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Progress Towards the Synthesis of Stabilized Carbonyl Oxides

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Progress Towards the Synthesis of Stabilized Carbonyl Oxides

By Marisa Weaver

An Honors Thesis submitted to the Faculty of the Department of Chemistry at the University of Redlands in partial fulfillment of the requirement for an Honors Bachelor of Science degree in Chemistry.

May 2010

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i. Abstract

Criegee proposed that the ozonolysis mechanism proceeds by means of a [3+2] cycloaddition, forming a carbonyl oxide and a carbonyl. This carbonyl oxide then recombines with the carbonyl, or a dipolarophile. Kuczkowski investigated the ozonolysis of vinyl ethers and found that recombination of the carbonyl oxide and the vinyl ether was observed. We are investigating a way to produce a carbonyl oxide and disconnect it from ozone to react with a dipolarophile by a [3+2] cycloaddition. In this work, silicon groups were used in efforts to stabilize the carbonyl oxide. Currently the synthesis of vinyl peroxidic enols which can tautomerize to carbonyl oxides are being attempted.

ii. Acknowledgements

I would like to thank everyone who has helped me in my efforts to reach the point I am today as I prepare to graduate from the University of Redlands. First and foremost, Dr. David Soulsby for guiding me with the research I have done on carbonyl oxide, Dr. Teresa Longin for advising me throughout my undergraduate career, Dr. Scott Serafin for showing me how chemistry can be fun, and Dr. Sandy Koonce, Dr. Barbara Murray, Dr. David Schrum for agreeing to be on my honors thesis committee. I would also like to thank Megan Kard and Cezar Rodarte for keeping me company in lab my first few semesters and Kevin Murphy and Patrick Medeira for joining us in lab for our last year at the U of R. Lastly, I would like to thank my family and the University of Redlands for supporting me through my college career and giving me encouragement to always reach a little higher than I thought I could manage.

1. Introduction

1.1 Discovery and Preparation of Ozone

The distinct odor produced in lightning storms began to attract the attention of chemists in the 1800's. Christian Friedrich Shönbein[1] investigated this new gas and called it ozone. Jacques-Louis Soret later confirmed that three oxygen atoms form ozone in 1867, Figure 1.[2]

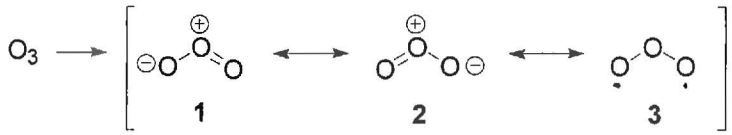

Figure 1: Ozone

Ozone is most commonly thought to be a hybrid of the two resonance structures **1** and **2** where the negative charge is delocalized over both terminal oxygen atoms in the molecule but can also be thought of as a diradical **3**. Originally ozone was an attractive area of study because it was a structurally interesting allotrope of oxygen and occurred naturally in the atmosphere. In the stratosphere, ozone absorbs UV radiation below 320 nm and decomposes to O_2 by the reaction shown in Figure # to produce oxygen.[3] Ozone has protective properties in the stratosphere, but in the troposphere it is a harmful pollutant because it a powerful oxidant, Figure 2.[3]

$$(1)\ O_3 + h\nu \rightarrow O_2 + O$$

$$(2)\ O + O_3 \rightarrow O_2$$

Figure 2: Reaction of UV radiation with O_3 to produce O_2

---

[1] Rubin, M. B. *Bull. Hist. Chem.* **2001**, *26(1)*, 40-56.
[2] Soret, J.L. *Annalen der Physik und Chemie.* **1867**, *208(9)*, 165-174.
[3] Miessler, G. L.; Tarr, D. A. *Inorganic Chemistry*; 3rd ed; Pearson Prentice Hall: New Jersey; 2004. p 632.

Initially, ozone was difficult to isolate in reasonable quantities to study. In the 1840's, it was typically obtained as a <1% solution in oxygen, but today, ozone generators can produce gaseous mixtures that are enriched by up to ~5% ozone.[1] The typical set-up for ozone generation and the reactions showing ozone formation are shown below, Figure 3.

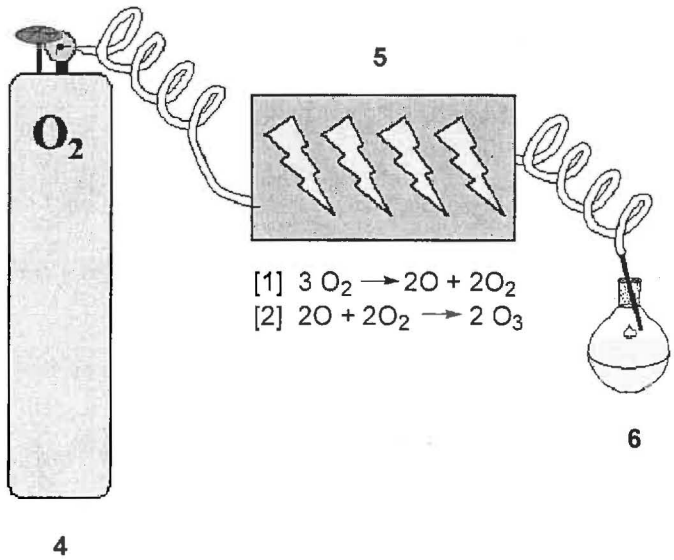

Figure 3: Ozone generator & reactions showing ozone formation

In an ozone generator, a source (**4**) first supplies oxygen to the generator (**5**). The oxygen then passes over an electrical discharge and forms oxygen enriched ozone, similar to the way ozone is produced in a lightning storm. The high voltage zone facilitates the reaction of oxygen to form as shown above.

The ozone can then be used as it exits the generator (**6**). The high oxidative power of ozone makes it a valuable reagent in organic synthesis for ozonolysis reactions[4] and structural elucidation.[1]

---

[4] Wade, Jr. L. G. *Organic Chemistry*. 6th edition. Pearson Prentice Hall: Upper Saddle River, NJ. 2006; p 362.

1.2 General Ozonolysis Reaction

Ozonolysis is a term that usually describes the reaction of ozone with an alkene, resulting in cleavage of the alkene (**7**) into two oxidized species, Figure 4.

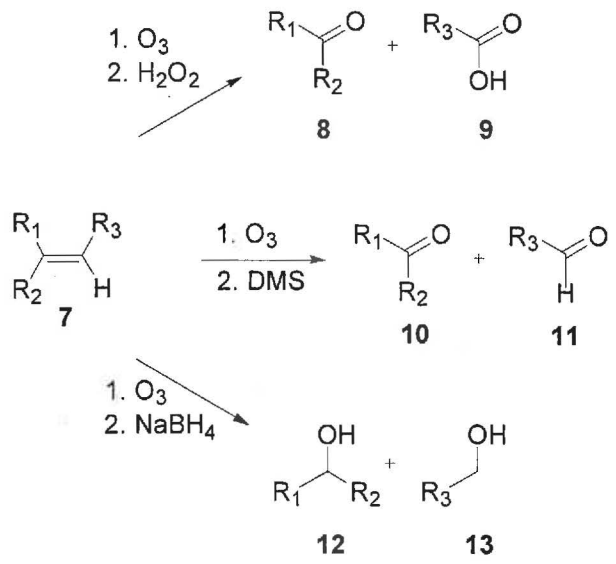

Figure 4: Cleavage of an alkene by ozonolysis

Dependant on whether the workup is oxidative or reductive, products such as alcohols (**12**, **13**), aldehydes (**11**), ketones (**8**, **10**) and carboxylic acids (**9**) are easily synthesized.[5] This is a useful way to oxidize alkenes because it provides a means to generate the carbonyl moieties through a reductive workup; as opposed to cleavage of an alkene with potassium permanganate which occurs under significantly harsher oxidative conditions.[4] An example of an ozonolysis reaction is illustrated in Figure 5.

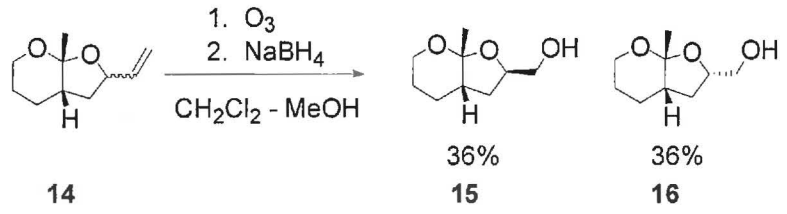

Figure 5: Ozonolysis reaction used for characterization

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[5] Laue, T.; Plagens, A. *Named Organic Reactions*. 2nd edition; John Wiley & Sons: New York; 1998. p 210-212.

In this previous reaction, **14** was obtained as a mixture of *cis*- and *trans*- isomers which could not be separated by column chromatography, however the ozonolyzed products were separable allowing characterization of the diastereomeric mixture.[6]

The ozonolysis mechanism consists of a series of two pericyclic reactions, and was first proposed by Criegee in 1945,[7] with further revisions in 1975.[8] The ozonolysis reaction occurs by means of two cycloadditions and a cycloreversion, forming two intermediate ozonides in the process, Figure 6.

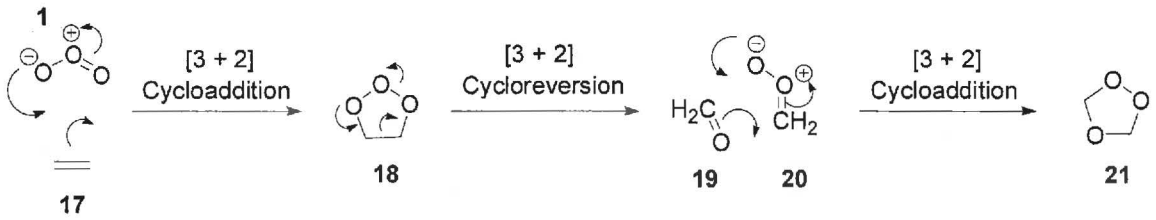

Figure 6: Criegee's mechanism of ozonolysis

The first step in the mechanism involves a [3+2] cycloaddition between ozone (**1**) and the alkene (**17**). The intermediate formed is a 1° ozonide (**18**). This then undergoes a [3+2] cycloreversion to form a carbonyl (**19**), and a carbonyl oxide (**20**). The reactive carbonyl oxide intermediate then quickly undergoes a second [3+2] cycloaddition to form a more stable 2° ozonide (**21**). As illustrated in Figure 3, the 2° ozonide produced after ozonolysis can then be used to produce a wide range of products depending on the workup. The structures of the 1° and 2° ozonides have been widely studied.[9] However, the carbonyl oxide has undergone relatively little study because of its reactivity. Figure 7

---

[6] Weaver, M.; Aponick, A. *Personal Communication.* University of Florida: NSF-REU Florida Program, 2008.
[7] Criegee, R.; Wenner, G. *Justus Liebigs Ann. Chem.* **1949**, *564*, 9-15.
[8] Criegee, R. V. *Angew. Chem.* **1975**, *87(21)*, 765-771.
[9] (a) Hoops, M. D.; Ault, B. S.; *J. Am. Chem. Soc.* **2009**, *131*, 2853-2863. (b) Taatjes, C. A.; Meloni, G.; Selby, T. M.; Trevitt, A. J.; Osborn, D. L.; Percival, C. J.; Shallcross, D. E. *J. Am. Chem. Soc.* **2008**, *130(36)*, 11883-11885.

shows the reaction energy diagram[10] is shown for the simple example ozonolysis reaction illustrated in Figure 6.

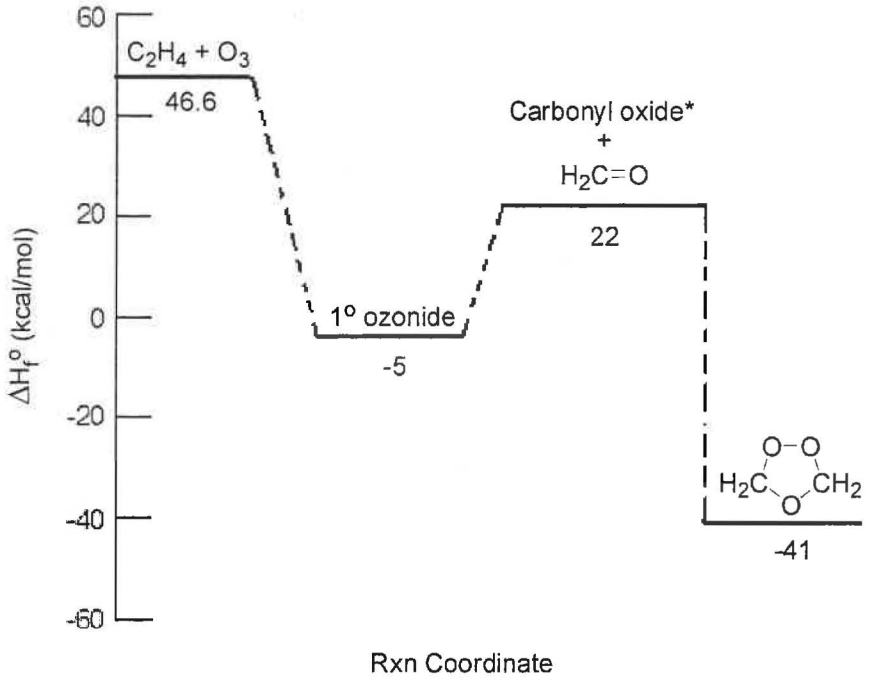

Figure 7: Energy diagram corresponding to ozonide formation[10]

The reaction between ozone and the alkene that starts through an exothermic reaction where the favored, lower-energy 1° ozonide is produced after the first cycloaddition. The second cycloreversion results in an unfavored higher energy intermediate consisting of a carbonyl and a carbonyl oxide. However a second cycloaddition then quickly occurs to produce a more stable 2° ozonide. The highly reactive carbonyl oxide is one of the most interesting components of the Criegee mechanism.

The carbonyl oxide has been proposed to exist in a few forms (**22**, **23**, **24**) or as a hybrid of all three (**25**) as shown in Figure 8.[11]

---

[10] Bailey, P. S. *Ozonation in Organic Chemistry: Olefinic Compounds*. Trahanovsky, W., Academic Press: New York, 1978; Vol. 1; p 129-130.
[11] Bunnelle, W. H. *Chem. Rev.* **1991**, *91*, 335-362.

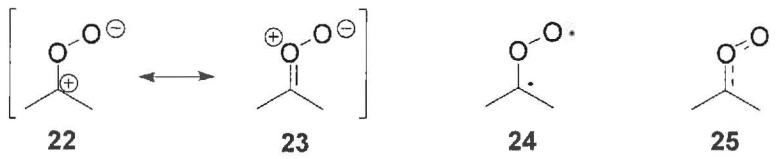

Figure 8: Carbonyl oxide resonance forms

The possible carbonyl oxide resonance forms consist of the Zwitterion – otherwise known as a 1,3-dipole (**22**), the Zwitterion resonance form (**23**), or the diradical (**24**). Although it is still not certain, calculations have been done that show the polar diradical (**24**) is more stable, and the zwitterionic forms (**22, 23**) lie at a higher energy but can be stabilized by π donors.[12] Since the carbonyl oxide is formed from the cycloreversion of 1° ozonides it can be difficult to predict which direction the 1° ozonide will undergo the cycloreversion. For symmetrical alkenes, this is not a problem, Figure **9**.[13]

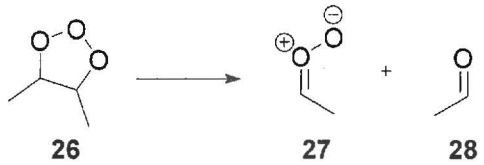

Figure 9: Reaction of symmetrical vs. unsymmetrical alkenes

Symmetrical alkene **26** undergoes cycloreversion and forms carbonyl oxide **27** and aldehyde **28** which can only recombine together one way. However, for unsymmetrical alkenes, mixtures of carbonyl oxides can result, Figure 10.[13]

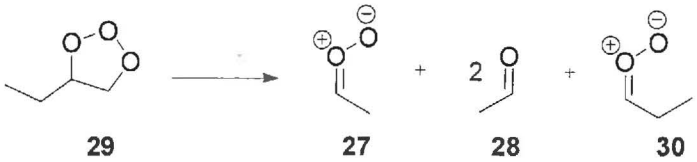

Figure 10: Reaction of symmetrical vs. unsymmetrical alkenes

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[12] Sander, W. *Angewandte Chemie Inernational Edition in English.* **2003**, *29(4)*, 344-354.
[13] Bailey, P. S.; *Ozonation in Organic Chemistry: Olefinic Compounds.* Trahanovsky, W. Academic Press: New York, 1978; Vol. 1; p 199-121.

Unsymmetrical alkene **29** undergoes cycloreversion and forms aldehyde **31** and carbonyl oxide **27**, but also carbonyl oxide **30**. The carbonyl oxides can recombine in two different ways so a unique product is not formed. Sometimes, one direction of cycloreversion is favored over another, but the outcome is difficult to predict.

1.3 Reactions Deviating from Normal Ozonolysis Conditions

Under certain reaction conditions and with certain substrates, the carbonyl oxide has been shown to deviate from the traditional ozonolysis mechanism.

1.3.1 Ozonolysis of Alkenes in the Presence of Nucleophiles

If nucleophiles are present during ozonolysis, it has been shown that the carbonyl oxide can undergo nucleophilic addition, Figure 11.[14]

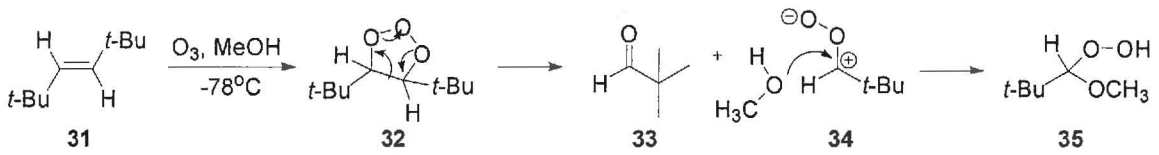

Figure 11: Nucleophilic addition to the carbonyl oxide

In this case, the symmetrical alkene (**31**) reacts with ozone to form the 1° ozonide (**32**). In the presence of methanol (CH_3OH), the methanol reacts as a nucleophile with the carbonyl oxide (**34**) and undergoes nucleophilic attack to form **35**, an α-alkoxyhydroperoxide.

1.3.2 Ozonolysis of Vinyl Ethers

Kuczkowski observed that when ethyl vinyl ether is exposed to ozone the carbonyl oxide reacts with the excess vinyl ether starting material.[15] This interesting result allows for the formation of β-hydroxyesters, which are difficult to produce using

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[14] Criegee, R. Schröder, G. *Chem. Ber.* **1960**, *23*, 689-700.
[15] Keul, H. Choi, H-S. Kuczkowski, R.L. *J. Org. Chem.* **1985**, *50*, 3365-3371.

other methods. An example of a carbonyl oxide reacting with a vinyl ether is illustrated in Figure 12.

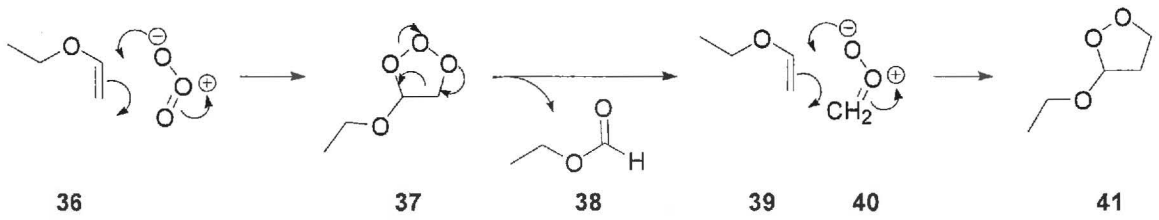


Figure 12: Reaction of ozone with vinyl ether

In Figure 12, the ethoxypropene (**36**) reacts with ozone and forms a 1° ozonide (**37**). After cycloreversion, a nonreactive dipolarophile, formate ester (**38**), and the carbonyl oxide (**40**) are formed. Since **39** is a more reactive dipolarophile it quickly undergoes cycloaddition to form the 2° ozonide product (**41**).

The reaction of the carbonyl oxide with the vinyl ether (**36**) shows that the carbonyl oxide can react with activated alkenes. But this reaction is limited because the carbonyl oxide always reacts with the dipolarophile starting material. However, if a carbonyl oxide can be produced and its lifetime increased, then ozone needn't be present during the reaction meaning that any dipolarophile could be added to generate a myriad of products.

In order to find ways to disconnect carbonyl oxides from the ozonolysis event, we investigated two approaches. The first approach involved partially disconnecting ozonolysis from the reaction. This was achieved by synthesizing a substrate that would contain an alkene that could be ozonolyzed, to give a resulting carbonyl oxide that was stabilized by a neighboring group, allowing ozone to be removed from the reaction environment. Then any dipolarophile could be added to the flask and the dipolarophile could then react with the stabilized carbonyl oxide. The removal of ozone from the

reaction environment would also allow other dipolarophiles that are oxidatively sensitive to be added to the reaction.

The second approach involves complete removal of ozone from formation of the carbonyl oxide using a tautomerization approach. If ozone can be completely removed, then there will be no chance for other dipolarophiles to be oxidized. These approaches could be applied to synthesis of many targets such as, (3*R**,5*S**,12*E*,14*E*,17*Z*)-3,5-Dimethyl-3,5-peroxydodeca-12,14,17-trienoic acid, a natural product isolated from the Philippine Sponge *Plakinastrella* sp, Figure 13.[16]

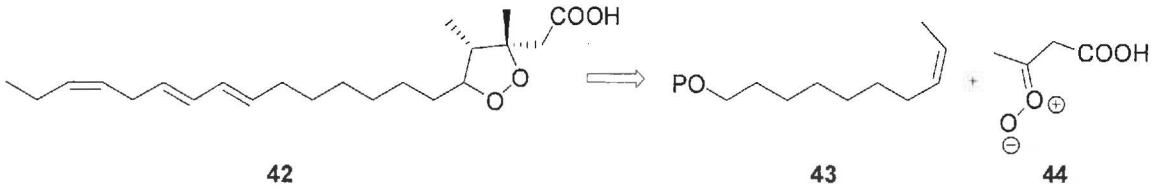


Figure 13: Possible disconnection of **42** to a carbonyl oxide intermediate

The natural product can be easily disconnected from the target (**42**) to alkene **43** and the carbonyl oxide **44**. If the carbonyl oxide **44** can be made with approach 1 or approach 2, it can react with **43**. Then to obtain product **42**, Grubb's metathesis can be used to add the remaining chain. The use of the carbonyl oxide in synthesis could significantly reduce the number of steps in synthesis of target molecules to provide quicker syntheses.

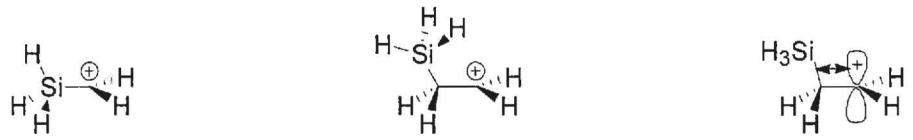
2. Approaches to Stabilize the Carbonyl Oxide

2.1.1 Stabilization Using Electron Donating Groups

Carbocations can be stabilized via inductive and hyperconjugative effects with inductive effects often dominating.[17] Wierschke et al. determined the magnitude of

[16] Qureshi, A.; Salva, J. Harper, M. K. Faulkner, D. J. *J. Nat. Prod.* **1998**, *61*, 1539-1542.

stabilization of carbocations through hyperconjugation of α-silicon or β-silicon groups, by using computational methods in the GAUSSIAN 80 program, Figure 14.[17]



45 **46** **47**

Figure 14: α- and β-Silicon stabilizing groups

Computational results showed that the β-silyl groups (**46**) stabilized the carbocation by 38.0 kcal/mol more than α-silyl groups (**45**), showing that hyperconjugation between the C-Si bond in **46** (β-silicon group) and the empty p-orbital is much greater than the hyperconjugation between the H-Si bond in **47** (α-silicon group) and the empty p-orbital. Therefore, the addition of a silyl group in an appropriate position could stabilize the carbonyl oxide long enough so as to partially disconnect the carbonyl oxide from the ozonolysis event.

2.1.2 Experimental Design, Results & Discussion

Kuzckowski et al. showed that the highly reactive carbonyl oxide produced from ozonolysis of ethyl vinyl ethers (Figure 12) did react with the remaining vinyl ether instead of the dipolarophile produced.[15] Knowing that unreactive dipolarophiles were produced our synthetic goal was to generate a vinyl ether that would produce a stabilized carbonyl oxide and an unreactive dipolarophile with an electron-donating group in the β-position that will stabilize the carbocation. After initial ozonolysis and subsequent removal of ozone any dipolarophile could be added to the stabilized carbonyl oxide. Another advantage to this method is that silicon groups are easily removed and replaced by a hydrogen.

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[17] Wierschke, S. G. Chandrasekhar, J. Jorgenson, W. L. *J. Am. Chem. Soc.* **1985**, *107*, 1496-1500.

A β-silicon group was chosen with the idea that the resulting hyperconjugation between the C-Si bond and the empty p-orbital could increase the lifetime of the highly reactive carbonyl oxide intermediate, Figure 15.

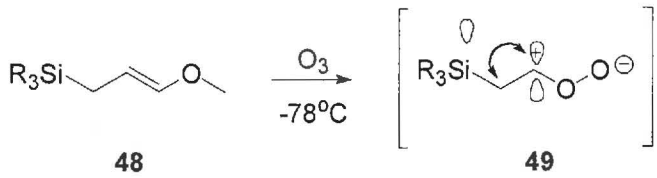


Figure 15: Stabilization of carbonyl oxide through hyperconjugation

The desired substrate, methyl silylvinyl ether (**43**) has an electron-rich β-silicon group and would generate a nonreactive formate ester upon ozonolysis. Provided the cycloreversion of the 1° ozonide cleaved in the desired direction, the β-silicon group should stabilize the δ-positive carbon atom (**49**) through hyperconjugation. We predicted that this interaction would keep the carbonyl oxide stable in the form of **49** long enough so that the vinyl ether would cleave entirely without reacting with starting material or the formate ester. After removal of ozone, another dipolarophile (such as an alkene) would be added to react with the stabilized carbonyl oxide.

The retrosynthesis of a vinyl ether similar to **48** is illustrated in Figure 16.

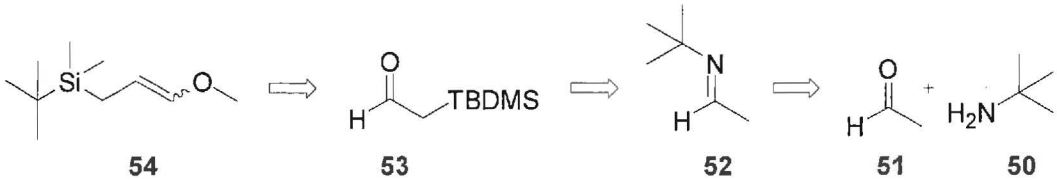


Figure 16: Retrosynthesis of methyl-silyl vinyl ether **54**

From **53** to **54** a Wittig reaction is used to generate the vinyl ether. Addition of the silyl group is achieved via deprotonation of the imine followed by hydrolysis. α-deprotonation of **52** allows addition of the silicon group.

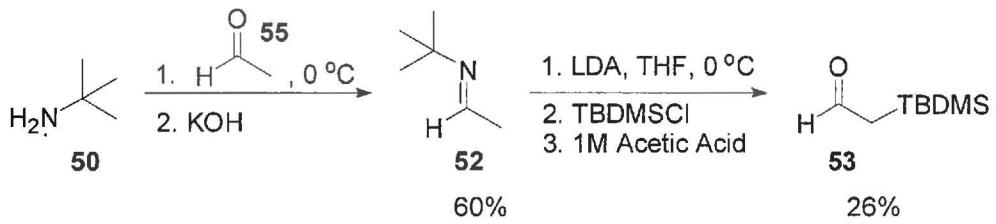


Figure 17: Synthesis of **54**

The first step in the synthesis of **54** is the formation of imine **52**, which is formed by addition of acetaldehyde (**55**) to *t*-butylamine (**50**), then subsequent addition of KOH at 0 °C. This reaction is left in the freezer overnight and gave the imine **52** in 60% yield after distillation. Subsequent deprotonation of the imine **52** with LDA, followed by addition of TBDMSCl and hydrolysis with acetic acid generated aldehyde **53**, in a low yield of 26% due to purification issues. Originally, a trimethylsilane (TMS) group was added to **52** as the stabilizing electron rich group, but the product was volatile and difficult to work with, so the TBDMS group was used instead.

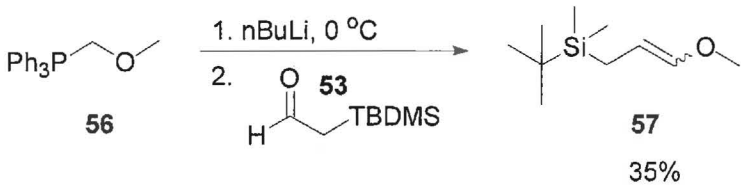


Figure 18: Synthesis of **57**

Finally, the transformation from **53** to **57** was done via a Wittig reaction involving the phosphorous ylide of **56** with nBuLi to give the vinyl ether **57** in a 35% yield.

Once **57** was prepared, some initial experiments were carried out in $CDCl_3$. Ozonolysis of **57** at –78°C to see if a stabilized carbonyl oxide could be generated. However, NMR analysis of the crude reaction indicated that the 1° ozonide underwent cycloreversion in both directions, Figure 19.

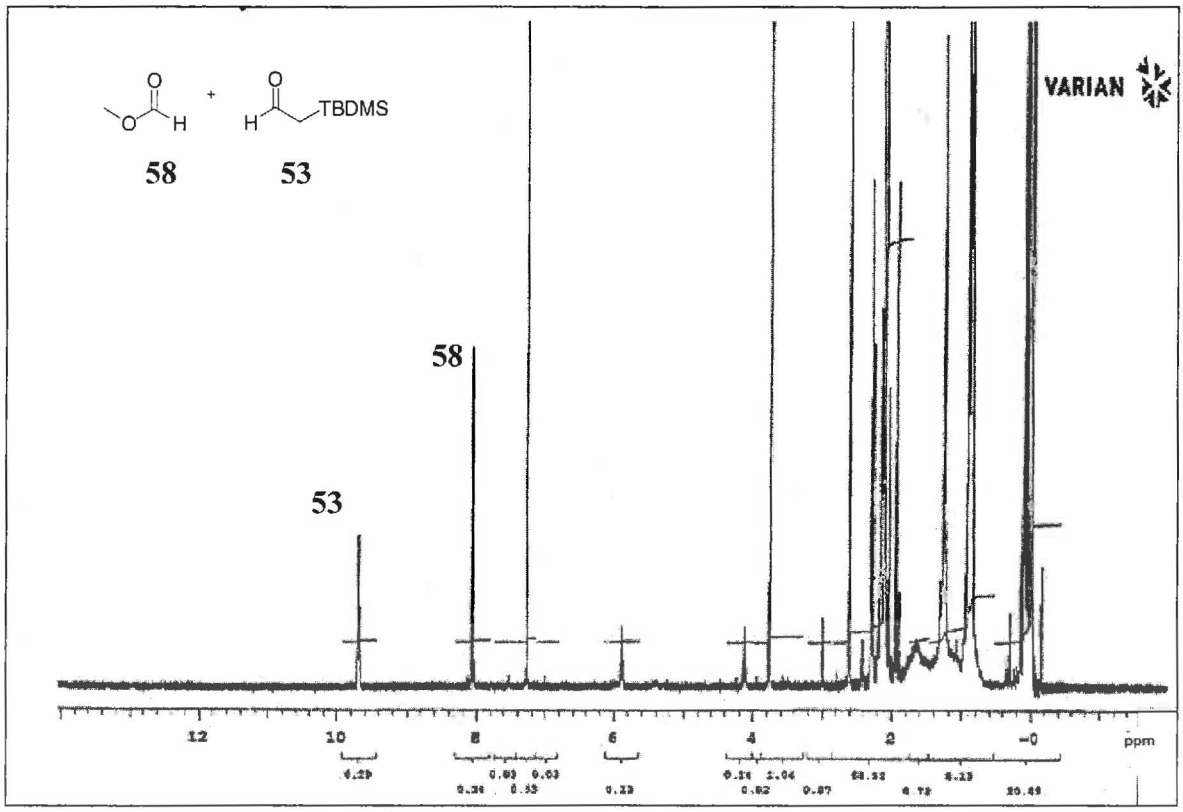


Figure 19: Crude NMR of ozonolysis of **54** in $CDCl_3$

As shown by the ^{1}H NMR spectrum, ozonolysis of **54** gave two identifiable products: methyl formate ester (**58**) and the aldehyde (**53**). The ozonolysis produced the desired unreactive formate ester, but there were no identifiable products of the carbonyl oxide reacting with dipolarophiles in the reaction. Unfortunately, the β-stabilization did not occur as expected. The cycloreversion of the 1° ozonide needed to be in the clockwise direction, but the ^{1}H NMR indicates that the cycloreversion occurred in both directions, Figure 20.

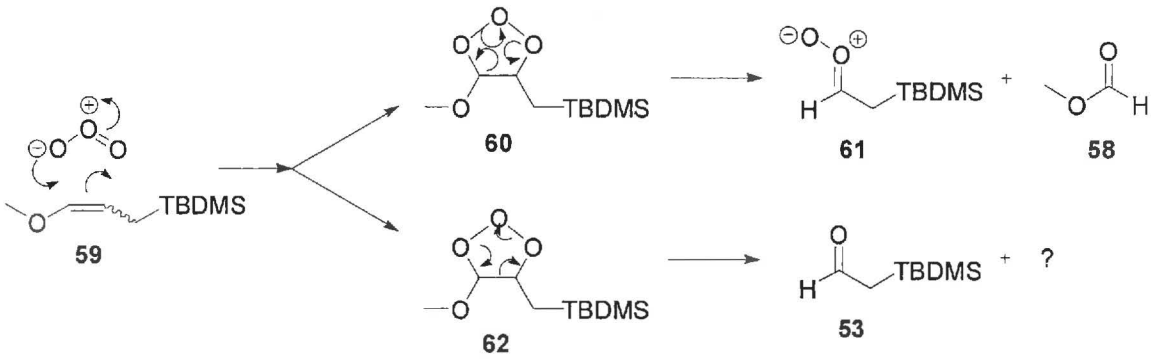


Figure 20: Predicted mechanisms of cycloreversion

Clearly the silicon changed the electronics of the 1° ozonide leading to competing pathways for cycloreversion. Since this first approach led to unclear results, a second approach that would disconnect ozone entirely from the reaction environment was investigated.

2.2.1 Synthesis of Carbonyl Oxides in the Absence of Ozone

Keto-enol tautomerization is a well-studied reaction, Figure 21.

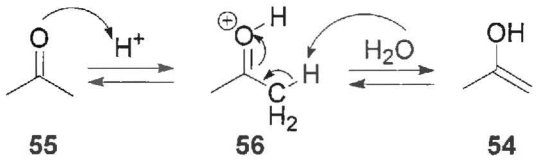


Figure 21: Keto-enol tautomerization mechanism

Although the ketone (**63**) is thermodynamically favored in most cases, there are cases where the enol (**65**) is favored; particularly when the α-hydrogen is unusually acidic. Protected enols can be generated via the addition of silyl protecting groups such as TMS or TBDMS, Figure 22.

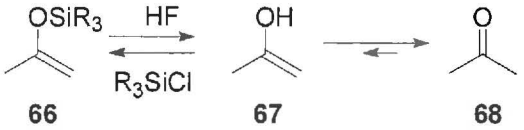


Figure 22: Derivatized enol (**66**) locked from tautomerization

Although **57** is locked in the derivatized enol, addition of HF gives **58** and can readily tautomerize to **59**. Since a vinyl peroxide resembles **58**, it is possible that tautomerization of the vinyl peroxide can be used to produce a carbonyl oxide.

2.2.2 Experimental Design, Results & Discussion

Since it is possible for enols to tautomerize to ketones, it seemed likely to us that a vinyl peroxide (**69**) could tautomerize and form carbonyl oxide (**71**).

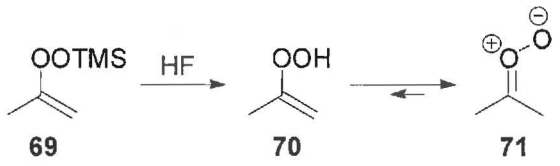


Figure 23: Tautomerization of a protected vinyl peroxide

If deprotection occurs and peroxy-enol tautomerization takes place in the presence of a dipolarophile, then the dipolarophile should react with the carbonyl oxide that is formed. With this approach, ozone is never present thereby eliminating the possibility of cleaving or oxidizing the dipolarophile.

2.2.2.i Substrates with Allyl Groups

Our initial approach to disconnect ozone from ozonolysis involved using allyl substrates to generate vinyl ethers, Figure 23.

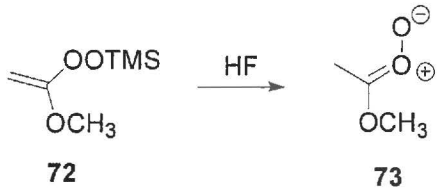


Figure 24: Tautomerization to carbonyl oxide in the absence of ozone

Retrosynthetic analysis shows that ozonolysis of **74** in the presence of methanol, would give would give a vinyl peroxide. Protection with TMS (**75**) and elimination of the bromine could form the vinyl peroxide (**76**), Figure 25.

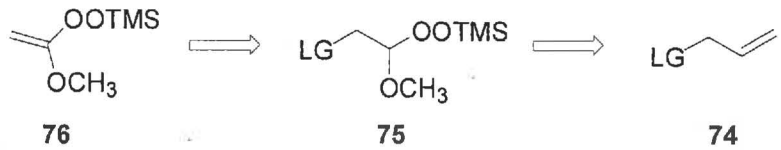


Figure 25: Preparation of a vinyl peroxy-enol (**76**)

The synthesis was carried out as shown in Figure 26.

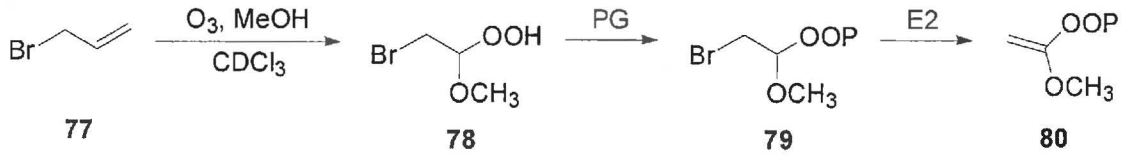


Figure 26: Synthesis of **76** using allyl bromide

Allyl bromide (**77**) was ozonolyzed in the presence of methanol to generate the methoxy-peroxide product (**78**), but it was difficult to see by NMR if the ozonolysis gave the desired product. So, instead of allyl bromide, allyl alcohol was used as a precursor where the –OH was transformed into an –OTs leaving group before ozonolysis, Figure 27.

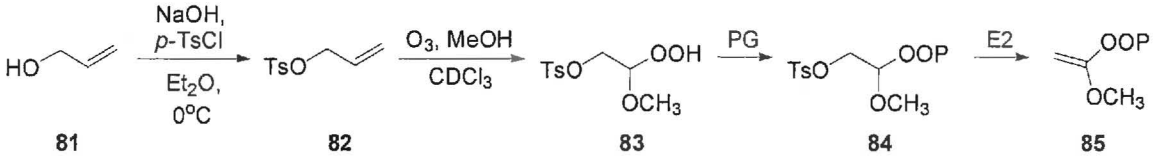


Figure 27: Synthesis of **85** using allyl alcohol (**81**)

Ozonolysis of allyl alcohol (**81**) was successful, however, it was unclear if the protection step was successful using this precursor. A variety of protecting groups were tried, but the NMR results for each reaction were unclear. There is a possibility that the $-OCH_3$ group might have been complicating the elimination step, so the focus was changed to cyclic substrates to generate peroxidic products from symmetrical cycloalkenes.[18]

[18] Terentev, A. O. Krylov, I. B. Borisov, D. A. Nikishin, G. I. *Synthesis*. **2007**, *19*, 2979-2986.

2.2.2.ii Substrates Using Cyclohexene Precursors

Similarly to the allyl precursors, our third approach was to use cyclic peroxidic precursors to generate carbonyl oxides in the absence of ozone. Carbonyl oxide **87** could be made similarly to the way described in previous work to react with dipolarophiles disconnected from the ozonolysis event, Figure 28.

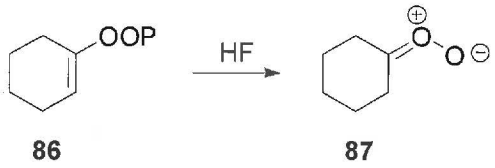


Figure 28: Carbonyl oxide production in the absence of ozone

Halogenated vinyl peroxides like **87** are known and can be obtained by addition of hydrogen peroxides and a halogen across a double bond, analogous to halohydrin formation (**88**). Our plan was to prepare **86** by elimination of **87** which was obtained from cyclohexene (**88**), Figure 29.

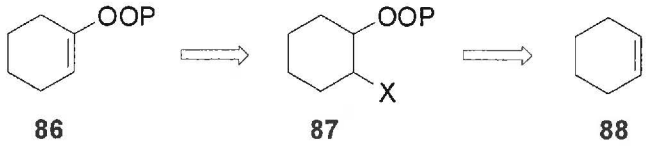


Figure 29: Retrosynthesis of **86** from cyclohexene (**88**)

Initial work to prepare **87** was done using iodine, but the iodine compound quickly decomposed to the 2-iodocyclohexanol product during purification. When bromine was used instead of iodine, the product was obtained after purification as seen by the α-H peak of the –COOH in the ^{1}H NMR. The synthesis is shown in Figure 30.

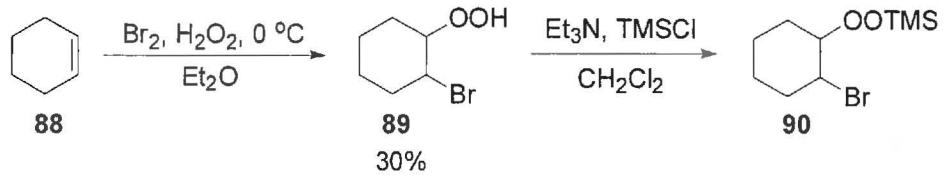


Figure 30: Synthesis of **87**

At this point, **89** has been synthesized, despite lower yields. It seems as though the protection to form **90** works best with Et_3N and TMSCl. So far, the difficulty with the synthesis of **90** lies with the ability to separate the similar isomers of **89**.

In order for the E2 elimination to occur, the bromine atom needs to be axial to the hydrogen with the OOTMS group on it (**90**), Figure 30. If the E2 elimination can occur, then the protected vinyl peroxide (**92**) can be produced, Figure 31.

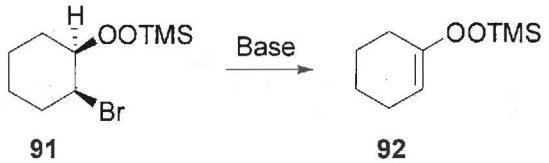


Figure 31: E2 to prepare **92**

Once **92** is produced, HF can be added and the possibility for the tautomerization is apparent and **92** can be used as a carbonyl oxide to react with other dipolarophiles.

3. Conclusion

In efforts to produce carbonyl oxides removed from ozone, our first approach using the hyperconjugation effect with the silicon group did not work as expected. The reason is unknown, but the electronics of the silicon probably influenced the reaction greatly. The two competing cycloreversion pathways led to the formation of the formate ester, but also regenerated the aldehyde precursor. Despite the formation of these two dipolarophiles, reaction between the dipolarophiles and the formed carbonyl oxides was not seen. With this unclear spectrum, another approach was investigated.

Our second approach involving the cyclohexene precursor (**92**) is promising, Figure 30. Since separation of the isomers of **90** has been difficult, using the cyclic peroxide, another synthetic approach that will not depend on the formation of a correct isomer will be investigated in future work.

If the carbonyl oxide can be disconnected from ozone in some capacity, a wide variety of products can be imagined, Figure 32.

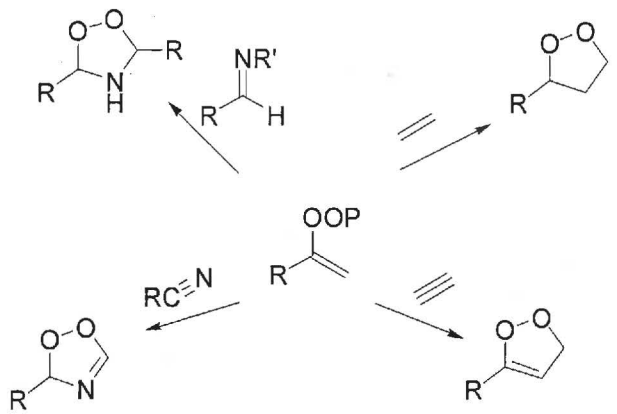


Figure 32: Carbonyl oxide tautomerization used to react with dipolarophiles

The carbonyl oxide could react with alkenes, alkynes, nitriles and imines. This diverse reaction scope can give rise to many of the functional groups found in synthetic targets.

4. Future Work

Currently, the halohydroperoxide (**89**) has been produced, but further purification is needed. Using our current approach to obtain the cyclic product (#), addition of the protecting group needs to be further refined and a base needs to be found to do the elimination reaction. After elimination, the tautomerization reaction can be tried to see if generation of a carbonyl oxide in the absence of ozone is possible.

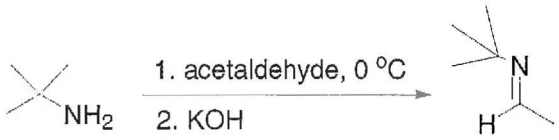
Another approach to obtain (**87**) would not require the specific anti-periplanar isomer. Instead, addition of silver oxide would remove the bromine. Subsequent

addition of an MH would remove the H from peroxide group and potentially allow the tautomerization to occur. This method is not yet fully developed, but is a potential way to produce the carbonyl oxide in the absence of ozone.

5. Experimental

All reactions were carried out in oven-dried glassware. Reactions were carried out in air, unless otherwise noted. Dichloromethane, hexanes, ethyl acetate and ethanol solvents were all used as received without further purification. THF was distilled from calcium hydride in the presence of benzophenone under nitrogen. Triethylamine and trimethylsilane were all distilled under nitrogen to purify the reagents. Flash column chromatography was performed using (size of particles) silicon dioxide. NMR spectra were recorded using a Varian-400MHz instrument and the NMR's were referenced to TMS.

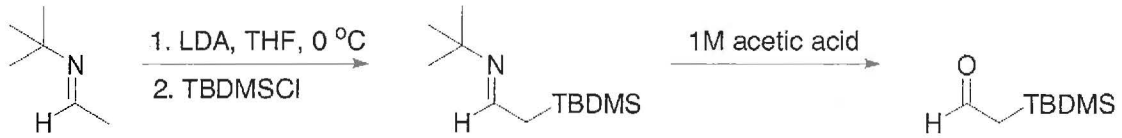
Preparation of *t*-butyl-ethylideneamine: [19]



To an oven-dried 250 mL RBF equipped with a stir bar was charged 38 mL (0.362 mmol, 1 eq.) of t-butyl amine. The flask was cooled to 0 °C. Then, over 1h 20.3 mL (0.362, 1 eq.) of acetaldehyde was added dropwise to reaction mixture at 0 °C with further stirring for 1h. 812 mg (0.0145 mmol, 0.04 eq.) KOH was added to reaction and the reaction was left in the freezer for 48h. The product was distilled under N_2 and the product was collected over the range 66 – 69 °C. ^{1}H NMR(400 MHz, $CDCl_3$, δ): 7.686 (q, J = 4.82 Hz, -C*H*, 1H), 1.956 (d, J = 4.84 Hz, -CH_3, 3H), 1.171 (s, -C(CH_3)$_3$, 9H).

[19] Campbell, K. N.; Sommers, A. H.; Campbell, B. K. *J. Am. Chem. Soc.* **1944**, *66(1)*, 82-84.

Preparation of *t*-butyldimethylsilanyl acetaldehyde:

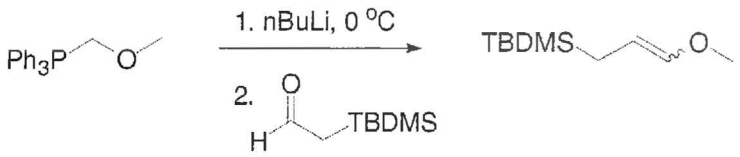


LDA was prepared by adding 8.86 mL (55.4 mmol, # eq.) freshly distilled diisopropylamine to an RBF charged with 60 mL THF and equipped with a stir bar. It was then cooled to –78 °C and 34.6 mL (55.4 mmol, 2 eq.) n-BuLi was added to the reaction over 20 minutes. After addition, the flask was warmed to RT and the solution was a dark yellow color.

The LDA solution was added dropwise to a RBF at –78 °C charged with 5g of the imine (50.4 mmol, 1eq.) and 20 mL THF. The solution was then stirred for 20 minutes at –78°C and 7.05 mL TMSCl (55.4 mmol, # eq.) in 20 mL THF was added at 0 °C. Then, this solution was warmed to RT. Following, 20 mL 1M acetic acid (100 mL, 2eq) was added to the solution and stirred for 48h.

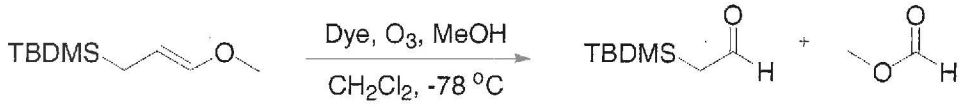
The organic layer was extracted with 3 x 50 mL dichloromethane. The organic layer was then washed with 20 mL water and 30 mL saturated sodium bicarbonate. The organic layer was dried over $MgSO_4$, concentrated and purified by column chromatography (SiO_2, pre-column with hexanes, then gradient column to 20:1 Hex:EtOAc). ^{1}H NMR(400 MHz, $CDCl_3$, δ): 9.70 (t, J = 4.4 Hz, -*H*C=O, 1H), 2.27 (d, J = 4.45 Hz, -CH_2, 2H), 0.924 (s, -C(CH_3)$_3$, 9H). ^{13}C NMR(100 MHz, $CDCl_3$, δ): 206.35 (H*C*=O), 41.97 (*C*H_2), 22.34 (*C*(CH_3)$_3$), 5.44 (C(*C*H_3)$_3$).

Preparation of *t*-Butyl-(3-methoxyallyl)-dimethylsilane:



An oven dried 50 mL RBF was charged with 418.23 mg methoxy-methyl triphenylphospine (1.22 mmol, 1 eq.) and 15 mL THF was cooled to 0 °C. The flask was pumped and purged with nitrogen. Then n-BuLi (0.67 mL, 1.34 mmol) was added dropwise over 30m. After addition, the reaction was warmed to RT then cooled back to 0 °C. Then, 193 mg *t*-butyldimethylsilanyl acetaldehyde (1.22 mmol, 1 eq.) in 5 mL THF was added to the reaction flask and the color changed from colorless to a light yellow orange. The solution warmed to RT, diluted with 15 mL Et_2O and quenched with 15 mL water. The organic layer was washed with 10 mL water. Then, the aqueous layer was extracted with 2 x 15 mL ether, and the combined organics were washed again with 10 mL water, dried over $MgSO_4$, filtered and concentrated. The product was purified by column chromotagraphy (SiO_2, 40:1 Hex:EtOAc). [cis-] ^{1}H NMR(400 MHz, $CDCl_3$, δ): 5.83 (d, J = 6.3 Hz, OC=C*H*, 1H), 4.35 (td, J = 8.3, 6.5 Hz, -CH_2C*H*, 1H), 3.549 (s, 3H), 1.448 (s, -CH_2, 2H), 0.946 (s, -C(CH_3)$_3$), 9H), 0.062 (s, Si(CH_3)$_2$). ^{13}C(100 MHz, $CDCl_3$, δ): 109.821 (OCH_3), 37.402, 29.178 (CH), 33.061 (CH_2), 20.598 (*C*(CH_3)$_3$), 6.475 (C(*C*H_3)$_3$). [trans-] ^{1}H NMR(400 MHz, $CDCl_3$, δ): 6.15 (d, J = 12.3 Hz, OC=C*H*, 1H), 4.73 (td, J = 8.3, 12.4 Hz, -CH_2C*H*, 1H), 3.486 (s, -CH_2, 2H), 2.169 (s, -OCH_3, 3H), 0.880 (s, -C(CH_3)$_3$, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 106.462 (OCH_3), 62.808, 20.754 (CH), 33.423 (CH_2), 18.734 (*C*(CH_3)$_3$), 6.628 (C(*C*H_3)$_3$).

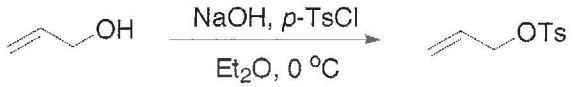
Preparation of 2-(*t*-Butyl-dimethylsilanyl)-1-methoxyeth-1-yl hydroperoxide:



To a 25 mL RBF, *t*-Butyl-(3-methoxy-allyl)-dimethyl-silane (17.4 mg, 0.093 mmol, 1eq.), MeOH (0.02 mL, 0.467 mmol, 5eq.) and a minimal amount of Sudan Red 78 dye were added. The solution was cooled to –78 °C. Ozone was bubbled through the

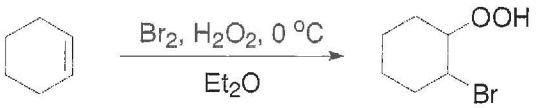
solution for 3 seconds, warmed to RT and concentrated. ^{1}H NMR(400 MHz, $CDCl_3$, δ): aldehyde 9.70 (t, J = 4.4 Hz, -*H*C=O, 1H), ester 8.2 (s, -OCH_3).

Preparation of toluene-4-sulfonic acid allyl ester: [20]



A 250 mL RBF was charged with allyl alcohol (1g, 17.2 mmol, 1 eq.), and 25 mL ether, then cooled to 0 °C. Then, 2.48 g NaOH (64.5 mmol, 3.75 eq.) in ether was added to the reaction. The reaction was stirred for 1 hour at 0 °C, then quenched with an ice-water mixture (20 mL). The organic layer was separated and washed with 2 x 25 mL portions of ice water, dried over $MgSO_4$, filtered, and concentrated. The product was purified using column chromatography (SiO_2, gradient to 10:1 Hex:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.80 (d, J = 7.8 Hz, -Ar H, 2H), 7.35 (d, J = 8.0 Hz, -Ar H, 2H), 5.82 (ddt, J = 16.7, 10.4, 6.3 Hz, 1H), 5.30 (d, J = 30.7 Hz, =C*H*, 1H), 5.27 (d, J = 23.6 Hz, =C*H*, 1H), 4.54 (d, J = 5.3 Hz, -CH_2, 2H), 2.451 (s, Ar CH_3, 3H). ^{13}C(100 MHz, $CDCl_3$, δ): 130.270 (OCH), 129.846, 127.945 (Ar H), 124.479 (Ar C), 70.762 (CH_2), 21.655 (CH_3).

Preparation of 2-Bromo-cyclohexyl hydroperoxide: [18]



An oven dried 250 mL RBF was charged with cyclohexene (2.46 mL, 24.29 mmol), and an ethereal solution of hydrogen peroxide (50 mLof H_2O_2 extracted with 3x25 mL portions of ether), then cooled to 0 °C. Following, Br_2 (1.245 mL, 24.29 mmol) was added in 50 mL of ether using a dropping funnel over a period of 10 minutes. The

[20] MacDowell, D. W. H.; Purpura, J. M. *J. Org. Chem.* **1986**, *51*, 183-188.

reaction was stirred at 0 °C for 2 hours, then evaporated in vaccuo. The product was purified by column chromotography (SiO_2, gradient to 4:1 Hex:CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.889 (s, -C*H*OOH, 1H), 5.026, 4.757, 4.53 (t, J = 3.5 Hz), 4.5 (t, J = 3.2 Hz), 4.210 (m), 3.986 (m), 1.10 – 2.47 (m, 8H).

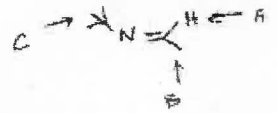
6. Appendix

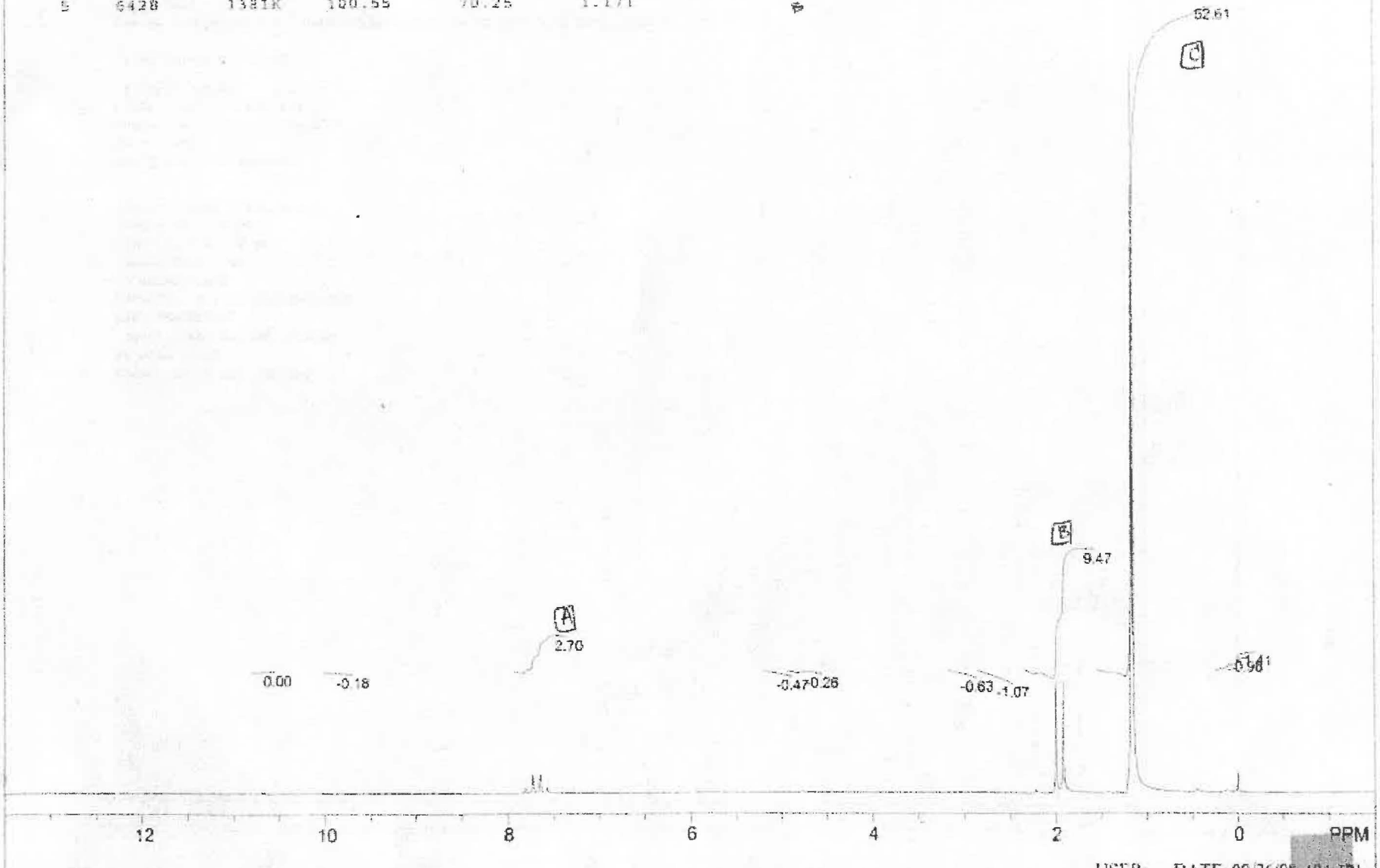
6.1 NMR Spectra

Interpolated Peak Listing

PEAK	INT	HEIGHT	REL. HT	HZ	PPM
1	3206	45046	3.28	463.61	7.726
2	3245	46655	3.41	458.79	7.645
3	8022	198186	14.43	119.77	1.996
4	8062	205512	15.00	114.93	1.915
5	6428	1381K	100.55	70.25	1.171

MGW-01-06





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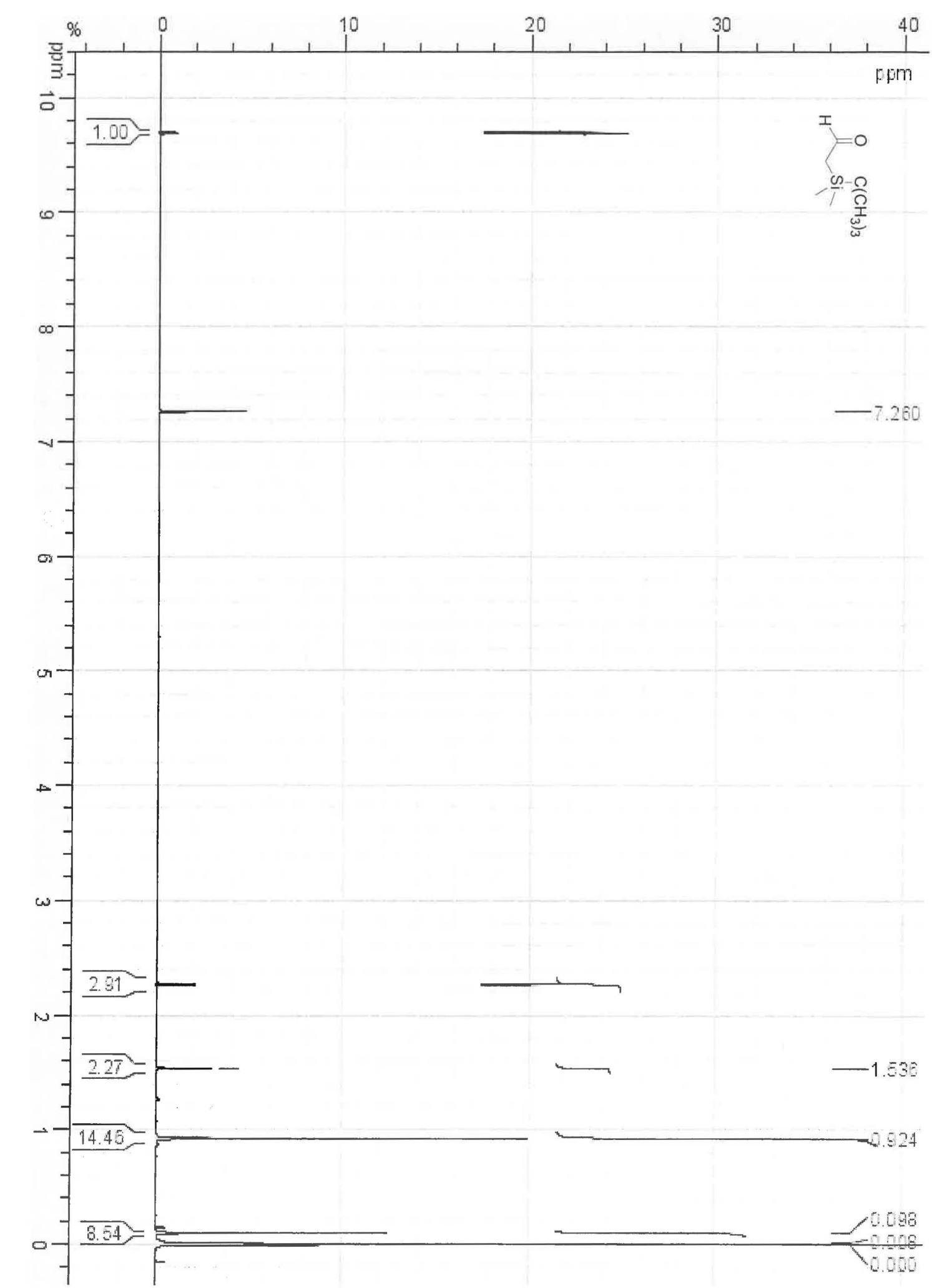
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2.27
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C(CH3)3
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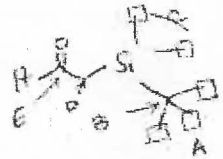
MGW-01-14 (#9-14)



VARIAN

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Automation directory: /home/walkup3/vnmrsys/studies/expl/auto_2009.01.23

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 26.0 C / 299.1 K
Sample #1, Operator: walkup3
File: 0106
VNMRS-400 "Varian-NMR"

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Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24309.8 Hz
256 repetitions
OBSERVE C13, 100.5422038 MHz
DECOUPLE H1, 399.8536141 MHz
Power 39 dB
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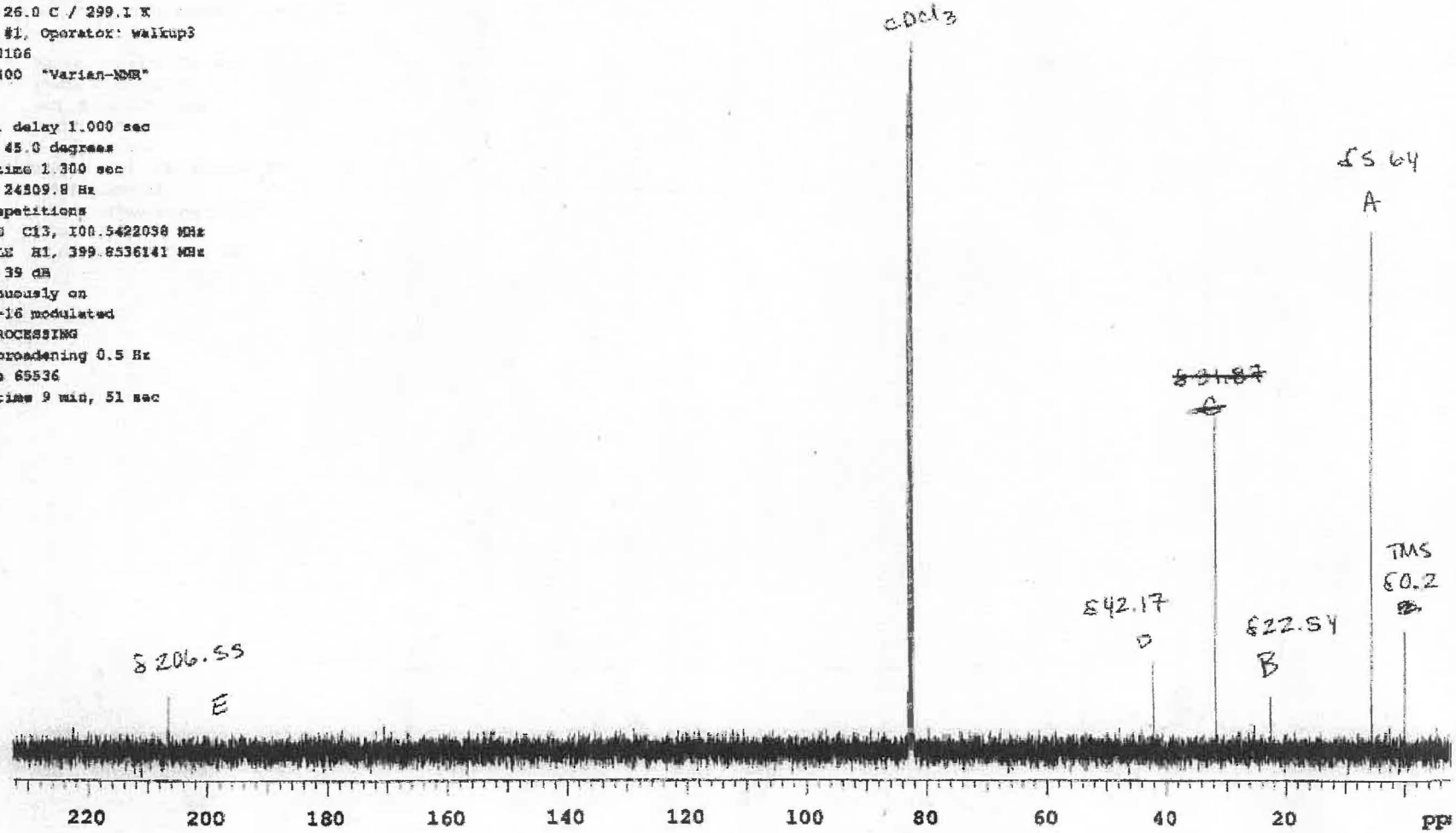

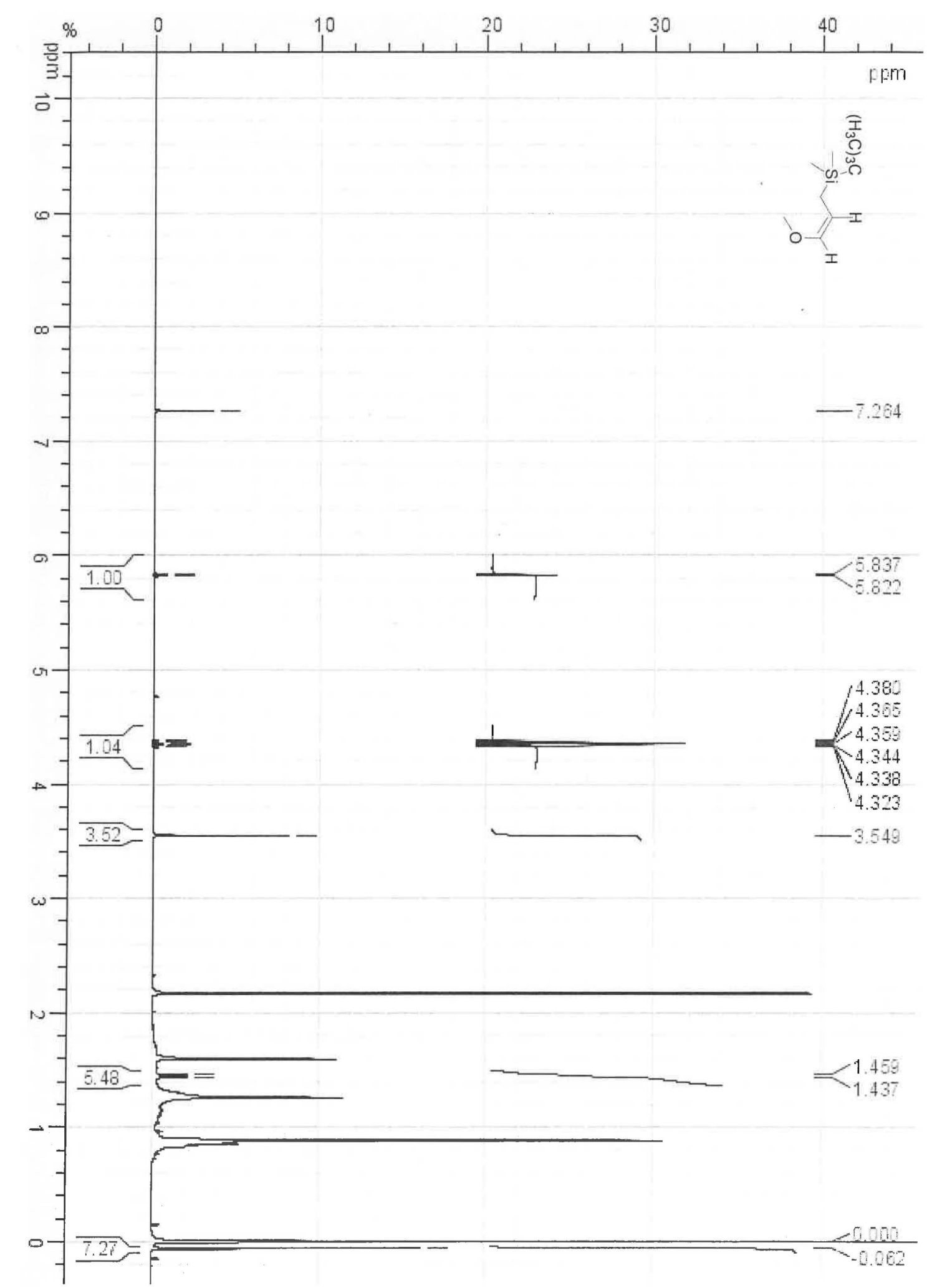
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4.359
4.344
4.338
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3.52
3.549
5.48
1.459
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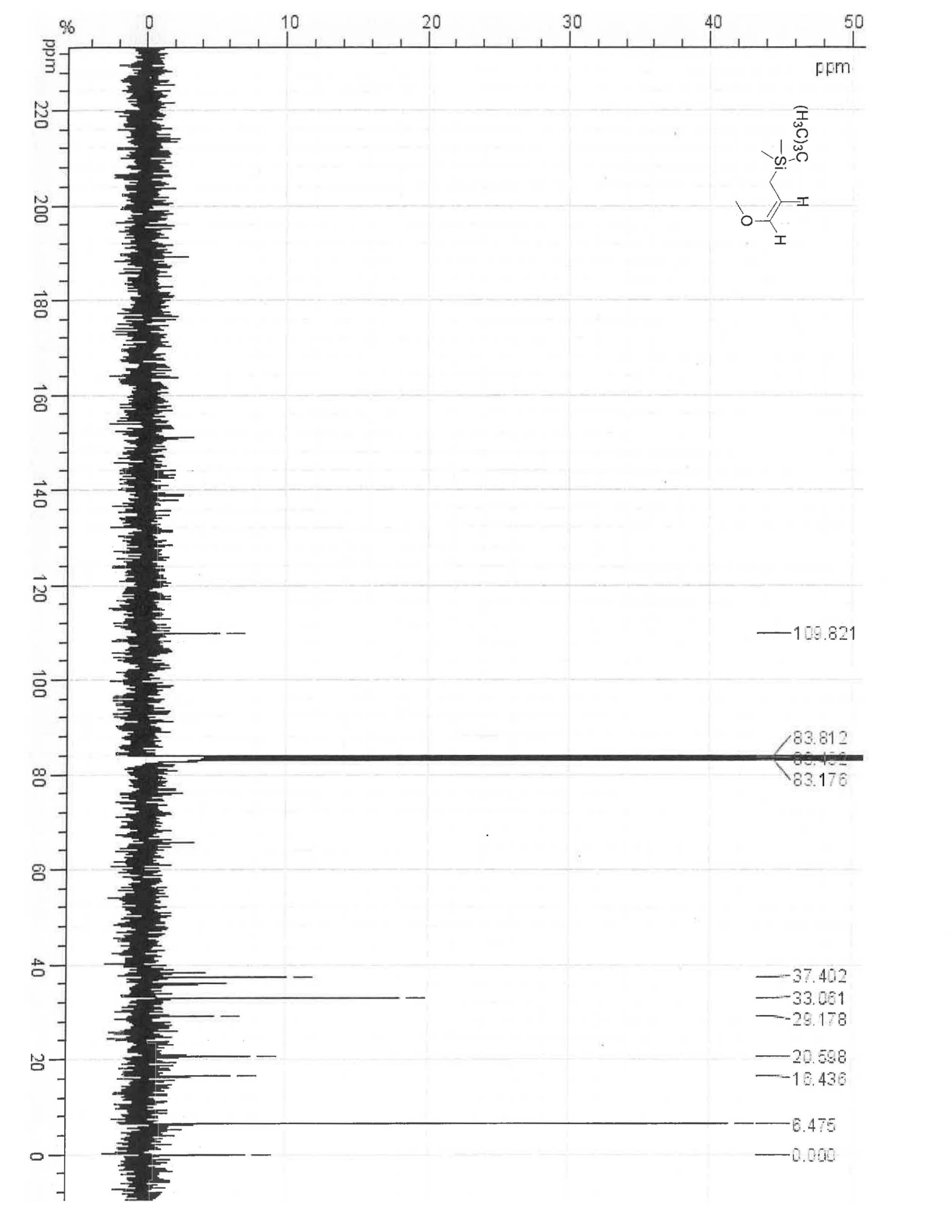
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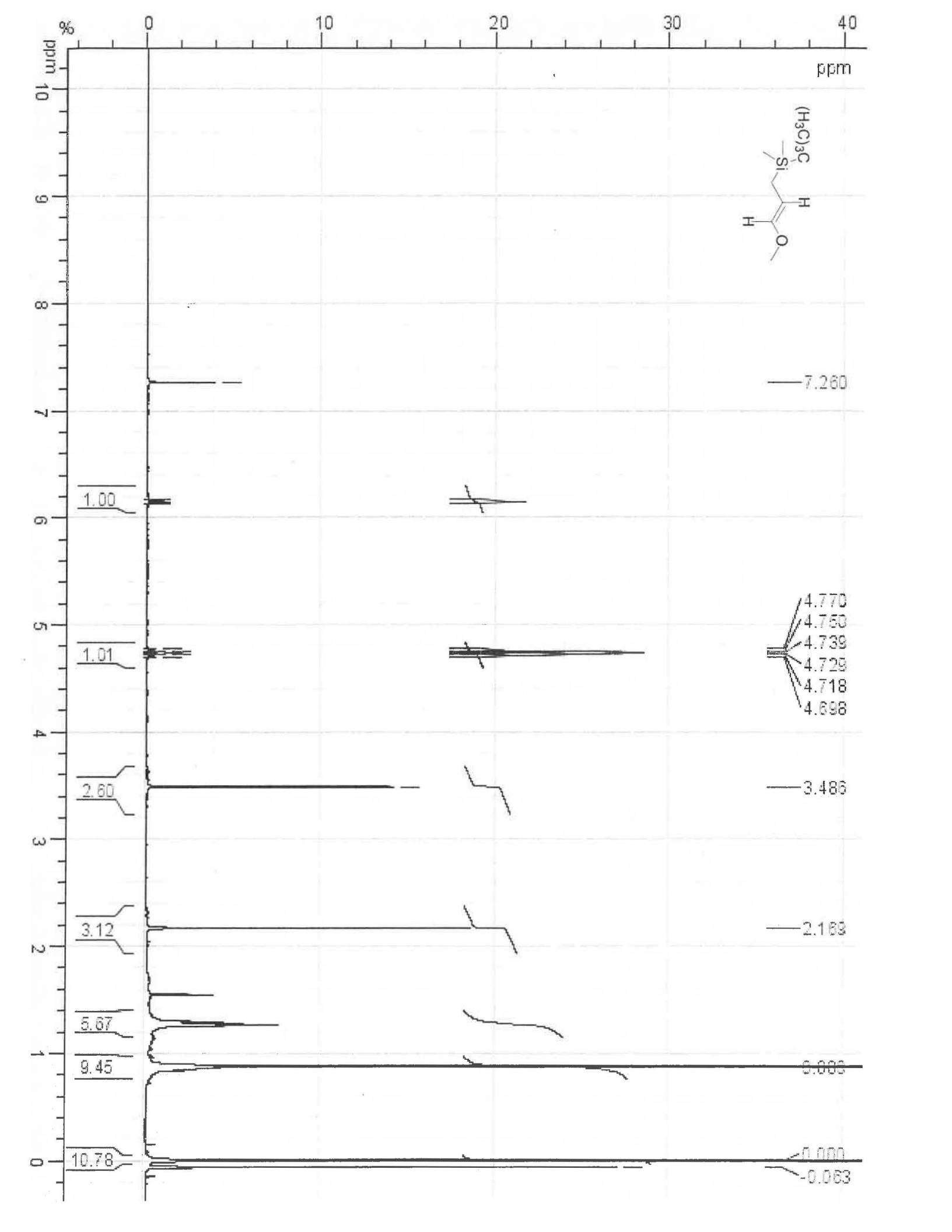
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H
H
O
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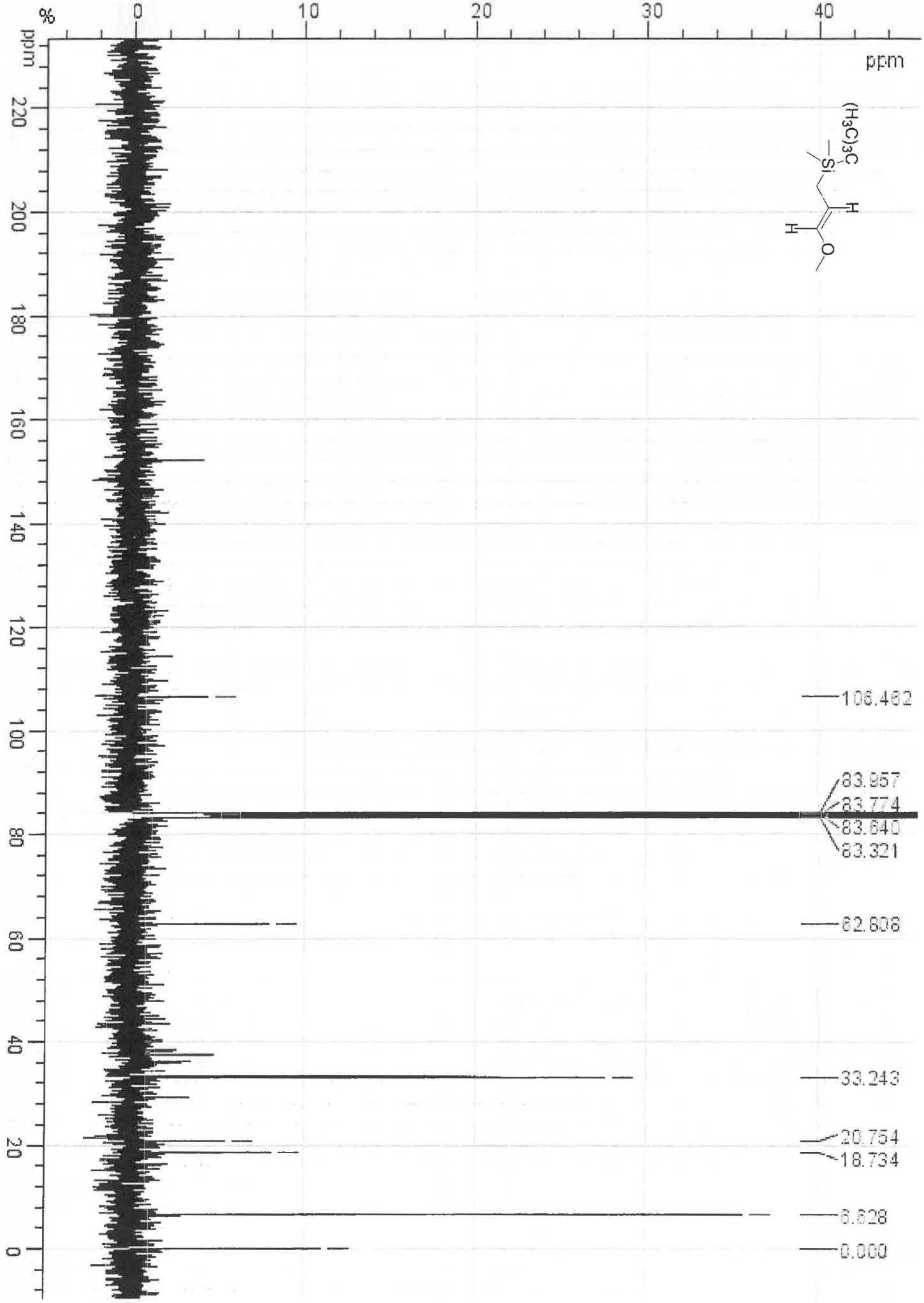
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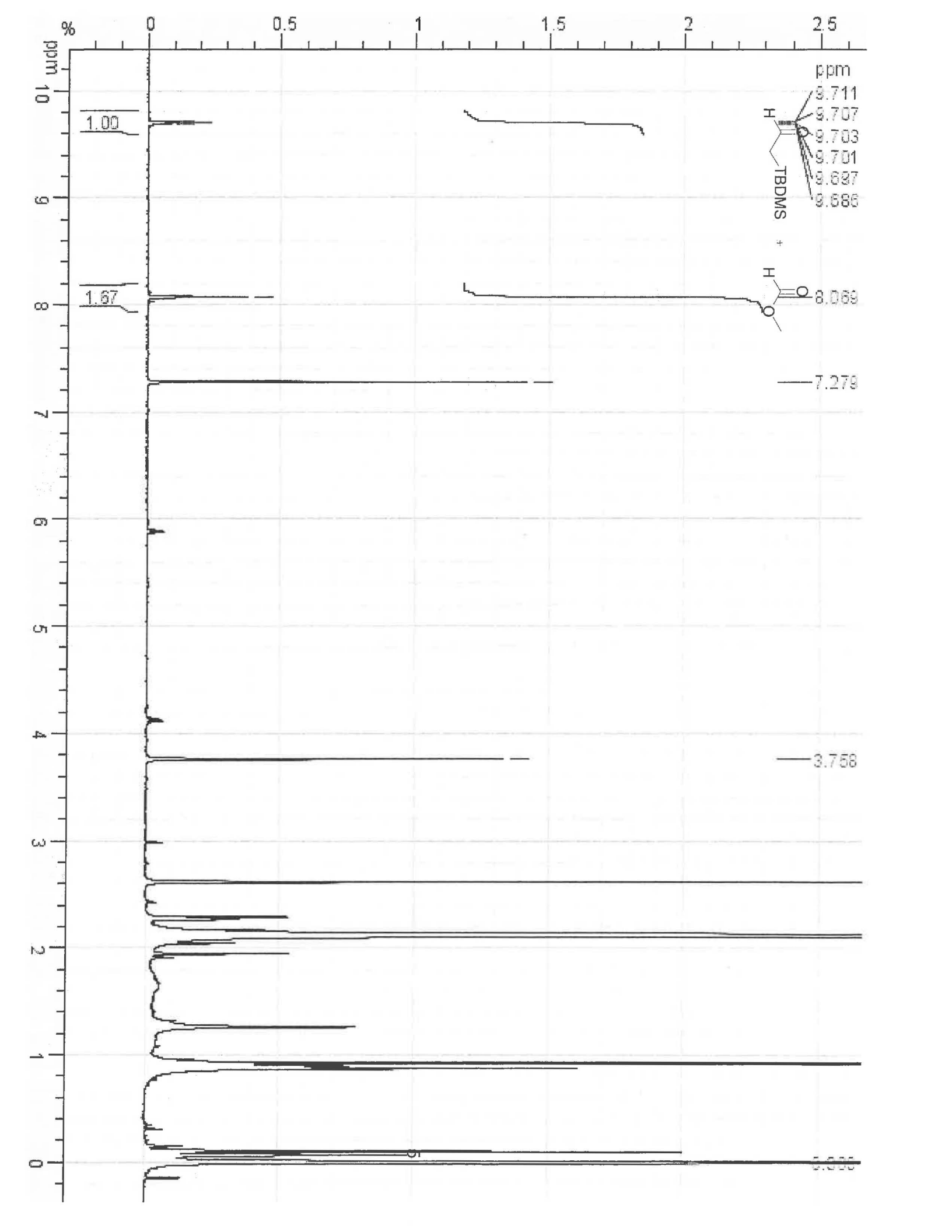
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1.67
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H
TBDMS
+
H
O
O
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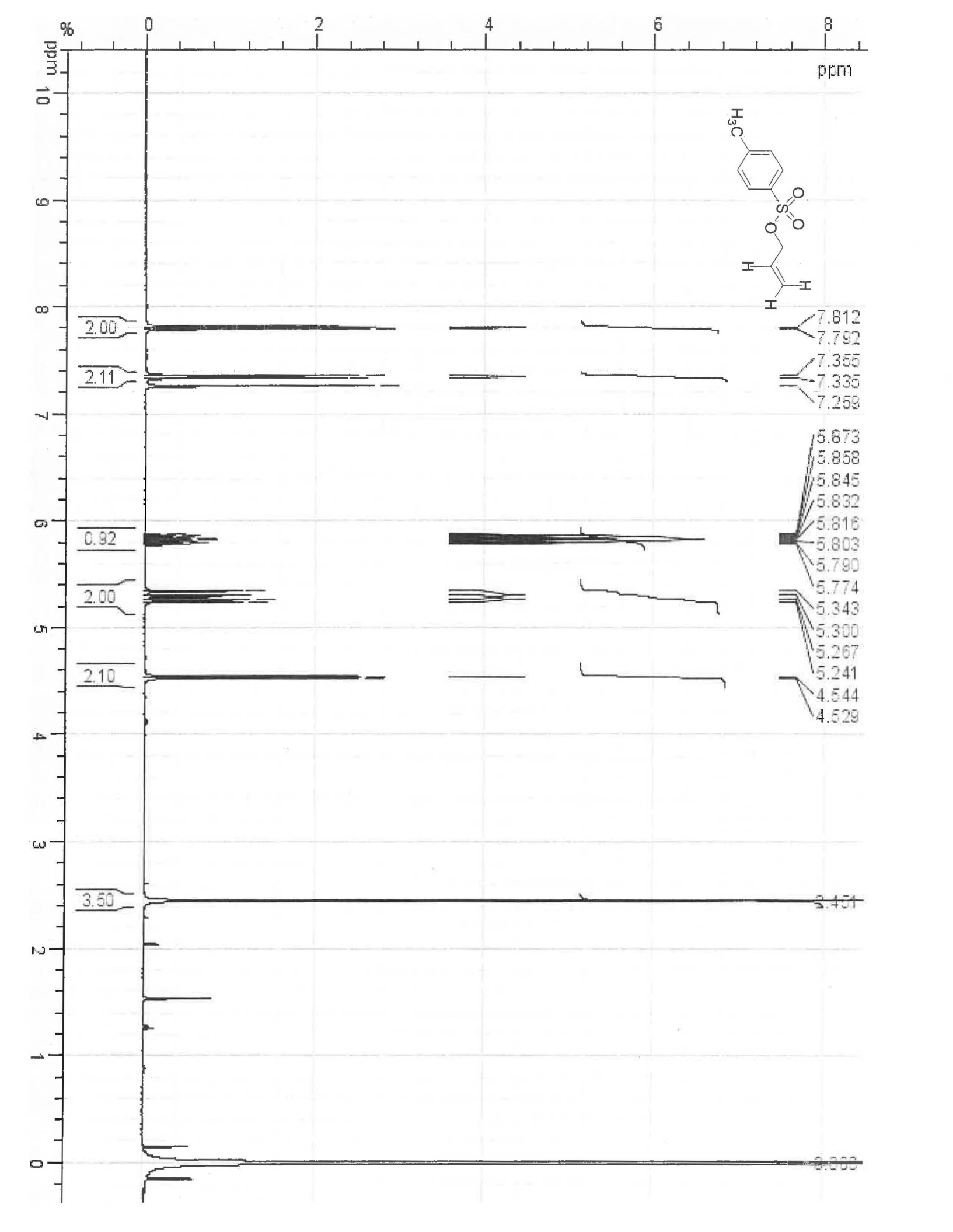
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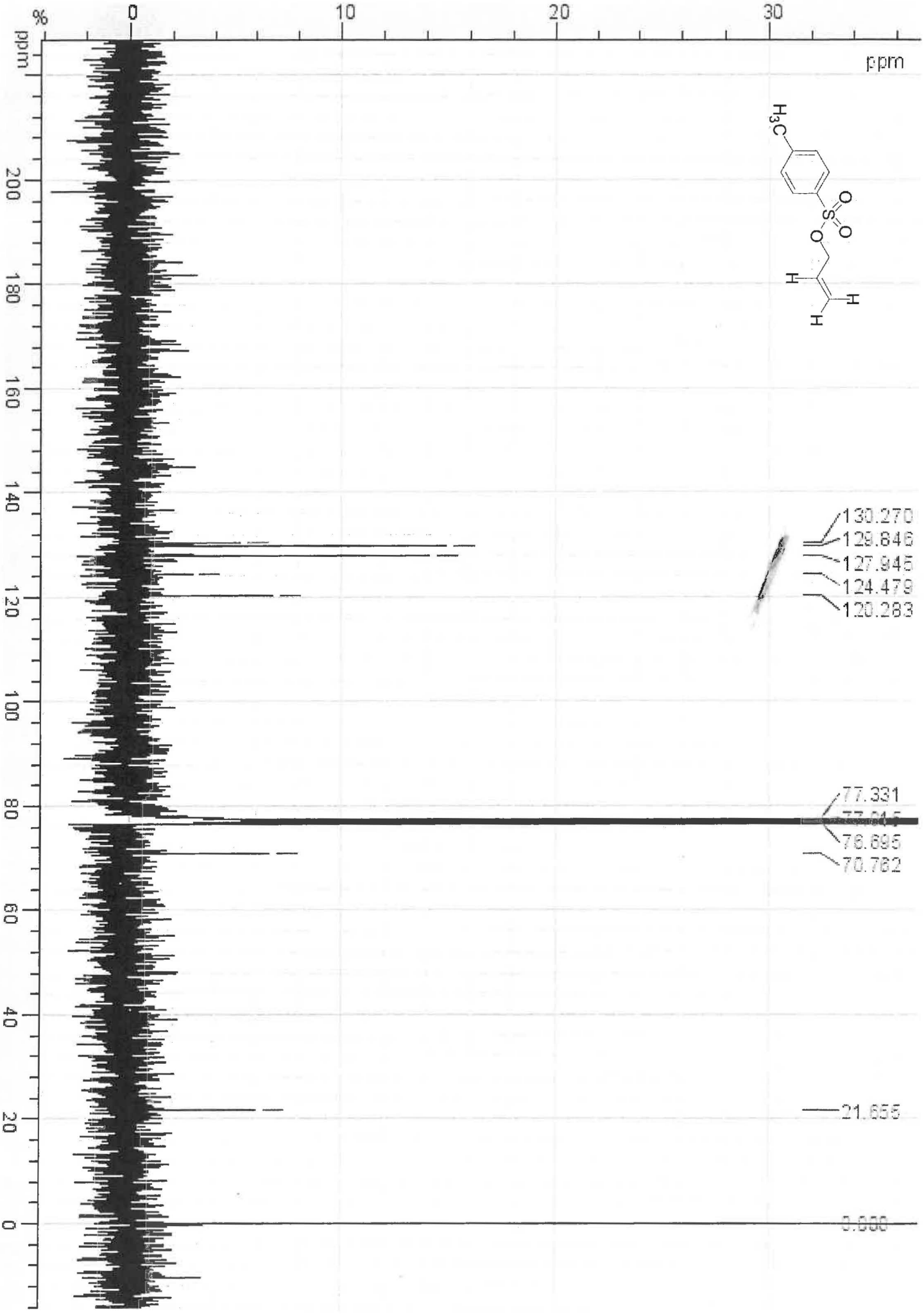
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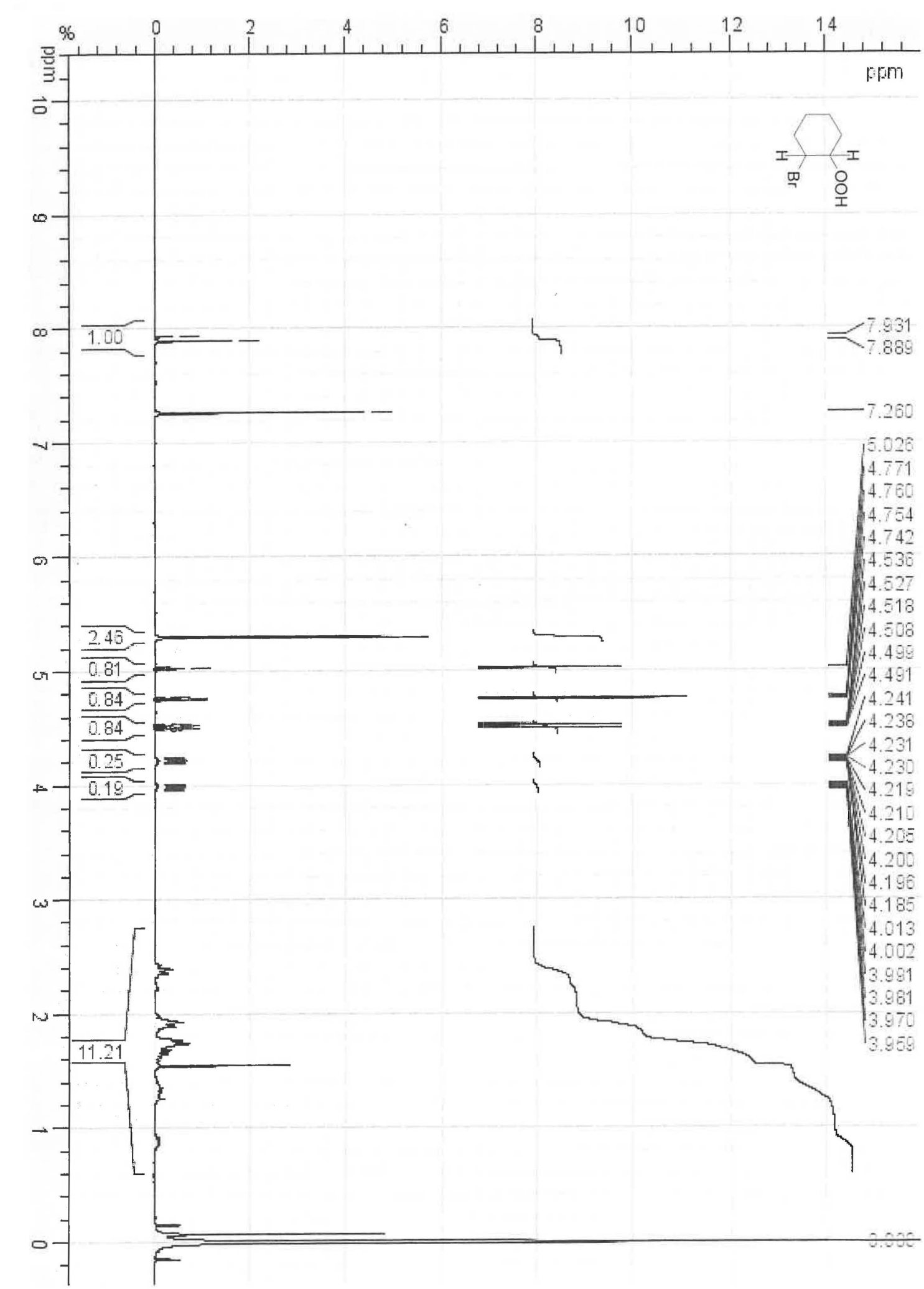
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0.84
0.25
0.19
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7.889
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5.026
4.771
4.760
4.754
4.742
4.536
4.527
4.518
4.508
4.499
4.491
4.241
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4.231
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4.219
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4.205
4.200
4.196
4.185
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4.002
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3.981
3.970
3.959
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