UNIVERSITY OF CALIFORNIA,
IRVINE

Syntheses of Acyclic *Plocamium* Polyhalogenated Monoterpentes, Evaluation of Biological Activity, and Formation of *E*-Vinyl Halides

Dissertation

Submitted in partial satisfaction of the requirements
for the degree of

Doctor of Philosophy

in Chemistry

by

Carl Vogel

Thesis Committee:
Professor Christopher Vanderwal, Chair
Professor Richard Chamberlin
Professor Sergey Pronin

2015

For my family.

‘There is no final word, unless some part of what’s done outlives those who did it.’

Table of Contents

List of Figures

List of Schemes

Acknowledgements

The first person that I need to thank is of course my advisor, Chris Vanderwal. He has proven time and again to be intelligent, creative, extraordinarily patient, and above all, a genuinely good-hearted person.

The Vanderwal lab is and always has been full of awesome people. Along with being excellent scientists, they made the whole experience a lot more enjoyable than it otherwise might have been: the day-to-day tasks made more enjoyable by gangster rap Friday and other shenanigans; celebratory outings to the pub and whiskey hour to commiserate our defeats. It is a special place to have worked in.

Everybody thanks the facilities, and for good reason. Without the top-notch facilities, and top-notch people running them, there wouldn't be a department. John Greaves deserves special thanks in my case. I can't actually think of a time where he was wrong, or gave up on obtaining a measurement on a compound I had made. With his retirement, UCI is truly losing a class act.

Along with the facilities, the UCI chemistry department at large is a wonderful place to conduct science. I have had the distinct privilege of being able to learn from Larry Overman over the past few years. Not many people get to say they had Larry teach their synthesis class, and I'm very grateful that I can.

Lastly, my family has been there for me the entire way. I am really bad at remembering to call, buy presents, and a whole host of other things a son and brother is supposed to be able to do, but they have all been supportive from beginning to end though all of it, and I cannot thank them enough.

Curriculum Vitae

Research Experience

University of California, Irvine

Graduate Student Research Assistant (July 2010–December 2015)

- Designed synthesis of a family of acyclic polyhalogenated monoterpenes, biologically active natural produts from the red algae genus *Plocamium*.
- Synthesized a number of natural products and analogues. Compounds have been sent to Dr. Fred Valeriote, a collaborator at the Henry Ford Medical Center in Detroit, for biological testing
- Key steps: diastereoselective dichlorination of a trisubstituted olefin, direct oxidative-cleavage of acetonide, multiple olefinations of base-sensitive intermediates

University of Illinois, Chicago

Undergraduate Research Assistant (February 2008–April 2010)

Visiting Research Specialist (April 2010–June 2010)

- Optimized method and expanded substrate scope of N–O and N–N bond formation from aryl azides using $FeBr_2$
- Explored methodology to synthesize a variety of nitrogen heterocycles from azides

Education

University of California, Irvine

PhD Candidate in Organic Chemistry (July 2010–December 2015)

- Research Advisor: Chris Vanderwal
- Research Project: Total Synthesis of *Plocamium* Polyhalogenated Monoterpenes and Biological Evaluation

University of Illinois, Chicago

B.S. in Chemistry (August 2006–May 2010)

- Research Advisor: Tom Driver
- Research Project: Intramolecular Fe(II)-Catalyzed N–O or N–N Bond Formation from Aryl Azides

Publications

Vogel, C. V.; Pietraszkiewicz, H.; Sabry, O. M.; Gerwick, W. H.; Valeriote, F. A.; Vanderwal, C. D. "Enantioselective, Divergent Syntheses of Several Polyhalogenated *Plocamium* Monoterpenes, and Evaluation of their Activity and Selectivity Toward Solid Tumors" *Angew. Chem. Int. Ed.* **2014**, *53*, 12205–12209.

Stokes, B. J.; **Vogel, C. V.**; Urnezis, L. K.; Pan, M.; Driver, T. G. "Intramolecular Fe(II)-Catalyzed N-O or N-N Bond Formation from Aryl Azides" *Org. Lett.* **2010**, *12*, 2884–2887.

Honor and Awards

University of California, Irvine

- 2015 St. Jude National Graduate Student Symposium Attendee
- 2013 NIH Ruth L. Kirschstein National Research Service Award (1F31CA174176-01)

University of Illinois, Chicago

- 2010 Ronald J. Baumgarten Award for Outstanding Students in Chemistry
- 2009 Herbert E. Paaren Summer Research Stipend
- 2009 Herbert E. Paaren Academic Scholarship
- 2009 National Organic Symposium Travel Stipend (ACS)

Presentations

- **Vogel, C. V.**; Pietraszkiewicz, H.; Sabry, O. M.; Gerwick, W. H.; Valeriote, F. A.; Vanderwal, C. D. "Divergent Syntheses of Acyclic Polyhalogenated *Plocamium* Monoterpenes and Evaluation of Activity for Solid Tumors" 249th ACS National Meeting and Exposition, Denver, Colorado; March 25, 2015.
- **Vogel, C. V.**; Vanderwal, C. D. "Progress Towards the Total Synthesis of Polyhalogenated Monoterpenes from the Red Algae *Plocamium Cartilagineum*" Graduate Student and Post-Doctoral Colloquium, University of California, Irvine; February 22, 2013.
- Stokes, B. J.; **Vogel, C. V.**; Urnezis, L. K.; Pan, M.; Driver, T. G. "Intramolecular Fe(II)-Catalyzed N–O or N–N Bond Formation from Aryl Azides" Chicago Organic Symposium, Northwestern University, Evanston; February 27, 2010 (Poster Presentation).
- Stokes, B. J.; **Vogel, C. V.**; Urnezis, L. K.; Pan, M.; Driver, T. G. "Intramolecular Fe(II)-Catalyzed N–O or N–N Bond Formation from Aryl Azides" National Organic Symposium, University of Colorado, Boulder; June 11, 2009 (Poster Presentation).

Teaching Experience

University of California, Irvine

Discussion Leader/Teaching Assistant (2012)

- Organic Chemistry I (Fall 2012)

Laboratory Instructor/Teaching Assistant (2010–2013)

- Organic Chemistry Laboratory III (Spring 2012, Spring 2013)
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- Organic Chemistry Laboratory II (Spring 2011, Winter 2012)
- Organic Chemistry Laboratory I (Fall 2010)

Abstract of the Dissertation

Syntheses of Acyclic *Plocamium* Polyhalogenated Monoterpentes, Evaluation of Biological Activity, and Formation of *E*-Vinyl Bromides

By

Carl Victor Vogel

Doctor of Philosophy in Chemistry

University of California, Irvine, 2015

Professor Chris Vanderwal, Chair

In chapter 1, background information on the acyclic *Plocamium* polyhalogenated monoterpenes, a group of natural products found in the red algae *Plocamium cartilagineum*, is given. Their discovery and relevant biological information is outlined, as well as previous work on related compounds.

The next chapter describes the initial synthetic route designed to access the acyclic *Plocamium* polyhalogenated monoterpenes. This includes the various attempts at synthesizing a suitable model system to test the key proposed dichlorination step. Although the first attempt to synthesize the desired system starting from the Zincke aldehyde does not afford the model stubstrate, a second strategy utilizing a known enynal does eventually lead to the desired model substrate. However, the key dichlorination step does not work, owing to undesirable reactivity of the diene. A new strategy had to be devised.

Chapter 3 describes the strategy that is ultimately successful at synthesizing the acyclic *Plocamium* polyhalogenated monoterpene natural products. Starting from a commercial mannitol derivative, the central chlorine-bearing stereocenters are installed, followed by functionalization of the C1-C2 alkene. Initially, a cross-metathesis reaction is proposed as a key disconnection.

Surprisingly, the cross-metathesis completely fails despite extensive experimentation with various reaction conditions, returning starting material nearly quantitatively in every case. Eventually, employing an oxidative cleavage followed by sequential olefinations successfully finished the natural products. To date, 9 natural products and 5 analogues have been synthesized. Biological activity of the compounds against a variety of solid tumor cell lines is also described.

The final chapter outlines attempts at developing new methodology to synthesize *E*-vinyl halides from an aldehyde in a single step. A lack of current viable methods was the driving force for developing new methodology. Variations of the Takai-Utimoto olefination are tested, as well as a modification of the Schlosser-modified Wittig olefination.

Chapter 1: Background

1.1 Discovery and Characterization

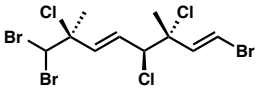


Figure 1. First characterized acyclic *Plocamium* polyhalogenated monoterpene.

The group of polyhalogenated monoterpenes is a large group of natural products, with both cyclic and acyclic architectures. The first example of the acyclic variety was isolated by Faulkner from the sea hare *Aplysia californica*, and the structure confirmed via X-ray crystallography (Figure **1**).[1] The authors suspected that the compound was being bioaccumulated by the sea hare, and was actually being produced by a red algae species, which they confirmed when the compound was isolated from the red algae *Plocamium coccinium*.[2] After the discovery of this first example, many more polyhalogenated monoterpenes were isolated by a number of groups.[3A–I] All of the reported examples contain two vicinal stereogenic chlorines, one secondary and one tertiary. Both the *syn* and *anti* versions are known in many cases. The left- and right-hand portions of the molecule can contain a range of halogenation patterns, up to six halogens total (Figure **2**).

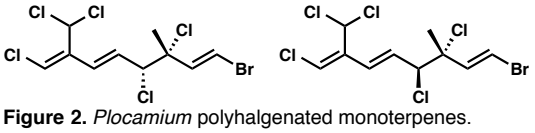


Figure 2. *Plocamium* polyhalgenated monoterpenes.

The characterization of molecules with complex halogenation patterns poses an unusual challenge: the determination of regiochemistry. Confirming the precise carbon to which each halogen is assigned to can be very difficult, especially when multiple types of halogen are present. Reassignments of regiochemistry are not uncommon. For example, in the case of violacene, a related cyclic monoterpene, the precise regiochemistry was only confirmed after X-ray crystallography revealed a misassignment.[4,5] A similar misassignment was discovered with chondrocole A, again being corrected after X-ray crystallography data was obtained (Figure **3**).[6,7]

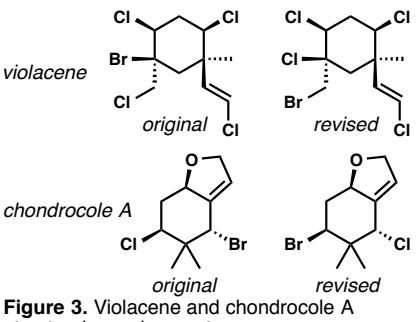
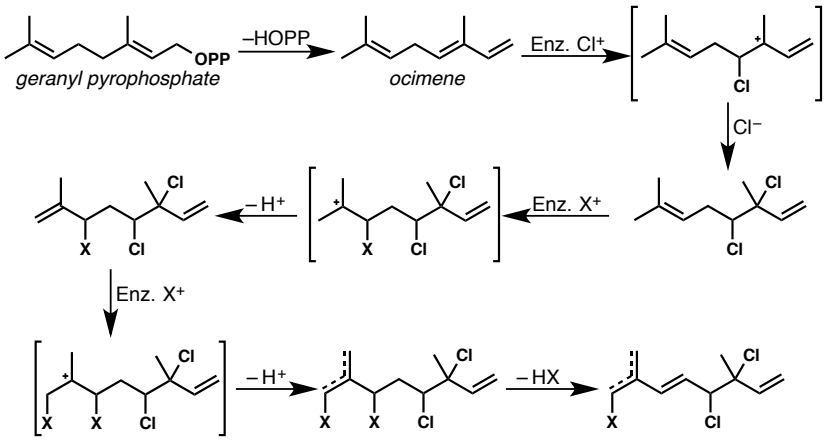


Figure 3. Violacene and chondrocole A structural reassignment.

Although X-ray crystallography data is generally the best way to elucidate stereochemical and regiochemical information for a structure, it is not always an option, as not all compounds are crystalline. Fortunately, Crews and coworkers discovered that while proton NMR data for polyhalogenated small molecules can be ambiguous, ^{13}C NMR data is much clearer idea of connectivity. They developed a system that can reliably predict the regiochemistry of halogen substituents based on ^{13}C NMR chemical shifts and carbon type, in cyclic or acyclic manifolds.[3E]

1.2 Biosynthesis

Although these compounds were discovered 40 years ago, very little is known about the biosynthetic pathway of the *Plocamium* polyhalogenated monoterpenes. However, a review by Crews hypothesizes a reasonable biosynthetic map based on other known biosynthetic pathways.[8] Ocimene is formed from geranyl pyrophosphate by loss of HOPP. The central alkene is then chlorinated or brominated via an enzyme-mediated electrophilic halogenation, and the carbocation is quenched by nucleophilic attack with chloride ion. A number of haloperoxidase enzymes are known and have been studied, although none of them have come from the algae species that produce acyclic polyhalogenated monoterpenes.[9,10] Although Crews did not hypothesize as to how some of the other oxidation states are reached in the biosynthesis, some assumptions can be made based on the other proposed pathways. A series of electrophilic halogenations,



Scheme 1. Possible biosynthesis of acyclic *Plocamium* polyhalogenated monoterpenes.

followed by loss of proton transposes the remaining trisubstituted alkene to the exocyclic position and installs the primary or vinyl halide, depending on the monoterpene in question. How the remaining left-hand halogens are installed is a mystery. Electrophilic halogenation might be difficult owing to the decreased electron density of the alkene because of the installed halide. The remaining halogens may be installed by single-electron processes, which seem more likely than a pathway using electrophilic halogenation. In any case, the final step in the biosynthesis is likely loss of HX to form the central alkene (Scheme **1**).

1.3 Biological Activity

One of the primary foci of study of this family of compounds is their biological activity. In nature, it is hypothesized that many of these compounds act as antifeedants to predatory organisms,[8,11] but a much wider and more interesting range of activity relevant to humans has been observed. These compounds have been found to exhibit antifungal, antimicrobial, antiplasmodial, and anticancer properties. More importantly, these compounds have been shown to be selectively active against solid tumors over leukemia and melanoma cell lines.[12,3I] The most notable example of selective cytotoxicity comes from the related compound halomon, which was isolated from another red algae, *Portieria hornemannii.*[13] When the National Cancer Institute subjected halomon and other related compounds to the NIH COMPARE algorithm, it showed significant selectivity for solid tumors over leukemia cell lines, and possessed little to no similarities in mechanism or structure to any known anticancer agents, being one of the earliest compounds tested. Because of this, halomon was taken into preclinical trials for the treatment of

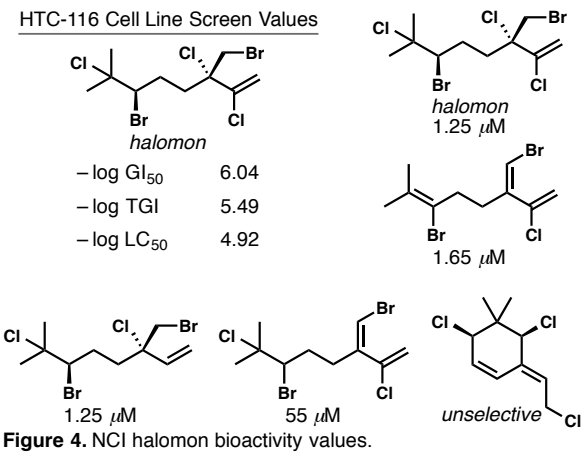
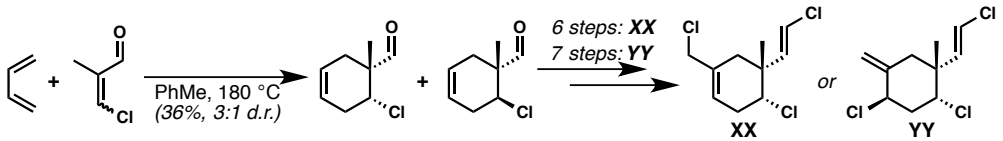


Figure 4. NCI halomon bioactivity values.

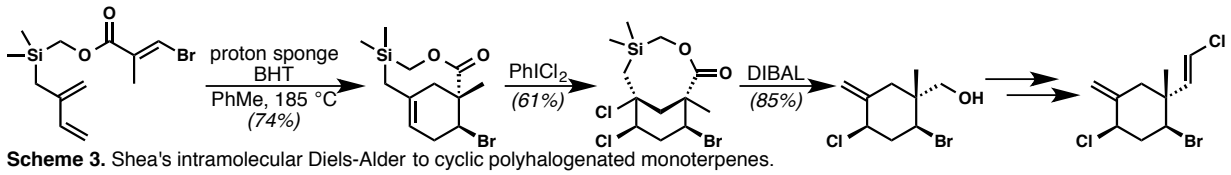
solid tumors. The studies showed that while halomon could be an effective anticancer agent, it also suffered from issues of bioavailability. Interestingly, the researchers also found that halomon is generally stable in mouse models, and is only toxic at extremely high dosage (Figure **4**).[14] Other compounds that were isolated were either not potent, or unselective. Unfortunately, obtaining sufficient amounts of halomon for in vivo testing was difficult, and the project was eventually abandoned.

1.4 Related Syntheses



Scheme 2. Williard's synthesis of cyclic polyhalogenated monoterpenes.

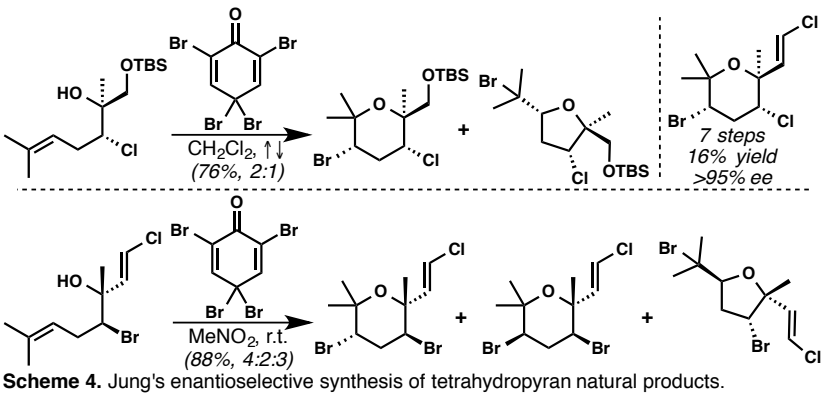
Although none of the acyclic *Plocamium* polyhalogenated monoterpenes had been synthesized when we started the research program, a number of related cyclic and acyclic members have been synthesized. The first report came from Williard and Laszlo in 1985 (Scheme **2**).[15] The key step in their strategy was a Diels–Alder cycloaddition, which set the desired stereochemistry at two of the four positions, which could be relayed into the other necessary positions to furnish two natural products. The original target, violacene could not be synthesized using this method, nor was enantioenriched material produced, but it was the first synthesis of any of the *Plocamium* monoterpene compounds. Shea and coworkers were able to develop a more efficient strategy for the synthesis of a cyclic member of the polyhalogenated monoterpenes (Scheme **3**).[16] Their strategy also relied on a Diels–Alder disconnection, however, Shea utilized an intramolecular variant, which circumvented any regiochemical issues an



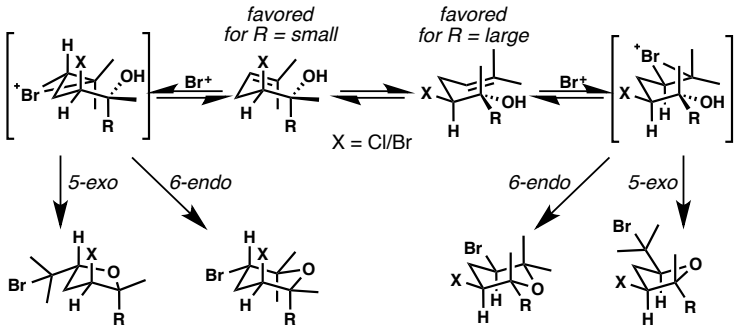
Scheme 3. Shea's intramolecular Diels-Alder to cyclic polyhalogenated monoterpenes.

intermolecular approach could have had. The additional functionality installed also made late-stage functionalization more selective, further increasing the efficiency of the strategy. The chlorination step of Shea's approach is particularly interesting. Due to the nature of the bridgehead olefin, dichlorination occurs via the *exo-syn* mode, correctly setting the desired relative stereochemistry.

The Jung group has published a number of strategies pertaining to both the cyclic and acyclic members of the polyhalogenated monoterpes. Rather than target the previously synthesized carbocyclic substrates, Jung's first and second reports targeted the related cyclic ethers (Scheme **4**).[17,18] The key step was a haloetherification reaction, closing the ring and installing one of the bromines in a single step. Jung's reasoning for the observed selectivities of the key haloetherification is minimization of 1,3-diaxial interactions (Scheme **5**). Along with being the first syntheses of the tetrahydropyran natural products, they were also the fist enantioselective syntheses of any member of the family.



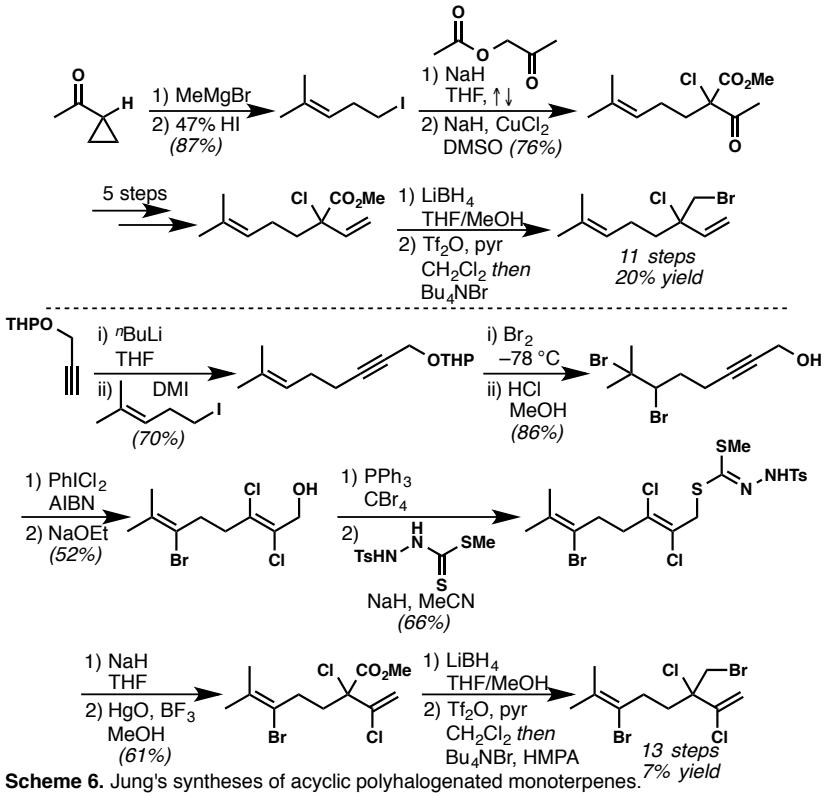
Scheme 4. Jung's enantioselective synthesis of tetrahydropyran natural products.



Scheme 5. Hypothesis for selectivity of haloetherification.

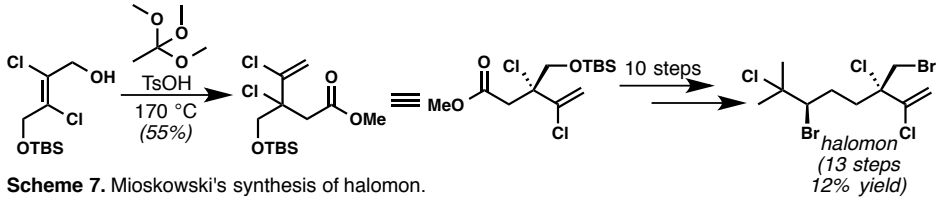
Jung was also the first to report the synthesis of an acyclic member.[19] Depending on the desired substitution pattern, different starting materials were needed, but the overall strategy of joining the left- and right-hand fragments, ultimately leading to reduction and installation of the primary bromide holds for

both members synthesized (Scheme **6**). Unfortunately, relatively high step counts are needed to install just a few halogens, and without enantiocontrol.



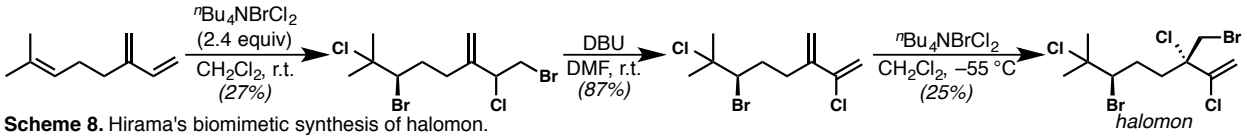
Scheme 6. Jung's syntheses of acyclic polyhalogenated monoterpenes.

Although halomon has garnered attention from a number of different groups, at the outset of our studies, only two had successfully synthesized it. The first synthesis was Mioskowski's in 1998, using a Johnson–Claisen rearrangement to install the key tertiary chloride (Scheme **7**).[20] The synthesis is relatively long, and separation of the final product is extremely cumbersome, requiring multiple rounds of HPLC.



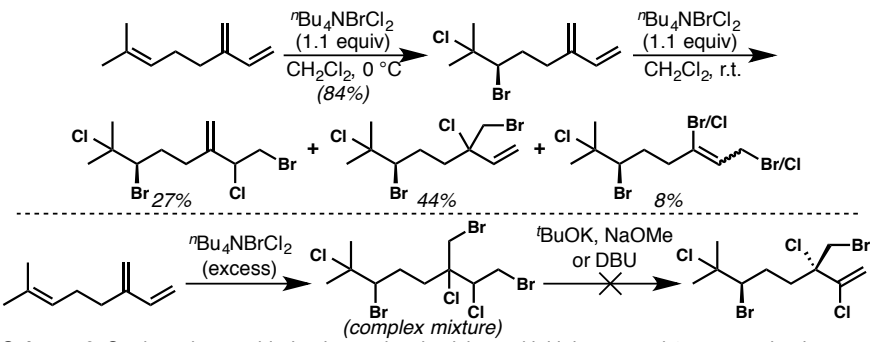
Scheme 7. Mioskowski's synthesis of halomon.

Hirama's synthesis of halomon drastically reduces the number of steps by using a biomimetic strategy (Scheme **8**).[21] Starting from myrcene, double bromochlorination/elimination/bromochlorination furnishes halomon in an impressive three steps.

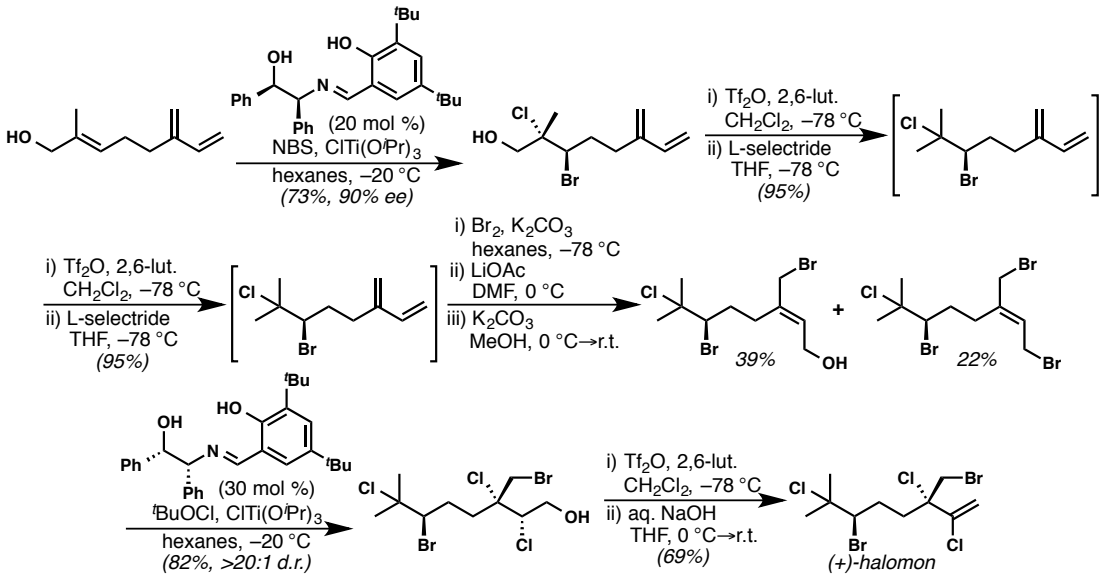


Scheme 8. Hirama's biomimetic synthesis of halomon.

The authors found that while bromochlorination of the trisubstituted olefin was exceptionally selective, bromochlorination of the diene always led to a mixture of products, hence the one-pot procedure (Scheme **9**). Initially, Hirama proposed a two-step synthesis of halomon, in which all of the halogens would be installed in a single step, followed by regioselective elimination of HBr to give the desired final product. However, the initial triple-bromochlorination yielded a complex mixture, and the subsequent elimination did not work under any circumstances. Additionally, the authors note that separation of the final product from the undesired diastereomers and isomers is tedious.



Scheme 9. Study on bromochlorination regioselectivity and initial proposed 2-step synthesis.



Scheme 10. Burns' synthesis of halomon.

In 2015, Burns published the first enantioselective synthesis of halomon (Scheme **10**).[22] The main advantage of the Burns synthesis is regio- and stereoselectivive installation of the halogens, thanks to the Ti-mediated halogenation protocol the lab developed, which will be

discussed later in this chapter. Unfortunately, functionalization of the diene gives a mixture of products, echoing the problems faced by Hirama. However, despite the longer step count and product mixture resulting from unselective diene functionalization, the Burns synthesis is still marks a major advance in the synthesis of acyclic polyhalogenated monoterpenes.

1.5 Introduction to Dichlorination Methodology

The ability to control the stereoselectivity of halogenation reactions is an important aspect of natural product synthesis. In most cases, only one halogen is installed, and is ultimately used as a functional handle to install other desired groups. However, in a number of natural products, including the *Plocamium* polyhalogenated monoterpenes that are the subject of this dissertation, halogen-bearing stereogenic carbons are a main structural feature of the final product. Another well-known group of natural products that include stereogenic halogens is the chlorosulfolipids (Figure **5**). Several groups have made significant contributions to the synthesis of various members of this family of compounds, including the Vanderwal and Carreira groups.[23] The biggest challenge is installation of the various chlorine atoms along the backbone, where specific stereochemistry is required. However, with careful planning, it is possible to use other functionality in the molecule to direct dichlorination reactions to favor the desired stereochemistry.

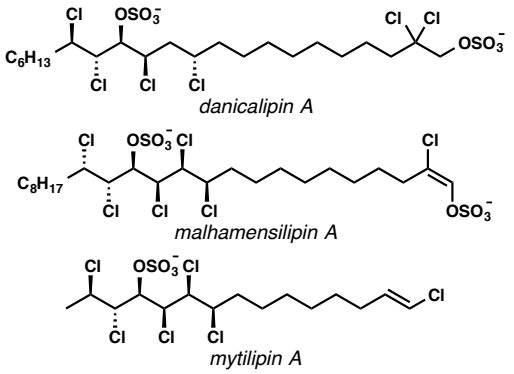


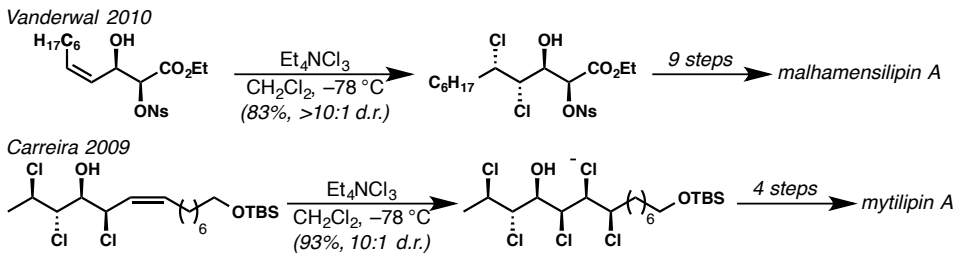
Figure 5. Several chlorosulfolipids.

1.6 Alkene Dichlorination

Several methods are available for the stereoselective installation of vicinal chlorides from an alkene. In 1997, Mioskowski first reported dichlorination reactions using Et_4NCl_3, which is easily prepared by bubbling chlorine gas through a solution of Et_4NCl in CH_2Cl_2.[24] This reagent

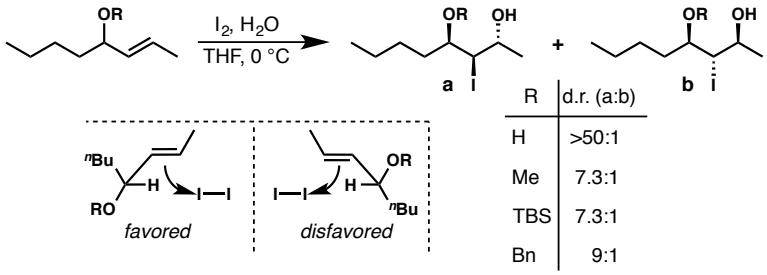
is somewhat hygroscopic, but otherwise stable, and can be weighed out on the benchtop, making it much more user-friendly than chlorine gas. Et_4NCl_3 was shown to dichlorinate various alkenes and alkynes, as well as oxidize activated alcohols.

Syntheses of the chlorosulfolipids by the Carreira and Vanderwal groups have used this reagent as a means to install several of the requisite chlorine atoms (Scheme **11**).[25] In both examples, the nearby oxygen functionality influences the diastereoselectivity of the dichlorination to give the desired stereochemistry. In the case of the synthesis of malhamensilipin A by Vanderwal, the alcohol is enantioenriched, thereby rendering the synthesis enantioselective.



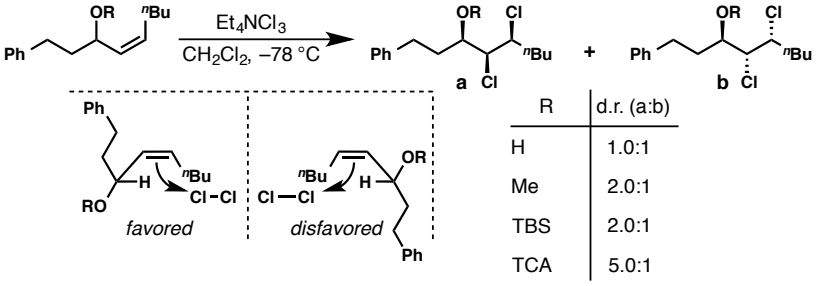
Scheme 11. Examples of utilizing Et_4NCl_3 in the synthesis of the chlorosulfolipids.

Although the precise mechanism of alkene dichlorination with Et_4NCl_3 is still unknown, the selectivity likely follows the model proposed by Chamberlin for iodohydroxylation (Scheme **12**).[26] The primary governing factor for stereochemistry is minimization of 1,3-allylic ($A^{1,3}$) strain, with the regiochemistry being dictated by the alkene substituents, while the stereochemistry is directed by the allylic alcohol. Chamberlin's model for iodohydroxylation proposed that the iodonium intermediate is preferentially formed on the same alkene face as the oxygen functionality. This both minimized the $A^{1,3}$ strain between the alkene substituents and the large ^{n}Bu-group, and allows the oxygen



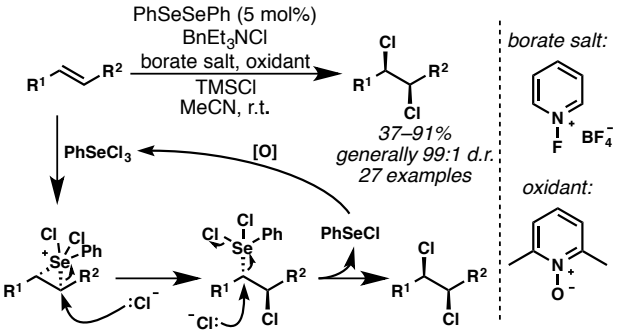
Scheme 12. Chamberlin's studies on the selectivity of iodo diol formation.

lone pair to stabilize the iodonium ion. Nucleophilic attack of the iodonium occurs almost exclusively at the least sterically-hindered position, unless otherwise electronically disfavored. The Vanderwal group performed similar studies on dichlorination of allylic alcohols, with results supporting Chamberlin's conclusions (Scheme **13**).[27]



Scheme 13. Vanderwal's studies on the selectivity of alkene dichlorination.

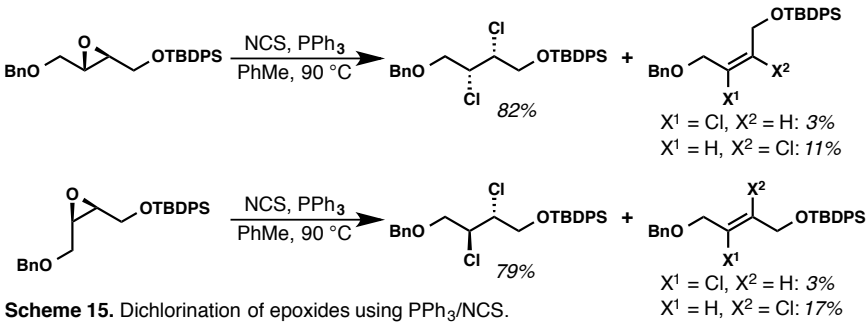
In 2015, Denmark reported a catalytic method for *syn*-dichlorination, using a combination of chloride sources and a selenium catalyst (Scheme **14**).[28] This is accomplished by exploiting a mechanism that differs from other dichlorination reagents. The mechanism of *anti*-dichlorination of an *E*-alkene with Et_4NCl_3 can be explained by nucleophilic ring-opening of a chloronium intermediate. However, Denmark's method does not go through a chloronium intermediate. Instead, a seleniranium intermediate is formed, followed by nucleophilic ring-opening to form a (β-chloro)phenylselenium dichloride species. The selenium is then displaced by a second equivalent of nucleophilic to form the *syn*-dichloride species. This method has the potential to be extremely useful in situations where the *Z*-alkene is difficult to synthesize, as well as provide new mechanistic framework for asymmetric catalysis in the future.



Scheme 14. Denmark's selenium catalyzed *syn*-dichlorination.

1.7: Epoxide chlorination

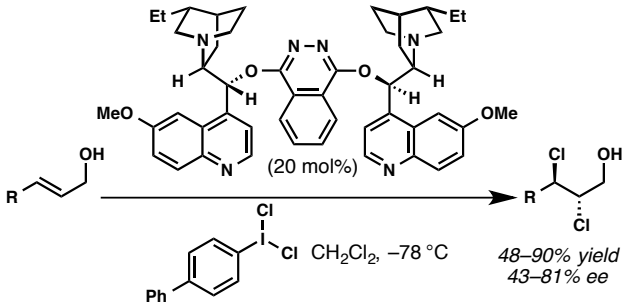
Another method, first reported by Isaacs and Kirkpatrick, chlorinates epoxides using a mixture of PPh_3 and CCl_4. [29] An improvement developed by Iranpoor and later studied by Yoshimitsu replaces the CCl_4 with NCS (Scheme **15**).[30] This method is well suited for cases where nearby oxygen functionality is not easily accessed in an enantioselective manner, or the oxygen functionality is not desired in the final product. The fact that this method uses NCS as the sole source of chlorine and takes advantage of well-established alkene epoxidation protocols for the source of enantioselectivity make it an attractive alternative in some situations, and was successfully used in Yoshimitsu's synthesis of hexachlorosulfolipid (mytilipin A).[31] Unfortunately, the necessary epoxidation adds a step to the sequence of dichloride formation. Additionally, the dichlorination step is sensitive to other oxygen functionality in the molecule, and is prone side product formation resulting from elimination, both of which can lead to significantly diminished yields.



Scheme 15. Dichlorination of epoxides using PPh_3/NCS.

1.8 Asymmetric Dichlorination

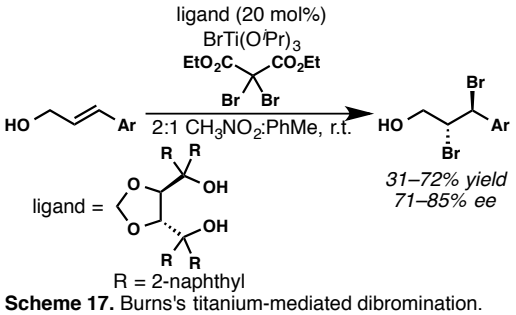
Recently, several methods of asymmetric dihalogenation of alkenes have been published. In 2011, Nicolaou reported a method which uses the dimeric cinchona alkaloid derivative $(DHQ)_2PHAL$ to impart enantioselectivity (Scheme **16**).[32] It is proposed that the catalyst interacts with the allylic alcohol of the substrate, while simultaneously activating the chlorinating reagent $PhICl_2$. Unfortunately, only modest selectivity is observed, and the substrate



Scheme 16. Nicolaou's enantioselective alkene dichlorination.

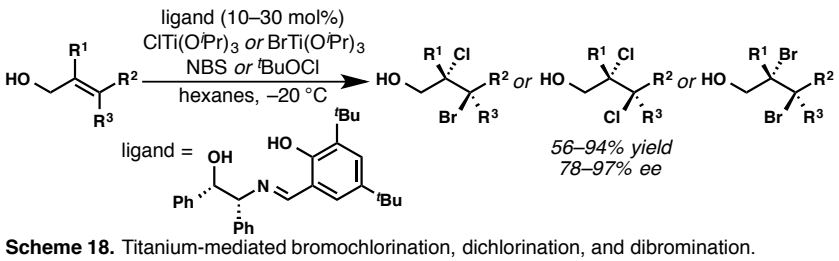
scope is limited to primary allylic alcohols, usually on a styrenyl system. Moreover, dichlorination of *Z*-alkenes leads to diminished yield and selectivity, further limiting the synthetic utility of the method.

In 2013, Burns reported the enantioselective dibromination of allylic alcohols (Scheme **7**).[33] Although this reaction was the first report of its kind, it did not mark a significant improvement over the method developed by Nicolaou. The substrate scope was still limited to styrenyl systems, and only gave modest enantioselectivity. The main difference between the two methods, other than the halides installed, was the source of bromine. Burns used an α,α-dibromocarbonyl as the electrophilic bromine source, which was only reactive once activated by a titanium species containing the nucleophilic bromine bound to the alkene substrate.

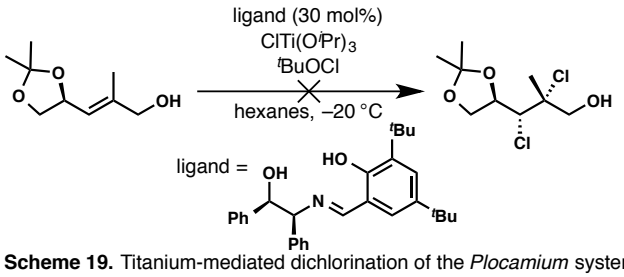


Scheme 17. Burns's titanium-mediated dibromination.

The first major advance in enantioselective dihalogenation was reported by Burns in 2015, which could accomplish both bromochlorinations and dichlorinations in the highest enantioselectivities reported to date (Scheme **18**).[34] However, the largest advantage that this improvement showed over the initial to dibromination method was the ability to enantioselectively dihalogenate non-styrenyl systems. We attempted this dichlorination methodology in the hopes of switching the diastereoselectivity (Scheme **19**). Although the method failed in the context of the



Scheme 18. Titanium-mediated bromochlorination, dichlorination, and dibromination.



Scheme 19. Titanium-mediated dichlorination of the *Plocamium* system.

acyclic *Plocamium* polyhalogenated, it is arguably the first synthetically useful method reported in the literature.

1.9 Conclusion

The polyhalogenated monoterpene family of natural products is both structurally diverse and biologically relevant. There is still much to learn about the biosynthesis of these molecules, along with a need to screen as many members as possible for potential biological activity. While a number of groups have published synthetic efforts towards these molecules, many of them successful, none of the previous syntheses are amenable to the more structurally complex *Plocamium* polyhalogenated monoterpenes. However, the dihalogenation methodologies highlighted in the previous syntheses, as well as the other methods discussed, give a solid platform to develop a successful strategy.

1.10 References

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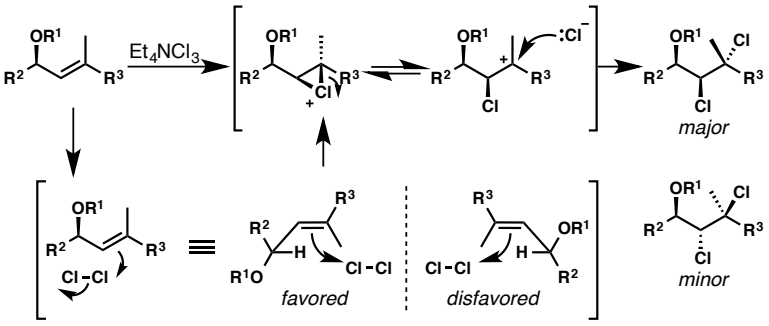
Chapter 2: Initial retrosynthesis and dichlorination of model system

2.1 Introduction

In the previous chapter, the group of acyclic *Plocamium* polyhalogenanted monoterpenes was outlined. The interesting biological activity and structural complexity motivated us to develop a general synthesis to access as many members of the group as possible. Several other syntheses of related molecules were also highlighted, but it was clear to us that adopting a strategy based on one of the previously reported syntheses would not be viable. In this chapter, the initial retrosynthesis will be discussed, as well as the various attempts to synthesize the desired dichlorination model system.

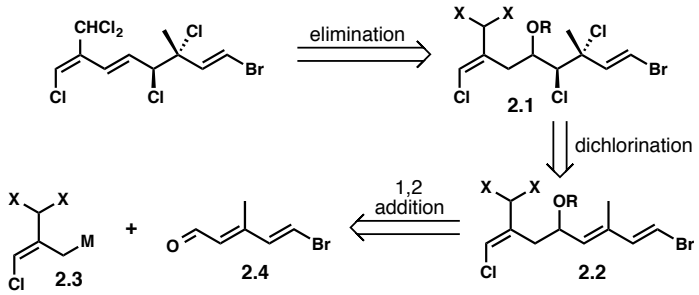
2.2 Initial retrosynthesis

At the start of our synthetic efforts, the key question that we needed to answer was how to install the central chlorines in a stereoselective manner. Based on the previous precedent, we believed that the strategy with the highest chance of success was to use Et_4NCl_3 to dichlorinate a trisubstituted olefin (Scheme **1**). In order to achieve the desired selectivity, we imagined nearby oxygen functionality could direct the diastereoselectivity, and with the proper method of preparation, provide a means for an enantioselective synthesis starting from a chiral alcohol. There were no examples of a diastereoselective dichlorination on trisubstituted olefins, but we believed that it would follow the same trends as previously reported on the dichlorination of disubstituted olefins. Before we could start experimenting to find the best conditions to install the desired stereogenic chlorines though, the requisite trisubstituted alkene needed to be installed with suitable functional handles



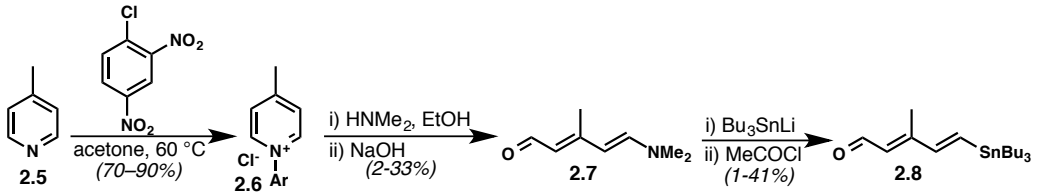
Scheme 1. Proposed mechanism for stereoselectivity of dichlorination.

to install the necessary flanking functionality (Scheme **2**). For the initial retrosynthesis, we imagined that the final alkene could be installed via elimination of allylic alcohol **2.1**, which could be used to direct the dichlorination of **2.2**. 1,2-addition of a nucleophilic organometallic reagent analogous to **2.3** into aldehyde **2.4** would construct the dichlorination precursor. The aldehyde bore a striking resemblance to the *δ*-tributylstannyl-*α*,*β*,*γ*,*δ*-unsaturated aldehydes derived from Zincke aldehydes as previously reported by the Vanderwal lab, which might serve as a convenient precursor.[1]



Scheme 2. Initial retrosynthesis.

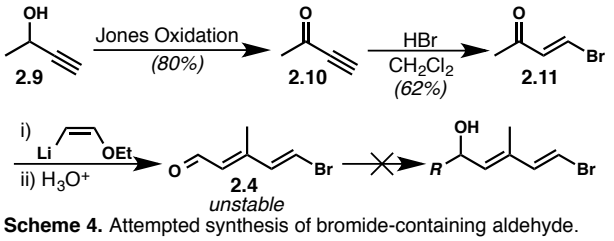
Following the protocol, 4-picoline (**2.5**) was heated with 2,4-dinitrochlorobenzene to form pyridinium salt **2.6** (Scheme **3**). Subsequent treatment with aqueous NaOH formed the desired Zincke aldehyde (**2.7**). Although the procedure is straightforward, **2.7** is sensitive to acidic and basic conditions, as well as silica chromatography. Moreover, the dinitroaniline byproduct, which negatively impacts formation of the stannane, is difficult to remove. However, with clean material, the stannylation reaction performs as reported, and the requisite vinylstannane **2.8** could be isolated.



Scheme 3. Synthesis of stannane-containing aldehyde.

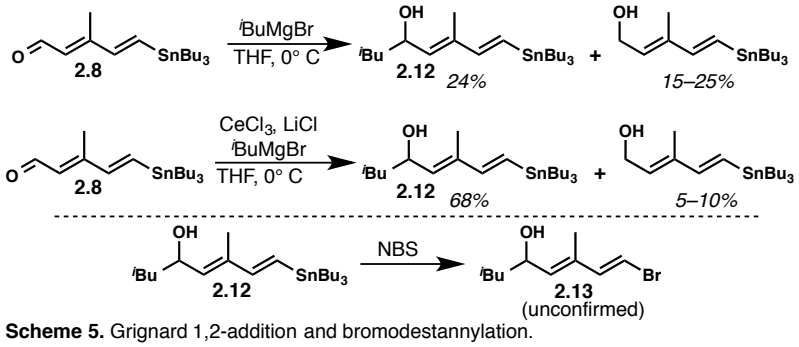
Concurrently, another method to synthesize the desired aldehyde containing the vinyl bromide was being evaluated (Scheme **4**). Jones oxidation of commercial alcohol **2.9** cleanly gave ynone **2.10**. Subsequent treatment of alkyne **2.10** with HBr afforded **2.11**. 1,2-addition of

the vinyllithium species[2] followed by mildly acidic workup generated the desired aldehyde **2.4** after elimination of ethanol. Unfortunately, we found that **2.4** is extremely unstable, and does not tolerate most workup conditions, nor does it survive the 1,2-addition reaction.



Scheme 4. Attempted synthesis of bromide-containing aldehyde.

Because vinylstannane **2.8** was relatively stable, we decided to subject it to the 1,2-addition conditions (Scheme **5**). Gratifyingly, 1,2-addition of ^{i}BuMgBr into **2.8** was successful, but was complicated by a number of byproducts arising primarily from reduction, but also from 1,4- and 1,6-addition. Employing the use of $CeCl_3$ as a Lewis acid alleviated these problems, giving the desired 1,2-addition product **2.12**.[3] Although the stannane was relatively stable with the aldehyde present, once the secondary alcohol was formed, protodestannylation became an issue, and product loss was evident. Even so, initial experiments indicated stannane **2.12** could be subjected to bromodestannylation conditions to synthesize desired vinyl bromide **2.13**,[4] but not enough material could be produced to properly isolate and characterize the products.



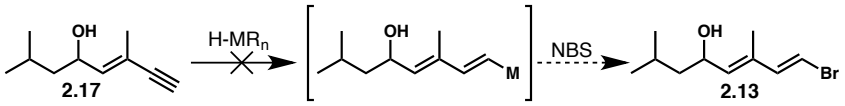
Scheme 5. Grignard 1,2-addition and bromodestannylation.

The sequence starting from 4-picoline successfully produced the desired model diene **2.13**, but there were multiple problems with reproducibility and low yield. A larger amount of material was needed to properly screen the dichlorination conditions, so a new strategy was devised which avoided many of the problematic reactions and intermediates.

2.3 Enynal Strategy

Scheme 6. Acid-catalyzed rearrangement, oxidation, and 1,2-addition.

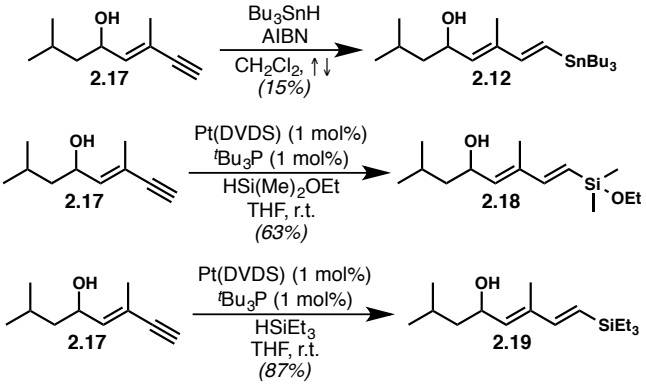
The second strategy to produce the desired model substrate relied on the use of known alkyne **16.2** instead of the vinylstannane (Scheme **6**). Using known procedures, commercially available tertiary alcohol **2.14** could be rearranged under acidic conditions to give primary alcohol **2.15**.[5] Subsequent oxidation uneventfully produced desired aldehyde **2.16**, but the 1,2-addition suffered from a significant amount of reduction byproduct.[6] Thankfully, as with the vinylstannane, once $CeCl_3$ was added as a Lewis acid, the yield of desired addition product **2.17** rose significantly. Alternatively, we found that running the reaction in Et_2O alleviated the need for $CeCl_3$, greatly simplifying reaction setup.



H-MR_n = catecholborane, 9-BBN
DIBAL, $LiAlH_4$, Cp_2ZrHCl

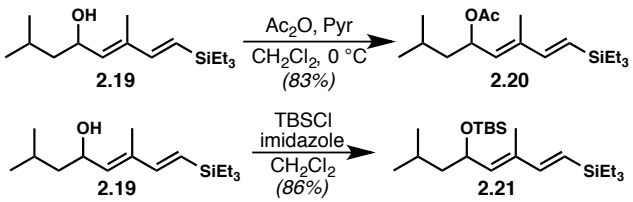
Scheme 7. Unsuccessful hydrometallation attempts.

With the requisite alkyne in hand, we found that hydrometallation of the enyne was much more challenging than originally anticipated (Scheme **7**). Hydroalumination was unsuccessful under all tested conditions,[7] as were hydroboration[8] and hydrozirconation,[9] each primarily returning alkyne **2.17**. Protection of the secondary alcohol did not change the outcome of any of the reactions. Hydrostannylation was met with a small amount of success,[10] but the resulting vinylstannane **2.12** suffered from the same issues of protodestannylation as before (Scheme **8**). Coupled with a low



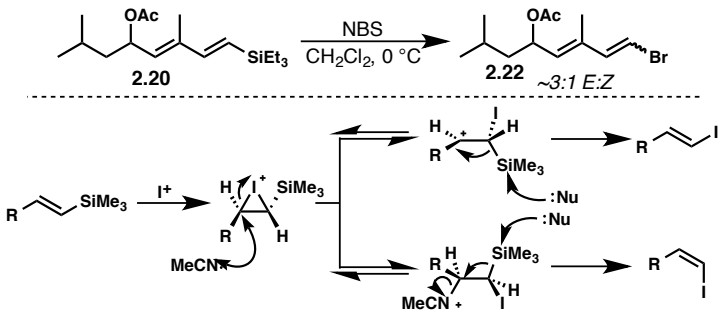
Scheme 8. Alkyne hydrostannylation and hydrosilylation.

yield, the stannane was discarded in favor of a silane. Pt-catalyzed hydrosilylation was by far the most efficient hydrometallation condition, with reproducable yields of 80% and above.[11] Vinylsilane **2.19** was found to have a more desirable combination of stability and reactivity relative to **2.18**, which tended to dimerize under the reaction conditions and during purification. At this point, the secondary alcohol **2.19** was protected as either the acetate (**2.20**) or TBS ether (**2.21**) in order to prevent oxidation (Scheme **9**).

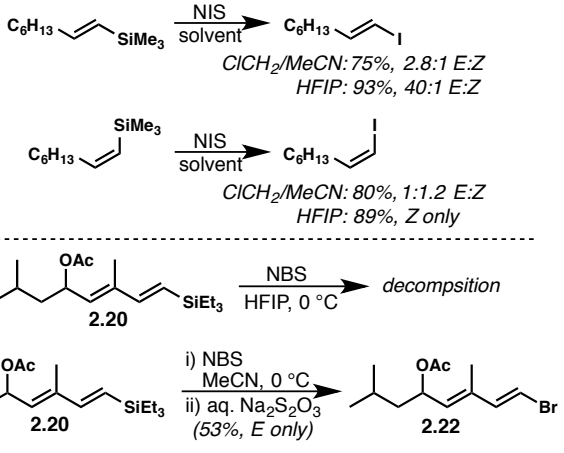


Scheme 9. Alcohol acetylation and silylation.

Bromodesilylation proved to be more difficult than bromodestannylation (Scheme **10**). Although the suppressed reactivity of silane relative to the stannane ensured that premature demetallation was not an issue, this same property also complicated the installation of the vinyl bromide. While bromodestannylation of stannane **2.12** gave exclusively the *E*-bromide, bromodesilylation of silane **2.20** initially gave a mixture of the *E*- and *Z*-bromide. This scrambling of alkene geometry is a known issue for iododesilylation reactions. The first study of this reaction by Kishi hypothesized the loss of stereochemistry was a result of nucleophilic attack of the iodonium intermediate by the solvent or other exogenous nucleophile, followed by anti-



Scheme 10. Unselective bromodesilylation and Kishi's model for inversion.

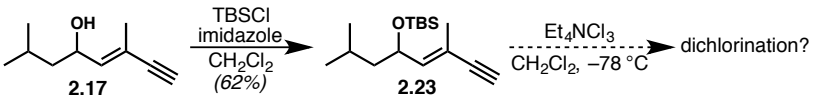


Scheme 11. Zakarian's study and successful bromodesilylation.

elimination of the silane.[12] Zakarian found that when hexafluoroisopropanol (HFIP) was used instead of MeCN or $ClCH_2CN$, complete retention of stereochemistry was observed in most cases (Scheme **11**).[13] This is likely due to the high polarity but low nucleophilicity of HFIP, which can activate NIS but not open the iodonium intermediate. However, in our case, use of HFIP led to complete decomposition of **2.20**. Thankfully, Kishi and Zakarian also independently reported that halodesilylation reactions were sensitive to the steric bulk of the allylic position, greatly favoring retention of alkene geometry under more standard conditions. Simply running the reaction in MeCN instead of CH_2Cl_2, and quenching with aqueous $Na_2S_2O_3$ ensured complete retention of stereochemistry to give the desired *E*-bromide **2.22**.

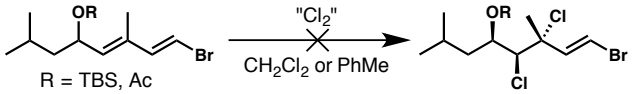
2.4 Dichlorination

With the ability to produce sufficient quantities of the dichloriantion precursor, we evaluated conditions to install the necessary secondary and tertiary stereogenic chlorides. Prior to completing the synthesis of the desired model system, we subjected the enyne to dichorination conditions to find out if the trisubstituted alkene could be successfully dichlorinated in the presence of the alkyne (Scheme **12**). Unfortunately, no distinguishable products could be isolated from the reaction mixture. Therefore, we could not draw any meaningful conclusions as to reaction rates. We next evaluated the originally designed model system (Scheme **13**). Despite a multitude of conditions tested, we were never able to detect, let alone isolate, any desired dichlorination product. The products observed depended greatly on the protecting group used. Dichlorination of silyl-protected alcohols yielded an intractable mixture of products under all tested conditions. When acetate-protected alcohol **2.22** was used, three

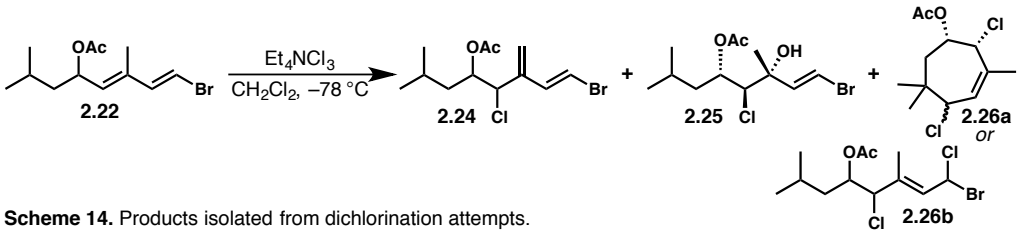


2.17 2.23

Scheme 12. Attempted enyne dichlorination.

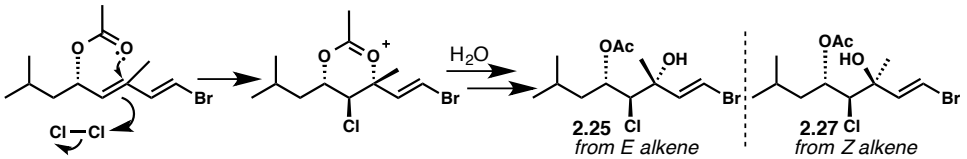


Scheme 13. Unsuccessful dichlorination conditions.



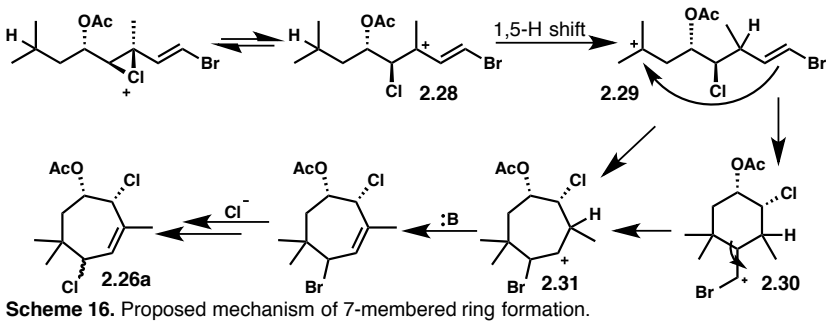
Scheme 14. Products isolated from dichlorination attempts.

major products could be isolated, but only when Et_4NCl_3 was used as the dichlorination reagent (Scheme **14**). The first product identified was exocyclic alkene **2.24**, resulting from the deprotonation and elimination of the chloronium intermediate. A second product was a



Scheme 15. Proposed mechanism of chlorohydrin formation.

chlorohydrin, bearing anti,anti stereochemistry of the stereotriad (**2.25**) when the *E*-alkene is subjected to the dichlorination conditions, and anti,syn (**2.27**) using the *Z*-alkene (Scheme **15**). The relative stereochemistry of each was confirmed by X-ray crystallography. We believe the acetate functionality actually participates in the initial attack of the electrophilic chlorine. The resultant oxocarbenium ion can either be attacked by some exogenous nucleophile, or by H_2O, forming the tertiary alcohol.



Scheme 16. Proposed mechanism of 7-membered ring formation.

The final isolable component from the reaction mixture generated from the acetate protected substrate was more difficult to identify. The isolated compound is either the 1,4-dichlorination product **2.26b,** or 7-membered ring **2.26a**. The best explanation for the formation of **2.26a** involved a 1,5-hydride shift of **2.28**, followed by cyclization of **2.29**, and subsequent elimination. The cyclization could reasonably occur by either direct formation of the 7-

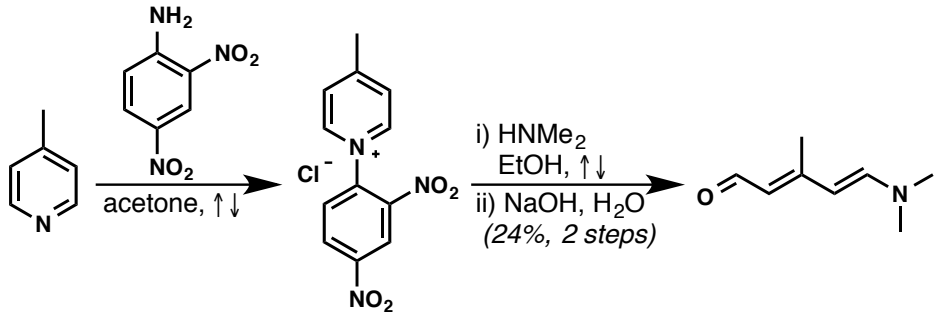
membered ring **2.31**, or formation of 6-membered ring **2.30** followed by a ring expansion. The plausibility of the hydride shift is much less certain. There are a number of reports of 1,5-hydride shifts in the literature, and they have been well studied in the context of taxane ring systems.[14] However, in all literature reports, the substrates that undergo these 1,5-hydride shifts are cyclic. It is unknown if acyclic substrates can adopt a conformation that allows a 1,5-hydride shift to occur. There are also no examples of a 1,5-hydride shift being promoted by chloronium formation. In our case, even though the substrate seems poised to undergo this type of transformation, we do not have direct evidence that the proposed hydride shift occurs. Because of this, the most likely structure is **2.26b**.

2.5 Conclusion

We successfully evaluated the viability of the diene dichlorination strategy, but ultimately the route had to be abandoned due to the failure of the key dichlorination reaction. The Zincke aldehyde route, although successful, was not able to produce enough material to properly test the key dichlorination. Thankfully, an alternative route successfully produced the necessary model system for dichlorination in six steps with 9% overall yield of model substrate **2.22**. We learned that while diene systems could potentially serve as dichlorination precursors, they are prone to a number of side reactions that significantly complicate the desired dichlorination.

2.6 Experimental Procedures

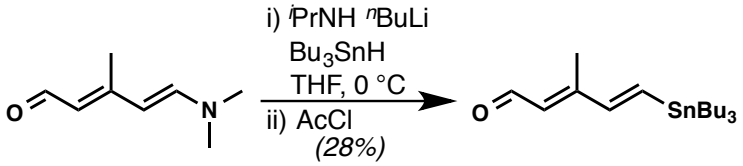
^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using Bruker DRX spectrometers at either 500 or 600 MHz (1H) and 125 MHz (13C). The chemical shifts are reported in parts per million (ppm) using the deuterated solvent as the internal reference. Coupling constants are reported in Hertz (Hz) and the peak multiplicity is listed as follows: s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet. Infrared spectra were obtained using a Perkin-Elmer Spectrum RXI FT-IR instrument. High-resolution mass spectra were obtained with a Waters LCT Premier mass spectrometer. All column chromatography was performed using Dynamic Adsorbents 230-400 mesh silica gel (SiO_2) with the indicated solvent system, unless otherwise noted. All reactions were carried under an argon atmosphere using flame-dried or oven-dried glassware. All solvents were dried by passing through activated alumina columns.



(2E,4E)-3-Methyl-5-N,N-dimethylamino-2,4-pentadien-1-al (2.7)

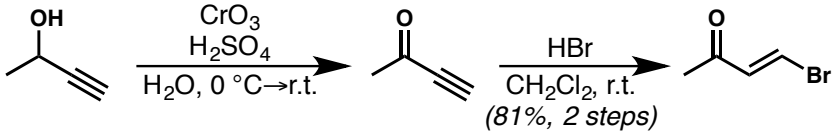
In a 1 L round bottom flask, 4-picoline (10.0 mL, 9.56 g, 102.7 mmol, 1 equiv.) was dissolved in acetone (200 mL), and 2,4-dinitrochlorobenze (20.79 g, 102.65 mmol, 1 equiv.) was added in a single portion. The flask was fitted with a reflux condenser and the mixture was heated at reflux overnight. The reaction was cooled to room temperature, and the acetone removed in vacuo to give a purple goo. EtOH (250 mL) was added to dissolve the purple goo, followed by dropwise addition of Me_2NH (40% wt/wt in H_2O, 31.2 mL) with stirring. Vessel was sealed and stirred overnight at room temperature. Ice water (250 mL) was added, stirred for 1 h, 4M NaOH (50

mL) added, stirred 5 min, filtered through Hirsch funnel to remove black solids, extracted with CH_2Cl_2 (3 x 75 mL), the organic layer dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (9:1 CH_2Cl_2:MeOH) afforded a 3:1 mixture of (2E/Z,4E)-3-Methyl-5-N,N-dimethylamino-2,4-pentadien-1-al (**2.7**) as a purpleish solid (3.50 g, 24%). *E*-isomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.86 (d, *J* = 8.7, 1H), 6.91 (d, *J* = 13.3, 1H), 5.75 (d, *J* = 8.7, 1H), 5.11 (d, *J* = 13.3, 1H), 2.93 (s, 6H), 2.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.3, 149.7, 146.5, 124.8, 120.5, 101.0, 21.6, 12.5.



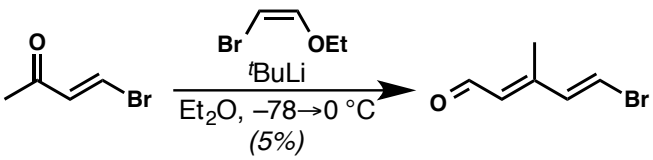
(2*E*,4*E*)- 5-(tributylstannyl)- 3-methyl-2,4-pentadien-1-al (2.8)

To a flask containing ^{i}Pr$_2$NH (0.39 mL, 0.281 g, 2.8 mmol, 1.3 equiv) in THF (10 mL) at 0 °C was added ^{n}BuLi (2.5M in hexanes, 1.04 mL, 2.6 mmol, 1.2 equiv) and stirred 10 minutes. Bu_3SnH (0.65 mL, 0.703 g, 2.4 mmol, 1.1 equiv) was added dropwise, stirred 15 min. (2E,4E)-3-Methyl-5-N,N-dimethylamino-2,4-pentadien-1-al (**2.7**) in 10 mL THF was added dropwise, the reaction mixture was warmed to r.t. and stirred 10 min. Quenched with AcCl (4 mL), washed with saturated aqueous $NaHCO_3$ (10 mL), extracted with CH_2Cl_2, the organic layer dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (98:2 hexanes:EtOAc) afforded (2*E*,4*E*)- 5-(tributylstannyl)- 3-methyl-2,4-pentadien-1-al (**2.8**) as a yellow oil (0.234 g, 28%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.15 (d, *J* = 8.1, 1H), 7.03 (d, *J* = 19.3, 1H), 6.68 (d, *J* = 19.4, 1H), 5.91 (d, *J* = 8.1, 1H), 2.25 (s, 3H), 1.51 (t, *J* = 7.8, 6H), 1.32 (q, *J* = 7.3, 6H), 0.96 (appar. t, *J* = 8.2, 6H), 0.90 (t, *J* = 7.3, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.4, 154.5, 148.9, 141.8, 129.3, 29.2, 27.4, 13.8, 12.6, 9.8.



(E)-1-bromo-1-buten-3-one (2.11)

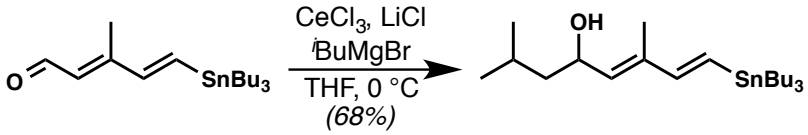
To an Erlenmeyer flask containing CrO_3 (4.362 g, 43.6 mmol, 1.26 equiv) was added H_2O (78 mL) followed by 18M H_2SO_4 (15.6 mL). This solution was added dropwise over 30 min to a flask containing 3-butyn-2-ol (2.496 g, 3.0 mL, 34.6 mmol, 1.0 equiv) in 4.5M H_2SO_4 (100 mL, prepared from 78 mL H_2O + 22.8 mL H_2SO_4) stirring at 0 °C. After addition, reaction was brought to r.t. and stirred 4h. Quenched with solid $NaHCO_3$ (added in portions until fizzing stopped), extracted with CH_2Cl_2 (3 x 45 mL), the organic layer dried over $MgSO_4$ and filtered. To the CH_2Cl_2 solution containing methyl ethynyl ketone (**2.10**) was added 48% aq. HBr (20 mL) at r.t., and the mixture stirred 2.5 h. Quenched with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2 (3 x 30 mL), the organic layer dried over $MgSO_4$, filtered and carefully concentrated in vacuo to afford (E)-1-bromo-1-buten-3-one (**2.11**) as a yellow solid (4.193 g, 81%). This compound melts at body-temperature, and can be stored neat at –20 °C with minimal decomposition, slowly turning brown. It rapidly decomposes at r.t. into a black fuming tar. R_f = 0.83, 4:1 hexanes:EtOAc; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, J = 14.1, 1H), 6.79 (d, J = 14.1, 1H), 2.26 (s, 3H).



(2*E*,4*E*)-5-bromo-3-methylpenta-2,4-dien-1-al (2.4)

To a solution of cis-1-bromo-2-ethoxyethylene (0.234 g, 1.55 mmol, 1.0 eq) in dry Et_2O (15 mL) was added ^{t}BuLi (2.45 mL, 1.4 M, 3.10 mmol, 2.0 eq) over 25 min at –78 °C. After addition was completed, the reaction was allowed to stir for 30 min at –78 °C, at which point the solution was

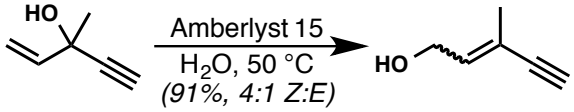
cannulated into a flask containing 1-bromo-1-buten-3-one (**2.11**) (0.230 g, 1.55 mmol, 1.0 eq) in Et_2O (15 mL) at –78 °C. Reaction was stirred for 1 h at –78 °C, then brought to 0 °C and stirred for 30 min, then warmed to room temperature. Reaction was filtered through a plug of silica with CH_2Cl_2 eluent under a stream of argon. Flash chromatography (SiO_2, 95:5 hexanes:Et_2O) afforded (2*E*,4*E*)-5-bromo-3-methylpenta-2,4-dien-1-al (**2.4**) as an air-sensitive yellow oil (13 mg, 5%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.12 (d, *J* = 7.9, 1H), 6.90 (q, *J* = 14.0, 8.8, 2H), 5.93 (d, *J* = 8.5, 1H), 2.26 (d, *J* = 1.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.1, 140.4, 129.9, 125.5, 110.0, 29.8.



(5*E*,7*E*)-2,6-dimethyl-8-(tributylstannyl)octa-5,7-dien-4-ol (2.12)

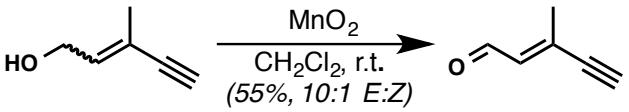
To a flask containing anhydrous $CeCl_3$ (0.320 g, 1.30 mmol, 5.0 eq) and LiCl (0.116 g, 2.74 mmol, 10.5 eq) was added THF (3.0 mL). Suspension was stirred at room temperature for 18 h, at which point (2*E*,4*E*)-3-Methyl-5-(tributylstannyl)-2,4-pentadien-1-al (**2.8**) (0.102 g, 0.26 mmol, 1.0 eq) in THF (1.0 mL) was added via syringe and stirred at room temperature for 30 min, then cooled to 0 °C. *i*BuMgBr (0.40 mL, 2.0 M, 0.75 mmol) was then added dropwise via syringe at 0 °C. The solution was stirred at 0 °C for 30 min and quenched with H_2O (1 mL). Extracted with CH_2Cl_2 (3 x 3 mL) and washed with H_2O (2 x 2 mL), then dried over $MgSO_4$. Flash chromatography (SiO_2, 98:2 hexanes:EtOAc) afforded (5*E*,7*E*)-2,6-dimethyl-8-(tributylstannyl)octa-5,7-dien-4-ol (**2.12**) as a pale yellow oil (80 mg, 68%) contaminated with minor *Z* isomer (4:1 *E*:*Z*). *E*-isomer (R_f = 0.55, 4:1 hexanes:EtOAc), ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.53 (d, *J* = 19.3, 1H, C7-*H*), 6.24 (d, *J* = 19.3, 1H, C8-*H*), 5.42 (d, *J* = 8.7, 1H, C5-*H*), 4.61–4.56 (m, 1H, C4-*H*), 1.81 (s, 3H, C10-*H*), 1.74–1.66 (m, 1H, C3-*H*), 1.58–1.46 (m, 8H, C3-

H, C2-*H*, C11-*H*), 1.31 (q, *J* = 7.3, 6H, C1-*H*), 0.98–0.86 (m, 21H, C11–14-*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.3 (C5), 136.7 (C6), 134.5 (C7), 128.3 (C8), 67.3 (C4), 46.7 (C3), 29.2 (C11), 27.4 (C10), 24.6 (C2), 23.1 (C12), 22.6 (C13), 13.8 (C1), 9.5 (C14); *Z*-isomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (d, *J* = 19.2, 1H), 6.34 (d, *J* = 19.2, 1H), 5.32 (d, *J* = 8.8), 4.81–4.76 (m, 1H), 1.84 (s, 3H), 1.74–1.66 (m, 1H), 1.58–1.46 (m, 8H), 1.31 (q, *J* = 7.3), 0.98–0.86 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5, 135.5, 132.2, 131.8, 65.6, 46.9, 30.7, 29.2, 24.6, 23.1, 22.6, 13.8, 9.5; IR (thin film) ν 3676, 3278, 2956, 2925, 2870, 2853, 1566, 1464, 1376, 985 cm^{-1}; attempts to find parent peak in MS failed due to fragmentation.



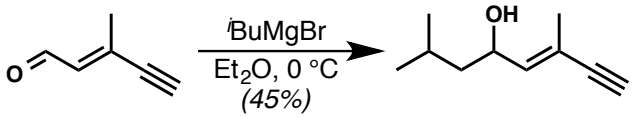
3-methyl-2-penten-4-yn-1-ol (2.15)

To a flask containing 3-methyl-1-penten-4-yn-3-ol (**2.14**) (2.458 g, 25.6 mmol, 1.0 equiv) was added H_2O (20 mL), followed by Amberlyst 15 (3.0 g). Stirred at 50 °C at ~350 rpm overnight. Cooled to room temperature, filtered through a sintered glass funnel to remove the Amberlyst 15, the solids washed with CH_2Cl_2, the aqueous layer extracted with CH_2Cl_2 (3 x 25 mL), the combined organic extracts washed with saturated aqueous $NaHCO_3$ (15 mL), dried over $MgSO_4$ and concentrated in vacuo to afford 4:1 *Z:E* mixture of 3-methyl-2-penten-4-yn-1-ol (**2.15**) as a yellow oil (2.244 g, 91%). *Z*-isomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95 (t, *J* = 6.8, 1H), 4.33 (d, *J* = 6.8, 2H), 3.17 (s, 1H), 1.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5, 120.1, 82.3, 81.9, 61.4, 23.1.



3-methyl-1-penten-4-yn-3-al (2.16)

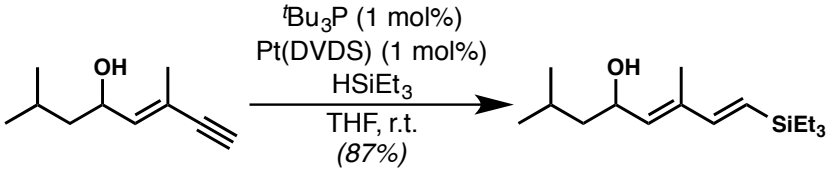
To a solution of 3-methyl-1-penten-4-yn-3-ol (**2.15**) (0.501 g, 5.21 mmol, 1 equiv) in CH_2Cl_2 (50 mL) was added MnO_2 (4.521 g, 52 mmol, 10 equiv) in a single portion. The flask was capped, covered in aluminum foil, and stirred overnight at room temperature. The reaction was filtered though a plug of silica gel in a sintered glass funnel, the filter cake rinsed with CH_2Cl_2 (3 x 15 mL), and the resulting solution carefully concentrated in vacuo, with the water bath being kept at 0 °C to prevent product loss to afford 3-methyl-1-penten-4-yn-3-al (**2.16**) as a pale yellow oil (0.270 g, 2.87 mmol, 55%). *E*-isomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.03 (d, J = 8.1, 1H), 6.23 (d, J = 8.1, 1H), 3.56 (s, 1H), 2.14 (d, J = 1.4, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.7, 141.1, 136.8, 88.0, 80.1, 24.7.



(*E*)-2,6-dimethyloct-5-en-7-yn-4-ol (2.17)

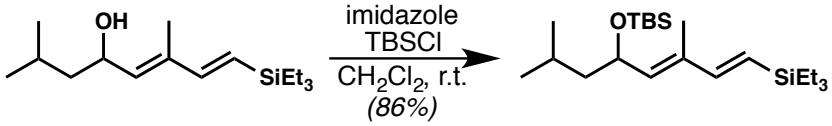
To a solution of 3-methyl-1-penten-4-yn-3-al (**2.16**) (0.296 g, 3.15 mmol, 1 equiv) in Et_2O (10 mL) at 0 °C was added ^{i}BuMgBr (2.0 M in Et_2O, 2.2 mL, 1.4 equiv) dropwise over 10 minutes. The reaction mixture was stirred for 45 minutes and quenched with H_2O (5 mL). Extracted with Et_2O (3 x 10 mL), the organic extracts dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (98:2 hexanes:EtOAc) afforded (*E*)-2,6-dimethyloct-5-en-7-yn-4-ol (**2.17**) as a clear oil (0.216 g, 45%). *E*-isomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (d, J = 9.3, 1H), 4.68 (q, J = 7.5, 1H), 3.14 (s, 1H), 1.88 (d, J = 1.3, 3H), 1.69 (septet, J = 6.7, 1H), 1.62 (br s, OH), 1.51

(quintet, J = 6.9, 1H), 1.32 (quintet, J = 6.4, 1H), 0.94 (d, J = 1.9, 3H), 0.93 (d, J = 1.9, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.0, 118.9, 82.2, 81.9, 69.1, 45.9, 24.7, 23.2, 23.1, 22.7.



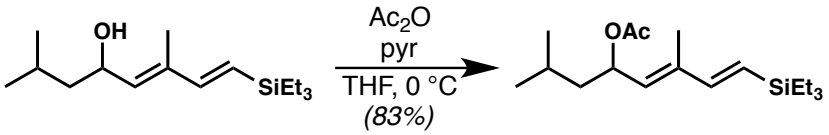
(5*E*,7*E*)-8-(triethylsilane)-2,6-dimethyl-5,7-octadiene-4-ol (2.19)

To a flask charged with ^{t}Bu$_3$P (0.004g, 0.02 mmol, 1 mol%) was added Pt(DVDS) (202.5µL, 0.02 mmol, 1 mol%, 2% soln. in xylenes), THF (15 mL), and triethylsilane (1.4 mL, 8.56 mmol, 4 eq). Solution was stir for 30 min at room temperature, then (*E*)-2,6-dimethyloct-5-en-7-yn-4-ol (**2.17**) (0.327 g, 2.14 mmol, 1.0 eq) in THF (5.0 mL) was added dropwise via syringe over 30 min. Solution was stirred for 18 h at room temperature then concentrated *in vacuo*. Flash chromatography (SiO_2, 98:2 hexanes:EtOAc) afforded (5*E*,7*E*)-8-(triethylsilane)-2,6-dimethyl-5,7-octadiene-4-ol (**2.19**) as a yellow oil (0.501 g, 87%). (R_f = 0.55, 4:1 hexanes:EtOAc) ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (d, J = 19.0, 1H, C7-*H*), 5.89 (d, J = 19.0, 1H), 5.37 (d, J = 8.8, 1H), 4.77 (m, 1H), 1.84 (s, 3H), 1.67 (m, 1H), 1.53 (m, 1H), 1.44 (s, OH), 1.30 (m, 1H), 0.93 (d, J = 6.5, 6H, and q, J = 7.9, 9H); ^{13}C NMR (125 MHz, CDCl3): δ 141.1, 135.4, 133.4, 128.0, 65.8, 47.0, 24.7, 23.1, 22.7, 20.2, 7.5, 3.6; IR (thin film) ν 2955, 2936, 2911, 2876, 1724, 1680, 1458, 1415, 1368, 1238, 1061, 1005 cm^{-1}; attempts to find parent peak in MS failed due to fragmentation.



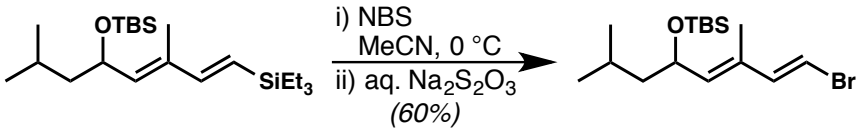
(5*E*,7*E*)-8-(triethylsilane)-2,6-dimethyl-4-(*tert*-butyldimethylsiloxy)-5,7-octadiene (2.21)

To a solution of (5*E*,7*E*)-8-(triethylsilane)-2,6-dimethyl-5,7-octadiene-4-ol (**2.19**) (0.105 g, 0.39 mmol, 1.0 eq) in CH_2Cl_2 (12 mL) was added imidazole (0.054 g, 0.80 mmol, 2.0 eq) and stirred at room temperature for 10 min, then TBSCl (0.106 g, 0.70 mmol, 1.8 eq) and the solution stirred at room temperature for 5 h. Solution was diluted with hexanes (5 mL), rinsed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over $MgSO_4$, concentrated in vacuo, then filtered through a plug of silica with hexane eluent to afford (5*E*,7*E*)-8-(triethylsilane)-2,6-dimethyl-4-(*tert*-butyldimethylsiloxy)-5,7-octadiene (**2.21**) as a clear oil (0.129 g, 86%) contaminated with minor C5 *Z*-isomer (9:1 *E*:*Z*). *E*-isomer (R_f = 0.28, hexanes) ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (d, *J* = 19.0, 1H, C8-*H*), 5.81 (d, *J* = 19.0, 1H, C7-*H*), 5.32 (d, *J* = 8.9, 1H, C5-*H*), 4.74 (td, *J* = 8.3, 6.0, 1H, C4-*H*), 1.81 (s, 3H, C9-*H*), 1.66 (m, 1H, C3-*H*), 1.49 (m, 1H, C3-*H*), 1.20 (m, 1H, C2-*H*), 0.95 (t, *J* = 7.8, 12H, C11-*H*), 0.92 (d, *J* = 1.1, 6H, C1-*H*), 0.87 (s, 9H, C13-*H*), 0.60 (q, *J* = 7.7, 6H, C10-*H*), 0.10 (s, 6H, C12-*H*), 0.02 (t, *J* = 8.2, 12H, C11-*H*); ^{13}C NMR (125 MHz, CDCl3): δ 141.7 (C5), 135.1 (C7), 132.6 (C6), 126.5 (C8), 66.6 (C4), 48.0 (C3), 26.1 (C9), 25.9 (C12), 25.8 (C12), 24.3 (C10), 23.3 (C10), 22.5 (C10), 20.0 (C2), 7.5 (C1), 3.7 (C11), –2.8 (C13), –3.4 (C13), –4.0 (C13), –4.7 (C14); *Z*-isomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.51 (d, *J* = 19.1, 1H), 5.70 (d, *J* = 19.1, 1H), 5.43 (d, *J* = 8.6, 1H), 4.53 (td, *J* = 8.3, 6.0, 1H), 1.81 (s, 3H), 1.66 (m, 1H), 1.49 (m, 1H), 1.20 (m, 1H), 0.95 (t, *J* = 7.8, 12H), 0.92 (d, *J* = 1.1, 6H), 0.87 (s, 9H), 0.60 (q, *J* = 7.7, 6H), 0.10 (s, 6H), 0.02 (t, *J* = 8.2, 12H); ^{13}C NMR (125 MHz, CDCl3): δ 149.7, 144.5, 137.7, 133.6, 68.1, 47.6, 26.0, 25.9, 25.8, 24.3, 23.3, 22.5, 20.0, 7.5, 3.7, –2.8, –3.4, –4.0, –4.7; IR (ATIR) ν 2953, 2928, 2876, 2857, 1464, 1252, 1067, 1003 cm^{-1}; HRMS (CI/NH_4^+) *m / z* calcd for $C_{22}H_{46}OSi_2^+$ 382.3087 (M^+), found 382.3092 (M^+).



(5*E*,7*E*)-8-(triethylsilane)-2,6-dimethyl-4-acetoxy 5,7-octadiene (2.20)

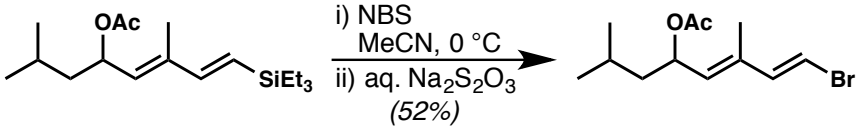
To a solution of (5*E*,7*E*)-8-(triethylsilane)-2,6-dimethyl-5,7-octadiene-4-ol (**2.19**) (0.266 g, 0.99 mmol, 1.0 eq) in THF (10 mL) at 0 °C was added pyridine (0.32 ml, 3.98 mmol, 4.0 eq) and stirred for 5 min. Acetic anhydride (0.20 ml, 1.99 mmol, 2.0 eq) was added and allowed to stir at 0 °C for 4 h. Solution was transferred to a separatory funnel containing saturated aqueous $NaHCO_3$ (5 mL), extracted with CH_2Cl_2 (3x 15 mL), washed with brine (10 mL), dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (SiO_2, 98:2 hexanes:EtOAc) afforded (5*E*,7*E*)-8-(triethylsilane)-2,6-dimethyl-4-acetoxy 5,7-octadiene (**2.20**) as a pale yellow oil (0.255 g, 83%). (R_f = 0.69, 5:1 hexanes:EtOAc); 5*E*-isomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (d, *J* = 19.0, 1H), 5.90 (d, *J* = 19.0, 1H), 5.29 (d, *J* = 9.1, 1H), 2.02 (s, 3H), 1.84 (s, 3H), 1.63–1.54 (m, 2H), 1.39–1.34 (m, 1H), 0.95 (t, *J* = 8.0, 9H), 0.91 (d, *J* = 7.2, 3H and d, *J* = 6.7, 3H), 0.61 (q, *J* = 7.9, 6H); ^{13}C NMR (125 MHz, CDCl3): δ 170.4, 141.3, 136.8, 128.7, 128.4, 68.7, 44.2, 24.5, 22.7, 22.6, 21.4, 20.0, 7.4, 3.5; accurate mass (CI/NH_4^+) *m / z* calcd for $C_{18}H_{34}O_2SiNa$ 333.2226 $(M + Na)^+$, found 333.2219 $(M + Na)^+$.



(5*E*/5*Z*,7*E*)-8-bromo-2,6-dimethyl-4-(*tert*-butyldimethylsiloxy) 5,7-octadiene (S2.1)

To a solution of (5*E*,7*E*)-8-(triethylsilane)-2,6-dimethyl-4-(*tert*-butyldimethylsiloxy)-5,7-octadiene (**2.21**) (0.399 g, 1.04 mmol) in 3:1 MeCN:CH_2Cl_2 (16 mL) at 0 °C was added a solution of NBS (0.185 g, 1.04 mmol, 1.0 eq) in a single portion. The reaction mixture was stirred at 0 °C for 2 h, warmed to r.t., covered in aluminum foil and stirred overnight. The

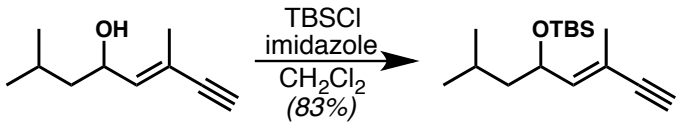
reaction mixture was cooled back to 0 °C, quenched with a saturated aqueous solution of $Na_2S_2O_3$ (2.0 mL), stirred 10 minutes, extracted with CH_2Cl_2 (3 x 5 mL), the organic layer washed with brine (1 x 5 mL), dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (SiO_2, 100:0–99:1 hexanes:EtOAc) afforded (5*E*/5*Z*,7*E*)-8-bromo-2,6-dimethyl-4-(*tert*-butyldimethylsiloxy) 5,7-octadiene (**S2.1**) as a pale yellow oil (0.217 g, 60%); *E*-isomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (d, *J* = 13.6, 1H), 6.32 (d, *J* = 13.6, 1H), 5.31 (d, *J* = 8.7, 1H), 4.54 (q, *J* = 8.1, 1H), 1.80 (s, 3H), 1.67 (septet, *J* = 6.8, 1H), 1.49 (appar quintet, *J* = 6.5, 1H), 1.18 (appar quintet, *J* = 5.7, 1H), 0.91 (appar t, *J* = 6.4, 3H), 0.87 (s, 9H), 0.04 (s, 3H), –0.01 (s, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 136.1, 134.6, 129.6, 107.7, 67.0, 47.8, 26.0, 24.3, 23.5, 22.4, 20.1, –3.9, –4.6.



(5*E*/5*Z*,7*E*)-8-bromo-2,6-dimethyl-4-acetoxy 5,7-octadiene (2.22)

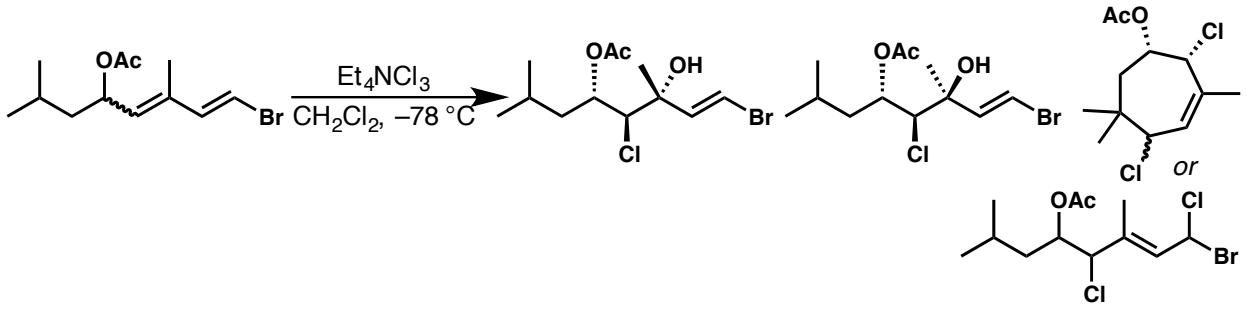
To a solution of (5*E*,7*E*)-8-(triethylsilane)-2,6-dimethyl-4-acetoxy 5,7-octadiene (**2.20**) (0.264 g, 0.85 mmol) in MeCN (7 mL) at 0 °C was added a solution of NBS (0.151 g, 0.85 mmol, 1.0 eq) in MeCN (3 mL) dropwise over 5 min, and reaction mixture was stirred at 0 °C for 2 h. A saturated aqueous solution of $Na_2S_2O_3$ (2.0 mL) was added and the mixture warmed to r.t., extracted with CH_2Cl_2 (2 x 5 mL), the organic layer washed with brine (1 x 5 mL), dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (SiO_2, 100:0–99:1 hexanes:EtOAc) afforded (5*E*/5*Z*,7*E*)-8-bromo-2,6-dimethyl-4-acetoxy 5,7-octadiene (**2.22**) as a pale yellow oil (0.124 g, 52%) as a 4:1 mixture of 5*E*:5*Z* isomers. (R_f = 0.60, 5:1 hexanes:EtOAc); *E*-isomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.69 (d, *J* = 13.8, 1H), 6.31 (d, *J* = 13.8, 1H), 5.63–5.58 (m, 1H), 5.32 (d, *J* = 9.1, 1H), 2.00 (s, 3H), 1.84 (s, 3H), 1.59 (appar octet, *J* = 7.0, 2H), 1.34 (appar

nonet, J = 6.6, 1H), 0.91 (d, J = 2.9, 3H), 0.90 (d, J = 2.9, 3H),); ^{13}C NMR (125 MHz, CDCl3): δ 170.4, 141.1, 131.6, 109.3, 106.6, 69.4, 43.6, 24.5, 22.8, 22.6, 21.3, 12.9.



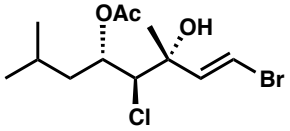
(*E*)-2,6-dimethyl-4-(*tert*-butyldimethylsiloxy)-oct-5-en-7-yn (2.23)

To a solution of (*E*)-2,6-dimethyloct-5-en-7-yn-4-ol (**2.17**) (50 mg, 0.33 mmol, 1.0 eq) in CH_2Cl_2 (3 mL) at room temperature was added imidazole (32 mg, 0.40 mmol, 1.2 eq) and stirred for 5 min, then TBSCl (67 mg, 0.36 mmol, 1.1 eq) was added and the solution stirred at room temperature for 3 h. Solution was diluted with hexanes (5 mL), rinsed with saturated aqueous $NaHCO_3$ (2 mL) and brine (2 mL), dried over $MgSO_4$, concentrated in vacuo, then filtered through a plug of silica with hexane eluent to afford (*E*)-2,6-dimethyl-4-(*tert*-butyldimethylsiloxy)-oct-5-en-7-yn (**2.23**) as a clear oil (62 mg, 83%) contaminated with minor *Z*-isomer (9:1 *E*:*Z*). *E*-isomer (R_f = 0.74, 4:1 hexanes:EtOAc) ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.64 (d, J = 8.8, 1H), 4.65–4.61 (m, 1H), 3.11 (s, 1H), 1.84 (s, 3H), 1.71–1.62 (m, 1H), 1.48–1.42 (m, 1H), 1.25–1.20 (m, 1H), 0.92 (d, J = 6.6, 3H), 0.89 (d, J = 6.6, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, CDCl3): δ 143.4, 116.3, 82.5, 81.3, 69.9, 47.1, 26.0, 25.9, 24.2, 23.4, 22.9, 22.4, –4.2, –4.9; *Z*-isomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (dd, J = 8.87, 1.0, 1H), 4.45–4.40 (m, 1H), 2.77 (s, 1H), 1.80 (d, J = 1.3, 3H), 1.71–1.62 (m, 1H), 1.48–1.42 (m, 1H), 1.25–1.20 (m, 1H), 0.92 (d, J = 6.6, 3H), 0.89 (d, J = 6.6, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, CDCl3): δ 143.3, 115.7, 86.3, 74.3, 67.5, 46.9, 25.9, 24.1, 23.4, 22.9, 22.2, –4.2, –4.9; IR (thin film) ν 2955, 2927, 2856, 1466, 1362, 1256, 1076, 998, 837, 776 cm^{-1}; HRMS (EI/DCM) *m/z* calculated for $C_{10}H_{31}OSi$ $(M + H)^+$ 267.2704, found 267.2709 $(M + H)^+$.



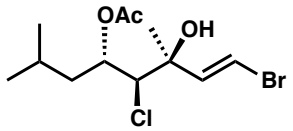
2.24, 2.25, and 2.26a/226b

To a solution of (5*E*/5*Z*,7*E*)-8-bromo-2,6-dimethyl-4-acetoxy 5,7-octadiene (**2.22**) (0.015 g, 0.036 mmol) in CH_2Cl_2 (1.0 mL) at –78 0 °C was added a solution of Et_4NCl_3 (0.016 g, 0.066 mmol, 1.8 eq) in CH_2Cl_2 (0.75 mL) dropwise over 10 min. The reaction mixture was allowed to stir at –78 0 °C for 3 h, then was quenched with saturated aqueous $Na_2S_2O_3$ (0.5 mL). Extracted with CH_2Cl_2 (3 x 2 mL), washed with brine (1 x 1 mL), dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (100:0–95:5 hexanes:EtOAc) afforded **2.24** as a colorless crystalline solid, **2.25** as a colorless crystalline solid, and **2.26** as a colorless oil.



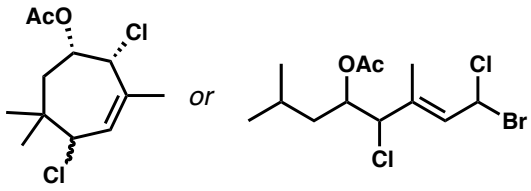
(±)(3*R*,4*S*,5*S*,1*E*)-4-chloro-5-acetoxy-3,7-dimethyl-1-en-3-ol (2.24)

(R_f = 0.41, 5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.49 (d, *J* = 13.4, 1H), 6.32 (dd, *J* = 13.4, 1.1, 1H), 5.17 (appar dq, *J* = 10.3, 1.9, 1H), 4.10 (d, *J* = 3.6, 1H), 2.40 (d, *J* = 1.0, 1H), 2.08 (s, 3H), 1.73 (t, *J* = 10.8, 1H), 1.61 (appar td, *J* = 10.2, 1.9, 1H), 1.42 (s, 3H), 0.92 (d, *J* = 6.4, 3H), 0.85 (d, *J* = 6.1, 3H)); ^{13}C NMR (125 MHz, CDCl3): δ 171.4, 138.8, 107.3, 75.5, 72.3, 71.2, 38.6, 28.5, 24.4, 23.8, 21.6, 21.3; IR (ATIR) ν 3287, 2954, 2924, 2852, 1718, 1624, 1464, 1373, 1242 cm^{-1}; accurate mass (CI/NH_4^+) *m / z* calcd for $C_{12}H_{20}BrClO_3NH_4$ 344.0628 $(M+NH_4)^+$, found 382.0638 $(M+NH_4)^+$.



(±)(3*S*,4*S*,5*S*,1*E*)-4-chloro-5-acetoxy-3,7-dimethyl-1-en-3-ol (2.25

(R_f = 0.27, 5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.44 (d, *J* = 13.5, 1H), 6.32 (d, *J* = 13.5, 1H), 5.33–5.30 (m, 1H), 4.04 (d, *J* = 2.9, 1H), 2.57 (s, 1H), 2.09 (s, 3H), 1.77 (qd, *J* = 10.7, 3.2, 1H), 1.63–1.57 (m, 1H), 1.46 (s, 3H), 0.93 (d, *J* = 6.5), 0.89 (d, *J* = 6.4); ^{13}C NMR (125 MHz, CDCl3): δ 171.2, 140.6, 107.7, 76.0, 71.7, 71.3, 39.2, 26.3, 24.6, 23.8, 21.6, 21.3; accurate mass (CI/NH_4^+) *m / z* calcd for $C_{12}H_{20}BrClO_3NH_4$ 344.0628 $(M+NH_4)^+$, found 382.0638 $(M+NH_4)^+$.



(±)(3*R*,4*S*)-3,7-dichloro-4-acetoxy-2,6,6-trimethylcycloheptene (2.26a/2.26b)

(R_f = 0.59, 5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.41 (dd, *J* = 9.8, 2.5, 1H), 6.14 (d, *J* = 9.8, 1H), 5.27 (tt, *J* = 6.8, 3.1, 1H), 4.27 (d, *J* = 6.8, 1H), 2.10 (s, 3H), 1.83 (d, *J* = 1.2, 3H), 1.55–1.50 (m, 1H), 1.24–1.19 (m, 1H), 0.92 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (125 MHz, CDCl3): δ 170.5, 134.4, 131.5, 71.7, 67.8, 51.9, 41.2, 24.7, 23.5, 21.9, 21.1, 13.4; IR (ATIR) ν 2956, 2924, 1741, 1641, 1466, 1370, 1227 cm^{-1}; accurate mass (CI/NH_4^+) *m / z* calcd for $C_{12}H_{18}Cl_2O_2NH_4$ 282.1028 $(M+NH_4)^+$, found 282.1018 $(M+NH_4)^+$.

2.7 References

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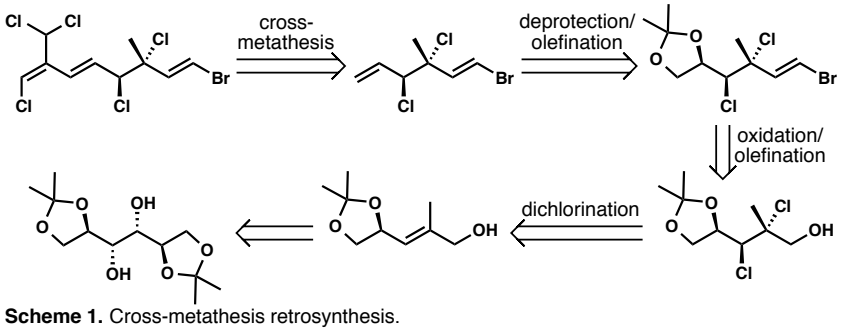
Chapter 3: Mannitol Route

3.1 Introduction

In the previous chapter, the original synthetic strategy relying on the dichlorination of a diene derived from an enynal was discussed. With this result, we decided that the next strategy needed to avoid diene dichlorination in favor of the reaction of single alkene. Although the 1,2-addition to marry the eastern and western portions of the molecule conveniently installed a secondary alcohol to direct the dichlorination, we were unsure if rendering this addition asymmetric as a means to develop an enantioselective synthesis was feasible. Additionally, a nucleophile sufficiently functionalized to complete the synthesis post 1,2-addition would have been both difficult to obtain, and might have greatly complicated the addition.

With those concerns in mind, we conceived of another approach that avoided many of those problems altogether (Scheme **1**). Instead of a 1,2-addition to join the eastern and western fragments, we envisioned a cross-metathesis could serve the same purpose while avoiding the problems of functional group tolerance associated with reagents for carbonyl addition. The requisite terminal alkene could be installed a number of ways, but we settled on a Corey–Winter olefination for the initial retrosynthesis. The terminal alkene would ultimately be derived from an acetonide-protected diol. The C1-C2 alkene would be installed post-dichlorination to avoid the issues we had observed in the prior system. The acetonide would direct the dichlorination of the nearby olefin, which brought us back to a known precursor.[1] Because we were able to take the starting materials back to a

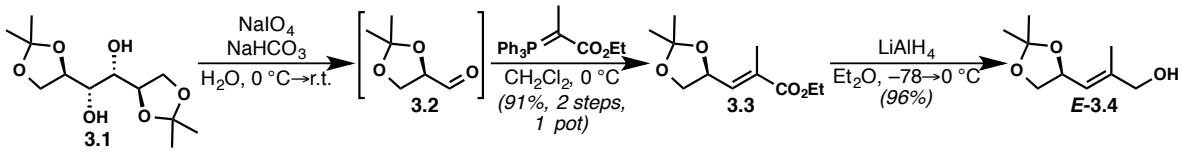


Scheme 1. Cross-metathesis retrosynthesis.

known derivative of mannitol, an asymmetric reaction in order to install the alcohol was unnecessary. Moreover, we would be able to quickly and easily test the key dichlorination step, without the need to design and synthesize a model system.

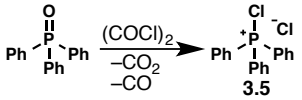
3.2 Dichlorination Precursor Synthesis

The procedure for the synthesis of the dichlorination precursor depends on which dichloride diastereomer is desired, and therefore, which olefin isomer is needed. To access the *E*-olefin, we were fortunate to be able to use the previously published work of Fukumoto to access the desired allylic alcohol (Scheme **2**).[1] Starting from diisopropylidine *D*-mannitol (**3.1**), oxidative cleavage of the vicinal diol with $NaIO_4$ furnished *R*-glyceraldehyde acetonide (**3.2**). A solution of the stabilized Wittig reagent in CH_2Cl_2 can be added directly to the crude reaction mixture to give the desired *E*-alkene **3.3**. Once purified, the isolated Wittig product **3.3** was subjected to $LiAlH_4$ reduction conditions to provide the desired allylic alcohol ***E*-3.4** in excellent yields. Although Fukumoto performed the reduction using DIBAL in CH_2Cl_2, we preferred $LiAlH_4$ for cost reasons, and the workup procedure is simplified.



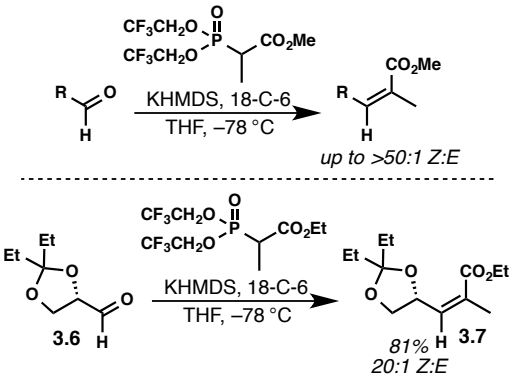
Scheme 2. Synthesis of *E*-alkene dichlorination precursor.

Initially, alkene **3.3**, resulting from the Wittig olefination, was purified by flash chromatography. On larger scale, this method of purification became cumbersome, and removal of all phosphine byproducts proved difficult. Thankfully, a chromatography-free method of phosphine removal had already been developed by Gilheany.[2] Treatment of triphenylphosphine oxide with oxalyl chloride forms the dichloride salt **3.5**, which is much less soluble and readily precipitates out of solution (Scheme **3**). This



Scheme 3. Dichlorophosphonium salt formation.

salt can be removed via filtration through celite or silica. In our case, the crude product mixture was first triturated with hexanes to remove the majority of the phosphine oxide, filtered, followed by addition of oxalyl chloride to convert the remaining phosphine oxide to the dichloride salt, which has decreased solubility and makes it much easier to remove via filtration through silica. This improved purification procedure was substantially easier to accomplish than chromatography on scales over 10 g.

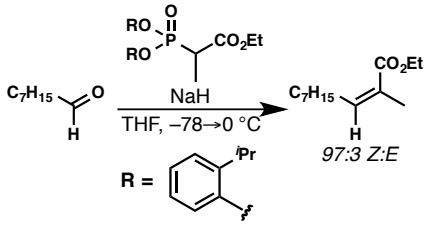


Scheme 4. Still–Gennari HWE and use by Roush.

In order to access the *Z*-alkene, which leads to the *syn*-dichloride, a *Z*-selective olefination procedure was necessary. The most well-known *Z*-selective olefination procedure is the Still-Gennari modification of the Horner–Wadsworth–Emmons (HWE) olefination (Scheme **4**). This method uses an electron-deficient phosphonate along with a potassium counterion sequestered with 18-crown-6 (18-c-6). Selectivities of >20:1 *Z:E* can be achieved depending on the exact phosphonate and aldehyde used, making it one of the most selective methods for *Z*–olefin construction.[3] This method was used by Roush on a similar aldehyde (**3.6**) in the synthesis of olefin **3.7**, achieving 81% yield with 20:1 *Z:E* selectivity.[4]

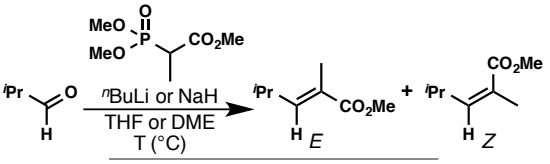
There are, however, a few issues associated with the Still–Gennari modification. The first problem is that the selectivity can be very sensitive to the aldehyde substitution. A significant drop in the *Z:E* ratio is observed in reactions involving branched, saturated aldehydes. In the case of glyceraldehyde acetonide, we observed an 8:1 *Z:E* ratio at best. However, the primary reason for our avoiding the Still-Gennari HWE modification was cost. The fluorinated phosphonate is expensive, even when starting from the requisite trifluoroethanol. Additionally, the 18-c-6 is also expensive, and is generally used in excess to achieve the highest *Z* selectivity possible. On the

scales that we needed to push forward with the synthesis (~3 g aldehyde), the cost of each reaction would have exceeded $1200, thus rendering this method prohibitively expensive.



Scheme 5. Ando olefination.

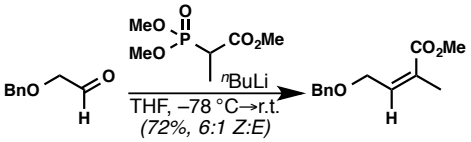
Another *Z*-selective method of olefin construction involving the modification of an HWE phosphonate is the Ando method (Scheme **5**).[5] In this iteration, the traditionally alkyl groups of the phosphonate are replaced with aryl groups. Originally, phenyl groups were used, but a later report indicated that bulky ortho-substituents further increased the *Z*-selectivity. While these aryl-substituted phosphonates are less expensive to obtain than the fluorinated phosphonates used in Still–Gennari, their synthesis is more complex, as is the purification. One large drawback of the Ando method is the extensive optimization that is often necessary to give the highest selectivity and yield possible. A number of bases are competent for the reaction, but as we discovered, selectivity can vary between each. Unfortunately, we never found conditions that gave satisfactory selectivity and yield for our substrate using this method.



base	solvent	T (°C)	*E:Z*
*n*BuLi	THF	–78	*1:3*
*n*BuLi	THF	23	*5.3:1*
NaH	THF	–78	*1:1*
NaH	THF	23	*4.3:1*
*n*BuLi	DME	–78	*1:1*
*n*BuLi	DME	23	*12:1*
NaH	DME	–78	*1:1*
NaH	DME	23	*5:1*

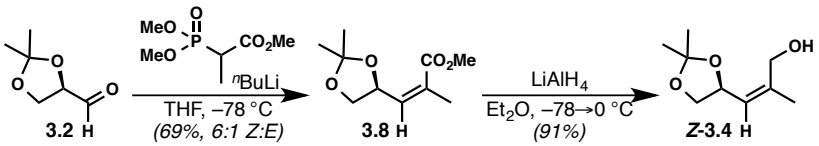
Scheme 6. Heathcock's study on the effect of counterion.

There is one other method available to selectively construct the *Z*-olefin we desired. We were made aware of this method through members of the Shea lab, Leah Cleary and Jennifer Pitzen. Heathcock has conducted a study of the effect of the counterion, temperature, and solvent on the selectivity of HWE olefinations (Scheme **6**).[6] He found that although the *E*-isomer is generally favored, at low temperature, using a lithium conterion in THF favors the *Z*-isomer in some cases, and



Scheme 7. Shea group's *Z*-selective HWE.

appears to benefit from α-alkoxy groups. The use of other counterions or DME resulted in favoring the *E*-isomer. Alpha-substitution could also be tolerated. This method was used in a publication by the Shea group to install a trisubstituted olefin in their studies on the synthesis of *N*-methylwelwitindolinone B isothiocyanate (Scheme **7**).[7]

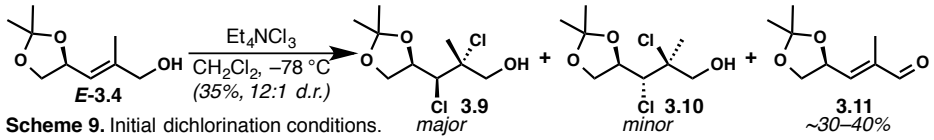


Scheme 8. Synthesis of *Z*-alkene dichlorination precursor.

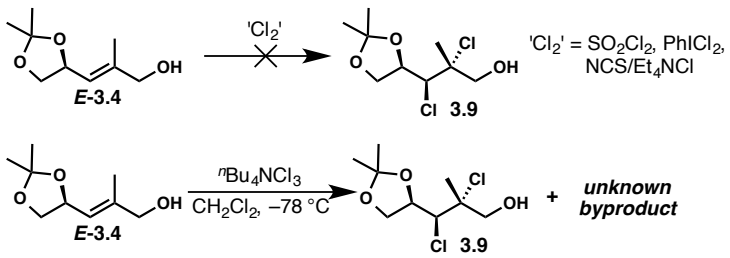
We were glad to see that the method works equally well on glyceraldehyde acetonide, giving a respectable 6:1 *Z:E* ratio with 69% isolated yield for the *Z*-alkene **3.8**, nearly identical to the Shea group's report (Scheme **8**). Moreover, this method is very cost-effective, utilizing inexpensive, readily available reagents. Reduction of the ester to the primary alcohol was carried out in the same manner as before to give the dichlorination precursor ***Z*-3.4**.

3.3 Dichlorination

At this point, we subjected the *E*-olefin to dichlorination conditions using Et_4NCl_3[8] (Scheme **9**). The initial results were very positive, with the desired dichloride **3.9** isolated in 35% yield as a single diastereomer from an initial 12:1 mixture of *syn,anti* (**3.9**) and *anti,anti* (**3.10**) products. While the selectivity was excellent, other side reactions were prevalent. A portion of the starting material was likely being consumed though deprotection of the acetonide, as evidenced by the presence of polar byproducts by TLC. However, the most prevalent side-product was oxidation of the primary alcohol to enal **3.11**, which would not undergo the dichlorination of the

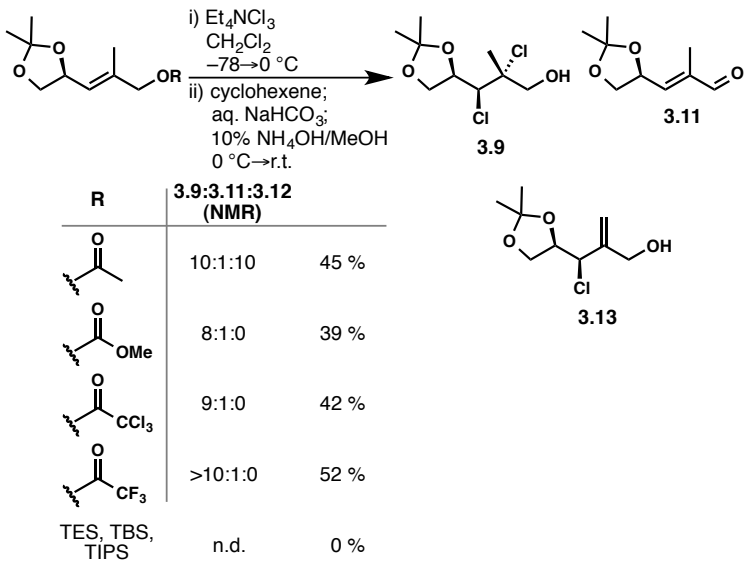


Scheme 9. Initial dichlorination conditions.



Scheme 10. Dichlorination reagent screening.

alkene. Other dichlorinating reagents were also tested, including SO_2Cl_2, $PhICl_2$, and combinations of NCS with nucleophilic chloride sources, but these alternate conditions did not give the desired dichloride product (Scheme **10**). Curiously, when $^{n}Bu_4NCl_3$ was employed, a mixture of the desired dichlorination product **3.9** and another inseparable product with the same mass and similar chemical shifts was produced. Although the enal byproduct was not as prevalent, the inability to separate the desired dichloride from the unknown compound led us to find an alternative solution.

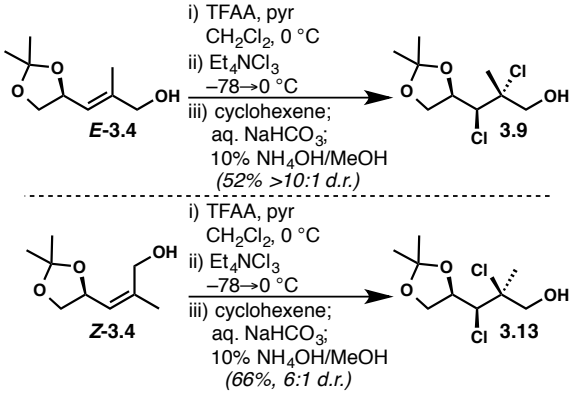


R	3.9:3.11:3.12 (NMR)	
O	10:1:10	45 %
O, OMe	8:1:0	39 %
O, CCl_3	9:1:0	42 %
O, CF_3	>10:1:0	52 %
TES, TBS, TIPS	n.d.	0 %

Scheme 11. Dichlorination protecting group screen.

Because other dichlorination conditions did not work, the obvious next step was to protect the alcohol to prevent oxidation (Scheme **11**). Strangely, when the alcohol was protected as the silyl ether, no dichlorination product was observed, and the oxidation product **3.11** was still present. When the protecting group was changed to a carbonyl based group, some improvement was seen. While acetate gave a mixture of the desired dichlorination (**3.9**) and elimination (**3.12**) products, very little of the oxidation product (**3.11**) was observed. Carbonate and trichloroacetate groups led to further improvement in yield. Finding that electron-poor groups led to higher yields, trifluoroacetate was used next. Previous reports by the Vanderwal lab stated that while trifluoroacetate can give desirable selectivity, it is too labile to survive purification.[9] However, we decided that this ease of removal could be an advantage, opening up the opportunity to carry out the protection-dichlorination-deprotection sequence in a single pot

(Scheme **12**). After very little optimization, we were able to carry out this sequence to give a 52% isolated yield of desired *anti*-dichloride **3.9** as a single diastereomer. Additionally, we found that quenching the reaction with a sacrificial alkene, in this case cyclohexene, resulted in cleaner crude material compared to that obtained from a reductive quench such as aqueous $Na_2S_2O_3$. Thankfully, dichlorination of the *Z*-alkene ***Z*-3.4** could be carried out under the previously optimized conditions to give desired *syn*-dichloride **3.13** in 66% yield. Unfortunately, the *syn,syn* and *anti,syn* diastereomers could not be separated, and the 6:1 mixture was carried on.



Scheme 12. Optimized dichlorination conditions.

Although we were relatively confident of our stereochemical assignments of each compound, the unambiguous evidence of stereochemistry provided by crystallography was highly desirable. After a number of different aromatic groups and other functionality were appended to the alcohol in an attempt to induce crystal formation, we found that appending a mesylate group onto each of the *anti*-dichlorides induced crystal formation suitable for X-ray analysis (Figure **1**). Various functional groups were appended to the alcohol of the *syn*-dichlorides, but crystal formation of these diastereomers eluded us at this point.

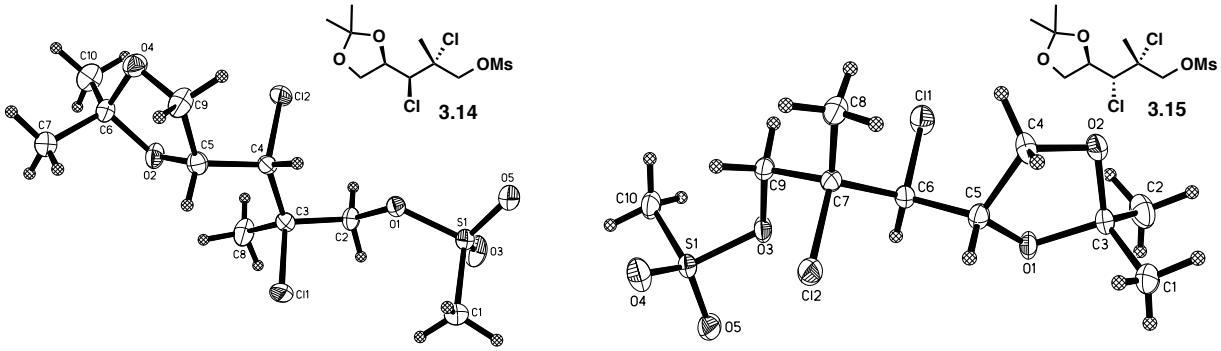
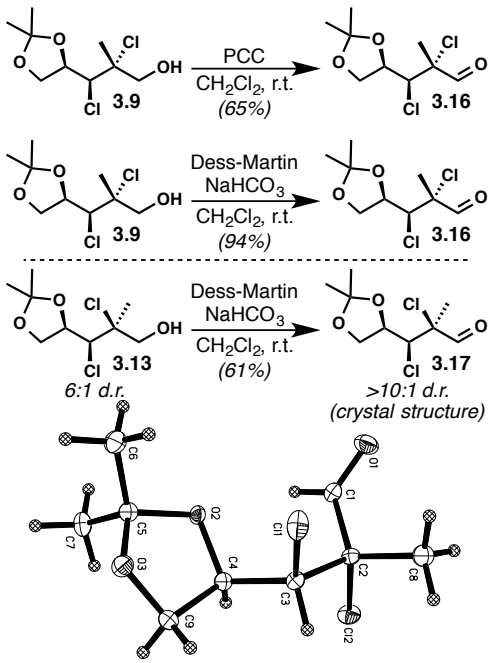


Figure 1. Mesylate derivatives used to confirm stereochemistry via X-Ray crystallography.

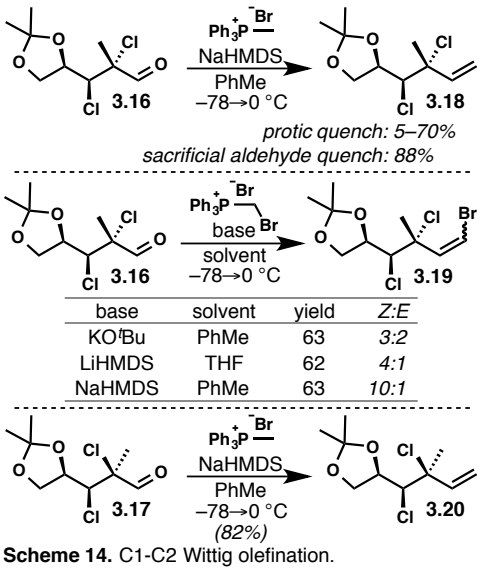
3.4 Oxidation/Olefination

With the Cl-bearing stereocenters installed, were next considered oxidation of the primary alcohol to the aldehyde (Scheme **12**). Although PCC oxidation was successful, it was slow and required a large excess of reagent to reach full conversion. Dess–Martin periodinane proved to be vastly superior, with much higher yields and shorter reaction times. We also found that the *syn*-dichloride diastereomers could be separated after oxidation to afford the *syn,syn* diastereomer **3.17** in >10:1 d.r. Moreover, we found that upon purification, aldehyde **3.17** spontaneously crystalized to form crystals suitable for X-ray analysis, confirming the relative and absolute stereochemistry of the isolated *syn*-diastereomer.



Scheme 13. Oxidation and *syn*-dichloride crystal structure.

With the aldehyde in hand, we set about finding suitable conditions to install the C1-C2 olefin (Scheme **14**). Early on, Wittig olefination proved to be a suitable method to install both the terminal olefin (**3.18**, **3.20**) and the *Z*-bromide (**3.19**). NaHMDS was superior to lithium bases with increased yield and, in the case of the *Z*-bromide, selectivity. Toluene also provided a boost in reactivity over THF. The main problem that we encountered was when the reaction was performed on over 250 mg of the aldehyde, the yield dropped drastically. We discovered that the problem stemmed from the quench. If a proton source

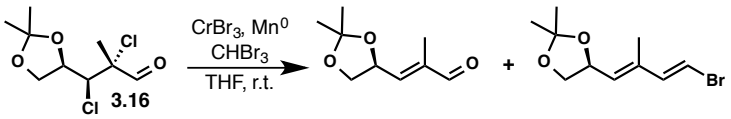


base	solvent	yield	*Z:E*
KO^{t}Bu	PhMe	63	*3:2*
LiHMDS	THF	62	*4:1*
NaHMDS	PhMe	63	*10:1*

Scheme 14. C1-C2 Wittig olefination.

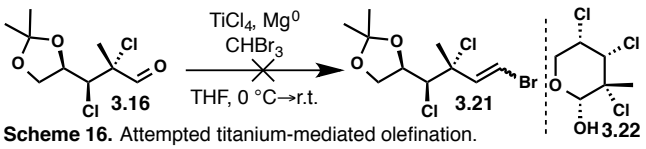
was used to quench the reaction (H_2O, MeOH, or AcOH), the problem was generally exacerbated. Eventually, we found that the best way to quench was to use a sacrificial aldehyde, usually hexanal, to react with the remaining active Wittig reagent, alleviating the problems associated with a protic quench.

For other targets, we required a selective synthesis of *E*-vinyl bromides. Although we attempted to modify the conditions of the Wittig olefination to favor the *E*-bromide, we were unable to completely switch the selectivity, and a mixture of alkene isomers was the only result we obtained. Although a number of methods for installing *E*-vinyl halides exist, the primary one is the Cr(II)-mediated Takai–Utimoto olefination (Scheme **15**). Once we were able to find a reliable source of the necessary $CrBr_3$, we were able to perform the olefination on simple aldehydes with good selectivity and yield. However, when employing dichloride **3.16**, the only products that we observed arose from reductive dechlorination. Significant modification of the reaction conditions and procedure did not result in formation of the desired alkene.



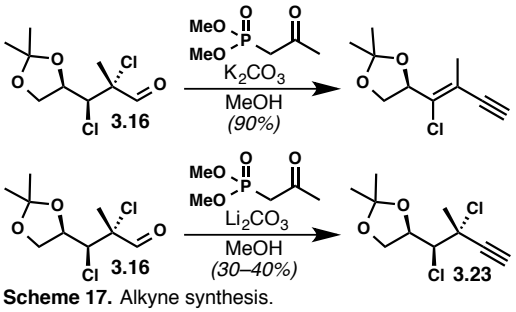
Scheme 15. Attempted Takai-Utimoto olefination.

One reported method for the installation of *E*-vinyl halides is a titanium-mediated olefination (Scheme **16**).[10,11] Similar in function to the Tebbe[12] and Petasis[13] reagents, a titanium species is formed in situ for the olefination. However, in our hands, even on simple aldehyde model systems, the olefination did not take place. When attempted on aldehyde **3.16**, the only product that we isolated appeared to have suffered from deprotection of the acetonide, followed by a cyclization event to form tetrahydropyran **3.22**, although we did not rigorously confirm this.



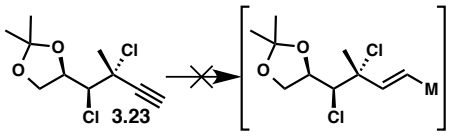
Scheme 16. Attempted titanium-mediated olefination.

The next method of *E*-bromide installation that we attempted was hydrometallation of an alkyne. A variety of different metal hydrides can be added to alkynes to give the vinyl-metal species. Subsequent bromodemetallation furnishes the *E*-bromide.



Scheme 17. Alkyne synthesis.

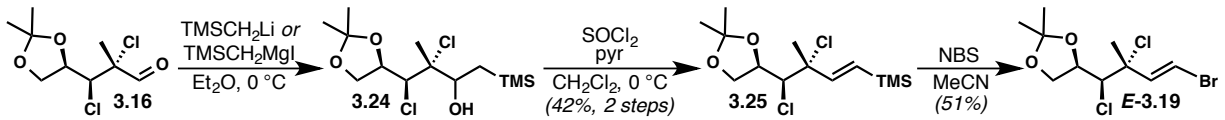
Alkynylation of aldehyde **3.16** was initially challenging (Scheme **17**). Standard conditions using the Ohira–Bestmann reagent along with K_2CO_3 resulted in elimination.[14] Lowering the temperature and using a more powerful base did not alleviate the problem. Eventually, we found that simply switching the base to Li_2CO_3 allowed us to synthesize the desired alkyne **3.23** in 30–40% yield. Unfortunately, the alkyne did not undergo hydrometallation under any conditions tested (Scheme **18**). Generally speaking, one of two results was observed: recovery of the unreacted alkyne **3.23**, or complete decomposition with no isolable products. Standard hydroalumination conditions using DIBAL only led to recovery of starting material, while Hoveyda's Ni-catalyzed hydroalumination led to decomposition.[15] Pd-catalyzed hydrostannylation[16] gave an intractable mixture of products, while Pt-catalyzed hydrosilylation[17] led to complete decomposition, with no observable products via NMR. Hydrozirconation using Schwartz's reagent[18] also led to only decomposition, presumably through deprotection of the acetonide and subsequent reactivity.



conditions	solvent	result
DIBAL	hexane	s.m.
$Ni(PPh_3)_2Cl_2$ DIBAL	THF	decomp
$Pd(PPh_3)_2Cl_2$ Bu_3SnH	THF	decomp
Cp_2ZrHCl	CH_2Cl_2	decomp
Pt(DVDS), $^tBu_3P$ Et_3SiH	CH_2Cl_2	decomp

Scheme 18. Alkyne hydrometallation attempts.

At this point, we had to find an alternative way to install the desired *E*-bromide. Although the literature was sparse, we had found a few reports of secondary alcohol dehydration using thionyl chloride and pyridine to give *E*-vinylsilanes in high selectivity (Scheme **19**).[19] We

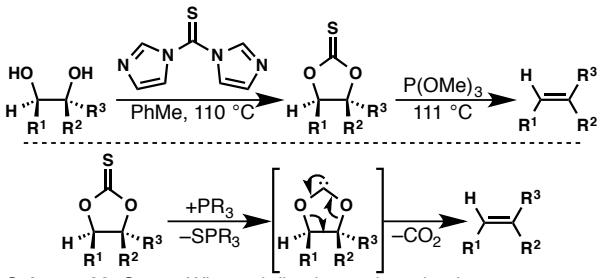


Scheme 19. *E*-bromide synthesis via vinylsilane.

decided that this was a reasonable course of action, and subjected aldehyde **3.16** to Grignard addition using $TMSCH_2MgI$ or the equivalent alkyllithium. Although the 1,2-addition proceeded using either the Grignard or alkyllithium, the Grignard reagent proved to be superior, resulting in much higher conversion to **3.24**. Although we were unable to isolate the secondary alcohol **3.24**, this issue proved inconsequential. After workup and concentration, the crude reaction mixture containing **3.24** was subjected to the dehydration conditions, and we successfully synthesized and isolated vinylsilane **3.25** in reasonable yield and excellent *E*-selectivity. Subsequent bromodesilylation yielded the desired *E*-bromide ***E*-3.19**.

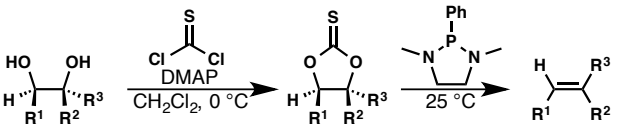
3.5 Acetonide Deprotection and Corey–Winter Olefination

With the C1-C2 alkene installed, we now had to find a way to install the terminal olefin necessary for the cross metathesis. The primary concern at this point was the sensitivity of the chlorides to elimination, so conditions that were relatively neutral were a priority. One of the more interesting possibilities was the Corey–Winter olefination (Scheme **20**).[20] After installation of a thiocarbonate, treatment with trimethyl phosphite forms the alkene. After the initial report by Corey and Winter, Horton showed that a carbene intermediate is likely, with extrusion of CO_2 as the final step of the mechanism, supporting the original hypothesis of Corey.[21] The original conditions, which called for trimethyl phosphite, have the disadvantage of requiring elevated temperatures. Fortunately, Corey and Hodgson found that the reaction can be performed at room



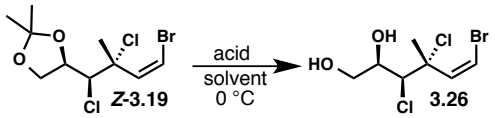
Scheme 20. Corey–Winter olefination and mechanism.

temperature if a diazaphospholidine is used in place of the phosphite (Scheme **21**).[22]

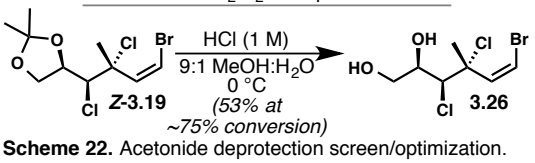


Scheme 21. Corey–Winter olefination with Hopkins protocol.

Now that we had a plan for the alkene installation, we proceeded to find suitable conditions to deprotect acetonide ***Z*-3.19** to the necessary diol **3.26** (Scheme **22**). A number of different conditions were tested, most of which caused decomposition. THF was a particularly poor solvent, the use of which led to rapid decomposition under acidic conditions. We eventually settled on 1.0 M HCl in MeOH, stopping the reaction before complete conversion to minimize the amount of decomposition. At ~75% conversion, we were able to isolate 53% of the diol **3.26**, while recovering ~20% of acetonide ***Z*-3.19**.

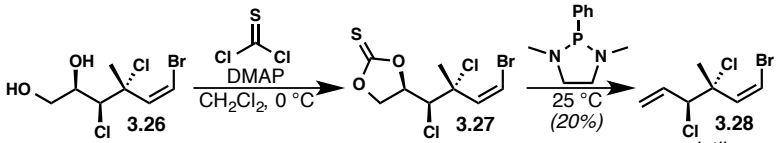


acid (1 M)	solvent	result
AcOH	THF	<50% conversion
AcOH	MeOH	<50% conversion
AcOH	CH_2Cl_2	decomp.
TsOH	THF	decomp.
TsOH	MeOH	decomp.
TsOH	CH_2Cl_2	decomp.
HCl	THF	prod. + decomp
HCl	MeOH	prod. + s.m.
HCl	CH_2Cl_2	prod. + s.m.



Scheme 22. Acetonide deprotection screen/optimization.

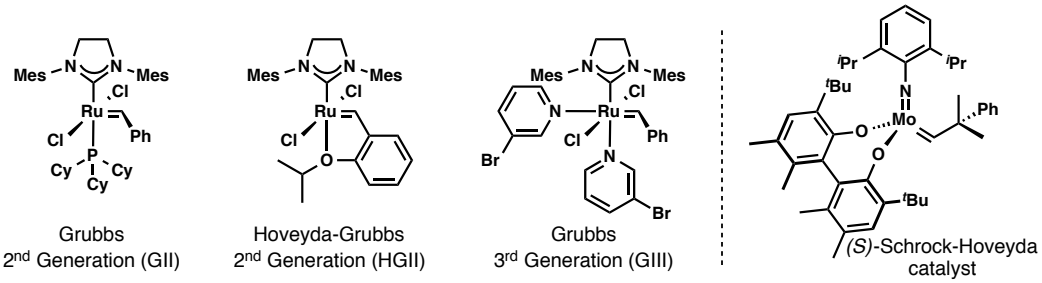
With the diol in hand, the thiocarbonate could be synthesized in two possible ways. While 1,1-thiocarbonyldiimidazole is a user-friendly reagent, it requires elevated temperatures in order to install the thiocarbonate. Because of this, we opted to use a combination of thiophosgene and DMAP (Scheme **23**). Although thiophosgene is much more toxic, it is much more reactive, which enables formation of the thiocarbonate below room temperature, and quenching excess reagent is straightforward. Using this protocol, thiocarbonate **3.27** could be formed in short order. Unfortunately, purification was an issue, and eventually we opted to carry on the crude reaction mixture after workup. Treatment of the mixture with neat diazaphospholidine as described



Scheme 23. Corey–Winter olefination with Hopkins protocol.

by the Hopkins protocol, followed by filtration through silica with CH_2Cl_2, cleanly afforded the desired terminal alkene **3.28**. Yields were typically 20–30%, but we believe this was due to the volatility of the product, rather than poor reaction efficiency. The fact that this reaction occurs selectively is surprising, given that the electron-rich phosphorous species does not interact with the allylic halides.

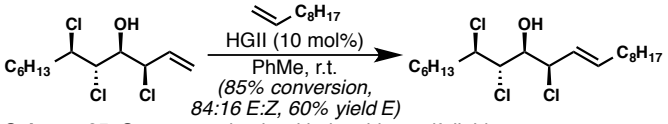
3.6 Cross-Metathesis Attempts



Type I alkene: rapid homodimerization; homodimers participate in cross-metathesis
Type II alkene: slow homodimerization; homodimers do not participate in cross-metathesis
Type III alkene: no homodimerization

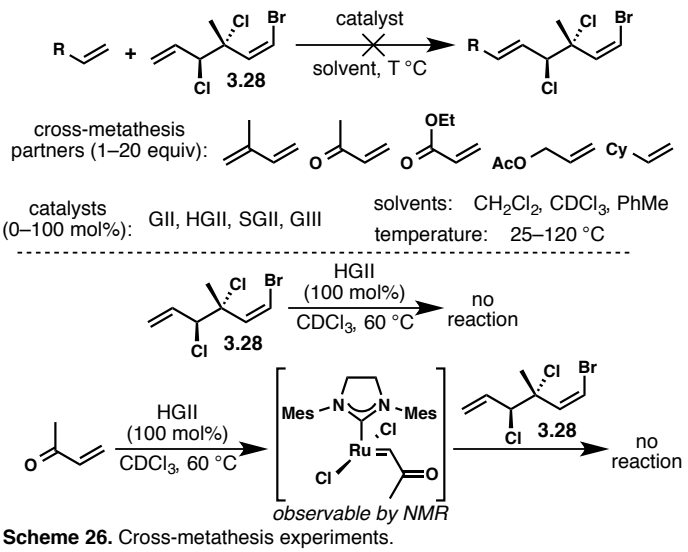
Scheme 24. Alkene metathesis catalysts and olefin types.

With the necessary terminal alkene in hand, we were able to test the key cross-metathesis step. We limited our screening to the Grubbs-type catalysts, as the presence of numerous chlorine atoms on our substrate might be an issue for the extremely reactive Schrock-type catalysts (Scheme **24**). Because cross-metathesis reactions of isoprene are known to be difficult,[23] we tested the viability of the cross-metathesis with simpler partners before extensively exploring the synthesis of the chlorinated isoprene unit. We chose a selection of alkenes of different types (I, II, III), as well as variants of the ruthenium alkylidene cross-metathesis catalysts.[24,25] The cross-metathesis of complex substrates had been successful in the Vanderwal group in the context of the chlorosulfolipids (Scheme **25**).[26] Based on this precedent, as well as other reports of successful cross-metathesis with allylic chlorides,[27] we were confident in our strategy. However, even after



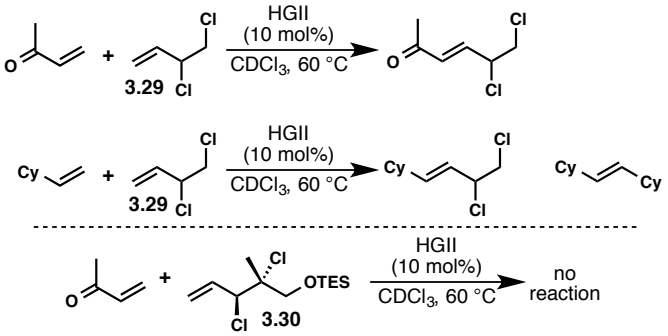
Scheme 25. Cross-metathesis with the chlorosulfolipids.

extensive screening efforts, we did not observe the desired reactivity (Scheme **26**). In fact, in almost every case, we recovered terminal alkene **3.28** nearly quantitatively. Even when stoichiometric amounts of Hoveyda-Grubbs II catalyst were used, we saw no reactivity. NMR experiments showed that the catalyst does not initiate onto the dichloride-containing terminal alkene, even at the stoichiometric loading. It was possible that the dichloride-containing alkene could not initiate onto the catalyst, but could undergo cross-metathesis with pre-activated catalyst. However, when we performed this experiment, no reactivity was observed, and starting material recovered.



Scheme 26. Cross-metathesis experiments.

We next hypothesized that the vinyl bromide could be inhibiting the catalyst. It has been reported that certain bromide species can inhibit the catalyst, blocking the open coordination site on the bottom face of the catalyst.[28] However, the two chlorine atoms could also be inhibiting reactivity. To test this, we employed commercial dichloride **3.29** under catalytic conditions with two different cross-metathesis partners (Scheme **27**). In both cases, the reaction proceeded smoothly, indicating that if we removed the vinyl bromide from our substrate, the cross-metathesis might proceed. To do this, we simply protected the primary alcohol as the silyl ether, and performed the

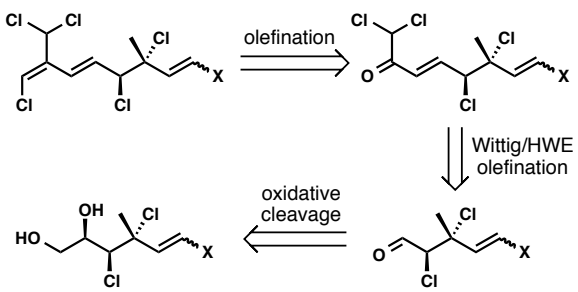


Scheme 27. Cross-metathesis without vinyl bromide.

deprotection/Corey–Winter olefination sequence to arrive at cross-metathesis substrate **3.30** devoid of the vinyl bromide. However, even with this change, the substrate did not undergo the cross-metathesis, and the majority of the starting material was recovered. We were, and still are, perplexed by this lack of reactivity. The only difference between the unreactive alkene and other dichlorides that we know are competent cross-metathesis substrates is the presence of the tertiary chloride.

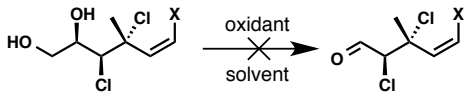
3.7 Revised Retrosynthesis: Oxidative Cleavage/Olefination Sequence

With the cross-metathesis strategy abandoned, we needed to find a new convergent step (Scheme **28**). After considering a range of options, we realized that the diol originally constructed for the Corey–Winter olefination could instead undergo an oxidative-cleavage reaction to give an aldehyde. With the aldehyde, a variety of more traditional olefination reaction conditions became available. However, the Vanderwal group has some experience with these types of β-chloro aldehydes, which readily eliminate even under mild conditions. Still, we had the material on hand to test the oxidative cleavage and general stability of the aldehyde, so we went forward with this new strategy.



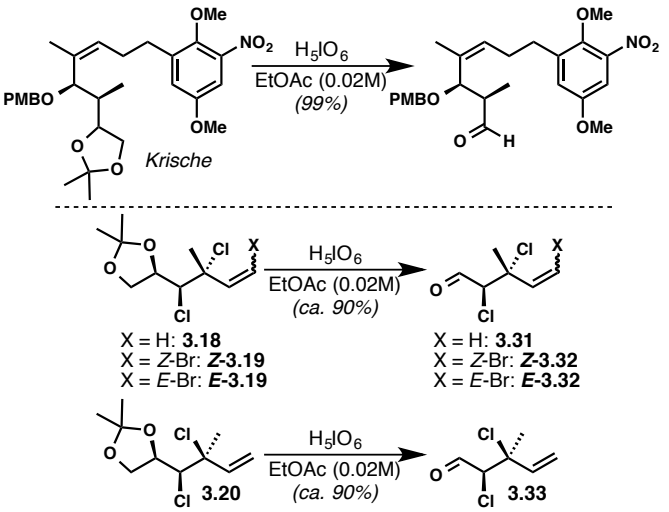
Scheme 28. Revised retrosynthesis.

The oxidative cleavage proved to be more difficult than we originally anticipated (Scheme **29**). Standard conditions employing $NaIO_4$ did not produce the desired aldehyde. Similarly, $Pb(OAc)_4$ and H_5IO_6 also failed to react with the diol to form the aldehyde. After testing a number of variations for standard oxidative cleavage, we found that the deprotection/oxidative cleavage could be performed in a single pot using H_5IO_6. We were first



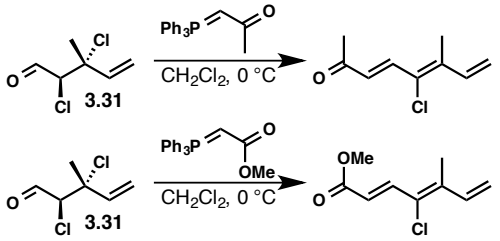
oxidants: $NaIO_4$, $Pb(OAc)_4$, H_5IO_6
solvents: THF, H_2O, MeCN, Me_2CO, CH_2Cl_2, PhH
Scheme 29. Attempted diol oxidative cleavage.

encouraged to test this protocol after seeing a report by Krische and coworkers on another sensitive aldehyde (Scheme **30**). In their case, the product aldehyde was not prone to elimination, but it did have an α-stereocenter that could be easily epimerized. Under the optimized conditions, the aldehyde was produced in high yield without epimerizing the alpha-stereocenter.[29] Gratifyingly, when we followed the protocol reported by Krische, aldehydes **3.31**, ***Z*-3.32**, ***E*-3.32**, and **3.33** were produced in consistently high yields, with very little elimination product observed. While we were initially worried about product stability, the aldehydes were tstable enough to be concentrated and stored at –20 °C.



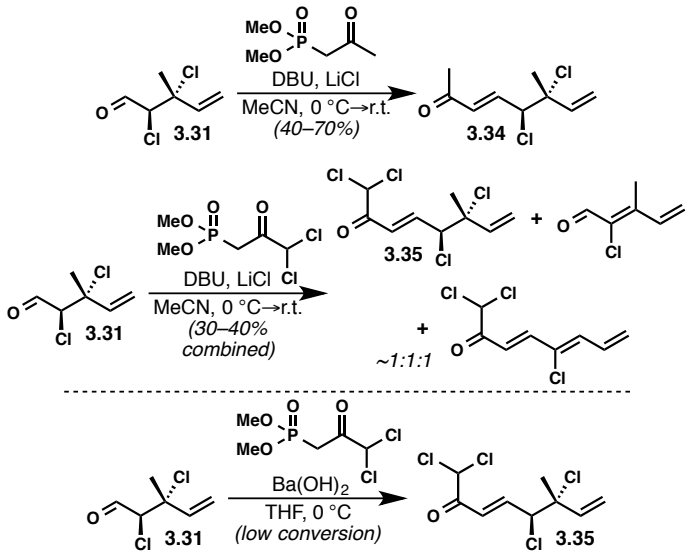
Scheme 30. Direct Oxidative cleavage precedent and results.

With the aldehyde in hand, we went about evaluating olefination conditions (Scheme **31**). The easiest to test was the Wittig olefination to install the enone. To screen possible conditions, we used the simplified methyl ketone or ester functionality in place of the dichloromethyl group. Unfortunately, the Wittig reagent was not reactive enough at the temperatures below which elimination of aldehyde **3.31** occurred. We then moved to the Horner–Wadsworth–Emmons olefination. A number of protocols have been reported that are good for base-sensitive aldehydes. One of the most popular methods is the Masamune–Roush olefination, which features the use of DBU and excess LiCl in MeCN (Scheme **32**).[30] When the methyl ketone HWE reagent was used under these conditions, the desired enone **3.34** was



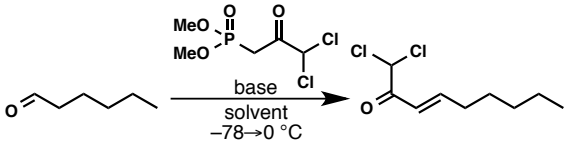
Scheme 31. Attempted Wittig olefination.

produced in satisfactory yields, although large amounts of elimination byproducts were present. We figured that we could optimize against the elimination byproducts, so we forged ahead and utilized the necessary dichloromethyl phosphonate. However, when the dichloromethyl HWE reagent was used, problems started to arise. The decreased reactivity of the HWE reagent was clear, with reaction times being significantly longer. Because of this, the elimination byproducts of both enone **3.35** product and aldehyde **3.31** were present in roughly equal proportions to the desired product. Varying the amine base, equivalents, temperature, and time did not lead to better results. In the same vein of reasoning, $Ba(OH)_2$ is also known to be a useful reagent for base-sensitive systems.[31] Unfortunately, while there was very little elimination at low conversion, the elimination products appeared again at high conversion.



Scheme 32. Masamune–Roush HWE and $Ba(OH)_2$.

Finding a mild base that prevented elimination but promoted olefination seemed like a tall order. We changed our strategy to finding conditions that drastically increased the reactivity of the HWE reagent, which would allow us to run the reaction at much lower temperatures (Scheme **33**). To give us a general idea of the reactivity trends of the dichloromethyl phosphonate, we subjected hexanal to the HWE conditions to determine relative reaction rates. We found that NaHMDS and KHMDS performed

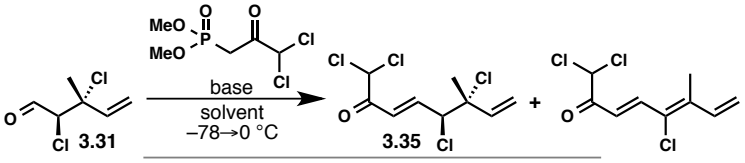


base: NaHMDS ≈ KHMDS > ^{n}BuLi > KO^{t}Bu
solvent: PhMe > THF

Scheme 33. General reactivity trends for HWE reagent.

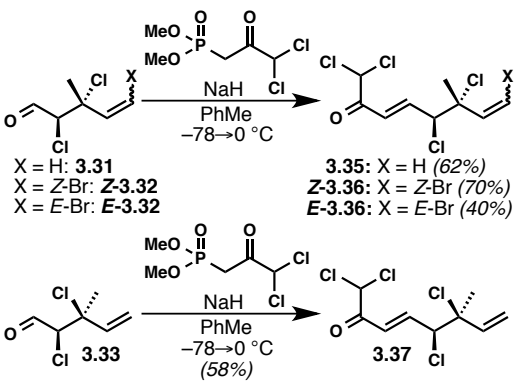
similarly, while ^{n}BuLi and KO^{t}Bu were much slower. We also found a significant increase in reaction rate in PhMe over THF.

With this knowledge in hand, we decided to evaluate the olefination on the real system (Scheme **34**). The first reactions that were run under this new protocol showed promising results, with the product enone **3.35** clearly forming at a faster rate than elimination in all cases, and the reactivity trends that we had found for the model aldehyde holding true for the aldehyde in the real scenario. Although NaHMDS performed well for the olefination, if all of the byproduct amine was not removed, the product would completely eliminate upon concentration. Thankfully, NaH showed very similar reactivity to NaHMDS, and the byproduct H_2 could not interfere with the reaction, so it was the base of choice for further optimization (Scheme **35**). After varying temperature, reagent equivalents, and time, we were able to optimize the yield to over 60% in the best cases, with the majority of the elimination byproducts being easily removed in a single round of chromatography. Limiting the purification steps was necessary to suppress the amount of product lost to elimination.



base	solvent	conversion	desired:elimination
^{n}BuLi	THF	~40%	3:1
^{n}BuLi	PhMe	~80%	>10:1
NaH	THF	~60%	1:1
NaH	PhMe	100%	>10:1

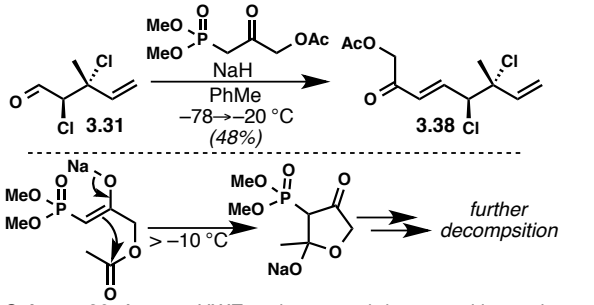
Scheme 34. HWE olefination testing on real system.



Scheme 35. HWE olefination.

Using the HWE olefination as a key part of the synthesis allowed us the opportunity for late-stage diversification of substrates by simply changing the substituents on the phosphonate (Scheme **36**). One group that we desired to install was oxygen functionality in place of the dichlorides. A handful of natural products contained either an acetate or aldehyde at that

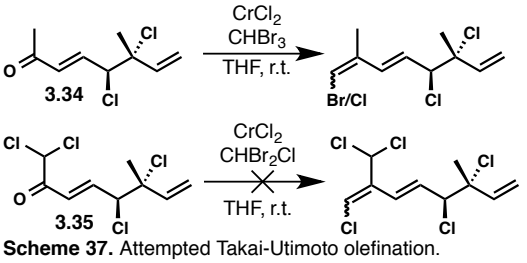
position. We first attempted to install the oxygen using a phosphonate with silyl ether functionality, but this reagent proved difficult to synthesize. Fortunately, replacing the silane with an acetate allowed for a much more straightforward synthesis of the reagent. With the acetoxy group present, however, the HWE reaction was ill-behaved, presumably due to either inter- or intramolecular olefination of the deprotonated phosphonate onto the acetate functionality. Eventually, we found that with careful control of temperature, we could largely prevent decomposition of the reagent, and produce the desired enone **3.38**.



Scheme 36. Acetoxy HWE and proposed decomposition pathway.

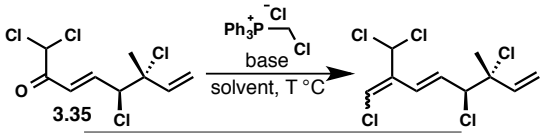
3.8 Final Olefination to Install C7-C8 Alkene

With the ketone in place, we focused our attention to installing the final olefin to complete the synthesis. We were worried about the sensitivity of the ketone to basic conditions, so our initial efforts focused on neutral conditions (Scheme **37**). Although the Takai–Utimoto olefination is typically used on aldehydes, it can be used to form vinyl halides on ketones. Indeed, when we ran the first few reactions on enone **3.34**, we were able to identify the vinyl halide. Unfortunately, when dichloromethyl enone **3.35** was used, we saw no conversion to the desired vinyl halide, even when substantially altering the reaction conditions. In most cases, reduction of alkyl chlorides by the Cr(II) species is slow. However, it is known that chlorides alpha to carbonyl groups are much more readily reduced. Furthermore, vicinal dihalides are prone to rapid reduction.



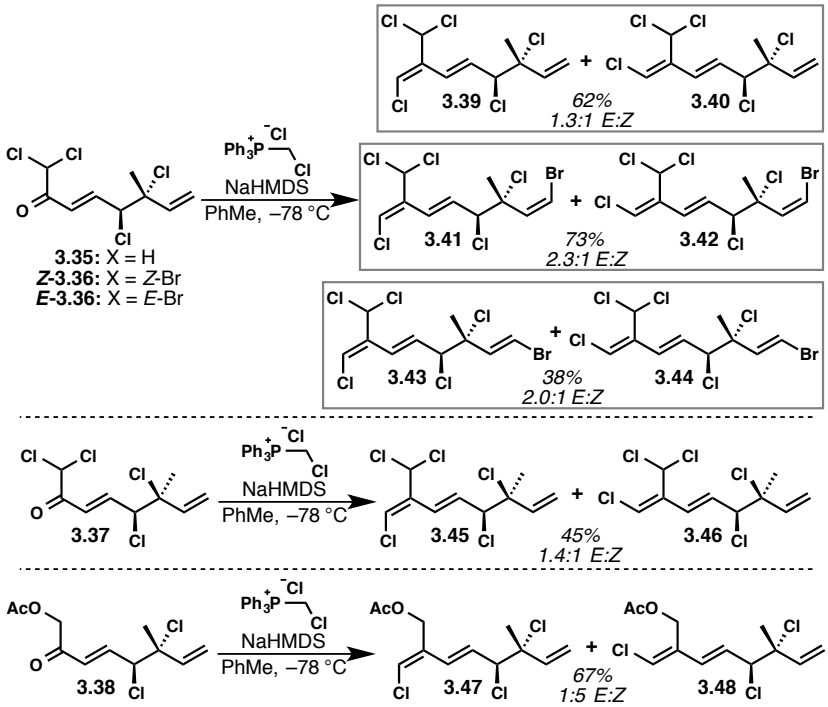
Scheme 37. Attempted Takai-Utimoto olefination.

The range of reactions to install vinyl halides onto ketones is limited. Although we were worried about the basicity of the reaction conditions, we decided to try standard Wittig olefination conditions (Scheme **38**). After a brief survey of bases and solvents, we found that, as before, the best combination for reactivity was NaHMDS in PhMe. With the base and solvent chosen, we optimized the installation of the final vinyl chloride (Scheme **39**). We were delighted when we found that the desired vinyl chloride could be installed relatively cleanly. Although there was very little selectivity for either the *E*- or *Z*-vinyl chloride, this was somewhat inconsequential, as in many cases both isomers are natural products, and they can be separated by standard-phase HPLC. The reaction proved to be robust for all of the substrates necessary, to furnish a variety of natural products and analogues from a standard protocol.



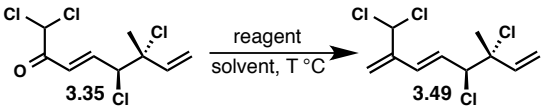
base	solvent	T °C	conversion
KO^{t}Bu	THF	–20	< 20%
KO^{t}Bu	PhMe	–78	< 20%
NaHMDS	THF	–20	< 20%
NaHMDS	PhMe	–78	> 95%

Scheme 38. Vinyl chloride Wittig screening.



Scheme 39. Vinyl chloride installation to furnish natural products.

Installation of the 1,1-disubstituted olefin proved more difficult. We first tried a range of methylenating reagent that are known to be non-basic (Scheme **40**). Unfortunately, these Ti- and Zn-

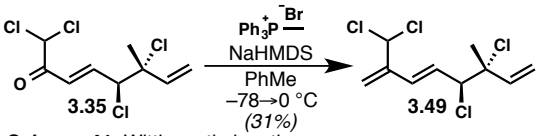


reagent: Tebbe, Petasis, Nysted
solvent: THF, PhMe
T °C: 25–120 °C

slow conversion (< 80 °C)
or decomposition (> 80 °C)

Scheme 40. Methylenation attempts with nonbasic reagents.

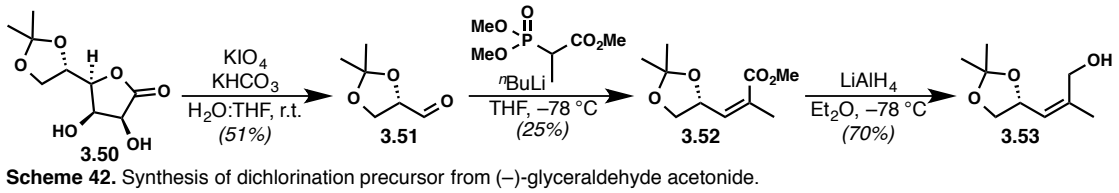
based reagents were not reactive enough to efficiently form the desired alkene. Higher temperatures led to only decomposition. We eventually tried the Wittig reaction. The unsubstituted Wittig reagent is much more basic, and less nucleophilic, so elimination byproducts were more prevalent. However, with careful control of temperature, the desired olefin **3.49** could be isolated in serviceable yields (Scheme **41**).



Scheme 41. Wittig methylenation.

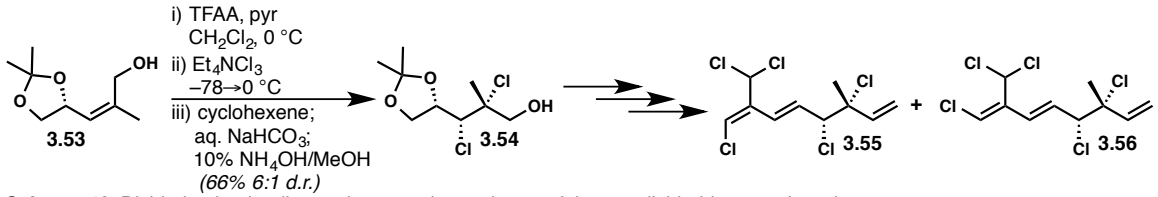
3.9 Synthesis of the Natural Enantiomer of the *Syn*-Dichloride Natural Products

With the syntheses of a number of the natural products completed, we turned our attention to an issue with the current route: when using the mannitol derivative as the starting material, the incorrect enantiomer of the *syn*-dichloride natural product is synthesized.



Scheme 42. Synthesis of dichlorination precursor from (–)-glyceraldehyde acetonide.

Thankfully, there are known procedures to access (–)-glyceraldehyde acetonide (**3.51**) from ascorbic acid derivative **3.50** (Scheme **42**). Although the protocols utilizing $NaIO_4$ are more widely cited,[32] careful monitoring of pH is required, as well as a tedious workup procedure. We found that methods that use KIO_4 are much easier to carry out, as well as higher yielding.[33,34] The subsequent olefination and reduction were lower yielding than before, but enough material could be produced to carry on with the synthesis.



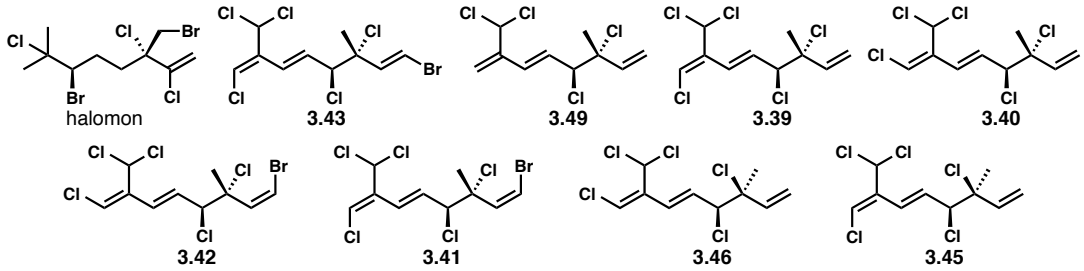
Scheme 43. Dichlorination leading to the natural enantiomer of the *syn*-dichloride natural products.

Thankfully, dichlorination of **3.53** gave results essentially identical to the opposite enantiomer, comparable in both yield and diastereoselectivity (Scheme **43**). The subsequent steps were carried out without issue, furnishing the natural enantiomer of the *syn*-series natural products. Moreover, the measured optical rotation of each compound compared favorably with the previously synthesized *syn*-compounds, with opposite sign but similar magnitude.

3.10 Biological activity against solid tumors

Compound	H116	H125	MCF-7	LNCaP	OVC-5	U251N	MDA	PANC-1	HepG2	IC_{50} [μg mL^{-1}]
halomon	*	*		*	*	*	*		*	0.37
3.43		*		*	*	*	*		*	1.3
3.49	*	*		*	*	*				15
3.39	*	*	*	*	*	*	*		*	1.3
3.40	*	*	*	*	*	*				3.6
3.42	*	*		*	*	*	*			3.5
3.41		*		*	*	*				1.4
3.46	*	*		*	*	*	*			8.3
3.45	*	*	*	*	*	*	*		*	8.5

* Indicates selectivity for the cell line over CCRF–CEM leukemia cell lines according to zone diffusion assay.
H116: HCT-116 human colon carcinoma
H125: human non-small-cell lung carcinoma
MCF-7: human breast adenocarcinoma
LNCaP: androgen-sensitive human prostate adenocarcinoma
OVC-5: OVCAR-5 human ovary carcinoma
U251N: human glioblastoma
MDA: MDA-MB-231 human breast carcinoma
PANC-1: human pancreatic carcinoma
HepG2: human hepatocellular carcinoma
IC_{50}: H116 cell line only



Scheme 44. Activity against solid tumors.

Through collaboration with Dr. Fred Valeriote at the Henry Ford Hospital in Detroit, MI, we have been able to study the effect of the synthesized acyclic *Plocamium* polyhalogenated monoterpenes on a number of solid tumor cell lines (Scheme **44**). Dr. Valeriote, along with Halina Pietraszkiewicz, measured the selectivity of each compound in the table for the given cell line over CCRF–CEM leukemia cell lines using a zone-diffusion assay. Halomon was used as a

benchmark. It is important to note that the sample of **3.43** used in the assay was isolated from the red algae, while the other *Plocamium* compounds were synthesized. Although we are in the early stages of the studies, we are encouraged by the selectivity of several compounds, as well as promising potency.

3.11 Conclusion

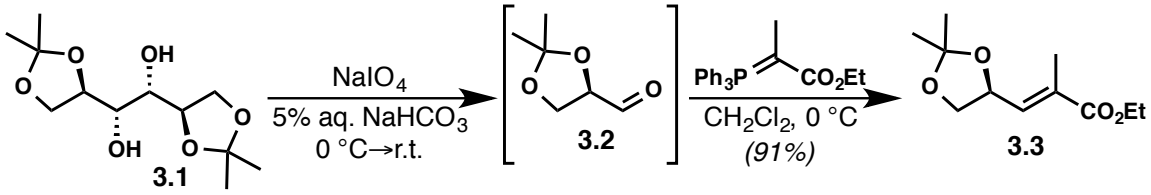
We successfully developed a divergent synthesis of the acyclic *Plocamium* polyhalogenated monoterpenes starting from chiral pool starting materials, with a longest linear sequence of nine steps except for the *E*-bromides. Currently, nine natural products and five analogues have been synthesized, with more potentially on the horizon. We are continually sending new samples to Dr. Valeriote for testing.

3.12 Experimentals

All reactions were performed in oven-dried (140 °C) or flame-dried glassware under an atmosphere of dry argon unless otherwise noted. Reaction solvents including dichloromethane (CH_2Cl_2, Fisher, HPLC Grade), hexane (Fisher, HPLC Grade), diethyl ether (Et_2O, Fisher, BHT stabilized HPLC Grade), tetrahydrofuran (THF, Fisher, HPLC Grade), and toluene (PhMe, Fisher, HPLC Grade) were dried by percolation through a column packed with neutral alumina and a column packed with Q5 reactant, a supported copper catalyst for scavenging oxygen, under a positive pressure of argon. Solvents for workup and chromatography were: hexanes (Fisher or EMD, ACS Grade), *n*-pentane (J.T.Baker, BAKER ANALYZED®), ethyl acetate (Fisher, ACS Grade), dichloromethane (DCM, Fisher, ACS Grade), and methanol (Fisher, ACS Grade). Reactions that were performed open to air utilized solvent dispensed from a wash bottle, and no precautions were taken to exclude water. Column chromatography was performed using EMD Millipore 60 Å (0.040-0.063 mm) mesh silica gel (SiO_2). The following reagents were distilled from the indicated drying agents under Ar prior to use: triethylamine (EMD, CaH_2), trifluoroacetic anhydride (Oakwood, P_2O_5). Tetraethylammonium trichloride was prepared according to literature procedure.[8]

^1H NMR and ^{13}C NMR spectra were recorded on Bruker GN500 (500 MHz, ^1H; 125 MHz, ^{13}C), Bruker CRYO500 (500 MHz, ^1H; 125 MHz, ^{13}C), and Bruker AVANCE600 (600 MHz, ^1H; 150 MHz, ^{13}C) spectrometers at 298 K. ^1H and ^{13}C spectra were referenced to residual chloroform (7.26 ppm, ^1H; 77.2 ppm, ^{13}C). Chemical shifts are reported in ppm and multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br s (broad singlet). Coupling constants, *J*, are reported in Hertz. Infrared (IR) spectra were recorded on a Perkin-Elmer spectrum RX1 FT-IR instrument in NaCl cells and peaks are reported in cm^{-1}.

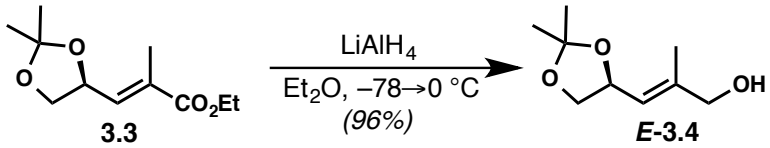
Mass spectroscopy was performed by the University of California Mass Spectrometry Facility. Accurate mass spectra were recorded on a Waters LCT Premier spectrometer and Data are reported in the form of (m/z). Optical rotation data was obtained on a Jasco P-1010 digital polarimeter using the sodium D-line filter (589 nm). Analytical thin-layer chromatography was performed on Merck silica gel 60 F_{254} TLC plates. Visualization was accomplished with UV(254), potassium permanganate ($KMnO_4$), *p*-anisaldehyde, and 2,4-dinitrophenylhydrazine (DNP) staining solutions. Analytical HPLC was performed on an Agilent 1100 series instrument utilizing a Grace Altima silica 5μ column with visualization at 254 nm. Semi-preparative HPLC was performed on an Agilent 1100 series instrument utilizing a Grace Altima silica 5μ 250 x 22 mm column with visualization at 254 nm.



Ethyl (2*E*,4*S*)-4,5-Isopropylidenedioxy-2-methylpent-2-enoate (3.3)

To a solution of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**3.1**) (8.24 g, 31.4 mmol, 1.0 equiv.) in 5% aq. $NaHCO_3$ (120 mL) open to air was added $NaIO_4$ (8.06 g, 37.7 mmol, 1.2 equiv.) portionwise at 0 °C. The solution was warmed to r.t. and stirred for 1 h. The reaction mixture was tcooled to 0 °C, and (carbethoxyethylidene)triphenylphosphorane[2] (25.0 g, 69.0 mmol, 2.2 equiv.) in CH_2Cl_2 (40 mL) was added and the reaction was stirred vigorously at 0 °C for 4 h. The reaction was extracted with CH_2Cl_2 (3 x 40 mL), the organic extract washed with H_2O (1 x 50 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude mixture was triturated with hexanes (100 mL) and filtered. The remaining solid was washed several times with hexanes (5 x 25 mL), and the resulting solution concentrated in vacuo to half of the original volume. The

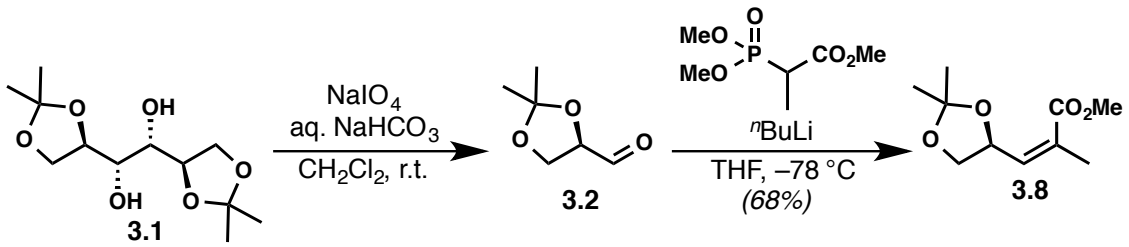
remaining phosphine oxide was removed following the procedure reported by Gilheany.[3] Oxalyl chloride (2 mL) was added to the crude mixture in hexanes and stirred 30 minutes at r.t. The orange solid was removed by filtration through a plug of SiO_2 with CH_2Cl_2 eluent. Concentration in vacuo afforded crude (2*E*,4*S*)-4,5-isopropylidenedioxy-2-methylpent-2-enoate (**3.3**) as a clear oil (12.27 g, 91%), which was used without further purification. The spectral data matched those previously reported by Fukumoto[1]. R_f = 0.58, 4:1 pentane:EtOAc; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68 (dd, *J* = 8.1, 1.3, 1H), 4.86 (appar. q, *J* = 7.7, 6.5, 1H), 4.20 (qd, *J* = 7.2, 2.0, 2H), 4.15 (dd, *J* = 8.2, 6.3, 1H), 3.63 (t, *J* = 8.0, 1H), 1.89 (d, *J* = 1.3, 3H), 1.45 (s, 3H), 1.41 (s, 3H), 1.29 (t, *J* = 7.1, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 138.2, 131.2, 109.9, 72.9, 68.9, 61.0, 26.8, 26.0, 24.4, 13.2.



(2*E*,4*S*)-4,5-Isopropylidenedioxy-2-methylpent-2-en-1-ol (*E*-3.4)

To a round bottom flask charged with $LiAlH_4$ (2.38 g, 62.6 mmol, 1.1 equiv.) was added Et_2O (150 mL), and the suspension was cooled to –78 °C. A solution of **3.3** (12.20 g, 56.9 mmol, 1.0 equiv.) in Et_2O (50 mL) was added via cannula over a period of 10 minutes. Once the addition was complete, the reaction was stirred at –78 °C for 1 h, warmed to 0 °C, and stirred an additional 30 min. The reaction was quenched by the slow addition of saturated aq. Na_2SO_4 (~15 mL) until the bubbling ceased and a white suspension formed. The solids were filtered off through celite, and the solid residue washed with several portions of EtOAc (5 x ~40 mL). The resulting organic solution was dried over $MgSO_4$ and concentrated in vacuo to afford (2*E*,4*S*)-4,5-isopropylidenedioxy-2-methylpent-2-en-1-ol (***E*-3.4**) as a clear, viscous oil (10.14 g, 97 %), that could be used without further purification. The spectral data matched those previously

reported by Fukumoto[1]. R_f = 0.13, 4:1 pentane:EtOAc; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.58 (appar. dq, *J* = 8.6, 1.4, 1H), 4.83 (m, 1H), 4.08 (dd, *J* = 8.1, 6.0, 1H), 4.03 (d, *J* = 5.9, 2H), 3.55 (t, *J* = 8.1, 1H), 1.74 (d, *J* = 1.3, 3H), 1.42 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.1, 122.2, 109.2, 72.6, 69.5, 67.8, 26.9, 26.2, 14.2.

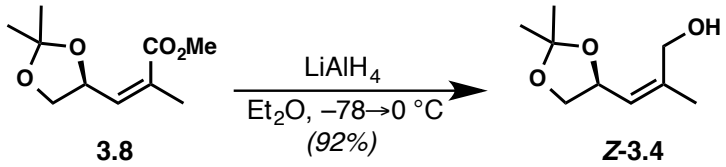


Methyl (2*Z*,4*S*)-4,5-Isopropylidenedioxy-2-methylpent-2-enoate (3.8)

To a solution of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**3.1**) (2.066 g, 7.9 mmol, 1.0 equiv.) in CH_2Cl_2 (18 mL) open to air was added sat. aq. $NaHCO_3$ (0.8 mL) at r.t., and the resulting mixture was stirred for 5 min. $NaIO_4$ (3.369 g, 15.8 mmol, 2.0 equiv.) was added in portions over a period of 5 min. The resulting mixture was stirred at r.t. for 2 h. After this time, $MgSO_4$ (~1.5 g) was added and the mixture was stirred for 30 min at r.t. The slurry was filtered through a sintered glass frit, and the solids were rinsed and mixed thoroughly with with CH_2Cl_2 (5 x 20 mL). The solution was concentrated in vacuo, and the crude glyceraldehyde acetonide was used without further purification (it is best used immediately, but storage at –20 °C for 18–36 h is acceptable; long-term storage is not advised).

To a round bottom flask charged with trimethyl 2-phosphonopropionate (4.326 g, 22.1 mmol, 1.4 equiv) was added THF (80 mL), and the solution was cooled to –78 °C. ^{n}BuLi (2.48 M in hexane, 8.8 mL, 22.1 mmol, 1.4 equiv) was added dropwise over a period of 5 min, with a yellow color forming towards the end of the addition. The solution was stirred for 1 h, and the crude glyceraldehyde acetonide in THF (20 mL) was added over a period of 10 minutes, running

the solution down the interior wall of the flask, and the mixture was stirred for 6 h at –78 °C. The reaction was quenched by the slow addition of 5% AcOH in MeOH (~15 mL) at –78 °C, followed by warming to r.t. H_2O (25 mL) was added, and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (2 x 15 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (SiO_2, 98:2 hexanes:EtOAc) separated the alkene isomers (6:1 *Z*:*E*) and afforded methyl (2*Z*,4*S*)-4,5-isopropylidenedioxy-2-methylpent-2-enoate (**3.8**) as a clear oil (2.187 g, 68%). The spectral data matched those previously reported by Fukumoto[1]. R_f = 0.64, 4:1 pentane:EtOAc; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.09 (d, *J* = 6.8, 1H), 5.26 (q, *J* = 6.8, 1H), 4.31 (dd, *J* = 8.0, 6.9, 1H), 3.74 (s, 3H), 3.59 (dd, *J* = 8.0, 7.0, 1H), 1.93 (s, 3H), 1.45 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 142.9, 129.1, 109.5, 74.1, 69.7, 51.9, 26.8, 25.6, 20.2.

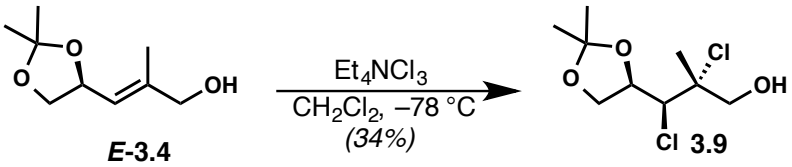


3.8 **Z-3.4**

(2*Z*,4*S*)-4,5-Isopropylidenedioxy-2-methylpent-2-en-1-ol (*Z*-3.4)

To a round bottom flask charged with $LiAlH_4$ (0.204 g, 5.4 mmol, 1.1 equiv.) was added Et_2O (20 mL), and the suspension was cooled to –78 °C. A solution of **3.8** (0.979 g, 4.9 mmol, 1.0 equiv.) in Et_2O (5 mL) was added dropwise over a period of 10 minutes. Once the addition was complete, the reaction was stirred at –78 °C for 1 h, warmed to 0 °C, and stirred an additional 30 min. The reaction was quenched by the slow addition of saturated aq. Na_2SO_4 (~3 mL) until the bubbling ceased and a white suspension formed. The solids were filtered off through celite, and the solid residue washed with several portions of EtOAc (5 x ~10 mL). The resulting organic solution was dried over $MgSO_4$ and concentrated in vacuo to afford (2*Z*,4*S*)-4,5-isopropylidenedioxy-2-methylpent-2-en-1-ol (***Z*-3.4**) as a clear, viscous oil The spectral data

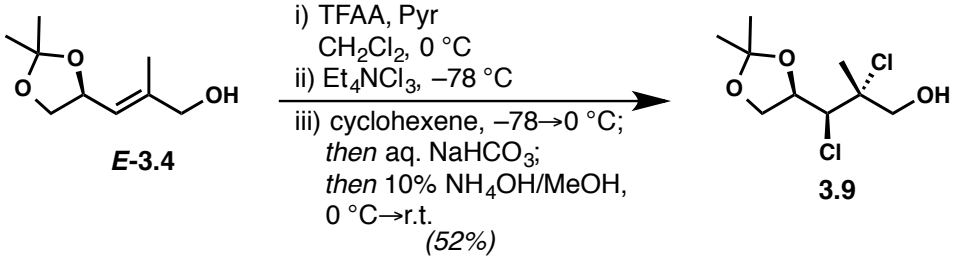
matched those previously reported by Fukumoto[1]. (0.774 g, 92 %). R_f = 0.23, 4:1 pentane:EtOAc; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35 (d, *J* = 8.4, 1H), 4.84–4.89 (m, 1H), 4.22 (d, *J* = 12.4, 1H), 4.13 (dd, *J* = 12.3, 3.4, 1H), 4.07 (dd, *J* = 8.1, 6.0, 1H), 3.54 (t, *J* = 8.0, 1H), 1.85 (d, *J* = 1.3, 3H), 1.42 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.5, 125.2, 109.3, 72.1, 69.9, 62.1, 26.9, 26.1, 21.8.



***E*-3.4** **3.9**

(2*R*,3S,4*R*)-Dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-ol (3.9)

Procedure A: To a solution of ***E*-3.4** (1.56 g, 9.0 mmol, 1.0 equiv.) in CH_2Cl_2 (90 mL) at –78 °C was added a solution of Et_4NCl_3[1] (3.86 g, 16.3 mmol, 1.8 equiv.; ~1.05 equiv. actvite 'Cl_2') in CH_2Cl_2 (20 mL) dropwise over 5 min. The solution was allowed to stir at –78 °C for 2 h, quenched with saturated aq. $Na_2S_2O_3$ (10 mL), and extracted with CH_2Cl_2 (2 x 20 mL). The organic extracts were washed with H_2O (3 x 15 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (SiO_2, 85:13:2–80:15:5 pentane:CH_2Cl_2:EtOAc) afforded (2*R*,3S,4*R*)-dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-ol (**3.9**) as an off-white solid (0.751 g, 34%).



***E*-3.4** **3.9**

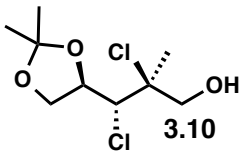
Procedure B: To a solution of ***E*-3.4** (2.13 g, 12.4 mmol, 1.0 equiv.) in CH_2Cl_2 (40 mL) at 0 °C was added trifluoroacetic anhydride (2.1 mL, 14.9 mmol, 1.2 equiv.) dropwise via syringe. The solution was stirred for 15 min at 0 °C, then pyridine (1.0 mL, 12.4 mmol, 1.0 equiv.) was added

dropwise via syringe. The mixture was stirred for an additional 30 min at 0 °C.

Meanwhile, Et_4NCl_3[1] (4.39 g, 18.6 mmol, 1.5 equiv.; ~1.05 equiv. active 'Cl_2') was added to a separate flask containing Na_2SO_4 (1 large spatula scoop) which had been oven-dried for 2 hours, then cooled in a dessicator. The flask was sealed, purged with Ar, and CH_2Cl_2 (15 mL) was added. The canary-yellow solution was allowed to sit for 30 min, with occasional swirling to ensure the Et_4NCl_3 was completely dissolved.

The reaction mixture containing protected allylic alcohol ***E*-3.4** was cooled to –78 °C, at which point the solution of Et_4NCl_3 was decanted off of the Na_2SO_4 via syringe and added to the reaction mixture over a period of 5 min. After the addition was complete, the pale-yellow reaction mixture was stirred for 1.5 h at –78 °C, warmed to 0 °C and stirred an additional 15 minutes. After the allotted time, cyclohexene (1.0 mL) was added to the reaction mixture at 0 °C, and the yellow color quickly dissipated. A solution of saturated aqueous $NaHCO_3$ (10 mL) was added at 0 °C, and the reaction mixture was warmed to r.t. and stirred for 20 min. A 10% solution of NH_4OH in MeOH (4 mL) was added and the reaction mixture was stirred for 45 minutes at r.t. The crude reaction mixture was extracted with CH_2Cl_2 (3 x 15 mL). The organic extracts were with brine (1 x 20 mL), dried over $MgSO_4$, and concentrated in vacuo. To ease purification, the crude mixture was dissolved in MeOH (10 mL), cooled to 0 °C, and excess $NaBH_4$ was added, the solution warmed to r.t. and stirred 1 h (this step reduces all aldehyde byproducts to more easily separated products). Saturated aqueous $NaHCO_3$ (5 mL) was added, and the reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (SiO_2, 85:10:5–70:20:10

pentane:CH_2Cl_2:EtOAc) afforded (2*R*,3S,4R)-dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-ol (**3.9**) as as a clear oil, which forms a crystalline solid over a period of several hours (1.62 g, 52%). R_f = 0.33, 4:1 pentane:EtOAc; $[\alpha]_D^{25}$ –27.9° (*c* 0.91, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.79 (td, *J* = 6.7, 1.5, 1H), 4.24 (d, *J* = 1.4, 1H), 4.13 (dd, *J* = 8.2, 6.9, 1H), 3.92 (m, 2H), 3.73 (dd, *J* = 12.4, 5.0, 1H), 2.35 (br s, 1H), 1.68 (s, 3H), 1.48 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 110.7, 76.3, 74.1, 69.3, 18.1, 64.2, 26.0, 25.8, 22.3; IR (thin film) 3447, 2986, 2937, 2883, 1456 cm^{-1}; Accurate Mass (ESI/MeOH) *m / z* calculated for $C_9H_{16}{}^{35}Cl_2O_3Na$ 265.0374 $(M + Na)^+$, found 265.0372 $(M + Na)^+$.

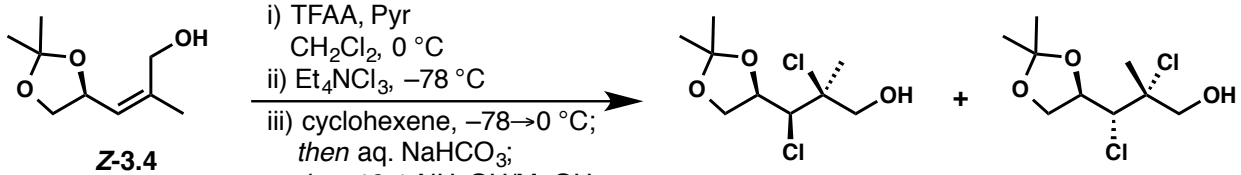


3.10

(2*S*,3*R*,4*R*)-Dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-ol (3.10)

When the above reaction (procedure **B**) was conducted on 2 g (~12 mmol) scale, a small amount (~100 mg) of the minor diastereomer was isolated.

R_f = 0.36, 4:1 pentane:EtOAc; $[\alpha]_D^{25}$ +45.1° (*c* 0.89, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.55 (appar. q, *J* = 7.4, 1H), 4.20 (dd, *J* = 8.9, 6.2, 1H), 4.15 (d, *J* = 7.7), 3.96–3.99 (m, 2H), 3.79 (dd, *J* = 12.0, 8.8, 1H), 2.72 (dd, *J* = 8.7, 6.7, 1H), 1.69 (s, 3H), 1.44 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 110.9, 75.6, 73.6, 69.7, 68.7, 66.6, 26.5, 26.2, 26.0.



***Z*-3.4** **3.13** **S3.1**

(2*S*,3*S*,4*R*)-Dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-ol (3.13) +

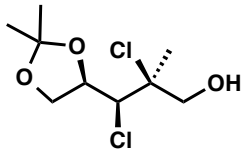
(2*R*,3*R*,4*R*)-Dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-ol (S3.1)

To a solution of ***Z*-3.4** (0.320 g, 1.90 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) at 0 °C was added trifluoroacetic anhydride (0.31 mL, 2.2 mmol, 1.2 equiv.) dropwise via syringe. The solution was stirred 15 min at 0 °C, then pyridine (0.15 mL, 1.9 mmol, 1.0 equiv.) was added dropwise via syringe, and the mixture was stirred an additional 15 min at 0 °C.

Meanwhile, Et_4NCl_3[1] (1.15 g, 4.9 mmol, 1.8 equiv.; 1.05 equiv. active 'Cl_2') was added to a separate flask containing Na_2SO_4 (1 large spatula scoop) which had been oven-dried for 2 hours, then cooled in a dessicator. The flask was sealed and purged with Ar, and CH_2Cl_2 (5 mL) was added. The canary-yellow solution was allowed to sit for 30 min, swirling to ensure the Et_4NCl_3 was completely dissolved.

The reaction mixture containing the protected allylic alcohol ***Z*-3.4** was cooled to –78 °C, at which point the solution of Et_4NCl_3 was decanted off of the Na_2SO_4 via syringe and added to the reaction mixture over a period of 5 min. After the addition was complete, the pale-yellow reaction mixture was stirred for 1.5 h at –78 °C, warmed to 0 °C and stirred an additional 15 minutes. After the allotted time, cyclohexene (0.25 mL) was added to the reaction mixture at 0 °C, and the yellow color quickly dissipated. A solution of saturated aqueous $NaHCO_3$ (5 mL) was added at 0 °C, and the reaction mixture was warmed to r.t. and stirred for 20 min. A 10% solution of NH_4OH in MeOH (3 mL) was added, and the reaction mixture was stirred for 45 min at r.t. The crude reaction mixture was extracted with CH_2Cl_2 (3 x 5 mL) and the organic extracts were washed with brine (1 x 10 mL), dried over $MgSO_4$, and concentrated in vacuo. To ease purification, the crude mixture was dissolved in MeOH (5 mL), cooled to 0 °C, and excess $NaBH_4$ was added, the solution was warmed to r.t. and stirred 1 h (this step reduces all aldehyde

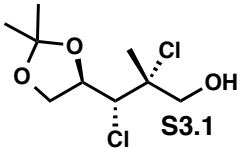
byproducts to more easily separated products). Saturated aqueous $NaHCO_3$ (5 mL) was added, and the reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL), dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (SiO_2, 85:10:5–70:20:10 pentane:CH_2Cl_2:EtOAc) afforded a 6:1 mixture of (2*S*,3*S*,4*R*)-dichloro-4*R*,5-isopropylidenedioxy-2-methylpentan-1-ol (**3.13**) and (2*R*,3*R*,4*R*)-dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-ol (**S3.1**) as a clear oil (0.296 g, 66%). Separation was accomplished for characterization purposes by oxidizing the primary alcohol (Dess–Martin periodane), separating the diastereomers via flash chromatography, then reducing each back to the alcohol ($NaBH_4$). In general the mixture was used without separation in the subsequent step.



3.13

(2*S*,3*S*,4*R*)-Dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-ol (3.13)

R_f = 0.36, 4:1 pentane:EtOAc; $[\alpha]_D^{25}$ –5.5° (*c* 0.95, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.88 (t, *J* = 6.8, 1H), 4.15 (dd, *J* = 8.2, 7.0, 1H), 4.07 (s, 1H), 3.99 (d, *J* = 12.8, 1H), 3.93 (dd, *J* = 8.3, 6.6, 1H), 3.68 (d, *J* = 12.4, 1H), 3.40 (br s, 1H), 1.72 (s, 3H), 1.49 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 111.1, 74.7, 73.2, 67.9, 67.8, 67.1, 27.5, 25.8, 25.7; IR (thin film) 2991, 2937, 2886, 1743, 1455, cm^{-1}; Accurate Mass (ESI/MeOH) *m / z* calculated for $C_9H_{16}Cl_2O_3Na$ 265.0374 $(M + Na)^+$, found 265.0373 $(M + Na)^+$.

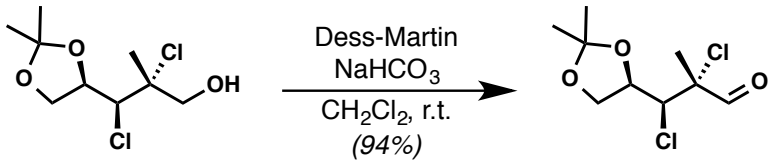


S3.1

(2*R*,3*R*,4*R*)-Dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-ol (S3.1)

R_f = 0.37, 4:1 pentane:EtOAc; $[\alpha]_D^{25}$ +14.4° (*c* 0.98, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ

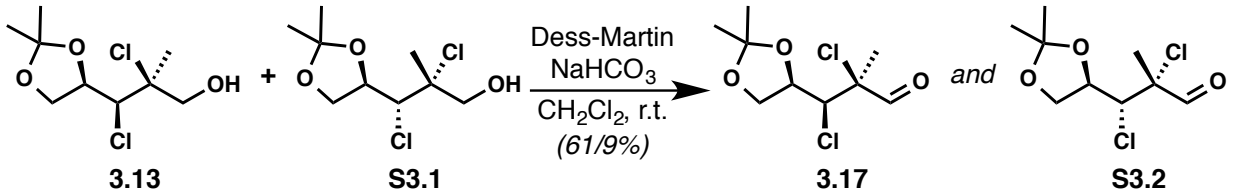
4.36 (appar. q, *J* = 6.7, 1H), 4.23 (dd, *J* = 9.0, 6.2, 1H), 4.20 (d, *J* = 8.3, 1H), 4.00 (dd, *J* = 9.0, 7.0, 1H), 3.89 (d, *J* = 4.3, 2H), 2.66 (br s, 1H), 1.71 (s, 3H), 1.44 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 111.1, 75.8, 74.7, 70.1, 69.2, 68.2, 26.4, 26.0, 23.4.



3.9 **3.16**

(2*R*,3*S*,4*R*)-Dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-al (3.16)

To a solution of **3.9** (1.48 g, 6.1 mmol, 1.0 equiv.) in CH_2Cl_2 (40 mL) open to air was added $NaHCO_3$ (1.54 g, 18.4 mmol, 3.0 equiv.) in one portion, followed by Dess–Martin periodinane (3.35 g, 7.9 mmol, 1.3 equiv.) in one portion. The reaction mixture was stirred for 4 h at r.t. Saturated aqueous $NaHCO_3$ (10 mL) was added and the biphasic mixture was stirred for 30 min. The crude reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were washed with H_2O (15 mL) and brine (15 mL), followed by drying over $MgSO_4$ and concentration in vacuo. Flash chromatography (SiO_2, 90:10:0–85:10:5 pentane:CH_2Cl_2:EtOAc) afforded (2*R*,3*S*,4*R*)-dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-al (**3.16**) as a clear, colorless oil (1.40 g, 94%). (R_f = 0.62, 4:1 pentane:EtOAc); $[\alpha]_D^{25}$ +26.9° (*c* 0.99, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.28 (s, 1H), 4.75 (td, *J* = 6.6, 2.1, 1H), 4.22 (d, *J* = 2.1, 1H), 4.14 (dd, *J* = 8.3, 6.9, 1H), 3.95 (dd, *J* = 8.4, 6.4, 1H), 1.78 (s, 3H), 1.45 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.9, 110.9, 73.1, 72.0, 67.5, 63.0, 26.0, 25.7, 19.1; IR (thin film) 2989, 2938, 2888, 1742, 1456, cm^{-1}; Accurate Mass (CI/CH_2Cl_2) *m / z* calculated for $C_9H_{14}{}^{35}Cl_2O_3H$ 241.0398 $(M + H)^+$, found 241.0400 $(M + H)^+$.

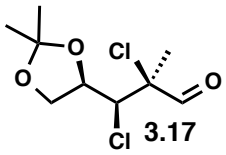


(2*S*,3*S*,4*R*)-Dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-al + (3.13)

(2*R*,3*R*,4*R*)-Dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-al (S3.1)

To a solution of **XX** + **XX** (0.953 g, 3.92 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL) open to air was added $NaHCO_3$ (0.988 g, 11.76 mmol, 3.0 equiv.) in one portion, followed by Dess–Martin periodinane (2.161 g, 5.10 mmol, 1.3 equiv.) in one portion. The reaction mixture was stirred for 4 h at r.t. Saturated aqueous $NaHCO_3$ (10 mL) was added and the biphasic mixture was stirred for 30 min. The crude reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were washed with H_2O (15 mL) and brine (15 mL), followed by drying over $MgSO_4$ and concentration in vacuo. Flash chromatography (SiO_2, 90:10:0–85:10:5 pentane:CH_2Cl_2:EtOAc) afforded (2*S*,3*S*,4*R*)-dichloro-4*R*,5-isopropylidenedioxy-2-methylpentan-1-al **(3.17)** as a colorless, crystalline solid (0.574 g, 61%*) and (2*R*,3*R*,4*R*)dichloro-4*R*,5-isopropylidenedioxy-2-methylpentan-1-al (**S3.2**) as a clear oil (0.087 g, 9%*).

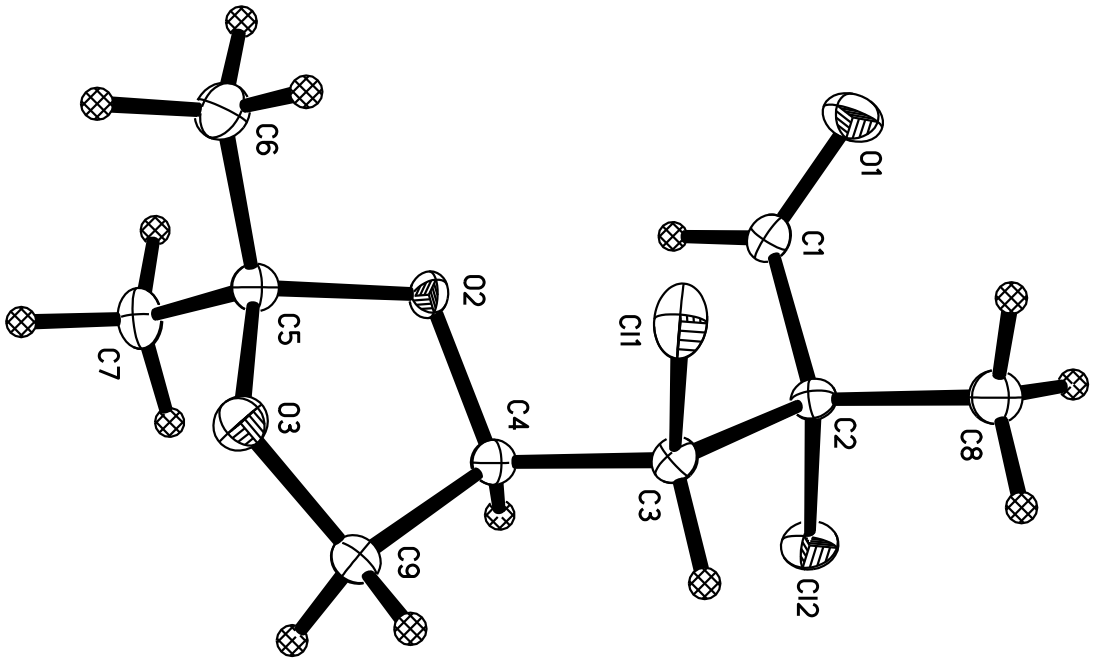
*Isolated yields; multiple rounds of chromatography were generally needed to sufficiently separate the diastereomers. The first round of chromatography yielded a mixture of the diastereomers free of other byproducts (0.816 g, 86%).

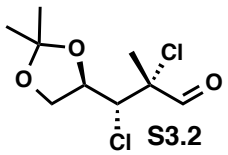


(2*S*,3*S*,4*R*)-Dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-al (3.17)

R_f = 0.62, 4:1 pentane:EtOAc; $[\alpha]_D^{25}$ –80.2° (*c* 0.96, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 9.58 (s, 1H), 4.92 (td, *J* = 5.4, 1.6, 1H), 4.13 (dd, *J* = 8.2, 7.2, 1H), 4.11 (d, *J* = 1.6, 1H), 3.96

(dd, J = 8.4, 5.8, 1H), 1.80 (s, 3H), 1.44 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.1, 111.2, 73.9, 73.6, 67.3, 66.8, 25.7, 25.4, 24.1; IR (thin film) 2988, 2938, 2888, 1733 cm^{-1}; Accurate Mass (CI/CH_2Cl_2) m / z calculated for $C_9H_{14}{}^{35}Cl_2O_3H$ 241.0398 $(M + H)^+$, found 241.0398 $(M + H)^+$. Crystals suitable for X-ray analysis were obtained by slow evaporation of CH_2Cl_2 (**cdv31**).

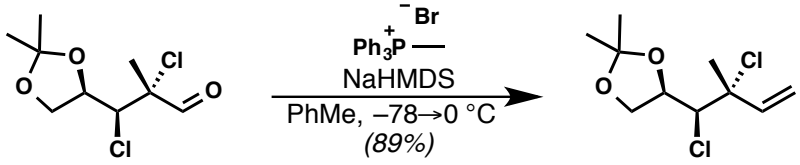




S3.2

(2*R*,3*R*,4*R*)-Dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-al (S3.2)

R_f = 0.71, 4:1 pentane:EtOAc; $[\alpha]_D^{25}$ +30.0° (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 9.28 (s, 1H), 4.24–4.15 (m, 3H), 4.04–4.00 (m, 1H), 1.73 (s, 3H), 1.42 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.9, 111.7, 76.1, 74.0, 68.6, 65.9, 26.6, 25.1, 18.7; IR (thin film) 2990, 2936, 2853, 1739 cm^{-1}; Accurate Mass (CI/CH_2Cl_2) *m / z* calculated for $C_9H_{14}{}^{35}Cl_2O_3H$ 241.0398 $(M + H)^+$, found 241.0398 $(M + H)^+$.

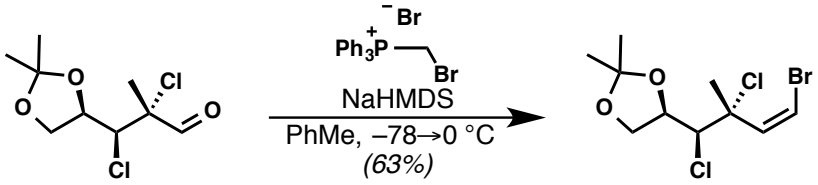


3.16 **3.18**

(3*R*,4*S*,5*R*)-Dichloro-5,6-isopropylidenedioxy-3-methylbutene (3.18)

Methyltriphenylphosphonium bromide (1.333 g, 3.73 mmol, 1.8 equiv.) was heated at 110 °C under vacuum for 4 h in the reaction vessel, with subsequent cooling to room temperature, followed by addition of PhMe (25 mL). The suspension was cooled to 0 °C, and NaHMDS (1.0 M in THF, 2.9 mL, 2.90 mmol, 1.4 equiv.) was added driopwise via syringe. The mixture quickly turned canary yellow, and was stirred for 1 h at 0 °C. The yellow suspension was cooled to –78 °C, and **3.16** (0.504 g, 2.09 mmol, 1.0 equiv.) in PhMe (5 mL) was added dropwise to the solution of the ylide and stirred at –78 °C for 1 h. The temperature was raised to 0 °C and the reaction progress was carefully monitored by TLC until the starting material was consumed (~25–30 min). The reaction was cooled to –78 °C, and hexanal (0.1 mL) in PhMe (1.0 mL) was added. The reaction was stirred at –78 °C for 15 min, then 0 °C for 15 min. H_2O (10 mL) was added, and the crude mixture was extracted with hexanes (3 x 20 mL). The combined organic

extracts were washed with brine (15 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (SiO_2, 90:10:0–89:10:1 hexanes:CH_2Cl_2:EtOAc) afforded (3*R*,4*S*,5*R*)-dichloro-5,6-isopropylidenedioxy-3-methylbutene (**3.18**) as a clear oil (0.449 g, 89%). R_f = 0.62, 9:1 pentane:EtOAc; $[\alpha]_D^{25}$ +7.2° (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03 (dd, *J* = 17.0, 10.6, 1H), 5.39 (d, *J* = 17.0, 1H), 5.23 (d, *J* = 10.6, 1H), 4.84 (td, *J* = 6.7, 2.0, 1H), 4.11 (t, *J* = 6.9, 1H), 3.95 (d, *J* = 1.9, 1H), 3.84 (t, *J* = 7.2, 1H), 1.81 (s, 3H), 1.45 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.3, 115.5, 110.4, 74.1, 72.7, 68.1, 26.1, 25.9, 23.9; IR (thin film) 3097, 2989, 2937, 2884, 1455 cm^{-1}; Accurate Mass (CI/CH_2Cl_2) *m / z* calcd for $C_{10}H_{17}{}^{35}Cl_2O_2$ 239.0606 $(M + H)^+$, found 239.0599 $(M + H)^+$.

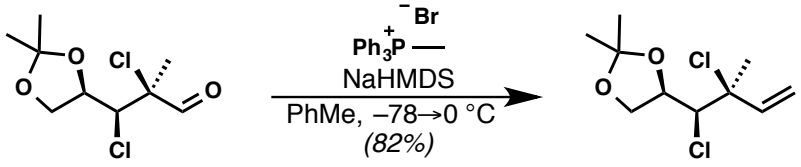


3.16 **Z-3.19**

(*Z*)-(3*R*,4*S*,5*R*)-Dichloro-5,6-isopropylidenedioxy-1-bromo-3-methylbutene (*Z*-3.19)

To a suspension of (bromomethyl)triphenylphosphonium bromide (0.724 g, 1.7 mmol, 1.6 equiv., dried under vacuum at 110 °C for 4 h. prior to use) in PhMe (8 mL) was added NaHMDS (0.84 M in THF, 1.9 mL, 1.5 mmol, 1.5 equiv.) at –78 °C, and the mixture was stirred for 2 h, changing to a bright yellow over time. A solution of **3.16** (0.254 g, 1.1 mmol, 1.0 equiv.) in PhMe (2 mL) was added dropwise via syringe over 5 min. The reaction mixture was allowed stir for 1 h at –78 °C, then warmed slowly to 0 °C (over ~3 h, achieved by ceasing addition of dry ice to the cooling bath) and stirred an additional 30 min. The reaction was quenched by the addition of 5% AcOH in MeOH (1 mL). The crude mixture was extracted with hexanes (3 x 10 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (1 x 10 mL), dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (SiO_2, 90:10:0–89:10:1

hexanes:CH_2Cl_2:EtOAc) afforded a 10:1 *Z*:*E* mixture of (*Z*/*E*)-(3*R*,4*S*,5*R*)-dichloro-5,6-isopropylidenedioxy-3-methylbut-1-ene (***Z*-3.19**) as a clear, colorless oil (0.213 g, 63%). *Z*-isomer: R_f = 0.62, 9:1 pentane:EtOAc; $[\alpha]_D^{25}$ +9.6° (*c* 0.99, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.51 (d, *J* = 8.3, 1H), 6.40 (d, *J* = 8.3, 1H), 4.80 (td, *J* = 6.8, 2.2, 1H), 4.53 (d, *J* = 2.1, 1H), 4.2 (dd, *J* = 8.2, 6.8, 1H), 3.96 (dd, *J* = 8.2, 7.0, 1H), 2.08 (s, 3H), 1.54 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.2, 136.6, 110.1, 73.8, 70.3, 68.0, 67.1, 26.7, 26.0, 25.8; IR (thin film) 2986, 1654, 1457, 1372 cm^{-1}; Accurate Mass (EI/CH_2Cl_2) *m* / *z* calcd for $C_9H_{12}Br^{35}Cl_2O_2$ 300.9398 $(M - CH_3)^+$, found 300.9411 $(M - CH_3)^+$.

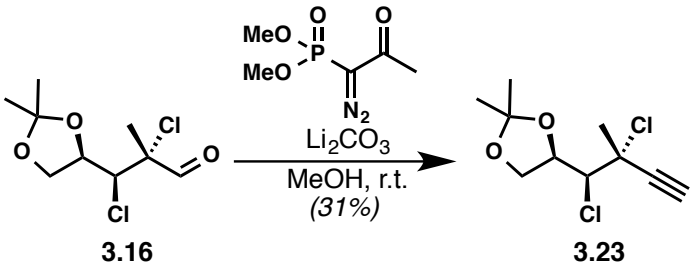


3.17 **3.20**

(3*S*,4*S*,5*R*)-Dichloro-5,6-isopropylidenedioxy-3-methylbutene (3.20)

Methyltriphenylphosphonium bromide (0.433 g, 1.21 mmol, 1.8 equiv.) was heated at 110 °C under vacuum for 4 h. in the reaction vessel, with subsequent cooling to room temperature, followed by addition of PhMe (6 mL). The suspension was cooled to 0 °C, and NaHMDS (0.9 M in THF, 1.0 mL, 0.9 mmol, 1.4 equiv.) was added dropwise via syringe. The solution quickly turned canary yellow, and was stirred for 1 h at 0 °C. The yellow suspension was cooled to –78 °C, and **3.17** (0.162 g, 0.67 mmol, 1.0 equiv.) in PhMe (2 mL) was added dropwise to the solution of the ylide. The mixture was stirred at –78 °C for 1 h, then the temperature was raised to 0 °C and the reaction progress was carefully monitored by TLC until the starting material was consumed (~25–30 min). The reaction was cooled to –78 °C, and hexanal (0.1 mL) in PhMe (1.0 mL) was added. The reaction was stirred at –78 °C for 15 min, then 0 °C for 15 min. H_2O (10 mL) was added, and the crude mixture was extracted with hexanes (3 x 25 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and concentrated in vacuo.

Flash chromatography (SiO_2, 90:10:0–89:10:1 hexanes:CH_2Cl_2:EtOAc) afforded (3*S*,4*S*,5*R*)-dichloro-5,6-isopropylidenedioxy-3-methylbutene (**3.20**) as a clear oil (0.132 g, 82%). R_f = 0.55, 9:1 pentane:EtOAc; $[\alpha]_D^{25}$ –50.5° (*c* 0.97, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.21 (dd, *J* = 17.1, 10.7, 1H), 5.43 (d, *J* = 17.0, 1H), 5.29 (d, *J* = 10.7, 1H), 4.62 (td, *J* = 6.7, 2.7, 1H), 4.08 (dd, *J* = 8.2, 6.7, 1H), 4.02 (d, *J* = 2.7, 1H), 3.87 (dd, *J* = 8.1, 7.1, 1H), 1.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 116.7, 110.3, 74.7, 72.9, 69.7, 68.2, 27.6, 26.1, 25.9; IR (thin film) 2989, 2936, 2886, 1456, 1412, 1372 cm^{-1}; Accurate Mass (CI/CH_2Cl_2) *m / z* calcd for $C_{10}H_{17}{}^{35}Cl_2O_2$ 239.0606 $(M + H)^+$, found $(M + H)^+$.

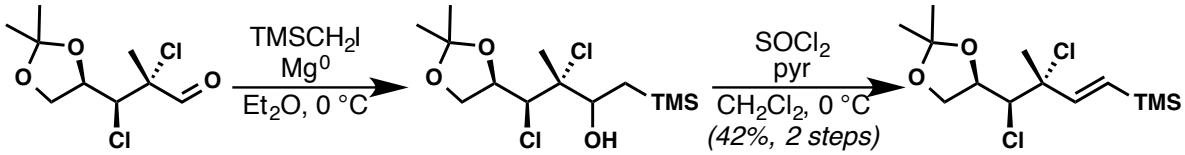


3.16 **3.23**

(3*R*,4*S*,5*R*)-Dichloro-5,6-isopropylidenedioxy-3-methylbutyne (3.23)

To a suspension of Li_2CO_3 (0.574 g, 7.8 mmol, 10 equiv.) in MeOH (4 mL) was added Ohira–Bestmann reagent (0.222 g, 1.16 mmol, 1.5 equiv.) in MeOH (4 mL). The suspension was stirred 5 minutes, and **3.16** (0.187 g, 0.78 mmol, 1.0 equiv.) in MeOH (2 mL) was added. The flask was covered in foil, and the mixture stirred for 48 h at r.t. The mixture was diluted with CH_2Cl_2 (XX mL), the Li_2CO_3 filtered off through a sintered glass funnel, and the resulting solution concentrated. Flash chromatography (SiO_2, 90:10:0–89:10:1 hexanes:CH_2Cl_2:EtOAc) afforded (3*R*,4*S*,5*R*)-Dichloro-5,6-isopropylidenedioxy-3-methylbutyne (**3.23**) as a clear oil (0.058 g, 31%). R_f = 0.53, 9:1 pentane:EtOAc; $[\alpha]_D^{25}$ –6.8° (*c* 0.81, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.77 (td, *J* = 6.7, 3.2, 1H), 4.17 (dd, *J* = 8.4, 6.5, 1H), 4.10 (d, *J* = 3.3, 1H), 3.95 (dd, *J* = 8.4, 6.8, 1H), 2.77 (s, 1H), 1.98 (s, 3H), 1.47 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 110.4, 83.8, 75.3, 74.5, 68.1, 67.8, 62.6, 29.4, 26.2, 25.9; IR (thin film) 2988, 2955, 2897, 2103,

1614 cm^{-1}; Accurate Mass (CI/CH_2Cl_2) *m / z* calcd for $C_{10}H_{14}{}^{35}Cl_2O_2NH_4$ 254.0715 $(M + NH_4)^+$, found 254.0718 $(M + NH_4)^+$.



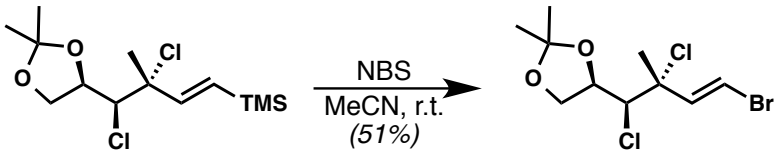
3.16 **3.24** **3.25**

(*E*)-(3*R*,4*S*,5*R*)-Dichloro-5,6-isopropylidenedioxy-1-(trimethylsilyl)-3-methylbutene (3.25)

A flask containing Mg^0 (powder, 0.608 g, 25.0 mmol, 50 equiv.) was flame-dried under vacuum 3x, cooled, and backfilled with argon. Et2O (7 mL) was added, and the suspension cooled to 0 °C. $TMSCH_2I$ (0.93 mL, 6.3 mmol, 13 equiv.) was added dropwise. The flask was briefly warmed to initiate the Grignard formation, and once bubbles were seen forming, inserted back into the ice bath. Once the addition was complete, the mixture was stirred for 1 h at 0 °C. Stirring was stopped and the solids allowed to settle. Half of the total volume was drawn into a syringe and added dropwise to a flask containing **3.16** (0.119 g, 0.49 mmol, 1.0 equiv.) in Et_2O (8 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C, quenched with 10% aq. NH_4Cl (~5 mL), H_2O added (~10 mL), extracted with Et_2O (3 x 10 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude mixture was subjected to the next reaction without further purification.

To a flask containing crude alcohol **3.24** was added CH_2Cl_2 (6 mL). The solution was cooled to 0 °C, and $SOCl_2$ (0.1 mL, 1.4 mmol, 2.5 equiv.) was added dropwise. The mixture was stirred 5 min., and pyridine (0.25 mL 3.1 mmol, 6.3 equiv.) was added over 30 sec. The reaction mixture was stirred for 1.5 h, quenched with sat. aq. $NaHCO_3$ (~10 mL), extracted with CH_2Cl_2, the combined organic extracts washed with sat. aq. $NaHCO_3$ (~10 mL), dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (SiO_2, 90:10:0–89:10:1 hexanes:CH_2Cl_2:EtOAc) afforded (*E*)-(3*R*,4*S*,5*R*)-Dichloro-5,6-isopropylidenedioxy-1-(trimethylsilyl)-3-methylbutene

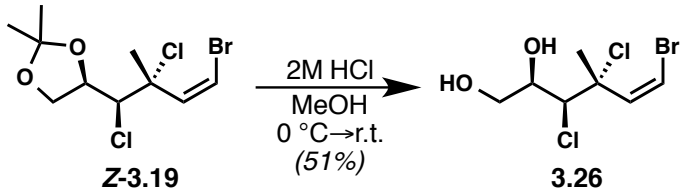
(**3.25**) as a clear oil (0.065 g, 42%). R_f = 0.39, 9:1 pentane:EtOAc; $[\alpha]_D^{25}$ +19.8° (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.10 (d, *J* = 18.5, 1H), 6.02 (d, *J* = 18.5, 1H), 4.80 (td, *J* = 6.8, 2.8, 1H), 4.09 (dd, *J* = 8.2, 6.6, 1H), 3.96 (d, *J* = 2.79, 1H), 3.83 (dd, *J* = 8.2, 7.0, 1H), 1.80 (s, 3H), 1.46 (s, 3H), 1.38 (s, 3H), 0.102 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.1, 130.6, 110.3, 77.2, 74.5, 73.9, 68.3, 68.2, 26.2, 25.9, 24.4, –1.3; IR (thin film) XXXX cm^{-1}; Accurate Mass (CI/CH_2Cl_2) *m / z* calcd for $C_{13}H_{24}{}^{35}Cl_2O_2SiNH_4$ 328.1266 $(M + NH_4)^+$, found 328.1260 $(M + NH_4)^+$.



3.25 ***E*-3.19**

(*E*)-(3*R*,4*S*,5*R*)-Dichloro-5,6-isopropylidenedioxy-1-bromo-3-methylbutene (*E*-3.19)

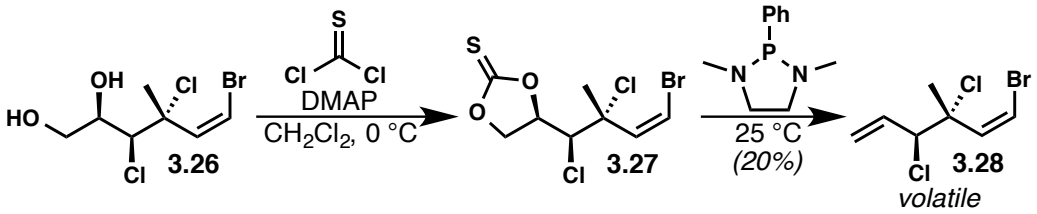
To a flask containing **3.25** (0.065 g, 0.21 mmol, 1.0 equiv.) in MeCN (5 mL) was added NBS (0.185 g, 1.04 mmol, 5 equiv.) in a single portion. The flask was sealed, covered in foil, and the reaction mixture stirred 48 h at r.t. The reaction was quenched with sat. aq. $Na_2S_2O_3$ (~2mL) and H_2O (~5 mL), extracted with CH_2Cl_2 (3 x ~10 mL), the combined organic extracts washed with brine (~5 mL), dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (SiO_2, 90:10:0–89:10:1 hexanes:CH_2Cl_2:EtOAc) afforded (*E*)-(3*R*,4*S*,5*R*)-Dichloro-5,6-isopropylidenedioxy-1-bromo-3-methylbutene (***E*-3.19**) as a clear oil (0.034 g, 42%). R_f = 0.41, 9:1 pentane:EtOAc; $[\alpha]_D^{25}$ +17.0° (*c* 1.04, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.54 (d, *J* = 13.5, 1H), 6.44 (d, *J* = 13.6, 1H), 4.82 (td, *J* = 6.7, 2.1, 1H), 4.12 (dd, *J* = 8.2, 6.7, 1H), 3.94 (d, *J* = 2.1, 1H), 3.87 (dd, *J* = 8.2, 6.7, 1H), 1.82 (s, 3H), 1.46 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.3, 110.7, 109.5, 72.5, 68.05, 68.01, 26.0, 25.8, 24.6; IR (thin film) 3088, 2987, 2935, 2884, 1725, 1621 cm^{-1}; Accurate Mass (CI/CH_2Cl_2) *m / z* calcd for $C_{10}H_{15}{}^{79}Br^{35}Cl_2O_2H$ 316.9711 $(M + H)^+$, found 316.9720 $(M + H)^+$.



***Z*-3.19** **3.26**

(*Z*)-(3*S*,4*R*)dichloro-6-bromo-4-methyl-5-hexene-1,2*R*-diol (3.26)

To a solution of (0.933 g, 2.93 mmol) in wet MeOH (20 mL) at 0 °C was added a solution of 2M HCl (2.0 mL) in MeOH (6 mL) cooled to 0 °C dropwise via pipette. The reaction mixture was allowed to stir and warm over 18 h, at which point saturated aqueous $NaHCO_3$ (5 mL) was carefully added to avoid bubbling over. The crude mixture was extracted with EtOAc (3 x 10 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash Chromatography (90:10–80:20 hexanes:EtOAc) afforded (*Z*)-(3*S*,4*R*)dichloro-6-bromo-4-methyl-5-hexene-1,2*R*-diol **3.26** as an off-white solid (0.436 g, 53%). (R_f = 0.22, 4:1 hexane:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.46 (d, *J* = 8.2, 1H), 6.34 (d, *J* = 8.2, 1H), 4.52–4.48 (m, 1H), 4.27–4.22 (m, 1H), 4.11 (d, *J* = 4.6, 1H), 3.76 (d, *J* = 4.1, 1H), 3.74 (d, *J* = 4.1, 1H), 2.21 (d, *J* = 4.4, 1H), 1.61 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.3, 107.8, 85.4, 79.0, 71.5, 70.8, 23.1; accurate mass (ES–/MeOH) *m / z* calcd for $C_7H_{10}{}^{79}Br^{35}Cl_2O_2$ 274.9241 $(M - H)^-$, found 274.9248 $(M–H)^-$.

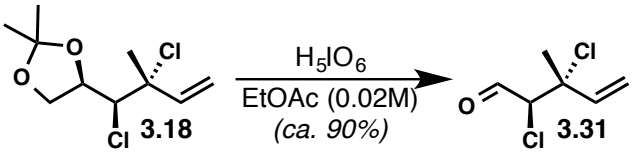


(*Z*)-(3*R*,4*S*)dichloro-1-bromo-3-methyl-1,5-hexadiene (3.28)

To a flask containing diol **3.26** (0.436 g, 1.57 mmol, 1.0 equiv.) was added CH_2Cl_2 (15 mL), followed by DMAP (0.498 g, 4.08 mmol, 2.6 equiv.). The mixture was cooled to 0 °C, and thiophosgene (0.16 mL, 2.08 mmol, 1.3 equiv) dropwise via syringe. The reaction mixture was stirred for 1.5 h at 0 °C, warmed to r.t., and SiO_2 added. The solvent was evaporated, the SiO_2

loaded onto a short plug of silica, and eluted with CH_2Cl_2 to afford crude thiocarbonate **3.27**, which was subjected to the next reaction without further purification.

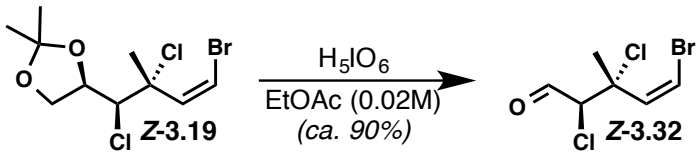
To a vial containing thiocarbonate **3.27** was added 1,3-dimethyl-2-phenyl-1,3,2-diazophospholidine (0.75 mL). The reaction mixture was stirred at r.t. for 18 h, at which time the crude mixture was diluted with CH_2Cl_2 (5 mL) and filtered through a small plug of silica with pentane as the eluent, and the resulting solution concentrated in vacuo. Flash chromatography (pentane) afforded **3.28** as a colorless oil (0.093 g, 33%). (R_f = 0.22, 4:1 hexane:EtOAc); *Z*-isomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.52 (d, *J* = 8.4, 1H), 6.39 (d, *J* = 8.4, 1H), 6.05 (ddd, *J* = 10.2, 8.1, 6.7, 1H), 5.46 (d, *J* = 16.8, 1H), 5.35 (d, *J* = 10.2, 1H), 4.9 (d, *J* = 8.1, 1H), 1.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.2, 133.3, 120.7, 109.6, 70.6, 68.5, 26.2; IR (thin film) 2923, 2850, 2359, 1448 cm^{-1}; attempts to find parent peak in MS failed due to fragmentation.



(2*S*,3*R*)-2,3-Dichloro-3-methylpent-4-enal (3.31)

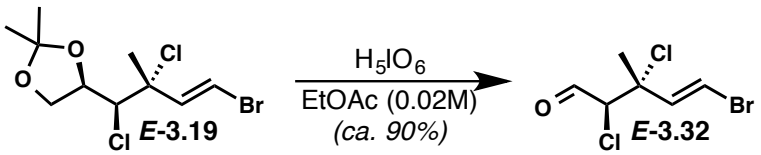
To a suspension of H_5IO_6 (0.315 g, 1.38 mmol, 2.0 equiv.) in EtOAc (15 mL) open to air was added **3.18** (0.166 g, 0.69 mmol, 1.0 equiv.) in EtOAc (5 mL) at r.t. The suspension was stirred at r.t. for 2 h, with the reaction mixture gradually turning white and cloudy over time. Solid Na_2SO_4 was added to the reaction mixture, followed by pentane (20 mL). The suspension was stirred vigorously for 10 min at r.t., and filtered through a plug of 10:1 celite:SiO_2 with CH_2Cl_2 eluent. Concentration in vacuo afforded (2*S*,3*R*)-2,3-dichloro-3-methylpent-4-enal (**3.31**) as a pale yellow oil (0.195 g, 89%), which was used without further purification. Although unstable

to silica gel chromatography, **3.31** can be stored neat at –20 °C for at least one month with minimum decomposition (<5%). R_f = 0.62, 9:1 pentane:EtOAc; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.50 (d, *J* = 3.6, 1H), 6.02 (dd, *J* = 16.9, 10.6, 1H), 5.47 (d, *J* = 16.9, 1H), 5.35 (d, *J* = 10.6, 1H), 4.23 (d, *J* = 3.6, 1H), 1.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.6, 138.3, 117.8, 69.01, 68.97, 26.0; an accurate mass could not be obtained owing to fragmentation.



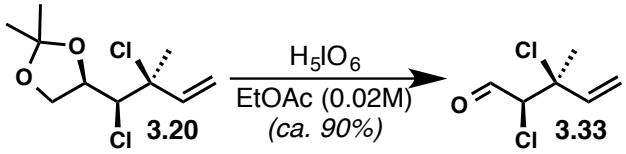
(2*S*,3*R*,*Z*)-5-Bromo-2,3-dichloro-3-methylpent-4-enal (*Z*-3.32)

To a suspension of H_5IO_6 (0.090 g, 0.39 mmol, 2.0 equiv.) in EtOAc (4 mL) open to air was added ***Z*-3.19** (0.062 g, 0.19 mmol, 1.0 equiv.) in EtOAc (2 mL) at r.t. The suspension was stirred at r.t. for 2 h, with the reaction mixture gradually turning white and cloudy over time. Solid Na_2SO_4 was added to the reaction, followed by pentane (10 mL). The suspension was stirred vigorously for 10 min at r.t., and was filtered through a plug of 10:1 celite:SiO_2 with CH_2Cl_2 eluent. Concentration in vacuo afforded (2*S*,3*R*,*Z*)-5-bromo-2,3-dichloro-3-methylpent-4-enal (**XX**) as a pale yellow oil (0.042 g, 87%), which was used without further purification. Although unstable to silica gel chromatography, ***Z*-3.32** can be stored neat at –20 °C for at least one month with minimum decomposition (<5%). R_f = 0.51, 9:1 pentane:EtOAc; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.60 (d, *J* = 2.7, 1H), 6.57 (d, *J* = 8.5, 1H), 6.48 (d, *J* = 8.4, 1H), 4.91 (d, *J* = 2.6, 1H), 2.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.5, 135.1, 111.0, 68.0, 67.6, 26.9; an accurate mass could not be obtained owing to fragmentation.



(2*S*,3*R*,*E*)-5-Bromo-2,3-dichloro-3-methylpent-4-enal (*E*-3.32)

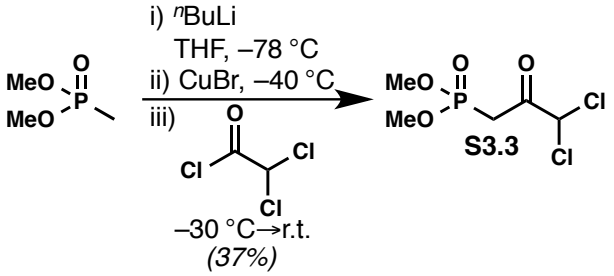
To a suspension of H_5IO_6 (0.169 g, 0.52 mmol, 2.0 equiv.) in EtOAc (8 mL) open to air was added ***E*-3.19** (0.082 g, 0.26 mmol, 1.0 equiv.) in EtOAc (4 mL) at r.t. The suspension was stirred at r.t. for 2 h, with the reaction mixture gradually turning white and cloudy over time. Solid Na_2SO_4 was added to the reaction, followed by pentane (10 mL). The suspension was stirred vigorously for 10 min at r.t., and filtered through a plug of celite with CH_2Cl_2 eluent. Concentration in vacuo afforded (2*S*,3*R*,*E*)-5-bromo-2,3-dichloro-3-methylpent-4-enal (***E*-3.32**) as a pale yellow oil (0.057 g, 90%), which was used without further purification. Although unstable to silica gel chromatography, ***E*-3.32** can be stored neat at –20 °C for at least one month with minimum decomposition (<5%). R_f = 0.54, 9:1 pentane:EtOAc; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.51 (d, *J* = 3.4, 1H), 6.64 (d, *J* = 13.6, 1H), 6.42 (d, *J* = 13.6, 1H), 4.26 (d, *J* = 3.4, 1H), 1.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.0, 137.3, 111.5, 68.7, 68.5, 26.0; an accurate mass could not be obtained owing to fragmentation.



(2*S*,3*S*)-2,3-Dichloro-3-methylpent-4-enal (3.33)

To a suspension of H_5IO_6 (0.144 g, 0.63 mmol, 2.0 equiv.) in EtOAc (5 mL) open to air was added **3.20** (0.076 g, 0.32 mmol, 1.0 equiv.) in EtOAc (3 mL) at r.t. The suspension was stirred at r.t. for 2 h, with the reaction mixture gradually turning white and cloudy over time. Solid Na_2SO_4 was added to the reaction mixture, followed by pentane (10 mL). The suspension was

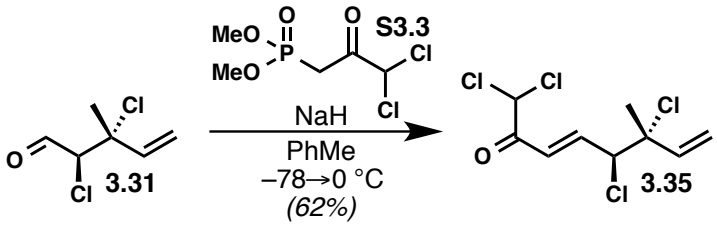
stirred vigorously for 10 min. at r.t., and was filtered through a plug of 10:1 celite:SiO_2 with CH_2Cl_2 eluent. Concentration in vacuo afforded (2*S*,3*S*)-2,3-dichloro-3-methylpent-4-enal (**3.33**) as a pale yellow oil (0.049 g, 91%), which was used without further purification. Although unstable to flash chromatography, (2*S*,3*S*)-2,3-dichloro-3-methylpent-4-enal **(3.33)** can be stored neat at –20 °C for at least one month with minimum decomposition (<5%). R_f = 0.62, 9:1 pentane:EtOAc; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.47 (d, *J* = 3.8, 1H), 6.10 (dd, *J* = 16.8, 10.7, 1H), 5.52 (d, *J* = 16.8, 1H), 5.38 (d, *J* = 10.7, 1H), 4.24 (d, *J* = 3.8, 1H), 1.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.6, 136.7, 118.4, 69.14, 69.08, 28.0; an accurate mass could not be obtained owing to fragmentation.



Dimethyl (3,3-dichloro-2-oxopropyl)phosphonate (S3.3)

^{n}BuLi (2.72 M in THF, 19.6 mL, 53.3 mmol, 1.1 equiv.) was added to a round bottom flask containing THF (175 mL). The resulting solution was cooled to –78 °C, and dimethyl methylphosphonate (6.01 g, 48.4 mmol, 1.05 equiv.) in THF (25 mL) was added dropwise via syringe. The reaction was stirred at –78 °C for 20 min, and CuBr (13.9 g, 96.9 mmol, 2.0 equiv.) was added in a single portion. The resulting suspension was warmed to –40 °C, and the reaction was stirred for 2 h. At this point, dichloroacetyl chloride (4.4 mL, 46.2 mmol, 1.0 equiv.) was added dropwise at –40 °C. The temperature was raised to –30 °C and held there for 4 h. At this point, the reaction was allowed to warm to r.t. overnight. The reaction was quenched by addition of H_2O (~30 mL), stirred 15 minutes, and filtered through a sintered glass filter funnel. The crude mixture was extracted with EtOAc (3 x 40 mL) and the combined organic extracts were

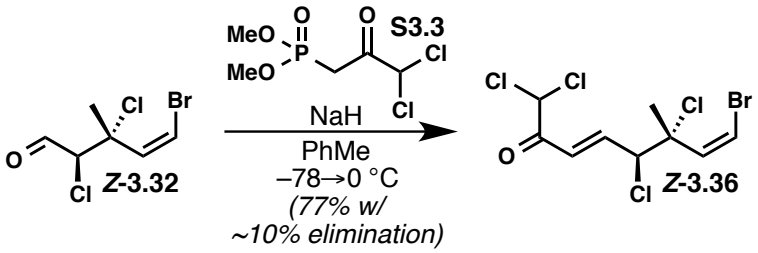
washed with H_2O (3 x 40 mL) and brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography (SiO_2, 90:10–50:50 hexanes:EtOAc, then 90:10–60:40 EtOAc:acetone) afforded dimethyl (3,3-dichloro-2-oxopropyl)phosphonate (**S3.3**) as a yellow oil (4.22 g, 37 %). R_f = 0.23, 3:2 pentane:EtOAc; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.12 (s, 1H), 3.82 (d, J = 11.3, 6H), 3.46 (d, J = 21.9, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.1, 70.1, 53.6, 35.0; IR (thin film) 3291, 2959, 2855, 1742, 1459 cm^{-1}; Accurate Mass (ESI/MeOH) *m / z* calcd for $C_5H_9{}^{35}Cl_2O_4PNa$ 256.9513 $(M + Na)^+$, found 256.9507 $(M + Na)^+$.



(5*S*,6*R*,*E*)-1,1,5,6-Tetrachloro-6-methylocta-3,7-dien-2-one (3.35)

NaH (~60% in oil, 0.052 g, 1.29 mmol, 2.5 equiv.) was washed with hexanes (3 x 2 mL) to remove the oil. PhMe (5 mL) was added, and the suspension was cooled to 0 °C. Phosphonate **S3.3** (0.603 g, 2.57 mmol, 5.0 equiv.) in PhMe (2 mL) was added via syringe, and the yellow solution was stirred at 0 °C for 1 h. The phosphonate solution was cooled to –78 °C, and **3.31** (0.086 g, 0.51 mmol, 1.0 equiv.) in PhMe (3 mL) was added dropwise. The resulting solution was stirred at –78 °C for 1 h. The temperature was raised to –20 °C over a period of ~30 min and stirred 1 h, then raised to 0 °C and stirred 30 min, and finally to r.t. and stirred 30 min. The reaction was quenched by the addition of 5% aq. AcOH (2 mL) and the mixture was extracted with pentane (3 x 5 mL). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (2 x 5 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (SiO_2, 98:1.8:0.2 pentane:CH_2Cl_2:EtOAc) afforded (5*S*,6*R*,*E*)-1,1,5,6-tetrachloro-6-methylocta-3,7-dien-2-one (**3.35**) as a colorless oil (.087 g, 62%), with a small amount of delta-elimination

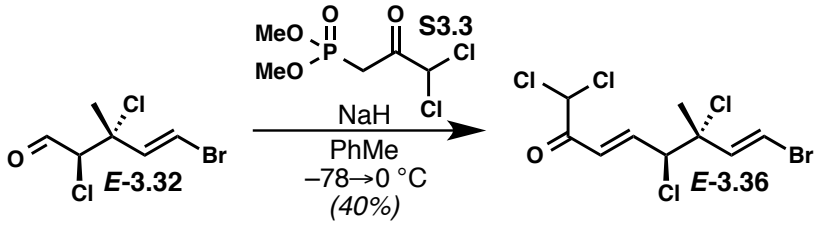
product still present. R_f = 0.63, 9:1 pentane:EtOAc; $[\alpha]_D^{25}$ –8.9° (*c* 0.85, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 15.3, 7.7, 1H), 6.87 (d, *J* = 15.3, 1H), 6.04 (dd, *J* = 17.0, 10.6, 1H), 5. 93 (s, 1H), 5.45 (d, *J* = 17.0, 1H), 5.33 (d, *J* = 10.6, 1H), 4.66 (d, *J* = 7.6, 1H), 1.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.8, 144.8, 139.3, 125.4, 117.3, 77.2, 69.4, 66.6, 24.7; IR (thin film) 3076, 2925, 2853, 1711, 1637, 1581 cm^{-1}; Accurate Mass (CI/CH_2Cl_2) *m / z* calcd for $C_9H_{10}{}^{35}Cl_4ONH_4$ 291.9829 $(M + NH_4)^+$, found 291.9815 $(M + NH_4)^+$.



(5*S*,6*R*,3*E*,7*Z*)-1,1,5,6-Tetrachloro-8-bromo-6-methylocta-3,7-dien-2-one (*Z*-3.36)

NaH (~60% in oil, 0.017g, 0.44 mmol, 2.5 equiv.) was washed with hexanes (3 x 1 mL) to remove the oil residue. PhMe (3 mL) was added, and the suspension was cooled to 0 °C. Phosphonate **S3.3** (0.204 g, 0.87 mmol, 5.0 equiv.) in PhMe (2 mL) was added via syringe, and the yellow solution was stirred at 0 °C for 1 h. The phosphonate solution was cooled to –78 °C, and ***Z*-3.32** (0.043 g, 0.17 mmol, 1.0 equiv.) in PhMe (3 mL) was added dropwise. The resulting solution was stirred at –78 °C for 1 h. The temperature was raised to –20 °C over a period of ~30 min and stirred 1 h, then raised to 0 °C and stirred 30 min, and finally to r.t. and stirred 30 min. The reaction was quenched by the addition of 5% aq. AcOH (2 mL) and the mixture was extracted with pentane (3 x 5 mL). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (2 x 5 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (SiO_2, 98:1.8:0.2 pentane:CH_2Cl_2:EtOAc) afforded (5*S*,6*R*,3*E*,7*Z*)-1,1,5,6-tetrachloro-8-bromo-6-methylocta-3,7-dien-2-one (***Z*-3.36**) as a colorless oil (.042 g, 77%), with ~10% delta-elimination product present. R_f = 0.59, 9:1 pentane:EtOAc; $[\alpha]_D^{25}$ –42.0° (*c* 0.25, $CHCl_3$); ^1H

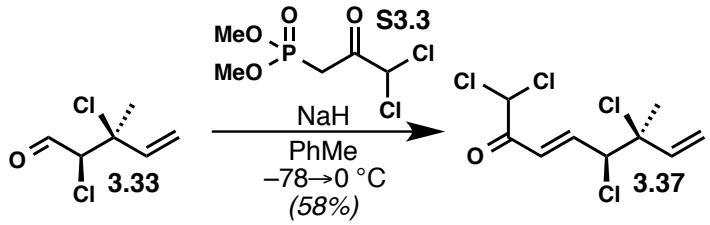
NMR (500 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 15.3, 7.3, 1H), 6.93 (dd, *J* = 15.2, 0.8, 1H), 6.54 (d, *J* = 8.4, 1H), 6.34 (d, *J* = 8.4, 1H), 5.94 (s, 1H), 5.28 (dd, *J* = 7.3, 0.9, 1H), 1.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.7, 144.4, 136.0, 125.6, 110.6, 69.8, 65.0, 26.4; IR (thin film) 3074, 2924, 2852, 1710, 1635, 1594 cm^{-1}; Accurate Mass (CI/CH_2Cl_2) *m / z* calcd for $C_9H_9Br^{35}Cl_4ONH_4$ 369.8935 $(M + NH_4)^+$, found 369.8946 $(M + NH_4)^+$.



(5*S*,6*R*,3*E*,7*Z*)-1,1,5,6-Tetrachloro-8-bromo-6-methylocta-3,7-dien-2-one (*E*-3.36)

NaH (~60% in oil, 0.031 g, 0.78 mmol, 3.3 equiv.) was washed with hexanes (3 x 1 mL) to remove the oil residue. PhMe (3 mL) was added, and the suspension was cooled to 0 °C. Phosphonate **S3.3** (0.365 g, 1.55 mmol, 6.7 equiv.) in PhMe (3 mL) was added via syringe, and the yellow solution was stirred at 0 °C for 1 h. The phosphonate solution was cooled to –78 °C, and ***E*-3.32** (0.057 g, 0.23 mmol, 1.0 equiv.) in PhMe (3 mL) was added dropwise. The resulting solution was stirred at –78 °C for 1 h. The temperature was raised to –20 °C over a period of ~30 min and stirred 1 h, then raised to 0 °C and stirred 30 min, and finally to r.t. and stirred 30 min. The reaction was quenched by the addition of 5% aq. AcOH (2 mL) and the mixture was extracted with pentane (3 x 8 mL). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (2 x 5 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (SiO_2, 98:1.8:0.2 pentane:CH_2Cl_2:EtOAc) afforded (5*S*,6*R*,3*E*,7*Z*)-1,1,5,6-tetrachloro-8-bromo-6-methylocta-3,7-dien-2-one (***E*-3.36**) as a colorless oil (.0.26 g, 32%) contaminated with elimination byproducts. R_f = 0.59, 9:1 pentane:EtOAc; $[\alpha]_D^{25}$ –42.0° (*c* 0.25, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 15.3, 7.3, 1H), 6.93 (dd, *J* = 15.2, 0.8, 1H), 6.54 (d, *J* = 8.4,

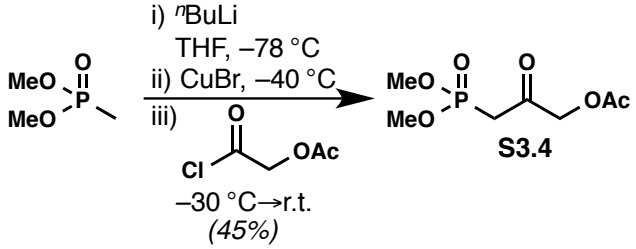
1H), 6.34 (d, J = 8.4, 1H), 5.94 (s, 1H), 5.28 (dd, J = 7.3, 0.9, 1H), 1.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.7, 144.4, 136.0, 125.6, 110.6, 69.8, 65.0, 26.4; IR (thin film) 3074, 2924, 2852, 1710, 1635, 1594 cm^{-1}; Accurate Mass (CI/CH_2Cl_2) m / z calcd for $C_9H_9Br^{35}Cl_4ONH_4$ 369.8935 $(M + NH_4)^+$, found 369.8946 $(M + NH_4)^+$.



(5*S*,6*S*,*E*)-1,1,5,6-Tetrachloro-6-methylocta-3,7-dien-2-one (3.37)

NaH (~60% in oil, 0.028 g, 0.71 mmol, 1.8 equiv.) was washed with dry hexanes (3 x 1 mL) to remove the oil. PhMe (3 mL) was added, and the suspension was cooled to 0 °C. Phosphonate **S3.3** (0.32 g, 2.57 mmol, 3.5 equiv.) in PhMe (1 mL) was added via syringe, and the yellow solution was stirred at 0 °C for 1 h. The phosphonate solution was cooled to –78 °C, and **3.33** (0.065 g, 0.39 mmol, 1.0 equiv.) in PhMe (2 mL) was added dropwise. The resulting solution was stirred at –78 °C for 1 h. The temperature was raised to –20 °C over a period of ~30 min and stirred 1 h, then raised to 0 °C and stirred 30 min, and finally to r.t. and stirred 30 min. The reaction was quenched by the addition of 5% aq. AcOH (2 mL) and the mixture was extracted with pentane (3 x 5 mL). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (2 x 5 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (SiO_2, 98:1.8:0.2 pentane:CH_2Cl_2:EtOAc) afforded (5*S*,6*S*,*E*)-1,1,5,6-tetrachloro-6-methylocta-3,7-dien-2-one (**3.37**) as a colorless oil (.063 g, 58%), with a small amount of delta-elimination product still present. R_f = 0.55, 9:1 pentane:EtOAc; $[\alpha]_D^{25}$ –58.9° (*c* 0.97, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (dd, J = 15.4, 7.9, 1H), 6.84 (d, J = 15.3, 1H), 6.04 (dd, J = 16.9, 10.6, 1H), 5.92 (s, 1H), 5.48 (d, J = 16.9, 1H), 5.36 (d, J = 10.7, 1H), 4.68 (d, J = 7.9, 1H), 1.83 (s, 3H); ^{13}C

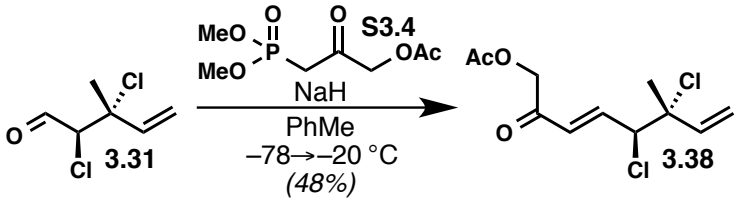
NMR (125 MHz, $CDCl_3$) δ 184.8, 145.0, 136.9, 125.2, 118.4, 71.5, 69.4, 67.0, 27.9; IR (thin film) 2988, 2954, 2926, 2854, 1711, 1637 cm^{-1}; Accurate Mass (CI/CH_2Cl_2) *m / z* calcd for $C_9H_{10}{}^{35}Cl_4ONH_4$ 291.9829 $(M + NH_4)^+$, found 291.9815 $(M + NH_4)^+$.



Dimethyl (3-acetoxy-2-oxopropyl)phosphonate (S3.4)

^{n}BuLi (2.5 M in THF, 24 mL, 60.0 mmol, 1.05 equiv.) was added to a round bottom flask containing THF (175 mL). The resulting solution was cooled to –78 °C, and dimethyl methylphosphonate (7.89 g, 64.0 mmol, 1.1 equiv.) in THF (25 mL) was added dropwise via syringe. The reaction was stirred at –78 °C for 20 min, and CuBr (16.59 g, 116.0 mmol, 2.0 equiv.) was added in a single portion. The resulting suspension was warmed to –40 °C, and the reaction was stirred for 2 h. At this point, acetoxyacetyl chloride (6.2 mL, 57.8 mmol, 1.0 equiv.) was added dropwise at –40 °C. The temperature was raised to –30 °C and held there for 4 h. At this point, the reaction was allowed to warm to r.t. overnight. The reaction was quenched by addition of H_2O (~30 mL), stirred 15 minutes, and filtered through a sintered glass filter funnel. The crude mixture was extracted with EtOAc (3 x 40 mL) and the combined organic extracts were washed with H_2O (3 x 40 mL) and brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography (SiO_2, 90:10–50:50 hexanes:EtOAc, then 90:10–60:40 EtOAc:acetone) afforded dimethyl (3-acetoxy-2-oxopropyl)phosphonate (**S3.4**) as a yellow oil (5.80 g, 45 %). R_f = 0.25, EtOAc; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.82 (s, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 3.15 (s, 1H), 3.11 (s, 1H), 2.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.3 (d), 170.2, 72.0 (d), 68.4, 40.8 (d), 24.1 (d), 24.0 (d); Accurate Mass (ESI/MeOH) *m / z* calcd for

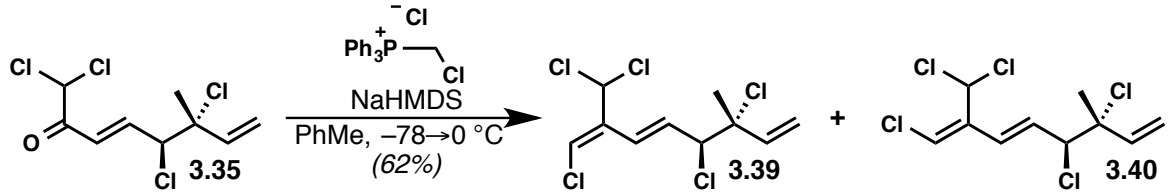
$C_7H_{13}O_6PNa$ 247.0347 $(M + Na)^+$, found 247.0341 $(M + Na)^+$.



(5*S*,6*R*,*E*)-5,6-dichloro-6-methyl-2-oxoocta-3,7-dien-1-yl acetate (3.38)

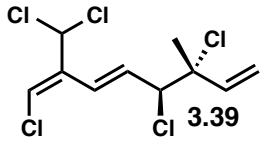
NaH (~60% in oil, 0.018 g, 0.44 mmol, 3.3 equiv.) was washed with dry hexanes (3 x 1 mL) to remove the oil. PhMe (5 mL) was added, and the suspension was cooled to –78 °C. Phosphonate **S3.4** (0.172 g, 0.77 mmol, 6.6 equiv.) in PhMe (5 mL) was added via syringe, and the suspension was slowly warmed to between –20 and –10 °C, at which point the suspension bubbled vigorously, and quickly turned into a homogenous solution. Once the solution turned completely clear, it was immediately cooled back to –78 °C. Aldehyde **3.31** (0.025 g, 0.15 mmol, 1.0 equiv.) in PhMe (6 mL) was added dropwise. The resulting solution was stirred at –78 °C for 2 h. The temperature was raised to –20 °C over a period of ~1 h and stirred 48 h. The reaction was quenched by the addition of 5% aq. AcOH (2 mL) and the mixture was extracted with pentane (3 x 5 mL). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (2 x 5 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (SiO_2, 90:8:25 pentane:CH_2Cl_2:EtOAc) afforded (5*S*,6*R*,*E*)-5,6-dichloro-6-methyl-2-oxoocta-3,7-dien-1-yl acetate (**3.38**) as a colorless oil (.019 g, 48%), with a small amount of delta-elimination product still present. R_f = 0.31, 9:1 pentane:EtOAc; $[\alpha]_D^{25}$ –7.2° (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (dd, *J* = 15.6, 7.7, 1H), 6.43 (dd, *J* = 15.6, 1.1, 1H), 6.02 (dd, *J* = 17.0, 10.6, 1H), 5.44 (d, *J* = 17.0, 1H), 5.31 (d, *J* = 10.6, 1H), 4.85 (s, 2H), 4.57 (dd, *J* = 7.7, 1.1, 1H), 2.19 (s, 3H), 1.74 (s, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.0, 170.3, 141.0, 139.4, 128.9, 117.2, 71.3, 67.5, 66.9, 24.8, 20.6; IR (thin film) 2923, 2852, 1745, 1697, 1634 cm^{-1}; Accurate Mass

(CI/CH_2Cl_2) *m / z* calcd for $C_{11}H_{14}{}^{35}Cl_2O_3NH_4$ 282.0664 $(M + NH_4)^+$, found 282.0662 $(M + NH_4)^+$.



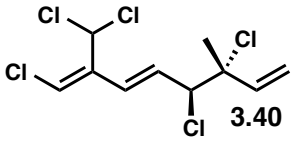
(1*E*,3*E*,5*S*,6*R*)-1,5,6-Trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (3.39) + **(1*Z*,3*E*,5*S*,6*R*)-1,5,6-Trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (3.40)**

To a suspension of (chloromethyl)triphenylphosphonium chloride (0.178 g, 0.51 mmol, 3.5 equiv., dried under vacuum at 120 °C for 4 h prior to use) in PhMe (9 mL) at 0 °C was added NaHMDS (0.86 M in THF, 0.45 mL, 0.39 mmol, 2.6 equiv.). The solution quickly turned yellow, and was allowed to stir at 0 °C for 2 h. The ylide solution was cooled to –78 °C, and a solution of **3.35** (0.040 g, 0.14 mmol, 1.0 equiv.) in PhMe (3 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 1 h, warmed to 0 °C, and stirred for 1 h, at which point the reaction was quenched by the addition of 5% aq. AcOH (2 mL). The crude mixture was extracted with pentane (3 x 8 mL), and the combined organic extracts washed with saturated $NaHCO_3$ (10 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (SiO_2, pentane) afforded a 1.3:1 mixture of (1*E*,3*E*,5*S*,6*R*)-1,5,6-trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (**3.39**) and (1*Z*,3*E*,5*S*,6*R*)-1,5,6-trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (**3.40**) as a clear oil (0.027 g, 62%), which were separated via semi-preparative HPLC. Analytical HPLC conditions: hexanes, 1.0 mL/min at 50 bar, (tR min): major = 6.38 (*E*), minor = 5.87 (*Z*). Semi-preparative HPLC conditions: hexanes, 20 mL/min at 40 bar, 50 μL injection, (tR min): major = 7.26 (*E*), minor = 6.58 (*Z*). 15 mg of the mixture was subjected HPLC conditions; 5.7 mg **3.40** was recovered, and 7.9 mg **3.39** was recovered.



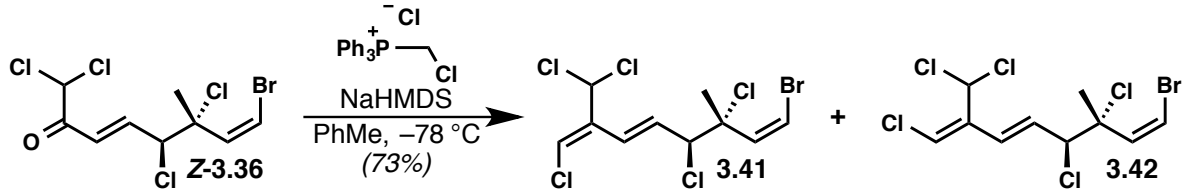
(1*E*,3*E*,5*S*,6*R*)-1,5,6-Trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (3.39)

R_f = 0.19, pentane; $[\alpha]_D^{25}$ –32.0° (*c* 0.84, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.76 (s, 1H), 6.63 (d, *J* = 16.2, 1H), 6.49, (dd, *J* = 16.2, 8.6, 1H), 6.40 (s, 1H), 6.10 (dd, *J* = 17.1, 10.6, 1H), 5.42 (d, *J* = 17.1, 1H), 5.31 (d, *J* = 10.6, 1H), 4.59 (d, *J* = 8.6), 1.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.5, 136.1, 132.0, 124.4, 124.0, 116.7, 71.9, 69.6 (2C), 25.2; Accurate Mass (CI/CH_2Cl_2) *m / z* calcd for $C_{10}H_{11}{}^{35}Cl_5NH_4$ 323.9647 $(M + NH_4)^+$, found 323.9640 $(M + NH_4)^+$.



(1*Z*,3*E*,5*S*,6*R*)-1,5,6-Trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (3.40)

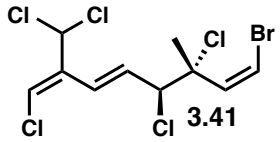
R_f = 0.21, pentane; $[\alpha]_D^{25}$ –6.2° (*c* 0.77, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.97 (s, 1H), 6.355 (m, 1H), 6.349 (m, 1H), 6.31 (s, 1H), 6.08 (dd, *J* = 17.1, 10.6, 1H), 5.42 (d, *J* = 17.1, 1H), 5.30 (d, *J* = 10.7, 1H), 4.55 (dd, *J* = 6.1, 1.4, 1H), 1.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.6, 137.8, 130.5, 126.9, 119.5, 116.7, 72.0, 69.0, 65.7, 25.2; Accurate Mass (CI/CH_2Cl_2) *m / z* calcd for $C_{10}H_{11}{}^{35}Cl_5NH_4$ 323.9647 $(M + NH_4)^+$, found 323.9644 $(M + NH_4)^+$.



(1*E*,3*E*,5*S*,6*R*,7*Z*)-8-Bromo-1,5,6-trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (3.41) +

(1*Z*,3*E*,5*S*,6*R*,7*Z*)-8-Bromo-1,5,6-trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (3.42)

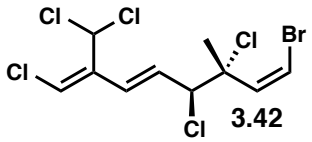
To a suspension of (chloromethyl)triphenylphosphonium chloride (0.093 g, 0.27 mmol, 3.7 equiv., dried under vacuum at 120 °C for 4 h prior to use) in PhMe (2.5 mL) at 0 °C was added NaHMDS (0.82 M in THF, 0.21 mL, 0.17 mmol, 2.2 equiv.). The solution quickly turned yellow, and was allowed to stir at 0 °C for 1 h. The ylide solution was cooled to –78 °C, and a solution of ***Z*-3.36** (0.025 g, 0.07 mmol, 1.0 equiv.) in PhMe (2 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 4 h. After this time, the cooling bath was removed and the reaction mixture was immediately quenched with 5% aq. AcOH (~2 mL). The resulting brownish orange mixture was stirred for 15 min. Additional 5% aq. AcOH (~2 mL) was added, and the crude mixture was extracted with pentane (3 x 5 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (5 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (SiO_2, pentane) afforded a 2.3:1 mixture of (1*E*,3*E*,5*S*,6*R*,7*Z*)-8-bromo-1,5,6-trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (**3.41**) and (1*Z*,3*E*,5*S*,6*R*,7*Z*)-8-bromo-1,5,6-trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (**3.42**) as a clear oil (0.020 g, 73%), which were separated via preparative HPLC. Stirring the *Z*-isomer with activated charcoal in pentane was used to remove the residual elimination products that could not be separated via HPLC. Analytical HPLC conditions: hexanes, 1.0 mL/min at 50 bar, (tR min): major = 4.55 (*E*), minor = 4.17 (*Z*). Semi-preparative HPLC conditions: hexanes, 10 mL/min at 40 bar, 50 μL injection, (tR min): major = 13.78 (*E*), minor = 12.25 (*Z*). 19 mg of the mixture was subjected to HPLC conditions; 4.5 mg **3.42** (contaminated with elimination product) and 7.6 mg **3.41** were recovered.



3.41

(1*E*,3*E*,5*S*,6*R*,7*Z*)-8-Bromo-1,5,6-trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (3.41)

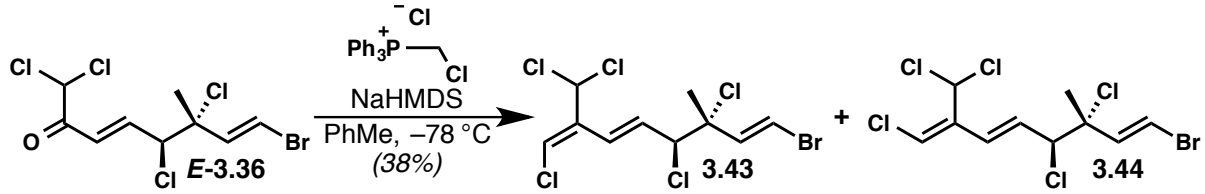
R_f = 0.23, pentane; $[\alpha]_D^{25}$ –28.7° (*c* 0.42, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (s, 1H), 6.70 (d, *J* = 16.2, 1H), 6.56 (d, *J* = 8.4, 1H), 6.54 (dd, *J* = 16.2, 8.2, 1H), 6.42 (d, *J* = 8.4, 1H), 6.40 (s, 1H), 5.10 (d, *J* = 8.3, 1H), 2.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1, 136.0, 131.4, 124.6, 124.4, 110.0, 69.6 (2C), 68.0, 26.4; Accurate Mass (CI/CH_2Cl_2) *m / z* calcd for $C_{10}H_{10}Br^{35}Cl_5NH_4$ 401.8752 $(M + NH_4)^+$, found 401.8769 $(M + NH_4)^+$.



3.42

(1*Z*,3*E*,5*S*,6*R*,7*Z*)-8-Bromo-1,5,6-trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (3.42)

R_f = 0.27, pentane; $[\alpha]_D^{25}$ –32.1° (*c* 0.80, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (s, 1H), 6.55 (d, *J* = 8.5, 1H), 6.41 (m, 3H), 6.33 (s, 1H), 5.07 (d, *J* = 5.4, 1H), 2.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 136.1, 129.9, 127.3, 119.6, 109.9, 70.8, 67.4, 65.7, 26.4; Accurate Mass (CI/CH_2Cl_2) *m / z* calcd for $C_{10}H_{10}Br^{35}Cl_5NH_4$ 401.8752 $(M + NH_4)^+$, found 401.8769 $(M + NH_4)^+$.

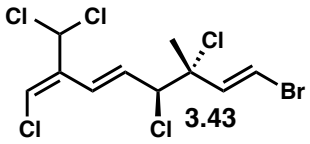


(1*E*,3*E*,5*S*,6*R*,7*E*)-8-Bromo-1,5,6-trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (3.43) +

(1*Z*,3*E*,5*S*,6*R*,7*E*)-8-Bromo-1,5,6-trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (3.44)

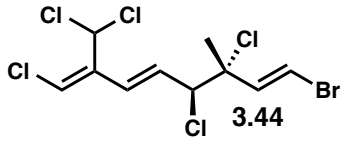
To a suspension of (chloromethyl)triphenylphosphonium chloride (0.103 g, 0.30 mmol, 4.0 equiv., dried under vacuum at 120 °C for 4 h prior to use) in PhMe (2.5 mL) at 0 °C was added NaHMDS (0.90 M in THF, 0.29 mL, 0.26 mmol, 3.5 equiv.). The solution quickly turned yellow, and was allowed to stir at 0 °C for 1 h. The ylide solution was cooled to –78 °C, and a solution of ***E*-3.36** (0.026 g, 0.07 mmol, 1.0 equiv.) in PhMe (2 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 4 h. After this time, the cooling bath was removed and the reaction mixture was immediately quenched with 5% aq. AcOH (~2 mL). The resulting brownish orange mixture was stirred for 15 min. Additional 5% aq. AcOH (~2 mL) was added, and the crude mixture was extracted with pentane (3 x 5 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (5 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (SiO_2, pentane) afforded a 2.0:1 mixture of (1*E*,3*E*,5*S*,6*R*,7*E*)-8-bromo-1,5,6-trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (**3.43**) and (1*Z*,3*E*,5*S*,6*R*,7*E*)-8-bromo-1,5,6-trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (**3.44**) as a clear oil (0.011 g, 38%), which were separated via preparative HPLC. Analytical HPLC conditions: hexanes, 1.0 mL/min at 50 bar, (tR min): major = 6.17 (*E*), minor = 5.77 (*Z*). Semi-preparative HPLC conditions: hexanes, 5.0 mL/min at 60 bar, 50 μL injection, (tR min): major = 20.32 (*E*), minor =

19.00 (*Z*). 10 mg of the mixture was subjected to HPLC conditions; 3 mg **3.44** and 6 mg **3.43** were recovered.



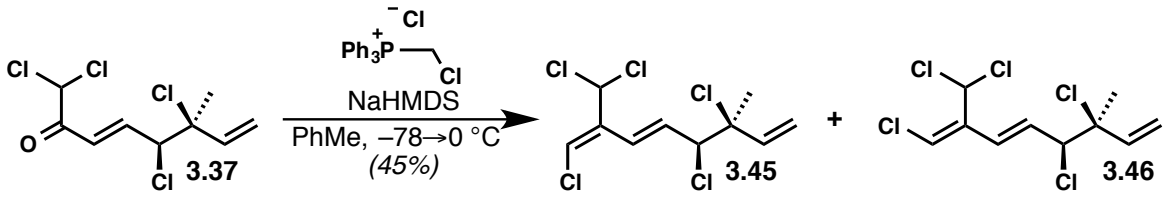
(1*E*,3*E*,5*S*,6*R*,7*E*)-8-Bromo-1,5,6-trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (3.43)

R_f = 0.22, pentane; $[\alpha]_D^{25}$ –20.2° (*c* 0.35, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.77 (s, 1H), 6.64 (d, *J* = 16.2, 1H), 6.58 (d, *J* = 13.6, 1H), 6.50–6.45 (m, 2H), 6.40 (s, 1H), 4.58 (d, *J* = 8.5, 1H), 1.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 136.0, 131.3, 124.6, 124.5, 110.4, 71.6, 69.7, 68.9, 25.4; Accurate Mass (CI/CH_2Cl_2) *m / z* calcd for $C_{10}H_{10}Br^{35}Cl_5NH_4$ 401.8752 $(M + NH_4)^+$, found 401.8769 $(M + NH_4)^+$.



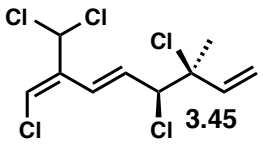
(1*Z*,3*E*,5*S*,6*R*,7*E*)-8-Bromo-1,5,6-trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (3.44)

R_f = 0.27, pentane; $[\alpha]_D^{25}$ –3.1° (*c* 0.29, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (s, 1H), 6.57 (d, *J* = 13.6, 1H), 6.45 (d, *J* = 13.6, 1H), 6.35–6.32 (m, 3H), 4.54 (d, *J* = 7.1, 1H), 1.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 137.7, 129.7, 127.5, 119.8, 110.3, 71.7, 68.4, 65.6, 25.4; Accurate Mass (CI/CH_2Cl_2) *m / z* calcd for $C_{10}H_{10}Br^{35}Cl_5NH_4$ 401.8752 $(M + NH_4)^+$, found 401.8769 $(M + NH_4)^+$.



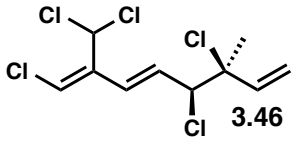
(1*E*,3*E*,5*S*,6*S*)-1,5,6-Trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (3.45) + **(1*Z*,3*E*,5*S*,6*S*)-1,5,6-Trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (3.46)**

To a suspension of (chloromethyl)triphenylphosphonium chloride (0.128 g, 0.37 mmol, 4.0 equiv., dried under vacuum at 120 °C for 4 h prior to use) in PhMe (2 mL) at 0 °C was added NaHMDS (1.0 M in THF, 0.23 mL, 0.23 mmol, 2.5 equiv.). The solution quickly turned yellow, and was allowed to stir at 0 °C for 2 h. The ylide solution was cooled to –78 °C, and a solution of **3.37** (0.026 g, 0.09 mmol, 1.0 equiv.) in PhMe (1 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 3 h. After this time, the cooling bath was removed and the reaction mixture was immediately quenched by adding 5% aq. AcOH (~2 mL). The resulting yellowish-orange mixture was stirred for 15 min. Additional 5% aq. AcOH (~2 mL) was added, and the crude mixture was extracted with pentane (3 x 5 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (5 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (SiO_2, pentane) afforded a 1:1.4 mixture of (1*Z*,3*E*,5*S*,6*S*)-1,5,6-trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (**3.45**) and (1*E*,3*E*,5*S*,6*S*)-1,5,6-trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (**3.46**) as a clear oil (0.013 g, 45%), which were separated via semi-preparative HPLC. Analytical HPLC conditions: hexanes, 1.0 mL/min at 50 bar, (tR min): major = 4.55 (*E*), minor = 4.27 (*Z*). Semi-preparative HPLC conditions: hexanes, 10 mL/min at 40 bar, 50 μL injection, (tR min): major = 11.82 (*E*), minor = 10.86 (*Z*). 13 mg of the mixture were subjected HPLC conditions; 5 mg **3.46** was recovered, and 7 mg **3.45** was recovered.



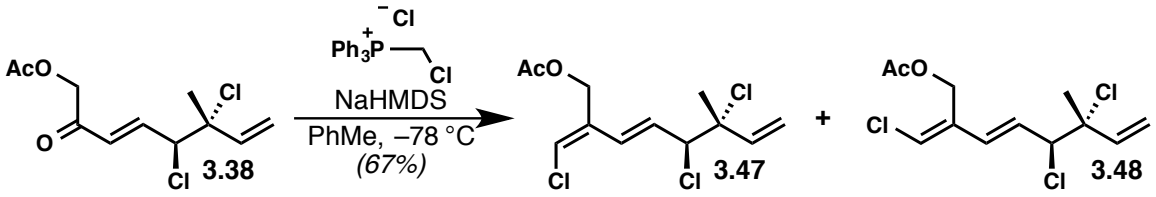
(1*E*,3*E*,5*S*,6*S*)-1,5,6-Trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (3.45)

R_f = 0.18, pentane; $[\alpha]_D^{25}$ –58.8° (*c* 0.59, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76 (s, 1H), 6.63 (d, *J* = 16.2, 1H), 6.46 (dd, *J* = 16.2, 8.7, 1H), 6.39 (s, 1H), 6.11 (dd, *J* = 16.9, 10.7, 1H), 5.48 (d, *J* = 16.9, 1H), 5.34 (d, *J* = 10.6, 1H), 4.61 (d, *J* = 8.7, 1H), 1.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 136.1, 132.1, 124.4, 123.9, 117.6, 72.2, 69.7, 69.5, 27.7; IR (thin film) 3092, 3067, 2984, 2954, 2925, 2852, 1580 cm^{-1}; Accurate Mass (CI/CH_2Cl_2) *m / z* calcd for $C_{10}H_{11}{}^{35}Cl_4$ 270.9615 $(M - Cl)^+$, found 270.9609 $(M - Cl)^+$.



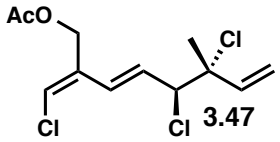
(1*Z*,3*E*,5*S*,6*S*)-1,5,6-Trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (3.46)

R_f = 0.21, pentane; $[\alpha]_D^{25}$ –28.3° (*c* 0.38, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.33–6.34 (m, *J* = 5.3, 2.2 2H), 6.30 (s, 1H), 6.10 (dd, *J* = 16.9, 10.7, 1H), 5.47 (d, *J* = 16.9, 1H), 5.33 (d, *J* = 10.6, 1H), 4.57 (dd, *J* = 5.2, 2.4, 1H), 1.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 137.8, 130.7, 126.9, 119.4, 117.5, 72.3, 69.2, 65.7, 27.7; IR (thin film) 3093, 3067, 2955, 2924, 2853, 1572 cm^{-1}; Accurate Mass (CI/CH_2Cl_2) *m / z* calcd for $C_{10}H_{11}{}^{35}Cl_4$ 270.9615 $(M - Cl)^+$, found 270.9609 $(M - Cl)^+$.



(2*E*,3*E*,5*S*,6*R*)-5,6-dichloro-2-(chloromethylene)-6-methylocta-3,7-dien-1-yl acetate (3.47) + **(2*Z*,3*E*,5*S*,6*R*)-5,6-dichloro-2-(chloromethylene)-6-methylocta-3,7-dien-1-yl acetate (3.48)**

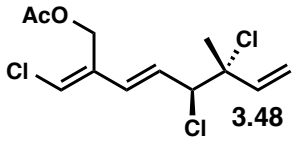
To a suspension of (chloromethyl)triphenylphosphonium chloride (0.140 g, 0.40 mmol, 6.5 equiv., dried under vacuum at 120 °C for 4 h prior to use) in PhMe (2 mL) at 0 °C was added NaHMDS (1.0 M in THF, 0.36 mL, 0.36 mmol, 5.8 equiv.). The solution quickly turned yellow, and was allowed to stir at 0 °C for 2 h. The ylide solution was cooled to –78 °C, and a solution of **3.38** (0.017 g, 0.06 mmol, 1.0 equiv.) in PhMe (1 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 3h. After this time, the reaction mixture was quenched by adding 10% AcOH in MeOH(~2 mL), and the cooling bath removed. The resulting yellowish-orange mixture was stirred 15 min. H_2O (~3 mL) was added, and the crude mixture was extracted with pentane (3 x 5 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (5 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (SiO_2, 97:2:1 pentane:CH_2Cl_2:EtOAc) afforded a 1:5 mixture of (2*E*,3*E*,5*S*,6*R*)-5,6-dichloro-2-(chloromethylene)-6-methylocta-3,7-dien-1-yl acetate (**3.47**) and (2*Z*,3*E*,5*S*,6*R*)-5,6-dichloro-2-(chloromethylene)-6-methylocta-3,7-dien-1-yl acetate (**3.48**) as a clear oil (0.013 g, 67%), which were separated via preparative TLC (9:1 pentane:EtOAc).



(2*E*,3*E*,5*S*,6*R*)-5,6-dichloro-2-(chloromethylene)-6-methylocta-3,7-dien-1-yl acetate (3.47)

(R_f = 0.36, 9:1 pentane:EtOAc); $[\alpha]_D^{25}$ XX° (*c* XX, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76 (d, *J* = 15.9, 1H), 6.41 (s, 1H), 6.059 (dd, *J* = 17.1, 10.7, 1H), 6.056 (dd, *J* = 15.9, 8.8, 1H), 5.41

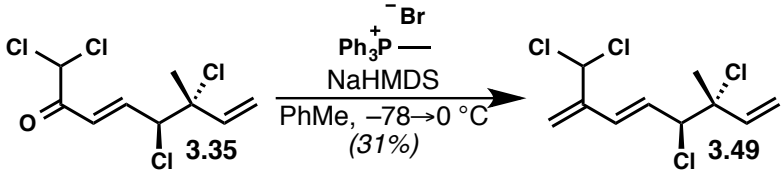
(d, J = 17.0, 1H), 5.28 (d, J = 10.6, 1H), 4.79 (dd, J = 12.8, 0.9, 1H), 4.74 (dd, J = 12.8, 0.6, 1H), 4.57 (dd, J = 8.8, 0.4, 1H), 2.08 (s, 3h), 1.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 139.8, 132.5, 129.2, 127.3, 123.4, 116.5, 69.5, 68.3, 63.2, 29.9, 25.2; IR (thin film) 3069, 2958, 2928, 2856, 1742 cm^{-1}; Accurate Mass (CI/CH_2Cl_2) m/z calcd for $C_{12}H_{15}{}^{35}Cl_3O_2NH_4$ 314.0481 $(M + NH_4)^+$, found 314. 0485 $(M + NH_4)^+$.



3.48

(2*Z*,3*E*,5*S*,6*R*)-5,6-dichloro-2-(chloromethylene)-6-methylocta-3,7-dien-1-yl acetate

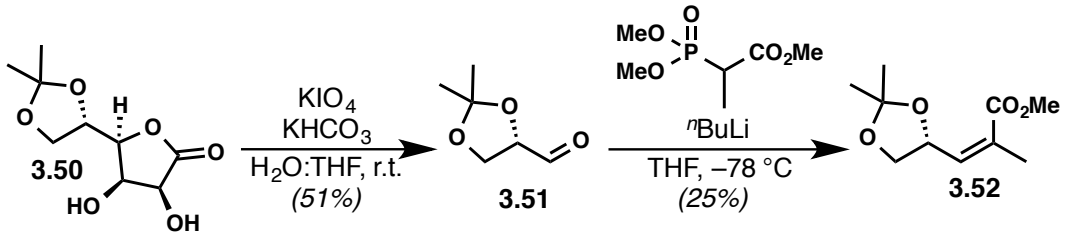
(R_f = 0.40, 9:1 pentane:EtOAc); $[\alpha]_D^{25}$ –38.2° (*c* 0.76, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.43 (s, 1H), 6.25 (d, J = 15.6, 1H), 6.05 (dd, J = 17.1, 10.7, 1H), 5.97 (dd, J = 15.6, 8.7, 1H), 5.39 (d, J = 17.1, 1H), 5.27 (d, J = 10.7), 4.96 (d, J = 4.4, 2H), 4.49 (d, J = 8.8, 1H), 2.08 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 139.8, 134.6, 131.5, 127.0, 125.5, 116.4, 72.1, 69.3, 58.5, 24.9, 20.9; IR (thin film) 3069, 2958, 2928, 2856, 1742 cm^{-1}; Accurate Mass (CI/CH_2Cl_2) m/z calcd for $C_{12}H_{15}{}^{35}Cl_3O_2NH_4$ 314.0481 $(M + NH_4)^+$, found 314.0485 $(M + NH_4)^+$.



(5*S*,6*R*,*E*)-5,6-Dichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (3.49)

To a suspension of methyltriphenylphosphonium bromide (0.057 g, 0.16 mmol, 4 equiv., dried under vacuum at 120 °C for 4 h prior to use) in PhMe (1 mL) at 0 °C was added NaHMDS (0.81 M in THF, 0.15 mL, 0.12 mmol, 3 equiv.). The solution quickly turned yellow, and was allowed to stir at 0 °C for 2 h. The ylide solution was cooled to –78 °C, and a solution of **3.35** (0.011 g, 0.04 mmol, 1.0 equiv.) in PhMe (0.5 mL) was added dropwise. The reaction mixture was stirred

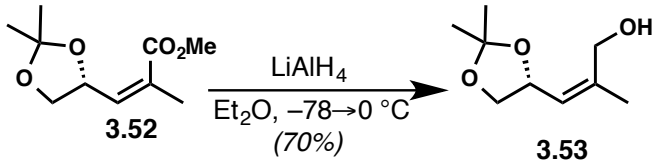
at –78 °C for 1 h, and gradually warmed to 0 °C over a period of 6 h, then to r.t. overnight. Upon warming, the reaction mixture turned from yellow to brown to green. The reaction was quenched with 5% aq. AcOH (1 mL) and the mixture was extracted with pentane (3 x 3 mL). The organic extracts were washed with saturated aq. $NaHCO_3$ (2 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (SiO_2, pentane) afforded (5*S*,6*R*,*E*)-5,6-Dichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (**3.49**) as a clear oil (0.003 g, 31%). R_f = 0.19, pentane; $[\alpha]_D^{25}$ –2.7° (*c* 1.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35 (d, *J* = 15.9, 1H), 6.34 (s, 1H), 6.23 (dd, *J* = 15.9, 8.6, 1H), 6.09 (dd, *J* = 17.1, 10.7, 1H), 5.56 (s, 1H), 5.41 (d, *J* = 17.1, 1H), 5.39 (s, 1H), 5.29 (d, *J* = 10.7, 1H), 4.55 (d, *J* = 8.6, 1H), 1.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.1, 139.6, 129.7, 129.1, 118.6, 116.6, 72.1, 71.0, 69.4, 25.2; Accurate Mass (CI/CH_2Cl_2) *m / z* calcd for $C_{10}H_{12}{}^{35}Cl_4NH_4$ 290.0037 $(M + NH_4)^+$, found 290.0026 $(M + NH_4)^+$.



Methyl (2*Z*,4*R*)-4,5-Isopropylidenedioxy-2-methylpent-2-enoate (3.52)

To a flask containing KIO_4 (9.83 g, 43 mmol, 2.1 equiv) and $KHCO_3$ (4.27 g, 43 mmol, 2.1 equiv.) was added H_2O (25 mL). To the slurry was added dropwise a solution of *L*-5,6-*O*-isopropylidene-gulono-1,4-lactone (5.03 g, 23 mmol, 1.0 equiv) in H_2O:THF (10:25 mL) at r.t. and stirred for 5 h. The reaction mixture was capped and stored at 5 °C overnight. The solids were filtered off through a sintered glass funnel and washed with CH_2Cl_2 (3 x ~25 mL). The filtrate was extracted with CH_2Cl_2 (3 x ~25 mL), dried over $MgSO_4$ and carefully concentrated in vacuo to give crude *S*-2,3-*O*-isopropylidene-glyceraldehyde (1.52 g, 51%) which was used immediately without further purification.

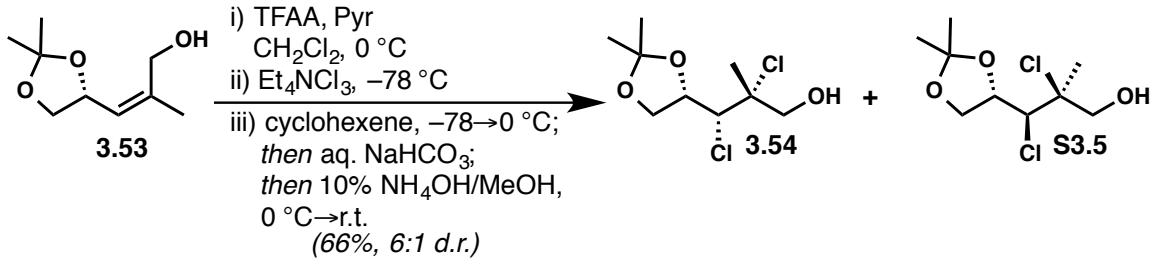
To a round bottom flask charged with trimethyl 2-phosphonopropionate (3.902 g, 19.9 mmol, 1.7 equiv.) was added THF (80 mL), and the solution was cooled to –78 °C. ^{n}BuLi (2.50 M in hexane, 8.0 mL, 20.0 mmol, 1.7 equiv) was added dropwise over a period of 5 min, with a yellow color forming towards the end of the addition. The solution was stirred for 1 h, and the crude glyceraldehyde acetonide in THF (20 mL) was added over a period of 10 minutes, running the solution down the interior wall of the flask, and the mixture was stirred for 6 h at –78 °C. The reaction was quenched by the slow addition of 5% AcOH in MeOH (~15 mL) at –78 °C, followed by warming to r.t. H_2O (25 mL) was added, and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (2 x 15 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (SiO_2, 98:2 hexanes:EtOAc) separated the alkene isomers (6:1 *Z*:*E*) and afforded methyl (2*Z*,4*R*)-4,5-isopropylidenedioxy-2-methylpent-2-enoate (**3.52**) as a clear oil (0.584 g, 24%). R_f = 0.64, 4:1 pentane:EtOAc; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.09 (d, *J* = 6.8, 1H), 5.26 (q, *J* = 6.8, 1H), 4.31 (dd, *J* = 8.0, 6.9, 1H), 3.74 (s, 3H), 3.59 (dd, *J* = 8.0, 7.0, 1H), 1.93 (s, 3H), 1.45 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 142.9, 129.1, 109.5, 74.1, 69.7, 51.9, 26.8, 25.6, 20.2.



(2*Z*,4*R*)-4,5-Isopropylidenedioxy-2-methylpent-2-en-1-ol (3.53)

To a round bottom flask charged with $LiAlH_4$ (0.122 g, 3.22 mmol, 1.1 equiv.) was added Et_2O (20 mL), and the suspension was cooled to –78 °C. A solution of **3.52** (0.584 g, 2.92 mmol, 1.0 equiv.) in Et_2O (5 mL) was added dropwise over a period of 10 minutes. Once the addition was

complete, the reaction was stirred at –78 °C for 1 h, warmed to 0 °C, and stirred an additional 30 min. The reaction was quenched by the slow addition of saturated aq. Na_2SO_4 (~3 mL) until the bubbling ceased and a white suspension formed. The solids were filtered off through celite, and the solid residue washed with several portions of EtOAc (5 x ~10 mL). The resulting organic solution was dried over $MgSO_4$ and concentrated in vacuo to afford (2*Z*,4*R*)-4,5-isopropylidenedioxy-2-methylpent-2-en-1-ol (**3.53**) as a clear, viscous oil (0.352 g, 70%). R_f = 0.23, 4:1 pentane:EtOAc; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35 (d, *J* = 8.4, 1H), 4.84–4.89 (m, 1H), 4.22 (d, *J* = 12.4, 1H), 4.13 (dd, *J* = 12.3, 3.4, 1H), 4.07 (dd, *J* = 8.1, 6.0, 1H), 3.54 (t, *J* = 8.0, 1H), 1.85 (d, *J* = 1.3, 3H), 1.42 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.5, 125.2, 109.3, 72.1, 69.9, 62.1, 26.9, 26.1, 21.8.



(2*R*,3*R*,4*S*)-Dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-ol (3.54) +

(2*S*,3*S*,4*S*)-Dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-ol (S3.5)

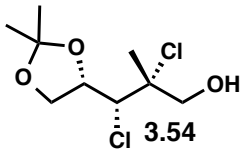
To a solution of **3.53** (0.357 g, 2.07 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) at 0 °C was added trifluoroacetic anhydride (0.31 mL, 2.2 mmol, 1.1 equiv.) dropwise via syringe. The solution was stirred 15 min at 0 °C, then pyridine (0.18 mL, 2.2 mmol, 1.05 equiv.) was added dropwise via syringe, and the mixture was stirred an additional 15 min at 0 °C.

Meanwhile, Et_4NCl_3 (0.981 g, 4.1 mmol, 2.0 equiv.; 1.05 equiv. active 'Cl_2') was added to a separate flask containing Na_2SO_4 (1 large spatula scoop) which had been oven-dried for 2 hours, then cooled in a dessicator. The flask was sealed and purged with Ar, CH_2Cl_2 (5 mL) was added.

The canary-yellow solution was allowed to sit for 30 min, swirling to ensure the Et_4NCl_3 was completely dissolved.

The reaction mixture containing the alkene was cooled to –78 °C, at which point the solution of Et_4NCl_3 was decanted off of the Na_2SO_4 via syringe and added to the reaction mixture over a period of 5 min. After the addition was complete, the pale-yellow reaction mixture was stirred for 1.5 h at –78 °C, then warmed to 0 °C and stirred an additional 15 minutes. After the allotted time, cyclohexene (0.25 mL) was added to the reaction mixture at 0 °C, and the yellow color quickly dissipated. A solution of saturated aqueous $NaHCO_3$ (5 mL) was added at 0 °C, and the reaction mixture was warmed to r.t. and stirred for 20 min. A 10% solution of NH_4OH in MeOH (3 mL) was added, and the reaction mixture was stirred for 45 min at r.t. The crude reaction mixture was extracted with CH_2Cl_2 (3 x 5 mL) and the organic extracts were washed with brine (1 x 10 mL), dried over $MgSO_4$, and concentrated in vacuo. To ease purification, the crude mixture was dissolved in MeOH (5 mL), cooled to 0 °C, and excess $NaBH_4$ was added. The solution was warmed to r.t. and stirred 1 h (this step reduces all aldehyde byproducts to more easily separated products). Saturated aqueous $NaHCO_3$ (5 mL) was added, and the reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL), dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (SiO_2, 85:10:5–70:20:10 pentane:CH_2Cl_2:EtOAc) afforded a 6:1 mixture of (2*R*,3*R*,4*S*)-dichloro-4*R*,5-isopropylidenedioxy-2-methylpentan-1-ol (**3.54**) and (2*S*,3*S*,4*S*)-dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-ol (**S3.5**) as a clear oil (0.331 g, 66%). Separation was accomplished for characterization purposes by oxidizing the primary alcohol (Dess–Martin periodane), separating the diastereomers via flash chromatography, then reducing each back to the alcohol ($NaBH_4$). In general the mixture was used without separation in the

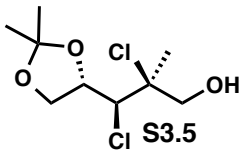
subsequent step.



3.54

(2*R*,3*R*,4*S*)-Dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-ol (3.54)

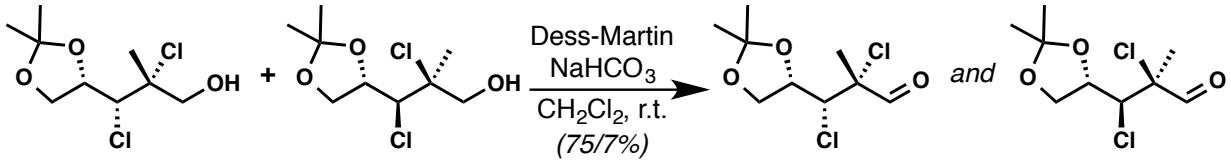
R_f = 0.36, 4:1 pentane:EtOAc; $[\alpha]_D^{25}$ +19.3° (*c* 1.01, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 4.88 (t, *J* = 6.8, 1H), 4.15 (dd, *J* = 8.2, 7.0, 1H), 4.07 (s, 1H), 3.99 (d, *J* = 12.8, 1H), 3.93 (dd, *J* = 8.3, 6.6, 1H), 3.68 (d, *J* = 12.4, 1H), 3.40 (br s, 1H), 1.72 (s, 3H), 1.49 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 111.1, 74.7, 73.2, 67.9, 67.8, 67.1, 27.5, 25.8, 25.7; IR (thin film) 2991, 2937, 2886, 1743, 1455, cm^{-1}; Accurate Mass (ESI/MeOH) *m / z* calculated for $C_9H_{16}Cl_2O_3Na$ 265.0374 $(M + Na)^+$, found 265.0373 $(M + Na)^+$.



S3.5

(2*S*,3*S*,4*S*)-Dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-ol (S3.5)

R_f = 0.37, 4:1 pentane:EtOAc; $[\alpha]_D^{25}$ –25.5° (*c* 0.99, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 4.36 (appar. q, *J* = 6.7, 1H), 4.23 (dd, *J* = 9.0, 6.2, 1H), 4.20 (d, *J* = 8.3, 1H), 4.00 (dd, *J* = 9.0, 7.0, 1H), 3.89 (d, *J* = 4.3, 2H), 2.66 (br s, 1H), 1.71 (s, 3H), 1.44 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 111.1, 75.8, 74.7, 70.1, 69.2, 68.2, 26.4, 26.0, 23.4.



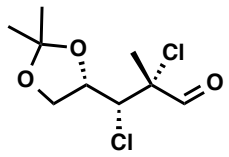
3.54 **S3.5** **S3.6** **S3.7**

(2*R*,3*R*,4*S*)-Dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-al + (S3.6)

(2*S*,3*S*,4*S*)-Dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-al (S3.7)

To a solution of **3.54** + **S3.5** (0.953 g, 3.92 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL) open to air was

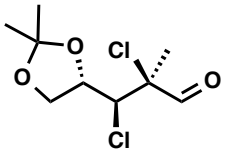
added $NaHCO_3$ (0.343 g, 4.08 mmol, 3.0 equiv.) in one portion, followed by Dess–Martin periodinane (0.808 g, 1.91 mmol, 1.4 equiv.) in one portion. The reaction mixture was stirred for 4 h at r.t. Saturated aqueous $Na_2S_2O_3$ (~10 mL) was added and the biphasic mixture was stirred for 30 min. The crude reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), followed by drying over $MgSO_4$ and concentration in vacuo. Flash chromatography (SiO_2, 90:10:0–85:10:5 pentane:CH_2Cl_2:EtOAc) afforded (2*R*,3*R*,4*S*)-dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-al (**S3.6**) as a colorless, crystalline solid (0.245 g, 75%) and (2*S*,3*S*,4*S*)dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-al (**S3.7**) as a clear oil (0.024 g, 7%).



S3.6

(2*R*,3*R*,4*S*)-Dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-al (S3.6)

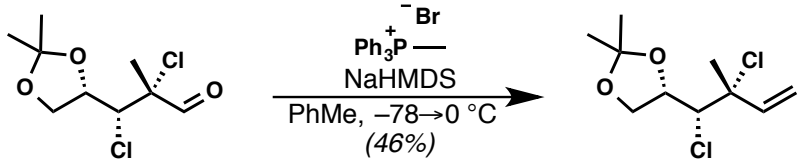
R_f = 0.62, 4:1 pentane:EtOAc; $[\alpha]_D^{25}$ +93.2° (*c* 1.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.58 (s, 1H), 4.92 (td, *J* = 5.4, 1.6, 1H), 4.13 (dd, *J* = 8.2, 7.2, 1H), 4.11 (d, *J* = 1.6, 1H), 3.96 (dd, *J* = 8.4, 5.8, 1H), 1.80 (s, 3H), 1.44 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.1, 111.2, 73.9, 73.6, 67.3, 66.8, 25.7, 25.4, 24.1; IR (thin film) 2988, 2938, 2888, 1733 cm^{-1}; accurate Mass (CI/CH_2Cl_2) *m / z* calculated for $C_9H_{14}{}^{35}Cl_2O_3H$ 241.0398 $(M + H)^+$, found 241.0398 $(M + H)^+$.



S3.7

(2*S*,3*S*,4*S*)-Dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-al (S3.7)

R_f = 0.71, 4:1 pentane:EtOAc; $[\alpha]_D^{25}$ –44.1° (*c* 0.94, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 9.28 (s, 1H), 4.24–4.15 (m, 3H), 4.04–4.00 (m, 1H), 1.73 (s, 3H), 1.42 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.9, 111.7, 76.1, 74.0, 68.6, 65.9, 26.6, 25.1, 18.7; IR (thin film) 2990, 2936, 2853, 1739 cm^{-1}.

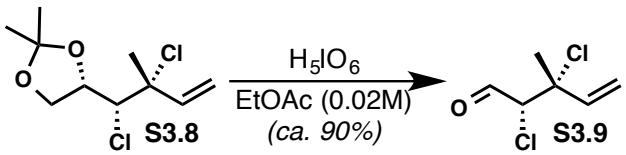


S3.6 **S3.8**

(3*R*,4*R*,5*S*)-Dichloro-5,6-isopropylidenedioxy-3-methylbutene (S3.8)

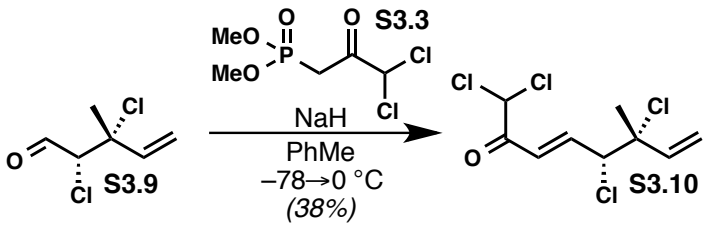
Methyltriphenylphosphonium bromide (0.377 g, 1.06 mmol, 1.8 equiv.) was heated at 110 °C under vacuum for 4 h. in the reaction vessel, with subsequent cooling to room temperature, followed by addition of PhMe (8 mL). The suspension was cooled to 0 °C, and NaHMDS (1.0 M in THF, 0.88 mL, 0.88 mmol, 1.5 equiv.) was added dropwise via syringe. The solution quickly turned canary yellow, and was stirred for 1 h at 0 °C. The yellow suspension was cooled to –78 °C, and **S3.6** (0.141 g, 0.59 mmol, 1.0 equiv.) in PhMe (2 mL) was added dropwise to the solution of the ylide. The mixture was stirred at –78 °C for 1 h, then the temperature was raised to 0 °C and the reaction progress was carefully monitored by TLC until the starting material was consumed (~25–30 min). The reaction was cooled to –78 °C, and hexanal (0.1 mL) in PhMe (1.0 mL) was added. The reaction was stirred at –78 °C for 15 min, then 0 °C for 15 min. H_2O (10 mL) was added, and the crude mixture was extracted with hexanes (3 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and concentrated in vacuo.

Flash chromatography (SiO_2, 90:10:0–89:10:1 hexanes:CH_2Cl_2:EtOAc) afforded (3*R*,4*R*,5*S*)-dichloro-5,6-isopropylidenedioxy-3-methylbutene (**S3.8**) as a clear oil (0.064 g, 46%). R_f = 0.55, 9:1 pentane:EtOAc; $[\alpha]_D^{25}$ +55.2° (*c* 1.19, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.21 (dd, *J* = 17.1, 10.7, 1H), 5.43 (d, *J* = 17.0, 1H), 5.29 (d, *J* = 10.7, 1H), 4.62 (td, *J* = 6.7, 2.7, 1H), 4.08 (dd, *J* = 8.2, 6.7, 1H), 4.02 (d, *J* = 2.7, 1H), 3.87 (dd, *J* = 8.1, 7.1, 1H), 1.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 116.7, 110.3, 74.7, 72.9, 69.7, 68.2, 27.6, 26.1, 25.9; IR (thin film) 2989, 2936, 2886, 1456, 1412, 1372 cm^{-1}; accurate Mass (CI/CH_2Cl_2) *m / z* calcd for $C_{10}H_{17}{}^{35}Cl_2O_2$ 239.0606 $(M + H)^+$, found 239.0600 $(M + H)^+$.



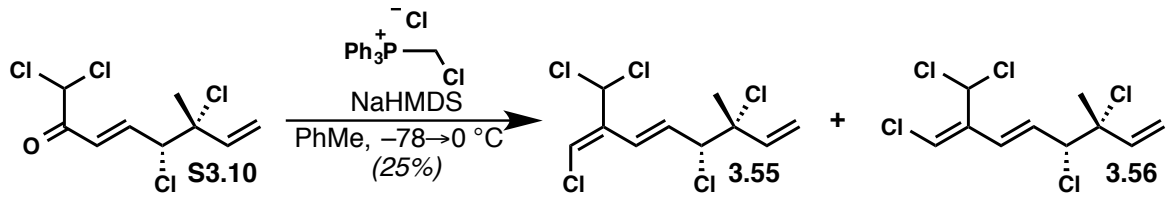
(2*R*,3*R*)-2,3-Dichloro-3-methylpent-4-enal (S3.9)

To a suspension of H_5IO_6 (0.122 g, 0.54 mmol, 2.0 equiv.) in EtOAc (5 mL) open to air was added **S3.8** (0.064 g, 0.27 mmol, 1.0 equiv.) in EtOAc (3 mL) at r.t. The suspension was stirred at r.t. for 2 h, with the reaction mixture gradually turning white and cloudy over time. Solid Na_2SO_4 was added to the reaction mixture, followed by pentane (10 mL). The suspension was stirred vigorously for 10 min. at r.t., and filtered through a plug of celite with pentane eluent. Concentration in vacuo afforded (2*R*,3*R*)-2,3-dichloro-3-methylpent-4-enal (**XX**) as a pale yellow oil (0.040 g, 90%), which was used without further purification. Although unstable to flash chromatography, (2*S*,3*S*)-2,3-dichloro-3-methylpent-4-enal **(XX)** can be stored neat at –20 °C for at least one month with minimum decomposition (<5%). R_f = 0.62, 9:1 pentane:EtOAc; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.47 (d, *J* = 3.8, 1H), 6.10 (dd, *J* = 16.8, 10.7, 1H), 5.52 (d, *J* = 16.8, 1H), 5.38 (d, *J* = 10.7, 1H), 4.24 (d, *J* = 3.8, 1H), 1.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.6, 136.7, 118.4, 69.14, 69.08, 28.0.



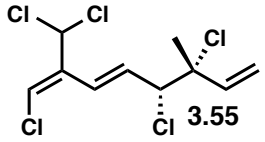
(5*R*,6*R*,*E*)-1,1,5,6-Tetrachloro-6-methylocta-3,7-dien-2-one (S3.10)

NaH (~60% in oil, 0.024 g, 0.60 mmol, 2.5 equiv.) was washed with dry hexanes (3 x 1 mL) to remove the oil. PhMe (3 mL) was added, and the suspension was cooled to 0 °C. Phosphonate **S3.3** (0.280 g, 1.19 mmol, 5 equiv.) in PhMe (1 mL) was added via syringe, and the yellow solution was stirred at 0 °C for 1 h. The phosphonate solution was cooled to –78 °C, and **S3.9** (0.040 g, 0.24 mmol, 1.0 equiv.) in PhMe (2 mL) was added dropwise. The resulting solution was stirred at –78 °C for 1 h. The temperature was raised to –20 °C over a period of ~30 min and stirred 1 h, then raised to 0 °C and stirred 30 min, and finally to r.t. and stirred 30 min. The reaction was quenched by the addition of 5% aq. AcOH (2 mL) and the mixture was extracted with pentane (3 x 5 mL). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (2 x 5 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (SiO_2, 98:1.8:0.2 pentane:CH_2Cl_2:EtOAc) afforded (5*R*,6*R*,*E*)-1,1,5,6-tetrachloro-6-methylocta-3,7-dien-2-one (**S3.10**) as a colorless oil (.025 g, 38%), with a small amount of delta-elimination product still present. R_f = 0.55, 9:1 pentane:EtOAc; $[\alpha]_D^{25}$ +59.0° (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 15.4, 7.9, 1H), 6.84 (d, *J* = 15.3, 1H), 6.04 (dd, *J* = 16.9, 10.6, 1H), 5.92 (s, 1H), 5.48 (d, *J* = 16.9, 1H), 5.36 (d, *J* = 10.7, 1H), 4.68 (d, *J* = 7.9, 1H), 1.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.8, 145.0, 136.9, 125.2, 118.4, 71.5, 69.4, 67.0, 27.9; IR (thin film) 2988, 2954, 2926, 2854, 1711, 1637 cm^{-1}; accurate Mass (CI/CH_2Cl_2) *m / z* calcd for $C_9H_{10}{}^{35}Cl_4ONH_4$ 291.9829 $(M + NH_4)^+$, found 291.9817 $(M + NH_4)^+$.



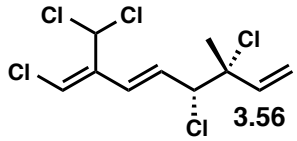
(1*E*,3*E*,5*R*,6*R*)-1,5,6-Trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (3.55) + **(1*Z*,3*E*,5*R*,6*R*)-1,5,6-Trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (3.56)**

To a suspension of (chloromethyl)triphenylphosphonium chloride (0.110 g, 0.32 mmol, 3.5 equiv., dried under vacuum at 120 °C for 4 h prior to use) in PhMe (2 mL) at 0 °C was added NaHMDS (1.0 M in THF, 0.27 mL, 0.27 mmol, 3.0 equiv.). The solution quickly turned yellow, and was allowed to stir at 0 °C for 2 h. The ylide solution was cooled to –78 °C, and a solution of **S3.10** (0.025 g, 0.09 mmol, 1.0 equiv.) in PhMe (1.5 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 3 h, warmed to room temperature, and stirred 30 minutes. After this time, the cooling bath was removed and the reaction mixture was quenched by adding 5% aq. AcOH (~2 mL). The resulting yellowish-orange mixture was stirred for 5 min. Additional 5% aq. AcOH (~2 mL) was added, and the crude mixture was extracted with pentane (3 x 5 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (5 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (SiO_2, pentane) afforded a 1.6:1 mixture of (1*E*,3*E*,5*R*,6*R*)-1,5,6-trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (**3.55**) and (1*Z*,3*E*,5*R*,6*R*)-1,5,6-trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (**3.56**) as a clear oil (0.007 g, 25%), which were separated via semi-preparative HPLC. Analytical HPLC conditions: hexanes, 1.0 mL/min at 50 bar, (tR min): major = 5.53 (*E*), minor = 5.12 (*Z*). Semi-preparative HPLC conditions: hexanes, 5 mL/min at 60 bar, 50 μL injection, (tR min): major = 18.51 (*E*), minor = 17.50 (*Z*). 6 mg of the mixture were subjected HPLC conditions; 2 mg **3.56** was recovered, and 3 mg **3.55** was recovered.



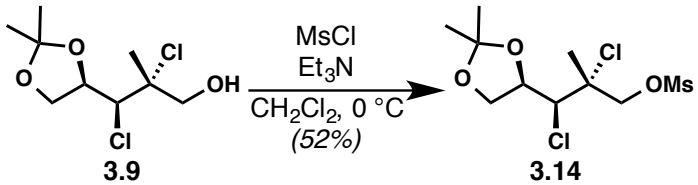
(1*E*,3*E*,5*R*,6*R*)-1,5,6-Trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (3.55)

R_f = 0.18, pentane; $[\alpha]_D^{25}$ +93.8° (*c* 0.37, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.76 (s, 1H), 6.63 (d, *J* = 16.2, 1H), 6.46 (dd, *J* = 16.2, 8.7, 1H), 6.39 (s, 1H), 6.11 (dd, *J* = 16.9, 10.7, 1H), 5.48 (d, *J* = 16.9, 1H), 5.34 (d, *J* = 10.6, 1H), 4.61 (d, *J* = 8.7, 1H), 1.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 136.1, 132.1, 124.4, 123.9, 117.6, 72.2, 69.7, 69.5, 27.7; IR (thin film) 3092, 3067, 2984, 2954, 2925, 2852, 1580 cm^{-1}.



(1*Z*,3*E*,5*R*,6*R*)-1,5,6-Trichloro-2-(dichloromethyl)-6-methylocta-1,3,7-triene (3.56)

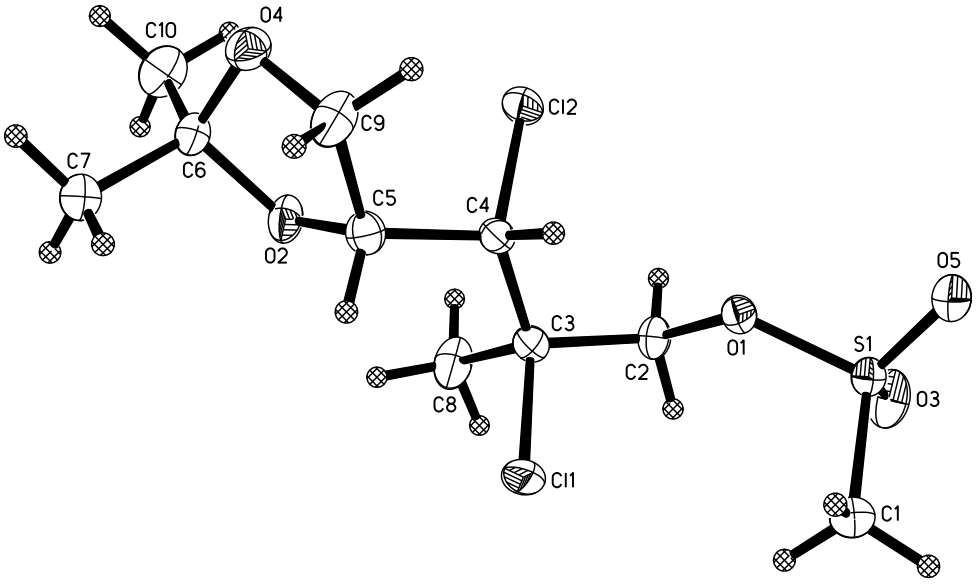
R_f = 0.21, pentane; $[\alpha]_D^{25}$ +34.1° (*c* 0.38, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.33–6.34 (m, *J* = 5.3, 2.2 2H), 6.30 (s, 1H), 6.10 (dd, *J* = 16.9, 10.7, 1H), 5.47 (d, *J* = 16.9, 1H), 5.33 (d, *J* = 10.6, 1H), 4.57 (dd, *J* = 5.2, 2.4, 1H), 1.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 137.8, 130.7, 126.9, 119.4, 117.5, 72.3, 69.2, 65.7, 27.7; IR (thin film) 3093, 3067, 2955, 2924, 2853, 1572 cm^{-1}.

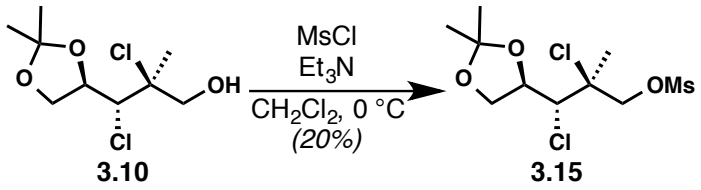


(2*S*,3*R*,4*R*)-Dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-methanesulfonate (3.14)

To a solution of **3.9** (0.070 g, 0.29 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) at 0 °C was added MsCl (0.1 mL, 1.3 mmol, 4.5 equiv.) and the mixture was stirred for 15 min at 0 °C. Et_3N (0.5 mL, 3.6 mmol, 12 equiv.) was added dropwise and the reaction mixture was stirred for an additional 15

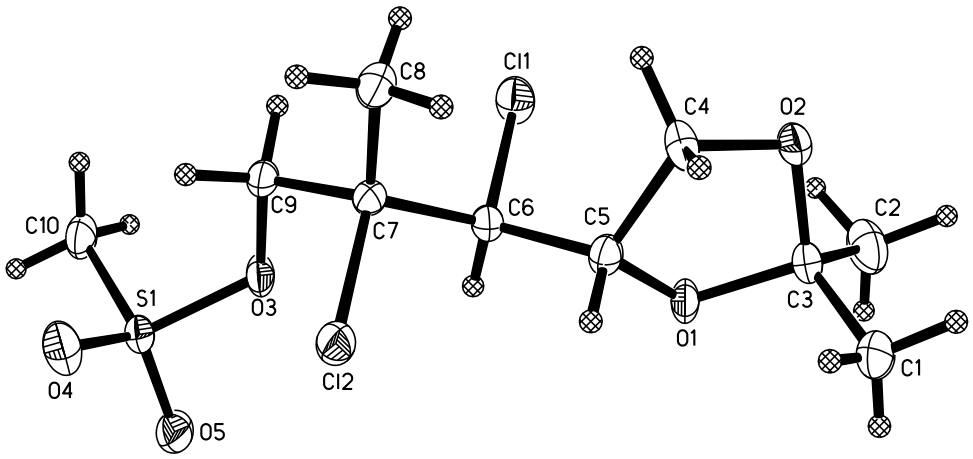
min at 0 °C, turning slightly orange over time. The reaction was quenched by the addition of saturated aq. $NaHCO_3$ (3 mL). The crude mixture was extracted with CH_2Cl_2 (3 x 5 mL), the combined organic extracts were washed with saturated aq. $NaHCO_3$ (5 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (SiO_2, 85:10:5 hexanes:CH_2Cl_2:EtOAc) afforded (2*S*,3*R*,4*R*)-dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-methanesulfonate (**3.14**) as a white solid (0.049 g, 52%). R_f = 0.23, 4:1 pentane:EtOAc; $[\alpha]_D^{25}$ –22.5° (*c* 0.99, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.84 (t, *J* = 6.7, 1H), 4.55 (d, *J* = 10.9, 1H), 4.29 (d, *J* = 10.9, 1H), 4.15 (s, 1H), 4.14 (t, *J* = 8.1, 1H), 3.90 (t, *J* = 6.7, 1H), 3.10 (s, 3H), 1.71 (s, 3H), 1.47 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 110.9, 74.8, 73.6, 70.7, 67.9, 63.5, 37.8, 26.0, 25.8, 22.2; IR (thin film) 2998, 2960, 2937, 2894, 1455, cm^{-1}; Accurate Mass (ESI/MeOH) *m / z* calculated for $C_{10}H_{18}{}^{35}Cl_2O_5SNa$ 343.0150 $(M + Na)^+$, found 343.0149 $(M + Na)^+$. Crystals suitable for X-ray analysis were obtained by slow evaporation of a solution in CH_2Cl_2 (**cdv28**).





(2*R*,3*S*,4*R*)-Dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-methanesulfonate (3.15)

To a solution of (**3.10**) (0.072 g, 0.29 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) at 0 °C was added MsCl (0.1 mL, 1.3 mmol, 4.5 equiv.) and the mixture was stirred for 15 min at 0 °C. Et_3N (0.5 mL, 3.6 mmol, 12 equiv.) was added dropwise and the reaction mixture was stirred for an additional 15 min at 0 °C, turning slightly orange over time. The reaction was quenched by the addition of saturated aq. $NaHCO_3$ (3 mL). The crude mixture was extracted with CH_2Cl_2 (3 x 5 mL), the combined organic extracts were washed with saturated aq. $NaHCO_3$ (5 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (SiO_2, 85:10:5 hexanes:CH_2Cl_2:EtOAc) afforded (2*S*,3*R*,4*R*)-dichloro-4,5-isopropylidenedioxy-2-methylpentan-1-methanesulfonate (**3.15**) as a white solid (0.019 g, 20%). R_f = 0.26, 4:1 pentane:EtOAc; $[\alpha]_D^{25}$ +22.2° (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.62 (d, *J* = 10.0, 1H), 4.55 (q, *J* = 6.5, 1H), 4.47 (d, *J* = 10.1, 1H), 4.20 (dd, *J* = 8.8, 6.5, 1H), 4.11 (d, *J* = 7.5, 1H), 3.99 (dd, *J* = 8.5, 6.7, 1H), 3.07 (s, 3H), 1.74 (s, 3H), 1.44 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 110.1, 76.1, 73.8, 69.6, 68.5, 65.8, 37.8, 26.5, 26.3, 25.8; IR (thin film) 2997, 2962, 2937, 2893, 1453, cm^{-1}; Accurate Mass (ESI/MeOH) *m / z* calculated for $C_{10}H_{18}{}^{35}Cl_2O_5SNa$ 343.0150 $(M + Na)^+$, found 343.0148 $(M + Na)^+$. Crystals suitable for X-ray analysis were obtained by slow evaporation of a solution in CH_2Cl_2 (**cdv30**).


C8
Cl1
C4
O2
C9
C7
C6
C5
C2
C10
S1
O3
O1
C3
O4
Cl2
C1
O5

3.13 References

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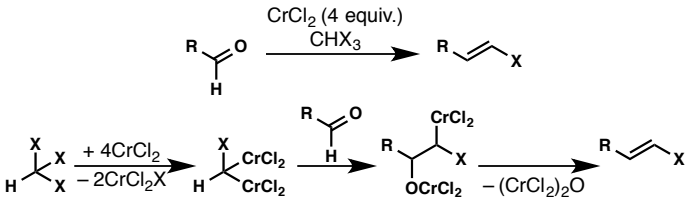
Chapter 4: Studies on *E*-vinyl bromide formation

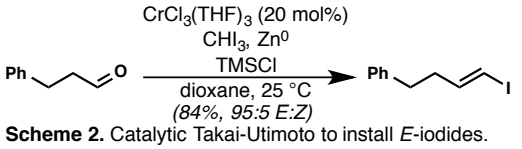
4.1 Takai-Utimoto Olefination



Scheme 1. General reaction mechanism of the Takai-Utimoto olefination.

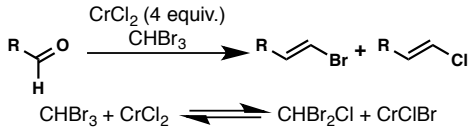
In the previous chapter, the difficulties in synthesizing the C1-C2 *E*-vinyl bromide were discussed. Though this experience, we were struck by the lack of reliable methods for their synthesis, especially ones that were a single step. To our knowledge, the only method that is a single step is the Takai-Utimoto olefination, which utilizes Cr(II) to form a carbene-like nucleophile, 1,2-addition into an aldehyde, followed by anti-elimination to form the *E*-olefin (Scheme **1**).[1] This method has a number of positive attributes, most importantly neutral conditions. The chromium nucleophile is almost completely nonbasic, making it well-suited for olefinating easily enolizable aldehydes and other base-sensitive functionality. It is also selective for aldehydes over ketones, with the ketone being recovered completely unreacted in most cases.

However, there are also a number of problems with the Takai-Utimoto olefination, most of them centered around the Cr(II) necessary for the reaction. The first difficulty is that Cr(II) is moisture and air sensitive, necessitating storage in a glovebox. This problem can be partially dealt with by generating the Cr(II) species in situ via reduction of the less sensitive Cr(III) species. However, the reduction is slow, greatly extending overall reaction times and requiring larger amounts of reagent. Second, commercial $CrCl_2$ is expensive, with prices generally over $10/g. This cost is exacerbated by the fact that because Cr(II) is a single-electron reductant, four equivalents are needed for every one equivalent of substrate, and generally six are used in order to ensure the reaction goes to completion. There are a few



Scheme 2. Catalytic Takai-Utimoto to install *E*-iodides.

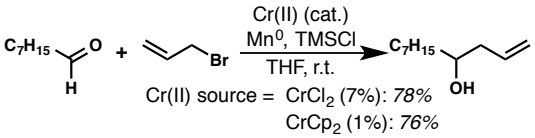
reports of the Takai-Utimoto olefination catalytic in chromium,[2,3] but they are very limited in scope (Scheme **2**). The last problem occurs when trying to install vinyl bromides, the vinyl chloride is a major byproduct. This happens due to competing Finklestein reaction between the halomethane and $CrCl_2$ or other chloride sources, forming $CHClBr_2$. The Cr(II) then preferentially reduces the bromides, resulting in chloride installation (Scheme **3**). This can be remedied by using $CrBr_3$ and perforing and in-situ reduction, but we found that sourcing high quality $CrBr_3$ is much more difficult, and even more costly.



Scheme 3. Finklestein leading to vinyl chloride

4.2 Attempts at Improving the Takai-Utimoto Olefination

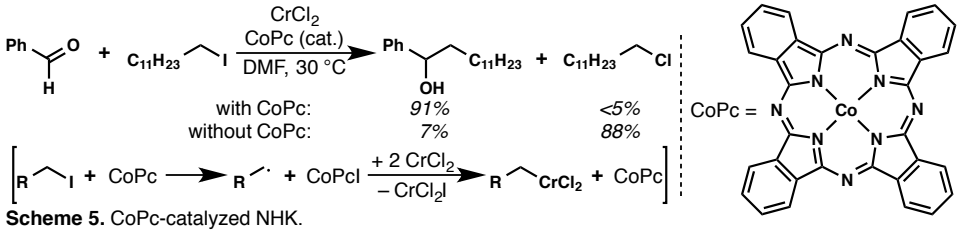
We decided that it would be a worthwhile endeavor to try and improve the Takai-Utimoto olefination to bring down the cost. The primary way to do this would be improving the catalytic methods and render them more general. Although there are only a handful of reports on the Takai-Utimoto olefination catalytic in chromium, there is a large body of work for the Nozaki-Hiyama-Kishi (NHK) coupling catalytic in Cr, which bears a number of mechanistic and practical similarities to the olefination. The main reason for developing a NHK variant catalytic in chromium was to develop an asymmetric variant. Fürstner reported much of the pioneering work in this area (Scheme **4**).[4,5] The first issue was to find a way to exchange and trap the oxygen bound to chromium, which returns the Cr(III) back to a state that it can be reduced. This was done by adding TMSCl to the reaction mixture. Next, he found that the chromium source had a large impact on the catalytic efficiency, and While $CrCl_2$ was competent, $CrCp_2$ gave superior turnover numbers. Presumably, the Cp ligands increase the solubility of the chromium species, increasing the reaction rate. The identity of the



Scheme 4. $CrCl_2$ vs $CrCp_2$ in Ni-free NHK.

stoichiometric reductant was also important, as the formed metal salt should be as nonreactive as possible. Mn^0 proved to be superior to Zn^0, due to its reduced Lewis acidity.

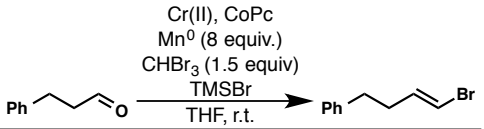
Takai and Utimoto also reported on improvements to the NHK coupling reaction. Their relevant contribution focused on the Finklestein side reaction, which can be a major issue in cases where the halide species is slow to reduce. However, another report indicated that while Cr(II) can be slow to reduce alkyl halides, it is able to trap the formed carbon radical extremely quickly (Scheme **5**).[6] Using this concept, Takai and Utimoto developed a method that uses the



Scheme 5. CoPc-catalyzed NHK.

Cr(II) to trap a radical that is first formed by a cobalt species. The reduction of the alkyl iodide by cobalt is extremely fast, and the subsequent trapping of the alkyl iodide by Cr(II) gives the nucleophilic species that is slow to form under the conditions that only use Cr(II).[7]

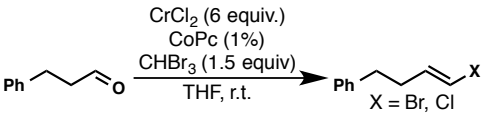
With this knowledge in hand, we decided to test these concepts on the Takai-Utimoto reaction conditions. Preliminary results on model aldehydes indicated that the methods developed in order to improve the NHK coupling reaction also applied to the olefination favorably (Scheme **6**). We found that the olefination could take place with catalytic amounts of chromium when the conditions first developed for the catalytic NHK. We opted to use TMSBr in place of TMSCl because we found that the exogenous chloride displaced the bromine of $CHBr_3$, ultimately leading to vinyl chloride installation. Much like Fürstner



Cr(II)	CoPc	TMSBr	result
$CrCl_2$ (10%)	1%	2.5 equiv.	<10% conversion
$CrCp_2$ (10%)	1%	2.5 equiv.	50% conversion
$CrCp_2$ (2%)	1%	2.5 equiv.	<10% conversion
$CrCp_2$ (10%)	none	2.5 equiv.	50% conversion
$CrCp_2$ (10%)	1%	none	<10% conversion

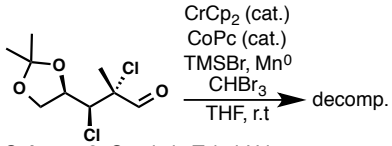
Scheme 6. Catalytic Takai-Utimoto olefination screening.

reported, while $CrCl_2$ could be used in catalytic quantities, $CrCp_2$ was substantially more efficient. We also found that the CoPc had no effect on the reaction outcome when a catalytic amount of $CrCp_2$ was used. However, addition of CoPc to the conditions using stoichiometric amounts of $CrCl_2$ drastically decreased the formation of the vinyl chloride byproduct (Scheme **7**). This was an important discovery, as $CrCp_2$ is much more sensitive and more expensive than $CrCl_2$. It is also important to note that a combination of $CrCl_3$ and Mn^0 could be used in place of the $CrCl_2$ with nearly identical results.

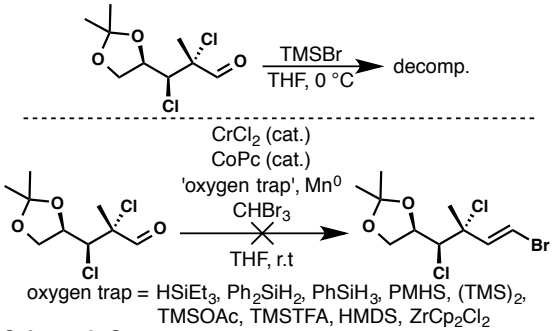


Scheme 7. CoPc in stoichiometric Takai-Utimoto.

We were excited to test these conditions on the *Plocamium* system to see if any would be an improvement over the standard conditions, which gave only reductive dechlorination products (Scheme **8**). Unfortunately, with the more complex system used in the synthesis of the *Plocamium* natural products, we saw no desired product under any circumstance. $CrCp_2$ seemed too reactive to tolerate the oxygen and halogen functionality of this system, and using $CrCl_2$ with the cobalt catalyst either returned starting material or only led to reductive dechlorination products. The TMSBr necessary for the catalytic variant of this reaction was also a problem, and led to deprotection of the acetonide in a control reaction lacking the other reagents (Scheme **9**). We attempted to find another suitable oxygen trap, but the milder reagents were not effective at exchanging the oxygen off of chromium, and more powerful reagents again led to only decomposition. Because the changes we had made did not seem to improve the reactivity in the context of complex natural product synthesis, we decided to shelve this



Scheme 8. Catalytic Takai-Utimoto attempt on *Plocamium* monoterpene system.

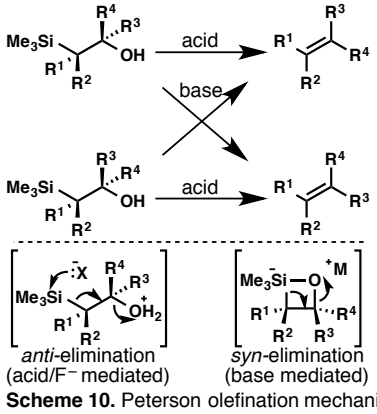


Scheme 9. Oxygen trap screen.

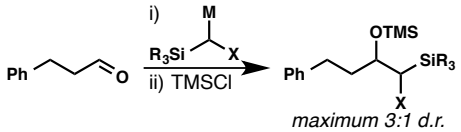
idea and move on to other possible reactions.

4.3 Peterson olefination.

Another potential option to install vinyl halides was using the Peterson olefination (Scheme **10**). First reported in 1968, this reaction takes advantage of silicon's affinity for oxygen, transforming a β-hydroxy silane into an olefin.[8,9] It has been known for some time that the alkene geometry is a result of the type of elimination, which can be reagent controlled. Acidic and fluorine-mediated conditions lead to the *anti*-elimination product by activation of oxygen or silicon, respectively. Under basic conditions, the *syn*-elimination product forms, due to coordination of the adjacent oxygen to silicon. This aspect of the Peterson olefination is both an asset and a liability. Due to this nature of the elimination, the stereochemistry of the alkene is directly related to the β-hydroxy silane diastereomer. If the functionality is synthesized by a method with high diastereoselectivity, a single alkene isomer can be formed. However, a mixture of β-hydroxy silane diastereomers will result in a mixture of alkene isomers. Still, we thought this hurdle could be overcome, and ran some preliminary experiments to test if a single diastereomer could be formed via 1,2-addition of an organometallic (Scheme **11**). Despite many attempts at influencing the selectivity, nothing ever significantly changed. The size of the silane had the largest effect, but the differences were modest. Moreover, we found that the 1,2-addition product was not stable. If the oxygen were not capped with a protecting group at low temperature, the addition product would completely decompose upon workup.

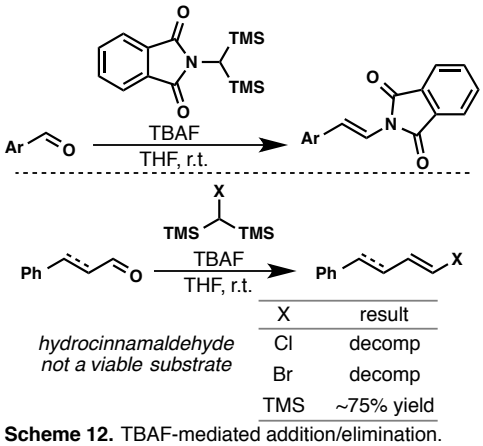


Scheme 10. Peterson olefination mechanism.



Scheme 11. Diastereoselective 1,2-addition attempts.

One interesting report that we found showed that some groups could be installed via Peterson olefination with excellent *E*-selectivity when bis-silanes were used along with a fluorine source (Scheme **12**). [10 11] Presumably, the fluorine would activate one of the silicon atoms and make the carbon-silicon bond nucleophilic enough to attack an aldehyde. The resulting silyl ethe would deprotect under the conditions, and the Peterson olefination would occur with the remaining silane to give exclusively the *E*-alkene. We attempted this protocol with a number of different heteroatoms. All of the halides failed. Only in the case when the heteroatom was another silicon was the desired *E*-olefin isolated. Unfortunately, this reaction was not useful for enolizable aldehydes such as hydrocinnamaldehyde, which rapidly decompose.

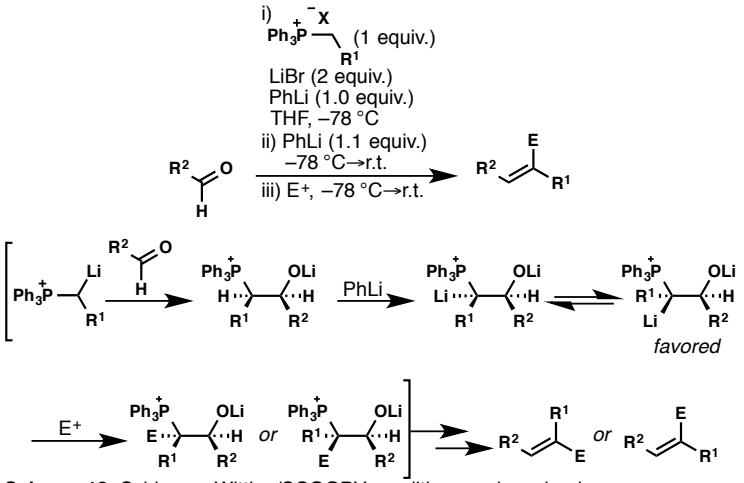


X	result
Cl	decomp
Br	decomp
TMS	~75% yield

Scheme 12. TBAF-mediated addition/elimination.

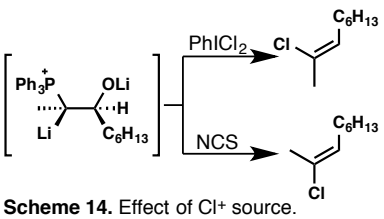
4.4 SCOOPY-Wittig Olefination

We had one more idea for a new method of *E*-bromide installation, which stemmed from an attempted Schlosser-modification of the Wittig reaction (Scheme **13**).[12] Although ulikely, we thought that the Schlosser-Wittig might be a competent method to install the vinyl halide stereoselectively. As expected, this did not work. However, it did lead us to a variant of the Schlosser-Wittig that showed promise. In 1969, Schlosser reported on a modification of his the original method, where instead of quenching the reaction

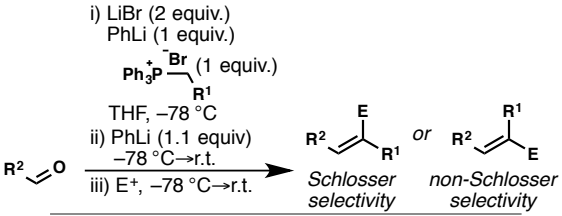


Scheme 13. Schlosser-Witting/SCOOPY conditions and mechanism.

with a proton source, another electrophile such as an aldehyde could be added to form an additional C-C bond.[13] He later coined this method 'α-substitution plus carbonyl olefination via β-oxido phosphorus ylids', or SCOOPY.[14] This proved to be a powerful method for stereoselective olefin synthesis, and a report by Corey demonstrated this, including one particularly interesting result. He was able to install a vinyl chloride using the Schlosser-Wittig by quenching the reaction with an electrophilic chlorine source, forming a new C-Cl bond (Scheme **14**).[15] More interestingly though was the change in alkene geometry observed when different chlorine sources were use. If the chlorine source was $PhICl_2$, the *Z*-olefin formed, analogous to quenching with a hydrogen source. However, when NCS was used as the quench, formation of the *E*-olefin was favored. Corey did not discuss why this was the case. When searching for more literature on the subject, we came across a series of reports by Hodgsen studying the SCOOPY modification of the Schlosser-Wittig (Scheme **15**).[16,17,18] In these studies, the aldehyde, Wittig reagent, and electrophile were all probed for their effect on olefin geometry. The aldehyde had very little effect on the selectivity, while the Wittig reagent and electrophile had a profound effect on selectivity. Based on the reports, H and Me give the Schlosser selectivity, while larger substituents can give non-Schlosser selectivity depending on the electrophile used. We though it was strange that electrophilic bromine sources had not been tested with the unsubstitutued Wittig reagent. We were curious to see if using a combination of



Scheme 14. Effect of Cl^+ source.

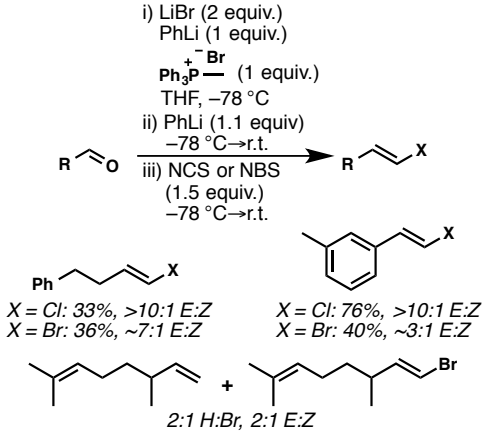


E^+	E	R^1	selectivity
$BrCF_2CF_2Br$	Br	Me	Schlosser
$BrCF_2CF_2Br$	Br	>Me	non-Schlosser
$BrCH_2OAc$	CH_2OAc	Me	Schlosser
$BrCH_2OAc$	CH_2OAc	>Me	Schlosser
$BrCH_2OAc$	CH_2OAc	H	Schlosser

Scheme 15. Hodgson's SCOOPY studies.

the Corey and Hodgsen protocols, we could selectively obtain *E*-bromides on disubstituted olefins.

With a general sense of what conditions to use, we began to test the feasibility of the method to install *E*-bromides (Scheme **16**). Very little had to be altered in order to obtain promising results. Using the standard conditions reported by Hodgson, we were able to obtain selectivities for the *E*-bromide or chloride that were as good or better than the selectivity seen in the Takai-Utimoto olefination performed on the same substrates. There are still a number of problems that need to be ironed out before we could publish a report on this new method. The yields are typically below 40%, and alpha-substitution is a significant problem, with both lower selectivity and yield. However, there is still opportunity to optimize the method, which could ultimately provide a much-needed alternative to the Takai-Utimoto olefination.



Scheme 16. Initial results of SCOOPY *E*-bromide installation.

4.5 Conclusion

The installation of *E*-vinyl bromides still poses a significant challenge, especially in a step-economical fashion. We saw this as an opportunity to develop a new method to add to the synthetic toolbox. After several unsuccessful ideas were tested, we landed in the area of SCOOPY-olefinations, and have seen some promising initial results for both selectivity and yield. If the SCOOPY method proves to be difficult to optimize, we may test a few other ideas that involve combinations of other known olefination and halogenation methods.

4.6 Experimental procedures

All reactions were performed in oven-dried (140 °C) or flame-dried glassware under an atmosphere of dry argon unless otherwise noted. Reaction solvent tetrahydrofuran (THF, Fisher, HPLC Grade) was dried by percolation through a column packed with neutral alumina and a column packed with Q5 reactant, a supported copper catalyst for scavenging oxygen, under a positive pressure of argon. Solvents for workup and chromatography were: *n*-pentane (J.T.Baker, BAKER ANALYZED®) and Et_2O (Fisher, ACS Grade). Column chromatography was performed using EMD Millipore 60 Å (0.040-0.063 mm) mesh silica gel (SiO_2). CoPc and $CrCp_2$ were purchased from Aldrich. $CrCl_2$ was purchased from Strem. $CHBr_3$ was washed with concentrated H_2SO_4 until the acid layer was no longer colored, sat. aq. $NaHCO_3$, H_2O, dried over Na_2SO_4 and distilled over P_2O_5 prior to use.

^1H NMR and ^{13}C NMR spectra were recorded on Bruker GN500 (500 MHz, ^1H; 125 MHz, ^{13}C) and Bruker CRYO500 (500 MHz, ^1H; 125 MHz, ^{13}C) spectrometers at 298 K. ^1H spectra were referenced to residual chloroform (7.26 ppm, ^1H). Chemical shifts are reported in ppm and multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br s (broad singlet). Coupling constants, *J*, are reported in Hertz. Analytical thin-layer chromatography was performed on Merck silica gel 60 F_{254} TLC plates. Visualization was accomplished with UV(254), potassium permanganate ($KMnO_4$), and *p*-anisaldehyde staining solutions.

Method A: General procedure for Takai–Utimoto catalytic in $CrCp_2$

In a glovebox, vial was charged with $CrCp_2$ (0.003 g, 10 mol%) and Mn^0 powder (0.082 g, 1.5 mmol, 10 equiv.). Once outside of the glovebox, THF (1 mL) was added to form a suspension. In a separate vial, aldehyde (0.15 mmol, 1 equiv.) was dissolved in THF (1.0 mL), followed by the addition of $CHBr_3$ (50 μL, 0.23 mmol, 1.5 equiv.) and TMSBr (80 μL, 0.38 mmol, 2.5 equiv.). The resulting solution was added to the metal slurry via syringe and stirred 12 h at r.t. The crude mixture was diluted with Et_2O (5 mL) and filtered through a plug of cotton with Et_2O eluent. The resulting solution was washed with 5% aq. AcOH (1 X 5 mL), washed with saturated aq. $NaHCO_3$ (1 X 5 mL), the organic extract dried over $MgSO_4$ and concentrated in vacuo.

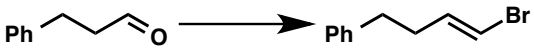
Method B: General procedure for Takai–Utimoto promoted by CoPc

In a glovebox, flask was charged with $CrCl_2$ (0.165 g, 1.34 mmol, 6 equiv.) and CoPc (0.001 g,1 mol%). Once outside of the glovebox, THF (2 mL) was added. In a separate vessel, aldehyde (0.22 mmol, 1 equiv.) was dissolved in THF (1 mL), followed by addition of $CHBr_3$ (39 μL, 0.43 mmol, 2.0 equiv.). The resulting solution was added to the metal slurry via syringe and stirred 12 h at r.t. The crude mixture was diluted with Et_2O (5 mL) and filtered through a plug of cotton with Et_2O eluent. The resulting solution was washed with 5% aq. AcOH (1 X 5 mL), washed with saturated aq. $NaHCO_3$ (1 X 5 mL), the organic extract dried over $MgSO_4$ and concentrated in vacuo.

Method C: General procedure for SCOOPY-Wittig olefination

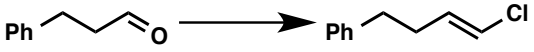
LiBr (0.191 g, 2.2 mmol, 2.2 equiv) was flame dried (3x), cooled to r.t., and the vessel backfilled with Ar. The LiBr was dissolved in THF (6 mL), and the solution added to the reaction flask

containing Wittig reagent (0.357 g, 1.0 mmol, 1 equiv. dried under vacuum at 120 °C for 2h). The mixture was stirred for 30 min, cooled to –78 °C, and PhLi (1.8M in Bu_20, 0.58 mL, 1.05 mmol, 1.05 equiv.) was added dropwise. The reaction mixture was stirred for 1h, warmed to r.t. and stirred 30 min, and cooled back to –78 °C. Aldehyde (1.0 mmol, 1 equiv.) in THF (2 mL) was added dropwise, and the reaction mixture stirred for 2h. PhLi (1.8M in Bu_20, 0.61 mL, 1.1 mmol, 1.1 equiv.) was added dropwise and the reaction mixture stirred for 30 min, warmed to r.t. and stirred an additional 30 min. The orange-red solution was cooled to –78 °C and cannulated to a separate flask containing N-halosuccinimide (2.0 mmol, 2.0 equiv.) in THF (2 mL) at –78 °C, slowly running the solution down the wall of the flask. The resulting mixture was warmed to r.t. over 2.5h, and stirred at r.t. overnight. The reaction was quenched with H_2O (4 mL), extracted with Et_2O (3 x 10 mL), the combined organic extracts dried over $MgSO_4$ and concentrated in vacuo.



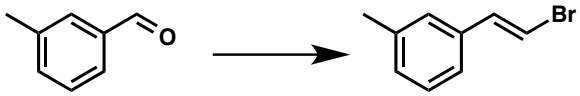
(4-bromobut-3-en-1-yl)benzene

Method A: ~10%, ~3:1 *E:Z*; Method B: ~15%, ~3:1 *E:Z*; Method C: 36%, ~7:1 *E:Z*. R_f = 0.82, pentane. The spectra matched that previously reported by Yan[19]; *E*-isomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.27 (m, 2H), 7.23–7.16 (m, 3H), 6.22 (dt, *J* = 13.6, 7.2, 1H), 6.05 (dt, *J* = 13.6, 1.4, 1H), 2.72 (t, *J* = 7.5, 2H), 2.39–2.34 (m, 2H).



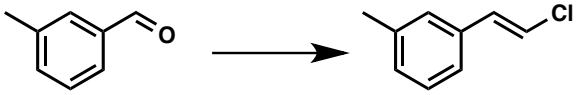
(4-chlorobut-3-en-1-yl)benzene

Method C: 33%, ~10:1 *E:Z*. R_f = 0.80, pentane. The spectra matched that previously reported by Yan[20]; *E*-isomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.27 (m, 2H), 7.23–7.16 (m, 3H), 5.98–5.90 (m, 2H), 2.71 (t, *J* = 7.4, 2H), 2.40–2.35 (m, 2H).



(*E*)-1-(2-bromovinyl)-3-methylbenzene

Method C: 40%, ~3:1 *E:Z*. R_f = 0.78, pentane. The spectra matched that previously reported by Adimurthy[21]; *E*-isomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (t, *J* = 8.0, 1H), 7.10–7.02 (m, 4H), 6.74 (d, *J* = 14.0, 1H), 2.33 (s, 3H).



(*E*)-1-(2-chlorovinyl)-3-methylbenzene

Method C: 76%, ~10:1 *E:Z*. R_f = 0.76, pentane. The spectra matched that previously reported by Schlosser[22]; *E*-isomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (t, *J* = 7.8, 1H), 7.11–7.07 (m, 3H), 6.79 (d, *J* = 13.7, 1H), 6.62 (d, *J* = 13.7, 1H), 2.34 (s, 3H).

4.7 References

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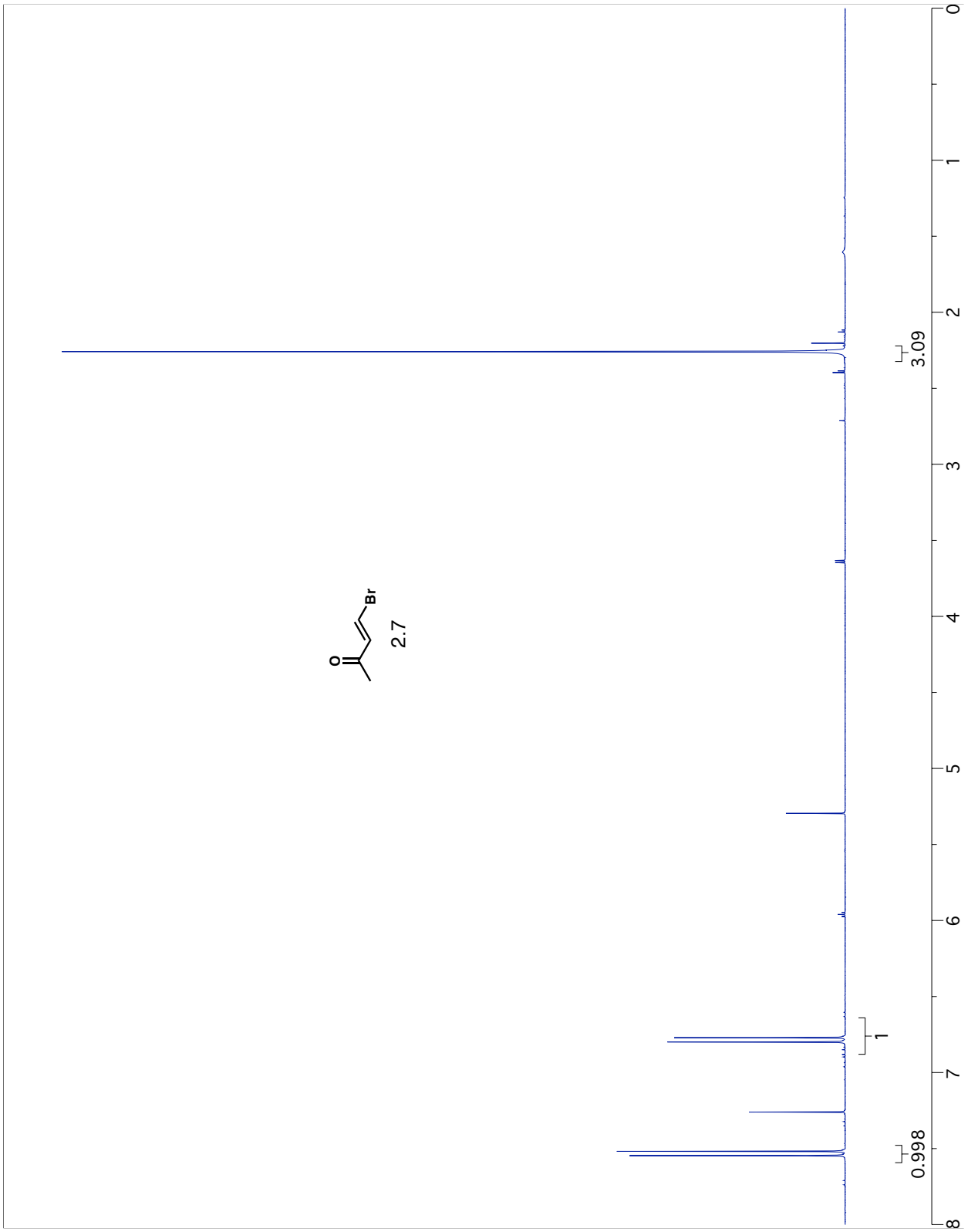
Thesis Conclusion

Our work in the synthesis of the acyclic *Plocamium* polyhalogenated monoterpenes has granted a general strategy that is amenable to the entire group of natural products. To date, 9 natural products and 5 unnatural isomers have been synthesized, most of which have been tested or are currently being tested for activity against solid tumor cell lines. Using our general approach, a variety of analogues can be synthesized to optimize the biological properties of the compounds, with a goal of developing clinical candidates for the treatments of solid tumors.

Appendix A: NMR Spectra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7
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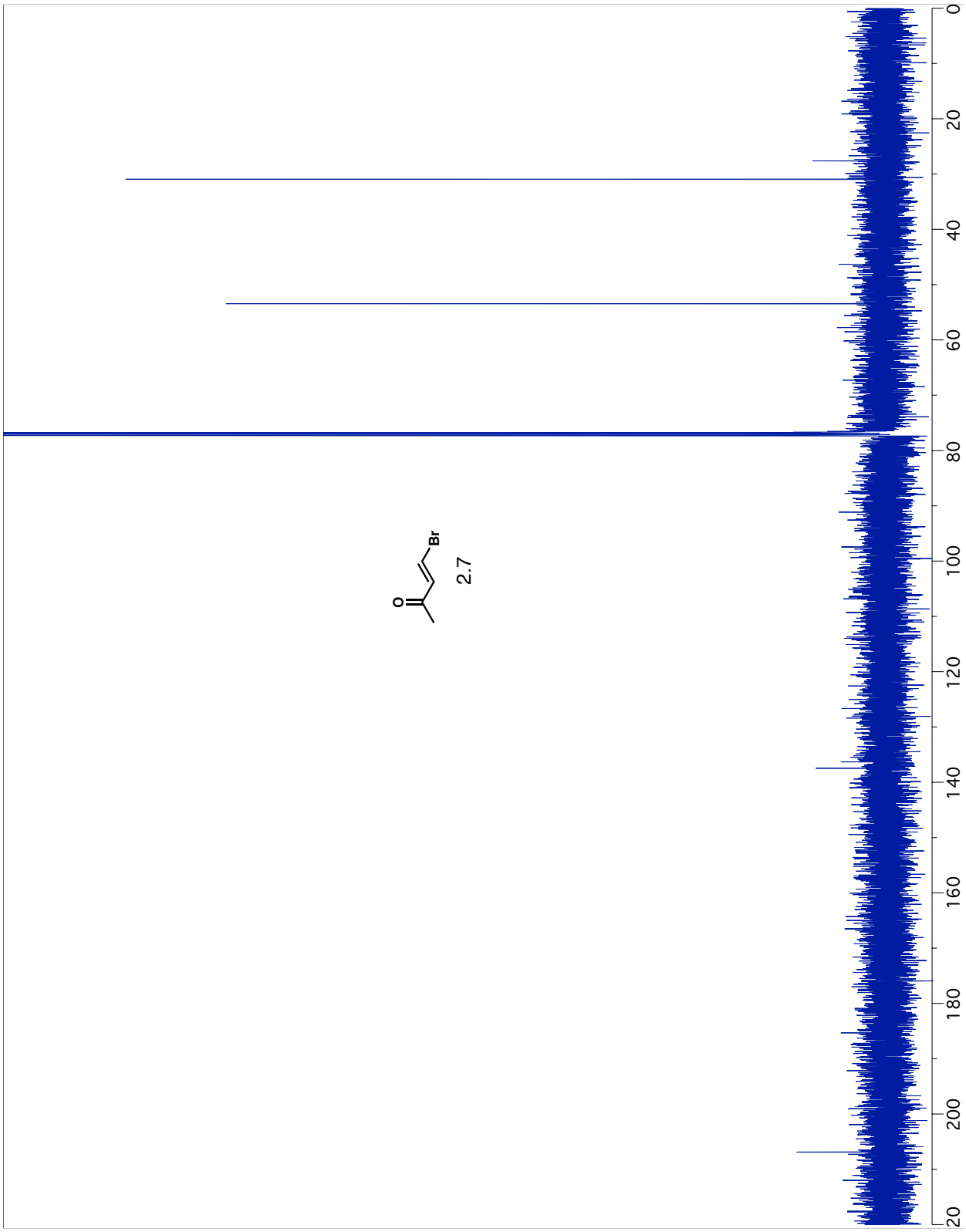
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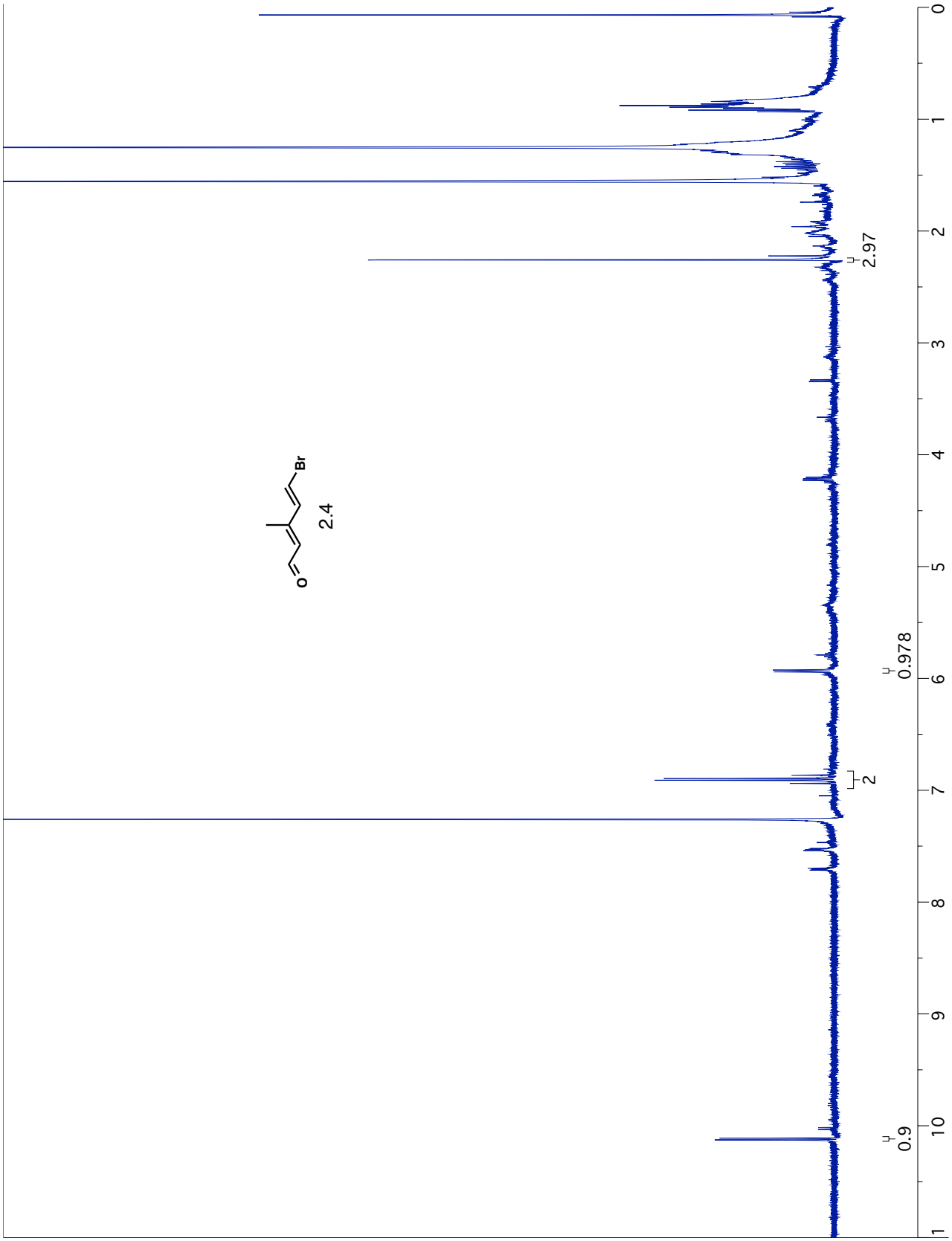
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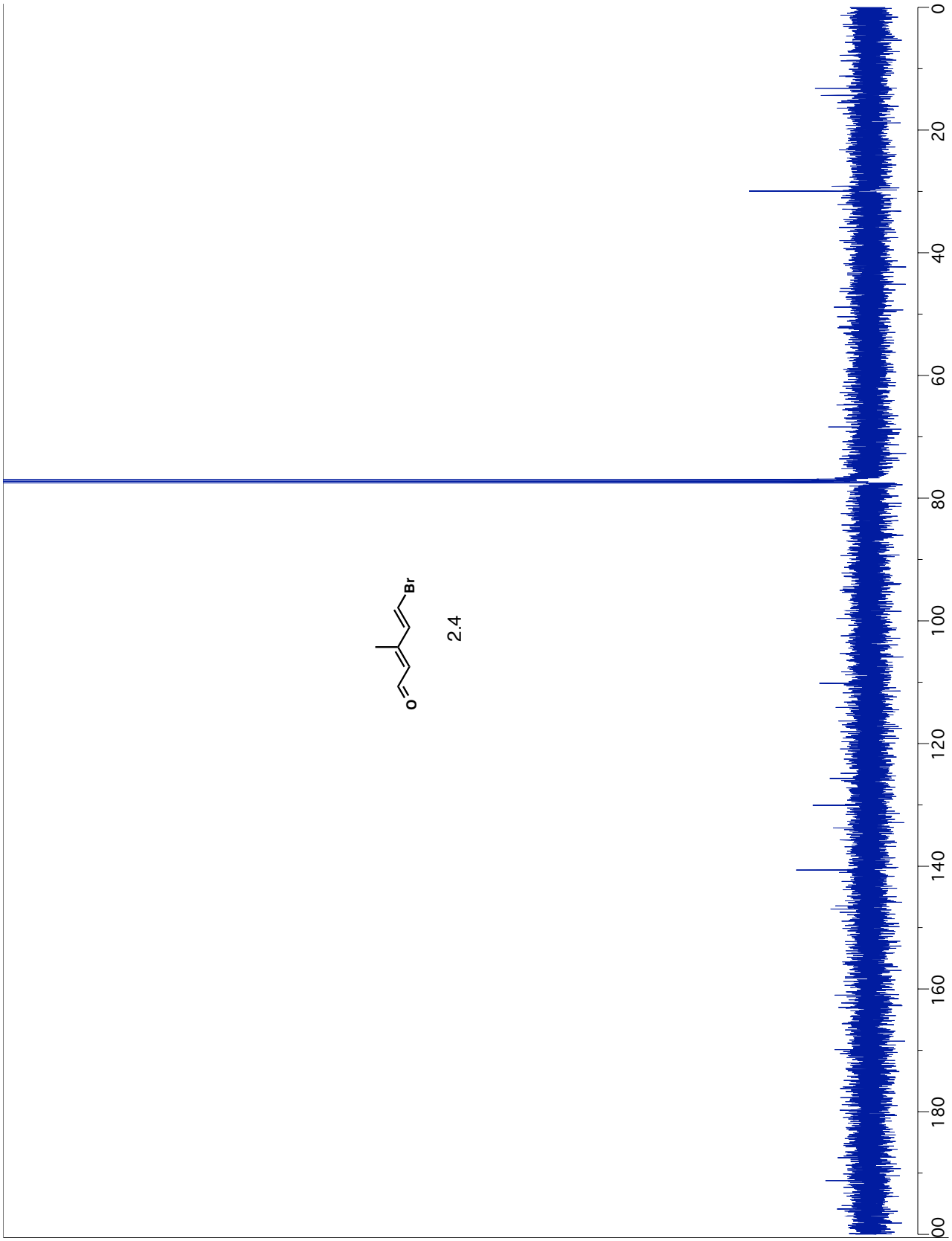
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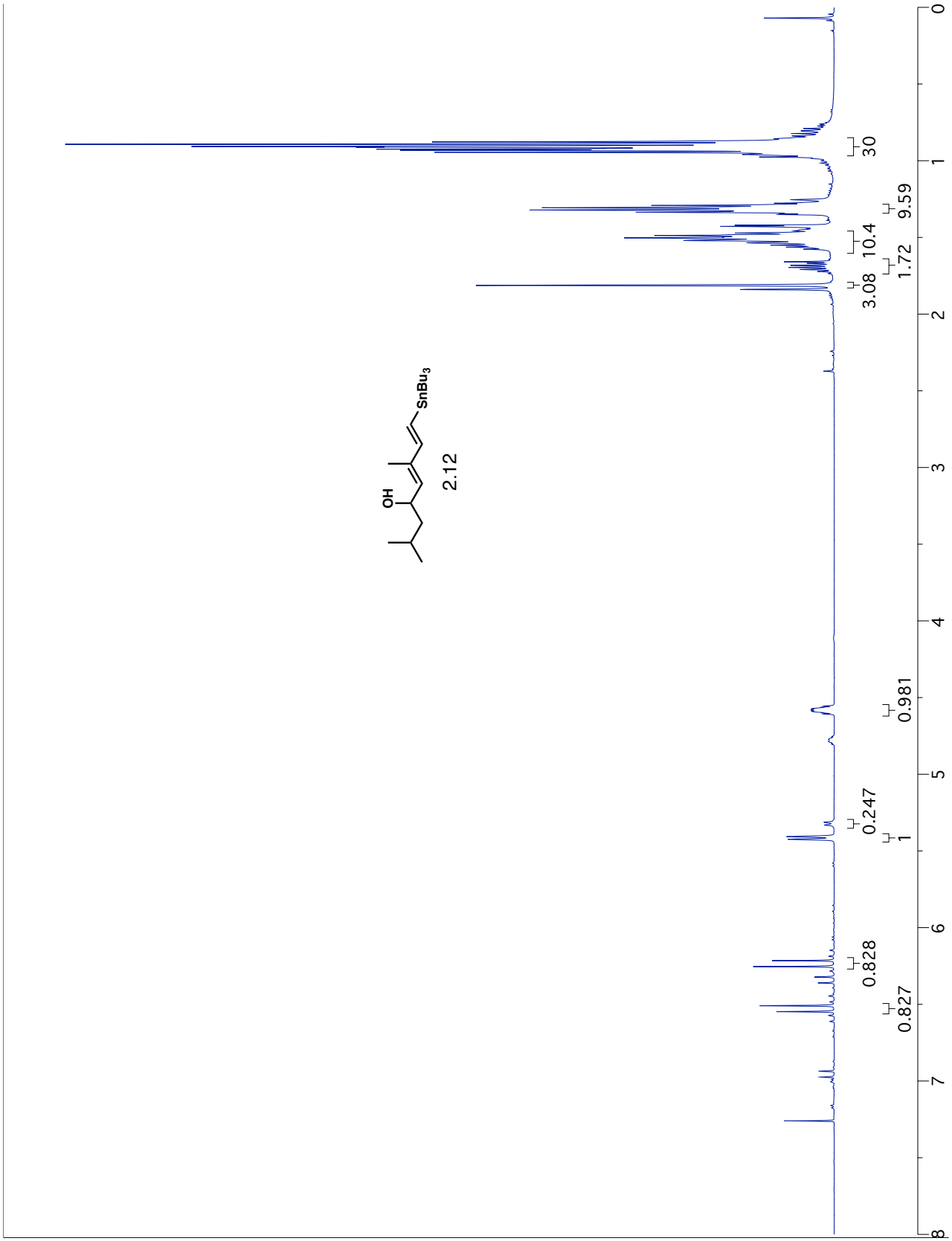
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3
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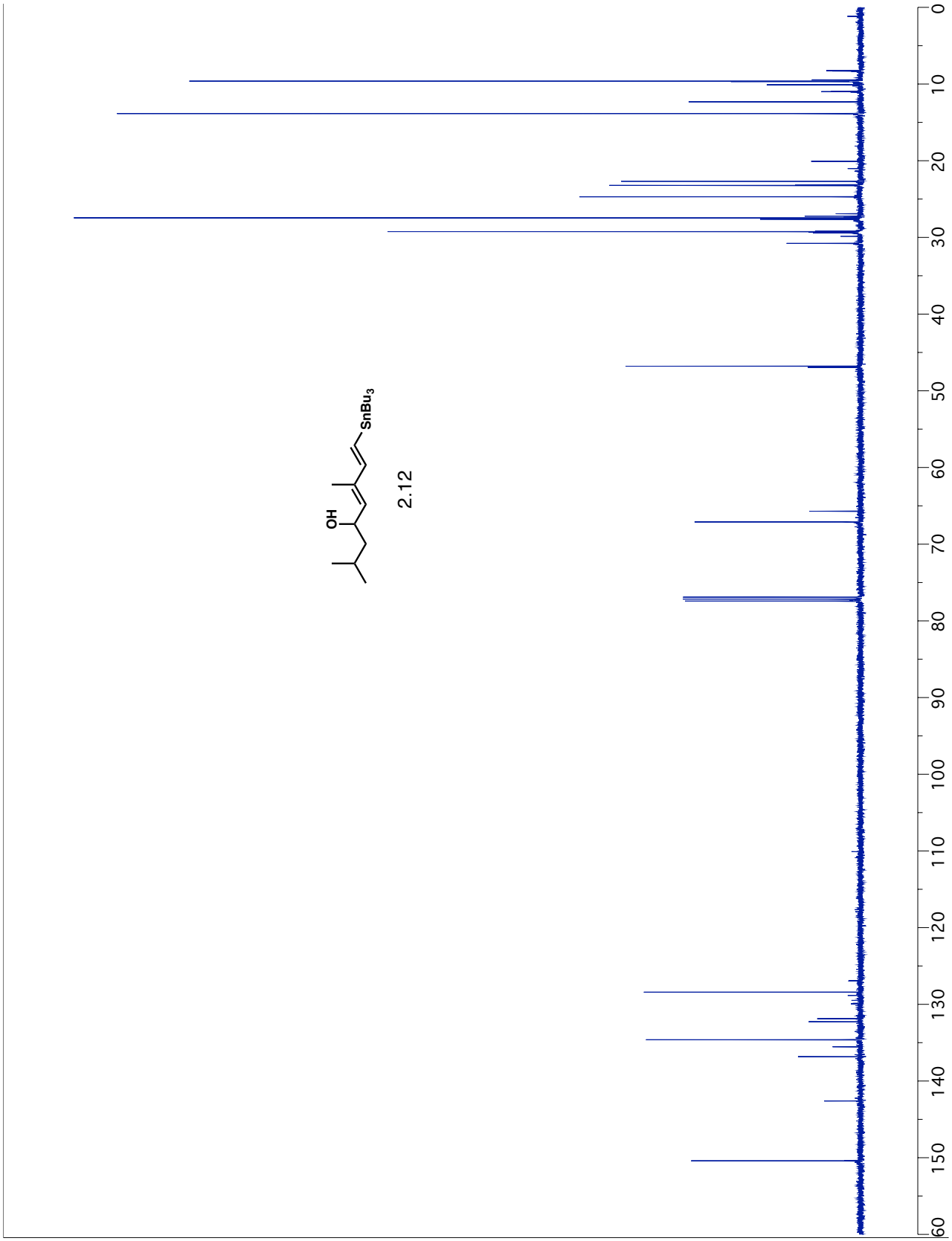
5
6
7
8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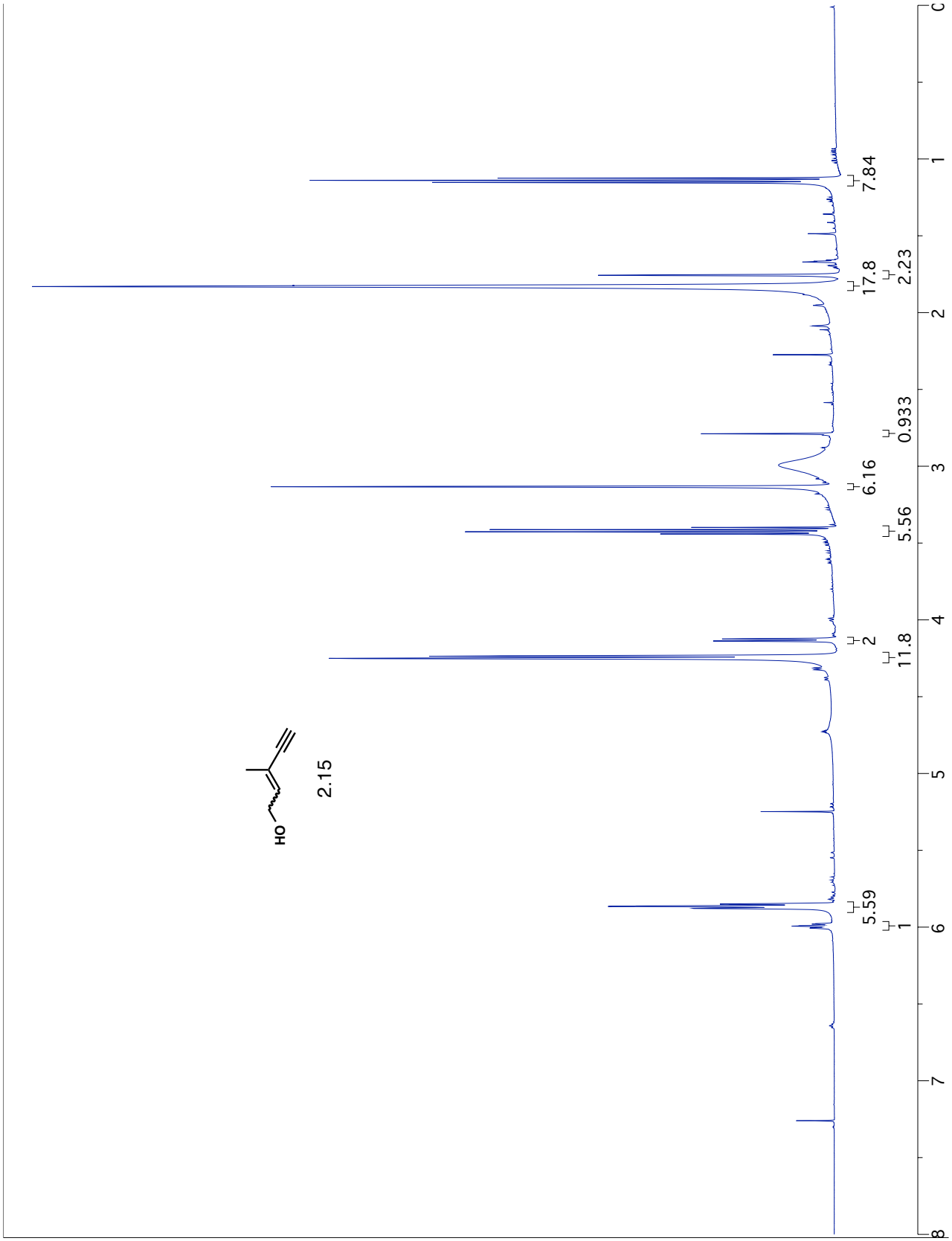
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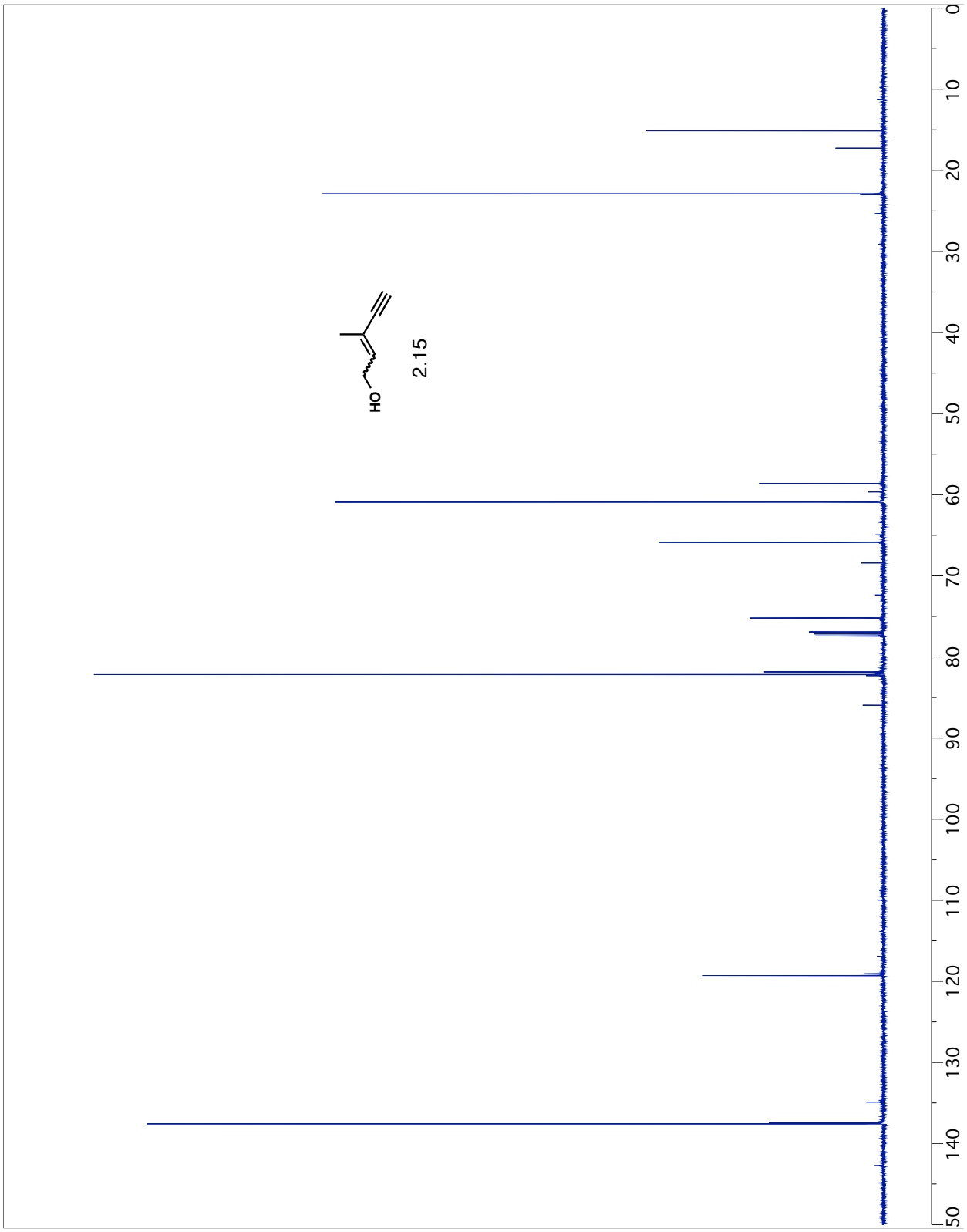
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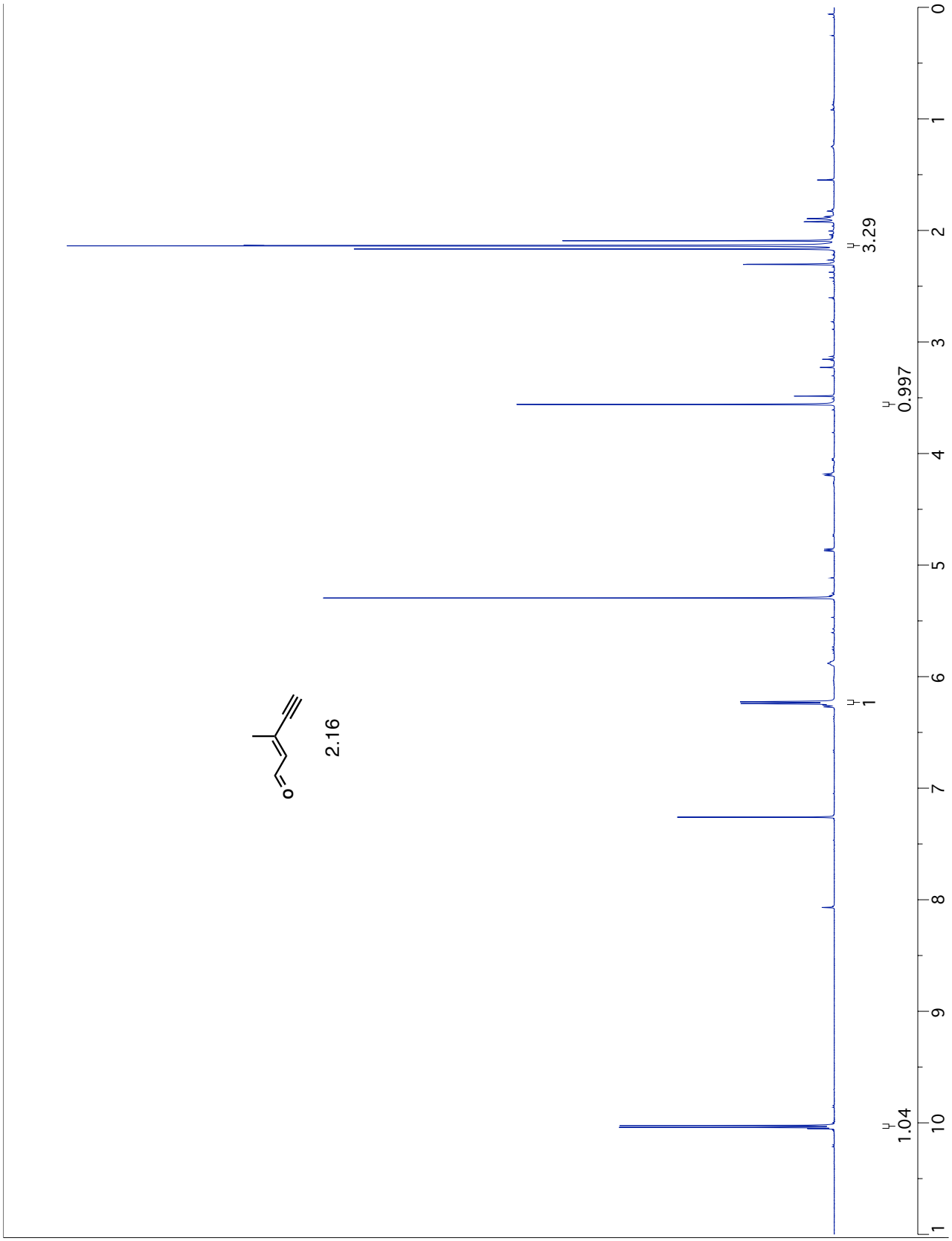
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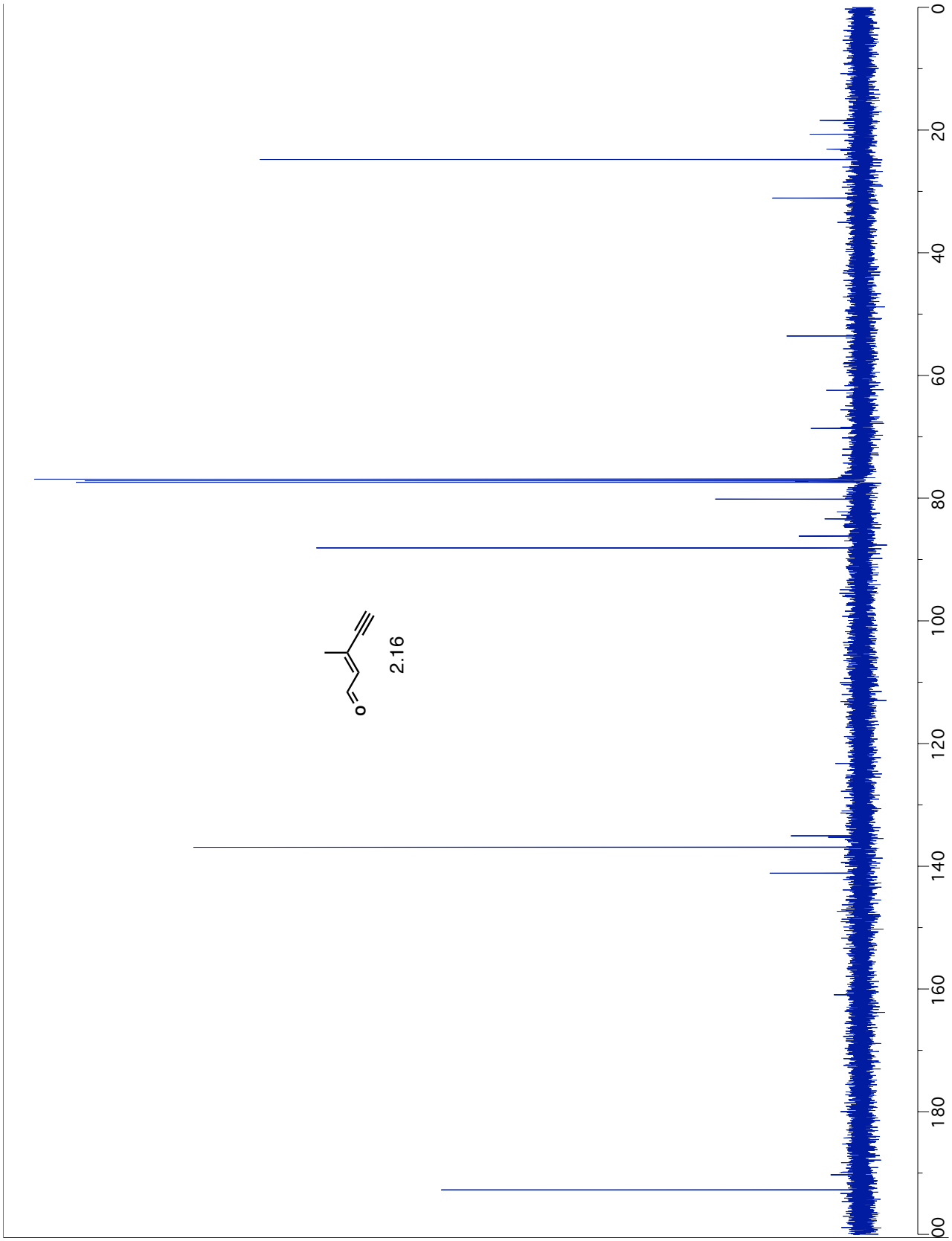
9
10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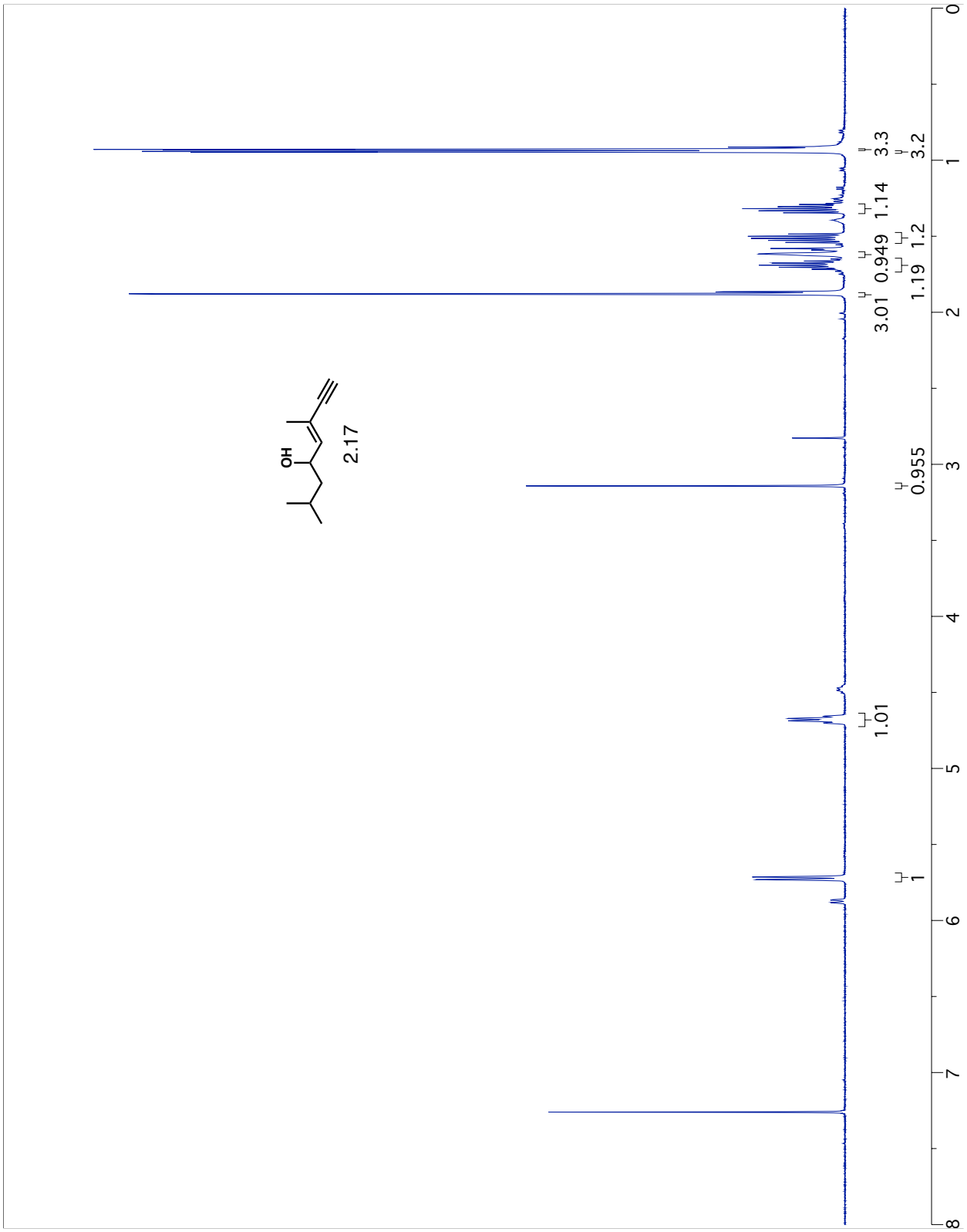
00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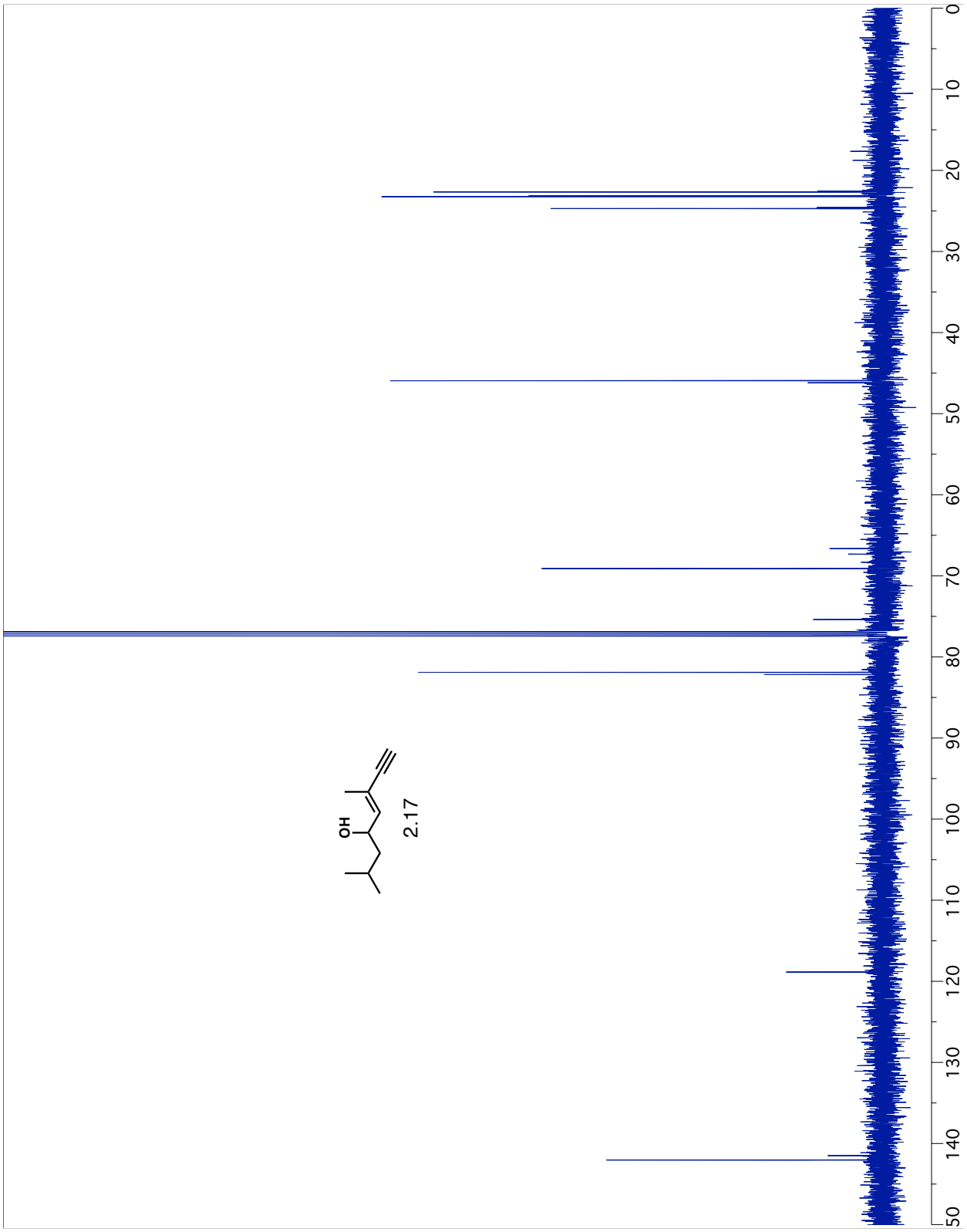
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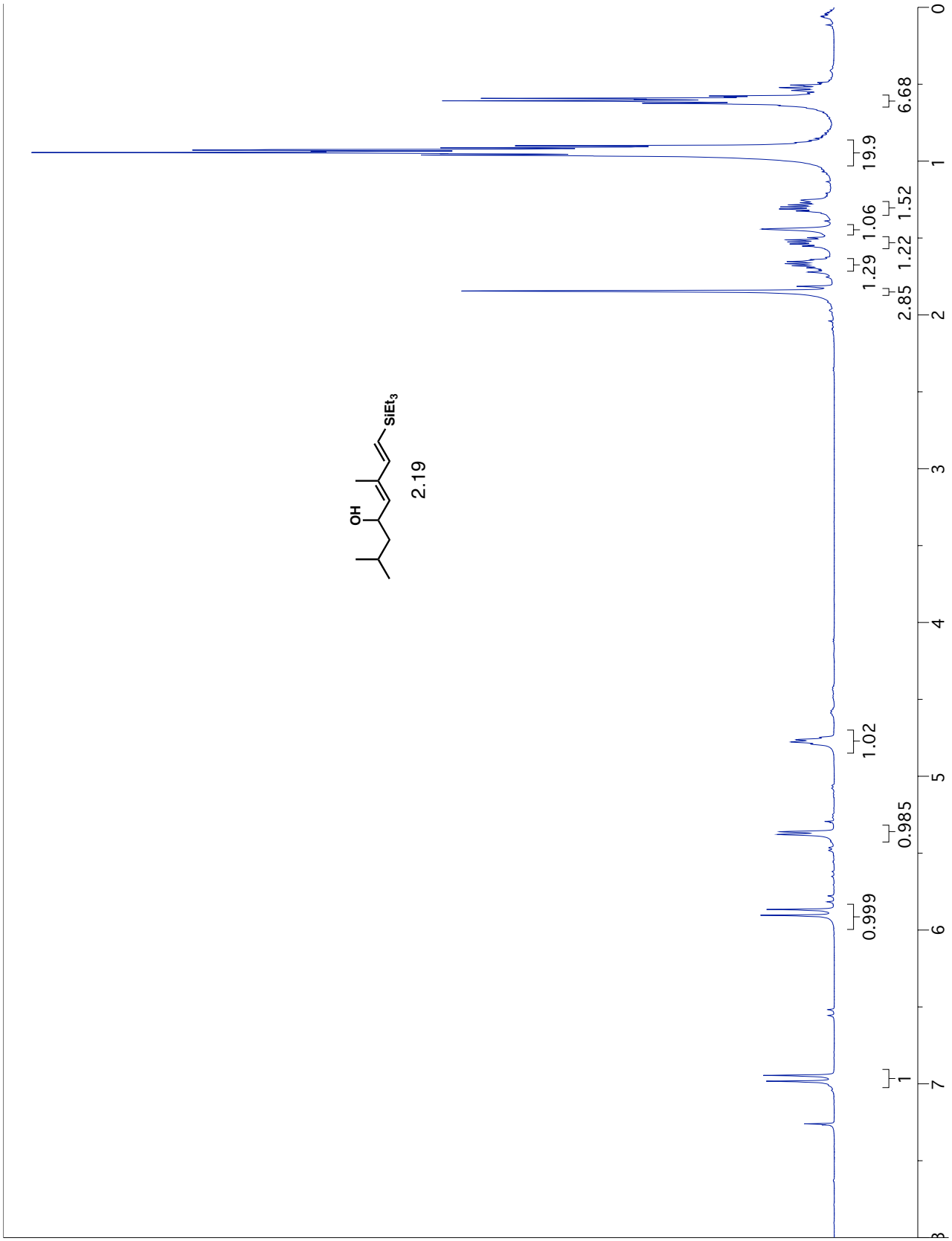
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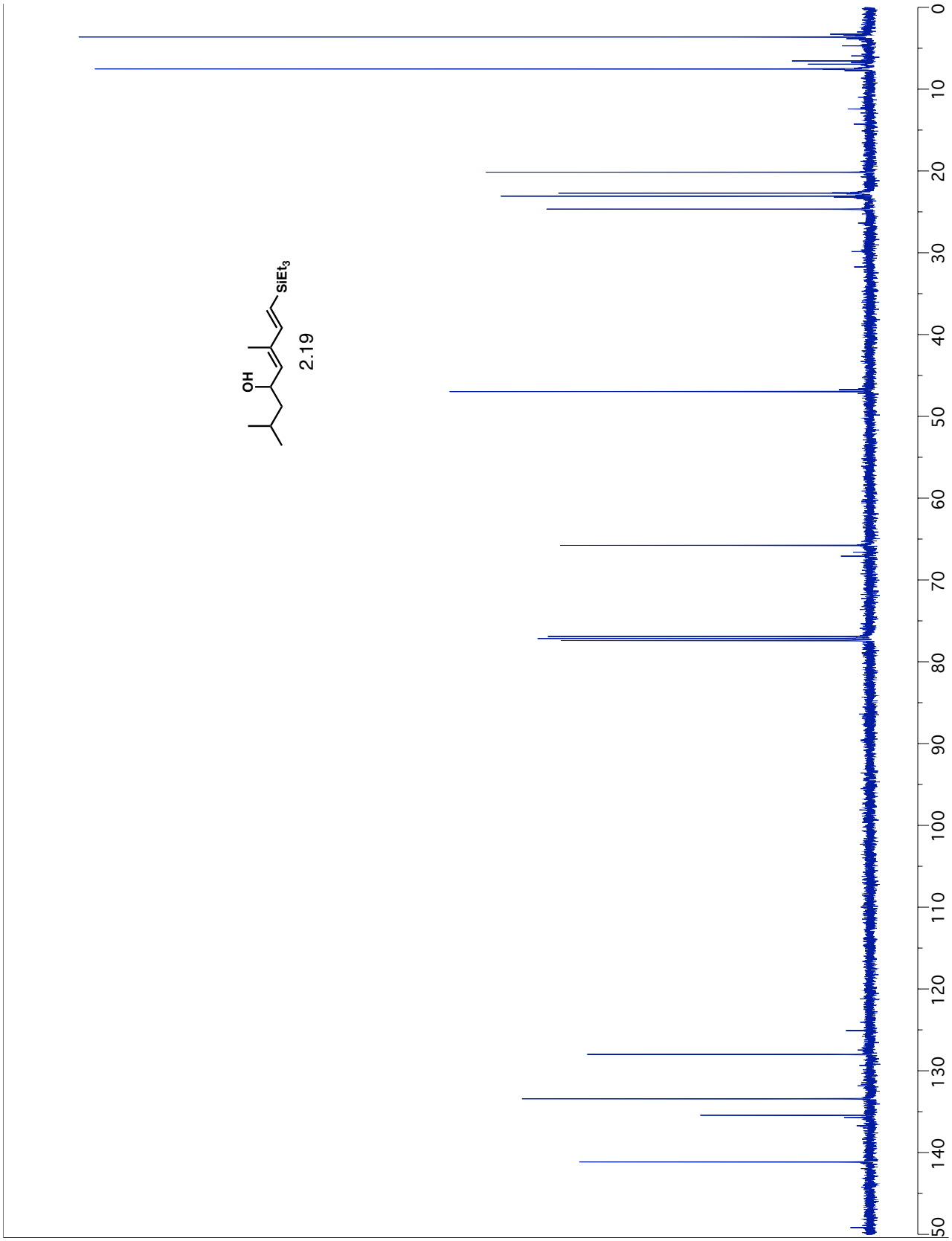
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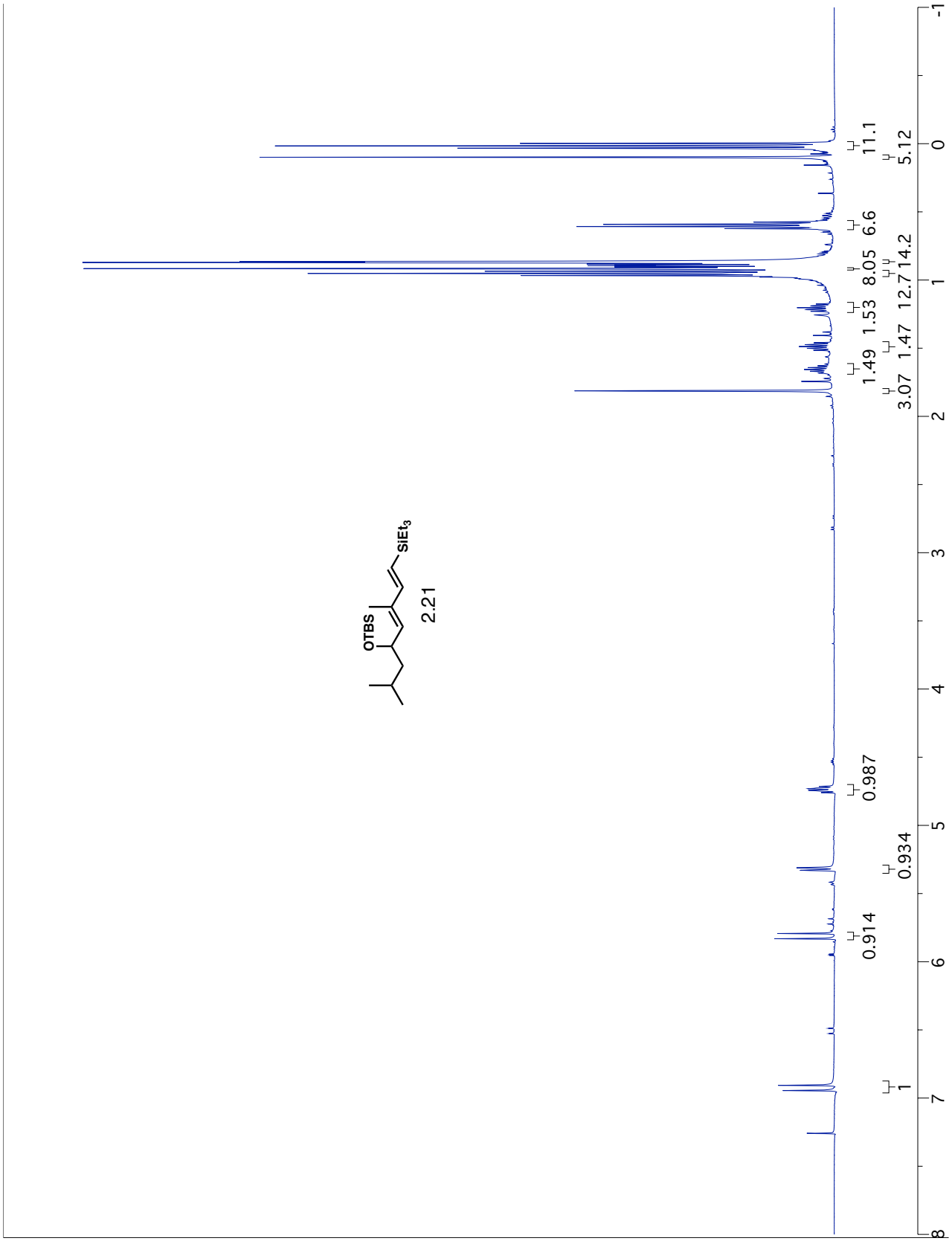
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6
7
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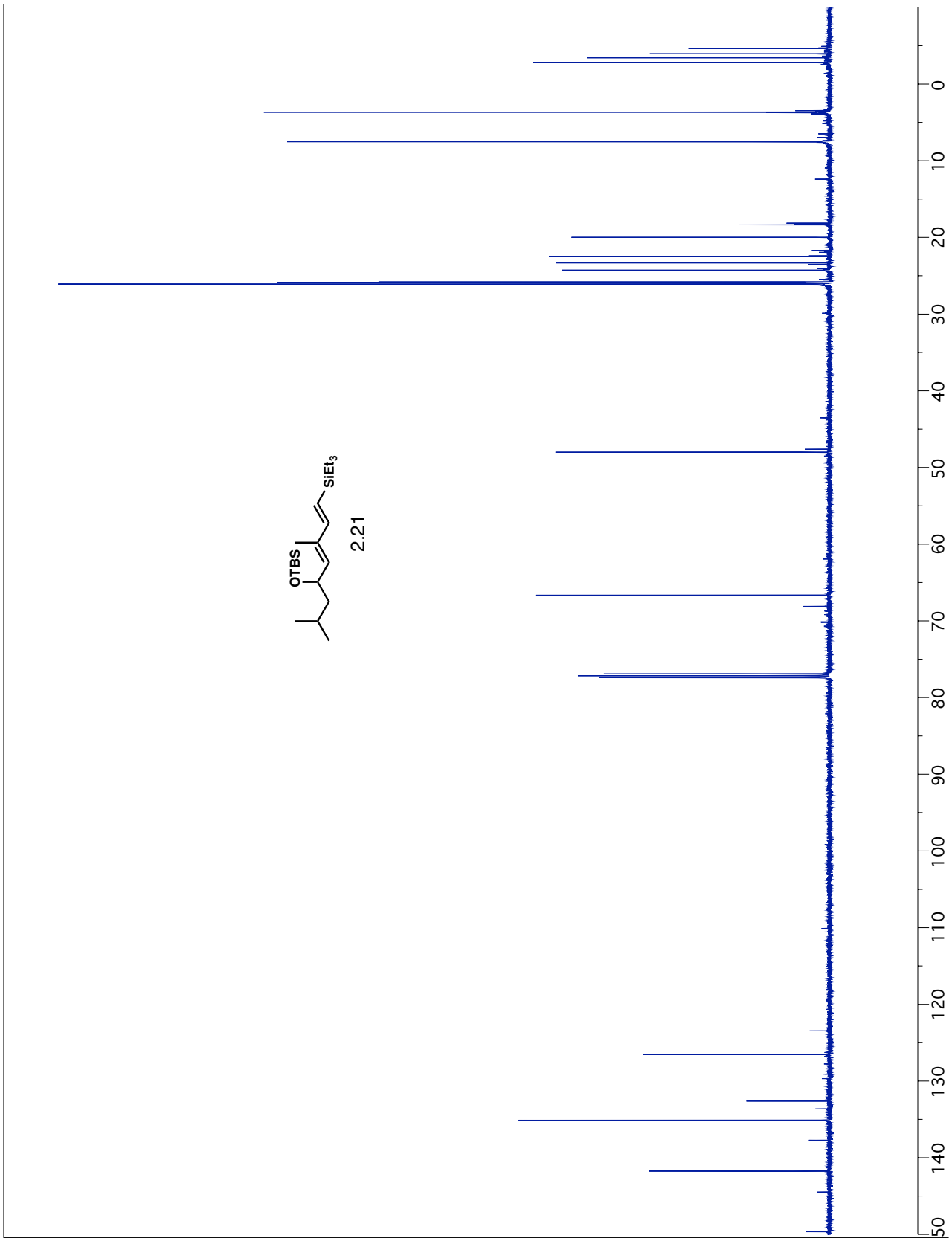
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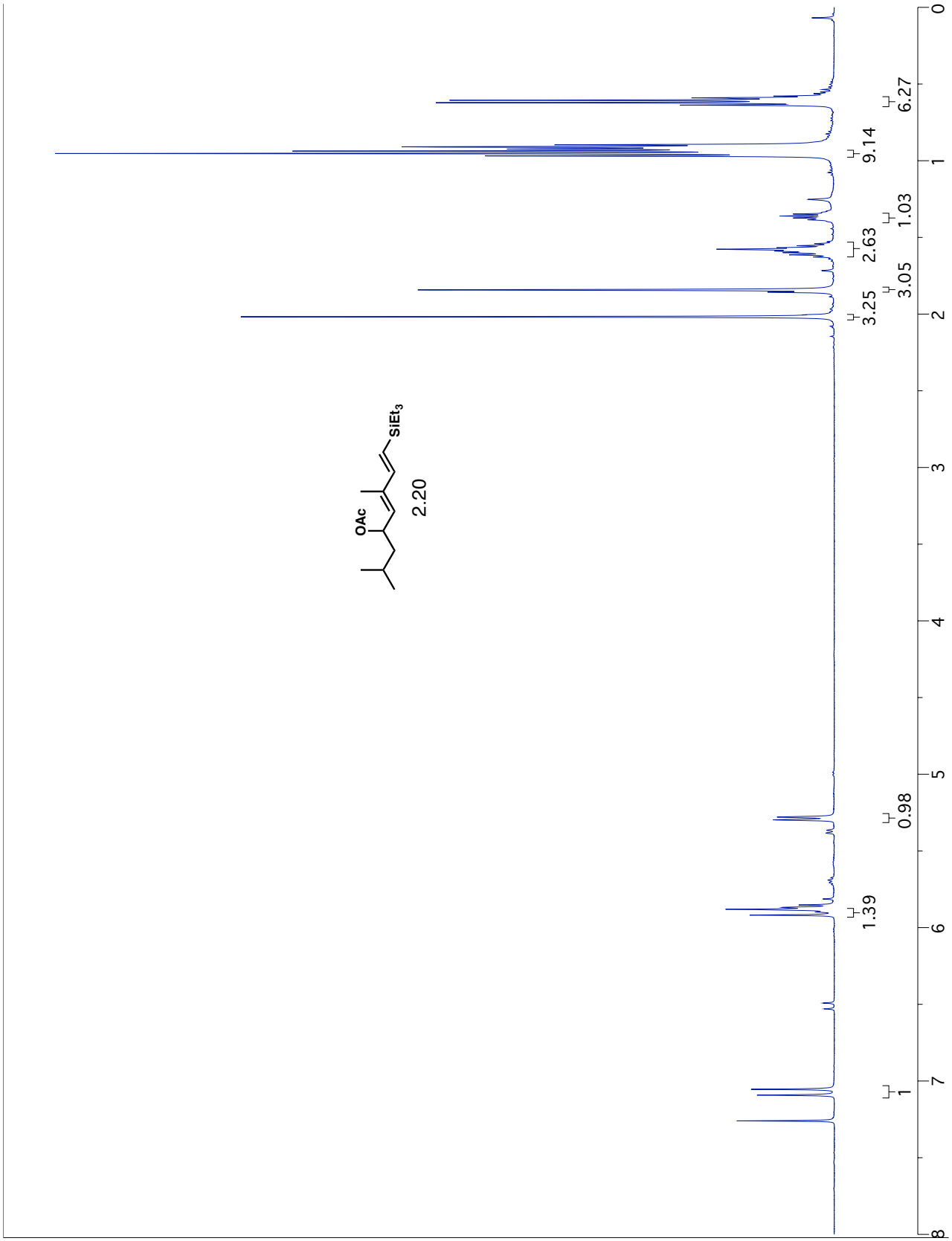
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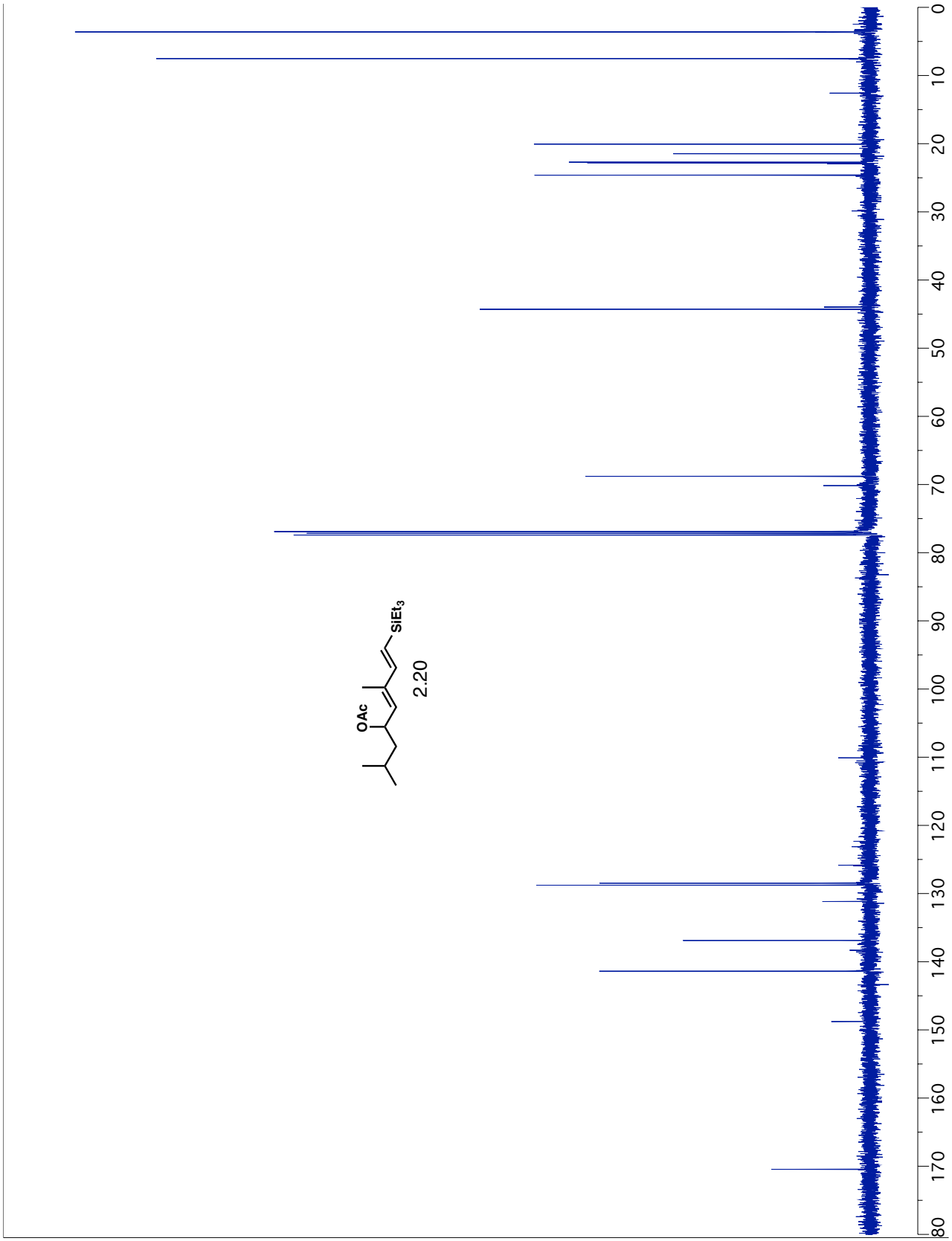
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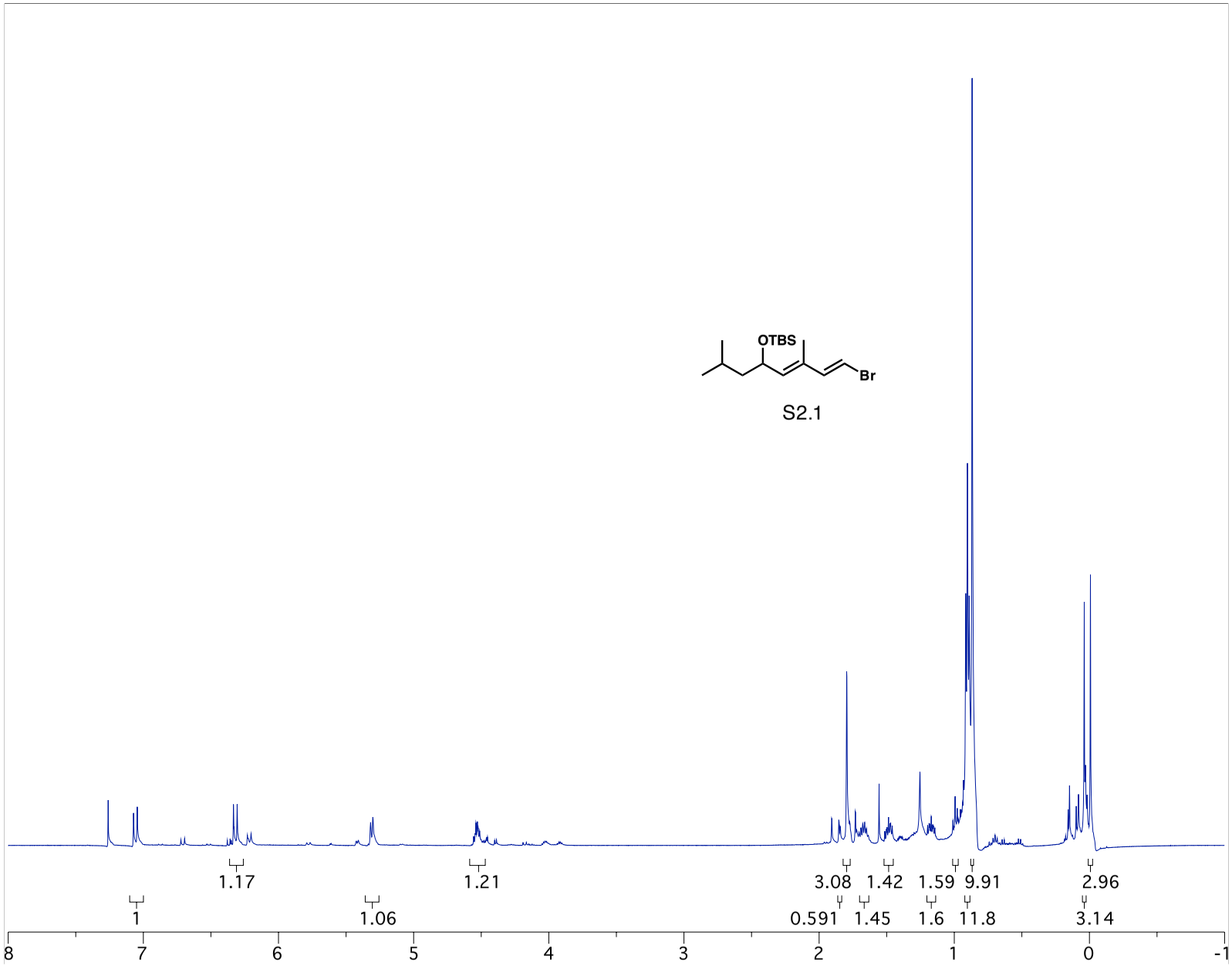
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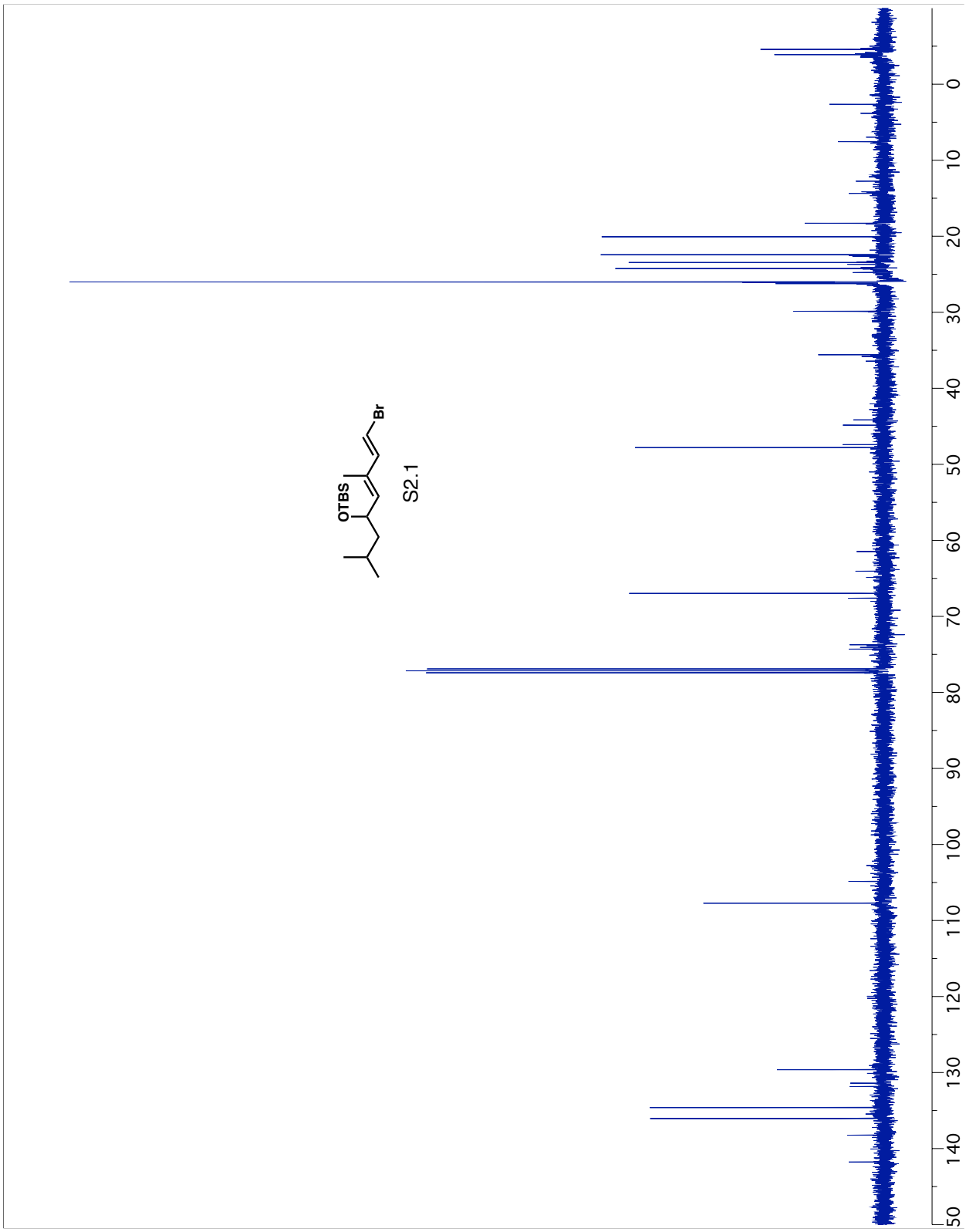
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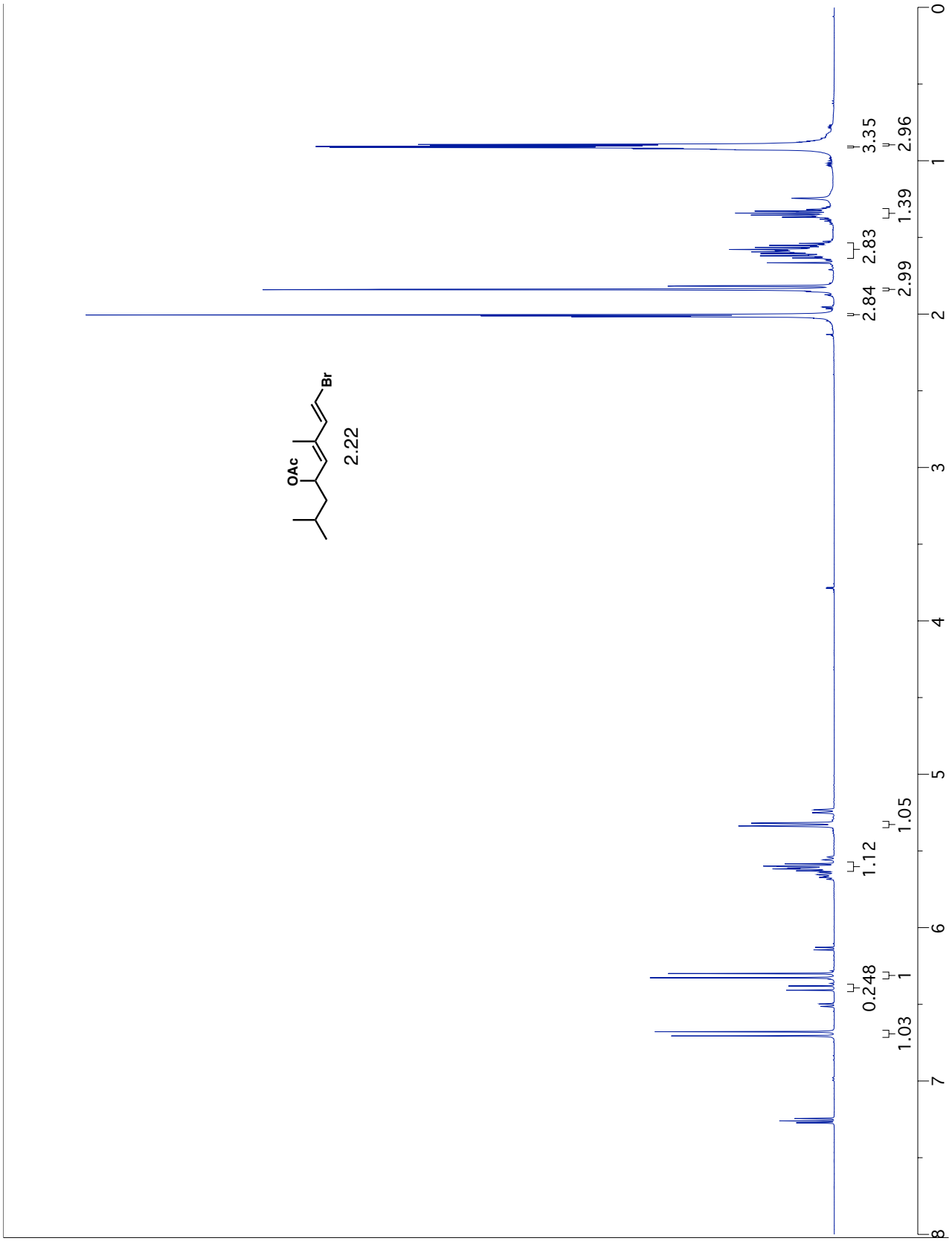
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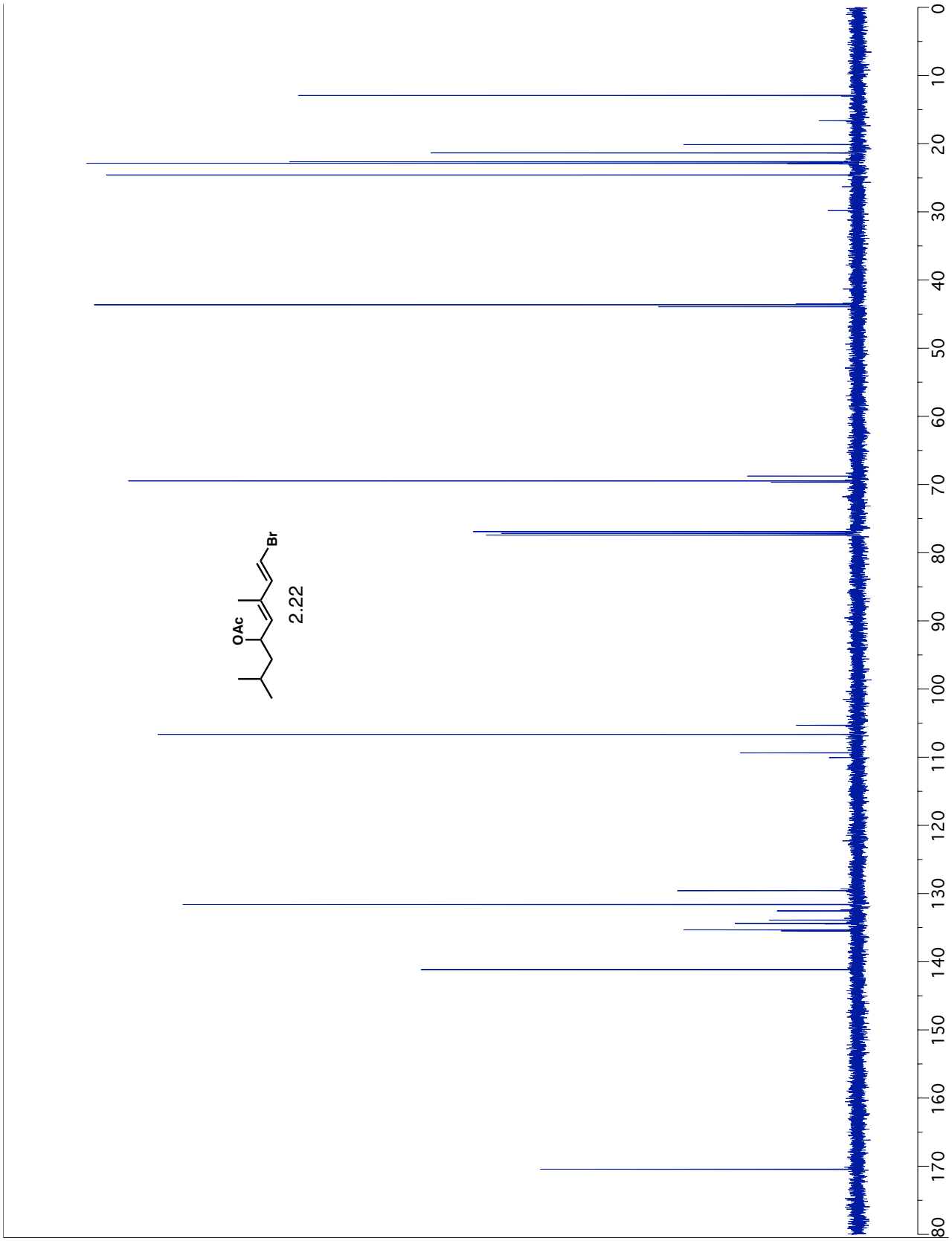
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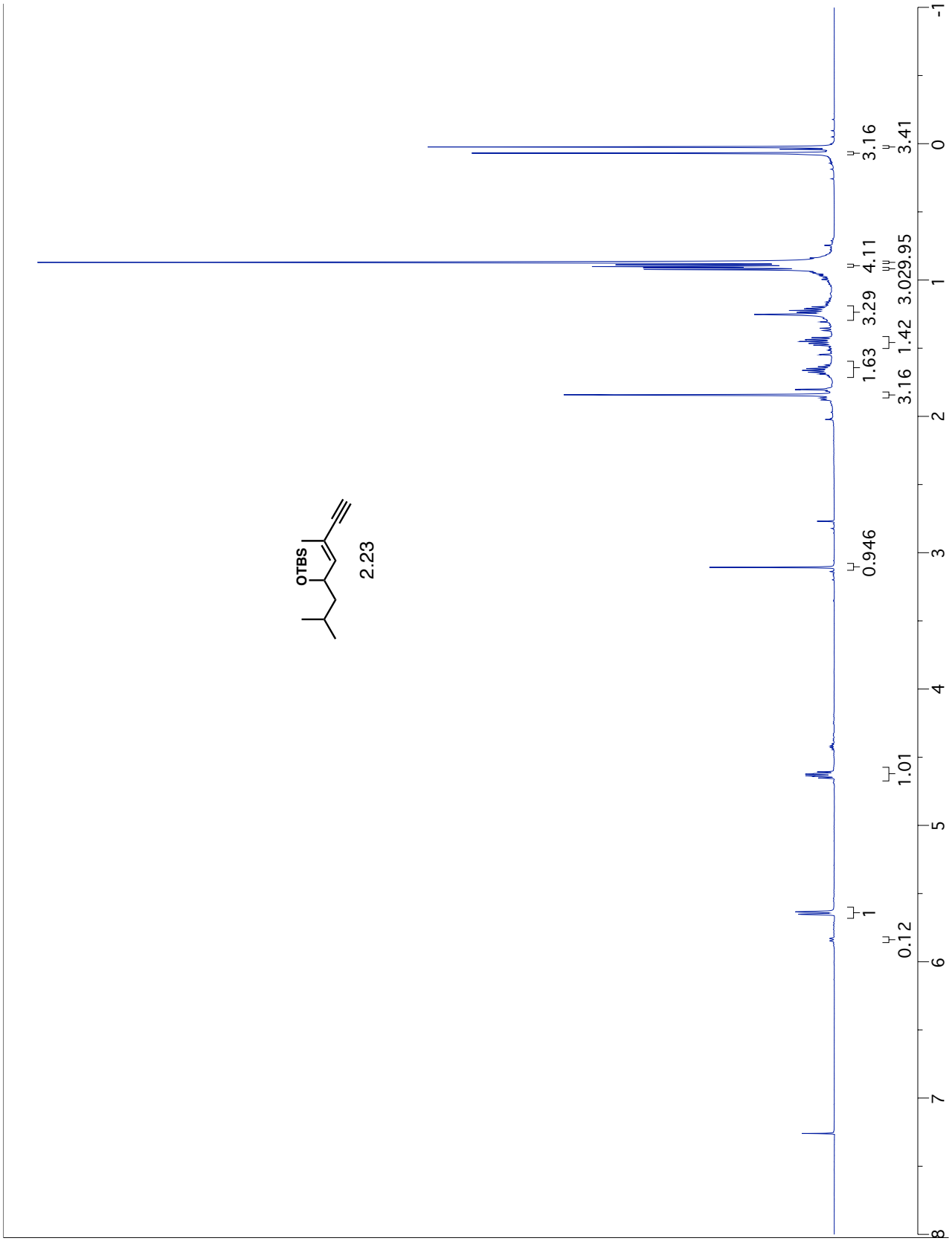
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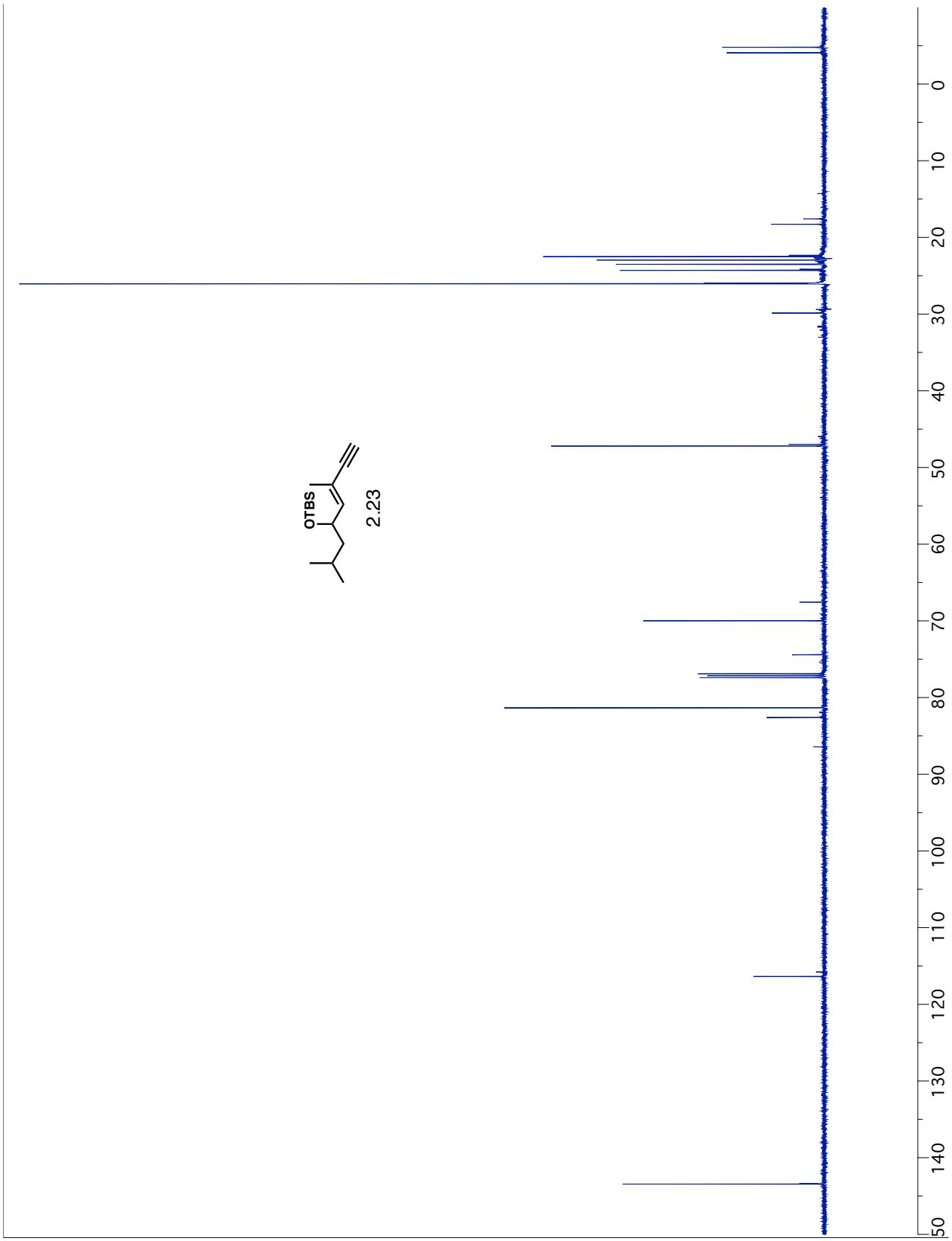
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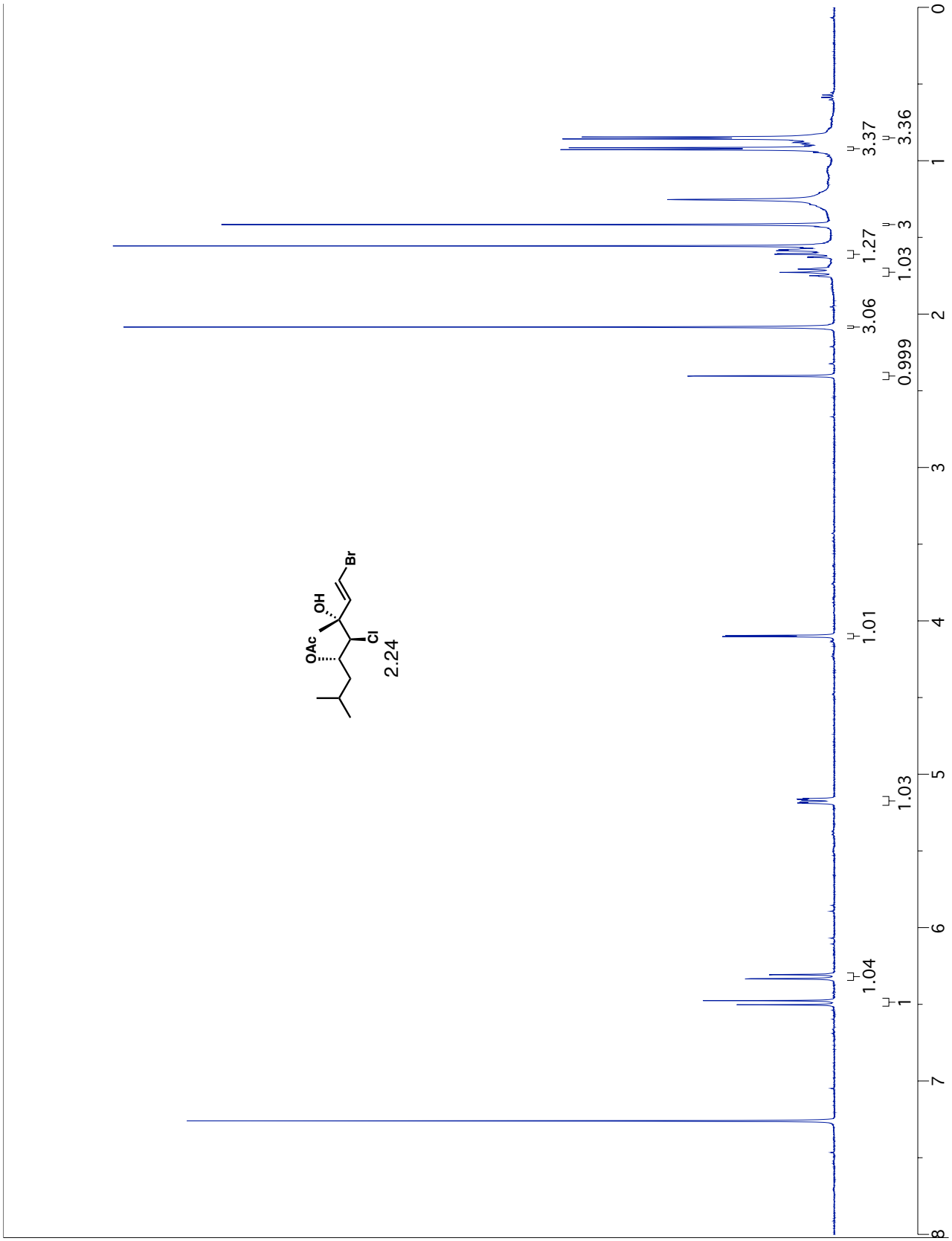
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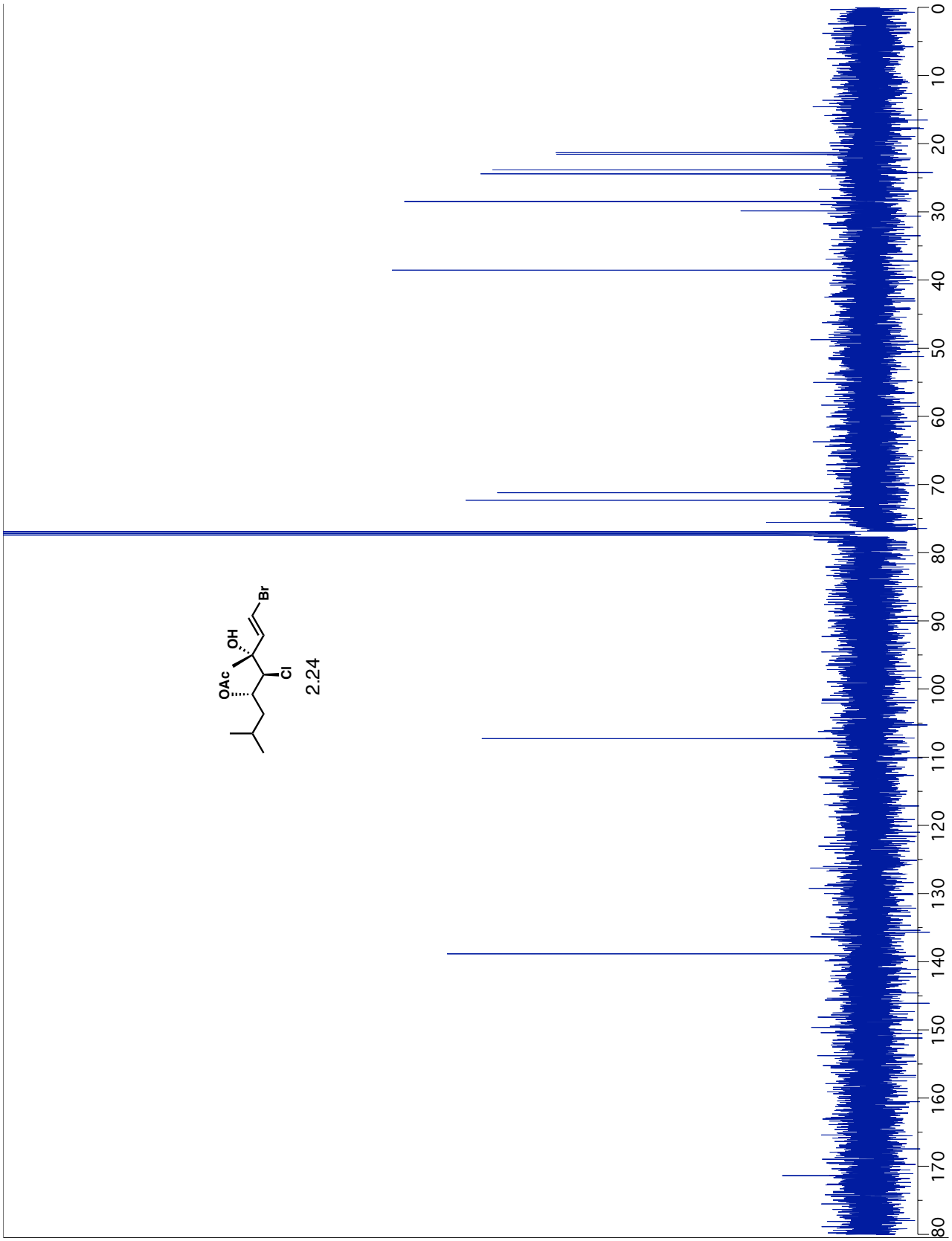
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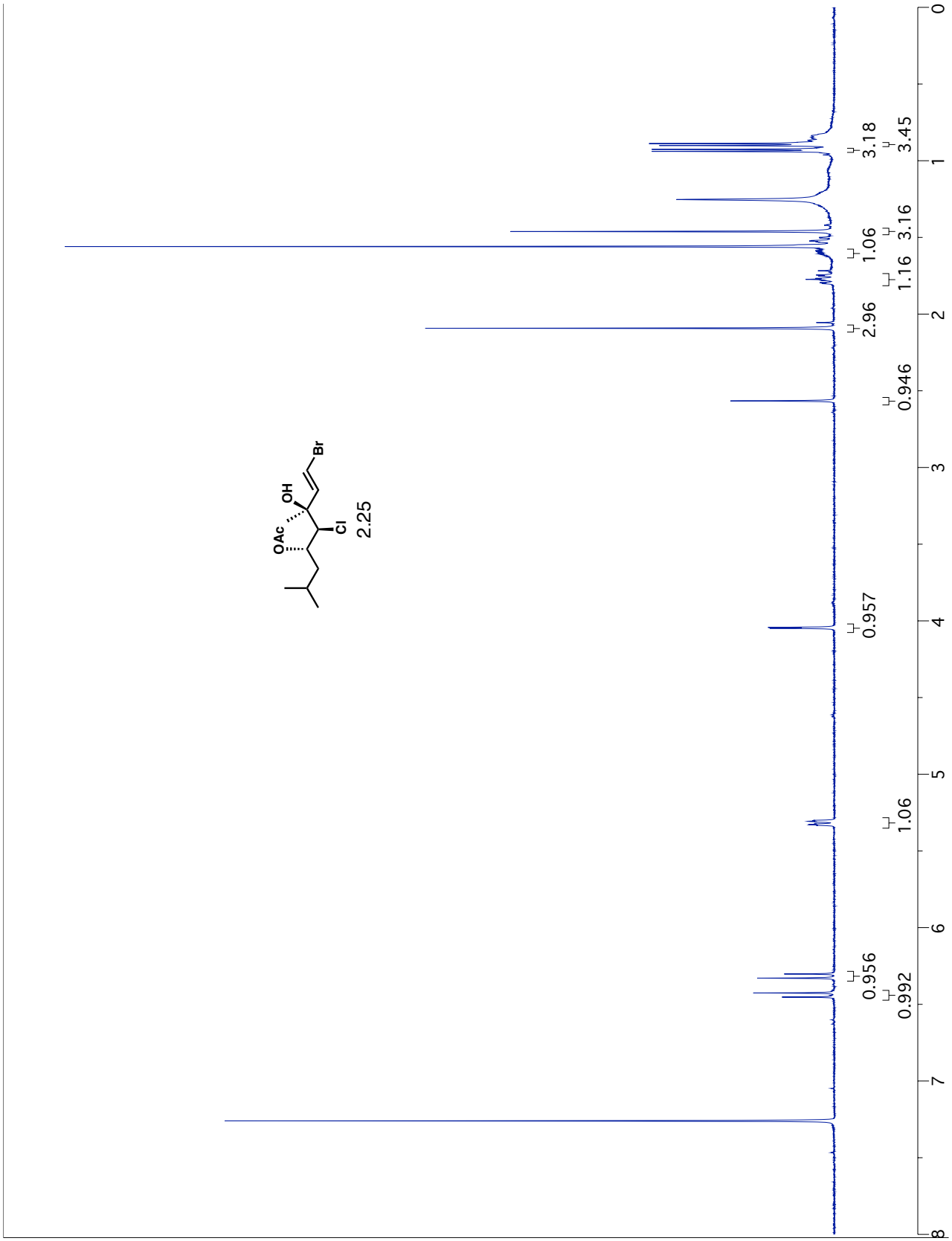
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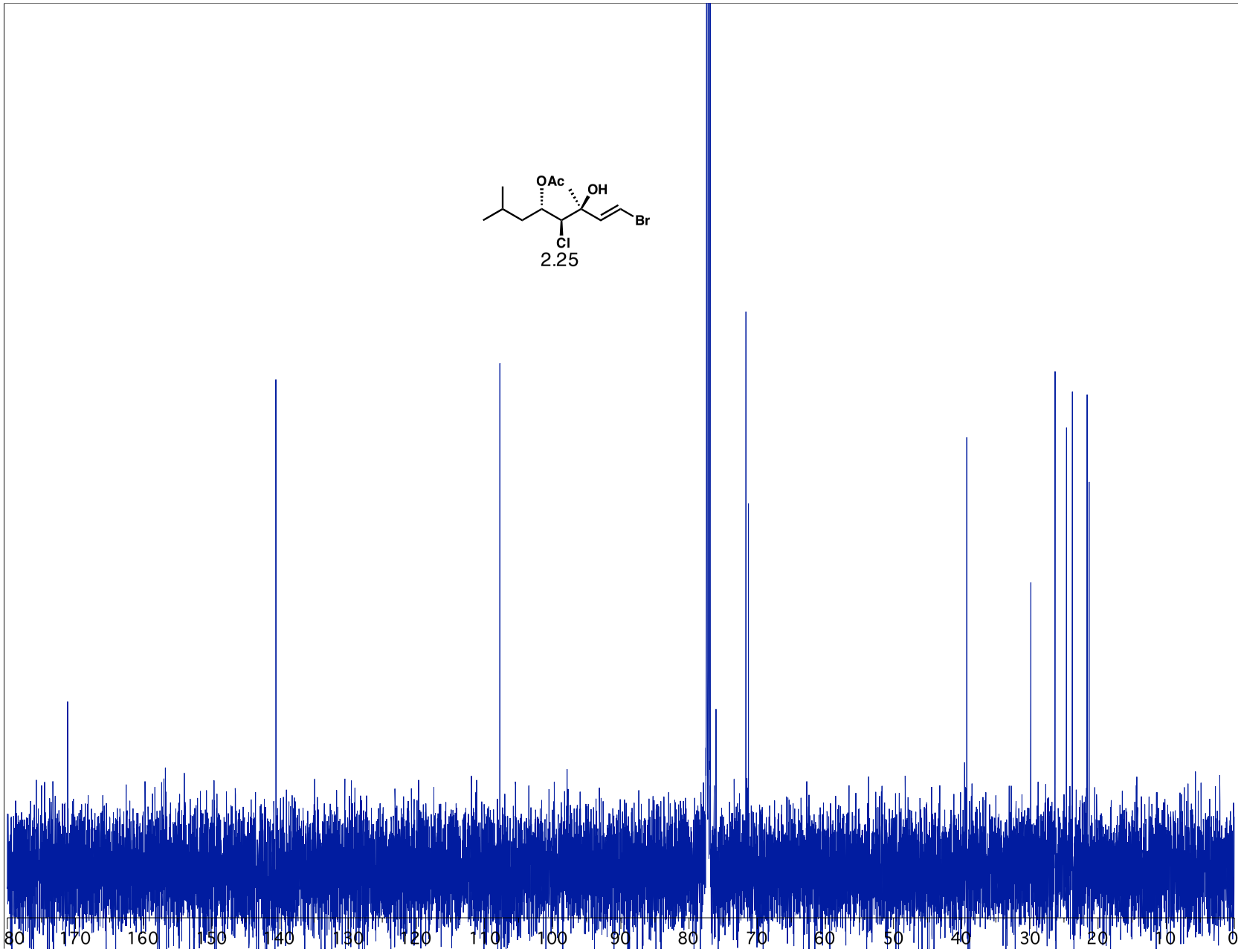
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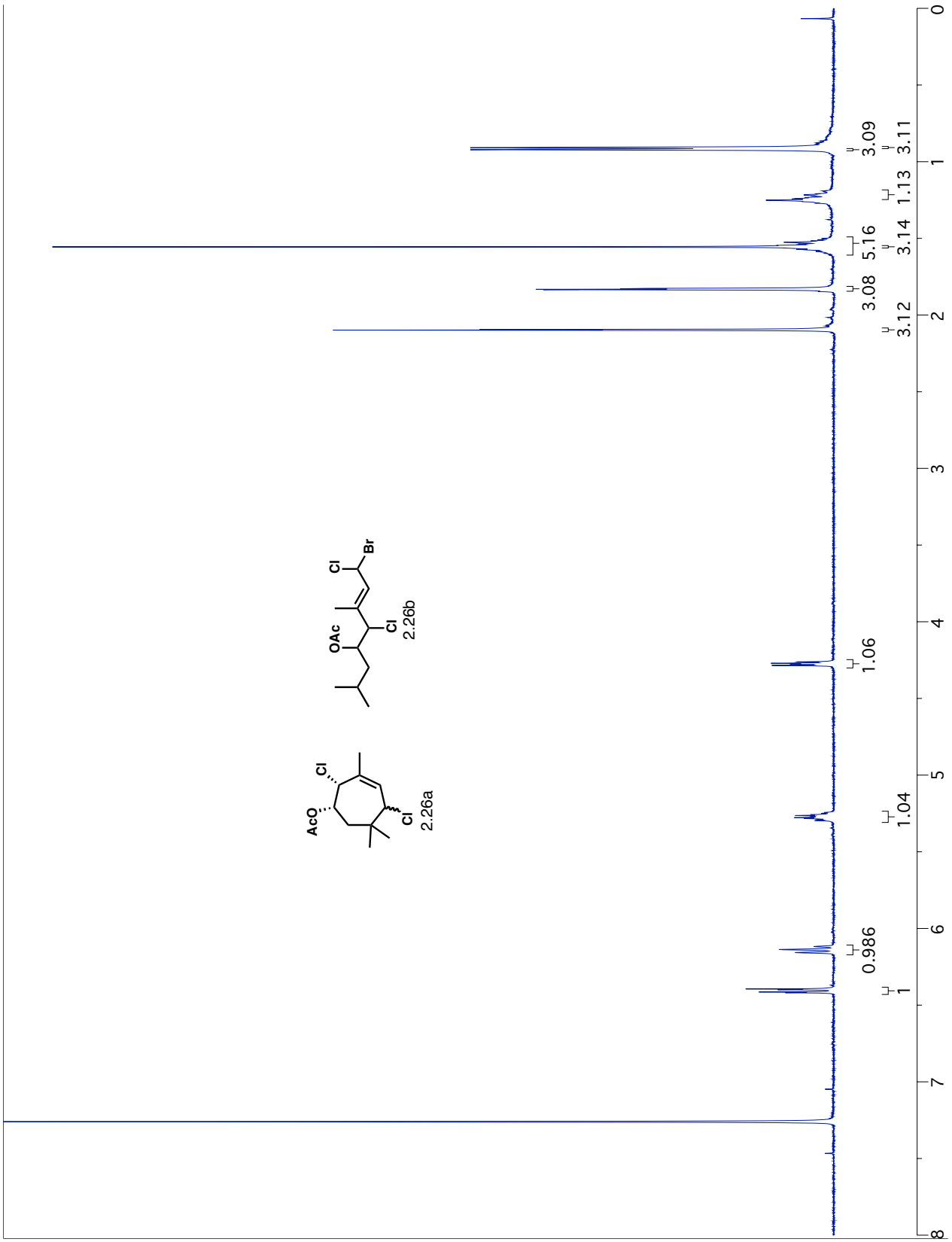
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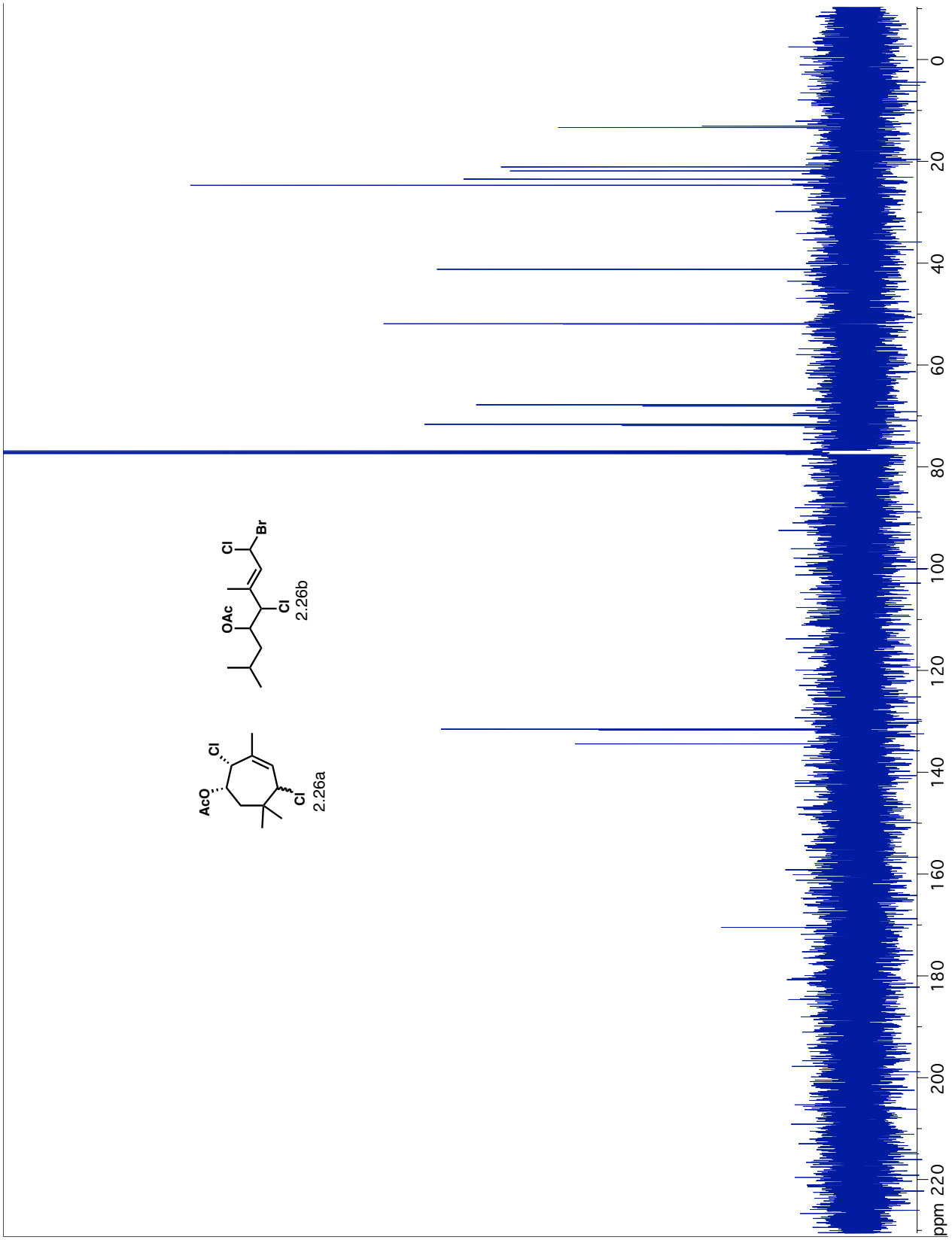
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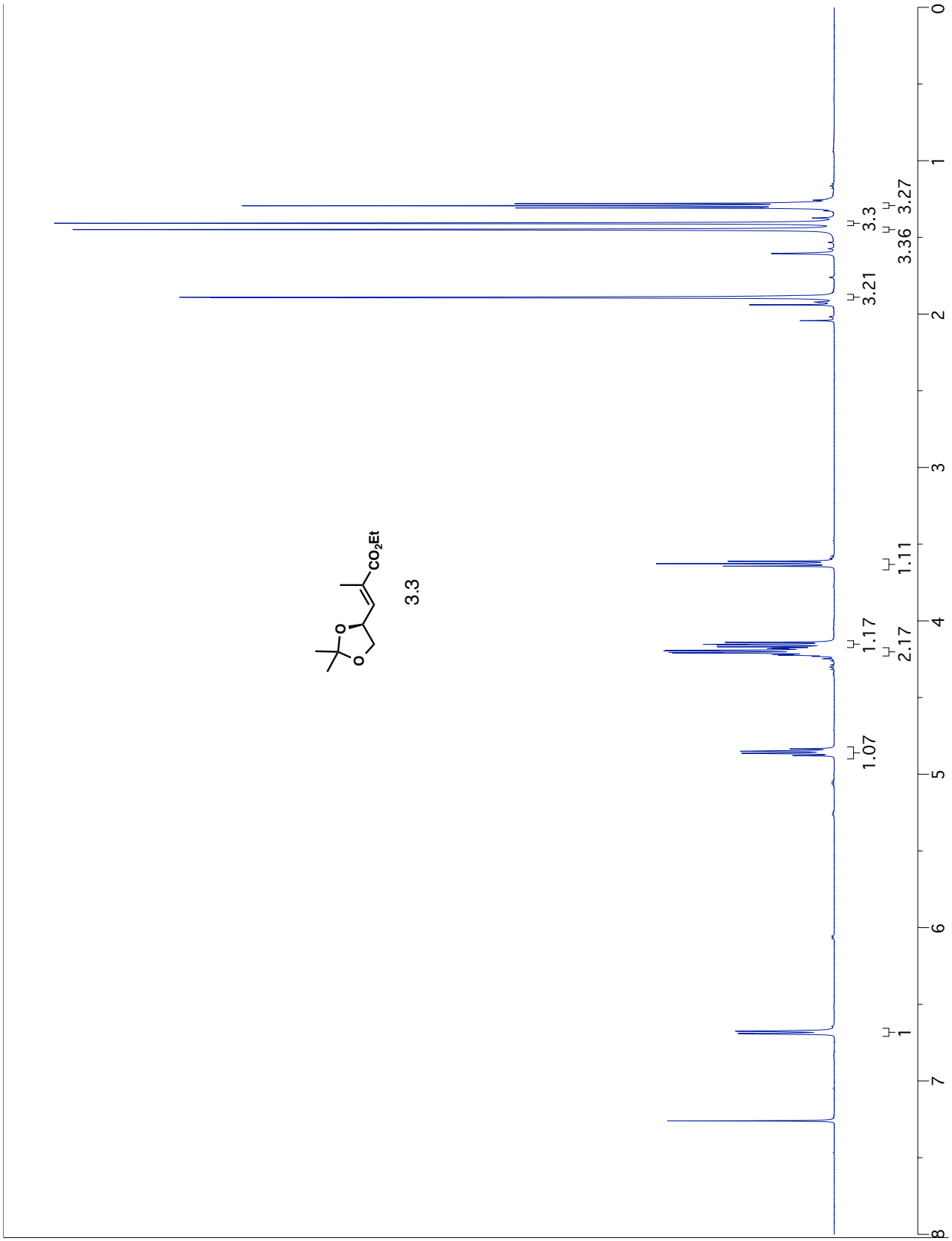
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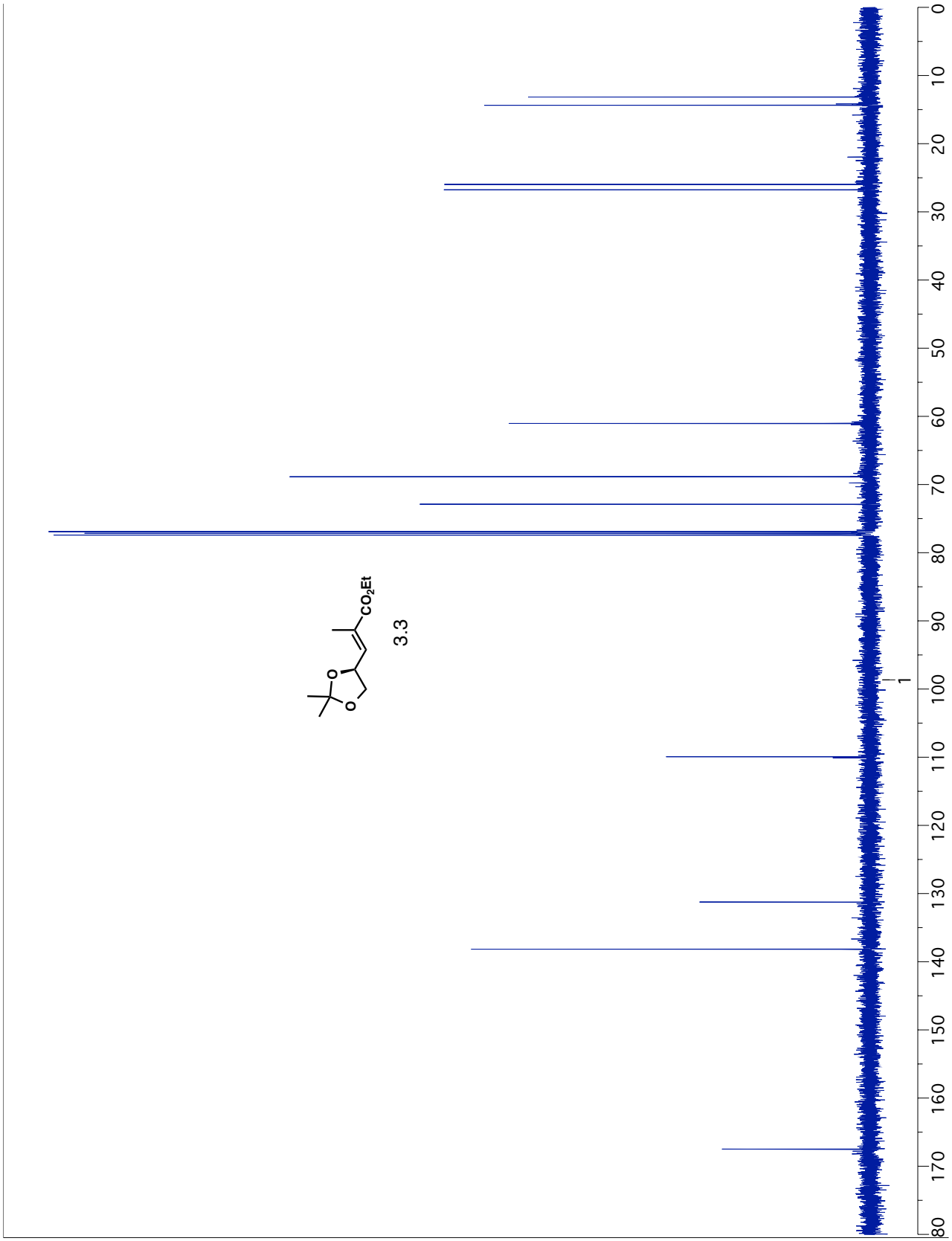
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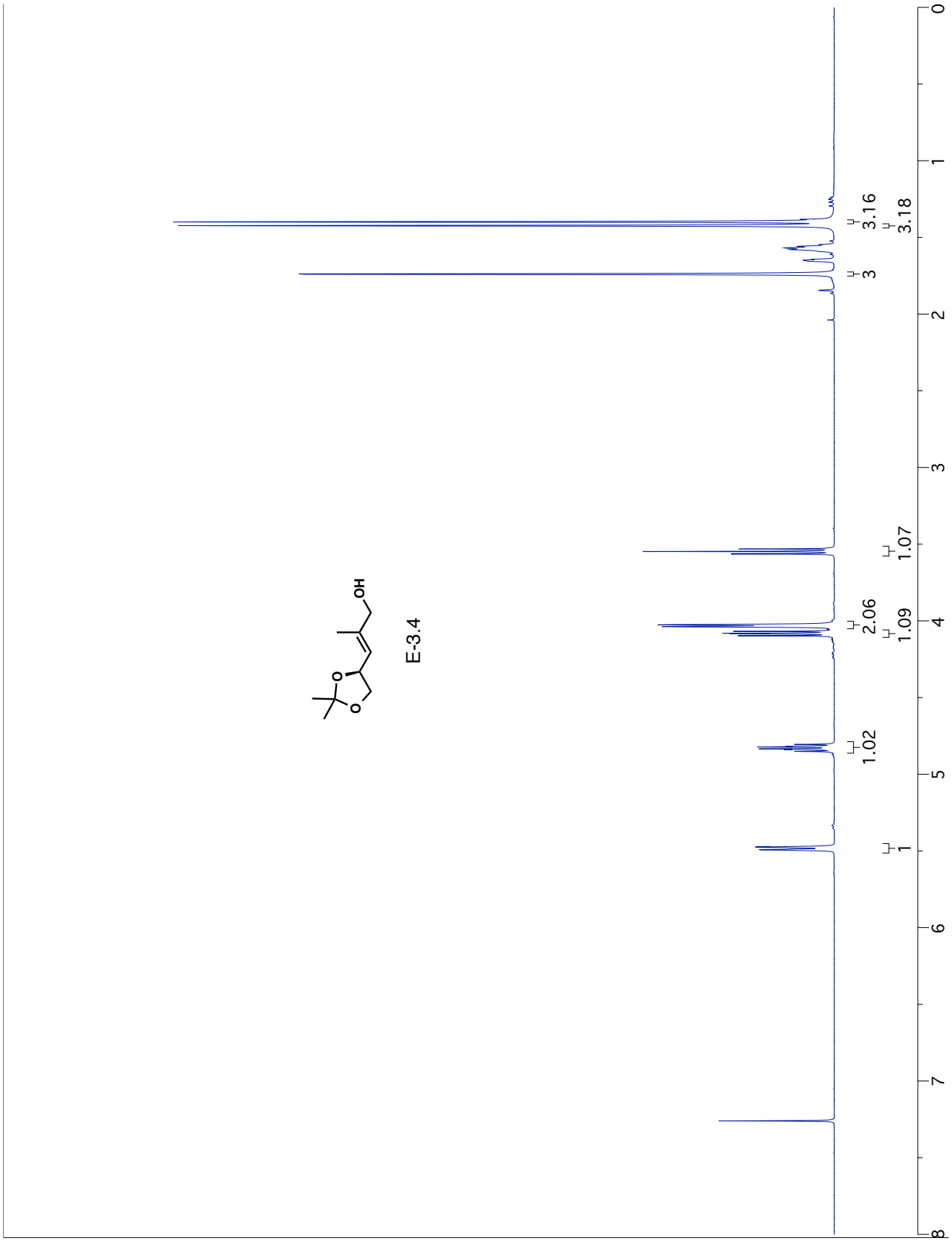
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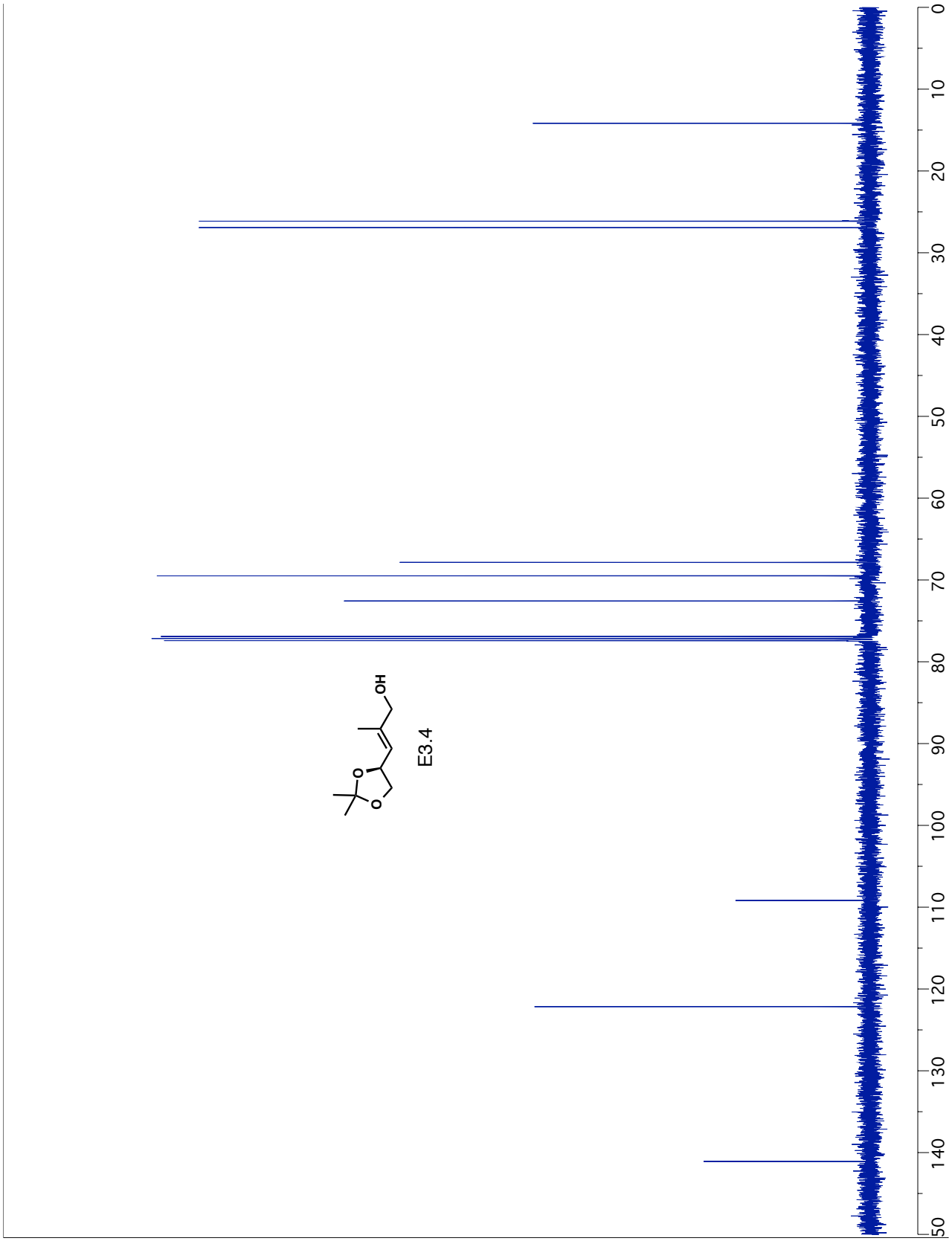
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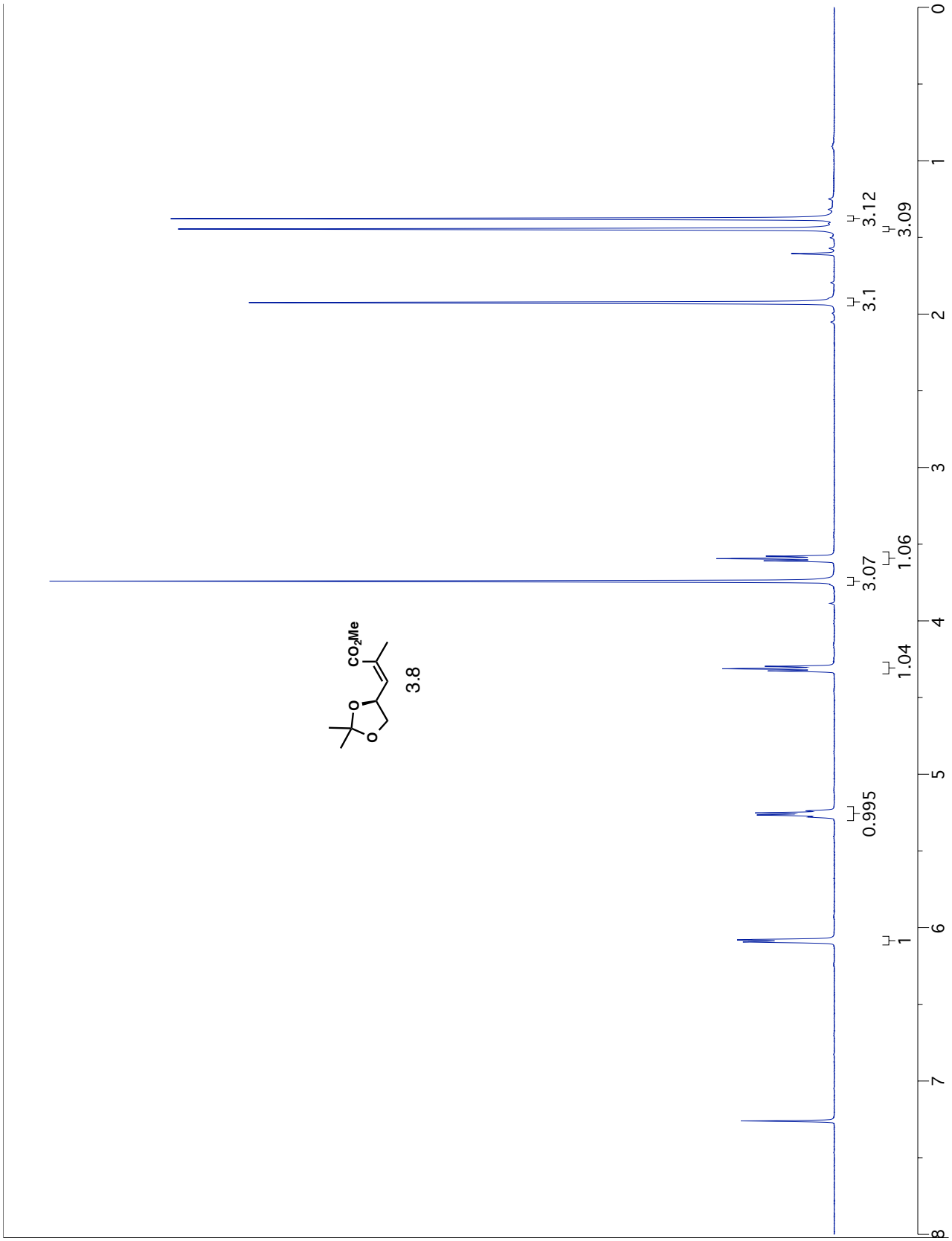
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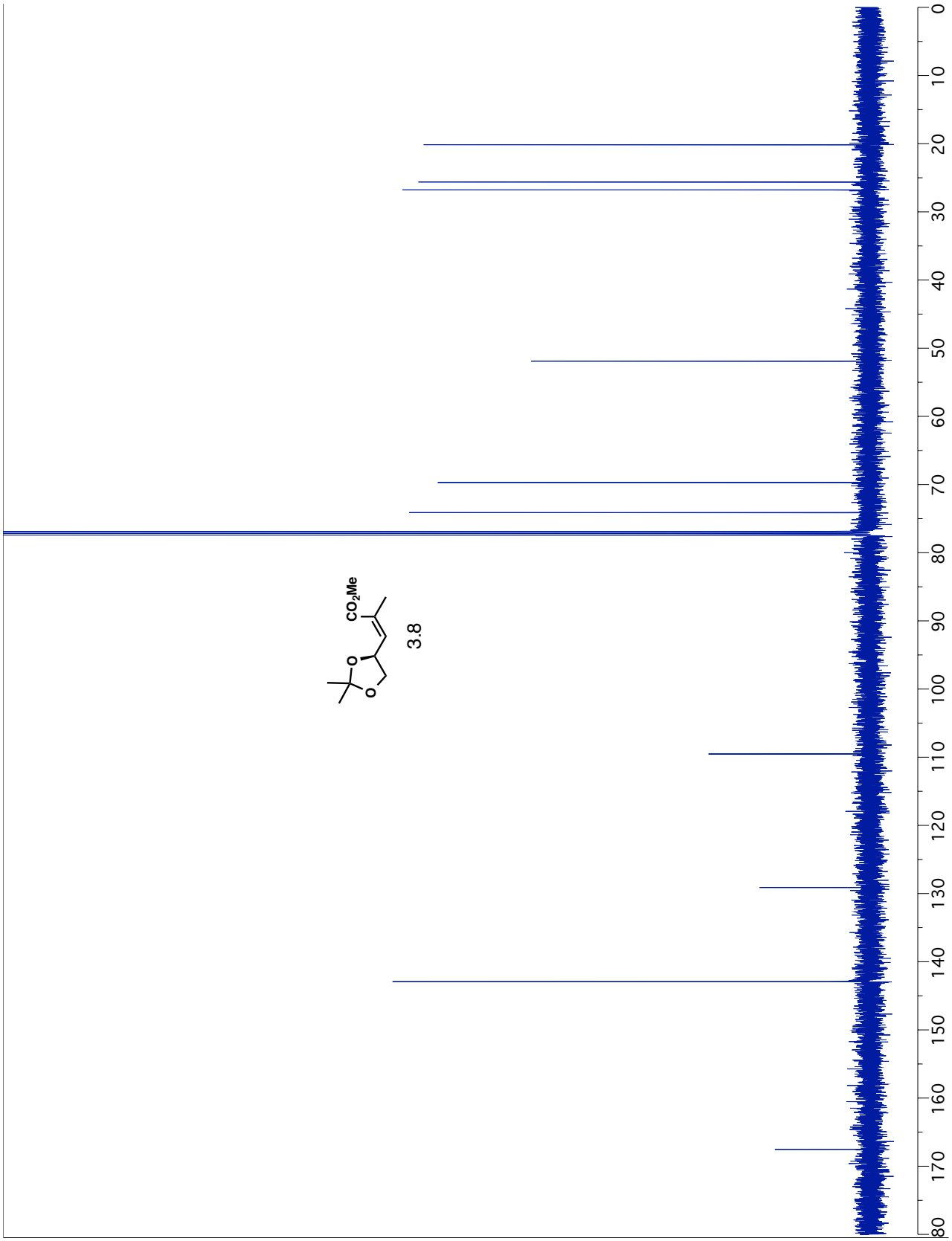
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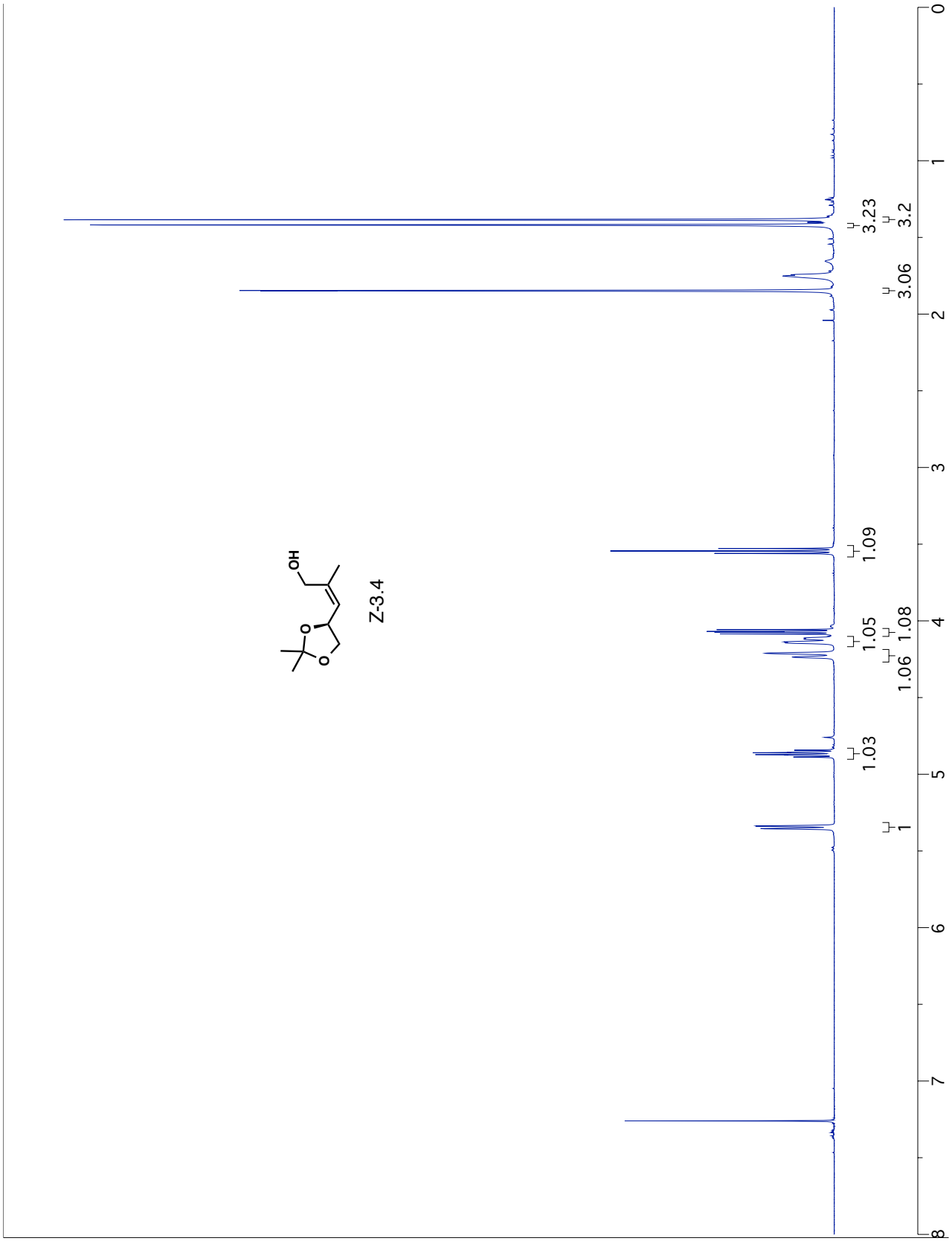
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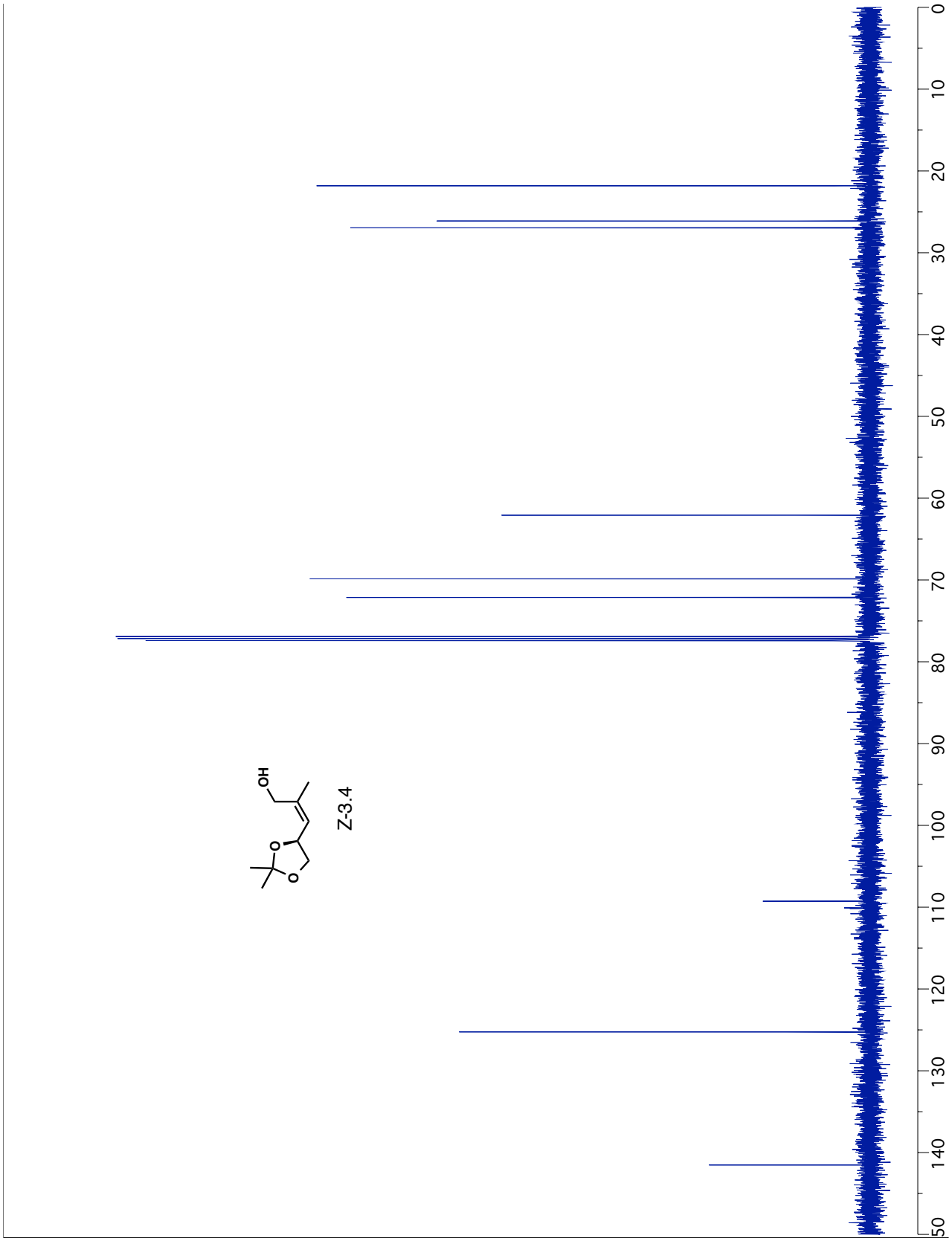
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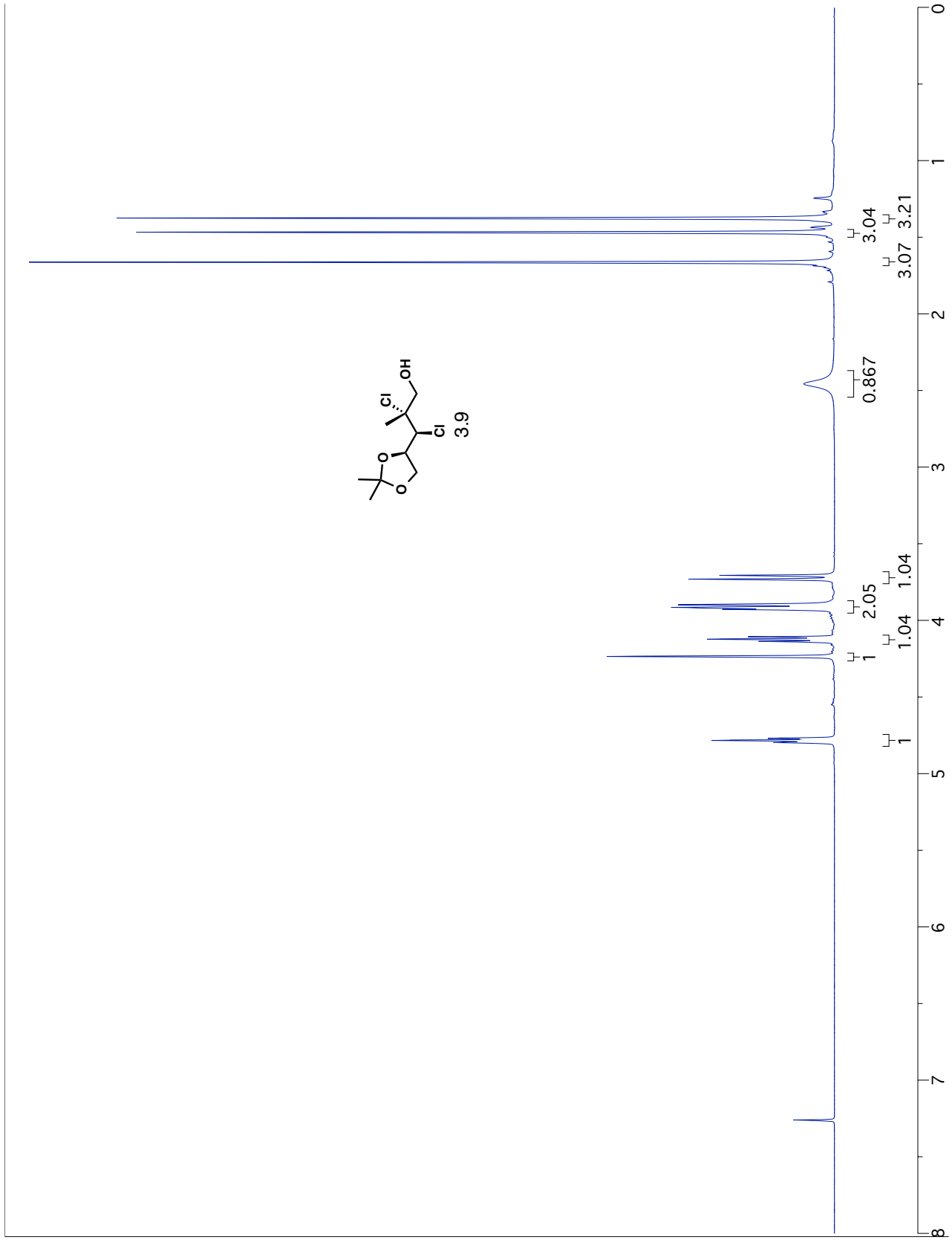
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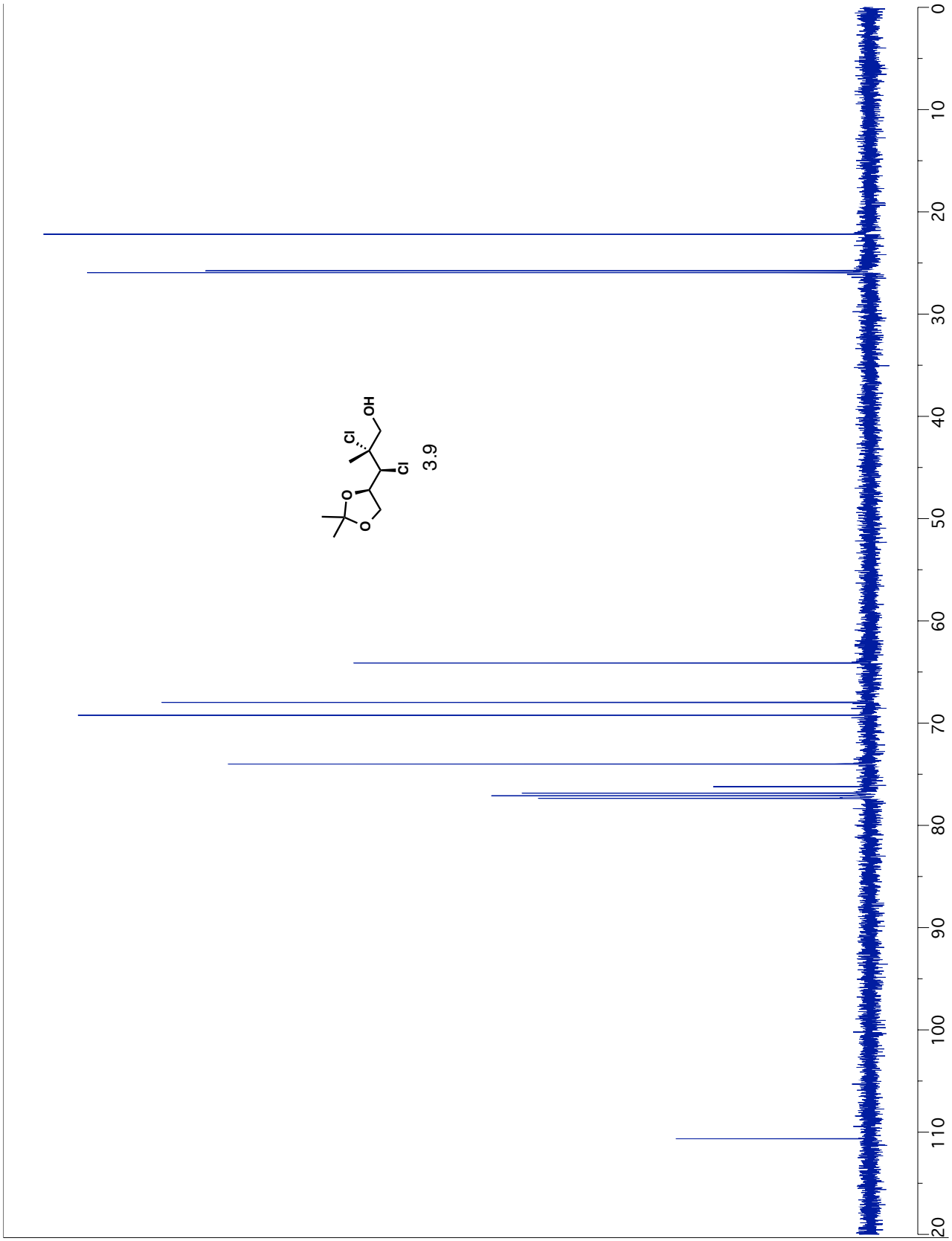
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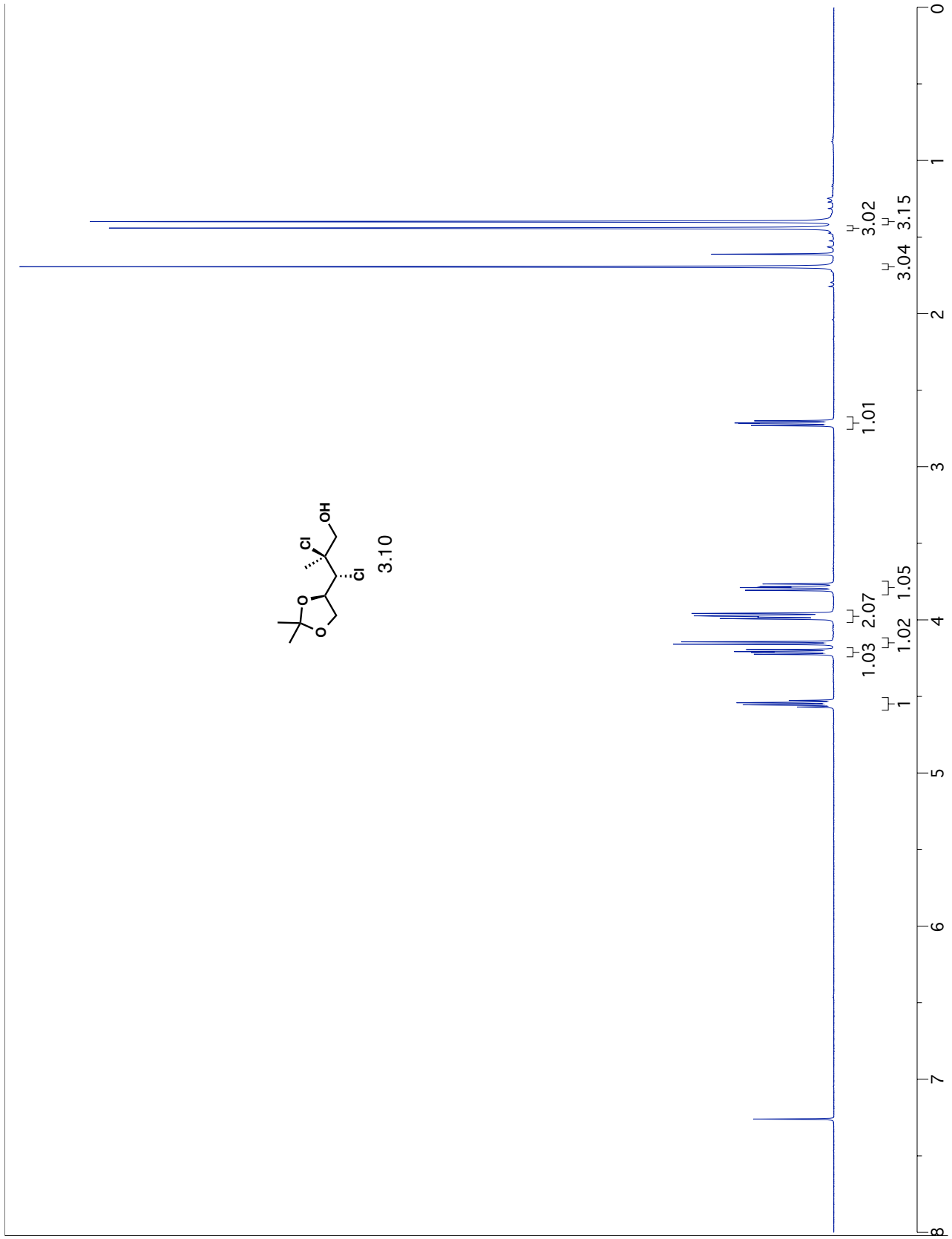
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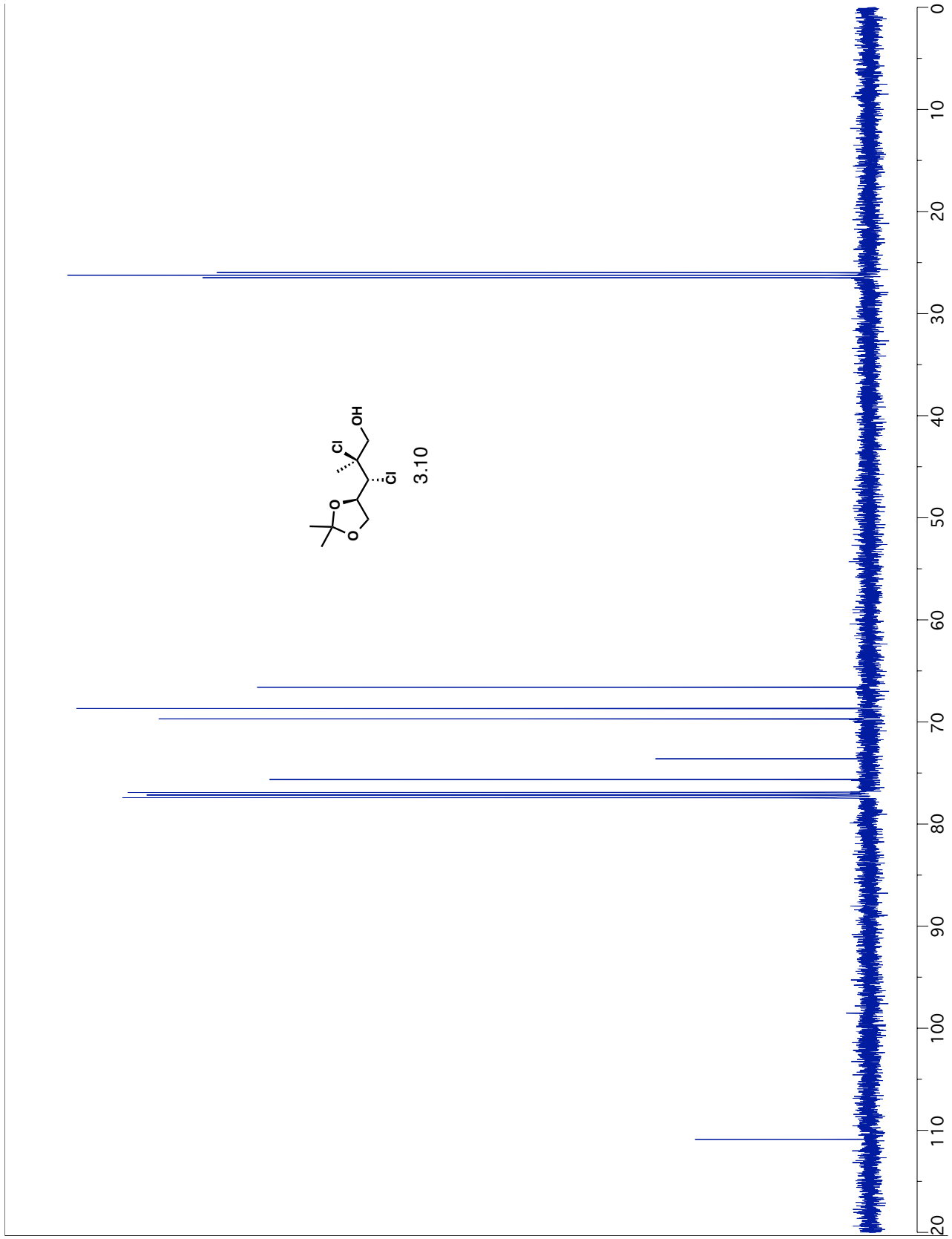
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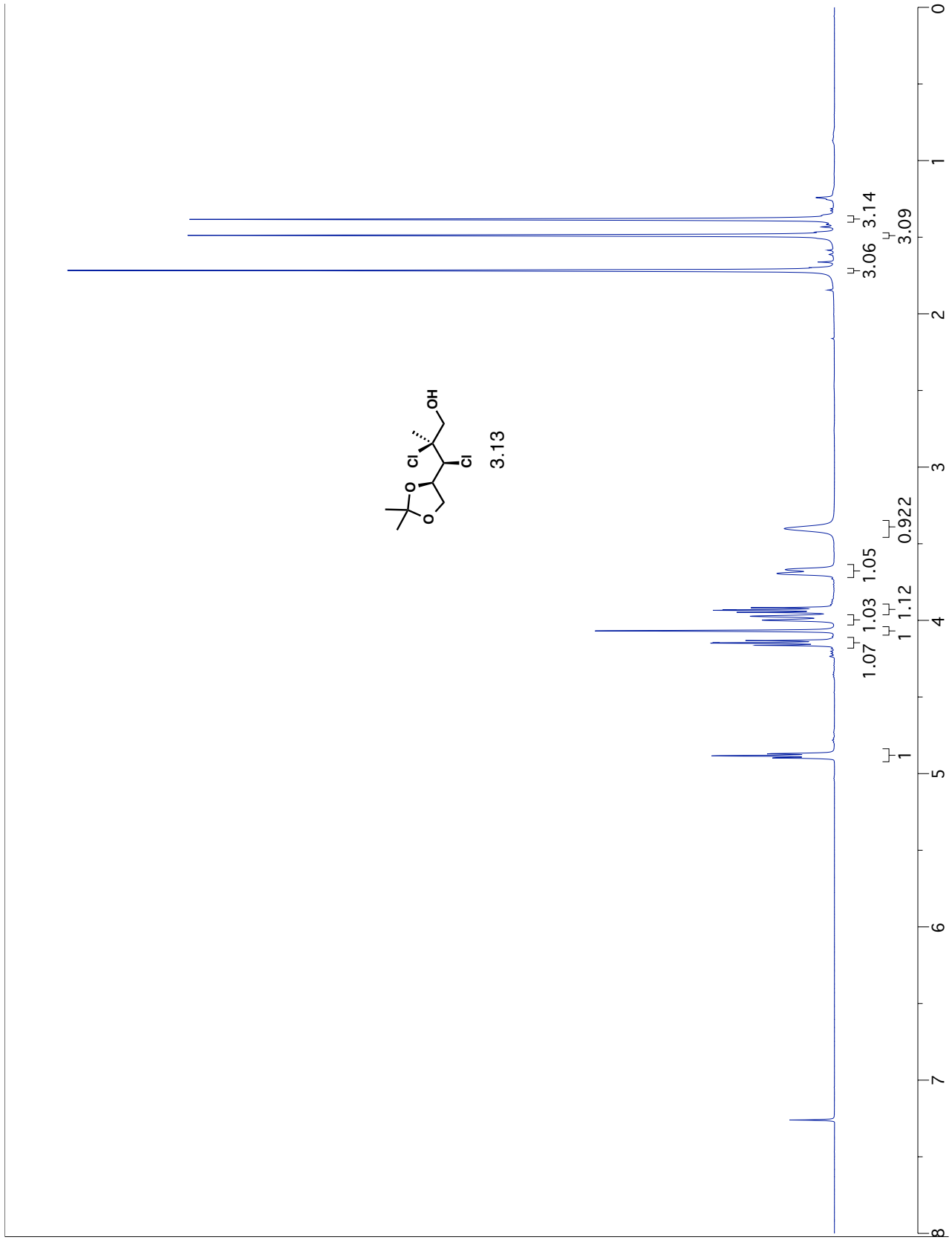
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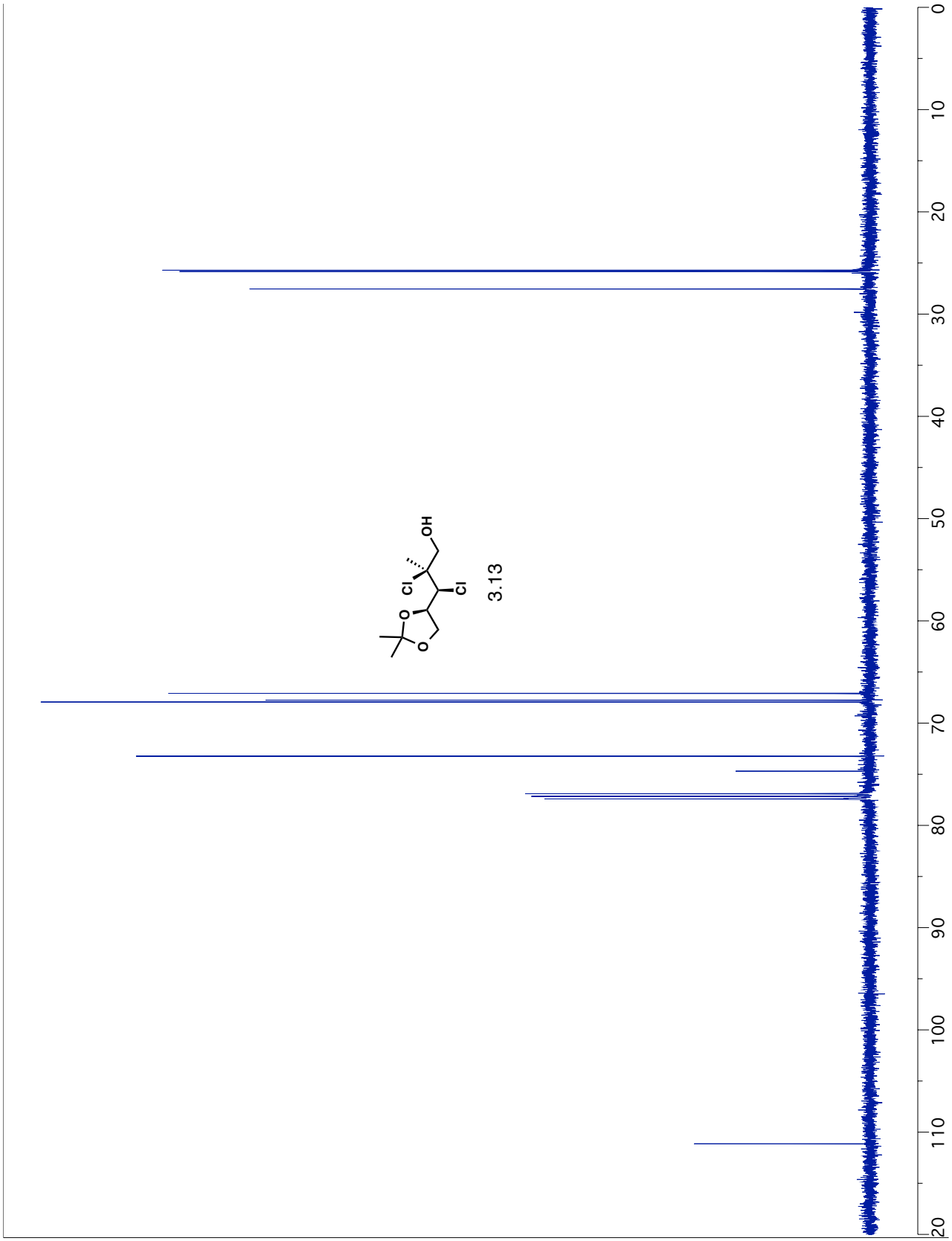
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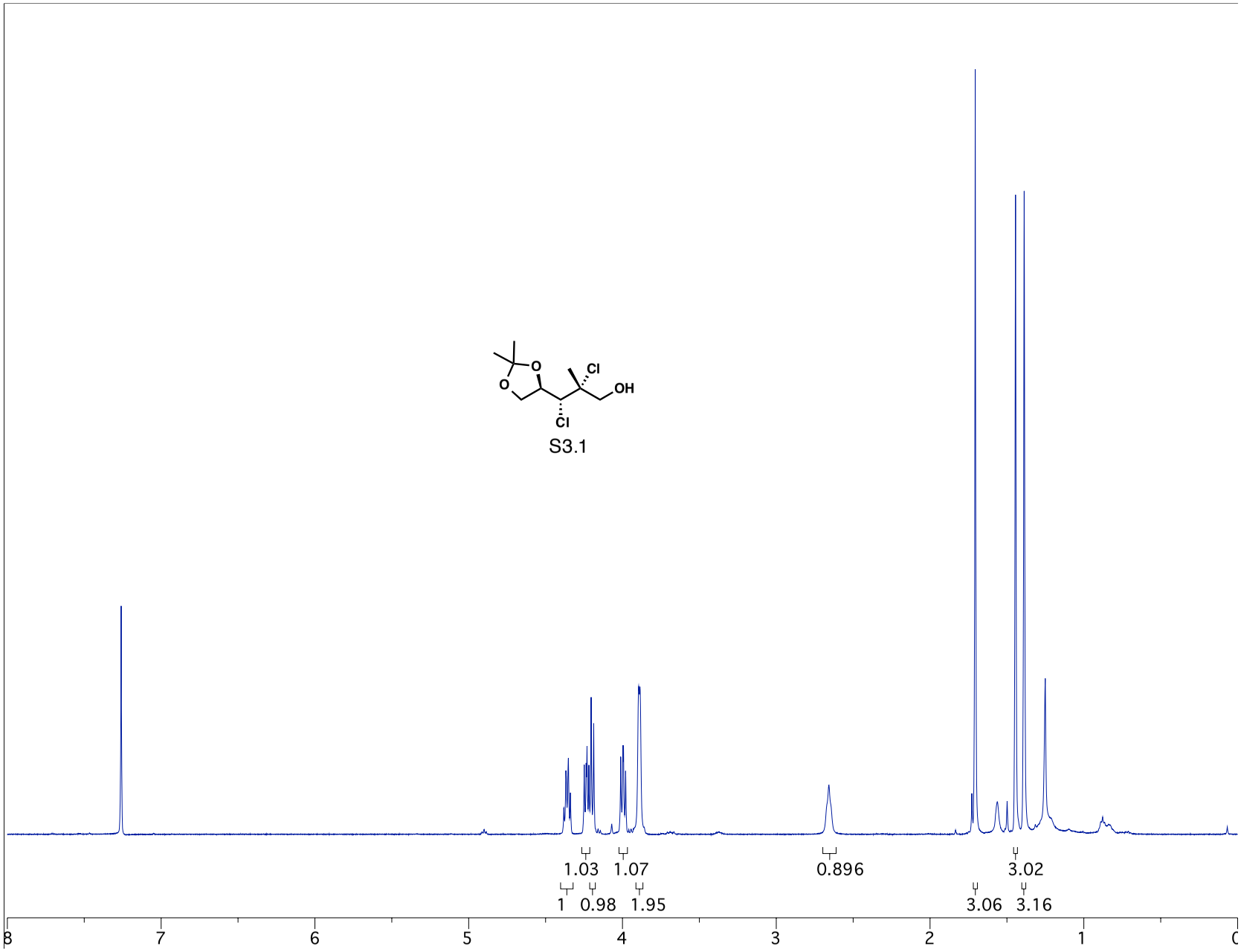
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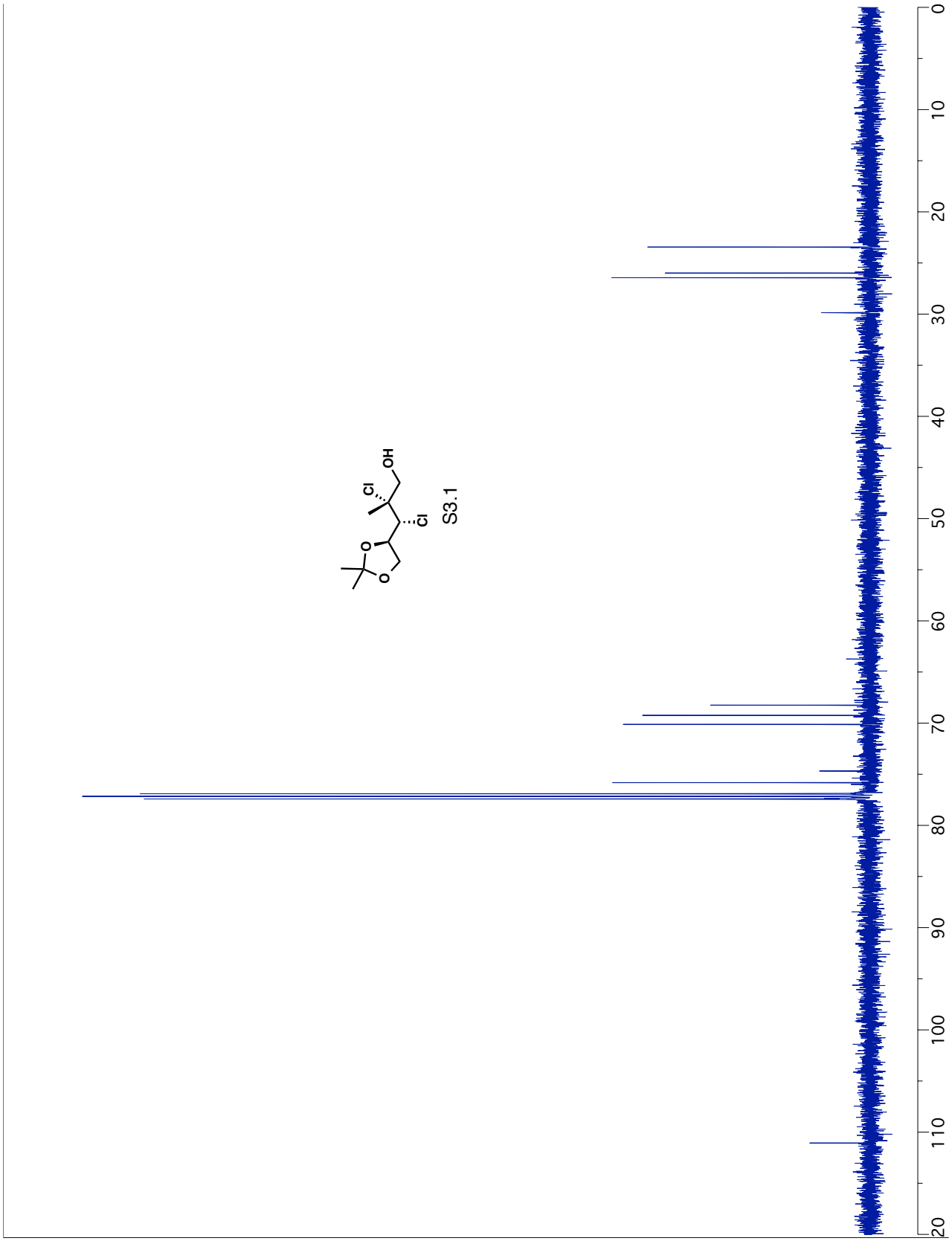
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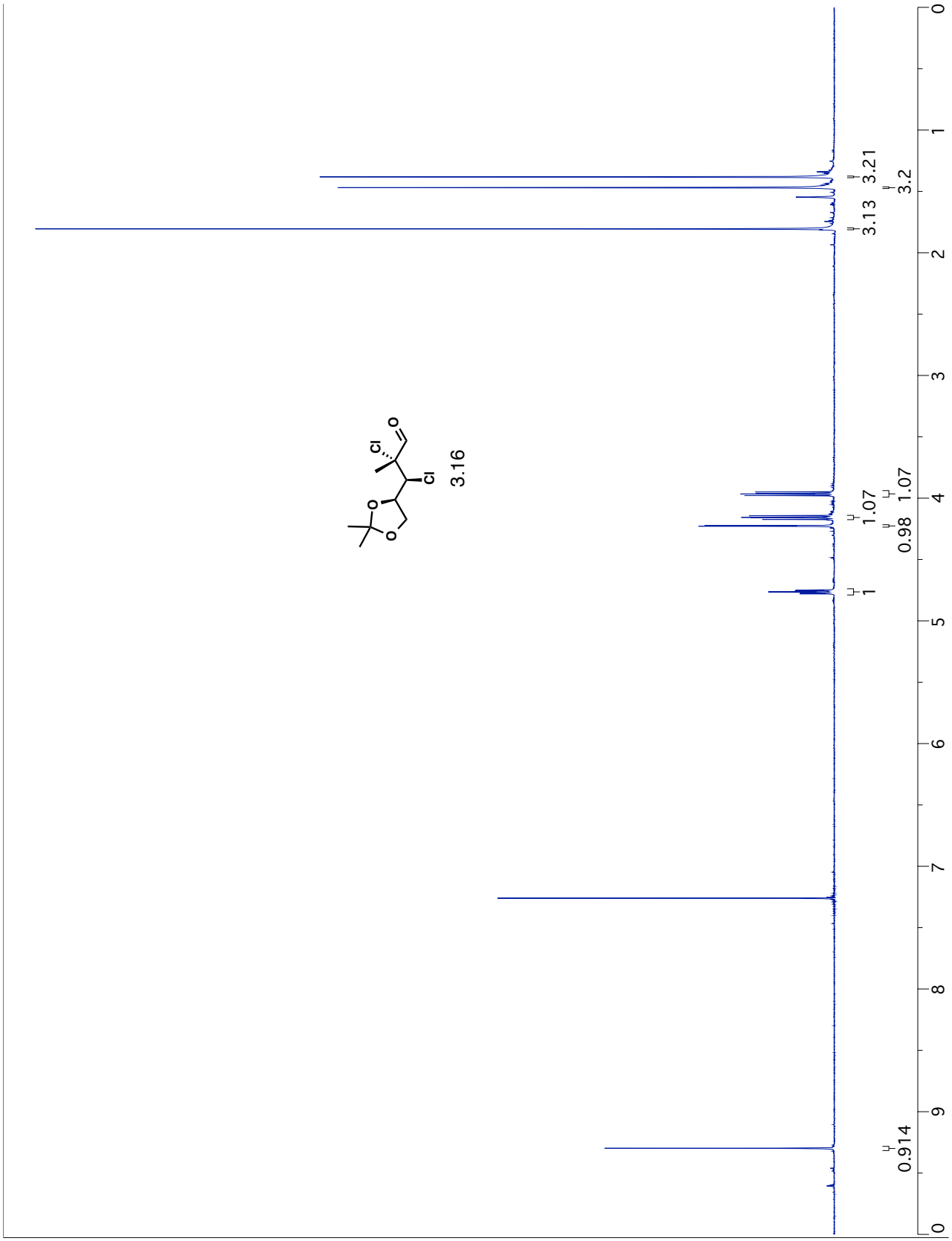
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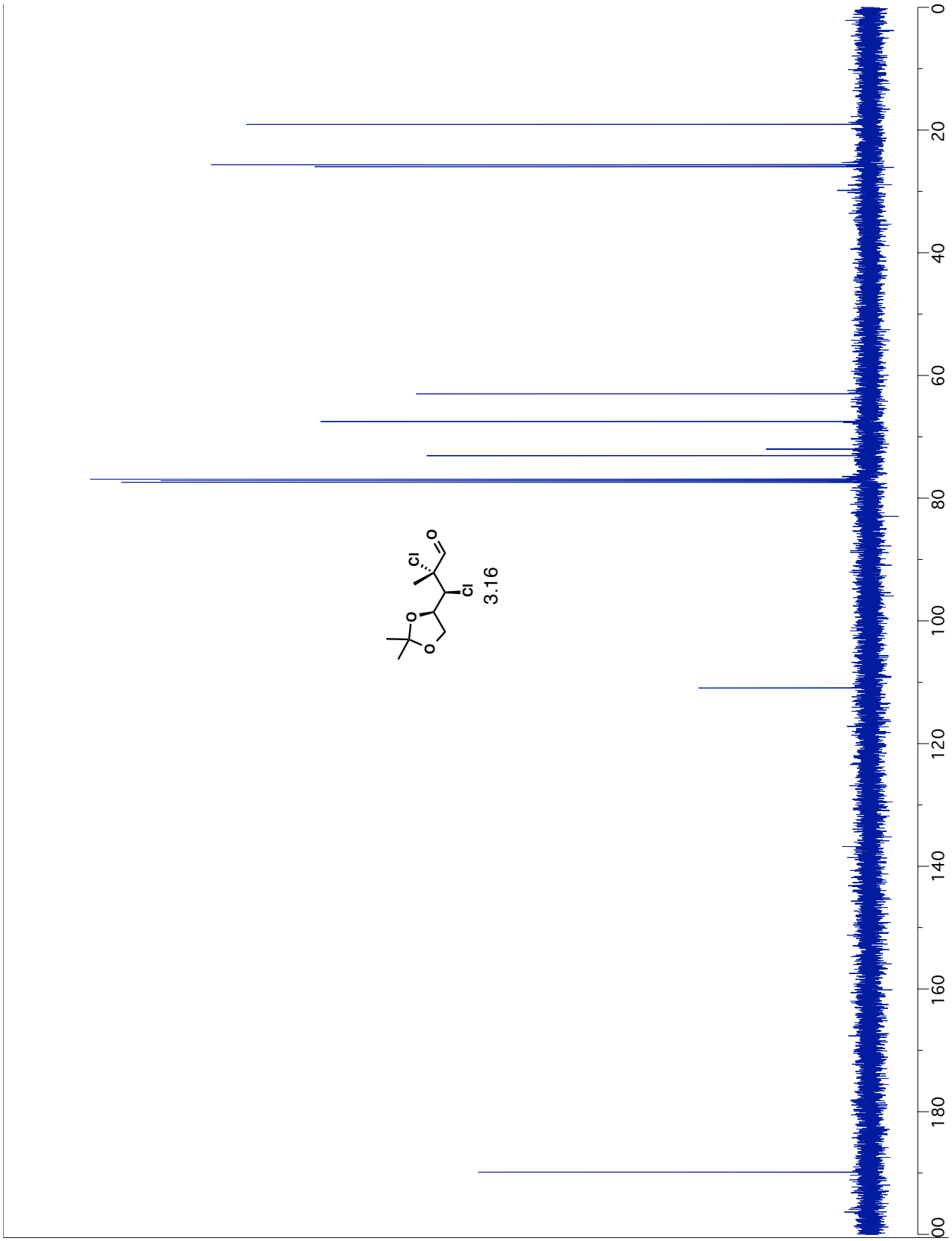
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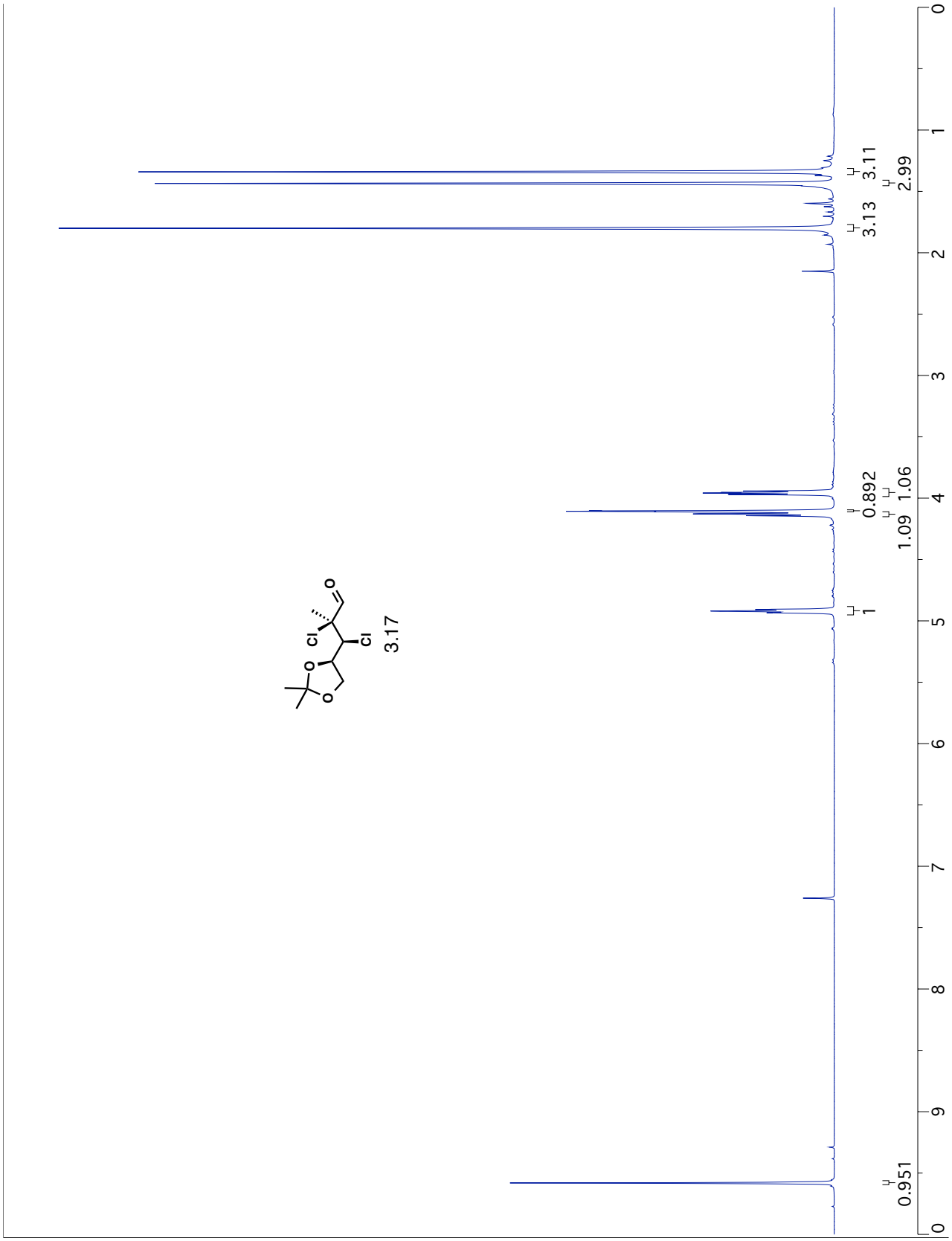
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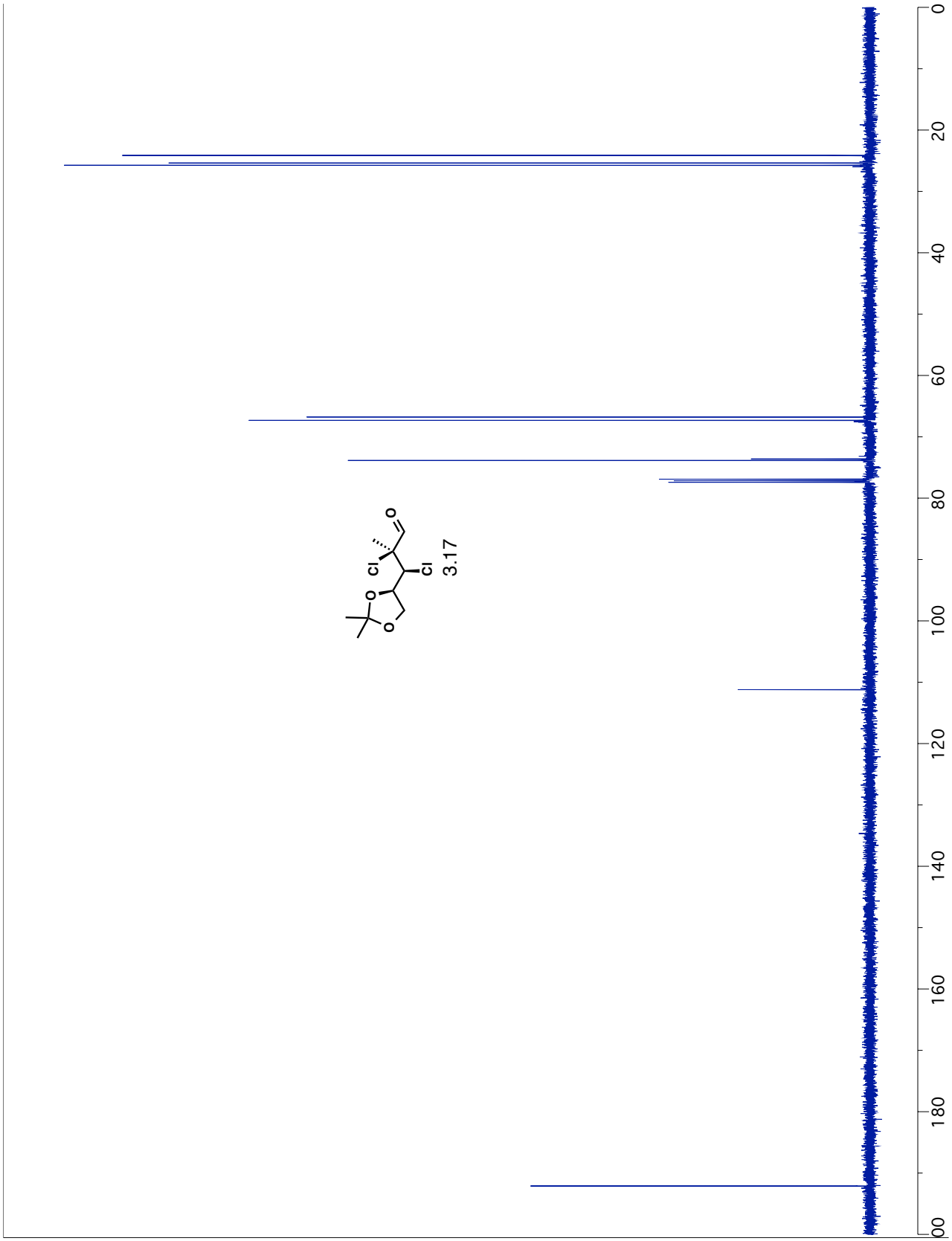
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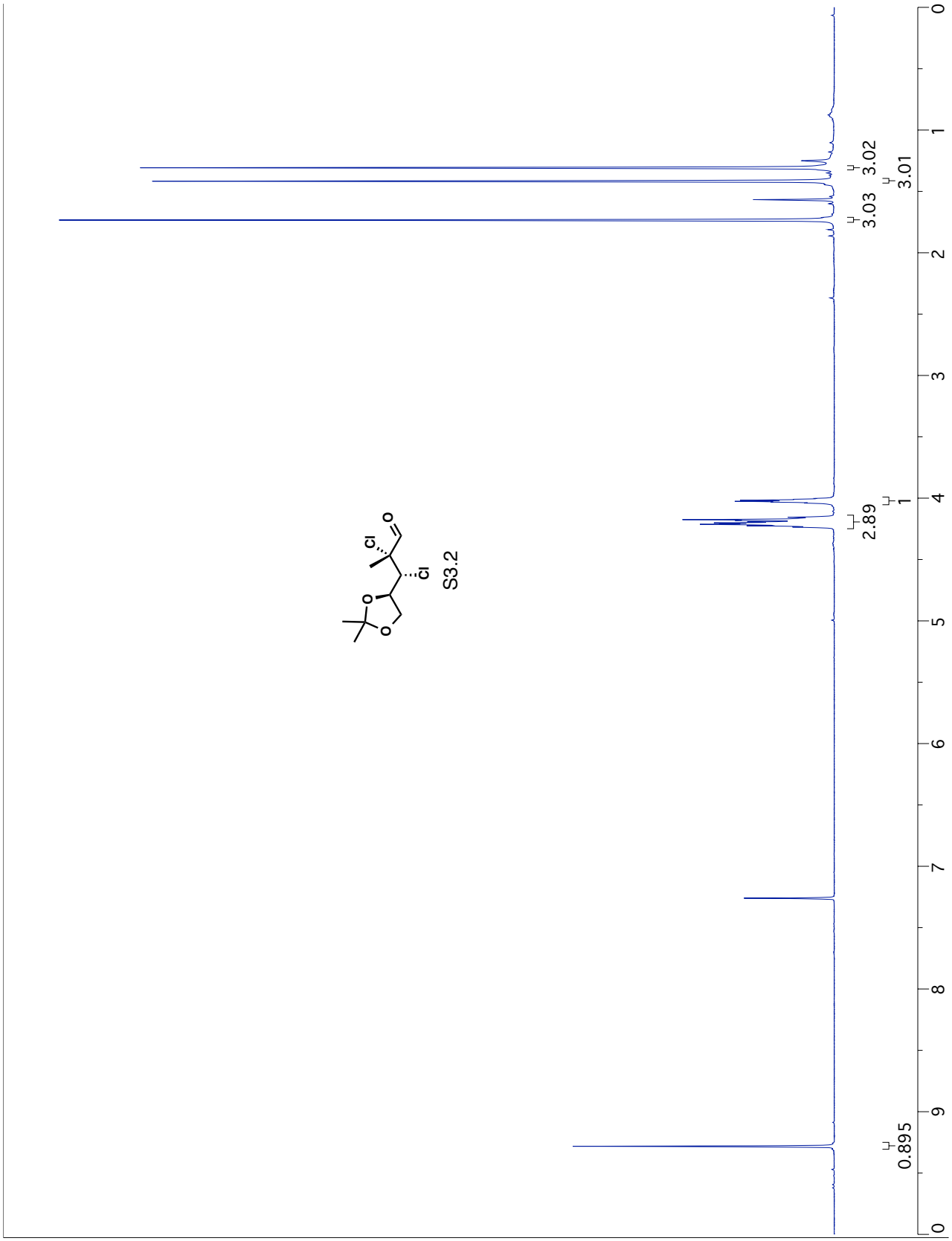
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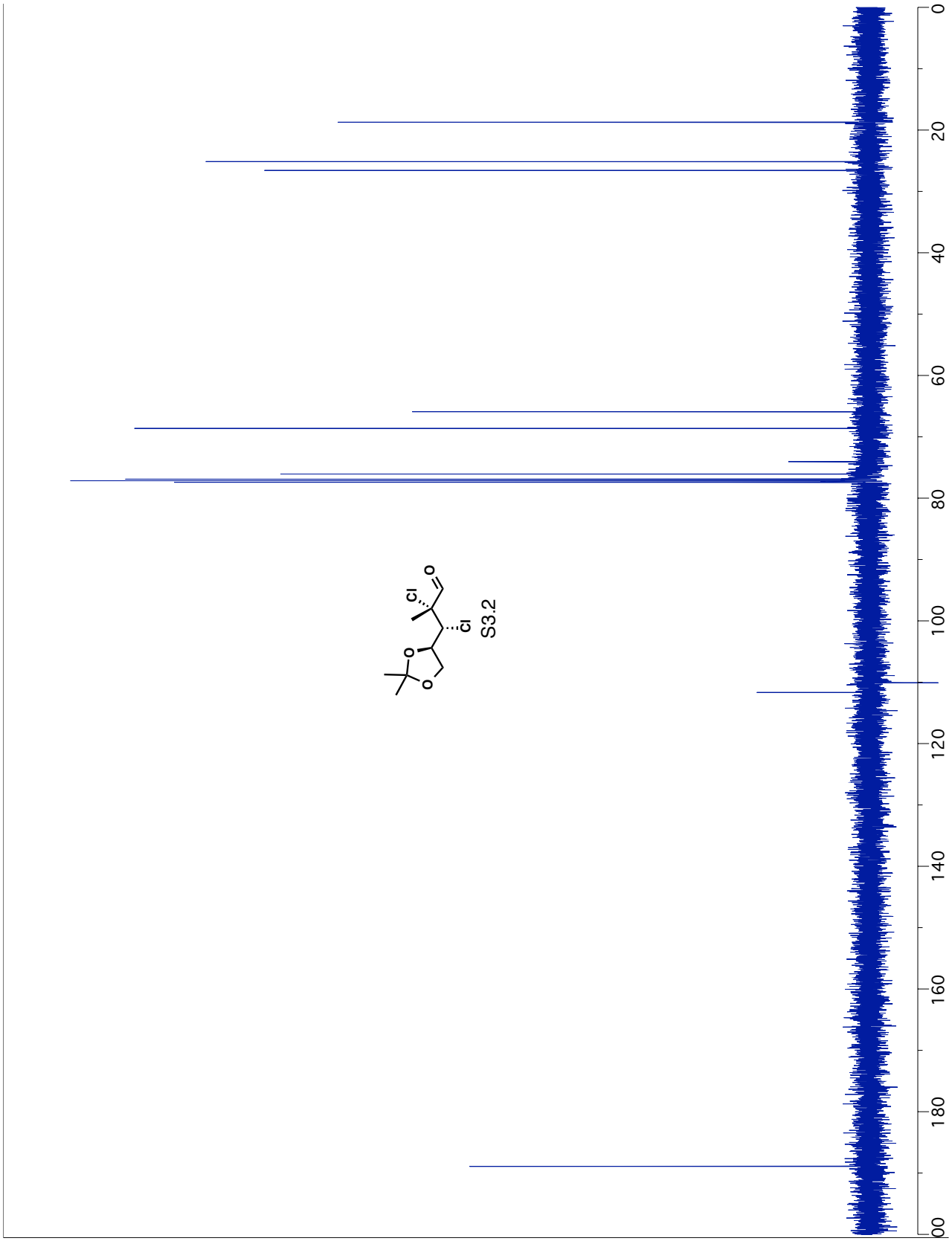
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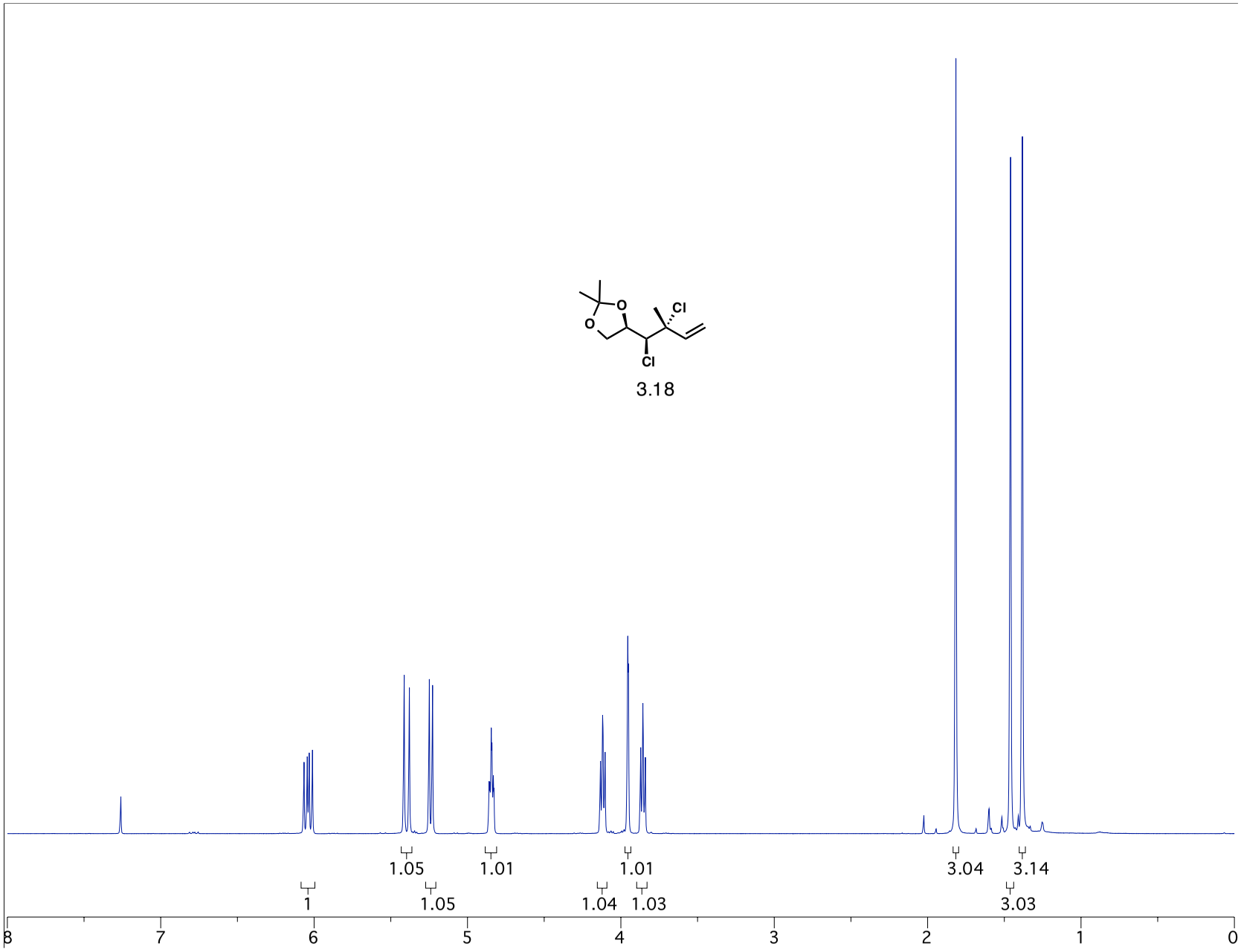
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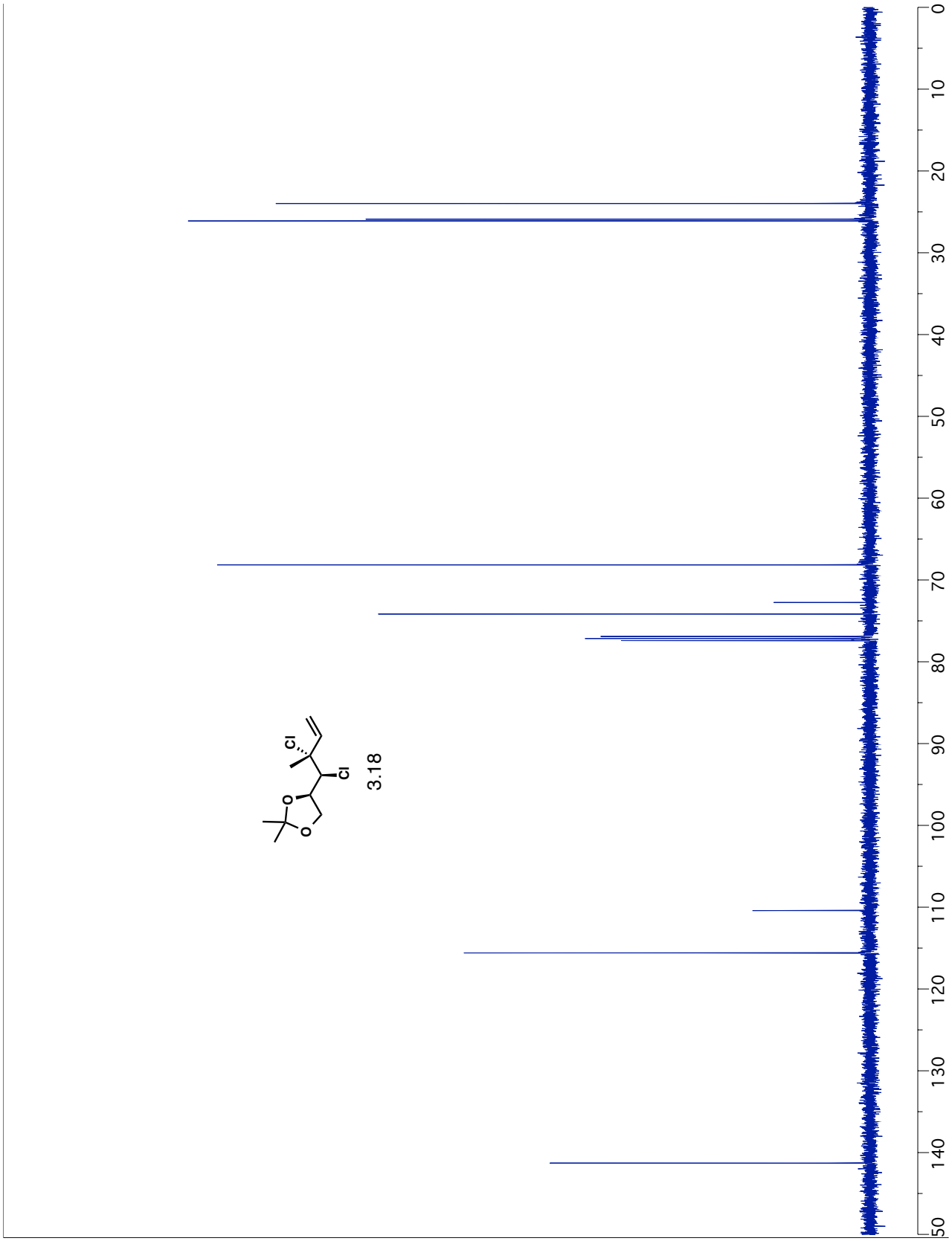
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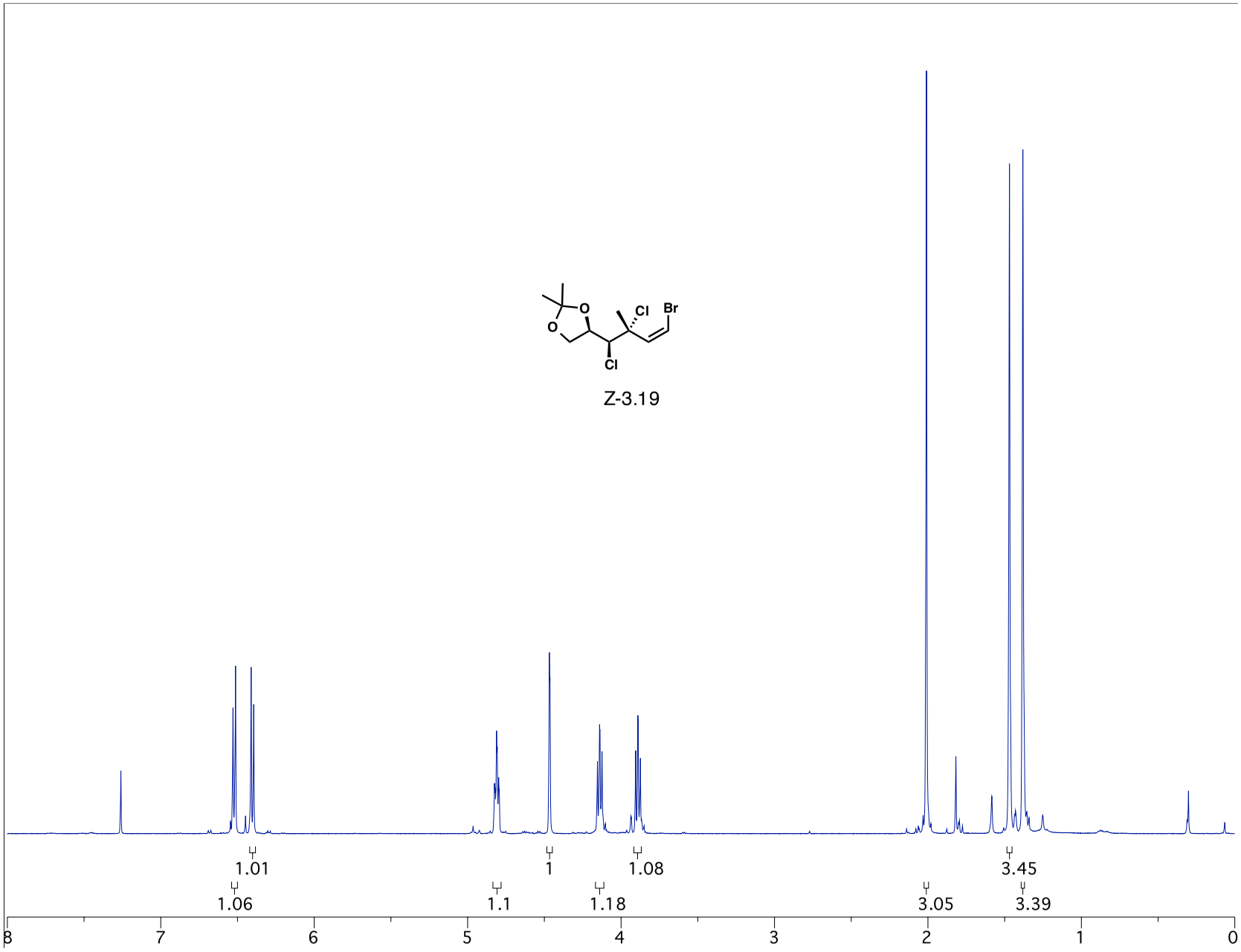
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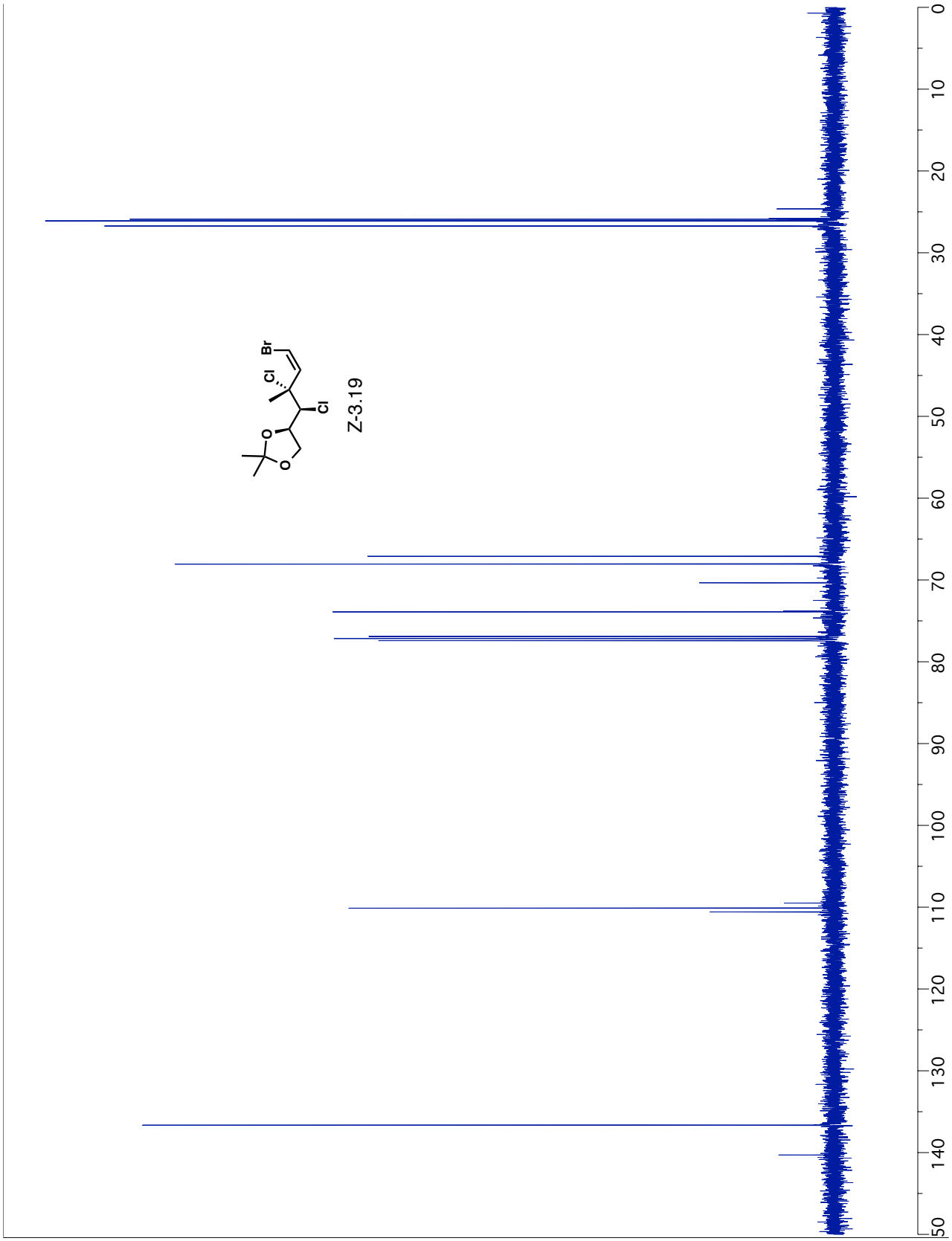
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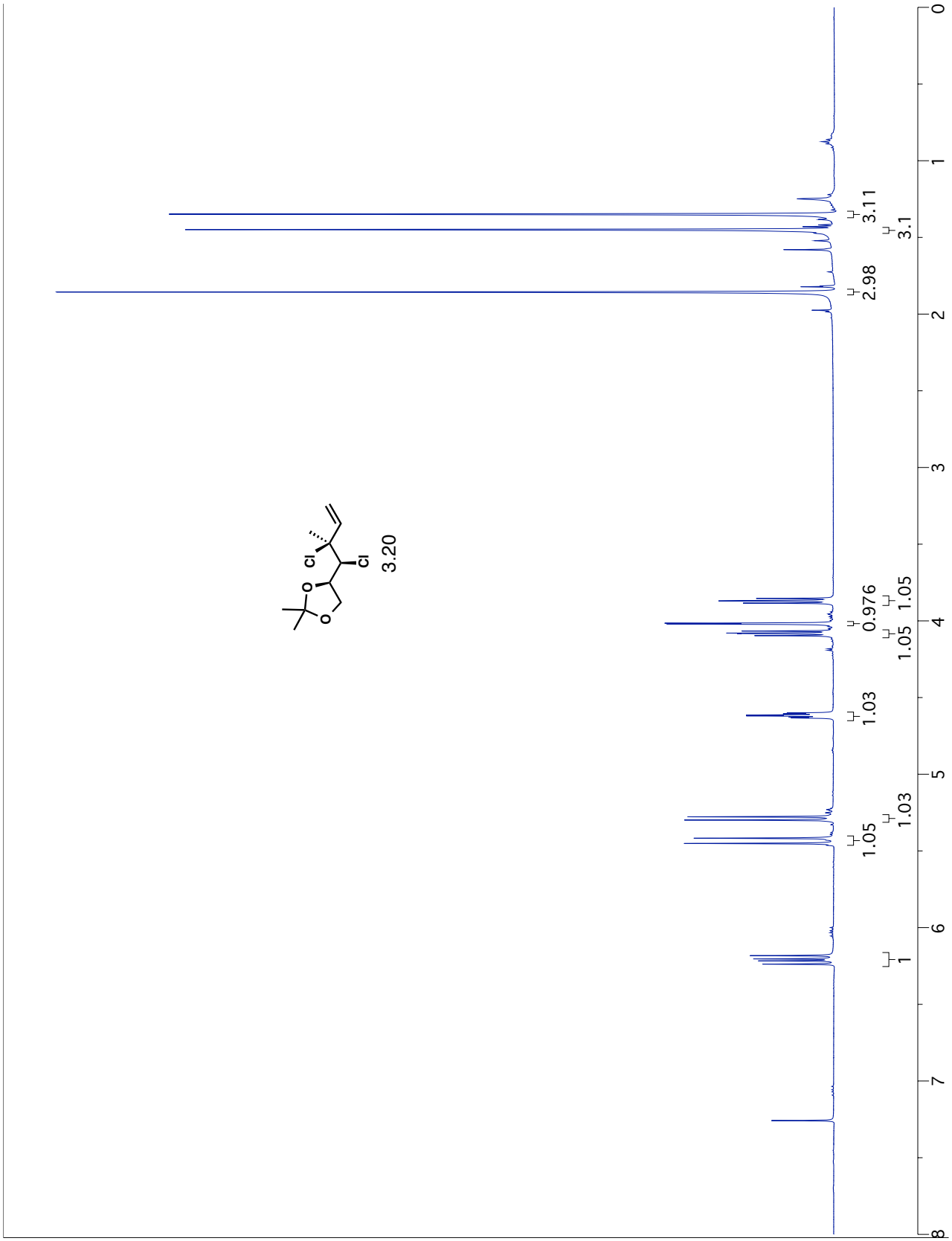
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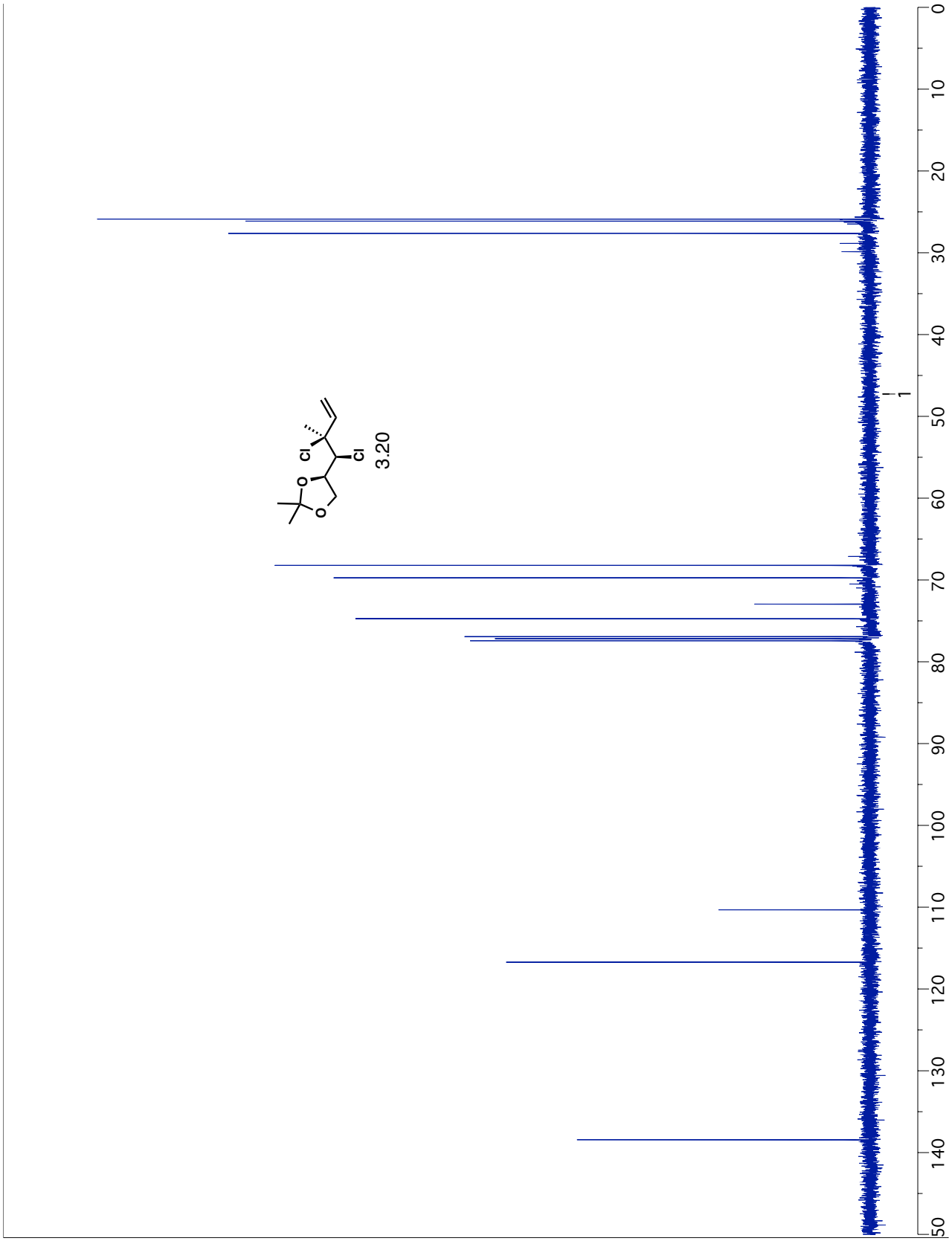
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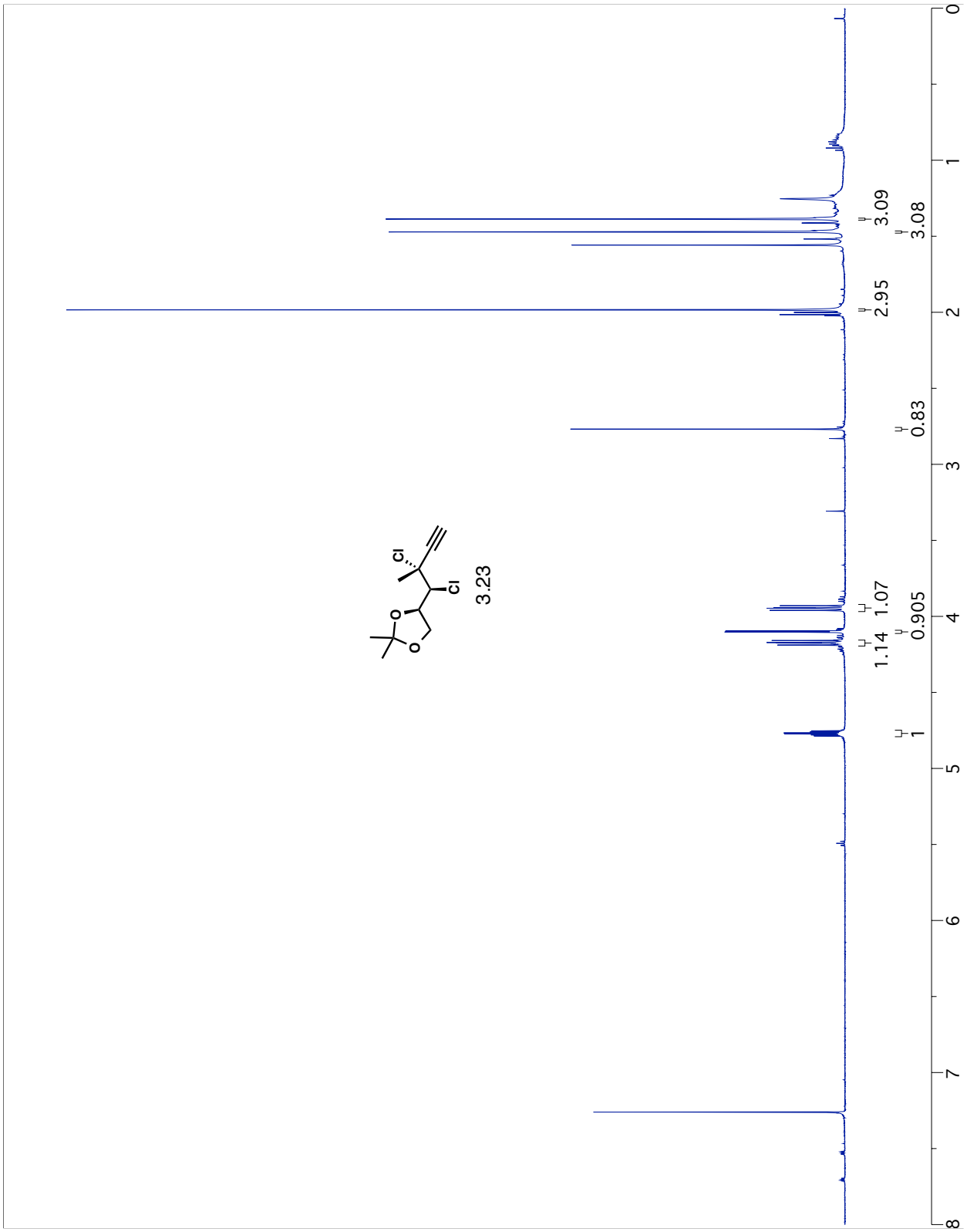
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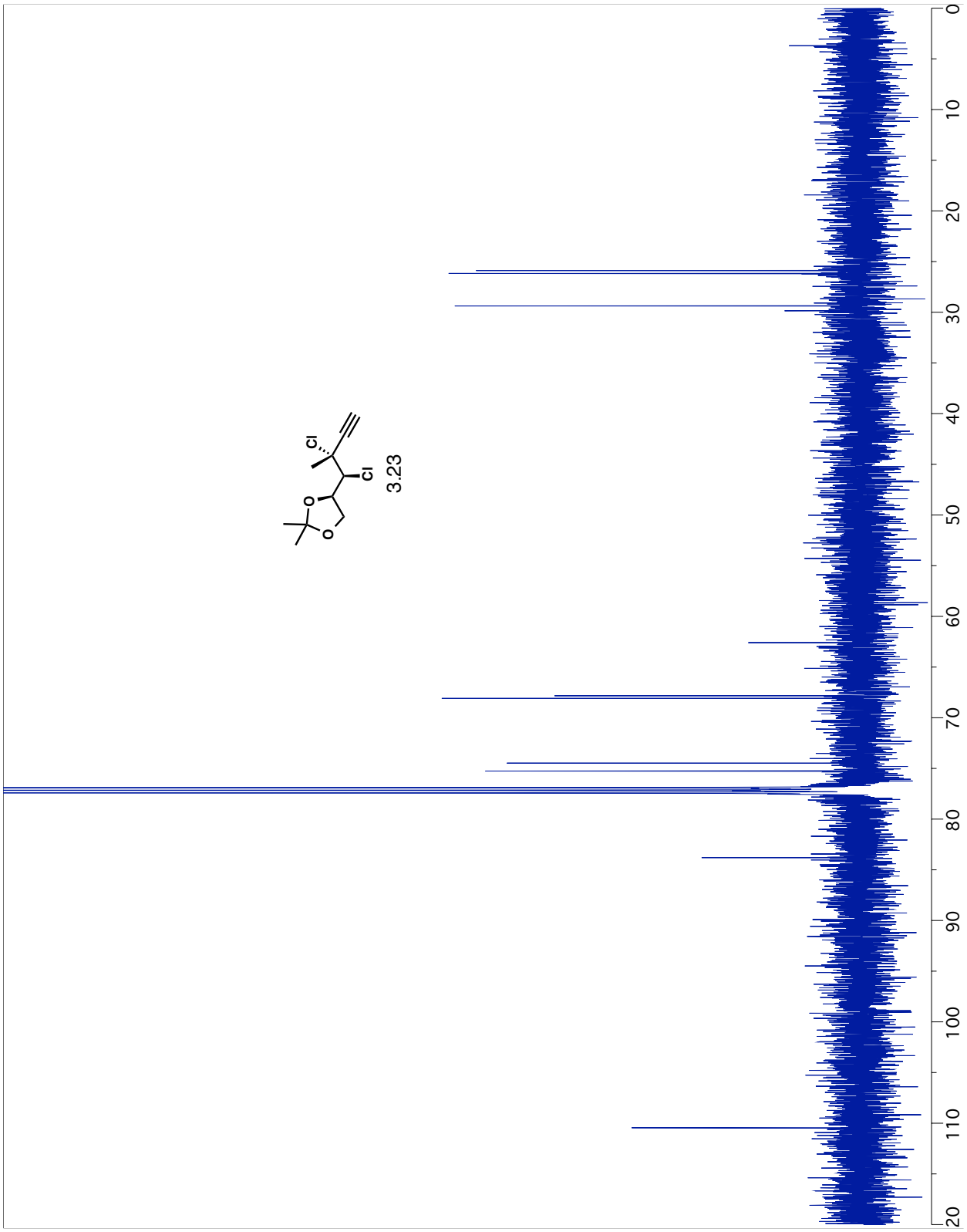
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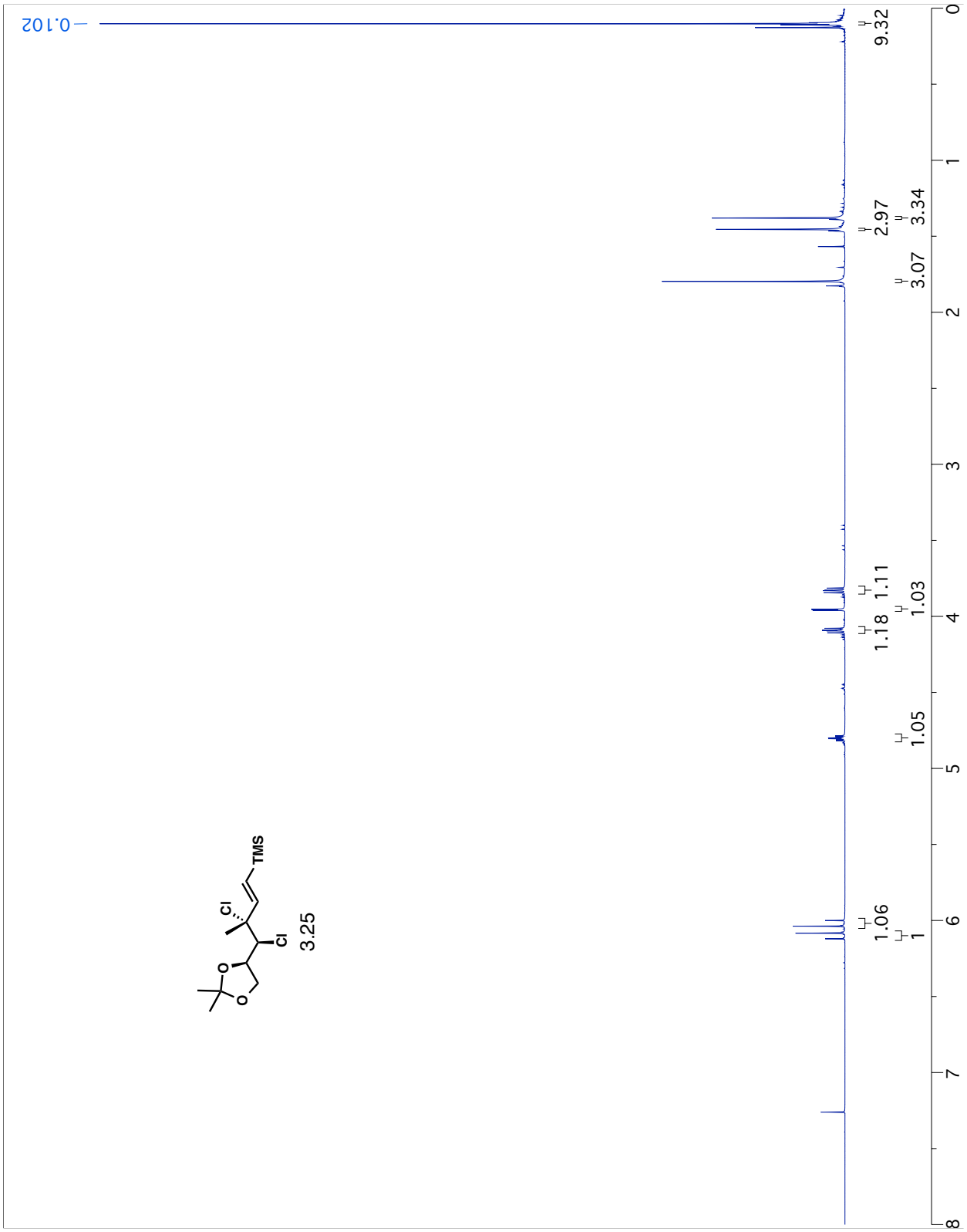
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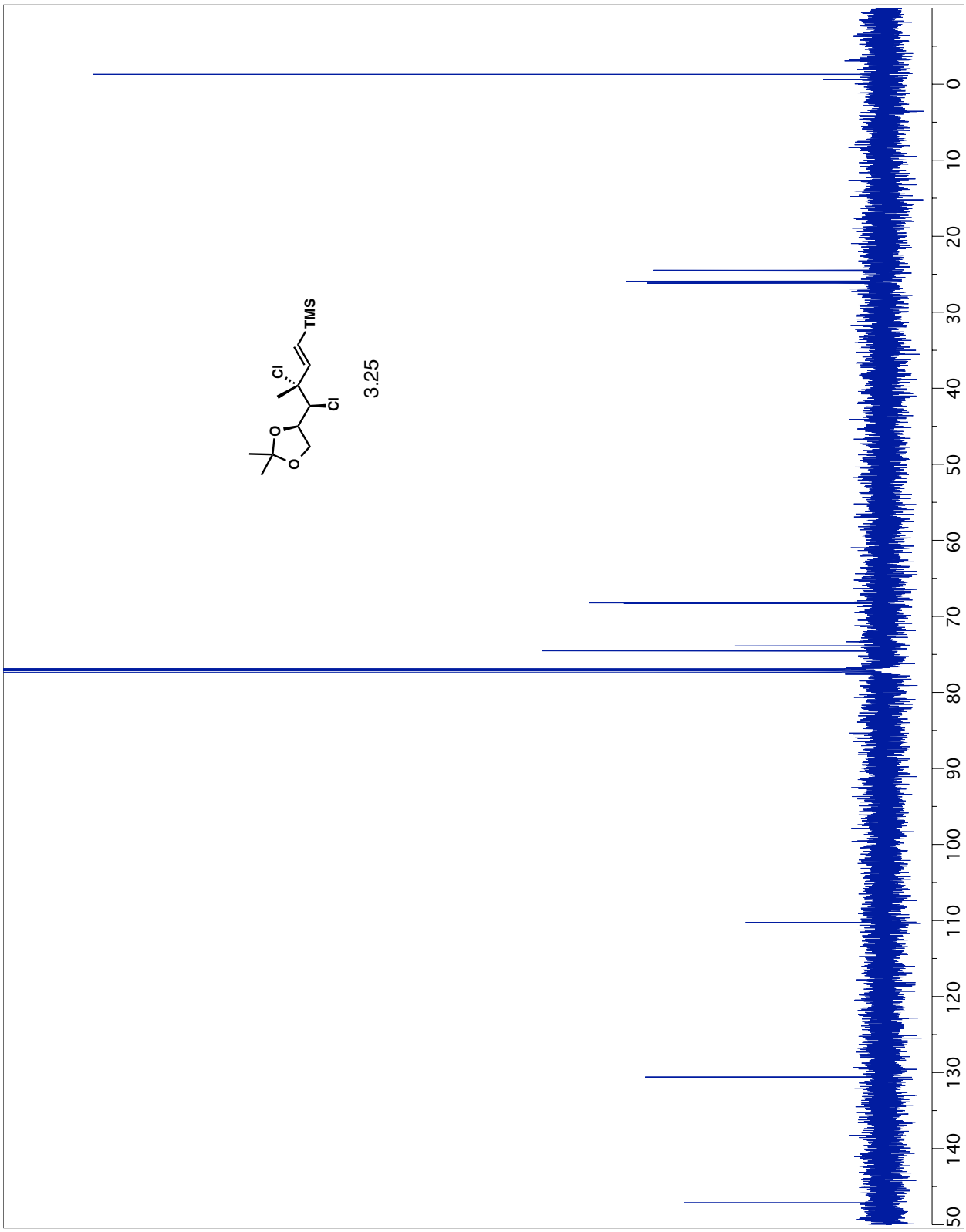
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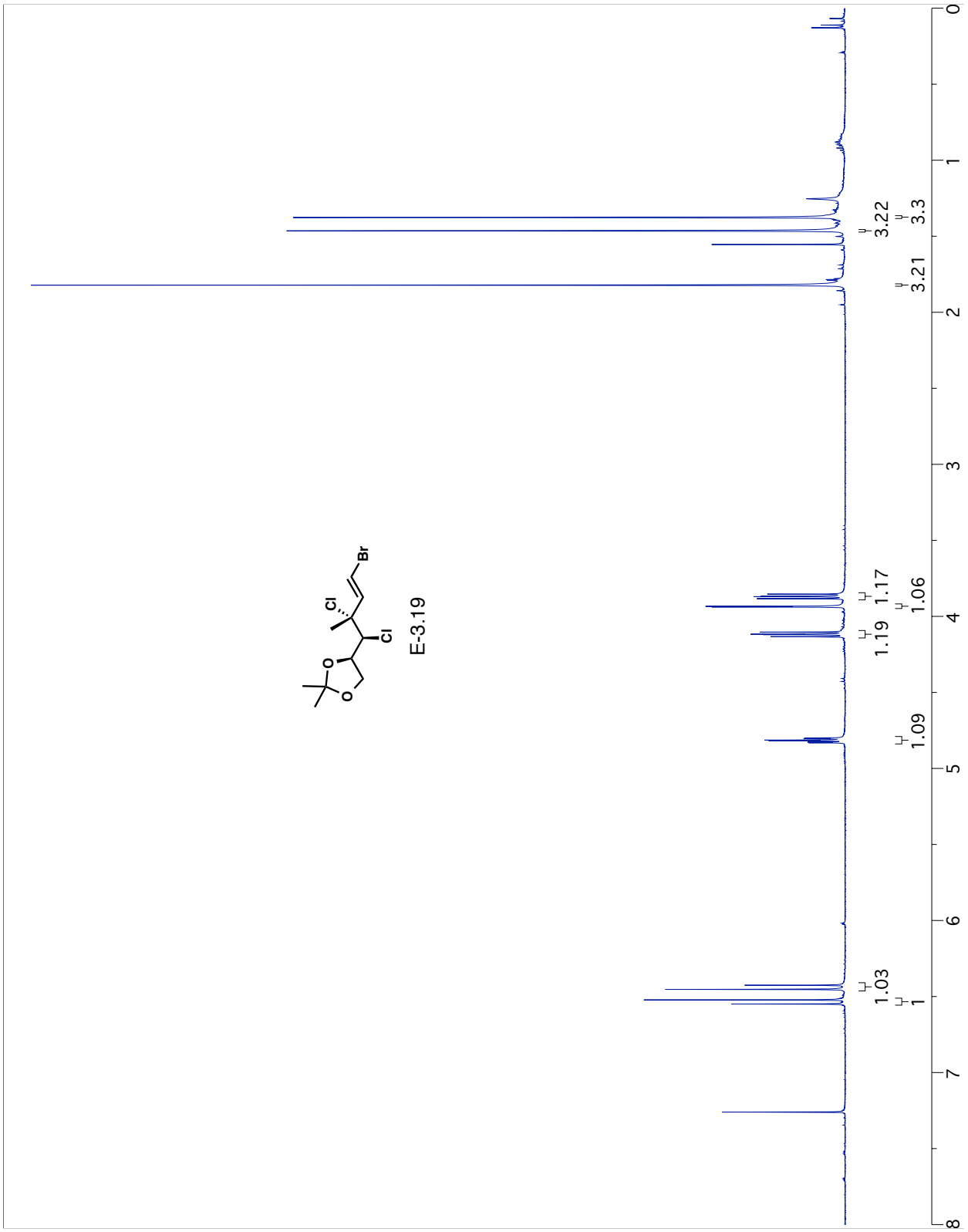
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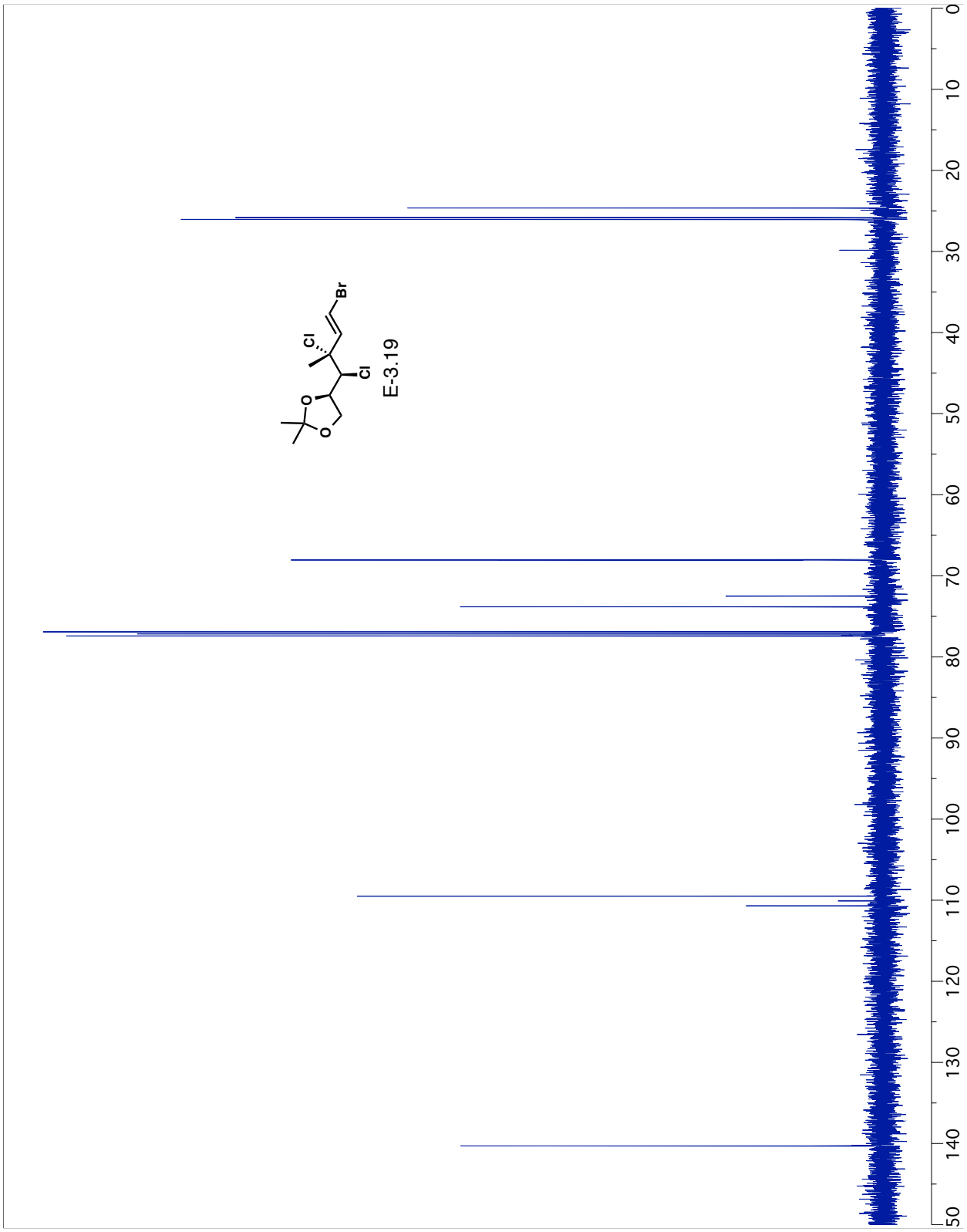
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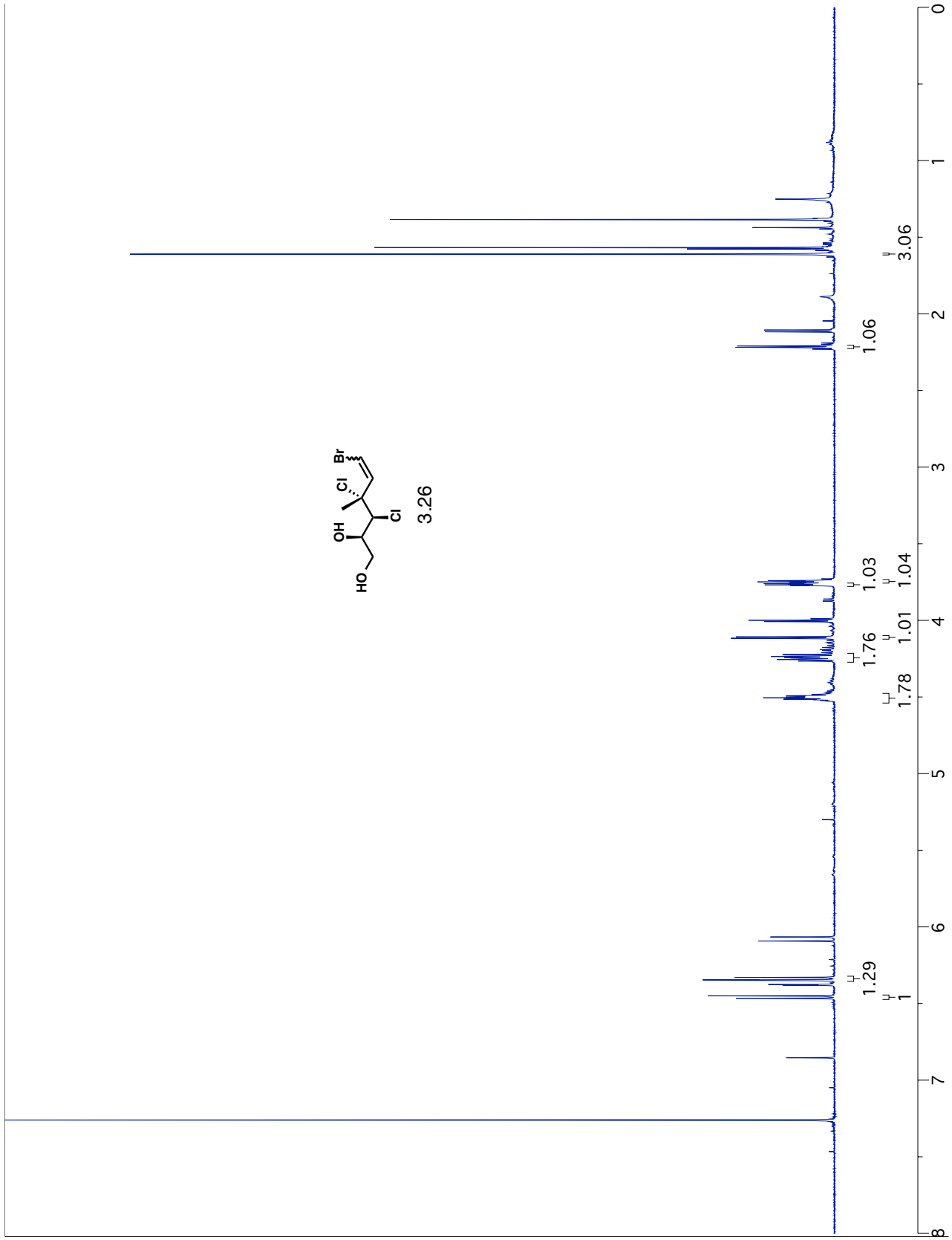
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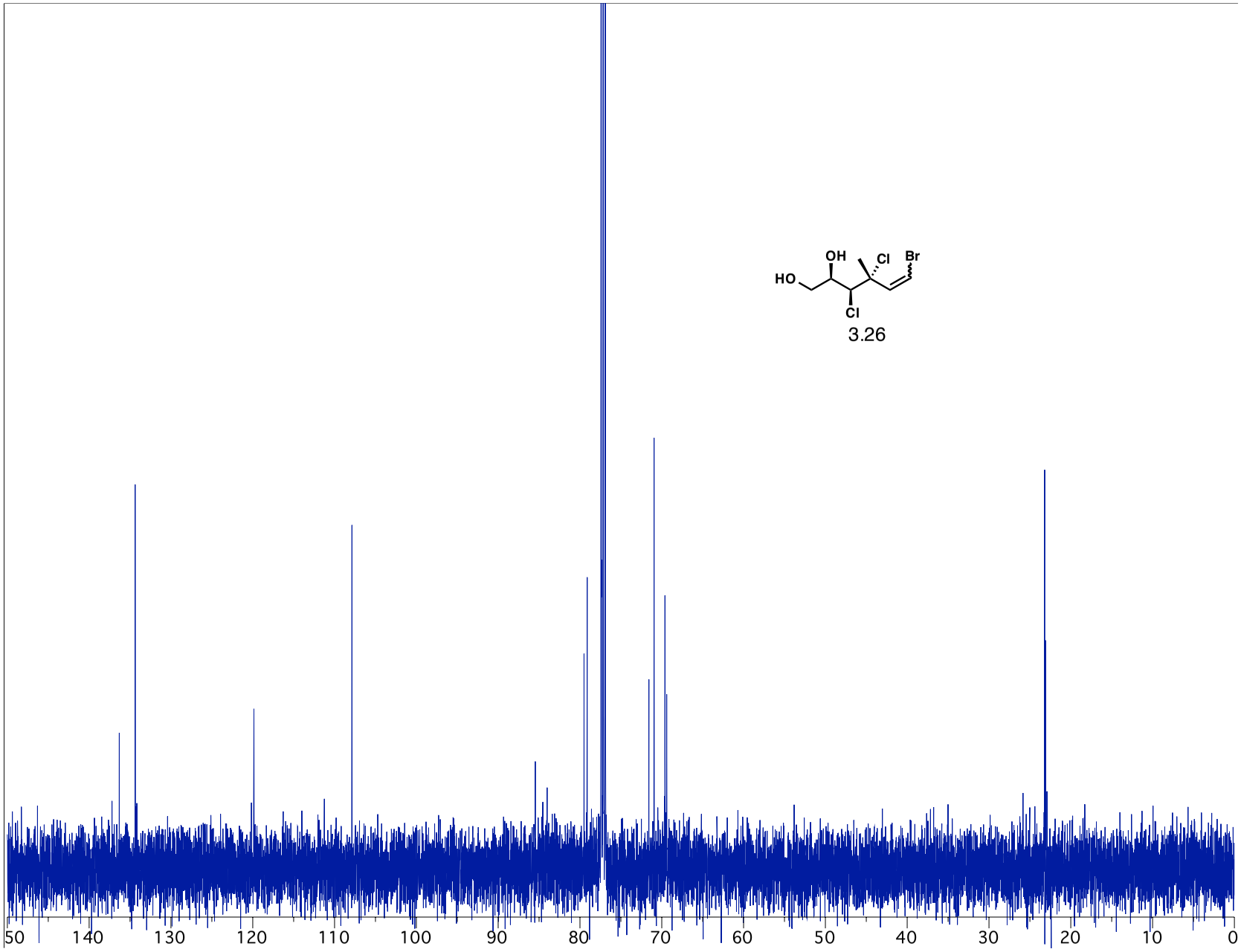
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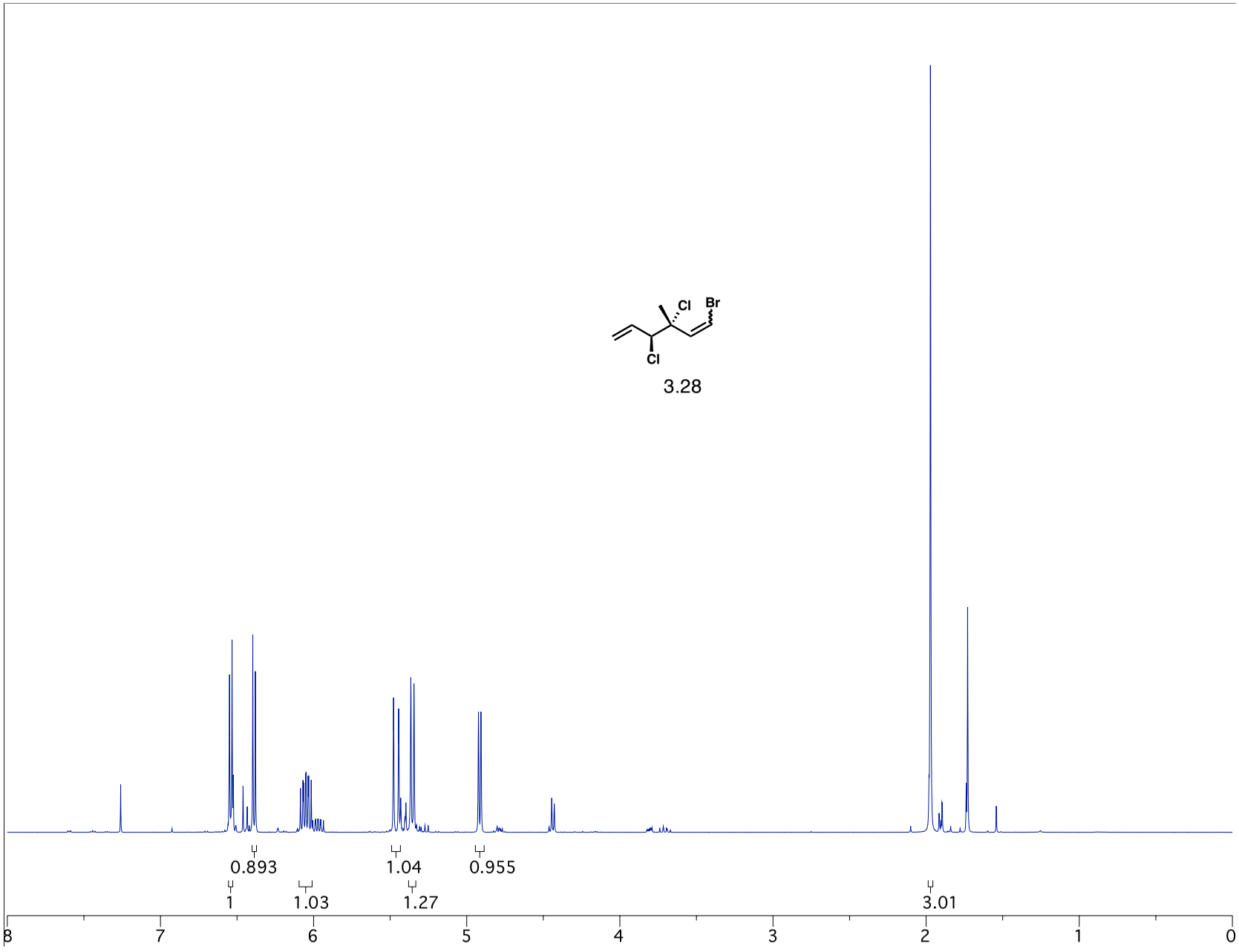
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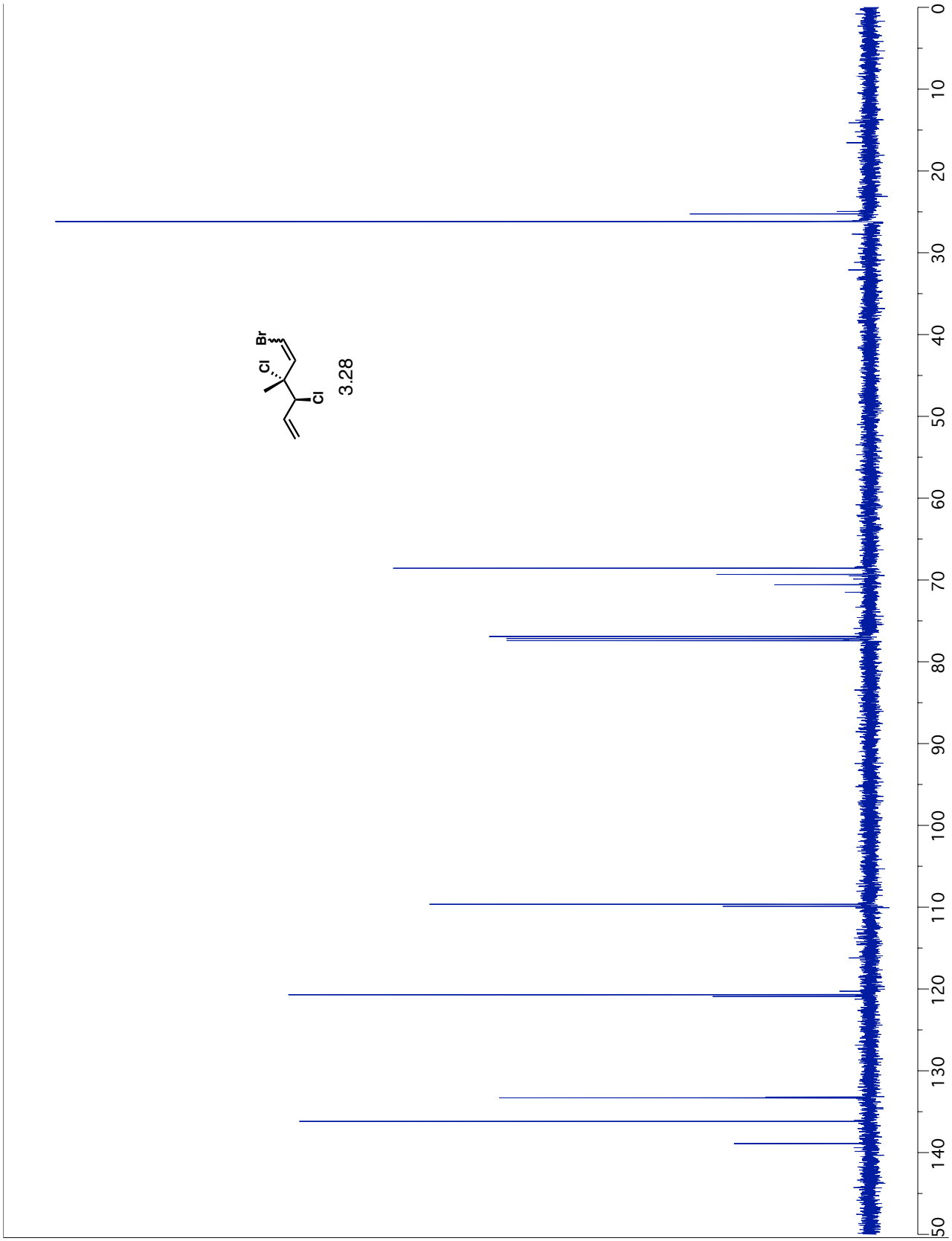
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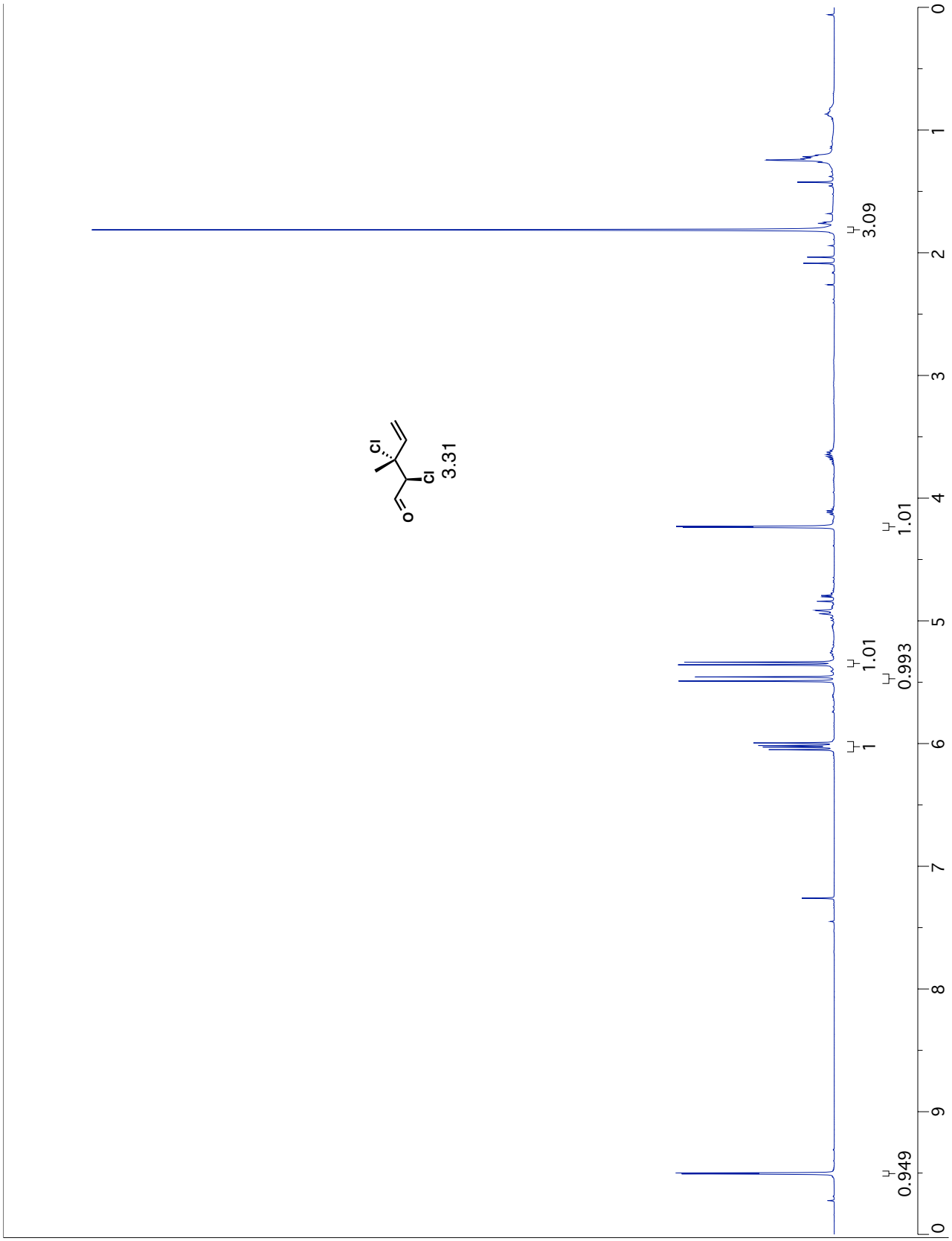
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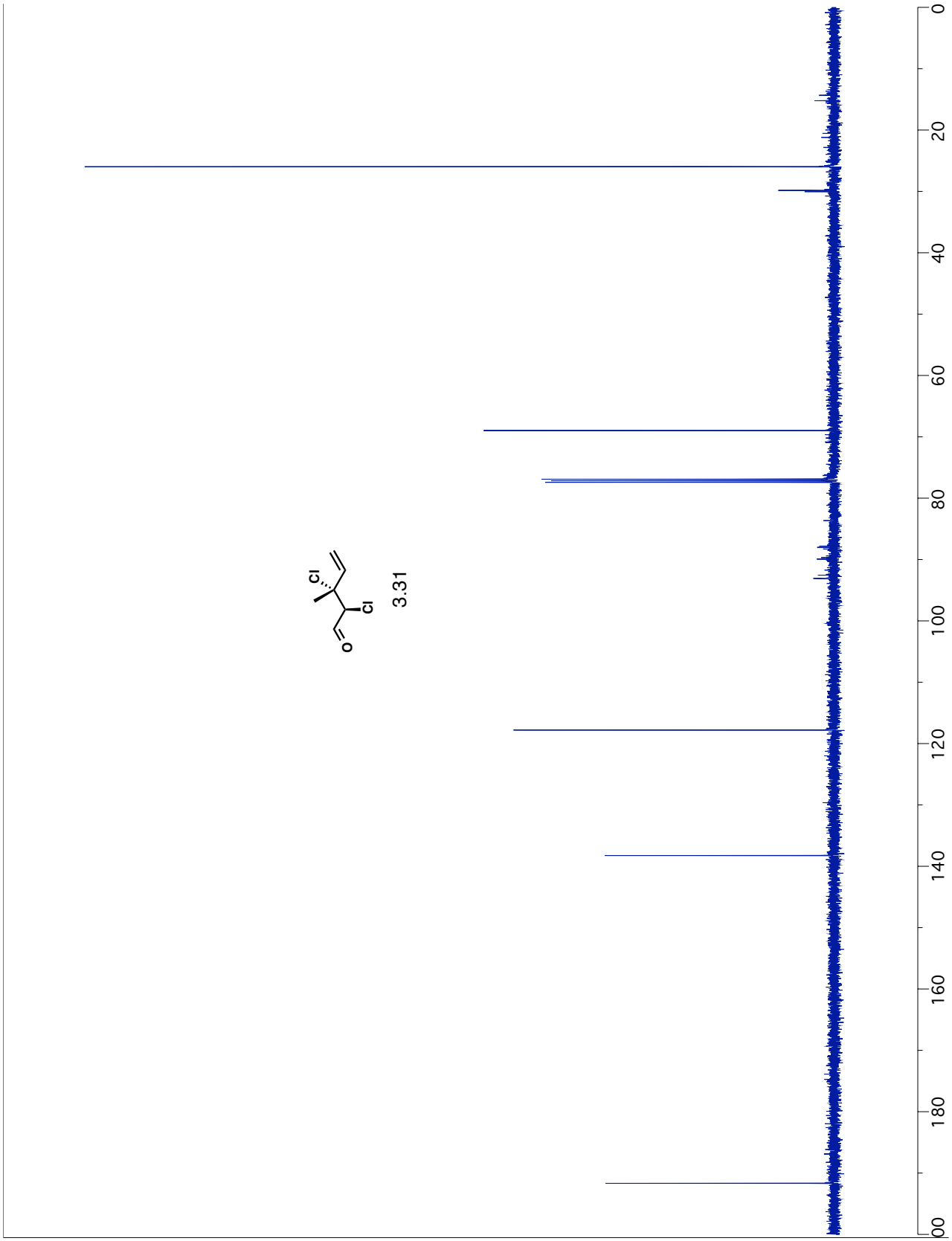
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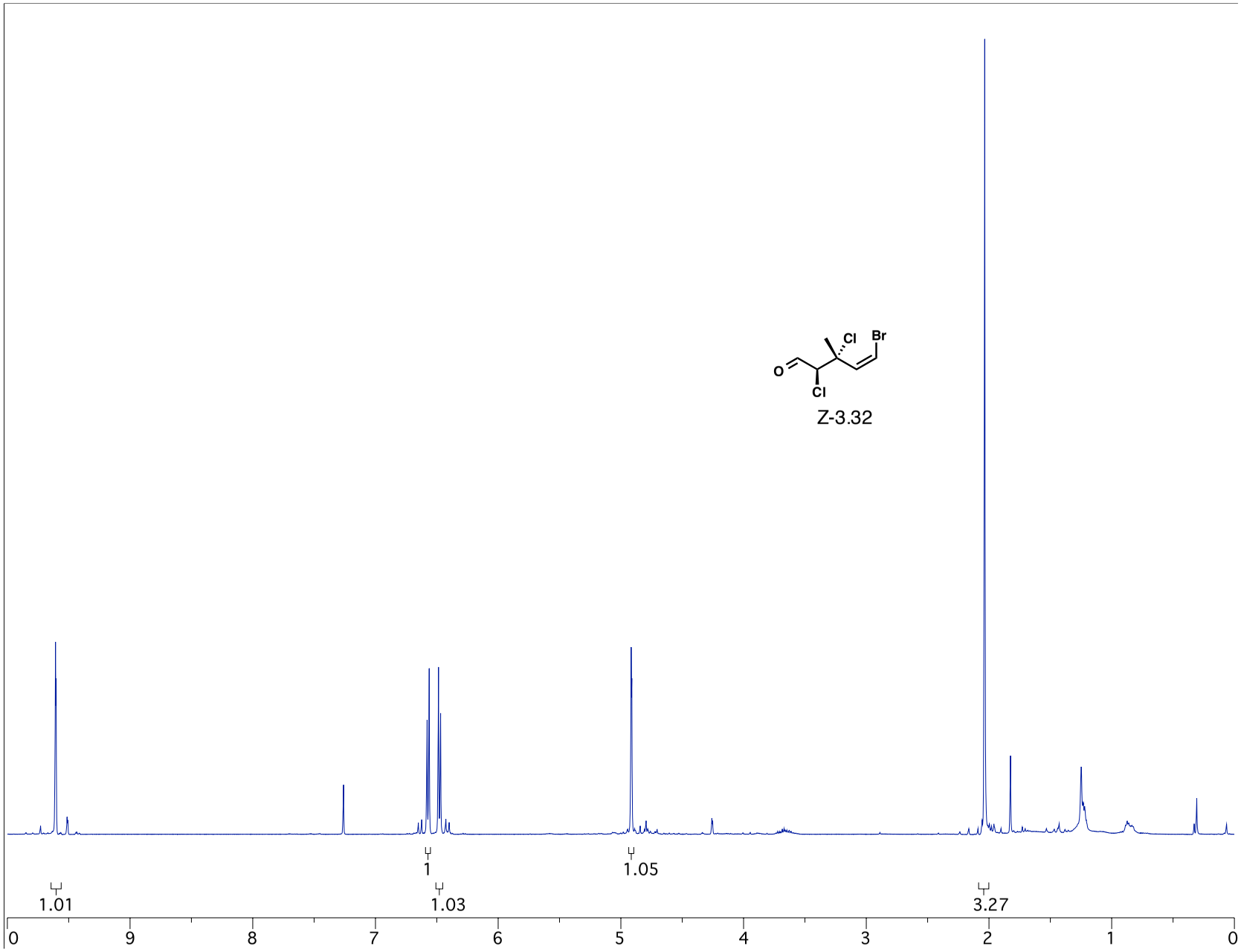
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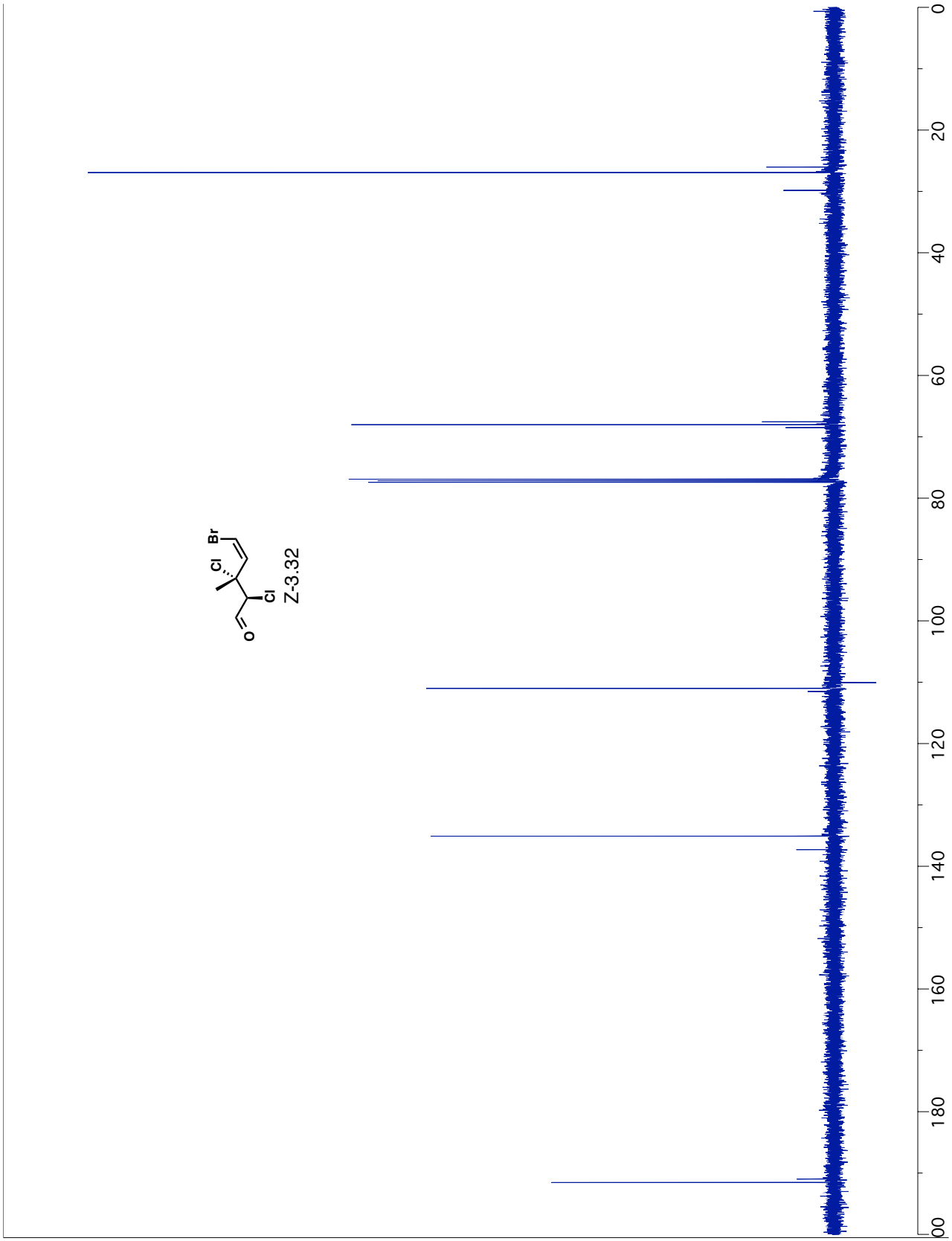
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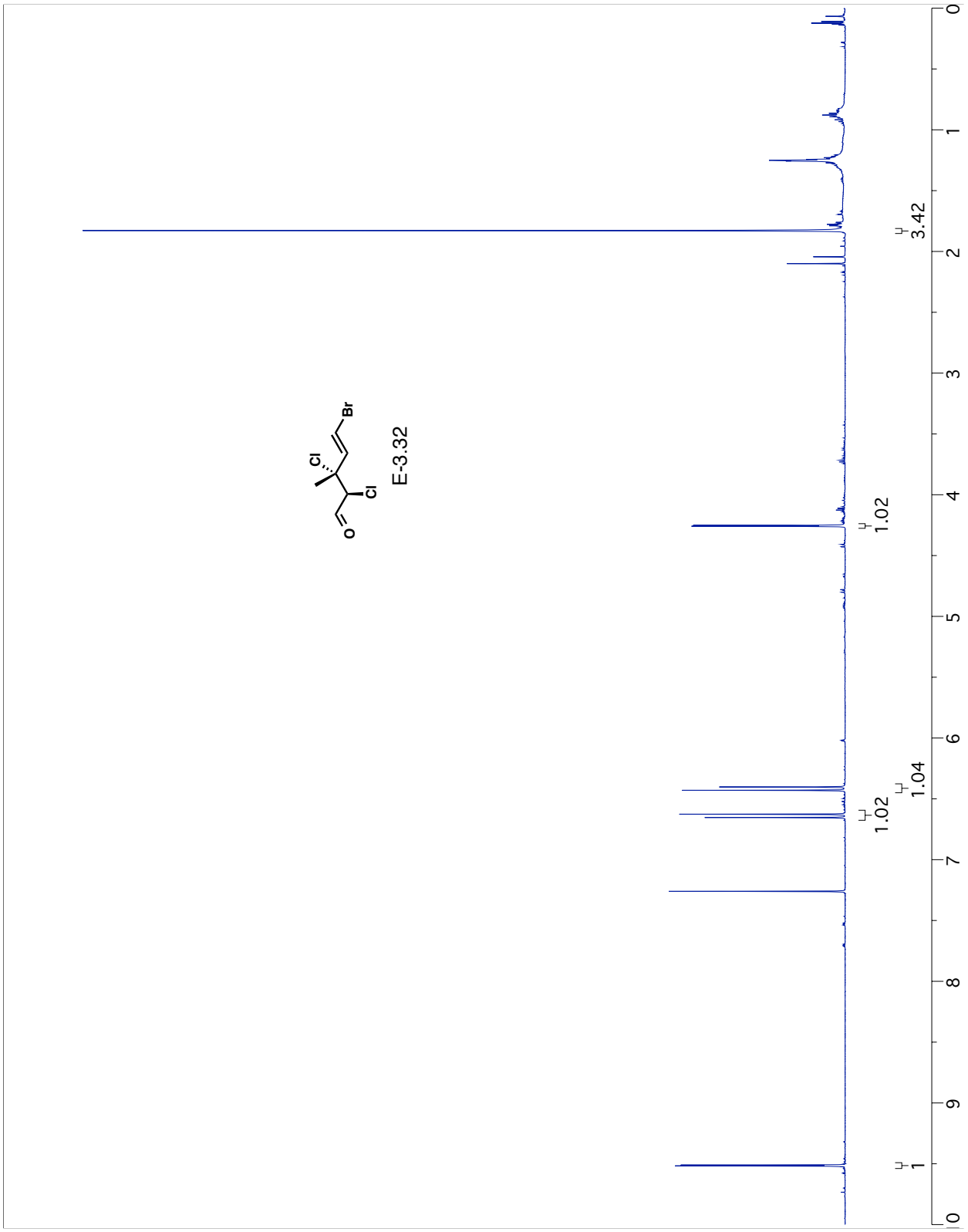
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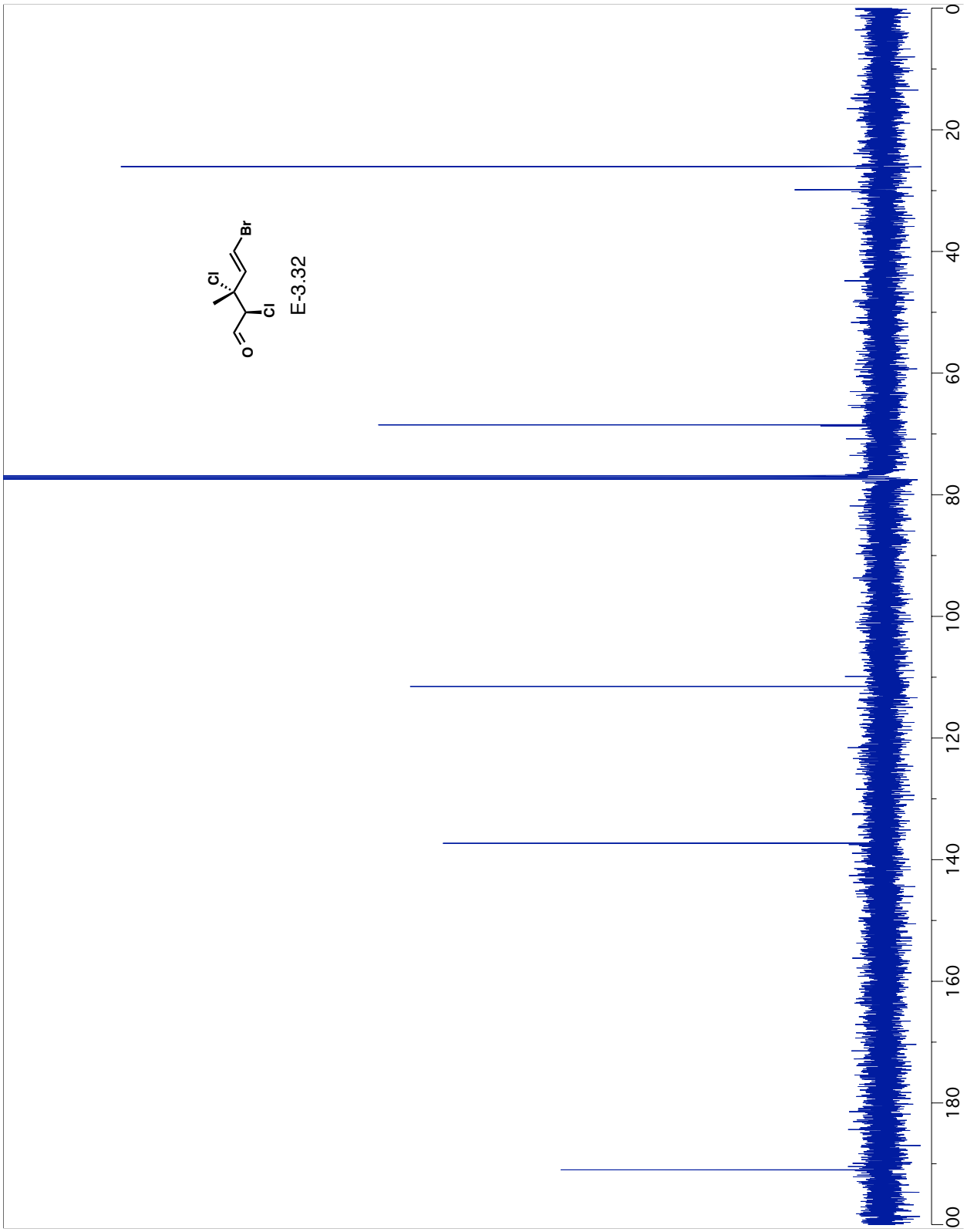
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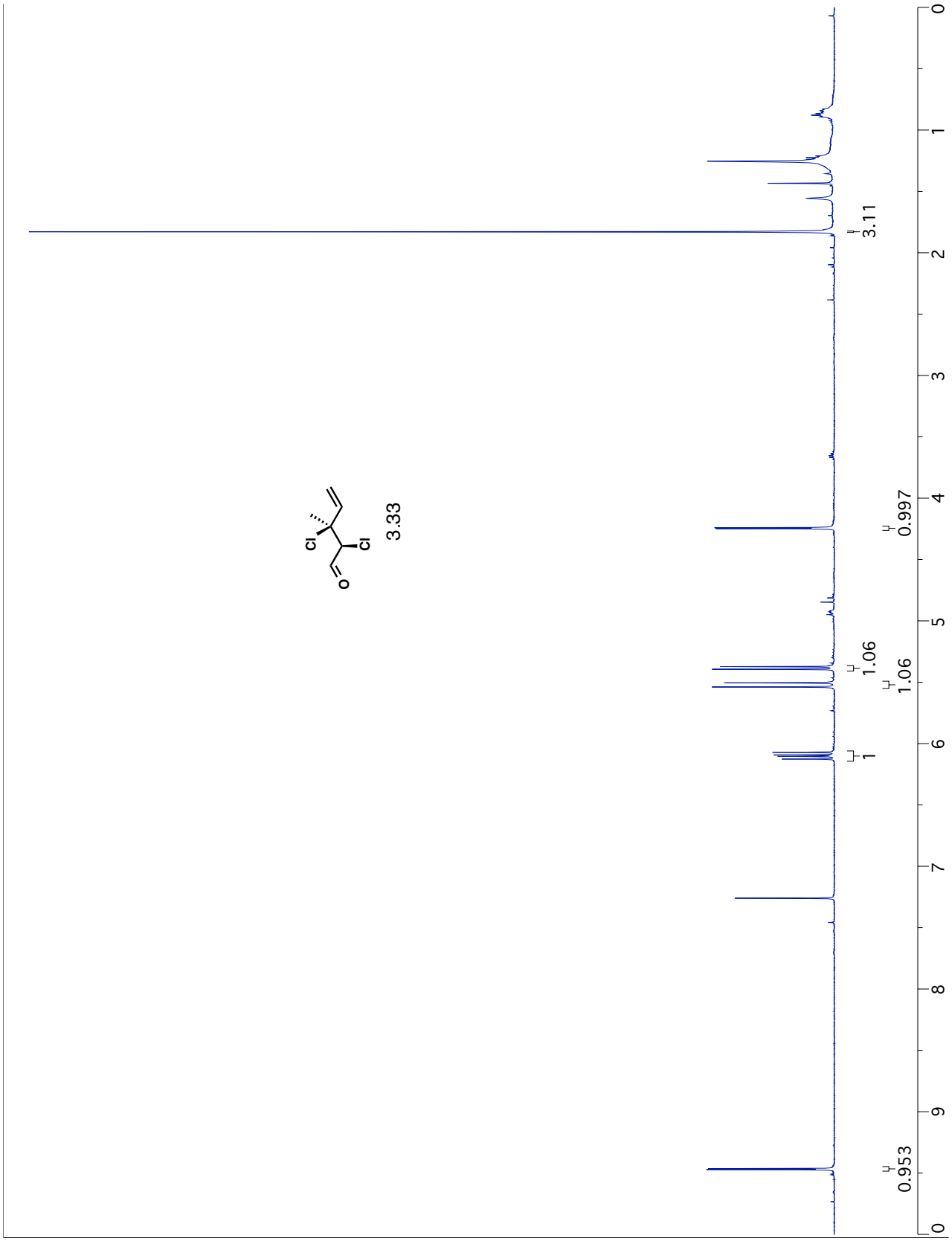
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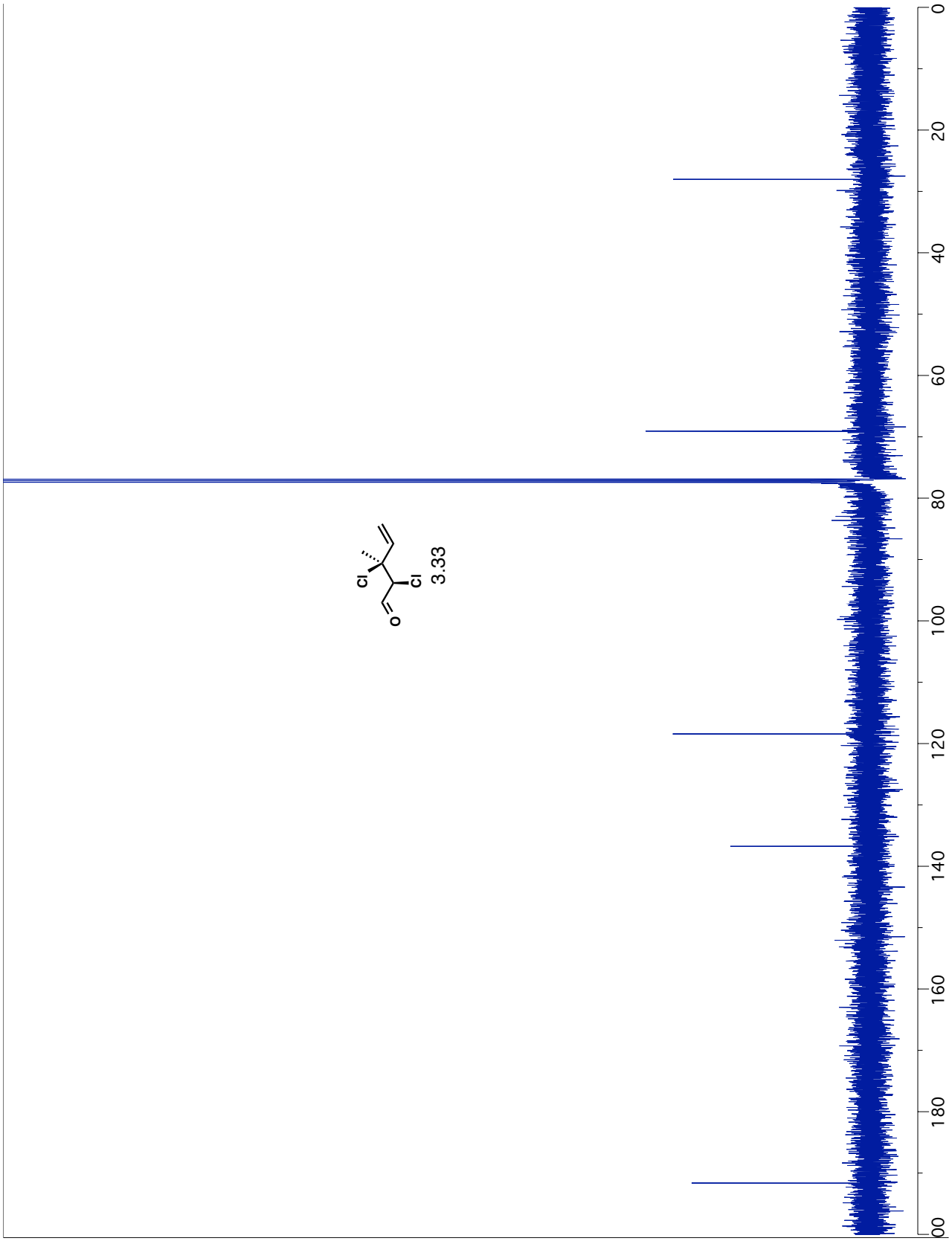
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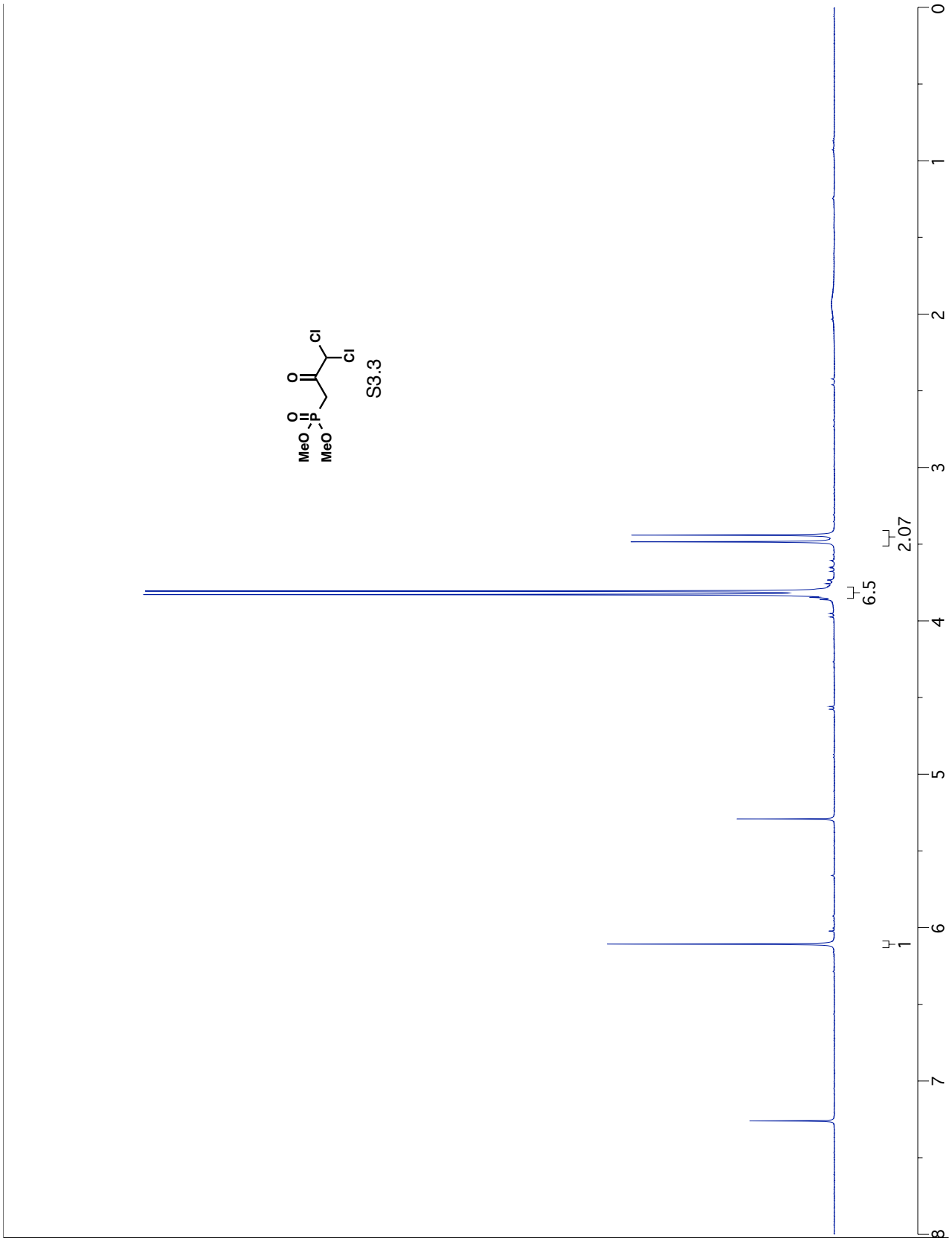
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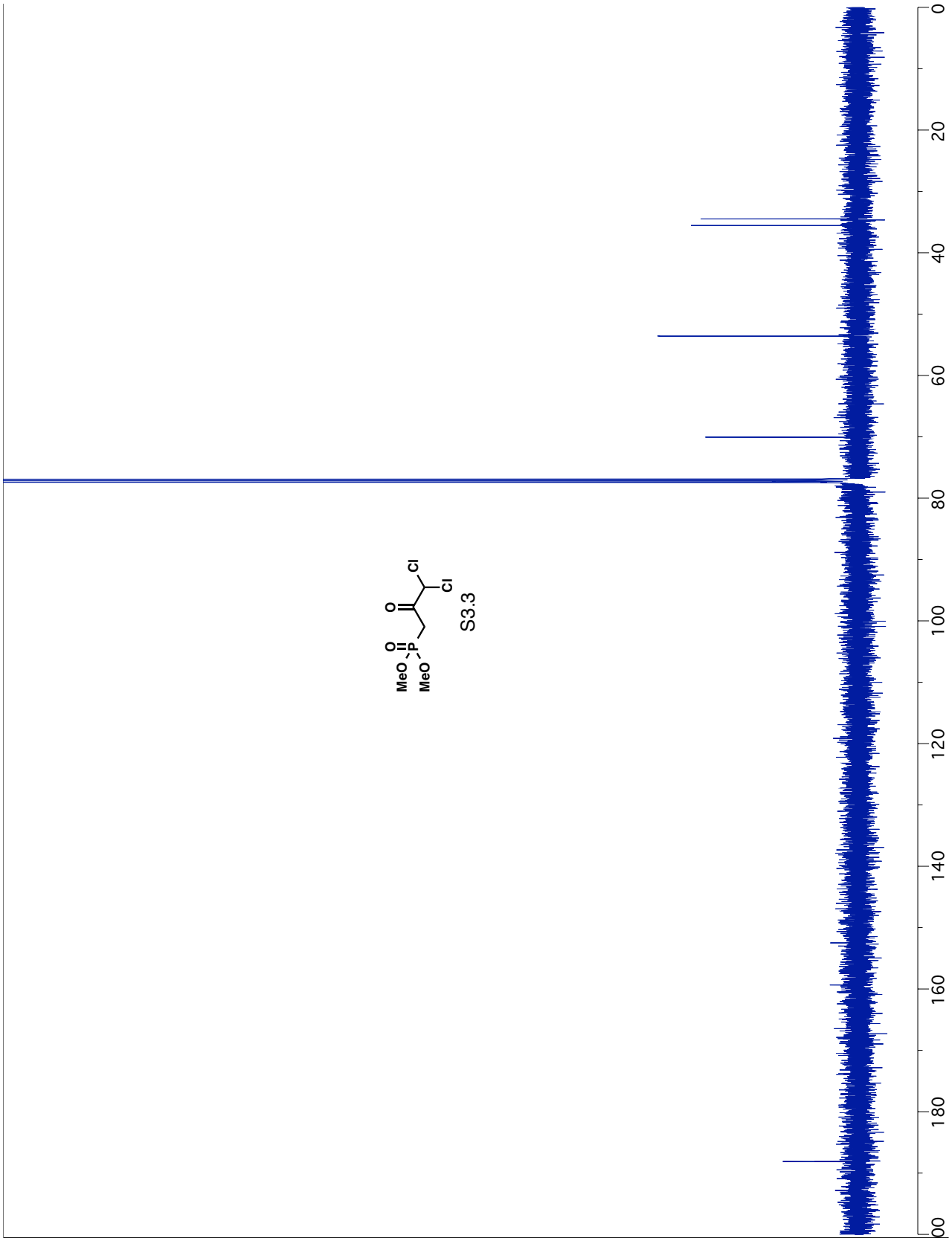
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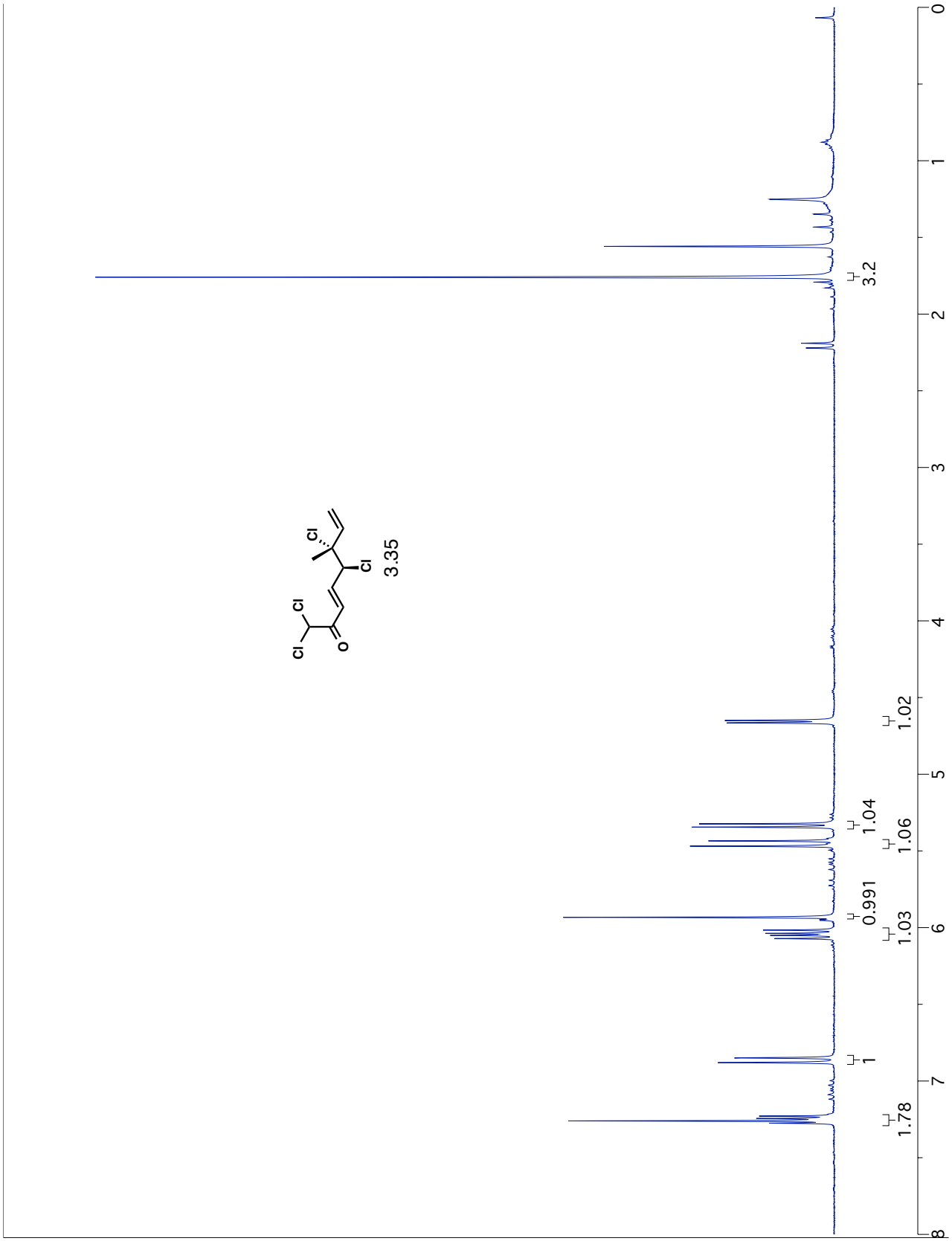
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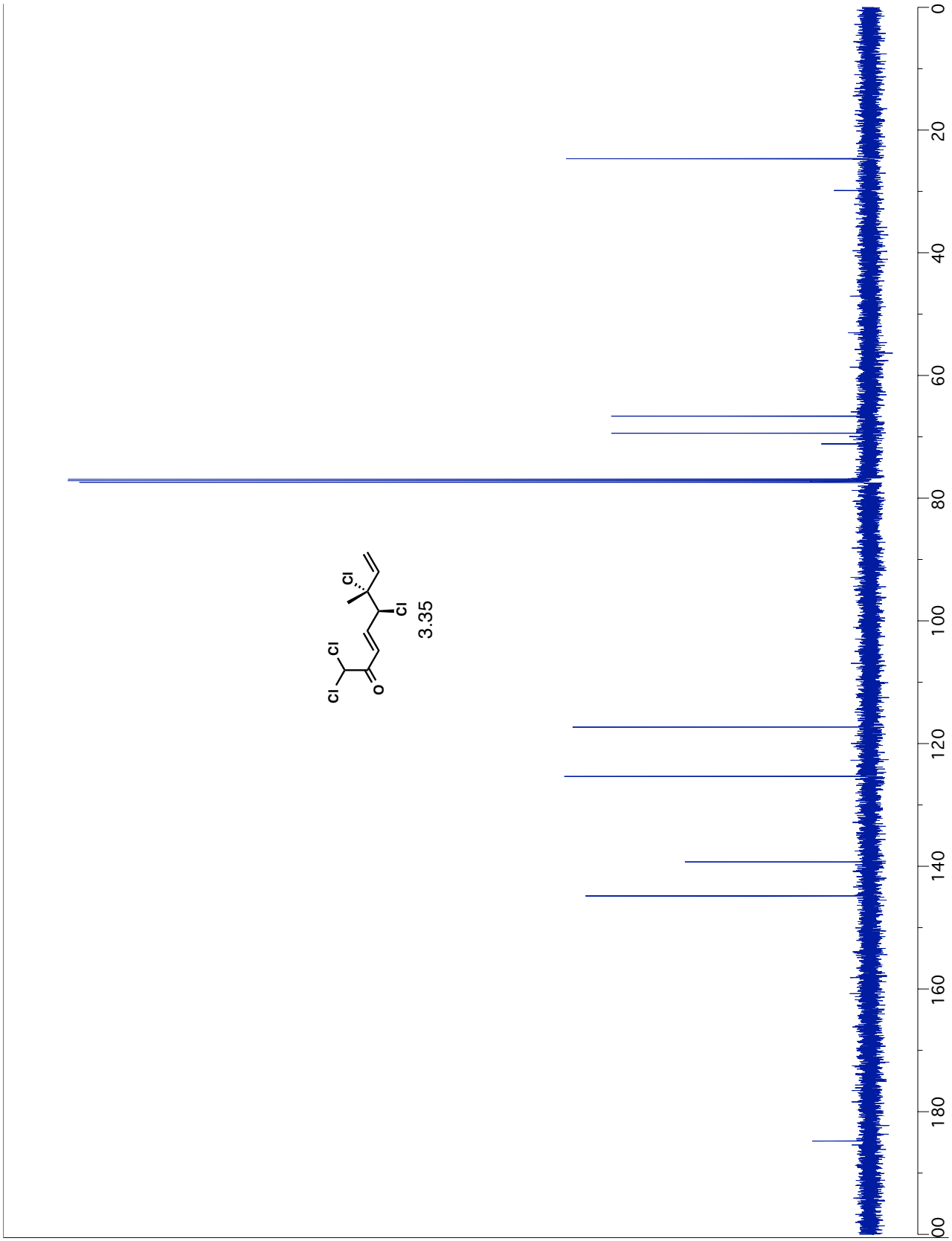
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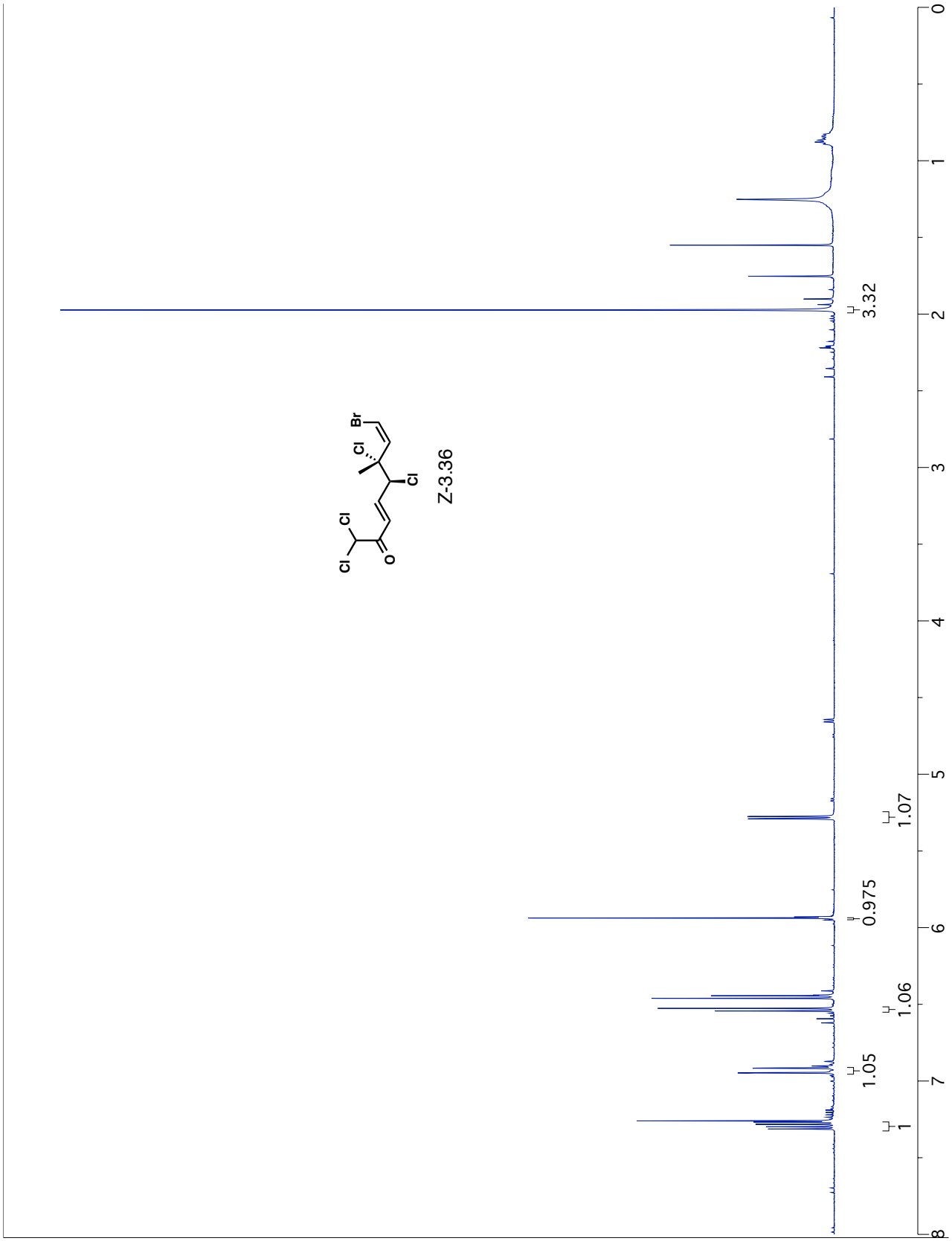
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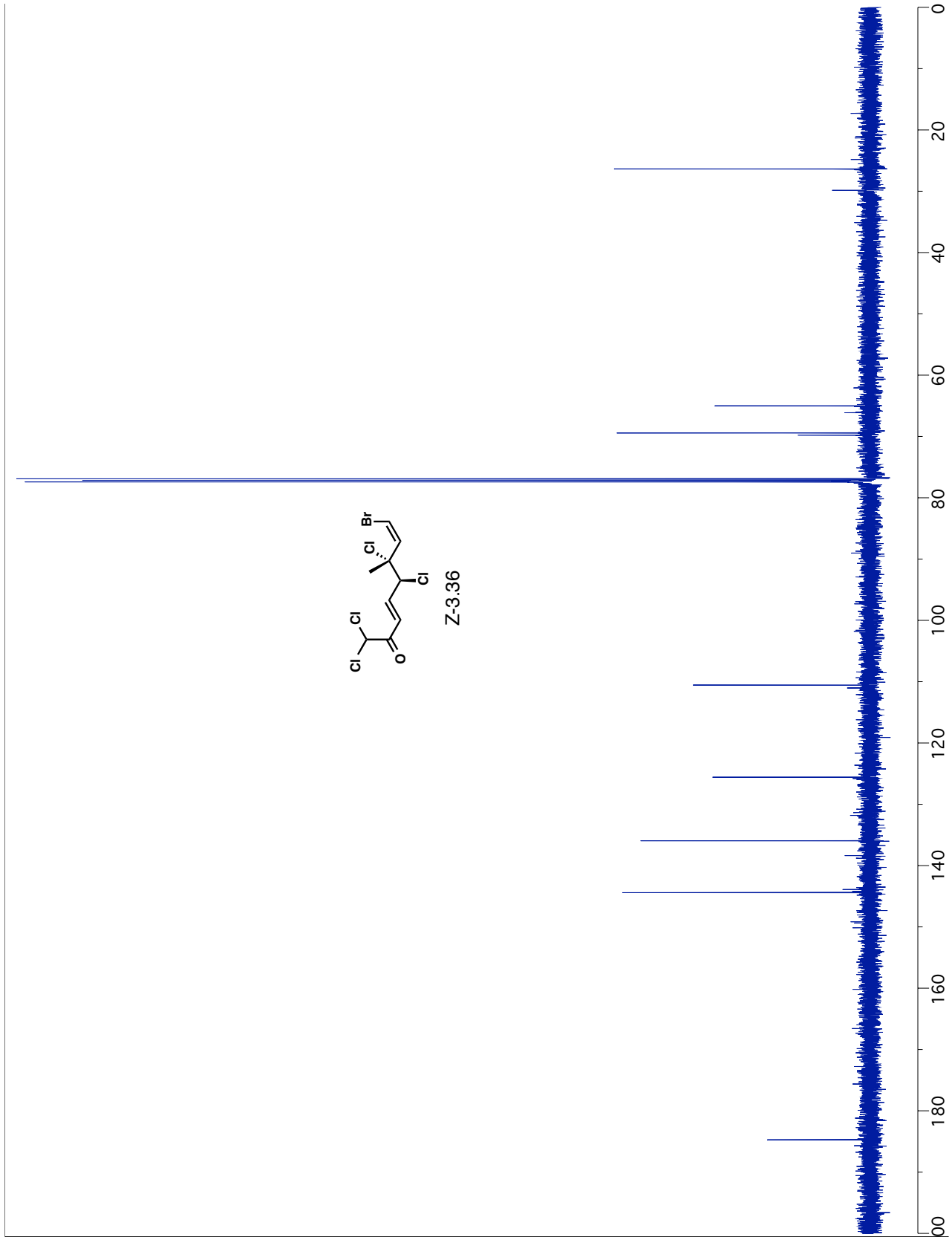
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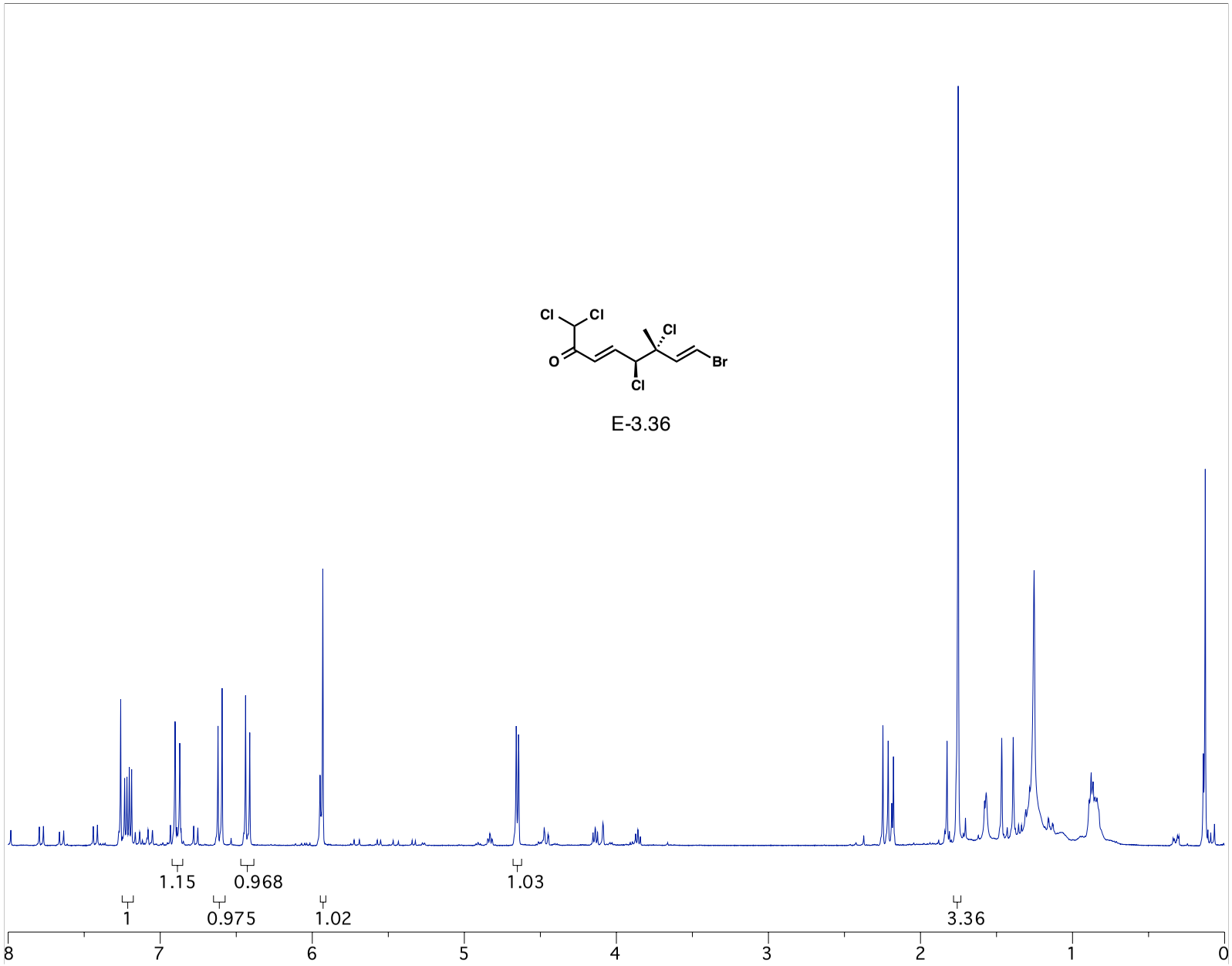
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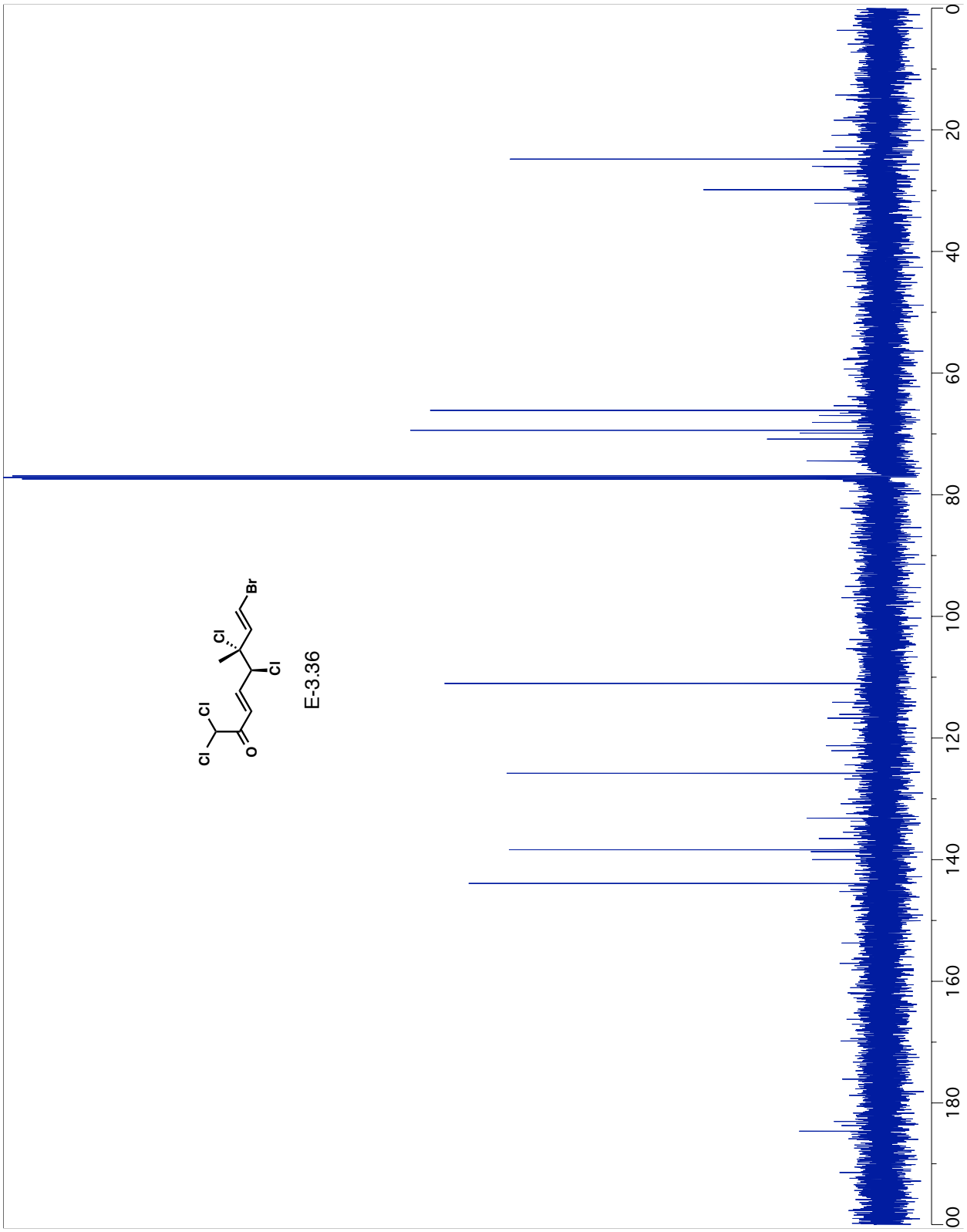
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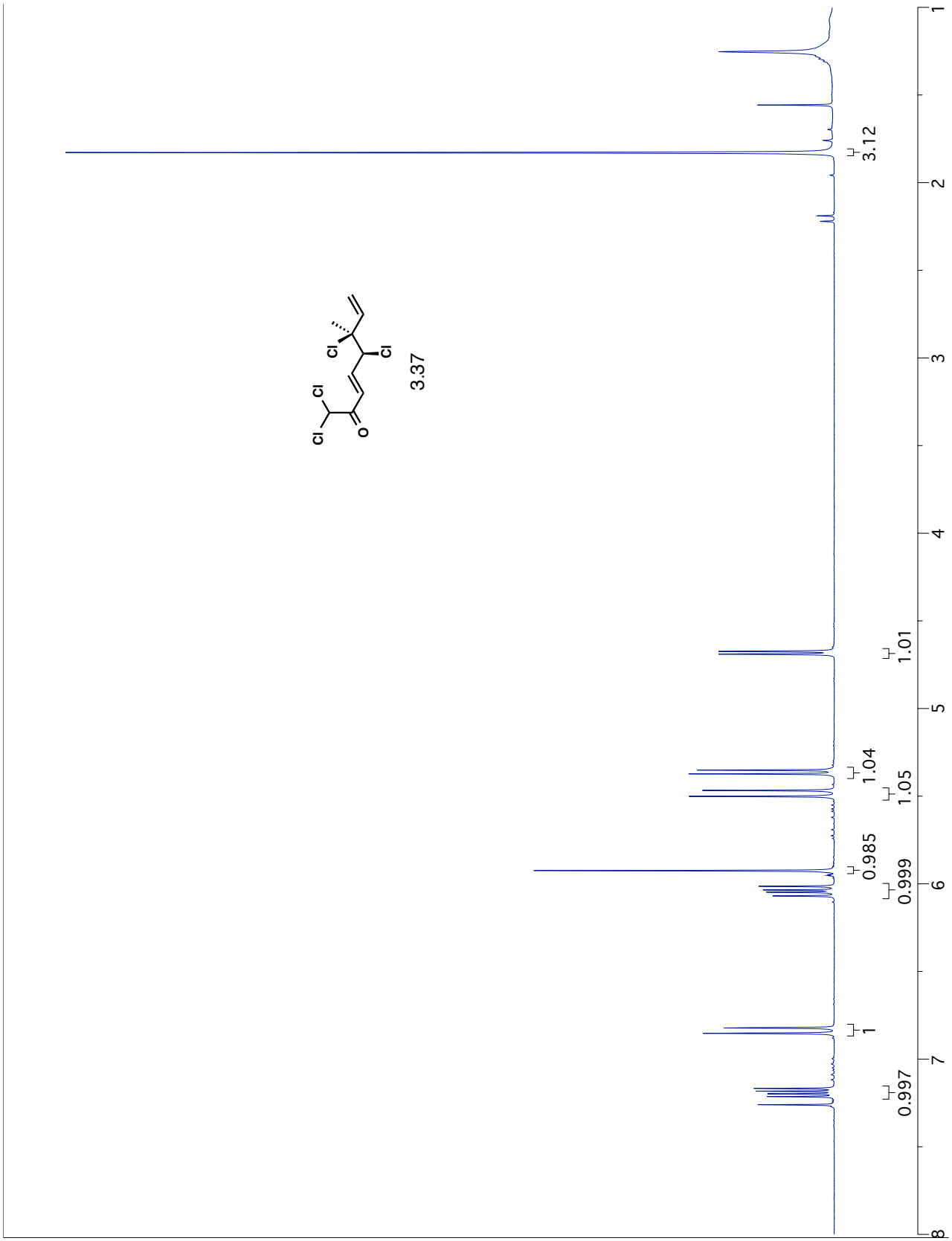
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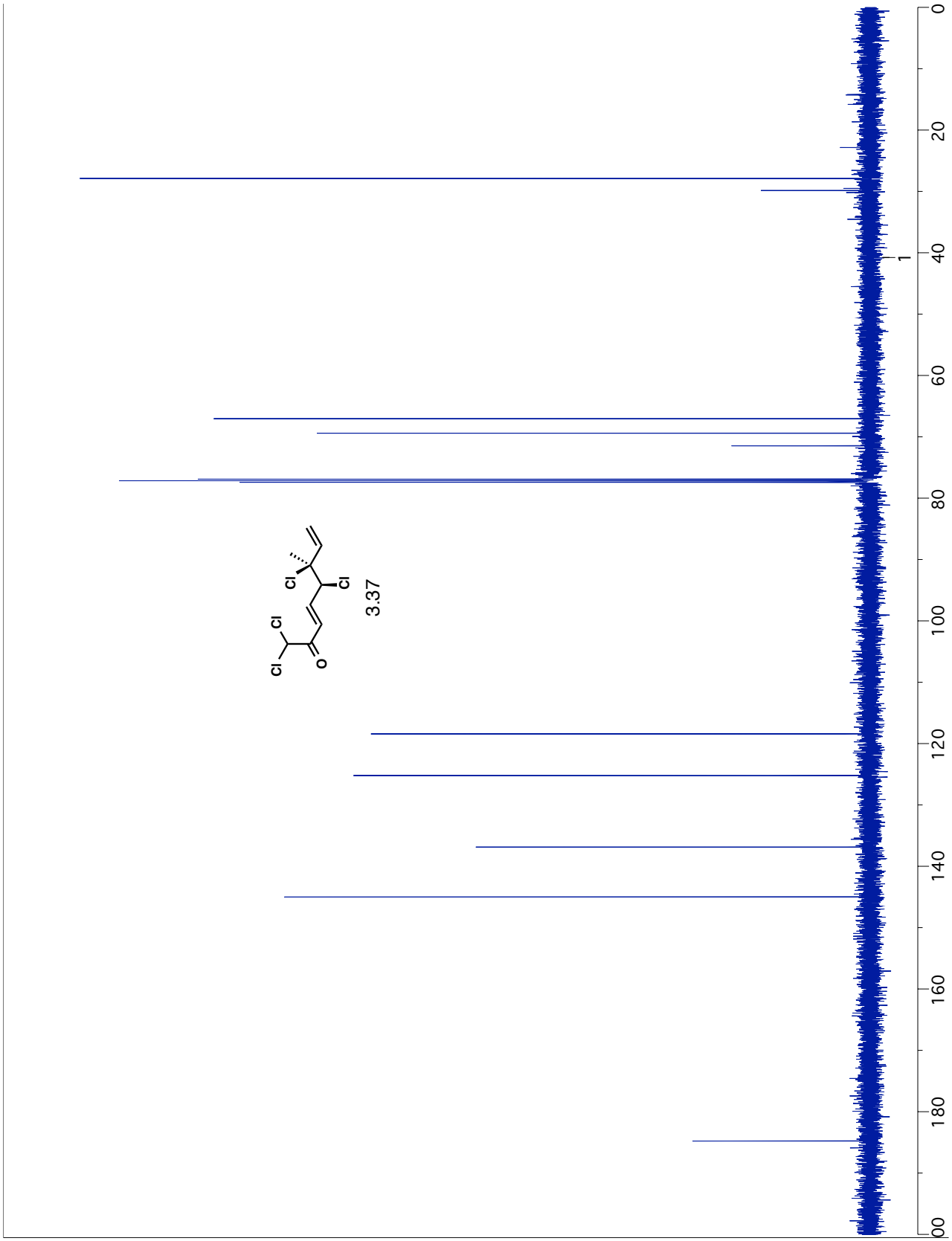
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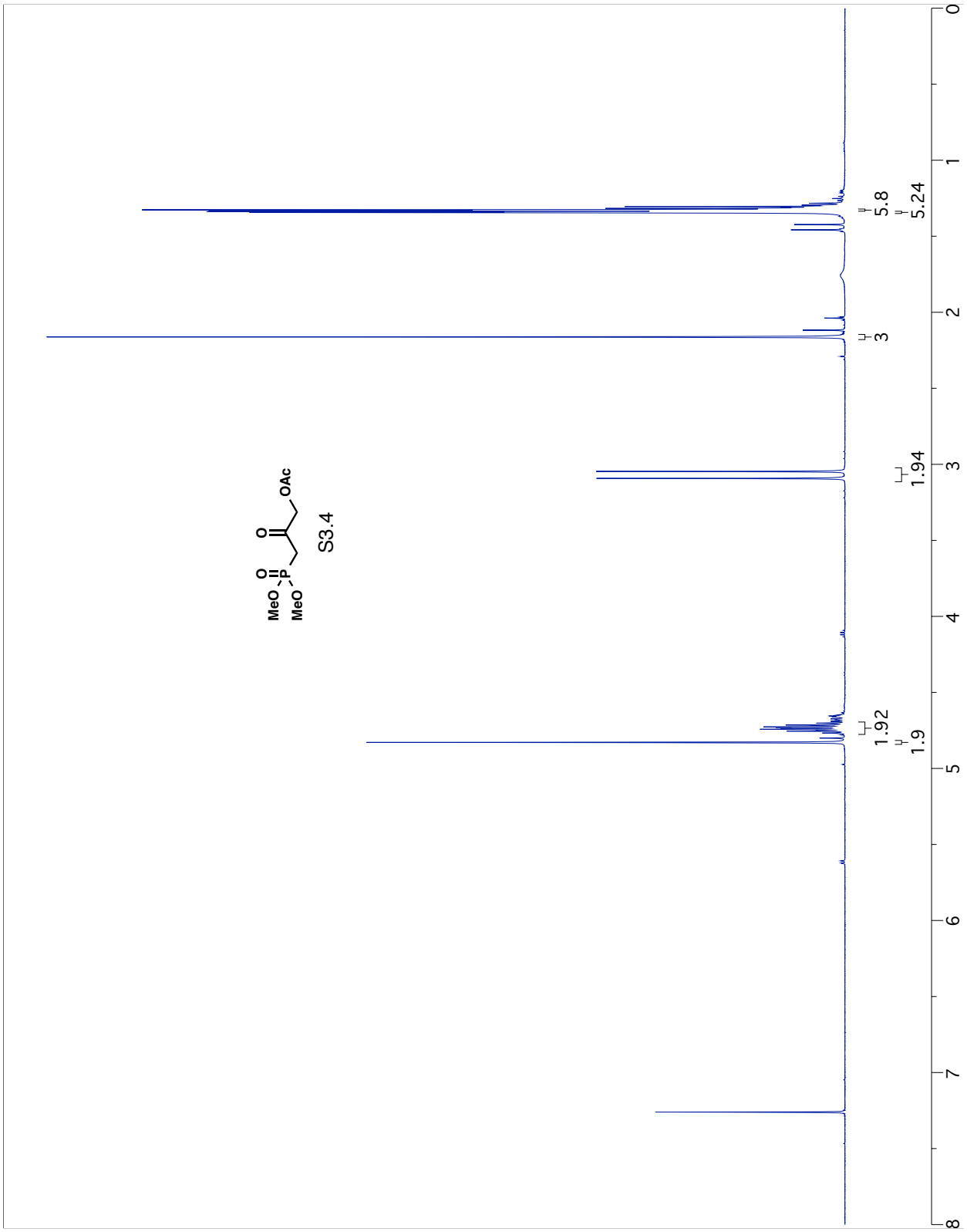
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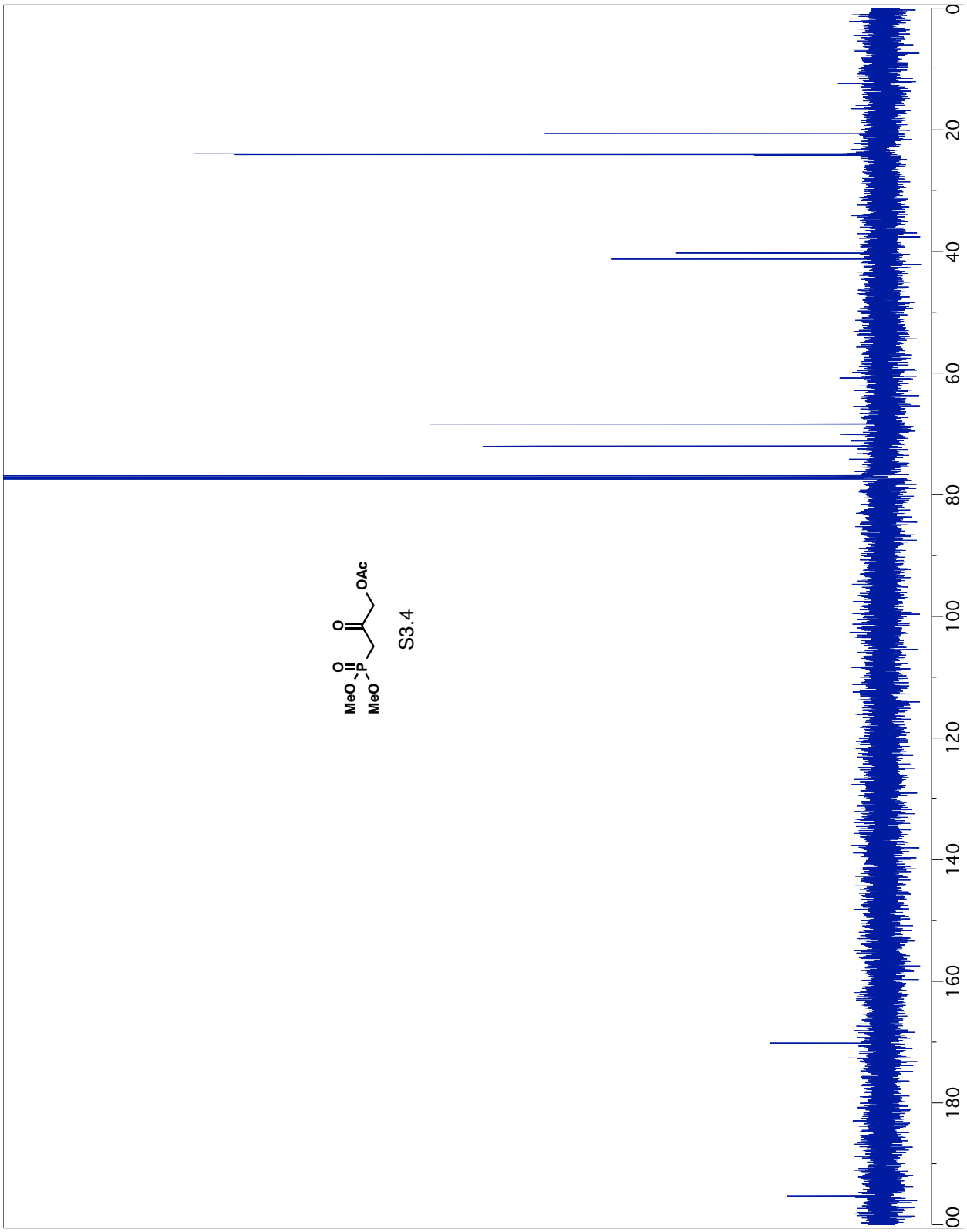
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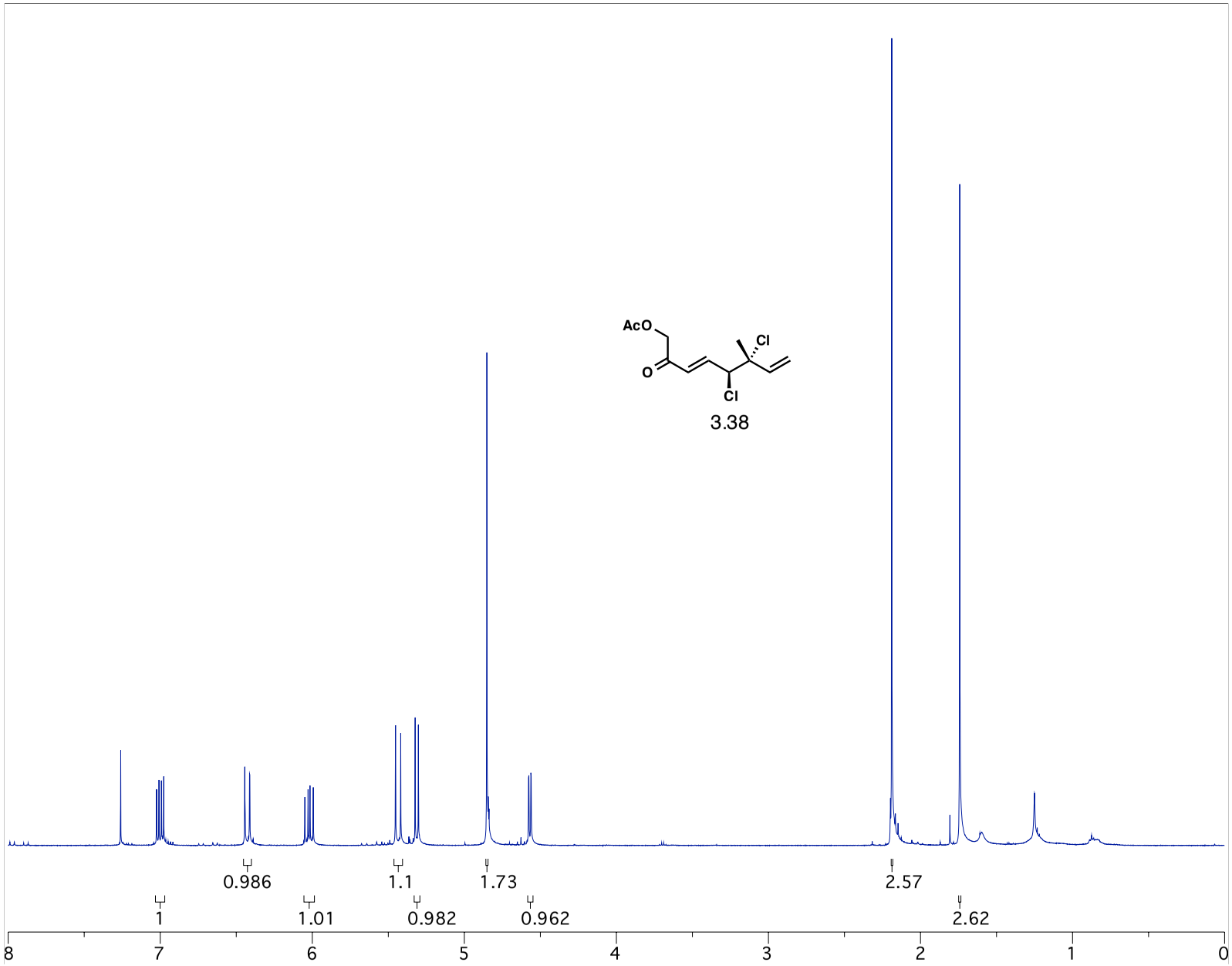
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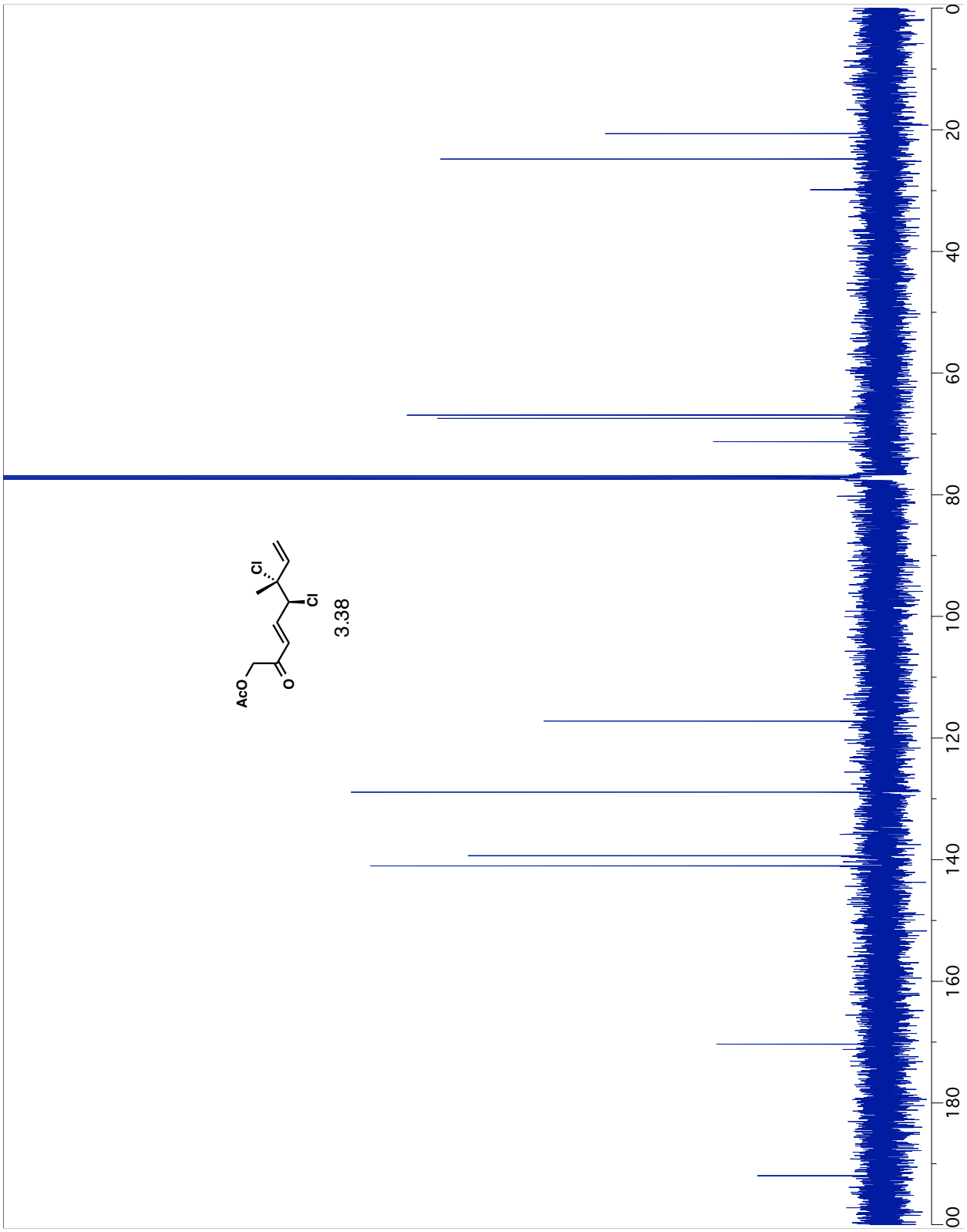
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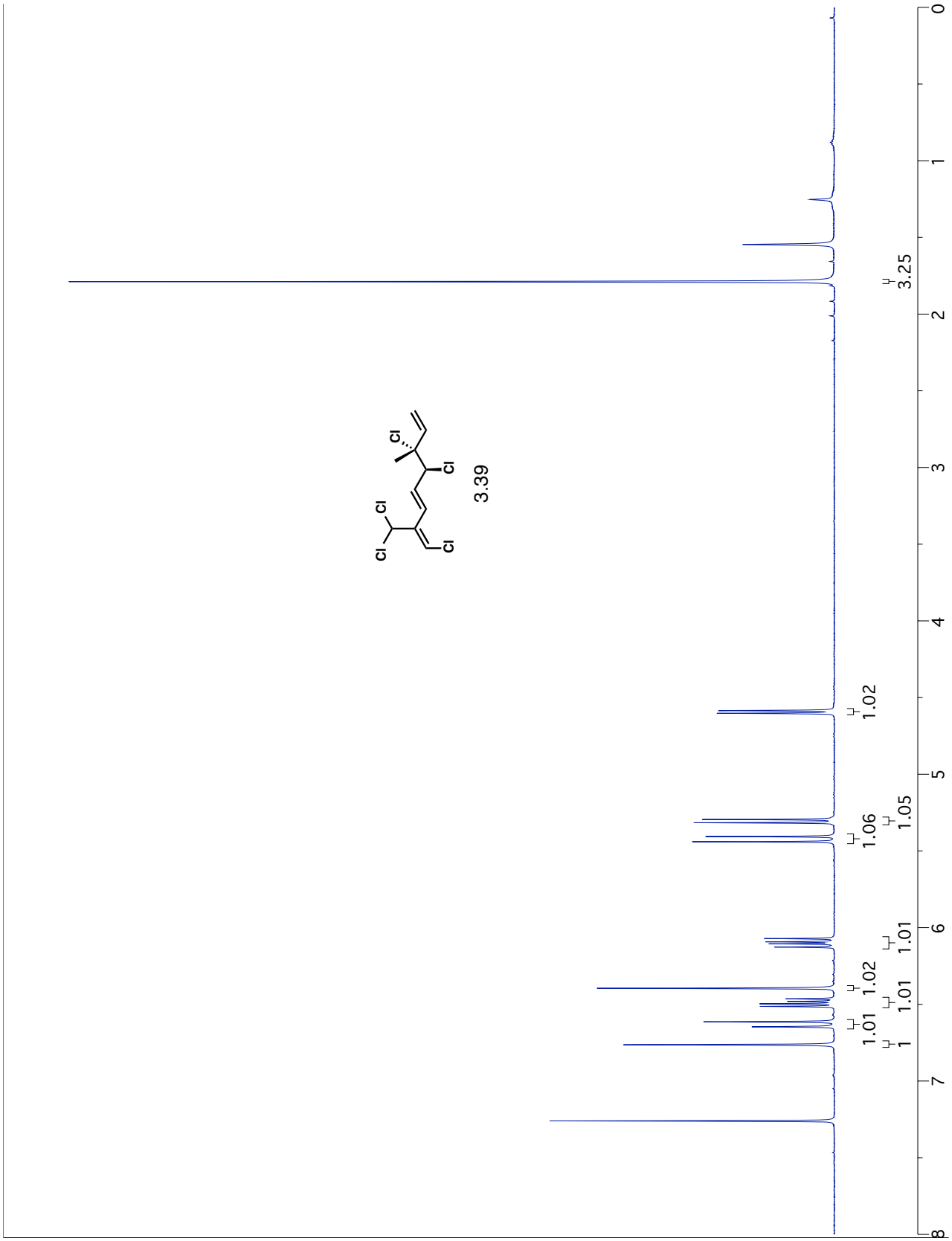
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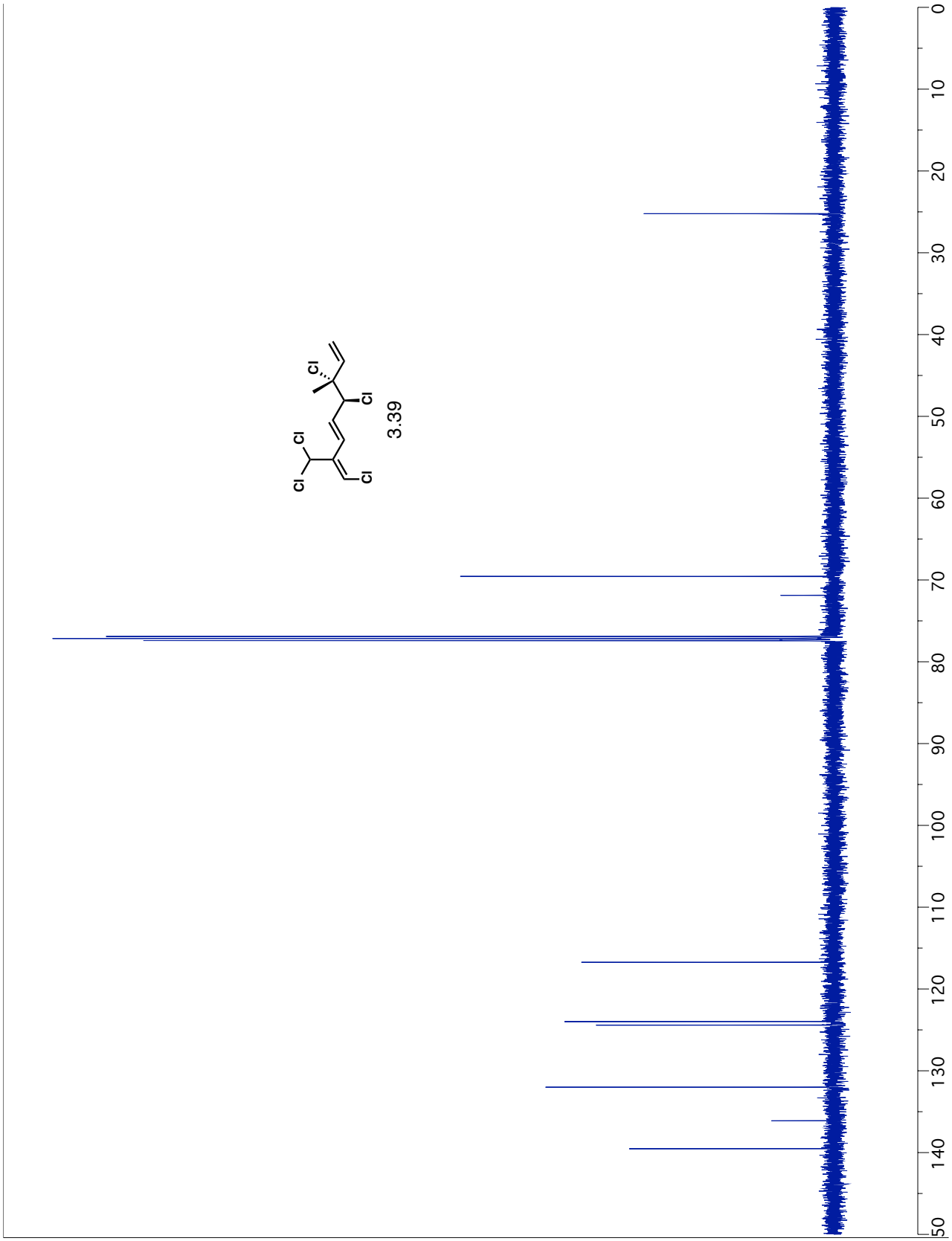
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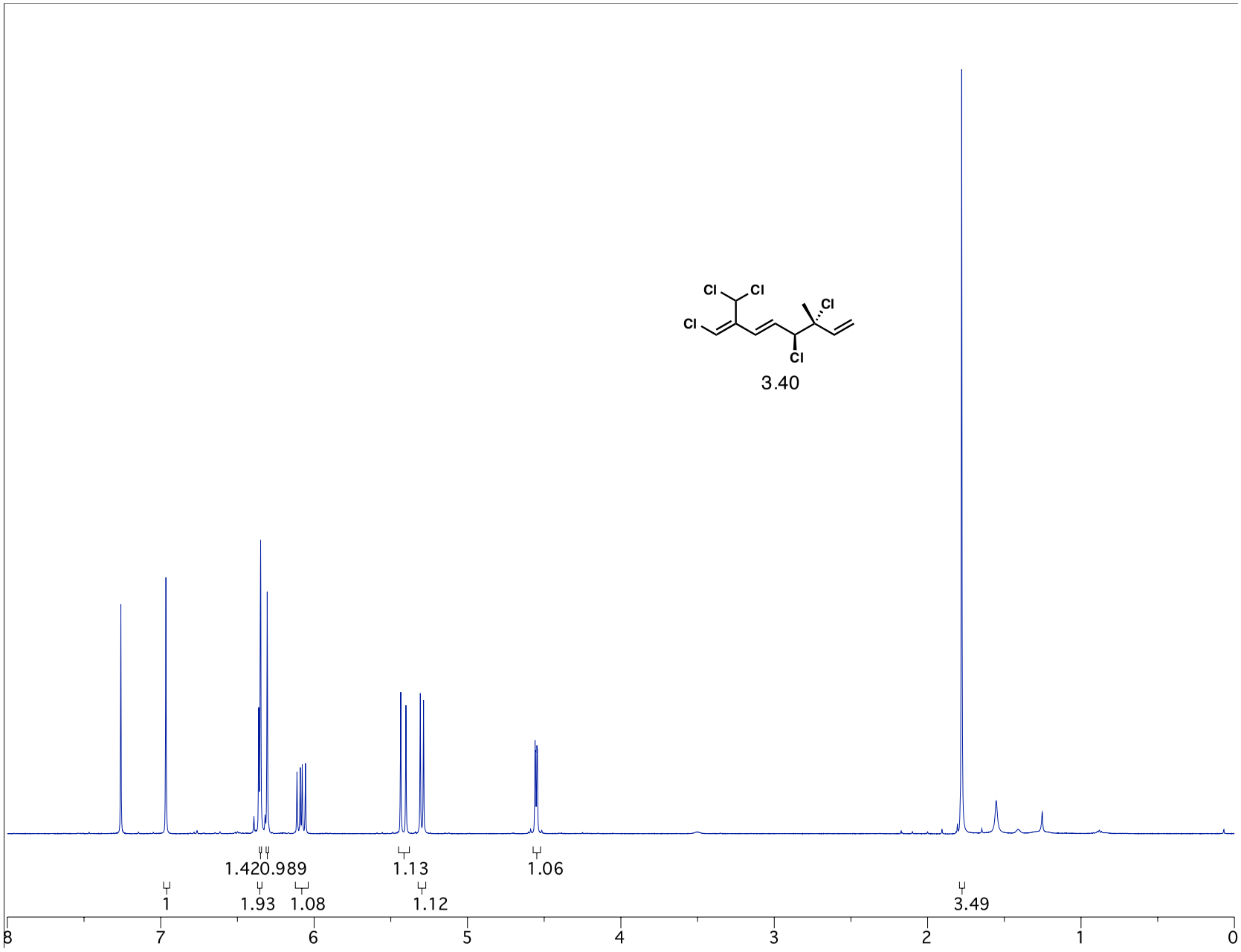
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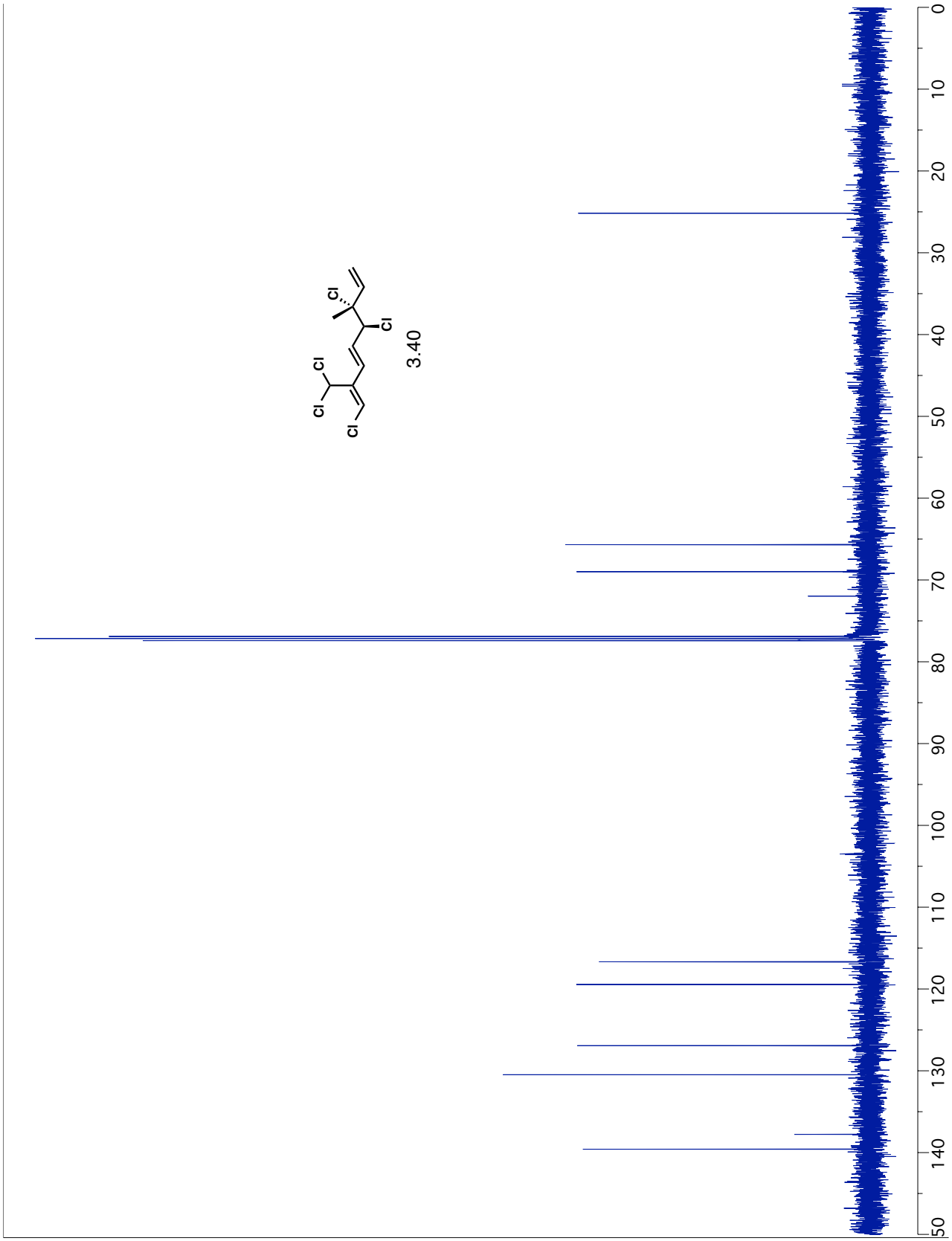
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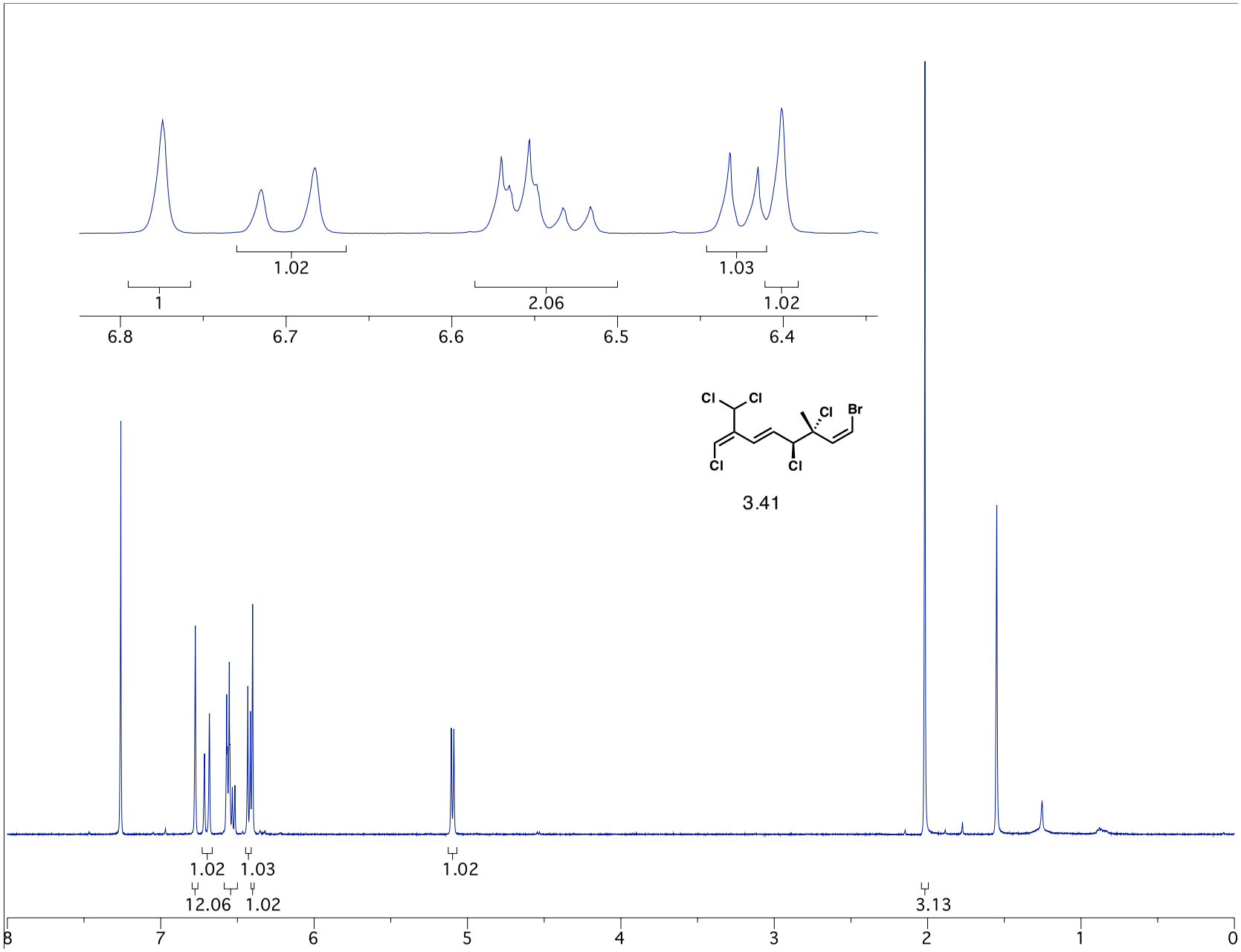
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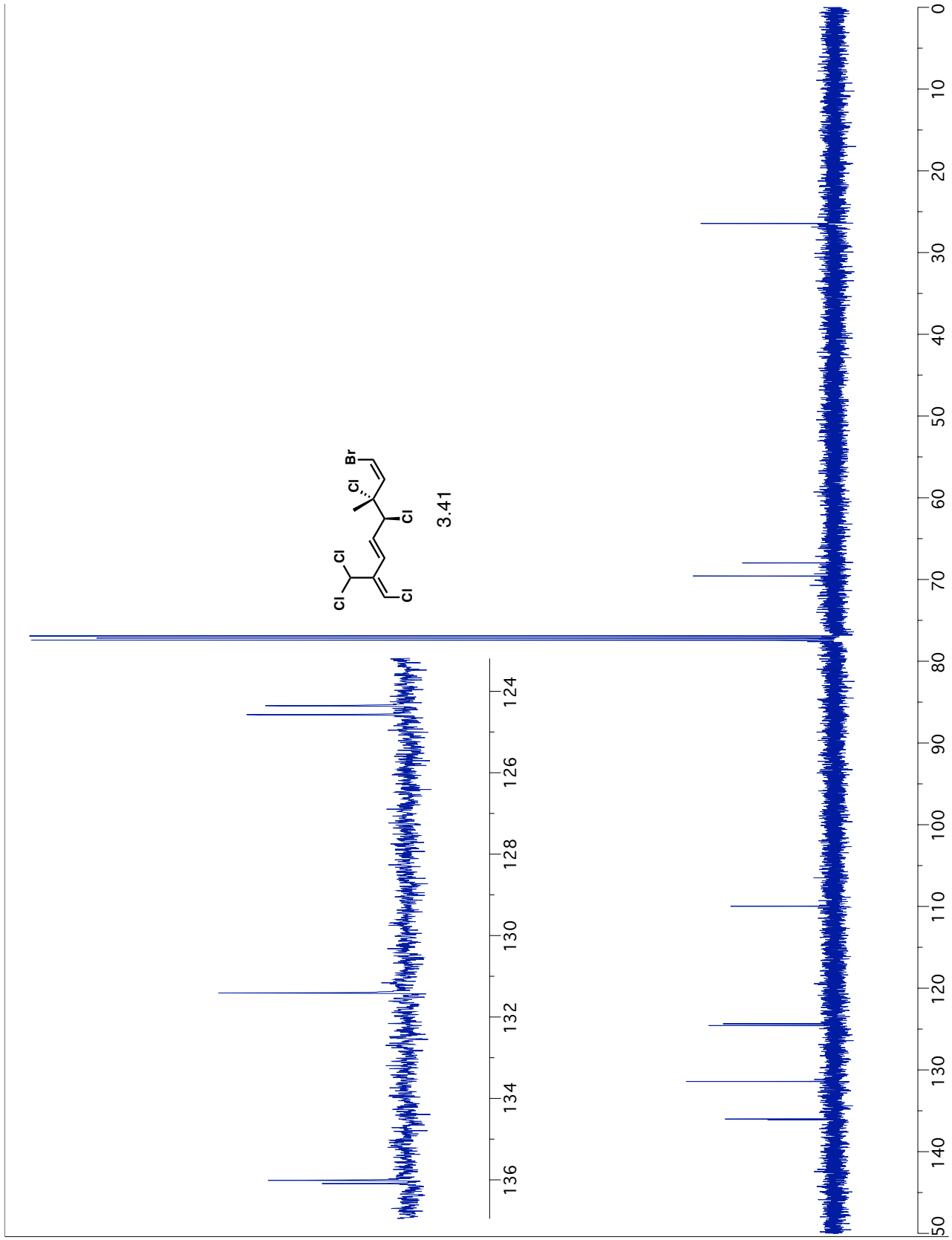
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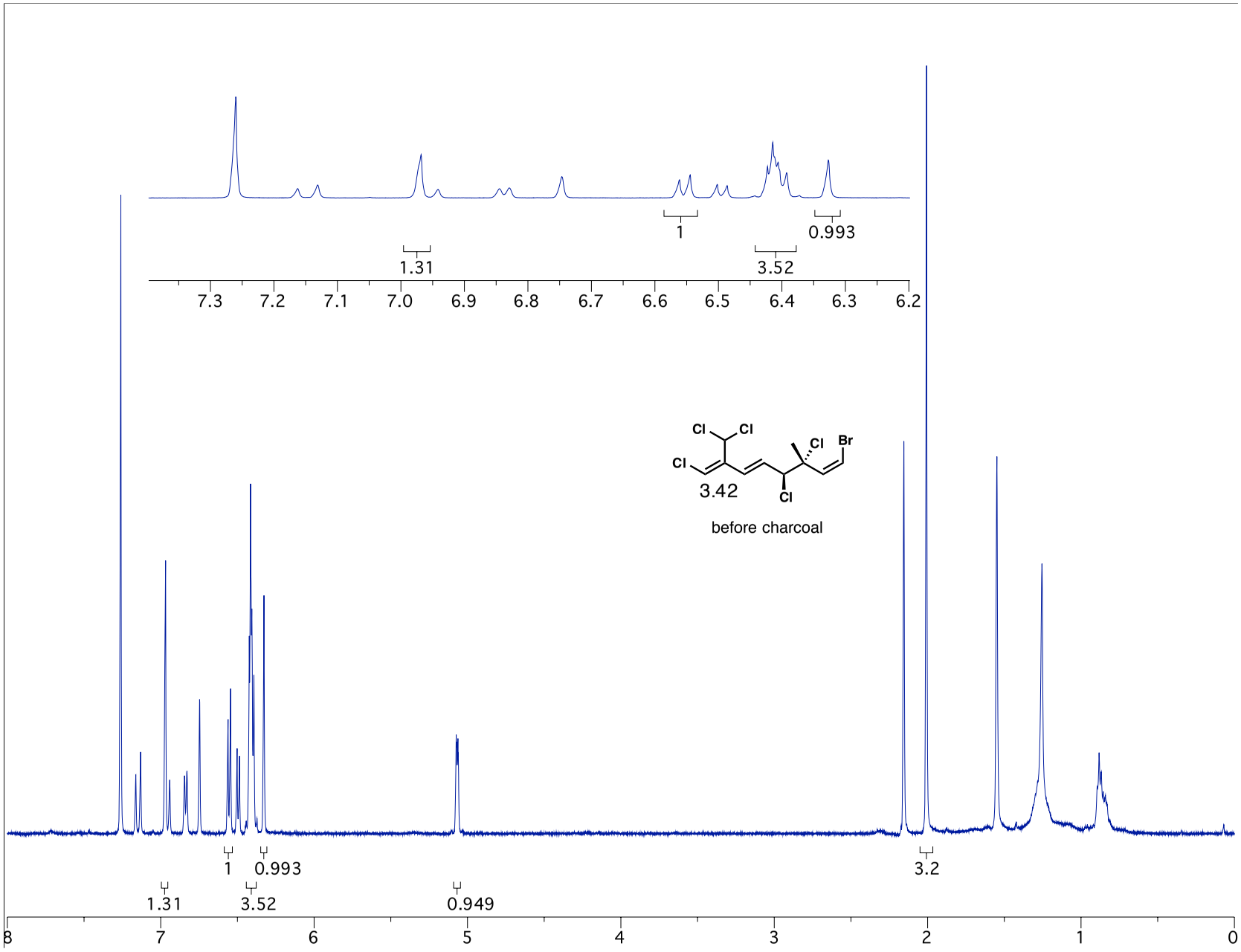
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6.4
6.3
6.2
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Cl
Cl
Cl
Br
3.42
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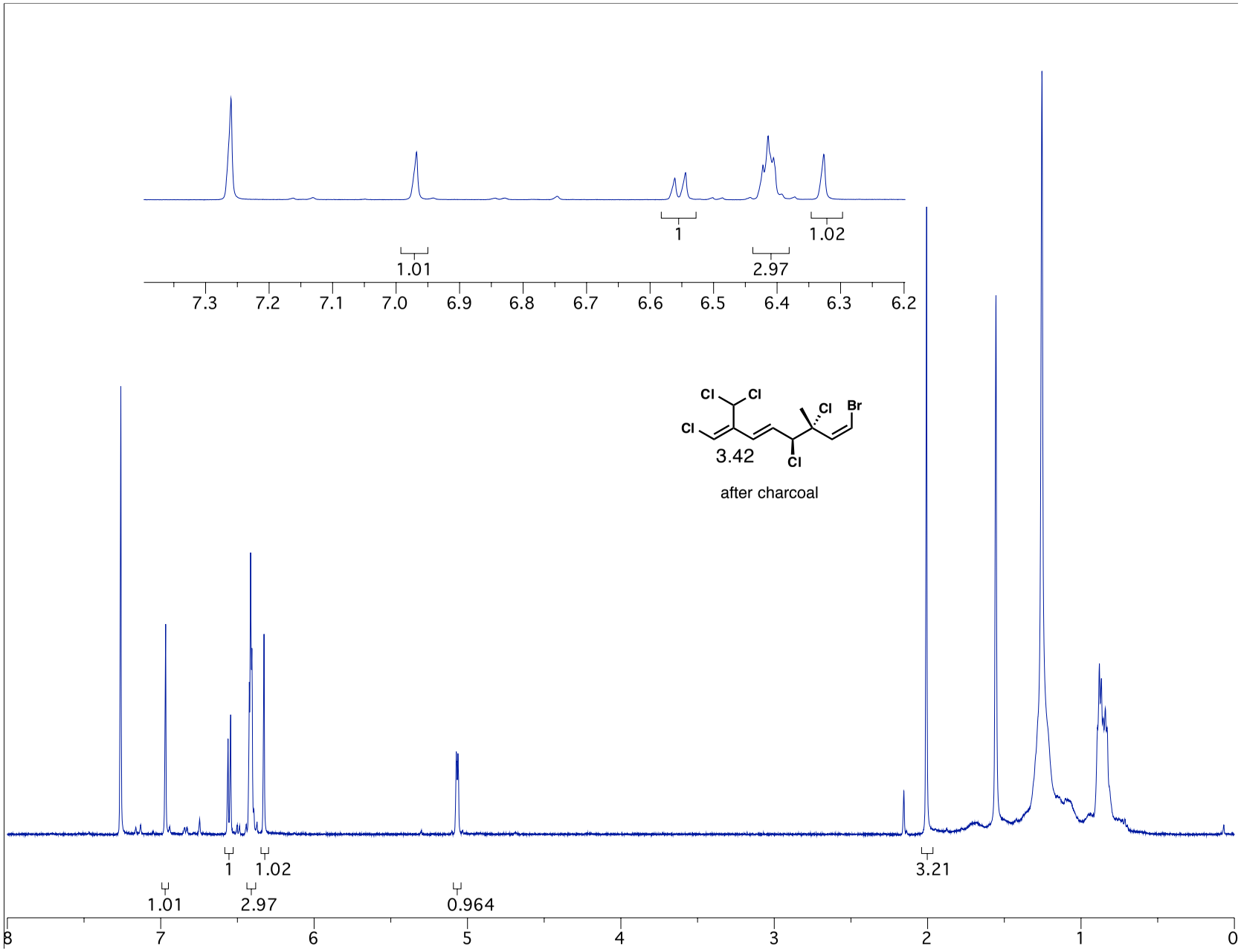
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6.7
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6.5
6.4
6.3
6.2
Cl
Cl
Cl
Br
Cl
3.42
Cl
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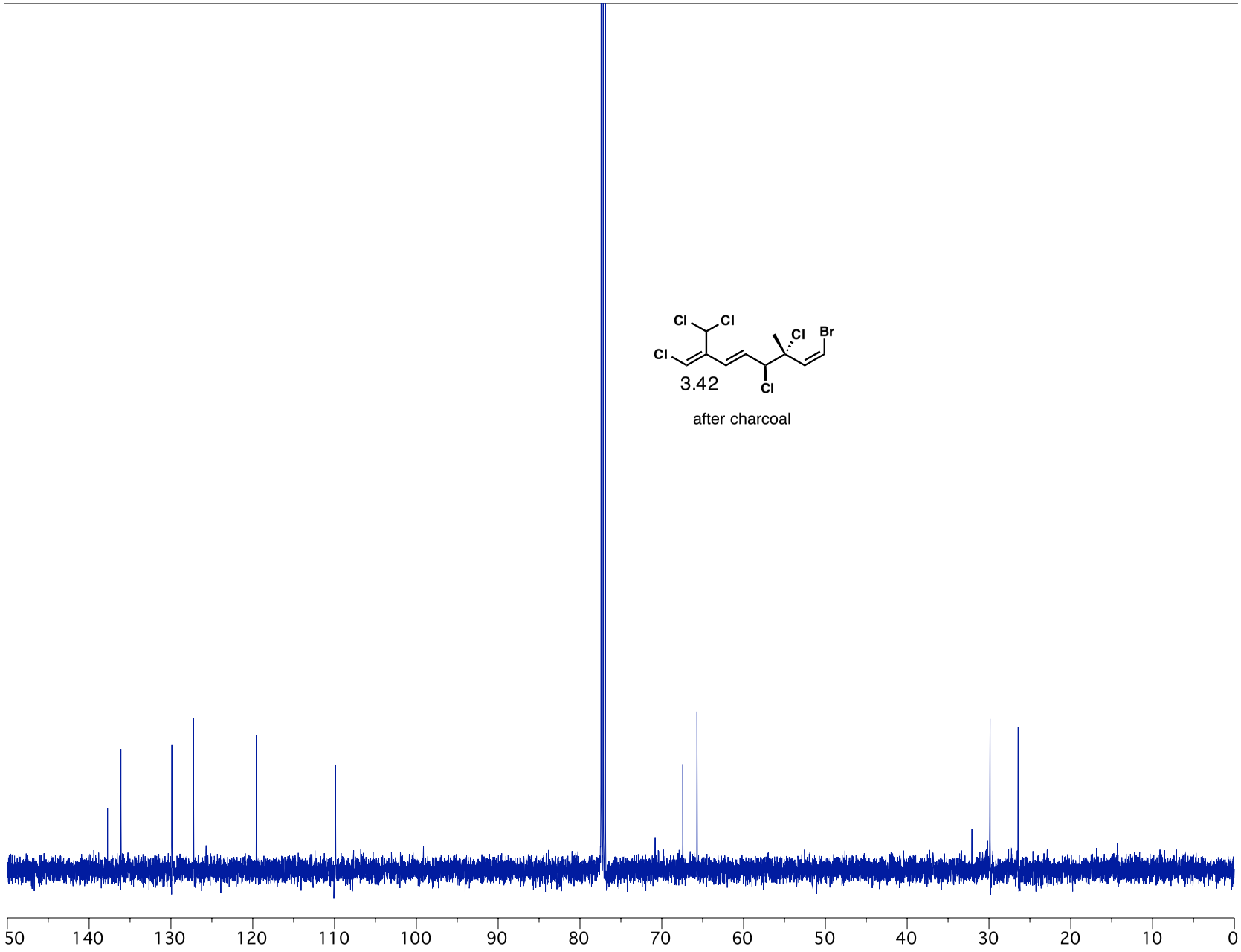
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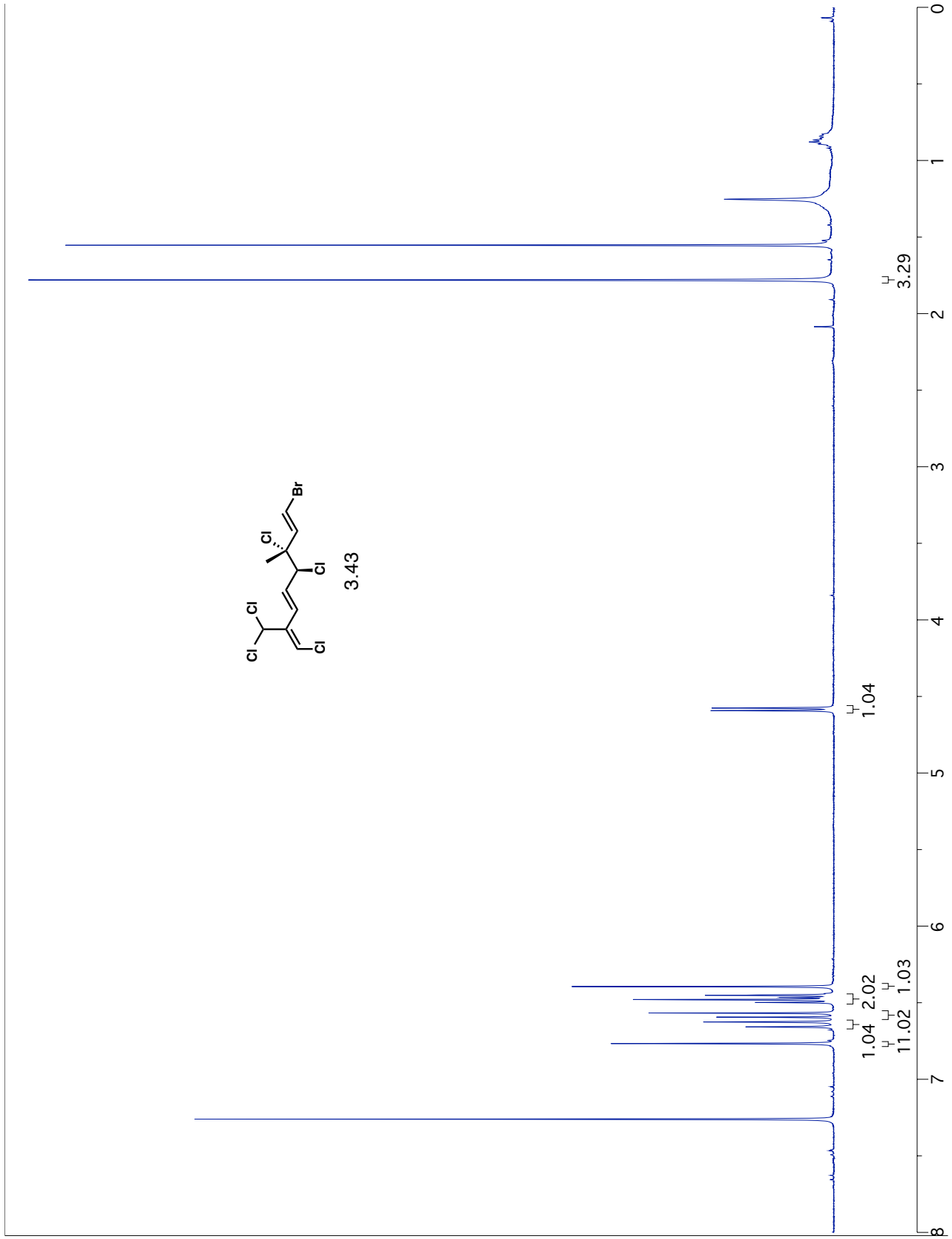
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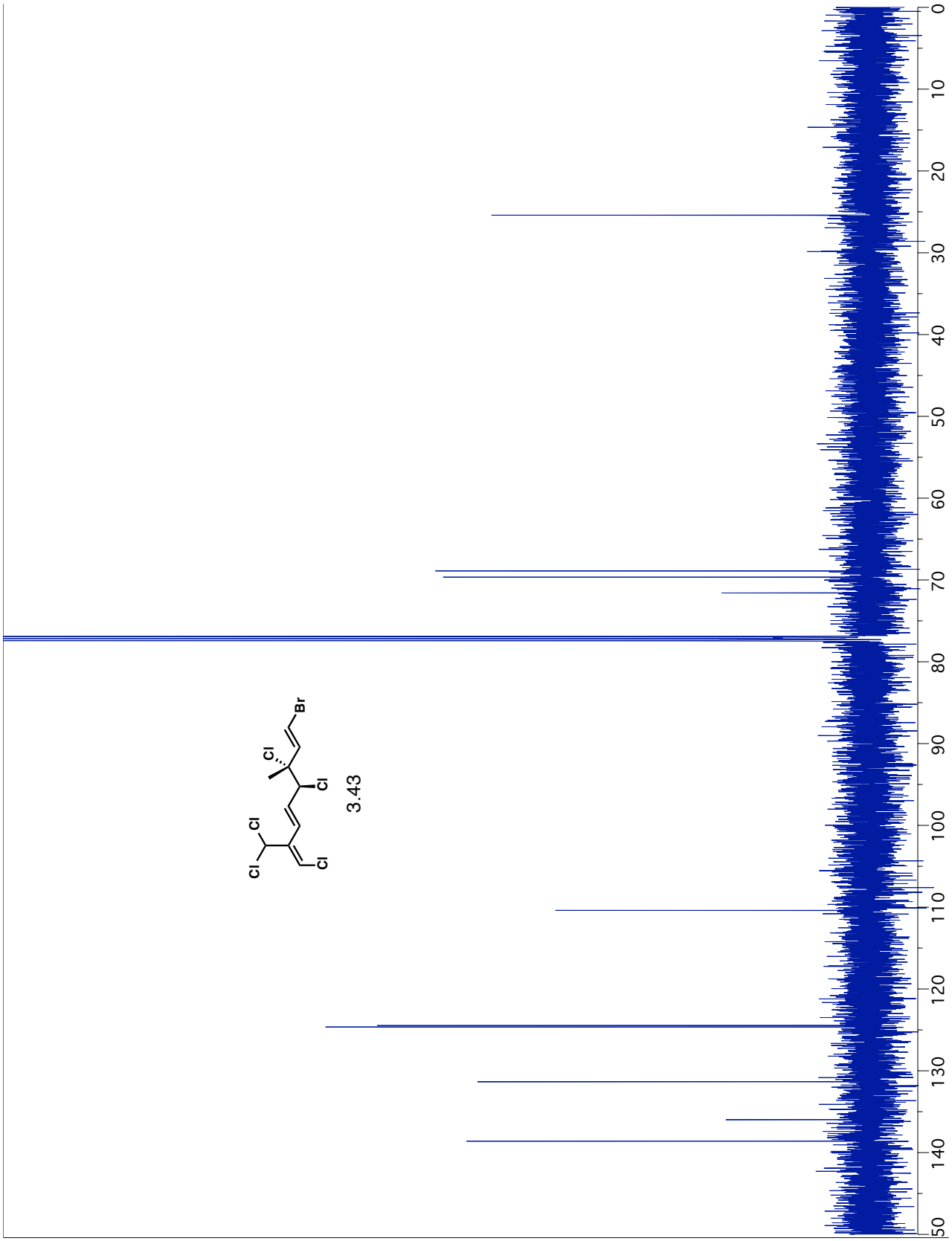
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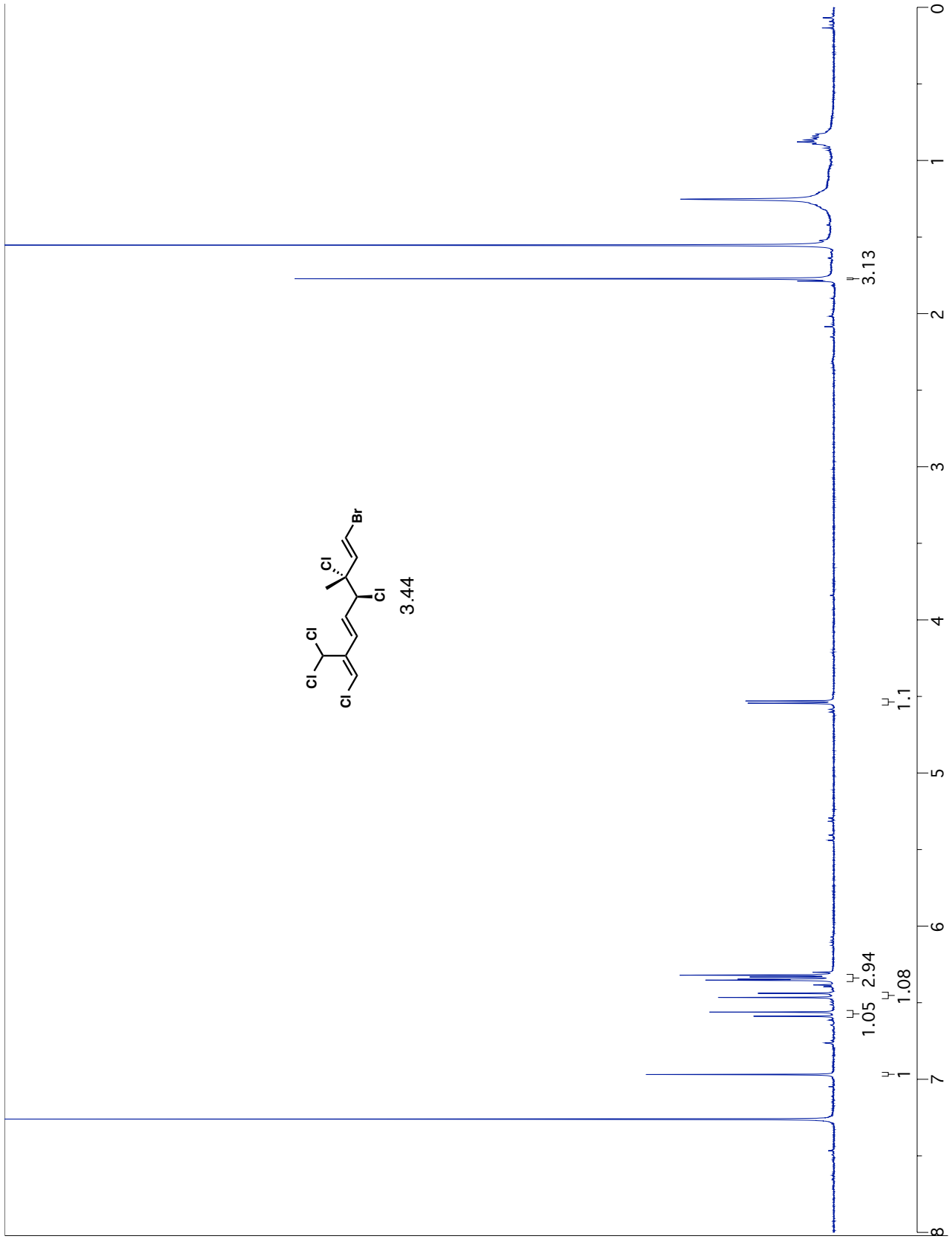
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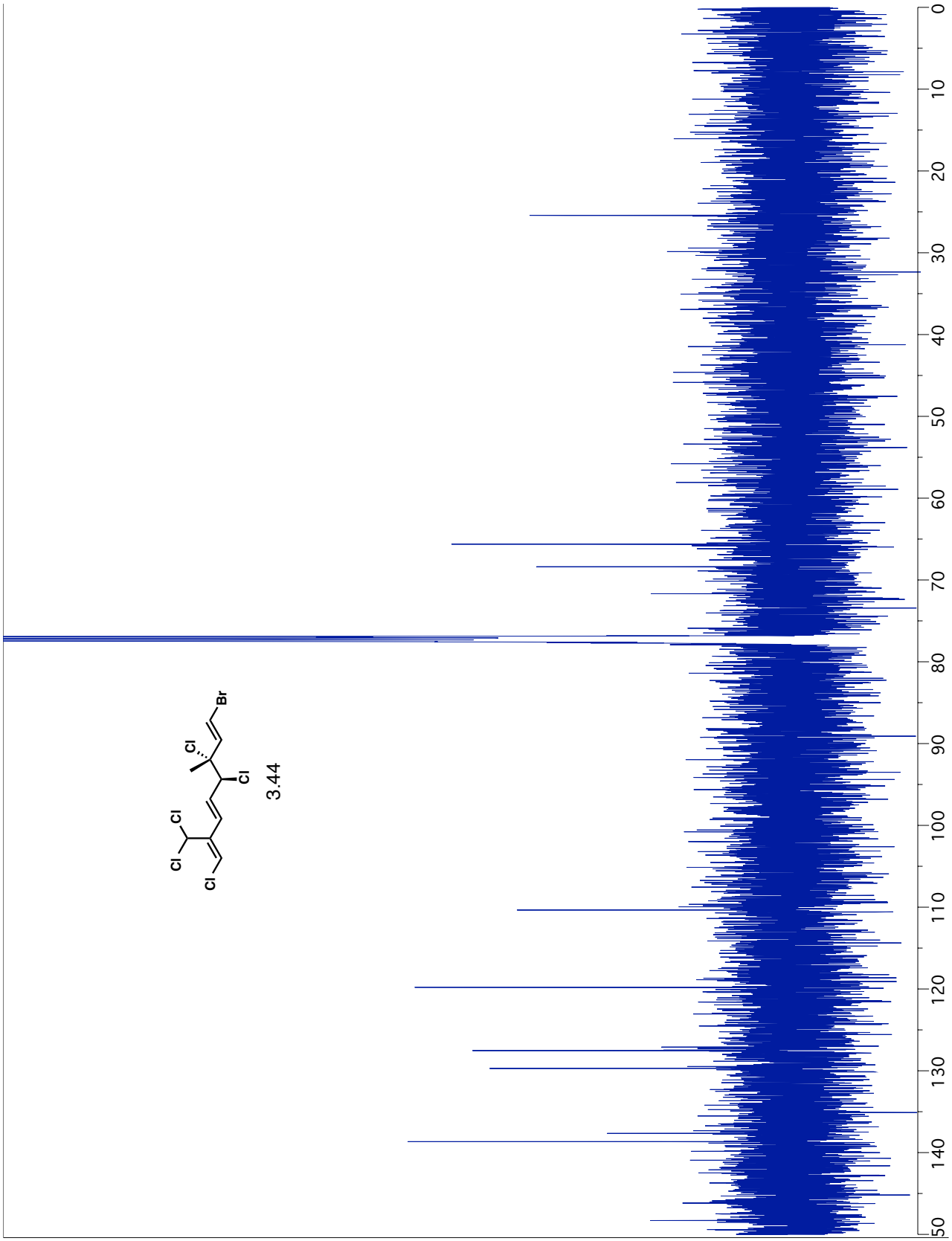
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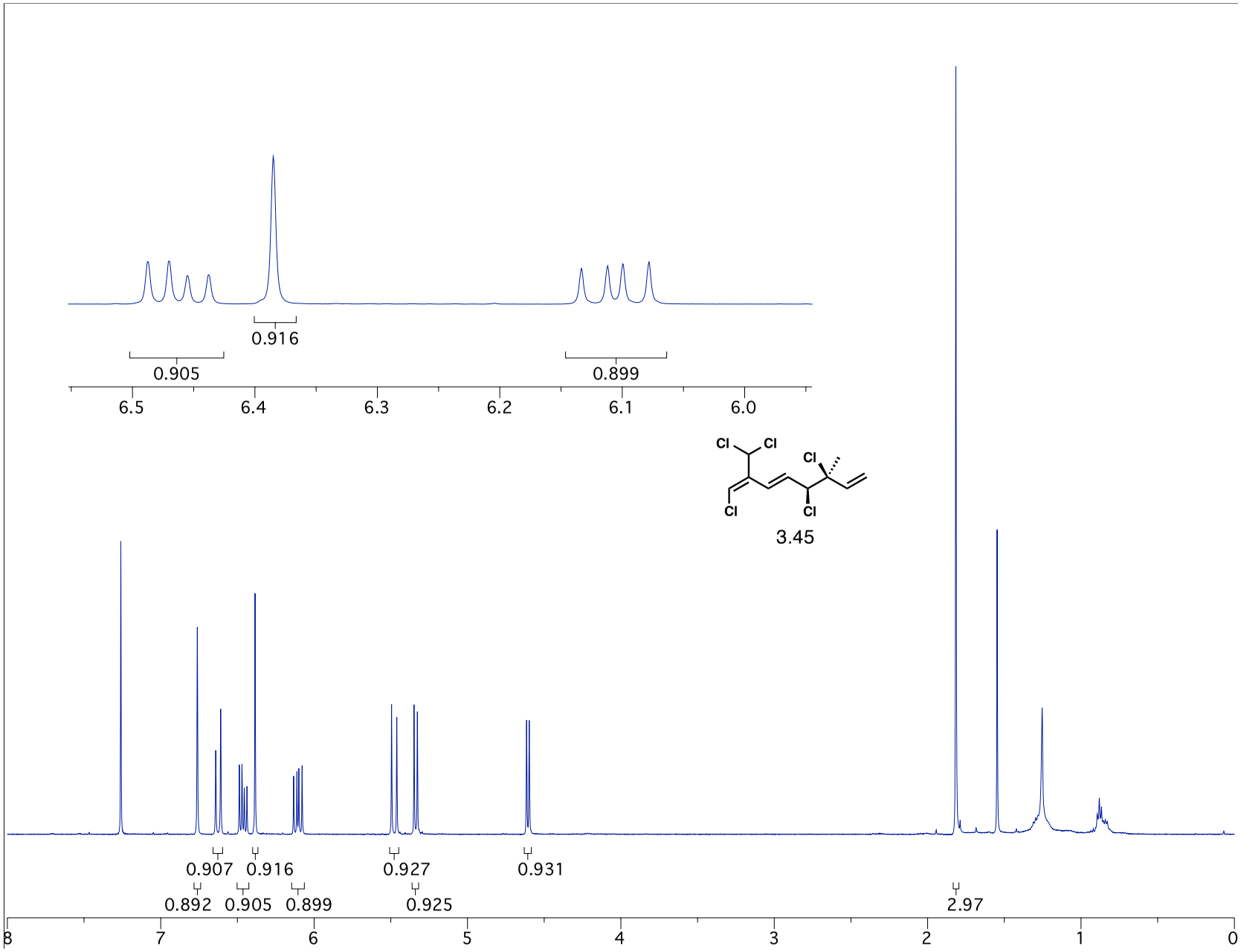
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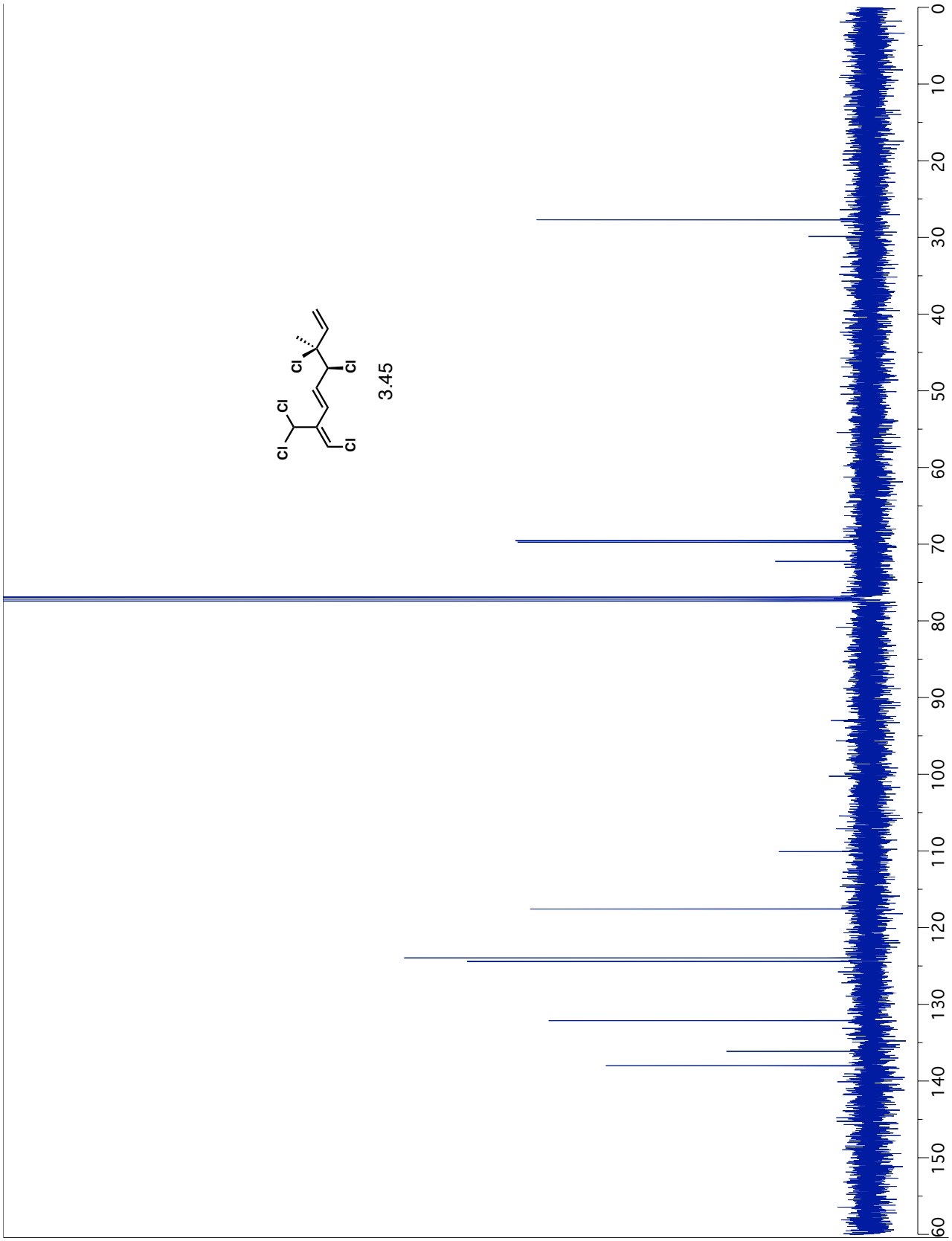
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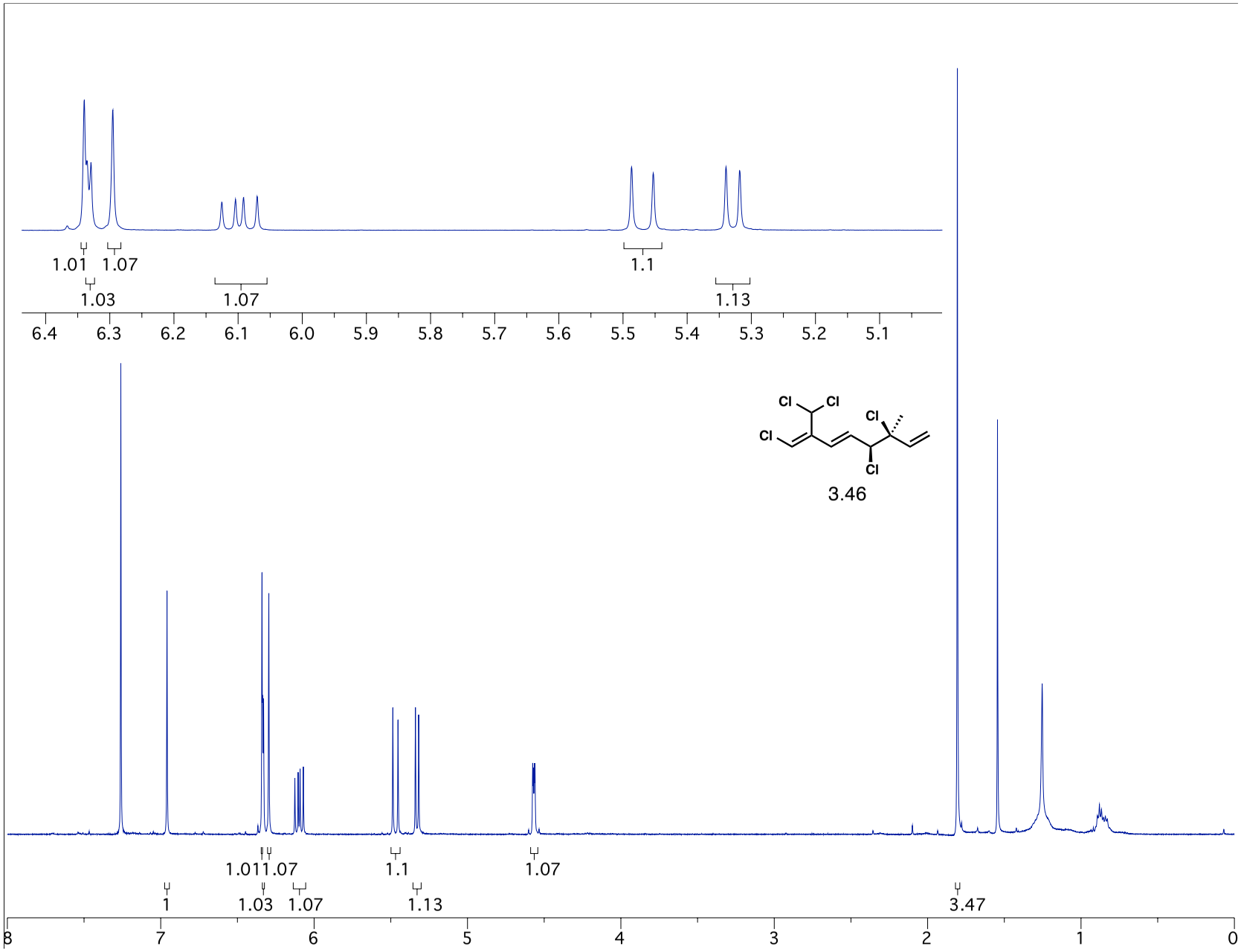
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5.3
5.2
5.1
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Cl
Cl
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1.07
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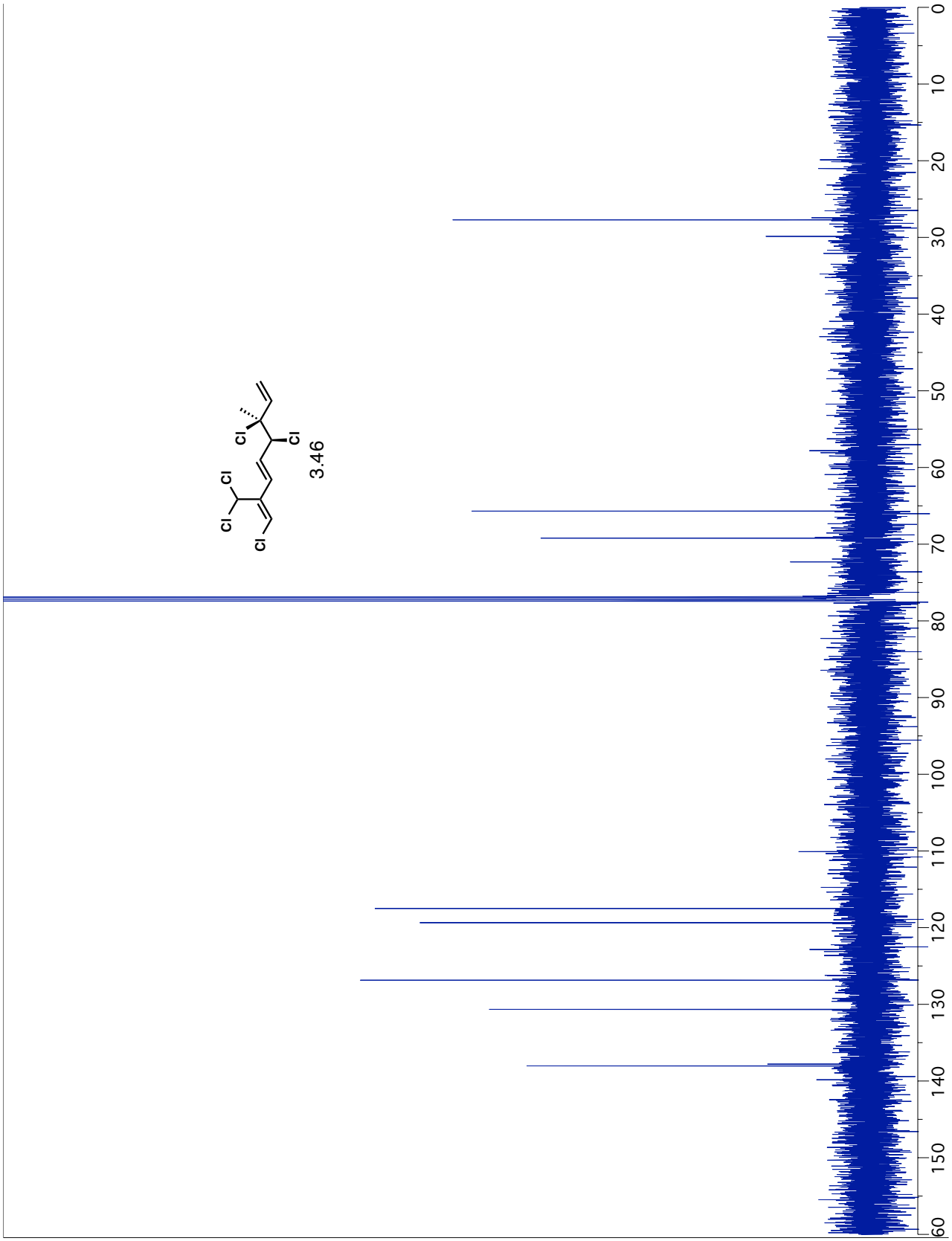
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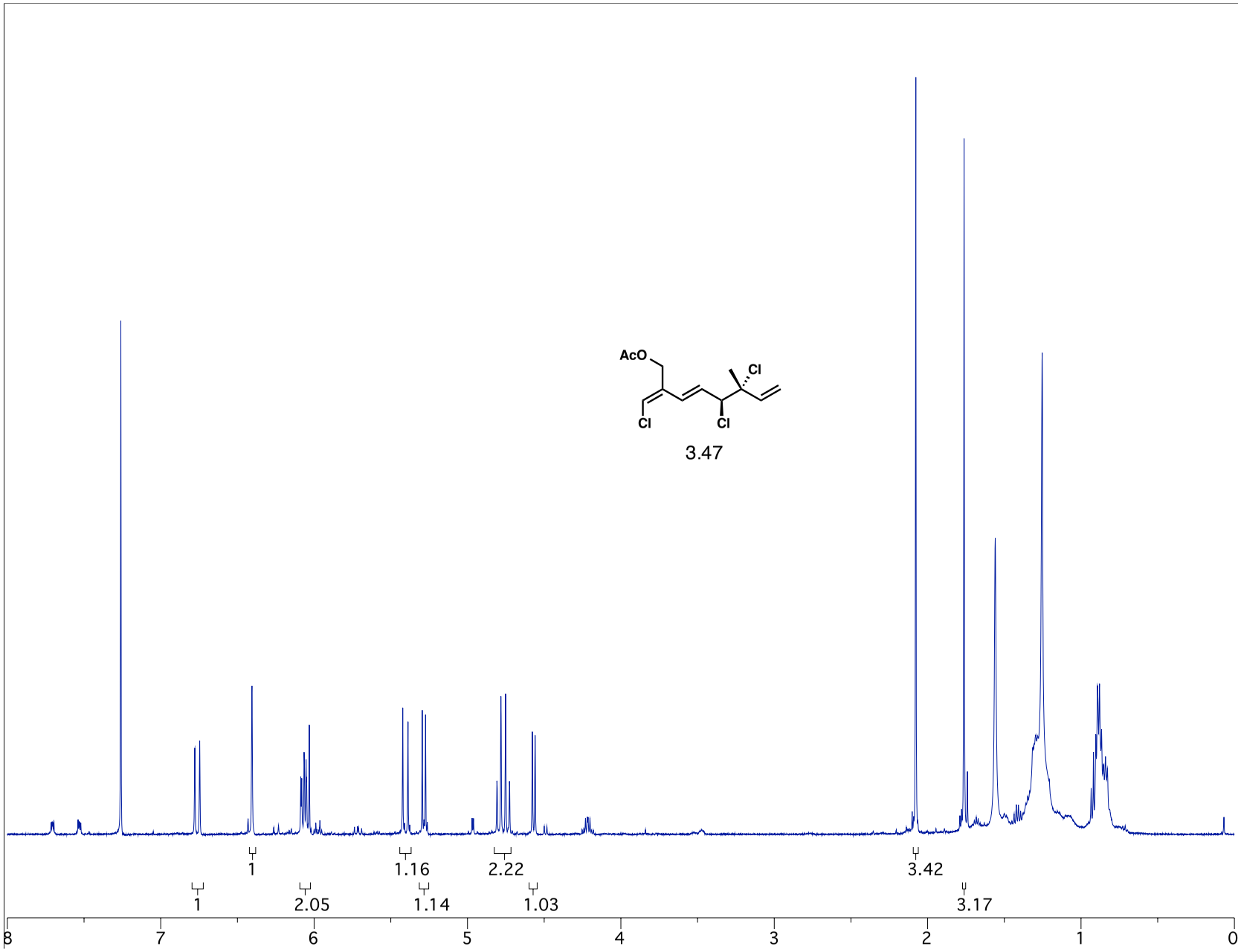
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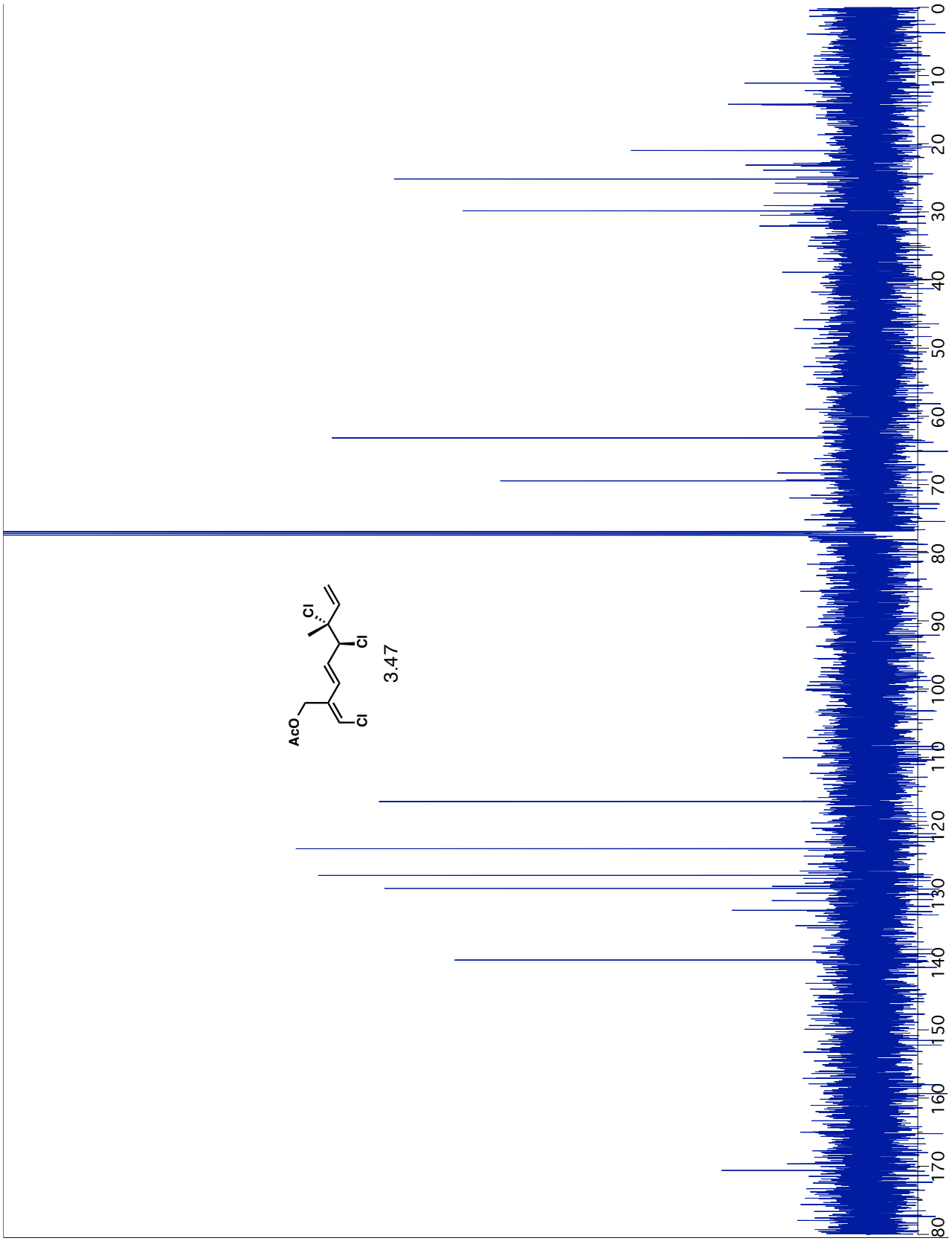
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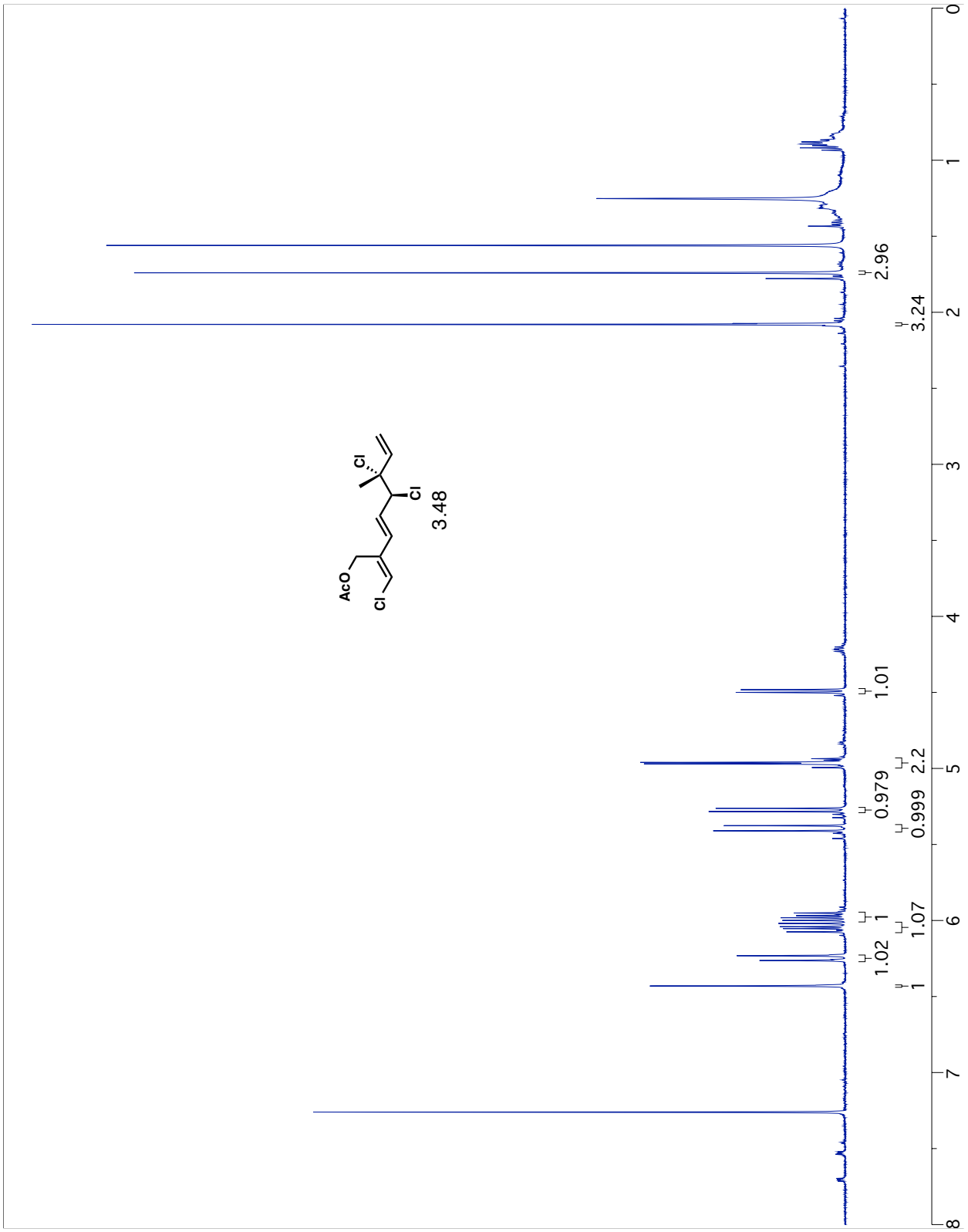
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6
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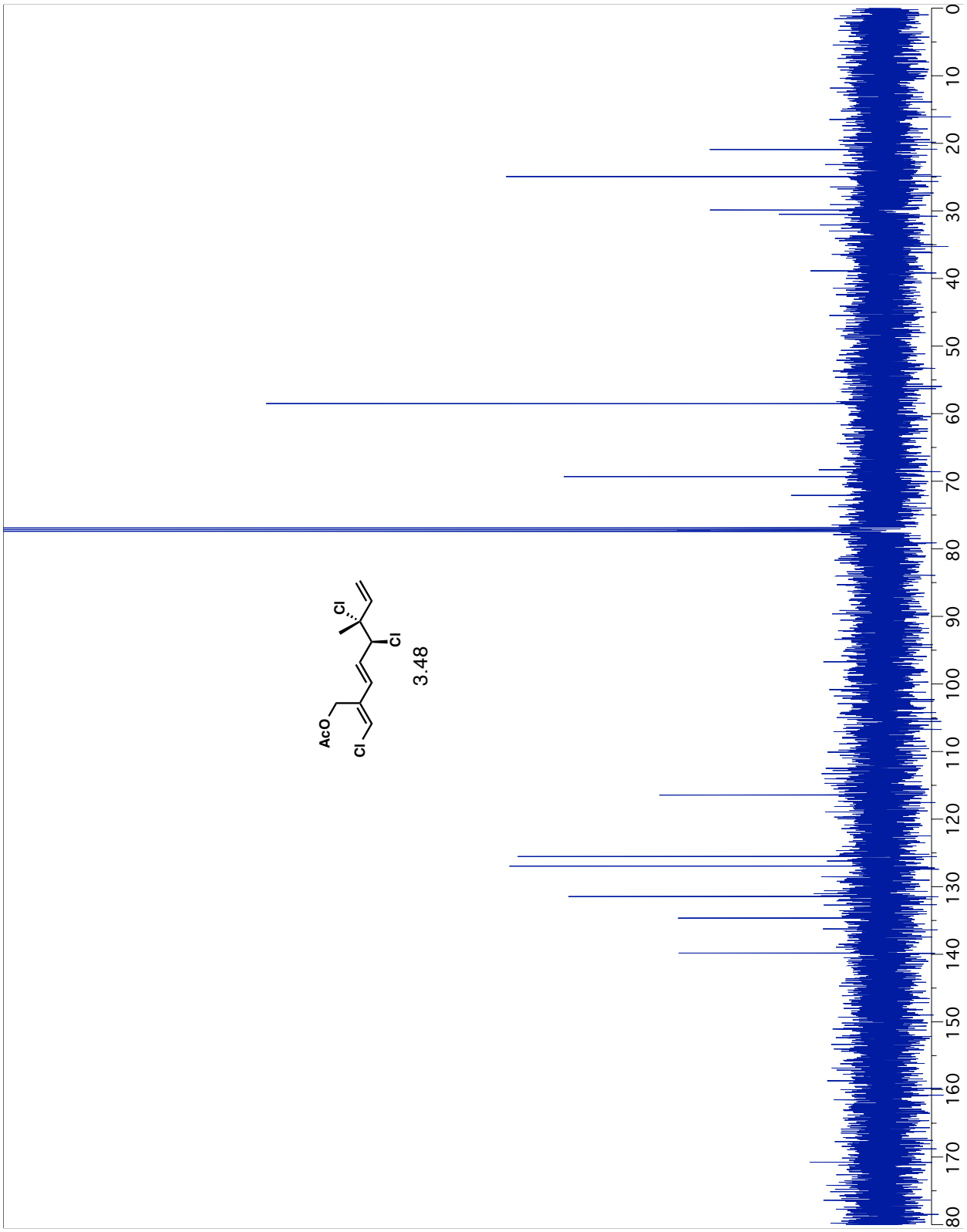
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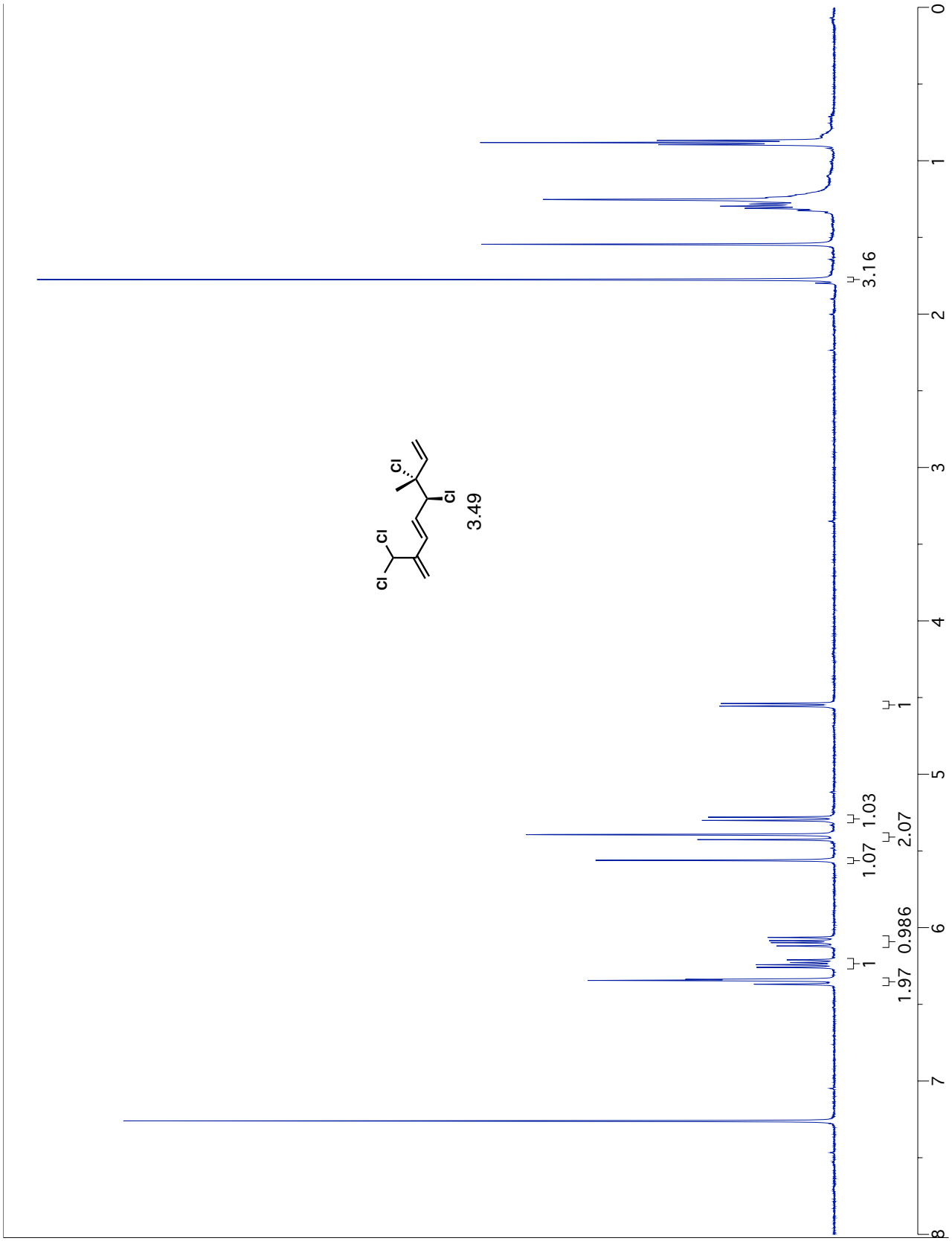
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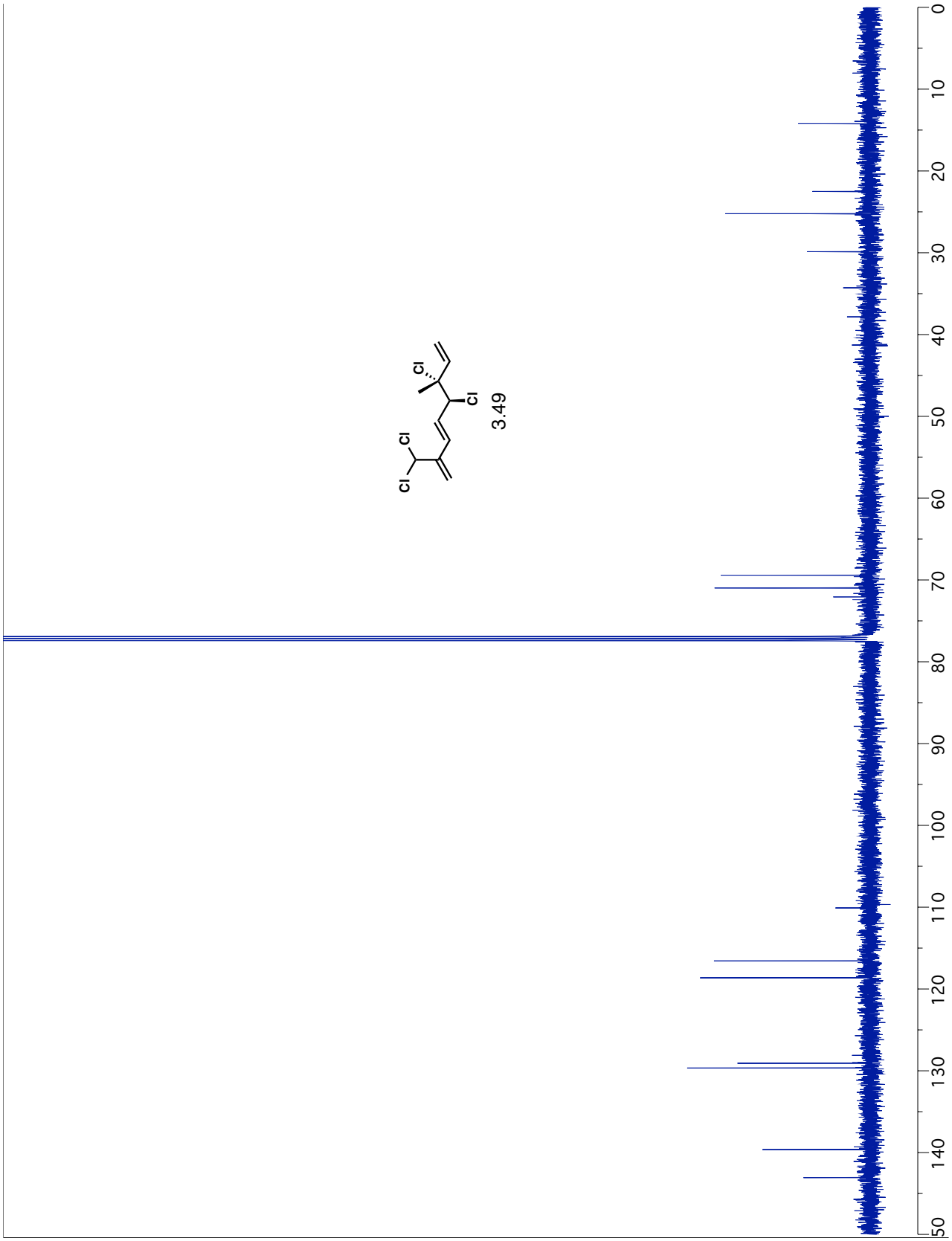
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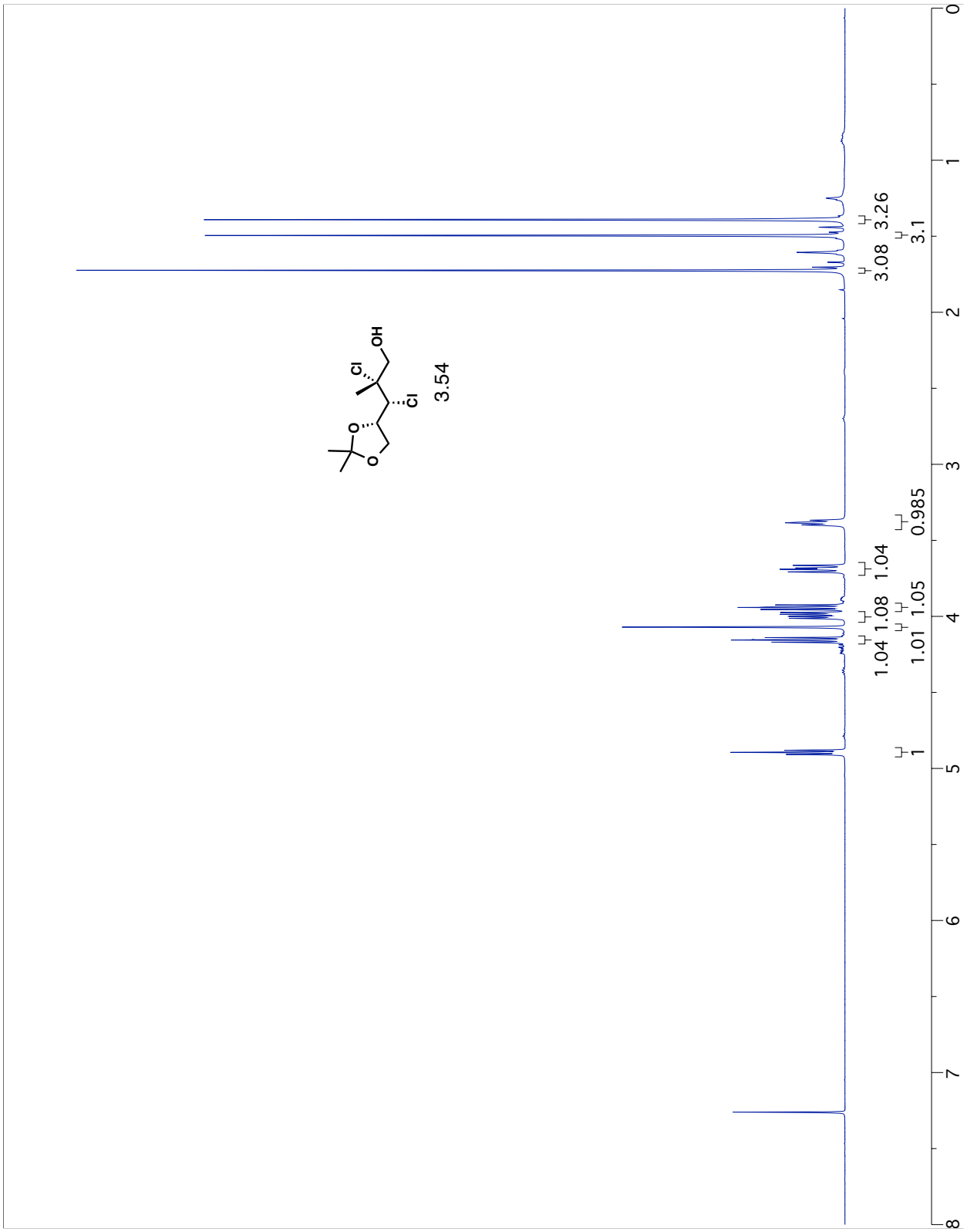
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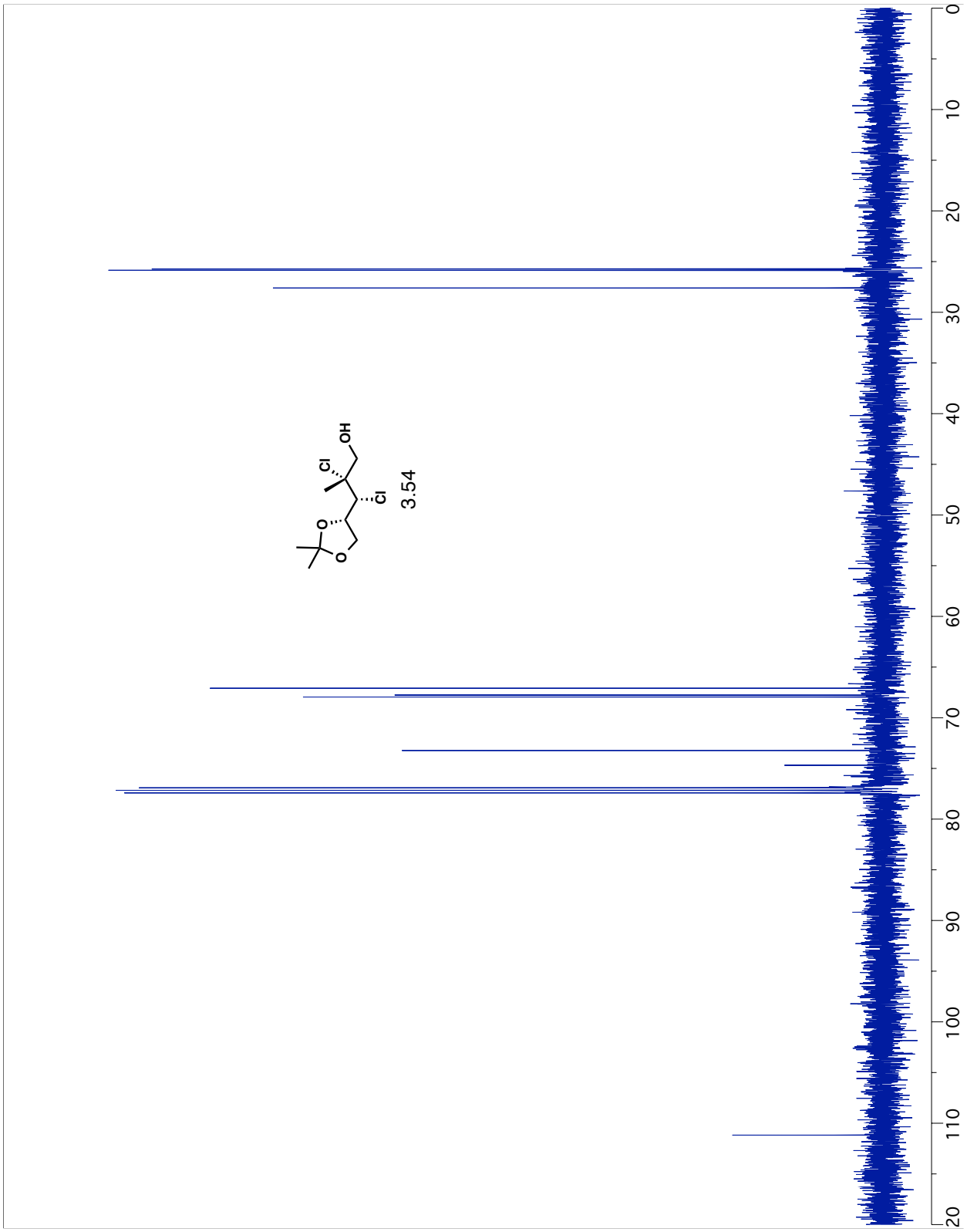
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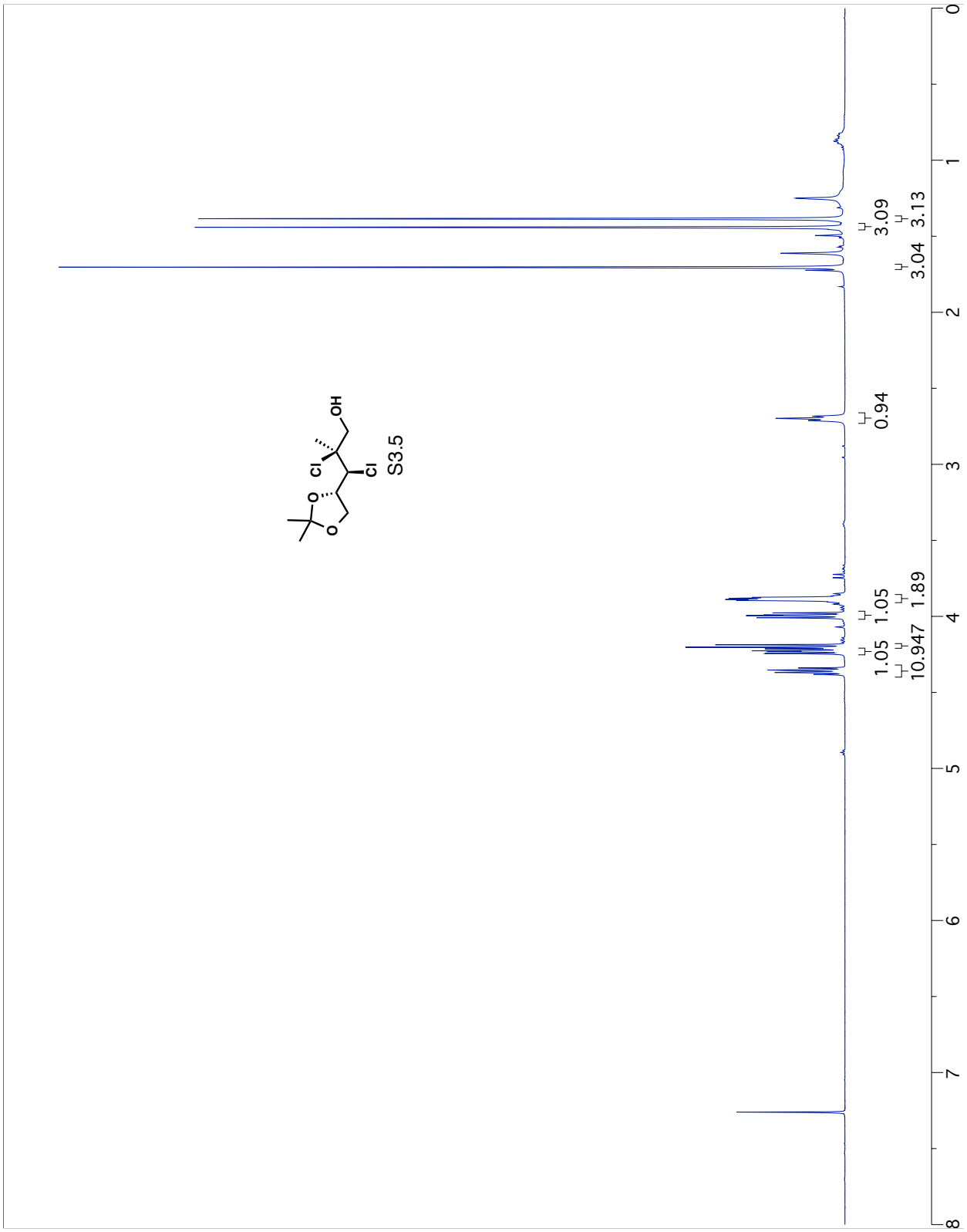
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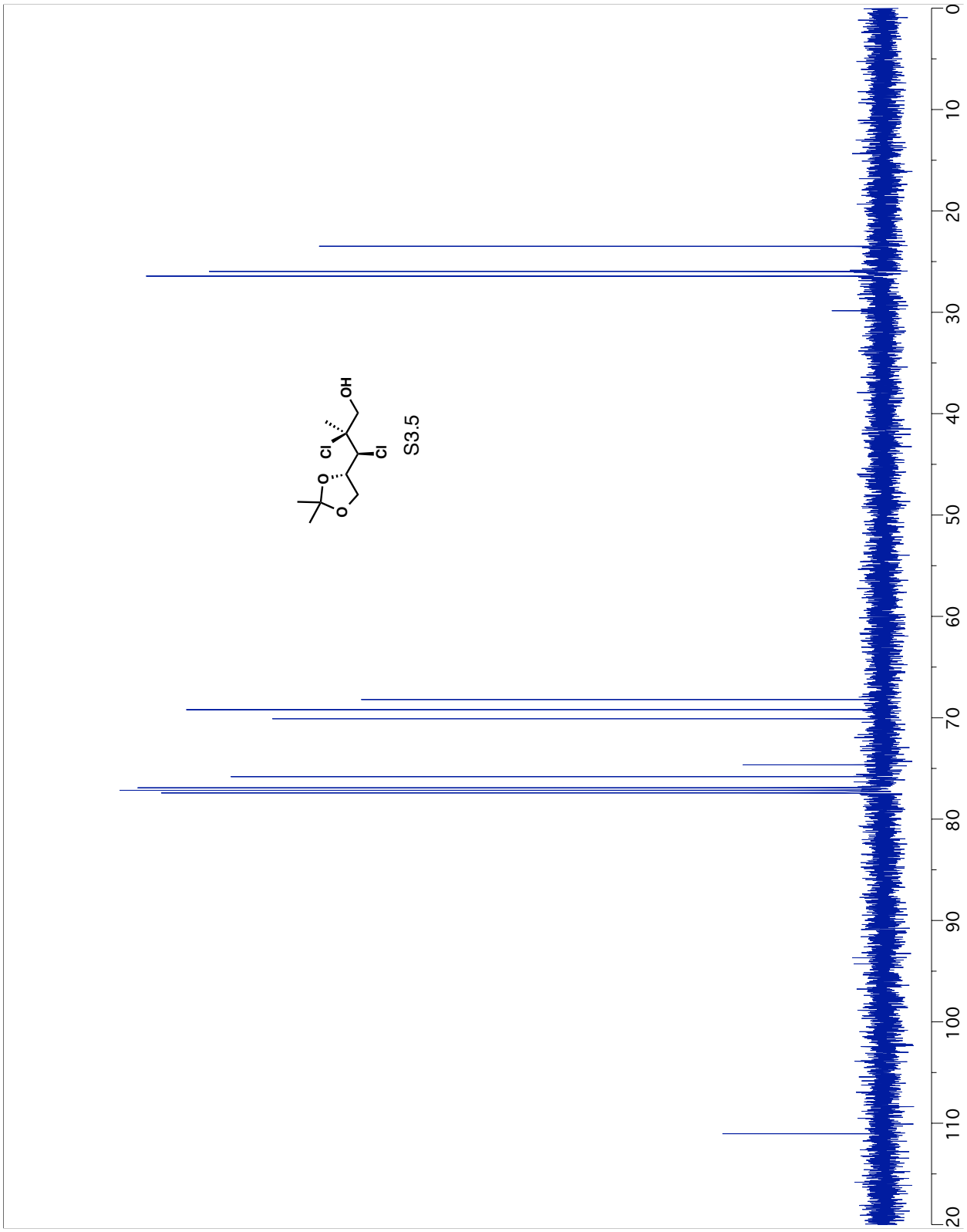
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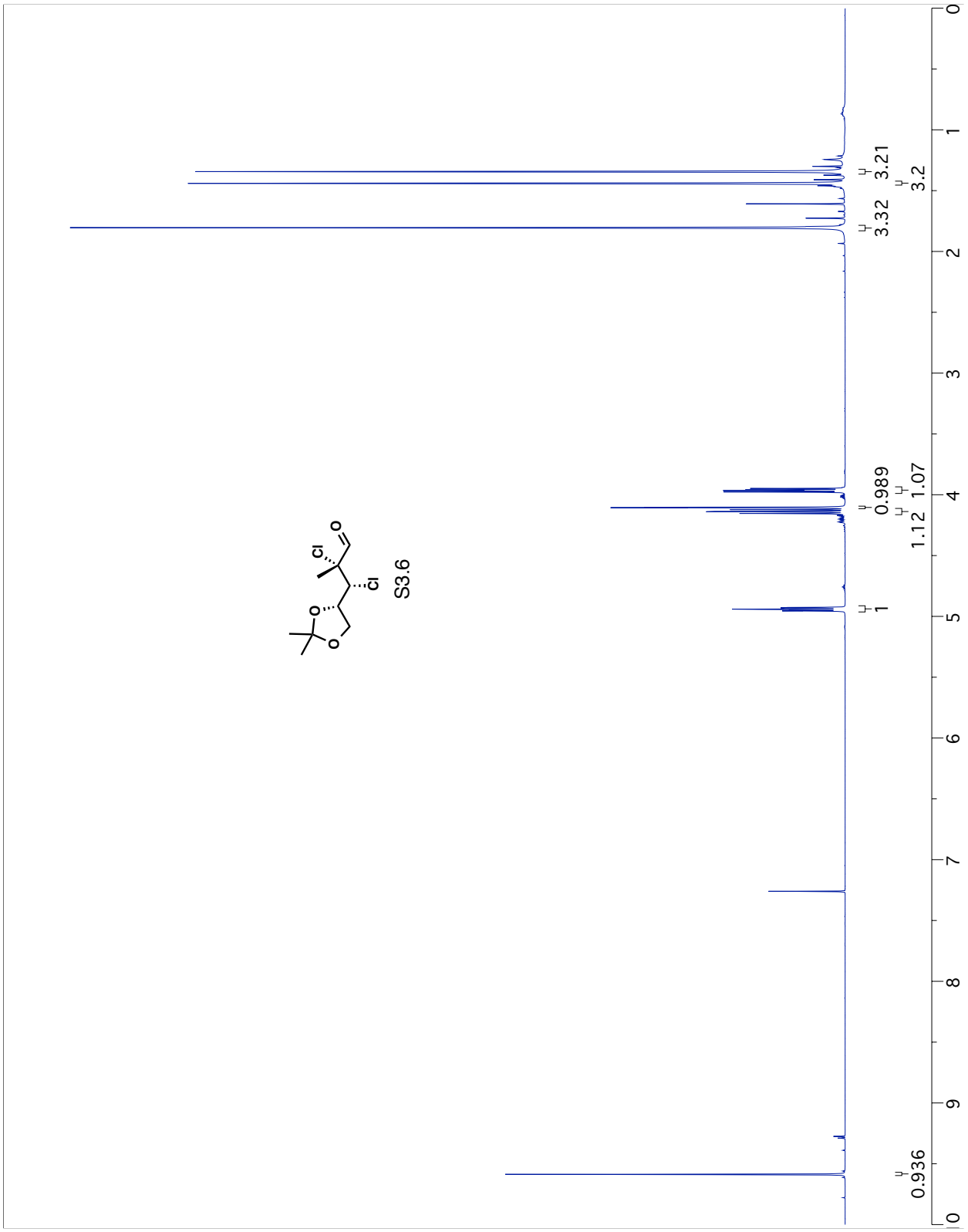
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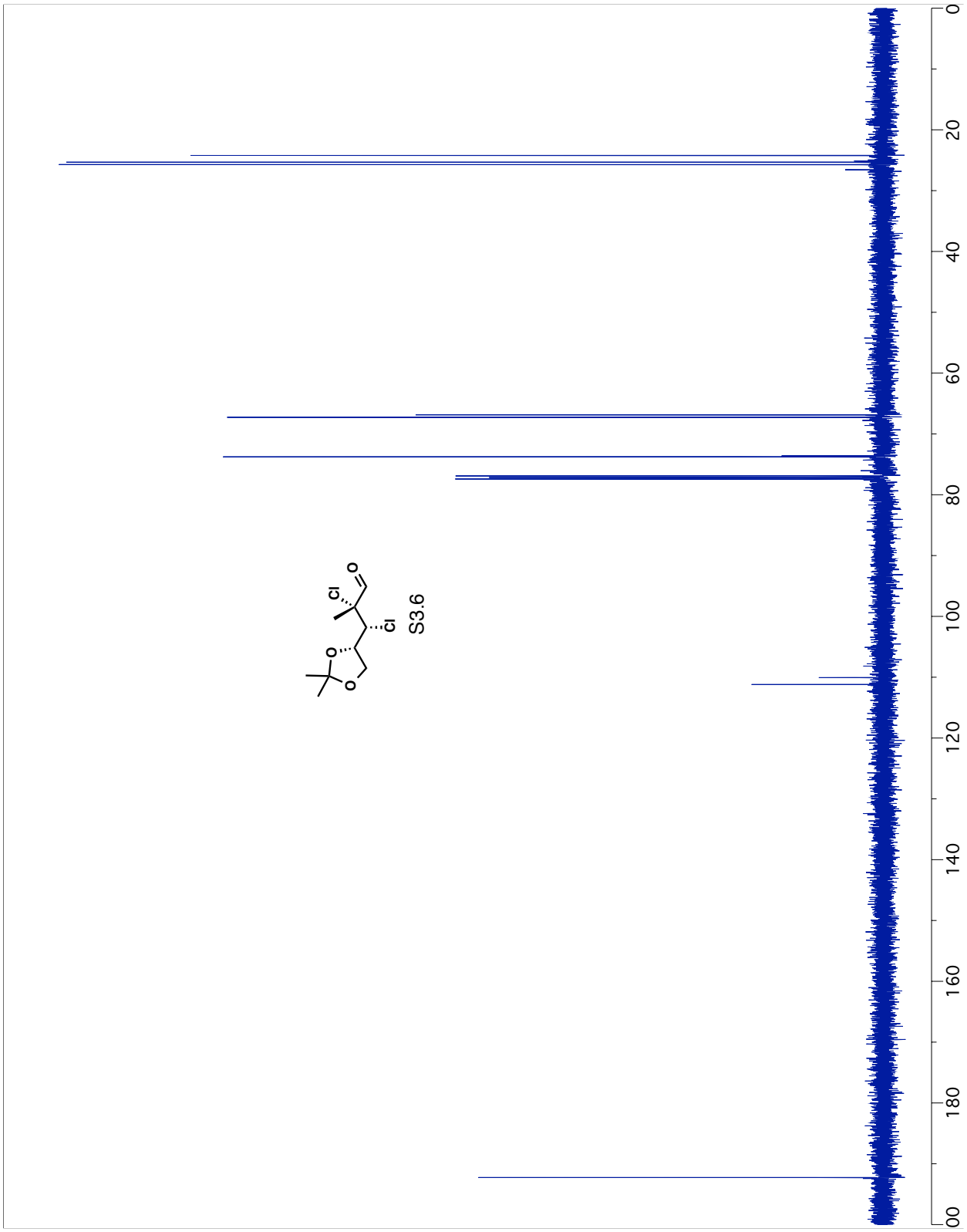
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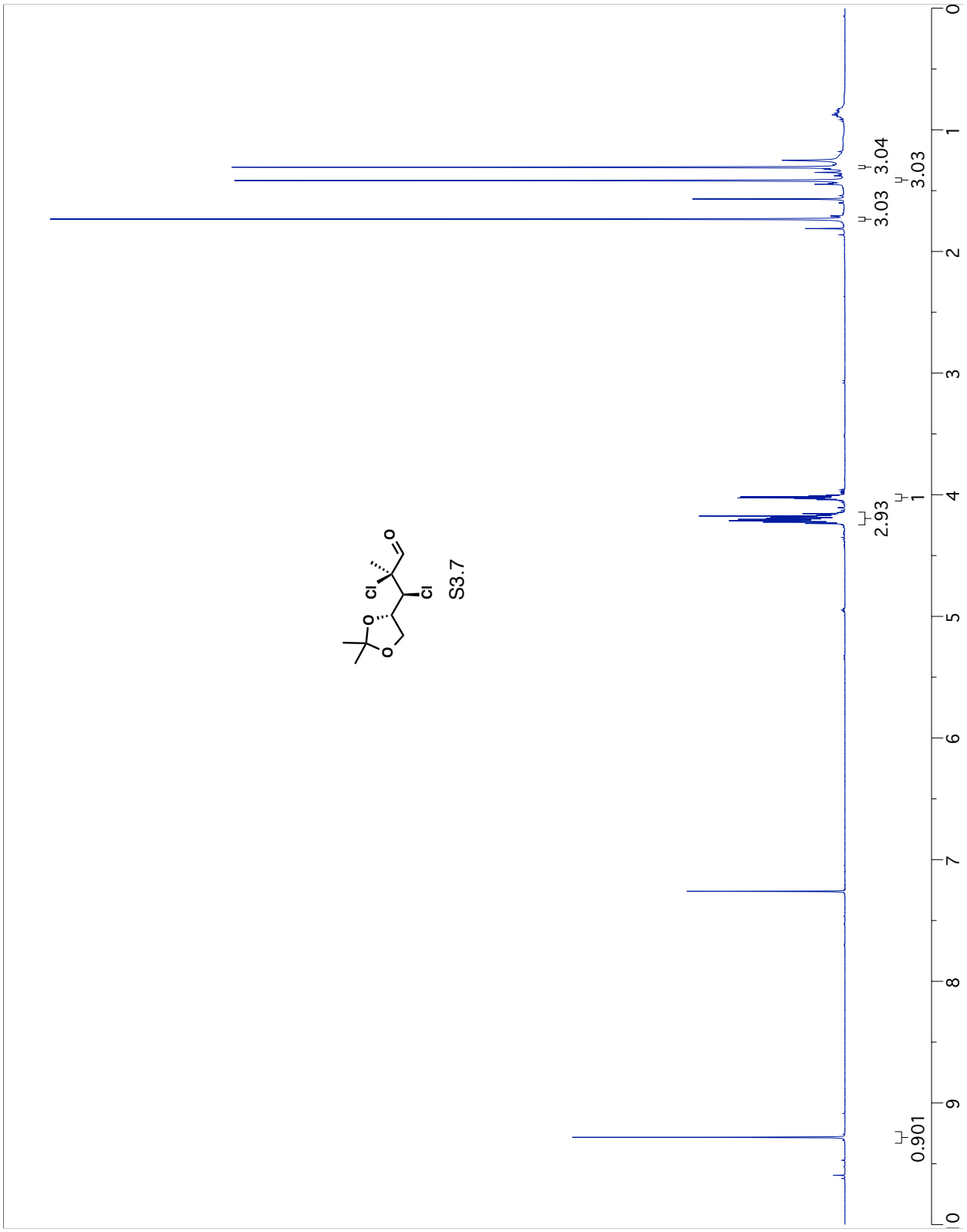
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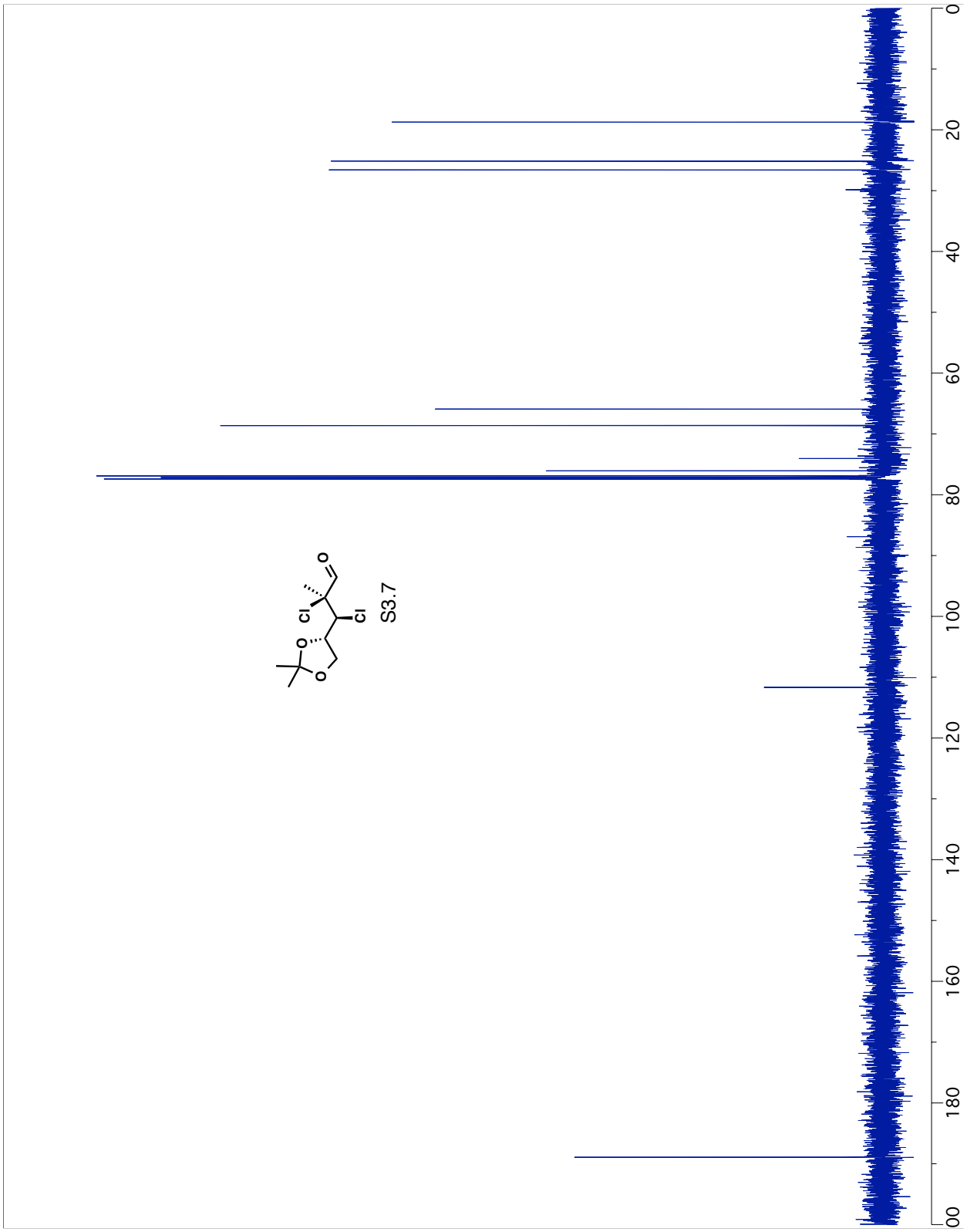
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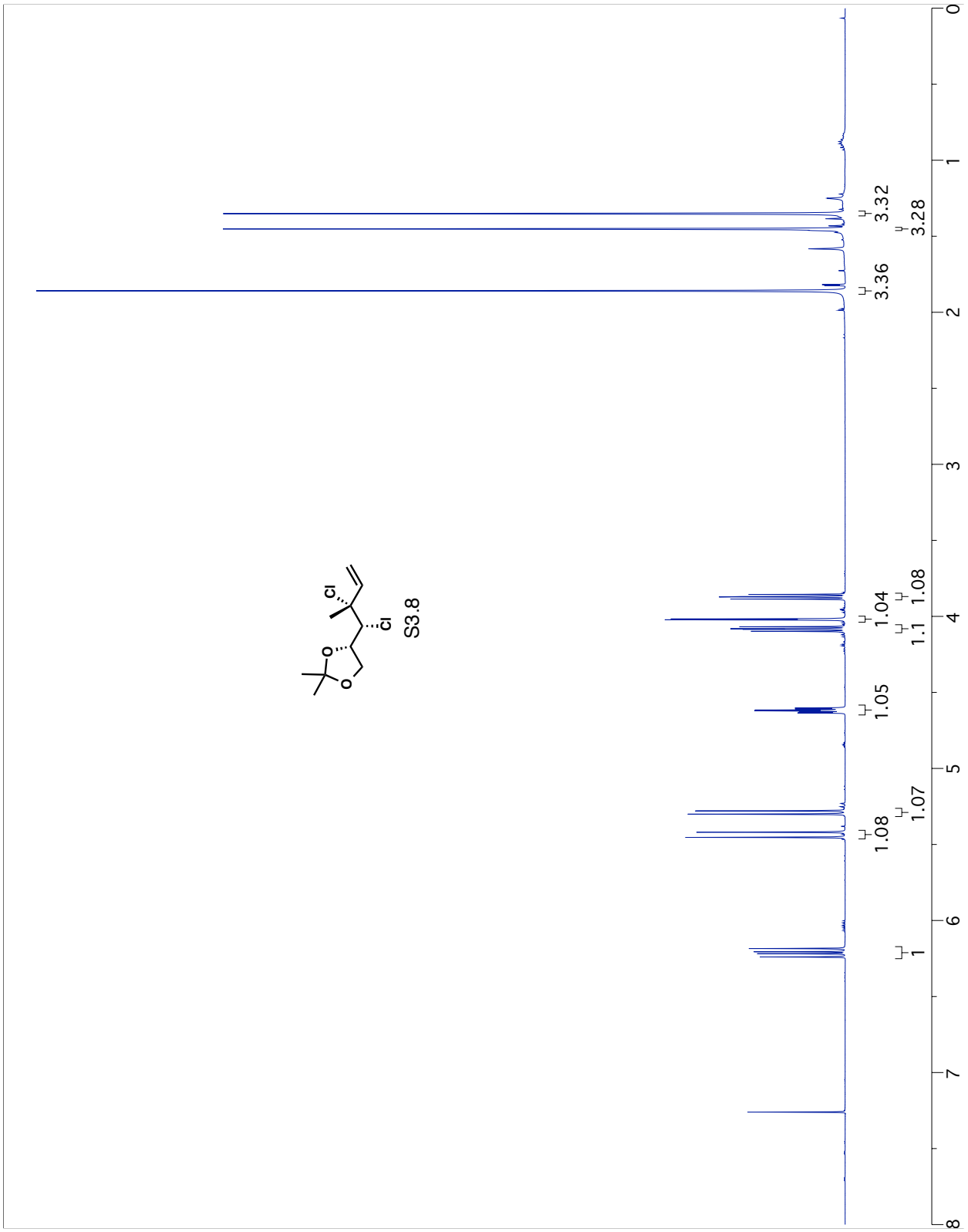
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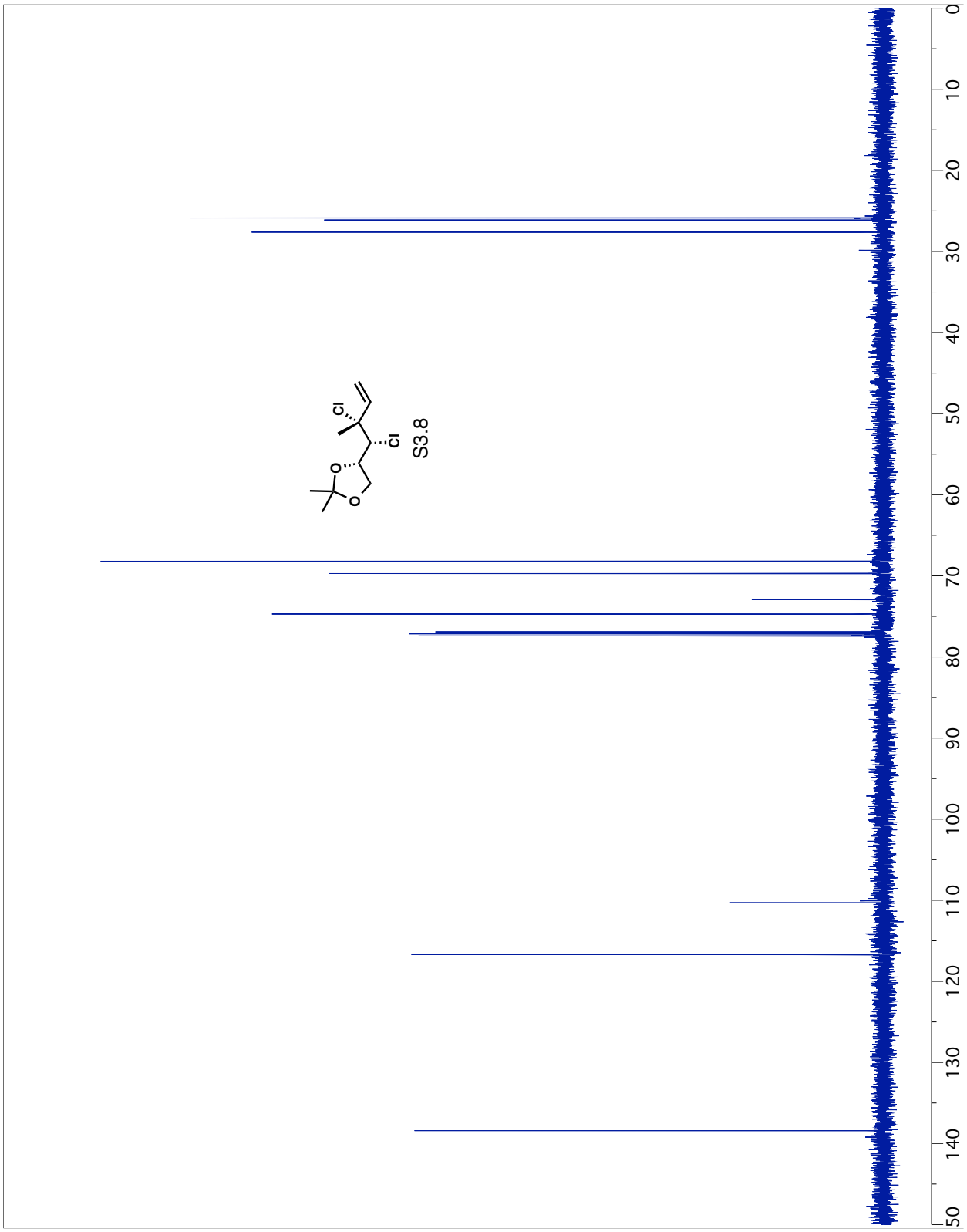
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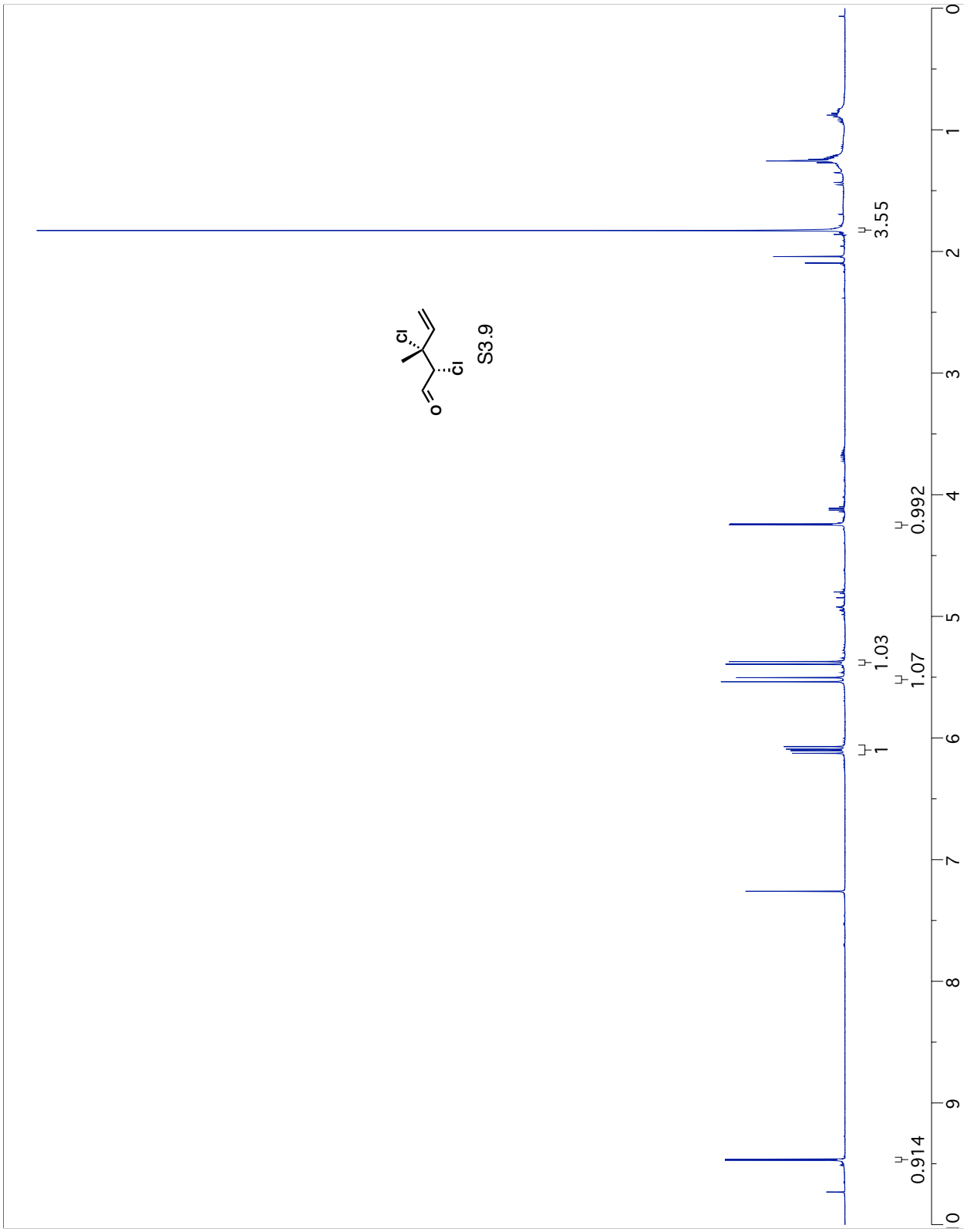
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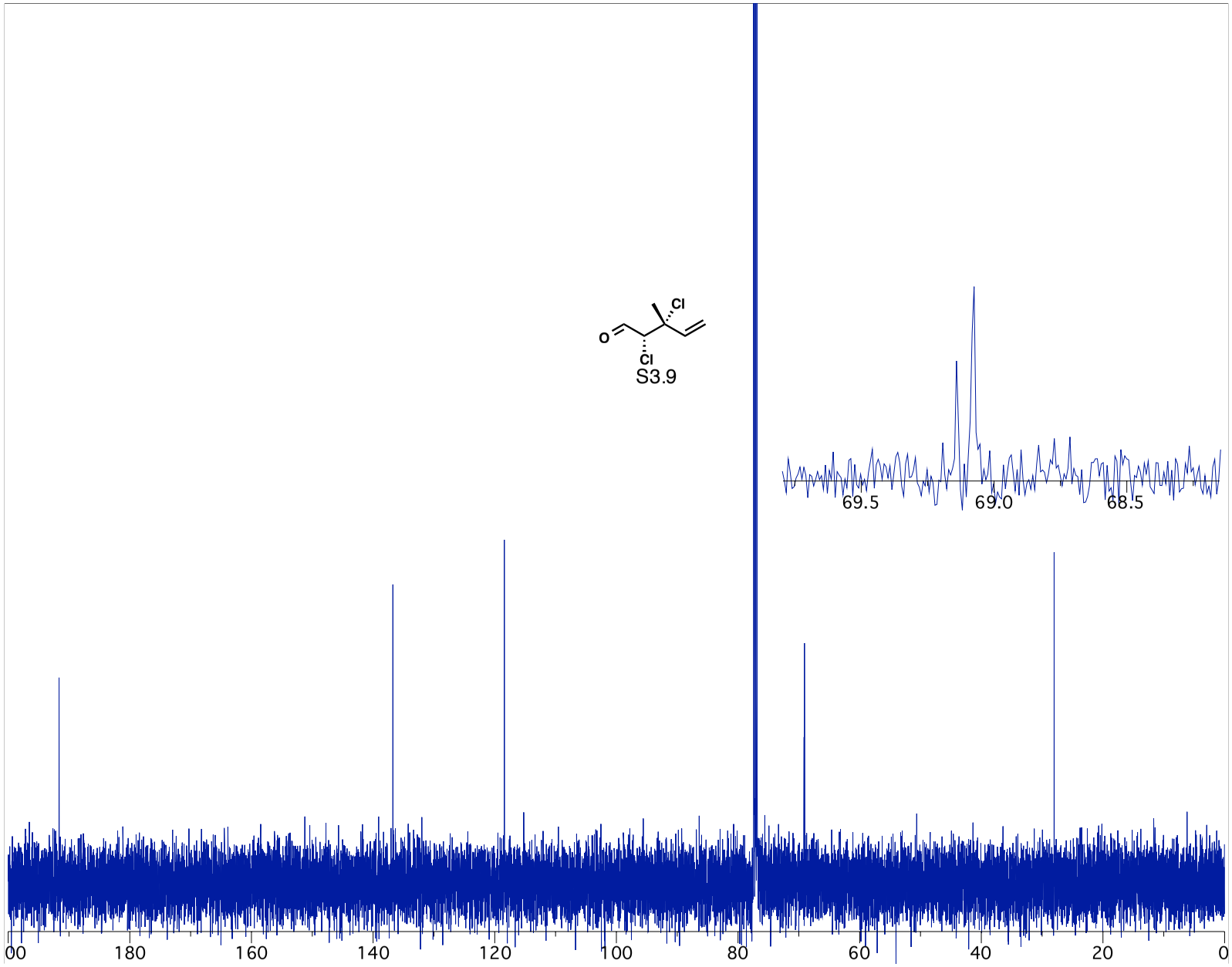
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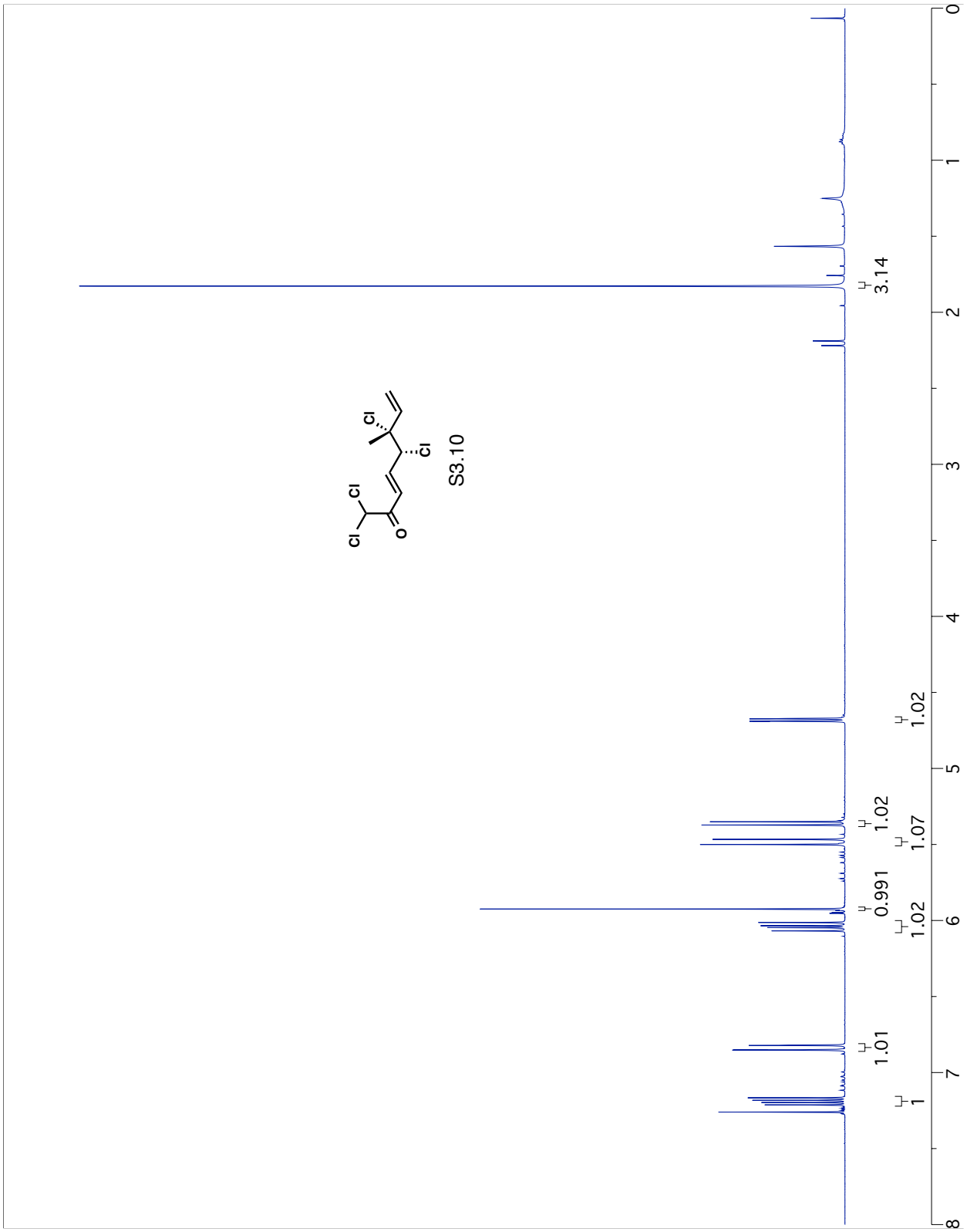
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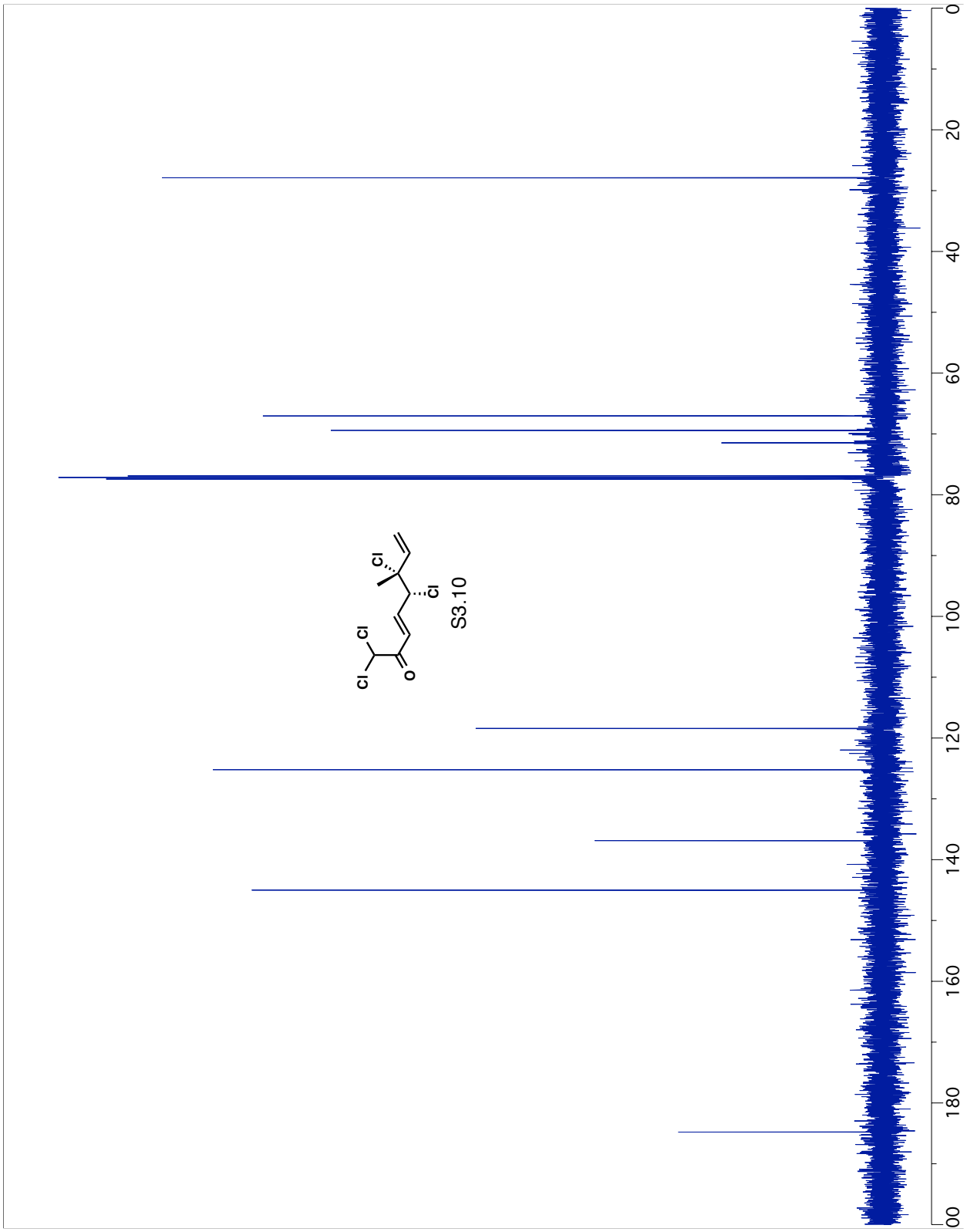
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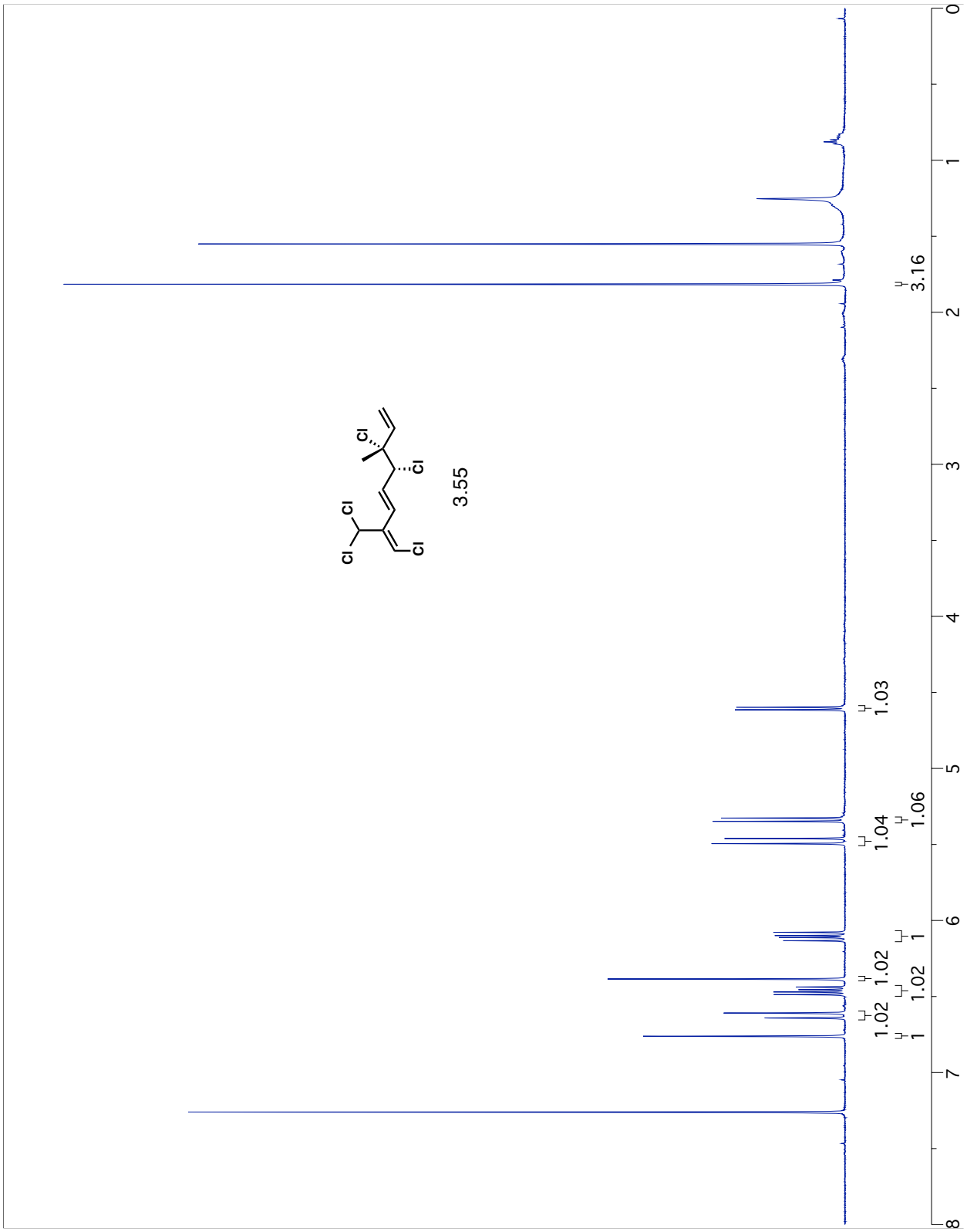
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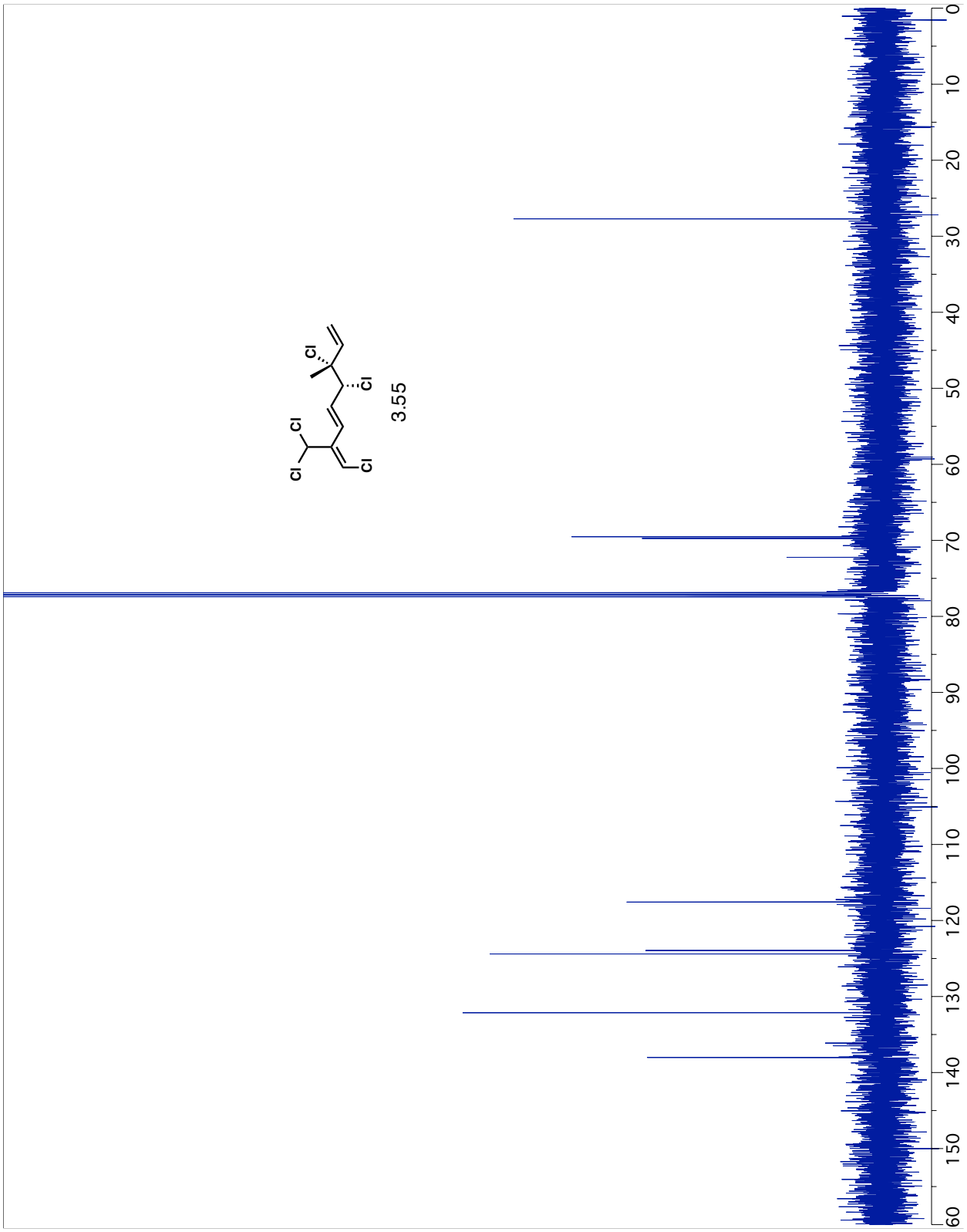
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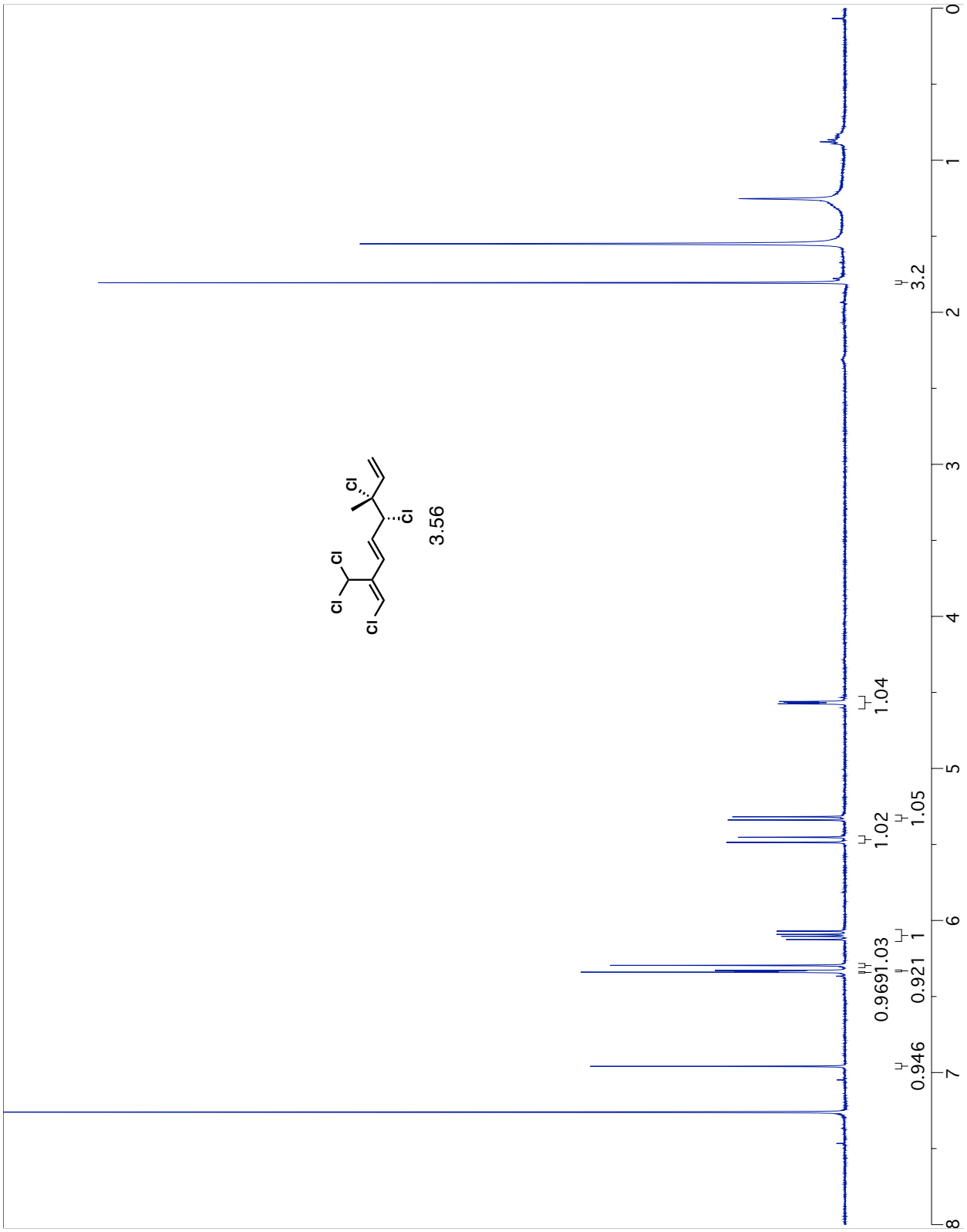
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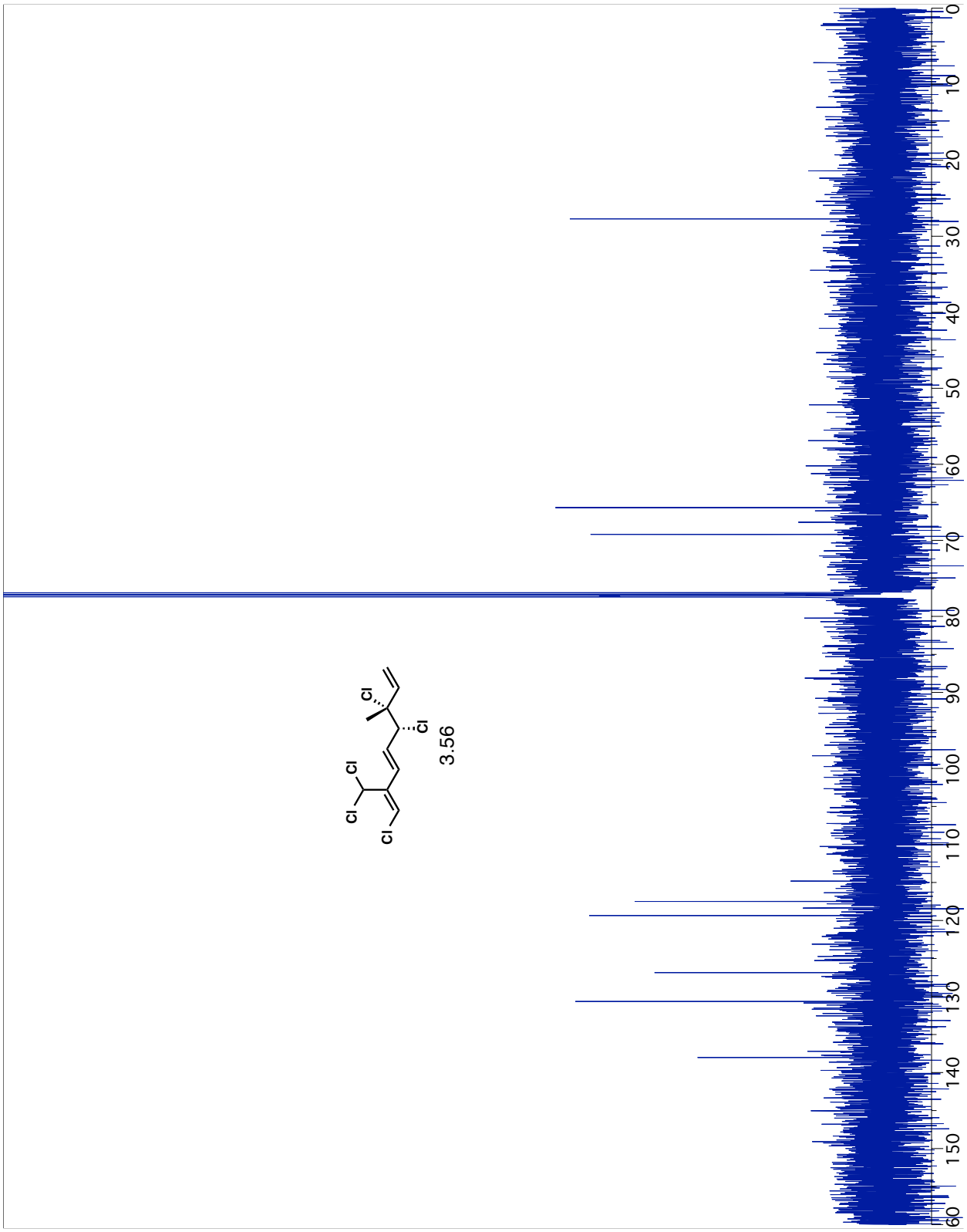
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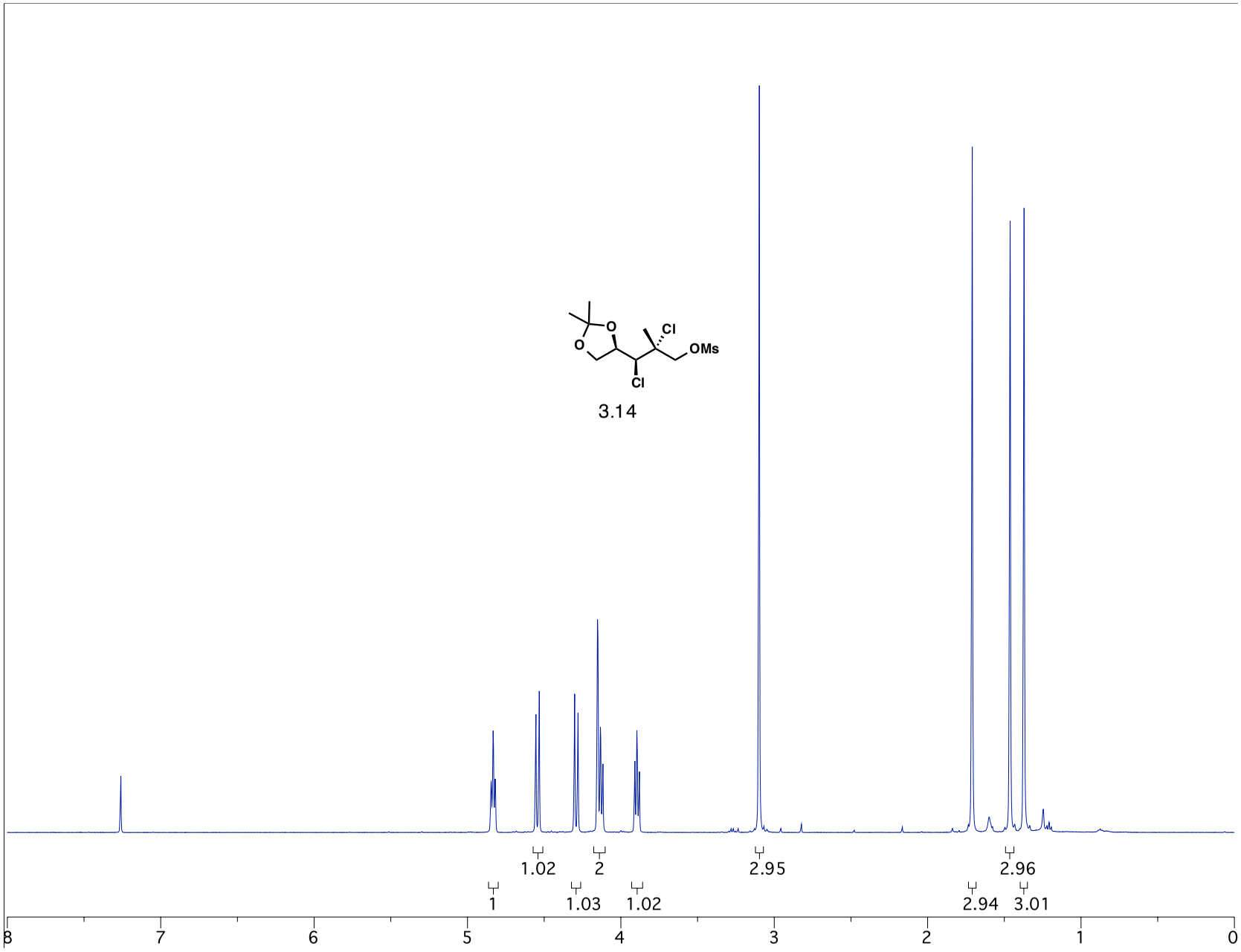
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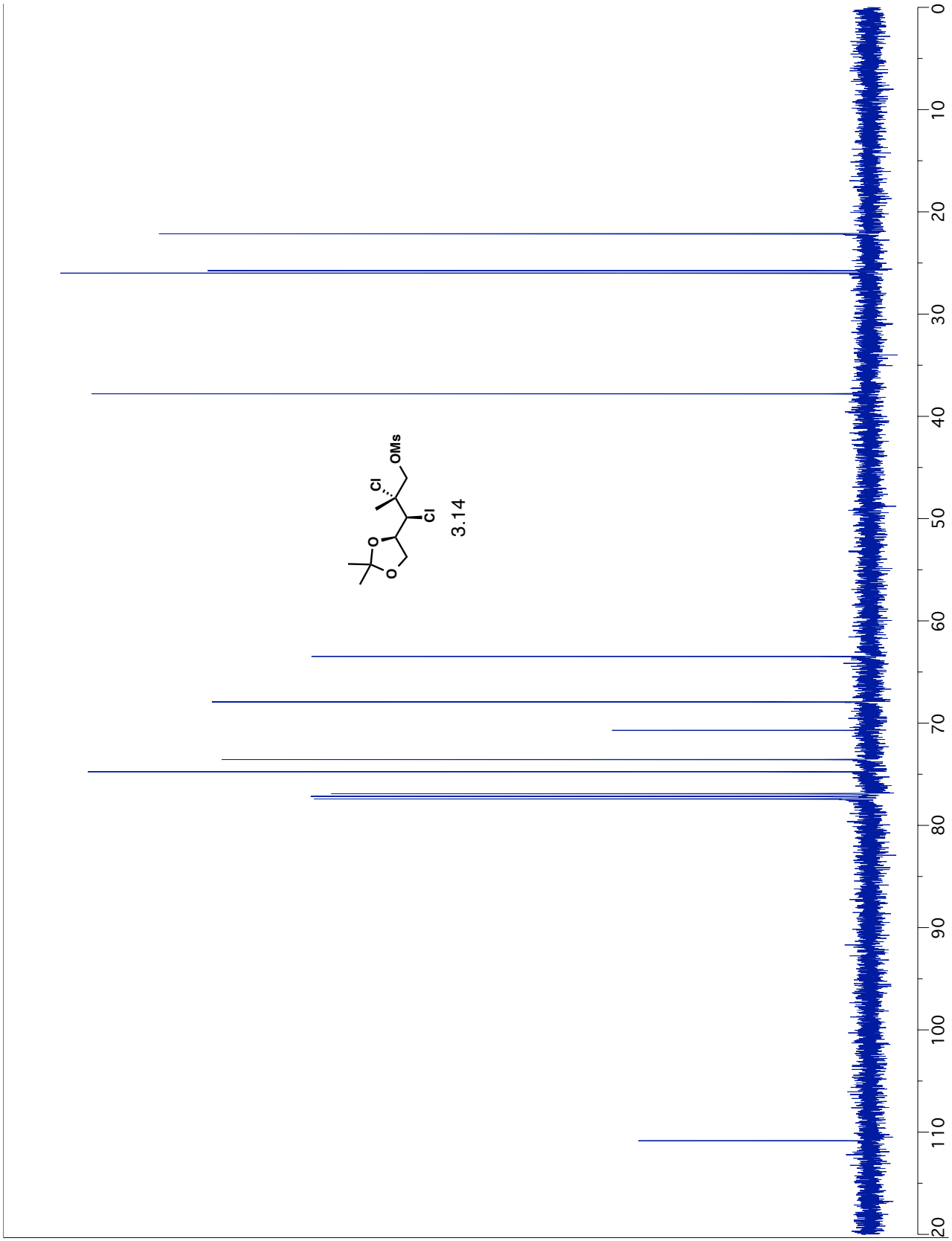
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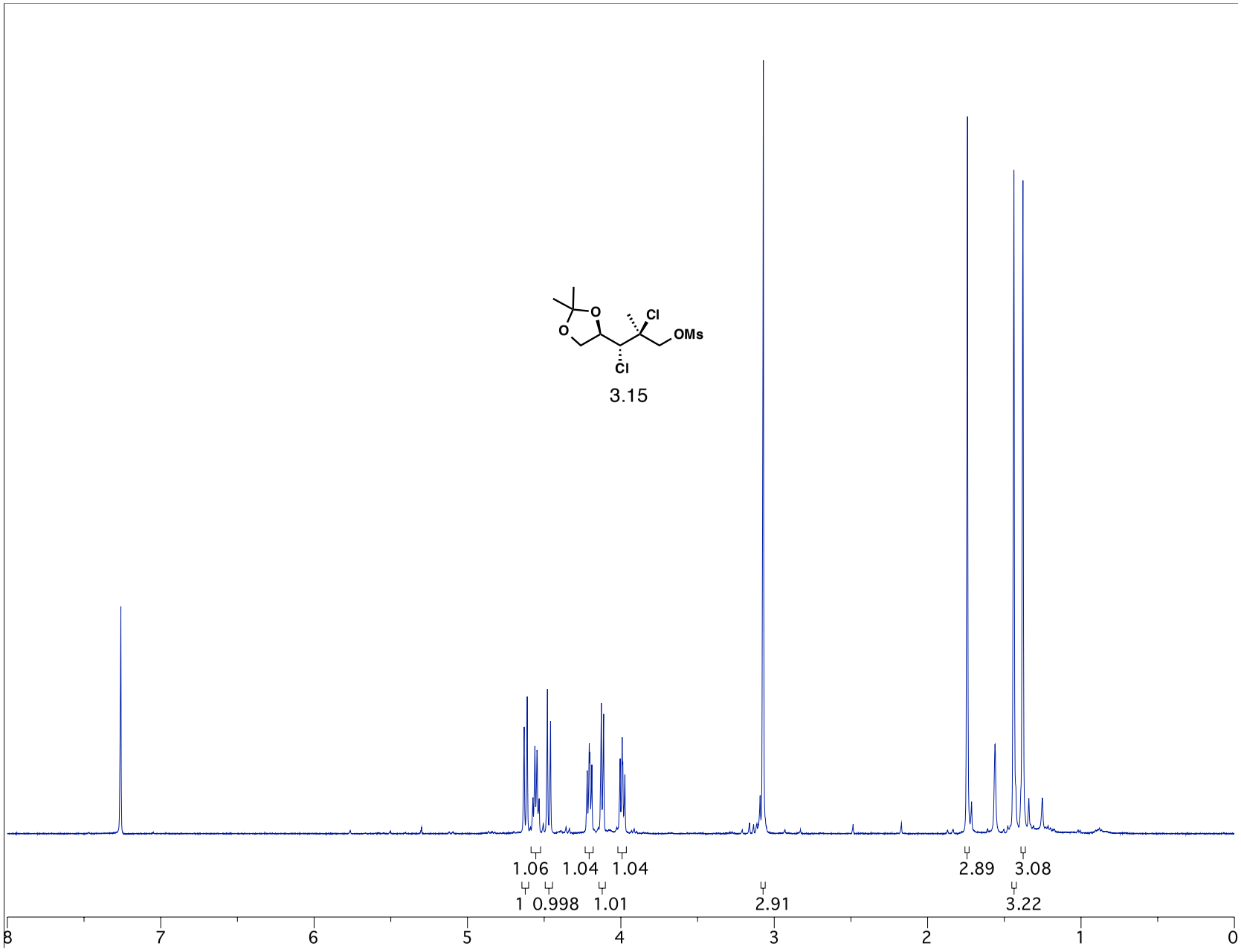
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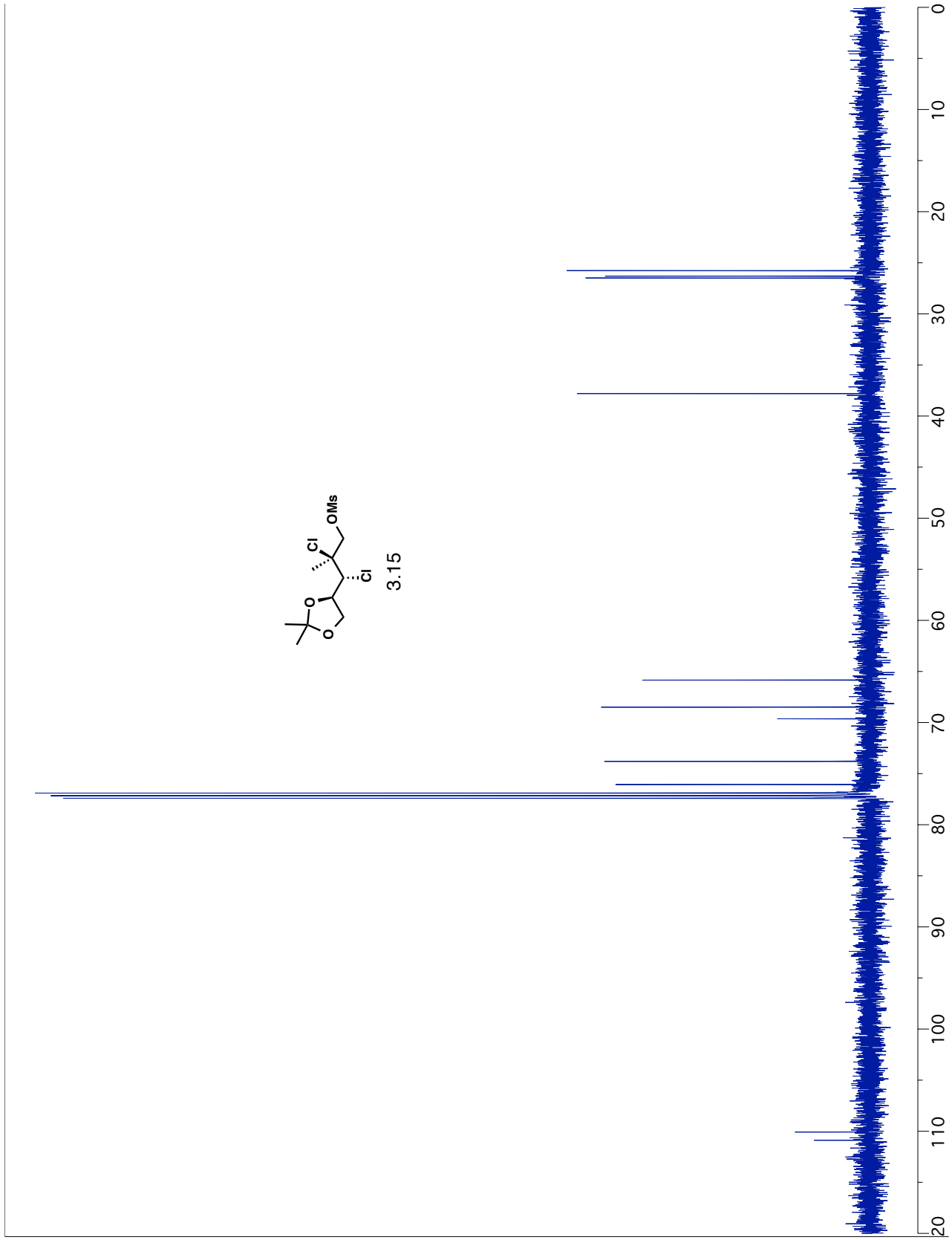
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