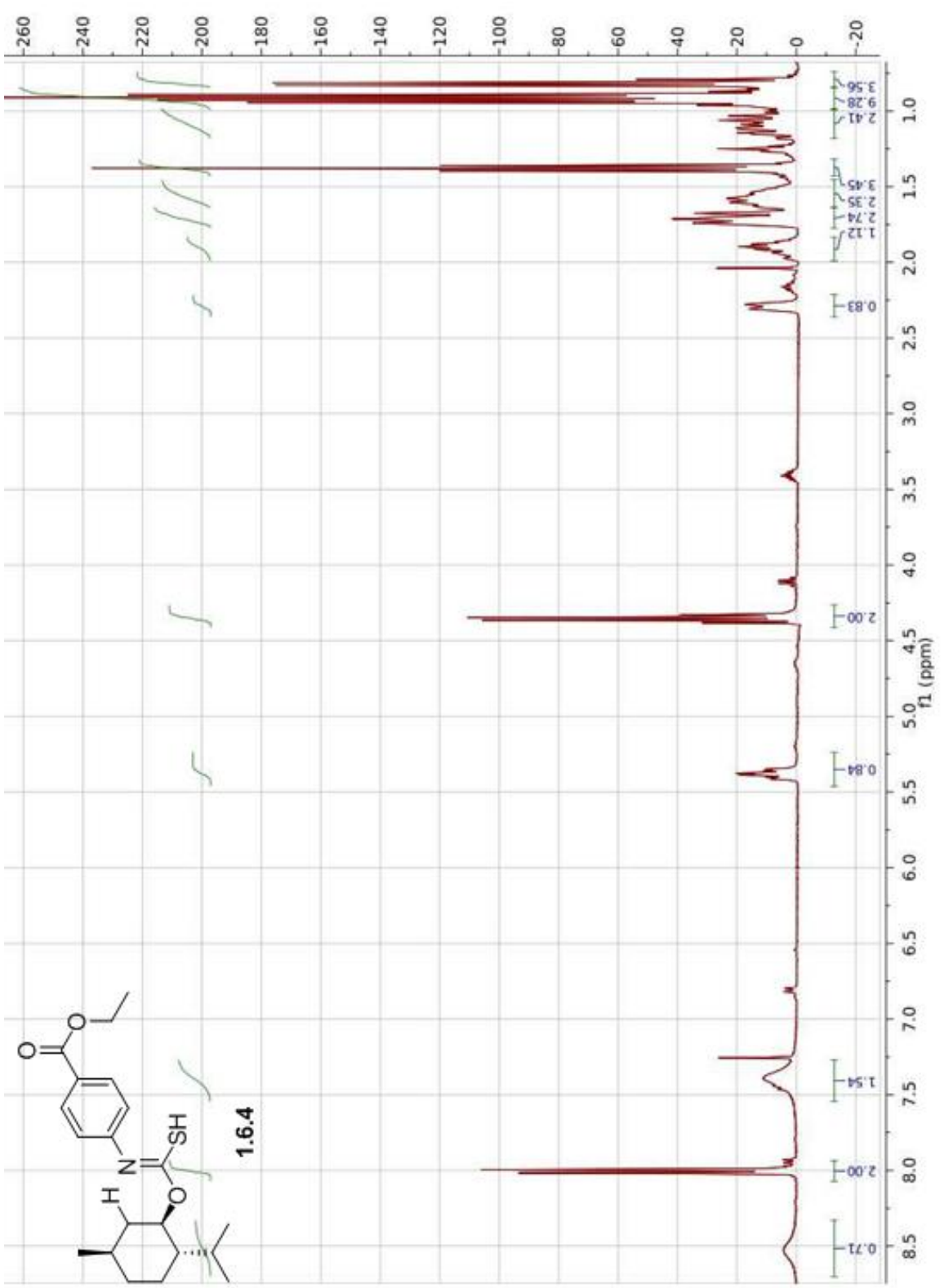
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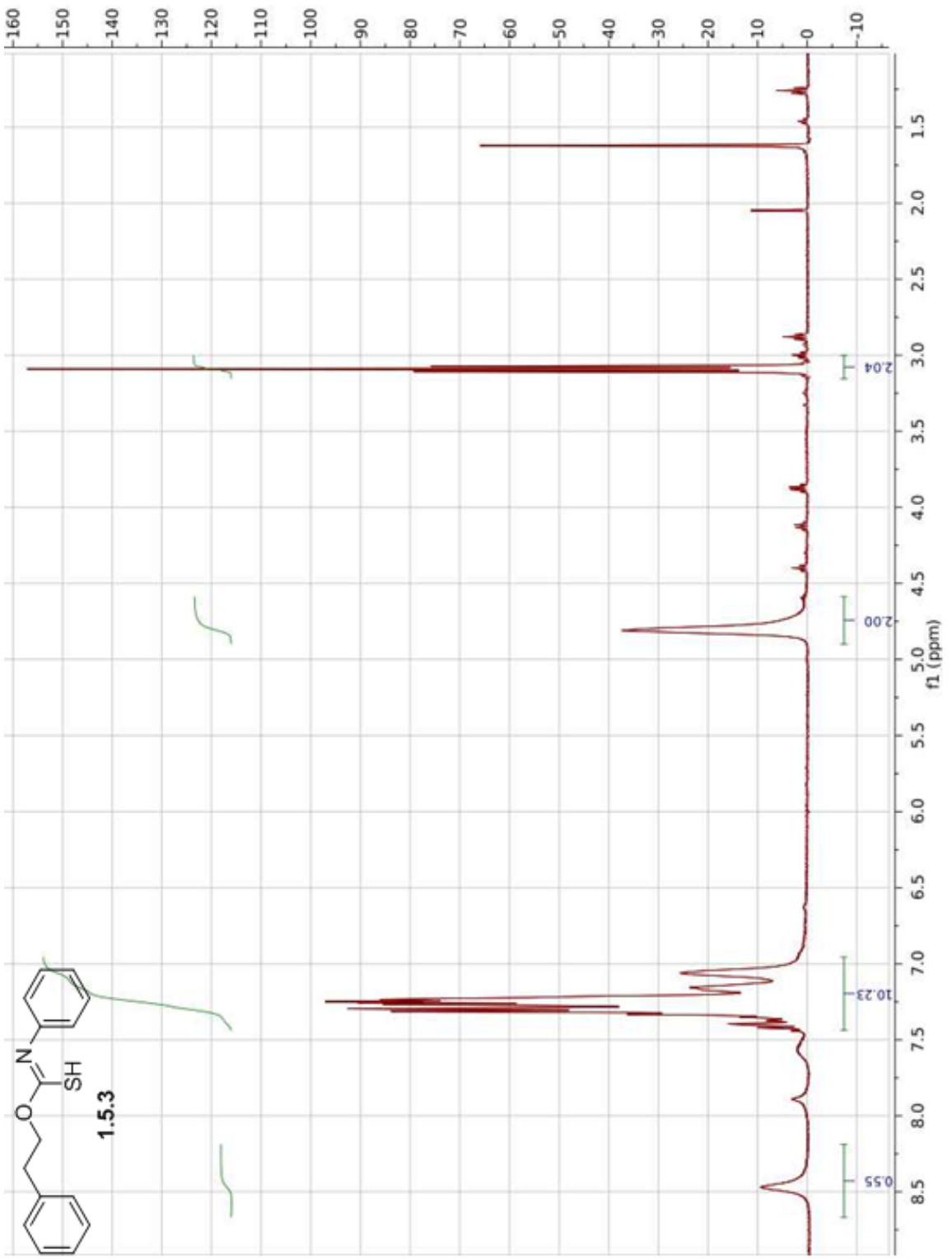
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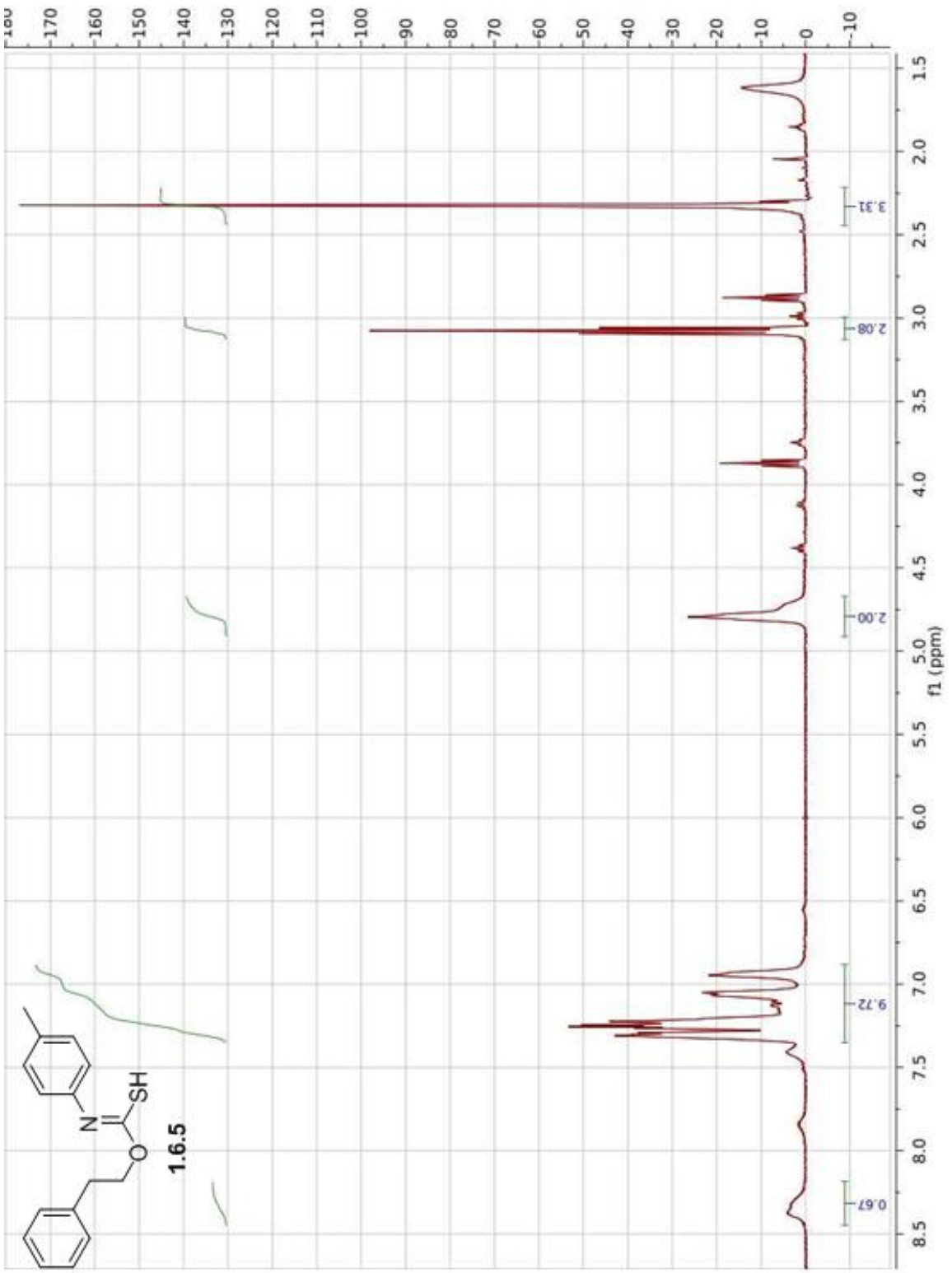
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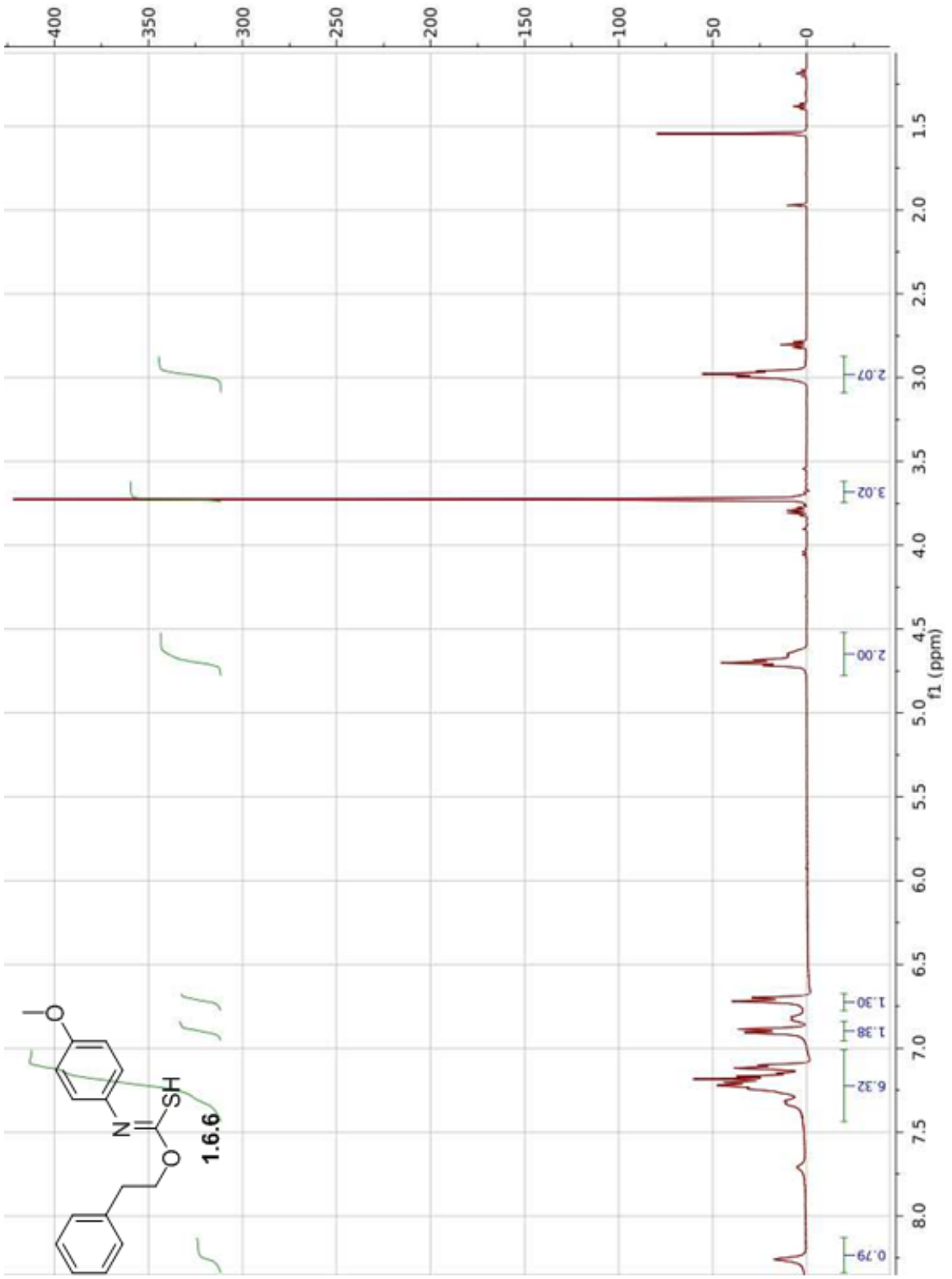
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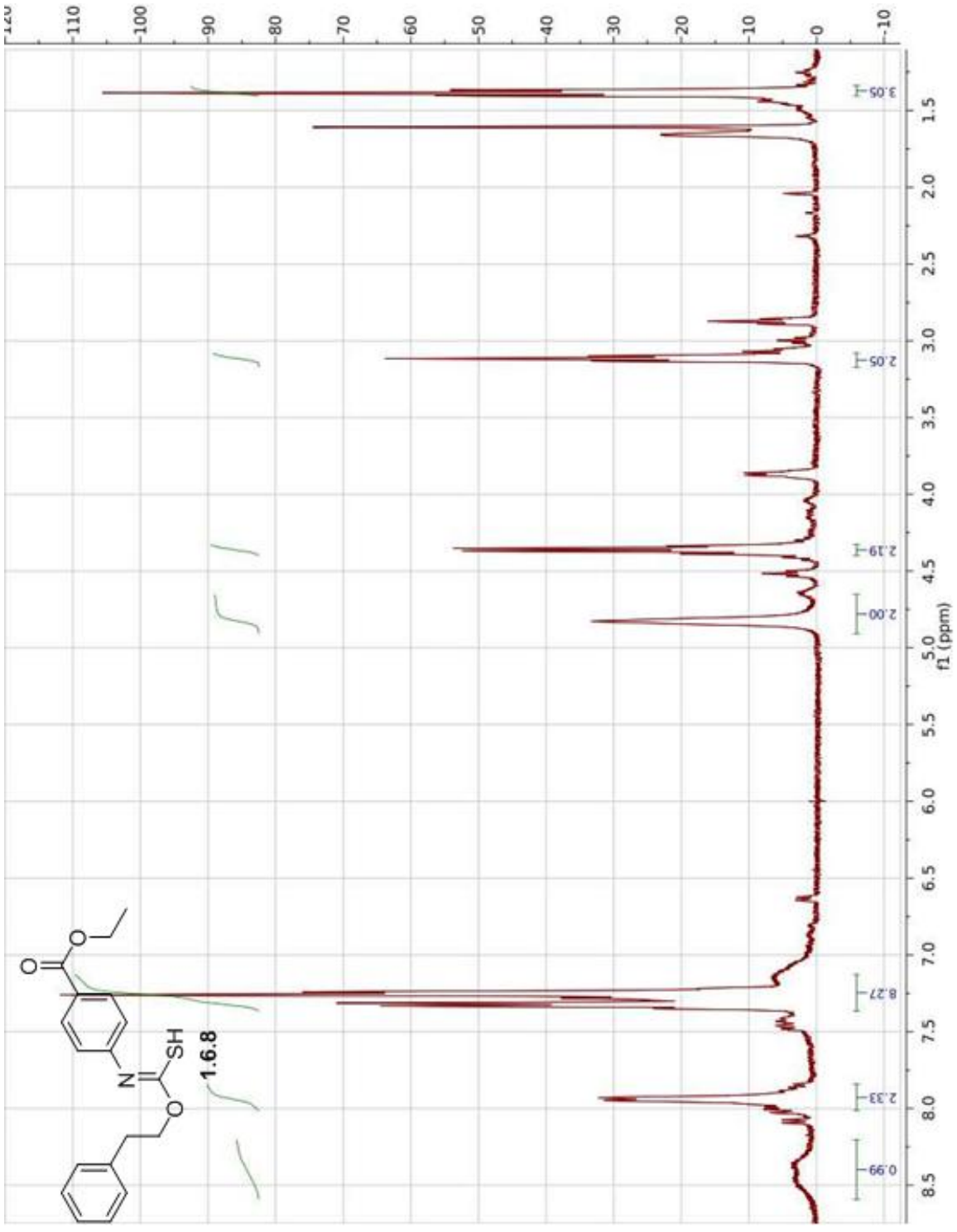
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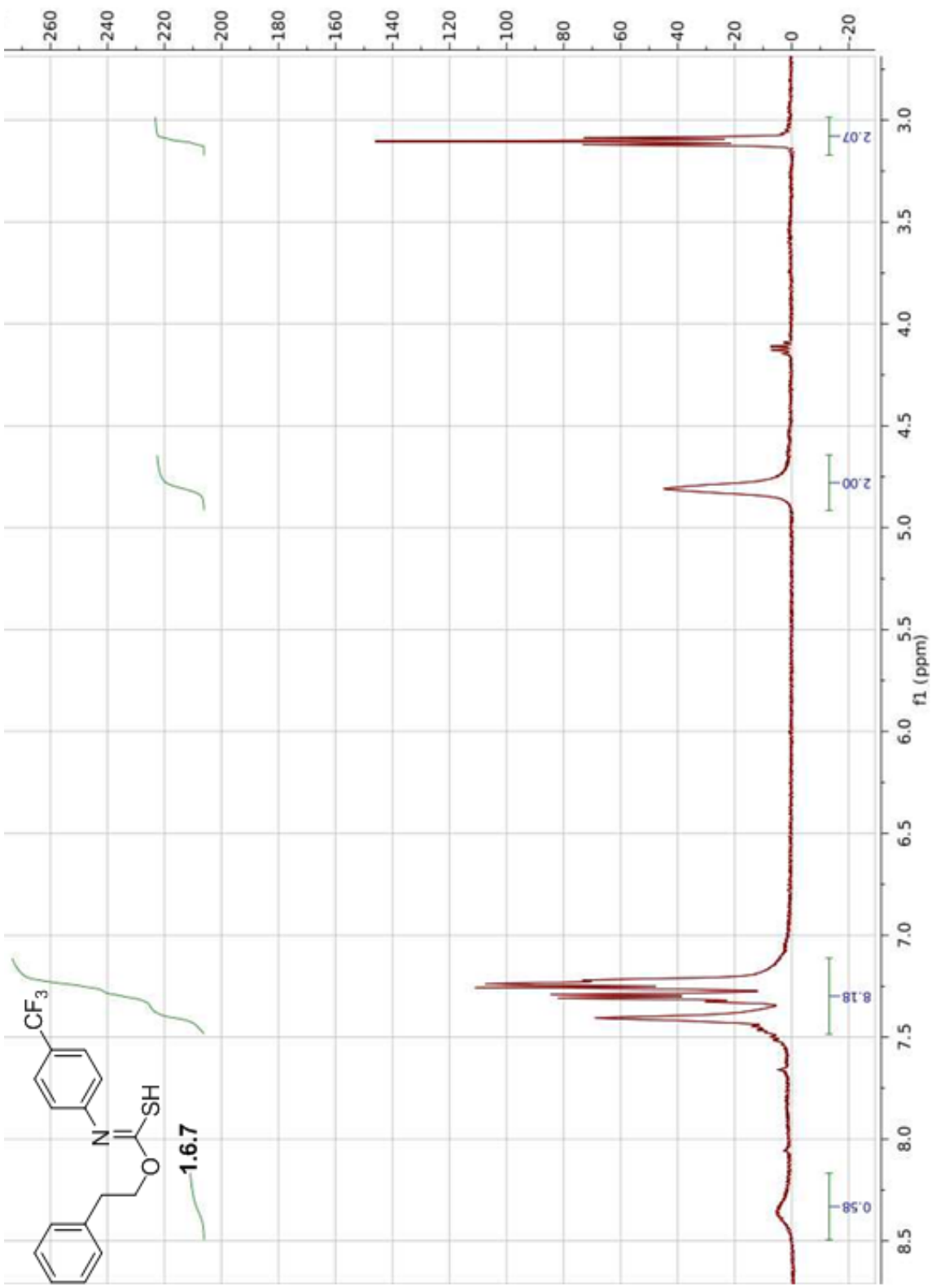
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O
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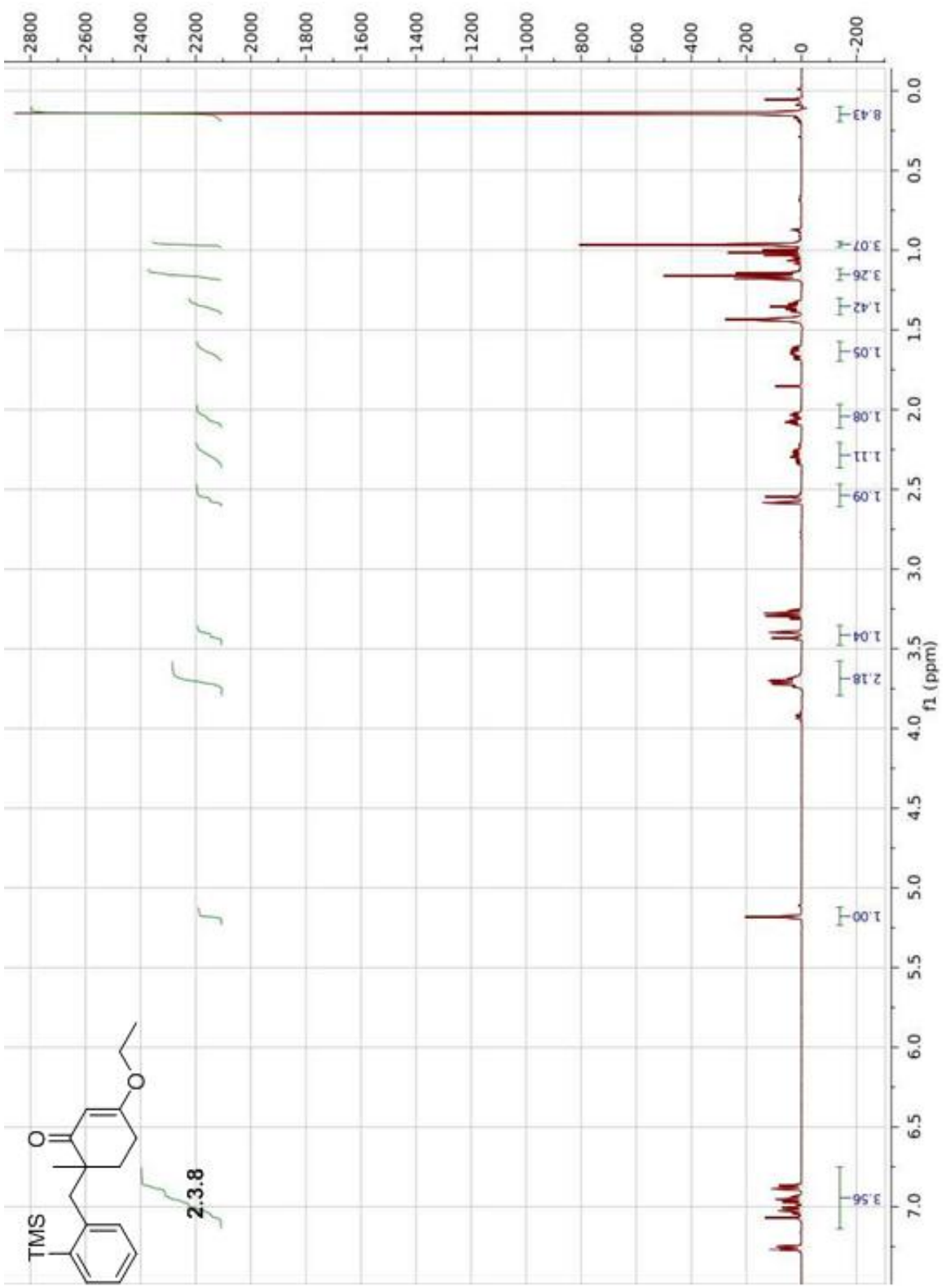
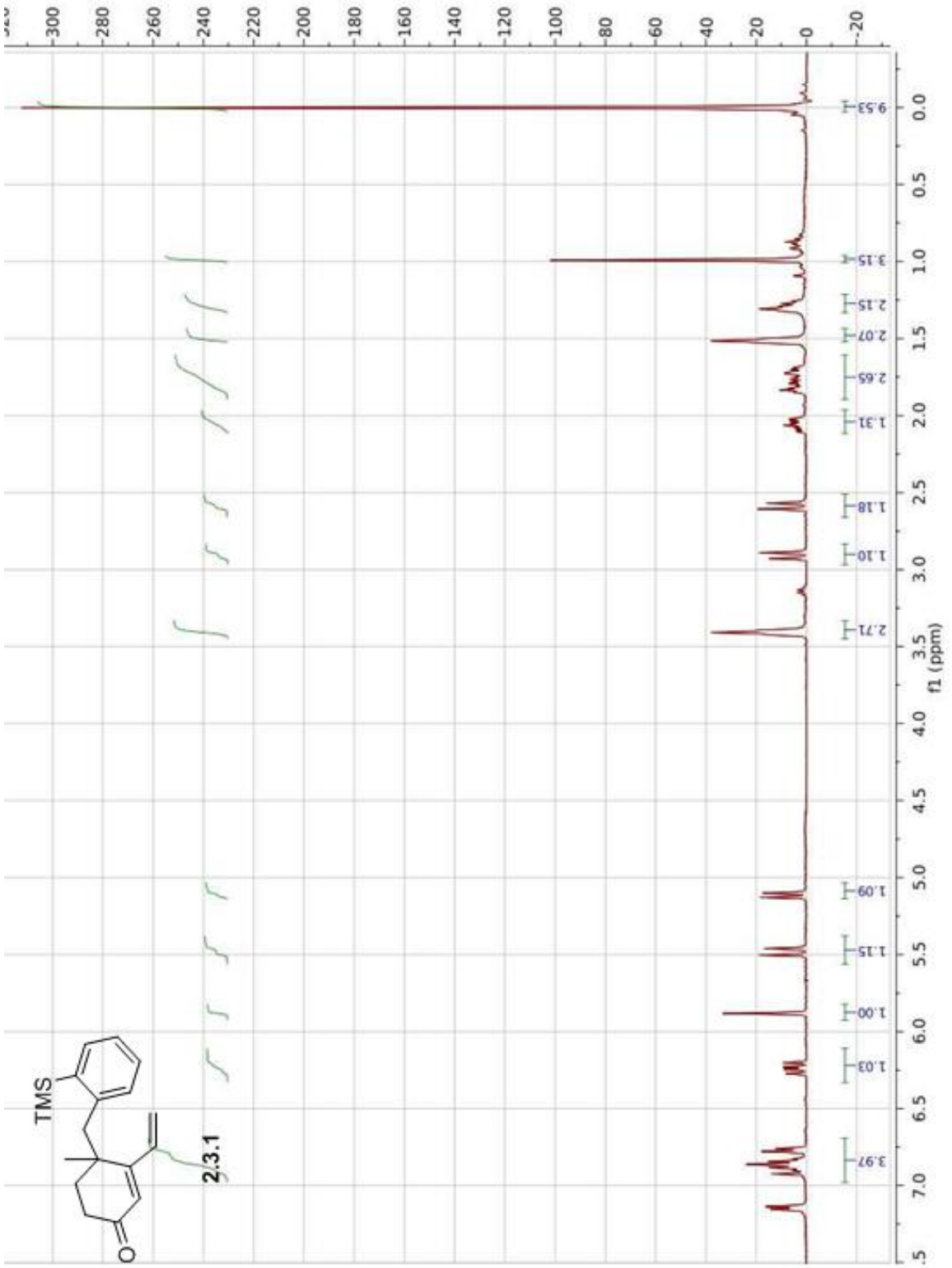
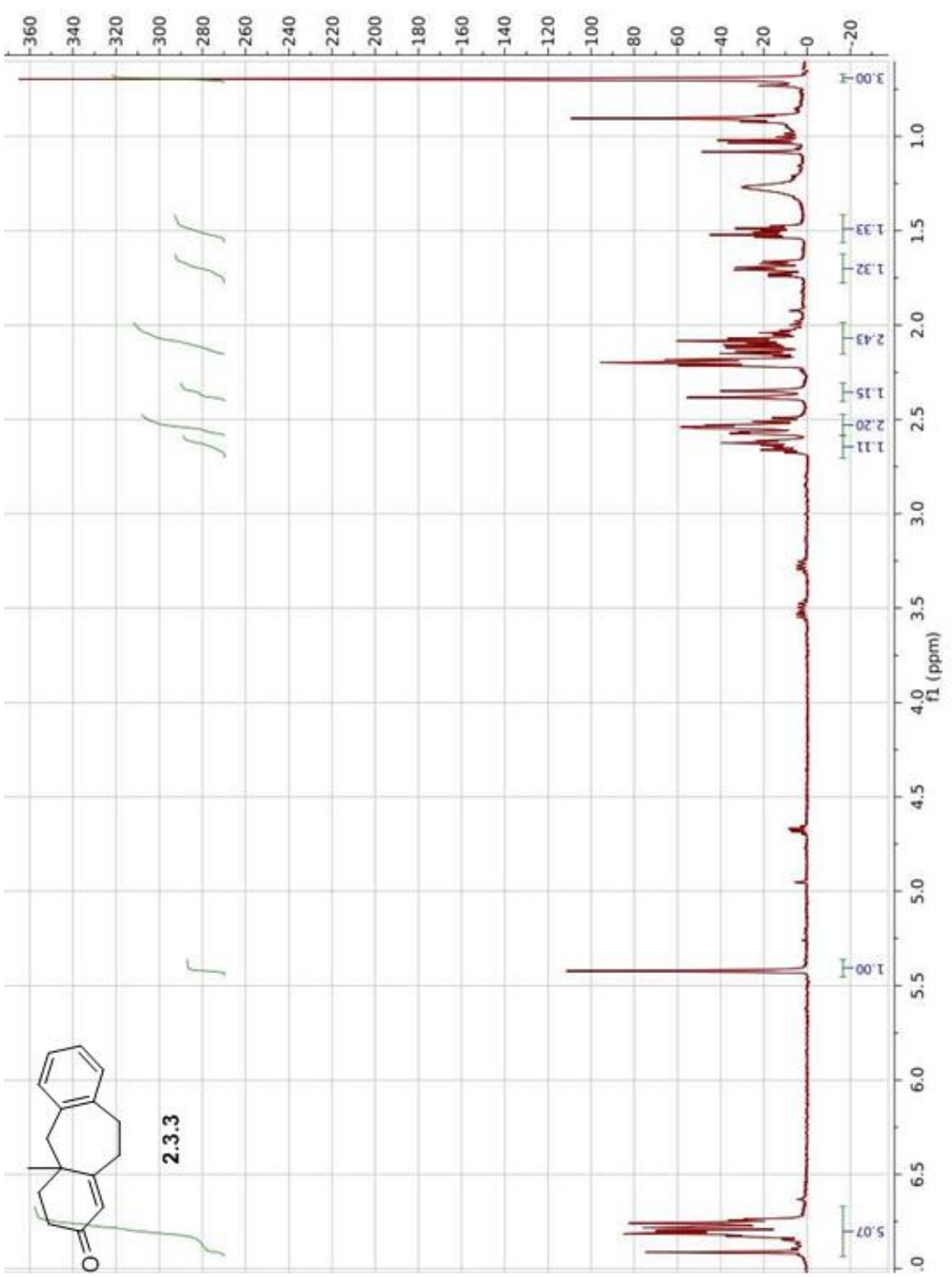
APPENDIX B

^{1}H NMR SPECTRA RELEVANT TO CHAPTER II


TMS
O
O
2.3.8
f1 (ppm)


TMS
O
2.3.1
f1 (ppm)


2.3.3
O
f1 (ppm)
5.07
1.00
1.11
2.20
1.15
2.43
1.32
1.33
3.00