FORMATION AND REACTIVITY OF ALLENES AND SPIRODIEPOXIDES

by

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and approved by

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ABSTRACT OF THE DISSERTATION

FORMATION AND REACTIVITY OF ALLENES AND SPIRODIEPOXIDES

By YUE ZHANG

Dissertation Director:
Professor Lawrence J. Williams

Disclosed are the studies on allene and functionalized medium sized ring synthesis as well as applications of spirodiepoxide based methods. A new method of making allenes via C-C bond fragmentation was developed by which, most notably, an enantioenriched functionalized cyclic allene was synthesized. Mechanistic studies provide a framework for understanding this reaction in relation to other known modes of fragmentation. The synthesis of a chiral cyclononadienone was completed. This product has been shown to be a key intermediate towards many members of the xenicane family. Three epoxomicin analogues were synthesized. The issue of selectivity in allene oxidation was addressed in the course of this study. A model study towards erythronolide A was completed in which the feasibility of selective double cuprate addition to a bis[spirodiepoxide] macrolactone controlled by the macrocyclic environment was demonstrated. Lastly, the development of new reactions using spirodiepoxides to directly access densely functionalized structures in single- or two-flask procedures is reported.

Dedication

To My Family

Acknowledgement

I would like to express my sincerest thanks to Professor Lawrence J. Williams for his valuable ideas, advice, and discussions, as well as his generous support. It has been a privilege to work under his guidance and a great pleasure working for him.

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I would like to thank the entire Williams group for their friendship and help during the past six years, it was a great experience to work with them.

Finally, I would like to especially thank my mother Xu, Ling, my father Zhang, Zude and my auntie Xu, Rong for their unconditional love and unwavering support during these often difficult times. Without you, this work would not have been possible.

Table of Contents

List of Tables

List of Figures and Schemes

CHAPTER ONE

Allene Synthesis via C-C Fragmentation: Method and Mechanistic Insight

The rich structural and reactive properties of allenes complement the chemistry of alkenes and alkynes and render them uniquely versatile synthetic intermediates.[1] Allenes are also present in many natural products, about 150 allenic or cumulenic natural products have been discovered (Figure 1.1)[2]. These natural products often exhibit impressive activities as mechanism-based enzyme inhibitors, cytotoxins, or antiviral agents. Furthermore, allenes are also relevant to certain biosynthetic pathways.[3]

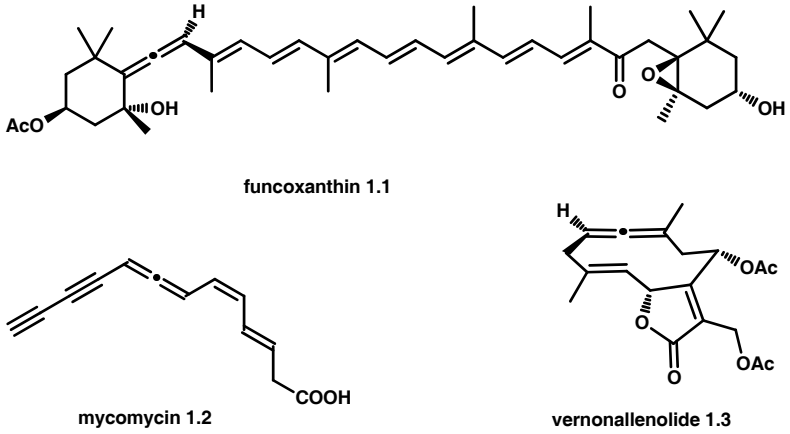

Figure 1.1 Allenic natural products

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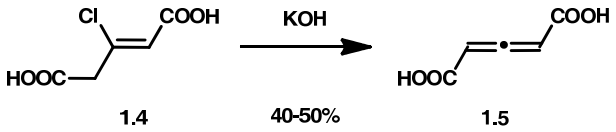
[1] (a) Hashmi, A. S. K., in Krause, N.; Hashmi, A. S. K. *Modern Allene Chemistry*, Vol. 1; Wiley-VCH Verlag: Weinhelm, 2004, pp 3-36. (b) Ma, S.; in Krause, N.; Hashmi, A. S. K. *Modern Allene Chemistry*, Vol. 2; Wiley-VCH Verlag: Weinhelm, 2004, pp 595-684. (c) Wei, L.–L.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773. (d) Brummond, K. M.; DeForrest, J. E. *Synthesis* **2007**,*6*, 795. (e) Kim, H.; Williams, L. J. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 870.

[2] (a) Krause, N.; Hoffmann-Roder, A.; in Krause, N.; Hashmi, A. S. K. *Modern Allene Chemistry*, Vol. 2; Wiley-VCH Verlag: Weinhelm, 2004, pp 997-1017. (b) Hu, G.; Liu, K.; Williams, L. J. *Org. Lett.* **2008**, *10*, 5493.

[3] (a) Corey, E. J.; D'Alarco, M.; Matsuda, S. P.; Lansbury, Jr.,P. T.; Yamada, Y. *J. Am. Chem. Soc.* **1987**, *109*, 289. (b) Song, W.C.; Brash, A. R. *Science*, **1991**, *253*, 781.



Scheme 1.1 First synthesis of allene by Burton and von Pechmann

In 1875, van't Hoff has already predicted the correct structures of allenes and higher cumulenes as well as their unique chiral property.[4] Although allenes now are considered stable compounds, most chemists thought of allenes as highly unstable before the 20th century. The first synthesis of an allene was reported in 1887 by Burton and von Pechmann (Scheme 1.1). Not surprisingly, their initiative was to challenge van't Hoff's concept. However, the structures of allenes were not confirmed until IR and Raman spectroscopy became available. Due to the spectral similarity between allenes and their isomers, quite a few natural products were assigned incorrectly. For example, our group revised the structure of brosimum allene in 2008 by using both experimental and computational methods (Figure 1.2).[2b]

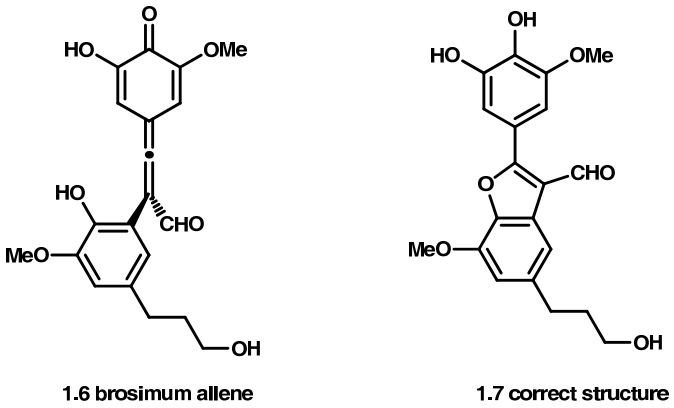
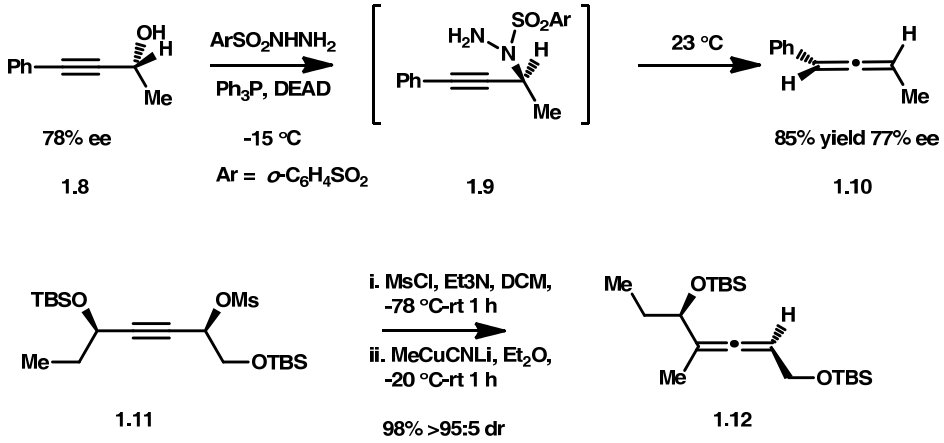


Figure 1.2 Structural revision of brosimum allene

[4] J. H. Van't Hoff, *La Chimie dans L'Espace*, Bazendijk, Rotterdam, **1875**.

Despite being discovered over a century ago, allene chemistry wasn't heavily and rapidly developed until last 20 years. Moreover, the methods for their preparation and strategies for their application are still limited. The most useful stereoselective methods for allene synthesis are the S_N2' displacement of propargylic esters by organocuprates and rearrangement of propargyl diazenes (Scheme 1.2).[5] In the course of our studies,[6] we identified instances where available approaches are not expedient and, consequently, developed a new entry to allenes via C-C fragmentation.



Scheme 1.2 General ways to make allenes

Olefin-forming C-C fragmentation (**1.13→1.14**, Scheme 1.3) was recognized in natural product degradation studies, for example by Eschenmoser,[7] and significantly developed by Grob.[8] Recently, Dudley reported that *β*-triflyl-α,β-unsaturated ketones also undergo efficient C-C fragmentation to give alkynes (**1.15→1.16**). This fragmentation strategy has

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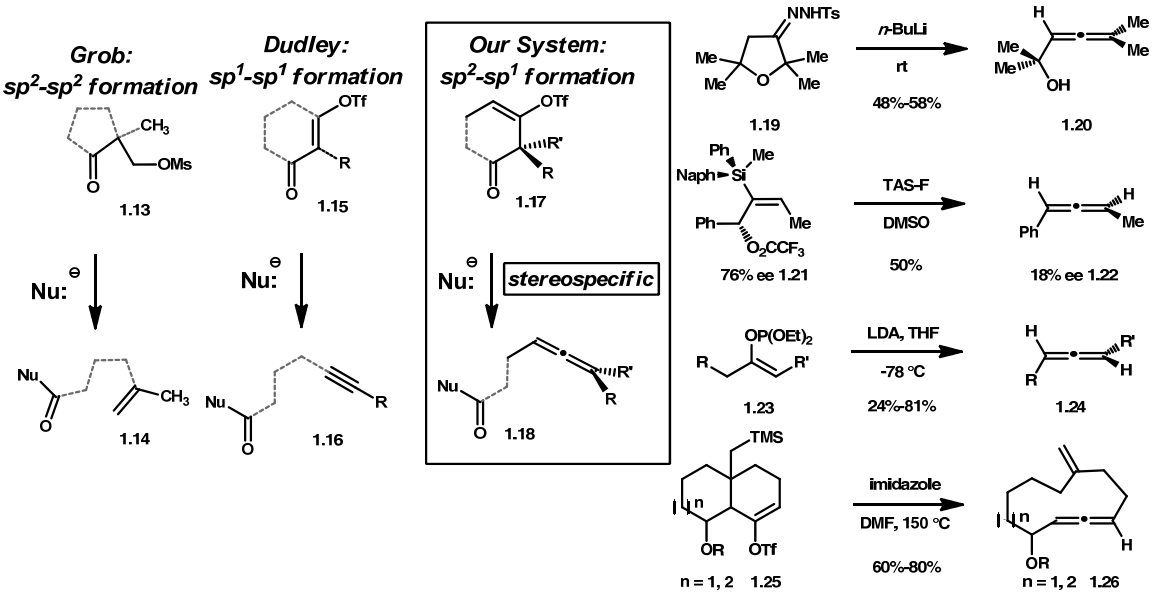
[5] (a) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492; See also. (b) Ready, J. M.; Pu, X. *J. Am. Chem. Soc.* **2008**, *130*, 10874. (c) Furstner, A.; Mendez, M. *Angew. Chem, Int. Ed.* **2003**, *115*, 5513. (d) Burton, B. S.; von Pechmann, H. *Ber. Dtsch. Chem. Ges* **1887**, *20*, 145. (e) Ghosh, P.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.*, **2007**, *129*, 2438. (f) Rona, P.; Crabbé, P. *J. Am. Chem. Soc.* **1969**, *91*, 3289.

[6] (a) Shangguan, N.; Kiren, S.; Williams, L. J. *Org. Lett.* **2007**, *9*, 1093. (b) Kolakowski, R. V.; Williams, L. J. *Tetrahedron Lett.* **2007**, *48*, 4761. (c) Wang, Z.; Shangguan, N.; Cusick, J. R.; Williams, L. J. *Synlett* **2008**, *2*, 213.

[7] Eschenmoser, A.; Frey, A. *Helv. Chim. Acta.* **1952**, *35*, 1660.

[8] (a) Grob, C.A.; Kiefer, H.R.; Lutz, H.J.; Wilkens, H. J. *Helv. Chim. Acta,* **1967***, 50*, 416. (b) Grob, C. A. *Angew. Chem., Int. Ed.* **1969**, *8*, 535.

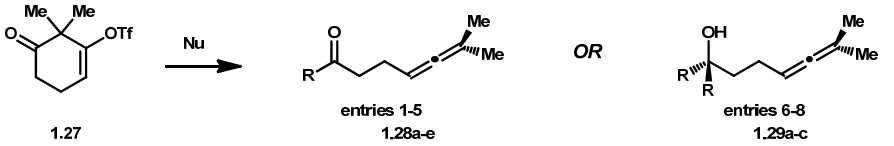
not been applied to allene synthesis. Allenes have been accessed by a variety of anion-initiated and thermolytic fragmentation reactions of suitably functionalized alkenes. For example, Agosta generated the allene **1.20** via fragmenting the tosylhydrazone tetrahydrofuran **1.19**.[9] McGarvey demonstrated that by fragmenting a chiral silyl triflate **1.21** with fluoride source could generate allene **1.22** selectively.[10] Brummond reported vinyl phosphate esters could be fragmented to allenes with LDA (**1.23→1.24)**. Kuwajima also showed a thermal degradation method to generate cyclic allenes (**1.25→1.26**).[11] Recently, we wondered whether vinyl triflates would fragment to give the corresponding allenes via a framework that complements the Eschenmoser/Grob and Dudley reactions (**1.17→1.18**) and whether this transformation could be used to prepare allenes stereospecifically.



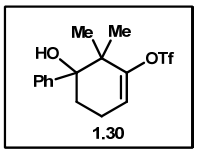
Scheme 1.3 Fragmentation to alkenes, alkynes and allenes

[9] Foster, A. M.; Agosta, W. C. *J. Org. Chem.* **1972**, *37*, 61
[10] Torres, E.; Larson, G. L.; McGarvey, G. J. *Tetrahedron Lett.* **1988**, *29*, 1355.
[11] (*a*) Brummond, K. M.; Dingess, E. A.; Kent, J. L. *J. Org. Chem.* **1996**, *61*, 6096. (*b*) Brummond, K. M.; Wan, H.; Kent, J. L. *J.Org. Chem.* **1998**, *63*, 6535.

Table 1.1 Nucleophilic induced alllene fragmentation



entry	R-	product	yield (%)	entry	R-	product	yield (%)
1	Ph	1.28a	76[a]	6	Ph	1.29a	86[f]
2	Ph, O	1.28b	78[b]	7	nBu	1.29b	81[g]
3	EtO, O	1.28c	89[c]	8	S, S	1.29c	74[h]
4	S, S	1.28d	87[d]				
5	TMS	1.28e	75[e]				



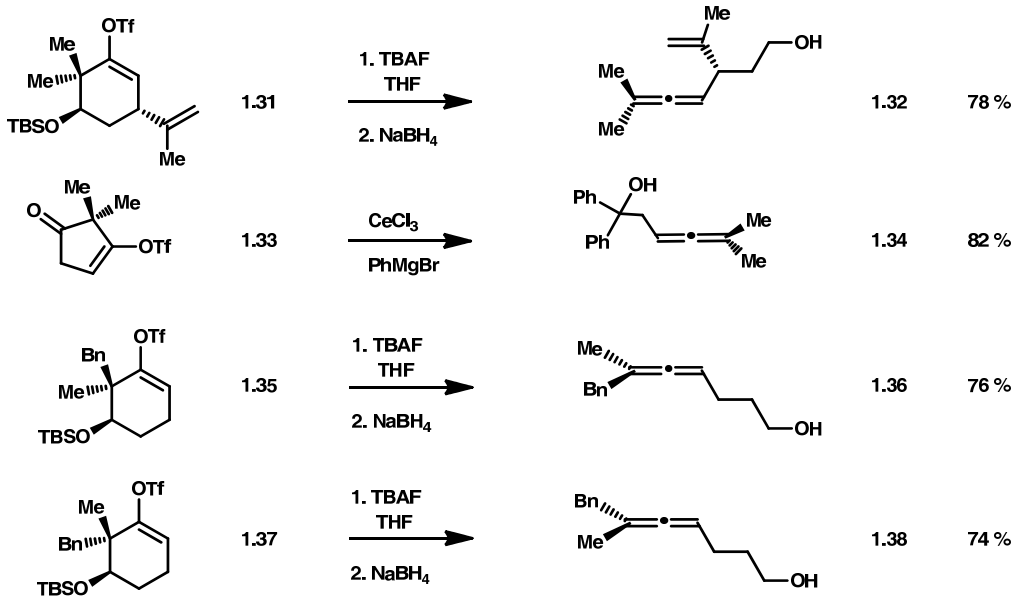
Reactions and conditions: [a] 1.0 equiv of PhLi, 45 min, THF -78 °C - rt, 1 h. [b] 1.3 equiv of NaHMDS, 1.3 equiv of $PhCOCH_3$, THF, -78 °C, 15 min. [c] 1.4 equiv of LiHMDS, 1.3 equiv of EtOAc, THF, -78 °C, 15 min. [d] 1.1 equiv of *n*BuLi, 1.2 equiv of dithiane, THF, -78 °C - rt, 1 h. [e] 1.1 equiv of *n*BuLi, 1.2 equiv of TMSCCH, THF, -78 °C - rt, 1 h. [f] 3.0 equiv of $CeCl_3$, 3.0 equiv of PhMgBr, THF, -78 °C - rt, 1 h. *g* 3.0 equiv of $CeCl_3$, 3.0 equiv of *n*BuLi, THF, -78 °C - rt. [h] 3.0 equiv of *n*BuLi, 3.0 equiv of dithiane, THF, -78 °C - rt.

Addition of carbon nucleophiles to the carbonyl of **1.27** generated a transient alkoxide that induced fragmentation/allene formation (Table 1.1). Use of approximately stoichiometric quantities of nucleophile gave allenic ketones **1.28a-e**. Use of excess reagent gave allenic alcohols **1.29a-c**. Organolithium and Grignard reagents, including alkyl, aryl, and alkynyl nucleophiles, smoothly added and induced fragmentation. Ketone and ester enolates also added as did dithiane anions. Use of cerium chloride was necessary to suppress competitive enolate formation of this substrate in instances where hard carbon nucleophiles were used.[12] Addition of alkoxides or lithiated amines as nucleophiles for carbonyl addition, which in principle would give ester or amide products, gave recovered **1.27** or complex mixtures (not shown). As suggested by the

[12] Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.

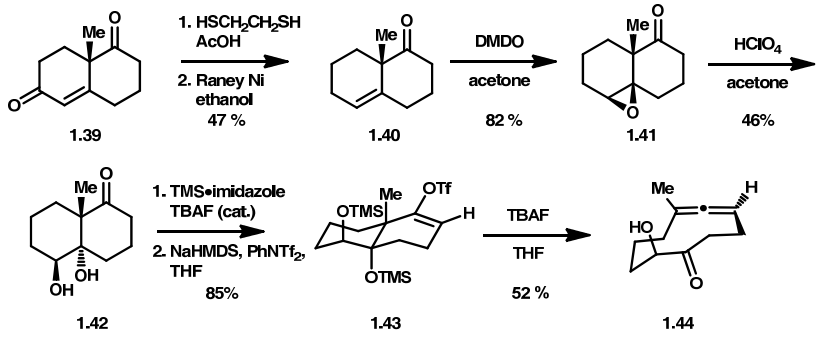
selective preparation of compounds **1.28** and **1.29**, fragmentation appears rate limiting for at least some substrates. For example, when a reaction mixture of **1.27** with $CeCl_3$ (2.5 equiv) and PhLi (2.5 equiv) at -78 °C was quenched after 10 min, the nonfragmented tertiary alcohol **1.30** was isolated in 20 % yield (Table 1.1, see inset). These data demonstrate that allenes form rapidly from carbon nucleophile addition/vinyl triflate fragmentation for suitable substrates.

Scheme 1.4 shows the conversion of other vinyl triflates to allenes and that stereogenic allenes form stereospecifically. Exposure of carvone-derived silyl ether **1.31** to fluoride led to rapid and clean formation of allenic aldehyde. For convenience, the reaction mixture was then treated with reducing agent, which gave the corresponding acyclic alcohol **1.32**. Excess phenyl magnesium bromide smoothly added to cyclopentenone **1.33** to give allenic alcohol **1.34**.



Scheme 1.4 Vinyl triflate to allene fragmentation

The fragmentations are stereospecific. Highly enantioenriched acyclic vinyl triflates **1.35** and **1.37** fragmented upon treatment with fluoride to give the corresponding enantioenriched allenes. Mosher ester analysis showed that in this fragmentation allene **1.38** was not formed from **1.35→1.36** and allene **1.36** was not formed from **1.37→1.38.**



Scheme 1.5 Synthesis of cyclic allene

With the success of synthesizing acyclic allenes, we targeted a cyclic allene (**1.44)** that could be achieved by fragmenting precursor **1.43** (Scheme 1.5). The synthesis commenced with commercial Wieland–Miescher ketone **1.39**. After condensation with dithiol and desulfurization with Raney nickel, olefin **1.40** was obtained in 47 % combined yield. DMDO oxidation gave a single diastereomer (**1.41)** in 82 % yield. Acid catalyzed epoxide opening generated diol **1.42**. Subsequent TMS protection and triflation gave the vinyl triflate **1.43** in 85 % combined yield. Gratifyingly, the transient alkoxide generated by TMS cleavage induced fragmentation to afford the 10-membered allene **1.44** in 52 % yield as a single isomer. The reaction efficiency for these more complex substrates is primarily a reflection of triflate hydrolysis as a competing side reaction. Thus, the precursor diol ketone **1.42** was also isolated from the reaction mixture. The yield of **1.44**, base on recovered **1.42**, was 85 %.

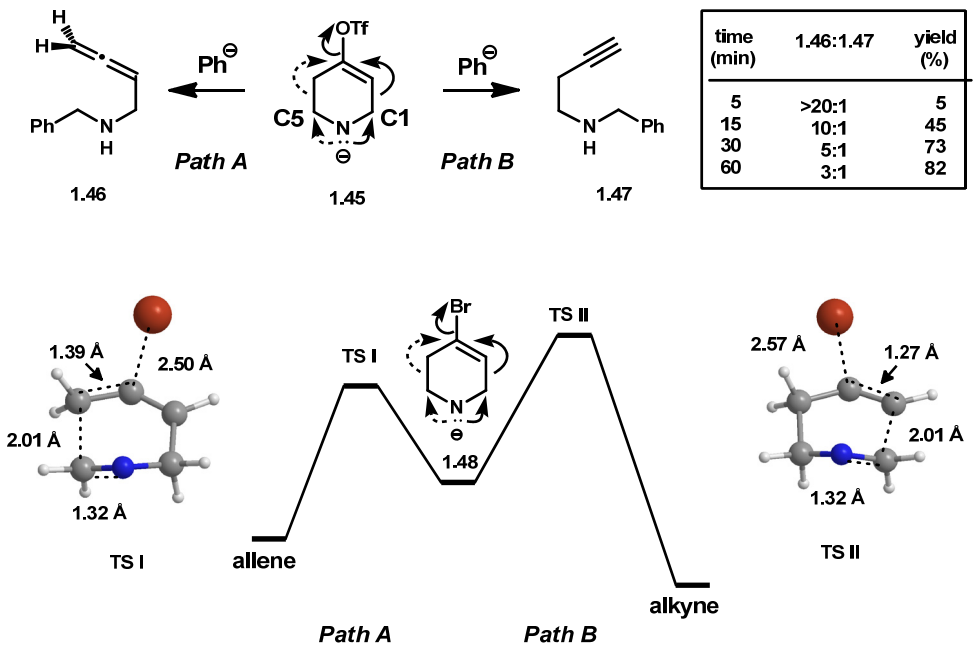


Figure 1.3 Fragmentation and mechanistic insight of vinyl triflate

We were interested in the mechanism of fragmentation as well. My coworker, Dr. Kolakowski, studied this reaction to help understanding the fragmentation reaction (Figure 1.3). In principle, anionic *O*-triflyl piperidone **1.45** could give an allene of type **1.46** or an alkyne of type **1.47** (*cf.* Dudley fragmentation). The corresponding trifluoroacetate salt was treated with excess PhMgBr in diethyl ether at -20 °C.[13] Only **1.46** was observed after 5 min (>20:1, **1.46**:**1.47**, 5% yield, 5% conversion). As the reaction proceeded, **1.47** became evident and the ratio of **1.46**:**1.47** gradually decreased. After 1 h the ratio of **1.46**:**1.47** was 3:1 (82% yield, 82% conversion). The increase in alkyne is readily understood in terms of the known propensity of terminal allenes to isomerize to terminal alkynylides under strongly basic conditions.[1] These data demonstrate that fragmentation of this system favors allene over alkyne formation.

[13] The immediate fragmentation products (not observed) are imines. Use of THF accelerated the isomerization process (1 h: **1.46**:**1.47** = 1:1, 85% yield, 85% conversion).

Why does the allene form faster than the alkyne? Computed transition states were found for allene and alkyne formation using B3LYP/6-31G+(2d,2p).[14] The $\delta\Delta H^{\ddagger}_{calc}$ for the computed transition structures **TSI** and **TSII** was 2.39 kcal/mol, favoring allene formation.[15,16] Moreover, the optimized ground state energy of **1.48** indicates, by NBO analysis, a greater positive charge on C5 than on C1.[14a,17] Hence the calculated transition structures are consistent with a rationale wherein the triflate polarizes the carbon framework. Despite proper stereoelectronics for both pathways, the sp^3 network, being more polarized than the sp^2 network, interacts more strongly with the anionic nitrogen and, as a result, allene formation becomes the kinetically more facile pathway.

We have shown that suitably functionalized vinyl triflates serve as precursors to allenes by way of direct fragmentation or as part of an addition/cascade reaction. Mechanistic studies provide a framework for understanding this reaction in relation to other known modes of fragmentation, and as such, these findings complement methods of alkene and alkyne synthesis that rely upon C-C fragmentation. This work is complementary to allene synthesis methods that use alkyne precursors, provides access to highly enantioenriched allenes, including cyclic allenes and is stereospecific.

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[14] (a) Frisch, M. J.; *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004. Exchange potentials: (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. Correlation functional: (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Re*V. *B* **1988**, *37*, 785.

[15] Caution must be exercised in light of the known difficulties in calculating allene and alkyne ground states. (See: Wodrich, M. D.; Corminboeuf, C.; Schleyer, P. V. R. *Org. Lett.* **2006**, *8*, 3631.) The good correlation between $\Delta H^{\ddagger}_{calc}$ and experiment is likely due in part to the degree of separation that exists between the transition states and the product ground states.

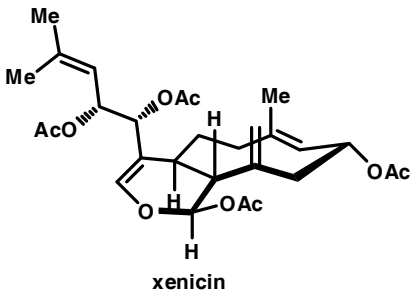
[16] Transition states for chlorine and fluorine substituted piperidines were calculated and compared with the bromine substituted TS I (see Supporting Information). The enthalpy of the reaction for the series was -F 13.5 kcal/mol, -Cl 9.2 kcal/mol, and -Br 8.3 kcal/mol, consistent with leaving group ability.

[17] Weinhold, F. Landis, C. *Valency and Bonding*; Cambridge University Press: Cambridge, U.K., 2005.

CHAPTER TWO

Structure and Reactivity of a Chiral Cyclononadienone

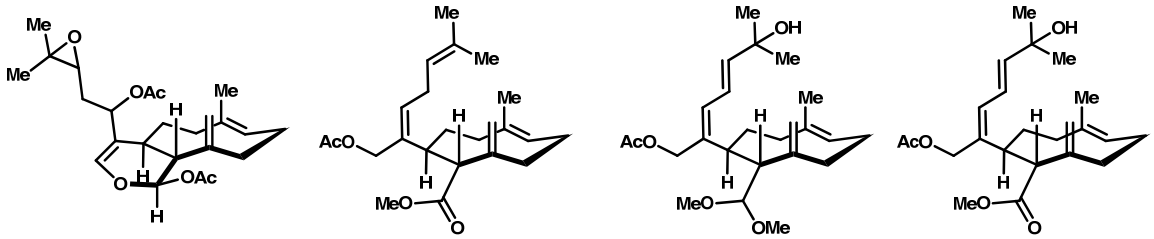
In 1977, F. J. Schmitz *et al*. isolated a diterpenoid from *Xenia elongata* named xenicin (**2.1**), the first isolated member of the xenicane family. The structure was determined by x-ray crystallography.[18] The structural characteristics of the xenicane family is the nine-member carbocyclic skeleton. To date more than 150 natural products have been isolated within this family.



xenicin

Figure 2.1

Recently, Falkowski *et al.* isolated four new xenicane members (Figure 2.2) from *Xenia elongata*. These compounds were found to be cytotoxic. They showed strong ability to induce cell apoptosis, which makes them potential anti cancer drugs. This was the first report to show that the compounds belonging to this family cause cell death by apoptotic induction.[19]

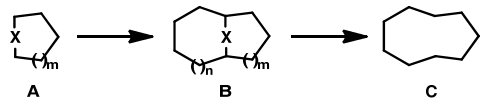


2.2 new isolate 1 | 2.3 new isolate 2 | 2.4 new isolate 3 | 2.5 new isolate 4

Figure 2.2 New isolates

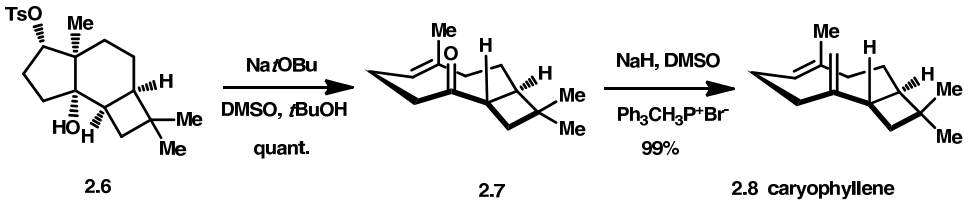
[18] Vanderah, D. J.; Steudler, P. A.; Ciereszko, L. S.; Schmitz, F. J.; Ekstrand, J. D.; Van der Helm, D. *J. Am. Chem. Soc.* **1977**, *17*, 5780.
[19] Andrianasolo, E. H.; Haramaty, L.; Degenhardt, K.; Mathew, R.; White, E.; Lutz, R.; Falkowski, P. *J. Nat. Prod.* **2007**, *70*, 1551.

Despite the biological activities of the xenicane family, the number of total synthesis related to this family is very limited, due primarily to the nine membered core structure. The problem of the synthesis of nine-membered cycloalkanes primarily stems from destabilizing trans-annular interactions. [20] Most synthetic strategies to prepare cyclononanes and their derivatives deal with this structural congestion by initial formation of a smaller ring to which a second ring is then fused (**A→B**, Scheme 2.1). In subsequent maneuver, the small ring connectivity is removed and the nine-member ring connectivity is left intact (B→C).



Scheme 2.1 Strategies to prepare cyclononanes

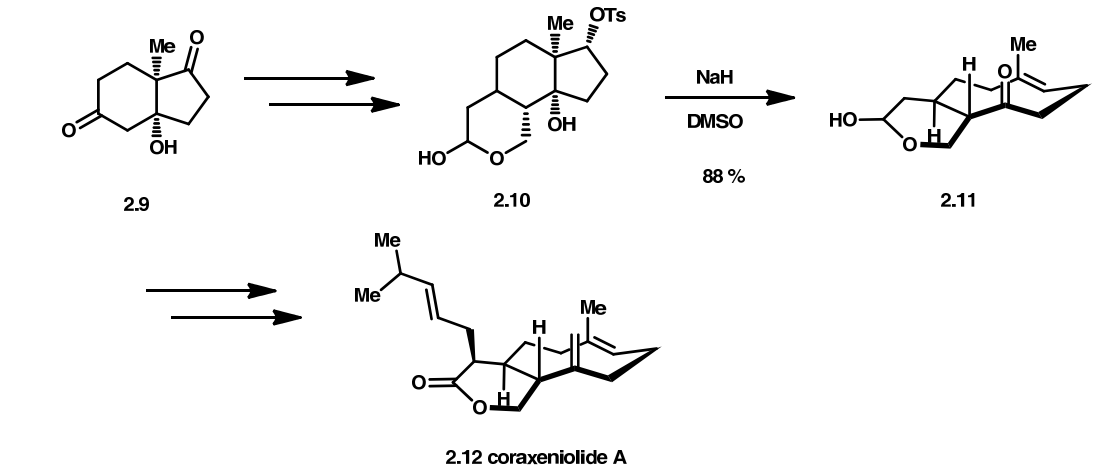
In 1964, Corey *et al.* applied this strategy to a racemic synthesis of natural product caryophyllene (Scheme 2.2).[21] They successfully fragmented tricyclic tosylate **2.6** with methylsulfinylcarbanion. And continuously stirring the reaction mixture at room temperature for 17 hrs generated the epimerization product **2.7** quantitatively in one step. Subsequent Wittig olefination yielded the natural product caryophyllene **2.8**.



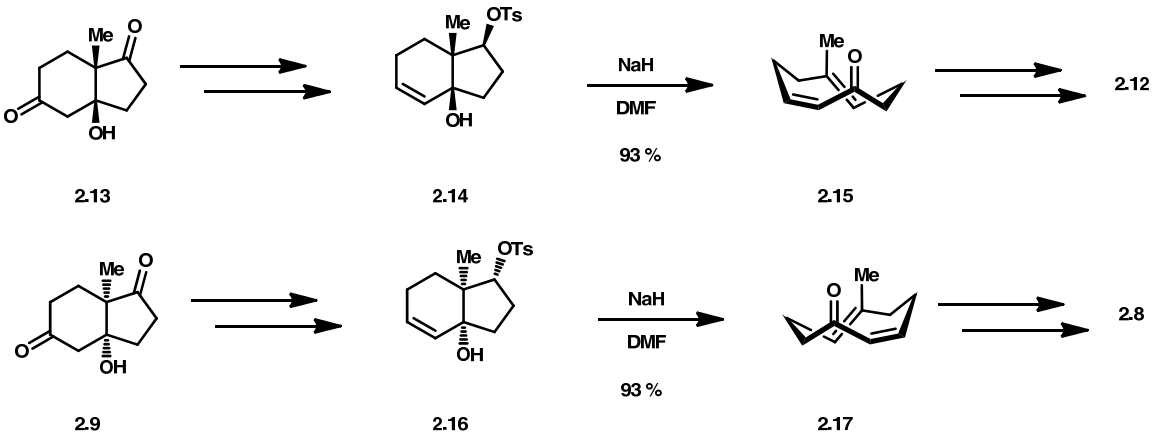
Scheme 2.2 First total synthesis of caryophyllene

[20] Prelog, V.; Schenker, K. *Helv. Chim. Acta* **1952**, *35*, 2044-2053; Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981.
[21] (a) Corey, E. J.; Mitra, R. B.; Uda, H. *J. Am. Chem. Soc.* **1963**, *85*, 362; (b) Corey, E. J.; Mitra, R. B.; Uda, H. *J. Am. Chem. Soc.* 1964, **86**, 485.

Following a similar idea, Leumann *et al.* synthesized coraxeniolide A in 2000.[22] Tricyclic fragmentation precursor was synthesized from enantiomerically pure (+)-Hajos-Parrish ketone.[23] Base induced fragmentation gave trans cyclononane **2.11** in very good yield. This product was then converted to coraxeniolide A in a few steps.



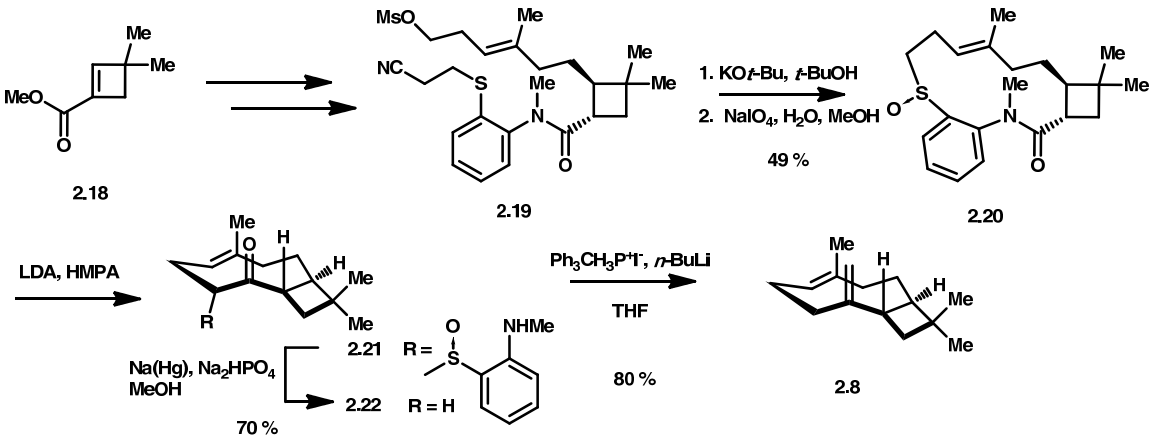
Scheme 2.3 First total synthesis of coraxeniolide A



Scheme 2.4 Total synthesis of caryophyllene and coraxeniolide A

[22] Renneberg, D.; Pfander, H.; Leumann, C. J. *J. Org. Chem.* **2000**, 65.
[23] Hajos, Z. G.; Parish, D. R. *Org. Synth. Col.* **1990**, *7*, 363.

In 2008, Corey *et al.* revisited the syntheses of caryophyllene and coraxeniolide A (scheme 2.4).[24] Starting from enantiomerically pure (+)-Hajos-Parrish ketone **2.13** they finished coraxeniolide A **2.12** in 12 steps in 3.1 % overall yield. While the (-)-Hajos-Parrish ketone led to caryophyllene **2.8** in 13 steps in 10 % overall yield. In both syntheses they built the 9-member core **2.15** and **2.17** which are configurationally enantiomeric. Both enantiomers were then decorated to coraxeniolide A and caryophyllene respectively. The properties and reactivity of these interesting cyclononadienones (**2.15** and **2.17**) will be discussed later in this chapter.



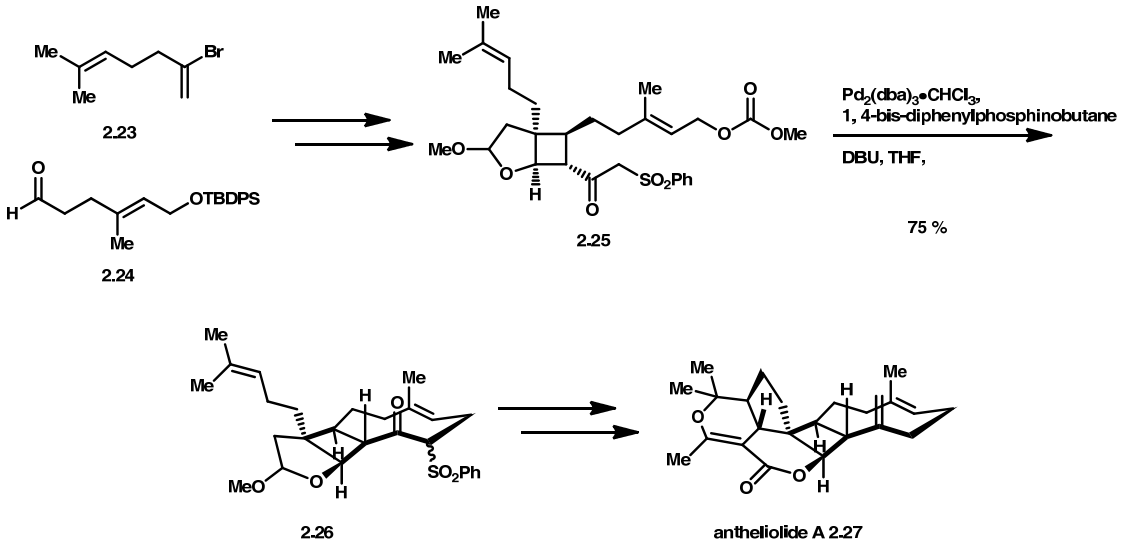
Scheme 2.5 Oshis's total synthesis of caryophyllene

A ring contraction method was also used to construct the 9-member ring skeleton. In 1984, Oishi *et al.* synthesized caryophyllene by contracting a 13-membered ring to a 9-membered ring (Sheme 2.5).[25] They started with the known cyclobutenyl ester **2.18** and converted it to the cyclization precursor **2.19** in 13 steps. Treatment with potassium *tert*-butoxide resulted in the cleavage of the S-protecting group and the concomitant formation of a 13-membered ring sulfide by an intra-molecular S_N2 displacement of the

[24] Larionov, O. V.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 2954.
[25] Ohtsuka, Y.; Niitsuma, S.; Tadokoro, H.; Hayashi, T.; Oishi, T. *J. Org. Chem.* **1984**, *49*, 2326.

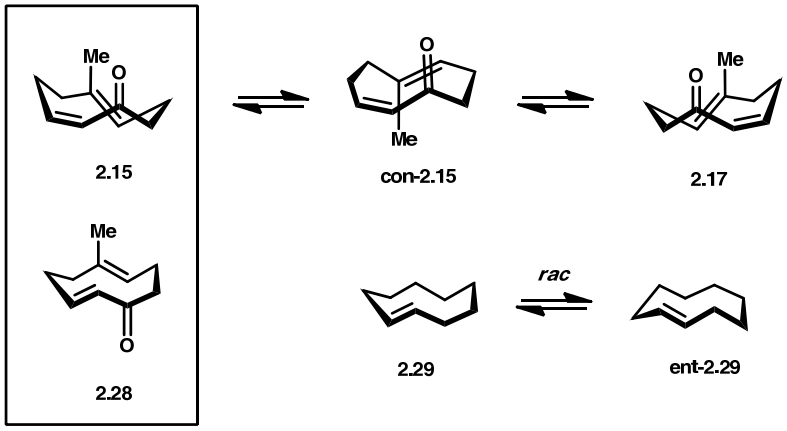
mesylate. Further oxidation of the sulfide using sodium periodate gave the corresponding sulfoxide **2.20**. Lithium diisoproylamide promoted the intramolecular acyl transfer ring contraction reaction and the following sodium amalgam desulfurization afforded the nine-membered ring ketone **2.22** in 70 % yield. The Wittig olefination of **2.22** provided caryophyllene **2.8**.

In 2006, Corey's group used an intra-molecular cyclization reaction to construct the 9-memembered ring in the synthesis of antheliolide A.[26] Starting with vinylic bromide **2.23** and aldehyde **2.24** the fragmentation precursor **2.25** was made in 12 steps in 17 % yield. The Palladium catalyzed intra-molecular Tsuji-Trost reaction gave the 9-memembered core of antheliolide A in 75 % yield. The core was then converted to antheliolide A **2.27** in 14 more steps in a total of 0.019 % yield from the starting material.



Scheme 2.6 Total synthesis of antheliolide A

[26] Mushti, C. S.; Kim, J.-H.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 14050-14052.



Scheme 2.7 Possible cyclononadienone racemization pathway

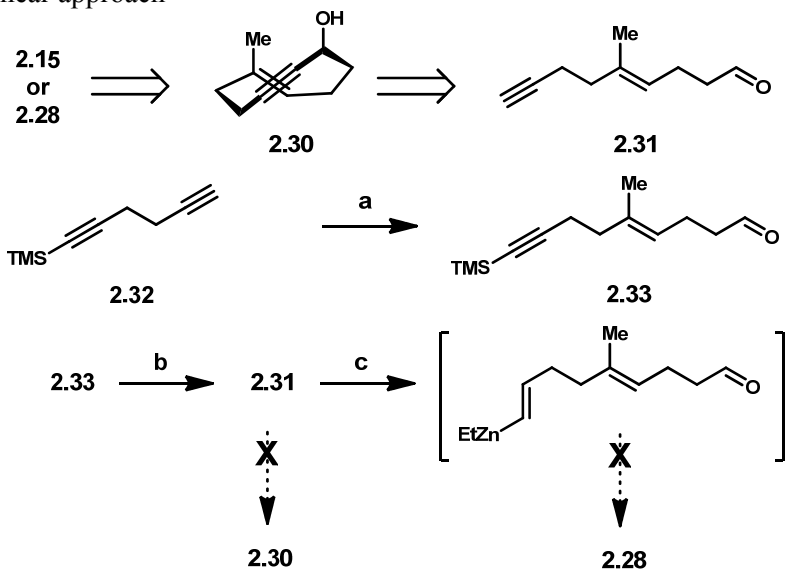
Our interest in the synthesis of nine-membered ring-containing natural products was piqued by the recognition that strategies to access such targets are lacking. We were further attracted to the problem by reports of isolates, for example, **2.2**-**2.5**. Most of the molecules in this class have not been studied in detail due to the paucity of materials obtained from the organisms that produce them coupled with difficulty associated with their chemical synthesis.

Cope and others recognized that in order for *trans*-cyclononene and related ring system to racemize, they must undergo a potentially slow conformational interconversion (**2.29→ent-2.29**).[27] This substance was shown to have a racemization half-life of approximately 4 min at 0 °C, and 6 s at 25 °C. We wondered if more functionalized constructs, for example, **2.15** and analogous structures (*e.g.*, **2.28**), would racemize more slowly than the parent compound. In the case of **2.15**, the racemization process could well be step-wise for example, conversion of **2.15** to **con-2.15** and then to **2.17**. In favorable cases, species such as **2.15** could be prepared directly in enatioenriched form or

[27] Cope, A. C.; Banholzer, K.; Keller, H.; Pawson, B. A.; Whang, J. J.; Winkler, H. J. S. *J. Am. Chem. Soc.* **1965**, *87*, 3644-3649.

resolved by dynamic kinetic methods. Importantly, stereoselective transformations of this substance should be possible when racemization is slow. Hence, this strategy aims to convert traditional chirality into conformational chirality[28] and then to new center chirality.

Scheme 2.8 Linear approach



Reactions and conditions: (a) (i) Cp_2ZrCl_2, $AlMe_3$, $(CH_2Cl)_2$, 25 °C; (ii) $CuLi(hexynyl)_2$, acrolein, HMPA, TMSCl, -78 °C to -30 °C, 30%; (b) TBAF, AcOH, THF, 0 °C, 93%; (c) dicyclohexylboran, hexanes, diethylzinc, 0 °C.

We prepared **2.15** and initiated the study of its structure and reactivity. Originally, our synthesis focused on direct cyclization of an acyclic precursor (**2.31**, Scheme 2.8). The presence of the trans-olefin in **2.31** complicates this strategy, since the olefin geometry necessarily projects the termini in opposite directions. Still, this route benefits from avoidance of transannular strain. The single flask conversion of known diyne **2.32** by way of a carbometalation/transmetalation/conjugate addition sequence[29] gave ynal **2.33** (30 %, unoptimized). Unfortunately, cyclization of the desiylated ynal gave complex

[28] It has long been recognized that conformers will be chiral in the absence of free rotation. van 't Hoff, J. H. The Arrangement of Atoms in Space; Longmans, Green, and CO: 39 Paternoster Row, London, New York and Bombay, 1898. p 54.
[29] Lipshutz, B. H.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 7440–7441.

mixture of products that did not include the desired cyclononenes (**2.31** →**2.28**, **2.30**). We suspect enolization of the aldehyde is a problem for this transformation. The deprotection of **2.33** requires neutral conditions, which also suggests that the aldehyde is not stable under basic conditions.

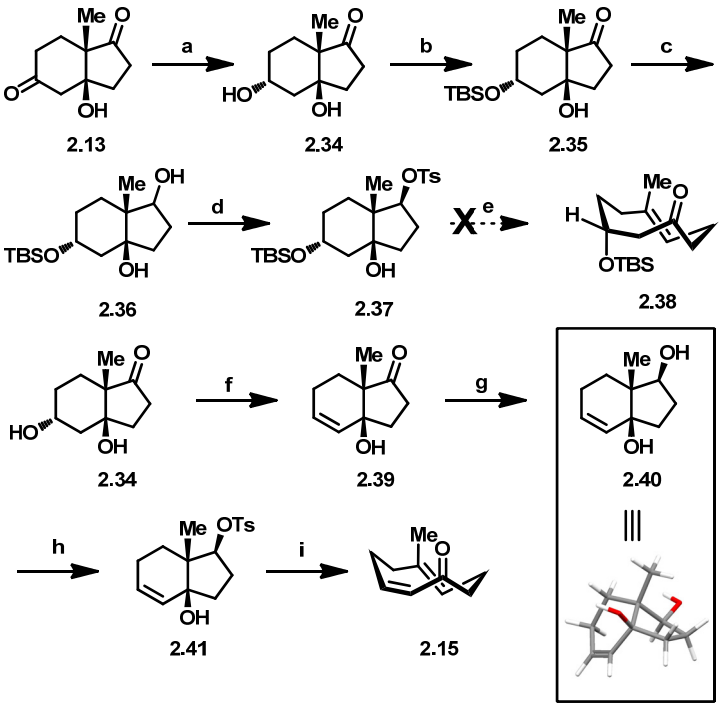
An alternative route to enantioenriched **2.15** is shown in scheme 2.9. Use of ketone **2.13** followed by eventual fragmentation would enable access to enones of type **2.15**. At the outset of this work, it was unclear that the dissymmetric structure would be sufficiently stable to be converted stereoselectively to enantioenriched product; however, this route coincided with that of Corey and Lavinov in their elegant (and stereoselective!) syntheses of caryophyllene and coraxeniolide A.[24] Briefly, ketone **2.13** was prepared in enantioenriched form,[23] reduced, protected, reduced again (→**2.36**), and then activated for fragmentation (→**2.37**). Tosylate **2.37** did not undergo fragmentation under standard conditions[30] or at elevated temperatures. We reasoned the problem could be the torsion angle is not close enough to 180° for fragmentation. Molecular modeling also suggests that **2.37** is highly constrained and the (HO)CCCO(Ts) torsion angle is 139°.[31] Nevertheless, we examined olefinic analog **2.41**, which was calculated to have a much better geometry with a torsion angle of 165.1°. Furthermore, the crystal structure analysis showed that the torsion angle of compound **2.40**, the precursor of **2.41**, is 164.7°.

[30] Grob fragmentation conditions, see also Ref. 21, 22, 24; (a) Paquette, L. A.; Yang, Jiong.; Long, Y. O. *J. Am. Chem. Soc.* **2002**, *124*, 6542-6543; (b) Winkler, J. D.; Quinn, K. J.; MacKinnon, C. H.; Hiscock, S. D.; McLaughlin, E. C. *Org. Lett.* **2003**, *5*, 1805-1808; (c) Molander, G. A.; Huérou, Y. L.; Brown, G. A. *J. Org. Chem.* **2001**, *66*, 4511-4516.

[31] Calculations used (DFT-B3LYP 6-31G(d, p)). (a) All structures were fully optimized by analytical gradient methods using the GAUSSIAN 03 suites, (a) Frisch, M. J.; Trucks, G. W.; Schlege, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C., et al. GAUSSIAN *03*, Revision E.01; Gaussian: Wallingford, CT, 2004; Density functional (DFT) calculations used the exchange potentials of: (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648; the correlation functional of: (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

Pleasingly, treatment of **2.41** under standard conditions gave the desired cyclononadienone **2.15**.

Scheme 2.9 Synthesis of cyclononadienone



Reactions and conditions: (a) $NaBH_4$, methanol, 0 °C, 77%; (b) TBSCl, imidazole, DMAP, CH_2Cl_2, 0 °C to rt, 82%; (c) $Li_{(s)}$, $NH_{3(l)}$, reflux; (d) TsCl, pyridine, DMAP, $CHCl_3$, 0 °C to rt, 2 steps 33%; (e) KH, THF, rt to reflux; NaH, THF, rt to reflux; NaH, DMF, rt; NaH, DMSO, rt; (f) (i) MsCl, TEA, 0 °C; (ii) DBU neat, 80 °C, 53% (from **2.34**); (g) $Li_{(s)}$, $NH_{3(l)}$, reflux, 40%; (h) TsCl, pyridine, DMAP, $CHCl_3$, 0 °C to rt, 80%; (i) NaH, DMSO, rt, 60%.

Further analysis provided several insights into the structure and reactivity of **2.15**. This substance is a low melting crystalline solid that is difficult to manipulate in crystalline form, and we have been unsuccessful in obtaining crystallographic data for this material. The optical rotation [α_D = -17.0] is in agreement with the earlier report. The highest directly observed enantiopurity of **2.15** was 87 % *ee*. This was achieved by chiral HPLC analysis immediately upon extraction from the fragmentation followed by filtration

through a plug of silica gel. Alternatively, oxidative trapping of **2.15** with dimethyldioxirane right after extraction of the fragmentation mixture gave epoxide **2.42**[32] in 90 % *ee*. Although a small degree of racemization takes place during HPLC analysis, this method was used to evaluate the stability of **2.15**. Much slower than *trans*-cyclononene, compound **2.15** racemizes with $t_{1/2}$ = 32 h, 23 °C ($k_{rac} = 3.0 \times 10^{-6}$ s^{-1}, Table 2.1 and Figure 2.3).

Entry	Time (h)	*ee* (%)
1	0	84.4
2	5.5	74.2
3	9.25	68.0
4	23	51.0
5	33.5	40.6

Table 2.1 Racemization of cyclononadienone

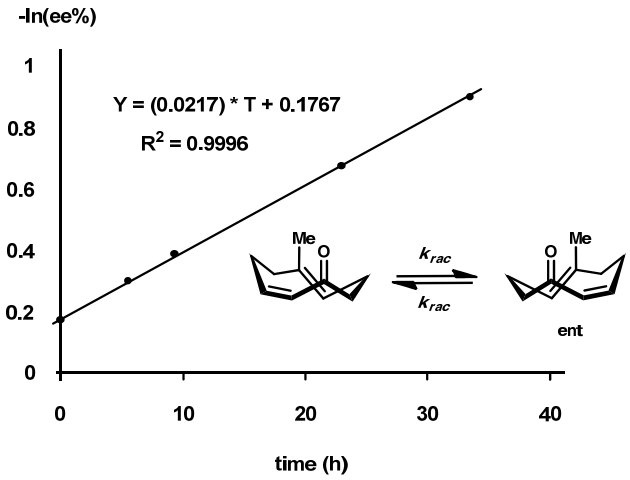


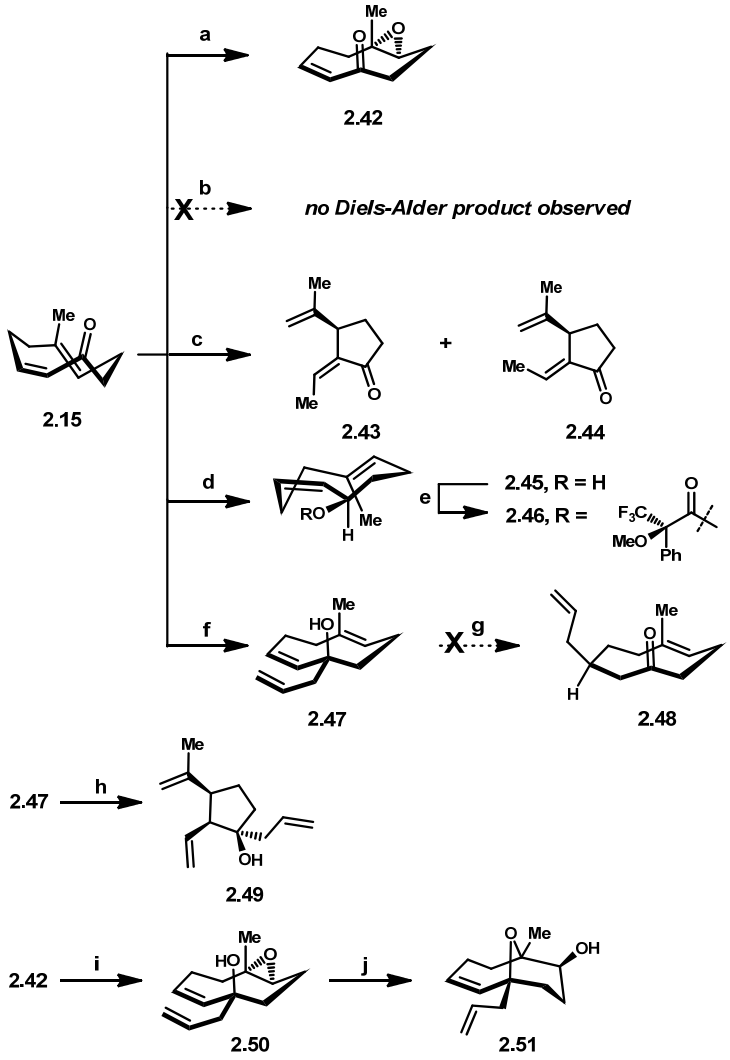
Figure 2.3 Plot of -ln(*ee*%) versus time[33]

NMR analysis strongly suggested that the structure represented as **2.15** is the dominant conformer in solution.[34] Presumably, **2.15** racemizes by way of **con-2.15**, though we have

[32] This compound was characterized by single crystal X-ray diffraction. Crystallographic data for compound **2.40**, **2.42**, and **2.45** have been deposited with the Cambridge Crystallographic Data Center, Nos. CCDC 712607 (**2.40**), CCDC 712606 (**2.42**), and CCDC 712605 (**2.45**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).
[33] Bada, J. L.; Protsch, R. Proc. Nat. Acad. Sci. 1973, 70, 1331–1334. We define half-life as *ee* = 50 %.
[34] NOSEY analysis shows the olefin protons as proximal, cf. 24.

not observed this or other related species. For example, variable temperature ^{1}H NMR analysis of **2.15** proved invariant from 25 °C to 55 °C. Consistent with these observations, computational analysis suggests that **2.15** is more stable than **con-2.15** by 4.2 kcal/mol.[31]

Scheme 2.10 Reactivity of cyclononadienone and its derivatives



Reactions and conditions: (a) DMDO, $CHCl_3$, 0 °C, 96%; (b) cyclopentadiene, rt/Lewis acid (see text), toluene, -78 °C to rt; (c) cyclopentadiene, toluene, 130 °C, 60%, 2:1; (d) $NaBH_4$, methanol, 0 °C, 93%; (e) (*R*)-Mosher's acid, DCU, DMAP, CH_2Cl_2, rt, 80%; (f) allylmagnesium chloride, THF, 0 °C to rt, 75%; (g) KH, 18-crown-6, THF, reflux; (h) toluene, 130 °C; (i) allylmagnesium chloride, THF, -78 °C, 75%; (j) KH, 18-crown-6, THF, -78 °C to rt, 90%.

As indicated above, DMDO epoxidation gave **2.42** in high yield (96 %). Indeed, dissymmetric ketone **2.15** participates in a number of stereoselective transformations. Our initial attempts focused on Diel-Alder reaction in the presence of cyclopentadiene, which did not react at room temperature. Lewis acids Me_2AlCl, Et_2AlCl and $AlCl_3$ also failed to promote this reaction.[35] No cyclopentadiene cycloaddition product was observed at elevated temperatures. Instead, **2.43** and **2.44** were obtained. These α,β-unsaturated ketones are derived from Cope rearrangement of **2.15** followed by isomerization. Stereoselective hydride reduction of **2.15** gave the corresponding alcohol **2.45** as a crystalline solid with no deterioration in enatiomeric purity, according to Mosher ester analysis (**2.46**).[36] Allylation produced **2.47** (75 %). Compound **2.47** failed to undergo anion-accelerated oxy-Cope rearrangement at low temperature, and at higher temperature, only the transannular Cope product, trisubstituted cyclopentene **2.49**, was obtained. To further demonstrate the versatility of **2.15**, and to evaluate a potential alternative oxy-Cope sequence, **2.15** was epoxidized and then allylated to give **2.50**. Upon subjection to anion-accelerated oxy-Cope conditions, the transannular epoxide-opened product **2.51** was cleanly obtained (90 %). Transannular cyclization of **2.50** to **2.51** occurs slowly at low temperature. Indeed, when the allylation of **2.42** was run at 0 °C, **2.51** was obtained in 76 % yield (Scheme 2.10).

These studies elaborate earlier findings on cyclononadienone **2.15**, including several stereoselective transformations and insight into the structure of this interesting class of

[35] (a) Murray, L. M.; O' Brien, P.; Taylor, R. J. K. *Org. Lett.* **2003**, *5*, 1943; (b) Jeroncic, L. O.; Cabal, M-P.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 387; (c) Although these Lewis acids failed, trityl perchlorate was effective at promoting conjugate addition to this enone (Ref. 24).

[36] For example, reduction of **2.15** (in one instance enone of 60% *ee* was used) provided **2.45** from which **2.46** was prepared as a mixture of diastereomers (dr = 4:1, corresponding to 60% *ee* of **2.45**). Crystallographic structure determination of **2.45** revealed this material to be a disordered solid composed of both enantiomers (see Ref. 32).

synthetically useful intermediates. Importantly, **2.42**-**2.51** are derived from **2.15**, and are obtained in enatioenriched form. Many dissymmetric compounds related to **2.15** should be readily accessible.

CHAPTER THREE

Spirodiepoxides: Synthesis of Epoxomicinoids

Epoxomicin, a peptide produced by the actinomycete strain No. Q996-17 (isolated from a soil sample collected from Andhra Pradesh State, India). Since its isolation in 1992 epoxomicin has drawn lots of attention because of its activity against solid tumors derived from B16 melanoma.[37] Epoxomicin family includes only a few linear peptides. The structural similarities are: a threonine or serine segment and an α', β'-epoxyketone derived from leucine or γ', δ'-dehydroleucine. Eponemycin **3.2**, epopromycin A **3.3** and epopropromycin B **3.4** (Figure 3.1) are included in this family. These compounds are also identified based on their ability to inhibit plant cell wall synthesis.[38,39] The α', β'-epoxyketone motif is believed to be crucial for biological activities.[40]

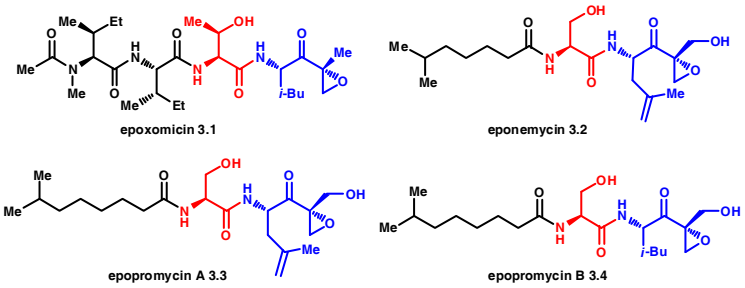


Figure 3.1 The epoxomicin family

The biological profile of epoxomicin also includes proteasome inhibition[39,41,42], immune regulation[43] and anti-inflammatory properties.[44]

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[37] Hanada, M.; Sugawara, K.; Kaneta, K.; Toda, S.; Nishiyama, Y.; Tomita, K.; Yamamoto, H.; Konishi, M.; Oki, T. *J. Antibiot.* **1992**, *52*, 1746.
[38] Tsuchiya, K.; Kobayashi, S.; Nishikiori, T.; Nakagawa, T.; Tatsuta, K.; *J. AntiBiot.* **1997**, *50*, 261.
[39] Sin, N.; Kim, K.-B.; Elofsson, M.; Meng, L.-H.; Auth, H.; Kwok, B. H. B.; Crews, C. M. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2283.
[40] Sugawara, K.; Hatori, M.; Nishiyama, Y.; Tomita, K.; Kamei, H.; Konishi, M.; Oki, T. *J. AntiBiot.* **1990**, *43*, 8.
[41] Spaltenstein, A.; Leban, J. J.; Huang, J. J.; Reinhardta, K. R.; Viverosb, O. H.; Sigafoosb, J.; Crouchc, R. *Tetrahedron Lett.* **1996**, *37,* 1343.

During the study of the biological activities of epoxomicin, Crews *et al.* cocrystallized epoxomicin with the yeast *S. cerevisiae* 20S proteasome (Figure 3.2), which provides a framework to understand the intriguing selectivity of this proteasome inhibitor class. Crews discovered the following mechanism (Schem 3.2). Epoxomicin reacts with to the 20S proteasome results in formation of a morpholino adduct between the epoxyketone parmacophore and the active site amino terminal Thr 1 of the β5 subunit. He further suggested that attack by Thr1 Oγ on epoxomicin results in hemiacetal formation followed by subsequent cyclization of Thr 1 N onto the epoxide resulting in an inversion of C2 and formation of the adduct.[42]

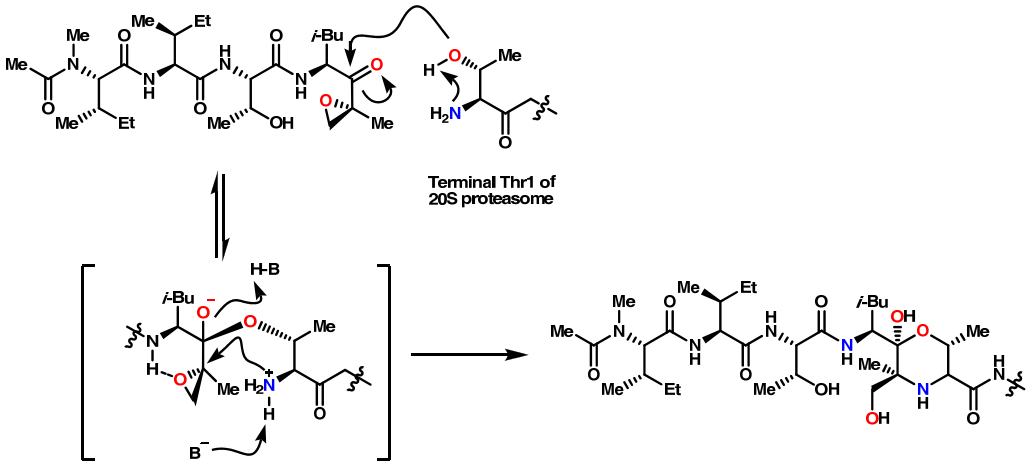

Figure 3.2 Proposed mechanism

Crews *et al.* completed the first total synthesis of epoxomicin in 1999. They started construction of the epoxy-β-aminoketone motif with addition of vinly bromide to known Weinreb amide **3.5**[45] which resulted in formation of the unsaturated ketone **3.6** (Scheme

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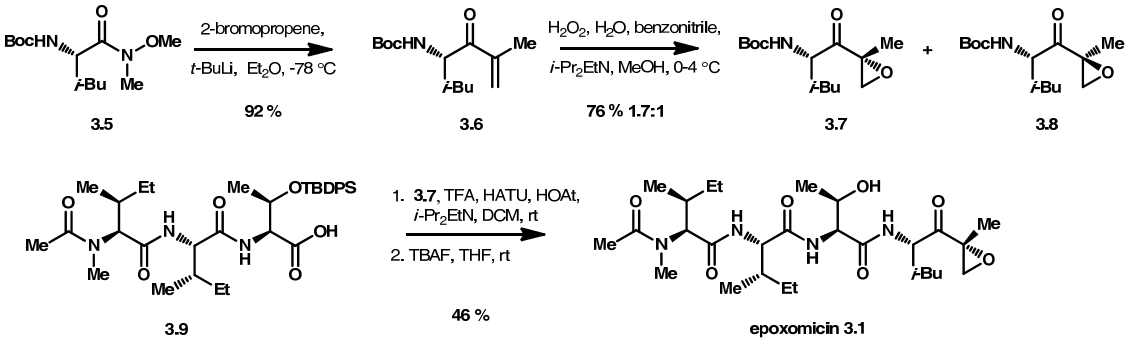
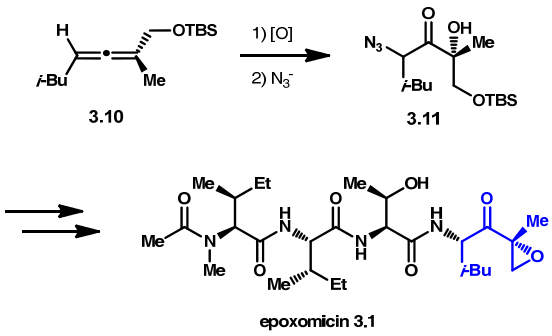
[42] Groll, M.; Kim, K.-B.; Kairies, N.; Huber, R.; Crews, C. M. *J. Am. Chem. Soc.* **2000**, *122*, 1237.
[43] Schwarez, K.; de Giuli, R.; Schmidtke, G.; Kostka, S.; van den Broek, M.; Kim, K.-B.; Crews, C. M.; Kraft, R.; Groettrup, M. *J. Immunol.* **1999**, *162*, 6147.
[44] Meng, L.-H.; Mohan, R.; Kwok, B. H. B.; Elofsson, M.; Sin, N.; Crews, C. M. *Proc. Natl. Acad. Sci.***1999**, *96*, 10403.
[45] Fehrentz, J.-A.; Castro, B. *Synthesis* 1983, 676.

3.1). Subsequent epoxidation with hydrogen peroxide furnished a mixture of epoxides **3.7** and **3.8** (1.7:1), which were separated by column. The TBDPS-protected tripeptide acid **3.9** was prepared using standard peptide synthesis methods in good yields. Removal of the Boc group of **3.7** by brief treatment with neat trifluoroacetic acid gave the deprotected TFA salt. Without purification the TFA salt was then coupled to tripeptide **3.9** with HATU and HOAt to give TBDPS protected epoxomicin. Removal of the TBDPS group with TBAF finished epoxomicin **3.1**.



Scheme 3.1 First total synthesis of epoxomicin



Scheme 3.2 Total synthesis of epoxomicin via spirodiepoxide

In 2004, the Williams' group reported the first application of spirodiepoxides (SDEs) in total synthesis (Scheme 3.2).[46] Epoxomicin was synthesized using SDE intermediates with the longest linear sequence of 12 steps and 26 % overall yield. The main focus of the

[46] Katukojvala, S.; Barlett, K. N.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.* **2004**, *126*, 15348.

synthesis was construction of the epoxide motif (highlighted in blue). Allene **3.10** was treated with DMDO to give SDE intermediate, followed by nucleophilic opening by azide furnished α-azido, α'-hydroxy ketone **3.11**. The latter was then converted to epoxomicin **3.1** in five additional steps.

Use of SDE methodologies allows for simple systems to be elaborated to much more complex and densely functionalized motifs via oxidation of relatively simpler allene substrates.[47] In order to further understand the structure and reactivity of this group, the focus has been on stereoselective allene oxidation, spirodiepoxide transformations, and development of a mechanistic framework to rationalize and predict the behavior of this functionality. The research findings disclosed here focus on solvent, oxidant and substrate-dependent allene epoxidation and the application of these findings to the synthesis of analogs of the proteasome inhibitor epoxomicin.[48]

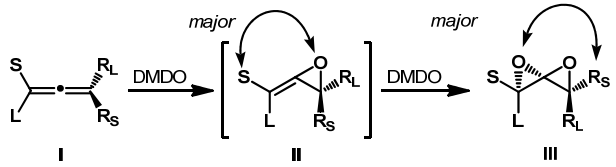
Scheme 3.3 shows a simple steric model for allene to spirodiepoxide conversion (**I** → **II** → **III**).[49] This model assumes that the site of first oxidation is selective, e.g., the $\mathbf{R_S}/\mathbf{R_L}$ terminus in the case of **I**. The preferred approach of oxidant occurs on the same side as the small substituent on the non-reacting terminus of the allene, or allene oxide (see arrows). Prior studies support the above model and suggest that the first oxidation is selective (**I** → **II,** ~10:1) and that the second is not (**II** → **III**, ~1:1).[49] It is noteworthy that these foundational studies focused exclusively on achiral and racemic allenic

[47] (a) Lotesta, S. D.; Hou, Y.; Williams, L. J. *Org. Lett.* **2007**, *9*, 869. (b) Ghosh, P.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.* **2007**, *129*, 2438. (c) Shangguan, N.; Kiren, S.; Williams, L. J. *Org. Lett.* **2007**, *9*, 1093. (d) Lotesta, S. D.; Kiren, S.; Williams, L. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 7108. (e) Wang, Z.; Shangguan, N.; Cusick, J. R.; Williams, L. J. *Synlett* **2008**, *2*, 213. (h) Ghosh, P.; Zhang, Y.; Emge, T. J.; Williams, L. J. *Org. Lett.* **2009**, *11*, 4402. (i) Ghosh, P.; Cusick, J. R.; Inghrim, J.; Williams, L. J. *Org. Lett.,* **2009**, *11*, 4672. (i) Duffy, R. J.; Morris, K. A.; Romo, D. Tetrahedron **2009**, *65*, 5879.

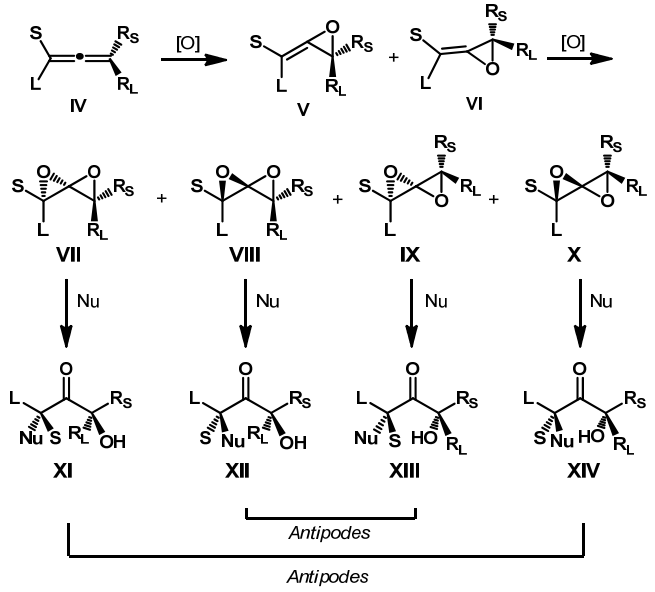
[48] Yue Zhang, Joseph R. Cusick, Partha Ghosh, Ning Shangguan, Sreenivas Katukojvala, Jennifer Inghrim, Thomas J. Emge, and Lawrence J. Williams J. *J. Org. Chem.* **2009**, *74*, 7707.

[49] Crandall, J. K.; Batal, D. J.; Sebesta, D. P.; Lin, F. *J. Org. Chem.* **1991**, *56*, 1153.

hydrocarbons, where the allene was the sole stereogenic moiety and the substituents were simple linear or branched alkanes. These observations are consistent with the notion that allene epoxidation (i.e., allene oxide formation) is slower and more selective than allene oxide epoxidation.[50]



Scheme 3.3 Allene diepoxidation model



Scheme 3.4 Allene oxidation followed by nucleophile opening model

Spirodiepoxide formation represents an unusually complex set of stereochemical possibilities.[51] Although many interesting outcomes are possible, we focus on the complexities related to epoxidation of stereogenic allenes. In principle, an enantiopure allene can give as many as four diastereomeric spirodiepoxides, even in instances where

[50] Although the rationale that allene oxide epoxidation is faster than allene epoxidation appears compelling, unambiguous exceptions are known; see, for example: (a) Camp, R. L.; Green, F. D. *J. Am. Chem. Soc.* **1968**, *90*, 7349. (b) Crandall, J. K.; Machleder, W. H. *J. Heterocycl. Chem.* **1969**, *6*, 777. (c) Marshall, J. A.; Tang, Y. *J. Org. Chem.* **1994**, *59*, 1457.

[51] Note that the central spirodiepoxide carbon will be stereogenic in all but the most symmetric of structures.

the first oxidation is regioselective (**IV** → **V** + **VI** → **VII** – **X**, Scheme 3.4). Upon substitution, which for simplicity we will assume occurs regioselectively and with inversion of configuration, the minor isomers IX and X give rise to the antipodal isomers of the products derived from the major spirodiepoxide products VII and VIII. Hence, *high enantiopurity of the allene precursor will not ensure high enantiopurity of the spirodiepoxide substitution products.*

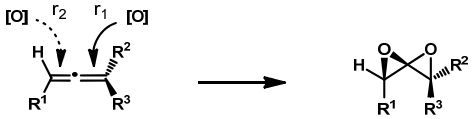
In order for a single spirodiepoxide to be formed both the first and second oxidations must be fully face selective (e.g., **IV** → **V** → **VII**). The intrinsic reactivity of the allene and allene oxide will tend to favor selective first epoxidation and less selective second epoxidation.[52] For instance, oxidation of a stereogenic trisubstituted allene will likely give a preponderance of two spirodiepoxides owing to the high site and stereoselectivity expected for the first epoxidation (S = H, Scheme 3.4). Clearly, allene epoxidation must be selective for spirodiepoxides to be efficiently applied to the synthesis of stereochemically elaborate products.

Our work on functionalized allene indicates that spirodiepoxide formation may be highly stereoselective. Table 3.1 and 3.2 summarize solvent and oxidant dependence as well as the effect of a chiral center adjacent to a stereogenic allene. These results are described along with a stereochemical model that accounts for these findings (Figure 3.3).

---

[52] (a) Although symmetric 1,3-disubstituted allenes will give two spirodiepoxides in instances where the first oxidation is highly selective and the second oxidation is not, 1,3-disubstituted allenes that lack symmetry will give three spirodiepoxides. (b) The possible outcomes of substitution for the major spirodiepoxides derived from enantiopure C2-symmetric allenes constitute another interesting scenario. The expected product for the C_2-symmetric spirodiepoxide is an α-hydroxy-α'-substituted ketone as a single enantiomer (unless the α'-substituent is hydroxyl!). Substitution of the non-C_2-symmetric spirodiepoxide product will give a racemic mixture, unless only one of the enatiotopic termini is opened in the process.

Table 3.1 Stereoselective spirodiepoxide formation: influence of dioxirane and solvent



3.12a R^1 = *i*-Bu, R^2,R^3 = *n*-Bu
3.12b R^1,R^2 = *n*-Bu, R^3 = H
3.12c R^1,R^2 = *i*-Pr, R^3 = H

3.13
(major)

entry	allene	conditions	selectivity[a] r_1	selectivity[a] r_2
1	**3.12a**	DMDO/DME	5:1	na
2	**3.12a**	DMDO/hexane	9:1	na
3	**3.12a**	DMDO/acetone	10:1	na
4	**3.12a**	DMDO/CH_2Cl_2	>20:1	na
5	**3.12a**	DMDO/$CHCl_3$	>20:1	na
6	**3.12a**	DMDO/CCl_4	>20:1	na
7	**3.12a**	DMDO/*t*-BuOH	>20:1	na
8	**3.12b**	DMDO/acetone	10:1	1.1:1
9	**3.12b**	DMDO/CH_2Cl_2	>20:1	1.8:1
10	**3.12b**	DMDO/$CHCl_3$	>20:1	2.0:1
11[b]	**3.12b**	DMDO/CCl_4	>20:1	1.4:1
12[c]	**3.12b**	MEDO/MEK	14:1	1.3:1
13	**3.12b**	DEDO/DEK	16:1	1.5:1
14	**3.12c**	DMDO/acetone	10:1	2.5:1
15	**3.12c**	DMDO/CH_2Cl_2	>20:1	3.3:1
16	**3.12c**	DMDO/$CHCl_3$	>20:1	5.0:1
17	**3.12c**	DMDO/CCl_4	>20:1	2.0:1
18	**3.12c**	DMDO/*t*-BuOH	>20:1	4.6:1

[a]Ratios determined by ^{1}H NMR. [b]MEDO: methylethyldioxirane, MEK: methyl ethyl ketone. [c]DEDO: diethyldioxirane, DEK: diethyl ketone. The allenes used here were racemic.

We focused on the use of dioxirane oxidants in this study. Dimethyldioxirane (DMDO) was prepared as a dilute solution in acetone (~ 0.10 M)[53] and extracted into halogenated solvent. The resultant comparatively concentrated solutions (~ 0.3 M) contained only trace quantities of residual acetone (<3 %).[54] These solutions were diluted to 0.1 M by addition of the solvents indicated in Table 3.1. Methylethyldioxirane (MEDO) and diethyldioxirane (DEDO) were prepared as solutions in their parent ketones. In contrast to acetone solutions of DMDO, these other dioxiranes are not readily extracted into

[53] The supporting information in ref 47b describes in detail the method used to prepare DMDO.
[54] Ferrer, M.; Gibert, M.; Sánchez-Baeza, F.; Messeguer, A. *Tetrahedron Lett.* **1996**, *37*, 3585.

halogenated solvent, and consequently, solvent studies were not conducted for these oxidants.[55]

Consistent with the analysis outlined above, achiral allenes such as **3.12a**[47c] give two diastereoisomeric spirodiepoxides (Table 3.1, entries 1-7). Such oxidations enable the direct determination of face selectivity for the first epoxidation of an allene. For electron-rich allenes where $R_L = R_S$ (Scheme 3.4), the first oxidation should take place at the more substituted terminus. Since $R_L = R_S$ (Scheme 3.4) the two faces of the second π-bond are equivalent and only two diastereomeric spirodiepoxides are formed. The ratio is apparent upon inspection of the ^{1}H NMR of the mixture. Although DMDO/acetone solutions give good selectivity for the first oxidation (r_1 = 10:1) and is superior to solvents such as DME and hexanes (entries 1-3), DMDO in chlorinated solvents and *tert*-butyl alcohol gives excellent selectivity for the first oxidation (r_1 > 20:1).

Oxidation of allene **3.12b** with DMDO in acetone gave four products in an approximate ratio of 11:10:1.1:1. This is understood as reflecting a selective first oxidation for which $r_1 \approx$ 10:1 and a unselective second oxidation for which $r_2 \approx$ 1.1:1 (entry 8, Table 3.1). Again acetone was found to be inferior to halogenated solvents for these oxidations. Interestingly, chloroform is slightly superior to the other halogenated solvent combinations examined (entries 8-11). MEDO and DEDO are also superior to acetone but less selective than DMDO/chloroform (entries 12 and 13). For these oxidants, the

[55] For the synthesis of MEDO and DEDO, see: (a) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847. Other methods of oxidation were also evaluated, such as the use of Shi's fructose-derived catalyst, Jacobsen's (salen)manganese(III) catalyst, as well as trifluoromethyl methyl dioxirane (TFDO). Oxidation with these reagents was difficult to reproduce and led to the formation of several products. For the Shi oxidation, see: (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (c) Zhu, Y.; Tu, Y.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 7819. For the Jacobsen epoxidation, see: (d) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (e) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063. For the original preparation of TFDO and its use as an oxidant, see: (f) Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc.* **1989**, *111*, 6749.

selectivity of the first epoxidation is improved significantly and that of the second oxidation is improved slightly relative to acetone. These data may reflect subtle solvent effects and are consistent with the increased steric bulk of MEDO and DEDO in comparison to DMDO. We also examined branched allene **3.12c**. Similar trends were observed, albeit with generally higher selectivity (entries 14-18). Although only modestly improved, the face selectivity of the second oxidation of unfunctionalized alkyl allenes is superior in halogenated solvent (entries 15-17). Branching improves the face selectivity of the second oxidation,[49,56] which is further enhanced in halogenated solvent and tert-butyl alcohol (e.g., compare entries 10 and 16). DMDO in chlorinated solvent, however, is the most selective and convenient dioxirane system studied to date.[57]

The face selectivity of chiral trisubstituted allenes is shown in Table 3.2. The first oxidation is outstanding for each substrate (r_1 > 20:1). In our synthesis of epoxomicin, low temperature oxidation of silyl ethers of type **3.10** gave four spiodiepoxides with two major isomers in modest ration in DMDO/acetone along with minor isomers.[58] DMDO/chloroform oxidation gave only two spirodiepoxides (2:1). This ratio was higher for the allene bearing branched substituents (**3.20**, 3.3:1) . However, divergent results were observed from the related stereoisomeric allenes **3.16a**[47b] and **3.16b**. One isomer

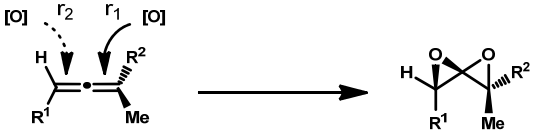
[56] Spirodiepoxide formation from di-tert-butylallene is high (~9:1), even in acetone.

[57] Structure assignments of the diastereomeric spirodiepoxides described in Table 3.1 are based on analogy to other spirodiepoxides. There is strong evidence to support these assignments. Although Crandal and coworkers (ref 49) provided rigorous proof of structure of a spirodiepoxide derivative in only one instance, all of that work was supported by compelling, albeit circumstantial, spectroscopic evidence and the logical force of the steric model itself. Our work (ref 46,47), especially the communication related to the present work (ref 46), provides numerous unambiguous structural proofs of spirodiepoxide derivatives, including both major and minor isomers, by chemical correlation, total synthesis, or crystallographic analysis. Without exception, these data support the steric models presented here.

[58] Structures for the major isomers listed in Table 3.2 were assigned as follows: A derivative of 3.10 was correlated to the natural product epoxomicin (ref 46). Spectral data for compound 3.20 matched reported data for this material (ref 48). The major isomer of compound **3.18** was derivatized and thence correlated to the natural product erythromycin (ref 47b). One of the two azide derivatives obtained from the mixture of spirodiepoxides **3.21b** (compound 3.34) was crystallized and subjected to single-crystal X-ray analysis. Spirodiepoxides **3.21a**, the other isomer of **3.21b**, and **3.22** were based on close analogy to the major isomer of **3.23**.

showed enhanced selectivity upon epoxidation (**3.16a**, 5:1), whereas a 1:1 mixture was obtained from the epimer (**3.16b**). Replacement of the methyl group on the stereogenic carbon of **3.16a** with ethyl further improved selectivity (**3.17**, 6:1) as did replacement of the electron donating alkyl group R_1 with hetero functionality[47b] (**3.18**, 8:1). Thus, selectivity of the second oxidation depends on the allene substitution pattern and relative stereochemistry of proximal substituents.[57,59]

Table 3.2 Stereoselective spirodiepoxide formation: influence of allene structure



entry	allene	R^1	R^2	product	selectivity[a] r_1	r_2
1	**3.14**	*i*-Bu	CH_2OTBS	**3.19**	>20:1	2:1
2	**3.15**	*i*-Pr	*i*-Pr	**3.20**	>20:1	3.3:1
3	**3.16a**	*i*-Bu		**3.21a**	>20:1	5:1
4	**3.16b**	*i*-Bu		**3.21b**	>20:1	1:1
5	**3.17**	*i*-Bu		**3.22**	>20:1	6:1
6	**3.18**	CH_2OTBS		**3.23**	>20:1	8:1

[a]Ratios determined by ^{1}H NMR.

[59] ^{1}HNMR analysis of the mixture derived from DMDO/acetone gave an approximate ratio of 2:1 for the major isomers. The major and minor isomer signals were not baseline resolved. There was no evidence of minor products formed in DMDO/chloroform.

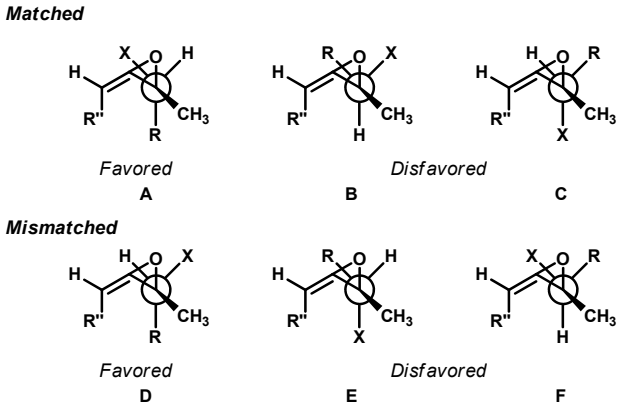


Figure 3.3 Model for diastereoselectivity

In contrast to the data in Table 3.1, the stereoselective oxidations shown in Table 3.2 are not well rationalized by the earlier model (Scheme 3.3), The observed selectivities are modest but follow distinct trends. Consequently, we suggest a refined model for stereo selectivity (Figure 3.3). Oxygen atom transfer to the more substituted terminus of the allene would give the expected allene oxide, based on steric considerations. The presence and nature of branching combined with intrinsic conformational preferences gives rise to the possibility of cooperative (matched) or competitive (mismatched) diastereoselectivity in the second oxidation. In light of the data we favor a rationale based on (1) the allene oxide O-C_{sp3} bond as highly polarized,[50,60] (2) arrangements that represent electronically stabilized conformations as preferred, and (3) these ground-state conformational and stereoelectronic considerations as relevant to low energy transition states.

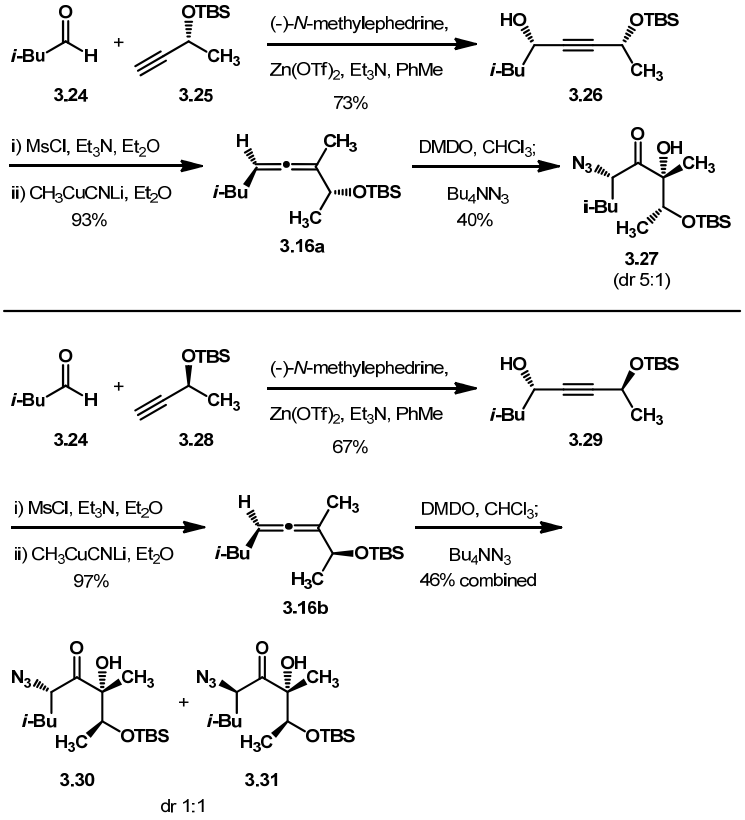
In the absence of overriding factors, the best vicinal electron-donating substituent (R) will be oriented antiperiplanar to the highly polarized allene oxide O-C_{sp^3} (A, Figure 3.3). Conversely, the conformation should be relatively destabilized with an electron-

[60] The high degree of polarization in the allene oxide C-O bond is consistent with facile formation of the oxyallyl zwitterions from this functionality. See: (a) Mann, J. *Tetrahedron* **1986**, *42*, 4611. (b) Wei, L.-L.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773.

withdrawing sustituent (X) arranged antiperiplanar to the allene oxide O-C_{sp^3} bond (C). The presence of an alkyl substituent on the allene oxide O-C_{sp^3} terminus may provide a secondary conformational bias; however, the steric bulk of this group, relative to a hydrogen substituent, should reduce face selectivity in addition to any conformational bias it might otherwise induce (compare Table 3.1, entry 16 with table 3.2, entry 2). The apparent matched and mismatched cases of **3.16a** and **3.16b** are consistent with this model. In both cases, the methyl substituent attached to the allene will project only the methyl hydrogen near one face of the reacting double bond. Compound **3.16a** would project a methyl group near the opposite face of the allene oxide double bond. In contrast, **3.16b** would project only the methine hydrogen near the double bond. Thus the two faces of the double bond for **3.16b** would be nearly indistinguishable, whereas **3.16a** would be comparatively biased. The introduction of R with greater bulk could well increase selectivity, as observed (compare entries 3 and 5, Table 3.2). In addition to these steric and stereoelectronic factors, the intrinsic reactivity of the double bond contributes to epoxidation face selectivity. Since the reactivity of the allene oxide is high, selectivity is often low. Introduction of flanking hetero functionality, as in **3.18** (entry 6) gives rise to higher selectivity (*cf.* entry 5).

Scheme 3.5 summarizes the route employed to prepare elaborated epoxomicin analogues. Asymmetric zinc mediated alkynylation of isovaleraldehyde with **3.25** or **3.28** gave a single diastereomeric product, even though this aldehyde is not α-branched. We have found to obtain good yields in Carreira alkynylations. It is essential to use high-purity aldehyde. In this case distillation is adequate and the aldehyde so obtained can be stored

for months at low temperature. Without distillation, isovaleryl aldehyde gave adol-related products under Carreira alkynylation conditions.[61]



Scheme 3.5 Synthesis of azides

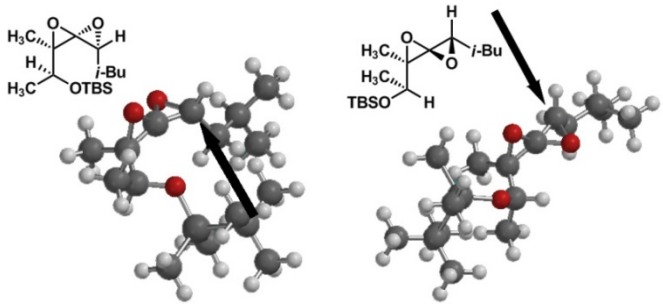


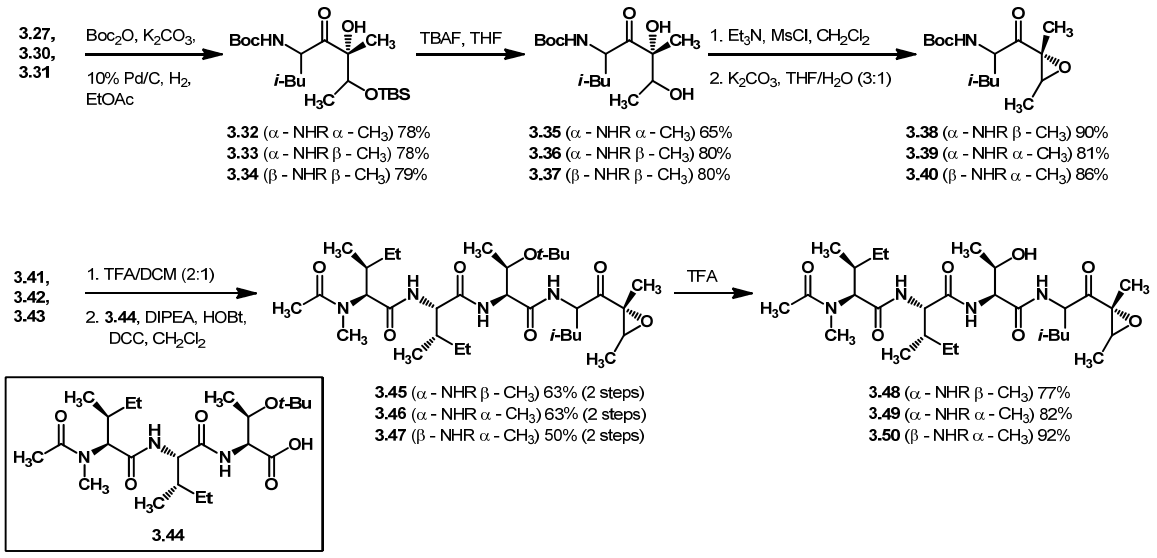
Figure 3.4 Steric influence on major vs minor spirodiepoxide reactivity

[61] (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806. (b) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687. (c) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605. (d) Sasaki, H.; Boyall, D.; Carreira, E. M. *Helv. Chim. Acta* **2001**, *84*, 964. See also: (e) Kirkham, J. E. D.; Courtney, T. D. L.; Lee, V.; Baldwin, J. E. *Tetrahedron* **2005**, *61*, 7219.

Conversion of the propargyl alcohol to the allene gave **3.16a** and **3.16b**. Spirodiepoxidation of these allenes, as described above, was followed by azide opening to give **3.27** from **3.16a**, which was readily isolated from the minor diastereomer (dr = 5:1). In contrast, **3.16b** gave two separable isomers in a 1:1 ratio. Crystallographic analysis established the relative stereochemistry of **3.30** and **3.31**. Interestingly, the diastereomeric spirodiepoxides derived from **3.16a**, as well as the spirodiepoxides derived from **3.16b**, convert to the azide products at significantly different rates. This is consistent with the relative accessibility of the reactive terminus of the spirodiepoxide. As illustrated for the major and minor isomeric spirodiepoxides, derived from **3.16a** in Figure 3.4, the major isomer is less accessible to an external nucleophile than the minor isomer (see arrows). In our total synthesis of epoxomicin (Scheme 3.2) both spirodipoxide isomers reacted completely and both azide products decomposed slowly upon silica gel chromatography, with the minor isomer being lost at a greater rate than the major isomer.[46] In contrast, spirodiepoxides derived from congeners **3.16a** and **3.16b** reacted slowly with azide, probably due to steric considerations, and the reaction did not reach completion. This is reflected in the isolated yields of the products. The azides products, however, were well behaved on silica gel and did not decompose upon chromatography.

Azides **3.27**, **3.30** and **3.31** were taken through the following sequence (Scheme 3.6). Reduction of the azide with concomitant Boc protection (→**3.32-3.34**), and then epoxide formation by mesylation of the secondary alcohol followed by cyclization gave the modified warheads (**3.38-3.40**). Boc group removal was followed by coupling to known

tripeptide **3.41** (→**3.42**-**3.44**). The targets **3.45**-**3.48** were arrived at via deprotection of the *tert*-butyl ether using TFA.



Scheme 3.6 Synthesis of epoxomicinoids

In summary, we have evaluated substrate-dependent formation of spirodiepoxides by way of dioxirane epoxidation. A framework for understanding and predicting face selectivity was outlined. To date, the most convenient dioxirane method for spirodiepoxidation is exposure to DMDO/chloroform solutions. The first oxidation proceeds with excellent face selectivity (>20:1). The second oxidation may proceed with good selectivity (up to 8:1) depending on substrate. These methods were applied to the preparation of three epoxomicin analogues. In addition to providing a simple procedure for improved allene epoxidation, the present work provides a foundation for the systematic evaluation of substrate- and reagent-directed methods for spirodiepoxide formation.

CHAPTER FOUR

Modeling a Macrocyclic Bis[Spirodiepoxide]

Strategy to Erythronolide A

Erythromycin is a macrolide antibiotic that has an antimicrobial spectrum similar to or slightly wider than that of penicillin. It is often used for people who have an allergy to penicillin. It is a secondary metabolite produced by soil inhibiting actinomycete family of a strain of *Saccharopolyspora erythraea* (formerly known as *Streptomyces erythraea*). It was first isolated in 1952 by J. M. McGuire and coworkes at Eli Lilly from some soil samples provided by Abelardo Aguilar.[62] The product was launched as commercial antibiotic by Eli Lilly under the brand name llosone® in the same year.

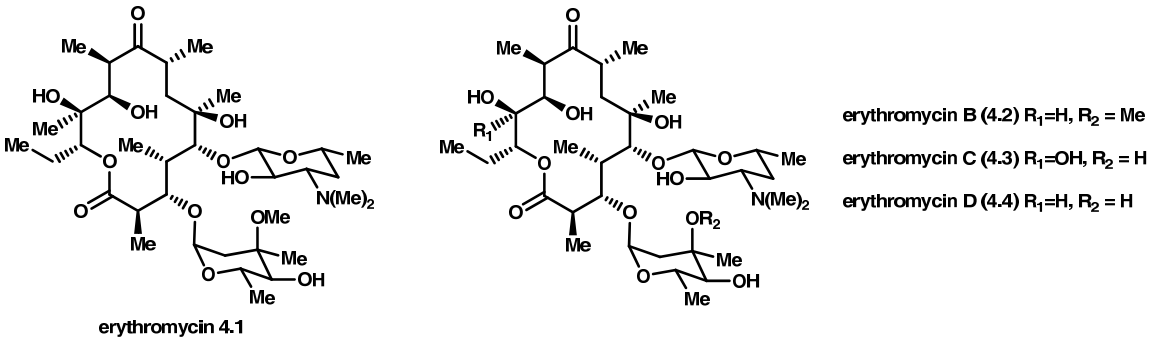


Figure 4.1 Erythromycins

The erythromycin family includes erythromycin **4.1** (also known as erythromycin A) and its congeners erythromycin B, erythromycin C, and erythromycin D (**4.2-4.4**). (Figure 4.1). [63] Erythromycin is composed of a 14-membered macrolactone, known as

[62] McGuire, J. M.; Bunch, R. L.; Anderson, R. C.; Boaz, H. E.; Flynn, E. H.; Powell, H. M.; Smith, J. W. *Antibiot. Chemother.* **1952**, *2*, 281.
[63] (a) Wiley, P. F.; Gerzon, K.; Flynn, E. H.; Sigal, M. V., Jr.; Weaver, O.; Quarck, U. C.; Chauvette, R. R.; Monahan, R. *J. Am. Chem. Soc.* **1957**, *79*, 6062. (b) Wiley, P. F.; Gerzon, K.; Flynn, E. H.; Sigal, M. V., Jr.; Weaver, O.; Monahan, R. Gerzon, K. *J. Am. Chem. Soc.* **1957**, *79*, 6070. (c) Wiley, P. F.; Richard, G.; Pettinga, C. W.; Gerzon, K.

erythronolide A **4.5** to which has sugar cladinose attached at C-3 and desosamine at C-5. (Figure 4.2).[63a]

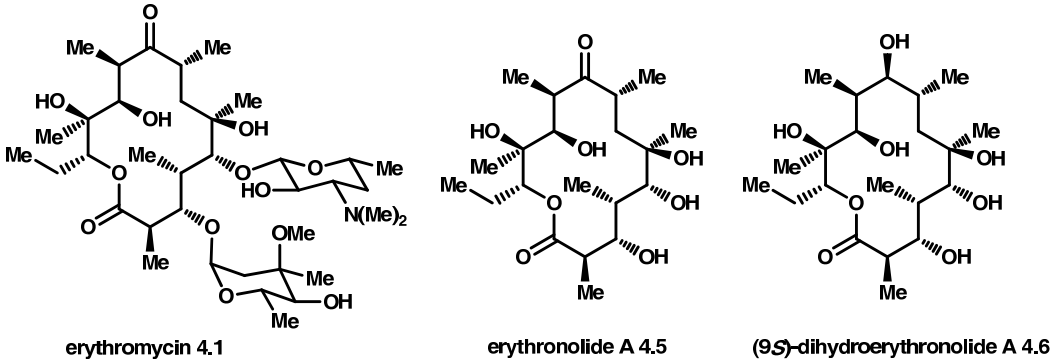


Figure 4.2 Erythronolides

Wiley *et al*. first completely assigned structure **4.1** by degradation study.[63a] The structure was then confirmed by Harris et al. in 1965 by X-ray.[64] The derivative, erythronolide A **4.5**, contains 10 stereocenters. (9*S*)-dihydroerythronolide A **4.6** is an advanced synthetic precursor of erythronolide A **4.5**, with a hydroxyl group at C9. The synthesis of **4.1** from **4.6** is known.[65]

Since its discovery, erythromycin has been widely used as a broad-spectrum antibiotic and has been known to block protein synthesis. However, the molecular details were not revealed until an X-ray crystal structure of ribosome-erythromycin was resolved.[66,67] Figure 4.3 shows the blocking of protein translation by binding of erthyromycin to the 50S ribosomal subunit.

J. Am. Chem. Soc. **1957**, *79*, 6074. (d) Majer, J.; Martin, J. R.; Egan, R. S.; Corcoran, J. W. *J. Am. Chem. Soc.* **1977**, *99*, 1620.

[64] Harris, D. R.; McGeachin, S. G.; Mills, H. H. *Tetrahedron Lett.* **1965**, *6*, 679.

[65] Toshima, K.; Nozaki, Y.; Mukaiyama, S.; Tamai, T.; Nakata, M.; Tatsuta, K.; Kinoshita, M. *J. Am. Chem. Soc.* **1995**, *117*, 3717.

[66] Ban, N.; Nissen, P.; Hansen, J.; Moore, P. B.; Steitz, T. A. *Science* **2000**, *289*, 905.

[67] Katz, L.; Ashley, G. W. *Chem. Rev.* **2005**, *105*, 499.

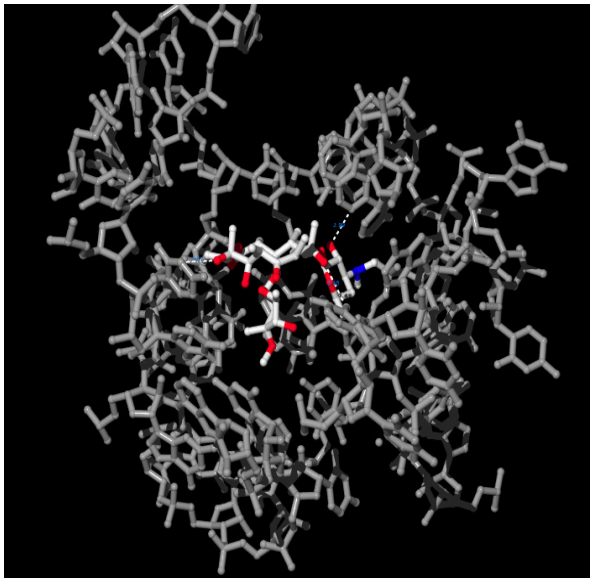


Figure 4.3 Crystal structure of erythromycin-ribosome complex

The first total synthesis of erythromycin A was completed by Woodward in 1981, 30 years later after the isolation.[68] To date, numerous syntheses of compounds from the erythromycin family have been achieved. The routes to this archetypal macrocyclic polypropionate form a gallery of elegant methods for chemical synthesis.[69]

Our study focuses on the total synthesis of (9*S*)-dihydroerythronolide A. Here we present a model study that explores a new strategy to this target.

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[68] R. B. Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B. W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H. *J. Am. Chem. Soc*. **1981**,*103*, 3215.

[69] (a) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569. (b) Paterson, I.; Rawson, D. J. *Tetrahedron Lett.* **1989**, *30*, 7463. (c) Mulzer, J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1452. (d) Stürmer, R.; Ritter, K.; Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 101. (e) Martin, S. F.; Hida, T.; Kym, P. R.; Loft, M.; Hodgson, A. *J. Am. Chem. Soc.* **1997**, *119*, 3193. (f) Evans, D. A.; Kim, A. S.; Metternich, R.; Novack, V. J. *J. Am. Chem. Soc.* **1998**, *120*, 5921. (g) Peng, Z.-H.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 6018. (h) Hergenrother, P. J.; Hodgson, A.; Judd, A. S.; Lee, W.-C.; Martin, S. F. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 3278. (i) Muri, D.; Lohse-Fraefel, N.; Carreira, E. M. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 4036.

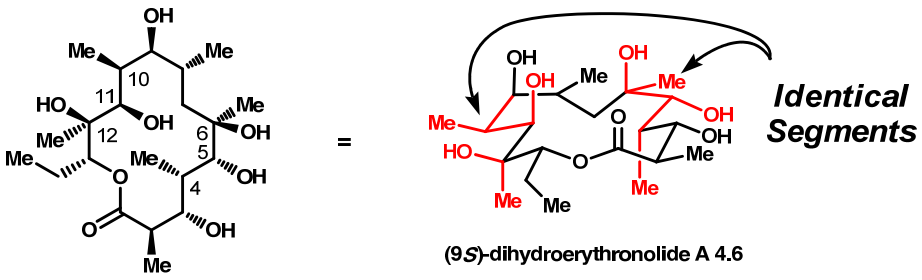
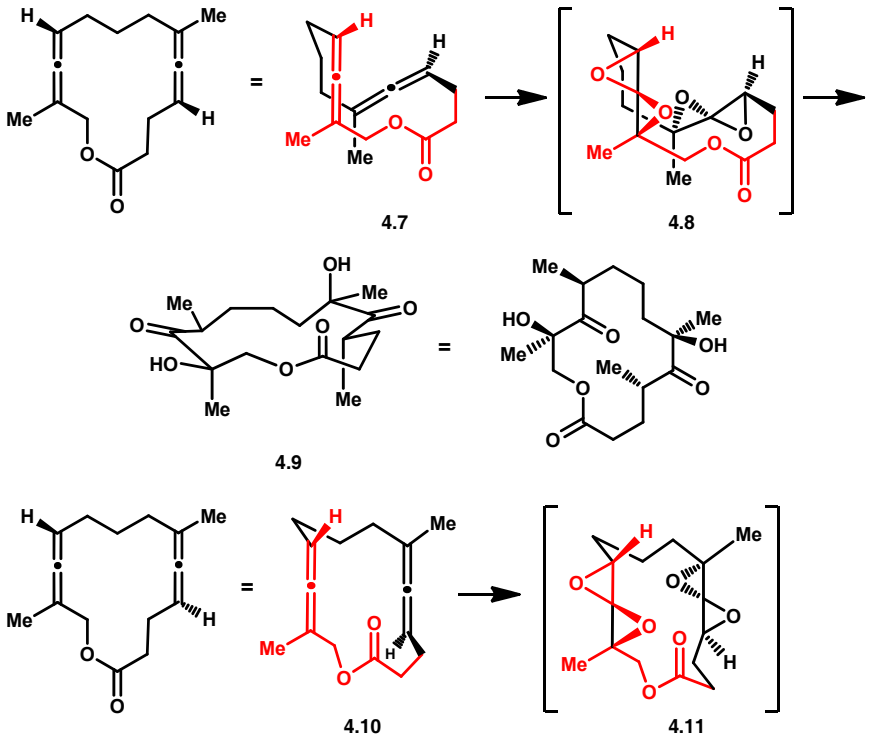


Figure 4.4 Identical Segments in (9*S*)-dihydroerythronolide A

Our aim was to evaluate a strategy of simultaneous formation of the identical C4-C6 and C10-C12 segments in a macrocyclic context. In this case, oxidation would be followed by elaboration of the twin motifs. Late stage introduction of heterofunctionality introduces significant risks related to planning flexibility.[70] However, this approach has the potential advantage to significantly increase tempo and efficiency.



Scheme 4.1 Synthetic plan

[70] Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; John Wiley & Sons, Inc., New York, **1995**, *pp* 4.

Our primary target was compound **4.9** (Scheme 4.1, *cf.* **4.6**). Oxidation of allene **4.7** to the corresponding spirodiepoxide[71] **4.8**, followed by nucleophilic opening (→**4.9**), suggested a direct means of entry to the goal structure. Of course, in the total synthesis the requisite functionality at C1,C2, C8, C9 and C13 would need to be installed probably prior to the epoxidation sequence.

Many of the planned steps of this strategy seemed highly speculative, since there is little precedent to guide expectations with regard to the formation and stability of macrocyclic bis[allenes] of type **4.7**[72] and bis[spirodiepoxides] of type **4.8**,[73] and necessarily, nucleophilic substitution of **4.8**. However, the possibility of the successful conversion of **4.8** to **4.9**, and the implications of the sequence on strategic planning of this and other targets, encouraged us to proceed with this model study. The stereochemical outcome of the epoxidation/addition sequence became the focal point, and the epoxidation of both allene **4.7** and isomer **4.10** was evaluated.

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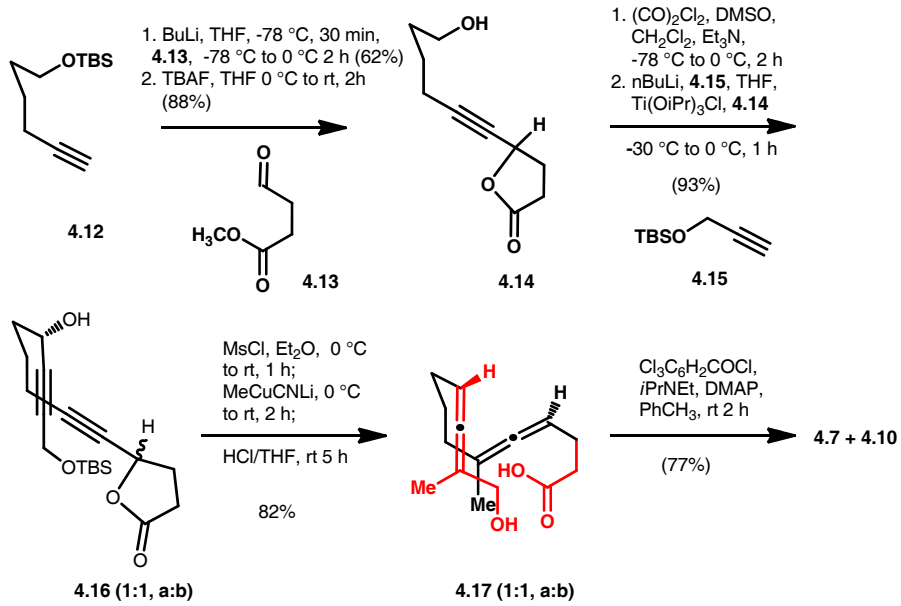
[71] (a) Katukojvala, S.; Barlett, K. N.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.* **2004**, *126*, 15348-15349; (b) Lotesta, S. D.; Hou, Y.; Williams, L. J. *Org. Lett.* **2007**, *9*, 869-872; (c) Ghosh, P.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.* **2007**, *129*, 2438-2439; (d) Lotesta, S. D.; Kiren, S.; Sauers, R. R.; Williams, L. J. *Angew. Chem., Int. Ed. Engl.* **2007**, *46*, 7108-7111; (e) Shangguan, N.; Kiren, S.; Williams, L. J. *Org. Lett.* **2007**, *9*, 1093-1096. (f) Wang, Z.-H.; Shangguan, N.; Cusick, J. R.; Williams, L. J. *Synlett* **2008**, *2*, 213-216.

[72] For cyclic bis[allenes], see: (a) Garratt, P. J.; Nicolaou, K. C.; Sondheimer, F. ***J. Chem. Soc. D****., Chem. Commum.* **1970**, 1219-1220; (b) Baker, R.; Garratt, P. J.; Nicolaou, K. C.; Sondheimer, F. *Tetrahedron Lett.* **1972**, 3425–3428; (c) Garratt, P. J.; Nicolaou, K. C.; Sondheimer, F. *J. Am. Chem. Soc.* **1973**, *95*, 4582–4592.

[73] (a) No bis[spirodiepoxides] are known. The only cyclic spirodiepoxide reported was derived from 1,2-cyclononadiene. (b) Crandall, J. K.; Batal, D. J.; Sebesta, D.P.; Ling, F. *J. Org. Chem.* **1991**, *56*, 1153-1166.



Scheme 4.2 Synthesis of seco acids

The synthesis of **4.7** and **4.10** began with commercial aldehyde **4.13**.[74] and readily available alkyne **4.12**.[75] (Scheme 4.2) Careful lithium alkynylide addition to **4.13** minimized competitive addition to the ester moiety and effected spontaneous lactone formation, which we recognized might be sufficiently reactive to serve as an allene precursor. Removal of the silyl group (→**4.14**) and then oxidation of the primary alcohol gave the corresponding aldehyde. The combination of titanium chloride triisopropoxide and lithium alkynylide[76] derived from **4.15** effected the selective conversion of this aldehyde to a 1:1 mixture of propargyl alcohols **4.16** without complication from the moderately electrophilic lactone.

[74] Also conveniently prepared from γ-butyrolactone, see: Corey, E. J.; Albright, J. O.; Barton, A. E.; Hashimoto, S.-I. *J. Am. Chem. Soc.* **1980**, *102*, 1435–1436.
[75] This known substance was prepared from the corresponding alcohol. Marron, B. E.; Spanevello, R. A.; Elisseou, M. E.; Serhan, C. N.; Nicolaou, K. C. *J. Org. Chem.* **1989**, *54*, 5522-5527.
[76] Reetz. M. T. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556-569.

We explored the single flask conversion of the two propargyl moieties in **4.16** to the corresponding double allene of **4.17**. Even though not highly activated, the propargyl lactone could serve as the immediate precursor to the corresponding C4-C6 allene. The goal, therefore, was to activate the C10-C12 propargyl alcohol and then to add excess cuprate directly to the reaction vessel. This proved successful. Furthermore, it was unnecessary to isolate the silyl ether product. Instead, subsequent addition of aqueous acid in tetrahydrofuran to the reaction mixture effected silyl cleavage and provided seco acid **4.17**, as a 1:1 mixture of isomers, in excellent overall yield. Thus, the sequential addition of reagents for propargyl alcohol activation, subsequent allene formation, and then deprotection effected the single flask conversion of **4.16** to **4.17** in 82% overall yield.

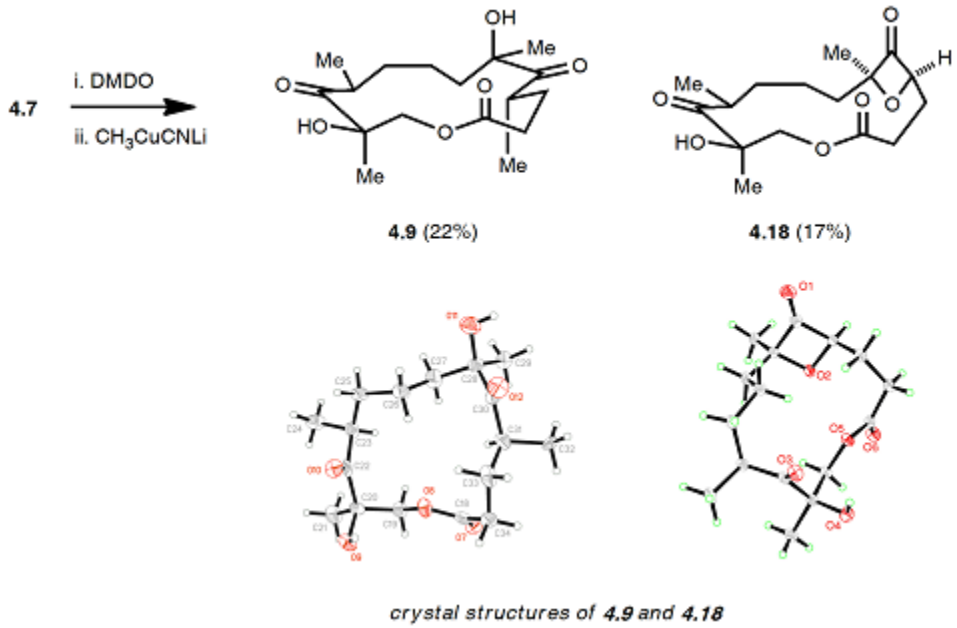
Macrolactonization often requires high temperature, high dilution, and very slow addition of reagent.[77] Cyclization of **4.17** occurred readily at room temperature, with slow addition of reagents over 2 h and a final concentration of substrate of 0.01 M. This simple procedure gave the macrocyclic bis[allenes] **4.7** and **4.10** in a 1:1 ratio as a separable mixture in good yield. Both **4.7** and **4.10** proved to be stable, well-behaved oils.

Molecular modeling of **4.7** suggests that its low energy conformer closely resembles the structure shown in Scheme 4.1. The intrinsic facial bias for approach of reagent to the π-faces of an allene appears to be reinforced by cyclization.[78] Still, the selective conversion of **4.7** to bis[spirodiepoxide] **4.8** was not ensured, as each oxygen would be delivered to

[77] Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911-939.

[78] For a discussion of intrinsic bias and stereochemical models of spirodiepoxide formation, see: Zhang, Y.; Cusick, J. R.; Ghosh, P.; Shangguan, N.; Katukojvala, S.; Inghrim, J.; Emge, T. J.; Williams, L. J. ***2009***, *74*, 7707-7714..

the substrate sequentially, and the topography and conformation of each possible intermediate on the path to **4.8** differ somewhat.



Scheme 4.3 Synthesis of erythronolide model

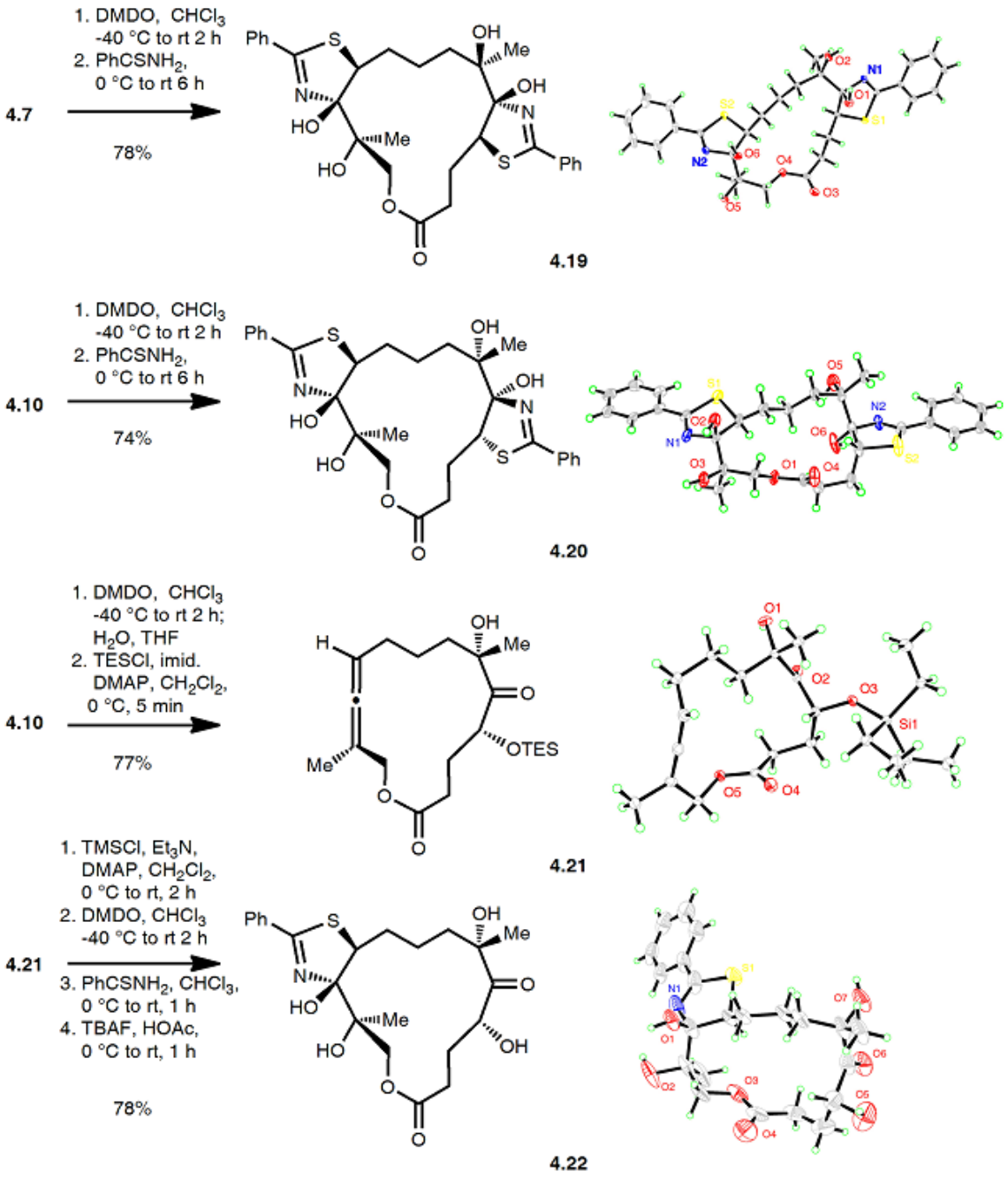
The synthesis of the erythronolide model proceeded smoothly. Structure assignments, including the relative stereochemistry of **4.7** and **4.10**, are inferred but unambiguous based on X-ray crystallographic analysis, as described below and illustrated in Schemes 4.3 and 4.4. Exposure of **4.7** to DMDO (6 equiv) followed by addition of the methyl cuprate to the spirodiepoxide[71c] gave **4.9** (Scheme 4.3). Hence, exhaustive epoxidation of the cyclic bis[allene] generated the corresponding bis[spirodiepoxide] and effected the conversion of the two allene axes of chirality into six stereogenic centers. The 22 % isolated yield of **4.9** represents the combined overall efficiency for the introduction of four oxygens as the bis[spirodiepoxide] and its subsequent conversion to the two ketones,

two tertiary alcohols and two methyl groups and thereby the selective installation of four noncontiguous stereocenters.[79]

Several other minor products were also observed. The most abundant of these, **4.18**, was found to contain an oxetanone in the C4-C6 sector and the desired substitution in the C10-C12 sector. The only published report of oxetanone formation from spirodiepoxide rearrangement (a single example) was effected under flash vacuum pyrolysis conditions.[73b] Presumably, **4.18** arises from Lewis acid mediated rearrangement of the spirodiepoxide.

In contrast to the conversion of **4.7** to **4.9**, epoxidation of **4.7** followed by reaction with thiobenzamide gave a 78% yield of **4.19**, a functionalized bis[thiazoline] (Scheme 4.4).[71d] Two rings and six stereogenic centers were installed by this exercise. The stereochemistry of the aminols at C5 and C11 is consistent with minimization of steric repulsion of the thiazoline substituents.

[79] All products were obtained as single isomers, including **4.9** and **4.18-4.22**. There was no evidence of the formation of stereoisomeric mixtures.

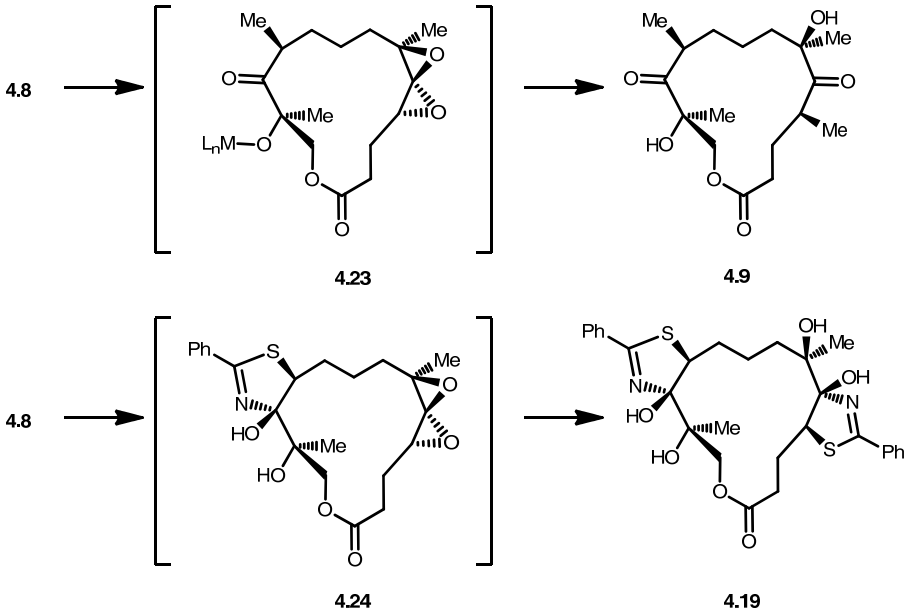


Scheme 4.4 Reactions of macrocyclic allenes

The behavior of **4.10** mirrored that of **4.7**. Molecular modeling suggested that the rendering shown in Scheme 4.1 is a good approximation of the low energy conformer for

this substance. DMDO oxidation of **4.10** gave the isomeric bis[spirodiepoxide], which we assign as **4.11**. Addition of thiobenzamide to this bis[spirodiepoxide] gave bis[thiazoline] **4.20** in excellent yield as well (74%, Scheme 4.4). In the course of these studies, we noticed that the DMDO oxidation of **4.7** and **4.10** led to rapid and selective formation of mono[spirodiepoxide] intermediates. The second allene oxidized slowly at low temperature. Hence, in the presence of only 3 equiv of DMDO at 0 °C the mono[spirodiepoxide] was efficiently prepared. As shown for **4.10**, selective generation of the mono[spirodiepoxide] followed by addition of water gave the corresponding ketodiol. This substance is an oil at room temperature. The TES ether, **4.21**, however, is a crystalline solid. X-ray analysis of this material established that the spirodiepoxide was derived from the more electronrich allene. The mono[spirodiepoxidation] was stereoselective, as expected given the conversion of **4.10** to **4.15**; water addition and silyl protection were regioselective; and the overall yield of **4.21** from **4.10** was 77%. The differences in allene oxidation rates offer the opportunity to incorporate two divergent nucleophiles to the macrocyclic core. Accordingly, **4.21** was silylated and then converted to the corresponding spirodiepoxide. Thiobenzamide addition to the spirodiepoxide followed by liberation of the secondary and tertiary alcohols gave **4.22**. Crystallographic analysis of this material unambiguously confirmed the structural assignment. The efficiency of these transformations, which is good for **4.9** and excellent for **4.19**-**4.22**, coupled with the structural diversity and complexity of the macrolides obtained illustrate the advantage of the macrocycle scaffold strategy. We suggest that the difference in efficiency for the formation of **4.9** and **4.19** from **4.7** stems from the behavior of the corresponding intermediates (e.g., **4.23** and **4.24**, Scheme 4.5). The intermediate derived

from cuprate addition (**4.23**) differs substantially from the intermediate derived from thiobenzamide addition (**4.24**). Since cuprate addition to spirodiepoxides is accompanied by precipitation of the product complex, rate retardation associated with heterogeneous cuprate addition to species such as **4.23** could lower the overall yield for the conversion of **4.7** to **4.9** and increase the likelihood of side product formation (cf. **4.18**, Scheme 4.5). In contrast, the thiazoline intermediates, e.g., **4.24**, are soluble. Regardless, this strategy provides rapid and stereoselective access to targets of high complexity.



Scheme 4.5 Possible pathways

In summary, elaborated macrocycles **4.9** and **4.19**-**4.22** were prepared from scaffolds **4.7** and **4.10**. These precursors were readily obtained in a seven-step sequence that included the efficient single flask conversion of the two propargyl moieties to the seco acid (**4.16**→**4.17**). Whereas **4.21** and **4.22** were fashioned via multistep manipulations, model compound **4.9** and related structures **4.14** and **4.15** were prepared in one oxidation/addition maneuver, for a total of eight steps from commercial reagents. This

strategy and studies on fully elaborated scaffolds are encouraging us to pursuit the total synthesis of natural product with a similar strategy.

CHAPTER FIVE

Spirodiepoxides: Direct Access to Highly Functionalized Diverse Targets

Spirodiepoxides (SDEs) were reported as intermediates in 1966 by Crandall's group in the oxidation of allenes with peracetic acid.[80] The formation of SDE was demonstrated to proceed via allene oxide **5.2**, which was converted to ketone **5.3** and cyclopropanone **5.4** under acidic conditions (Figure 5.1). Further oxidation lead to compound **5.6**, **5.7** and **5.8**, which were presumably generated from SDE **5.5** under acidic conditions.

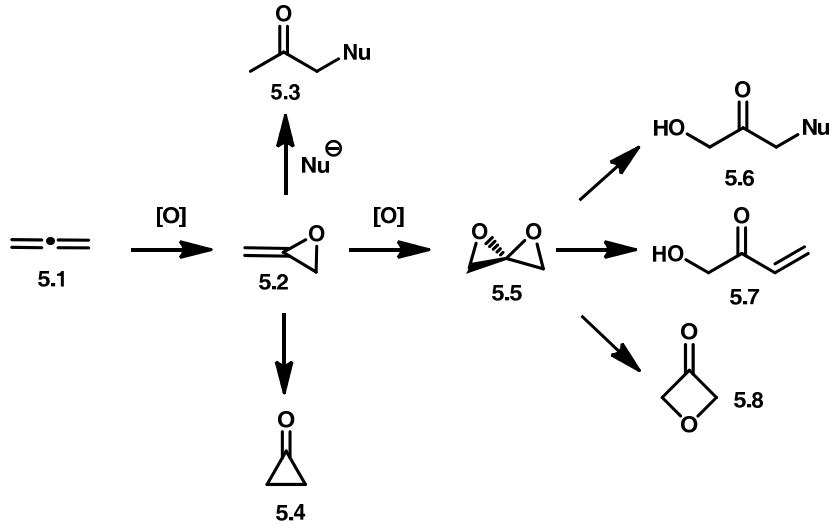


Figure 5.1 Products of allene oxidation with peracetic acid

Crandall also reported an isolable SDE in 1968.[81] Oxidation of the tetrasubstituted allene **5.9** under weakly acidic conditions (*m*CPBA) produced the first isolable SDE in 40 % yield (Scheme 5.1). In most cases, oxidation of an allene under these conditions leads to many products such as oxetanones and enones with almost no selectivity.

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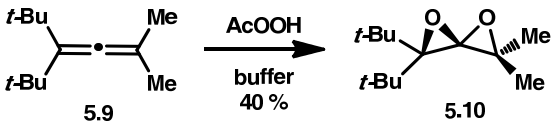
[80] (a) Crandall, J. K.; Machleder, W. H. *Tetrahedron Lett.* **1966**, *7*, 6037. (b) Crandall, J. K.; Machleder, W. H. *J. Am. Chem. Soc.* **1968**, *90*, 7292.
[81] Crandall, J. K.; Machleder, W. H.; Thomas, M. J. *J. Am. Chem. Soc.* **1968**, *90*, 7346.



Scheme 5.1 First isolated SDE

In 1985 Murry reported a method to make dimethyldioxirane (DMDO) as a practical oxidant.[82] DMDO provides neutral oxidation conditions to convert allenes to SDEs with very good yields.[83] Although in principle many interesting and complex structures can be generated from SDEs, selectivity is a serious problem for the use of SDEs as synthetic intermediates. Stereoselective synthesis and opening of SDEs is not well developed; only very limited SDE studies were reported before this decade.[84]

In 2004, the Williams group utilized a SDE strategy for the total synthesis of epoxomicin as stated in chapter three.[85] In 2007, the group successfully developed carbon nucleophile addition to SDEs using organocuprates with good yields.[86] This methodology was applied in a model study towards the synthesis of (9*S*)-dihydroerythronolide A, which was discussed in chapter four.[87] Furthermore, the SDE chemistry was also utilized in the syntheses of psymberin, *epi*-citreodiol and motifs of pectenotoxin.[88] All of the referenced work shows that SDEs enable access to highly functionalized targets of considerable structural diversity in few steps. This chapter will discuss several new and interesting transformations of SDEs.

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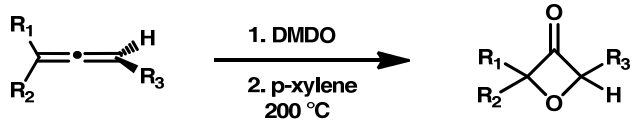
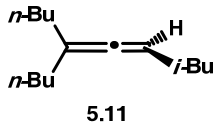
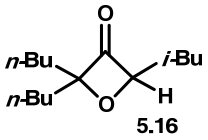
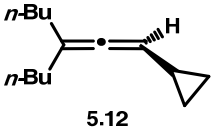
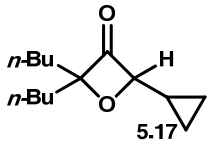
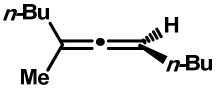
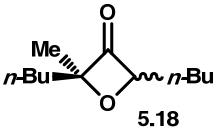
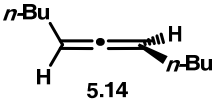
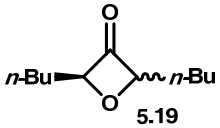
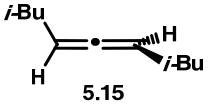
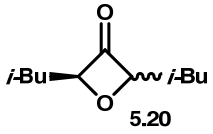
[82] Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847.
[83] Crandall, J. K.; Batal, D. J.; Sebesta, D. P.; Lin, F. *J. Org. Chem.* **1991**, *56*, 1153.
[84] a) Crandall, J. K.; Batal, D. J.; Lin, F.; Riex, T.; Nadol, G. S.; Ng, R. A. *Tetrahedron* **1992**, *48*, 1427. b) Crandall, J. K.; Rambo, E. *Tetrahedron Lett.* **1994**, *35*, 1489. c) Crandall, J. K.; Rambo, E. *Tetrahedron* **2002**, *58*, 7027.
[85] Katukojvala, S.; Barlett, K. N.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.* **2004**, *126*, 15348.
[86] Ghosh, P.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.* **2007**, *129,* 2438.
[87] Ghosh, P.; Zhang, Y.; Emge, T. J.; Williams, L. *Org. Lett.* **2009**, *19,* 4402.
[88] (a) Shangguan, N.; Kiren, S.; Williams, L. J. *Org. Lett.* **2007**, *9 ,* 1093; (c) Ghosh, P; Cusick, J. R.;Inghrim, J.; Williams, L. J. *Org. Lett.,* **2009**, *11,* 4672. (b) Lotesta, S. D.; Hou, Y.-Q.and Williams, L. J. *Org. Lett.* **2007**, *9*, 869; (c) Joyasawal, S.; Lotesta, S. D.; Akhmedov, N. G.; Williams, L. J. *Org. Lett.* **2010**, *12*, 988.

Table 5.1 Oxetanone formation



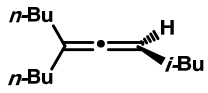
Allenes	Products	Yields
 5.11	 5.16	78%
 5.12	 5.17	81%
 5.13	 5.18	50% (*cis*:*trans* =2:1)
 5.14	 5.19	20% (*cis*:*trans* =2:1)
 5.15	 5.20	50% (*cis*:*trans* =2:1)

One of the SDE degradation products observed under acidic conditions is an oxetanone. We found that trisubstituted SDEs under thermal conditions rearrange to form oxetanones. As shown in Table **5.1**, trisubstituted SDEs derived from allenes **5.11-5.13** could generate oxetanones **5.16-5.18** at elevated temperature with good yields, whereas disubstituted SDEs **5.14** and **5.15** give low yields of oxetanones. The diastereomeric ratio of **5.18**, **5.19** and **5.20** is 2:1, which is consistent with the ratio of the parent spirodiepoxides.[89] Moreover, the major isomer of **5.19** (*cis*) gave two diastereomeric products upon reduction with sodium borohydride, whereas the minor (*trans*) gave a single reduction product. Hence, we propose that oxetanone formation is concerted

[89] NMR showed the ratio of spirodiepoxides derived from allene **5.13**, **5.14** and **5.15** are 2:1.

without involving complete charge separation. Calculations showed that there is a single barrier in this transformation. The frequency calculation of the transition structure also showed that the vibrational mode of the transition state is very similar to one vibrational mode of the SDE, supporting the proposal that the rearrangement is a concerted process.

Table 5.2 Heteroatom nucleophiles

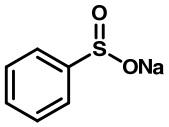
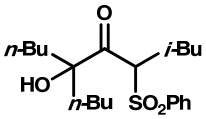
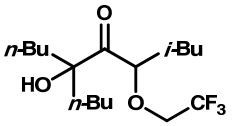
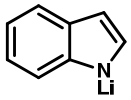
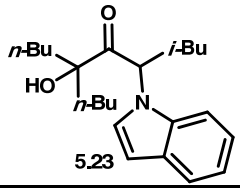


5.11

DMDO

then Nu^-

Product

Nucleophiles	Products	Yields
	 5.21	50%[a]
CF_3CH_2ONa	 5.22	75%[b]
	 5.23	50%[c]

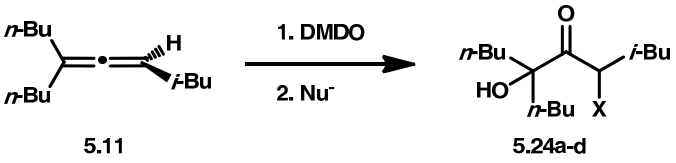
Conditions: Allene **5.11** was oxidized by DMDO in chloroform and the solvent was removed after the completion of the oxidation. The SDE was then added to following solutions. [a] 1.5 equiv of sodium benzene sulfinate, THF, 0 °C - rt, 1 h. [b] 1.5 equiv of NaH in CF_3CH_2OH, 0 °C - rt, 30 min. [c] 3.0 equiv of *n*-BuLi, 3.0 equiv of indole, THF, -78 °C - rt, 1 h.

Nucleophilic opening of SDEs using heteroatoms is known.[90] We studied the reaction using sodium benzene sulfinate, trifluoroethoxide and indolyl anion. The nucleophiles added to the SDE at the less hindered position in good yields. The indolyl anion added to

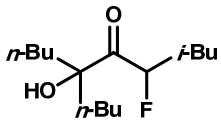
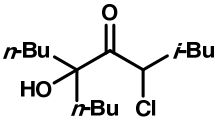
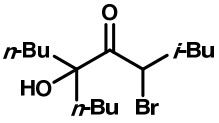
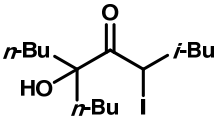
[90] Lotesta, S. D.; Kiren, S.; Sauers, R. R.; Williams, L. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 7108.

the SDE and gave the nitrogen addition product instead of the C-3 addition product, in contrast to single epoxide in the presence of Lewis acids.[91]

Table 5.3 Halide nucleophiles



5.11 5.24a-d

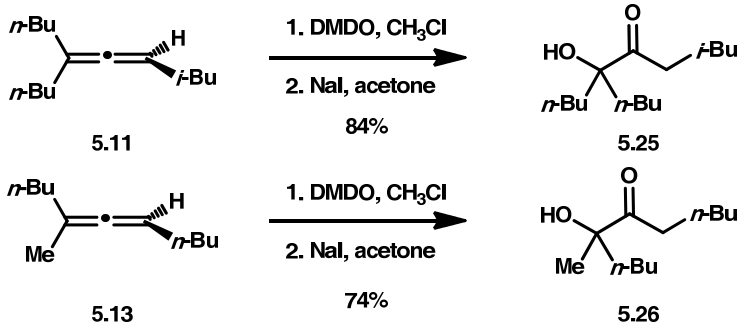
Nucleophiles	Products		Yields
TBAF		5.24a	51 %[a]
LiCl		5.24b	90 %[b]
LiBr		5.24c	90 %[c]
NaI		5.24d	20 %[d]

Conditions: Allene **5.11** was oxidized by DMDO in chloroform and the solvent was removed after the completion of the oxidation. [a] 3.0 equiv of TBAF, THF, 0 °C - rt, 1 h. [b] 2.0 equiv of LiCl, chloroform, 0 °C - rt, 30 min. [c] 2.0 equiv of LiBr, chloroform, 0 °C - rt, 1 h. [d] 2.0 equiv of NaI, acetonitrile, 0 °C - rt, 1 h.

Halide nucleophiles also react with SDEs (Table 5.3). F^-, Cl^- and Br^- all add to the SDE generated by allene **5.11** and form the corresponding halide adducts. Interestingly, sodium iodide reacts with SDEs in acetone and gives reduction products instead of the halide addition products (Scheme 5.2). In anhydrous acetonitrile, NaI adds to the SDE and gives the addition product, but it also gives reduction product **5.25** (20 %) and

[91] Westermaier, M; Mayr, H. *Chem. Eur. J.* **2008**, *14*, 1638.

oxetanone **5.16** (40 %). This could be a potential new method to make oxetanones to complement the thermal conditions.



Scheme 5.2 Reduction reaction

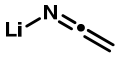
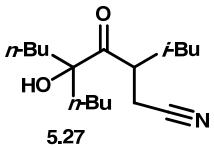
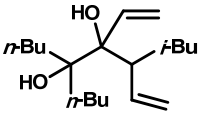
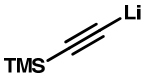
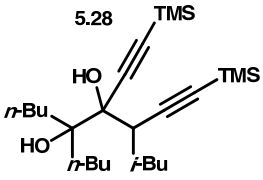
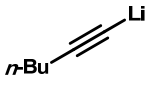
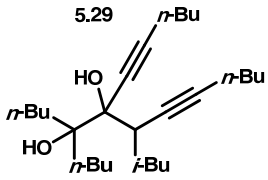
Carbon-carbon bond formation is fundamental to organic synthesis. We developed conditions for the addition of various alkyllithium reagents to SDEs. Under basic conditions, deprotonated acetonitrile, vinyllithium and alkynyllithium added to SDE **5.11** in good yields (Table 5.4). Unlike organocuprate reagents, alkyllithium reagents gave double addition products. The first equivalent added to the less hindered carbon of the SDE, and the second equivalent then added to the ketone generated by SDE opening. We were pleased to observe that the second addition takes place with very high selectivity (>10:1); however, we did not determine the relative stereochemistry of the major products **5.28-5.30**. Regardless of stereochemistry, the diastereoselectivity is unprecedented. Compound **5.28** is a precursor for anionic oxy-Cope rearrangement.[92] We treated compound **5.28** with potassium hydride in THF at 0 °C to afford *cis* alkene **5.33** in 60 % yield. Indeed, alkene **5.33** could be obtained in a single flask in 61% overall yield from allene **5.11** by simply adding 20 equivalents of HMPA to the vinyllithium addition reaction mixture (Scheme 5.3). The relative stereochemistry of diol **5.28** could not be

[92] (a) Paquette L. A. *Tetrahedron* **1997**, *53*, 13971; (b) Paquette L. A. *Synlett* **1990**, *2*, 67; (c) Paquette L. A. *Angew. Chem. Int. Ed. Engl.***1990**, *29*, 609.

confirmed since, in principle, the *cis* olefin can be generated from either diastereomer via chair (**5.31**) or boat (**5.32**)-like transition states. The polar Felkin-Anh model seems inadequate to explain the high selectivity.[93] Lithium coordination to the alkene has been suggested[94] and may be relevant, but has never accounted for such high selectivity. Further studies are needed to determine the stereochemistry of the diol. Even with the relative stereochemistry determined, however, the driving stereoelectronic effect is not obvious, as there may be media and/or aggregation at play and they may bear on the stereochemical outcome.

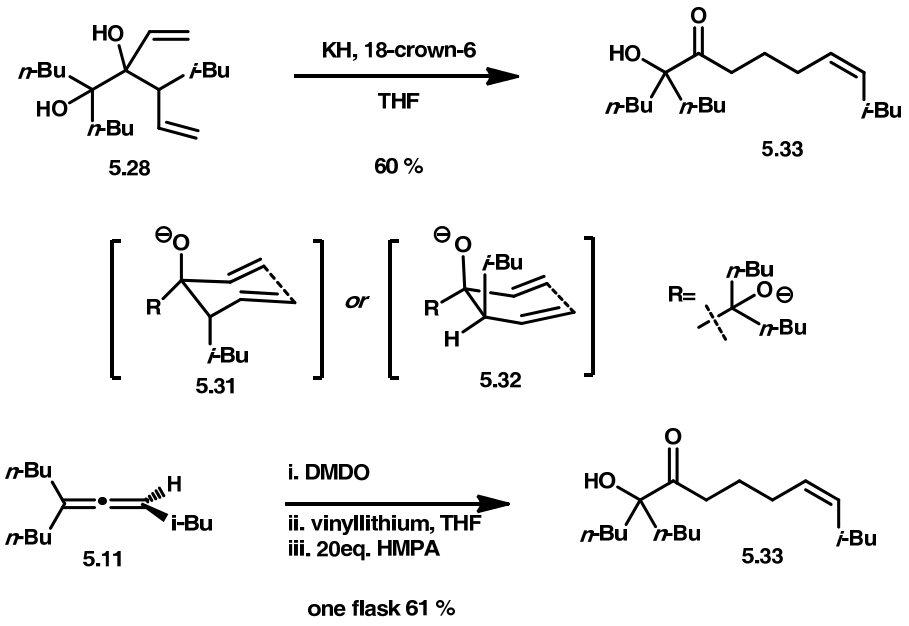
Table 5.4 Carbon nucleophiles

5.11

Nucleophiles	Products	Yields
	 5.27	51 %[a]
		77 %[b]
	 5.28	64 %[c]
	 5.29 5.30	71 %[d]

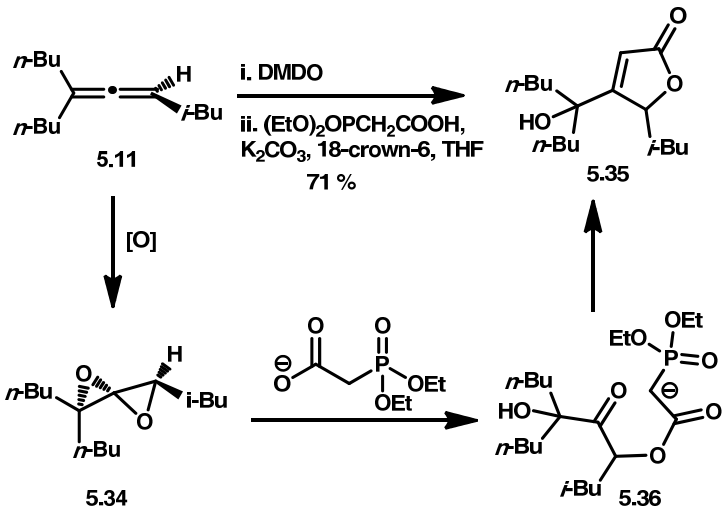
[93] (a) Anh, N. T.; Eisenstein, O.; Lefour, J-M.; Dau, M-E. *J. Am. Chem. Soc.* **1973**, *95*, 6146; (b) Mengel, A.; Reiser, O *Chem. Rev.* **1999**, *99*, 1191.
[94] Harris, C. R.; Kuduk, S. D.; Balog, A.; Savin, K.; Glunz, P. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 7050.

Conditions: Allene **5.11** was oxidized by DMDO in chloroform and the solvent was removed after the completion of the oxidation. [a] 3.0 equiv of acetonitrile, 3.0 equiv of LDA, THF, -78 °C - rt, 1 h. [b] 3.0 equiv of vinyllithium, THF, 0 °C - rt, 30 min. [c] 4.0 equiv of trimethylsilyl acetylene, 4.0 equiv of *n*-BuLi, THF, -78 °C – rt, 1 h. [d] 4.0 equiv of 1-hexyne, 4.0 equiv of *n*-BuLi, THF, -78 °C – rt, 1 h.



Scheme 5.3 Anionic oxy-Cope rearrangement

Butenolides are a class of unsaturated five membered lactones. They are part of many natural product structures (*c.f.* vitamin C). We demonstrated a method to make the butenolide from an allene via the SDE. Butenolide **5.35** could be produced in 71 % yield from allene **5.11** (Scheme 5.4). Allene **5.11** was oxidized by DMDO in chloroform as usual. The freshly formed SDE **5.34** was then added to the solution of potassium diethylphosphonoacetate. Presumably, the SDE is opened by the carboxylate, followed by sequential proton transfer and then intramolecular Horner-Wadsworth-Emmons reaction to give the butenolide **5.35** smoothly.



Scheme 5.4 Butenolide formation

In summary, we developed new and direct reactions using SDEs to synthesize densely functionalized structures in one or two flasks procedures. Allenes can be directly converted to a wide range of functional motifs facilitated by oxidation to their corresponding SDEs. Thermal rearrangement to oxetanones from trisubstituted SDEs was effective. We also explored a variety of possible nucleophiles for SDE opening, including heteroatoms and carbon nucleophiles. The divinyl addition product of a SDE in the presence of HMPA undergoes anion accelerated oxy-Cope rearrangement. Amphinucleophilic reagents can be used to give access to butenolides starting from an allene via the SDE. These examples further demonstrate that SDEs are very versatile intermediate that can be used to build complex molecules concisely.

General Procedure

Starting materials, reagents and solvents were purchased from commercial suppliers (Sigma-Aldrich and Fischer). All reactions were conducted in oven-dried (145 °C) glassware under an inert atmosphere of dry argon. The progress of reactions was monitored by silica gel thin layer chromatography (TLC) plates (pore size 60Å, 250 μm layer thickness, glass support, with fluorescent indicator, Silicycle) visualized under 254 nm UV and charred using vanillin or *p*-anisaldehyde stain. Products were purified by flash column chromatography (FCC) on 230-400 mesh, pore size 60Å, Silicycle, ultra pure silica gel. Infrared (FTIR) spectra were recorded on an ATI MattsonGenesis Series FT-Infrared spectrophotometer. Characterized reactant products were homogeneous by TLC. Proton nuclear magnetic resonance spectra ^{1}H NMR were recorded on either a Varian-400 *I-Nova* (400 MHz), or a Varian-500 *I-Nova* (500 MHz). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, n = nonet, td = triplet of a doublet, dt = doublet of a triplet, b = broad, m = multiplet), and coupling constants in Hz. ^{13}C NMR were recorded on either a Varian-300 instrument (75 MHz), a Varian-400 instrument (100 MHz), or a Varian-500 *I-Nova* (125 MHz). Proton chemical shifts are reported in ppm relative to tetramethylsilane (0 ppm) as the internal standard, Carbon chemical shifts are reported in ppm relative to $CDCl_3$ (77.0 ppm) as the internal standard, Mass spectra were recorded on a Finnigan LCQ-DUO.

Computational Experimental Details

Electronic structure calculations, based on density functional theory (DFT), were carried out with the Gaussian 03 or 09 suite[1] of programs. We utilized the B3LYP functional[2] with 6-31++g(d,p), 6-31+g(d,p), 6-31g(2d,2p) and 6-31 g(d,p) basis sets.[3] Transition states were verified by observing the nature of the negative imaginary frequency.

(1) Gaussian 03, Revision E.01,
M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Wallingford CT, 2004.

Gaussian 09, Revision A.02,
M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

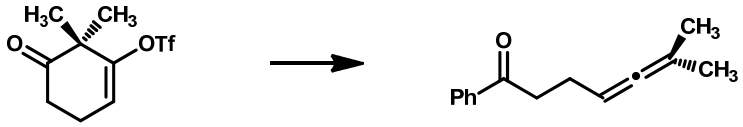
(2) Beche, A. D. *J. Chem. Phys.* **1993**, *98*, 5648; Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(3) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971,** *54,* 724; Hariharan, P. C.; Pople, J. A. *Mol. Phys.* **1974,** *27,* 209; 15. Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980,** *72,* 650; McLean, A. D.; Chandler, G. S. *J. Chem. Phys.* **1980,** *72,* 5639; Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. v. R. *J. Comp. Chem.* **1983**, *4*, 294.

Experimental Chapter One:

Protocol for the formation of triflates:

One of two methods was employed for the formation of the vinyl triflates used in this work. First the use of a stoichiometric amide base such as NaHMDS or LDA for the deprotonation of the corresponding ketone and than treatment with (bis)trifilamide.[95] Second we used 2,6-ditertbutyl-3-methylpyridine for deprotonation of the carbonyl compound and then treatment of the enolate with triflic anhydride.[96]

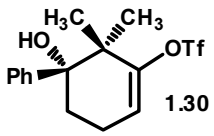


1.27 1.28a

6-methyl-1-phenylhepta-4,5-dien-1-one (1.28a): To an oven dried round bottom flask (15 ml) equipped with a magnetic stir bar and septum was added dry ether (1.3 ml) and vinyl triflate **1.27** (70 mg, 0.258 mmol) under an argon atmosphere. The reaction mixture was cooled to -78 °C, and 1.8 M phenyl lithium (145 µl, 0.290 mmol) was added dropwise via syringe. The reaction mixture was stirred for 1 h at -78 °C and additional 1 h at rt. The reaction mixture was dried *in vacuo* and subjected to flash column chromatography (hexanes 98 %: ethyl acetate 2 %) to provide a colorless oil (39 mg, 76 %); IR ν_{max}(KBr)/cm^{-1} 2907, 1967, 1687, 1597; δ_H (500 MHz, $CDCl_3$) 7.97 (2H, d, J = 8.0 Hz), 7.56 (1H, t, J = 7.34 Hz), 7.47 (2H, t, J = 7.6 Hz), 5.09 (1H, n, J = 2.8 Hz), 3.06 (2H, t, J = 6.9 Hz), 2.43 (2H, qt, J = 7.03), 1.58 (3H, s), 1.57 (3H, s); δ_C (125 MHz,

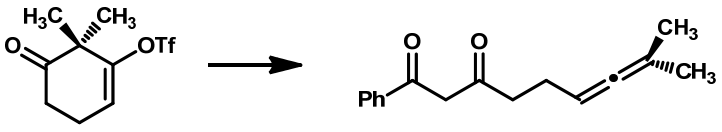
[95] Stang, P. J.; Treptow, W. *Synthesis* **1980**, 4, 283.
[96] Mcmurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, 24, 979.

$CDCl_3$) 201.9, 199.9, 137.5, 133.0, 128.7, 128.2, 96.9, 88.2, 37.4, 23.9, 20.8; (ESI/MS) *m/z* Calcd for $C_{28}H_{32}NaO_2$: 423.2 [M x 2 + Na]; found: 423.2.



1.30

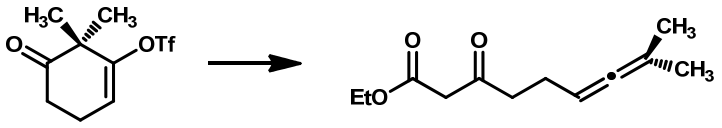
1.30 was isolated in 20 % yield when the reaction was quenched after stirring for 20 min at -78 °C. IR ν_{max}(KBr)/cm^{-1} 3447, 2909, 1447; δ_H (500 MHz, $CDCl_3$) 7.53 (2H, d, *J* =7.6 Hz), 7.38 (2H, t, *J* = 8.0 Hz), 7.31 (1H, t, *J* = 7.0 Hz), 5.83 (1H, dd, *J* = 2.5 Hz), 2.61 (1H, m), 2.53 (1H, m), 2.35 (1H, dt, *J* = 8.6 Hz), 1.88 (1H, s), 1.78 (1H, m), 1.14 (3H, s), 0.97 (3H, s); δ_C (125 MHz, $CDCl_3$) 154.5, 143.3, 127.9, 127.7, 127.3, 115.7, 77.8, 44.2, 30.5, 25.8, 20.7, 18.1; (ESI/MS) *m/z* Calcd for $C_{15}H_{17}F_3NaO_4S$: 373.1 [M + Na]; found: 373.1.



1.27 1.28b

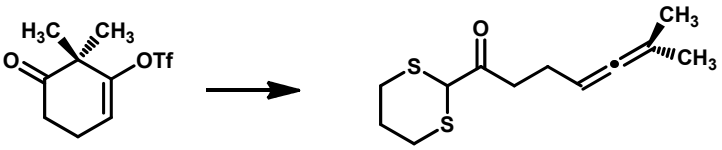
8-methyl-1-phenylnona-6,7-diene-1,3-dione (1.28b): To an oven dried round bottom flask (15 ml) equipped with a magnetic stir bar and septum was added dry THF (1.3 ml) and acetophenone (67 µl, 0.573 mmol). At -78 °C, 1.0 M NaHMDS (620 µl, 0.617 mmol) was added dropwise and stirred for 45 min. A solution of vinyl triflate **1.27** (120 mg, 0.441 mmol) in 1 ml of dry THF was added dropwise. The reaction mixture was stirred for an additional 1 h at -78 °C, and 1 h at rt. The reaction mixture was then dried *in vacuo* and subjected to flash column chromatography (hexanes 95 %: ethyl acetate 5%) to provide a colorless oil (83 mg, 78 %). IR ν_{max}(KBr)/cm^{-1} 3438, 2916, 1967, 1603; δ_H (500 MHz, $CDCl_3$) 7.89 (2H, d, *J* = 7.9 Hz), 7.53 (1H, t, *J* = 7.4 Hz), 7.46 (2H, t, *J* = 7.9 Hz), 5.05 (1H, n, *J* = 2.9 Hz), 2.54 (1H, t, *J* = 7.4 Hz), 2.36 (2H, d, *J* = 6.9 Hz), 1.65 (3H, s), 1.64 (3H, s); δ_C (125 $CDCl_3$, MHz) 202.1, 197.2, 182.9, 135.2, 132.4, 128.9, 128.2,

97.1, 96.5, 87.8, 38.6, 25.2, 20.9; (ESI/MS) *m/z* Calcd for $C_{32}H_{36}NaO_4$: 507.2 [M x 2 + Na]; found: 507.2.



1.27 1.28c

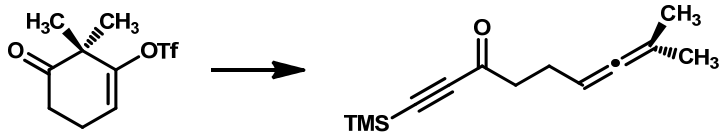
Ethyl 8-methyl-3-oxonona-6,7-dienoate (1.28c): To an oven dried round bottom flask (15 ml) equipped with a magnetic stir bar and septum was added dry THF (1.8 ml) and ethyl acetate (77 µl, 0.872 mmol). At -78 °C, 1.0 M NaHMDS (837 µl, 0.837 mmol) was added dropwise and stirred for 45 min. A solution of vinyl triflate **1.27** (95 mg, 0.350 mmol) in 1 ml of dry THF was added dropwise. The reaction mixture was stirred for an additional 1 h at -78 °C, and 1 h at rt. The reaction mixture was dried *in vacuo* and subjected to flash column chromatography (hexanes 95%: ethyl acetate 5%) to provide a colorless oil (61 mg, 83 %). IR ν_{max}(neat)/cm^{-1} 2981, 1968, 1744, 1717; δ_H (500 MHz, $CDCl_3$) 4.99 (1H, n, J = 2.9 Hz), 4.18 (2H, qt, J = 6.9 Hz), 3.43 (2H, s), 2.61 (2H, t, J = 6.8 Hz), 2.26 (2H, qt, J = 6.9 Hz), 1.65 (3H, s), 1.63 (3H, s), 1.27 (3H, t, J = 7.0); δ_C (125 MHz, $CDCl_3$) 202.4, 201.9, 167.5, 97.1, 87.7, 81.5, 49.6, 41.9, 23.2, 20.8, 14.3; (ESI/MS) *m/z* Calcd for $C_{24}H_{36}NaO_6$: 443.2 [M x 2 + Na]; found: 443.2.



1.27 1.28d

1-(1,3-dithian-2-yl)-6-methylhepta-4,5-dien-1-one (1.28d): To an oven dried round bottom flask (15 ml) equipped with a magnetic stir bar and septa was added dry THF (1.9

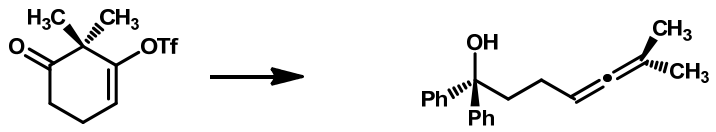
ml) and dithiane (56 mg, 0.463 mmol). At -40 °C, 2.5 M *n*-butyllithium (170 µl, 0.424 mmol) was added dropwise gradually warmed to -20 °C over the course of 1 h. The solution was cooled to -78 °C and vinyl triflate **1.27** (105 mg, 0.386 mmol) in 1 ml of dry THF was added dropwise. The reaction mixture was stirred for an additional 1 h at -78 °C, and 1 h at rt. The reaction mixture was dried *in vacuo* and subjected to flash column chromatography (hexanes 95%: ethyl acetate 5%) to provide a colorless oil (81 mg, 87 %). IR ν_{max}(neat)/cm^{-1} 3425.0, 2905, 1995, 1711, 1213; δ_H (500 MHz, $CDCl_3$) 5.02 (1H, n, J = 2.9 Hz), 4.26 (1H, s), 3.23 (2H, t, J = 6.4 Hz), 2.76 (2H, t, J = 7.4 Hz), 2.60 (2H, ddd, J = 2.7 Hz), 2.29 (2H, qt, J = 2.9 Hz), 2.06 (2H, m), 1.68 (3H, s), 1.67 (3H, s); δ_C (125 MHz, $CDCl_3$) 202.6, 201.8, 97.1, 87.8, 47.4, 39.5, 26.6, 25.5, 23.8, 20.9; (ESI/MS) *m/z* Calcd for $C_{24}H_{36}NaO_2S_4$: 507.0 [M x 2 + Na]; found: 507.0.



1.27 1.28e

8-methyl-1-(trimethylsilyl)nona-6,7-dien-1-yn-3-one (1.28e): To an oven dried round bottom flask (15 ml) equipped with a magnetic stir bar and septa was added dry THF (2.2 ml) and ethynyltrimethylsilane (75 µl, 0.529 mmol). At -78 °C, 2.5 M *n*-butyllithium (194 µl, 0.485 mmol) was added dropwise and maintained at 0 °C for 10 min. The solution was cooled to -78 °C and vinyl triflate 1**.27** (105 mg, 0.386 mmol) in 1 ml of dry THF was added dropwise. The reaction mixture was stirred for an additional 1 h at -78 °C, and 1 h at rt. The reaction mixture was dried *in vacuo* and subjected to flash column chromatography (hexanes 95%: ethyl acetate 5%) to provide a colorless oil (73 mg, 75 %). IR ν_{max}(neat)/cm^{-1} 2979, 2153, 1968, 1734, 1210; δ_H (500 MHz, $CDCl_3$) 5.01

(2H, n, *J* = 2.9 Hz), 2.64 (2H, t, *J* = 7.0 Hz), 2.34 (2H, qt, *J* = 7.0Hz), 1.67 (3H, s), 1.6 (3H, s), 0.25 (9H, s); δ_C (125 MHz, $CDCl_3$) 201.2, 187.5, 102.3, 97.6, 97.5, 87.5, 44.2, 23.8, 50.8, -0.4; (ESI/MS) *m/z* Calcd for $C_{13}H_{20}NaOSi$: 243.1 [M + Na]; found 243.1.

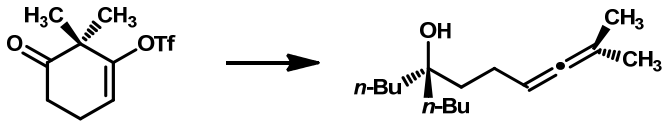


1.27 **1.29a**

6-methyl-1,1-diphenylhepta-4,5-dien-1-ol (1.29a): To a flamed dried round bottom flask (15 ml) equipped with a magnetic stir bar and septum, anhydrous $CeCl_3$[97] (360 mg, 1.466 mmol) was dispensed in an argon glove bag. The reaction flask was then gradually warmed to 130-145 °C over 30 min and held at that range for 30 min. The flask was cooled to rt, dry THF (1 ml) was added and the flask was sonicated for 1 h. At -78 °C, 1M phenylmagnesium bromide in ether (1.466 ml, 1.466 mmol) was added dropwise and stirred for 45 min. Vinyl triflate **1.27** (133 mg, 0.489 mmol) in 1 ml of dry THF was then added dropwise. The reaction mixture was stirred for an additional 1 h at -78 °C, and 1 h at rt. The reaction was quenched with saturated $NaHCO_3$ (10 ml) and extracted with ethyl acetate (3 X 15 ml), the organic portion was dried over Na_2SO_4. The resultant extract was dried *in vacuo* subjected to flash column chromatography (hexanes 95%: ethyl acetate 5%) to provide a colorless oil (117 mg, 86 %). IR ν_{max}(neat)/cm^{-1} 3473, 2932, 1965, 1446; δ_H (500MHz, $CDCl_3$) 7.43 (4H, d, *J* = 8.0 Hz), 7.33 (4H, d, *J* = 8.2 Hz), 7.24 (2H, d, *J* = 6.6 Hz), 5.01 (1H, n, *J* = 2.8 Hz), 2.40 (2H, t, *J* = 8.0 Hz), 2.29 (1H, s), 1.98 (2H, qt, *J* = 8.6 Hz), 1.70 (3H, s), 1.69 (3H,s); δ_C (125 MHz, $CDCl_3$) 201.8, 147.3, 128.4,

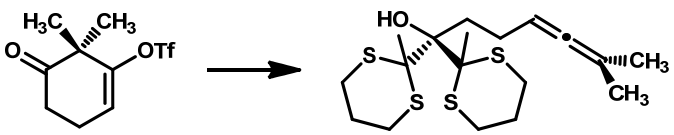
[97] For a detailed procedure on the preparation of anhydrous $CeCl_3$ used here see: Ballentine, S.; Hart, D. J. *Org. Syn., Coll. Vol.* 10, **2004**, 200.

127.0, 126.3, 96.0, 89.0, 78.6, 41.3, 24.2, 20.9; (ESI/MS) *m/z* Calcd for $C_{40}H_{44}NaO_2$: 578.9 [M x 2+ Na]; found: 578.9.



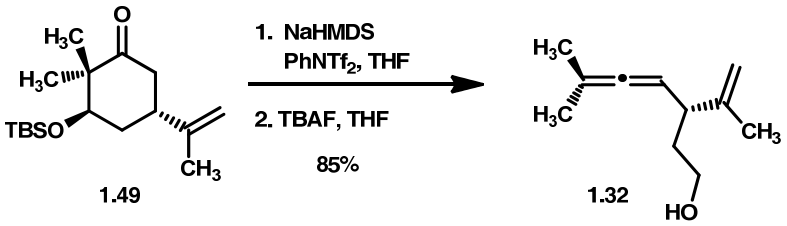
1.27 1.29b

5-butyl-10-methylundeca-8,9-dien-5-ol (1.29b): To a flamed dried round bottom flask (15 ml) equipped with a magnetic stir bar and septum, anhydrous $CeCl_3$ (299 mg, 1.212 mmol) was dispensed in an argon glove bag. The reaction flask was the gradually warmed to 130-145 °C over 30 min and held at that range for 30 min. The flask was cooled to rt, dry THF (1 ml) was added and the flask was sonicated for 1 h. At -78 °C, 2.5 M *n*-butyllithium (485 µl, 1.212 mmol) was added dropwise and stirred for 45 min. Vinyl triflate **1.27** (110 mg, 0.404 mmol) in 1 ml of dry THF was then added dropwise. The reaction mixture was stirred for an additional 1 h at -78 °C, and 1 h at rt. The reaction was quenched with satuarated $NaHCO_3$ (10 ml) and extracted with ethyl acetate (3 X 15 ml), the organic portion was dried over Na_2SO_4. The resultant extract was dried *in vacuo* subjected to flash column chromatography (hexanes 95 %: ethyl acetate 5%) to provide a colorless oil (78 mg, 81 %). IR ν_{max}(neat)/cm^{-1} 3403, 2932, 1967; δ_H (500 MHz, $CDCl_3$) 4.98 (2H, n, J = 2.9 Hz), 1.98 (2H, m), 1.68 (3H, s), 1.67 (3H, s), 1.63 (1H, bs), 1.52 (2H, m), 1.43 (4H, m), 1.28 (8H, m), 0.91 (6H, t, J = 7.2 Hz); δ_C (125 MHz, $CDCl_3$) 201.7, 95.7, 89.3, 74.7, 39.2, 38.8, 26.0, 23.8, 23.6, 21.0, 14.3; (ESI/MS) *m/z* Calcd for $C_{32}H_{60}NaO_2$: 500.1 [M x 2+ Na]; found: 500.1.



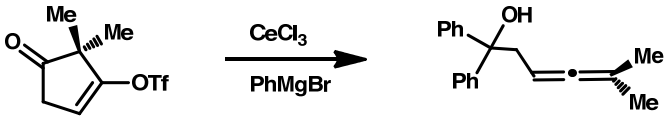
1.27 1.29c

6-methyl-1,1-bis(2-methyl-1,3-dithian-2-yl)hepta-4,5-dien-1-ol (1.29c): To an oven dried round bottom flask (15 ml) equipped with a magnetic stir bar and septum was added dry THF (2.1 ml) and methyldithiane (111 mg, 0.826 mmol). At -20 °C, 2.5 M *n*-butyllithium (0.294 µl, 0.735 mmol) was added dropwise, warmed to 22 °C and stirred for 30 min. The solution was cooled to -78 °C and vinyl triflate **1.27** (50 mg, 0.184 mmol) in 1 ml of dry THF was added dropwise. The reaction mixture was stirred at rt for 15 min at which time TLC indicated the consumption of the starting material. The reaction mixture was dried *in vacuo* and subjected to flash column chromatography (hexanes 95 %: ethyl acetate 5%) to provide a colorless oil (57 mg, 79 %). IR ν_{max}(neat)/cm^{-1} 3744, 2927, 1966, 1444, 1275; δ_H (400 MHz, $CDCl_3$) 5.02 (1H, n, J = 2.9 Hz), 3.45 (1H, s), 2.91 (8H, m), 2.34 (4H, m), 2.05 (6H, s), 1.93 (4H, m), 1.69 (6H, d, J = 2.9 Hz); δ_C (100 MHz, $CDCl_3$) 201.7, 95.27, 89.0, 85.7, 65.1, 34.4, 28.0, 27.6, 27.5, 27.2, 24.6, 21.1; (ESI/MS) *m/z* Calcd for $C_{18}H_{30}NaOS_4$: 413.1 [M+Na]; found: 413.2 .



(R)-6-methyl-3-(prop-1-en-2-yl)hepta-4,5-dien-1-ol (1.32): Unstable triflate **1.31** was synthesized from know ketone **1.49** and flushed through silica gel with hexanes and utilized for the next step without further purification. To an oven dried round bottom flask (10 ml) equipped with a magnetic stir bar and septum was added dry THF (0.580 ml) and vinyl triflate **1.31** (50 mg, 0.117 mmol). At 0 °C, was added 1 M TBAF in THF *cf.* 5 % H_2O (0.233 ml, 0.233 mmol) drop wise and warmed to 22 °C and stirred 1 h. At which time TLC indicated consumption of the starting material. The flask was then charged

with 2 ml of MeOH and excess $NaBH_4$ was added.[98] When the bubbling subsided the reaction mixture was dried *in vacuo* and subjected to flash column chromatography (hexanes 95 %: ethyl acetate 5%) to provide a colorless oil (17 mg, 75 %). IR ν_{max}(neat)/cm^{-1} 3416, 2973, 1966, 1413, 1212; δ_H (500 MHz, $CDCl_3$) 4.89 (1H, m), 4.80 (1H, m), 4.76 (1H, m), 3.67 (2H, t, J = 6.4 Hz), 2.82 (1H, qt, J = 7.4 Hz), 1.73 (2H, m), 1.71 (3H, s), 1.70 (6H, s), 1.69 (1H, bs); δ_C (125 MHz, $CDCl_3$) 201.7, 148.0, 111.0, 96.7, 91.9, 61.8, 44.4, 35.3, 21.0, 20.8, 19.5; (ESI/MS) *m/z* Calcd for $C_{11}H_{19}O$: 167.2 [M+H]; found 167.2.

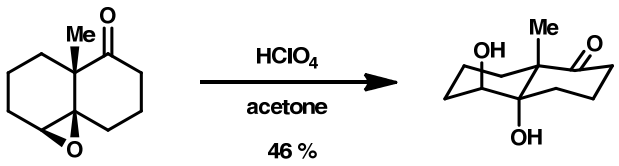


1.33 **1.34**

5-methyl-1,1-diphenylhexa-3,4-dien-1-ol (1.34): To a flamed dried round bottom flask (15 ml) equipped with a magnetic stir bar and septum, anhydrous $CeCl_3$ (360 mg, 1.466 mmol) was dispensed in an argon glove bag. The reaction flask was then gradually warmed to 130-145 °C over 30 min and held at that range for 30 min. The flask was cooled to rt, dry THF (1 ml) was added and the flask was sonicated for 1 h. At -78 °C, 1M phenylmagnesium bromide in ether (1.466 ml, 1.466 mmol) was added dropwise and stirred for 45 min. Vinyl triflate **1.33** (133 mg, 0.489 mmol) in 1 ml of dry THF was then added dropwise. The reaction mixture was stirred for an additional 1 h at -78 °C, and 1 h at rt. The reaction was quenched with saturated $NaHCO_3$ (10 ml) and extracted with ethyl acetate (3 X 15 ml), the organic portion was dried over Na_2SO_4. The resultant extract was dried *in vacuo* subjected to flash column chromatography (hexanes 95%: ethyl acetate 5%) to provide a colorless oil (117 mg, 86 %). IR ν_{max}(neat)/cm^{-1} 3462, 2925, 1974,; δ_H

[98] Note: The aldehyde was reduced *in situ* due to its inherent instability to silica chromatography.

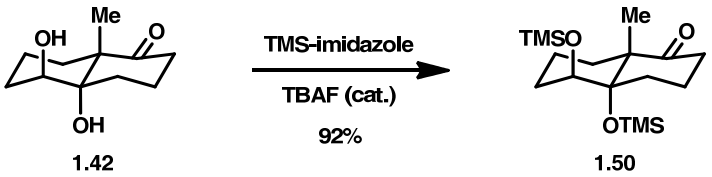
(500MHz, $CDCl_3$) 7.44 (4H, d, *J* = 7.8 Hz), 7.31 (4H, d, *J* = 8.3 Hz), 7.22 (2H, d, *J* = 6.9 Hz), 5.03 (1H, n, *J* = 2.8 Hz), 2.64 (2H, d, *J* = 9.1 Hz), 2.31 (1H, s), 1.68 (3H, s), 1.65 (3H,s); δ_C (125 MHz, $CDCl_3$) 201.8, 147.0, 128.6, 127.5, 126.3, 100.1, 88.5, 78.0, 41.1, 21.9; (ESI/MS) *m/z* Calcd for $C_{19}H_{20}O$: 551.7 [M x 2+ Na]; found: 551.5.



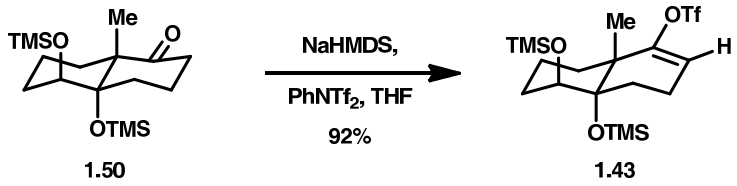
1.41 **1.42**

(4aS,5S,8aS)-4a,5-dihydroxy-8a-methyloctahydronaphthalen-1(2H)-one (1.42): To the solution of the epoxide **1.41** (740 mg, 4.1 mmol) in acetone (10 mL) at 0 °C, was added conc $HClO_4$ (1 ml) dropwise and stirred at that temperature for 1 h. The reaction was then neutralized with 10% NaOH. Acetone was evaporated and the reaction mixture was dissolved in water (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with brine (50 mL), dried *in vacuo* and subjected to flash column chromatography (hexanes 20 %: ethyl acetate 80 %) to give the diol **1.42** (370 mg, 46 % yield) as white crystal. IR ν_{max}(neat)/cm^{-1} 3444, 2927, 2871, 1697, 1456, 1089, 961; δ_H (400 MHz, CD_3OD) 3.51 (1H, t, *J* = 2.8 Hz), 2.80-2.63 (1H, m), 2.62-2.50 (1H, m), 2.20-1.71 (6H, m), 1.60-1.50 (1H, m), 1.49-1.41 (1H, m), 1.41-1.33 (1H, m), 1.38 (3H, d, *J* = 0.5 Hz), 1.31-1.23 (1H, m); δ_C (100 MHz, CD_3OD) 219.0, 77.8, 76.3, 53.0, 37.2, 30.8, 29.6, 28.4, 21.4, 20.8, 17.1; (ESI/MS) *m/z* Calcd for $C_{11}H_{18}NaO_3$: 221.1 [M+Na]; found: 221.1.[99]

[99] The stereochemistry of the diol **1.42** was confirmed by x-ray crystallography. Slow evaporation of a sample of diol **1.42** in minimum amount of EtOAc gave crystals suitable for X-ray analysis. CCDC 741826 contains the supplementary crystallographic data for diol **1.42**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

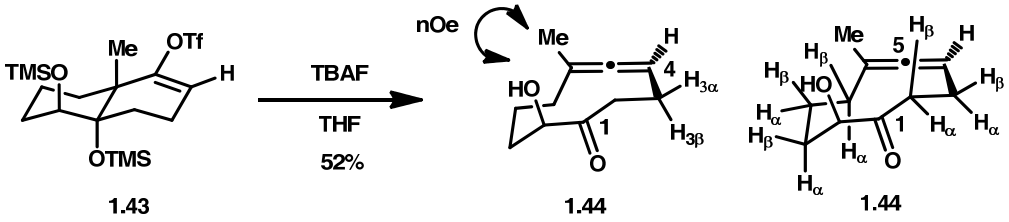


(4aS,5S,8aS)-8a-methyl-4a,5-bis(trimethylsilyloxy)octahydronaphthalen-1(2H)-one (1.50): Diol **1.42** (87mg, 0.439 mmol) was dissolved in 0.6 mL 1-(trimethylsilyl)-1H-imidazole at room temperature. Then two drops of TBAF (1.0 M solution in THF) was added. Reaction was stirred at room temperature for 2 h. The reaction was then quenched with water (30 mL), and extracted with DCM (3 x 30 mL). The combined organic phase was washed with water (20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvent and FCC purification using 5% EtOAc in hexanes gave bis silyl ether **1.50** (138 mg, 92% yield) as a colorless oil. IR ν_{max}(neat)/cm^{-1} 2954, 2872, 1716, 1455, 1251, 948, 840, 753; δ_H (500 MHz, $CDCl_3$) 3.64 (1H, t, J = 2.5 Hz), 2.62 (1H, ddd, J = 15.4, 11.2, 9.1 Hz), 2.45 (1H, ddd, J = 14.3, 11.9, 7.2 Hz), 2.21-2.14 (1H, m), 2.00-1.87 (3H, m), 1.84 (1H, ddd, J = 14.1, 4.6, 3.0 Hz), 1.81-1.68 (1H, m), 1.49-1.39 (2H, m), 1.40-1.22 (2H, m), 1.31 (3H, s), 0.12 (9H, s), 0.10 (9H, s); δ_C (125 MHz, $CDCl_3$) 216.4, 82.5, 75.1, 53.4, 35.7, 29.4, 29.2, 27.4, 21.0, 20.0, 16.0, 2.8(3), 0.4(3); ESI/MS) *m/z* Calcd for $C_{17}H_{34}NaO_3Si_2$: 365.2 [M+Na]; found 365.2.



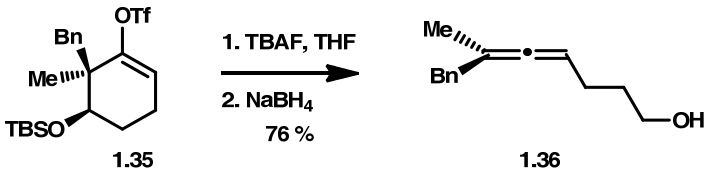
(4aS,5S,8aS)-8a-methyl-4a,5-bis(trimethylsilyloxy)-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl trifluoromethanesulfonate (1.43): To a solution of ketone **1.50** (114 mg, 0.333 mmol) in THF (1 mL), cooled at -78 °C, was added NaHMDS (1.0

M, 0.50 mL, 0.50 mmol). The solution was stirred at -78 °C for 45 min. $PhNTf_2$ (143 mg, 0.40 mmol) in 1 mL THF solution was then added dropwise to the reaction mixture. The reaction mixture was then slowly warmed up to 0 °C over 2 h. The reaction was then quenched with saturated NH_4Cl (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic phase was washed with water (20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvent and FCC purification using 4% Et_2O in hexanes gave triflate **1.43** (152 mg, 92% yield) as a colorless oil. IR ν_{max}(neat)/cm^{-1} 2955, 2873, 1416, 1209, 1088, 942, 840, 754; δ_H (500 MHz, $CDCl_3$) 5.49 (1H, t, *J* = 3.7 Hz), 3.70 (1H, t, *J* = 2.7 Hz), 2.30-2.15 (3H, m), 1.98 (1H, dtd, *J* = 11.2, 5.2, 2.7 Hz), 1.89 (1H, td, *J* = 13.1, 3.4 Hz), 1.82-1.69 (1H, m), 1.50-1.41 (2H, m), 1.4-1.32 (2H, m), 1.35 (3H, s), 0.12 (9H, s), 0.10 (9H, s); δ_C (125 MHz, $CDCl_3$) 156.8, 118.7 (1C, q, *J* = 320 Hz), 112.7 (1C, d, *J* = 0.9 Hz), 78.8, 74.8, 44.0, 29.2, 27.6, 26.6, 23.7, 20.9, 16.1, 2.6(3), 0.3(3); ESI/MS) *m/z* Calcd for $C_{15}H_{26}F_3O_6SSi$: 419.1 [M+H_2O-TMS]; found 419.5.



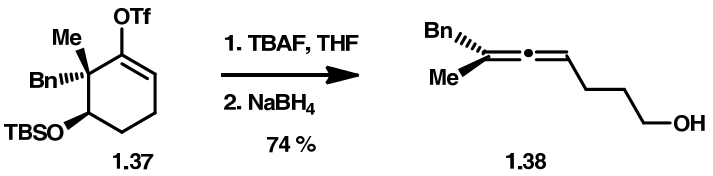
10-hydroxy-6-methylcyclodeca-4,5-dienone (1.44): To a solution of triflate **1.43** (60 mg, 0.126 mmol) in THF (1 mL), was added TBAF (1.0 M, 0.50 mL, 0.50 mmol) in one portion and stirred at rt for 15 min. The reaction was then quenched with saturated NH_4Cl (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic phase was washed with brine (5 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvent and FCC purification using 20% EtOAc in hexanes gave allene **1.44** (12 mg, 52% yield) as a colorless oil. IR ν_{max}(neat)/cm^{-1} 3417, 2925, 2855, 1964, 1705, 1445, 1043, 926, 774; δ_H

(500 MHz, $CDCl_3$) 5.13-5.07 (1H, m, $\mathbf{H_4}$), 4.21 (1H, dt, J = 7.3, 3.6 Hz, $\mathbf{H_{10}}$), 3.33 (1H, d, J = 3.5 Hz, O**H**), 2.73-2.64 (1H, m, $\mathbf{H_{2\beta}}$), 2.73-2.64 (1H, m, $\mathbf{H_{3\alpha}}$), 2.61-2.53 (1H, m, $\mathbf{H_{2\alpha}}$), 2.28-2.17 (1H, m, $\mathbf{H_{3\beta}}$), 2.28-2.17 (1H, m, $\mathbf{H_{9\alpha}}$), 2.17-2.09 (1H, m, $\mathbf{H_{7\alpha}}$), 2.04-1.96 (1H, m, $\mathbf{H_{7\beta}}$), 1.94-1.87 (1H, m, $\mathbf{H_{9\beta}}$), 1.87-1.77 (1H, m, $\mathbf{H_{8\alpha}}$), 1.60-1.50 (1H, m, $\mathbf{H_{8\beta}}$), 1.57 (3H, d, J = 2.9 Hz, C$\mathbf{H_3}$); δ_C (125 MHz, $CDCl_3$) 211.7 ($\mathbf{C_1}$), 203.3 ($\mathbf{C_5}$), 102.0 ($\mathbf{C_6}$), 88.4 ($\mathbf{C_4}$), 76.1 ($\mathbf{C_{10}}$), 34.7 ($\mathbf{C_2}$), 34.4 ($\mathbf{C_7}$), 32.3 ($\mathbf{C_{10}}$), 23.5 ($\mathbf{C_3}$), 18.7 ($\mathbf{C_9}$), 17.9 ($\mathbf{C_{11}}$); ESI/MS) *m/z* Calcd for $C_{11}H_{16}NaO_2$: 203.1 [M+Na]; found 203.1.



(*S*)-6-methyl-7-phenylhepta-4,5-dien-1-ol (1.36): To an oven dried round bottom flask (15 ml) equipped with a magnetic stir bar and septum was added dry THF (5 ml) and vinyl triflate **1.35** (270 mg, 0.64 mmol). At 0 °C, was added 1 M TBAF in THF *cf.* 5 % H_2O (3.2 ml, 3.2 mmol) dropwise and warmed to 22 °C and stirred for 1 h. At which time TLC indicated consumption of the starting material. The flask was then charged with 2 ml of MeOH and excess $NaBH_4$ was added. When the bubbling subsided the reaction mixture was concentrated *in vacuo* and subjected to flash column chromatography (hexanes 95 %: ethyl acetate 5%) to provide a colorless oil 76 %, $[\alpha]_D^{25}$ +24.9 (*c* 1.2, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 3582, 3360, 2933, 1981, 1494, 1381, 1212, 1145, 1029, 665; δ_H (500 MHz, $CDCl_3$) 7.35 – 7.14 (5H, m), 5.02 (1H, m), 3.60 (2H, td, J = 1.8, 6.6 Hz), 3.26 (2H, s), 2.02 (2H, m), 1.64 (3H, d, J = 2.8 Hz), 1.61 (2H, t, J = 7.2 Hz); δ_C (500 MHz, $CDCl_3$) 202.8, 135.9, 129.8, 129.2, 128.4, 126.3, 99.8, 89.9, 62.8, 41.7, 32.4, 25.8, 19.2 ; (ESI/MS) *m/z* Calcd for $C_{14}H_{19}O$: 203.3 [M+H]; found: 203.3. ^{1}H, and ^{19}F NMR showed one enantiomer. ^{19}F NMR (CDCl3, 470 MHz) of the corresponding (*S*)-MTPA

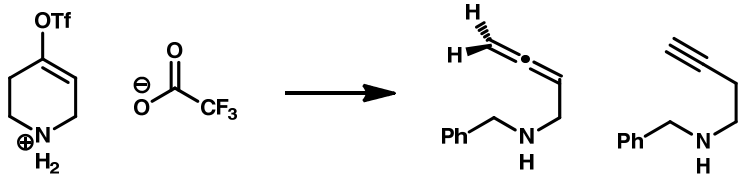
ester : δ -72.02 (*s*, F); δ_H (500 MHz, $CDCl_3$) 7.56 – 7.16 (10H, m), 4.98 (1H, m), 4.28 (m, 2H), 3.56 (1H, s), 3.26 (2H, d, *J* = 2.7 Hz), 1.98 (2H, dq, *J* = 2.3, 7.6 Hz), 1.64 (3H, d, *J* = 3.7 Hz); (ESI/MS) *m/z* Calcd for $C_{24}H_{25}F_3NaO_3$: 441.2 [M+Na]; found: 441.4.



1.37 1.38

(*R*)-6-methyl-7-phenylhepta-4,5-dien-1-ol (1.38): 74 %, $[\alpha]_D^{25}$ -22.3 (*c* 0.9, $CHCl_3$). Corresponding Mosher ester analysis of enantiomeric allenes **1.36** and **1.38** using ^1H, and ^{19}F NMR showed one enantiomer. ^{19}F NMR (CDCl3, 470 MHz) of the corresponding (*S*)-MTPA ester : δ -71.89 (*s*, F).

Typical procedure for mechanistic study:



1.45 1.46 1.47

***N*-benzylbuta-2,3-dien-1-amine (1.46), *N*-benzylbut-3-yn-1-amine (1.47):** To an oven dried round bottom flask (15 ml) equipped with a magnetic stir bar and septum was added piperidinevinylOTf **1.45**, **(**220 mg, 0.637 mmol). Dry ether (6.40 ml) was added via syringe and under an argon atmosphere. The partially dissolved solid was cooled to -20 °C at which time (1.05 µl, 3.19 mmol) of 3.0 M phenyl magnesium bromide in ether was slowly added via syringe. The cooling bath was then removed and the turbid reaction mixture began to dissolve. After 1 h the reaction was quenched with saturated $NaHCO_3$ (5 ml). The reaction mixture was then added to a separatory funnel followed by ether (10 ml) and an additional portion of saturated $NaHCO_3$ (10 ml). The ethereal layer was

separated and the organic layer was extracted with 3 X 10 ml portions of ether. The ethereal layers were combined and dried over anhydrous Na_2SO_4, filtered and dried *in vacuo*. Flash column chromatography of the resultant oil with (dichloromethane 97 % : $MeO^-NH_4^+$ 2%) as a solvent provided a slightly off white oil (85 mg, 84 %) of a combined mixture of allene **1.46** and alkyne **1.47**. **1.46** IR ν_{max}(KBr)/cm^{-1} 3374, 2922, 1955, 1454 δ_H (500 MHz, $CDCl_3$) 7.37 (4H, m), 5.18 (1H, q, *J* = 2.2 Hz), 4.89 (2H, dt, *J* = 6.6 Hz), 3.39 (2H, dt, *J* =2.2 Hz), δ_C (125 MHz, $CDCl_3$) 208.7, 140.1, 128.7, 128.5 127.2, 89.5, 76.3, 53.3, 47.4 ; (ESI/MS) *m/z* Calcd for $C_{11}H_{14}N$: 160.1 [M+H]; found: 160.1. **1.47** IR ν_{max}(KBr)/cm^{-1} 3307, 3063, 2918, 2098, 1203 δ_H (500 MHz, $CDCl_3$) 7.33 (4H, m), 3.85 (1H, q, *J* = 2.2 Hz), 2.84 (2H, t, *J* = 6.6 Hz), 2.43 (2H, td, 2.4 Hz), 2.2 (1H, bs), 2.08 (1H, td, *J* = 2.0 Hz); δ_C (125 MHz, $CDCl_3$) 140.2, 128.5, 127.5, 89.5, 76.3, 53.3, 47.4, 19.5; (ESI/MS) *m/z* Calcd for $C_{11}H_{14}N$: 160.1[M+H]; found: 160.1.

Computational Experimental Details

Calculated ground and TS states and ΔH for the piperidine halogen series.

4-bromo-1,2,3,6-tetrahydropiperidide

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.710520	-1.201619	0.074192
2	6	0	2.260387	-1.200110	0.045420
3	7	0	2.870292	-0.011932	-0.419715
4	6	0	2.273680	1.086742	0.239832
5	6	0	0.732769	1.285120	-0.081701
6	6	0	0.066659	-0.044176	-0.009456
7	1	0	2.312730	1.020734	1.370740
8	1	0	2.776766	2.030370	-0.031938
9	1	0	0.606453	1.723222	-1.083262
10	1	0	0.283945	1.985642	0.642523
11	1	0	2.528825	-1.474509	1.116623
12	1	0	2.577034	-2.066754	-0.561225
13	1	0	0.190270	-2.153755	0.172204
14	35	0	-1.932347	-0.015348	-0.008497

SCF Done: E(RB+HF-LYP) = -2821.19494633

4-bromo-1,2,3,6-tetrahydropiperidide TS I

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.811697	-1.092137	0.052705
2	6	0	2.379978	-1.264529	0.097830
3	7	0	3.072144	-0.154390	-0.462708
4	6	0	2.779366	0.966142	0.189199
5	6	0	0.825290	1.404901	-0.039666
6	6	0	0.306348	0.115235	0.015457
7	1	0	2.684305	0.960817	1.294275

8	1	0	3.229630	1.888317	-0.192921
9	1	0	0.739377	1.926407	-0.996569
10	1	0	0.628188	2.062749	0.811263
11	1	0	2.621654	-1.442665	1.171135
12	1	0	2.626780	-2.187616	-0.445563
13	1	0	0.220148	-2.000103	0.056345
14	35	0	-2.196319	-0.025853	-0.010062

Low frequencies --- -295.9546 -4.2714

Zero-point correction	0.106347 (Hartree/Particle)
Thermal correction to Energy	0.113565
Thermal correction to Enthalpy	0.114509
Thermal correction to Gibbs Free Energy	0.073168
Sum of electronic and zero-point Energies	-2821.075333
Sum of electronic and thermal Energies	-2821.068115
Sum of electronic and thermal Enthalpies	-2821.067171
Sum of electronic and thermal Free Energies	-2821.108512

SCF Done: E(RB+HF-LYP) = -2821.18167997

4-bromo-1,2,3,6-tetrahydropiperidide TS II

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	2.017564
3	7	0	1.259301	0.000000	2.433321
4	6	0	1.956440	1.131256	1.933710
5	6	0	2.295206	0.977000	0.368390
6	6	0	1.110688	0.509359	-0.339151
7	1	0	1.382821	2.080253	2.019948
8	1	0	2.918727	1.266413	2.446604
9	1	0	3.122394	0.269236	0.235754
10	1	0	2.633831	1.952288	0.003286
11	1	0	-0.593832	0.933565	2.019239
12	1	0	-0.594456	-0.891066	2.243135
13	1	0	-0.882482	-0.395455	-0.474851
14	35	0	1.710816	0.786954	-2.819961

Low frequencies --- -315.3985 -8.1281 -0.0149 -0.0148 0.0080 11.4756

Zero-point correction	0.106624 (Hartree/Particle)
Thermal correction to Energy	0.113946
Thermal correction to Enthalpy	0.114890
Thermal correction to Gibbs Free Energy	0.073264
Sum of electronic and zero-point Energies	-2821.071594
Sum of electronic and thermal Energies	-2821.064272
Sum of electronic and thermal Enthalpies	-2821.063327
Sum of electronic and thermal Free Energies	-2821.104954

SCF Done: E(RB+HF-LYP) = -2821.17821776

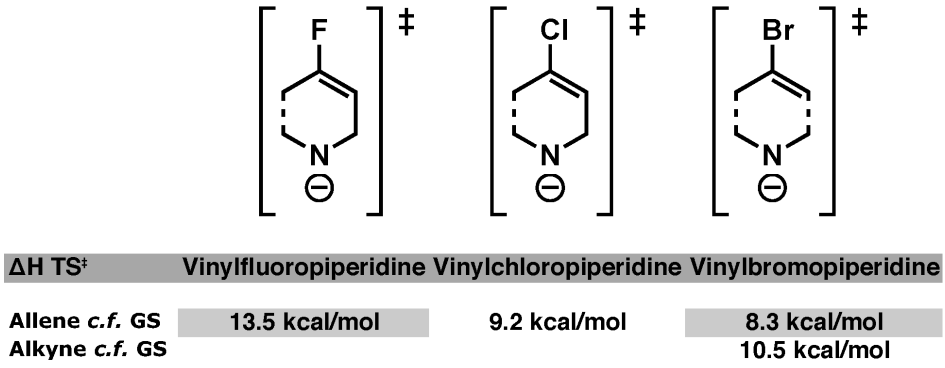


Figure 1 Calculated TS states and ΔH for the piperidine halogen series.

4-fluoro-1,2,3,6-tetrahydropiperidide

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.298299	-1.228027	0.063618
2	6	0	-1.240698	-1.182022	0.047852
3	7	0	-1.816303	0.037989	-0.405098
4	6	0	-1.179540	1.121701	0.249647
5	6	0	0.353366	1.269124	-0.094785
6	6	0	0.969034	-0.084710	-0.029520
7	1	0	-1.670577	2.075077	-0.010625
8	1	0	-1.207856	1.053281	1.383299
9	1	0	0.860293	1.941042	0.622785
10	1	0	0.477609	1.703209	-1.099138
11	1	0	-1.600886	-2.024202	-0.568930
12	1	0	-1.530974	-1.455392	1.114333
13	1	0	0.823923	-2.178426	0.172570
14	9	0	2.373315	-0.084101	-0.022164

SCF Done: E(RB+HF-LYP) = -349.305781532

4-fluoro-1,2,3,6-tetrahydropiperidide TS (analogous to TS I)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.524619
3	7	0	1.391286	0.000000	1.947007
4	6	0	1.896464	1.221373	1.849477
5	6	0	1.530265	1.963448	-0.147000
6	6	0	0.800738	0.858047	-0.675586
7	1	0	1.318384	2.089773	2.228541
8	1	0	2.978835	1.326248	1.979309
9	1	0	2.404527	2.264389	-0.731403
10	1	0	0.949440	2.813717	0.209306
11	1	0	-0.564353	0.870405	1.948510
12	1	0	-0.506401	-0.909746	1.878337
13	1	0	-0.415781	-0.857264	-0.526029
14	9	0	1.155214	0.469001	-2.003693

Low frequencies --- -321.1759 -22.3101 -15.8295

Zero-point correction	0.107617 (Hartree/Particle)
Thermal correction to Energy	0.113811
Thermal correction to Enthalpy	0.114755
Thermal correction to Gibbs Free Energy	0.077599
Sum of electronic and zero-point Energies	-349.176664
Sum of electronic and thermal Energies	-349.170469
Sum of electronic and thermal Enthalpies	-349.169525
Sum of electronic and thermal Free Energies	-349.206682

SCF Done: E(RB+HF-LYP) = -349.284280603

4-chloro-1,2,3,6-tetrahydropiperidide

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.104118	-1.208530	0.067032
2	6	0	1.647929	-1.198314	0.044693
3	7	0	2.257402	-0.001891	-0.408749
4	6	0	1.646490	1.095164	0.246064

5	6	0	0.113297	1.284146	-0.091694
6	6	0	-0.547745	-0.052465	-0.018175
7	1	0	1.676180	1.028545	1.378322
8	1	0	2.152609	2.039426	-0.018544
9	1	0	-0.004318	1.713030	-1.098472
10	1	0	-0.356269	1.982510	0.622769
11	1	0	1.917396	-1.481005	1.115058
12	1	0	1.976308	-2.057431	-0.566742
13	1	0	-0.420543	-2.158681	0.171063
14	17	0	-2.383983	-0.033716	-0.013514

SCF Done: E(RB+HF-LYP) = -709.663483888

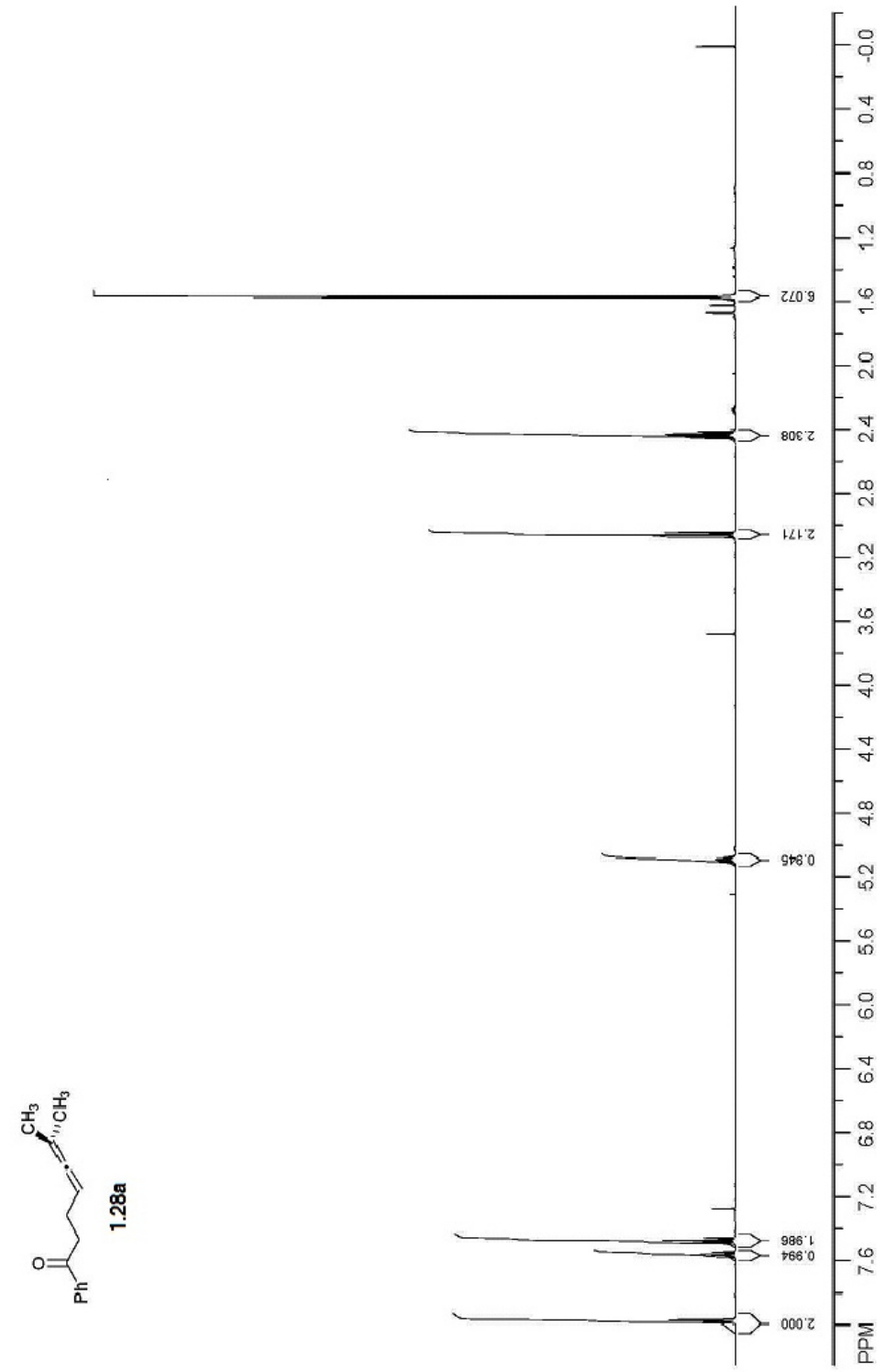
4-chloro-1,2,3,6-tetrahydropiperidide TS (analogous to TS I)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.142288	-1.106034	0.082269
2	6	0	1.716818	-1.255070	0.098669
3	7	0	2.375585	-0.141164	-0.491051
4	6	0	2.076629	0.982813	0.160215
5	6	0	0.135679	1.393970	-0.005484
6	6	0	-0.368984	0.097548	0.061825
7	1	0	2.033060	0.983908	1.269725
8	1	0	2.506863	1.906439	-0.241844
9	1	0	0.008144	1.912722	-0.959283
10	1	0	-0.048951	2.048931	0.850726
11	1	0	1.981794	-1.414917	1.170085
12	1	0	1.965605	-2.181727	-0.437692
13	1	0	-0.442968	-2.017794	0.081459
14	17	0	-2.755719	-0.054634	-0.040046

Low frequencies --- -301.1029 -3.3624

Zero-point correction	0.106409 (Hartree/Particle)
Thermal correction to Energy	0.113575
Thermal correction to Enthalpy	0.114520
Thermal correction to Gibbs Free Energy	0.074133
Sum of electronic and zero-point Energies	-709.542443
Sum of electronic and thermal Energies	-709.535277
Sum of electronic and thermal Enthalpies	-709.534333
Sum of electronic and thermal Free Energies	-709.574719

SCF Done: E(RB+HF-LYP) = -709.648852263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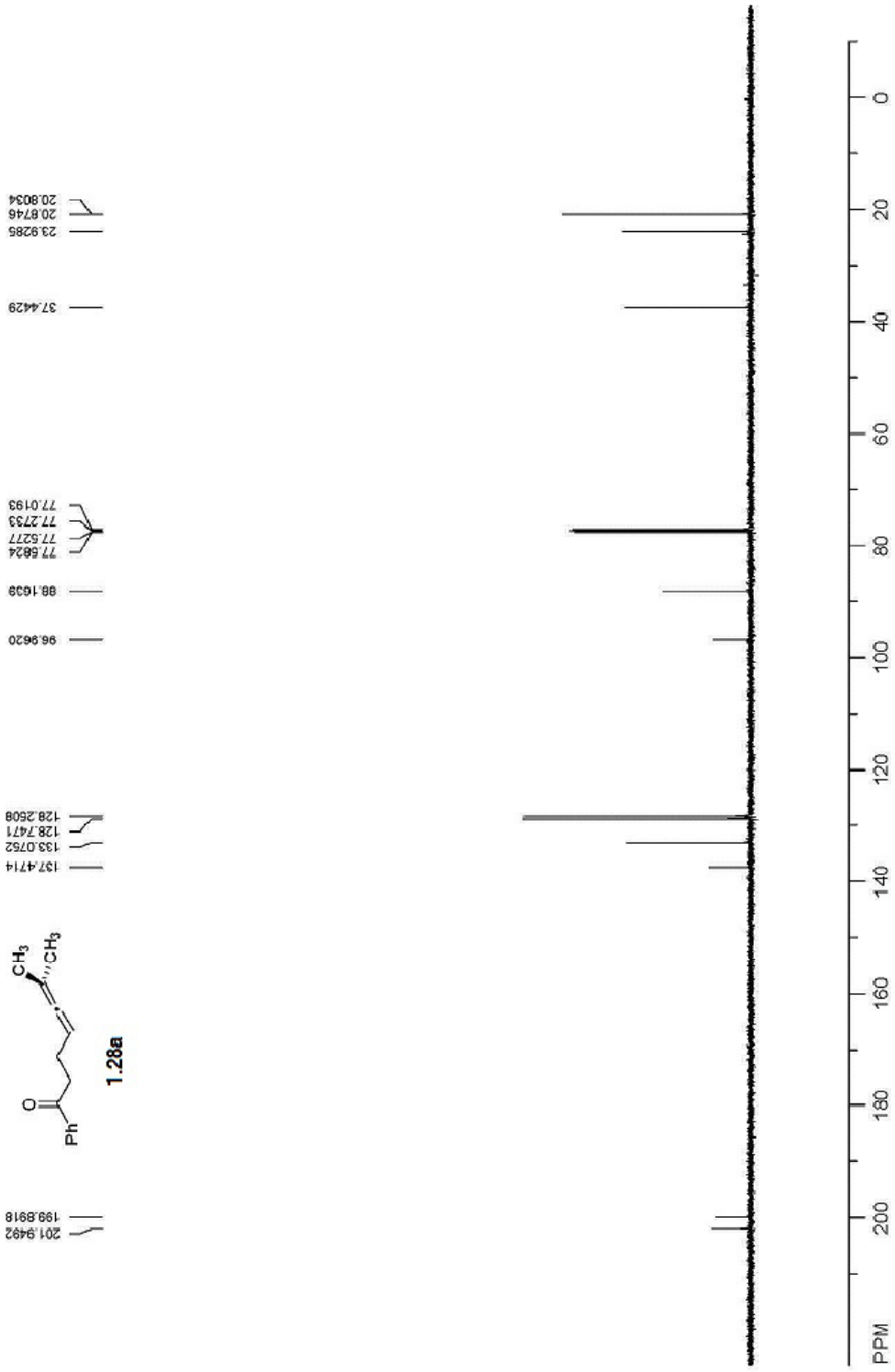
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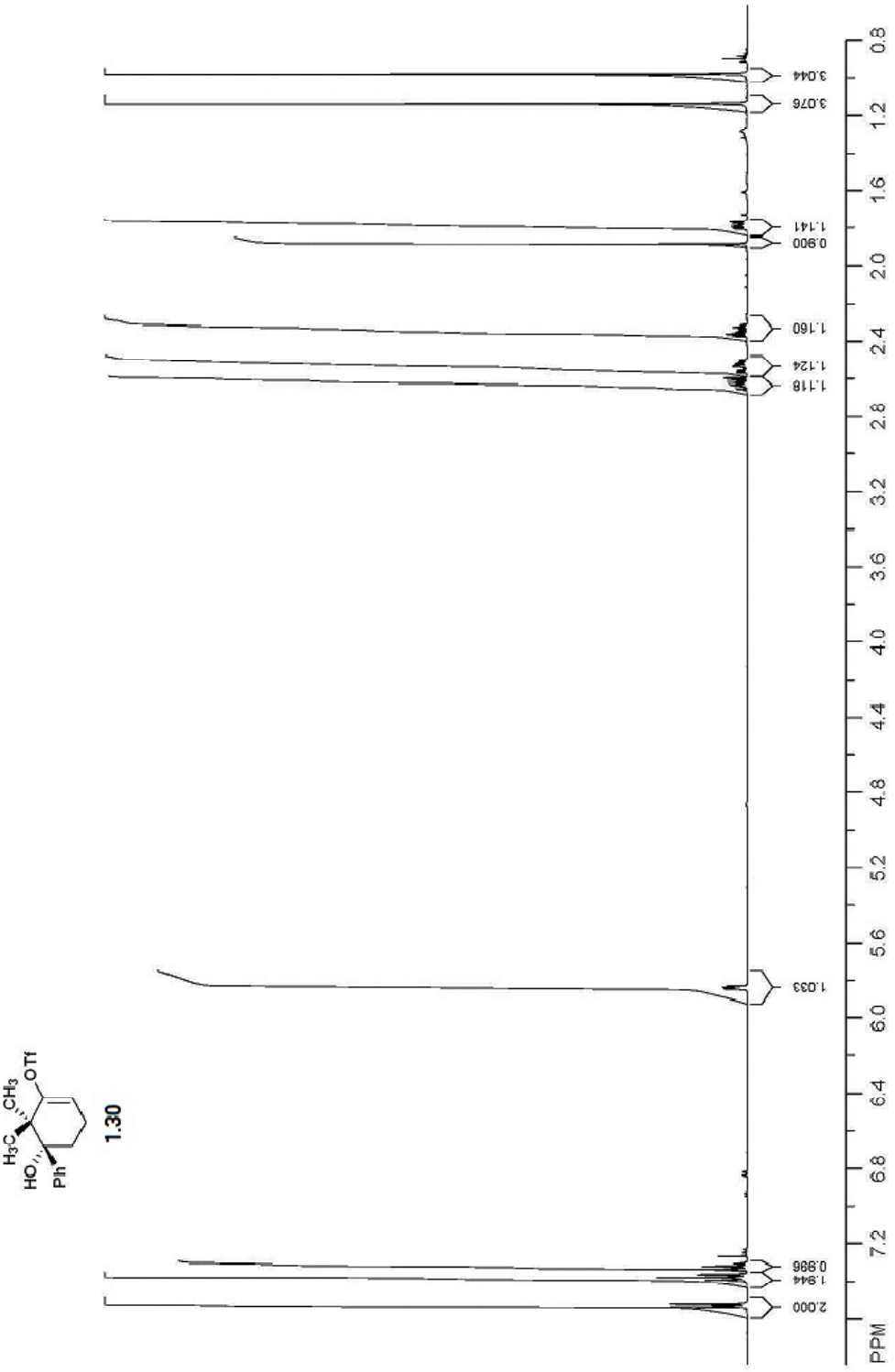
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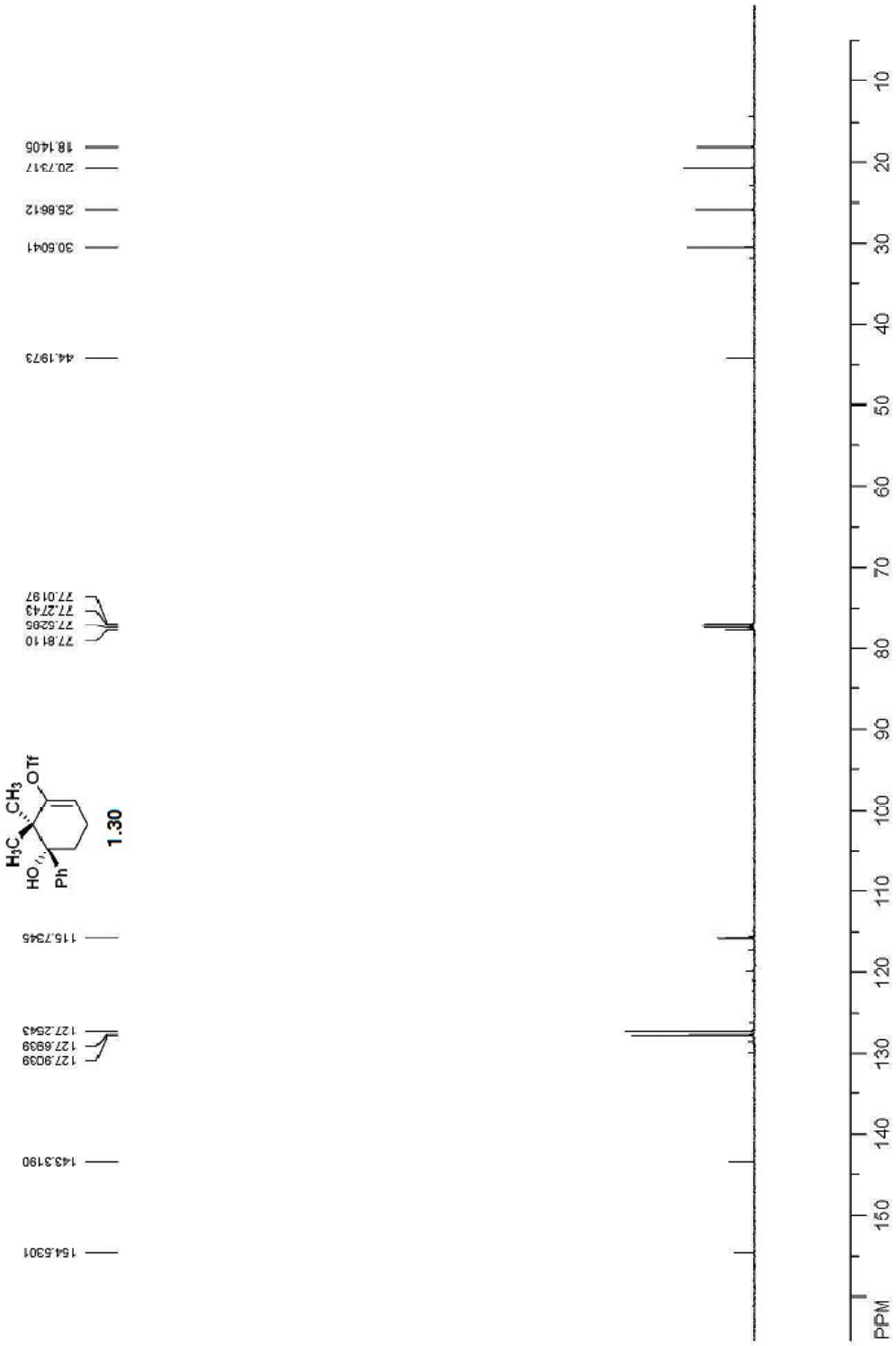
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CH3
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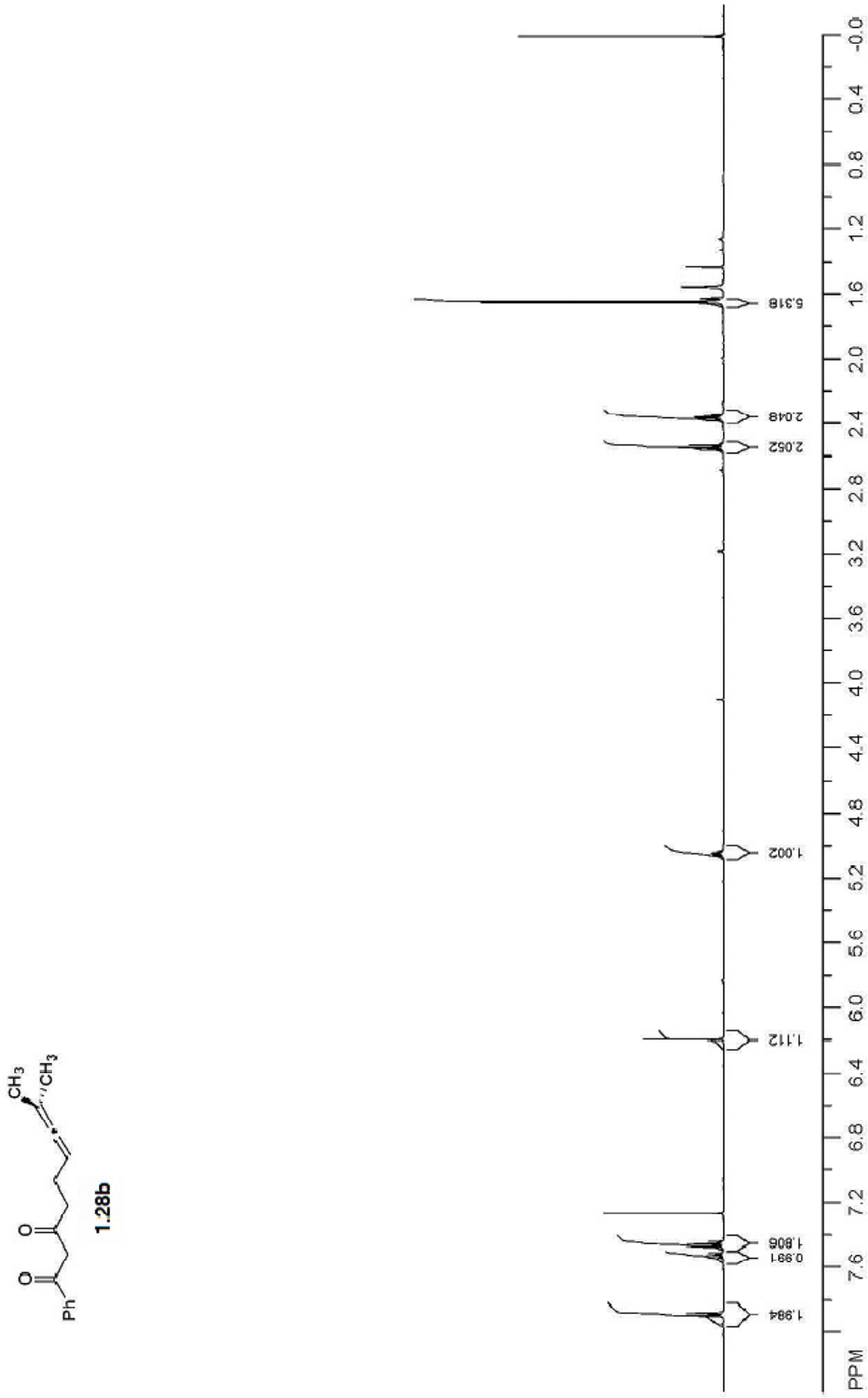
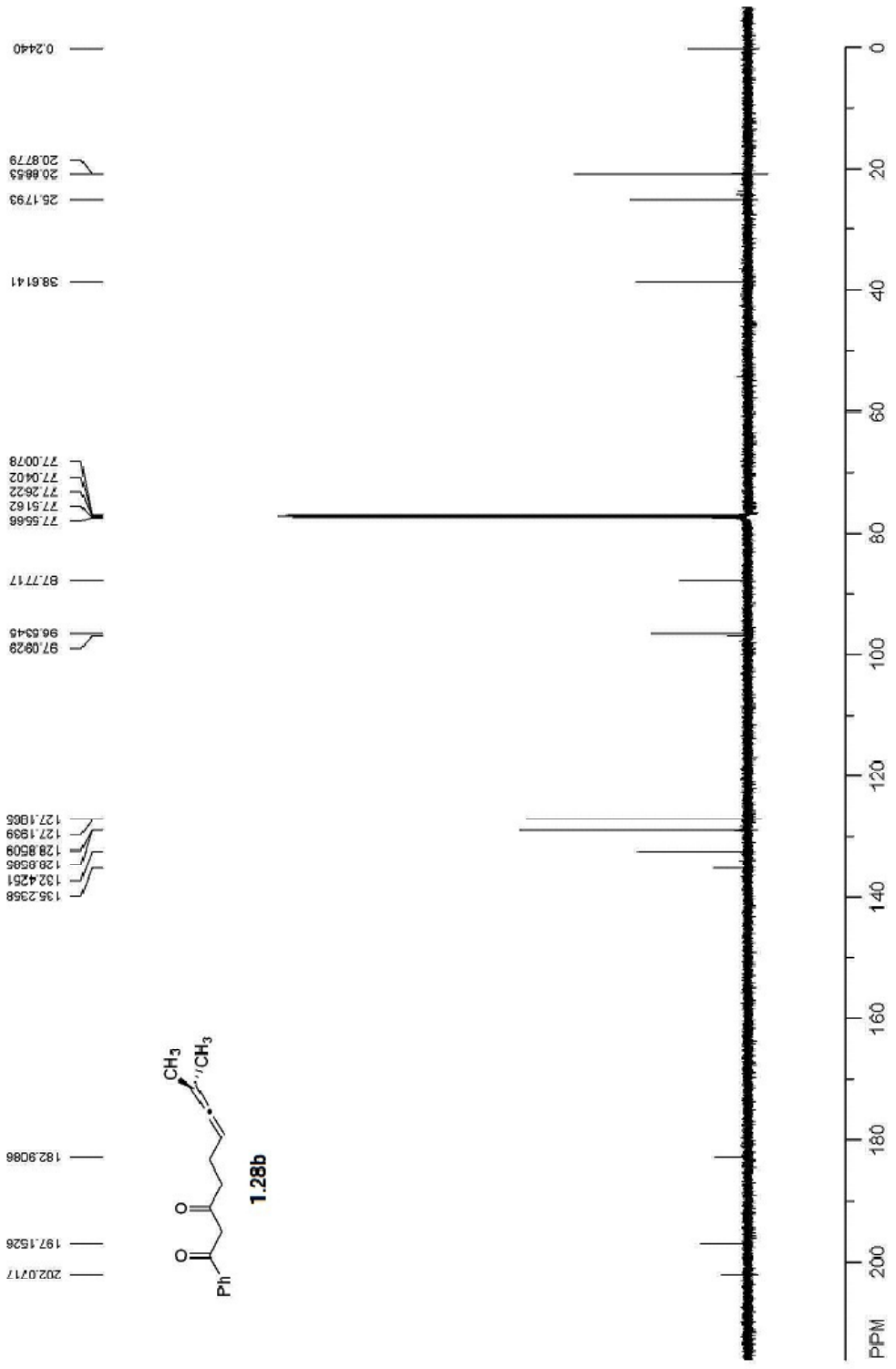
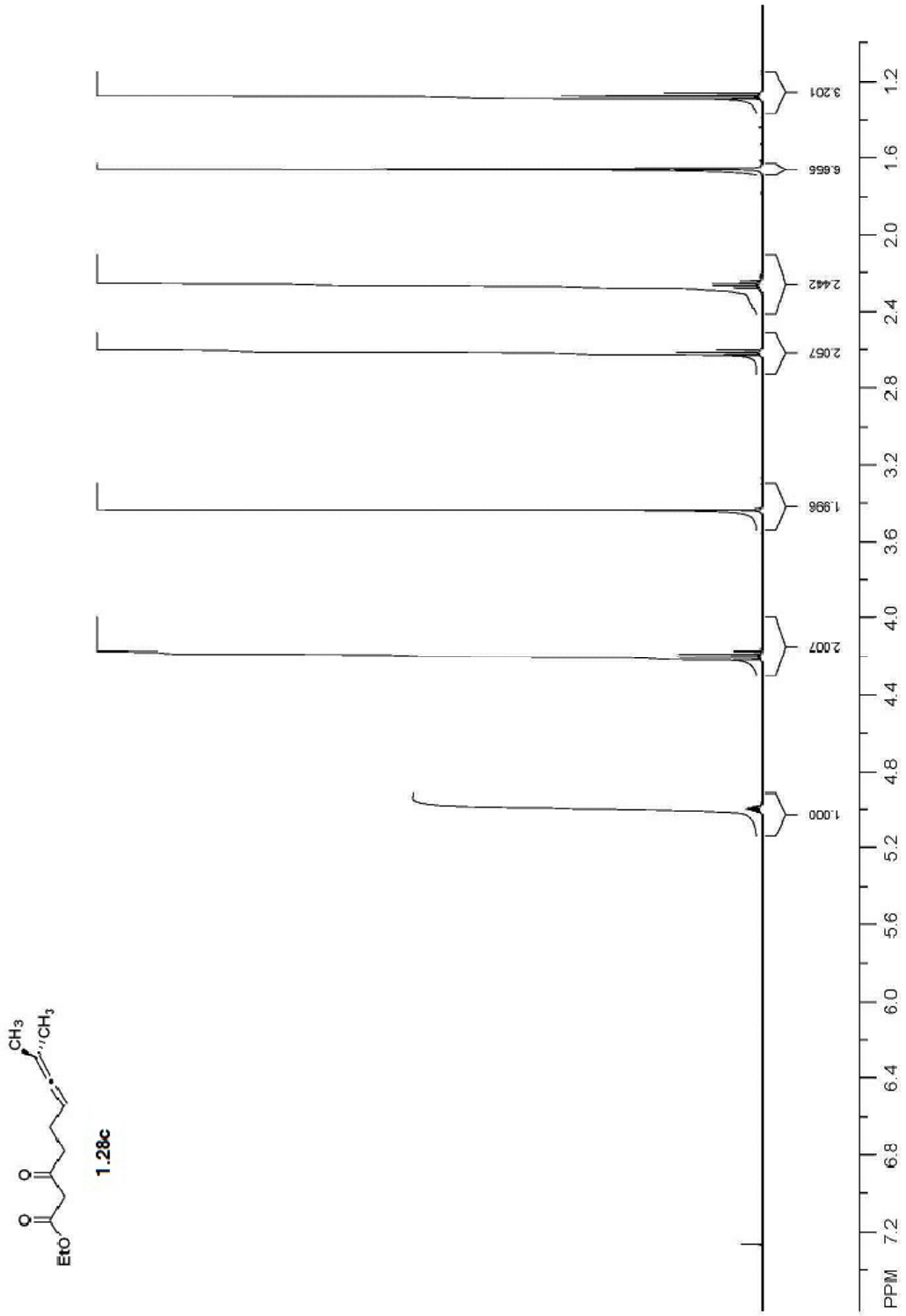
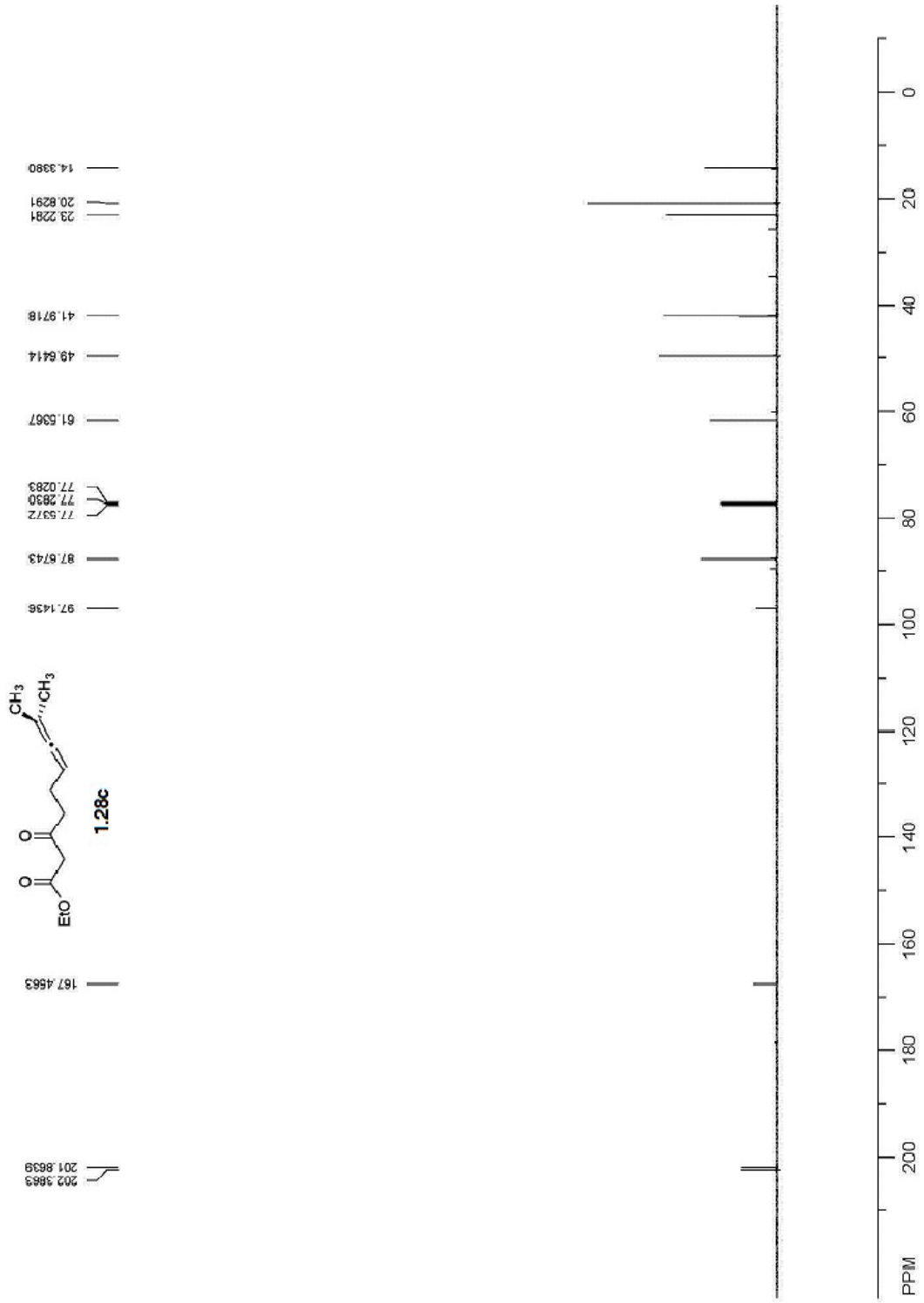
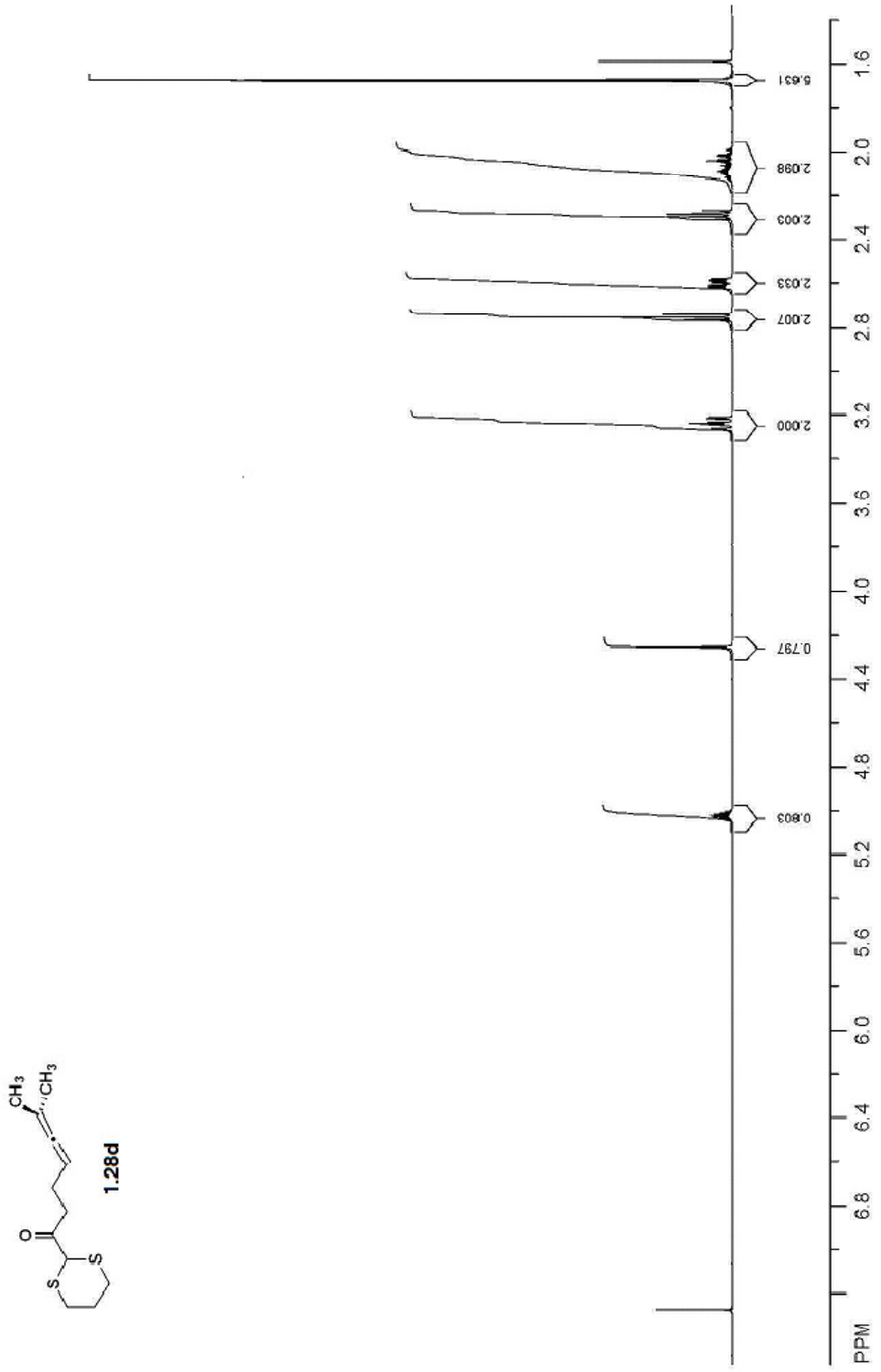
HO
Ph
PPM
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150

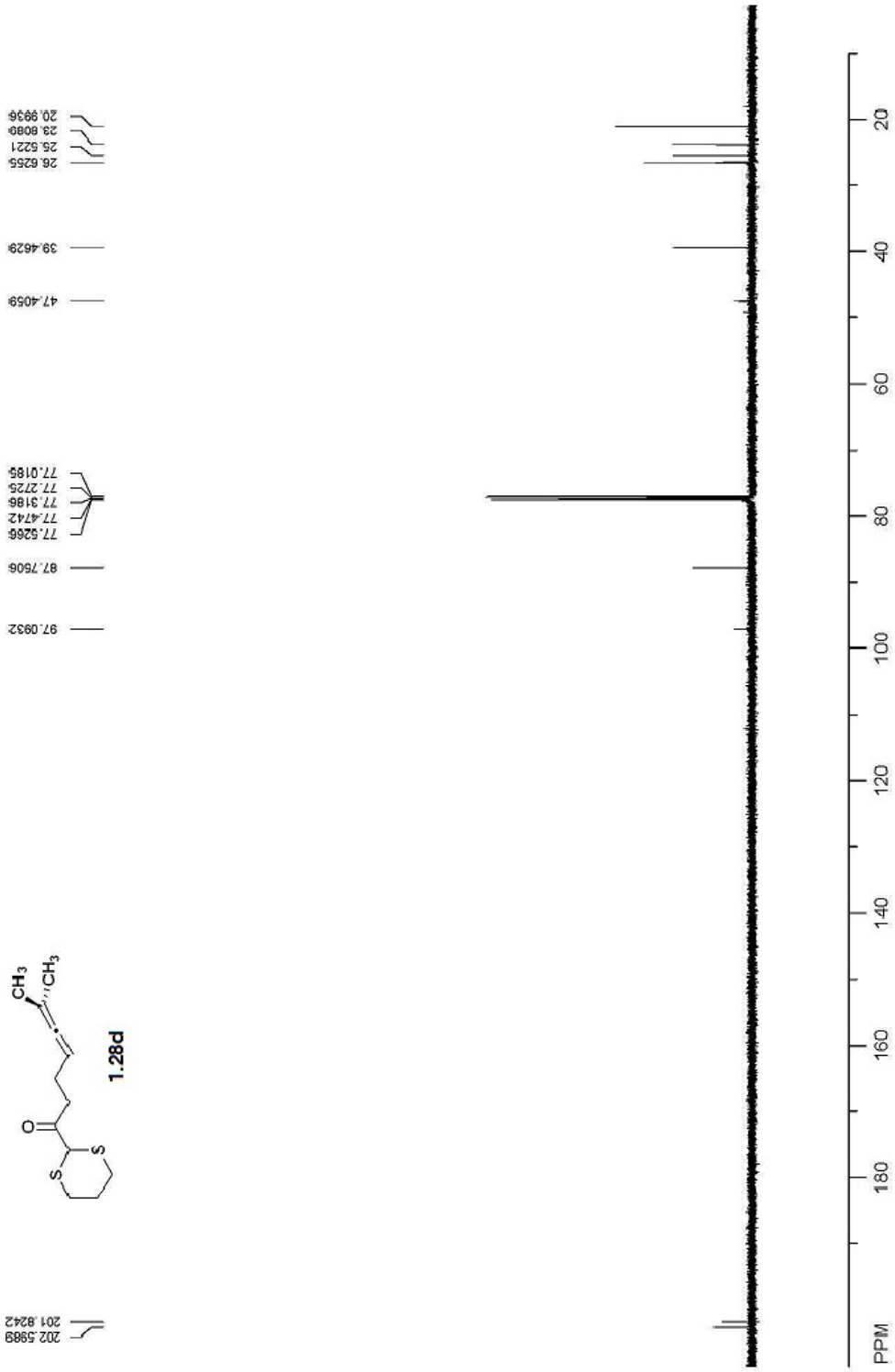

CH3
CH3
O
O
Ph
1.28b
5.318
2.048
2.052
1.002
1.112
1.806
0.991
1.984
PPM
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
-0.0

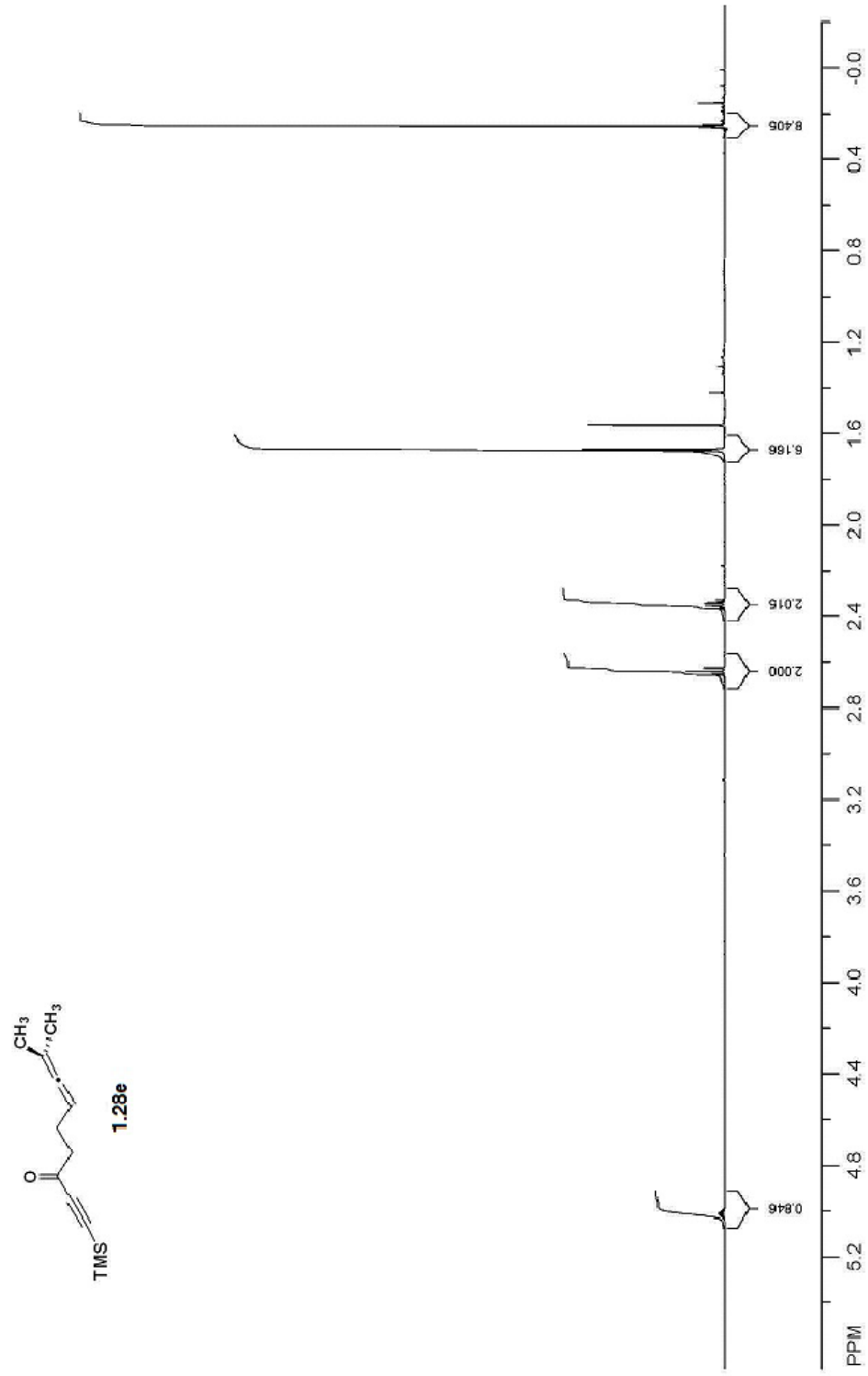

0.2440
20.8779
20.8853
26.1793
38.6141
77.0078
77.0402
77.2622
77.5162
77.5566
87.7717
96.5345
97.0929
127.1865
127.1899
128.8509
128.8586
132.4261
136.2358
182.9086
197.1526
202.0717
1.28b
CH3
CH3
O
O
Ph
0
20
40
60
80
100
120
140
160
180
200
PPM

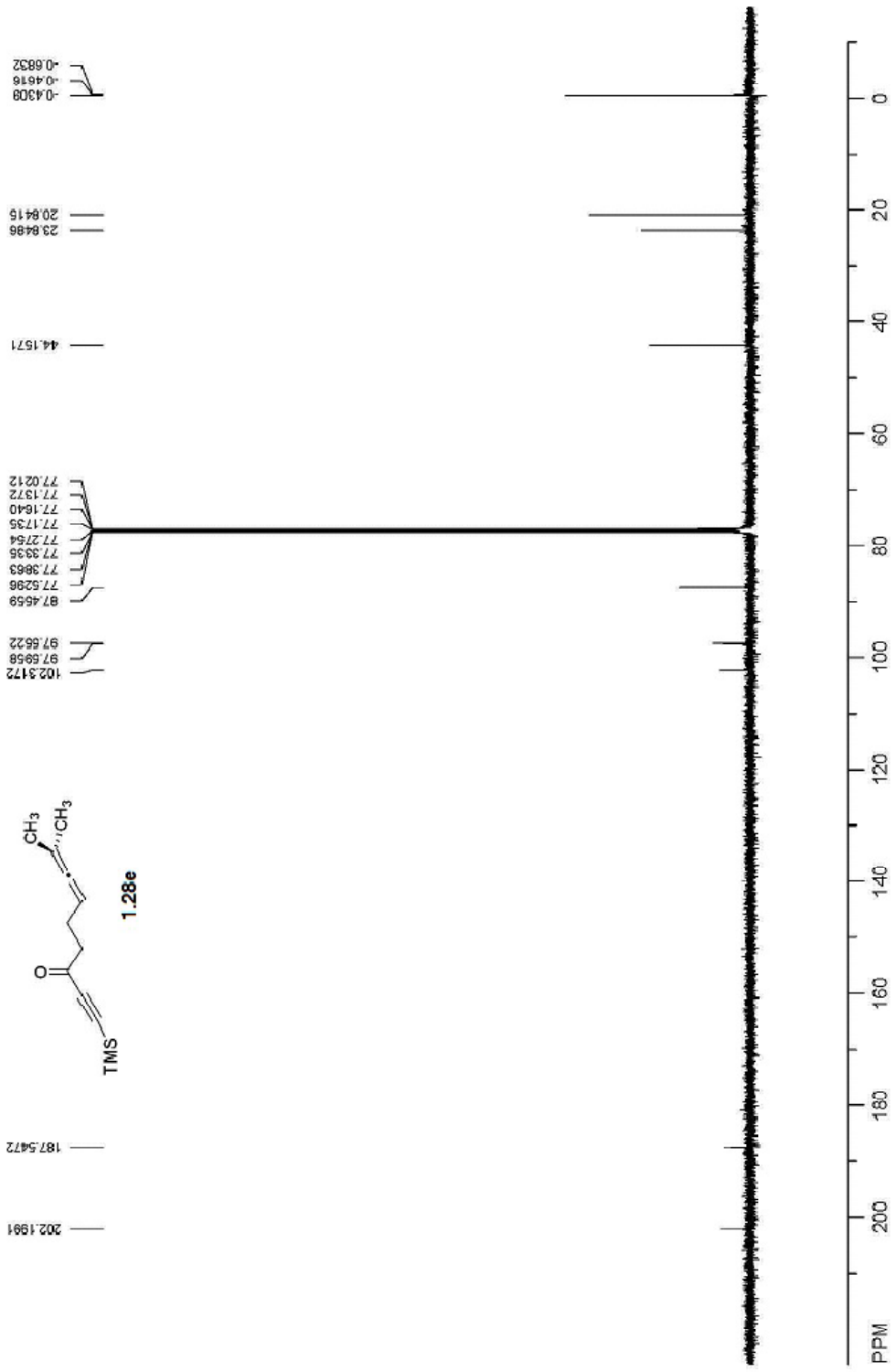

CH3
CH3
O
O
EtO
1.28c
3.201
6.656
2.442
2.057
1.998
2.007
1.000
PPM
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2

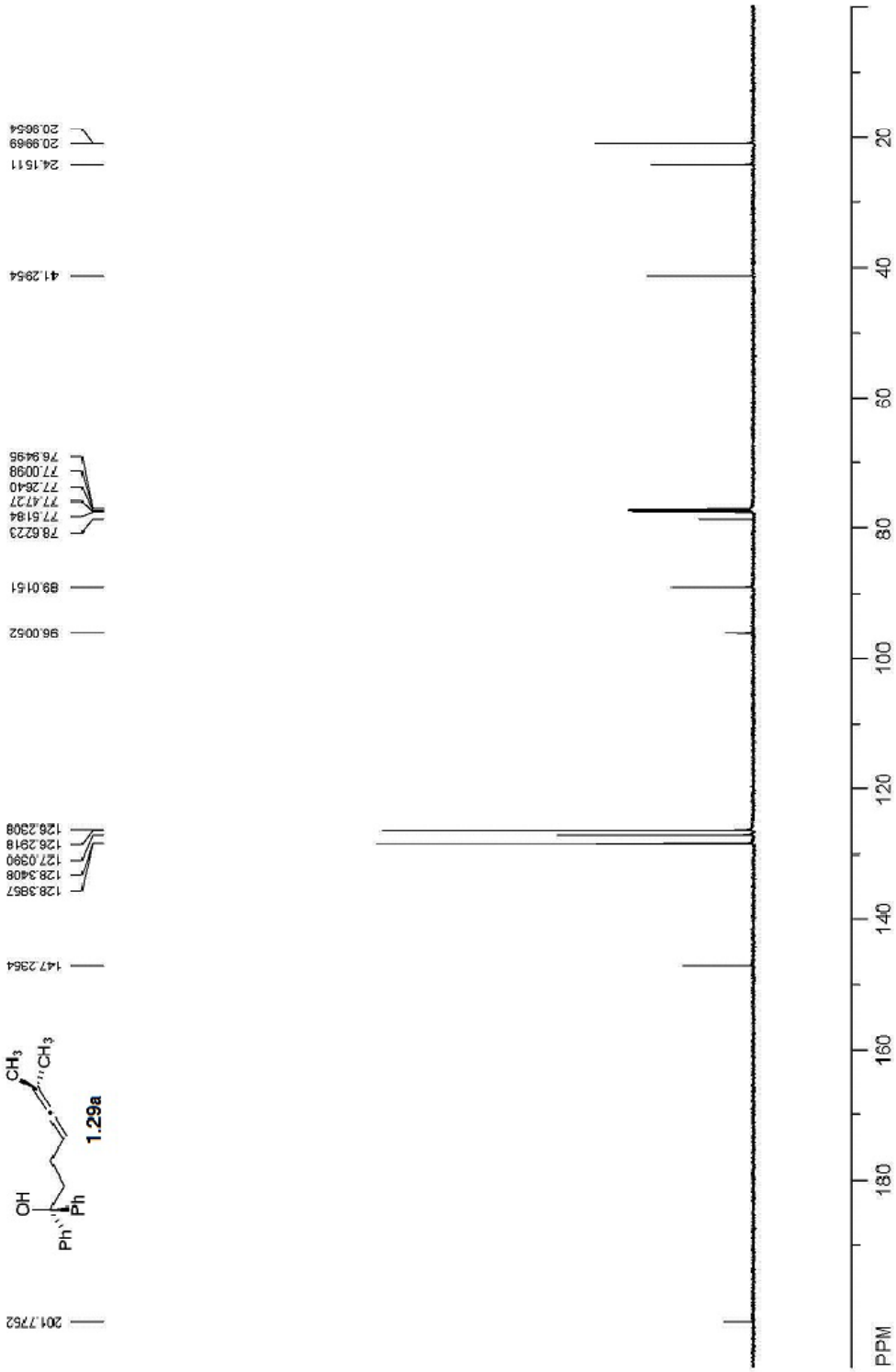

14.3380
20.8291
23.2281
41.9718
49.6414
61.5367
77.0283
77.2830
77.5372
87.6743
97.1436
167.4663
201.8639
202.3883
1.28c
EtO
O
O
CH3
CH3
PPM
0
20
40
60
80
100
120
140
160
180
200

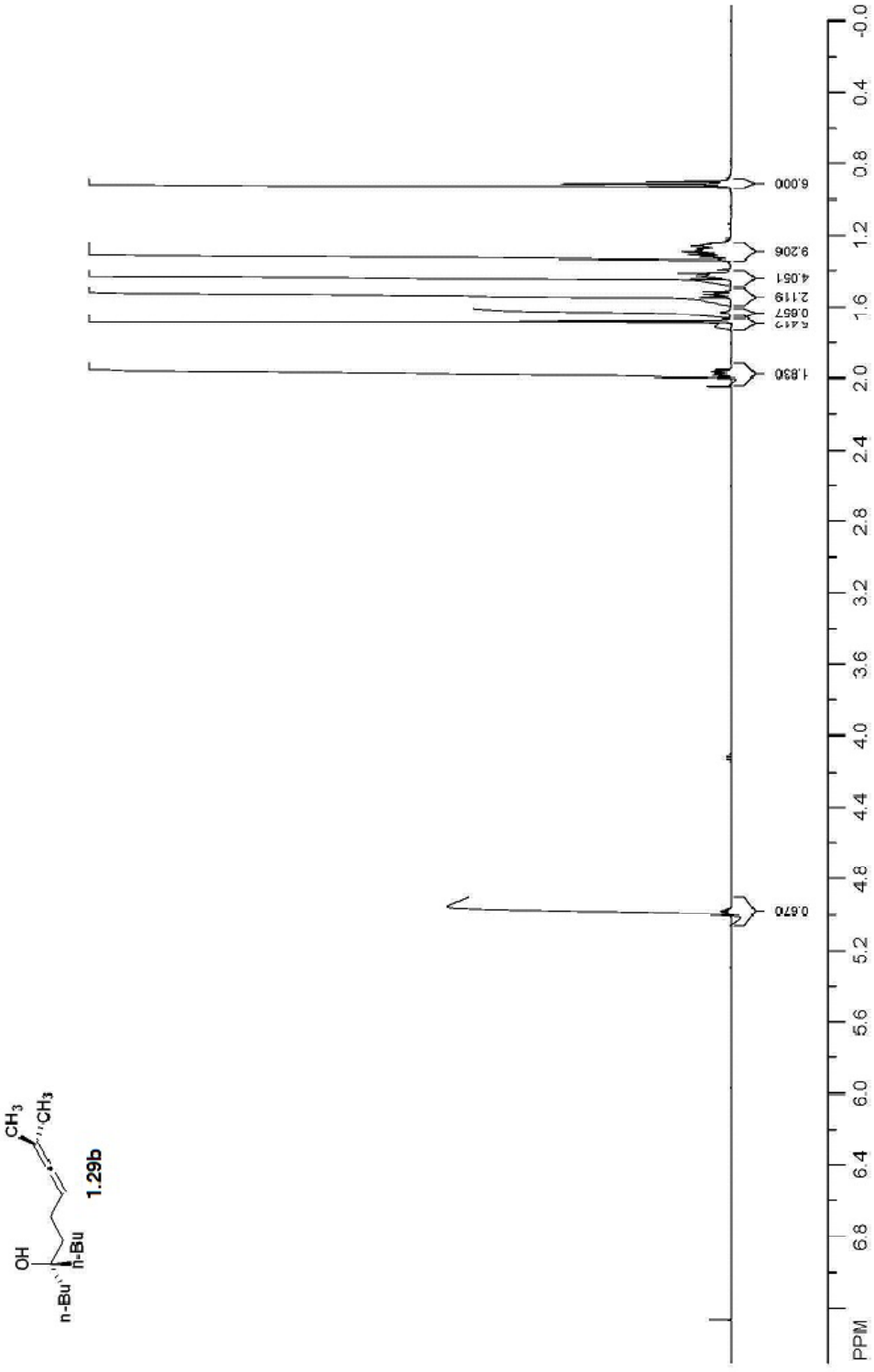

6.631
2.098
2.003
2.033
2.007
2.000
0.797
0.803
PPM
1.6
2.0
2.4
2.8
3.2
3.6
4.0
4.4
4.8
5.2
5.6
6.0
6.4
6.8
CH3
CH3
O
S
S
1.28d

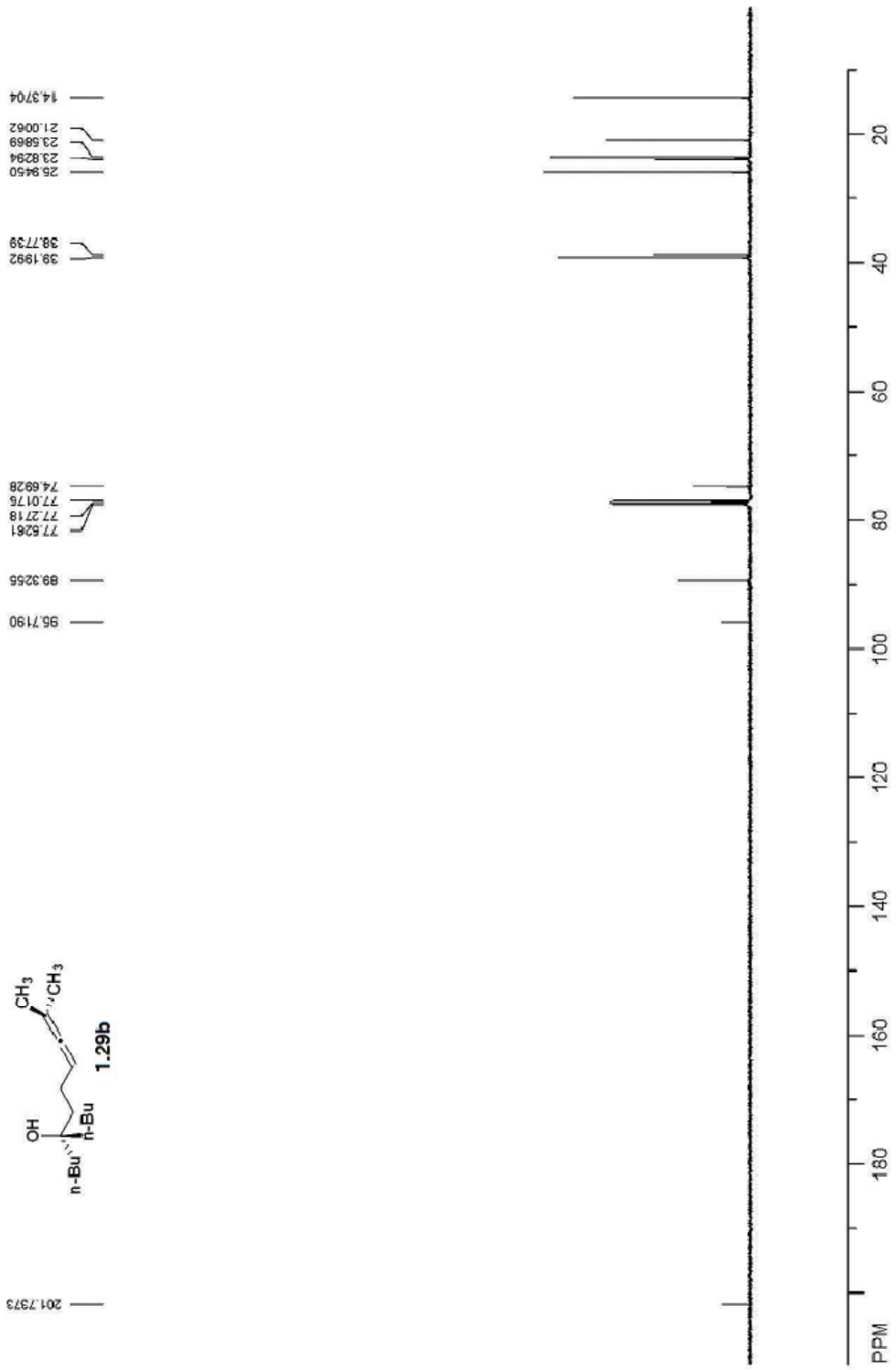

1.28d
202.5989
201.8242
97.0932
87.7506
77.5286
77.4742
77.3186
77.2725
77.0185
47.4059
39.4629
26.6256
25.5221
23.8089
20.9936
PPM

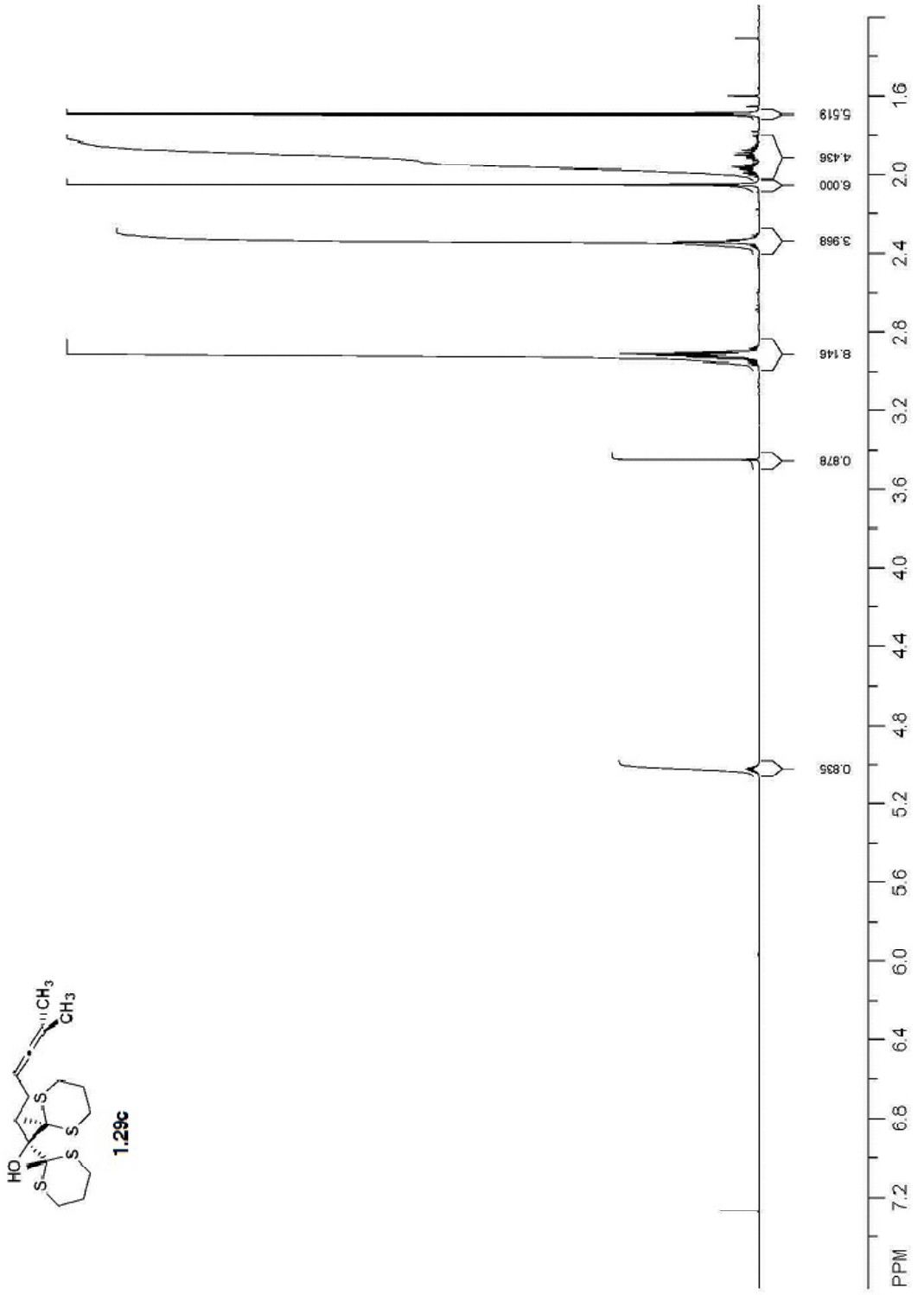

CH3
CH3
O
TMS
1.28e
8.406
6.166
2.015
2.000
0.846
PPM
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
-0.0


-0.4308
-0.4676
-0.6852
20.8415
23.8486
44.1571
77.0212
77.1372
77.1640
77.1735
77.2754
77.3336
77.3863
77.5296
87.4659
97.6522
97.6958
102.3172
187.5472
202.1991
CH3
CH3
O
TMS
1.28e
0
20
40
60
80
100
120
140
160
180
200
PPM

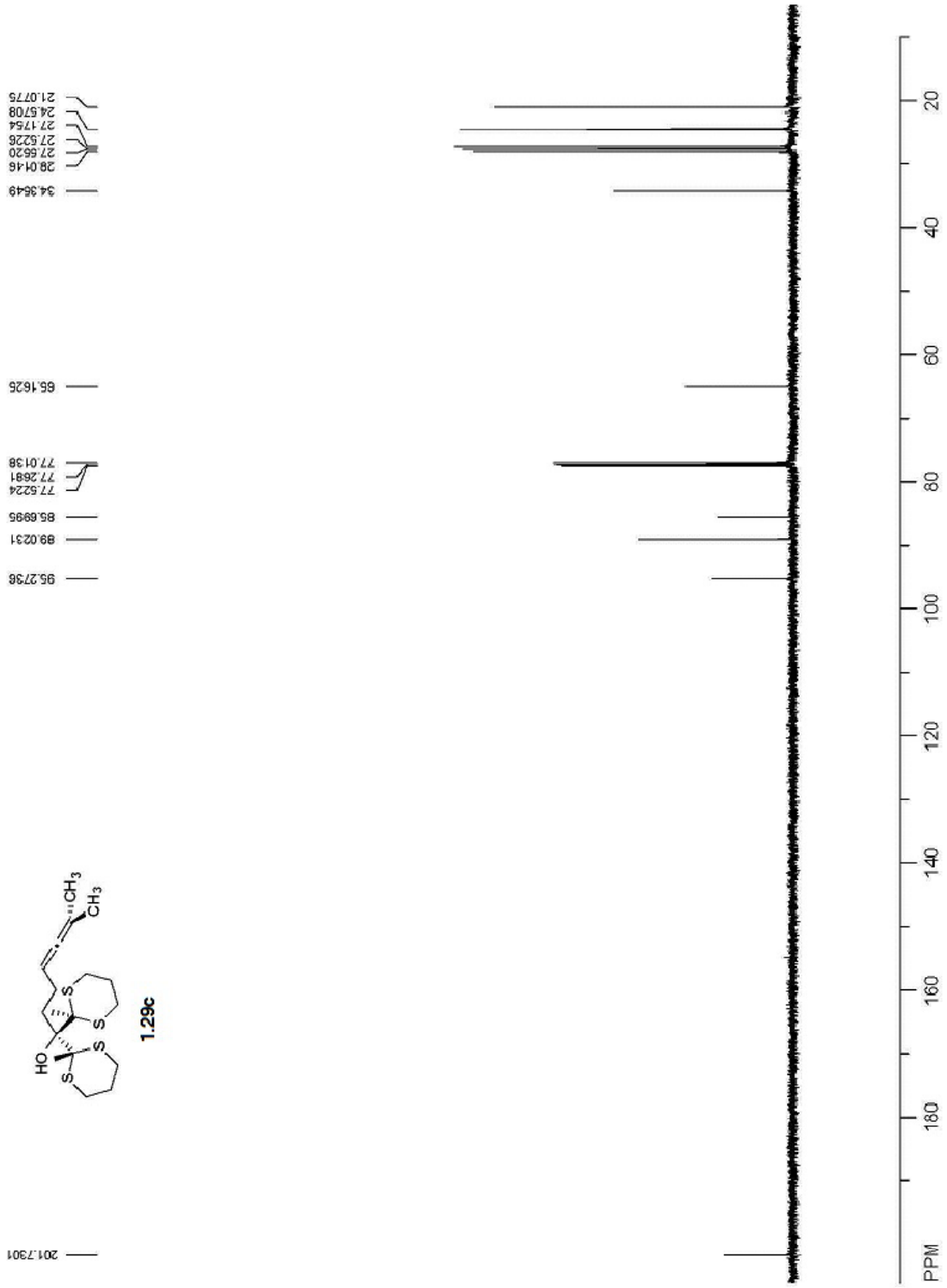

20.9654
24.1511
41.2954
76.9495
77.0098
77.2640
77.4727
77.5184
78.6223
89.0151
96.0052
128.2308
128.2918
127.0390
128.3408
128.3857
147.2364
201.7752
1.29a
OH
Ph
Ph
CH3
CH3
PPM
20
40
60
80
100
120
140
160
180

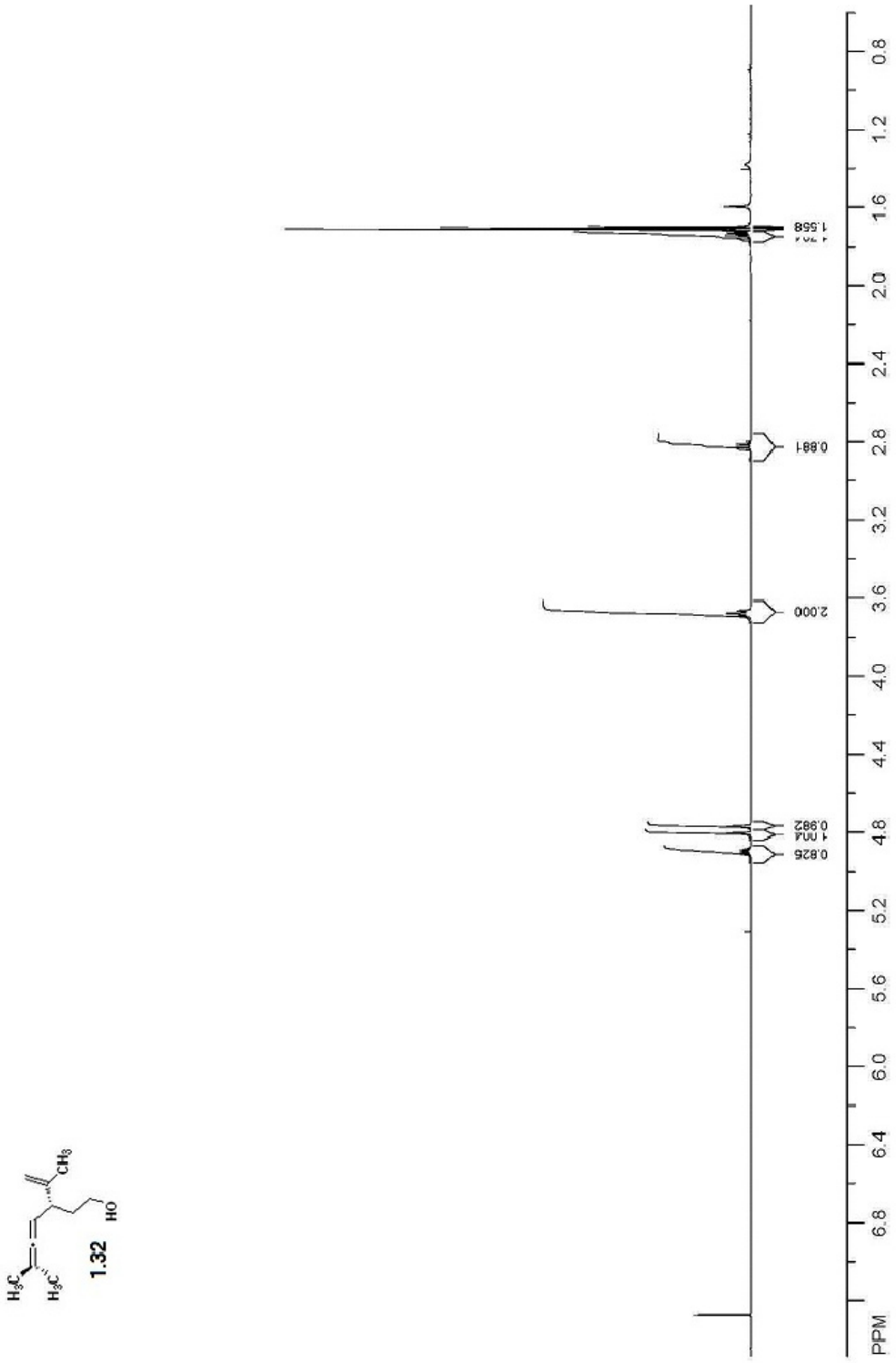

CH3
CH3
OH
n-Bu
n-Bu
1.29b
6.000
9.206
4.051
2.119
0.857
2.413
1.850
0.870
PPM
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
-0.0


14.3704
21.0062
23.5869
23.8294
25.9450
39.1992
38.7739
74.6928
77.0175
77.2718
77.5261
89.3255
95.7190
201.7373
OH
n-Bu
n-Bu
CH3
CH3
1.29b
PPM
20
40
60
80
100
120
140
160
180

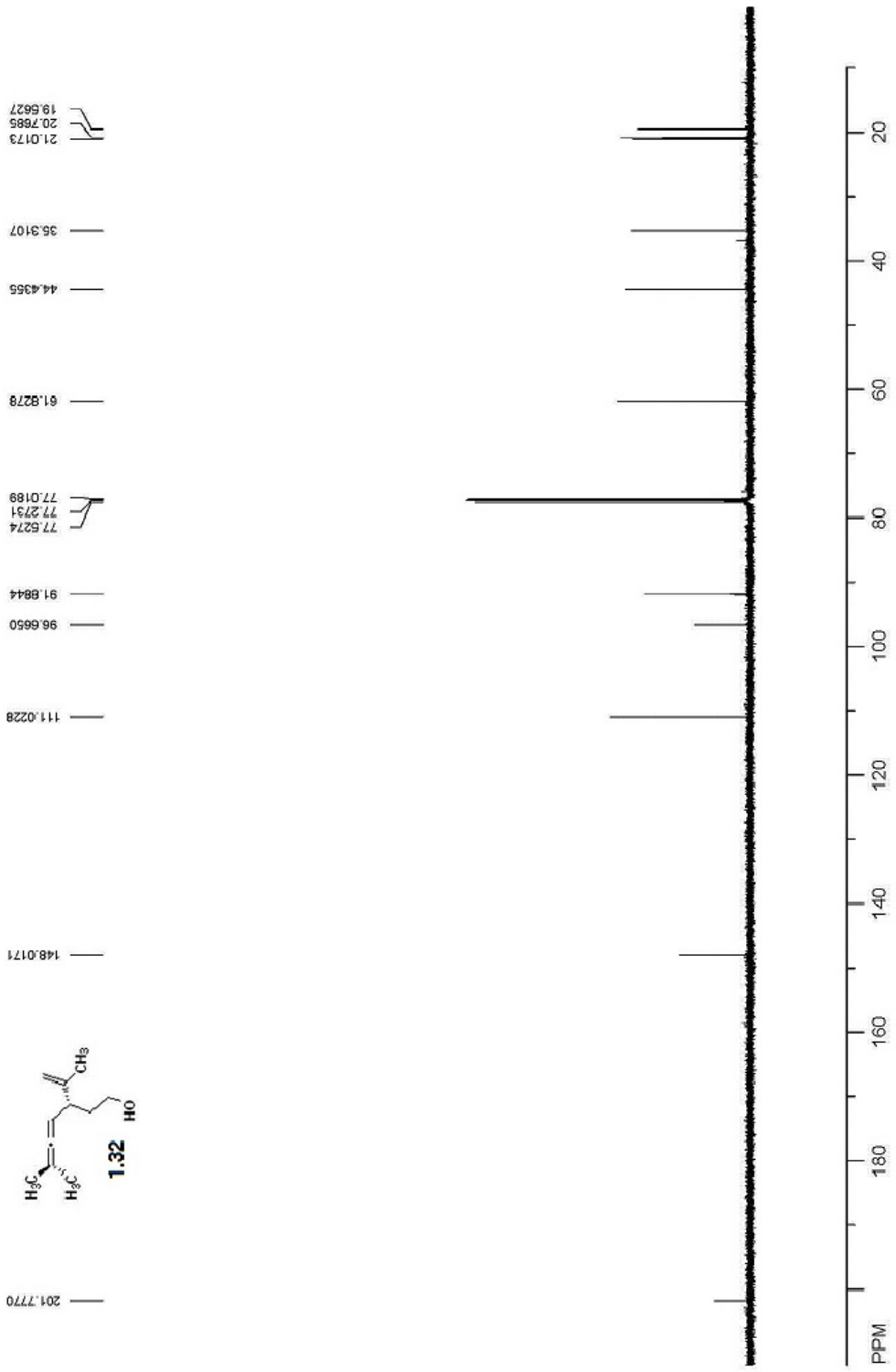

5.519
4.436
6.000
3.968
8.146
0.878
0.835
PPM
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
HO
S
S
S
S
CH3
CH3

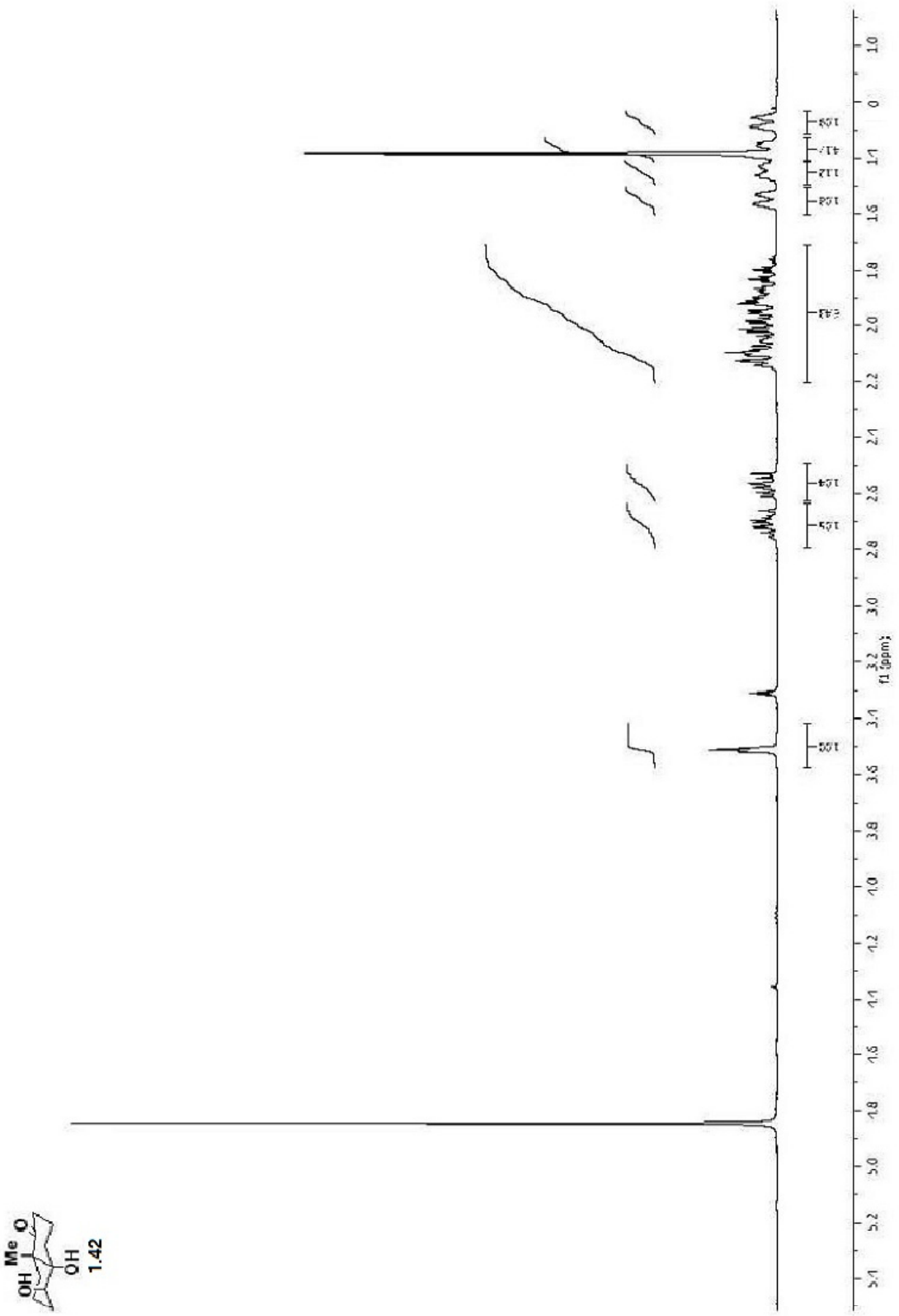
1.29c

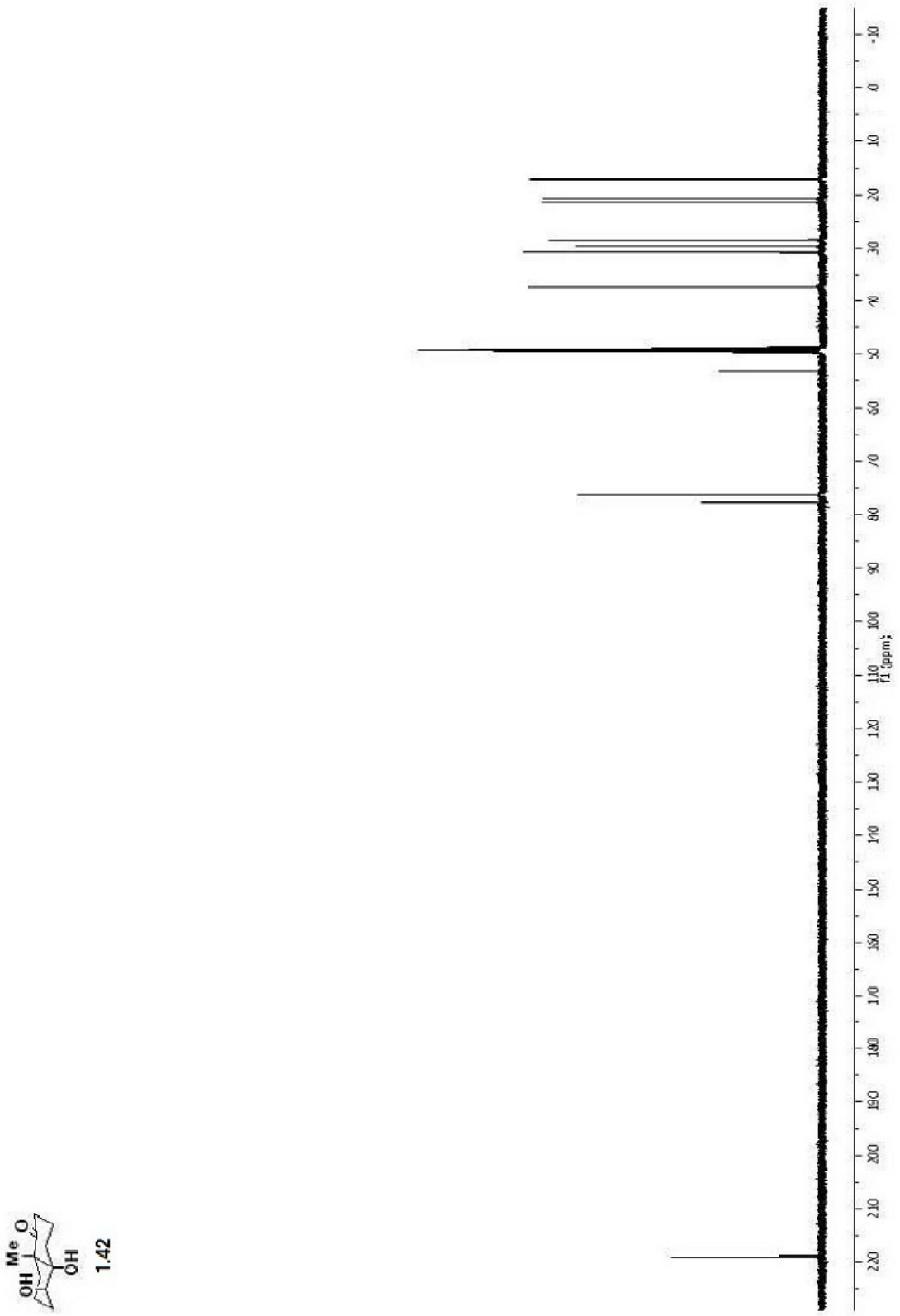

201.7301
95.2736
89.0231
86.6995
77.5224
77.2681
77.0138
65.1625
34.3649
28.0146
27.6620
27.5228
27.1754
24.5708
21.0775
PPM
20
40
60
80
100
120
140
160
180
HO
S
S
S
S
CH3
CH3
1.29c

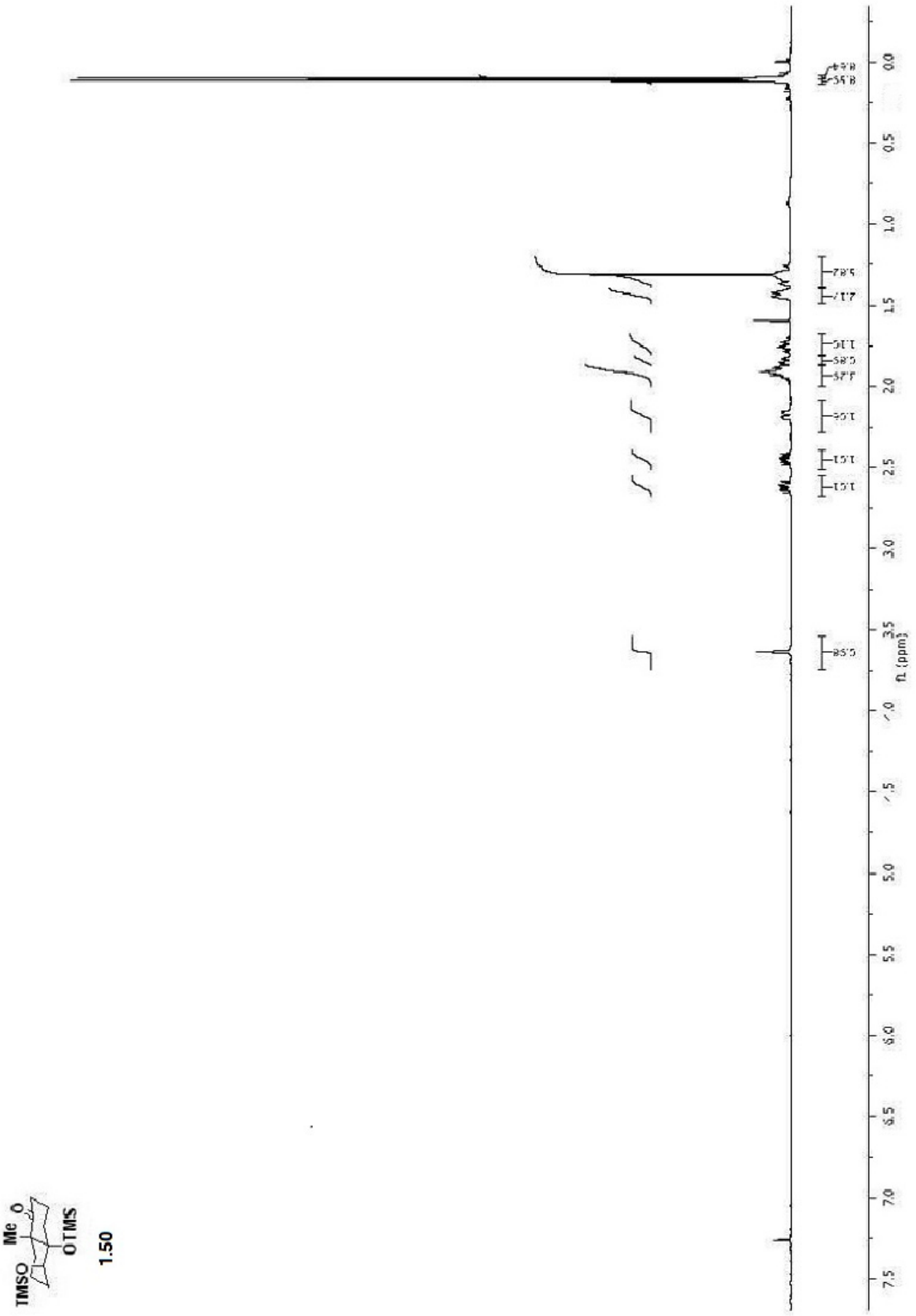

1.558
0.881
2.000
0.826
1.004
0.982
PPM
0.8
1.2
1.6
2.0
2.4
2.8
3.2
3.6
4.0
4.4
4.8
5.2
5.6
6.0
6.4
6.8
CH3
HO
H3C
H3C

1.32

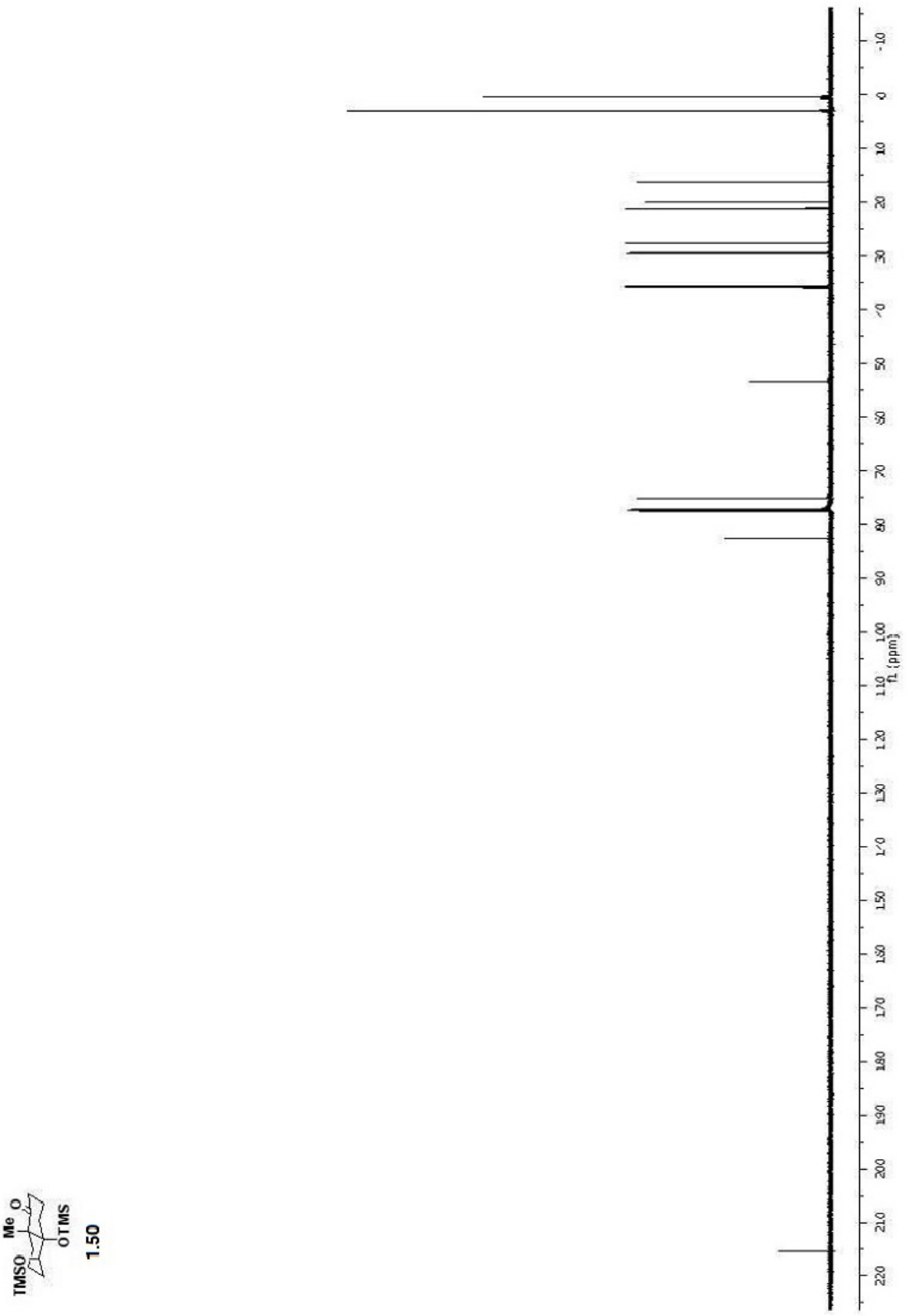

1.32
OH
CH3
H3C
H3C
201.7770
148.0171
111.0228
96.6650
91.8844
77.6274
77.2731
77.0189
61.8278
44.4355
36.3107
21.0173
20.7686
19.5627
PPM
20
40
60
80
100
120
140
160
180

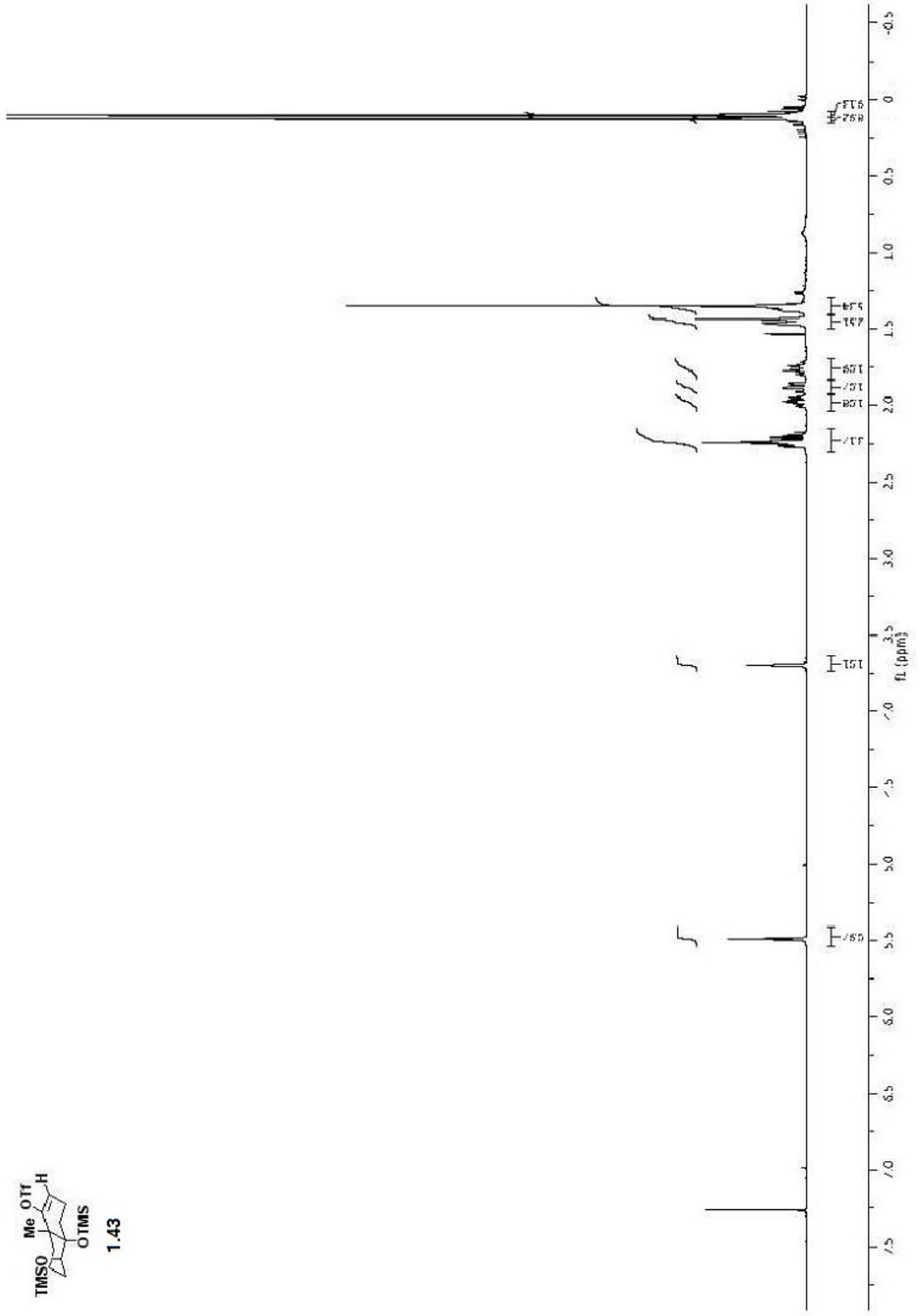

Me
O
OH
OH
1.42
f1 (ppm)


Me
O
OH
OH
1.42
f1 (ppm)

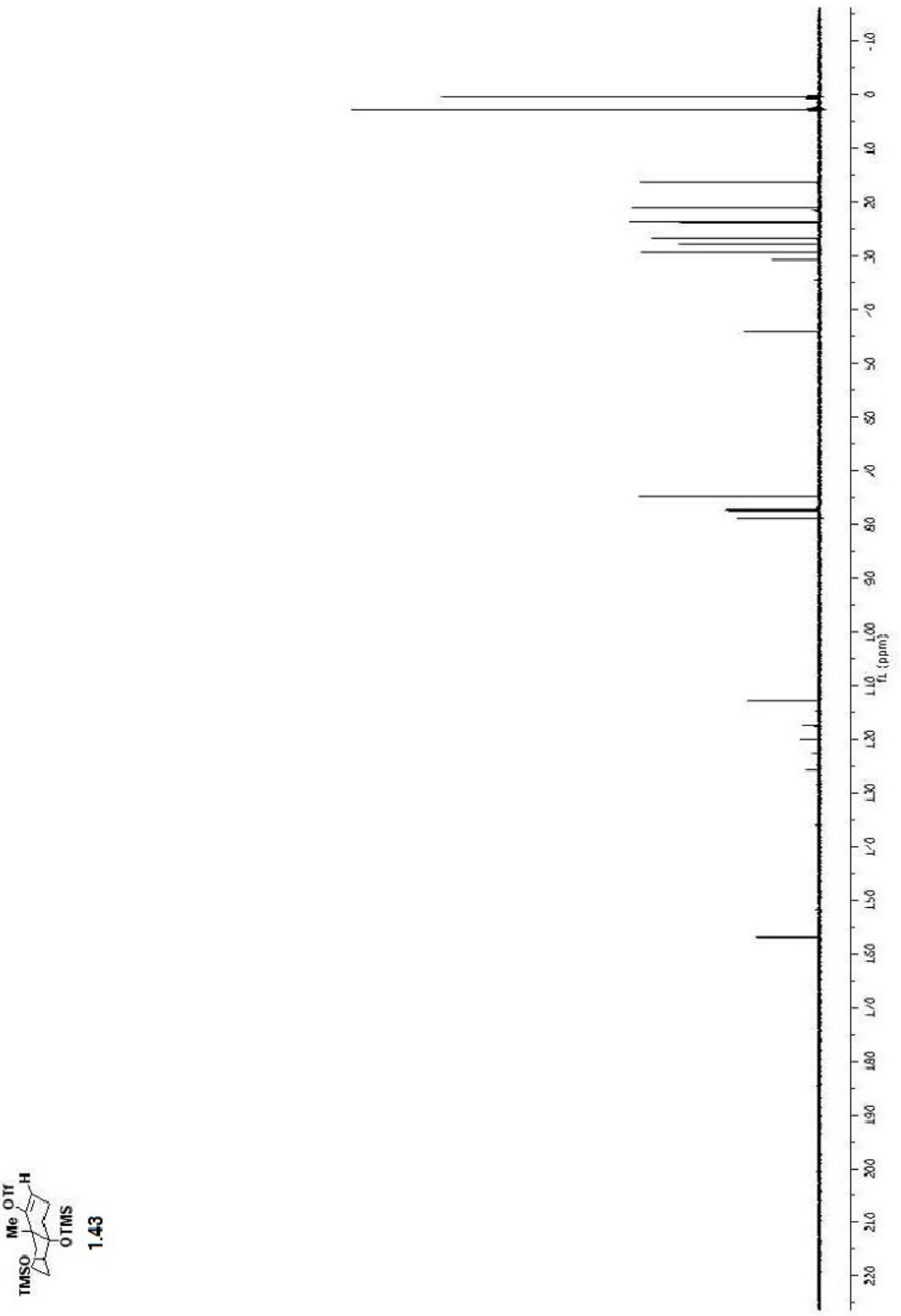


1.50

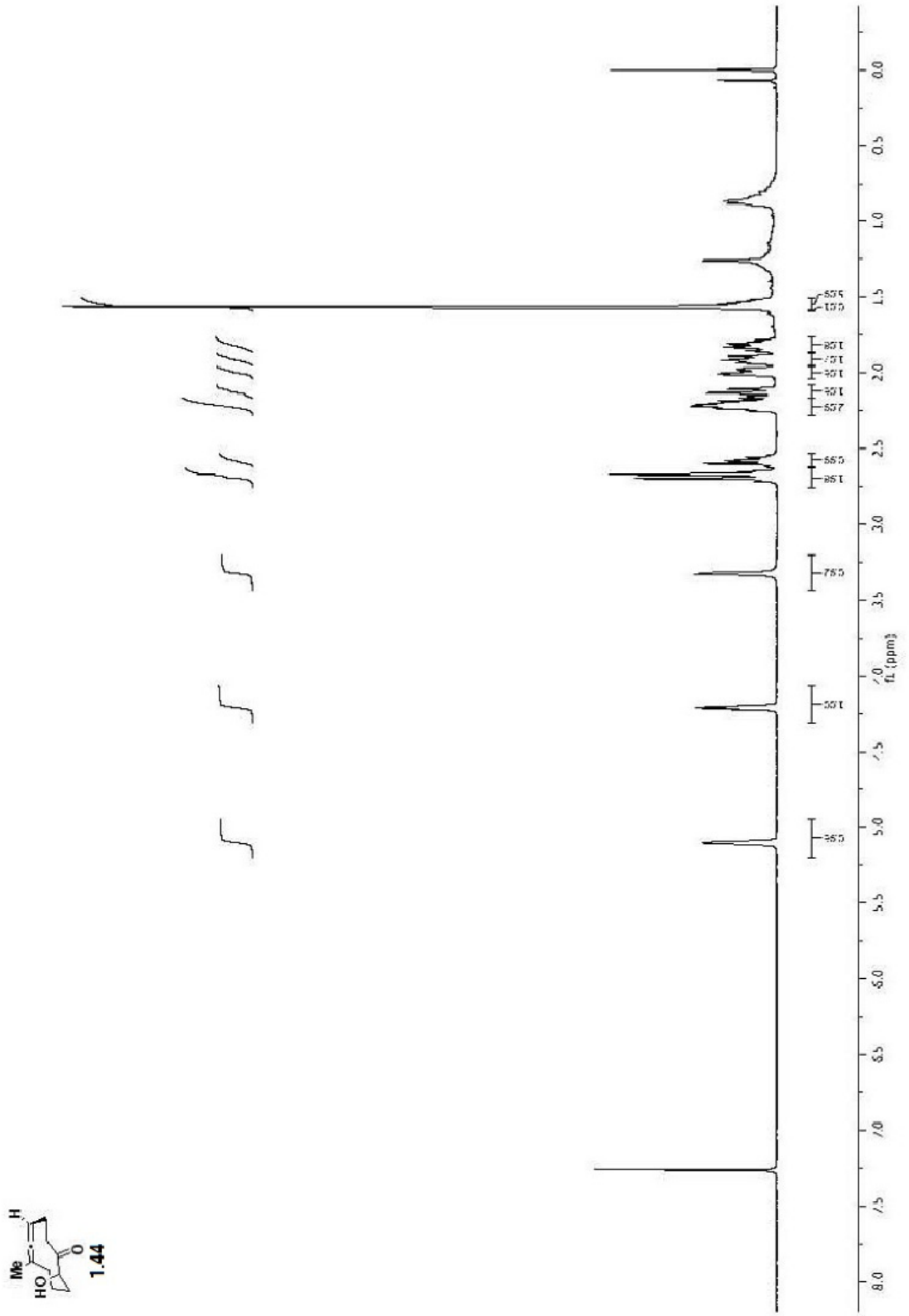

TMSO
Me
O
OTMS
1.50
f1 (ppm)

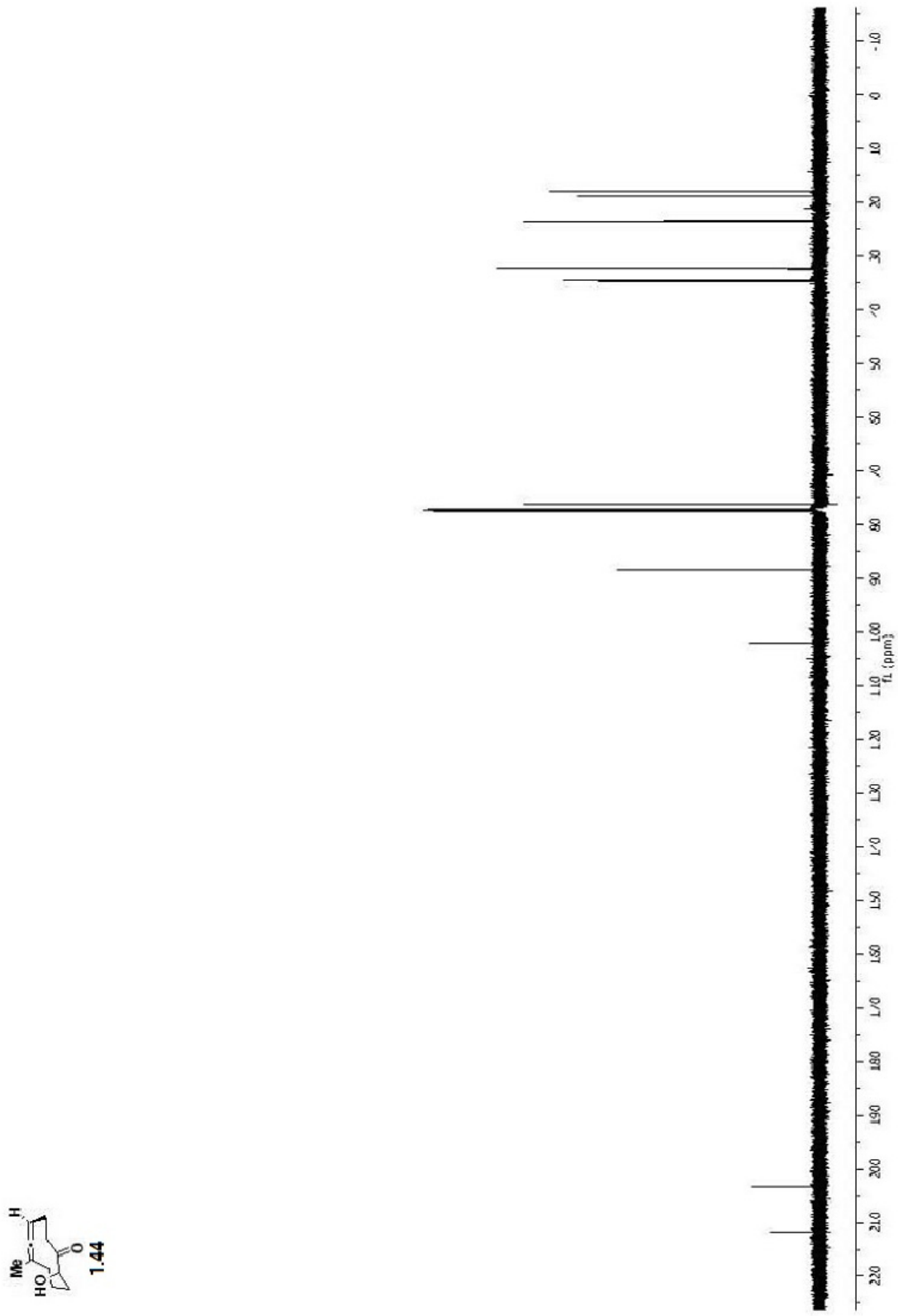


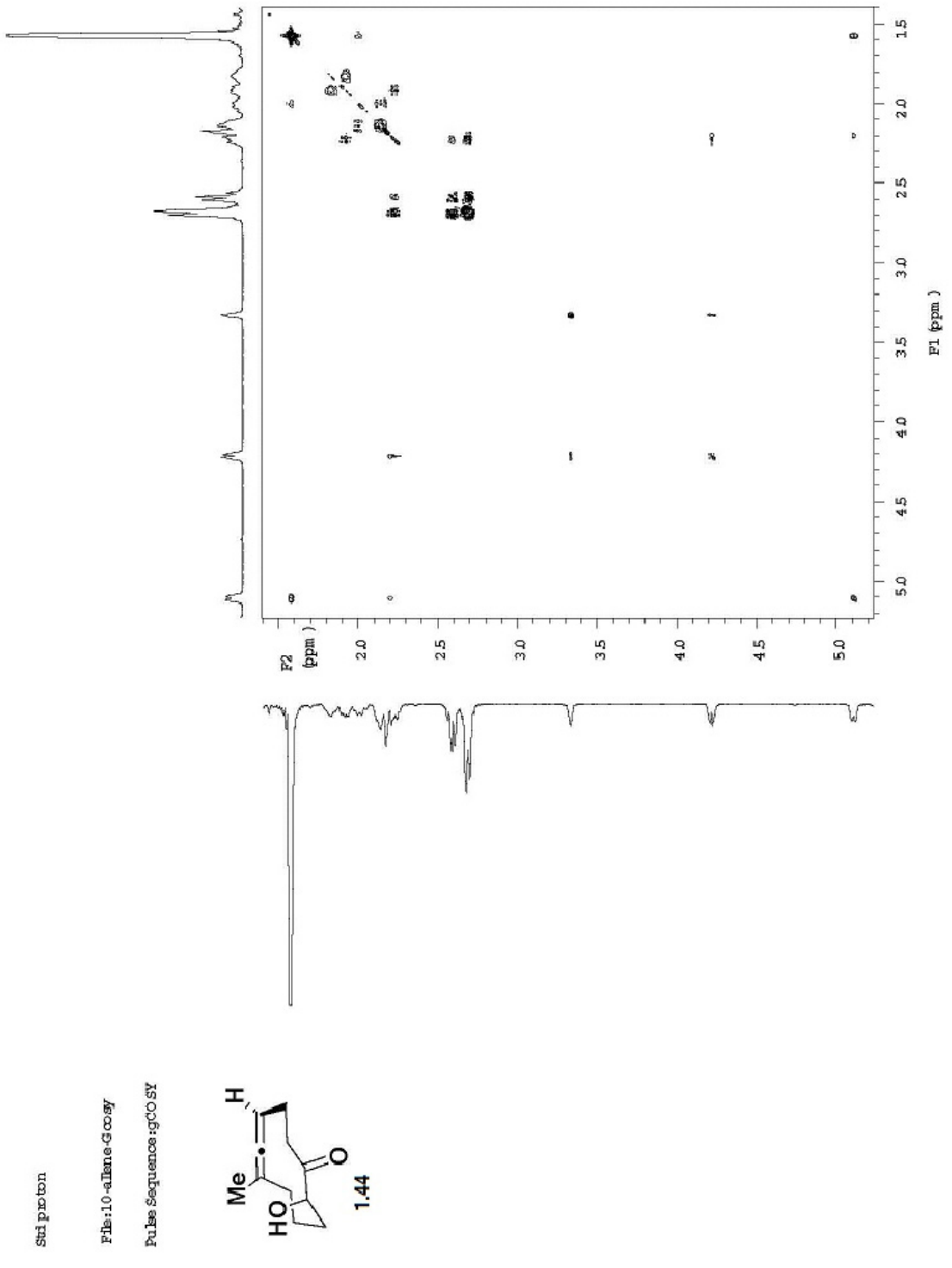
1.43

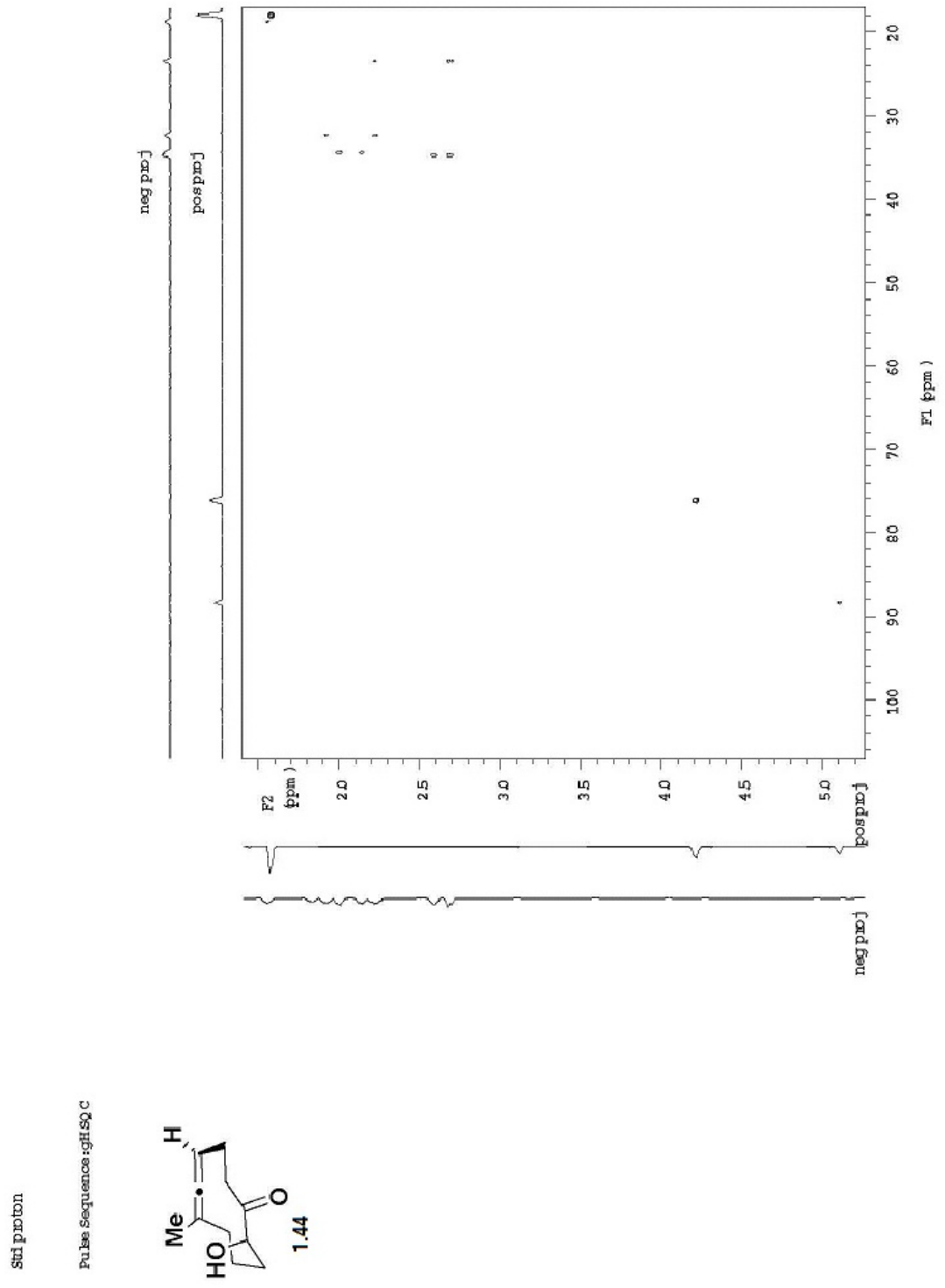


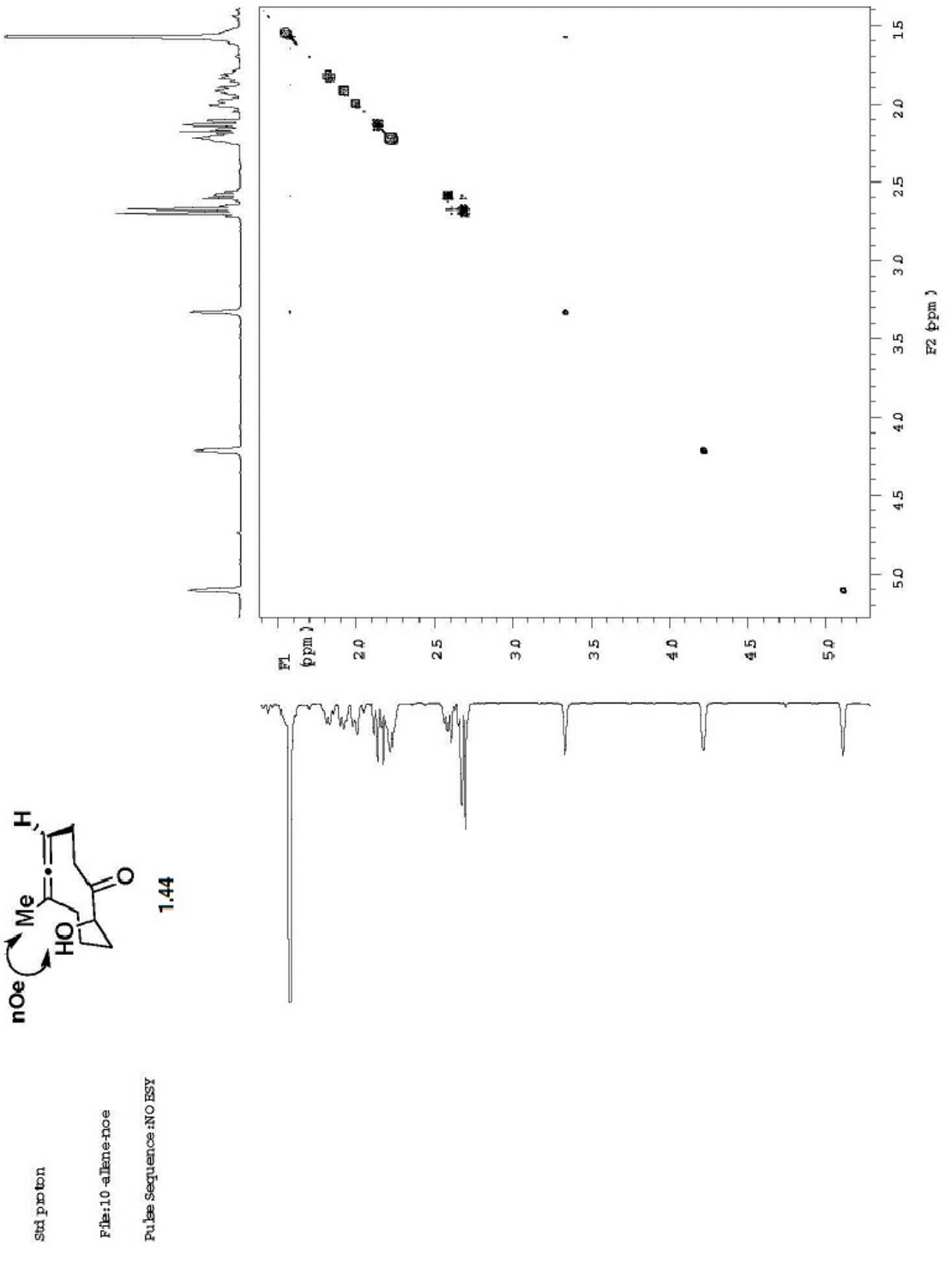
1.43


Me
H
HO
O
1.44
f1 (ppm)

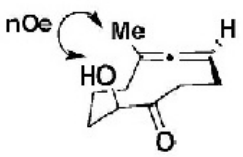

Me
H
HO
O
1.44
f1 (ppm)


Std proton
File:10-allene-Gcosy
Pulse Sequence: gCOSY
Me
H
HO
O
1.44
F2 (ppm)
F1 (ppm)

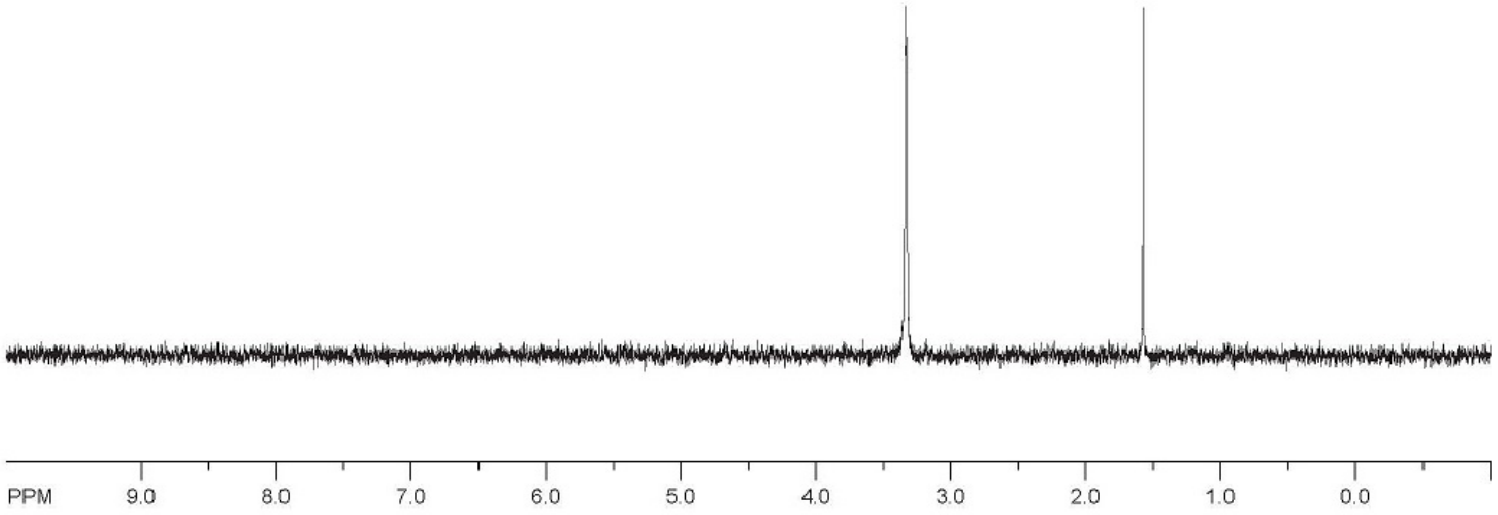

Std proton
Pulse Sequence: gHSQC
Me
H
HO
O
1.44
neg proj
posproj
F2 (ppm)
F1 (ppm)


Std proton
File:10-allene-noe
Pulse Sequence:NOESY
nOe
Me
H
HO
O
1.44
F1 (ppm)
F2 (ppm)

SpinWorks 2.5: NOESY1D

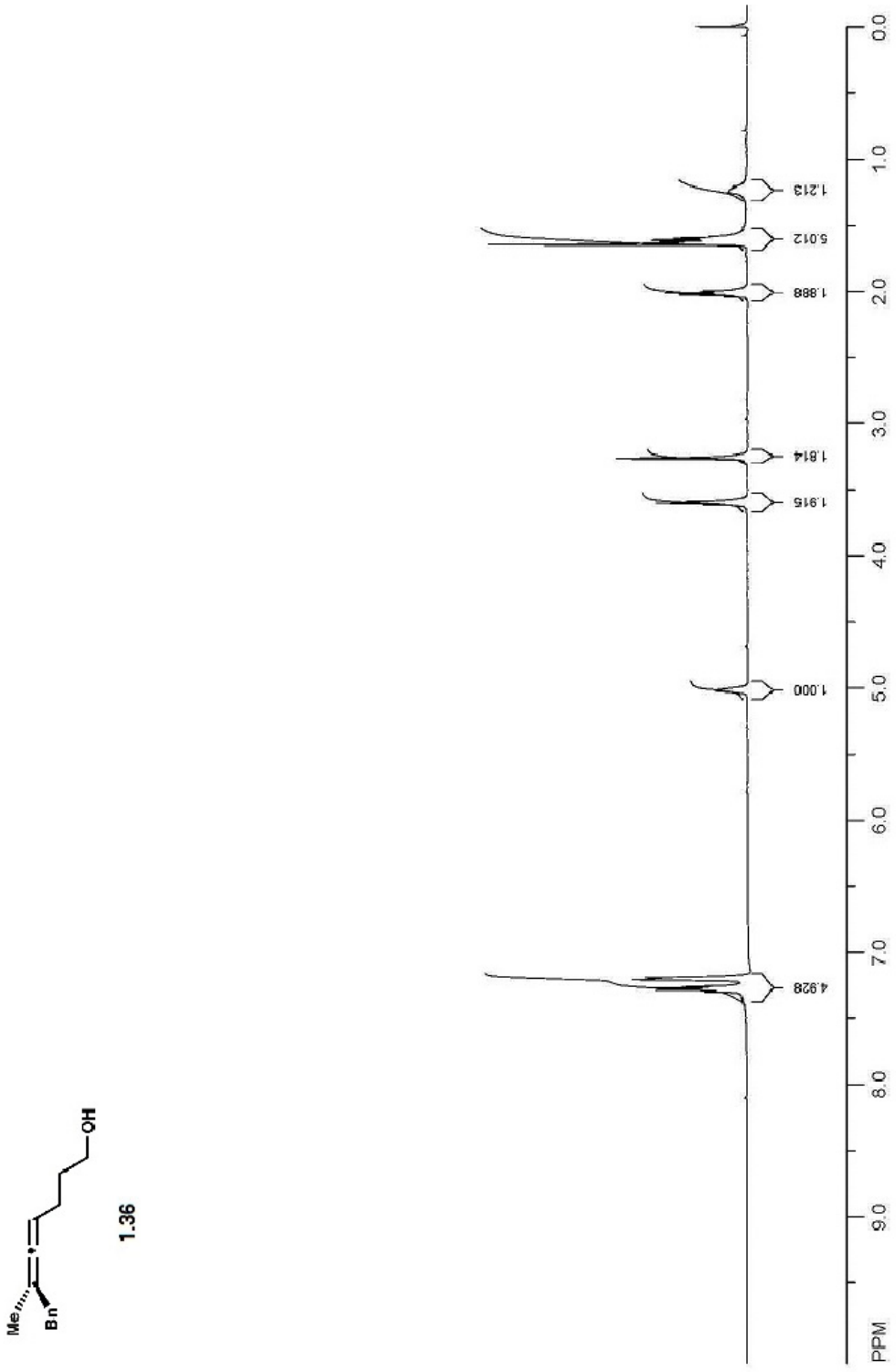


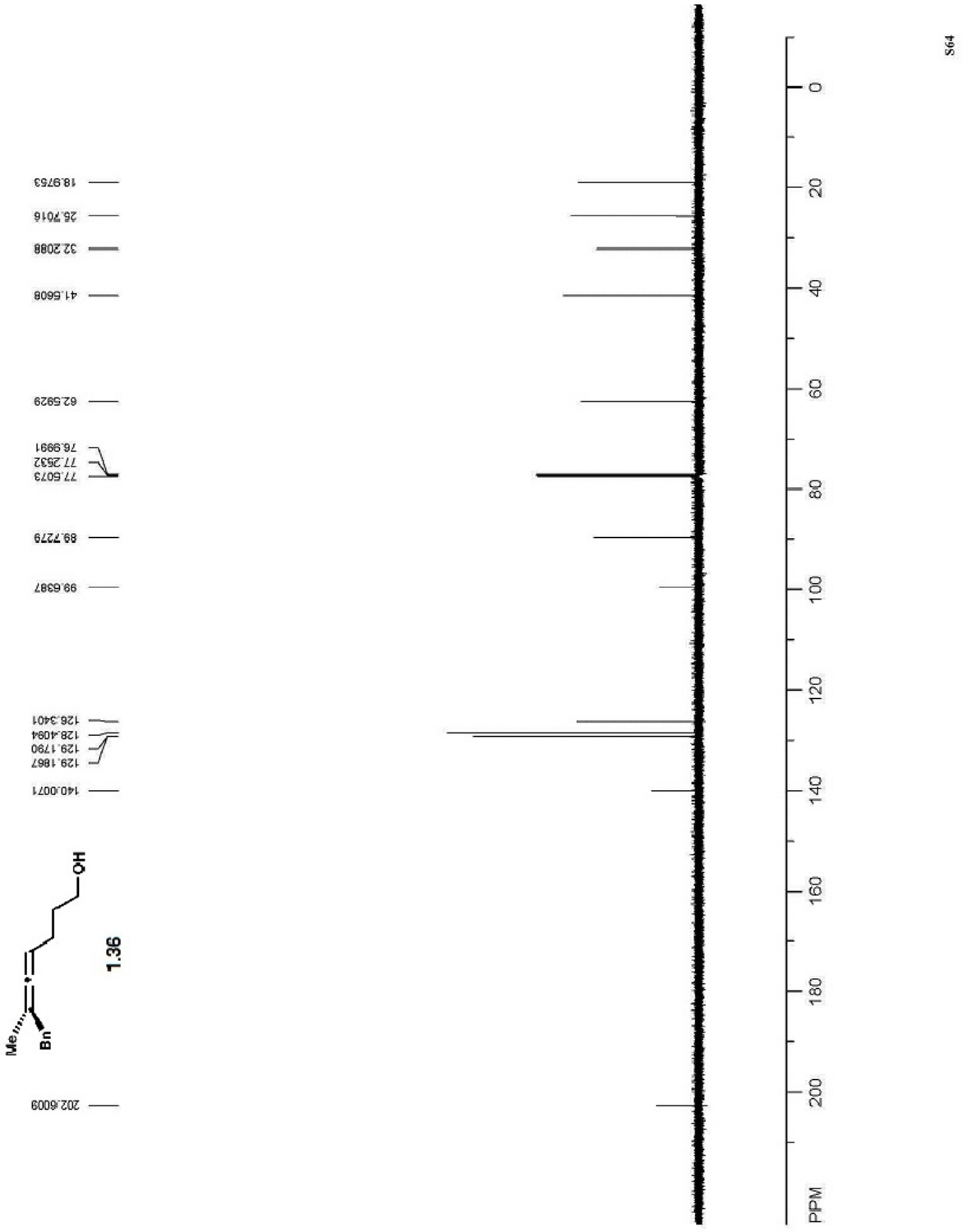
1.44

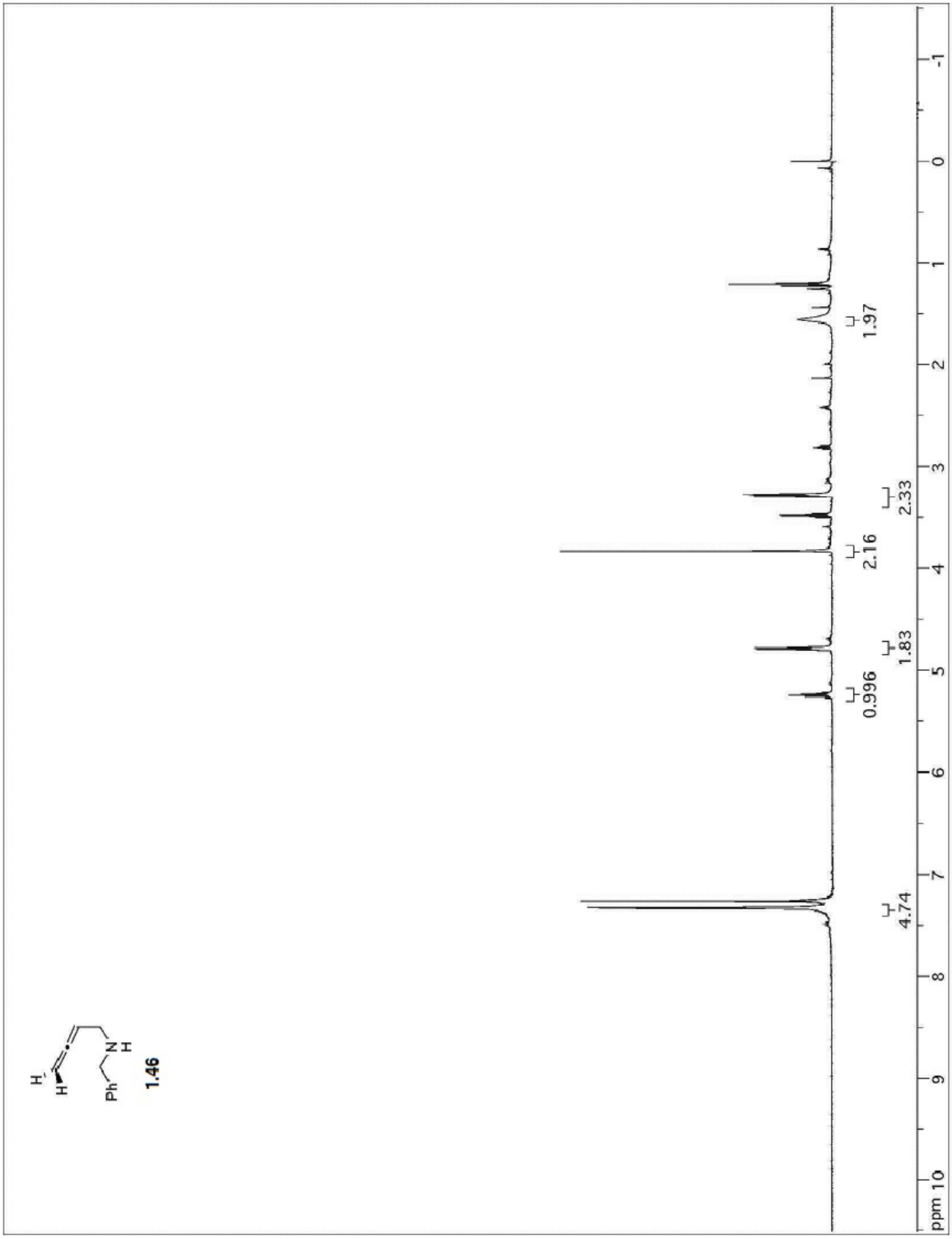


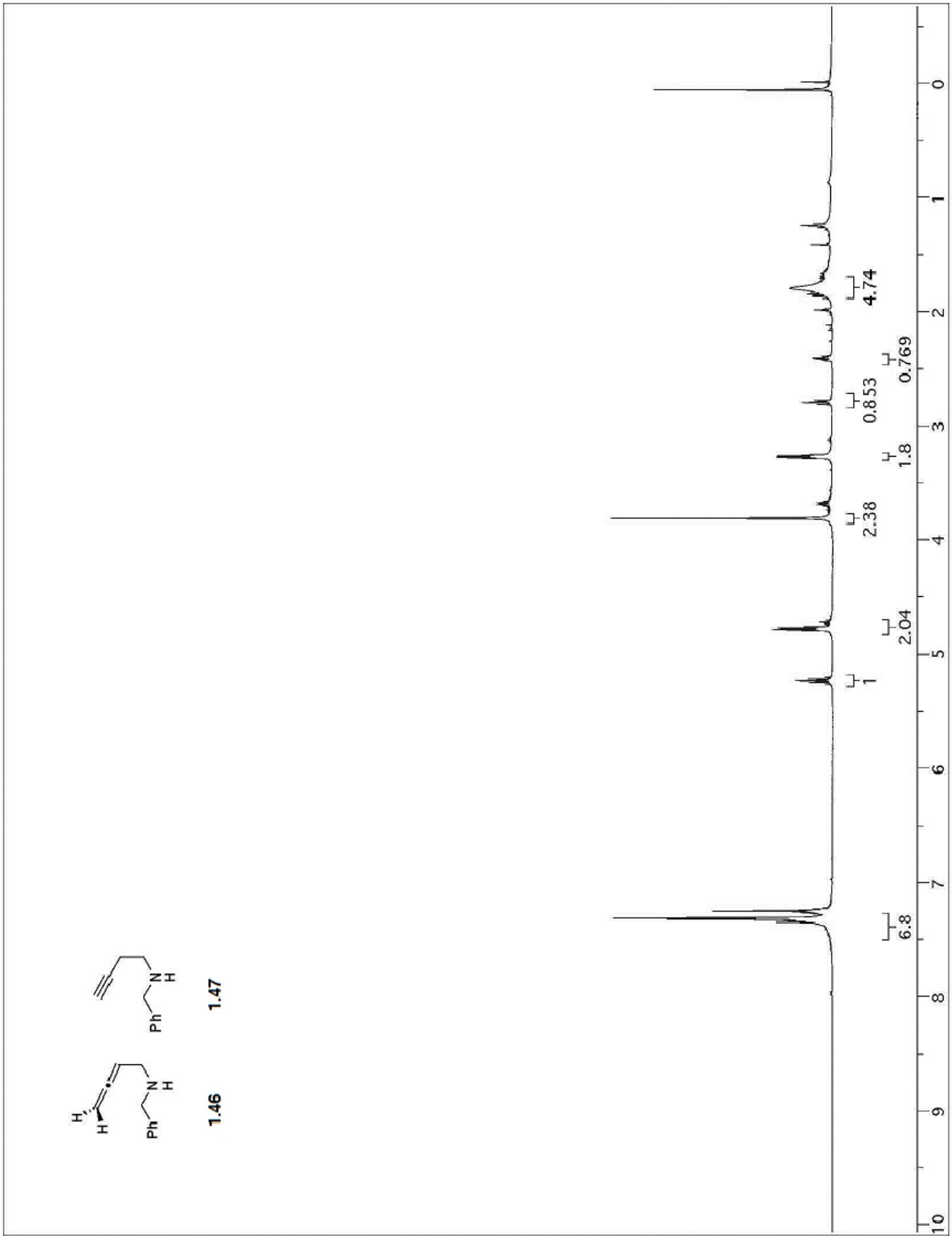
file: D:\Documents and Settings\Yue\Desktop\ir-33.fid\fid block# 1 expt: "NOESY1D"
transmitter freq.: 499.772123 MHz
time domain size: 32018 points
width: 8012.82 Hz = 16.032948 ppm = 0.250260 Hz/pt
number of scans: 64

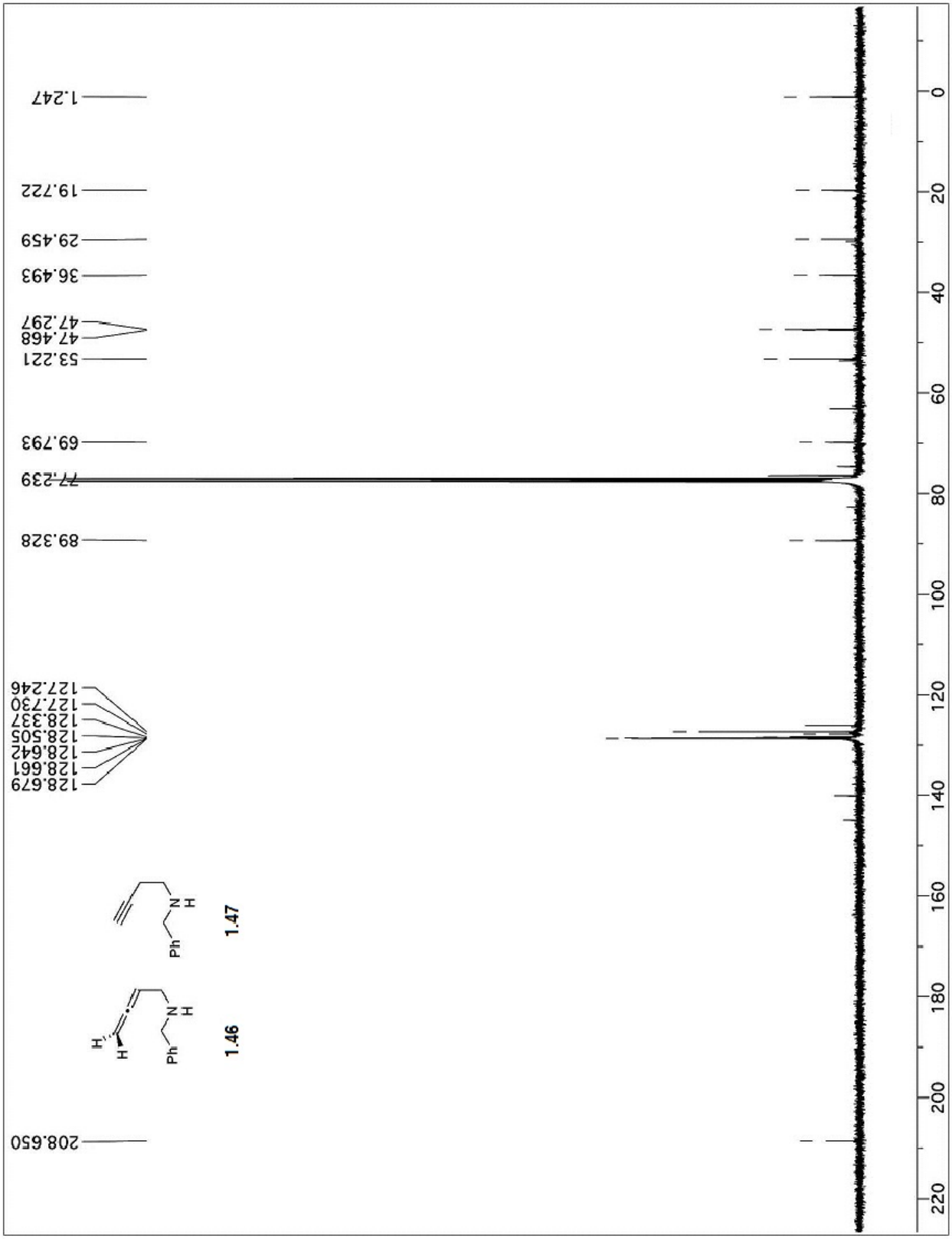
freq. of 0 ppm: 499.769124 MHz
processed size: 32768 complex points
LB: 0.501 GB: 0.0000
Hz/cm: 219.898 ppm/cm: 0.44000


OH
Me
Bn
1.36
1.213
5.012
1.888
1.814
1.915
1.000
4.928
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
PPM

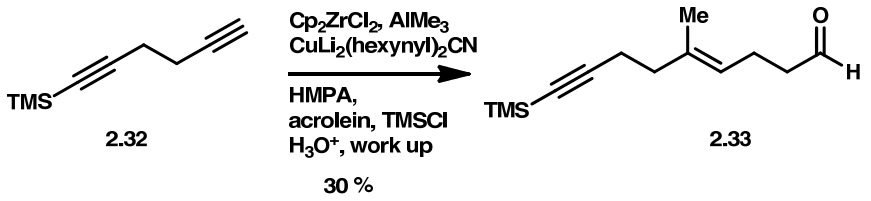

S64
PPM
0
20
40
60
80
100
120
140
160
180
200
18.9753
26.7016
32.2088
41.5608
62.5929
76.9991
77.2532
77.5073
89.7279
99.6387
126.3401
128.4094
129.1790
129.1867
140.0071
202.6009
OH
Me
Bn
1.36


1.46
4.74
0.996
1.83
2.16
2.33
1.97
ppm

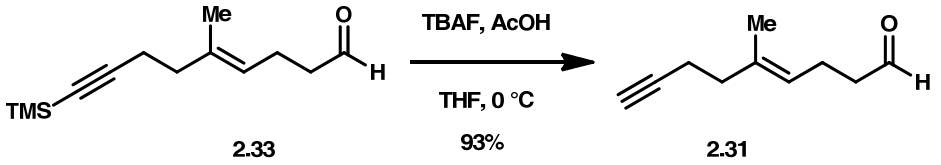

1.46
1.47
6.8
2.04
1
2.38
1.8
0.853
0.769
4.74


1.247
19.722
29.459
36.493
47.297
47.468
53.221
69.793
77.239
89.328
127.246
127.730
128.337
128.505
128.642
128.661
128.679
208.650
1.47
1.46
Ph
N
H
Ph
N
H
H
H
0
20
40
60
80
100
120
140
160
180
200
220

Experimental Chapter Two:

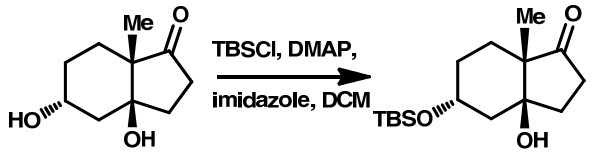


(E)-5-methyl-9-(trimethylsilyl)non-4-en-8-ynal (2.33): To a suspension of Cl_2ZrCp_2 (117mg, 0.4 mmol) in 1,2-dichloroethane (5 mL) was slowly added 2.0M $AlMe_3$ (0.8 ml, 1.6 mmol) at 0 °C. After all Cl_2ZrCp_2 was completed dissolved, diyne **2.32** (200 mg, 1.33 mmol) was added slowly to the flask and stirred for 8 h from 0 °C to rt. A 1.0 M solution of $CuCN_2$•2LiCl was prepared by adding a LiCl (85 mg, 2.0 mmol) in 1 mL THF solution to a flame dried flask with CuCN (89 mg, 1.0 mmol) with stirring. The vinylalane solution was dried by vacuum and added 5 mL THF and then cooled to -25 °C. 0.1 mL of the 1.0 M $CuCN_2$•2LiCl solution was added dropwise at -25 °C followed HMPA (0.23 mL, 1.3 mmol). A solution of TMSCl (75 mg, 1.3 mmol) and acrolein (0.17 mL, 1.3 mmol) in THF was then added. The reaction was stirred for another 1 h at -25 °C. The reaction was then added 10 % HCl (5 mL) and stirred at 0 °C for 30 min. The reaction mixture was then added 20 mL water and extracted with Et_2O (3 x 20 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. Evaporation of solvent and flash column chromatography with (hexanes 85 %: ethyl acetate 15 %) to give the aldehyde **2.33** (89 mg, 30 % yield) as a colorless oil. δ_H (400 MHz, $CDCl_3$) 9.77 (1 H, t, *J* = 1.6 Hz), 5.20-5.13 (1 H, m), 2.50-2.44 (2 H, m), 2.40-2.26 (4 H, m), 2.22-2.16 (2 H, m), 1.64 (3 H, s), 0.14 (9 H, m).



2.33 2.31

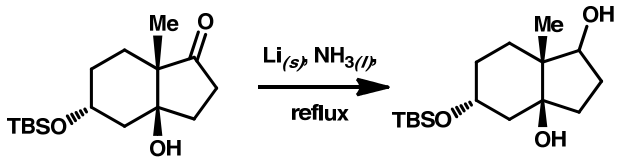
(E)-5-methylnon-4-en-8-ynal (2.31): To a solution of TMS alkyne **2.33** (75 mg, 0.34mmol) in THF (1 mL) at 0 °C, was added a mixture of TBAF (1.0 M, 0.50 mL, 0.50 mmol) and acetic acid (29 μL, 0.5mmol) slowly. The reaction mixture was stirred for 1 h at 0 °C before quenched with water (20 mL). The reaction mixture was then added 20 mL water and extracted with Et_2O (3 x 20 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. Evaporation of solvent and flash column chromatography with (hexanes 80 %: ethyl acetate 20 %) to give the aldehyde **2.31** (47 mg, 93 % yield) as a colorless oil. δ_H (400 MHz, $CDCl_3$) 9.77 (1 H, t, J = 1.5 Hz), 5.20-5.15 (1 H, m), 2.52-2.44 (2 H, m), 2.40-2.31 (2 H, m), 2.31-2.24 (2 H, m), 2.24-2.16 (2 H, m), 1.94 (1 H, t, J = 1.9 Hz), 1.64 (3 H, s); δ_C (125 MHz, $CDCl_3$) 202.4, 135.0, 123.5, 84.0, 68.5, 43.8, 38.2, 20.8, 17.4, 15.8.



2.34 2.35

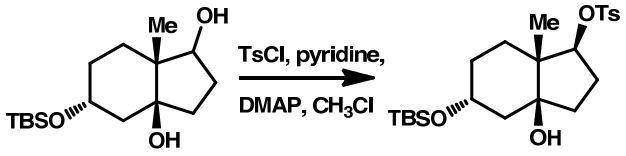
(3aS,5R,7aS)-5-((tert-butyldimethylsilyl)oxy)-3a-hydroxy-7a-methyloctahydro-1H-inden-1-one (2.35): To a solution of diol **2.34** (95 mg, 0.52 mmol) in DCM (2 mL) at

0 °C was added imidazole and TBSCl. The reaction for stirred for 1 h from 0 °C to rt before quenched with water (20 mL). The mixture was extracted with DCM (20x3 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. Evaporation of solvent and flash column chromatography with (hexanes 75 %: ethyl acetate 25 %) to give ketone **2.35** (126 mg, 82 % yield) as a colorless oil. δ_H (500 MHz, $CDCl_3$) 4.03-3.95 (1 H, m), 2.56-2.41 (2 H, m), 2.40-2.24 (1 H, m), 1.92-1.83 (2 H, m), 1.81-1.74 (1 H, m), 1.68-1.60 (2 H, m), 1.48 (1 H, bs), 1.37-1.29 (1 H, m), 1.29-1.21 (1 H, m), 1.01 (3 H, s), 0.88 (9 H, s), 0.07 (3 H, s), 0.05 (3 H, s); δ_C (125 MHz, $CDCl_3$) 220.3, 78.9, 67.0, 52.6, 43.2, 34.2, 33.2, 30.2, 27.2, 25.8(3), 25.8, 18.0, -4.82, -4.87.



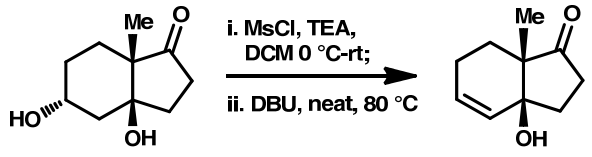
2.35 2.36

(3aS,5R,7aR)-5-((tert-butyldimethylsilyl)oxy)-7a-methyloctahydro-1H-indene-1,3a-diol (2.36): A flame dried flask with $Li_{(s)}$ (50 mg, 7 mmol) was cooled with dry ice bath and cold finger. $NH_{3(g)}$ was purged slowly to the flask until the flask is half full. Ketone **2.35** (85 mg, 0.285 mmol) in 2 mL THF was added slowly to the refluxing ammonia solution and stirred for 30 min. The reaction mixture was then warmed slowly until most of ammonia was evaporated. The reaction mixture was quenched with MeOH slowly with dry ice bath. Water (20 mL) was then added and extracted with EtOAc (20 mLx3). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. Evaporation of solvent and flash column chromatography with (hexanes 50 %: ethyl acetate 50 %) to give diol **2.36** (80 mg, 93 % yield, 1:1 *cis*:*trans*) as a colorless oil.



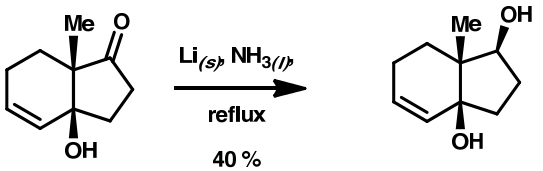
2.36 2.37

(1S,3aS,5R,7aR)-5-((tert-butyldimethylsilyl)oxy)-3a-hydroxy-7a-methyloctahydro-1H-inden-1-yl 4-methylbenzenesulfonate (2.37): To a solution of diol **2.36** (80 mg, 0.266 mmol) in 1 mL chloroform was added pyridine (45 µL, 0.80 mmol), TsCl (102 mg, 0.53 mmol) and DMAP (2 mg, 16 µmol). The reaction was then stirred for 5 h before quenched with water 20 mL. The mixture was extracted with DCM (20x3 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. Evaporation of solvent and flash column chromatography with (hexanes 70 %: ethyl acetate 30 %) to give tosylate **2.37** (43 mg, 36 % yield) as a colorless oil. δ_H (500 MHz, $CDCl_3$) 7.79 (2 H, d, J = 8.2 Hz), 7.34 (2 H, d, J = 8.2 Hz), 4.78-4.71 (1 H, m), 3.90-3.82 (1 H, m), 2.45 (3 H, s), 2.11-1.94 (2 H, m), 1.85-1.70 (2 H, m), 1.70-1.60 (1 H, m), 1.47-1.38 (1 H, m), 1.30-1.16 (2 H, m), 1.48 (1 H, bs), 1.37-1.29 (1 H, m), 1.29-1.21 (1 H, m), 0.92 (3 H, s), 0.86 (9 H, s), 0.03 (3 H, s), 0.02 (3 H, s); δ_C (125 MHz, $CDCl_3$) 144.6, 134.1, 129.7(2), 127.8(2), 86.2, 79.6, 67.2, 46.7, 42.7, 36.8, 29.8, 26.9, 25.8(3), 21.6, 18.0, 15.2, -4.85, -4.88.



2.34 53 % 2.39

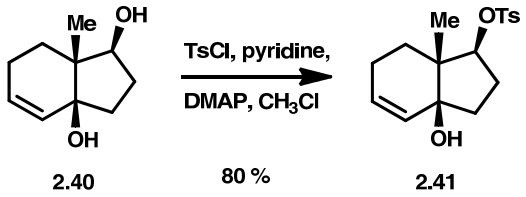
(3aS,7aS)-3a-hydroxy-7a-methyl-2,3,3a,6,7,7a-hexahydro-1H-inden-1-one (2.39): To a solution of diol **2.34** (7.7 g, 42 mmol) in 150 mL chloroform was added TEA (7 mL, 50 mmol) and MsCl (3.9mL, 50 mmol) slowly at 0 °C. TsCl (24 mg, 0.126 mmol) and DMAP (1 mg, 8.19 μmol). The reaction was then stirred for 1 h from 0 °C to rt before quenched with water 200 mL. The mixture was extracted with DCM (200 mLx3). The combined organic layer was washed with brine (100 mL) and dried over Na_2SO_4. Solvent was removed to give crude mesylate (11 g, quant.) as a yellow oil. The crude mesylate was added DBU (32 mL, 209 mmol). The reaction was heated to 80 °C for 5 h. The reaction was quenched with water 200 mL and extracted with DCM (200mLx3). The combined organic layer was washed with 1N HCl (50 mL), water (50 mL), brine (50 mL) and dried over Na_2SO_4. Evaporation of solvent and flash column chromatography with (hexanes 80 %: ethyl acetate 20 %) to give olefin **2.39** [5.55 g (64% purity), 70 % yield] as a colorless oil. The observed NMR data were identical with literature values.



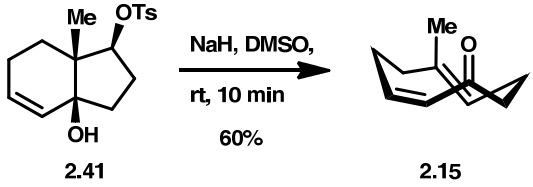
2.39 2.40

(1S,3aS,7aR)-7a-methyl-2,3,3a,6,7,7a-hexahydro-1H-indene-1,3a-diol (2.40): A flame dried flask with $Li_{(s)}$ (1g mg, 144 mmol) was cooled with dry ice bath and cold finger. $NH_{3(g)}$ was purged slowly to the flask until the flask is half full. Ketone **2.39** (3 g, 9 mmol) in 10 mL THF was added slowly to the refluxing ammonia solution and stirred for 30 min. The reaction mixture was then warmed slowly until most of ammonia was evaporated. The reaction mixture was quenched with MeOH slowly with dry ice bath. Water (50 mL) was then added and extracted with EtOAc (20 mLx3). The combined organic layer was

washed with brine (10 mL) and dried over Na_2SO_4. Evaporation of solvent and flash column chromatography with (hexanes 60 %: ethyl acetate 40 %) to give diol **2.40** (19 mg, 40 % yield) as a white crystal. The observed NMR data were identical with literature values.

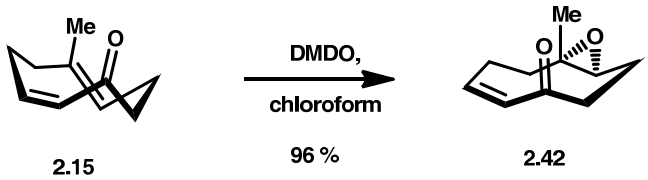


(1S,3aS,7aR)-3a-hydroxy-7a-methyl-2,3,3a,6,7,7a-hexahydro-1H-inden-1-yl4-methyl benzenesulfonate (2.41): To a solution of diol **2.40** (1.68 g, 10 mmol) in 10 mL chloroform was added pyridine (2.4 mL, 30 mmol), TsCl (3.8 g, 20 mmol) and DMAP (122 mg, 1.0 mmol). The reaction was then stirred for 5 h before quenched with water 100 mL. The mixture was extracted with DCM (100x3 mL). The combined organic layer was washed with brine (50 mL) and dried over Na_2SO_4. Evaporation of solvent and flash column chromatography with (hexanes 70 %: ethyl acetate 30 %) to give tosylate **2.41** (2.5 g, 80 % yield) as a colorless oil. The observed NMR data were identical with literature values.

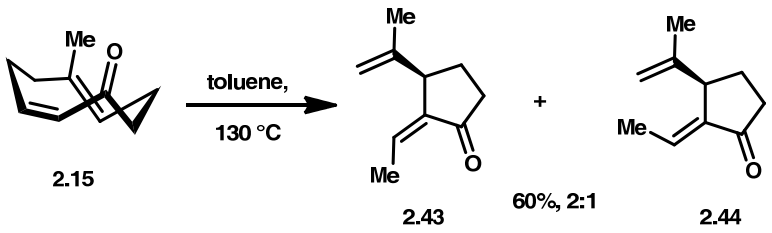


(-)(2Z,6E)-6-methylcyclonona-2,6-dienone (2.15): NaH (37 mg, 60 %, 0.93 mmol) in a flame dried flask was rinsed with hexanes 3 times under argon. DMSO (1 mL) was added to the flask, and the suspension was heated to 65-70 °C under argon for 45 min. The solution was then cooled to rt and added to a solution of tosylate 2.41 (200 mg, 0.62

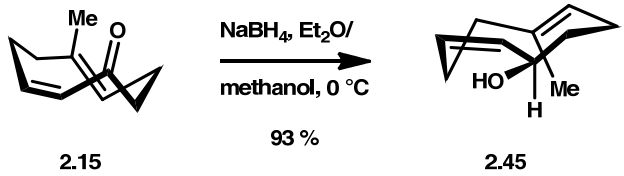
mmol) in 2 mL DMSO slowly. The reaction was stirred at rt for 10 min and then quenched with 20 mL NH_4Cl. The mixture was extracted with Et_2O (20 mLx3). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. Evaporation of solvent and flash column chromatography with (pentane 90 %: Et_2O 10 %) to give tosylate **2.41** (56 mg, 60 % yield) as a colorless oil. The observed NMR data were identical with literature values.



(1S,9S,Z)-9-methyl-10-oxabicyclo[7.1.0]dec-5-en-4-one (2.42): To cyclononadienone **1** (50 mg, 0.333 mmol) was added DMDO in chloroform (2.5 ml, 0.2 M, 0.5 mmol) at 0 °C. After 5 min the reaction mixture was concentrated and purified by flash chromatography (20% EtOAc/Hexanes) to give epoxide **2.42** (53 mg, 96 %) as a white crystalline solid. IR ν_{max}(neat)/cm^{-1} 2936, 1690, 1625, 1453, 1177, 980, 747; δ_H (500 MHz, $CDCl_3$) 6.28 (1 H, dd, *J* = 12.3, 1.3 Hz), 5.81 (1 H, ddd, *J* = 12.2, 9.1, 7.6 Hz), 3.10 (1 H, dd, *J* = 11.8, 2.3 Hz), 2.77 (1 H, td, *J* = 11.5, 7.7 Hz), 2.77 (1 H, td, *J* = 11.5, 7.7 Hz), 2.72-2.62 (2 H, m), 2.40 (1 H, ddd, *J* = 11.4, 7.5, 1.5 Hz), 2.28-2.20 (1H, m), 2.16-2.05 (2 H, m), 1.65 (1 H, qd, *J* = 11.7, 7.5 Hz), 1.20 (3 H, s), 0.97 (1 H, dd, *J* = 12.5, 11.8 Hz); δ_C (125 MHz, $CDCl_3$) 206.5, 136.8, 134.9, 61.1, 59.3, 37.4, 35.9, 24.3, 21.8, 17.0; *m/z* (ESIMS) found: 167 $(M+H)^+$; calc'd: 167. HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH=90/10, Flow Rate = 1 mL/min, UV = 230 nm, t_R = 13.1 min and t_R = 27.9 min (major, 90% *ee*).

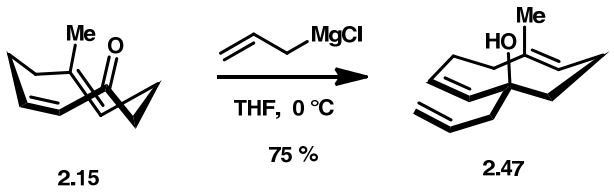


(Z)-2-ethylidene-3-(prop-1-en-2-yl)cyclopentanone (2.43) and (E)-2-ethylidene-3-(prop-1-en-2-yl)cyclopentanone (2.44): Ketone 2.15 (20 mg, 0.13 mmol) in 2 ml toluene was heated to 130 °C in a sealed tube for 1 h. The reaction mixture was purified with flash chromatography (hexanes 95 %: Et_2O 5 %) to give enone **2.43** (8 mg, 40 %) as a colorless. δ_H (500 MHz, $CDCl_3$) 5.98-5.88 (1 H, m), 4.89-4.86 (1 H, m), 4.83-4.80 (1 H, m), 3.45-3.36 (1 H, m), 2.42-2.33 (1 H, m), 2.32-2.22 (1 H, m), 2.16 (2 H, dd, J = 7.4, 2.5 Hz), 2.07-1.98 (1 H, m), 1.87-1.77 (1 H, m), 1.66 (3 H, s), 1.34-1.17 (1 H, m); δ_C (125 MHz, $CDCl_3$) 208.4, 145.8, 137.6, 136.9, 113.4, 50.8, 38.8, 25.2, 18.6, 14.3; Continue eluting with 10% Et_2O/hexanes gave ketone **2.44** (4 mg, 20 %) as a colorless oil. δ_H (500 MHz, $CDCl_3$) 6.78 (1 H, qd, J = 6.8, 2.3 Hz), 4.80-4.77 (1 H, m), 4.83-4.80 (1 H, m), 3.57-3.52 (1 H, m), 2.43-2.33 (1 H, m), 2.33-2.24 (1 H, m), 2.11-2.00 (1 H, m), 1.95-1.86 (1 H, m), 1.79-1.75 (4 H, m), 1.36-1.23 (2 H, m); δ_C (125 MHz, $CDCl_3$) 206.7, 145.5, 140.0, 134.2, 111.3, 45.9, 36.6, 25.2, 20.5, 14.7.

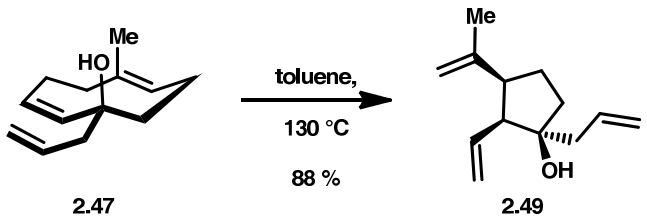


(R,2Z,6E)-6-methylcyclonona-2,6-dienol (2.45): To a solution of ketone 2.15 (85 mg, 0.57 mmol) in 10% methanol-ether (1 mL) was cooled to 0 °C and add $NaBH_4$, (10 mg, 0.28 mmol for 30 min. The solution was concentrated and purified with flash

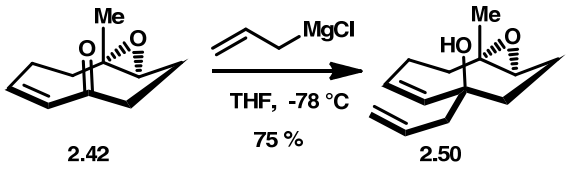
chromatography (hexanes 90 %: EtOAc 10 %) to give alcohol **2.45** (80 mg, 93 %) as a white crystal. δ_H (500 MHz, $CDCl_3$) 5.52-5.45 (1 H, m), 5.35-5.28 (1 H, m), 5.19-5.12 (1 H, m), 3.81-3.75 (1 H, m), 2.46-2.33 (1 H, m), 2.20-2.13 (1 H, m), 2.12-2.07 (1 H, m), 2.07-1.96 (3 H, m), 1.95-1.85 (1 H, m), 1.71 (3 H, s), 1.59-1.51 (1 H, m); δ_C (125 MHz, $CDCl_3$) 138.7, 131.9, 129.5, 125.8, 68.1, 42.1, 36.3, 27.5, 24.7, 16.9.



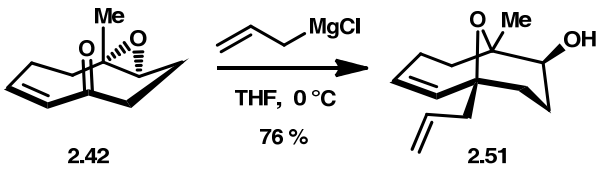
(R,2Z,6Z)-1-allyl-6-methylcyclonona-2,6-dienol (2.47): To a solution of ketone **2.15** (22 mg, 0.146 mmol) in THF (0.5 mL) at 0 °C was added allylmagnesium chloride (2.0 M, in THF, 0.11 ml, 0.22 mmol). After 1 h the reaction was quenched with saturated NH_4Cl, extracted with ether (3x10 mL), the organic fractions were combined, dried over Na_2SO_4, filtered, concentrated, and then the residue was purified by flash chromatography (3% EtOAc/Hexanes) to yield alcohol **2.47** (21 mg, 75 % yield) as a colorless oil. IR ν_{max}(neat)/cm^{-1} 3562, 2924, 1725, 1638, 1448, 996, 915, 743; δ_H (500 MHz, $CDCl_3$) 5.83 (1 H, dddd, *J* = 17.0, 10.2, 8.5, 6.1 Hz), 5.37 (1 H, dd, *J* = 12.7, 1.2 Hz), 5.29-5.03 (4 H, m), 2.43 (1 H tdd, *J* = 12.6, 11.9, 6.3), 2.32 (1 H, ddt, *J* = 13.6, 6.1, 1.3 Hz), 2.20, (1 H, qdd, *J* = 5.5, 2.5, 1.3 Hz), 2.17-2.05 (4 H, m), 1.93 (1 H, ddd, *J* = 13.8, 11.9, 6.3 Hz), 1.85 (1 H, ddd, *J* = 13.8, 6.3, 1.6 Hz), 1.74 (3 H, t, *J* = 1.2 Hz), 1.56 (1 H, br s), 1.58-1.51 (1 H, dt, *m*); δ_C (125 MHz, $CDCl_3$) 139.9, 134.1, 131.5, 127.9, 125,4, 118.6, 76.4, 48.6, 44.0, 36.2, 27.1, 25.1 17.0; *m/z* (ESIMS) found: 175 $(M\text{-}OH)^+$; calc'd: 175.



(1S,2S,3S)-1-allyl-3-(prop-1-en-2-yl)-2-vinylcyclopentanol (2.49): Ketone 2.15 (24 mg, 0.125 mmol) in 1 ml toluene was heated to 130 °C in a sealed tube for 2 h. The reaction mixture was purified with flash chromatography (hexanes 95 %: EtOAc 5 %) to give alcohol **2.49** (21 mg, 88 %) as a colorless. δ_H (400 MHz, $CDCl_3$) 5.99-5.84 (1 H, m), 5.74-5.58 (1 H, m), 5.23-5.01 (4 H, m), 4.81 (1 H, s), 4.75 (1 H, s), 2.67-2.55 (2 H, m), 2.37-2.29 (2 H, m), 2.07-1.93 (1 H, m), 1.82-1.62 (4 H, m), 1.68 (3 H, s); δ_C (100 MHz, $CDCl_3$) 145.5, 135.2, 134.0, 118.6, 118.4, 110.2, 81.1, 55.2, 49.0, 46.7, 38.1, 26.2, 23.2.

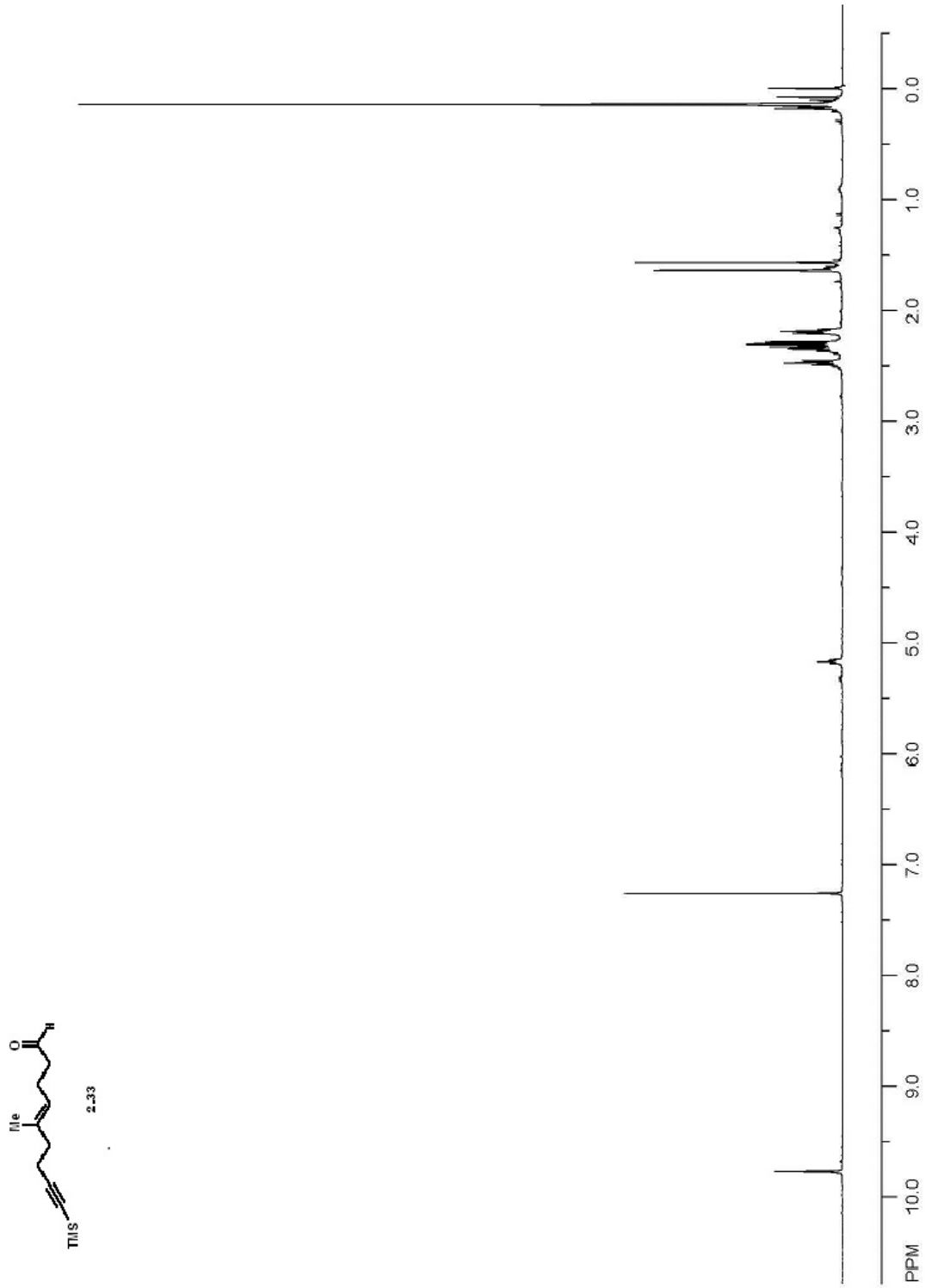


(1S,4R,9R,Z)-4-allyl-9-methyl-10-oxabicyclo[7.1.0]dec-5-en-4-ol (2.50): To a solution of epoxide **2.42** (7 mg, 0.042 mmol) in THF (0.5 mL) at -78 °C was added allylmagnesium chloride (2.0 M, in THF, 32 μL, 0.062 mmol). After 1 h the reaction was quenched with methanol at -78 °C, diluted with 15 mL water and extracted with ether (3x10 mL), the organic fractions were combined, dried over Na_2SO_4, filtered, concentrated, and then the residue was purified by flash chromatography (20 % EtOAc/Hexanes) to yield alcohol **2.50** (6.6 mg, 75 % yield) as a colorless oil.



2.42 2.51

(1R,6R,7S)-1-allyl-6-methyl-10-oxabicyclo[4.3.1]dec-2-en-7-ol (2.51): To a solution of epoxide **2.42** (20 mg, 0.133 mmol) in THF (0.5 mL) at 0 °C was added allylmagnesium chloride (2.0 M in THF, 90 µl, 0.18 mmol). The mixture was stirred at 0 ^{o}C for 1 h. The reaction was then quenched with saturated NH_4Cl, extracted with ether (3x10 mL), the organic fractions were combined, dried over Na_2SO_4, filtered, concentrated, and then the residue was purified by flash chromatography (25% EtOAc/Hexanes) to yield bicyclic alcohol **2.51** (19 mg, 76 % yield) as a white solid. IR ν_{max}(neat)/cm^{-1} 3424, 2932, 1639, 1440, 1078, 912; δ_H (500 MHz, $CDCl_3$) 5.95-5.80 (2 H, m), 5.13-4.99 (3 H, m), 3.35 (1 H, br s), 2.61-2.51 (1 H, m), 2.31-2.14 (3 H, m), 1.93-1.66 (5 H, m), 1.64-1.55 (1 H, m), 1.32-1.25 (1 H, m), 1.20 (3 H, s); δ_C (125 MHz, $CDCl_3$) 134.4, 134.0, 130.3, 117.4, 78.2, 75.6, 70.0, 48.6, 38.8, 27.0, 26.5, 23.3, 21.1; *m/z* (ESIMS) found: 231 $(M+Na)^+$; calc'd: 231.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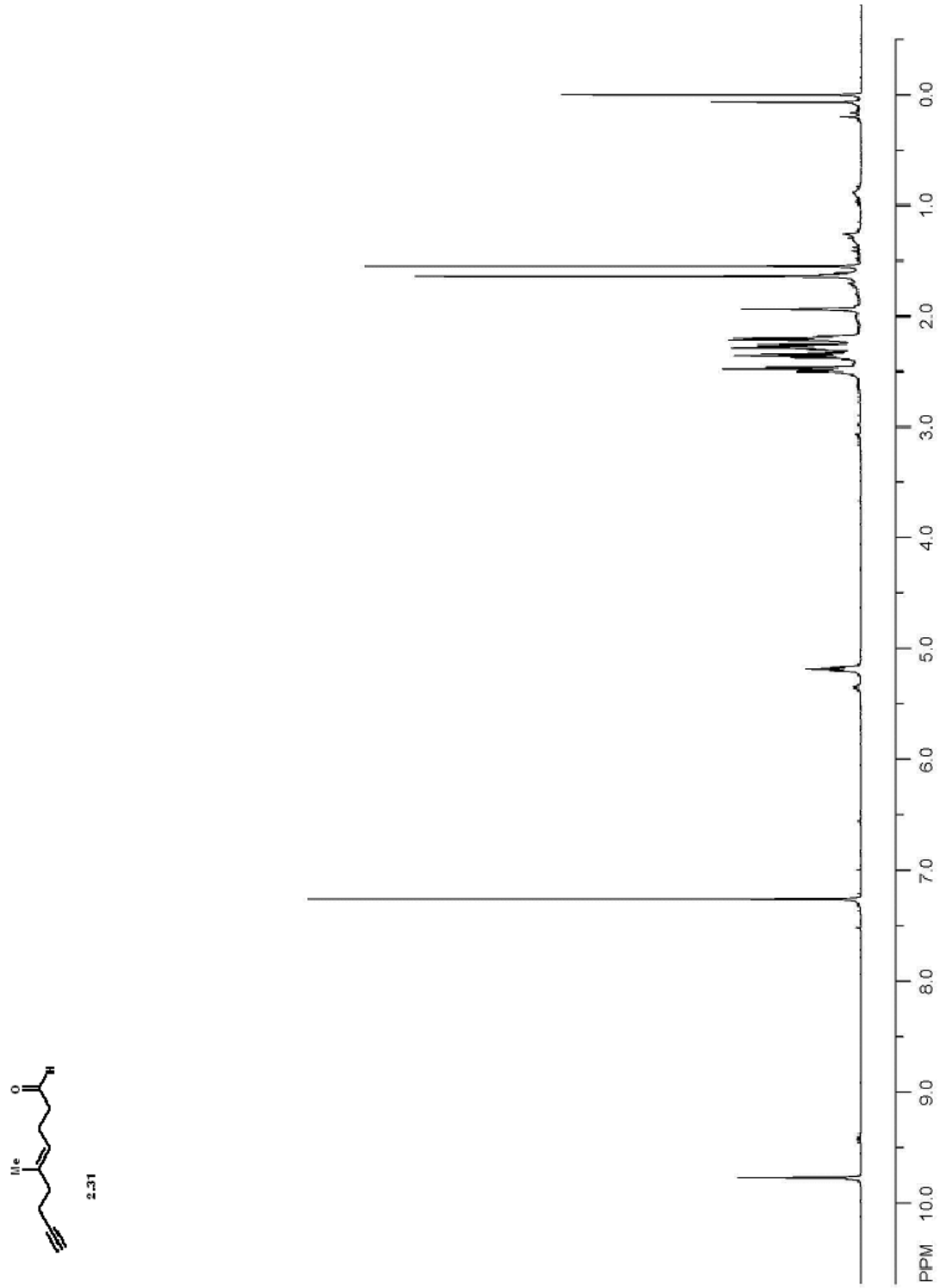
1.0
0.0
PPM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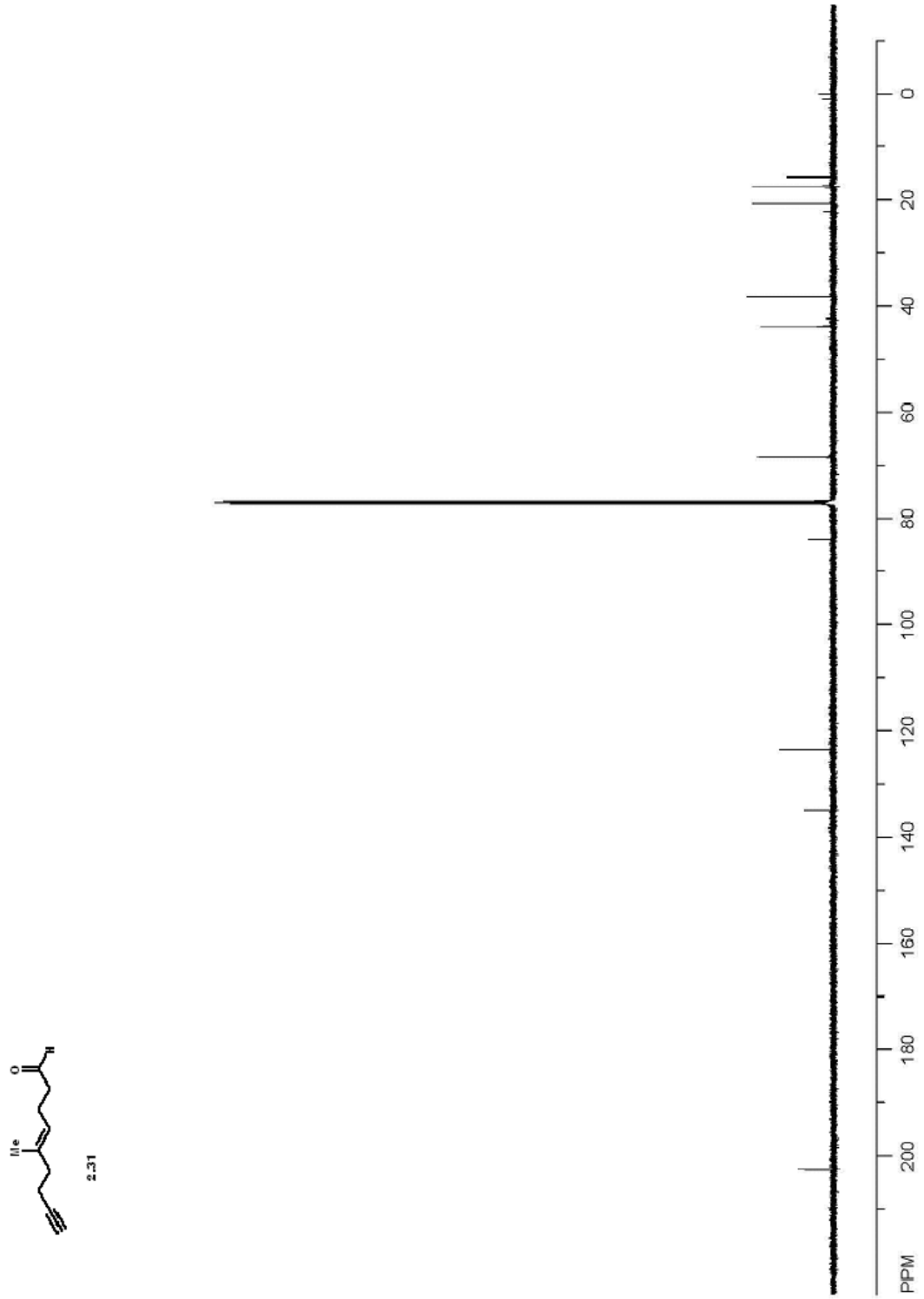
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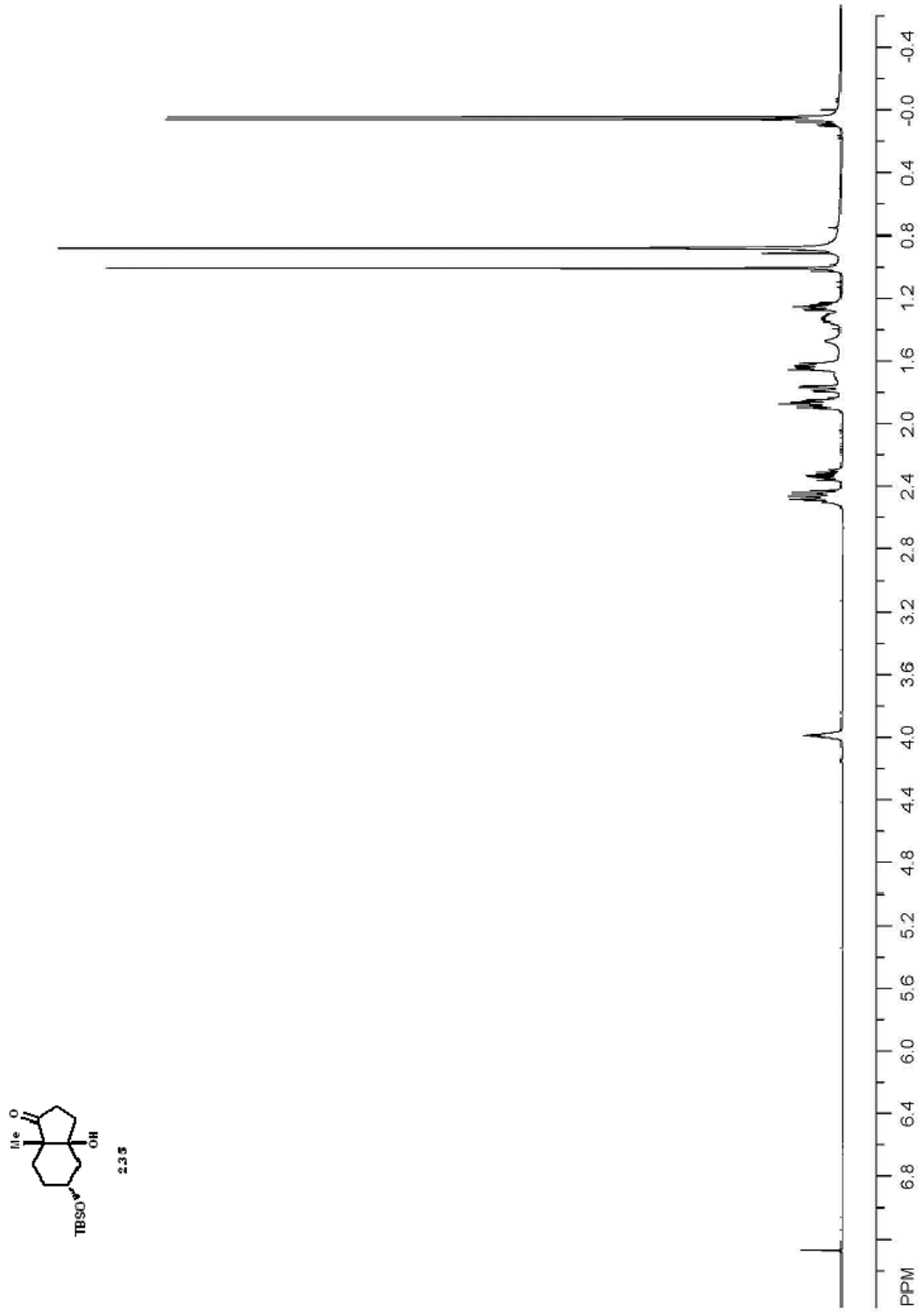
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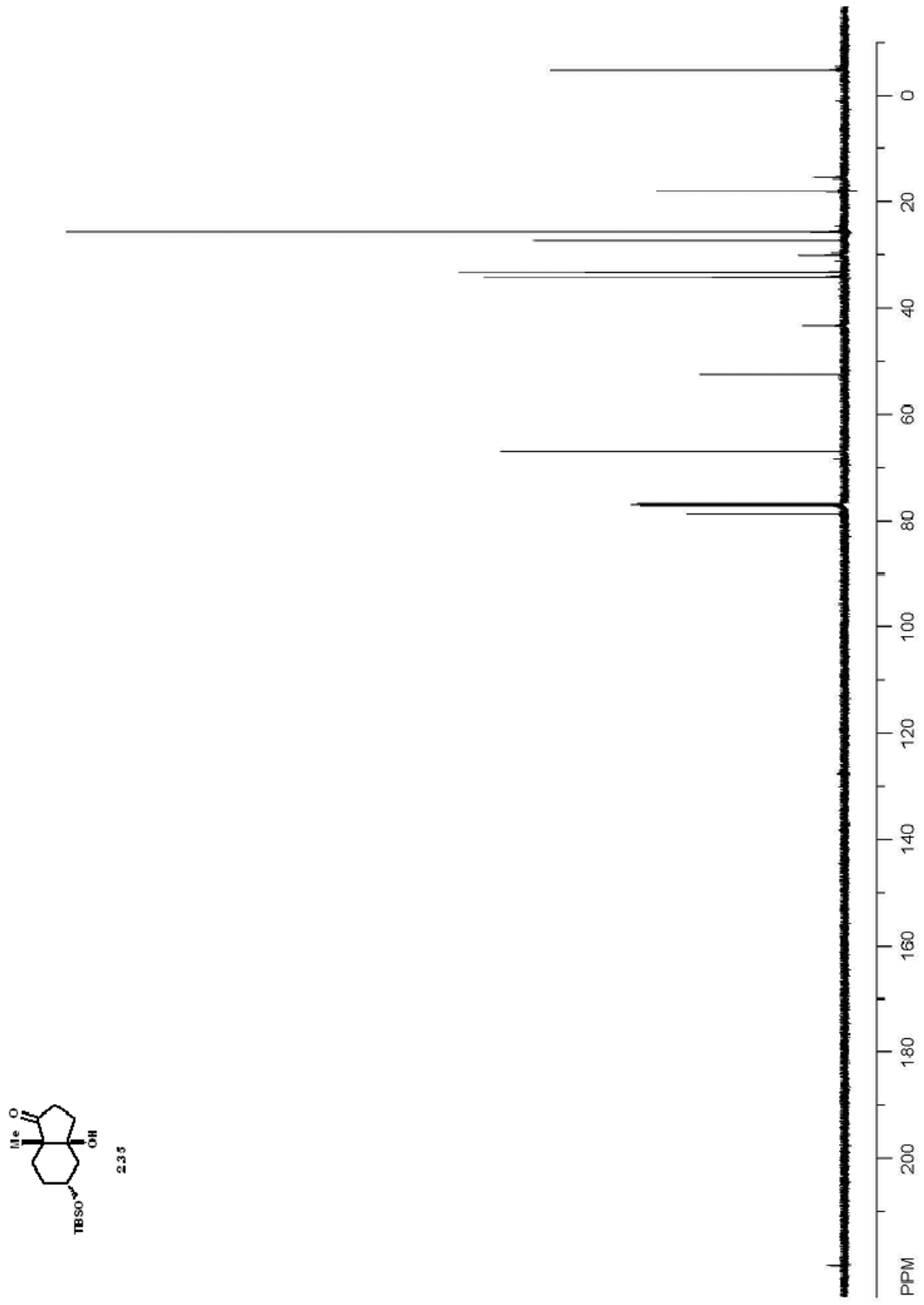
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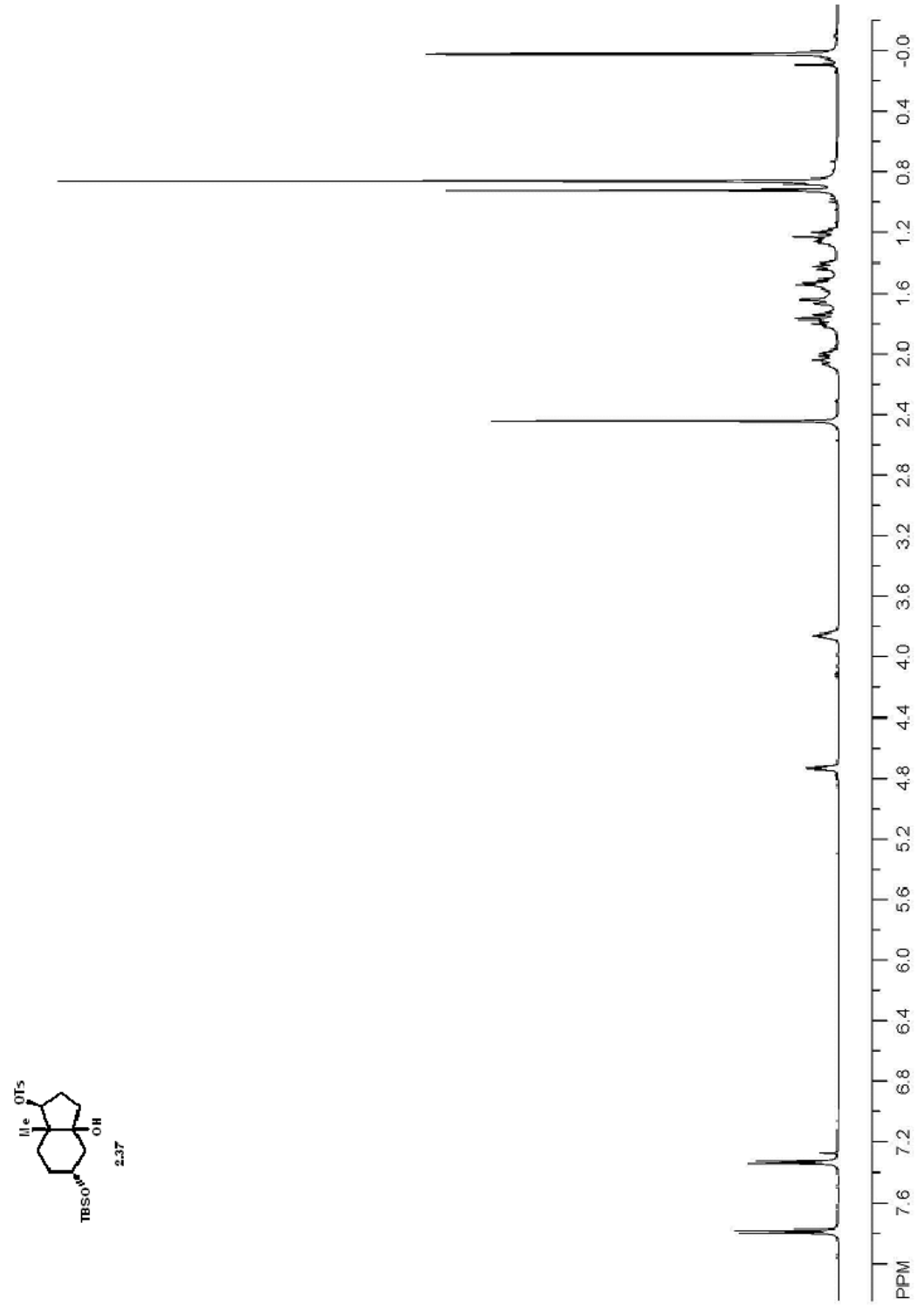
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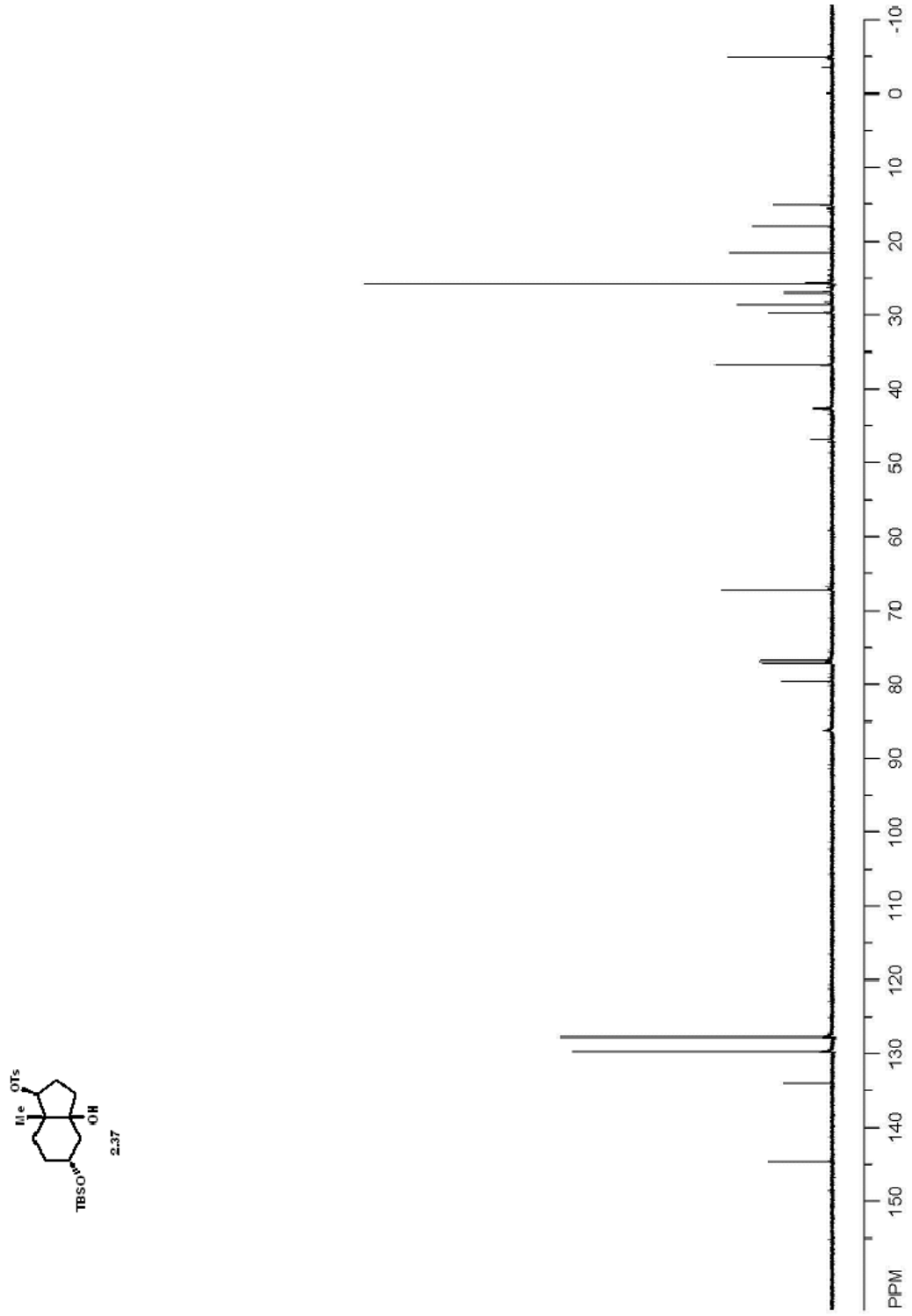
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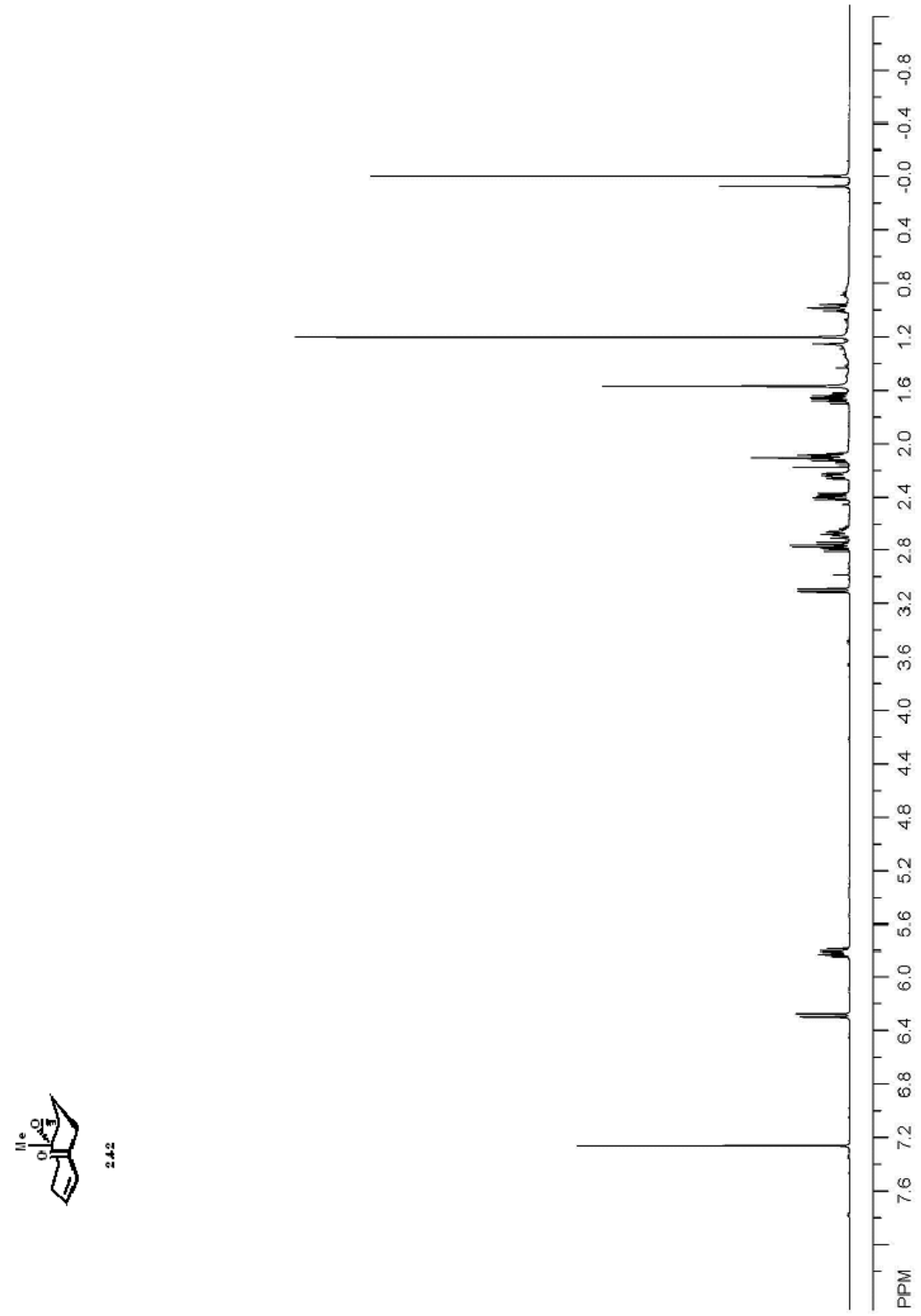
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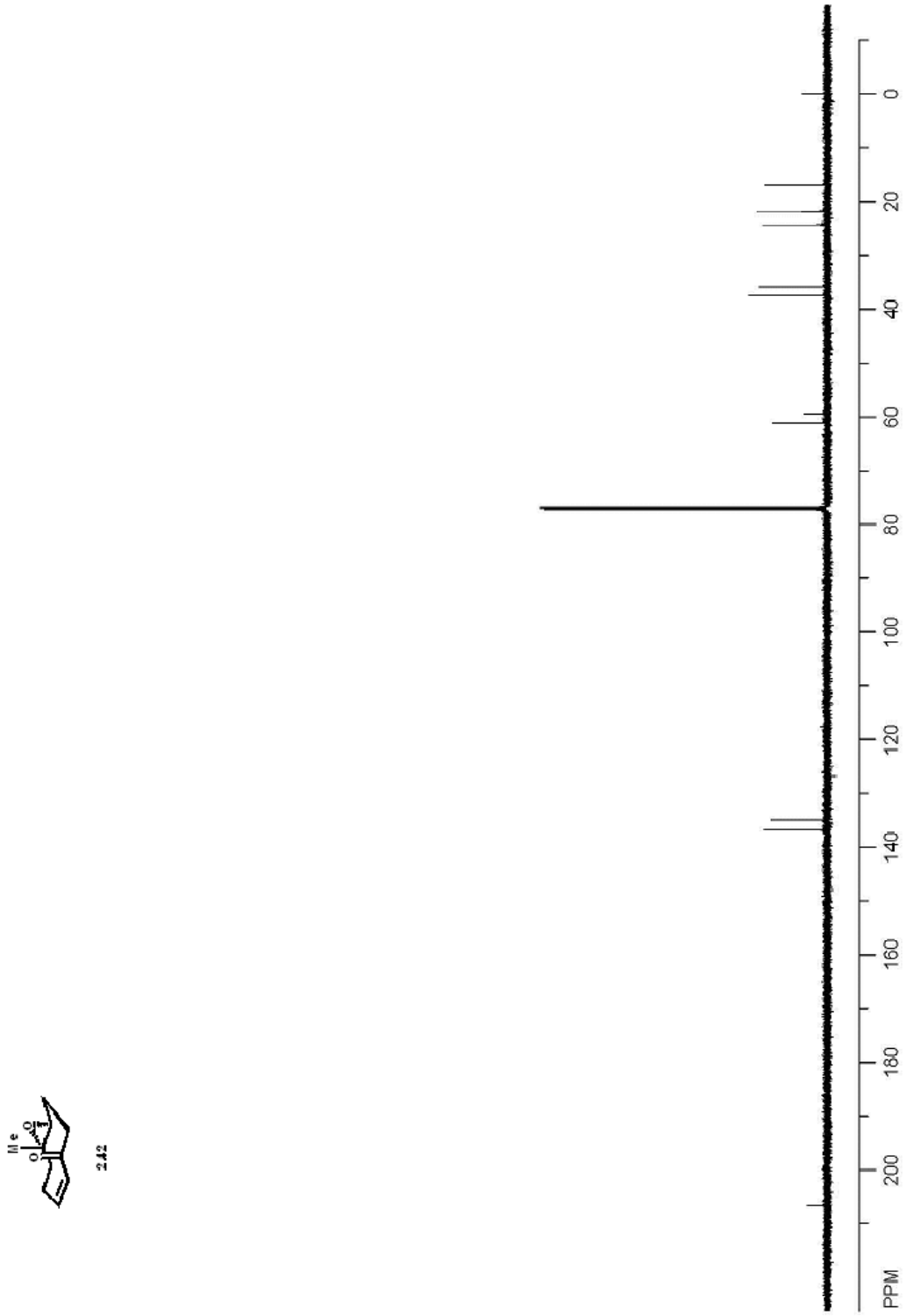
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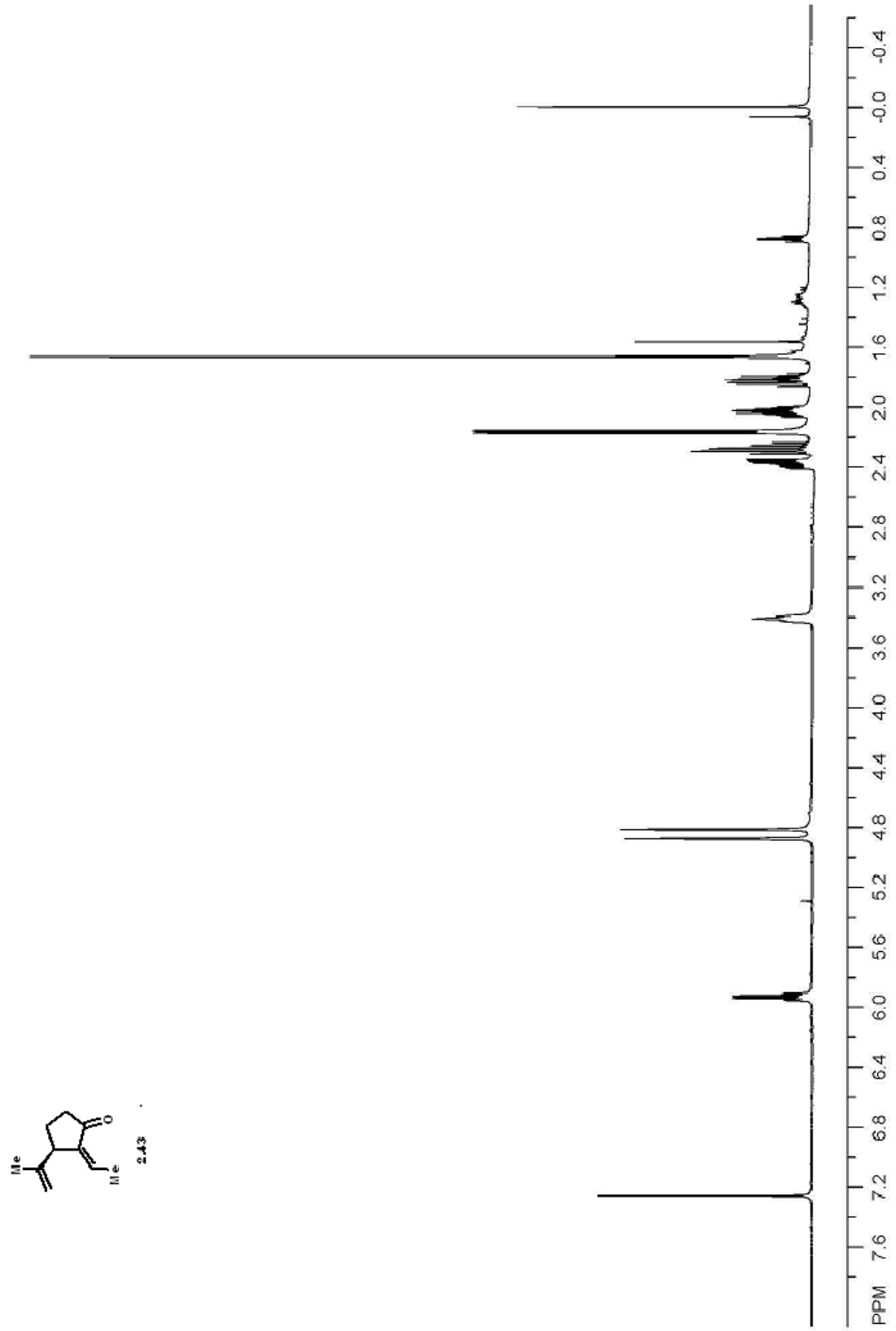
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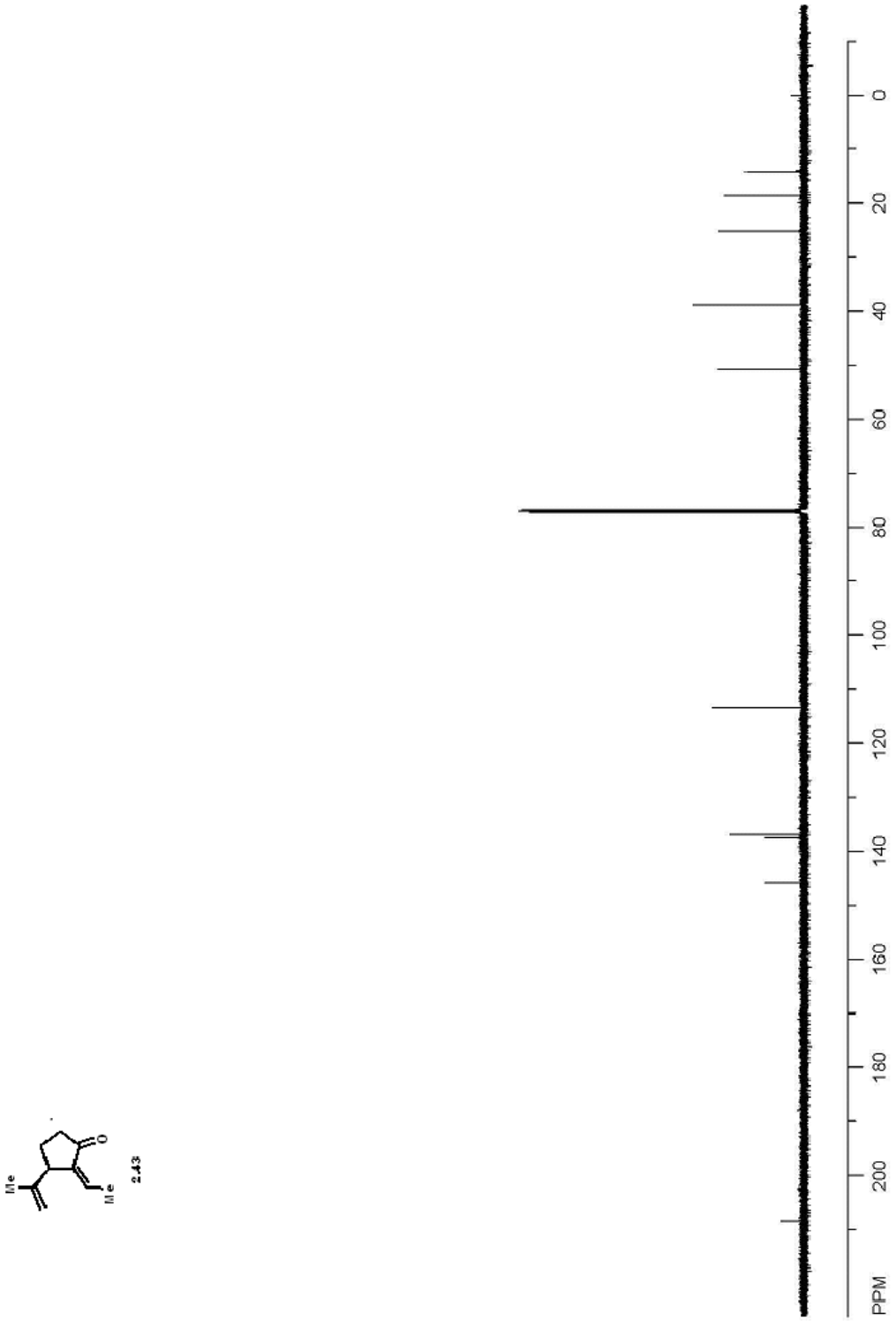
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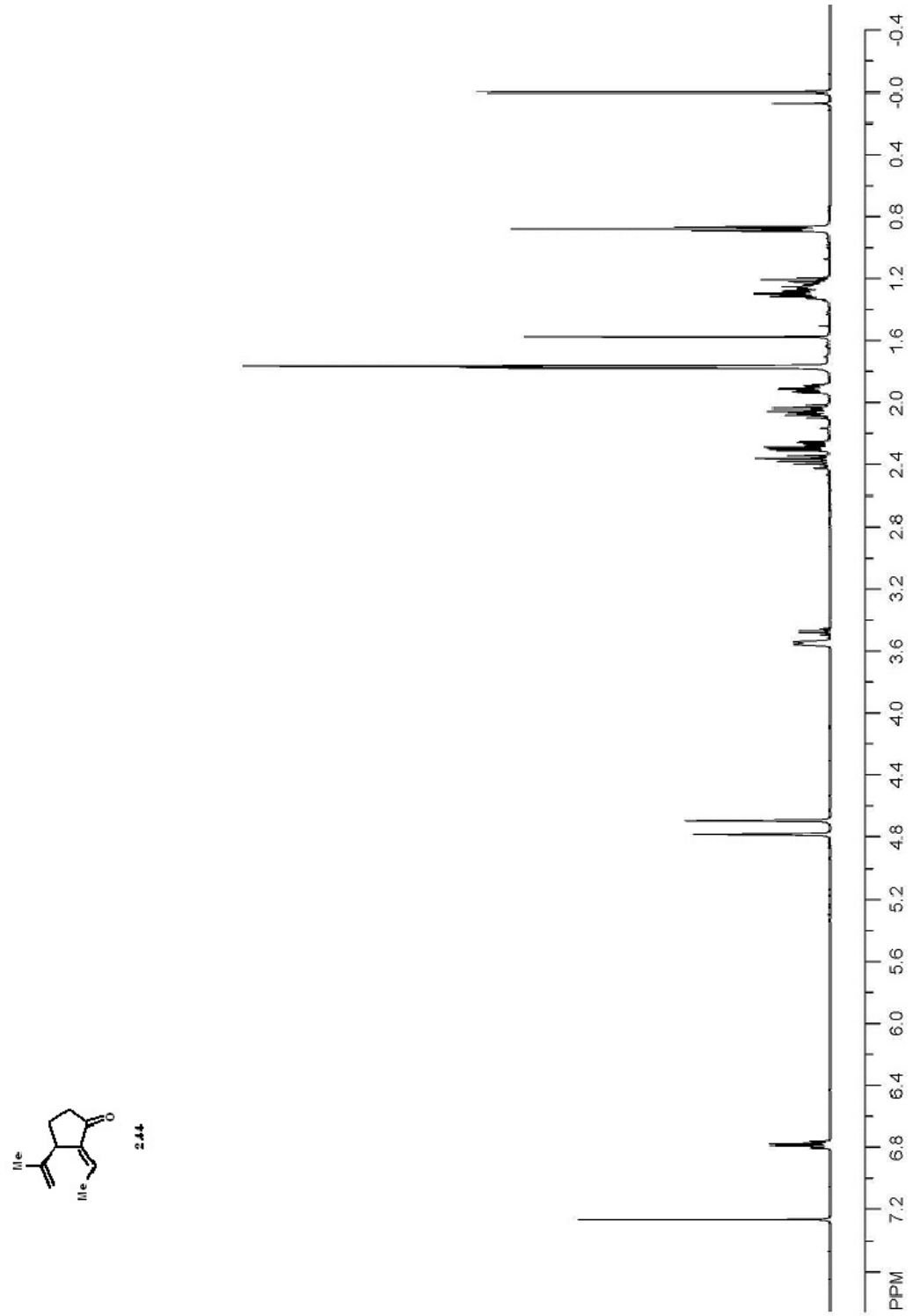
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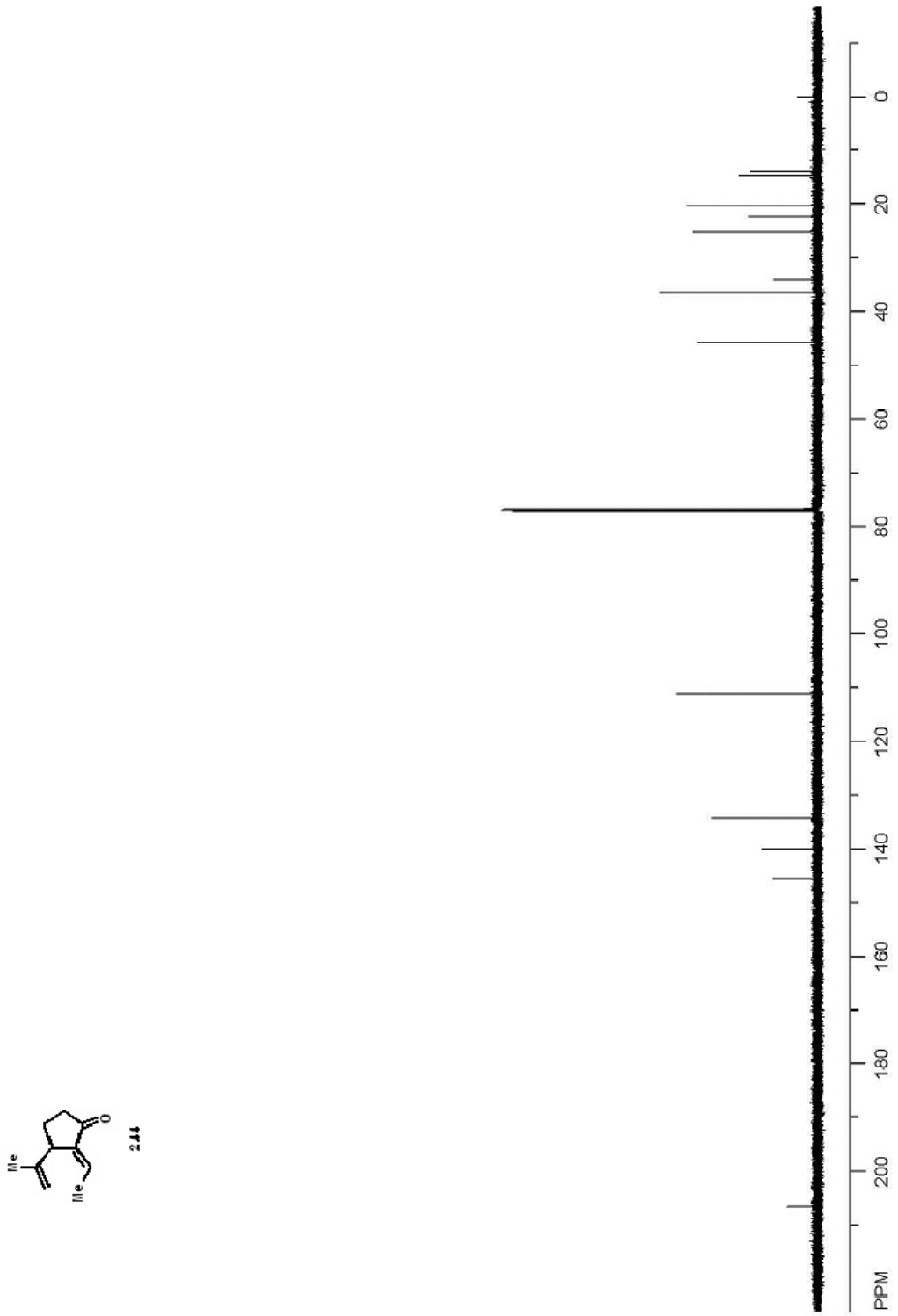
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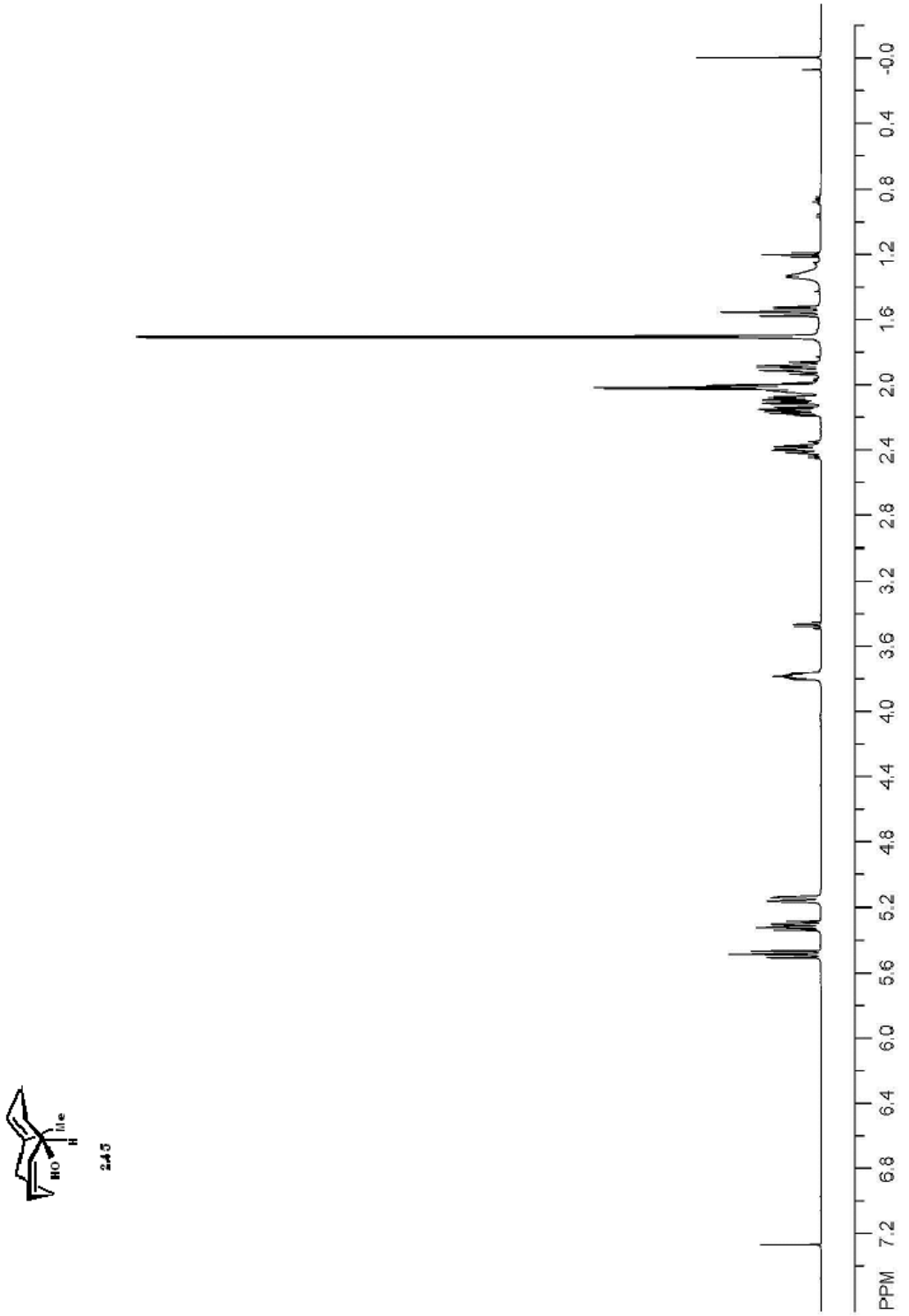
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H
243
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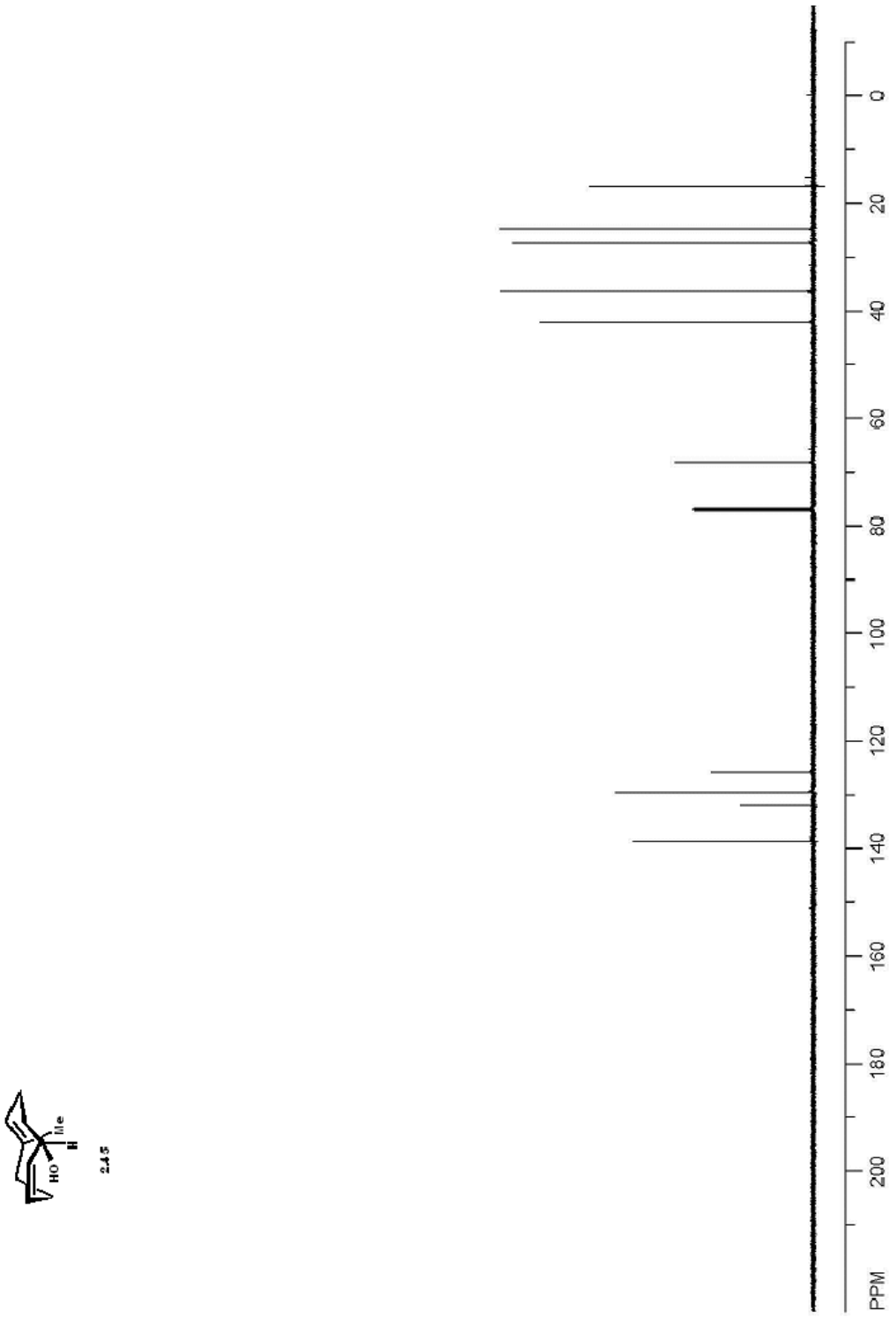
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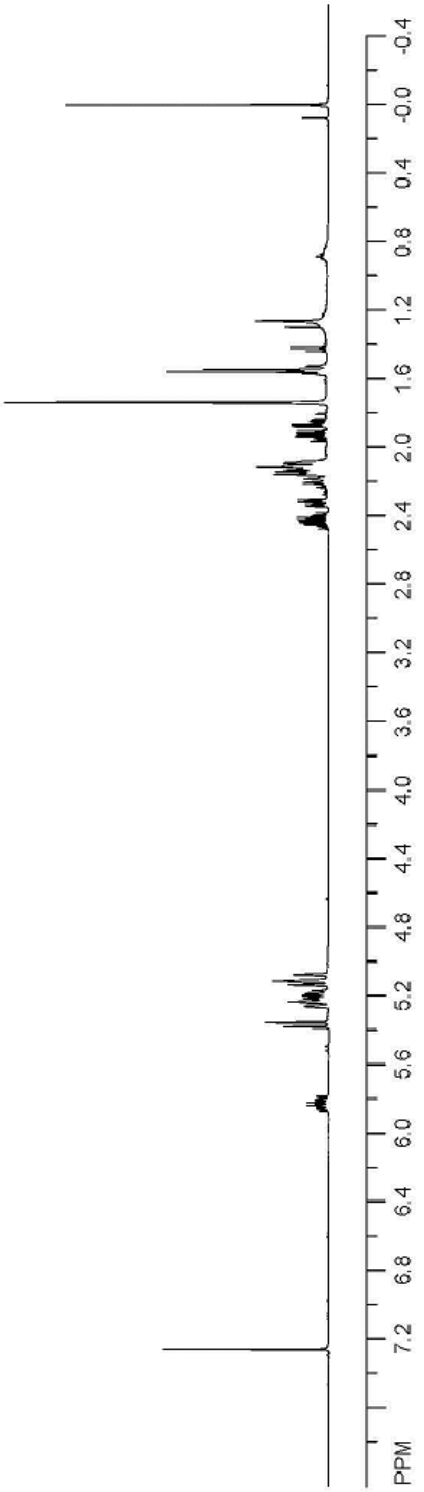

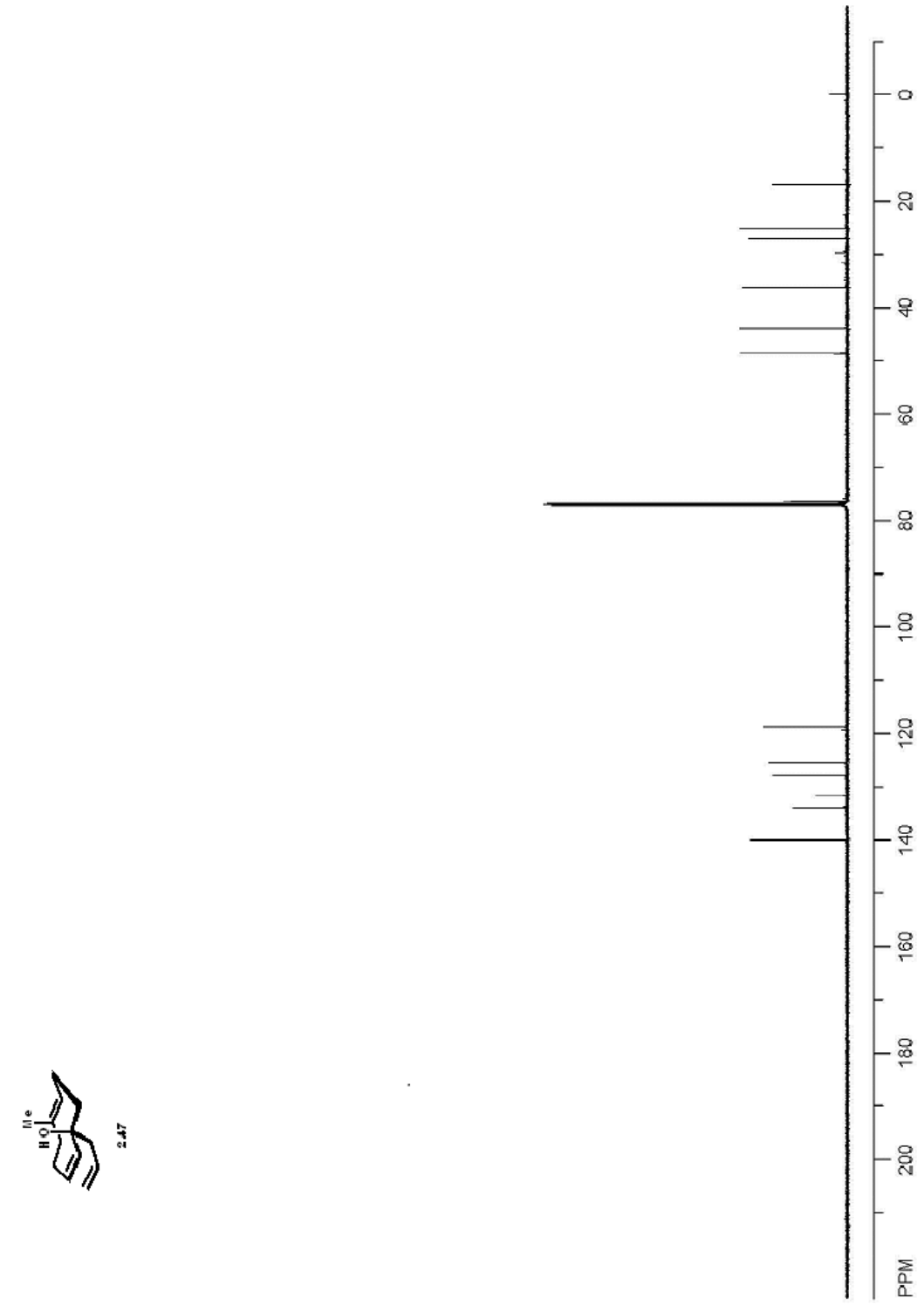
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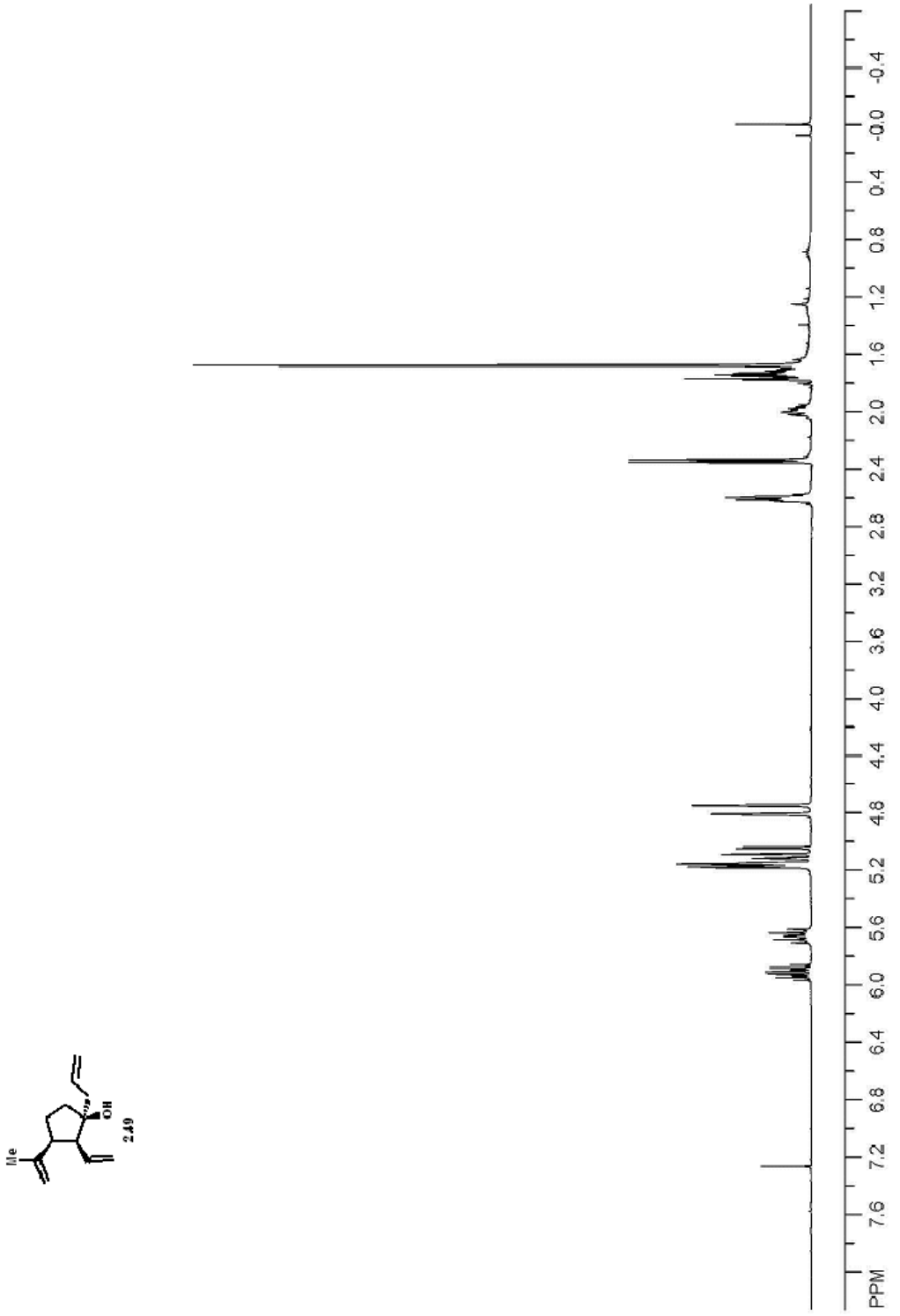
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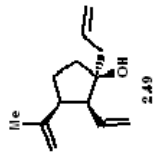
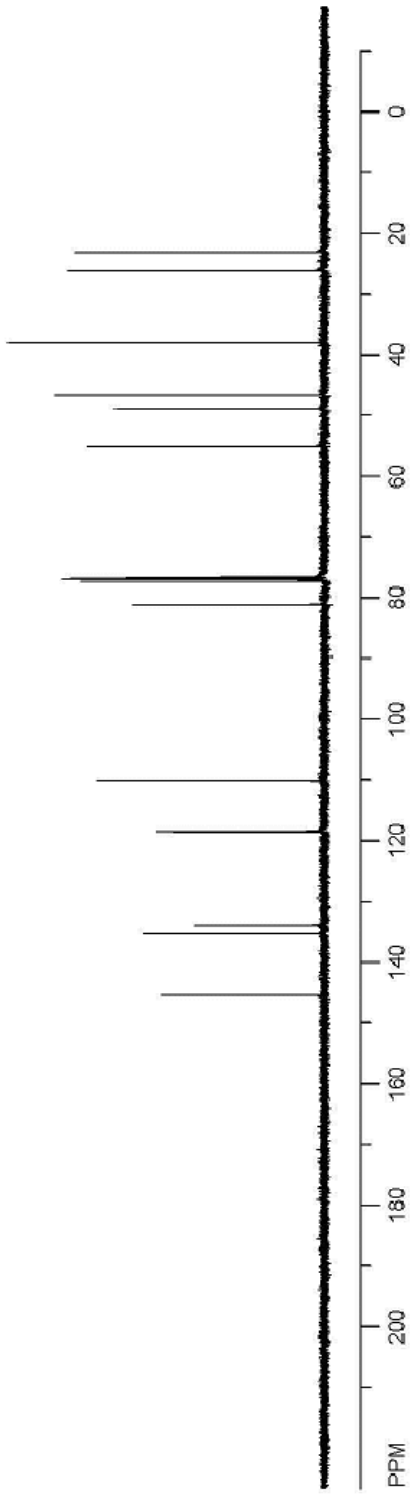
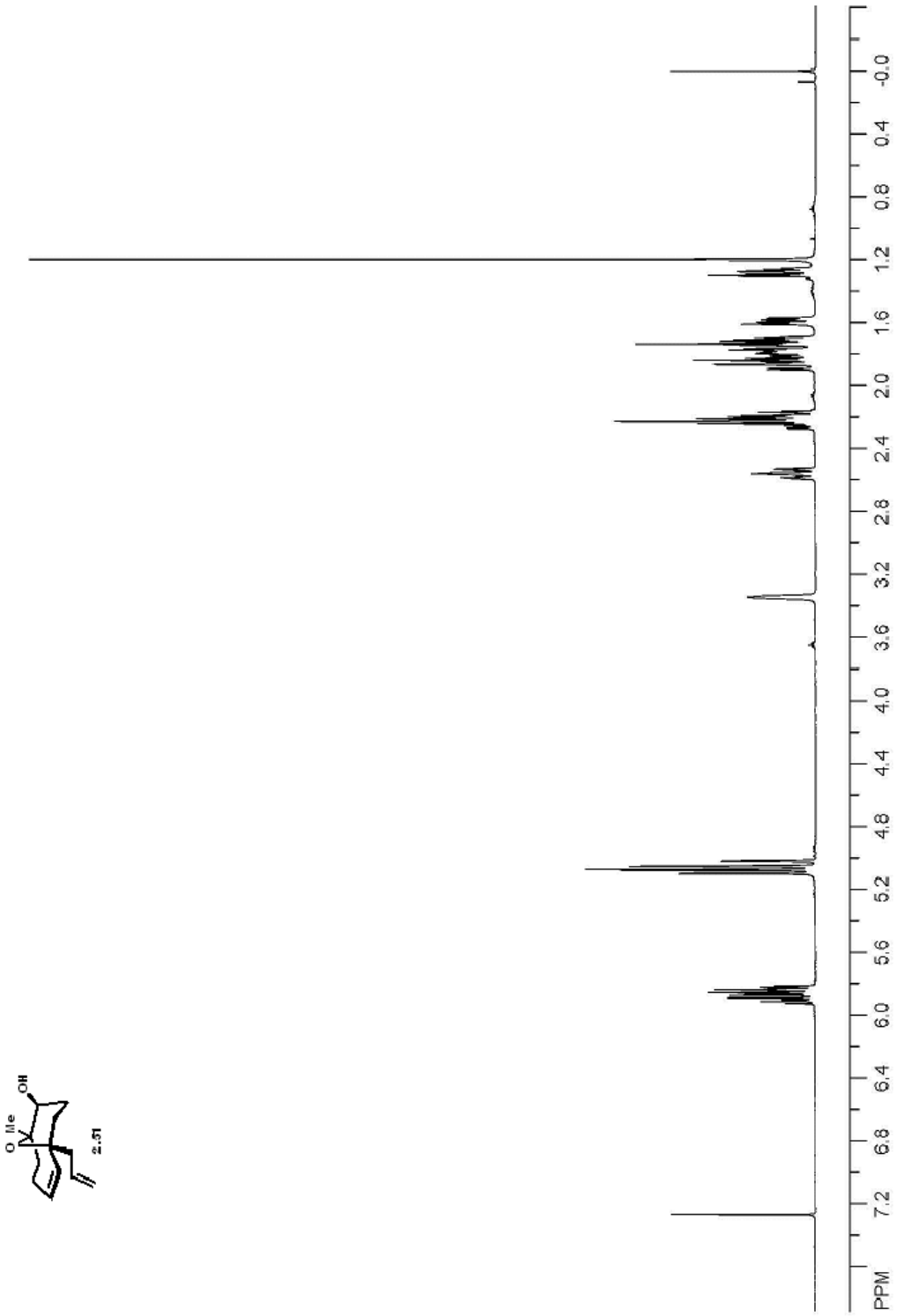


2.49

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4.8
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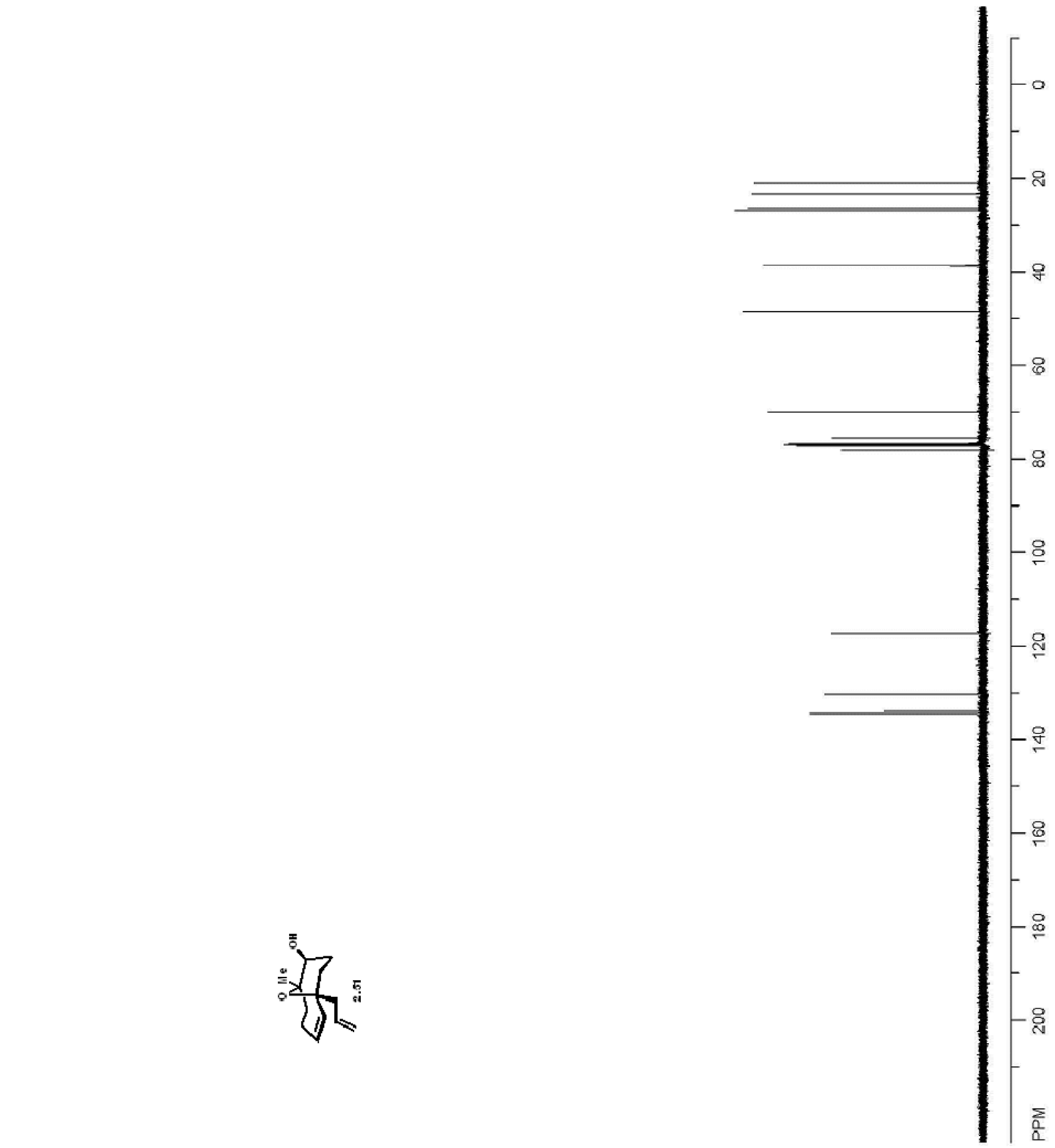
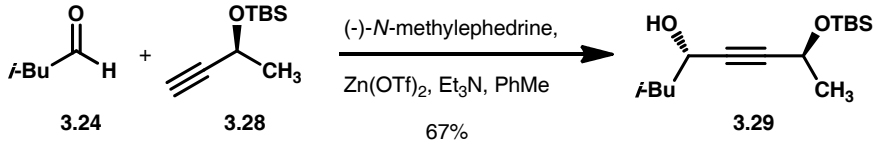

OH
O Me
2.51
PPM
0
20
40
60
80
100
120
140
160
180
200

Experimental Chapter Three:

General procedure for preparation of spirodiepoxides from allenes:

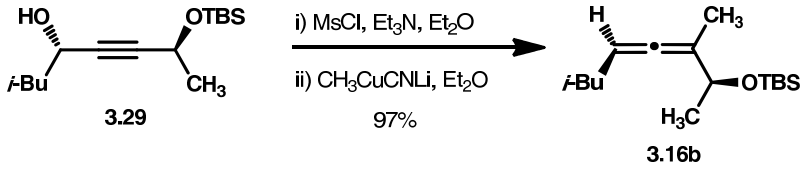
Dimethyldioxirane (DMDO) was prepared[6] (~0.10 M) or extracted into halogenated solvent ($CHCl_3$ ~0.30 M, CH_2Cl_2 ~0.38 M, CCl_4 ~0.25 M). This solution (3 equiv.) was added drop-wise to a solution of the allene cooled to -40 °C and dissolved in the same solvent such that the final concentration of DMDO was ~0.10 M. The reaction was stirred under nitrogen and allowed to warm to room temperature (21 °C) over 2 h. The solvent was evaporated and the resulting epoxide was dried under vacuum and used without further purification.



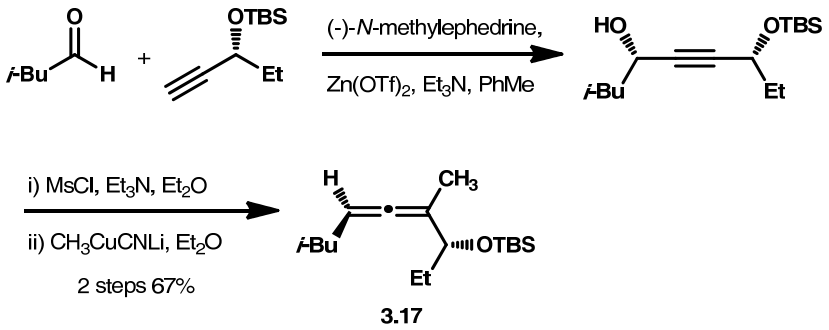
3.24 3.28 3.29

Propargyl Alcohol 3.29: A suspension of $Zn(OTf)_2$ (600 mg, 1.65 mmol), (-)-*N*-methylephedrine (355 mg, 1.98 mmol) and Et_3N (0.20 mL, 2.01 mmol) in toluene (5 mL) was stirred at room temperature for 30 min. TBS-protected *(S)*-3-butyn-2-ol **3.28** (360 mg, 1.95 mmol) was added in one portion and the reaction stirred for 2 h. Isovaleraldehyde (130 mg, 1.51 mmol) was added in one portion and the reaction was stirred overnight at room temperature. The reaction was diluted with EtOAc (50 mL), washed with saturated aqueous NH_4Cl (4 x 5 ml), dried over anhydrous $MgSO_4$, and then evaporated to give the crude product. FCC with 5% ethyl acetate-hexane gave 271 mg of propargyl alcohol **3.29** (1.00 mmol, 67%) as a clear colorless oil. $[\alpha]_D$ -64 (c = 3.6, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 3352, 1468, 1252; δ_H (400 MHz, $CDCl_3$) 4.54 (1H, qd, *J* = 6.5, 1.5 Hz), 4.46-4.38 (1H, m), 1.91-1.77 (1H, m), 1.76 (1H, d, *J* = 5.5 Hz), 1.66-1.49

(2H, m), 1.40 (3H, d, J = 6.5 Hz), 0.94 (3H, d, J = 6.7 Hz), 0.92 (3H, d, J = 6.7 Hz), 0.90 (9H, s), 0.13 (3H, s), 0.12 (3H, s); δ_C (100 MHz, $CDCl_3$) 87.4, 84.4, 61.0, 59.0, 46.8, 25.8, 25.4, 24.7, 22.5 (2), 18.2, -4.3, -4.9; MS (ESI): *m/z* calculated for $C_{15}H_{30}O_2SiNa$ $[MNa]^+$ 293.2; found 293.2.

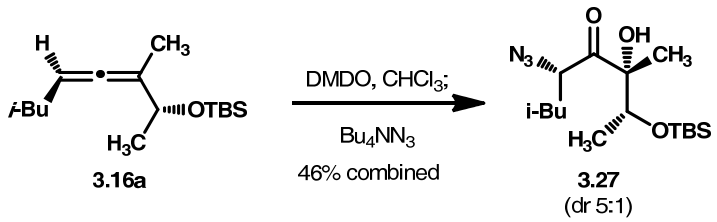


Allene 3.16b: To a solution of propargyl alcohol **3.29** (195 mg, 0.721 mmol) in Et_2O (5 mL) was added Et_3N (0.2 ml, 1.44 mmol) dropwise. The solution was cooled to 0 °C, MsCl (0.11 mL, 1.42 mmol) was added dropwise, and the reaction stirred for 1 h from 0 °C to room temperature. After the reaction was completed, as judged by TLC, the solution was cooled to 0 °C. CuCN (269 mg, 3.00 mmol) in Et_2O (5 mL) was cooled to 0 °C and a solution of 1.6 M MeLi in Et_2O (1.9 mL, 3.04 mmol) was then added. The cuprate was then added dropwise, via syringe to the above mesylate. The resultant mixture was allowed to warm to room temperature over 1 h and was then quenched with saturated aqueous NH_4Cl (5 ml) and extracted with Et_2O (3 x 10 ml). The organic extracts were combined, dried over anhydrous $MgSO_4$, and then concentrated. FCC purification of the crude product with pentane gave 187 mg of allene **3.16b** (0.696 mmol, 97%) as a colorless oil. $[\alpha]_D$ +32 (c = 3.3, $CHCl_3$); IR ν_{max} (neat) /cm^{-1} 1967, 1255, 1085; δ_H (500 MHz, $CDCl_3$) 5.05-5.00 (1H, m), 4.29 (1H, qd, J = 6.3, 1.2 Hz), 1.85 (2H, dd, J = 7, 7 Hz), 1.65 (3H, d, J = 2.9 Hz), 1.70-1.58 (1H, m), 1.24 (3H, d, J = 6.3 Hz), 0.91 (6H, d, J = 6.6 Hz), 0.89 (9H, s), 0.05 (3H, s), 0.04 (3H, s); δ_c (125 MHz, $CDCl_3$) 200.9, 102.6, 89.4, 70.5, 38.6, 28.4, 25.9(3), 23.0, 22.2, 22.2, 18.2, 13.6, -4.7, -5.0; MS (ESI): *m/z* calculated for $C_{16}H_{32}OSiH$ $[MH]^+$ 269.2; found 269.2.



3.17

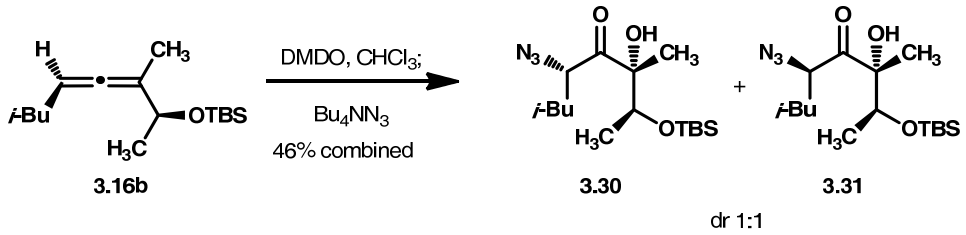
Allene 3.17: This allene was prepared following the procedure for **3.29** and **3.16b** above, except as noted below. For alkynylation: $Zn(OTf)_2$ (170 mg, 0.458 mmol), (-)-*N*-methylephedrine (101 mg, 0.561 mmol), Et_3N (0.08 mL, 0.571 mmol), TBS-protected *(R)*-1-pentyn-3-ol (110 mg, 0.554 mmol), isovaleraldehyde (37 mg, 0.426 mmol). The crude propargyl alcohol was taken on without purification (79 mg, 0.277 mmol). For mesylation: Et_3N (0.05 ml, 0.360 mmol), MsCl (25 μL, 0.316 mmol). Allene formation: CuCN (95 mg, 1.061 mmol), 1.6 M MeLi in Et_2O (0.69 mL, 1.108 mmol). FCC purification using pentane gave 75 mg of allene **3.17** (0.266 mmol, 62% 2 steps) as a colorless oil. $[\alpha]_D$ +35 (*c* = 3.1, $CHCl_3$); IR ν_{max} (neat) /cm^{-1} 1967, 1255, 1085; δ_H (500 MHz, $CDCl_3$) 4.93-4.86 (1H, m), 3.95 (1H, t, *J* = 6.6 Hz), 1.85 (2H, t, *J* = 7.2 Hz), 1.65-1.53 (1H, m), 1.56 (3H, d, *J* = 3 Hz), 1.53-1.40 (2H, dq, *J* = 6.6, 7.2 Hz), 0.87 (6H, d, *J* = 6.6 Hz), 0.85 (9H, s), 0.80 (3H, t, *J* = 7.5 Hz), 0.00 (6H, s); δ_c (125 MHz, $CDCl_3$) 201.9, 101.0, 89.1, 76.4, 38.7, 29.5, 26.1 (3), 22.5, 22.4, 18.5, 13.3, 10.5, -4.4, -4.8; MS (ESI): *m/z* calculated for $C_{17}H_{34}OSiH$ $[MH]^+$ 283.2; found 283.2.



3.16a **3.27** (dr 5:1)

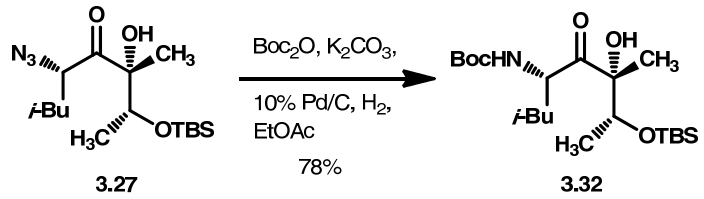
Azide 3.27: DMDO in $CHCl_3$ (0.2 M, 14 mL, 2.80 mmol) was added to the known allene **3.16a** (290 mg, 1.08 mmol) at -40 °C. The reaction mixture was allowed to stir from -40

°C to room temperature over 2 h. Solvent was dried under vacuum and the crude spirodiepoxide was dissolved in dry $CDCl_3$ (5 mL) and cooled to -20 °C. A solution of tetrabutylammonium azide (313 mg, 1.10 mmol) in dry $CHCl_3$ (5 mL) was added and stirred for 1 h from -20 °C to room temperature. Solvent was evaporated to about 1 mL. The crude product in $CHCl_3$ was purified by FCC using 50% DCM-hexane to give 150 mg of azide **3.27** (0.437 mmol, 40%) as a colorless oil. $[\alpha]_D$ -17 (*c* = 0.96, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 3487, 2107, 1682; δ_H (400 MHz, $CDCl_3$) 4.36 (1H, dd, *J* = 10.7, 2.9 Hz), 3.86 (1H, q, *J* = 6.3 Hz), 2.83 (1H, s), 1.94-1.78 (1H, m), 1.79-1.68 (1H, m), 1.60-1.46 (1H, m), 1.33 (3H, s), 1.09 (3H, d, *J* = 6.3 Hz), 1.01 (3H, d, *J* = 1.9 Hz), 0.99 (3H, d, *J* = 1.8 Hz), 0.92 (9H, s), 0.12 (3H, s), 0.11 (3H, s); δ_C (100 MHz, $CDCl_3$) 212.2, 81.9, 73.8, 62.7, 38.7, 25.8(3), 25.6, 24.6, 23.3, 21.1, 18.3, 18.1, -4.0, -4.8; MS (ESI): *m/z* calculated for $C_{16}H_{33}N_3O_3SiNa$ $[MNa]^+$ 366.2; found 366.2.



Azides 3.30 and 3.31: 294 mg of azides **3.30** and **3.31** (0.856 mmol, dr 1:1, 44% combined yield) were obtained as a colorless oil from 522 mg of **3.16b** (1.94 mmol) using the same procedure as in allene **3.16a**. Azides **3.30** and **3.31** were separated by FCC using 50% DCM-hexane. **3.30**: $[\alpha]_D$ +82 (*c* = 0.50, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 3533, 2112, 1724; δ_H (500 MHz, $CDCl_3$) 4.23 (1H, dd, *J* = 10.8, 3.3 Hz) 4.17 (1H, q, *J* = 6.3 Hz), 3.32 (1H, s), 1.90-1.80 (1H, m), 1.80-1.73 (1H, m), 1.66-1.58 (1H, m), 1.20 (3H, s), 1.12 (3H, d, *J* = 6.3 Hz), 1.01 (3H, d, *J* = 6.6 Hz), 0.99 (3H, d, *J* = 6.5 Hz), 0.88 (9H, s),

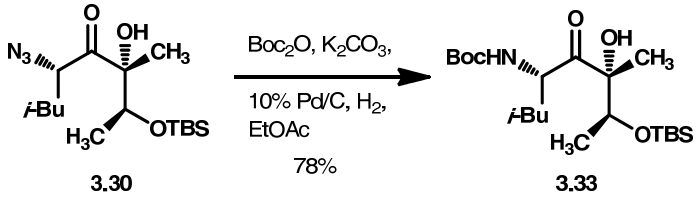
0.09 (3H, s), 0.04 (3H, s); δ_C (125 MHz, $CDCl_3$) 213.3, 82.0, 72.5, 61.8, 38.4, 25.7(3), 25.5, 23.2, 21.4, 21.1, 17.8, 17.0, -4.2, -5.0; MS (ESI): *m/z* calculated for $C_{16}H_{33}N_3O_3SiNa$ $[MNa]^+$ 366.2; found 366.2. **3.31**: $[\alpha]_D$ -16 (*c* = 0.44, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 3527, 2108, 1724; δ_H (500 MHz, $CDCl_3$) 4.41 (1H, dd, *J* = 10.9, 2.9 Hz), 4.22 (1H, q, *J* = 6.3 Hz), 3.36 (1H, s), 1.92-1.80, (1H, m), 1.64-1.56 (1H, m), 1.46-1.38 (1H, m), 1.23 (3H, s), 1.13 (3H, d, *J* = 6.3 Hz), 0.99 (3H, d, *J* = 6.7 Hz), 0.97(3H, d, *J* = 6.6 Hz), 0.88 (9H, s), 0.11 (3H, d), 0.03 (3H, d); δ_C (125 MHz, $CDCl_3$) 212.3, 81.8, 71.6, 60.0, 38.8, 25.8(3), 25.3, 23.2, 21.4, 21.2, 17.8, 17.2, -4.4, -4.7; MS (ESI): *m/z* calculated for $C_{16}H_{33}N_3O_3SiNa$ $[MNa]^+$ 366.2; found 366.2.



3.27 3.32

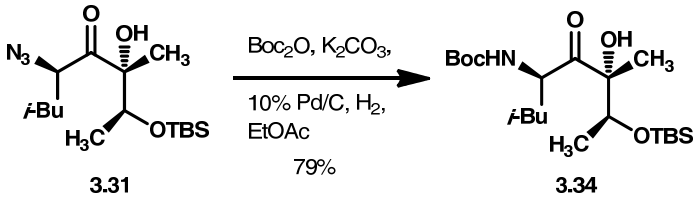
***tert*-butyl-Carbamate 3.32:** To a solution of azide **3.27** (293 mg, 0.853 mmol) in EtOAc was added K_2CO_3 (354 mg, 2.561 mmol), $(Boc)_2O$ (1.16 mg, 5.32 mmol) and 10% Pd/C (54 mg). The resultant suspension was then hydrogenated under 1 atm pressure overnight. The reaction mixture was filtered through a pad of silica gel and the solvent was evaporated. FCC purification using 4% EtOAc-hexane gave 278 mg of *tert*-butyl-carbamate **3.32** (0.666 mmol, 78%) as a clear oil. $[\alpha]_D$ +34 (*c* = 0.70, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 3543, 3438, 3390, 1712; δ_H (500 MHz, $CDCl_3$) 4.98 (2H, bs), 3.85 (1H, q, *J* = 6.2 Hz), 2.85 (1H, s), 1.83-1.68 (2H, m), 1.41 (9H, s), 1.33(3H, s), 1.20-1.10 (1H, m), 1.07 (3H, d, *J* = 6.2 Hz), 1.02 (3H, d, *J* = 6.2 Hz), 0.92 (3H, d, *J* = 6.5 Hz), 0.90 (9H, s), 0.089 (3H, s), 0.085 (3H, s); δ_C (100 MHz, $CDCl_3$) 214.9, 155.3, 81.9, 79.3, 73.5,

55.6, 41.2, 28.3(3), 25.8(3), 25.2, 23.6, 23.3, 21.2, 18.3, 18.0, -4.2, -4.8; MS (ESI): *m/z* calculated for $C_{21}H_{43}NO_5SiNa$ $[MNa]^+$ 440.3; found 440.3.



3.30 **3.33**

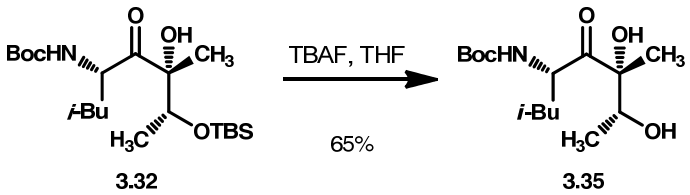
***tert*-butyl-Carbamate 3.33:** 42 mg of *tert*-butyl carbamate **3.30** (0.101 mmol, 84%) was obtained as a white crystalline solid from 41 mg of **3.30** (0.119 mmol) using the same procedure as in azide **3.27**. $[\alpha]_D$ +43 (*c* = 0.60, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 3539, 3434, 3382, 1708; δ_H (500 MHz, $CDCl_3$) 5.17 (1H, d, *J* = 9.1 Hz), 4.94-4.88 (1H, m), 4.19 (1H, q, *J* = 6.3 Hz), 3.34 (1H, s), 1.80-1.70 (2H, m), 1.41 (9H, s), 1.23-1.16 (1H, m), 1.19(3H, s), 1.11 (1H, d, *J* = 6.3 Hz), 1.04 (3H, d, *J* = 5.9 Hz), 0.91 (3H, d, *J* = 6.3 Hz), 0.84 (9H, s), 0.06 (3H, s), -0.04 (3H, s); δ_C (125 MHz, $CDCl_3$) 216.1, 155.0, 82.0, 79.1, 72.7, 55.2, 42.4, 28.3(3), 25.8(3), 25.0, 23.8, 21.6, 21.4, 17.8, 16.7, -4.5, -4.9; MS (ESI): *m/z* calculated for $C_{21}H_{43}NO_5SiNa$ $[MNa]^+$ 440.3; found 440.3.



3.31 **3.34**

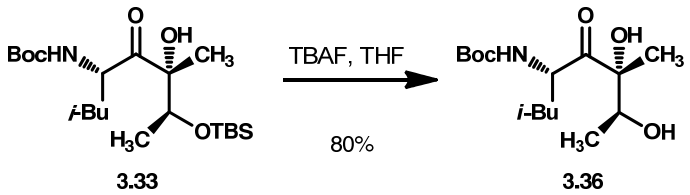
***tert*-butyl-Carbamate 3.34:** 47 mg of *tert*-butyl carbamate **3.31** (0.113 mmol, 79%) was obtained as a white crystalline solid from 49 mg of **3.34** (0.143 mmol) using the same procedure as in azide **3.27**. $[\alpha]_D$ +7 (*c* = 0.44, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 3441, 3396, 1713; δ_H (500 MHz, $CDCl_3$) 5.05-4.94 (1H, m), 4.88 (1H, d, *J* = 9.2 Hz) 4.33 (1H, q, *J* = 6.3 Hz), 3.13 (1H, s), 1.42 (9H, s), 1.18 (3H, s), 1.16-1.04 (2H, m), 1.13 (3H, d, *J* = 6.3 Hz), 1.00 (3H, d, *J* = 6.5 Hz), 0.91 (3H, d, *J* = 6.7 Hz), 0.86 (9H, s), 0.09 (3H, s), -0.02

(3H, s); δ_C (125 MHz, $CDCl_3$) 214.8, 155.3, 82.2, 79.4, 70.5, 52.8, 41.0, 28.3(3), 25.8(3), 25.1, 23.6, 21.3, 21.1, 17.8, 16.9, -4.5, -4.55; MS (ESI): *m/z* calculated for $C_{21}H_{43}NO_5SiNa$ $[MNa]^+$ 440.3; found 440.3.



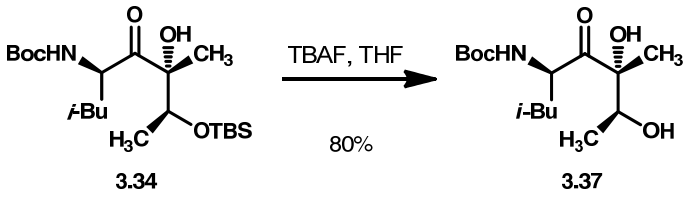
3.32 **3.35**

Diol 3.35: To a solution of *tert*-butyl-carbamate **3.32** (82 mg, 0.20 mmol) in THF (2 mL) was added TBAF (0.4 mL, 1 M solution in THF) at 0 °C and stirred for 1 h from 0 °C to room temperature. The reaction mixture was quenched by NH_4Cl (4 mL) and extracted with EtOAc (3 x 5 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and evaporated to give the crude product. FCC purification using 20% EtOAc-hexane gave 39 mg of diol **3.35** (0.13 mmol, 65%) as a white crystal. $[\alpha]_D$ +8 (*c* = 0.16, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 3323, 1714, 1674; δ_H (500 MHz, $CDCl_3$) 4.99 (1H, d, *J* = 7.6 Hz), 4.75-4.69 (1H, m), 4.47(1H, d, *J* = 11.3 Hz), 4.16 (1H, s), 3.58 (1H, dq, *J* = 11.3, 6.6 Hz), 1.81-1.71 (1H, m), 1.73-1.65 (1H, m), 1.41 (9H, s), 1.28 (3H, s), 1.22-1.15 (1H, m), 1.13 (3H, d, *J* = 6.7 Hz), 0.98 (3H, d, *J* = 6.4 Hz), 0.93 (3H, d, *J* = 6.5 Hz); δ_C (125 MHz, $CDCl_3$) 215.7, 157.2, 82.7, 80.8, 74.6, 55.7, 39.3, 28.2(3), 25.2, 23.4, 21.9, 21.0, 16.1; MS (ESI): *m/z* calculated for $C_{15}H_{29}NO_5Na$ $[MNa]^+$ 326.2; found 326.2.



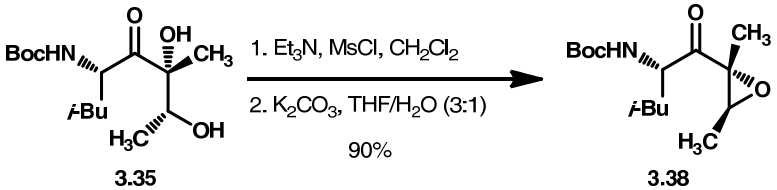
3.33 **3.36**

Diol 3.36: 31 mg of diol **3.36** (0.102 mmol, 80%) was obtained as a white crystalline solid from 53 mg of **3.33** (0.127 mmol) using the same procedure as in *tert*-butyl carbamate **3.32**. $[\alpha]_D$ +1.9 (*c* = 0.13, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 3363, 1716, 1683; δ_H (500 MHz, $CDCl_3$) 4.84 (1H, d, *J* = 7.1 Hz), 4.76-4.70 (1H, m), 4.41(1H, d, *J* = 3.9 Hz), 3.98 (1H, qd, *J* = 6.4, 3.9 Hz), 3.71 (1H, s), 1.82-1.71 (1H, m), 1.74-1.67 (1H, m), 1.41 (9H, s), 1.26-1.18 (1H, m), 1.22 (3H, s), 1.17 (3H, d, *J* = 6.4 Hz), 1.00 (3H, d, *J* = 6.3 Hz), 0.96 (3H, d, *J* = 6.5 Hz); δ_C (125 MHz, $CDCl_3$) 217.9, 157.0, 82.2, 80.8, 71.7, 55.3, 38.9, 28.2(3), 25.2, 23.4, 21.5, 20.9, 15.5; MS (ESI): *m/z* calculated for $C_{15}H_{29}NO_5Na$ $[MNa]^+$ 326.2; found 326.2.



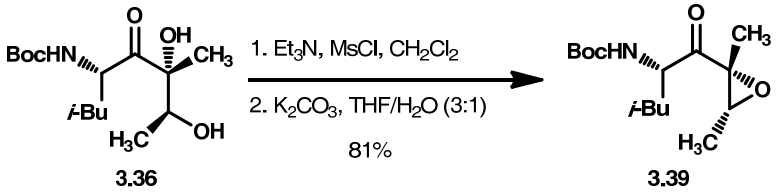
3.34 **3.37**

Diol 3.37: 50 mg of diol **3.37** (0.165 mmol, 80%) was obtained as a white crystalline solid from 86 mg of **25** (0.206 mmol) using the same procedure as in *tert*-butyl carbamate **3.32**. $[\alpha]_D$ +1 (*c* = 0.10, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 3370, 1708, 1692; δ_H (500 MHz, $CDCl_3$) 5.02 (1H, d, *J* = 8.4 Hz), 4.83-4.76 (1H, m), 4.09-4.02 (1H, qd, *J* = 6.9, 6.9 Hz), 3.89 (1H, s), 3.47 (1H, d, *J* = 7.6 Hz), 1.81-1.71 (1H, m), 1.48-1.30 (2H, m), 1.41 (9H, s), 1.37 (3H, s), 1.18 (3H, d, *J* = 6.5 Hz), 0.96 (3H, d, *J* = 6.5 Hz), 0.93 (3H, d, *J* = 6.7 Hz); δ_C (125 MHz, $CDCl_3$) 214.8, 156.4, 82.0, 80.8, 71.7, 52.4, 40.4, 28.2(3), 24.9, 23.4, 21.5, 21.1, 16.3; MS (ESI): *m/z* calculated for $C_{15}H_{29}NO_5Na$ $[MNa]^+$ 326.2; found 326.2.



3.35 **3.38**

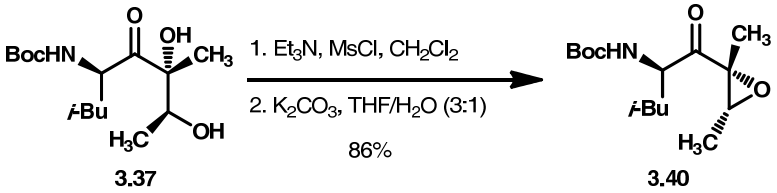
Epoxide 3.38: To a solution of diol **3.35** (26 mg, 0.086 mmol) in DCM (1 mL) was added Et_3N (24 µL, 0.17 mmol) and cooled to 0 °C. Methanesulfonyl chloride (13 µL, 0.17 mmol) was added dropwise and stirred under argon from 0 °C to room temperature for 1 h. The reaction mixture was extracted with DCM (2 x 5 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and evaporated to give the crude mesylate. The crude mesylate and K_2CO_3 (100 mg, 0.724 mmol) in THF-water (3:1, 4 mL) was stirred at room temperature for 4 h. The reaction mixture was extracted with EtOAc (3 x 5 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and evaporated. FCC purification using 10% EtOAc-hexane gave 22 mg of epoxide **3.38** (0.077 mmol, 90% 2 steps) as a colorless oil. $[\alpha]_D$ + 5.8 (*c* = 0.56, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 3379, 1709; δ_H (500 MHz, $CDCl_3$) 4.83 (1H, d, *J* = 8.8 Hz), 3.42 (1H, q, *J* = 5.3 Hz), 1.88-1.67 (1H, m), 1.52-1.45 (1H, m), 1.45 (3H, s), 1.41 (9H, s), 1.37 (3H, d, *J* = 5.4 Hz), 1.16-1.09 (1H, m), 0.97 (3H, d, *J* = 6.6 Hz), 0.93 (3H, d, *J* = 6.7 Hz); δ_C (125 MHz, $CDCl_3$) 210.5, 155.6, 79.6, 62.8, 56.9, 51.7, 40.3, 28.3(3), 25.1, 23.4, 21.3, 13.6, 12.8; MS (ESI): *m/z* calculated for $C_{15}H_{27}NO_4Na$ $[MNa]^+$ 308.2; found 308.2.



3.36 3.39

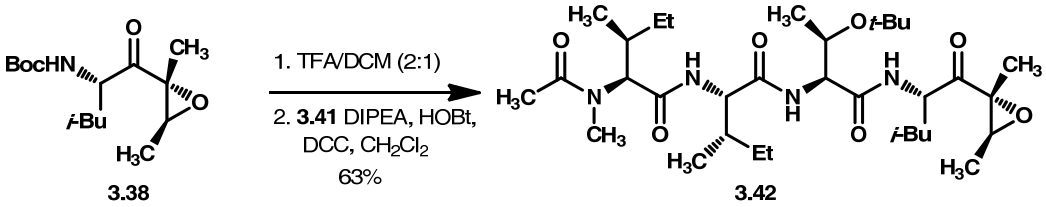
Epoxide 3.39: 22 mg of epoxide **3.39** (0.077 mmol, 81% 2 steps) was obtained as a crystalline solid from 29 mg of **3.36** (0.096 mmol) using the same procedure as in diol **3.35**. $[\alpha]_D$ +25 (*c* = 0.12, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 3376, 1707; δ_H (500 MHz, $CDCl_3$) 4.88 (1H, d, *J* = 8.9 Hz), 4.88-4.71 (1H, m), 3.09 (1H, q, *J* = 5.7 Hz), 1.85-1.72 (1H, m),

1.70-1.60 (1H, m), 1.51 (3H, s), 1.43 (9H, s), 1.35 (3H, d, J = 5.5 Hz), 1.18-1.11 (1H, m), 1.04 (3H, d, J = 6.5 Hz), 0.96 (3H, d, J = 6.7 Hz); δ_C (125 MHz, $CDCl_3$) 209.3, 155.5, 79.6, 64.0, 56.1, 51.7, 39.7, 28.2(3), 25.1, 23.4, 21.2, 19.8, 13.9; MS (ESI): *m/z* calculated for $C_{15}H_{27}NO_4Na$ $[MNa]^+$ 308.2; found 308.1.



3.37 3.40

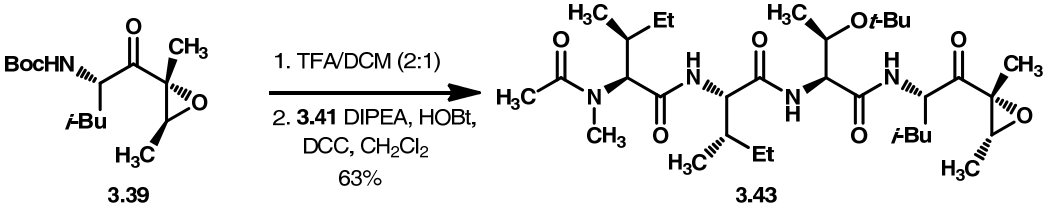
Epoxide 3.40: 29 mg of epoxide **3.40** (0.102 mmol, 86% 2 steps) was obtained as a white crystalline solid from 36 mg of **3.37** (0.119 mmol) using the same procedure as in diol **26**. $[\alpha]_D$ +11 (c = 0.11, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 3358, 1707; δ_H (500 MHz, $CDCl_3$) 4.85 (1H, d, J = 8.6 Hz), 4.63-4.56 (1H, m), 3.06 (1H, q, J = 5.5 Hz), 1.78-1.67 (1H, m), 1.60 (3H, s), 1.57-1.52 (1H, m), 1.42 (9H, s), 1.41-1.34 (1H, m), 1.19 (3H, d, J = 5.5 Hz), 0.97 (3H, d, J = 6.5 Hz), 0.94 (3H, d, J = 6.7 Hz); δ_C (125 MHz, $CDCl_3$) 207.1, 155.3, 79.9, 64.9, 61.2, 54.7, 39.7, 28.3(3), 24.7, 23.3, 21.5, 19.2, 14.2; MS (ESI): *m/z* calculated for $C_{15}H_{27}NO_4Na$ $[MNa]^+$ 308.2; found 308.2.



3.38 3.42

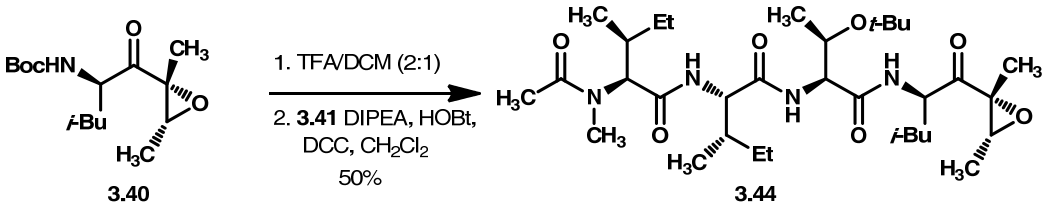
Tetrapeptide 3.45: To epoxide **3.38** (18 mg, 0.063 mmol) at 0 °C was added DCM/TFA (2:1, 0.3 ml) and stirred under argon for 25 min. Solvent was evaporated at 0 °C under vacuum and the residue was azeotroped with benzene and dried to give the amine salt. To the amine salt and tripeptide acid **3.41** (32 mg, 0.070 mmol) in DCM (2 mL) was added diisopropylethylamine (37 μL, 0.21 mmol) at 0 °C and stirred. After 2 min, 1-

hydroxybenzotriazole (HOBt) (19 mg, 0.141 mmol) was added at room temperature. Dicyclohexylcabrodiimide (DCC) (15 mg, 0.073 mmol) was added and stirred at room temperature under argon for 5 h. The reaction was diluted with EtOAc (50 mL) and the precipitated urea by-product was filtered off. Filtrate was washed with saturated aqueous $NaHCO_3$, water, brine, dried over anhydrous Na_2SO_4 and then evaporated. FCC purification using 60% EtOAc-hexane gave 25 mg of tetrapeptide **3.42** (0.040 mmol, 63% 2 steps) as a white solid. $[\alpha]_D$ -3 (*c* = 0.30, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 3295, 1721, 1633, 1538; δ_H (500 MHz, $CDCl_3$) 7.60 (1H, d, *J* = 7.5 Hz), 6.96 (1H, d, *J* = 5.6 Hz) 6.68 (1H, d, *J* = 6.7 Hz), 4.62 (1H, d, *J* = 11.4 Hz), 4.55-4.50 (1H, m), 4.28 (1H, dd, *J* = 5.5, 3.9 Hz), 4.24 (1H, dd, *J* = 8.1, 6.0 Hz), 4.21 (1H, dd, *J* = 6.5, 3.9 Hz), 3.52 (1H, q, *J* = 5.4 Hz), 2.93 (3H, s), 2.18-2.10 (1H, m), 2.10 (3H, s), 2.03-1.95 (1H, m), 1.72-1.64 (1H, m), 1.57-1.49 (1H, m), 1.45 (3H, s), 1.38 (3H, d, *J* = 5.4 Hz), 1.38-1.32 (2H, m), 1.28 (9H, s), 1.30-1.20 (1H, m), 1.16-0.90 (2H, m), 1.07 (3H, d, *J* = 6.4 Hz), 0.97-0.92 (9H, m), 0.91-0.84 (9H, m); δ_C (125 MHz, $CDCl_3$) 209.1, 172.2, 170.7, 170.4, 169.6, 75.4, 65.9, 63.2, 61.6, 58.0, 57.1, 57.0, 50.9, 39.6, 36.2, 32.0, 31.3, 28.1(3), 25.4, 24.6, 24.3, 23.4, 21.9, 21.3, 16.6, 15.7, 15.6, 13.6, 12.8, 11.3, 10.4; MS (ESI): *m/z* calculated for $C_{33}H_{60}N_4O_7Na$ $[MNa]^+$ 647.4; found 647.5.



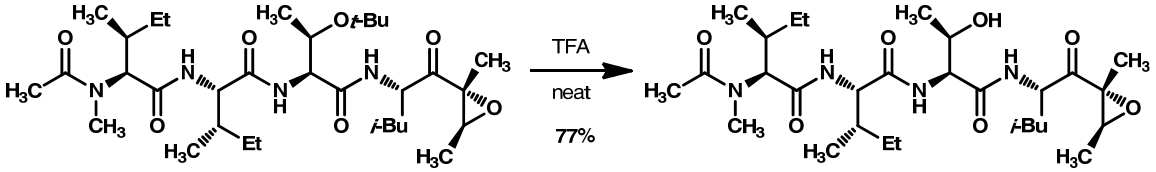
Tetrapeptide 3.43: 27 mg of tetrapeptide **3.43** (0.043 mmol, 62% 2 steps) was obtained as a white crystalline solid from 20 mg of **3.39** (0.070mmol) using the same procedure as in epoxide **3.38**. $[\alpha]_D$ -10 (*c* = 0.60, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 3296, 1722, 1633, 1538;

δ_H (500 MHz, $CDCl_3$) 7.58 (1H, d, *J* = 8.3 Hz), 7.04 (1H, d, *J* = 5.5 Hz) 6.68 (1H, br. s), 4.97-4.87 (1H, m), 4.58 (1H, d, *J* = 11.2 Hz), 4.32 (1H, dd, *J* = 5.5, 5.4 Hz), 4.26 (1H, dd, *J* = 8.2Hz, 5.9 Hz), 4.22 (1H, dd, *J* = 6.5 , 3.9 Hz), 3.09 (1H, q, *J* = 5.7 Hz), 2.95 (3H, s), 2.18-2.10 (1H, m), 2.11 (3H, s), 2.08-1.99 (1H, m), 1.72-1.64 (2H, m), 1.51 (3H, s), 1.41 (3H, d, *J* = 5.7 Hz), 1.38-1.32 (2H, m), 1.30 (9H, s), 1.30-1.20 (1H, m), 1.16-0.90 (2H, m), 1.08 (3H, d, *J* = 6.4 Hz), 0.97-0.84 (18H, m); δ_C (125 MHz, $CDCl_3$) 207.8, 172.2, 170.7, 170.4, 169.3, 75.3, 65.7, 64.1, 62.0, 61.2, 58.0, 57.3, 55.2, 39.1, 36.1, 32.2, 31.3, 28.1(3), 25.3, 24.6, 24.2, 23.4, 22.0, 21.1, 19.9, 16.6, 15.7, 15.5, 13.8, 11.3, 10.3; MS (ESI): *m/z* calculated for $C_{33}H_{60}N_4O_7Na$ $[MNa]^+$ 647.4; found 647.6.



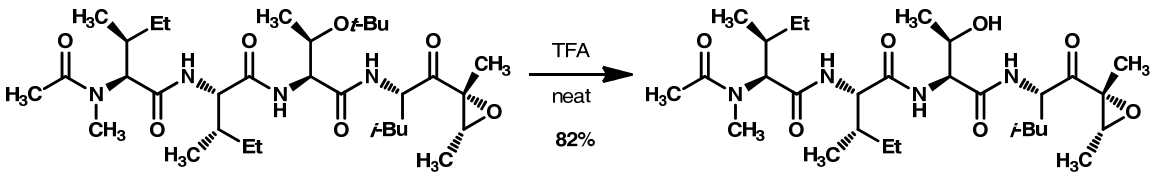
Tetrapeptide 3.44: 24 mg of tetrapeptide **3.44** (0.038 mmol, 50% 2 steps) was obtained as a white crystalline solid from 22 mg of **3.40** (0.077 mmol) using the same procedure as in epoxide **3.38**. $[\alpha]_D$ -8 (*c* = 0.29, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 3303, 1724, 1632, 1537; δ_H (500 MHz, $CDCl_3$) 7.29 (1H, d, *J* = 7.4 Hz), 7.01 (1H, d, *J* = 5.7 Hz) 6.74 (1H, br. s), 4.88-4.82 (1H, m), 4.62 (1H, d, *J* = 11.4 Hz), 4.29-4.21 (3H, m), 3.05 (1H, q, *J* = 5.5 Hz), 2.94 (3H, s), 2.18-2.10 (1H, m), 2.12 (3H, s), 2.05-1.95 (1H, m), 1.84-1.67 (1H, m), 1.62-1.56 (1H, m), 1.57 (3H, s), 1.50-1.30 (2H, m), 1.30-1.20 (1H, m), 1.24 (9H, s), 1.20-0.90 (2H, m), 1.20 (3H, d, *J* = 5.5 Hz), 0.99 (3H, d, *J* = 6.3 Hz), 0.97-0.93 (9H, m), 0.91-0.84 (9H, m); δ_C (125 MHz, $CDCl_3$) 205.9, 172.3, 170.72, 170.71, 168.8, 75.4, 65.6, 65.2, 61.7, 61.1, 58.3, 57.5, 53.9, 39.4, 36.2, 32.0, 31.3, 28.2(3), 24.63, 24.58, 24.4, 23.4, 22.0,

21.0, 19.4, 17.6, 15.8, 15.7, 14.5, 11.3, 10.3; MS (ESI): *m/z* calculated for $C_{33}H_{60}N_4O_7Na$ $[MNa]^+$ 647.5; found 647.6.



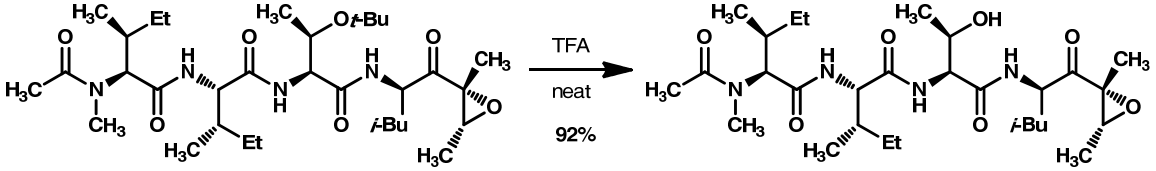
3.42 3.45

Epoxomicinoid 3.45: To tetrapeptide **3.42** (20 mg, 0.032 mmol) was added TFA (0.3 mL). The solution was allowed to stir at 0 °C for 10 min then was stirred for another 10 min without the ice bath. Solvent was evaporated at room temperature and azeotroped with benzene. FCC purification using EtOAc gave 14 mg of **3.42** (0.025 mmol, 77%) as a white solid. $[\alpha]_D$ -36 (*c* = 0.60, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 3295, 1716, 1643, 1538; δ_H (500 MHz, $CDCl_3$) 7.18 (1H, d, *J* = 7.7 Hz), 7.14 (1H, d, *J* = 8.0 Hz), 6.92 (1H, d, *J* = 7.0 Hz), 4.68-4.56 (2H, m), 4.43 (1H, dd, *J* = 7.7, 2.7 Hz), 4.30-4.20 (2H, m), 3.52 (1H, d, *J* = 3.4 Hz), 3.46 (1H, q, *J* = 5.4 Hz), 2.97 (3H, s), 2.16-2.07 (1H, m), 2.11 (3H, s), 2.05-1.95 (1H, m), 1.70-1.60 (1H, m), 1.56-1.48 (1H, m), 1.45 (3H, s), 1.38 (3H, d, *J* = 5.4 Hz), 1.40-1.20 (2H, m), 1.15-1.05 (1H, m), 1.11 (3H, d, *J* = 6.5 Hz), 1.02-0.88 (2H, m), 0.94-0.84 (18H, m); δ_C (125 MHz, $CDCl_3$) 209.2, 172.2, 171.7, 170.7, 170.6, 66.5, 63.1, 61.7, 58.0, 57.1, 56.5, 51.0, 39.3, 36.1, 32.2, 31.8, 29.7, 25.1, 24.7, 24.6, 23.4, 22.0, 21.1, 17.8, 15.5, 13.6, 12.8, 11.1, 10.5; MS (ESI): *m/z* calculated for $C_{29}H_{52}N_4O_7Na$ $[MNa]^+$ 591.4; found 591.5.



3.43 3.46

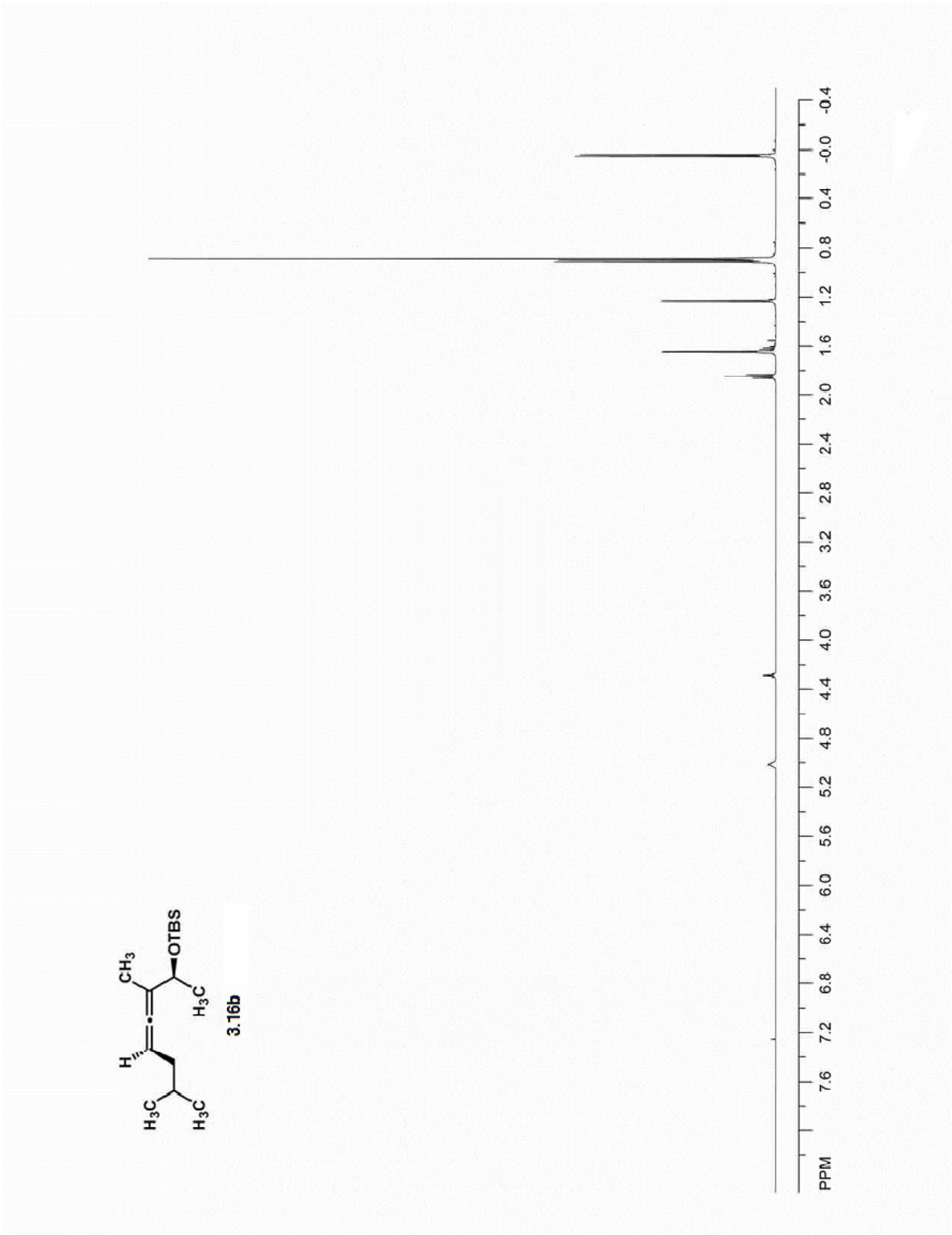
Epoxomicinoid 3.46: 15 mg of **3.46** (0.026 mmol, 82%) was obtained as white crystalline solid from 20 mg of **3.43** (0.032 mmol) using the same procedure as in tetrapeptide **3.42**. $[\alpha]_D$ -16 (*c* = 0.35, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 3293, 1716, 1633, 1538; δ_H (500 MHz, $CDCl_3$) 7.14 (1H, d, *J* = 8.0 Hz), 7.10 (1H, d, *J* = 8.8 Hz), 6.92 (1H, d, *J* = 7.6 Hz), 5.00-4.93 (1H, m), 4.62 (1H, d, *J* = 11.4, 2.7 Hz), 4.33-4.24 (2H, m), 4.27 (1H, dd, *J* = 8.1, 6.6 Hz), 3.61 (1H, br. s), 3.09 (1H, q, *J* = 5.7Hz), 2.98 (3H, s), 2.17-2.06 (1H, m), 2.11 (3H, s), 2.05-1.95 (1H, m), 1.75-1.60 (2H, m), 1.50 (3H, s), 1.44-1.20 (2H, m), 1.37 (3H, d, *J* = 5.7 Hz), 1.15-1.06 (1H, m), 1.13 (3H, d, *J* = 6.5 Hz), 1.04-0.88 (2H, m), 0.98 (3H, d, *J* = 6.2 Hz), 0.94 (3H, d, *J* = 6.3 Hz), 0.90-0.84 (12H, m), δ_C (125 MHz, $CDCl_3$) 208.2, 172.2, 171.6, 170.7, 170.6, 66.5, 64.1, 62.0, 61.3, 58.0, 56.7, 55.3, 38.6, 36.1, 32.3, 31.8, 25.2, 24.7, 24.5, 23.4, 22.1, 20.9, 19.9, 17.8, 15.6, 15.5, 13.9, 11.2, 10.5; MS (ESI): *m/z* calculated for $C_{29}H_{52}N_4O_7Na$ $[MNa]^+$ 591.4; found 591.4.



3.44 3.47

Epoxomicinoid 3.47: 7 mg of **3.47** (0.012 mmol, 92%) was obtained as white crystalline solid from 8.2 mg of **3.44** (0.013 mmol) using the same procedure as in tetrapeptide **3.42**. $[\alpha]_D$ -10 (*c* = 0.11, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 3294, 1719, 1638, 1532; δ_H (500 MHz, $CDCl_3$) 7.23 (1H, d, *J* = 7.1 Hz), 7.05 (1H, d, *J* = 5.1 Hz), 6.88 (1H, d, *J* = 7.8 Hz), 4.82-4.74 (1H, m), 4.49 (1H, d, *J* = 11.5 Hz), 4.40 (1H, qd, *J* = 6.5, 1.6 Hz), 4.25 (1H, dd, *J* = 7.8, 1.6 Hz), 4.11 (1H, dd, *J* = 5.6, 4.8 Hz), 3.14 (1H, br. s), 3.06 (1H, q, *J* = 5.5 Hz), 2.96 (3H, s), 2.21-2.06 (2H, m), 2.15 (3H, s), 1.87-1.77 (1H, m), 1.70-1.62 (1H, m), 1.59 (3H, s), 1.60-1.32 (2H, m), 1.30-1.06 (1H, m), 1.21 (3H, d, *J* = 5.5 Hz), 1.17 (3H, d, *J* = 6.5 Hz), 1.08-0.92 (2H, m), 1.00-0.85 (18H, m), δ_C (125 MHz, $CDCl_3$) 207.4, 172.7, 172.1,

171.1, 171.07, 67.1, 65.0, 63.1, 61.4, 59.9, 58.0, 55.6, 38.6, 35.7, 33.1, 31.3, 25.0, 24.7, 24.4, 23.4, 22.1, 21.0, 19.6, 18.9, 16.0, 15.8, 14.3, 11.6, 10.3; MS (ESI): *m/z* calculated for $C_{29}H_{52}N_4O_7Na$ $[MNa]^+$ 591.4; found 591.5.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PPM
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7.2
6.8
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5.6
5.2
4.8
4.4
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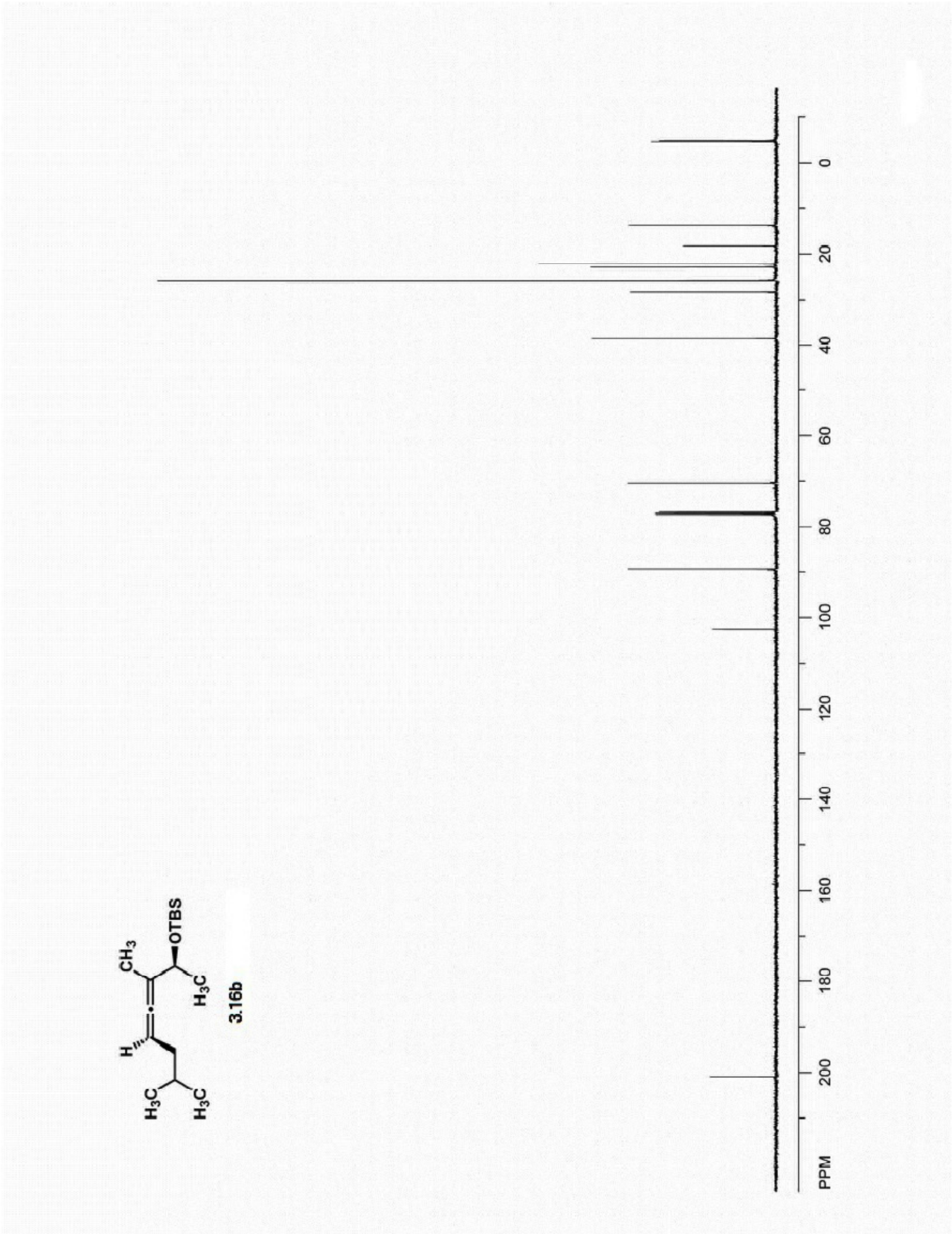
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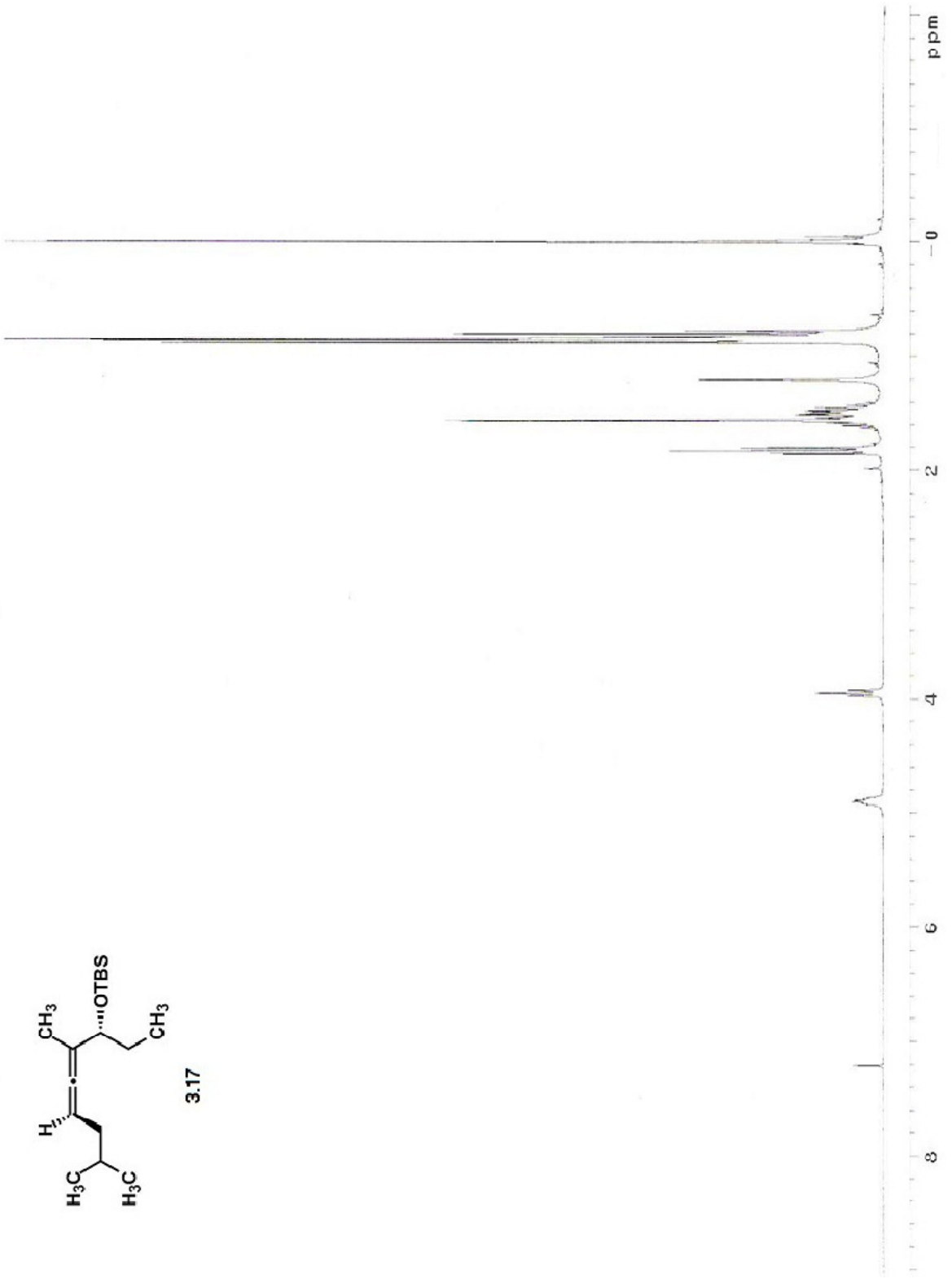

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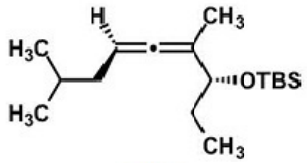
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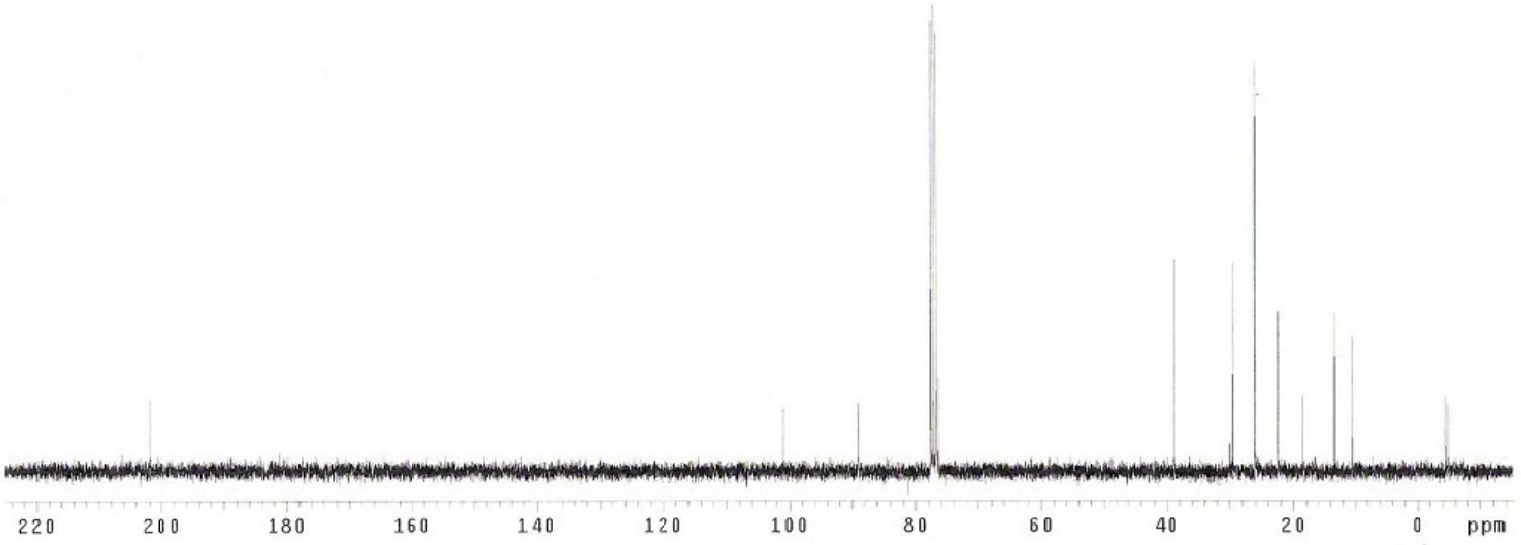
OTBS
H3C
CH3

3.17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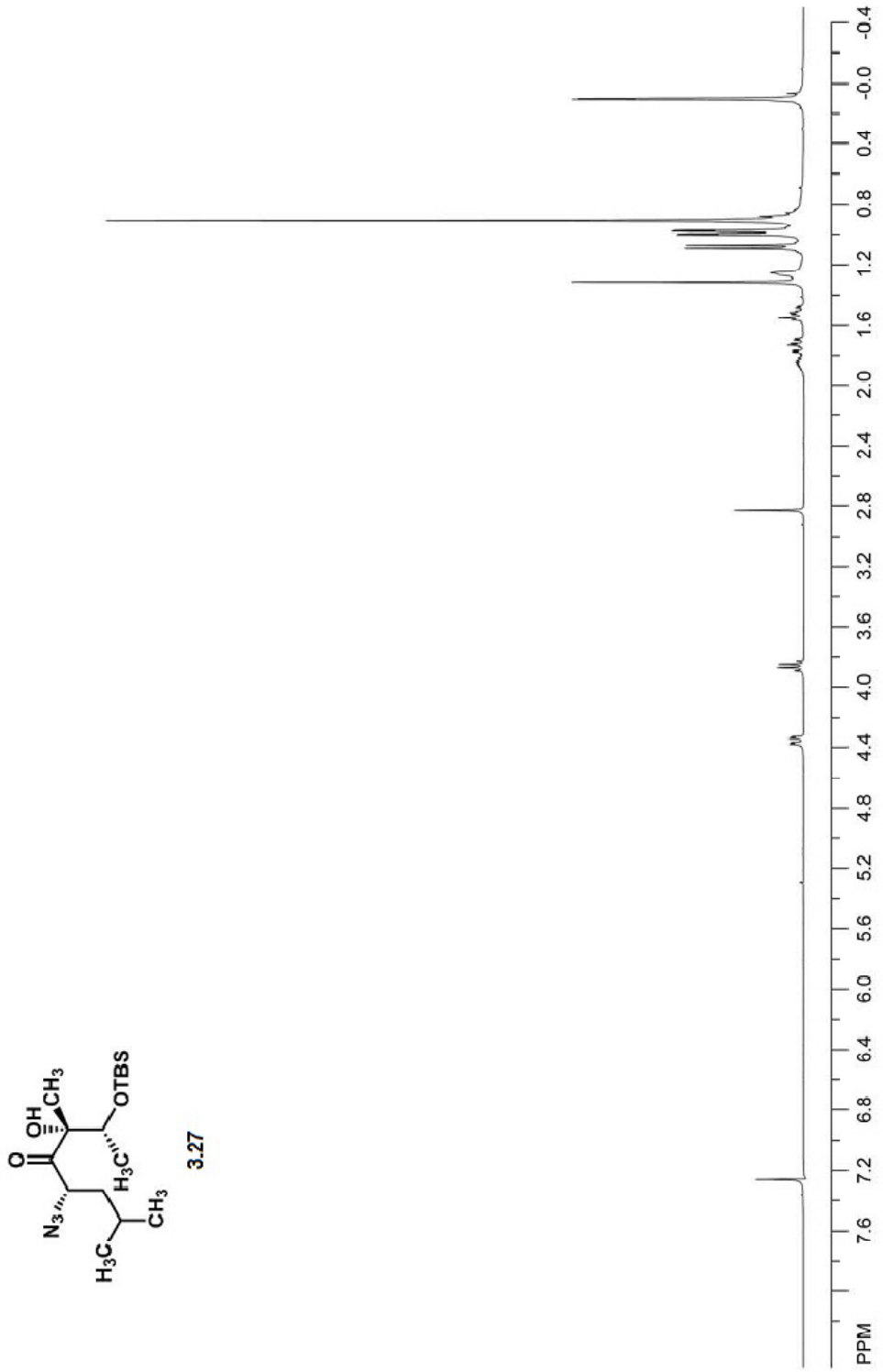
ppm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N3
H3C
CH3
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PPM
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5.6
5.2
4.8
4.4
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2.8
2.4
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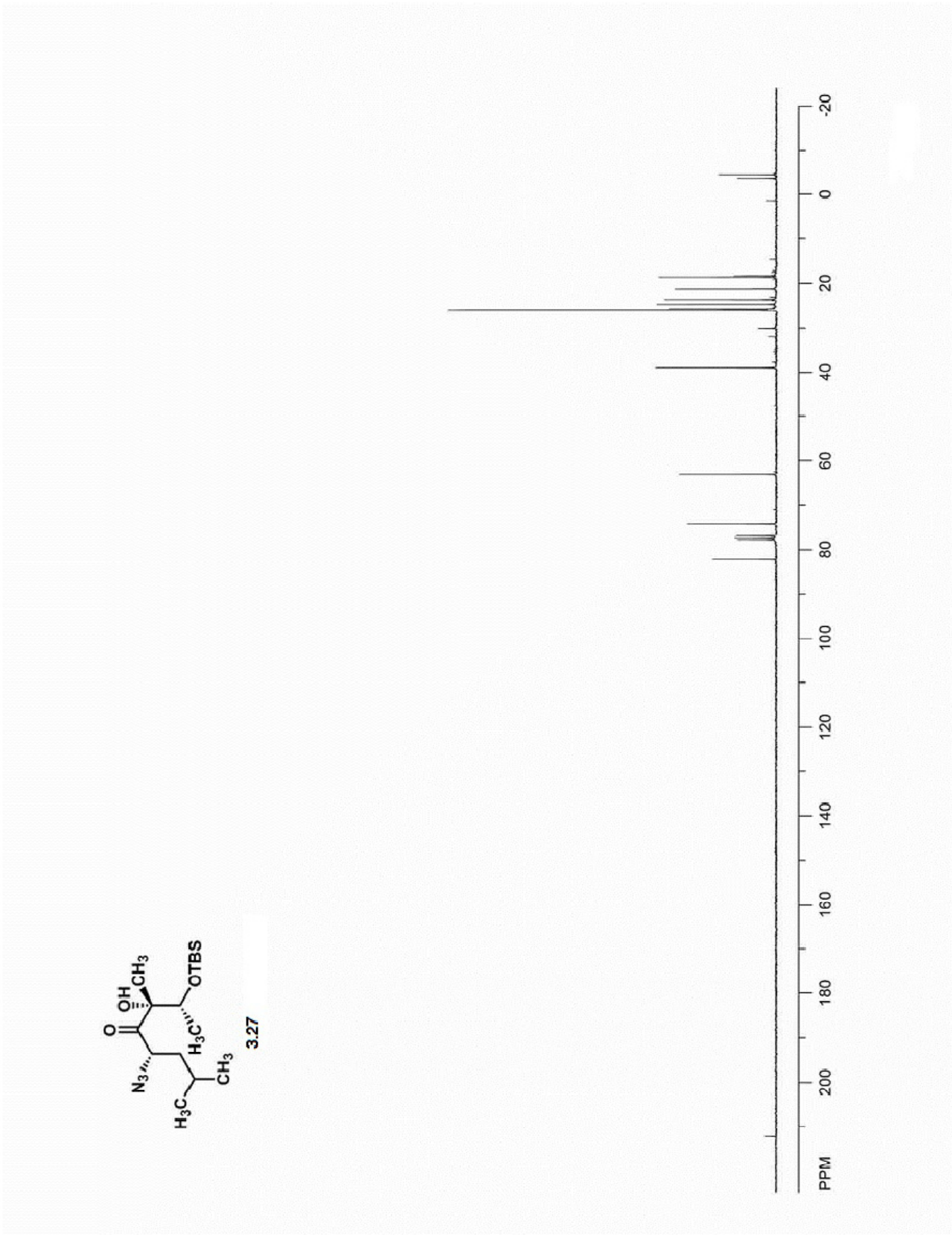
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PPM
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20
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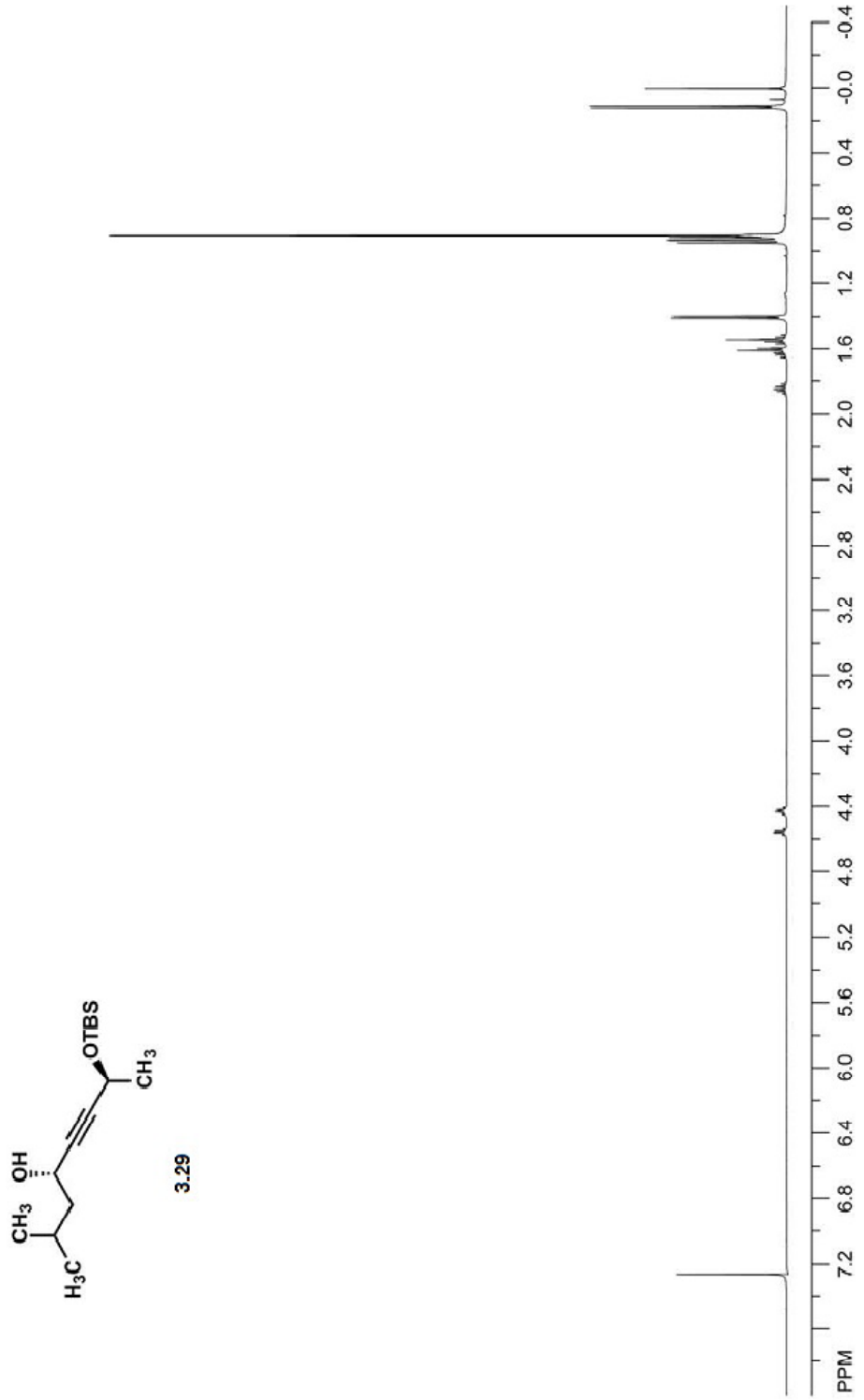
-20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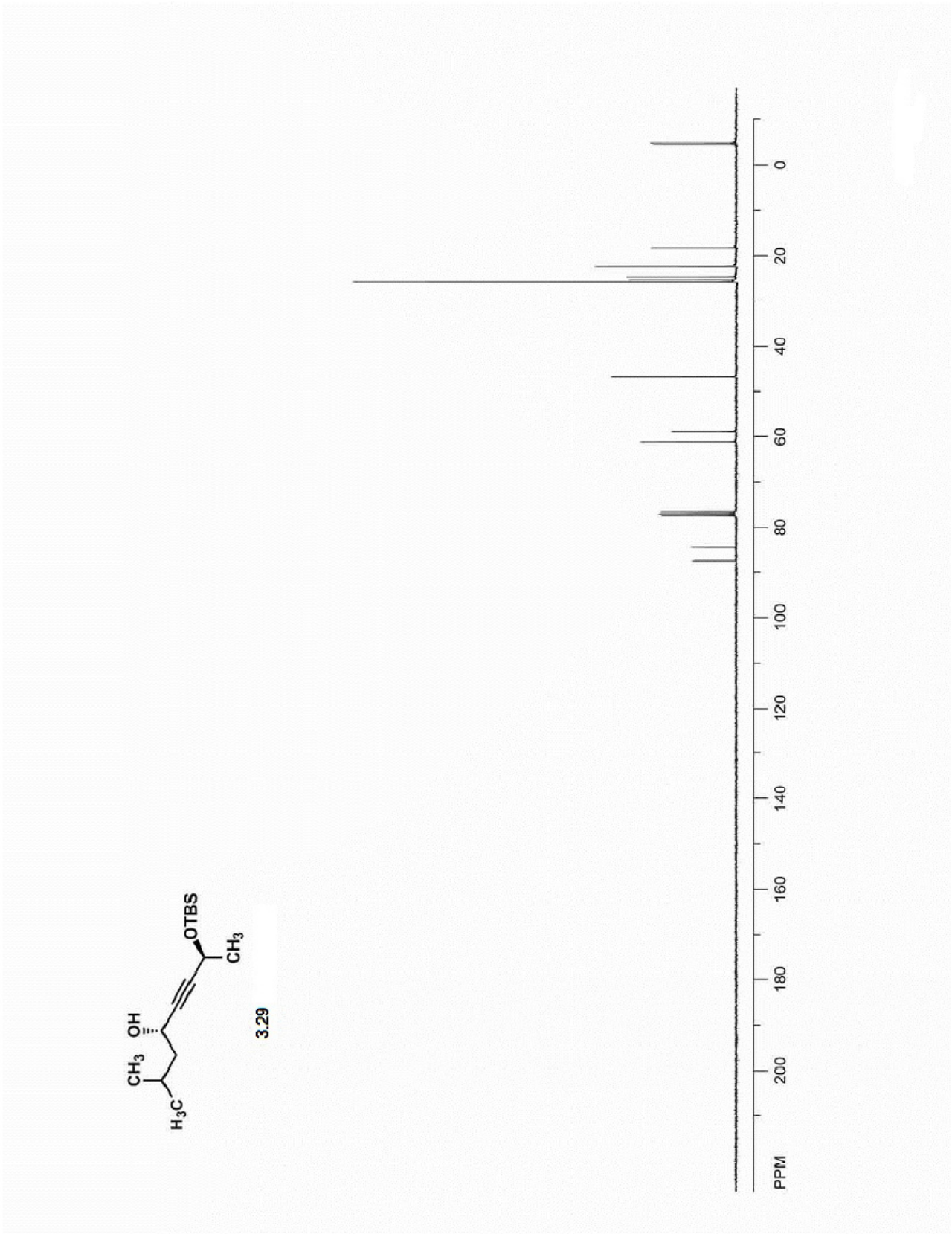
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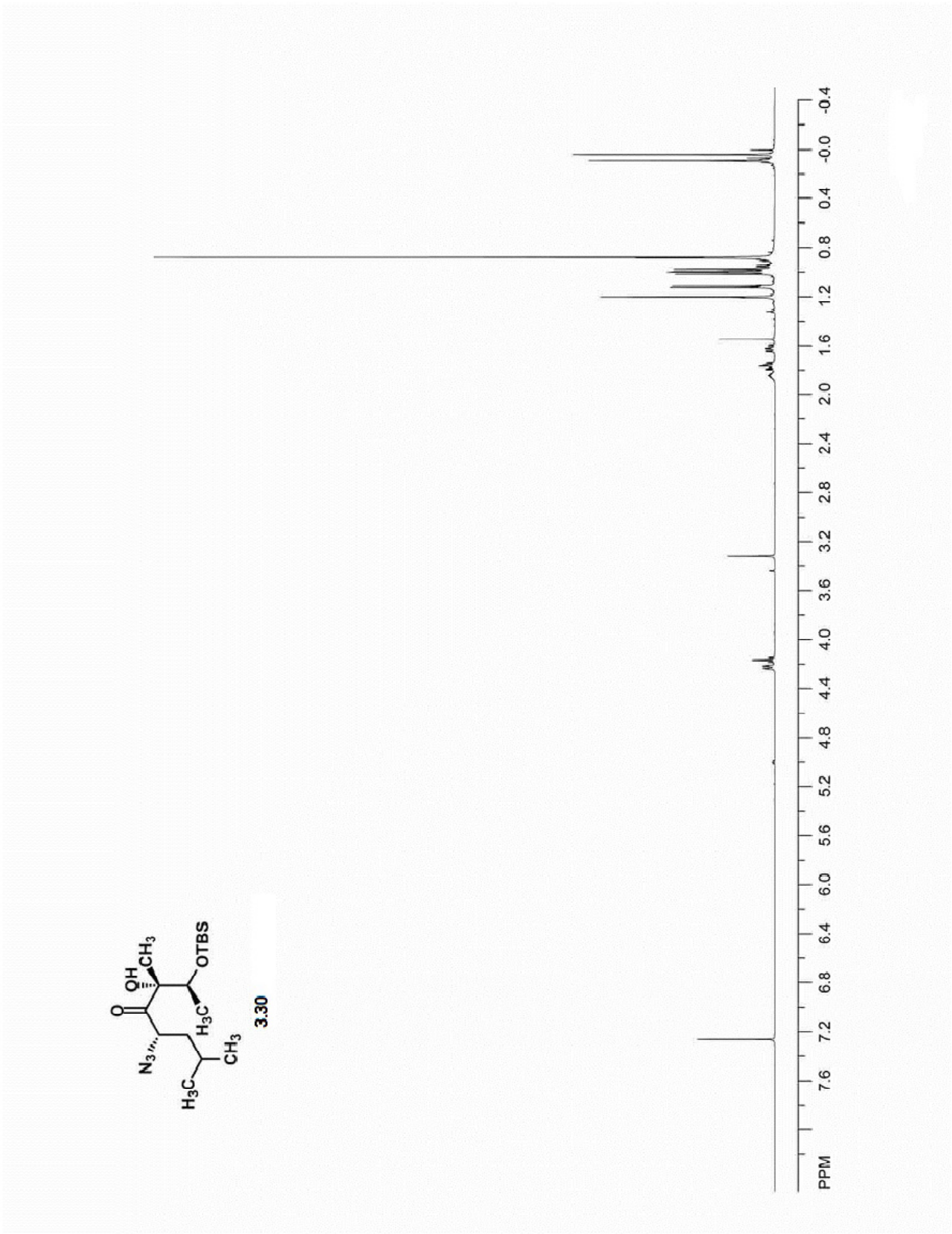
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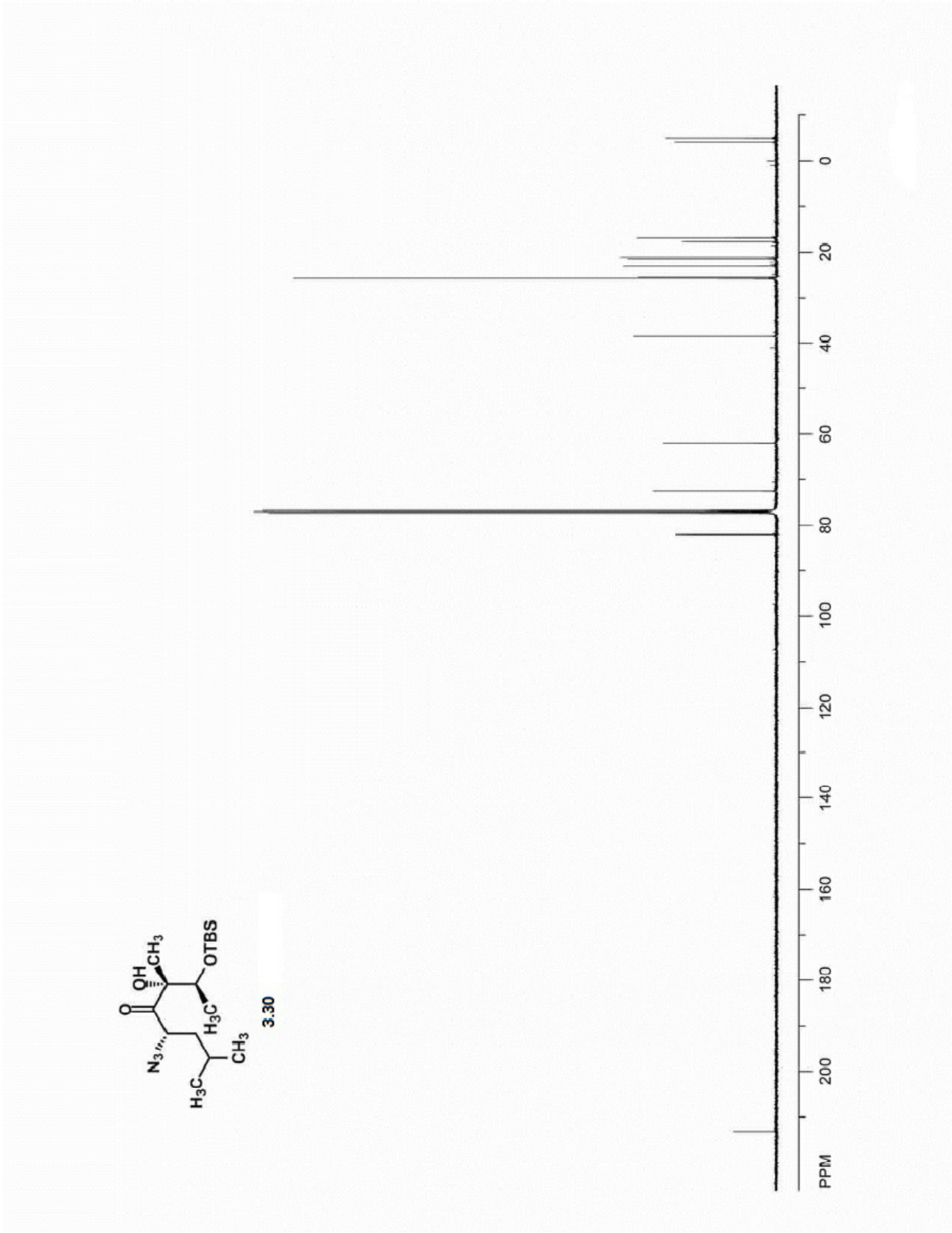
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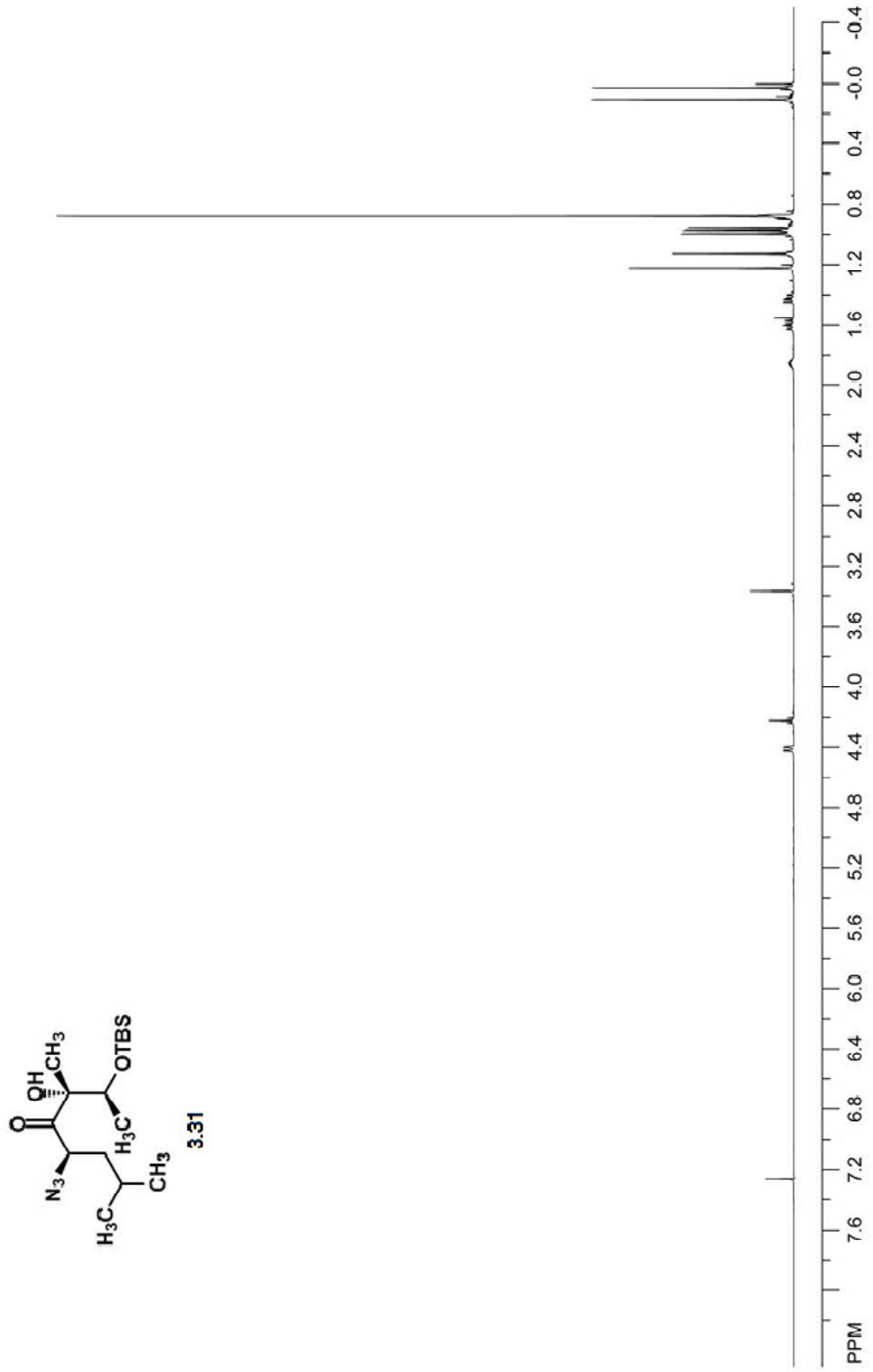
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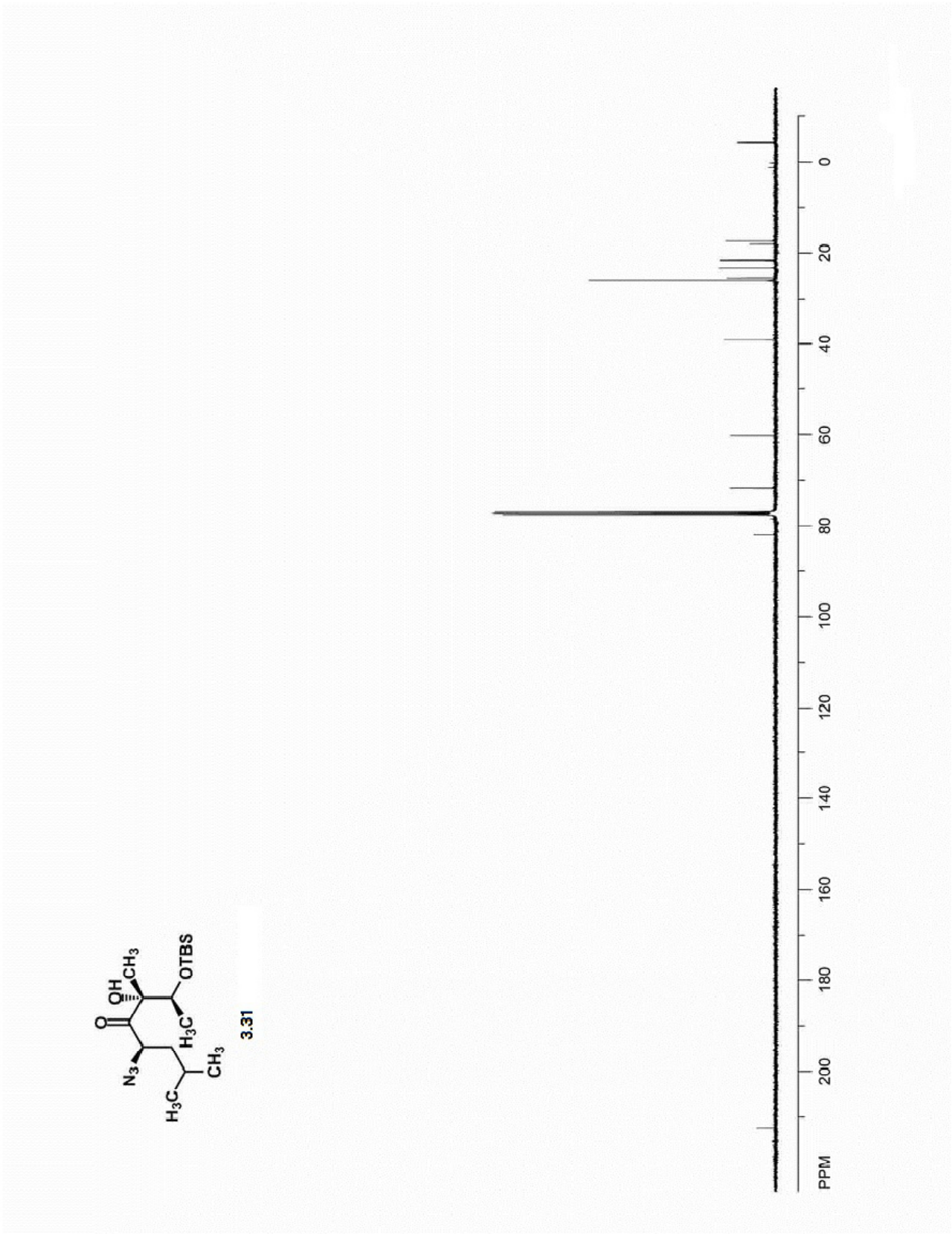
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PPM
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120
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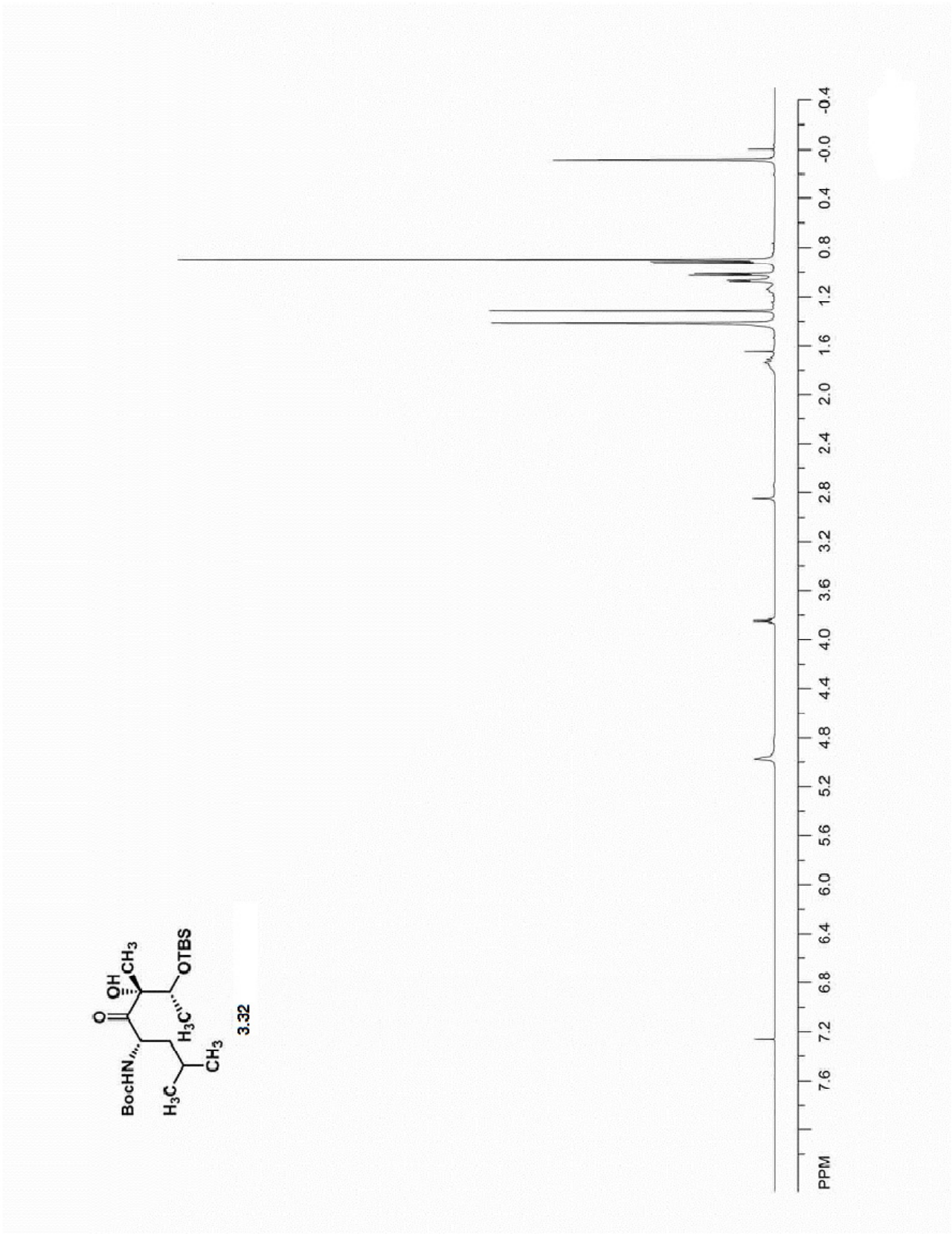
60
40
20
0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OH
CH3
O
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PPM
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5.2
4.8
4.4
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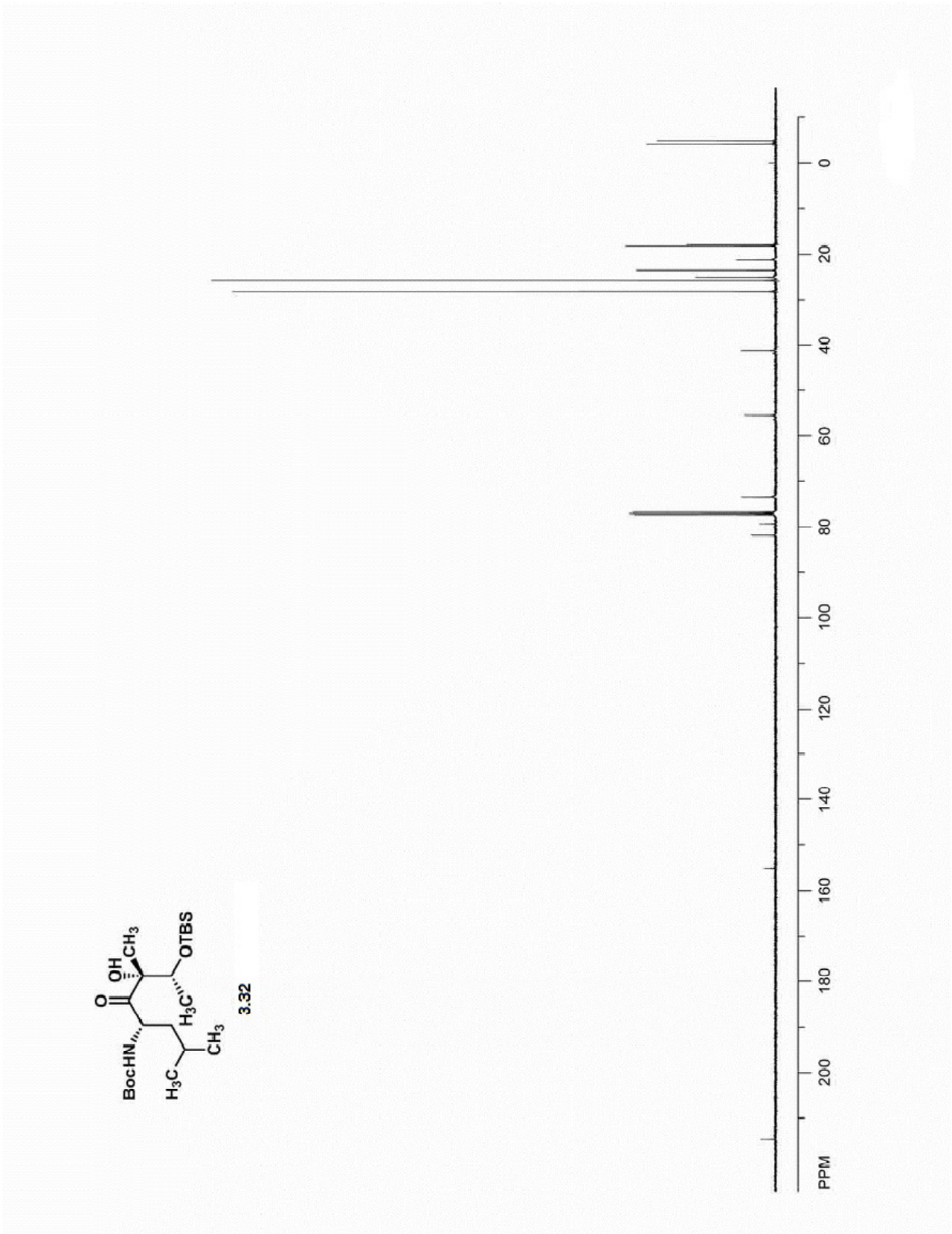
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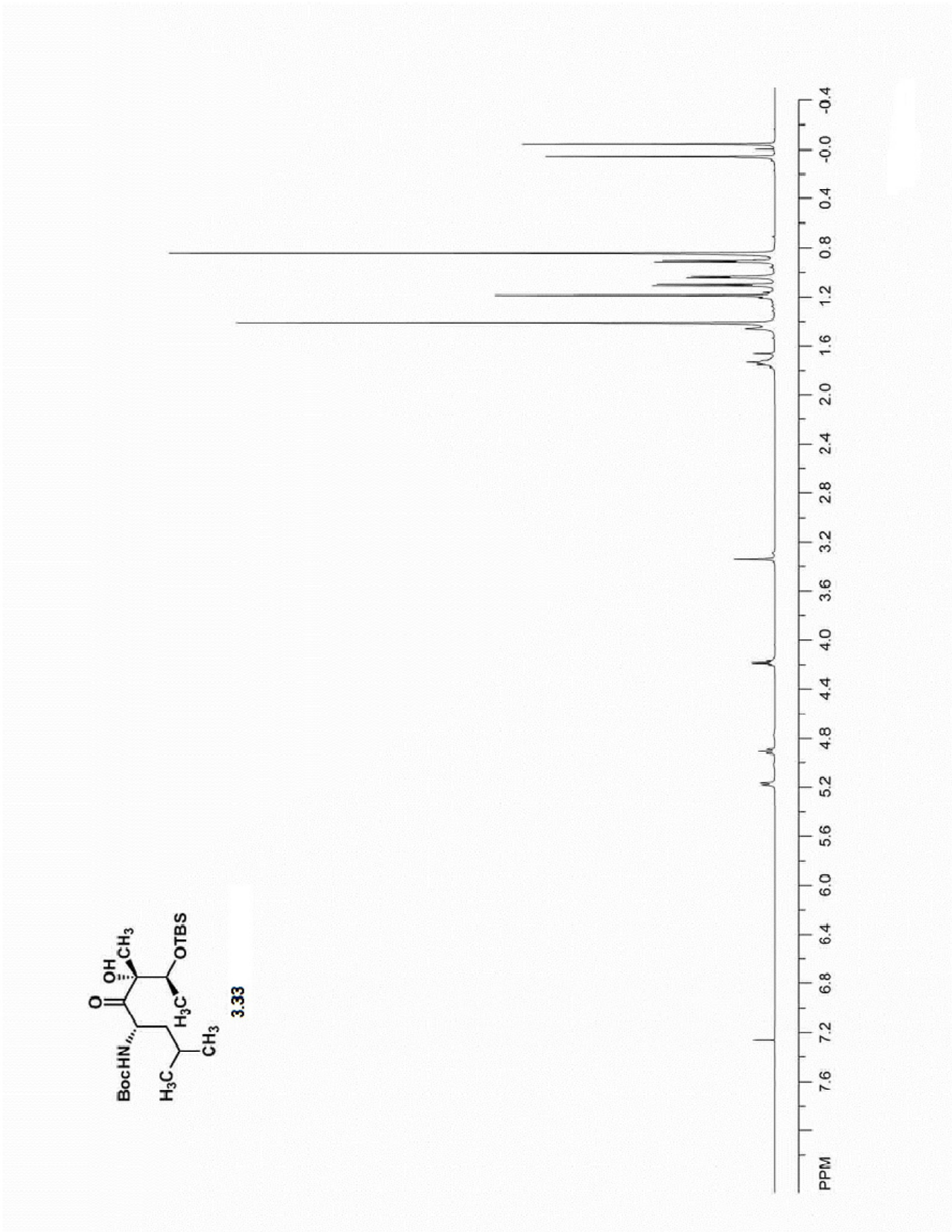
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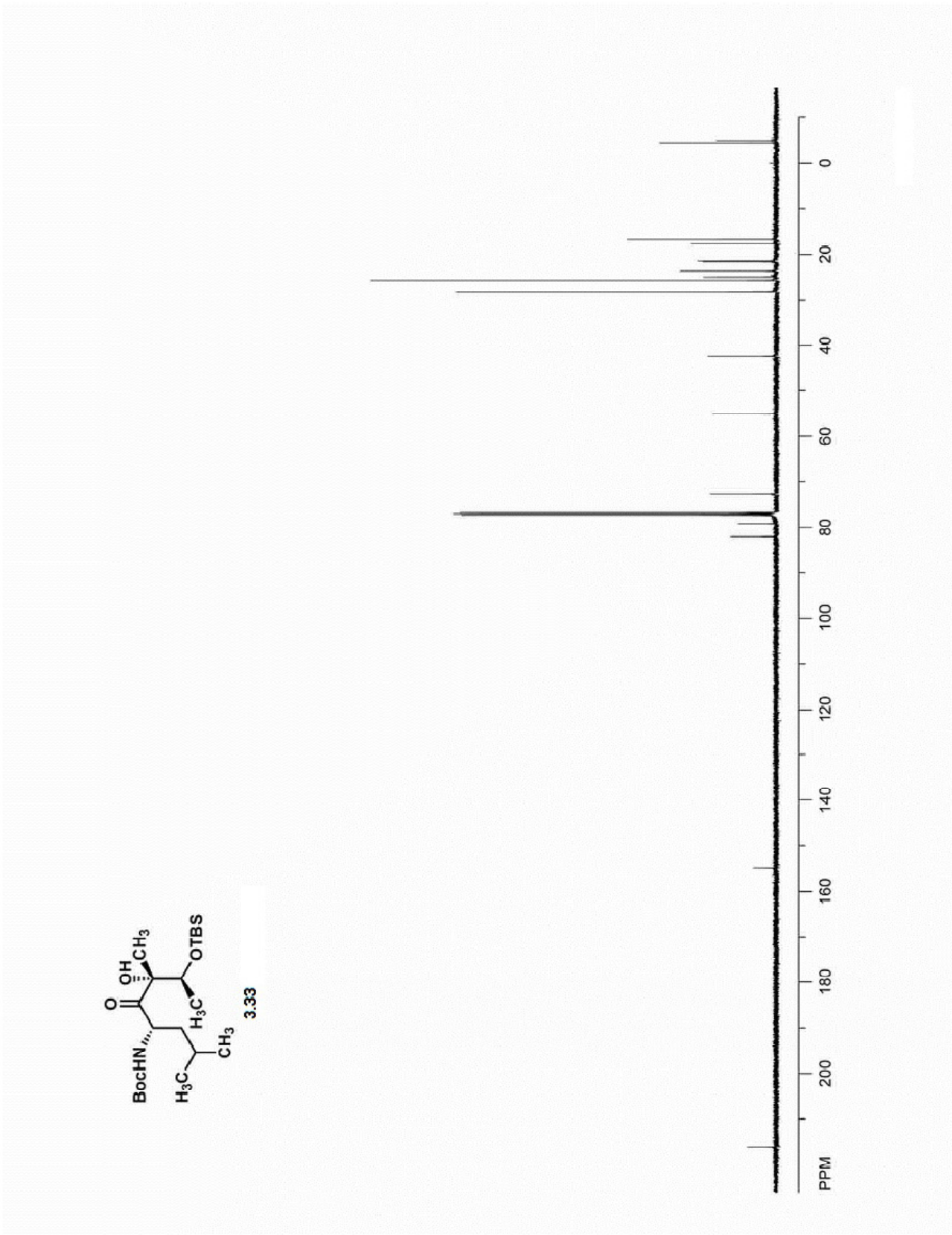
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180
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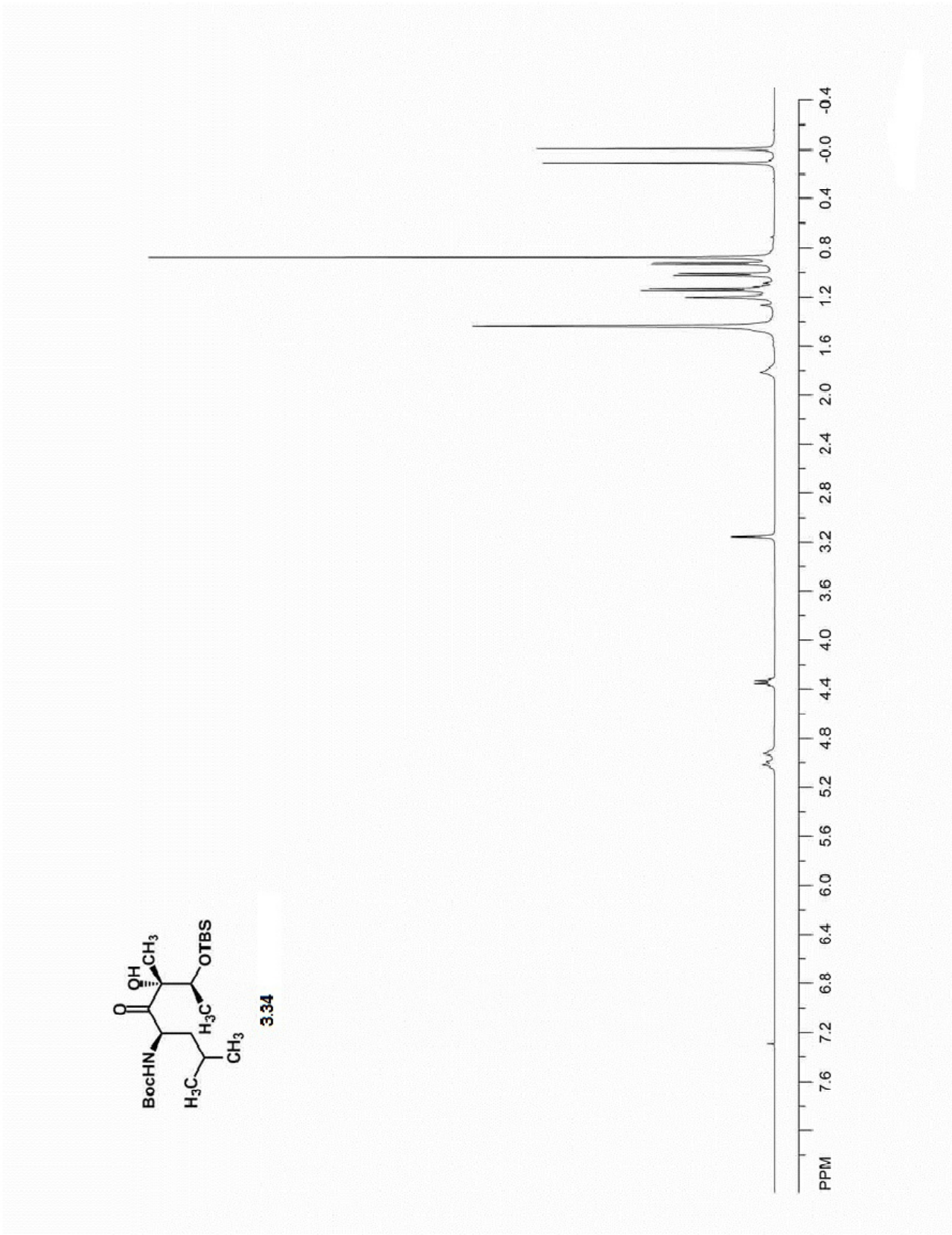
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5.2
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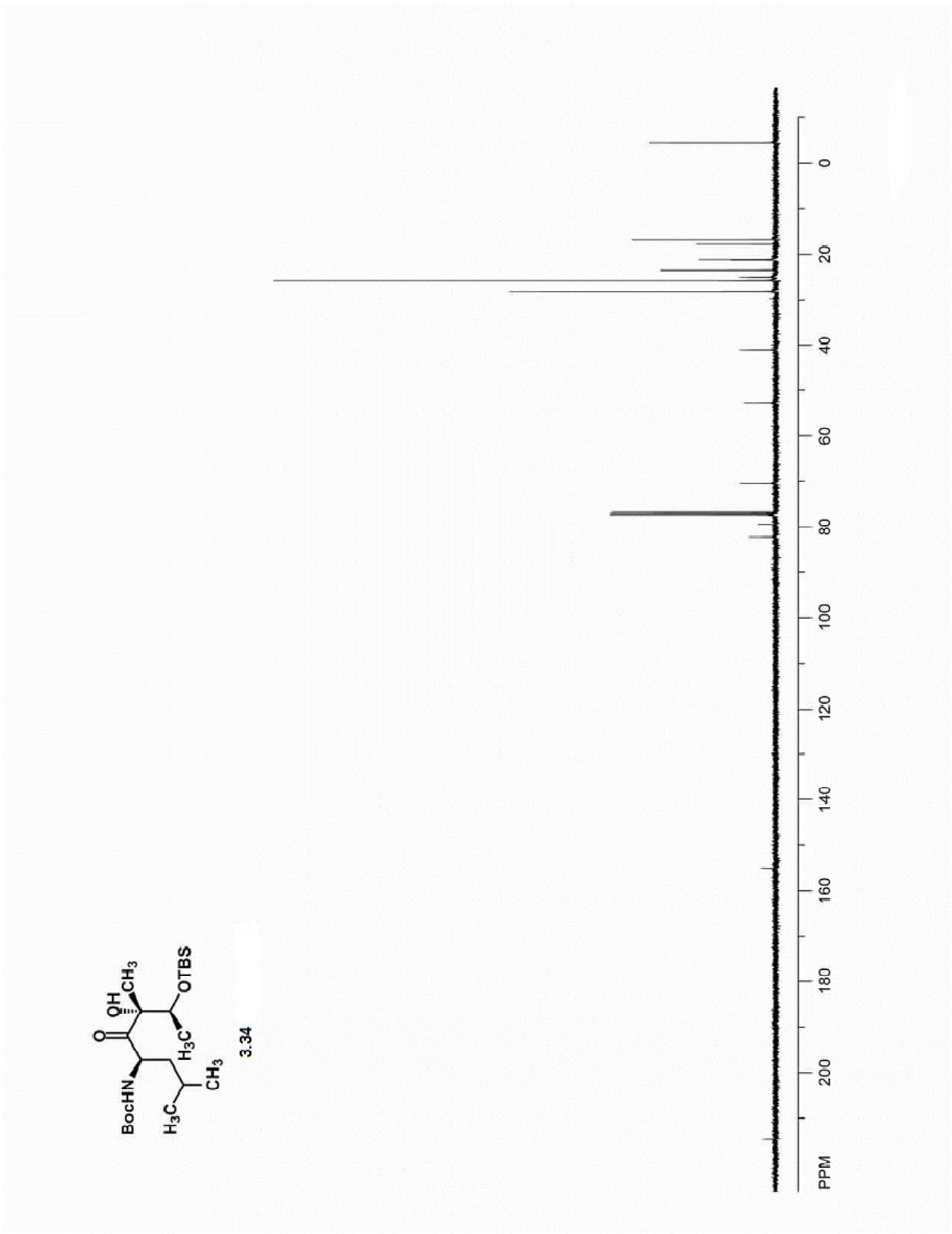
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PPM
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180
160
140
120
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60
40
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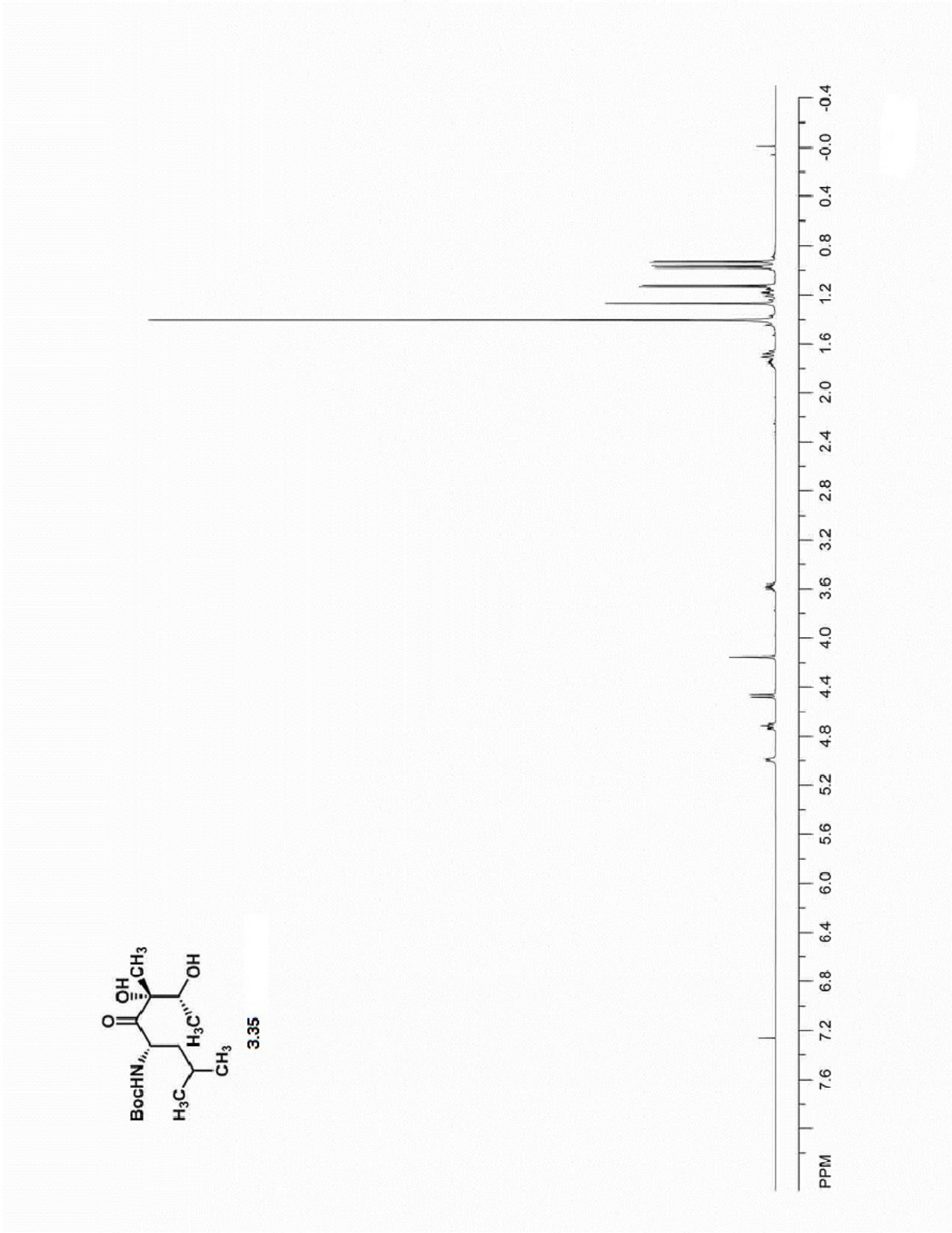
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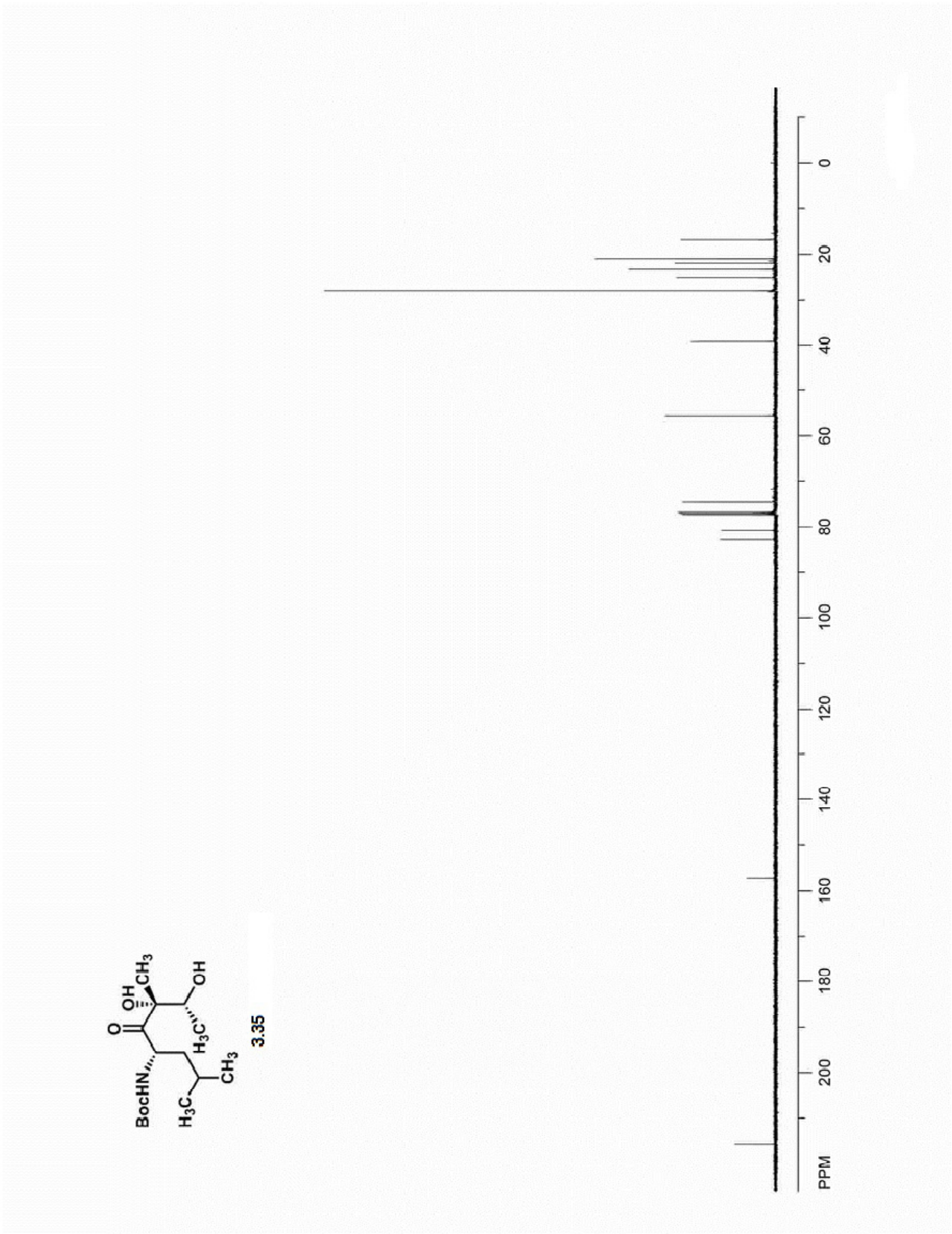
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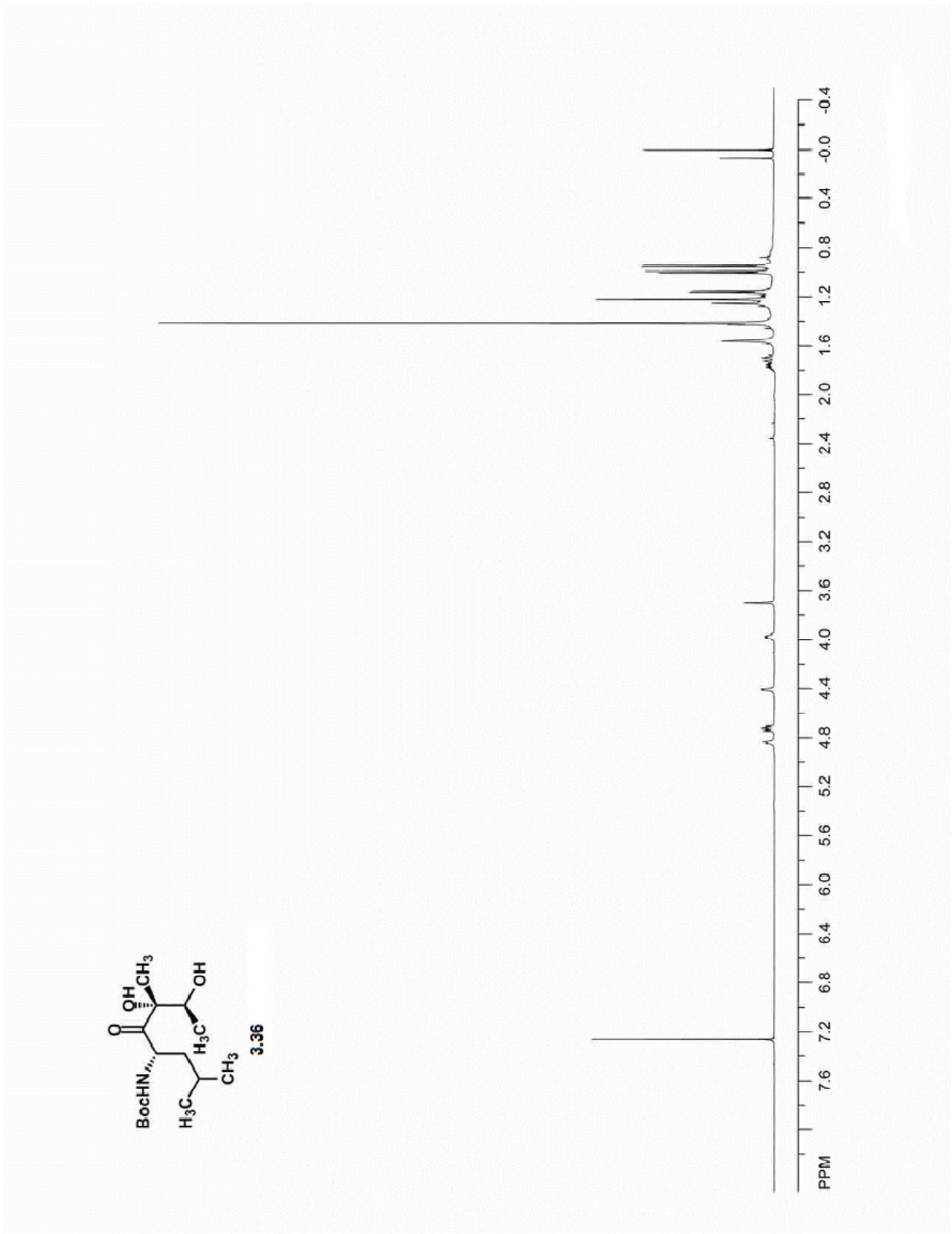
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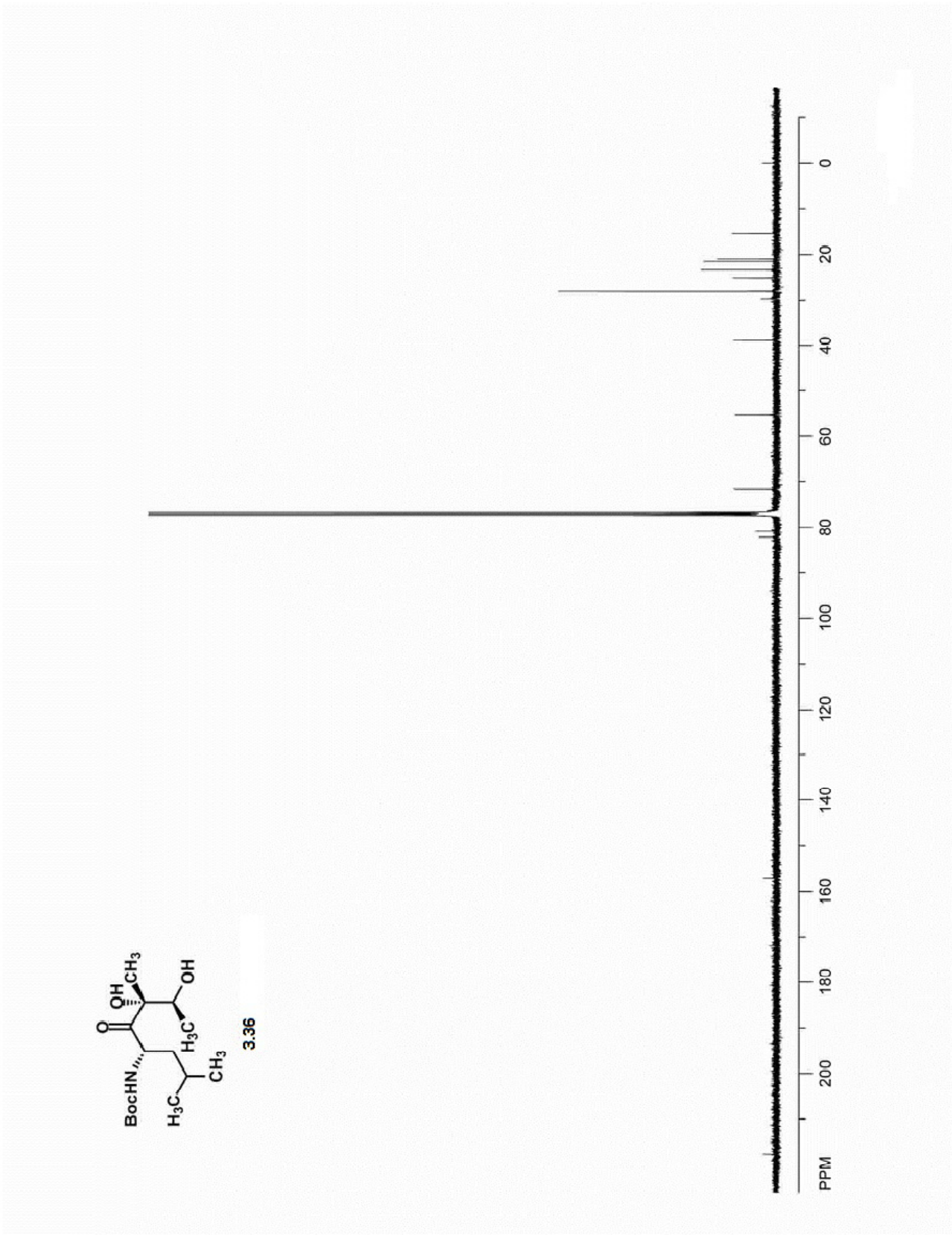
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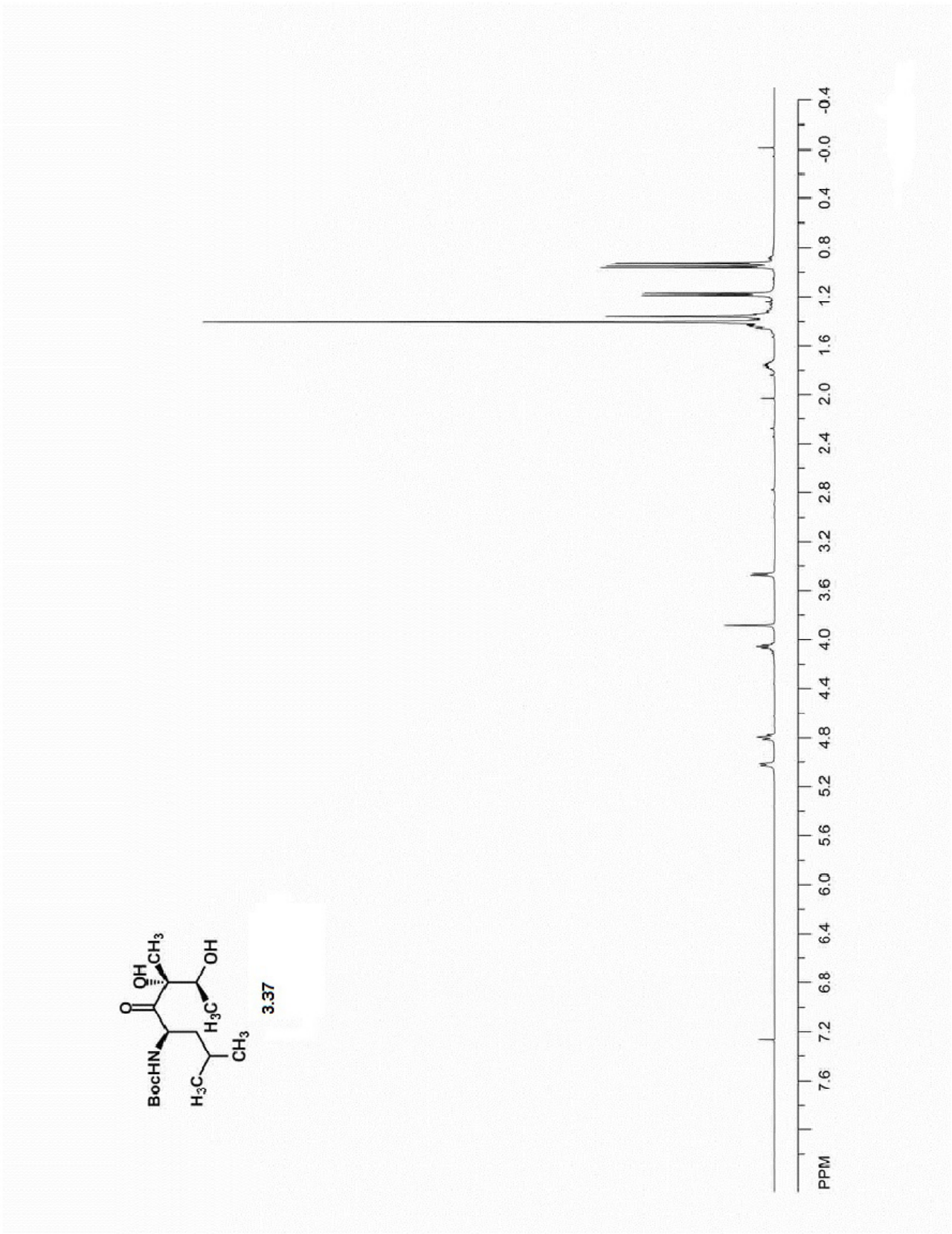
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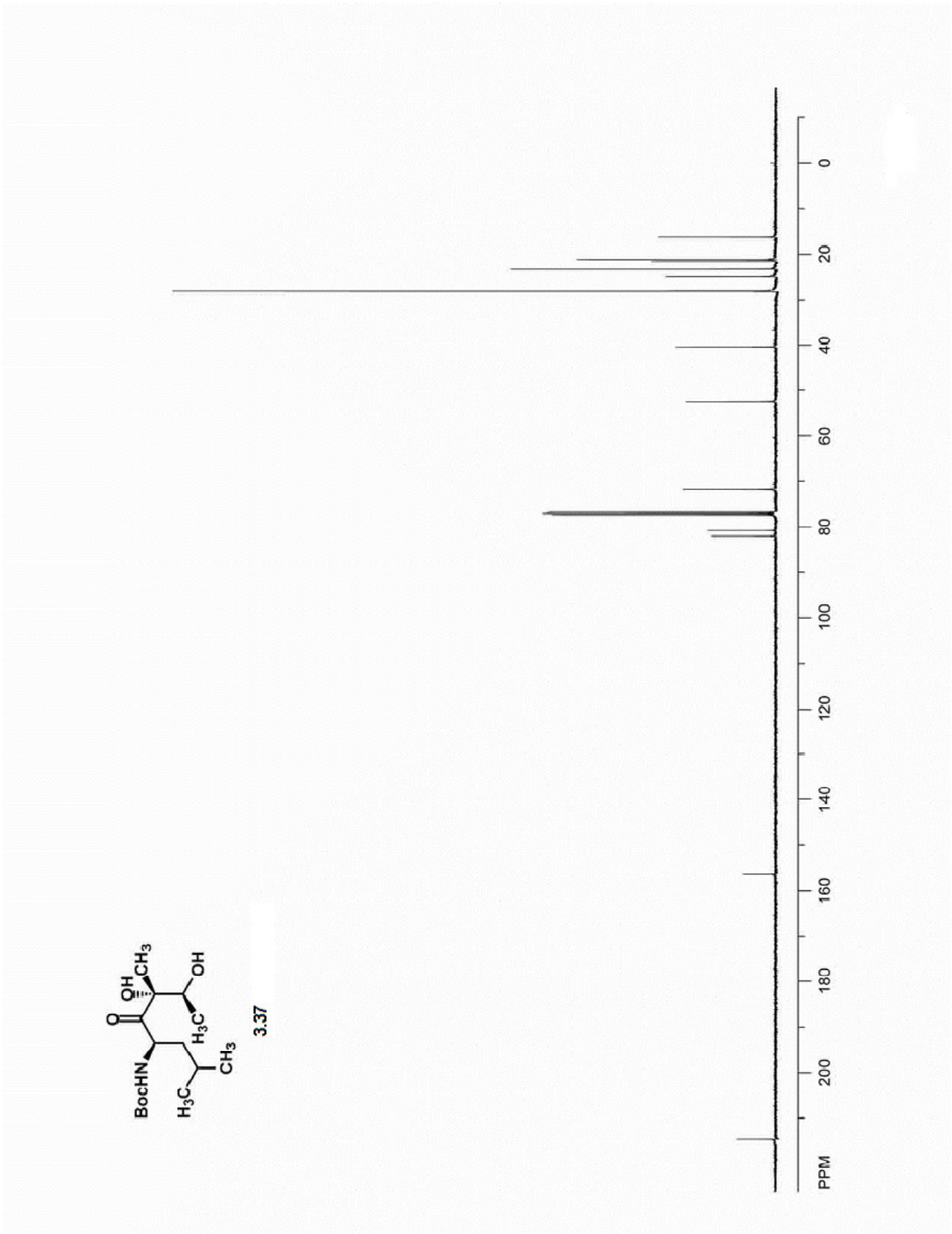
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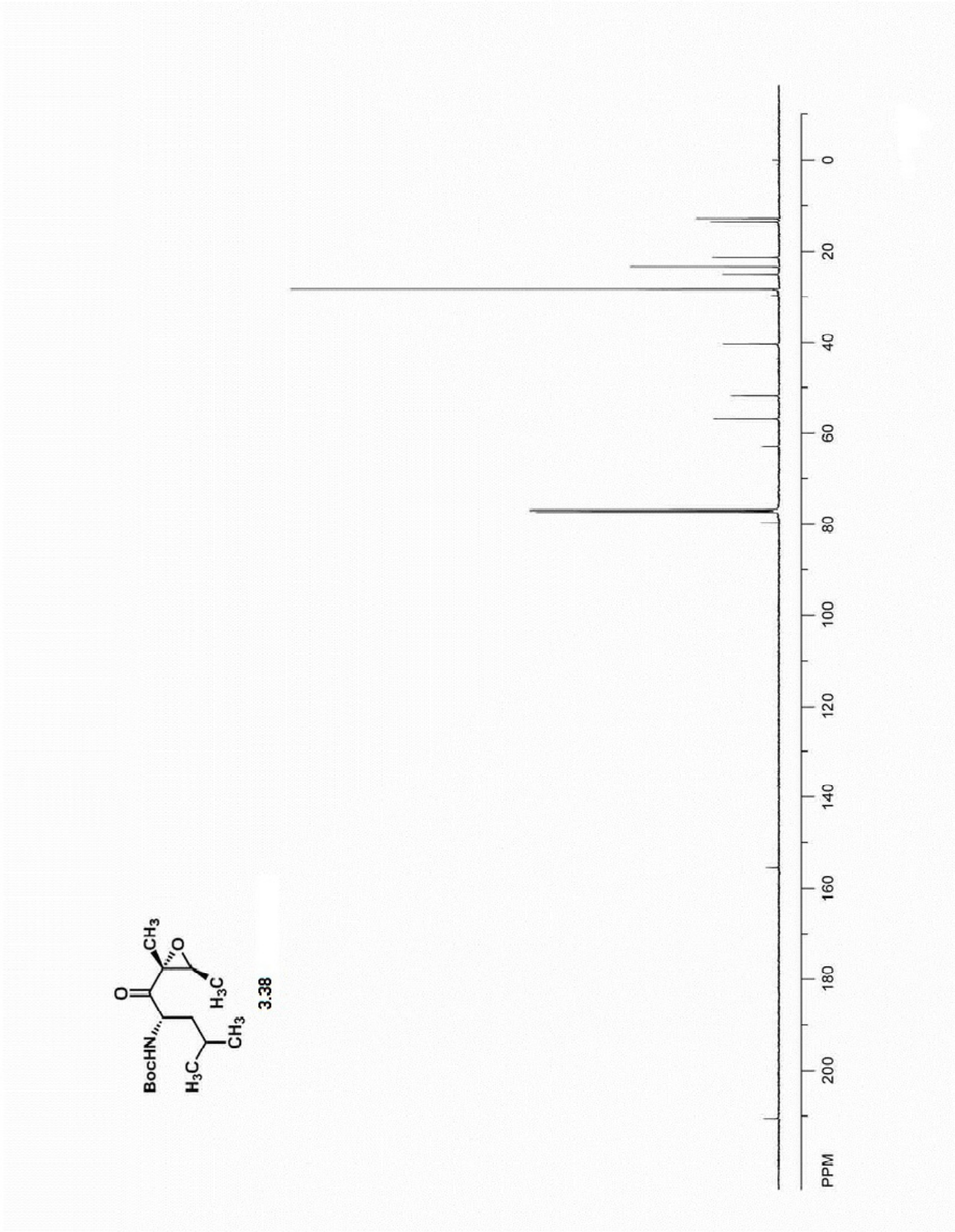
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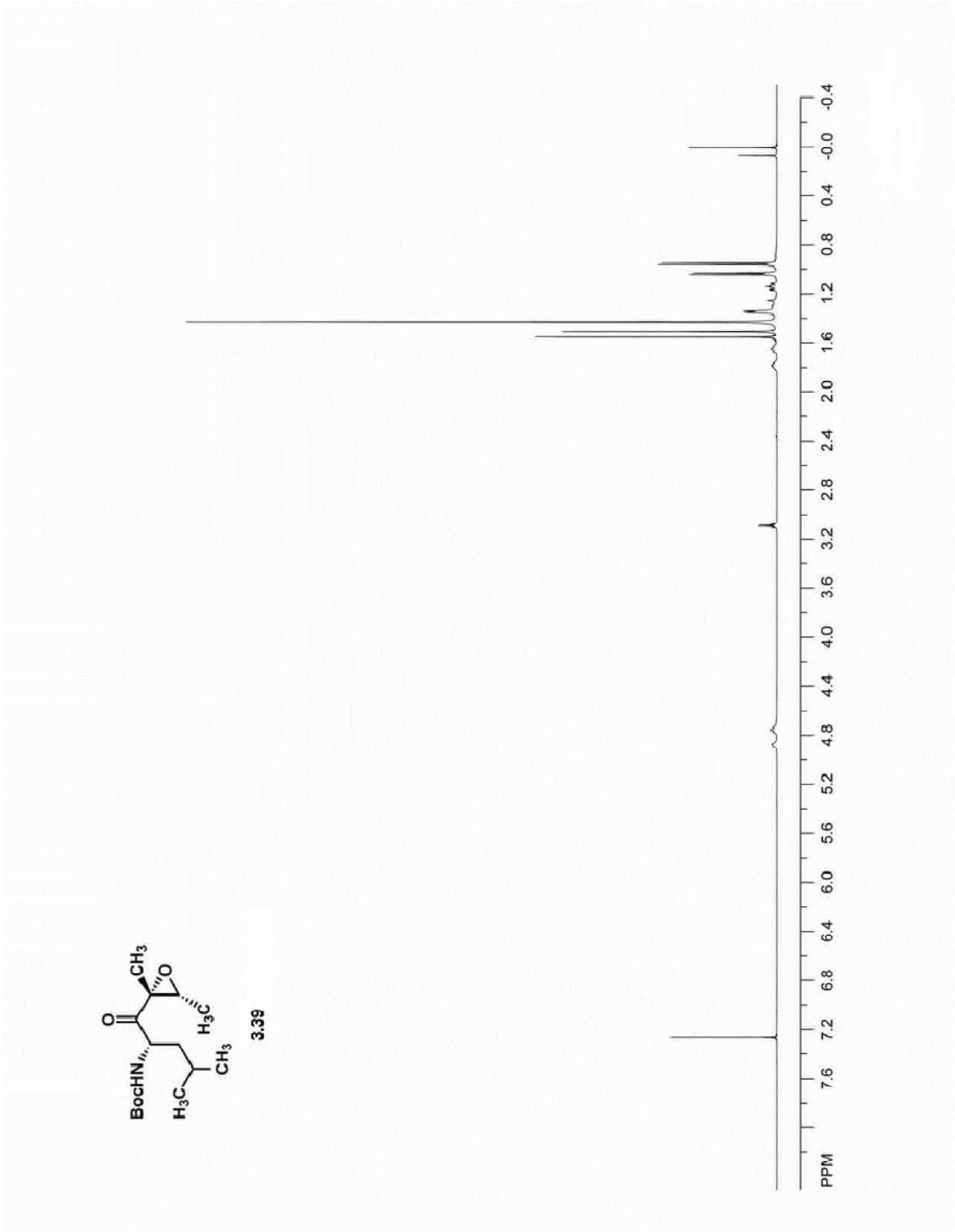
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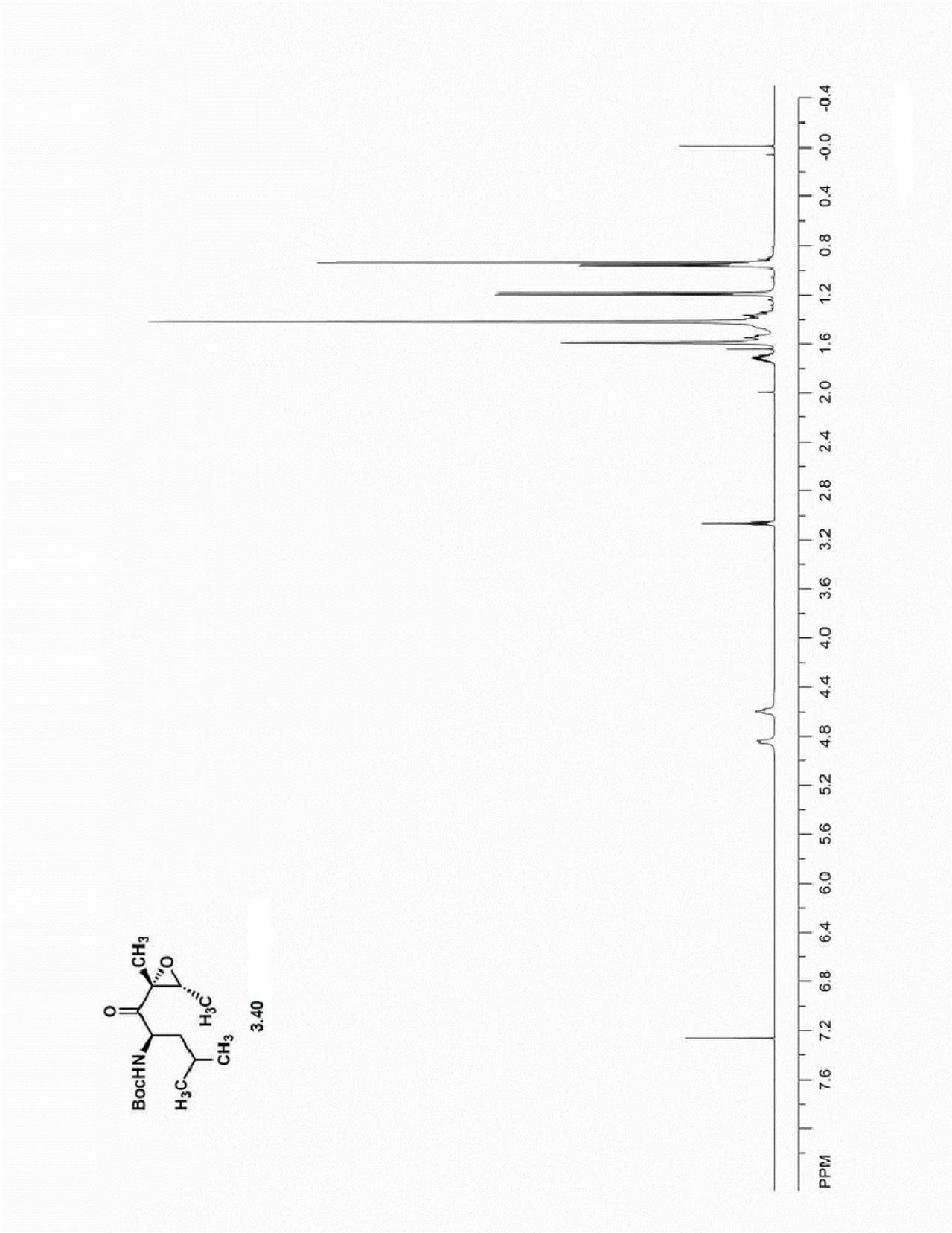
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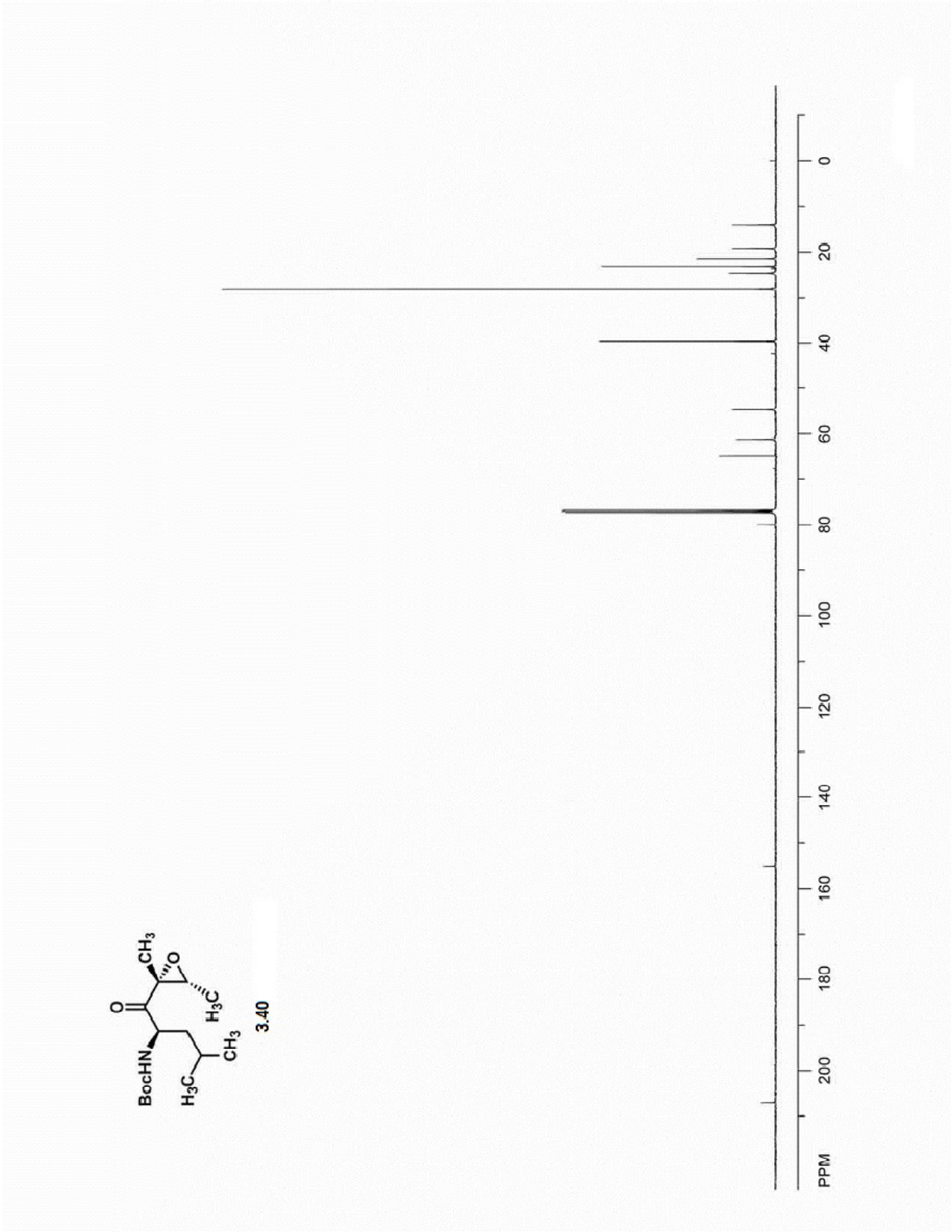
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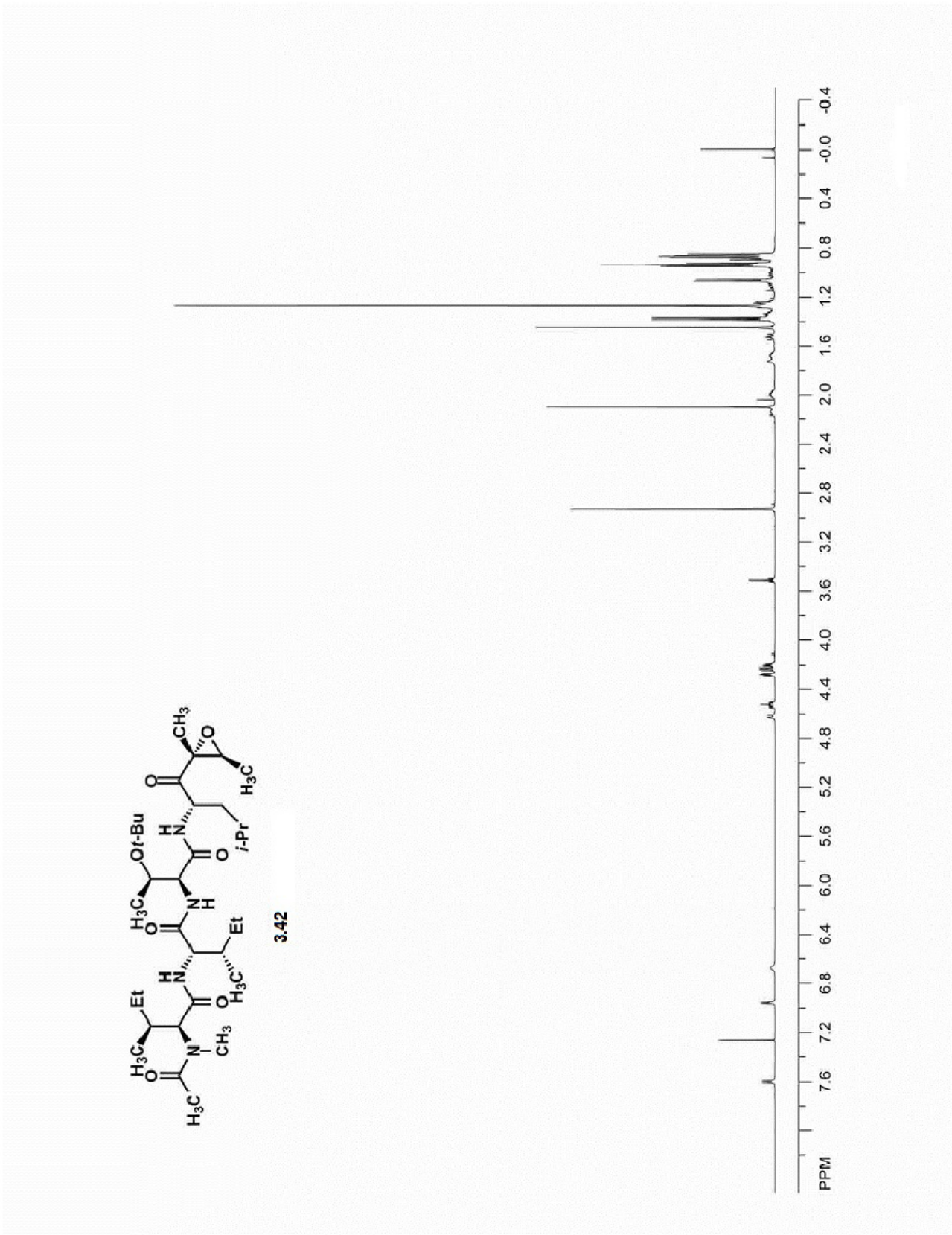
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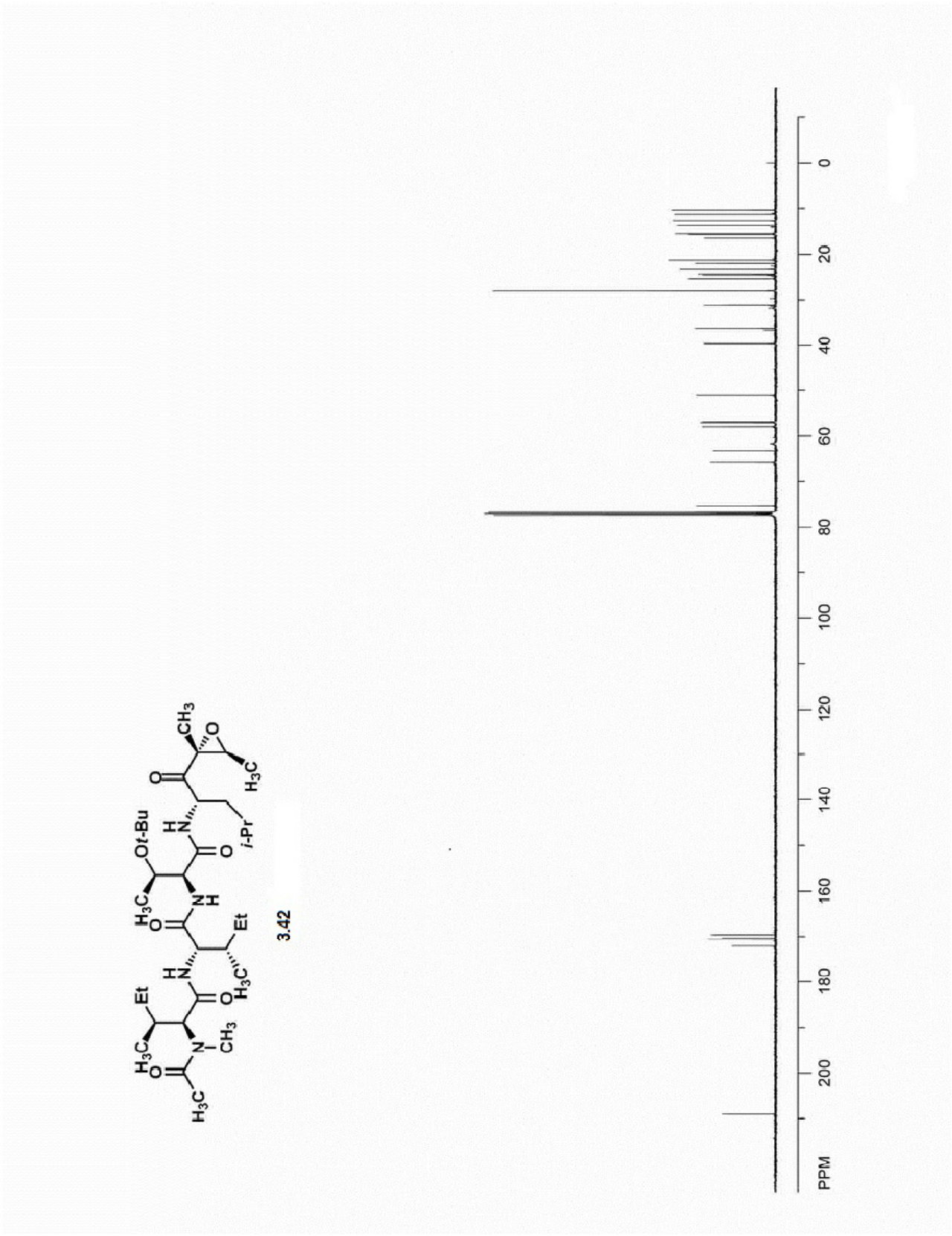
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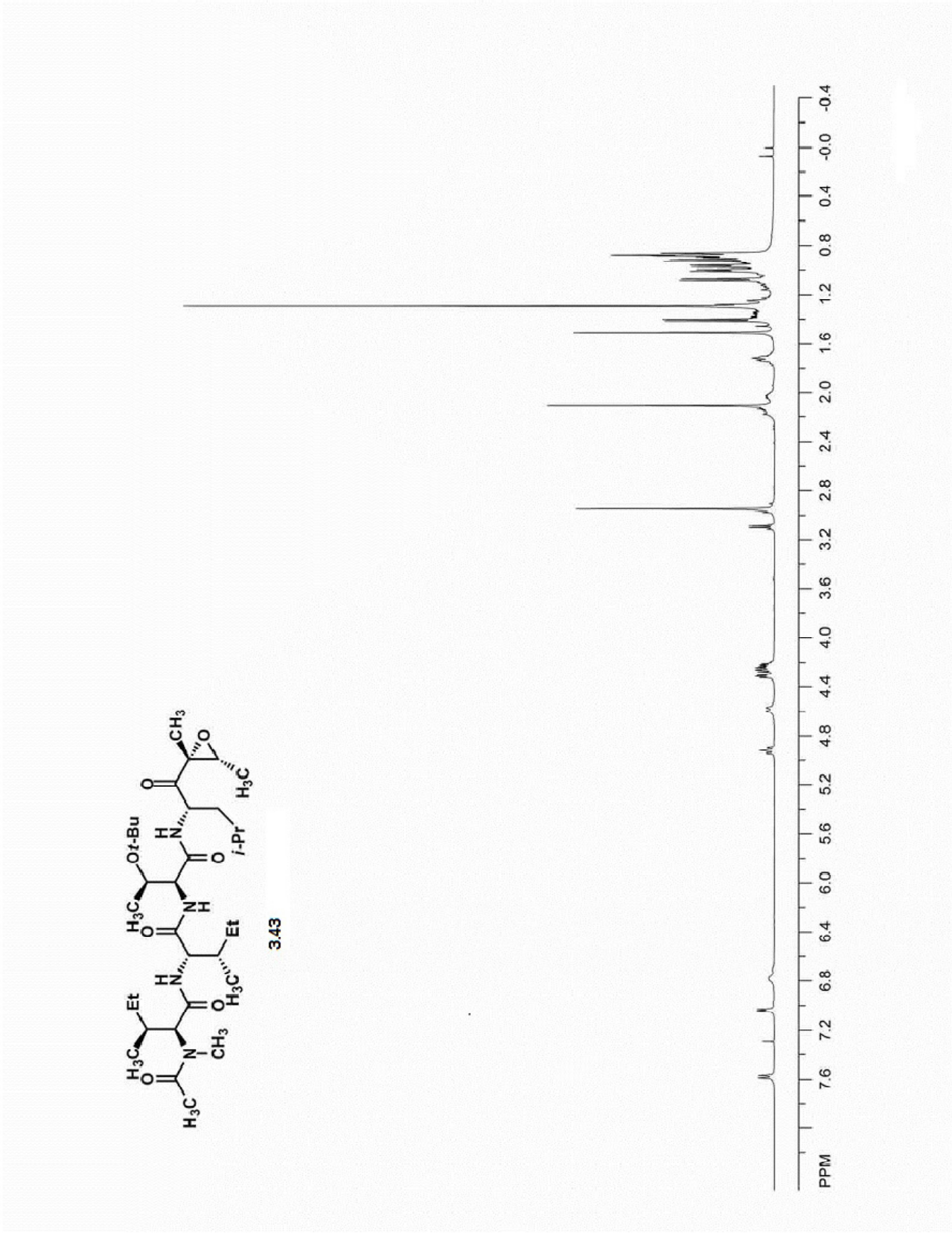
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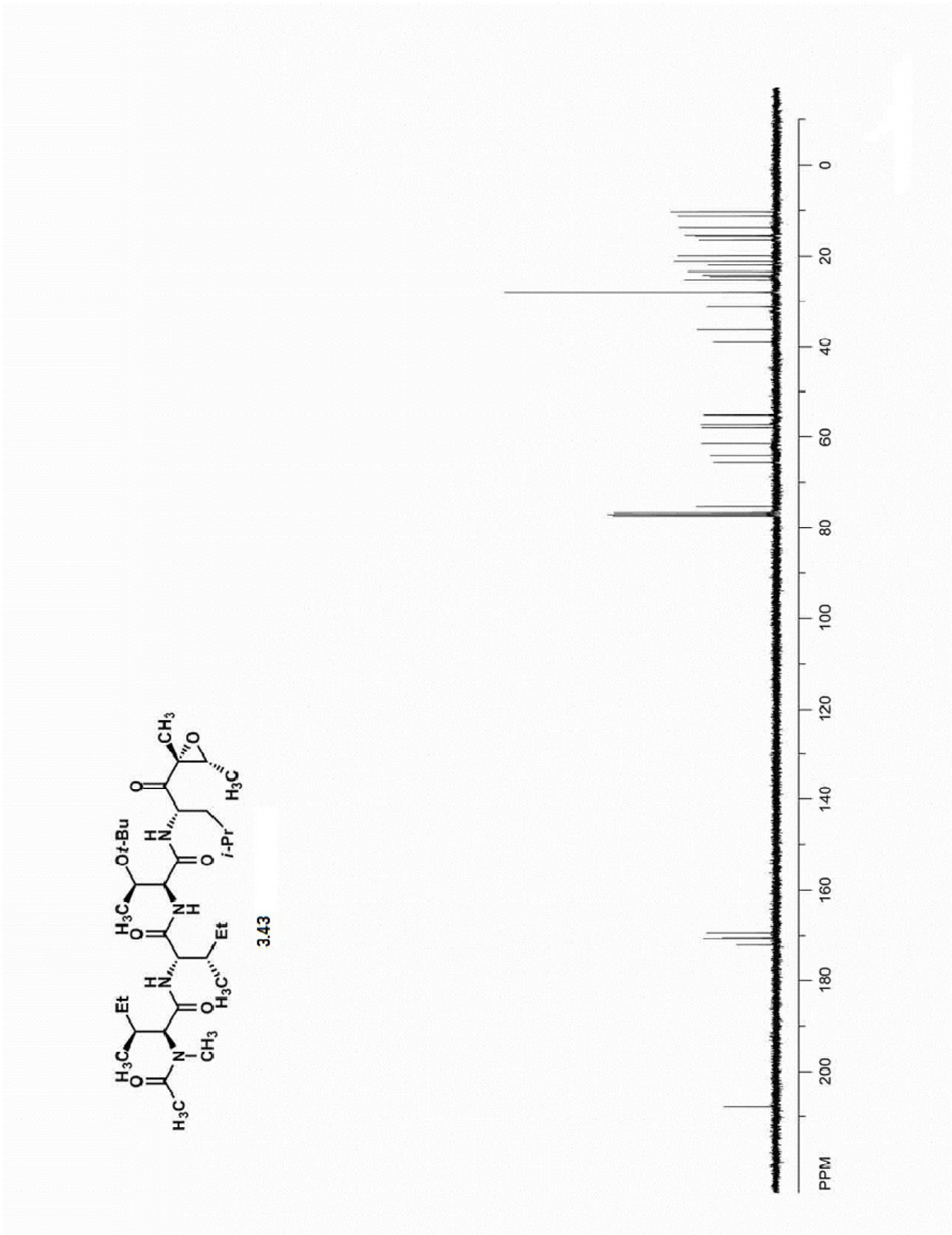
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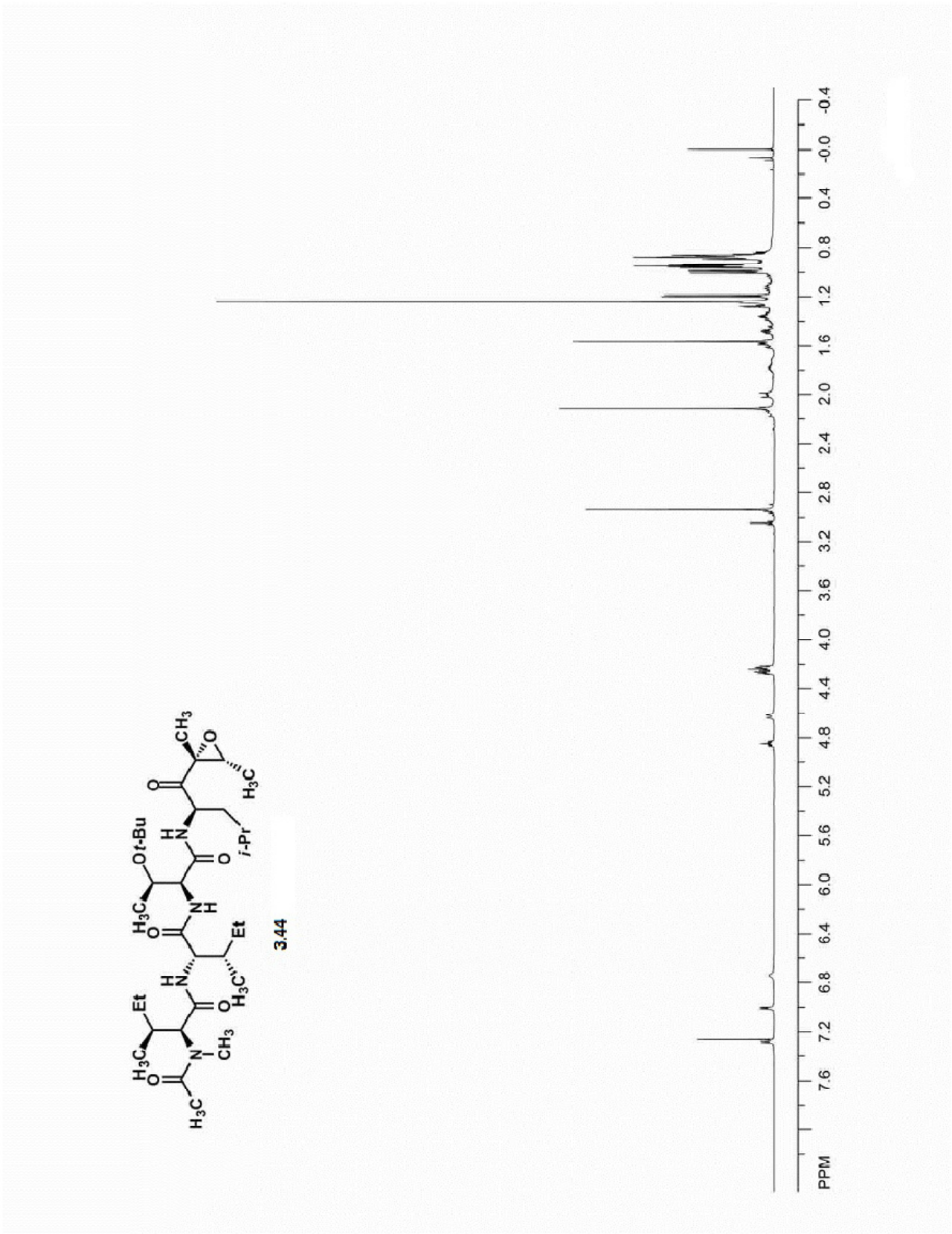

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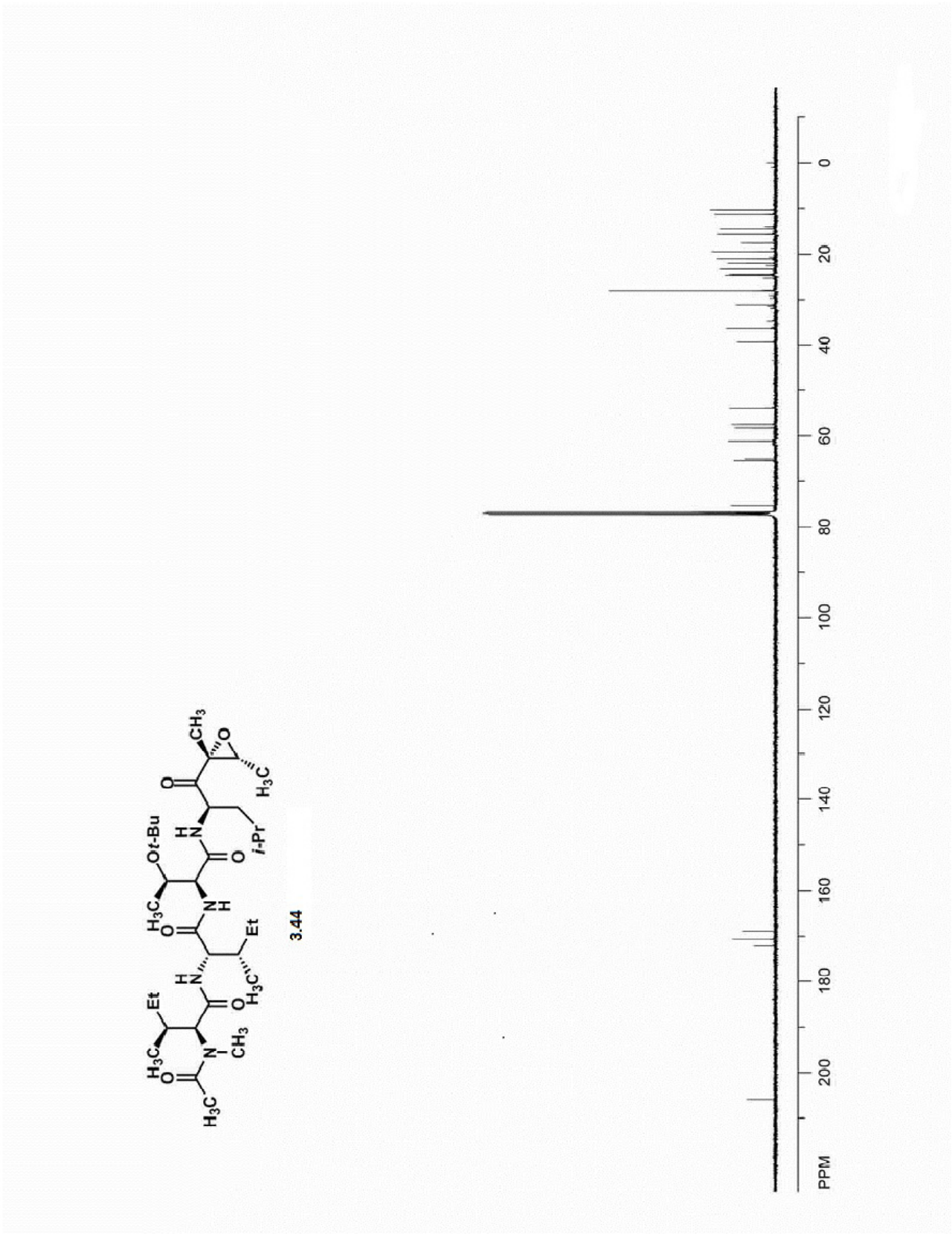
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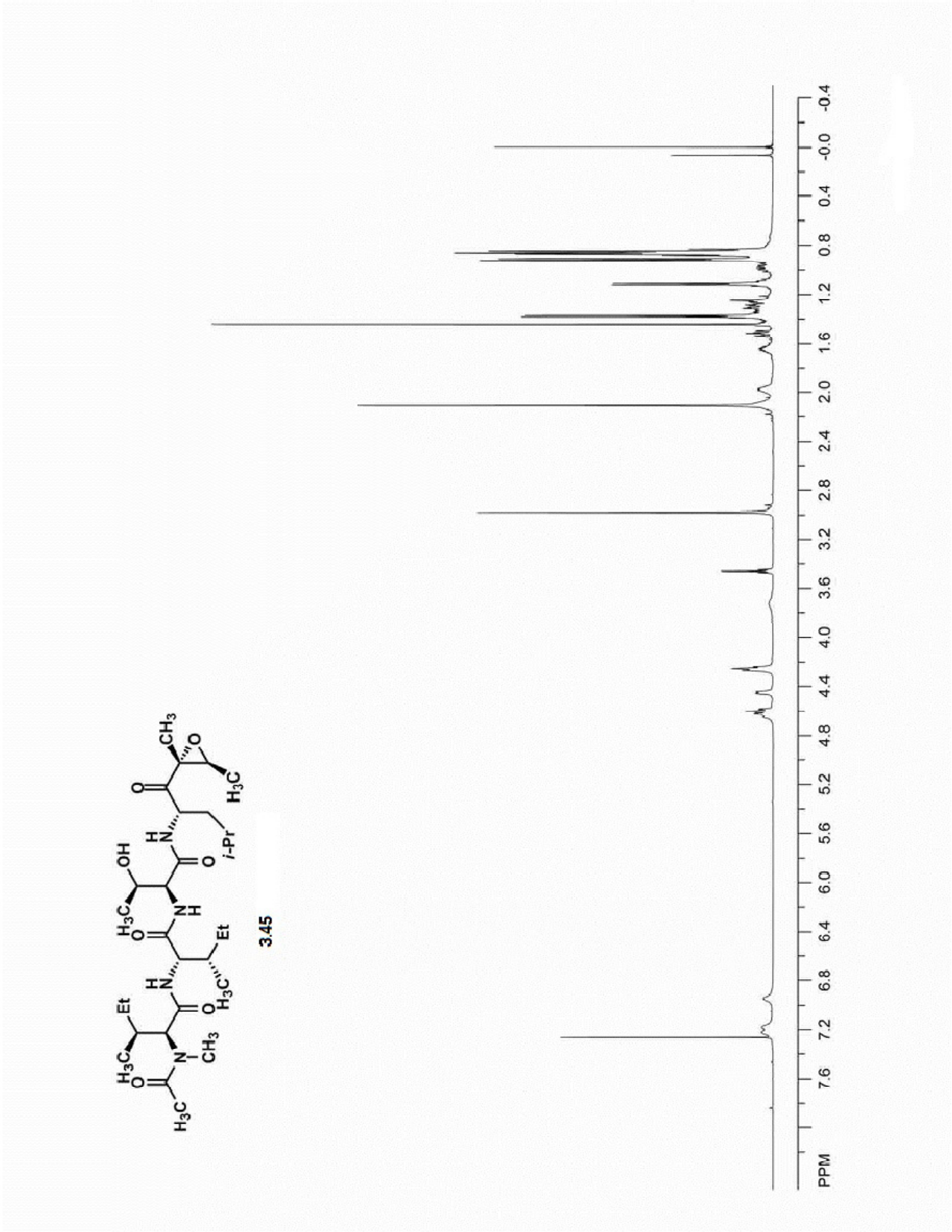
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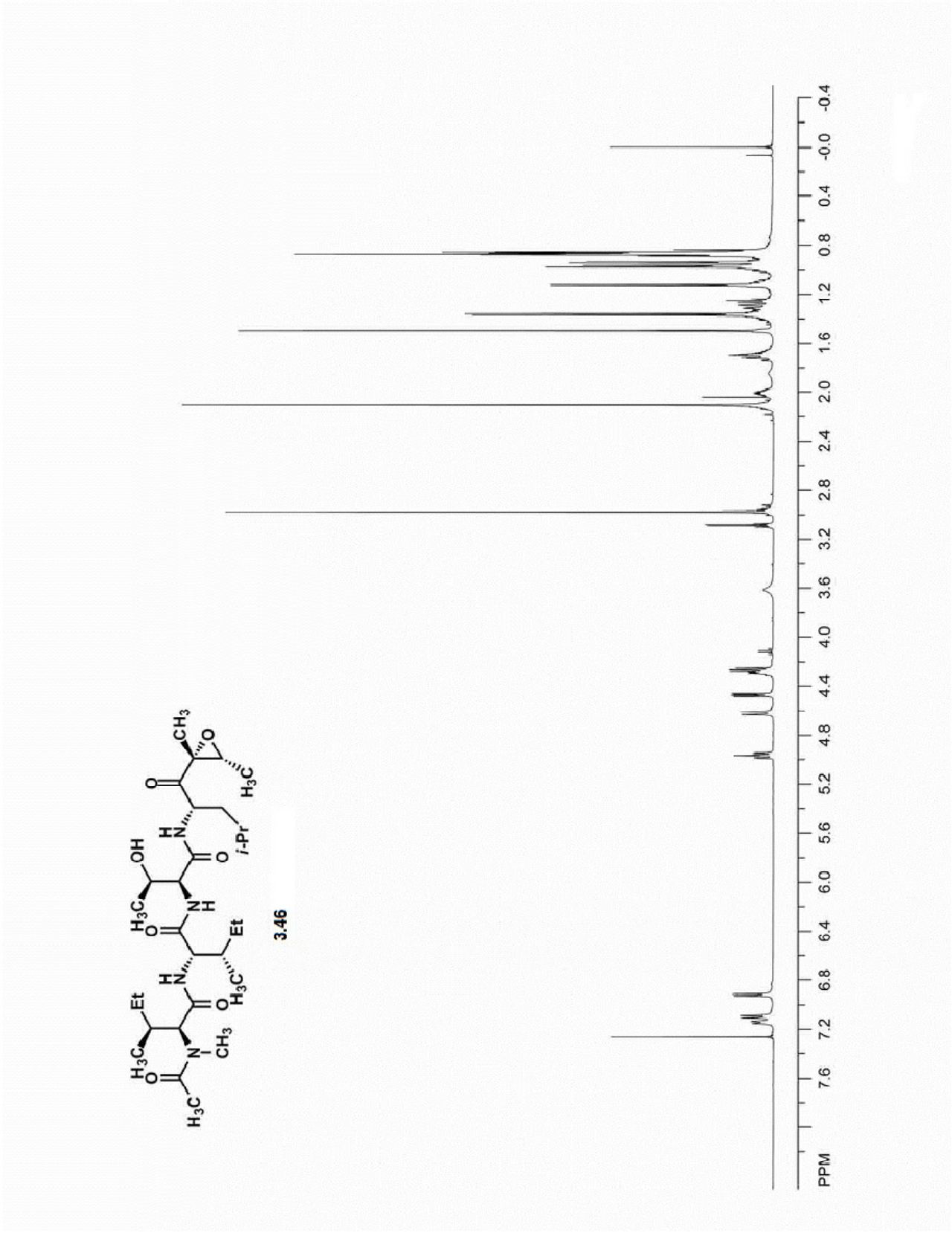
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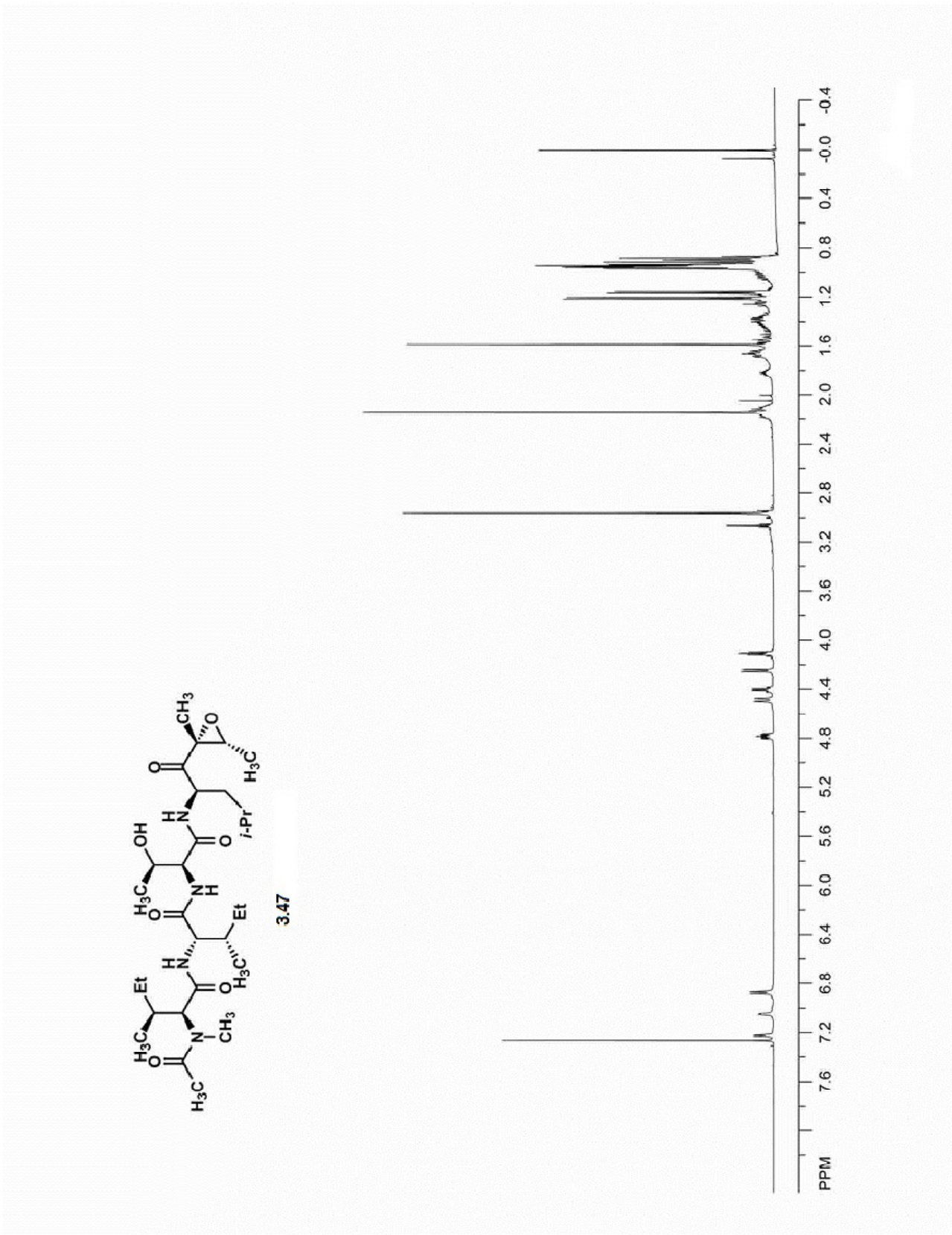
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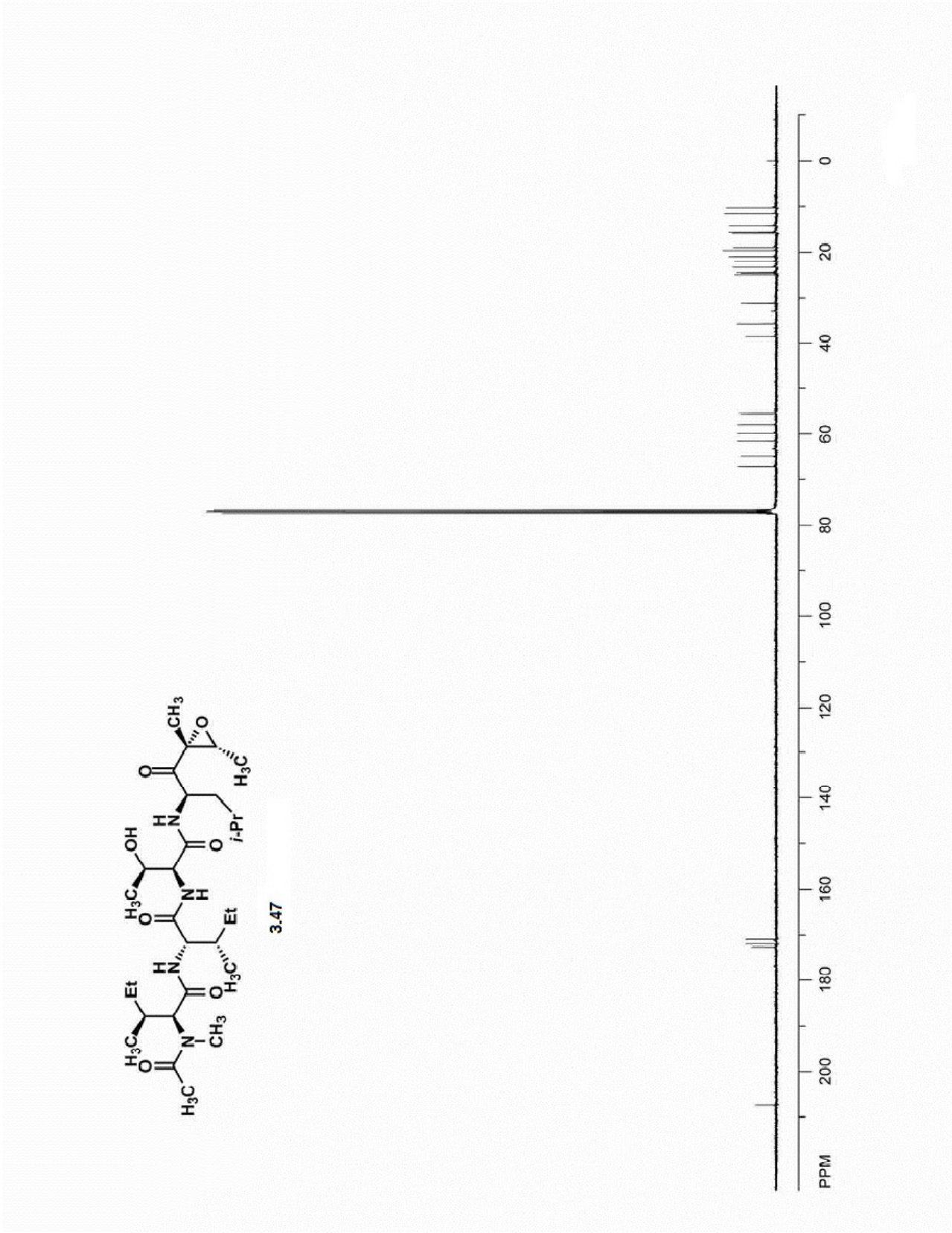
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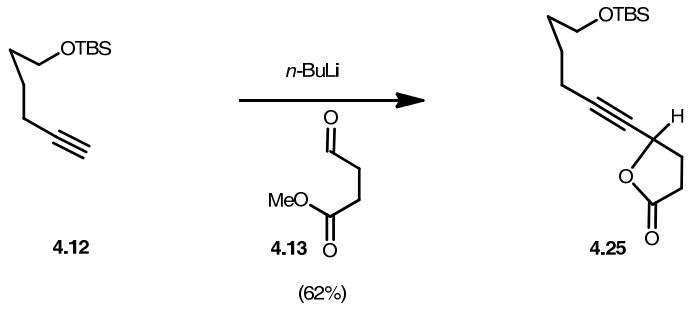
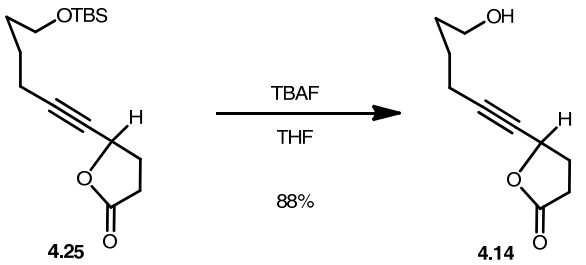
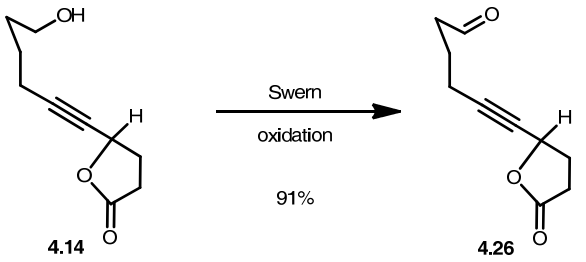
Experimental Chapter Four:



5-(6-(Tert-butyldimethylsilyloxy)hex-1-ynyl)dihydrofuran-2(3H)-one (4.25): To a solution of TBS protected 5-hexyne-1-ol **4.12** (9 g, 42.45 mmol) in dry THF (150 mL), cooled at -78 °C, was added *n*-BuLi (1.6 M, 28 mL, 44.8 mmol) slowly. The reaction was allowed to warm to 0 °C slowly over 30 minutes and then cooled back to -78 °C. A solution of methyl 4-oxobutanoate **4.13** (5 g, 43.1 mmol) in THF (150 mL) was then added to the reaction mixture dropwise. Upon completion of addition, the reaction mixture was slowly warmed to 0 °C over 2h. The reaction was then quenched with saturated NH_4Cl (50 mL) and extracted with Et_2O (3 x 100 mL). The combined organic phase was washed with water (100 mL), brine (50 mL) and dried over anhydrous $MgSO_4$. Evaporation of solvent and FCC purification using 15% EtOAc in hexanes gave the lactone **4.25** (7.78 g, 62% yield) as a colorless oil. IR ν_{max}(neat)/cm^{-1} 2245, 1786; δ_H (400 MHz, $CDCl_3$) 5.16-5.09 (1H, m), 3.65-3.60 (2H, t, J = 5.9 Hz), 2.72-2.60 (1H, m), 2.56-2.44 (2H, m), 2.30-2.22 (3H, m), 1.66-1.50 (4H, m), 0.893 (9H,s), 0.049 (6H, s); δ_C (100 MHz, $CDCl_3$) 176.2, 88.6, 76.6, 69.7, 62.5, 31.8, 30.1, 27.9, 25.9, 24.7, 18.5, 18.3, -5.3; *m/z* (ESIMS) found: 319.2, calc'd for $C_{16}H_{28}NaO_3Si$ $[M+Na]^+$: 319.2.

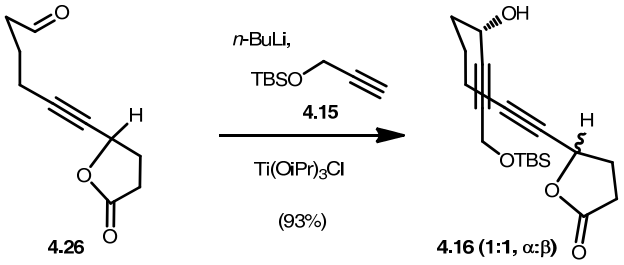


5-(6-Hydroxyhex-1-ynyl)dihydrofuran-2(3H)-one (4.14): To a solution of lactone **4.25** (7 g, 23.6 mmol) in THF (50 mL) was added (25 mL, 25 mmol) TBAF (1.0 M solution in THF) at 0 °C. The reaction mixture was warmed to room temperature and stirred for two hours at room temperature. The reaction was then quenched with saturated NH_4Cl (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic phase was washed with water (50 mL), brine (50 mL) and dried over anhydrous $MgSO_4$. Evaporation of solvent and FCC purification using 75% EtOAc in hexanes gave hydroxyl lactone **4.14** (3.76 g, 88% yield) as a colorless oil. IR ν_{max}(neat)/cm^{-1} 3424, 2244, 1782; δ_H (400 MHz, $CDCl_3$) 5.18-5.08 (1H, m), 3.66 (2H, t, *J* = 3.0 Hz), 2.72-2.60 (1H, m), 2.56-2.44 (2H, m), 2.30-2.22 (3H, m), 1.80(1H, s), 1.71-1.56 (4H, m); δ_C (100 MHz, $CDCl_3$) 176.4, 88.3, 76.7, 69.6, 62.1, 31.6, 30.0, 27.9, 24.5, 18.4; *m/z* (ESIMS) found: 205.1, calc'd for $C_{10}H_{14}NaO_3$ $[M+Na]^+$: 205.1.



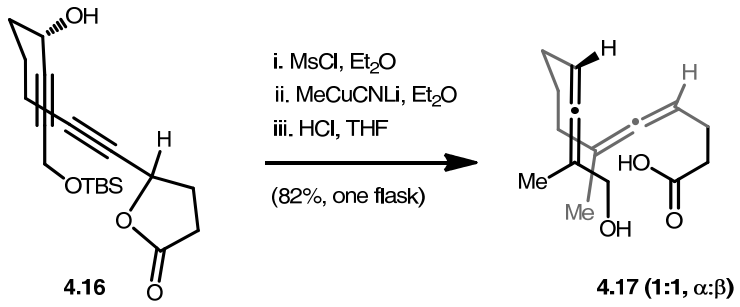
6-(5-Oxotetrahydrofuran-2-yl)hex-5-ynal (4.26): A solution of oxalyl chloride (1.1 mL, 12.6 mmol) in DCM (25 mL) was cooled to -78 °C. To that DMSO (1.75 mL, 24.7 mmol) was added slowly and stirred for 15 min at -78 °C. Then the alcohol **4.14** (1.5 g,

8.23 mmol) in DCM (5 mL) was added slowly and stirred for 15 min when Et_3N (5.7 mL, 41.2 mmol) was added. The reaction mixture was then warmed to 0 °C and allowed to stir for additional 30 min. The reaction was then quenched with water (15 mL) and extracted with DCM (2 x 50 mL). The combined organic phase was washed with water (15 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvent and FCC purification using 40% EtOAc in hexanes gave **4.26** (1.35 g, 91% yield) as a colorless oil. IR ν_{max}(neat)/cm^{-1} 2243, 1779, 1720; δ_H (400 MHz, $CDCl_3$) 9.81 (1H, t, J = 0.49 Hz), 5.18-5.08 (1H, m), 2.72-2.44 (5H, m), 2.36-2.20 (3H, m), 1.90-1.82 (2H, m); δ_C (100 MHz, $CDCl_3$) 201.5, 176.1, 87.3, 77.6, 69.4, 42.6, 30.0, 27.9, 20.6, 18.1; *m/z* (ESIMS) found: 181.1, calc'd for $C_{10}H_{13}O_3$ $[M+H]^+$: 181.1.



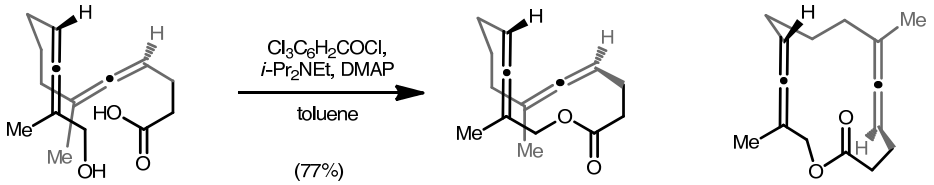
5-(9-(Tert-butyldimethylsilyloxy)-6-hydroxynona-1,7-diynyl)dihydrofuran-2(3H)-one (4.16): To a solution of TBS protected propargyl alcohol **4.15** (1.78 g, 10.5 mmol) in THF (45 mL) was added *n*-BuLi (2.5 M, 3.9 mL, 9.75 M) slowly at -40 °C. The reaction was slowly warmed up to room temperature and then cooled back to -40 °C. Aldehyde **4.26** (1.35 g, 7.5 mmol) in 10 mL THF was then added slowly to the reaction. The reaction mixture was then slowly warmed to room temperature over one hour. The reaction was then quenched with saturated NH_4Cl (20 mL) and extracted with Et_2O (3 x 100 mL). The combined organic phase was washed with water (50 mL), brine (50 mL) and dried over anhydrous $NaSO_4$. Evaporation of solvent and FCC purification using

30% EtOAc in hexanes gave bis[alkyne]s **4.16** (2.46 g, 1:1, 94% yield) as a colorless oil. IR ν_{max}(neat)/cm^{-1} 3415, 2243, 1778; δ_H (400 MHz, $CDCl_3$) 5.18-5.08 (1H, m), 4.48-4.40 (1H, m), 4.37-4.33 (2H,m), 2.72-2.60 (1H, m), 2.56-2.44 (2H, m), 2.36-2.20 (3H, m), 1.88-1.64 (5H, m), 0.91(9H, s), 0.12(6H, s); δ_C (100 MHz, $CDCl_3$) 176.2, 88.0, 85.3, 83.9, 77.98, 69.6, 61.9, 51.7, 36.5, 30.1, 27.9, 25.8, 23.8, 18.4, 18.3, -5.1; *m/z* (ESIMS) found: 373.2, calc'd for $C_{19}H_{30}NaO4Si$ $[M+Na]^+$: 373.2.



13-Hydroxy-6,12-dimethyltrideca-4,5,10,11-tetraenoic acid (4.17): To a solution of **4.16** (2.7 g, 7.5 mmol) in 50 mL ether was added Et_3N (1.56 mL, 11.2 mmol) and MsCl (0.87 mL, 11.2 mmol) respectively at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h at room temperature. The reaction was then cooled back to 0 °C and to that was added a solution of methyl cyanocuprate, prepared from CuCN (4 g, 44.7 mmol) and MeLi (28 mL, 44.8 mmol) in 75 ml Et_2O. The reaction mixture was then warmed to room temperature and stirred for 2 h. The reaction was then diluted with 75 ml THF and to that 10% HCl solution (12ml) was added and stirred for additional 5 h at room temperature. The reaction mixture was then diluted with Et_2O (200 ml), washed with water (3 x 50 ml) and dried over anhydrous $NaSO_4$.. Evaporation of solvent and FCC purification using 80% EtOAc in hexanes gave seco acids **4.17** (1.54 g, 1:1, 86% yield) as a colorless oil. IR ν_{max}(neat)/cm^{-1} 3342, 1966, 1710; δ_H (400 MHz, $CDCl_3$) 5.34-

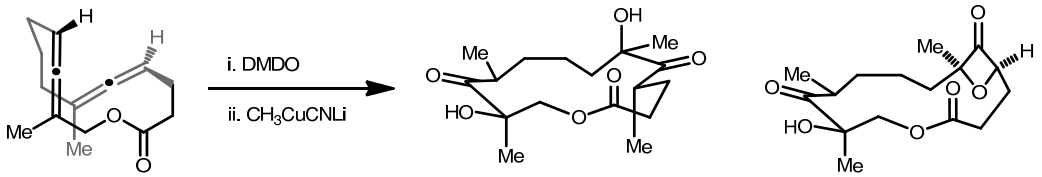
5.24 (1H, m), 5.14-5.06 (1H, m), 4.01 (2H, d, *J* = 3.1Hz), 2.50-2.36 (2H, m), 2.36-2.20 (2H, m), 2.10-1.86 (4H, m), 1.70 (3H, d, *J* = 2.8 Hz), 1.66 (3H, d, *J* = 2.8 Hz), 1.57-1.44 (2H, m); δ_C (100 MHz, $CDCl_3$) 200.9(200.9), 199.3(199.3), 177.9(177.8), 101.4(101.3), 100.6(100.5), 94.3(94.1), 89.0(89.0), 63.7(63.7), 33.3(33.3), 32.9(32.8), 28.7(28.6), 26.9(26.7), 24.0(23.9), 19.4(19.3), 15.7; *m/z* (ESIMS) found: 251.2, calc'd for $C_{15}H_{23}O_3$ $[M+H]^+$: 251.2.



4.17 **4.7** **4.10**

To a solution of seco acids **4.17** (500 mg, 2 mmol) in 20 mL toluene was added N,N-diisopropylethylamine (1.83 mL, 10 mmol) and 2,4,6 trichlorobenzoyl chloride (2.44 g, 10 mmol) were added respectively to above solution. The solution was stirred for 6 h at room temperature. 4-dimethylaminopyridine (DMAP, 2.45 g, 20 mmol) in 180 mL toluene was prepared in another flask. The actived ester was added dropwise to the DMAP solution using syringe pump over 2 h and stirred for 2 more hours at room temperature. The reaction was quenched with NH_4Cl (20 mL). The organic layer was decanted and the aqueous layer was extracted with Et_2OAc twice (100 mL). All the organic layers were combined and dried over Na_2SO_4. The crude product was purified by flash chromatography (4% EtOAc/Hexanes) to yield macro lactone **4.7** and **4.10** (354 mg, 1:1, 77% yield) as a colorless oil. After a second column 70 mg of **4.7** and 71 mg of **4.10** were obtained with 205 mg of mixture. **Bis[allene] macrolactone (4.7):** IR ν_{max}(neat)/cm^{-1} 1969, 1742; δ_H (400 MHz, $CDCl_3$) 5.30-5.18 (1H, m), 5.08-4.96 (1H, m),

4.84 (1H, d, *J* = 11.6 Hz), 4.23 (1H, dd, *J* = 11.6, 2.4 Hz), 2.56-2.22 (4H, m), 2.10-1.74 (4H, m), 1.75 (3H, d, *J* = 2.8 Hz), 1.66 (3H, d, *J* = 2.8 Hz), 1.64-1.42 (2H, m); δ_C (100 MHz, $CDCl_3$) 202.8, 200.8, 172.8, 101.3, 97.6, 91.9, 89.9, 66.2, 33.4, 32.5, 26.3, 24.8, 24.1, 19.8, 16.8; *m/z* (ESIMS) found: 255.1, calc'd for $C_{15}H_{20}NaO_2$ $[M+23]^+$: 255.1. **Iso-bis[allene] macrolactone (4.10):** IR ν_{max}(neat)/cm^{-1} 1968, 1740; δ_H (400 MHz, $CDCl_3$) 5.26-5.18 (1H, m), 5.06 (1H, d, *J* = 11.2 Hz), 5.04-4.94 (1H, m), 4.10 (1H, dd, *J* = 11.2, 2.4 Hz), 2.52-2.26 (4H, m), 2.66-1.80 (4H, m), 1.76 (3H, d, *J* = 3.2Hz), 1.67 (3H, d, *J* = 2.8 Hz), 1.64-1.36 (2H, m); δ_C (100 MHz, $CDCl_3$) 203.9, 201.8, 172.7, 100.9, 97.3, 91.6, 89.3, 66.2, 34.2, 32.9, 27.1, 26.0, 25.6, 19.8, 17.1; *m/z* (ESIMS) found: 233.2, calc'd for $C_{15}H_{21}O_2$ $[M+H]^+$: 233.2.

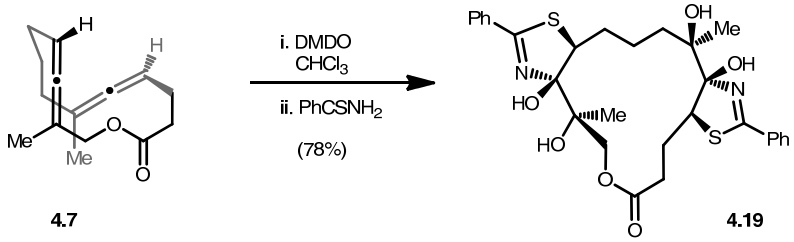


4.7 **4.9** (22%) **4.18** (17%)

To a solution of freshly prepared dimethyldioxirane (DMDO) in $CHCl_3$ (12.9 mL, 2.586 mmol) was added bis[allene] macrolactone **4.17** (120 mg, 0.517 mmol) in $CHCl_3$ dropwise at -40 °C. The reaction was stirred under nitrogen and let to warm to rt over 2 h. Solvent was evaporated and the resulting bis[SDE] was used as such for the next step. Lower order methyl cyanocuprate was prepared by adding MeLi (3.2 mL, 5.12 mmol) to a slurry of CuCN (460 mg, 5.86 mmol) in diethyl ether (50 mL) at -40 °C and then warming to 0 °C. The cuprate was cooled back to -40 °C and to that a ether solution (2 ml) of bis[SDE] was added slowly. The reaction was warmed to room temperature over 2 h. The reaction was then quenched with saturated NH_4Cl (10 mL) and extracted with

Et_2O (3 x 20 mL). The combined organic phase was washed with water (10 mL), brine (10 mL) and dried over anhydrous $MgSO_4$. Evaporation of solvent and FCC purification using 15% EtOAc in hexanes gave a mixture of **4** and **13** (63 mg) as colorless oil. Based on 1.4:1 ratio of the product mixture by ^1H NMR, the yield calculated for **4** and **13** are 22% and 16% respectively. **4.9** (white solid) and **4.18** (white solid) were then separated by 4 more FCC purification. **Model macrolactone (4.9):** MP 118 °C; IR ν_{max}(neat)/cm^{-1} 3473, 2938, 1737, 1706, 1457, 1374; δ_H (500 MHz, $CDCl_3$) 4.37 (1H, d, *J* = 12.0 Hz), 4.28 (1H, s), 4.22 (1H, d, *J* = 12.0 Hz), 4.04 (1H, s), 2.98-2.92 (1H, m), 2.78-2.72 (1H, m), 2.38 (2H, *J* = 6.5 Hz), 2.10-2.02 (1H, m), 1.90-1.82 (1H, m), 1.76-1.66 (2H, m), 1.44 (3H, s), 1.41 (3H, s), 1.38-1.24 (3H, m), 1.15 (3H, d, *J* = 7.0 Hz), 1.12 (3H, d, *J* = 7.0 Hz), 0.88-0.80 (1H, m); δ_C (125 MHz, $CDCl_3$) 217.8, 214.4, 172.1, 78.9, 77.9, 68.9, 41.1, 39.0, 38.3, 35.7, 31.6, 28.0, 25.6, 22.0, 20.8, 20.5, 18.6; *m/z* (ESIMS) found: 351.3, calc'd for $C_{17}H_{28}NaO_6$ $[M+Na]^+$: 351.2. Slow evaporation of a sample of **4.9** dissolved in 0.2 mL hexanes and minimum amount of DCM gave crystals suitable for single crystal X-ray analysis. **Oxetanone macrolactone (4.18)**: MP 151 °C; IR ν_{max}(neat)/cm^{-1} 3477, 2928, 1811, 1740, 1709, 1462; 5.42 (1H, dd, *J* = 4.5, 3.0 Hz), 4.35 (1H, d, *J* = 12.0 Hz), 4.25 (1H, s), 4.14 (1H, d, *J* = 12.0 Hz), 3.04-2.96 (1H, m), 2.51 (1H, ddd, *J* = 18.0, 8.0, 3.0 Hz), 2.36 (1H, ddd, *J* = 16.0, 10.0, 3.5 Hz), 2.20-2.08 (2H, m), 2.06-1.98 (1H, m), 1.76-1.68 (1H, m), 1.56- 1.50 (1H, m), 1.45 (6H, s), 1.36-1.28 (2H, m), 1.15 (3H, *J* = 6.5 Hz), 0.90-0.86 (1H, m); δ_C (125 MHz, $CDCl_3$) 215.7, 206.8, 172.3, 105.6, 96.0, 77.8, 68.9, 40.1, 36.2, 33.9, 30.6, 24.4, 23.2, 22.2, 21.6, 20.3.; *m/z* (ESIMS) found: 335.2, calc'd for $C_{16}H_{24}NaO_6$ $[M+Na]^+$: 335.1. Slow evaporation of a sample of **4.18** dissolved

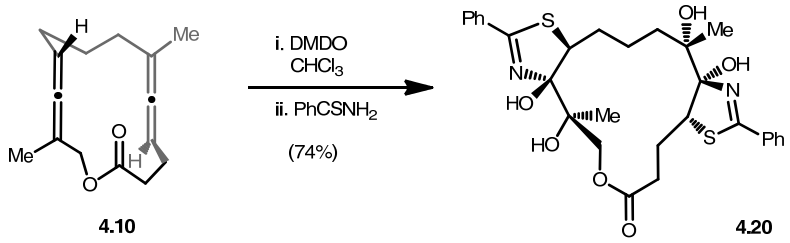
in 0.2 mL hexanes and minimum amount of DCM gave crystals suitable for single crystal X-ray analysis.



4.7 4.19

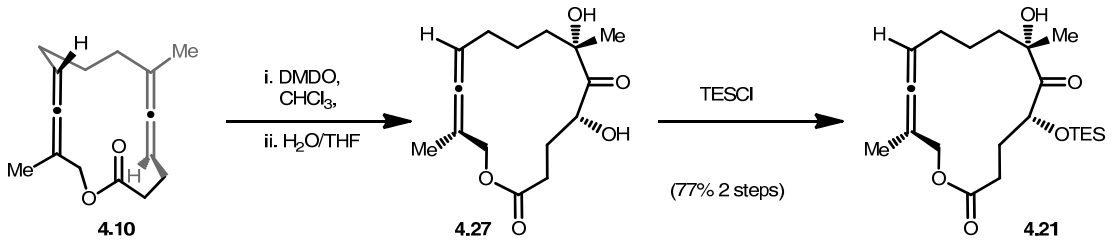
Bis[thiazoline] macrolactone (4.19): To a solution of freshly prepared dimethyldioxirane (DMDO) in $CHCl_3$ (3.22 mL, 0.645 mmol) was added bis[allene] macro lactone **4.7** (30 mg, 0.129 mmol) in $CHCl_3$ dropwise at -40 °C. The reaction was stirred under nitrogen and let to warm to rt over 2 h. Solvent was evaporated and the resulting bis[SDE] was dissolved in chloroform. thiobenzamide (70mg, 0.517mmol) was added at 0 °C and the reaction mixture was warmed to room temperature and stirred for 6h. Evaporation of the solvent followed by FCC using 15 % EtOAc in Hexanes gave the bis[thiazoline] **4.19** (58 mg, 78% yield) as a white solid. MP 78 °C ; IR ν_{max}(neat)/cm^{-1} 3442, 1735, 1604, 1576; δ_H (500 MHz, $CDCl_3$) 7.86-7.78 (4H, m), 7.52-7.38 (6H, m), 4.34 (1H, d, *J* = 11.6 Hz), 4.20 (1H, d, *J* = 11.6 Hz), 4.11 (1H, dd, *J* = 9.6, 3.8 Hz), 4.02-3.96 (1H, m), 3.73 (1H, s), 3.61 (1H, s), 3.18 (1H, s), 2.93 (1H, s), 2.70-2.58 (1H, m), 2.40-2.20 (3H, m), 2.10-1.96 (1H, m), 1.94-1.78 (1H, m), 1.76-1.54 (3H, m), 1.29 (3H, s), 1.30-1.20 (1H, m), 1.26 (3H, s); δ_C (125 MHz, $CDCl_3$) 171.3, 169.5, 168.8, 132.5, 132.4, 132.04, 131.97, 128.6, 128.5, 128.4, 128.3, 110.4, 110.0, 77.8, 76.2, 66.4, 53.7, 53.3, 36.2, 34.3, 33.0, 27.6, 27.0, 22.0, 21.5; *m/z* (ESIMS) found: 571.2, calc'd for $C_{29}H_{35}N_2O_6S_2$ $[M+H]^+$: 571.2. Slow evaporation of a sample of **4.19** dissolved in 0.2 mL

hexanes and minimum amount of DCM gave crystals suitable for single crystal X-ray analysis.



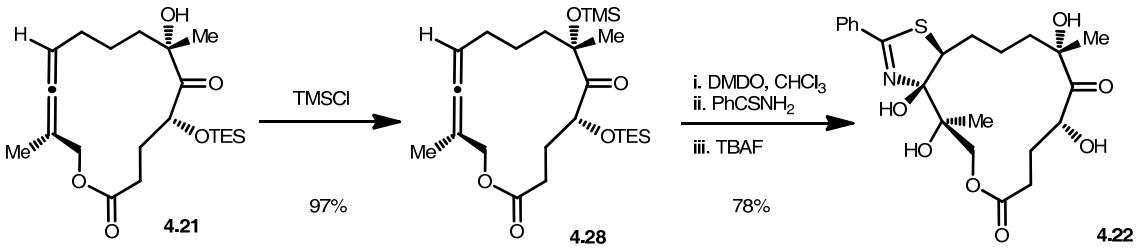
4.10 4.20

Iso-bis[thiazoline] 4.20: (55 mg, 74% yield) was prepared, using same procedure from bis[allene] macrolactone **4.10** (30 mg, 0.129 mmol). MP 158 °C; IR ν_{max}(neat)/cm^{-1} 3416, 1734, 1605, 1577; δ_H (400 MHz, $CDCl_3$) 7.84 (2H, d, *J* = 7.6 Hz), 7.80 (2H, d, *J* = 7.6 Hz), 7.54-7.34 (6H, m), 4.75 (1H, d, *J* = 11.6 Hz), 4.61 (1H, s), 4.50 (1H, s), 4.34 (1H, dd, *J* = 10.4, 2.8 Hz), 3.94 (1H, dd, *J* = 10.4, 4 Hz), 3.75 (1H, d, *J* = 4.0 Hz), 3.59 (1H, s), 3.05 (1H, s), 3.06-2.94 (1H, m) 2.58-2.40 (1H, m), 2.38-2.22 (1H, m), 2.22-1.88 (4H, m), 1.80-1.66 (1H, m), 1.60-1.40 (1H, m) 1.33 (3H, s), 1.22-1.06 (1H, m), 1.10 (3H, s); δ_C (100 MHz, $CDCl_3$) 172.6, 170.1, 168.1, 132.5, 132.3, 132.0, 131.9, 128.6, 128.5, 128.4, 128.3, 112.3, 110.3, 78.1, 76.7, 66.8, 50.0, 49.1, 34.6, 33.9, 33.6, 28.1, 21.5, 20.7, 20.6; *m/z* (ESIMS) found: 571.2, calc'd for $C_{29}H_{35}N_2O_6S_2$ $[M+H]^+$: 571.2. Slow evaporation of a sample of **4.20** dissolved in 0.2 mL hexanes and minimum amount of DCM gave crystals suitable for single crystal X-ray analysis.



4.10 4.27 4.21

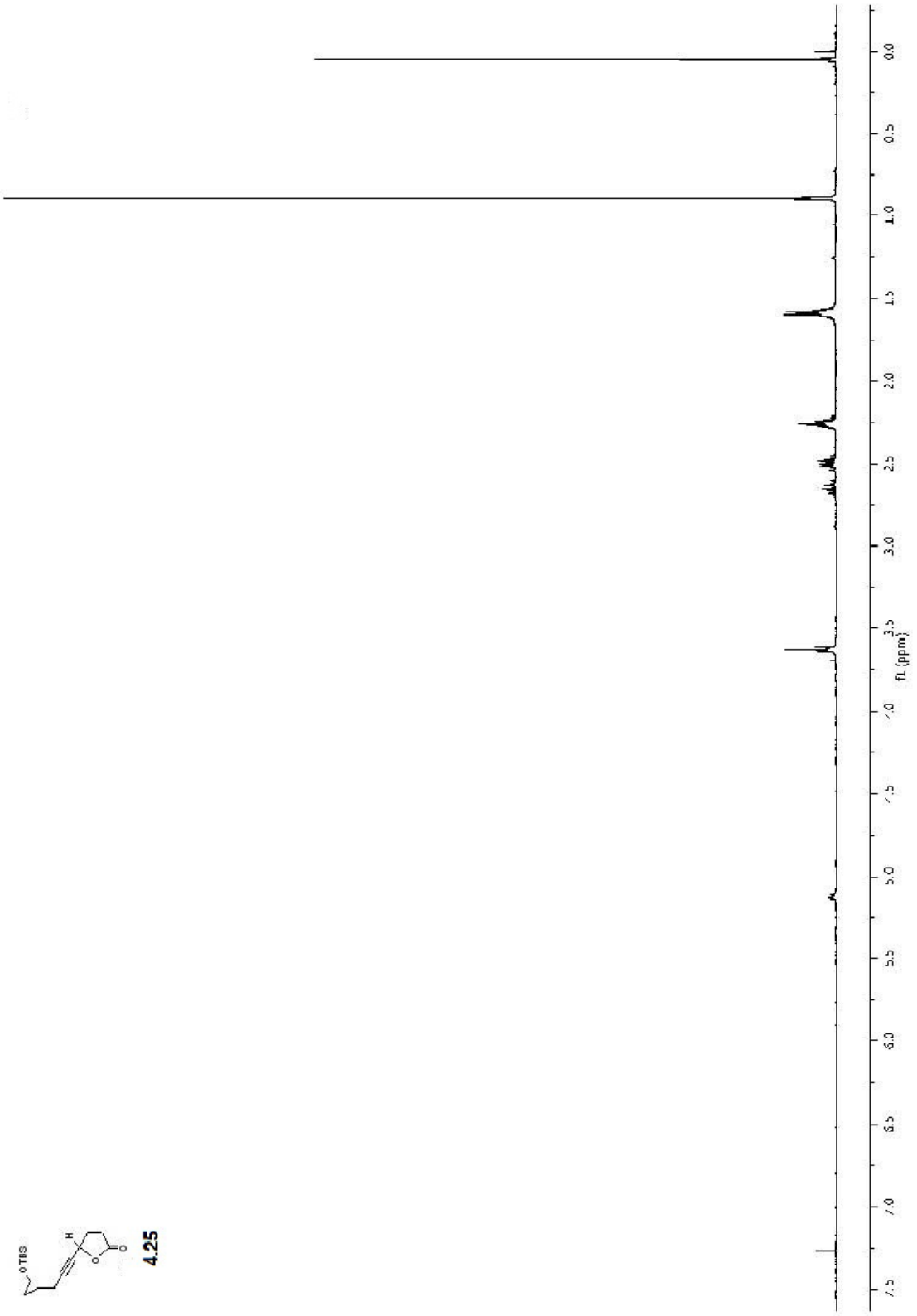
TES-allene macrolactone (4.21): To a solution of freshly prepared dimethyldioxirane (DMDO) in $CHCl_3$ (2.7 mL, 0.593 mmol) was added iso-bis[allene] macrolactone **4.10** (50 mg, 0.216 mmol) in $CHCl_3$ dropwise at -40 °C. The reaction was stirred under nitrogen and let to warm to 0 °C over 1 h. Solvent was evaporated and the resulting bis[SDE] was dissolved in 5 mL THF/water (1:1) solution at 0 °C and stirred for 30 minutes at 0 °C. The reaction mixture was then extracted in diethyl ether (3 x 20 mL). Evaporation of the solvent followed by FCC using 25% EtOAc in Hexanes gave the diol **4.27** (47mg, 78% yield) as a colorless oil. To a solution of diol **4.27** (38 mg, 0.135 mmol) in DCM (5 mL), cooled to 0 °C, was added imidazole (14 mg, 0.20 mmol), DMAP (2 mg, 0.016 mmol), and TESCl (24.4 mg, 0.16 mmol) at 0 °C. The reaction was stirred 5 minutes at 0 °C. Diluted with DCM (20 mL), washed with water (2 x 5 mL). Evaporation of the solvent followed by FCC using 10% EtOAc/Hexanes gave the compound **4.21** (55 mg, 99% yield) as a white solid. MP 54 °C; IR ν_{max}(neat)/cm^{-1} 3493, 2954, 1971, 1737, 1750; δ_H (500 MHz, $CDCl_3$) 5.28-5.20 (1H, m), 4.69 (1H, dd, *J* = 12.5, 3.5 Hz), 4.44 (1H, dd, *J* = 8.0, 4.0 Hz), 4.21 (1H, s), 4.20 (1H, dd, *J* = 12.0, 2.0 Hz), 2.40-2.28 (2H, m), 2.10-2.02 (2H, m), 1.98-1.90 (1H, m), 1.84-1.76 (1H, m), 1.71 (3H, d, *J* = 2.5 Hz), 1.70-1.60 (2H, m), 1.40 (3H, s), 1.26-1.16 (2H, m), 0.97 (9H, t, *J* = 8.0 Hz), 0.65 (6H, q, *J* = 8.0 Hz); δ_C (125 MHz, $CDCl_3$) 213.0, 202.5, 172.4, 96.6, 93.0, 80.1, 77.1, 64.9, 38.2, 30.0, 29.5, 28.3, 27.3, 23.5, 17.2, 6.9, 5.1. *m/z* (ESIMS) found: 397.1, calc'd for $C_{21}H_{37}O_5Si$ $[M+H]^+$: 397.2.



Diol-thiazoline macrolactone (4.22): To a solution of **4.21** (40 mg, 0.10 mmol) in DCM (5 mL), cooled to 0 °C, was added TEA (20 mg, 0.20 mmol), DMAP (2 mg, 0.016 mmol), and TMSCl (16 mg, 0.144 mmol) at 0 °C. The reaction was warmed to room temperature and stirred for 1 h. Diluted with DCM (20 mL), washed with water (2 x 5 mL). Evaporation of the solvent followed by FCC using 5% EtOAc/Hexanes gave silyl ether **4.28** (46 mg, 97% yield) as a colorless oil. IR ν_{max}(neat)/cm^{-1} 2954, 1970, 1739, 1248, 842; δ_H (400 MHz, $CDCl_3$) 5.20-5.12 (1H, m), 4.76 (1H, dd, *J* = 13.2, 3.2 Hz), 4.50 (1H, t, *J* = 6.0 Hz), 4.15 (1H, dd, *J* = 12.8, 2.4 Hz), 2.54-2.24 (4H, m), 2.14-2.10 (1H, m), 1.98-1.60 (5H, m), 1.70 (3H, d, *J* = 2.4 Hz), 1.39 (3H, s), 0.94 (9H, t, *J* = 8.0 Hz), 0.61 (6H, q, *J* = 8.0 Hz), 0.10 (9H, s); δ_C (100 MHz, $CDCl_3$) 209.9, 202.2, 172.6, 95.9, 92.8, 81.9, 72.8, 64.8, 38.7, 30.4, 29.7, 28.7, 25.7, 23.3, 17.0, 7.0, 5.3, 2.6; *m/z* (ESIMS) found: 491.3, calc'd for $C_{24}H_{44}NaO_5Si_2$ $[M+Na]^+$: 491.3.

To a solution of freshly prepared dimethyldioxirane (DMDO) in $CHCl_3$ (1.3 mL, 0.26 mmol) was added allene **4.28** (50 mg, 0.102 mmol) in $CHCl_3$ dropwise at -40 °C. The reaction was stirred under nitrogen and let to warm to rt over 2 h. Solvent was evaporated and the resulting SDE was dissolved in chloroform (3 mL). Thiobenzamide (41 mg, 0.3 mmol) was added at 0 °C and the reaction mixture was warmed to room temperature and stirred for 3 h. Solvent was evaporated and the reaction products was re-dissolved in THF (2 mL) and cooled to 0 °C. Three drops of 80% glacial acetic acid and TBAF (0.3 mL,

0.3 mmol) was added to the reaction. The reaction was then warmed to room temperature and stirred for 1 h. Diluted with ether (50 mL), washed with water (10 mL). Evaporation of the solvent followed by FCC using 15% EtOAc in Hexanes gave the diol-thiazoline **4.22** (36 mg, 78% yield) as a white solid. MP 151 °C; IR ν_{max}(neat)/cm^{-1} 3438, 2932, 1735, 1716, 1239; δ_H (500 MHz, $CDCl_3$) 7.80 (2H, d, *J* = 8.0 Hz), 7.50 (1H, t, *J* = 7.0 Hz), 7.41 (2H, t, *J* = 7.5 Hz), 4.75 (1H, bs), 4.55 (1H, d, *J* = 11.0 Hz), 3.96 (1H, dd, *J* = 5.5, 5.5 Hz), 3.90 (1H, d, *J* = 11.5 Hz), 3.84 (1H, s), 3.51 (1H, s), 3.11 (1H, s), 2.92 (1H, d, *J* = 4.5 Hz), 2.66-2.58 (1H, m), 2.44-2.32 (1H, m), 2.16-2.02 (4H, m), 1.90-1.82 (2H, m), 1.70-1.78 (2H, m), 1.46 (3H, s), 1.29 (3H, s); δ_C (125 MHz, $CDCl_3$) 215.3, 172.0, 170.6, 132.7, 132.3, 128.8 (2), 128.6 (2), 109.6, 79.7, 76.1, 70.4, 66.7, 54.2, 39.7, 32.1, 29.2, 29.1, 27.1, 26.9, 21.7; *m/z* (ESIMS) found: 452.2, calc'd for $C_{22}H_{30}NO_7S$ $[M+H]^+$: 452.2. Slow evaporation of a sample of **4.22** dissolved in 0.2 mL hexanes and minimum amount of DCM gave crystals suitable for single crystal X-ray analysis.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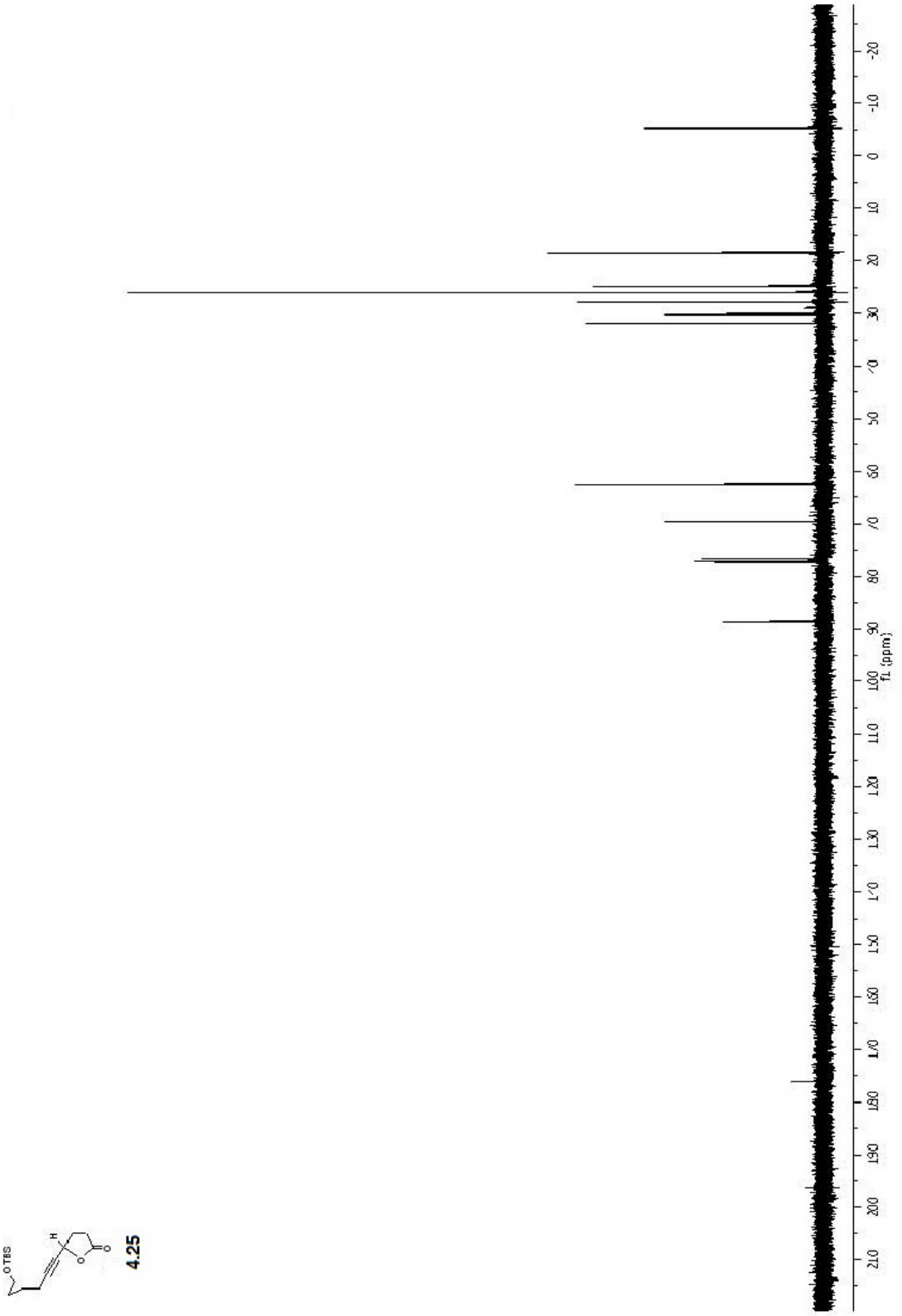
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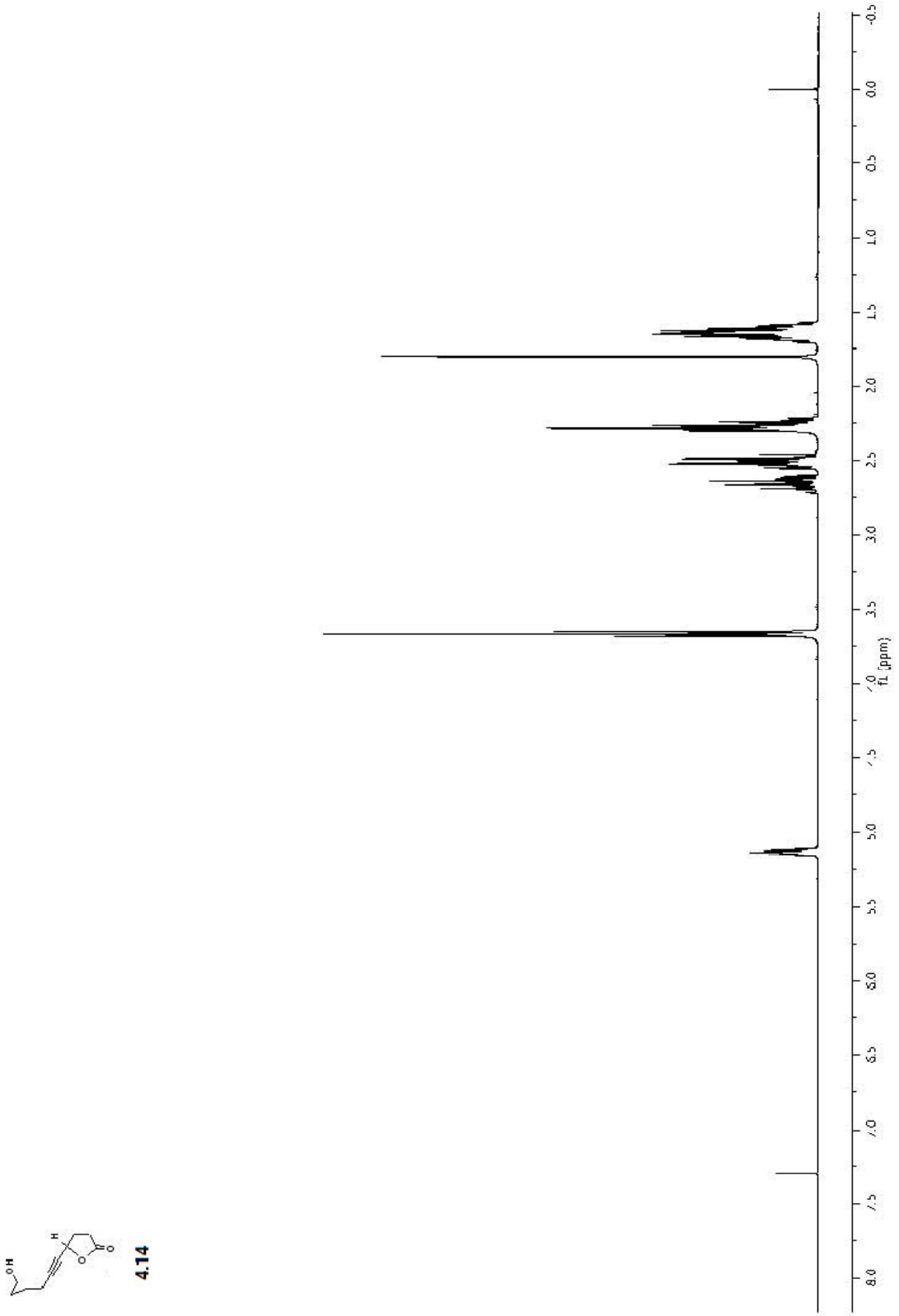

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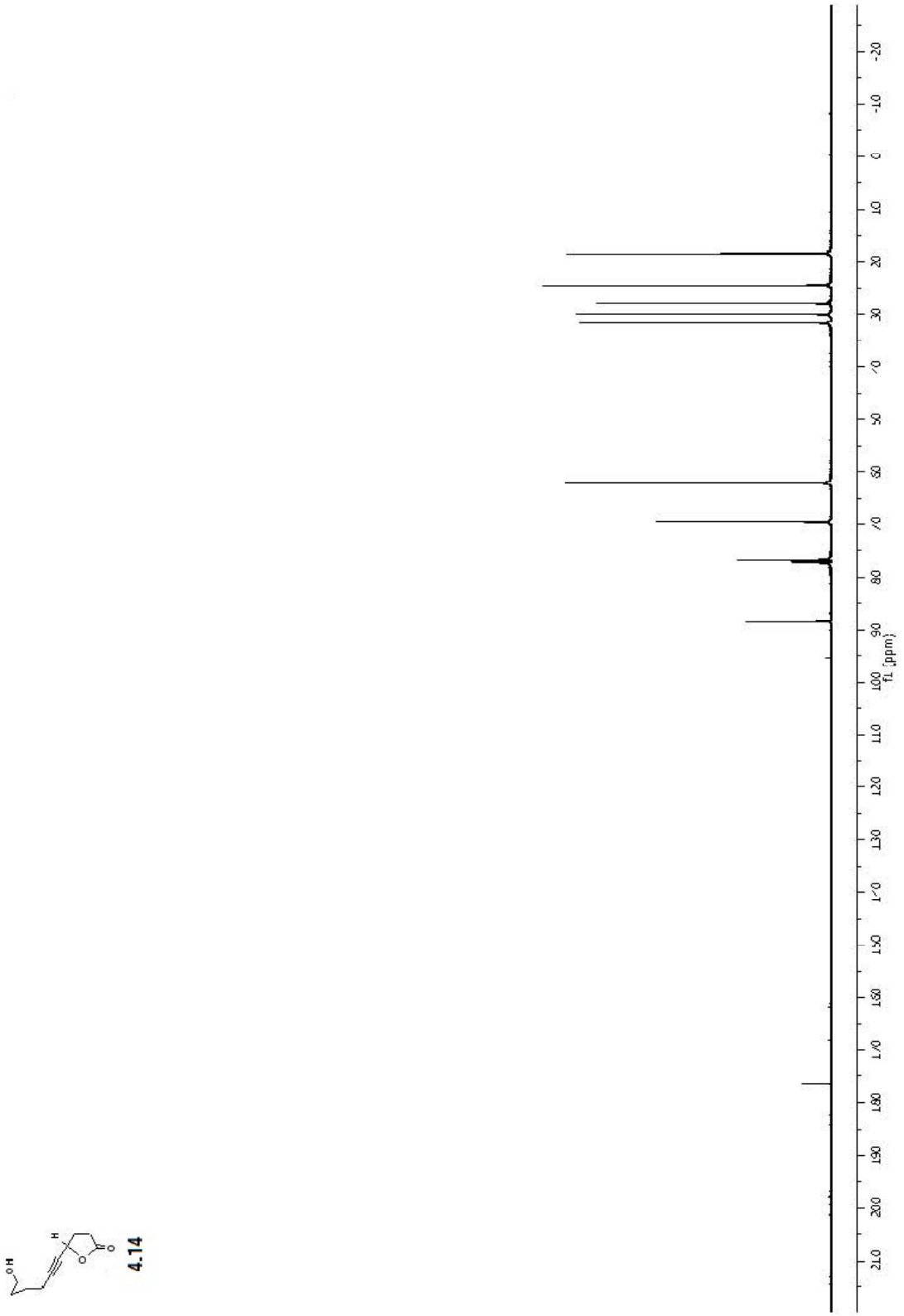

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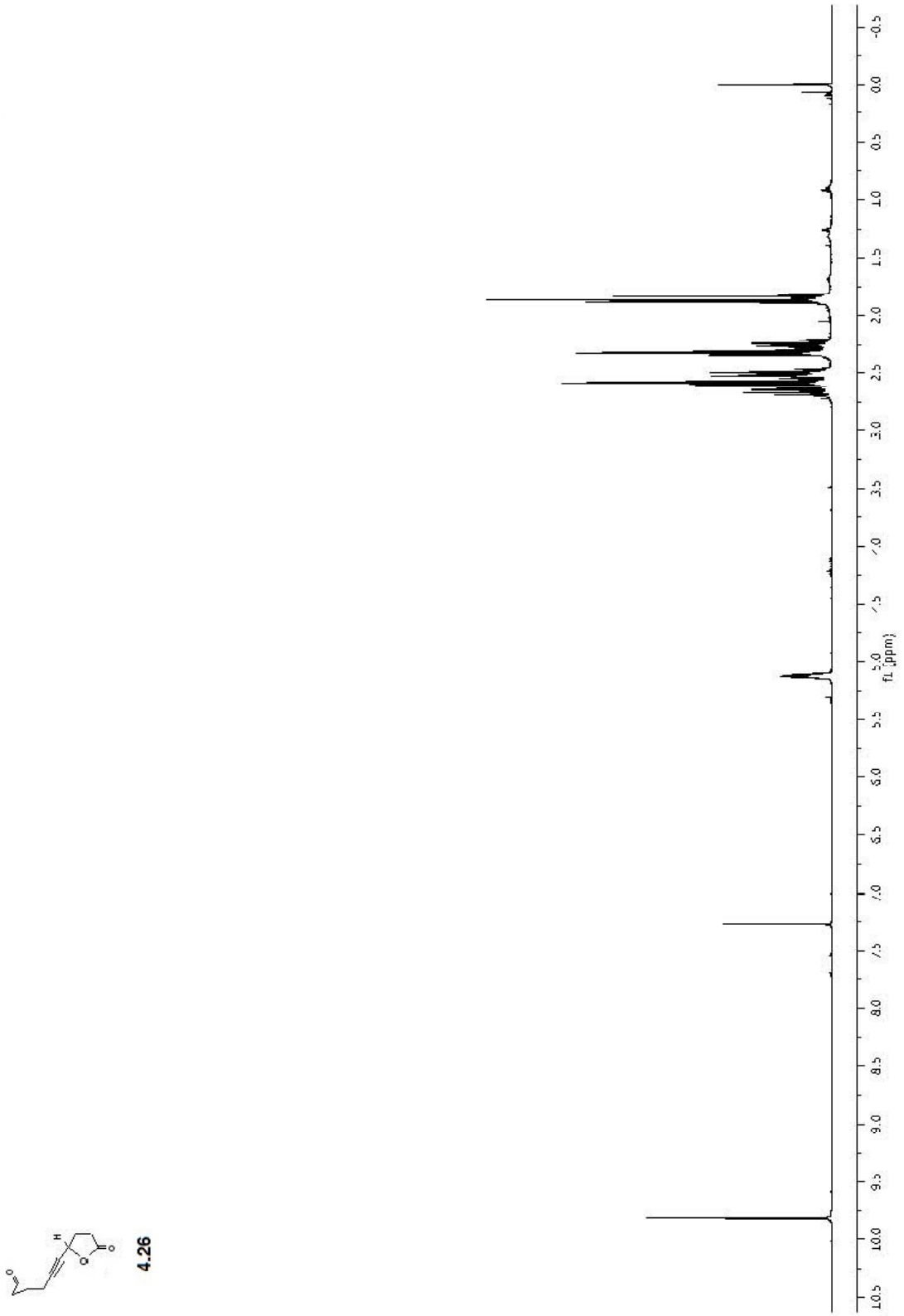
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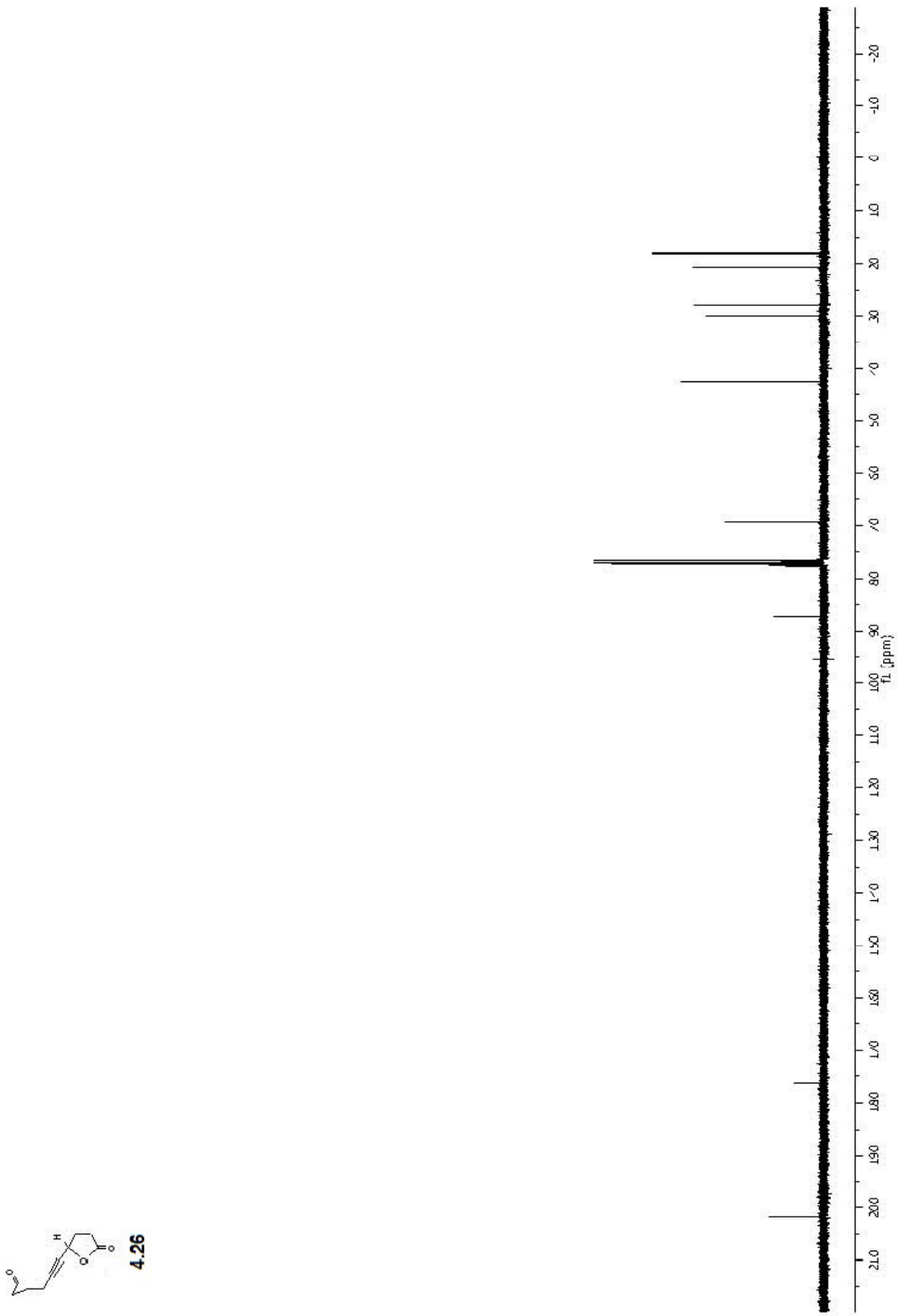
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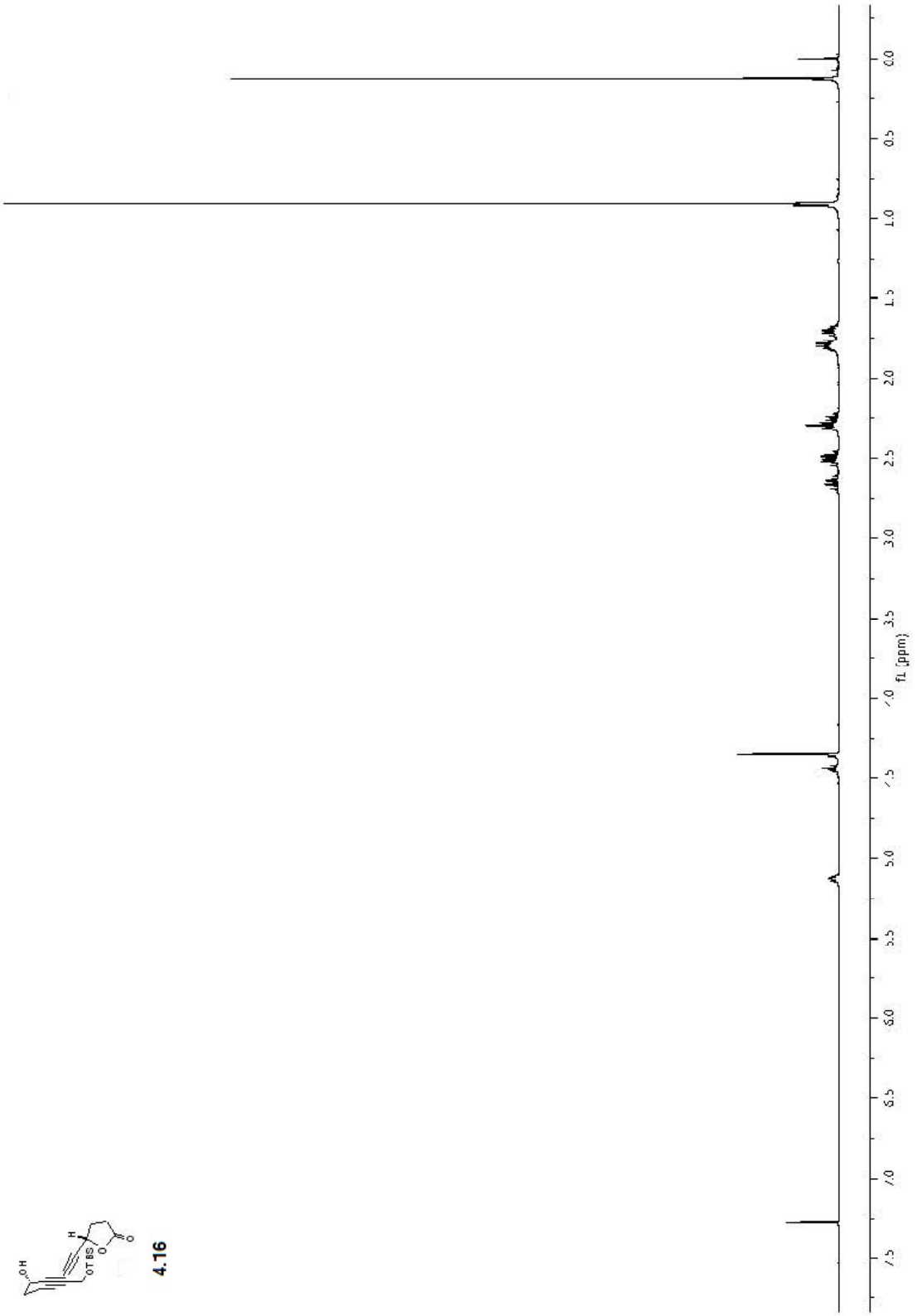
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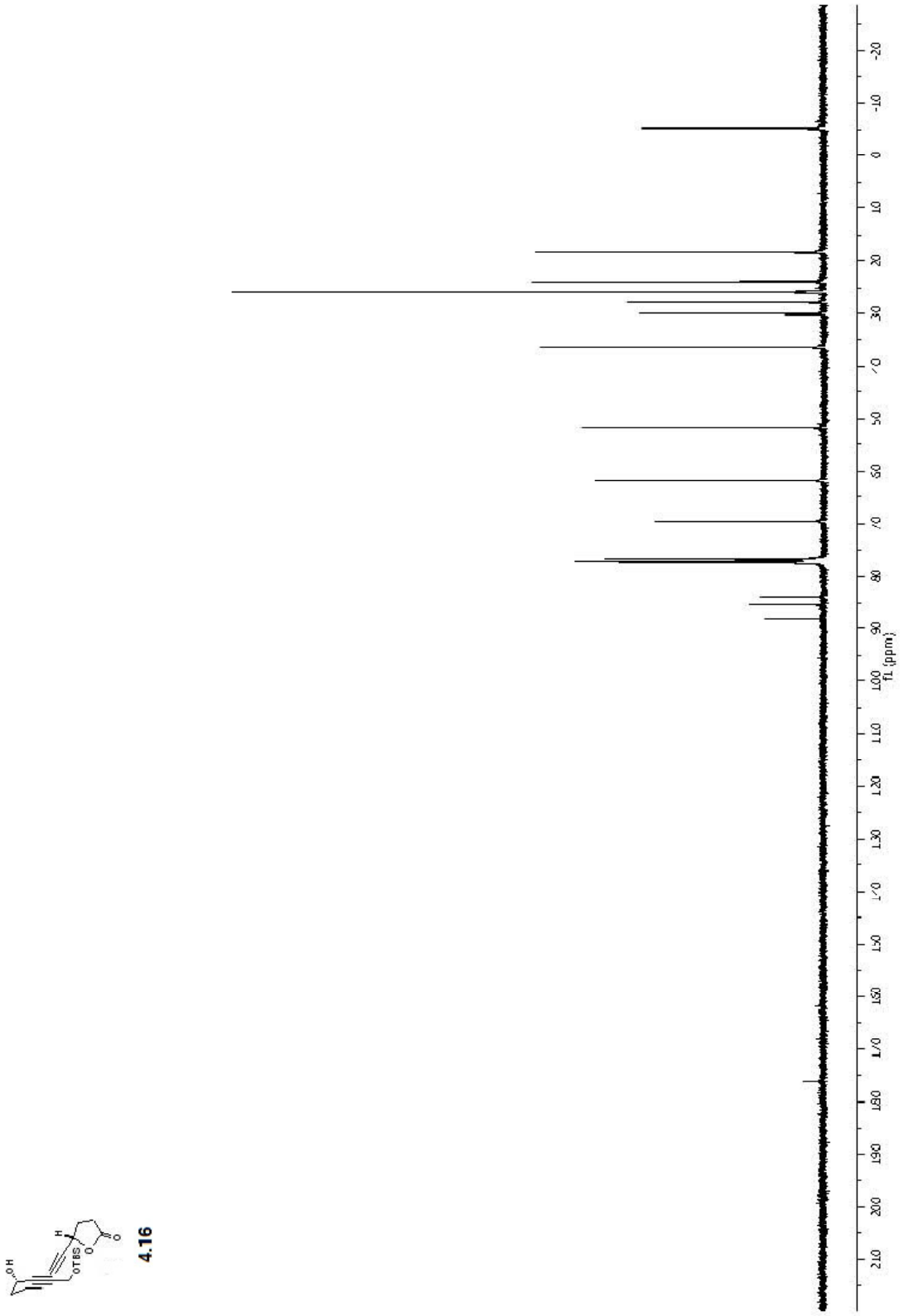
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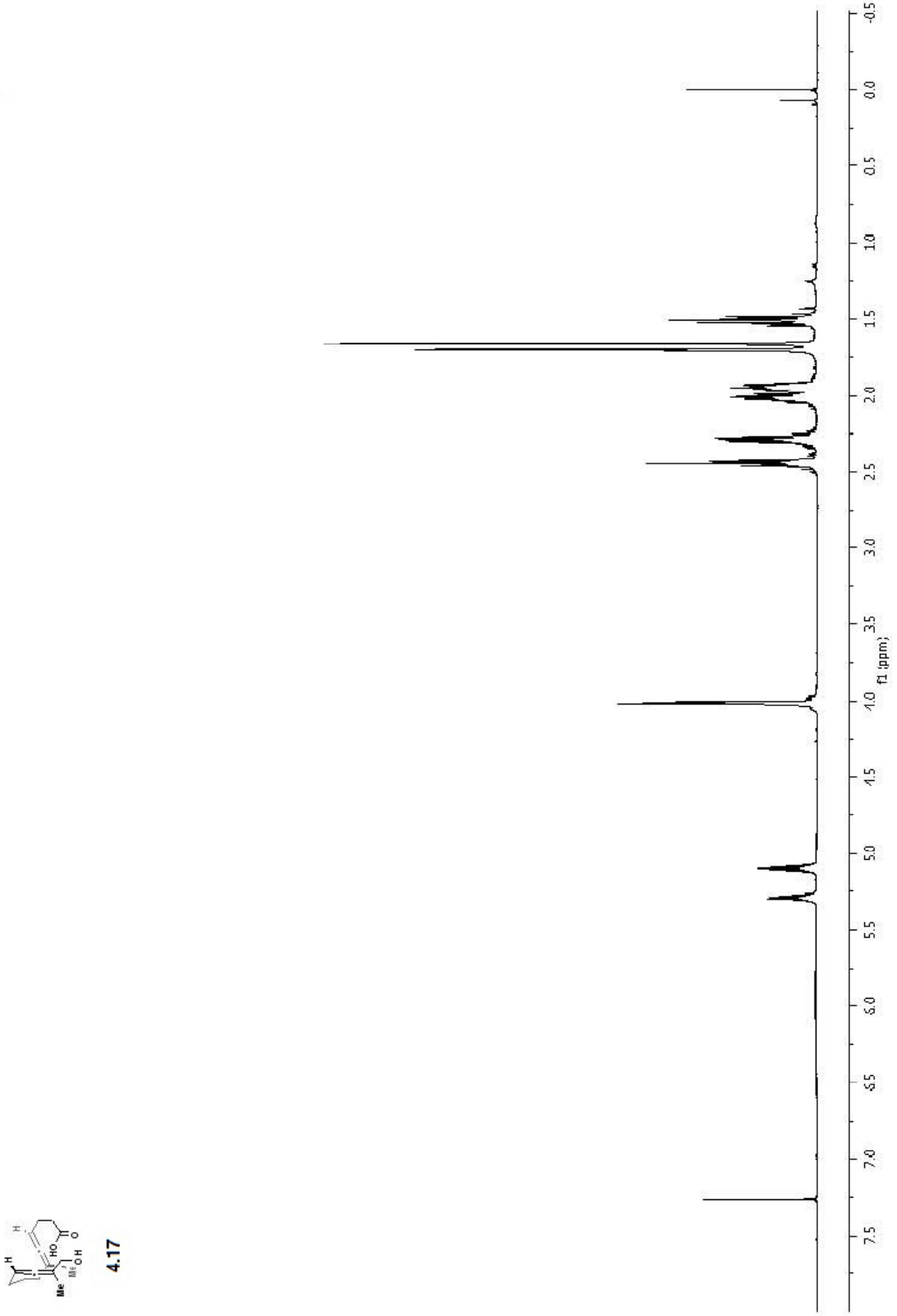
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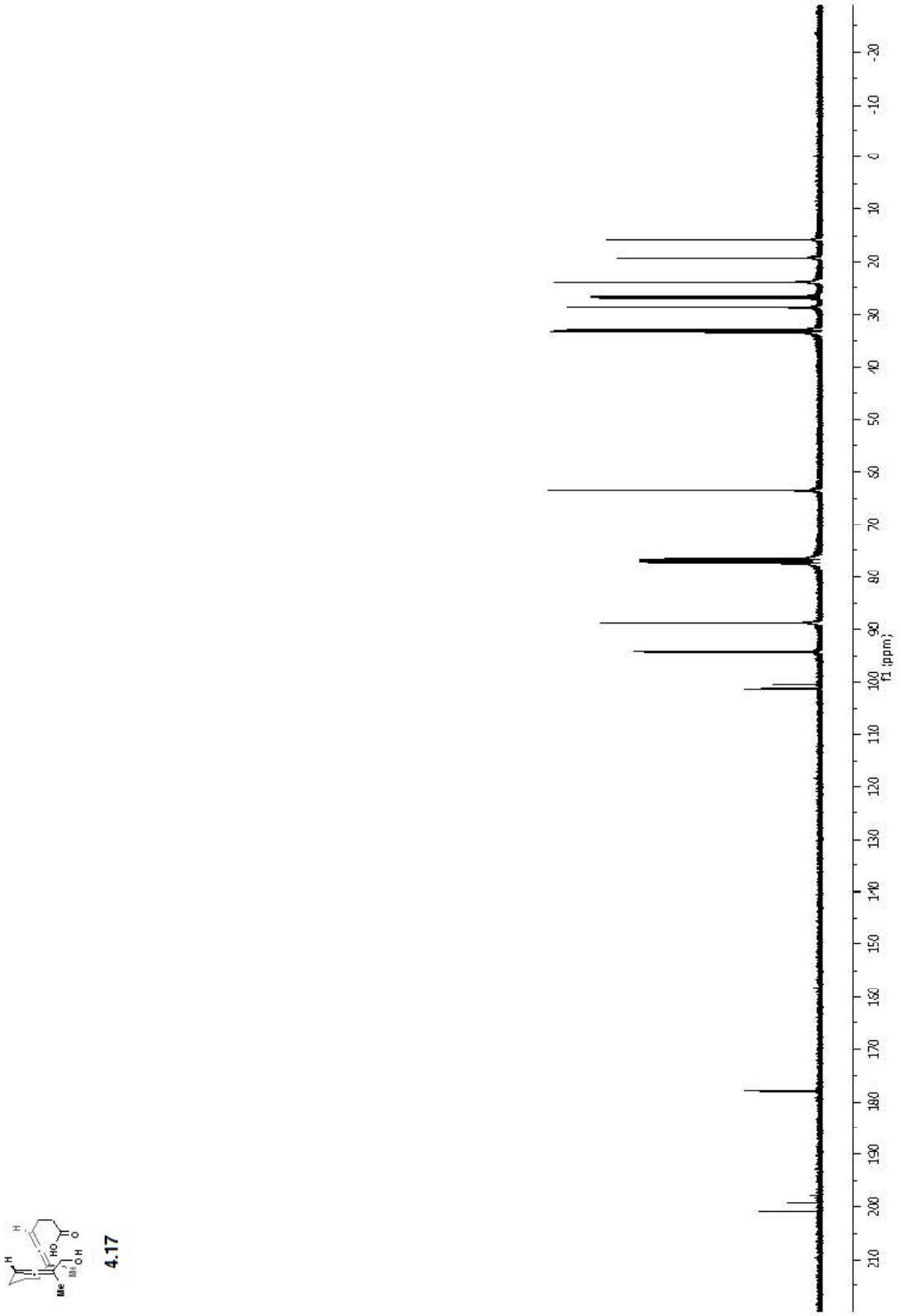

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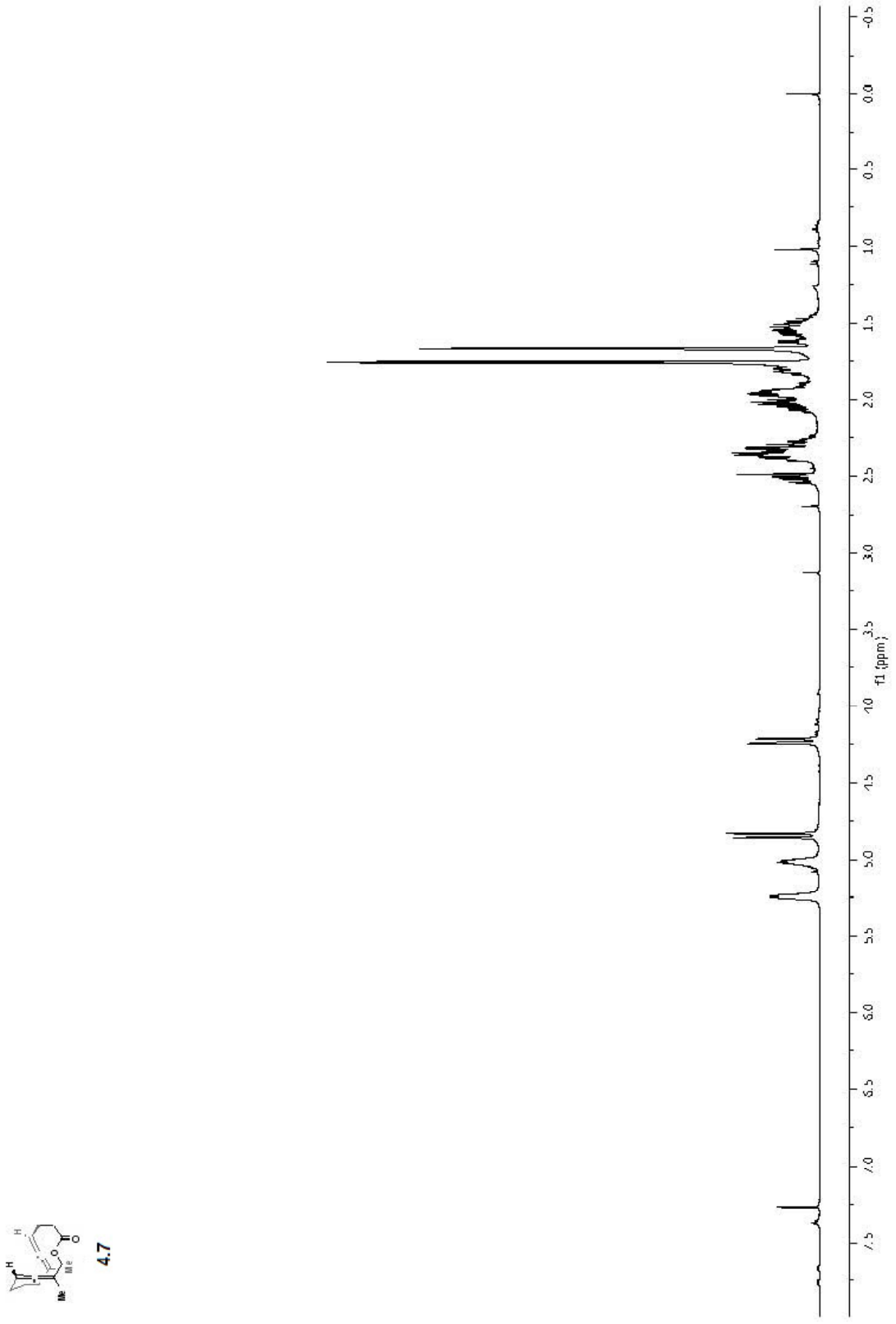
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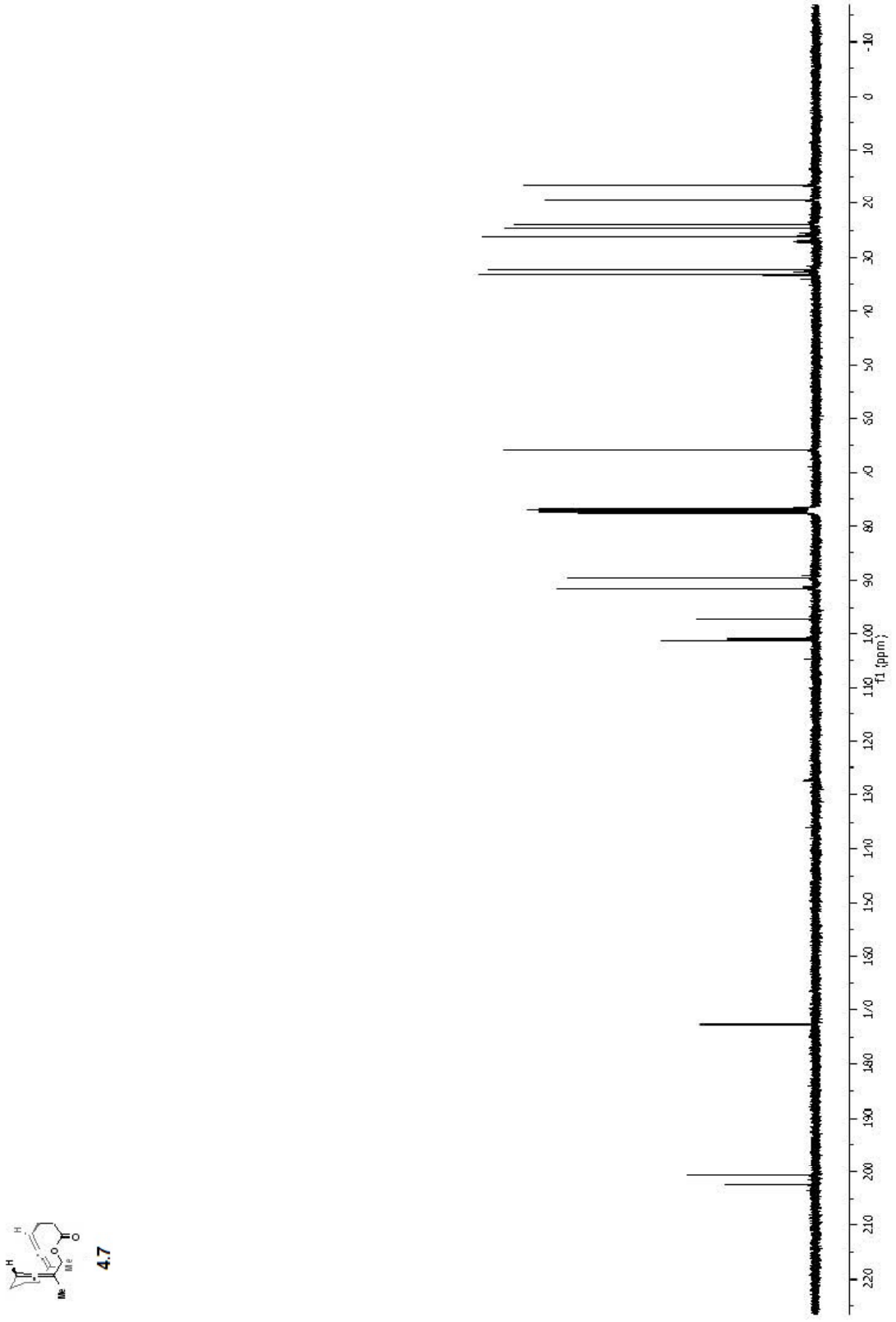
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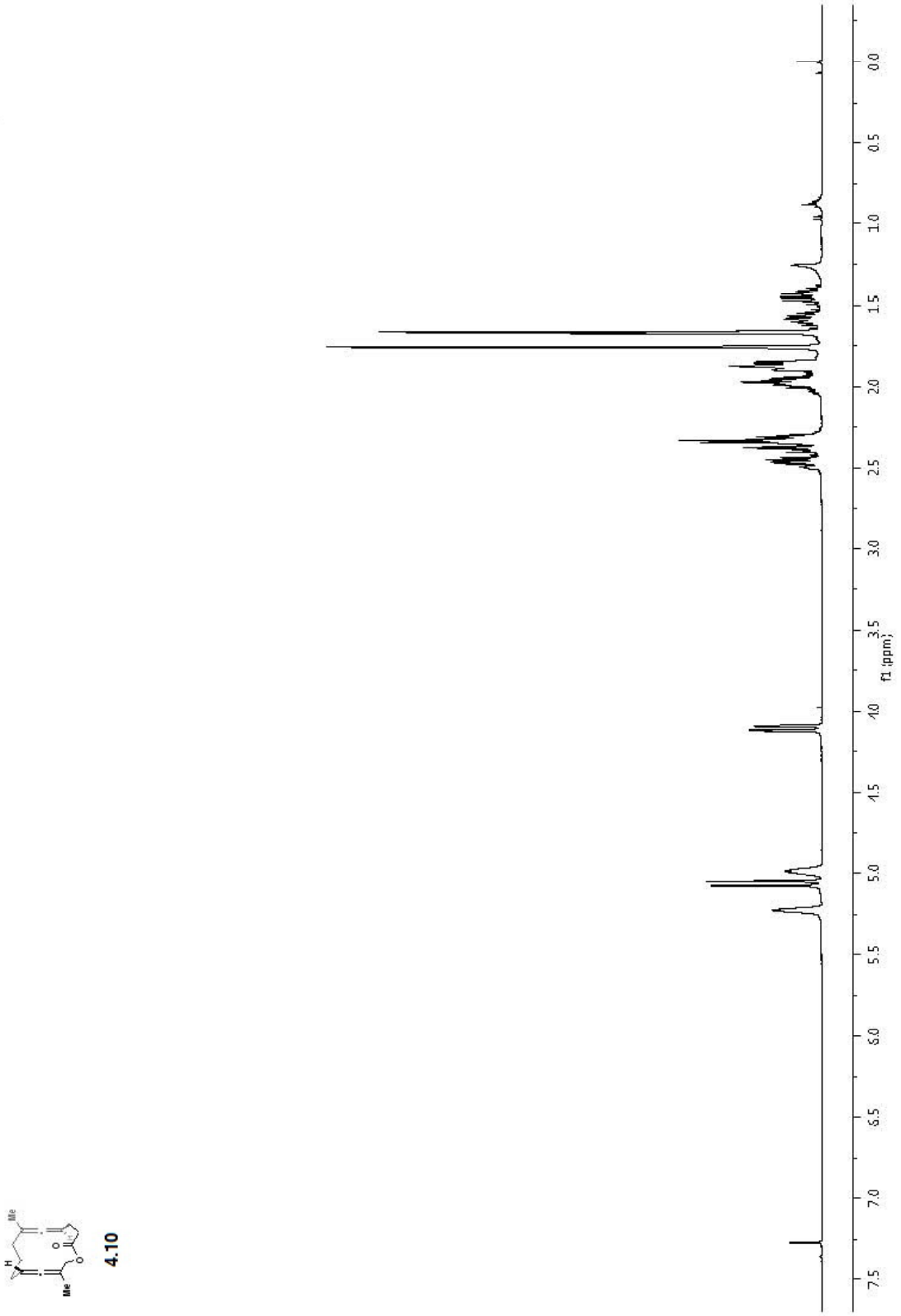
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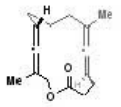
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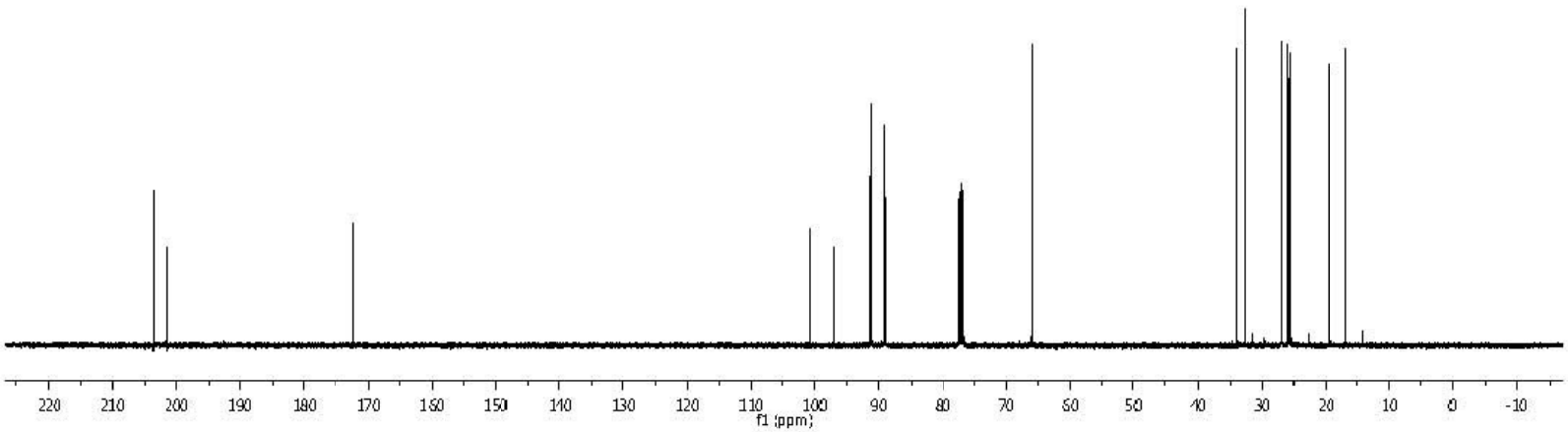
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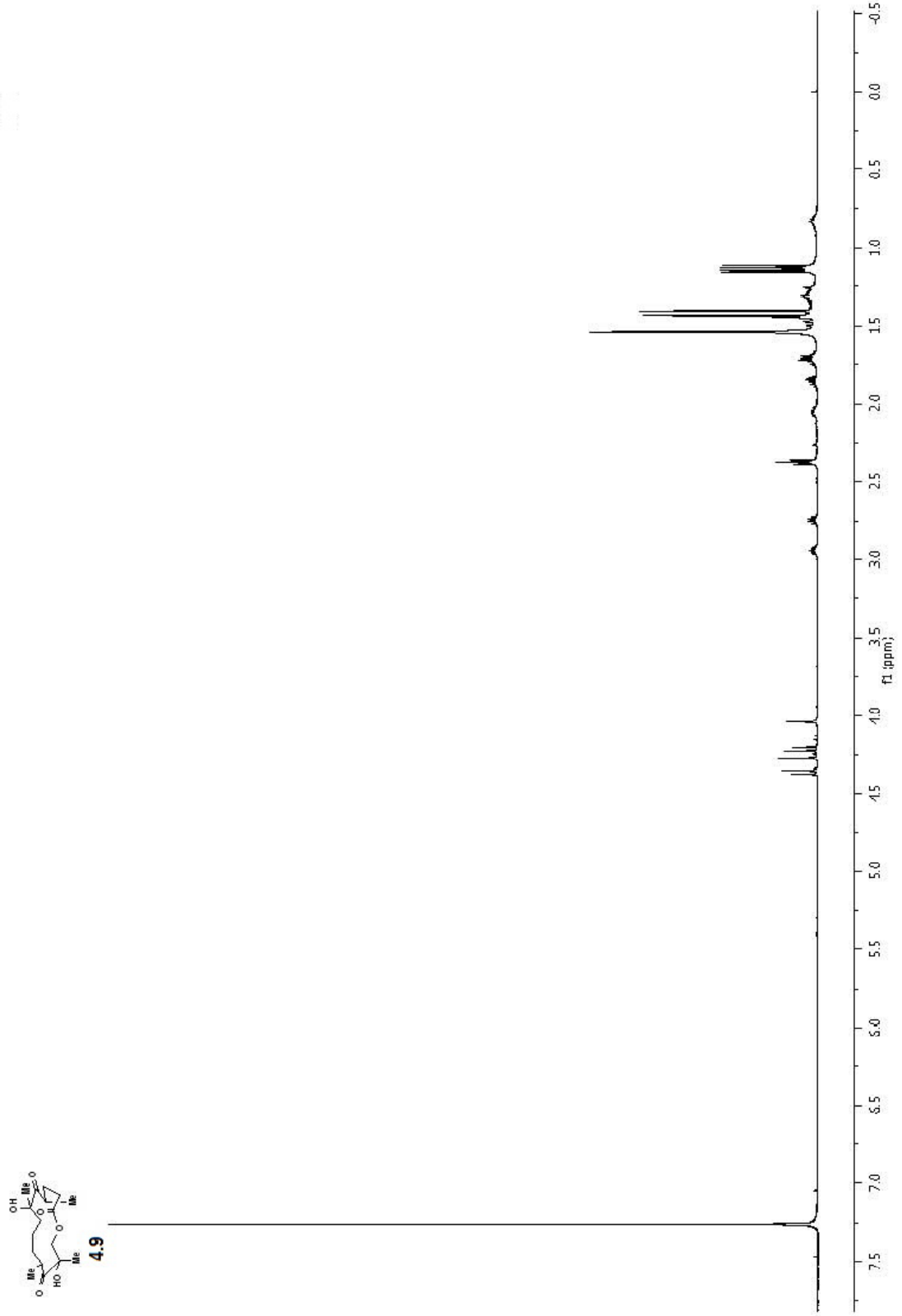
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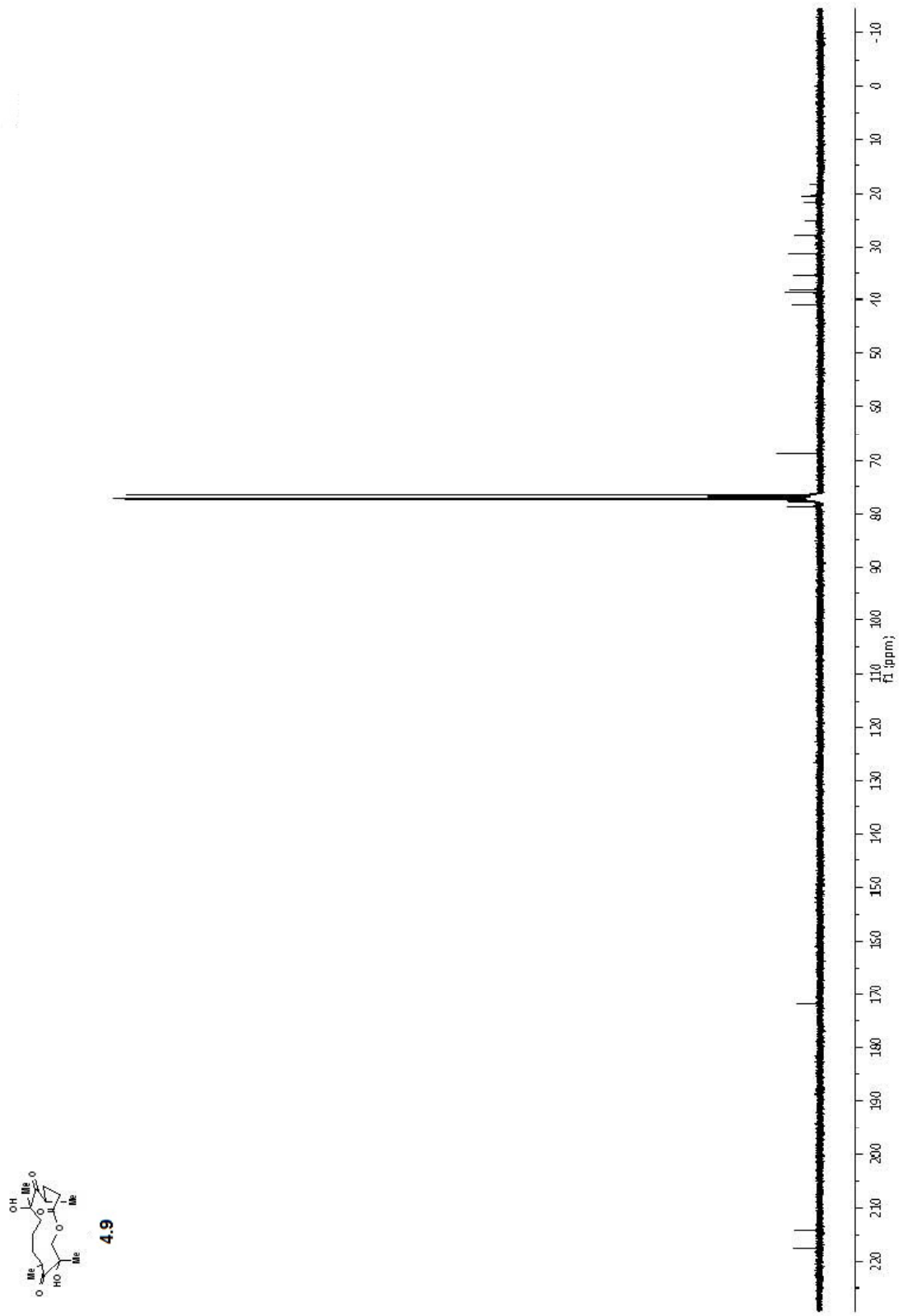
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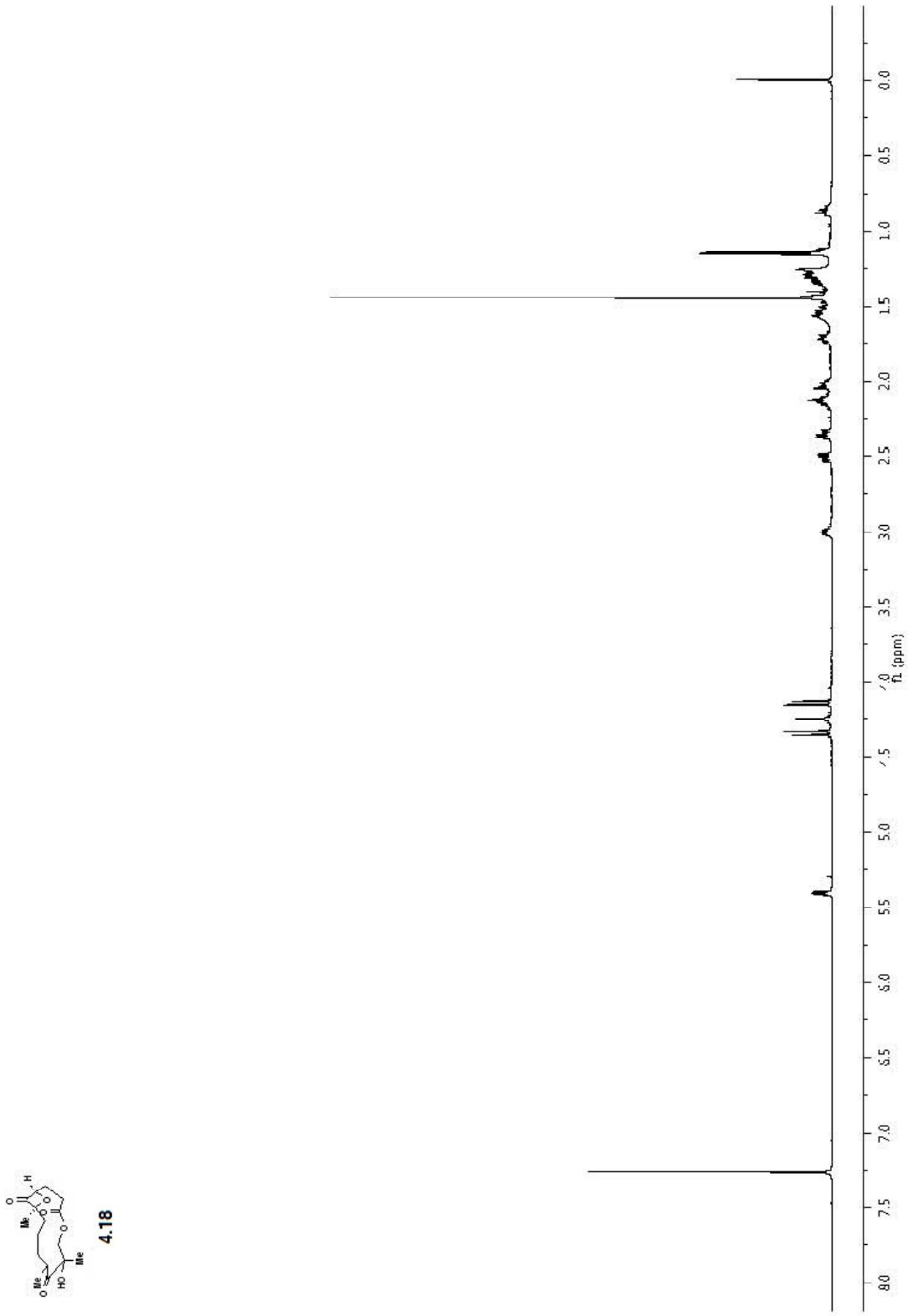
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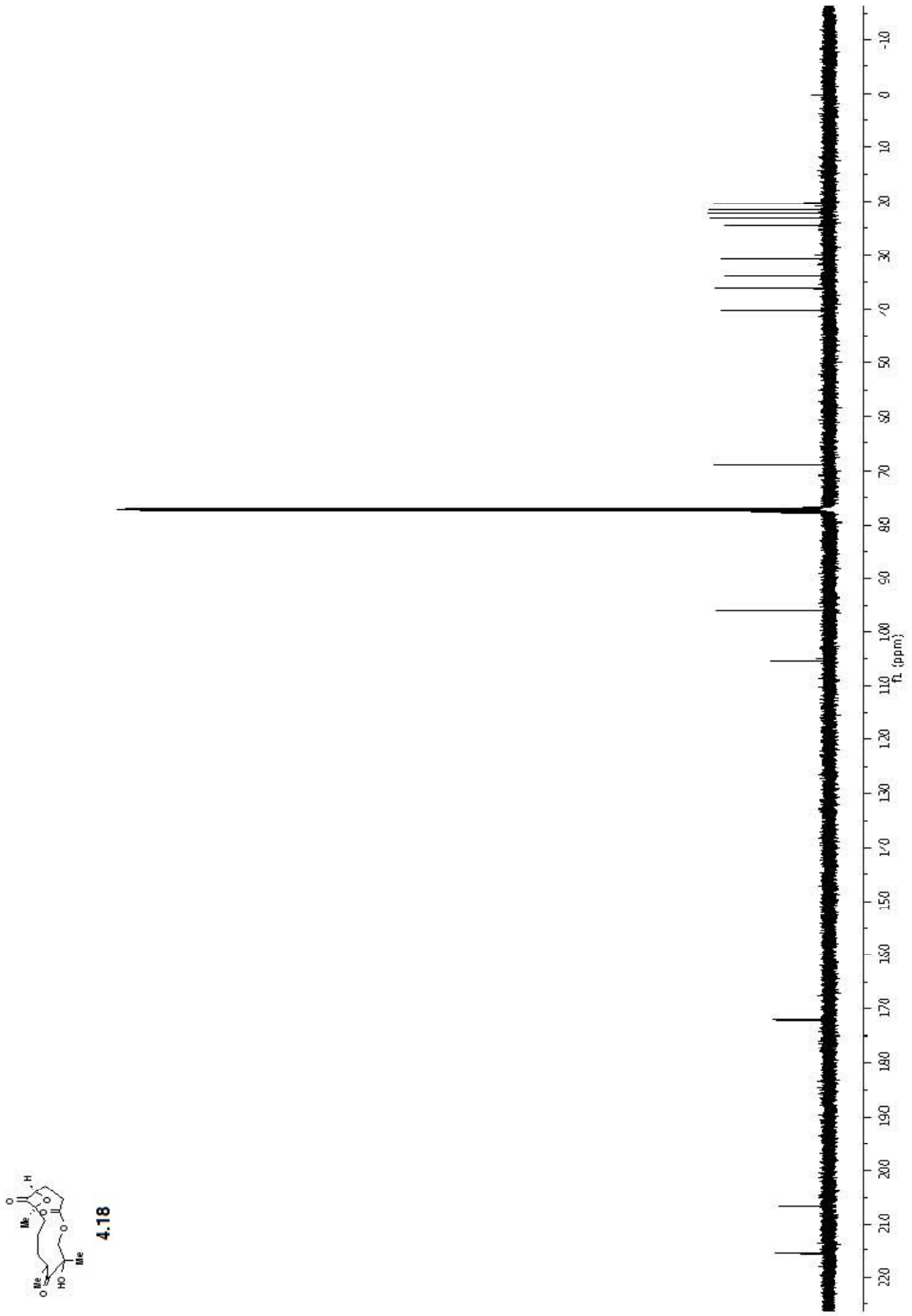
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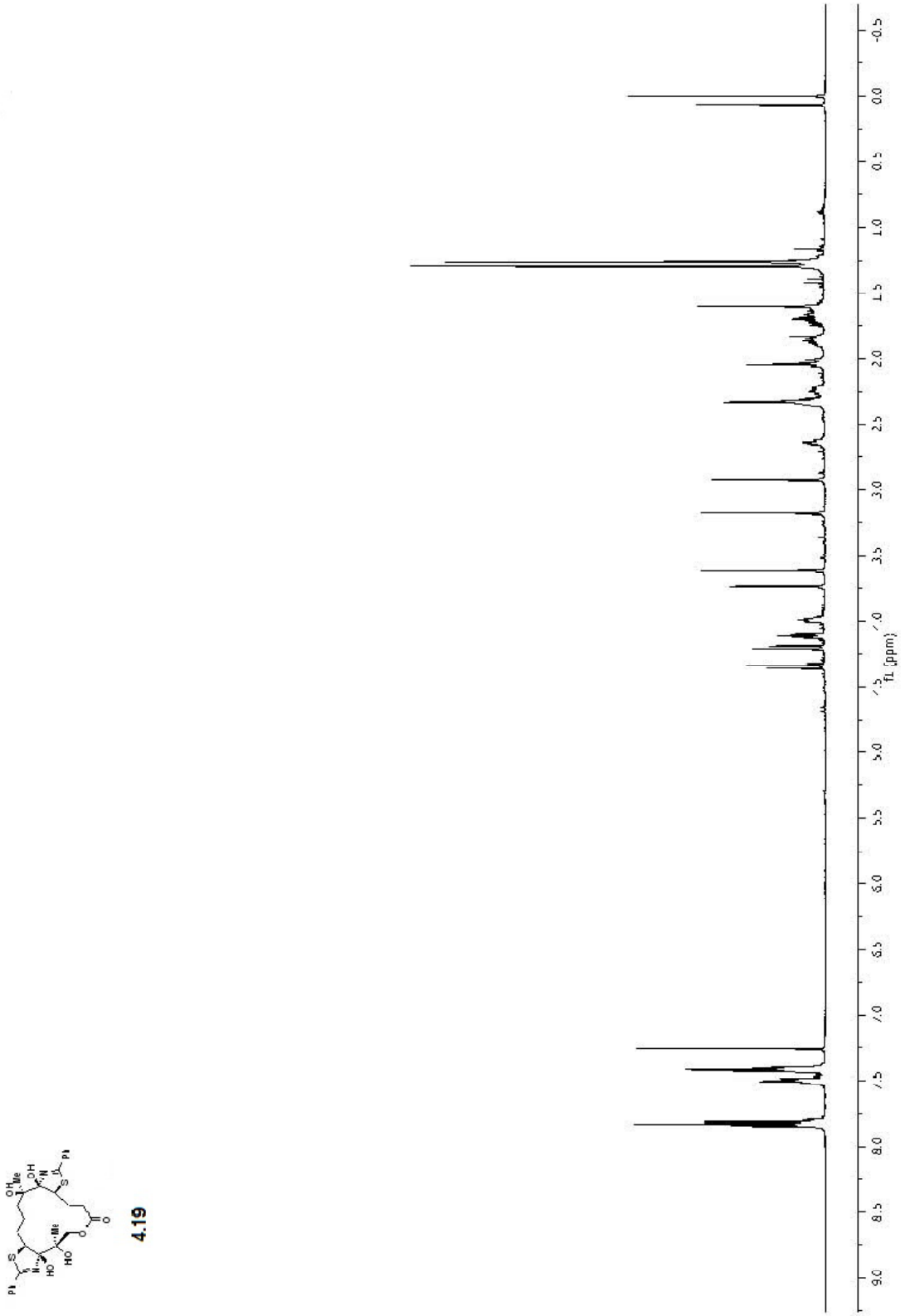
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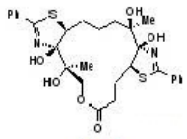

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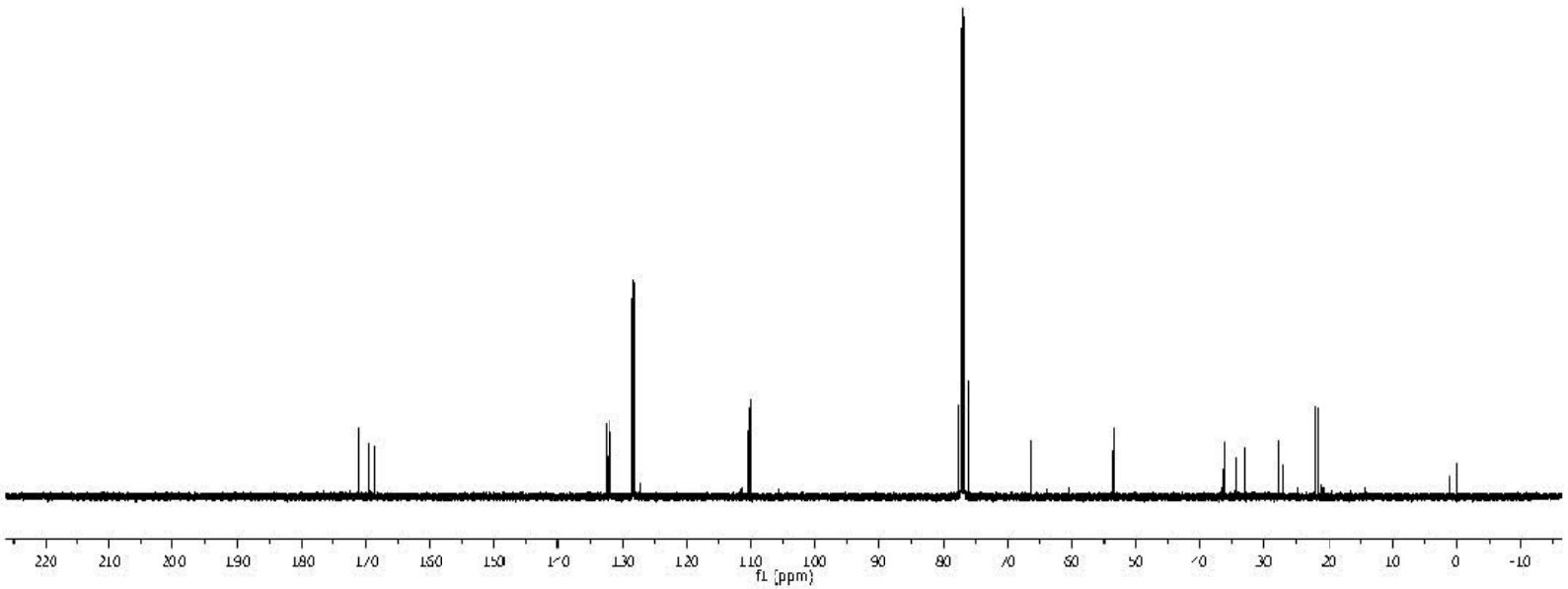
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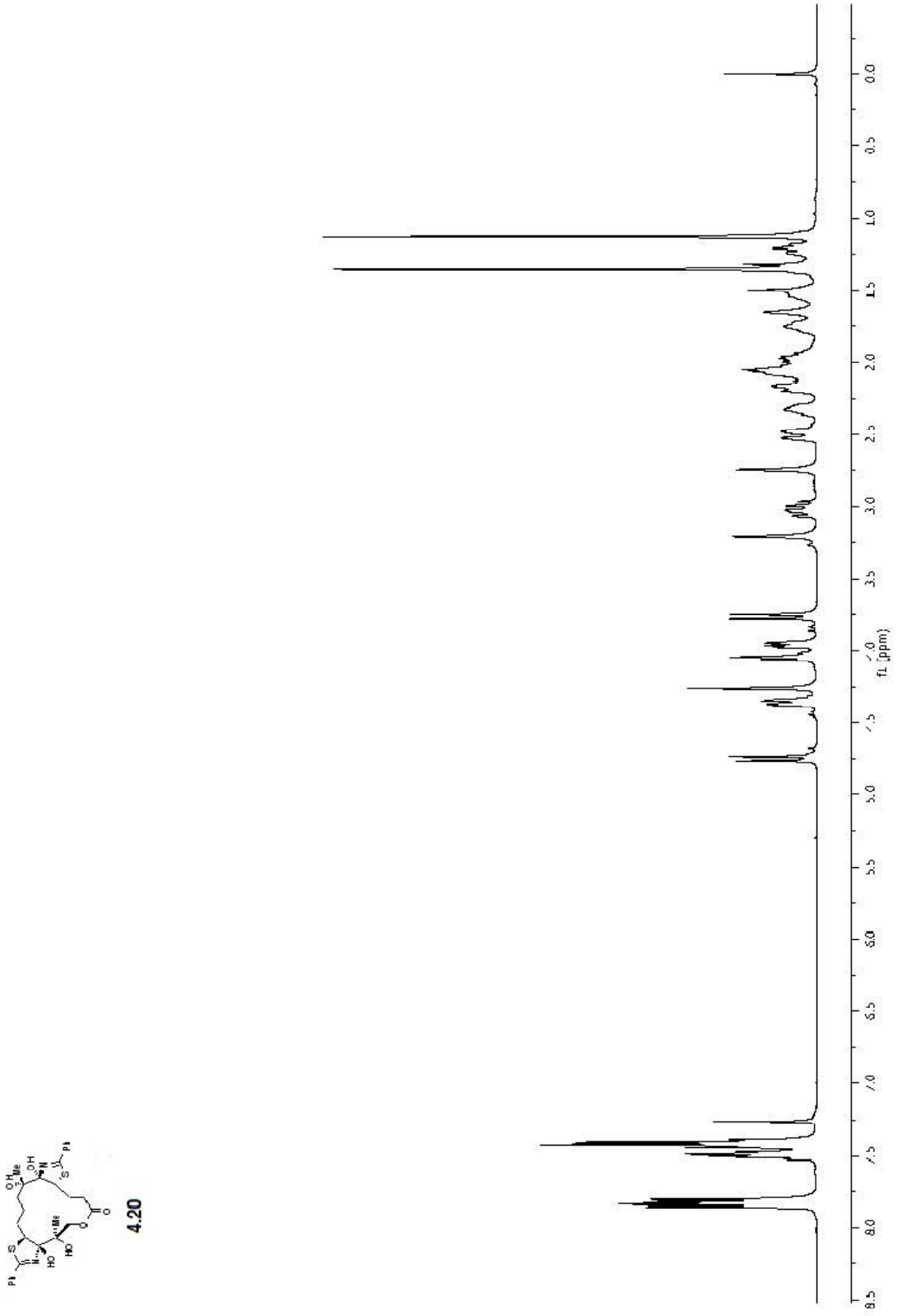
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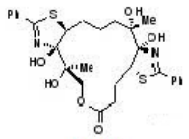

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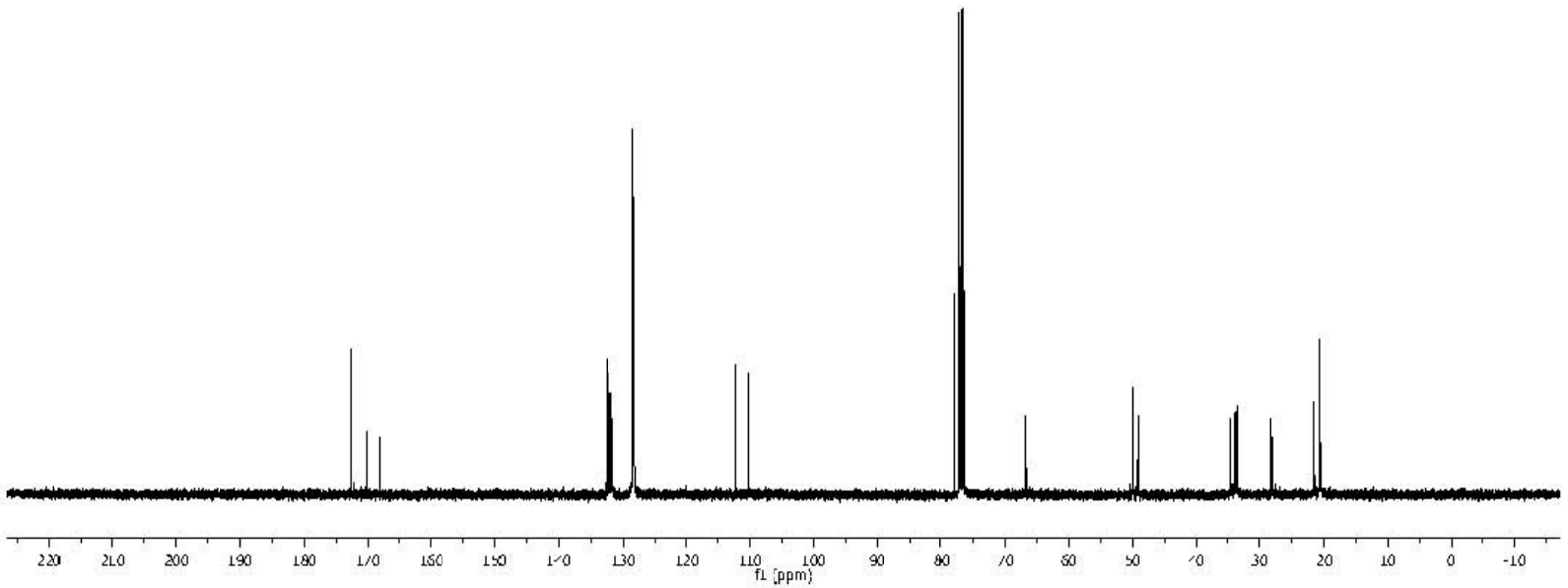
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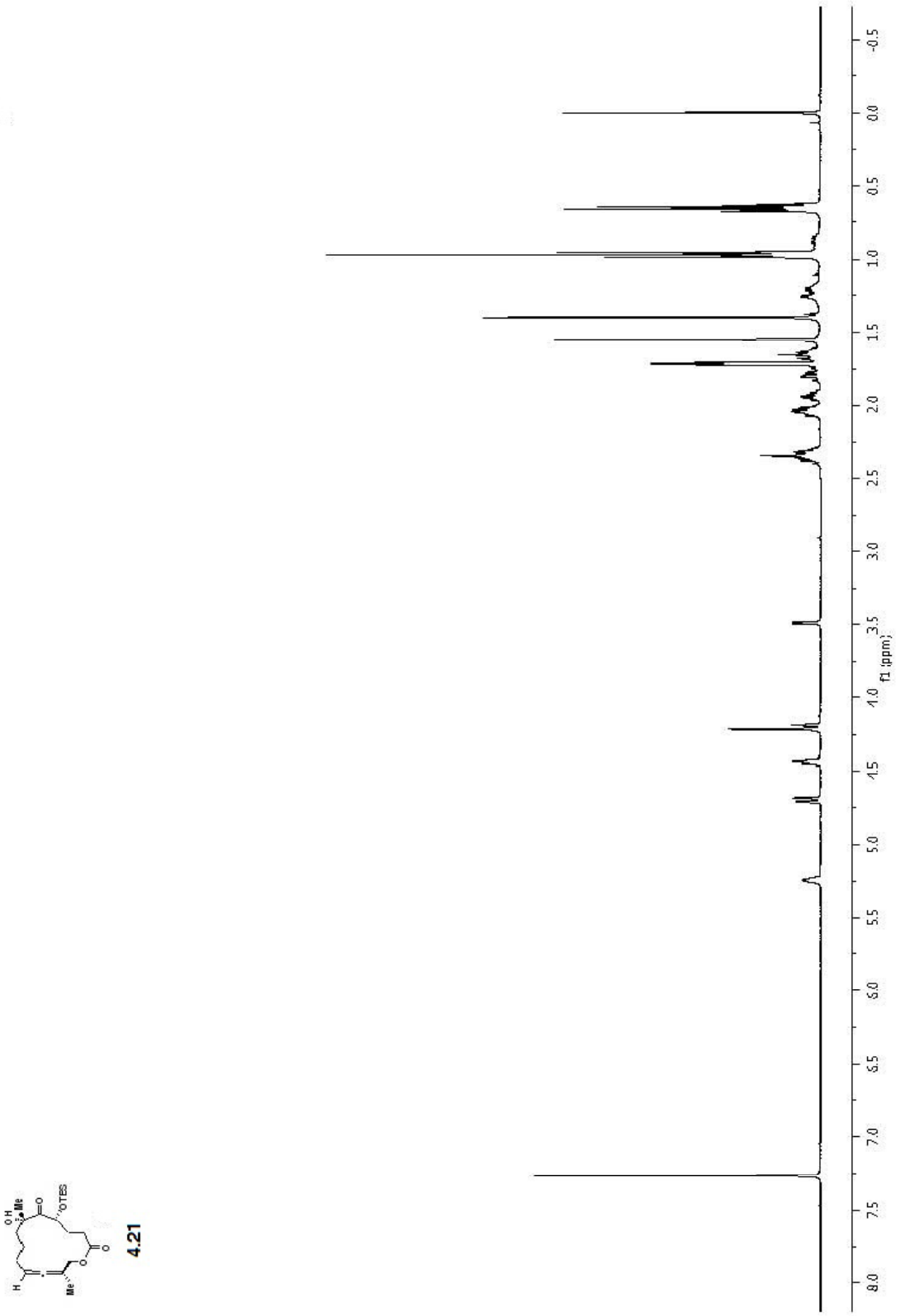
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H
Me
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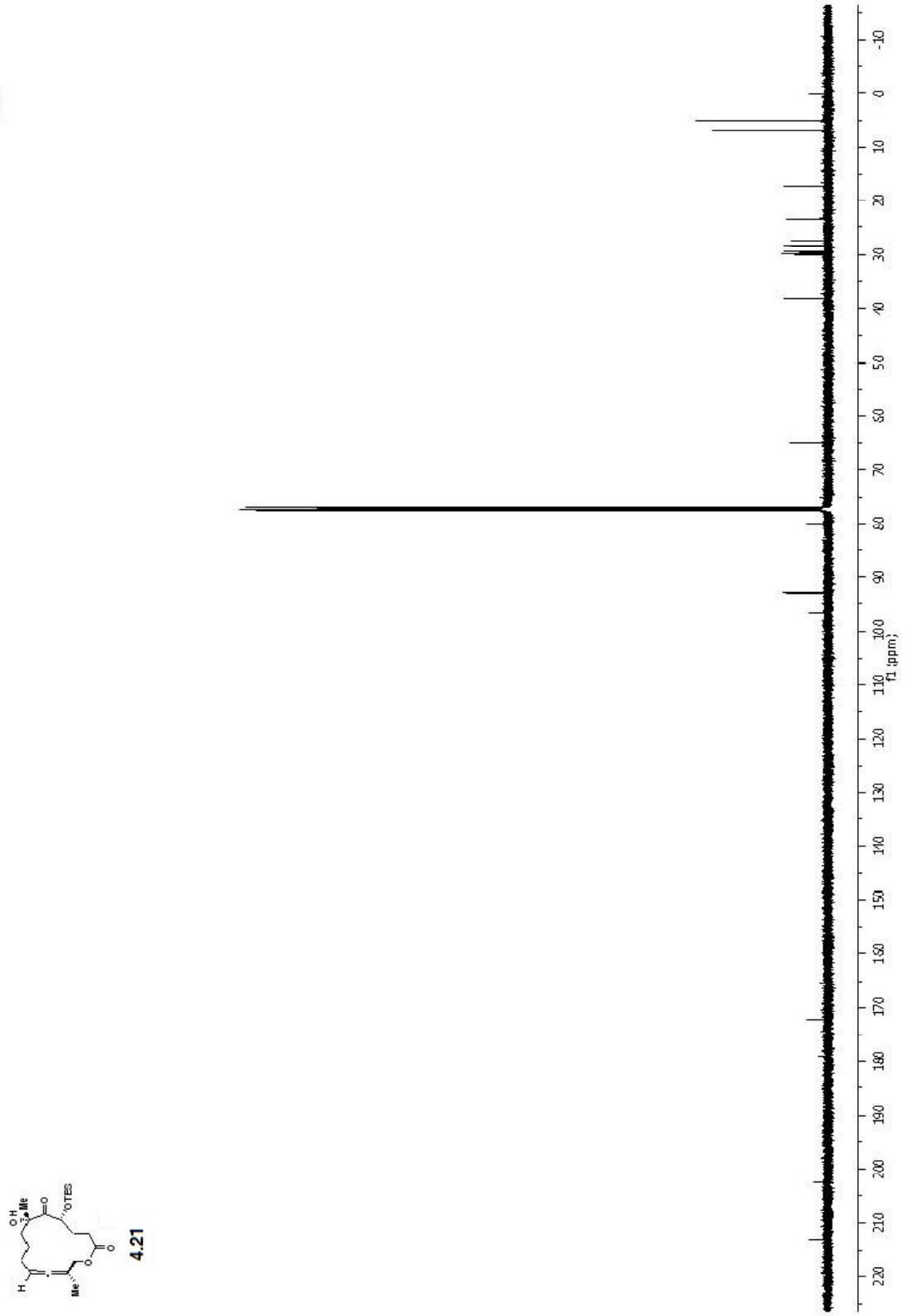
f1 (ppm)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O
OTES
O
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H
Me
4.21
f1 (ppm)
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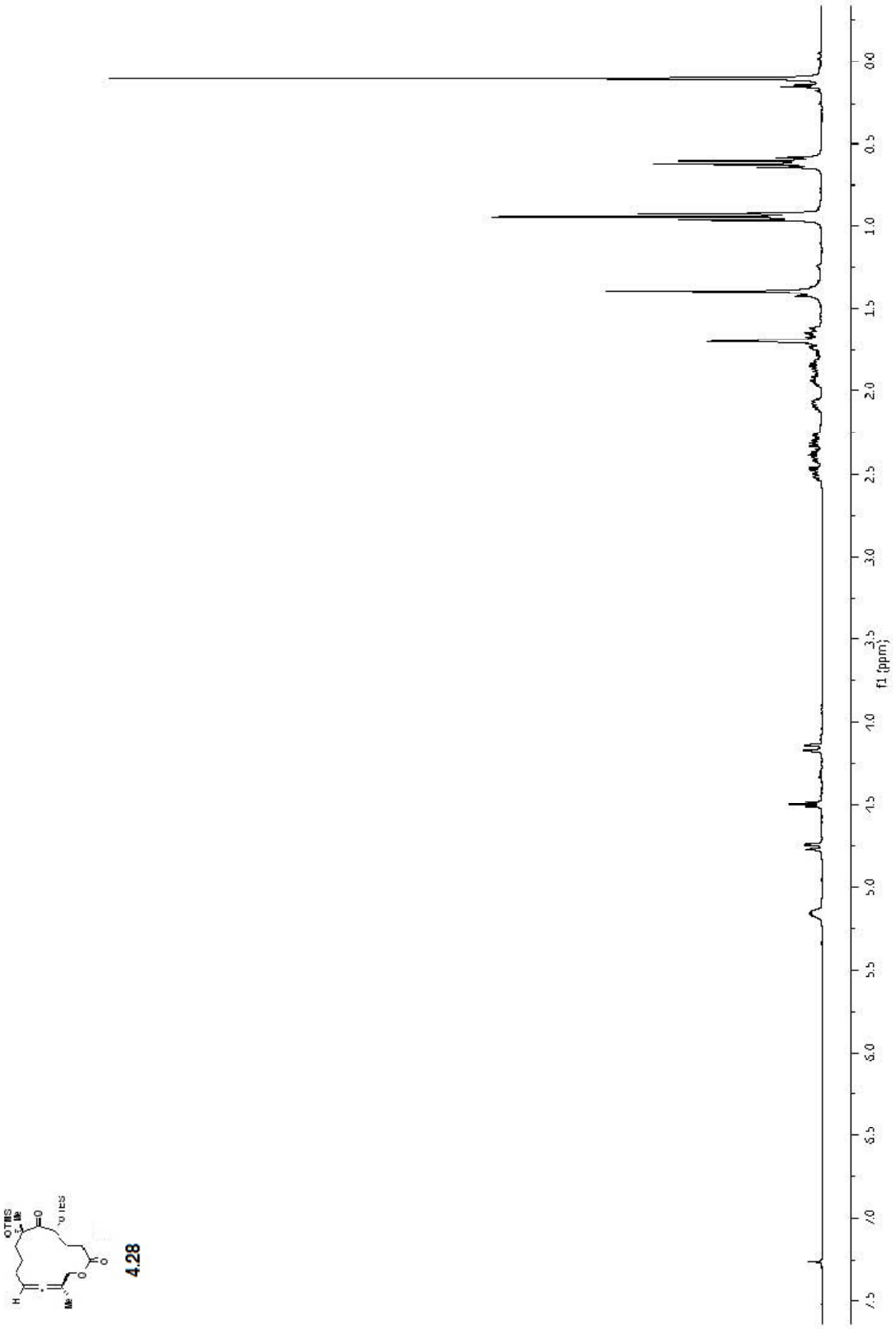
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OTES
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O
O
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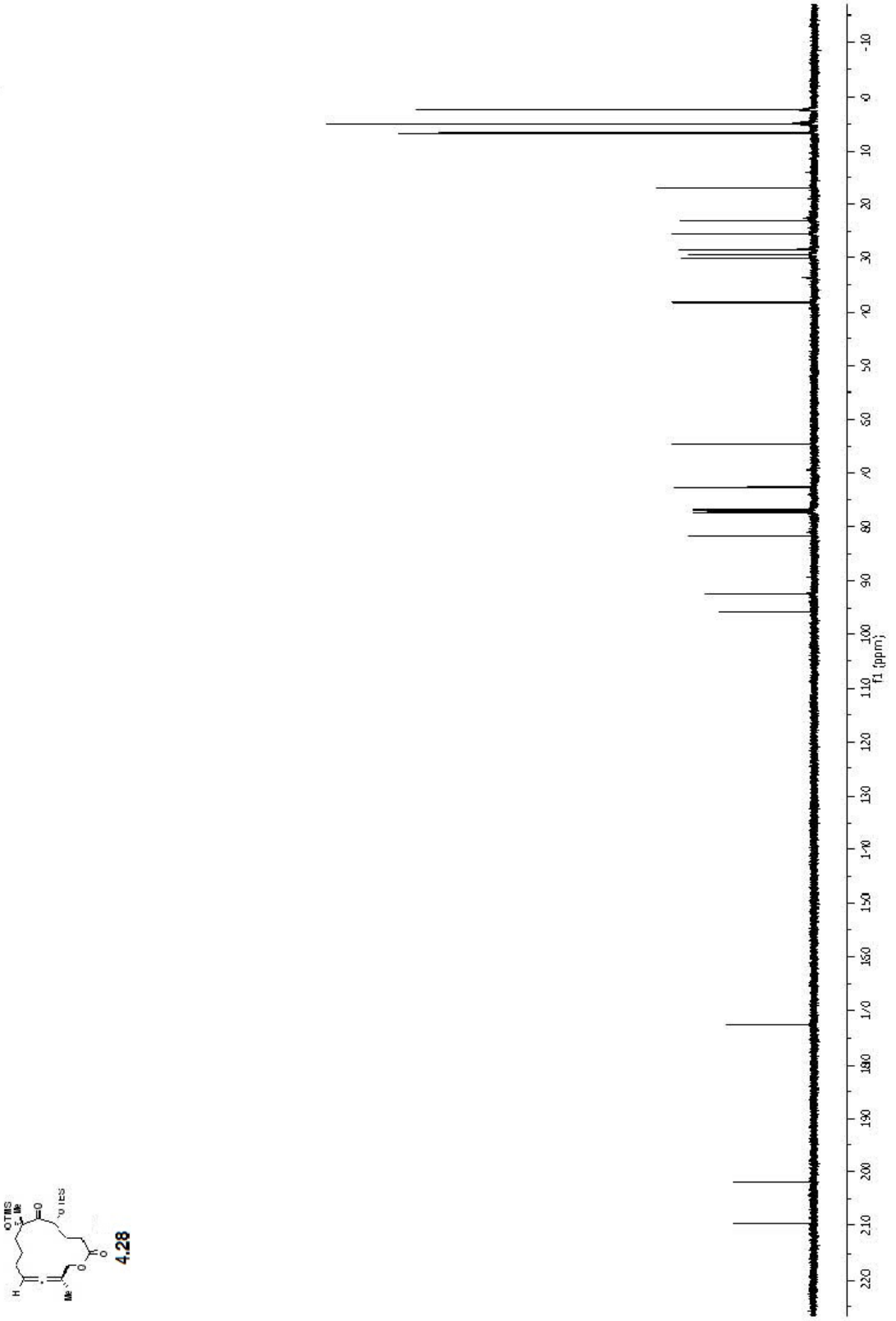
f1 (ppm)


OTBS
OTES
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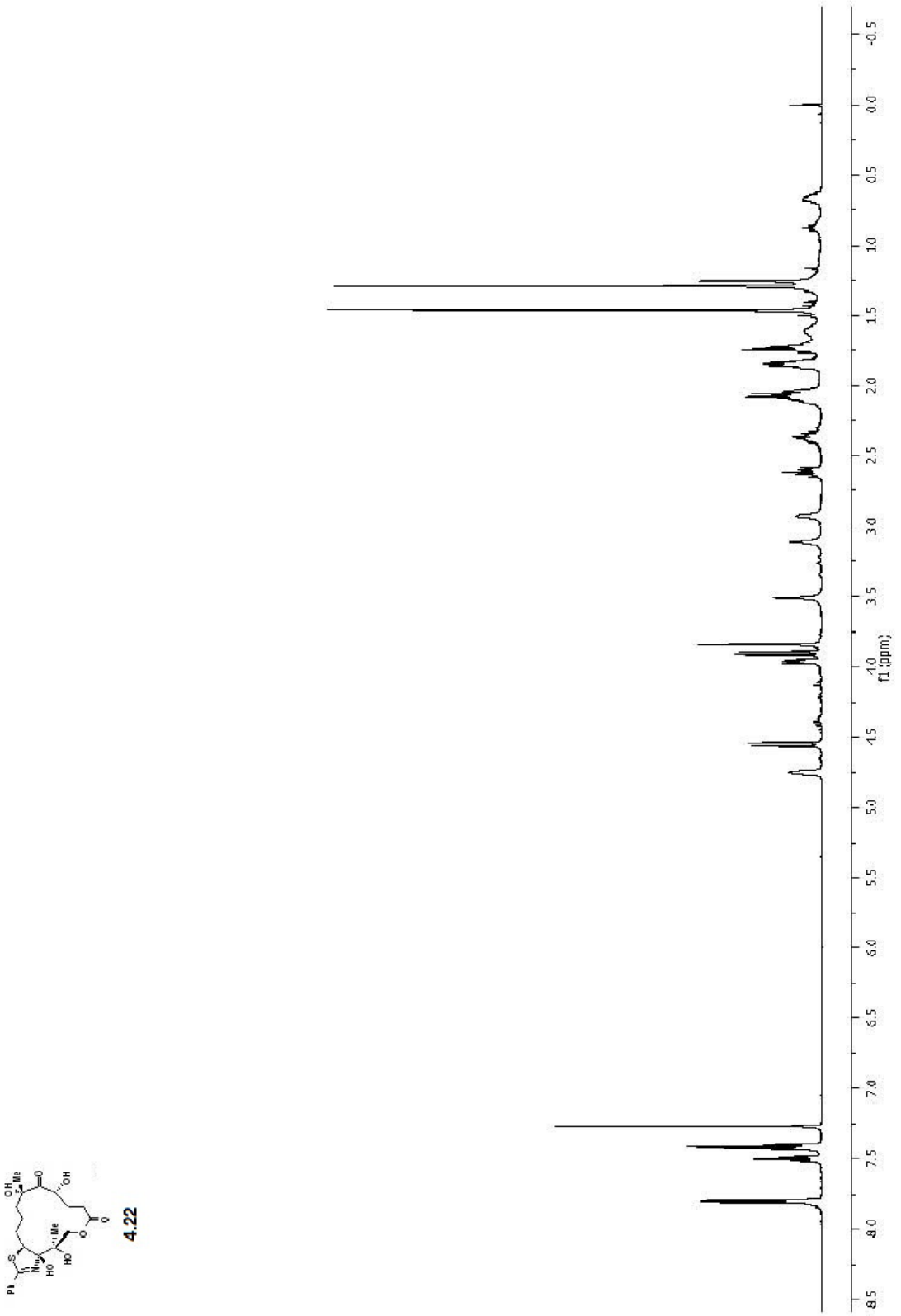
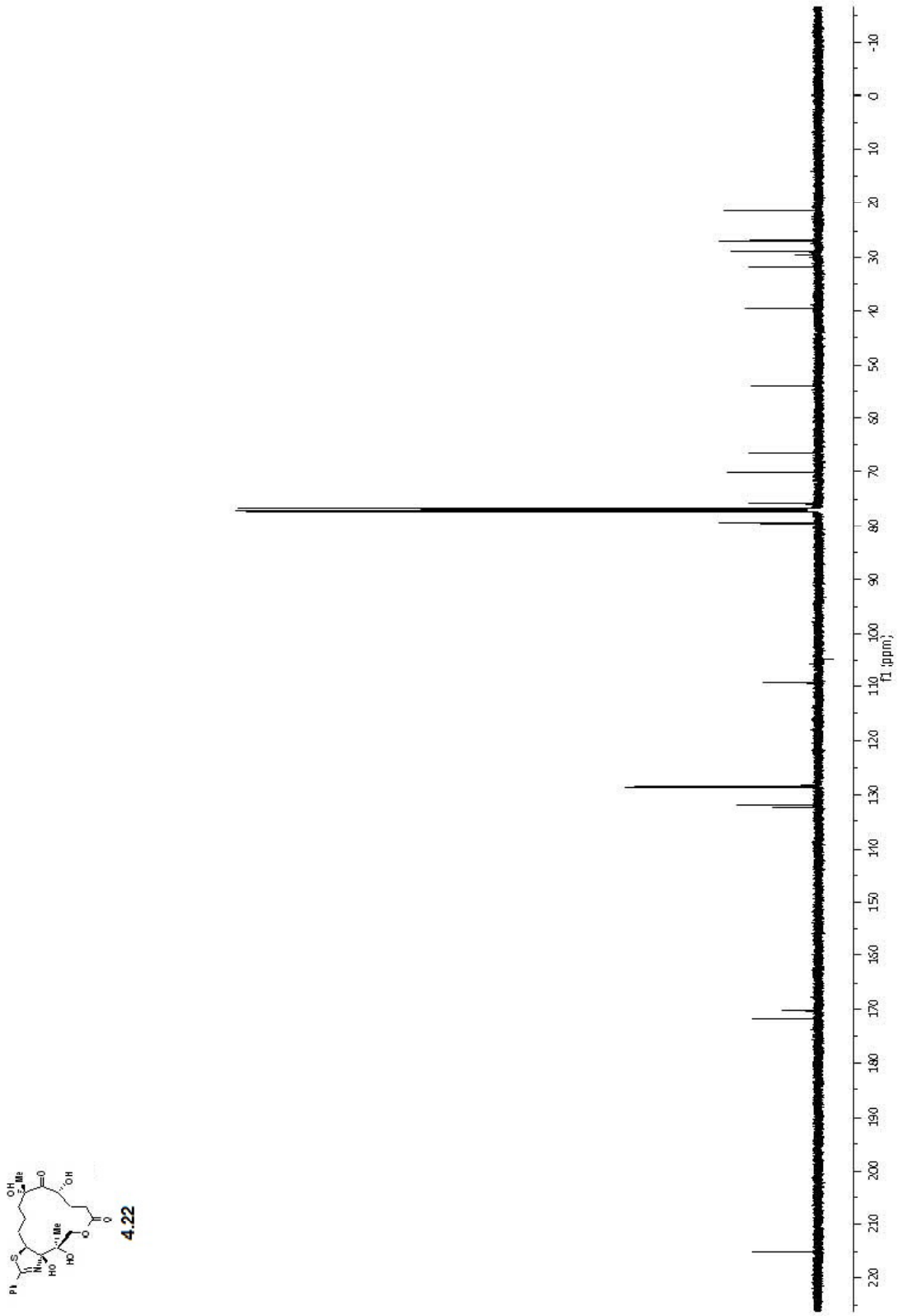
f1 (ppm)



4.22

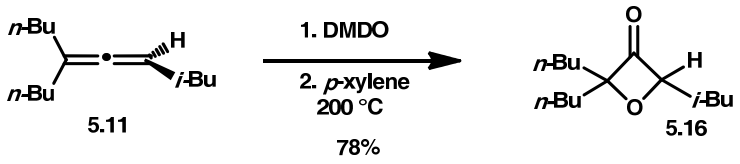


4.22

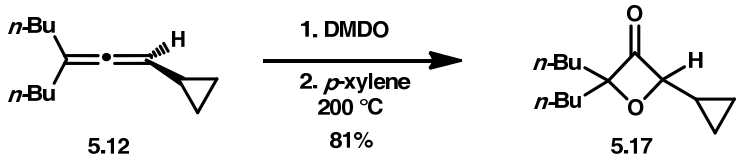
Experimental Chapter Five:

General procedure for preparation of oxetanones from allenes:

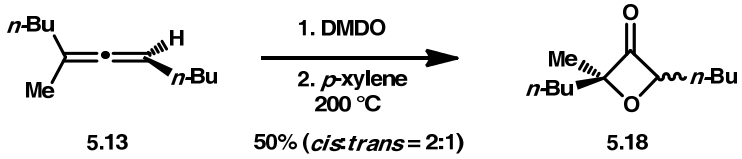
Dimethyldioxirane (DMDO) was prepared (~0.10 M) or extracted into halogenated solvent ($CHCl_3$ ~0.30 M, CH_2Cl_2 ~0.38 M, CCl_4 ~0.25 M). This solution (3 equiv.) was added drop-wise to a solution of the allene cooled to -40 °C and dissolved in the same solvent such that the final concentration of DMDO was ~0.10 M. The reaction was stirred under nitrogen and allowed to warm to room temperature (21 °C) over 2 h. The solvent was evaporated and the resulting SDE was dried and azerotroped under vacuum. The fresh prepared spirodiepoxide was then dissolved in *p*-xylene to make a 0.01 M solution and degassed and heated in a sealed tube at 200 °C for 2 h.



2,2-dibutyl-4-isobutyloxetan-3-one (5.16): Oxetanone **5.16** was prepared from allene **5.11** (20 mg, 0.083 mmol) using general procedure. The reaction mixture was concentrated and purified by flash chromatography (1% Et_2O/Hexanes) to give oxetanone **5.16** (18 mg, 78% yield) as a colorless oil. δ_H (500 MHz, $CDCl_3$) 5.23-5.19 (1 H, m), 1.88-1.42 (8 H, m), 1.41-1.17 (7 H, m), 0.99-0.88 (12 H, m); δ_C (125 MHz, $CDCl_3$) 210.1, 108.2, 95.9, 39.9, 35.3, 35.1, 25.9, 25.8, 25.1, 23.0(2), 22.9, 22.2, 13.9, 13.8.

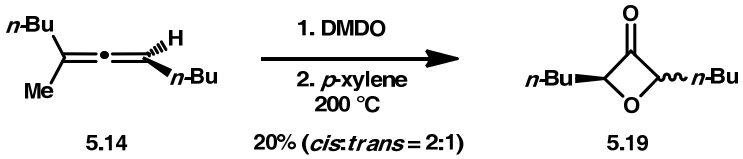


2,2-dibutyl-4-cyclopropyloxetan-3-one (5.17): Oxetanone **5.17** was prepared from allene **5.12** (20 mg, 0.10 mmol) using general procedure. The reaction mixture was concentrated and purified by flash chromatography (1% Et_2O/Hexanes) to give oxetanone **5.17** (19 mg, 81% yield) as a colorless oil. δ_H (400 MHz, $CDCl_3$) 4.55 (1 H, d, J = 8.8 Hz), 1.83-1.65 (4 H, m), 1.58-1.14 (8 H, m), 0.96-0.84 (7 H, m), 0.71-0.62 (2 H, m), 0.49-0.36 (2 H, m); δ_C (100 MHz, $CDCl_3$) 208.4, 107.8, 101.2, 34.9, 34.8, 25.7(2), 23.0, 22.9, 13.9, 13.8, 11.2, 2.6, 2.1.



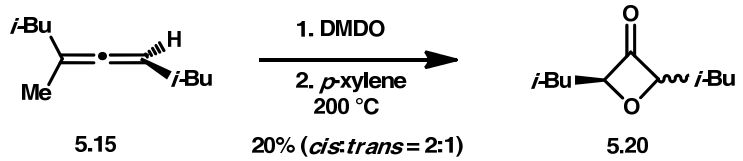
2,4-dibutyl-2-methyloxetan-3-one (5.18): Oxetanone **5.18** was prepared from allene **5.13** (20 mg, 0.12 mmol) using general procedure. The reaction mixture was concentrated and purified by flash chromatography (1% Et_2O/Hexanes) to give oxetanone **5.18** as a colorless oil of *cis* and *trans* oxetanones (12 mg, 50% yield, 2:1 *cis*:*trans*). *Cis* and *trans* isomers was separated by another column. ***Cis***: δ_H (500 MHz, $CDCl_3$) 5.19 (1 H, t, J = 6.9 Hz), 1.87-1.77 (2 H, m), 1.77-1.67 (2 H, m), 1.60-1.20 (8 H, m),1.47 (3 H, s), 0.92 (3 H, t, J = 7.2 Hz), 0.91 (3 H, t, J = 7.1 Hz); ***Trans***: δ_H (500 MHz, $CDCl_3$) 5.26 (1 H, dd, J = 8.0, 6.4 Hz), 1.87-1.66 (4 H, m), 1.53-1.22 (8 H, m),1.47 (3 H, s), 0.92 (3 H, t, J =

7.3 Hz), 0.91 (3 H, t, J = 7.1 Hz); δ_C (125 MHz, $CDCl_3$) 211.2, 104.8, 96.2, 36.4, 30.8, 27.0, 25.8, 22.9, 22.4, 21.5, 13.8(2).



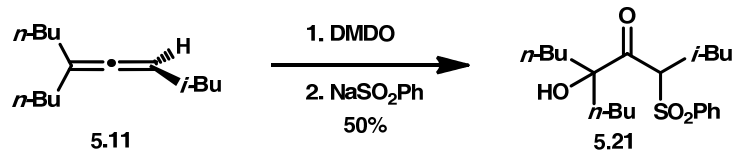
5.14 20% (*cis*:*trans* = 2:1) 5.19

2,4-dibutyloxetan-3-one (5.19): Oxetanone **5.19** was prepared from 20 mg allene **5.14** using general procedure. The reaction mixture was concentrated and crude NMR showed about 20% (2:1 *cis:trans*) of oxetanone products.



5.15 20% (*cis*:*trans* = 2:1) 5.20

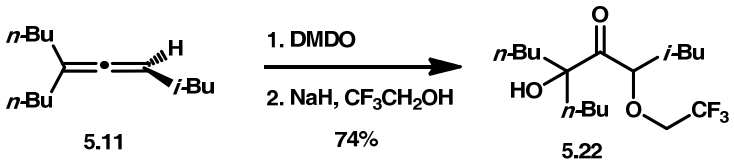
2,4-dibutyloxetan-3-one (5.20): Oxetanone **5.20** was prepared from allene **5.15** (20 mg, 0.12 mmol) using general procedure. The reaction mixture was concentrated and crude NMR showed about 20% (2:1 *cis:trans*) of oxetanone products.



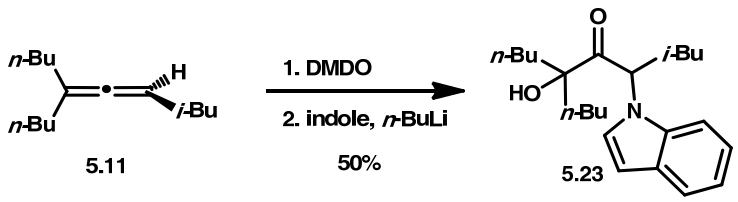
5.11 5.21

6-butyl-6-hydroxy-2-methyl-4-(phenylsulfonyl)decan-5-one (5.21): Allene **5.11** (20 mg, 0.083 mmol) was oxidized by DMDO using general procedure. The fresh prepared SDE was then dissolved in 0.5 mL THF and cooled to 0 °C. Sodium benzene sulfinate (20.5 mg, 0.125 mmol) was then added to above solution. The reaction was stirred for 1 h from 0 °C to rt. The reaction mixture was concentrated and purified by flash

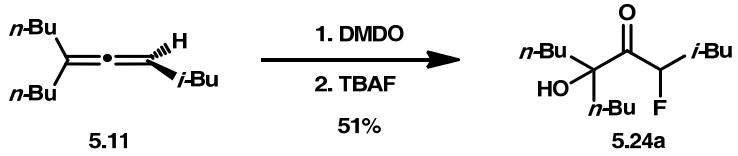
chromatography (4 % EtOAc/Hexanes) to give **5.21** (16 mg, 50 % yield) as a colorless oil.



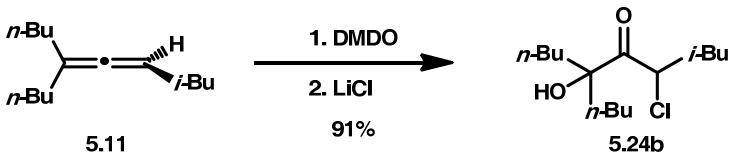
6-butyl-6-hydroxy-2-methyl-4-(phenylsulfonyl)decan-5-one (5.21): Allene **5.11** (20 mg, 0.083 mmol) was oxidized by DMDO using general procedure. Sodium hydride (5 mg, 60%, 0.125 mol) was added to 0.5 mL 2,2,2-trifluoroethanol at 0 °C. The fresh repaired SDE was dissolved in 0.2 mL 2,2,2-trifluoroethanol and added to above solution at 0 °C.s then added to above solution. The reaction was stirred for 30 min from 0 °C to rt. The reaction was quenched with saturated aq. NH_4Cl (2 ml), extracted with Et_2O (3 x 5 ml), dried over anhydrous Na_2SO_4 and evaporated to give crude product. Upon purification by flash chromatography (4 % EtOAc/Hexanes) gave **5.22** (21 mg, 74 % yield) as a colorless oil. IR ν_{max}(neat)/cm^{-1} 3497, 2960, 2874,1713, 1468, 1283, 1161, 670; δ_H (500 MHz, $CDCl_3$) 4.55 (1 H, dd, J = 8.9, 3.8 Hz), 4.00-3.90 (1 H, m), 3.69-3.60 (1 H, m), 2.57 (1 H, bs), 1.92-1.50 (7 H, m), 1.45-1.23 (6 H, m), 1.15-1.01 (2 H, m), 0.97 (3 H, d, J = 6.7 Hz), 0.96 (3 H, d, J = 6.7 Hz), 0.89 (3 H, t, J = 7.3 Hz), 0.88 (3 H, t, J = 7.2 Hz); δ_C (125 MHz, $CDCl_3$) 212.9, 123.8 (q, J = 279 Hz), 82.5 (d, J = 1.8 Hz), 81.2, 66.6 (m), 39.8, 39.6, 38.8, 38.7, 38.3, 25.5, 25.4, 24.5, 23.2, 22.9(2), 21.3, 13.9, 13.8; (ESI/MS) Calcd for *m/z* $C_{17}H_{32}F_3O_3^+$: 341.2 $[M+H]^+$; found 341.2.



6-butyl-6-hydroxy-4-(1H-indol-1-yl)-2-methyldecan-5-one (5.21): Allene **5.11** (20 mg, 0.083 mmol) was oxidized by DMDO using general procedure. To a solution of indole (30 mg, 0.25 mmol) in 0.5 mL THF was added 2.5 M *n*-BuLi (0.1 mL, 0.25 mmol) in hexanes solution at -78 °C slowly. The mixture was stirred at -78 °C for 45 min. The fresh repaired SDE was dissolved in 0.2 mL THF and added to above solution at -78 °C. The reaction was stirred for 2 h from -78 °C to 0 °C. The reaction was quenched with saturated aq. NH_4Cl (2 ml), extracted with Et_2O (3 x 5 ml), dried over anhydrous Na_2SO_4 and evaporated to give crude product. Upon purification by flash chromatography (10 % EtOAc/Hexanes) gave **5.23** (15 mg, 50 % yield) as a colorless oil. IR ν_{max}(neat)/cm^{-1} 3504, 2958, 2871, 1811, 1714, 1459, 738; δ_H (500 MHz, $CDCl_3$) 7.60 (1 H, d, J = 7.9 Hz), 7.42 (1 H, d, J = 8.3 Hz), 7.22 (1 H, td, J = 7.7, 1.1 Hz), 7.10 (1 H, td, J = 7.5, 0.8 Hz), 6.56 (1 H, d, J = 3.2 Hz), 5.62 (1 H, dd, J = 11.0, 3.8 Hz), 2.99 (1H, bs), 2.19 (1 H, td, J = 12.5, 3.8 Hz), 1.79-1.47 (5 H, m), 1.45-1.19 (6 H, m), 1.19-1.05 (1 H, m), 1.03-0.79 (12 H, m); 0.51 (2 H, t, J = 3.2 Hz); δ_C (125 MHz, $CDCl_3$) 211.0, 136.2, 128.5, 125.2, 121.9, 121.2, 119.8, 108.9, 103.1, 82.5, 77.2, 40.8, 38.7, 38.3, 25.5, 25.1, 24.2, 23.2, 22.9, 22.5, 21.8, 13.8, 13.5; (ESI/MS) Calcd for *m/z* $C_{23}H_{36}NO_2^+$: 358.3 $[M+H]^+$; found 358.3.

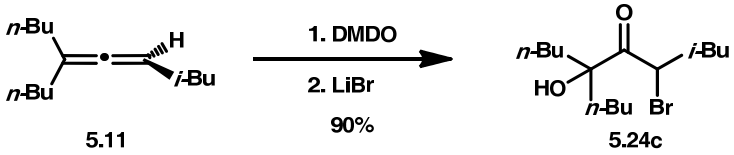


6-butyl-4-fluoro-6-hydroxy-2-methyldecan-5-one (5.24a): Allene **5.11** (20 mg, 0.083 mmol) was oxidized by DMDO using general procedure. The fresh prepared SDE was then dissolved in 0.5 mL THF and cooled to 0 °C. To above solution was added pre-dried (with molecular sieves) 1 M TBAF (0.17 mL, 0.17 mmol) solution in THF at 0 °C. The reaction was stirred for 2 h from 0 °C to rt. The reaction was quenched with saturated aq. NH_4Cl (2 ml), extracted with Et_2O (3 x 5 ml), dried over anhydrous Na_2SO_4 and evaporated to give crude product. Upon purification by flash chromatography (4 % EtOAc/Hexanes) gave **5.24a** (11 mg, 51 % yield) as a colorless oil. δ_H (500 MHz, $CDCl_3$) 5.15 (0.5 H, *J* = 9.7, 3.4 Hz), 5.05 (0.5 H, dd, *J* = 10.3, 2.8 Hz), 3.44 (1 H, bs), 1.95-1.83 (2 H, m), 1.81-1.60 (3 H, m), 1.47-1.21 (5 H, m), 0.99 (3 H, d, *J* = 6.6 Hz), 0.987 (3 H, d , *J* = 6.6 Hz), 0.890 (3 H, t, *J* = 7.3 Hz), 0.887 (3 H, t, *J* = 7.3 Hz); δ_C (125 MHz, $CDCl_3$) 212.8, 94.7, 93.2, 82.7, 82.6, 40.9, 40.8, 37.9, 37.9, 37.8, 25.8, 25.7, 24.6(d), 23.1, 22.9(d), 21.3, 13.9(2); (ESI/MS) Calcd for *m/z* $C_{15}H_{30}FO_2^+$: 261.2 $[M+H]^+$; found 261.2.



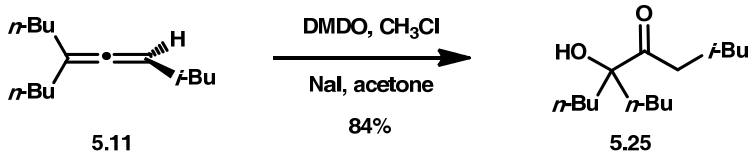
6-butyl-4-chloro-6-hydroxy-2-methyldecan-5-one (5.24b): Allene **5.11** (20 mg, 0.083 mmol) was oxidized by DMDO using general procedure. Lithium chloride (5.3 mg, 0.125 mmol) in a flask was flame dried and cooled. To above flask the fresh prepared SDE in 0.5 mL THF was added in one potion. The reaction was stirred for 2 h at rt. The reaction was quenched with saturated aq. NH_4Cl (2 ml), extracted with Et_2O (3 x 5 ml), dried over anhydrous Na_2SO_4 and evaporated to give crude product. Upon purification by flash

chromatography (4 % EtOAc/Hexanes) gave **5.24b** (21 mg, 91 % yield) as a colorless oil. IR ν_{max}(neat)/cm^{-1} 3513, 2958, 2872, 1720, 1467; δ_H (400 MHz, $CDCl_3$) 4.78 (1 H, dd, J = 10.2, 3.9 Hz), 3.00 (1 H, bs), 1.95-1.82 (2 H, m), 1.81-1.62 (4 H, m), 1.60-1.48 (1 H, m), 1.47-1.20 (10 H, m), 1.00-0.84 (12 H, m); δ_C (125 MHz, $CDCl_3$) 208.9, 82.8, 54.3, 41.9, 38.6, 38.5, 25.6, 25.5, 24.8, 23.1, 22.9(2), 21.1, 13.9(2); (ESI/MS) Calcd for *m/z* $C_{15}H_{30}ClO_2^+$: 277.2 $[M+H]^+$; found 277.2.



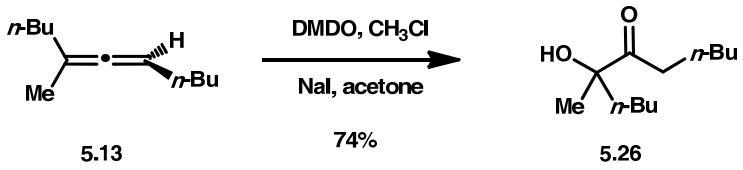
5.11 5.24c

4-bromo-6-butyl-6-hydroxy-2-methyldecan-5-one (5.24c): Allene **5.11** (20 mg, 0.083 mmol) was oxidized by DMDO using general procedure. Lithium bromide (11 mg, 0.125 mmol) in a flask was flame dried and cooled. To above flask the fresh prepared SDE in 0.5 mL THF was added in one potion. The reaction was stirred for 2 h at rt. The reaction was quenched with saturated aq. NH_4Cl (2 ml), extracted with Et_2O (3 x 5 ml), dried over anhydrous Na_2SO_4 and evaporated to give crude product. Upon purification by flash chromatography (4 % EtOAc/Hexanes) gave **5.24c** (24 mg, 90 % yield) as a colorless oil. IR ν_{max}(neat)/cm^{-1} 3513, 2958, 2872, 1720, 1467; δ_H (300 MHz, $CDCl_3$) 4.71 (1 H, t, J = 6.9 Hz), 2.98 (1 H, bs), 1.95-1.01 (26 H, m), 0.99-0.80 (12 H, m); δ_C (125 MHz, $CDCl_3$) 208.6, 82.7, 44.6, 41.9, 38.8, 38.4, 25.8, 25.6, 25.5, 22.9(3), 21.3, 14.1(2); (ESI/MS) Calcd for *m/z* $C_{15}H_{30}BrO_2^+$: 321.1, 323.1 $[M+H]^+$; found 321.1, 323.1.



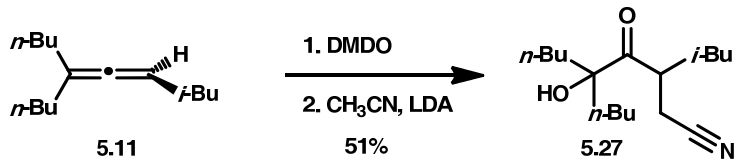
5.11 5.25

6-butyl-6-hydroxy-2-methyldecan-5-one (5.25): Allene **5.11** (20 mg, 0.083 mmol) was oxidized by DMDO using general procedure. The fresh prepared SDE was then dissolved in 0.5 mL acetone. Sodium iodide (25 mg, 0.166 mmol) was then added to above solution. The reaction was stirred for 30 min at rt. The reaction was quenched with saturated aq. NH_4Cl (2 ml), extracted with Et_2O (3 x 5 ml), dried over anhydrous Na_2SO_4 and evaporated to give crude product. Upon purification by flash chromatography (2 % EtOAc/Hexanes) gave know compound **5.25** (17 mg, 84 % yield) as a colorless oil. The observed NMR data were identical with literature values.



5.13 5.26

5-hydroxy-5-methylundecan-6-one (5.26): Allene **5.13** (20 mg, 0.10 mmol) was oxidized by DMDO general procedure. The fresh prepared SDE was then dissolved in 0.5 mL acetone. Sodium iodide (30 mg, 0.20 mmol) was then added to above solution. The reaction was stirred for 30 min at rt. The reaction was quenched with saturated aq. NH_4Cl (2 ml), extracted with Et_2O (3 x 5 ml), dried over anhydrous Na_2SO_4 and evaporated to give crude product. Upon purification by flash chromatography (2 % EtOAc/Hexanes) gave know compound **5.26** (15 mg, 74 % yield) as a colorless oil. The observed NMR data were identical with literature values.

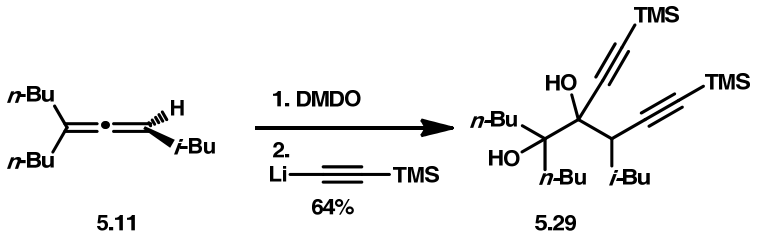


5.11 5.27

5-butyl-5-hydroxy-3-isobutyl-4-oxononanenitrile (5.27): Allene **5.11** (20 mg, 0.083 mmol) was oxidized by DMDO using general procedure. To a solution of diisopropylamine (36 µL, 0.25 mmol) in 0.5 mL THF at -78 °C was added 2.5 M *n*-BuLi (0.10 mL, 0.25 mmol) in hexanes solution slowly. The mixture was stirred at -78 °C for 45 min. Acetonitrile (13 µL, 0.25 mmol) was added to the LDA solution at -78 °C. The fresh prepared SDE was then dissolved in 0.2 mL THF and added to above solution. The reaction was stirred for 2 h from -78 °C to 0 °C . The reaction was quenched with saturated aq. NH_4Cl (2 ml), extracted with Et_2O (3 x 5 ml), dried over anhydrous Na_2SO_4 and evaporated to give crude product. Upon purification by flash chromatography (10 % EtOAc/Hexanes) gave compound **5.27** (12 mg, 51 % yield) as a colorless oil. IR ν_{max}(neat)/cm^{-1} 3488, 2958, 2932, 2872, 2252, 1709, 1467; δ_H (500 MHz, $CDCl_3$) 3.47-3.39 (1 H, m), 2.61 (1 H, dd, *J* = 16.9, 7.6 Hz), 2.51 (1 H, bs), 2.43 (1 H, dd, *J* = 16.9, 5.2 Hz), 1.77-1.52 (6 H, m), 1.45-1.24 (7 H, m), 1.16-1.04 (2 H, m), 0.96 (3 H, d, *J* = 3.1 Hz), 0.95 (3 H, d, *J* = 3.1 Hz), 0.90 (6 H, t, *J* = 7.3 Hz); δ_C (125 MHz, $CDCl_3$) 214.4, 118.3, 82.7, 40.2, 40.0, 38.3, 38.0, 25.6, 25.5, 23.3, 22.9(2), 18.6, 13.9; (ESI/MS) Calcd for *m/z* $C_{17}H_{32}NO_2^+$: 282.2 $[M+H]^+$; found 282.2.

6-butyl-2-methyl-4,5-divinyldecane-5,6-diol (5.28): Allene **5.11** (20 mg, 0.083 mmol) was oxidized by DMDO using general procedure. The fresh prepared SDE was dissolved in 0.5 mL THF. To above solution 2.8 M vinyllithium (0.12 mL, 0.333 mmol) in THF solution was added slowly at 0 °C The mixture was stirred for 1 h from 0 °C to rt. The

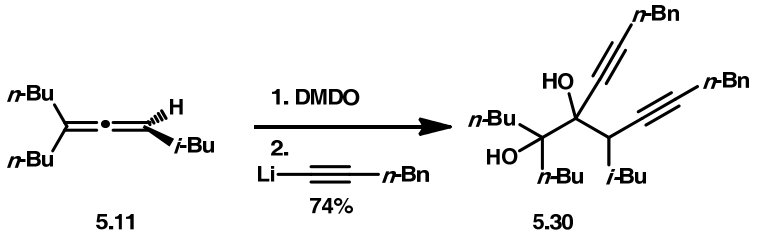
reaction was quenched with saturated aq. NH_4Cl (2 ml), extracted with Et_2O (3 x 5 ml), dried over anhydrous Na_2SO_4 and evaporated to give crude product. Upon purification by flash chromatography (10 % EtOAc/Hexanes) gave compound **5.28** (19 mg, 77 % yield) as a colorless oil. IR ν_{max}(neat)/cm^{-1} 3501, 3073, 2957, 2871, 1467, 922; δ_H (500 MHz, $CDCl_3$) 5.84-5.69 (2 H, m), 5.37 (1 H, dd, *J* = 17.1, 2.1 Hz), 5.24-5.17 (2 H, m), 5.12 (1 H, dd, *J* = 17.6, 1.8 Hz), 2.81 (1 H, bs), 2.42 (1 H, td, J = 10.6, 2.6 Hz), 2.00 (1 H, bs), 1.75-1.61 (2 H, m), 1.52-1.40 (3 H, m), 1.39-1.18 (10 H, m), 0.98-0.76 (12 H, m); δ_C (100 MHz, $CDCl_3$) 141.1, 139.3, 117.6, 115.0, 81.4, 79.5, 47.6, 38.2, 35.7, 34.8, 26.6, 26.2, 24.8, 24.2, 23.7, 23.5, 20.8, 14.1, 14.0; (ESI/MS) Calcd for *m/z* $C_{19}H_{37}O_2^+$: 297.3 $[M+H]^+$; found 297.3.



5.11 5.29

6-butyl-2-methyl-4,5-bis((trimethylsilyl)ethynyl)decane-5,6-diol (5.29): Allene **5.11** (20 mg, 0.083 mmol) was oxidized by DMDO using general procedure. To a solution of trimethylsilylacetylene (47 μL, 0.33 mmol) in 0.5 THF at -78 °C was added 2.5 M *n*-BuLi (0.133 mL, 0.33 mmol) in hexanes solution slowly. The fresh prepared SDE was then dissolved in 0.2 mL THF and added to above solution at -78 °C. The mixture was stirred for 1 h from -78 °C to 0 °C. The reaction was quenched with saturated aq. NH_4Cl (2 ml), extracted with Et_2O (3 x 5 ml), dried over anhydrous Na_2SO_4 and evaporated to give crude product. Upon purification by flash chromatography (2 % EtOAc/Hexanes) gave compound **5.29** (18 mg, 64 % yield) as a colorless oil. δ_H (400 MHz, $CDCl_3$) 3.55

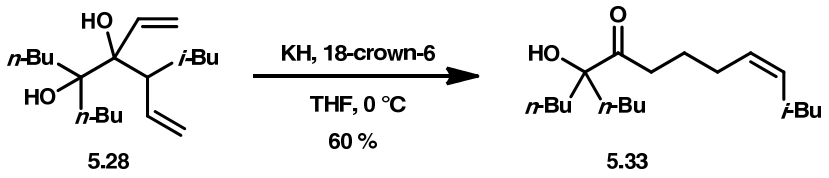
(1 H, bs), 3.25 (1 H, bs), 2.70-2.63 (1 H, m), 1.93-1.67 (6 H, m), 1.60-1.19 (9 H, m), 1.02-0.82 (12 H, m), 0.16 (9 H, s), 0.15 (9 H, s); δ_C (100 MHz, $CDCl_3$) 108.1, 106.1, 92.2, 91.5, 80.0, 76.6, 39.7, 38.9, 36.3, 34.6, 27.4, 25.8, 25.8, 25.7, 23.9, 23.9, 23.6, 23.5, 21.2 14.1(2), -0.1(3), -0.4 (3); (ESI/MS) *m/z* Calcd for $C_{25}H_{49}O_2Si_2$: 437.3 [M+H]; found 437.3.



5.11 5.30

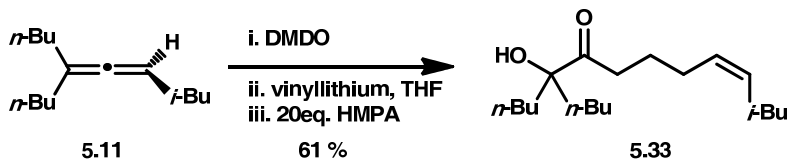
5-butyl-6-(hex-1-yn-1-yl)-7-isobutyltridec-8-yne-5,6-diol (5.30): Allene **5.11** (20 mg, 0.083 mmol) was oxidized by DMDO using general procedure. To a solution of 1-hexyne (37 µL, 0.33 mmol) in 0.5 THF at -78 °C was added 2.5 M *n*-BuLi (0.133 mL, 0.33 mmol) in hexanes solution slowly. The fresh prepared SDE was then dissolved in 0.2 mL THF and added to above solution at -78 °C. The mixture was stirred for 1 h from -78 °C to 0 °C. The reaction was quenched with saturated aq. NH_4Cl (2 ml), extracted with Et_2O (3 x 5 ml), dried over anhydrous Na_2SO_4 and evaporated to give crude product. Upon purification by flash chromatography (2 % EtOAc/Hexanes) gave compound **5.30** (25 mg, 74 % yield) as a colorless oil. IR ν_{max}(neat)/cm^{-1} 3501, 2957, 2871, 2234, 1685, 1467; δ_H (500 MHz, $CDCl_3$) 3.41 (1 H, bs), 3.22 (1 H, bs), 2.66-2.60 (1 H, m), 2.26-2.14 (4 H, m), 1.89-1.68 (7 H, m), 1.58-1.23 (16 H, m), 1.00-0.86 (18 H, m); δ_C (100 MHz, $CDCl_3$) 87.8, 87.0, 80.8, 80.5, 79.9, 76.3, 40.0, 38.0, 36.3, 34.5, 30.8, 30.4, 27.1, 25.9, 25.7, 24.0,

23.6, 22.0, 21.9, 21.1, 18.4(2), 14.1, 14.0, 13.5(2); (ESI/MS) *m/z* Calcd for $C_{27}H_{49}O_2^+$: 405.4 [M+H]; found 405.4.



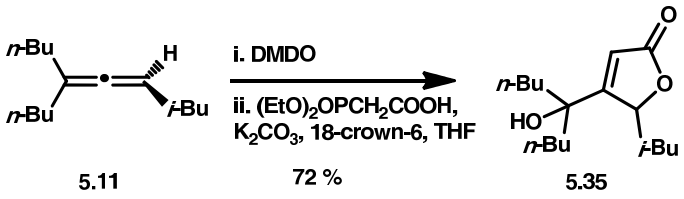
5.28 5.33

***(Z)*-5-butyl-5-hydroxy-13-methyltetradec-10-en-6-one (5.33):** To a suspension of potassium hydride (15 mg, 35%, 0.13 mmol) in 0.5 mL THF was added 18-crown-6 (34 mg, 0.13 mmol) at 0 °C. Diol **5.28** was dissolved in 0.2 mL THF and added to above solution at 0 °C. The reaction was stirred for 45 min at 0 °C. The reaction was quenched with saturated aq. NH_4Cl (2 ml), extracted with Et_2O (3 x 5 ml), dried over anhydrous Na_2SO_4 and evaporated to give crude product. Upon purification by flash chromatography (2 % EtOAc/Hexanes) gave compound **5.33** (15 mg, 60 % yield) as a colorless oil. IR ν_{max}(neat)/cm^{-1} 3482, 3007, 2956, 2871, 1704, 1455, 1086; δ_H (500 MHz, $CDCl_3$) 5.50-5.32 (2 H, m), 3.88 (1 H, bs), 2.45 (2 H, t, *J* = 7.5 Hz), 2.07 (2 H, q, *J* = 7.2 Hz), 1.92 (2 H, t, *J* = 6.9 Hz), 1.73-1.57 (8 H, m), 1.44-1.22 (7 H, m), 0.92-0.84 (12 H, m); δ_C (125 MHz, $CDCl_3$) 214.4, 129.8, 129.1, 81.5, 38.7(2), 36.4, 35.4, 28.6, 26.7, 25.5(2), 23.4, 22.9(2), 22.3(2), 13.9(2); (ESI/MS) *m/z* Calcd for $C_{19}H_{37}O_2^+$: 297.3 $[M+H]^+$; found 297.3.



5.11 61 % 5.33

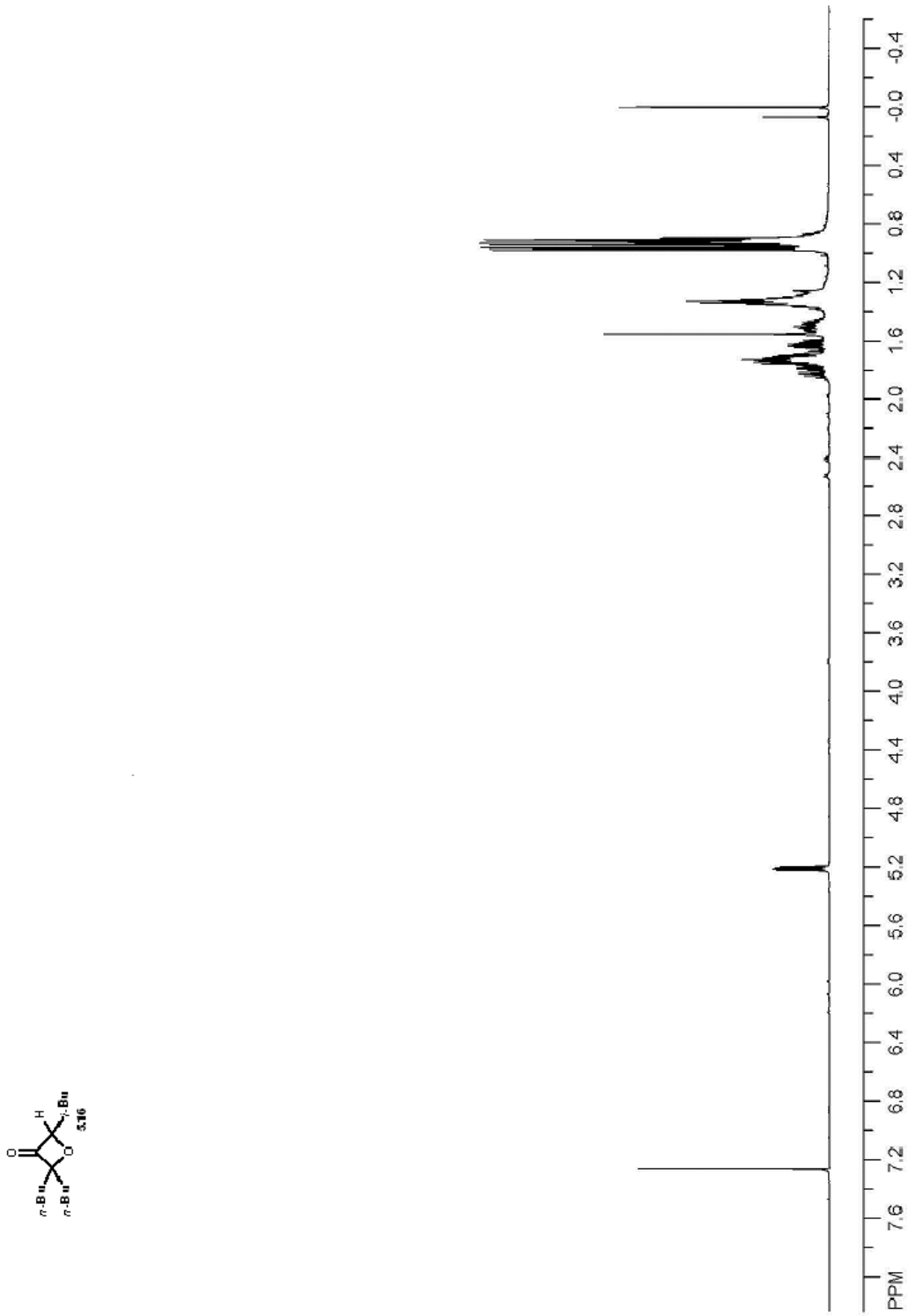
***(Z)*-5-butyl-5-hydroxy-13-methyltetradec-10-en-6-one (5.33):** Allene **5.11** (20 mg, 0.083 mmol) was oxidized by DMDO using general procedure. The fresh prepared SDE was dissolved in 0.5 mL THF. To above solution 2.8 M vinyllithium (0.12 mL, 0.333 mmol) in THF solution was added slowly at 0 °C The mixture was stirred for 1 h from 0 °C to rt. HMPA (0.3 mL, 1.6 mmol) was then added to the reaction mixture. The reaction was stirred at 0 °C for another hour. The reaction was stirred for 45 min at 0 °C. The reaction was quenched with saturated aq. NH_4Cl (2 ml), extracted with Et_2O (3 x 5 ml), dried over anhydrous Na_2SO_4 and evaporated to give crude product. Upon purification by flash chromatography (2 % EtOAc/Hexanes) gave compound **5.33** (15 mg, 61 % yield) as a colorless oil.



5.11 72 % 5.35

4-(5-hydroxynonan-5-yl)-5-isobutylfuran-2(5H)-one (5.35): Allene **5.11** (20 mg, 0.083 mmol) was oxidized by DMDO using general procedure. To a solution of diethylphosphonoacetic acid in 1 mL THF was added potassium carbonate (69 mg, 0.5 mmol) and 18-crown-6 (44 mg, 0.166 mmol). The mixture was stirred for 1 h at rt. The fresh prepared SDE was dissolved in 0.2 mL THF and added to above solution at rt. The reaction was stirred for 4 h at rt. The reaction was quenched with saturated aq. NH_4Cl (2 ml), extracted with Et_2O (3 x 5 ml), dried over anhydrous Na_2SO_4 and evaporated to give crude product. Upon purification by flash chromatography (15 % EtOAc/Hexanes) gave compound **5.35** (17 mg, 72 % yield) as a colorless oil. δ_H (400 MHz, $CDCl_3$) 5.77 (1 H, d, J = 1.6 Hz), 5.05 (1 H, dt, J = 10.9, 1.8 Hz), 2.06-1.88 (2 H, m), 1.74-1.60 (4 H, m), 1.43-

1.11 (10 H, m), 1.01 (3 H, d, J = 6.3 Hz), 0.97 (3 H, d, J = 6.3 Hz), 0.94-0.87 (6 H, m); δ_C (100 MHz, $CDCl_3$) 177.8, 172.8, 115.9, 82.6, 76.1, 42.5, 41.7, 41.2, 25.6(2), 25.4, 23.7, 22.9, 22.8, 21.1, 13.9(2); (ESI/MS) *m/z* Calcd for $C_{17}H_{30}O_3$: 283.2 [M+H]; found 283.2.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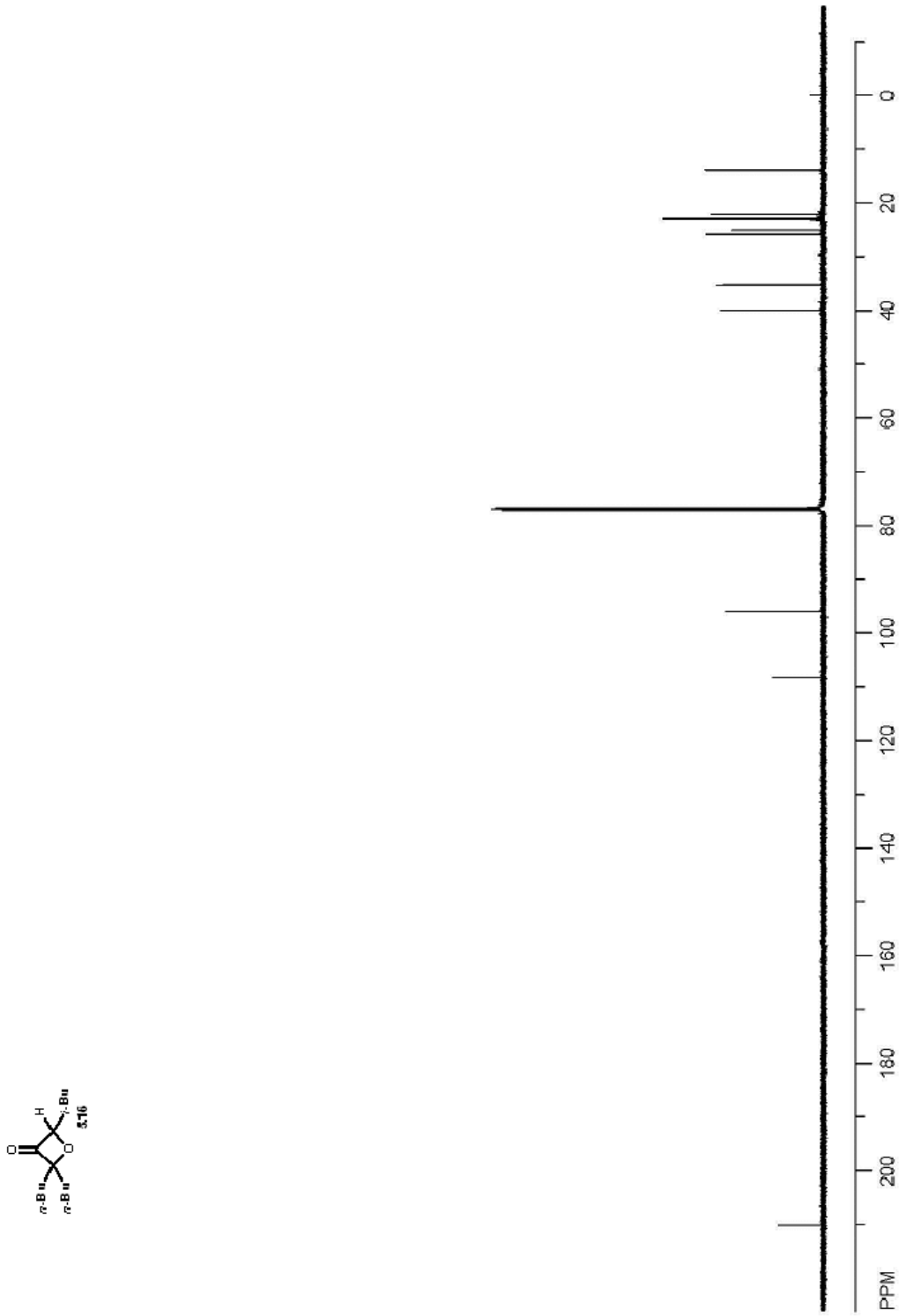
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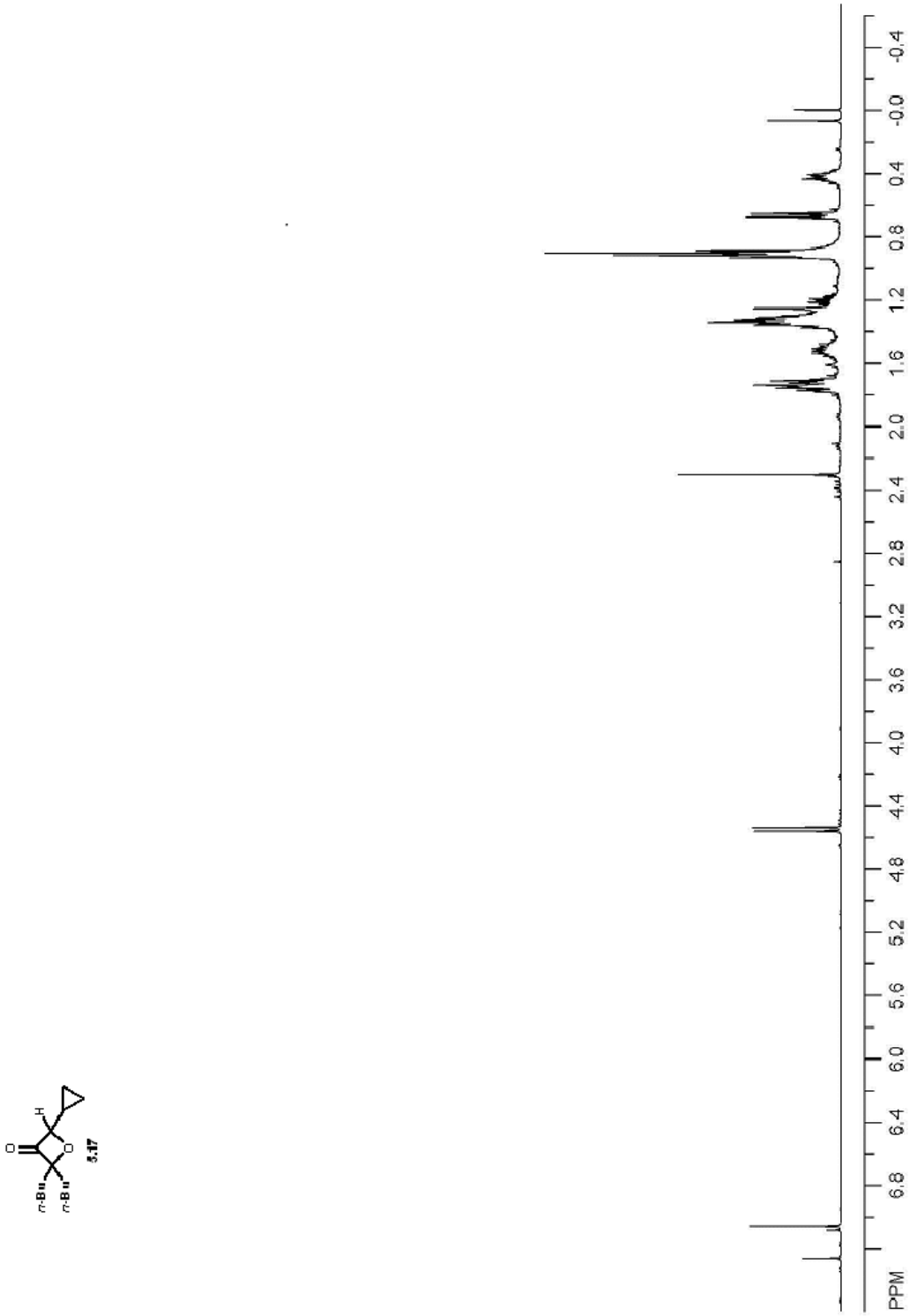
200

5.16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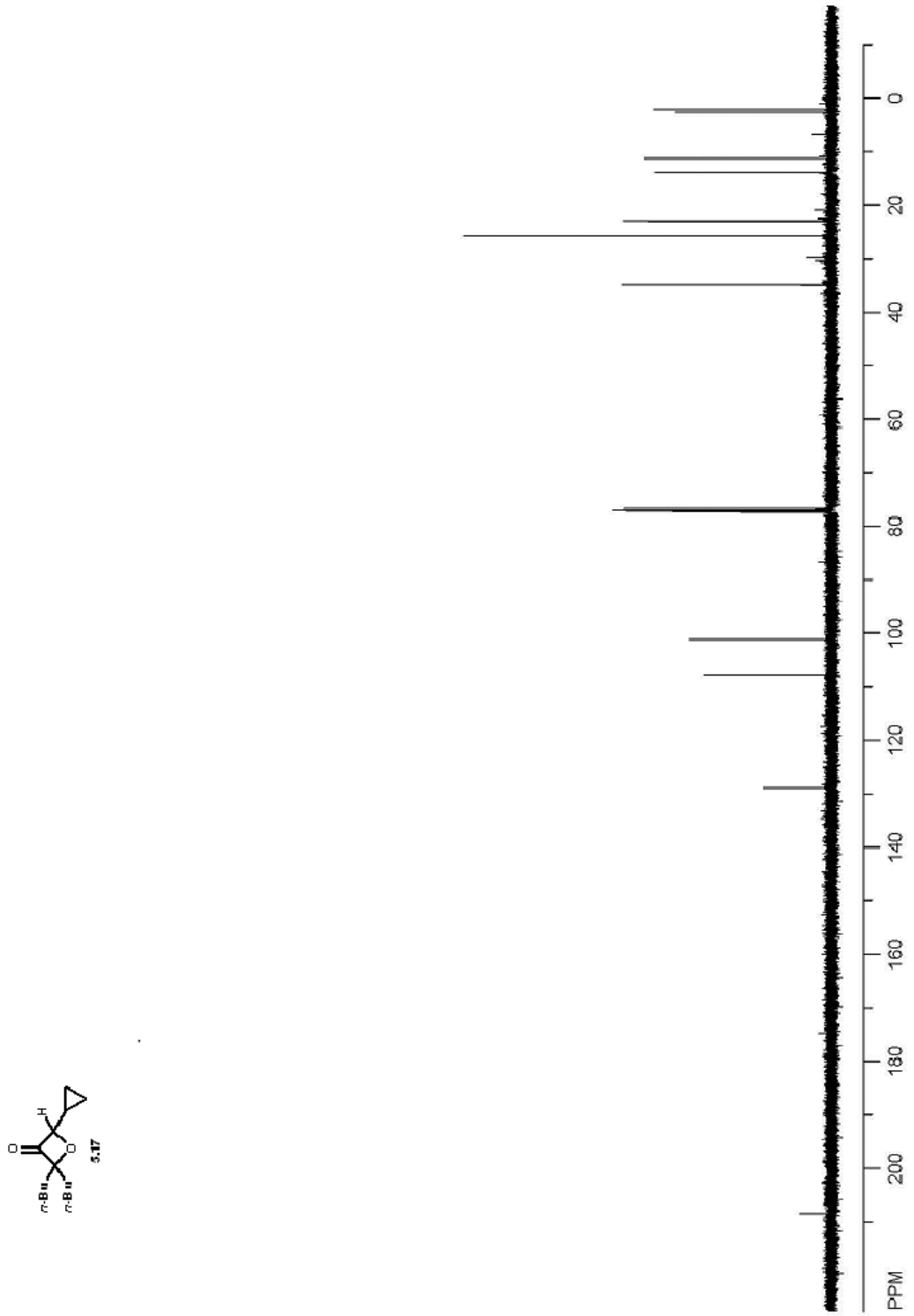
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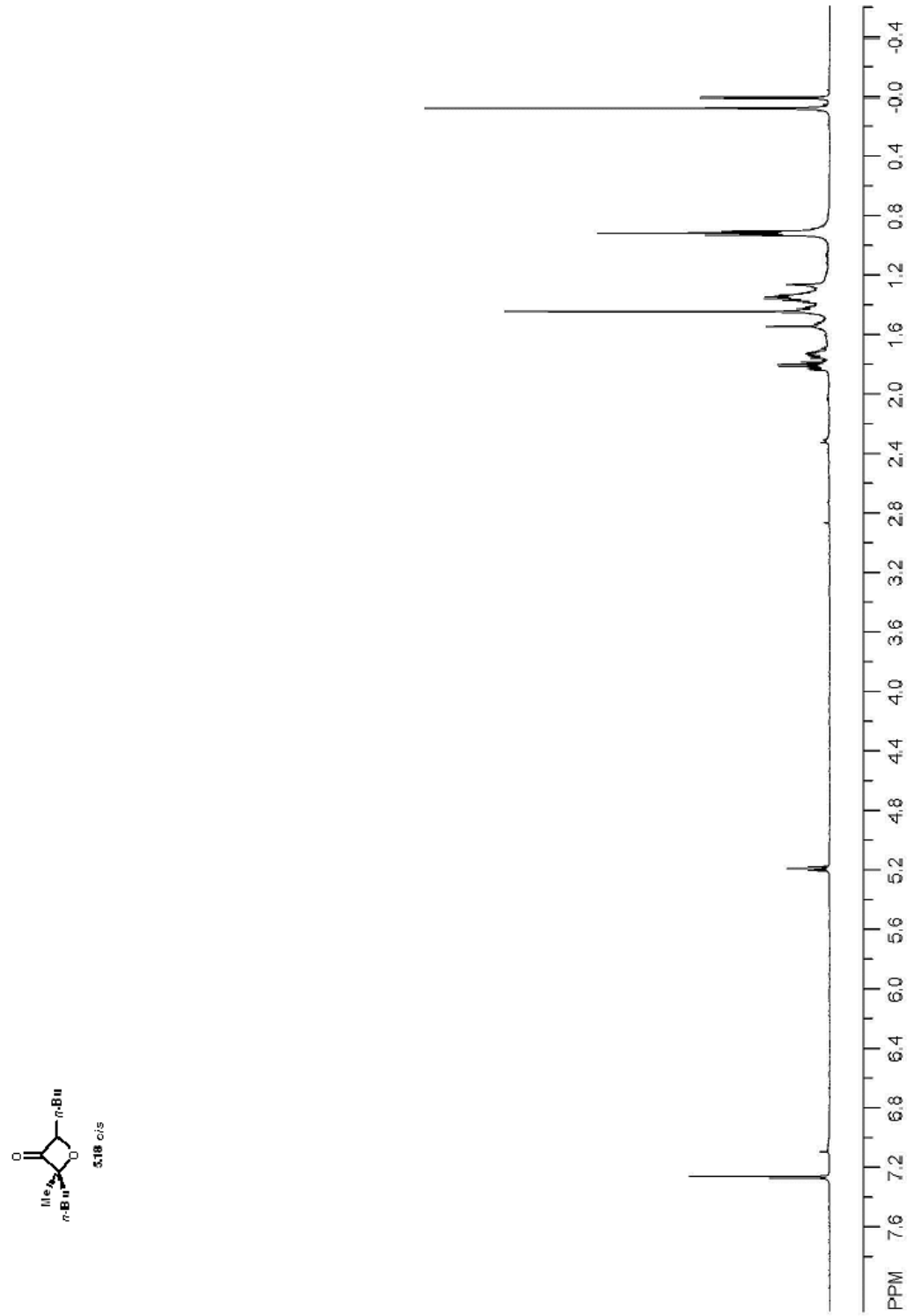
80
100
120
140
160
180
200


PPM
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6.8
6.4
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5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
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0.4
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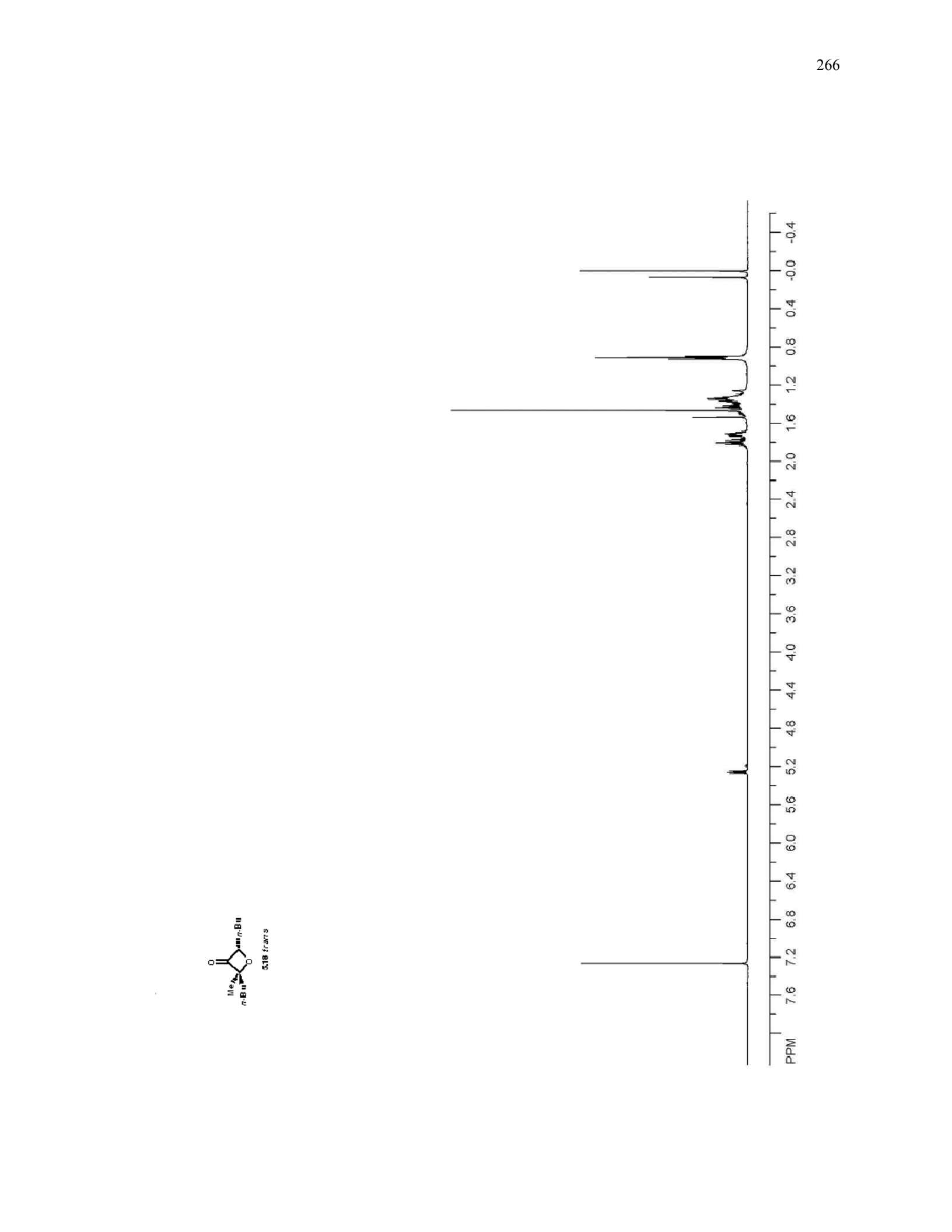
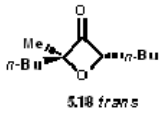
-0.4

O
O
O
Me
n-Bu
n-Bu

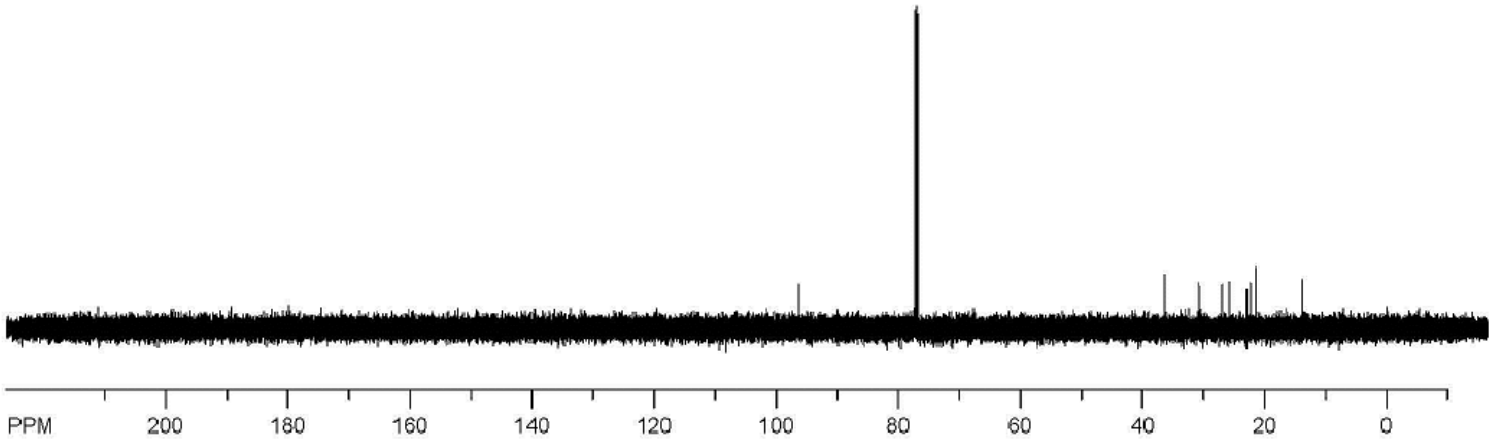
5.18 *cis*

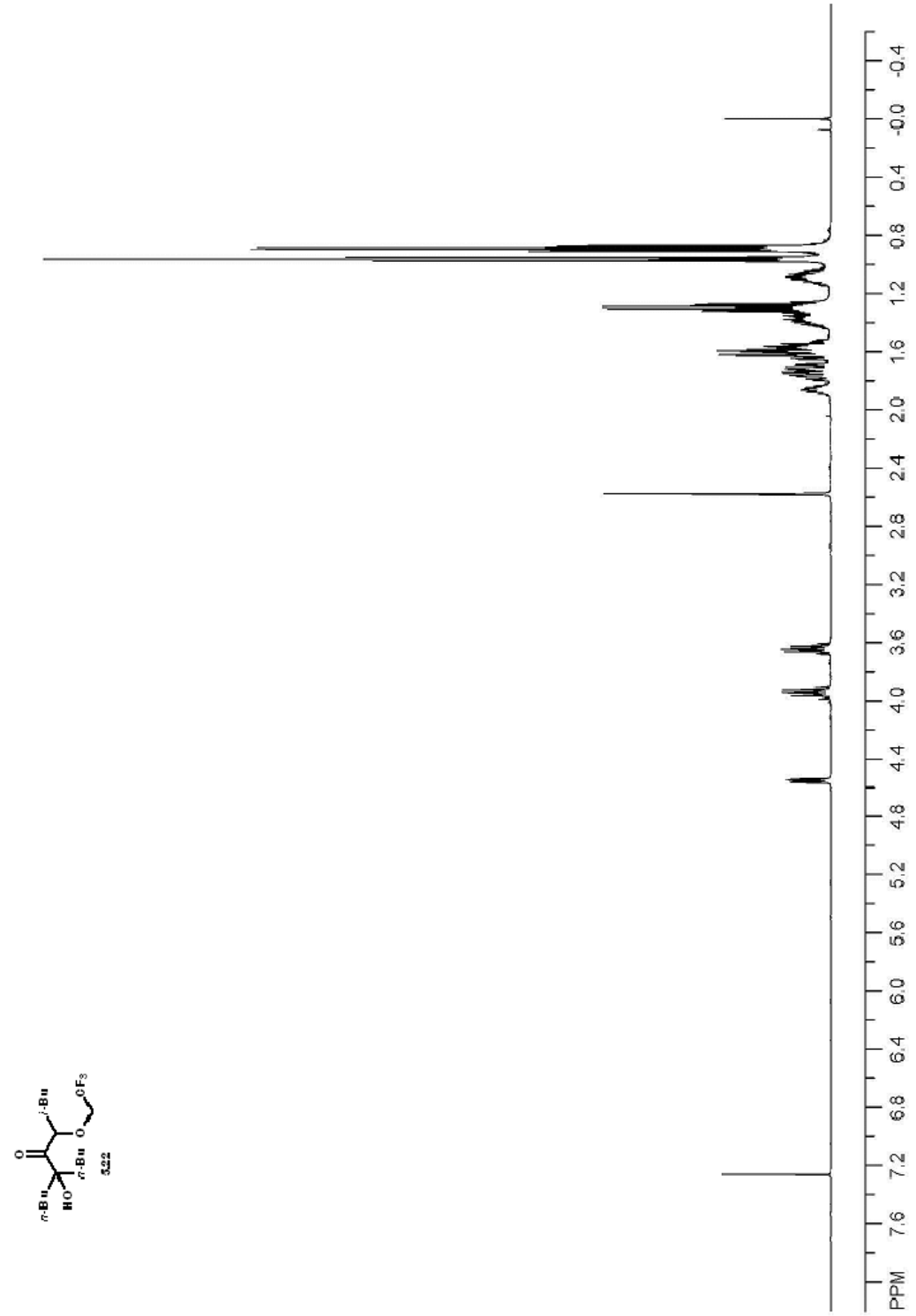


5.18 *trans*



5.18 *trans*

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6.4
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5.6
5.2
4.8
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2.8
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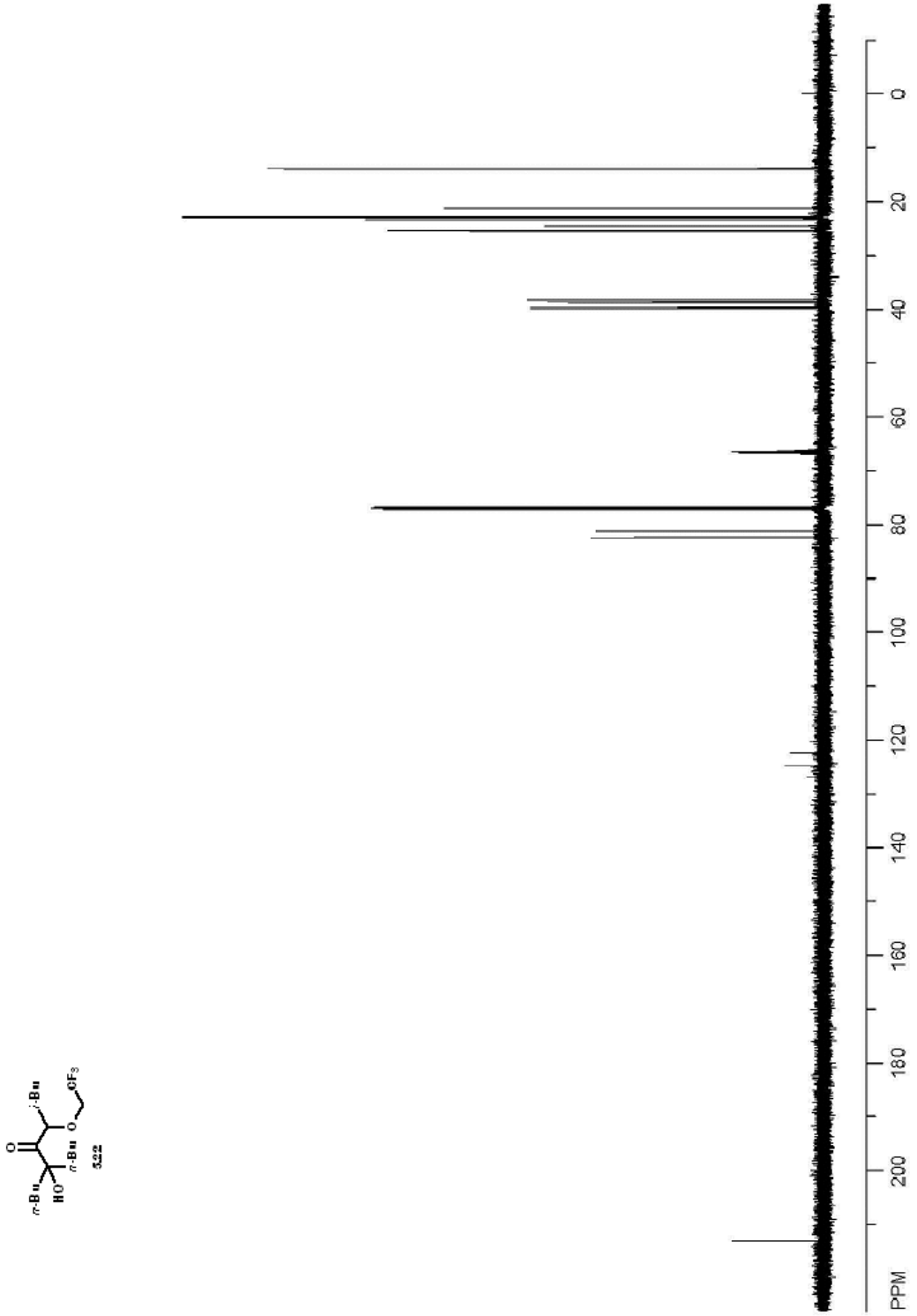
PPM
0
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n-Bu
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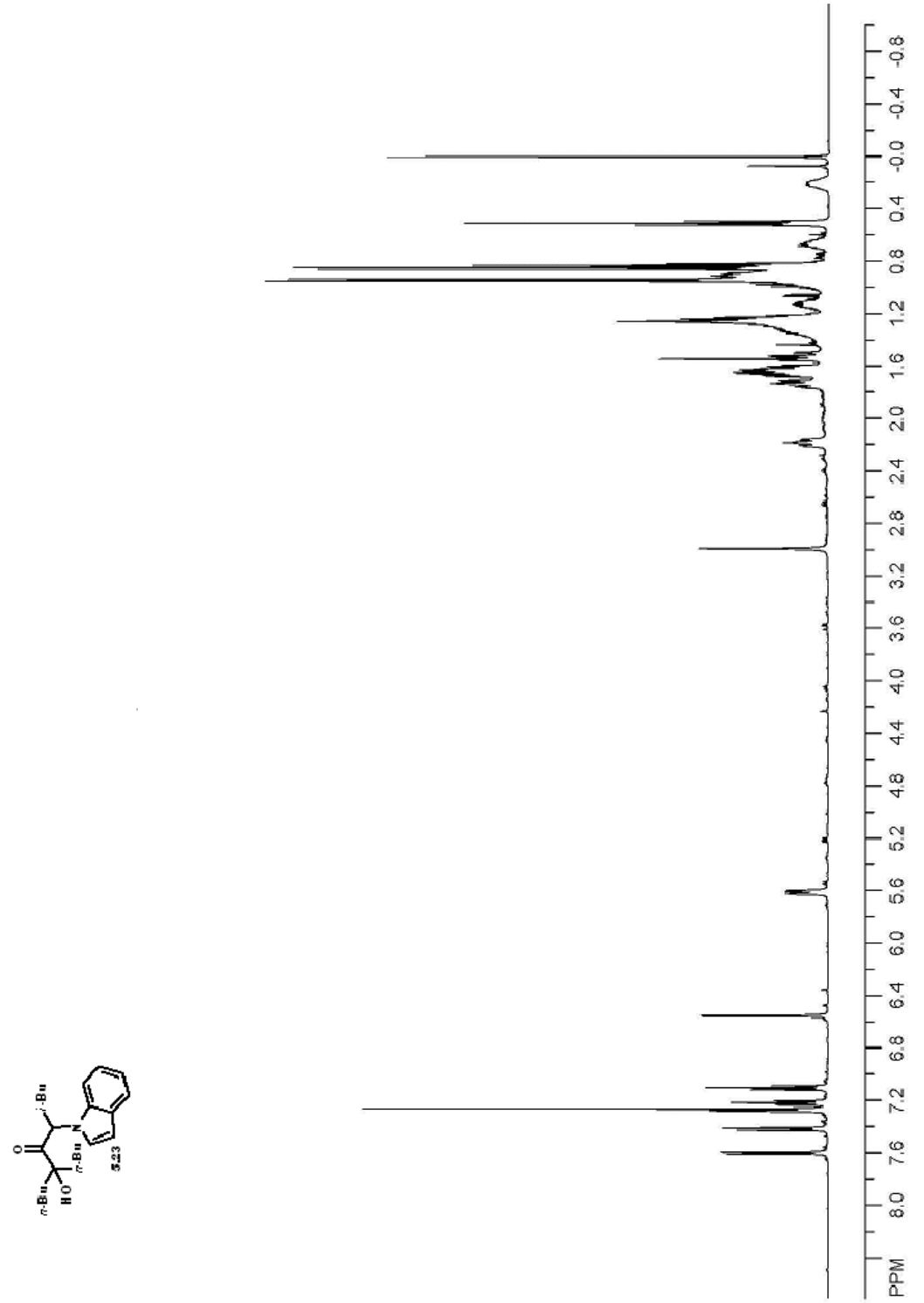
i-Bu
O
CF3
522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3.6
3.2
2.8
2.4
2.0
1.6
1.2
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-0.0
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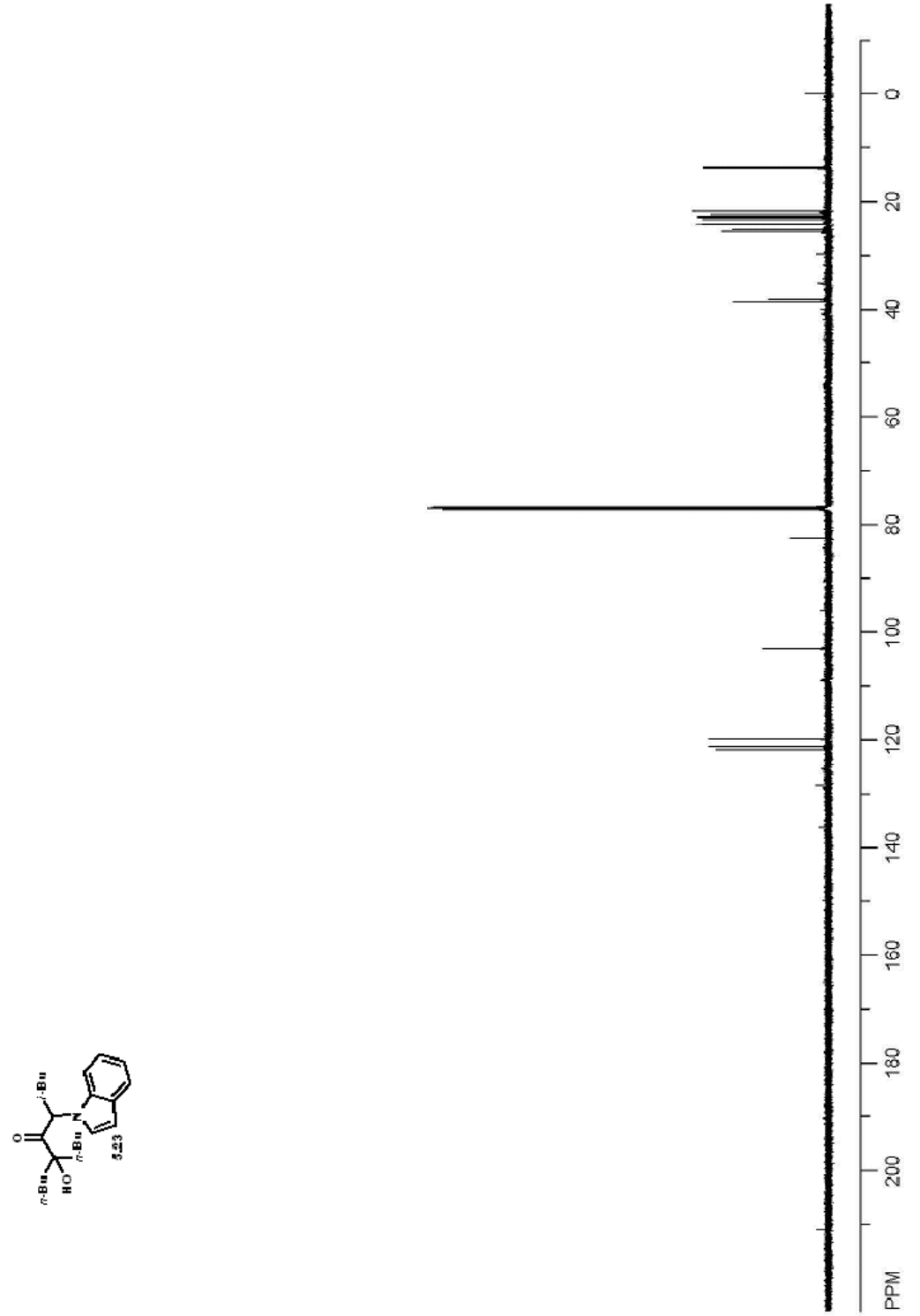
-0.8
n-Bu
i-Bu
n-Bu
HO
N
O
523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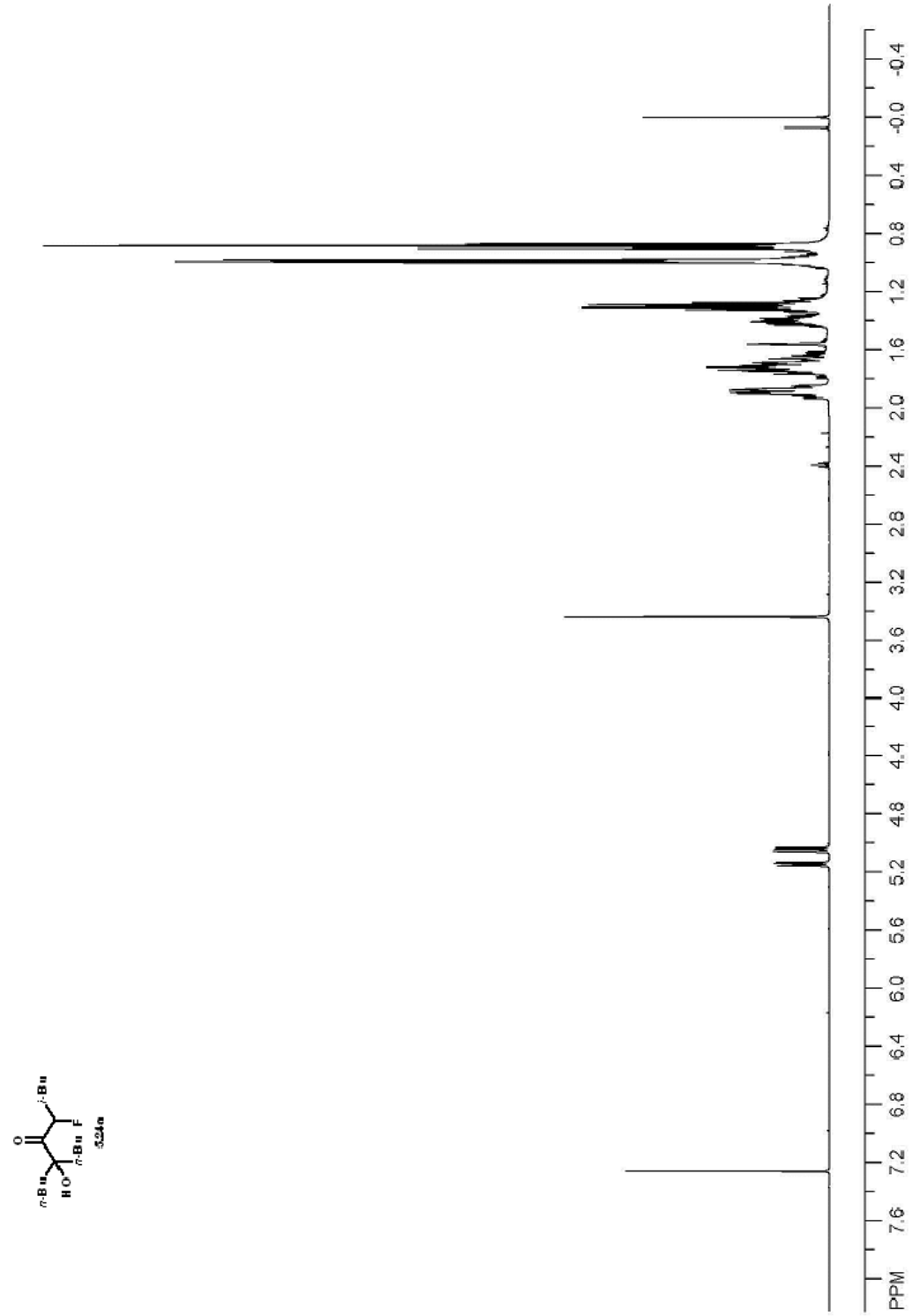
5.23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6.8
6.4
6.0
5.6
5.2
4.8
4.4
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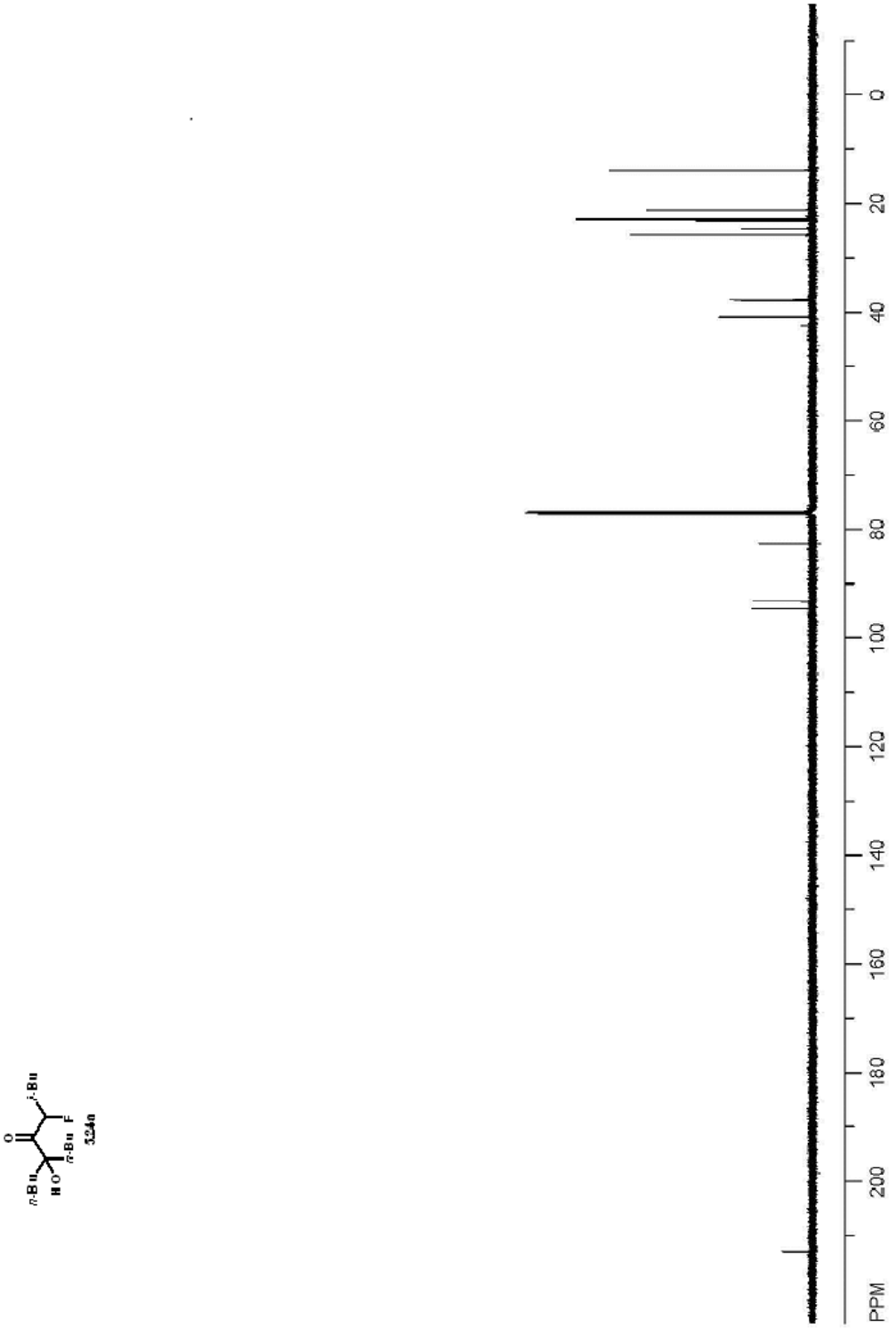
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
-0.0
-0.4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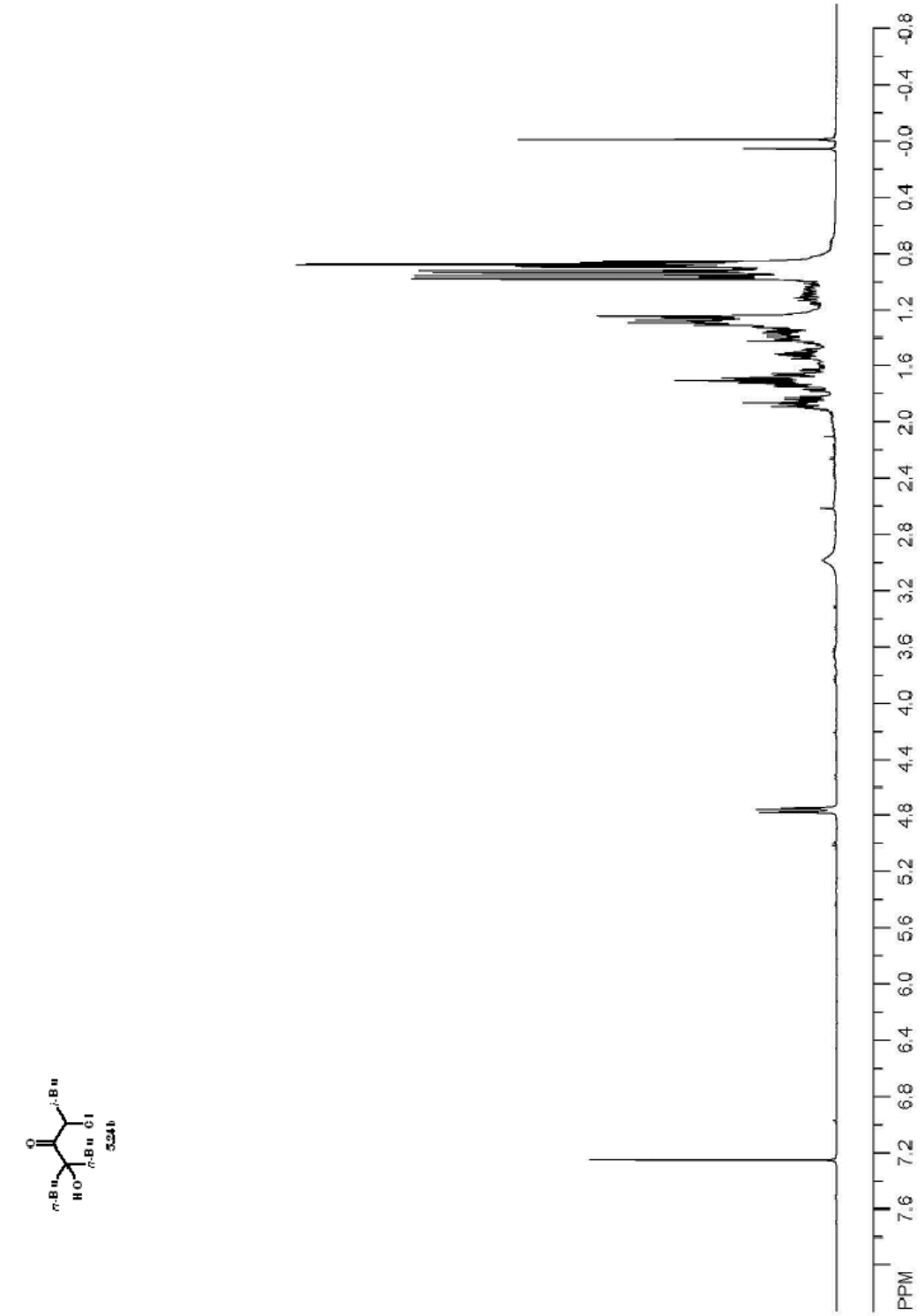
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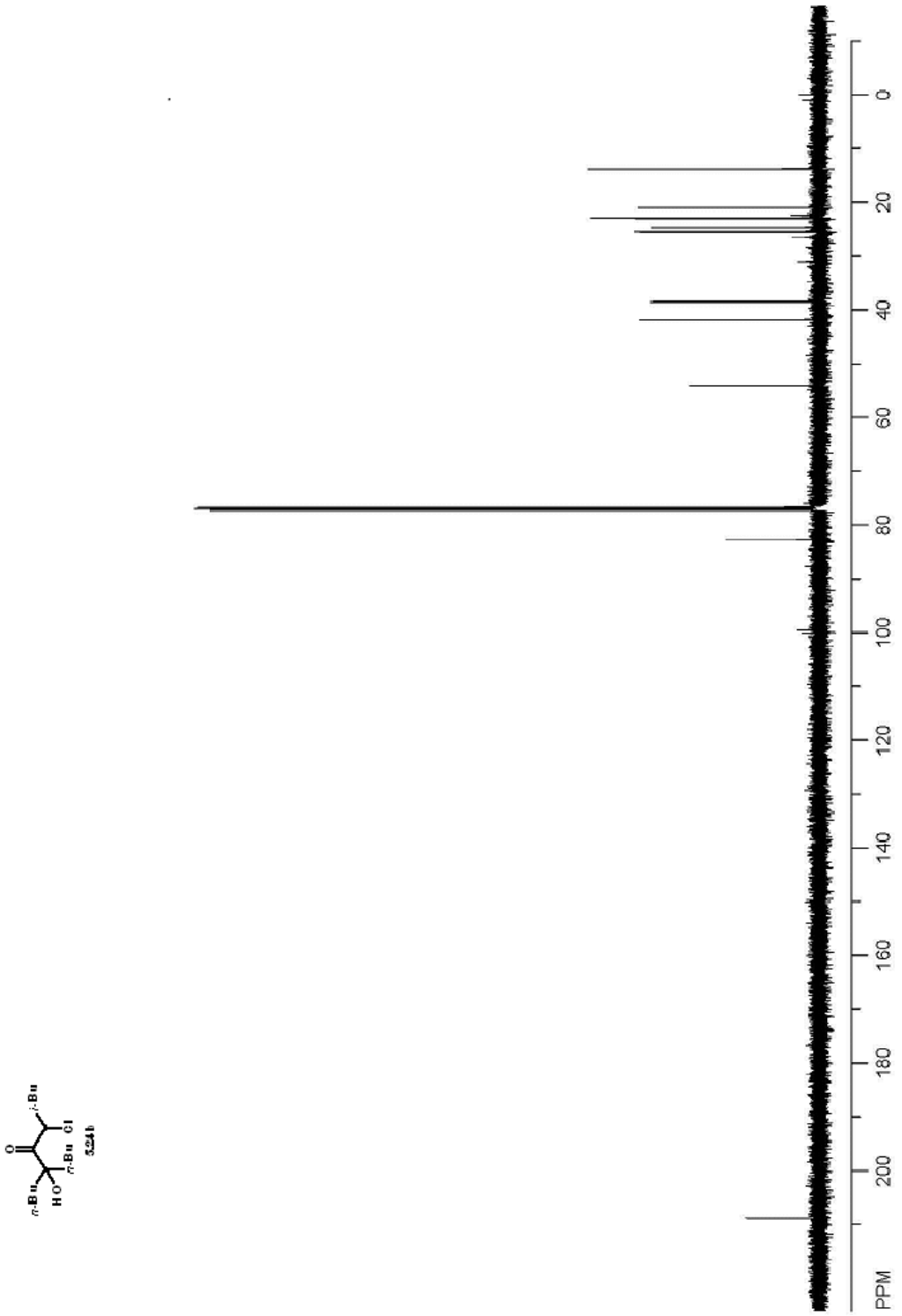
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
-0.0
-0.4
-0.8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40
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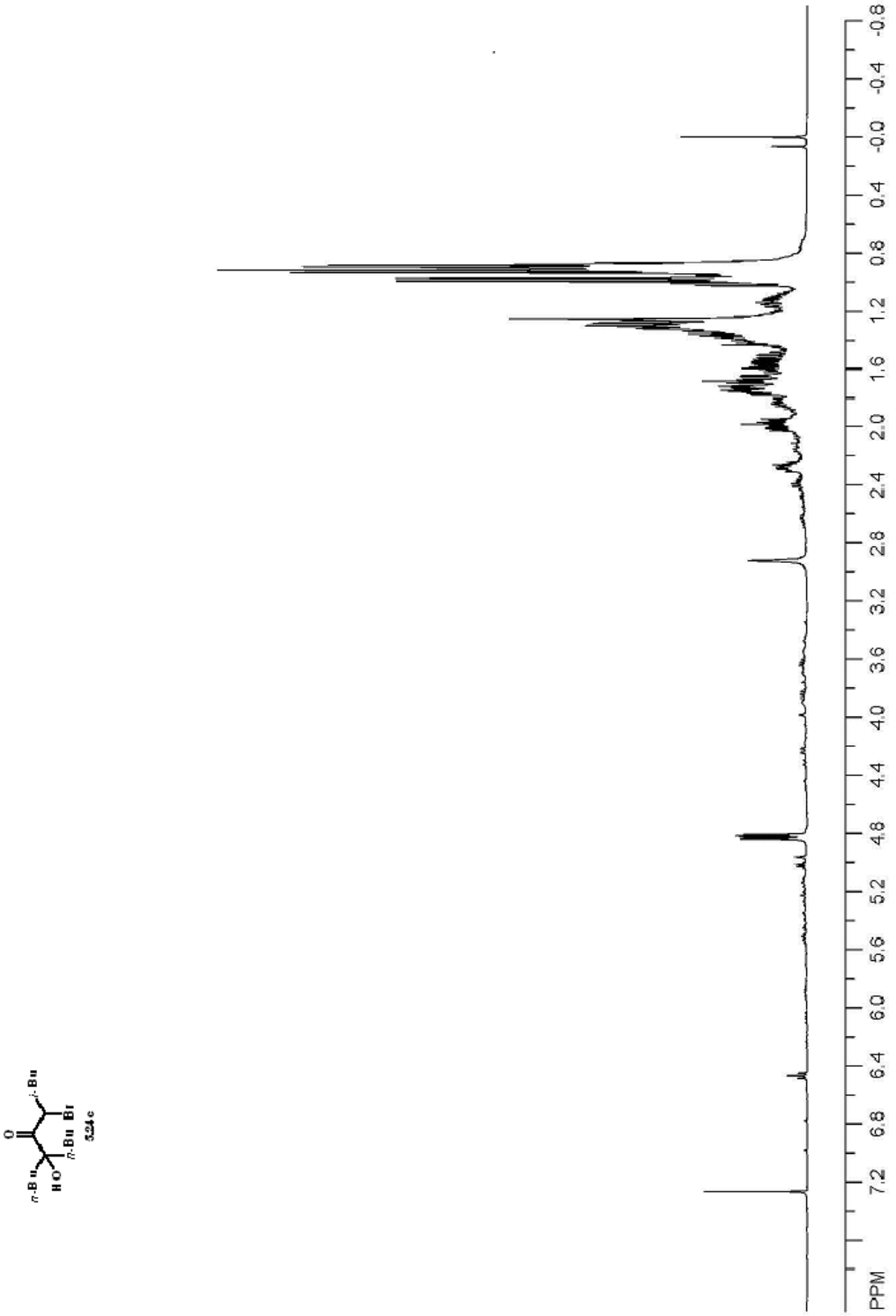
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6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
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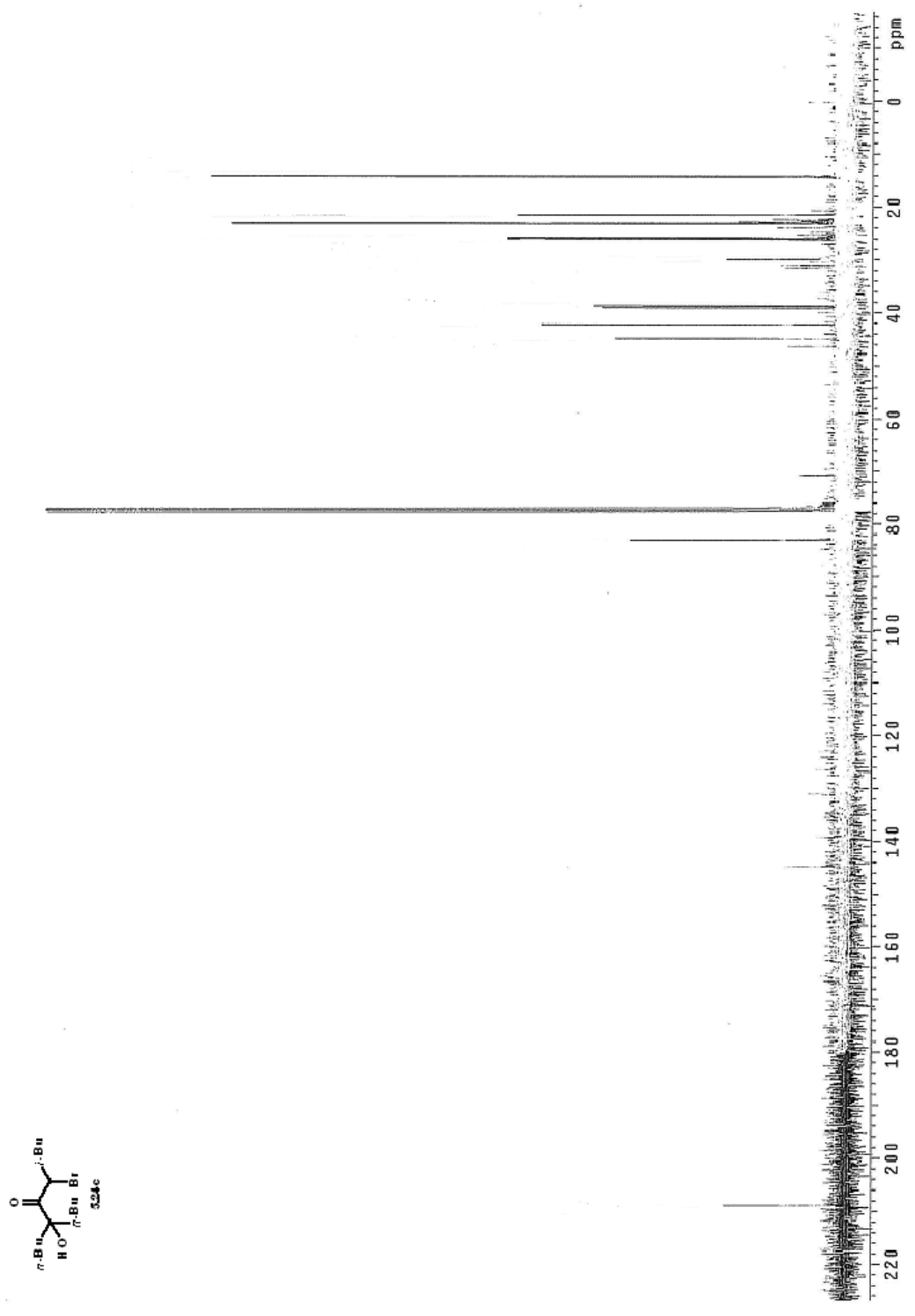
1.2
0.8
0.4
-0.0
-0.4
-0.8



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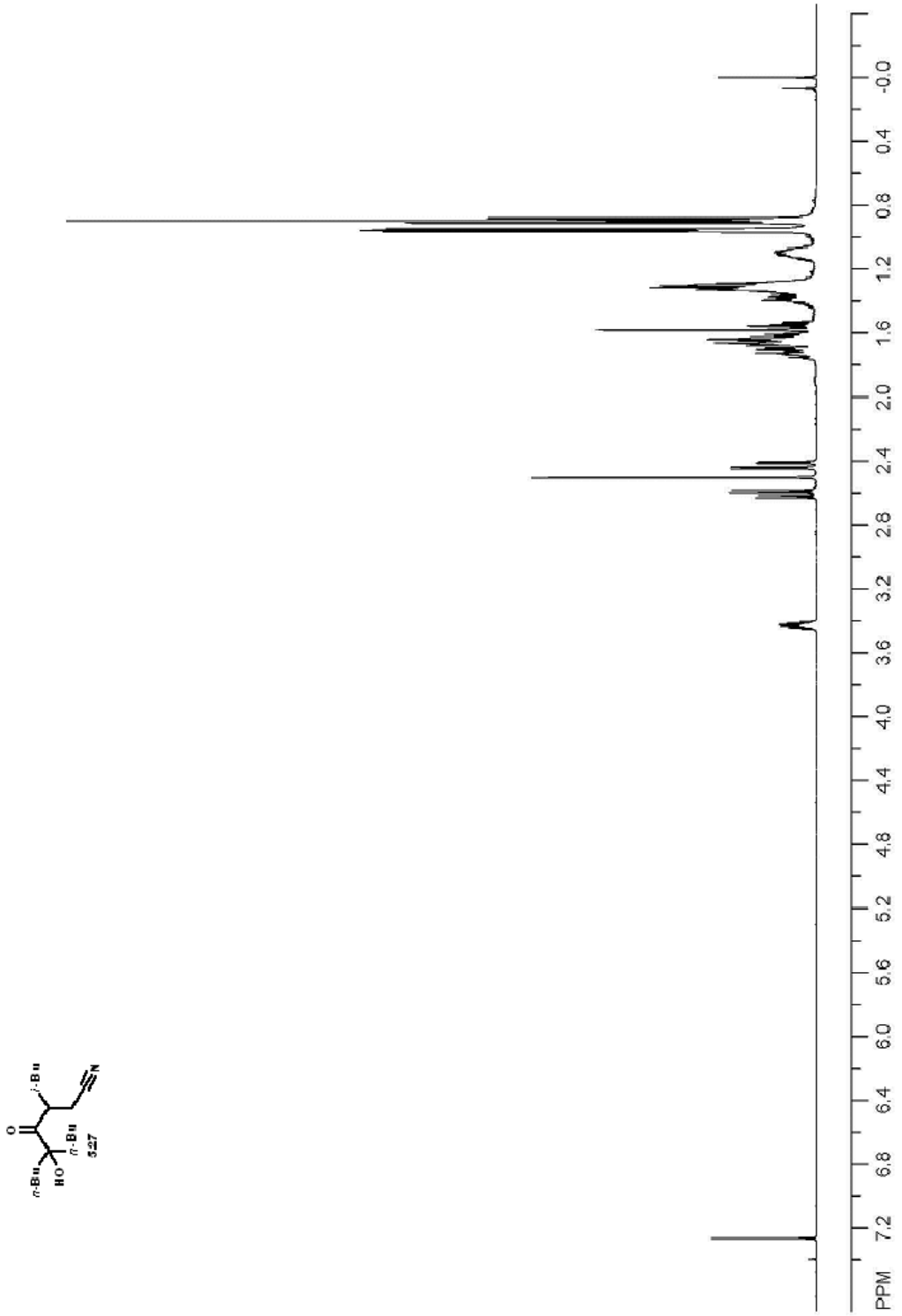
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6.8
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5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
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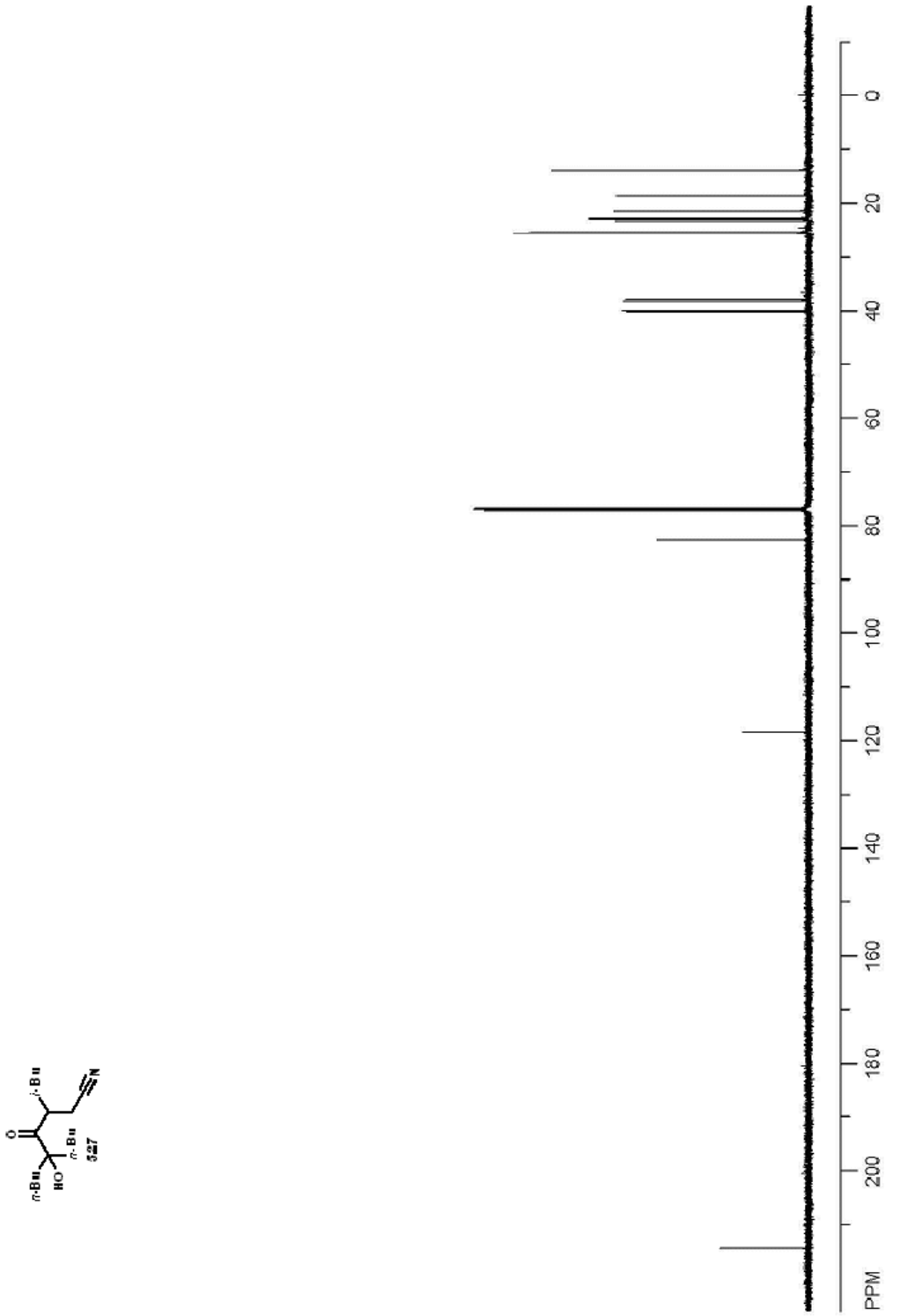
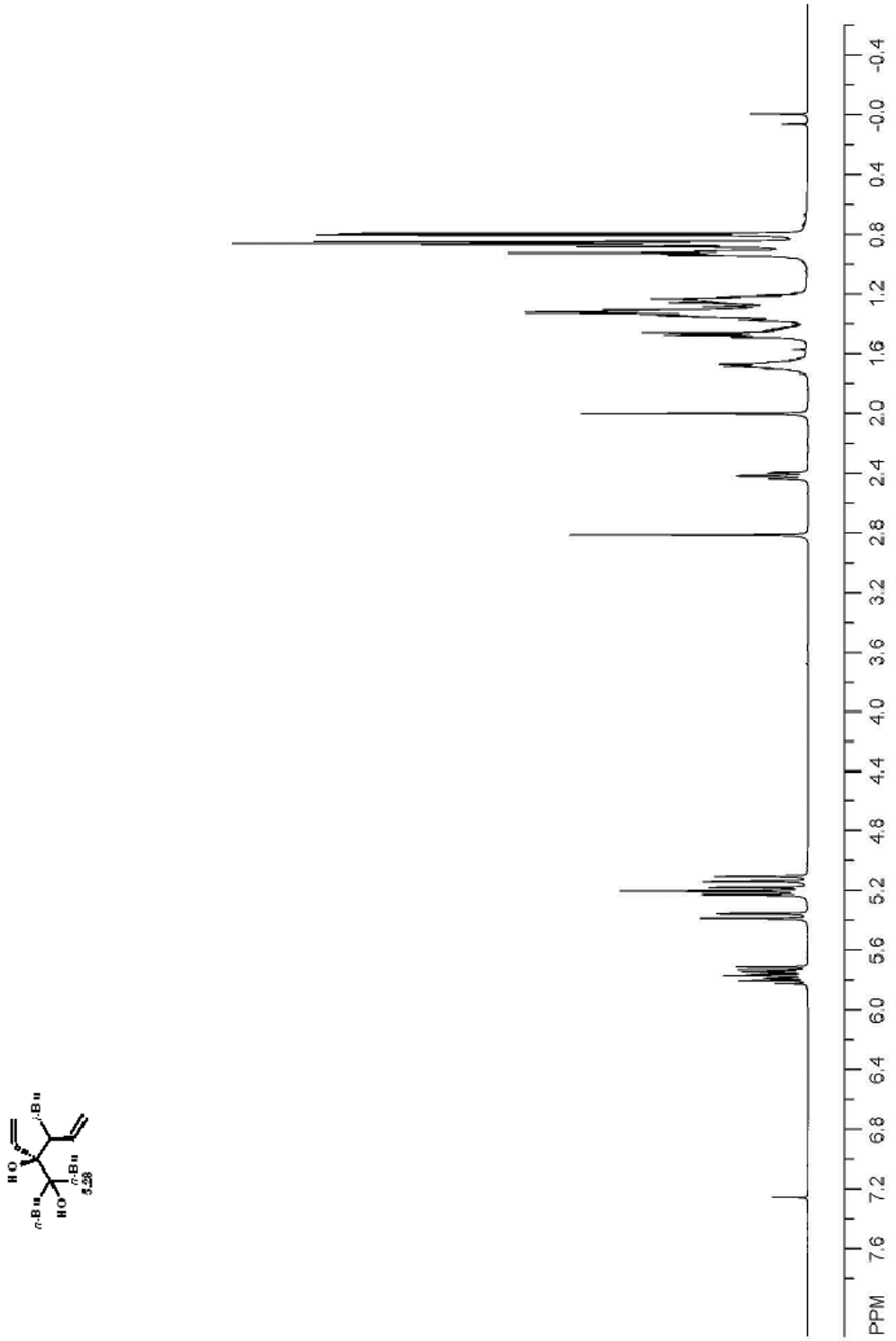
2.0
1.6
1.2
0.8
0.4
-0.0
O
i-Bu
n-Bu
HO
n-Bu
527
N



127


PPM
7.6
7.2
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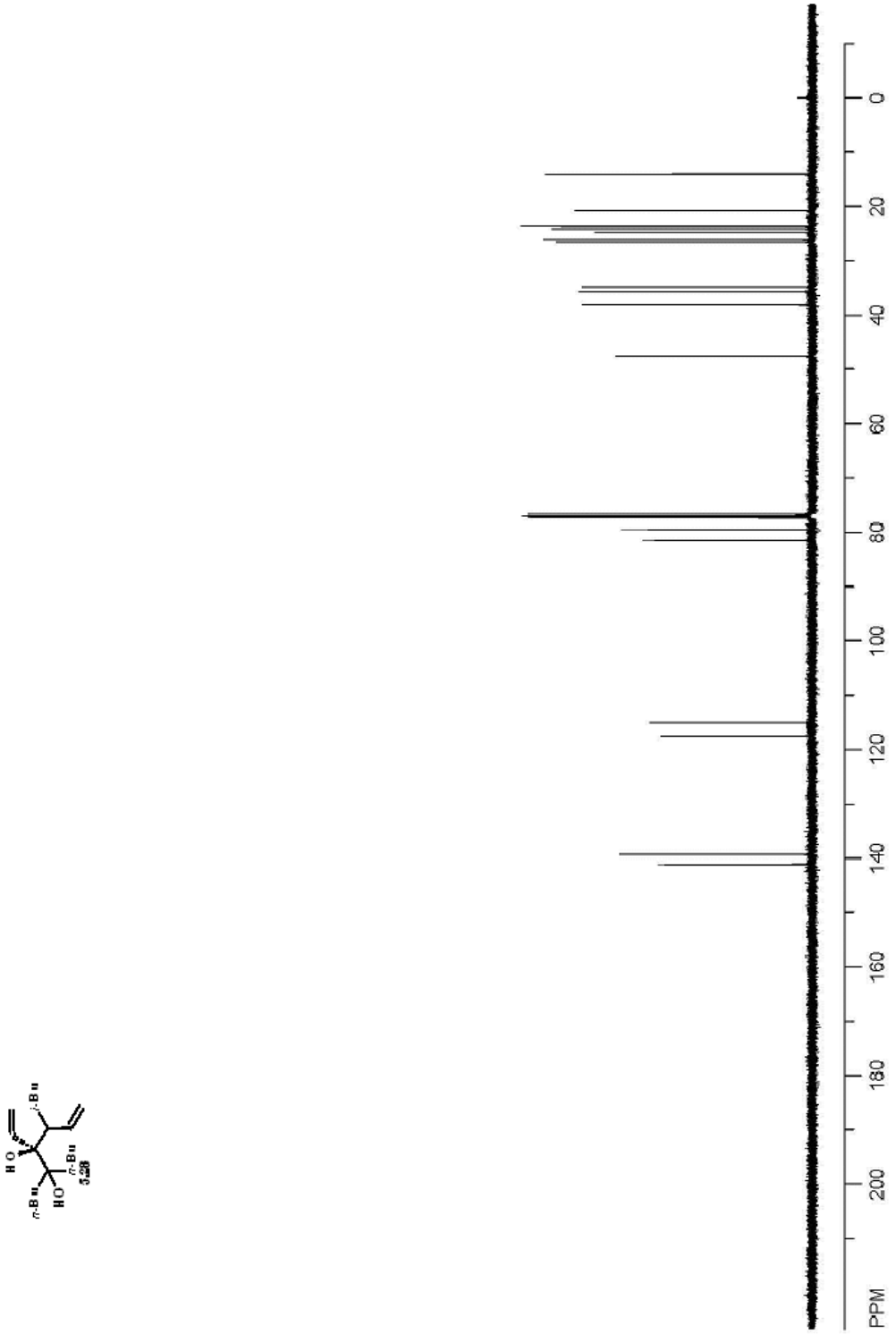
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
-0.0
-0.4


PPM
0
20
40
60
80
100
120
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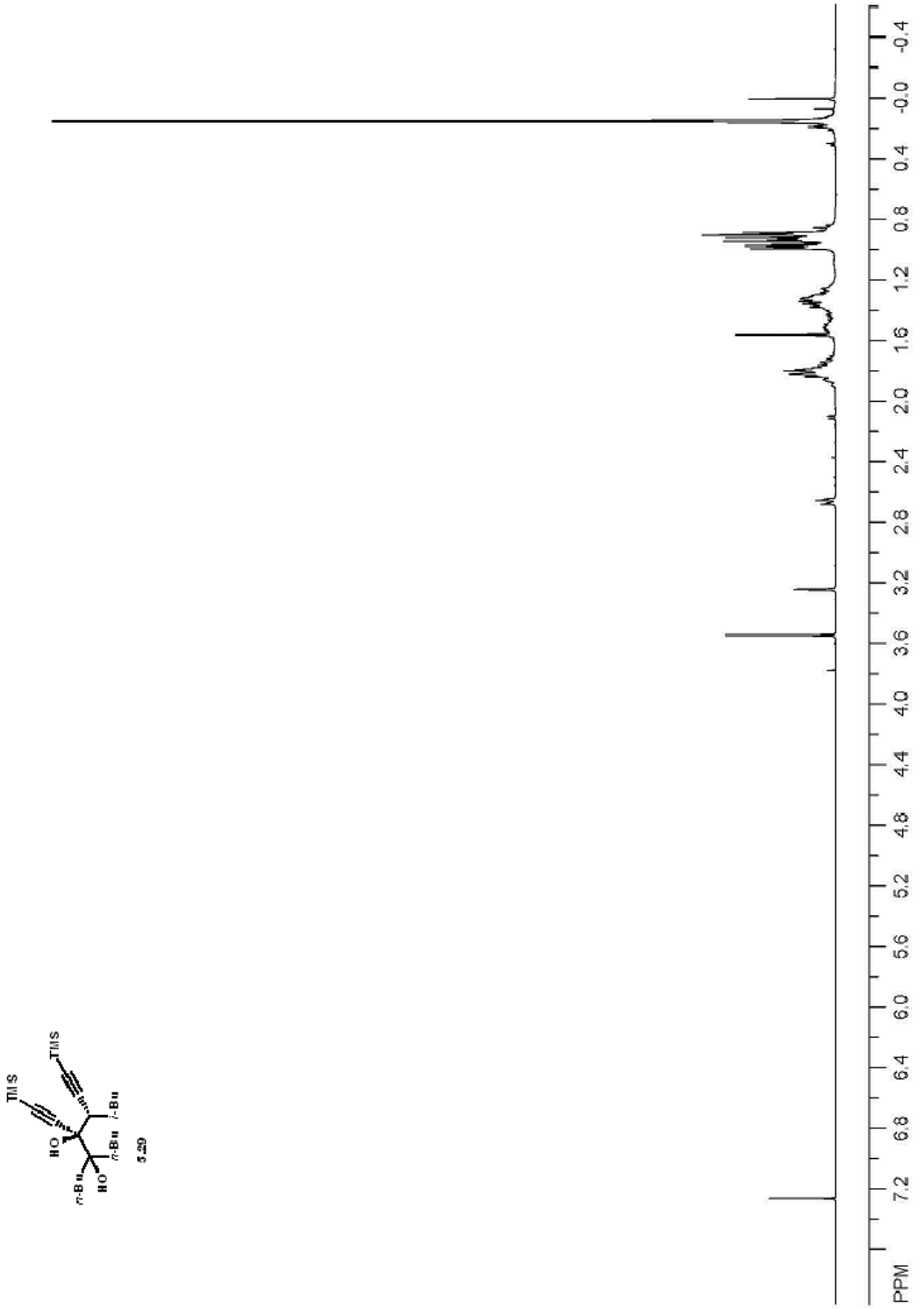
180
200


TMS
HO
n-Bu
HO
n-Bu
i-Bu
TMS
5.29
PPM
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6.8
6.4
6.0
5.6
5.2
4.8
4.4
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3.6
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2.8
2.4
2.0
1.6
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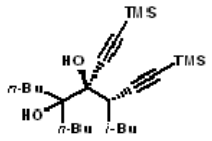
-0.4



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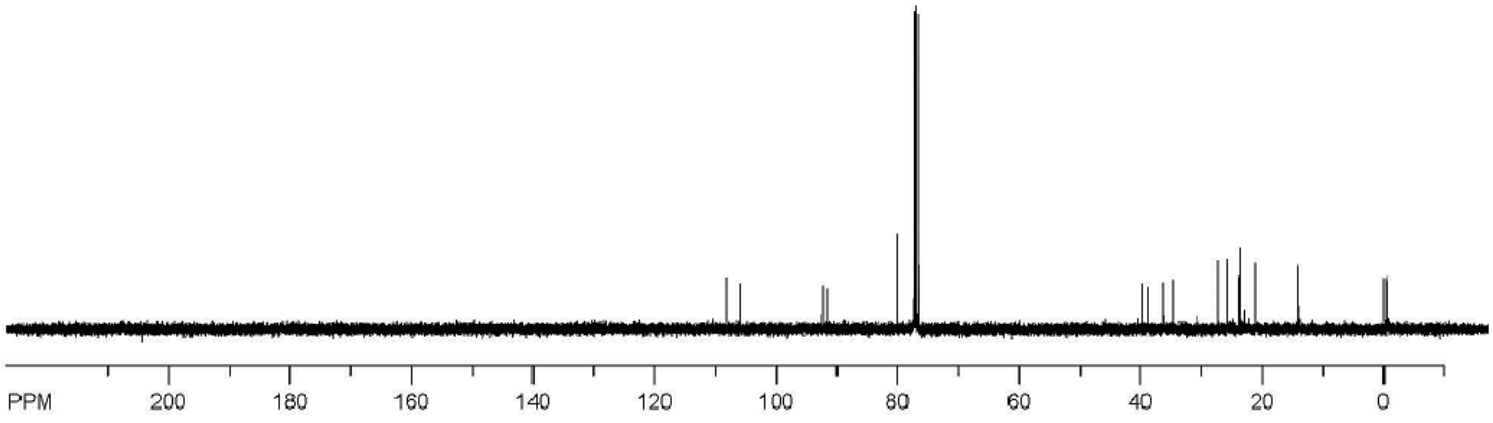
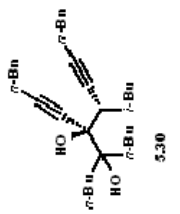
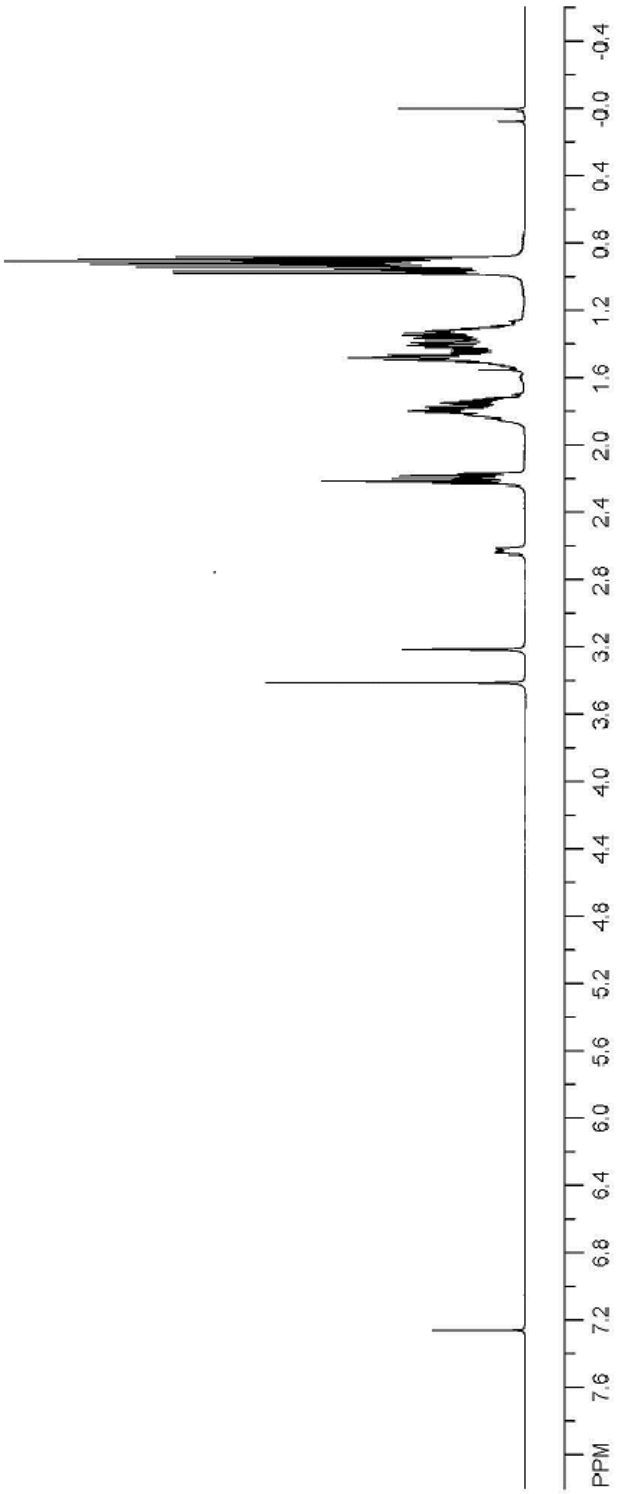



n-Bu
n-Bu
HO
n-Bu
n-Bu
HO
n-Bu
n-Bu

5.30


PPM
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6.4
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5.2
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4.4
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3.6
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2.4
2.0
1.6
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0.8
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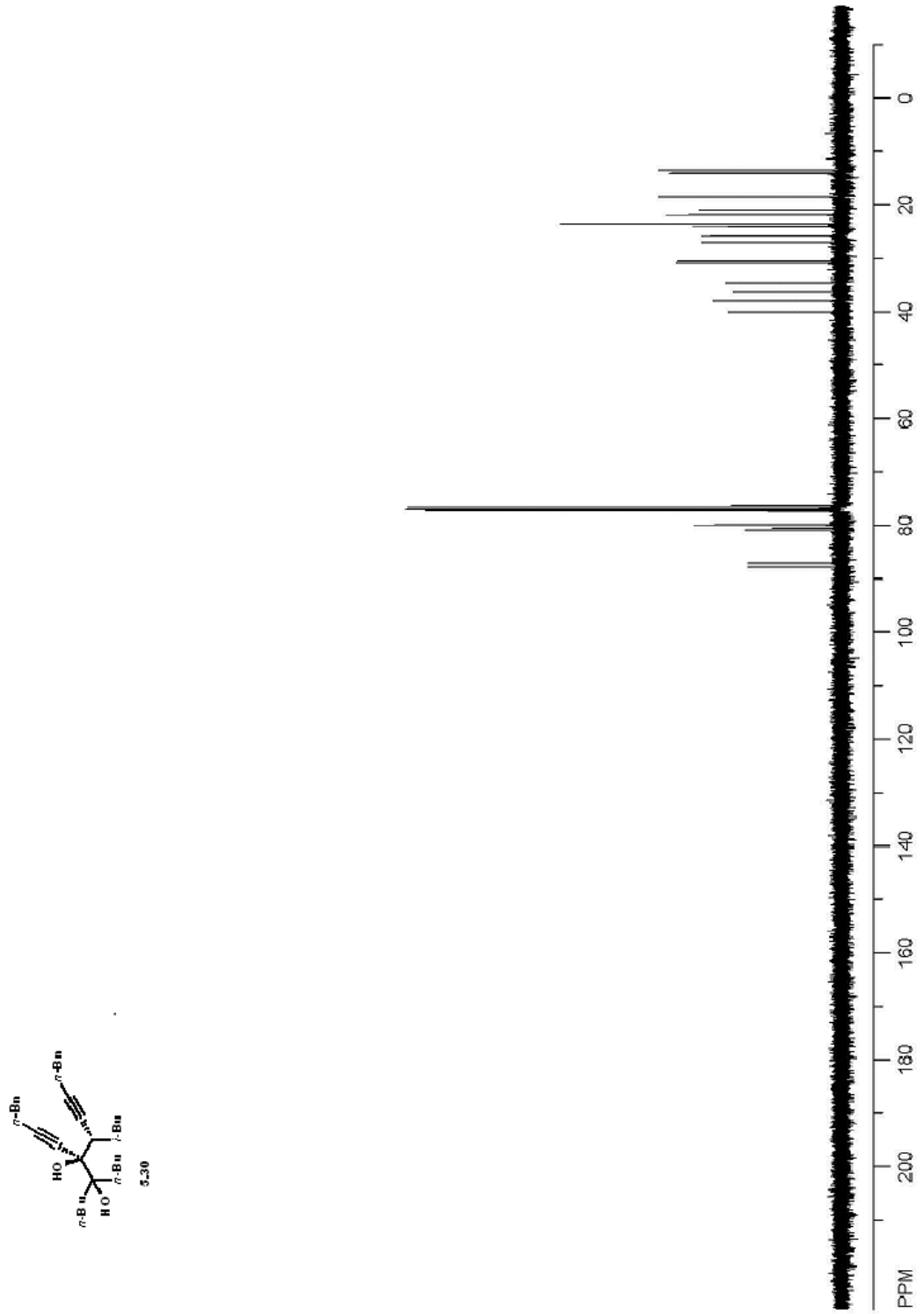
-0.0
-0.4


n-Bu
n-Bu
HO
n-Bu
i-Bu
n-Bu
HO
n-Bu
5.30
PPM
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60
80
100
120
140
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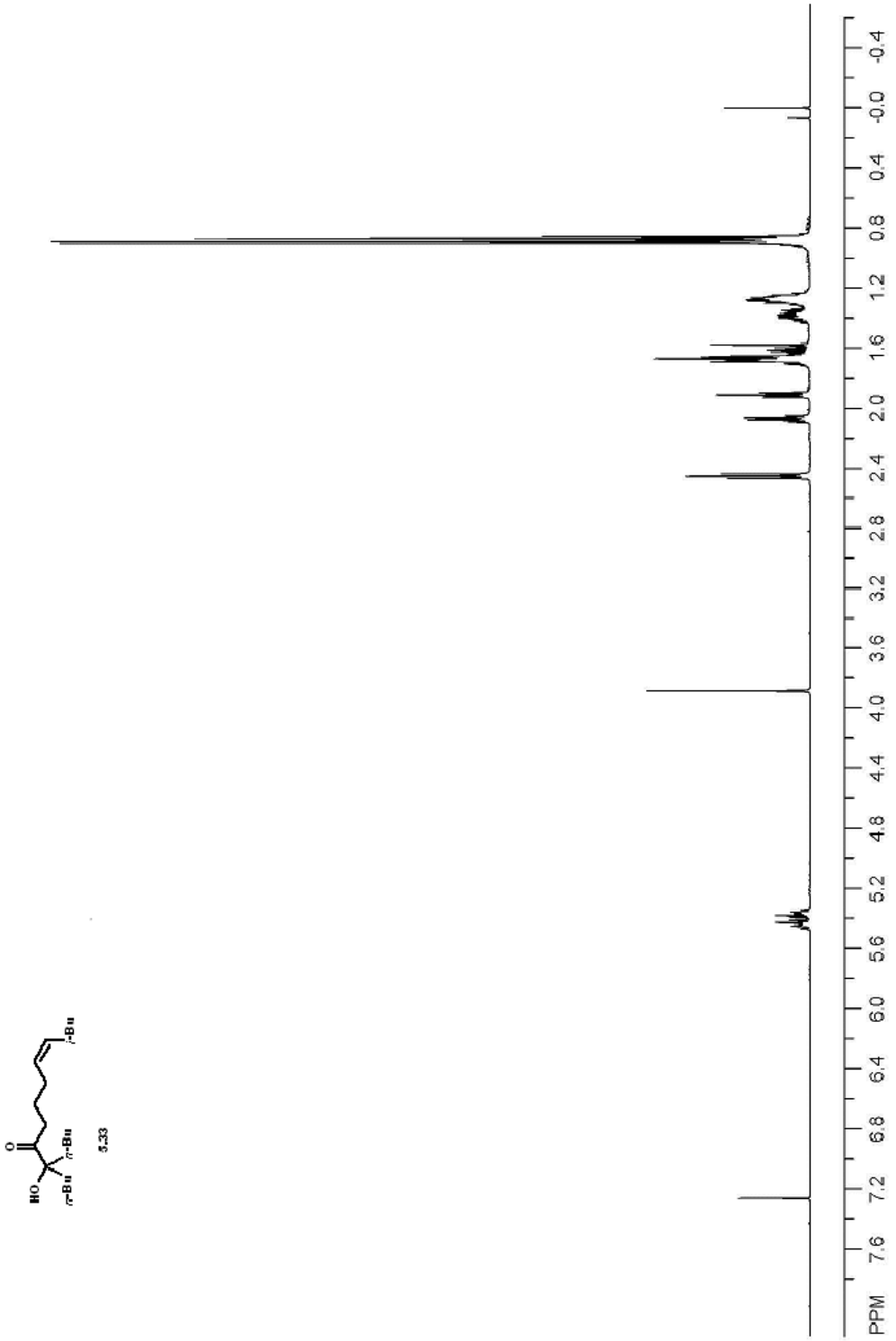
180
200


HO
n-Bu
n-Bu
i-Bu
5.33
PPM
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6.8
6.4
6.0
5.6
5.2
4.8
4.4
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1.6
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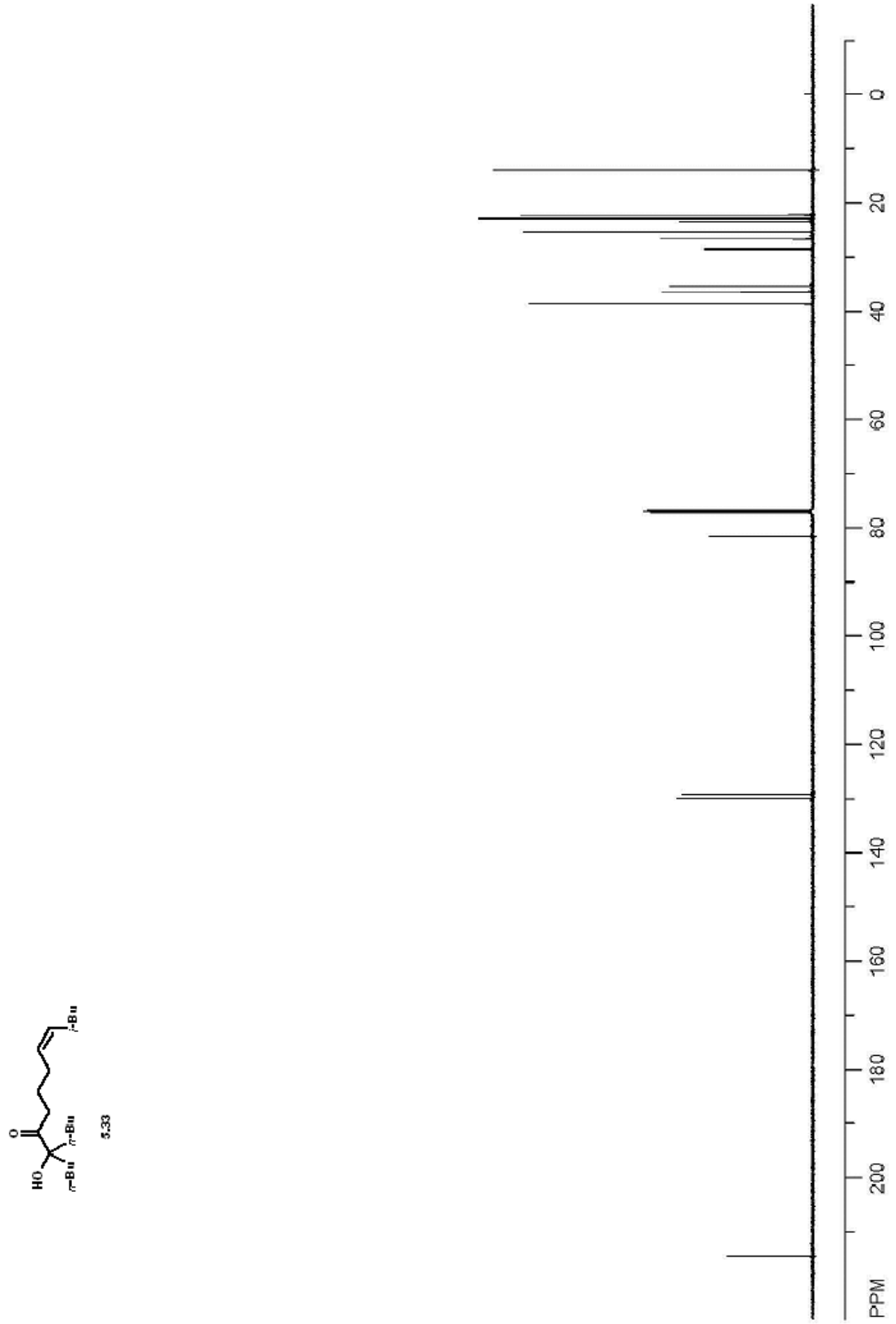
-0.4


HO
n-Bu
n-Bu
i-Bu
O
5.33
PPM
0
20
40
60
80
100
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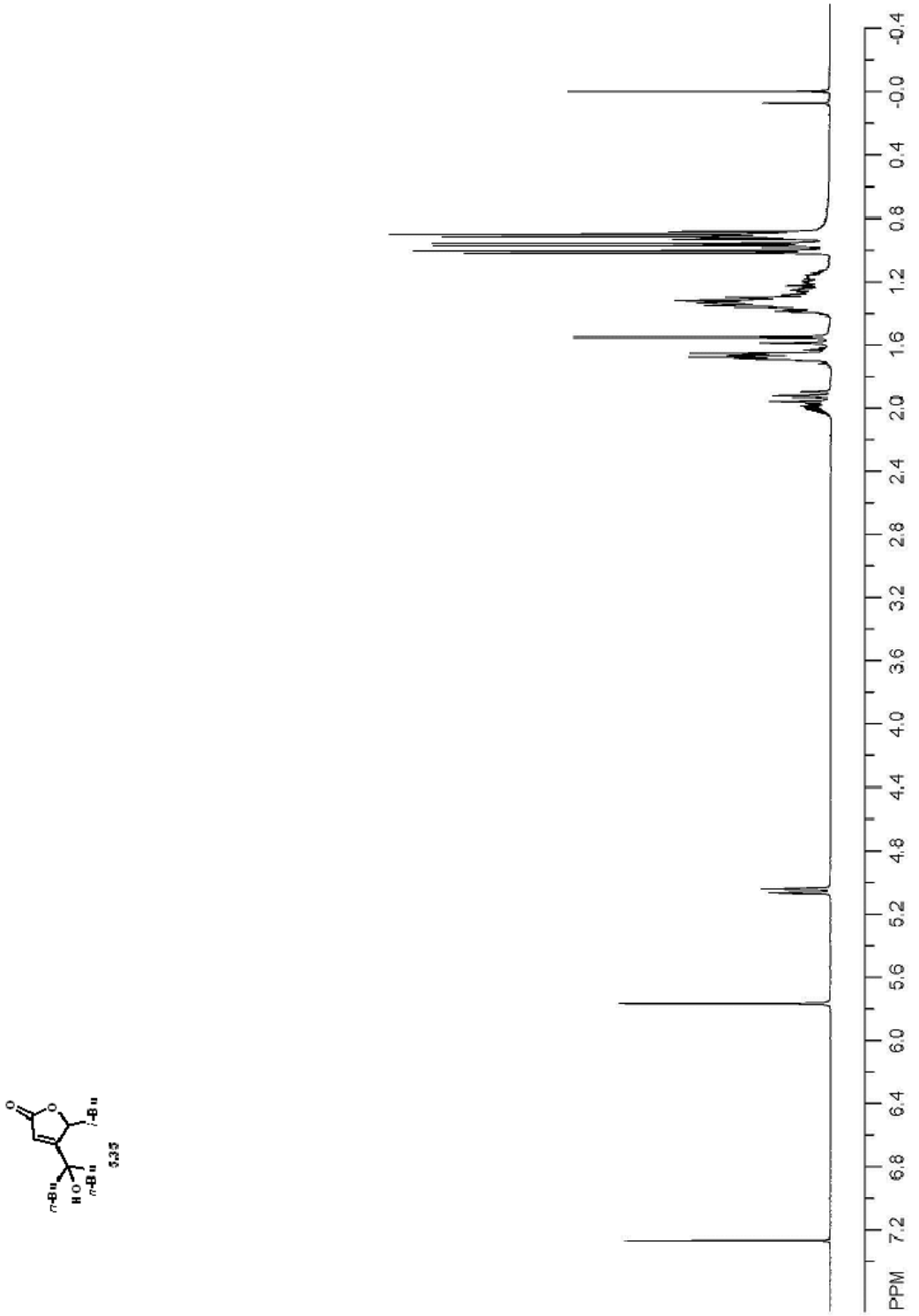
180
200


PPM
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5.2
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2.4
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1.6
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0.8
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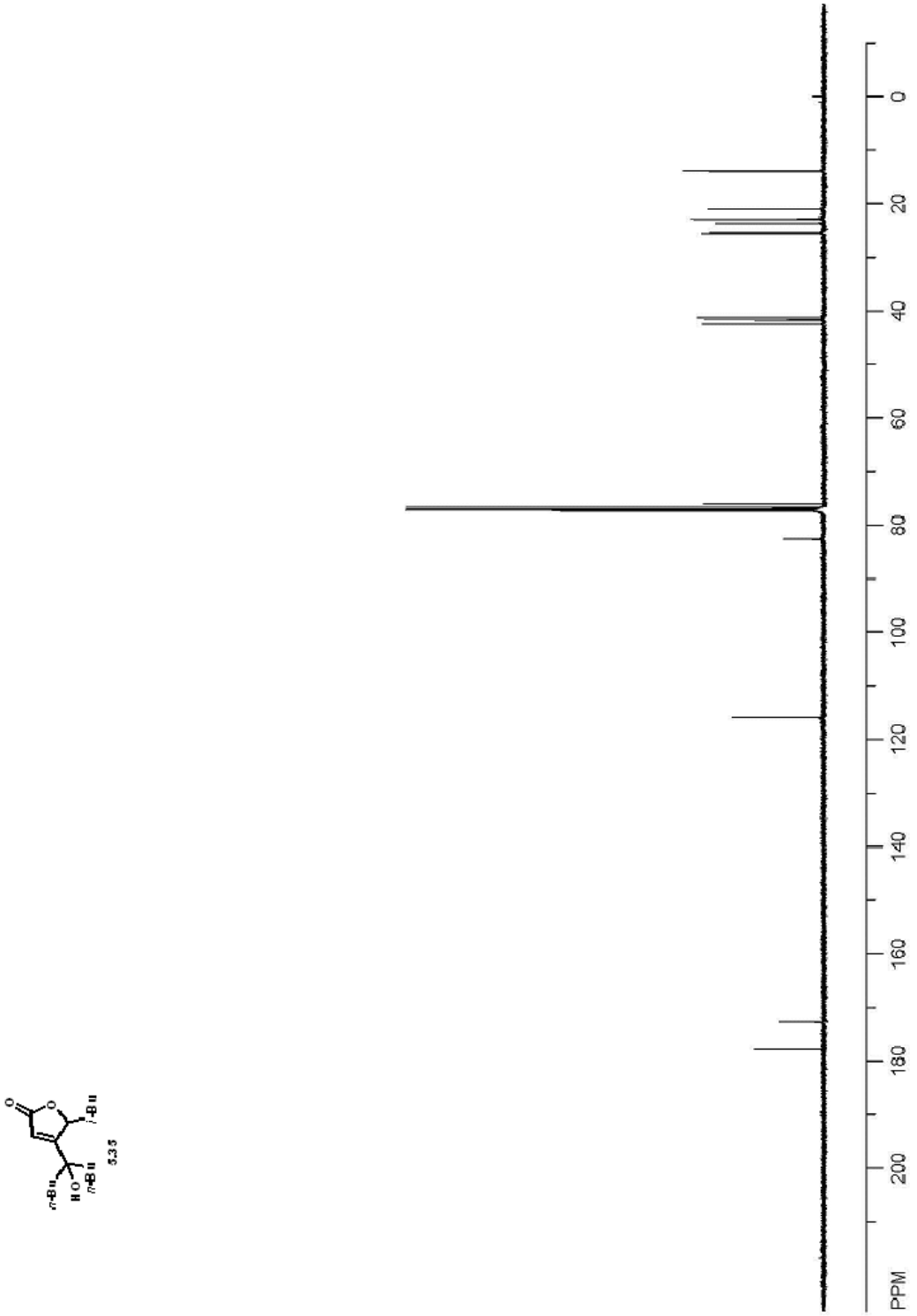
PPM
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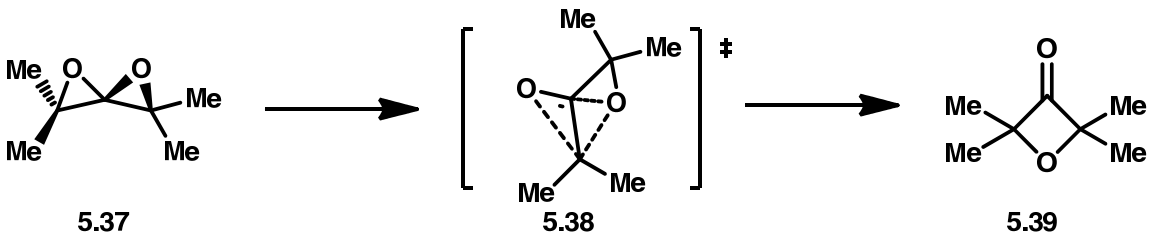

5.37 **5.38** **5.39**

Frequency calculation data for TS **5.38**:

B3LYP/6-31+g(d,p) optimized to TS

C	1.34901	0.13991	-0.02068
O	0.31427	-1.43217	-1.04694
C	0.04063	-0.41686	-0.34952
C	-1.25458	0.12836	0.12819
O	-0.5978	-0.39297	1.27025
C	-2.46601	-0.68411	-0.31677
H	-3.26094	-0.59277	0.43067
H	-2.85115	-0.3234	-1.27709
H	-2.19818	-1.73652	-0.41858
C	-1.53314	1.62536	0.20089
H	-1.82006	2.04129	-0.77138
H	-2.35795	1.79907	0.90076
H	-0.66701	2.16942	0.58652
C	2.29848	-0.70143	0.75133
H	3.22765	-0.87488	0.19384
H	2.57902	-0.13094	1.6486
H	1.84538	-1.64472	1.04543
C	1.85981	1.38466	-0.65291
H	2.72098	1.8003	-0.12312
H	2.20399	1.10112	-1.65984
H	1.0813	2.13775	-0.78548

Zero-point correction= 0.174848 (Hartree/Particle)
Thermal correction to Energy= 0.185674
Thermal correction to Enthalpy= 0.186618
Thermal correction to Gibbs Free Energy= 0.139516
Sum of electronic and zero-point Energies= -424.137067
Sum of electronic and thermal Energies= -424.126241
Sum of electronic and thermal Enthalpies= -424.125297
Sum of electronic and thermal Free Energies= -424.172399

Low frequencies --- -390.2328 -16.3469 -7.7231 -0.0008 0.0005 0.0006

Curriculum Vitae

Yue Zhang

EDUCATION

2004 – 2010	Rutgers, The State University of New Jersey, New Brunswick, Organic Chemistry, Ph.D.
1994 –1999	University of Science and Technology of China (USTC), China, Chemistry, B.S.

PUBLICATIONS

Zhang, Yue; Lotesta, Stephen; Emge, Thomas; Williams, Lawrence "Structure and Reactivity of a Chiral Cyclononadienone" *Tetrahedron Lett.* **2009**, *50*, 1882–1885.

Zhang, Yue; Cusick, Joseph; Ghosh, Partha; Williams, Lawrence *et al.* "Spirodiepoxides: Synthesis of Epoxomicinoids" *J. Org. Chem.* **2009**, *74,* 7707–7714.

Kolakowski, Robert; Manpadi, Madhuri; Zhang, Yue; Emge, Thomas; Williams, Lawrence "Allene Synthesis via C-C Fragmentation: Method and Mechanistic Insight" *J. Am. Chem. Soc.* **2009**, *131,* 12910–12911.

Ghosh, Partha; Zhang, Yue; Emge, Thomas; Williams, Lawrence "Modeling a Macrocyclic Bis[Spirodiepoxide] Strategy to Erythronolide A" *Org. Lett.* **2009**, *11,* 4402–4405.