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Sulfoxides as an intramolecular sulfenylating agent for indoles and diverse applications of the sulfide-sulfoxide redox cycle in organic chemistry

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SULFOXIDES AS AN INTRAMOLECULAR SULFENYLATING AGENT FOR INDOLES AND DIVERSE APPLICATIONS OF THE SULFIDE-SULFOXIDE REDOX CYCLE IN ORGANIC CHEMISTRY

By

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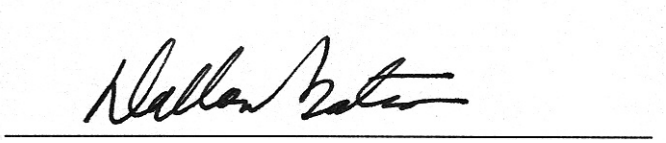
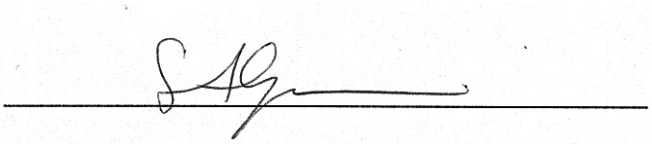
This dissertation, “Sulfoxides as an Intramolecular Sulfenylating Agent for Indoles and Diverse Applications of the Sulfide-Sulfoxide Redox Cycle in Organic Chemistry”, is hereby approved in partial fulfillment of the requirements of the degree of DOCTOR OF PHILOSOPHY in the field of Chemistry.

Department of Chemistry



Dissertation Advisor: Prof. Dallas K. Bates



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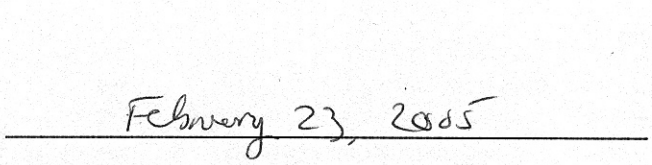

Date

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Abstract

This dissertation involves study of various aspects of sulfoxide chemistry. Specifically designed *t*-butyl and propanenitrile sulfoxides tethered to indole-2-carboxamide were used as a source of intramolecular sulfenylating agents to synthesize novel indolo[3,2-b]-1-5-benzothiazepinones which are structurally analogous to the other biologically active benzothiazepinones. This study reveals that the intramolecular cyclization of sulfoxide follows an electrophilic sulfenylation (Sulfoxide Electrophilic Sulfenylation, SES) reaction pathway. Evidence of the absence of sulfenic acid as a transient reactive intermediate in such intramolecular cyclization is also provided.

In another study, sulfoxide was used as a "protecting group" of thioether to synthesize 8-membered, indole substituted, thiazocine-2-acetic acid derivative via Ring Closing Metathesis (RCM). Protection (oxidation) of inert (to RCM) sulfide to sulfoxide followed by RCM produced cyclized product in good yields. Deprotection (reduction) of sulfoxide was achieved using Lawessons Reagent (L.R.). Application of the sulfide-sulfoxide redox cycle to solve the existing difficulties in using RCM methodology to thioethers is illustrated.

A new design of a "molecular brake", based on the sulfide-sulfoxide redox cycle is described. N-Ar rotation in simple isoindolines is controlled by the oxidation state of the proximate sulfur atom. Sulfide [S(II)] shows "free" [brake OFF] N-Ar rotation whereas sulfoxide displayed hindered [brake ON] N-Ar rotation. The semi-empirical molecular orbital (PM3) calculations revealed concerted pyramidalization of amidic nitrogen with N-Ar rotation.

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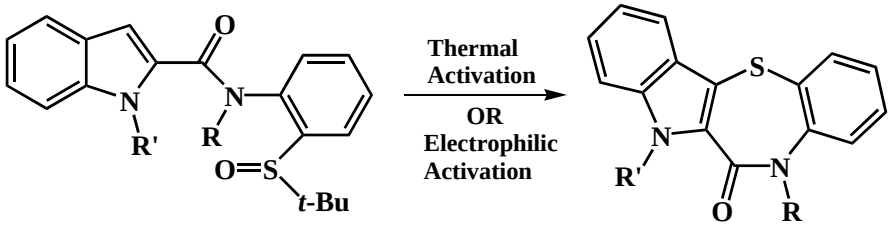
Unifying Theme

This dissertation is a combination of efforts in understanding different aspects of sulfoxide chemistry in chemically varying substrates. The chosen sulfoxide substrates are chemically diverse in nature, however, each substrate is specifically designed to suit the requirements of the intended study. Each study is included as a separate chapter (Chapters 2, 3 and 4) and hence the chronological order of compounds and references is restricted to each chapter and is not continued from one chapter to another. Background about principles and techniques used in each study is explained in the first chapter (Chapter 1). The following brief discussion is intended to give an idea of studied aspects of sulfoxide chemistry.

Sulfoxide is an important functional group in organic chemistry. To date numerous applications of sulfoxides in organic synthesis have been disclosed and further research is in progress. Our research group has an impact in specific reaction of sulfoxides, namely Sulfoxide Electrophilic Sulfenylation (SES) reaction. In the 1980's, our research group developed SES reaction to synthesize novel *N*,*S*-heterocycles, which commonly exist as substructures of more complex biologically active compounds. In this reaction, sulfoxide is used as an intramolecular sulfenylating agent. Mechanistically, during this reaction, sulfoxide is activated thermally (heating in a high boiling solvent) or electrophilically (by an electrophilic species) to produce *N*,*S*-heterocycle. Both electrophilic and thermal activation is mechanistically different and the electrophilic activation mechanism is well-known. However, the mechanism of thermal activation is still under study mainly because it takes place in absence of any other chemical reagent. We had proposed a mechanism of thermal activation of sulfoxides involving electrophilic addition of

nucleophile at sulfur producing sulfonium salt as a reactive intermediate. As opposed to our proposed mechanism, other studies (discussed later) involving thermal activation of sulfoxides proposed existence of sulfenic acid (R-S-OH) as a reactive intermediate in intramolecular cyclization reactions of sulfoxides. Both sulfonium salt and sulfenic acid are extremely reactive, hence difficult to isolate species. Their presence in the reaction mixture is usually derived by the identity of by-products obtained from the reaction. However, they share one thing in common; they both originate from a sulfoxide functional group. We have shown earlier that methyl and ethyl sulfoxides follow the SES reaction pathway (sulfonium salt as reactive intermediate), for thermal activation of *t*-butyl sulfoxides, however, the sulfenic acid pathway is more common in literature. Synthesis of benzisothiazolones has been achieved by intramolecular cyclizations of *t*-butyl sulfoxides and it was argued that these proceed via sulfenic acid. However, enough evidence to prove the presence of sulfenic acid was not provided. Hence, it is unclear whether or not intramolecular cyclizations of *t*-butyl sulfoxides generate sulfenic acid under thermal activation reaction conditions. Chapter 2 of this dissertation resolves some of these mechanistic issues regarding the presence of sulfenic acid as a reactive intermediate in intramolecular cyclization of sulfoxides. We employed thermal and electrophilic activation of appropriately designed *t*-butyl sulfoxides and achieved synthesis of benzothiazepinones (Figure 1), a novel heterocyclic system which was synthesized earlier in our research laboratory from corresponding ethyl sulfoxides.



R = H or CH_3

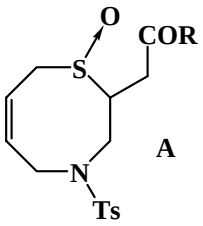
R' = H or CH_3

Figure 1

Importantly, we were able to prove that the *t*-butyl sulfoxides do not generate sulfenic acid during the intramolecular cyclization process under the employed reaction conditions.

This study emphasizes the importance of alkyl (*t*-butyl in this case) sulfoxides as intramolecular sulfenylating agents. In addition, it should be noted that if the sulfoxide is suitably substituted, it can be used to resolve some of the important mechanistic issues.

In our research laboratory, Sulfoxide Electrophilic Sulfenylation (SES) has also been applied to synthesize novel fused large ring heterocycles via ring expansion of sulfonium salt of sulfoxides. For a specific ring expansion study, we needed to synthesize an 8-membered ring sulfoxide substrate (**A**, Figure 2). We designed a new protocol to synthesize this novel 8-membered *N*,*S*-heterocycle via Ring Closing Metathesis (RCM) reaction in sulfide [S(II)] oxidation state, with eventual oxidation of sulfide to sulfoxide **A** in mind.



A

R = Indole

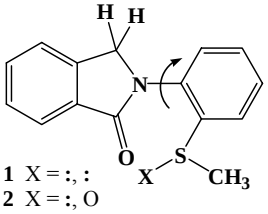
Figure 2

However, all our attempts to get successful RCM reaction with sulfide met with complete failure under varied reaction conditions. The main reason of such failure was the Ru-Sulfur coordination between sulfide substrate and the Ru-based (Grubbs 2nd generation) catalyst. To prevent such coordination, we envisioned sulfoxide as a "protecting group" for such thioethers. Indeed sulfoxide gave good yields of a cyclized product under standard RCM reaction conditions. Protection (oxidation) of sulfide and deprotection (reduction) of sulfoxide was achieved by conventional reagents, *m*-CPBA and Lawessons Reagent (L.R.) respectively. We were able to synthesize this 8-membered ring *N*,*S*-heterocycle with sulfur in sulfide oxidation

This concept is novel as it is the only example of using sulfoxide as a "protecting group" for thioether, which fails to produce the cyclized product via RCM.

The sulfide-sulfoxide redox cycle is a well-known process with various procedures available to achieve both, sulfide oxidation and sulfoxide reduction. Application of this relatively simple and well studied concept to solve existing difficulties in using RCM with thioethers is the most important outcome of this research (explained in Chapter 3).

Besides change in electronic effects caused by sulfide oxidation, steric effects also play a crucial role. Due to an increase in steric hindrance with the presence of oxygen in sulfoxides, molecular motions around the sulfur center would be affected. The understanding of the steric bulk of sulfoxide oxygen and the ease with which sulfide-sulfoxide redox cycle can be achieved (reversibility, in other words) is extremely important. It is this sulfide-sulfoxide redox cycle which is the basis of our design of the "molecular brake" (Chapter 4).



1 X = :, **:**
2 X = :, O
3 X = O, O

Figure 3

With the help of Dynamic NMR (DNMR) spectroscopy, we were able to show that the rate of N-Ar rotation in simple isoindolines (Figure 3) can be controlled with the oxidation state of proximate sulfur atom.

Sulfide [S(II)] shows "free" rotation [brake "OFF" mode] around the N-Ar bond, whereas sulfoxide displayed "hindered" rotation [brake "ON" mode]. Design of the molecular brake based on sulfide-sulfoxide redox cycle is one of the diverse applications of this redox chemistry. This molecular brake design can be a very useful component of the molecular machine, a molecular analog of any machine that we use in our everyday life. Further details about the design and its advantages will be discussed in Chapter 4.

This dissertation is a combination of various approaches in understanding the diverse applications of sulfoxides in organic chemistry. Although, all of the systems (Chapters) do not relate to each other directly, they all have a common thread, the presence of sulfoxide and its diverse applications.

Chapter 1

This Chapter includes a detailed introduction, along with some literature background of all the subsequent Chapters (Chapters 2, 3 and 4) that are included in this dissertation. In addition, some of the basic principles of the techniques used in following chapters (2, 3 and 4) are also covered. The Chapter is divided in three parts A, B and C and these notations are limited only to this Chapter. In addition, the compound numbers, schemes and figures are restricted to each part and are not continued from one part to another.

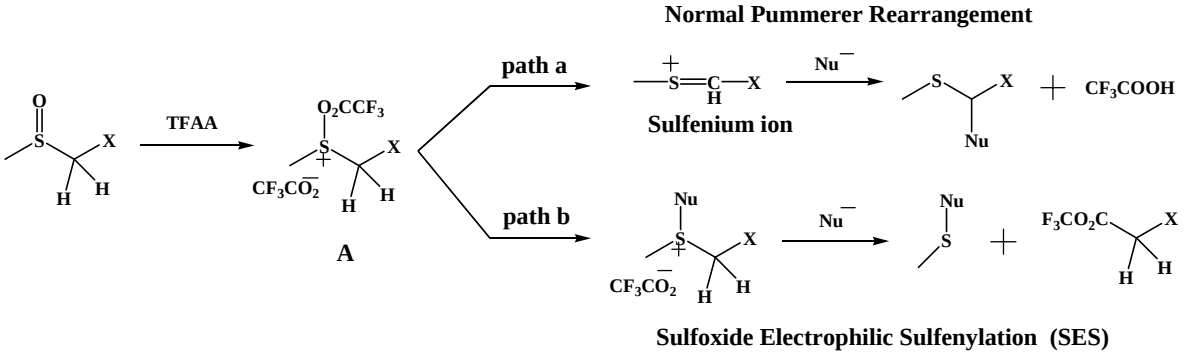
Part A: Sulfoxides as an intramolecular sulfenylating agent.

Part B: Sulfoxide as a protecting group.

Part C: Sulfoxide as a "molecular brake".

Part A: Sulfoxides as an intramolecular sulfenylating agent

As a part of our continuing efforts to synthesize novel *N*- and *N*,*S*-heterocycles, we have developed an intramolecular sulfenylation reaction, Sulfoxide Electrophilic Sulfenylation (SES) reaction. In this method, sulfenylation is carried out intramolecularly by a sulfoxide moiety. This reaction takes place under the normal Pummerer reaction conditions and was initially called "Interrupted Pummerer reaction".



Scheme 1

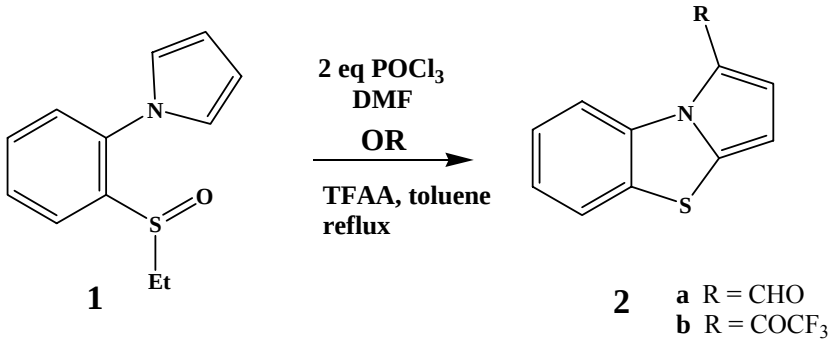
The mechanism of this reaction is shown in Scheme 1. In the Pummerer reaction, sulfoxide bearing an alpha-hydrogen is treated with anhydride, acyl halide, inorganic acids or other activating species. This converts the oxygen atom of sulfoxide into a better leaving group by forming species such as **A**. This species then looses a proton from the adjacent carbon producing sulfenium ion (path a, Scheme 1). Nucleophile then attacks the carbon producing alpha-substituted sulfide. Our research group has developed a method in which the path of the normal Pummerer reaction can be altered by varying sulfoxide substituent. Under identical reaction conditions as Pummerer reaction, sulfoxide bearing an alkyl (methyl, ethyl, etc.) group can follow path b in Scheme 1. During this path, nucleophile attacks *at sulfur* in species **A**, followed by alkyl group displacement to produce the *S*-heterocycle.

SES is a very attractive method to synthesize novel *N*,*S*-heterocycles. Conventional methods to carry out sulfenylation involve the use of a sulfide/positive halogen source or thiol/halogen[1], which results in polyhalogenated or polysulfenylated products when more than one unsubstituted site is available. SES products are always monosulfenylated because of the use of intramolecular sulfoxide functionality and relatively mild reaction conditions (explained later) compared to conventional methods.

History of Sulfoxide Electrophilic Sulfenylation (SES) reaction:

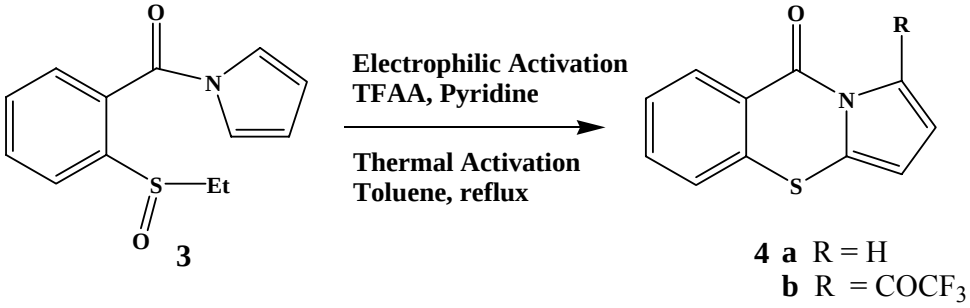
Our research group has synthesized a variety of *N*,*S*-heterocycles using SES methodology. One of the earliest example[2] of SES reaction is shown below (Scheme 2). Activation of ethyl sulfoxide using Vilsmeier-Haack reagent ($POCl_3$, DMF) to produce substituted pyrrolo[2,1-b]benzothiazole **2a** was the prominent feature of this reaction.

Compound **2b** was also synthesized from **1** later on[3] by using trifluroacetic anhydride (TFAA), in hot toluene, as an activating reagent instead of Vilsmeier-Haack reagent. The applications of this methodology were limited due to added functionality in the product in the form of aldehydic or trifluroacetyl moiety in **2a** and **2b** respectively.



Scheme 2

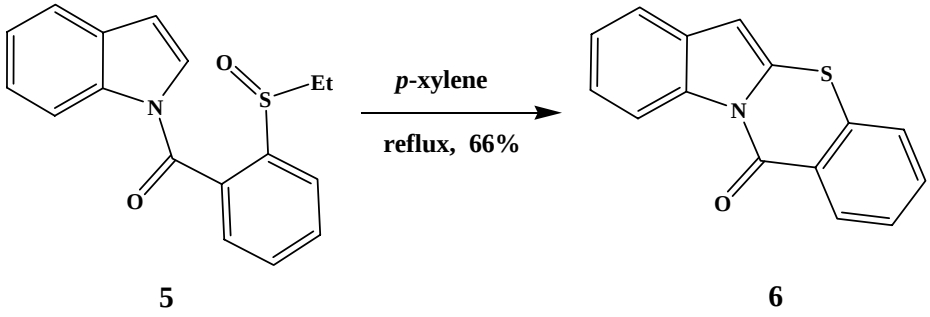
Some 6-membered *N,S*-heterocycles were also synthesized from corresponding ethyl sulfoxides using the SES method (Scheme 3).[4] Electrophilic activation (TFAA, large excess 3.7 eq) of **3** was carried out at room temperature (several hours) with pyridine (4 eq) as an acid scavenger to prevent the formation of **4b**. Unfortunately, in spite of this, **4b** was isolated in 83% yield with the absence of **4a**. However, reducing the amount of TFAA to slight excess (1.3 eq) in presence of pyridine (1.5 eq) at 0 °C produced **4a** in 55% yield along with **4b** (10%) and unchanged starting material. In addition to electrophilic activation, thermal activation (heating sulfoxide in high boiling solvents such as benzene, toluene, *p*-xylene) of sulfoxide **3** (in *p*-xylene) produced **4a** in 88% yield as well.



Scheme 3

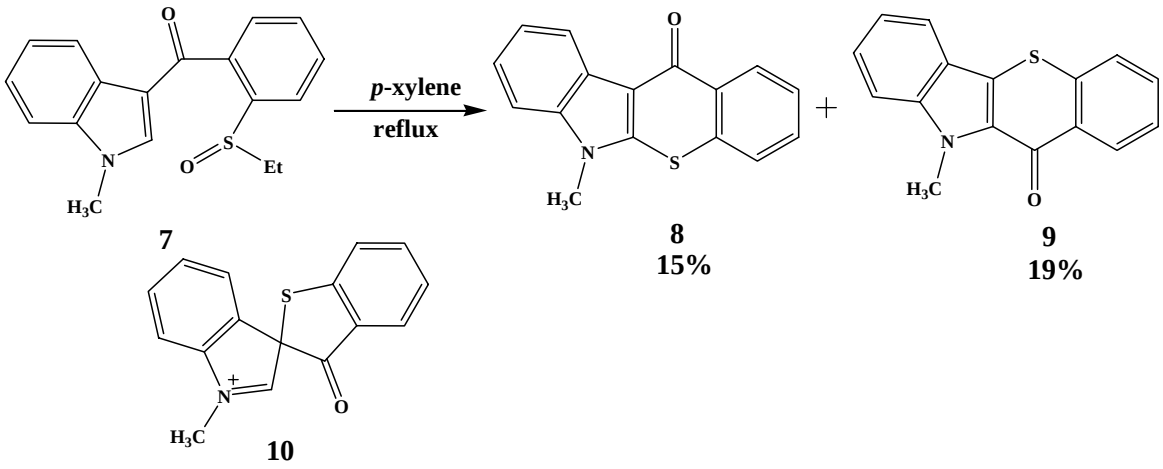
The advantage of this mode of sulfoxide activation is that no other reagent is necessary to carry out this cyclization and the product obtained is therefore unsubstituted heterocycle. Furthermore, the by-products obtained from these reactions are alkyl alcohols depending on the sulfoxide side chain. For example, in case of **3**, ethanol is produced as a by-product along with **4a**. The by-product can easily be removed from the reaction mixture during reaction (*p*-xylene, reflux, 140 °C), after reaction (during concentration of the reaction mixture under vacuo) or during work-up procedures.

As research progressed, synthesis of some indole containing heterocycles was achieved using thermal activation of **5** to produce **6** in 66% yield (Scheme 4).[5]



Scheme 4

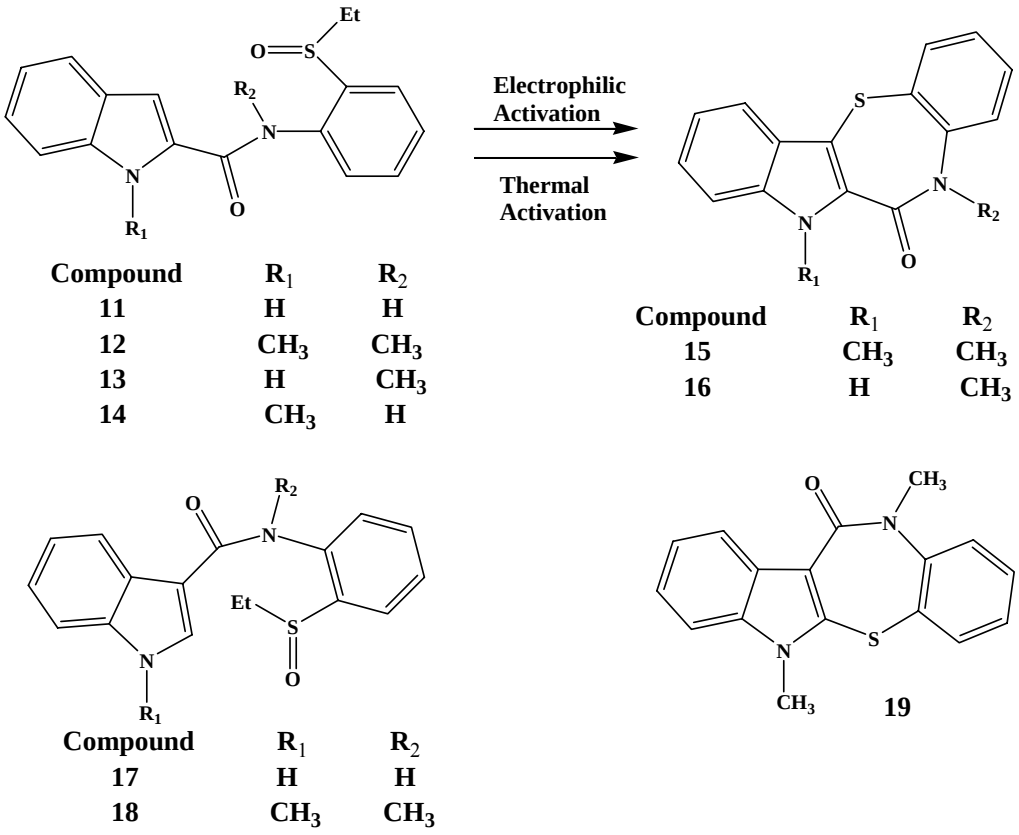
Other indole substrates produced rather unusual and mechanistically difficult to understand reaction products as shown in Scheme 5. Compound **7**, upon heating in *p*-xylene, produced **8** and **9** in 15% and 19% yields respectively.



Scheme 5

While **8** was the expected product, formation of **9** was explained on the basis of the spirocyclic intermediate such as **10**, followed by sulfur migration from the C-2 to C-3 position of the indole nucleus.

SES methodology was further extended towards synthesis of 7-membered ring thiazepinone compounds (Scheme 6). Ethyl sulfoxides tethered to indole-2-carboxamide derivatives (**11-14**) and indole-3-carboxamide derivatives (**17-18**) were synthesized and subjected to both electrophilic activation (TFAA, pyridine) and thermal activation (*p*-xylene, reflux).



Compound	R_1	R_2
11	**H**	**H**
12	**CH_3**	**CH_3**
13	**H**	**CH_3**
14	**CH_3**	**H**

Compound	R_1	R_2
15	**CH_3**	**CH_3**
16	**H**	**CH_3**

Compound	R_1	R_2
17	**H**	**H**
18	**CH_3**	**CH_3**

19

Scheme 6

Amidic substitution was essential in producing successful cyclization products, hence only **12** and **13** gave cyclized products **15** and **16** respectively, and no reaction was observed with **11** and **14**. A striking result of this work was the formation of **15** instead of **19** from 3-substituted indole carboxamide **18**. All of these results (contribution of Mary Mateo, former doctoral student of our laboratory) will be discussed in detail in Chapter 2.

Methods of Sulfoxide Activation:

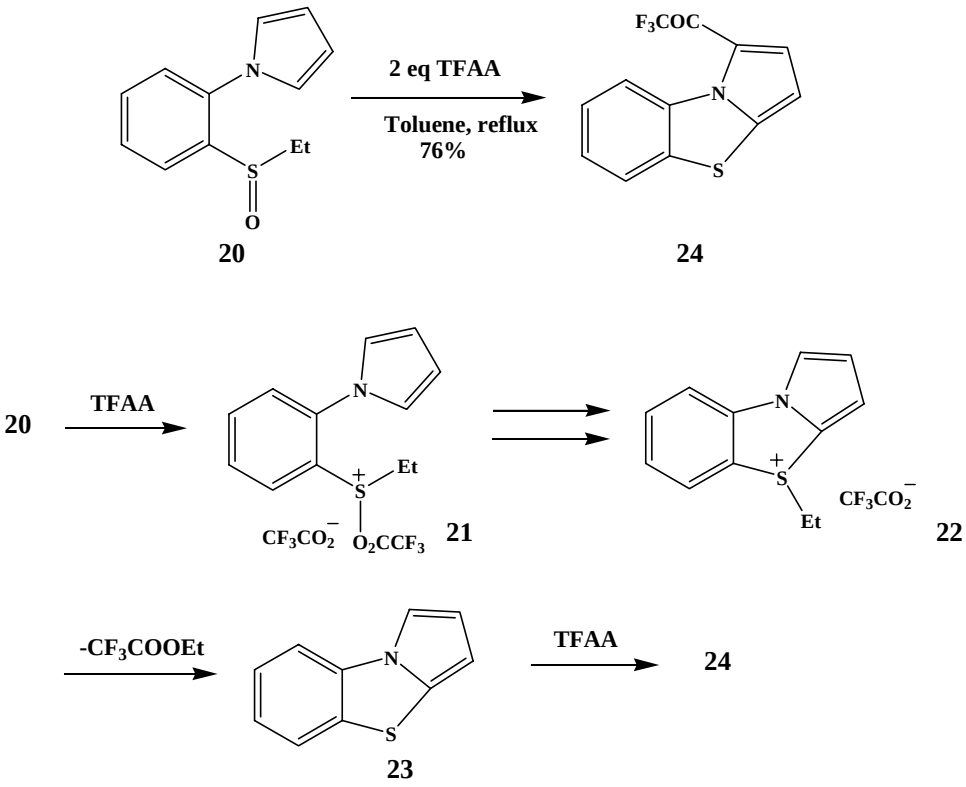
Common methods of sulfoxide activation involve electrophilic and thermal activation.

Electrophilic Activation:

As mentioned earlier, sulfoxides can be activated with the use of an electrophilic species. In all of the above-mentioned examples of SES reactions, we have used either TFAA or $POCl_3$/DMF as an electrophilic species. Activation of sulfoxide mainly involves conversion of oxygen of sulfoxide into a better leaving group. This also involves formation of an electron deficient sulfonium ion as an electrophilic intermediate. An electron rich heterocycle then attacks this electrophilic intermediate similar to an aromatic electrophilic substitution reaction producing, in our case, a nucleophile-sulfur bond. Displacement of the alkyl side chain then produces a parent heterocycle. However, as observed in the above-mentioned examples, any excess of an activating reagent then reacts with this parent heterocycle and incorporates added functionality in the heterocycle.

Thermal Activation:

In the past, we have performed thermal activation of alkyl (ethyl) sulfoxides by heating the sulfoxide in electron rich, high-boiling solvents such as benzene, toluene, *p*-xylene, etc. to produce novel *N,S*-heterocycles. These reactions proceed well in either the presence or the absence of TFAA. The presence of TFAA yields a trifluroacetylated heterocycle because excess of TFAA reacts with the initially formed parent heterocycle. For example, compound **20**, upon heating in refluxing toluene in the presence of TFAA, produced **24** in 76% yield (Scheme 7).[3]



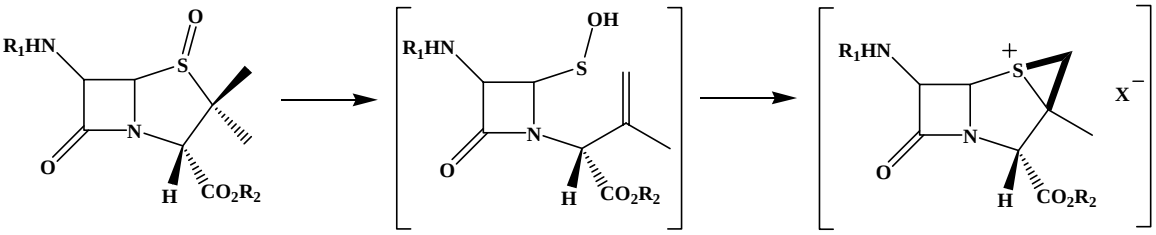
Scheme 7

We proposed that the reaction begins with the thermal activation of sulfoxide in the presence of TFAA to produce **21**, followed by a nucleophilic attack of the electron rich pyrrole ring on sulfur to produce sulfonium salt **22**. Sulfonium salt then undergoes thermal (toluene, reflux) displacement of the S-alkyl group to produce the parent heterocycle **23**, which due to the added electrophilic activating influence of sulfur, undergoes further substitution to yield **24**.

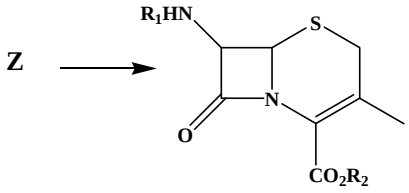
As discussed earlier, we have also carried out the thermal activation of ethyl sulfoxide in the absence of TFAA simply by heating sulfoxide in *p*-xylene. We believe, in the absence of TFAA, sulfoxide activation still takes place in a very similar fashion as described in Scheme 7. In the absence of TFAA, it is probable that acidic protons of

adjacent methylene carbons could intermolecularly protonate sulfoxide oxygen of another sulfoxide thereby activating it for the reaction.

There is literature precedence for another feasible mechanism of the thermal activation of sulfoxides in the case of penicillin to cephalosphorin conversions.[6] It was proposed that this reaction proceeds via a species called "sulfenic acid" as the reactive intermediate as shown in Scheme 8.



Penicillin Sulfoxide **Sulfenic acid intermediate** **Z**



Cephalosphorin

Scheme 8

Understanding of sulfenic acid chemistry is essential to study the mechanistic aspects of thermal activation of sulfoxides.

Introduction to the sulfenic acid chemistry:

Sulfenic acid is a highly reactive, difficult to isolate species, usually generated *in situ* by thermolysis of suitably substituted sulfoxide.[7] Sulfoxides with one or more hydrogens on a carbon beta to a sulfur atom undergo decomposition at moderate temperatures to produce an alkene and sulfenic acid (R-S-OH). A commonly accepted mechanism of sulfenic acid formation is stereospecific cis-elimination[8] as shown in Figure 1.

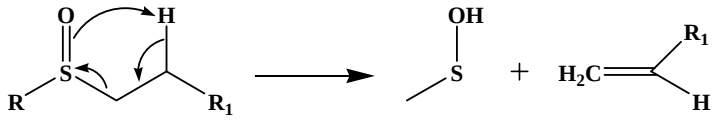
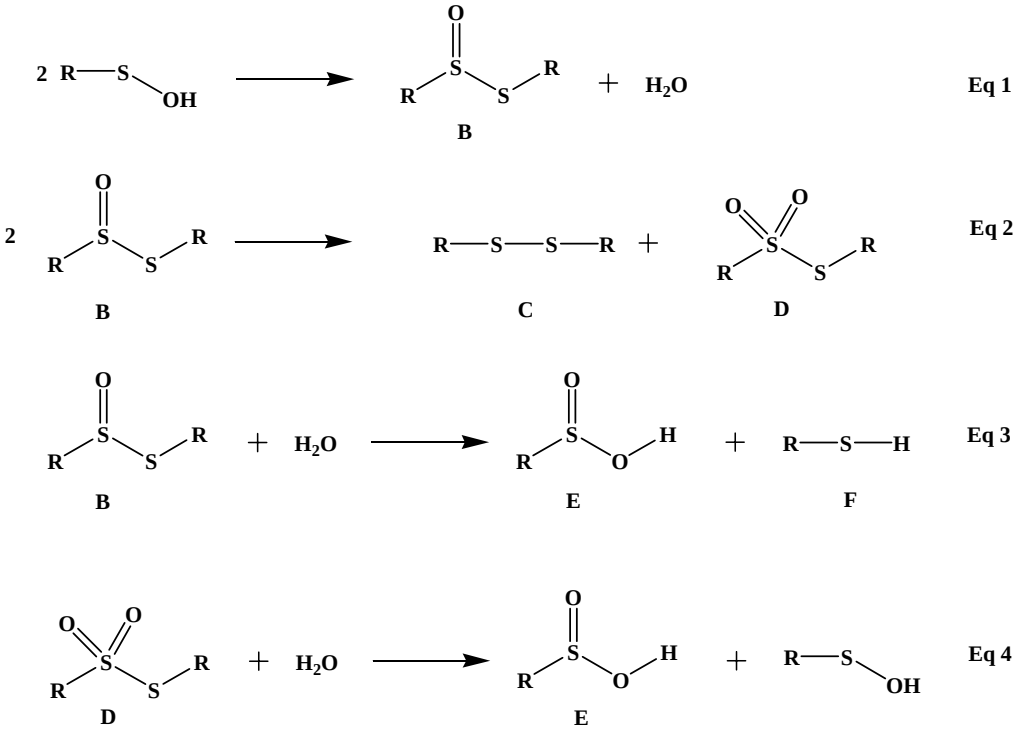


Figure 1

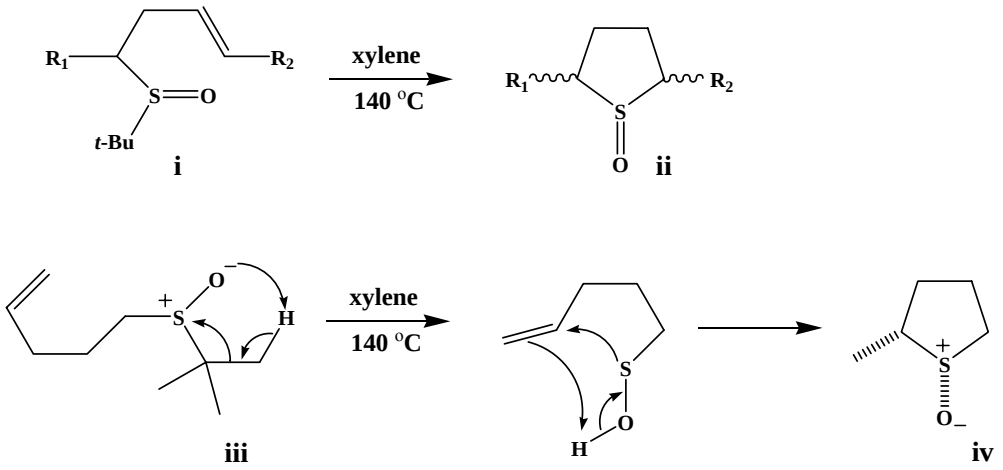
The temperature at which this thermolysis takes place varies with the R_1 group (Figure 1). The commonly studied alkyl group is the *t*-butyl group and some other examples of the functional group include the propanenitrile[9] group. Upon heating in high boiling solvents such as toluene, xylenes, etc., *t*-butyl sulfoxides undergo thermolysis to produce sulfenic acid with the elimination of isobutene. However, due to the steric bulk and the greater number of available beta-hydrogen atoms, *t*-butyl sulfoxides are capable of forming sulfenic acids even at low temperatures. [10]

As mentioned earlier, sulfenic acid is a very reactive species and hence undergoes a variety of reactions. Unfortunately, due to high reactivity, the principle reactions of sulfenic acids are not observed directly and most of the evidence for the existence of sulfenic acid has to be derived from the products obtained from a specific reaction.[11] Some of the basic reactions of sulfenic acid involve formation of thiosulfinate **B**

(equation 1). These thiosulfinate are unstable and thermally disproportionate in disulfides **C** (R-S-S-R) and thiosulfonates **D** (R-SO_2-S-R) as shown in equation 2. Thiosulfinate **B** and thiosulfonate **D** could also react with water (formed in equation 1) to produce sulfinic acid **E**, thiol (**F**) and a molecule of sulfenic acid (equation 3, 4).

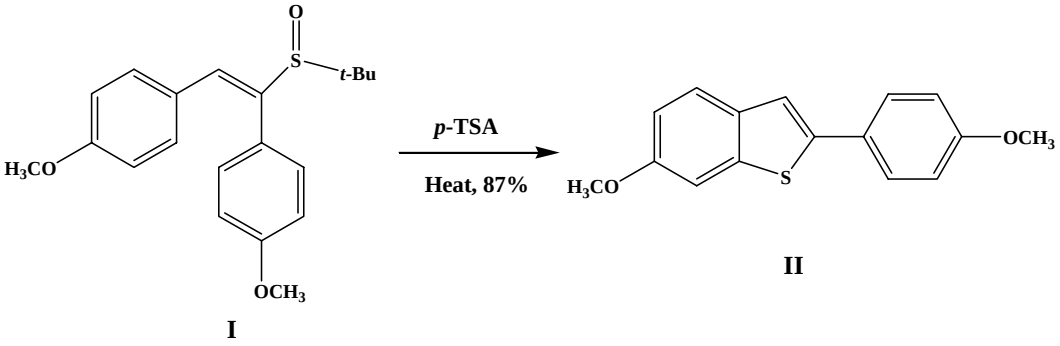


Synthetically useful reactions of sulfenic acids involve intramolecular and intermolecular additions of sulfenic acids to olefins and dienes. Examples of some of the known[12] reactions of sulfenic acids are shown in Scheme 9.



Scheme 9

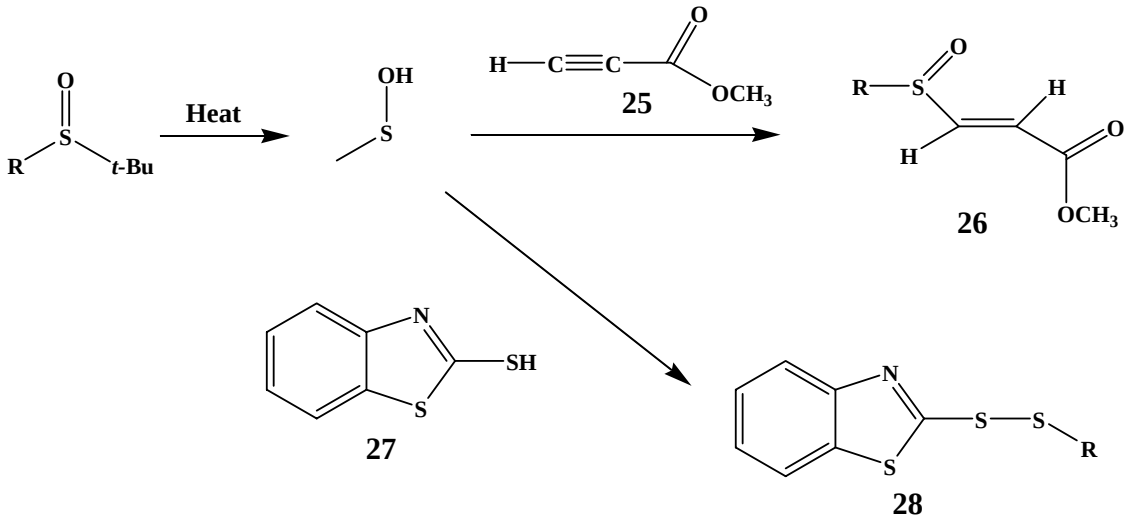
Sulfenic acid mediated intramolecular cyclizations have also been reported in the synthesis of benzothiophenes by heating styrenyl sulfoxide in the presence of *p*-TSA (Scheme 10).[13]



Scheme 10

The following reactions (Scheme 11) of sulfenic acids are of mechanistic importance. The presence of sulfenic acid in the reaction mixture can be confirmed by trapping it with alkyne or thiols. Methyl propiolate **(25)** is commonly used[8,11,14] alkyne whereas 2-

mercaptobenzothiazole **(27)** is an example[6] of thiol used as a sulfenic acid trapping agent. Scheme 11 shows the typical products that are obtained by such trapping experiments.



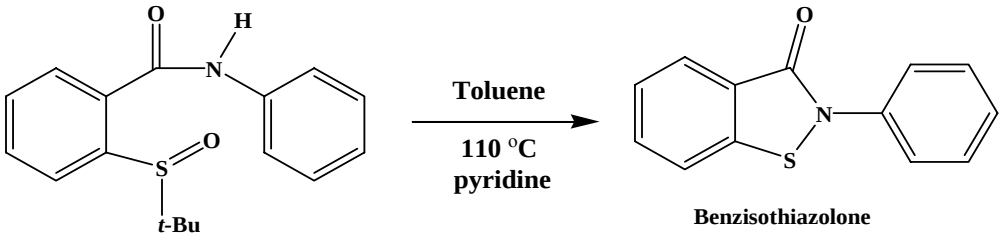
Scheme 11

Reaction of sulfenic acid with methyl propiolate can be seen as a reverse reaction of sulfenic acid formation and hence it is known[11] that the formation of thiosulfinates (**B**) and **26** are competitive reactions. Reactions of sulfenic acids and **27** are generally clean producing corresponding disulfide **(28)** in high yields.[6] These results indicate that **27** is a better sulfenic acid trap than methyl propiolate and avoids any complications in results.

Objective of this study:

Because of the similarity of the sulfoxide substituent (ethyl group in our studies and *t*-butyl in sulfenic acid chemistry) and the temperature (toluene, reflux) at which we performed our thermal activation of sulfoxides, it was thought that our thermal activation process might involve sulfenic acid as a reactive intermediate.

Furthermore, Wright and co-workers[15] synthesized specifically designed *t*-butyl sulfoxides and carried out thermal cyclization of these sulfoxides to produce benzisothiazolones (Scheme 12).



Scheme 12

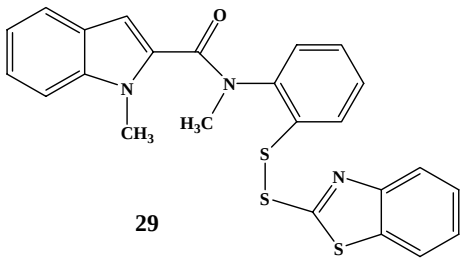
At the temperature of toluene reflux 100 °C, they postulated that, the *t*-butyl sulfoxides will undergo thermal elimination to produce sulfenic acid, which would cyclize with the loss of water, to produce the desired benzisothiazolones. However, enough evidence for the formation of sulfenic acid in the reaction mixture was not provided (for example by chemical means such as trapping experiments or any other type of experiments). In addition, unlike other reported sulfenic acid based cyclizations, this cyclization was carried out in a basic medium (pyridine).

The above example lacks enough experimental evidence to support the existence of sulfenic acid in the reaction mixture. A thorough understanding of sulfenic acid

chemistry along with experimental evidence is necessary to prove or disprove the presence of sulfenic acids as reactive intermediates in intramolecular cyclization reactions.

Our previous experience with intramolecular cyclizations using ethyl sulfoxides and the by-products obtained under those reaction conditions indicate that our thermal activation process follows the SES (formation of sulfonium salt) pathway. We obtained ethanol as a by-product in our cyclization reactions of ethyl sulfoxide. This is an indication of the absence of sulfenic acid (and corresponding alkene, ethene) being produced during the reaction. If sulfenic acid is to be produced in the reaction mixture, we would not have seen ethanol as a by-product of the reaction, as the ethene formed in the process of forming sulfenic acid would have been expelled (as a gas) from the reaction mixture.

Based on these observations, we persued the following study during which, we revisited our own system (discussed earlier, Scheme 6) and used *t*-butyl sulfoxides and propanenitrile sulfoxide (in one case) as intramolecular sulfenylating agents to carry out the synthesis of benzothiazepinones. The substituent effects and reactivity patterns were identical to the ones observed before for corresponding ethyl sulfoxides. Importantly, we performed a trapping experiment with 2-mercaptobenzothiazoles and were able to isolate thiazepinone **15** without any indication (by TLC) of the formation of a corresponding disulfide product **29**.



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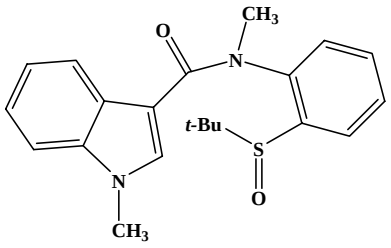
These results indicate that the products obtained in these cyclizations are SES reactions based on the attack of an electron rich heterocycle at the sulfoxide and do not involve a sulfenic acid mechanistic pathway. It is also probable that some results, which are reported in the literature (Wright and co-workers),[15] to proceed via sulfenic acid, in fact follow the SES path.

In addition to this, we also synthesized compound **30**, a *t*-butyl derivative of compound **18**, in an attempt to understand the formation of **15** from **18**. However, **30** did not produce **18** under the reaction conditions used and we think that structural changes (by replacing the ethyl group) due to the bulky *t*-butyl group could be the reason behind this.



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All of the above results of *t*-butyl, propanenitrile and ethyl sulfoxides along with experimental details and spectroscopic data are included in Chapter 2.

This research along with contribution from Mary Eggers (Mateo), former doctoral student in our research laboratory was presented at the ACS National Meeting,

Jog, P. V.; Bates, D. K.; Eggers, M. E. *Book of Abstracts,* 228th ACS National Meeting, Philadelphia, PA August 22-26, 2004. ORGN-675.

This research is also submitted for publication,

Bates, D. K.; Eggers, M. E.; Jog, P. V. *J. Org. Chem*. Submitted for publication.

Part B: Sulfoxide as a protecting group

This part covers the important aspects involved in the synthesis of thiazocine-2-acetic acid derivatives via Ring Closing Metathesis (RCM).

Introduction:

Application of organometallic chemistry in organic synthesis is ever increasing. Inorganic metal complexes act as catalysts in a variety of organic reactions. Alkene metathesis is one such well-known organic reaction, catalyzed by various types of tungsten-, molybdenum-, and ruthenium-based organometallic complexes. Initially, application of this reaction was limited in polymer chemistry with a Ring-Opening Metathesis Polymerization (ROMP) reaction. Soon after, an interesting reaction, namely, Ring Closing Metathesis (RCM) was discovered and within few years, it became the most powerful synthetic tool in carbon-carbon (C-C) bond forming reactions. Application of RCM is not only limited to the synthesis of novel compounds, but it has also proved to be the better alternative approach towards previously known systems. Subsequent chapter (Chapter 3) describes the new protocol, to synthesize thiazocine-2-acetic acid derivatives via RCM.

Mechanism of RCM:

The mechanism of RCM involves a series of alternating [2+2] cycloaddition and cycloreversion reactions between substrate and catalytic species (metal alkylidiene) (Figure 1).[16] Also, there is some evidence of metalacyclobutanes as reactive intermediates.[17] In alkene metathesis, all the individual steps of the catalytic cycle are

reversible, however, ring-closing metathesis is a forward driven reaction due to an increase in entropy in going from one substrate to two products.

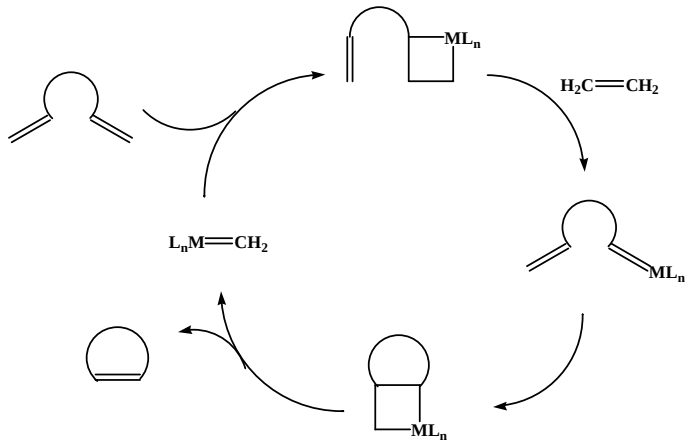


Figure 1: Mechanism of Ring Closing Metathesis.

Catalysts used in RCM:

RCM catalysts can be categorized as tungsten- (W), molybdenum- (Mo), or ruthenium- (Ru) based depending on the central transition metal atom in the complex. Tungsten-based catalysts **A** are less commonly used in RCM chemistry.[16] Alkoxy imido Mo complexes **B** are the earlier developed catalysts[17] followed, later on, by benzylidene Ru complexes **C** by Grubbs and co-workers[18] (Figure 2). Due to their air and moisture sensitivity, short storage life and poor functional group tolerance, Mo complexes are limitedly used. However, they show pronounced metathesis activity towards a variety of substrates in varying steric and electronic environments. In contrast, Ru complexes show greater tolerance to varied functionalities from esters, ketones, acetals, ethers to even more polar alcohols, aldehydes and carboxylic acids.

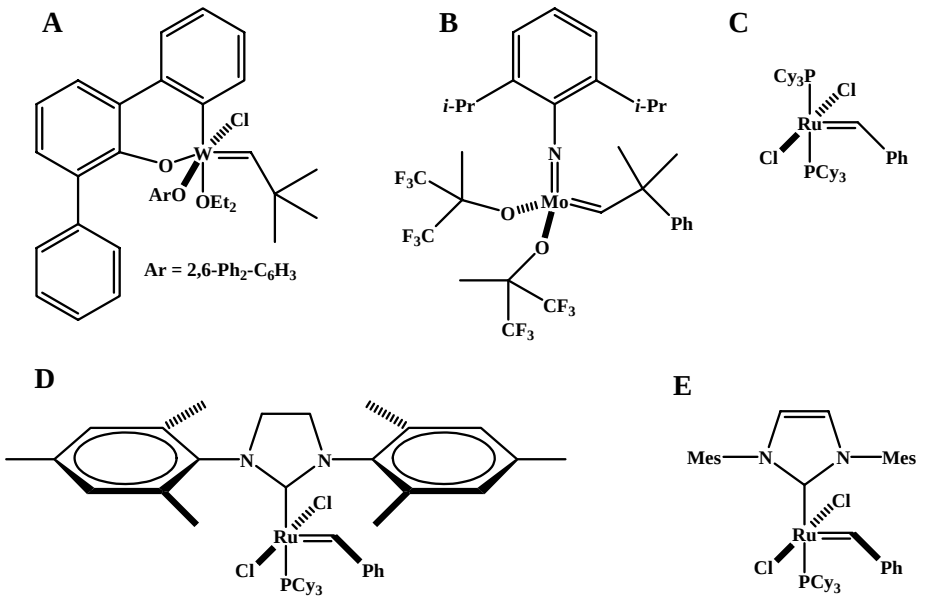


Figure 2: Various catalysts used in RCM.

This increased tolerance to functional groups, along with their ready availability and ease of handling, has made these Ru complexes commercially available over their Mo counterparts.

Later on, the focus of this research was shifted towards making more efficient, more functional group tolerant and air and moisture stable catalysts. Grubbs 2nd generation catalysts **D**[19] and **E**[20] are the examples of such modern and efficient catalysts. The important feature of **D** and **E** is the presence of bulky electron donating imidazole and imidazoline ligand, which increases the ring-closing metathesis activity while retaining air and moisture stability. These complexes also show greater functional group and heteroatom compatibility compared to catalyst **C**.

Factors affecting RCM reaction:

Suppression of the competitive metathesis based polymerization of reactant under reaction conditions is important, in achieving successful RCM. This is achieved by performing the reaction under high dilution conditions. There is literature precedence that RCM is strongly favored over intermolecular polymerization by preexisting conformational constrains in the substrate.[21] The choice of catalyst also plays an important role and often depends on the functional group in substrate and steric demands.[22] Ring size of the expected product, steric effect, effect of certain functional groups and the presence of heteroatom are some other important aspects governing the success of RCM chemistry.[23] Discussion in this chapter is restricted to the application of RCM to sulfur containing substrates.

RCM as applied to sulfur containing substrates:

There is a lot of ongoing research towards synthesizing *S*-heterocycles using RCM methodology. This increasing interest is mainly due to well-known biologically active and synthetically useful (as intermediates) *S*-heterocycles.[23] Our interest in *S*-heterocycles is centralized on the application of Sulfoxide Electrophilic Sulfenylation (SES) reaction in synthesizing novel *N*, *S*-heterocycles. SES is a novel sulfenylation method developed in our research laboratory, and uses sulfoxides as intramolecular sulfenylating agents.[24]

In order to synthesize a novel 12-membered ring *N,S*-heterocycle using SES methodology, we needed its immediate precursor, a thiazocine acetic acid derivative sulfoxide **3** (Scheme 1). Sulfoxide **3** is a novel 8-membered ring *N,S*-heterocycle. Synthesis of higher membered heterocycles, specifically, 8-membered compounds still

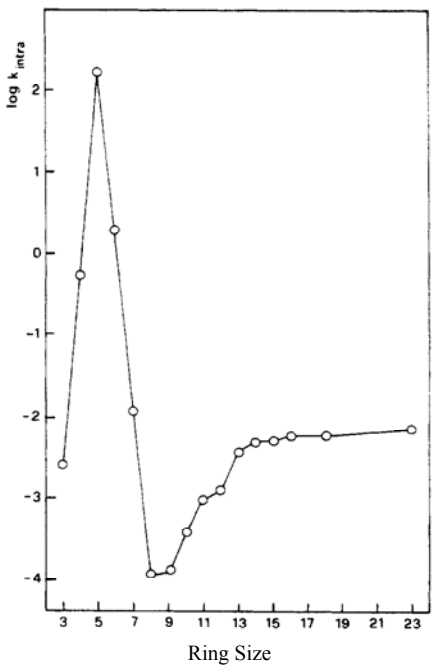


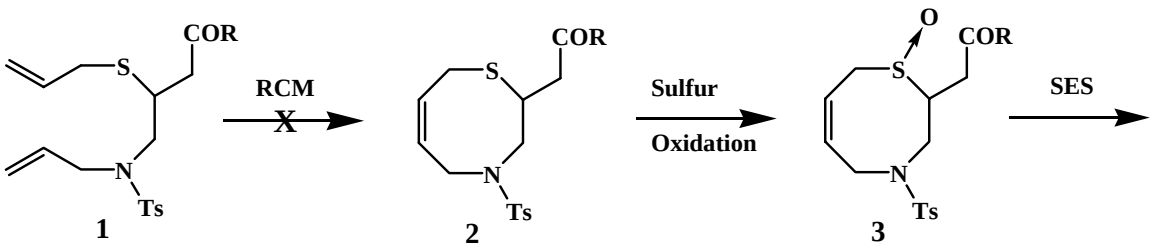
Figure 3: Adapted from Ref 25

remain as a formidable task. Figure 3 is an illustrative example of the difficulties involved in the synthesis of 8-membered heterocycles.[25] In this graph, the rate of cyclization (lactonization from ω-bromoalkanoate) was plotted against the ring size (3 to 23) of the product obtained, which shows the decrease in the rate of lactonization for 8-membered ring heterocycles by a factor of 10^6. In addition, the absence of examples with sulfur containing (as a nucleophile) systems displays the intensity of the problems encountered specifically, in synthesizing 8-membered ring *S*-heterocycles.

However, there are examples in literature about 8-membered *S*-heterocycles. In one case, intramolecular cyclization of α,ω-dibromoalkanes in presence of $Na_2S{\cdot}9H_2O$ was used to make 7-15 membered ring thiacycloalkanes (48% yield of 8-membered thiacycloalkane).[26] The other example used [2,3] the sigmatropic rearrangement of sulfur ylides to synthesize the 8-membered *S*-heterocycle.[27] Additionally, examples of *S*-, *N*,*S*-, *N*,*O*- *O*,*O*-, *N*,*N*-hetrocycles, which are structurally analogous to **3** are also scarce.[25,28] The need for 8–membered *N*,*S*-heterocycles is increasing due to their occurrence in biologically active compounds as a substructure. This prompted us to design a suitable method for the synthesis of the 8-membered ring *N*,*S*-heterocycles.

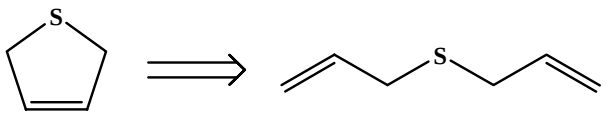
RCM has proven its wide applicability in synthesizing medium-sized *N*,*O*-heterocyclic systems.[28] We decided to apply RCM methodology to synthesize the 8-membered ring *N*-

S-heterocycle **2**, with the hope that if this, otherwise improbable to achieve synthesis of the 8-membered heterocycle is successful, then RCM can be a very important synthetic tool in making other (9,10-membered and so on..) macrocyclic systems. We decided to employ RCM to synthesize rarely studied sulfur compounds of the type **2** with subsequent oxidation of sulfur to give sulfoxide **3** (Scheme 1). Retro-synthetic analysis gave us the structure of the RCM precursor as **1**. However, our efforts to get the cyclized product **2,** met with complete failure under varied RCM reaction conditions. Although, we were disappointed, the result was not unexpected looking at the volume of literature[29] available about failures of sulfur containing compounds to produce successful RCM results.



Scheme 1 **R = OCH_3, Indole, Indoline**

Basset and co-workers[30] reported ring-closing metathesis on sulfur containing substrates as early as 1995. Diallyl sulfides of the type **4** gave successful cyclized products with catalyst **A**. The same substrate, with catalyst **B** gave better yields than **A**, however, catalyst **C** did not produce a cyclized product.



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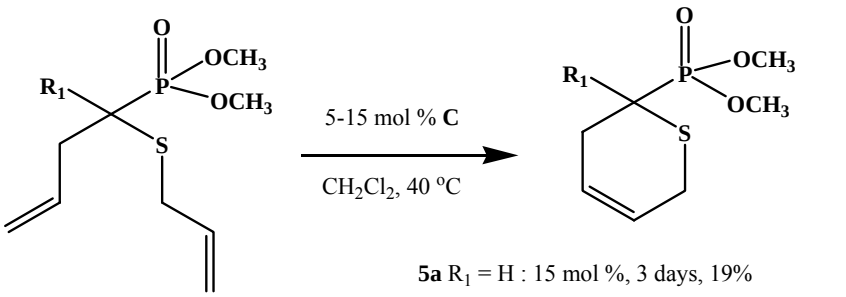
The main reason for the failure of catalyst **C** was Ru-S(II) lone pair coordination, resulting in catalyst deactivation (poisoning). It was believed that, such Mo-S (II) coordination was avoided in case of catalyst **B** due to steric bulk around the central Mo atom.[16] This example demonstrates the effect of changing the catalyst in order to get improved results. Unfortunately, due to financial constrains, instrumentation requirements, timeline of research, etc., it is not always possible for chemists to do such change readily.

As mentioned earlier, research in the development of a more efficient catalyst has answered these questions to some extent. For example, Grubb's 2nd generation catalysts **D** and **E** showed improved heteroatom and functional group tolerance than generation one catalyst **C**. The added air and moisture stability along with the commercial availability of **D** and **E** has increased their wide use over air senstitive and non-commercially available Mo-based catalysts.

Inspite of this, there is still no assurance of successful RCM chemistry on sulfur substrates as evident from unsuccessful cyclizations of some diallyl sulfides with catalyst **E**[31]and our own example (Scheme 1), which uses catalyst **D**. It is extremely discouraging for a chemist to see such unsuccessful results considering the time, labor and cost of chemicals involved in the synthesis of its precursors.

In parallel to the catalyst development studies, there are some reports where substrate modifications were helpful in getting successful results to synthesize *S*-heterocycles using RCM. For example, introduction of bulky *t*-butyl ester replacing hydrogen gave an almost quantitative yield (99%) of the cyclized product **5a** compared to a mere 19% of **5b** when R_1 = H. with catalyst **C** (Scheme 2).[32]



5a R_1 = H : 15 mol %, 3 days, 19%

5b R_1 = -CO_2-*t*-bu : 5 mol %, 20 hours, 99%

Scheme 2

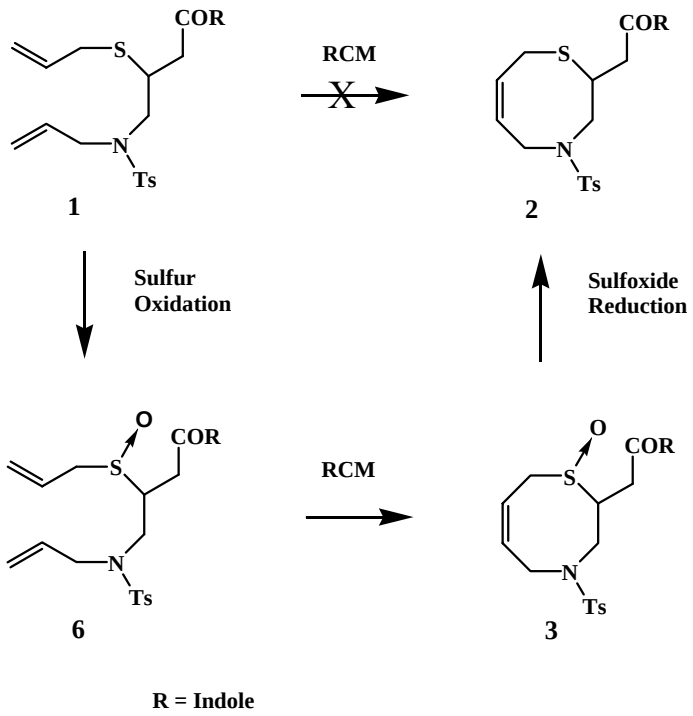
Some other substrate modifications include complete oxidation of sulfides to corresponding sulfones. Sulfones tend to give much better results compared to their sulfide analogs.[33] The success of these examples lies in avoiding the Ru-S(II) coordination by the steric bulk of *t*-butyl ester in one case (Scheme 2) and by the absence of lone pairs on sulfur, in case of sulfones.

An interesting point to note in both the above-mentioned examples is that success was achieved after making irreversible or permanent substrate modifications. This is important because, if the RCM reaction with S(II) containing substrates is to fail, then it may not always be possible for a chemist to make such irreversible substrate modifications. Furthermore, introduction of added functionality (for example, *t*-butyl ester in Scheme 2) could cause severe interference during the synthetic steps to be followed after RCM in any given reaction scheme depending on the chemical nature of functionality. Additionally, the need of sulfur (II) in the target compound is very high, as many of the biologically active *S*-heterocycles are in the form of sulfides. These issues, not only restrict the chemists ability in making their originally intended target compound but it also limits the scope of RCM as applied to sulfur chemistry.

Change in the oxidation state of sulfur, is an attractive approach, but sulfone is not the only choice, specifically because the reduction of sulfone to produced desired sulfide is difficult to persue. Hence, we sought to carry out partial or incomplete (intermediate) oxidation of sulfide to get sulfoxide. Rather surprisingly, RCM studies on sulfoxides are rarely seen. To the best of our knowledge, prior to our work, there were only two reports of such studies with equal results of success[34] and failure.[35] It may be recalled that our earlier proposed reaction scheme involved reaction steps as RCM→ Sulfur oxidation→SES in that order (Scheme 1). After unsuccessful RCM results on sulfide **1,** we exchanged the first two steps of the proposed scheme and carried out partial sulfur oxidation first, followed by RCM on sulfoxide **6**. We were pleased to see that sulfoxide **6** sucessfully produced RCM cyclized sulfoxide **3** (Scheme 3). This success gave us one of our intended targets (compound **3**), however, unsuccessful RCM on **1** precluded us in getting our other intended product, sulfide **2**. The idea of incomplete or partial oxidation of sulfide plays a crucial role here because, unlike previously reported substrate modifications, this modification is reversible. Individual oxidation and reduction steps are irreversible but the concept of performing these steps in a way shown below (Scheme 3) makes this modification reversible. For example, we achieved the reduction of sulfoxide **3** using Lawesson's Reagent (L.R.) and were able to successfully synthesize the intended sulfide **2**.

The idea of using sulfoxide as an intermediate is advantageous, as there are plenty of reagents available to carry out sulfur oxidation and sulfoxide reduction.[36] Such redox reactions are relatively cheap (in terms of cost of chemicals), less labor intensive and easy to perform. Importantly, by this approch, the change in catalyst is not required,

which avoids the handling of the air sensitive catalyst and the need of a sophisticated instrumentation facility for such handling.



Scheme 3

In other words, sulfoxide protects sulfur, presumably by preventing Ru-S(II) coordination during the RCM reaction thereby acting as a "protecting group" of sulfide. Based on all the advantages mentioned above, it is clear that using sulfoxide as a "protecting group" is the method of choice where RCM fails to produce the cyclized product with corresponding sulfide. It extends the scope and applicability of RCM on various sulfur containing substrates. It is even worth revisiting some of the earlier unsuccessful results with sulfides and applying this methodology. Importantly, with this

powerful tool in hand, chemists will no longer have to make compromises in synthesizing their intended target compound, especially if it happens to be a sulfide [S(II)].

The demonstration of this concept with the most sensitive substrate (**3)** of this series, along with other synthetic efforts towards thiazocine-2-acetic acid derivatives was published in the following article:

Bates, D. K.; Li, X.; Jog, P. V. *J. Org. Chem*. **2004**, *69*, 2750.

This research was also presented at the ACS National Meeting,

Bates, D. K.; Li, X.; Jog, P. V. *Book of Abstracts,* 227th ACS National Meeting,

Anaheim, CA March 28-April 1, 2004. ORGN-80.

My most important contribution was developing the redox protecting scheme for the indirect sulfide RCM methodology. This involved finding a suitable reagent, reaction conditions along with preparation of sulfide **2** (Scheme 3) and thorough spectroscopic characterization. I also synthesized various diene RCM precursors for exploratory work on scope and utility of this methodology. Due to space restrictions, thorough spectroscopic characterization such as COSY, HETCOR spectra of **2** along with the detailed chemical shift and the coupling constant information is included as an appendix 3 to this dissertation and is not included in the published article.

Part C: Sulfoxide as a "molecular brake"

This part of the chapter demonstrates one of the unique applications of sulfide-sulfoxide redox chemistry.

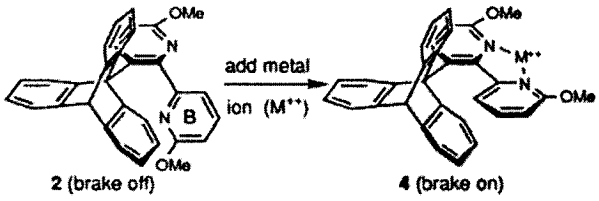
Introduction:

Recently, there has been a lot of research interest in the area of molecular manufacturing[37] to develop specific molecular systems with precisely positioned atoms and functional groups to achieve a desired behavior. The ultimate, rather far away, aim of this research is to synthesize a molecular analog of what we use in our everyday life, a machine.[38] The idea of a molecular machine is based on the same principles as of any vehicle, appliances or even biological systems, muscles, etc. Molecular machines can achieve varied functions such as catalysis, nanoscale manipulations, information storage, and many more.[39] In addition, an important factor, which adds a driving force to this research, is the nanoscale dimension of the molecular systems. In short, a lot can be achieved, if we were to make a nanoscale molecular machine to perform as many varied tasks as mentioned above.

The initial research in the designing of the molecular machine was challenging, mainly because there was nothing specifically known about any design. Equally important, as applicable to any machine, was to gain control over rather contineous molecular motions. Hence, the attention was shifted towards making smaller individual components first, with the ultimate assembling of each of these, to produce a complete molecular machine. This approach is commonly called as a bottom-up approach.

The integral component of the molecular machine is a "molecular brake". Kelley et al., were the early investigators of the molecular brake.[40] Their design of the molecular brake

involved a triptycene unit attached to a bipyridine unit. (Figure 1, adapted from reference 40).



Brake "OFF" Brake "ON"

Figure 1: Example of the molecular brake

With the help of dynamic NMR spectroscopy (DNMR), they were able to show that the external addition of a metal ion solution (Hg^{+} ion) was capable of restricting the free rotation of the triptycene unit (brake "ON" mode). Disengagement of the brake was achieved with the addition of an EDTA solution, which selectively complexed the added metal ion resulting in the removal of the metal ion, from the system and free rotation of the triptycene unit (brake "OFF" mode).

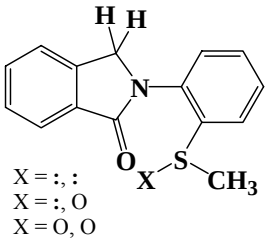


Figure 2: Isoindolines

Based on our knowledge of sulfur chemistry, we envisioned a molecular brake involving a sulfide-sulfoxide redox cycle. We designed a system Isoindoline-1-ones (Figure 2, detailed discussion about our design can be found in chapter 4), in which N-Aryl rotation was varied with the oxidation of the proximate sulfur atom. Dynamic spectroscopy studies on these compounds revealed that, sulfide [oxidation state of S(II)] shows free N-Aryl rotation while corresponding sulfoxide/sulfone resulted in hindered N-Ar rotation.

This approach is novel for many reasons, first, it will add on to the current research of molecular brakes by giving a viable alternative to the scientists in this field, where the earlier example of the molecular brake (external addition of metal ion as rotation obstructive tool) could not be used. Secondly, since sulfur oxidation or reduction can be achieved easily by both chemical and electrochemical means, this type of molecular brake can be used to engage or disengage the brake externally (redox chemical reaction) or internally (redox electrochemical reaction). Importantly, our molecular brake satisfies the basic requirements of a molecular brake. Steric hindrance of sulfoxide oxygen provides the required hindrance to the free rotational process (N-Ar rotation) a brake "ON" mode and the ease of sulfide-sulfoxide redox chemistry gives the essential reversibility to the whole process.

The synthesis and characterization of isoindolines will be explained later (Chapter 4, supporting information), but before we go further it is important to understand some basic concepts and applications of dynamic NMR (DNMR) spectroscopy as applied to the research in the field of molecular machines.

Principles and Applications of Dynamic NMR Spectroscopy[41]:

Dynamic NMR spectroscopy is a valuable tool for the chemists studying intramolecular motions. Intramolecular motions involve bond rotations, heteroatom inversions, ring inversions, etc. Although it is well known that the rotations about single bonds are rapid, there are examples of sterically or electronically hindered single bond rotations. Amides are probably the most widely studied example of functional groups by dynamic NMR

spectroscopy[42] and dimethylformamide (DMF, Figure 3) is the most common compound studied among other amides.

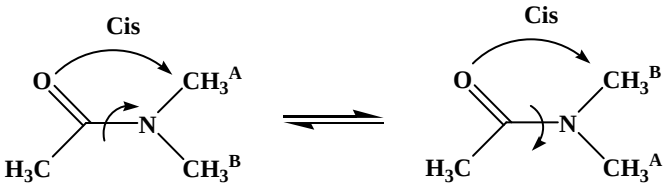


Figure 3: Dimethylformamide (DMF) with diastereotopic methyl grops.

The two methyl groups in DMF show separate signals in its ^{1}H NMR spectrum at room temperature. In this compound, due to amide resonance, the rotation about the amide bond is hindered. Methyl group cis to oxygen (Figure 3) is in a magnetically different environment than the methyl group trans to oxygen, which results in the two signals being separate. Chemically speaking, both methyl groups are identical. Such pairs of groups of atomic nuclei are called diastereotopic. If one of the groups is replaced by a different group then the compound forms a pair of diastereoisomers.

Another example of such class of compounds include the compound of the type **1** (Figure 4).

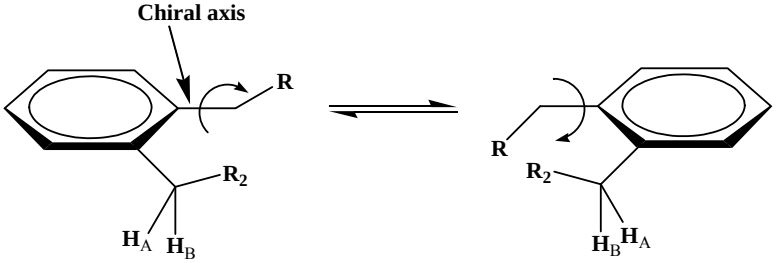
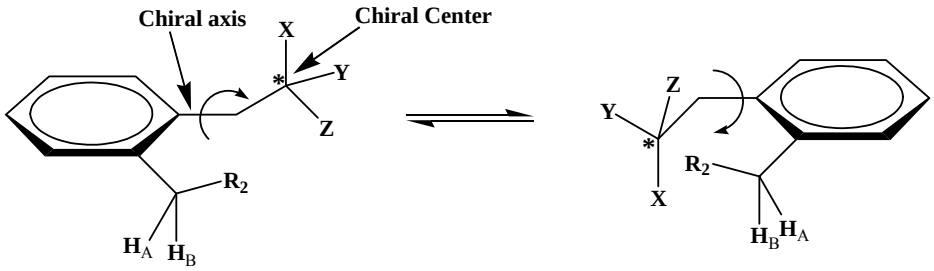


Figure 4: Schematic of enantiomeric rotational isomers.

The molecule of the type **1** and **2** are called enantiomeric rotational isomers, because of the presence of the chiral axis. If a molecule in such a case is unsymmetrically substituted and adopts non-planar conformation, then it is probable for the two groups (H_A and H_B in this case) to be magnetically nonequivalent (hence diastereotopic to each other) and give rise to two separate signals in the NMR spectra. The exact signal separation depends on the barrier to rotation about the chiral axis, a measure of ease by which these isomers interconvert. In addition, such magnetic nonequivalence is often temperature dependent (linear with temperature), in a specific range of temperatures, which is useful in quantification of the rotational barrier. This temperature dependence is non-linear for the molecules containing more than one stereogenic unit. For example, if the compounds similar to **1** contain additional stereocenter (eg. chiral center), in addition to the existing chiral axis, then such molecule shows conformational isomers when the rate of rotation is slow and configurational isomers when the rate of rotation is high (compound **3**, Figure 5). Analysis of such systems with the dynamic NMR technique could be quite problematic and the NMR spectrum often displays unusual variations with changes in temperature.



3 **Only conformational isomers shown**

Figure 5

The direct consequence of the hindered rotation is often encountered in ^{1}H NMR spectrum that shows some broad peaks in addition to normal sharp peaks. If the temperature is raised, the broad signal sharpens and if it is lowered, the original signal splits into one or more signals. Such behavior is an indication of an exchange in nuclei sites taking place at the temperature at which the spectrum is recorded. As temperature is raised, the rotation becomes faster due to an external supply of heat; similarly, a slow rotation is the result of cooling. A fast exchange limit is said to be reached when there is no further sharpening of the signal with a rise in temperature. Similarly, a stage at which the exchange of nuclei is negligibly small is called a slow exchange limit. It is in between these fast and slow exchange limits where dynamic NMR spectroscopy is valuable. The spectra recorded between these limits directly reflect the rate of exchange of nuclei. The most important temperature value for a dynamic NMR chemist is coalescence temperature. It is the temperature at which two signals coalsce (merge) to give one peak and it is denoted as Tc. Coalescence temperature gives information about the rate of exchange of nuclei (Eq 1). Equation 1 can only be used for the uncoupled nuclei. However, for the coupled systems (such as H_A and H_B) equation 2 should be used to obtain the value of the rate of exchange. Using this value of the rate of exchange, the free energy of activation $\Delta G^{\mp}$ of exchange can be evaluated (Eq 3) along with other thermodynamic entities such as $\Delta H^{\mp}$ and $\Delta S^{\mp}$.[5]

$$k_C = 2.22(\Delta \nu_{AB}) \tag{1}$$

$$k_C = 2.22\sqrt{(\nu_A - \nu_B)^2 - 6J_{AB}{}^2} \tag{2}$$

$$\Delta G^{\mp} = 4.575 \times 10^{-3} T_C \left[10.319 + \log\left(\frac{T_C}{k} \right) \right] \quad (3)$$

Free energy of activation $\Delta G^{\mp}$ is the most common way to express the intensity of hindered rotation. For example, the amide rotation in DMF has a free energy of activation of about 21.5 kcal/mol (89.9 kJ/mol),[43] a value as high as that is an indication of highly hindered rotation. This is an example of a high rotational barrier value due to a preexisting constrain in the molecule. Extrapolating the same concept, it is reasonable to say that if for a specific molecule, the rotational barrier of a given rotation increases due to structural modification in the molecule or external stimuli, then that is the result of enforced restriction of the rotation about that bond.

It is well known that dynamic NMR spectroscopy is an invaluable technique to study intramolecular motions with activation energies of 5-25 kcal/mol (21-104 kJ/mol), which corresponds to about 10^{-4} to 10^{10} sec^{-1} rate of exchange. Isomers interconverting at such rates are impossible to isolate as separate entities at room temperature.

It is extremely important to mention here that all the things said above, about fast and slow rotations are strictly based on what is being observed at the NMR time scale. For example, a slow rotation at the NMR time scale actually means that the rate of exchange is slower than the limit detectable by the dynamic NMR spectroscopy technique. Detection of slow or fast rotation often depends on the strength of the magnetic field under which the study is performed.

Line Shape Analysis[41]:

As mentioned earlier, the rate of exchanging nuclei can be calculated from the coalescence temperature (Tc), however it is always desirable to analyze data further to obtain the rate of exchange at various temperatures. Total line shape analysis is the method most commonly used to get the rate of exchange in the range of coalescence temperature. Line shape analysis is often performed with specifically designed computer software.[44] The computing program requires the values of chemical shifts, coupling constant and the experimentally recorded spectrum at any given temperature. It then simulates the signal shapes (line shape) and generates a "theoretical" spectrum at that temperature. This theoretical spectrum is a good visual match of the experimental spectrum, and more importantly, it provides the value of the rate of exchange at that temperature. Similar analysis near the range of coalescence temperature (usually 10 °C below and 2-3 °C above coalescence temperature) gives reliable data of the exchange rate. Plotting a graph (lnk vs 1/T) of such data gives a value of the free energy of activation ($\Delta G^{\mp}$), which eventually gives the estimate of other thermodynamic parameters such as $\Delta H^{\mp}$ and $\Delta S^{\mp}$.

Computational Methods:

A variety of computational methods such Molecular Mechanics (for example MM+), Semi-empirical (for example, PM3), *ab-initio* (for example, STO3-G), etc. have been employed in evaluating the rotational barrier about sterically hindered rotations. A major advantage of computational methods is that it gives an exact nature of steric strain caused due to the precise positioning of the atoms during the complete rotational process

(dihedral angles ranging from 0° to 360°). This information is rarely available from the experimental methods. Furthermore, computational study helps to compare the data obtained from experimental techniques.

A chemist often has to make a choice of the computational method to be used for computation, based on available computational software sophistication and the time involved in doing the calculations. Molecular mechanics (MM+) is a popular method because of its high-speed ability to do calculations, however, data obtained from this method may not compare well with the experimental techniques and hence can be intriguing. In the MM+ method, molecules are treated as mechanical parts with atoms as spheres and bonds as springs. Such treatment, sometime results in false, unrealistic energy minima (local minima). A semi-empirical method (eg. PM3) is based on the experimentally derived parameters and although it takes more time than MM+, it provides more accurate results than the MM+ method. A highly sophisticated method is an *ab-initio* method of computation, which works best for highly complex molecules. This method provides accurate, intense (sometimes unnecessary) data but suffers from serious limitations in terms of the enormous time taken to do the calculations. Based on this information, it is easy to infer that within any given time limit, the semi-empirical (PM3) method is the best suitable for moderately complex molecules.

Among others, amides are the most commonly studied functional group by computational methods. There are reports of electronic and steric effects of nitrogen substitution on hindered amide rotations.[45] There is a lot of interest in studying structure and geometries of strained amides.[46] Particularly, in understanding how the rotation about such strained amide bonds takes place and if there is any change in hybridization of

amidic nitrogen during the rotational process. While the study is still in progress, there are reports of otherwise sp^2 hybridized amidic nitrogen undergoing change in hybridization from sp^2 to sp^3 as the substituent on nitrogen rotates.[46]

As noted by Streitwieser, Jr., A.; Heathcock, C. H.:

> Ammonia itself and amines generally have a pyramidal structure (Section 23.1); the H—N—H bond angle in ammonia is 107.1°. The most effective conjugation of the nitrogen lone pair with the benzene ring would be obtained for a lone pair in a *p*-orbital parallel to the *p*-orbitals of the aromatic π-system. However, lone pairs are generally more stable in orbitals having some *s*-character. In the case of aniline, an energy compromise is reached in which the lone-pair orbital has more *p*-character than in ammonia but in which the orbital retains some *s*-character. As a result, the NH_2 group in aniline is still pyramidal but with a larger H—N—H angle (113.9°) than in ammonia. The H—N—H plane intersects the plane of the benzene ring at an angle of 39.4°.
>
> --Streitwieser, Jr., A.; Heathcock, C. H. in *Introduction to Organic Chemistry,* (3rd ed., Macmillan Publishing Company, New York, NY **1985**.)

This effect applies, not only to anilines but also to amides. To avoid the concept of rehybridization (sp^3 in alkyl amines and sp^2 in aryl amines, etc.) the concept of "nitrogen pyramidalization" was introduced. In this terminology, a pure sp^3 hybridized nitrogen is said to have 100% pyramidalization. Any "flattening" of the nitrogen geometry decreases pyramidalization. Thus, planar nitrogen is said to have 0% of pyramidalization. Nitrogen pyramidalization is a conformational change that the molecule undergoes to minimize the steric interactions during rotation of the substituent. Nitrogen pyramidalization often results in reducing the rotational barrier of rotations. Rankin and Boyd[47] developed a method to quantify nitrogen pyramidalization by measuring the virtual dihedral angle in

case of prolyl amides. The arrows drawn (Figure 6), show how the virtual dihedral angle is defined. This value of this angle is ±180° for sp^2 hybridized nitrogen and ±120° for the sp^3 nitrogen.

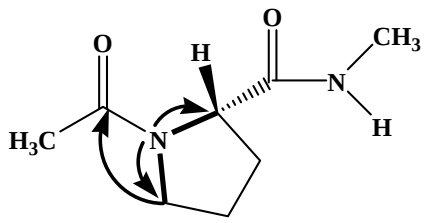


Figure 6: Definition of virtual dihedral angle as defined in prolyl amide.

The extent of nitrogen pyramidalization is a varying factor and it depends on the size of the substituent and its interaction with rest of the molecule during the rotational process. As the size of the substituent increases, its interaction with the rest of the molecule gets severe during its rotation. To reduce this sterically induced strain, nitrogen pyramidalization also increases and results in lowering the rotational barrier value of such process. However, if the steric strain is intentionally introduced in the molecule, then in that case, nitrogen pyramidalization partially nullifies the induced steric strain, giving less than the expected increase in the rotational barrier value.

It is reasonable to expect that nitrogen pyramidalization occurs only when there is a strong interaction between neighboring groups. Depending on the nature and size of the substituent, pyramidalization can occur only a few times during the complete rotational process (dihedral angles ranging from 0° to 360°). In other words, rotation and pyramidalization are concerted or correlated events. Correlated rotations are known to show less than expected rotational barrier values.[46c]

Lunazzi and co-workers[48] developed a graphical method to show the presence of correlated rotations in molecules with the aid of computational methods. A 2D energy contour plot is plotted after driving the two dihedral angles under study (from 0° to 360°) and obtaining the energy of the molecule at each fixed pair of dihedral angle. At each fixed pair of dihedral angle, the rest of the molecule is allowed to relax to its minimum energy conformation. A schematic of the 2D energy contour plot is shown in Figure 7. For example, let's assume that the contour plot obtained after driving dihedral angles A and B during such study looks like the one shown in Figure 7a. Then, since the line joining the energy minima is parallel to one axis (axis B in figure 7a) and perpendicular to another axis (axis A in Figure 7a), it can be deduced that the two rotations are noncorrelated to each other. In case of dihedral angles C and D however, (Figure 7b) such line is diagonal to one axis (axis D in figure 7b) and hence it can be said that the two rotations are correlated or geared.

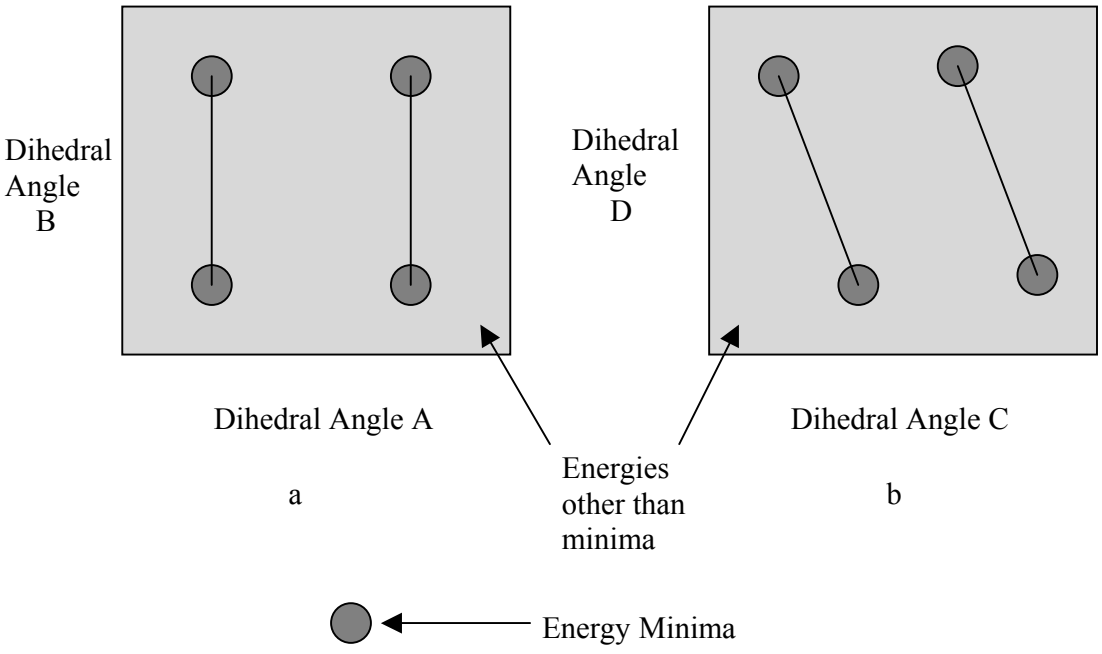


Figure 7: Schematic of 2D contour plot.

Lunazzi and co-workers used[48] this type of graphical notation to show the correlated or noncorrelated rotation between any given dihedral angles. We have designed a varient of this type of graph and plotted one dihedral angle involving complete rotation against another dihedral angle involved in nitrogen pyramidalization (virtual dihedral angle), while making sure (during the calculations) that both the dihedral angles cover the entire range of possible values. Detailed information of our results, along with the specific dihedral angles studied can be found in Chapter 4.

All of the above discussion is helpful in understanding our sulfide-sulfoxide redox mediated molecular brake design which is published in the following article:

Jog, P. V.; Brown, R. E.; Bates, D. K. *J. Org. Chem*. **2003**, *68*, 8240.

This research was also presented at the ACS National Meeting, New Orleans, LA.,

Jog, P. V.; Brown, R. E.; Bates, D. K. *Book of Abstracts,* 225th ACS National Meeting, New Orleans, LA March 23-27, 2003. ORGN-541.

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Chapter 2

Sulfoxides as a sulfenylating agent

Intramolecular Sulfoxide Electrophilic Sulfenylation (SES) of 2- and 3- Indole Carbanilides: Formation of Indolo[3,2-*b*]-1,5-benzothiazepinones

Bates, D. K.; Eggers, M. E.; Jog, P. V. *J. Org. Chem.* Submitted for publication.

The contribution of Parag Jog to this work included synthesis of all compounds containing *t*-butyl and 2-cyanoethyl groups as well as studies of thermal and TFAA activated reactions of the penultimate sulfoxide derivatives. He also did all of the work related to detection of sulfenic acid intermediates.

Approved by co-author Dallas K. Bates

Intramolecular Sulfoxide Electrophilic Sulfenylation (SES) of 2- and 3- Indole Carbanilides: Formation of Indolo[3,2-*b*]-1,5-benzothiazepinones

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Abstract

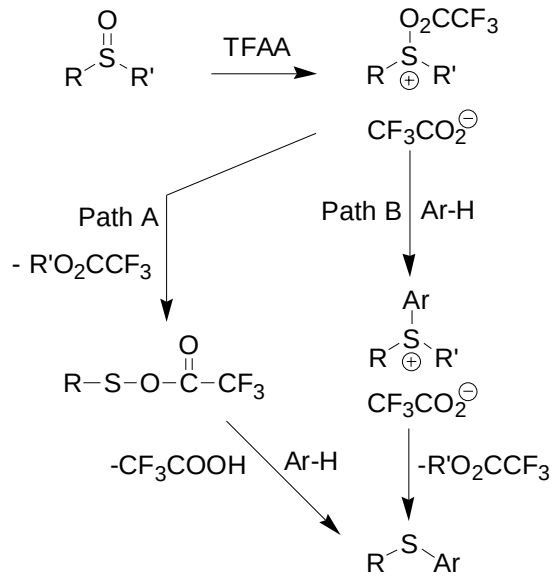
A series of *N*-[2-(alkylsulfinyl)phenyl]-1*H*-indole-2-carboxamides was prepared in which the indole and amidic nitrogens were either unsubstituted (**2ab**), partially substituted (indole N-H, amide N-Me, (**4ab**) and indole N-Me, amide N-H, (**6ab**), or fully substituted (indole N-Me, amide N-Me, (**8abc**). When these compounds were heated in an inert solvent (chloroform for *t*-butyl sulfoxides or *p*-xylene for ethyl sulfoxides) or treated with trifluoroacetic anhydride, all compounds (**4ab**, **8abc**) in which the amidic nitrogen was methylated cyclize to indolo[3,2-*b*]-1,5-benzothiazepinones (**9** or **10**, depending on indolic substitution). Successful cyclization was attributed to an ability of the N-Me amides to readily adopt a conformation conducive to cyclization, which other derivatives were unable to achieve. The same pattern of reactivity was observed with *N*-[2-(alkylsulfinyl)phenyl]-1*H*-indole-3-carboxamides (**15a**, **17ab**) under the same reaction conditions and the same product (**10**) was produced from (**17a**) upon heating in *p*-xylene. Rearrangement of a 3*H*-indolinium spirocyclic intermediate is proposed to account for this result. Accumulating evidence, including cyclization in the presence of a sulfenic acid trapping agent, suggests these reactions take place via an sulfonium salt intermediate (electrophilic sulfur of sulfoxide attacked by a nucleophile) rather than via a sulfenic acid intermediate.

Introduction

Sulfoxides are widely used as electrophilic sulfenylating agents for alkenes and aromatic (and heteroaromatic) systems. There are two general mechanistic pathways by which sulfoxides are activated to become sulfenylating agents and both occur with reagents and conditions typical for the Pummerer Reaction.[1] Many reported 'anomalous' reaction products from Pummerer Reactions are electrophilic sulfenylation reactions, with the 'anomalous' pathway favored by the presence of a proximate nucleophilic group[2] or a non-acidic hydrogen atom on the carbon α to the sulfoxide.[3]

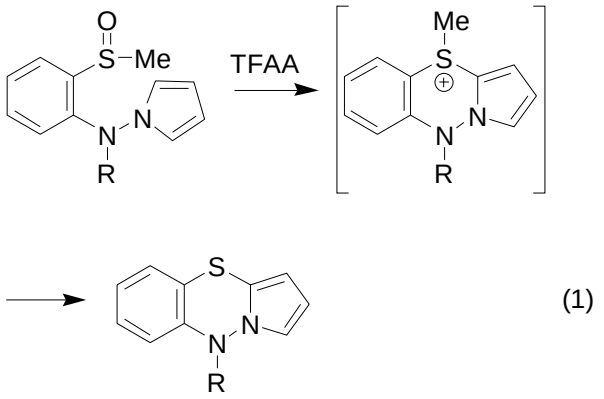
One pathway to sulfenylation involves sulfenic acid intermediates. Treatment of a sulfoxide with an anhydride or trace of acid/heat in an inert solvent may form a mixed anhydride of a sulfenic acid ($RSOCOCF_3$, RSOAc, etc.) or a sulfenic acid (RSOH, which presumably forms, *in situ*, $RSOH_2^+$ as the active sulfenylating agent),[4] which are reported to react with alkenes[5,6] or arenes[7] via electrophilic addition or electrophilic substitution, respectively. The other mechanistic pathway to sulfenylation with sulfoxides involves direct (nucleophilic) attack at (electrophilic) sulfur in an activated sulfoxide (R_2S-$O_2CCF_3^+$ or R_2S-OH^+) forming an intermediate sulfonium salt which is dealkylated, either *in situ* or as a separate step, to form the sulfenylation product. These two pathways are shown in Scheme 1. There are numerous examples of electrophilic sulfenylations of aromatics[8] and heteroaromatics[9] utilizing this approach.

Scheme 1. Alternative Pathways to Electrophilic Sulfenylation with Sulfoxides[/a]

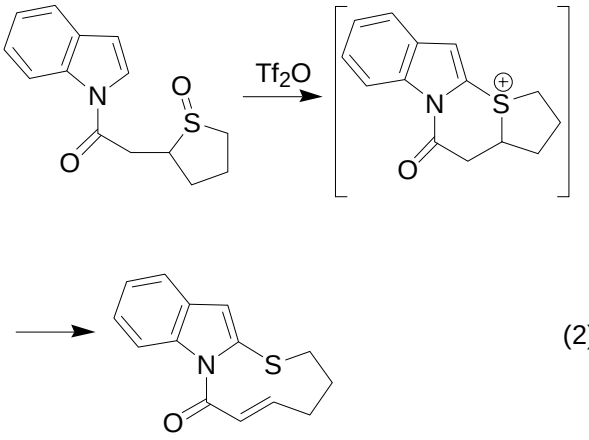


[/a] Illustrated with trifluoroacetic anhydride as the sulfoxide activator. Other reagents may be used (see text).

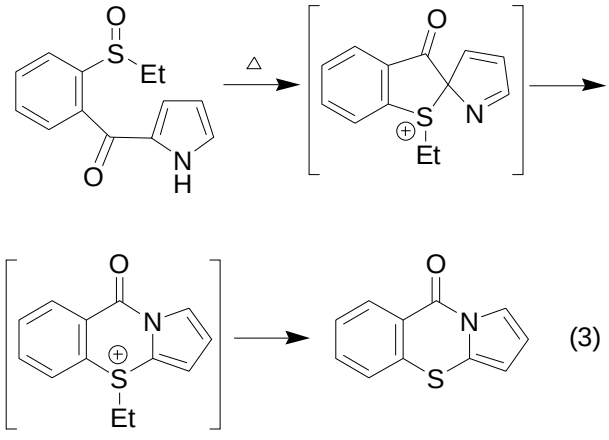
We have exploited this chemistry (sulfoxide electrophilic sulfenylation-SES) followed by variations in the mode of dealkylation to prepare new *N,S*-heterocyclic systems: SES/displacement[10] (eq 1) and SES/ring enlargement[11] (eq 2). We have also observed a third variant, SES/rearrangement[12] in a pyrrole system (eq 3). In this process, a minor product under all conditions tried was the rearranged product shown. Its formation was rationalized as resulting from rearrangement of an initially formed spirocyclic intermediate.



(1)



(2)



(3)

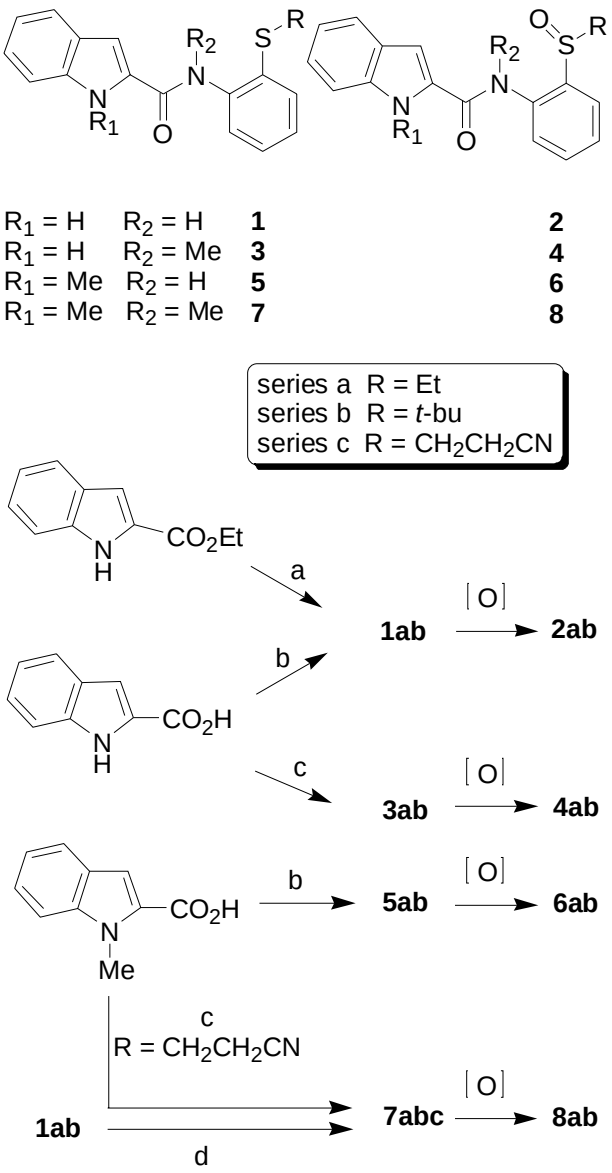
In this article we describe a study of SES/rearrangement cascade in a series of 2- and 3-substituted indole compounds. Indoles exhibit a strong preference for electrophilic attack at C-3 even when that position is already substituted. The 3-substituted target compounds

were selected to attempt to enhance rearrangement processes because 3,3-spirocyclic and other 3,3-disubstituted-3*H*-indolinium species resulting from indole/electrophile interactions are a common occurrence throughout indole chemistry.[13] In each series, sulfoxides containing ethyl, *t*-butyl, and propanenitrile alkyl group were prepared. The latter two types of sulfoxides, having non-acidic alkyl groups, should undergo SES reactions (not Pummerer chemistry) but would be expected to dealkylate under milder conditions than ethyl substituted compounds.[14] These compounds are of interest because *t*-butyl and propanenitrile sulfoxides also very easily thermally decompose to sulfenic acid derivatives[15] providing a potential opportunity to study their relevance as intermediates in these reactions.

Results and Discussion

Several related (ethyl, *t*-butyl, and 2-propanenitrile) sulfoxides tethered to C-2 or C-3 of indole were prepared with indole and amidic nitrogen atoms in differing degrees of methylation. Preparation and reactions of the C-2 and C-3 substituted compounds are discussed separately below.

Scheme 2[/a]



[/a] conditions: (a) 2-ethylthioaniline, $AlMe_3$, toluene, reflux (b) $SOCl_2$, Et_2O, 2-(alkylthio)aniline, rt (c) $SOCl_2$, Et_2O, *N*-methyl-2-(alkylthio)aniline, rt (d) 50% NaOH, CH_3I, *n*-Bu_4NHSO_4, toluene.

Indoles substituted at C-2

Indole-2-carboxylic acid chloride, formed *in situ* by reaction of indole-2-carboxylic acid with thionyl chloride at room temperature[16], and a 2-(alkylthio)aniline[17] produced sulfides **1ac** in modest yields. Problems have been reported in reaction of indole

carboxylic acids with thionyl chloride[18] and use of the unstable acid chloride (and consequent low yield of amide) could be avoided by trimethylaluminum-catalyzed condensation[19] of 2-(alkylthio)anilines and ethyl indole-2-carboxylate. For example, **1a** was obtained in 92% yield by this approach. Oxidations were accomplished using standard methodologies: a slow, but selective, multi-phase reaction using $NaIO_4$ in CH_2Cl_2/MeOH/H_2O [3a]; potassium peroxy monosulfate (Oxone) in THF/MeOH/H_2O[20]; or *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane.[21]

Monoalkylated compounds bearing the methyl substituent on the amide (**4ab**) were prepared similarly replacing the aniline component with an *N*-methyl-2-(alkylthio)aniline,[22] followed by sulfur oxidation.

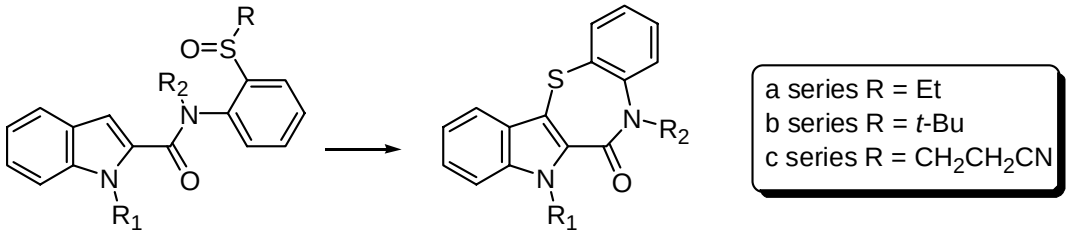
Monoalkylated compounds bearing the methyl substituent on the indole (**6ab**) were prepared similarly using alkylthioanilines and *N*-methylindole carboxylic acid, followed by oxidation.

N,*N'*-Dimethylated compounds (**8ab**) were prepared by dialkylation of amides (**1ab**) by catalytic phase transfer methylation, followed by oxidation. Sulfide (**1c**) decomposed under phase transfer conditions (retro-Michael) so compound **8c** was prepared in low yield by reaction of 1-methyl-1*H*-indole-2-carboxylic acid chloride with 2-propanenitrile-2-(methylaminophenyl)sulfide).

When the sulfoxides were subjected to cyclization conditions [either activation by electrophilic species (TFAA) or thermally (refluxing in chloroform or *p*-xylene)] clear patterns of reactivity emerge. For unknown reasons, thermal conditions always produced lower yield of product than with TFAA activation. As expected, in successful reactions, *t*-butyl sulfoxide derivatives cyclize thermally in refluxing chloroform whereas ethyl

sulfoxide derivatives require much higher temperatures (refluxing in *p*-xylene). In addition, as shown in Table 1, a substituent at the amidic nitrogen is essential for cyclization of all sulfoxides. Interestingly, in every case, the ^{1}H NMR spectrum of a sulfoxide that successfully cyclizes was very poorly resolved. This is indicative of conformational interconversion between two or more rotomers taking place on the millisecond time-scale at 25 ^{o}C. Recording ^{1}H NMR spectra at 100 ^{o}C showed fewer, sharper peaks as expected for an increased rate of interconversion in a dynamic process.[24] It seems logical that conformational flexibility could help the molecule readily obtain the geometry required for indole pi electron – sulfoxide sulfur atom interaction and it is well known that *N*, *N*-dialkyl amides have lower barriers to C(O)-N rotation as well as higher energy, non-planar ground states (hence the lower rotational barrier) than primary or secondary amides.[25]

Table 1. Correlation of Cyclization and Spectral Data for Sulfoxides



2ab R_1 = H R_2 = H
4ab R_1 = H R_2 = Me
6ab R_1 = Me R_2 = H
8abc R_1 = Me R_2 = Me

-
9 R_1 = H R_2 = Me
-
10 R_1 = Me R_2 = Me

Sulfoxide	Cyclization product % yield (TFAA, thermal)	^{1}H NMR (rt)	$\upsilon_{S=O}$ (cm^{-1})
2a	none	sharp	1009
2b	none	sharp	985
4a	**9** (75, 56)	broad	1041
4b	**9** (100, 58)	broad	1040
6a	none	sharp	1003
6b	none	sharp	999
8a	**10** (90, 22)	broad	1025
8b	**10** (100, 66)	broad	1039
8c	**10** (50, 41)	broad	1039

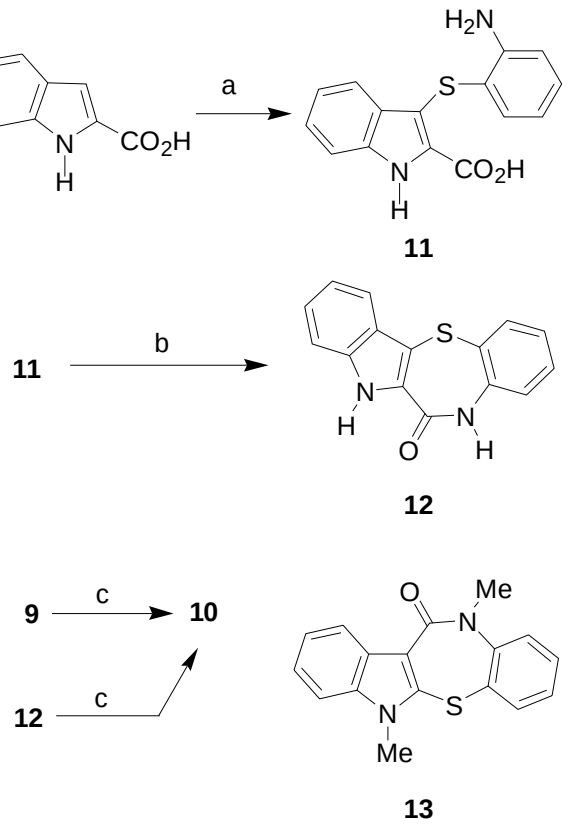
Sulfoxides which bear only a proton on the amidic nitrogen (**2ab**, **6ab**) produced either decomposition products or were recovered unchanged. This may be due to factors preventing the sulfoxide sulfur atom and the indole pi-system from assuming the correct conformation for cyclization. There is evidence of S=O---H-N intramolecular hydrogen-bonding in ^{1}H NMR and IR spectra of these compounds. Sulfoxide peaks in the IR

spectra of **2ab** and **6ab** appear at a lower frequency, which is to be expected if the oxygen of the sulfoxide is involved in hydrogen bonding[26] (Table 1). Additionally, ^{1}H NMR spectra of **2ab** and **6ab** showed sharp and well-resolved peaks in contrast to ^{1}H NMR spectra of compounds in which the amidic nitrogen was methylated. Compounds in which the amidic site is methylated (but still contain an indole N-H) (**4ab**) cyclize both thermally and with TFAA activation to produce the same product, assigned the structure 10,11-dihydro-10-methyl-12*H*-indolo[3,2-*b*]-1,5-benzothiazepin-11-one (**9**). The failure of compounds containing amidic N-H to cyclize is also attributable to the large energy difference in the *cis*- and *trans*- amide isomers, with the unfavorable (for cyclization) *trans*-isomer preferred. Not only are these compounds 'locked' into an arrangement wherein the sulfoxide oxygen is hydrogen bonded the amidic NH, but the energy barrier to interconversion of the *cis*- and *trans*- amide forms is formidable. On the other hand, the amidic N(Me) compounds not only exhibit lower rotational barriers to *cis*-/*trans*-amide isomer interconversion, but the literature[25b] suggests that these compounds probably exist predominately in the *cis*-form (which in this case places the sulfoxide and indole entities near one another).

Compounds **8abc** gave a compound assigned the structure 10,11-dihydro-10,12-dimethylindolo[3,2-*b*]-1,5-benzothiazepin-11-one (**10**). Thermal conditions consistently produced lower yield of product than with TFAA activation with all sulfoxides. For reasons that are unclear, 2-propanenitrile compounds were inferior to both ethyl and *t*-butyl sulfoxides and were not pursued further. As with product **9**, spectral data clearly shows cyclization was effected, however, additional proof of structure was sought due to the possibilities of scrambling of the acyl and sulfur locations either during the reaction

or subsequent equilibration[27,28] leading to compounds that would exhibit very similar spectral properties. Fortunately, the likely rearrangement product (**13**) is a known compound. The UV spectrum and melting point of our cyclization product differs considerably from that of **13** reported by Grandolini and co-workers[29] ruling out this alternative isomer. In addition, **10** was synthesized via an unambiguous route (Scheme 3). Using the technique described by Atkinson,[30] amino acid **11** was readily prepared. Refluxing **11** in toluene using SiO_2 as catalyst[31] gave **12** which on catalytic phase transfer methylation gave a product chromatographically and spectroscopically identical to the cyclization product (**10)**, clearly establishing the sites of attachment of the sulfur and carbonyl groups on the indole ring. Catalytic phase transfer methylation of **9** also produced **10** (76%) confirming the structure of that product as well.

Scheme 3[/a]



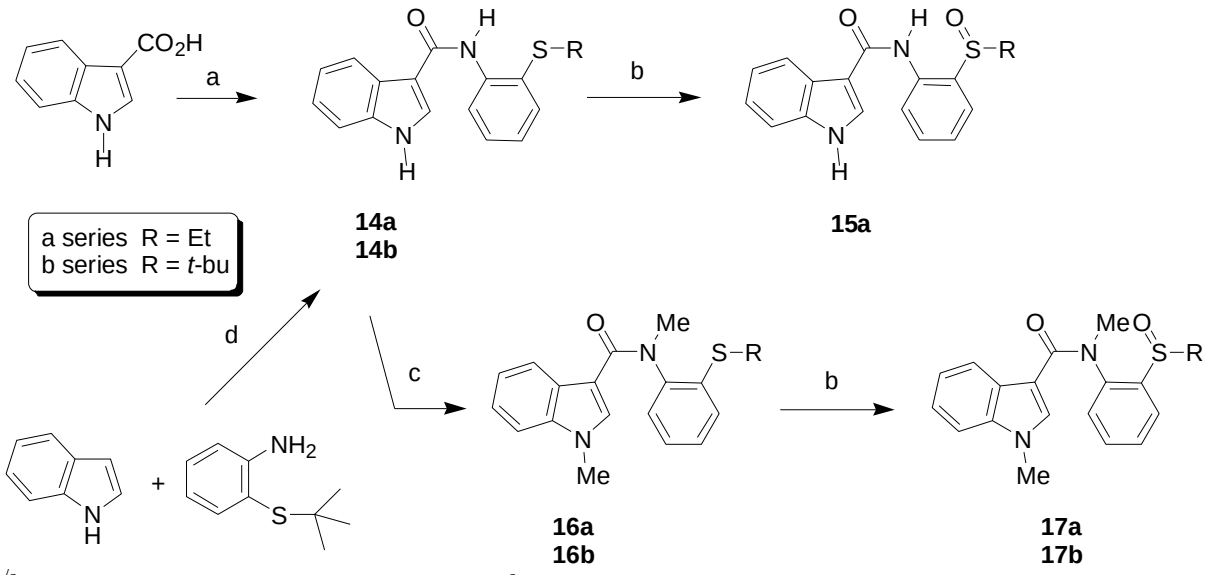
[/a] conditions: (a) 2,2'-diaminodiphenyldisulfide, NaH, DMF (b) SiO_2, toluene, reflux (c) *n*-Bu_4NHSO_4, 50% NaOH, CH_3I, toluene, reflux.

Indoles substituted at C-3

3-Substituted indole sulfoxides were of great interest due to the propensity of indoles to react with electrophiles at C-3. The synthesis of sulfoxides (**15a**, **17ab**) is outlined in Scheme 4. Indole-3-carboxylic acid[32] was converted to the acid chloride *in situ* with the use of oxalyl chloride and then reacted with 2-(ethylthio)aniline to produce sulfide **14a** which was oxidized to sulfoxides **15a**. Catalytic phase transfer methylation of **14a** to **16a** followed by oxidation gave sulfoxide **17a**. We encountered reproducibility problems with the reported preparation of 3-indole carboxylic acid so the *t*-butyl analogue was prepared by a different route. Indole and 2-(*t*-butylthio)aniline in the presence of triphosgene and

pyridine directly produced (**14b**) in 33% yield. Methylation and oxidation provided (**17b**).

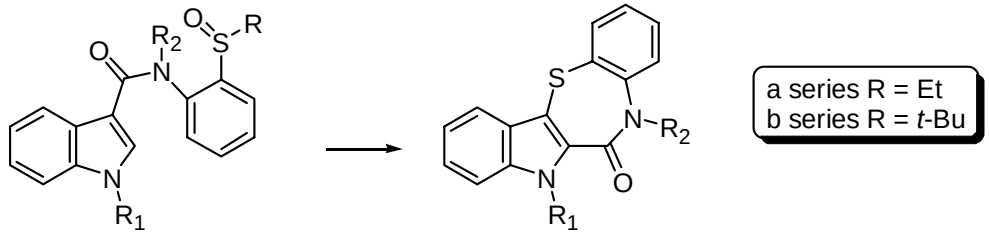
Scheme 4[/a]



[/a] Conditions: (a) 1. $(COCl)_2$, THF, 0 ^oC 2. $ArNH_2$, CH_2Cl_2 (b) Oxone or m-CPBA (c) 50% NaOH, CH_3I, *n*-Bu_4NHSO_4, toluene (d) 1. triphosgene, toluene/CH_2Cl_2/pyr 2. $ArNH_2$, CH_2Cl_2.

Cyclizations of sulfoxides **15a, 17ab** was attempted under both thermal and electrophilic activation. As shown in Table 2, results in this series were mixed. Like its 2-substituted indole counterpart the compound with an amidic N-H (**15a**) did not cyclize under any conditions used. Compound **17a**, which had a broad ^1H NMR spectrum, gave a cyclized product in good yield, but decomposed under TFAA activation. The *t*-butyl sulfoxide **17b**, although it had the same ^1H NMR and IR patterns as successfully cyclized sulfoxides, decomposed under both thermal and TFAA activation.

Table 2. Correlation of Cyclization and Spectral Data for Sulfoxides

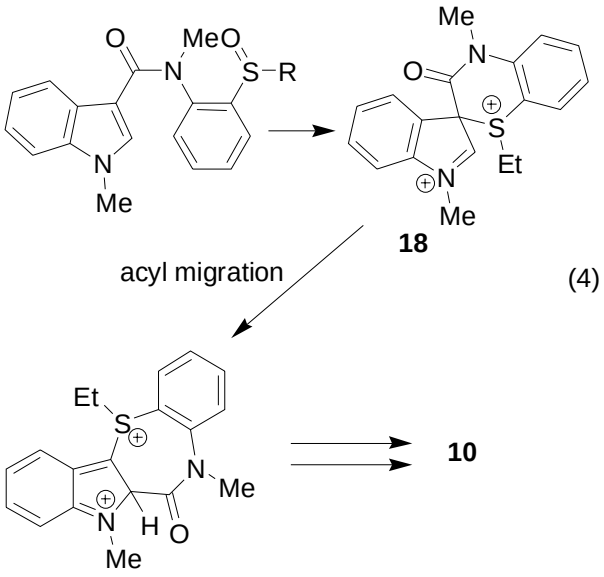


15a R_1 = H R_2 = H -
17ab R_1 = Me R_2 = Me **10** R_1 = Me R_2 = Me

Sulfoxide	Product% yield (TFAA, thermal)	^{1}H NMR (rt)	$\upsilon_{S=O}$ (cm^{-1})
15a	none	sharp	1003
17a	**10** (none, 67%)	broad	1014
17b	none	broad	1030

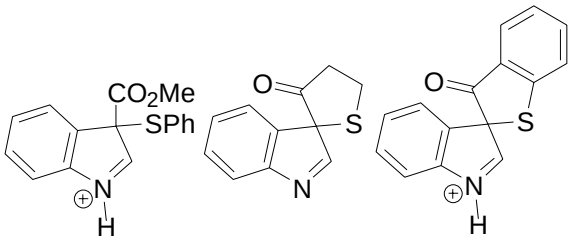
The product obtained from heating **17a** under reflux for 15 h in *p*-xylene (67% yield after chromatography) proved *to be identical to **10**, the cyclization product from the 2-substituted indole sulfoxide*. Mechanistically, there are several explanations for such a phenomenon. (a) migration of the acyl-amide group from C-3 to C-2 of indole prior to cyclization (**17a → 8a → 10**). However, heating the sulfide **7a** (which cannot cyclize via SES) for 12 h in *p*-xylene showed no evidence of acyl migration (95% recovery of unchanged starting material). There is literature precedence for acyl migration from C-3 to C-2 in indoles but typically much more strongly acidic conditions than used here are required.[33] (b) Initial formation of **13** by direct cyclization to C-2, followed by rearrangement to **10** upon prolonged heating in *p*-xylene, as we had observed previosly in another indolic system.[27] However, authentic **13** (synthesized as reported by Grandolini and co-workers[29]) showed no sign of rearrangement to **10** after 22 h in refluxing *p*-

xylene. Even after an additional 24 h at reflux in 0.1% TFA in *p*-xylene solution resulted in 92% recovery of unchanged starting material. (c) Initial formation of a 3*H*-spirocyclic intermediate (such as **18**) during SES at C-3, followed by *acyl migration* to C-2 and loss of a proton to give **10** (eq 4).



Formation of product **10** via a spirocyclic intermediate runs contrary to expectations based on the literature available. For example, formation of methyl 2-phenylthioindole-3-carboxylate from sulfenyl chloride and methyl indole-3-carboxylate is proposed to occur by way of preferential sulfur migration in the 3*H*-indolium species (**19**), although no evidence was provided to support this speculation.[34] Additionally, Nagarajan[35] proposed a spirocyclic intermediate (**20**) followed by preferential sulfur migration to C-2 to explain formation of 2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indol-4-one from 3-(3-indolylthio)propanoic acid. However, Hamel and co-workers[36a] have shown that 3-(3-indolylthio)propanoic acid isomerizes to the 2-isomer prior to cyclization. This work also established a generalization about reaction conditions for cyclizations involving 3-indolylthioalkanoic acids: when conducted in PPA C-3 to C-2 thioalkyl migration occurs

prior to cyclization, but with PPE in CH_2Cl_2, migration is minimal. An apparent anomaly to this behavior, for which no formal explanation could be provided, involves 2-(3-indolylthio)benzoic acid.[28]



19 **20** **21**

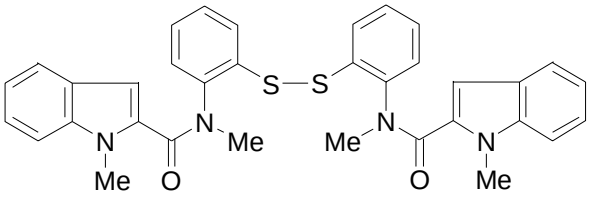
Formation of **10** via a spirocyclic intermediate requires migration of the acyl-amide group to occur in preference to an arylsulfonium group (or arylthio group).[37] It also seems plausible that a similar intermediate from **21** could explain the apparently anamolous behavior reported by Hamel.[28] Both 3-acylindoles[33] and simple 3-alkylthio- and 3-arylthioindoles[36] undergo acid-catalyzed conversion, respectively, to their 2-substituted counterpart in these thermodynamically-controlled processes. However, when both groups are present at indole C-2/C-3, the thermodynamically more stable product can not be determined by inspection and in both Hamel's work and this work, neither the product nor the alternative isomer is interconverted under the conditions the reaction. Thus, the product that forms predominately could be a kinetic product derived by migration in a spirocyclic intermediate of the group having the greater migratory appitude: a resonance-stabilized acylium species [phenylacylium species (in the case of Hamel's cyclization) or of an amidic acyl (isocyanato) group in the present work in prefernce to a sulfur species]. Although the scant data available suggests sulfur substituents have a greater migratory aptitude than ester, aldehyde and alkyl ketone

groups, no information is available concerning the potentially more stable migrating groups amide or phenyl ketone.[38]

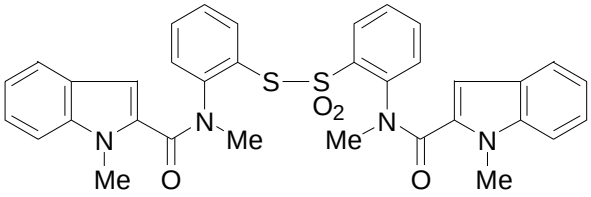
Eliminating the sulfenic acid pathway for SES chemistry

Formation of sulfenic acids from sulfoxides and their sulfenylation of a nucleophilic nitrogen atom (to prepare a series of benzoisothiazolones) has been reported[39] to occur under nearly the same conditions reported here (trichloroacetic anhydride/pyridine or refluxing toluene/pyridine). Glucosulfinylpropanenitriles[40] as well as *t*-butyl alkyl sulfoxides,[41] upon heating in an inert solvent, generate transient sulfenic acids which have been trapped using methyl propiolate or other alkynes.

To explore the possibility that **10** may also form via a transient sulfenic acid, we conducted thermal reactions of **8b** in the presence of a sulfenic acid trapping agent. When (**8b**) was refluxed in chloroform in the presence of 2-mercaptobenzothiazole as a trapping agent[42] (1 molar equiv) cyclization product **10** was obtained in 31% yield (compared to 66% yield in the absence of the trapping agent) and no disulfide product is observed. In some cases when *t*-butyl sulfoxides were refluxed in *p*-xylene, minor amounts of **22** and **23** were isolated in addition to cyclized product. These compounds are indicative of sulfenic acid formation,[43] but were never detected in reactions of ethyl sulfoxides. Yields of cyclized product from *t*-butyl sulfoxides were considerably lower when they were found in the crude reaction product. We believe sulfenic acids are **not** intermediates in these sulfenylation reactions and are instead formed as an undesired side reaction; it is important to conduct reactions under conditions below the threshold for sulfenic acid formation to obtain optimal yields of cyclized products.



22



23

Conclusions

Contrary to expectations, both 2- and 3- indolecarbanilides (**8abc** and **17a**) undergo cyclization to produce the same product - indolo[3,2-*b*]-1,5-benzothiazepin-11-one (**10**). For the 3-indolecarbanilides, the possibility of indole substituent migration before or after cyclization was eliminated and a 3*H*-indolium spirocyclic intermediate, with preferential migration of the carbonyl-containing moiety from C-3 to C-2, is proposed to rationalize the results. We also discovered that successful cyclization in this series requires the *absence* of an amidic N-H in the compounds. The lack of reactivity of compounds containing an amidic N-H is attributed to N-H---O=S hydrogen bonding and a lower energy *trans*-amide conformation, both of which enforce a molecular geometry that prevents the sulfoxide sulfur atom from achieving an orientation conducive to interaction with indole pi-electrons. By extrapolation, if compounds containing an amidic N-H are required, one should consider introducing an easily removable amidic alkyl substituent (*e.g.*, benzyl) into the SES substrate.

The reaction conditions used in this study have been reported to produce sulfenic acid intermediates and some authors have suggested a sulfenic acid pathway for some

sulfenylation reactions of sulfoxides. Trapping experiments using benzothiazole and previous observations[10b,11] suggest that both thermal and electrophile-activated sulfenylation reactions (including those with *t*-butyl sulfoxides) take place via a sulfonium salt pathway, not sulfenic acid intermediates.

Experimental Section

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were determined in $CDCl_3$ solutions unless otherwise indicated. IR spectra were recorded in KBr pellets for solid samples and neat on NaCl plates for liquid samples. Mass spectra were recorded at 70 eV (EI) unless indicated otherwise.

***N*-[2-(ethylthio)phenyl]-1*H*-indole-2-carboxamide (1a). Method A.** To a well-stirred solution of indole-2-carboxylic acid (10.0 g, 60 mmol) in Et_2O (194 mL) at 0 ^{o}C under a drying tube was added dropwise, $SOCl_2$ (9.6 mL, 140 moles, 2.2 eq.) neat over 5 min. The mixture was allowed to warm to room temperature. After stirring an additional 2 h, volatiles were removed in vacuo leaving a yellow solid which was redissolved in Et_2O (96 mL) and added to a well-stirred solution of 2-(ethylthio)aniline (2 eq. 18.4 g, 0.12 moles) in Et_2O (96 mL) over 8 min at 0 ^{o}C. The resulting yellow slurry was stirred for 50 min at 0 ^{o}C and at room temperature for 30 min at which time the mixture was diluted with EtOAc (100 mL). The combined organics were washed with 5% aq HCl (3 x 150 mL), 5% aq. $NaHCO_3$ (3 x 150 mL), H_2O (2 x 100 mL), dried (Na_2SO_4) and the solvent evaporated in vacuo to yield a wet orange solid. Column chromatography (1:1 $CHCl_3$:hexanes) gave a yellow solid, **1a** (5.7 g, 32%). Analytically pure material could be obtained by recrystallization from acetone: mp 153-155 ^{o}C; IR 3350, 3298, 1654 cm^{-1}; ^{1}H NMR (200 MHz) δ 10.09 (1H, d, J = 0.6 Hz), 9.51 (1H, s), 8.60 (1H, dd, J = 1, 6 Hz),

7.65 (1H, dd, J = 0.6, 8 Hz), 7.53 (1H, dd, J = 1, 6 Hz), 7.44 (1H, dd, J = 0.6, 8 Hz), 7.00-7.40 (5H, m), 2.76 (2H, q, J = 7 Hz), 1.18 (3H, t, J = 7 Hz,); ^{13}C NMR δ 160.2, 140.1, 137.6, 136.3, 131.5, 131.0, 128.1, 125.4, 124.6, 123.2, 122.6, 121.3, 120.4, 112.8, 103.4, 31.3, 15.3; MS [m/z (relative intensity] 296 (M^+, 54), 235 (75), 153 (100); Anal. Calcd for $C_{17}H_{16}N_2OS$: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.70; H, 5.55; N, 9.34.

Method B. To a N_2-flushed flask containing toluene (123 mL) was added trimethyl-aluminum (2.0 M in hexane, 21 mL, 42 mmol, 1.14 eq.) via a syringe dropwise. *CAUTION: pyrophoric.* This solution was cooled to 5 ^{o}C and 2-(ethylthio)aniline (5.7 g, 37 mmol) in toluene (18 mL) was added dropwise. After stirring 20 min at 5 ^{o}C, the solution allowed to warm to room temperature over a 45-min period. To the resulting solution was added dropwise ethyl indole-2-carboxylate (7.0 g, 37 mmol) in toluene (62 mL) and CH_2Cl_2 (18 mL). When the addition was complete the reaction mixture was heated to reflux. After refluxing 16 h, the cooled solution was hydrolyzed by slow addition of 2% aq. HCl (45 mL). The layers were separated and the aqueous layer extracted with EtOAc (3 x 50 mL). The combined organics were washed with saturated NaCl and then with H_2O, dried (Na_2SO_4) and the solvent evaporated in vacuo to yield a yellow solid (9.8 g, 92%) as a single spot on TLC which was identical to the compound prepared above (^{1}H NMR and mixed melting point).

***N*-[2-(ethylsulfinyl)phenyl]-1*H*-indole-2-carboxamide (2a).** To a well-stirred solution of **1a** (0.5 g, 1.5 mmol) in THF/MeOH (2.5 mL/ 1 mL) at 0 ^{o}C was added all at once a solution of Oxone in H_2O (2.5 mL). The resulting mixture was stirred at 0 ^{o}C for 5 min then at room temperature for 2.5 h then extracted with CH_2Cl_2 (2 x 10 mL). The combined organics were washed with H_2O, dried (Na_2SO_4) and the solvent removed in

vacuo to yield a light yellow solid which was recrystallized in MeOH to yield a very faint yellow solid, **2a** (0.3 g, 58%): mp 156-157 ^{o}C; IR 3289, 3168, 1662, 1009 cm^{-1}; ^{1}H NMR (200 MHz) δ 11.84 (1H, s, br), 10.29 (1H, s, br), 8.80 (1H, dd, J= 1, 8 Hz), 7.10-7.72 (8H, m, containing 1H at δ 7.45, dd, J = 1, 8 Hz), 3.07-3.19 (2H, dm), 1.26 (3H, t, J = 7 Hz); ^{13}C NMR δ 160.4, 141.6, 133.0, 131.2, 128.2, 127.7, 127.2, 127.1, 125.4, 125.1, 123.5, 122.9, 121.1, 112.4, 104.8, 48.9, 7.8; MS [m/z (relative intensity)] 312 (M^{+}, 63), 283 (20), 144 (100). Anal Calcd for $C_{17}H_{16}N_2O_2S$: C, 65.36, H, 5.16, N, 8.97. Found: C, 65.35, H, 5.33, N, 8.86.

***N*-[2-(*tert*-butylsulfinyl)phenyl]-*N*-methyl-1*H*-indole-2-carboxamide (4b).** To an ice-cooled solution of **3b** (5.0 g, 14.8 mmol) in CH_2Cl_2 (150 mL) was added slowly a solution of *m*-CPBA (77%, 1.1 eq, 21.1 mmol, 3.6 g) in CH_2Cl_2 (50 mL). The resulting mixture was stirred at 0 ºC for 15 min and then put it in a freezer (-8 ^{o}C) overnight. The reaction mixture was then poured into 5% $NaHCO_3$ solution (150 mL) and extracted with CH_2Cl_2 (200 mL). The combined organic layer was washed with distilled water, dried, and concentrated in vacuo. Column chromatography (EtOAc-hexane, 9:1) gave yellowish white solid which was recrystallized (hexane) to give a white solid (3.68 g, 70%): mp 114-116 ºC; IR 3453, 1624 cm^{-1}; ^{1}H NMR and ^{13}C NMR was not well-resolved due to presence of rotational isomers; MS [m/z (rel. intensity)] 144 (6), 56 (58), 41 (100).

***N*-[2-(ethylthio)phenyl]-*N*,1-dimethyl-1*H*-indole-2-carboxamide (7a).** To a well-stirred suspension of **1a** (5.2 g; 17 mmol) and tetra-*n*-butylammonium sulfate (0.6 g; 2 mmol; 0.1 eq.) in toluene (22 mL) was added 50% aq. NaOH solution (22 mL) in one portion. The resulting two-layer mixture was heated to reflux and a solution of CH_3I (5.4 g; 38 mmol; 2.2 eq) in toluene (5 mL) added dropwise over 5 min. This mixture was

refluxed for 24 h, cooled to room temperature and the layers separated. The organic layer was washed with H_2O several times (until washings were neutral to litmus), dried (Na_2SO_4) and the solvent evaporated in vacuo to yield a brown solid which was filtered through a silica gel column (1:1 $CHCl_3$:hexanes as eluent) to give **7a** (4.7 g, 82%) as a white solid. Recrystallization (acetone) gave pure **7a**: mp 127-128 ^oC; IR 1635 cm^{-1}; ^1H NMR (200 MHz) δ 6.95-7.38 (8H, m), 6.07 (1H, s), 3.97 (3H, s), 3.41 (3H, s), 2.80 (2H, apparent qd, J = 7.2, 4.9, 2.3 Hz,), 1.20 (2H, t, J = 7.3 Hz); ^{13}C NMR δ 164.6, 143.1, 138.4, 136.5, 132.3, 129.0, 128.8, 128.6, 127.9, 126.5, 123.7 122.2, 120.1, 110.1, 107.1, 37.2, 32.0, 26.4, 14.2; MS [m/z (relative intensity)] 324 (M+, 2), 158 (100); Anal. Calcd for $C_{19}H_{20}N_2OS$: C, 70.34; H, 6.21; N, 8.63. Found: C, 70.27; H, 6.34; N, 8.58.

10,11-Dihydro-10-methyl-12*H*-indolo[3,2-*b*][1,5]benzothiazepin-11-one (9) from 4a.

Method A (Thermal Cyclization). A solution of **4a** (1.7 g, 5 mmol) in *p*-xylenes (66 mL) was heated under reflux for 12 h. Upon cooling to room temperature, the solution was filtered to give a green solid, **9** (0.8 g, 56%): mp 290 ^oC (dec); IR 3228, 1618 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 12.13 (1H, s, br), 7.15-7.67 (8H, m), 3.51 (3H, s); MS [m/z (relative intensity)] 280 (M^+, 100). Anal Calcd. for $C_{16}H_{12}N_2OS$: C, 68.55, H, 4.31, N, 9.51. Found: C, 68.63, H, 4.65, N, 9.91.

Method B (excess of TFAA). The reaction was carried out as for **8** from TFAA (0.2 mL, 1.2 mmol, 3.75 eq) in CH_2Cl_2 (2 mL), pyridine (0.1 mL, 1.2 mmol, 4 eq.), **4a** (0.10 g, 0.3 mmol) in CH_2Cl_2 (1 mL). Stirring at 0 ^oC for 15 min, then at room temperature for 0.5 h, to yielded **9** as a yellow solid (0.3 g, 75%).

10,11-dihydro-10-methyl-12*H*-indolo[3,2-*b*]-1,5-benzothiazepin-11-one (9) from 4b.

Method A (Thermal Cyclization): A solution of **4b** (0.73 g, 2.1 mmol) in chloroform (75 mL) was heated under reflux for 64 hours. The solution was allowed to cool to room temperature and the solid formed was filtered and air dried to give white solid **9** (0.33 g, 58%): mp 295 ºC (dec); IR 1619 cm^{-1}; ^{1}H NMR δ 10.61 (broad, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 8.28 Hz, 1H), 7.17-7.19 (m, 2H), 7.11 (dt, J = 6.99, 1.07 Hz, 1H), 6.95-7.03 (m, 2H), 3.44 (s, 3H); ^{13}C NMR could not be taken due to insolubility of **9** in common solvents. MS [m/z (rel. intensity)] 280 [M^{+}, 100], 248(27).

Method B (Electrophilic Activation). To a well-stirred solution of TFAA (0.45 g, 2.1 mmol, 3.75 eq.) in CH_2Cl_2 (20 mL) at 0 °C was added pyridine (0.18 g, 2.3 mmol, 4 eq.), neat via syringe. The reaction vessel was kept under a drying tube throughout the reaction. To the resulting yellow solution was added, a solution of **4b** (0.20 g, 0.57 mmol) in CH_2Cl_2 (15 mL) which was previously cooled to 0 °C. This was stirred at 0 °C for 15 min then at room temperature for 30 min. The solution was poured onto 10% Na_2CO_3 (30 mL) and stirred for 5 min. The layers were separated and the aqueous layer washed with CH_2Cl_2 (30 mL). The combined organics were washed with 5% aqueous solution of HCl (3 X 40 mL), 10% aqueous solution of Na_2CO_3 (1 X 40 mL), H_2O and dried over sodium sulfate. The solvent was removed in vacuo to yield pure yellow solid, **9** (0.16 g, 100%).

10,11-Dihydro-10,12-dimethylindolo[3,2-*b*][1,5]benzothiazepin-11-one (10) from 8a.

Method A (Thermal Cyclization). A solution of **8a** (1.0 g, 3 mmol) in *p*-xylenes (35 mL) was heated under reflux for 30 h. After solvent evaporation in vacuo, the brown

solid was passed thru a silica gel column ($CHCl_3$) to give **10** (0.2 g, 22%): mp 198-200 ^oC; IR 1627 cm^{-1}; ^1H NMR (200 MHz) δ 7.77 (1H, d, J = 0.9 Hz), 7.73 (1H, d, J = 0.9 Hz), 7.08 - 7.58 (6H, m), 3.91 (3H, s), 3.62 (3H, s); ^{13}C NMR δ 163.5, 146.0, 138.2, 137.4, 132.3, 131.0, 128.9, 126.2, 125.8, 125.5, 125.0, 120.6, 120.3, 117.5, 110.1, 38.6, 31.6; MS [m/z (relative intensity)] 294 (M+, 100). Anal. Calcd for $C_{17}H_{14}N_2OS$: C, 69.36; H, 4.79; N 9.52. Found: C, 69.35; H, 4.89; N, 9.28.

Method B (excess of TFAA). To a well-stirred solution of TFAA (1.4 mL, 11 mmol, 3.75 eq) in CH_2Cl_2 (17 mL) at 0 ^oC was added pyridine (1 mL, 12 mmol, 4 eq.), neat via a syringe. To this solution was added, **8a** (1 g, 3 mmol) in CH_2Cl_2 (9 mL) which had been previously cooled to 0 ^oC. After stirring at 0 ^oC for 15 min then at room temperature for 3 h., the solution was poured onto a 10% aqueous Na_2CO_3 (30 mL) and stirred for 5 min. The layers were separated and the aqueous layer washed with CH_2Cl_2 (1 x 30 mL). The combined organics were washed with 5% HCl (3 x 40 mL), 10% Na_2CO_3 (1 x 40 mL), H_2O and dried (Na_2SO_4). The solvent was removed in vacuo to yield a relatively pure yellow solid **10** (0.8 g, 90%). mp 196-198 ^oC.

Trapping experiment. To a solution of **8b** (0.1 g, 0.27 mmol) in chloroform (50 mL) was added 2-mercaptobenzothiazole (1.0 eq., 0.27 mmol, 45.0 mg) and the resulting mixture was heated under reflux for 72 h (until no starting material on TLC). The solution was allowed to cool to room temperature and the solvent evaporated in vacuo to yield a brown solid. Column chromatography (CH_2Cl_2) gave white solid **10** (0.025 g, 32%).

3-[(2-aminophenyl)thio]-1*H*-indole-2-carboxylic acid (11). To a well-stirred suspension of NaH (1.1 g, 45 mmol, 3.0 eq) in DMF (30 mL) under N_2 at room

temperature was added dropwise a solution of indole-2-carboxylic acid (2.4 g, 15 mmol) in DMF (10 mL). After the evolution of H_2 had ceased, a solution of 2,2'-diaminodiphenyldisulfide (15 mmol) in DMF (5 mL) was added dropwise and the dark colored solution was heated at 50 ^oC for 24 h, then poured to H_2O (75 mL) and extracted with Et_2O (3 x 50 mL). The aqueous layer was acidified to pH ~5-6 precipitating a light brown solid (**11**, 4.1 g, 93%). The solid was used in the next step without purification.

10,11-Dihydro-10,12*H*-indolo[3,2-*b*][1,5]benzothiazepin-11-one (12). A suspension of **11** (5g, 17.6 mmol) and SiO_2 (column chromatographic grade, 20 g) in toluene (250 mL) was heated under reflux for 13 h under a Dean-Stark trap. The partially cooled reaction mixture was filtered through a sintered glass funnel (10-15 μ) and the SiO_2 washed with 1:1 CH_2Cl_2: MeOH (50 mL) and then with MeOH (2 x 30 mL). The combined organics were evaporated *in vacuo* and the light brown solid recrystallized to produce **12** (2.95 g, 63%) as an off-white solid: mp 237-239 ^oC (50% EtOH); IR 3414, 3197, 1654 cm $^{-1}$; ^1H NMR (200 MHz) δ 12.14 (1H, s, br), 10.46 (1H, s, br), 7.12-7.70 (8H, m); ^{13}C NMR δ 164.7, 142.3, 137.6, 133.0, 131.5, 130.6, 130,3, 127.0, 126.9, 126.8, 126.3, 125.2, 121.8, 120.8, 114.0; MS [m/z (relative intensity)] 266 (M+, 100). Anal. calcd for $C_{15}H_{10}N_2OS$: C, 67.65, H, 3.78, N, 10.52. Found: C, 67.48, H, 4.12, N, 10.42.

***N*-[2-(ethylthio)phenyl]-1*H*-indole-3-carboxamide (14a).** To a magnetically stirred solution of indole-3-carboxylic acid (1.5 g, 9 mmol) in THF (20 mL) at 0 ^oC was added dropwise neat oxalyl chloride (2.3 g, 18 mmol, 2 eq.). After 12 h at room temperature, the solvent was evaporated *in vacuo* and the yellow residue (in dichloroethane (40 mL)) was added to a mechanically stirred solution of 2-(ethylthio)aniline (2.8 g, 18 mmol, 2 eq) in dichloroethane (30 mL). After 5 h at room temperature, the mixture was washed with 5%

HCl (3 x 50 mL), 5% $NaHCO_3$ (3 x 50 mL), H_2O and dried (Na_2SO_4). The solvent was evaporated *in vacuo* to leave a dark brown oil. Column chromatography ($CHCl_3$) produced **14a** as a faint brown solid, (0.9 g, 35%): mp 103-105 ^oC; IR 3352, 3216, 1638 cm^{-1}; ^1H NMR (200 MHz) δ 9.31 (1H, s), 8.66 (1h, dd, J = 1.3, 7 Hz), 8.31-8.36 (1H, m), 7.88 (1h, d, J = 3 Hz), 7.58, (1H, dd, J = 1.4, 6.2 Hz), 7.25-7.48 (4H, m), 7.07 (1H, td, J = 1.4, 6.2 Hz), 2.78 (2H, q, J = 7 Hz), 1.20 (3H, t, J = 7 Hz); ^{13}C NMR δ 165.4, 141.5, 138.2, 136.8, 131.0, 130.8, 125.8, 125.1, 124.4, 124.3, 123.3, 121.8, 121.2, 113.9, 113.5, 31.7, 16.1; MS [m/z (relative intensity)] 296 (M^+, 12), 153 (100). Anal. Calcd. for $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44; N, 9.45. Found: C, 68.49; H, 5.62; N, 9.44.

***N*-[2-(*tert*-butylthio)phenyl]-1*H*-indole-3-carboxamide (14b).** Triphosgene (1.1 g, 3.66 mmol) was dissolved in toluene (5 mL). This was added to a well-stirred solution of indole (1.3 g, 11.0 mmol) and pyridine (0.88 g, 11.0 mmol) in CH_2Cl_2 (40 mL) dropwise over 30 min at 25 °C. The resulting dark red mixture was stirred for 3.5 h at 25 °C under drying tube. At this point, the solvent was evaporated in vacuo to half of its volume and an additional CH_2Cl_2 (10 mL) was added. To this, was added a solution of 2-(*tert*-butylthio)aniline (4.0 g, 22.1 mmol) in CH_2Cl_2 (25 mL) dropwise. The resulting dark green mixture was stirred at room temperature under a drying tube for 4 h. The reaction mixture was washed with 5% HCl (3 x 50 mL), 5% Na_2CO_3 (3 x 50 mL), H_2O (1 x 50 mL) and dried over sodium sulfate. The solvent was removed in vacuo to get a dark solid, which was purified by column chromatography (CH_2Cl_2) to give white solid (1.20 g, 33%): mp 185-187 °C; IR 3335, 1637 cm^{-1}; ^1H NMR δ 9.88 (broad, 1H), 9.64 (broad, 1H), 8.76 (d, J = 7.88 Hz, 1H), 8.46 (d, J = 7.88 Hz, 1H), 7.89 (d, J = 2.64 Hz, 1H), 7.58 (d, J = 7.74 Hz, 1H), 7.46 (t, J = 7.03 Hz, 2H), 7.32 (t, J = 7.03 Hz, 1H), 7.25 (t, J = 7.74

Hz, 1H), 7.08 (t, J = 7.74 Hz, 1H), 1.27 (s, 9H); ^{13}C NMR δ 163.6, 142.1, 138.7, 136.8, 130.8, 129.5, 124.3, 123.0, 121.8, 120.3, 120.2, 120.0, 112.6, 112.4, 48.5, 31.0, 30.8; MS [m/z (rel. intensity)] 324 [M^+, 13], 268 (6), 144 (100), 125 (24), 57 (5).

***N*-[2-(ethylsulfinyl)phenyl]-1*H*-indole-3-carboxamide (15a).** (96%): mp 60-61 ^{o}C; IR 3217, 3168, 1652, 1003 cm^{-1}; ^{1}H NMR (200 MHz) δ 11.15 (1H, s); 9.72 (1H, s), 8.71 (1H, d, J = 8 Hz), 8.40-8.45 (1H, m , cont. J = 3 Hz), 7.90 (1H, d, J = 3 Hz), 7.06-7.60 (6H, m, cont. J = 1, 8 Hz), 3.02-3.24 (2H, dm), 1.18 (3H, t, J = 7 Hz); ^{13}C NMR δ 164.9, 142.8, 137.8, 134.1, 128.8, 128.2, 127.3, 125.6, 124.4, 124.0, 123.8, 123.1, 122.7, 113.1, 113.0, 49.3, 8.8; MS [m/z (relative intensity)] 312 (M^+, 15), 144 (100). Anal. Calcd. for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97. Found: C, 65.48; H, 5.23; N, 8.99.

***N*-[2-(ethylthio)phenyl]-*N*,1-dimethyl-1*H*-indole-3-carboxamide (16a).** To a stirred suspension of **14a** (1.8 g, 6.1 mmol) and tetra-*n*-butylammonium sulfate in toluene (10 mL) was added 50% aqueous NaOH (7 mL) in one portion. After reflux for 2 h, a solution of CH_3I (1.9 g, 13.3 mmol, 2.2 eq.) in toluene (2 mL) was added and the mixture heated under reflux for an additional 17 h. The organics were collected, washed with H_2O until neutral to litmus, dried (Na_2SO_4), the volatiles removed *in vacuo*, and the brown solid chromatographed ($CHCl_3$) to produce **16a** (1.8 g, 90%) as an off-white solid: mp 172-173 ^{o}C (acetone); IR 1621 cm^{-1}; ^{1}H NMR (200 MHz) δ 8.41-8.46 (1H, m), 7.12-7.34 (7H, m), 6.06 (1H, d, J = 0.6 Hz), 3.49 (3H, s), 3.38 (3H, s), 2.90 (2H, apparent qd, J = 7.1, 0.2 Hz), 1.27 (3H, t, J = 7.0 Hz); ^{13}C NMR δ 166.7, 143.6, 138.4, 136.8, 132.6, 130.3, 124.4, 124.2, 127.5, 126.7, 123.5, 123.2, 122.0, 110.0 109.8 37.3, 33.8, 26.2, 14.5; MS [m/z (relative intensity)] 324 (M^+, 3), 158 (100). Anal. Calcd. for $C_{19}H_{20}N_2OS$: C, 70.34; H, 6.21; N, 8.63. Found: C, 70,28; H, 6.41; N, 8.69.

***N*-[2-(*tert*-butylthio)phenyl]-*N*,1-dimethyl-1*H*-indole-3-carboxamide (16b).** To a well-stirred suspension of **14b** (1.1 g, 3.4 mmol) and tetra-*n*-butylammonium hydrogen sulfate (0.3 eq, 1 mmol, 0.35 g) in toluene (100 mL) was added all at once 50% NaOH (aq) solution (100 mL). The resulting two layer mixture was heated under reflux at which a solution of iodomethane (2.5 eq, 8.5 mmol, 1.20 g) in toluene (10 mL) was added dropwise over 5 min. The resulting two phase mixture was maintained at reflux for 87 h. It was cooled to room temperature and the layers separated. The organic layer was washed with water several times (until washings were neutral to litmus), dried over sodium sulfate and evaporated in vacuo to yield an off-white solid. Purification by column chromatography (chloroform:ether, 9:1) gave white compound (0.87 g, 73%): mp 156-158 ºC; IR 1630 cm^{-1}; ^{1}H NMR δ 8.34-8.41 (m, 1H), 7.59 (d, J = 7.72 Hz, 1H), 7.31-7.39 (m, 2H), 7.28 (ddd, J = 7.71, 2.12 Hz, 1H), 7.17-7.22 (m, 2H), 7.10-7.16 (m, 1H), 5.81 (s, 1H), 3.43 (s, 6H), 1.29 (s, 9H); ^{13}C NMR δ 166.1, 147.6, 136.5, 136.0, 131.6, 129.0, 128.9, 128.2, 127.3, 122.6, 122.3, 121.0, 109.8, 108.9, 46.7, 32.8, 31.6; MS [m/z (rel. intensity)] 295 (12), 263 (21), 158 (100).

***N*-[2-(ethylsulfinyl)phenyl]-*N*,1-dimethyl-1*H*-indole-3-carboxamide (17a).** (72%). mp 188-189 ^{o}C (acetone); IR 1627, 1014 cm^{-1}; ^{1}H NMR (200 MHz, taken at 100 ^{o}C in DMSO-d_6) δ 8.25-8.31 (1H, m), 7.96-8.01 (1H, m), 7.19-7.60 (7H, m), 6.25 (1H, s), 3.54 (3H, s), 3.46 (3H, s), 2.56-2.80 (2H, m, cont. J = 6.6 Hz), 1.12 (3H, t, J = 6.6 Hz); ^{13}C NMR δ 167.0, 143.3, 143.1, 137.4, 133.5, 133.2, 133.0, 130.3, 121.9, 124.3, 123.7, 123.1, 123.0, 110.6, 110.5, 50.8, 49.5, 34.5, 7.3; MS [m/z (relative intensity)] 340 (M+, 0.2), 158 (100). Anal. Calcd for $C_{19}H_{20}N_2O_2S$: C, 67.03; H, 5.92; N, 8.23. Found: C, 67.25; H, 6.10;N, 8.27.

***N*-[2-(*tert*-butylsulfinyl)phenyl]-*N*,1-dimethyl-1*H*-indole-3-carboxamide (17b).** To an ice-cooled solution of **16b** (0.82 g, 2.30 mmol) in CH_2Cl_2 (50 mL) was added slowly a solution of *m*-CPBA (77%, 1.1 eq, 3.32 mmol, 0.57 g) in CH_2Cl_2 (10 mL). The resulting mixture was stirred at 0 ºC for 15 min and then put it in a freezer (-8 ^oC) overnight. The reaction mixture was then poured into 5% $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2 (50 mL). The combined organic layer was washed with distilled water, dried, and concentrated in vacuo. Column chromatography (acetone:CH_2Cl_2, 1:1) gave white solid (0.42 g, 49%): mp 159-160 ºC; IR 1631, 1030 cm^{-1}; ^1H NMR and ^{13}C NMR was not well-resolved due to presence of rotational isomers; MS [m/z (rel. intensity)] 294 (35), 158 (100).

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Supporting Information Available: Experimental procedures for 2-(ethylthio)-*N*-methylaniline, 2-(*tert*-butylthio)-*N*-methylaniline, ethyl *N*-methylindole-2-carboxylate,

1b, **2b**, **3ab**, **4a**, **5ab**, **6ab**, **7bc**, **8abc**, and the thermal and TFAA-promoted cyclization of **8b**; ^{1}H NMR and ^{13}C NMR spectra for **1b-3b, 5b-8b, 7c, 10, 14b,** and **16b**; ^{1}H NMR for **4b** and **9.** This material is available free of charge via the internet at http://pubs.acs.org.

Chapter 3

Sulfoxide as a "protecting group"

Simple Thiazocine-2-acetic acid Derivatives via Ring Closing Metathesis

Bates, D. K.; Li, X.; Jog, P. V. *J. Org. Chem.* **2004**, *69*, 2750.

The contribution of Parag Jog to this work mainly involved design and execution of the use of sulfoxides as protecting groups in RCM chemistry. To my knowledge use of the sulfide ←→ sulfoxide redox cycle has never been applied as a protecting group strategy. His work is very significant in this respect as the full potential of this approach to other areas where the S(II) oxidation state poses problems remains to be determined. He also conducted extensive NMR studies to assign all chemical shifts and coupling constants to the sulfide thiazocine derivative.

Approved by co-author Dallas K. Bates

JOC*Article*

Simple Thiazocine-2-acetic Acid Derivatives via Ring-Closing Metathesis

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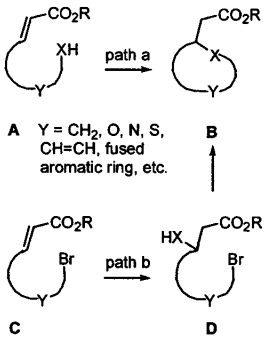
A new protocol for synthesis of 2-heterocylylacetic acid derivatives involving conjugate addition of allyl mercaptan to an acrylate containing a tethered olefinic site followed by RCM (ring-closing metathesis) is described. In this series, sulfanyl derivatives were unreactive, while sulfoxide and sulfone analogues provided the corresponding thiazocines in fair to excellent yields. Use of the sulfoxide oxidation state as a protecting group for sulfides inert to RCM is demonstrated also. Thus, oxidation of sulfide **9** [*N*-allyl-*N*-[2-(allylthio)-4-(1*H*-indol-1-yl)-4-oxobutyl]-4-methylbenzenesulfonamide] followed by cyclization yielded the corresponding thiazocine sulfoxide **12**. Deprotection (deoxygenation) of **12** was accomplished using Lawesson's reagent, producing 1-[[4-[4-(methylphenyl)sulfonyl]-3,4,5,8-tetrahydro-2*H*-1,4-thiazocin-2-yl]acetyl]-1*H*-indole (**21**) in 67% unoptimized yield.

Introduction

Heterocylylacetic acid derivatives are a diverse and important group of compounds. In addition to examples of NSAIDS (Myalex/fenclozic acid)[1] (including COX-2 specific inhibitors)[2] and nonbenzodiazepine hypnotics (Ambien/zolpidem),[3] compounds acting as blood platelet aggregation inhibitors,[4] aldose reductase inhibitors,[5] antimicrobial agents,[6] TACE inhibitors,[7] and medicinal chelating agents[8] and many others exhibiting useful biological activity have been reported. Many synthetic efforts have concentrated on five-, six-, seven-, and eight-membered ring examples of **B** (Y = $(CH_2)_n$, X = O) because of their prominence as building blocks for synthesis of fused polyether marine toxins (e.g., ciguatoxin)[9] and other natural products.[10] Compounds **B** (X = S) have also been prepared, but examples are scarce. Of the synthetic approaches developed, most target a specific member and are not general. Common general protocols (typically applicable only to five-, six-, and seven-membered ring compounds) involve conjugate addition to an α,β-unsaturated ester. Specifically, Michael addition of N-, O-, or S-centered nucleophiles to tethered acrylates[11] (**A**, eq 1, path a) or Michael addition of a protected nucleophile to an acrylate (for example, **C**) followed by deprotection and cyclization[12] (eq 1, path b)[13] have been used extensively.



(1)

Here we describe a new protocol for assembling compounds of type **B** making use of conjugate addition followed by ring-closing metathesis (RCM) (eq 2). This approach is illustrated by preparation of 2-thiazocinyl-

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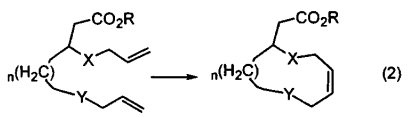
acetic acid derivatives and should be readily adaptable to other analogues as well. The specific target compounds were chosen because RCM has been shown to be an excellent methodology for N- and O-containing medium-sized ring synthesis[14] and eight-membered rings are the smallest simple *S*- and *N,S*-cycloalkanes for which conventional synthetic approaches fail.[15]

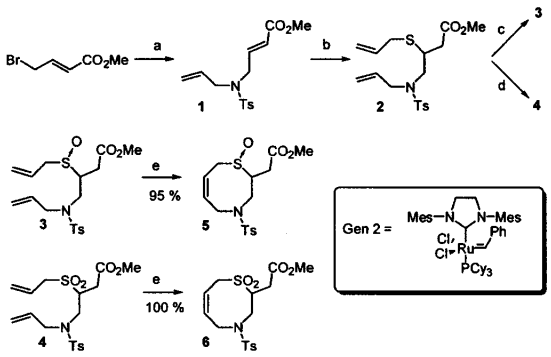


(2)

E X = S (no RCM), SO, SO_2 Y = N-Ts n = 1 **F**

Although olefin metathesis has experienced explosive growth, reports of applications of RCM to sulfur-containing compounds are comparatively rare. Initial work found the Grubbs first generation catalyst inferior to Mo- and W-based catalysts with respect to sulfur(II) tolerance.[16,17] Although Mo-based catalysts are quite tolerant of sulfur-(II) sites in the substrate, the highly active N-heterocyclic carbene catalysts such as Grubbs' second generation catalyst (Gen 2; see Scheme 1) are more widely used as a result of their improved tolerance for sulfur(II) and their air and moisture stability. Numerous examples of additional successful RCM reactions of sulfides, disulfides, and dithioacetals using Ru/carbene complexes have been reported.[18] The literature suggests the sulfonyl oxidation state (sulfones,[19] sulfonamides,[20] etc.[21]) is better tolerated in RCM substrates than lower oxidation states of sulfur. Deactivation via Ru-sulfonyl oxygen coordination does not occur (even though Ru-sulfonyl ligation to assist ring closure has been suggested).[22] In contrast to the body of work available for sulfides and sulfones,

SCHEME 1 [a]



[a] Reagents: (a) *N*-tosylallylamine, NaOH, TBAH, DCM, rt, 100%; (b) allyl mercaptan, NaOMe, MeOH, reflux, 68%; (c) $NaIO_4$, acetone/water, 22 h, rt, 35%; (d) Oxone (3 equiv), MeOH/water, 3 d, rt, 58%; (e) 5 mol % Gen 2, DCM, reflux (6 h for **5**, 8 h for **6**).

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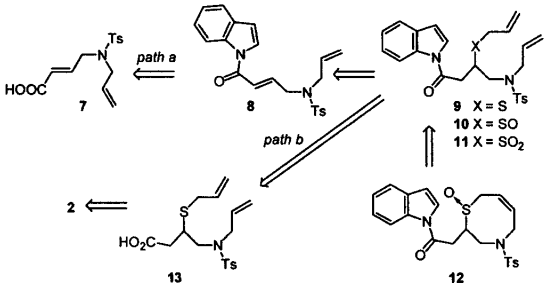
sulfoxides have been studied very little. DMSO treatment has been proposed[23] as a means of removing Ru-containing contaminants from RCM reaction mixtures, presumably due to coordination Ru. Only two reports of RCM chemistry applied to sulfoxides have been reported. One was successful[24] and the other was not.[19a] Therefore, sulfur-containing substrates for this study were prepared not only in the sulfanyl and sulfonyl oxidation states but also in the sulfinyl state as well.

Results and Discussion

Reaction of methyl 4-bromocrotonate with *N*-tosylallylamine[25] under phase transfer conditions followed by conjugate addition of allyl mercaptan provided the key intermediate **2** in 68% overall yield (Scheme 1). Oxidation of **2** to sulfoxide **3** (obtained as a 1:1 mixture of diastereomers) and sulfone **4** was readily accomplished by conventional means. Although **2** failed to undergo RCM[26] (Gen 2 catalyst),[27] both sulfone **4** *and sulfoxide* **3** cyclized [to thiazocines **6** and **5** (obtained as a 2:3 mixture of diastereomers), respectively] in excellent yield.

SCHEME 2. Alternative Pathways to Thiazocine 12



With this success in hand we applied the methodology to preparation of acyl indole **12** (Scheme 2), a system useful for SES/ring opening studies.[28] Preparation of this target demonstrates some of the potential obstacles in syntheses of RCM substrates of the type shown in eq 2. Thus, sulfide **9** was prepared in three steps from **1** in 19% overall yield, realizing path a in Scheme 2. The low yield is due to poor conversion of the acid chloride of **7** to the acylindole. The problem stems from the lability of the initially formed acylindole to nucleophilic attack; no acylation procedure attempted involving a strong nucleophile (OH^-) or nucleophilic solvent (H_2O) gave satisfactory yields of **8**. Alternative acylation conditions were not thoroughly explored because an alternative process forming the labile acylindole later in the sequence was developed. Reversing the order of the reactions leading to **9** (forward synthesis version of path b, Scheme 2) did not improve overall yield because ester hydrolysis of **2** to **13** proceeded in poor yield as a result of unavoidable (in our hands) retro-Michael addition of allyl mercaptan.

These difficulties were overcome using the well-known[29] stability of indoline amides relative to their indole amide counterpart and the ease of conversion of the former to the latter.[30] Execution of this strategy led to **9** in 44% yield (from **1**, path a in Scheme 3). Reversing the sequence of Michael addition and indoline oxidation (path b, Scheme 3) was not effective. Although Michael addition of allyl mercaptan to **14** proceeded very cleanly, subsequent reaction of **15** with DDQ gave not only oxidation of the indoline but also retro-Michael addition providing mainly compound **8**.

Oxidation[31] of indole **9** with 1 or 2 equiv of *m*-CPBA gave the corresponding sulfoxide (**10**, 72%, 2:3 inseparable mixture of diastereomers) or sulfone (**11**, 99%). Treatment of these compounds with Gen 2 (10 mol % for the sulfoxide and 5 mol % for the sulfone) produced the corresponding thiazocinyl acetamide derivatives **12** and **16** in 48% and 89%, respectively (Scheme 4). Compound **12** was isolated as a 2:3 mixture of diastereomers.

(20) (a) Wanner, J.; Harned, A. M.; Probst, D. A.; Poon, K. W. C.; Klein, T. A.; Snelgrove, K. A.; Hanson, P. R. *Tetrahedron Lett.* **2002**, *43*, 917–921. (b) Yao, Q. *Angew. Chem., Int. Ed.* **2000**, *39*, 3896–3898. (c) Long, D. D.; Termin, A. P. *Tetrahedron Lett.* **2000**, *41*, 6743–6747. (d) Lane, C.; Snieckus, V. *Synlett* **2000**, 1294–1296. (e) Hanson, P. R.; Probst, D. A.; Robinson, R. E.; Yau, M. *Tetrahedron Lett.* **1999**, *40*, 4761–4764. (f) Paquette, L. A.; Leit, S. M. *J. Am. Chem. Soc.* **1999**, *121*, 8126–8927. (g) Fuerstner, A. *Chem. Commun.* **1998**, 1315–1316. (h) Cerezo, S.; Cortes, J.; Moreno-Manus, M.; Pleixats, R.; Roglans, A. *Tetrahedron* **1998**, *54*, 14869–14884. (i) Visser, M. S.; Heron, N. M.; Didiuk, M. T.; Sagal, J. F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 4291–4298.

(21) Sulfonates: Karsch, S.; Schwab, P.; Metz, P. *Synlett* **2002**, 2019–2022.

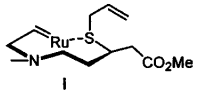
(22) Paquette, L. A.; Fabris, F.; Tae, J.; Gallucci, J. C.; Hofferberth, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 3391–3398. Also see: Marco-Contelles, J.; de Opazo, E. *J. Org. Chem.* **2000**, *65*, 5416–5419 and references therein.

(23) Ahn, Y. M.; Yang, K.; Georg, G. I. *Org. Lett.* **2001**, *3*, 1411–1413.

(24) Cachoux, F.; Ibrahim-Ouali, M.; Santelli, M. *Synlett* **2002**, 1987–1990.

(25) *N*-Tosyl compounds appear to be superior to alkyl-, benzoyl-, or ethoxycarbonyl-protected amines in RCM processes: (a) Kinderman, S. S.; van Maarseveen, J. H. Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Org. Lett.* **2001**, *3*, 2045–2048. (b) van Otterlo, W. A. L.; Pathak, R.; de Konig, C. B. *Synlett* **2003**, 1859–1861.

(26) Starting material (**2**) was recovered unchanged quantitatively. The lack of reactivity is probably not due to Ru coordination with the ester [no reaction was observed when $Ti(OiPr)_4$ was added to the RCM reaction according to Fuerstner's protocol (Fuerstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130–9136) and both S-oxidized counterparts to the sulfide (**3** and **4**) readily undergo RCM]. The problem is more likely due to inactivation of the catalyst by coordination of the Ru to S(II). Coordination/inactivation could occur intermolecularly prior to interaction of the Ru with the olefinic sites or intramolecularly, perhaps as shown in structure **i**.



i

The latter process (involving coordination of ruthenium to hydroxyl oxygen via a six-membered ring rather than the eight-membered ring as in **i**) has been suggested previously (for example, Washburn, D. G.; Heidebrecht, R. W.; Martin, S. F. *Org. Lett.* **2003**, 5, 3523–3525) to explain Grubbs' catalyst inactivation. This process seems less likely in the present context because of the size of the ring involved and the necessity to invoke selective reaction of the *N*-allylic olefinic site, even though the *S*-allylic olefinic site is sterically and electronically similar.

(27) (a) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783–3784. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.

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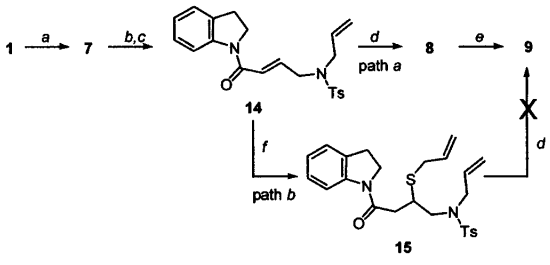
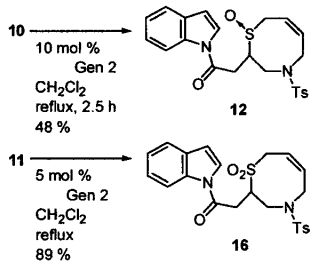
(31) (a) Portoghese, P. S.; Telang, V. G. *Tetrahedron* **1971**, *27*, 1823–1829. (b) Johnson, C. R.; Diefenbach, H.; Keiser, J. E.; Sharp, J. C. *Tetrahedron* **1969**, *25*, 5649–5653.

SCHEME 3. Acylindole 9 via Oxidation of Indoline Amide 8[a]

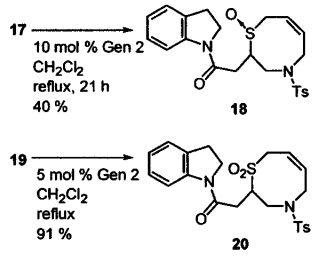


[a] Reagents: (a) LiOH, THF/H_2O, 0 °C, 95%; (b) oxalyl chloride, THF, 24 h, 0 °C; (c) indoline, pyridine, DMAP, 64%; (d) DDQ, dioxane, 70 °C, 3 d, 89%; (e) allyl mercaptan, Et_3N, CH_2Cl_2, 80%; (f) allyl mercaptan, NaOMe, MeOH/THF, 15 min, 0 °C, 95%.

SCHEME 4. RCM of Acylindoles 10 and 11

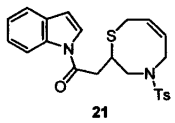


SCHEME 5. RCM of Indoline Amides 17 and 19



This pattern of reactivity was duplicated in the corresponding indoline analogues. Thus, treatment of **15** with either 1 or 2 equiv of *m*-CPBA gave the corresponding sulfoxide **17** (as an inseparable 2:3 ratio of diastereomers) or sulfone (**19**). Treatment of these compounds with Gen 2 (10 mol % for the sulfoxide and 5 mol % for the sulfone) produced the corresponding thiazocines **18** and **20** in 40% and 91%, respectively (Scheme 5). Compound **18** was isolated as a 3:4 mixture of diastereomers.

In view of the mixed history of success with S(II) substrates in RCM processes, our current results on successful RCM on sulfoxides where the corresponding sulfides fail, the abundance of simple oxidation procedures for the sulfide to sulfoxide transformation,[32] and the ease of the reverse deoxygenation process[32] suggest sulfoxides may be useful protecting groups for thioethers undergoing RCM.[33] As a demonstration of the concept, the most labile sulfoxide in the series (compound **12**) was treated with Lawesson's reagent[34] to produce sulfide **21** in 67% yield.



In conclusion, sulfone and sulfoxide derivatives of compound **E** (Y = *N*-Ts, eq 2) undergo RCM in good to excellent yield with Grubbs second generation catalyst, providing a new route to (1,4-thiazocinyl)-2-acetic acid derivatives. Sulfide derivatives in the series do not undergo RCM with Grubbs' second generation catalyst, but such compounds are available through a protection/deprotection sequence involving the corresponding sulfoxide. Application of the methodology to other 2-heterocyclyl acetic acid derivatives is underway.

Experimental Section

Methyl (2*E*)-4-[Allyl[(4-methylphenyl)sulfonyl]amino]-but-2-enoate (1). To a well-stirred mixture of *N*-allyl-4-methylbenzensulfonamide (0.42 g, 2 mmol), powdered NaOH (2.0 equiv, 0.16 g, 4 mmol), and tetrabutylammonium hydrogen sulfate (0.06 equiv, 0.04 g) in CH_2Cl_2 (15 mL) was added dropwise a solution of methyl γ-bromocrotonate (1.5 eq, 0.537 g, 3 mmol) in CH_2Cl_2 (5 mL) in an ice–water bath. The resulting mixture was stirred at 0 °C for 5 min and at room temperature for 2 h. After filtering, the filtrate was washed with distilled water, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Column chromatography on silica gel (EtOAc/hexane, 1:4) gave 0.62 g (100%) of **1** as a white solid: mp 58–60 °C; IR 1724 cm^{-1}; ^1H NMR δ 7.65 (d, 2H, J = 8.0 Hz), 7.27 (d, 2H, J = 8.0 Hz), 6.68 (dt, 1H, J = 15.6, 6.0 Hz), 5.87 (d, 1H, J = 15.6 Hz), 5.55 (m, 1H), 5.13–5.07 (m, 2H), 3.87 (d, 2H, J = 6.0 Hz), 3.75 (d, 2H, J = 6.4 Hz), 3.68 (s, 3H), 2.38 (s, 3H); ^{13}C NMR δ 166.0, 143.6, 142.6, 136.7, 132.1, 129.8, 127.1, 123.4, 119.7, 51.6, 50.4, 47.2, 21.4; MS [*m*/*z*] 278 (M^+). Anal. Calcd for $C_{15}H_{19}O_4NS$: C, 58.23; H, 6.19; N, 4.53. Found: C, 58.36; H, 6.32; N, 4.53.

Methyl 4-[Allyl[(4-methylphenyl)sulfonyl]amino]-3-(allylthio)butanoate (2). To a well-stirred solution of allyl mercaptan (5.0 equiv, 0.20 mL, 2.5 mmol) and MeONa (1.1 equiv, 0.03 g, 0.6 mmol) in methanol (7 mL) was added a solution of **1** (0.16 g, 0.5 mmol) in MeOH (4 mL) at room temperature. The resulting mixture was refluxed for 3 h, cooled, poured into ice water, and extracted with EtOAc. The combined organic layers were washed with distilled water, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Column chromatography on silica gel (EtOAc/hexane, 1:4) gave 0.13 g (68%) of **2** as an oily liquid: IR 1739 cm^{-1}; ^1H NMR δ 7.65 (d, 2H, J = 8.0 Hz), 7.27 (d, 2H, J = 8.0 Hz), 5.74 (m, 1H), 5.48 (m, 1H), 5.16–5.03 (m, 4H), 3.80–3.76 (m, 2H), 3.67 (s, 3H), 3.37 (dd, 1H, J = 14.0, 10.0 Hz), 3.22 (m, 1H), 3.14 (d, 2H, J = 6.8 Hz), 3.09 (dd, 1H, J = 14.0, 4.8 Hz), 2.87 (dd, 1H, J = 16.4, 4.8 Hz), 2.49 (dd, 1H, J = 16.4, 8.4 Hz), 2.39 (s, 3H); ^{13}C NMR δ 171.9, 143.5, 136.4, 134.4, 132.4, 129.7, 127.2, 119.7, 117.4, 51.7, 51.6, 51.5, 39.1, 37.4, 34.8, 21.4; MS [*m*/*z* (rel intensity)] 228 (78), 224 (79), 155 (100).

Methyl 4-[Allyl[(4-methylphenyl)sulfonyl]amino]-3-(allylsulfinyl)butanoate (3). To an ice-cooled solution of **2**

(32) For leading references see Jog, P. V.; Brown, R. E.; Bates, D. K. *J. Org. Chem.* **2003**, *68*, 8240–8243.

(33) Gladysz and co-workers have reported use of a cationic rhenium compound that serves both as a protecting group for S(II) and RCM catalyst for thioethers: Martin-Alvarez, J. M.; Hampel, F.; Arif, A. M.; Gladysz, J. A. *Organometallics* **1999**, *18*, 955–957.

(34) (a) Bartsch, H.; Erker, T. *Tetrahedron Lett.* **1992**, *33*, 199–200. (b) Tewari, N.; Kumar, Y.; Thaper, R. K.; Khanna, J. M. *Synth. Commun.* **1996**, *26*, 1169–1173.

(0.81 g, 2.12 mmol) in acetone (12 mL) was added a solution of sodium periodate (1.05 equiv, 0.48 g, 2.23 mmol) in H_2O (6 mL) at 0 °C. The resulting mixture was stirred at room temperature for 22 h and concentrated in vacuo. The residue was diluted with H_2O (40 mL) and extracted with $CHCl_3$. The combined organic layers were washed with distilled water, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Column chromatography on silica gel (EtOAc) gave 0.30 g (35%) of **3** as a colorless sticky liquid (mixture of two diastereomers in a 1:1 ratio): IR 1725 cm^{-1}; ^1H NMR δ 7.66 (d, 2H, J = 7.6 Hz), 7.29 (d, 2H, J = 7.6 Hz), 5.85 (m, 1H), 5.55−5.39 (m, 3H), 5.19−5.11 (m, 2H), 3.82−3.75 (m, 2H), 3.70 (s, 3H), 3.69 (s, 3H), 3.60 (dd, 1H, J = 12.0, 6.8 Hz), 3.51 (m, 1H), 3.41 (dd, 2H, J = 13.6, 7.6 Hz), 3.27 (dd, 1H, J = 14.8, 7.6 Hz), 2.96 (dd, 1H, J = 18.0, 5.2 Hz), 2.89 (dd, 1H, J = 18.0, 5.6 Hz), 2.79 (dd, 1H, J = 18.0, 8.0 Hz), 2.52 (dd, 1H, J = 18.0, 6.4 Hz), 2.40 (s, 3H); ^{13}C NMR δ 171.9, 171.4, 143.9, 135.6, 135.5, 132.1, 132.0, 129.9, 129.8, 127.4, 127.3, 125.9, 125.8, 123.9, 123.8, 120.5, 120.4, 54.6, 53.9, 53.4, 52.4, 52.3, 52.2, 52.1, 52.0, 47.4, 44.6, 32.0, 28.3, 21.5; MS [*m/z* (rel intensity)] 224 (47), 155 (66).

Methyl 4-[Allyl[(4-methylphenyl)sulfonyl]amino]-3-(allylsulfonyl)butanoate (4). To an ice-cooled solution of **2** (0.73 g, 1.91 mmol) in MeOH (15 mL) was added a solution of Oxone (3.0 equiv, 3.52 g, 5.73 mmol) in H_2O (15 mL) at 0 °C. The resulting cloudy slurry was stirred at room temperature for 3 d. After filtering, the filtrate was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Column chromatography on silica gel (EtOAc/hexane, 2:3) gave 0.46 g (58%) of **4** as a colorless sticky liquid: IR 1739 cm^{-1}; ^1H NMR δ 7.67 (d, 2H, J = 8.0 Hz), 7.31 (d, 2H, J = 8.0 Hz), 5.89 (m, 1H), 5.54−5.40 (m, 3H), 5.19−5.12 (m, 2H), 4.07 (m, 1H), 3.85−3.76 (m, 4H), 3.73 (s, 3H), 3.45−3.42 (m, 2H), 2.99 (dd, 1H, J = 18.0, 6.4 Hz), 2.84 (dd, 1H, J = 18.0, 5.6 Hz), 2.42 (s, 3H); ^{13}C NMR δ 171.0, 144.2, 135.3, 131.7, 131.0, 127.5, 125.5, 123.9, 120.8, 58.3, 56.1, 52.5, 52.4, 46.1, 30.9, 21.5; MS [*m/z* (rel intensity)] 260 (5), 224 (1), 155 (8).

Methyl [4-(4-Methylphenylsulfonyl]-1-oxido-3,4,5,8-tetrahydro-2H-1,4-thiazocin-2-yl]acetate (5). To a solution of **3** (0.26 g, 0.65 mmol) in CH_2Cl_2 (10 mL) was added a solution of commercial Gen 2 catalyst (5% mol, 0.028 g) in CH_2Cl_2 (4 mL) under a nitrogen atmosphere. The resulting mixture was refluxed for 6 h. The mixture was cooled to room temperature and concentrated in vacuo. Column chromatography of the residue on silica gel (EtOAc) gave 0.23 g (95%) of **5** separable mixture of two diastereomers in a 2:3 ratio both of which were viscous, tacky semiliquids. Minor diastereomer (higher R_f): IR 1733 cm^{-1}; ^1H NMR δ 7.65 (d, 2H, J = 8.0 Hz), 7.31 (d, 2H, J = 8.0 Hz), 5.84 (dd, 1H, J = 11.2, 4.0 Hz), 5.57 (m, 1H), 4.14 (d, 2H, J = 8.8 Hz), 4.00−3.76 (m, 3H), 3.70 (s, 3H), 3.48 (m, 1H), 3.04 (d, 1H, J = 14.8 Hz), 2.83 (dd, 1H, J = 16.4, 6.4 Hz), 2.44 (dd, 1H, J = 16.4, 8.0 Hz), 2.40 (s, 3H); ^{13}C NMR δ 170.6, 144.2, 133.5, 133.1, 130.0, 127.4, 119.0, 53.1, 52.2, 49.2, 45.5, 44.2, 33.3, 21.5; MS [*m/z* (rel intensity)] 371 (M^+, 9), 216 (8), 155 (68). Major diastereomer (lower R_f): IR 1736 cm^{-1}; ^1H NMR δ 7.59 (d, 2H, J = 8.4 Hz), 7.30 (d, 2H, J = 7.6 Hz), 5.87−5.74 (m, 2H), 4.30 (dd, 1H, J = 14.0, 8.0 Hz), 4.21 (d, 1H, J = 18.0 Hz), 3.92 (dd, 1H, J = 14.0, 8.0 Hz), 3.65 (s, 3H), 3.60−3.50 (m, 3H), 3.14−3.07 (m, 2H), 2.60 (dd, 1H, J = 17.2, 9.2 Hz), 2.40 (s, 3H); ^{13}C NMR δ 171.0, 144.2, 134.1, 132.2, 130.0, 127.1, 118.8, 55.6, 52.2, 49.7 48.6, 47.9, 31.8, 21.5; MS [*m/z* (rel intensity)] 371 (M^+, 15), 216 (11), 155 (56).

Methyl [4-(4-Methylphenylsulfonyl]-1,1-dioxido-3,4,5,8-tetrahydro-2H-1,4-thiazocin-2-yl]acetate (6). To a solution of **4** (0.40 g, 0.96 mmol) in CH_2Cl_2 (10 mL) was added a solution of commercial Gen 2 catalyst (5% mol, 0.041 g) in CH_2Cl_2 (5 mL) under a nitrogen atmosphere. The resulting mixture was refluxed for 8 h. The mixture was cooled to room temperature and concentrated in vacuo. Column chromatography of the residue on silica gel (EtOAc/hexane, 2:3) gave 0.38 g (100%) of **6** as a white solid: mp 155−7 °C; IR 1740 cm^{-1}; ^1H NMR δ 7.63 (d, 2H, J = 8.0 Hz), 7.29 (d, 2H, J = 8.0 Hz), 5.77−5.66 (m, 2H), 4.39 (m, 1H), 4.12−3.94 (m, 3H), 3.77−3.69 (m, 2H), 3.66 (s, 3H), 3.22 (dd, 1H, J = 14.4, 2.8 Hz), 3.03 (dd, 1H, J = 16.8, 3.6 Hz), 2.41−2.35 (m, 4H); ^{13}C NMR δ 170.2, 144.3, 134.4, 132.7, 130.0, 127.3, 118.7, 55.6, 52.8, 52.1, 49.4, 49.0, 29.0, 21.3; MS [*m/z* (rel intensity)] 232 (14), 155 (32). Anal. Calcd for $C_{16}H_{21}O_6NS_2$: C, 49.60; H, 5.46; N, 3.62. Found: C, 49.54; H, 5.56; N, 3.64.

1-[[4-[4-(Methylphenyl)sulfonyl]-3,4,5,8-tetrahydro-2H-1,4-thiazocin-2-yl]acetyl]-1H-indole (21). To a solution of **12** (see Supporting Information for preparation; 30.8 mg, 0.0675 mmol) in CH_2Cl_2 (5 mL) was added portionwise a freshly solution of Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide, 27.3 mg, 0.0654 mmol] in CH_2Cl_2 (3 mL). The mixture was stirred at room temperature until TLC indicated the reaction was complete (15 min), at which time solvent was evaporated in vacuo. One milliliter of methanol was added, and the mixture was stirred (1 min) during which time the product was obtained as a white solid (20.0 mg, 67%): mp 177−178.5 °C; ^1H NMR δ 8.39 (d, 1H, J = 7.9 Hz), 7.61 (d, 2H, J = 8.2 Hz), 7.55 (d, 1H, J = 7.3 Hz), 7.40 (d, 1H, J = 3.6 Hz), 7.34−7.26 (m, 4H), 6.65 (d, 1H, J = 3.6 Hz), 5.79 (ddd, 1H, J = 11.3, 7.6, 2.7 Hz), 5.66 (ddd, 11.3, 4.0, 3.7 Hz), 4.37 (dd, 1H, J = 13.1, 8.6 Hz), 4.25 (dd, 1H, J = 17.7, 3.7 Hz), 3.99−3.94 (m, 1H), 3.77 (dd, 1H, J = 13.1, 9.2 Hz), 3.55 (dd, 1H, J = 17.7, 4.0 Hz), 3.36 (dd, 1H, J = 13.1, 2.7 Hz), 3.23−3.17 (m, 2H), 3.04 (dd, 1H, J = 16.4, 8.2 Hz), 2.38 (s, 3H); ^{13}C NMR δ 168.3, 143.9, 135.8, 135.0, 130.6, 130.1, 128.1, 127.3, 125.6, 125.5, 124.5, 124.2, 121.2, 116.7, 110.1, 58.1, 49.4, 38.3, 37.0, 27.2, 21.7; MS [*m/z*, rel int)]: 440 (6), 117 (100).

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Supporting Information Available: Full experimental details for preparation of compounds **7−12** and **14−20** and selective spectroscopic and analytical data for these compounds and copies of ^1H and ^{13}C NMR spectra for compounds **1−12** and **14−21**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO035692Z

Chapter 4

Sulfoxide as a "molecular brake"

A Redox-Mediated Molecular Brake: Dynamic NMR Study of 2-[2-(Methylthio)phenyl]isoindolin-1-one and *S*-Oxidized Counterparts

Jog, P. V.; Brown, R. E.; Bates, D. K. *J. Org. Chem.* **2003**, *68*, 8240.

JOC*Note*

A Redox-Mediated Molecular Brake: Dynamic NMR Study of 2-[2-(Methylthio)phenyl]isoindolin-1-one and *S*-Oxidized Counterparts

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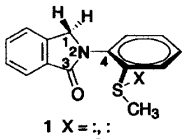
Abstract: A redox-mediated molecular brake based on the sulfide−sulfoxide redox cycle is illustrated by modulation of the rotation rate of an N−Ar "shaft" by varying the oxidation state of sulfur in 2-[2-(sulfur-substituted)phenyl]-isoindolin-1-ones. N−Ar rotational barriers in methylsulfinyl (**2**) and methylsulfonyl (**3**) derivatives (13.6 kcal mol^{-1}) are ~5 kcal mol^{-1} higher than sulfide **1**. Rate reduction for N−Ar rotation is ~10^4 s^{-1} (280 K) upon oxidation. Correlated *N*-pyramidalization/N−Ar rotation reduces the effectiveness of the brake by decreasing the energy barrier to N−Ar bond rotation.

Rotational motion is an integral behavior of molecules. Controlling these motions in a reproducible fashion is a key design element for molecular machines. For a molecular brake,[1] an integral component of a molecular machine, reversibility and hindrance to motion are the two most important aspects. Recently, organic molecules designed specifically to achieve certain desired motions leading to a molecular motor have been reported.[2] For example, a ratcheted "drive shaft" containing intramolecular features which allow rotation of the shaft in only one direction has been reported,[3] and approaches to intramolecular brakes based upon changes of pH,[4] metal ion concentration,[1,5] or coordination number (or oxidation state of the metal)[6] have been disclosed.

We now wish to introduce the concept of an organic-based redox-mediated molecular brake. The system is based on the sulfide−sulfoxide redox cycle and is illustrated in a minimalist system by modulation of the rate of rotation of an N−Ar "shaft" by varying the oxidation state of a proximate sulfur atom in 2-[2-(sulfur-substituted)phenyl]isoindolin-1-ones **1**−**3**. Oxidized sulfur acts as the braking mode (rotation hindered) while the reduced [S(II)] counterpart shows "free" rotation. This approach is attractive because there are numerous high-yield chemical and electrochemical processes for both sulfur oxidation to sulfoxide[7,8] and sulfoxide deoxygenation to sulfide.[9,10] Thus, the processes of applying and removing the brake are readily reversible, easily controllable actions.



1 X = :, :
2 X = O, :
3 X = O, O

Simple isoindolin-1-ones exist as enantiomeric rotational isomers with slow rotation about the aryl C−N bond giving rise to diastereotopic methylene protons.[11] Ortho-substitution of the aryl group of 2-phenylisoindolin-1-one with sulfur-containing groups (compounds **1**−**3**) had a pronounced line broadening effect on methylene proton signals in the ^{1}H NMR spectra (25 °C) (Figure 1) indicating the sulfur oxidation level dramatically affects the rate of rotation about the N−Ar bond in these compounds.

On cooling below −20 °C, the methylene "bump" in sulfone (**3**) splits into an AB quartet ($\Delta\nu$ =191.5 Hz and J_{AB} = 16.8 Hz at 400 MHz in the absence of exchange)

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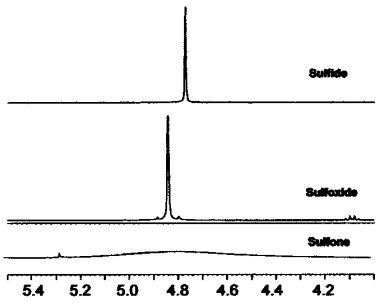

FIGURE 1. ^{1}H NMR spectra of isoindolin-1-one sulfide (**1**), sulfoxide (**2**), and sulfone (**3**) (400 MHz, $CDCl_3$, 25 °C).

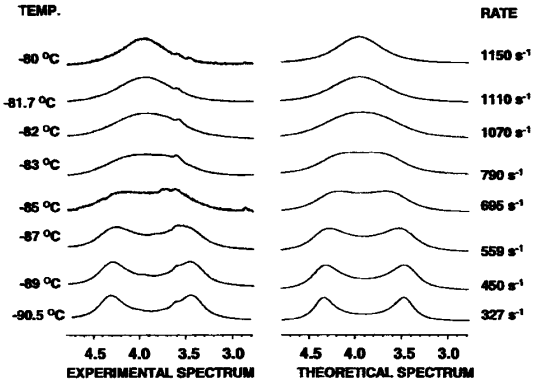

FIGURE 2. Line-shape analysis of **1**.

TABLE 1. NMR Parameters and Thermodynamic Data for Isoindolin-1-ones (1–3)

compd	T_C (K)	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (cal mol^{-1})	$\Delta G^{\ddagger}$ [c] (kcal mol^{-1})	$\Delta G^{\ddagger}$ [d] (kcal mol^{-1}) (computed)
1[a]	<188	8.10	−1.5	8.4 (8.6)	9.2, 9.0
2[b]	280			(13.6)	10.4, 11.9
3[b]	295	12.2	4.9	13.6 (13.7)	17.2, 13.5

[a] NMR in toluene-d_8. [b] NMR in $CDCl_3$. [c] Experimental value from line-shape analysis or (coalescence measurement). [d] Calculated from minima on either side of the transition state.

with a coalescence temperature (T_c) of 22 °C. These data provide a value of 13.7 kcal/mol (57.2 kJ/mol) for the free energy of activation ($\Delta G^{\ddagger}$) of **3**. Line-shape analysis of spectra obtained at various temperatures confirms this value ($\Delta G^{\ddagger}$ = 13.6, 56.9 kJ/mol) and allows calculation of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ (Table 1). Similarly, sulfide (**1**) gives T_c = −85 °C (188 K) and $\Delta G^{\ddagger}$ = 8.56 kcal/mol (35.8 kJ/mol) [$\Delta G^{\ddagger}$ = 8.40 kcal/mol (35.1 kJ/mol) by line-shape analysis]. The rate data obtained from line-shape analysis of ^{1}H NMR spectra of **1** are shown in Figure 2.

Analyses of the variable-temperature (VT) ^{1}H NMR spectra of sulfoxide **2** were problematic. The methylene signals appeared as an AB quartet in the absence of exchange (H_a = 4.95, H_b = 4.85, J = 16.78 Hz, $CDCl_3$, −60 °C). As the sample was warmed these peaks gradually collapsed to a single broad peak and, upon further heating, decoalesced into another AB quartet (H_a = 4.86, H_b = 4.80, J = 16.78 Hz, $CDCl_3$, 50 °C). Throughout this process, the centerline of the absorptions migrated linearly upfield, becoming constant in appearance and chemical shift at about 120 °C ($CDBr_3$). This behavior is unique to the sulfoxide; both the sulfide and the sulfone showed classical decoalescence upon warming from the absence of exchange regime to give a singlet having a chemical shift equal to the average values for H_a and H_b in the low-temperature AB quartet. In analogy with sulfide (**1**) and sulfone (**3**), coalescence of the low-temperature AB quartet in sulfoxide (**2**) is a physical manifestation of increased N−Ar rotation. However, in **2**, even as H_a and H_b rapidly exchange, they are diastereotopic due to the presence of the chiral sulfoxide moiety, hence the reappearance of separate signals for H_a and H_b at higher temperatures. In other words, as noted by Lunazzi,[12] sulfoxides which contain a chiral center and also a stereogenic axis (in our case the N−Ar bond) will display a set of conformational enantiomers (or atropisomers) at low temperature (under conditions of slow exchange) and a pair of configurational enantiomers when exchange is rapid.

For sulfoxide **2**, $\Delta G^{\ddagger}$ and k were determined at the coalescence temperature (280 K, 13.6 kcal mol^{-1} and 1.3 × 10^2 s^{-1}, respectively). By comparison, k_{280} for **1** and **3** are 1.6 × 10^6 and 1.4 × 10^2 s^{-1}, respectively. As expected from the scant literature available,[13] the sulfoxide and sulfone barriers to rotation are very similar. Thus, at 280 K, oxidation of sulfide **1** to either the sulfoxide **2** or sulfone **3** slows this rate of rotation by about 10^4 s^{-1}.[14]

Based on a "rigid shaft" model, we had expected an increase in rotational barrier of more than 5 kcal/mol upon sulfur oxidation. Examination in models of the N−Ar rotation reveals a severe steric interaction during

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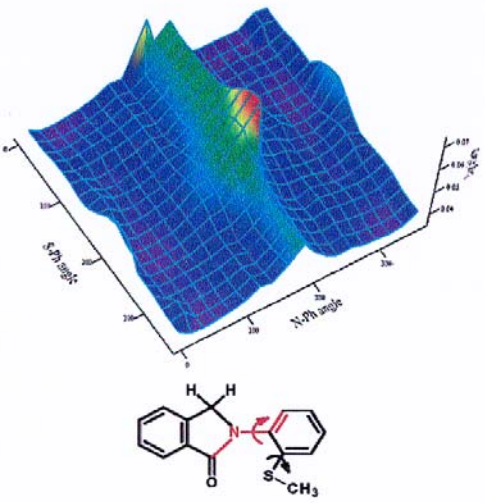

FIGURE 3. Potential energy surface plot for **1** (Gaussian 98).

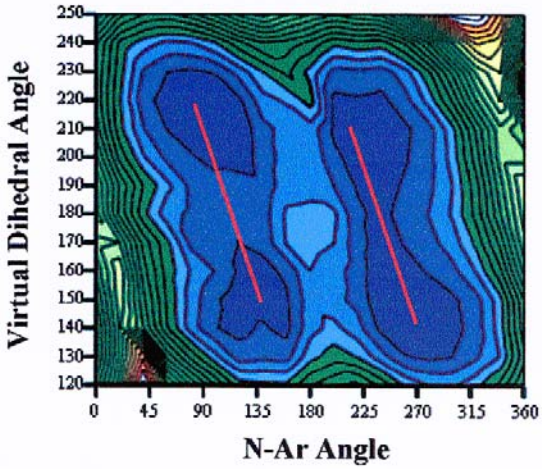

FIGURE 4. Surface plot of N−Ar angle and virtual dihedral angle for **1**.

the passage of the ortho substituents over the carbonyl group during rotational interconversion of enantiomers. Transition-state nitrogen pyramidalization to avoid steric interactions during rotational motion has been reported.[15] To get a better picture of rotational processes and to determine theoretical rotational barriers, semiempirical molecular orbital calculations were performed on compounds **1**−**3**.[16] Figure 3 shows the potential energy surface diagram for sulfide **1** for concurrent N−Ar and S−Ar rotations, with central maxima and minima on either side indicating noncorrelated N−Ar and S−Ar rotations.[17] The calculated barrier is ~9 kcal/mol for passage of *o*-SMeAr over the carbonyl group, which matches well with the values obtained from experimental work (~8.5 kcal mol^{-1}). Similar calculations were performed on **2** and **3** (Table 1). These values also agree quite well with experimental results but are not as close as for **1**. Theoretical values may deviate slightly from the experimental values due to chirality considerations or parametrizations in the PM3 program. The barrier to passage of *o*-SMeAr over the methylene portion of the isoindolinone is calculated to be much lower than for passage over the carbonyl (3.3 kcal mol^{-1}).

A major finding of the calculations is that pyramidalization of the amidic nitrogen is predicted in all three 2-(*o*-substituted phenyl)isoindolinone derivatives. This process cannot be observed by NMR in our model systems. Calculations show the degree of nitrogen pyramidalization[18] in the highest energy conformations greatly increases with the initial oxidation from −S− to S=O (9.6° to 13.3°), but changes little upon further oxidation (13.3° to 13.9° in the sulfone). One can visualize nitrogen pyramidalization during N−Ar bond rotation in our model system as a "wobbling" rotating shaft rather than a rigid rotating shaft. At torsion angles where steric repulsion of the indolinone ring and *o*-Ar substituent is minimal, N-pyramidalization is also minimal. However as the steric interaction increases so does N-pyramidalization.

The calculations suggest (and it is reasonable to expect) N−Ar rotation and N-pyramidalization to be coupled or correlated motions. The coordinated movement of two proximate groups in order to minimize steric interactions during rotation of these groups is termed correlated or cogwheel rotation and is a well-studied phenomenon.[17,19−21] Motions in which rotation is coupled to nitrogen inversion

(14) As a practical matter, oxidation to the sulfone state offers little or no increase in the barrier to rotation, while methods for converting sulfones to sulfides are not nearly as diverse nor simply executed as for sulfoxide deoxygenation. This is why our focus is on the S ↔ S=O redox cycle even though DNMR studies are, in general, easier to conduct on sulfone derivatives.

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(18) Different measures have been used to describe nitrogen pyramidalization: (a) Degree of pyramidalization equals 360 − Σ bond angles to the nitrogen atom (Ganguly, B.; Freed, D. A.; Kozlowski, M. C. *J. Org. Chem.* **2001**, *66*, 1103). (b) Measurement of a virtual dihedral angle (Rankin, K. N.; Boyd, R. J. *J. Phys. Chem. A* **2002**, *106*, 11168) and (c) measurement of the distance from the nitrogen atom to the plane containing by the three atoms bonded to nitrogen (Schweizer, W. B.; Procter, G.; Kaftory, M.; Dunitz, J. D. *Helv. Chim. Acta* **1978**, *61*, 2783).

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have been studied extensively by both experimental and computational methods[22] and correlated rotation−nitrogen pyramidalization has been studied computationally.[23] Lunazzi[17] has developed a graphical method to demonstrate correlated bond rotations by generating a contour map of the potential energy surface described by incremental rotations of the dihedral angles about the bonds suspected of correlated rotation. Correlated rotation is present when the rotation pathways (indicated by lines joining energy minima) run diagonal to the $x-y$ axes and parallel to each other. To demonstrate computationally the correlated nature of N−Ar rotation and N-pyramidalization in **1**−**3**, we have developed a variant of the Lunazzi graphical approach: a "virtual dihedral angle" is plotted against the N−Ar torsion angle. Rankin and Boyd[18b] introduced the virtual dihedral angle as a means of quantitating nitrogen pyramidalization. The virtual dihedral angle given by C1−N2−C3−C4 (see structure **1**) in compounds **1**−**3** having a value of 180° corresponds to planar nitrogen (flat, sp^2, degree of pyramidalization[18a] = 0°) and a value of 120° corresponds to tetrahedral nitrogen (sp^3, degree of pyramidalization = 31.5°). In the calculations (PM3), the virtual dihedral angle and the N−Ar torsion angle were locked, and then the other angles and bond distances were allowed to relax to their minima for each of the locked values. The N−Ar torsion angle values were fixed in 20° increments from 0 to 360° and virtual dihedral angle values were fixed in 10° increments from −90° to +90°. The resulting plot (Figure 4) has the appearance of a Lunazzi diagram, but relates N−Ar rotation to N-pyramidalization. Thus, diagonal lines joining the energy minima in Figure 4 are indicative of correlated motions.

Redox disengagement/engagement of the molecular brake can be observed in situ in an NMR tube. Addition of a solution of Lawesson's reagent[9k] (in $CDCl_3$) to an NMR sample of compound **2** equilibrated to −40 °C in the NMR probe leads to a rapid replacement of the AB quartet (δ 4.95) observed for the methylene hydrogen atoms in the "stopped" sulfoxide with a broad singlet (δ 4.78) corresponding to the methylene hydrogen atoms in sulfide **1** as rotation about the N−Ar bond takes place. Conversely engagement of the brake may be observed by addition of a solution of *m*-CPBA (in $CDCl_3$) to an NMR sample of compound **1** equilibrated to −40 °C in the NMR probe. This leads to a rapid replacement of the broad singlet (δ 4.78) corresponding to the methylene hydrogen atoms in the slowly rotating sulfide with an AB quartet (δ 4.95) corresponding to the methylene hydrogen atoms in the absence of N−Ar rotation in sulfoxide **2**. These reagents are nearly ideal for these experiments because the reactions are rapid (even at −40 °C), quantitative, and exhibit no interfering peaks in the region δ 4−5. A sample spectrum from titration of **1** with *m*-CPBA to approximately 80% conversion at −40 °C in an NMR tube is shown in Figure 5 (Supporting Information). The redox conversions may also be monitored by changes in intensity of the methyl signals in **1** (δ 2.41) and **2** (δ 3.05).

In conclusion, we have shown that the rate of N−Ar rotation in isoindolin-1-ones **1**−**3** is controlled by the oxidation state of sulfur in a proximate ortho substituent. The rate difference between sulfane and the sulfinyl/sulfonyl forms is $\sim 10^4$ s^{-1}. The model compounds are shown computationally to undergo correlated N-pyramidalization and C−N bond rotation. As the *o*-Ar substituent passes the plane of the isoindolinone, N-pyramidalization reaches maximum, but the nitrogen becomes planar when the isoindolinone and Ar groups are nearly orthogonal. Pyramidalization of nitrogen causes the redox brake to be less effective than expected. Design of a system in which shaft element flexing (in the form of atom pyramidalization) is avoided should provide more dramatic rate reductions using this molecular brake concept.

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Supporting Information Available: Experimental details for preparation and characterization of compounds **1**−**3**, ^1H and ^{13}C NMR spectra for compounds **1**−**3**, 3D potential energy surface plots for **2** and **3**, PM3-computed *Z*-matrices for the lowest energy conformation of compounds **1**−**3** (when N−Ar and S−Ar torsion angles are locked and incremented), 2D surface plots of N−Ar torsion angle vs virtual dihedral angle for **2** and **3**, rate data for **3** from line-shape analysis, and PM3-computed *Z*-matrices for the lowest energy conformation of compounds **1**−**3** (when N−Ar and the virtual dihedral angle torsion angle are locked and incremented). This material is available free of charge via the Internet at http://pubs.acs.org.

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Future Directions

The use of sulfoxide as a source of intramolecular sulfenylating agents was well-known. Different modes (electrophilic and thermal) of sulfoxide activation were also well documented. However, the following observation warrants further study in understanding the actual process of sulfoxide activation. Mass spectrometric analysis of *t*-butyl, propane nitrile, and ethyl sulfoxides, which successfully produced a cyclized product in reaction conditions, was eventful. These sulfoxides, which are proven to have several rotomeric isomers in solution, ambiguously yet cleanly produce the intended cyclized product (based on M+ values) directly from solid samples during the mass spectrometric data collection. Further work is necessary to understand this phenomenon, especially because this phenomenon was observed for only those sulfoxides, which successfully produced the cyclized product under both electrophilic and thermal reaction conditions in the laboratory.

In chapter 3, sulfoxide was introduced as a "protecting group" for thioether which was unreactive under RCM reaction conditions. A well-known Ru-S(II) coordination was presumably avoided in the sulfoxide oxidation state. The next step in this research is to define the scope and utility of this approach. It is important to note that in an example described in chapter 3, one of the unsaturated components in the RCM diene precursor was directly attached to a sulfur atom. It would be interesting to apply this methodology of using sulfoxide as a protecting group to a sulfur containing system in which either of the alkene components is not directly attached to the sulfur atom. The results obtained from such an experiment would provide more insight in understanding the exact nature of

the interaction between the Ru-based catalyst and the sulfur containing substrate. Precisely, the validity of using sulfoxide as a protecting group of thioether needs to be tested with respect to the precise positioning of both the alkenes undergoing RCM reaction and the sulfur atom in substrate.

As discussed in chapter 4, nitrogen pyramidalization lowers the rotational barrier in sulfoxide, which results in a lower than expected increase in the rotational barrier. A system where nitrogen pyramidalization can be avoided should provide a more effective molecular brake based on the sulfide-sulfoxide redox cycle. If nitrogen pyramidalization is unavoidable, then the sulfide [S(II)] oxidation state of such system should have even lower barrier than Isoindoline **1** in chapter 4 to be a more efficient molecular brake than the one described in chapter 4 based on this redox cycle.

Appendix 1

Intramolecular Sulfoxide Electrophilic Sulfenylation (SES) of 2- and 3- Indole Carbanilides: Formation of Indolo[3,2-*b*]-1,5-benzothiazepinones

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Supplemental Information

(Compound numbers correspond to the numbers in the article:

Bates, D. K.;Eggers, M. E.; Jog, P. V. *J. Org. Chem.* Submitted for publication)

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2-(ethylthio)-*N*-methylaniline. Sodium metal (29.9 g, 260 mmol) was added to MeOH (390 mL) over 30 min with vigorous stirring. After H_2 evolution was complete (10 min), neat 2-(ethylthio)aniline (40.3 g, 260 mmol) was added dropwise then this solution was added dropwise to a well-stirred suspension of paraformaldehyde (10.9 g, 360 mmol) in MeOH (260 mL). After stirring 7 h at room temperature, neat $NaBH_4$ (9.1 g, 0.26 mol) was added to the reddish brown mixture. After refluxing 45 min, 1 M KOH (400 mL) was added to the cooled orange solution, which was then stirred for 30 min. This mixture was reduced to ½ its original volume in vacuo and poured into a saturated NaCl solution (200 mL). Extraction with CH_2Cl_2 (3 x 200 mL) followed by washing the combined organic layers with saturated aqueous NaCl, drying (Na_2SO_4) and solvent evaporation in vacuo produced a brown liquid. Flash chromatography (1:1 $CHCl_3$:hexanes) gave pure 2-(ethylthio)-*N*-methylaniline (18.2 g, 42%): IR 3390 cm^{-1}; ^1H NMR (200 MHz) δ 7.18-7.41 (2H, m), 6.57- 6.67 (2H, m), 5.10 (1H, s, br), 2.86 (3H, s), 2.70 (2H, q, J = 7.3 Hz), 1.20 (3H, t, J = 7.3 Hz); ^{13}C NMR δ 150.8, 136.6, 130.6, 117.9, 117.1, 110.1, 31.2, 29.5, 15.5; MS [m/z (relative intensity)] 167 (M+, 100).

2-(*tert*-butylthio)-*N*-methylaniline. A mixture of 2-(*tert*-butylthio)aniline (3.5 g, 19 mmol) and 100 mL of glacial acetic acid was heated under reflux for 14 h. The reaction mixture was cooled to room temperature and poured onto an ice-water mixture. The organic layer was extracted with chloroform (2 x 250 mL), washed with water (2 x 250 mL) and dried over sodium sulfate. Evaporation of solvent in vacuo gave ***N*-[2-(*tert*-butylthio)phenyl]acetamide** as a brown liquid. (4.2 g, 97%): IR 3343, 1693 cm^{-1}; ^1H NMR δ 8.79 (broad, 1H), 8.44 (d, J = 8.16, 1H), 7.46 (ddd, J = 7.72, 1.67, 0.40 Hz, 1H),

7.34 (dt, J = 7.52, 1.64 Hz, 1H), 6.99 (dt, J = 7.61, 1.33 Hz, 1H), 2.16 (s, 3H), 1.25 (d, J = 0.67 Hz, 9H); ^{13}C NMR δ 167.9, 141.4, 138.5, 130.7, 123.1, 119.7, 119.5, 48.2, 30.9, 30.8, 24.8; MS [m/z (rel. intensity)] 223 [M^+, 16], 125 (100), 57 (36).

To a well-stirred suspension of *N*-[2-(*tert*-butylthio)phenyl]acetamide (12.8 g, 57 mmol) and tetra-*n*-butylammonium hydrogen sulfate (0.2 eq, 11.5 mmol, 3.89 g) in toluene (250 mL) was added all at once 50% NaOH aqueous solution (500 mL). The resulting two layer mixture was heated under reflux at which a solution of iodomethane (excess, (2.0 eq), 114 mmol, 16.3 g) in toluene (40 mL) was added dropwise over 15 min. The resulting two phase mixture was maintained at reflux for 24 h. It was cooled to room temperature and the layers separated. The organic layer was washed with water several times (until washings were neutral to litmus), dried over sodium sulfate and evaporated in vacuo to yield ***N*-[2-(*tert*-butylthio)phenyl]-*N*-methylacetamide** as an off-white solid (8.5 g, 63%): mp 56-58 ºC; IR 1651 cm^{-1}; ^{1}H NMR δ 7.63 (dd, J = 7.23, 1.37 Hz, 1H), 7.31 (ddd, J = 7.45, 1.85 Hz, 1.18 Hz, 1H), 7.27 (ddd, J = 7.45, 1.89, 1.18 Hz, 1H), 7.18 (ddd, J = 6.86, 1.81, 0.94 Hz, 1H), 3.18 (dd, J = 1.37, 0.3 Hz, 3H), 1.75 (dd, J = 1.45, 0.35 Hz, 3H), 1.34 (d, J = 1.35 Hz, 9H); ^{13}C NMR δ 170.8, 146.6, 136.6, 133.5, 129.0, 128.5, 127.8, 47.2, 37.1, 31.7, 31.6, 22.7; MS [m/z (rel. intensity)] 181 (34), 57 (17).

To a solution of *N*-[2-(*tert*-butylthio)phenyl]-*N*-methylacetamide (8.3 g, 35 mmol) in 95% ethanol (400 mL) was added a solution of 30% aqueous HCl (70 mL). The resulting reaction mixture was refluxed for 6 d. The cooled reaction mixture was neutralized with 30% aqueous NaOH solution untill pH=8. Organic layer was extracted with chloroform (2 x 250 mL), washed with water (2 x 400 mL) and dried over sodium sulfate. Evaporation of solvent in vacuo gave 2-(*tert*-butylthio)-*N*-methylaniline as brown liquid

(5.7 g, 83%): IR 3400 cm^{-1}; ^{1}H NMR δ 7.41 (dd, J = 7.44, 1.63 Hz, 1H), 7.29 (dt, J = 7.38, 1.67 Hz, 1H), 6.60-6.67 (m, 2H), 5.37 (broad, 1H), 2.87 (s, 3H), 1.33 (s, 9H); ^{13}C NMR δ 151.9, 139.1, 130.7, 115.7, 115.2, 109.3, 47.3, 30.8, 30.2; MS [m/z (rel. intensity)] 195 (16), 139 (100), 57 (13).

Ethyl *N*-methylindole-2-carboxylate. To a well-stirred solution of ethyl indole-2-carboxylate (5.0 g, 26 mmol), CH_3I (11.2 g, 79 mmol, 3 eq) and tetra-*n*-butylammonium sulfate (9.0 g, 26 mmol, 1 eq) in toluene (50 mL) at 0 °C was added 50% aqueous NaOH (25 mL) in one portion. The resulting two-phase mixture was heated to reflux for 1 h and, after cooling, the layers separated. The organic layer was washed with 5% HCl (2 x 50 mL), H_2O (1 x 50 mL), dried (Na_2SO_4) and the solvent evaporated in vacuo to yield a wet yellow solid. Column chromatography ($CHCl_3$) and collection of the higher R_f component gave ethyl *N*-methylindole-2-carboxylate (4.2 g, 80%) as an off-white solid: mp 59-60 °C; IR 1704 cm^{-1}; ^{1}H NMR δ 7.70 (1H, dd, J = 0.8, 7 Hz), 7.17-7.39 (4H, m), 4.40 (2H, q, J = 7 Hz), 4.08 (3H, s), 1.43 (3H, t, J = 7 Hz); MS [m/z (relative intensity)] 203 (M^+, 46), 89 (100). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.82; H, 6.45; N, 6.89. Found: C, 70.76; H, 6.47; N, 6.98.

***N*-[2-(*tert*-butylthio)phenyl]-1*H*-indole-2-carboxamide (1b).** To a well-stirred solution of indole-2-carboxylic acid (4.25 g, 26.4 mmol) in ether (100 mL) at 0 °C under a drying tube was added dropwise thionyl chloride neat (3 x 3.66 g portionwise over 12 h, 3.5 eq.). The reaction mixture was allowed to stir at room temperature during 12 h. The resulting clear yellow solution was evaporated in vacuo to produce yellow solid (4.50 g,

95%). This solid was redissolved in ether (100 mL) and added to a well-stirred solution of 2-(*tert*-butylthio)aniline (1.2 eq, 5.64 g, 31 mmol) in dioxane-water-ether (40-5-50 mL) mixture over 10 min at room temperature. The reaction mixture was stirred at room temperature for 3 h and then diluted with ethyl acetate (150 mL). The combined organics were washed with 5% HCl (aq, 3 x 150 mL), 5% $NaHCO_3$ (aq, 3 x 150 mL), water (2 x 150 mL) dried over sodium sulfate and solvent evaporated in vacuo to yield a off-white solid. Recrystallization with hexane gave white compound (6.1 g, 71%): mp 191-193 ºC; IR 3453, 1660 cm^{-1}; ^1H NMR δ 10.4 (broad, 1H), 9.9 (broad, 1H), 8.80 (d, J = 8.16 Hz, 1H), 7.76 (d, J = 7.91 Hz, 1H), 7.61 (d, J = 7.91 Hz, 1H), 7.54 (d, J = 7.91 Hz, 1H), 7.49 (d, J = 7.91 Hz, 1H), 7.32 (t, J = 7.35 Hz, 1H), 7.09-7.22 (m, 3H), 1.36 (s, 9H); ^{13}C NMR δ 159.5, 141.2, 138.7, 137.0, 131.1, 130.9, 127.7, 124.8, 123.5, 122.1, 120.8, 120.5, 119.6, 112.2, 102.9, 48.5, 30.9; MS [m/z (rel. intensity)] 324 [M^+, 9], 144 (100), 89 (20), 57 (14). Anal. Calc. for $C_{19}H_{20}N_2OS$: C, 70.34; H, 6.21; N, 8.63. Found: C, 70.21; H, 6.43; N, 8.56.

***N*-[2-(*tert*-butylsulfinyl)phenyl]-1*H*-indole-2-carboxamide (2b).** To an ice-cooled solution of **1b** (5.10 g, 15.7 mmol) in CH_2Cl_2 (150 mL) was added slowly a solution of *m*-CPBA (77%, 1.1 eq, 22.4 mmol, 3.9 g) in CH_2Cl_2 (50 mL). The resulting mixture was stirred at 0 ºC for 15 min and then put it in a freezer (-8 ^oC) overnight. The reaction mixture was then poured into 5% $NaHCO_3$ solution (150 mL) and extracted with CH_2Cl_2 (200 mL). The combined organic layer was washed with distilled water, dried, and concentrated in vacuo. Column chromatography (EtOAc-hexane, 3:7) gave yellowish white solid which was recrystallized (hexane) to give a white solid (3.51 g, 66%): mp

228-230 ºC (dec); IR 1664 cm^{-1}; ^{1}H NMR δ 12.1 (broad, 1H), 9.46 (broad, 1H), 8.74 (dd, J = 8.34, 0.62 Hz, 1H), 7.72 (d, J = 8.15 Hz, 1H), 7.53 (dt, J = 8.49, 1.70 Hz, 1H), 7.44 (d, J = 8.25, 0.83 Hz, 1H), 7.26-7.31 (m, 2H), 7.09-7.19 (m, 3H), 1.28 (s, 9H); ^{13}C NMR δ 159.6, 142.5, 136.7, 132.4, 131.1, 128.8, 127.9, 124.8, 122.6, 122.4, 122.3, 120.8, 120.7, 111.8, 104.2, 59.1, 23.4; MS [m/z (rel. intensity)] 340 [M^{+}, 1], 144 (100), 89 (26), 57 (18). Anal. Calc. for $C_{19}H_{20}N_2O_2S$: C, 67.03; H, 5.92; N, 8.23. Found: C, 67.04; H, 6.07; N, 8.18.

***N*-[2-(ethylthio)phenyl]-*N*-methyl-1*H*-indole-2-carboxamide (3a).** This compound was prepared analogously to compound **1a**. The crude orange solid was chromatographed ($CHCl_3$) to give **3a** as a yellow solid (38%): mp 188-190 ^{o}C (acetone); IR 3316, 1611 cm^{-1}; ^{1}H NMR (200 MHz) δ 9.73 (s, 1H, br), 6.95-7.49 (8H, m), 5.25 (1H, s), 3.45 (3H, s), 2.88 (2H, apparent qd, J=7.3, 0.1 Hz), 1.24 (3H, t, J = 7 Hz); ^{13}C NMR δ 163.3, 142.3, 138.7, 136.5, 130.5, 130.3, 130.2, 128.8, 128.3, 127.2, 125.2, 123.0, 120.9, 112.6, 107.2, 38.1, 26.7, 14.7; MS [m/z (relative intensity)] 310 (M^{+}, 15), 249 (100). Anal. Calcd for $C_{18}H_{18}N_2OS$: C, 69.65, H, 5.84, N, 9.02. Found: C, 69.53, H, 5.95, N, 8.86.

***N*-[2-(*tert*-butylthio)phenyl]-*N*-methyl-1*H*-indole-2-carboxamide (3b).** To a well-stirred solution of indole-2-carboxylic acid (3.75 g, 23 mmol) in ether (100 mL) at 0 °C under a drying tube was added dropwise thionyl chloride neat (3 x 3.23 g portionwise over 12 h, 82 mmol, 3.5 eq.). The reaction mixture was allowed to stir at room temperature during 12 h. The resulting clear yellow solution was evaporated in vacuo to produce yellow solid (4.0 g, 96%). This solid was redissolved in ether (100 mL) and

added to a well-stirred solution of *N*-[2-(tert-butylthio)phenyl]-*N*-methylamine (1.1 eq, 5.0 g, 26 mmol) in dioxane-water-ether (40-5-50 mL) mixture over 10 min at room temperature. The reaction mixture was stirred at room temperature for 3 h and then diluted with ethyl acetate (150 mL). The combined organics were washed with 5% HCl (aq, 3 x 150 mL), 5% $NaHCO_3$ (aq, 3 x 150 mL), water (2 x 150 mL) dried over sodium sulfate and solvent evaporated in vacuo to give yellowish white solid, which was recrystallized (EtOAc) to give a white solid (5.94 g, 79%): mp 213-214 ºC; IR 3454, 1622 cm^{-1}; ^1H NMR δ 9.37 (broad, 1H), 7.69 (dd, J = 7.24, 1.79 Hz, 1H), 7.37-7.47 (m, 3H), 7.35 (d, J = 8.35 Hz, 1H), 7.30 (d, J = 8.35 Hz, 1H), 7.17 (t, J = 7.43 Hz, 1H), 6.96 (t, J = 7.40 Hz, 1H), 5.11 (s, 1H), 3.45 (s, 3H), 1.29 (s, 9H); ^{13}C NMR δ 162.6, 146.3, 137.2, 135.2, 134.4, 129.9, 129.4, 128.9, 128.4, 127.7, 124.3, 122.1, 120.0, 111.5, 106.3, 47.1, 38.7, 31.8; MS [m/z (rel. intensity)] 338 [M^+, 6], 249 (41), 144 (100), 89 (25). Anal. Calc. for $C_{20}H_{22}N_2OS$: C, 70.97; H, 6.55; N, 8.28. Found: C, 70.82; H, 6.54; N, 8.17**.**

***N*-[2-(ethylsulfinyl)phenyl]-*N*-methyl-1*H*-indole-2-carboxamide (4a).** (59%): mp 177-179 ^oC (acetone); IR 3282, 1628, 1041 cm^{-1}; ^1H NMR (200 MHz taken at 100 ^oC in DMSO-d_6) δ 9.53 (1H, s, br), 8.04-8.09 (1H, m), 6.95- 7.73 (7H, m), 5.39 (1H, s), 3.48 (3H, s), 2.5 -2.8 (2H, m, cont. J = 6.5 Hz), 1.13 (3H, t, J = 6.4 Hz); ^{13}C NMR δ 164.2, 143.4, 142.3, 137.7, 134.4, 132.0, 131.7, 130.5 129.2, 129.1, 126.9, 124.1, 122.4, 113.8, 108.8, 50.1, 40.6, 7.6; MS [m/z (relative intensity)] 326 (M^+, 8), 249 (100). Anal. Calcd for $C_{18}H_{18}N_2O_2S$: C, 66.23, H, 5.56, N, 8.58. Found: C, 65.98, H, 5.70, N, 8.26.

***N*-[2-(ethylthio)phenyl]-1-methyl-1*H*-indole-2-carboxamide (5a).** This compound was prepared analogously to compound **9** from toluene (15 mL), trimethylaluminum (2.0 M in hexane, 2.5 mL, 4.96 mmol, 1.14 eq.), 2-(ethylthio)aniline (0.7 g, 4.4 mmol) in toluene (2 mL), ethyl *N*-methylindole-2-carboxylate (0.9 g, 4.4 mmol) in toluene (7 mL) and CH_2Cl_2 (5 drops). The orange oil **5a** (1.1 g, 84%) solidified on standing: mp 86-87.5 ^oC (light yellow solid, acetone/hexane); IR 3321, 1660 cm^{-1}; ^1H NMR (200 MHz) δ 9.49 (1H, d, J = 1 Hz), 8.56 (1H, dd, J = 1, 7 Hz), 7.72 (1H, dd, J = 1, 7 Hz), 7.59 (1H, dd, J = 2, 6 Hz), 7.05-7.42 (8H, m, containing 1H, d , dd, J = 2, 6 Hz), 4.14 (3H, s), 2.83 (2H, q, J = 7 Hz), 1.25 (3H, t, J = 7 Hz); ^{13}C NMR δ 161.5, 141.2, 140.3, 136.8, 133.2, 131.1, 127.3, 125.2, 123.3, 123.0 120.9, 111.5, 105.9, 33.0, 31.9, 16.2; MS [m/z (relative intensity)] 310 (M^+, 7), 158 (100). Anal. Calcd for $C_{18}H_{18}N_2OS$: C, 69.57; H, 5.84; N, 9.02. Found: C, 69.23; H, 5.95; N, 9.06.

***N*-[2-(*tert*-butylthio)phenyl]-1-methyl-1*H*-indole-2-carboxamide (5b).** To a well-stirred solution of 1-methyl-1*H*-indole-2-carboxylic acid (3.25 g, 18.6 mmol) in ether (100 mL) at 0 °C under a drying tube was added dropwise thionyl chloride neat (3 x 2.6 g portionwise over 12 h, 3.5 eq.). The reaction mixture was allowed to stir at room temperature during 12 h. The resulting clear yellow solution was evaporated in vacuo to produce yellow solid (3.0 g, 84%). This solid was redissolved in ether (100 mL) and added to a well-stirred solution of 2-(*tert*-butylthio)aniline (1.1 eq, 3.69 g, 20.4 mmol) in dioxane-water-ether (40-5-50 mL) mixture over 10 min at room temperature. The reaction mixture was stirred at room temperature for 3 h and then diluted with ethyl acetate (150 mL). The combined organics were washed with 5% HCl (aq, 3 x 150 mL),

5% $NaHCO_3$ (aq, 3 x 150 mL), water (2 x 150 mL) dried over sodium sulfate and solvent evaporated in vacuo to yield a greenish solid which was purified by column chromatography (chloroform: hexane, 8:2) to give pale yellow solid (3.71 g, 59%): mp 86-88 ºC; IR 3326, 1670 cm^{-1}; ^1H NMR δ 9.78 (broad, 1H), 8.65 (dd, J = 8.34, 1.19 Hz, 1H), 7.74 (dt, J = 8.07, 0.88 Hz, 1H), 7.58 (dd, J = 7.74, 1.58 Hz, 1H), 7.42-7.49 (m, 2H), 7.37 (ddd, J = 6.79, 1.12 Hz, 1H), 7.20 (ddd, J = 6.88, 1.15 Hz, 1H), 7.13 (s, 1H), 7.10 (dt, J = 7.53, 1.40 Hz, 1H), 4.14 (s, 3H), 1.34 (s, 9H); ^{13}C NMR δ 160.0, 141.6, 139.4, 138.6, 131.9, 130.8, 126.0, 124.5, 123.3, 122.1, 120.7, 120.4, 119.4, 110.2, 104.6, 48.4, 31.7, 30.9; MS [m/z (rel. intensity)] 338 [M^+, 7], 158 (100), 89 (29), 57 (12). Anal. Calc. for $C_{20}H_{22}N_2OS$: C, 70.97; H, 6.55; N, 8.28. Found: C, 70.88; H, 6.79; N, 8.22.

***N*-[2-(ethylsulfinyl)phenyl]-1-methyl-1*H*-indole-2-carboxamide (6a).** (73%): mp 96-99 ^oC (acetone); IR (KBr) 3219, 1667, 1003 cm^{-1}; ^1H NMR (200 MHz) δ 11.60 (1H, s, br), 8.67 (1H, d, J = 8 Hz), 7.08-7.71 (8H, m), 4.15 (3H, s), 3.02-3.22 (2H, dm, cont. J = 7 Hz), 1.24 (3H, t, J = 7 Hz); ^{13}C NMR δ 162.0, 142.4, 140.9, 133.8, 132.3, 128.0, 127.3, 126.2, 125.9, 124.2, 123.8, 123.7, 121.7, 111.4, 107.0, 49.6, 33.1, 8.7; MS [m/z/(relative intensity) 326 (M^+, 10), 158 (100). Anal. Calcd for $C_{18}H_{18}N_20_2S$: C, 66.23; H, 5.56; N 8.58. Found: C, 65.88, H, 5.63, N, 8.77.

***N*-[2-(*tert*-butylsulfinyl)phenyl]-1-methyl-1*H*-indole-2-carboxamide (6b).** To an ice-cooled solution of **5b** (4.0 g, 11.8 mmol) in CH_2Cl_2 (150 mL) was added slowly a solution of *m*-CPBA (77%, 1.1 eq, 16.8 mmol, 2.90 g) in CH_2Cl_2 (50 mL). The resulting mixture was stirred at 0 ºC for 15 min and then put it in a freezer (-8 ^oC) overnight. The

reaction mixture was then poured into 5% $NaHCO_3$ solution (150 mL) and extracted with CH_2Cl_2 (200 mL). The combined organic layer was washed with distilled water, dried, and concentrated in vacuo. Column chromatography (chloroform-ether, 9:1) gave white solid (2.6 g, 62%): mp 135-137 ºC; IR 1669 cm^{-1}; ^1H NMR δ 11.87 (broad, 1H), 8.69 (dd, J = 8.49, 0.99 Hz, 1H), 7.71 (dt, J = 8.05, 0.96 Hz, 1H), 7.51 (dt, J = 7.21, 1.74 Hz, 1H), 7.35-7.41 (m, 2H), 7.33 (dt, J = 6.80, 1.07 Hz, 1H), 7.12-7.18 (m, 2H), 7.10 (dt, J = 7.26, 1.03 Hz, 1H), 4.14 (s, 3H), 1.28 (s, 9H); ^{13}C NMR δ 160.1, 142.5, 139.6, 132.3, 131.3, 128.7, 126.1, 124.5, 122.6, 122.4, 122.1, 120.9, 120.5, 110.1, 106.0, 59.1, 31.9, 23.4; MS [m/z (rel. intensity)] 354 [M^+, 2], 158 (100), 89 (16). Anal. Calc. for $C_{20}H_{22}N_2O_2S$: C, 67.77; H, 6.26; N, 7.90. Found: C, 68.09; H, 6.22; N, 7.88.

***N*-[2-(*tert*-butylthio)phenyl]-*N*,1-dimethyl-1*H*-indole-2-carboxamide (7b).** To a well-stirred suspension of **1b** (6.5 g, 20 mmol) and tetra-*n*-butylammonium hydrogen sulfate (0.3 eq, 6 mmol, 2.0 g) in toluene (250 mL) was added all at once 50% NaOH (aq) solution (200 mL). The resulting two layer mixture was heated under reflux at which a solution of iodomethane (2.5 eq, 50 mmol, 7.11 g) in toluene (10 mL) was added dropwise over 5 min The resulting two phase mixture was maintained at reflux for 24 h. It was cooled to room temperature and the layers separated. The organic layer was washed with water several times (until washings were neutral to litmus), dried over sodium sulfate and evaporated in vacuo to yield an off-white solid. Recrystallization with hexane gave white compound (5.6 g, 79%): mp 105-106 ºC; IR 3007, 1636 cm^{-1}; ^1H NMR δ 7.48 (d, J = 7.99 Hz, 1H), 7.42 (dt, J = 7.33, 1.42 Hz, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.29 (d, J = 8.24 Hz, 2H), 7.17 (q, J = 7.72 Hz, 2H), 6.95 (t, J = 7.43 Hz, 1H), 5.72

(s, 1H), 4.02 (s, 3H), 3.49 (s, 3H), 1.24 (s, 9H); ^{13}C NMR δ 164.4, 148.4, 138.3, 137.9, 132.4, 131.5, 129.6, 126.9, 126.8, 126.0, 123.3, 121.7, 119.5, 109.7, 106.8, 46.5, 38.4, 31.6, 31.4; MS [m/z (rel. intensity)] 263 (100), 158 (80), 89 (33). Anal. Calc. for $C_{21}H_{24}N_2OS$: C, 71.55; H, 6.86; N, 7.95. Found: C 71.79; H 7.06; N 7.91.

***N*-{2-[(2-cyanoethyl)thio]phenyl}-*N*,1-dimethyl-1*H*-indole-2-carboxamide (7c).** To a well-stirred solution of 1-methyl-1*H*-indole-2-carboxylic acid (0.65 g, 3.71 mmol) in ether (50 mL) at 0 °C under a drying tube was added dropwise thionyl chloride neat (3 x 0.5 g portionwise over 12 h, 3.5 eq.). The reaction mixture was allowed to stir at room temperature during 12 h. The resulting clear yellow solution was evaporated in vacuo to produce yellow solid (0.6 g, 84%). This solid was redissolved in ether (50 mL) and added to a well-stirred solution of 2-propanenitrile-2-(methylaminophenyl)sulfide (1.1 eq, 0.65 g, 3.38 mmol) in dioxane-water-ether (20-3-25 mL) mixture over 10 min at room temperature. The reaction mixture was stirred at room temperature for 3 h and then diluted with ethyl acetate (150 mL). The combined organics were washed with 5% HCl (aq, 3 x 150 mL), 5% $NaHCO_3$ (aq, 3 x 150 mL), water (2 x 150 mL) dried over sodium sulfate and solvent evaporated in vacuo to yield a sticky solid which was purified by column chromatography (chloroform: Ether, 9:1) to give white solid (0.35 g, 27%): mp 124-125 ºC; IR 2240, 1635 cm^{-1}; ^{1}H NMR δ 6.92-7.80 (m, 8H), 5.95 (s, 1H), 3.98 (s, 3H), 3.44 (s, 3H), 2.41 (s, 2H), 2.30 (s, 2H); ^{13}C NMR was not well-resolved due to presence of rotational isomers; MS [m/z (rel. intensity)] 349 [M^+, 3], 263 (72), 158 (100), 89 (24). Anal. Calc. for $C_{20}H_{19}N_3OS$: C, 68.74; H, 5.48; N, 12.02. Found: C 68.80; H 5.58; N 11.87.

***N*-[2-(ethylsulfinyl)phenyl]-*N*,1-dimethyl-1*H*-indole-2-carboxamide (8a). (**95%); mp 165-167 ^{o}C (acetone); IR 1633, 1052, 1025 cm^{-1}; ^{1}H NMR (200 MHz, taken at 100 ^{o}C) δ 7.87-7.91 (1H, m), 7.50-7.56 (2H, m), 7.24-7.43 (4H, m), 7.03 - 7.08 (1H, m), 6.14 (1H, s), 3.97 (3H, s), 3.40 (3H, s), 2.65 (2H, m, containing J = 7 Hz), 1.19 (3H, t, J = 7 Hz); ^{13}C NMR δ 163.0, 141.8, 138.8, 133.1, 132.0, 129.5, 129.3, 129.0, 126.9, 126.8, 124.9, 122.6, 121.0, 110.6, 108.8, 49.2, 39.0, 32.3, 7.0; MS [m/z (relative intensity)] 340 (M^{+}, 1), 158 (100). Anal. Calcd for $C_{19}H_{20}N_20_2S$: C, 67.02; H, 6.11; N, 8.00. Found: C, 67.03; H, 5.92; N, 8.23.

***N*-[2-(*tert*-butylsulfinyl)phenyl]-*N*,1-dimethyl-1*H*-indole-2-carboxamide (8b).** To an ice-cooled solution of **7b** (5.38 g, 15.2 mmol) in CH_2Cl_2 (150 mL) was added slowly a solution of *m*-CPBA (77%, 1.1 eq, 21.7 mmol, 3.74 g) in CH_2Cl_2 (50 mL). The resulting mixture was stirred at 0 ºC for 15 min and then put it in a freezer (-8 ^{o}C) overnight. The reaction mixture was then poured into 5% $NaHCO_3$ solution (150 mL) and extracted with CH_2Cl_2 (200 mL). The combined organic layer was washed with distilled water, dried, and concentrated in vacuo. Column chromatography (EtOAc-hexane, 6:4) gave yellowish white solid which was recrystallized (hexane) to give a white solid (3.42 g, 61%): mp 125-127 ºC; IR 3003, 1639 cm^{-1}; ^{1}H NMR and ^{13}C NMR were not well-resolved due to presence of rotational isomers; MS [m/z (rel. intensity)] 158 (100), 89 (26). Anal. Calc. for $C_{21}H_{24}N_2O_2S$: C, 68.45; H, 6.56; N, 7.60. Found: C 68.30; H 6.64; N 7.51.

***N*-{2-[(2-cyanoethyl)sulfinyl]phenyl}-*N*,1-dimethyl-1*H*-indole-2-carboxamide (8c).** To an ice-cooled solution of **7c** (0.2 g, 0.57 mmol) in CH_2Cl_2 (50 mL) was added slowly

a solution of *m*-CPBA (77%, 1.1 eq, 0.81 mmol, 0.141 g) in CH_2Cl_2 (50 mL). The resulting mixture was stirred at 0 ºC for 15 min and then put it in a freezer (-8 ^oC) overnight. The reaction mixture was then poured into 5% $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2 (75 mL). The combined organic layer was washed with distilled water, dried, and concentrated in vacuo. Column chromatography (EtOAc:hexane, 9:1) gave sticky liquid (0.15 g, 72%): IR 1637, 1039 cm^{-1}; ^1H NMR and ^{13}C NMR were not well-resolved due to presence of rotational isomers; MS [m/z (rel. intensity)] 312 (15), 294 (38), 158 (100), 53 (99).

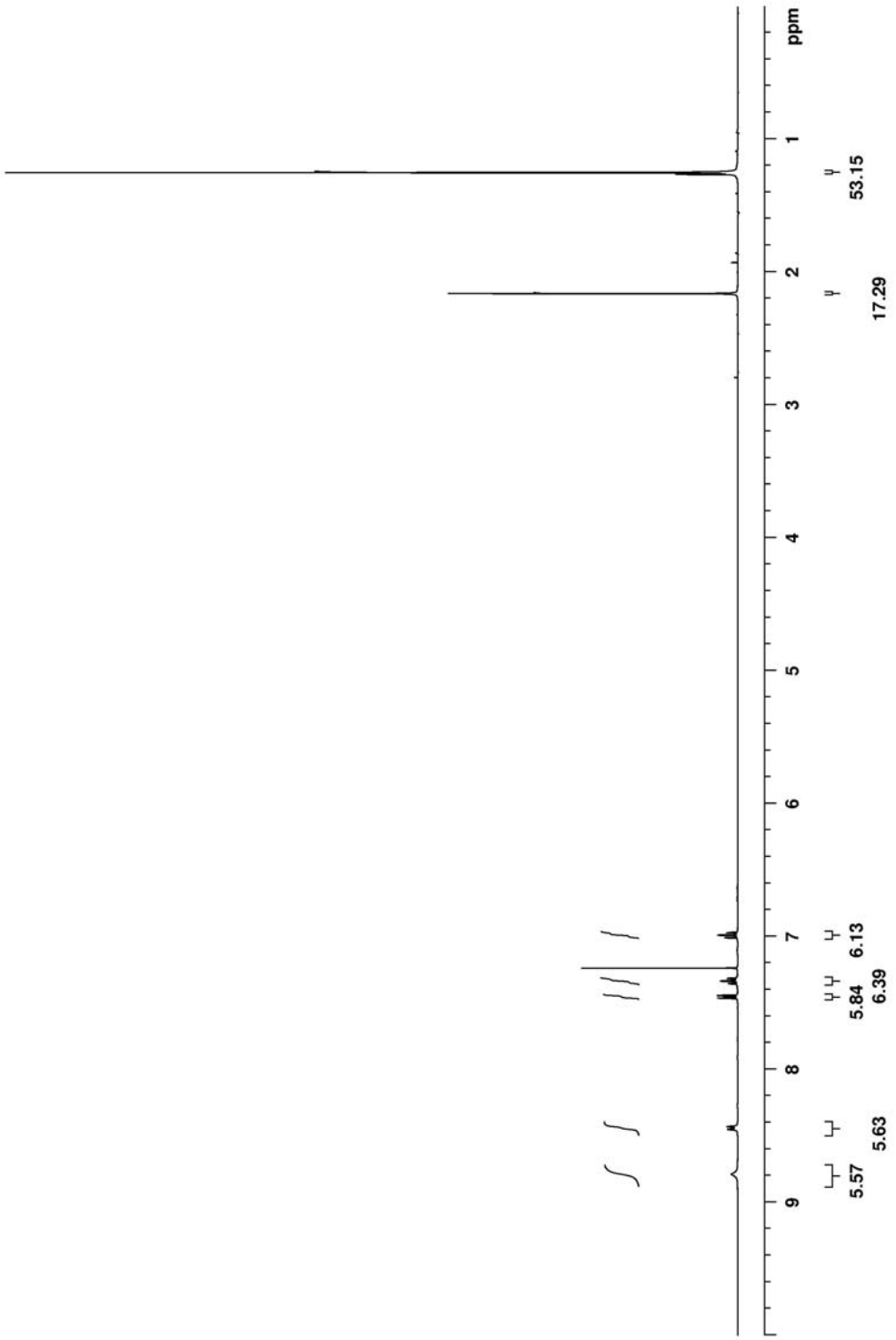
10,11-dihydro-10,12-dimethylindolo[3,2-*b*]-1,5-benzothiazepin-11-one (10) from 8b.

Method A (Thermal Cyclization): A solution of **8b** (0.3 g, 0.82 mmol) in chloroform (50 mL) was heated under reflux for 6 d. The solution was allowed to cool to room temperature and the solvent evaporated in vacuo to yield a brown solid. Column chromatography ($CHCl_3$: ether, 9:1) gave white solid (0.16 g, 67%): mp 196-198 ºC; IR 1624 cm^{-1}; ^1H NMR δ 7.73 (dt, J = 8.06, 0.93 Hz, 1H), 7.54 (dd, J = 7.75, 0.8 Hz), 7.26-7.34 (m, 4H), 7.17 (ddd, J = 8.11, 4.54, 1.12 Hz, 2H), 3.91 (s, 3H), 3.61 (s, 3H); ^{13}C NMR δ 163.4, 146.0, 138.2, 137.4, 132.3, 131.0, 128.9, 126.2, 125.8, 125.5, 125.0, 120.6, 120.2, 117.5, 110.1, 38.6, 31.6; MS [m/z (rel. intensity)] 294 [M^+, 100].

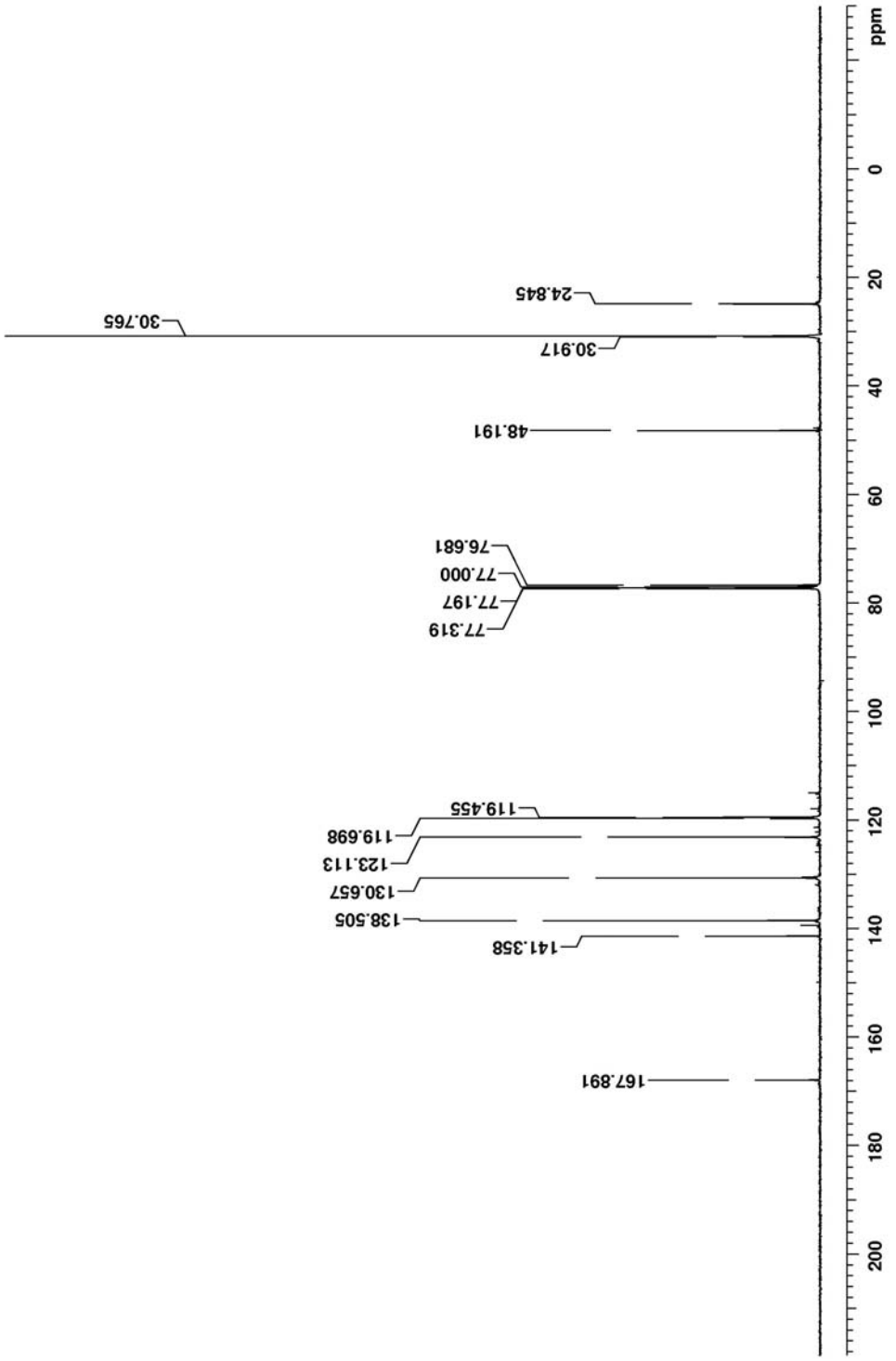
Method B (Electrophilic Activation): To a well-stirred solution of TFAA (0.64 g, 3.1 mmol, 3.75 eq.) in CH_2Cl_2 (20 mL) at 0 °C was added pyridine (0.25 g, 3.2 mmol, 4 eq.), neat via syringe. The reaction vessel was kept under a drying tube throughout the reaction. To the resulting yellow solution was added, a solution of **8b** (0.3 g, 0.82 mmol) in CH_2Cl_2 (15 mL) which was previously cooled to 0 °C. This was stirred at 0 °C for 15

min then at room temperature for 3 h. The solution was poured onto 10% Na_2CO_3 (25 mL) and stirred for 5 min. The layers were separated and the aqueous layer washed with CH_2Cl_2 (30 mL). The combined organics were washed with 5% aqueous solution of HCl (3 X 40 mL), 10% aqueous solution of Na_2CO_3 (1 X 40 mL), H_2O and dried over sodium sulfate. The solvent was removed in vacuo to yield pure yellow solid, **10** (0.23 g, 100%).

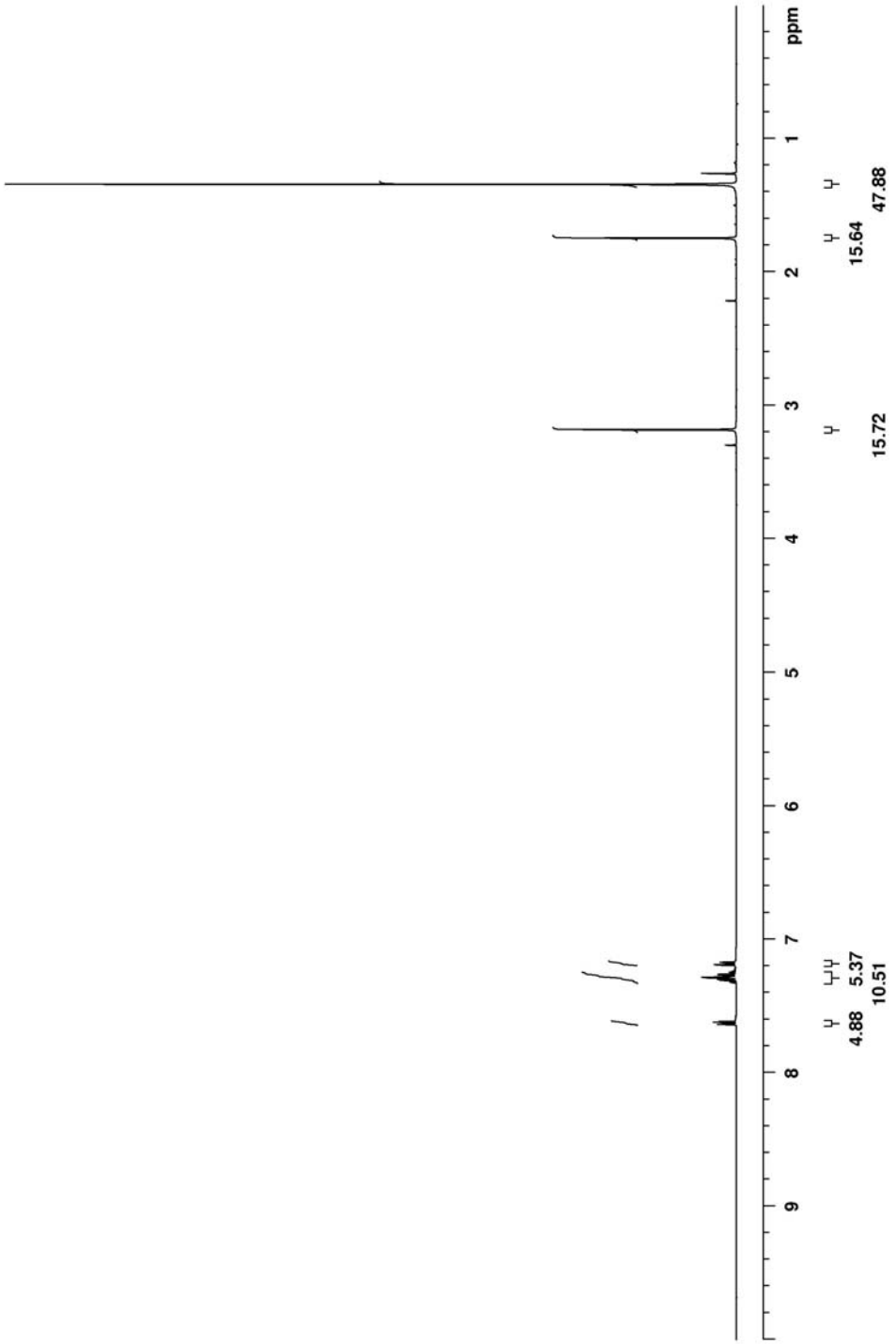
^{1}H NMR Spectrum of ***N*-[2-(*tert*-butylthio)phenyl]acetamide**



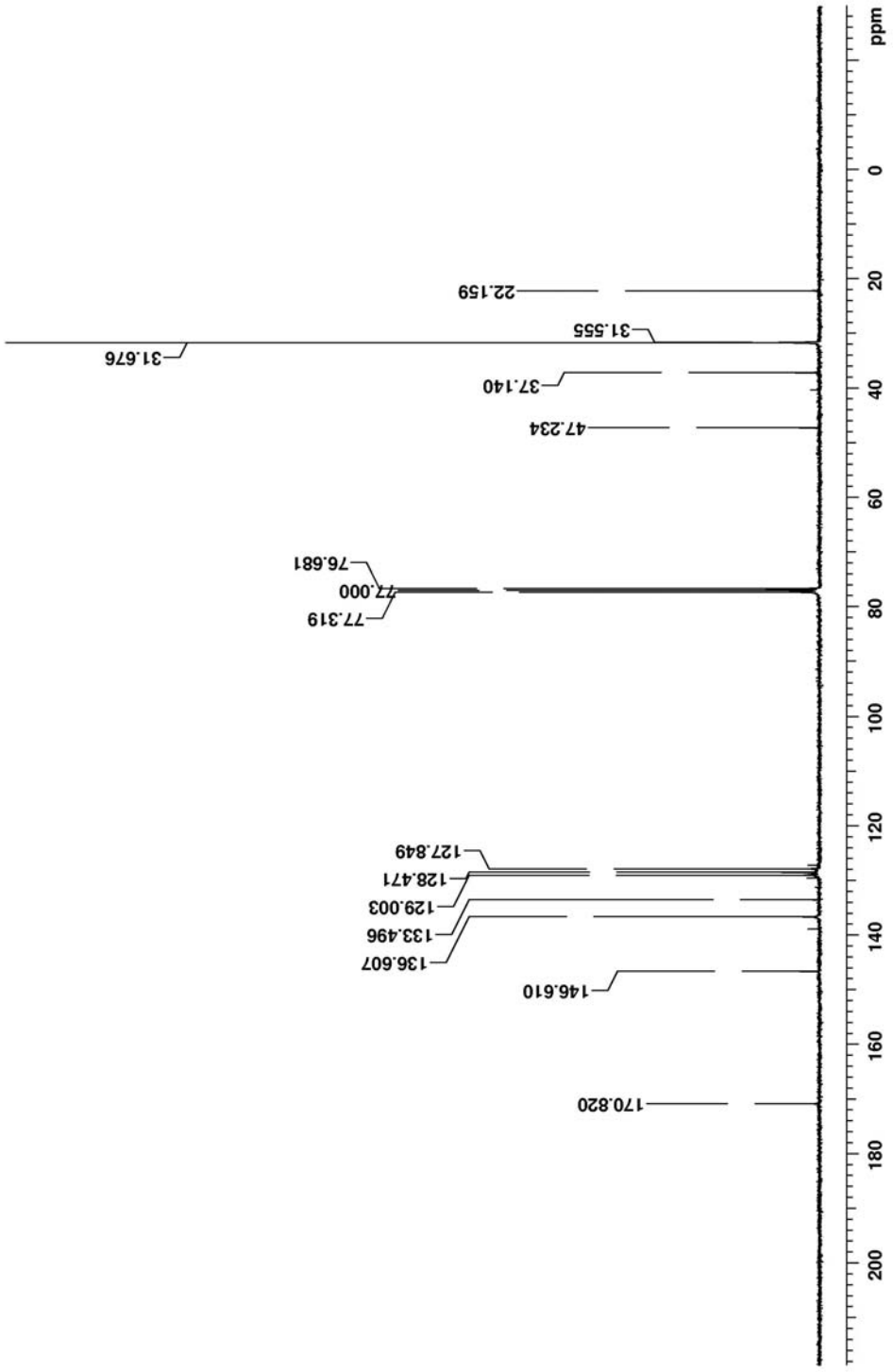
^{13}C NMR Spectrum of ***N*-[2-(*tert*-butylthio)phenyl]acetamide**



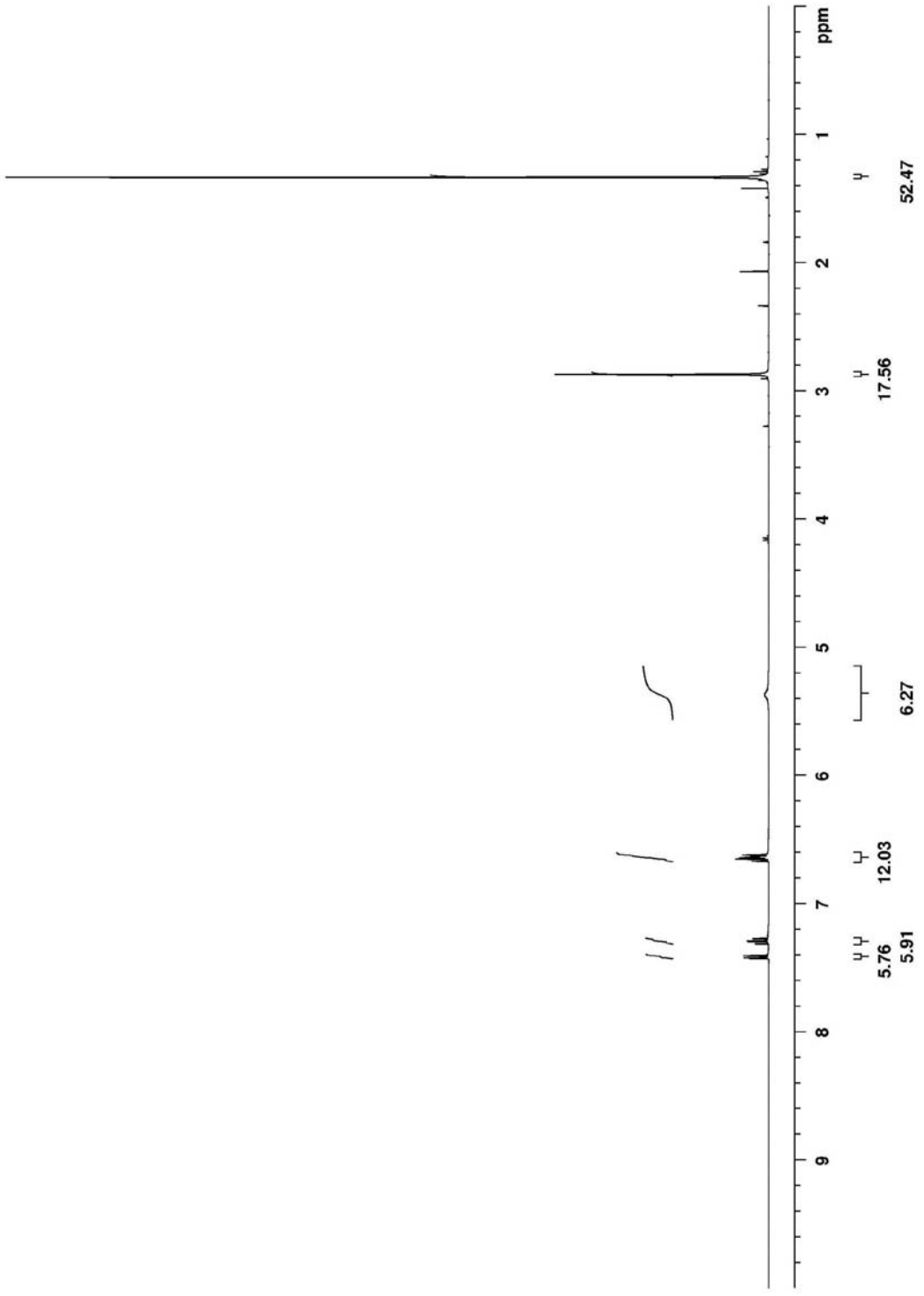
^{1}H NMR Spectrum of ***N*-[2-(*tert*-butylthio)phenyl]-*N*-methylamide**



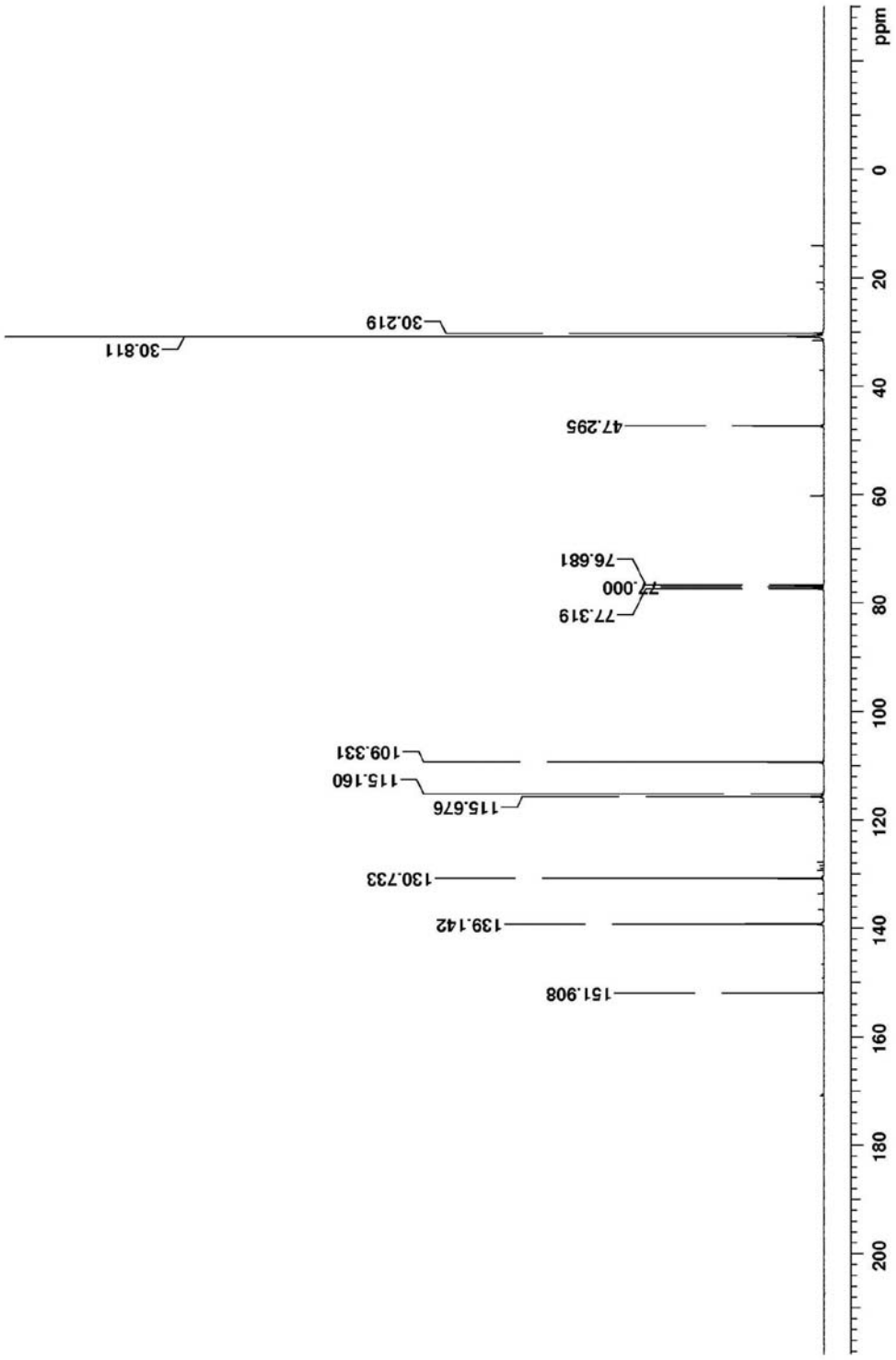
^{13}C NMR Spectrum of ***N*-[2-(*tert*-butylthio)phenyl]-*N*-methylamide**



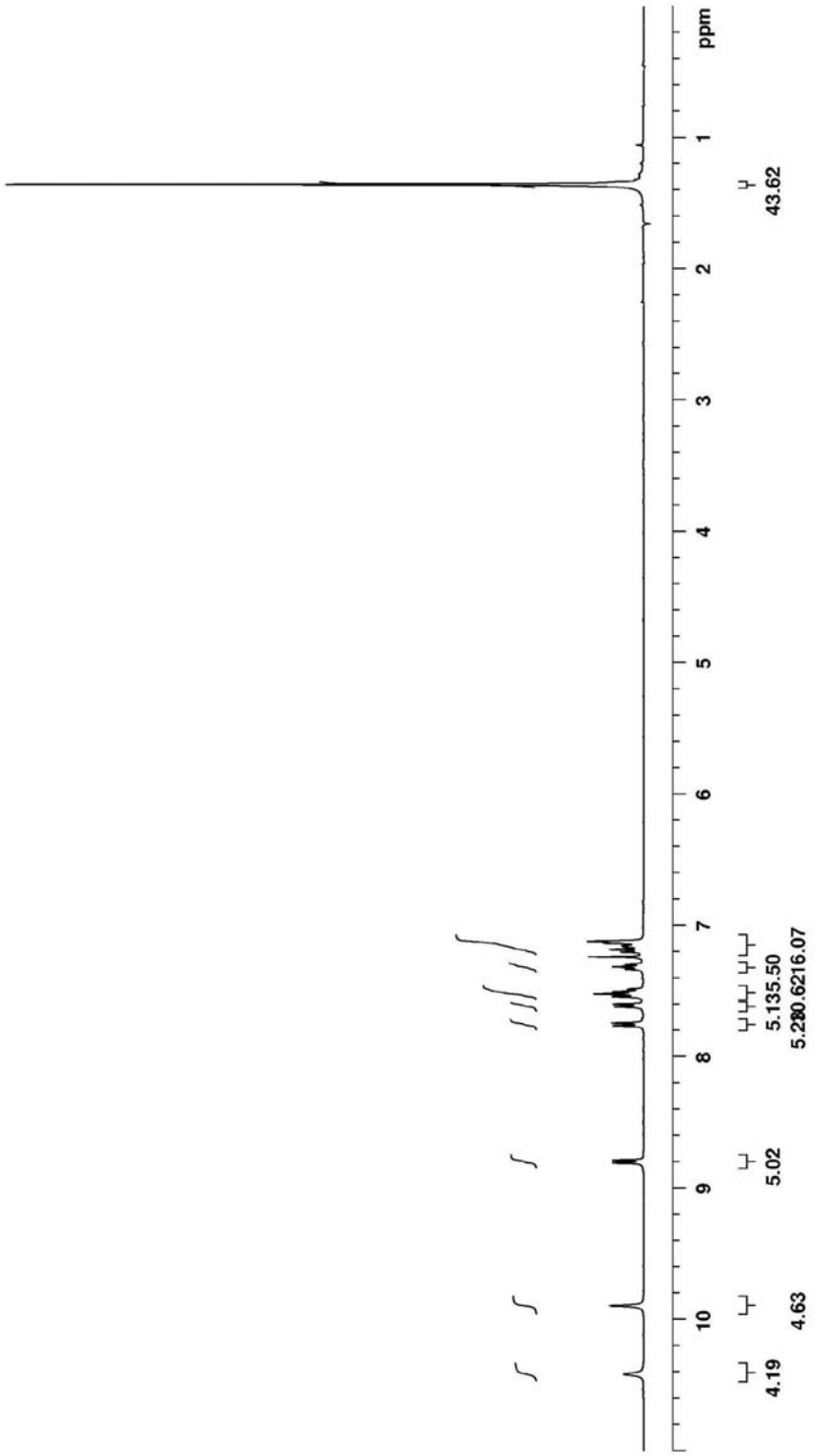
^{1}H NMR Spectrum of ***N*-[2-(*tert*-butylthio)phenyl]-*N*-methylamine**



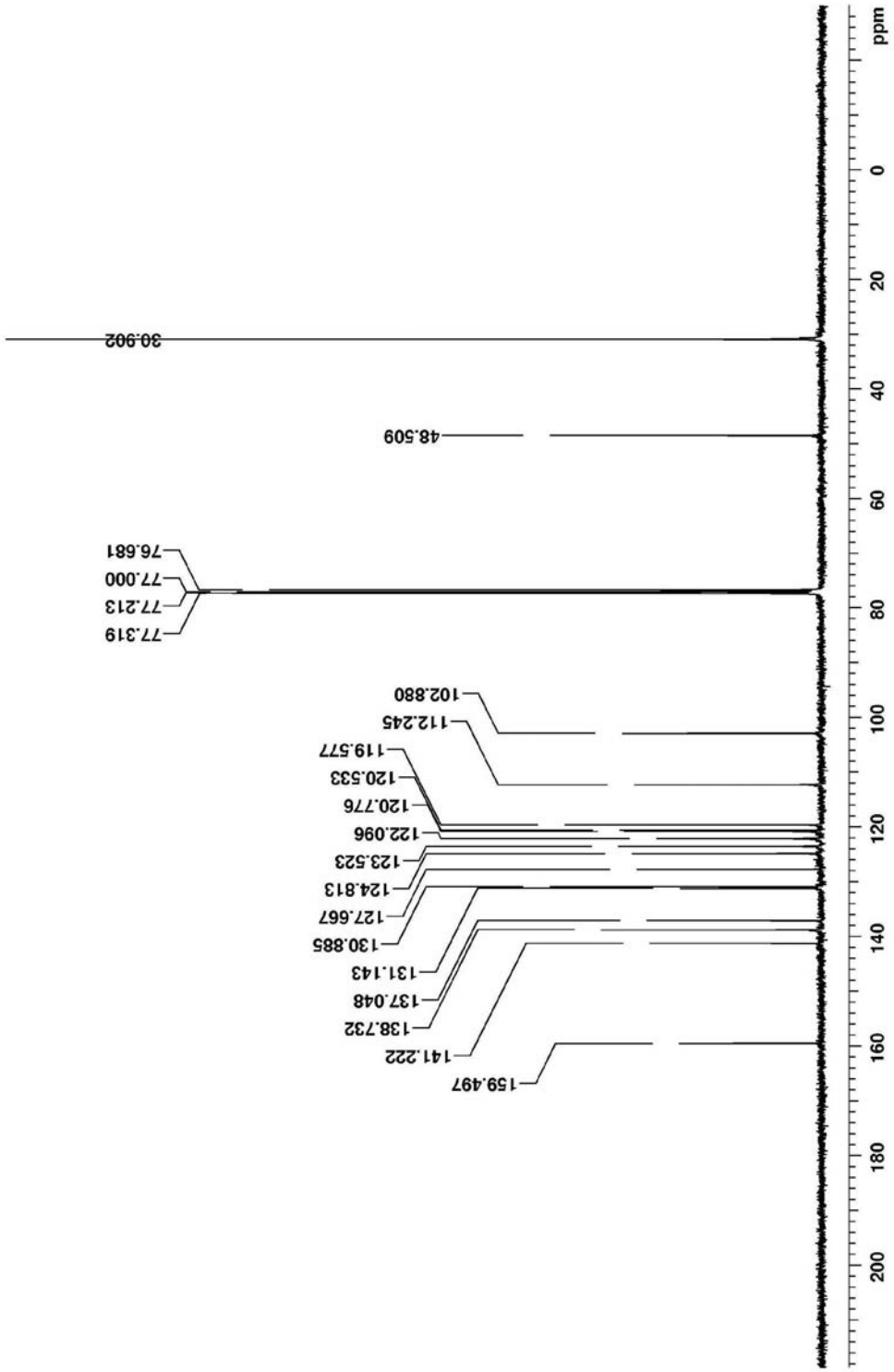
^{13}C NMR Spectrum of ***N*-[2-(*tert*-butylthio)phenyl]-*N*-methylamine**



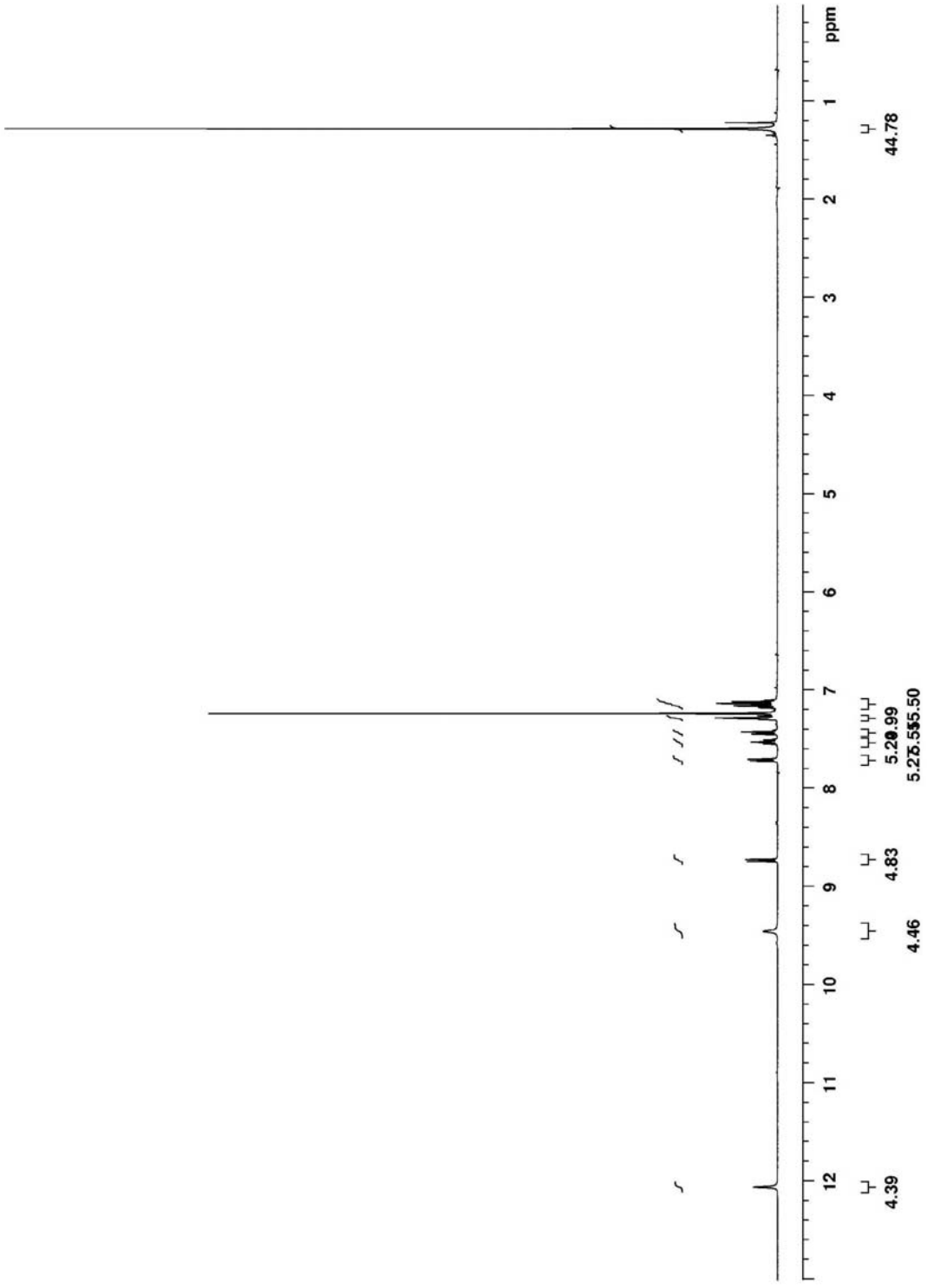
^{1}H NMR Spectrum of **1b**



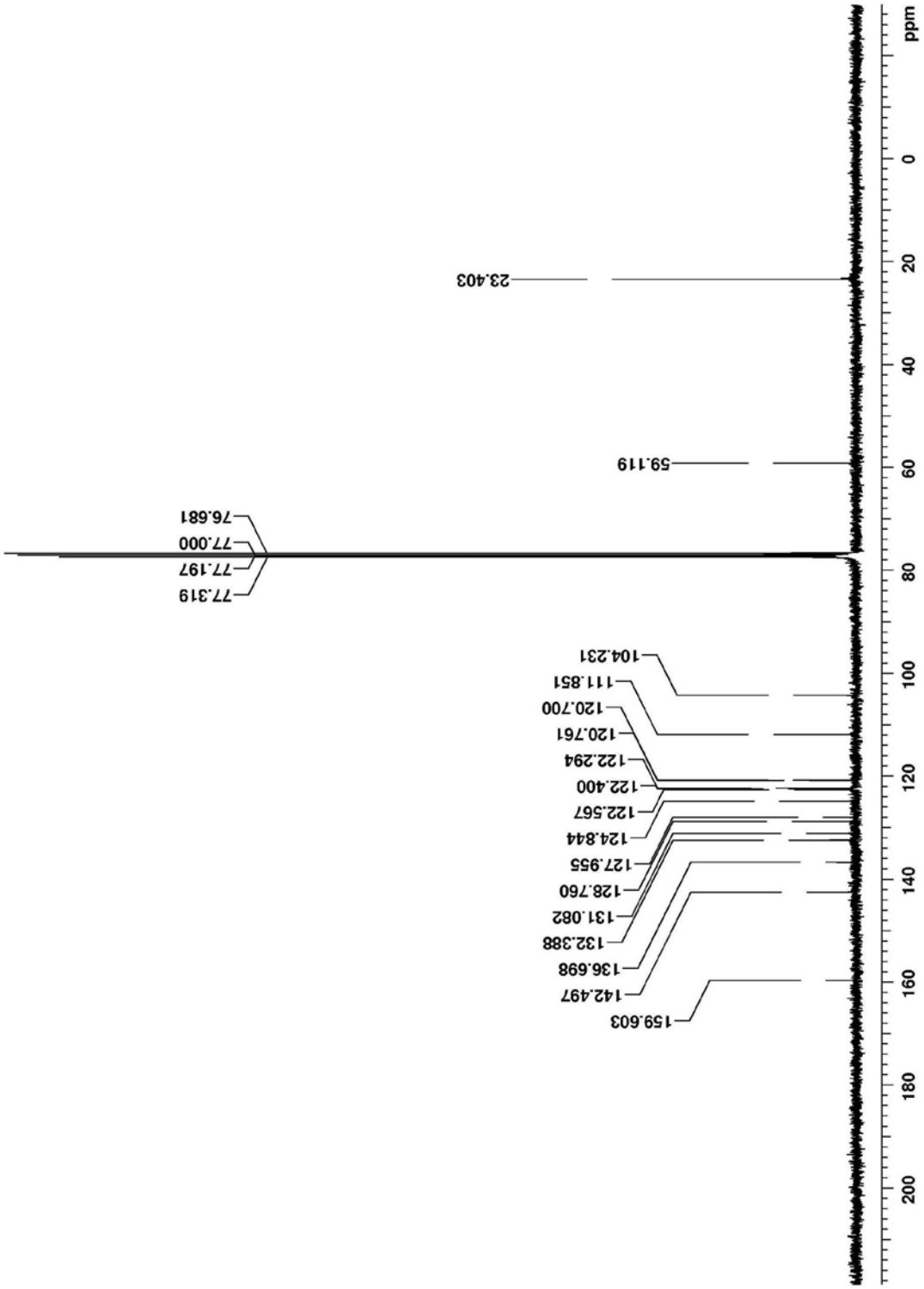
^{13}C NMR Spectrum of **1b**



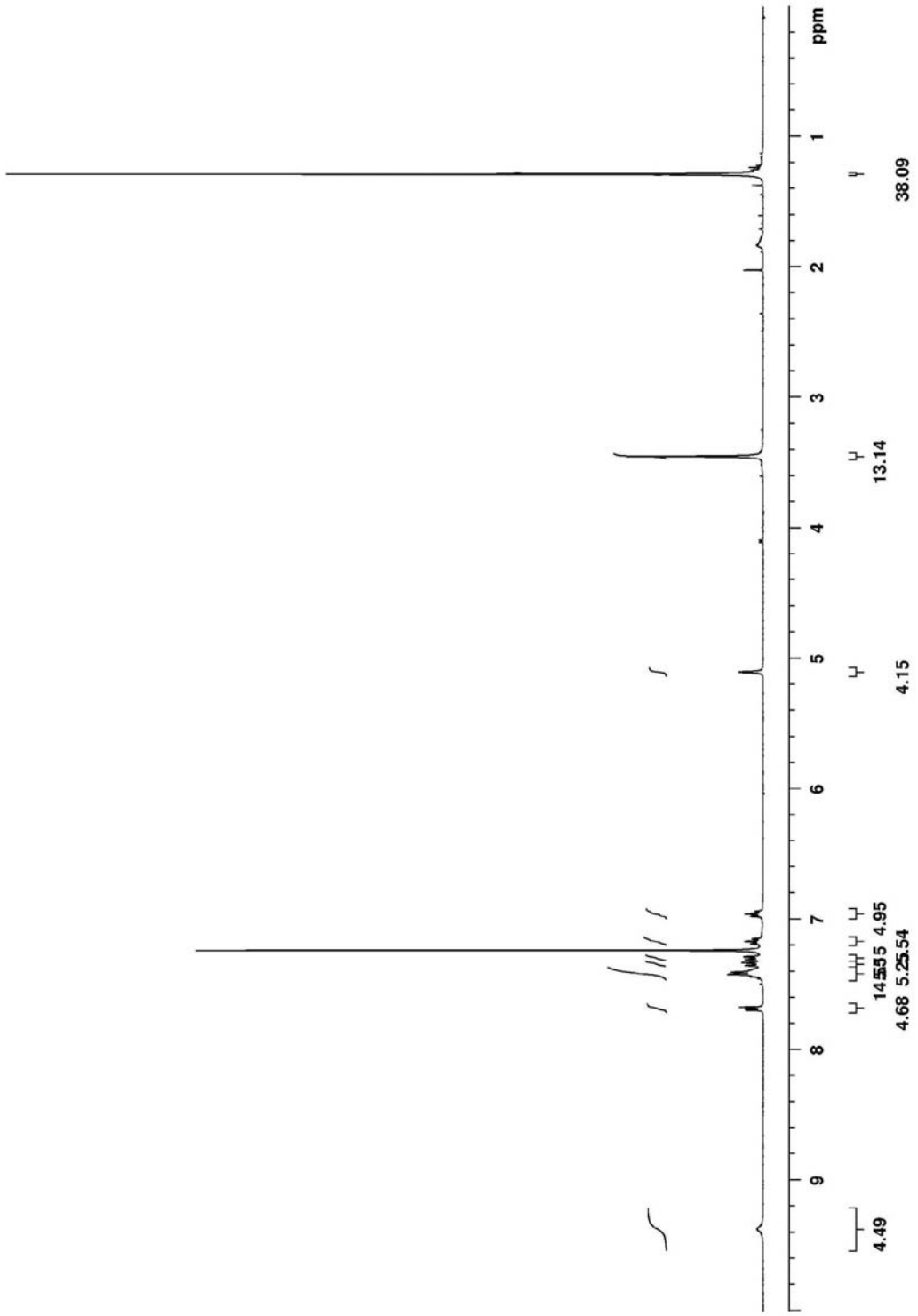
^{1}H NMR Spectrum of **2b**



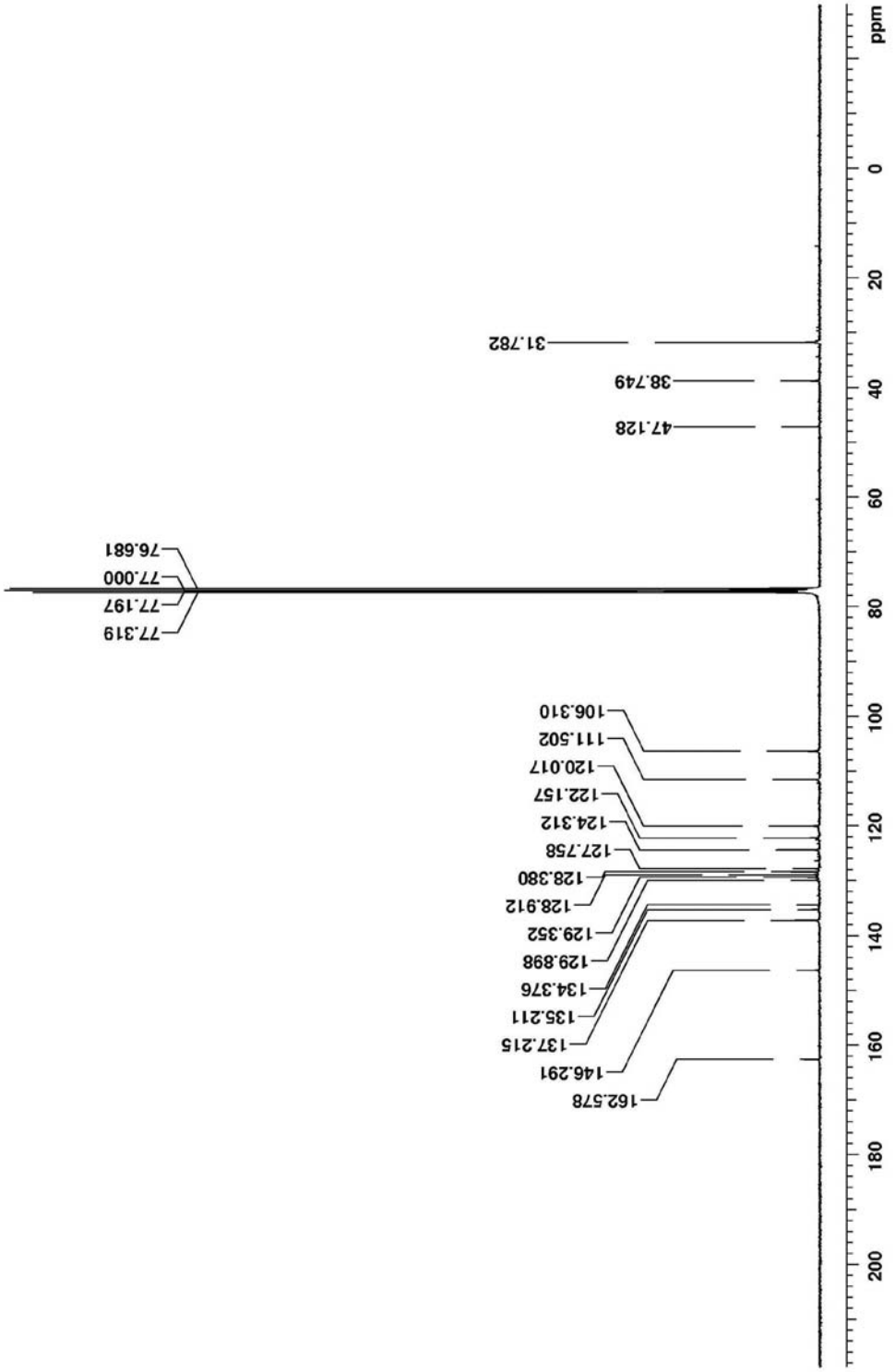
^{13}C NMR Spectrum of **2b**



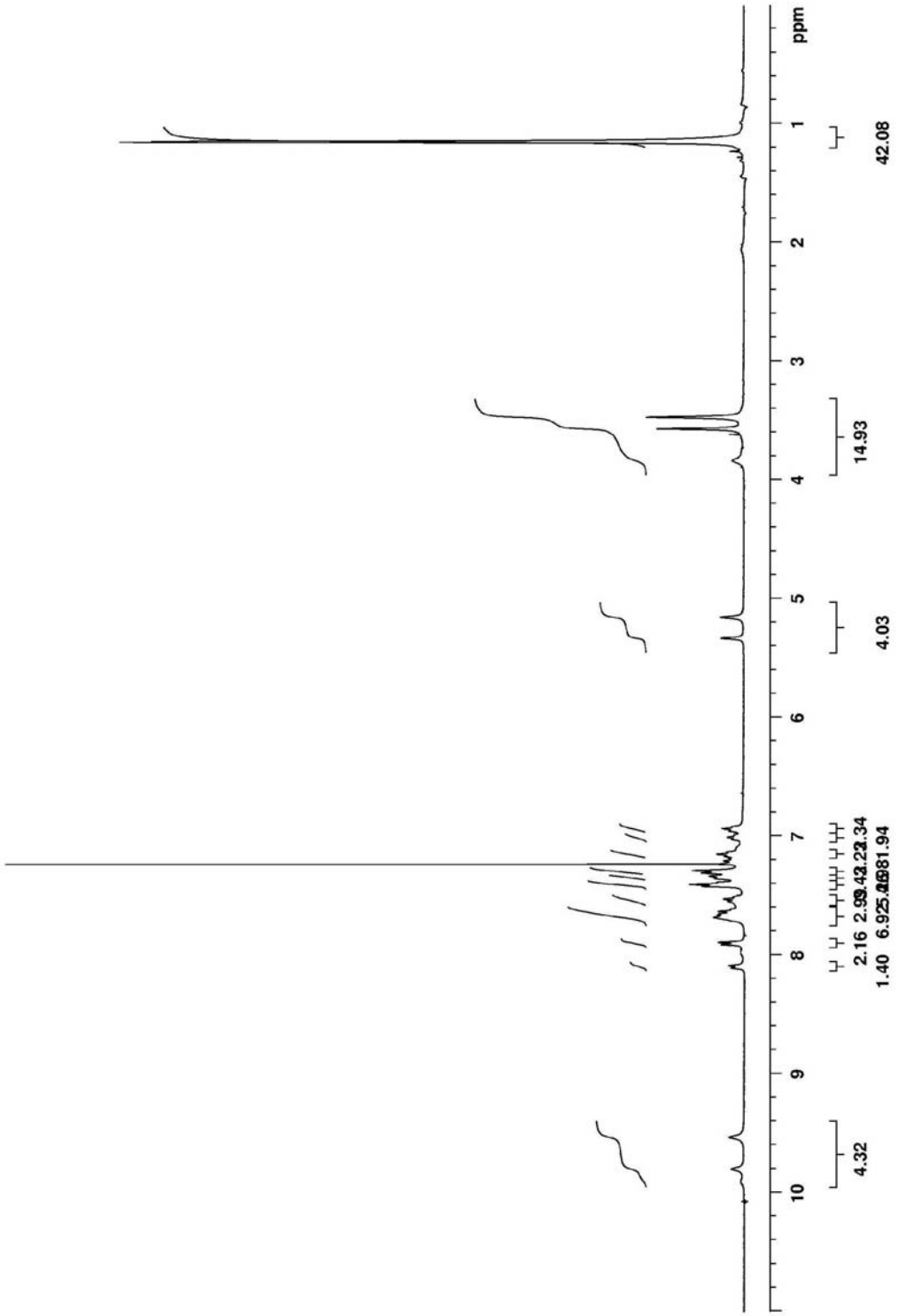
^{1}H NMR Spectrum of **3b**



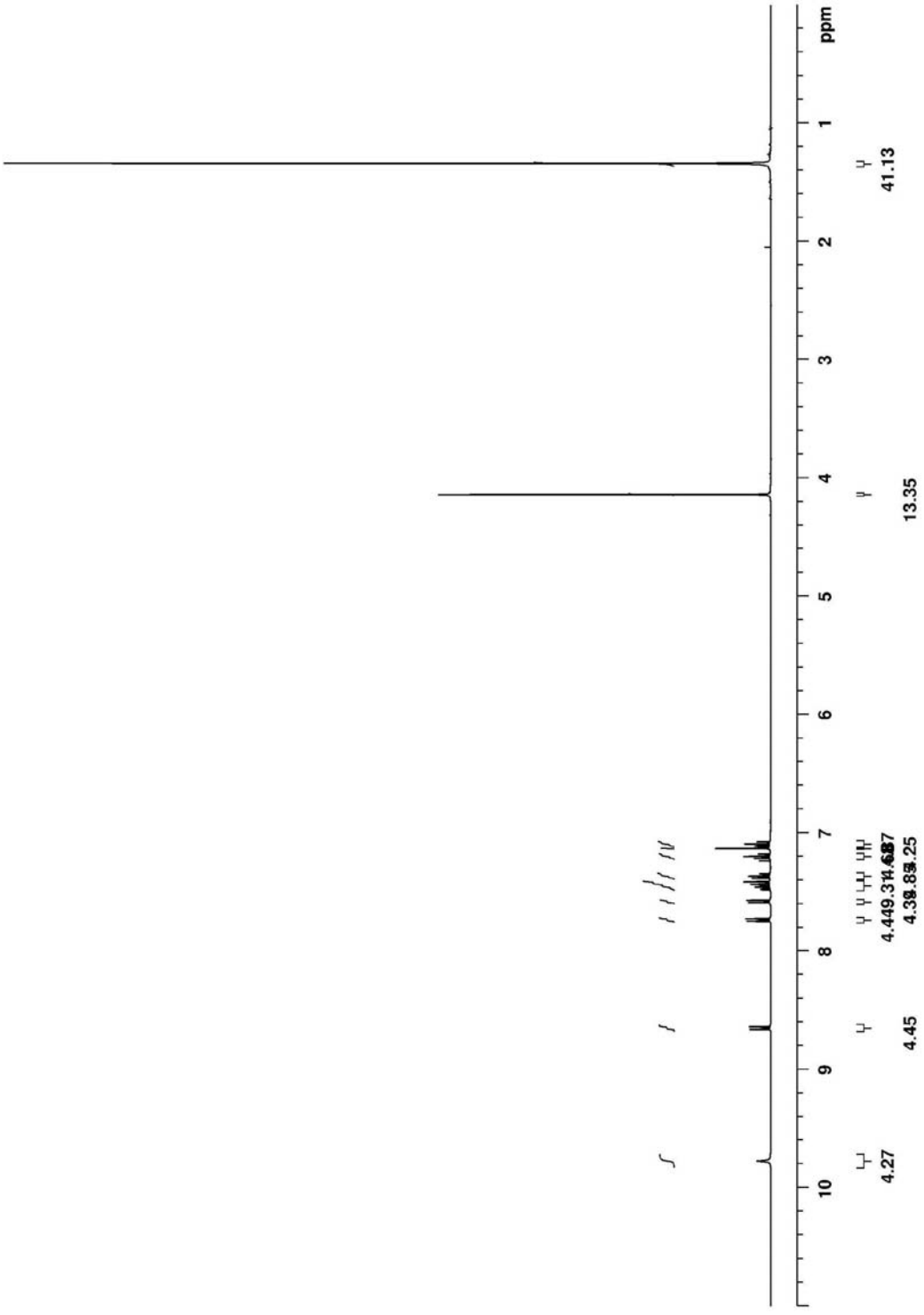
^{13}C NMR Spectrum of **3b**



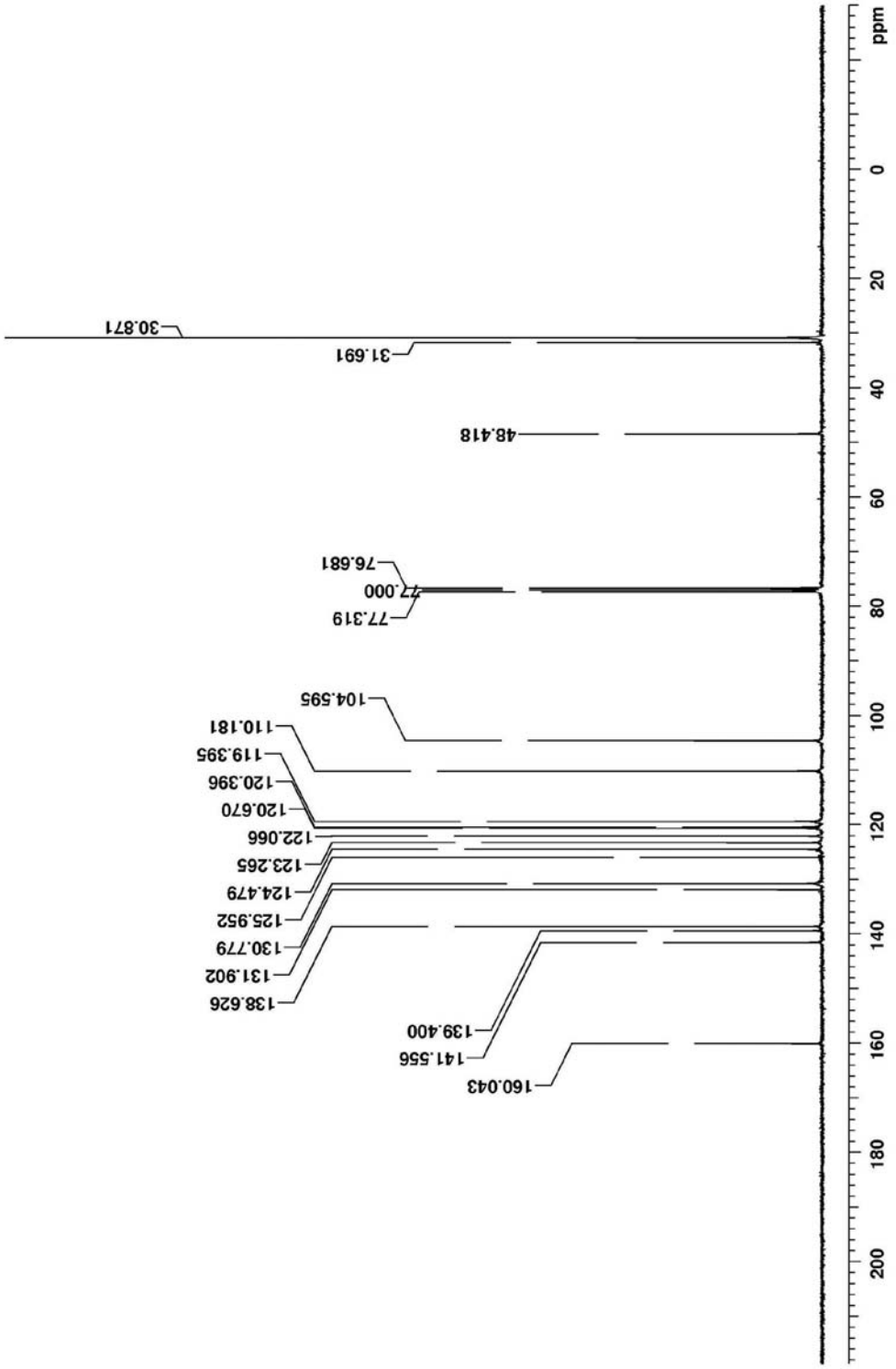
^{1}H NMR Spectrum of **4b**



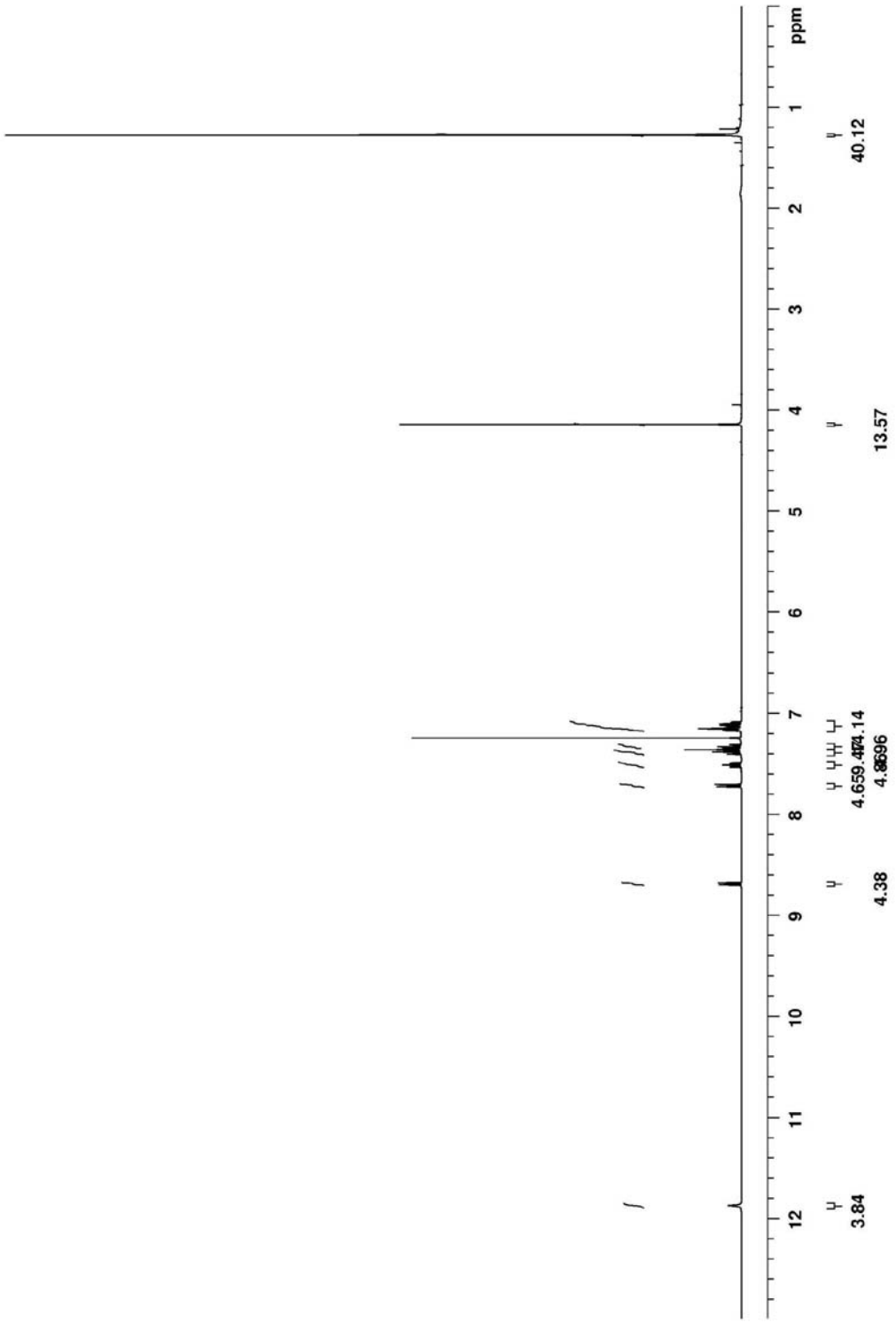
^{1}H NMR Spectrum of **5b**



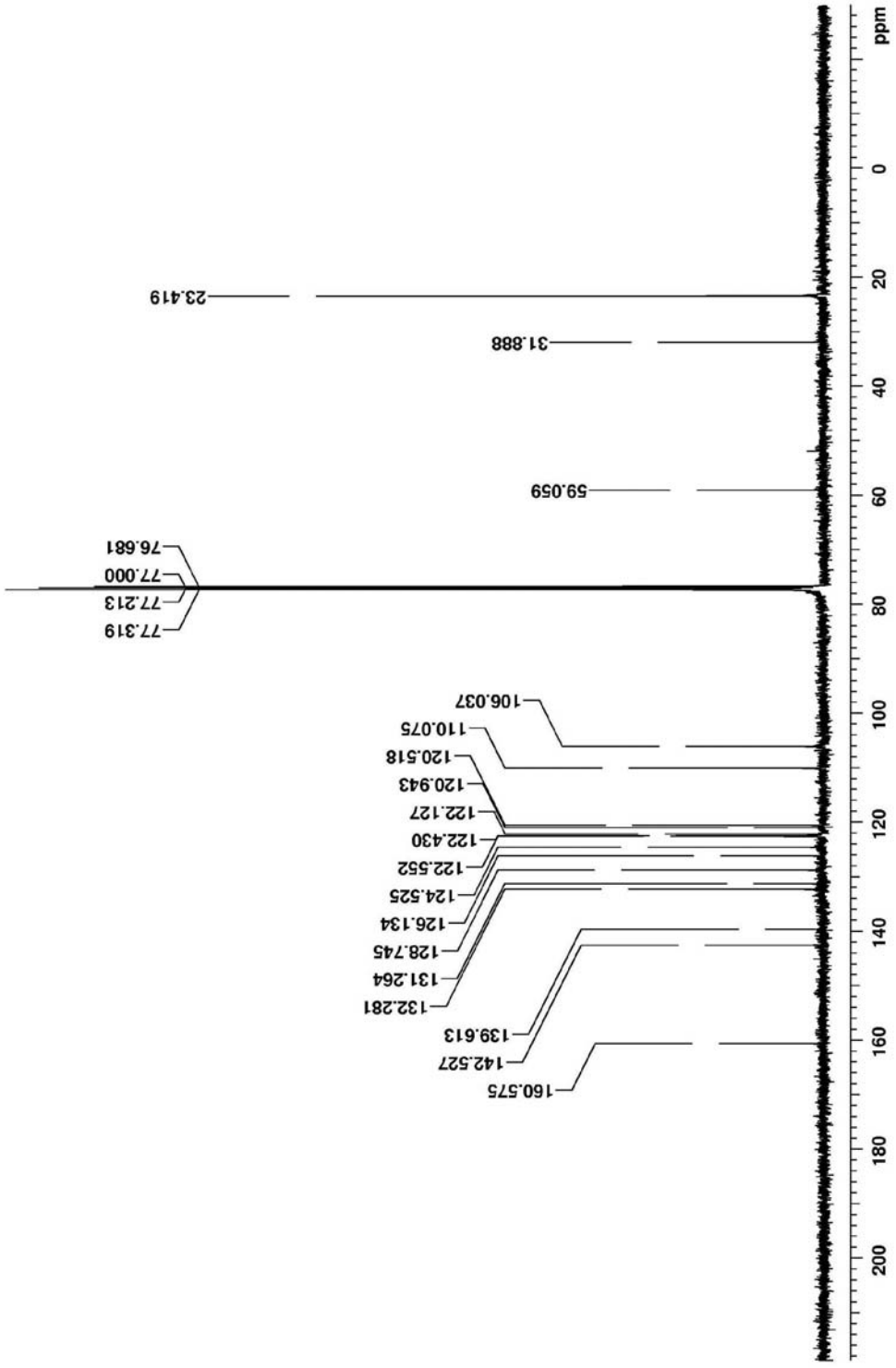
^{13}C NMR Spectrum of **5b**



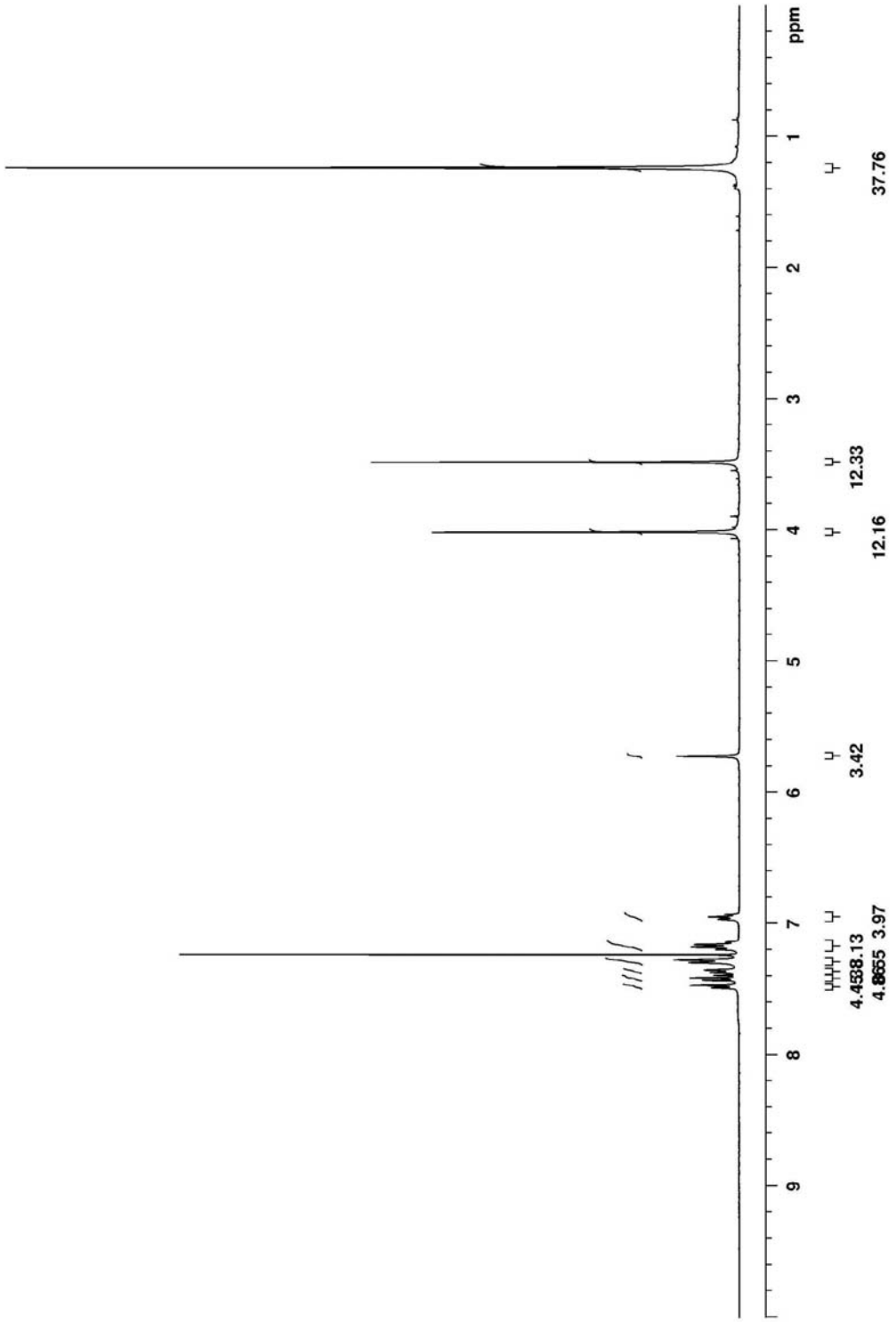
^{1}H NMR Spectrum of **6b**



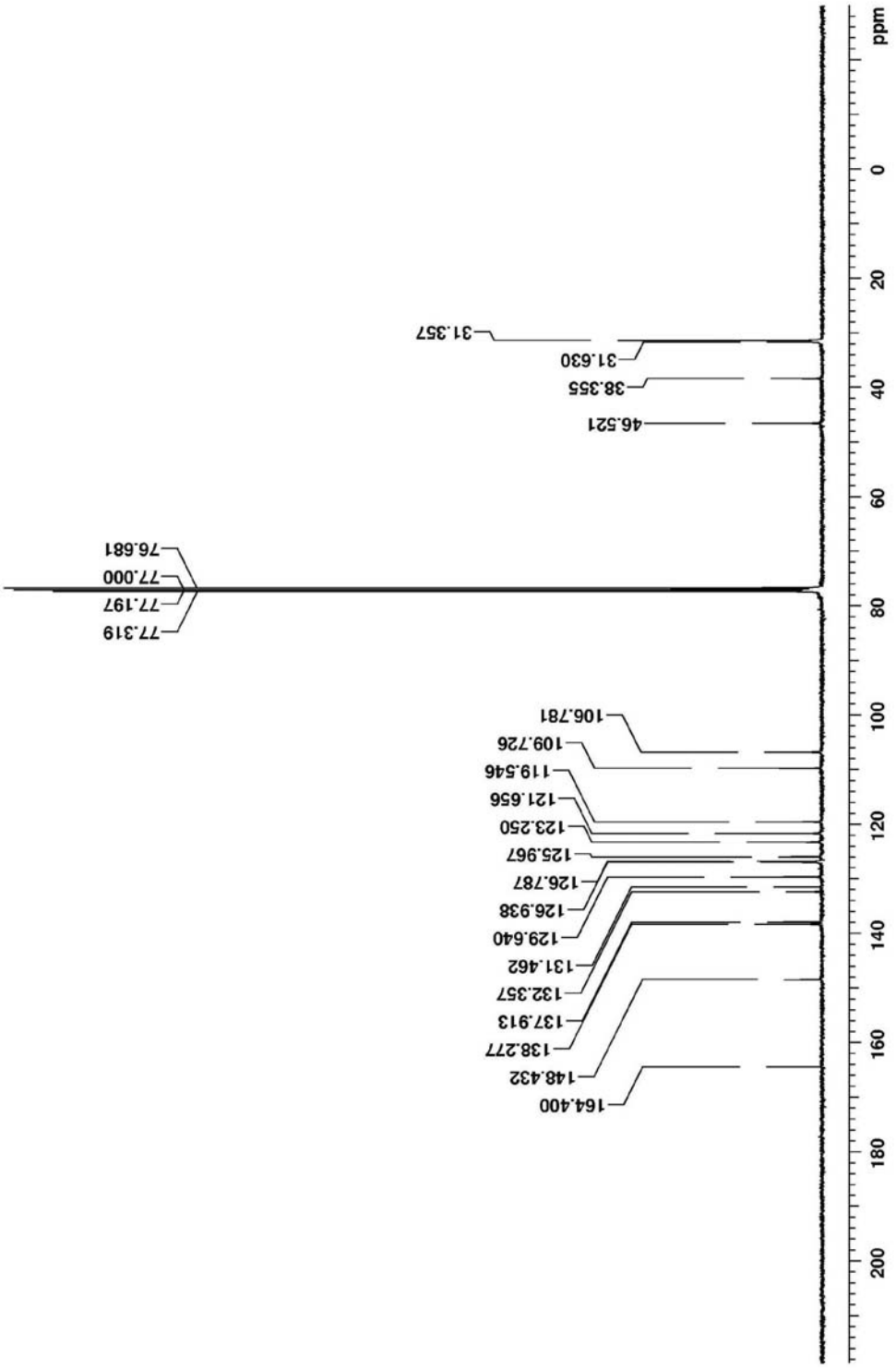
^{13}C NMR Spectrum of **6b**



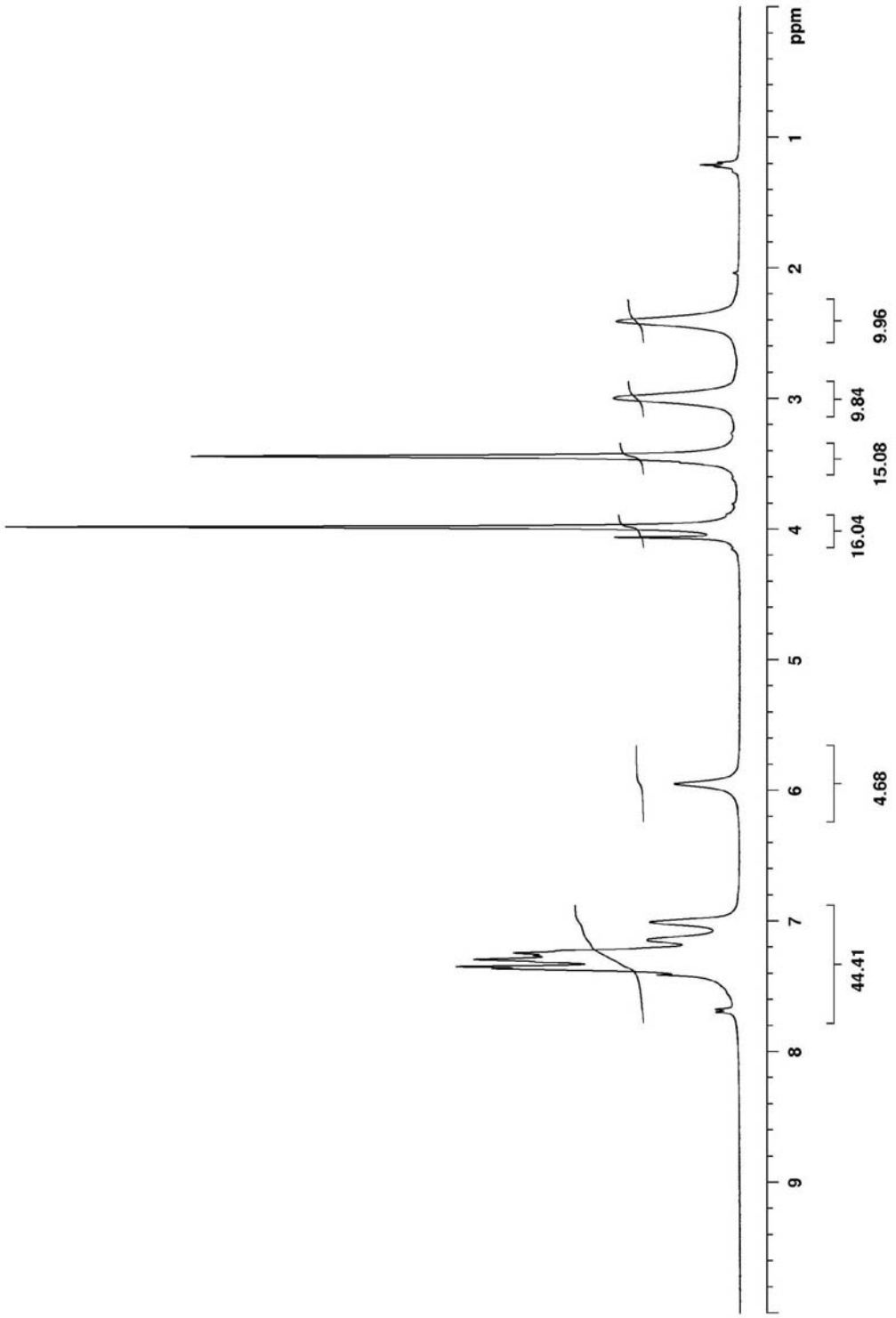
^{1}H NMR Spectrum of **7b**



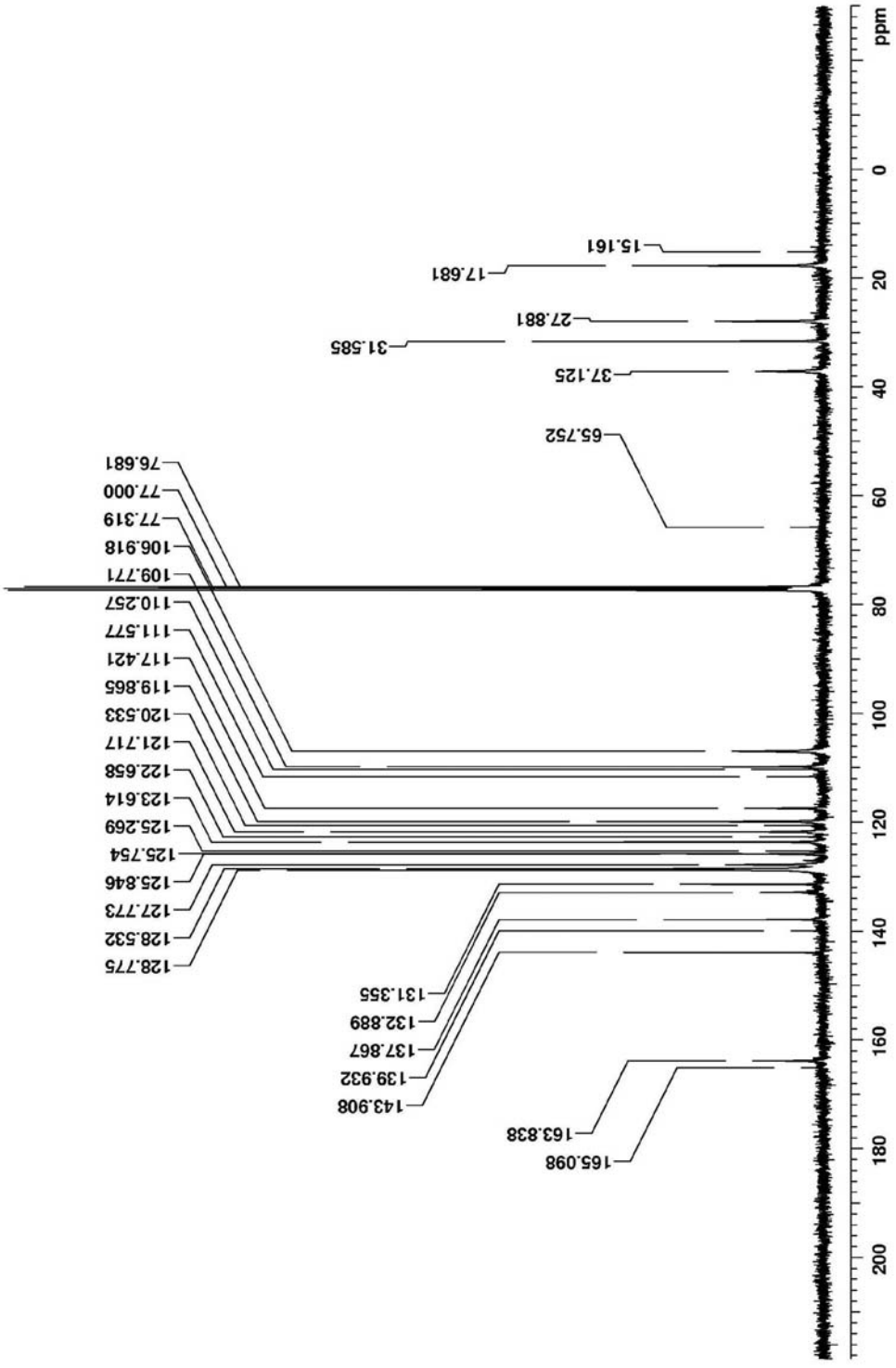
^{13}C NMR Spectrum of **7b**



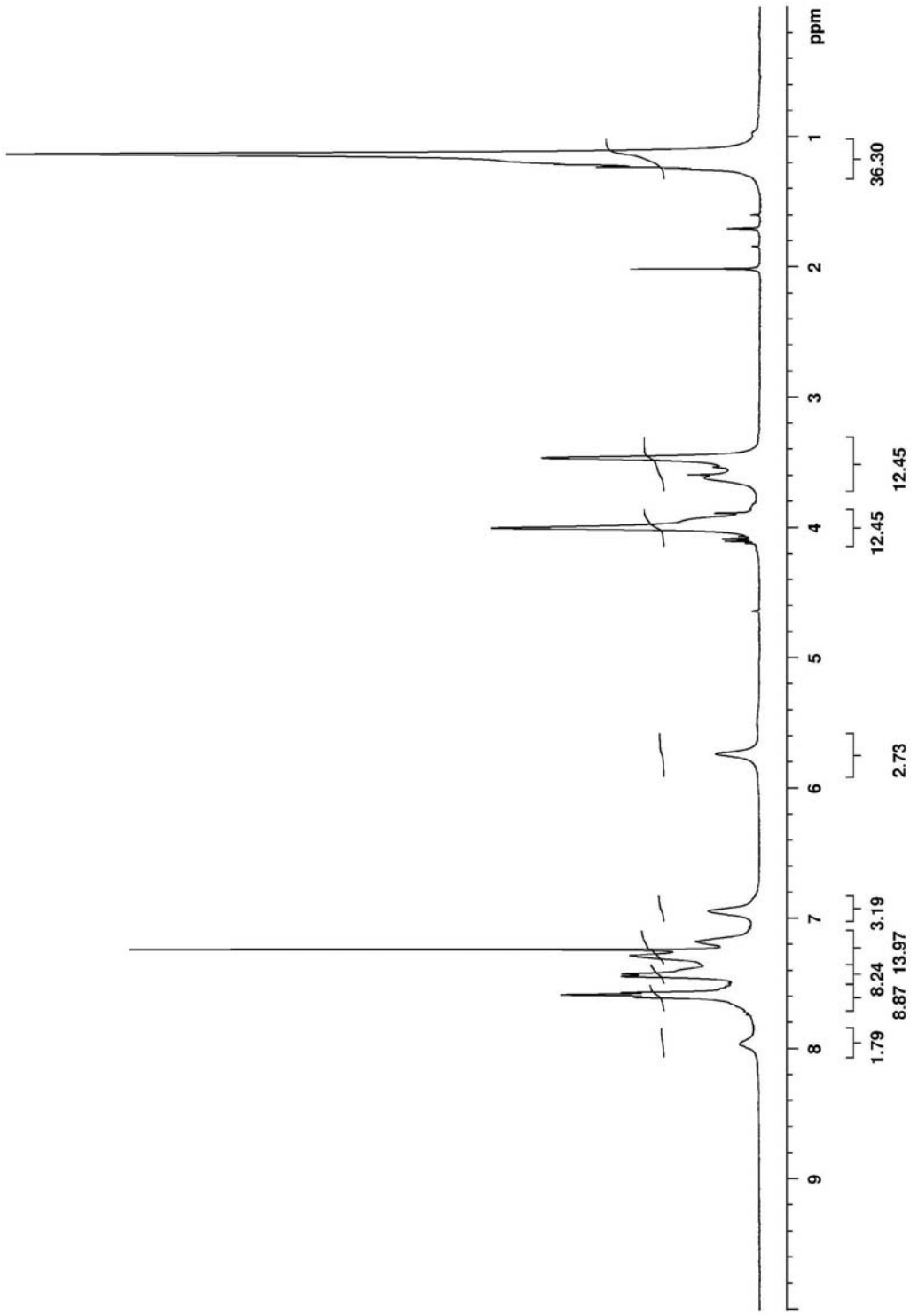
^{1}H NMR Spectrum of **7c**



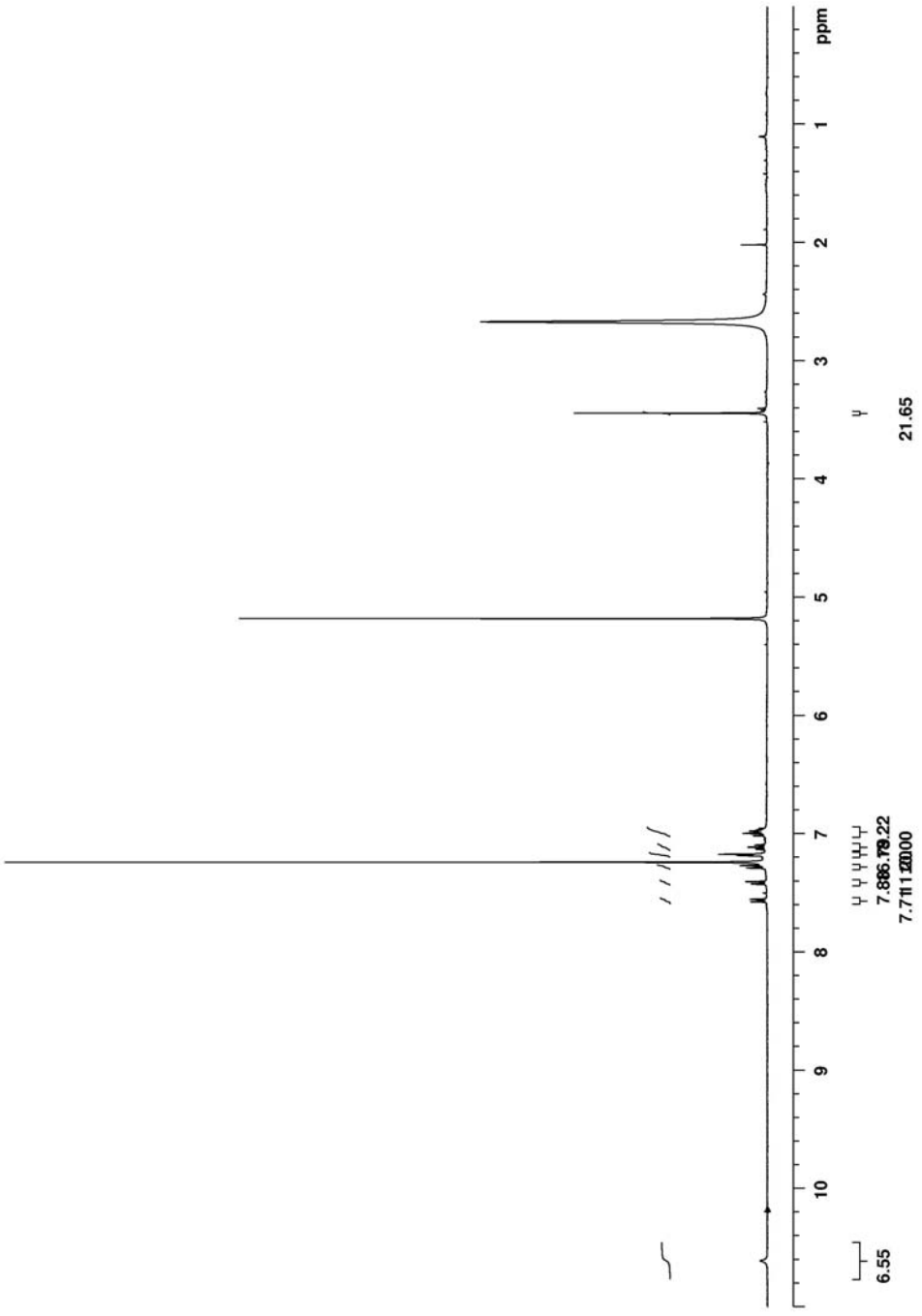
^{13}C NMR Spectrum of **7c**



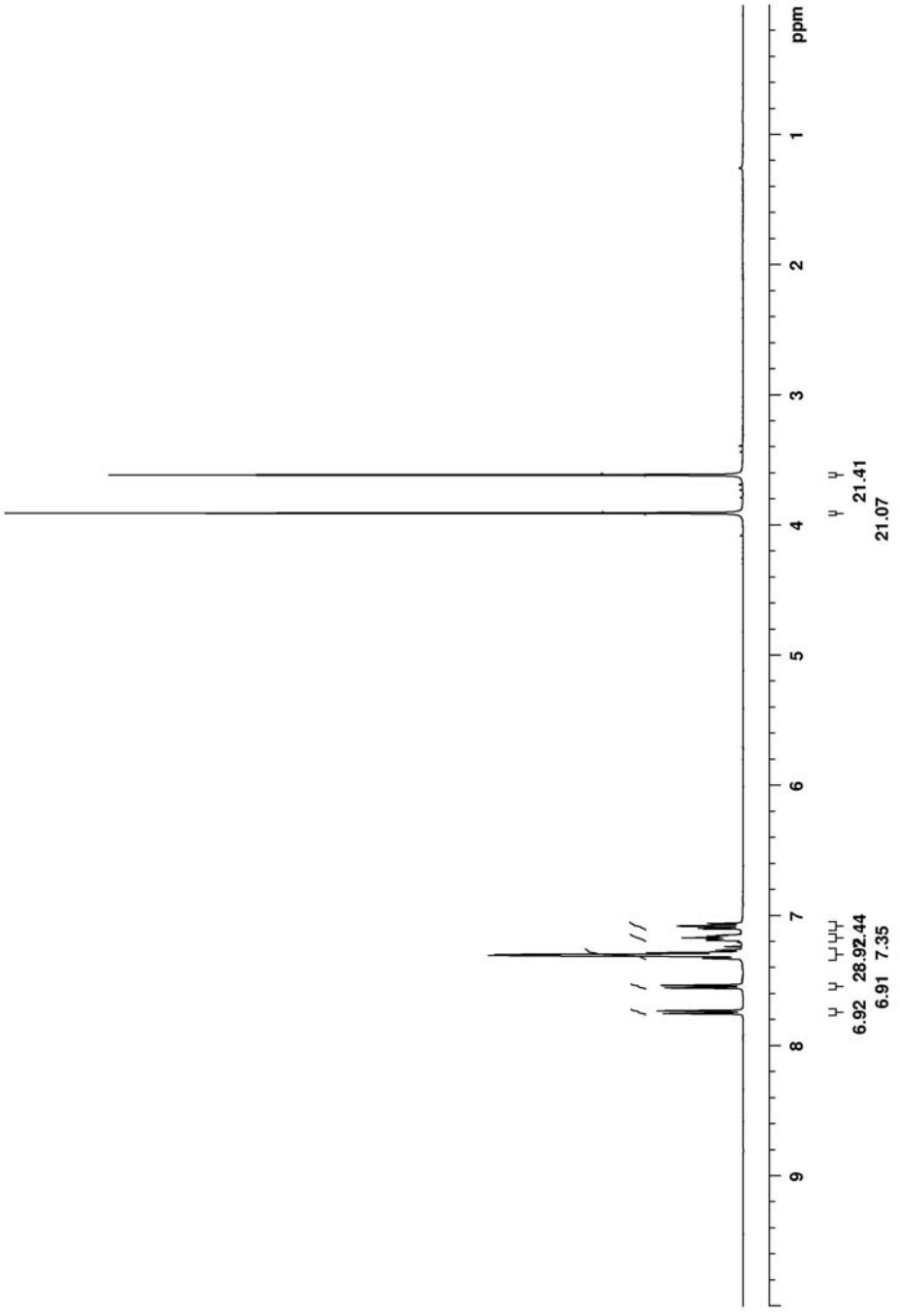
^{1}H NMR Spectrum of **8b**



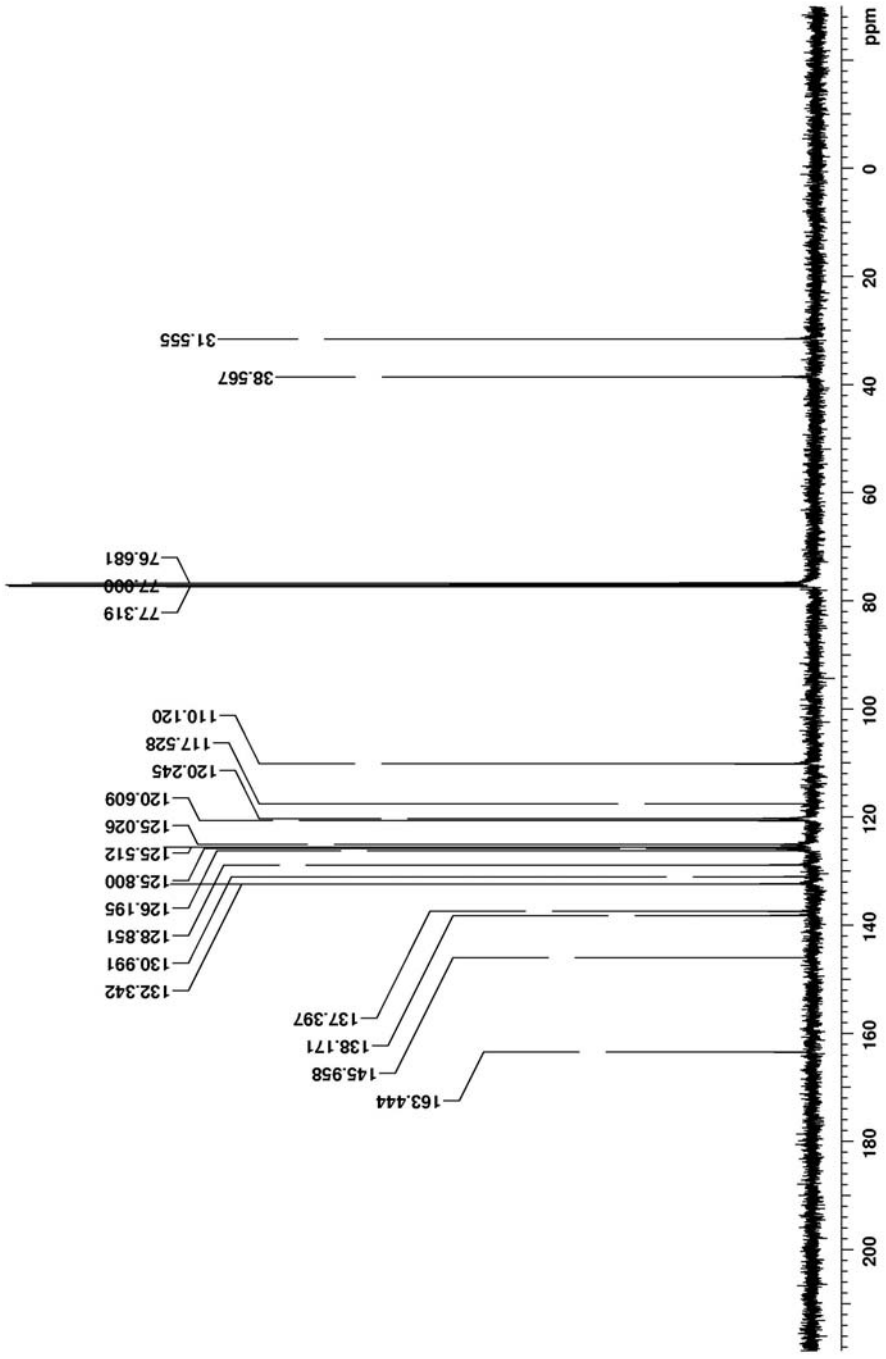
^{1}H NMR Spectrum of **9**



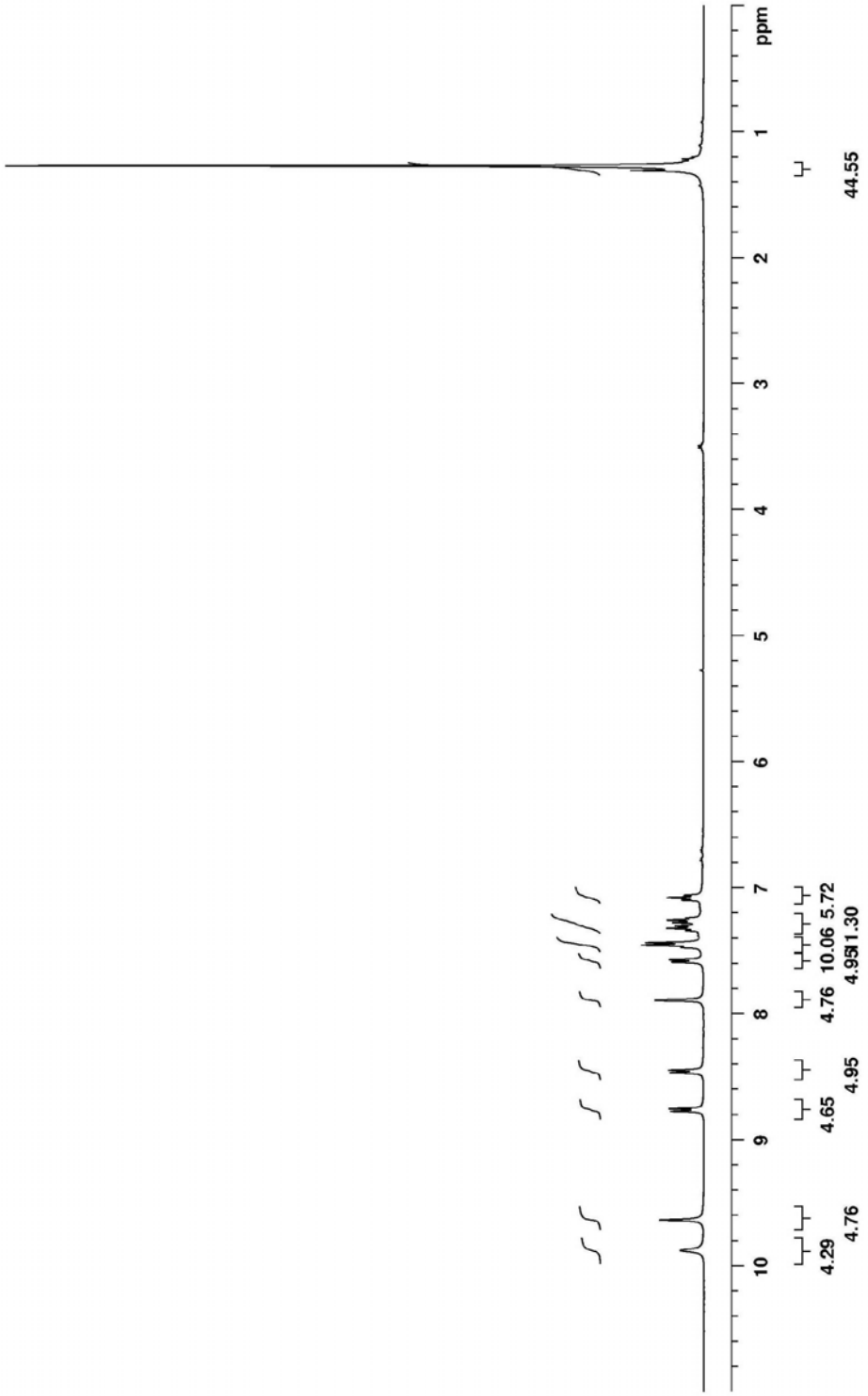
^{1}H NMR Spectrum of **10**



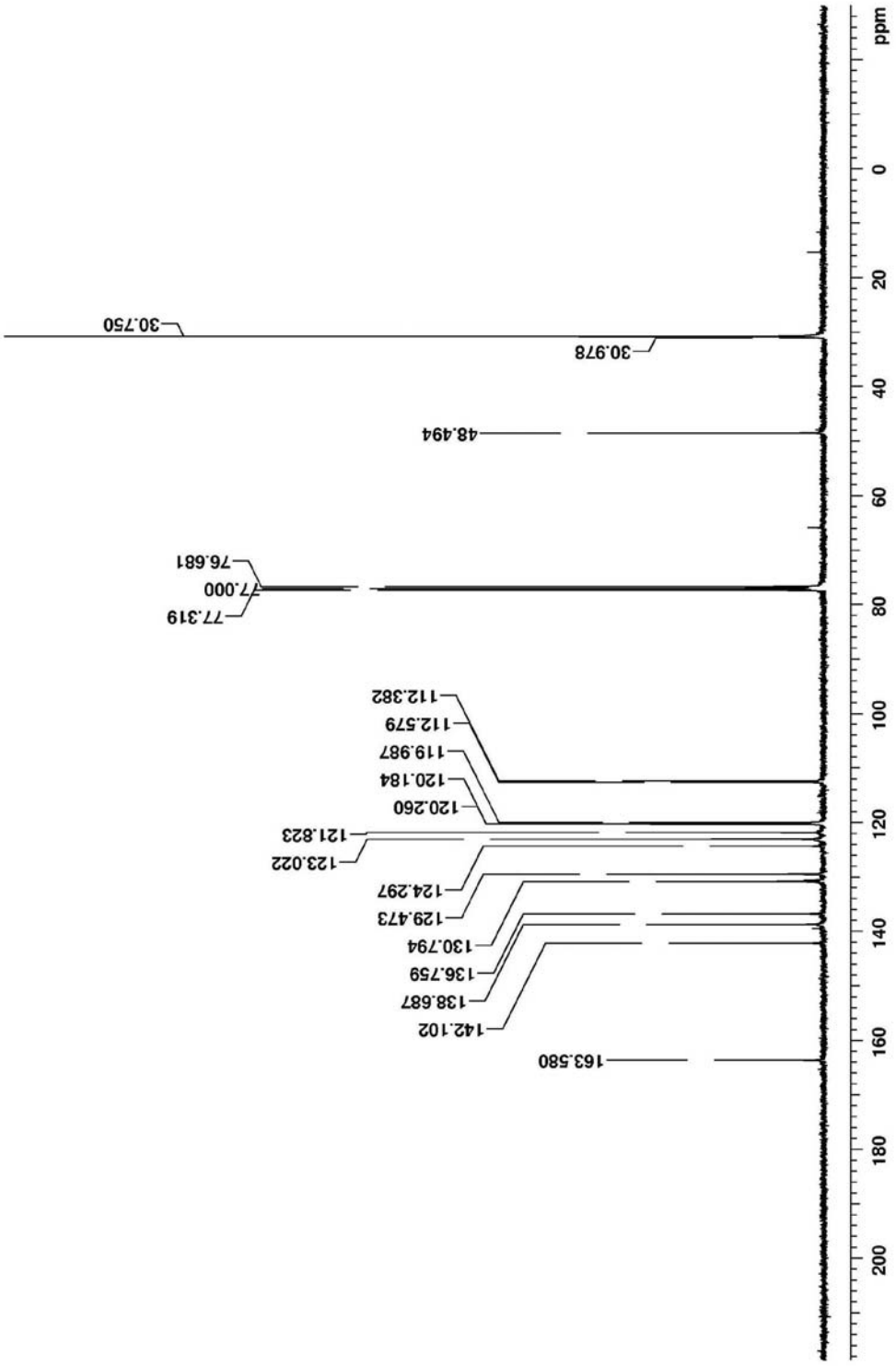
^{13}C NMR Spectrum of **10**



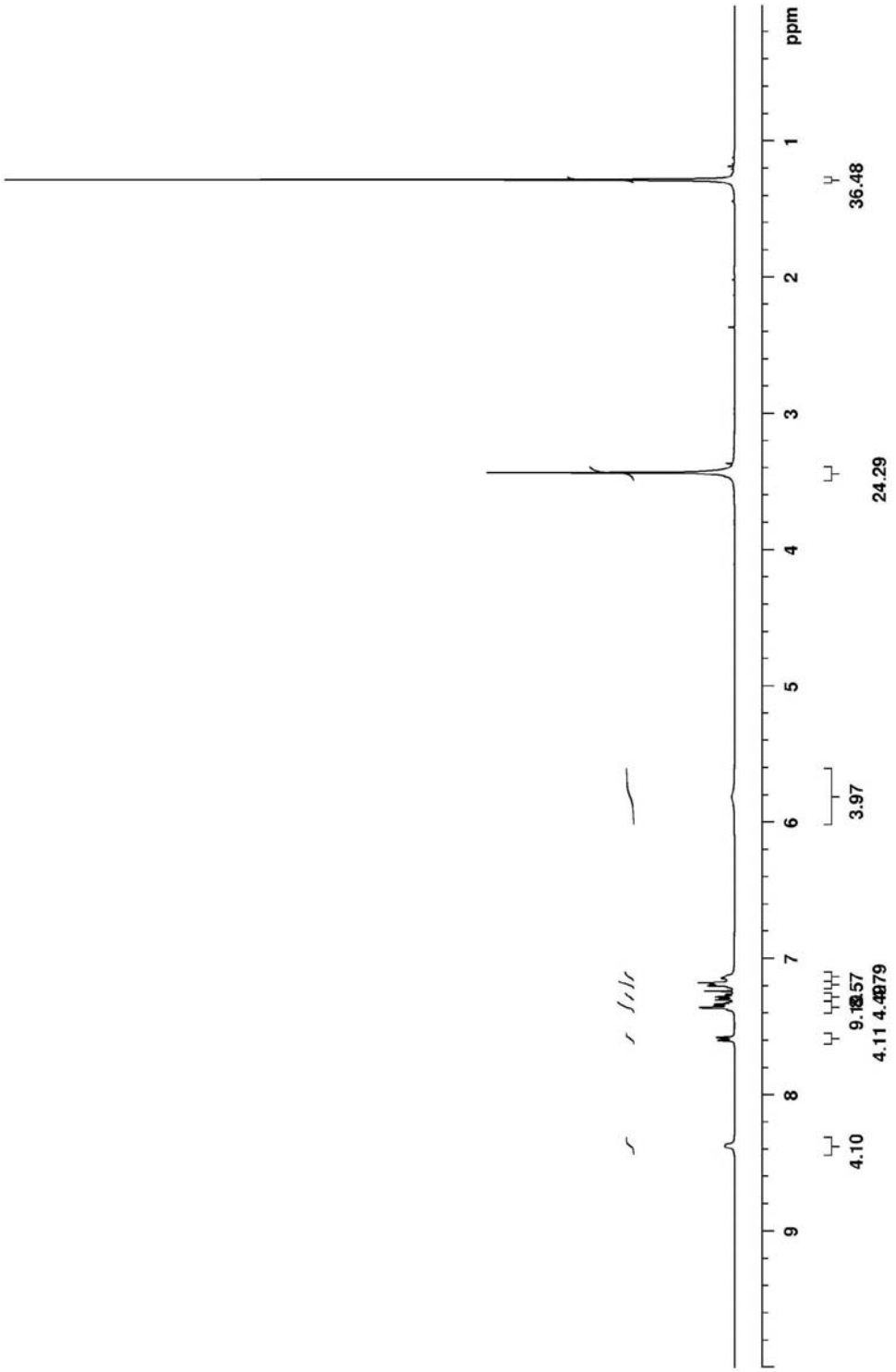
^{1}H NMR Spectrum of **14b**



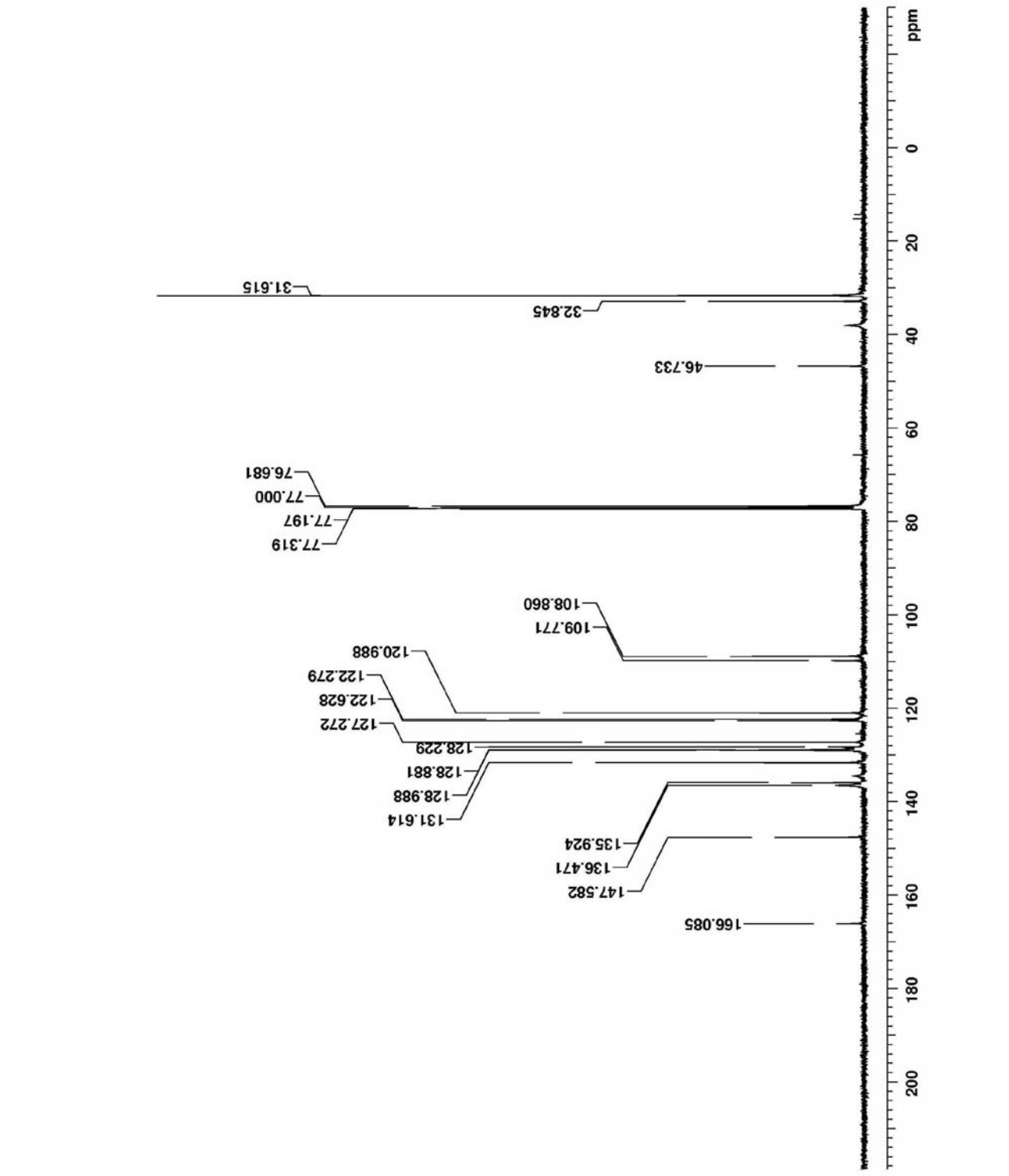
^{13}C NMR Spectrum of **14b**



^{1}H NMR Spectrum of **16b**



^{13}C NMR Spectrum of **16b**



Appendix 2

Simple Thiazocine-2-acetic Acid Derivatives via Ring Closing Metathesis

Dallas K. Bates,* Xiaofen Li and Parag V. Jog

Supplemental Information

(Compound numbers correspond to the numbers in the article:

Bates, D. K.; Li, X.; Jog, P. V. *J. Org. Chem.* **2004**, *69*, 2750)

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Experimental Section (Introduction and compounds 7-12 and 13-20)

All reagents were used without purification unless otherwise noted. Silica gel (70-230 mesh, 60 Å) was used for column chromatography. Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. IR spectra were recorded in chloroform solution. NMR spectra were recorded in $CDCl_3$ solution unless otherwise noted (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz). Mass spectra were obtained under electron impact at 70 eV. Gen2 refers to Grubbs' second Generation catalyst [CAS registry number 246047-72-3, 1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)(tricycohexylphosphine)ruthenium]. Methyl γ-bromocrotonate was prepared according to the literature:[35] ^{1}H NMR δ 6.95 (m, 1H), 5.99 (dt, 1H, *J* = 15.6, 1.2 Hz), 3.97 (dd, 2H, *J* = 7.6, 1.2 Hz), 3.71 (s, 3H); ^{13}C NMR δ 165.9, 141.9, 124.1, 51.8, 29.0. *N*-Allyl-4-methylbenzensulfonamide was prepared according to the literature: mp 62-63 ^{o}C (lit.[36] 63-65 ^{o}C); ^{1}H NMR δ 7.73 (d, 2H, *J* = 8.0 Hz), 7.29 (d, 2H, *J* = 8.0 Hz), 5.70 (m, 1H), 5.14 (dd, 1H, *J* = 17.2, 1.2 Hz), 5.08 (dd, 1H, *J* = 9.2, 1.2 Hz), 4.50 (br s, 1H), 3.56 (t, 2H, *J* = 6.0 Hz), 2.41 (s, 3H); ^{13}C NMR δ 143.5, 137.0, 133.0, 129.7, 127.1, 117.7, 45.8, 21.5.

(2*E*)-4-[allyl[(4-methylphenyl)sulfonyl]amino]but-2-enoic acid (7). To an ice-cooled solution of $LiOH{\cdot}H_2O$ (1.5 eq, 0.95 g, 22.5 mmol) in H_2O (40 mL) and THF (40 mL) was added at 0 ^{o}C a solution of **1** (4.64 g, 15 mmol) in THF (40 mL). This mixture was stirred at 0 ^{o}C for 3 h under a nitrogen atmosphere, then extracted with EtOAc. The aqueous layer was acidified with 5% HCl solution followed by extraction with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to

give 4.22 g (95%) of **7** as a white solid, which was used directly for preparation of **8** or **14**. ^{1}H NMR δ 7.68 (d, 2H, *J* = 8.0 Hz), 7.30 (d, 2H, *J* = 8.0 Hz), 6.81 (dt, 1H, *J* = 15.6, 5.6 Hz), 5.85 (dt, 1H, *J* = 15.6, 1.6 Hz), 5.59 (m, 1H), 5.17-5.10 (m, 2H), 3.93 (dd, 2H, *J* = 5.6, 1.6 H z), 3.79 (d, 2H, *J* = 6.4 Hz), 2.42 (s, 3H); ^{13}C NMR δ 174.6, 145.3, 143.8, 136.7, 132.2, 129.8, 127.2, 119.9, 117.6, 50.6, 47.3, 21.6.

***N*-allyl-*N*-[(2*E*)-4-(1*H*-indol-1-yl)-4-oxobut-2-enyl]-4-methylbenzenesulfonamide (8).** Method 1: To an ice-cooled solution of **7** (0.71 g, 2.4 mmol) in THF (25 mL) was added dropwise oxalyl chloride (12.0 eq, 2.52 mL, 28.9 mmol) at 0 ^{o}C. The resulting mixture was stirred at room temperature for 24 h and concentrated *in vacuo*. The residue was used directly for the following reaction. To a well-stirred mixture of indole (1.1 eq, 0.31 g, 2.7 mmol), powdered NaOH (1.5 eq, 0.14 g, 3.6 mmol) and tetrabutylammonium hydrogen sulfate (0.01 eq, 0.01 g) in CH_2Cl_2 (15 mL) was added dropwise a solution of above residue in CH_2Cl_2 (10 mL) in an ice-water bath. The resulting mixture was stirred at 0 ^{o}C for 15 min and at room temperature for 3 h, poured into ice-water, and extracted with CH_2Cl_2. The combined organic layers were washed with distilled water, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Column chromatography on silica gel (EtOAc/hexane, 1:9) gave 0.24 g (25%) of **8** as a sticky liquid.

Method 2: To a solution of **14** (1.10 g, 2.78 mmol) in dioxane (50 mL) was added a solution of DDQ (6.0 eq, 3.78 g, 16.68 mmol) in dioxane (30 mL) at 55 ^{o}C through a syringe. The resulting mixture was then heated to 70 ^{o}C and stirred for 3 days. The mixture was vacuum filtered and the filtrate was concentrated *in vacuo*. The residue was then stirred in MeOH (60 mL) at room temperature for 1 h. After the evaporation of

MeOH, the residue was diluted with CH_2Cl_2 (100 mL), washed with 5% $NaHCO_3$ solution followed by distilled water and concentrated *in vacuo*. Column chromatography on silica gel (EtOAc/hexane, 1:4) gave 0.98 g (89%) of **8** as a sticky liquid: IR 1690 cm^{-1}; ^1H NMR δ 8.45 (d, 1H, *J* = 7.6 Hz), 7.72 (d, 2H, *J* = 8.4 Hz), 7.55 (d, 1H, *J* = 7.6 Hz), 7.39 (d, 1H, *J* = 4.0 Hz), 7.36-7.25 (m, 4H), 6.98 (dt, 1H, *J* = 15.2, 5.2 Hz), 6.76 (dt, 1H, *J* = 15.2, 1.6 Hz), 6.64 (dd, 1H, *J* = 4.0, 0.8 Hz), 5.64 (m, 1H), 5.19-5.14 (m, 2H), 4.05 (dd, 2H, *J* = 5.2, 1.6 Hz), 3.85 (d, 2H, *J* = 6.4 Hz), 2.39 (s, 3H); ^{13}C NMR δ 163.3, 144.1, 143.8, 136.7, 135.7, 132.3, 130.6, 130.0, 127.2, 125.1, 124.6, 123.9, 123.0, 120.9, 119.9, 116.7, 109.4, 50.9, 47.7, 21.5; MS [m/z (rel intensity)] 394 (M^+, 27), 278 (8), 239 (13), 155 (69), 123 (6), 117 (60).

***N*-allyl-*N*-[2-(allylthio)-4-(1*H*-indol-1-yl)-4-oxobutyl]-4-methylbenzenesulfonamide (9).** To an ice-cooled solution of allyl mercaptan (1.2 eq, 0.07 mL, 0.9 mmol) and Et_3N (1.2 eq, 0.125 mL, 0.9 mmol) in CH_2Cl_2 (10 mL) was added a solution of **8** (0.30 g, 0.75 mmol) in CH_2Cl_2 (6 mL) at 0 ^oC. The resulting mixture was stirred at 0 ^oC for 15 min and at room temperature for 6 h, then diluted with CH_2Cl_2, washed with 5% HCl solution followed by distilled water. The organic layer was dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Column chromatography on silica gel (EtOAc/hexane, 1:4) gave 0.28 g (80%) of **9** as a sticky liquid: IR 1705 cm^{-1}; ^1H NMR δ 8.47 (d, 1H, *J* = 8.0 Hz), 7.67 (d, 2H, *J* = 8.0 Hz), 7.55 (d, 1H, *J* = 7.6 Hz), 7.47 (d, 1H, *J* = 4.0 Hz), 7.36-7.26 (m, 4H), 6.64 (d, 1H, *J* = 3.6 Hz), 5.76 (m, 1H), 5.56 (m, 1H), 5.23-5.02 (m, 4H), 3.89-3.78 (m, 2H), 3.57-3.46 (m, 3H), 3.29-3.06 (m, 4H), 2.40 (s, 3H); ^{13}C NMR δ 169.3, 143.7, 136.3, 135.7, 134.5, 132.5, 130.4, 129.8, 127.3,

125.0, 124.7, 123.7, 120.8, 120.0, 117.6, 116.7, 109.3, 52.0, 51.8, 39.1, 38.6, 35.5, 21.5; MS [m/z (rel intensity)] 313 (65), 224 (72), 155 (89), 117 (68).

***N*-allyl-*N*-[2-(allylsulfinyl)-4-(1*H*-indol-1-yl)-4-oxobutyl]-4-methylbenzenesulfonamide (10).** To an ice-cooled solution of **9** (1.5 g, 3.21 mmol) in CH_2Cl_2 (25 mL) was added slowly a solution of *m*-CPBA (1.0 eq) in CH_2Cl_2 (20 mL). The resulting mixture was stirred at 0 ^oC for 15 min and put in a freezer (-20 ^oC) overnight. The reaction mixture was then poured into 5% $NaHCO_3$ solution. After separating and saving the organic layer, the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with distilled water, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Column chromatography on silica gel (EtOAc/hexane, 3:2) gave 1.12 g (72%) of **10** as a sticky liquid (as a mixture of two diastereomers in a 2:3 ratio): IR 1698 cm^{-1}, ^1H NMR δ 8.38 (d, 1H, *J* = 7.6 Hz), 7.69 (d, 2H, *J* = 8.0 Hz), 7.55 (d, 1H, *J* = 7.6 Hz), 7.47 (d, 1H, *J* = 3.6 Hz), 7.36-7.25 (m, 4H), 6.67 (d, 1H, *J* = 4.0 Hz), 5.97 (m, 1H), 5.59 (m, 1H), 5.48-5.43 (m, 2H), 5.22 (dd, 1H, *J* = 17.2, 1.2 Hz), 5.16 (dd, 1H, *J* =10.0, 1.2 Hz), 3.86 (d, 2H, *J* = 6.4 Hz), 3.79 (m, 1H), 3.69 (m, 1H), 3.64-3.59 (m, 2H), 3.57 (m, 1H), 3.48 (m, 1H), 3.43 (dd, 1H, *J* = 7.2, 2.0 Hz), 2.39 (s, 3H); ^{13}C NMR δ 168.6, 144.0, 135.6, 132.4, 130.4, 130.0, 127.4, 127.2, 126.0, 125.3, 124.4, 124.0, 123.9, 121.1, 120.5, 116.5, 110.2, 54.2, 52.5, 51.0, 44.7, 34.1, 21.5.

***N*-allyl-*N*-[2-(allylsulfonyl)-4-(1*H*-indol-1-yl)-4-oxobutyl]-4-methylbenzenesulfonamide (11).** To an ice-cooled solution of **9** (0.28 g, 0.60 mmol) in CH_2Cl_2 (8 mL) was added a solution of *m*-CPBA (2.0 eq) in CH_2Cl_2 (6 mL). The

resulting mixture was stirred at room temperature for 12 h and poured into 5% $NaHCO_3$ solution. After separating and saving the organic layer, the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with distilled water, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Column chromatography on silica gel (EtOAc/hexane, 3:7) gave 0.17 g (57%) of **11** as a sticky liquid: IR 1703 cm^{-1}; ^1H NMR δ 8.42 (d, 1H, *J* = 8.0 Hz), 7.68 (d, 2H, *J* = 8.0 Hz), 7.56 (d, 1H, *J* = 7.6 Hz), 7.48 (d, 1H, *J* = 4.0 Hz), 7.35-7.33 (m, 1H), 7.30-7.26 (m, 3H), 6.67 (dd, 1H, *J* = 4.0, 0.4 Hz), 5.93 (m, 1H), 5.59-5.48 (m, 3H), 5.23 (dd, 1H, *J* = 17.2, 1.2 Hz), 5.16 (dd, 1H, *J* = 10.0, 1.2 Hz), 4.37 (m, 1H), 3.99-3.78 (m, 4H), 3.70-3.59 (m, 2H), 3.53-3.46 (m, 2H), 2.39 (s, 3H); ^{13}C NMR δ 168.0, 144.2, 135.6, 135.2, 131.8, 130.5, 130.0, 127.5, 125.7, 125.3, 124.4, 124.1, 124.0, 121.1, 121.0, 116.5, 110.2, 58.8, 54.9, 52.4, 46.2, 32.6, 21.5.

1-[[4-[4-(methylphenyl)sulfonyl]-1-oxido-3,4,5,8-tetrahydro-2*H*-1,4-thiazocin-2-yl]acetyl]-1*H*-indole (12). To a solution of **10** (0.79 g, 1.63 mmol, 1:1 ratio) in CH_2Cl_2 (10 mL) was added a solution of Gen 2 catalyst (10% mol, 0.14 g) in CH_2Cl_2 (8 mL) under a nitrogen atmosphere. The resulting mixture was refluxed for 2.5 h, cooled to room temperature and concentrated *in vacuo*, Column chromatography of the residue on silica gel (EtOAc) gave 0.36 g (48%) of **12** as a white solid (a mixture of two diastereomers in a 2:3 ratio): mp 149-51 ^oC.

minor diastereomer: ^1H NMR δ 8.39 (d, 1H, *J* = 8.0 Hz), 7.66 (d, 2H, *J* = 8.4 Hz), 7.54 (d, 1H, *J* = 7.6 Hz), 7.41 (d, 1H, *J* = 4.0 Hz), 7.35-7.25 (m, 4H), 6.64 (d, 1H, *J* = 4.0 Hz), 5.90 (m, 1H), 5.64 (m, 1H), 4.42 (m, 1H), 4.17-3.79 (m, 5H), 3.47 (dd, 1H, *J* = 17.2, 6.0 Hz), 3.09-3.03 (m, 2H), 2.36 (s, 3H).

major diastereomer: IR 1702 cm^{-1}; ^1H NMR δ 8.32 (d, 1H, *J* = 8.4 Hz), 7.59 (d, 2H, *J* = 8.4 Hz), 7.54 (d, 1H, *J* = 7.2 Hz), 7.47 (d, 1H, *J* = 4.0 Hz), 7.34-7.26 (m, 4H), 6.66 (d, 1H, *J* = 4.0 Hz), 5.95 (dt, 1H, *J* = 11.6, 3.2 Hz), 5.84 (m, 1H), 4.44 (m, 1H), 4.30 (d, 1H, *J* = 18.4 Hz), 3.99 (dd, 1H, *J* = 14.0, 8.8 Hz), 3.91 (m, 1H), 3.83 (dd, 1H, *J* = 17.2, 2.4 Hz), 3.74-3.64 (m, 2H), 3.26 (dd, 1H, *J* = 14.0, 2.4 Hz), 3.16 (dd, 1H, *J* = 17.2, 10.0 Hz), 2.39 (s, 3H); ^{13}C NMR δ 168.0, 167.5, 144.2, 144.1, 135.6, 135.5, 134.0, 133.7, 132.7, 130.4, 130.1, 130.0, 127.4, 127.1, 125.4, 125.3, 124.3, 124.1, 124.0, 121.1, 118.8, 116.4, 116.3, 110.3, 110.2, 55.4, 51.2, 49.9, 49.2, 48.8, 48.1, 46.2, 44.6, 34.7, 33.6, 21.46. Anal. Calcd for $C_{23}H_{24}O_5N_2S_2$: C, 60.51; H, 5.30; N, 6.14. Found: C, 60.18; H, 5.43; N, 6.00 (on diastereomer mixture).

***N*-Allyl-*N*-[(2*E*)-4-(2,3-dihydro-1*H*-indol-1-yl)-4-oxobut-2-enyl]-4-methylbenzenesulfonamide (14).** To an ice-cooled solution of **7** (0.68 g, 2.3 mmol) in THF (25 mL) was added dropwise oxalyl chloride (12.0 eq, 2.41 mL, 27.66 mmol) at 0 ^oC. The resulting mixture was stirred at room temperature for 24 h then concentrated *in vacuo* and the residue was used directly in the following reaction. To an ice-cooled solution of indoline (1.2 eq, 0.33 g, 2.8 mmol), pyridine (10.0 eq, 1.88 mL, 23.1 mmol) and DMAP (0.05 g) in CH_2Cl_2 (15 mL) was added slowly a solution of the above residue in CH_2Cl_2 (15 mL) at 0 ^oC. The resulting mixture was stirred at 0 ^oC for 15 min and at room temperature overnight. The solution was poured into 5% aqueous HCl and extracted with CH_2Cl_2. The combined organic layers were washed with 5% HCl solution followed by distilled water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatography on silica gel (EtOAc/hexane, 2:3) gave 0.59 g (64%) of **14** as a

white solid: mp 123-5 ^{o}C; IR 1666 cm^{-1}; ^{1}H NMR δ 8.22 (d, 1H, *J* = 7.2 Hz), 7.69 (d, 2H, *J* = 8.4 Hz), 7.28 (d, 2H, *J* = 8.0 Hz), 7.17 (t, 2H, *J* = 7.6 Hz), 7.00 (t, 1H, *J* = 7.6 Hz), 6.77 (dt, 1H, *J* = 14.8, 5.2 Hz), 6.37 (d, 1H, *J* = 14.8 Hz), 5.61 (m, 1H), 5.15-5.11 (m, 2H), 4.10-4.05 (m, 2H), 3.98 (d, 2H, *J* = 4.8 Hz), 3.81 (d, 2H, *J* = 6.4 Hz), 3.16 (t, 2H, *J* = 7.6 Hz), 2.39 (s, 3H); ^{13}C NMR δ 163.2, 143.6, 142.7, 140.2, 136.9, 132.3, 131.5, 129.8, 127.5, 127.1, 124.5, 123.9, 119.6, 117.4, 50.4, 48.0, 47.6, 27.9, 21.4; MS [m/z (rel intensity)] 396 (M^{+}, 10), 241 (4), 155 (29), 119 (83). Anal. Calcd for $C_{22}H_{24}O_3N_2S$: C, 66.64; H, 6.10; N, 7.07. Found: C, 66.56; H, 6.16; N, 7.07.

***N*-allyl-*N*-[2-(allylthio)-4-(2,3-dihydro-1*H*-indol-1-yl)-4-oxobutyl]-4-methylbenzenesulfonamide (15).** To an ice-cooled solution of allyl mercaptan (3.0 eq, 0.36 mL, 4.5 mmol) and sodium methoxide (1.12 eq, 0.09 g, 1.7 mmol) in MeOH (15 mL) and THF (5 mL) was added a solution of **14** (0.59 g, 1.5 mmol) in THF (10 mL) at 0 ^{o}C. The resulting mixture was stirred at 0 ^{o}C for 15 min. The solution was then poured into ice water and extracted with CH_2Cl_2. The combined organic layers were washed with distilled water, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Column chromatography on silica gel (EtOAc/hexane, 3:7) gave 0.67 g (95%) of **15** as a sticky liquid: IR 1659 cm^{-1}; ^{1}H NMR δ 8.22 (d, 1H, *J* = 8.8 Hz), 7.65 (d, 2H, *J* = 8.4 Hz), 7.27 (d, 2H, *J* = 8.4 Hz), 7.16 (t, 2H, *J* = 7.2 Hz), 6.98 (t, 1H, *J* = 7.2 Hz), 5.78 (m, 1H), 5.49 (m, 1H), 5.19-5.04 (m, 4H), 4.11-4.05 (m, 2H), 3.84 (d, 2H, *J* = 6.4 Hz), 3.55-3.42 (m, 2H), 3.28-3.13 (m, 5H), 3.00 (dd, 1H, *J* = 16.8, 4.4 Hz), 2.65 (dd, 1H, *J* = 16.8, 7.6 Hz), 2.39 (s, 3H); ^{13}C NMR δ 168.7, 143.4, 143.0, 136.7, 134.6, 132.3, 131.3, 129.7, 127.4,

127.2, 124.5, 123.6, 119.8, 117.4, 117.0, 51.5, 51.4, 48.1, 39.0, 38.7, 35.4, 27.9, 21.5; MS [m/z (rel intensity)] 315 (25), 224 (21), 155 (52), 119 (65).

1-[[4-[4-(methylphenyl)sulfonyl]-1,1-dioxido-3,4,5,8-tetrahydro-2*H*-1,4-thiazocin-2-yl]acetyl]-1*H*-indole (16). To a solution of **11** (0.07 g, 0.14 mmol) in CH_2Cl_2 (4 mL) was added a solution of commercial Gen 2 catalyst (5% mol, 0.006 g) in CH_2Cl_2 (3 mL) under a nitrogen atmosphere. The mixture was refluxed until TLC showed the reaction to be complete, cooled to room temperature and concentrated *in vacuo*. Column chromatography of the residue on silica gel (EtOAc/hexane, 3:2) gave 0.06 g (91%) of **16** as a white solid: mp 237-9 ^oC; IR 1711 cm^{-1}; ^1H NMR δ 8.32 (d, 1H, *J* = 8.0 Hz), 7.65 (d, 2H, *J* = 8.4 Hz), 7.55 (d, 1H, *J* = 7.2 Hz), 7.45 (d, 1H, *J* = 4.0 Hz), 7.34-7.25 (m, 4H), 6.67 (d, 1H, *J* = 4.0 Hz), 5.88 (d, 1H, *J* = 12.4 Hz), 5.79 (m, 1H), 4.80 (m, 1H), 4.42-4.35 (m, 2H), 4.02-3.92 (m, 2H), 3.79-3.73 (m, 2H), 3.22 (dd, 1H, *J* = 13.2, 3.2 Hz), 3.03 (dd, 1H, *J* = 17.6, 10.8 Hz), 2.39 (s, 3H); ^{13}C NMR δ 167.1, 144.4, 135.5, 133.8, 130.4, 130.2, 127.3, 125.4, 124.3, 124.1, 121.2, 117.7, 116.3, 110.6, 60.4, 53.1, 49.8, 49.1, 30.2, 21.5. Anal. Calcd for $C_{23}H_{24}O_5N_2S_2$: C, 58.46; H, 5.12; N, 5.93. Found: C, 58.18; H, 5.28; N, 5.76.

***N*-allyl-*N*-[2-(allylsulfinyl)-4-(2,3-dihydro-1*H*-indol-1-yl)-4-oxobutyl]-4-methylbenzenesulfonamide (17).** To an ice-cooled solution of **15** (0.85 g, 1.81 mmol) in CH_2Cl_2 (20 mL) was added slowly a solution of *m*-CPBA (1.0 eq) in CH_2Cl_2 (10 mL). The resulting mixture was stirred at 0 ^oC for 15 min and put in a freezer (-20 ^oC) overnight. The reaction mixture was then poured into 5% $NaHCO_3$ solution. After

separating and saving the organic layer, the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with distilled water, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Column chromatography on silica gel (EtOAc) gave 0.87 g (99%) of **17** as a sticky liquid (a mixture of two diastereomers present in a ratio of 2:3).

minor diastereomer: IR 1656 cm^{-1}; ^1H NMR δ 8.14 (d, 1H, *J* = 7.6 Hz), 7.67 (d, 2H, *J* = 8.0 Hz), 7.28 (d, 2H, *J* = 8.0 Hz), 7.18-7.15 (m, 2H), 7.00 (m, 1H), 5.95 (m, 1H), 5.53 (m, 1H), 5.44-5.40 (m, 2H), 5.21 (dd, 1H, *J* = 17.2, 1.6 Hz), 5.14 (dd, 1H, *J* = 10.0, 0.8 Hz), 4.12-4.06 (m, 2H), 3.84 (d, 2H, *J* = 6.8 Hz), 3.70-3.54 (m, 4H), 3.38 (dd, 1H, *J* = 13.2, 3.6 Hz), 3.20 (t, 2H, *J* = 8.4 Hz), 3.12 (dd, 1H, *J* = 17.6, 4.4 Hz), 2.91 (dd, 1H, *J* = 17.6, 8.0 Hz), 2.39 (s, 3H); ^{13}C NMR δ 167.8, 143.8, 142.6, 135.9, 132.3, 131.2, 129.9, 127.4, 127.3, 126.3, 124.7, 124.0, 123.6, 120.3, 116.9, 54.3, 52.1, 51.3, 48.0, 44.7, 34.2, 27.9, 21.5.

major diastereomer: IR 1656 cm^{-1}; ^1H NMR δ 8.17 (d, 1H, *J* = 8.8 Hz), 7.68 (d, 2H, *J* = 8.0 Hz), 7.28 (d, 2H, *J* = 8.0 Hz), 7.17 (m, 2H), 7.01 (td, 1H, *J* = 7.2, 1.6 Hz), 5.87 (m, 1H), 5.53-5.39 (m, 3H), 5.22-5.11 (m, 2H), 4.17-4.06 (m, 2H), 3.87-3.84 (m, 3H), 3.59 (dd, 1H, *J* = 14.4, 9.2 Hz), 3.54 (dd, 1H, *J* = 13.6, 8.0 Hz), 3.40 (dd, 1H, *J* = 12.8, 7.2 Hz), 3.30 (dd, 1H, *J* = 14.4, 6.4 Hz), 3.22-3.13 (m, 3H), 2.68 (dd, 1H, *J* = 18.0, 4.8 Hz), 2.39 (s, 3H); ^{13}C NMR δ 168.1, 143.8, 142.8, 135.9, 132.4, 132.0, 131.3, 129.9, 127.3, 127.2, 126.0, 124.7, 123.9, 120.4, 116.9, 54.9, 52.1, 51.7, 48.0, 29.0, 28.0, 21.5; MS [m/z (rel intensity)] 396 (9), 241 (9), 155 (35), 119 (100) for diastereomer mixture.

1-[[4-[4-(methylphenyl)sulfonyl]-1-oxido-3,4,5,8-tetrahydro-2*H*-1,4-thiazocin-2-yl]acetyl]indoline (18). To a solution of **17** (0.58 g, 1.193 mmol) in CH_2Cl_2 (12 mL) was added a solution of commercial Gen 2 catalyst (10% mol, 0.10 g) in CH_2Cl_2 (10 mL) under a nitrogen atmosphere. The resulting mixture was refluxed for 21 h, cooled to room temperature and concentrated *in vacuo*. Column chromatography of the residue on silica gel (EtOAc) gave 0.22 g (40%) of **18** as a mixture of two diastereomers in a 3:4 ratio).

minor diastereomer: ^{1}H NMR δ 8.14 (d, 1H, *J* = 7.6 Hz), 7.67 (d, 2H, *J* = 8.0 Hz), 7.28 (d, 2H, *J* = 8.0 Hz), 7.19-7.15 (m, 2H), 7.02 (m, 1H), 5.89 (dt, 1H, *J* = 11.6, 3.2 Hz), 5.64 (m, 1H), 4.47 (m, 1H), 4.21-3.71 (m, 7H), 3.19 (t, 2H, *J* = 8.4 Hz), 3.04-2.95 (m, 2H), 2.57 (dd, 1H, *J* = 17.2, 4.0 Hz), 2.39 (s, 3H); ^{13}C NMR δ 166.7, 144.0, 142.5, 134.2, 134.0, 131.2, 130.0, 127.5, 127.4, 124.7, 124.2, 118.9, 116.9, 49.1, 48.0, 46.6, 44.6, 37.5, 34.9, 28.0, 21.5.

major diastereomer: IR 1655 cm^{-1}; ^{1}H NMR δ 8.06 (d, 1H, *J* = 8.0 Hz), 7.59 (d, 2H, *J* = 8.8 Hz), 7.27 (d, 2H, *J* = 8.0 Hz), 7.17-7.11 (m, 2H), 7.00 (m, 1H), 5.88 (dt, 1H, *J* = 11.6, 4.0 Hz), 5.80 (m, 1H), 4.39 (m, 1H), 4.28-3.61 (m, 7H), 3.30 (td, 2H, *J* = 14.0, 2.8 Hz), 3.18 (t, 2H, *J* = 8.4 Hz), 2.66 (dd, 1H, *J* = 16.8, 10.0 Hz), 2.38 (s, 3H); ^{13}C NMR δ 167.3, 144.1, 142.4, 134.2, 134.0, 132.7, 130.0, 127.4, 127.1, 124.7, 124.1, 118.5, 116.7, 55.6, 49.8, 48.6, 48.3, 48.0, 33.5, 28.0, 21.5; MS [m/z (rel intensity)] 155 (26), 119 (88) for diastereomer mixture.

***N*-allyl-*N*-[2-(allylsulfonyl)-4-(2,3-dihydro-1*H*-indol-1-yl)-4-oxobutyl]-4-methylbenzenesulfonamide (19).** To an ice-cooled solution of **15** (0.62 g, 1.32 mmol) in CH_2Cl_2 (20 mL) was added a solution of *m*-CPBA (2.0 eq) in CH_2Cl_2 (10 mL). The

resulting mixture was stirred at room temperature for 16 h, poured into 5% $NaHCO_3$ solution. After separating and saving the organic layer, the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with distilled water, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Column chromatography on silica gel (EtOAc/hexane, 3:7) gave 0.62 g (94%) of **19** as a sticky liquid: IR 1658 cm^{-1}; ^1H NMR δ 8.17 (d, 1H, *J* = 8.0 Hz), 7.68 (d, 2H, *J* = 8.4 Hz), 7.28 (d, 2H, *J* = 8.4 Hz), 7.19-7.16 (m, 2H), 7.01 (td, 1H, *J* = 7.6, 0.8 Hz), 5.91 (m, 1H), 5.56-5.43 (m, 3H), 5.21 (dd, 1H, *J* = 17.2, 1.2 Hz), 5.14 (dd, 1H, *J* = 10.0, 1.2 Hz), 4.28 (m, 1H), 4.18-4.06 (m, 2H), 3.96-3.77 (m, 4H), 3.64 (dd, 1H, *J* = 14.4, 9.6 Hz), 3.45 (dd, 1H, *J* = 14.4, 5.2 Hz), 3.20 (t, 2H, *J* = 8.4 Hz), 3.13 (dd, 1H, *J* = 18.0, 6.4 Hz), 3.05 (dd, 1H, *J* = 18.0, 5.6 Hz), 2.40 (s, 3H); ^{13}C NMR δ 167.1, 144.0, 142.6, 135.6, 131.7, 131.3, 129.9, 127.4, 125.4, 124.7, 124.1, 124.0, 120.6, 116.8, 58.5, 54.9, 51.8, 47.9, 45.7, 32.6, 27.9, 21.5; MS [m/z (rel intensity)] 347 (16), 155 (43), 119 (100).

1-[[4-[4-(methylphenyl)sulfonyl]-1,1-dioxido-3,4,5,8-tetrahydro-2*H*-1,4-thiazocin-2-yl]acetyl]indoline (20). To a solution of **19** (0.31 g, 0.62 mmol) in CH_2Cl_2 (10 mL) was added a solution of commercial Gen 2 catalyst (5% mol, 0.026 g) in CH_2Cl_2 (5 mL) under a nitrogen atmosphere. The mixture was refluxed until TLC showed the reaction to be complete, then cooled to room temperature and concentrated *in vacuo.* Column chromatography of the residue on silica gel (EtOAc) gave 0.26 g (89%) of **20** as a white solid: mp 267-9 ^oC; IR 1651 cm^{-1}; ^1H NMR δ 8.05 (d, 1H, *J* = 8.0 Hz), 7.65 (d, 2H, *J* = 8.4 Hz), 7.29 (d, 2H, *J* = 8.0 Hz), 7.15 (dd, 2H, *J* = 15.6, 7.6 Hz), 7.01 (td, 1H, *J* = 7.6, 1.2 Hz), 5.86 (d, 1H, *J* = 11.6 Hz), 5.75 (m, 1H), 4.85 (dd, 1H, *J* = 13.6, 7.2 Hz), 4.41 (d,

1H, *J* = 19.6 Hz), 4.06-4.02 (m, 2H), 3.97-3.85 (m, 2H), 3.69 (d, 2H, *J* = 19.2 Hz), 3.26-3.17 (m, 4H), 2.51 (dd, 1H, *J* = 17.2, 10.4 Hz), 2.39 (s, 3H); ^{13}C NMR δ 166.2, 144.3, 142.4, 134.0, 131.3, 130.1, 127.4, 127.2, 124.8, 124.3, 117.4, 116.7, 53.1, 52.9, 49.7, 49.2, 47.9, 29.9, 27.9, 21.5; MS [m/z (rel intensity)] 474 (M^+, 1), 155 (26), 119 (100). Anal. Calcd for $C_{23}H_{26}O_5N_2S_2$: C, 58.21; H, 5.52; N, 5.90. Found: C, 57.98; H, 5.69; N, 5.85.

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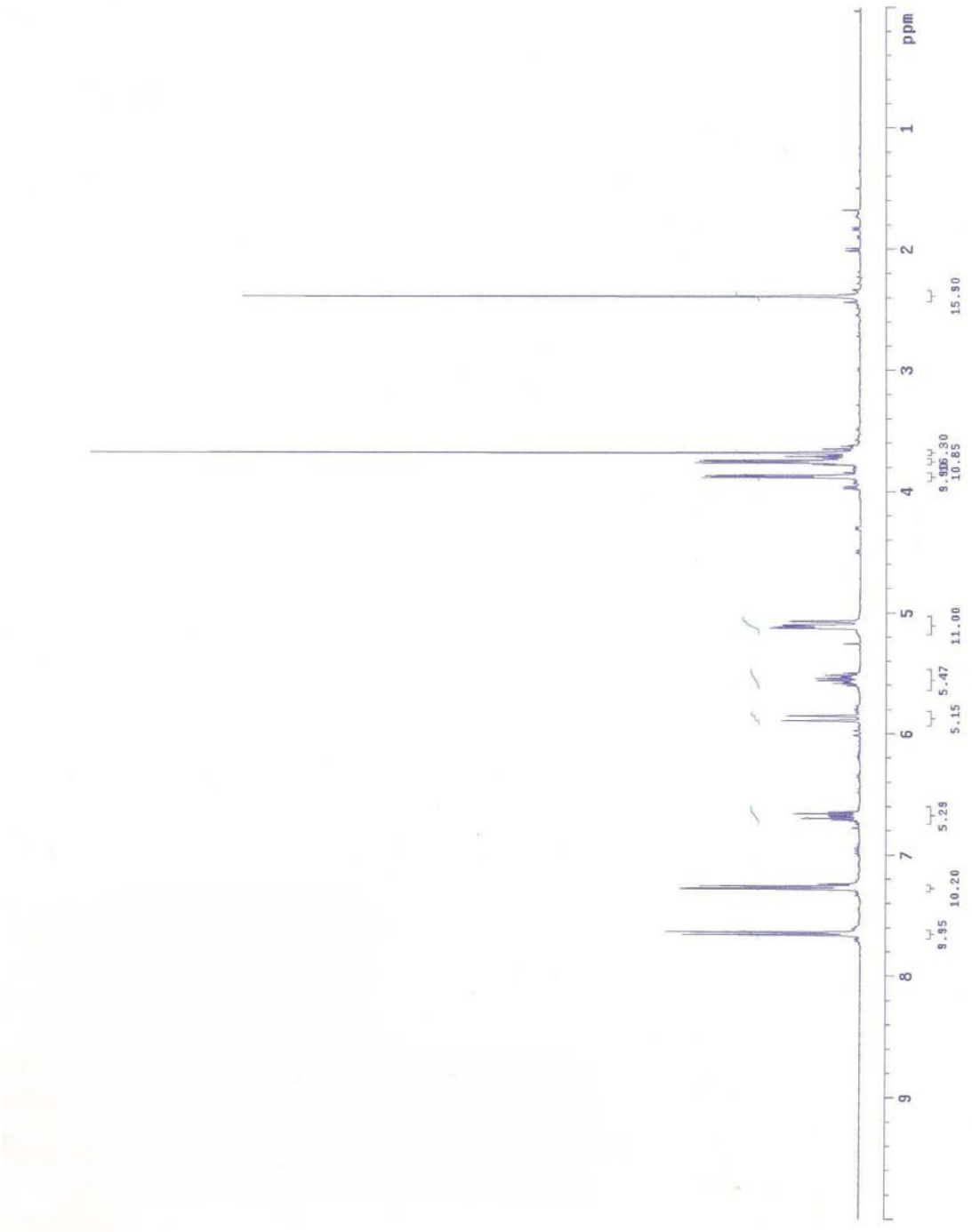
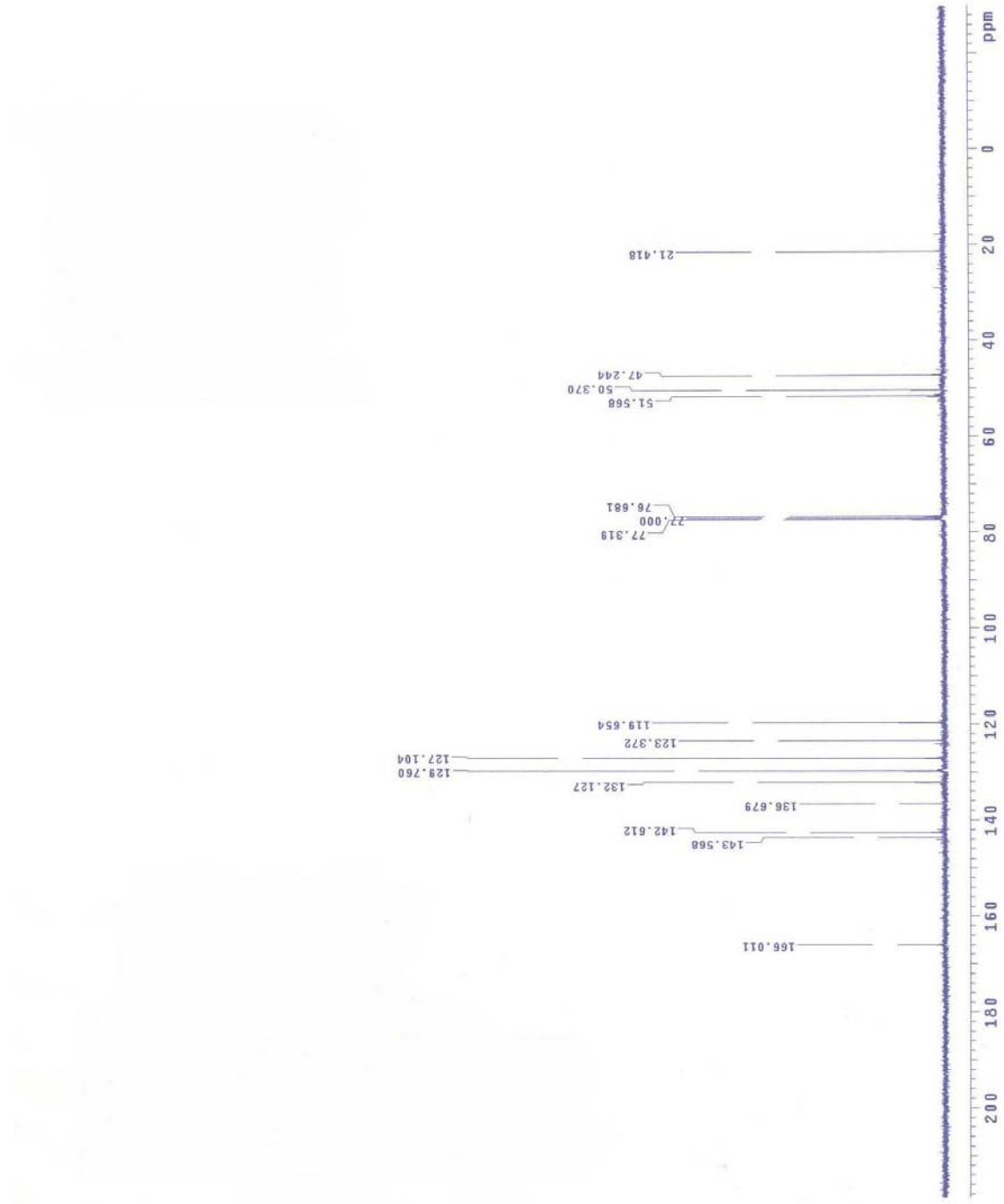
37. Dang, H. S.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1493-1498.

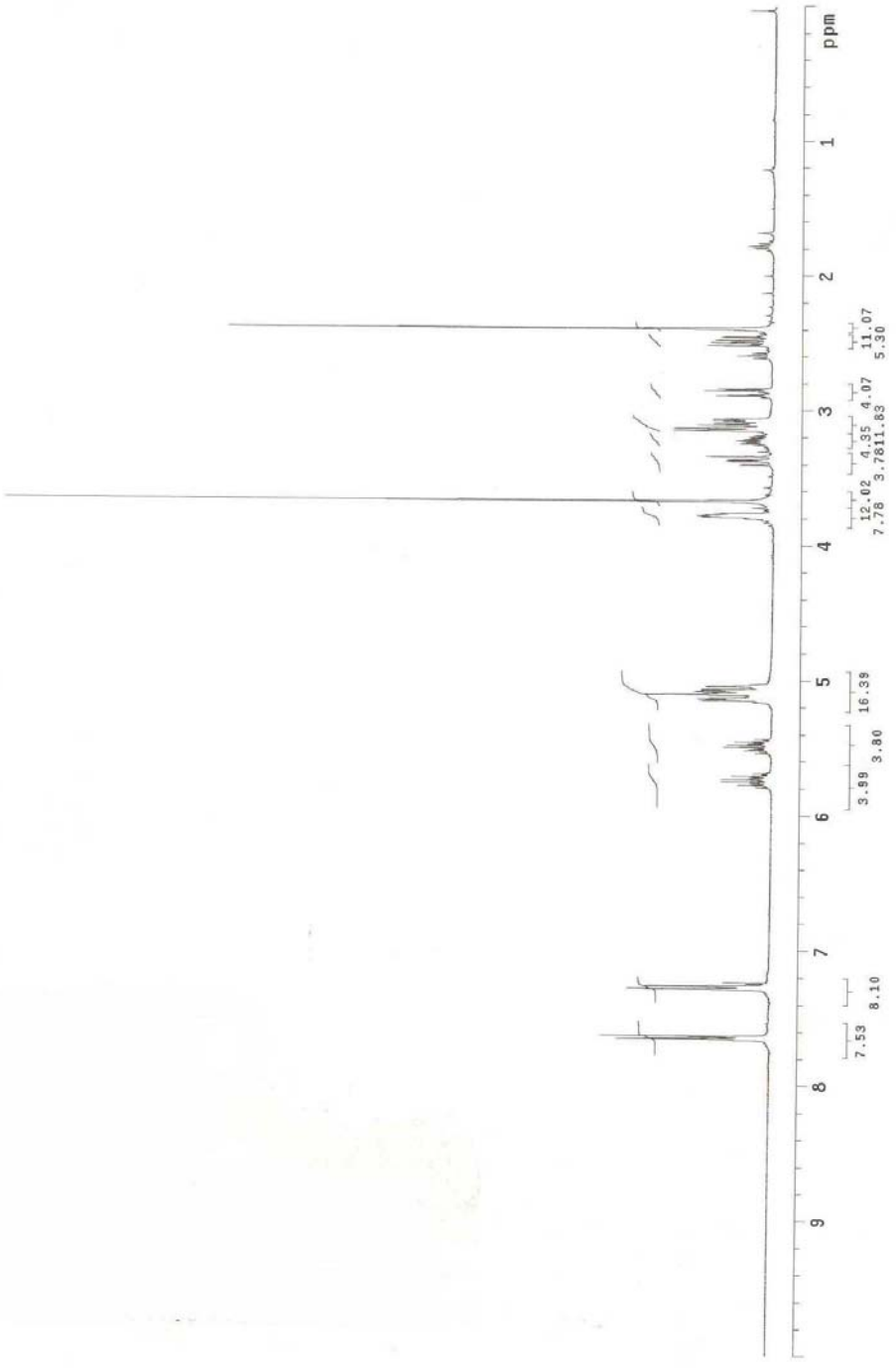
^{1}H NMR Spectrum of 1



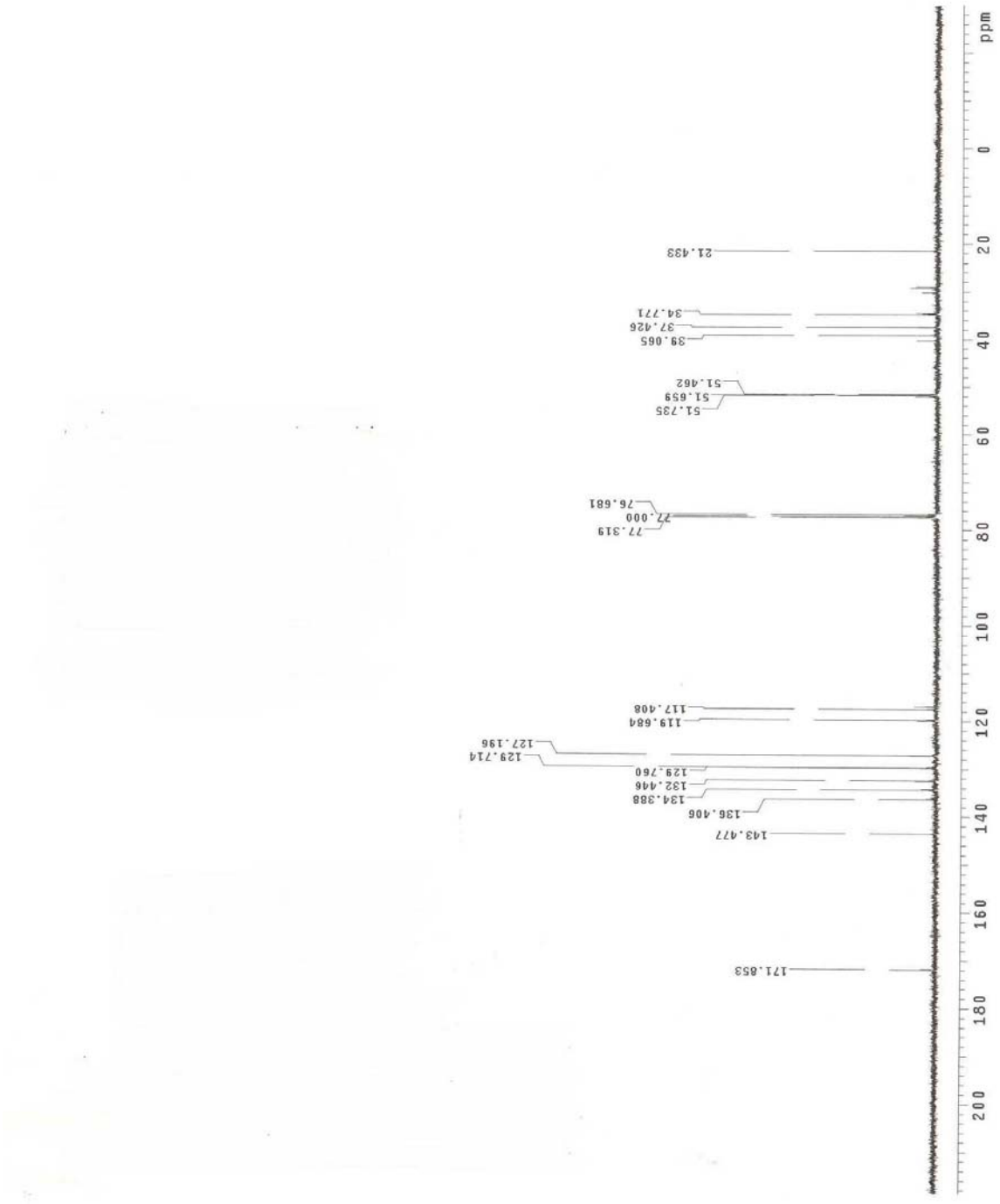
^{13}C NMR Spectrum of 1



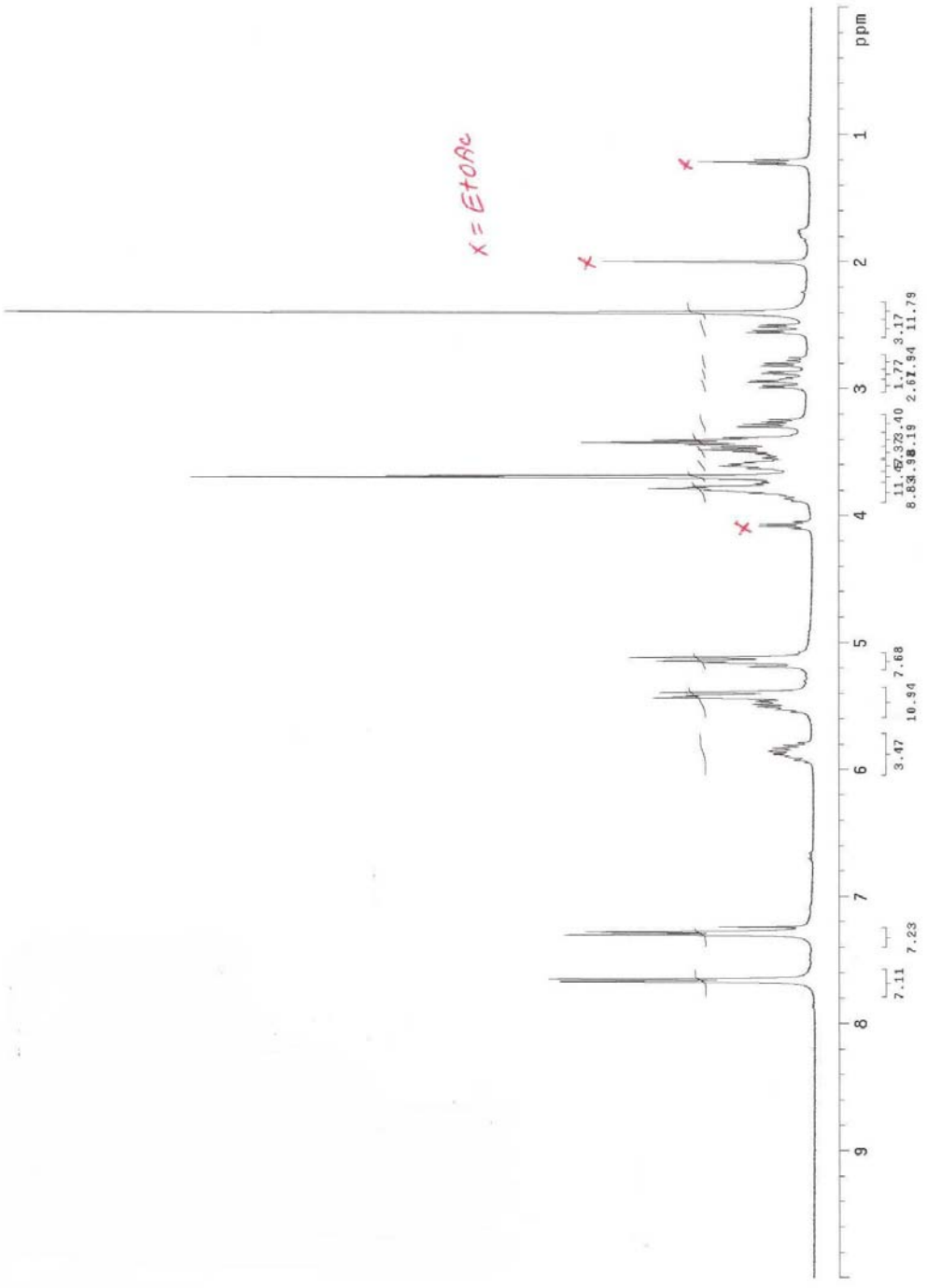
^{1}H NMR Spectrum of 2



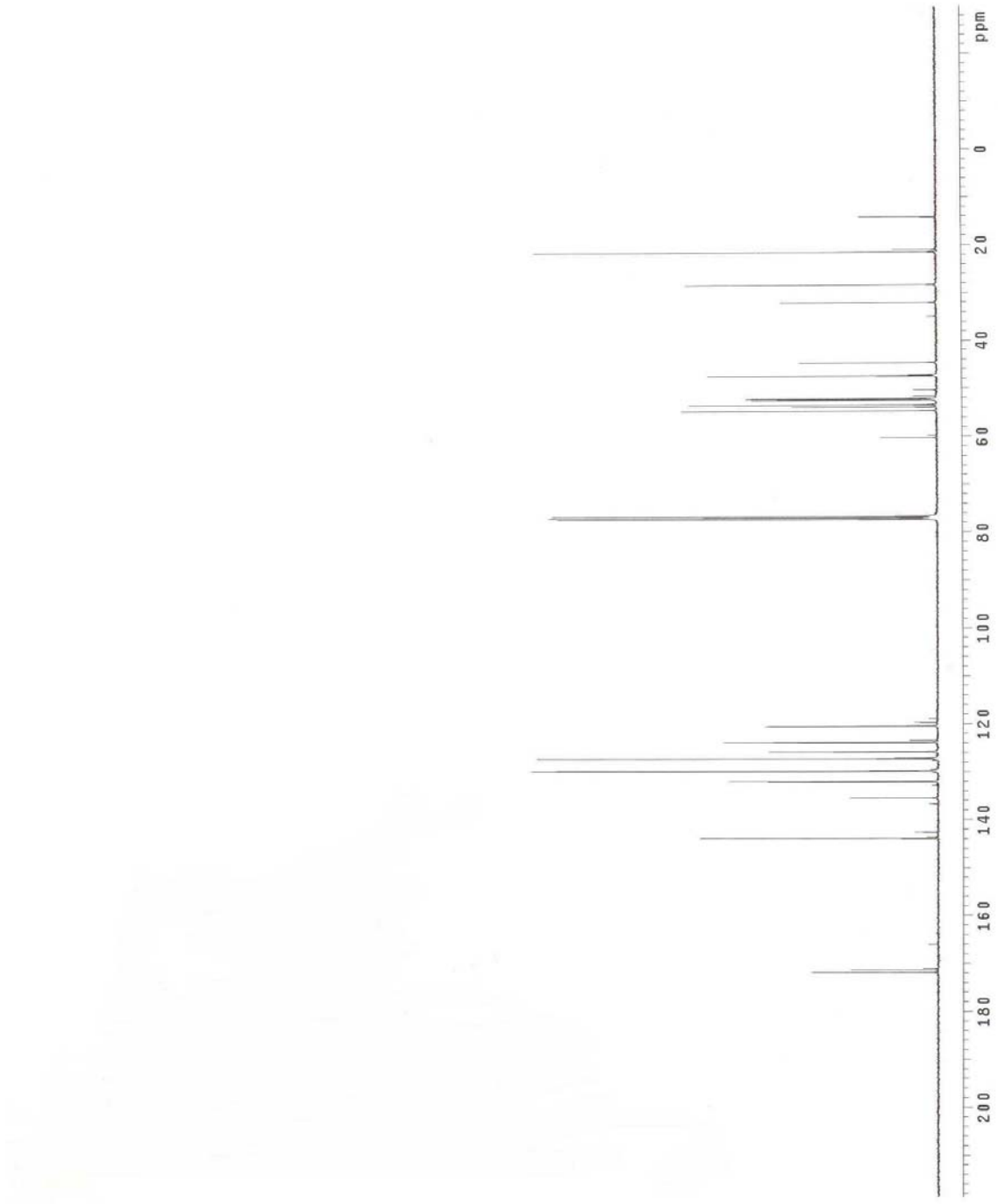
^{13}C NMR Spectrum of 2



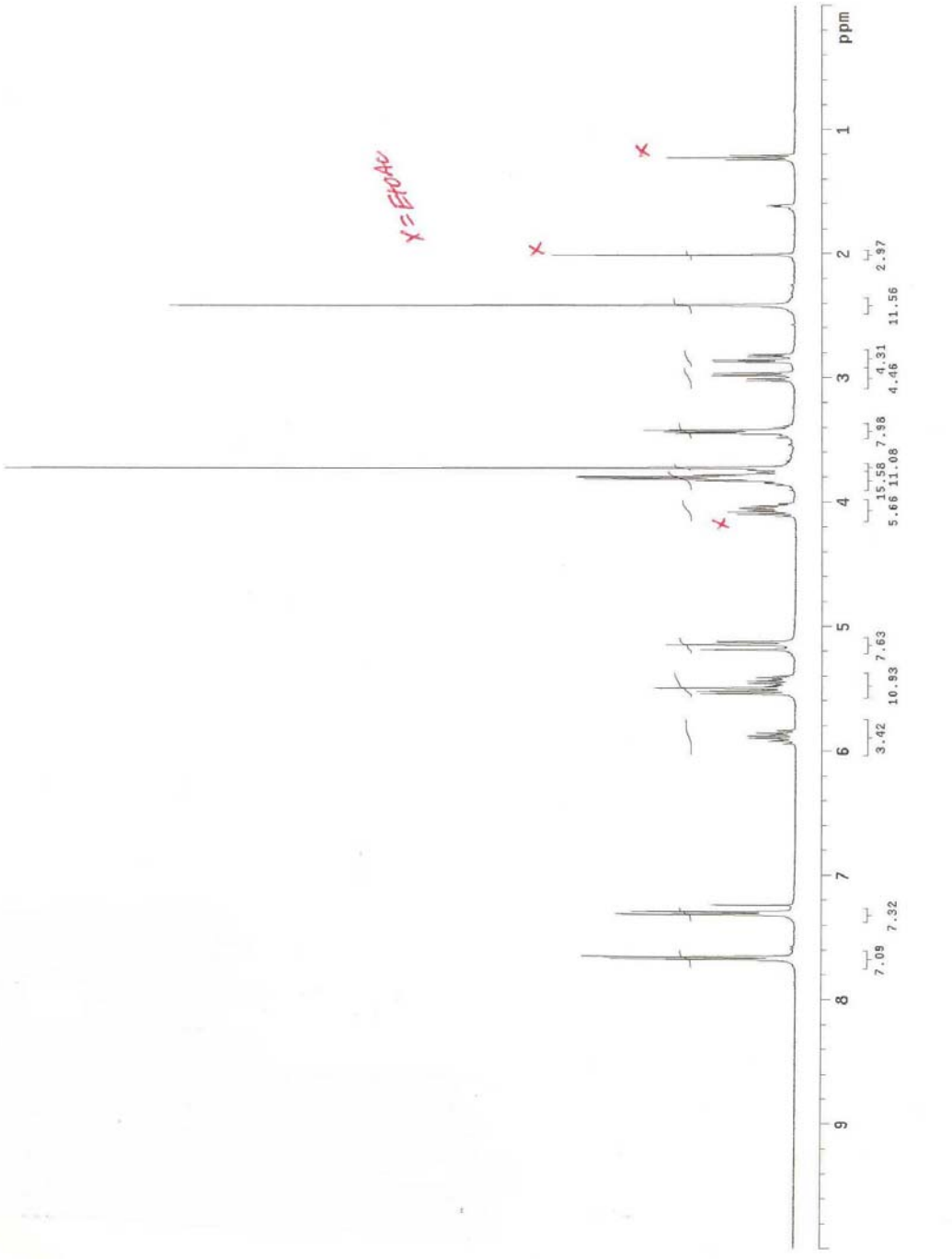
^{1}H NMR Spectrum of 3



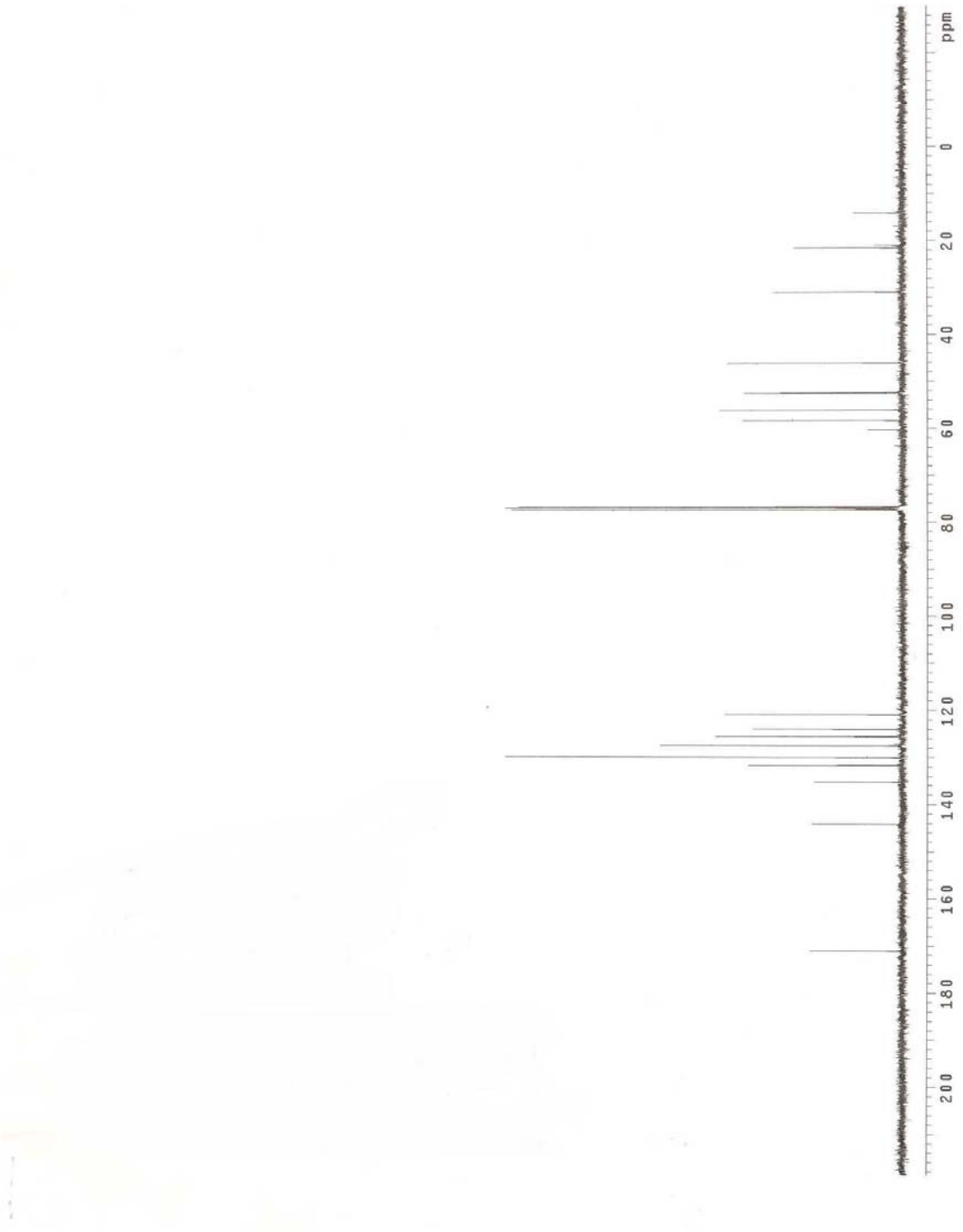
^{13}C NMR Spectrum of 3



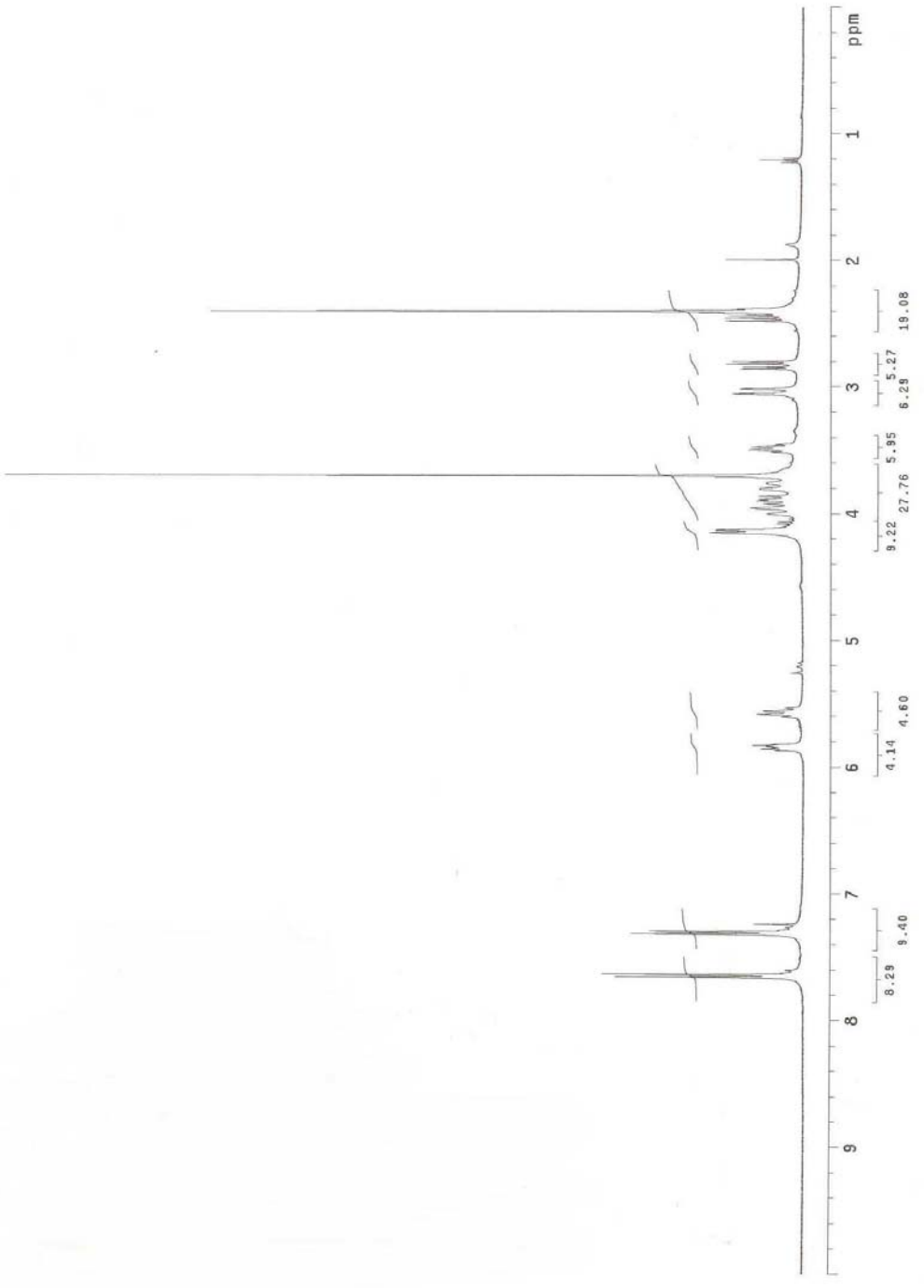
^{1}H NMR Spectrum of 4



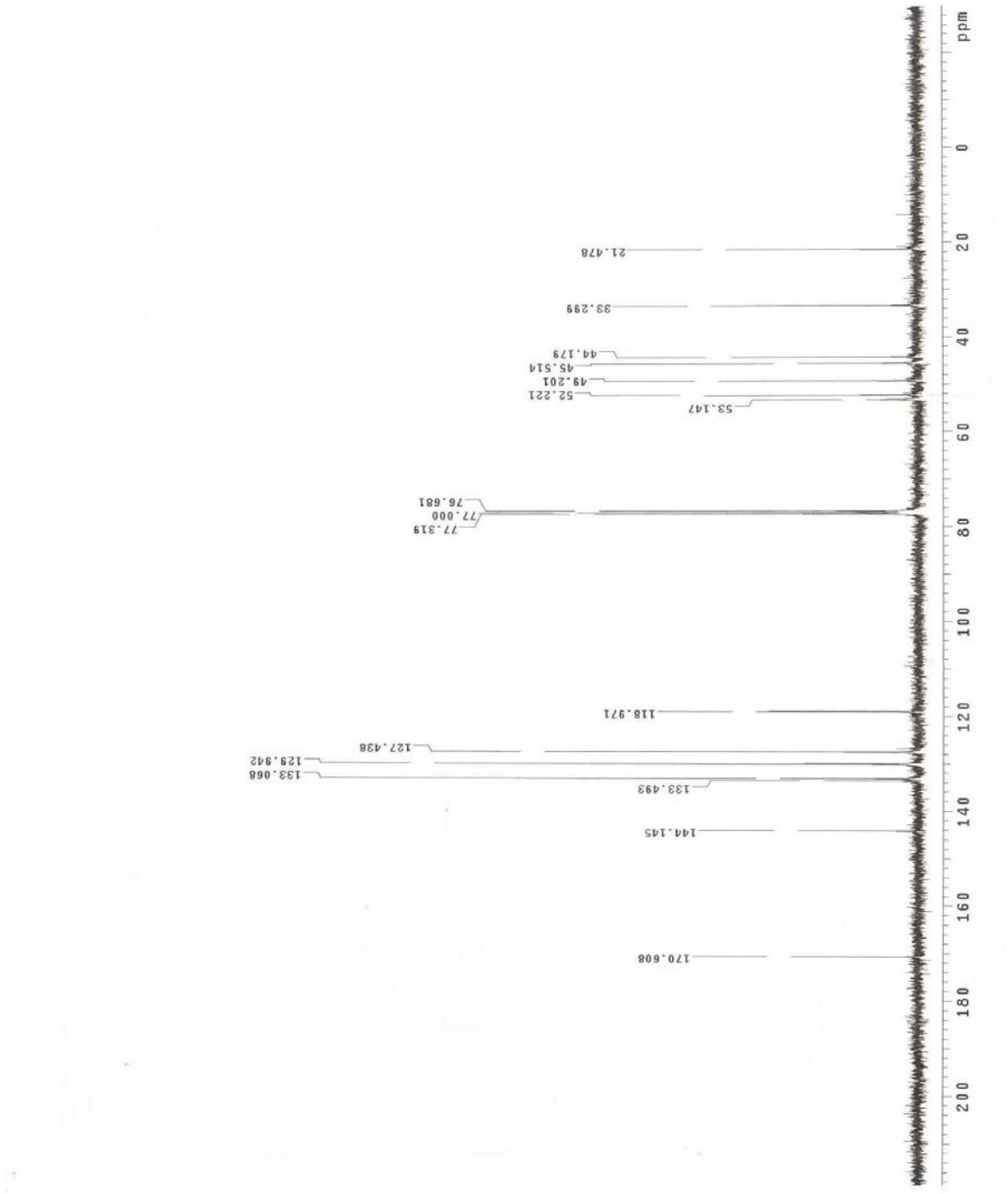
^{13}C NMR Spectrum of 4



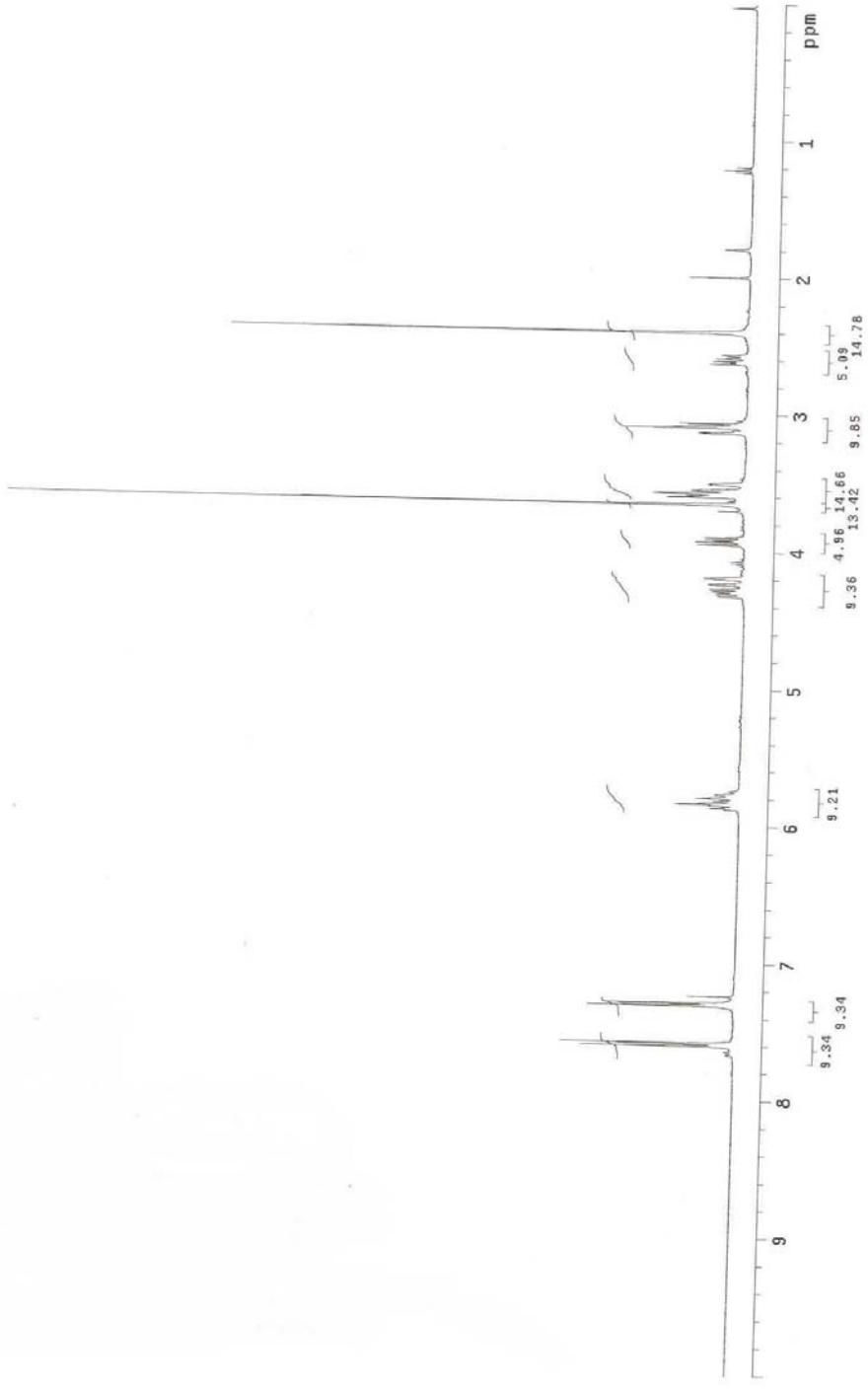
^{1}H NMR Spectrum of 5 (High R_f diastereomer)



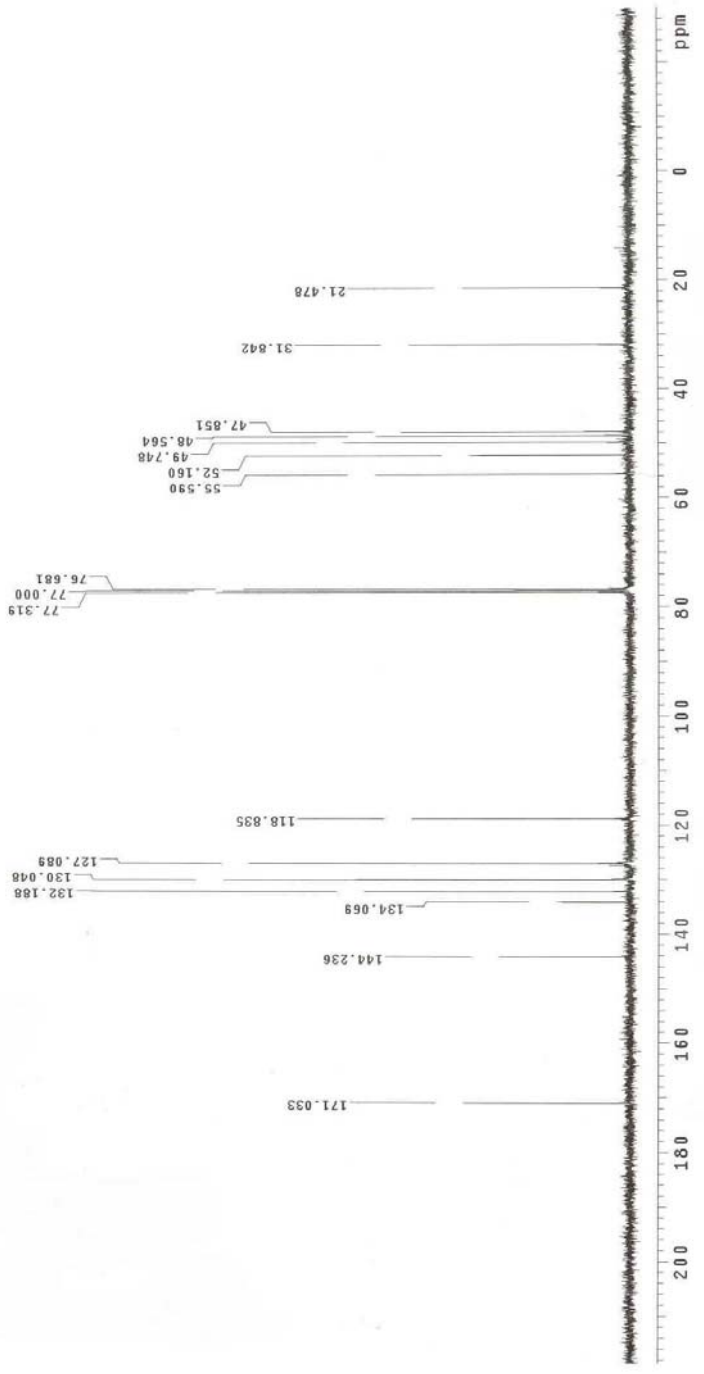
^{13}C NMR Spectrum of 5 (High R_f diastereomer)



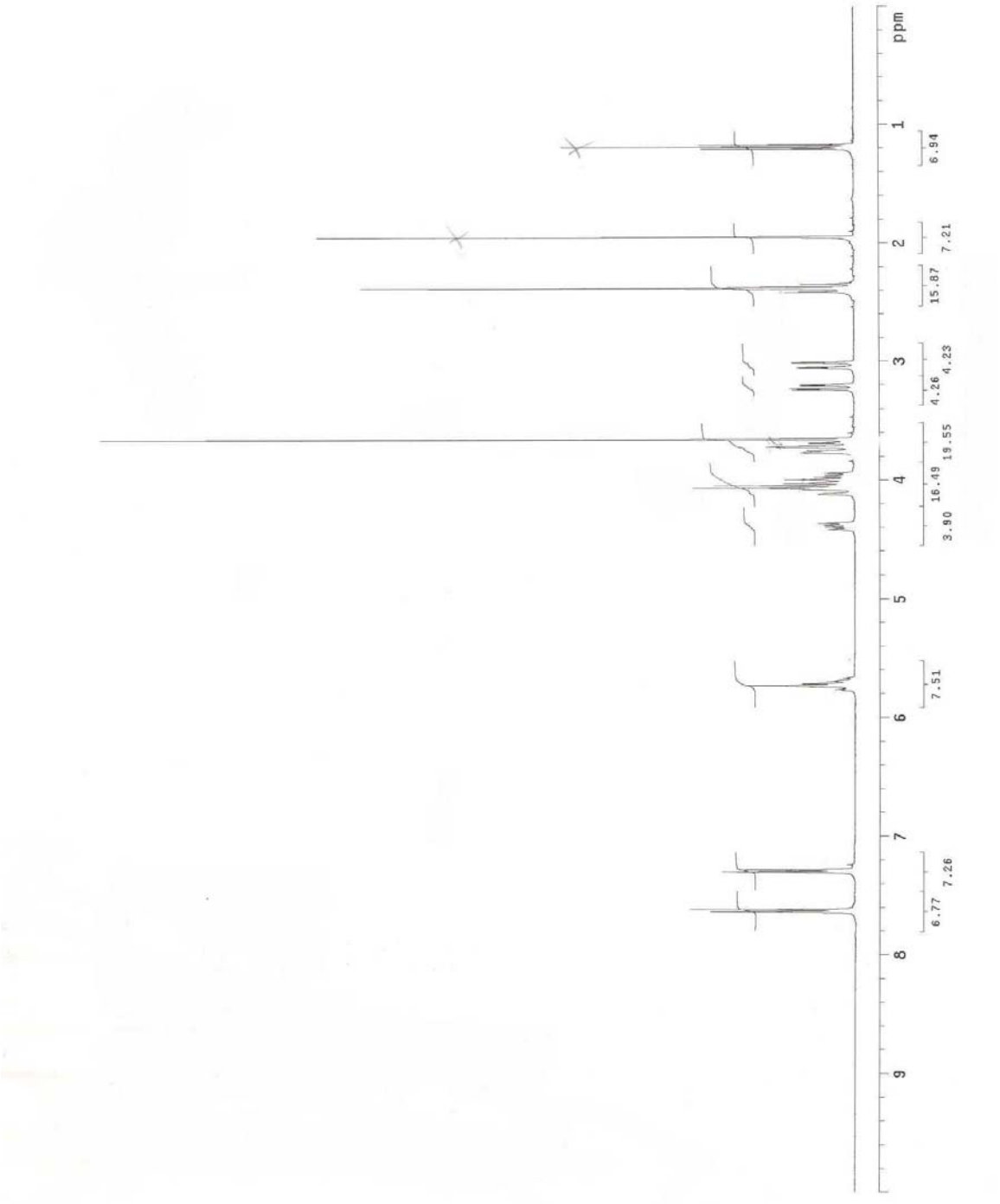
^{1}H NMR Spectrum of 5 (Low R_f diastereomer)



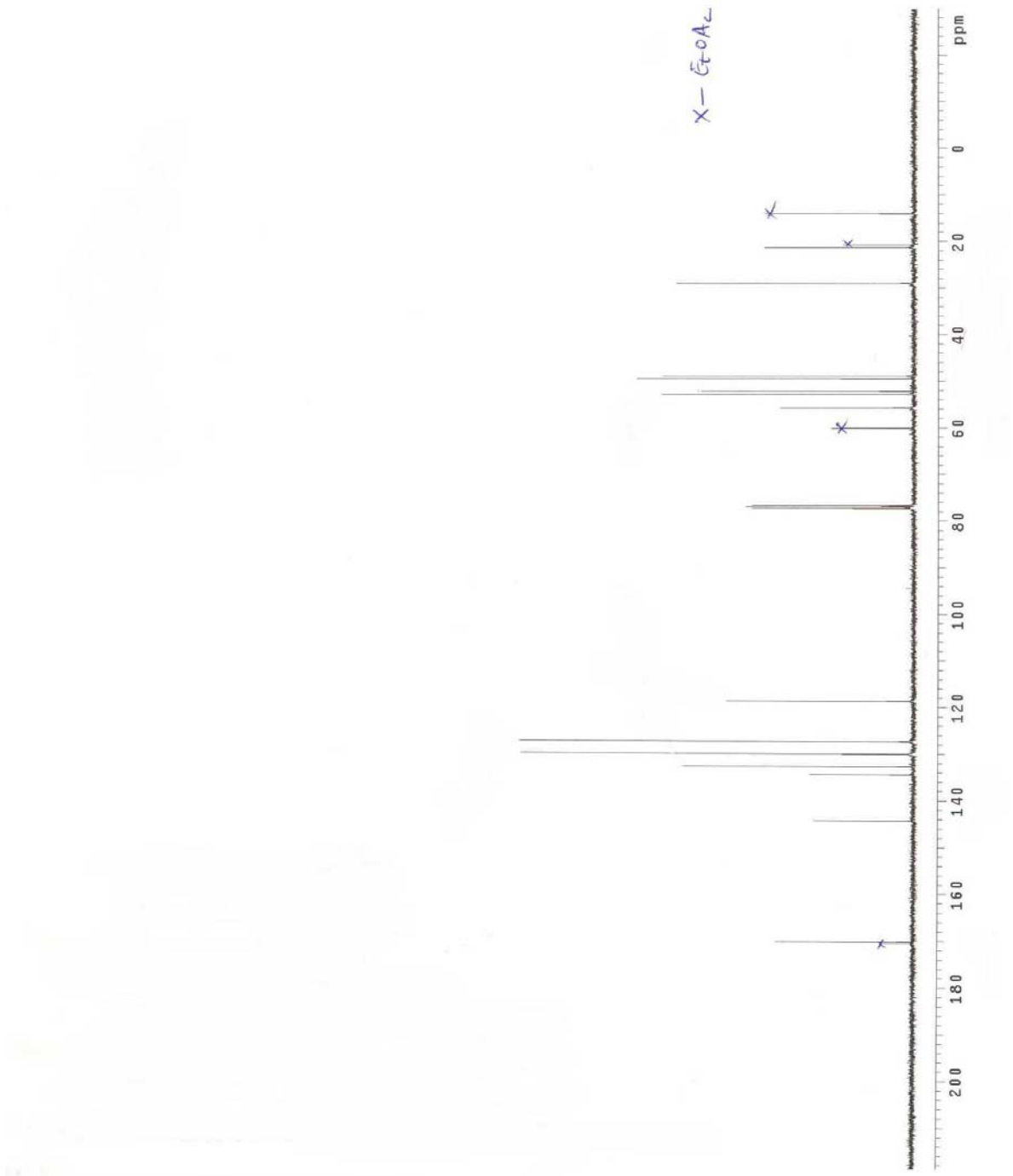
^{13}C NMR Spectrum of 5 (Low R_f diastereomer)



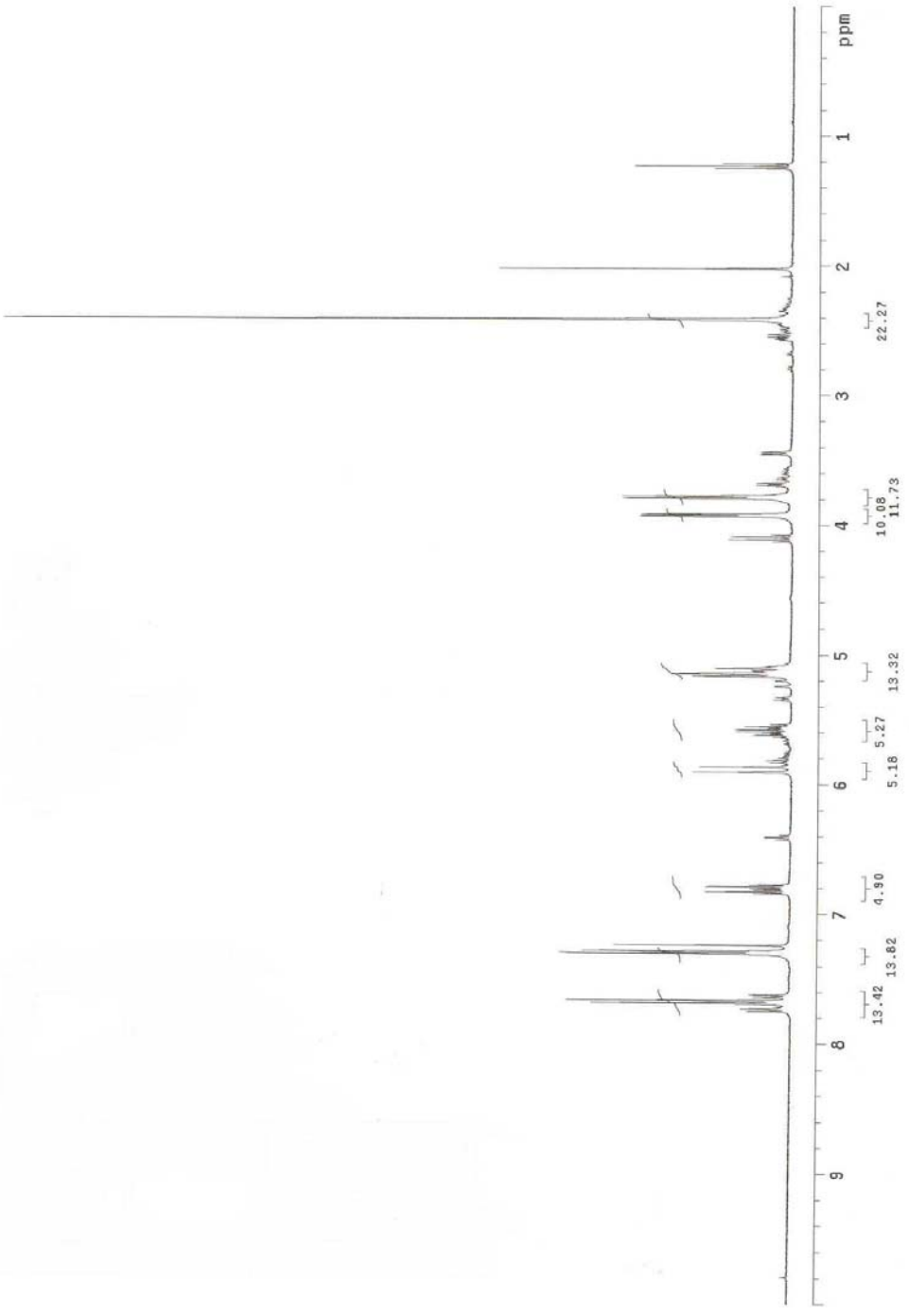
^{1}H NMR Spectrum of 6



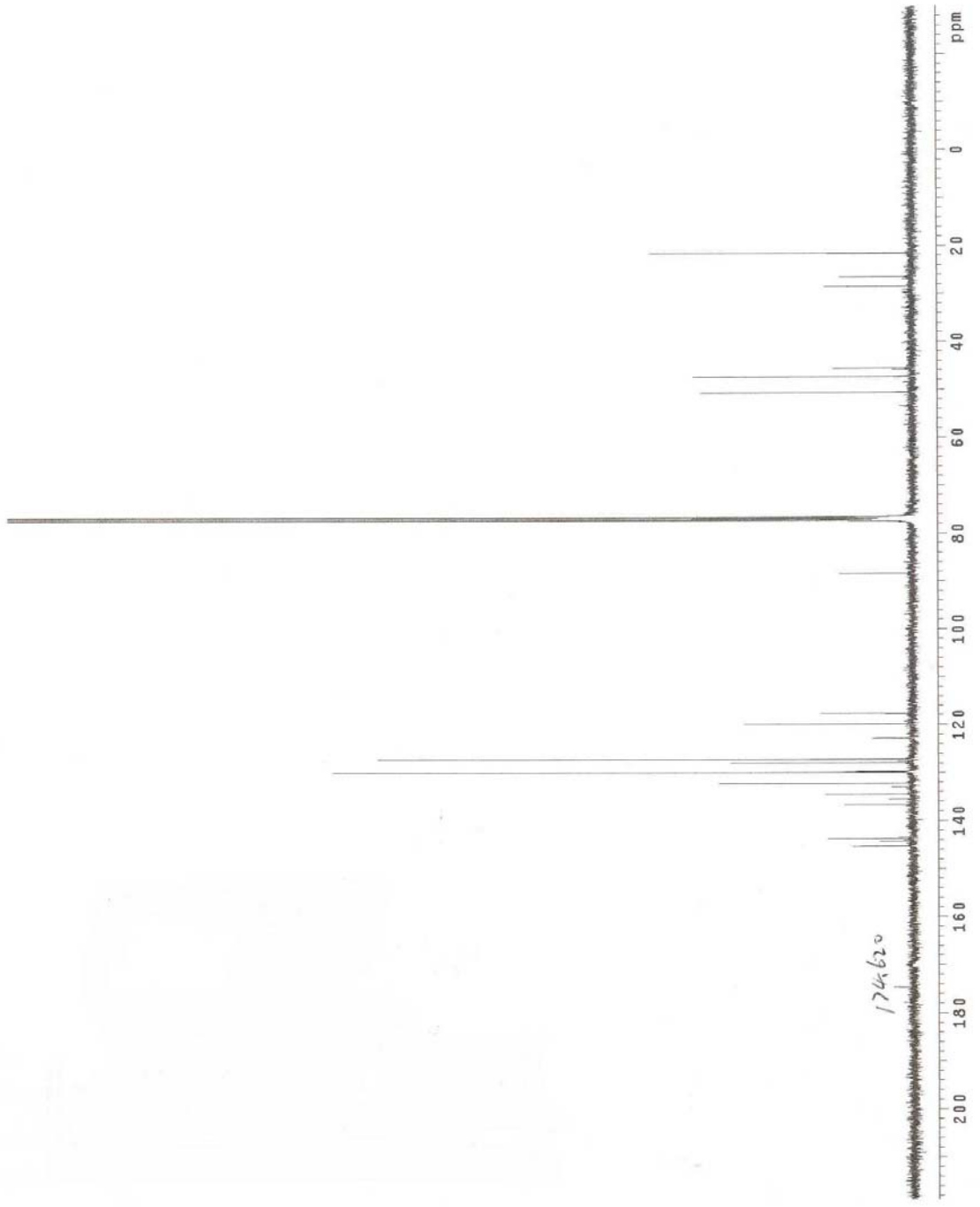
^{13}C NMR Spectrum of 6



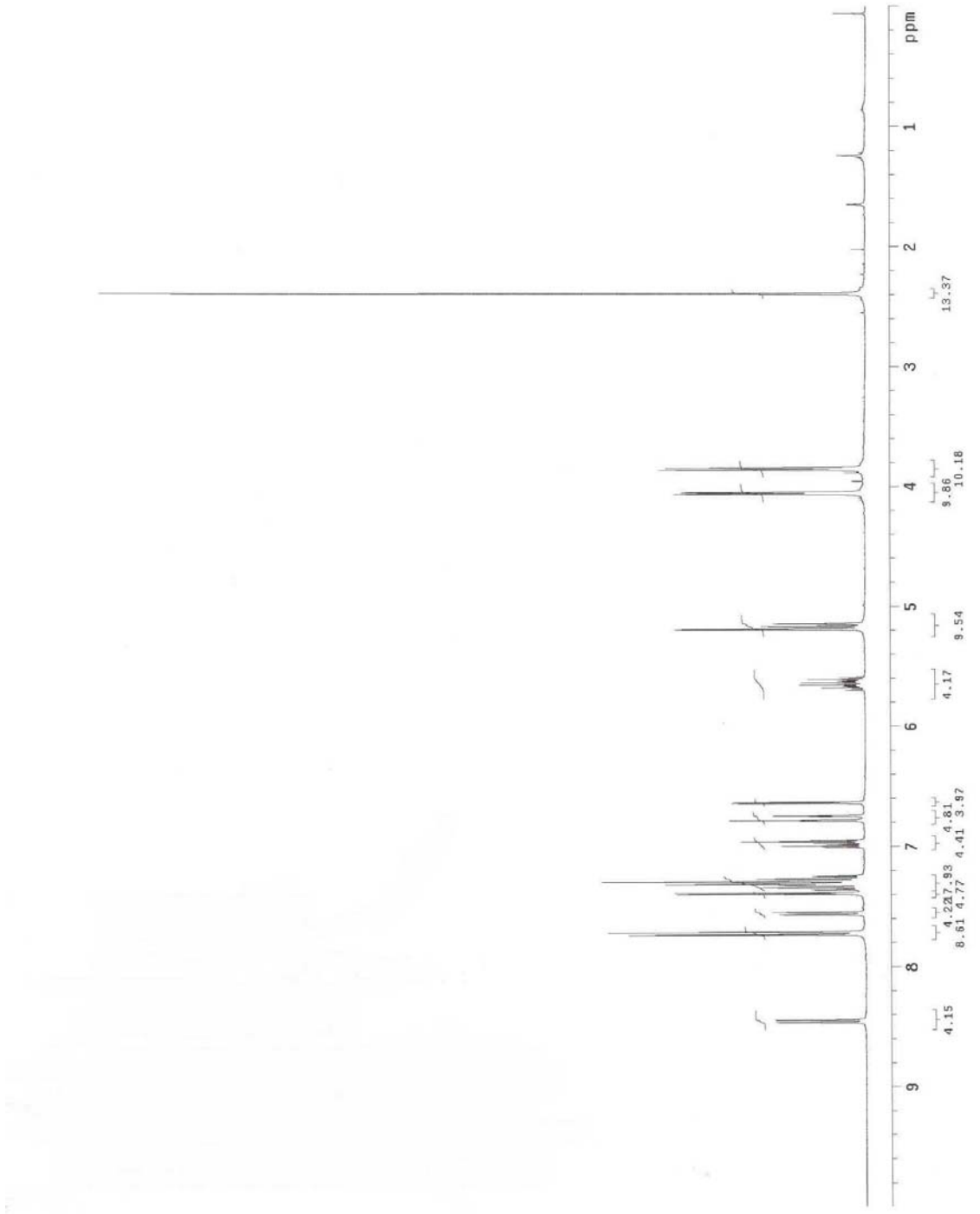
^{1}H NMR Spectrum of 7



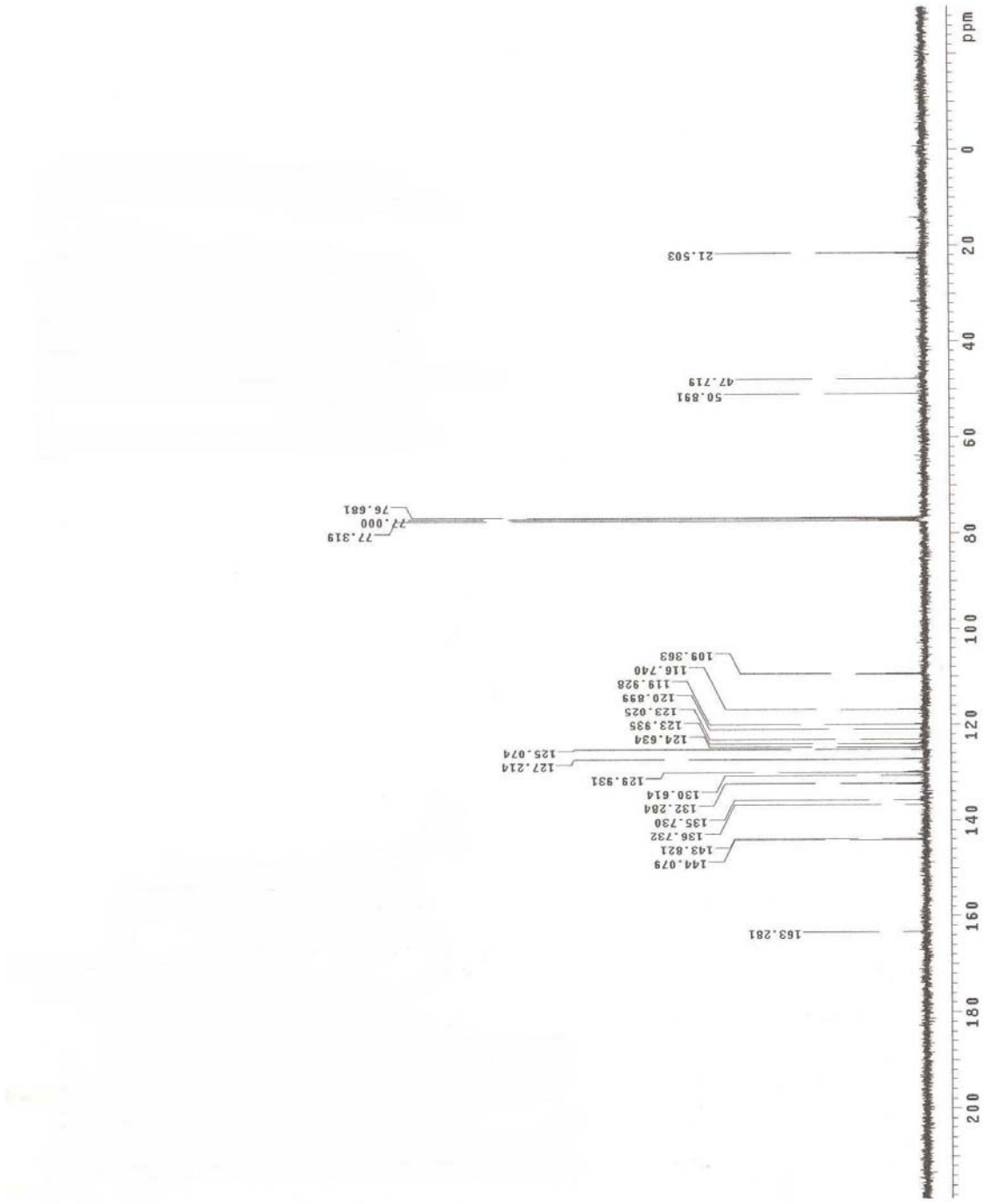
^{13}C NMR Spectrum of 7



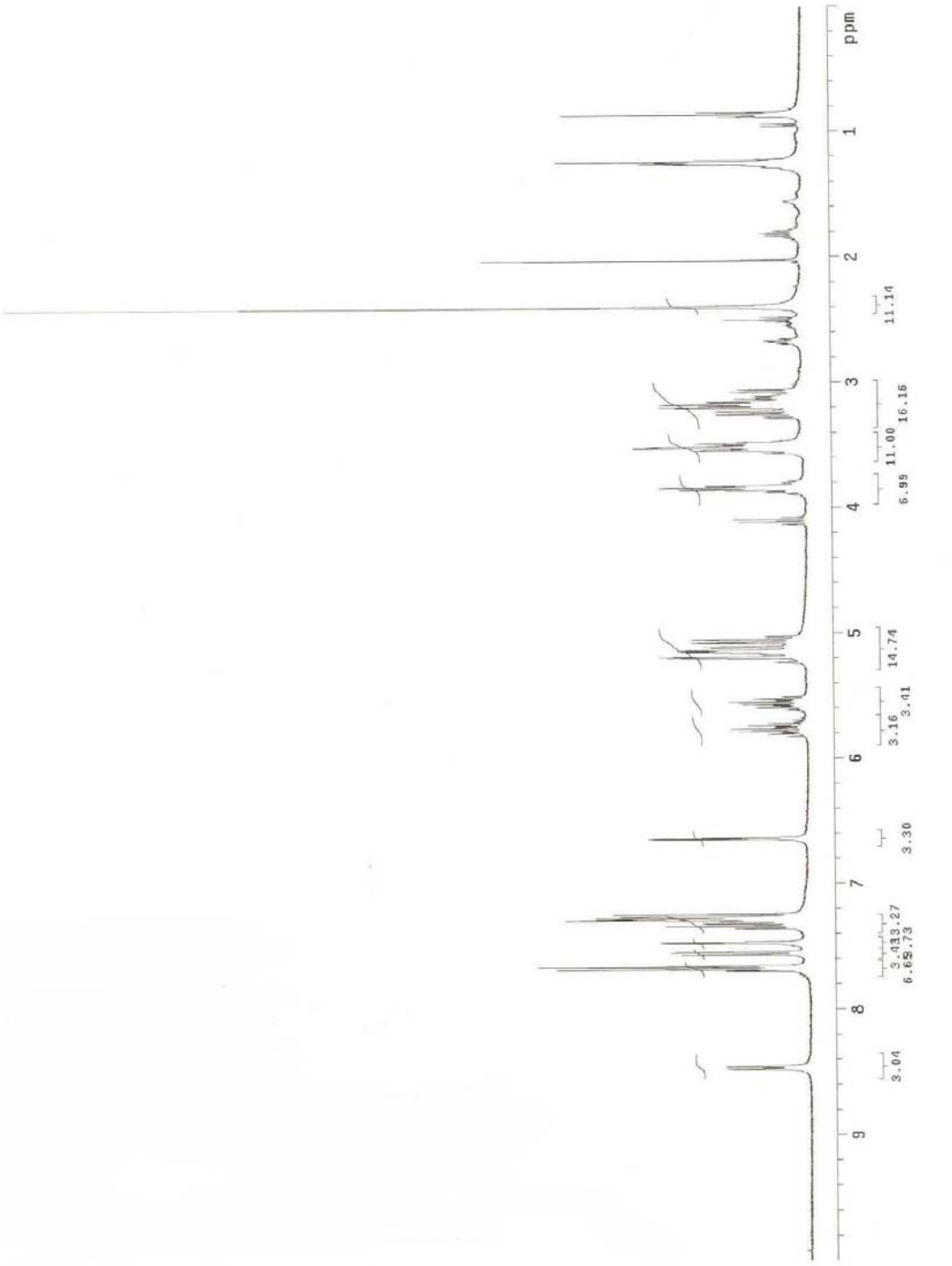
^{1}H NMR Spectrum of 8



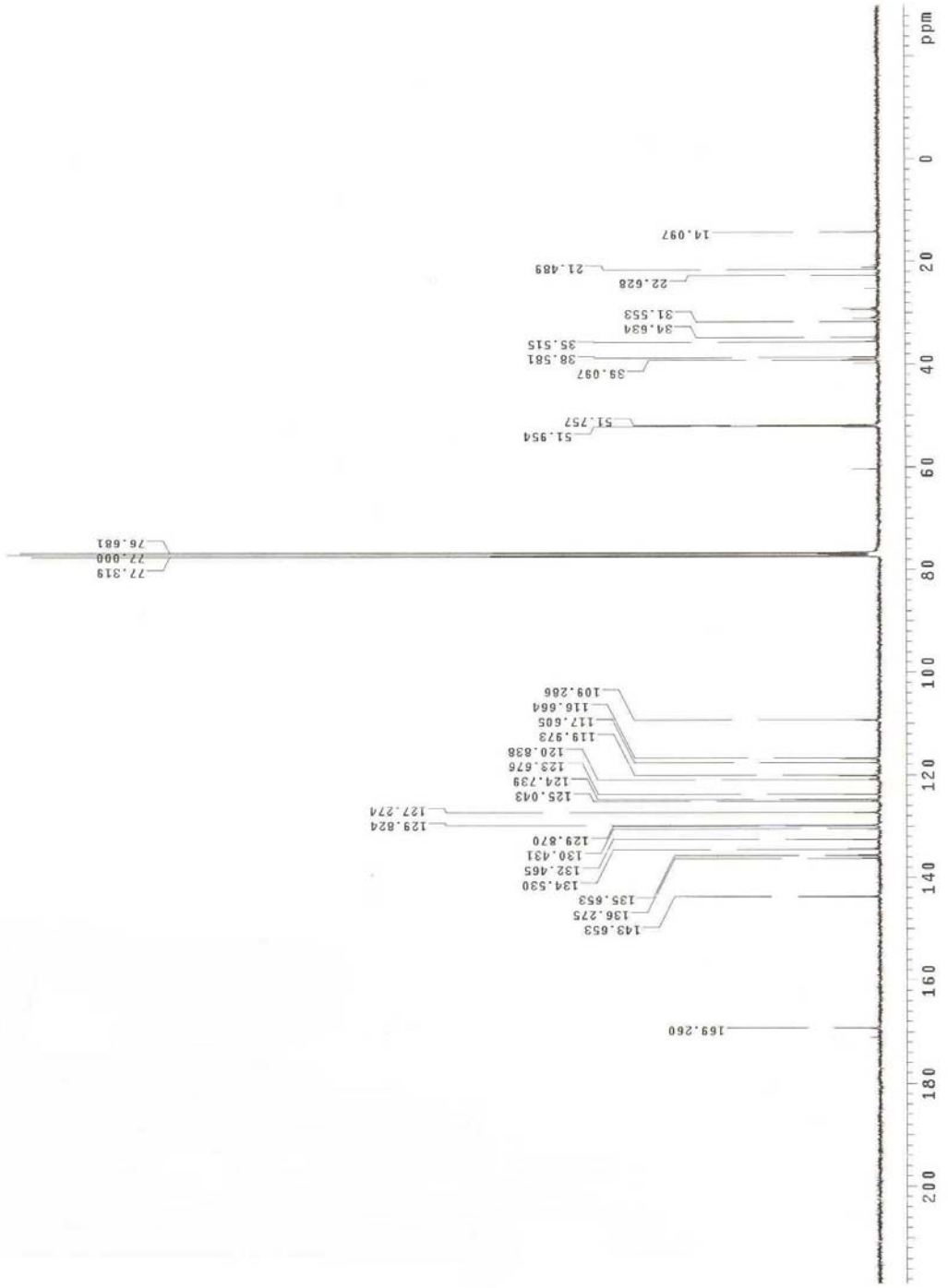
^{13}C NMR Spectrum of 8



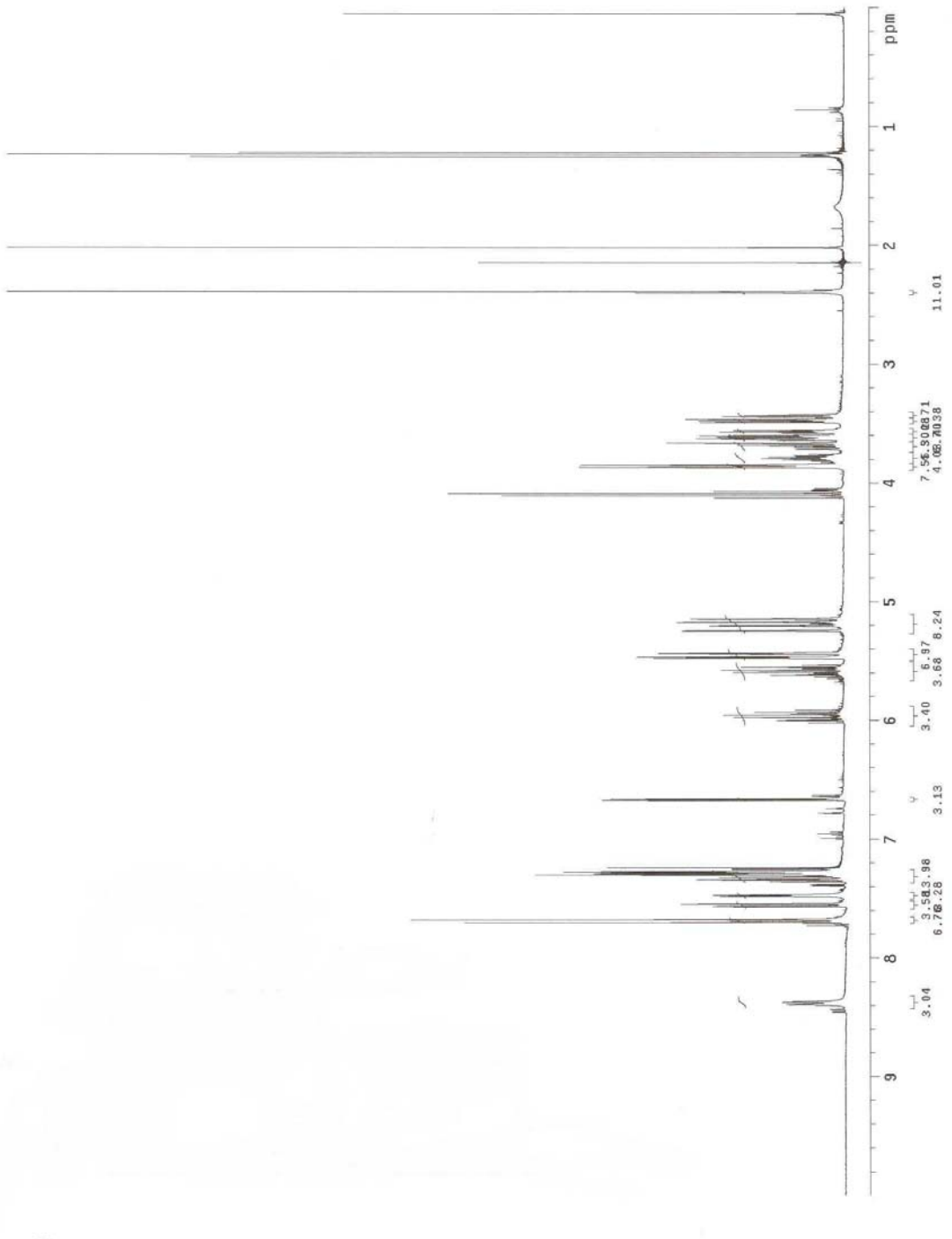
^{1}H NMR Spectrum of 9



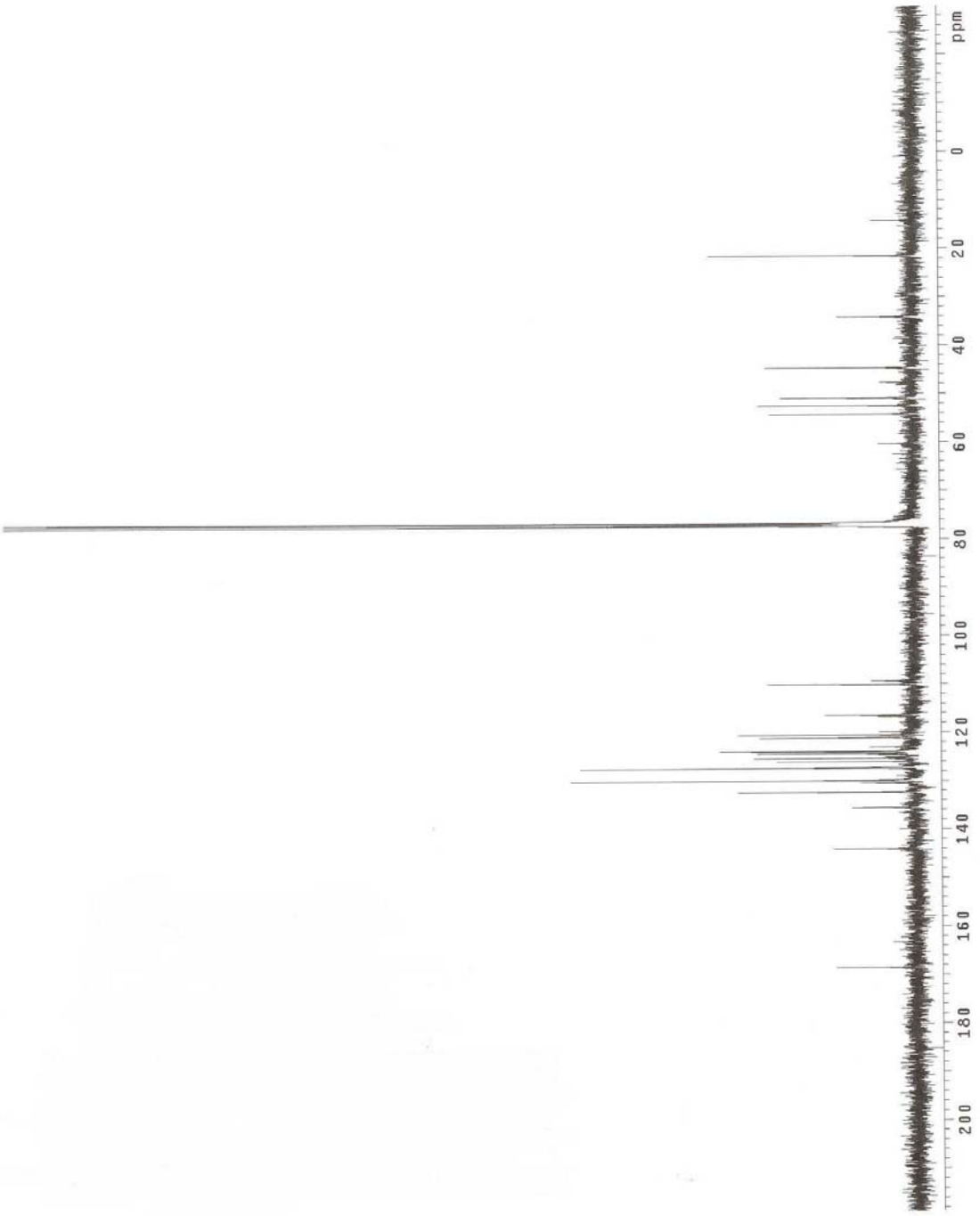
^{13}C NMR Spectrum of 9



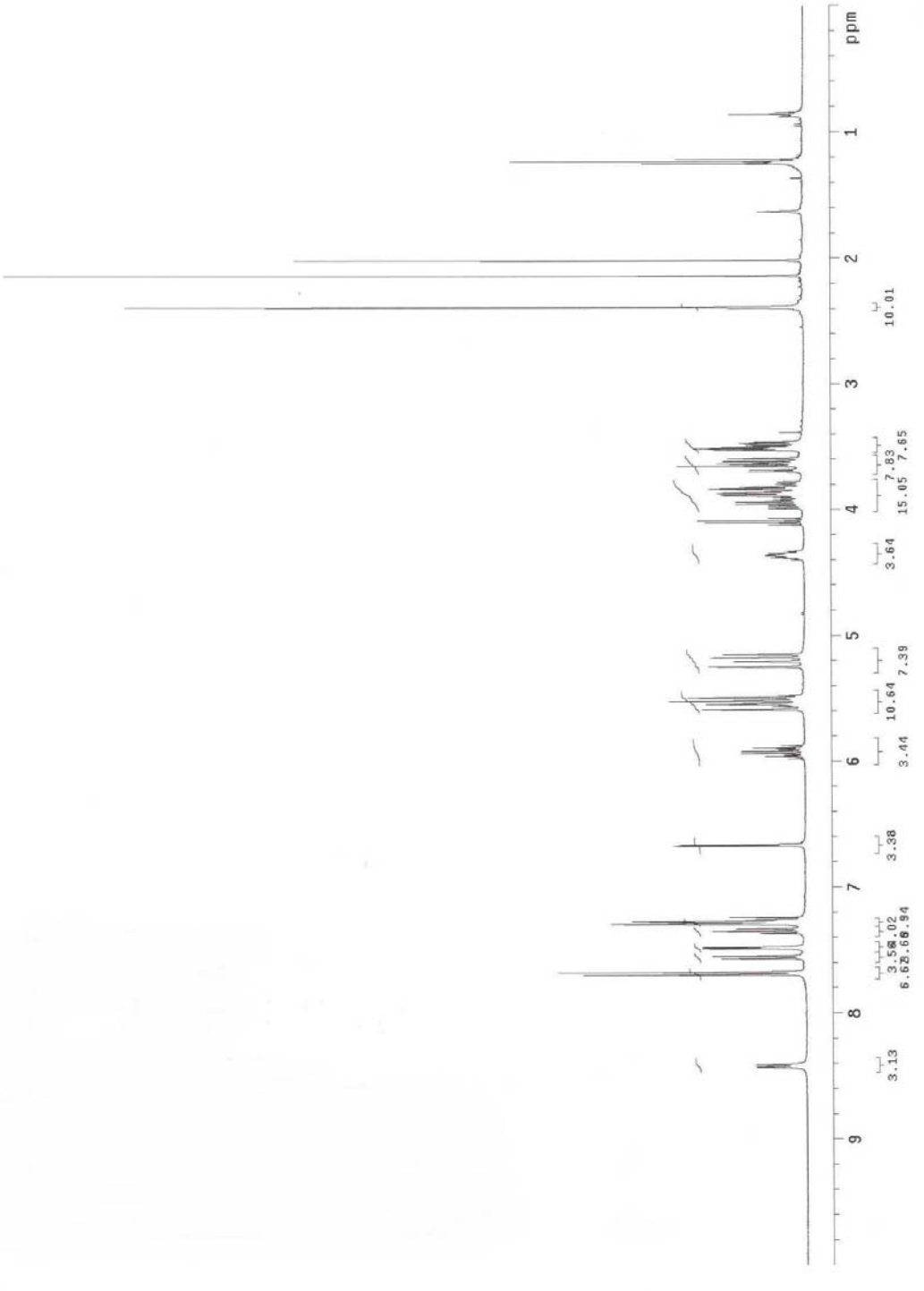
^{1}H NMR Spectrum of 10



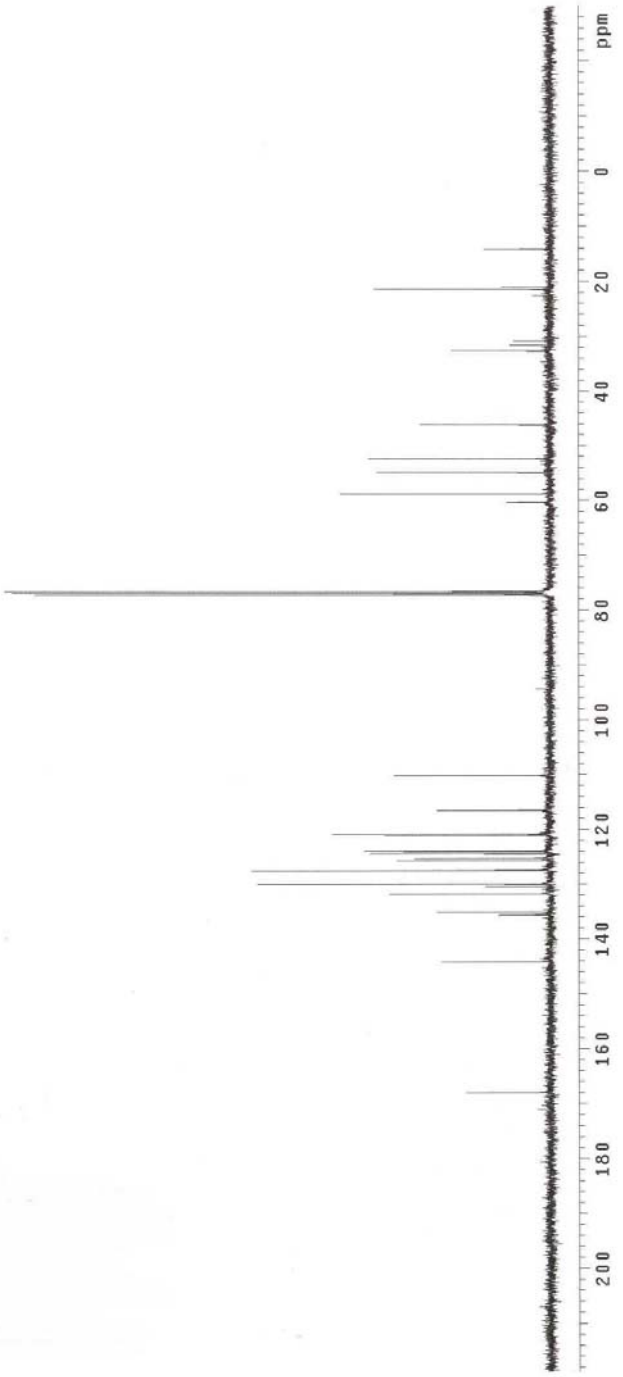
^{13}C NMR Spectrum of 10



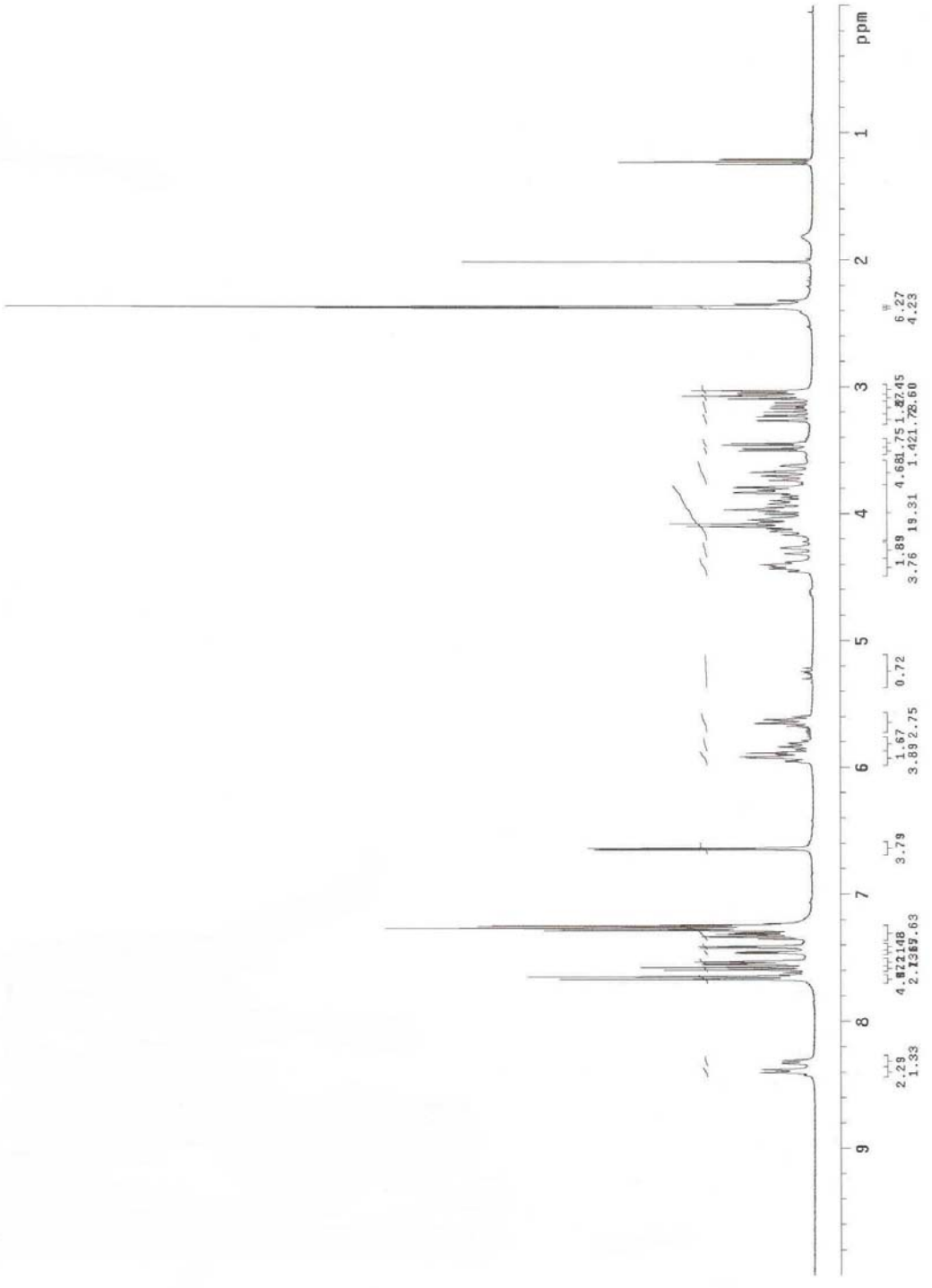
^{1}H NMR Spectrum of 11



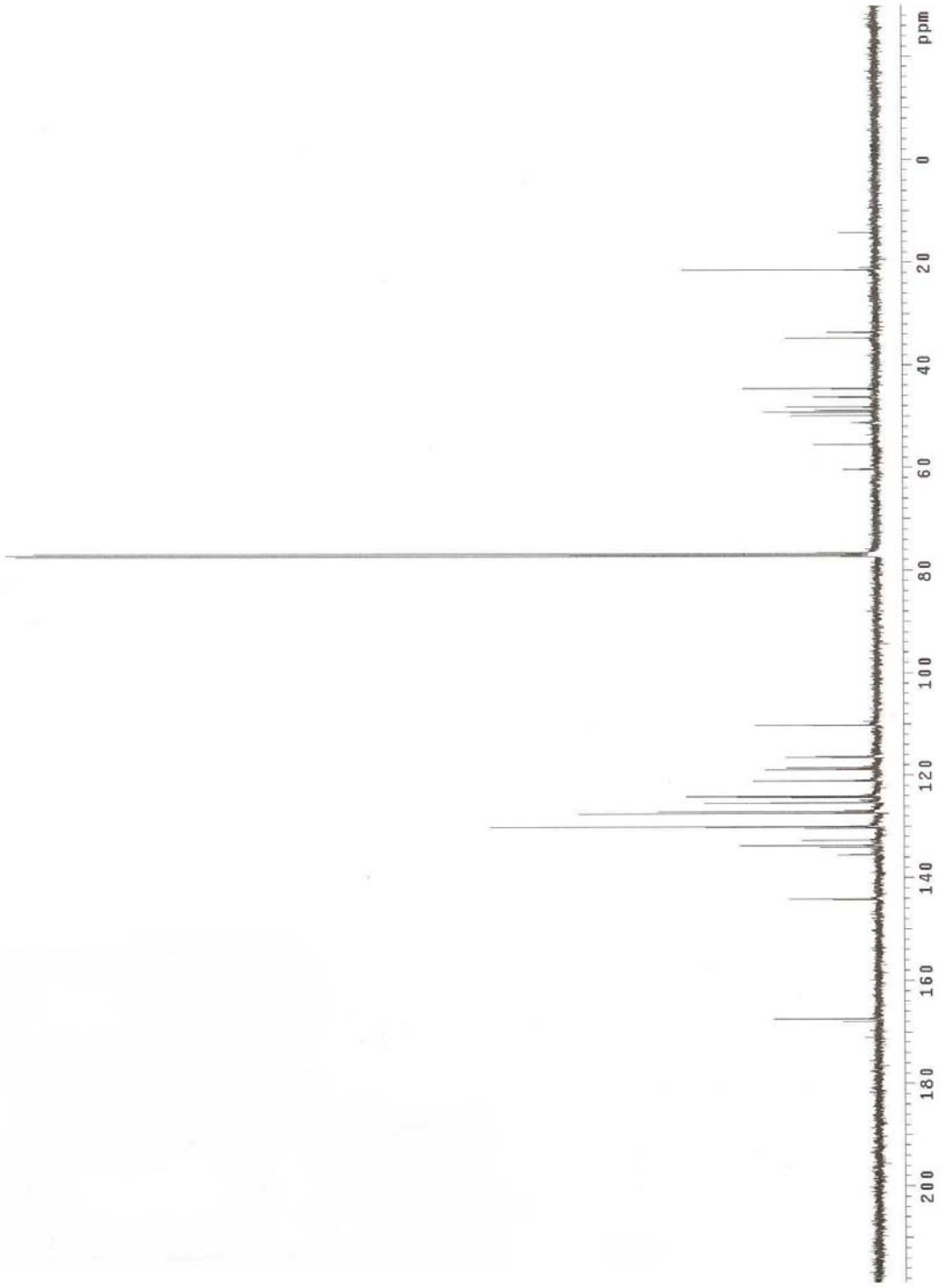
^{13}C NMR Spectrum of 11



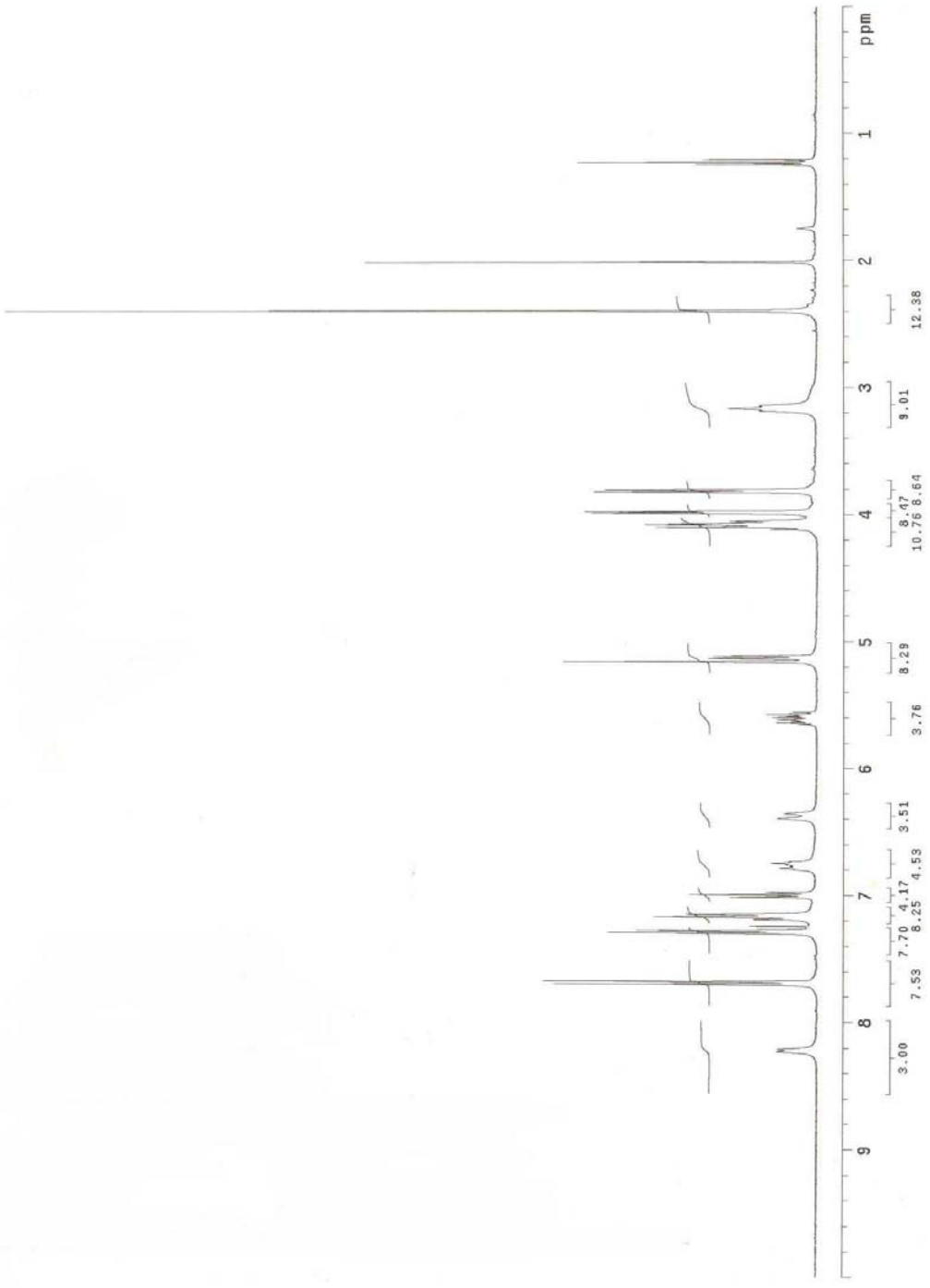
^{1}H NMR Spectrum of 12



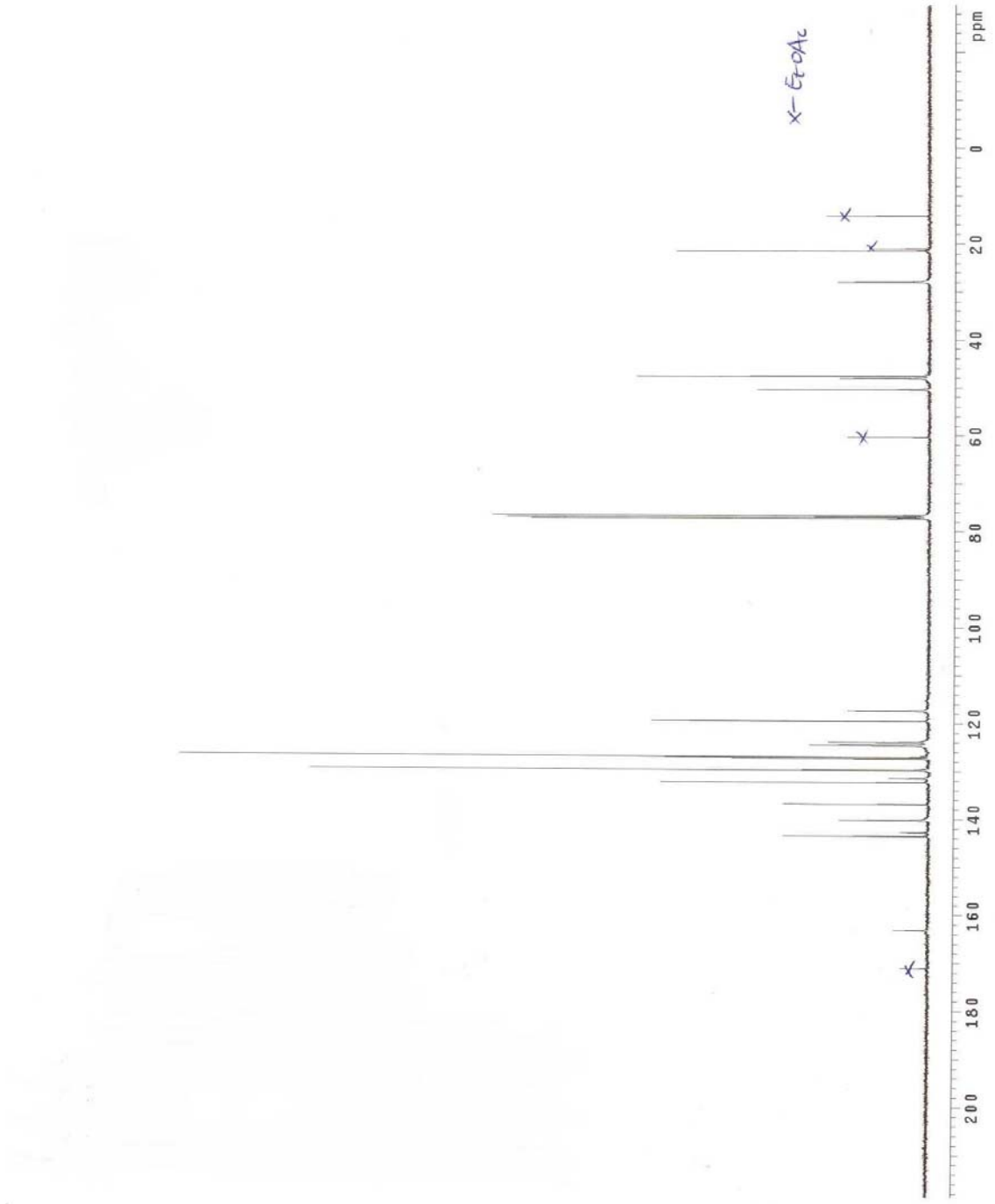
^{13}C NMR Spectrum of 12



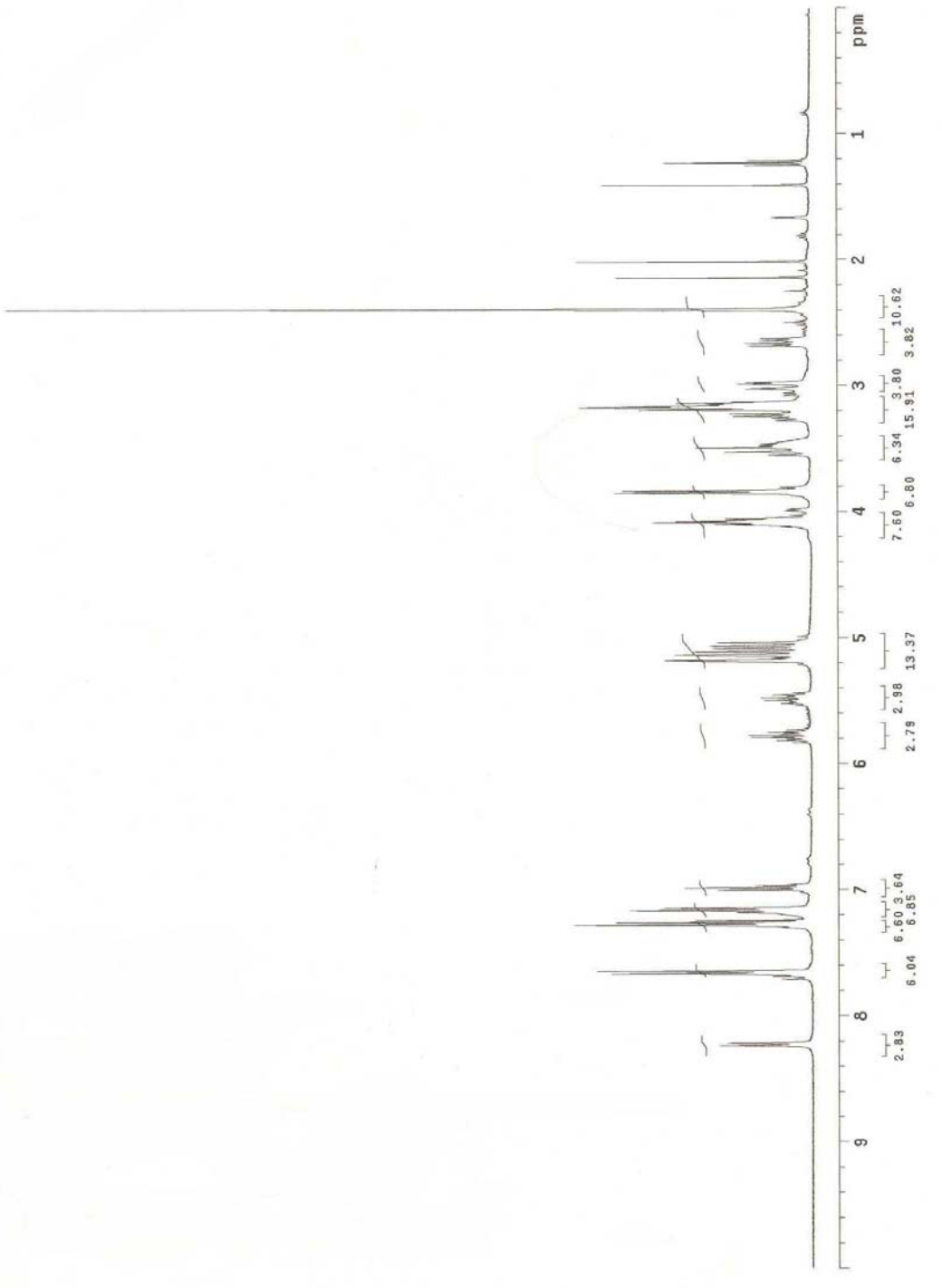
^{1}H NMR Spectrum of 14



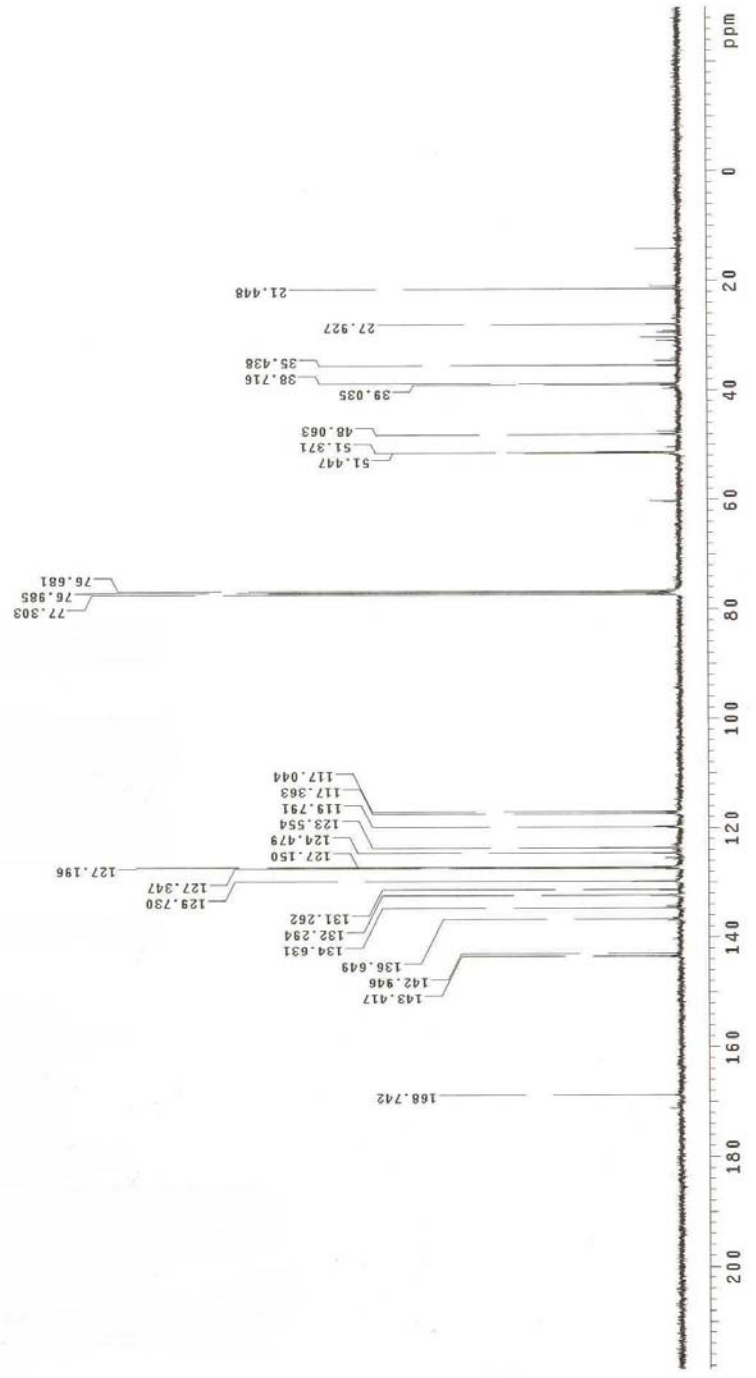
^{13}C NMR Spectrum of 14



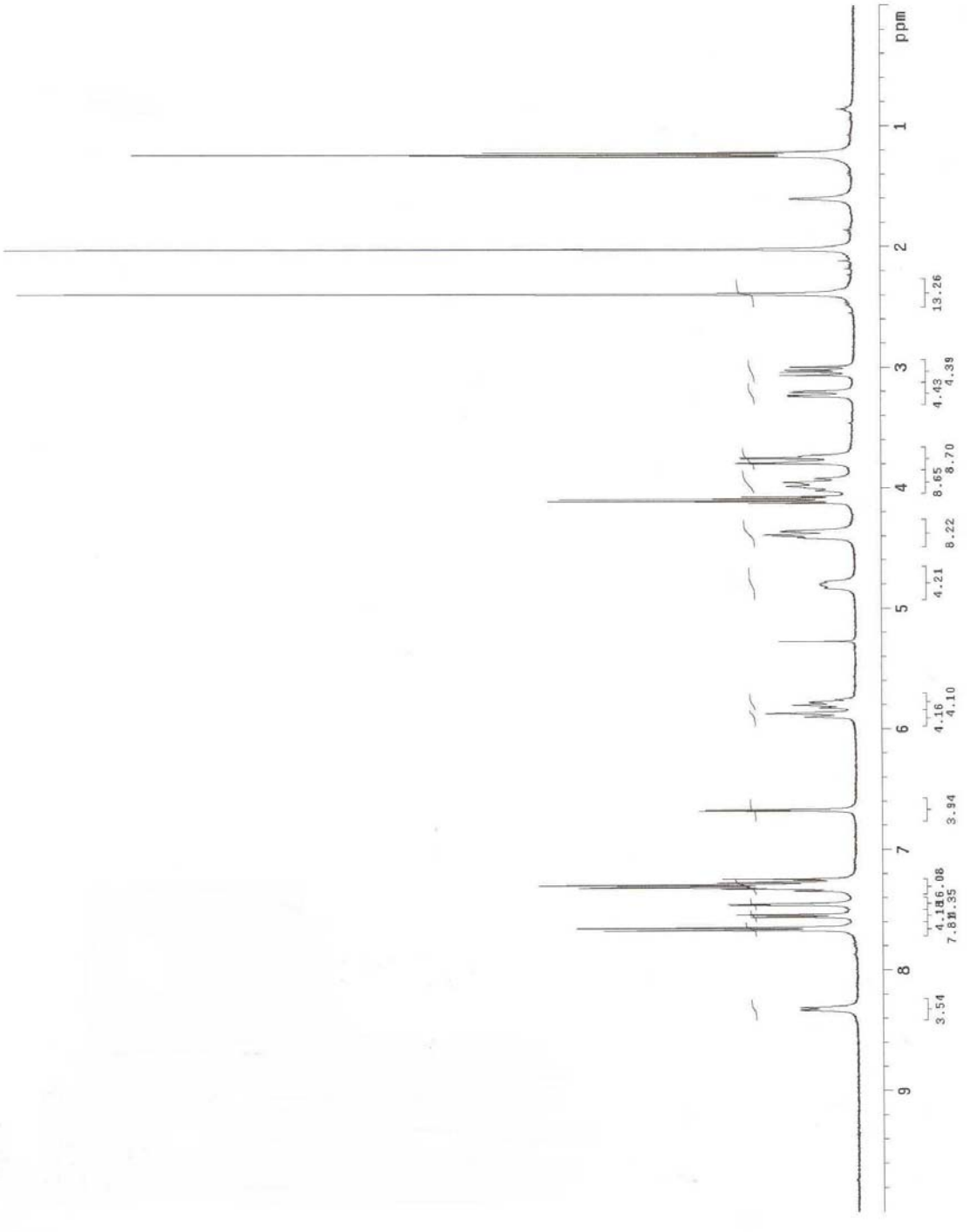
^{1}H NMR Spectrum of 15



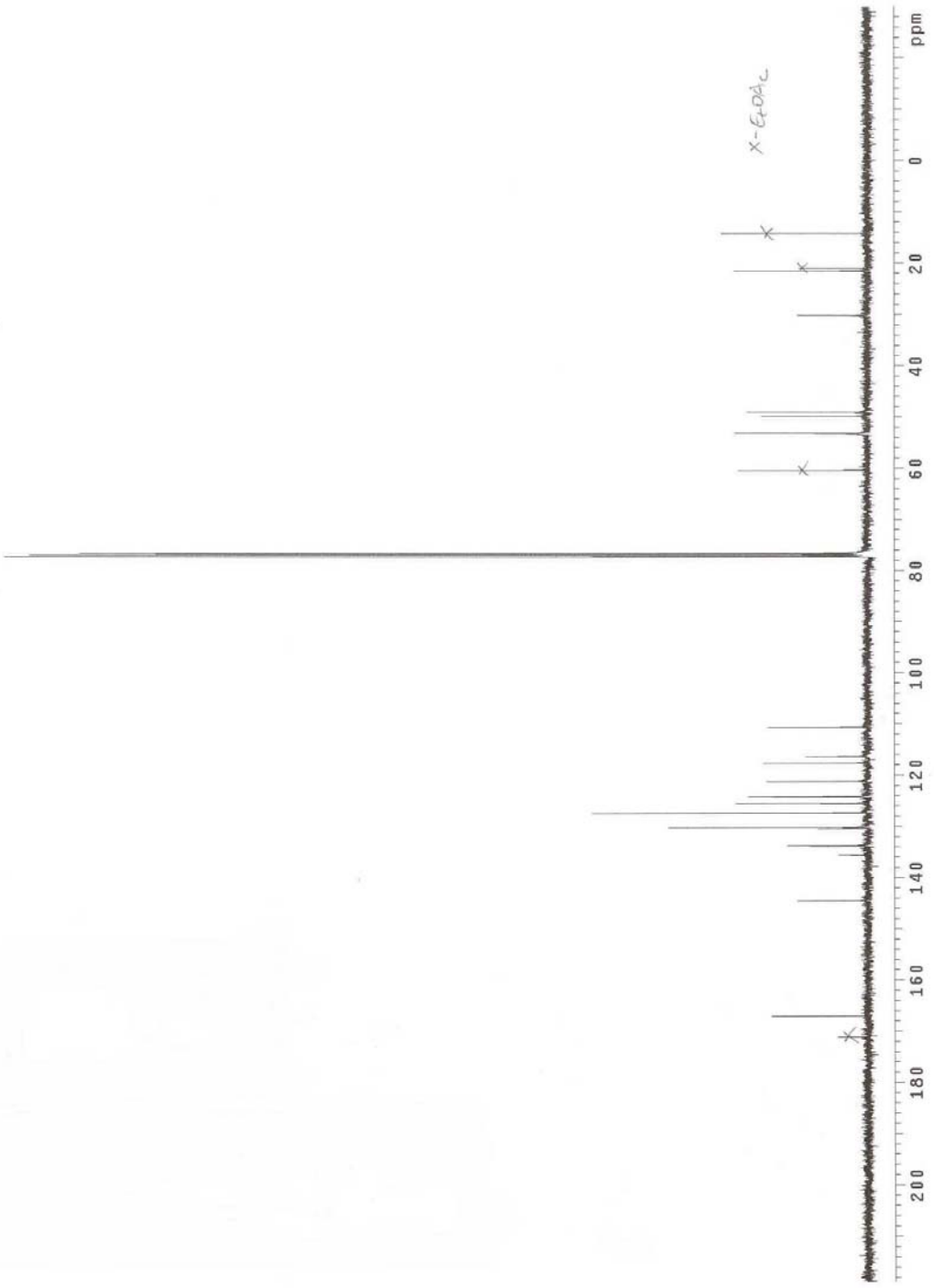
^{13}C NMR Spectrum of 15



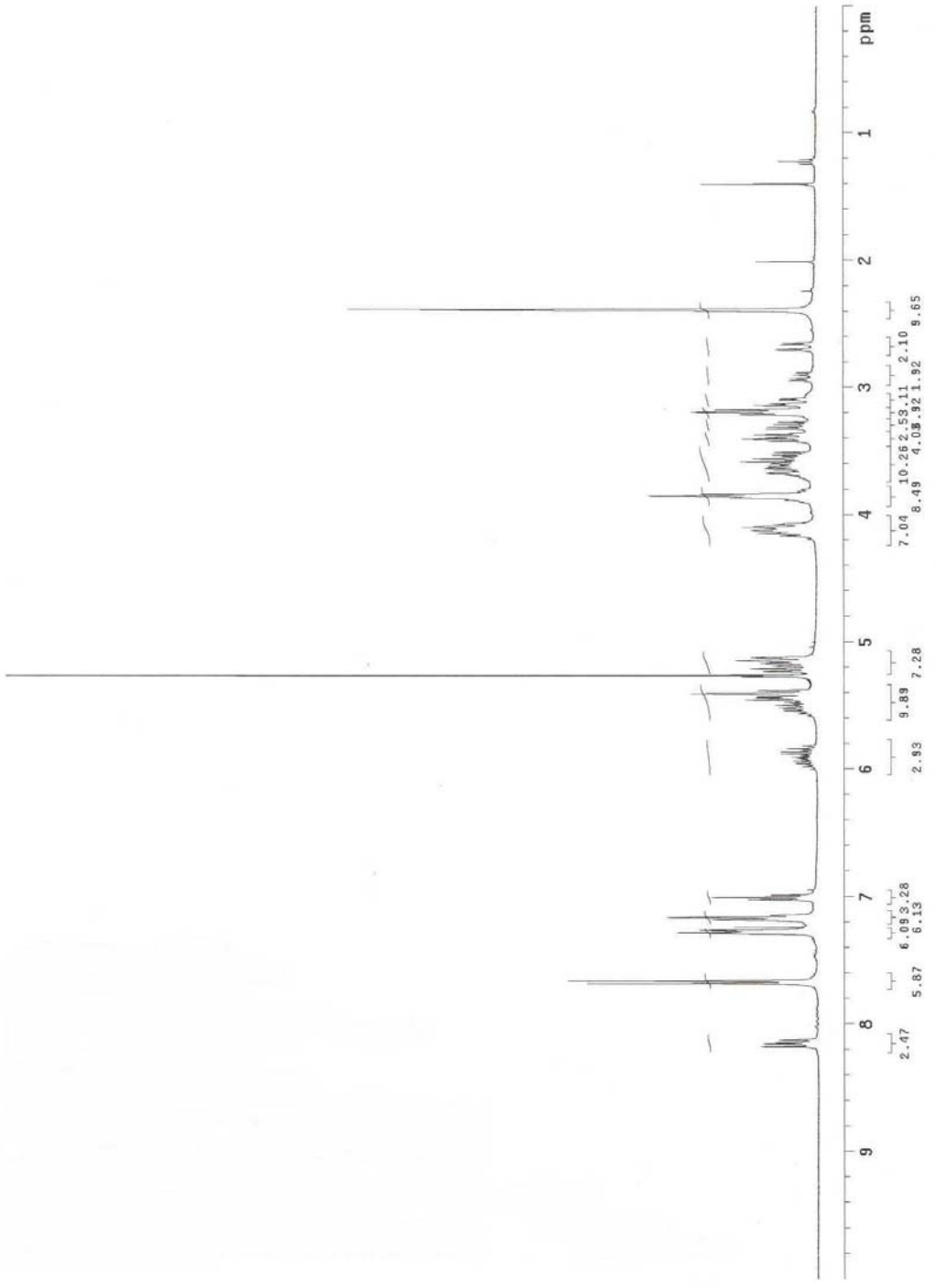
^{1}H NMR Spectrum of 16



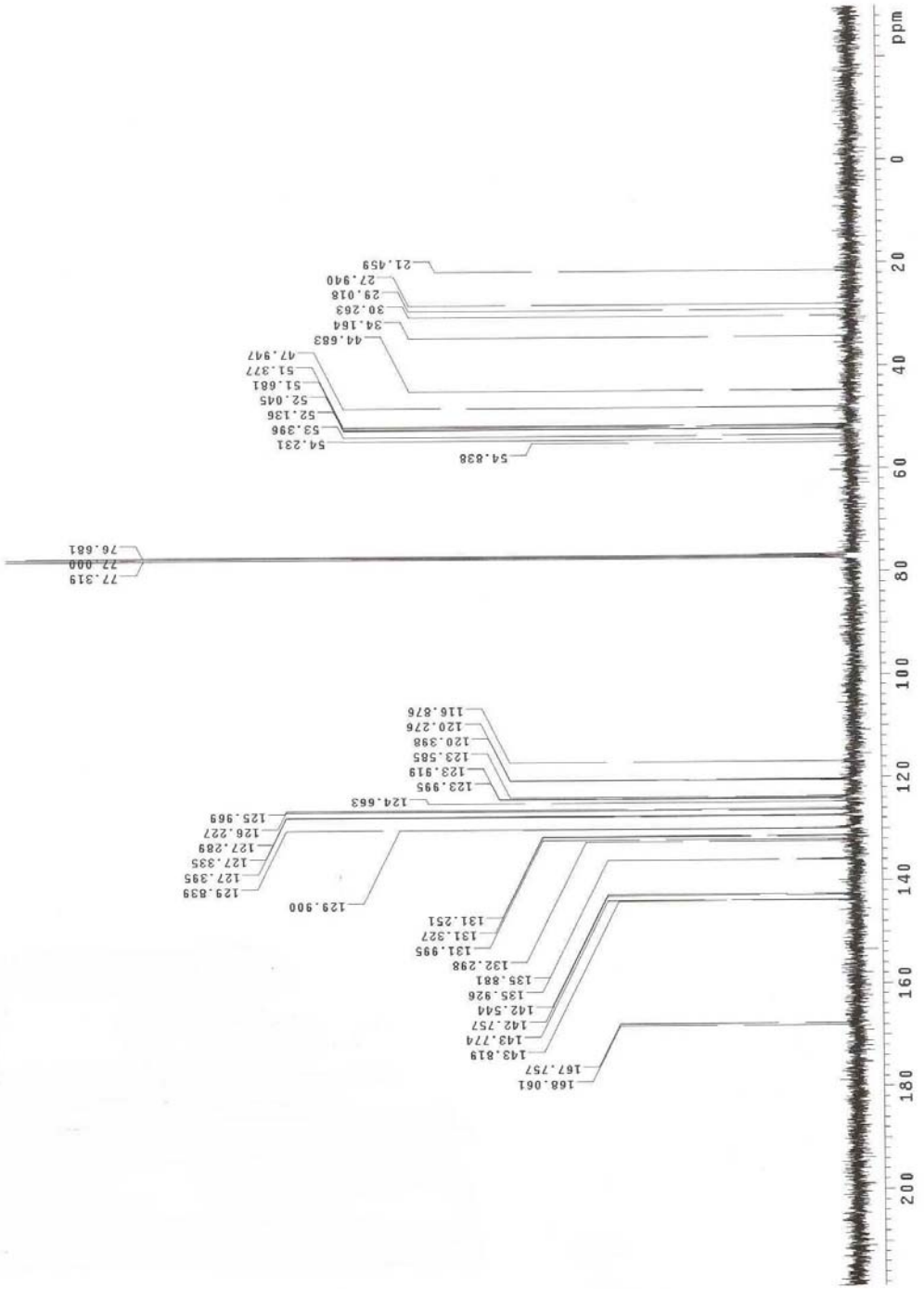
^{13}C NMR Spectrum of 16



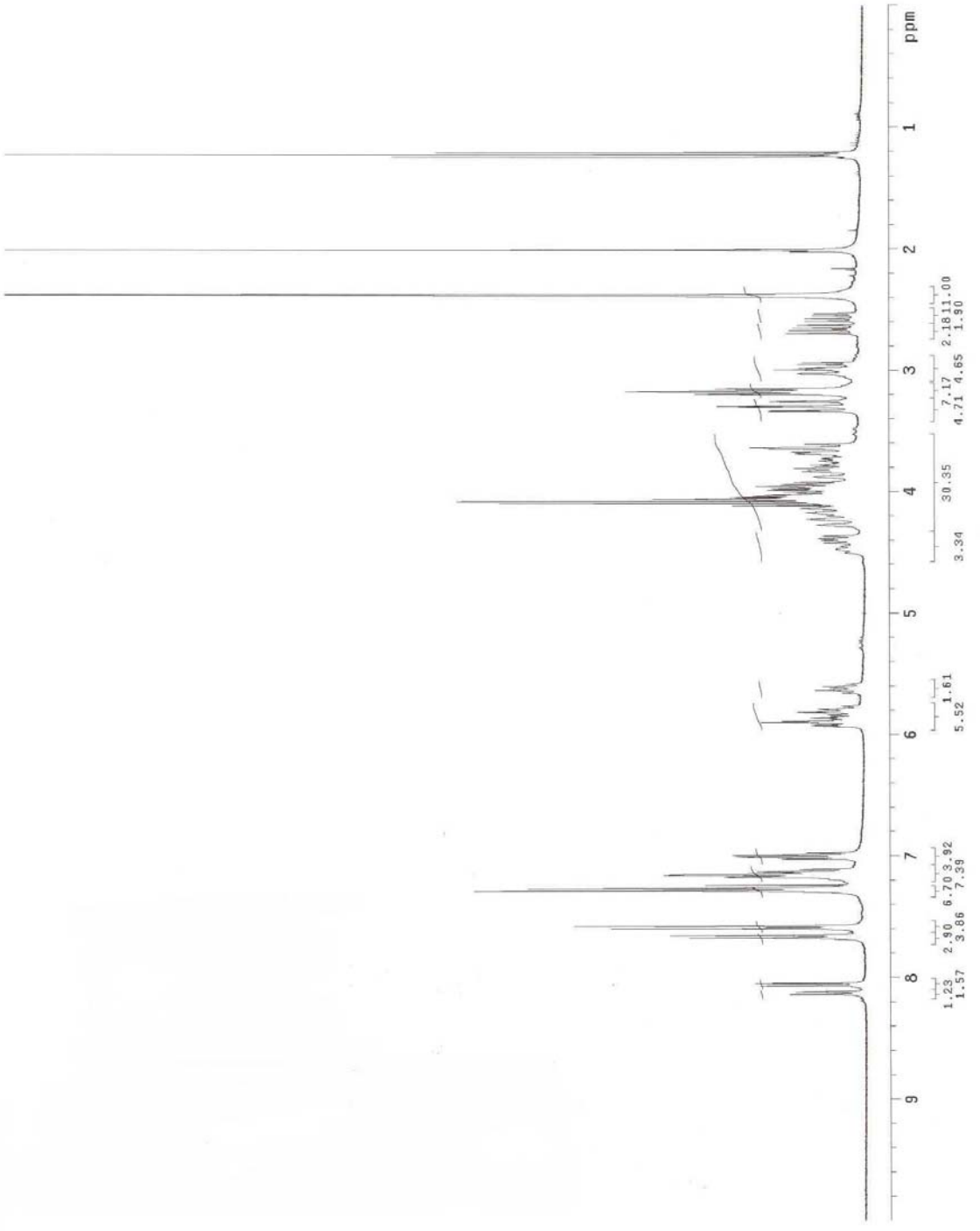
^{1}H NMR Spectrum of 17



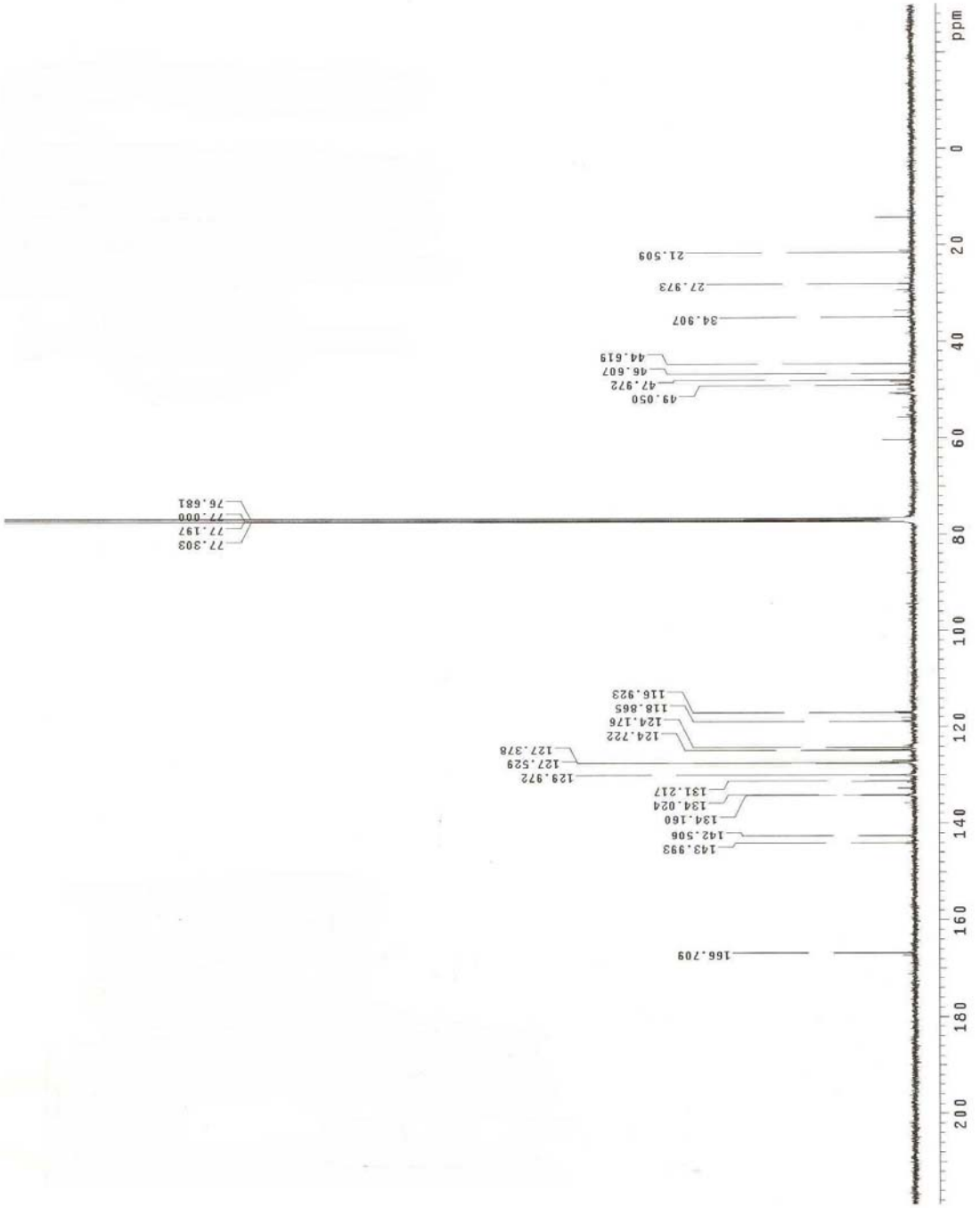
^{13}C NMR Spectrum of 17



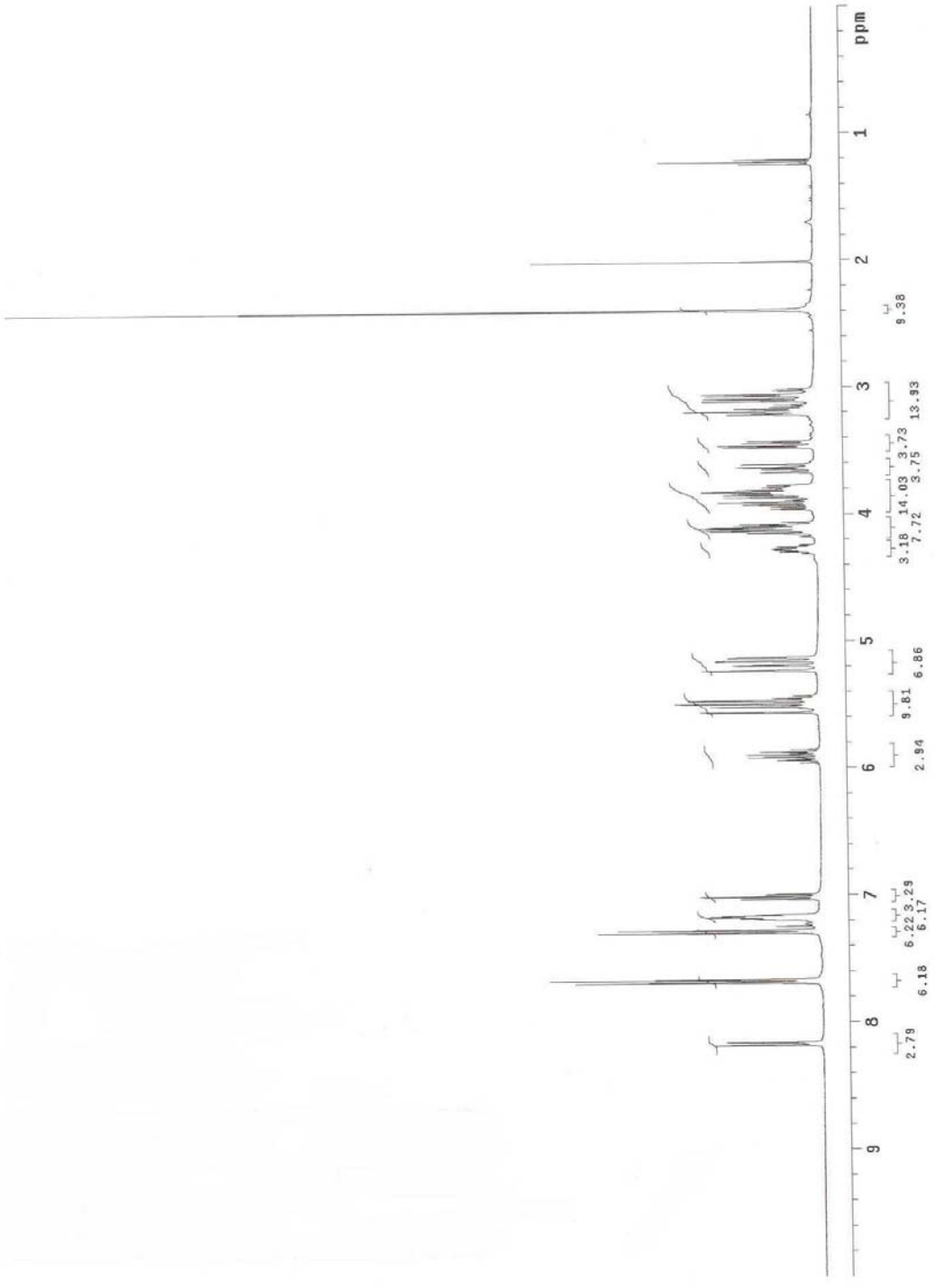
^{1}H NMR Spectrum of 18



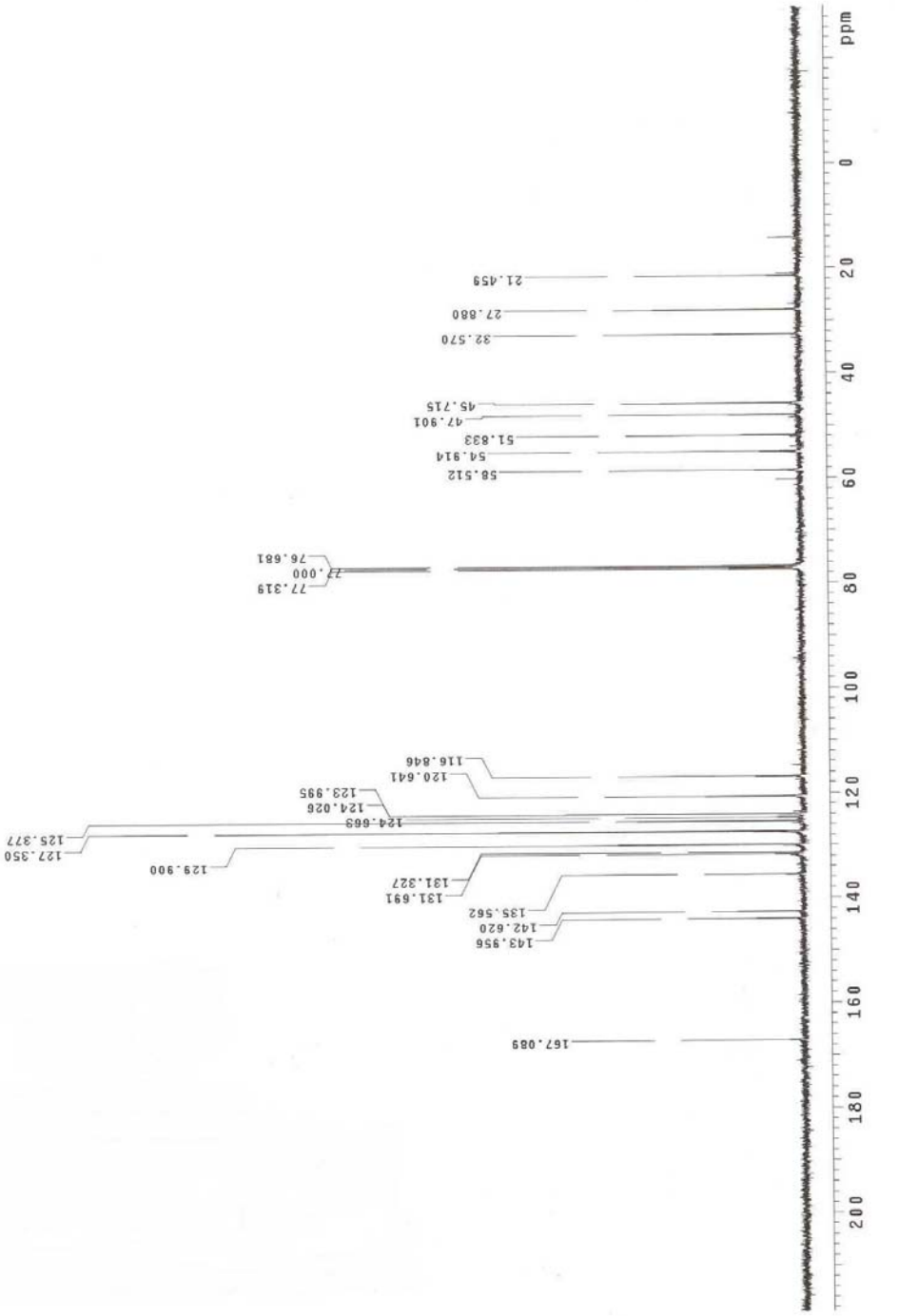
^{13}C NMR Spectrum of 18



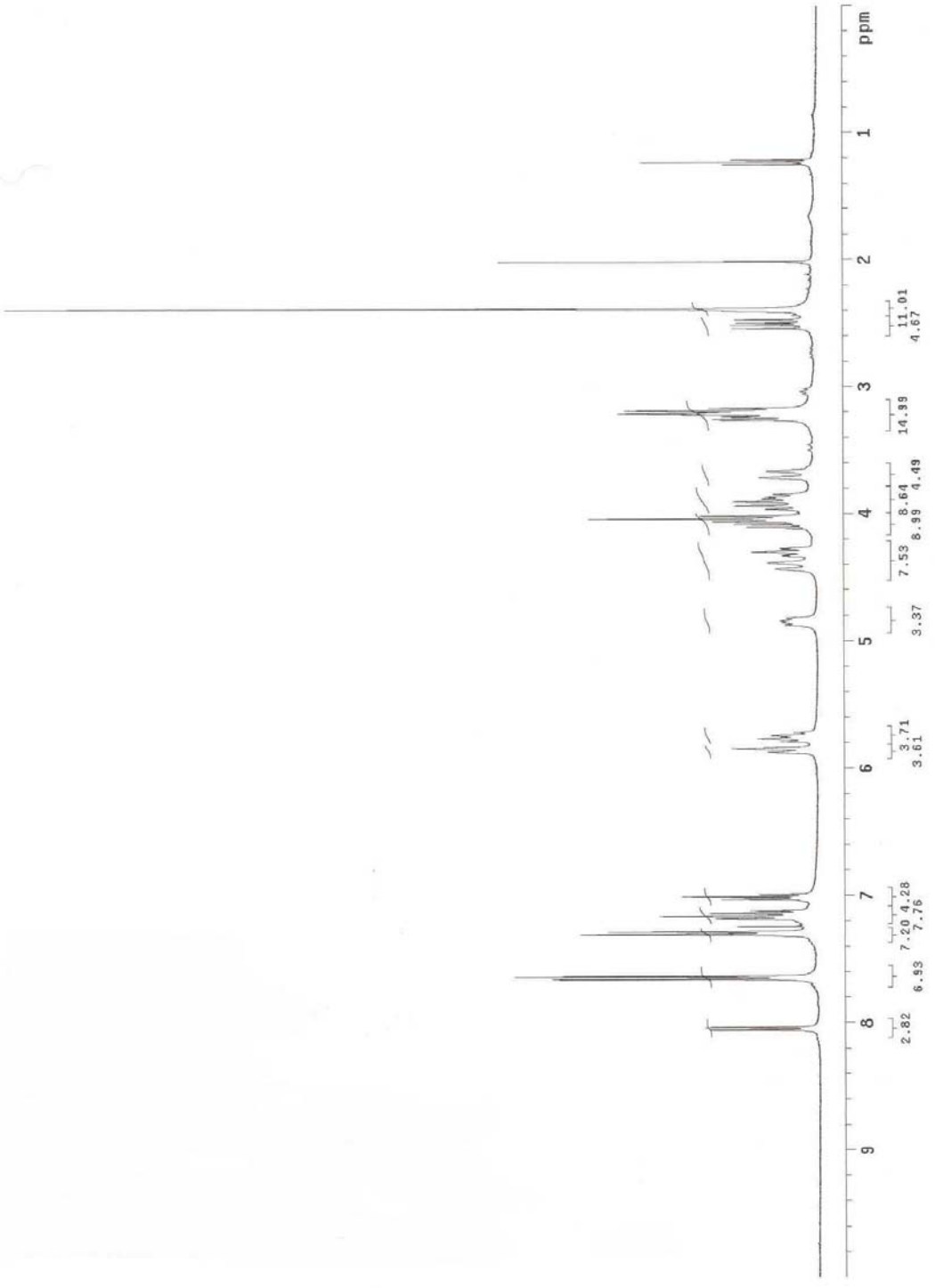
^{1}H NMR Spectrum of 19



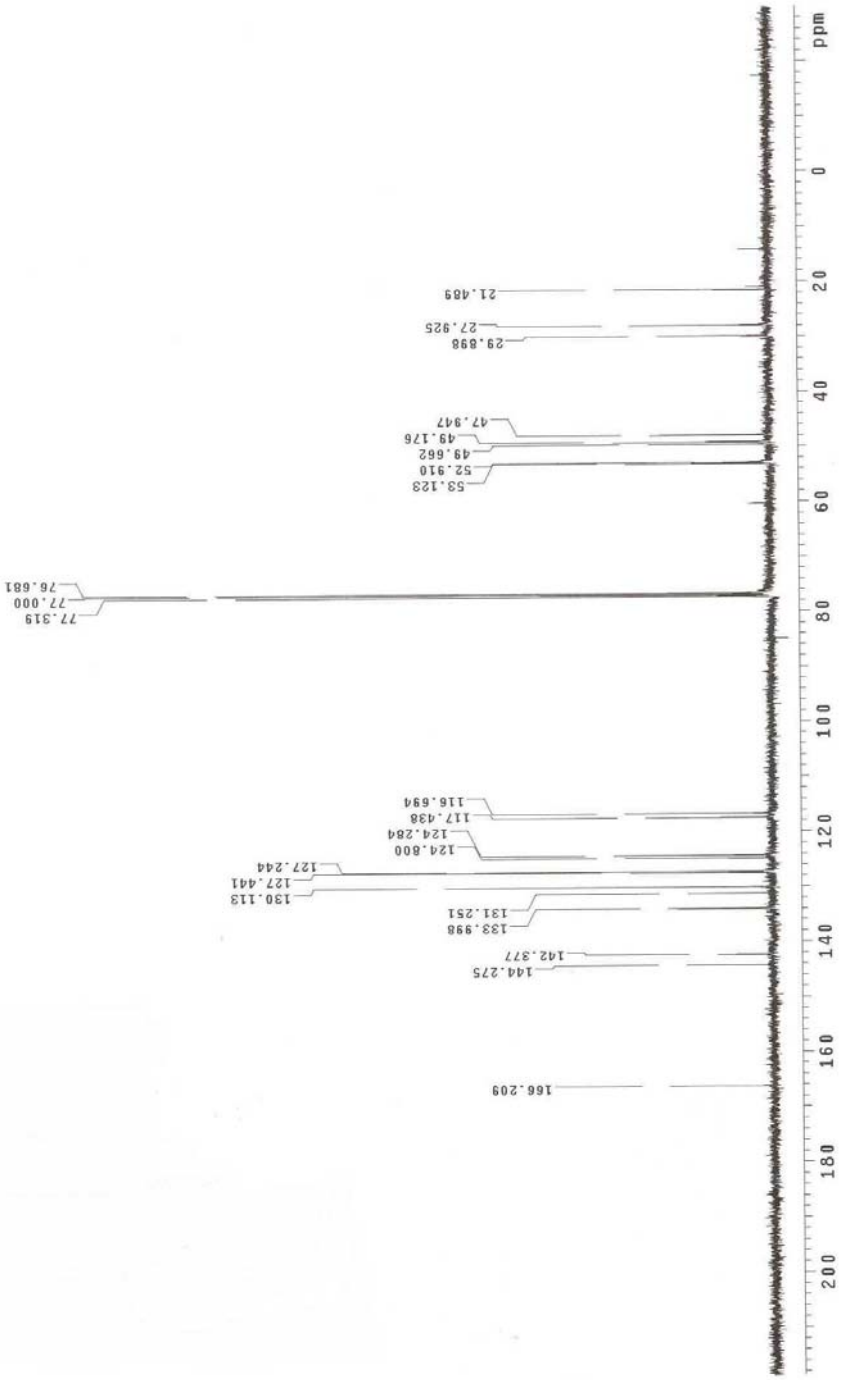
^{13}C NMR Spectrum of 19



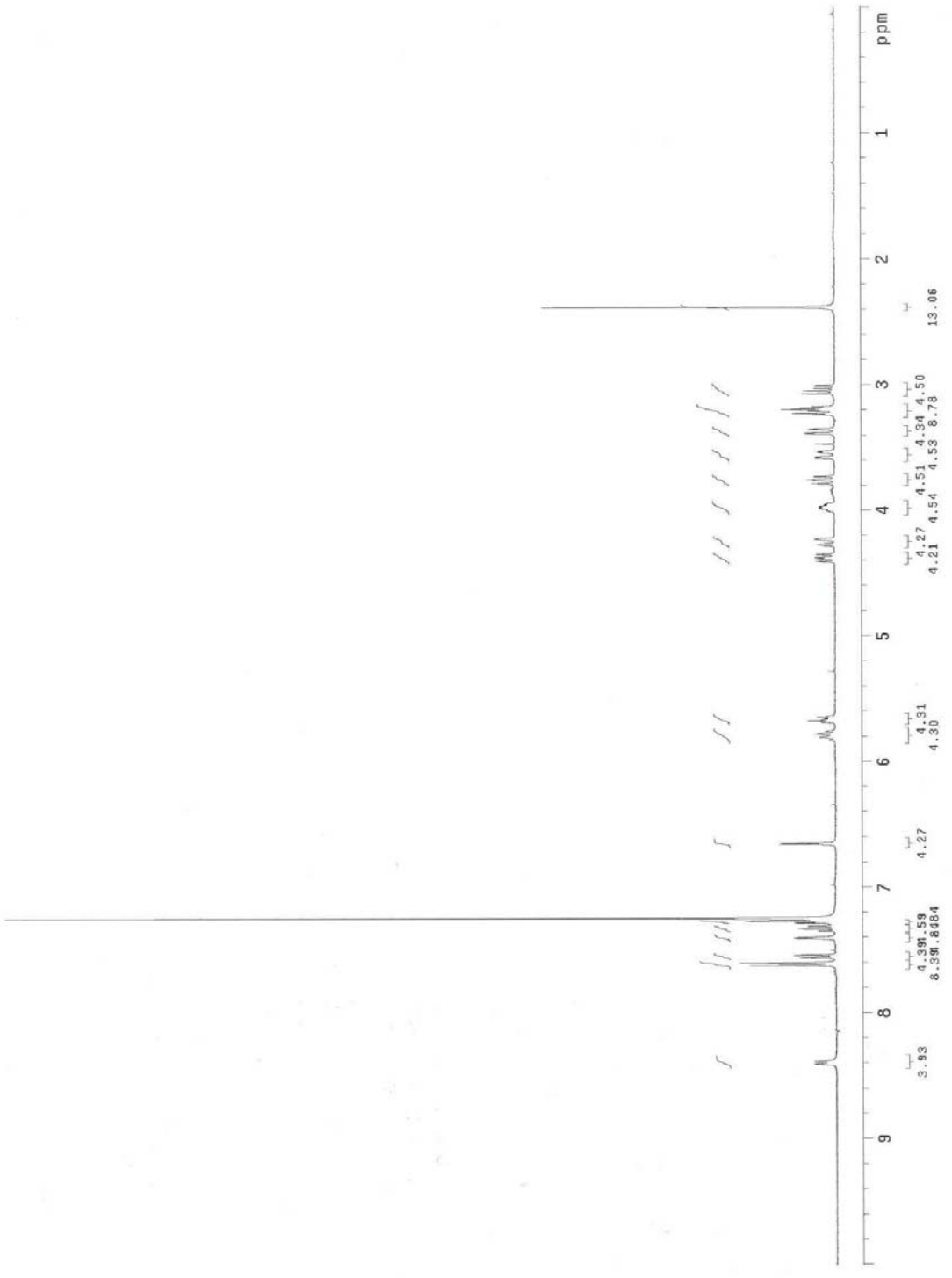
^{1}H NMR Spectrum of 20



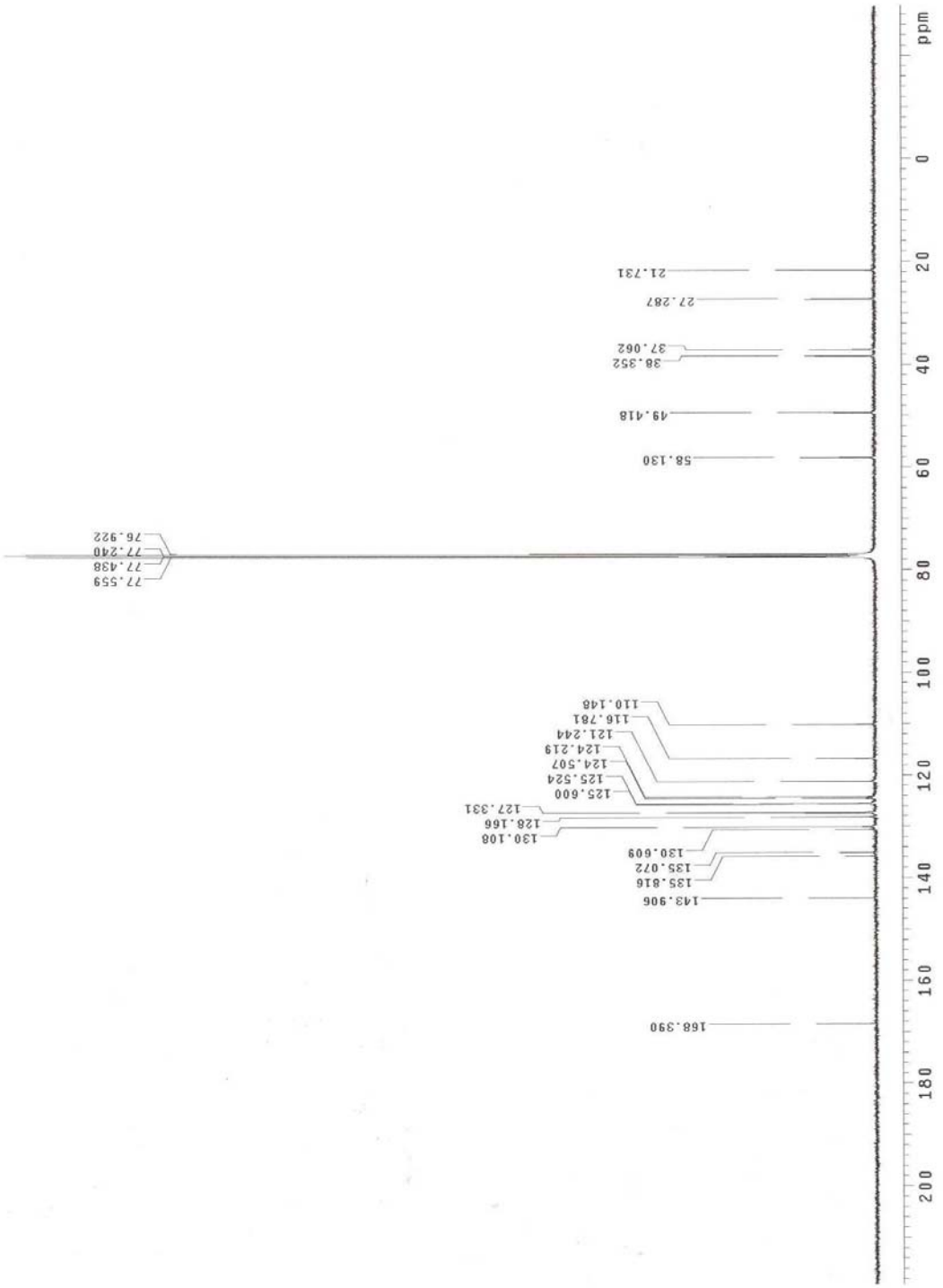
^{13}C NMR Spectrum of 20



^{1}H NMR Spectrum of 21



^{13}C NMR Spectrum of 21



Appendix 3

Simple Thiazocine-2-acetic Acid Derivatives via Ring Closing Metathesis

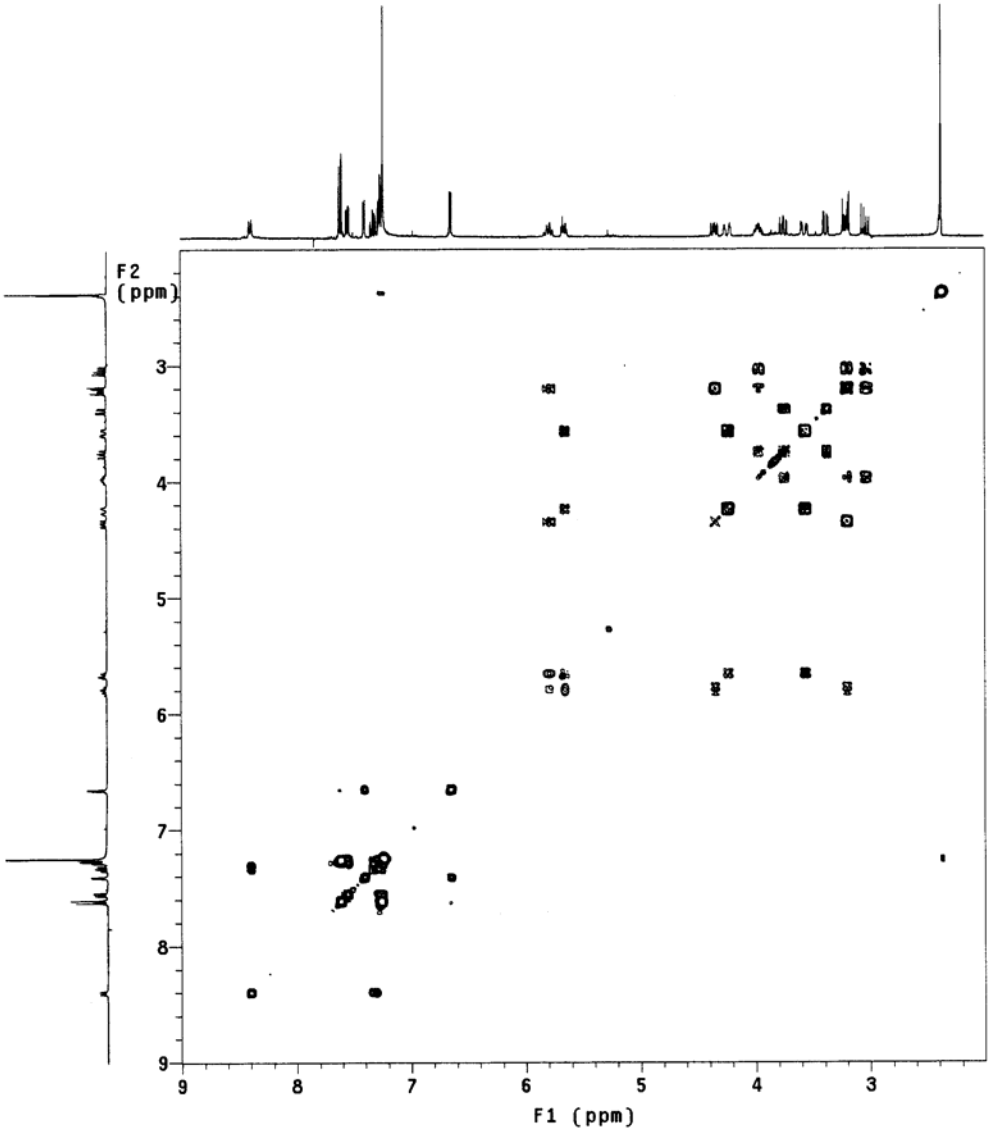
Dallas K. Bates,* Xiaofen Li and Parag V. Jog

Additional Supplemental Information

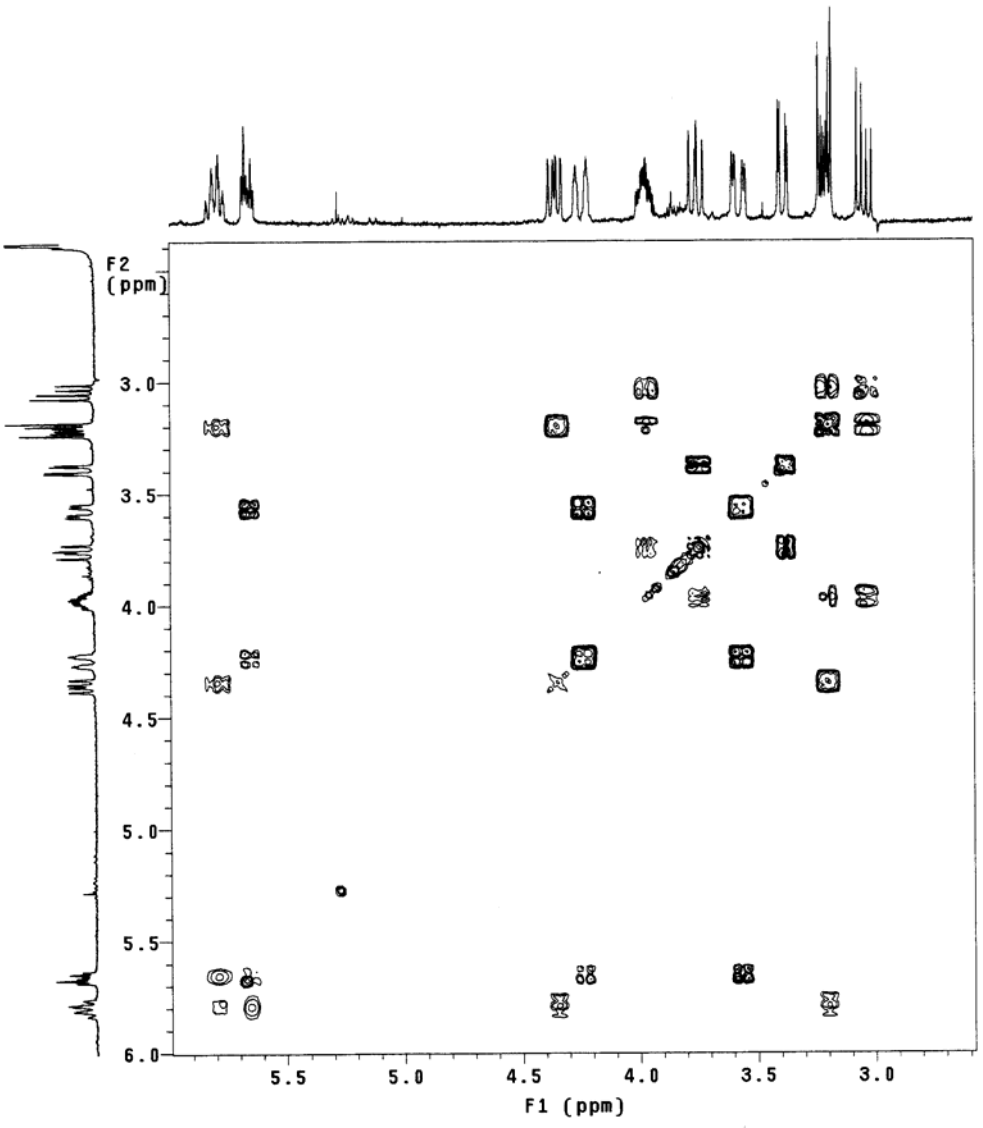
(Compound numbers correspond to the numbers in the article:

Bates, D. K.; Li, X.; Jog, P. V. *J. Org. Chem*. **2004**, *69*, 2750)

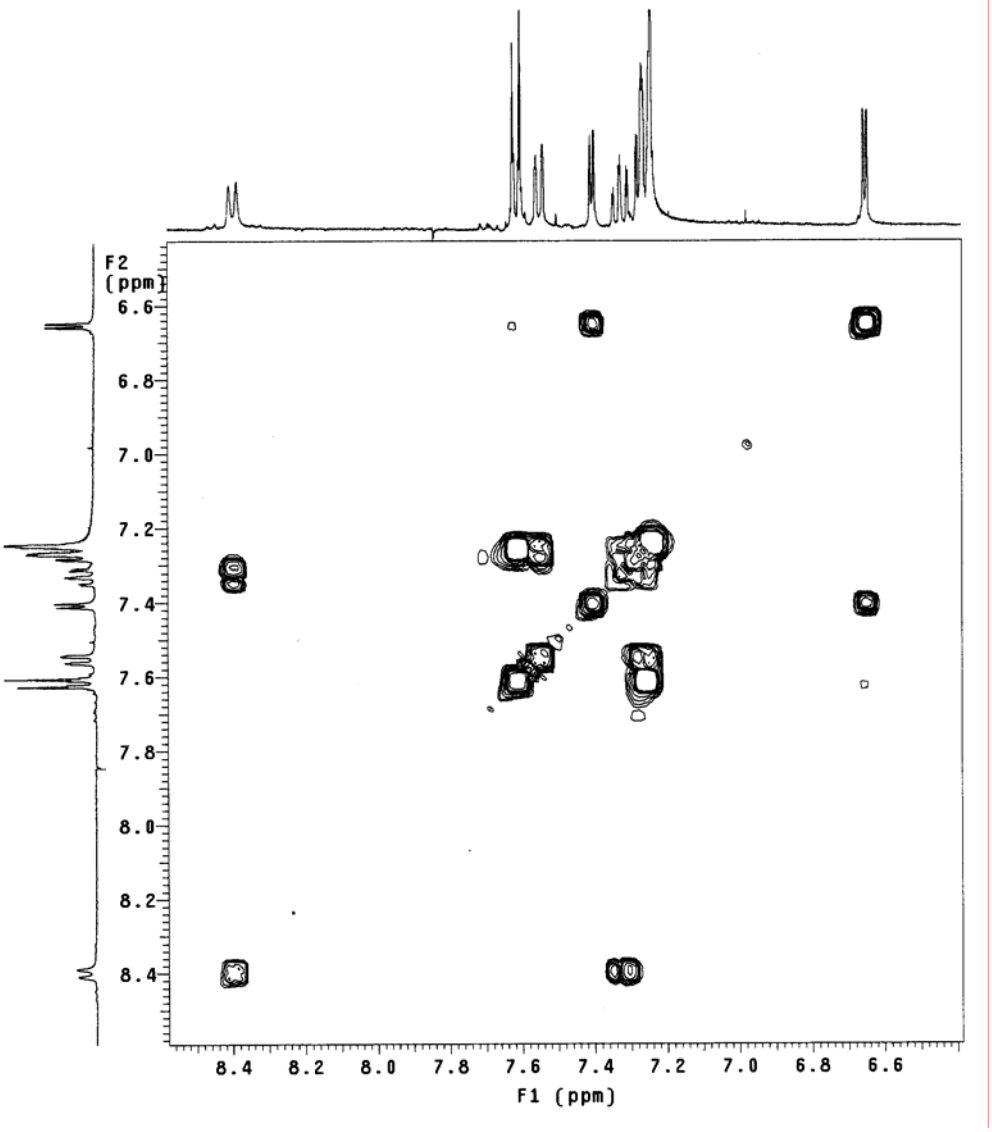
^{1}H-^{1}H COSY NMR Spectrum of **21**



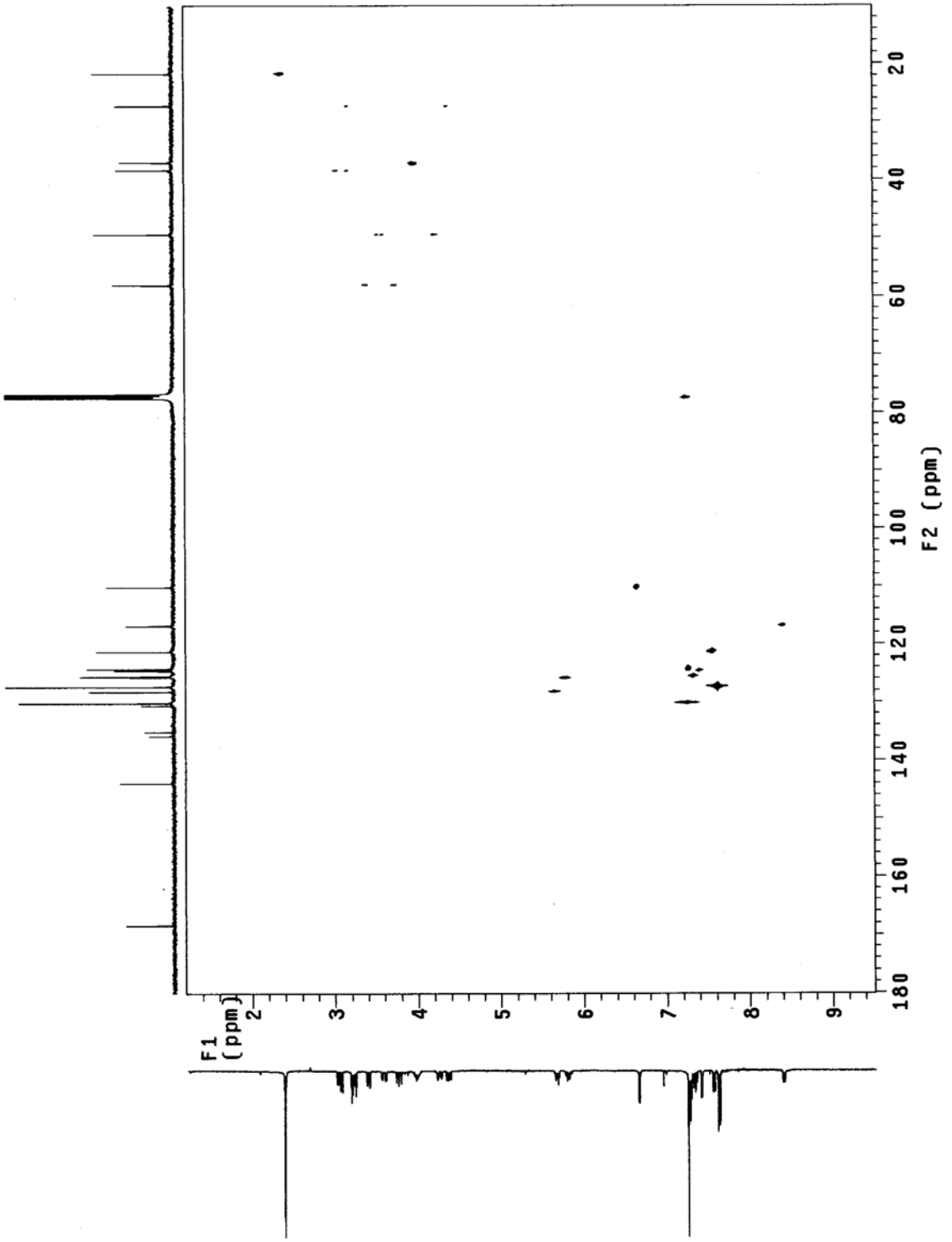
^{1}H-^{1}H COSY NMR Spectrum of **21** (Expansion 1)



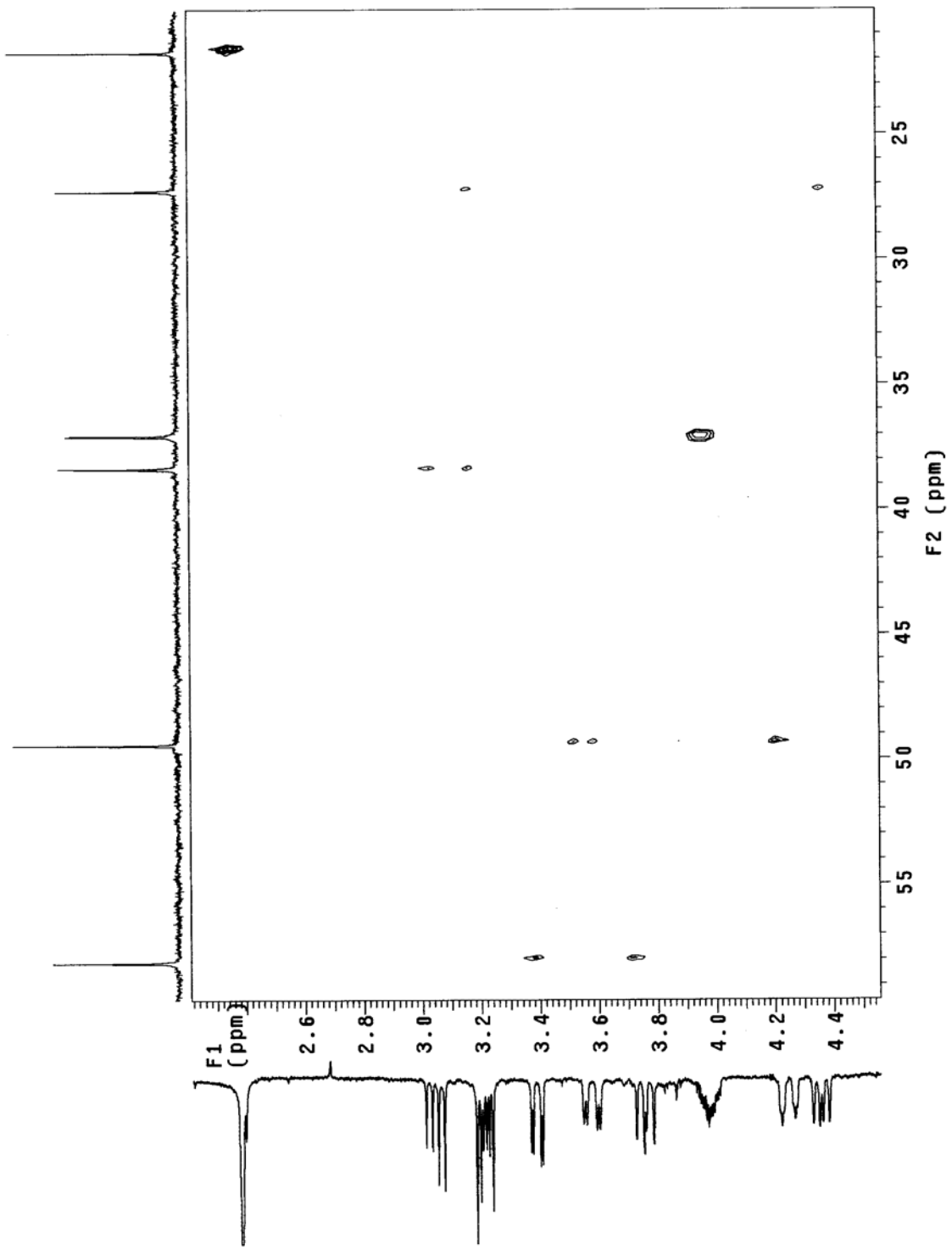
^{1}H-^{1}H COSY NMR Spectrum of **21** (Expansion 2)



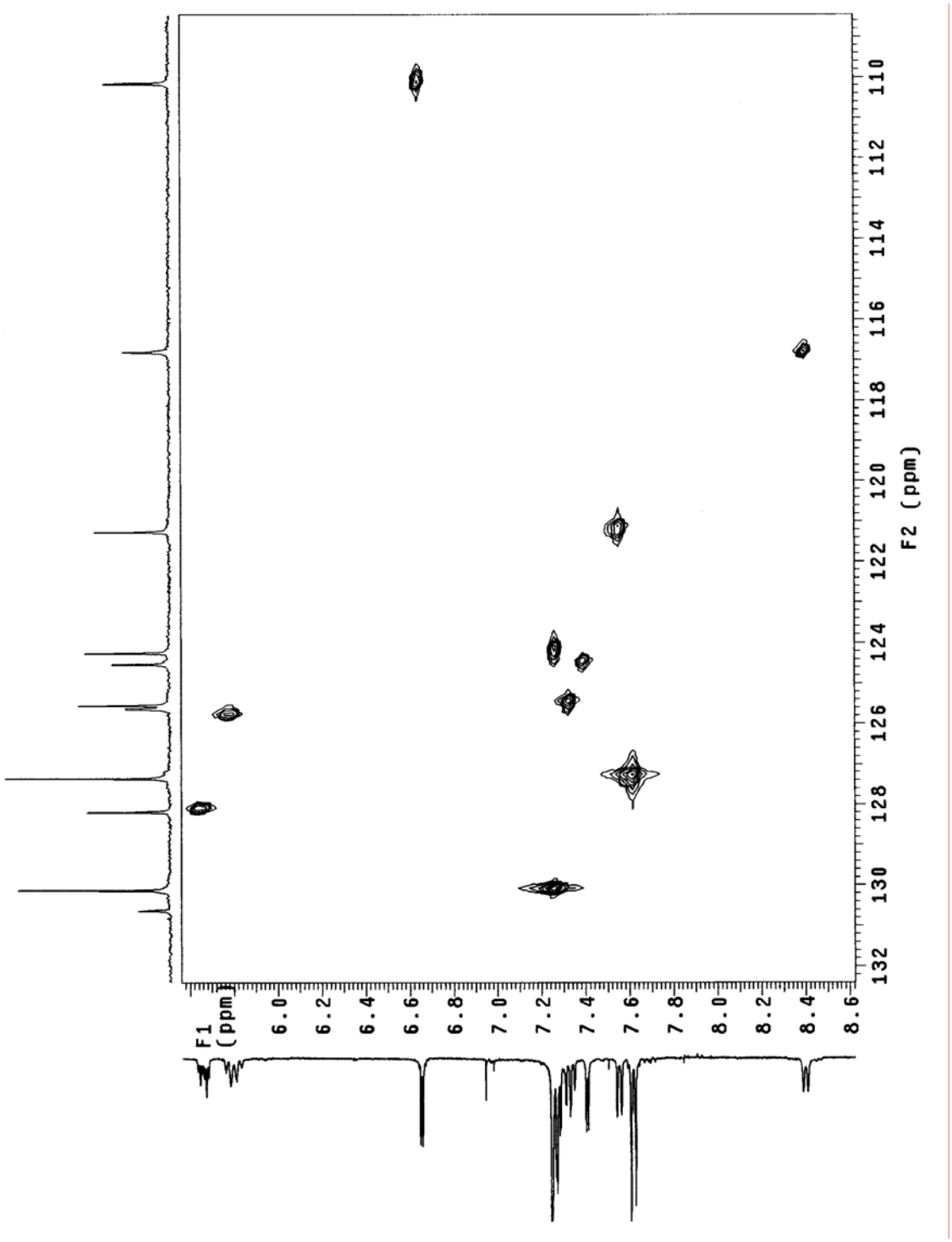
^{1}H-^{13}C HETCOR NMR Spectrum of **21**



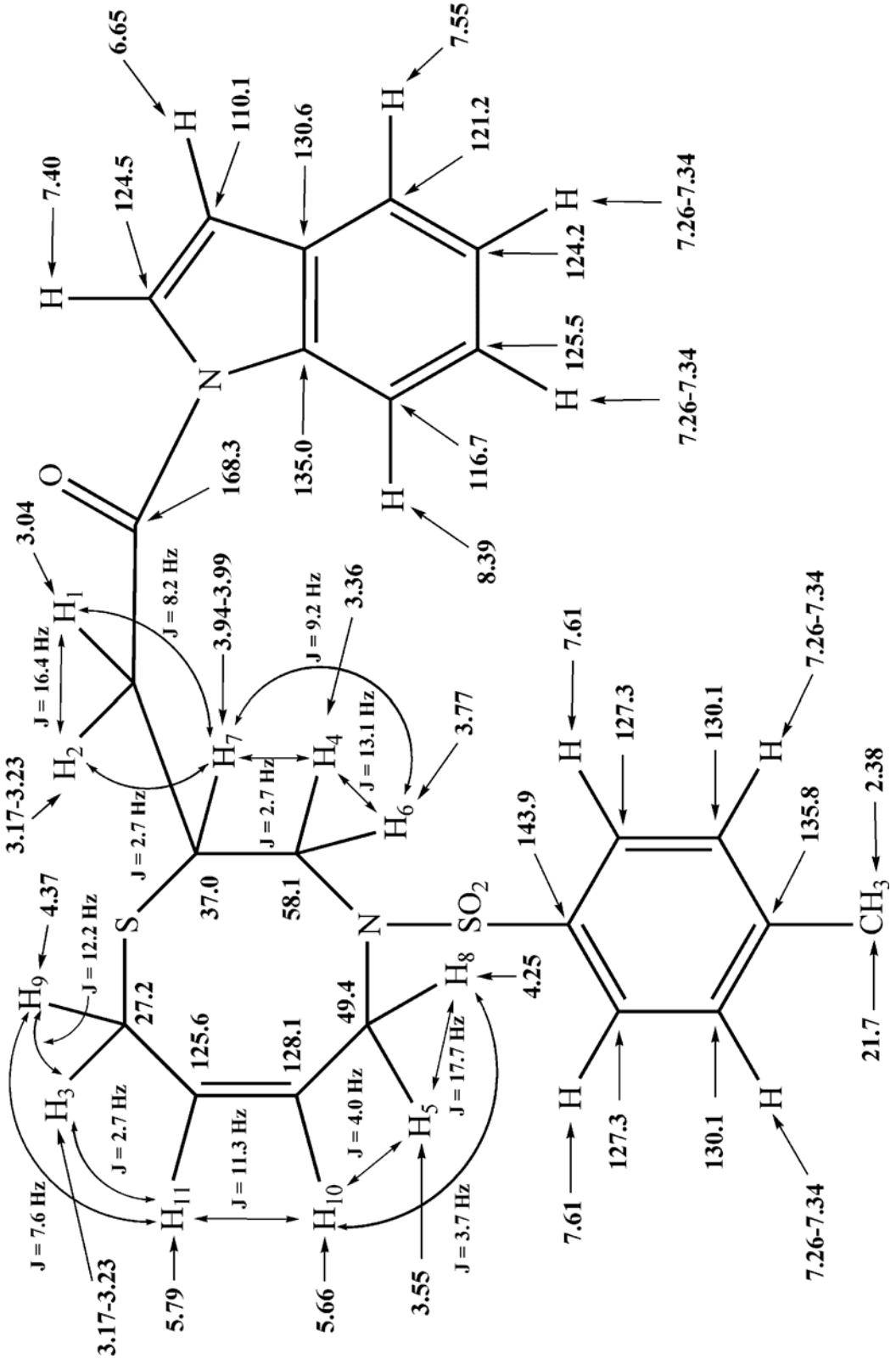
^{1}H-^{13}C HETCOR NMR Spectrum of **21** (Expansion 1)



^{1}H-^{13}C HETCOR NMR Spectrum of **21** (Expansion 2)



Peak Assignments in Compound 21



Appendix 4

A Redox-Mediated Molecular Brake: Dynamic NMR Study of 2-[2-(Methylthio)phenyl]isoindolin-1-one and *S*-Oxidized Counterparts

Parag V. Jog, Richard E. Brown and Dallas K. Bates*

(Compound numbers correspond to the numbers in the article:

Jog, P. V.; Brown, R. E.; Bates, D. K. *J. Org. Chem.* **2003**, *68*, 8240)

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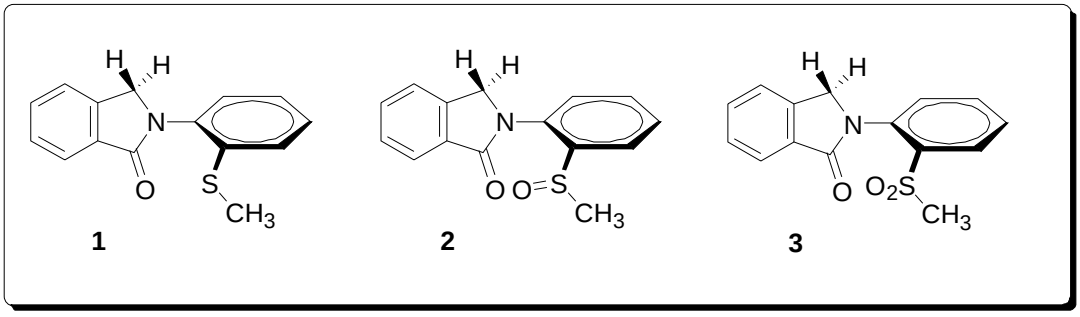


Experimental Section

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise noted) and were recorded at 400 MHz or 100 MHz, respectively. Mass spectra were obtained by electron impact (70 eV), relative intensities are given in parenthesis. IR spectra were recorded in chloroform solution. Column chromatography was carried out on silica gel (0.06-0.20 mm, pore diameter ~ 6 nm). Organic phases were dried over anhydrous Na_2SO_4. Phthalaldehyde, 2-aminothiophenol, *m*-chloroperbenzoic acid were commercial samples and used without further purification.

2-[2-(methylthio)phenyl]isoindolin-1-one (1). *o*-Phthalaldehyde (4 mmol, 0.5 g) in AcOH (20 mL) was heated to reflux. To this was added dropwise 2-(methylthio)aniline (1.4 g, 10 mmol) in 2 mL of AcOH. After 20 min at reflux the mixture was poured into water and extracted with EtOAc. The organic layer was washed sequentially with 2*N* HCl, saturated $NaHCO_3$ and brine and then dried. Solvent was evaporated and the crude orange-red solid was purified by column chromatography (benzene/EtOAc, 80/20) and recrystallization (EtOAc) to give a white solid (0.32 g, 30 %): mp 153-154 ºC; IR ν 1692 cm^{-1}; ^{1}H NMR δ 2.40 (s, 3H), 4.77 (s, 2H), 7.21-7.38 (m, 4H), 7.49 (t, J = 7.94 Hz, 2H), 7.58 (dt, J = 7.62, 0.89 Hz, 1H), 7.94 (d, J = 7.56 Hz, 1H); ^{13}C NMR δ 15.5, 52.2, 123.0, 124.6, 126.1, 126.9, 128.3, 129.1, 129.1, 132.0, 132.3, 136.1, 138.3, 142.0, 168.3; MS (EI) [m/z (rel. intensity)] 255 [M^+, 43], 208 (100), 180 (25). Anal. Calc. for $C_{15}H_{13}$ NOS: C, 70.56; H, 5.13; N, 5.49. Found: C, 70.80; H, 5.32; N, 5.59.

2-[2-(methylsulfinyl)phenyl]isoindolin-1-one (2). To an ice-cooled solution of **1** (0.1 g, 0.39 mmol) in CH_2Cl_2 (20 mL) was added slowly a solution of *m*-CPBA (1.1eq, 0.43 mmol, 0.074 g) in CH_2Cl_2 (5 mL). The resulting mixture was stirred at 0 ºC for 15 min

and then put it in a freezer (-8 ^{o}C) overnight. The reaction mixture was then poured into 5% $NaHCO_3$ solution (40 mL) and extracted with CH_2Cl_2 (40 mL). The combined organic layer was washed with distilled water, dried, and concentrated in vacuo. Column chromatography (EtOAc) gave yellowish white solid (0.082 g, 77 %), which was recrystallized (EtOAc-hexane, 8:2) to give a white solid: mp 161-162 ºC; IR ν 1698 cm^{-1}; ^{1}H NMR δ 2.88 (s, 3H), 4.84 (s, 2H), 7.29 (dd, J = 7.67, 1.44 Hz, 1H), 7.50–7.64 (m, 5H), 7.89 (d, J = 7.46 Hz, 1H), 8.11 (dd, J= 7.64, 1.67 Hz, 1H); ^{13}C NMR δ 43.3, 53.4, 123.2, 124.6, 125.5, 127.4, 128.8, 129.8, 131.3, 132.5, 132.7, 135.2, 141.7, 144.9, 169.1; MS (EI) [m/z (rel. intensity)] 271 [M^{+}, 23], 254 (100), 238 (77), 208 (53). Anal. Calc. for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16. Found: C, 66.18; H, 4.94; N, 4.97.

2-[2-(methylsulfonyl)phenyl]isoindolin-1-one (3). To an ice-cooled solution of **1** (0.10 g, 0.39 mmol) in CH_2Cl_2 (20 mL) was added a solution of *m*-CPBA (2.2 eq, 0.86 mmol, 0.15 g) in CH_2Cl_2 (10 mL). The resulting mixture was stirred at room temperature for 18 h, then poured into 5% $NaHCO_3$ (40 mL) solution. The aqueous layer was extracted with CH_2Cl_2 (30 mL). The combined organic layer was washed with distilled water, dried, and concentrated in vacuo. Column chromatography (EtOAc: hexane, 6:4) gave yellowish white solid (0.091 g, 82%), which was recrystallized (EtOAc-hexane, 7:3) to give a white solid: mp 186-187 ºC; IR ν 1694 cm^{-1}; ^{1}H NMR δ 3.15 (s, 3H), 4.84 (br, 2H), 7.39 (dd, J= 7.83, 1.2 Hz, 1H), 7.48-7.53 (m, 2H), 7.59-7.64 (m, 2H), 7.74 (dt, J = 7.65, 4.6 Hz, 1H), 7.89 (d, J = 7.59 Hz, 1H), 8.17 (d, J = 7.94, 1.48 Hz, 1H); ^{13}C NMR δ 44.2, 55.5, 123.2, 124.4, 128.5, 129.8, 131.1, 131.5, 131.7, 132.5, 135.3, 137.8, 140.0, 142.6, 169.8; MS (EI) [m/z (rel. intensity)] 287 [M^{+}, 34], 208 (100), 179 (17), 105 (50). Anal. Calc. for $C_{15}H_{13}NO_3S$: C, 62.70; H, 4.56; N, 4.87. Found: C 62.69; H 4.59; N 4.76.

Computational procedures. Rate constants at the coalescense temperature (k_c) were calculated using the standard equation for an AB coupled system (eq 1). $\Delta G^{\mp}$ (in Kcal mol^{-1}) was calculated from rate constants obtained by line shape analysis of the methylene protons in ^{1}H NMR spectra taken at various temperatures using eq 2. Probe temperatures were measured using a neat methanol sample and automated calibration procedures. Plotting $\log\frac{k}{T} vs \frac{1}{1000T}$ gives $\Delta H^{\mp}$ (in Kcal mol^{-1}) as –4.576 times the slope and $\Delta S^{\mp}$ (in cal mol^{-1}) was calculated according to eq 3. For a detailed discussion of these procedures see: (a) Sandstrom, J. *Dynamic NMR Spectroscopy*; Academic Press: New York, 1982, pp. 84-100. (b) Nelson, J. H. *Nuclear Magnetic Resonance Spectroscopy*; Prentice Hall: Upper Saddle River, NJ, 2003, Chapter 11.

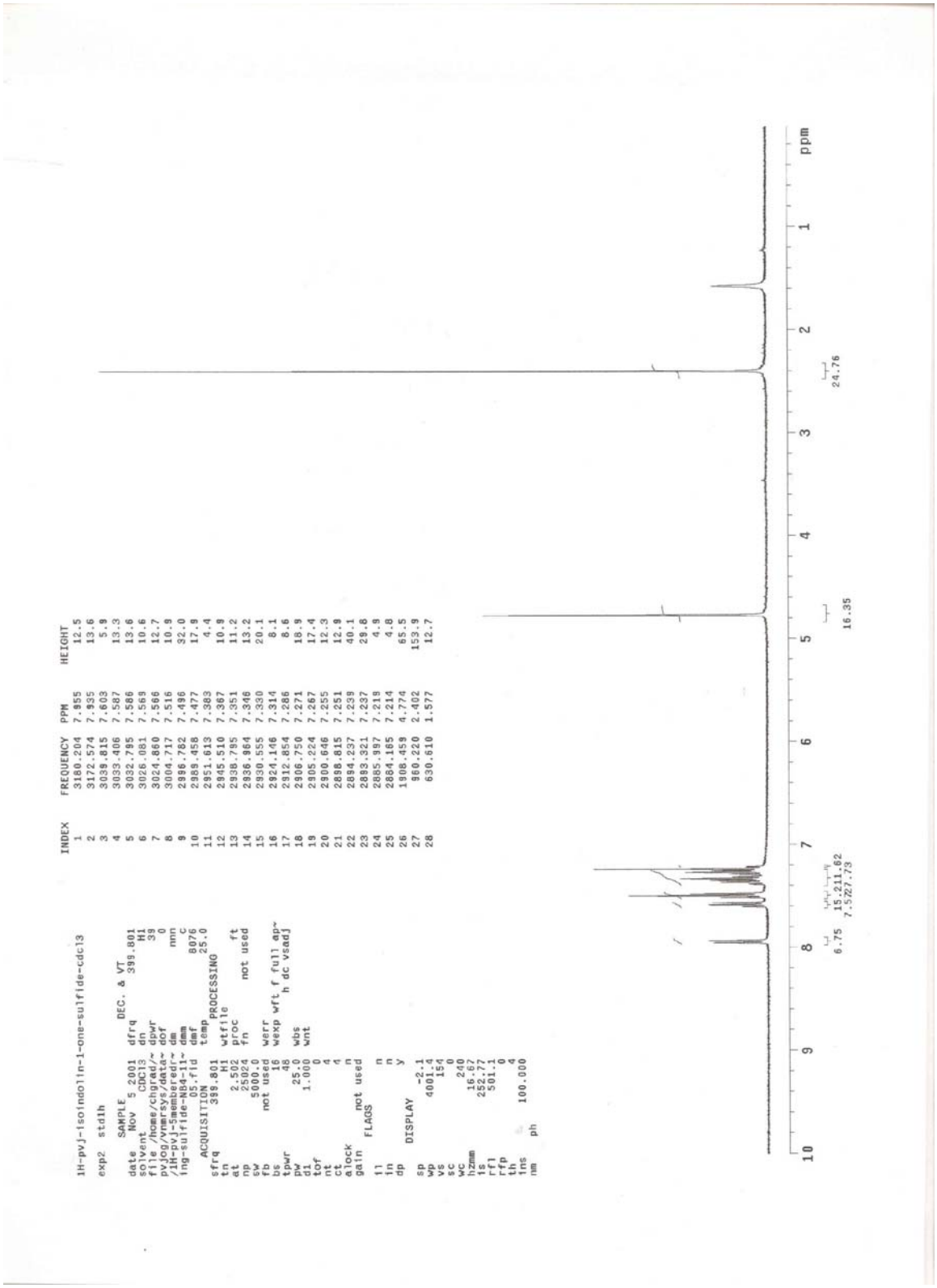
$$k_C = 2.22\sqrt{(\nu_A - \nu_B)^2 - 6J_{AB}{}^2} \quad (1)$$

$$\Delta G^{\mp} = 4.575\times10^{-3}T\left[10.319 + \log\left(\frac{T}{k}\right)\right] \quad (2)$$

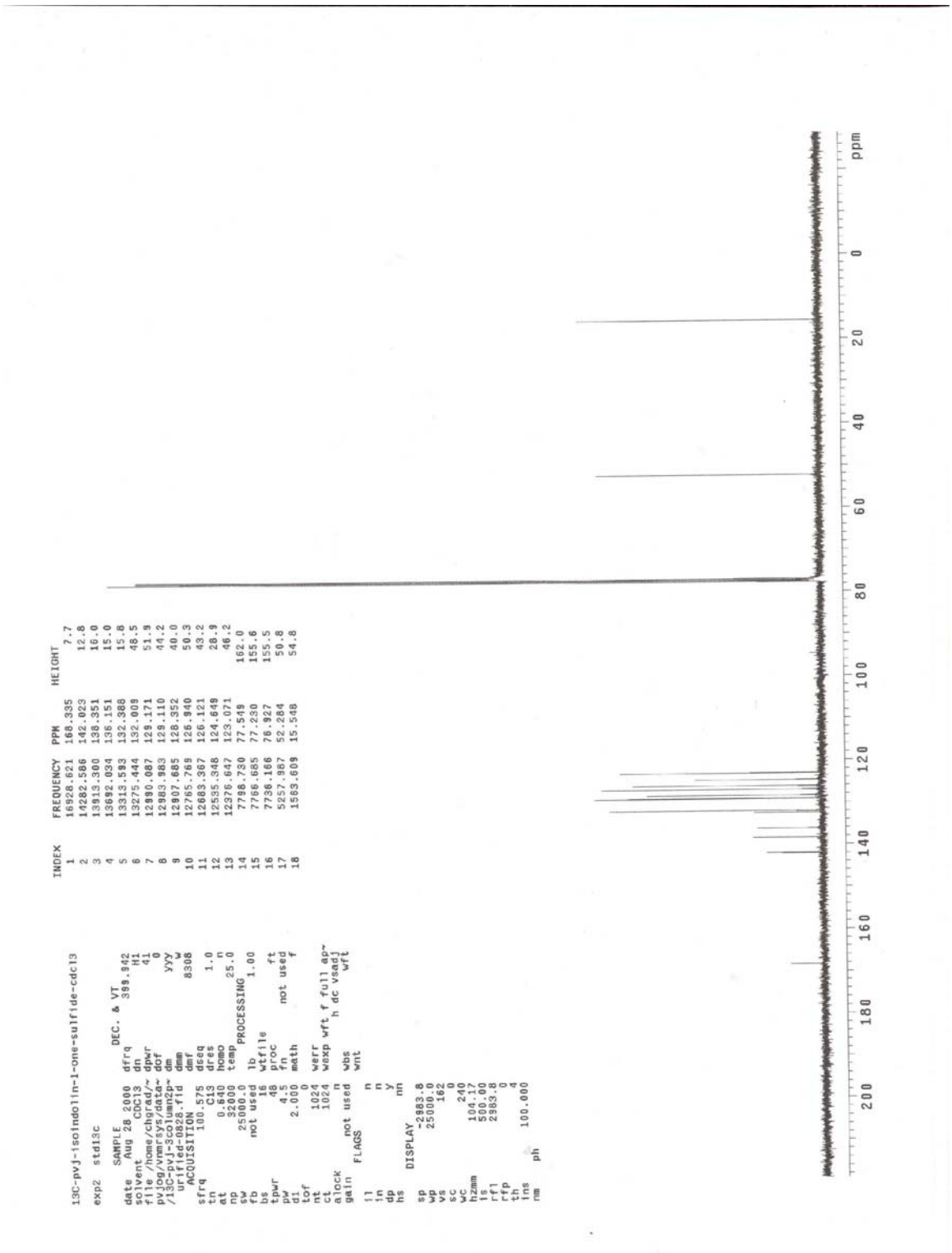
$$\Delta S^{\mp} = 4.576\log\frac{k}{T} + \frac{\Delta H^{\mp}}{T} - 47.218 \quad (3)$$

Structures **1, 2** and **3** were optimized in PM3 by driving the N-Ar and S-Ar torsion angles in 20 ° steps from 0 ° to 360 ° and allowing the other angles and bond distances to relax to their minima for each fixed value of the torsion angles. The barriers ($\Delta G^{\mp}$) were computed by locating the transition state (saddle point) by the QST3 method followed by frequency calculations of the minima on either side of the transition state and at the transition state (TS). Z-matrices for minima on both sides of the TS and for the TS are provided in the Supplemental Information (pp 224-232).

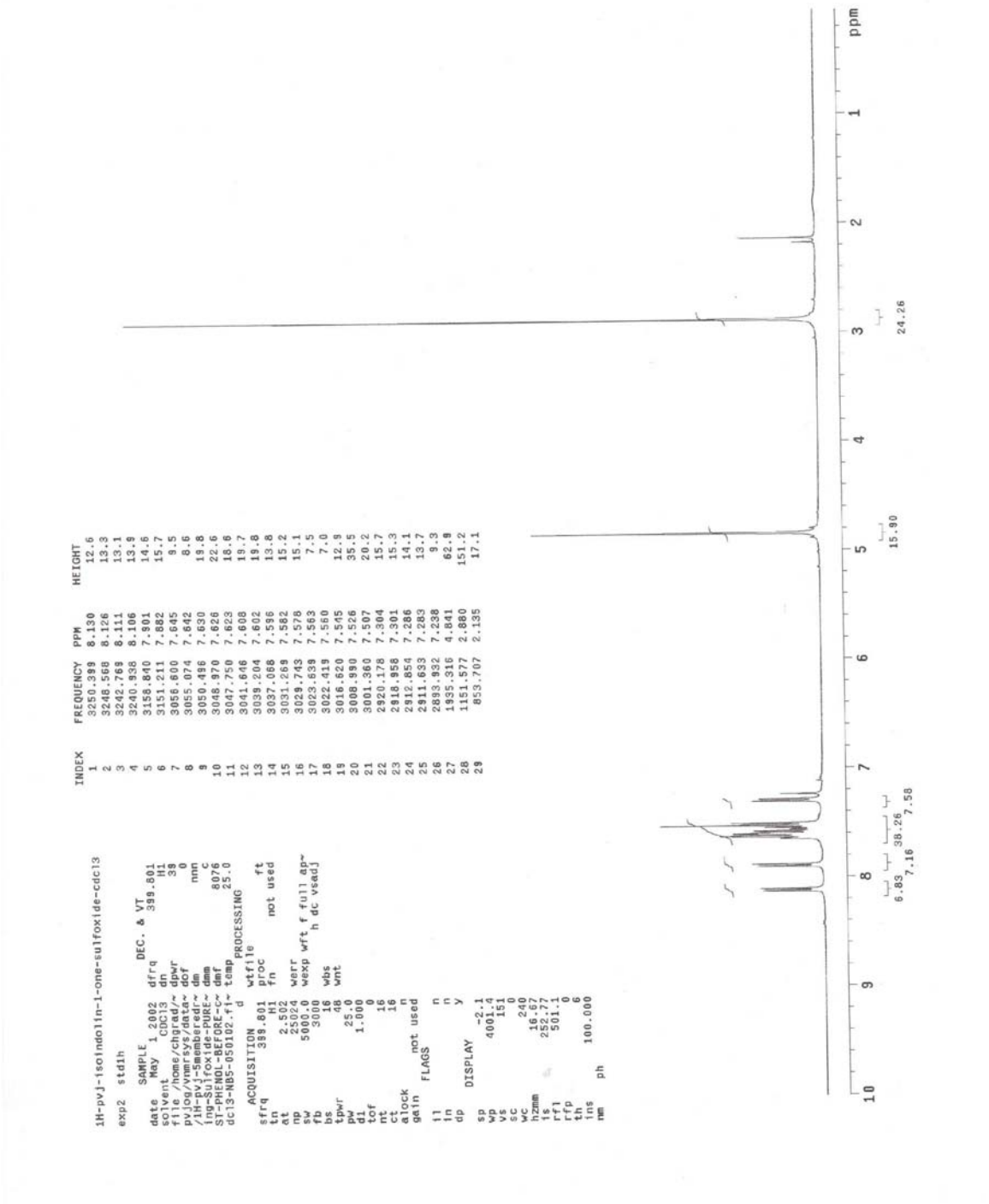
^{1}H NMR Spectrum of **1**



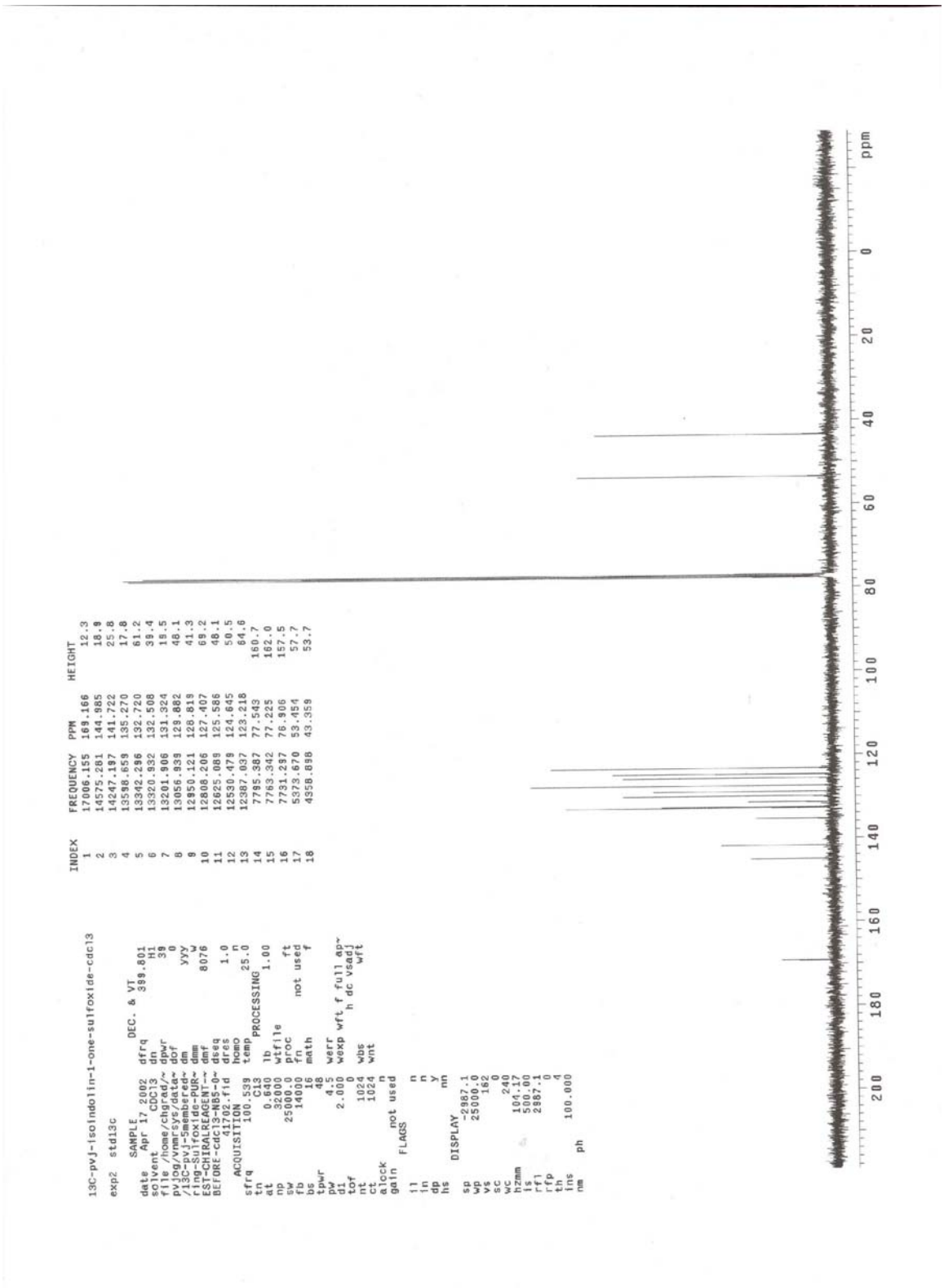
^{13}C NMR Spectrum of **1**



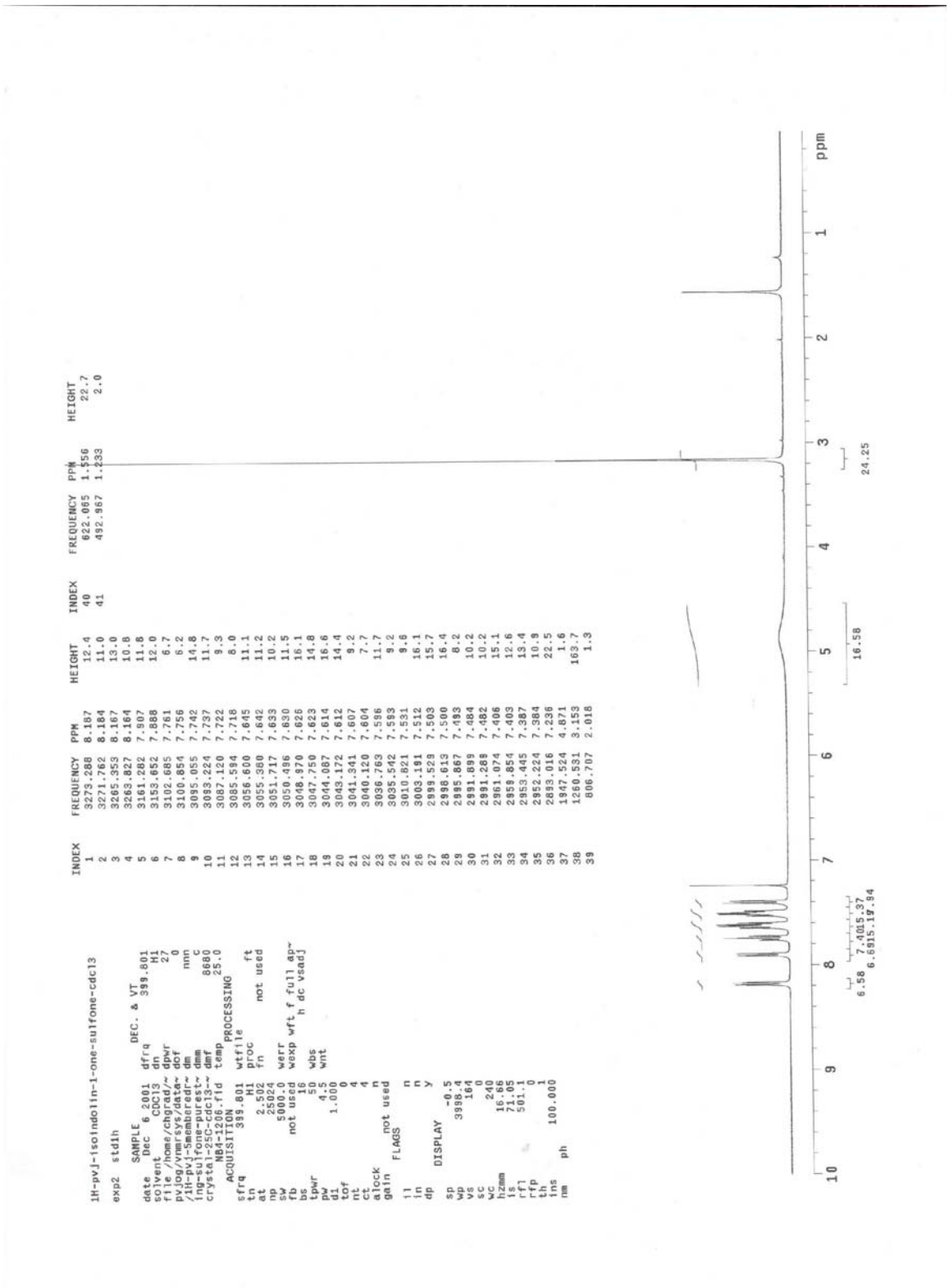
^{1}H NMR Spectrum of **2**



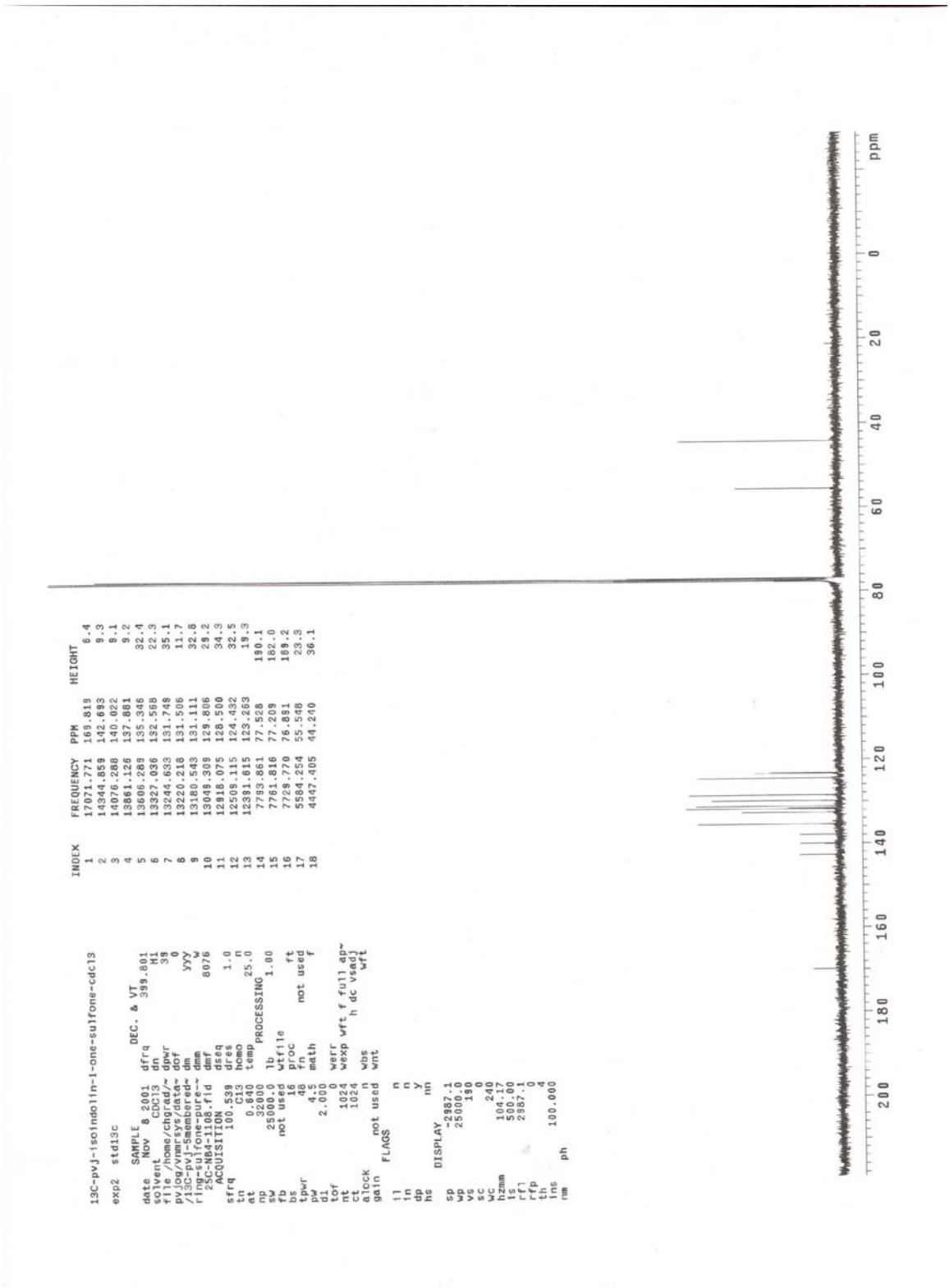
^{13}C NMR Spectrum of **2**



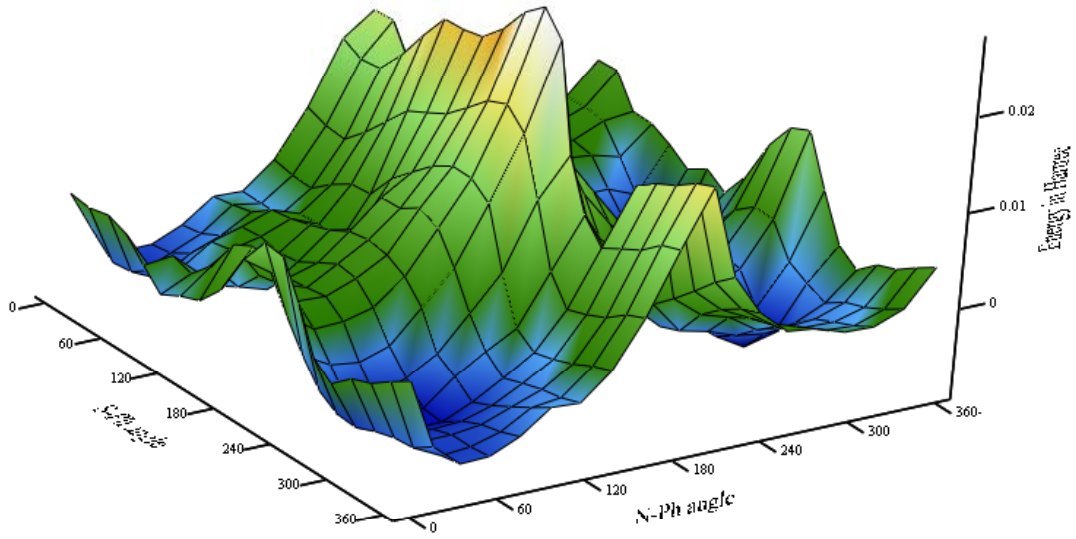
^{1}H NMR Spectrum of **3**



^{13}C NMR Spectrum of **3**

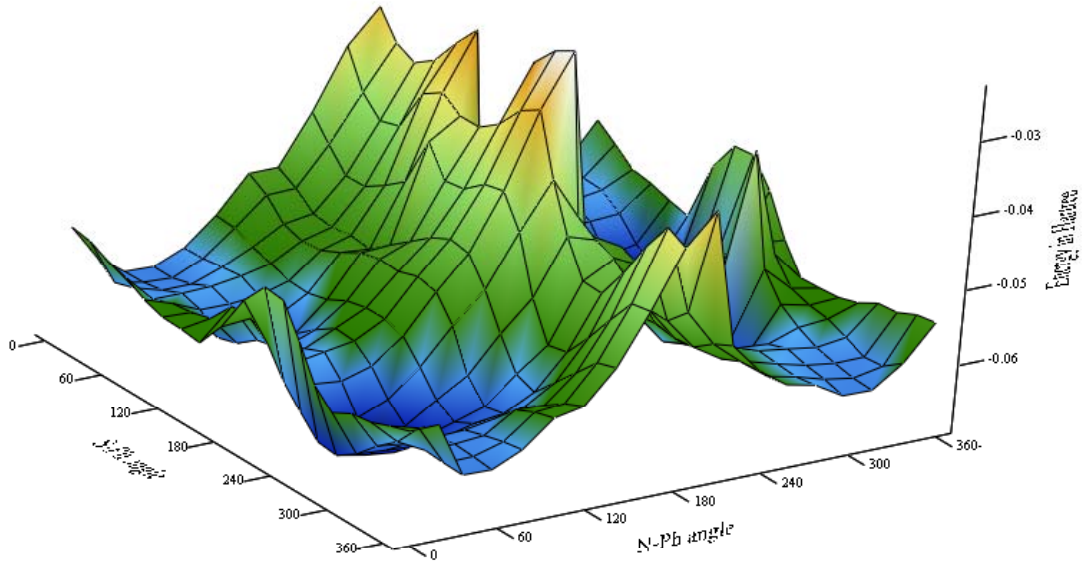


Potential Energy Surface Plot for Sulfoxide **2**



(z, s, q)

Potential Energy Surface Plot for Sulfone **3**



(z, v, w)

Z-matrix for **1** [N-Ar & S-Ar locked] (Lowest Energy Conformation)

```
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 h   2 hc3       1 hch3
 h   2 hc4       3 hch4       1 dih4
 s   2 sc5       3 sch5       1 dih5
 c   5 cs6       2 csc6       4 dih6
 c   6 cc7       5 ccs7       2 dih7
 c   7 cc8       6 ccc8       5 dih8
 c   8 cc9       7 ccc9       6 dih9
 c   9 cc10      8 ccc10      7 dih10
 c  10 cc11      9 ccc11      8 dih11
 n  11 nc12     10 ncc12      9 dih12
 c  12 cn13     11 cnc13     10 dih13
 c  13 cc14     12 ccn14     11 dih14
 c  14 cc15     13 ccc15     12 dih15
 c  15 cc16     14 ccc16     13 dih16
 c  16 cc17     15 ccc17     14 dih17
 c  17 cc18     16 ccc18     15 dih18
 c  18 cc19     17 ccc19     16 dih19
 c  19 cc20     18 ccc20     17 dih20
 h  18 hc21     17 hcc21     16 dih21
 h  20 hc22     19 hcc22     18 dih22
 h  20 hc23     19 hcc23     18 dih23
 h  17 hc24     18 hcc24     19 dih24
 h  16 hc25     17 hcc25     18 dih25
 h  15 hc26     14 hcc26     19 dih26
 o  13 oc27     14 occ27     19 dih27
 h  10 hc28     11 hcc28     12 dih28
 h   9 hc29     10 hcc29     11 dih29
 h   8 hc30      9 hcc30     10 dih30
 h   7 hc31      8 hcc31      9 dih31

        ch2        1.10030
        hc3        1.09627
        hch3      108.22882
        hc4        1.09548
        hch4      107.98874
        dih4      116.05034
        sc5        1.80450
        sch5      107.46093
        dih5     -122.80381
        cs6        1.77180
        csc6      104.68279
        dih6      273.94890
        cc7        1.39784
        ccs7      121.14130
        dih7      340.00000
        cc8        1.38719
        ccc8      121.44158
        dih8     -178.14156
        cc9        1.39036
        ccc9      119.92977
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        cc10       1.38814
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        cc11       1.40013
        ccc11     120.43985
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        ncc12     119.98005
        dih12    -178.86414
        cn13       1.44925
        cnc13     123.18632
        dih13      40.00000
        cc14       1.48613
        ccn14     106.28642
        dih14    -153.21541
        cc15       1.38357
        ccc15     129.70692
        dih15    -174.86795
        cc16       1.39713
        ccc16     118.05980
        dih16    -179.83891
        cc17       1.39069
        ccc17     120.86810
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        ccc18     121.05078
        dih18      0.04480
        cc19       1.38323
        ccc19     118.18847
        dih19      0.10850
        cc20       1.49561
        ccc20     128.80482
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        hcc21     120.89667
        dih21    -179.79813
        hc22       1.10957
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        dih22      57.76910
        hc23       1.10793
        hcc23     111.99601
        dih23     -63.50499
        hc24       1.09540
        hcc24     119.32075
        dih24    -179.96237
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        hcc25     119.69272
        dih25     179.91169
        hc26       1.09533
        hcc26     120.72678
        dih26    -179.87909
        oc27       1.21465
        occ27     129.64647
        dih27    -177.22970
        hc28       1.09724
        hcc28     120.23132
        dih28      -0.25801
        hc29       1.09497
        hcc29     119.97327
        dih29     179.33372
        hc30       1.09494
        hcc30     120.17359
        dih30    -179.97353
        hc31       1.10200
        hcc31     119.28782
        dih31    -179.60645
```

Z-matrix for **1** [N-Ar & S-Ar locked]-Lowest Energy Conformation
(other side of the Transition State)

0 1

h			
c	1 ch2		
h	2 hc3	1 hch3	
h	2 hc4	3 hch4	1 dih4
s	2 sc5	3 sch5	1 dih5
c	5 cs6	2 csc6	4 dih6
c	6 cc7	5 ccs7	2 dih7
c	7 cc8	6 ccc8	5 dih8
c	8 cc9	7 ccc9	6 dih9
c	9 cc10	8 ccc10	7 dih10
c	10 cc11	9 ccc11	8 dih11
n	11 nc12	10 ncc12	9 dih12
c	12 cn13	11 cnc13	10 dih13
c	13 cc14	12 ccn14	11 dih14
c	14 cc15	13 ccc15	12 dih15
c	15 cc16	14 ccc16	13 dih16
c	16 cc17	15 ccc17	14 dih17
c	17 cc18	16 ccc18	15 dih18
c	18 cc19	17 ccc19	16 dih19
c	19 cc20	18 ccc20	17 dih20
h	18 hc21	17 hcc21	16 dih21
h	20 hc22	19 hcc22	18 dih22
h	20 hc23	19 hcc23	18 dih23
h	17 hc24	18 hcc24	19 dih24
h	16 hc25	17 hcc25	18 dih25
h	15 hc26	14 hcc26	19 dih26
o	13 oc27	14 occ27	19 dih27
h	10 hc28	11 hcc28	12 dih28
h	9 hc29	10 hcc29	11 dih29
h	8 hc30	9 hcc30	10 dih30
h	7 hc31	8 hcc31	9 dih31

ch2	1.09521
hc3	1.10046
hch3	107.43616
hc4	1.09643
hch4	108.13139
dih4	116.30416
sc5	1.80446
sch5	113.36711
dih5	-124.71193
cs6	1.77176
csc6	104.47674
dih6	156.37300
cc7	1.39795
ccs7	121.13414
dih7	340.00000
cc8	1.38714
ccc8	121.48684
dih8	-178.59292
cc9	1.39027
ccc9	119.91684
dih9	0.30620
cc10	1.38809
ccc10	119.80609
dih10	-0.07069
cc11	1.40019
ccc11	120.47830
dih11	0.09825
nc12	1.44817
ncc12	119.89669
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cn13	1.45040
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dih14	-207.53316
cc15	1.38359
ccc15	129.71296
dih15	-185.19813
cc16	1.39712
ccc16	118.05721
dih16	-180.15880
cc17	1.39070
ccc17	120.86550
dih17	0.09091
cc18	1.39721
ccc18	121.05022
dih18	-0.02993
cc19	1.38326
ccc19	118.19311
dih19	-0.09453
cc20	1.49557
ccc20	128.80335
dih20	-180.33293
hc21	1.09438
hcc21	120.89301
dih21	-180.21847
hc22	1.10780
hcc22	112.00740
dih22	63.47436
hc23	1.10916
hcc23	112.70075
dih23	-57.88287
hc24	1.09539
hcc24	119.32389
dih24	-180.02871
hc25	1.09522
hcc25	119.69281
dih25	180.09458
hc26	1.09534
hcc26	120.72589
dih26	-180.16468
oc27	1.21447
occ27	129.63091
dih27	-182.74933
hc28	1.09727
hcc28	120.22351
dih28	0.46814
hc29	1.09497
hcc29	119.98013
dih29	180.38169
hc30	1.09494
hcc30	120.18186
dih30	-179.70674
hc31	1.10206
hcc31	119.27032
dih31	-179.33

Z-matrix for **1** [N-Ar & S-Ar locked] (Transition State)

```
0 1
 h
 c   1 ch2
 h   2 hc3       1 hch3
 h   2 hc4       1 hch4       3 dih4
 s   2 sc5       1 sch5       3 dih5
 c   5 cs6       2 csc6       4 dih6
 c   6 cc7       5 ccs7       2 dih7
 c   7 cc8       6 ccc8       5 dih8
 c   8 cc9       7 ccc9       6 dih9
 c   9 cc10      8 ccc10      7 dih10
 c   6 cc11      5 ccs11      2 dih11
 n  11 nc12      6 ncc12      5 dih12
 c  12 cn13      11 cnc13     6 dih13
 c  13 cc14      12 ccn14     11 dih14
 c  14 cc15      13 ccc15     12 dih15
 c  15 cc16      14 ccc16     13 dih16
 c  16 cc17      15 ccc17     14 dih17
 c  17 cc18      16 ccc18     15 dih18
 c  14 cc19      13 ccc19     12 dih19
 c  12 cn20      11 cnc20     6 dih20
 h  18 hc21      17 hcc21     16 dih21
 h  20 hc22      12 hcn22     11 dih22
 h  20 hc23      12 hcn23     11 dih23
 h  17 hc24      16 hcc24     15 dih24
 h  16 hc25      15 hcc25     14 dih25
 h  15 hc26      14 hcc26     13 dih26
 o  13 oc27      12 ocn27     11 dih27
 h  10 hc28      9 hcc28      8 dih28
 h   9 hc29      8 hcc29      7 dih29
 h   8 hc30      7 hcc30      6 dih30
 h   7 hc31      6 hcc31      5 dih31

  ch2       1.096500
  hc3       1.095300
  hch3      108.279
  hc4       1.095800
  hch4      108.038
  dih4      116.613
  sc5       1.806980
  sch5      106.835
  dih5      -121.419
  cs6       1.774350
  csc6      103.566
  dih6      -65.629
  cc7       1.402980
  ccs7      113.860
  dih7      -80.000
  cc8       1.383890
  ccc8      121.945
  dih8      -167.543
  cc9       1.391820
  ccc9      119.114
  dih9      1.229
  cc10      1.383731
  ccc10     119.935
  dih10     -3.221
  cc11      1.406218
  ccs11     126.822
  dih11     108.433
  nc12      1.448799
  ncc12     127.185
  dih12     -13.679
  cn13      1.478770
  cnc13     125.317
  dih13     -3.546
  cc14      1.483710
  ccn14     108.296
  dih14     126.389
  cc15      1.383850
  ccc15     129.947
  dih15     -175.077
  cc16      1.397120
  ccc16     117.940
  dih16     -178.826
  cc17      1.390980
  ccc17     120.875
  dih17     0.237
  cc18      1.397160
  ccc18     121.050
  dih18     -0.203
  cc19      1.402776
  ccc19     108.787
  dih19     5.953
  cn20      1.523247
  cnc20     112.780
  dih20     128.384
  hc21      1.094360
  hcc21     120.923
  dih21     -179.905
  hc22      1.107700
  hcn22     108.251
  dih22     106.849
  hc23      1.108970
  hcn23     113.030
  dih23     -11.940
  hc24      1.095420
  hcc24     119.626
  dih24     179.891
  hc25      1.095259
  hcc25     119.441
  dih25     -179.847
  hc26      1.095240
  hcc26     120.801
  dih26     1.136
  oc27      1.210421
  ocn27     122.107
  dih27     -64.649
  hc28      1.098219
  hcc28     117.944
  dih28     -177.593
  hc29      1.095250
  hcc29     120.096
  dih29     177.200
  hc30      1.094580
  hcc30     120.432
  dih30     179.880
  hc31      1.098531
  hcc31     118.543
  dih31     10.603
```

Z-matrix for **2** [N-Ar & S-Ar locked] (Lowest Energy Conformation)

```
0 1
 h
 c   1 ch2
 h   2 hc3       1 hch3
 h   2 hc4       3 hch4       1 dih4
 s   2 sc5       4 sch5       3 dih5
 o   5 os6       2 osc6       1 dih6
 c   5 cs7       2 csc7       1 dih7
 c   7 cc8       5 ccs8       2 dih8
 c   8 cc9       7 ccc9       5 dih9
 c   9 cc10      8 ccc10      7 dih10
 c  10 cc11      9 ccc11      8 dih11
 c  11 cc12     10 ccc12      9 dih12
 n  12 nc13     11 ncc13     10 dih13
 c  13 cn14     12 cnc14     11 dih14
 c  14 cc15     13 ccn15     12 dih15
 c  15 cc16     14 ccc16     13 dih16
 c  16 cc17     15 ccc17     14 dih17
 c  17 cc18     16 ccc18     15 dih18
 c  18 cc19     17 ccc19     16 dih19
 c  19 cc20     18 ccc20     17 dih20
 c  20 cc21     19 ccc21     18 dih21
 h   8 hc22     9 hcc22      10 dih22
 h   9 hc23     10 hcc23     11 dih23
 h  10 hc24     11 hcc24     12 dih24
 h  11 hc25     12 hcc25     13 dih25
 h  21 hc26     20 hcc26     19 dih26
 h  21 hc27     20 hcc27     19 dih27
 h  19 hc28     18 hcc28     17 dih28
 h  18 hc29     19 hcc29     20 dih29
 h  17 hc30     18 hcc30     19 dih30
 h  16 hc31     15 hcc31     20 dih31
 o  14 oc32     15 occ32     20 dih32

      ch2        1.10134
      hc3        1.09530
      hch3      107.87237
      hc4        1.09661
      hch4      106.98438
      dih4      115.61616
      sc5        1.82361
      sch5      109.12847
      dih5     -124.12739
      os6        1.55430
      osc6      103.54371
      dih6     -170.36889
      cs7        1.81353
      csc7       99.20021
      dih7      -62.34639
      cc8        1.39511
      ccs8      119.82700
      dih8      260.00000
      cc9        1.39024
      ccc9      121.18599
      dih9      182.70993
      cc10       1.38955
      ccc10     120.02758
      dih10      -0.37211
      cc11       1.38963
      ccc11     119.87169
      dih11      -0.40344
      cc12       1.39855
      ccc12     120.02754
      dih12      0.56045
      nc13       1.45486
      ncc13     120.03917
      dih13    -178.40211
      cn14       1.45796
      cnc14     121.62636
      dih14     300.00000
      cc15       1.48572
      ccn15     106.24593
      dih15    -210.52975
      cc16       1.38343
      ccc16     129.69823
      dih16    -186.31504
      cc17       1.39752
      ccc17     118.04530
      dih17     179.98928
      cc18       1.39043
      ccc18     120.88130
      dih18      0.05553
      cc19       1.39767
      ccc19     121.04680
      dih19      -0.02548
      cc20       1.38282
      ccc20     118.17325
      dih20      -0.13061
      cc21       1.49554
      ccc21     128.81170
      dih21     180.11303
      hc22       1.10096
      hcc22     119.41420
      dih22     180.50051
      hc23       1.09533
      hcc23     120.13650
      dih23     179.81577
      hc24       1.09529
      hcc24     119.90238
      dih24    -179.45886
      hc25       1.09667
      hcc25     120.48748
      dih25      2.17593
      hc26       1.11309
      hcc26     113.13319
      dih26     -56.53884
      hc27       1.10853
      hcc27     111.87746
      dih27     64.76130
      hc28       1.09444
      hcc28     120.84958
      dih28     179.87908
      hc29       1.09554
      hcc29     119.30489
      dih29    -180.09249
      hc30       1.09541
      hcc30     119.69885
      dih30    -179.92354
      hc31       1.09550
      hcc31     120.76047
      dih31     179.98403
      oc32       1.21189
      occ32     130.05433
      dih32          -184.01239
```

Z-matrix for **2** [N-Ar & S-Ar locked]-Lowest Energy Conformation
(other side of the Transition State)

0 1

h			
c	1 ch2		
h	2 hc3	1 hch3	
h	2 hc4	3 hch4	1 dih4
s	2 sc5	4 sch5	3 dih5
o	5 os6	2 osc6	1 dih6
c	5 cs7	2 csc7	1 dih7
c	7 cc8	5 ccs8	2 dih8
c	8 cc9	7 ccc9	5 dih9
c	9 cc10	8 ccc10	7 dih10
c	10 cc11	9 ccc11	8 dih11
c	11 cc12	10 ccc12	9 dih12
n	12 nc13	11 ncc13	10 dih13
c	13 cn14	12 cnc14	11 dih14
c	14 cc15	13 ccn15	12 dih15
c	15 cc16	14 ccc16	13 dih16
c	16 cc17	15 ccc17	14 dih17
c	17 cc18	16 ccc18	15 dih18
c	18 cc19	17 ccc19	16 dih19
c	19 cc20	18 ccc20	17 dih20
c	20 cc21	19 ccc21	18 dih21
h	8 hc22	9 hcc22	10 dih22
h	9 hc23	10 hcc23	11 dih23
h	10 hc24	11 hcc24	12 dih24
h	11 hc25	12 hcc25	13 dih25
h	21 hc26	20 hcc26	19 dih26
h	21 hc27	20 hcc27	19 dih27
h	19 hc28	18 hcc28	17 dih28
h	18 hc29	19 hcc29	20 dih29
h	17 hc30	18 hcc30	19 dih30
h	16 hc31	15 hcc31	20 dih31
o	14 oc32	15 occ32	20 dih32

ch2	1.09664
hc3	1.09649
hch3	107.79691
hc4	1.09613
hch4	107.67140
dih4	115.26090
sc5	1.82015
sch5	113.79521
dih5	-124.04437
os6	1.55766
osc6	104.05640
dih6	85.50938
cs7	1.81315
csc7	99.63681
dih7	193.80876
cc8	1.39509
ccs8	119.82092
dih8	260.00000
cc9	1.39015
ccc9	121.21552
dih9	181.63503
cc10	1.38946
ccc10	119.99494
dih10	-0.15081
cc11	1.38944
ccc11	119.85499
dih11	0.57367
cc12	1.39890
ccc12	120.08958
dih12	-0.25717
nc13	1.45738
ncc13	119.90203
dih13	-180.74428
cn14	1.46098
cnc14	119.92638
dih14	60.00000
cc15	1.48358
ccn15	106.80321
dih15	-144.08230
cc16	1.38379
ccc16	129.78477
dih16	-175.00663
cc17	1.39715
ccc17	118.02809
dih17	180.04681
cc18	1.39075
ccc18	120.86742
dih18	-0.08525
cc19	1.39744
ccc19	121.05986
dih19	0.07119
cc20	1.38313
ccc20	118.18491
dih20	0.11656
cc21	1.49611
ccc21	128.76282
dih21	180.20338
hc22	1.10103
hcc22	119.43878
dih22	180.01546
hc23	1.09531
hcc23	120.16159
dih23	180.32260
hc24	1.09527
hcc24	119.89841
dih24	-180.25913
hc25	1.09674
hcc25	120.48839
dih25	-1.06252
hc26	1.10853
hcc26	111.93514
dih26	-63.35717
hc27	1.10678
hcc27	112.26433
dih27	57.60945
hc28	1.09456
hcc28	120.88112
dih28	180.15011
hc29	1.09557
hcc29	119.31253
dih29	-179.91646
hc30	1.09539
hcc30	119.69713
dih30	-180.04044
hc31	1.09542
hcc31	120.77150
dih31	179.97922
oc32	1.21322
occ32	130.00511
dih32	-178.09089

Z-matrix for **2** [N-Ar & S-Ar locked] (Transition State)

```
0 1
 h
 c   1 ch2
 h   2 hc3       1 hch3
 h   2 hc4       3 hch4       1 dih4
 s   2 sc5       3 sch5       4 dih5
 o   5 os6       2 osc6       1 dih6
 c   5 cs7       2 csc7       1 dih7
 c   7 cc8       5 ccs8       6 dih8
 c   8 cc9       7 ccc9       5 dih9
 c   9 cc10      8 ccc10      7 dih10
 c  10 cc11      9 ccc11      8 dih11
 c   7 cc12      8 ccc12      9 dih12
 n  12 nc13      7 ncc13      8 dih13
 c  13 cn14      12 cnc14     7 dih14
 c  14 cc15      13 ccn15     12 dih15
 c  15 cc16      14 ccc16     13 dih16
 c  16 cc17      15 ccc17     14 dih17
 c  17 cc18      16 ccc18     15 dih18
 c  18 cc19      17 ccc19     16 dih19
 c  15 cc20      14 ccc20     13 dih20
 c  13 cn21      14 cnc21     15 dih21
 h   8 hc22      7 hcc22      12 dih22
 h   9 hc23      8 hcc23      7 dih23
 h  10 hc24      9 hcc24      8 dih24
 h  11 hc25      12 hcc25     13 dih25
 h  21 hc26      13 hcn26     14 dih26
 h  21 hc27      13 hcn27     14 dih27
 h  19 hc28      20 hcc28     21 dih28
 h  18 hc29      19 hcc29     20 dih29
 h  17 hc30      18 hcc30     19 dih30
 h  16 hc31      15 hcc31     14 dih31
 o  14 oc32      13 ocn32     21 dih32

ch2       1.096780
hc3       1.096430
hch3      107.641
hc4       1.095801
hch4      107.807
dih4      -115.637
sc5       1.821640
sch5      113.034
dih5      -124.649
os6       1.571731
osc6      103.173
dih6      104.233
cs7       1.818280
csc7      100.900
dih7      -151.203
cc8       1.400960
ccs8      110.337
dih8      5.992
cc9       1.381290
ccc9      122.665
dih9      -177.428
cc10      1.391639
ccc10     118.609
dih10     0.332
cc11      1.384120
ccc11     119.891
dih11     1.584
cc12      1.402553
ccc12     118.881
dih12     -2.477
nc13      1.452680
ncc13     128.169
dih13     -173.352
cn14      1.466101
cnc14     127.376
dih14     -3.881
cc15      1.482800
ccn15     108.405
dih15     133.065
cc16      1.384400
ccc16     129.834
dih16     -177.514
cc17      1.396809
ccc17     117.925
dih17     -179.190
cc18      1.391310
ccc18     120.883
dih18     0.226
cc19      1.397120
ccc19     121.064
dih19     -0.096
cc20      1.402509
ccc20     108.913
dih20     3.313
cn21      1.523925
cnc21     106.686
dih21     -4.485
hc22      1.120990
hcc22     114.589
dih22     175.797
hc23      1.094440
hcc23     120.510
dih23     -179.835
hc24      1.095301
hcc24     120.204
dih24     -179.060
hc25      1.098290
hcc25     120.549
dih25     -6.119
hc26      1.108090
hcn26     108.555
dih26     -115.341
hc27      1.109179
hcn27     112.762
dih27     125.726
hc28      1.094490
hcc28     120.981
dih28     -0.089
hc29      1.095581
hcc29     119.325
dih29     179.808
hc30      1.095410
hcc30     119.675
dih30     -179.992
hc31      1.095360
hcc31     120.827
dih31     0.677
oc32      1.212820
ocn32     122.994
dih32     166.499
```

Z-matrix for **3** [N-Ar & S-Ar locked] (Lowest Energy Conformation)

```
0 1
 h
 c   1 ch2
 h   2 hc3       1 hch3
 h   2 hc4       1 hch4       3 dih4
 s   2 sc5       1 sch5       4 dih5
 o   5 os6       2 osc6       3 dih6
 o   5 os7       2 osc7       3 dih7
 c   5 cs8       2 csc8       3 dih8
 c   8 cc9       5 ccs9       2 dih9
 c   9 cc10      8 ccc10      5 dih10
 c  10 cc11      9 ccc11      8 dih11
 c  11 cc12     10 ccc12      9 dih12
 c  12 cc13     11 ccc13     10 dih13
 n  13 nc14     12 ncc14     11 dih14
 c  14 cn15     13 cnc15     12 dih15
 c  15 cc16     14 ccn16     13 dih16
 c  16 cc17     15 ccc17     14 dih17
 c  17 cc18     16 ccc18     15 dih18
 c  18 cc19     17 ccc19     16 dih19
 c  19 cc20     18 ccc20     17 dih20
 c  20 cc21     19 ccc21     18 dih21
 c  21 cc22     20 ccc22     19 dih22
 h   9 hc23     10 hcc23     11 dih23
 h  10 hc24     11 hcc24     12 dih24
 h  11 hc25     12 hcc25     13 dih25
 h  12 hc26     13 hcc26     14 dih26
 h  22 hc27     21 hcc27     20 dih27
 h  22 hc28     21 hcc28     20 dih28
 h  20 hc29     19 hcc29     18 dih29
 h  19 hc30     20 hcc30     21 dih30
 h  18 hc31     19 hcc31     20 dih31
 h  17 hc32     16 hcc32     21 dih32
 o  15 oc33     16 occ33     21 dih33

      ch2        1.09971
      hc3        1.09952
      hch3     106.21738
      hc4        1.09959
      hch4     105.97175
      dih4    -112.40045
      sc5        1.78959
      sch5     111.98676
      dih5    -124.63797
      os6        1.47390
      osc6     108.64523
      dih6     131.88368
      os7        1.47044
      osc7     110.11663
      dih7       3.20854
      cs8        1.80548
      csc8     102.43726
      dih8    -113.17858
      cc9        1.39880
      ccs9     117.65770
      dih9     240.00000
      cc10       1.38930
      ccc10    121.73317
      dih10    182.60748
      cc11       1.38945
      ccc11    120.00626
      dih11      0.46026
      cc12       1.38878
      ccc12    119.66164
      dih12     -0.10997
      cc13       1.39911
      ccc13    120.10613
      dih13     -0.47293
      nc14       1.45603
      ncc14    119.47104
      dih14   -180.31466
      cn15       1.45872
      cnc15    120.43549
      dih15     60.00000
      cc16       1.48247
      ccn16    106.60514
      dih16   -146.45113
      cc17       1.38404
      ccc17    129.73281
      dih17   -175.14111
      cc18       1.39682
      ccc18    118.03437
      dih18   -179.96996
      cc19       1.39096
      ccc19    120.85873
      dih19     -0.11570
      cc20       1.39722
      ccc20    121.07655
      dih20      0.07727
      cc21       1.38338
      ccc21    118.20547
      dih21      0.14110
      cc22       1.49586
      ccc22    128.68415
      dih22   -179.68976
      hc23       1.10086
      hcc23    118.78132
      dih23    180.46665
      hc24       1.09548
      hcc24    120.14084
      dih24    180.06867
      hc25       1.09543
      hcc25    120.02478
      dih25    179.58515
      hc26       1.09695
      hcc26    120.44742
      dih26     -0.88799
      hc27       1.10810
      hcc27    112.02833
      dih27    -63.47290
      hc28       1.10898
      hcc28    112.63312
      dih28     58.05908
      hc29       1.09467
      hcc29    120.91787
      dih29   -179.68163
      hc30       1.09557
      hcc30    119.31294
      dih30   -179.95191
      hc31       1.09533
      hcc31    119.69677
      dih31    179.91773
      hc32       1.09532
      hcc32    120.77368
      dih32   -179.96664
      oc33       1.21398
      occ33    130.36602
      dih33     -178.22304
```

Z-matrix for **3** [N-Ar & S-Ar locked]-Lowest Energy Conformation
(other side of the Transition State)

0 1

h			
c	1 ch2		
h	2 hc3	1 hch3	
h	2 hc4	1 hch4	3 dih4
s	2 sc5	1 sch5	4 dih5
o	5 os6	2 osc6	3 dih6
o	5 os7	2 osc7	3 dih7
c	5 cs8	2 csc8	3 dih8
c	8 cc9	5 ccs9	2 dih9
c	9 cc10	8 ccc10	5 dih10
c	10 cc11	9 ccc11	8 dih11
c	11 cc12	10 ccc12	9 dih12
c	12 cc13	11 ccc13	10 dih13
n	13 nc14	12 ncc14	11 dih14
c	14 cn15	13 cnc15	12 dih15
c	15 cc16	14 ccn16	13 dih16
c	16 cc17	15 ccc17	14 dih17
c	17 cc18	16 ccc18	15 dih18
c	18 cc19	17 ccc19	16 dih19
c	19 cc20	18 ccc20	17 dih20
c	20 cc21	19 ccc21	18 dih21
c	21 cc22	20 ccc22	19 dih22
h	9 hc23	10 hcc23	11 dih23
h	10 hc24	11 hcc24	12 dih24
h	11 hc25	12 hcc25	13 dih25
h	12 hc26	13 hcc26	14 dih26
h	22 hc27	21 hcc27	20 dih27
h	22 hc28	21 hcc28	20 dih28
h	20 hc29	19 hcc29	18 dih29
h	19 hc30	20 hcc30	21 dih30
h	18 hc31	19 hcc31	20 dih31
h	17 hc32	16 hcc32	21 dih32
o	15 oc33	16 occ33	21 dih33

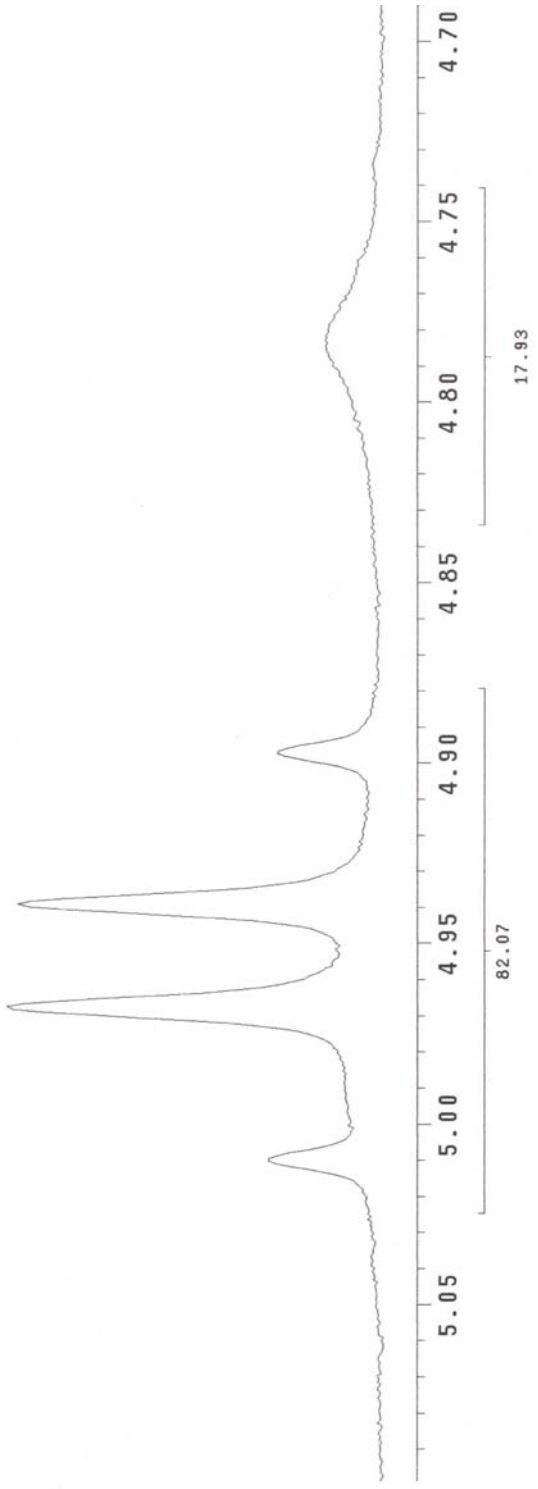
ch2	1.09970
hc3	1.10231
hch3	105.74564
hc4	1.09789
hch4	105.95278
dih4	-112.75818
sc5	1.79502
sch5	111.21516
dih5	-122.87967
os6	1.47375
osc6	107.64784
dih6	185.40933
os7	1.45920
osc7	109.80237
dih7	57.35084
cs8	1.80967
csc8	101.71621
dih8	-60.86019
cc9	1.39996
ccs9	116.74231
dih9	240.00000
cc10	1.38894
ccc10	121.96251
dih10	181.94320
cc11	1.38929
ccc11	119.97856
dih11	0.39892
cc12	1.38823
ccc12	119.53758
dih12	0.48979
cc13	1.39977
ccc13	120.24649
dih13	-0.14237
nc14	1.45672
ncc14	19.11798
dih14	-182.08878
cn15	1.46750
cnc15	19.84711
dih15	300.00000
cc16	1.48528
ccn16	06.28676
dih16	-212.02691
cc17	1.38346
ccc17	129.66633
dih17	-187.26582
cc18	1.39762
ccc18	118.02603
dih18	-180.32705
cc19	1.39040
ccc19	120.88550
dih19	0.06610
cc20	1.39770
ccc20	121.04128
dih20	0.02836
cc21	1.38284
ccc21	118.15817
dih21	-0.11619
cc22	1.49550
ccc22	128.75587
dih22	-180.46183
hc23	1.10117
hcc23	118.50807
dih23	180.27528
hc24	1.09549
hcc24	120.15787
dih24	180.86882
hc25	1.09538
hcc25	120.08803
dih25	180.43433
hc26	1.09709
hcc26	120.38783
dih26	-1.02120
hc27	1.11203
hcc27	112.37338
dih27	-56.47234
hc28	1.10830
hcc28	112.04060
dih28	64.74615
hc29	1.09439
hcc29	120.84516
dih29	-180.22042
hc30	1.09551
hcc30	119.30561
dih30	-180.00989
hc31	1.09541
hcc31	119.69926
dih31	180.18099
hc32	1.09556
hcc32	120.76542
dih32	-180.24083
oc33	1.20973
occ33	130.02882
dih33	-186.76067

Z-matrix for **3** [N-Ar & S-Ar locked] (Transition State)

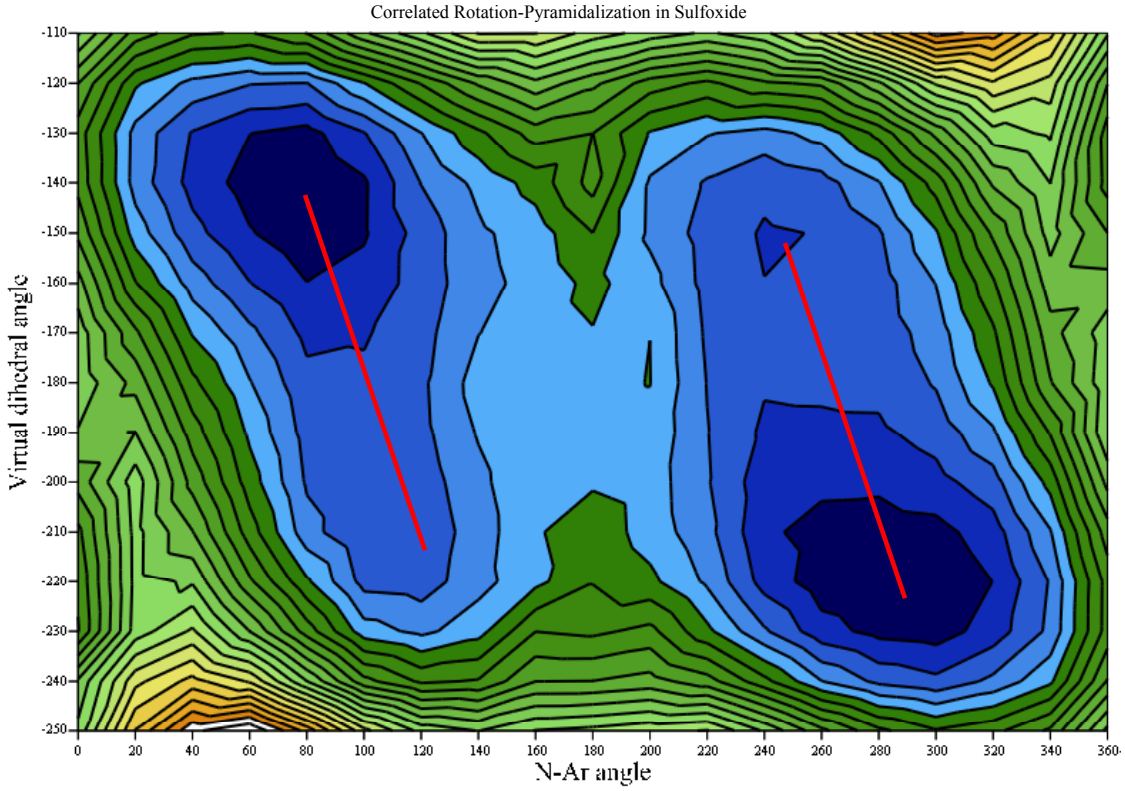
```
0 1
 h
 c   1 ch2
 h   2 hc3       1 hch3
 h   2 hc4       3 hch4       1 dih4
 s   2 sc5       3 sch5       1 dih5
 o   5 os6       2 osc6       4 dih6
 o   5 os7       2 osc7       4 dih7
 c   5 cs8       2 csc8       4 dih8
 c   8 cc9       5 ccs9       6 dih9
 c   9 cc10      8 ccc10      5 dih10
 c  10 cc11      9 ccc11      8 dih11
 c  11 cc12     10 ccc12      9 dih12
 c   8 cc13      9 ccc13     10 dih13
 n  13 nc14      8 ncc14      9 dih14
 c  14 cn15     13 cnc15      8 dih15
 c  15 cc16     14 ccn16     13 dih16
 c  16 cc17     15 ccc17     14 dih17
 c  17 cc18     16 ccc18     15 dih18
 c  18 cc19     17 ccc19     16 dih19
 c  19 cc20     18 ccc20     17 dih20
 c  16 cc21     15 ccc21     14 dih21
 c  14 cn22     15 cnc22     16 dih22
 h   9 hc23      8 hcc23     13 dih23
 h  10 hc24      9 hcc24      8 dih24
 h  11 hc25     10 hcc25      9 dih25
 h  12 hc26     13 hcc26     14 dih26
 h  22 hc27     14 hcn27     15 dih27
 h  22 hc28     14 hcn28     15 dih28
 h  20 hc29     21 hcc29     22 dih29
 h  19 hc30     20 hcc30     21 dih30
 h  18 hc31     19 hcc31     20 dih31
 h  17 hc32     16 hcc32     15 dih32
 o  15 oc33     14 ocn33     22 dih33

ch2       1.100849
hc3       1.098890
hch3      106.006
hc4       1.100061
hch4      105.962
dih4      112.294
sc5       1.786330
sch5      114.114
dih5      -124.023
os6       1.470110
osc6      110.626
dih6      -134.467
os7       1.477129
osc7      108.060
dih7      -6.084
cs8       1.812850
csc8      103.415
dih8      109.750
cc9       1.408819
ccs9      111.067
dih9      122.586
cc10      1.381291
ccc10     123.568
dih10     -178.699
cc11      1.390710
ccc11     118.887
dih11     -0.068
cc12      1.380629
ccc12     119.163
dih12     3.842
cc13      1.409000
ccc13     116.943
dih13     -6.076
nc14      1.454090
ncc14     129.566
dih14     -166.547
cn15      1.474890
cnc15     128.925
dih15     -4.888
cc16      1.480160
ccn16     108.764
dih16     128.314
cc17      1.384155
ccc17     129.875
dih17     -174.318
cc18      1.397320
ccc18     117.828
dih18     -179.263
cc19      1.390990
ccc19     120.914
dih19     0.060
cc20      1.397420
ccc20     121.080
dih20     -0.262
cc21      1.402138
ccc21     108.789
dih21     5.973
cn22      1.529506
cnc22     105.710
dih22     -8.079
hc23      1.103960
hcc23     119.015
dih23     175.163
hc24      1.094950
hcc24     120.472
dih24     -179.613
hc25      1.095320
hcc25     120.493
dih25     -177.180
hc26      1.099151
hcc26     120.428
dih26     -10.627
hc27      1.109131
hcn27     112.960
dih27     128.767
hc28      1.108030
hcn28     108.372
dih28     -112.168
hc29      1.094310
hcc29     121.022
dih29     0.413
hc30      1.095461
hcc30     119.297
dih30     179.726
hc31      1.095340
hcc31     119.673
dih31     179.591
hc32      1.095350
hcc32     120.843
dih32     1.106
oc33      1.210931
ocn33     121.728
dih33     161.262
```

Figure 6. Partial ^{1}H NMR of **1** (and **2**) [-40 ^{o}C, $CDCl_3$] with *m*-CPBA as a limiting reagent (0.85 equiv) after ~5 min.

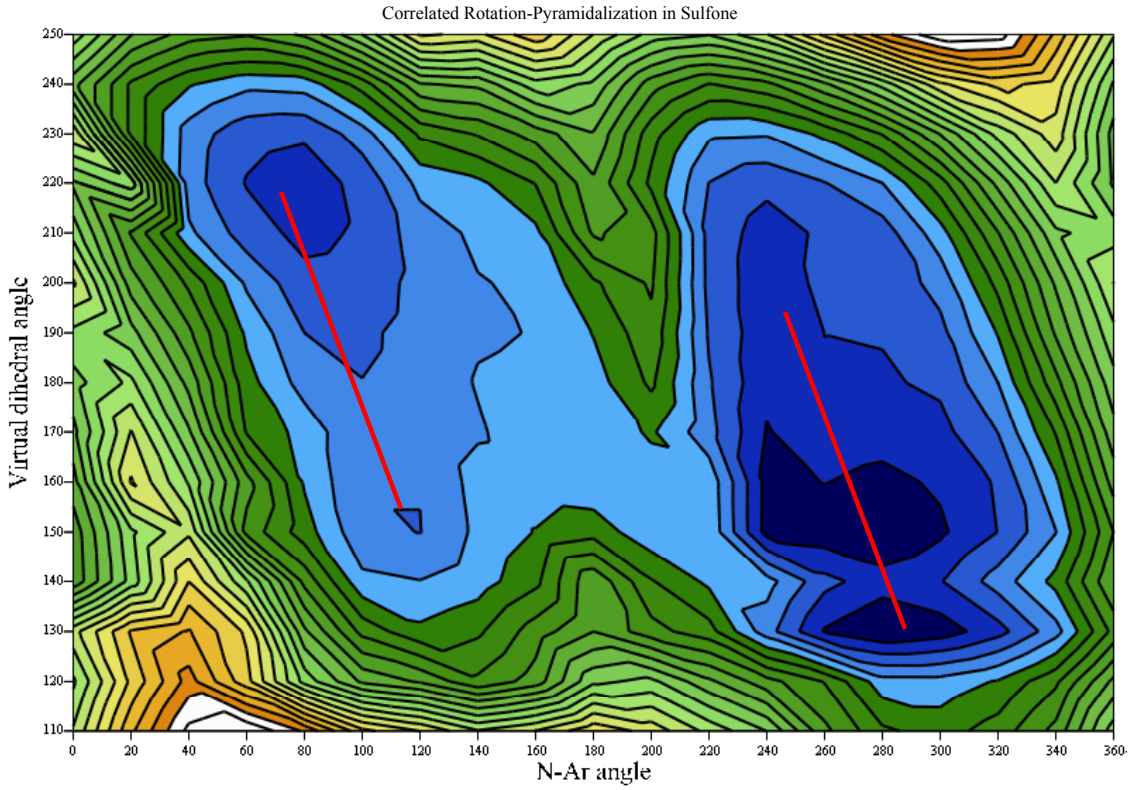


N-Ar torsion angle *vs* virtual dihedral angle for **2**



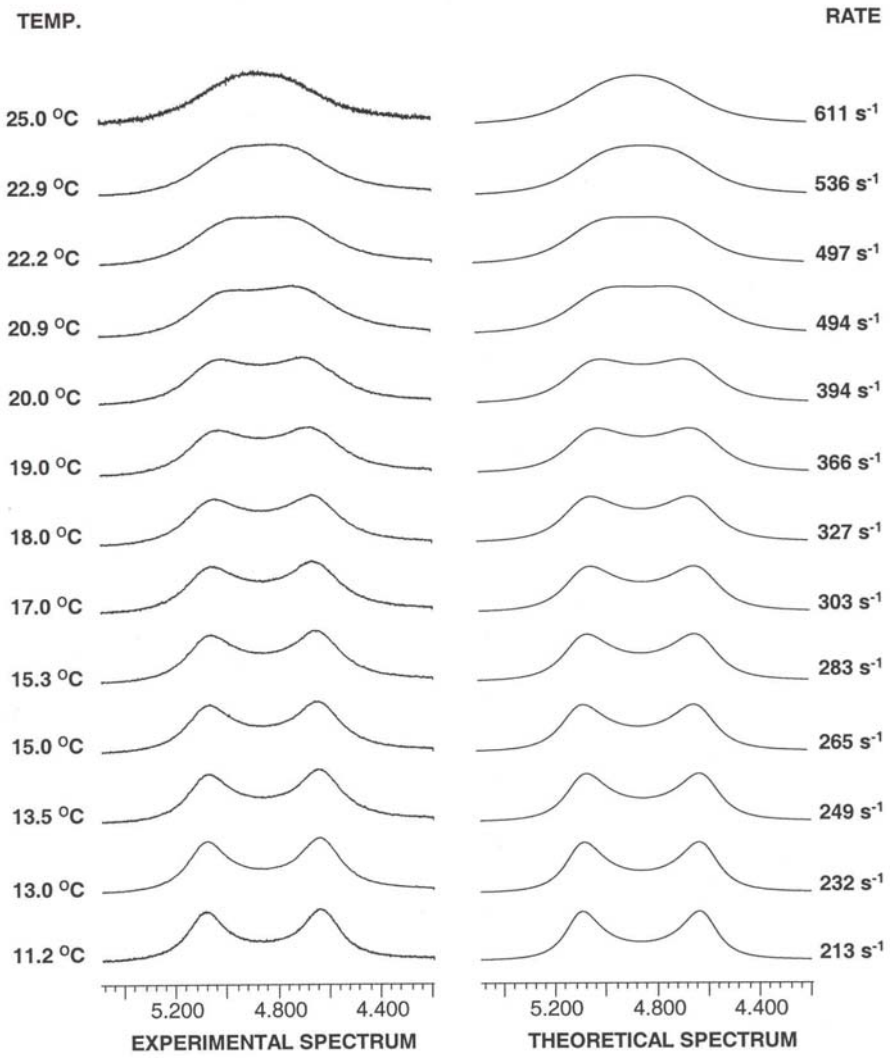
(q, w, z)

N-Ar torsion angle *vs* virtual dihedral angle for **3**



(q, w, z)

Line-shape analysis for **3**



Z-matrix for **1** (N-Ar & Virtual Dihedral Angle locked)-Lowest Energy Conformation

```
0 1
 c
 n   1 nc2
 c   2 cn3       1 cnc3
 c   2 cn4       1 cnc4       3 dih4
 c   4 cc5       2 ccn5       1 dih5
 c   5 cc6       4 ccc6       2 dih6
 c   6 cc7       5 ccc7       4 dih7
 c   7 cc8       6 ccc8       5 dih8
 c   8 cc9       7 ccc9       6 dih9
 s   9 sc10      8 scc10      7 dih10
 c  10 cs11      9 csc11      8 dih11
 h  11 hc12     10 hcs12      9 dih12
 h  11 hc13     10 hcs13      9 dih13
 h  11 hc14     10 hcs14      9 dih14
 c   3 cc15     2 ccn15       1 dih15
 c  15 cc16     3 ccc16       2 dih16
 c  16 cc17    15 ccc17       3 dih17
 c  17 cc18    16 ccc18      15 dih18
 c  18 cc19    17 ccc19      16 dih19
 c   1 cc20     2 ccn20       3 dih20
 h  19 hc21    18 hcc21      17 dih21
 h  18 hc22    17 hcc22      16 dih22
 h  17 hc23    16 hcc23      15 dih23
 h  16 hc24    15 hcc24       3 dih24
 o   3 oc25     2 ocn25       1 dih25
 h   5 hc26     4 hcc26       2 dih26
 h   6 hc27     5 hcc27       4 dih27
 h   7 hc28     6 hcc28       5 dih28
 h   8 hc29     7 hcc29       6 dih29
 h   1 hc30     2 hcn30       3 dih30
 h   1 hc31     2 hcn31       3 dih31

      nc2       1.50975
      cn3       1.45978
      cnc3    108.89349
      cn4       1.45190
      cnc4    115.49531
      dih4    220.00000
      cc5       1.40060
      ccn5    120.34846
      dih5    100.00000
      cc6       1.38813
      ccc6    120.32517
      dih6    180.30749
      cc7       1.39057
      ccc7    119.99521
      dih7      0.13847
      cc8       1.38826
      ccc8    119.88847
      dih8     -0.83974
      cc9       1.39864
      ccc9    121.15526
      dih9      0.65545
      sc10      1.77391
      scc10   115.13803
      dih10  -182.92343
      cs11      1.80565
      csc11   104.79719
      dih11   121.01170
      hc12      1.09502
      hcs12   112.92958
      dih12   -53.82583
      hc13      1.09690
      hcs13   106.58306
      dih13   187.62173
      hc14      1.09534
      hcs14   113.32572
      dih14    68.90601
      cc15      1.48438
      ccn15   106.75227
      dih15     8.05609
      cc16      1.38385
      ccc16   129.75096
      dih16  -185.05184
      cc17      1.39697
      ccc17   118.04217
      dih17  -180.06020
      cc18      1.39085
      ccc18   120.85820
      dih18     0.07523
      cc19      1.39719
      ccc19   121.05840
      dih19    -0.03954
      cc20      1.49509
      ccn20   104.07437
      dih20    -7.77877
      hc21      1.09453
      hcc21   120.91192
      dih21   179.85103
      hc22      1.09548
      hcc22   119.62039
      dih22   179.92606
      hc23      1.09528
      hcc23   119.44568
      dih23  -180.02428
      hc24      1.09535
      hcc24   120.74788
      dih24    -0.14571
      oc25      1.21366
      ocn25   123.56947
      dih25   184.69508
      hc26      1.09723
      hcc26   120.38630
      dih26     1.02506
      hc27      1.09520
      hcc27   119.85616
      dih27  -179.86280
      hc28      1.09501
      hcc28   120.15262
      dih28  -180.29603
      hc29      1.09809
      hcc29   119.88264
      dih29  -179.21689
      hc30      1.10803
      hcn30   112.44261
      dih30   113.49984
      hc31      1.10844
      hcn31   108.42942
      dih31  -127.97887
```

Z-matrix for **2** (N-Ar & Virtual Dihedral Angle locked)-Lowest Energy Conformation

```
0 1
c
n   1 nc2
c   2 cn3      1 cnc3
c   2 cn4      1 cnc4      3 dih4
c   4 cc5      2 ccn5      1 dih5
c   5 cc6      4 ccc6      2 dih6
c   6 cc7      5 ccc7      4 dih7
c   7 cc8      6 ccc8      5 dih8
c   8 cc9      7 ccc9      6 dih9
s   9 sc10     8 scc10     7 dih10
o  10 os11     9 osc11     8 dih11
c  10 cs12     9 csc12     8 dih12
h  12 hc13    10 hcs13    11 dih13
h  12 hc14    10 hcs14    11 dih14
h  12 hc15    10 hcs15    11 dih15
c   3 cc16     2 ccn16     1 dih16
c  16 cc17     3 ccc17     2 dih17
c  17 cc18    16 ccc18     3 dih18
c  18 cc19    17 ccc19    16 dih19
c  19 cc20    18 ccc20    17 dih20
c   1 cc21     2 ccn21     3 dih21
h  20 hc22    19 hcc22    18 dih22
h  19 hc23    18 hcc23    17 dih23
h  18 hc24    17 hcc24    16 dih24
h  17 hc25    16 hcc25     3 dih25
o   3 oc26     2 ocn26     1 dih26
h   5 hc27     4 hcc27     2 dih27
h   6 hc28     5 hcc28     4 dih28
h   7 hc29     6 hcc29     5 dih29
h   8 hc30     7 hcc30     6 dih30
h   1 hc31     2 hcn31     3 dih31
h   1 hc32     2 hcn32     3 dih32

nc2        1.50780
cn3        1.46060
cnc3     108.99248
cn4        1.45591
cnc4     115.57518
dih4     -140.00000
cc5        1.39903
ccn5     119.73399
dih5      80.00000
cc6        1.38930
ccc6     120.14908
dih6     -179.95374
cc7        1.38938
ccc7     119.81206
dih7       0.21161
cc8        1.38996
ccc8     119.99130
dih8      -0.53188
cc9        1.39567
ccc9     121.31522
dih9       0.13450
sc10       1.81380
scc10    119.27278
dih10    -174.97989
os11       1.55492
osc11    105.05411
dih11      2.37140
cs12       1.82252
csc12    100.13442
dih12    -104.63445
hc13       1.10017
hcs13    111.02151
dih13    190.15458
hc14       1.09546
hcs14    114.24206
dih14    -47.66955
hc15       1.09687
hcs15    108.92310
dih15     71.80602
cc16       1.48530
ccn16    106.43772
dih16      9.98057
cc17       1.38353
ccc17    129.72086
dih17    173.83040
cc18       1.39744
ccc18    118.03958
dih18    179.92783
cc19       1.39052
ccc19    120.87865
dih19      0.05810
cc20       1.39760
ccc20    121.04756
dih20     -0.02686
cc21       1.49548
ccn21    103.94507
dih21     -9.72510
hc22       1.09445
hcc22    120.85500
dih22    179.88917
hc23       1.09554
hcc23    119.64446
dih23    179.93527
hc24       1.09541
hcc24    119.42383
dih24    179.95733
hc25       1.09550
hcc25    120.76097
dih25     -0.16359
oc26       1.21180
ocn26    123.57681
dih26    -172.35769
hc27       1.09677
hcc27    120.44826
dih27      0.75426
hc28       1.09527
hcc28    119.92624
dih28    -179.59390
hc29       1.09532
hcc29    120.15927
dih29    179.89879
hc30       1.10120
hcc30    119.28023
dih30    -179.14006
hc31       1.11234
hcn31    108.53149
dih31    -129.97678
hc32       1.10843
hcn32    112.51186
dih32    111.49100
```

Z-matrix for **3** (N-Ar & Virtual Dihedral Angle locked)-Lowest Energy Conformation

```
0 1
c
n   1 nc2
c   2 cn3      1 cnc3
c   2 cn4      1 cnc4      3 dih4
c   4 cc5      2 ccn5      1 dih5
c   5 cc6      4 ccc6      2 dih6
c   6 cc7      5 ccc7      4 dih7
c   7 cc8      6 ccc8      5 dih8
c   8 cc9      7 ccc9      6 dih9
s   9 sc10     8 scc10     7 dih10
o  10 os11     9 osc11     8 dih11
o  10 os12     9 osc12     8 dih12
c  10 cs13     9 csc13     8 dih13
h  13 hc14    10 hcs14    12 dih14
h  13 hc15    10 hcs15    12 dih15
h  13 hc16    10 hcs16    12 dih16
c   3 cc17     2 ccn17     1 dih17
c  17 cc18     3 ccc18     2 dih18
c  18 cc19    17 ccc19     3 dih19
c  19 cc20    18 ccc20    17 dih20
c  20 cc21    19 ccc21    18 dih21
c   1 cc22     2 ccn22     3 dih22
h  21 hc23    20 hcc23    19 dih23
h  20 hc24    19 hcc24    18 dih24
h  19 hc25    18 hcc25    17 dih25
h  18 hc26    17 hcc26     3 dih26
o   3 oc27     2 ocn27     1 dih27
h   5 hc28     4 hcc28     2 dih28
h   6 hc29     5 hcc29     4 dih29
h   7 hc30     6 hcc30     5 dih30
h   8 hc31     7 hcc31     6 dih31
h   1 hc32     2 hcn32     3 dih32
h   1 hc33     2 hcn33     3 dih33

nc2          1.50527
cn3          1.44679
cnc3       110.25045
cn4          1.45191
cnc4       118.26006
dih4       150.00000
cc5          1.39955
ccn5       118.76147
dih5       280.00000
cc6          1.38865
ccc6       120.17543
dih6       180.43492
cc7          1.38943
ccc7       119.62737
dih7        -0.22696
cc8          1.38907
ccc8       119.98758
dih8        -0.24592
cc9          1.39914
ccc9       121.81343
dih9         0.23831
sc10         1.80502
scc10      117.45896
dih10     -178.51055
os11         1.46922
osc11      110.10983
dih11      130.58371
os12         1.47372
osc12      108.75719
dih12        2.07529
cs13         1.78958
csc13      101.70444
dih13     -112.38465
hc14         1.09965
hcs14      112.14765
dih14      115.81963
hc15         1.09956
hcs15      112.17576
dih15       -3.55484
hc16         1.10000
hcs16      113.90818
dih16     -124.00706
cc17         1.48301
ccn17      106.29511
dih17       -6.02150
cc18         1.38395
ccc18      129.66198
dih18     -176.11360
cc19         1.39682
ccc19      118.03828
dih19     -179.87980
cc20         1.39094
ccc20      120.86398
dih20       -0.12616
cc21         1.39717
ccc21      121.07761
dih21        0.06926
cc22         1.49620
ccn22      103.28453
dih22        5.60369
hc23         1.09462
hcc23      120.91318
dih23     -179.63482
hc24         1.09553
hcc24      119.60882
dih24     -179.81812
hc25         1.09530
hcc25      119.44171
dih25     -179.96762
hc26         1.09530
hcc26      120.76568
dih26        0.19854
oc27         1.21568
ocn27      123.06084
dih27      176.48206
hc28         1.09697
hcc28      120.41018
dih28       -0.19398
hc29         1.09543
hcc29      120.05234
dih29      179.69153
hc30         1.09548
hcc30      120.15398
dih30     -180.12789
hc31         1.10091
hcc31      118.70130
dih31     -179.46263
hc32         1.10926
hcn32      109.08437
dih32      125.42292
hc33         1.10783
hcn33      112.04193
dih33     -115.34331
```

Appendix 5

Step by step guide to convert and analyze NMR spectra from VNMR to gNMR

There are 3 different programs, which you have to use,

1. gCVT: This program is used to import spectrum from VNMR (which is our NMR processing software.
2. gSPG: This is the program in which imported spectra from gCVT opens up. In this program you can process your spectrum. For example, you can adjust your spectra for Line width, Phasing and other things. Be sure to SAVE your spectrum after you think it's perfect for processing in gNMR.
3. gNMR: This is the program which gives your theoretical and experimental spectrum

Now, following are the instructions for using gCVT program:

(Before doing this you might want to make a NEW sub-folder (as gSPG) in your main folder where you have your all VNMR spectrums for that particular compound. But you can do this later.)

1. Open gCVT program.
2. Along with gCVT program a window opens up which says Convert File. There are 4 different options in this window.
    i) VNMR Parameter file: procpar file
    ii) VNMR spectrum file: NONE
    iii) VNMR FID file: fid file

iv) VNMR text file: text file

Now, next to each of those there is a browse option. Click on that and go to your own spectrum file from VNMR.

When you open your file you may not see all your spectrum files. Therefore click on 'all files' then you will be able to see all your files.

For each of the above type select particular file from your spectrum EXCEPT FOR SPECTRUM file.

After you fill in all the file names click on GO. Then you will see some series of messages in gCVT window, which shows you the progress of your processing. (It's very fast..) Then it will give you a message

" generating spectrum by unweighted FFT

Phasing will probably be incorrect." Click OK.

This will open up your gSPG program and you will see your spectrum but with phasing totally wrong. You will have to phase this spectrum.

Now we are in gSPG program:

1. Try clicking on Spectrum menu and then Auto phase. This might be helpful but not for sure.
2. If the spectrum doesn't look good then Click on Spectrum Menu and then Phase. One window will open up. In this window it's usually good idea to Select – Quick phasing option. Then by clicking on

i) Left Phase

ii) Right phase

iii) Pivot phase

Adjust your spectrum till it looks as good as a normal NMR spectrum in VNMR.

When you are satisfied Click on Done.

Now if you are planning to simulate Whole Spectrum then at this stage you will have to SAVE this spectrum. Be sure to SAVE your spectrum after you think it's perfect for processing in gNMR.

As I am more interested in only methylene protons (i.e. 4.2-5.5 ppm) I will do the following:

i) Put the cursor on 4.2 ppm

ii) Drag the cursor till 5.5 ppm

iii) Click anywhere in the middle, this will show now only 4.2-5.5 ppm of the spectrum

iv) Click on Spectrum Menu, Reduce followed by Sub spectrum, this will now kind of enlarge your spectrum

v) If you want your spectrum in this enlarged form for the processing in gNMR then you will have to save this spectrum. I usually save this as same name which I used to save spectra in gSPG with added name as

*-sub

Now you are ready to process this spectrum in gNMR to get,

i) theoretical and experimental spectrum comparison

ii) rate of exchange process.

Repeat all of the above procedure for all your spectra at each temperature.

All these things are usually done as follows:

Open gNMR program now.

1. gNMR program opens up with a small window with title Welcome to gNMR inside the main big window.
2. Click on "start with an empty molecule".
3. GO to gSPG program where you have your experimental spectrum and note down the ppm values for the two peaks.(note: you can put the cursor on the peak and it's ppm value will appear in the left corner of the spectrum window)
4. In gNMR in document1-molecule1 window.
5. Enter approximate ppm value for 1st peak in column for δ (The one, which you noted down in step 3 above). Press Enter. **Also remember to keep this ppm value as variable. To do this, type any alphabetical letter in the window exactly below your ppm value window.**
6. Enter the approximate ppm value for 2nd peak in column for δ (the one which you noted down in step 3 above). Press Enter. **Also remember to keep this ppm value as variable. To do this, type any *(must be different from the letter which you used in step 5)* alphabetical letter in the window which exactly below your ppm value window.**

7. Click on Spectrum. Spectrum with 2 peaks (sharp) will appear.
8. Click on Settings – Spectrum, a small window will appear inside which you will see all the spectrum parameters like,

    i) Line width

    ii) Scale

    iii) From ppm

    iv) To ppm

    v) Verticle size

9. In from-ppm put 4.2 ppm (this comes from the spectrum which you saved in your gSPG program) **REFER to page 2 above.**
10. In to –ppm put 5.5 ppm (this comes from the spectrum which you saved in your gSPG program) **REFER to page 2 above.**
11. Click on OK
12. New spectrum window appears in which you have to scroll horizontally to see your 2nd peak. Therefore close this spectrum window by clicking on **X**

    Again in document 1-molecule1 window click on spectrum. Now you will see your spectrum with 2 peaks in one window without doing scroll. (The height of the 2 peaks might be different but don't worry!)
13. Now go to Settings—Spectrum—Iteration your Left hand side you will see that Iteration is in blue.
14. In right hand side it shows Spectrum: None

15. Click on File. Go and find out your corresponding gSPG spectrum which you saved as *-sub file above.
16. Click OK. A message will appear saying “Spectrometer frequency mismatch. Adjust automatically?” say OK to this.
17. You will now see that your experimental spectrum is now on TOP and theoretical Spectrum is now on BOTTOM in your spectrum 1 window.
18. In Spectrum –Settings window in Display choose option as Overlapping. Click on Apply Check “full line shape iteration” and click OK. You will see in Spectrum window that one spectrum is in Red color.
19. Next to your UNDO—REDO icons there is one icon, which is for exchange click on that icon and one exchange window opens up.

    Rate: type any number (I usually type 100)

    Iter? : incompl

    1-2 : 2-1

    2-1 : 1-2

After you type all these things the 2nd option Iter? Will change from Incoml to Fixed. Change that option by scrolling down to variable. Then, Click on Recalculate.

20. Now you will see that spectrum window has changed and you will see 2 sets of peaks not overlapping exactly.
21. **IMPORTANT:** In your left hand corner you will see a minimized window which is a LOG window open that window and adjust it’s size so that you can clearly see your spectrum iteration.
22. **IMPORTANT: you will see that in the spectrum window**

RED color spectrum: theoretical Spectrum has a base line UP certain height from your experimental BLACK Spectrum there for to fix that problem go to Settings—Spectrum—Baseline and you will see 3 options:

Phase(0):

Phase (1):

Height :

In any height window 1st type very small number say 0.01 and click Apply.

Now you will see that in spectrum window both the peaks RED and BLACK have nearly same Baseline Height. If you still see a very large difference in base line height then try typing very small number in Phase(0) and then in Phase (1) in same order. Try one at a time. Sometimes you have to type number in all of the above 3 windows. IMPORTANT: also be sure to check Iterate on Baseline in Settings—Spectrum—Iteration option. This is below "full line shape iteration", which you checked earlier. Click on APPLY—OK

23. Now you are all set to do iteration. Click on **Iterate—GO** you will see movement in two spectrums to match exactly with each other. At the same time you will see something is going on in LOG window and also in Exchange window. At the end of the matching you will now see that two spectrums match exactly and in exchange window you will see the exchange rate of this process. Take down this value and remember this value is for particular spectrum, which was recorded at particular temperature.

SAVE your Results in gNMR.

Sometimes if you see in gNMR Log window you will see that Error in Rate measurement is very high. To minimize the error you can do one thing. Go to your Molecule window where you put your ppm value initially and remove the alphabetical

letters which have put in there at the beginning and then again click on Iterate—GO. Again same calculations will be performed but this time you will see that the error in K measurement is very less. Till today I haven't been able to find out the reasoning behind this but this is just my observation.

24. **Repeat ALL these steps (1-23) for all of your recorded spectrums in VNMR to get exchange rate at all that temperature.**
25. **Plot graph of lnk vs 1/T in excel and calculate ΔG value from slope.**

Step by step guide to perform PM3 Semi-empirical calculations using Gaussian™

The following steps were followed to do the semi-empirical PM3 molecular orbital calculations on all of the isoindolines (**1-3,** Chapter 4).

1. Draw the structure in HyperChem™ v 6.02.
2. Import the structure in Gaussian™ 1998.
3. Optimize the structure using PM3 semi-empirical molecular orbital calculation method.
4. Define the z-matrix of the structure using z-mat editor in molden (program used to see the structure of the molecule).
5. Identify the two dihedral angles which you would like to study.
6. In gaussian, do the geometry optimization calculations by holding each of the dihedral angle at its fixed value and allowing rest of the molecule to relax to its minimum energy conformation. For example, rotate one dihedral angle from 0 to 360° while holding the other dihedral angle at any particular fixed value between 0 to 360°. Energies in the form of eigenvalues (in atmic units) would be provided during these calculations in the ".log" file of each of these calculations.
7. Plot a 3D surface plot (preferably in MathCad™) of the energy values obtained at each of the data point versus two dihedral angle values at the same data point.
8. Locate the minimum (on either side of the maxima) and maximum energy conformation on the surface plot (using the obtained energy values) and further

single point frequency calculations on each of these points were performed. This is necessary as the calculations performed in PM3 are the gas phase calculations.

9. From the energy valus obtained from the frequency calculations rotational barrier was evaluated, after converting atomic units into kcal/mol.
10. Identical calculations were performed in a study, which showed correlated nitrogen pyramidalization and N-Ar rotation by making the only change in one dihedral angle. Instead of using S-Ar angle as one dihedral angle and N-Ar as the other in **1**-**3**, virtual dihedral angle was used along with N-Ar as the second dihedral angle.