Selective, Nickel-Catalyzed Carbon-Carbon Bond-Forming Reactions of Alkynes

by

Karen M. Miller

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Submitted to the Department of Chemistry
in Partial Fulfillment of the Requirements
for the Degree of

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Signature of Author ______________________________
Department of Chemistry
May 16, 2005

Certified by ______________________________
Timothy F. Jamison
Paul M. Cook Career Development Associate Professor of Chemistry
Thesis Supervisor

Accepted by ______________________________
Robert W. Field
Chairman, Department Committee on Graduate Students

This doctoral thesis has been examined by a committee in the Department of Chemistry as follows:

Professor Stephen L. Buchwald ______________________________
Chairman

Professor Timothy F. Jamison ______________________________
Thesis Supervisor

Professor Gregory C. Fu ______________________________

To Mom and Dad, Mike, Nat, and Ryan

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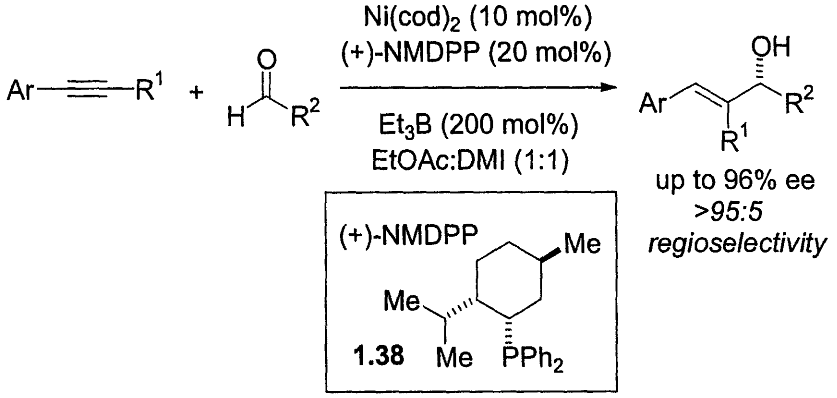
ABSTRACT

Catalytic addition reactions to alkynes are among the most useful and efficient methods for preparing diverse types of substituted olefins. Controlling both regioselectivity and (*E*/*Z*)-selectivity in such transformations presents a significant challenge. In reactions that also involve the creation of a new stereocenter, the development of enantioselective processes is highly desirable. Several novel, nickel-catalyzed carbon-carbon bond-forming reactions of alkynes that display excellent regioselectivity and (*E*/*Z*)-selectivity are described. These reactions afford synthetically useful allylic and homoallylic alcohols, often with high enantioselectivity.

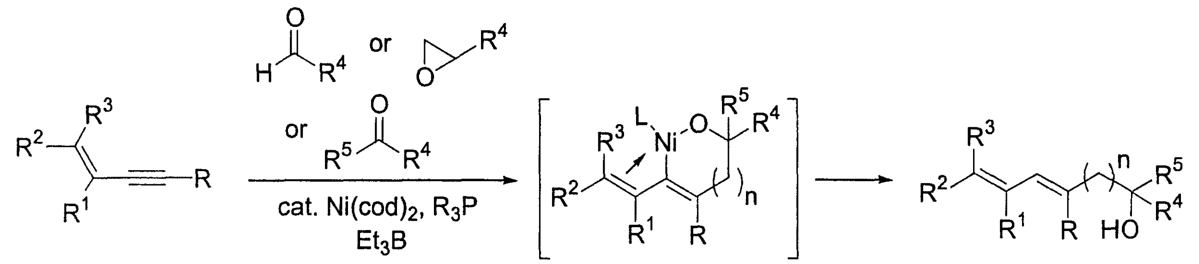
A highly enantioselective method for the nickel-catalyzed reductive coupling of alkynes and aldehydes has been realized using the commercially available (+)-neomenthyldiphenylphosphine as a chiral ligand. Allylic alcohols are afforded with complete (*E*/*Z*)-selectivity, generally >95:5 regioselectivity, and in up to 96% ee. In conjuction with ozonolysis, this process is complementary to existing methods of enantioselective α-hydroxy ketone synthesis.



In alkene-directed, nickel-catalyzed reductive couplings of 1,3-enynes with aldehydes and epoxides, the conjugated alkene dramatically enhances reactivity and uniformly directs regioselectivity, independent of the nature of the other alkyne substituent (aryl, alkyl (1°, 2°, 3°)) or the degree of alkene substitution (mono-, di-, tri-, and tetrasubstituted). The highly substituted 1,3-diene products are useful in organic synthesis and, in conjunction with a Rh-catalyzed, site-selective hydrogenation, afford allylic and homoallylic alcohols that previously could not be

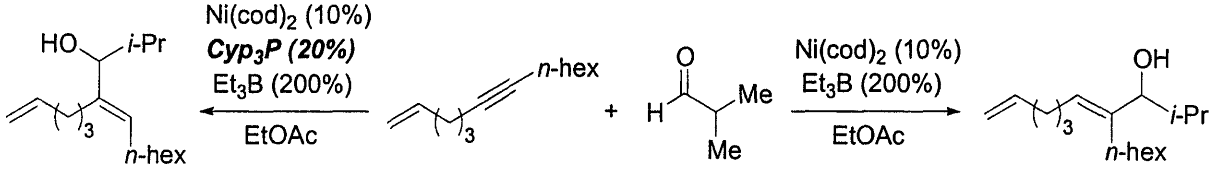
prepared in high regioselectivity (or at all) with related Ni-catalyzed alkyne coupling reactions. Enantiomerically enriched terminal epoxides can be employed to afford enantiomerically enriched homoallylic alcohols.

P-chiral, monodentate ferrocenyl phosphine ligands are efficient promoters of catalytic, asymmetric reductive coupling reactions of 1,3-enynes with aromatic aldehydes *and with ketones*. The latter represents the first catalytic intermolecular reductive coupling of alkynes and ketones, asymmetric or otherwise, to be reported. Both of these methods afford chiral 1,3-dienes in excellent regioselectivity and modest enantioselectivity.



typically >95:5 regioselectivity
epoxides - >99% ee
aldehydes - up to 58% ee
ketones - up to 70% ee

Nickel-catalyzed reductive couplings of 1,6-enynes and aldehydes also display very high (>95 : 5) regioselectivity. Use of a monodentate phosphine as an additive leads to formation of the opposite regioisomer in equal and opposite selectivity (5 : >95). These results provide strong evidence for an interaction between the remote alkene and the metal center during the regioselectivity-determining step.



>95:5 regioselectivity

>95:5 regioselectivity

Thesis Supervisor: Timothy F. Jamison

Title: Paul M. Cook Career Development Associate Professor of Chemistry

PREFACE

Portions of this thesis have appeared in the following articles that were co-written by the author, and are reproduced in part with permission from:

Catalytic Asymmetric Reductive Coupling of Alkynes and Aldehydes: Enantioselective Synthesis of Allylic Alcohols and α-Hydroxy Ketones. Miller, Karen M.; Huang, Wei-Sheng; Jamison, Timothy F. *J. Am. Chem. Soc.* **2003**, *125*, 3442-3443. Copyright 2003 American Chemical Society.

Catalytic Reductive Carbon-Carbon Bond-Forming Reactions of Alkynes. Miller, Karen M.; Molinaro, Carmela; Jamison, Timothy F. *Tetrahedron: Asymmetry* **2003**, *14*, Special Issue: "Asymmetric Syntheses on a Process Scale," 3619-3625. Copyright 2003 Elsevier Science.

Alkene-Directed, Nickel-Catalyzed Alkyne Coupling Reactions. Miller, Karen M.; Luanphaisarnnont, Torsak; Molinaro, Carmela; Jamison, Timothy F. *J. Am. Chem. Soc.* **2004**, *126*, 4130-4131. Copyright 2004 American Chemical Society.

Ligand-Switchable Directing Effects of Tethered Alkenes in Nickel-Catalyzed Additions to Alkynes. Miller, Karen M.; Jamison, Timothy F. *J. Am. Chem. Soc.* **2004**, *126*, 15342-15343. Copyright 2004 American Chemical Society.

Catalytic, Asymmetric Reductive Coupling of 1,3-Enynes and Aromatic Aldehydes. Miller, Karen M.; Colby, Elizabeth, A.; Woodin, Katrina S. *Submitted for publication.*

Highly Regioselective, Catalytic Asymmetric Reductive Coupling of 1,3-Enynes and Ketones. Miller, Karen M.; Jamison, T. F. *Submitted for publication.*

ACKNOWLEDGMENTS

I can't recall exactly when I fell in love with science, but I think it was probably sometime around the sixth grade, when I developed an extreme affection for manatees and all things marine and mammalian and proclaimed daily with gusto that I was destined to be a marine biologist. Several years later, after the realization that my poor swimming ability and aversion to diving probably necessitated a dream career shift, I took my first chemistry class from Dr. Tim Simpson, the only member of the faculty with a PhD at my small-town VT high school. His demonstrations were always the highlight of the class – blowing up coffee cans full of hydrogen underneath a lab bench so they wouldn't hit the ceiling while telling us how much more fun it was back in the day when he and his buddies did the same thing with H_2-filled garbage bags – and with anyone who showed the slightest enthusiasm for the subject, he was all too willing to go the extra mile. He and my biology teacher, Mr. Cameron, stayed after school many an afternoon helping me with an individual project my Senior year – I got it in my head that I was going to improve upon the "burning cashews in coffee cans" high school lab calorimetry experiment by building a more efficient, but inexpensive, calorimeter. We burned some Cheerios and nearly set fire to a lot more than that in the process, but in the end I did get a nice temperature plot, so we were happy.

I will be eternally grateful to whoever it happened to be in the Admissions Office at Dartmouth College that read my application and decided to make a space for me in the Class of 2000. At Dartmouth I became a singer, a costume designer, and yes, a chemist (though there were times the former two almost won out). I have Professors David Lemal and Gordon Gribble to thank for teaching me the beauty of organic chemistry; they were both outstanding lecturers and their introductory organic courses were arguably the best I took at Dartmouth. It was when I realized that this subject, which was the bane of every pre-med's existence, was the one that I loved most that I knew I belonged in a chemistry lab and not in a hospital.

Dr. Heidi Hassinger, who was a graduate student in Professor Gribble's lab at the time, was my first research mentor and led me to believe that this subject which I enjoyed was also something that I was good at, which for me was a huge boost of confidence. I took on an independent project in Professor Lemal's laboratory, and this was an incredibly valuable experience for me, mostly because it didn't work. The perseverance and ability to work through disappointment that I learned while on that project served me well during my years in graduate school.

I was also very fortunate to have the opportunity to work as an intern for a summer in Oncology Medicinal Chemistry at Wyeth Research in Pearl River, NY. It was after my time there that I decided to go to graduate school, and my mentor, Dr. Daniel Wang, along with his supervisor, Dr. Diane Boschelli, were invaluable contributors to my development as a scientist. I truly appreciate the continued support and career advice they have offered over the years.

Graduate school has been a bit of a roller-coaster ride, but many of my amazing colleagues have ensured that there were more upward slopes than down. I am grateful to Dr. Wei-Sheng Huang for taking me under his wing when I first joined the lab, and to Andrew Knox for putting up with me, being an incredibly enjoyable person to share a bench with, and teaching

me that the Scots really did in fact invent everything. I have been truly fortunate to work with a couple of exceptional undergraduates, Mr. Justin Cohen and Mr. Torsak Luanphaisarnnont, and I greatly appreciated both their commitment and their enthusiasm for their work. Thanks to Dr. Aaron Skaggs, Dr. Graham Simpson, Ryan Moslin, Chudi Ndubaku, Jim Trenkle, Victor Gehling, and Sze Sze Ng for making lab an enjoyable place to be, and thanks to the newbies Katrina Woodin, Aaron Van Dyke, and Andrew Lauer, for being great labmates and also for reminding me how much better grad school gets after the first year is over (really, it does).

I appreciate the contributions of Dr. Wei-Sheng Huang, Robert Jackson, Chudi Ndubaku, Elizabeth Colby, Katrina Woodin, Dr. Johann Chan, Dr. Sejal Patel, and Valer Jeso to advancing methodology for the catalytic, asymmetric reductive coupling of alkynes and aldehydes, and I thank Dr. Carmela Molinaro and Torsak Luanphaisarnnont for assisting with the development of alkene-directed coupling reactions of 1,3-enynes. I thank Ryan Moslin for his contributions to the development of catalytic reductive couplings of 1,6-enynes and aldehydes and for allowing me to include portions of his work in this thesis. Thanks to Jim Trenkle for his willingness to proofread part of this thesis, and to Elizabeth Colby and Tim Heffron for comparing notes on thesis preparation.

To my advisor, Professor Tim Jamison, I owe special thanks, not only for accepting me into his group those many long years ago, but also for his unyielding support and enthusiasm for my work. It has been a pleasure working with and learning from such a gifted chemist, writer, and public speaker. I also thank Professors Steve Buchwald and Greg Fu for their continued support over the years, their helpful and insightful suggestions, and for taking the time to actually read my thesis.

Finally, I am grateful to those I love, Mom and Dad, my brother Mike, my sister Nat, and my fiancé Ryan, without whom I never would have come this far. Mom and Dad, thanks for trying to understand what exactly it is that I do everyday and, when it still doesn't make sense, thinking that it's great anyway. Mike, thanks for showing me how to be a good student and have fun too, and Nat, thanks for showing me what it really means to be courageous and follow your dreams. Ryan, the last three years have been wonderful and I look forward to many more. Your love, encouragement, and support mean everything to me – thank you.

TABLE OF CONTENTS

ABBREVIATIONS

Ac	acetyl
Ar	aryl
atm	atmospheres
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butoxy carbonyl
Bu	butyl
°C	degree (Celsius)
cod	cyclooctadiene
Cp	cyclopentadiene
Cy	cyclohexyl
Cyp	cyclopentyl
δ	chemical shift in parts per million
DAIB	(dimethylamino)isoborneol
DBU	1,8-diazabicyclo[5.4.0]-7-undecene
DCC	dicyclohexylcarbodiimide
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	*N,N'*-dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
DuPhos	(–)-1,2-bis((2*R*,5*R*)-2,5-dimethylphospholano)benzene
ee	enantiomeric excess
Et	ethyl
eq	equation
Fc	ferrocenyl
g	grams
GC	gas chromatography
h	hours
Hept	heptyl
Hex	hexyl
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
i-Pr	isopropyl
IR	infrared
L	liters
m	meta
m	milli
μ	micro
M	molar
Me	methyl

Me-BPE	(+)-1,2-bis((2R,5R)-2,5-dimethylphospholano)ethane
MIB	(*N*-morpholino)isoborneol
MHz	megahertz
min	minutes
mol	moles
Ms	mesyl
MTBE	methyl *tert*-butyl ether
n	normal
NMDPP	neomenthyldiphenylphosphine
NMR	nuclear magnetic resonance
n.d.	not determined
nOe	nuclear Overhauser effect
o	ortho
Oct	octyl
p	para
Pent	pentyl
Ph	phenyl
sat.	saturated
t_R	retention time
t-Bu	*tert*-butyl
tert	tertiary
temp	temperature
TMS	trimethylsilyl
TBS	*tert*-butyl dimethylsilyl
TBAF	tetrabutylammonium fluoride
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	tosyl
wt	weight

Chapter 1

Catalytic, Asymmetric Reductive Coupling of Alkynes and Aldehydes

Introduction

Allylic alcohols are useful starting materials in organic synthesis[1] and are prevalent in complex natural products.[2] Accordingly, numerous catalytic enantioselective methods of allylic alcohol synthesis have been described and can be divided into three general classes: kinetic resolution of chiral allylic alcohols, carbonyl reduction, and carbonyl addition reactions. In recent years, the latter class has attracted a great deal of attention as such reactions simultaneously construct a new stereocenter and a carbon-carbon bond, thus facilitating convergent organic synthesis.

The Nozaki-Hiyama-Kishi reaction is one of the most well-studied and versatile methods for the generation of allylic alcohols and represents a powerful tool in organic synthesis.[3,4] Originally, this Cr(II)/Ni(II)-mediated addition of alkenyl halides to aldehydes required the stoichiometric generation of an alkenylchromium(III) reagent; however, in 1996, Fürstner reported the first examples of Cr(II)/Ni(II) coupling reactions that were catalytic in chromium, paving the way for the development of a catalytic, enantioselective variant.[5] Kishi and co-workers achieved this goal in 2002, when they reported enantioselectivities of up to 71% in the coupling of aldehyde **1.1** and alkenyl halide **1.2** in the presence of chiral chromium complex **1.3** (Scheme 1).[6]

Another strategy that has been widely employed for the enantioselective synthesis of allylic alcohols is the catalytic, asymmetric addition of alkenylzinc reagents to aldehydes.[7] Oppolzer has demonstrated that alkenylzinc reagents can be generated efficiently via

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[1] (a) Brückner, R., in *Comprehensive Organic Synthesis*, Trost, B. M., Ed. Pergamon: New York, 1991, vol. 6, Ch. 4.6, 873-908. (b) Hill, R. K., *ibid.*, vol. 5, Ch. 7.1, 785-826. (c) Wipf, P., *ibid.*, vol. 5, Ch. 7.2, 827-873. (d) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307-1370.

[2] (a) Epothilones: Bollag, D. M.; McQueney, P. A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazarides, E.; Woods, C. M. *Cancer Res.* **1995**, *55*, 2325-2333. (b) (–)-Terpestacin: Oka, M.; Iimura, S.; Tenmyo, O.; Sawada, Y.; Sugawara, M.; Ohkusa, N.; Yamamoto, H.; Kawano, K.; Hu, S.-L.; Fukagawa, Y.; Oki, T. *J. Antibiotics* **1993**, *46*, 367-373. (c) (+)-Acutiphycin: Barchi, Jr., J. J.; Moore, R. E.; Patterson, G. M. L. *J. Am. Chem. Soc.* **1984**, *106*, 8193-8197.

[3] Review: Fürstner, A. *Chem. Rev.* **1999**, *99*, 991-1045.

[4] (a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179-3181. (b) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644-5646. (c) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048-6050.

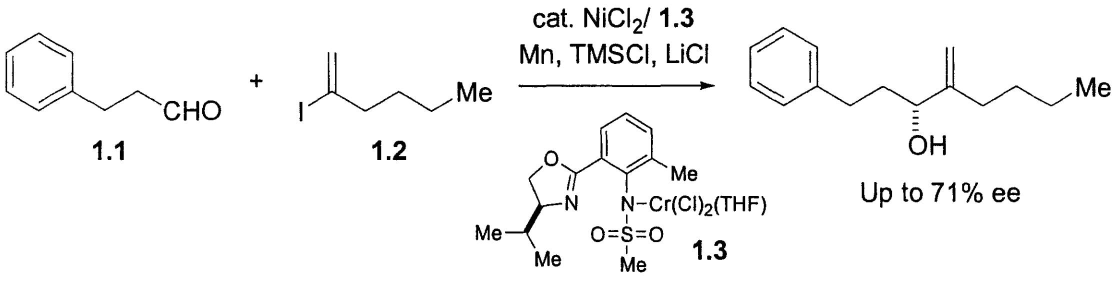
[5] (a) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 2533-2534. (b) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349-12357.

[6] Choi, H. W.; Nakajima, K.; Demeke, D.; Kang, F. A.; Jun, H. S.; Wan, Z. K.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4435-4438.

[7] For a recent review on catalytic, asymmetric organozinc additions to carbonyl compounds, see: Pu, L.; Yu, H. B. *Chem. Rev.* **2001**, *101*, 757-824.

hydroboration of a terminal alkyne followed by transmetallation to zinc (Scheme 2).[8] Additions of these species to aldehydes proceed in high enantioselectivity to afford *(E)*-disubstituted allylic alcohols when conducted in the presence Noyori's (–)-DAIB ligand[9] (**1.4**) (Figure 1). Walsh has shown that Nugent's (–)-MIB ligand[10] (**1.5**) is also effective in promoting highly enantioselective additions of alkenylzinc reagents to aldehydes, and has used the chiral allylic alcohols generated to synthesize enantiomerically enriched allylic amines, α-amino acids, γ-unsaturated β-amino acids, epoxy alcohols, and β-hydroxy aldehydes.[11] Bräse,[12] Chan,[13] Ha,[14] and Yang[15] have also reported catalytic additions of alkenylzinc reagents to aldehydes that employ the Oppolzer protocol in conjunction with [2.2]paracyclophane-based **1.6**, aminonaphthol **1.7**, amino alcohol **1.8**, and β-amino thiol **1.9** as chiral ligands, respectively.

Scheme 1.



A related reaction, developed by Wipf and co-workers, commences with hydrozirconation of a terminal alkyne using Cp_2ZrHCl (Schwartz's reagent[16]). Following transmetallation to zinc, the alkenylzinc reagents can be added to aldehydes in the presence of

---

[8] (a) Oppolzer, W.; Radinov, R. N. *Helv. Chim. Acta* **1992**, *75*, 170-173. (b) Use in intramolecular cyclization reactions: Oppolzer, W.; Radinov, R. N.; El-Sayed, E. *J. Org. Chem.* **2001**, *66*, 4766-4770.

[9] (a) Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed.* **1991**, *30*, 49-69. (b) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071-6072.

[10] (a) Nugent, W. A. *J. Chem. Soc., Chem. Commun.* **1999**, 1369-1370. (b) Rosner, T.; Sears, P. J.; Nugent, W. A.; Blackmond, D. G. *Org. Lett.* **2000**, *2*, 2511-2513.

[11] (a) Chen, Y. K.; Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 12225-12231. (b) Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 10677-10683. (c) Lurain, A. E.; Carroll, P. J.; Walsh, P. J. *J. Org. Chem.* **2005**, *70*, 1262-1268. (d) Jeon, S.-J.; Chen, Y. K.; Walsh, P. J. *Org. Lett.* **2005**, 1729-1732.

[12] (a) Review: Bräse, S.; Dahmen, S.; Höfener, S.; Lauterwasser, F.; Kreis, M.; Ziegert, R. E. *Synlett* **2004**, 2647-2669. (b) Dahmen, S. D.; Bräse, S. *Org. Lett.* **2001**, *3*, 4119-4122.

[13] Ji, J.-X.; Qiu, L.-Q.; Yip, C. W.; Chan, A. S. C. *J. Org. Chem.* **2003**, *68*, 1589-1590.

[14] Ko, D.-Y.; Kang, S.-W.; Kim, K. H.; Chung, Y.; Ha, D.-C. *Bull. Korean Chem. Soc.* **2004**, *25*, 35-36.

[15] Tseng, S.-L.; Yang, T.-K. *Tetrahedron: Asymmetry* **2005**, *16*, 773-782.

[16] Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679-680.

thiophenol ligand **1.10**.[17] The Wipf protocol has been successfully employed in the synthesis of several complex natural products.[18]

Scheme 2.

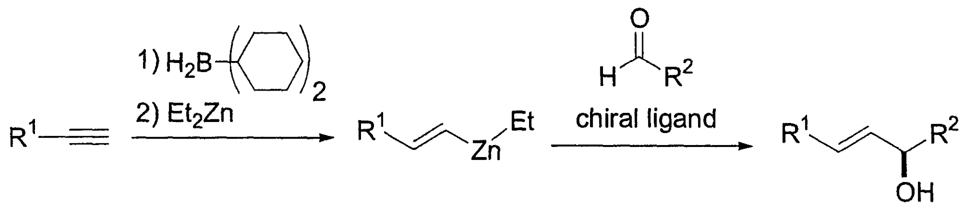
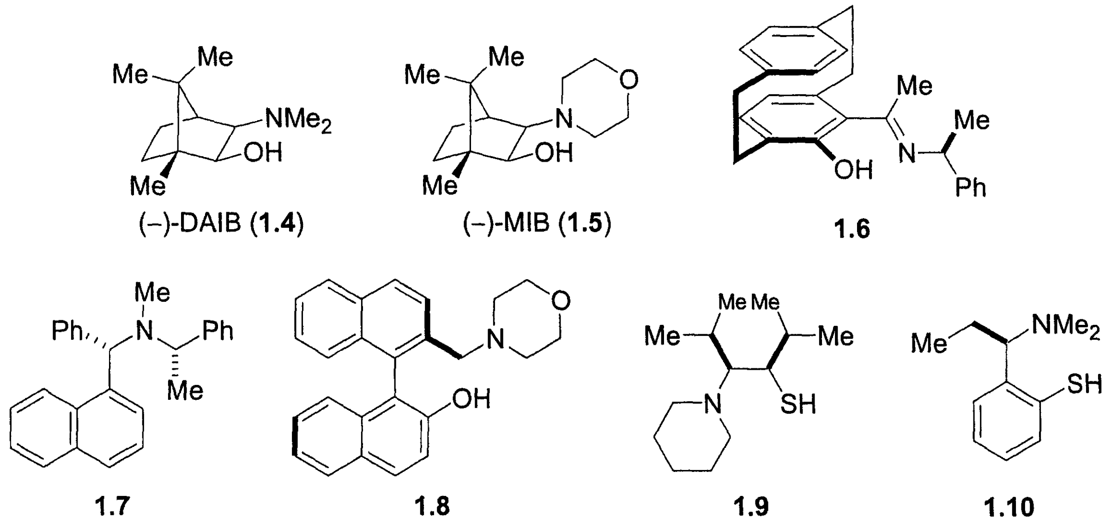


Figure 1. Ligands for the asymmetric, catalytic addition of alkenylzinc reagents to aldehydes.



Despite the versatility and synthetic utility of enantioselective alkenylzinc additions to aldehydes, these methods suffer two major drawbacks. The first is that this class of reactions has been shown to be effective only with terminal alkynes, as use of internal alkynes can result in diminished *E*/*Z* selectivities.[19] The second is that, although these methods are catalytic with

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[17] (a) Review: Wipf, P.; Kendall, C. *Chem. Eur. J.* **2002**, *8*, 1778-1784. (b) Wipf, P.; Ribe, S. *J. Org. Chem.* **1998**, *63*, 6454-6455.

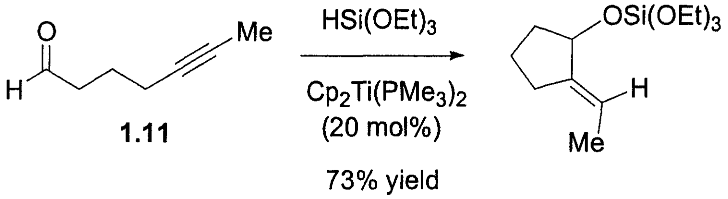
[18] (a) Lobatamide C: Shen, R.; Lin, C. T.; Bowman, E. J.; Bowman, B. J.; Porco, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 7889-7901. Shen, R.; Lin, C. T.; Porco, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 5650-5651. (b) Leucascandrolide A: Wipf, P.; Reeves, J. T. *Chem. Commun.* **2002**, 2066-2067. (c) Halichlorine: Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1999**, *38*, 3542-3545.

[19] Wipf, P.; Xu, W. J. *Tetrahedron Lett.* **1994**, *35*, 5197-5200.

respect to the chiral ligand employed, they each require stoichiometric quantities of transition metal to effect the reaction.[20]

High *E*-selectivities have been observed in several transition metal-mediated reductive coupling reactions of internal alkynes and aldehydes, allowing for the efficient synthesis of trisubstituted allylic alcohols.[21] Sato has shown that reactions of chiral titanium-alkyne complexes with carbonyl compounds generate enantiomerically enriched allylic alcohols, but selectivities in these couplings are low (<40% ee).[22]

Scheme 3.



Crowe and Rachita were the first to report a successful transition metal-catalyzed reductive coupling of alkynes and aldehydes, namely the cyclization of ynal **1.11** using a catalytic amount of $Cp_2Ti(PMe_3)_2$ and triethoxysilane as a stoichiometric reducing agent (Scheme 3).[23] Montgomery and Oblinger later reported that such cyclizations also proceed efficiently in the presence of catalytic amounts of $Ni(cod)_2$ and PBu_3 when diethylzinc is employed as a stoichiometric reducing agent.[24,25] Work done in our laboratory revealed that, when triethylborane (Et_3B) was used as the reducing agent, *intermolecular* nickel-catalyzed reductive coupling of alkynes and aldehydes could be achieved.[26,27] High regioselectivities were

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[20] Shibasaki recently reported an enantioselective alkenylation of aldehydes catalyzed by a chiral CuF complex that employs air- and moisture-stable alkenylsilanes as nucleophiles: Tomita, D.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 4138-4139.

[21] (a) Buchwald, S. L.; Watson, B. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1987**, *10*, 2544-2546. (b) Van Wagenen, B. C.; Livinghouse, T. *Tetrahedron Lett.* **1989**, *30*, 3495-3498. (c) Takagi, K.; Rousset, C. J.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 1440-1442. (d) Takayanagi, Y.; Yamashita, K.; Yoshida, Y.; Sato, F. *Chem. Commun.* **1996**, 1725-1726. (e) Takai, K.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1990**, *55*, 1707-1708. Kataoka, Y.; Miyai, J.; Oshima, K.; Takai, K. Utimoto, K. *J. Org. Chem.* **1992**, *57*, 1973-1981.

[22] (a) Review: Sato, F.; Urabe, H.; Okamoto, S. *Synlett* **2000**, 753-775. (b) Takayanagi, Y.; Yamashita, K.; Yoshida, Y.; Sato, F. *Chem. Commun.* **1996**, 1725-1726.

[23] Crowe, W. E.; Rachita, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 6787-6788.

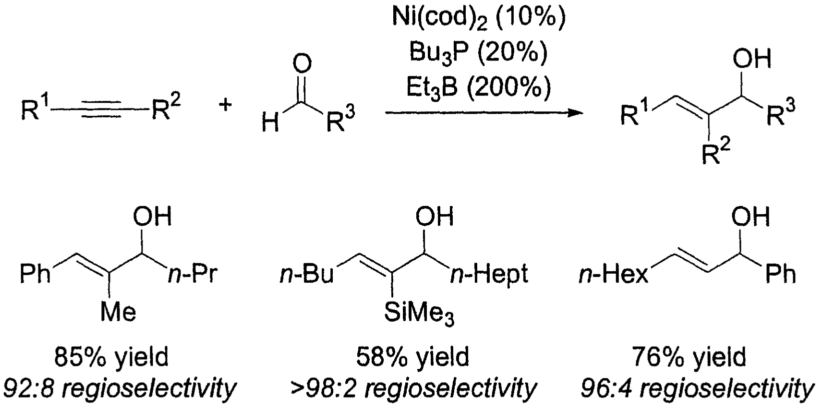
[24] Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065-9066.

[25] Montgomery has also reported the use of triethylsilane as a reducing agent in these couplings: Tang, X. Q.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 6068-6069.

[26] Huang, W.-S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221-4223.

observed for terminal alkynes and internal alkynes substituted with either an aryl (Ar-C≡C-R) or a trimethylsilyl (R-C≡C-SiMe$_3$) group, and both aromatic and aliphatic aldehydes functioned as coupling partners (Scheme 4).

Scheme 4.



Although catalytic, asymmetric carbonyl addition reactions are among the most studied and useful methods of enantioselective carbon–carbon bond formation,[28] very few examples of such processes that are catalyzed by complexes of group 10 metals have been reported. In addition to the Nozaki-Hiyama-Kishi reaction, examples include Pd(II)- and Pt(II)-catalyzed aldol[29] and ene[30] processes, and Ni(0)-catalyzed 1,3-dien-ω-al cyclizations.[31,32] In the following pages, we will discuss our efforts toward the development of a new member of this unusual class of reactions – a nickel-catalyzed, asymmetric reductive coupling of alkynes and aldehydes.[33,34]

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[27] Other examples of nickel-catalyzed intermolecular reductive coupling of alkynes and aldehydes have since been reported: (a) Takai, K.; Sakamoto, S.; Isshiki, T. *Org. Lett.* **2003**, *5*, 653 – 655. (b) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698-3699.

[28] See ref 7 and: (a) *Comprehensive Asymmetric Catalysis;* Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999. (b) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000.

[29] (a) Gorla, F.; Togni, A.; Venanzi, L. M.; Abinati, A.; Lianza, F. *Organometallics* **1994**, *13*, 1607-1616. (b) Sodeoka, M.; Ohrai, K.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 2648-2649. (c) Fujimura, O. *J. Am. Chem. Soc.* **1998**, *120*, 10032-10039. (d) Motoyama, Y.; Kawakami, H.; Shimozono, K.; Aoki, K.; Nishiyama, H. *Organometallics* **2002**, *21*, 3408-3416.

[30] (a) Hao, J.; Hatano, M.; Mikami, K. *Org. Lett.* **2000**, *2*, 4059-4062. (b) Koh, J. H.; Larsen, A. O.; Gagné, M. R. *Org. Lett.* **2001**, *3*, 1233-1236.

[31] Sato, Y.; Saito, N.; Mori, M. *J. Am. Chem. Soc.* **2000**, *122*, 2371-2372.

[32] Acylation (cyclic anhydride desymmetrization): Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 174-175.

[33] For recent reviews on nickel-catalyzed reductive couplings and cyclizations, see: (a) Miller, K. M.; Molinaro, C.; Jamison, T. F. *Tetrahedron: Asymmmetry* **2003**, *14*, 3619-3625. (b) Ikeda, S.-i. *Angew. Chem. Int. Ed.* **2003**, *42*, 5120-5122. (c) Montgomery, J. *Angew. Chem. Int. Ed.* **2004**, *43*, 2-20.

[34] Concurrently with our work, another system for the catalytic, asymmetric reductive coupling of alkynes and aldehydes was developed. Using a class of novel, *P*-chiral ferrocenyl monophosphines, couplings of alkyl-

Evaluation of Reaction Parameters

Chiral Phosphine Ligands

Work toward the development of an asymmetric, catalytic reductive coupling of alkynes and aldehydes began with an evaluation of chiral phosphine ligands in the reductive coupling of 1-phenyl-1-propyne (**1.12**) and *n*-butyraldehyde (**1.13**) (Table 1).[35] While nickel complexes of the chiral bidentate phosphine ligands BINAP (**1.14**),[36] Me-BPE (**1.15**),[37] and Me-DUPHOS (**1.16**)[38] did not effect the reaction, a variety of chiral monodentate phosphines were effective (Figure 2).[39]

Desired allylic alcohol **1.17** was isolated in excellent yield in the presence of α-pinene-derived phosphine **1.18**; however, the enantioselectivity was very low (Table 1, entry 1).[40] Enantioselectivity improved somewhat with β-pinene-derived phosphine **1.19**, but chemical yield decreased significantly (entry 2).[41] Burk's chiral phospholane (**1.20**),[37] which has proven an effective chiral ligand in nickel-catalyzed reductive cyclizations of ω-formyl-1,3-dienes and aldehydes,[31] afforded **1.17** in 0% ee (entry 3). Very low chemical yield and low enantioselectivity were obtained using binaphthol-derived aminophosphine ligand **1.21** (entry 4).[42,43]

A series of prolinol-derived phosphines (**1.22-1.25**) developed by Hiroi and Tomioka[44] was synthesized and evaluated (entries 5-8).[45] Certain members of this series (e.g. **1.24**,[44d] entry 7) promoted the reductive coupling in high yield and modest enantioselectivity; however,

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substituted alkynes (alkyl–C≡C–alkyl') and aldehydes were realized in up to 68%ee: Colby, E. A.; Jamison, T. F. *J. Org. Chem.* **2003**, *68*, 156-166.

[35] Dr. Wei-Sheng Huang contributed to this portion of the project (Table 1, entries 3, 4, and 12, and attempted couplings with ligands **1.13**, **1.14**, and **1.15**).

[36] Takaya, H.; Akutagawa, S.; Noyori, R. *Org. Synth.* **1989**, *67*, 20-32.

[37] Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Organometallics* **1990**, *9*, 2653-2655.

[38] Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518-8519.

[39] For reviews on the use of chiral monodentate phosphines in asymmetric catalysis, see: (a) Kagan, H. B.; Lagasse, F. *Chem. Pharm. Bull.* **2000**, *48*, 315-324. In asymmetric hydrogenation, specifically: (b) Borner, A.; Komarov, I. V. *Angew. Chem. Int. Ed.* **2001**, *40*, 1197-1200. (c) Jerphagnon, T.; Renaud, J.-L.; Bruneau, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2101-2111.

[40] Ligand **1.18** was prepared by Mr. Valer Jeso.

[41] Ligands **1.19** and **1.27** were prepared by Dr. Johann Chan.

[42] Chieffi, A.; Kamikawi, K.; Åhman, J.; Fox, J. M.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1897-1900.

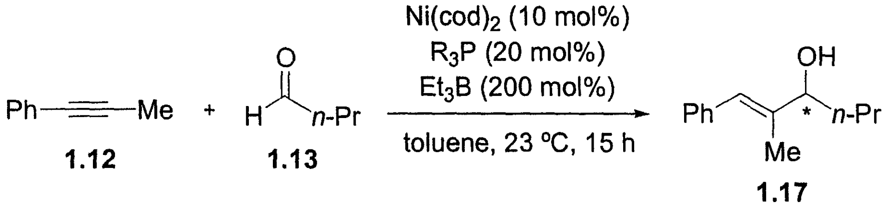
[43] We thank the laboratory of Professor Stephen L. Buchwald for graciously providing a sample of **20**.

[44] (a) Hiroi, K.; Abe, J. Chem. Pharm. Bull. 1991, 39, 616-621. (b) Hiroi, K.; Hidaka, A.; Sezaki, R.; Imamura, Y. *Chem. Pharm. Bull.* **1997**, *45*, 769-777. (c) Hiroi, K.; Suzuki, Y.; Abe, I. *Chem. Lett.* **1999**, 149-150. (d) Kanai, M.; Nakagawa, Y.; Tomioka, K. *Tetrahedron* **1999**, *55*, 3843-3854.

[45] Ligands **1.22-1.25** were prepared by Dr. Sejal Patel.

regioselectivities dropped below 90:10 in most cases. Phosphine **1.26**, prepared from *cis*-aminoindanol, provided only modest chemical yield and low enantioselectivity (entry 9), and Hayashi's ferrocenyl phosphine **1.27**,[46] while providing **1.17** in excellent yield, resulted in very low enantioselectivity (entry 10).

Table 1. Evaluation of chiral phosphine ligands in the asymmetric catalytic reductive coupling of 1-phenyl-1-propyne (**1.12**) and *n*-butyraldehyde (**1.13**).[a]



entry	R_3P	yield (%)[b]	ee (%)[c]	regioselectivity[d]
1	**1.18**	85	7	91:9
2	**1.19**	44	29	90:10
3	**1.20**	32	0	n/a
4	**1.21**	7	24	n/a
5	**1.22**	10	25	91:9
6	**1.23**	60	36	88:12
7	**1.24**	73	36	88:12
8	**1.25**	46	36	82:18
9	**1.26**	35	9	90:10
10	**1.27**	90	5	88:12
11	**1.28**	**97**	**50**	**95:5**

[a] Experimental procedure: A solution of Et_3B in toluene (2 M, 1 mmol, 0.5 mL) was added to a flask containing $Ni(cod)_2$ (0.05 mmol) and R_3P (0.1 mmol). The reaction was stirred 5 min at 23 °C, and then **1.13** (1 mmol) was added, followed by **1.12** (0.5 mmol). After 15 h, sat. aqueous NH_4Cl (2 mL) and 1 M HCl (0.5 mL) were added and the mixture was extracted with EtOAc (3 x 10 mL). Crude material was purified by silica gel chromatography. [b] Yield of isolated product. [c] Determined by HPLC analysis using Chiralcel OD column. [d] Determined by ^1H NMR.

The best result obtained in our initial ligand evaluation was obtained when the commercially available (+)-neomenthyldiphenylphosphine (NMDPP, **1.28**) was employed. Although first prepared by Morrison over 30 years ago, this chiral monophosphine has thus far

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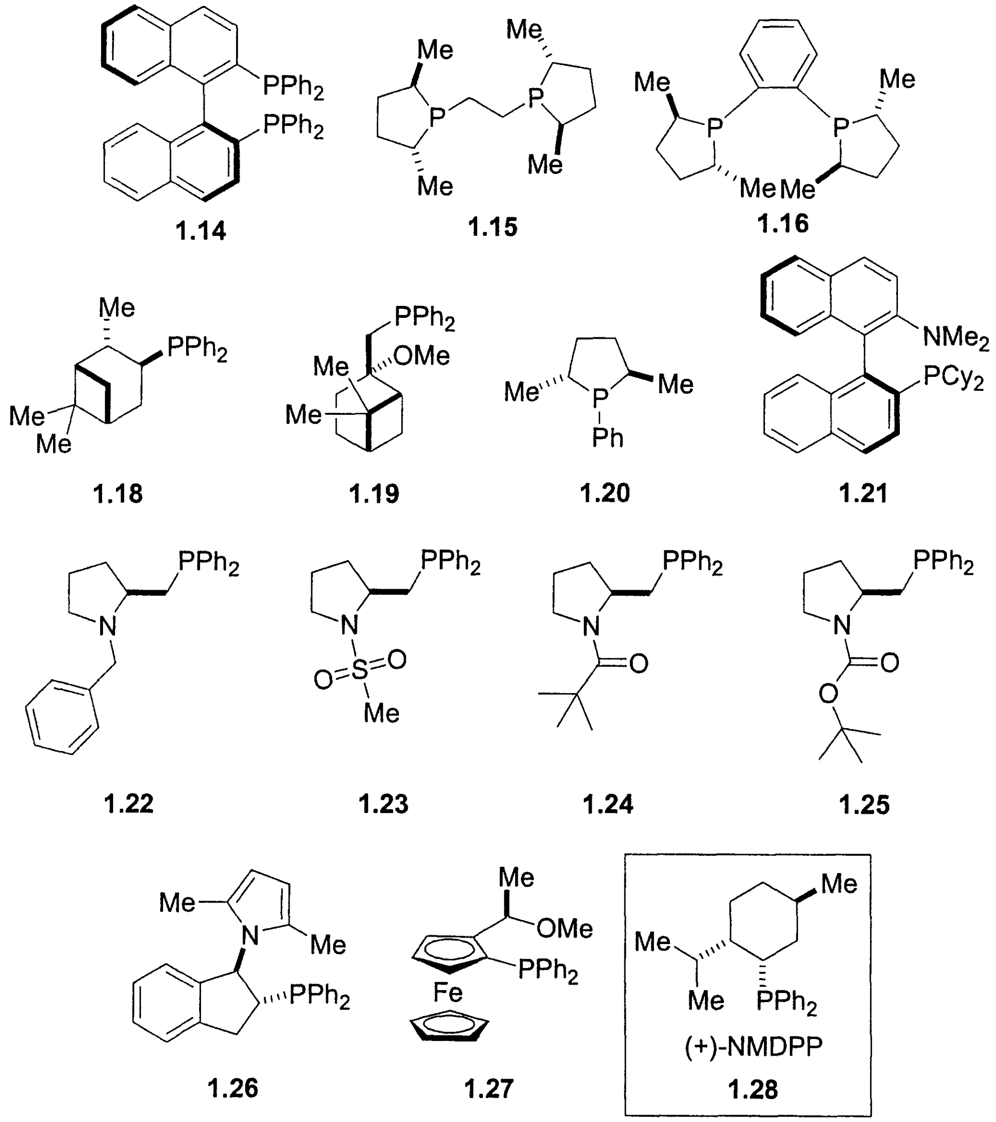
[46] (a) Hayashi, T.; Kumada, M. *Acc. Chem. Res.* **1982**, *15*, 395-401. (b) Hayashi, T.; Hayashizaki, K.; Kiyoi, T.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8153-8156.

found only limited utility in asymmetric catalysis;[47] nevertheless, use of NMDPP afforded allylic alcohol **1.17** in excellent yield and regioselectivity and in 50% ee (entry 11). As this was the highest enantioselectivity yet observed, we chose to evaluate other reaction parameters while using this chiral ligand in an attempt to improve enantioselectivity.

Figure 2. Chiral phosphines evaluated in the nickel-catalyzed reductive coupling of alkynes and aldehydes.



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[47] (a) Morrison, J. D.; Burnett, R. E.; Aguiar, A. M.; Morrow, C. J.; Philips, C. *J. Am. Chem. Soc.* **1971**, *93*, 1301-1303. (b) Blum, J.; Eisen, M.; Schumann, H.; Gorella, B. *J. Mol. Catal.* **1989**, *56*, 329-337. (c) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402-3415.

Solvent, Catalyst Loading, and Temperature

A variety of solvents were evaluated in the reductive coupling of **1.12** and **1.13** at 23 °C (Table 2, entries 1-6). Enantioselectivities varied only slightly with change in solvent at this temperature, and reactivities were excellent, with the exception of a reaction conducted in benzene (entry 2). Several experiments were conducted in MTBE to determine the effect of catalyst loading on yield and enantioselectivity (entries 6-9). Lowering the catalyst loading from 10 mol% Ni(cod)$_2$/ 20 mol% NMDPP to 2.5 mol% Ni(cod)$_2$/ 5 mol% NMDPP had no effect on yield or selectivity at 23 °C (entries 6-8); However, decreasing the nickel: ligand ratio to 1:1 (10 mol% Ni(cod)$_2$/ 10 mol% NMDPP) did have a detrimental effect on enantioselectivity (entry 9). An experiment performed with 10:20 catalyst loading that was quenched after only 1 h revealed that reaction conversion at this point was quite high (entry 10), and suggested that the reactivity of the system might tolerate reduced temperatures. A reaction conducted in MTBE at –30 °C revealed a significant temperature dependence on enantioselectivity, and **1.17** was formed in 65% ee (entry 11).

Table 2. Evaluation of catalyst loading, solvent, and temperature in the catalytic asymmetric reductive coupling of **1.12** and **1.13**.[a]

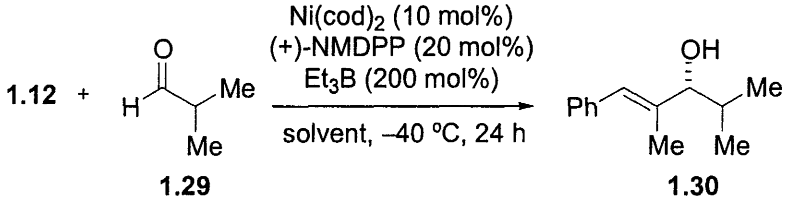
entry	Ni(cod)$_2$ (mol%)	NMDPP (mol%)	solvent	temp (°C)	yield (%)[b]	ee (%)[c]
1	10	20	toluene	23	97	50
2	"	"	benzene	"	49	53
3	"	"	THF	"	90	50
4	"	"	EtOAc	"	85	48
5	"	"	acetone	"	85	51
6	"	"	MTBE	"	91	50
7	5	10	"	"	86	50
8	2.5	5	"	"	91	50
9	10	10	"	"	86	45
10[d]	10	20	"	"	75	50
11	"	"	"	-30	45	65
12	"	"	THF	"	32	66
13	"	"	acetone	"	39	73
14	**"**	**"**	**toluene**	"	**69**	**65**

[a] Experimental procedure: A solution of Et$_3$B in solvent (2 M, 1 mmol, 0.5 mL) was added to a flask containing Ni(cod)$_2$ and (+)-NMDPP (amounts as specified). The reaction was stirred 5 min at 23 °C and, if noted, placed in a pre-cooled –30 °C bath. **1.13** (1 mmol) was added, followed by **1.12** (0.5 mmol). Experiments conducted at 23 °C were quenched after 15 h by addition of sat. aqueous NH$_4$Cl (2 mL) and 1 M HCl (0.5 mL); those at –30 °C were quenched after 24 h. Crude material was purified by silica gel chromatography. [b] Yield of isolated product (**1.17**). Regioselectivity was >95:5 in every case as determined by ^{1}H NMR. [c] Determined by HPLC analysis using Chiralcel OD column. [d] Reaction quenched after 1 h.

At reduced temperature, more variation of reaction yield and enantioselectivity was observed with change in solvent, and the highest selectivities were seen when either THF or acetone were employed (entries 12 and 13). However, these solvents afforded low chemical yields, and toluene was chosen for further study as it provided the highest yield at reduced temperature (entry 14).

Upon switching the aldehyde coupling partner from unbranched **1.13** to α-branched isobutyraldehyde (**1.29**), a remarkable improvement in enantioselectivity was observed. By cooling the reaction slightly further to –40 °C, the corresponding reductive coupling product **1.30** could be formed in *90% ee* (Table 3, entry 1). Unfortunately, a much lower chemical yield was obtained in this coupling reaction (29%), so a more extensive evaluation of solvents was undertaken.

Table 3. Solvent evaluation in the catalytic asymmetric reductive coupling of **1.12** and isobutyraldehyde (**1.29**).[a]



entry	solvent	yield (%)[b]	ee (%)[c,d]
1	toluene	29	90
2	*m*-xylene	30	86
3	THF	11	91
4	MTBE	40	85
5	anisole	36	86
6	**EtOAc**	**38**	**90**
7	*t*-BuOAc	30	87
8	acetone	22	95
9	none[e]	27	87

[a] Experimental procedure: A solution of Et$_3$B in solvent (2 M, 1 mmol, 0.5 mL) was added to a flask containing Ni(cod)$_2$ (0.05 mmol) and (+)-NMDPP (0.1 mmol). The reaction was stirred 10 min at 23 °C and then placed in a pre-cooled –40 °C bath. After 10 min, **1.29** (1 mmol) was added, followed by **1.12** (0.5 mmol). After 24 h, sat. aqueous NH$_4$Cl (2 mL) and 1 M HCl (0.5 mL) were added and the mixture was extracted with EtOAc (3 x 10 mL). Crude material was purified by silica gel chromatography. [b] Yield of isolated product. Regioselectivities were >95:5 in all cases as determined by ^{1}H NMR. [c] Determined by HPLC analysis using Chiralcel OD column. [d] Absolute configuration determined to be (*R*) by Mosher's ester analysis. [e] Reaction conducted on 1 mmol scale and quenched after 48 h.

Use of *m*-xylene in place of toluene resulted in a decrease in enantioselectivity (Table 3, entry 2). THF afforded a small improvement in enantioselectivity, but chemical yield dropped significantly to 11% (entry 3). While MTBE afforded the best yield, enantioselectivity in this solvent was lower (entry 4), and anisole performed similarly (entry 5). Use of EtOAc resulted in an improved yield and with no loss in enantioselectivity relative to toluene (entry 6), but enantioselectivity obtained in *t*-BuOAc did decrease (entry 7). Acetone led to the highest levels of enantioselection observed, albeit in low chemical yield (entry 8). Finally, an experiment was conducted in the absence of added solvent, but no improvement in yield or enantioselectivity was observed (entry 9). Upon conclusion of these studies, EtOAc was chosen for further study as it provided the optimal balance between reactivity and enantioselectivity.[48]

Additive Effects

Several additives or co-solvents were investigated in an attempt to increase reactivity in the reductive coupling of **1.12** and **1.29** while maintaining the high levels of enantioselectivity observed at low temperature (Table 4). Addition of either DMF or DMA to the reaction resulted in a complete loss in reactivity (entries 2 and 3). Coupling was observed in the presence of the protic additives MeOH and H_2O; however yields and enantioselectivities were diminished, and significant side product formation was observed (entries 4 and 5).[49]

The addition of 200 mol% of the polar aprotic cyclic urea DMPU (**1.31**, Figure 3) resulted in a slight *increase* in yield with no loss in enantioselectivity (entry 6). Increasing the amount of DMPU to 400 mol% resulted in further improvements to the yield and also a small increase in enantioselectivity (entry 7). Due to the positive results obtained with this additive, its five-membered ring analog, 1,3-dimethylimidazolidinone (DMI, **1.32**), was investigated under identical conditions. Use of this additive led to further enhancements in yield, providing **1.30** in

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[48] It is worthy of note that coupling reactions of alkynes and aldehydes can be carried out efficiently in both ketone (acetone) and ester (EtOAc, *t*-BuOAc) solvents. Reactions conducted in these solvents both at 23 °C and at reduced temperatures proceed with complete chemoselectivity (i.e., no coupling of the alkyne with a solvent molecule is observed).

[49] The use of protic solvents in nickel-catalyzed coupling reactions of this type tends to induce formation of the corresponding "alkylative" coupling product (transfer of Et from Et_3B instead of H). See Table 4 for details. For examples of the Ni-catalyzed, three-component coupling of alkynes, imines, and organoboron reagents in the presence of protic solvents, see: (a) Patel, S. J.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2003**, *42*, 1364-1367. (b) Patel, S. J.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2004**, *43*, 3941-3944.

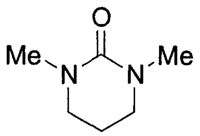
56% yield and 90% ee (entry 8).[50] Use of DMI as the exclusive reaction solvent did lead to significant enhancements in both yield and enantioselectivity relative to those obtained in EtOAc alone at 0 °C (entries 9 and 10); however, its relatively high freezing point (–1 °C) prevented its use as the exclusive reaction solvent at low temperatures. The dramatic effect of temperature on both chemical yield and enantioselectivity in this reaction is demonstrated by comparing experimental results obtained at –40 °C vs. 0 °C (entries 1 and 10).

Table 4. Evaluation of additive effects in the coupling of **1.12** and **1.29**.[a]

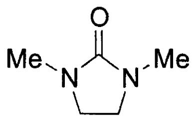
Entry	Solvent	Additive	Temp (°C)	Yield[b] (%)	ee[c] (%)	Regioselectivity[d]
1	“	“	–40	38	90	>95:5
2	“	DMF (200%)	“	<10	n.d.	n.d.
3	“	DMA (200%)	“	<10	n.d.	n.d.
4	“	MeOH (100%)	“	20[e]	77	>95:5
5	“	H_2O (50%)	“	20[f]	83	>95:5
6	“	DMPU (200%)	“	43	90	>95:5
7	“	DMPU (400%)	“	50	92	>95:5
8	“	DMI (400%)	“	56	90	>95:5
9	DMI	none	0	95	79	>95:5
10	EtOAc	none	“	90	72	91:9

[a] Experimental procedure: A solution of Et_3B in solvent (2 M, 1 mmol, 0.5 mL) and the additive were added to a flask containing $Ni(cod)_2$ (0.05 mmol) and (+)-NMDPP (0.1 mmol). The reaction was stirred for 5 min at 23 °C and then placed in a bath which had been cooled to the appropriate temperature. After 10 min, **1.29** (1 mmol) was added, followed by **1.12** (0.5 mmol). Experiments conducted at 0 °C were quenched after 6 h by addition of sat. aqueous NH_4Cl (2 mL) and 1 M HCl (0.5 mL); those at –40 °C were quenched after 24 h. Crude material was purified by silica gel chromatography. [b] Yield of isolated product (**1.30**). [c] Enantioselectivities determined by HPLC analysis using Chiralcel OD column. [d] Determined by ^1H NMR integration. [e] Both reductive and alkylative (transfer of Et from Et_3B instead of H) coupling products were observed, in a 67:33 ratio. [f] Both reductive and alkylative (transfer of Et from Et_3B instead of H) coupling products were observed, in a 58:42 ratio.

Figure 3. Effective additives in the catalytic, asymmetric reductive coupling of alkynes and aldehydes.



DMPU (**1.31**)



DMI (**1.32**)

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[50] Uneyama has reported a Pd-catalyzed tert-butoxycarbonylation of trifluoroacetimidoyl iodides in which the use of DMI as an additive led to improved chemical yields: Amii, H.; Kishikawa, Y.; Kageyama, K.; Uneyama, K. *J. Org. Chem.* **2000**, *65*, 3404-3408.

Further experimentation with this EtOAc:DMI solvent system revealed a unique correlation between enantioselectivity and addition rate of the aldehyde coupling partner (Table 5). At –25 °C, using EtOAc as the exclusive reaction solvent, no change in enantioselectivity is observed with change in rate of aldehyde addition (entries 2 and 3). However, when the EtOAc:DMI solvent system is employed, a dramatic effect is observed. As seen at –40 °C, a reaction conducted using EtOAc:DMI displayed enhanced reactivity and enantioselectivity relative to a reaction conducted in EtOAc alone (entries 2 and 4). This enhancement was greatly magnified, however, when the aldehyde was added to the reaction in a dropwise fashion over 8 h, and allylic alcohol **1.30** was isolated *in 95% yield and 90% ee.* These optimized conditions were then employed in reactions with other coupling partners.

Table 5. Cooperative effects of solvent composition and mode of aldehyde addition on yield and enantioselectivity.[a]

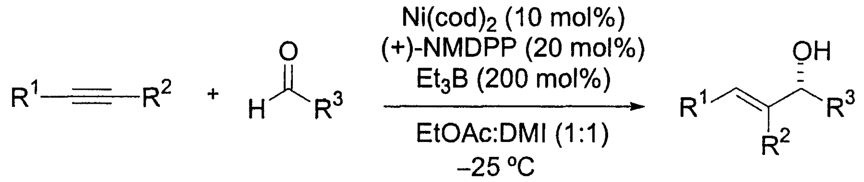
entry	solvent	Temp (°C)	*i*–PrCHO addition time	regioselectivity[b]	yield (%)	ee (%)[c]
1	EtOAc	–40	<2 min	>95:5	56	90
2	"	–25	"	>95:5	86	82
3	"	"	8 h	>95:5	74	82
4[d]	EtOAc/DMI	"	<2 min	>95:5	94	84
5[d]	**EtOAc/DMI**	**"**	**8 h**	**>95:5**	**95**	**90**

[a] Experimental procedure: A solution of $Ni(cod)_2$ (0.05 mmol), (+)-NMDPP (0.10 mmol), and Et_3B (1.0 mmol) in EtOAc (0.5 mL) or EtOAc/DMI (1:1, total volume 0.50 mL) was cooled to –25 °C. **1.12** (0.50 mmol) was added, and then **1.29** (1.0 mmol) was added via syringe over the time specified. After 36 h, sat. aqueous NH_4Cl (2 mL) and 1 M HCl (0.5 mL) were added and the mixture was extracted with EtOAc (3 x 10 mL). Crude material was purified by silica gel chromatography. [b]Determined by ^1H NMR. [c] Determined by chiral HPLC analysis using Chiralcel OD column. [d] A 1:1 ratio of EtOAc and DMI was used.

Substrate Scope and Limitations

This catalytic, asymmetric reductive coupling of alkynes and aldehydes affords trisubstituted allylic alcohols corresponding to exclusive cis addition to the alkyne in excellent regioselectivity and in up to 96% ee (Table 6). Branched aldehydes provide high yields and enantioselectivities in reductive couplings with 1-phenyl-1-propyne (entries 1 and 2); however, enantioselectivities are diminished when aromatic or α-unbranched aldehydes are employed (entries 3 and 4).

Table 6. Asymmetric catalytic reductive coupling of alkynes and aldehydes.[a]



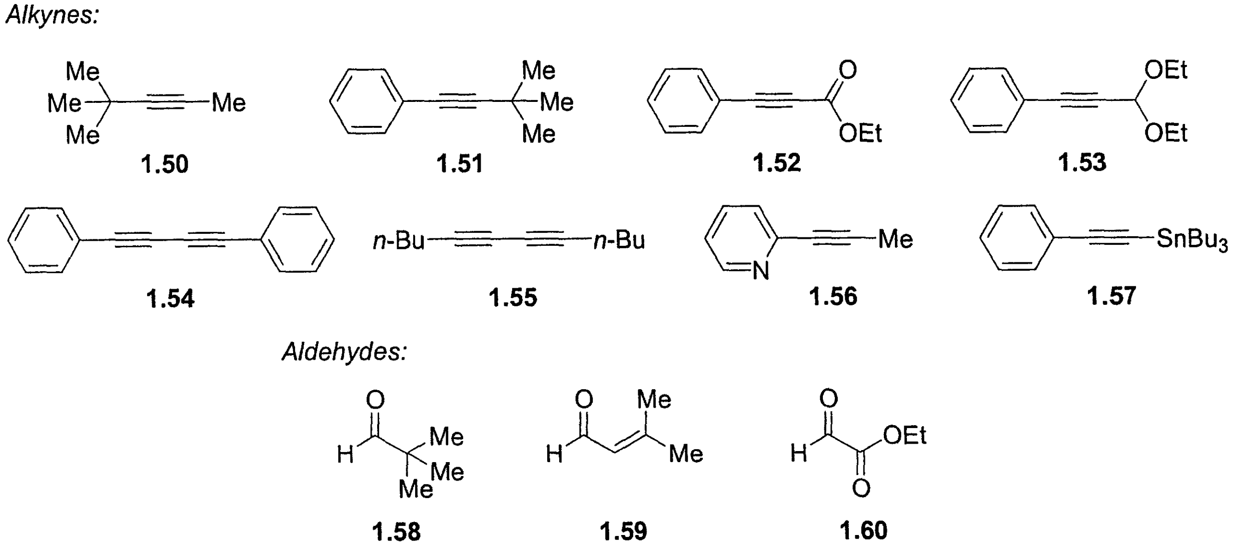
entry	R^1	R^2	R^3	Product	yield (%),[b] regioselectivity[c]	ee (%)[d]
1	Ph	Me	*i*–Pr	**1.30**	95 (>95:5)	90[e]
2	"	"	Cy	**1.33**	97 (>95:5)	90
3	"	"	Ph	**1.34**	79 (91:9)	73
4	"	"	*n*–Pr	**1.17**	82 (>95:5)	65
5	(*p*–MeO)Ph	"	*i*–Pr	**1.35**	80 (>95:5)	88
6	(*p*–Cl)Ph	"	"	**1.36**	75 (>95:5)	83
7	(*p*-CF_3)Ph	"	"	**1.37**	78 (>95:5)	81
8	(*o*-Me)Ph	"	"	**1.38**	86 (>95:5)	84
9	1-naphthyl	"	"	**1.39**	93 (>95:5)	90
10	Ph	Et	"	**1.40**	81 (>95:5)	93
11[f]	Ph	Et	Cy	**1.41**	78 (>95:5)	89
12	"	*n*–Pr	*i*–Pr	**1.42**	74 (>95:5)	92
13	"	*i*–Pr	"	**1.43**	58[g] (>95:5)	92
14	"	cyclopropyl	"	**1.44**	67 (>95:5)	92
15	"	CH_2OTBS	"	**1.45**	59 (>95:5)	85
16	"	CH_2NHBoc	"	**1.46**	60 (>95:5)	96
17	"	$SiMe_3$	*n*–Pr	**1.47**	43[g] (>95:5)	92
18	*n*–Pr	*n*–Pr	*i*–Pr	**1.48**	35[g] (–)	42
19	Ph	H	"	**1.49**	15 (>95:5)	75

[a] Experimental procedure: A solution of $Ni(cod)_2$ (0.05 mmol), (+)-NMDPP (0.10 mmol), and Et_3B (1.0 mmol) in EtOAc/DMI (1:1, total volume 0.50 mL) was cooled to –25 °C. The alkyne (0.50 mmol) was added, and then the aldehyde (1.0 mmol) was added dropwise via syringe over 8 h. After 36 h, sat. aqueous NH_4Cl (2 mL) and 1 M HCl (0.5 mL) were added and the mixture was extracted with EtOAc (3 x 10 mL). Crude material was purified by silica gel chromatography. [b] Yield of isolated product. [c] Determined by ^1H NMR. [d] Determined by chiral HPLC or GC analysis. [e] Absolute configuration determined to be (*R*) by Mosher's ester analysis. [f] Performed on 5.0 mmol scale. [g] Some alkylative coupling (transfer of Et from Et_3B instead of H) was observed.

Significant variation of the alkyne aromatic group (R^1) is tolerated (entries 5-9). Electron-donating (entries 5 and 8), electron-withdrawing (entries 6 and 7), and *ortho* substituents (entries 8 and 9) are accomodated, and 1-naphthyl-1-propyne proved particularly effective (entry 9). The other alkyne substituent (R^2) can also be varied considerably (entries 10-17). Alkynes possessing both linear (entries 10-12) and branched (entries 13 and 14) alkyl groups (including cyclopropyl) are efficient coupling partners. Protected alcohols, protected amines, and $SiMe_3$ groups are accommodated (entries 15-17), and CH_2NHBoc-substituted allylic alcohol **1.46** was isolated in 96% ee, our best selectivity to date (entry 16). The latter coupling has been performed on a gram-scale (10 mmol), and afforded **1.46** in 44% yield (1.35 g) and >98% ee following recrystallization.[33a]

In contrast to our group's recent studies with chiral ferrocenyl phosphine ligands,[34] NMDPP affords lower enantioselectivities in coupling reactions that involve aliphatic internal alkynes such as 4-octyne (entry 18). In addition, coupling products derived from terminal alkynes (entry 19) are isolated in very low yield due to competing nickel-catalyzed alkyne oligomerization reactions (entry 19).[51] Other alkynes that did not couple effectively under these conditions include: *tert*-butyl-substituted alkynes **1.50** and **1.51**, ethyl phenylpropiolate (**1.52**), diethyl acetal **1.53**, diynes **1.54** and **1.55**, 2-prop-1-ynyl-pyridine (**1.56**), and (phenylethynyl)tributyltin (**1.57**) (Figure 4). Aldehydes that were not effective coupling partners include pivaldehyde (**1.58**), 3-methyl-crotonaldehyde (**1.59**), and ethyl glyoxylate (**1.60**).

Figure 4. Ineffective coupling partners in catalytic asymmetric reductive coupling.



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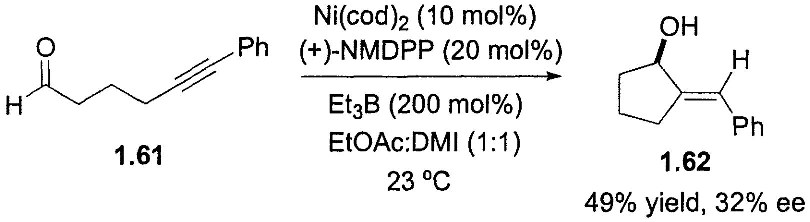
[51] Reviews: (a) Jolly, P. W.; Wilke, G. *The Organic Chemistry of Nickel*; Wiley: New York, 1975; Vol. 2, Chapter 2. (b) Jolly, P. W. In *Comprehensive Organometallic Chemistry*; Wilkinson, G.; Stone, F. G. A.; Abel, E. W., Eds.; Pergamon: New York, 1982; Vol. 8, p 649-670. (c) Winter, M. J. In *The Chemistry of the Metal-Carbon Bond*; Hartley, F. R.; Patai, S., Eds.; Wiley: Chichester, 1985; Vol. 3, Chapter 5.

Intramolecular Reductive Couplings

Our initial reports on the asymmetric catalytic reductive coupling of alkynes and aldehydes have presented only intermolecular examples.[52] Corresponding *intramolecular* couplings of ynals are of interest both from a mechanistic standpoint and because they would allow for the one-step preparation of enantiomerically enriched cyclic allylic alcohols containing an exocyclic alkene moiety.[53,54] However, subjection of ynal **1.61** to the conditions developed for the intermolecular, catalytic asymmetric reductive coupling afforded allylic alcohol **1.62** in only 32% ee (Scheme 5). Unfortunately, attempts to improve both yield and enantioselectivity in this coupling proved unsuccessful.[55] Ynals which would lead to the analogous 6, 7, and 8 membered ring-containing allylic alcohols were also synthesized, but exposure to reductive coupling conditions in these cases led only to reisolation of starting material.

Scheme 5.



Reaction Mechanism

While the mechanism for the catalytic, asymmetric reductive coupling of alkynes and aldehydes has yet to be elucidated, discussions of related reductive coupling reactions in the literature have largely focused on two possible reaction pathways (Scheme 6).[56] In Path A, oxidative addition of Ni(cod)$_2$ to Et$_3$B followed by subsequent β-hydride elimination is presumed to generate a nickel hydride ("Ni–H") species which can then perform a hydrometallation of the

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[52] See ref 33a and: Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442-3443.

[53] For preparation of such compounds using asymmetric reduction of prochiral enones, see: Simpson, A. F.; Bodkin, C. D.; Butts, C. P.; Armitage, M. A.; Gallagher, T. *J. Chem. Soc. Perkin Trans. 1* **2000**, *18*, 3047 – 3054.

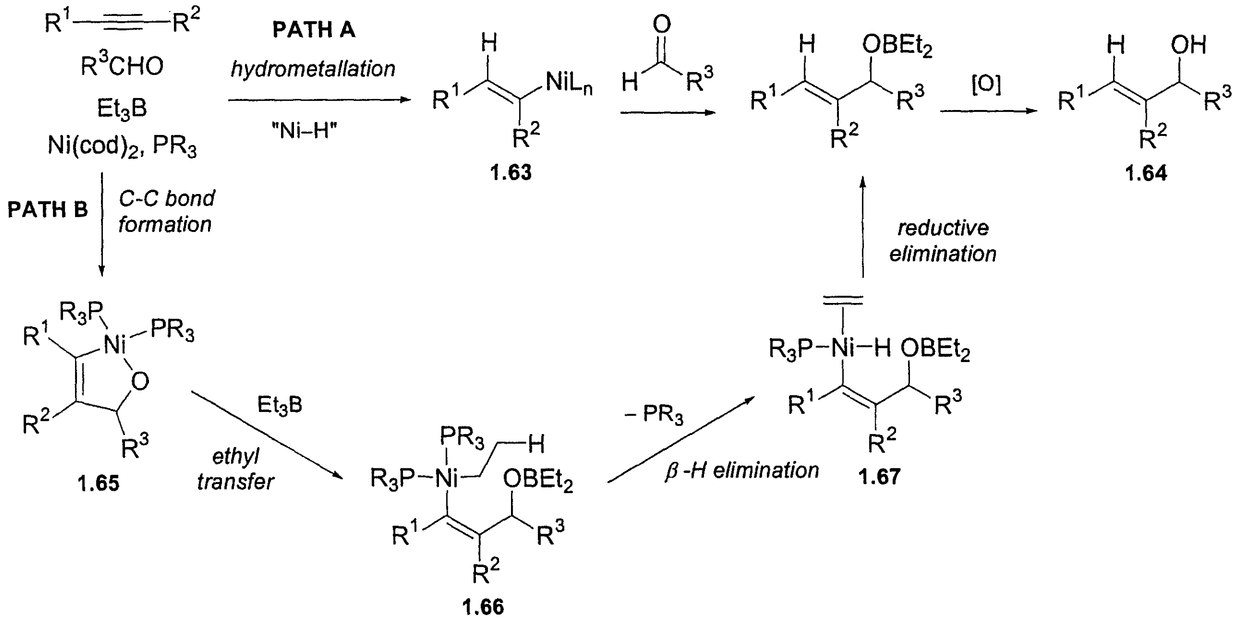
[54] For nickel-catalyzed reductive cyclizations of ynals in the presence of an achiral phosphine ligand, see ref 24.

[55] Yield was improved slightly (to 57%) by using Et$_2$Zn as a reducing agent (see ref 26); however, under these conditions, no enantioselectivity was observed.

[56] For an excellent overview of proposed mechanisms in this and related Ni-catalyzed reductive couplings and cyclizations, see ref 33c.

alkyne to afford alkenyl nickel species **1.63**. This complex then adds to the aldehyde and affords the observed allylic alcohol **1.64** upon oxidative work-up and resulting cleavage of the O–B bond.

Scheme 6. Two proposed mechanistic pathways for the catalytic, asymmetric reductive coupling of alkynes and aldehydes.



In Path B, coordination of the alkyne and the aldehyde to the metal center precedes a C–C bond-forming, oxidative cyclization to provide oxanickelacyclopentene **1.65**.[57,58] Transmetalation of Et_3B to **1.65** (resulting in transfer of an ethyl group to the nickel and simultaneous generation of an O–B bond) affords alkyl nickel species **1.66**. β-Hydride elimination of the ethyl group generates nickel hydride species **1.67** which, upon reductive elimination and oxidative work-up, provides **1.64**. Several factors,[59] including the dependence of

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[57] While a nickelacycle of this type has yet to reported in the literature, a number of related "nickelalactones" derived from reaction of Ni(0), an alkyne, and CO_2 have been characterized: (a) Burkhart, G.; Hoberg, H. *Angew. Chem. Int. Ed.* **1982**, *21*, 76. (b) Hoberg, H.; Schaefer, D.; Burkhart, G. *J. Organomet. Chem.* **1982**, *228*, C21-C24. (c) Hoberg, H.; Schaefer, D.; Burkhart, G.; Kruger, C.; Romao, M. J. *J. Organomet. Chem.* **1984**, *266*, 203-224. (d) Walther, D.; Bräunlich, G.; Kempe, R.; Sieler, J. *J. Organomet. Chem.* **1992**, *436*, 109-119. (e) Langer, J.; Fischer, R.; Görls, H.; Walther, D. *J. Organomet. Chem.* **2004**, *689*, 2952-2962.

[58] Recently, a related nickelacycle resulting from the first observed oxidative cyclization of an alkene and an aldehyde with Ni(0) was reported: Ogoshi, S.; Oka, M.-a.; Kurosawa, H.; *J. Am. Chem. Soc.* **2004**, *126*, 11802-11803.

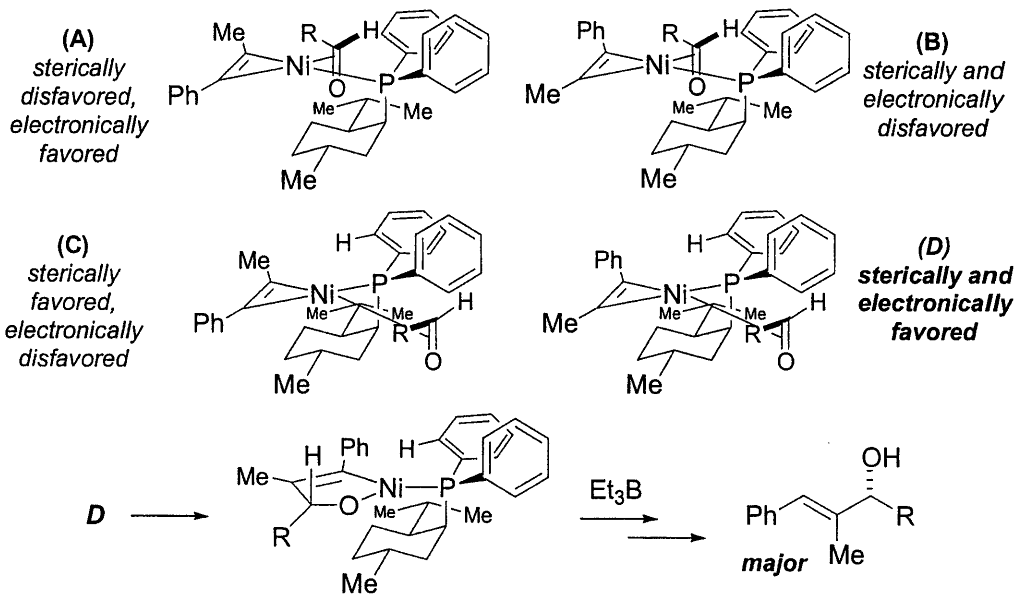
[59] See refs 24, 49a, and: Hratchian, H. P.; Chowdhury, S. K.; Gutiérrez-García, V. M.; Amarasinghe, K. K. D.; Heeg, M. J.; Schlegel, H. B.; Montgomery, J. *Organometallics* **2004**, *23*, 4636-4646.

regioselectivity on aldehyde structure (*cf.* Table 6, entries 1 and 3), suggest that this latter pathway or a variant thereof is most likely operating.[60]

Model for Enantioselectivity

The sense of asymmetric induction in these couplings is consistent with the model shown in Scheme 7. Several lines of evidence point to an oxametallacyclopentene intermediate,[59] arising from nickel complexes such as **A**–**D**. Both the axial placement and the orientation of a metal-PPh_2 group over the cyclohexyl ring of NMDPP have been observed in the solid state.[61] Rotation of one of the phenyl groups of the ligand to avoid interaction with the isopropyl group places a C–H bond in the ligand plane on one side of the metal, disfavoring aldehyde coordination (**A** and **B**). π-Complexation of the aldehyde to the less encumbered side (**C** or **D**) of the metal while orienting the aldehyde H toward the phenyl ring of NMDPP and the R group away from it appears to minimize steric interactions.

Scheme 7. Proposed steric and electronic control in catalytic asymmetric reductive couplings.



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[60] The production of ethylene is observed in these coupling reactions, which is consistent with a transfer of H from Et_3B via either Path A or Path B. See Experimental Section for details.

[61] Whittall, I. R.; Humphrey, M. G.; Samoc, M.; Luther-Davies, B.; Hockless, D. C. R. *J. Organomet. Chem.* **1997**, *544*, 189-196.

The high enantioselectivity uniquely provided by NMDPP in these couplings can thus be explained by a cooperative effect between steric properties of the ligand and electronic differences of the alkyne substituents. Two of the four modes of aldehyde coordination (**A** and **C**) are inconsistent with the sense and degree of regioselectivity observed in these couplings (i.e., such coordination would lead to C–C bond formation proximal to the Ph group, rather than proximal to the Me group, *cf.* Table 6).[62] Of the remaining two, one is more accessible (**D**). Rotation of the aldehyde by about 90 degrees in the transition state followed by oxametallacyclopentene formation leads to the major enantiomer observed.

Synthesis of Enantiomerically Enriched α-Hydroxy Ketones

The ozonolysis of allylic alcohols generated via the catalytic, asymmetric reductive coupling of alkynes and aldehydes provides ready access to enantiomerically enriched α-hydroxy ketones. Subjection of allylic alcohol **1.41** to standard ozonolysis conditions resulted in conversion to α-hydroxy ketone **1.68**, whose TBS ether was originally developed by Masamune for use in asymmetric aldol reactions,[63] in high yield and with complete preservation of enantiomeric purity (Scheme 8).

To further illustrate the utility of this approach, allylic alcohol **1.46** was converted into α-hydroxy ketone **1.69**, whose α–amino–α'–hydroxy pattern is found in molecules targeted against trypanosomes, parasites that cause African sleeping sickness upon transmission from tsetse flies,[64] and in aerothionin natural products with anti-tuberculosis activity.[65]

Common methods of α-hydroxy ketone synthesis via asymmetric catalysis involve dihydroxylation or epoxidation of ketone enolate derivatives.[66] However, these approaches are not well suited for cases in which the regioselectivity of enolate formation is poor or favors an

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[62] We believe that the observed regioselectivity in these couplings is due primarily to the electronic difference between the two alkyne substituents. For related examples and further discussion, see Chapter 2.

[63] (a) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566-1568. (b) Masamune, S.; Hirama, M.; Mori, S.; Ali, S. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568-1571.

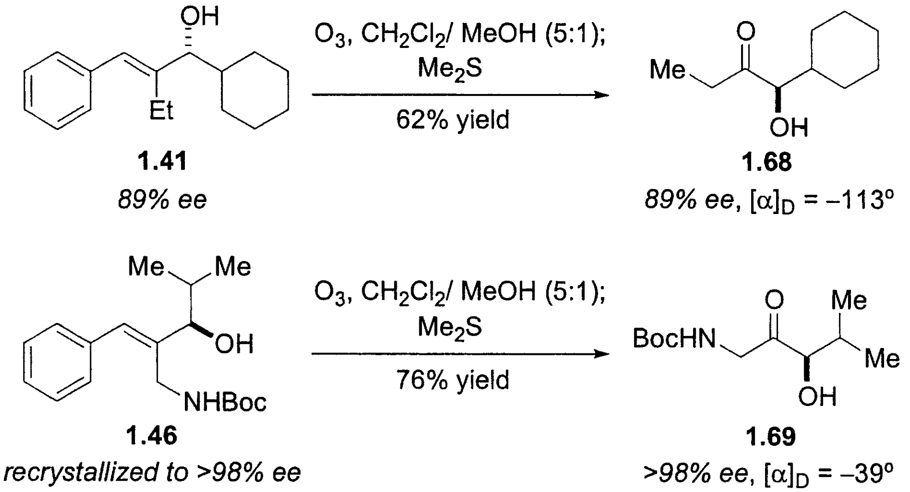
[64] (a) Eisenthal, R.; Game, S.; Holman, G. D. *Biochem. Biophys. Acta* **1989**, *985*, 81-89. (b) Azéma, L.; Bringaud, F.; Blonski, C.; Périé, J. *Bioorg. Med. Chem.* **2000**, *8*, 717-722.

[65] Ciminiello, P.; Costantino, V.; Fattorusso, Magno, S.; Mangioni, A.; Pansini, M. *J. Nat. Prod.* **1994**, *57*, 705-712.

[66] (a) Hashiyama, T.; Morikawa, K.; Sharpless, K. B. *J. Org. Chem.* **1992**, *57*, 5067-5068. (b) Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 7819-7822. (c) Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919-934.

undesired isomer. The catalytic, enantioselective reductive coupling/ozonolysis approach summarized above circumvents this issue[67] and is therefore complementary.

Scheme 8.



Conclusion

In summary, we have developed a catalytic, asymmetric reductive coupling of alkynes and aldehydes that allows for rapid and efficient access to enantiomerically enriched allylic alcohols. Upon ozonolysis, α-hydroxy ketones are generated which are useful building blocks in organic synthesis. The work described herein may also prove valuable in aiding the development of asymmetric variants of other nickel/phosphine-catalyzed reactions.

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[67] For another method that obviates regioselective enolization, see: Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **2002**, *124*, 7376-7389.

Experimental Section

General Methods. 1,5-Bis(cyclooctadiene) nickel (0) [Ni(cod)$_2$], tetrakis(triphenylphosphine) palladium(0) [Pd(PPh$_3$)$_4$], and copper iodide (98%) were purchased from Strem Chemicals, Inc. (*S*)-(+)-Neomenthyldiphenylphosphine (NMDPP) was either purchased from Strem Chemicals or prepared as previously reported.[68] Triethylborane (98%) was purchased from Aldrich Chemical Co. 1-Phenyl-1-propyne, 1-phenyl-1-butyne, 1-phenyl-1-pentyne, 1-phenyl-2-(trimethylsilyl)acetylene, 4-octyne, phenylacetylene and all aldehydes were purchased from either Aldrich Chemical Co. or Alfa Aesar. All aldehydes were distilled prior to use. Methylene chloride, pyrrolidine, and 1,3-dimethylimidazolidinone (DMI) were distilled over calcium hydride; tetrahydrofuran was distilled from a blue solution of sodium benzophenone ketyl; ethyl acetate was distilled over magnesium sulfate under argon atmosphere. Solutions of Et$_3$B were prepared by first degassing the appropriate solvent (sparged with Ar for 15 min) and then adding neat Et$_3$B.

Analytical thin layer chromatography (TLC) was performed using silica gel 60 F254 aluminum plates precoated with a fluorescent indicator or EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was accomplished with UV light and aqueous cerium molybdate, ethanolic phosphomolybdic acid, or aqueous potassium permanganate. Liquid chromatography was performed using a forced flow (flash chromatography)[69] of the indicated solvent system on Silicycle Silica Gel (230-400 mesh). ^{1}H and ^{13}C NMR spectra were recorded in deuterochloroform (CDCl$_3$), unless otherwise noted, on a Varian Inova 500 MHz instrument. Chemical shifts of ^{1}H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of CDCl$_3$ (77.0 ppm). Infrared (IR) spectra were recorded on a Perkin-Elmer 2000 FT-IR System transform spectrometer. High Resolution mass spectra (HMRS) were obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. HPLC was performed on a Hewlett-Packard 1100 chromatograph equipped with a variable wavelength detector and Chiralcel OD or OJ column. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 589 nm. Low temperatures were maintained using a Thermo Neslab CC-65 immersion cooler equipped with Cryotrol temperature controller.

Preparation of Alkyne Coupling Partners.

Representative procedure for preparation of 1-aryl-1-propynes.[70] 1-Methoxy-4-prop-1-ynyl-benzene: 4-Iodoanisole (5.1g, 15 mmol), Pd(PPh$_3$)$_4$ (350 mg, 0.3 mmol), and copper iodide (29 mg, 0.15 mmol) were added to an argon-filled, 250 mL three-necked round-bottom flask. Pyrrolidine (20 mL) was added and the resulting solution cooled to –78 C. The flask was then evacuated, and 1-propyne was bubbled in slowly via syringe. After 2-3 minutes, the flask was removed from the cold bath and allowed to warm slowly to ambient temperature. Once ambient

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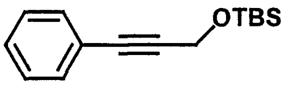
[68] Both enantiomers of NMDPP can be prepared on multi-gram scale in two steps from menthol (MsCl, Et$_3$N; then Na^0, PPh$_3$): Senaratne, K. P. A. Synthesis of cycloalkyldiarylphosphines. US Patent 5,710,340, April 29, 1996.

[69] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

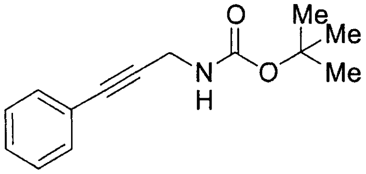
[70] Modification of procedure reported in: Pschirer, N. G.; Bunz, U. H. F. *Tetrahedron Lett.* **1999**, *40*, 2481-2484.

pressure had been reached, the propyne source was removed and the flask placed under an argon atmosphere. After stirring overnight, the solution was filtered through Celite and the solvent removed *in vacuo*. The residue was extracted with ether from a solution of saturated ammonium chloride, dried and condensed, and then subjected to flash chromatography on silica gel (50:1 hexanes: ethyl acetate) to provide the title compound as a clear liquid (75% yield, 1.46 g). Spectral data matched that previously reported.[2]



***tert*-Butyl-dimethyl-(3-phenyl-prop-2-ynyloxy)-silane:** Iodobenzene (3.06g, 1.68 mL, 15 mmol), palladium tetrakis(triphenylphosphine) (350 mg, 0.3 mmol), and copper iodide (29 mg, 0.15 mmol) were added to an argon-filled, 100 mL round-bottom flask and pyrrolidine (20 mL) was added. Propargyl alcohol (0.84 g, 0.87 mL, 15 mmol) was added and the solution allowed to stir at ambient temperature overnight. The solution was then filtered through Celite and the solvent removed *in vacuo*. The residue was extracted with ether from a solution of saturated ammonium chloride, dried and condensed, and then subjected to column chromatography in 4:1 hexanes: ethyl acetate to provide 3-phenyl-prop-2-yn-1-ol as a clear liquid (1.78 g).

This alcohol was dissolved in 15 mL dimethylformamide, and tert-butyldimethylsilyl chloride (4.07 g, 27 mmol) was added. Once the solid had dissolved, imidazole (1.84 g, 27 mmol) was added and the mixture was allowed to stir at ambient temperature overnight. The reaction was then quenched with water, and the organics extracted with hexanes, rinsed with brine, dried and concentrated. Column chromatography in 50:1 hexanes: ethyl acetate provided the title compound as a clear oil (66% yield over two steps, 2.43g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 - 7.45 (m, 2H); 7.31 – 7.33 (m, 3H); 4.56 (s, 2H); 0.96 (s, 9H); 0.19 (s, 6H).



(3-phenyl-prop-2-ynyl)-carbamic acid *tert*-butyl ester : Tetrakis(triphenylphosphine) palladium(0) (508 mg, 0.44 mmol) and copper iodide (42 mg, 0.22 mmol) were added to a 100 mL oven-dried, single-necked flask. N-*t*-butoxycarbonylprop-2-ynylamine[71] (3.41 g, 22.00 mmol) dissolved in pyrrolidine (40 mL) was then added, followed by iodobenzene (2.47 mL, 22.00 mmol). The reaction mixture was heated 16 h at 40 °C, then cooled and concentrated under reduced pressure. To the resulting oil was added saturated aqueous NH_4Cl (40 mL), and the mixture was extracted with diethyl ether (3 x 50 mL), dried and concentrated. The resulting oil was purified by flash chromatography on silica gel (5-17% EtOAc/hexanes) to give a yellow solid. Recrystallization from 20% EtOAc/hexanes provided analytically pure (3-phenyl-prop-2-ynyl)-carbamic acid *tert*-butyl ester as white needles (3.18 g, 63% yield). R_f = 0.50 (17% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.41 (m, 2H); 7.33 – 7.29 (m, 3H); 4.80

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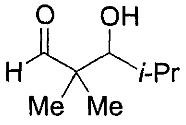
[71] Prepared in one step from propargylamine hydrochloride: Khan, S. I.; Grinstaff, M. W. *J. Am. Chem. Soc.* **1999**, *121*, 4704 - 4705.

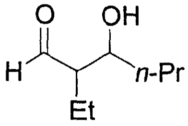
(bs, 1H); 4.17 (d, J = 4.5 Hz, 2H); 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 131.9, 128.5, 128.5, 122.9, 85.5, 83.3, 80.2, 31.4, 28.6; IR (film): 3338, 2978, 2932, 1699, 1599, 1519, 1491, 1456, 1392, 1367, 1276, 1250, 1170 cm^{-1}; HRMS (ESI) *m/z* 254.115 [$(M + Na)^+$ calcd for $C_{14}H_{17}NO_2$: 254.116]; mp: 94–95 °C.

Standard Experimental Procedure for Asymmetric Catalytic Reductive Coupling of Alkynes and Aldehydes.

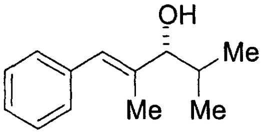
In a glovebox, $Ni(cod)_2$ (14 mg, 0.05 mmol), and (+)-NMDPP (32 mg, 0.1 mmol) were placed into a 50 mL oven-dried, single-necked round-bottom flask, which was then sealed with a rubber septum. The flask was removed from the glovebox, placed under argon, and Et_3B (2.0 M in ethyl acetate, 0.5 mL, 1 mmol) and DMI (0.5 mL) were added via syringe. The resulting solution was stirred 10 min at ambient temperature and then the reaction flask was placed in a precooled, −25 °C isopropanol bath. The solution was stirred 15 min, and then the alkyne (0.5 mmol) was added. The aldehyde (1.0 mmol) was then added over 8 h either portionwise (hourly) or continually in a dropwise fashion via syringe pump (the two modes of addition are functionally equivalent). The reaction was stirred an additional 36 h at −25 °C, at which point saturated aqueous NH_4Cl (3 mL) and 1M HCl (0.5 mL) were added. The mixture was diluted with ethyl acetate (10 mL) and water (5 mL), and the organic layer was extracted (3 x 20 mL), dried and condensed. The crude mixture was purified by flash chromatography on silica gel using a solvent gradient (hexanes: ethyl acetate; 50:1 to 10:1). Additional chromatography (toluene: EtOAc; 10:1) was sometimes necessary to completely remove aldehyde Aldol dimers **1.70** or **1.71**, which are common reaction byproducts.



1.70



1.71



(*E*)-2,4-Dimethyl-1-phenyl-pent-1-en-3-ol (1.30). In the reductive coupling of 1-phenyl-1-propyne (58 mg, 0.5 mmol, 63 μL) and isobutyraldehyde (72 mg, 1.0 mmol, 90 μL) at −25 °C, the standard procedure was used with portionwise addition of the aldehyde over 8 h (10 μl portions). Silica gel chromatography afforded the title compound as a clear oil (91 mg, 95% yield, 90% ee, >95:5 regioselectivity). R_f = 0.22 (10:1 hexanes: ethyl acetate). Absolute configuration was determined to be (*R*) via Mosher's ester analysis (vide infra).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 -7.37 (m, 5H), 6.48 (s, 1H), 3.80 (d, J = 8 Hz, 1H), 1.87-1.93 (m, 1H), 1.87 (s, 3H), 1.05 (d, J = 6.5 Hz, 3H), 0.91 (d, J = 6.5 Hz, 3H).

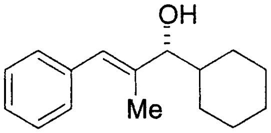
^{13}C NMR (125 MHz, $CDCl_3$) δ 139.86, 137.79, 129.19, 128.31, 127.06, 126.62, 84.34, 31.58, 19.75, 18.59, 13.45.

IR (thin film NaCl): 3396, 3057, 3024, 2958, 2871, 1600, 1491, 1447, 1382, 1295 cm^{-1}.

HRMS (ESI) *m/z* 213.125 [$(M + Na)^+$; calcd for $C_{13}H_{18}O$: 213.125].

Chiral HPLC analysis (Chiralcel OD, hexanes: 2-propanol, 98:2, 1 mL/min): t_R[(*R*)-**1.30**] = 13.8 min; t_R[(*S*)-**1.30**] = 15.6 min.

[α]D = –47.27 (25 °C, 589 nm, 1.00 g/100 mL, $CHCl_3$).



(*E*)-1-Cyclohexyl-2-methyl-3-phenyl-prop-2-en-1-ol (1.33). In the reductive coupling of 1-phenyl-1-propyne (58 mg, 0.5 mmol, 63 μL) and cyclohexanecarboxaldehyde (112 mg, 1.0 mmol, 121 μL) at –25 °C, the standard procedure was used with syringe pump addition of the aldehyde over 8 h. Silica gel chromatography afforded the title compound as a clear oil (125 mg, 97% yield, 90% ee, >95:5 regioselectivity). R_f = 0.25 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.36 (m, 5H); 6.44 (s, 1H); 3.84 (d, *J* = 8 Hz, 1H); 2.04 – 2.08 (m, 1H); 1.87 (s, 3H); 1.67 – 1.83 (m, 4H); 1.54 – 1.59 (m, 2H); 1.17 – 1.30 (m, 2H); 0.98 – 1.06 (m, 2H).

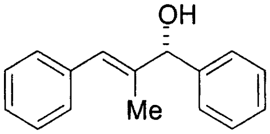
^{13}C NMR (125 MHz, $CDCl_3$) δ 139.58, 137.74, 129.17, 128.29, 127.25, 126.59, 83.47, 41.08, 29.91, 29.24, 26.65, 26.38, 26.20, 13.33.

IR (thin film NaCl): 3395, 3081, 3056, 3023, 2934, 2852, 1944, 1722, 1599, 1575, 1494, 1449 cm^{-1}.

HRMS (EI) *m/z* 230.167 [M^+; calcd for $C_{16}H_{22}O$: 230.167].

Chiral HPLC analysis (Chiralcel OD, hexanes: 2-propanol, 98.5:1.5, 0.5 mL/min): t_R[(*R*)-**1.33**] = 36.5 min; t_R[(*S*)-**1.33**] = 40.6 min.

[α]D = –19.05 (25 °C, 589 nm, 1.05 g/100 mL, $CHCl_3$).



(*E*)-2-Methyl-1,3-diphenyl-prop-2-en-1-ol (1.34). In the reductive coupling of 1-phenyl-1-propyne (58 mg, 0.5 mmol, 64 μL) and benzaldehyde (106 mg, 1.0 mmol, 102 μL) at –25 °C, the standard procedure was used with portionwise addition of the aldehyde over 8 h. Silica gel chromatography afforded the title compound as a clear oil (88 mg, 79% yield, 73% ee, 91:9 regioselectivity). R_f = 0.41 (5:1 hexanes: ethyl acetate). Spectral data were identical to those previously reported.[72]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.19 (m, 10H); 6.72 (s, 1H); 5.22 (s, 1H); 1.94 (bs, 1H); 1.67 (d, *J* = 1.5 Hz, 3H).

Chiral HPLC analysis (Chiralpak AD, hexanes: 2-propanol, 99:1, 0.5 mL/min): t_R[(*R*)-**1.34**] = 70.7 min; t_R[(*S*)-**1.34**] = 66.2 min.

[α]D = –2.48 (25 °C, 589 nm, 1.09 g/100 mL, $CHCl_3$).

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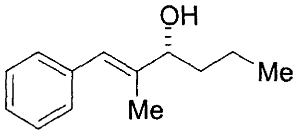
[72] Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron* **1998**, *54*, 2411.

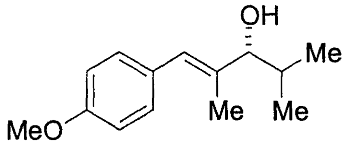


(*E*)-2-Methyl-1-phenyl-hex-1-en-3-ol (1.17). In the reductive coupling of 1-phenyl-1-propyne (58 mg, 0.5 mmol, 64 μL) and butyraldehyde (72 mg, 1.0 mmol, 90 μL) at −10 °C, the standard procedure was used with portionwise addition of the aldehyde over 6 h (15 μl portions). The reaction was quenched after 10 h. Silica gel chromatography afforded the title compound as a clear oil (78 mg, 82% yield, 65% ee, >95:5 regioselectivity). R_f = 0.46 (5:1 hexanes: ethyl acetate). Spectral data were identical to those previously reported.[73]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 – 7.26 (m, 5H); 6.38 (s, 1H); 4.07 (t, J = 6 Hz, 1H); 1.88 (bs, 1H); 1.77 (d, J = 1 Hz, 3H); 1.54 (dt, J = 6.9, 7.2 Hz, 2H); 1.44 – 1.19 (m, 2H); 0.87 (t, J = 7 Hz, 3H).

Chiral HPLC analysis (Chiralcel OD, hexanes: 2-propanol, 98:2, 1 mL/min): t_R[(*R*)-**1.17**] = 14.8 min; t_R[(*S*)-**1.17**] = 16.0 min.

$[\alpha]_D$ = −3.37 (25 °C, 589 nm, 1.01 g/100 mL, $CHCl_3$).



(*E*)-1-(4-Methoxy-phenyl)-2,4-dimethyl-pent-1-en-3-ol (1.35). In the reductive coupling of 1-methoxy-4-propynyl-benzene (73 mg, 0.5 mmol, 72 μL) and isobutyraldehyde (72 mg, 1.0 mmol, 90 μL) at −25 °C, the standard procedure was used with portionwise addition of the aldehyde over 8 h (10 μl portions). Silica gel chromatography afforded the title compound as a clear oil (87 mg, 80% yield, 88% ee, >95:5 regioselectivity). R_f = 0.38 (5:1 hexanes: ethyl acetate). Ozonolysis of **1.35** (see below for a representative experimental procedure) provided *p*-anisaldehyde in >90% yield, confirming the structural integrity of the aromatic system.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, J = 9 Hz, 2H); 6.89 (d, J = 9 Hz, 2H); 6.40 (s, 1H); 3.82 (s, 3H); 3.77 (d, J = 7.5 Hz, 1H); 1.87 (sept., J = 7 Hz, 1H); 1.86 (s, 3H); 1.04 (d, J = 7 Hz, 3H); 0.88 (d, J = 7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.28, 138.18, 130.35, 126.61, 113.73, 84.58, 55.46, 31.61, 19.74, 18.72, 13.37. (The presence of five sp^2 signals for the vinyl arene instead of the expected six suggests that two of the signals are isochronous.)

IR (thin film NaCl): 3425, 2958, 2870, 2836, 1608, 1511, 1466, 1297, 1250 cm^{-1}.

HRMS (ESI) *m/z* 243.137 [$(M + Na)^+$; calcd for $C_{14}H_{26}O_2$: 243.136].

Chiral HPLC analysis of the corresponding chloroacetate (**5a**) (Chiralcel OJ, hexanes: 2-propanol, 98:2, 1 mL/min): t_R[(*R*)- **5a**] = 19.8 min; t_R[(*S*)- **5a**] = 26.7 min.

$[\alpha]_D$ = −4.44 (25 °C, 589 nm, 0.90 g/100 mL, $CHCl_3$).

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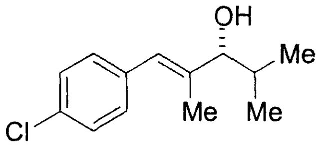
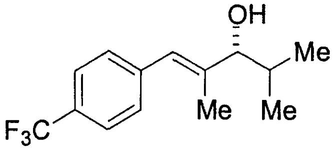
[73] Huang, W.-S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221-4223.



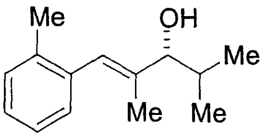
(*E*)-1-(4-Chloro-phenyl)-2,4-dimethyl-pent-1-en-3-ol (1.36). In the reductive coupling of 1-chloro-4-propynyl-benzene (75 mg, 0.5 mmol, 75 μL) and isobutyraldehyde (72 mg, 1.0 mmol, 90 μL) at −25 °C, the standard procedure was used with portionwise addition of the aldehyde over 8 h (10 μl portions). Silica gel chromatography afforded the title compound as a clear oil (83 mg, 75% yield, 83% ee, >95:5 regioselectivity). R_f = 0.45 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 9 Hz, 2H); 7.21 (d, *J* = 9 Hz, 2H); 6.41 (s, 1H); 3.79 (d, *J* = 7.5 Hz, 1H); 1.89 (sept., *J* = 7 Hz, 1H); 1.84 (s, 3H); 1.03 (d, *J* = 7 Hz, 3H); 0.89 (d, *J* = 7 Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 140.6, 136.2, 132.3, 130.5, 128.5, 125.8, 84.1, 31.6, 19.8, 18.4, 13.6.
IR (thin film NaCl): 3406, 2960, 2871, 1491, 1467, 1366 cm^{-1}.
HRMS (EI) *m/z* 224.096 [M^+; calcd for $C_{13}H_{17}ClO$: 224.096].
Chiral HPLC analysis of the corresponding chloroacetate (**1.36a**) (Chiralcel OD, hexanes: 2-propanol, 99.5:0.5, 1 mL/min): t_R[(*R*)-**1.36a**] = 10.9 min; t_R[(*S*)-**1.36a**] = 14.3 min.
$[\alpha]_D$ = −13.33 (25 °C, 589 nm, 1.05 g/100 mL, $CHCl_3$).



(*E*)-1-(4-trifluoromethyl-phenyl)-2,4-dimethyl-pent-1-en-3-ol (1.37). In the reductive coupling of 1-(trifluoromethyl)-4-propynyl-benzene (92 mg, 0.5 mmol, 95 μL) and isobutyraldehyde (72 mg, 1.0 mmol, 90 μL) at −25 °C, the standard procedure was used with portionwise addition of the aldehyde over 8 h (10 μl portions). Silica gel chromatography afforded the title compound as a clear oil (114 mg, 78% yield, 81% ee, >95:5 regioselectivity).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8 Hz, 2H); 7.38 (d, *J* = 8 Hz, 2H); 6.50 (s, 1H); 3.83 (d, *J* = 7.5 Hz, 1H); 1.91 (sept., *J* = 7 Hz, 1H); 1.86 (s, 3H); 1.03 (d, *J* = 6.5 Hz, 3H); 0.92 (d, *J* = 6.5 Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 142.20, 141.40, 129.33, 125.62, 125.27, 125.23 (q, *J* = 16), 83.81, 21.52, 19.77, 18.25, 13.70.
^{19}F NMR ($CFCl_3$ reference): δ −62.015.
IR (thin film NaCl): 3388, 2963, 2873, 1616, 1469, 1410, 1328 cm^{-1}.
HRMS (EI) *m/z* 258.122 [M^+; calcd for $C_{14}H_{17}F_3O$: 258.123].
Chiral HPLC analysis (Chiralcel OD, hexanes: 2-propanol, 98:2, 1 mL/min): t_R[(*S*)-**1.37**] = 8.4 min; t_R[(*R*)-**1.37**] = 9.5 min.



(*E*)-1-(2-Methyl-phenyl)-2,4-dimethyl-pent-1-en-3-ol (1.38). In the reductive coupling of 1-(*o*-tolyl)-1-propyne (65 mg, 0.5 mmol, 64 µL) and isobutyraldehyde (72 mg, 1.0 mmol, 90 µL) at −25 °C, the standard procedure was used with portionwise addition of the aldehyde over 8 h (10 µl portions). Silica gel chromatography afforded the title compound as a clear oil (88 mg, 86% yield, 84% ee, >95:5 regioselectivity).

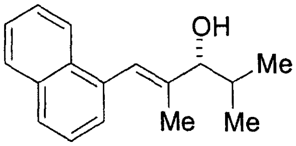
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 – 7.18 (m, 4H); 6.46 (s, 1H); 3.84 (d, *J* = 7.5 Hz, 1H); 2.25 (s, 3H); 1.90 (sept., *J* = 7 Hz, 1H); 1.70 (s, 3H); 1.06 (d, *J* = 7 Hz, 3H); 0.93 (d, *J* = 7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 139.86, 137.01, 136.57, 129.95, 129.40, 126.90, 126.15, 125.51, 83.93, 31.49, 20.20, 19.80, 18.60, 13.06.

IR (thin film NaCl): 3408, 3018, 2958, 2871, 1601, 1483, 1459, 1381, 1011 cm^{-1}.

HRMS (ESI) *m/z* 227.140 [(M + Na)$^+$; calcd for $C_{14}H_{20}O$: 227.141].

Chiral HPLC analysis (Chiralcel OD, hexanes: 2-propanol, 99.5:0.5, 0.3 mL/min): t$_R$[(*S*)-**1.38**] = 13.7 min; t$_R$[(*R*)-**1.38**] = 12.8 min.



(*E*)-2,4-Dimethyl-1-naphthalen-1-yl-pent-1-en-3-ol (1.39). In the reductive coupling of 1-prop-1-ynyl-napthalene (166 mg, 1 mmol, 164 µL) and isobutyraldehyde (144 mg, 2.0 mmol, 180 µL) at −25 °C, the standard procedure was used with syringe pump addition of the aldehyde over 8 h. Silica gel chromatography afforded the title compound as a clear oil (223 mg, 93% yield, 90% ee, >95:5 regioselectivity). R$_f$ = 0.16 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 - 7.98 (m, 1H); (7.86 – 7.88 (m, 1H); 7.78 (d, *J* = 8 Hz, 1H); 7.45 – 7.51 (m, 3H); 7.34 (d, *J* = 7 Hz, 1H); 6.91 (s, 1H), 3.98 (d, *J* = 7 Hz, 1H); 1.98 (sept, *J* = 6.5 Hz, 1H); 1.72 (s, 3H); 1.70 (d, *J* = 3 Hz, 1H); 1.13 (d, *J* = 6.5 Hz, 3H); 1.03 (d, *J* = 6.5 Hz, 3H).

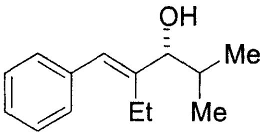
^{13}C NMR (125 MHz, $CDCl_3$) δ 141.68, 135.10, 133.74, 132.19, 128.60, 127.30, 126.85, 126.01, 125.92, 125.46, 125.18, 125.01, 83.82, 31.62, 19.94, 18.54, 13.49.

IR (thin film NaCl): 3580, 3407, 3058, 2958, 2870, 1927, 1816, 1655, 1591, 1507, 1467, 1385 cm^{-1}.

HRMS (ESI) *m/z* 263.1397 [(M + Na)$^+$; calcd for $C_{17}H_{20}O$: 263.1406].

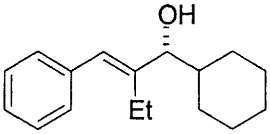
Chiral HPLC analysis (Chiralcel OD, hexanes: 2-propanol, 98:2, 1 mL/min): t$_R$[(*R*)-**1.39**] = 9.8 min; t$_R$[(*S*)-**1.39**] = 11.1 min.

$[\alpha]_D$ = −21.67 (25 °C, 589 nm, 0.30 g/100 mL, $CHCl_3$).



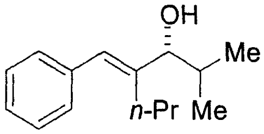
(*E*)-4-Benzylidene-2-methyl-hexan-3-ol (1.40). In the reductive coupling of 1-phenyl-1-butyne (130 mg, 1 mmol, 142 μL) and isobutyraldehyde (114 mg, 2.0 mmol, 180 μL) at −25 °C, the standard procedure was used with syringe pump addition of the aldehyde over 8 h. Silica gel chromatography afforded the title compound as a clear oil (166 mg, 81% yield, 93% ee, >95:5 regioselectivity). R_f = 0.28 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 – 7.36 (m, 5H); 6.49 (s, 1H); 3.92 (d, *J* = 6.5 Hz, 1H); 2.35 – 2.43 (m, 1H); 2.19 – 2.25 (m, 1H); 1.92 – 1.97 (m, 1H); 1.13 (t, *J* = 7.5 Hz, 3H); 1.02 (d, *J* = 6.5 Hz, 3H); 0.97 (d, *J* = 6.5 Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 146.08, 137.93, 128.83, 128.41, 126.60, 126.31, 82.05, 32.00, 21.77, 20.16, 17.80, 14.17.
IR (thin film NaCl): 3427, 3056, 3023, 2965, 2872, 1945, 1720, 1648, 1599, 1493, 1468, 1382 cm^{-1}.
HRMS (ESI) *m/z* 227.140 [(M + Na)$^+$; calcd for $C_{14}H_{20}O$: 227.141].
Chiral HPLC analysis (Chiralcel OD, hexanes: 2-propanol, 98:2, 1 mL/min): t_R[(*R*)-**1.40**] = 12.5 min; t_R[(*S*)-**1.40**] = 14.4 min.
[α]$_D$ = −22.50 (25 °C, 589 nm, 0.20 g/100 mL, $CHCl_3$).



(*E*)-2-benzylidene-1-cyclohexyl-butan-1-ol (1.41): In the reductive coupling of 1-phenyl-1-butyne (651 mg, 5 mmol, 710 μL) and cyclohexanecarboxaldehyde (1.12 g, 10.0 mmol, 1.21 mL) at −25 °C, the standard procedure was used with syringe pump addition of the aldehyde over 8 h. Silica gel chromatography afforded the title compound as a clear oil (0.95 g, 78% yield, 89% ee, >95:5 regioselectivity). R_f = 0.24 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.36 (m, 5H); 6.45 (s, 1H); 3.93 (d, *J* = 7 Hz, 1H); 2.37 (m, 1H); 2.24 (m, 1H); 2.00 (d, *J* = 12.5 Hz, 1H); 1.55 – 1.82 (m, 6H); 1.18 – 1.29 (m, 2H); 1.13 (t, *J* = 7.5 Hz, 3H); 1.04 – 1.10 (m, 2H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 145.77, 137.86, 128.83, 128.42, 128.15, 126.63, 81.71, 41.82, 30.41, 28.54, 26.71, 26.51, 26.33, 21.71, 14.26.
IR (thin film NaCl): 3407, 3055, 3023, 2927, 2851, 1599, 1493, 1448, 1308, 1261, 1173 cm^{-1}.
HRMS (ESI) *m/z* 267.173[(M + Na)$^+$; calcd for $C_{17}H_{24}O$: 267.172].
Chiral HPLC analysis (Chiralcel OD, hexanes: 2-propanol, 98:2, 1 mL/min): t_R[(*R*)-**1.41**] = 11.8 min; t_R[(*S*)-**1.41**] = 13.2 min.
[α]$_D$ = −29.50 (25 °C, 589 nm, 1.00 g/100 mL, $CHCl_3$).



(E)-4-Benzylidene-2-methyl-heptan-3-ol (1.42). In the reductive coupling of 1-phenyl-1-pentyne (144 mg, 1 mmol, 159 μL) and isobutyraldehyde (114 mg, 2.0 mmol, 180 μL) at −25 °C, the standard procedure was used with syringe pump addition of the aldehyde over 8 h. Silica gel chromatography afforded the title compound as a clear oil (156 mg, 72% yield, 92% ee, >95:5 regioselectivity). R_f = 0.28 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.35 (m, 2H); 7.22 – 7.27 (m, 3H), 6.50 (s, 1H), 3.90 (d, J = 6.5 Hz, 1H); 2.28 – 2.33 (m, 1H); 2.12 – 2.17 (m, 1H); 1.93 (sept, J = 7 Hz, 1H); 1.50 – 1.56 (m, 2H); 1.01 (d, J = 7 Hz, 3H); 0.95 (d, J = 7 Hz, 3H); 0.92 (t, J = 7 Hz, 3H).

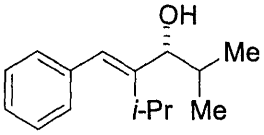
^{13}C NMR (125 MHz, $CDCl_3$) δ 144.81, 138.02, 128.83, 128.40, 128.11, 126.57, 82.14, 32.01, 31.15, 22.74, 20.16, 17.78, 14.76.

IR (thin film NaCl): 3431, 3056, 3024, 2959, 2871, 1944, 1649, 1600, 1576, 1493, 1468, 1380 cm^{-1}.

HRMS (ESI) *m/z* 241.156 [(M + Na)$^+$; calcd for $C_{15}H_{22}O$: 241.156].

Chiral GC analysis (Chiraldex B-PH, column = 125 °C, injector = 200 °C, flow (H_2) = 3 mL/min): t_R[(R)-**1.42**] = 74.7 min; t_R[(S)-**1.42**] = 72.5 min.

$[\alpha]_D$ = −26.55 (25 °C, 589 nm, 1.13 g/100 mL, $CHCl_3$).



(E)-4-Benzyl-2,5-dimethyl-hexan-3-ol (1.43). In the reductive coupling of 3-methyl-1-phenyl-but-1-yne (50 mg, 0.35 mmol, 60 μL) and isobutyraldehyde (50 mg, 0.7 mmol, 70 μL) at 0 °C, the standard procedure was used with portionwise addition of the aldehyde over 7 h (10 μL portions). Silica gel chromatography afforded a clear oil found to be a 5:4 mixture of reductive (**1.43**) and alkylative[74] (**1.43a**) coupling products by ^{1}H NMR (47 mg, 58% combined yield, 92% ee reductive, >95:5 regioselectivity). Additional chromatography provided pure **1.43** for analysis. R_f (**1.43**) = 0.23 (10:1 hexanes: ethyl acetate). R_f (**1.43a**) = 0.28 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.36 (m, 5H); 6.62 (s, 1H); 3.89 (d, J = 6.5 Hz, 1H); 3.10 (sept, J = 7 Hz, 1H); 2.00 (sept, J = 7 Hz, 1H); 1.20 (d, J = 7 Hz, 3H); 1.10 (d, J = 6.5 Hz, 3H); 1.04 (d, J = 7 Hz, 3H); 0.95 (d, J = 7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 150.52, 138.10, 128.96, 128.32, 126.61, 125.31, 75.67, 33.51, 28.76, 21.87, 21.66, 20.47, 18.48.

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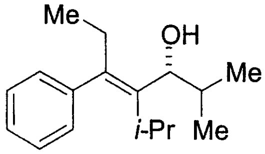
[74] Transfer of Et from Et_3B instead of H.

IR (thin film NaCl): 3444, 3080, 3056, 3023, 2960, 2871, 1600, 1576, 1494, 1465, 1444, 1384, 1364, 1029, 1000 cm^{-1}.

HRMS (ESI) *m/z* 241.157 [$(M + Na)^+$; calcd for $C_{15}H_{22}O$: 241.156].

Chiral HPLC analysis (Chiralcel OD, hexanes: 2-propanol, 98:2, 1 mL/min): t_R[(*R*)-**1.43**] = 10.7 min; t_R[(*S*)-**1.43**] = 9.4 min.

$[\alpha]_D$ = +45.00 (25 °C, 589 nm, 0.03 g/100 mL, $CHCl_3$).



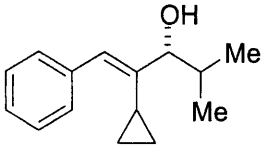
(*E*)-4-Isopropyl-2-methyl-5-phenyl-heptan-3-ol (1.43a).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.34 (m, 3H); 7.08 (d, *J* = 6.5 Hz, 2H); 3.96 (d, *J* = 9 Hz, 1H); 2.75 – 2.81 (m, 1H); 2.43 – 2.50 (sept, *J* = 7 Hz, 1H); 2.25 – 2.33 (m, 1H); 2.17 – 2.22 (m, 1H); 1.15 (d, *J* = 6.5 Hz, 3H); 0.96 (d, *J* = 7 Hz, 3H); 0.93 (d, *J* = 7 Hz, 3H); 0.86 (d, *J* = 7 Hz, 3H); 0.83 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 143.81, 142.10, 141.59, 128.85, 128.06, 126.28, 76.56, 33.58, 31.41, 28.49, 22.61, 22.15, 20.83, 20.73, 12.58.

IR (thin film NaCl): 3462, 3077, 3056, 3018, 2959, 2932, 2872, 1598, 1490, 1465, 1441, 1382, 1363, 1255, 1101, 1075 cm^{-1}.

HRMS (ESI) *m/z* 269.187 [$(M + Na)^+$; calcd for $C_{17}H_{26}O$: 269.188].

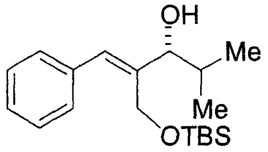


(*E*)-2-cyclopropyl-4-methyl-1-phenyl-pent-1-en-3-ol (1.44). In the reductive coupling of cyclopropylphenylacetylene (142 mg, 1.0 mmol) and isobutyraldehyde (144 mg, 2.0 mmol, 180 μL) at −25 °C, the standard procedure was used except that the scale was doubled. Silica gel chromatography afforded the allylic alcohol as a clear oil (145 mg, 67% yield, 92% ee, >95:5 regioselectivity).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.5 Hz, 2H); 7.34 (t, *J* = 7.5 Hz, 2H); 7.22 (t, *J* = 7.5 Hz, 1H); 6.62 (s, 1H); 3.81 (d, *J* = 6.5 Hz, 1H); 2.09 (sept., *J* = 7 Hz, 1H); 1.59 (m, 1H); 1.00 (t, *J* = 7 Hz, 6H); 0.80 – 0.70 (m, 2H); 0.50 – 0.41 (m, 2H).

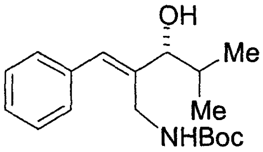
^{13}C NMR (125 MHz, $CDCl_3$) δ 143.49, 137.61, 129.56, 128.00, 127.45, 126.55, 79.73, 32.34, 20.28, 17.07, 11.79, 7.71, 6.90.

Chiral HPLC analysis (Chiralcel OD, hexanes: 2-propanol, 98.5:1.5, 0.8 mL/min): t_R[(*S*)-**1.44**] = 23.5 min; t_R[(*R*)-**1.44**] = 24.8 min.



(*Z*)-2-(tert-Butyl-dimethyl-silanyloxymethyl)-4-methyl-1-phenyl-pent-1-en-3-ol (1.45). In the reductive coupling of *tert*-butyl-dimethyl-(3-phenyl-prop-2-ynyloxy)-silane (246 mg, 1 mmol, 226 µL) and isobutyraldehyde (114 mg, 2.0 mmol, 180 µL) at −25 °C, the standard procedure was used with syringe pump addition of aldehyde over 8 h. Silica gel chromatography afforded the title compound as a clear oil (188 mg, 59% yield, 85% ee, >95:5 regioselectivity). R_f = 0.57 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.36 (m, 2H), 7.24 – 7.28 (m, 3H), 6.62 (s, 1H), 4.50 (d, *J* = 11.5 Hz, 1H), 4.37 (d, *J* = 11.5 Hz, 1H), 3.84 (d, *J* = 8.5 Hz, 1H), 1.98 – 2.02 (sept, *J* = 7 Hz, 1H), 1.09 (d, *J* = 7 Hz, 3H); 0.09 (m, 12H), 0.06 (d, *J* = 6 Hz, 6H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 140.39, 136.80, 130.44, 129.11, 128.33, 127.28, 83.96, 60.39, 32.78, 25.99, 19.99, 19.00, 18.29, -5.41.
IR (thin film NaCl): 3451, 2956, 2929, 2858, 1471, 1386, 1362, 1255 cm^{-1}.
HRMS (ESI) *m/z* 343.207 [$(M + Na)^+$; calcd for $C_{19}H_{32}O_2Si$: 343.206].
Chiral HPLC analysis (Chiralcel OD, hexanes: 2-propanol, 99.5:0.5, 0.2 mL/min): t_R[(*R*)-**1.45**] = 53.2 min; t_R[(*S*)-**1.45**] = 46.9 min.
$[\alpha]_D$ = −14.81 (25 °C, 589 nm, 1.08 g/100 mL, $CHCl_3$).



(*E*)-(1-Benzylidene-2-hydroxy-3-methyl-butyl)-carbamic acid *tert*-butyl ester (1.46).

0.5 mmol scale: In the reductive coupling of (3-phenyl-prop-2-ynyl)-carbamic acid *tert*-butyl ester (231 mg, 1 mmol) and isobutyraldehyde (114 mg, 2.0 mmol, 180 µL), $Ni(cod)_2$, NMDPP, and Et_3B in EtOAc were combined at room temperature and then cooled to −25 °C . The alkyne was then added as a solution in DMI (1 mL), and the aldehyde was added via syringe pump over 8 h. Silica gel chromatography afforded the title compound as a white solid (183 mg, 60% yield, 96% ee, >95:5 regioselectivity). R_f = 0.17 (5:1 hexanes: ethyl acetate).

10 mmol scale: In a glovebox, $Ni(cod)_2$ (280 mg, 1.00 mmol), and (+)-NMDPP (648 mg, 2.00 mmol) were placed into a 100 mL oven-dried, single-necked round-bottom flask, which was then sealed with a rubber septum. The flask was removed from the glovebox, placed under argon, and ethyl acetate (10 mL), and Et_3B (2.90 mL, 20.00 mmol) were added sequentially via syringe. The resulting solution was stirred 10 min at room temperature and then placed in a precooled bath at −25 °C. The solution was stirred 15 min at this temperature, and then a solution of (3-phenyl-prop-2-ynyl)-carbamic acid *tert*-butyl ester (2.31 g, 10.00 mmol) in DMI (10 mL) was added dropwise via syringe. Isobutyraldehyde (1.80 mL, 20.00 mmol) was then added dropwise over 8 h via syringe pump. The reaction was stirred an additional 36 h at −25 °C, at which point saturated aqueous NH_4Cl (20 mL) and 1M HCl (5 mL) were added. The organic layer was then extracted with EtOAc (3 x 50 mL), dried and concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel (hexanes: ethyl acetate; 50:1 to 10:1) to afford a 3:1 mixture of the title compound (94% ee) and isobutyraldehyde aldol dimer. Recrystallization of this solid from 5:1 hexanes:EtOAc provided **1.46** as a white solid (1.35 g, 44% yield, >98% ee). The supernatant was concentrated and further purified by flash chromatography on silica gel to yield an additional 0.24 g of **1.46** (52% overall yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.37 (m, 2H), 7.23 – 7.28 (m, 3H); 6.62 (s, 1H); 4.86 (bs, 1H); 4.02 (dd, *J* = 15, 7 Hz, 1H); 3.85 – 3.91 (m, 2H); 1.92 (sept, *J* = 7.5 Hz, 1H); 1.43 (s, 9H); 1.06 (d, *J* = 7 Hz, 3H); 0.91 (d, *J* = 7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 156.52, 140.02, 136.79, 130.92, 128.78, 128.65, 127.39, 82.66, 79.94, 37.93, 32.47, 28.58, 20.01, 18.78.

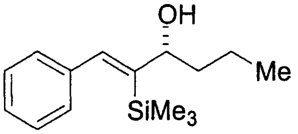
IR (thin film NaCl): 3287, 3082, 2952, 1670, 1559, 1265, 1183 cm^{-1}.

HRMS (ESI) *m/z* 328.187 [(M + Na)$^+$; calcd for $C_{18}H_{27}NO_3$: 328.188].

Chiral HPLC analysis (Chiralcel OD, hexanes: 2-propanol, 98:2, 1 mL/min): t_R[(*R*)-**1.46**] = 21.7 min; t_R[(*S*)-**1.46**] = 27.1 min.

$[\alpha]_D$ = –2.78 (25 °C, 589 nm, 0.90 g/100 mL, $CHCl_3$).

mp: 140–141 °C.



(Z)-1-Phenyl-2-trimethylsilanyl-hex-1-en-3-ol (1.47). In the reductive coupling of 1-phenyl-2-(trimethylsilyl)-acetylene (87 mg, 0.5 mmol, 98 μL) and butyraldehyde (72 mg, 1.0 mmol, 90 μL) at –25 °C, the standard procedure was used with portionwise addition of the aldehyde over 8 h. Silica gel chromatography afforded a clear oil which was found to be a 75:25 mixture of reductive (**1.47**) and alkylative[74] (**1.47a**) allylic alcohol coupling products by ^{1}H NMR (55 mg, 43% combined yield, 92% ee reductive, >95:5 regioselectivity). Additional chromatography provided pure **1.47** for analysis. R_f(**1.47**) = 0.33 (10:1 hexanes: ethyl acetate). R_f(**1.47a**) = 0.41 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (s, 1H); 7.19 – 7.32 (m, 5H); 4.41 – 4.43 (m, 1H); 1.43 – 1.70 (m, 3H); 0.92 – 1.01 (m, 4H); –0.02 (s, 9H).

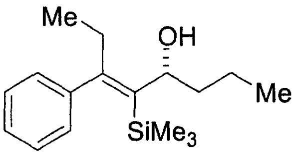
^{13}C NMR (125 MHz, $CDCl_3$) δ 147.51, 140.40, 140.25, 128.71, 127.99, 127.12, 75.78, 40.29, 19.42, 14.29, 1.05.

IR (thin film NaCl): 3364, 3057, 3024, 2958, 1593, 1491 cm^{-1}.

HRMS (ESI) *m/z* 271.149 [(M + Na)$^+$; calcd for $C_{15}H_{24}OSi$: 271.149].

Chiral HPLC analysis (Chiralcel OD, hexanes: 2-propanol, 98:2, 1 mL/min): t_R[(*R*)-**14**] = 13.5 min; t_R[(*S*)-**14**] = 5.4 min.

$[\alpha]_D$ = +66.00 (25 °C, 589 nm, 1.00 g/100 mL, $CHCl_3$).



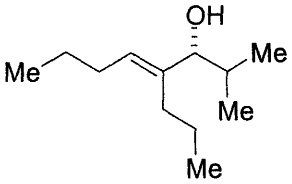
(Z)-6-Phenyl-5-trimethylsilanyl-octan-4-ol (**1.47a**).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.31 (m, 3H); 7.09 (d, J = 6.5 Hz, 2H); 4.73 (m, 1H); 2.40 – 2.47 (m, 2H); 1.78 – 1.84 (m, 1H); 1.52 – 1.60 (m, 3H); 1.39 – 1.45 (m, 1H); 1.01 (t, J = 7 Hz, 3H); 0.87 (t, J = 6.5 Hz, 3H), –0.19 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.74, 144.84, 140.17, 129.35, 127.86, 126.97, 74.39, 39.78, 29.58, 20.16, 14.36, 12.94, 2.60.

IR (thin film NaCl): 3609, 3473, 3077, 3057m 3024, 2959, 2872, 1584, 1488, 1457, 1442, 1407, 1374, 1246, 1136. 1072, 1022 cm^{-1}.

HRMS (ESI) m/z 299.180 [(M + Na)$^+$; calcd for $C_{17}H_{28}OSi$: 299.180].



(E)-2-Methyl-4-propyl-oct-4-en-3-ol (1.48). In the reductive coupling of 4-octyne (110 mg, 1 mmol, 146 μL) and isobutyraldehyde (114 mg, 2.0 mmol, 180 μL) at −25 °C, the standard procedure was used with syringe pump addition of aldehyde over 8 h. Silica gel chromatography afforded a clear oil which was found to be a 32:68 mixture of reductive (**1.48**) and alkylative[74] (**1.48a**) allylic alcohol coupling products by ^{1}H NMR (88 mg, 35% combined yield, 42% ee reductive). The two compounds were inseparable by silica gel chromatography. R_f = 0.38 (10:1 hexanes: ethyl acetate). Spectral data for **1.48** matches that previously reported.[75]

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.36 (t, J = 7 Hz, 0.45H); 4.13 (d, J = 9.5 Hz, 1H); 3.65 (d, J = 7 Hz, 0.45H); 2.12 – 2.20 (m, 1H); 1.88 – 2.08 (m, 7.2H); 1.75 – 1.81 (m, 1H); 1.35 – 1.47 (m, 5.6H); 1.07 (d, J = 6.5 Hz, 3H); 0.90 – 0.98 (m, 10H); 0.84 (d, J = 7 Hz, 1.4H); 0.75 (d, 6.5, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 141.36, 140.32, 134.35, 127.94, 82.96, 77.90, 34.23, 32.22, 31.81, 30.31, 30.08, 29.85, 25.02, 23.94, 23.47, 23.20, 22.18, 20.09, 20.01, 19.71, 18.28, 15.26, 14.91, 14.74, 14.47, 14.14.

HRMS (ESI) m/z 235.202 [(M + Na)$^+$; calcd for $C_{14}H_{28}O$: 235.203].

Chiral GC analysis was performed on the chloroacetate derivative of **1.48** (**1.48b**): (Chiraldex B-PH column, 90 °C for 30 min then 140 °C for 15 min): t_R[(R)-**1.48b**] = 38.4 min; t_R[(S)-**1.48b**] = 38.9 min.

$[\alpha]_D$ = –10.00 (25 °C, 589 nm, 0.30 g/100 mL, $CHCl_3$).

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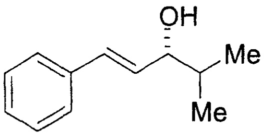
[75] Colby, E. C.; Jamison, T. F. *J. Org. Chem.* **2003**, 68, 156 – 166.

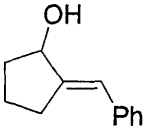


(*E*)-4-methyl-1-phenyl-1-penten-3-ol (1.49). In the reductive coupling of phenylacetylene (102 mg, 1 mmol, 110 μL) and isobutyraldehyde (114 mg, 2.0 mmol, 180 μL) at −25 °C, the standard procedure was except that the scale was doubled and the aldehyde was added in one portion at the beginning of the reaction (no slow addition). Silica gel chromatography afforded the title compound as a clear oil (30 mg, 15% yield, 75% ee, >95:5 regioselectivity). Spectral data for **1.49** matches that previously reported.[76]

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.59 (d, J = 16 Hz, 1H); 6.25 (dd, J = 16, 7 Hz, 1H); 4.04 (t, J = 6.5 Hz, 1H); 1.84 (sept., J = 6 Hz, 1H); 1.00 (d, J = 7 Hz, 3H); 0.96 (d, J = 7 Hz, 3H).

Chiral HPLC analysis (Chiralcel OD, hexanes: 2-propanol, 98:2, 1 mL/min): t$_R$[(*R*)-**1.44**] = 21.99 min; t$_R$[(*S*)-**1.44**] = 40.38 min.

Intramolecular Reductive Cyclization of Ynal 1.61



(*E*)-2-Benzylidene-cyclopentan-1-ol (1.62): To Ni(cod)$_2$ (14 mg, 0.05 mmol) and (+)-NMDPP (32 mg, 0.1 mg) at 23 °C was added EtOAc (1 mL), DMI (1 mL), and Et$_3$B (1.0 mmol, 0.15 mL). This solution was stirred 5 min at 23 °C and then a solution of 6-phenyl-hex-5-ynal[77] (**1.61**) in EtOAc (0.5 mL) was added. After 15 h, the reaction was stirred 30 min open to air to promote oxidation of the catalyst. Purification via flash chromatography on silica gel afforded the title compound as a white solid (49% yield, 43 mg, 32% ee). Spectral data matched those previously reported.[78]

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.33 – 7.39 (m, 4H); 7.20 – 7.25 (m, 1H); 6.59 (m, 1H); 4.61 (m, 1H); 2.71 – 2.79 (m, 1H); 2.56 – 2.63 (m, 1H); 1.93 – 2.15 (m, 2H); 1.62 – 1.80 (m, 2H).

Chiral HPLC analysis of the corresponding chloroacetate derivative (**1.62a**) (Chiralcel OD, hexanes: 2-propanol, 98:2, 1 mL/min): t$_R$[*major*] = 20.4 min; t$_R$[*minor*] = 22.5 min.

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[76] Yang, W. K.; Cho, B. T. *Tetrahedron: Asymmetry* **2000**, *11*, 2947-2953.

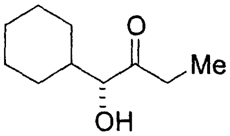
[77] Mahandru, G. M.; Skauge, A. R. L.; Chowdhury, S. K.; Amarasinghe, K. K. D.; Heeg, M. J.; Montgomery, J. *J. Am. Chem. Soc.* **2003**, *125*, 13481-13485.

[78] Clive, D. L. J.; Yang, W.; MacDonald, A. C.; Wang, Z.; Cantin, M. *J. Org. Chem.* **2001**, *66*, 1966-1983.

Observation of Ethylene Production

In a glovebox, Ni(cod)$_2$ (28 mg, 0.1 mmol), and (+)-NMDPP (64 mg, 0.2 mmol) were placed into a 50 mL oven-dried, single-necked round-bottom flask, which was then sealed with a rubber septum. The flask was removed from the glovebox, placed under argon, and EtOAc (1 mL) was added, followed by Et$_3$B (0.3 mL, 2 mmol). The mixture was stirred 5 min, and then isobutyraldehyde (114 mg, 2.0 mmol, 180 μL) was added. A double-ended needle was inserted into the flask, keeping the tip above the level of the liquid, and the other end was inserted into an NMR tube that had been filled with CDCl$_3$ (1 mL, degassed), fitted with a septum, and placed under argon. The needle was immersed in the liquid, and then 1-phenyl-1-butyne (130 mg, 1 mmol, 142 μL) was added to the reaction flask. The argon line was removed from the reaction flask, and gas production was observed immediately. Steady bubbling was observed through the solvent in the NMR tube for ~45 min. At this point, the needle was removed and ^{1}H NMR analysis of the tube showed a prominent singlet at 5.4 ppm corresponding to ethylene.

Synthesis of Enantiomerically Enriched α-Hydroxy Ketones



1-Cyclohexyl-1-hydroxy-butan-2-one (1.68): Alcohol **1.41** (315 mg, 1.3 mmol) was dissolved in CH$_2$Cl$_2$:MeOH (5:1, 10 mL), and the solution was cooled to –78 °C. Ozone was bubbled through the cooled solution until a blue color was obtained (~5 min). Argon was then bubbled through (10 min), and methyl sulfide (6.5 mmol, 0.48 mL) was added. The reaction was allowed to warm to room temperature and stir overnight. Removal of solvent followed by flash chromatography on silica gel (5:1 hexanes:ethyl acetate) afforded the title compound as a clear oil (62% yield, 138 mg, 0.81 mmol). Spectral and optical rotation data agreed with those previously reported.[79]

^{1}H NMR (500 MHz, CDCl$_3$) δ 4.06 (s, 1H); 3.41 (s, 1H); 2.41 – 2.57 (overlapping dq, J = 19, 7.5 Hz, 2H); 1.64 – 1.83 (m, 5H); 1.48 (dq, J = 12.5, 4 Hz, 1H); 1.17 – 1.35 (m, 5H); 1.13 (td, J = 7.5, 2 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 212.99, 80.75, 41.65, 31.65, 30.30, 26.77, 26.21, 26.05, 25.32, 7.83.

Chiral GC analysis (Alltech B-PH, column = 95 °C, injector = 200 °C, flow (H$_2$) = 2 mL/min): t$_R$[(*R*)-**1.68**] = 32.7 min; t$_R$[(*S*)-**1.68**] = 34.2 min.

$[\alpha]_D$ = –112.5 (25 °C, 589 nm, 1.0 g/100 mL, CHCl$_3$). Reported value: –128.03.[79a]

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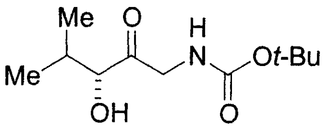
[79] (a) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566-1568. (b) Weiberth, F. J.; Hall, S. S. *J. Org. Chem.* **1985**, *50*, 5308-5314.



(3-Hydroxy-4-methyl-2-oxo-pentyl)-carbamic acid *tert*-butyl ester (1.69): Alcohol **1.46** (179 mg, 0.59 mmol) was dissolved in CH_2Cl_2:MeOH (5:1, 5 mL), and the solution was cooled to –78 °C. Ozone was bubbled through the cooled solution until a blue color was obtained (~5 min), and then argon was bubbled through (10 min). Methyl sulfide (3.0 mmol, 0.22 mL) was then added, and the reaction was allowed to warm to room temperature and stir overnight. Removal of solvent followed by flash chromatography on silica gel (5:1 hexanes:ethyl acetate) afforded the title compound as a clear oil (76% yield, 103 mg, 0.45 mmol). R_f = 0.45 (2:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.19 (bs, 1H); 4.05 – 4.23 (m, 3H); 3.06 (bs, 1H); 2.14 (m, 1H); 1.46 (s, 9H); 1.12 (d, J = 7 Hz, 3H); 0.79 (d, J = 7 Hz, 3H).

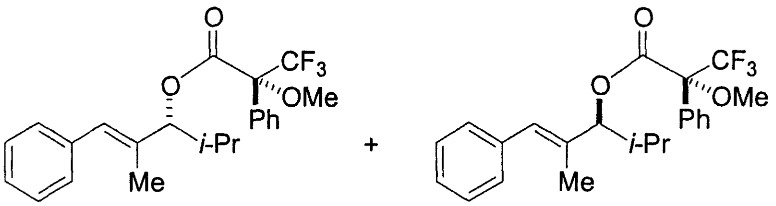
^{13}C NMR (125 MHz, $CDCl_3$) δ 208.10, 155.83, 80.36, 79.89, 47.61, 32.04, 31.80, 28.49, 22.87, 19.83, 15.18, 14.35. Spectrum showed a mixture of rotomers.

IR (thin film NaCl): 3426, 2975, 2934, 2876, 1695, 1510, 1393, 1368, 1252, 1168, 1020 cm^{-1}.

HRMS (ESI) *m/z* 254.136[(M + Na)$^+$; calcd for $C_{11}H_{24}NO_4$: 254.136].

Chiral HPLC analysis of the corresponding benzoate **1.69a** (Chiralcel OJ, hexanes: 2-propanol, 95:5, 0.3 mL/min): t_R[(*R*)-**1.69a**] = 55.3 min; t_R[(*S*)-**1.69a**] = 61.6 min.

$[\alpha]_D$ = –112.5 (25 °C, 1.0 g/100 mL, $CHCl_3$).



(major) (minor)

Absolute Configuration Determination of 1.30 via Mosher's Ester Analysis.[80] Alcohol **1.30** (85 mg, 0.45 mmol, 64% ee) was dissolved in CH_2Cl_2 (10 mL). (+)-Mosher's acid (116 mg, 0.5 mmol), dicyclohexylcarbodiimide (103 mg, 0.5 mmol), and DMAP (~1 mg) were added sequentially, and the reaction was heated to reflux and stirred overnight. Once cooled completely, it was concentrated in vacuo, resuspended in hexanes:ethyl acetate (5:1), and filtered through $MgSO_4$. This filtrate was further diluted with hexanes, then washed with 1M HCl, saturated $NaHCO_3$, and brine. The organic layer was dried and concentrated, then subjected to silica gel chromatography (50:1 hexanes: ethyl acetate) to yield a mixture of diastereomers (119 mg, 65% yield, ~85:15 diastereoselectivity). Shielding of the alkenyl group and deshielding of the isopropyl group in the major diastereomer suggested an absolute configuration of (*R*) for **1.30** (see Figure 1).

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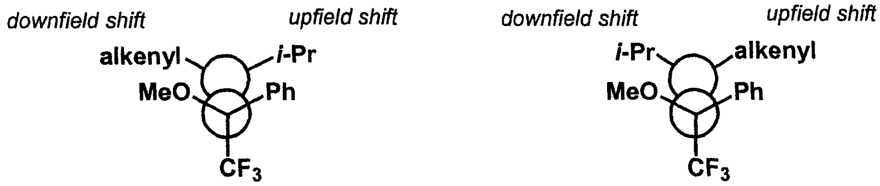
[80] (a) Mosher, H. S.; Dale, J. A. *J. Am. Chem. Soc.* **1973**, *95*, 512-519. (b) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543-2549.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.54 (m, 12H); 6.61 (s, 1H); 6.53 (s, 0.17H); 5.22 (d, J = 9.5 Hz, 1H); 5.12 (d, J = 9 Hz, 0.17H); 3.60 (s, 0.59H), 3.54 (s, 3H); 2.08 (m, 1.22H); 1.85 (d, J = 1.5 Hz, 3H); 1.67 (d, J = 1.5 Hz, 0.53H); 1.03 (d, J = 7 Hz, 0.57); 0.92 (d, J = 7 Hz, 0.55); 0.91(d, J = 6.5 Hz, 3H); 0.89 (d, J = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.31, 136.99, 134.40, 134.25, 132.79, 130.93, 130.67, 129.72, 129.67, 129.22, 129.20, 128.54, 128.49, 128.41, 128.35, 127.63 (d, J = 4.5), 127.49, 127.16, 127.06, 124.85, 122.56, 88.39, 88.09, 55.94, 55.59 (d, J = 4.5), 30.24, 30.04, 19.17, 19.12, 19.00, 18.78, 13.99, 13.79.

IR (thin film NaCl): 3062, 3027, 2966, 2875, 2849, 1746, 1600, 1576, 1493, 1471, 1450, 1389, 1370, 1326, 1270, 1170, 1123, 1081 cm^{-1}.

Figure 1. Determination of absolute configuration using (*R*)-(+)-Mosher's acid.



Absolute configuration *R*

Observed

Absolute configuration *S*

Chapter 2

Alkene-Directed, Nickel-Catalyzed Coupling Reactions

Introduction

As carbon-carbon double bonds can be transformed into a vast array of other functional groups, alkenes are among the most important and versatile organic compounds. While many simpler alkenes are commodity chemicals, those that are highly substituted are generally less available.[1] The controlled addition of two groups across an alkyne triple bond is an important strategy for the synthesis of these olefins,[1d] and several of these transformations are catalyzed by low valent nickel complexes.[2,3] In intermolecular cases, regioselectivity, one of the chief challenges in all alkyne addition reactions, is generally governed by electronic and/or steric differences between the two alkyne substituents (Scheme 1).[4] In cases in which the alkyne is substituted with two similar yet distinct groups, low to nonexistent regioselectivity is often observed, drastically reducing the reaction's overall efficiency.[5,6]

Our group has recently reported a series of intermolecular, nickel-catalyzed reductive coupling reactions of alkynes that display excellent regioselectivity when electronically

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[1] (a) *Modern Carbonyl Olefination: Methods and Applications*; Takeda, T., Ed.; Wiley-VCH: Weinheim, 2004. (b) *Metal-catalyzed Cross-coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. (c) *Handbook of Metathesis*; Grubbs, R. H., Ed.; John Wiley & Sons: New York, 2003. (d) *Preparation of Alkenes: A Practical Approach*; Williams, J. M. J., Ed.; Oxford University Press: Oxford, 1996.

[2] Ni-catalyzed reductive couplings and cyclizations: (a) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065-9066. (b) Huang, W.-S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221-4223. (c) Takai, K.; Sakamoto, S.; Isshiki, T. *Org. Lett.* **2003**, *5*, 653-655. (d) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442-3443. (e) Patel, S. J.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2003**, *42*, 1364-1367. (f) Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 8076-8077. (g) Patel, S. J.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2004**, *43*, 3941-3944. (h) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698-3699.

[3] Other Ni-catalyzed alkyne addition reactions: (a) Tsuda, T.; Kiyoi, T.; Saegusa, T. *J. Org. Chem.* **1990**, *55*, 2554-2558. (c) Stüdemann, T.; Ibrahim-Ouali, M.; Knochel, P. *Tetrahedron* **1998**, *54*, 1299-1316. (e) Louie, J.; Gibby, J. E.; Farnworth, M. V.; Tekavec, T. N. *J. Am. Chem. Soc.* **2002**, *124*, 15188-15189. (d) Han, L.-B.; Zhang, C.; Yazawa, H.; Shimada, S. *J. Am. Chem. Soc.* **2004**, *126*, 5080-5081. (e) Nakao, Y.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 13904-13905. (f) Kimura, M.; Ezoe, A.; Mori, M.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 201-209. (g) Shimizu, K.; Takimoto, M.; Sato, Y.; Mori, M. *Org. Lett.* **2005**, *7*, 195-197.

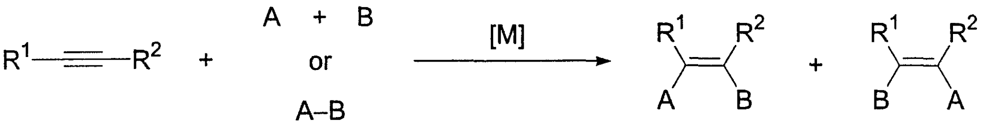
[4] Alkyne additions catalyzed by metals other than nickel that display electronic or steric control of regioselectivity: (a) Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fugiwara, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7252-7263. (b) Masui, D.; Kochi, T.; Tang, Z.; Ishii, Y.; Mizobe, Y.; Hidai, M. *J. Organomet. Chem.* **2001**, *620*, 69-79. (c) Huddleston, R. R.; Yang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 11488-11489. (d) Jang, H.-Y.; Huddleston, R. R.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4664-4668.

[5] A few notable exceptions exist: (a) Molander, G. A.; Retsch, W. H. *Organometallics* **1995**, *14*, 4570 – 4575. (b) Yamanoi, S.; Seki, K.; Matsumoto, T.; Susuki, K. *J. Organomet. Chem.* **2001**, *624*, 143–150. (c) Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111 – 124 and references therein. (d) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2001**, *123*, 12726 – 12727.

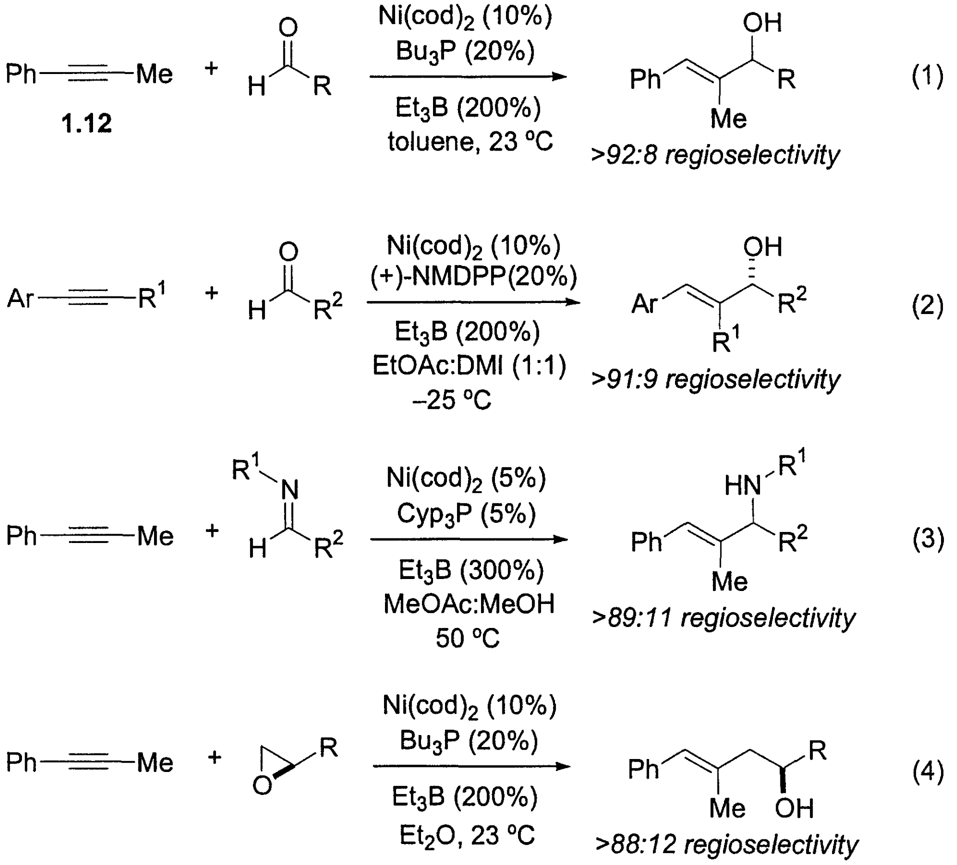
[6] For a highly regioselective carbolithiation of alkynes directed by remote heteroatoms, see: Hojo, M.; Murakami, Y.; Aihara, H.; Sakuragi, R.; Baba, Y.; Hosomi, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 621-623.

differentiable, aryl-substituted alkynes such as 1-phenyl-1-propyne (**1.12**) are employed (Scheme 2). Such couplings allow for the highly regioselective synthesis of allylic alcohols (eq 1 and 2),[2b,d] allylic amines (eq 3),[2e,g] and homoallylic alcohols (eq 4),[2f] often in high enantioselectivity.

Scheme 1. Regioselectivity in catalytic addition reactions to alkynes.



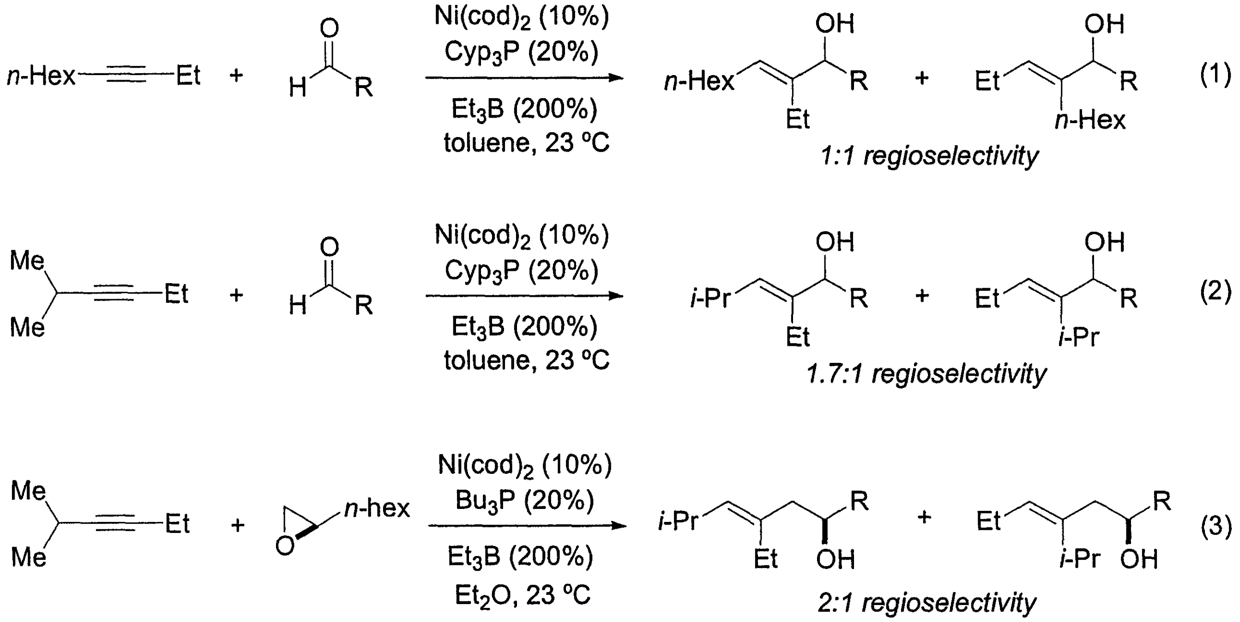
Scheme 2. Catalytic reductive coupling reactions of aryl-substituted alkynes.



Conversely, in reductive coupling reactions of alkynes that contain two electronically similar but distinct substituents (e.g., alkyl–C≡C–alkyl'), no regioselectivity is observed when these substituents are of similar size (Scheme 3, equation 1), and increased steric bulk on one of the alkyne substituents affords only modest regioselectivity (equations 2 and 3).[7] As the efficient construction of substituted olefins of this type is highly desirable due to their presence in a variety of complex natural products,[8] the development of new methodology that allows for improved regioselectivities in these couplings has been a subject of ongoing research in our group.

A ligand-based approach to controlling regioselectivity in couplings of this type has been developed which utilizes *P*-chiral ferrocenyl monodentate phosphines of general structure **A** (Scheme 4).[9] The reductive coupling of 1-cyclohexyl-1-propyne (**2.1**) and isobutyraldehyde was found to afford allylic alcohols **2.2a** and **2.2b** in up to 5.7: 1 regioselectivity and 55% ee when conducted in the presence of ligand **2.3**. This strategy has been successfully applied in the total synthesis of (–)-terpestacin.[10]

Scheme 3. Catalytic reductive couplings of alkynes that contain two electronically similar substituents.



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[7] For a recent report on highly regioselective, titanium-mediated reductive couplings of alkyl–C≡C–alkyl' alkynes and aldehydes, see: Bahadoor, A. B.; Flyer, A.; Micalizio, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 3694-3695.

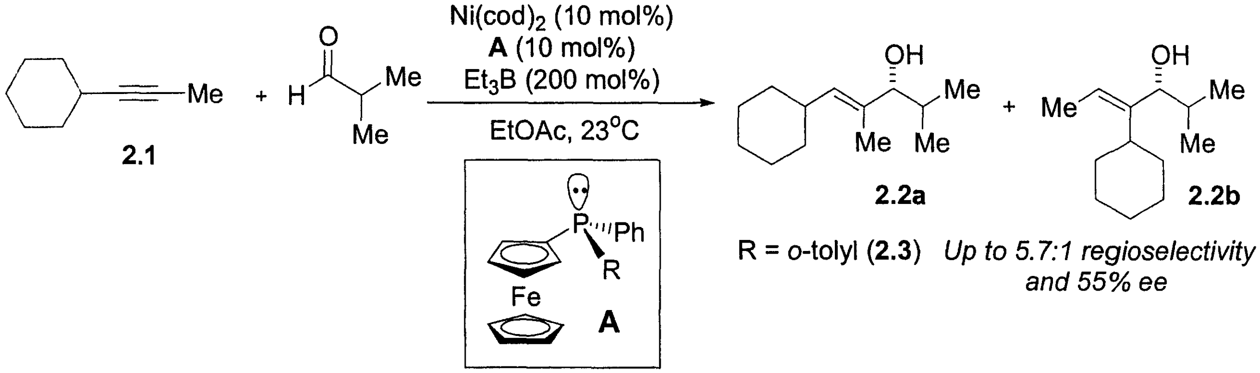
[8] For example: (a) (–)-Terpestacin: Oka, M.; Iimura, S.; Tenmyo, O.; Sawada, Y.; Sugawara, M.; Ohkusa, N.; Yamamoto, H.; Kawano, K.; Hu, S.-L.; Fukagawa, Y.; Oki, T. *J. Antibiotics* **1993**, *46*, 367-373. (b) (+)-Acutiphycin: Barchi, Jr., J. J.; Moore, R. E.; Patterson, G. M. L. *J. Am. Chem. Soc.* **1984**, *106*, 8193-8197.

[9] Colby, E. A.; Jamison, T. F. *J. Org. Chem.* **2003**, *68*, 156-166.

[10] (a) Chan, J. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 11514-11515. (b) Chan, J. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 10682-10691.

In an effort to probe the origin of high regioselectivity in reductive couplings of aryl-substituted alkynes, the use of 1,3-enynes as coupling partners was explored.[11] This work has led to the development of a new strategy for selective olefin synthesis, whereby a transient interaction between a conjugated alkene and a transition metal[12] dramatically enhances reactivity and uniformly directs regioselectivity. In conjunction with a site-selective, Rh-catalyzed hydrogenation of conjugated dienes, this work also affords a novel approach to overcoming poor or undesired regioselectivity in coupling reactions of alkynes.

Scheme 4.



Evaluation of Reaction Parameters

At the time that our studies commenced, only scattered examples of the use of 1,3-enynes as substrates in transition metal-catalyzed reactions existed in the literature.[13] We were therefore pleased to find that the reductive coupling of 1-decen-3-yne (**2.4**) and isobutyraldehyde occurred readily in the presence of catalytic amounts of Ni(cod)$_2$ and tri-*n*-octylphosphine (*n*-Oct$_3$P) and a stoichiometric quantity of triethylborane (Et$_3$B) (Table 1, entry 1). Dienol **2.5** was isolated in 54% yield and excellent regioselectivity (>95:5); unfortunately, some erosion of *E*/*Z* selectivity

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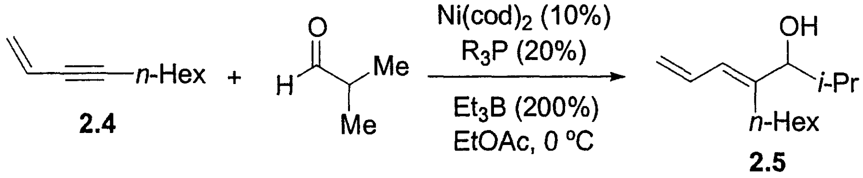
[11] Two other groups have recently reported intermolecular reductive coupling reactions that employ 1,3-enynes as coupling partners. See refs 2h and 4d.

[12] Crystallographic evidence for a similar interaction in a related group 10 (Pt) complex: Benyunes, S. A.; Brandt, L.; Fries, A.; Green, M.; Mahon, M. F.; Papworth, T. M. T. *J. Chem. Soc. Dalton Trans.* **1993**, 3785-3793.

[13] Catalytic enyne additions (internal alkynes): (a) Campi, E. M.; Jackson, W. R. *Aust. J. Chem.* **1989**, *42*, 471-478. (b) Dérien, S.; Clinet, J.-C.; Duñach, E.; Périchon, J. *J. Organomet. Chem.* **1992**, *424*, 213-224. (c) Van den Hoven, B. G.; Alper, H. *J. Org. Chem.* **1999**, *64*, 3964-3968. (d) Han, J. W.; Tokunaga, N.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 12915-12916.

in the newly formed double bond was observed. The use of other monodentate phosphine ligands also provided **2.5** in excellent regioselectivity (entries 2-5), and more sterically encumbered phosphines such as tricyclopentylphosphine (Cyp_3P, entry 3), tricyclohexylphosphine (Cy_3P, entry 4), and diphenyl(ferrocenyl)phosphine (Ph_2FcP, entry 5) led to improved *E*/*Z* selectivities. A coupling with the chiral monodentate phosphine (+)-neomenthyldiphenylphosphine (NMDPP, **1.28**) also provided **2.5** in high yield with excellent regio- and *E*/*Z* selectivity; however, very low enantioselection was observed (entry 6).

Table 1. Evalulation of monodentate phosphines as ligands in the nickel-catalyzed reductive coupling of 1-decen-3-yne (**2.4**) and isobutyraldehyde.



entry	R_3P	Yield (%)[b]	Regioselectivity[c]	*E*/*Z*[c]
1	*n*-Oct_3P	54	>95:5	90:10
2	Bn_3P	48	>95:5	93:7
3	**Cyp_3P**	**59**	**>95:5**	**>95:5**
4	Cy_3P	59	>95:5	95:5
5	Ph_2FcP	60	>95:5	95:5
6[d]	(+)-NMDPP	70	>95:5	>95:5

[a] Experimental Procedure: To a solution of $Ni(cod)_2$ (0.05 mmol), R_3P (0.10 mmol), and Et_3B (1 mmol) in EtOAc (0.5 mL) at 0 °C was added *i*-PrCHO (1.0 mmol) and **2.4** (0.50 mmol). The solution stirred 6 h at 0 °C and was then stirred 30 min open to the air to promote oxidation of the catalyst. Crude material was purified by silica gel chromatography. [b] Yield of isolated product. [c] Regioselectivity and *E*/*Z* selectivity were determined by ^1H NMR. [d] **2.5** was isolated in <5% ee.

Substrate Scope and Limitations

Investigation of a series of vinyl-substituted 1,3-enynes (**2.6-2.9**) in nickel-catalyzed reductive couplings with isobutyraldehyde revealed that the alkene imparts exquisite regioselectivity regardless of the nature or size of the other alkyne substituent (Table 2, entries 1-5).[14,15] In related coupling reactions of alkynes of the general form Ar–C≡C–alkyl, the

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[14] Enynes **2.4, 2.6-2.9** were synthesized using a modified Negishi coupling of vinyl bromide with the appropriate terminal alkyne: Negishi, E. -I.; Okukado, M.; Lovich, S. F.; Luo, F. -T. *J. Org. Chem.* **1984**, *49*, 2629-2632. Enynes **2.12-2.14, 2.16** were synthesized via Sonogashira cross-coupling of the appropriate vinyl

regioselectivity is generally very high (>95:5) and favors C-C bond formation distal to the aromatic group (*cf.* Scheme 2).[4d,g-i] It was therefore quite unexpected that the coupling of 3-buten-1-ynyl-benzene (**2.6**) caused a *complete reversal* in this sense of regioselectivity to favor C–C bond formation proximal to the aryl substituent and distal to the electronically similar and smaller vinyl substituent (entry 1).

Similar regioselectivities are observed with primary (*n*-Hex, entry 1), secondary (*i*-Pr, Cy, entries 2 and 3), and even tertiary alkyl groups (*t*-Bu, entry 4) opposite the vinyl substituent and, as demonstrated by *t*-Bu–C≡C–CH=CH$_2$ (**2.9**, entry 4), such enynes also display a remarkable increase in reactivity. Other alkynes with *tert*-alkyl substituents (*t*-Bu–C≡C–alkyl and Ar–C≡C–*t*-Bu) do not undergo reductive coupling under similar conditions.[16] Of even further significance is that few examples of catalytic carbon-carbon bond-forming reactions of *tert*-alkyl–C≡C–R alkynes are known,[4a,e,g,17] and in none of these, nickel-catalyzed or otherwise, is C-C bond formation favored adjacent to a *tert*-alkyl group.[18,19]

1,1-Disubstituted (entry 6), (Z)- and (*E*)-disubstituted (entries 7-9), trisubstituted (entry 10), and tetrasubstituted (entry 11) olefins all direct reductive couplings of alkynes in the same manner, and in a minimum regioselectivity of 86:14. As several examples of intermolecular nickel-catalyzed coupling reactions of aldehydes and 1,3-dienes have been reported,[20] it is also

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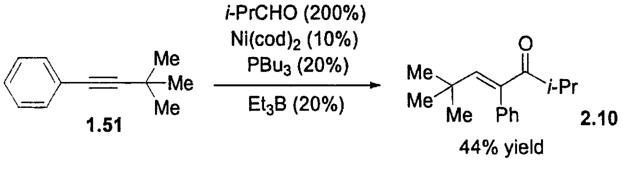
iodide with either 1-propyne (**2.12-2.13**), 1-butyne (**2.14**), or 1-hexyne (**2.16**). Enyne **2.15** was synthesized by POCl$_3$-promoted elimination of 1-propynyl-1-cyclohexanol: Inman, W. D.; Sanchez, K. A. J.; Chaidez, M. A.; Paulson, D. R. *J. Org. Chem.* **1989**, *54*, 4872 – 4881.

[15] Mr. Torsak Luanphaisarnnont assisted with the preparation of enynes **2.4, 2.6-2.9.**

[16] 4,4-Dimethyl-2-pentyne (**1.50**) does not couple under these conditions, and 1-phenyl-3,3-dimethyl-1-butyne (**1.51**) affords exclusively hydroacylation product **2.10** (regioselectivity was confirmed by ozonolysis).



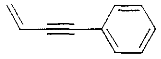
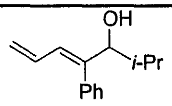
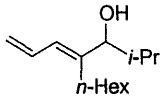
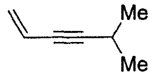
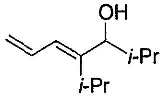
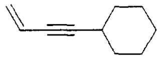
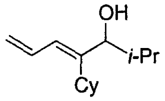
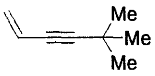
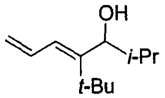
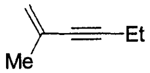
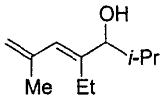
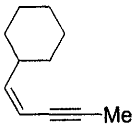
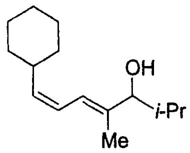
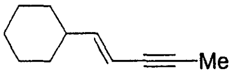
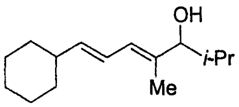
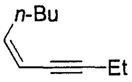
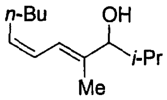
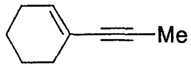
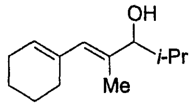
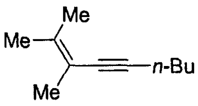
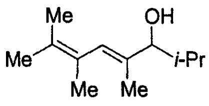
[17] (a) Johnson, J. R.; Cuny, G. D.; Buchwald, S. L. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1760-1761. (b) Jackson, W. R.; Lovel, C. G. *J. Chem. Soc., Chem. Commun.* **1982**, 1231-1232.

[18] For examples in which an addition to a *tert*-alkyl–C≡C–R alkyne generates *two* C–C bonds regioselectively, see refs 3e and 3g.

[19] (a) Addition of organometallic reagents to ynones and ynoate esters: Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Tetrahedron Organic Chemistry Series 9; Pergamon Press: Oxford, 1992. (b) See ref 13d for preferential C-Si bond formation adjacent to *t*-butyl.

[20] (a) Kimura, M.; Ezoe, A.; Shibata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4033-4034. (b) Takimoto, M.; Hiraga, Y.; Sato, Y.; Mori, M. *Tetrahedron Lett.* **1998**, *39*, 4543-4546. (c) Tamaru, Y. *J. Organomet. Chem.* **1999**, *576*, 215-231. (d) Shibata, K.; Kimura, M.; Kojima, K.; Tanaka, S.; Tamaru, Y. *J. Organomet.*

Table 2. Alkene-directed, nickel-catalyzed reductive coupling of 1,3-enynes and aldehydes.[a]

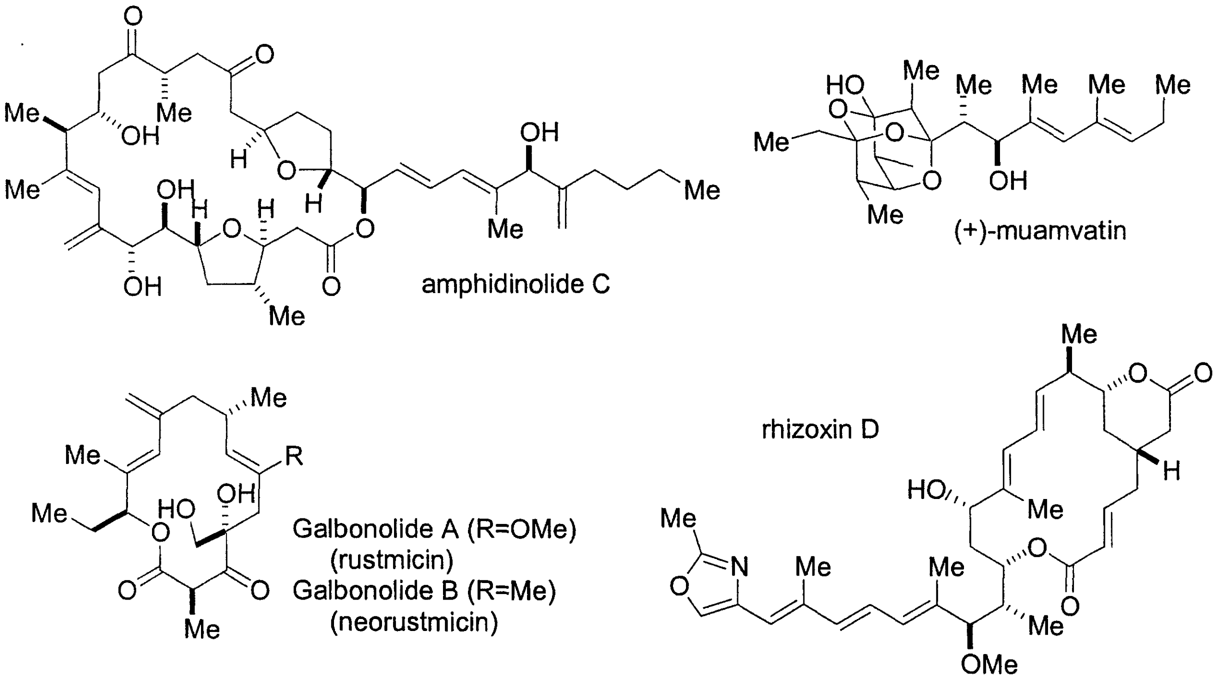
entry	enyne		product		yield (%)[b]	regioselectivity[c]
1		**2.6**		**2.17**	71	95:5
2	**2.4**			**2.5**	64	>95:5
3		**2.7**		**2.18**	64	>95:5
4[d]		**2.8**		**2.19**	63	>95:5
5[d]		**2.9**		**2.20**	69	>95:5
6		**2.11**		**2.21**	71	95:5
7		**2.12**		**2.22**	89	95:5
8		**2.13**		**2.23**	86	86:14
9		**2.14**		**2.24**	58	95:5
10		**2.15**		**2.25**	79	90:10
11[d]		**2.16**		**2.26**	88	95:5

[a] Experimental Procedure: To a solution of Ni(cod)$_2$ (0.05 mmol), Cyp$_3$P (0.10 mmol) and Et$_3$B (1 mmol) in EtOAc (0.5 mL) at 0 °C was added *i*-PrCHO (1.0 mmol) and the enyne (0.50 mmol). The solution was stirred 6-15 h and warmed gradually to room temperature. Crude material was purified by silica gel chromatography. [b] Yield of isolated product. [c] Regioselectivity was determined by ^{1}H NMR. [d] (+)-NMDPP (**1.28**, 0.10 mmol) employed as ligand.

Chem. **2001**, *624*, 348-353. (e) Sato, Y.; Sawaki, R.; Saito, N.; Mori, M. *J. Org. Chem.* **2002**, *67*, 656-662. (f) Sawaki, R.; Sato, Y.; Mori, M. *Org. Lett.* 2004, 6, 1131-1133.

noteworthy that the diene products do not undergo further reaction with another molecule of aldehyde under these conditions. 1,3-Dienols of the type constructed using these coupling reactions are found in a variety of complex natural products with interesting biological activity (Figure 1),[21] and are useful intermediates for Diels-Alder reactions,[22] catalytic epoxidations[23] and dihydroxylations,[24] and other important reactions.[25,26]

Figure 1. Biologically active natural products that contain 1,3-dienols or their derivatives.



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[21] (a) Amphidinolide C: Kobayashi, J.; Ishibashi, M.; Walchli, M. R.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Ohizumi, Y. *J. Am. Chem. Soc.* **1988**, *110*, 490-494. (b) Galbonolides: Sakoh, H.; Jona, H.; Sugimoto, Y.; Imamura, H.; Sakuraba, S.; Yamada, K.; Morishima, H. *Chem. Pharm. Bull.* **2004**, *52*, 992-994 and references therein. (c) (+)-Muamvatin: Roll, D. M.; Biskupiak, J. E.; Mayne, C. L.; Ireland, C. M. *J. Am. Chem. Soc.* **1986**, *108*, 6680-6682. (d) Rhizoxin D: Iwasaki, S.; Namikoshi, M.; Kobayashi, H.; Furukawa, J.; Okuda, S. *Chem. Pharm. Bull.* **1986**, *34*, 1387-1390.

[22] (a) W. Oppolzer, in *Comprehensive Organic Synthesis, Vol. 5* (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, U. K., **1991**, Chapter 4.1, pp.315 – 400. (b) W. R. Roush, in *Comprehensive Organic Synthesis, Vol. 5* (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, U. K., **1991**, Chapter 4.4, pp. 513 – 550.

[23] (a) Chang, S.; Lee, N. H.; Jacobsen, E. N. *J. Org. Chem.* **1993**, *58*, 6939-6941. (b) Frohn, M.; Dalkiewicz, M.; Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 2948-2953.

[24] Xu, D. Q.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570-7571.

[25] (a) Kimura, M.; Ezoe, A.; Shibata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4033-4034. (b) Sato, Y.; Sawaki, R.; Saito, N.; Mori, M. *J. Org. Chem.* **2002**, *67*, 656-662.

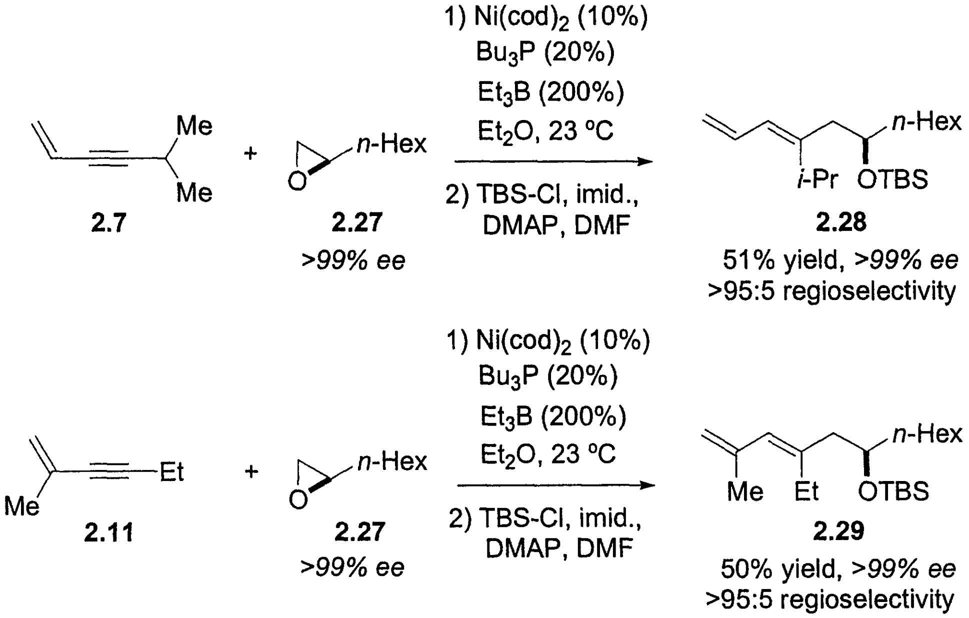
[26] For the preparation of dienes of opposite olefin geometry via three-component Ni-catalyzed coupling of alkynes, aldehydes, and vinyl zirconium reagents, see: Ni, Y.; Amarasinghe, K. K. D.; Montgomery, J. *Org. Lett.* **2002**, *4*, 1743-1745.

Alkene-Directed, Reductive Couplings of 1,3-Enynes and Epoxides[27]

Our group recently reported a catalytic reductive coupling of aryl-substituted alkynes and epoxides that occurs with retention of configuration at the epoxide stereocenter (*cf.* Scheme 2, eq 4).[2f] The ready availability of terminal epoxides in >99% ee[28] makes this an attractive strategy for preparing enantiomerically pure homoallylic alcohols in high regioselectivity.

Terminal epoxides were also found to undergo coupling in high regioselectivity and with retention of configuration when 1,3-enynes were employed (Scheme 5). (+)-1-Octene oxide (**2.27**) was coupled with enynes **2.7** and **2.11** to afford, following alcohol protection, enantiomerically pure TBS ethers **2.28** and **2.29** in >95:5 regioselectivity. These reactions provide access to 3,5-dienols of the type found in the marine natural product (–)-pateamine A, which has attracted attention due to its potent immunosuppressant properties (Figure 2).[29]

Scheme 5.



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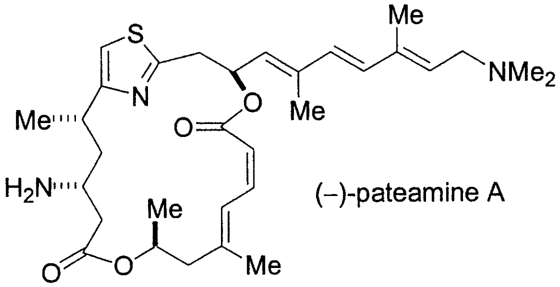
[27] This portion of the work was done in collaboration with Dr. Carmela Molinaro.

[28] (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936-938. (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307-1315.

[29] (a) Isolation: Northcote, P. T.; Blunt, J. W.; Munroe, M. H. G.; *Tetrahedron Lett.* **1991**, *32*, 6411-6414. Syntheses: (b) Romo, D.; Rzasa, R. M.; Shea, H. A.; Park, K.; Langenhan, J. M.; Sun, L.; Akheiser, A.; Liu, J. O. *J. Am. Chem. Soc.* **1998**, *120*, 12237-12254. (c) Remunian, M. J.; Pattenden, G. *Tetrahedron Lett.* **2000**, *41*, 7367-7371.

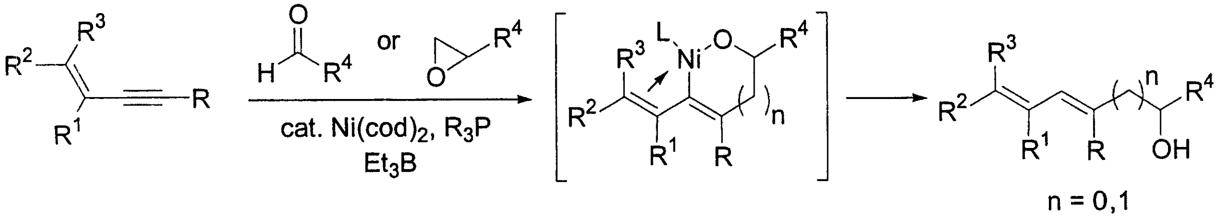
Figure 2.



Reaction Mechanism

The dramatic enhancement of reactivity (e.g. Table 2, entry 5) and the invariant sense and degree of regioselectivity (in particular the complete turnover vs. Ph; Table 2, entry 1) are not consistent with a purely steric and/or electronic phenomenon.[30] Conversely, these trends exhibit all the hallmarks of directed reactions[31] and can be explained by complexation of the alkene to the metal center during the regioselectivity-determining step (Scheme 6).[32]

Scheme 6.



While we have no direct evidence to support an interaction of this type, Green and co-workers have hypothesized based on X-ray crystallographic data that cationic (1,2,3-η)-*trans*-butadienyl complexes such as **2.30** (Figure 3) exhibit some localized bonding from the platinum

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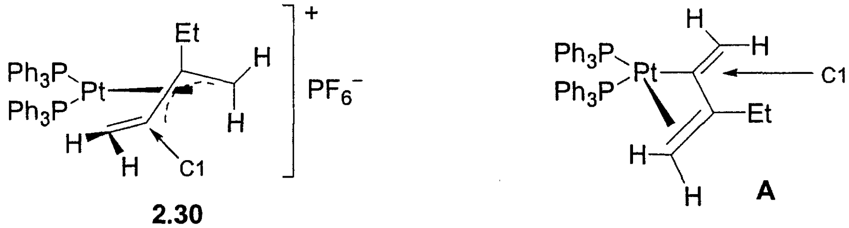
[30] Saito and co-workers have demonstrated that Pt(0)-enyne complexes exhibit enhanced reactivity (nucleophilicity) relative to analogous Pt(0)-monoyne complexes: Saito, S.; Tando, K.; Kabuto, C.; Yamamoto, Y. *Organometallics* **2000**, *19*, 3740-3743.

[31] Reviews: (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307-1370. (b) Kauffmann, T. *Synthesis* **1995**, 745-755. (c) Catellani, M.; Chiusoli, G. P.; Costa, M. *J. Organomet. Chem.* **1995**, *500*, 69-80. (d) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 2206-2225.

[32] Pörschke and co-workers have shown that Pd(0)-vinylacetylene complexes exist as a mixture of two isomers, one that is η^2-CH≡CH$_2$ bound and one that is η^2-CH=CH$_2$ bound, and suggested that their isomerization occurs intramolecularly via a transition state in which both alkyne and alkene are bound to the metal. It is presumed that similar complexation in a Ni(0)-enyne complex, followed by aldehyde insertion, would regioselectively afford the oxametallacycle depicted. Schager, F.; Bonrath, W.; Pörschke, K.-R.; Kessler, M.; Krüger, C.; Seevogel, K. *Organometallics* **1997**, *16*, 4276-4286.

center to carbon 1 (C1) that is best illustrated by formalism **A**, which contains a similar metal-olefin interaction to that which we propose.[33]

Figure 3.



2.30 **A**

Site-Selective, Rh-Catalyzed Hydrogenation of 1,3-Dienols

Unsymmetrical dialkylacetylenes (alkyl–C≡C–alkyl') are non-regioselective in nearly *all* catalytic reactions when the two substituents are of similar steric demand.[5] In cases where the two groups are well differentiated (e.g., electronically), the inaccessibility of the disfavored regioisomer limits the scope of many methods. Despite the importance of trisubstituted and tetrasubstituted olefins, the synthetic accessibility of dialkylacetylenes, and a plethora of useful catalytic alkyne addition reactions, there is no general strategy for controlling regioselectivity in these situations.

In conjunction with a rhodium-catalyzed, site-selective hydrogenation (Table 3), catalytic reductive couplings of 1,3-enynes and aldehydes address both of these problems. Examples of selective reduction of unsymmetrical 1,3-dienes are distributed only sparsely throughout the literature,[34] and we were therefore pleasantly surprised to find that Wilkinson's catalyst[35] [$(Ph_3P)_3RhCl$] under H_2 (1 atm) smoothly converted diene **2.5** into allylic alcohol **2.31** in excellent yield (entry 1). Protection of the alcohol was not required; however, reduction of the corresponding TBS ether **2.32** proceeded in similarly high yield (entry 2). Dienes **2.17**-**2.20** and **2.29** were similarly reduced (entries 3-6, 8), and the isopropenyl groups of dienes **2.21** and **2.29** were reduced selectively under slightly higher H_2 pressure (entries 7 and 9). In this way, it was

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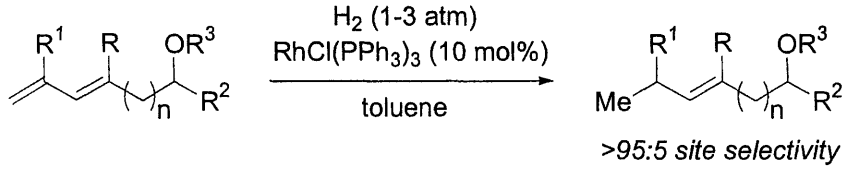
[33] Benyunes, S. A.; Brandt, L.; Fries, A.; Green, M.; Mahon, M. F.; Papworth, T. M. T. *J. Chem. Soc. Dalton Trans.* **1993**, 3785-3793.

[34] (a) Schrock, R. R.; Osborn, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 4450-4455. (b) Wender, P. A.; Holt, D. A. *J. Am. Chem. Soc.* **1985**, *107*, 7771-7772. (c) Choudary, B. M.; Sharma, G. V. M.; Bharathi, P. *Angew. Chem. Int. Ed.* **1989**, *28*, 465-466.

[35] (a) Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G. *J. Chem. Soc. A* **1966**, 1711-1732. (b) Osborn, J. A.; Wilkinson, G. *Inorg. Synth.* **1967**, *10*, 67-71.

possible to prepare the disfavored regioisomer in the nickel-catalyzed reductive coupling of an Ar–C≡C–alkyl alkyne (*cf.* Scheme 2) in >95:5 regioselectivity (entry 6), as well as *t*-Bu-substituted alkenes (entry 5), previously inaccessible via these nickel-catalyzed methods (vide supra).

Table 3. Selective reduction of dienes **2.17-2.27** with Wilkinson's catalyst[a]



entry	diene	R	R^1	n	R^2	R^3	alkenol	Yield (%)
1	**2.5**	*n*-Hex	H	0	*i*-Pr	H	**2.31**	92
2	**2.32**	*n*-Hex	H	0	*i*-Pr	TBS	**2.33**	98
3	**2.17**	Ph	H	0	*i*-Pr	H	**2.34**	80
4	**2.18**	*i*-Pr	H	0	*i*-Pr	H	**2.35**	76
5	**2.19**	Cy	H	0	*i*-Pr	H	**2.36**	87
6	**2.20**	*t*-Bu	H	0	*i*-Pr	H	**2.37**	83
7[b]	**2.21**	Et	Me	0	*i*-Pr	H	**2.38**	96
8	**2.28**	*i*-Pr	H	1	*n*-Hex	TBS	**2.39**	85
9[b]	**2.29**	Et	Me	1	*n*-Hex	TBS	**2.40**	94

[a] Experimental Procedure: A solution of $RhCl(PPh_3)_3$ (0.02 mmol) and diene (0.2 mmol) in toluene (1 mL) was placed under 1 atm H_2 and stirred 2 h. Crude material was purified by silica gel chromatography. [b] 3 atm of H_2 was employed.

This procedure also circumvents the poor regioselectivity observed with certain alkyne classes and can be used to prepare regioisomeric pairs of allylic alcohols, such as **2.35** and **2.38** (entries 3 and 7), and homoallylic alcohols (entries 8 and 9) with complete selectivity. While low regioselectivity is observed in the coupling of *i*-Pr–C≡C–Et and isobutyraldehyde (**2.38**:**2.35** = 1.7:1, *cf.* Scheme 3, eq 2), enyne **2.7** and its complement **2.11** can be converted over two steps to isomerically pure **2.35** and **2.38**, respectively (Scheme 7).

A number of conditions were investigated for the selective reduction of the (*Z*)-disubstituted olefin of diene **2.24**; however, all attempts afforded poor conversion and/or complex mixtures of 1,2 and 1,4 addition to the diene as well as overreduction of the resultant monoenes. These conditions were also not effective for the selective reduction of more substituted dienes such as **2.25** and **2.26**.

Scheme 7.

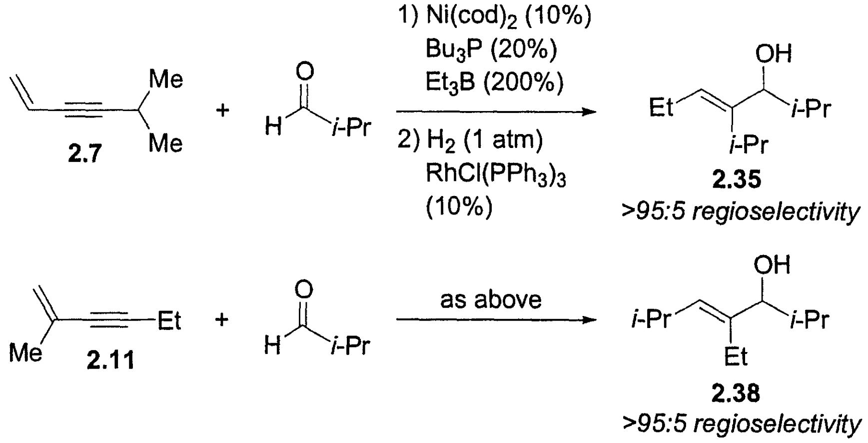
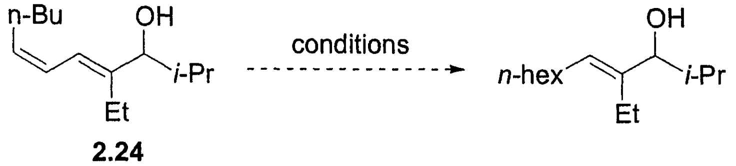


Table 4. Attempted selective reductions of dienol **2.24**.



Conditions	Results
$RhCl(PPh_3)_3$, 1 atm, 15 h[a]	~50% conversion, product mixture
$RhCl(PPh_3)_3$, 2 atm, 24 h	1,2 + overreduction + other
$RhCl(PPh_3)_3$, 3.4 atm, 20 h[a]	complex mixture (1,2 is major)
Pd/C, toluene:MeOH, 1 atm, 1.5 h	1,2 + 1,4 + overreduction
Pd/C, 1 atm, toluene, 30 min	1,2 + 1,4 + overreduction
PtO_2, 1 atm, 10 min	1,2 + 1,4 + overreduction
diimide, 25 °C, 15 h	recovered starting material
diimide, 85 °C, 15 h	complex mixture

[a] Reaction of the corresponding TBS ether.

Conclusion

Substrate-directed reactions are of tremendous importance to selective chemical synthesis.[31] In the case of nickel-catalyzed alkyne coupling reactions, an alkenyl group dramatically enhances reactivity and completely controls regioselectivity, enabling the regiocontrolled preparation of a variety of functionalized conjugated dienes that have broad application in organic synthesis. A novel, site-selective hydrogenation yields allylic and homoallylic alcohols that cannot be obtained in high regioselectivity (or at all) from the corresponding alkynes using these methods. Finally, this alkene-directing effect may be applicable to other catalytic reactions of alkynes.

Experimental Section

General Methods. All reactions were performed under an oxygen-free atmosphere of nitrogen or argon with rigid exclusion of moisture from reagents and glassware. Bis(1,5-cyclooctadiene)nickel (0) [$Ni(cod)_2$], tricyclopentylphosphine (Cyp_3P), (*S*)-(+)-neomenthyldiphenylphosphine (NMDPP), $RhCl(PPh_3)_3$ (Wilkinson's catalyst), and tetrakis(triphenylphosphine) palladium(0) [$Pd(PPh_3)_4$] were purchased from Strem Chemicals, Inc. and used without further purification. Triethylborane (98%), tributylphosphine, 1,2-epoxyoctane, vinyl bromide, 1-ocytne, phenylacetylene, cyclohexanecarboxaldehyde, and 4-(dimethylamino)-pyridine (DMAP) were purchased from Aldrich Chemical Co. and used as received. Imidazole, *tert*-butyldimethylsilyl chloride (TBSCl), and carbon tetrabromide were purchased from Alfa Aesar and used as received. 3-Methyl-1-butyne and 3,3-dimethyl-1-butyne were purchased from GFS Chemicals and used without further purification. Isobutyraldehyde was purchased from Alfa Aesar and distilled over magnesium sulfate prior to use. Zinc chloride ($ZnCl_2$) was purchased from Alfa Aesar and dried in vacuo at 150 °C for 16 h prior to use. 2-Methyl-1-hexen-3-yne (**2.11**) was purchased from Aldrich Chemical Co. and distilled prior to use. 2-Methyl-3-hexyne was prepared by $LiNH_2/NH_3$ deprotonation of 3-methyl-1-butyne followed by addition of ethyl bromide.[36] Tetrahydrofuran, diethyl ether and toluene were freshly distilled over blue solutions of sodium/benzophenone ketyl. Methylene chloride and pyrrolidine were distilled over calcium hydride; ethyl acetate was distilled over magnesium sulfate under argon atmosphere. Dimethylformamide, 99.9+% was purchased from Aldrich Chemical Co. and dried over activated molecular sieves (3 Å) prior to use.

Analytical thin layer chromatography (TLC) was performed on silica gel 60 F_{254} aluminum plates precoated with a fluorescent indicator or EM reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was accomplished with UV light and ethanolic phosphomolybdic acid (PMA) or aqueous potassium permanganate. Liquid chromatography was performed using a forced flow (flash chromatography)[37] of the indicated solvent system on Silicycle silica gel 60 (230 – 400 mesh). ^1H and ^{13}C NMR spectra were recorded on Varian Inova 300 and 500MHz and Bruker Advance 400MHz instruments. Infrared (IR) spectra were recorded as a thin film between NaCl plates on a Perkin-Elmer Model 2000 FT-IR System transform spectrometer. High resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. GC analysis was performed on a Varian CP-3800 gas chromatograph fitted with Chiraldex B-PH, B-DA, and G-TA capillary columns. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter at 589 nm.

Enyne Synthesis. General procedure for the synthesis of 1-buten-3-ynes:[38] In an oven-dried, 100 mL round-bottom flask, a terminal alkyne (15 mmol) was dissolved in THF (15 mL) and cooled to 0 °C. Then *n*-BuLi (15 mmol, 6 mL of 2.5 M solution in hexanes) was added dropwise, and the mixture was stirred 30 min at 0 °C. A solution of dry $ZnCl_2$ (2.04 g, 15 mmol) in THF (10 mL) was added via cannula and the mixture was allowed to warm to room temperature. In a 250 mL round bottom flask, vinyl bromide (25 mmol, 25 mL of a 1 M solution

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[36] Procedure supplied by GFS Chemicals, Inc., P.O. Box 245, Powell, OH 43065.

[37] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

[38] Negishi, E. –I.; Okukado, M.; Lovich, S. F.; Luo, F. –T. *J. Org. Chem.* **1984**, *49*, 2629-2632.

in THF) and $Pd(PPh_3)_4$ (0.69g, 0.6 mmol) were combined. The alkynyl zinc solution was transferred to the palladium solution via cannula. The bright yellow solution was stirred 2 h and then quenched with 1 M HCl (75 mL). The organics were extracted with pentanes (2 x 75 mL), washed with saturated NaCl, dried over $MgSO_4$, and filtered. Pentanes were removed via distillation, and the residue was then distilled under reduced pressure to provide the desired 1-buten-3-yne.

1-Decen-3-yne[38] (2.4): The standard procedure was followed. Thus, 1-octyne (2.21 mL, 15 mmol) provided after reaction and purification the title compound (0.95 g, 7.0 mmol, 47% yield) as a clear liquid. ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 17.4, 10.8, 2.1 Hz, 1H); 5.54 (dd, *J* = 17.4, 2.3 Hz, 1H); 5.37 (dd, *J* = 10.8, 2.3 Hz, 1H); 2.29 (dt, *J* = 10.2, 2.1 Hz, 2H); 1.48 – 1.57 (m, 2H); 1.25 – 1.44 (m, 6H); 0.89 (t, *J* = 7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 125.65, 117.86, 91.49, 76.48, 31.57, 28.86, 28.80, 22.77, 19.55, 14.28.

3-Buten-1-ynyl-benzene[39] (2.6): The general procedure was followed except that the scale was doubled. Thus, phenylacetylene (3.3 mL, 30 mmol) provided after reaction and purification the title compound (2.24 g, 17 mmol, 58% yield) as a clear liquid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.46 (m, 2H); 7.29 – 7.34 (m, 3H); 6.02 (dd, *J* = 17.4, 11.1 Hz, 1H); 5.73 (ddd, *J* = 17.4, 2.1, 0.5 Hz, 1H); 5.54 (ddd, *J* = 11.1, 2.1, 0.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.77, 128.52, 128.50, 127.14, 123.31, 117.38, 90.16, 88.28.

5-Methyl-1-hexen-3-yne (2.7): The general procedure was followed except that the reaction was performed on 50 mmol scale. Thus, 3-methyl-1-butyne (5.13 mL, 50 mmol) provided after reaction and purification the title compound (1.30 g, 23 mmol, 46% yield) as a clear liquid. ^1H NMR (300 MHz, $CDCl_3$) δ 5.79 (ddd, *J* = 17.5, 13, 2 Hz, 1H); 5.55 (dd, *J* = 17.5, 2.5 Hz, 1H); 5.38 (dd, *J* = 11, 2 Hz, 1H); 2.68 (doublet of septets, *J* = 7, 2 Hz, 1H); 1.20 (d, *J* = 7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 125.63, 117.80, 96.73, 78.65, 23.11, 21.25. IR (thin film NaCl): 3101, 3011, 2971, 2933, 2874, 2228, 1832, 1609, 1466, 1411, 1383, 1364, 1319, 1292, 1190, 1135, 1105, 1071, 974, 916 cm^{-1}.

3-Buten-1-ynyl-cyclohexane (2.8): Cyclohexanecarboxaldehyde (2.28g, 20 mmol, 2.44 mL) and triphenylphosphine (17.28g, 66 mmol) were dissolved in CH_2Cl_2 (80 mL) and cooled to 0 °C. A solution of carbon tetrabromide (14.68g, 44 mmol) in CH_2Cl_2 was added over 10 min, and the reaction was stirred 1.5 h at 0 °C. Hexanes (600 mL) was added, and the precipitated triphenylphosphine oxide was removed by filtration through a pad of silica gel. Removal of solvent in vacuo provided 1,1-dibromo-2-cyclohexylethene as a clear oil (5.43 g, 20 mmol, 100% yield). The 1,1-dibromo-2-cyclohexylethene was dissolved in THF (40 mL) and cooled to –78 °C. Then *n*-BuLi (55 mmol, 22 mL of a 2.5 M solution in hexanes) was added dropwise, and the solution was stirred 1 h at –78 °C, then warmed to 0 °C and stirred for an additional 45 min. Dried $ZnCl_2$ (3.4 g, 25 mmol) in THF (12 mL) was then added via cannula and the solution was allowed to warm to room temperature. The alkynyl zinc was then transferred via cannula into a solution of vinyl bromide (40 mmol, 40 mL of a 1M solution in THF) and palladium tetrakis (0.93 g, 0.80 mmol). The bright yellow solution was stirred overnight at room temperature. The reaction was quenched with 1M HCl (100 mL), and the organics were extracted with pentane (2x

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[39] Padwa, A.; Caruso, T.; Nahm, S.; Rodriguez, A. *J. Am. Chem. Soc.* **1982**, *104*, 2865-2871.

100 mL), washed with saturated NaCl, dried over $MgSO_4$, and filtered. Pentanes were removed via distillation, and the residue was distilled under reduced pressure to provide the title compound (0.61 g, 5.42 mmol, 47% yield) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (ddd, J = 29, 18, 1 Hz, 1H); 5.57 (ddd, J = 29, 5, 1 Hz, 1H); 5.38 (dd, J = 18, 4 Hz, 1H); 2.42 – 2.53 (m, 1H); 1.65 – 1.88 (m, 4H); 1.22 – 1.58 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 125.55, 117.89, 95.46, 79.35, 32.84, 29.85, 26.07, 25.15. IR (thin film NaCl): 3099, 3009, 2932, 2855, 2663, 2224, 1829, 1608, 1449, 1362, 1349, 1298, 1234, 1168, 973, 914 cm^{-1}.

5,5-Dimethyl-1-hexen-3-yne[40] (2.9): The general procedure was followed except that the reaction was performed on 50 mmol scale. Thus, 3,3-dimethylbutyne (6.1 mL, 50 mmol) provided after reaction and purification the title compound (2.14 g, 20 mmol, 40% yield) as a clear liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (dd, J = 17.4, 10.8 Hz, 1H); 5.52 (J = 17.4, 2.4 Hz, 1H); 5.35 (dd, J = 10.8, 2.4 Hz, 1H); 1.24 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 125.48, 117.84, 99.44, 77.94, 31.81, 31.12.

(*Z*)-Pent-1-en-3-ynyl-cyclohexane (2.12): $Pd(PPh_3)_4$ (277 mg, 0.24 mmol) and copper iodide (23 mg, 0.12 mmol) were added to a 250 mL, three-necked round-bottom flask under inert atmosphere. Pyrrolidine (16 mL) was added, followed by (*Z*)-(2-iodo-ethenyl)cyclohexane[41] (1.9 g, 8 mmol). The mixture was cooled to –78 °C and the flask was then evacuated. The vacuum outlet was closed, and with the flask still evacuated, propyne was bubbled in slowly. The flask was removed from the cold bath and allowed to warm gradually to room temperature. Propyne was bubbled in until atmospheric pressure was reached, at which point the reaction was placed under argon and stirred for 15 h. The reaction was then diluted with Et_2O (75 mL) and saturated aqueous NH_4Cl (75 mL). The organics were extracted with Et_2O (2 x 75 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude oil. Purification via flash chromatography on silica gel (100% hexanes) provided the title compound as a clear liquid (0.86 g, 73% yield). R_f = 0.50 (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.64 (t, J = 10 Hz, 1H); 5.32 (dd, J = 11, 2 Hz, 1H); 2.56 (m, 1H); 1.99 (d, J = 1.5 Hz, 3H); 1.73 – 1.65 (m, 5H); 1.38 – 1.29 (m, 2H); 1.22 – 1.16 (m, 1H); 1.14 – 1.04 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.44, 107.32, 89.46, 76.74, 39.22, 32.61, 26.21, 25.92, 4.70. IR (thin film NaCl): 3015, 2925, 2852, 2213, 1710, 1681, 1620, 1449, 1401 cm^{-1}. HRMS (EI) *m/z* 148.125 [M^+; calcd for $C_{11}H_{16}$: 148.126].

(*E*)-Pent-1-en-3-ynyl-cyclohexane (2.13): Procedure for the preparation of **2.12** was followed, except that (*E*)-(2-iodo-ethenyl)cyclohexane[42] (10 mmol) was employed, and the scale was adjusted accordingly (61% yield, 0.91 g). R_f = 0.39 (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (dd, J = 16, 7 Hz, 1H); 5.39 (dt, J = 16, 1.5 Hz, 1H); 2.00 (m, 1H); 1.93 (d, J = 2 Hz, 3H); 1.74 – 1.63 (m, 5H); 1.30 – 1.22 (m, 2H); 1.19 – 1.13 (m, 1H); 1.12 – 1.03 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.18, 107.59, 84.47, 78.75, 41.35, 32.56, 26.22, 26.04, 4.42. HRMS (EI) *m/z* 148.126 [M^+; calcd for $C_{11}H_{16}$: 148.126].

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[40] Han, J. W.; Tokunaga, N.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 12915-12916.

[41] Stork, G. S.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173 - 2174.

[42] Takai, K.; Ichiguchi, T.; Hisaka, S. *Synlett* **1999**, 1268-1270.

(*Z*)-Dec-5-en-3-yne (2.14): $Pd(PPh_3)_4$ (166 mg, 0.14 mmol) and copper iodide (14 mg, 0.07 mmol) were added to a 250 mL, three-necked round-bottom flask under inert atmosphere. Pyrrolidine (15 mL) was added, followed by (*Z*)-1-iodo-1-hexene[43] (1.51 g, 7.2 mmol). The mixture was cooled to –78 °C and the flask was then evacuated. The vacuum outlet was closed, and with the flask still evacuated, 1-butyne was bubbled in slowly. The flask was removed from the cold bath and allowed to warm gradually to room temperature. 1-Butyne was bubbled in until atmospheric pressure was reached, at which point the reaction was placed under argon and stirred for 15 h. The reaction was then diluted with Et_2O (75 mL) and saturated aqueous NH_4Cl (75 mL). The organics were extracted with Et_2O (2 x 75 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo (an ice bath was used for the latter as product is volatile). Purification via flash chromatography on silica gel (100% hexanes) provided the title compound as a clear liquid (0.34 g, 34% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 – 5.85 (m, 1H); 5.42 – 5.46 (m, 1H); 2.36 (dq, *J* = 7.5, 2.5 Hz, 2H); 2.30 (q, *J* = 7 Hz, 2H); 1.35 – 1.43 (m, 4H); 1.19 (t, *J* = 7.5 Hz, 3H); 0.92 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.92, 109.40, 95.90, 76.90, 31.25, 29.89, 22.47, 14.33, 14.14, 13.44.

1-prop-1-ynyl-cyclohexene[44] (2.15): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98 (s, 1H); 2.10 – 2.00 (m, 4H); 1.94 (s, 3H); 1.62 – 1.50 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.1, 121.1, 82.7, 81.6, 29.6, 25.6, 22.5, 21.7, 4.11.

(*E*)-2,3-dimethyl-non-2-en-4-yne (2.16): $Pd(PPh_3)_4$ (277 mg, 0.24 mmol) and copper iodide (23 mg, 0.12 mmol) were added to a 100 mL, oven-dried round-bottom flask under inert atmosphere. Pyrrolidine (24 mL) was added, followed by 1-hexyne (1.38 mL, 12 mmol) and 2-iodo-3-methyl-2-butene[45] (2.52g, 12 mmol). The mixture was heated to 50 °C and stirred for 15 h. The reaction was then cooled and diluted with Et_2O (100 mL) and saturated aqueous NH_4Cl (100 mL). The organics were extracted with Et_2O (2 x 75 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude oil. Purification via flash chromatography on silica gel (100% hexanes) provided the title compound as a clear liquid (1.52 g, 84% yield). R_f = 0.44 (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (t, *J* = 7 Hz, 2H); 1.92 (s, 3H); 1.78 (s, 3H); 1.72 (s, 3H); 1.56 – 1.49 (m, 2H); 1.48 – 1.41 (m, 2H); 0.93 (t, *J* = 7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.20, 112.13, 91.45, 82.47, 31.46, 23.61, 22.20, 19.94, 19.39, 19.14, 13.87. IR (thin film NaCl): 2959, 2931, 2873, 2862, 1682, 1466, 1458, 1445, 1372, 1329 cm^{-1}.

Standard Experimental Procedure for the Catalytic Reductive Coupling of Enynes and Aldehydes. In a glovebox, $Ni(cod)_2$ (14 mg, 0.5 mmol), and Cyp_3P (28 μL, 0.1 mmol) were placed into a 25 mL oven-dried, single-necked round-bottom flask, which was then sealed with a rubber septum. The flask was removed from the glovebox, placed under argon, and ethyl acetate (0.5 mL) was added via syringe, followed immediately by Et_3B (0.15 mL, 1.0 mmol). The resulting solution was stirred 5 min at ambient temperature and then cooled to 0 °C. Once the solution had cooled, isobutyraldehyde (90 μL, 1.0 mmol) was added dropwise via microsyringe.

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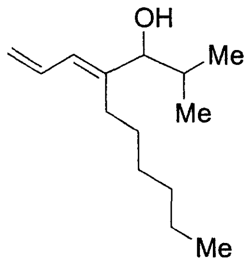
[43] Dieck, H. A.; Heck, R. F. *J. Org. Chem.* **1975**, *40*, 1083-1090.

[44] Inman, W. D.; Sanchez, K. A. J.; Chaidez, M. A.; Paulson, D. R. *J. Org. Chem.* **1989**, *54*, 4872-4881.

[45] Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14844-14845.

After stirring 5 min, the enyne (0.5 mmol) was added. The reaction was allowed to gradually warm to room temperature over 4 h, and the reaction continued to stir until complete by TLC (6 – 15 h). The septa was then removed and the reaction opened to air for 30 min to promote quenching of the catalyst. The crude mixture was purified by flash chromatography on silica gel using a solvent gradient (hexanes: ethyl acetate; 50:1 to 10:1). Note: Compounds formed are prone to rapid (over 2-3 days) decomposition, and so should either be used immediately or stored as solutions in benzene at –20 °C.



(4*E*)-4-Hexyl-2-methyl-hepta-4,6-dien-3-ol (2.5): In the reductive coupling of **2.4** (68 mg, 0.5 mmol) and isobutyraldehyde, the standard procedure was used. Silica gel chromatography afforded the title compound as a clear oil (67 mg, 64% yield, >95:5 regioselectivity, >95:5 *E*/*Z*). $R_f = 0.53$ (10:1 hexanes: ethyl acetate).

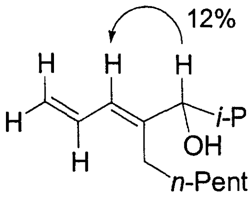
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.60 (m, 1H); 6.04 (d, $J = 11$ Hz, 1H); 5.21 (dd, $J = 17, 2$ Hz, 1H); 5.11 (dd, $J = 10, 2$ Hz, 1H); 3.76 (d, $J = 6.5$ Hz, 1H); 2.22 – 2.16 (m, 1H); 2.11 – 2.05 (m, 1H); 1.83 (oct., $J = 7$ Hz, 1H); 1.46 – 1.41 (m, 2H); 1.36 – 1.25 (m, 4H); 0.95 (d, $J = 6.5$ Hz, 3H); 0.90 – 0.88 (m, 6H).

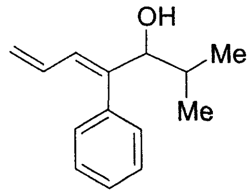
^{13}C NMR (125 MHz, $CDCl_3$) δ 145.21, 132.88, 126.70, 117.12, 82.04, 32.04, 31.88, 30.63, 30.10, 28.71, 22.88, 20.08, 17.88, 14.32.

IR (thin film NaCl): 3428, 2958, 2930, 2872, 2860, 1717, 1700, 1669, 1467, 1380, 1366, 1265, 1174, 1015 cm^{-1}.

HRMS (EI) *m/z* 210.198 [M^+; calcd for $C_{14}H_{26}O$: 210.198].

Irradiation of the carbinol methine proton resulted in a 12% nOe of the closest vinyl proton, consistent with an *E* olefin geometry in the observed allylic alcohol regioisomer.





(4*E*)-4-Phenyl-2-methyl-hepta-4,6-dien-3-ol (2.17): In the reductive coupling of **2.6** (64 mg, 0.5 mmol) and isobutyraldehyde, the standard procedure was used. Silica gel chromatography afforded the title compound as a clear oil (72 mg, 71% yield, 95:5 regioselectivity, >95:5 *E*/*Z*).

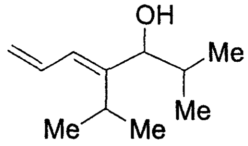
R_f = 0.27 (10:1 hexanes: ethyl acetate). The structure of the title compound was confirmed by ozonolysis, which provided α-hydroxyisovalerophenone[46] as the major product.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.40 (m, 2H); 7.29 – 7.33 (m, 1H); 7.22 – 7.24 (m, 2H); 6.25 – 6.37 (m, 2H); 5.31 (dd, J = 15.5, 2 Hz, 1H); 5.06 (dd, J = 10, 2 Hz, 1H); 4.18 (dd, J = 5, 5 Hz, 1H); 1.65 (d, J = 5 Hz, 1H); 1.63 (oct., J = 6.5 Hz, 1H); 0.92 (d, J = 6.5 Hz, 3H); 0.90 (d, J = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 145.22, 138.44, 134.04, 129.44, 128.37, 128.29, 127.50, 118.31, 81.46, 31.54, 20.04, 16.72.

IR (thin film NaCl): 3427, 3082, 3057, 3036, 2961, 2930, 2871, 1951, 1814, 1637, 1602, 1494, 1467, 1442, 1419, 1385, 1366, 1293, 1137, 1074, 998 cm^{-1}.

HRMS (EI) *m/z* 202.134 [M$^+$; calcd for $C_{14}H_{18}O$: 202.135].



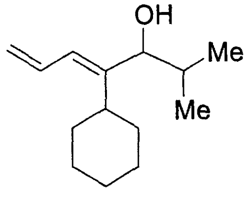
(4*E*)-4-Isopropyl-2-methyl-hepta-4,6-dien-3-ol (2.18): In the reductive coupling of **2.7** (47 mg, 0.5 mmol) and isobutyraldehyde the standard procedure was used. Silica gel chromatography afforded the title compound as a clear oil (54 mg, 64% yield, >95:5 regioselectivity, >95:5 *E*/*Z*). R_f = 0.30 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.80 – 6.72 (m, 1H); 6.03 (dd, J = 11, 0.5 Hz, 1H); 5.20 (ddd, J = 17, 2, 0.5 Hz, 1H); 5.12 (ddd, J = 10, 2, 0.5 Hz, 1H); 3.78 (dd, J = 7, 1.5 Hz, 1H); 2.82 (sept., J = 7 Hz, 1H); 1.86 (oct., J = 7 Hz, 1H); 1.18 (d, J = 7.5 Hz, 3H); 1.12 (d, J = 7.5 Hz, 3H); 0.99 (d, J = 7 Hz, 3H); 0.90 (d, J = 7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 149.73, 132.87, 125.84, 117.46, 79.17, 32.26, 28.83, 22.25, 22.08, 20.42, 17.84.

IR (thin film NaCl): 3456, 3086, 2962, 2933, 2874, 1743, 1729, 1640, 1595, 1466, 1418, 1374, 1244, 1170, 1130, 1105, 1047, 993 cm^{-1}.

HRMS (EI) *m/z* 168.151 [M$^+$; calcd for $C_{11}H_{20}O$: 168.151].



(4*E*)-4-Cyclohexyl-2-methyl-hepta-4,6-dien-3-ol (2.19): In the reductive coupling of **2.8** (136 mg, 1.0 mmol) and isobutyraldehyde (180 μL, 2.0 mmol), the standard procedure was used except that the scale was doubled and (+)-NMDPP (64 mg, 0.2 mmol) was employed as the phosphine ligand. Silica gel chromatography afforded the title compound as a clear oil (131 mg, 63% yield, >95:5 regioselectivity, >95:5 *E*/*Z*). R_f = 0.36 (10:1 hexanes: ethyl acetate).

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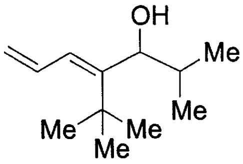
[46] Chincilla, R.; Falvello, L. R.; Galindo, N.; Nájera, C. *J. Org. Chem.* **2000**, *65*, 3034-3041.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 – 6.75 (m, 1H); 6.04 (d, J = 11.5 Hz, 1H); 5.20 (dd, J = 16.5, 2 Hz, 1H); 5.11 (dd, J = 10, 2 Hz, 1H); 3.78 (dd, J = 7, 3.5 Hz, 1H); 2.42 (tt, J = 12, 3.5 Hz, 1H); 1.85 (oct., J = 7 Hz, 1H); 1.82 – 1.59 (m, 4H); 1.54 (dq, J = 12.5, 3.5 Hz, 1H); 1.44 (dq, J = 12.5, 3.5 Hz, 1H); 1.35 – 1.25 (m, 3H); 1.21 (tt, J = 13, 3.5 Hz, 1H); 0.98 (d, J = 6.5 Hz, 3H); 0.89 (d, J = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 149.10, 133.06, 126.11, 117.36, 79.72, 40.02, 32.21, 32.18, 32.08, 27.16, 27.13, 26.33, 20.51, 17.79.

IR (thin film NaCl): 3420, 3084, 2928, 2853, 2668, 1809, 1729, 1636, 1593, 1449, 1420, 1384, 1365, 1260, 1140 cm^{-1}.

HRMS (EI) *m/z* 208.183 [M$^+$; calcd for $C_{14}H_{24}O$: 208.182].



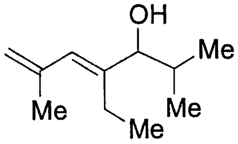
(4*E*)-4-*tert*-Butyl-2-methyl-hepta-4,6-dien-3-ol (2.20): In the reductive coupling of **2.9** (54 mg, 0.5 mmol) and isobutyraldehyde, the standard procedure was used except that (+)-NMDPP (32 mg, 0.1 mmol) was employed as the phosphine ligand. Silica gel chromatography afforded the title compound as a clear oil (63 mg, 69% yield, >95:5 regioselectivity, >95:5 *E*/*Z*). R$_f$ = 0.33 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 – 6.92 (m, 1H); 6.11 (d, J = 11.5 Hz, 1H); 5.13 (dt, J = 16.5, 1 Hz, 1H); 5.10 (dd, J = 10, 2 Hz, 1H); 4.02 (t, J = 5 Hz, 1H); 1.81 (oct., J = 6.5 Hz, 1H); 1.21 (s, 9H); 0.95 (d, J = 6 Hz, 3H); 0.94 (d, J = 7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 150.91, 134.39, 126.12, 118.03, 76.98, 35.96, 33.46, 31.34, 20.55, 16.79.

IR (thin film NaCl): 3432, 3086, 2958, 2872, 1813, 1630, 1584, 1470, 1366, 1230, 1206, 1133 cm^{-1}.

HRMS (EI) *m/z* 182.167 [M$^+$; calcd for $C_{12}H_{22}O$: 182.167].



(4*E*)-4-Ethyl-2,6-dimethyl-hepta-4,6-dien-3-ol (2.21): In the reductive coupling of 2-methyl-1-hexen-3-yne (**2.11**) (47 mg, 0.5 mmol) and isobutyraldehyde, the standard procedure was used. Silica gel chromatography afforded the title compound as a clear oil (60 mg, 71% yield, 95:5 regioselectivity, 95:5 *E*/*Z*). R$_f$ = 0.40 (10:1 hexanes: ethyl acetate).

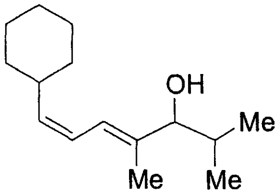
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (s, 1H); 4.96 (sext., J = 1 Hz, 1H); 4.87 (t, J = 1 Hz, 1H); 3.77 (dd, J = 7, 3 Hz, 1H); 2.33 (dq, J = 13.5, 7.5 Hz, 1H); 2.14 (dq, J = 14, 7.5 Hz, 1H);

1.88 (s, 3H); 1.86 (oct., *J* = 7 Hz, 1H); 1.41 (d, *J* = 3.5 Hz, 1H); 1.09 (t, *J* = 7 Hz, 3H); 0.96 (d, *J* = 6.5 Hz, 3H); 0.90 (d, *J* = 7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 144.74, 141.91, 128.18, 114.52, 82.18, 31.94, 23.76, 21.73, 20.11, 17.87, 15.04.

IR (thin film NaCl): 3407, 3081, 2966, 2935, 2873, 1633, 1599, 1464, 1373, 1292, 1246, 1172, 1127, 1071, 1011 cm^{-1}.

HRMS (ESI) *m/z* 267.113 [(M + Na)$^+$; calcd for $C_{13}H_{21}ClO_2$: 267.112] (HRMS was determined for the corresponding chloroacetate derivative).



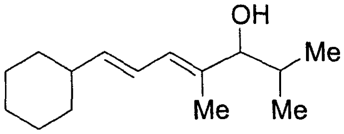
(*Z*),(*E*)-7-cyclohexyl-2,4-dimethyl-hepta-4,6-dien-3-ol (2.22): In the reductive coupling of **2.12** (74 mg, 0.5 mmol) and isobutyraldehyde, the standard procedure was used. Silica gel chromatography afforded the title compound as a clear oil (99 mg, 89% yield, 95:5 regioselectivity, >95:5 *E*/*Z*). R$_f$ = 0.32 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.26 (d, *J* = 12 Hz, 1H); 6.10 (t, *J* = 13 Hz, 1H); 5.32 (t, *J* = 10 Hz, 1H); 3.70 (d, *J* = 8 Hz, 1H); 2.45 (m, 1H); 1.82 (sept., *J* = 7 Hz, 1H); 1.73 (s, 3H); 1.70 – 1.60 (m, 4H); 1.35 – 1.25 (m, 3H); 1.22 – 1.16 (m, 1H); 1.13 – 1.04 (m, 2H); 1.00 (d, *J* = 7 Hz, 3H); 0.82 (d, *J* = 7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.92, 138.63, 122.14, 122.09, 84.18, 36.78, 33.45, 33.40, 31.52, 26.21, 26.07 (two isochronous signals), 19.67, 18.69, 12.05.

IR (thin film NaCl): 3372, 3016, 2924, 2851, 1717, 1605, 1448, 1381, 1317, 1297, 1258, 1101, 1010 cm^{-1}.

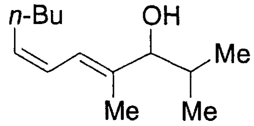
HRMS (EI) *m/z* 222.197 [M$^+$; calcd for $C_{15}H_{26}O$: 222.198].



(*E*),(*E*)-7-cyclohexyl-2,4-dimethyl-hepta-4,6-dien-3-ol (2.23): In the reductive coupling of **2.13** (74 mg, 0.5 mmol) and isobutyraldehyde, the standard procedure was used. Silica gel chromatography afforded the title compound as a clear oil (96 mg, 86% yield, 86:14 regioselectivity, >95:5 *E*/*Z*). R$_f$ = 0.17 (10:1 hexanes: ethyl acetate).

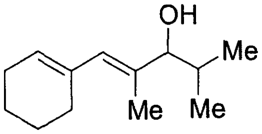
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.22 (dd, *J* = 11, 15 Hz, 1H); 5.96 (d, *J* = 11 Hz, 1H); 5.64 (dd, *J* = 15, 7 Hz, 1H); 3.63 (d, *J* = 6.5 Hz, 1H); 2.05 – 2.00 (m, 1H); 1.81 (sept., *J* = 7 Hz, 1H); 1.64 – 1.76 (m, 7 H); 1.23 – 1.36 (m, 2H); 1.04 – 1.23 (m, 4H); 0.99 (d, *J* = 6.5 Hz, 3H); 0.80 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 141.17, 136.93, 127.34, 123.44, 84.08, 41.32, 33.17, 31.48, 26.35, 26.23, 19.66, 18.76, 12.12.
IR (thin film NaCl): 3407, 2923, 2852, 1676, 1449, 1382, 1296, 1258, 1171, 1104, 1011 cm^{-1}.
HRMS (EI) *m/z* 222.197 [M$^+$; calcd for $C_{15}H_{26}O$: 222.198].



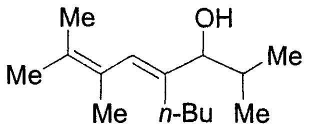
4-Ethyl-2-methyl-undeca-4,6-dien-3-ol (2.24): In the reductive coupling of **2.14** (68 mg, 0.5 mmol) and isobutyraldehyde, the standard procedure was used. Silica gel chromatography afforded the title compound as a clear oil (61 mg, 58% yield, 95:5 regioselectivity, >95:5 *E*/*Z*). R$_f$ = 0.32 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.27 – 6.18 (m, 2H); 5.51 – 5.46 (m, 1H); 3.78 (dd, *J* = 7, 3 Hz, 1H); 2.24 – 2.10 (m, 4H); 1.83 (oct., *J* = 7 Hz, 1H); 1.43 (d, *J* = 3 Hz, 1H); 1.40 – 1.24 (m, 6H); 1.08 (t, *J* = 7.5 Hz, 3H); 0.98 (d, J = 6.5 Hz, 3H); 0.91 (t, *J* = 7 Hz, 3H); 0.87 (d, *J* = 6.5 Hz, 3H).
^{13}C NMR (125 MHz, CDCl$_3$) δ 145.19, 132.62, 123.94, 121.10, 82.83, 32.02, 31.99, 27.50, 22.54, 21.09, 21.11, 18.14, 14.99, 14.20.
IR (thin film NaCl): 3404, 3018, 2960, 2931, 2873, 1717, 1700, 1684, 1670, 1653, 1647, 1604, 1467, 1379, 1366, 1315, 1292, 1258, 1176, 1081, 1049, 1011 cm^{-1}.
HRMS (EI) *m/z* 210.198 [M$^+$; calcd for $C_{14}H_{26}O$: 210.198].



(*E*)-1-cyclohex-1-enyl-2,4-dimethyl-pent-1-en-3-ol (2.25): In the reductive coupling of **2.15** (60 mg, 0.5 mmol) and isobutyraldehyde, the standard procedure was used. Silica gel chromatography afforded the title compound as a clear oil (77 mg, 79% yield, 90:10 regioselectivity). R$_f$ = 0.42 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, CDCl$_3$) δ 5.75 (s, 1H); 5.63 (s, 1H); 3.61 (dd, *J* = 14, 5 Hz, 1H); 2.13 (m, 4H); 1.88 - 1.78 (m, 1H); 1.78 (s, 3H); 1.67 - 1.56 (m, 4H); 1.46 (d, *J* = 5 Hz, 1H); 1.02 (d, *J* = 11 Hz, 3H); 0.83 (d, *J* = 11 Hz, 3H).
^{13}C NMR (125 MHz, CDCl$_3$) δ 136.26, 135.06, 130.19, 127.36, 84.94, 31.47, 29.47, 25.80, 23.14, 22.37, 19.72, 18.85, 13.36.
IR (thin film NaCl): 3379, 3026, 2927, 2870, 2834, 1648, 1459, 1448, 1437, 1380, 1366, 1296, 1243, 1170, 1133, 1113, 1077, 1010 cm^{-1}.
HRMS (EI) *m/z* 194.167 [M$^+$; calcd for $C_{13}H_{22}O$: 194.167].



(*E*)-(*E*)-4-butyl-2,6,7-trimethyl-octa-4,6-dien-3-ol (2.26): In the reductive coupling of **2.16** (75 mg, 0.5 mmol) with isobutyraldehyde, the standard procedure was used except that (+)-NMDPP (64 mg, 0.2 mmol) was employed as the phosphine ligand. After 6 h, standard work-up followed by silica gel chromatography afforded the title compound as a clear oil (99 mg, 88% yield, 95:5 regioselectivity, >95:5 *E*/*Z*). R_f = 0.36 (10:1 hexanes: ethyl acetate).

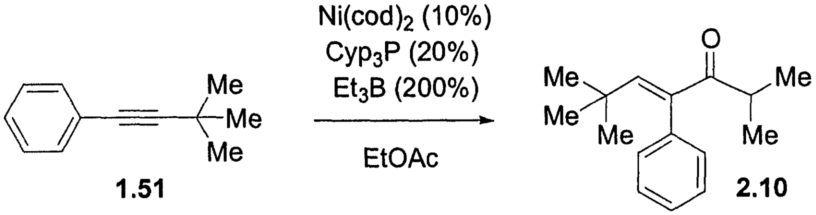
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92 (s, 1H); 3.75 (ddd, *J* = 7, 4, 1 Hz, 1H); 1.99 – 2.05 (m, 1H); 1.90 – 1.82 (m, 2H); 1.70 (bs, 6H); 1.62 (bs, 3H); 1.24 – 1.40 (m, 5H); 0.96 (d, *J* = 7 Hz, 3H); 0.91 (d, *J* = 7 Hz, 3H); 0.88 (t, *J* = 7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 141.69, 129.16, 126.97, 125.80, 81.53, 31.89, 31.27, 28.97, 23.45, 22.12, 20.14, 19.08, 17.88, 14.12.

IR (thin film NaCl): 3432, 2959, 2872, 2723, 1629, 1467, 1379, 1290, 1247, 1168, 1128, 1010 cm^{-1}.

HRMS (ESI) *m/z* 247.204 [$(M + Na)^+$; calcd for $C_{15}H_{28}O$: 247.203].

Attempted Reductive Coupling of 1.51.



2,6,6-Trimethyl-4-phenyl-hept-4-en-3-one (2.10): In a glovebox, $Ni(cod)_2$ (14 mg, 0.5 mmol), and Bu_3P (28 μL, 0.1 mmol) were placed into a 25 mL oven-dried, single-necked round-bottom flask, which was then sealed with a rubber septum. The flask was removed from the glovebox, placed under argon, and ethyl acetate (0.5 mL) was added via syringe, followed immediately by Et_3B (0.15 mL, 1.0 mmol). Isobutyraldehyde (90 μL, 1.0 mmol) was added dropwise via microsyringe at room temperature. After stirring 5 min, 1-phenyl-3,3-dimethyl-1-butyne (**1.51**, 0.5 mmol) was added. After 15 h, the septa was removed and the reaction opened to air for 30 min to promote quenching of the catalyst. Purification by flash chromatography on silica gel (hexanes: ethyl acetate; 50:1 to 10:1 gradient) afforded the title compound as a clear oil (38 mg, 33% yield, >95:5 regioselectivity). No desired allylic alcohol was observed, and regioselectivity of enone formation was confirmed by ozonolysis of **2.10** (3-methyl-1-phenyl-butane-1,2-dione[47] was isolated in 37% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.36 (m, 3H); 7.13 – 7.15 (m, 2H); 6.80 (s, 1H); 2.98 (sept., *J* = 7 Hz, 1H); 1.02 (d, *J* = 7 Hz, 6H); 0.93 (s, 9H).

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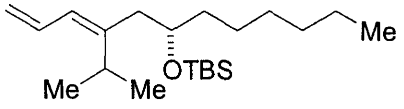
[47] Chang, C.-L.; Kumar, M. P.; Liu, R.-S. *J. Org. Chem.* **2004**, *69*, 2793-2796.

^{13}C NMR (125 MHz, $CDCl_3$) δ 206.65, 151.06, 139.45, 137.44, 130.33, 127.99, 127.47, 35.49, 34.45, 30.72, 19.38.

Reductive Coupling of 1,3-Enynes and Epoxides.



(3*E*)-*tert*-Butyl-(1-hexyl-3-isopropyl-hexa-3,5-dienyloxy)-dimethyl-silane (2.28): To $Ni(cod)_2$ (27 mg, 0.098 mmol) at 23 °C were added PBu_3 (40 μL, 0.16 mmol), Et_3B (200 μL, 2.11 mmol), (*S*)-1,2-epoxyoctane[48] (**2.27**, 100 μL, 0.65 mmol), and **2.7** (162 mg, 1.72 mmol). The brownish solution was stirred at 23 °C for 42 h. Et_2O (2 mL) was added, and the resulting solution was quenched with 2M aqueous NaOH (2 mL) and 30% aqueous H_2O_2 (drops). The resulting biphasic solution was vigorously stirred for 5 min. The layers were separated and the organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes to 19:1 hexanes:Et_2O solvent gradient) and protected as the TBS ether (TBSCl (140 mg, 1.42 mmol), imidazole (130 mg, 1.91 mmol), DMAP (130 mg, 1.06 mmol), THF (0.75 mL), DMF (0.25 mL)) to afford the title compound as a yellow liquid (112 mg, 51% yield, >95:5 regioselectivity, >99% ee).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.64 – 6.72 (m, 1H); 5.81 (d, J = 11.5 Hz, 1H); 5.10 (dd, J = 16.5, 1.5 Hz, 1H); 5.00 (dd, J = 10, 1.5 Hz, 1H); 3.82 (quin., J = 6 Hz, 1H); 3.01 (sept., J = 7 Hz, 1H); 2.18 (dd, J = 14.5, 6.5 Hz, 1H); 2.11 (dd, J = 15, 6.5 Hz, 1H); 1.24 – 1.55 (m, 10 H); 1.03 (d, J = 6.5 Hz, 3H); 1.01 (d, J = 6.5 Hz, 3H); 0.87 – 0.92 (m, 12H); 0.05 (s, 3H); 0.04 (s, 3H).

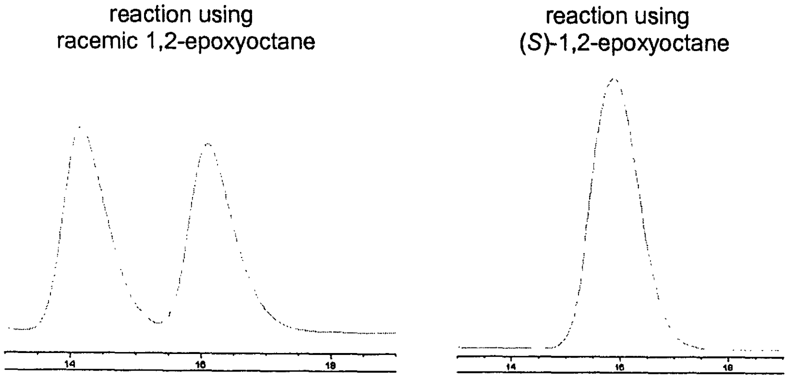
^{13}C NMR (125 MHz, $CDCl_3$) δ 145.24, 132.80, 127.23, 115.34, 72.00, 40.36, 37.40, 32.13, 29.74, 29.70, 26.16, 25.50, 22.86, 21.82, 21.23, 18.33, 14.34, -3.97, -4.19.

IR (thin film NaCl): 3085, 2958, 2929, 2857, 1800, 1638, 1592, 1463, 1378, 1361, 1254, 1092 cm^{-1}.

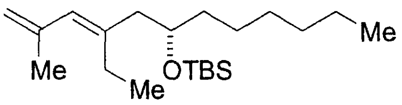
HRMS (ESI) *m/z* 361.289 [(M + Na)$^+$; calcd for $C_{21}H_{42}OSi$: 361.290].

$[\alpha]_D = -1.0$ (*c* 1.0, $CHCl_3$).

Chiral HPLC analysis:



HPLC (chiralcel-OD : 0.1% *i*PrOH/hexanes, 0.7 mL/min)



(3*E*)-*tert*-Butyl-(3-ethyl-1-hexyl-5-methyl-hexa-3,5-dienyloxy)-dimethyl-silane (2.29): To Ni(cod)$_2$ (22 mg, 0.08 mmol) at 23 °C were added PBu$_3$ (40 μL, 0.16 mmol), Et$_3$B (240 μL, 1.66 mmol), (*S*)-1,2-epoxyoctane[48] (**2.27**, 180 μL, 1.00 mmol), and **2.11** (100 μL, 0.80 mmol). The brownish solution was stirred 24 h at room temperature. Et$_2$O (2 mL) was added, and the resulting solution was quenched with 2M aqueous NaOH (2 mL) and 30% aqueous H$_2$O$_2$ (drops). The resulting biphasic solution was vigorously stirred for 5 min. The layers were separated and the organic phase was dried over MgSO$_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes to 19:1 hexanes:Et$_2$O solvent gradient) and protected as the TBS ether (TBSCl (225 mg, 1.50 mmol), imidazole (103 mg, 1.50 mmol), DMAP (183 mg, 1.50 mmol), and DMF (0.75 mL)) to afford the title compound as a clear liquid (135 mg, 50% yield, >95:5 regioselectivity, >99% ee). R_f = 0.13 (hexanes).

^{1}H NMR (500 MHz, CDCl$_3$) δ 5.64 (s, 1H); 4.90 (m, 1H); 4.76 (s, 1H); 3.77 (quin., *J* = 6 Hz, 1H); 2.12 – 2.25 (m, 4H); 1.84 (s, 3H); 1.25 – 1.50 (m, 10H); 1.02 (t, *J* = 7.5 Hz, 3H); 0.89 (t, *J* = 7.5 Hz, 3H); 0.89 (s, 9H); 0.05 (s, 3H); 0.03 (s, 3H).

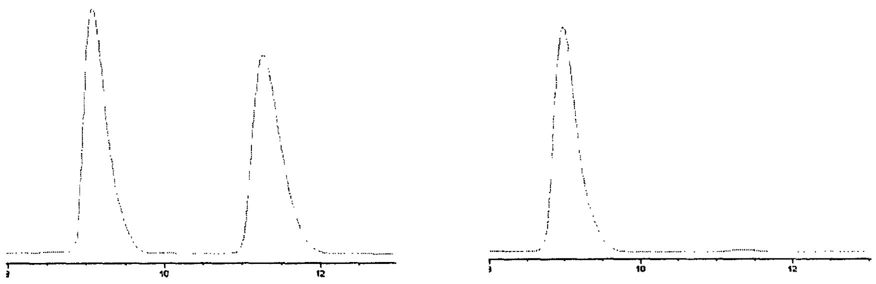
^{13}C NMR (125 MHz, CDCl$_3$) δ 142.32, 140.96, 129.97, 113.53, 71.54, 44.98, 37.45, 32.11, 29.71, 26.14, 25.45, 24.41, 23.94, 22.86, 18.35, 14.34, 13.88, –4.20, –4.29.

IR (thin film NaCl): 3.082, 2959, 2930, 2858, 1634, 1463, 1406, 1374, 1361, 1254, 1187, 1094, 1005 cm^{-1}.

HRMS (ESI) *m/z* 361.2891 [(M + Na)$^+$; calcd for C$_{21}$H$_{42}$OSi: 361.2891]. [α]$_D$ = –0.5 (*c* 1.0, CHCl$_3$).

[α]$_D$ = –0.5 (*c* 1.0, CHCl$_3$).

Chiral HPLC analysis was performed on the corresponding alcohol:



reaction using racemic 1,2-epoxyoctane

reaction using (*S*)-1,2-epoxyoctane

HPLC (chiralcel-OD : 0.2% *i*PrOH/hexanes, 1mL/min)

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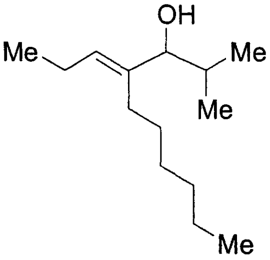
[48] Prepared via hydrolytic kinetic resolution: (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936-938; (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307-1315.

Standard Experimental Procedure for the Site-Selective Hydrogenation of 1,3-Dienes: In a glovebox, $RhCl(PPh_3)_3$ (11 mg, 0.012 mmol) was added to a 10 mL, oven-dried round-bottom flask. The flask was then removed from the glovebox and a solution of dienol (0.12 mmol) in toluene (1 mL) was added. H_2 was bubbled through the solution for 2-3 min, and it was then stirred under a balloon of H_2 until the reaction was complete by TLC analysis (2-3 h). The solution was then passed through a plug of Celite (EtOAc eluant), concentrated under reduced pressure, and purified by flash chromatography on silica gel using a solvent gradient (50:1 to 10:1 hexanes: EtOAc). Note: Certain dienes required higher pressures of H_2 to effect reduction; in these cases, a Lab-Crest® Pressure Reaction Vessel was employed.



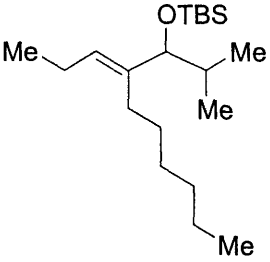
(*E*)-4-Hexyl-2-methyl-hept-4-en-3-ol (2.31): Using the standard procedure, $RhCl(PPh_3)_3$ (11 mg, 0.012 mmol) and **2.5** (25 mg, 0.12 mmol) after 3 h provided the title compound as a clear oil (23 mg, 92% yield). R_f = 0.41 (10:1 hexanes: ethyl acetate).

^1H NMR (500 MHz, $CDCl_3$) δ 5.34 (t, *J* = 7 Hz, 1H); 3.64 (d, *J* = 8 Hz, 1H); 2.09 – 1.92 (m, 4H); 1.78 (oct., *J* = 7 Hz, 1H); 1.42 – 1.24 (m, 8H); 0.98 (t, *J* = 8 Hz, 3H); 0.96 (d, *J* = 7 Hz, 3H); 0.89 (t, *J* = 7 Hz, 3H); 0.84 (d, *J* = 7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 140.83, 129.53, 82.93, 31.94, 31.79, 30.36, 30.20, 28.06, 22.91, 21.07, 20.09, 18.29, 14.65, 14.33.

IR (thin film NaCl): 3624, 3417, 2959, 2930, 2872, 1728, 1660, 1467, 1379, 1366, 1295, 1260, 1170, 1100, 1068, 1012 cm^{-1}.

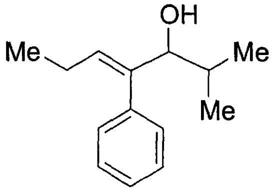
HRMS (ESI) *m/z* 235.203 [$(M + Na)^+$; calcd for $C_{14}H_{28}O$: 235.203].



***tert*-Butyl-(1-isopropyl-2-propylidene-octyloxy)-dimethyl silane (2.33):** A solution of **2.5** (0.25 mmol, 52 mg) and 2,6-lutidine (0.75 mmol, 87 μL) in CH_2Cl_2 (1.25 mL) was cooled to –78 °C and TBSOTf (0.38 mmol, 86 μL) was added. After 1 h, H_2O (5 mL) was added, and the organics were extracted with Et_2O (3 x 5 mL). The organics were dried and concentrated, and the crude mixture was purified by passing through a plug of silica gel (hexanes eluant) to afford the desired TBS ether (62 mg, 77 % yield). Then, using the standard procedure, **OTBS-2.5** (47 mg, 0.14 mmol) was hydrogenated with $RhCl(PPh_3)_3$ (13 mg, 0.014 mmol) and H_2 (1 atm) to afford after 2 h the title compound as a clear oil (40 mg, 85% yield). R_f = 0.41 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.24 (t, *J* = 7 Hz, 1H); 3.57 (d, *J* = 6.5 Hz, 1H); 2.06 – 1.99 (m, 2H); 1.97 – 1.89 (m, 2H); 1.69 (oct., *J* = 6.5 Hz, 1H); 1.40 – 1.25 (m, 8 H); 0.97 (t, *J* = 7.5 Hz, 3H); 0.90 (s, 9H); 0.86 (d, *J* = 7 Hz, 1H); 0.80 (d, *J* = 6.5 Hz, 1H); 0.02 (s, 3H); –0.04 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 140.07, 129.18, 83.36, 32.21, 31.99, 30.43, 30.19, 27.73, 26.20, 25.92, 22.95, 21.05, 20.35, 18.25, 14.61, 14.35, –3.96, –4.80.



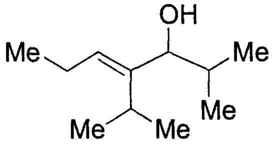
(*E*)-4-Phenyl-2-methyl-hept-4-en-3-ol (2.34): $RhCl(PPh_3)_3$ (14 mg, 0.015 mmol) and a solution of **2.17** (30 mg, 0.15 mmol) in toluene (1 mL) was placed in a reaction vessel and the vessel was charged with H_2 (3 atm). After 15 h, silica gel chromatography provided the title compound as a clear oil (24 mg, 80% yield). R_f = 0.32 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.37 (m, 2H); 7.26 – 7.31 (m, 1H); 7.17 – 7.20 (m, 2H); 5.68 (dt, *J* = 7.5 Hz, 1H); 4.00 (dd, *J* = 6, 6 Hz, 1H); 1.90 – 1.98 (m, 2H); 1.56 (sept., *J* = 6.5 Hz, 1H); 1.55 (d, *J* = 5 Hz, 1H); 0.95 (t, *J* = 7.5 Hz, 3H); 0.91 (d, *J* = 7 Hz, 3H); 0.90 (d, *J* = 7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 142.16, 138.98, 131.30, 129.41, 128.26, 127.03, 82.37, 31.88, 22.13, 20.07, 17.24, 14.64.

IR (thin film NaCl): 3418, 3080, 3056, 3022, 2961, 2871, 1947, 1809, 1600, 1574, 1494, 1461, 1442, 1385, 1366, 1292, 1259, 1174, 1142, 1123, 1082, 1012 cm^{-1}.

HRMS (ESI) *m/z* 227.140 [(M + Na)$^+$; calcd for $C_{14}H_{20}O$: 227.141].



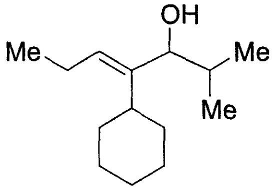
(*E*)-4-Isopropyl-2-methyl-hept-4-en-3-ol (2.35): Using the standard procedure, $RhCl(PPh_3)_3$ (12 mg, 0.013 mmol), **2.18** (43 mg, 0.25 mmol), and toluene (1.5 mL) after 2 h provided the title compound as a clear oil (33 mg, 76% yield). R_f = 0.38 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35 (t, *J* = 7 Hz, 1H); 3.64 (d, *J* = 8 Hz, 1H); 2.68 (sept., *J* = 7 Hz, 1H); 2.14 (dq, *J* = 7.5, 7.5 Hz, 1H); 2.13 (dq, *J* = 7.5, 7.5 Hz, 1H); 1.81 (oct., *J* = 7 Hz, 1H); 1.12 (d, *J* = 7.5 Hz, 3H); 1.05 (d, *J* = 7 Hz, 3H); 0.99 (d, *J* = 6.5 Hz, 3H); 0.99 (t, *J* = 7.5 Hz, 3H); 0.85 (d, *J* = 7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 145.99, 128.37, 79.46, 32.25, 28.19, 22.15, 21.80, 21.17, 20.47, 18.31, 14.76.

IR (thin film NaCl): 3616, 3406, 2961, 2933, 2873, 1730, 1661, 1465, 1382, 1365, 1291, 1252, 1169, 1109, 1067, 1013 cm^{-1}.

HRMS (EI) *m/z* 170.165[M$^+$; calcd for $C_{11}H_{22}O$: 170.167].



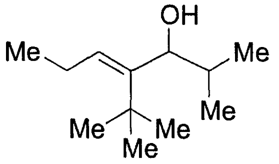
(*E*)-4-Cyclohexyl-2-methyl-hept-4-en-3-ol (2.36): Using the standard procedure, $RhCl(PPh_3)_3$ (17 mg, 0.018 mmol) and **2.19** (38 mg, 0.18 mmol) after 2.5 h afforded the title compound as a clear oil (33 mg, 87% yield). R_f = 0.34 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35 (t, *J* = 7.5 Hz, 1H); 3.65 (d, *J* = 8 Hz, 1H); 2.28 (tt, *J* = 12.5, 4 Hz, 1H); 2.15 (dq, *J* = 7.5, 7.5 Hz, 1H); 2.14 (dq, *J* = 7.5, 7.5 Hz, 1H); 1.81 (oct., *J* = 6.5 Hz, 1H); 1.79 – 1.52 (m, 4H); 1.50 (dq, *J* = 12.5, 4 Hz, 1H); 1.39 (dq, *J* = 12.5, 3.5 Hz, 1H); 1.34 – 1.12 (m, 4H); 0.99 (t, *J* = 7.5 Hz, 3H); 0.98 (d, *J* = 6.5 Hz, 3H); 0.85 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 145.32, 128.74, 80.13, 39.41, 32.17, 32.09, 31.80, 27.73, 27.22, 26.41, 21.37, 20.54, 18.27, 14.90.

IR (thin film NaCl): 3615, 3428, 2958, 2928, 2870, 2853, 1448, 1382, 1365, 1292, 1260, 1170, 1010 cm^{-1}.

HRMS (EI) *m/z* 210.197 [M$^+$; calcd for $C_{16}H_{26}O$: 210.198].



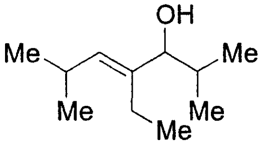
(*E*)-4-*tert*-Butyl-2-methyl-hept-4-en-3-ol (2.37): Using the standard procedure, $RhCl(PPh_3)_3$ (11 mg, 0.012 mmol) and **2.20** (23 mg, 0.124 mmol) after 1.5 h provided the title compound as a clear oil (19 mg, 83% yield). R_f = 0.30 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.40 (t, *J* = 7.5 Hz, 1H); 3.92 (t, *J* = 6 Hz, 1H); 2.40 – 2.23 (m, 2H); 1.80 (oct., *J* = 6.5 Hz, 1H); 1.18 (s, 9H); 1.00 (t, *J* = 7 Hz, 3H); 0.95 (d, *J* = 7 Hz, 3H); 0.90 (d, *J* = 7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 147.40, 128.98, 77.32, 35.48, 33.38, 30.91, 22.98, 20.58, 17.13, 15.09.

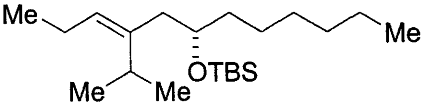
IR (thin film NaCl): 3612, 3424, 2959, 2872, 1727, 1641, 1469, 1397, 1383, 1364, 1305, 1260, 1228, 1198, 1173, 1122, 1099, 1015, 993 cm^{-1}.

HRMS (EI) *m/z* 184.182 [M$^+$; calcd for $C_{12}H_{24}O$: 184.182].



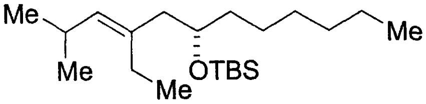
(*E*)-4-Ethyl-2,6-dimethyl-hept-4-en-3-ol (2.38): $RhCl(PPh_3)_3$ (17 mg, 0.018 mmol) and a solution of **2.21** (31 mg, 0.19 mmol) in toluene (1 mL) were placed in a reaction vessel and the vessel was charged with H_2 (3 atm). After 2 h, silica gel chromatography provided the title compound as a clear oil (30 mg, 96% yield). R_f = 0.31 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.14 (d, *J* = 10 Hz, 1H); 3.63 (d, *J* = 7 Hz, 1H); 2.62 – 2.54 (m, 1H); 2.10 – 1.99 (m, 2H); 1.78 (oct., *J* = 7 Hz, 1H); 1.73 (d, *J* = 2.5 Hz, 1H); 1.04 (t, *J* = 8 Hz, 3H); 0.98 (d, *J* = 7 Hz, 3H); 0.96 (d, *J* = 1.5 Hz, 3H); 0.95 (d, *J* = 1 Hz, 3H); 0.84 (d, *J* = 6.5 Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 140.07, 135.18, 82.90, 31.78, 26.95, 23.53, 23.46, 20.79, 20.09, 18.30, 15.43.
IR (thin film NaCl): 3395, 2960, 2871, 1467, 1378, 1363, 1293, 1248, 1169, 1131, 1102, 1070, 1018 cm^{-1}.
HRMS (ESI) *m/z* 170.166 [(M + Na)$^+$; calcd for $C_{11}H_{22}O$: 170.167].



(*E*)-*tert*-Butyl-(1-hexyl-3-isopropyl-hex-3-enyloxy)-dimethyl-silane (2.39): Using the standard procedure, $RhCl(PPh_3)_3$ (6 mg, 6.5 μmol) and **2.28** (46 mg, 0.14 mmol) after 2.5 h provided the title compound as a clear oil (39 mg, 85% yield). R_f = 0.18 (hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.07 (t, *J* = 7 Hz, 1H); 3.76 – 3.81 (m, 1H); 2.78 (sept., *J* = 7 Hz, 1H); 2.14 (dd, *J* = 14, 5 Hz, 1H); 1.95 – 2.08 (m, 3H); 1.24 – 1.56 (m, 10 H); 0.94 – 0.99 (m, 9H); 0.87 – 0.92 (m, 12H); 0.06 (s, 3H); 0.05 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 140.54, 128.42, 72.09, 40.62, 36.89, 32.13, 29.69, 29.15, 26.19, 25.51, 22.88, 21.85, 21.34, 20.88, 18.37, 14.92, 14.35, -3.92, -4.17.
IR (thin film NaCl): 2960, 2858, 1653, 1463, 1406, 1378, 1361, 1306, 1254, 1092, 1065, 1005 cm^{-1}.
HRMS (ESI) *m/z* 363.305 [(M + Na)$^+$; calcd for $C_{21}H_{44}OSi$: 363.305].
$[\alpha]_D = -1.3$ (*c* 1.0, $CHCl_3$).



(*E*)-*tert*-Butyl-(3-ethyl-1-hexyl-5-methyl-hex-3-enyloxy)-dimethyl-silane (2.40): $RhCl(PPh_3)_3$ (14 mg, 0.015 mmol) and a solution of **2.29** (50 mg, 0.15 mmol) in toluene (1 mL) were added to a reaction vessel and the vessel was charged with H_2 (3 atm). After 16 h, the solution was condensed and then purified via flash chromatography on silica gel (hexanes) to provide the title compound as a clear oil (47 mg, 94% yield). R_f = 0.17 (hexanes).

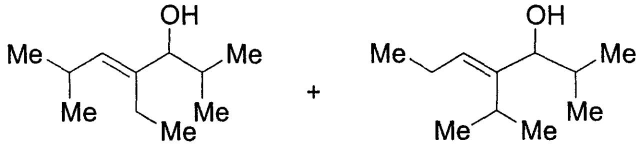
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.93 (d, *J* = 9 Hz, 1H); 3.72 (quin., *J* = 6 Hz, 1H); 2.48 – 2.55 (m, 1H); 2.15 (ddd, *J* = 14, 6.5, 1 Hz, 1H); 1.95 - 2.10 (m, 3H); 1.24 - 1.45 (m, 10 H); 0.97 (t, *J* = 8 Hz, 3H); 0.94 (d, *J* = 6.5 Hz, 3H); 0.93 (d, *J* = 6.5 Hz, 3H); 0.89 (t, *J* = 7 Hz, 3H); 0.89 (s, 9H); 0.04 (s, 3H); 0.04 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 136.03, 135.19, 71.61, 44.66, 36.98, 32.10, 29.94, 29.69, 27.07, 26.16, 25.41, 23.76, 23.68, 23.65, 22.86, 18.37, 14.34, 13.90, -4.15, -4.29.

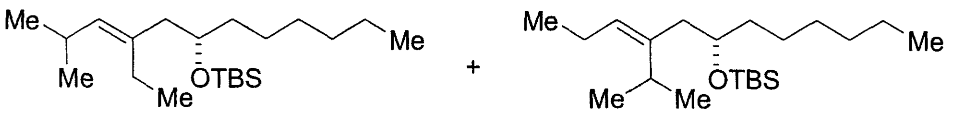
IR (thin film NaCl): 2958, 2858, 2709, 1740, 1662, 1465, 1406, 1376, 1361, 1255, 1190, 1093, 1005 cm^{-1}.

HRMS (ESI) *m/z* 363.3051 [(M + Na)$^+$; calcd for $C_{21}H_{44}OSi$: 363.3054].

$[\alpha]_D$ = –0.4 (*c* 1.0, $CHCl_3$).



Reductive coupling of 2-methyl-3-hexyne with isobutyraldehyde (2.38 + 2.35): In a glovebox, $Ni(cod)_2$ (14 mg, 0.5 mmol), and Cyp_3P (28 μL, 0.1 mmol) were placed into a 25 mL oven-dried, single-necked round-bottom flask, which was then sealed with a rubber septum. The flask was removed from the glovebox and placed under argon, and ethyl acetate (0.5 mL) was added via syringe, followed immediately by Et_3B (0.15 mL, 1 mmol). The resulting solution was stirred 5 min at ambient temperature and then cooled to 0 °C. Once the solution had cooled, isobutyraldehyde (90 μL, 1.0 mmol) was added dropwise via microsyringe. After stirring 5 min, 2-methyl-3-hexyne (48 mg, 0.5 mmol) was added. The reaction was allowed to gradually warm to 23 °C over 6 h. The septa was then removed, and the reaction was opened to air for 30 min to promote quenching of the catalyst. The crude mixture was purified by flash chromatography on silica gel using a solvent gradient (hexanes: ethyl acetate; 50:1 to 10:1) to afford a clear oil (64 mg, 75% yield) that was a 1.7:1 mixture of regioisomers **2.38** and **2.35**, respectively.



Reductive coupling of 2-methyl-3-hexyne with 1,2-epoxyoctane (2.30 + 2.29): To $Ni(cod)_2$ (55.8 mg, 0.20 mmol) at 23 °C were added PBu_3 (100 μL, 0.40 mmol), Et_3B (610 μL, 4.21 mmol), 1,2-epoxyoctane (380 μL, 2.49 mmol), and 2-methyl-3-hexyne (200 mg, 2.08 mmol). The brownish solution was stirred at 23 °C for 16 h. Et_2O (4 mL) was added, and the resulting solution was quenched with 2M aqueous NaOH (4 mL) and 30% aqueous H_2O_2 (drops). The resulting biphasic solution was vigorously stirred for 5 min. The layers were separated and the organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes to 9:1 hexanes:EtOAc solvent gradient) and protected as the TBS ether [TBSCl (395 mg, 2.62 mmol), imidazole (304 mg, 4.46 mmol), THF (10 mL), DMF (5 mL)] to afford a colorless liquid (344 mg, 49%) that was a 2:1 mixture of regioisomers **2.30** and **2.29**, respectively.

Chapter 3

Catalytic, Asymmetric Reductive Coupling Reactions of 1,3-Enynes: Enantioselective Synthesis of Chiral 1,3-Dienes

Introduction

1,3-Dienes are important and versatile intermediates in organic synthesis. They are able participants in an array of cycloaddition reactions, most notably the Diels-Alder reaction,[1,2,3] and there are a variety of efficient methods for preparing them.[4] Many of these, such as olefination reactions,[5,6] cross-couplings,[7,8] alkene/enyne metathesis,[9] and others,[10] facilitate convergent synthesis because they simultaneously construct a new carbon-carbon bond. Recently, our laboratory[11] and others[12] reported a new strategy for the synthesis of 1,3-dienes via transition metal-catalyzed reductive coupling reactions of 1,3-enynes and aldehydes. In addition to forming a new carbon-carbon bond, these methods also generate a stereogenic center,[13] allowing for efficient construction of chiral 1,3-dienes that have been widely employed in diastereoselective Diels-Alder reactions.[14,15]

---

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[3] (a) Oppolzer, W., in *Comprehensive Organic Synthesis,* Trost, B. M.; Fleming, I.; Eds. Pergamon Press: Oxford, U. K., 1991, Vol. 5, Chapter 4.1, pp. 315-400; (b) Roush, W. R. in *Comprehensive Organic Synthesis,* Trost, B. M.; Fleming, I.; Eds. Pergamon Press: Oxford, U. K., 1991, Vol. 5, Chapter 4.4, pp. 513-550.

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[11] See Chapter 2 and: Miller, K. M.; Luanphaisarnnont, T.; Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 4130-4131.

[12] (a) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698-3699; (b) Jang, H. Y.; Huddleston, R. R.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4664-4668.

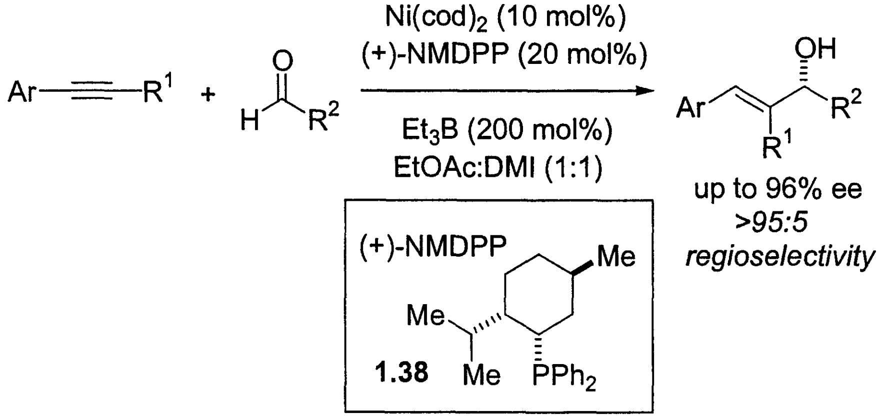
[13] For the synthesis of conjugated dienols via sequential Ni-catalyzed couplings, see: (a) Lozanov, M.; Montgomery, J. *J. Am. Chem. Soc.* **2002**, *124*, 2106-2107; (b) Ni, Y. K.; Amarasinghe, K. K. D.; Montgomery, J. *Org. Lett.* **2002**, *4*, 1743-1745.

[14] For leading references on chiral 1-substituted-1,3-dienes in intermolecular Diels-Alder reactions, see: (a) Barriault, L.; Thomas, J. D. O.; Clement, R. *J. Org. Chem.* **2003**, *68*, 2317-2323; (b) Adam, W.; Glaser, J.; Peters, K.; Prein, M. *J. Am. Chem. Soc.* **1995**, *117*, 9190-9193; (c) Datta, S. C.; Franck, R. W.; Tripathy, R.; Quigley, G. J.; Huang, L.; Chen, S.; Sihaed, A. *J. Am. Chem. Soc.* **1990**, *112*, 8472-8478; (d) Fisher, M. J.;

Previous work from our laboratory has shown that nickel-catalyzed reductive couplings of aryl-substituted alkynes (Ar–C≡C–R) with aldehydes are highly enantioselective when (+)-neomenthyldiphenylphosphine (NMDPP, **1.38**) is employed as a chiral ligand (Scheme 1).[16] We have also described a class of *P*-chiral, monodentate ferrocenyl phosphines (e.g., **3.1**, **3.2**; Figure 1) that are efficient promoters of related couplings of aliphatic internal alkynes (Alkyl–C≡C–Alkyl') and aldehydes,[17] and of multi-component coupling reactions of alkynes, imines, and organoboron reagents.[18]

The investigation of these chiral phosphines as ligands in reductive coupling reactions of 1,3-enynes has led to the development of methods for the catalytic, asymmetric reductive coupling of 1,3-enynes with both aldehydes *and ketones*. The latter represents the first catalytic intermolecular reductive coupling of alkynes and ketones, asymmetric or otherwise, to be reported and affords 1,3-dienes with an adjacent quaternary stereogenic center in excellent regioselectivity and modest enantioselectivity.

Scheme 1. Asymmetric, nickel-catalyzed reductive coupling of aryl alkynes and aldehydes.



Hehre, W. J.; Kahn, S. D.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4625-4633; (e) Tripathy, R.;. Franck, R. W.; Onan, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 3257-3262.

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[16] See Chapter 1 and: (a) Miller, K. M.; Huang, W. S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442-3443; (b) Miller, K. M.; Molinaro, C.; Jamison, T. F. *Tetrahedron: Asymmetry* **2003**, *14*, 3619-3625.

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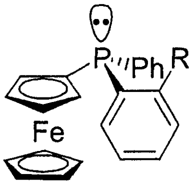
[18] Patel, S. J.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2004**, *43*, 3941-3944.

Figure 1.



(*R*)-**3.1** R = Me
(*R*)-**3.2** R = *i*-Pr

Catalytic Asymmetric Reductive Coupling of 1,3-Enynes and Aldehydes[19]

(+)-NMDPP Evaluation

Reductive couplings of a series of previously investigated 1,3-enynes[20] and isobutyraldehyde that were carried out using (+)-NMDPP as a chiral ligand afforded high regioselectivities and good to moderate yields, but enantioselectivities were typically quite low (Table 1). Aliphatic and aromatic aldehydes exhibited similarly poor selectivities, as demonstrated by the coupling of 2-methyl-1-hexen-3-yne (**2.11**) with both isobutyraldehyde and benzaldehyde (entries 5 and 6). However, enantioselectivity did increase with substitution on the alkene. 1-Prop-1-ynyl-cyclohexene (**2.15**) afforded coupling product in high yield and 68% ee when the previously optimized conditions[16] for the catalytic, asymmetric reductive coupling of aryl-substituted alkynes (Ar-C≡C-R) were employed (entry 8), and enyne **2.16**, containing a tetrasubstituted alkene, provided dienol **2.26** in 70% ee (entry 9).

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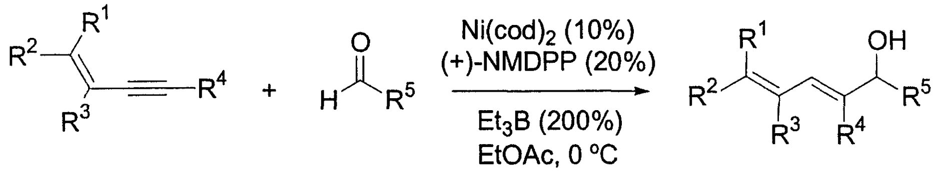
[19] This portion of the work was done in collaboration with Ms. Elizabeth A. Colby and Ms. Katrina S. Woodin.

[20] See Chapter 2 and ref 11.

Table 1. Catalytic, asymmetric reductive coupling of 1,3-enynes and aldehydes using (+)-NMDPP.[a]



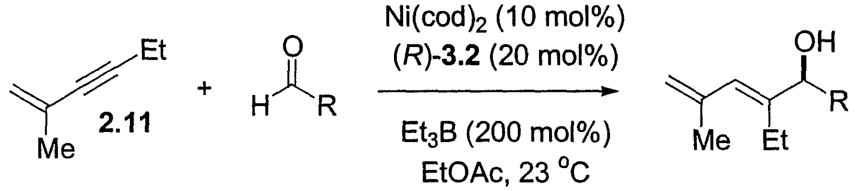
entry	R^1	R^2	R^3	R^4	enyne	R^5	dienol	Yield (%), Regioselectivity	ee (%)
1	H	H	H	*n*-Hex	**2.4**	*i*-Pr	**2.5**	70 (>95:5)	<5
2	"	"	"	*i*-Pr	**2.7**	"	**2.18**	37 (>95:5)	13
3	"	"	"	Cy	**2.8**	"	**2.19**	63 (>95:5)	17
4	"	"	"	*t*-Bu	**2.9**	"	**2.20**	69 (>95:5)	19
5	"	"	Me	Et	**2.11**	"	**2.21**	23 (>95:5)	15
6	"	"	"	"	**2.11**	Ph	**3.3**	16 (>95:5)	8
7	n-Bu	"	H	Et	**2.14**	*i*-Pr	**2.24**	61 (>95:5)	30
8[b]	H	$-C_4H_8-$		Me	**2.15**	"	**2.25**	80 (95:5)	68
9[b]	Me	Me	Me	Me	**2.16**	"	**2.26**	43 (>95:5)	70

[a] Experimental Procedure (see Supporting Information): A solution of $Ni(cod)_2$ (0.05 mmol), (+)-NMDPP (0.10 mmol) and Et_3B (1 mmol) in EtOAc (0.5 mL) was cooled to 0 °C. An enyne (0.50 mmol) followed by an aldehyde (1.0 mmol) were added via syringe, and the solution was stirred 6 h at 0 °C. Products were isolated following silica gel chromatography. Regioselectivities were determined by ^1H NMR and enantioselectivities by either chiral HPLC or chiral GC. [b] Experiment was run at −25 °C using 1:1 EtOAc:DMI (1 mL) as solvent and *i*-PrCHO was added over 8 h.

P-Chiral Ferrocenyl Monophosphine Evaluation

Reductive couplings of the commercially available enyne **2.11** were then investigated in the presence of *P*-chiral ferrocenyl monodentate phosphine ligands **3.1** and **3.2**. The coupling of **2.11** and isobutyraldehyde proceeded in very low enantioselectivity in the presence of ferrocenyl phosphine **3.1**, but regioselectivity remained high (Table 2, entry 1). When *benzaldehyde* was used, better enantioselectivity was observed (entry 2), and *ortho*-isopropylphenyl-substituted ferrocenyl phosphine **3.2** provided even higher levels of both reactivity and enantioselectivity (entry 3). A variety of aromatic aldehydes undergo reductive coupling with **2.11** under these conditions in excellent regioselectivity and modest enantioselectivity. Both electron-donating

Table 2. Catalytic, asymmetric reductive coupling reactions of **2.11** and aldehydes using *P*-chiral ferrocenyl monophosphine **3.2**.[a]



Entry	R	Dienol	Yield [%],[b] Regioselectivity[c]	ee [%][d]
1[e]	*i*-Pr	**2.21**	73 (>95:5)	9
2[e]	Ph	**3.3**	61 (>95:5)	36
3	"	"	66 (>95:5)	56[f]
4	*o*-MePh	**3.4**	71 (>95:5)	54
5	*p*-MePh	**3.5**	73 (>95:5)	56
6	*p*-OMePh	**3.6**	66 (>95:5)	56
7[g]	*p*-ClPh	**3.7**	54 (>95:5)	55
8[g]	*p*-CF$_3$Ph	**3.8**	62 (>95:5)	50
9[g]	*p*-(COMe)Ph	**3.9**	55 (>95:5)	56
10[g]	*p*-(CO$_2$Me)Ph	**3.10**	65 (>95:5)	53
11	1-naphthyl	**3.11**	52 (>95:5)	48
12	2-naphthyl	**3.12**	47 (>95:5)	58

[a] Experimental conditions: To a flask containing Ni(cod)$_2$ (0.05 mmol) and (*R*)-**3.2** (0.1 mmol) were added sequentially: EtOAc (0.5 mL), Et$_3$B (1.0 mmol), the aldehyde (1.0 mmol), and **2.11** (0.5 mmol). The reaction was stirred for 3 h at room temperature unless otherwise noted. [b] Yield of isolated product. [c] Determined by ^{1}H NMR. [d] Determined by HPLC analysis using Chiralcel OJ or Chiralpak AD-H column. [e] (*R*)-**3.1** was used in place of **3.2**. [f] Absolute configuration of the major enantiomer determined to be (*R*) via Mosher's ester analysis. [g] Reaction was conducted at 35 °C.[21]

(entries 4-6, 11-12) and electron-withdrawing[21] (entries 7-10) substituents are tolerated, and aromatic ketones and esters are also compatible (entries 9 and 10).

In our previously reported investigations,[11] we found that related coupling reactions of 1,3-enynes proceeded in excellent regioselectivity, regardless of the substitution pattern on the

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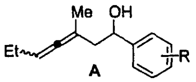
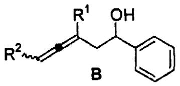
[21] In certain cases, coupling reactions conducted at 23 °C resulted in the formation of small amounts of allene-containing byproducts of the general form **A** (Table 1) or **B** (Table 2) and heating was required to eliminate their formation. Similar compounds have been reported by Sato *et al.* to be the exclusive product of addition reactions of 1,3-enyne-titanium complexes to aldehydes: Hamada, T.; Mizojiri, R.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2000**, *122*, 7138-7139.



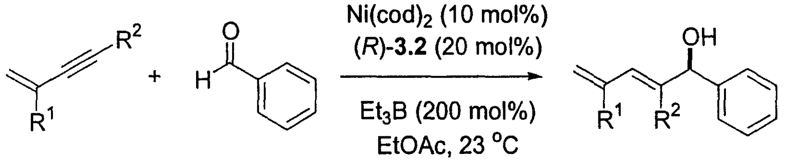
A



B

alkene or the size or nature of the other alkyne substituent. The same was found to be true in reactions promoted by ferrocenyl phosphine **3.2**, and a variety of vinyl-substituted enynes provided a single dienol regioisomer with moderate enantioselectivity (Table 3, entries 1-5), even when this required C–C bond formation to occur adjacent to sterically demanding *tert*-butyl[22] (entry 4) or trimethylsilyl (entry 5) groups.

Table 3. Catalytic, asymmetric reductive coupling reactions of 1,3-enynes with benzaldehyde.[a]



Entry	Enyne	R^1	R^2	Dienol	Yield [%],[b] Regioselectivity[c]	ee [%][d]
1[e]	**2.4**	H	*n*-Hex	**3.18**	66 (>95:5)	32
2	**2.8**	"	Cy	**3.19**	70 (>95:5)	42
3	**2.6**	"	Ph	**3.20**	58 (>95:5)	44
4[f]	**2.9**	"	*t*-Bu	**3.21**	66 (>95:5)	33
5[e]	**3.13**	"	$SiMe_3$	**3.22**	53 (>95:5)	14
6[g]	**3.14**	"	Cy	**3.23**	77 (>95:5)	55[h]
7	**3.15**	"	Ph	**3.24**	42 (>95:5)	54
8[f]	**3.16**	"	*t*-Bu	**3.25**	64 (>95:5)	52
9	**3.17**	"	$SiMe_3$	**3.26**	69 (>95:5)	28

[a] Experimental conditions: To a flask containing $Ni(cod)_2$ (0.05 mmol) and (*R*)-**3.2** (0.1 mmol) were added sequentially: EtOAc (0.5 mL), Et_3B (1.0 mmol), benzaldehyde (1.0 mmol), and the enyne (0.5 mmol). The reaction was stirred for 3 h at room temperature unless otherwise noted. [b] Yield of isolated product. [c] Determined by ^1H NMR. [d] Determined by HPLC analysis using Chiralcel OJ, OD, or Chiralpak AD-H column. [e] Reaction was conducted at 0 °C. [f] Reaction was conducted at 65 °C.[18] [g] Reaction was conducted at 38 °C.[18] [h] Absolute configuration of the major enantiomer determined to be (*R*) via Mosher's ester analysis.

To further investigate this pronounced directing effect, we synthesized a series of isopropenyl-substituted enynes that we had not previously investigated in nickel-catalyzed reductive coupling reactions. As in the case of their vinyl-substituted counterparts, all coupling reactions of these enynes proceeded in excellent regioselectivity (entries 7-10), and in every case the enantioselectivity surpassed that of the corresponding vinyl-substituted enyne (entries 2-5).

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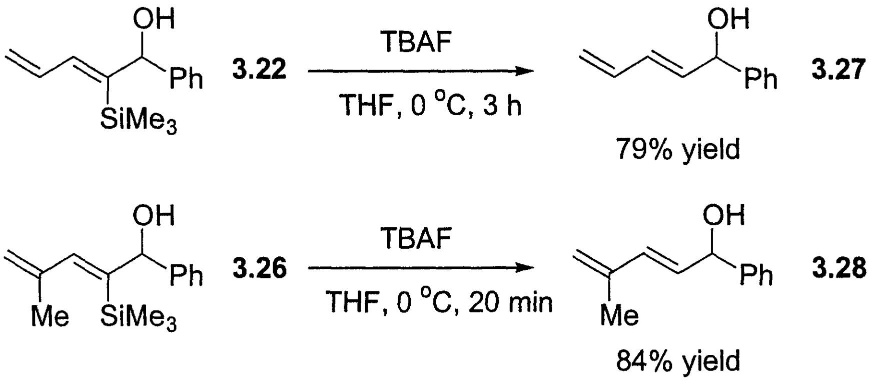
[22] Only one prior example of a catalytic carbon-carbon bond-forming reaction of a *tert*-alkyl–C≡C–R alkyne that

Protiodesilylation of Alkenylsilanes

While the 1-(trimethylsilyl)-substituted enynes investigated underwent coupling in low enantioselectivity (Table 2, entries 5 and 10), they are nevertheless worthy of note as they provide access to synthetically versatile, silyl-substituted conjugated dienes.[23] We have found that alkenylsilanes **3.22** and **3.26** are readily protiodesilylated under mild conditions to afford dienols **3.27** and **3.28**, respectively (Scheme 2). This two-step sequence affords an efficient route to functionalized 1,3-butadiene and isoprene units, respectively.[24] These products also correspond to the dienols expected from reductive coupling reactions of terminal enynes (H-C≡C–CR_2=CR_2), which are typically not effective coupling partners.

Scheme 2. Protiodesilylation of alkenylsilanes.



Conclusion

In summary, we have developed a catalytic, enantioselective reductive coupling of 1,3-enynes and aldehydes that is promoted by a *P*-chiral ferrocenyl monophosphine ligand and affords conjugated dienols in very high regioselectivity and modest enantioselectivity. A variety of aromatic aldehydes serve as coupling partners, and novel enyne substitution was investigated. Trimethylsilyl-substituted dienols obtained via reductive coupling undergo protiodesilylation under mild conditions, increasing the scope of synthetically useful 1,3-dienes that can be accessed using this methodology.

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proceeds with this regioselectivity has been reported (see Chapter 2 and ref 10).

[23] Review: Luh, T.-Y.; Wong, K.-T. *Synthesis* **1993**, 349-370.

[24] For preparation of related compounds via the addition of 1-metallo-1,3-dienes to carbonyl compounds see: (a) 1-lithio-1,3-butadiene: Wender, P. A.; Sieburth, S. M. *Tetrahedron Lett.* **1981**, *22*, 2471-2474; (b) an isoprenylalane: Kozikowski, A. P.; Kitigawa, Y. *Tetrahedron Lett.* **1982**, *23*, 2087-2090.

Catalytic, Asymmetric Reductive Coupling of 1,3-Enynes and Ketones

Introduction

The enantioselective generation of quaternary stereocenters is generally a formidable challenge. Recently, several catalytic, asymmetric methods that achieve this goal have been developed,[25] and addition reactions to ketones have attracted significant attention, as they provide access to enantiomerically enriched tertiary alcohols.[26] Catalytic, asymmetric additions of alkyl,[27] aryl,[28] alkynyl,[29,30] and alkenyl[31] groups to ketones have been reported. The latter class is of particular interest as such reactions provide enantioselective access to allylic alcohols of high synthetic utility.

Walsh has reported highly enantioselective, catalytic additions of alkenylzirconium reagents (prepared by in situ hydrozirconation of a terminal alkyne) to ketones.[31,32] The catalytic, asymmetric reductive coupling of alkynes and ketones would provide a more direct approach, as both alkyne reduction and C–C bond formation occur in the same catalytic pathway and the stoichiometric use of a transition metal is avoided. Methods for the catalytic asymmetric reductive coupling of alkynes and aldehydes have been reported;[16,17] however, to the best of our

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[25] Reviews: (a) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037-2066. (b) Corey, E. J.; Guzmán-Pérez, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 388-401. (c) Christoffers, J.; Mann, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4591-4597. (d) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105-10146. (e) Ramón, D. J.; Yus, M. *Curr. Org. Chem.* **2004**, *8*, 149-183. (f) Douglas, C. J.; Overman, L. E. *J. Proc. Nat. Acad. Sci.* **2004**, *101*, 5363-5367.

[26] Review: Ramon, D. J.; Yus, M. *Ang. Chem. Int. Ed.* **2004**, *43*, 284-287.

[27] (a) Ramón, D. J.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 1239-1242. (b) Ramón, D. J.; Yus, M. *Tetrahedron* **1998**, *54*, 5651-5666. (c) Garcia, C.; LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970-10971. (d) Jeon, S.-J.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 9544-9545. (e) Betancort, J. M.; Garcia, C.; Walsh, P. J. *Synlett* **2004**, 749-760. (f) Jeon, S.-J.; Li, H.; Garcia, C.; LaRochelle, L. K.; Walsh, P. J. *J. Org. Chem.* **2005**, 448-455.

[28] (a) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445-446. (b) Garcia, C.; Walsh, P. J. *Org. Lett.* **2003**, *5*, 3641-3644. (c) Li, H.; Garcia, C.; Walsh, P. J. *J. Proc. Nat. Acad. Sci.* **2004**, *101*, 5425-5427.

[29] Reviews: (a) Pu, L. *Tetrahedron* **2003**, *59*, 9873-9886. (b) Cozzi, P. G.; Hilgraf, R.; Zimmerman, N. *Eur. J. Org. Chem.* **2004**, 4095-4105

[30] Examples: (a) Cozzi, P. G. *Angew. Chem. Int. Ed.* **2003**, *42*, 2895-2898. (b) Lu, G.; Li, X.; Jia, X.; Chan, W. L.; Chan, A. S. C. *Ang. Chem. Int. Ed.* **2003**, *42*, 5057. (c) Saito, B.; Katsuki, T. *Synlett* **2004**, 1557-1560. (d) Cozzi, P. G.; Alesi, S. *Chem. Commun.* **2004**, 2448-2449. (e) Zhou, Y.; Wang, R.; Xu, Z.; Yan, W.; Liu, L.; Kang, Y.; Han, Z. *Org. Lett.* **2004**, *6*, 4147-4149.

[31] (a) Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 6538-6539. (b) Anaya de Parrodi, C.; Walsh, P. J. *Synlett* **2004**, 2417-2420.

[32] For diastereoselective additions of alkenylzirconocenes to ketones and α-keto esters, respectively, see: (a) Chavez, D. E.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2001**, *40*, 3667-3670. (b) Wipf, P.; Stephenson, C. R. J. *Org. Lett.* **2003**, *5*, 2449-2452.

knowledge, *no examples of catalytic intermolecular reductive coupling of alkynes and ketones, asymmetric or otherwise, exist in the literature.*[33,34,35,36]

In catalytic reductive couplings of aldehydes and 1,3-enynes[11] (and other alkynes),[37] a pendant alkene enhances both the reactivity and the selectivity of the alkyne. We now disclose that catalytic intermolecular reductive couplings of 1,3-enynes and ketones also proceed efficiently and in modest enantioselectivity when conducted in the presence of catalytic amounts of a *P*-chiral, ferrocenyl monodentate phosphine ligand.

Ligand Evaluation

Initial attempts to promote the catalytic reductive coupling of enyne **2.4** and acetophenone using triethylborane as a stoichiometric reductant and catalytic amounts of both $Ni(cod)_2$ and tricyclopentylphosphine (Cyp_3P), a ligand that had proven particularly effective in promoting reductive couplings of 1,3-enynes and aldehydes, were completely unsuccessful. Only a trace of desired coupling product **3.29** was observed, even at elevated temperature (Table 4, entry 1). Similar results were obtained with both tris-*(o*-methoxyphenyl*)*phosphine ((*o*-anisyl)$_3$P, entry 2) and cyclohexyldiphenylphosphine ($CyPPh_2$, entry 3). To our delight, however, the use of (+)-NMDPP led to an efficient catalytic reductive coupling, affording the desired dienol in 68% yield and >95:5 regioselectivity, albeit in only 17% ee (entry 4).

P-chiral, ferrocenyl monodentate phosphines are effective in catalytic asymmetric coupling reactions of alkynes with both aldehydes[17] and imines.[18] Accordingly, we evaluated this family of phosphines in the ketone coupling reaction described above. Unlike the other achiral ligands evaluated, ferrocenyldiphenylphosphine ($FcPPh_2$) was effective at promoting the

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[33] For an example of nickel-catalyzed *intramolecular* reductive coupling of an alkyne and a ketone, see: Chan, J.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 10682-10691.

[34] For a recent report of a nickel-catalyzed intermolecular alkyne insertion into cyclobutanones, see: Murakami, M.; Ashida, S.; Takanori, M. *J. Am. Chem. Soc.* **2005**, *127*, 6932-6933.

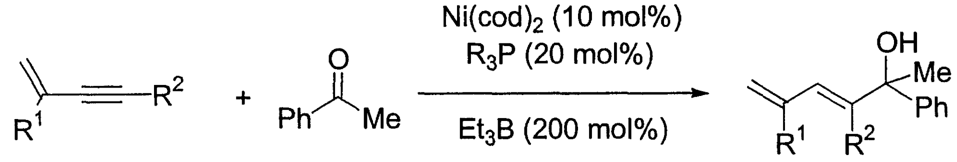
[35] Transition metal-*mediated* reductive coupling of alkynes and ketones: Titanium: (a) Ozerov, O. V.; Brock, C. P.; Carr, S. D.; Ladipo, F. T. *Organometallics*, **2000**, *19*, 5016-5025. Tantalum: (b) Kataoka, Y.; Miyai, J.; Oshima, K.; Takai, K.; Utimoto, K. *J. Org. Chem.* **1992**, *57*, 1973-1981. Zirconium: (c) Takahashi, T.; Xi, C.; Xi, Z.; Kageyama, M.; Fischer, R.; Nakajima, K.; Negishi, E. *J. Org. Chem.* **1998**, *63*, 6802-6806. (d) Buchwald, S. L.; Watson, B. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 2544-2546.

[36] Reductive cyclizations of alkynes and ketones promoted by samarium diiodide: Reviews: (a) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29-68. (b) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371-3403. Examples: (c) Molander, G. A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, *111*, 8236-8246. (d) Berndt, M.; Gross, S.; Hölemann, A.; Reissig, H.-U. *Synlett* **2004**, 422-438. (e) Hölemann, A.; Reissig, H.-U. *Synlett* **2004**, 2732-2735.

[37] See Chapter 4 and: Miller, K. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 15342-15343.

catalytic reductive coupling of **2.4** and acetophenone (entry 5), and the yield of the reaction of enyne **2.11** under the same conditions was significantly higher (entry 6). The introduction of a methyl group at the ortho position of one of the phenyl rings of $FcPPh_2$ (i.e., *P*-chiral ferrocenyl phosphine **3.1**) not only improved reaction yield, but also afforded the corresponding dienol **3.30** in 58% ee (entry 7).[38] The enhanced reactivity observed with phosphine **3.1** allowed for this coupling reaction to be conducted efficiently at room temperature, affording a further increase in enantioselectivity (64% ee, entry 8).

Table 4. Ligand evaluation in the reductive coupling of 1,3-enynes and acetophenone.[a]



2.4, 2.11

3.29, 3.30

entry	R^1	R^2	R_3P	temp (°C)	yield (%),[b] regioselectivity	ee (%)[c]
1	H	*n*-Hex	Cyp_3P	50	<2 (n.d.)	-
2	"	"	(*o*-anisyl)$_3$P	"	<2 (n.d.)	-
3	"	"	$CyPPh_2$	"	<2 (n.d.)	-
4	"	"	(+)-NMDPP	"	68 (>95:5)	17
5	"	"	$FcPPh_2$	"	44 (>95:5)	-
6	Me	Et	"	"	79 (>95:5)	-
7	"	"	**(*S*)-3.1**	35	89 (>95:5)	58
8	"	"	"	**23**	**69 (>95:5)**[d]	**64**

[a] Conditions: $Ni(cod)_2$ (0.05 mmol) and R_3P (0.1 mmol) were combined in a glovebox. The flask was removed and acetophenone (1.0 mmol) was added, followed by Et_3B (1.0 mmol). The flask was then placed in a heated bath at the specified temperature. The enyne (0.5 mmol) was added dropwise over 6 h via syringe pump, and after an additional 12 h, the reaction was stirred open to air for 30 min to promote oxidation of the catalyst. Silica gel chromatography afforded mixtures of desired product and acetophenone. [b] Yield and regioselectivity determined by ^1H NMR integration. [c] Determined by HPLC analysis, Chiralcel OJ column. [d] Isolated yield of pure **3.30** following treatment of crude reaction mixture with $NaBH_4$ at 0 °C.

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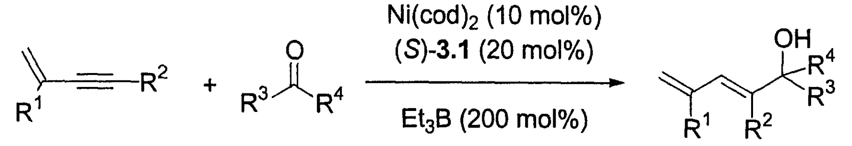
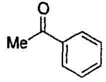
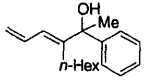
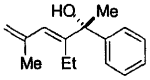
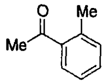
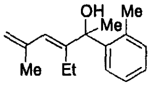
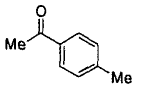
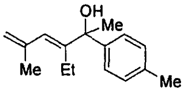
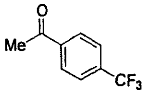
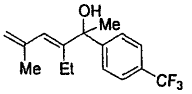
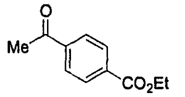
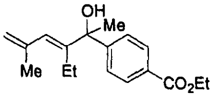
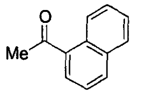
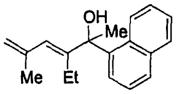
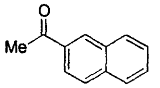
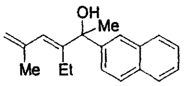
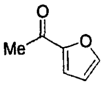
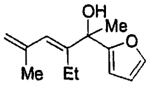
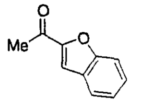
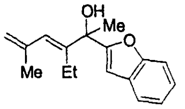
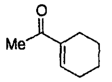
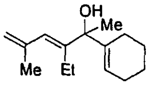
[38] Other substitution patterns on this aromatic ring led to *P*-chiral ferrocenyl phosphines of reduced efficacy (e.g. 2-

Table 5. Catalytic, asymmetric reductive coupling of 1,3-enynes and ketones.[a]



entry	enyne	ketone	dienol		yield (%),[b] regioselectivity[c]	ee (%)[d]
1[e]	**2.4**			**3.29**	62 (>95:5)	60
2	**2.11**	"		**3.30**	69 (>95:5)	64[e]
3	"			**3.31**	52 (>95:5)	47
4	"			**3.32**	71 (>95:5)	64
5	"			**3.33**	30 (>95:5)	56
6	"			**3.34**	60 (>95:5)	58
7	"			**3.35**	77 (>95:5)	46
8	"			**3.36**	65 (>95:5)	62
9	"			**3.37**	58 (>95:5)	40
10	"			**3.38**	58 (>95:5)	42
11	"			**3.39**	39 (>95:5)	70

[a] Conditions: At 23 °C, acetophenone (1.0 mmol) and Et$_3$B (1.0 mmol) were added to a flask containing Ni(cod)$_2$ (0.05 mmol) and (*S*)-**3.1** (0.1 mmol). The enyne (0.5 mmol) was added dropwise over 6 h via syringe pump. The reaction was stirred for an additional 12 h, and was then stirred open to air for 30 min to promote oxidation of the catalyst. Products were isolated following treatment of the crude mixtures with NaBH$_4$ (1.0 mmol) at 0 °C and were purified by silica gel chromatography. [b] Yield of isolated product. [c] Determined by ^{1}H NMR. [d] Determined by HPLC analysis, Chiralcel OJ or Chiralpak AD-H column. [e] (*R*)-**3.1** (0.1 mmol) was employed instead of (*S*)-**3.1**. [f] Absolute configuration determined to be (*S*) by conversion to (*R*)-2-hydroxy-2-phenyl-pentan-3-one (**3.41**, Scheme 4).

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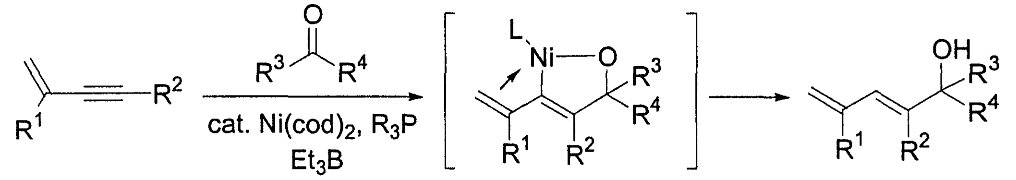
biphenyl, 28% yield, 18%ee; 2,5-dimethylphenyl, 76% yield, 50% ee; 2-*i*Pr-phenyl, 13% yield, 70% ee).

Substrate Scope

In addition to acetophenone, a variety of aromatic and heteroaromatic ketones undergo efficient catalytic asymmetric reductive coupling with **2.11** under these conditions (Table 5).[39,] Electron-donating (entries 3 and 4) and electron-withdrawing substituents on the aromatic ring are tolerated (entries 5 and 6), and aromatic esters are compatible (entry 6). Both 1- and 2-acetylnaphthalene couple effectively (entries 7 and 8), although ortho substitution leads to somewhat diminished enantioselectivity (entries 3 and 7). Heteroaromatic ketones 2-acetylfuran and benzofuran-2-yl methyl ketone can also be employed (entries 9 and 10). Interestingly, an α,β-unsaturated ketone, 1-acetyl-1-cyclohexene (entry 12), affords the best enantioselectivity observed (70% ee), albeit in moderate yield.[40] The unique reactivity observed with 1,3-enynes relative to other classes of alkynes and the high regioselectivity in these reactions suggests that these transformations may be directed by the neighboring alkene (Scheme 3).[41]

Scheme 3.



The products of these coupling reactions are enantiomerically enriched, chiral 1,3-dienes, a class of compounds whose utility in Diels-Alder cycloaddition reactions has been intensively studied.[14,15] A site-selective Rh-catalyzed hydrogenation of these dienols previously reported by our laboratory[11] provides access to trisubstituted allylic alcohols such as **3.40** that possess a quaternary carbinol stereogenic center, a class of allylic alcohols not previously accessible via any catalytic method (Scheme 4).[42] Ozonolysis of these compounds affords α-hydroxy ketones such as **3.41**, the TMS ether of which has been employed by Masamune in asymmetric Aldol

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[39] Ketones containing two alkyl substituents, such as cyclohexyl methyl ketone or cyclopropyl methyl ketone, afforded coupling products in very low yield (<10%) and α-keto esters were completely ineffective.

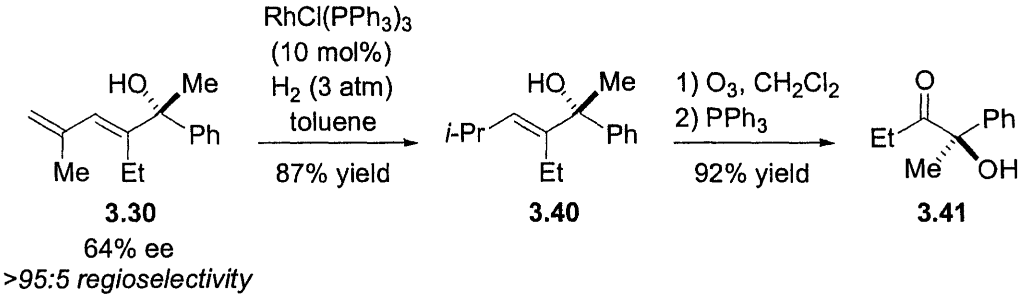
[40] Yield was improved by conducting this reaction at 35 °C: 55% yield, >95:5 regioselectivity, 63% ee.

[41] Alkynes that lack an alkenyl substituent, such as 1-phenyl-1-propyne or 4-octyne, do not couple under these conditions.

[42] For the singular example of the preparation of such compounds via antibody-catalyzed resolution, see: List, B.; Shabat, D.; Zhong, G.; Turner, J. M.; Li, A.; Bui, T.; Anderson, J.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **1999**, *121*, 7283-7291.

reactions.[43] This two-step procedure also allowed for assignment of the configuration of the major enantiomer of dienol **3.30** as *S*.[44]

Scheme 4.



Conclusion

In summary, we have developed the first catalytic, asymmetric reductive coupling of alkynes and ketones, a transformation in which 1,3-enynes are uniquely effective substrates. This transformation is highly regioselective and affords synthetically useful 1,3-dienes with an adjacent quaternary carbinol stereogenic center in moderate enantioselectivity. Finally, the *P*-chiral monodentate ferrocenyl phosphine that promotes this coupling reaction may find use in other asymmetric, nickel-catalyzed transformations.

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[43] Masamune, S.; Ali, S. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem. Int. Ed.* **1980**, *19*, 557-558.
[44] Harder, T.; Lohl, T.; Bolte, M.; Wagner, K.; Hoppe, D. *Tetrahedron Lett.* **1994**, *35*, 7365-7368.

Experimental Section

General Methods. Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of nitrogen or argon with rigid exclusion of moisture from reagents and glassware. Bis(1,5-cyclooctadiene)nickel (0) ($Ni(cod)_2$) and (+)-neomenthyldiphenylphosphine (NMDPP) were purchased from Strem Chemicals, Inc. and used without further purification. (*R*)-Ferrocenyl(2-methylphenyl)phenylphosphine (**3.1**) and (*R*)-Ferrocenyl(2-isopropylphenyl)-phenylphosphine (**3.2**) were prepared in five steps from (+)-ephedrine as previously reported;[45,46] (*S*)-enantiomers were prepared analogously from (–)-ephedrine. Triethylborane (Et_3B, 98%), and 2-methyl-1-hexen-3-yne (**2.11**) were purchased from Aldrich Chemical Co. and used as received. Enynes **2.4**, **2.6-2.9**, and **2.14-2.16** were prepared as described previously.[47] Benzaldehyde was purchased from Aldrich Chemical Co. and distilled prior to use. All other aldehydes and ketones were purchased from either Alfa Aesar or Aldrich Chemical Co. and used as received. Ethyl acetate was freshly distilled over $MgSO_4$ and was sparged with argon prior to use. Tetrahydrofuran and diethyl ether were freshly distilled over blue solutions of sodium/benzophenone ketyl, and dichloromethane was distilled over calcium hydride.

Analytical thin layer chromatography (TLC) was performed on silica gel 60 F_{254} aluminum plates precoated with a fluorescent indicator or EM reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was accomplished with UV light and ethanolic phosphomolybdic acid (PMA). Liquid chromatography was performed using a forced flow (flash chromatography)[48] of the indicated solvent system on Silicycle silica gel 60 (230 – 400 mesh). ^1H and ^{13}C NMR spectra were recorded in deuterochloroform ($CDCl_3$) on Varian Inova 300 and 500MHz instruments. Chemical shifts of ^1H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.23 ppm) on the δ scale. Infrared (IR) spectra were recorded as a thin film between NaCl plates on a Perkin-Elmer Model 2000 FT-IR System transform spectrometer. High resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. HPLC was performed on a Hewlett-Packard 1100 chromatograph equipped with a variable wavelength detector and either a Chiralcel OD-H, OJ, or Chiralpak AD-H column. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter at 589 nm.

Catalytic Asymmetric Reductive Coupling of Conjugated Enynes and Aldehydes Using (+)-NMDPP (Table 1).

Standard Procedure: In a glovebox, $Ni(cod)_2$ (14 mg, 0.5 mmol), and (+)-NMDPP (32 mg, 0.1 mmol) were placed into a 25 mL oven-dried, single-necked round-bottom flask, which was then sealed with a rubber septum. The flask was removed from the glovebox, placed under argon,

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[45] Colby, E. A.; Jamison, T. F. *J. Org. Chem.* **2003**, *68*, 156-166.

[46] Patel, S. J.; Jamison, T. F. *Angew. Chem.-Int. Edit.* **2004**, *43*, 3941-3944.

[47] See Chapter 2, Experimental Section.

[48] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

and ethyl acetate (0.5 mL) was added via syringe, followed immediately by Et_3B (0.15 mL, 1.0 mmol). The resulting solution was stirred 5 min at ambient temperature and then cooled to 0 °C. Once the solution had cooled, isobutyraldehyde (90 μL, 1.0 mmol) was added dropwise via microsyringe. After stirring 5 min, the enyne (0.5 mmol) was added. The reaction was stirred 6 h at 0 °C, and then the septa was removed and the reaction stirred 30 min open to air to promote quenching of the catalyst. The crude mixture was purified by flash chromatography on silica gel using a solvent gradient (hexanes: ethyl acetate; 50:1 to 10:1). Note: Compounds formed are prone to rapid (over 2-3 days) decomposition, and so should either be used immediately or stored as solutions in benzene at –20 °C.

2.5: The standard procedure afforded the title compound as a clear oil (74 mg, 70% yield, >95:5 regioselectivity, < 5% ee). Chiral HPLC analysis (Chiralcel OJ, hexanes: 2-propanol, 99.5:0.5, 0.8 mL/min): t_R[*major*] = 5.83 min; t_R[*minor*] = 6.52 min.

2.18: The standard procedure afforded the title compound as a clear oil (31 mg, 37% yield, >95:5 regioselectivity, 13% ee). Chiral HPLC analysis (Chiralcel OJ, hexanes: 2-propanol, 99.5:0.5, 0.4 mL/min): t_R [*major*] = 12.48 min; t_R[*minor*] = 13.76 min.

2.19: The standard procedure (double scale) afforded the title compound as a clear oil (131 mg, 63% yield, >95:5 regioselectivity, 17% ee). Chiral HPLC analysis (Chiralcel OD, hexanes: 2-propanol, 99.5:0.5, 0.6 mL/min): t_R[*minor*] = 6.81 min; t_R[*major*] = 7.45 min.

2.20: The standard procedure afforded the title compound as a clear oil (63 mg, 69% yield, >95:5 regioselectivity, 19% ee,). Chiral GC analysis (B-PH, 105 °C, 2.7 mL/min): t_R[*minor*] = 2.45 min; t_R[*major*] = 2.64 min.

2.21: The standard procedure afforded the title compound as a clear oil (19 mg, 23% yield, >95:5 regioselectivity, 15% ee). Chiral HPLC analysis (Chiralcel AD, hexanes: 2-propanol, 99.5:0.5, 0.5 mL/min): t_R[*major*] = 23.96 min; t_R[*minor*] = 25.26 min.

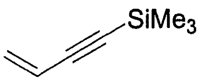
2.24: The standard procedure afforded the title compound as a clear oil (60 mg, 61% yield, >95:5 regioselectivity, 30% ee). Chiral HPLC analysis (Chiralcel OJ, hexanes: 2-propanol, 99:1, 0.4 mL/min): t_R[*minor*] = 10.16 min; t_R[*major*] = 11.70 min.

2.25: In a glovebox, $Ni(cod)_2$ (14 mg, 0.05 mmol), and (+)-NMDPP (32 mg, 0.1 mmol) were placed into a 50 mL oven-dried, single-necked round-bottom flask, which was then sealed with a rubber septum. The flask was removed from the glovebox, placed under argon, and Et_3B (2.0 M in ethyl acetate, 0.5 mL, 1 mmol) and DMI (0.5 mL) were added via syringe. The resulting solution was stirred 10 min at ambient temperature and then the reaction flask was placed in a precooled, –25 °C isopropanol bath. The solution was stirred 15 min, and then the alkyne (0.5 mmol) was added. The aldehyde (1.0 mmol) was then added over 8 h via syringe pump. The reaction was stirred an additional 36 h at –25 °C, at which point saturated aqueous NH_4Cl (3 mL) and 1M HCl (0.5 mL) were added. The mixture was diluted with ethyl acetate (10 mL) and water (5 mL), and the organic layer was extracted (3 x 20 mL), dried and condensed. The crude mixture was purified by flash chromatography on silica gel using a solvent gradient (hexanes: ethyl acetate;

50:1 to 10:1) to afford the title compound as a clear oil (78 mg, 80% yield, >95:5 regioselectivity, 68% ee). Chiral HPLC analysis (Chiralcel OJ, hexanes: 2-propanol, 99:1, 1 mL/min): t_R[*minor*] = 5.31 min; t_R[*major*] = 5.92 min.

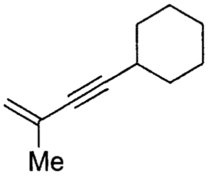
2.26: The procedure as described for **2.25** was employed (double scale) to afford the title compound as a clear oil (96 mg, 43% yield, >95:5 regioselectivity, 70% ee). Chiral GC analysis (G-TA, 90 °C, 5.0 mL/min): t_R[*minor*] = 24.23 min; t_R[*major*] = 25.17 min.

Preparation of 1,3-enynes.



3-Buten-1-ynyl-trimethyl silane[49] (3.13): DBU (35 mmol, 5.2 mL) was added dropwise to a solution of 4-(trimethylsilyl)but-3-yn-1-ynyl tosylate (35 mmol, 1.04 g)[50] in DMSO (40 mL) at 0 °C. After stirring for 12 h at ambient temperature, water (5 mL) was added, and the solution was extracted with diethyl ether (3 x 10 mL). The combined extracts were dried with $MgSO_4$. Kugelrohr distillation (60 °C, 20 Torr) afforded the title compound as clear liquid (1.87 g, 43% yield). Spectral data were consistent with those previously reported.

General procedure for synthesis of enynes 3.14, 3.16, and 3.17:[51] Terminal alkyne (30 mmol) was dissolved in 30 mL THF and cooled to 0 °C. A solution of *n*-butyllithium (12.0 mL, 2.5 M in hexane, 30 mmol) was added slowly and the solution was stirred 30 min at 0 °C. A solution of dry $ZnCl_2$ (4.08 g, 30 mmol) in THF (20 mL) was transferred to the lithium acetylide solution via cannula and the mixture was warmed to ambient temperature over 10 minutes. In a separate flask, 2-bromopropene (4.4 mL, 6.1 g, 50 mmol) and $Pd(PPh_3)_4$ (1.38 g, 1.2 mmol) were dissolved in THF (50 mL). The zinc acetylide was transferred to the palladium solution via cannula. The solution was stirred 18 h at ambient temperature, and then 1 N HCl was added (100 mL). Pentane was added (350 mL) and the layers were separated. The organic phase was washed with H_2O (10 x 100 mL) to remove residual THF, filtered through Celite, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification via Kugelrohr distillation under reduced pressure afforded the 1,3-enyne.



(3-Methyl-3-buten-1-ynyl)-cyclohexane (3.14): Prepared according to the general procedure (3.36 g, 22.7 mmol, 76% yield). R_f = 0.33 (hexanes). ^1H NMR (500 MHz, C_6D_6) δ 5.16 – 5.17

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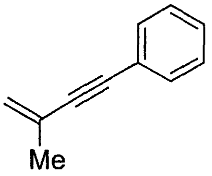
[49] Mayr, H.; Kuhn, O.; Schleirf, C.; Ofial, A. R. *Tetrahedron* **2000**, *56*, 4219-4229.

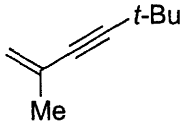
[50] Negishi, E.-i.; Boardman, L. D.; Sawada, H.; Bagheri, V.; Stoll, A. T.; Tour, J. M.; Rand, C. L. *J. Am. Chem. Soc.* **1988**, *110*, 5383-5396.

[51] Miller, K. M.; Luanphaisarnnont, T.; Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 4130-4131.

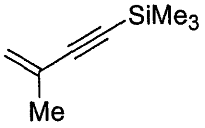
(m, 1H), 4.95 – 4.96 (m, 1H), 2.30 - 2.33 (m, 1H), 1.73 – 1.74 (m, 3H), 1.63 – 1.70 (m, 2H), 1.51 – 1.60 (m, 2H), 1.27 – 1.39 (m, 3H), 1.05 – 1.16 (m, 3H).
^{13}C NMR (125 MHz, C_6D_6) δ 128.3, 120.5, 93.9, 82.8, 33.5, 30.3, 26.7, 25.5, 24.5.
IR (thin film NaCl): 3095, 2931, 2855, 2219, 1615, 1449 cm^{-1}.
HRMS (EI) *m/z* 148.1246 [M^+; calcd for $C_{11}H_{16}$: 148.1247].



(3-Methyl-3-buten-1-ynyl)-benzene[52] (3.15): 2-Methyl-4-phenyl-3-butyn-2-ol[53] (3.28 g, 20.4 mmol) was dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C. Triethylamine (6.40 mL, 44.9 mmol) and methanesulfonyl chloride (1.74 mL, 22.4 mmol) were added via syringe, and the mixture was allowed to warm to ambient temperature over 2 h. After stirring an additional 22 h at ambient temperature, the reaction was quenched with H_2O (30 mL). The layers were separated and the organic phase was washed with 1 N HCl (2 x 50 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified via column chromatography (elution with hexane) and subsequent Kugelrohr distillation (1.74 g, 60% yield, pale yellow oil). Spectral data were consistent with those previously reported.



2,5,5-Trimethyl-1-hexen-3-yne (3.16): Prepared according to the general procedure (30 mmol scale, 1.59 g, 43% yield). Spectral data were consistent with those previously reported.[54]



Trimethyl-(3-methyl-3-buten-1-ynyl)-silane (3.17): Prepared according to the general procedure (30 mmol scale, 2.30 g, 55% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.34 – 5.35 (m, 1H), 5.24 – 5.25 (m, 1H), 1.88 – 1.89 (m, 3H), 0.19 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$)

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[52] Krijnen, E. S.; Zuilhof, H.; Lodder, G. *J. Org. Chem.* **1994**, *59*, 8139-8150.

[53] Prepared according to: Yu, W.-Y.; Alper, H. *J. Org. Chem.* **1997**, *62*, 5684-5687.

[54] (a) Stang, P. J.; Kowalski, M. H. *J. Am. Chem. Soc.* **1989**, *111*, 3356-3362. (b) Horner, M. G.; Rudolph, M. J.; Wolff, S.; Agosta, W. C. *J. Am. Chem. Soc.* **1992**, *114*, 6034-6047.

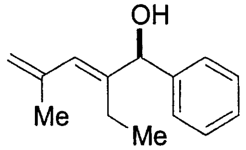
δ 127.1, 123.1, 106.6, 93.1, 23.5, 0.2 (3C). Spectral data were consistent with those previously reported.[55]

Standard Experimental Procedures for Catalytic, Asymmetric Reductive Coupling of 1,3-Enynes and Aldehydes Using Ferrocenyl Phosphine 3.2.

Procedure A (liquid aldehydes): In a glovebox, Ni(cod)$_2$ (14 mg, 0.5 mmol) and (*R*)-**3.2**[46] (42 mg, 0.1 mmol) were placed into a 10 mL oven-dried, single-necked round-bottom flask, which was then sealed with a rubber septum. The flask was removed from the glovebox, placed under argon, and ethyl acetate (0.5 mL) was added via syringe, followed immediately by Et$_3$B (0.15 mL, 1.0 mmol). The resulting solution was stirred 5 min, and then the aldehyde (1.0 mmol) was added dropwise via microsyringe. After stirring 5 min, the enyne (0.5 mmol) was added. The reaction was allowed to stir 3 h at 23 °C, at which point the septa was removed and the reaction was stirred 30 min open to air to promote quenching of the catalyst. The crude mixture was purified by flash chromatography on silica gel using a solvent gradient (hexanes: ethyl acetate; 50:1 to 10:1). Note: Dienols formed are prone to gradual decomposition, and so should be stored as solutions in benzene at –20 °C.

Procedure B (solid aldehydes): In a glovebox, Ni(cod)$_2$ (14 mg, 0.5 mmol), (*R*)-**3.2**[46] (42 mg, 0.1 mmol), and the aldehyde (1.0 mmol) were placed into a 10 mL oven-dried, single-necked round-bottom flask, which was then sealed with a rubber septum. The flask was removed from the glovebox, placed under argon, and ethyl acetate (0.5 mL) was added via syringe, followed immediately by Et$_3$B (0.15 mL, 1.0 mmol). The resulting solution was stirred 5 min, and then the enyne (0.5 mmol) was added dropwise via microsyringe. The reaction was allowed to stir 3 h at 23 °C, at which point the septa was removed and the reaction was stirred 30 min open to air to promote quenching of the catalyst. The crude mixture was purified by flash chromatography on silica gel using a solvent gradient (hexanes: ethyl acetate; 50:1 to 10:1). Note: Dienols formed are prone to gradual decomposition, and so should be stored as solutions in benzene at –20 °C.

2.21 (Table 1, entry 1): In the reductive coupling of **2.11** (47 mg, 0.5 mmol, 63 μL) and isobutyraldehyde (72 mg, 1.0 mmol, 90 μL), Procedure A was used. Silica gel chromatography afforded the title compound as a clear oil (61 mg, 73% yield, 9% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R$_f$ = 0.31 (10:1 hexanes: ethyl acetate).



(+)-(2*E*)-2-Ethyl-4-methyl-1-phenyl-penta-2,4-dien-1-ol (3.3): In the reductive coupling of **2.11** (47 mg, 0.5 mmol, 63 μL) and benzaldehyde (106 mg, 1.0 mmol, 101 μL), Procedure A was used. Silica gel chromatography afforded the title compound as a clear oil (62 mg, 66% yield,

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[55] Also reported in the literature to be prepared by silylation of 2-methyl-1-buten-3-yne: Rehn, S.; Ofial, A. R.; Mayr, H. *Synthesis* **2003**, 1790-1796.

56% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R$_f$ = 0.31 (10:1 hexanes: ethyl acetate). Absolute configuration of the major enantiomer was determined to be (*R*) via Mosher's ester analysis (vide infra).

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.34 – 7.41 (m, 4H); 7.27 – 7.31 (m, 1H); 6.18 (s, 1H); 5.23 (s, 1H); 4.99 (s, 1H); 4.91 (s, 1H); 2.29 (dq, *J* = 15, 7.5 Hz, 1H); 2.00 (dq, *J* = 15, 7.5 Hz, 1H); 1.91 (s, 3H); 1.87 (s, 1H); 0.94 (t, *J* = 7.5 Hz, 3H).

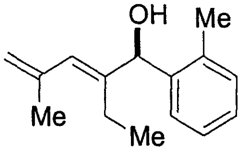
^{13}C NMR (125 MHz, CDCl$_3$) δ 144.41, 142.62, 141.81, 128.59, 127.85, 127.59, 126.97, 114.96, 77.94, 23.73, 21.73, 14.73.

IR (thin film NaCl): 3364, 3084, 3063, 3029, 2967, 2935, 2875, 1949, 1632, 1601, 1493, 1453, 1374, 1243, 1190, 1167, 1074, 1058, 1024 cm^{-1}.

HRMS (EI) *m/z* 202.135 [M$^+$; calcd for $C_{14}H_{18}O$: 202.135].

Chiral HPLC analysis (Chiralcel OJ, hexanes: 2-propanol, 99:1, 0.8 mL/min): t$_R$[*major*] = 26.18 min; t$_R$[*minor*] = 23.87 min.

[α]$_D$ = + 32.0 (23 °C, 589 nm, 1.03 g/100 mL, CHCl$_3$).



(+)-(2*E*)-2-Ethyl-4-methyl-1-*o*-tolyl-penta-2,4-dien-1-ol (3.4): In the reductive coupling of **2.11** (47 mg, 0.5 mmol, 63 μL) and *o*-tolualdehyde (120 mg, 1.0 mmol, 116 μL), Procedure A was used. Silica gel chromatography afforded the title compound as a clear oil (77 mg, 71% yield, 54% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R$_f$ = 0.34 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.48 (dd, J = 8, 2 Hz, 1H); 7.14 – 7.26 (m, 3H); 6.03 (s, 1H); 5.42 (s, 1H); 4.97 – 5.00 (m, 1H); 4.89 (t, J = 1 Hz, 1H); 2.30 – 2.39 (m, 4H); 2.00 – 2.09 (m, 1H); 1.89 (s, 3H); 1.74 – 1.78 (m, 1H); 0.93 (t, J = 7.5 Hz, 3H).

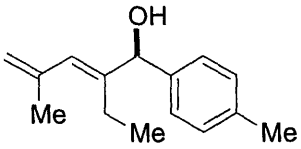
^{13}C NMR (125 MHz, CDCl$_3$) δ 143.44, 141.86, 140.31, 136.11, 130.63, 128.76, 127.69, 126.48, 126.29, 114.80, 74.50, 23.72, 21.95, 19.53, 14.62.

IR (thin film NaCl): 3346, 3077, 3022, 2966, 2935, 2875, 1632, 1603, 1488, 1460, 1374, 1285, 1244, 1161, 1112, 1075, 1054, 1022 cm^{-1}.

HRMS (EI) *m/z* 216.151 [M$^+$; calcd for $C_{15}H_{20}O$: 216.151].

Chiral HPLC analysis (Chiralpak AD-H, hexanes: 2-propanol, 98:2, 0.6 mL/min): t$_R$[*major*] = 21.29 min; t$_R$[*minor*] = 19.99 min.

[α]$_D$ = +12.0 (23 °C, 589 nm, 1.00 g/100 mL, CHCl$_3$).



(+)-(2*E*)-2-Ethyl-4-methyl-1-*p*-tolyl-penta-2,4-dien-1-ol (3.5): In the reductive coupling of **2.11** (47 mg, 0.5 mmol, 63 μL) and *p*-tolualdehyde (120 mg, 1.0 mmol, 118 μL), Procedure A was used. Silica gel chromatography afforded the title compound as a clear oil (79 mg, 73% yield, 56% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R_f = 0.32 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.5 Hz, 2H); 7.16 (d, *J* = 8.5 Hz, 2H); 6.18 (s, 1H); 5.19 (s, 1H); 4.99 (m, 1H); 4.91 (d, *J* = 1 Hz, 1H); 2.36 (s, 3H); 2.26 – 2.34 (m, 1H); 1.92 – 2.01 (m, 1H); 1.91 (s, 3H); 1.83 (s, 1H); 0.94 (t, *J* = 7.5 Hz, 3H).

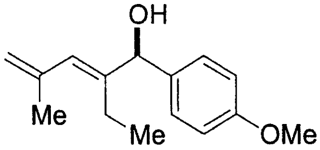
^{13}C NMR (125 MHz, $CDCl_3$) δ 144.49, 141.89, 139.72, 137.57, 129.29, 127.18, 126.95, 114.82, 77.62, 23.77, 21.83, 21.37, 14.70.

IR (thin film NaCl): 3363, 3082, 2966, 2934, 2874, 1632, 1512, 1454, 1374, 1300, 1243, 1167, 1111, 1077, 1020 cm^{-1}.

HRMS (EI) *m/z* 216.151 [M^+; calcd for $C_{15}H_{20}O$: 216.151].

Chiral HPLC analysis (Chiralcel OJ, hexanes: 2-propanol, 98:2, 1.0 mL/min): t_R[*major*] = 13.24 min; t_R[*minor*] = 10.70 min.

$[\alpha]_D$ = +38.1 (23 °C, 589 nm, 1.00 g/100 mL, $CHCl_3$).



(+)-(2*E*)-2-Ethyl-1-(4-methoxy-phenyl)-4-methyl-penta-2,4-dien-1-ol (3.6): In the reductive coupling of **2.11** (47 mg, 0.5 mmol, 63 μL) and *p*-anisaldehyde (136 mg, 1.0 mmol, 121 μL), Procedure A was used. Silica gel chromatography (use of a 3:1 toluene:hexanes to toluene gradient was required to remove unreacted aldehyde) afforded the title compound as a clear oil (77 mg, 66% yield, 56% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R_f = 0.38 (5:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.34 (m, 2H); 6.86 – 6.92 (m, 2H); 6.18 (s, 1H); 5.18 (d, *J* = 3 Hz, 1H); 4.99 (s, 1H); 4.91 (s, 1H); 3.82 (s, 3H); 2.26 – 2.35 (m, 1H); 1.92 – 1.99 (m, 1H); 1.92 (s, 3H); 1.85 (d, *J* = 3.5 Hz, 1H); 0.94 (t, *J* = 7.5 Hz, 3H).

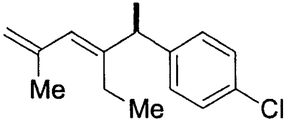
^{13}C NMR (125 MHz, $CDCl_3$) δ 159.32, 144.53, 141.88, 134.82, 128.28, 126.95, 114.78, 113.94, 77.23, 55.47, 23.77, 21.86, 14.65.

IR (thin film NaCl): 3407, 3079, 2966, 2935, 2875, 2836, 1611, 1585, 1511, 1463, 1373, 1303, 1249, 1172, 1110, 1076, 1037 cm^{-1}.

HRMS (EI) *m/z* 232.146 [M^+; calcd for $C_{15}H_{20}O_2$: 232.146].

Chiral HPLC analysis (Chiralpak AD-H, hexanes: 2-propanol, 98:2, 1.0 mL/min): t_R[*major*] = 21.38 min; t_R[*minor*] = 24.96 min.

$[\alpha]_D$ = + 34.3 (23 °C, 589 nm, 1.00 g/100 mL, $CHCl_3$).



(+)-(2*E*)-1-(4-Chloro-phenyl)-2-ethyl-4-methyl-penta-2,4-dien-1-ol (3.7): In the reductive coupling of **2.11** (47 mg, 0.5 mmol, 63 μL) and 4-chlorobenzaldehyde (141 mg, 1.0 mmol), Procedure B was used, but the reaction was conducted at 35 °C (i.e. the reaction flask was placed in a 35 °C oil bath prior to addition of the enyne and then stirred at this temperature for the duration of the reaction.) Silica gel chromatography afforded the title compound as a clear oil (64 mg, 54% yield, 55% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R_f = 0.24 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.35 (m, 4H); 6.13 (s, 1H); 5.20 (s, 1H); 5.00 – 5.01 (m, 1H); 4.91 (t, J = 1 Hz, 1H); 2.21 – 2.30 (m, 1H); 1.96 – 2.05 (m, 1H); 1.91 (s, 3H); 1.73 (d, J = 3 Hz, 3H); 0.93 (t, J = 7.5 Hz, 3H).

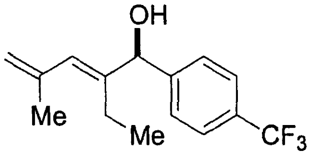
^{13}C NMR (125 MHz, $CDCl_3$) δ 144.19, 141.60, 141.10, 133.49, 128.69, 128.31, 128.29, 115.29, 77.55, 23.63, 21.55, 14.80.

IR (thin film NaCl): 3360, 3083, 2967, 2935, 2875, 1903, 1633, 1597, 1490, 1456, 1408, 1374, 1242, 1167, 1091, 1015 cm^{-1}.

HRMS (EI) *m/z* 236.097 [M^+; calcd for $C_{14}H_{17}ClO$: 236.096].

Chiral HPLC analysis (Chiralpak AD-H, hexanes: 2-propanol, 98:2, 1.0 mL/min): t_R[*major*] = 14.73 min; t_R[*minor*] = 12.80 min.

$[\alpha]_D$ = + 17.0 (23 °C, 589 nm, 1.00 g/100 mL, $CHCl_3$).



(+)-(2*E*)-2-Ethyl-4-methyl-1-(4-trifluoromethyl-phenyl)-penta-2,4-dien-1-ol (3.8): In the reductive coupling of **2.11** (47 mg, 0.5 mmol, 63 μL) and 4-(trifluoromethyl)benzaldehyde (174 mg, 1.0 mmol, 137 μL), Procedure A was used, except that the reaction was conducted at 35 °C (i.e. the reaction flask was placed in a 35 °C oil bath prior to addition of the enyne and then stirred at this temperature for the duration of the reaction.) Silica gel chromatography afforded the title compound as a clear oil (84 mg, 62% yield, 50% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R_f = 0.56 (7:3 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 8 Hz, 2H); 7.53 (d, J = 8 Hz, 2H); 6.14 (s, 1H); 5.28 (d, J = 3.5 Hz, 1H); 5.02 (s, 1H); 4.93 (s, 1H); 2.22 – 2.26 (m, 1H); 2.02 – 2.07 (m, 1H); 1.96 (d, J = 3.5 Hz, 1H); 1.91 (s, 3H); 0.94 (t, J = 6.5 Hz, 3H).

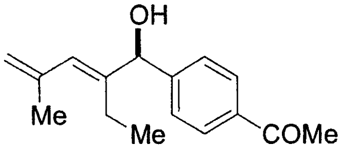
^{13}C NMR (125 MHz, $CDCl_3$) δ 144.48, 141.97, 131.27, 129.56, 127.59, 125.97, 125.94 (q, J = 16 Hz), 116.06, 78.41, 24.06, 21.93, 15.34 (two of the ^{13}C signals are isochronous).

IR (thin film NaCl): 3363, 2967, 2932, 1620, 1461, 1414, 1375, 1326, 1166, 1129, 1068, 1018 cm^{-1}.

HRMS (EI) *m/z* 270.122 [M^+; calcd for $C_{15}H_{17}F_3O$: 270.123].

Chiral HPLC analysis (Chiralcel OD-H, hexanes: 2-propanol, 98:2, 1 mL/min): t_R[*major*] = 10.25 min; t_R[*minor*] = 8.79 min.

$[\alpha]_D$ = +3.0 (23 °C, 589 nm, 1.0 g/100 mL, $CHCl_3$).



(+)-(2*E*)-1-[4-(2-Ethyl-1-hydroxy-4-methyl-penta-2,4-dienyl)-phenyl]-ethanone (3.9): In the reductive coupling of **2.11** (47 mg, 0.5 mmol, 63 μL) and 4-acetylbenzaldehyde (148 mg, 1.0 mmol), Procedure B was used, except that the reaction was conducted at 35 °C (i.e. the reaction flask was placed in a 35 °C oil bath prior to addition of the enyne and then stirred at this temperature for the duration of the reaction.) Silica gel chromatography afforded the title compound as a clear oil (67 mg, 55% yield, 56% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R_f = 0.30 (7:3 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.5 Hz, 2H); 7.50 (d, *J* = 8.5 Hz, 2H); 6.13 (s, 1H); 5.29 (s, 1H); 5.01 (dd, *J* = 2.5, 1.5 Hz, 1H); 4.92 (t, *J* = 1 Hz, 1H); 2.61 (s, 3H); 2.22 – 2.25 (m, 1H); 2.02 – 2.2.05 (m, 1H); 2.02 (d, *J* = 2.5 Hz, 1H); 1.90 (s, 3H); 0.92 (t, *J* = 7.5 Hz, 3H).

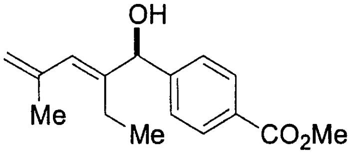
^{13}C NMR (125 MHz, $CDCl_3$) δ 198.41, 148.29, 144.33, 141.80, 136.80, 129.32, 128.92, 127.21, 115.78, 78.35, 27.17, 23.85, 21.73, 15.16.

IR (thin film NaCl): 3448, 2965, 2932, 1683, 1607, 1573, 1501, 1411, 1359, 1304, 1269, 1205, 1075, 1016 cm^{-1}.

HRMS (EI) *m/z* 244.146 [M$^+$; calcd for $C_{16}H_{20}O_2$: 244.146].

Chiral HPLC analysis (Chiralcel OJ, hexanes: 2-propanol, 98:2, 1 mL/min): t_R[*major*] = 55.73 min; t_R[*minor*] = 77.66 min.

$[\alpha]_D$ = +1.3 (23 °C, 589 nm, 0.76 g/100 mL, $CHCl_3$).

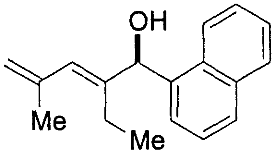


(+)-(2*E*)-4-(2-Ethyl-1-hydroxy-4-methyl-penta-2,4-dienyl)-benzoic acid methyl ester (3.10): In the reductive coupling of **2.11** (47 mg, 0.5 mmol, 63 μL) and methyl 4-formylbenzoate (164 mg, 1.0 mmol), Procedure B was used, except that the reaction was conducted at 35 °C (i.e. the reaction flask was placed in a 35 °C oil bath prior to addition of the enyne and then stirred at this temperature for the duration of the reaction.) Silica gel chromatography afforded the title compound as a clear oil (84 mg, 65% yield, 53% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R_f = 0.40 (7:3 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.5 Hz, 2H); 7.47 (d, *J* = 8 Hz, 2H); 6.13 (s, 1H); 5.28 (d, *J* = 3.5 Hz, 1H); 5.00 (dd, *J* = 2.5, 1.5 Hz, 1H); 4.91 (t, *J* = 1 Hz, 1H); 3.92 (s, 3H); 2.12 – 2.26 (m, 1H), 2.02 – 2.07 (m, 1H); 1.97 (d, *J* = 3.5 Hz, 1H); 1.59 (s, 3H); 0.91 (t, J = 7.5 Hz, 3H).

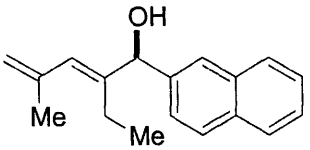
^{13}C NMR (125 MHz, $CDCl_3$) δ 167.21, 147.85, 144.05, 141.51, 129.78, 129.36, 128.83, 126.73, 115.38, 77.97, 52.23, 23.52, 21.39, 14.80.

IR (thin film NaCl): 3460, 2965, 1723, 1611, 1577, 1437, 1412, 1374, 1285, 1192, 1114, 1019 cm^{-1}.
HRMS (EI) *m/z* 260.140 [M$^+$; calcd for $C_{16}H_{20}O_3$: 260.141].
Chiral HPLC analysis (Chiralcel OJ, hexanes: 2-propanol, 98:2, 1 mL/min): t_R[*major*] = 36.26 min; t_R[*minor*] = 51.94 min.
[α]$_D$ = +1.9 (23 °C, 589 nm, 1.6 g/100 mL, $CHCl_3$).



(+)-(2*E*)-2-Ethyl-4-methyl-1-naphthalen-1-yl-penta-2,4-dien-1-ol (3.11): In the reductive coupling of **2.11** (47 mg, 0.5 mmol, 63 μL) and 1-naphthaldehyde (156 mg, 1.0 mmol, 136 μL), Procedure A was used. Silica gel chromatography (use of a 3:1 toluene:hexanes to toluene gradient was required to remove unreacted aldehyde) afforded the title compound as a clear oil (65 mg, 52% yield, 48% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R$_f$= 0.41 (5:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 – 8.20 (m, 1H); 7.87 – 7.90 (m, 1H); 7.82 (d, *J* = 8.5 Hz, 1H); 7.67 (d, *J* = 7.5 Hz, 1H); 7.47 – 7.55 (m, 3H); 6.23 (s, 1H); 5.97 (d, *J* = 4 Hz, 1H); 4.99 – 5.02 (m, 1H); 4.92 (t, *J* = 1 Hz, 1H); 2.36 – 2.44 (m, 1H); 2.01 – 2.09 (m, 1H); 1.98 (d, *J* = 4.5 Hz, 1H); 1.91 (s, 3H); 0.93 (t, *J* = 7.5 Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 143.97, 141.87, 137.79, 134.06, 131.53, 129.02, 128.97, 128.66, 126.30, 125.78, 125.57, 124.79, 123.89, 114.93, 74.56, 23.74, 22.29, 14.72.
IR (thin film NaCl): 3348, 3050, 2966, 2934, 2874, 1632, 1598, 1510, 1457, 1395, 1373, 1260, 1163, 1057, 1001 cm^{-1}.
HRMS (EI) *m/z* 252.150 [M$^+$; calcd for $C_{18}H_{20}O$: 252.151].
Chiral HPLC analysis (Chiralcel OJ, hexanes: 2-propanol, 98:2, 1.0 mL/min): t_R[*major*] = 25.73 min; t_R[*minor*] = 28.33 min.
[α]$_D$ = +26.0 (23 °C, 589 nm, 1.00 g/100 mL, $CHCl_3$).



(+)-(2*E*)-2-Ethyl-4-methyl-1-naphthalen-2-yl-penta-2,4-dien-1-ol (3.12): In the reductive coupling of **2.11** (47 mg, 0.5 mmol, 63 μL) and 2-naphthaldehyde (156 mg, 1.0 mmol), Procedure B was used. Silica gel chromatography (use of a 3:1 toluene:hexanes to toluene gradient was required to remove unreacted aldehyde) afforded the title compound as a clear oil (59 mg, 47% yield, 58% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R$_f$= 0.44 (5:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 – 7.90 (m, 4H); 7.46 – 7.52 (m, 3H); 6.24 (s, 1H); 5.40 (d, *J* = 3.5 Hz, 1H); 5.01 (m, 1H); 4.94 (s, 1H); 2.28 – 2.36 (m, 1H); 2.01 – 2.09 (m, 1H); 1.98 (d, *J* = 3.5 Hz, 1H); 1.93 (s, 3H); 0.96 (t, *J* = 7.5 Hz, 3H).

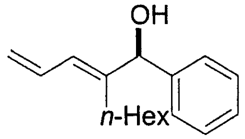
^{13}C NMR (125 MHz, $CDCl_3$) δ 144.31, 141.81, 140.02, 133.44, 133.19, 128.35, 128.23, 128.09, 127.88, 126.31, 126.11, 125.67, 125.01, 115.13, 78.16, 23.72, 21.75, 14.82.

IR (thin film NaCl): 3375, 3056, 2967, 2934, 2874, 1725, 1633, 1601, 1508, 1456, 1373, 1270, 1244, 1161, 1122, 1077, 1042 cm^{-1}.

HRMS (EI) *m/z* 252.151 [M^+; calcd for $C_{18}H_{20}O$: 252.151].

Chiral HPLC analysis (Chiralcel OJ, hexanes: 2-propanol, 98:2, 1.0 mL/min): t_R[*major*] = 39.71 min; t_R[*minor*] = 36.88 min.

$[\alpha]_D$ = +23.0 (23 °C, 589 nm, 1.00 g/100 mL, $CHCl_3$).



(+)-(2*E*)-2-Hexyl-1-phenyl-penta-2,4-dien-1-ol (3.18): In the reductive coupling of **2.4** (64 mg, 0.5 mmol) and benzaldehyde (106 mg, 1.0 mmol, 101 μL), Procedure A was used, except that the reaction was conducted at 0 °C (i.e. the reaction flask was placed in a 0 °C ice bath prior to addition of the aldehyde and enyne and was stirred at this temperature for the duration of the reaction.) Silica gel chromatography afforded the title compound as a clear oil (81 mg, 66% yield, 32% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R_f = 0.58 (7:3 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.38 (m, 3H); 7.27 – 7.30 (m, 2H); 6.57 – 6.65 (m, 1H); 6.32 (d, *J* = 11 Hz, 1H); 5.29 (dd, *J* = 17, 2 Hz, 1 H); 5.21 (d, *J* = 3 Hz, 1H); 5.17 (dd, *J* = 11, 2 Hz, 1H); 2.13 – 2.18 (m, 1 H); 1.92 – 1.97 (m, 1 H); 1.94 (d, *J* = 3.5 Hz, 1H); 1.19 – 1.31 (m, 10H); 0.86 (t, *J* = 7 Hz, 3H).

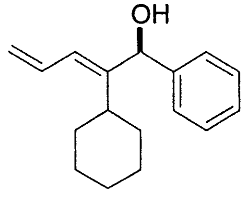
^{13}C NMR (125 MHz, $CDCl_3$) δ 144.80, 142.43, 132.85, 128.58, 127.90, 126.97, 117.83, 77.80, 31.73, 30.00, 29.75, 28.569, 22.76, 14.27.

IR (thin film NaCl): 3424, 3063, 3030, 2956, 2929, 2858, 1703, 1657, 1598, 1496, 1454, 1378, 1319, 1272, 1204, 1025 cm^{-1}.

HRMS (EI) *m/z* 244.182 [M^+; calcd for $C_{17}H_{24}O$: 244.1822].

Chiral HPLC analysis (Chiralcel OJ, hexanes: 2-propanol, 99.5:0.5, 0.5 mL/min): t_R[*major*] = 37.42 min; t_R[*minor*] = 41.77 min.

$[\alpha]_D$ = +21.9 (23 °C, 589 nm, 0.96 g/100 mL, $CHCl_3$).



(+)-(2*E*)-2-Cyclohexyl-1-phenyl-penta-2,4-dien-1-ol (3.19): In the reductive coupling of **2.8** (67 mg, 0.5 mmol, 77 μL) and benzaldehyde (106 mg, 1.0 mmol, 101 μL), Procedure A was used. Silica gel chromatography (toluene: hexanes; 3:1) afforded the title compound as a clear yellow oil (86 mg, 70% yield, 42% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R$_f$ = 0.19 (9:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.26 – 7.39 (m, 5H); 6.74-6.82 (ddd, *J* = 16.8, 11.1, 10.0 Hz, 1H), 6.23 (dd, *J* = 11.1, 0.8 Hz, 1H); 5.29 (d, *J* = 3.2 Hz, 1H); 5.24 (dd, *J* = 16.8, 2.0 Hz, 1H); 5.15 (dd, *J* = 10.0, 2.0 Hz, 1H); 2.41 – 2.46 (m, 1H), 1.81 (d, *J* = 3.7 Hz, 1H), 1.72 – 1.76 (m, 1H), 1.48 – 1.66 (m, 4H), 1.33 – 1.35 (m, 1H), 1.07 – 1.28 (m, 5H).

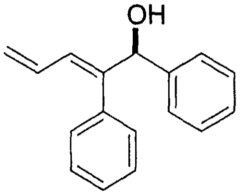
^{13}C NMR (125 MHz, CDCl$_3$) δ 148.7, 142.8, 132.8, 128.4 (2C), 127.7, 127.2 (2C), 126.4, 118.0, 75.7, 40.1, 32.3, 32.2, 27.09, 27.06, 26.2.

IR (thin film NaCl): 3421, 3062, 3029, 2927, 2852, 1660, 1449 cm^{-1}.

HRMS (EI) *m/z* 242.1671 [M$^+$; calcd for $C_{17}H_{22}O$: 242.1665].

Chiral HPLC analysis (Chiralcel OD-H, hexanes: 2-propanol, 98:2, 0.8 mL/min): t$_R$[*major*] = 16.47 min; t$_R$[*minor*] = 18.16 min.

[α]$_D$ = +2.5 (23 °C, 589 nm, 0.80 g/100 mL, CHCl$_3$).



(+)-(2*E*)-1,2-Diphenyl-penta-2,4-dien-1-ol (3.20): In the reductive coupling of **2.6** (64 mg, 0.5 mmol, 68 μL) and benzaldehyde (106 mg, 1.0 mmol, 101 μL), Procedure A was used. Silica gel chromatography afforded the title compound as a clear yellow oil (69 mg, 58% yield, 44% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R$_f$ = 0.13 (9:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.20 – 7.34 (m, 7H); 7.01 – 7.05 (m, 3H), 6.54 (d, *J* = 11.0 Hz, 1H), 6.26 – 6.34 (ddd, *J* = 16.9, 11.0, 10.1 Hz, 1H), 5.51 (s, 1H); 5.36 (dd, *J* = 16.9, 2.0 Hz, 1H); 5.11 (dd, *J* = 10.1, 2.0 Hz, 1H); 2.35 (s, 1H).

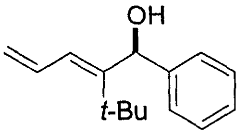
^{13}C NMR (125 MHz, CDCl$_3$) δ 145.1, 141.9, 137.7, 134.0, 129.6 (2C), 128.4 (2C),128.2 (2C), 127.9, 127.8, 127.5, 127.0 (2C), 119.0, 78.1.

IR (thin film NaCl): 3402, 3060, 3031, 2927, 1667, 1600, 1493, 1450 cm^{-1}.

HRMS (EI) *m/z* 236.1193 [M$^+$; calcd for $C_{17}H_{16}O$: 236.1196].

Chiral HPLC analysis (Chiralcel OD-H, hexanes: 2-propanol, 98:2, 1.0 mL/min): t$_R$[*major*] = 17.47 min; t$_R$[*minor*] = 22.45 min.

[α]$_D$ = +2.5 (23 °C, 589 nm, 1.6 g/100 mL, CHCl$_3$).



(+)-(2*E*)-2-tert-Butyl-1-phenyl-penta-2,4-dien-1-ol (3.21): In the reductive coupling of **2.9** (54 mg, 0.5 mmol, 73 μL) and benzaldehyde (106 mg, 1.0 mmol, 101 μL), Procedure A was used except that the reaction was conducted at 65 °C in the following manner: a solution of Ni(cod)$_2$, (*R*)-**3.2**, EtOAc and Et_3B was prepared at room temperature as described in the general procedure, then heated to 65 °C in an oil bath for 5 min before simultaneous addition of aldehyde and enyne. Silica gel chromatography afforded the title compound as a clear pale yellow oil (71 mg, 66% yield, 33% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R_f = 0.13 (9:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.40 (m, 4H), 7.28 – 7.30 (m, 1H), 7.00 – 7.08 (m, 1H), 6.35 (d, *J* = 11.6 Hz, 1H), 5.47 (d, *J* = 4.6 Hz, 1H), 5.17 – 5.22 (m, 2H), 1.75 (d, *J* = 4.6 Hz, 1H), 1.20 (s, 9H).

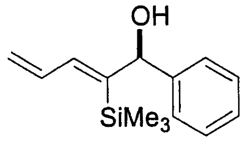
^{13}C NMR (125 MHz, $CDCl_3$) δ 149.8, 143.5, 134.2, 128.7 (2C), 127.8, 127.7, 127.6 (2C), 118.6, 75.3, 35.8, 31.4 (3C).

IR (thin film NaCl): 3355, 3085, 3029, 2957, 2872, 1630, 1601, 1453 cm^{-1}.

HRMS (EI) *m/z* 216.1509 [M$^+$; calcd for $C_{15}H_{20}O$: 216.1508].

Chiral HPLC analysis (Chiralcel OJ, hexanes: 2-propanol, 95:5, 1.0 mL/min): t_R[*major*] = 13.24 min; t_R[*minor*] = 7.11 min.

[α]$_D$ = +5.0 (23 °C, 589 nm, 1.0 g/100 mL, $CHCl_3$).



(2*E*)-1-Phenyl-2-(trimethyl-silanyl)-penta-2,4-dien-1-ol (3.22): In the reductive coupling of **3.13** (62 mg, 0.5 mmol) and benzaldehyde (106 mg, 1.0 mmol, 101 μL), the standard procedure was used, except that the reaction was conducted at 0 °C (i.e. the reaction flask was placed in a 0 °C ice bath prior to addition of the aldehyde and enyne and was stirred at this temperature for the duration of the reaction.) Silica gel chromatography afforded the title compound as a clear oil (62 mg, 53% yield, 14% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R_f = 0.64 (7:3 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.37 (m, 5 H); 6.94 (d, *J* = 11.5 Hz, 1H); 6.74 – 6.81 (m, 1H); 5.40 (d, *J* = 3 Hz, 1H); 5.33 (dd, *J* = 16.5, 1.5 Hz, 1H); 5.29 (dd, *J* = 10, 1.5 Hz, 1H); 1.90 (d, J = 4.5 Hz, 1H); 0.04 (s, 9H) ppm.

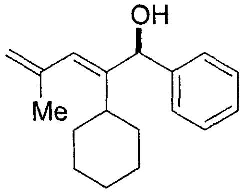
^{13}C NMR (125 MHz, $CDCl_3$) δ 145.96, 142.85, 141.08, 135.60, 128.52, 127.78, 127.48, 120.13, 78.40, 0.73 ppm.

IR (thin film NaCl): 3372, 3061, 3086, 3029, 2956, 2927, 2855, 1602, 1569, 1493, 1453, 1408, 1250, 1190, 1064, 1032, 841 cm^{-1}.

HRMS (EI) *m/z* 231.112 [(M – H)$^+$; calcd for $C_{14}H_{18}O$: 231.120].

Chiral HPLC analysis (Chiralcel OD-H, hexanes: 2-propanol, 98:2, 1 mL/min): t_R[*major*] = 11.14 min; t_R[*minor*] = 12.27 min.

[α]$_D$ = +2.3 (23 °C, 589 nm, 0.87 g/100 mL, $CHCl_3$).



(+)-(2*E*)-2-Cyclohexyl-4-methyl-1-phenyl-penta-2,4-dien-1-ol (3.23): In the reductive coupling of **3.14** (74 mg, 0.5 mmol, 80 μL) and benzaldehyde (106 mg, 1.0 mmol, 101 μL), Procedure A was used except that the reaction was conducted at 38 °C in the following manner: a solution of Ni(cod)$_2$, (*R*)-**3.2**, EtOAc and Et$_3$B was prepared at ambient temperature as described in the general procedure, then heated 5 min in a 38 °C oil bath before simultaneous addition of enyne and aldehyde. Silica gel chromatography afforded the title compound as a clear oil (98 mg, 77% yield, 55% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R$_f$ = 0.12 (9:1 hexanes: ethyl acetate). Absolute configuration of the major enantiomer was determined to be (*R*) via Mosher's ester analysis (vide infra).

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.37 – 7.41 (m, 2H); 7.30 – 7.36 (m, 2H); 7.26 – 7.29 (m, 1H), 6.03 (s, 1H); 5.35 (d, *J* = 4.0 Hz, 1H); 4.99 – 5.00 (m, 1H); 4.79 – 4.80 (m, 1H); 2.77 – 2.83 (m, 1H), 1.86 – 1.87 (m, 3H); 1.67 – 1.79 (m, 2H); 1.61 – 1.64 (m, 3H), 1.55 (qd, *J* = 12.5, 3.4 Hz, 1H), 1.07 – 1.34 (m, 5H).

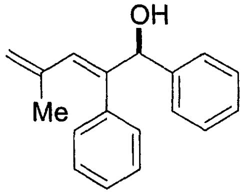
^{13}C NMR (125 MHz, CDCl$_3$) δ 148.1, 143.7, 141.9, 128.7, 128.5 (2C), 127.6, 127.3 (2C), 114.1, 73.7, 40.2, 32.7, 32.5, 26.9, 26.8, 26.3, 24.3.

IR (thin film NaCl): 3387, 3029, 2927, 2851, 1631, 1602, 1449 cm^{-1}.

HRMS (EI) *m/z* 256.1821 [M$^+$; calcd for C$_{18}$H$_{24}$O: 256.1822].

Chiral HPLC analysis (Chiralcel AD-H, hexanes: 2-propanol, 98:2, 1.0 mL/min): t$_R$[*major*] = 16.70 min; t$_R$[*minor*] = 13.14 min.

[α]$_D$ = +2.5 (23 °C, 589 nm, 1.2 g/100 mL, CHCl$_3$).



(+)-(2*E*)-4-Methyl-1,2-diphenyl-penta-2,4-dien-1-ol (3.24): In the reductive coupling of **3.16** (71 mg, 0.5 mmol, 76 μL) and benzaldehyde (106 mg, 1.0 mmol, 101 μL), Procedure A was used. Silica gel chromatography afforded the title compound as a clear yellow oil (53 mg, 42% yield, 54% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R$_f$ = 0.15 (9:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.25 – 7.32 (m, 5H); 7.19 – 7.23 (m, 3H); 6.91 – 6.93 (m, 2H), 6.55 (s, 1H); 5.42 (s, 1H); 4.98 (s, 1H); 4.94 (s, 1H); 2.23 (s, 1H), 1.39 (s, 3H).

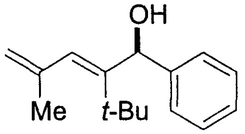
^{13}C NMR (125 MHz, CDCl$_3$) δ 143.1, 141.9, 141.8, 138.3, 129.9 (2C), 129.8, 128.3 (2C), 127.70 (2C), 127.69, 127.3, 126.9 (2C), 119.0, 79.5, 22.3.

IR (thin film NaCl): 3419, 3060, 3029, 2963, 2932, 2873, 1663, 1598, 1450 cm^{-1}.

HRMS (EI) *m/z* 250.1342 [M$^+$; calcd for C$_{18}$H$_{18}$O: 250.1352].

Chiral HPLC analysis (Chiralcel AD-H, hexanes: 2-propanol, 98:2, 1.0 mL/min): t_R[*major*] = 18.80 min; t_R[*minor*] = 20.49 min.

$[\alpha]_D$ = +1.3 (23 °C, 589 nm, 3.0 g/100 mL, $CHCl_3$).



(+)-(2*E*)-2-*tert*-Butyl-4-methyl-1-phenyl-penta-2,4-dien-1-ol (3.25): In the reductive coupling of **3.16** (61 mg, 0.5 mmol, 81 μL) and benzaldehyde (106 mg, 1.0 mmol, 101 μL), Procedure A was used except that the reaction was conducted at 65 °C in the following manner: a solution of $Ni(cod)_2$, (*R*)-**3.2**, EtOAc and Et_3B was prepared at ambient temperature as described in the general procedure, then heated 5 min in a 65 °C oil bath before simultaneous addition of enyne and aldehyde. Silica gel chromatography (3:1 toluene: hexanes) afforded the title compound as a clear pale yellow oil (74 mg, 64% yield, 52% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R_f = 0.09 (3:1 toluene: hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.43 (m, 2H); 7.34 – 7.37 (m, 2H); 7.27 – 7.30 (m, 1H), 6.11 – 6.12 (m, 1H), 5.42 (d, *J* = 4.6 Hz, 1H), 4.90 – 4.91 (m, 1H); 4.79 – 4.80 (m, 1H), 1.86 – 1.87 (m, 3H); 1.76 (m, 1H), 1.18 (s, 9H).

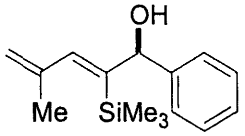
^{13}C NMR (125 MHz, $CDCl_3$) δ 148.8, 144.9, 144.1, 130.5, 128.6 (2C), 127.6, 127.4 (2C), 113.2, 74.5, 36.6, 31.1 (3C), 24.4.

IR (thin film NaCl): 3375, 3081, 3029, 2964, 2870, 1622, 1453 cm^{-1}.

HRMS (EI) *m/z* 230.1661 [M^+; calcd for $C_{16}H_{22}O$: 230.1665].

Chiral HPLC analysis (Chiralcel OJ, hexanes: 2-propanol, 95:5, 1.0 mL/min): t_R[*major*] = 6.37 min; t_R[*minor*] = 5.12 min.

$[\alpha]_D$ = +3.6 (23 °C, 589 nm, 1.1 g/100 mL, $CHCl_3$).



(+)-(2*Z*)-4-Methyl-1-phenyl-2-trimethylsilanyl-penta-2,4-dien-1-ol (3.26): In the reductive coupling of **3.17** (69 mg, 0.5 mmol, 88 μL) and benzaldehyde (106 mg, 1.0 mmol, 101 μL), Procedure A was used. Silica gel chromatography (toluene: hexanes; 3:1) afforded the title compound as a clear oil (85 mg, 69% yield, 28% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R_f = 0.21 (9:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.36 (m, 4H); 7.26 – 7.27 (m, 1H); 6.81 (s, 1H); 5.34 (d, *J* = 1.4 Hz, 1H); 4.92 – 4.93 (m, 1H); 4.89 – 4.90 (m, 1H); 1.85 – 1.86 (m, 3H); 1.79 (s, 1H); 0.01 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 143.7, 143.1, 142.4, 128.5 (2C), 127.8, 127.7 (2C), 114.2, 77.8, 23.2, 1.1 (3C).

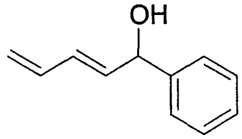
IR (thin film NaCl): 3391, 3030, 2966, 2898, 1601, 1492, 1453 cm^{-1}.

HRMS (EI) *m/z* 245.1363 [(M – H)$^+$; calcd for $C_{15}H_{22}OSi$: 245.1362].

Chiral HPLC analysis (Chiralcel OD-H, hexanes: 2-propanol, 99:1, 1.0 mL/min): t$_R$[*major*] = 18.19 min; t$_R$[*minor*] = 13.74 min.

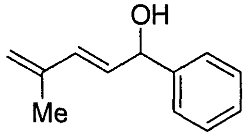
$[\alpha]_D$ = +4.5 (23 °C, 589 nm, 0.67 g/100 mL, $CHCl_3$).

Protiodesilylation of Dienyl Alcohols 3.22 and 3.26.



1-Phenyl-penta-2,4-dien-1-ol (3.27): A solution of **3.22** (0.37 mg, 0.16 mmol) in THF in (1.6 mL) was cooled to 0 °C. Tetrabutylammonium fluoride (0.4 mL, 1.0 M in THF, 0.4 mmol) was added dropwise via syringe and the solution was stirred 1 h at 0 °C. H_2O was added (2 mL) and the mixture was partitioned between EtOAc (15 mL) and brine (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (1 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel using a solvent gradient (hexanes: ethyl acetate; 93:7 to 90:10) to afford the title compound as a clear, colorless oil (20 mg, 79% yield). Spectral data were consistent with those previously reported.[56]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.41 (m, 5H); 6.29 – 6.43 (m, 2H); 5.89 – 5.94 (m, 1H); 5.12 – 5.32 (m, 3H); 1.98 (d, *J* = 6 Hz, 1H).



(–)-(2*E*)-4-Methyl-1-phenyl-penta-2,4-dien-1-ol (3.28): A solution of **3.26** (78 mg, 0.32 mmol) in THF (2.85 mL) was cooled to 0 °C. Tetrabutylammonium fluoride (0.35 mL, 1.0 M in THF, 0.35 mmol) was added dropwise via syringe and the solution was stirred 10 min at 0 °C. H_2O was added (2 mL) and the mixture was partitioned between EtOAc (15 mL) and brine (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (1 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel using a solvent gradient (hexanes: ethyl acetate; 93:7 to 90:10) to afford the title compound as a clear, colorless oil (46 mg, 84% yield, 25% ee, >95:5 regioselectivity, >95:5 *E/Z*). R_f = 0.09 (9:1 hexanes: ethyl acetate).

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[56] Carreño, M. C.; García-Cerrada, S.; Urbano, A.; Di Vitta, C. *J. Org. Chem.* **2000**, 65, 4355-4363.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.41 (m, 4H), 7.29 – 7.32 (m, 1H), 6.42 (d, J = 15.7 Hz, 1H), 5.84 (dd, J = 15.7, 6.7 Hz, 1H), 5.27 (dd, J = 6.7, 2.0 Hz, 1H), 5.04 (s, 2H), 2.27 (d, J = 2.0 Hz, 1H), 1.86 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 143.1, 141.5, 133.7, 131.7, 128.7 (2C), 127.8, 126.4 (2C), 117.5, 75.2, 18.7.

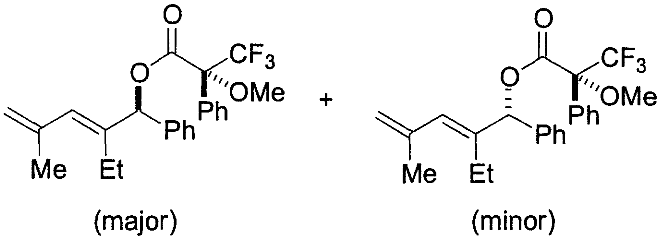
IR (thin film NaCl): 3357, 3083, 3029, 2919, 2851, 1609, 1451 cm^{-1}.

HRMS (EI) *m/z* 174.1039 [M$^+$; calcd for $C_{12}H_{14}O$: 174.1036].

Chiral HPLC analysis (Chiralcel OD-H, hexanes: 2-propanol, 99.5:0.5, 0.7 mL/min): t_R[*major*] = 7.94 min; t_R[*minor*] = 8.49 min.

$[\alpha]_D$ = –11.2 (23 °C, 589 nm, 1.0 g/100 mL, $CHCl_3$).

Absolute Configuration Determination of 3.3 via Mosher's Ester Analysis.[57]



Alcohol **3.3** (22 mg, 0.11 mmol, 56% ee) was dissolved in CH_2Cl_2 (4 mL). (+)-Mosher's acid (47 mg, 0.20 mmol), dicyclohexylcarbodiimide (45 mg, 0.22 mmol), and DMAP (3 mg, 0.022 mmol) were added sequentially, and the reaction was stirred at ambient temperature overnight. The reaction mixture was then washed through a plug of silica with CH_2Cl_2 (50 mL) and concentrated in vacuo to yield a colorless oil (44 mg, 95% yield). A ^{1}H NMR spectrum showed the alkenyl peaks of the major diastereomer to be upfield (shielded) relative to the minor diastereomer indicating the *R* absolute configuration of **3.3**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.45 (m, 14H); 6.52 (s, 1.4H); 6.09 (s, 0.4 H); 5.89 (s, 1H); 5.01 (s, 0.4H); 4.97 (s, 1H); 4.89 (s, 0.4H); 4.81 (s, 1H); 3.54 (s, 1.2 H); 3.49 (s, 3H); 2.21 – 2.26 (m, 1.4H); 2.05 – 2.14 (m, 0.4H); 1.93 – 1.97 (m, 1H); 1.87 (s, 1.2H); 1.81 (s, 3H); 0.93 (t, J = 7.5 Hz, 1.2 H); 0.87 (t, J = 7.5 Hz, 3H).

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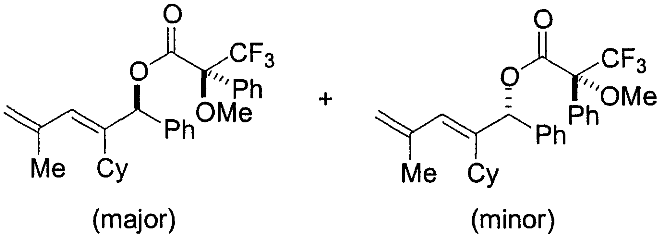
[57] (a) Mosher, H. S.; Dale, J. A. *J. Am. Chem. Soc.* **1973**, *95*, 512-519. (b) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543-2549.

Absolute Configuration Determination of 3.23 via Mosher's Ester Analysis.[57]



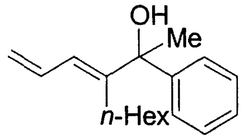
Alcohol **3.23** was dissolved in CH_2Cl_2 (0.6 mL). Triethylamine (10 μL), (*R*)-(−)- α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (Mosher acid chloride, 10 μL), and 4-dimethylaminopyridine (1 mg) were added sequentially. The mixture was stirred 2 h over which time a yellow color was assumed, and then the solvent was removed *in vacuo*. The crude residue was purified via silica gel chromatography (50:1 hexanes:EtOAc to 9:1 hexanes:EtOAc solvent gradient) to afford the product as a clear, colorless oil (11 mg, 61% yield, 3.6:1 dr). ^{1}H NMR analysis of the product clearly showed the alkenyl peaks of the major diastereomer to be downfield (deshielded) relative to the minor diastereomer indicating the *R* absolute configuration of **3.23**.

^{1}H NMR (500 MHz, C_6D_6) δ 7.29 – 7.44 (m, 10H), 6.64 (s, 1H, major), 6.62 (s, 1H, minor), 6.07 (br s, 1H, major), 5.83 (br s, 1H, minor), 5.02 (m, 1H, major), 4.98 (m, 1H, minor), 3.51 (s, 3H, major), 3.47 (s, 3H, minor), 2.77 – 2.83 (m, 1H), 1.85 (s, 3H, major), 1.77 (s, 3H, minor), 1.74 – 1.76 (m, 1H), 1.54 – 1.67 (m, 4H), 1.23 – 1.31 (m, 2H), 1.10 – 1.20 (m, 2H), 0.98 – 1.09 (m, 1H, major), 0.85 – 0.96 (m, 1H, minor).

Standard Experimental Procedures for Catalytic, Enantioselective Reductive Coupling of 1,3-Enynes and Ketones:

Procedure A (liquid ketones): In a glovebox, Ni(cod)$_2$ (0.05 mmol, 14 mg) and (*S*)-FcPPh(*o*-MePh) (**3.1**, 0.1 mmol, 28 mg) were added to a 10 mL, round-bottom flask equipped with a magnetic stir bar. The flask was sealed with a septum, removed from the glovebox, and placed under argon. The ketone (1.0 mmol) and Et_3B (1.0 mmol, 150 μL) were then added and the mixture was stirred 5 min to solubilize the ligand and metal. The enyne (0.5 mmol) was taken up in a microsyringe and then added to the flask over 6 h via syringe pump. The reaction was stirred an additional 12 h at 23 °C, and was then quenched by opening to the atmosphere, diluting with diethyl ether (2-3 mL), and stirring 1 h. The crude mixture was then filtered through a silica plug eluting with diethyl ether (25 mL), concentrated in vacuo, and redissolved in MeOH (5 mL). This solution was cooled to 0 °C in an ice bath, and then $NaBH_4$ (1.0 mmol, 38 mg) was added portionwise. The mixture was stirred 5-30 min until consumption of the excess ketone was complete by TLC, and was then concentrated in vacuo, taken up in diethyl ether (10 mL) and water (10 mL), extracted with diethyl ether (3 x 10 mL), dried over $MgSO_4$, and concentrated. Products were purified via flash chromatography on silica gel (50:1 hexanes: ethyl acetate to 10:1 hexanes: ethyl acetate gradient).

Procedure B (solid ketones): In a glovebox, Ni(cod)$_2$ (0.05 mmol, 14 mg), (*S*)-FcPPh(*o*-MePh) (**3.1**, 0.1 mmol, 28 mg), and the ketone (1.0 mmol) were added to a 10 mL, round-bottom flask equipped with a magnetic stir bar. The flask was sealed with a septum, removed from the glovebox, and placed under argon. Et$_3$B (1.0 mmol, 150 μL) and toluene (200 μL) were then added and the mixture was stirred 5 min to solubilize the ligand and metal. The enyne (0.5 mmol) was taken up in a microsyringe and then added to the flask over 6 h via syringe pump. The reaction was stirred an additional 12 h at 23 °C, and then quenched by opening to the atmosphere, diluting with diethyl ether (2-3 mL) and stirring 1 h. The crude mixture was then filtered through a silica plug eluting with diethyl ether (25 mL), concentrated in vacuo, and redissolved in MeOH (5 mL). This solution was cooled to 0 °C in an ice bath, and then NaBH$_4$ (1.0 mmol, 38 mg) was added portionwise. The mixture was stirred 5-30 min until consumption of the excess ketone was complete by TLC, and was then concentrated in vacuo, taken up in diethyl ether (10 mL) and water (10 mL), extracted with diethyl ether (3 x 10 mL), dried over MgSO$_4$, and concentrated. Products were purified via flash chromatography on silica gel (50:1 hexanes: ethyl acetate to 10:1 hexanes: ethyl acetate gradient).



(–)-(3*E*)-3-Allylidene-2-phenyl-nonan-2-ol (3.29): In the reductive coupling of **2.4** (68 mg, 0.5 mmol, 80 μL) and acetophenone (120 mg, 1.0 mmol, 117 μL), Procedure A was used, except that (*R*)-**3.1** was employed. Silica gel chromatography afforded the title compound as a clear oil (80 mg, 62% yield, 60% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R_f = 0.31 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.42 – 7.44 (m, 2H); 7.31 – 7.35 (m, 2H); 7.23 – 7.27 (m, 1H); 6.54 – 6.63 (m, 1H); 6.32 (d, *J* = 11 Hz, 1H); 5.28 (ddd, *J* = 17, 2, 0.5 Hz, 1H); 5.17 (ddd, *J* = 10, 2, 0.5 Hz, 1H); 1.93 – 2.08 (m, 2H); 1.80 (s, 1H); 1.72 (s, 3H); 1.12 – 1.30 (m, 8H); 0.84 (t, *J* = 7 Hz, 3H).

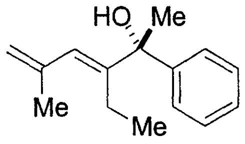
^{13}C NMR (125 MHz, CDCl$_3$) δ 148.21, 146.46, 133.52, 128.26, 127.11, 125.81, 124.74, 117.79, 77.94, 31.64, 30.16, 29.18, 29.14, 22.77, 14.27.

IR (thin film NaCl): 3455, 3085, 2956, 2931, 2859, 1811, 1681, 1639, 1600, 1493, 1447, 1416, 1372, 1269, 1217, 1159, 1099, 1063, 1028 cm^{-1}.

HRMS (EI) *m/z* 258.199 [M$^+$; calcd for C$_{18}$H$_{26}$O: 258.199].

Chiral HPLC analysis (Chiralcel OJ, hexanes: 2-propanol, 99:1, 0.6 mL/min): t$_R$[*major*] = 15.02 min; t$_R$[*minor*] = 20.26 min.

[α]$_D$ = –16.0 (23 °C, 589 nm, 1.00 g/100 mL, CHCl$_3$).



(*S*)-(+)-(3*E*)-3-Ethyl-5-methyl-2-phenyl-hexa-3,5-dien-2-ol (3.30): In the reductive coupling of **2.11** (47 mg, 0.5 mmol, 63 μL) and acetophenone (120 mg, 1.0 mmol, 117 μL), Procedure A was used. Silica gel chromatography afforded the title compound as a clear oil (75 mg, 69% yield, 64% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R_f = 0.36 (10:1 hexanes: ethyl acetate). Absolute configuration of the major enantiomer was determined to be (*S*) by conversion to (*R*)-2-hydroxy-2-phenyl-pentan-3-one (**3.41**, see below).

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.44 – 7.48 (m, 2H); 7.30 – 7.35 (m, 2H); 7.23 – 7.27 (m, 1H); 6.19 (s, 1H); 5.00 (m, 1H); 4.94 (m, 1H); 2.13 – 2.21 (m, 1H); 2.03 – 2.11 (m, 1H); 1.92 (s, 3H); 1.81 (s, 1H); 1.72 (s, 3H); 0.87 (t, *J* = 7 Hz, 3H).

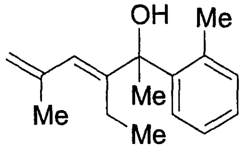
^{13}C NMR (125 MHz, CDCl$_3$) δ 147.66, 146.86, 142.28, 128.26, 127.03, 126.85, 125.78, 114.53, 78.40, 29.56, 23.85, 21.77, 15.65.

IR (thin film NaCl): 3456, 3084, 3060, 3027, 2970, 2936, 2875, 1634, 1601, 1493, 1447, 1372, 1166, 1108, 1067, 1028 cm^{-1}.

HRMS (EI) *m/z* 216.152 [M$^+$; calcd for $C_{15}H_{20}O$: 216.151].

Chiral GC analysis (B-PH, 135 °C, 1.5 mL/min): t_R[*major*] = 20.63 min; t_R[*minor*] = 20.18 min.

[α]$_D$ = +7.0 (23 °C, 589 nm, 1.00 g/100 mL, CHCl$_3$).



(–)-(3*E*)-3-Ethyl-5-methyl-2-*o*-tolyl-hexa-3,5-dien-2-ol (3.31): In the reductive coupling of **2.11** (47 mg, 0.5 mmol, 63 μL) and 2'-methylacetophenone (134 mg, 1.0 mmol, 131 μL), Procedure A was used. Silica gel chromatography afforded the title compound as a clear oil (60 mg, 52% yield, 47% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R_f = 0.46 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.57 – 7.60 (m, 1H); 7.16 – 7.22 (m, 2H); 7.10 – 7.16 (m, 1H); 6.01 (s, 1H); 4.96 (t, *J* = 2 Hz, 1H); 4.88 (d, *J* = 1 Hz, 1H); 2.39 (s, 3H); 2.21 – 2.29 (m, 1H); 2.11 – 2.19 (m, 1H); 1.86 (s, 3H); 1.78 (s, 1H); 1.76 (s, 3H); 0.89 (t, *J* = 7.5 Hz, 3H).

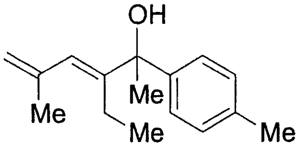
^{13}C NMR (125 MHz, CDCl$_3$) δ 147.05, 144.02, 142.37, 136.97, 132.30, 127.44, 127.17, 126.39, 125.66, 114.08, 78.82, 29.79, 23.76, 21.84, 21.63, 15.83.

IR (thin film NaCl): 3469, 3076, 2969, 2935, 2875, 1633, 1599, 1485, 1454, 1372, 1321, 1220, 1162, 1106, 1083, 1069, 1044 cm^{-1}.

HRMS (EI) *m/z* 230.166 [M$^+$; calcd for $C_{16}H_{22}O$: 230.167].

Chiral HPLC analysis (Chiralcel OJ, hexanes: 2-propanol, 99:1, 0.8 mL/min): t_R[*major*] = 10.55 min; t_R[*minor*] = 15.59 min.

[α]$_D$ = –11.0 (23 °C, 589 nm, 1.00 g/100 mL, CHCl$_3$).



(–)-(3*E*)-3-Ethyl-5-methyl-2-*p*-tolyl-hexa-3,5-dien-2-ol (3.32): In the reductive coupling of **2.11** (47 mg, 0.5 mmol, 63 μL) and 4'-methylacetophenone (134 mg, 1.0 mmol, 133 μL), Procedure A was used. Silica gel chromatography afforded the title compound as a clear oil (82 mg, 71% yield, 64% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R_f = 0.30 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.34 (d, *J* = 8.5 Hz, 2H); 7.14 (d, *J* = 8.5 Hz, 2H); 6.18 (s, 1H); 4.99 (s, 1H); 4.93 (s, 1H); 2.35 (s, 3H); 2.03 – 2.19 (m, 2H); 1.91 (s, 3H); 1.78 (s, 1H); 1.70 (s, 3H); 0.88 (t, *J* = 7 Hz, 3H).

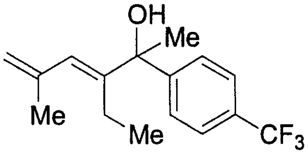
^{13}C NMR (125 MHz, CDCl$_3$) δ 147.79, 143.95, 142.35, 136.63, 128.96, 126.63, 125.72, 114.43, 78.27, 29.49, 23.87, 21.80, 21.23, 15.66.

IR (thin film NaCl): 3462, 3080, 2970, 2935, 2874, 1635, 1512, 1456, 1372, 1187, 1165, 1104, 1072, 1020 cm^{-1}.

HRMS (EI) *m/z* 230.168 [M$^+$; calcd for $C_{16}H_{22}O$: 230.167].

Chiral HPLC analysis (Chiralcel AD-H, hexanes: 2-propanol, 98:2, 1.0 mL/min): t_R[*major*] = 8.66 min; t_R[*minor*] = 9.76 min.

$[\alpha]_D$ = –4.0 (23 °C, 589 nm, 1.00 g/100 mL, CHCl$_3$).



(+)-(3*E*)-3-Ethyl-5-methyl-2-(4-trifluoromethyl-phenyl)-hexa-3,5-dien-2-ol (3.33): In the reductive coupling of **2.11** (47 mg, 0.5 mmol, 63 μL) and 4'-(trifluoromethyl)acetophenone (188 mg, 1.0 mmol), Procedure B was used. Silica gel chromatography afforded the title compound as a clear oil (43 mg, 30% yield, 56% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R_f = 0.26 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.58 (s, 4H); 6.17 (s, 1H); 5.02 (m, 1H); 4.94 (s, 1H); 2.14 – 2.24 (m, 1H); 1.98 – 2.08 (m, 1H); 1.91 (d, *J* = 1 Hz, 3H); 1.82 (s, 1H); 1.72 (s, 3H); 0.88 (t, *J* = 7.5 Hz, 3H).

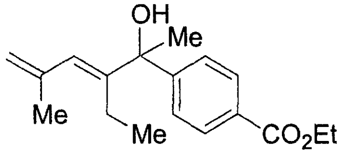
^{13}C NMR (125 MHz, CDCl$_3$) δ 150.98, 146.96, 141.94, 127.79, 126.15, 125.25, 125.23, 125.19, 125.17, 115.01, 78.39, 29.95, 23.75, 21.65, 15.76.

IR (thin film NaCl): 3452, 3082, 2974, 2938, 2877, 1618, 1453, 1411, 1374, 1328, 1166, 1127, 1101, 1072, 1016 cm^{-1}.

HRMS (EI) *m/z* 284.139 [M$^+$; calcd for $C_{16}H_{19}F_3O$: 284.138].

Chiral HPLC analysis (Chiralpak AD-H, hexanes: 2-propanol, 98:2, 0.8 mL/min): t_R[*major*] = 10.3 min; t_R[*minor*] = 8.3 min.

$[\alpha]_D$ = +15.0 (23 °C, 589 nm, 1.00 g/100 mL, CHCl$_3$).



(+)-4-[(2*E*)-2-Ethyl-1-hydroxy-1,4-dimethyl-penta-2,4-dienyl]-benzoic acid ethyl ester (3.34): In the reductive coupling of **2.11** (47 mg, 0.5 mmol, 63 μL) and ethyl 4-acetylbenzoate (192 mg, 1.0 mmol), Procedure B was used. Silica gel chromatography afforded the title compound as a clear oil (87 mg, 60% yield, 58% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R_f = 0.40 (5:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8 Hz, 2H); 7.53 (d, *J* = 8 Hz, 2H); 6.16 (s, 1H); 5.00 (t, *J* = 1 Hz, 1H); 4.93 (t, *J* = 1Hz, 1H); 4.38 (q, *J* = 7 Hz, 2H); 2.14 – 2.22 (m, 1H); 2.00 – 2.08 (m, 1H); 1.91 (t, *J* = 1 Hz, 3H); 1.85 (s, 1H); 1.72 (s, 3H); 1.40 (t, *J* = 7 Hz, 3H); 0.85 (t, *J* = 7.5 Hz, 3H).

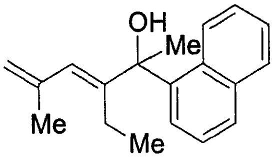
^{13}C NMR (125 MHz, $CDCl_3$) δ 166.74, 152.05, 147.08, 142.01, 129.56, 127.56, 125.78, 114.88, 78.45, 61.10, 29.77, 23.76, 21.63, 15.71, 14.57.

IR (thin film NaCl): 3480, 2980, 2937, 2876, 1942, 1716, 1609, 1575, 1504, 1449, 1408, 1369, 1277, 1182, 1109, 1020 cm^{-1}.

HRMS (EI) *m/z* 289.180 [(M + H)$^+$; calcd for $C_{18}H_{24}O_3$: 289.180].

Chiral HPLC analysis (Chiralpak AD-H, hexanes: 2-propanol, 98:2, 1.0 mL/min): t_R[*major*] = 19.94 min; t_R[*minor*] = 17.54 min.

[α]$_D$ = +17.0 (23 °C, 589 nm, 1.00 g/100 mL, $CHCl_3$).



(–)-(3*E*)-3-Ethyl-5-methyl-2-naphthalen-1-yl-hexa-3,5-dien-2-ol (3.35): In the reductive coupling of **2.11** (47 mg, 0.5 mmol, 63 μL) and 1-acetylnaphthalene (170 mg, 1.0 mmol, 152 μL), Procedure A was used. Silica gel chromatography afforded the title compound as a clear oil (102 mg, 77% yield, 46% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R_f = 0.26 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 – 8.42 (m, 1H); 7.83 – 7.86 (m, 1H); 7.78 – 7.80 (m, 2H); 7.41 – 7.48 (m, 3H); 6.24 (s, 1H); 4.96 (m, 1H); 4.88 (m, 1H); 2.12 – 2.30 (m, 2H); 2.08 (s, 1H); 1.93 (s, 3H); 1.86 (s, 3H); 0.82 (t, *J* = 7.5 Hz, 3H).

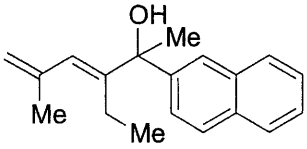
^{13}C NMR (125 MHz, $CDCl_3$) δ 148.27, 142.39, 141.80, 134.68, 131.24, 128.98, 128.78, 127.51, 126.97, 125.39, 125.06, 124.18, 114.18, 79.04, 30.45, 23.74, 22.04, 15.52.

IR (thin film NaCl): 3566, 3463, 3050, 2970, 2935, 2875, 1930, 1814, 1633, 1599, 1509, 1452, 1395, 1373, 1345, 1311, 1216, 1181, 1161, 1090, 1025 cm^{-1}.

HRMS (EI) *m/z* 266.167 [M$^+$; calcd for $C_{19}H_{22}O$: 266.167].

Chiral HPLC analysis (Chiralcel OJ, hexanes: 2-propanol, 98:2, 1.0 mL/min): t_R[*major*] = 10.78 min; t_R[*minor*] = 14.34 min.

[α]$_D$ = −3.0 (23 °C, 589 nm, 1.00 g/100 mL, CHCl$_3$).



(+)-(3*E*)-3-Ethyl-5-methyl-2-naphthalen-2-yl-hexa-3,5-dien-2-ol (3.36): In the reductive coupling of **2.11** (47 mg, 0.5 mmol, 63 μL) and 2-acetylnaphthalene (170 mg, 1.0 mmol), Procedure B was used. Silica gel chromatography afforded the title compound as a clear oil (87 mg, 65% yield, 62% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R$_f$ = 0.23 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.98 (s, 1H); 7.79 – 7.88 (m, 3H); 7.46 – 7.51 (m, 3H); 6.24 (s, 1H); 5.02 (t, *J* = 2 Hz, 1H); 4.96 (t, *J* = 1 Hz, 1H); 2.08 – 2.24 (m, 2H); 1.93 (s, 3H); 1.92 (s, 1H); 1.82 (s, 3H); 0.88 (t, *J* = 7.5 Hz, 3H).

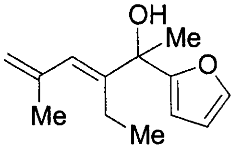
^{13}C NMR (125 MHz, CDCl$_3$) δ 147.49, 144.26, 142.25, 133.29, 132.59, 128.38, 127.93, 127.70, 127.32, 126.22, 125.99, 124.82, 123.88, 114.67, 78.60, 29.57, 23.85, 21.70, 15.75.

IR (thin film NaCl): 3456, 3057, 2970, 2935, 2874, 1632, 1600, 1506, 1450, 1373, 1311, 1272, 1246, 1188, 1157, 1113, 1070, 1054 cm^{-1}.

HRMS (EI) *m/z* 266.167 [M$^+$; calcd for $C_{19}H_{22}O$: 266.167].

Chiral HPLC analysis (Chiralcel OJ, hexanes: 2-propanol, 98:2, 1.0 mL/min): t$_R$[*major*] = 25.78 min; t$_R$[*minor*] = 32.81 min.

[α]$_D$ = +14.3 (23 °C, 589 nm, 1.05 g/100 mL, CHCl$_3$).



(−)-(3*E*)-3-Ethyl-2-furan-2-yl-5-methyl-hexa-3,5-dien-2-ol (3.37): In the reductive coupling of **2.11** (47 mg, 0.5 mmol, 63 μL) and 2-acetylfuran (110 mg, 1.0 mmol), Procedure B was used, except that no NaBH$_4$ workup was required. Following air quench, the crude reaction mixture was purified directly by silica gel chromatography. This afforded the title compound as a clear oil (60 mg, 58% yield, 40% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R$_f$ = 0.36 (5:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.36 (dd, *J* = 4, 2 Hz, 1H); 6.33 (dd, *J* = 3, 2 Hz, 1H); 6.25 (dd, *J* = 3.5, 1 Hz, 1H); 6.13 (s, 1H); 4.98 (m, 1H); 4.91 (s, 1H); 2.20 (q, *J* = 7 Hz, 2H); 2.17 (s, 1H); 1.89 (s, 3H); 1.69 (s, 3H); 0.85 (t, *J* = 7.5 Hz, 3H).

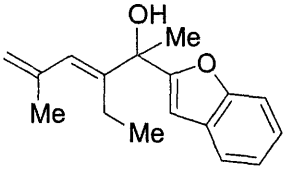
^{13}C NMR (125 MHz, CDCl$_3$) δ 158.67, 146.25, 142.09, 141.79, 126.68, 114.61, 110.41, 106.14, 74.65, 26.75, 23.83, 21.66, 15.16.

IR (thin film NaCl): 3437, 3118, 3081, 2974, 2938, 2877, 1690, 1633, 1503, 1452, 1373, 1239, 1156, 1119, 1072, 1011 cm^{-1}.

HRMS (EI) *m/z* 206.130 [M^+; calcd for $C_{13}H_{18}O_2$: 206.130].

Chiral HPLC analysis (Chiralcel OJ, hexanes: 2-propanol, 99:1, 0.8 mL/min): t_R[*major*] = 11.50 min; t_R[*minor*] = 10.61 min.

$[\alpha]_D$ = –15.0 (23 °C, 589 nm, 1.00 g/100 mL, $CHCl_3$).



(–)-(3*E*)-2-Benzofuran-2-yl-3-ethyl-5-methyl-hexa-3,5-dien-2-ol (3.38): In the reductive coupling of **2.11** (47 mg, 0.5 mmol, 63 μL) and benzofuran-2-yl methyl ketone (160 mg, 1.0 mmol), Procedure B was used. Silica gel chromatography afforded the title compound as a clear oil (74 mg, 58% yield, 42% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R_f = 0.23 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (dt, *J* = 7.5, 1 Hz, 1H); 7.46 (d, *J* = 8 Hz, 1H); 7.20 – 7.29 (m, 2H); 6.66 (d, *J* = 1 Hz, 1H); 6.19 (s, 1H); 5.00 (s, 1H); 4.93 (t, *J* = 1 Hz, 1H); 2.31 (s, 1H); 2.27 (dq, *J* = 7, 2.5 Hz, 2H); 1.90 (s, 3H); 1.79 (s, 3H); 0.90 (t, *J* = 7 Hz, 3H).

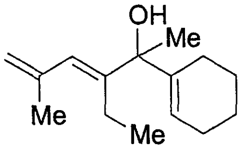
^{13}C NMR (125 MHz, $CDCl_3$) δ 161.43, 154.80, 145.64, 141.97, 128.45, 127.42, 124.32, 122.99, 121.21, 114.88, 111.52, 102.97, 75.14, 26.87, 23.78, 21.62, 15.45.

IR (thin film NaCl): 3438, 3082, 3036, 2971, 2937, 2875, 1893, 1778, 1634, 1597, 1581, 1454, 1373, 1333, 1304, 1250, 1216, 1165, 1116, 1072, 1008 cm^{-1}.

HRMS (EI) *m/z* 256.147 [M^+; calcd for $C_{17}H_{20}O_2$: 256.146].

Chiral HPLC analysis (Chiralcel OJ, hexanes: 2-propanol, 99.5:0.5, 0.5 mL/min): t_R[*major*] = 55.71 min; t_R[*minor*] = 50.81 min.

$[\alpha]_D$ = –13.3 (23 °C, 589 nm, 1.05 g/100 mL, $CHCl_3$).



(–)-(3*E*)-2-Cyclohex-1-enyl-3-ethyl-5-methyl-hexa-3,5-dien-2-ol (3.39): In the reductive coupling of **2.11** (47 mg, 0.5 mmol, 63 μL) and 1-acetyl-1-cyclohexene (124 mg, 1.0 mmol, 128 μL), Procedure A was used, but the reaction was conducted at 35 °C (note: the reaction flask was placed in a 35 °C oil bath prior to addition of the enyne and then stirred at this temperature for the duration of the reaction.) Silica gel chromatography afforded the title compound as a clear oil (60 mg, 55% yield, 63% ee, >95:5 regioselectivity, >95:5 *E*/*Z*). R_f = 0.29 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (s, 1H); 5.82 (sept., J = 1.5 Hz, 1H); 4.95 (m, 1H); 4.88 (m, 1H); 2.06 - 2.24 (m, 4H); 1.82 - 1.98 (m, 2H); 1.88 (t, J = 1 Hz, 3H); 1.52 – 1.62 (m, 4H); 1.44 (s, 3H); 1.02 (t, J = 7.5 Hz, 3H).

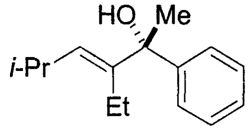
^{13}C NMR (125 MHz, $CDCl_3$) δ 146.68, 142.54, 141.39, 126.51, 121.70, 114.00, 78.93, 26.87, 25.48, 24.63, 23.95, 23.12, 22.52, 21.05, 15.60.

IR (thin film NaCl): 3458, 3079, 2968, 2932, 2858, 2837, 1633, 1449, 1372, 1270, 1245, 1139, 1116, 1091, 1042 cm^{-1}.

HRMS (EI) *m/z* 220.183 [M^+; calcd for $C_{15}H_{24}O$: 220.182].

Chiral HPLC analysis (Chiralpak AD-H, hexanes: 2-propanol, 98:2, 0.7 mL/min): t_R[*major*] = 10.07 min; t_R[*minor*] = 9.38 min.

$[\alpha]_D$ = –4.0 (23 °C, 589 nm, 1.00 g/100 mL, $CHCl_3$).



3-Ethyl-5-methyl-2-phenyl-hex-3-en-2-ol (3.40): $RhCl(PPh_3)_3$ (19 mg, 0.02 mmol) and a solution of diene **3.30** (0.21 mmol) in toluene (1 mL) were added to a Lab-Crest® Pressure Reaction Vessel and filled with H_2 (3 atm). After 2.5 h, the H_2 source was removed, and the solution was sparged with Ar and concentrated under reduced pressure. Purification by flash chromatography on silica gel using a solvent gradient (50:1 to 10:1 hexanes: EtOAc) afforded the title compound as a clear oil (40 mg, 87% yield). R_f = 0.35 (10:1 hexanes: ethyl acetate).

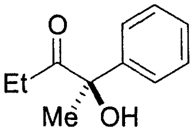
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.44 (m, 2H); 7.30 – 7.33 (m, 2H); 7.21 – 7.25 (m, 1H); 5.47 (d, J = 10 Hz, 1H); 2.53 – 2.64 (m, 1H); 1.93 – 2.01 (m, 1H); 1.82 – 1.90 (m, 1H); 1.74 (s, 1H); 1.66 (s, 1H); 1.03 (d, J = 6.5 Hz, 6 H); 0.86 (dt, J = 7.5, 1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 147.14, 143.11, 133.04, 128.14, 126.79, 125.70, 78.08, 29.69, 27.36, 23.45, 23.42, 21.53, 15.93.

IR (thin film NaCl): 3465, 3087, 3060, 3026, 2960, 2933, 2870, 1726, 1601, 1493, 1466, 1447, 1374, 1361, 1170, 1118, 1069, 1028 cm^{-1}.

HRMS (ESI) *m/z* 241.157 [$(M + Na)^+$; calcd for $C_{15}H_{22}O$: 241.156].

$[\alpha]_D$ = +25.7 (23 °C, 589 nm, 0.70 g/100 mL, $CHCl_3$).



(*R*)-2-Hydroxy-2-phenyl-pentan-3-one (3.41): Allylic alcohol **3.40** (30 mg, 0.14 mmol) was dissolved in CH_2Cl_2 (6 mL), and the solution was cooled to –78 °C. The cooled solution was sparged with ozone (O_3) until a blue color was obtained (~1 min), and was then sparged with argon until no trace of blue color remained (~5 min). Triphenylphosphine (0.7 mmol, 184 mg) was then added, and the reaction was allowed to stir overnight while warming gradually to room temperature. Removal of solvent in vacuo followed by flash chromatography on silica gel

(100:1 hexanes:DCM to 10:1 hexanes:EtOAc gradient) afforded the title compound as a clear oil (92% yield, 23 mg, 64% ee). Spectral data matched that previously reported.[58]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.46 (m, 2H); 7.36 – 7.40 (m, 2H); 7.30 – 7.38 (m, 1H); 4.64 (s, 1H); 2.45 – 2.52 (m, 1H); 2.32 – 2.40 (m, 1H); 1.80 (s, 3H); 0.99 (t, J = 7 Hz, 3H).

Chiral HPLC analysis (Chiralcel OD-H, hexanes: 2-propanol, 98:2, 1.0 mL/min): $t_R[\textit{major}]$ = 10.07 min; $t_R[\textit{minor}]$ = 11.18 min.

$[\alpha]_D = -194.3$ (23 °C, 589 nm, 0.70 g/100 mL, benzene). Previously reported $[\alpha]_D = -228.3$ (>95% ee, 20 °C, benzene).[44]

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[58] Brunner, H.; Stöhr, F. *Eur. J. Org. Chem.* **2000**, 2777-2786.

Chapter 4

Ligand-Switchable Directing Effects of Tethered Alkenes in Nickel-Catalyzed Additions to Alkynes

Introduction

Substrate-directable reactions are a very important class of selective organic transformations.[1] A temporary dative bond between a non-reacting functional group in the starting material and a reagent or catalyst can amplify (or reverse) selectivity by reinforcing (or changing) the low energy conformation of the transition state of the selectivity-determining step. Directing groups have been used to control reactivity and selectivity in a number of transition metal-catalyzed transformations, including hydroformylation of alkenes,[2] hydrostannation of alkynes,[3] Pauson–Khand-type reactions,[4] Heck reactions,[5] Pd-[6] and Ni-catalyzed[7] allylations, and C–H and C–C bond activation.[8]

While such neighboring group effects are typically mediated by a heteroatom, a few examples exist in which reactivity or selectivity is influenced by a remote alkene.[6c,e,9] Knochel has shown that alkenyl halides **4.1** undergo efficient, nickel-catalyzed cross-coupling reactions with dialkylzinc reagents, while their saturated analogs **4.2** do not afford cross-coupling products (Scheme 1).[9] He proposed that an interaction between the remote olefin and the metal center (**4.3**) delocalizes the *d* electrons of the nickel into the π^*-antibonding orbitals of the double bond, thus accelerating the reductive elimination of Ni(II) complexes **4.4** to provide coupling products **4.5**. The use of alkenes that were in conjugation with an electron-withdrawing substituent, *e.g.* an ester, further improved reaction efficacy.

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[1] Reviews: (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307-1370. (b) Kauffmann, T. *Synthesis* **1995**, 745-755. (c) Catellani, M.; Chiusoli, G. P.; Costa, M. *J. Organomet. Chem.* **1995**, *500*, 69-80. (d) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 2206-2225.

[2] (a) Review: Breit, B. *Chem. Eur. J.* **2000**, *6*, 1519-1524. (b) Krauss, I. J.; Wang, C. C.-Y.; Leighton, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 11514-11515.

[3] (a) Rice, M. B.; Whitehead, S. L.; Horvath, C. M.; Muchnij, J. A.; Maleczka, R. E. *Synthesis* **2001**, 1495-1504. (b) Marshall, J. A.; Bourbeau, M. P. *Tetrahedron Lett.* **2003**, *44*, 1087-1089.

[4] (a) Itami, K.; Mitsudo, K.; Yoshida, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 3481-3484. (b) Itami, K.; Mitsudo, K.; Fujita, K.; Ohashi, Y.; Yoshida, J.-i. *J. Am. Chem. Soc.* **2004**, *126*, 11058-11066.

[5] Review: Oestreich, M. *Eur. J. Org. Chem.* **2005**, 783-792.

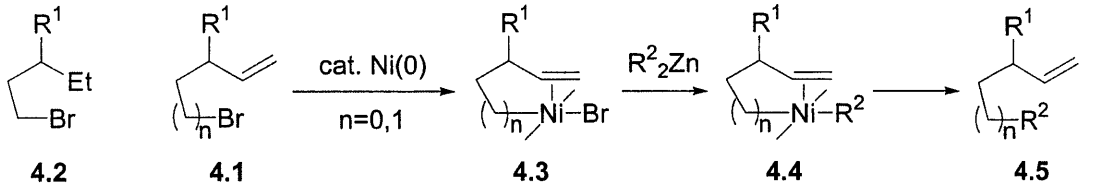
[6] (a) Krafft, M. E.; Fu, Z.; Procter, M. J.; Wilson, A. M. *Pure & Appl. Chem.* **1998**, *70*, 1083-1090. (b) Krafft, M. E.; Wilson, A. M.; Fu, Z.; Procter, M. J.; Dasse, O. A. *J. Org. Chem.* **1998**, *63*, 1748-1749. (c) Krafft, M. E.; Sugiura, M.; Abboud, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 9174-9175. (d) Krafft, M. E.; Lucas, M. C. *Chem. Commun.* **2003**, 1232-1233. (e) Nomura, N.; Tsurugi, K.; RajanBabu, T. V.; Kondo, T. *J. Am. Chem. Soc.* **2004**, *126*, 5354-5355.

[7] Didiuk, M. T.; Morken, J. P.; Hoveyda, A. H. *Tetrahedron* **1998**, *54*, 1117-1130.

[8] Review: Jun, C.-H.; Moon, C. W.; Lee, D.-Y. *Chem. Eur. J.* **2002**, *8*, 2422-2428.

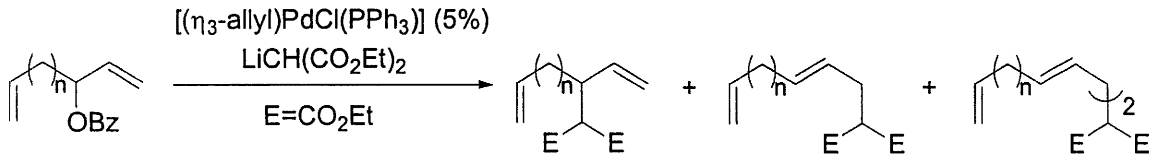
[9] (a) Devasagayaraj, A.; Studemann, T.; Knochel, P. *Angew. Chem. Int. Ed.* **1995**, *34*, 2723-2725. (b) Giovannini, R.; Stüdemann, T.; Devasagayaraj, A.; Dussin, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 3544-3553.

Scheme 1.



The ability of a remote alkene to direct regioselectivity in palladium-catalyzed allylations was elegantly demonstrated by Krafft (Scheme 2). An allylic acetate with a tethered alkene two methylene units away (**4.7**) selectively affords only one of three possible products, while acetates with other tether lengths (n = 1, 3; **4.6**, **4.8**) afford mixtures. Evaluation of the palladium catalyst employed revealed that altering the phosphine ligand (e.g., Cy_3P, Ph_3P, $(C_6F_5)_3P$, $(PhO)_3P$) had no effect on regioselectivity in allylations with **4.7**; however, in the presence of a bidentate phosphine, such as diphenylphosphinoethane (DPPE), capable of disrupting olefin coordination, product mixtures were observed.

Scheme 2.



4.6	n=1	72%	15	46	39
4.7	**n=2**	**69%**	**100**	**0**	**0**
4.8	n=3	71%	<2	59	41

We recently reported that nickel-catalyzed additions to 1,3-enynes proceed with unprecedented levels of reactivity and selectivity, and proposed that such additions are directed by the conjugated alkene.[10,11,12] Herein we report not only that a remote, *unconjugated* alkene can dictate regioselectivity, but also that the sense of regioselectivity can be completely *reversed*

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[10] Miller, K. M.; Luanphaisarnnont, T.; Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 4130-4131.

[11] Other examples of catalytic reductive coupling reactions of 1,3-enynes and aldehydes: (a) (Ni) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698-3699. (b) (Rh) Jang, H.-Y.; Huddleston, R. R.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4664-4668.

[12] Reviews of catalytic reductive coupling reactions: (a) Miller, K. M.; Molinaro, C.; Jamison, T. F. *Tetrahedron: Asymmetry* **2003**, *14*, 3619-3625. (b) Ikeda, S.-i. *Angew. Chem. Int. Ed.* **2003**, *42*, 5120-5122. (c) Jang, H.-Y.; Krische, M. J. *Acc. Chem. Res.* **2004**, *37*, 653-661. (d) Montgomery, J. *Angew. Chem. Int. Ed.* **2004**, *43*, 3890-3908.

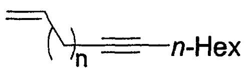
(from >95 : 5 to 5 : >95) by a substoichiometric amount of a phosphine additive. Simply put, the degree of regioselectivity is due entirely to a directing effect of an appropriately placed alkene, and the sense of the regioselectivity is due entirely to the presence (or absence) of a phosphine ligand.

Synthesis and Evaluation of Enyne Coupling Partners

Enyne Synthesis

A series of enynes was targeted in which the alkyne and the alkene were separated by 1-4 methylene units (Figure 1). Enyne **4.9** (n = 1) was obtained via copper-catalyzed allylation, and the remaining three enynes were accessed using the Sonogashira cross-coupling of alkynes and alkyl halides reported by Fu and Eckhardt (Scheme 3).[13] 1-Bromo-3-butene was found to be an ineffective substrate for cross-coupling, so enyne **4.10** (n = 2) was accessed via the coupling of (3-bromopropoxy)-*tert*-butyldimethylsilane and 1-octyne, followed by removal of the *tert*-butyldimethylsilyl group, oxidation, and olefination. Enynes **4.11** (n = 3) and **4.12** (n = 4) were obtained by cross-coupling with the corresponding unsaturated bromides directly.

Figure 1.



4.9 n=1
4.10 n=2
4.11 n=3
4.12 n=4

*Reductive Couplings of **4.9-4.12***

In our initial investigations, we examined reductive coupling reactions of **4.9-4.12** and isobutyraldehyde (Table 1, entries 1-4). In all cases, very low yields of the allylic alcohol products were observed in the absence of a phosphine ligand – with one striking exception (entry 3). Remarkably, a tether of three methylene groups (**4.11**) provides not only a dramatic increase in reactivity, but also complete selectivity for allylic alcohol regioisomer **4.15a**. Because of the marked difference in reactivity and selectivity for one (and only one) tether length, it is very unlikely that the infinitesimal differences in the steric and electronic properties of the alkyne substituents in **4.11** are responsible for this effect. Consistent with this notion is a control

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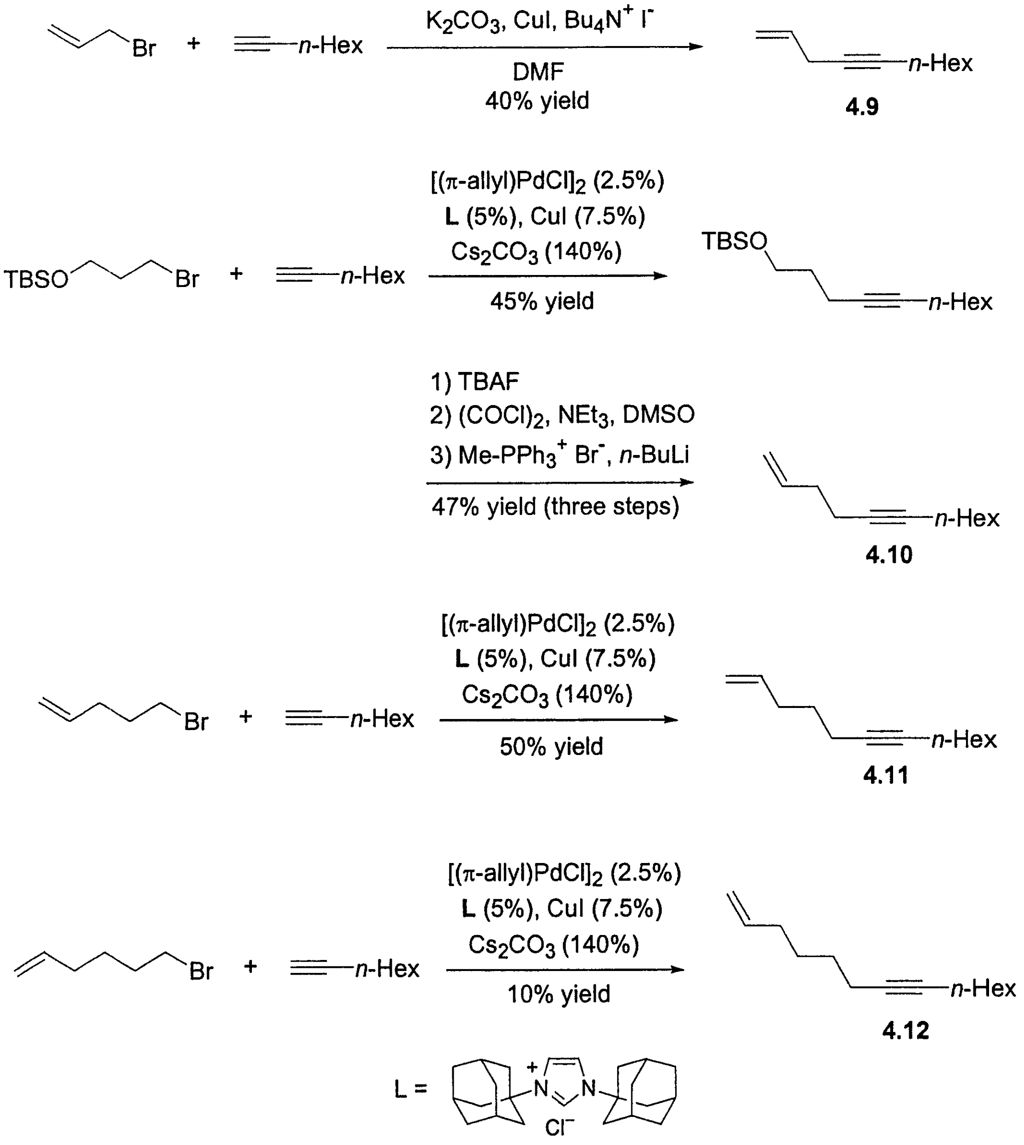
[13] Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642-13643.

experiment with the corresponding alkyne lacking the pendant alkene, 1,2-dihydro-**4.11** (**4.17**, entry 5). As expected, product yield was significantly diminished, and no regioselectivity was observed.

Scheme 3.



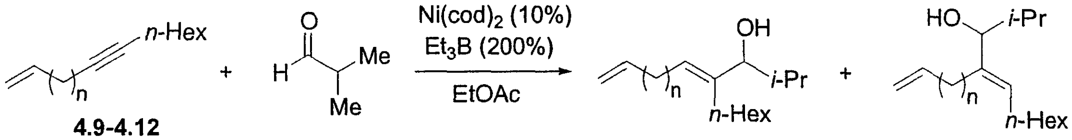
4.9

4.10

4.11

4.12

Table 1. Directing Effects of Tethered Alkenes.



4.9-4.12 **4.13a-4.16a** **4.13b-4.16b**

entry	alkyne	n	yield(%)	regioselectivity (**a** : **b**)
1	**4.9**	1	<5	n.d.
2	**4.10**	2	<5	n.d.
3	**4.11**	**3**	**53**	**>95:5**
4	**4.12**	4	<5	n.d.
5	*n*-Pent-C≡C-*n*-Hex (**4.17**)	n.a.	28	50:50

[a] Standard procedure: The alkyne (0.50 mmol) was added to a 0 °C solution of Ni(cod)$_2$ (0.05 mmol), *i*–PrCHO (1.00 mmol), and Et$_3$B (1.00 mmol) in EtOAc (0.5 mL), and the solution was allowed to stir 15 h at room temperature. [b] Determined by ^{1}H NMR and/or GC. [c] Some alkylative coupling (transfer of Et from Et$_3$B) also observed.

Substrate Scope

Table 2 illustrates the scope and utility of this directing effect.[14] Several aldehydes can be coupled with enyne **4.11** in high regioselectivity (entries 1-3) and a variety of 1,6-enynes serve as effective coupling partners (entries 4-8). In coupling reactions of *n*-alkyl–C≡C–*i*-Pr alkynes, the steric demand of the *i*-Pr group disfavors the regioisomer corresponding to **4.22** (~1:2 ratio),[15] while *n*-alkyl–C≡C–CH$_2$OTBS alkynes exhibit a twofold preference for the regioisomer corresponding to **4.24**, attributable to an electron-withdrawing effect of the propargylic oxygen. A tethered alkene, however, is sufficient to override (or reinforce) these "inherent" regioselectivities (entries 4 and 5). Heteroatoms that could compete with the alkene for binding to nickel do not erode regioselectivity but rather augment the versatility of this directable transformation (enynes **4.25-4.27**).

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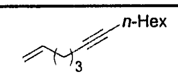
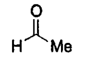
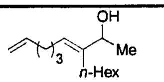
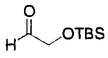
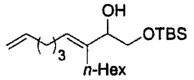
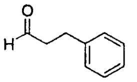
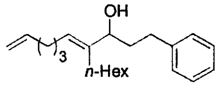
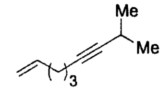
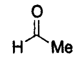
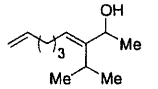
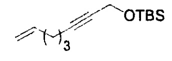
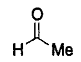
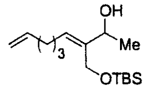
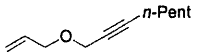
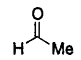
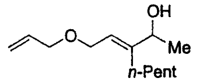
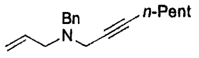
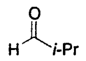
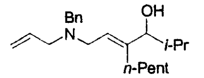
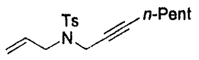
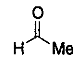
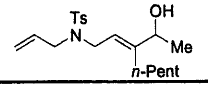
[14] Aromatic aldehydes couple in considerably reduced efficiency. An extended reaction time (40 h) was required for a 26% yield (>95:5 regioselectivity) in a coupling between **4.11** and benzaldehyde (PhCHO).

[15] See Chapter 2, Scheme 3, and: Colby, E. A.; Jamison, T. F. *J. Org. Chem.* **2003**, *68*, 156-166.

Table 2. Highly regioselective, catalytic reductive coupling reactions directed by a remote alkene.[a]

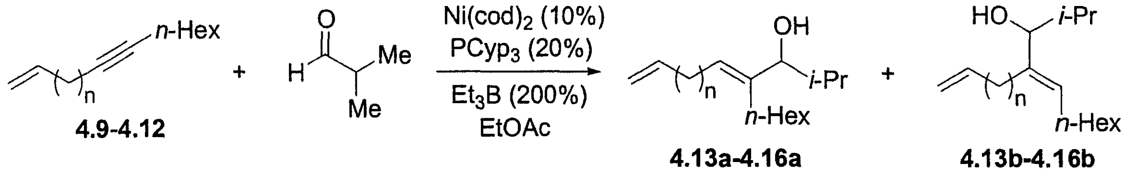
entry	enyne		aldehyde	product		yield (%), regioselectivity[b]
1		**4.11**			**4.18**	69 (>95:5)
2	"				**4.19**	58 (>95:5)
3	"				**4.20**	60 (>95:5)
4		**4.21**			**4.22**	64 (>95:5)
5		**4.23**			**4.24**	62 (>95:5)
6		**4.25**			**4.28**	60 (>95:5)
7		**4.26**			**4.29**	62 (>95:5)
8		**4.27**			**4.30**	68 (>95:5)

[a] Standard procedure: The alkyne (0.50 mmol) was added to a 0 °C solution of Ni(cod)$_2$ (0.05 mmol), the aldehyde (1.00 mmol), and Et$_3$B (1.00 mmol) in EtOAc (0.5 mL), and the solution was allowed to stir 15 h at room temperature. [b] Determined by ^{1}H NMR and/or GC.

Effect of a phosphine additive

The results of a set of coupling reactions employing an organophosphine were especially surprising and provide significant insight into the mechanistic framework of not only these directed reactions, but also nickel-catalyzed reductive coupling reactions of alkynes in general (Table 3). In contrast to the experiments summarized in Table 1 (no phosphine), enynes **4.9**, **4.10**, and **4.12** (n = 1, 2, 4, respectively) did undergo coupling with isobutyraldehyde when tricyclopentylphosphine (Cyp$_3$P) was employed, but in a non-regioselective fashion (entires 1, 2, and 4). However, with four carbon-carbon single bonds between the alkene and the alkyne (**4.11**), remarkably high regioselectivity was observed as before, but in this case with complete

Table 3. Effect of a phosphine additive in reductive coupling reactions of enynes **4.9-4.12**.[a]



entry	alkyne	n	yield(%)	regioselectivity (**a** : **b**)[b]
1	**4.9**	1	75	54:46
2	**4.10**	2	84	47:53
3	**4.11**	**3**	**45**	**5:>95**
4	**4.12**	4	50	50:50
5	**4.13**	n.a.	77	50:50

[a] Standard procedure: The alkyne (0.50 mmol) was added to a 0 °C solution of $Ni(cod)_2$ (0.05 mmol), *i*-PrCHO (1.00 mmol), and Et_3B (1.00 mmol) in EtOAc (0.5 mL), and the solution was allowed to stir 15 h at room temperature. [b] Determined by ^1H NMR and/or GC.

preference for the *other* regioisomer (**4.15b**, entry 3).[16,17] A control experiment using saturated alkyne **4.13** also provided further evidence for a temporary dative interaction between the remote alkene and the metal center (entry 5). The complete reversal in regioselectivity observed here is unprecedented. Trost has reported directed Pd-catalyzed enyne isomerizations in which the

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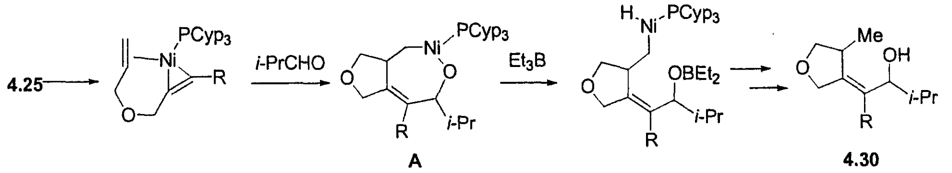
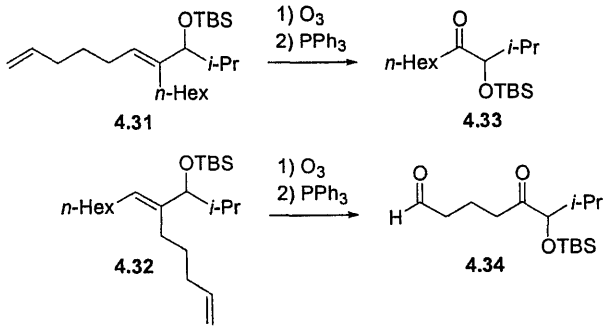
[16] Alkynes with a heteroatom in the tether (**4.25-4.27**) primarily afford products of phosphine-promoted carbocyclization, such as **4.30**. These may arise from a species akin to **A**, as shown below. See also Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 1286-1288.



[17] The identities of regioisomers **4.15a** and **4.15b** were conclusively established by performing ozonolysis of their TBS ethers **4.31** and **4.32**.

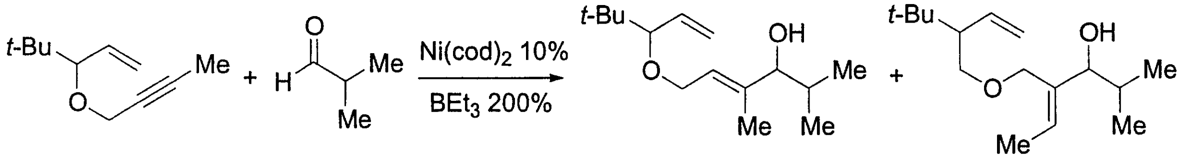


selectivity was flipped by an additive;[18] however, in this case, high regioselectivity was observed in only one direction (≥15:1 vs. 1:2.5).

Diastereoselective Couplings[19]

In order to probe the origin of the completely *ligand-switchable* regioselectivity observed in reductive couplings with **4.11**, the chiral enyne **4.35** was synthesized and investigated in reductive couplings with isobutyraldehyde (Scheme 4). In the absence of a phosphine ligand, regioisomer **4.36a** was formed and was isolated as a single diastereomer. The presence of Cyp_3P led to a complete switch in regioselectivity, affording allylic alcohol **4.36b**; however, in this case no diastereomeric preference was observed.

Scheme 4.



4.35 **4.36a** **4.36b**

ligand	**4.36a:4.36b**	*d.r.*
Cyp_3P	<5:95	50:50
none	>95:5	>95:5

Mechanistic Implications

The highly selective and switchable regioselectivities observed with enynes **4.11** and **4.35** can be explained by considering two different four-coordinate square planar nickel complexes as precursors to C-C bond formation (Scheme 5).[20] Intermediate **A** is consistent with the studies of Pörschke, who showed that 1,6-heptadiene and 1,6-heptadiyne chelate nickel in three-coordinate, approximately trigonal planar complexes in the solid state and in solution.[21] In the absence of a phosphine ligand, the aldehyde will coordinate *trans* to the alkene portion of the enyne, generating square planar complex **B**. Carbon-carbon bond formation then occurs to generate oxametallacycle **C**. As the olefin tether remains coordinated to the nickel during this step,

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[18] Trost, B. M.; Tanoury, G. J.; Lautens, M.; Chan, C.; MacPherson, D. T. *J. Am. Chem. Soc.* **1994**, *116*, 4255-4267.

[19] This portion of the work was carried out by Mr. Ryan T. Moslin.

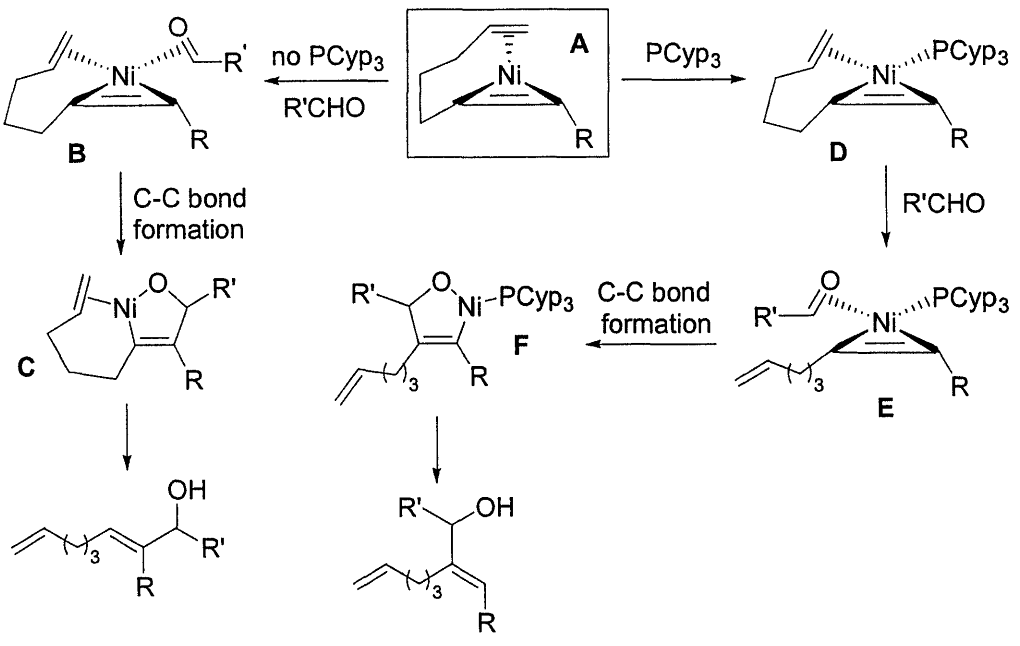
[20] This mechanistic rationale was developed in part by Mr. Ryan T. Moslin.

[21] (a) Proft, B.; Pörschke, K.-R.; Lutz, F.; Krüger, C. *Chem. Ber.* **1991**, *124*, 2667-2675. (b) Proft, B.; Pörschke, K.-R.; Lutz, F.; Krüger, C. *Chem. Ber.* **1994**, *127*, 653-655.

control of both regioselectivity and diastereoselectivity (if the tether contains a chiral substituent) is observed.

In the presence of Cyp$_3$P, however, square planar complex **D** is generated, and prior to C–C bond formation the aldehyde must displace the olefin to give complex **E**. Retention of stereochemistry during this displacement is expected;[22] thus, the tether still controls regioselectivity and directs for formation of oxametallacycle **F**. Since the olefin tether is not coordinated to the metal center during the C–C bond-forming step, a chiral tether has no appreciable influence on diastereoselectivity.

Scheme 5.



Phosphine Ligand Evaluation

An investigation of the effect of other monodentate phosphines on regioselectivity in the reductive coupling of **4.11** and isobutyraldehyde revealed some interesting trends. The regioselectivity displays a dramatic dependence on phosphine ligand employed, and exclusive formation of **4.15b** is limited to reactions with only a few phosphines (Group A, Table 4). A number of phosphines resulted instead in mixtures of regioisomers, favoring either **4.15b** (Group

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[22] In d^8, square-planar complexes, ligand substitution generally occurs through an associative pathway with retention of stereochemistry. Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, California, 1987, pp 241-244.

B) or **4.15a** (Group C). These observations suggest that the degree to which the olefin is able to control regioselectivity in these couplings is integrally linked to both the steric and electronic properties of the phosphine employed (Table 4).

Table 4. Effect of phosphine ligand on regioselectivity in reductive couplings of **4.11** and isobutyraldehyde.[a]

	entry	PR_3	**4.15a**	**4.15b**	yield[b]
Group A	**1**	**$PCyp_3$**	**5**	**>95**	**50**
	2	PCy_3	5	>95	30
Group B	3	$PFcPh_2$	40	60	20
	4	$PCyPh_2$	42	58	30
	5	PBu_3	42	58	75
Group C	6	P(*o*-anisyl)$_3$	65	35	75
	7	NMDPP	70	30	70
	8	" (10%)	87	13	65
	9	**none**	**>95**	**5**	**50**

[a] Conditions: 0.5 mmol scale, 10 mol% Ni(cod)$_2$, 20 mol% ligand, 100 mol% alkyne, 200 mol% *i*-PrCHO, 200 mol% Et_3B, EtOAc, 0 °C to RT, 15h. Regioselectivities determined by GC analysis. [b] 10-15% reductive cyclization product observed in all cases; yields are approximated based on ^{1}H NMR integration of the mixture.

Low regioselectivities observed with Group B phosphines are likely a result of preferential formation of a 2:1:1 R_3P:Ni:enyne complex of type **G** (Scheme 6), in which the olefin tether is not bound to nickel. In contrast, regioselectivities obtained when Group C phosphines are employed appear to result from competitive reaction of the enyne through two different olefin-bound nickel complexes, one with phosphine (i.e., **D**, Scheme 5) and one without (i.e., **B**, Scheme 5).[23] Supportive of this theory was an experiment run with only one equivalent of the Group C phosphine (+)-NMDPP (**1.38**) relative to nickel (entry 10), which displayed a stronger preference for formation of regioisomer **4.15a** than did a reaction with two equivalents (entry 9). In addition, chiral GC analysis of the two regioisomers formed in an (+)-NMDPP-promoted reaction showed that while regioisomer **4.15b** is formed in 26% ee, the ee of regioisomer **4.15a** is <5%.

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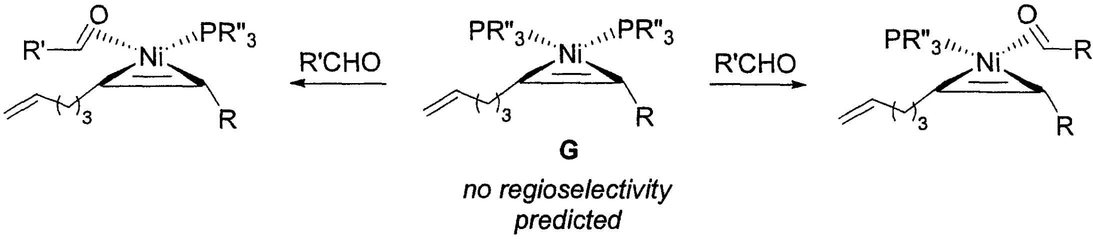
[23] ^{31}P NMR studies have suggested that NMDPP does not strongly associate with Ni in related systems (only a singlet corresponding to free phosphine is observed under numerous conditions.

Scheme 6.



Conclusion

Controlling regioselectivity in reductive couplings that involve alkynes of the type (alkyl-C≡C-alkyl') presents a significant challenge. The highly regioselective reductive couplings of 1,6-enynes and aldehydes reported herein not only represent the first examples of coupling reactions of this type, but also display a complete reversal in regioselectivity in the presence of certain monodentate phosphine ligands. These alkene-directed couplings afford allylic alcohols of high synthetic utility, and preliminary studies suggest that a chiral substituent between the alkene and the alkyne is capable of inducing high diastereoselectivity. This method also demonstrates that alkenes alone are viable promoters of reductive coupling reactions; thus, alkene-containing ligands may afford novel reactivity or selectivity in nickel-catalyzed reactions of this type.[24,25]

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[24] Use of alkene additives in other Group 10 metal-catalyzed reactions: Nickel: (a) Giovannini, R.; Knochel, P. *J. Am. Chem. Soc.* **1998**, *120*, 11186-11187. (b) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 174-175. Platinum: (c) Nakamura, I.; Bajracharya, G. B.; Wu, H.; Oishi, K.; Mizushima, Y.; Gridnev, I. D.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 15423-15430.

[25] (a) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11509-11510. (b) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628-1629.

Experimental Section

General Methods. Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of nitrogen or argon with rigid exclusion of moisture from reagents and glassware. Copper iodide, [(π-allyl)PdCl]$_2$, cesium carbonate, bis(cyclooctadienyl)- nickel(0) (Ni(cod)$_2$), and tricyclopentylphosphine (Cyp$_3$P) were purchased from Strem Chemicals, Inc. and used without further purification. 1,3-Bis(1-adamantyl)imidazolium chloride was either purchased from Strem Chemicals or prepared on multi-gram scale according to procedures described in the patent literature.[26] Triethylborane (Et$_3$B, 98%), 3-(bromopropoxy)-*tert*-butyldimethylsilane, tetrabutylammonium fluoride (1M in THF), oxalyl chloride, triethylamine, methyltriphenylphosphonium bromide, *n*-butyllithium (2.5M in hexanes), 6-bromo-1-hexene, 1-bromopentane, and 4-(dimethylamino)pyridine (DMAP) were purchased from Aldrich Chemical Co. and used as received. 1-Octyne, tetrabutylammmonium iodide, 5-bromo-1-pentene, methanesulfonyl chloride, allylamine, imidazole, *tert*-butyldimethylsilyl chloride, *p*-toluenesulfonyl chloride, and triphenylphosphine were purchased from Alfa Aesar and used as received. 3-Methyl-1-butyne and lithium amide were purchased from GFS Chemicals and used as received. Allyl bromide (Alfa Aesar) and benzyl bromide (Alfa Aesar) were filtered through a plug of silica gel prior to use. Isobutyraldehyde (Alfa Aesar), acetaldehyde (Aldrich), and 3-phenylpropionaldehyde (Alfa Aesar) were distilled over anhydrous MgSO$_4$ prior to use. (*tert*-Butyldimethylsilyloxy)acetaldehyde (Aldrich) was distilled prior to use. Tetrahydrofuran and diethyl ether were freshly distilled over blue solutions of sodium/benzophenone ketyl, toluene was freshly distilled over sodium metal, and dichloromethane was distilled over calcium hydride. Ethyl acetate was distilled over anhydrous MgSO$_4$ under argon atmosphere and sparged with argon prior to use. Dimethylformamide (99.9+%; Aldrich) was dried over activated molecular sieves (3 Å) prior to use. Methylsulfoxide (99.9%; Aldrich) and acetonitrile (99.8%; Aldrich) were used as received.

Analytical thin layer chromatography (TLC) was performed on silica gel 60 F$_{254}$ aluminum plates precoated with a fluorescent indicator or EM reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was accomplished with UV light and ethanolic phosphomolybdic acid (PMA) or aqueous potassium permanganate. Liquid chromatography was performed using a forced flow (flash chromatography)[27] of the indicated solvent system on Silicycle silica gel 60 (230 – 400 mesh). ^{1}H and ^{13}C NMR spectra were recorded in deuterochloroform (CDCl$_3$) on Varian Inova 300 and 500MHz instruments. Chemical shifts of ^{1}H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of CDCl$_3$ (77.23 ppm) on the δ scale. Infrared (IR) spectra were recorded as a thin film between NaCl plates on a Perkin-Elmer Model 2000 FT-IR System transform spectrometer. High resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. GC analysis was

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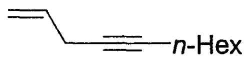
[26] Arduengo, III., Anthony J. Preparation of 1,3-disubstituted imidazolium salts. U. S. Patent 5,182,405, January 26, 1993.

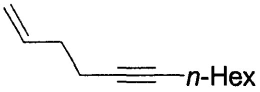
[27] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

performed on a Varian CP-3800 gas chromatograph fitted with Chiraldex B-PH, B-DA, and G-TA capillary columns.

Preparation of Starting Materials.



1-Undecen-4-yne[28] (4.9): A solution of 1-octyne (0.74 mL, 550 mg) in dimethylformamide was prepared and anhydrous K_2CO_3 (1.04 g, 7.5 mmol), copper iodide (95 mg, 0.5 mmol), and tetrabutylammonium iodide (1.85 g, 5 mmol) were added sequentially. Allyl bromide (0.56 mL, 0.79 g) was added and the mixture stirred overnight. The reaction was diluted with water (75 mL) and diethyl ether (75 mL). The organics were extracted twice with diethyl ether (2 x 50 mL), rinsed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Flash chromatography on silica gel (hexanes) afforded the title compound as a clear liquid (140 mg, 19% yield (60% BRSM)). $R_f = 0.40$ (hexanes). Spectral data matches that previously reported.[28] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 – 5.87 (m, 1H); 5.33 (dq, J = 17, 2 Hz, 1H); 5.10(dq, J = 9.5, 1.5 Hz, 1H); 2.93 – 2.97 (m, 2H); 2.20 (tt, J = 7, 2.5 Hz, 2H); 1.48 – 1.54 (m, 2H); 1.24 – 1.43 (m, 6H); 0.90 (t, J = 7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.62, 115.77, 83.19, 76.65, 31.60, 29.24, 28.80, 23.53, 22.79, 19.01, 14.29.



1-Docen-5-yne (4.10): According to the procedure described by Fu and Eckhardt,[29] in a glove box, 1,3-bis(1-adamantyl)imidazolium chloride (83 mg, 0.23 mmol), copper iodide (65 mg, 0.34 mmol), [(π-allyl)PdCl]$_2$ (42 mg, 0.11 mmol), and cesium carbonate (2.05 g, 6.3 mmol) were added to a sealed tube equipped with a stir bar. The tube was removed from the glovebox, and diethyl ether (6 mL) was added, followed by dimethylformamide (3 mL). The tube was placed under argon and 1-octyne (0.87 mL, 5.85 mmol) was added, followed by (3-bromopropoxy)-*tert*-butyldimethylsilane (1.04 mL, 4.5 mmol). The tube was sealed, placed in a 45 °C oil bath, and stirred vigorously for 16 h. Once the reaction had cooled it was diluted with diethyl ether (30 mL) and water (30 mL). The organics were extracted twice with diethyl ether (2 x 30 mL), rinsed with brine, dried over anhydrous $MgSO_4$, and concentrated. Flash chromatography on silica gel (hexanes) provided a brown oil. Kugelrohr distillation (180 °C at 0.1 Torr) provided *tert*-butyldimethyl-undec-4-ynyloxy-silane as a clear oil (585 mg, 46% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.70 (t, J = 6 Hz, 2H); 2.23 (tt, J = 7, 2.5 Hz, 2H); 2.14 (tt, J = 7, 2.5 Hz, 2H); 1.66 – 1.72 (m, 2H); 1.45 – 1.51 (m, 2H); 1.24 – 1.41 (m, 6H); 0.90 (t, J = 7 Hz, 3H); 0.90 (s, 9H); 0.06 (s, 6H).

tert-Butyldimethyl-undec-4-ynyloxy-silane (500 mg, 1.77 mmol) was dissolved in THF (18 mL) and the solution was cooled to 0 °C. Tetrabutylammonium fluoride (2.12 mL of 1M solution in THF) was added, and the mixture was stirred for one hour at 0 °C and an additional 45 minutes at room temperature. Brine was added, and the organics were then extracted with

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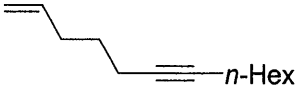
[28] Yamaguchi, R.; Kawasaki, H.; Yoshitome, T.; Kawanisi, M. *Chem. Lett.* **1982**, 1485-1486.

[29] Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642-13643.

ethyl acetate (3 x 30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated. Flash chromatography on silica gel (5:1 hexanes: ethyl acetate) provided undec-4-yn-1-ol as a clear oil (200 mg, 67% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.77 (t, J = 6 Hz, 2H); 2.29 (tt, J = 6.5, 2.5 Hz, 2H); 2.14 (tt, J = 7, 2.5 Hz, 2H); 1.72 – 1.77 (m, 2H); 1.61 (bs, 1H); 1.44 – 1.52 (m, 2H); 1.24 – 1.40 (m, 6H); 0.89 (t, J = 7 Hz, 3H).

Dichloromethane (12 mL) was added to oxalyl chloride (158 μL, 1.79 mmol) and the mixture was cooled to –78 °C. Methylsulfoxide (169 μL, 2.38 mmol) was added, followed by a solution of undec-4-yn-1-ol (200 mg, 1.19 mmol) in dichloromethane (4 mL). The reaction was stirred for 20 minutes at –78 °C, and then triethylamine (500 mL, 3.57 mmol) was added. The reaction was warmed to 0 °C and stirred for 30 minutes. The mixture was washed twice with water (2 x 25 mL), and then the organics were extraced with dichloromethane (2 x 30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude aldehyde was used immediately in the subsequent step.

A solution of methyltriphenylphosphonium bromide (429 mg, 1.2 mmol) in THF (5 mL) was cooled to 0 °C and *n*-BuLi (0.48 mL of a 2.5 M solution in hexanes) was added. After stirring for 30 minutes at 0 °C, the mixture was cooled to –78 °C, and a solution of the aldehyde in THF (1.5 mL) was added. The reaction was stirred for 15 minutes and then warmed to ambient temperature. A saturated aqueous solution of NH_4Cl (10 mL) was added, and the organics were extracted with diethyl ether (2 x 20 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. Flash chromatography on silica gel (hexanes) afforded the title compound as a clear oil (137 mg, 70% yield over two steps). R_f = 0.30 (hexanes). Spectral data matches that previously reported.[30] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 – 5.91 (m, 1H); 5.05 – 5.09 (m, 1H); 5.00 – 5.03 (m, 1H); 2.23 – 2.26 (m, 4H); 2.13 – 2.17 (m, 2H); 1.44 – 1.51 (m, 2H); 1.24 – 1.41 (m, 6H); 0.90 (t, J = 7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.53, 115.54, 81.01, 79.58, 33.62, 31.60, 29.30, 28.75, 22.80, 18.95, 18.87, 14.29.



1-Tridecen-6-yne (4.11): According to the procedure described by Fu and Eckhardt,[29] in a glove box, 1,3-bis(1-adamantyl)imidazolium chloride (370 mg, 1.0 mmol), copper iodide (290 mg, 1.5 mmol), [(π-allyl)PdCl]$_2$ (185 mg, 0.5 mmol), and cesium carbonate (9.1 g, 28 mmol) were added to a sealed tube equipped with a stir bar. The tube was removed from the glovebox, and diethyl ether (28 mL) was added, followed by dimethylformamide (14 mL). The tube was placed under argon and 1-octyne (3.85 mL, 26 mmol) was added, followed by 5-bromo-1-pentene (2.35 mL, 20 mmol). The tube was sealed, placed in a 45 °C oil bath, and stirred vigorously for 16 h. Once the reaction had cooled it was diluted with diethyl ether (100 mL) and water (100 mL). The organics were extracted twice with diethyl ether (2 x 100 mL), rinsed with brine, dried over anhydrous $MgSO_4$, and concentrated. Flash chromatography on silica gel yielded an orange oil. Kugelrohr distillation (125 °C at 20 Torr) afforded the title compound as a clear oil (2.03 g, 57% yield). R_f = 0.57 (hexanes). Spectral data matches that previously reported.[31] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 – 5.85 (m, 1H); 5.01 – 5.06 (m, 1H); 4.96 – 4.99

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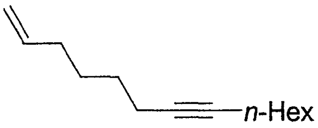
[30] Hara, S.; Satoh, Y.; Suzuki, A. *Chem. Lett.* **1982**, 1289-1290.

[31] Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 1245-1255.

(m, 1H); 2.12 – 2.19 (m, 6H); 1.58 (quin., J = 7 Hz, 2H); 1.48 (quin., J = 7 Hz, 2H); 1.24 – 1.42 (m, 6H); 0.90 (t, J = 7Hz, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 138.36, 115.14, 80.83, 79.96, 33.04, 31.60, 29.34, 28.77, 28.54, 22.81, 18.98, 18.41, 14.30.



1-Tetradecen-7-yne (4.12): According to the procedure described by Fu and Eckhardt,[4] in a glove box, 1,3-bis(1-adamantyl)imidazolium chloride (95 mg, 0.25 mmol), copper iodide (74 mg, 0.38 mmol), [(π-allyl)PdCl]$_2$ (47 mg, 0.13 mmol), and cesium carbonate (2.30 g, 7.00 mmol) were added to a sealed tube equipped with a stir bar. The tube was removed from the glovebox, and diethyl ether (6.7 mL) was added, followed by dimethylformamide (3.3 mL). The tube was placed under argon and 1-octyne (0.96 mL, 6.5 mmol) was added, followed by 6-bromo-1-hexene (0.67 mL, 5 mmol). The tube was sealed, placed in a 45 °C oil bath, and stirred vigorously for 16 h. Once the reaction had cooled it was diluted with diethyl ether (25 mL) and water (25 mL). The organics were extracted twice with diethyl ether (2 x 25 mL), rinsed with brine, dried over anhydrous MgSO$_4$, and concentrated. Flash chromatography on silica gel (hexanes) afforded the title compound as a clear oil (72 mg, 10% yield). R$_f$ = 0.40 (hexanes). Spectral data matches that previously reported.[32] ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.77 – 5.88 (m, 1H); 4.99 – 5.04 (m, 1H); 4.93 – 4.97 (m, 1H); 2.12 – 2.19 (m, 4H); 2.04 – 2.10 (m, 2H); 1.24 – 1.56 (m, 12H); 0.90 (t, J = 7 Hz, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 139.00, 114.64, 80.63, 80.18, 33.52, 31.60, 29.34, 28.80, 28.77, 28.26, 22.80, 18.98, 18.83, 14.29.

n-Pent—≡—*n*-Hex

6-Tridecyne (4.17): According to the procedure described by Fu and Eckhardt,[29] in a glove box, 1,3-bis(1-adamantyl)imidazolium chloride (95 mg, 0.25 mmol), copper iodide (74 mg, 0.38 mmol), [(π-allyl)PdCl]$_2$ (47 mg, 0.13 mmol), and cesium carbonate (2.30 g, 7.00 mmol) were added to a sealed tube equipped with a stir bar. The tube was removed from the glovebox, and diethyl ether (6.7 mL) was added, followed by dimethylformamide (3.3 mL). The tube was placed under argon and 1-octyne (0.96 mL, 6.5 mmol) was added, followed by 1-bromopentane (0.62 mL, 5 mmol). The tube was sealed, placed in a 45 °C oil bath, and stirred vigorously for 16 h. Once the reaction had cooled it was diluted with diethyl ether (25 mL) and water (25 mL). The organics were extracted twice with diethyl ether (2 x 25 mL), rinsed with brine, dried over anhydrous MgSO$_4$, and concentrated. Flash chromatography on silica gel (hexanes) yielded an orange oil. Kugelrohr distillation (120 °C at 20 Torr) afforded the title compound as a clear oil (372 mg, 41% yield). R$_f$ = 0.66 (hexanes). Spectral data matches that previously reported.[33] ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.12 - 2.17 (m, 4H); 1.44 – 1.52 (m, 4H); 1.24 – 1.41 (m, 10H); 0.90 (t, J = 7 Hz, 3H); 0.90 (t, J = 7 Hz, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 80.46, 80.45, 31.60, 31.30, 29.36, 29.09, 28.76, 22.80, 22.46, 18.98, 18.95, 14.29, 14.24.

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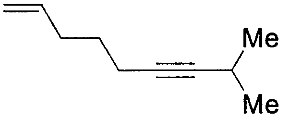
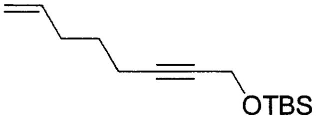
[32] Liu, Y.; Xi, C.; Hara, R.; Nakajima, K.; Yamazaki, A.; Kotora, M.; Takahashi, T. *J. Org. Chem.* **2000**, *65*, 6951-6957.

[33] Naruse, M.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1974**, *30*, 2159-2163.



8-Methyl-non-1-en-6-yne (4.21). According to the procedure described by Fu and Eckhardt,[29] in a glove box, 1,3-bis(1-adamantyl)imidazolium chloride (380 mg, 1.0 mmol), copper iodide (296 mg, 1.5 mmol), [(π-allyl)PdCl]$_2$ (188 mg, 0.5 mmol), and cesium carbonate (4.6 g, 14 mmol) were added to a sealed tube equipped with a stir bar. The tube was removed from the glovebox, and diethyl ether (13 mL) was added, followed by dimethylformamide (6.5 mL). The tube was placed under argon and 3-methyl-1-butyne (2.0 mL, 20 mmol) was added, followed by 5-bromo-1-pentene (1.18 mL, 10 mmol). The tube was sealed, placed in a 45 °C oil bath, and stirred vigorously for 16 h. Once the reaction had cooled it was diluted with diethyl ether (50 mL) and water (50 mL). The organics were extracted twice with diethyl ether (2 x 50 mL), rinsed with brine, dried over anhydrous MgSO$_4$, and concentrated. Flash chromatography on silica gel (hexanes) provided an orange oil. Kugelrohr distillation (115 °C at 20 Torr) afforded the title compound as a clear oil (656 mg, 48% yield). R_f = 0.52 (hexanes). ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.77 – 5.85 (m, 1H); 5.01 – 5.06 (m, 1H); 4.96 – 4.99 (m, 1H); 2.48 – 2.58 (m, 1H); 2.12 – 2.19 (m, 4H); 1.54 – 1.61 (m, 2H); 1.15 (d, J = 7 Hz, 6H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 138.38, 115.12, 86.61, 79.10, 33.00, 28.53, 26.82, 23.67, 20.74, 18.33. IR (thin film NaCl): 3079, 2971, 2936, 1642, 1465, 1362, 1321, 1257, 1154, 992, 913.



***tert*-Butyl-dimethyl-oct-7-en-2-ynyloxy-silane (4.23).** Lithium amide (604 mg, 26 mmol) was added under argon atmosphere to a 250 mL three-necked, round-bottom flask that had been fitted with a dry ice condenser, a mechanical stirrer, and an addition funnel. The flask was cooled to –78 °C and liquid ammonia (25 mL) was added. The mixture was then stirred, and *tert*-butyldimethyl(prop-2-ynyloxy) silane[34] (4.26 g, 25 mmol) was added dropwise over 10 minutes via the addition funnel. After stirring at –78 °C for 1 h, 5-bromo-1-pentene (2.96 mL, 25 mmol) was added dropwise over 10 minutes via the addition funnel. After 2 h at –78 °C, no conversion was observed, so the reaction was allowed to warm to –40 °C and stir for an additional 2 h. The reaction was quenched by addition of water (50 mL), diluted with diethyl ether (50 mL), and allowed to warm to ambient temperature overnight. Organics were then extracted with additional diethyl ether (2 x 50 mL), rinsed with brine (100 mL), dried and concentrated. Crude NMR revealed a ~3:1 mixture of starting alkyne:**4.23**. Distillation of the mixture (70 °C at 0.1 Torr) afforded the title compound as a clear oil (800 mg, 15% yield). R_f = 0.20 (hexanes). ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.76 (m, 1H); 5.04 (dq, J = 17, 2 Hz, 1H); 4.98 (d of quintets, J = 10, 1 Hz, 1H); 4.31 (t, J = 2 Hz, 2H); 2.23 (tt, J = 7, 2 Hz, 1H); 2.13 – 2.18 (m, 2H); 1.61 (quin., J = 7 Hz, 2H); 0.92 (s, 9H); 0.13 (s, 6H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 138.11, 115.33, 85.24, 79.12, 52.21, 33.01, 27.98, 26.24, 26.08, 18.39, –4.89.

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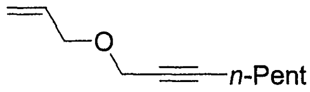
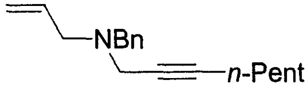
[34] Araki, Y.; Konoike, T. *J. Org. Chem.* **1997**, *62*, 5299-5309.

IR (thin film NaCl): 3079, 2931, 2898, 2858, 1642, 1473, 1463, 1390, 1362, 1254, 1140, 1082. HRMS (ESI) m/z 261.164 [(M + Na)$^+$; calcd for $C_{14}H_{26}OSi$: 261.165].



1-Allyloxy-oct-2-yne[35] (4.25). NaH (456 mg of a 57% dispersion in mineral oil, 11 mmol) was suspended in THF (5 mL) and 2-octyn-1-ol (0.87 mL, 10 mmol) in THF (2.5 mL) was added dropwise via syringe. The mixture was stirred for 30 minutes at ambient temperature, and then allyl bromide (1.04 mL, 12 mmol) was added. The mixture was stirred for 3 h at ambient temperature, at which point water (25 mL) and diethyl ether (25 mL) were added. The organic layer was collected, dried over anhydrous $MgSO_4$, and concentrated. Subsequent purification via flash chromatography on silica gel afforded the title compound as a clear liquid (650 mg, 39% yield). $R_f = 0.52$ (10:1 hexanes: ethyl acetate). Spectral data matches that previously reported.[35] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 – 5.97 (m, 1H); 5.29 – 5.33 (m, 1H); 5.20 – 5.23 (m, 1H); 4.15 (t, J = 2 Hz, 2H); 4.04 – 4.07 (m, 2H); 2.22 (tt, J = 7, 2 Hz, 2H); 1.49 – 1.56 (m, 2H); 1.24 – 1.40 (m, 4H); 0.90 (t, J = 7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.43, 117.87, 87.37, 75.95, 70.63, 57.96, 31.25, 28.52, 22.40, 18.95, 14.19.



Allyl-benzyl-oct-2-ynyl-amine (4.26). A solution of 2-octyn-1-ol (1.73 mL, 20 mmol) and triethylamine (3.35 mL, 24 mmol) in diethyl ether (40 mL) was prepared and cooled to 0 °C. Methanesulfonyl chloride (1.70 mL, 22 mmol) was then added dropwise, and the mixture was stirred at 0 °C for 20 min. Water (50 mL), 1M HCl (10 mL), and additional diethyl ether (25 mL) were added. The organic layer was then washed sequentially with saturated solutions of $NaHCO_3$ (50 mL) and NaCl (50 mL). The organic layer was dried, concentrated, and then added to neat allylamine (7.5 mL, 100 mmol) at 0 °C. The mixture was allowed to warm gradually to ambient temperature and stirred for 1.5 h. The reaction was then poured into diethyl ether (75 mL) and the resulting white solid was removed via filtration. The filtrate was concentrated and distilled (175 °C, 15 Torr) to provide allyl-oct-2-ynyl-amine as a clear liquid (1.42 g, 44% yield).

Allyl-oct-2-ynyl-amine (1.13 g, 6.84 mmol) was dissolved in acetonitrile (30 mL), and then anhydrous K_2CO_3 (1.89 g, 13.68 mmol) and benzyl bromide (0.98 mL, 8.21 mmol) were added. The mixture was stirred vigorously overnight. The solvent was removed *in vacuo* and the residue was dissolved in water (75 mL) and diethyl ether (75 mL). The organic layer was collected, rinsed with brine, dried, and concentrated. Subsequent purification via flash chromatography on silica gel (10:1 hexanes:ethyl acetate) afforded the title compound as a clear liquid (0.95 g, 54% yield). $R_f = 0.60$ (10:1 hexanes: ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.38 (m, 5H); 5.86 – 5.94 (m, 1H); 5.25 – 5.30 (m, 1H); 5.15 – 5.18 (m, 1H); 3.64 (s, 2H); 3.28 (t, J = 2 Hz, 2H); 3.17 (d, J = 6.5 Hz, 2H); 2.25 (dt, J = 7, 2 Hz, 2H); 1.53 – 1.59 (m, 2H); 1.32 – 1.46 (m, 4H); 0.93 (t, J = 7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.99, 129.44,

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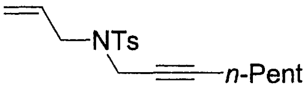
[35] Zhao, Z.; Ding, Y.; Zhao, G. *J. Org. Chem.* **1998**, *63*, 9285-9291.

128.44, 127.25, 118.06, 100.00, 86.06, 74.53, 57.39, 56.86, 41.98, 31.32, 28.95, 22.44, 18.92, 14.28. IR (thin film NaCl): 3065, 3029, 2957, 2931, 2860, 2815, 1643, 1495, 1455, 1432, 1368, 1327, 1253, 1117. HRMS (ESI) *m/z* 256.206 $[(M + H)^+$; calcd for $C_{18}H_{25}N$: 256.206].



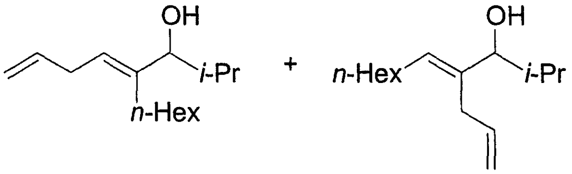
***N*-allyl-*N*-oct-2-ynyl-benzenesulfonamide (4.27).** Allyl-oct-2-ynyl-amine (1.013 g, 6.13 mmol) (see above entry for preparation) was dissolved in dichloromethane (7.5 mL) and triethylamine (1.28 mL, 9.15 mmol) was added. The solution was cooled to 0 °C and a solution of *p*-toluenesulfonyl chloride (1.40 g, 7.32 mmol) in dichloromethane (5.0 mL) was added. The mixture was allowed to warm to ambient temperature and stirred for 1 h. The reaction was quenched with phosphate buffer (pH 7), and the organics were extracted with additional dichloromethane (2 x 25 mL), washed with brine, dried over anhydrous $MgSO_4$, and concentrated. Subsequent purification via flash chromatography on silica gel (10:1 hexanes:ethyl acetate) afforded the title compound as a clear liquid (1.54 g, 79% yield). R_f = 0.40 (10:1 hexanes: ethyl acetate). ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.5 Hz, 2H); 7.29 (d, *J* = 8 Hz, 2H); 5.71 – 5.80 (m, 1H); 5.28 (dq, *J* = 17, 1.5 Hz, 1H); 5.23 (dq, *J* = 10, 1 Hz, 1H); 4.07 (t, *J* = 2.5 Hz, 2H); 3.81 (d, *J* = 7 Hz, 2H); 2.43 (s, 3H); 1.90 (tt, *J* = 7, 2 Hz, 2H); 1.16 – 1.29 (m, 6H); 0.88 (t, *J* = 7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.39, 136.39, 132.41, 129.51, 128.05, 119.80, 86.50, 72.47, 49.09, 36.55, 31.15, 28.25, 22.31, 21.73, 18.60, 14.17. IR (thin film NaCl): 3083, 2957, 2931, 2860, 1644, 1598, 1496, 1434, 1350, 1164, 1093. HRMS (ESI) *m/z* 320.169 $[(M + H)^+$; calcd for $C_{18}H_{25}NO_2S$: 320.168].

Alkene-Directed Reductive Coupling of Alkynes and Aldehydes.

General Procedure A (no additive): In a glovebox, $Ni(cod)_2$ (14 mg, 0.05 mmol) was placed into a 25 mL oven-dried, single-necked round-bottom flask, and the flask was then sealed with a rubber septum. The flask was removed from the glovebox, placed under argon, and ethyl acetate (0.5 mL) was added via syringe, followed immediately by Et_3B (0.15 mL, 1.0 mmol). The resulting solution was then cooled to 0 °C, and isobutyraldehyde (90 μL, 1.0 mmol) was added dropwise via microsyringe. After stirring 5 min, the enyne (0.5 mmol) was added. The reaction was allowed to gradually warm to room temperature and stir 15 h. The septa was then removed and the reaction stirred 30 min open to air to promote quenching of the catalyst. The crude mixture was purified by flash chromatography on silica gel using a solvent gradient (hexanes: ethyl acetate; 50:1 to 10:1).

General Procedure B (Cyp_3P additive): In a glovebox, $Ni(cod)_2$ (14 mg, 0.05 mmol), and Cyp_3P (28 μL, 0.1 mmol) were placed into a 25 mL oven-dried, single-necked round-bottom flask, which was then sealed with a rubber septum. The flask was removed from the glovebox, placed under argon, and ethyl acetate (0.5 mL) was added via syringe, followed immediately by Et_3B (0.15 mL, 1.0 mmol). The resulting solution was then cooled to 0 °C, and isobutyraldehyde (90 μL, 1.0 mmol) was added dropwise via microsyringe. After stirring 5 min, the enyne (0.5 mmol) was added. The reaction was allowed to gradually warm to room temperature and stir 15

h. The septa was then removed and the reaction was stirred 30 min open to air to promote quenching of the catalyst. The crude mixture was purified by flash chromatography on silica gel using a solvent gradient (hexanes: ethyl acetate; 50:1 to 10:1).



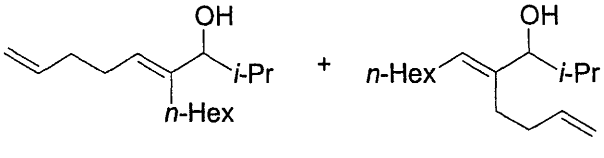
4-But-3-enylidene-2-methyl-decan-3-ol (4.13a) and **4-allyl-2-methyl-undec-4-en-3-ol (4.13b).** Procedure A (standard conditions): Reaction of isobutyraldehyde and **4.9** afforded <5% yield of **4.13a** and **4.13b**. Procedure B (half-scale): Reaction of isobutyraldehyde (45 μL, 0.5 mmol) and **4.9** (38 mg, 0.25 mmol) in the presence of Ni(cod)$_2$ (7 mg, 0.025 mmol), Cyp$_3$P (14 μL, 0.05 mmol), and Et$_3$B (75 μL, 0.5 mmol) in EtOAc (0.25 mL) afforded a 54:46 mixture of regioisomers **4.13a** and **4.13b** as a clear oil (42 mg, 75% yield). R$_f$ = 0.37 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, CDCl$_3$) δ 5.78 – 5.87 (m, 2H); 5.46 (t, J = 7.5 Hz, 1H); 5.40 (t, J = 7.5 Hz, 1H); 4.95 – 5.10 (m, 4H); 3.69 (d, J = 7 Hz, 1H); 3.66 (d, J = 7.5 Hz, 1H); 2.81 – 2.84 (m, 4H); 1.95 – 2.08 (m, 4H); 1.76 – 1.83 (m, 2H); 1.24 – 1.44 (m, 16H); 0.97 (d, J = 7 Hz, 3H); 0.96 (d, J = 6.5 Hz, 3H); 0.89 (t, J = 7 Hz, 3H); 0.89 (t, J = 7 Hz, 3H); 0.86 (d, J = 6.5 Hz, 3H); 0.82 (d, J = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 142.78, 137.94, 137.48, 137.33, 129.73, 124.84 (instrument peak), 124.54, 115.20, 114.90, 100.00 (instrument peak), 83.31, 82.75, 32.12, 31.95, 31.90, 31.78, 31.67, 30.22, 30.18, 29.80, 29.29, 28.07, 27.82, 22.89, 22.85, 20.12, 19.99, 18.41, 18.19, 14.32, 14.31.

IR (thin film NaCl): 3408, 3079, 2958, 2929, 2872, 2859, 1716, 1667, 1637, 1468, 1380, 1367, 1249, 1172, 1010.

HRMS (ESI) m/z 247.204 [(M + Na)$^+$; calcd for C$_{15}$H$_{28}$O: 247.203].



2-Methyl-4-pent-4-enylidene-decan-3-ol (4.14a) and **4-but-3-enyl-2-methyl-undec-4-en-3-ol (4.14b).** Procedure A (standard conditions): Reaction of isobutyraldehyde and **4.10** (82 mg, 0.5 mmol) afforded <5% yield of **4.14a** and **4.14b**. Procedure B (standard conditions): Reaction of isobutyraldehyde and **4.10** (82 mg, 0.5 mmol) afforded a 47:53 mixture of regioisomers **4.14a** and **4.14b** (100 mg, 84% yield). R$_f$ = 0.37 (10:1 hexanes: ethyl acetate).

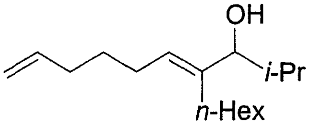
^{1}H NMR (500 MHz, CDCl$_3$) δ 5.79 – 5.90 (m, 2H); 5.39 (t, J = 7 Hz, 1H); 5.36 (t, J = 7 Hz, 1H); 5.00 – 5.06 (m, 2H); 4.96 – 4.99 (m, 2H); 3.66 (d, J = 7 Hz, 1H); 3.64 (d, J = 7 Hz, 1H);

1.93 – 2.20 (m, 12H); 1.73 – 1.83 (m, 2H); 1.24 – 1.43 (m, 16H); 0.97 (d, J = 7 Hz, 3H); 0.95 (d, J = 7 Hz, 3H); 0.89 (t, J = 7 Hz, 3H); 0.84 (d, J = 7 Hz, 3H); 0.83 (d, J = 7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 141.98, 140.29, 139.09, 138.63, 128.91, 126.85, 114.94, 114.71, 83.03, 82.81, 34.29, 34.19, 31.99, 31.92, 31.90, 31.79, 30.20, 30.18, 29.97, 29.29, 28.22, 27.83, 27.35, 27.22, 22.90, 22.86, 20.10, 20.02, 18.44, 18.23, 14.33, 14.31.

IR (thin film NaCl): 3421, 3078, 2957, 2928, 2871, 2858, 1824, 1726, 1641, 1467, 1415, 1380, 1366, 1295, 1247, 1169, 1129, 1008.

HRMS (ESI) *m/z* 261.220 [(M + Na)$^+$; calcd for $C_{16}H_{30}O$: 261.219].



4-Hexyl-2-methyl-deca-4,9-dien-3-ol (4.15a). Procedure A (half-scale): Reaction of isobutyraldehyde (45 μL, 0.5 mmol) and **4.11** (45 mg, 0.25 mmol) in the presence of $Ni(cod)_2$ (7 mg, 0.025 mmol) and Et_3B (75 μL, 0.5 mmol) in EtOAc (0.25 mL) afforded an 85:15 mixture of the title compound and the corresponding alkylative coupling product (transfer of an ethyl group instead of a hydrogen from Et_3B) (34 mg, 53% yield (46% reductive), >95:5 regioselectivity). Structure of **4.15a** was confirmed via ozonolysis (vide infra). An analytically pure sample of **4.15a** was obtained via flash chromatography on silica gel impregnated with 5% silver nitrate. R_f = 0.40 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 – 5.87 (m, 1H); 5.35 (t, J = 7.5 Hz, 1H); 4.99 – 5.04 (m, 1H); 4.95 – 4.98 (m, 1H); 3.66 (d, J = 7.5 Hz, 1H); 1.92 – 2.10 (m, 6H); 1.78 (oct., J = 7 Hz, 1H); 1.44 – 1.51 (m, 2H); 1.24 – 1.43 (m, 8H); 0.96 (d, J = 7 Hz, 3H); 0.89 (t, J = 7 Hz, 3H); 0.84 (d, J = 7 Hz, 3H).

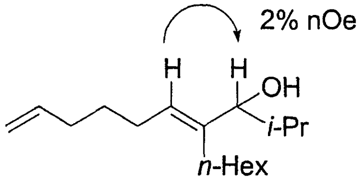
^{13}C NMR (125 MHz, $CDCl_3$) δ 141.79, 139.02, 127.43, 114.73, 82.89, 33.67, 31.91, 31.90, 31.82, 30.27, 30.18, 29.30, 28.17, 27.19, 22.90, 20.11, 18.26, 14.34.

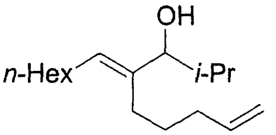
IR (thin film NaCl): 3623, 3428, 3078, 2956, 2929, 2871, 2859, 1823, 1641, 1468, 1379, 1365, 1295, 1246, 1169, 1130, 1116, 1007.

HRMS (ESI) *m/z* 275.235 [(M + Na)$^+$; calcd for $C_{17}H_{32}O$: 275.235].

Regioselectivity confirmed by GC analysis (chiral B-PH, 125 °C, 2.5 mL/min): 21.30, 22.06 min.

Irradiation of the vinyl proton resulted in a 2% nOe of the carbinol proton, consistent with an *E* olefin geometry in the observed allylic alcohol regioisomer.





2-Methyl-4-pent-4-enyl-undec-4-en-3-ol (4.15b). Procedure B (modification: aldehyde added over 3 h via syringe pump): Reaction of isobutyraldehyde and **4.11** (89 mg, 0.5 mmol) provided **4.15b** as a clear oil (57 mg, 45% yield). Following initial purification, flash chromatography on silica gel impregnated with 5% silver nitrate was required to remove minor impurities. Structure of **4.15b** was confirmed via ozonolysis (vide infra). R$_f$ = 0.40 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, CDCl$_3$) δ 5.79 – 5.87 (m, 1H); 5.36 (t, *J* = 7 Hz, 1H); 5.01 – 5.05 (m, 1H); 4.96 – 4.99 (m, 1H); 3.65 (d, *J* = 7 Hz, 1H); 1.95 – 2.13 (m, 6H); 1.78 (oct., *J* = 7 Hz, 1H); 1.46 – 1.56 (m, 2H); 1.24 – 1.40 (m, 8H); 0.96 (d, *J* = 7 Hz, 3H); 0.89 (t, *J* = 7 Hz, 3H); 0.83 (d, *J* = 7 Hz, 3H).

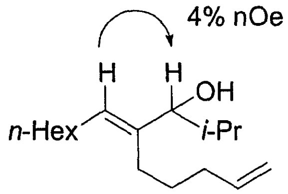
^{13}C NMR (125 MHz, CDCl$_3$) δ 140.95, 138.88, 128.39, 114.86, 83.05, 34.55, 31.98, 31.80, 29.99, 29.46, 29.28, 27.78, 27.53, 22.85, 20.08, 18.35, 14.32.

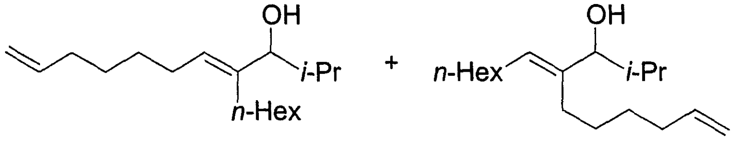
IR (thin film NaCl): 3415, 3077, 2956, 2928, 2858, 1823, 1722, 1641, 1467, 1379, 1366, 1297, 1249, 1168, 1113, 1010.

HRMS (ESI) *m/z* 275.235 [(M + Na)$^+$; calcd for $C_{17}H_{32}O$: 275.235].

Regioselectivity confirmed by GC analysis (chiral B-PH, 125 °C, 2.5 mL/min): 21.30, 22.06 min.

Irradiation of the vinyl proton resulted in a 4% nOe of the carbinol proton, consistent with an *E* olefin geometry in the observed allylic alcohol regioisomer.





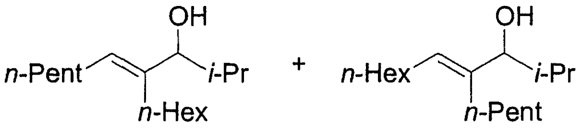
4-Hexyl-2-methyl-undeca-4,10-dien-3-ol (4.16a) and 4-hex-5-enyl-2-methyl-undec-4-en-3-ol (4.16b). Procedure A (reduced scale): Reaction of isobutyraldehyde (35 μL, 0.38 mmol) and **4.12** (36 mg, 0.19 mmol) in the presence of Ni(cod)$_2$ (5 mg, 19 μmol) and Et$_3$B (60 μL, 0.40 mmol) in EtOAc (200 μL) afforded <5% yield of **4.16a** and **4.16b**. Procedure B (reduced scale): Reaction of isobutyraldehyde (35 μL, 0.38 mmol) and **4.12** (36 mg, 0.19 mmol) in the presence of Ni(cod)$_2$ (5 mg, 19 μmol), Cyp$_3$P (11 μL, 38 μmol), and Et$_3$B (60 μL, 0.40 mmol) in EtOAc (200 μL) afforded a 50:50 mixture of regioisomers **4.16a** and **4.16b** as a clear oil (27 mg, 52% yield). R$_f$ = 0.46 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, CDCl$_3$) δ 5.77 – 5.86 (m, 2H); 5.36 (t, *J* = 7 Hz, 1H); 5.35 (t, *J* = 7 Hz, 1H); 4.98 – 5.04 (m, 2H); 4.93 – 4.96 (m, 2H); 3.65 (d, *J* = 7.5 Hz, 2H); 1.92 – 2.10 (m, 12H); 1.74 – 1.82 (m, 2H); 1.22 – 1.45 (m, 24H); 0.96 (d, *J* = 7 Hz, 3H); 0.96 (d, *J* = 6.5 Hz, 3H); 0.90 (t, $J = 7$ Hz, 3H); 0.89 (t, $J = 7$ Hz, 3H); 0.84 (d, $J = 7$ Hz, 3H); 0.83 (d, $J = 7$ Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 141.54, 141.11, 139.20, 139.17, 128.17, 127.71, 114.56, 114.51, 82.98, 82.94, 33.89, 33.81, 32.00, 31.93, 31.83, 31.82, 30.28, 30.20, 30.02, 29.70, 29.67, 29.50, 29.30, 28.85, 28.17, 27.92, 27.78, 27.58, 22.90, 22.86, 20.10, 20.09, 18.31, 18.29, 14.34, 14.32.

IR (thin film NaCl): 3438, 3078, 2957, 2929, 2858, 1821, 1714, 1660, 1641, 1467, 1415, 1379, 1366, 1296, 1247, 1169, 1102, 1009.

HRMS (ESI) *m/z* 289.251 [(M + Na)$^+$; calcd for $C_{18}H_{34}O$: 289.250].



4-Hexyl-2-methyl-dec-4-en-3-ol (4.37a) and 2-methyl-4-pentyl-undec-4-en-3-ol (4.37b). Procedure A (standard conditions): Reaction of isobutyraldehyde and **4.17** (90 mg, 0.5 mmol) afforded an 85:15 mixture of the title compounds and the corresponding alkylative coupling products (transfer of an ethyl group instead of a hydrogen from Et$_3$B) as a clear oil (36 mg, 28% yield (24% reductive), 51:49 mixture of regioisomers **4.37a** and **4.37b**). Procedure B (standard conditions): Reaction of isobutyraldehyde and **4.17** (90 mg, 0.5 mmol) afforded a 51:49 mixture of regioisomers **4.37a** and **4.37b** as a clear oil (98 mg, 77% yield). $R_f = 0.39$ (10:1 hexanes: ethyl acetate).

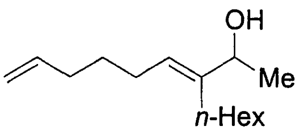
^{1}H NMR (500 MHz, CDCl$_3$) δ 5.35 (t, $J = 7$ Hz, 1H); 3.65 (d, $J = 7.5$ Hz, 1H); 1.92 – 2.07 (m, 4H); 1.78 (oct., $J = 7$ Hz, 1H); 1.24 – 1.44 (m, 14H); 0.96 (d, $J = 6$ Hz, 3H); 0.87 – 0.92 (m, 6H); 0.84 (d, $J = 6.5$ Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 141.33, 128.01, 83.01, 83.00, 32.71, 32.00, 31.93, 31.84, 31.83, 30.30, 30.20, 30.03, 30.00, 29.74, 29.30, 28.15, 28.10, 27.76, 27.72, 22.90, 22.86, 22.80, 22.74, 20.09, 18.32, 14.34, 14.32, 14.31, 14.30.

IR (thin film NaCl): 3624, 3423, 2957, 2927, 2872, 2859, 1713, 1661, 1467, 1379, 1366, 1297, 1244, 1169, 1105, 1008.

HRMS (ESI) *m/z* 277.251 [(M + Na)$^+$; calcd for $C_{17}H_{34}O$: 277.250].

Regioselectivity determined by GC analysis (chiral B-PH, 110 °C, 2.0 mL/min): 51.08, 52.04 min.



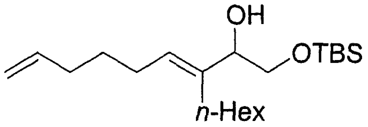
3-Hexyl-nona-3,8-dien-2-ol (4.18). Following Procedure A (modification: toluene used in place of EtOAc as the reaction solvent), reductive coupling of acetaldehyde (100 µl, 2 mmol) and **4.11** (89 mg, 0.5 mmol) afforded the title compound as a clear oil (77 mg, 69% yield, >95:5 regioselectivity). $R_f = 0.19$ (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, CDCl$_3$) δ 5.78 – 5.86 (m, 1H); 5.41 (t, J = 7 Hz, 1H); 4.99 – 5.05 (m, 1H); 4.94 – 4.98 (m, 1H); 4.23 (q, J = 6.5 Hz, 1H); 1.95 – 2.12 (m, 6H); 1.46 (quin., J = 7.5 Hz, 2H); 1.28 – 1.42 (m, 8H); 1.27 (d, J = 6.5 Hz, 3H); 0.90 (t, J = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 143.84, 139.00, 125.15, 114.72, 72.31, 33.65, 31.90, 30.11, 30.02, 29.22, 27.82, 27.13, 22.88, 22.58, 14.33.

IR (thin film NaCl): 3349, 3078, 2957, 2928, 2858, 1641, 1458, 1415, 1378, 1366, 1283, 1116, 1062.

HRMS (ESI) *m/z* 247.203 [(M + Na)$^+$; calcd for $C_{15}H_{28}O$: 247.203].



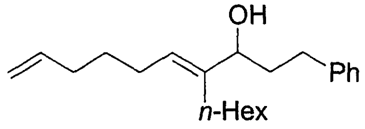
1-(*tert*-Butyl-dimethyl-silanyloxy)-3-hexyl-nona-3,8-dien-2-ol (4.19). Following Procedure A (modification: toluene used in place of EtOAc as the reaction solvent), reductive coupling of (*tert*-butyldimethylsilyloxy)acetaldehyde (190 μL, 1 mmol) and **4.11** (89 mg, 0.5 mmol) afforded the title compound as a clear oil (102 mg, 58% yield, >95:5 regioselectivity). R$_f$ = 0.42 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, CDCl$_3$) δ 5.77 – 5.86 (m, 1H); 5.48 (t, J = 7 Hz, 1H); 5.10 (dd, J = 17, 1 Hz, 1H); 4.96 (dt, J = 10, 1 Hz, 1H); 4.08 (dd, J = 8.5, 3 Hz, 1H); 3.64 (dd, J = 10, 3 Hz, 1H); 3.42 (dd, J = 10, 8.5 Hz, 1H); 2.03 – 2.12 (m, 5H); 1.87 – 1.94 (m, 1H); 1.47 (quin., J = 7.5 Hz, 2H); 1.24 – 1.40 (m, 8H); 0.91 (s, 9H); 0.89 (t, J = 7 Hz, 3H); 0.09 (s, 6H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 139.03, 138.39, 127.21, 114.68, 75.70, 67.27, 33.67, 31.91, 29.87, 29.78, 29.19, 28.58, 27.19, 26.11, 22.86, 18.52, 14.32, –5.08, –5.11.

IR (thin film NaCl): 3572, 3472, 3078, 2956, 2929, 2858, 1824, 1730, 1641, 1471, 1464, 1390, 1362, 1316, 1255, 1223, 1099, 1057, 1006, 992.

HRMS (ESI) *m/z* 377.284 [(M + Na)$^+$; calcd for $C_{21}H_{42}O_2Si$: 377.285].



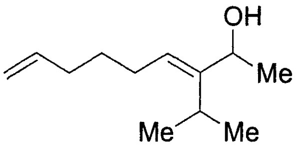
4-Hexyl-1-phenyl-deca-4,9-dien-3-ol (4.20). Following Procedure A (modification: toluene used in place of EtOAc as the reaction solvent), reductive coupling of 3-phenylpropionaldehyde (132 μL, 1 mmol) and **4.11** (89 mg, 0.5 mmol) afforded the title compound as a clear oil (95 mg, 60% yield, >95:5 regioselectivity). R$_f$ = 0.23 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.27 – 7.31 (m, 2H); 7.17 – 7.22 (m, 3H); 5.78 – 5.87 (m, 1H); 5.41 (t, J = 7 Hz, 1H); 5.00 – 5.04 (m, 1H); 4.95 – 4.98 (m, 1H); 4.05 (t, J = 6.5 Hz, 1H); 2.70 – 2.76 (m, 1H); 2.60 – 2.66 (m, 1H); 1.96 – 2.11 (m, 6H); 1.84 – 1.89 (m, 2H); 1.47 (quin., J = 7.5 Hz, 2H); 1.24 – 1.42 (m, 8H); 0.89 (t, J = 7 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 142.41, 142.39, 138.94, 128.65, 128.55, 126.82, 125.96, 114.78, 76.34, 37.59, 33.65, 32.52, 31.87, 30.20, 30.06, 29.93, 27.82, 27.19, 22.87, 14.32.

IR (thin film NaCl): 3360, 3077, 3064, 3027, 2954, 2928, 2858, 1940, 1821, 1727, 1641, 1604, 1496, 1455, 1415, 1378, 1301, 1154, 1048, 1031, 992.

HRMS (ESI) *m/z* 337.250 [(M + Na)$^+$; calcd for $C_{22}H_{34}O$: 337.250].



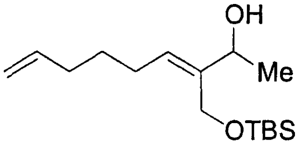
3-Isopropyl-nona-3,8-dien-2-ol (4.22). Following Procedure A (modification: toluene used in place of EtOAc as the reaction solvent), reductive coupling of acetaldehyde (100 μL, 1.8 mmol) and **4.21** (68 mg, 0.5 mmol) afforded the title compound as a clear oil (58 mg, 64% yield, >95:5 regioselectivity). R_f = 0.20 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, CDCl$_3$) δ 5.78 – 5.86 (m, 1H); 5.47 (t, *J* = 7 Hz, 1H); 4.99 – 5.04 (m, 1H); 4.95 – 4.98 (m, 1H); 4.30 (q, *J* = 6.5 Hz, 1H); 2.76 (sept., *J* = 7 Hz, 1H); 2.05 – 2.13 (m, 4H); 1.47 (quin., *J* = 7 Hz, 2H); 1.29 (d, *J* = 6.5 Hz, 3H); 1.11 (d, *J* = 7 Hz, 3H); 1.05 (d, *J* = 7 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 149.38, 138.99, 124.20, 114.74, 68.43, 33.65, 29.36, 28.20, 26.99, 24.19, 21.97, 21.71.

IR (thin film NaCl): 3361, 3078, 2962, 2929, 2872, 1824, 1641, 1460, 1415, 1365, 1304, 1282, 1217, 1150, 1111, 1060.

HRMS (ESI) *m/z* 205.156 [(M + Na)$^+$; calcd for $C_{12}H_{22}O$: 205.156].



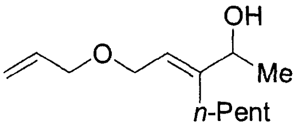
3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-nona-3,8-dien-2-ol (4.24). Following Procedure A (modification: toluene used in place of EtOAc as the reaction solvent), reductive coupling of acetaldehyde (100 μL, 1.8 mmol) and **4.23** (119 mg, 0.5 mmol) afforded the title compound as a clear oil (88 mg, 62% yield, >95:5 regioselectivity). R_f = 0.40 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, CDCl$_3$) δ 5.76 – 5.85 (m, 1H); 5.49 (t, *J* = 7.5 Hz, 1H); 4.99 – 5.04 (m, 1H); 4.95 – 4.98 (m, 1H); 4.31 – 4.40 (m, 3H); 2.00 – 2.10 (m, 4H); 1.48 (quin., *J* = 7.5 Hz, 2H); 1.34 (d, *J* = 6 Hz, 3H); 0.92 (s, 9H); 0.12 (s, 3H); 0.11 (s, 3H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 140.04, 138.70, 127.74, 114.94, 72.43, 60.20, 33.45, 28.94, 26.92, 26.07, 22.22, 18.36, –5.30.

IR (thin film NaCl): 3421, 3078, 2956, 2929, 2886, 2858, 1668, 1641, 1472, 1463, 1442, 1406, 1390, 1362, 1255, 1072.

HRMS (ESI) *m/z* 307.206 [(M + Na)$^+$; calcd for $C_{16}H_{32}O_2Si$: 307.206].



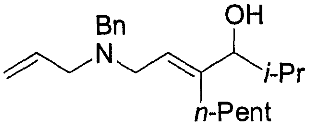
5-Allyloxy-3-pentyl-pent-3-en-2-ol (4.28). Following Procedure A (modifications: toluene used in place of EtOAc as the reaction solvent, and slow addition of the enyne over 3 h via syringe pump), reductive coupling of acetaldehyde (100 μL, 1.8 mmol) and **4.25** (83 mg, 0.5 mmol) afforded the title compound as a clear oil (64 mg, 60% yield, >95:5 regioselectivity). $R_f = 0.17$ (5:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 – 5.97 (m, 1H); 5.64 (t, $J = 6.5$ Hz, 1H); 5.27 – 5.32 (m, 1H); 5.19 – 5.22 (m, 1H); 4.27 (q, $J = 6.5$ Hz, 1H); 4.05 (d, $J = 6.5$ Hz, 2H); 3.99 (dt, $J = 6$, 1.5 Hz, 2H); 2.09 – 2.16 (m, 1H); 1.98 – 2.04 (m, 1H); 1.20 – 1.42 (m, 11H); 0.90 (t, $J = 7$ Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 147.75, 134.98, 121.25, 117.42, 71.63, 71.58, 66.49, 32.40, 29.97, 28.18, 22.66, 22.40, 14.24.

IR (thin film NaCl): 3392, 2957, 2932, 2861, 1647, 1459, 1367, 1212, 1065.

HRMS (ESI) *m/z* 235.166 [$(M + Na)^+$; calcd for $C_{13}H_{24}O_2$: 235.167].



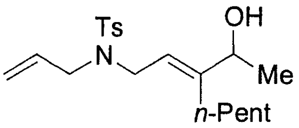
6-(Allyl-benzyl-amino)-2-methyl-4-pentyl-hex-4-en-3-ol (4.29). Following Procedure A (modification: toluene used in place of EtOAc as the reaction solvent), reductive coupling of isobutyraldehyde (90 μL, 1.0 mmol) and **4.26** (128 mg, 0.5 mmol) afforded the title compound as a clear oil (102 mg, 62% yield, >95:5 regioselectivity). $R_f = 0.22$ (5:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.36 (m, 4H); 5.86 – 5.95 (m, 1H); 5.52 (t, $J = 6.5$ Hz, 1H); 5.20 (dd, $J = 17.5$, 2 Hz, 1H); 5.16 (d, $J = 10$ Hz, 1H); 3.69 (d, $J = 7$ Hz, 1H); 3.57 (s, 2H); 3.12 (d, $J = 7$ Hz, 2H); 3.09 (d, $J = 6.5$ Hz, 2H); 1.97 – 2.04 (m, 1H); 1.89 – 1.95 (m, 1H); 1.79 (oct., $J = 7$ Hz, 1H); 1.22 – 1.38 (m, 6H); 0.95 (d, $J = 6.5$ Hz, 3H); 0.88 (t, $J = 7$ Hz, 3H); 0.86 (d, $J = 7$ Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 144.51, 139.70, 136.22, 129.16, 128.37, 127.04, 124.66, 117.67, 82.42, 58.28, 57.14, 50.91, 32.59, 31.71, 29.89, 28.45, 22.66, 20.14, 18.07, 14.29.

IR (thin film NaCl): 3423, 3065, 3028, 2956, 2930, 2870, 1643, 1495, 1455, 1366, 1255, 1118, 1073, 1012.

HRMS (ESI) *m/z* 330.279 [$(M + Na)^+$; calcd for $C_{22}H_{35}NO$: 330.279].



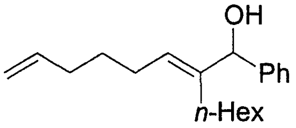
N-allyl-N-[3-(1-hydroxyethyl)-oct-2-enyl]-benzenesulfonamide (4.30). Following Procedure A (modification: toluene used in place of EtOAc as the reaction solvent), reductive coupling of acetaldehyde (200 µL, 3.6 mmol) and **4.27** (160 mg, 0.5 mmol) afforded the title compound as a clear oil (125 mg, 68% yield, >95:5 regioselectivity). R_f = 0.29 (3:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.5 Hz, 2H); 7.30 (d, *J* = 8.5 Hz, 2H); 5.64 – 5.73 (m, 1H); 5.26 (t, *J* = 7 Hz, 1H); 5.14 – 5.18 (m, 2H); 4.16 (q, *J* = 6.5 Hz, 1H); 3.86 (d, *J* = 6.5 Hz, 2H); 3.79 - 3.81 (m, 2H); 2.44 (s, 3H); 2.02 - 2.08 (m, 1H); 1.89 - 1.96 (m, 1H); 1.22 – 1.36 (m, 6H); 1.20 (d, *J* = 6.5 Hz, 3H); 0.89 (t, *J* = 7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 148.02, 143.44, 137.74, 133.39, 129.83, 127.45, 118.98, 118.87, 71.34, 49.90, 44.17, 32.36, 29.71, 27.98, 22.64, 22.40, 21.73, 14.24.

IR (thin film NaCl): 3521, 2957, 2931, 2870, 1644, 1598, 1495, 1446, 1418, 1402, 1343, 1305, 1289, 1264, 1213, 1159, 1119, 1092, 1059.

HRMS (ESI) *m/z* 388.192 [(M + Na)$^+$; calcd for $C_{20}H_{31}NO_3S$: 388.192].



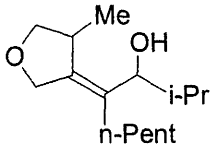
2-Hexyl-1-phenyl-octa-2,7-dien-1-ol (4.38). Following Procedure A (modification: toluene used in place of EtOAc as the reaction solvent), reductive coupling of benzaldehyde (106 µL, 1 mmol) and **4.11** (89 mg, 0.5 mmol) proceeded slowly and only minimal conversion was observed after 15 h. The reaction was allowed to stir at 23 °C for an additional 25 h prior to quenching. Flash chromatography on silica gel afforded the title compound as a clear oil (37 mg, 26% yield, >95:5 regioselectivity). R_f = 0.29 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 - 7.38 (m, 3H); 7.24 - 7.29 (m, 2H); 5.79 - 5.88 (m, 1H); 5.62 (t, *J* = 7 Hz, 1H); 5.17 (s, 1H); 5.02 (dq, *J* = 17, 1.5 Hz, 1H); 4.95 - 4.99 (m, 1H); 2.06 – 2.15 (m, 4H); 1.95 - 2.02 (m, 1H); 1.78 - 1.86 (m, 1H); 1.51 (quin., *J* = 7.5 Hz, 2H); 1.15 – 1.30 (m, 8H); 0.86 (t, *J* = 7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 142.94, 141.86, 138.97, 128.43, 127.58, 126.90, 126.77, 114.78, 78.32, 33.70, 31.76, 29.83, 29.65, 29.24, 28.04, 27.26, 22.78, 14.29.

IR (thin film NaCl): 3373, 3063, 3029, 2955, 2928, 2858, 1641, 1493, 1454, 1378, 1190, 1014, 911, 700.

HRMS (ESI) *m/z* 309.220 [(M + Na)$^+$; calcd for $C_{20}H_{30}O$: 309.219].



2-Methyl-4-(4-methyl-dihydro-furan-3-ylidene)-nonan-3-ol (4.30). Following Procedure B on half-scale, Ni(cod)$_2$ (7 mg, 25 μmol), Cyp$_3$P (14 μL, 50 μmol), ethyl acetate (0.25 mL) and Et$_3$B (75 μL, 0.50 mmol) were combined under argon and the resulting solution was cooled to 0 °C. Isobutyraldehyde (45 μL, 0.5 mmol) was added dropwise via microsyringe, followed by **4.25** (42 mg, 0.25 mmol). The reaction was allowed to gradually warm to room temperature and stir for 15 h. Formation of an allylic alcohol of analogous structure to **4.15b** was not observed. Rather, purification by flash chromatography on silica gel (hexanes: ethyl acetate; 10:1 to 5:1) provided carbocyclization product **4.30** as a clear oil (16 mg, 27% yield, >10:1 dr). R_f = 0.52 (3:1 hexanes: ethyl acetate).

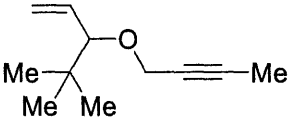
^{1}H NMR (500 MHz, CDCl$_3$) δ 4.45 (d, J = 13.5 Hz, 1H); 4.28 (d, J = 13.5 Hz, 1H); 3.98 (d, J = 9.5 Hz, 1H); 3.80 (dd, J = 8, 5 Hz, 1H); 3.70 (d, J = 9 Hz, 1H); 2.90 – 2.98 (m, 1H); 1.94 – 2.01 (m, 1H); 1.81 – 1.90 (m, 2H); 1.20 – 1.40 (m, 6H); 1.13 (d, J = 7 Hz, 3H); 1.10 (d, J = 6.5 Hz, 3H); 0.90 (t, J = 7 Hz, 3H); 0.81 (d, J = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 143.17, 131.78, 79.46, 75.94, 69.22, 36.16, 32.94, 31.58, 29.72, 29.17, 22.65, 21.05, 20.17, 19.82, 14.30.

IR (thin film NaCl): 3443, 2957, 2931, 2870, 1466, 1379, 1315, 1260, 1091, 1009.

HRMS (ESI) *m/z* 263.199 [(M + Na)$^+$; calcd for $C_{15}H_{28}O_2$: 263.198].

Diastereoselective Couplings of Chiral Enyne 4.35.



3-But-2-ynyloxy-4,4-dimethyl-pent-1-ene (4.35): NaH (1.32 g of a 58 wt% dispersion) was placed in a 250 mL round-bottom flask, washed with anhydrous hexanes, and dried in vacuo. THF (80 mL) was then added, followed by 4,4-dimethyl-pent-1-en-3-ol[36] (133 mg, 8 mmol). The mixture was stirred 4 h at 23 °C, and then 1-bromo-2-butyne (0.84 mL, 9.6 mmol) was added. After stirring 15 h, sat. NH$_4$Cl (aq) (100 mL) was added, and the organics were extracted with Et$_2$O (3 x 100 mL). The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated. Flash chromatography on silica gel (8:1 hexanes:Et$_2$O) afforded the title compound as a clear liquid (650 mg, 49% yield). ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.64 – 5.72 (m, 1H); 5.26 – 5.29 (m, 1H); 5.17 – 5.22 (m, 1H); 4.13 – 4.17 (m, 1H); 3.90 – 3.95 (m, 1H); 3.42 (d, J = 8 Hz, 1H); 1.86 (t, J = 2.5 Hz, 3H); 0.91 (s, 9H).

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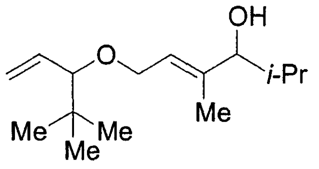
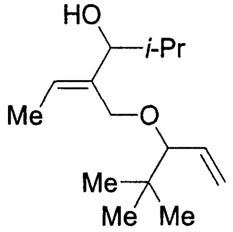
[36] Craig, D.; Pennington, M. W.; Warner, P. *Tetrahedron* **1999**, *55*, 13495-13512.



6-(1-*tert*-Butyl-allyloxy)-2,4-dimethyl-hex-4-en-3-ol (4.36a): In a glovebox, Ni(cod)$_2$ (5.5 mg, 0.02 mmol) was placed into a 10 mL oven-dried, single-necked round-bottom flask, and the flask was then sealed with a rubber septum. The flask was removed from the glovebox, placed under argon, and toluene (0.15 mL) was added via syringe, followed immediately by Et$_3$B (0.15 mL, 1.0 mmol). The resulting solution was then cooled to 0 °C, and isobutyraldehyde (18 μL, 0.2 mmol) was added dropwise via microsyringe, followed by enyne **4.35** (33 mg, 0.2 mmol). The reaction was allowed to gradually warm to room temperature and stir 15 h. The septa was then removed and the reaction was stirred 30 min open to air to promote quenching of the catalyst. Purification by flash chromatography on silica gel using a solvent gradient (hexanes: ethyl acetate; 12:1 to 5:1), afforded the title compound as a clear oil (3.1 mg, 6% yield, >95:5 regioselectivity, >95:5 diastereoselectivity).

^{1}H NMR (500 MHz, CDCl$_3$) δ 5.68 – 5.76 (m, 1H); 5.52 (t, J = 6 Hz, 1H); 5.26 (dd, J = 5.5, 1.5 Hz, 1H); 5.14 (d, J = 16.5 Hz, 1H); 4.08 (dd, J = 12.5, 5.5 Hz, 1H); 3.86 (dd, J = 12.5, 7 Hz, 1H); 3.64 (d, J = 8 Hz, 1H); 3.22 (d, J = 8.5 Hz, 1H); 1.72 – 1.82 (m, 1H); 1.61 (s, 3H); 1.60 (s, 1H); 0.99 (d, J = 6.5 Hz, 3H); 0.89 (s, 9H); 0.82 (d, J = 7 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 139.82, 136.47, 125.06, 118.45, 88.65, 83.80, 64.85, 34.58, 31.13, 26.32, 19.69, 18.65, 11.89.



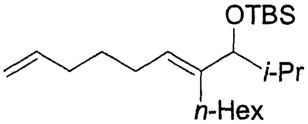
4-(1-*tert*-Butyl-allyloxymethyl)-2-methyl-hex-4-en-3-ol (4.36b): In a glovebox, Ni(cod)$_2$ (5.5 mg, 0.02 mmol) and Cyp$_3$P (5.6 μL, 0.02 mmol) were placed into a 10 mL oven-dried, single-necked round-bottom flask, and the flask was then sealed with a rubber septum. The flask was removed from the glovebox, placed under argon, and toluene (0.15 mL) was added via syringe, followed immediately by Et$_3$B (0.15 mL, 1.0 mmol). The resulting solution was then cooled to 0 °C, and isobutyraldehyde (18 μL, 0.2 mmol) was added dropwise via microsyringe, followed by enyne **4.35** (33 mg, 0.2 mmol). The reaction was allowed to gradually warm to room temperature and stir 15 h. The septa was then removed and the reaction was stirred 30 min open to air to promote quenching of the catalyst. Purification by flash chromatography on silica gel using a solvent gradient (hexanes: ethyl acetate; 12:1 to 5:1), afforded the title compound as a clear oil (6.2 mg, 13% yield, >95:5 regioselectivity, 50:50 diastereoselectivity).

^{1}H NMR (500 MHz, CDCl$_3$) δ 5.68 – 5.77 (m, 2H); 5.61 (q, J = 7 Hz, 2H); 5.32 (ddd, J = 10, 5, 1.5 Hz, 2H); 5.22 (d, J = 17.5 Hz, 2H); 4.29 (d, J = 11 Hz, 1H); 4.08 (d, J = 11 Hz, 1H);

3.94 (d, J = 10.5 Hz, 1H); 3.74 (d, J = 10.5 Hz, 1H); 3.25 (dd, J = 20.5, 8.5 Hz, 2H); 2.84 (dd, J = 13.5, 7 Hz, 2H); 1.75 – 1.88 (m, 2H); 1.68 (d, J = 7 Hz, 3H); 1.66 (d, J = 7 Hz, 3H); 1.60 (s, 2H); 1.03 (dd, J = 7, 7 Hz, 6H); 0.90 (s, 9H); 0.89 (s, 9H); 0.76 (dd, J = 7, 7 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 135.90, 135.87, 126.74, 126.70, 119.49, 119.27, 90.64, 90.56, 84.41, 84.30, 65.05, 64.89, 32.47, 32.38, 26.43, 26.30, 19.87, 19.85, 19.28, 13.37.

Structural confirmation of 4.15a via TBS protection and ozonolytic cleavage.



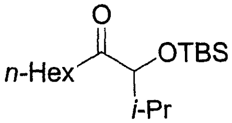
***tert*-Butyl-(1-isopropyl-2-hexyl-octa-2,7-dienyloxy)-dimethyl silane (4.31).** Alcohol **4.15a** (28 mg, 0.11 mmol) was dissolved in dimethylformamide (0.5 mL) and *tert*-butyldimethylsilyl chloride (33 mg, 0.22 mmol), imidazole (15 mg, 0.22 mmol), and 4-dimethylaminopyridine (27 mg, 0.22 mmol) were added sequentially. The mixture was allowed to stir overnight, and was then quenched by addition of water (2 mL) and diethyl ether (2 mL). The organics were extracted with additional diethyl ether (2 x 2 mL), dried over anhydrous $MgSO_4$, and concentrated. Flash chromatography on silica gel (10:1 hexanes:ethyl acetate) afforded the title compound as a clear oil (25 mg, 62% yield (95% based on recovered starting material)). R_f = 0.67 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 – 5.87 (m, 1H); 5.26 (t, J = 7 Hz, 1H); 4.99 – 5.04 (m, 1H); 4.95 – 4.97 (m, 1H); 3.60 (d, J = 6.5 Hz, 1H); 2.01 – 2.10 (m, 4H); 1.87 – 2.00 (m, 2H); 1.69 (oct., J = 6.5 Hz, 1H); 1.42 – 1.49 (m, 2H); 1.24 – 1.40 (m, 8H); 0.90 (s, 9H); 0.90 (t, J = 7 Hz, 3H); 0.85 (d, J = 6.5 Hz, 3H); 0.80 (d, J = 7 Hz, 3H); 0.02 (s, 3H); –0.05 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 141.05, 139.19, 127.00, 114.61, 83.17, 33.80, 32.22, 31.96, 30.40, 30.05, 29.40, 27.88, 27.21, 26.20, 22.94, 20.39, 18.49, 18.16, 14.35, –3.95, –4.77.

IR (thin film NaCl): 2957, 2929, 2858, 1642, 1472, 1383, 1361, 1254, 1128, 1054.

HRMS (ESI) *m/z* 389.323 [$(M + Na)^+$; calcd for $C_{23}H_{46}OSi$: 389.321].

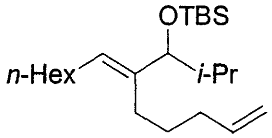


3-(*tert*-Butyl-dimethyl-silanoxy)-2-methyl-decan-4-one (4.33). *tert*-Butyldimethylsilyl ether **4.31** (17 mg, 46 μmol) was dissolved in dichloromethane (2 mL) and cooled to –78 °C. Ozone was then bubbled through the solution until a blue color was observed (<1 min). The solution was purged with argon for 5 min, and then triphenylphosphine (60 mg, 0.23 mmol) was added. The mixture was allowed to warm gradually to ambient temperature and stir overnight. Concentration of the solution and purification via flash chromatography on silica gel (1:1

hexanes:benzene) provided the title compound as a clear oil (7.5 mg, 54% yield). $R_f = 0.60$ (1:1 hexanes: benzene).

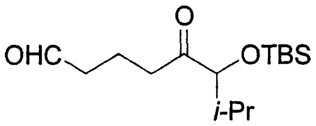
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (d, $J = 5.5$ Hz, 1H); 2.51 – 2.59 (m, 1H); 2.41 – 2.49 (m, 1H); 1.93 (oct., $J = 6.5$ Hz, 1H); 1.51 – 1.57 (m, 2H); 1.24 – 1.34 (m, 8H); 0.94 (s, 9H); 0.86 – 0.90 (m, 9H); 0.05 (s, 3H); 0.02 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 214.27, 83.90, 38.05, 32.82, 31.90, 29.24, 25.99, 23.23, 22.74, 19.17, 18.36, 17.71, 14.27, –4.57, –4.84.
IR (thin film NaCl): 2958, 2930, 2858, 1715, 1471, 1436, 1406, 1388, 1363, 1253, 1182, 1120, 1090, 1071.
HRMS (ESI) *m/z* 323.236 [$(M + Na)^+$; calcd for $C_{17}H_{36}O_2Si$: 323.238].

Structural confirmation of 4.15b via TBS protection and ozonolytic cleavage.



***tert*-Butyl-(1-isopropyl-2-pent-4-enyl-non-2-enyloxy)-dimethyl silane (4.32).** Alcohol **4.15b** (20 mg, 80 μmol) was dissolved in dimethylformamide (0.5 mL) and *tert*-butyldimethylsilyl chloride (24 mg, 0.16 mmol), imidazole (11 mg, 0.16 mmol), and 4-dimethylaminopyridine (20 mg, 0.16 mmol) were added sequentially. The mixture was allowed to stir overnight, and was then quenched by addition of water (2 mL) and diethyl ether (2 mL). The organics were extracted with additional diethyl ether (2 x 2 mL), dried over anhydrous $MgSO_4$, and concentrated. Flash chromatography on silica gel (hexanes) afforded the title compound as a clear oil (13 mg, 45% yield (91% based on recovered starting material)). $R_f = 0.55$ (hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 – 5.87 (m, 1H); 5.27 (t, $J = 7$ Hz, 1H); 5.00 – 5.04 (m, 1H); 4.95 – 4.97 (m, 1H); 3.59 (d, $J = 7$ Hz, 1H); 1.92 – 2.09 (m, 6H); 1.69 (oct., $J = 7$ Hz, 1H); 1.44 – 1.52 (m, 2H); 1.24 – 1.38 (m, 8H); 0.90 (s, 9H); 0.89 (t, $J = 7$ Hz, 3H); 0.86 (d, $J = 7$ Hz, 3H); 0.79 (d, $J = 7$ Hz, 3H); 0.02 (s, 3H); –0.05 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 140.24, 139.07, 127.98, 114.65, 83.40, 34.79, 32.26, 32.03, 30.02, 29.36, 29.29, 27.75, 27.26, 26.19, 22.89, 20.32, 18.48, 18.31, 14.33, –3.97, –4.78.
IR (thin film NaCl): 2957, 2929, 2857, 1642, 1472, 1383, 1361, 1251, 1128, 1054.
HRMS (ESI) *m/z* 389.320 [$(M + Na)^+$; calcd for $C_{23}H_{46}OSi$: 389.321].



6-(*tert*-Butyl-dimethyl-silanyloxy)-7-methyl-5-oxo-octanal (4.34). *tert*-Butyldimethylsilyl ether **4.32** (19 mg, 52 μmol) was dissolved in dichloromethane (2 mL) and cooled to –78 °C.

Ozone was then bubbled through the solution until a blue color was observed (<1 min). The solution was purged with argon for 5 min, and then triphenylphosphine (68 mg, 0.26 mmol) was added. The mixture was allowed to warm gradually to ambient temperature and stir overnight. Concentration of the solution and purification via flash chromatography on silica gel (10:1 hexanes:ethyl acetate) afforded the title compound as a clear oil (12 mg, 81% yield). $R_f = 0.30$ (10:1 hexanes: ethyl acetate).

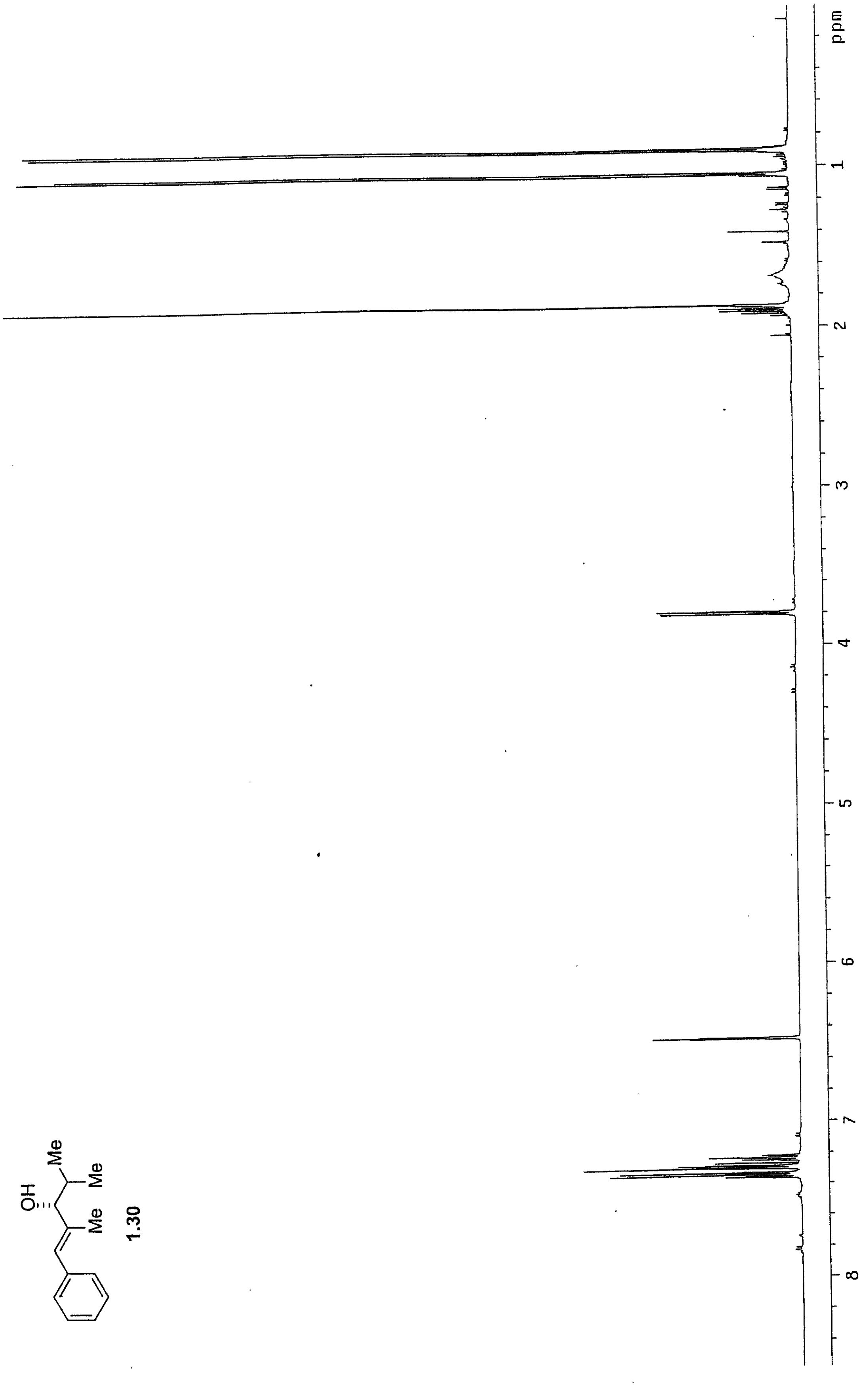
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (t, $J = 1.5$ Hz, 1H); 3.73 (d, $J = 5.5$ Hz, 1H); 2.62 – 2.68 (m, 1H); 2.47 – 2.55 (m, 2H); 1.86 – 1.95 (m, 3H); 0.93 (s, 9H); 0.89 (d, $J = 6.5$ Hz, 3H); 0.88 (d, $J = 7$ Hz, 3H); 0.05 (s, 3H); 0.01 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 213.36, 202.17, 83.73, 43.32, 36.94, 32.96, 25.97, 19.06, 18.32, 17.71, 15.76, –4.57, –4.83.

IR (thin film NaCl): 2959, 2932, 2859, 2716, 1726, 1472, 1389, 1366, 1254, 1183, 1088.

Appendix A.

^{1}H and ^{13}C NMR Spectra (Chapter 1)



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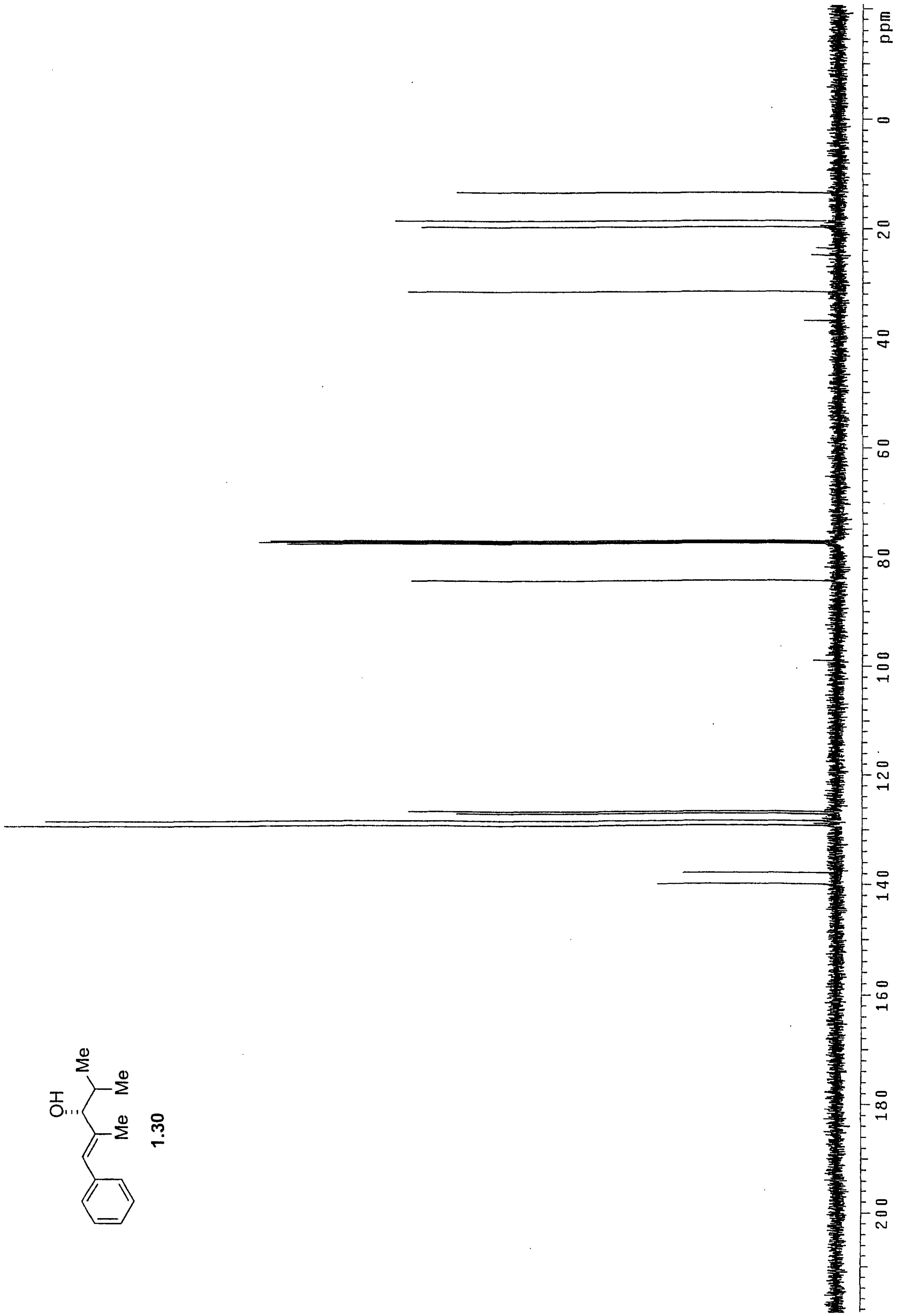

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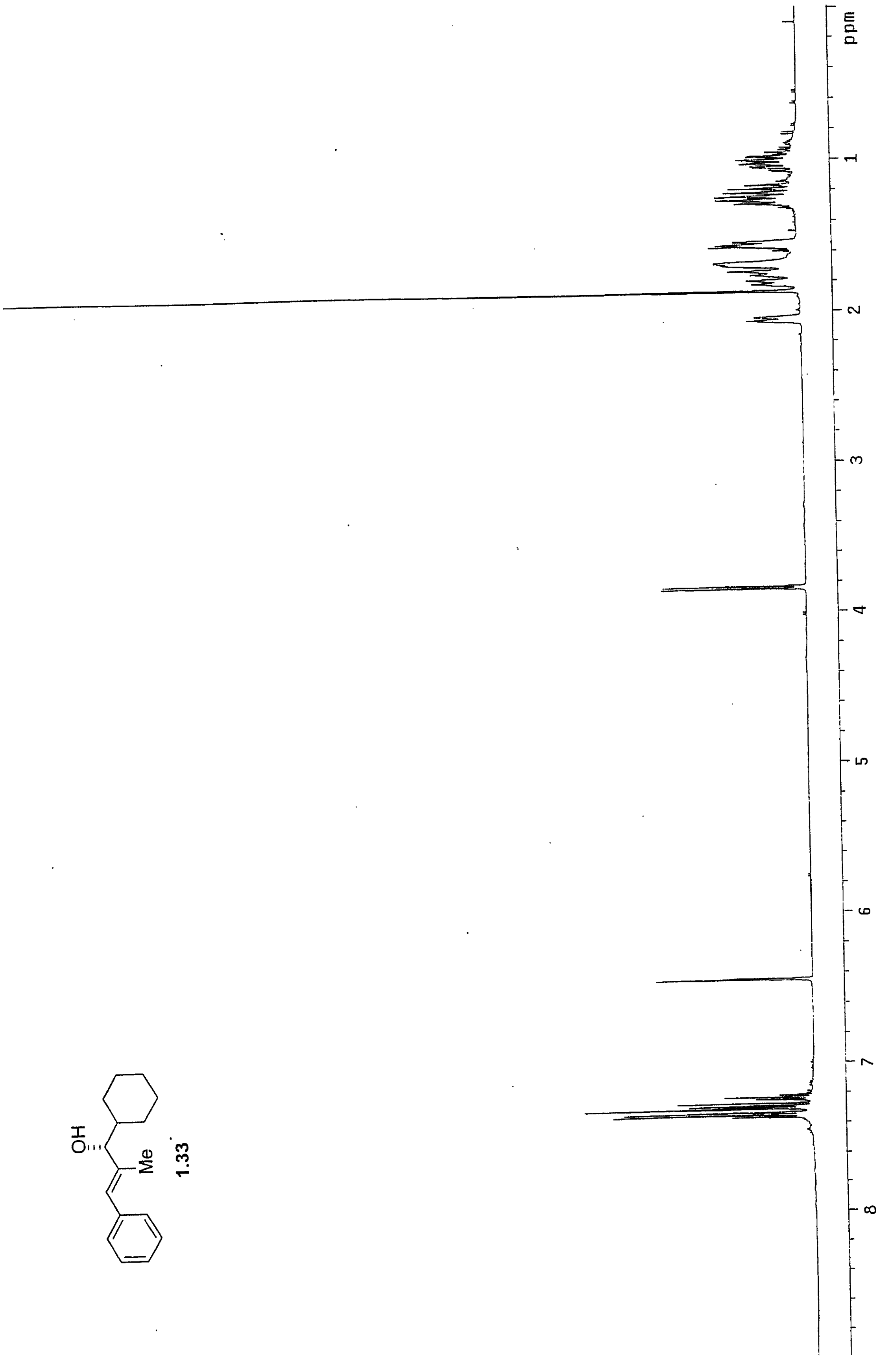

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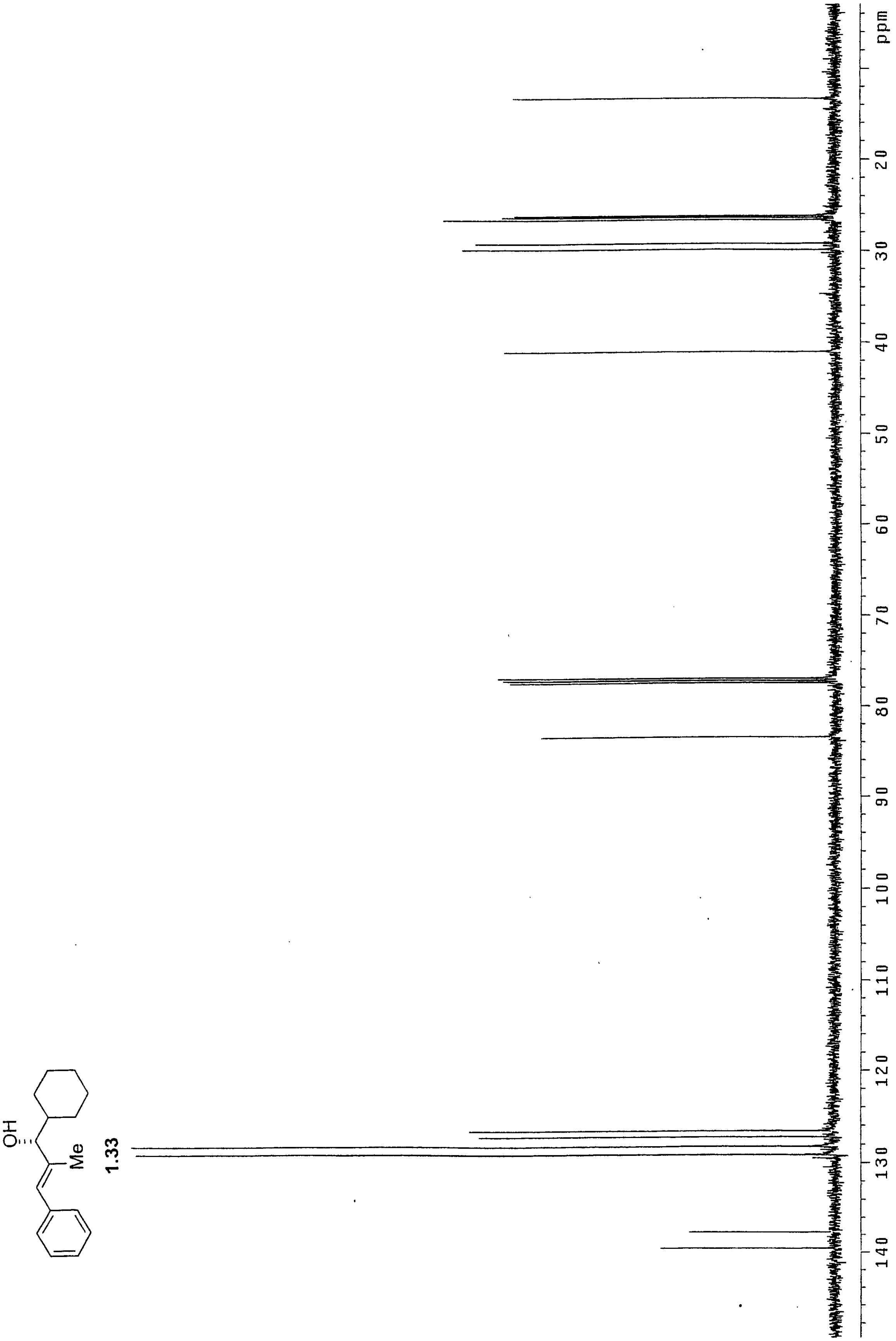

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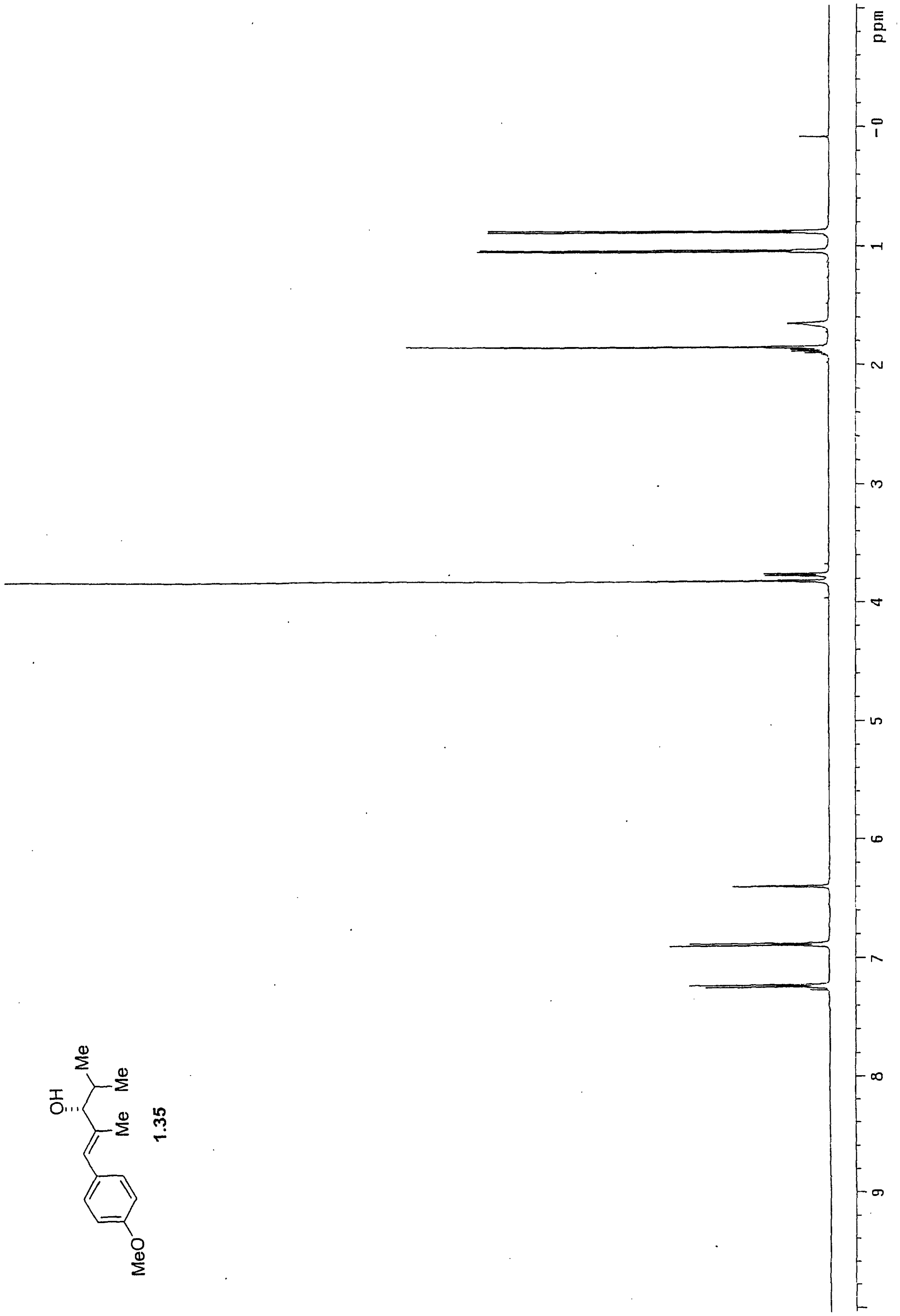

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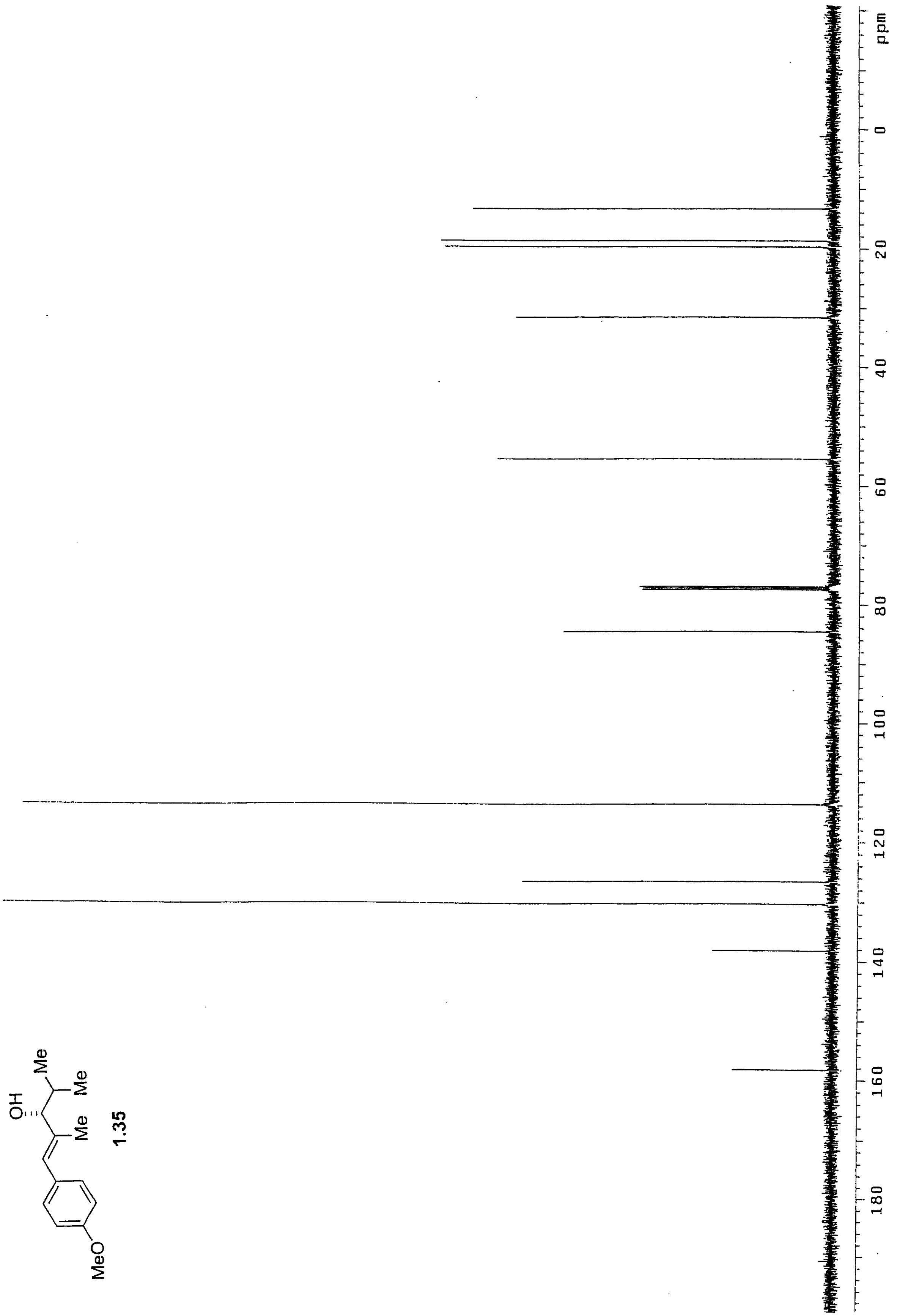
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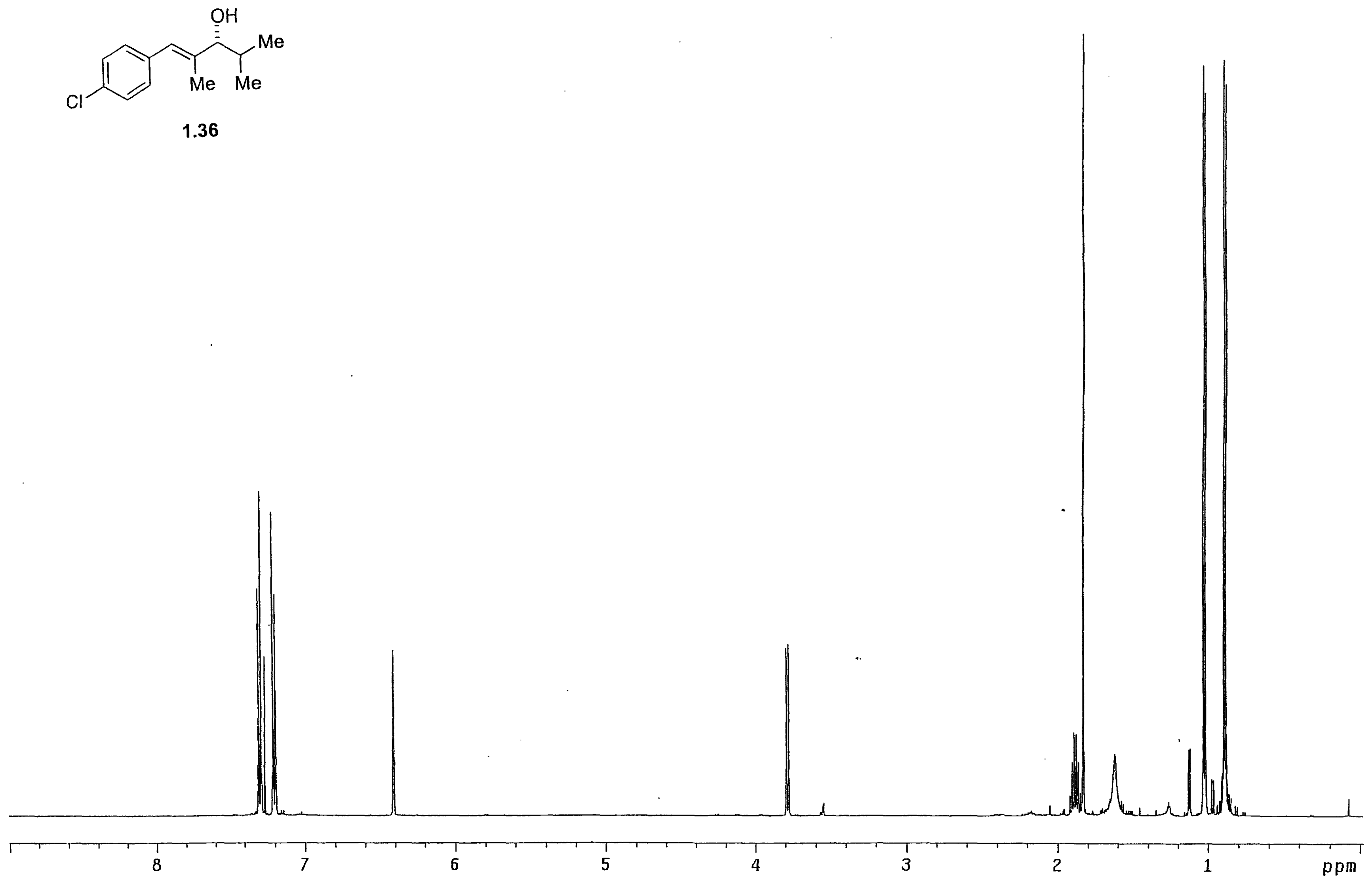

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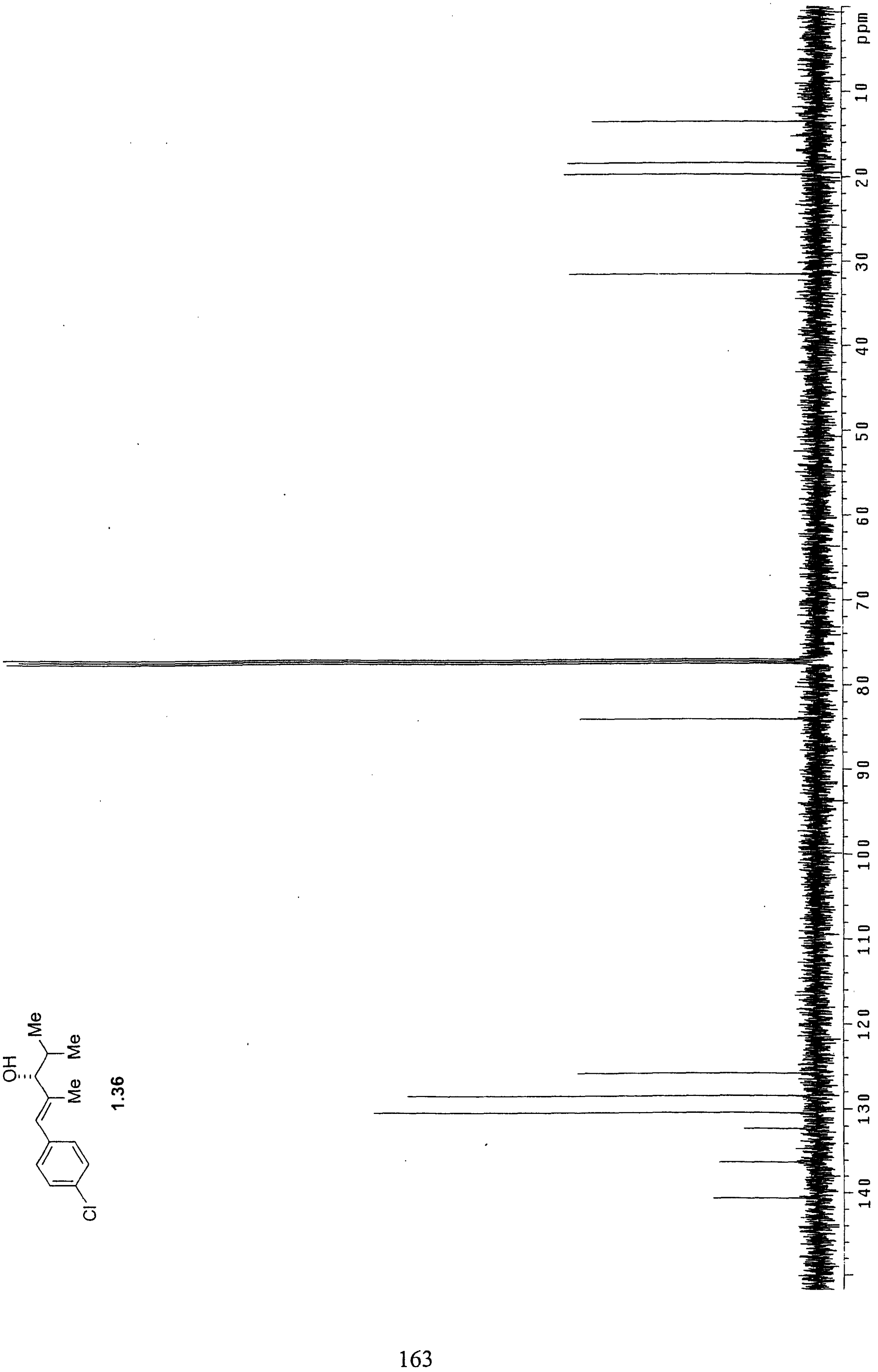

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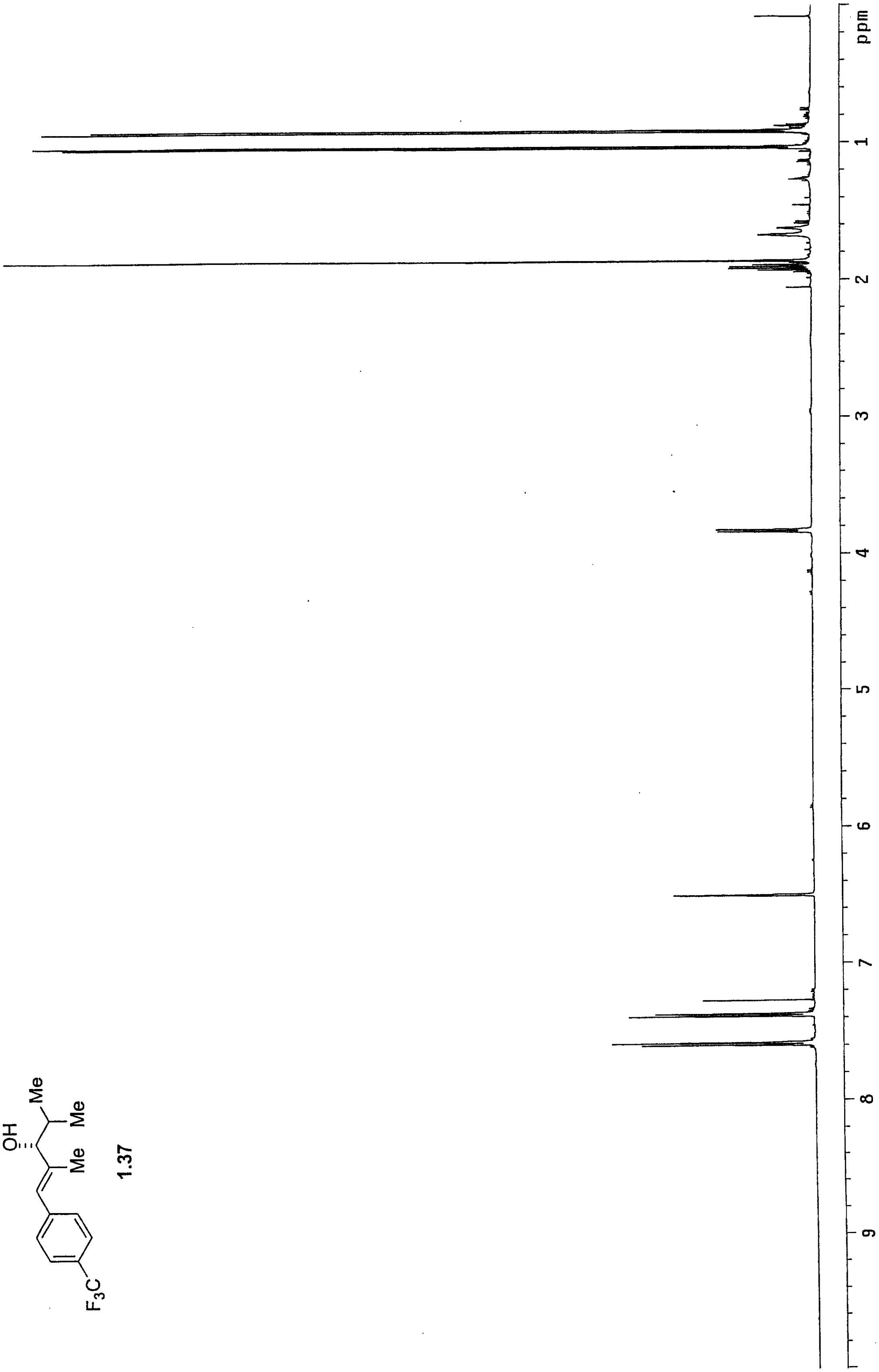
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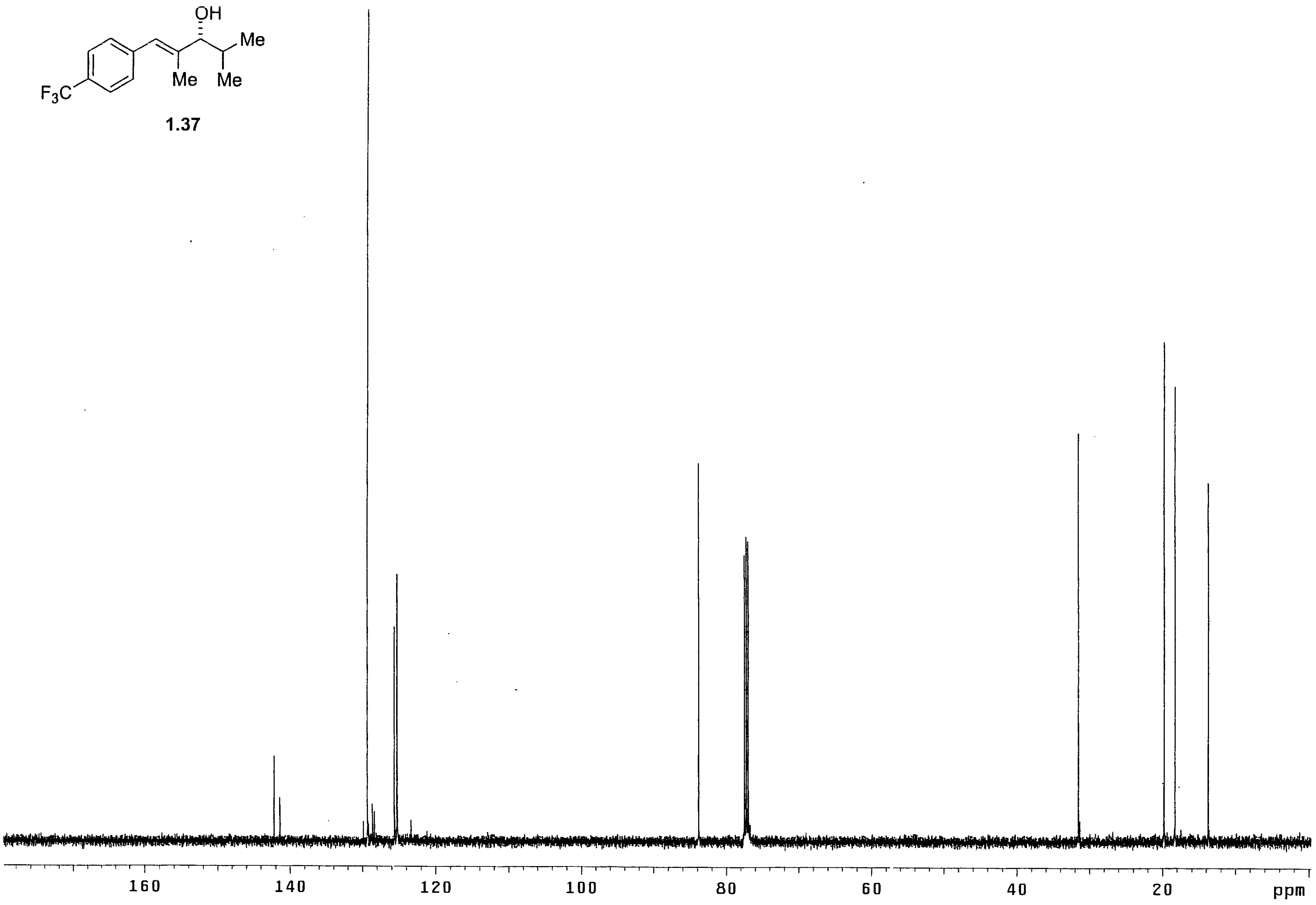

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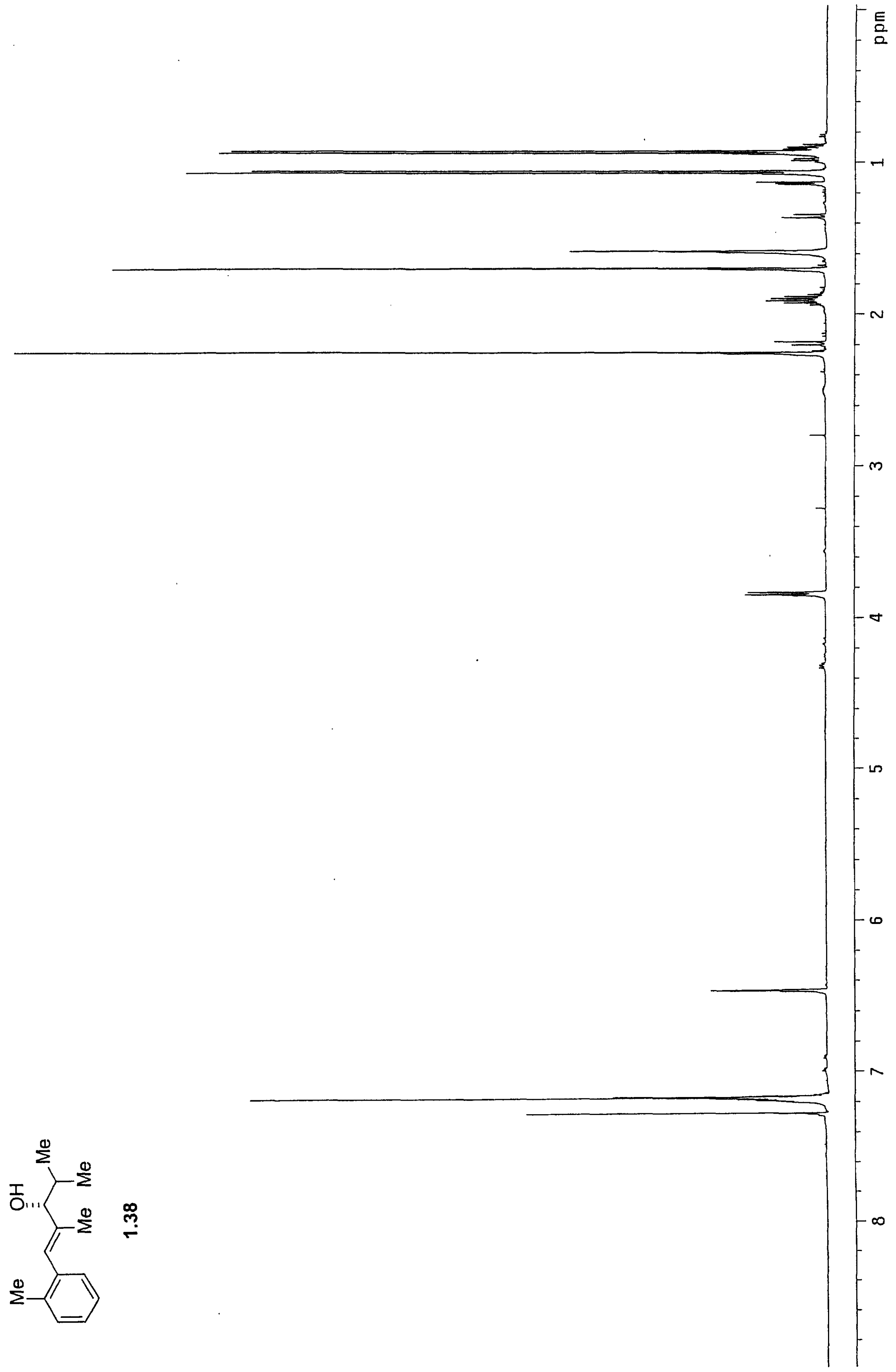

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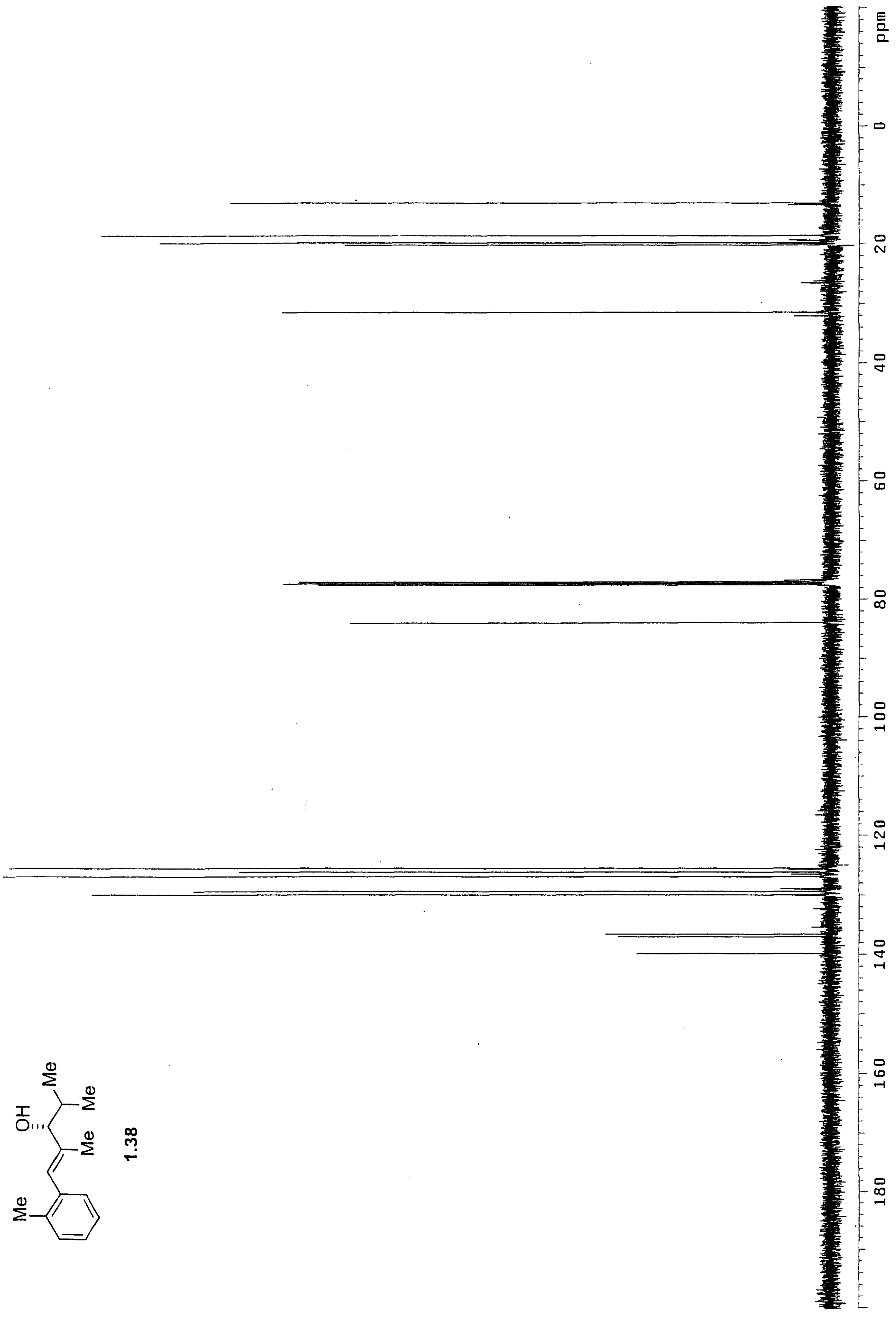

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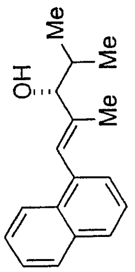

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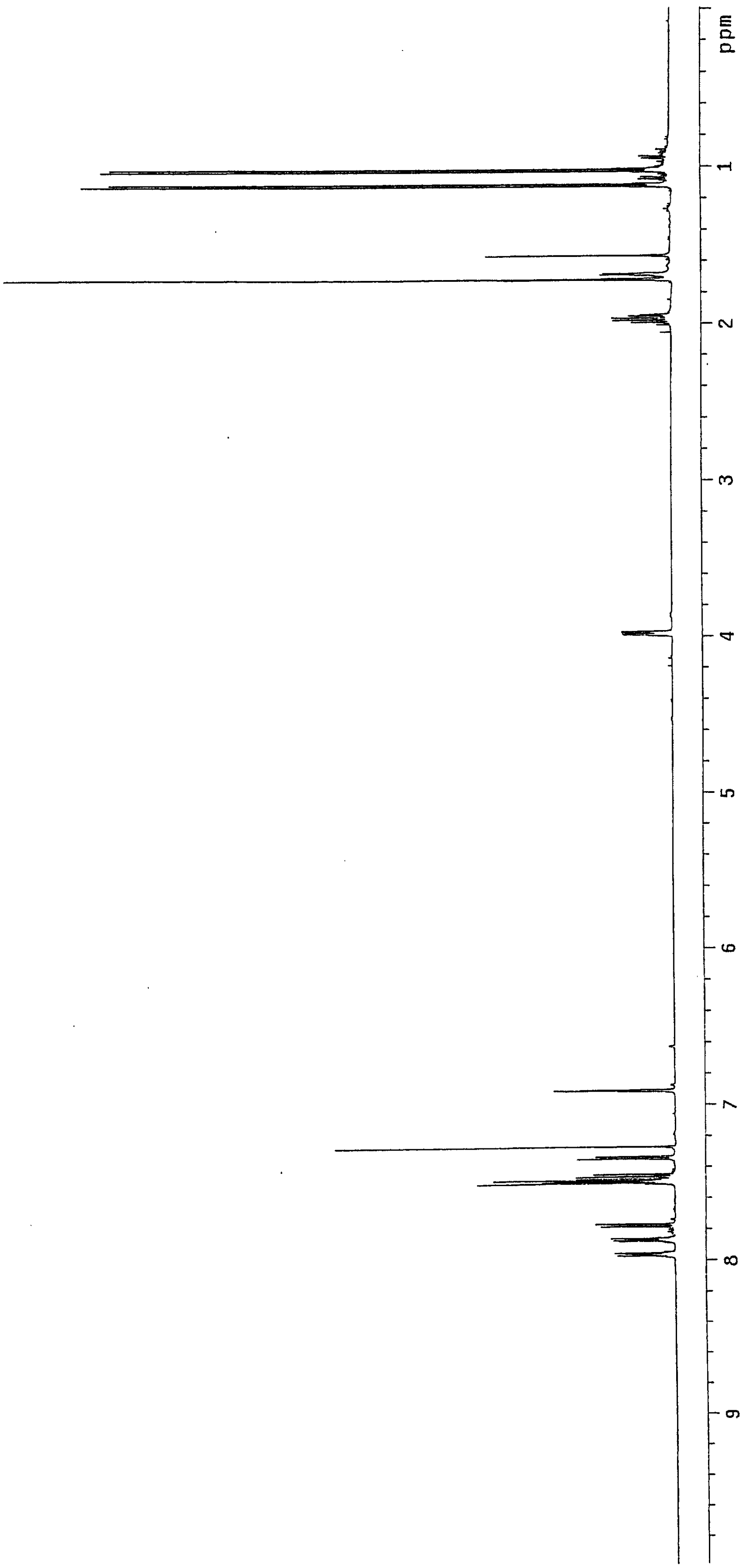

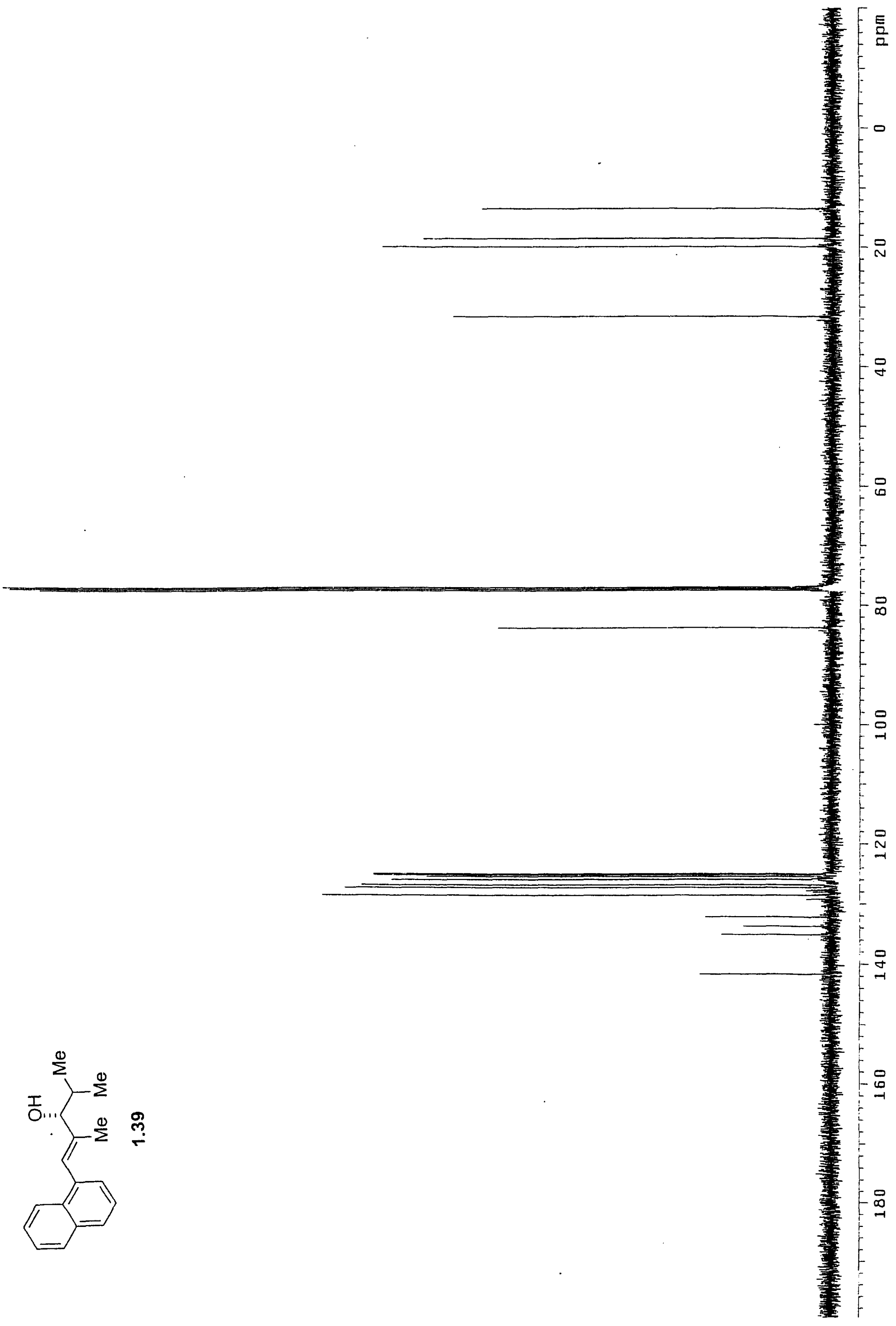

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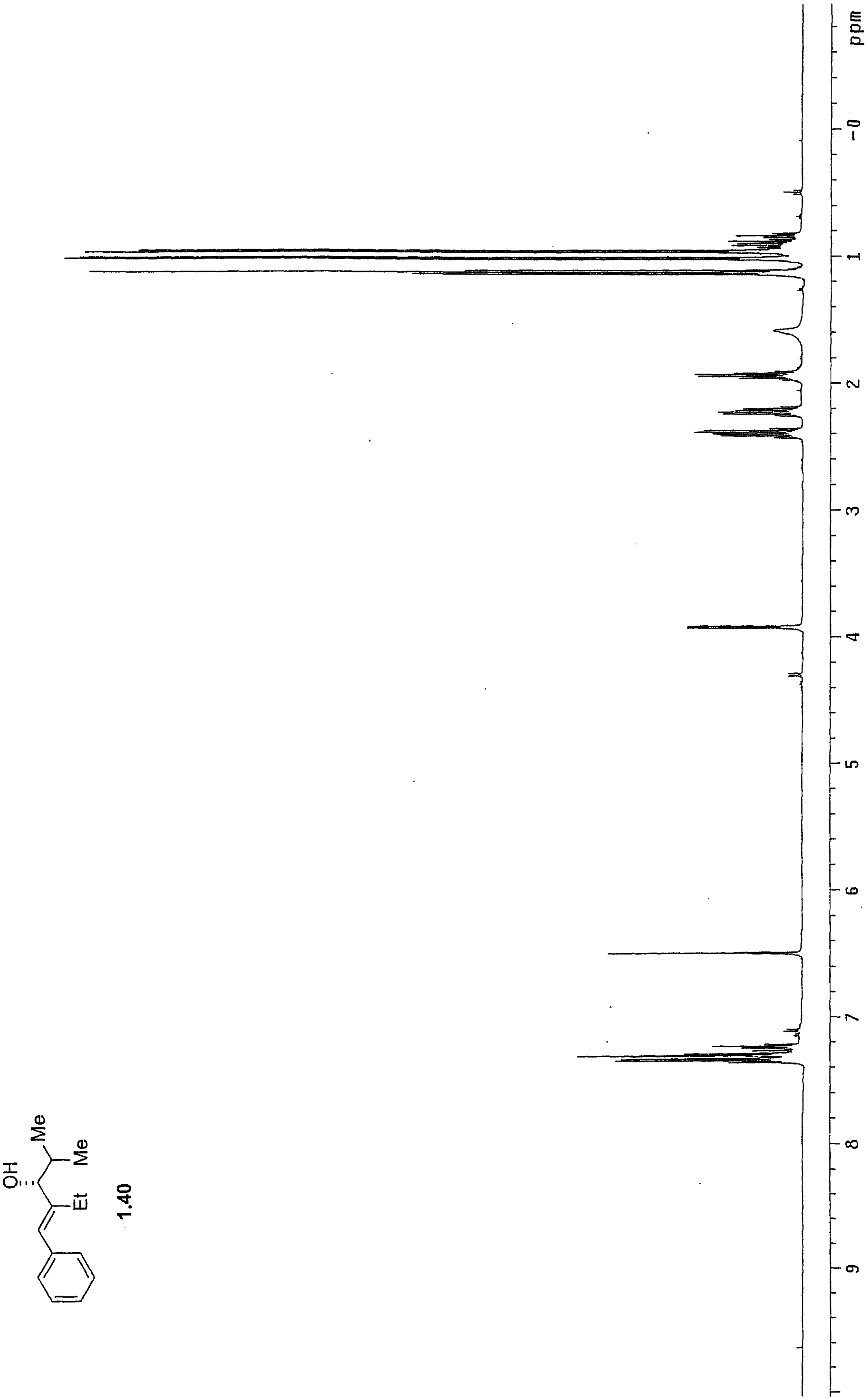

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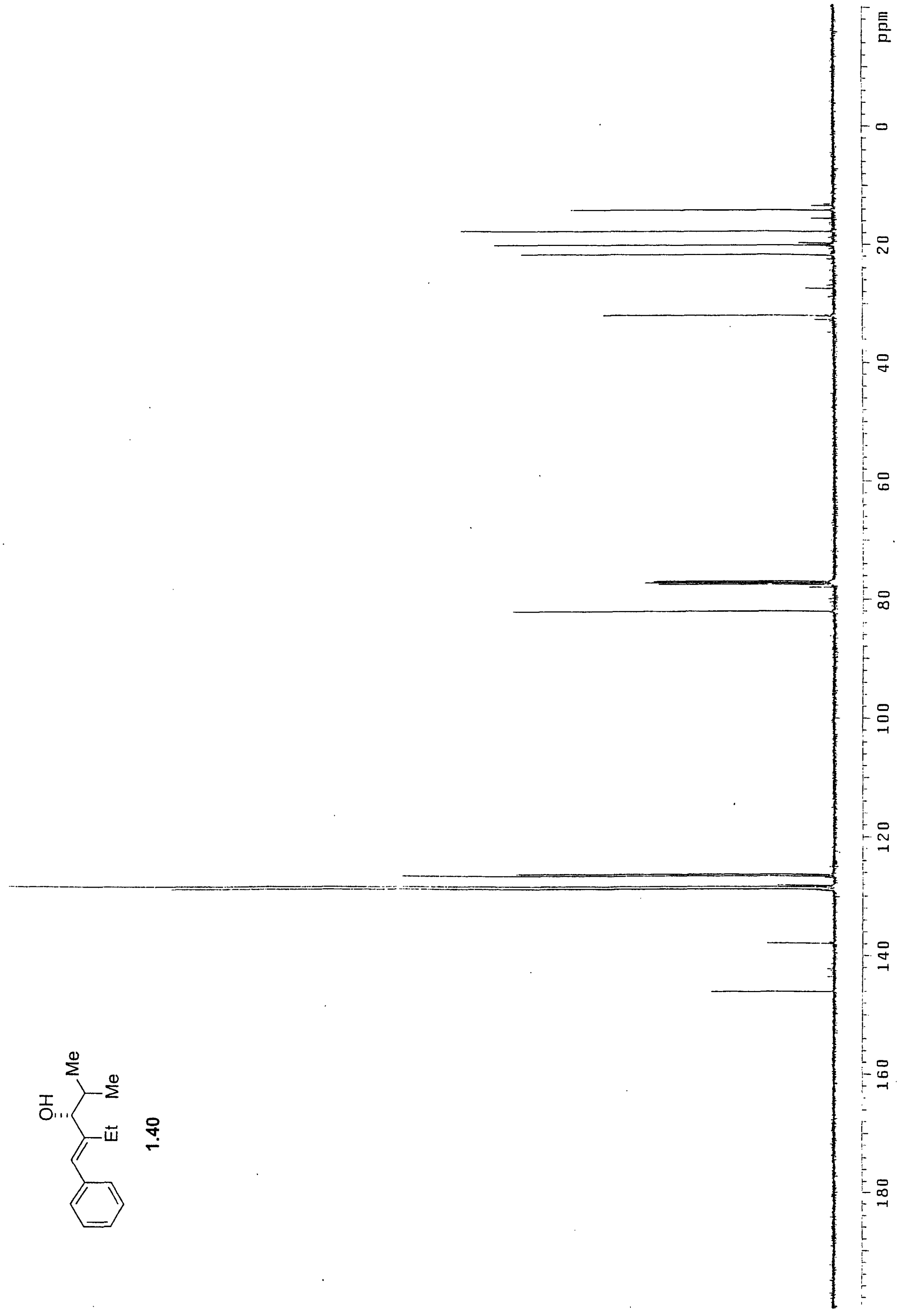

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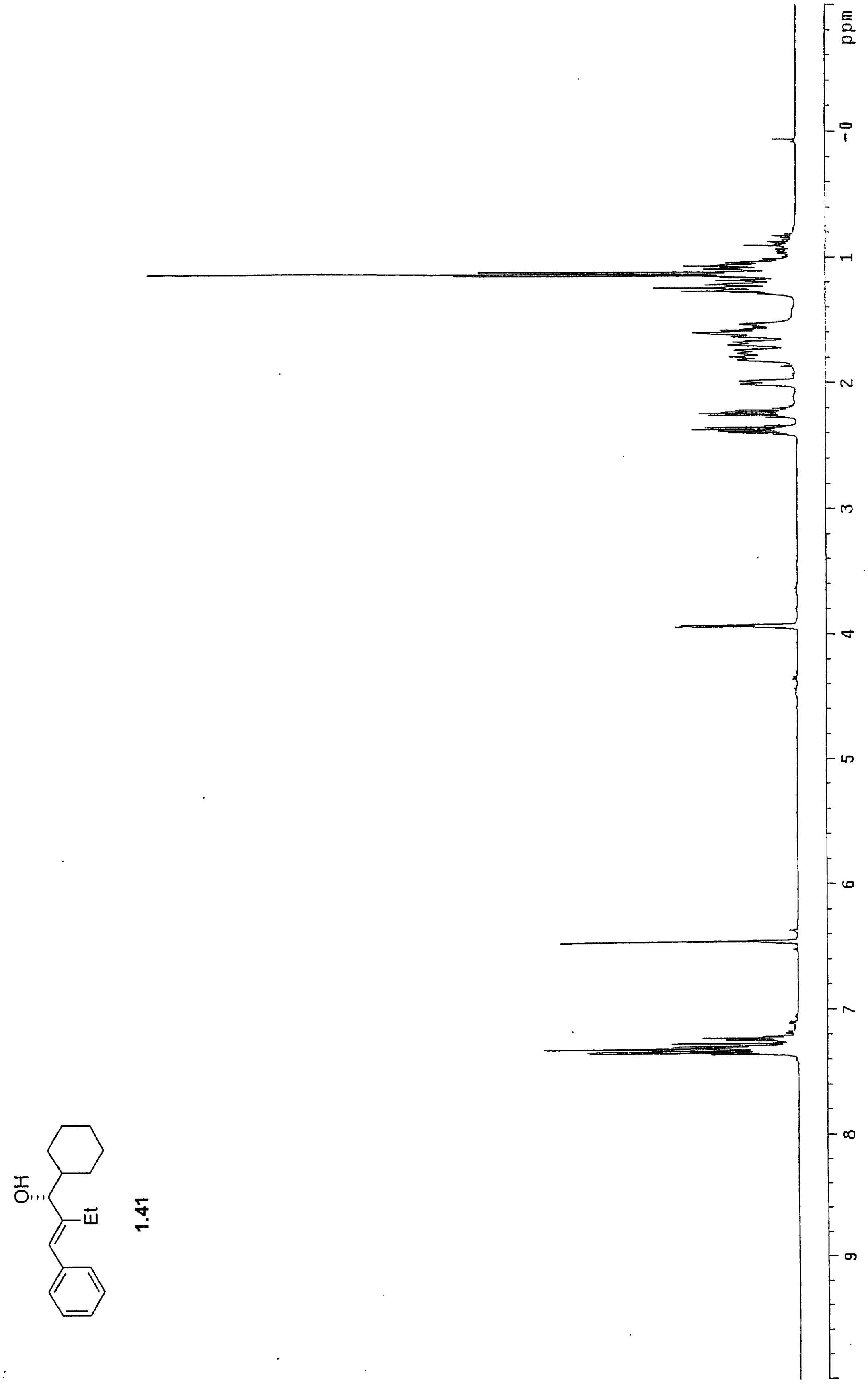

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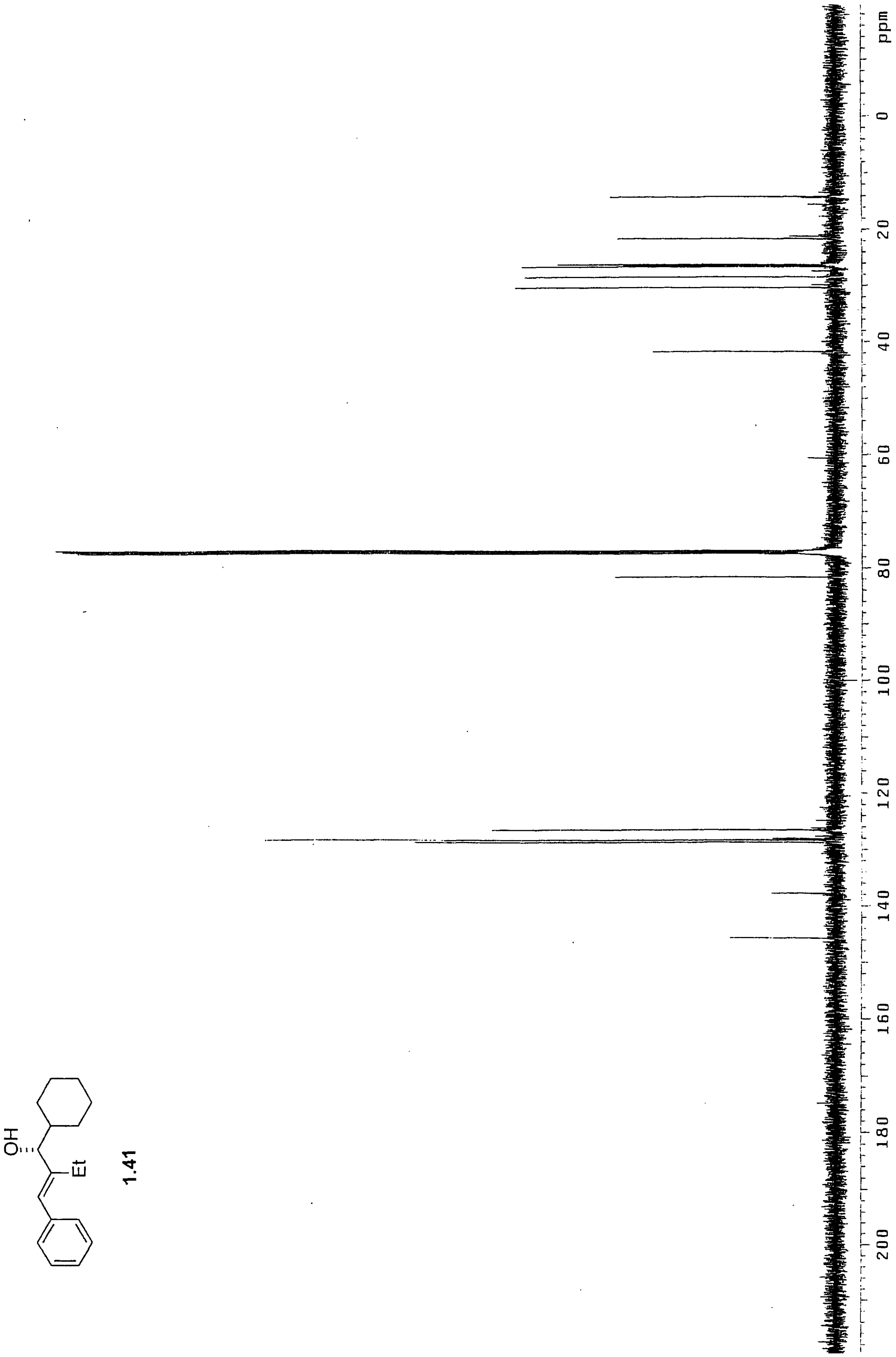

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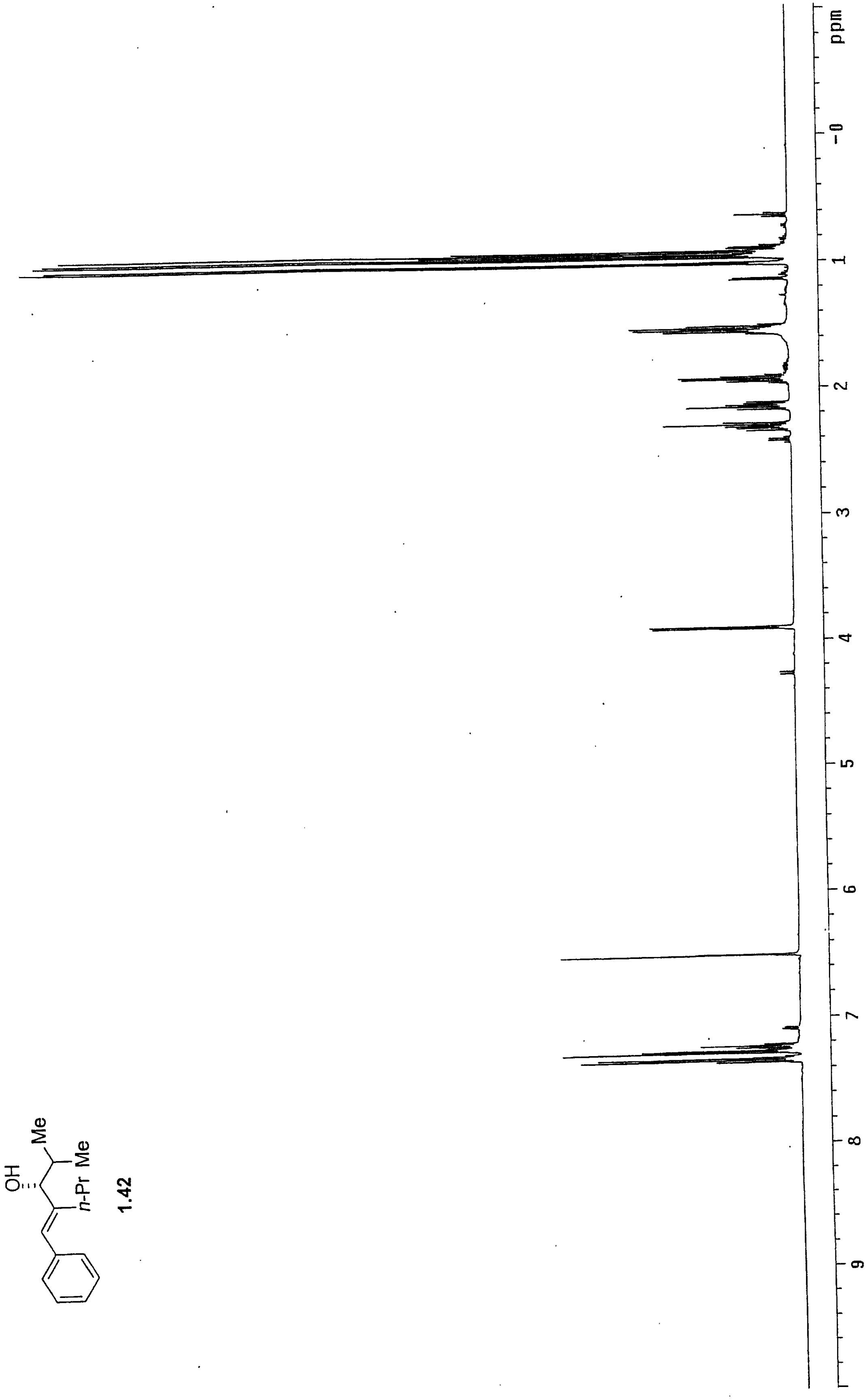

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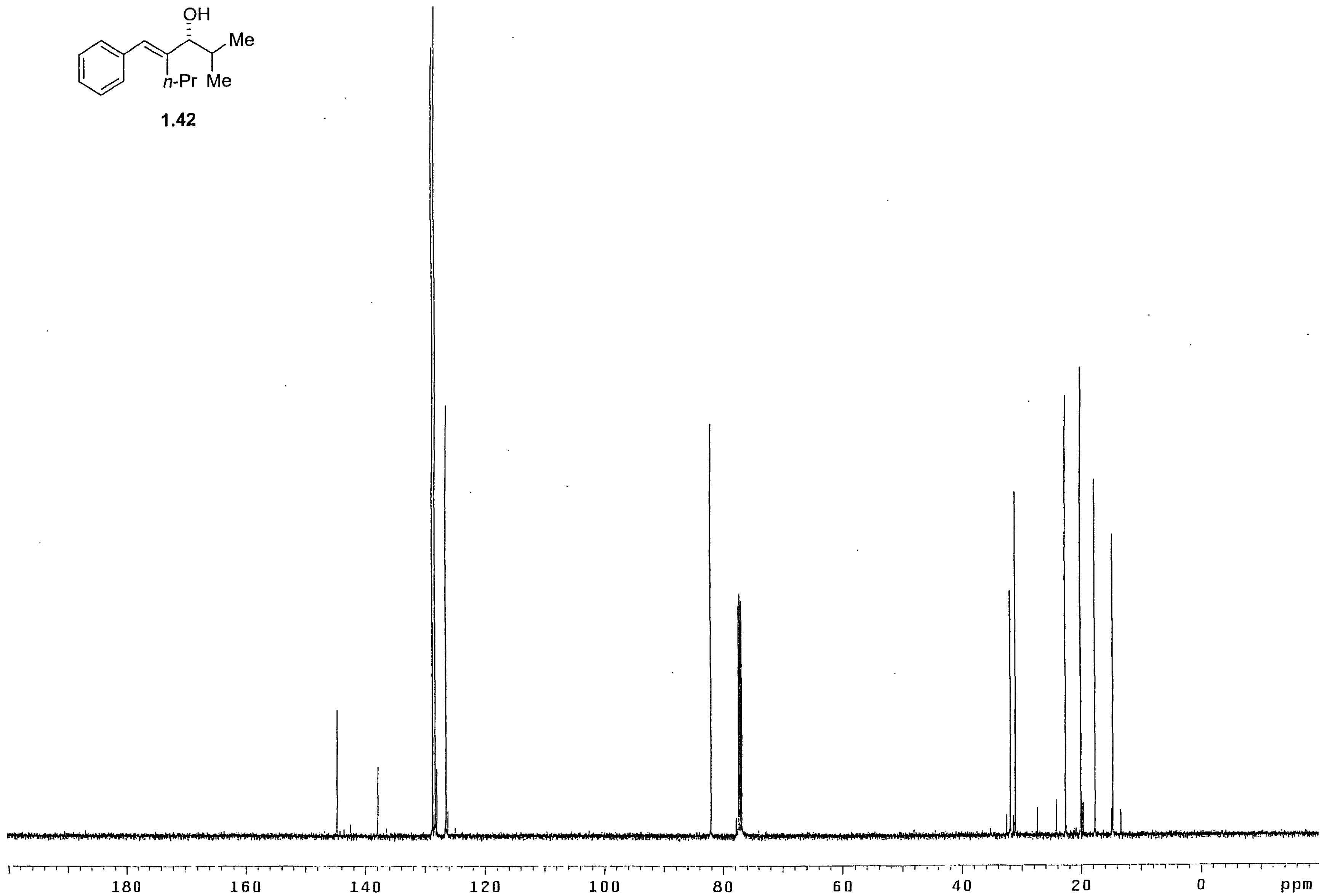

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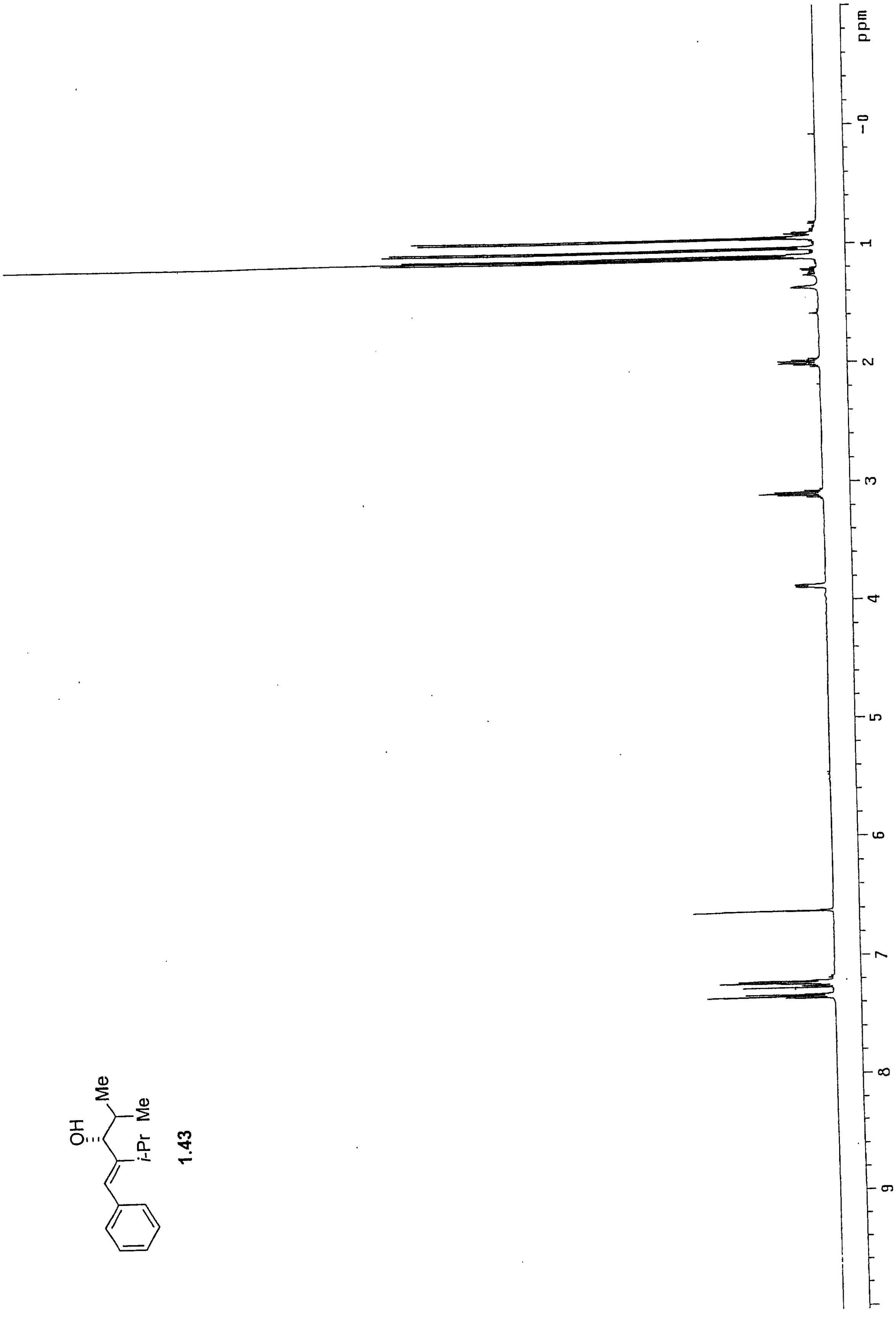

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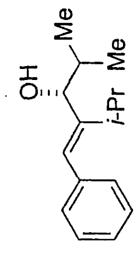

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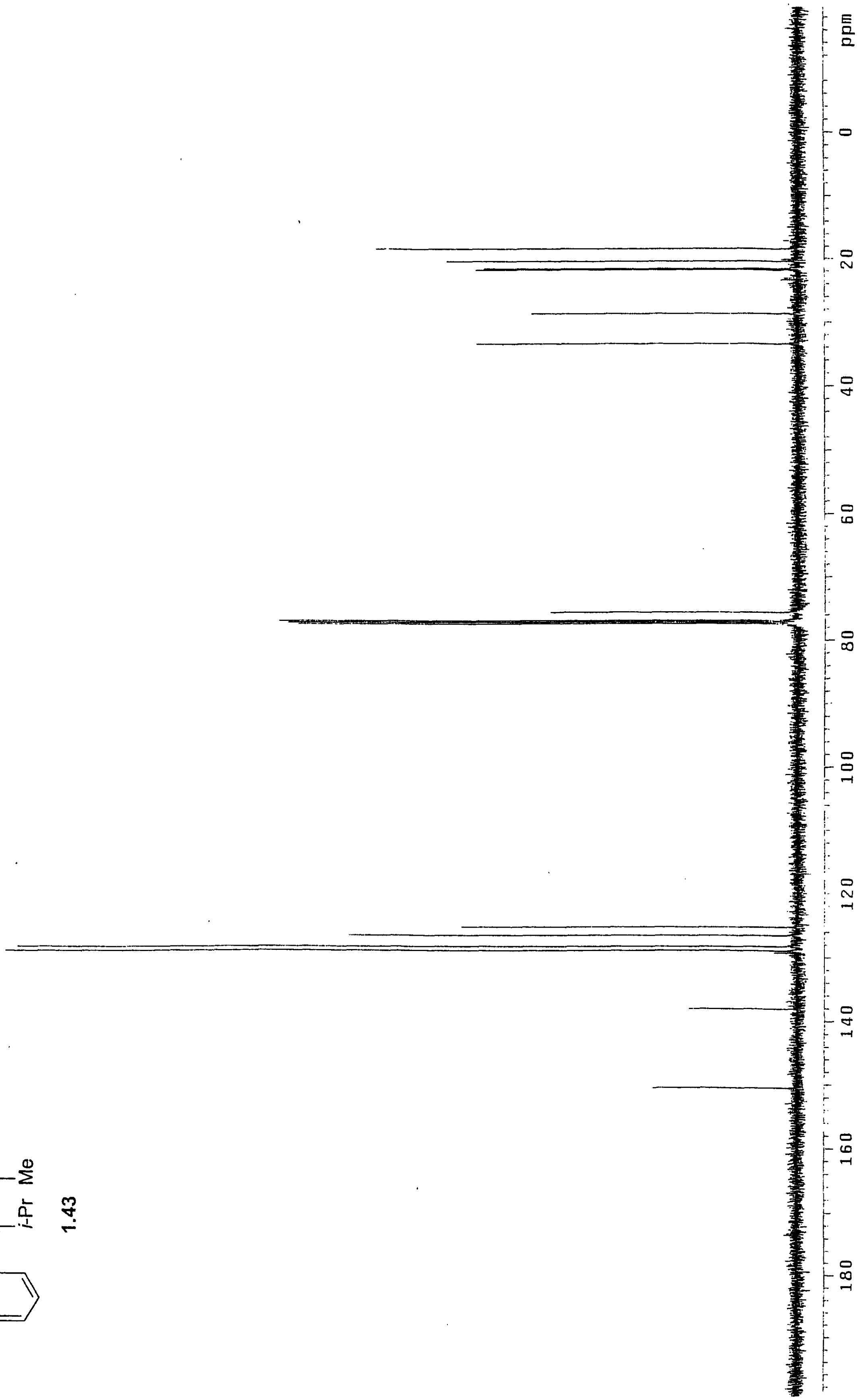

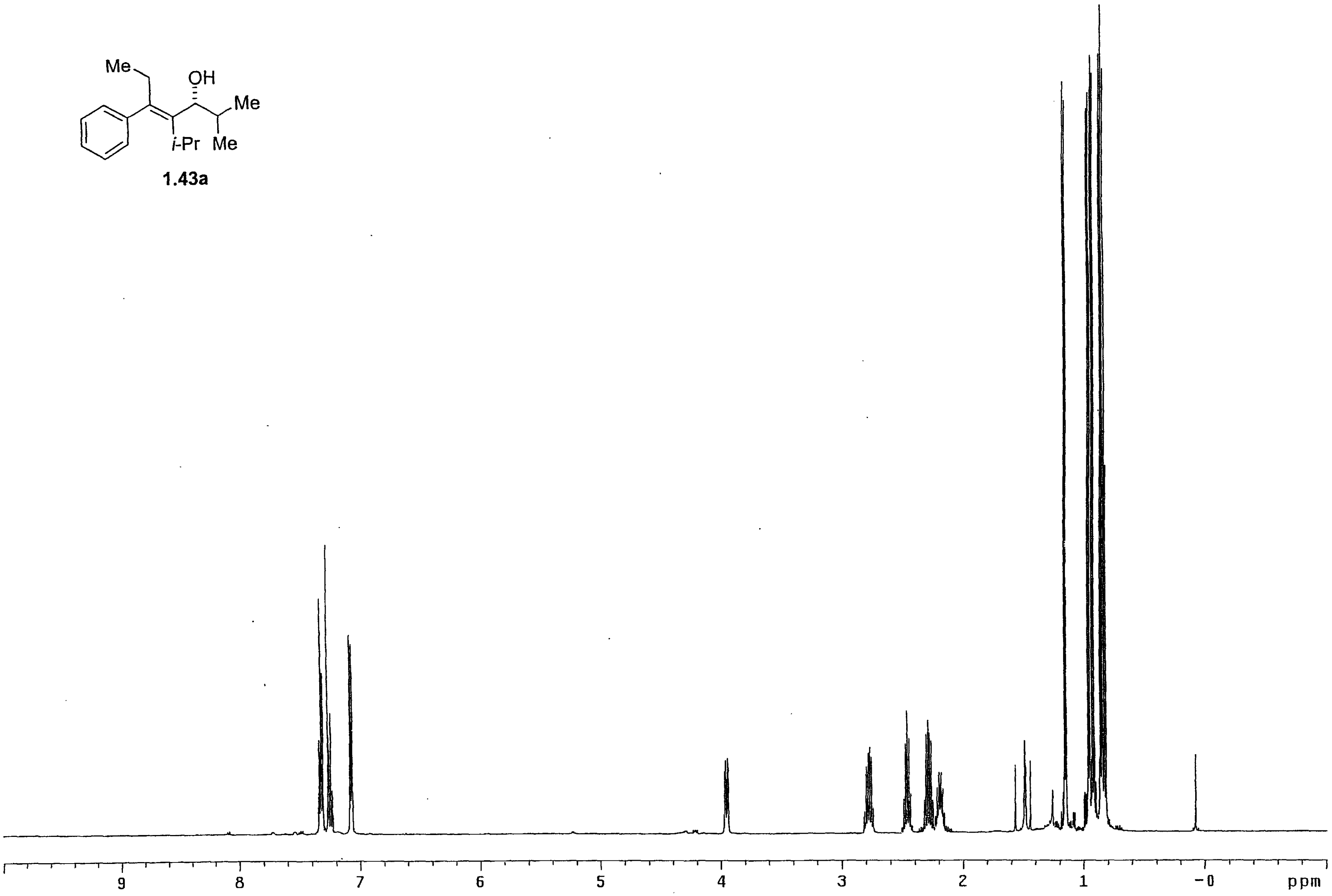Me
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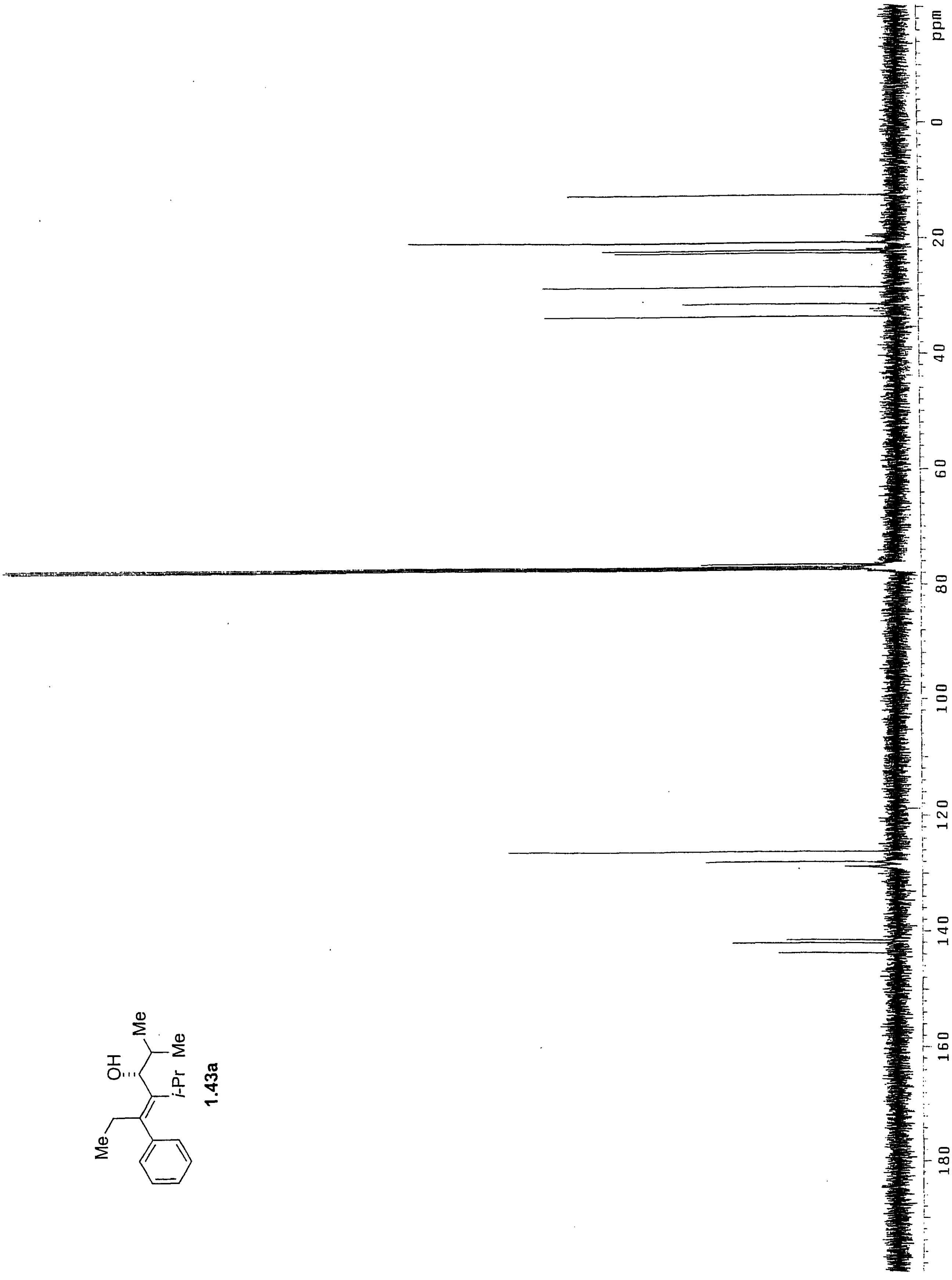

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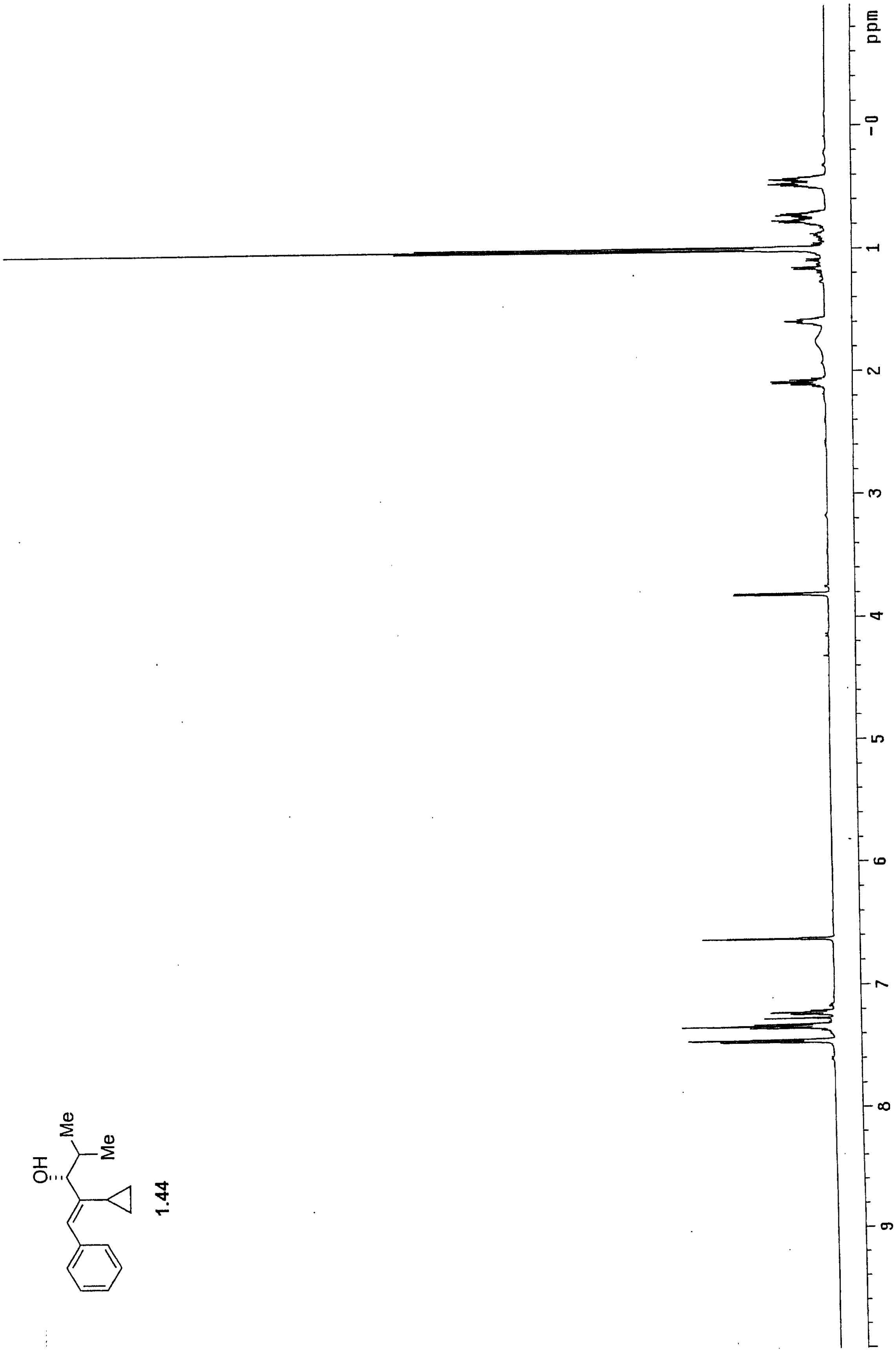

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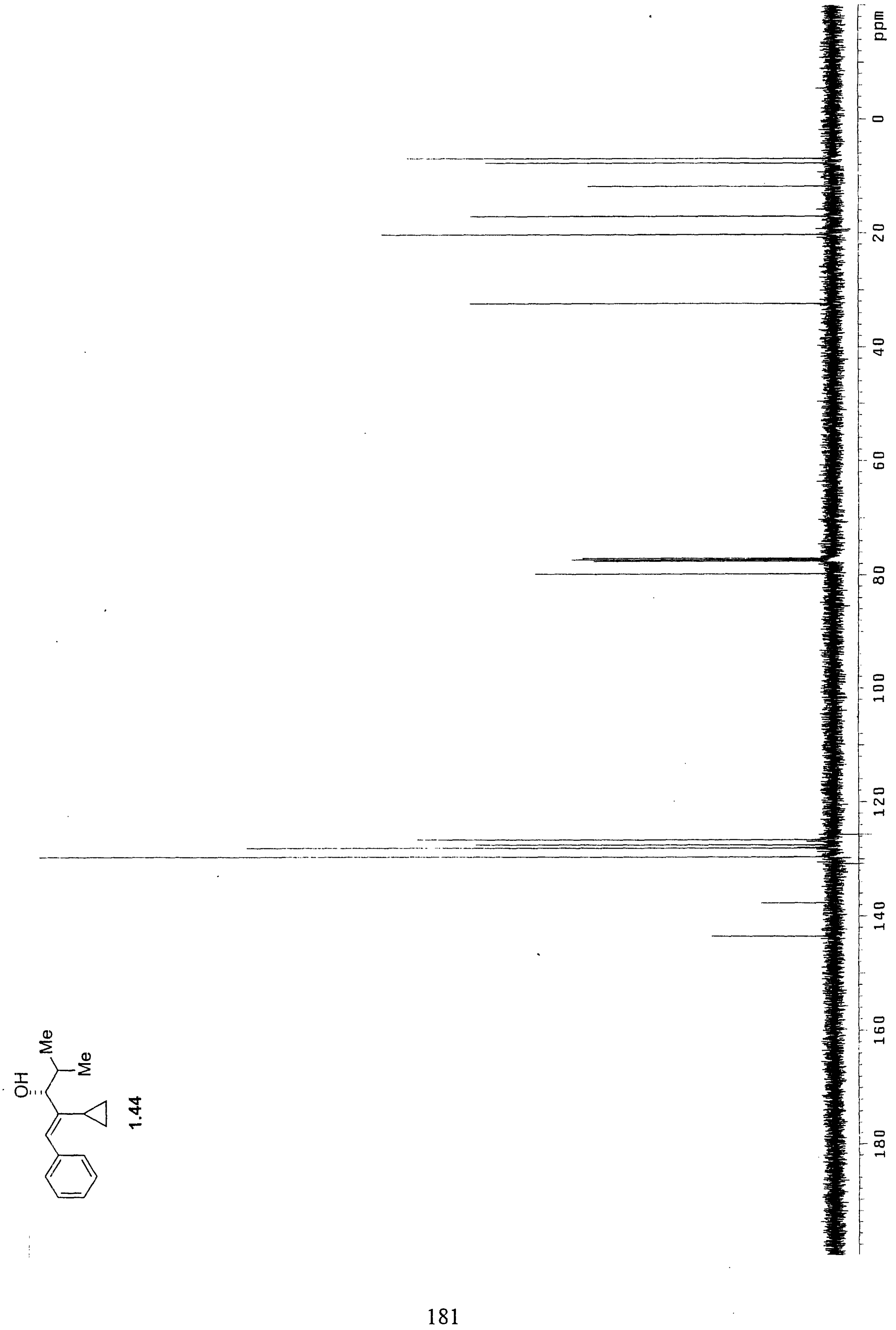

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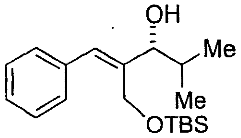

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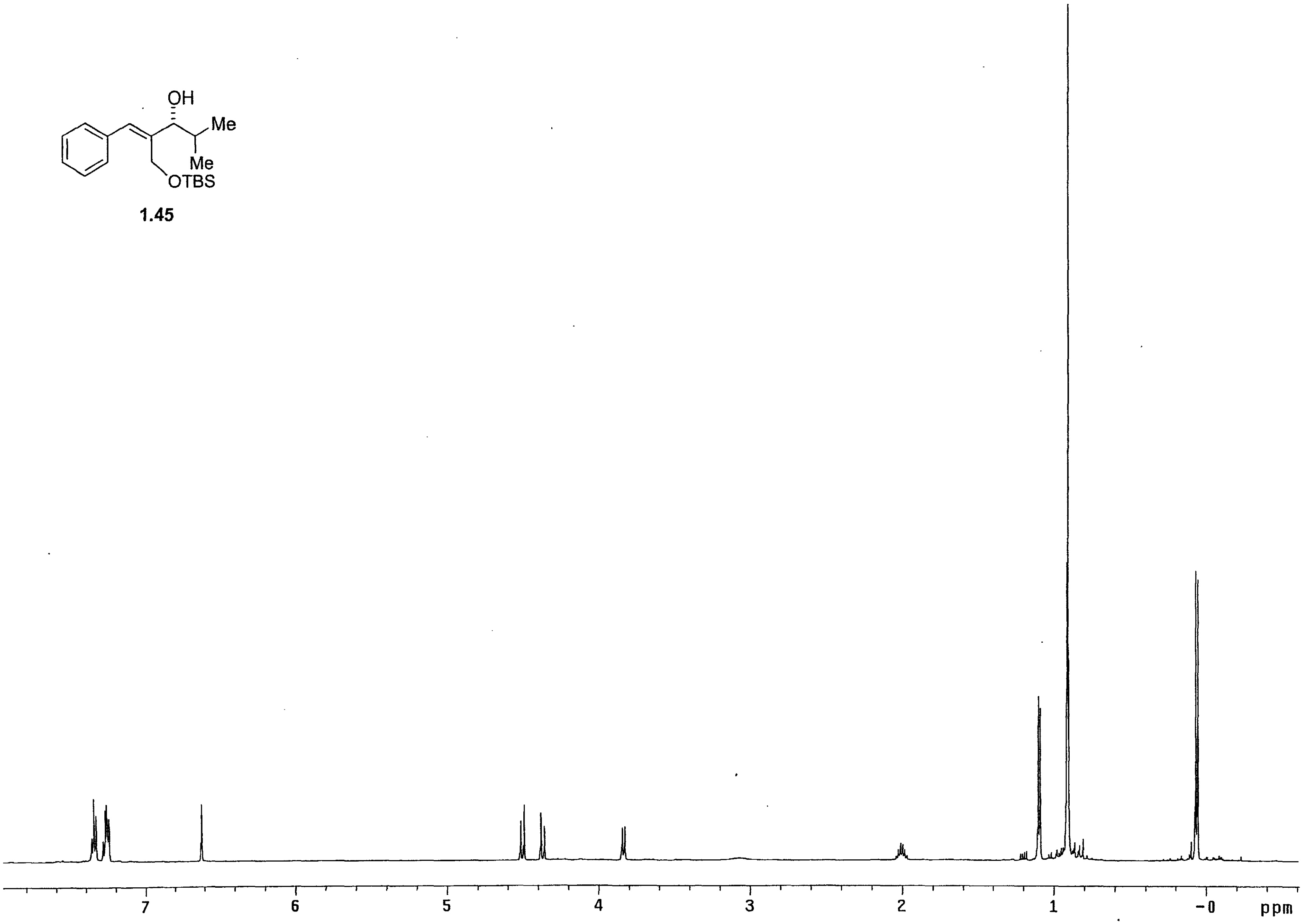

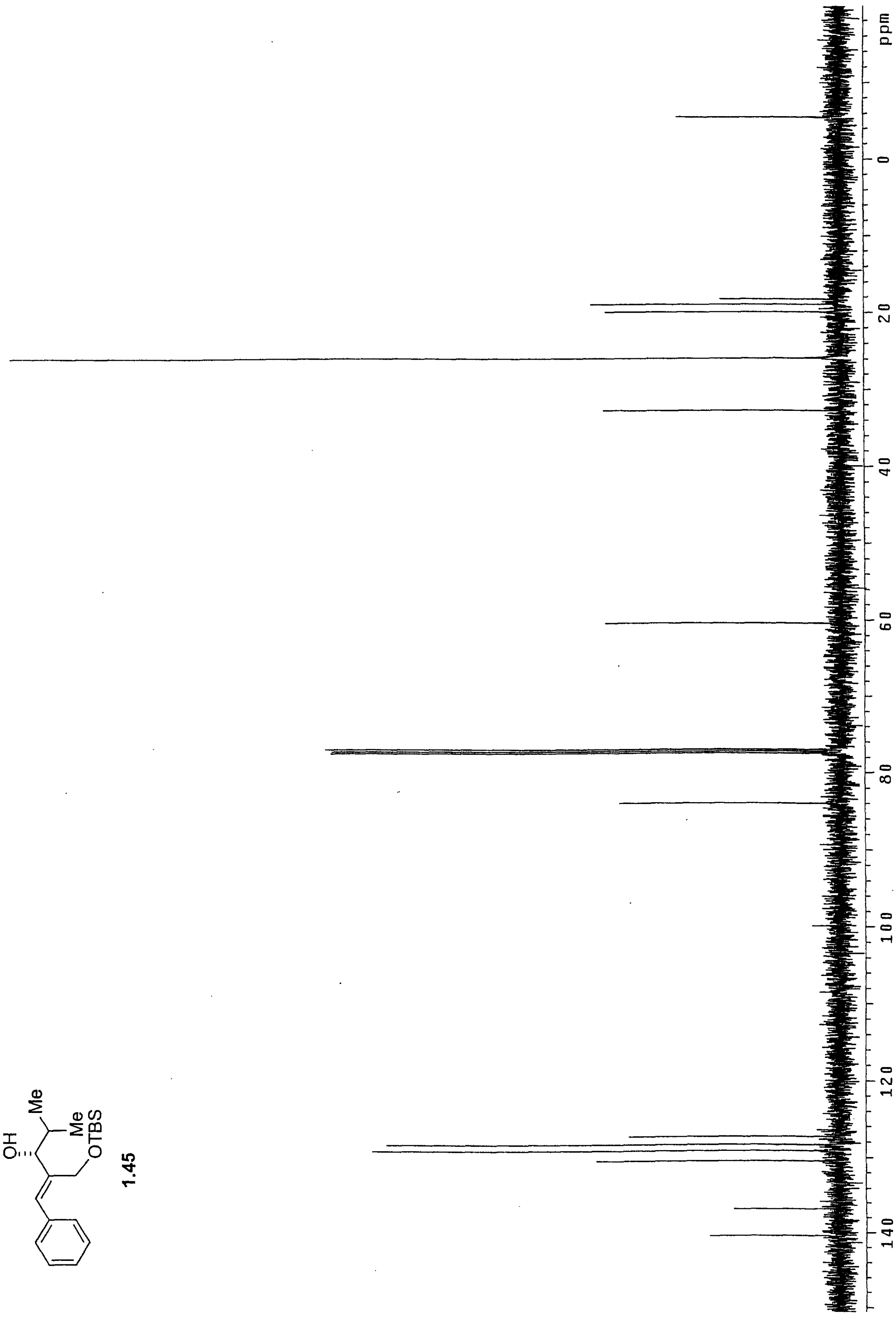
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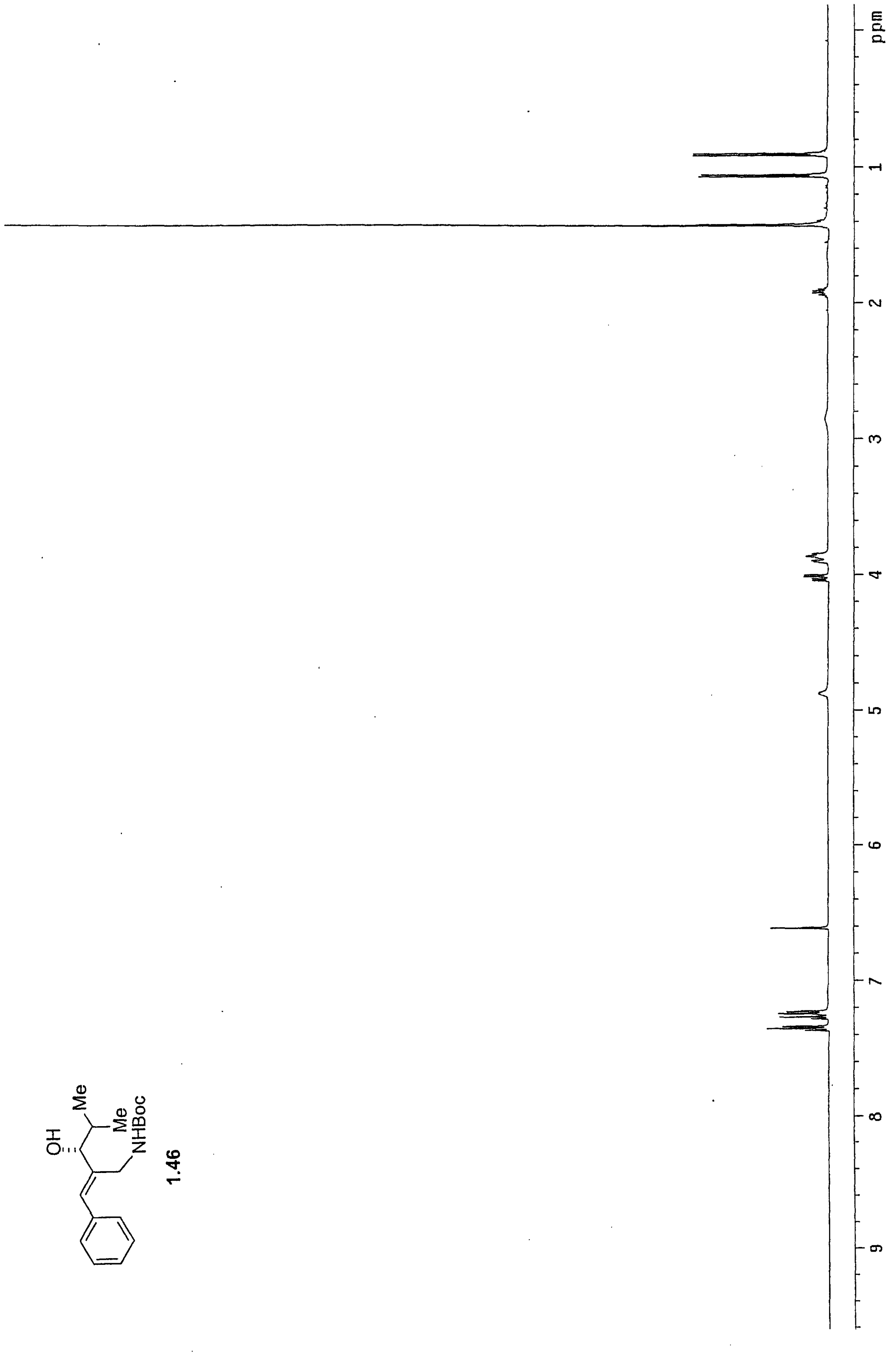

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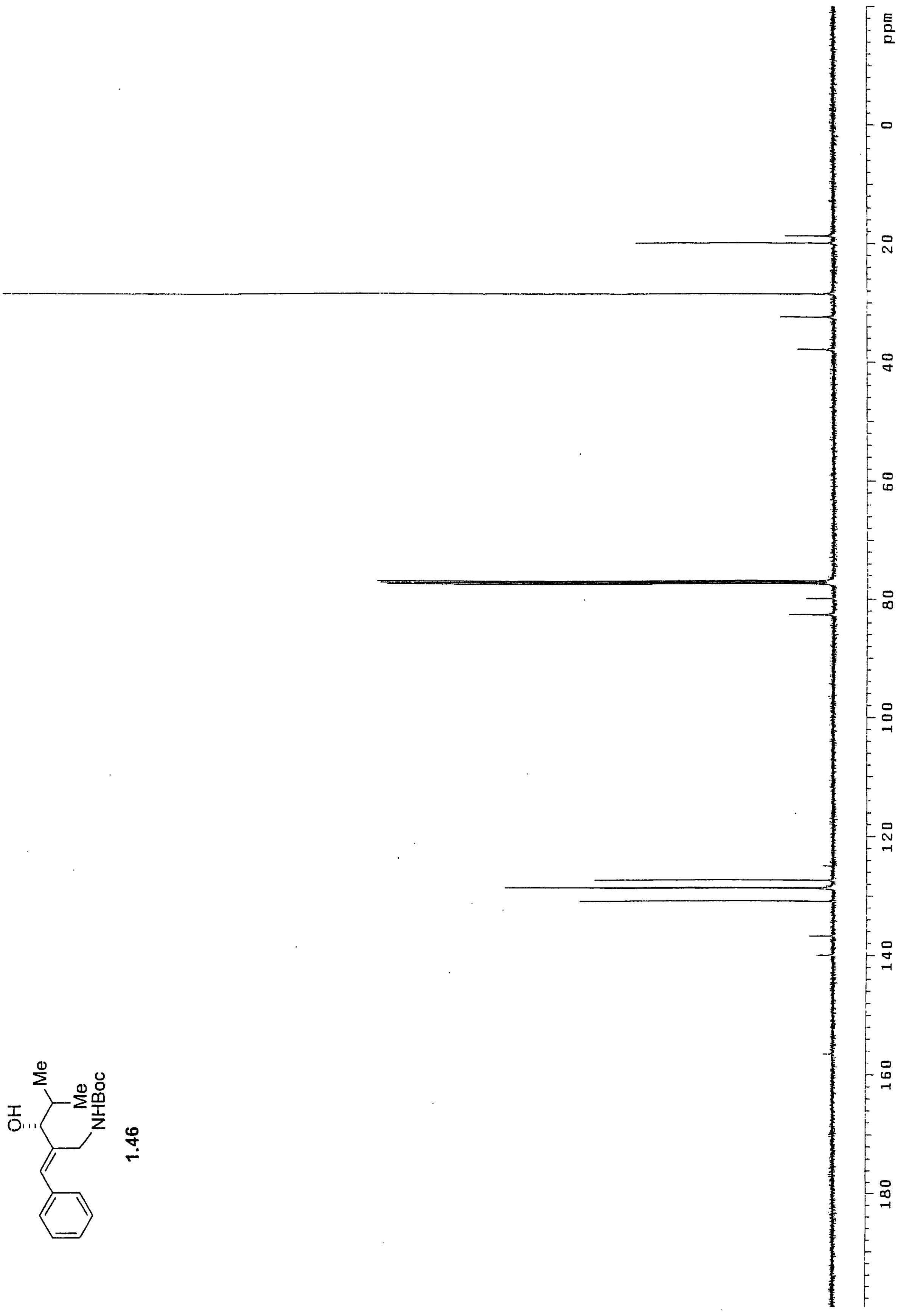

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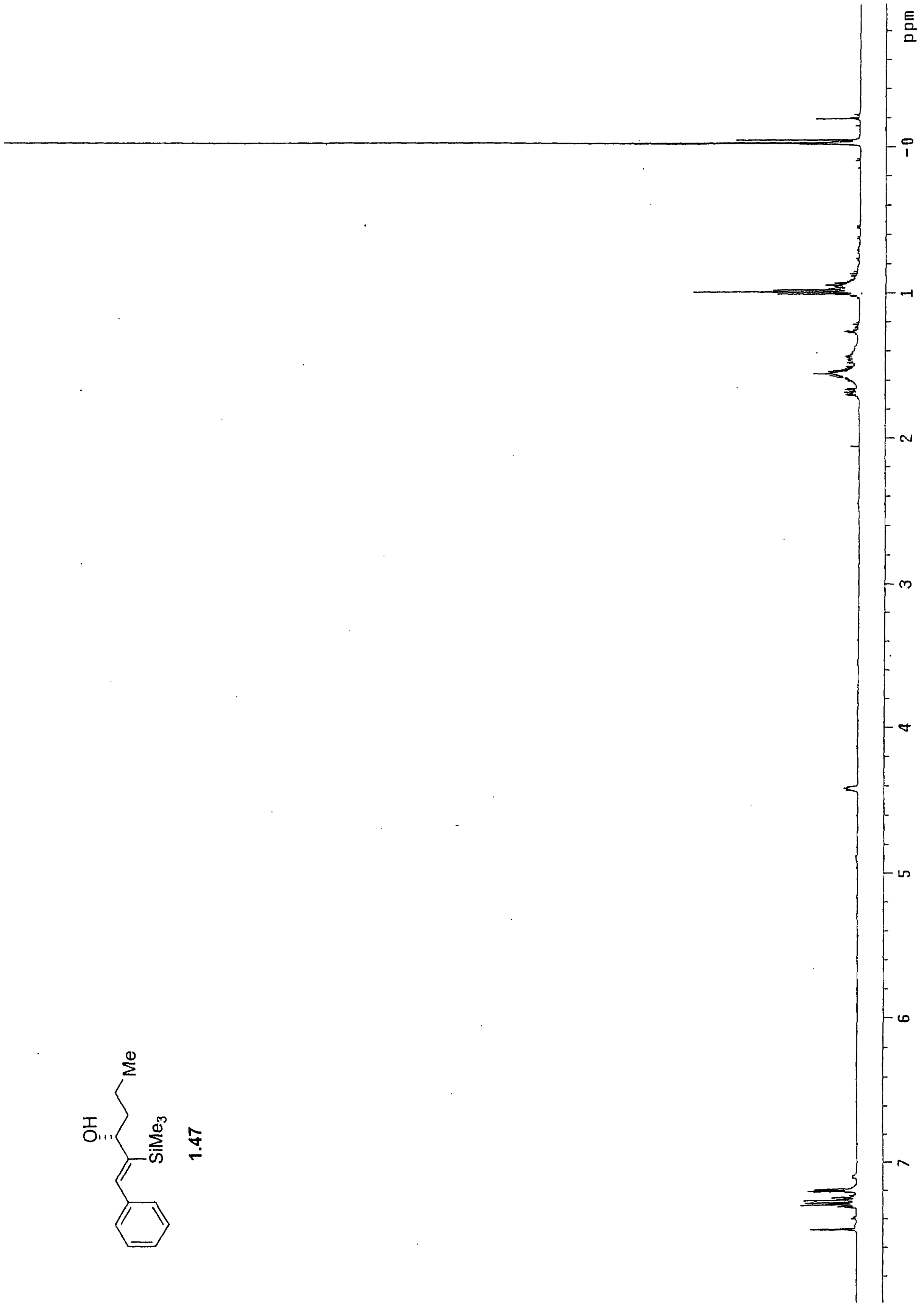

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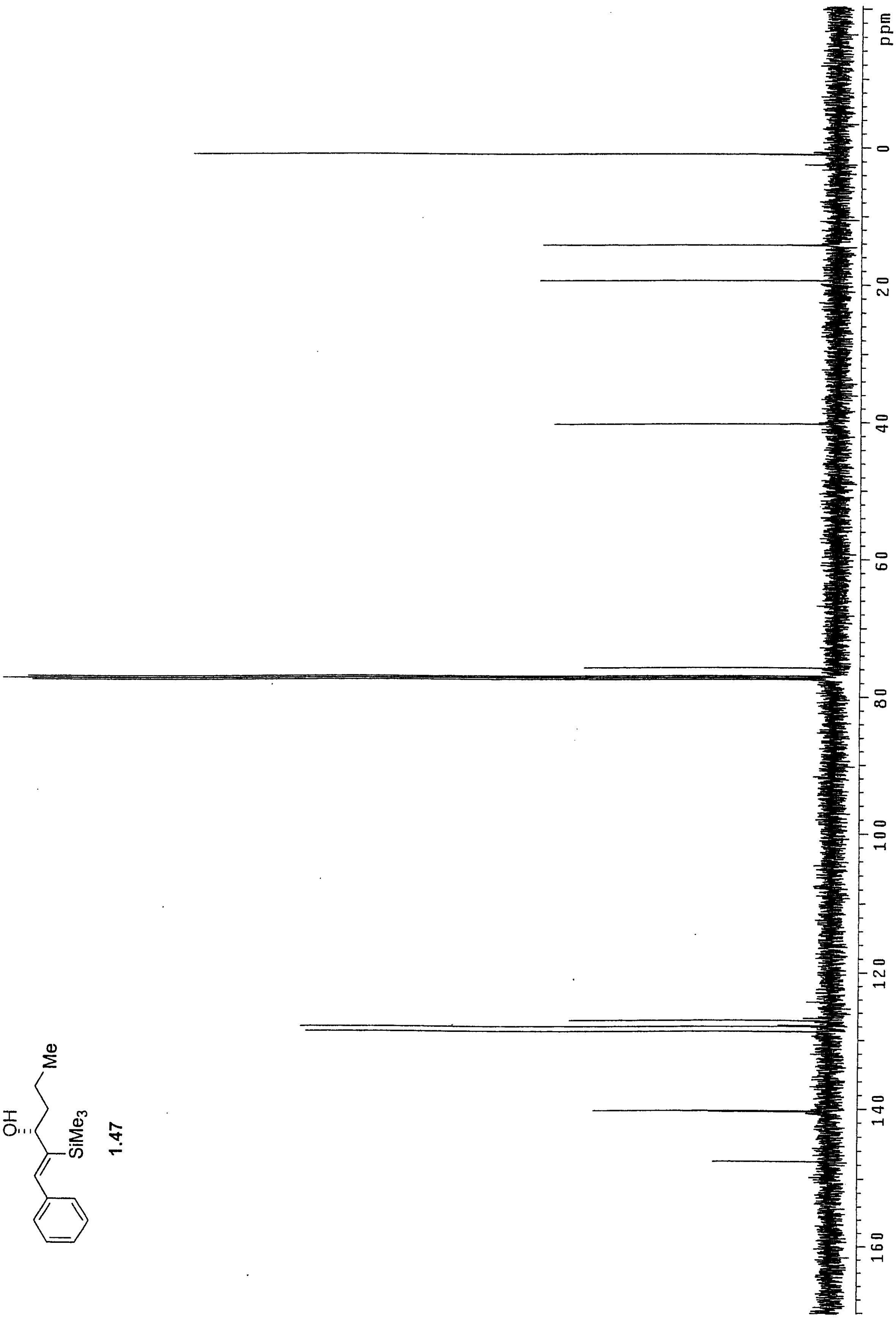

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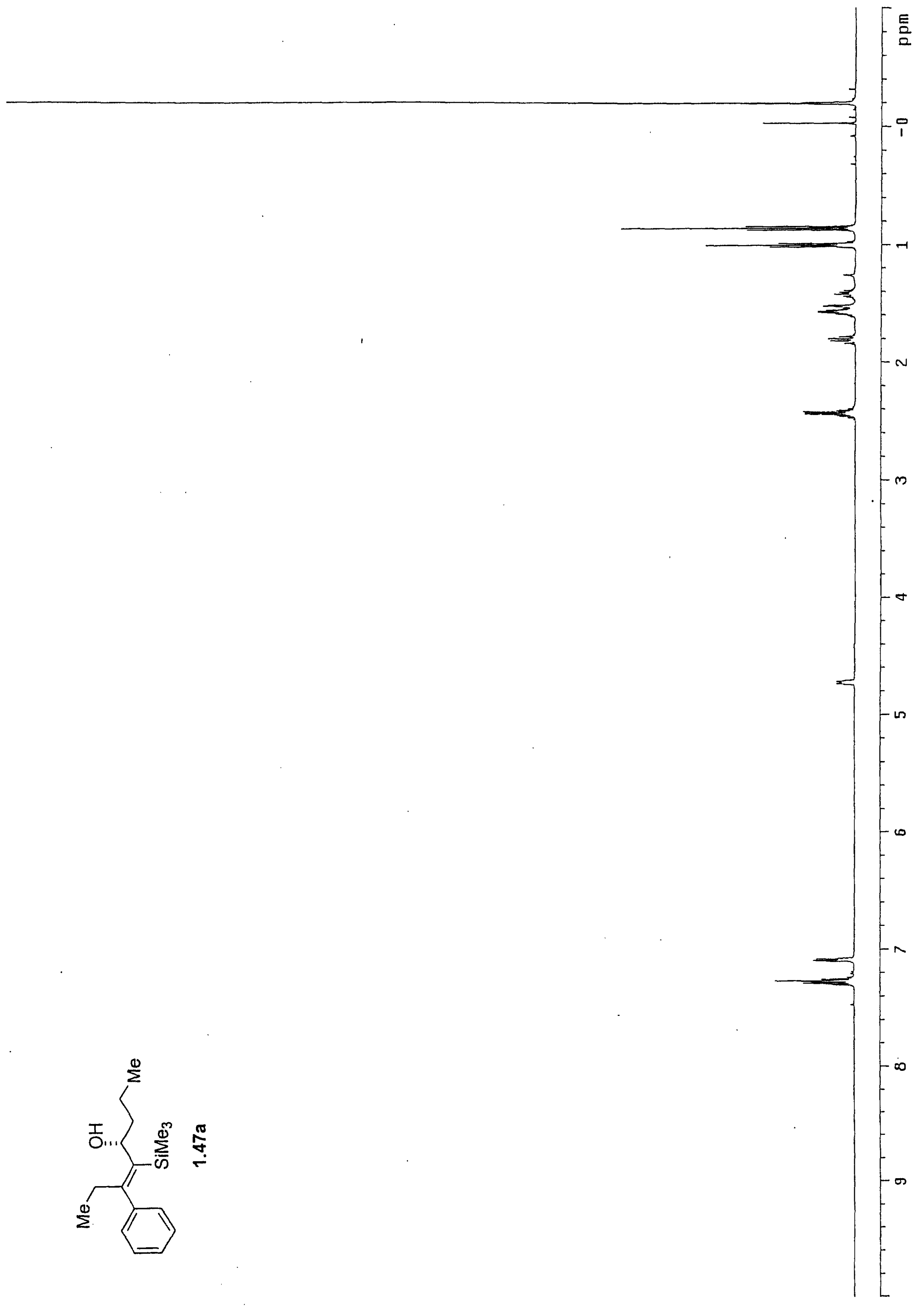

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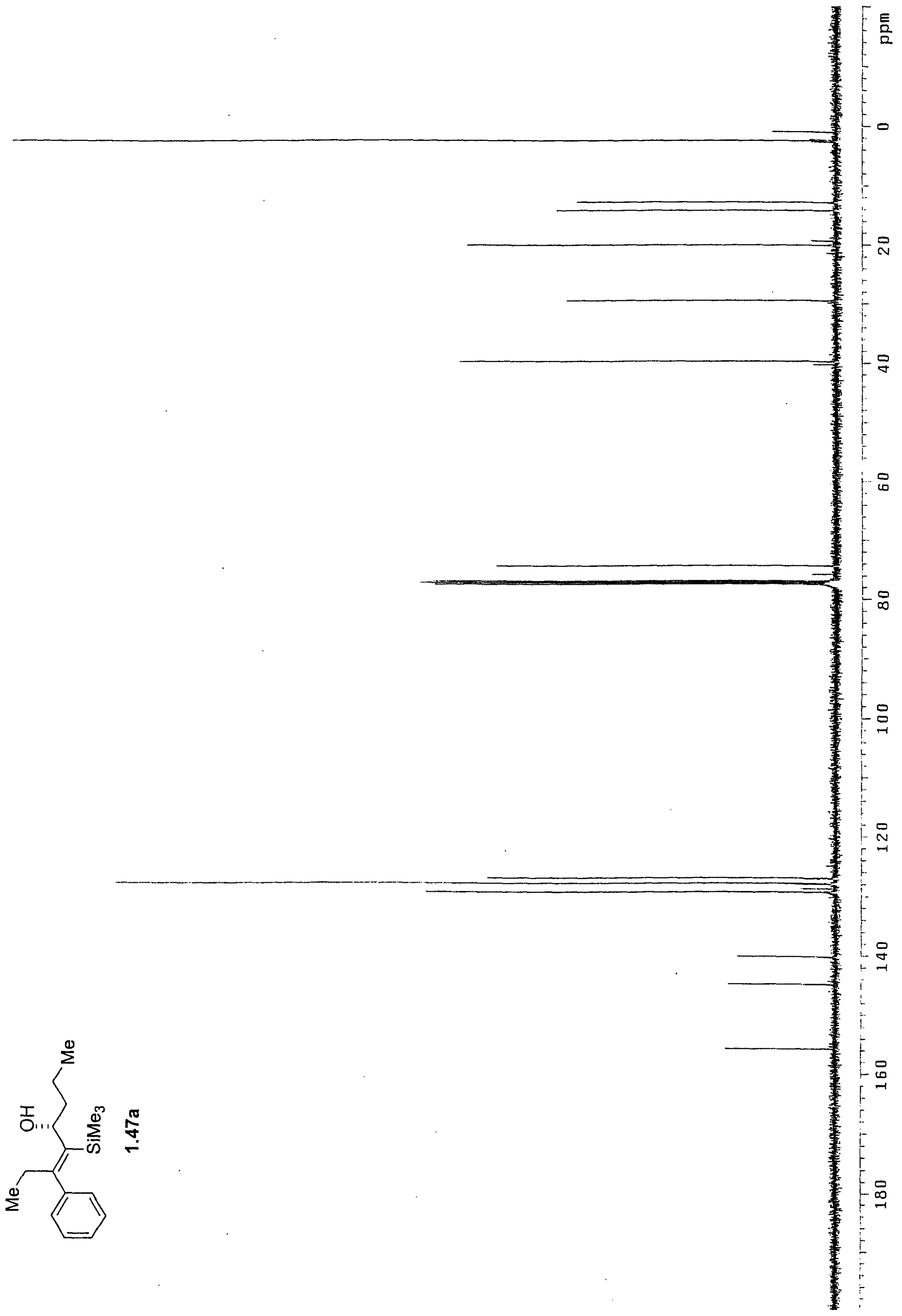

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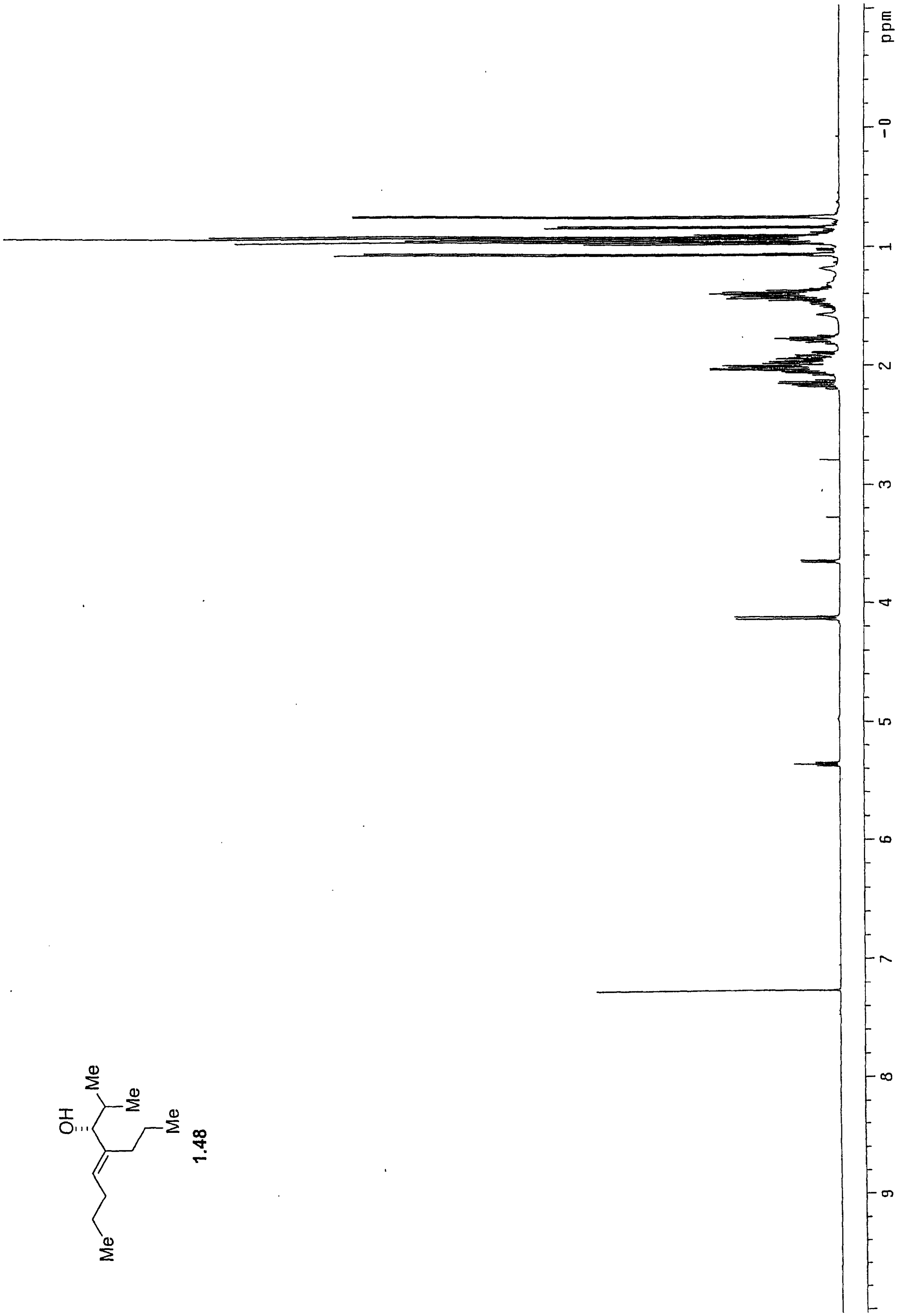

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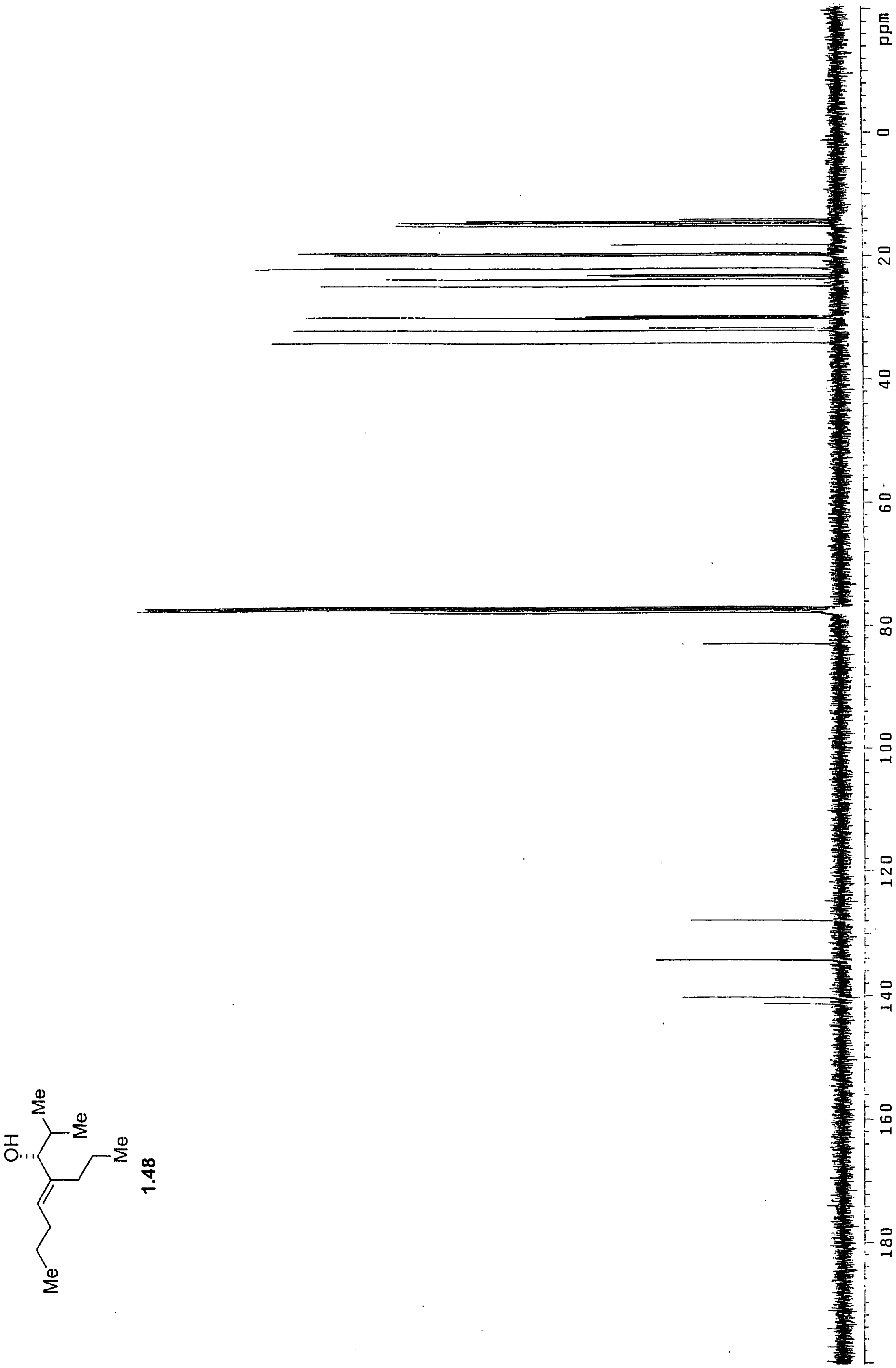

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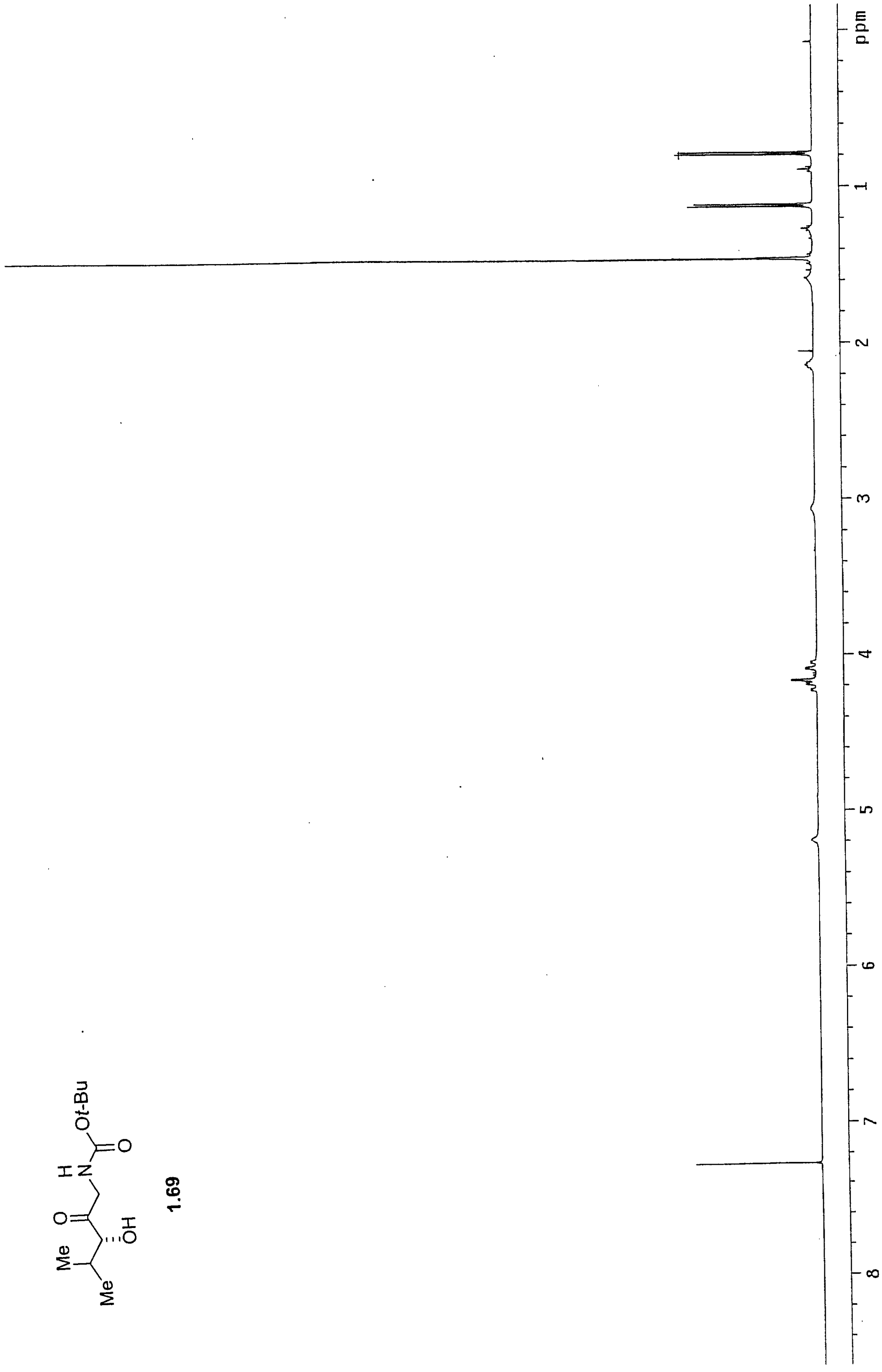

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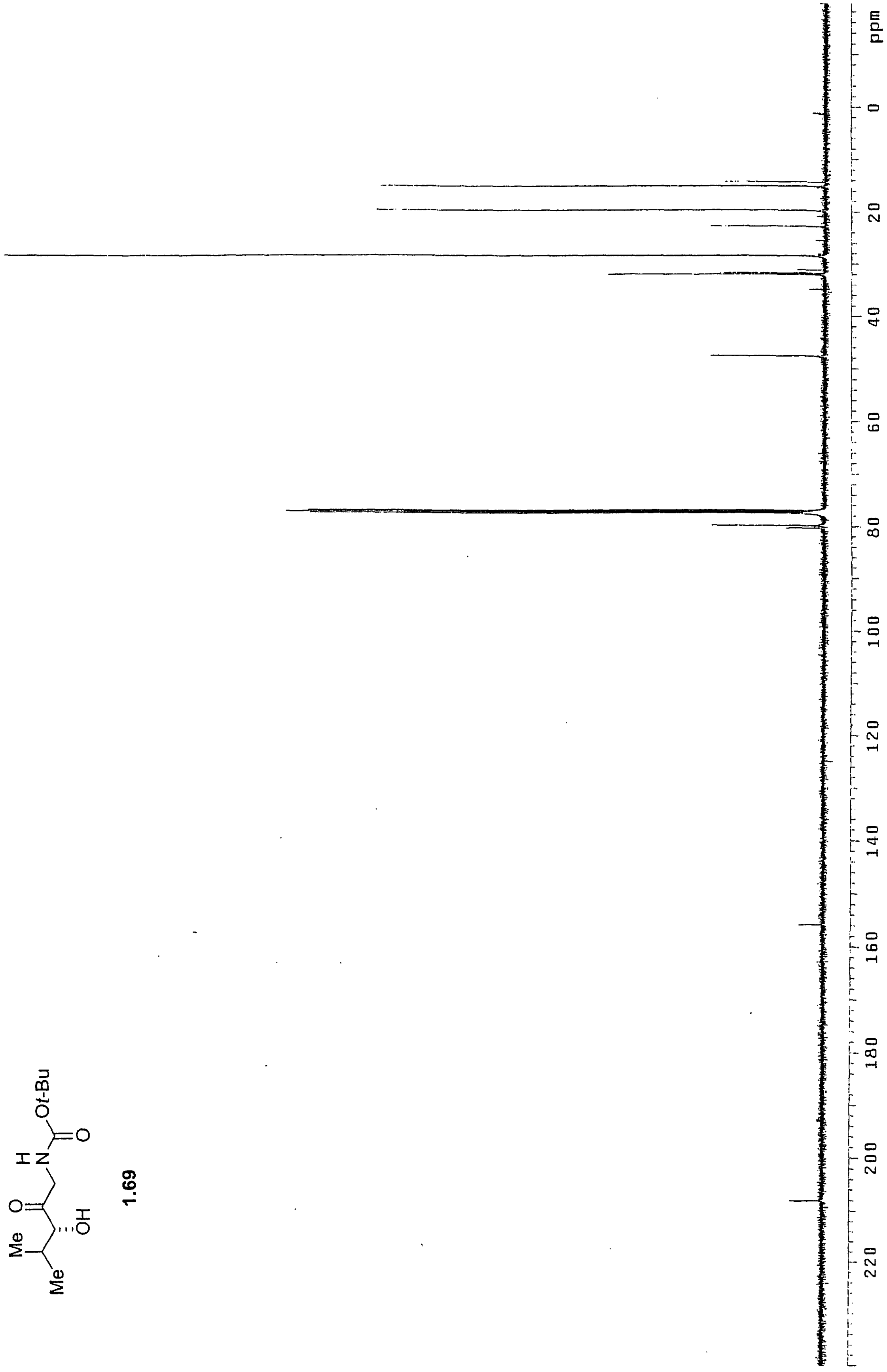

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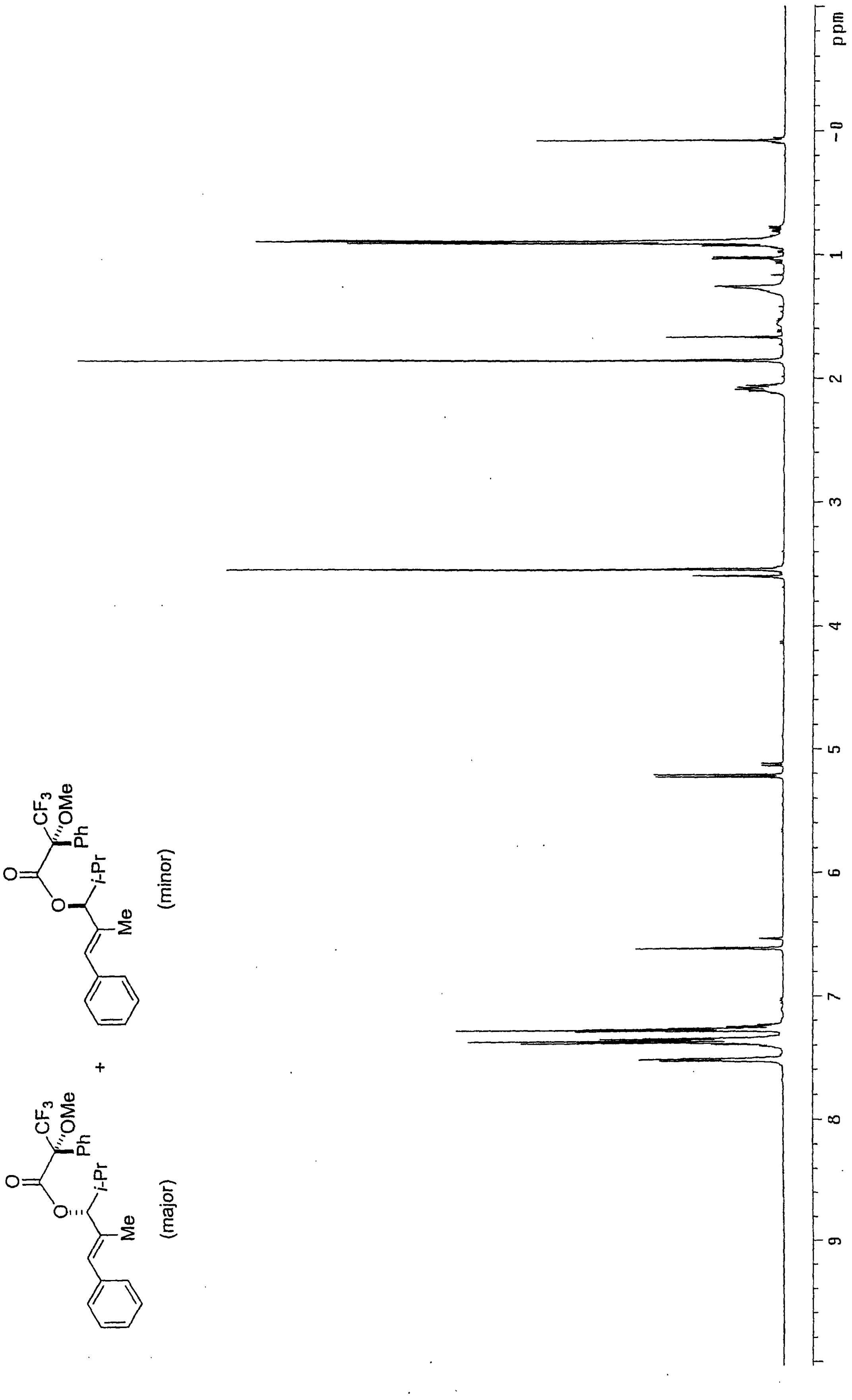
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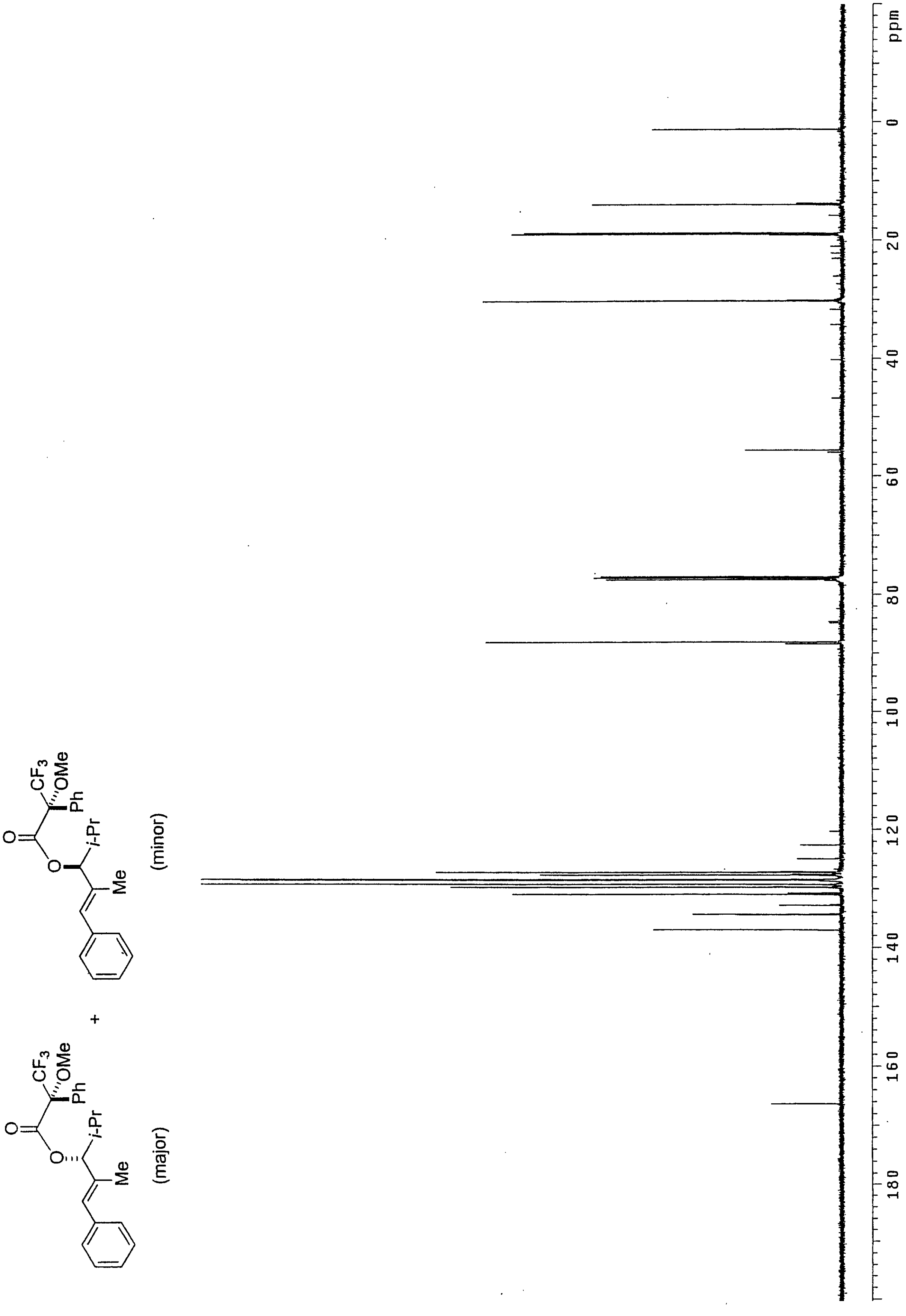
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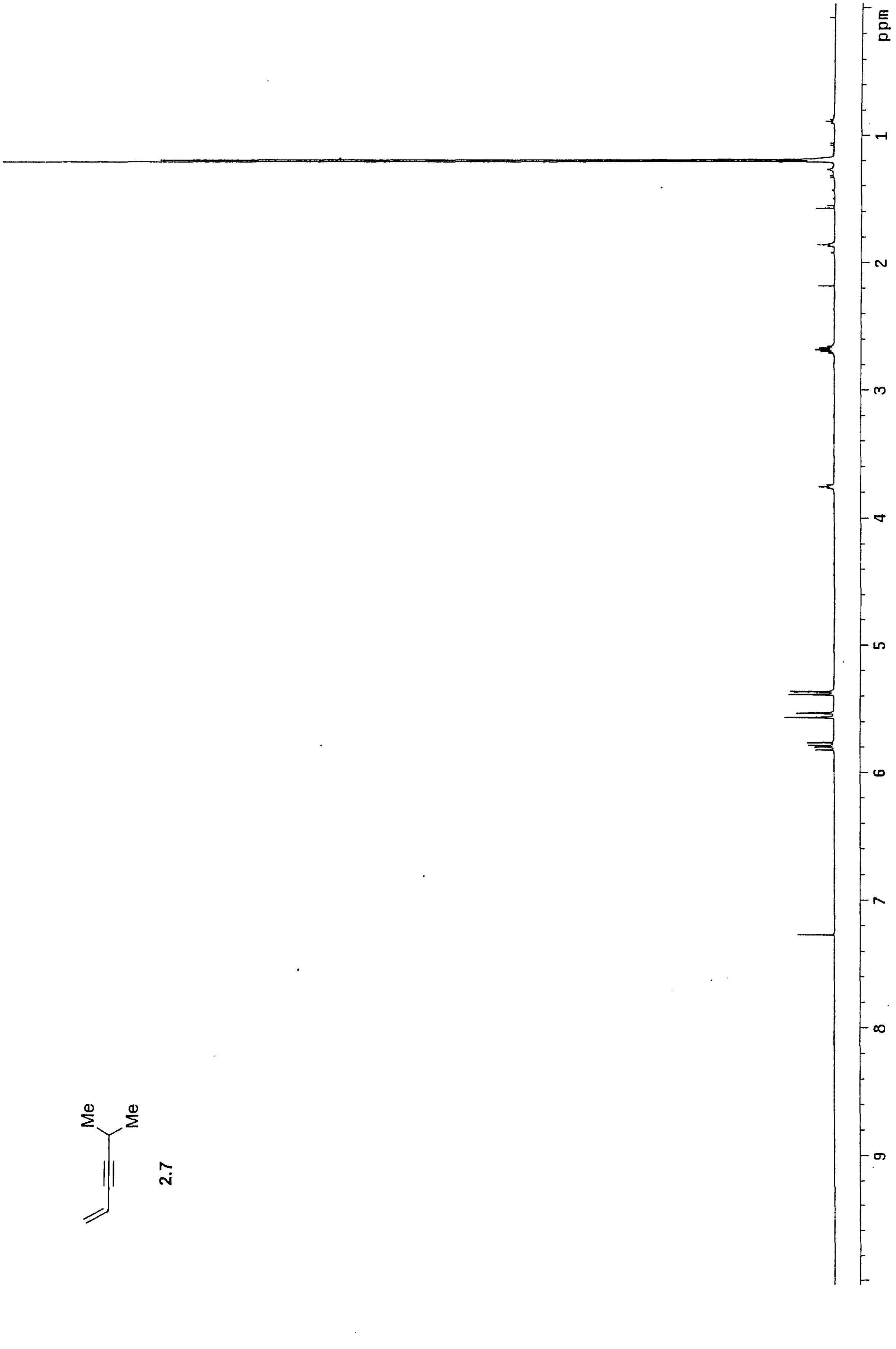
Appendix B.

^{1}H and ^{13}C NMR Spectra (Chapter 2)



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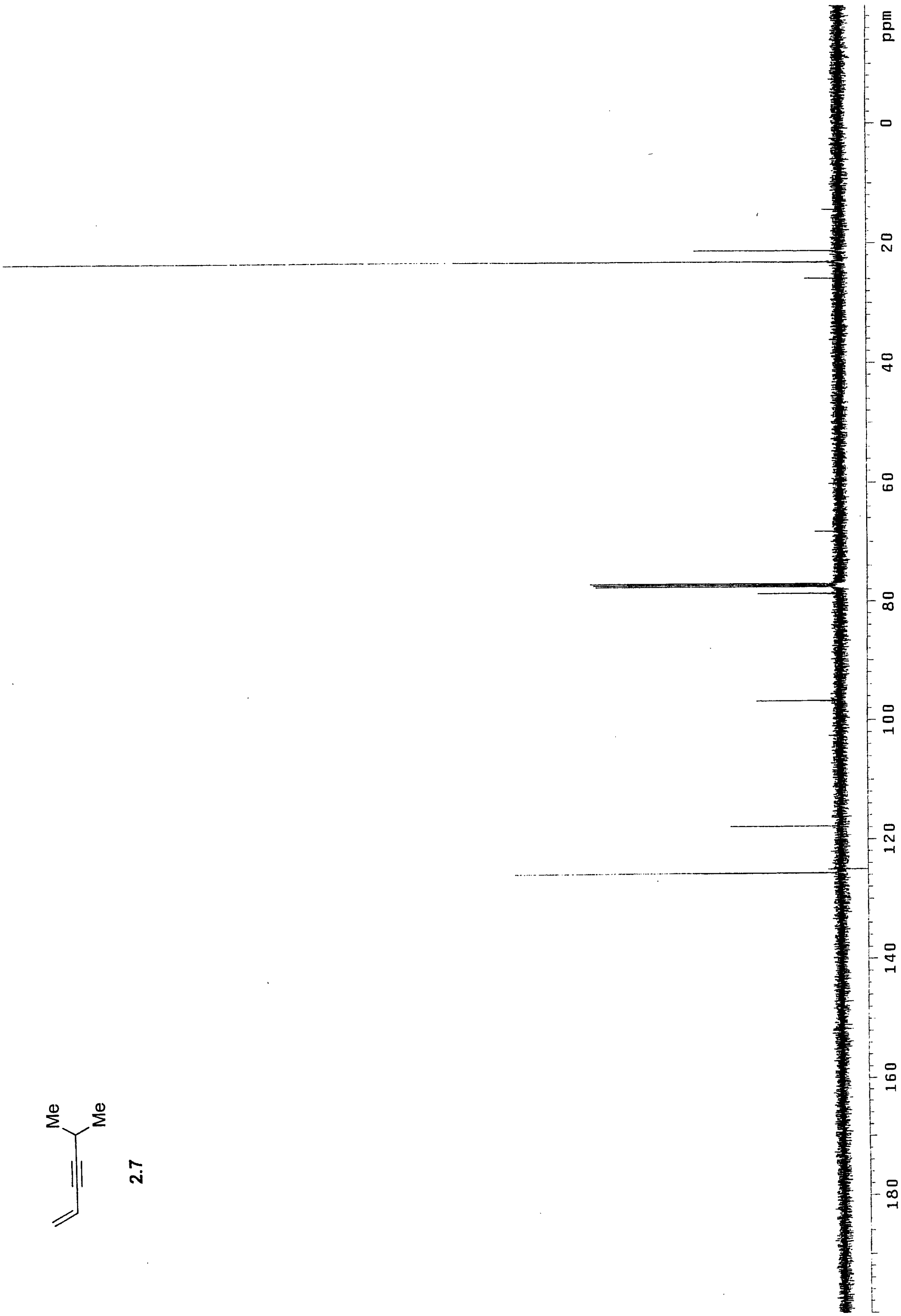

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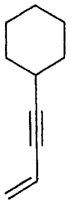

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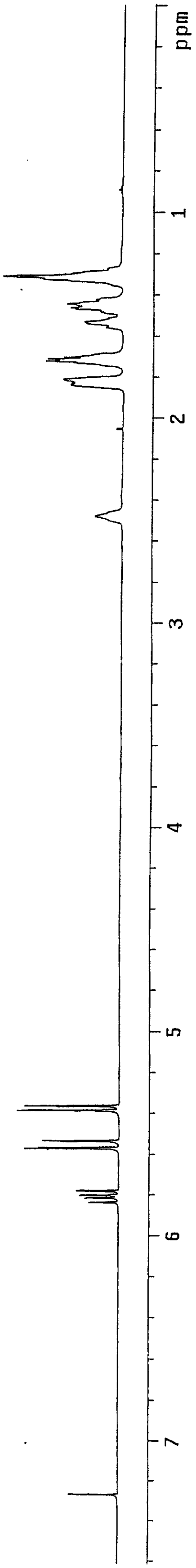

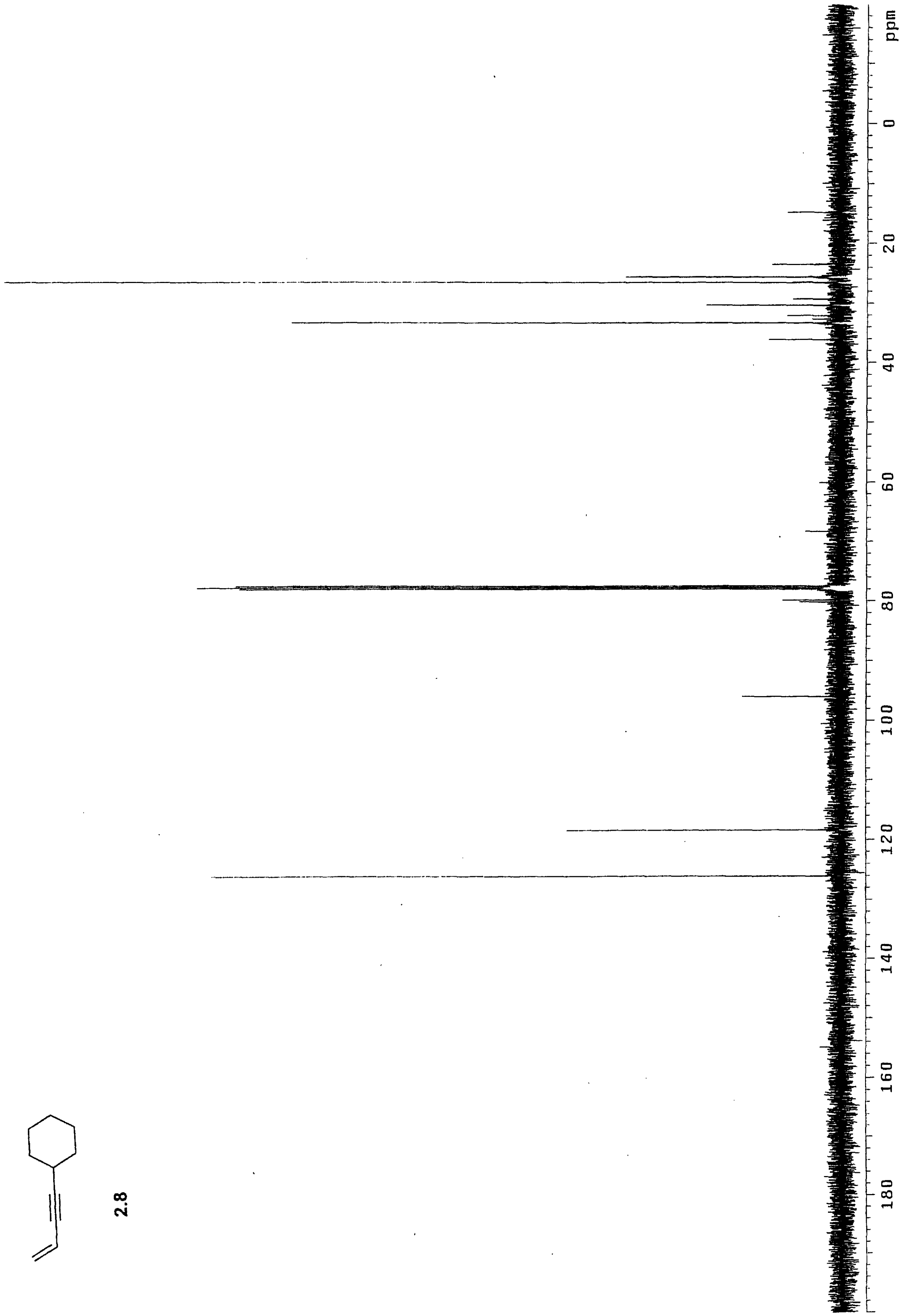

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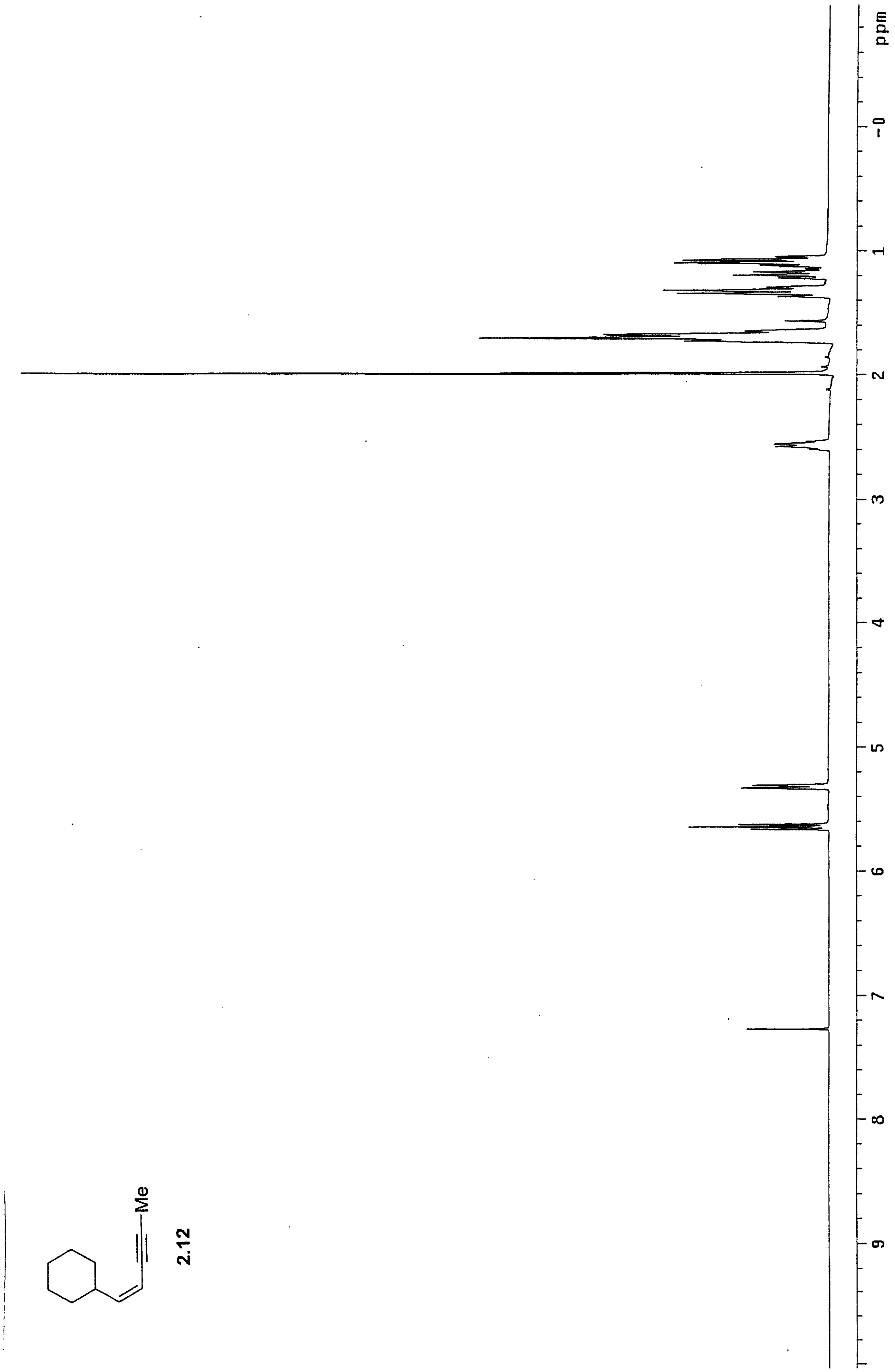

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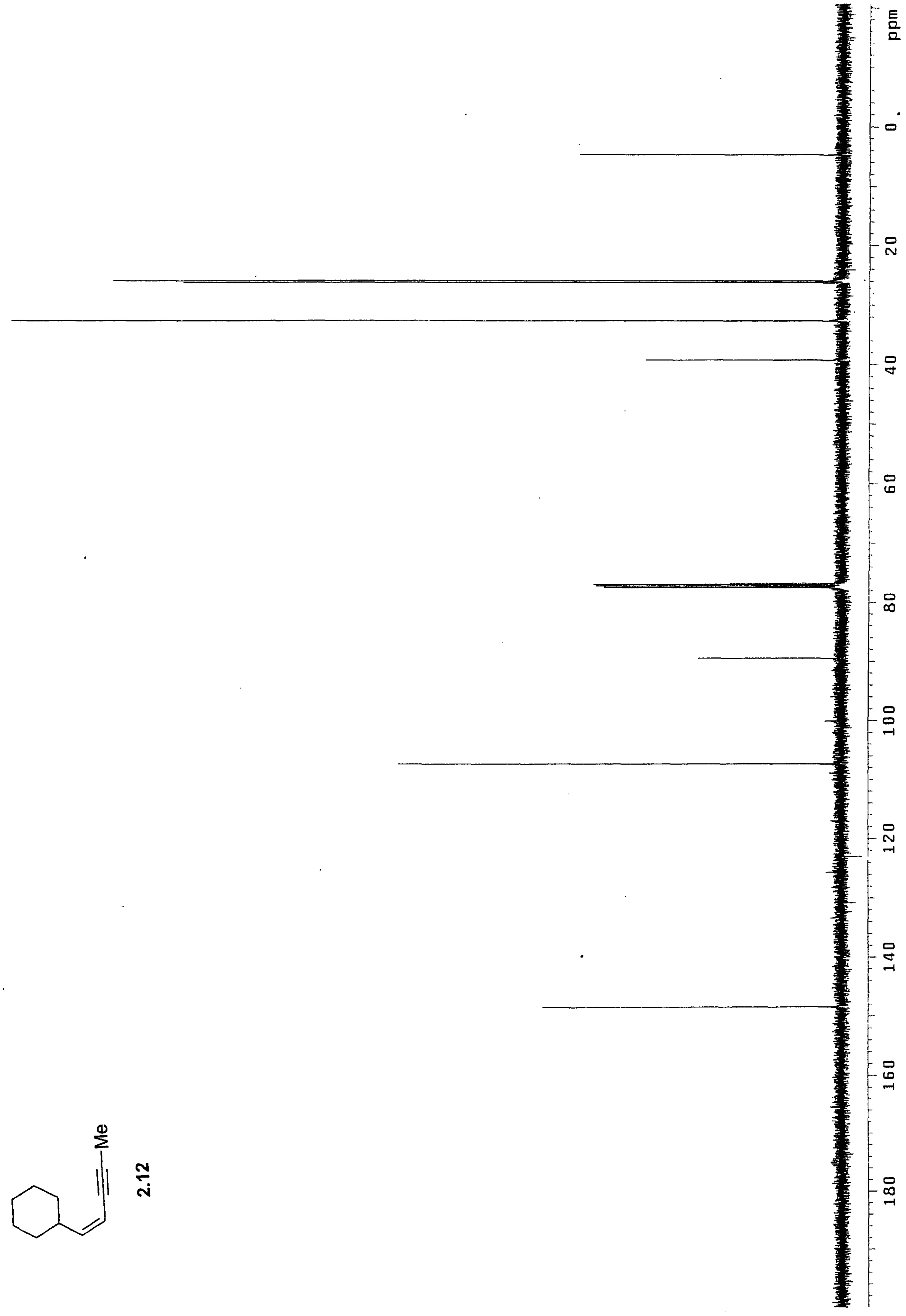
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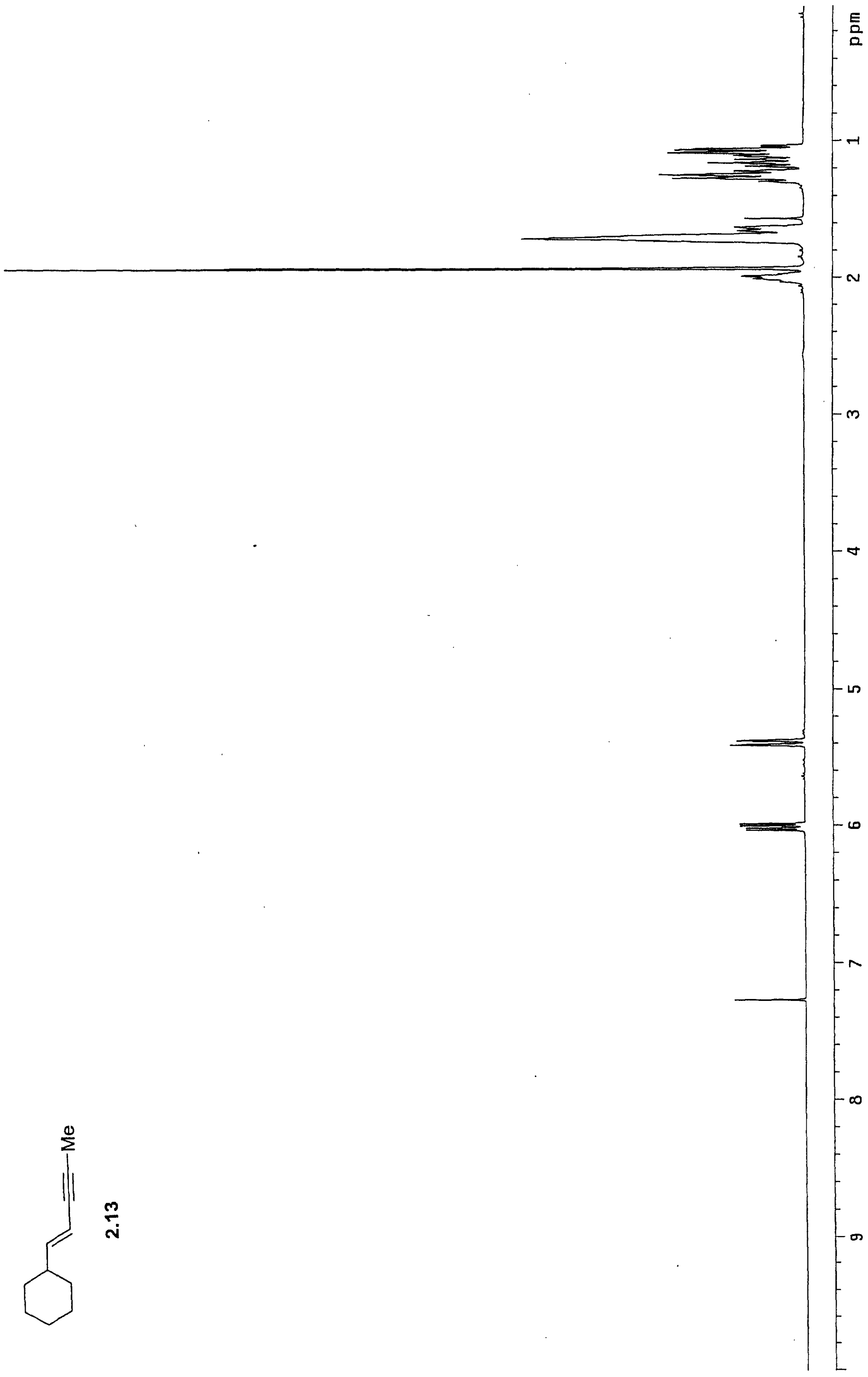

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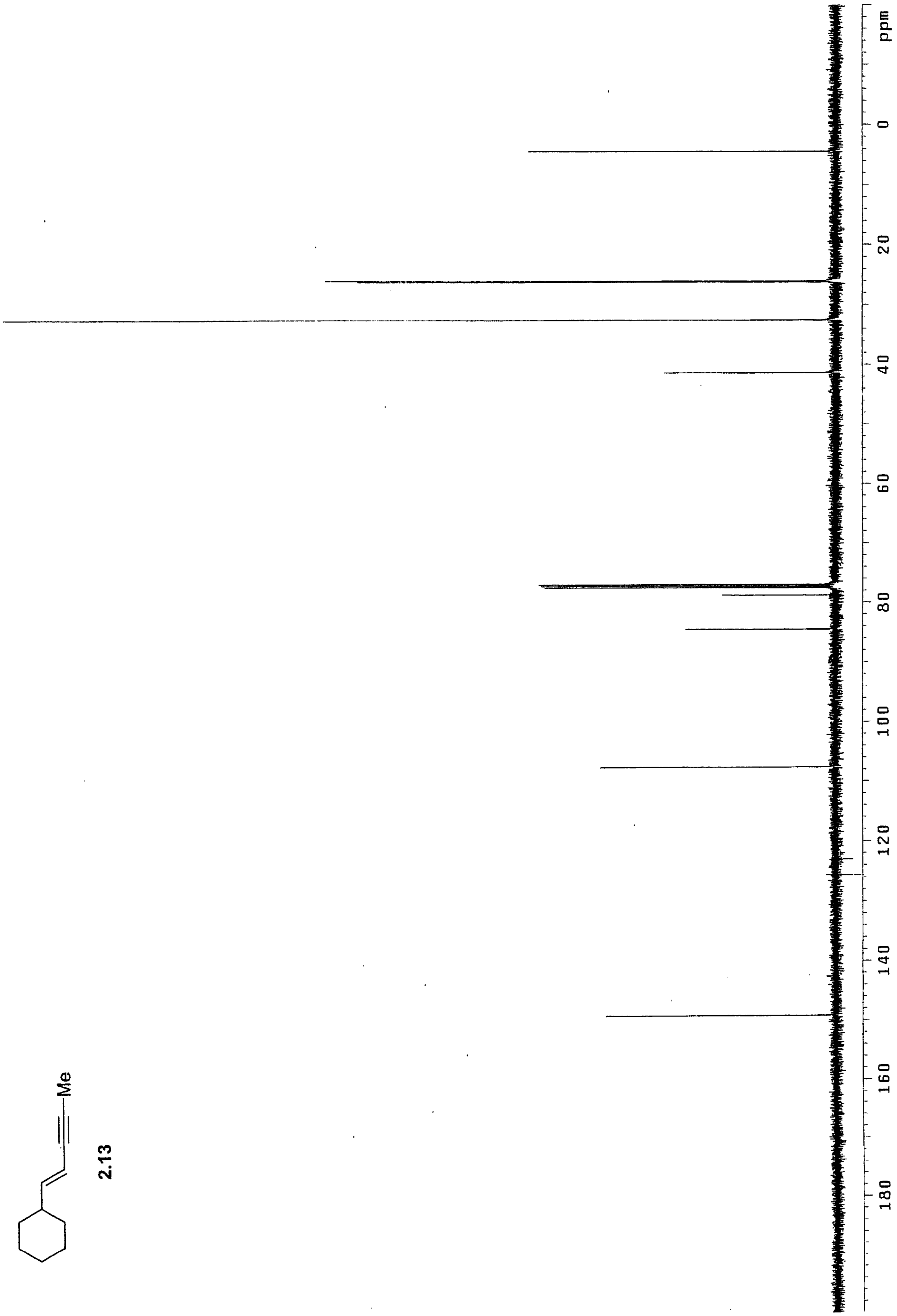

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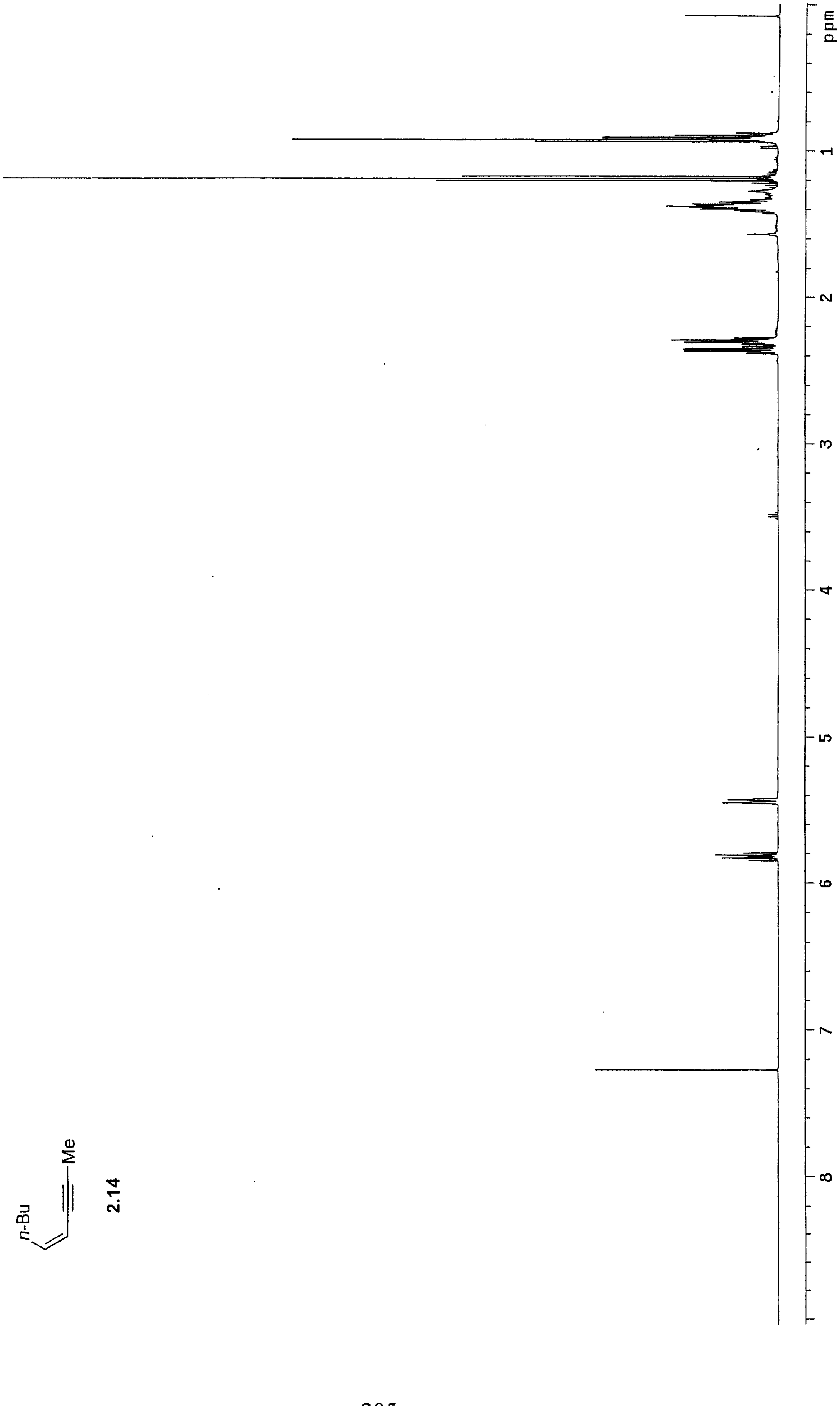

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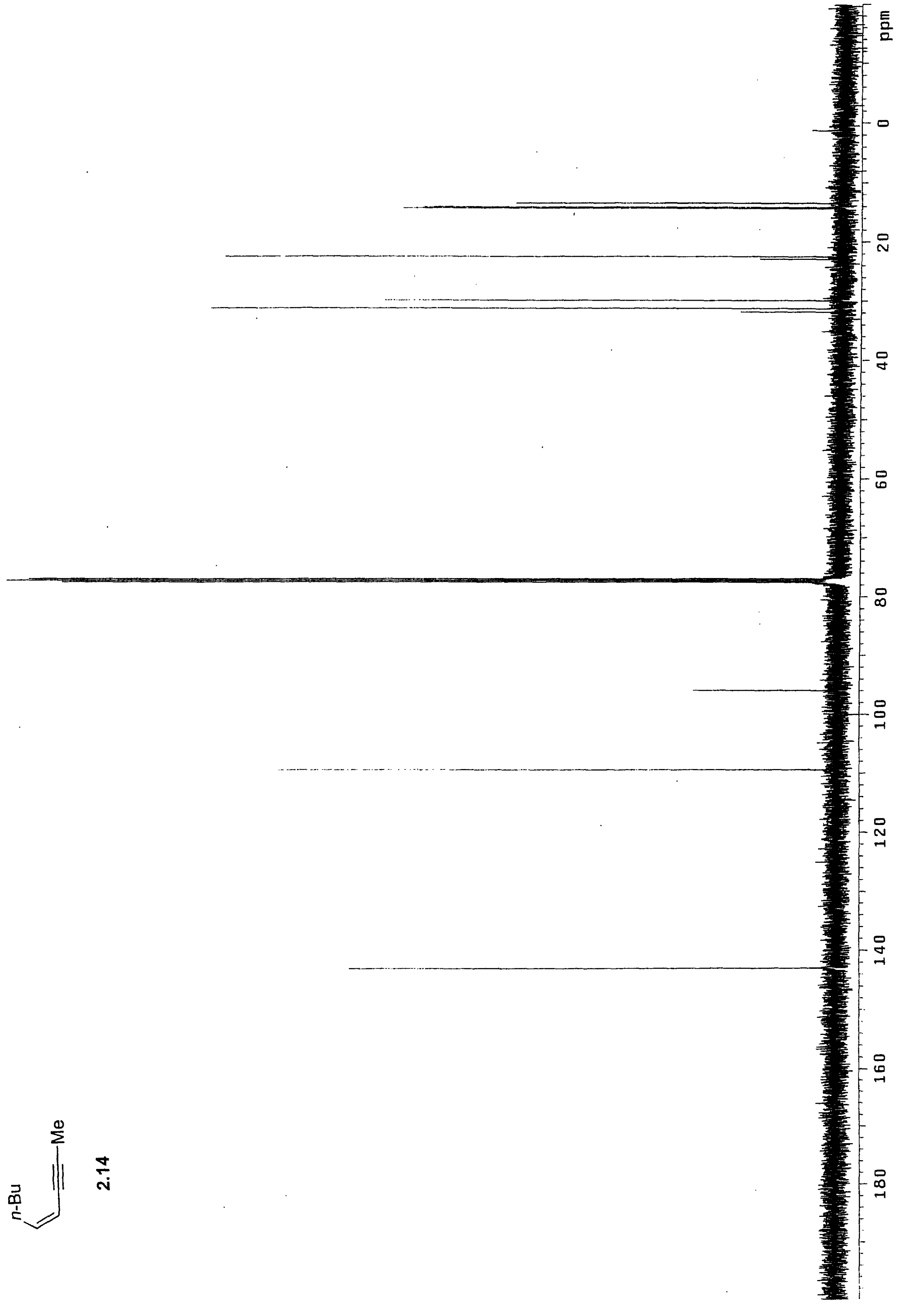

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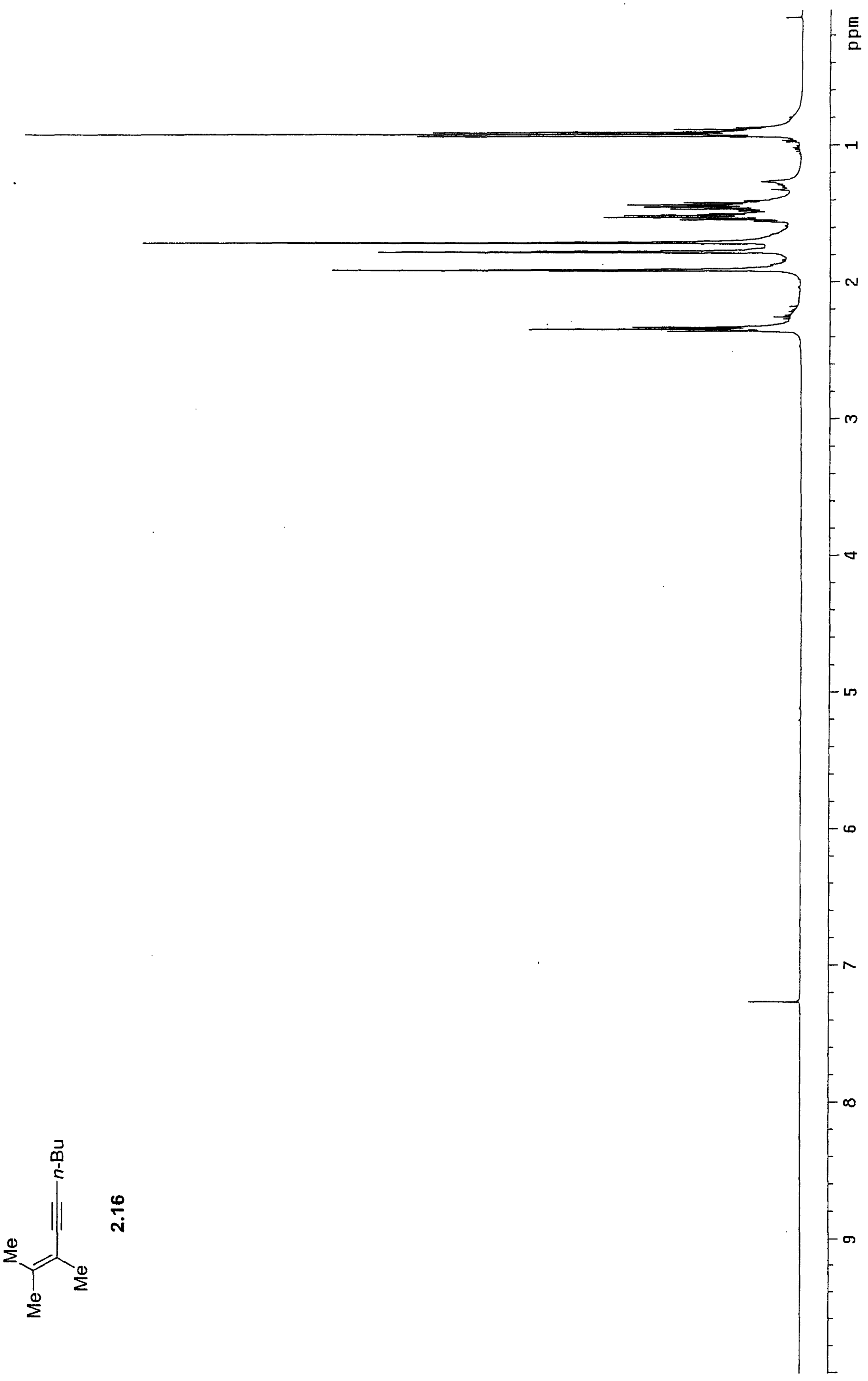

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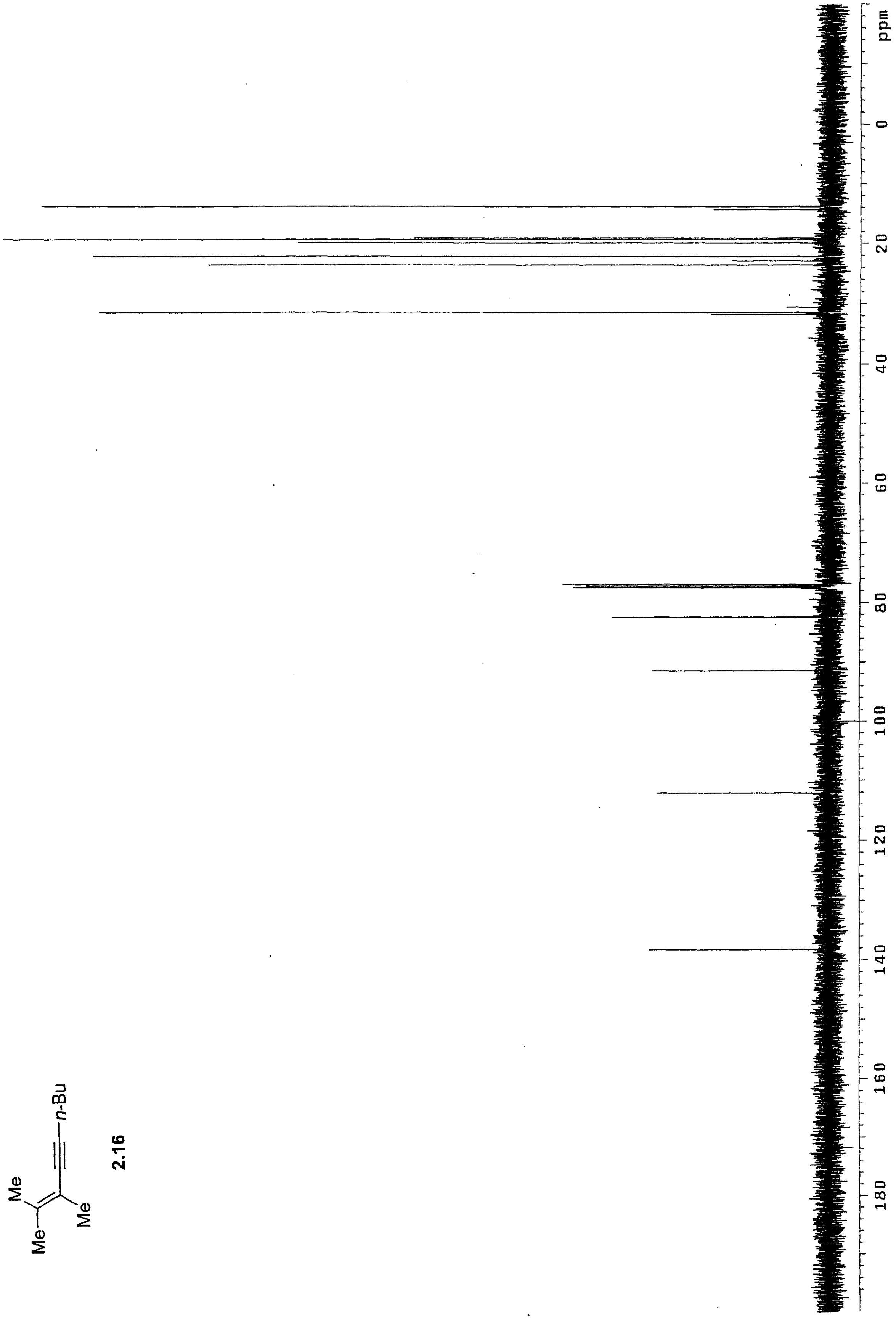

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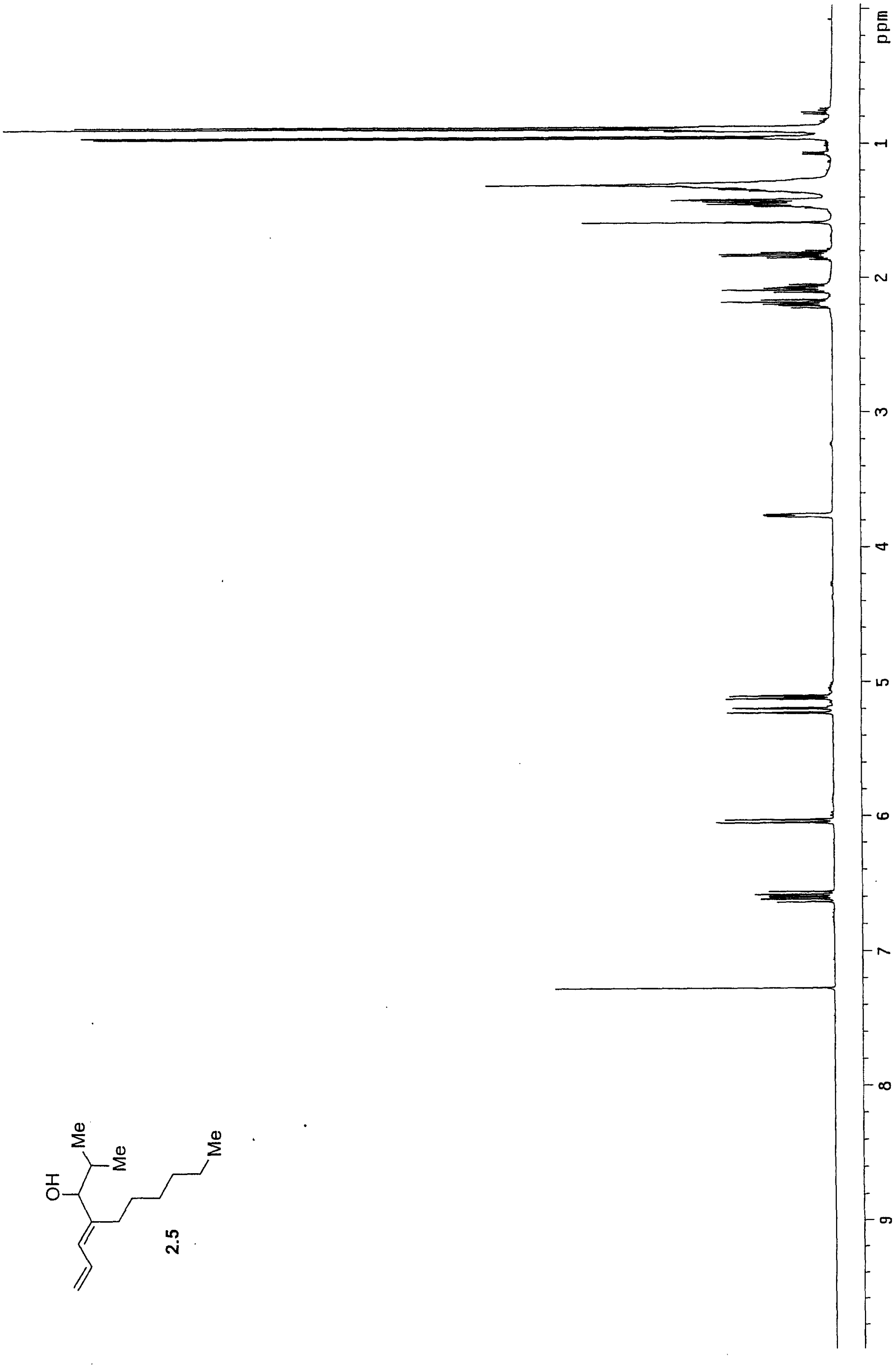
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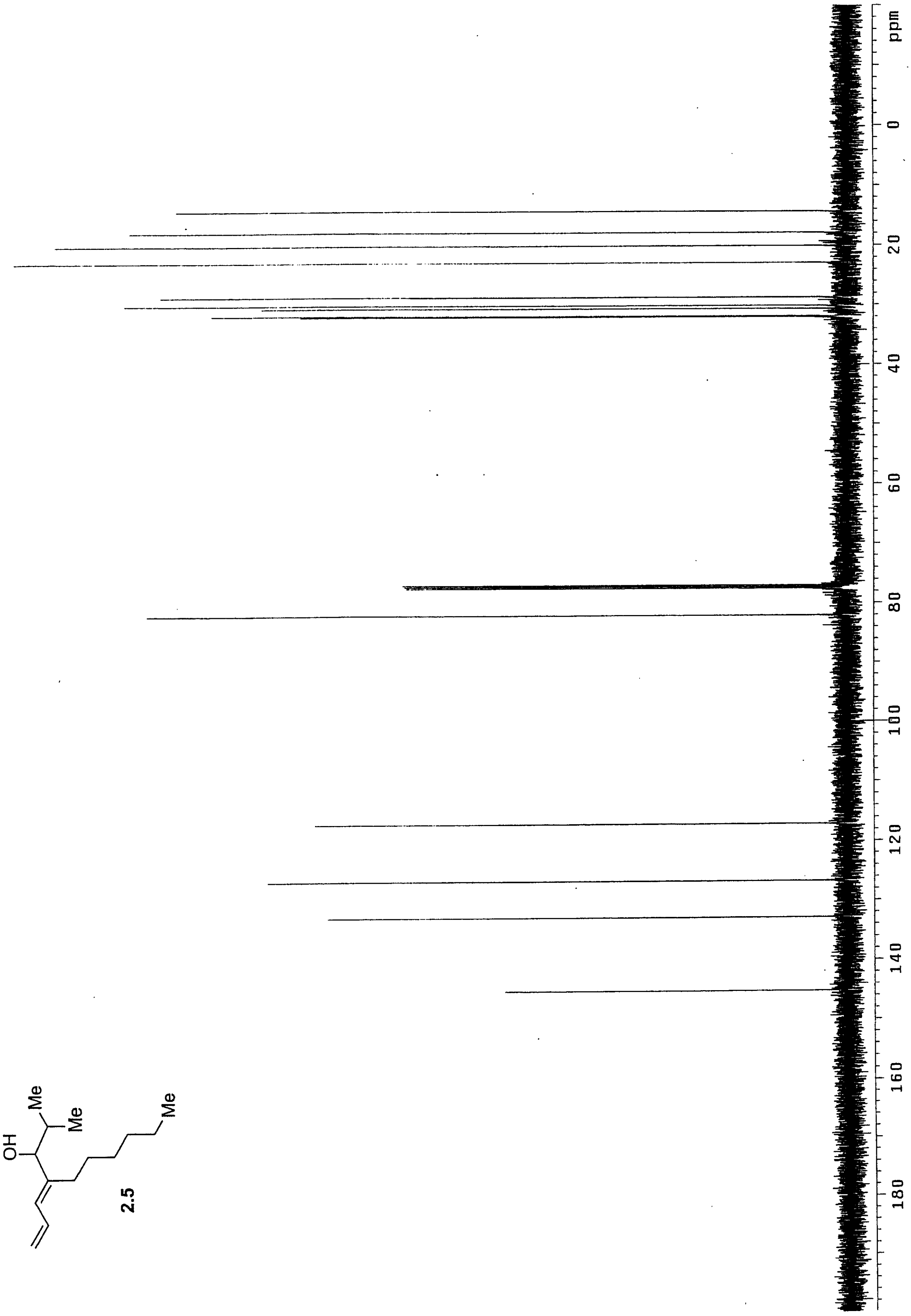

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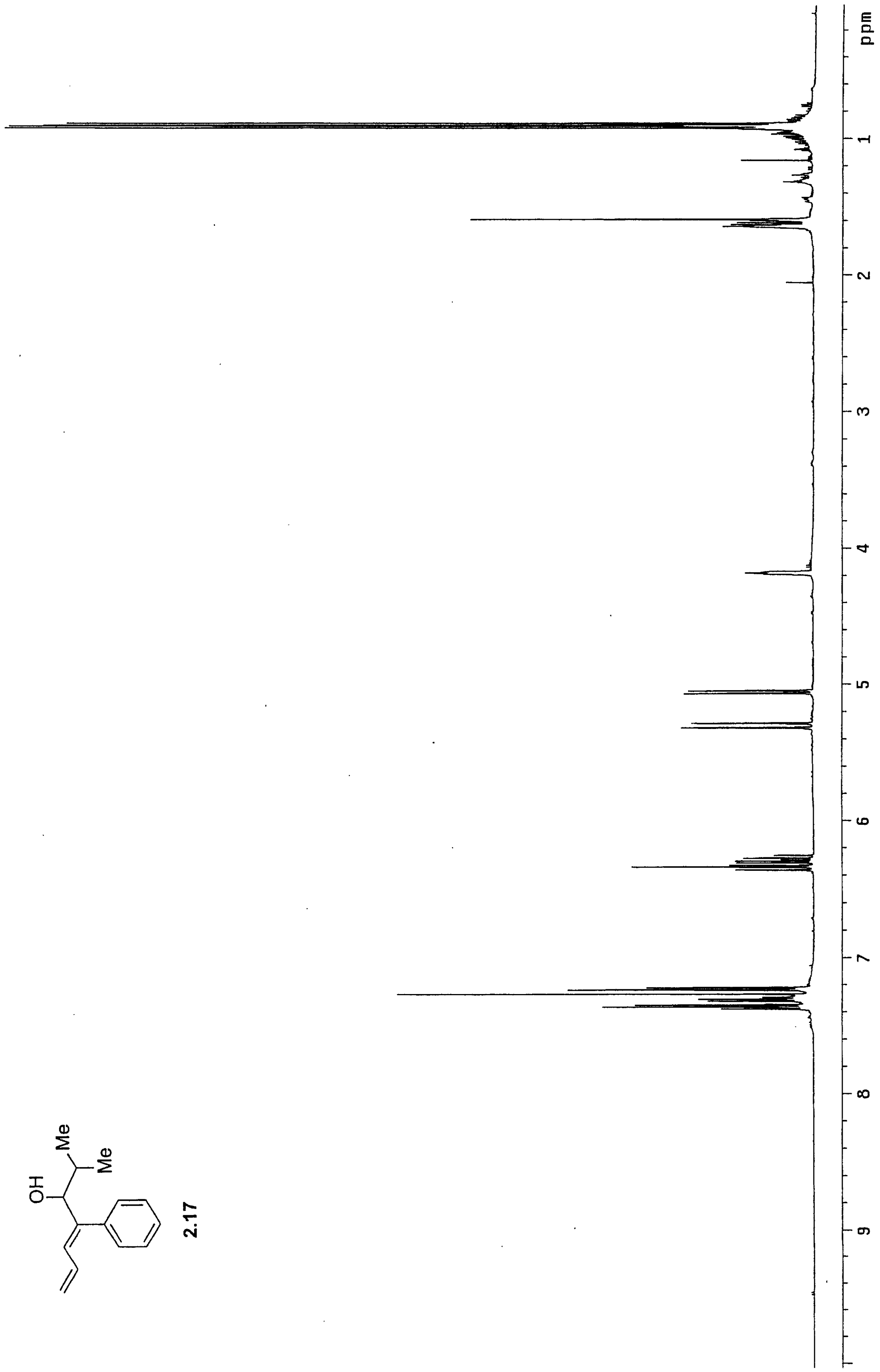

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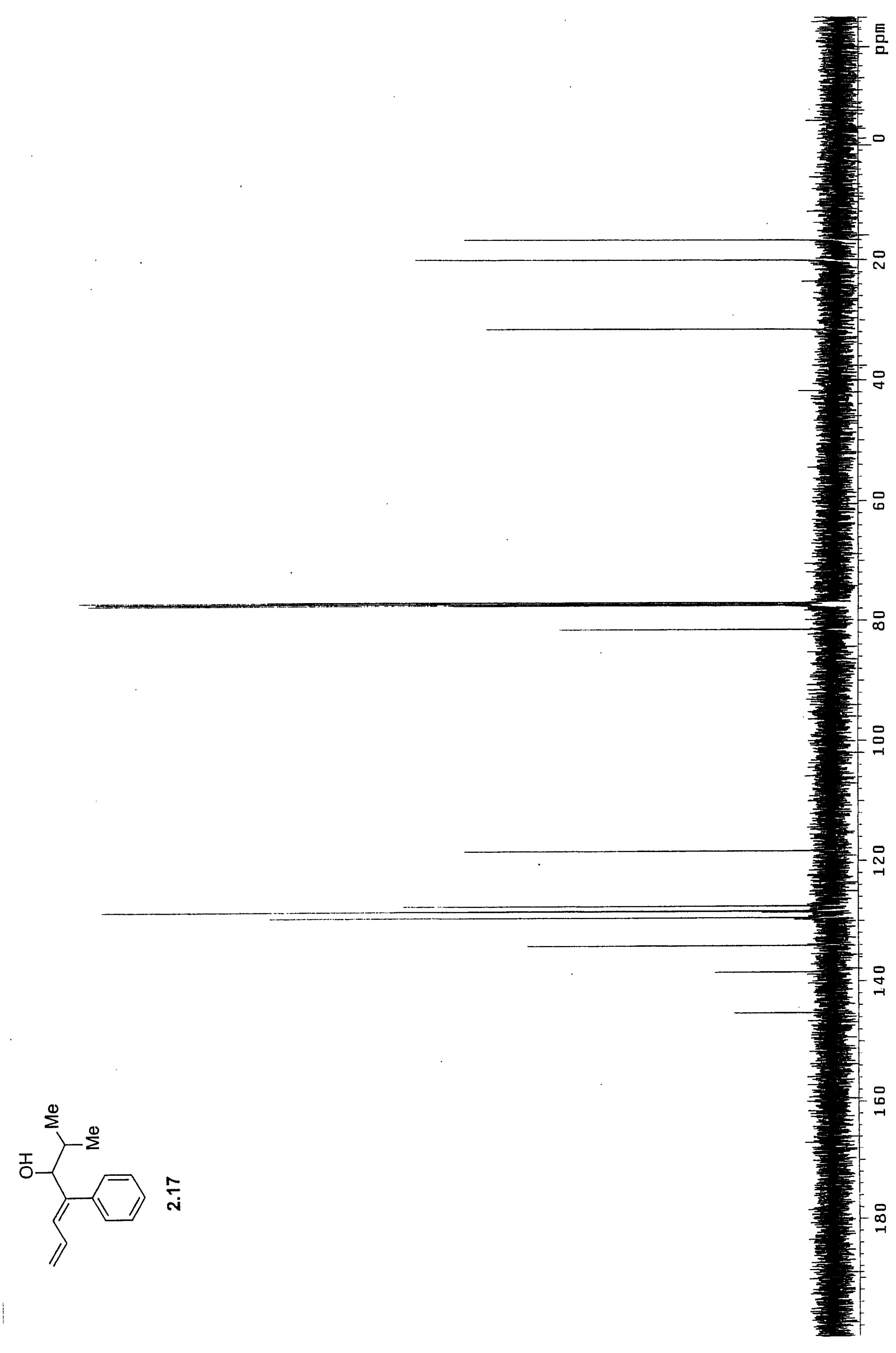

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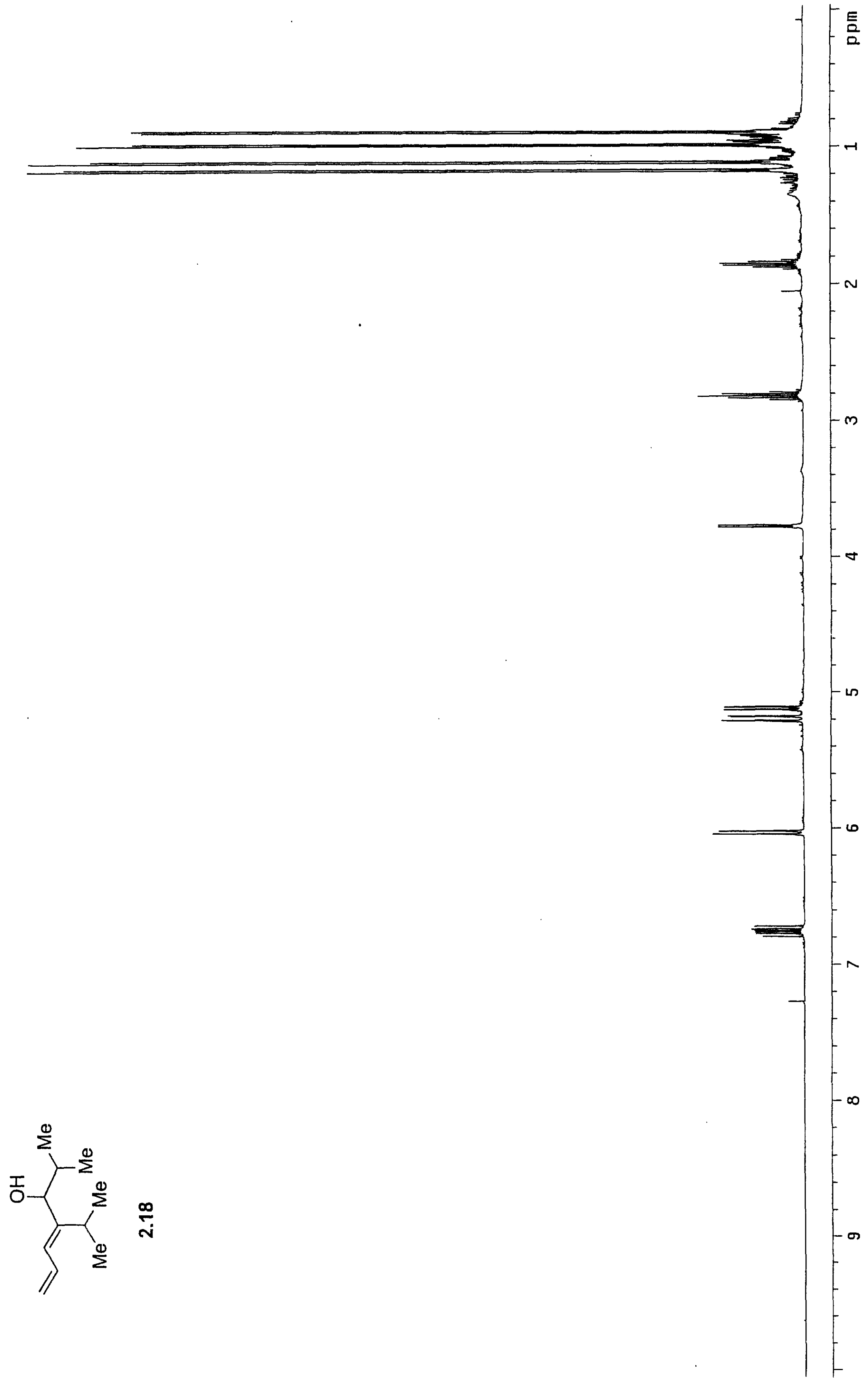

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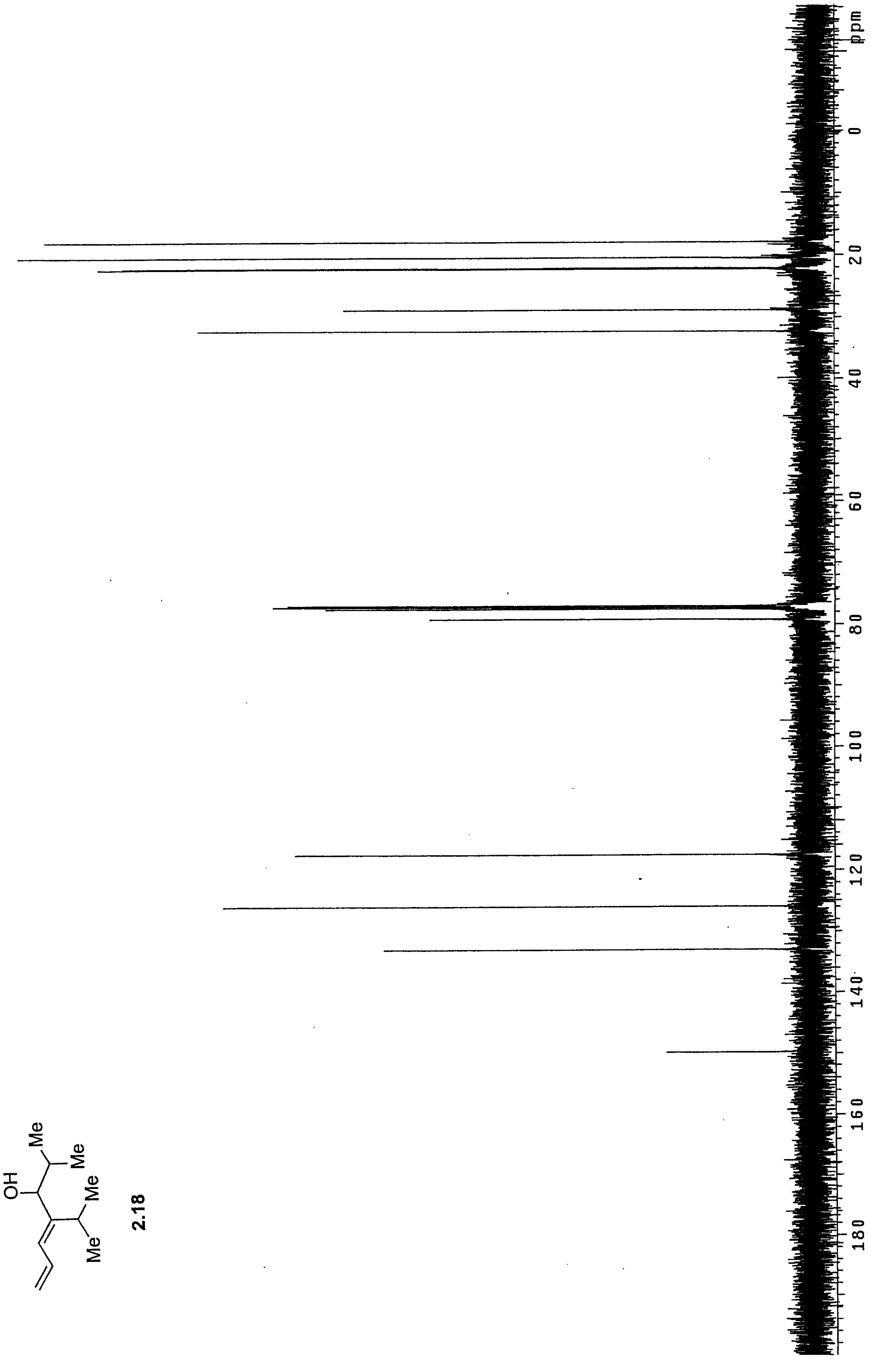

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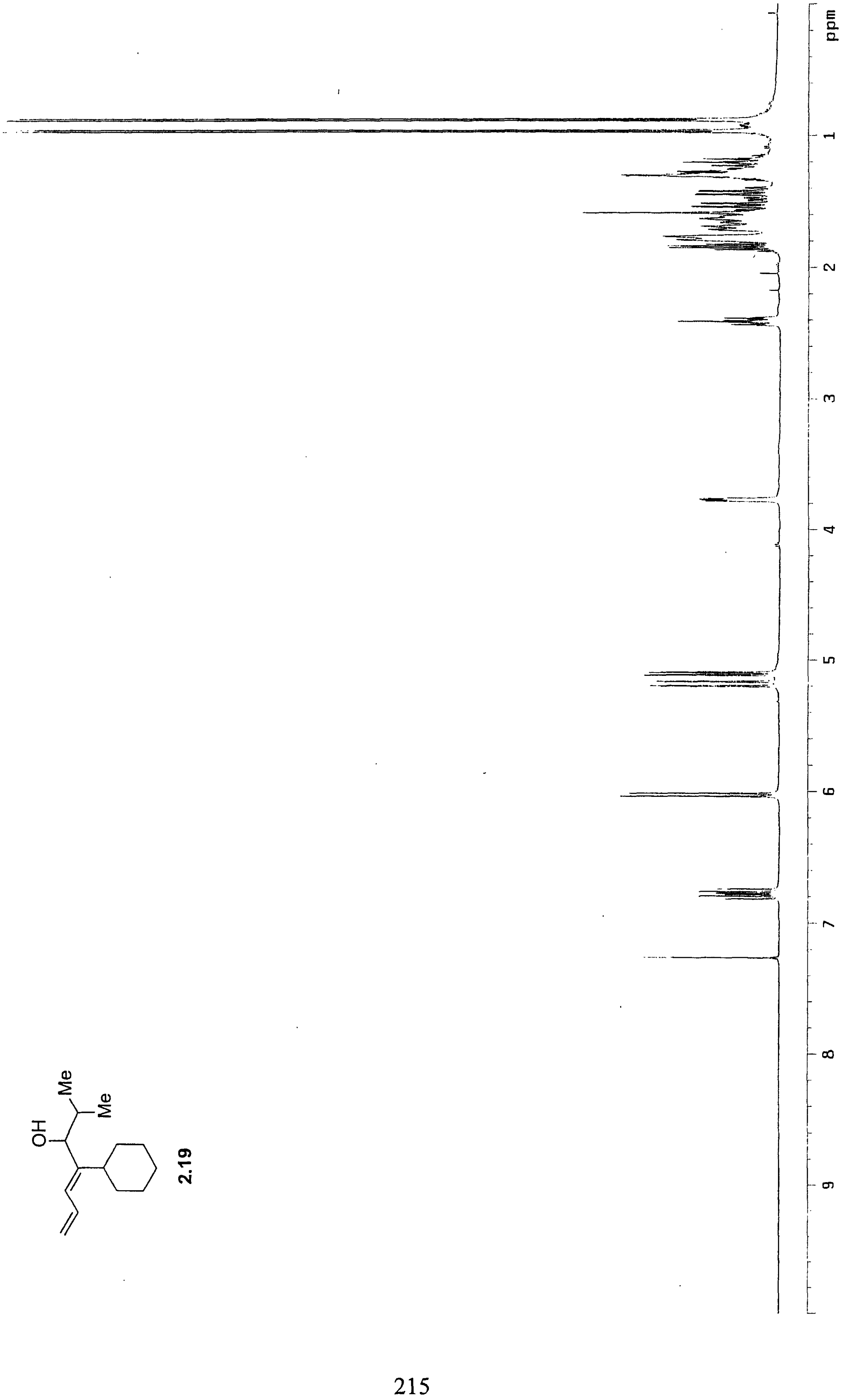

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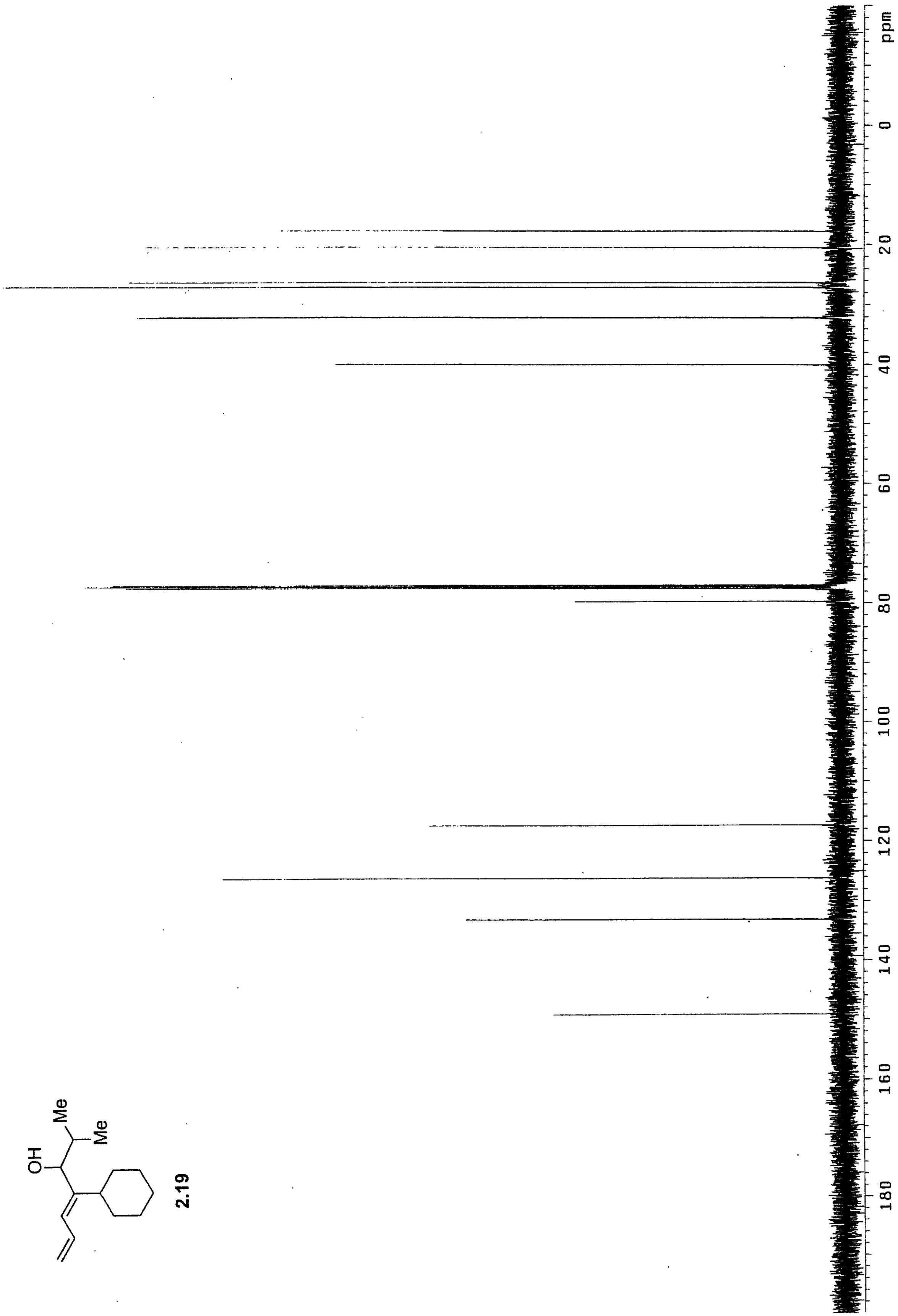

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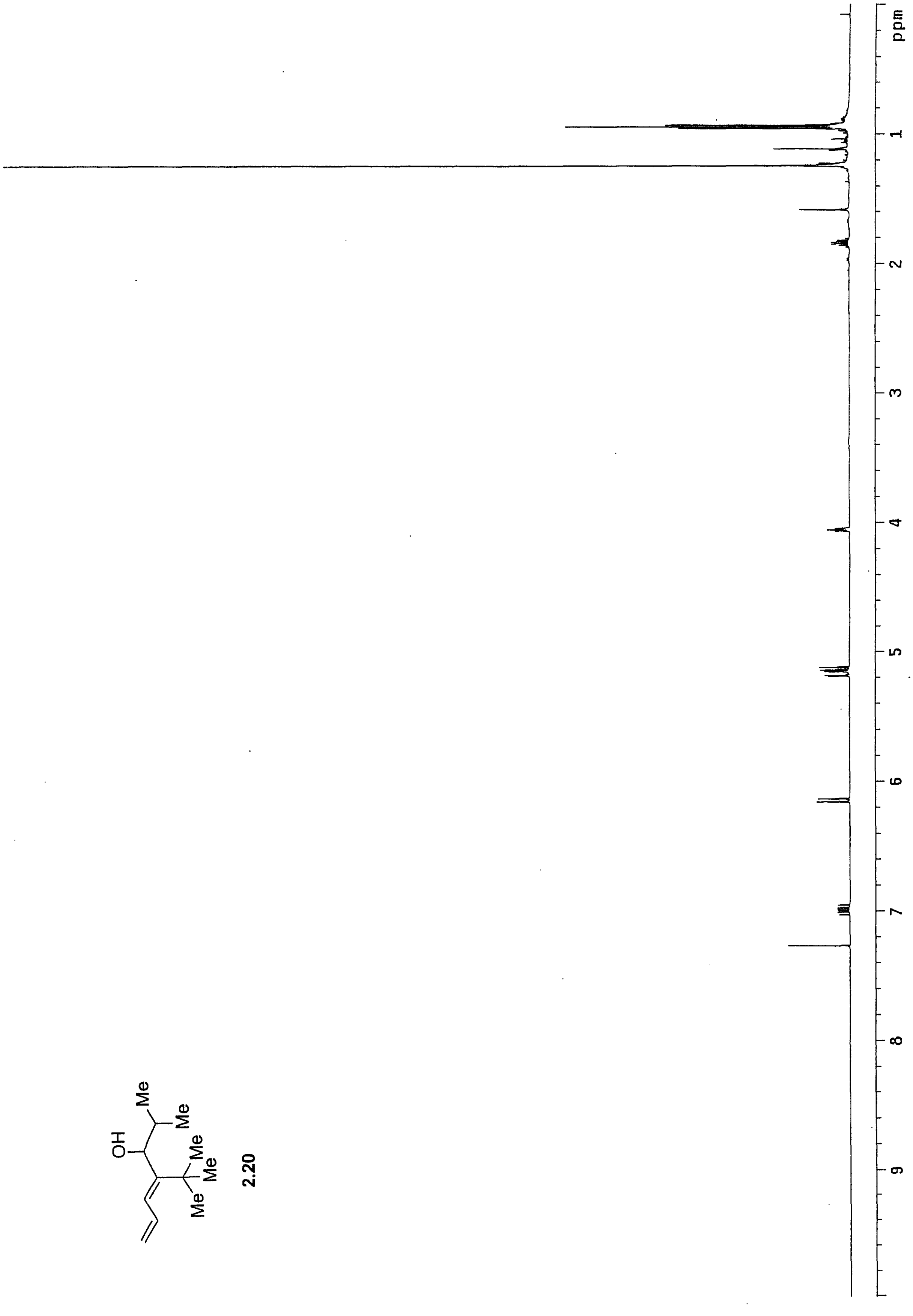

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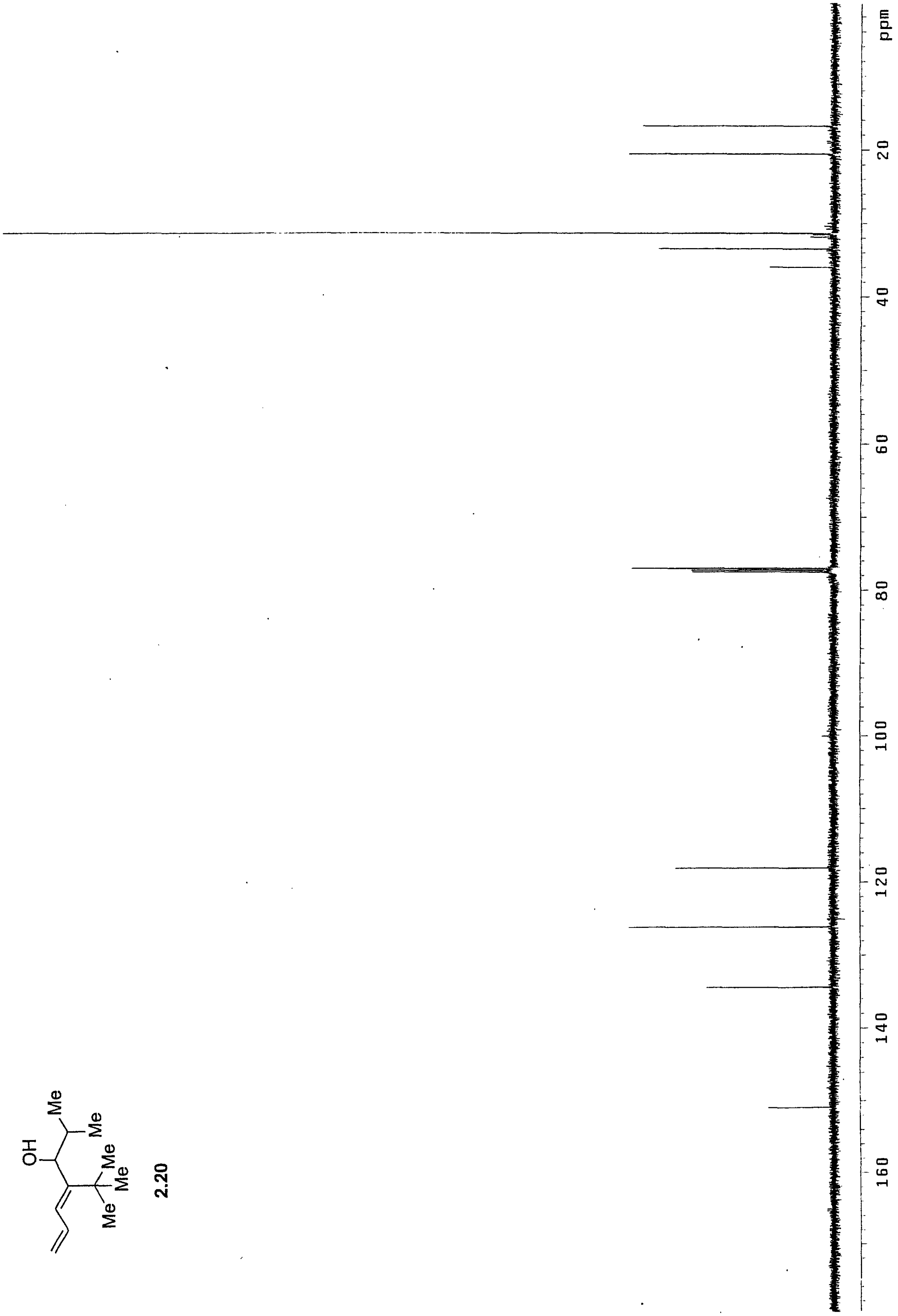

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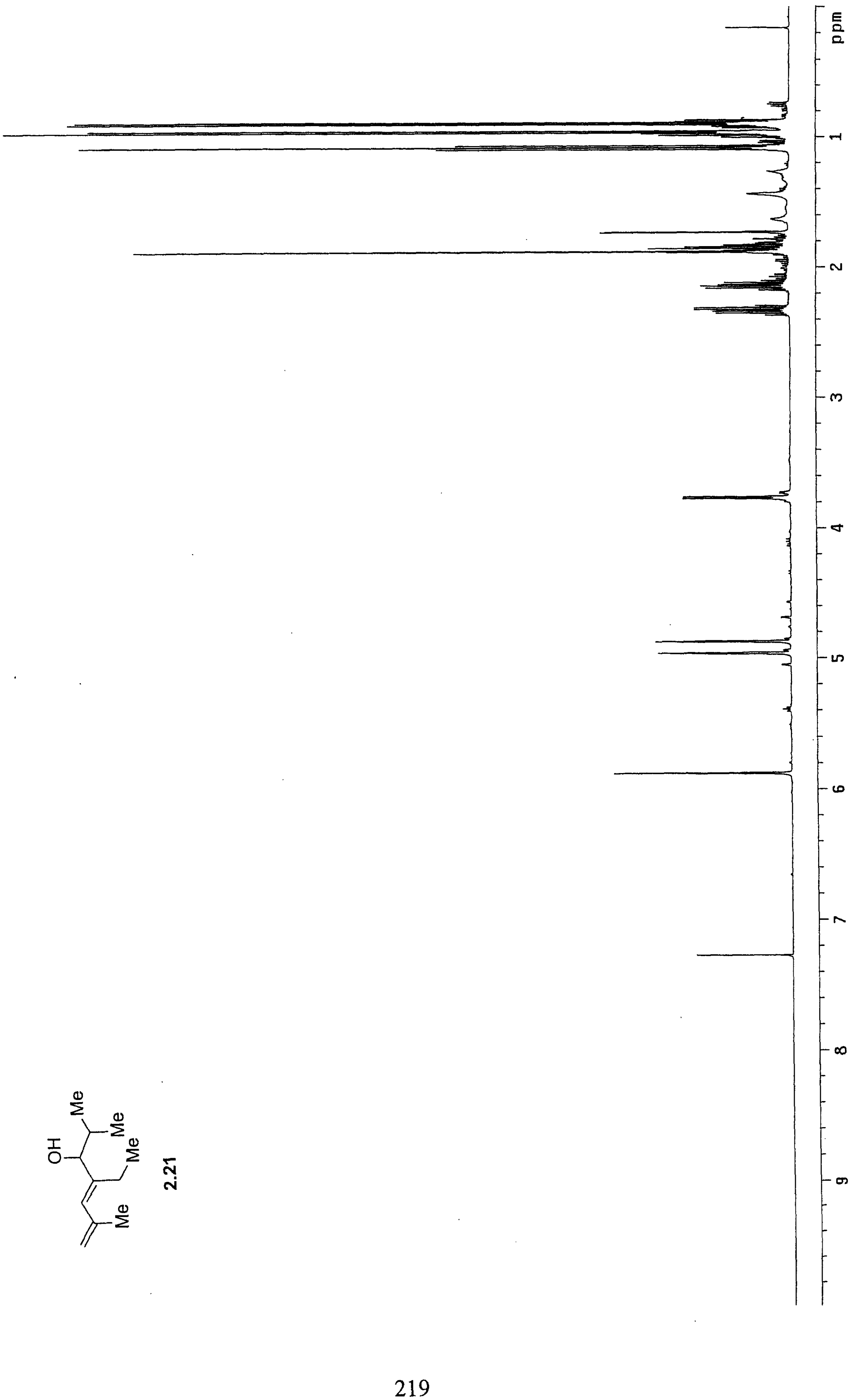

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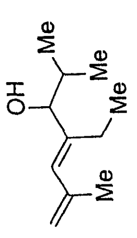

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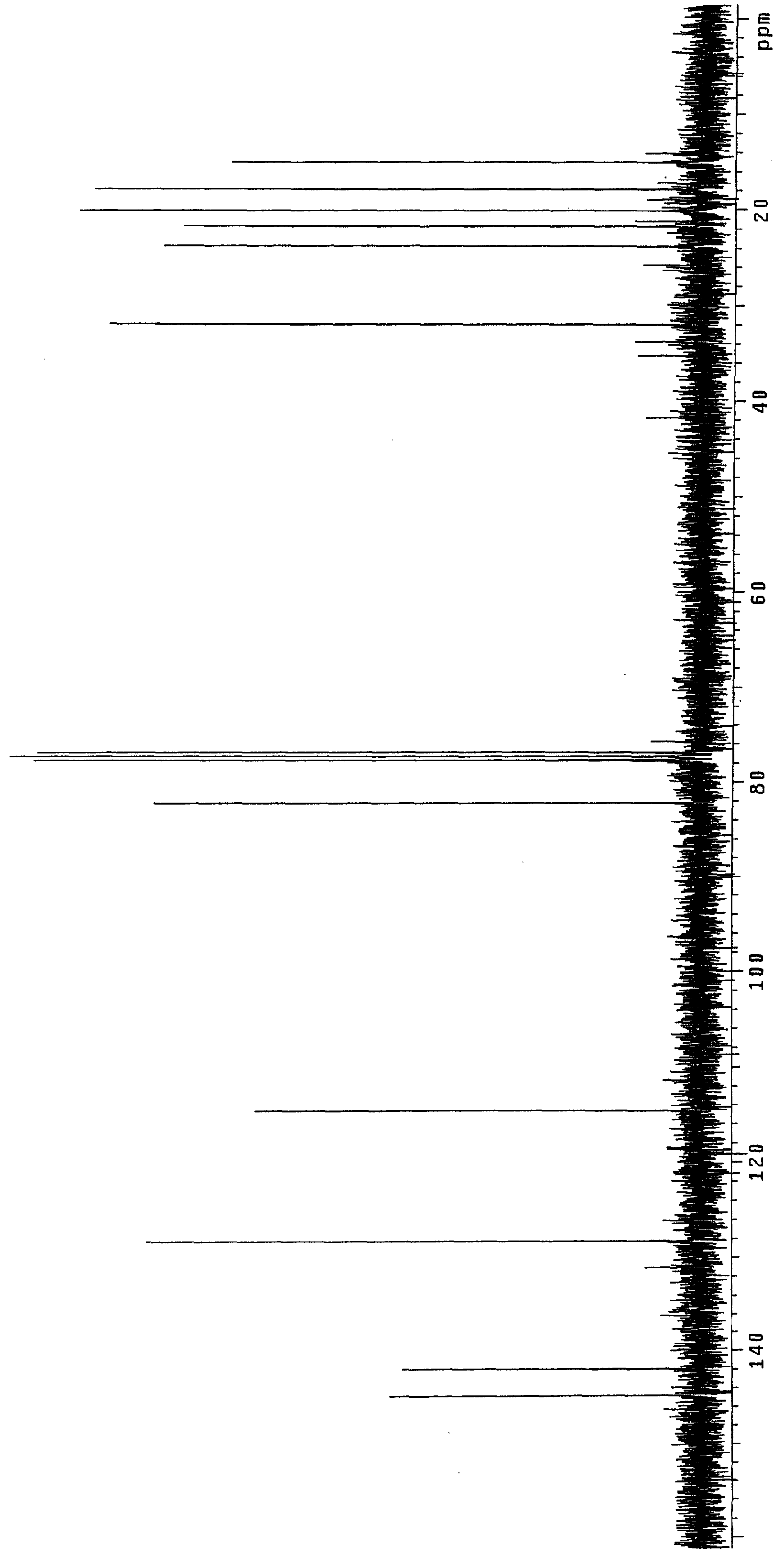

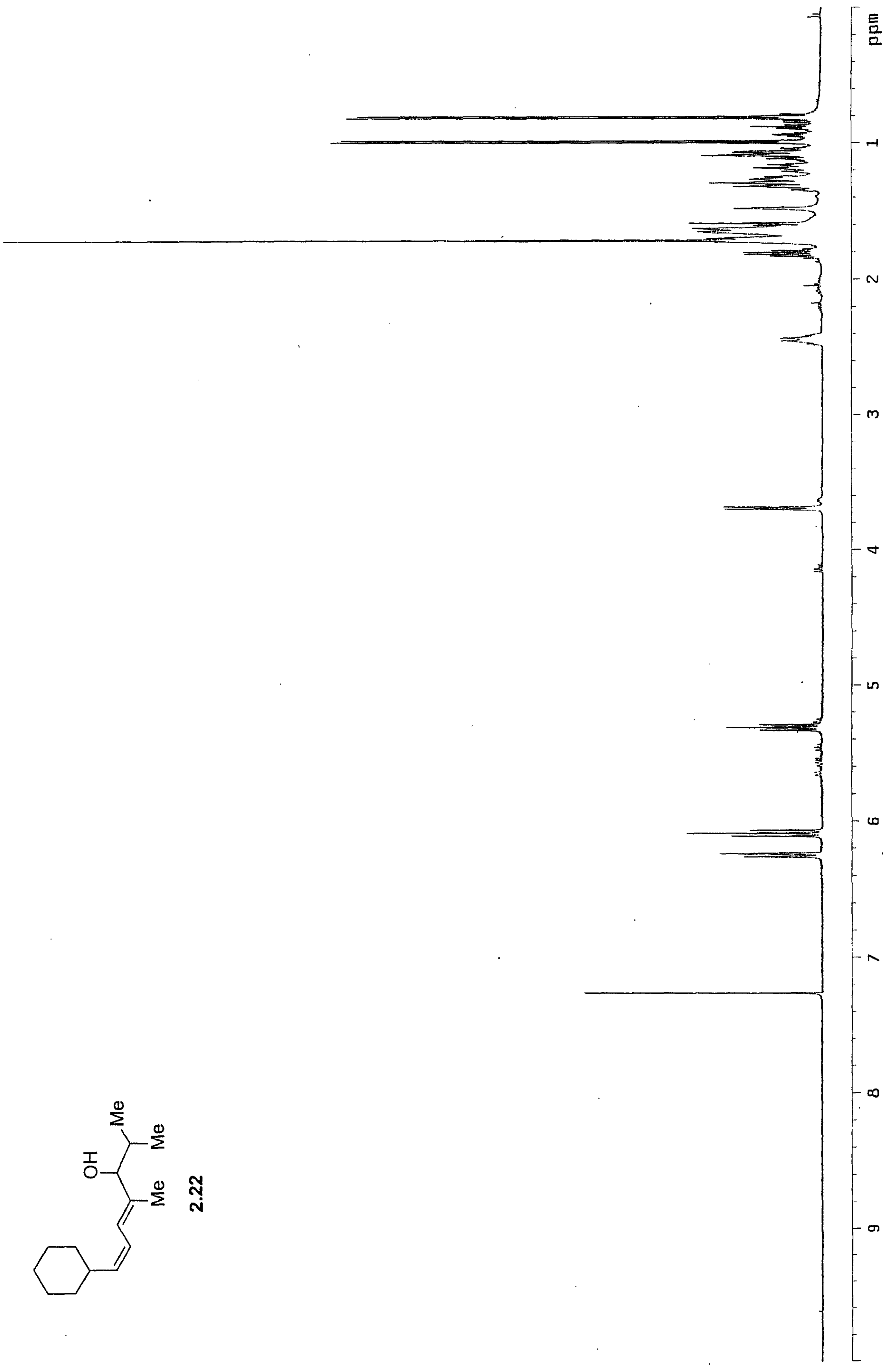

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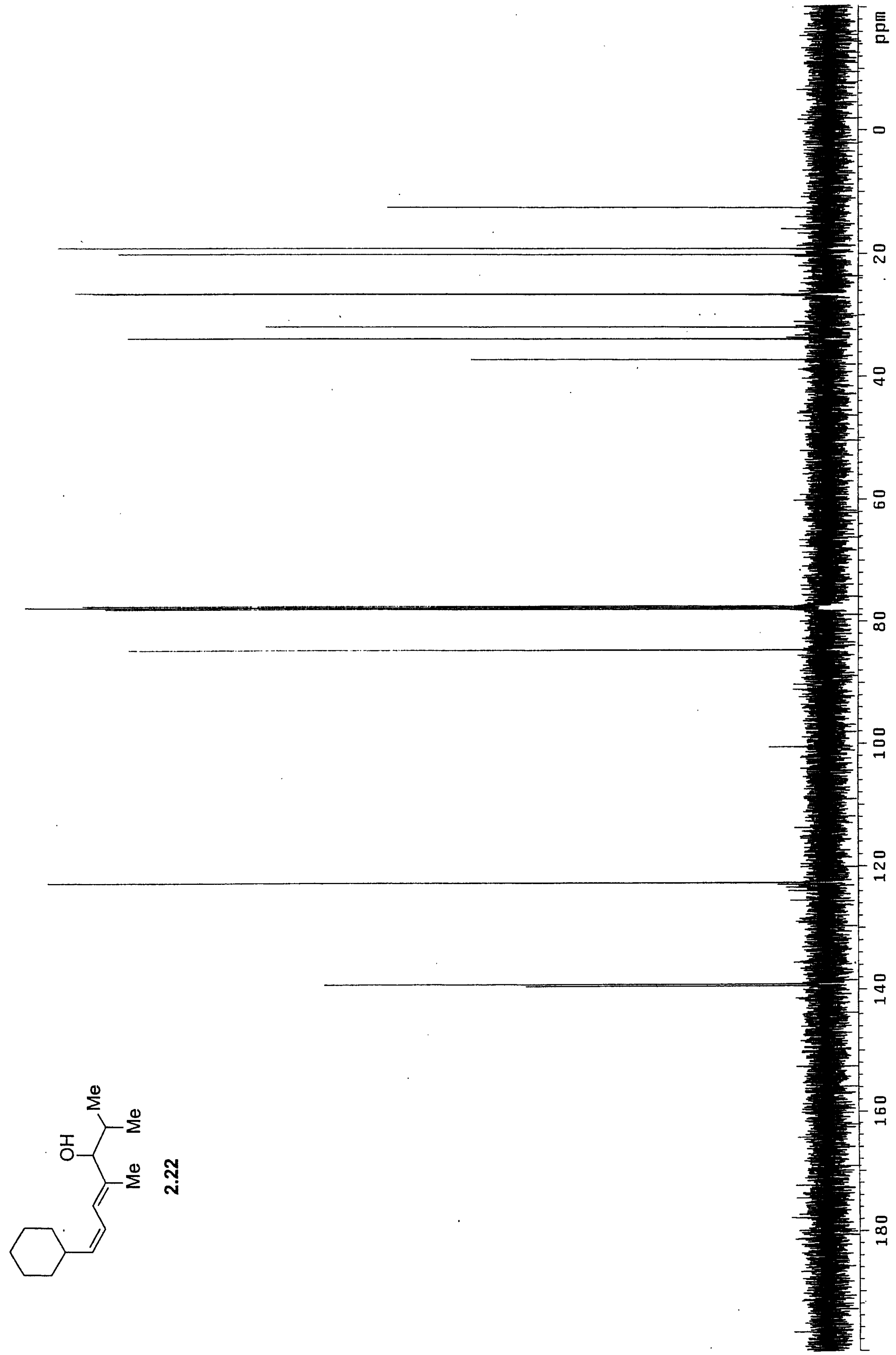

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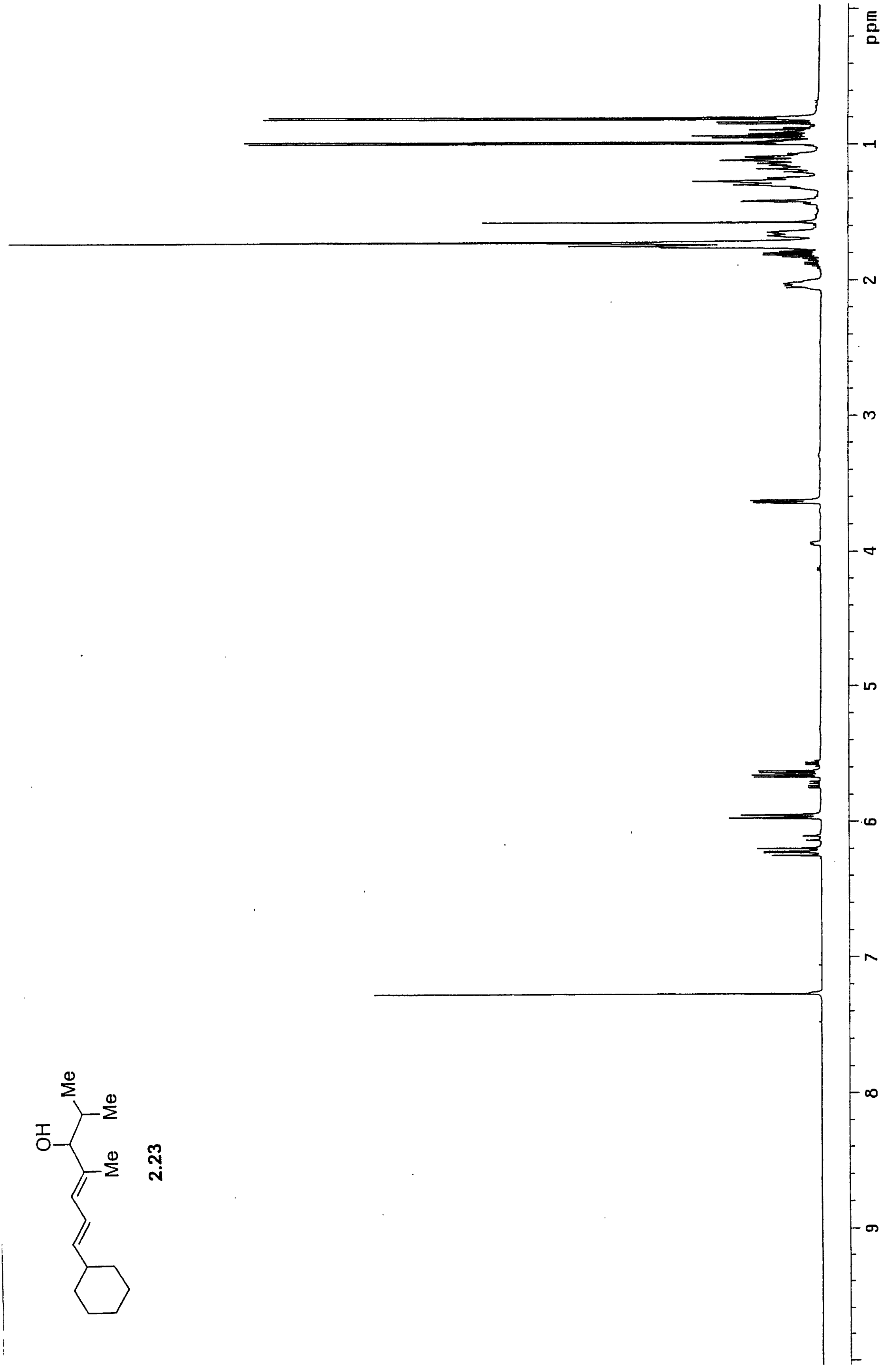
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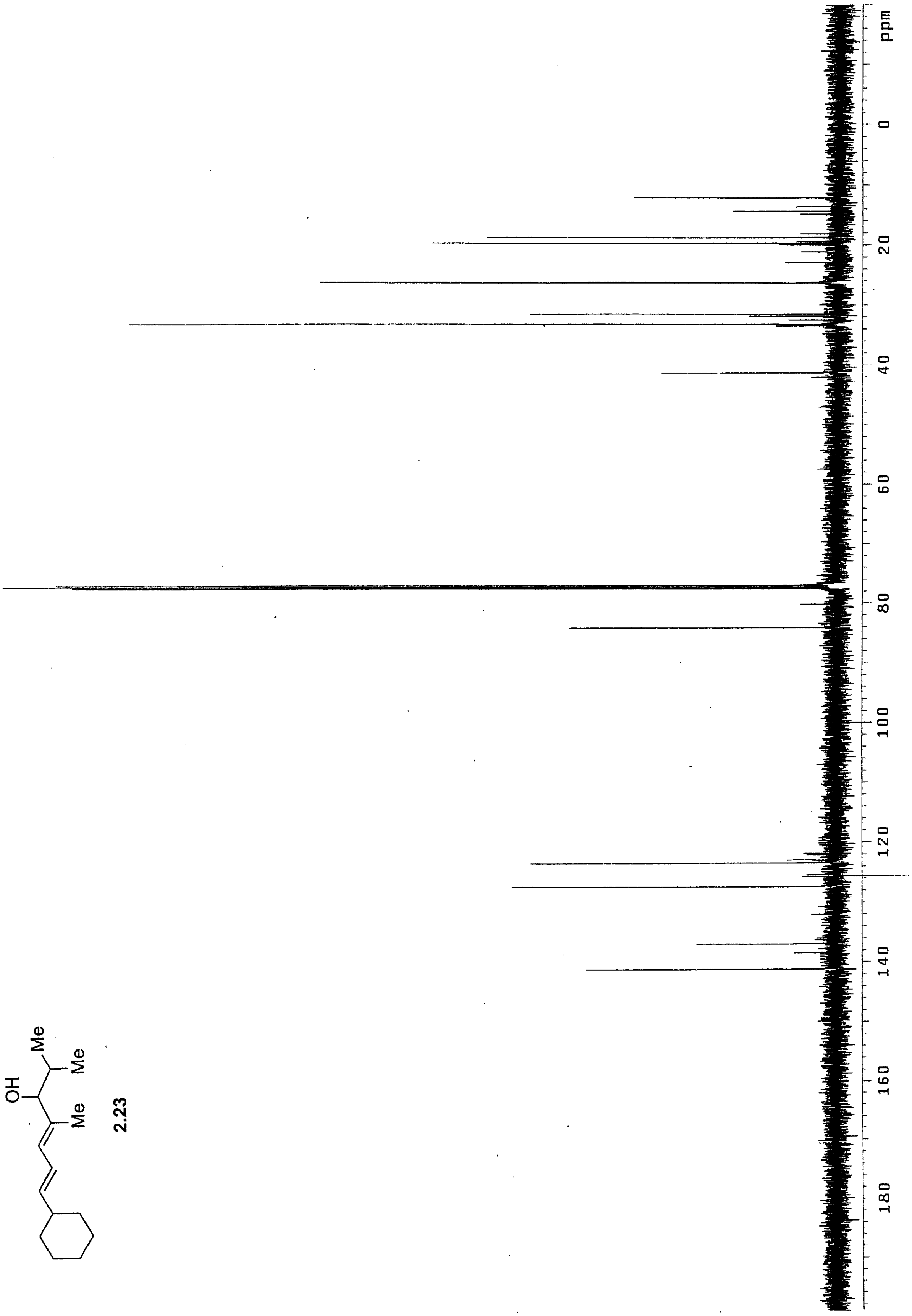

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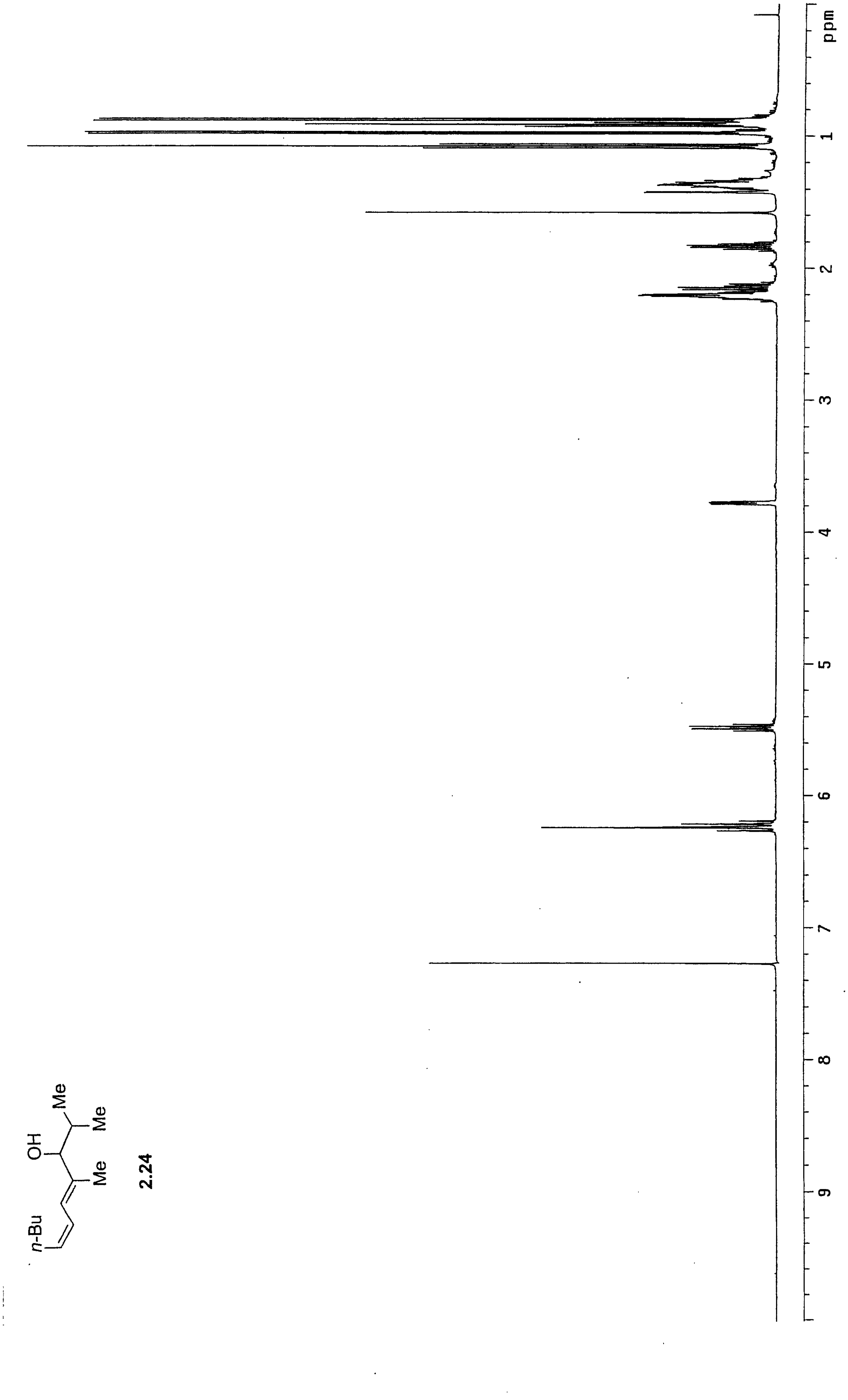

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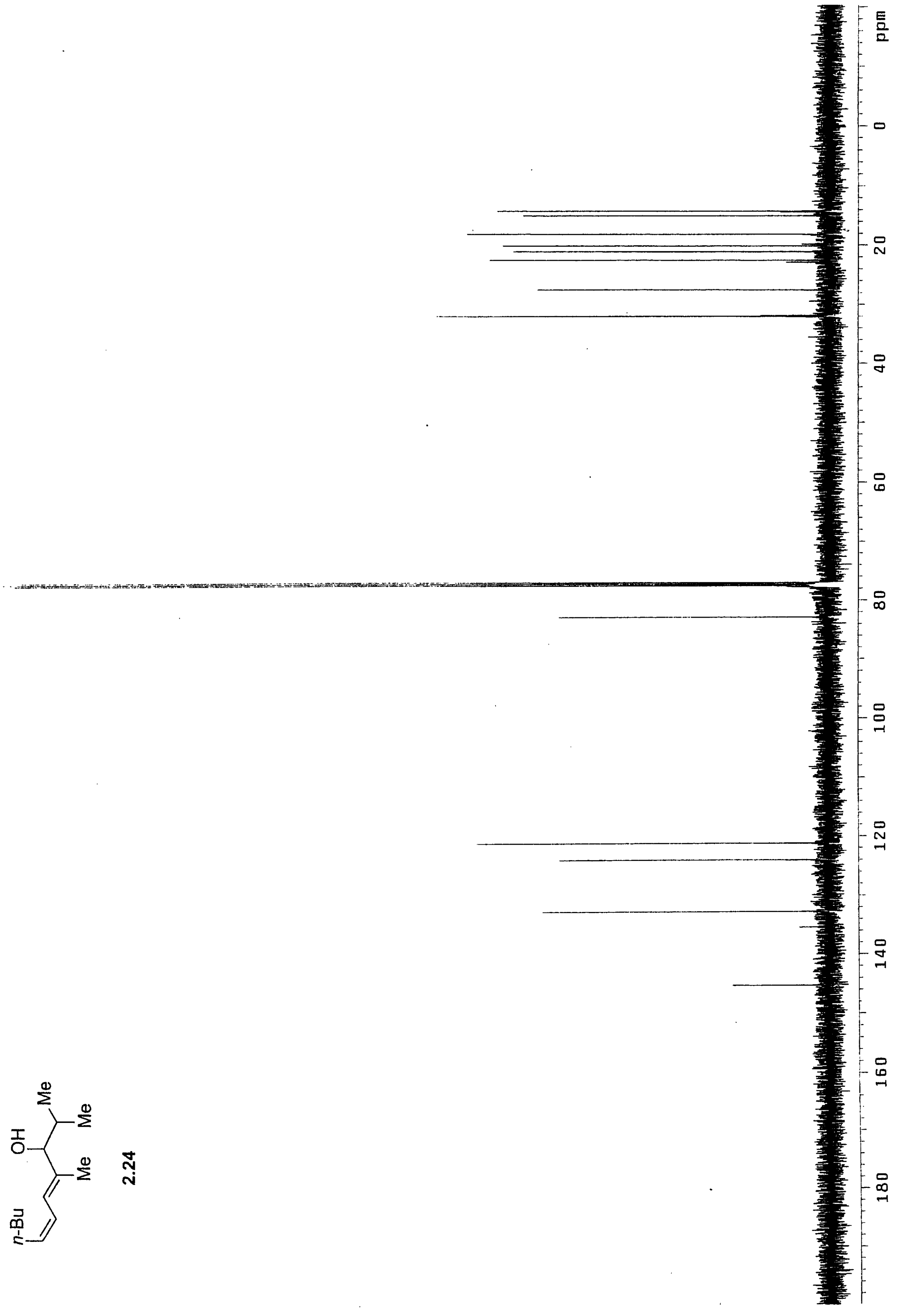

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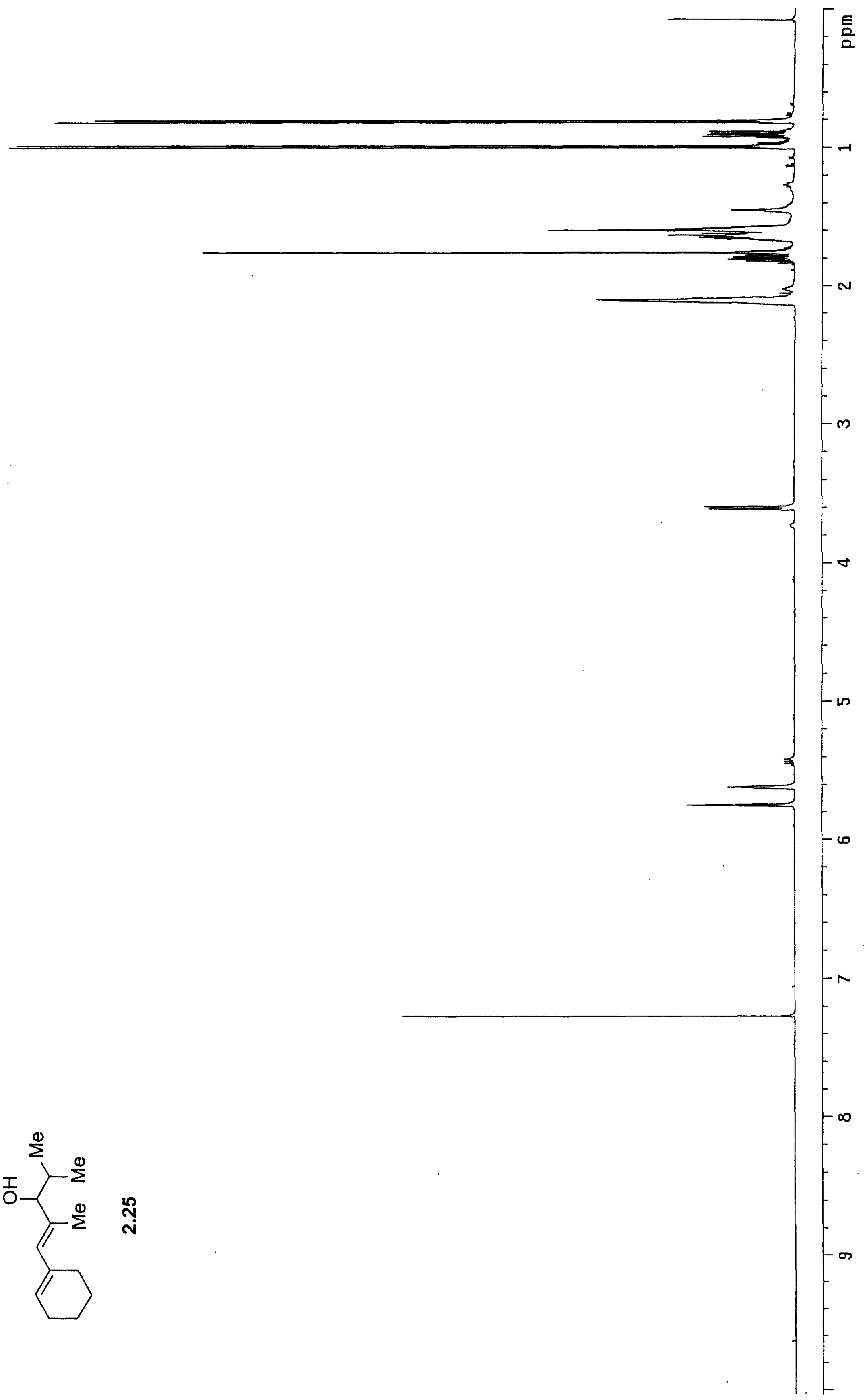

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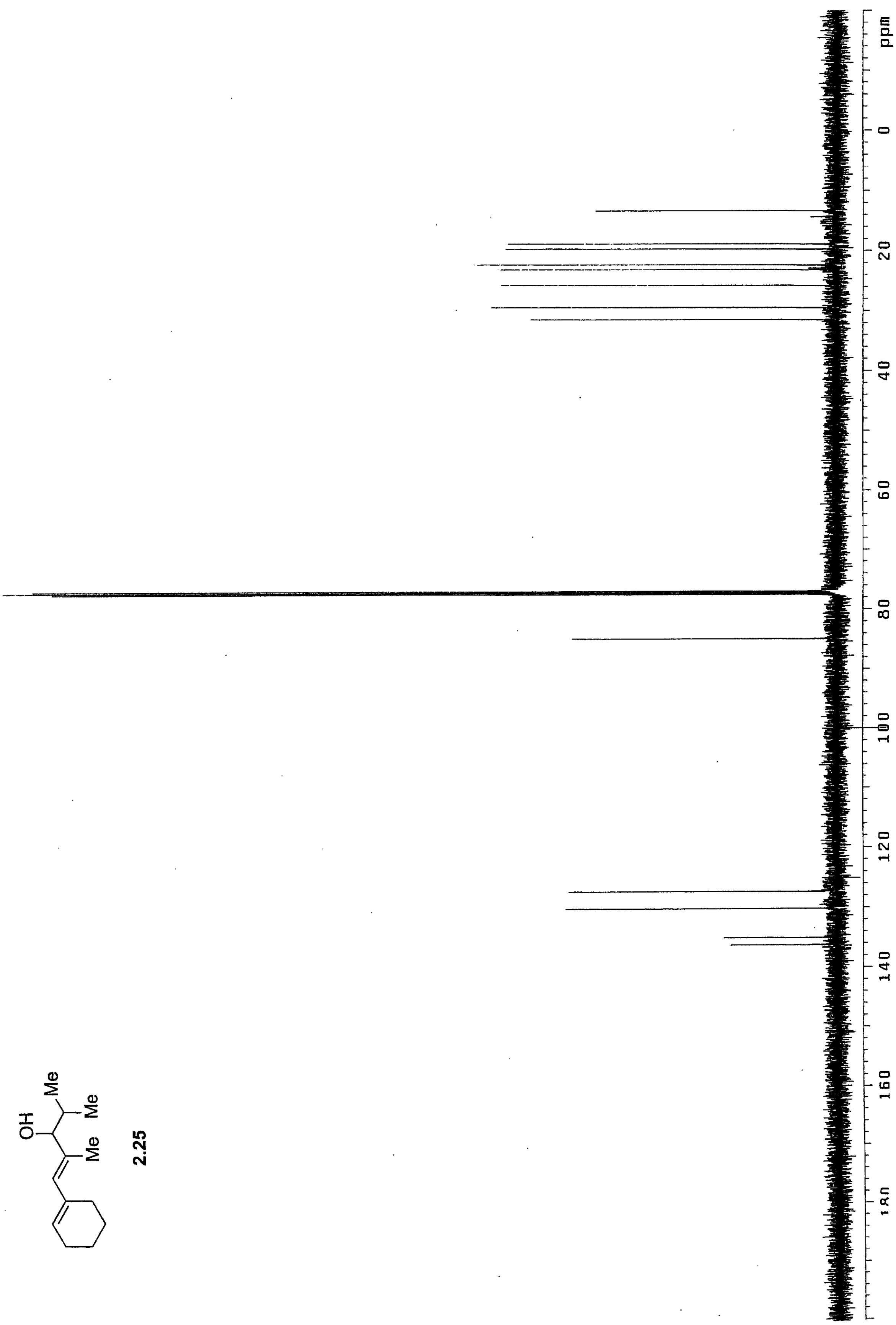

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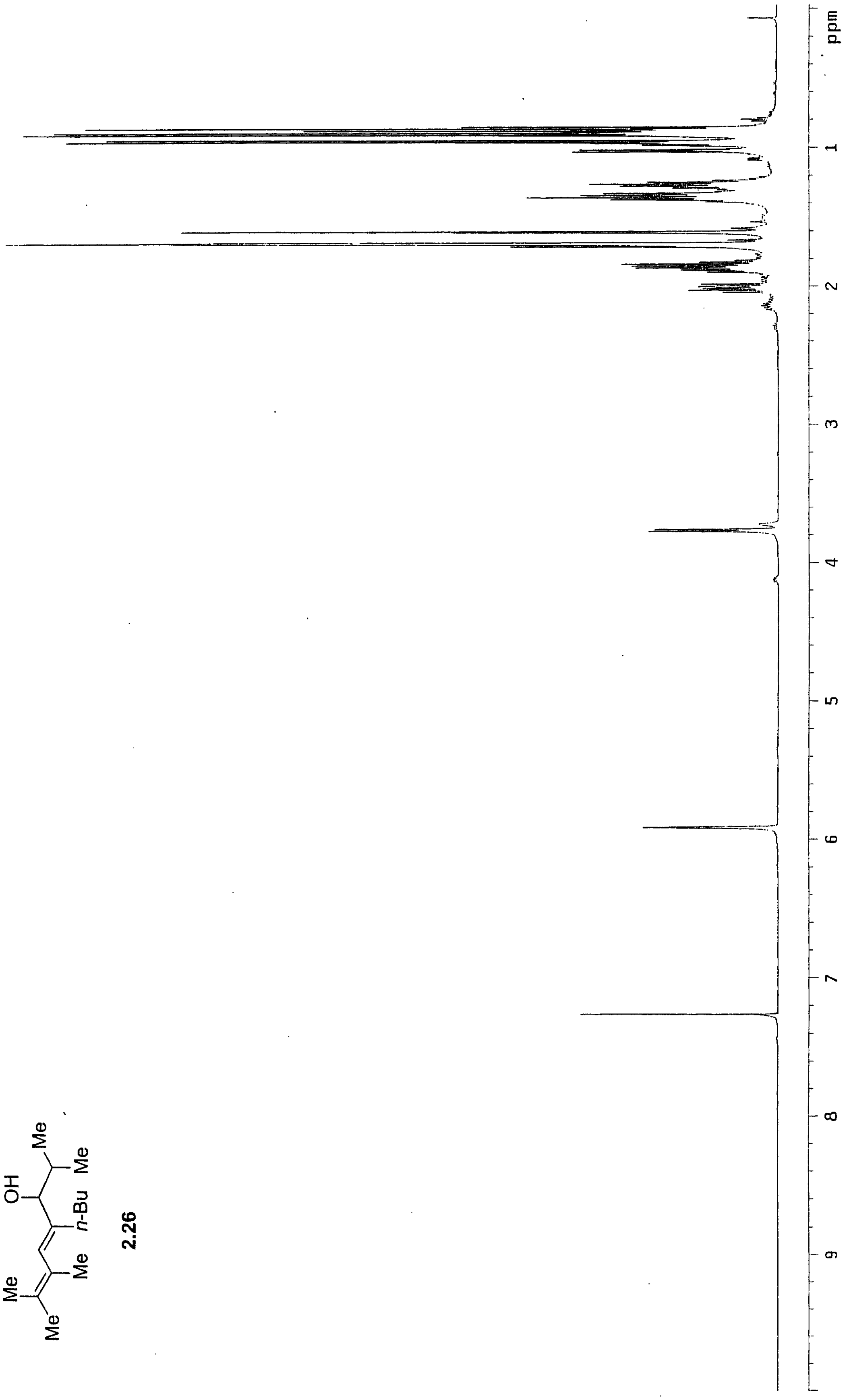

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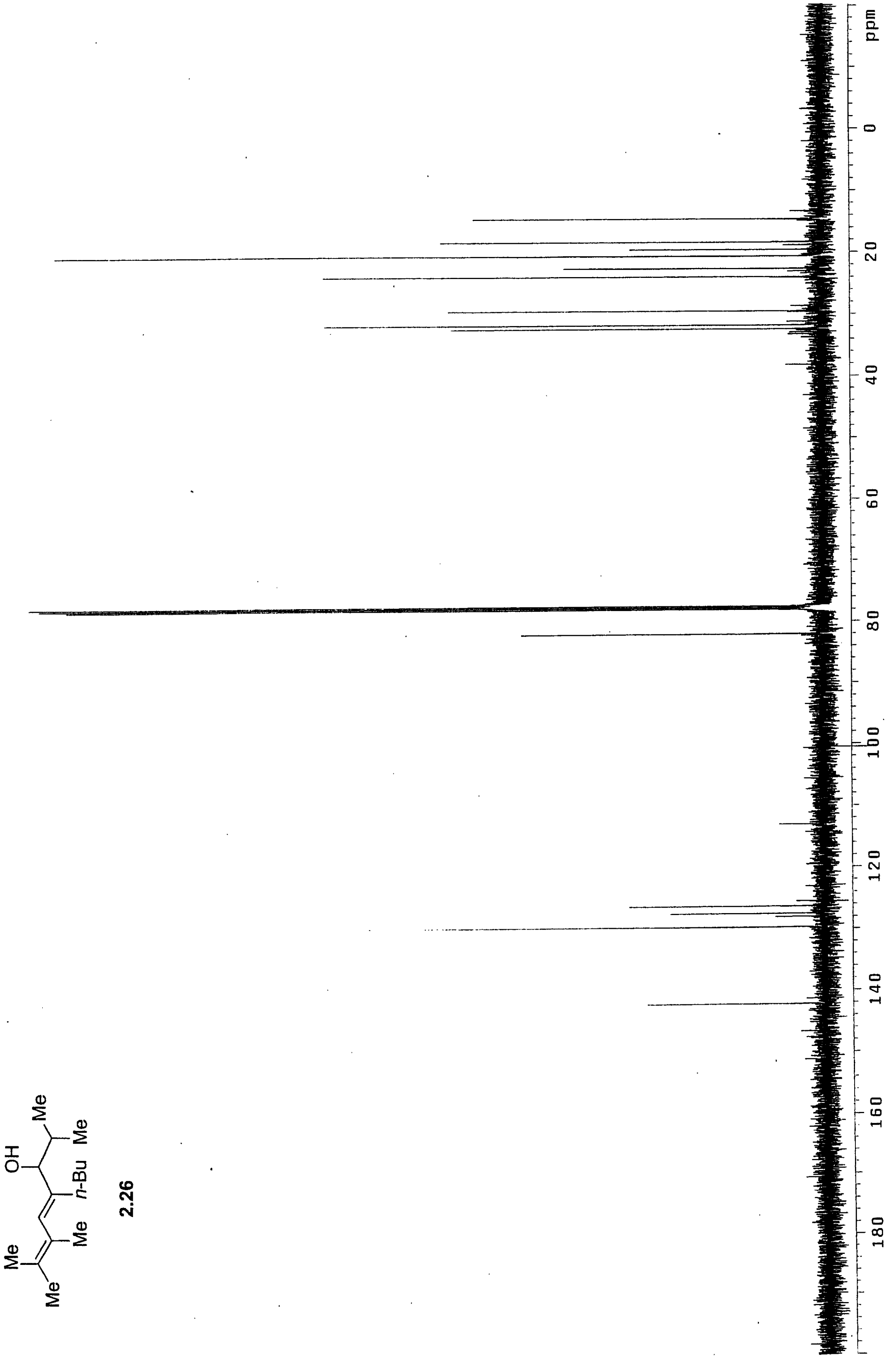

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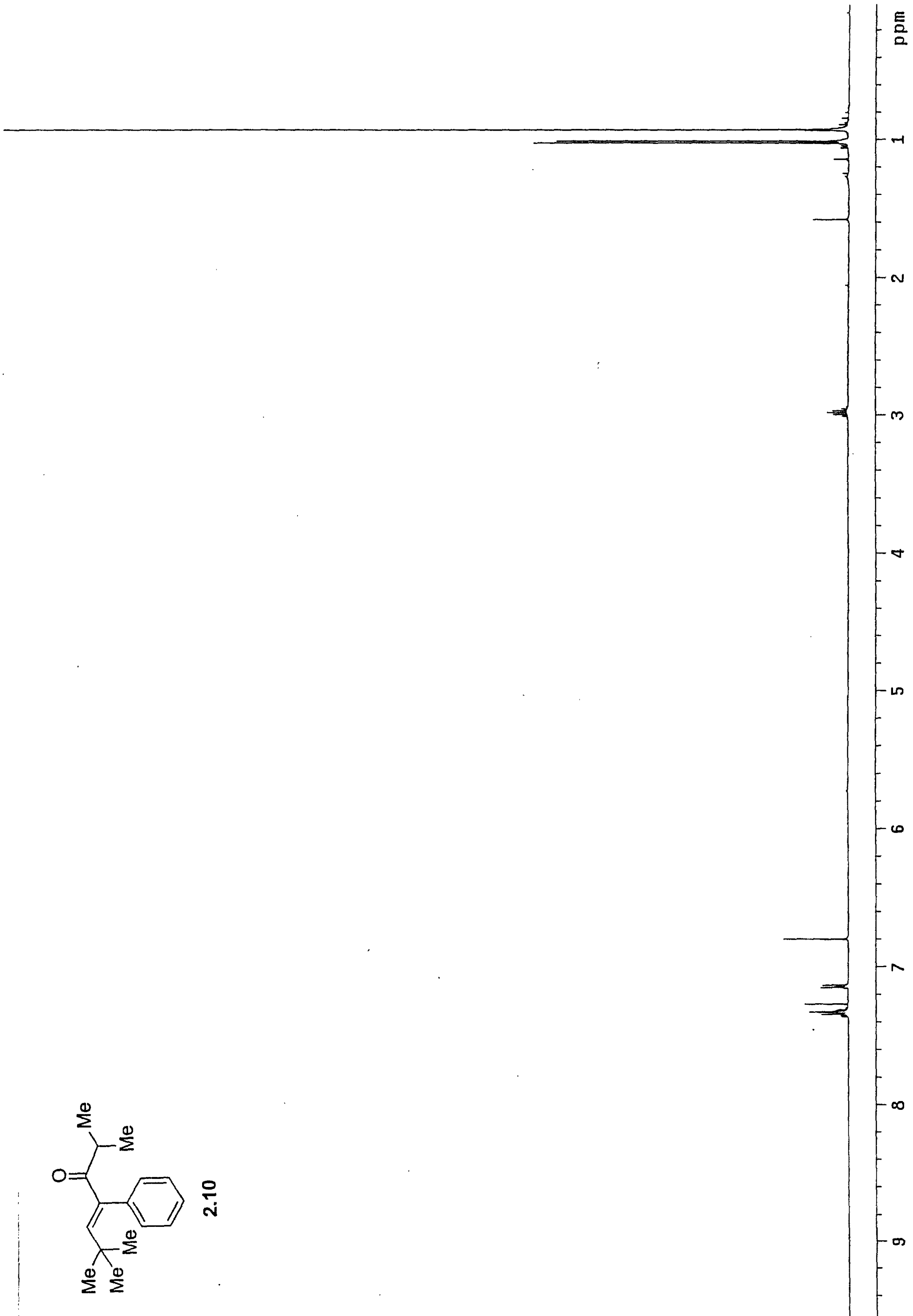
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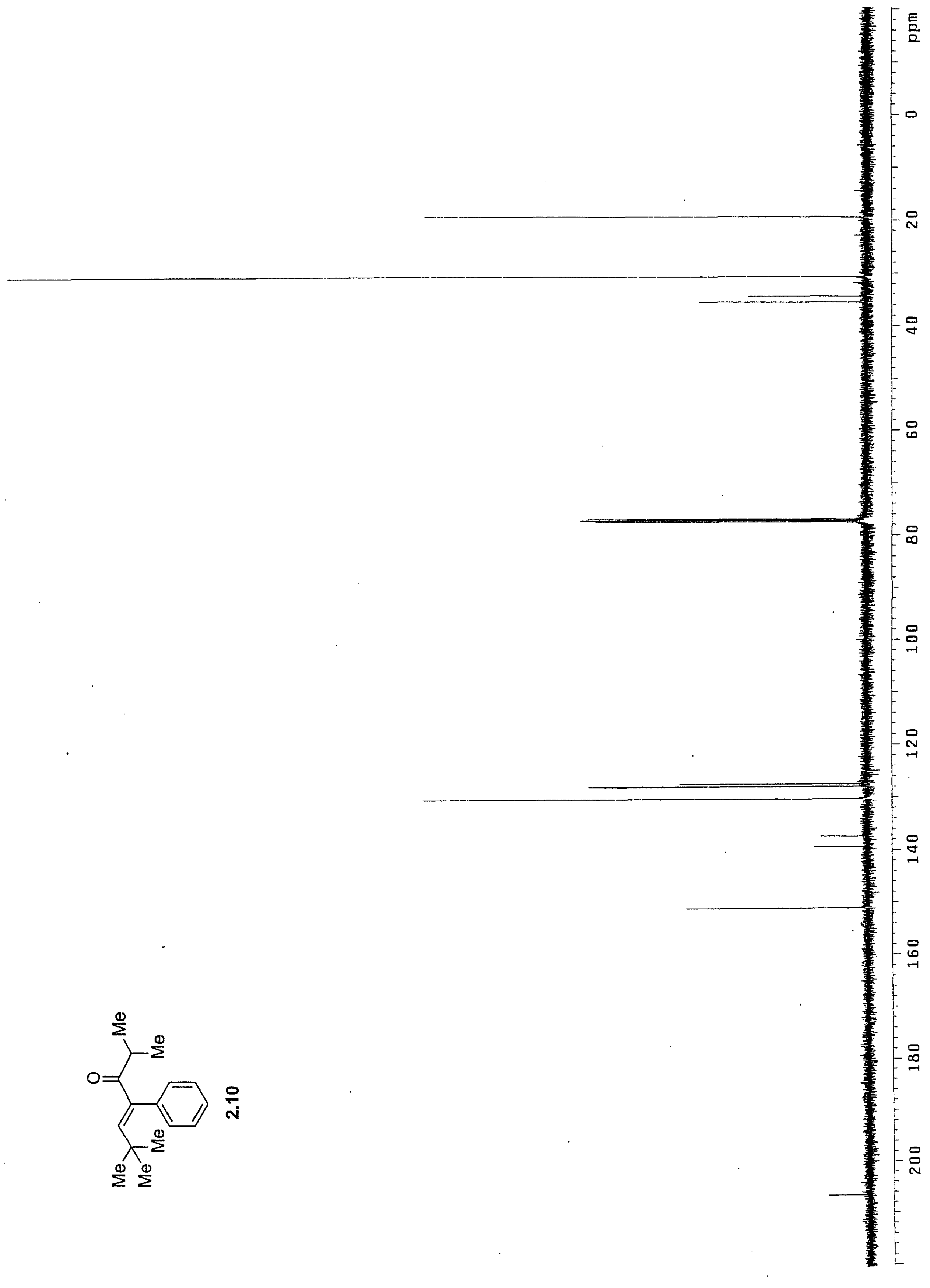

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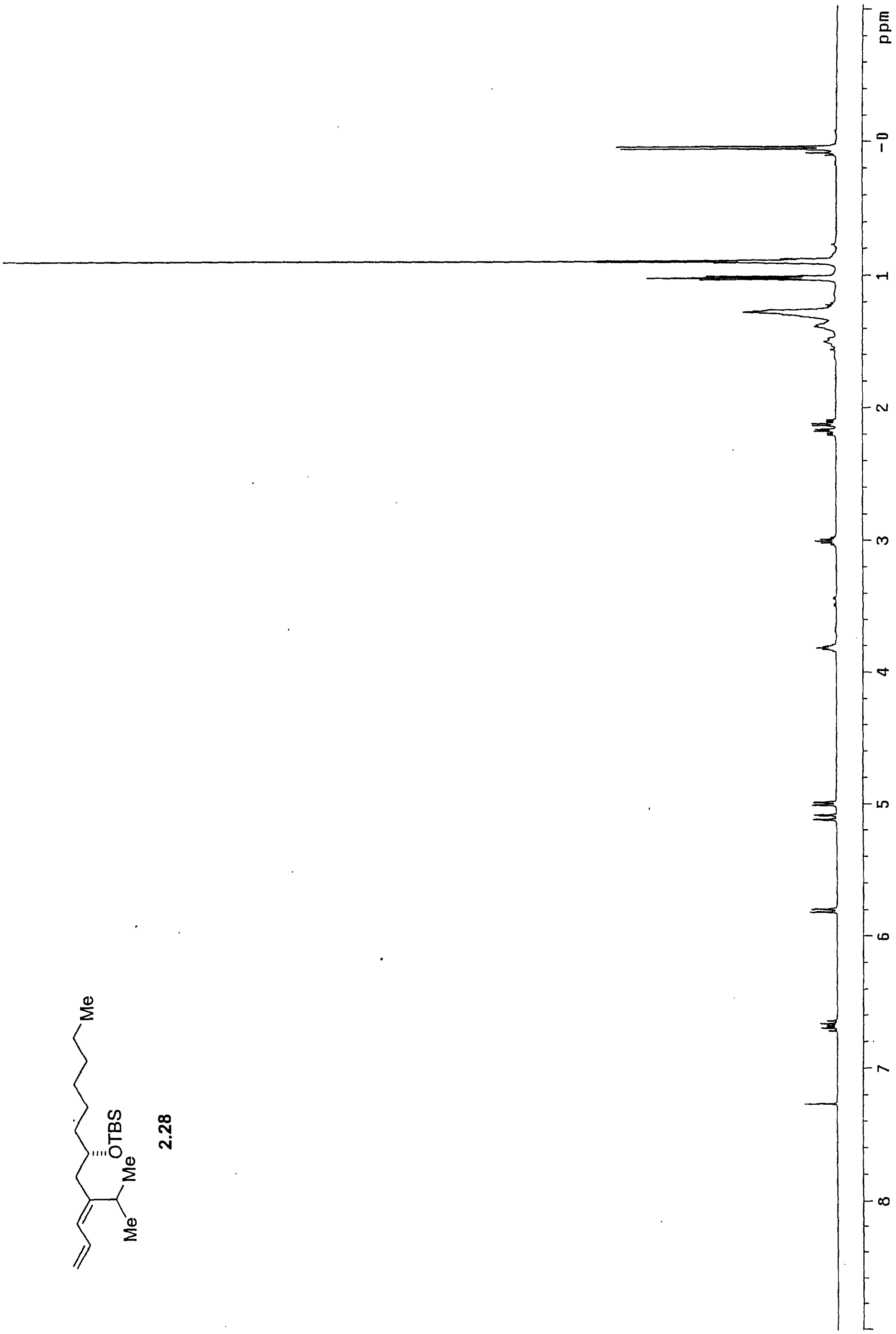

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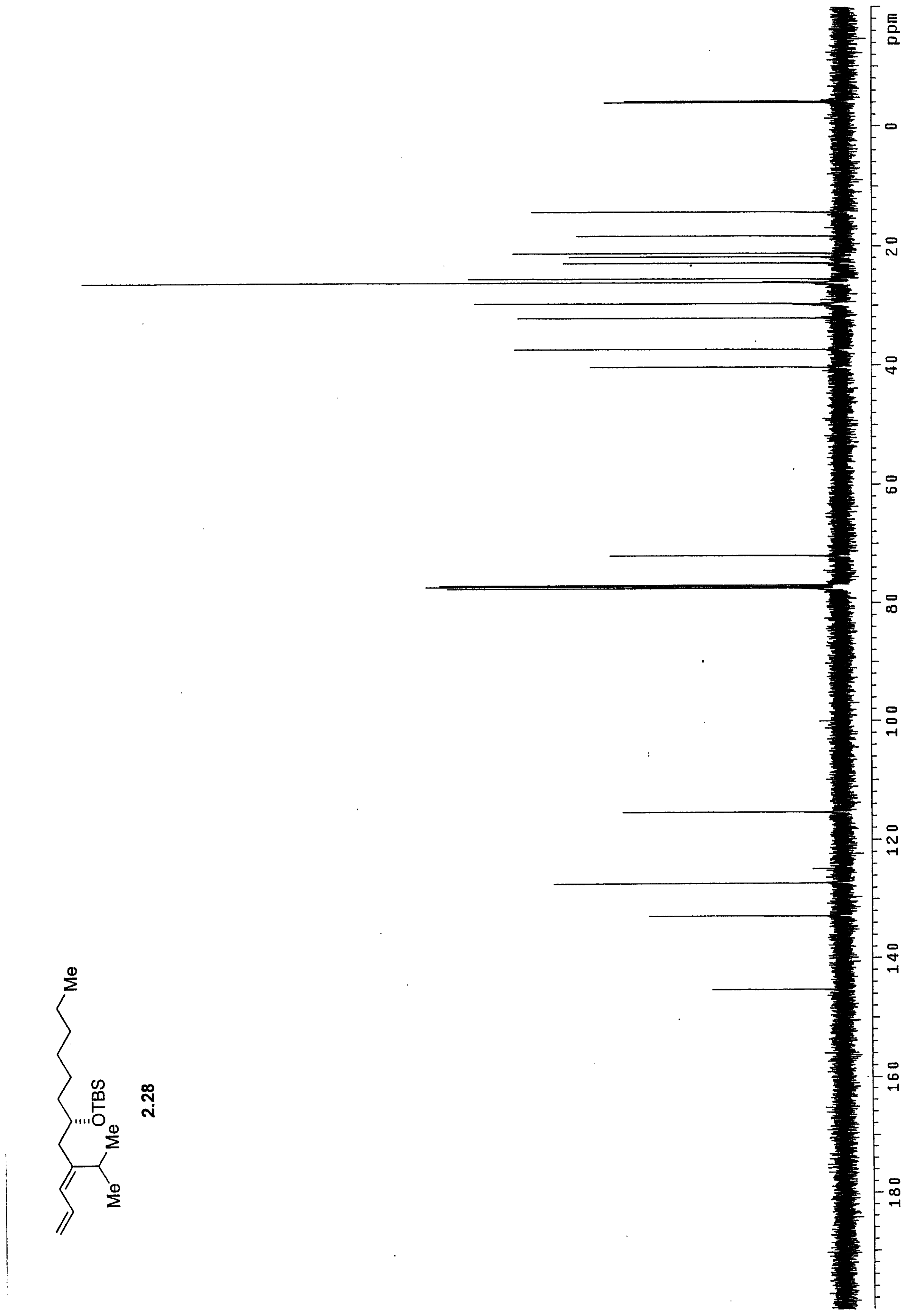

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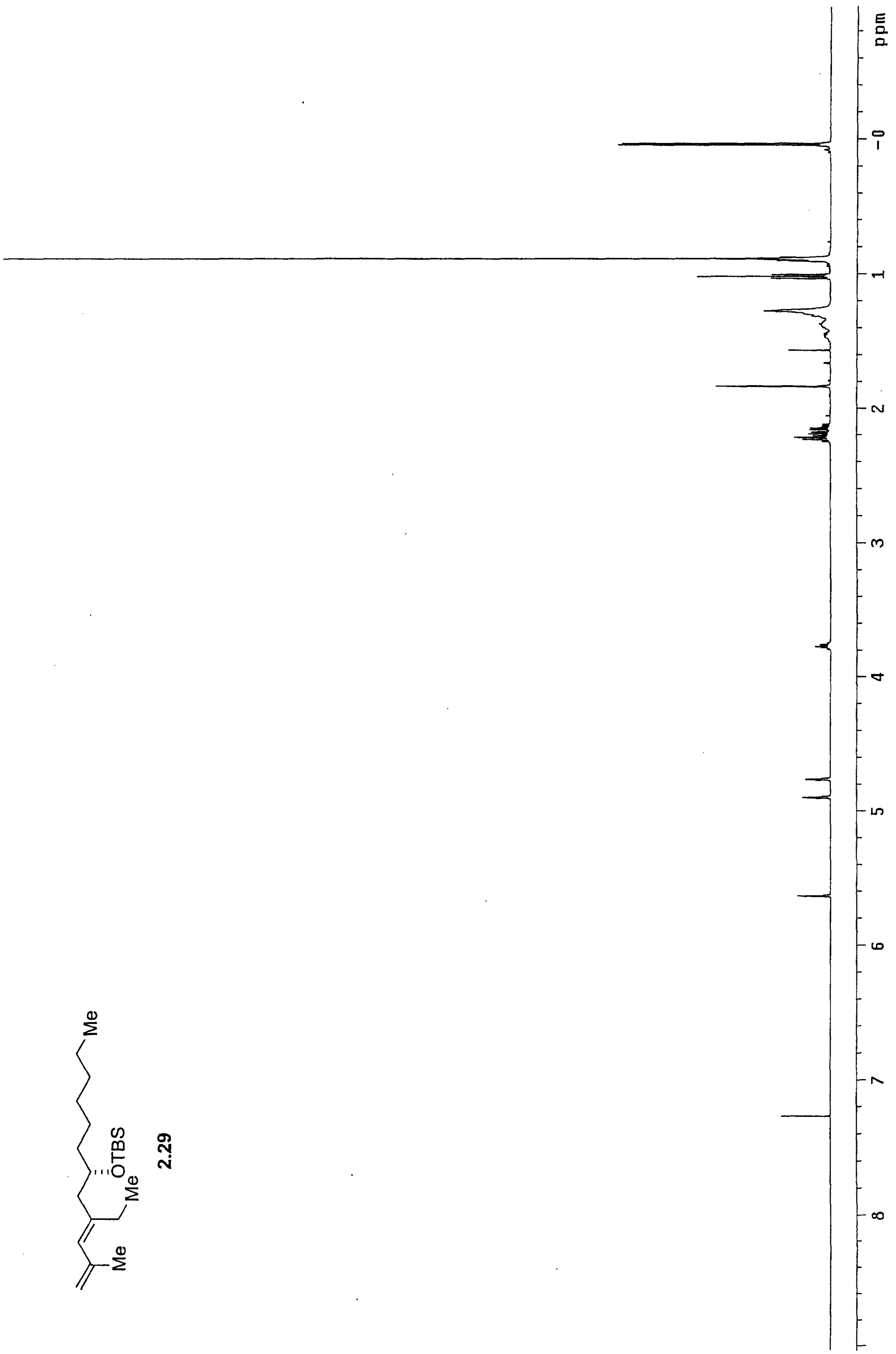

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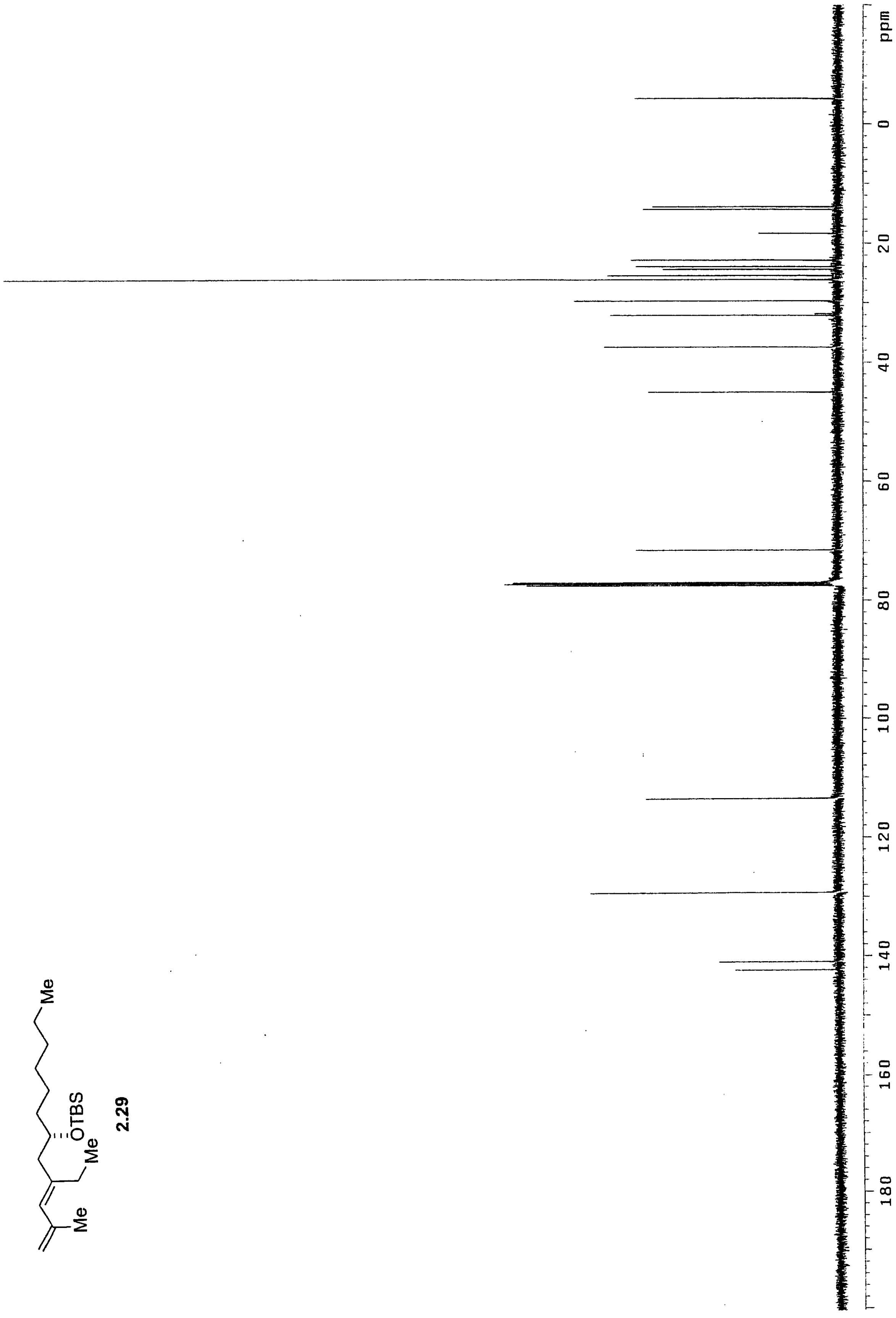

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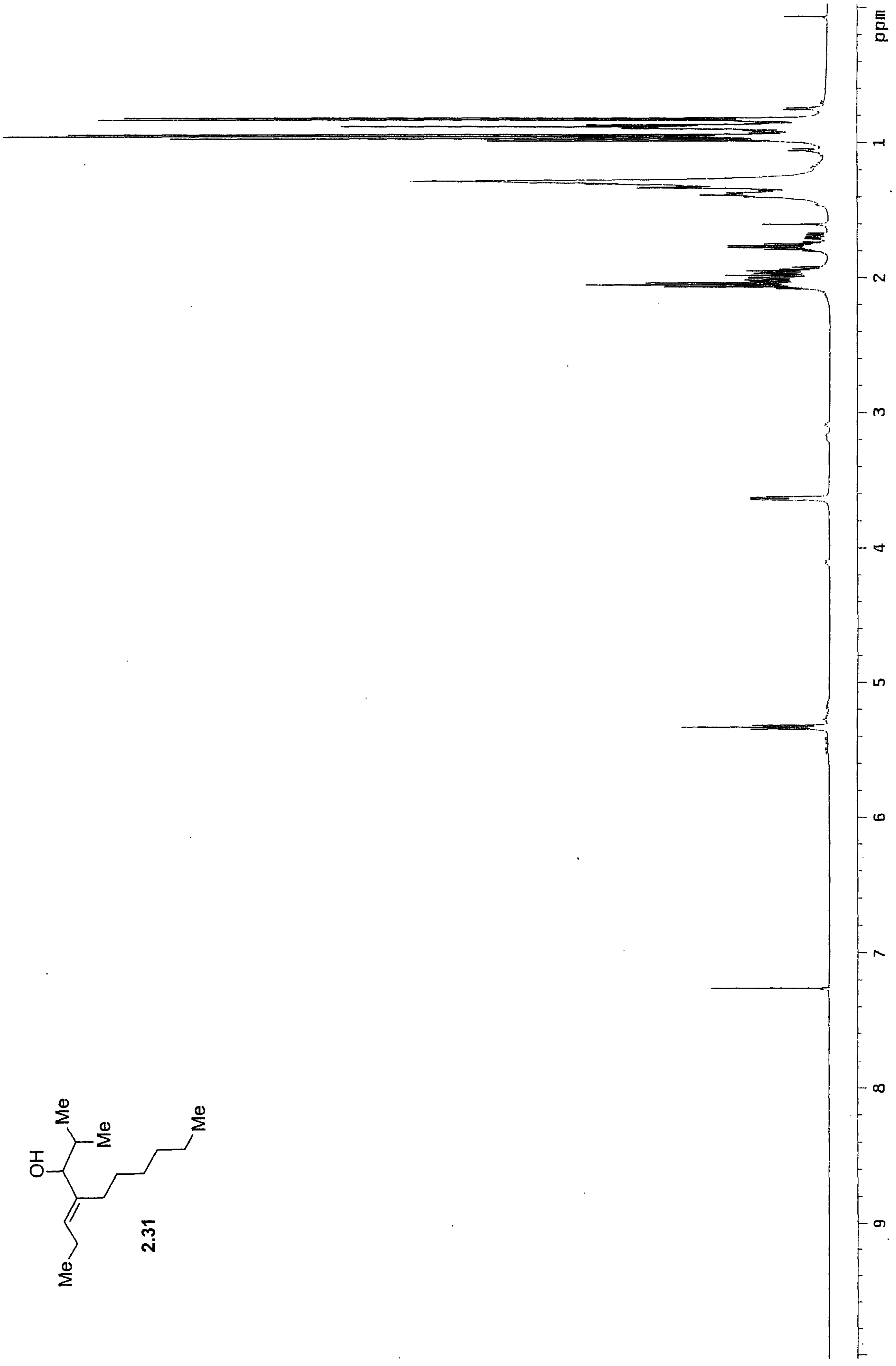

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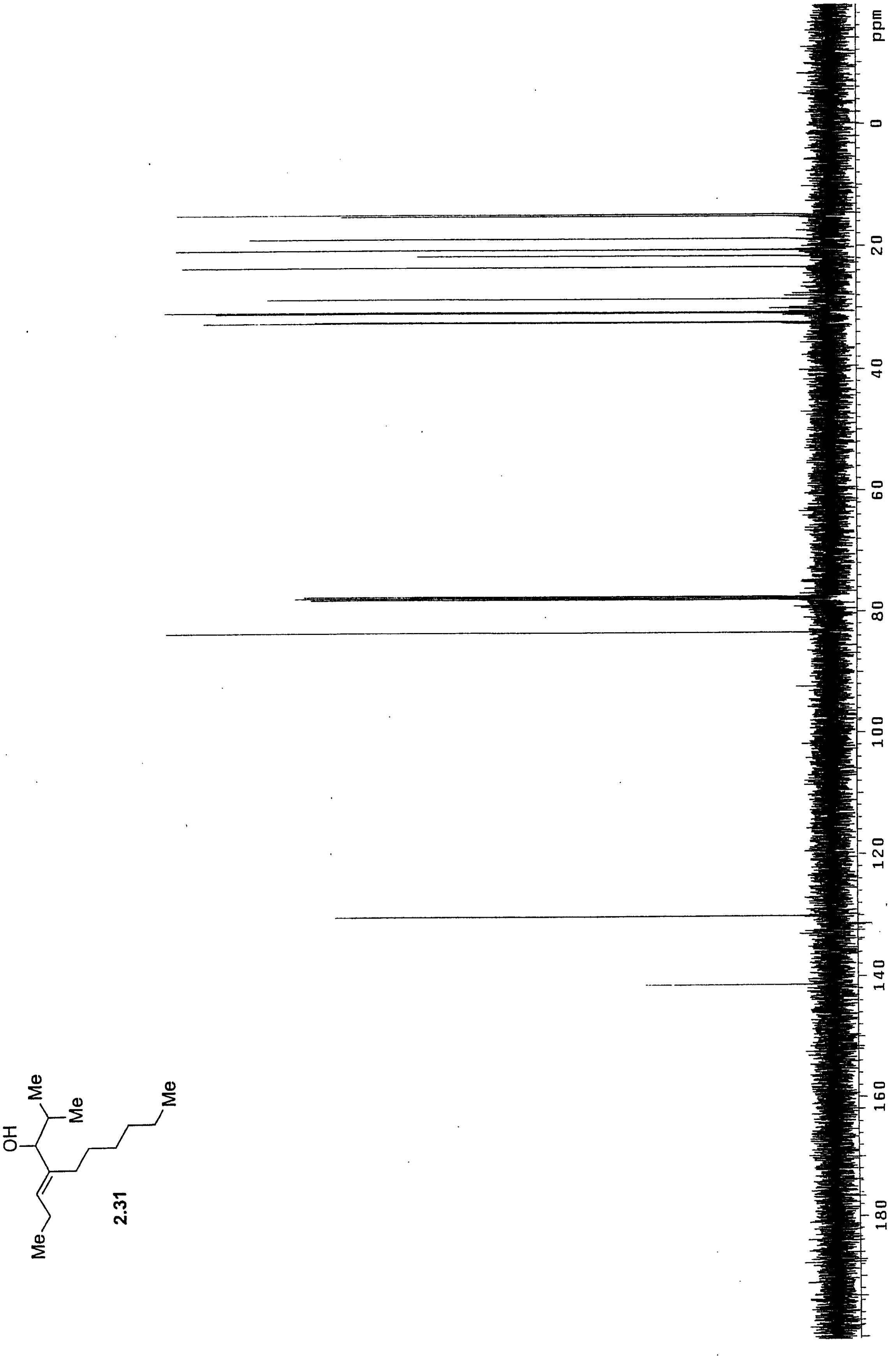

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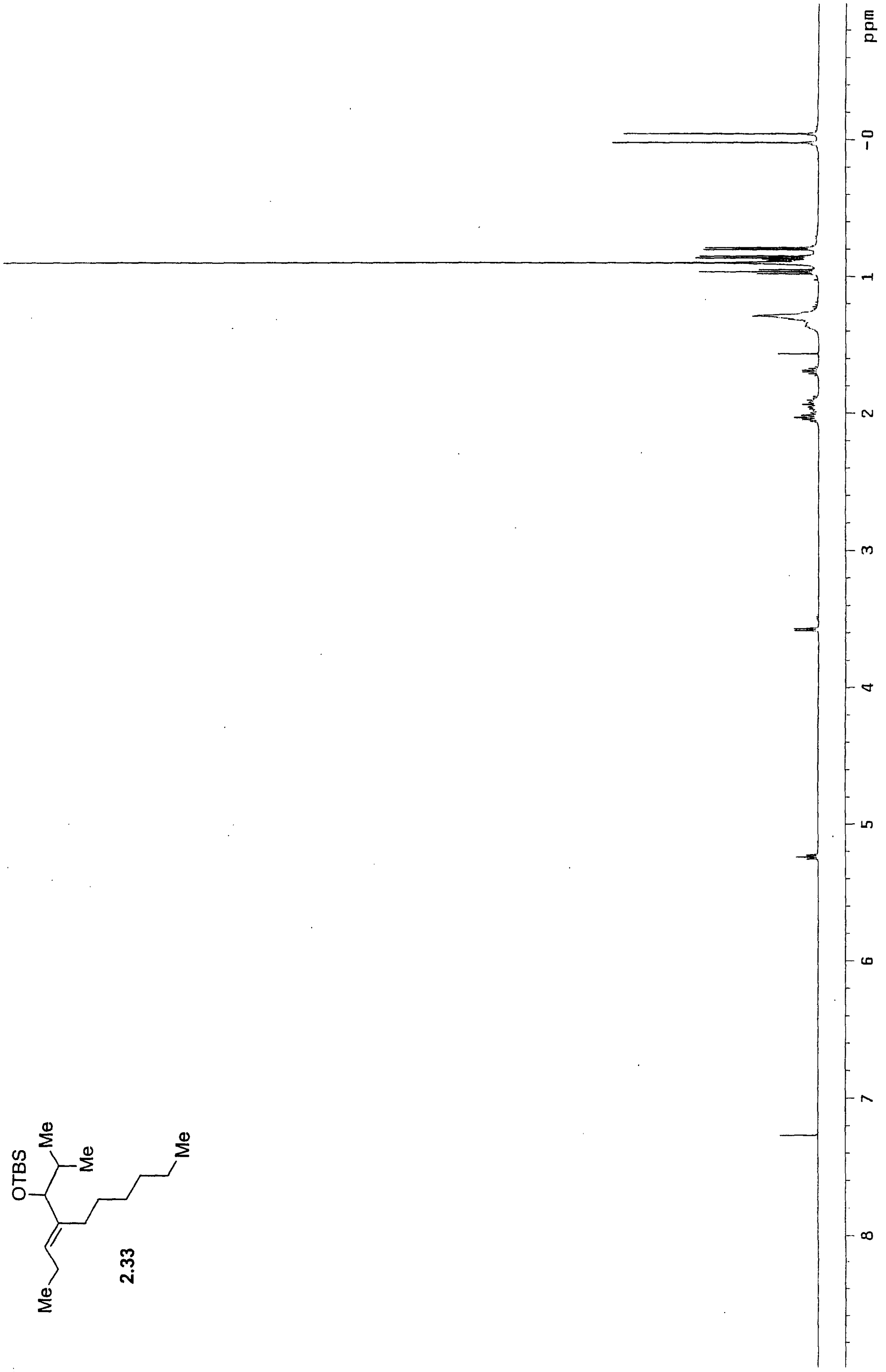

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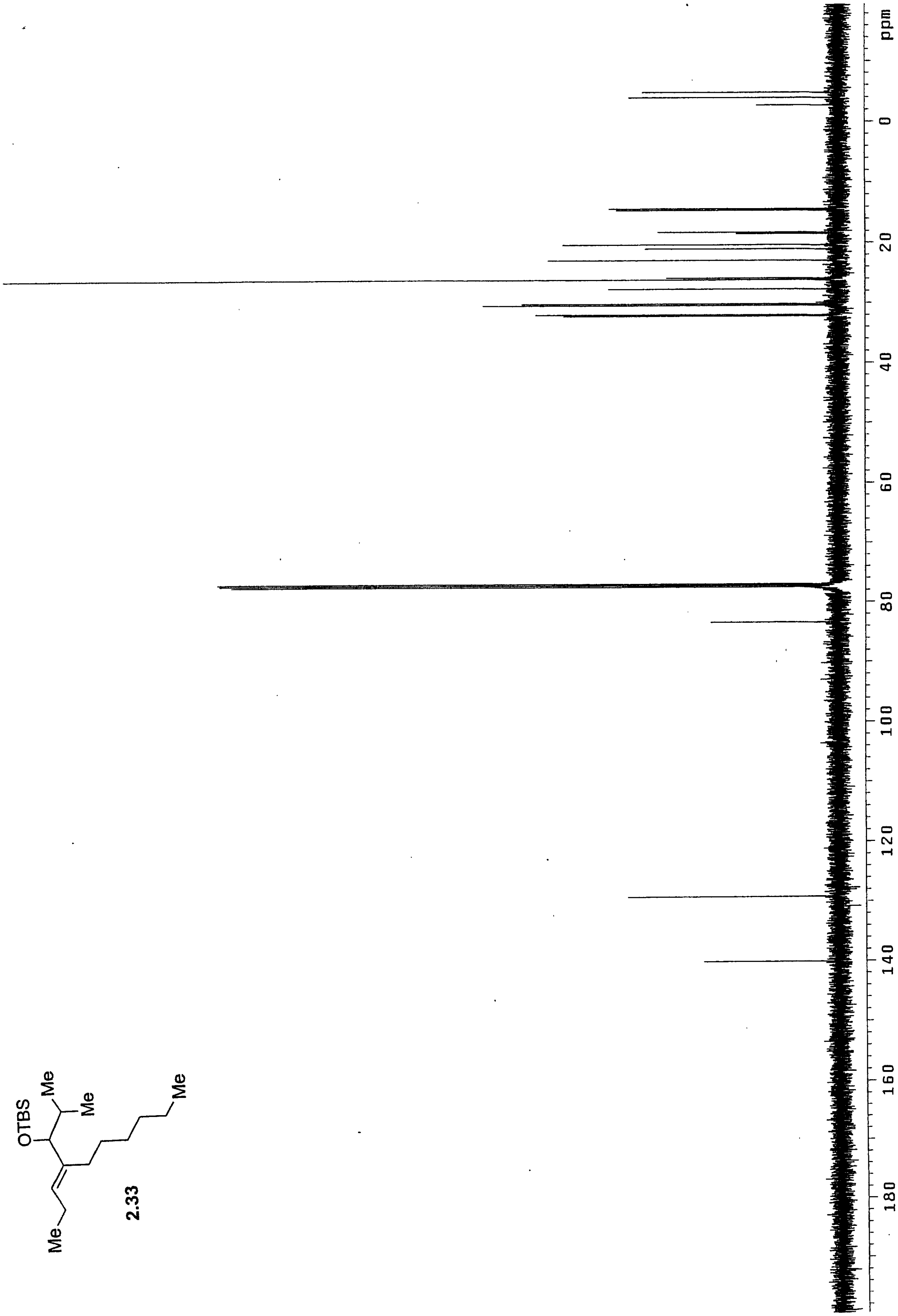

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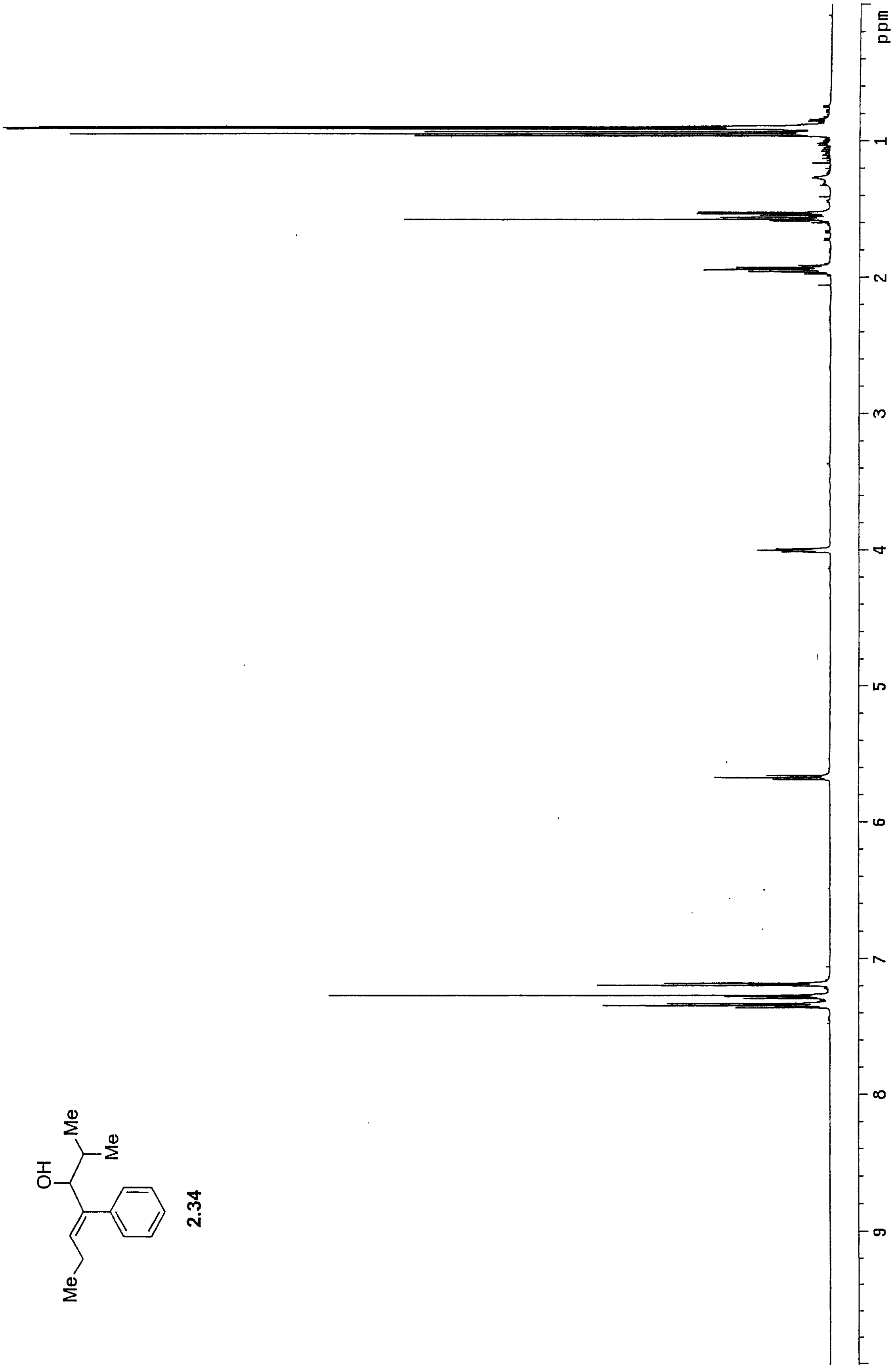

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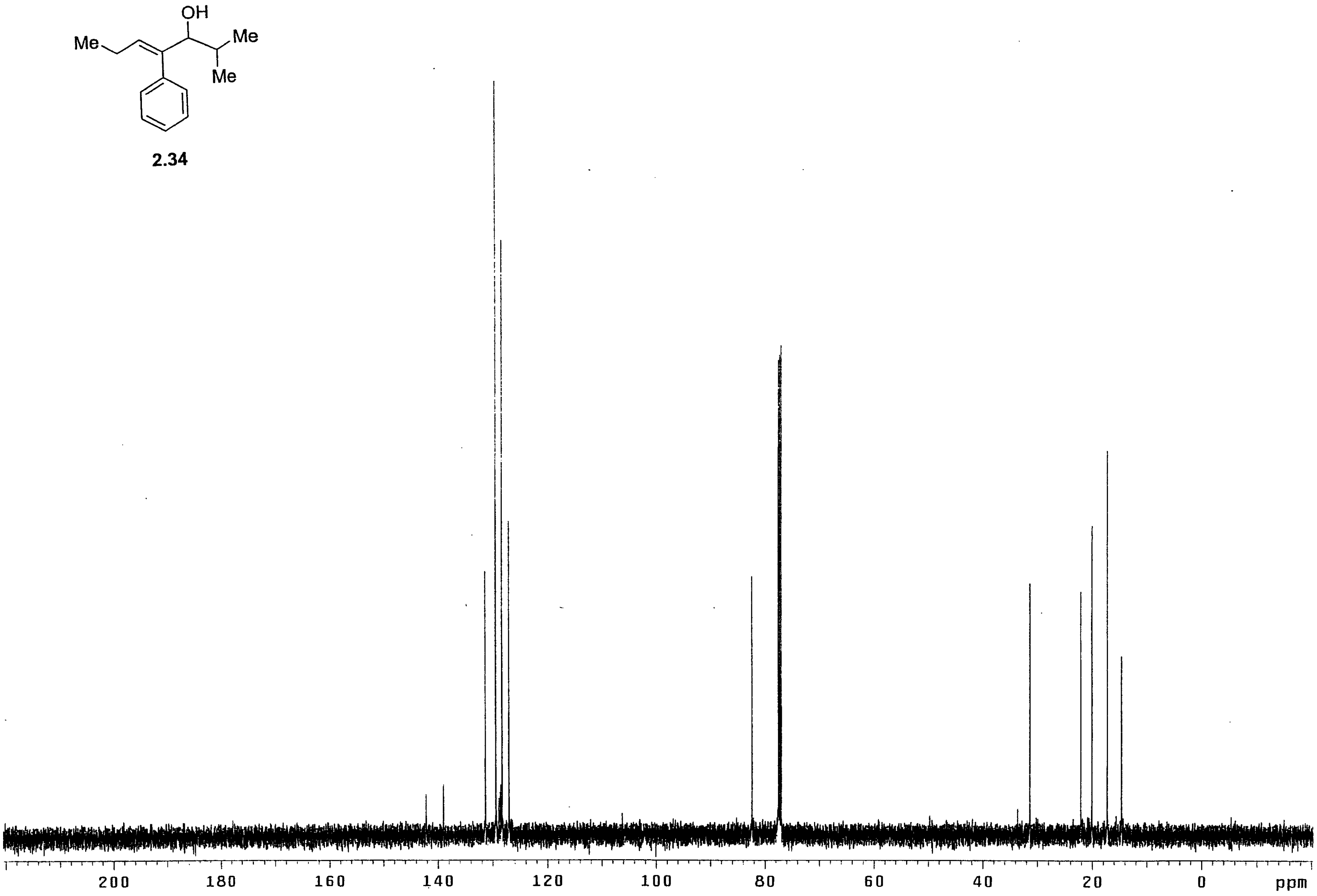

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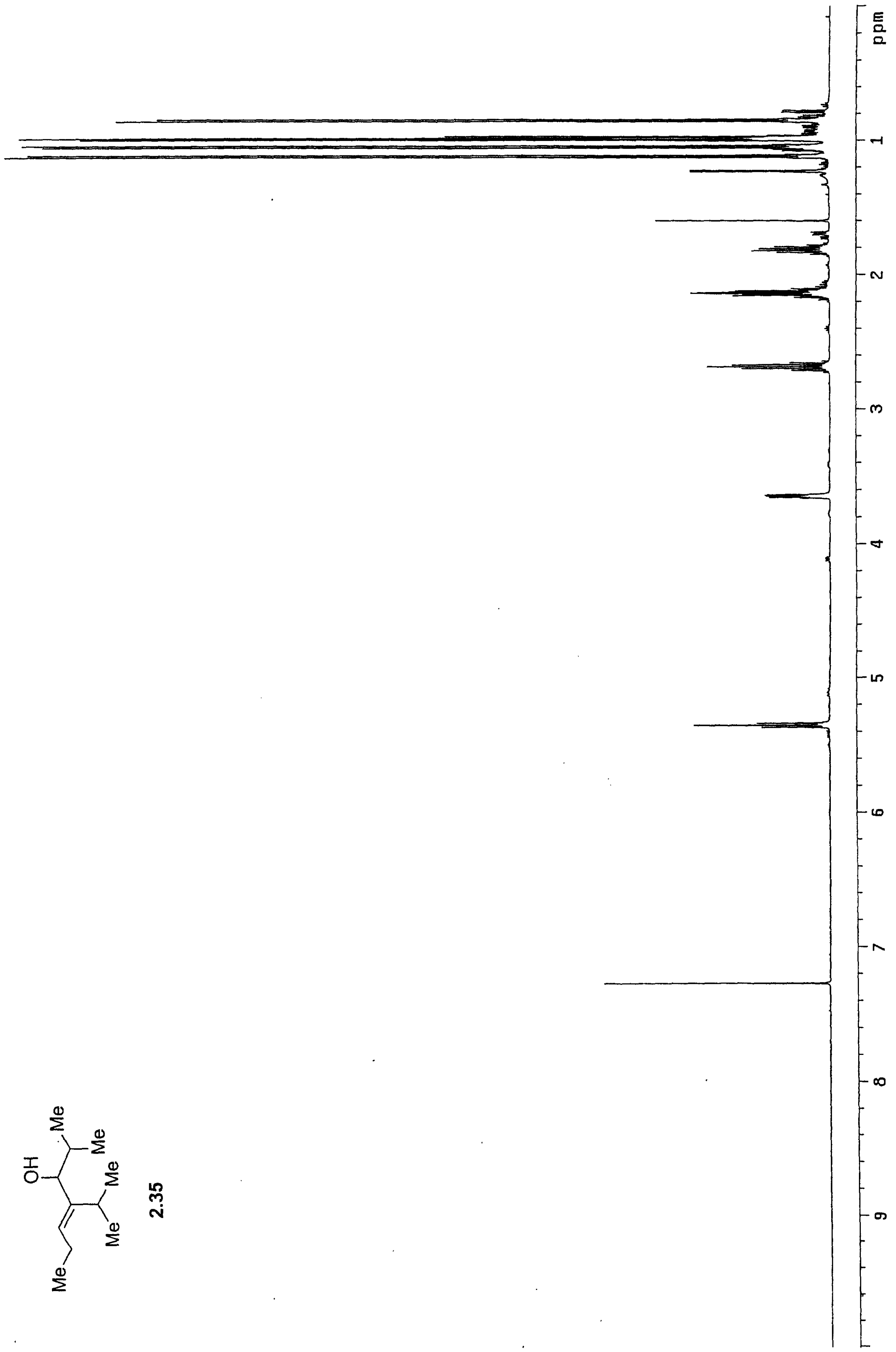

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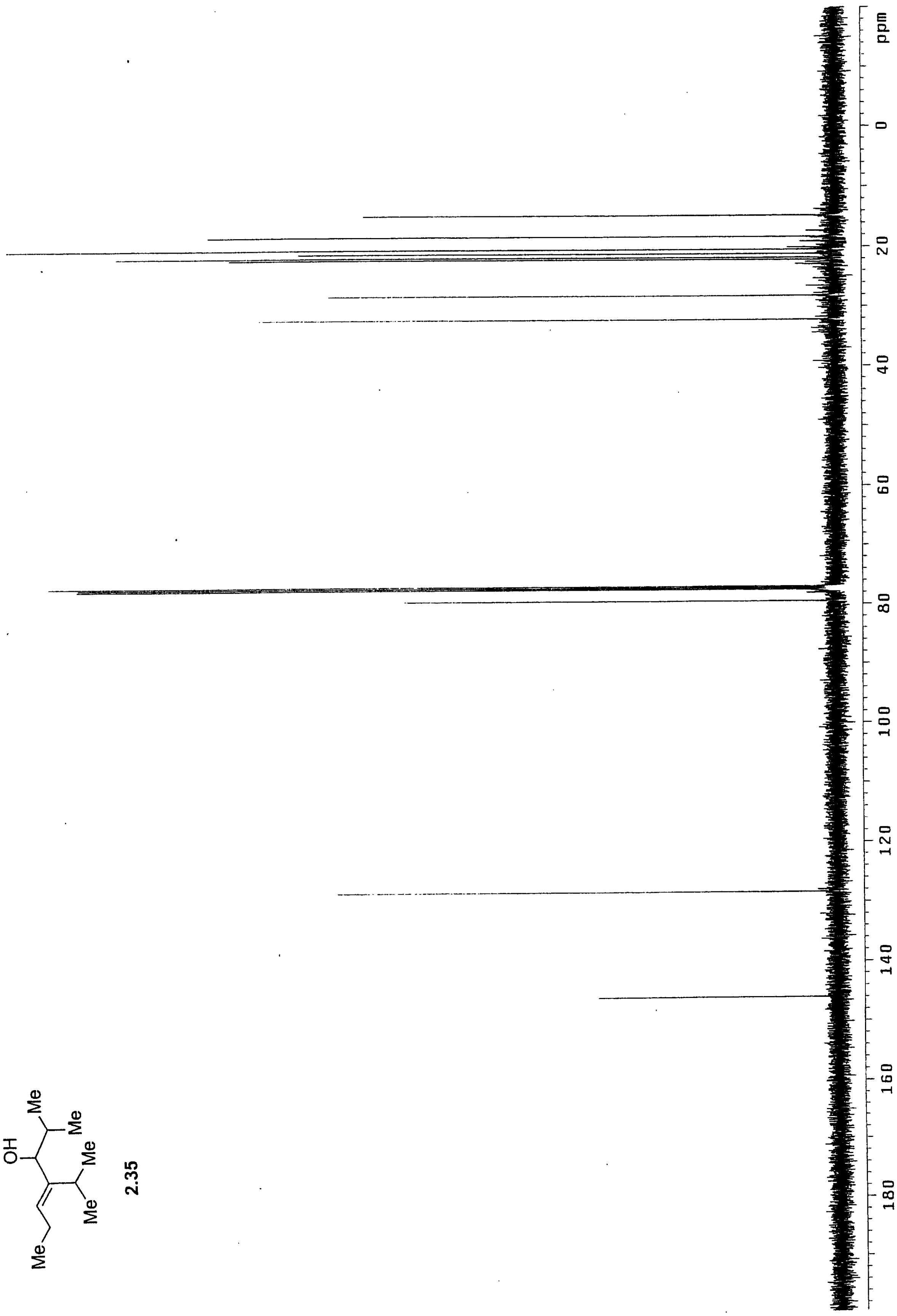

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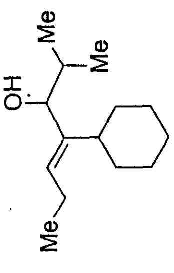

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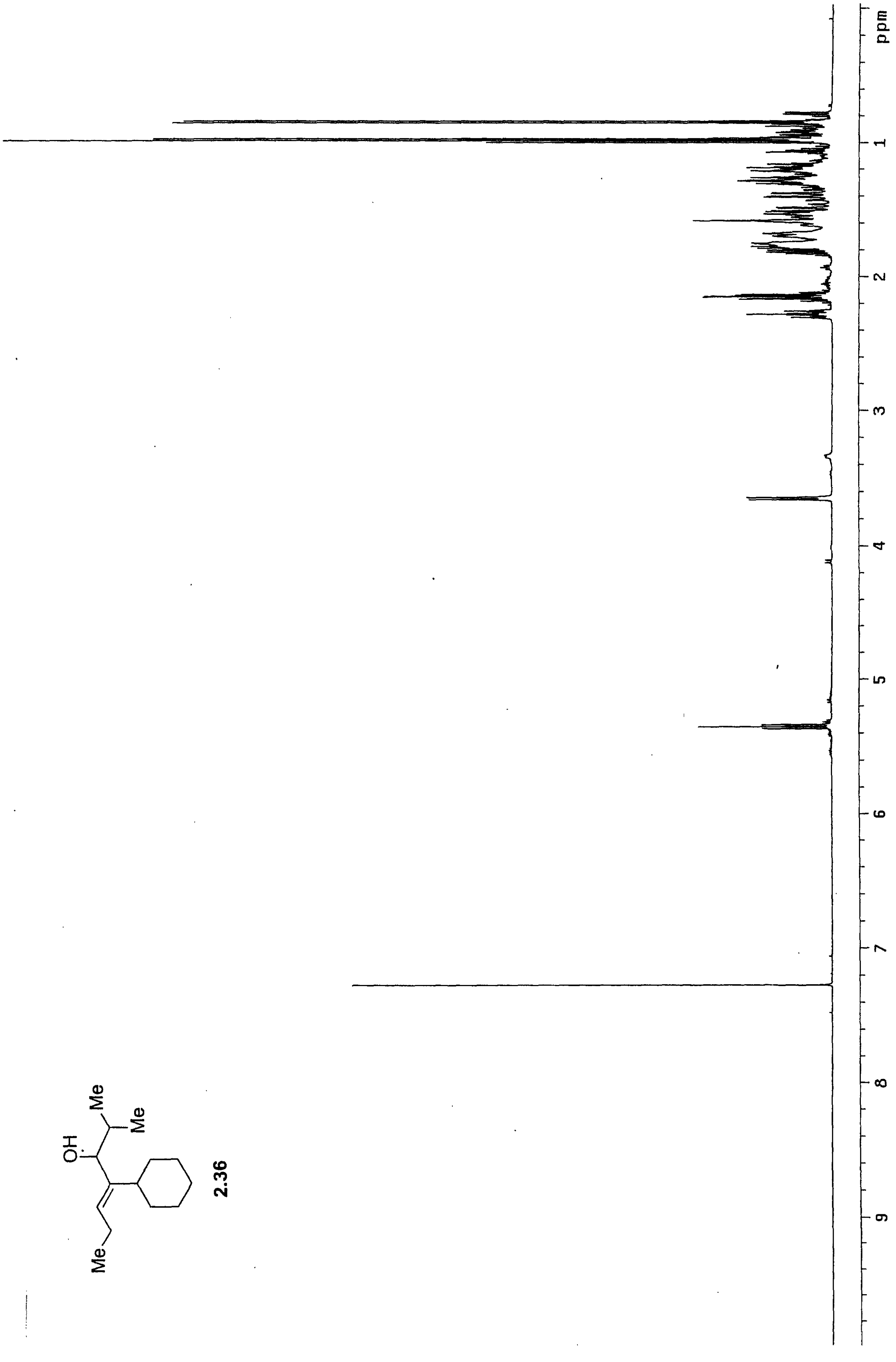

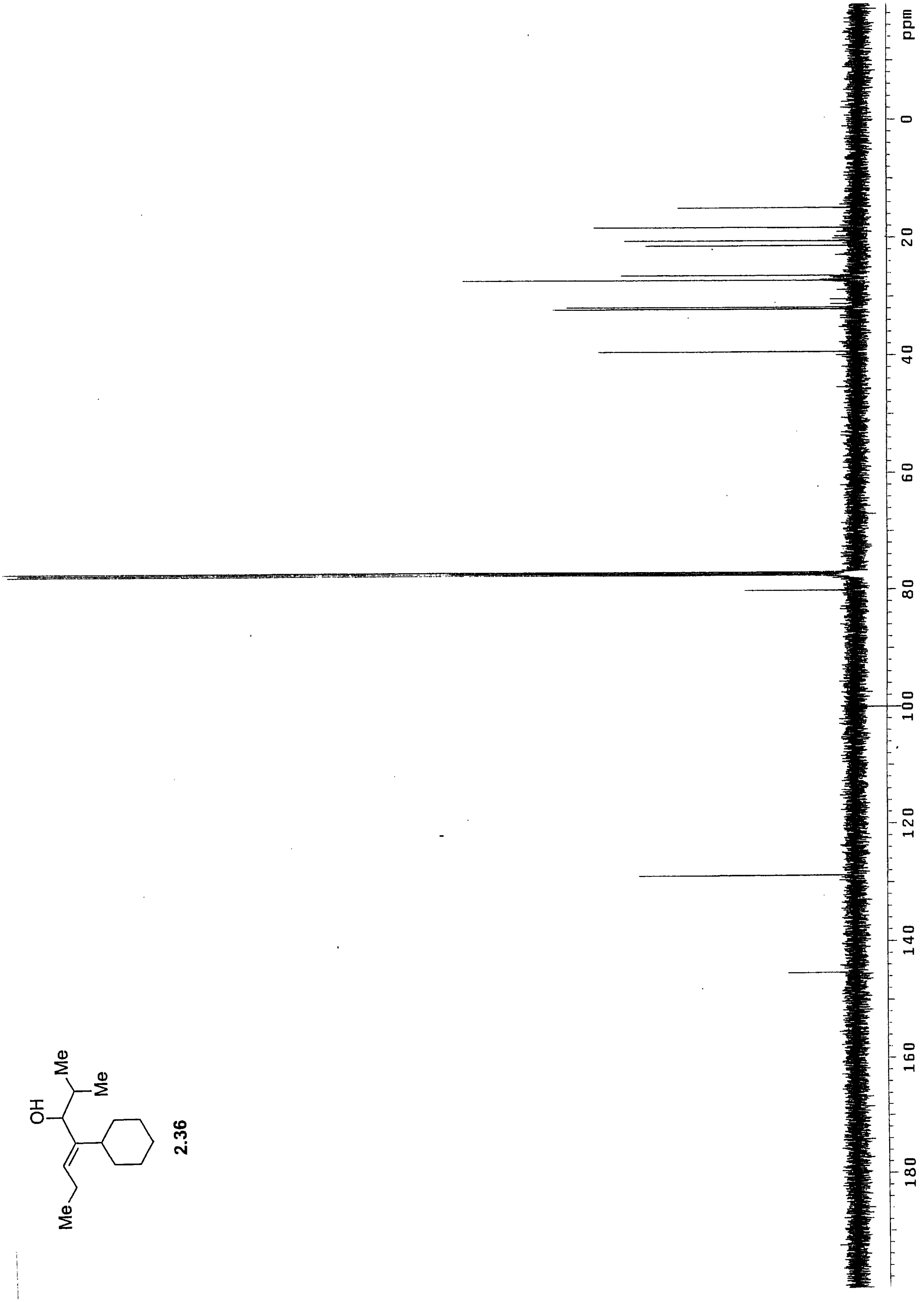

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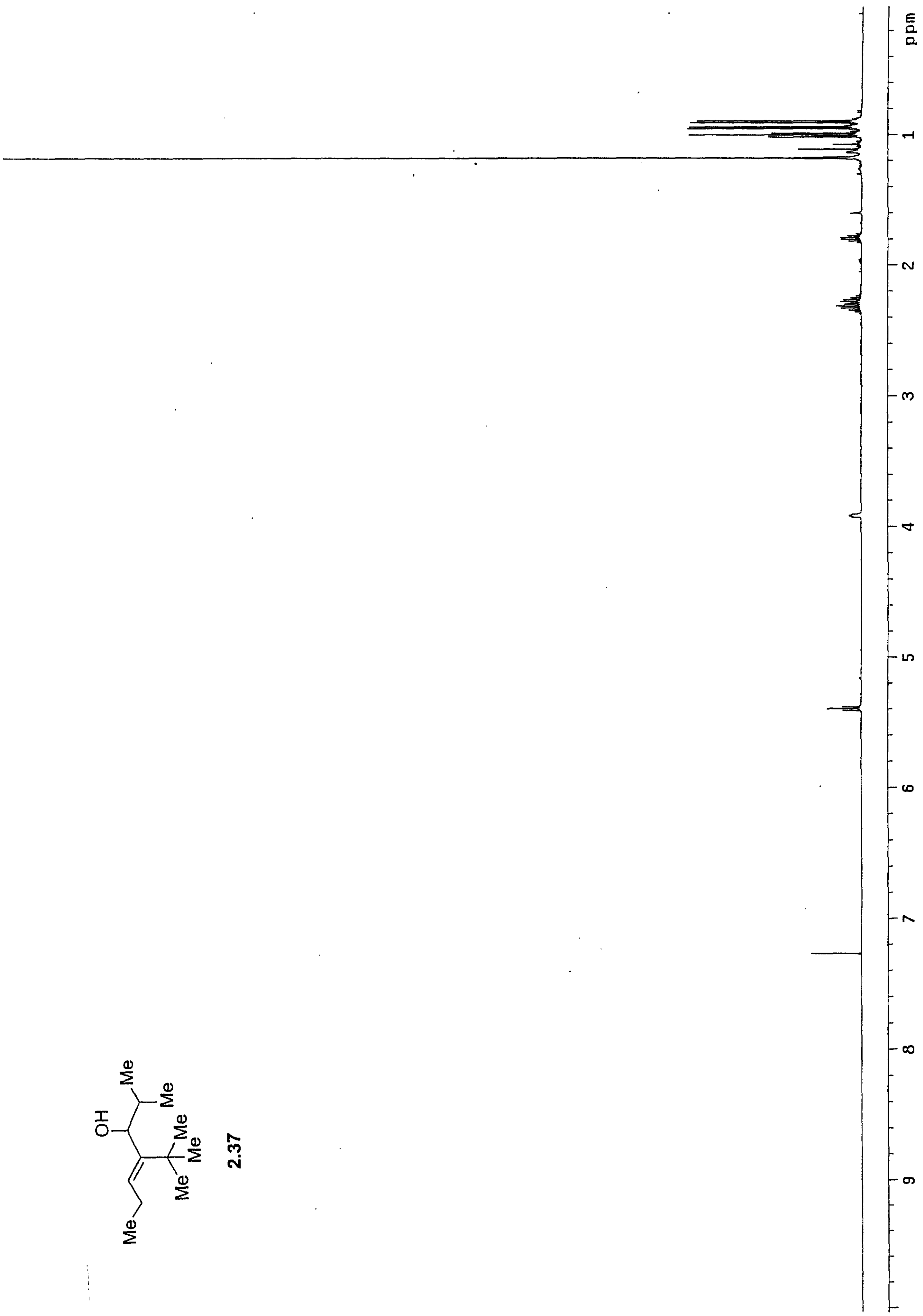

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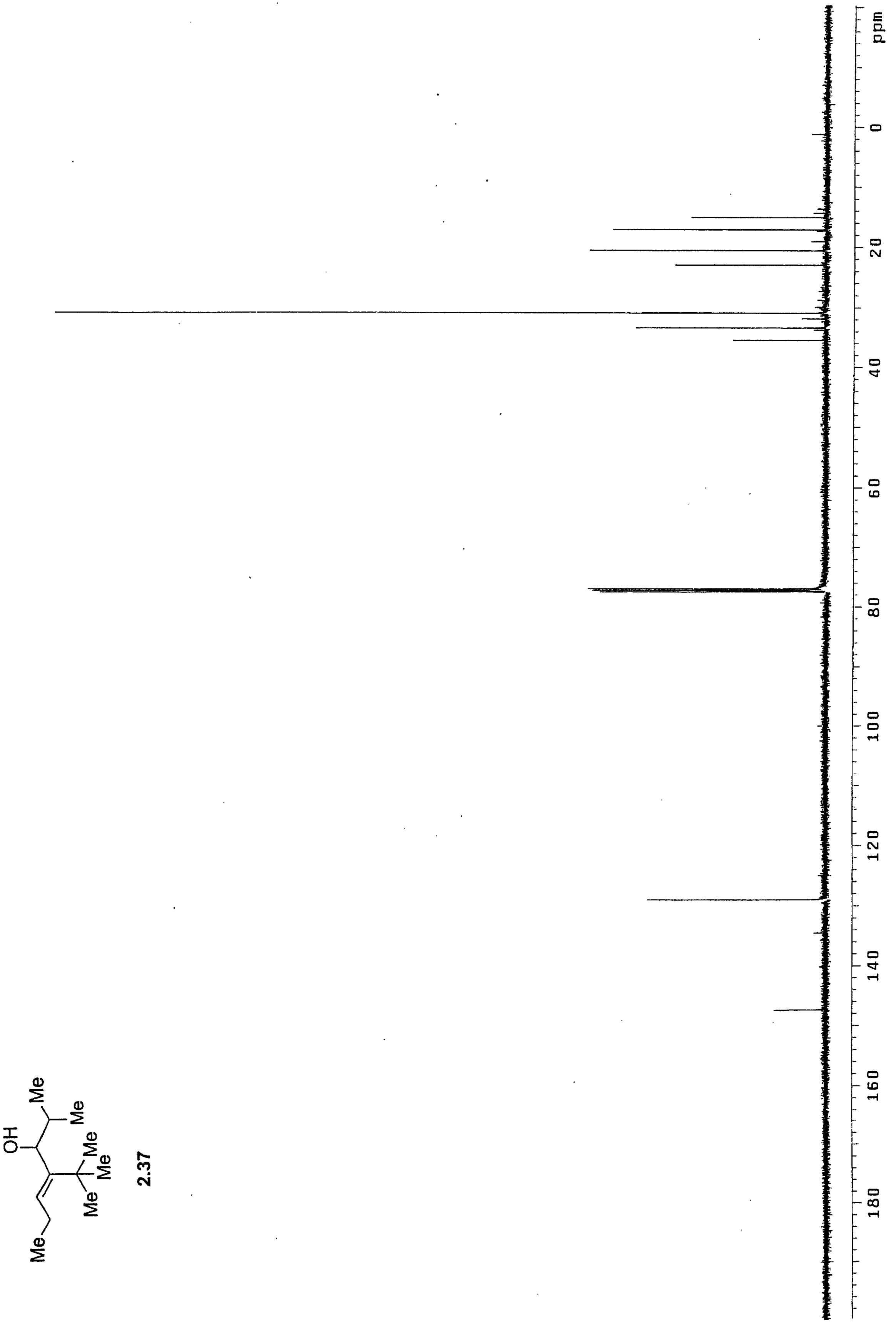

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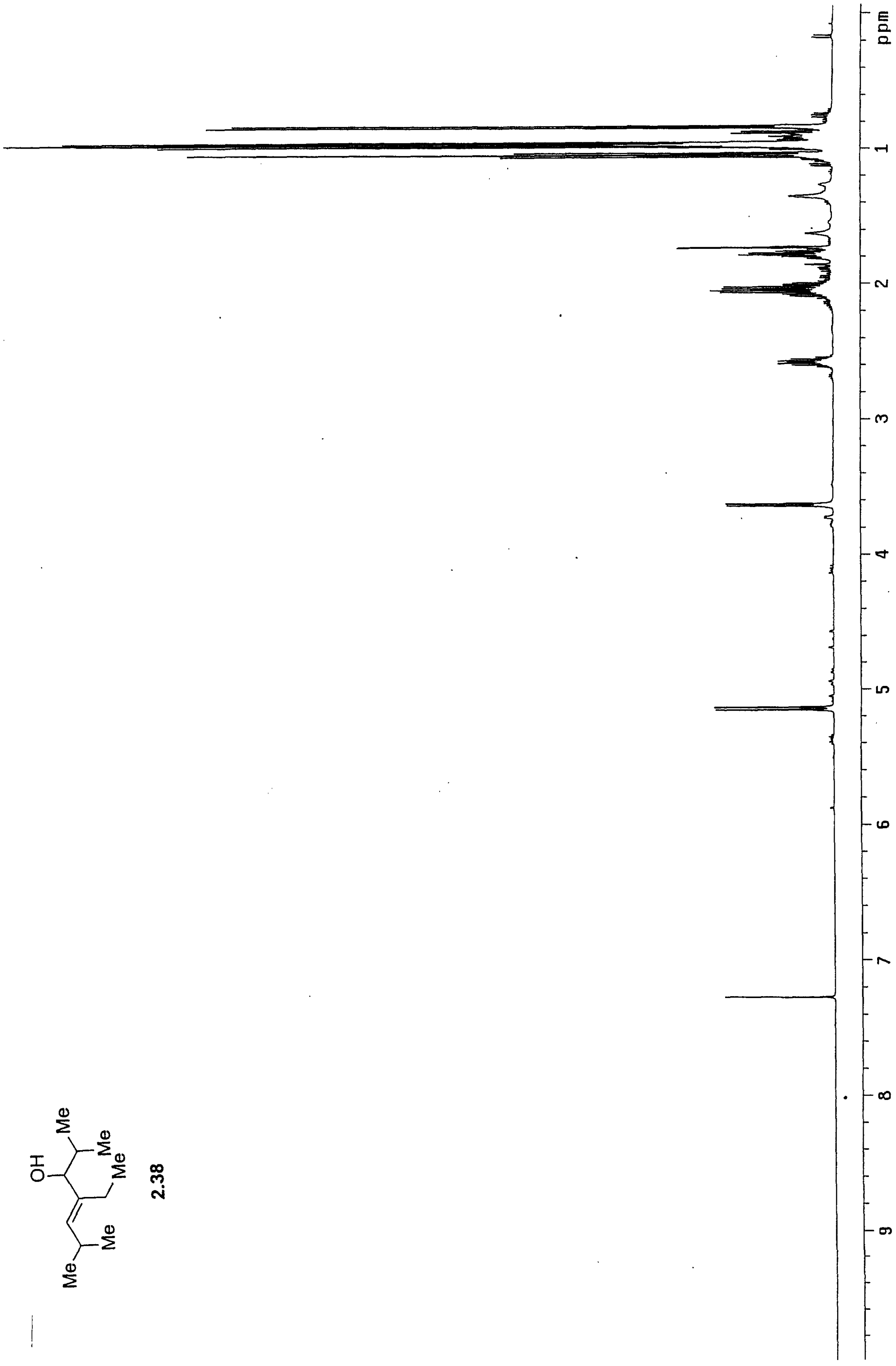

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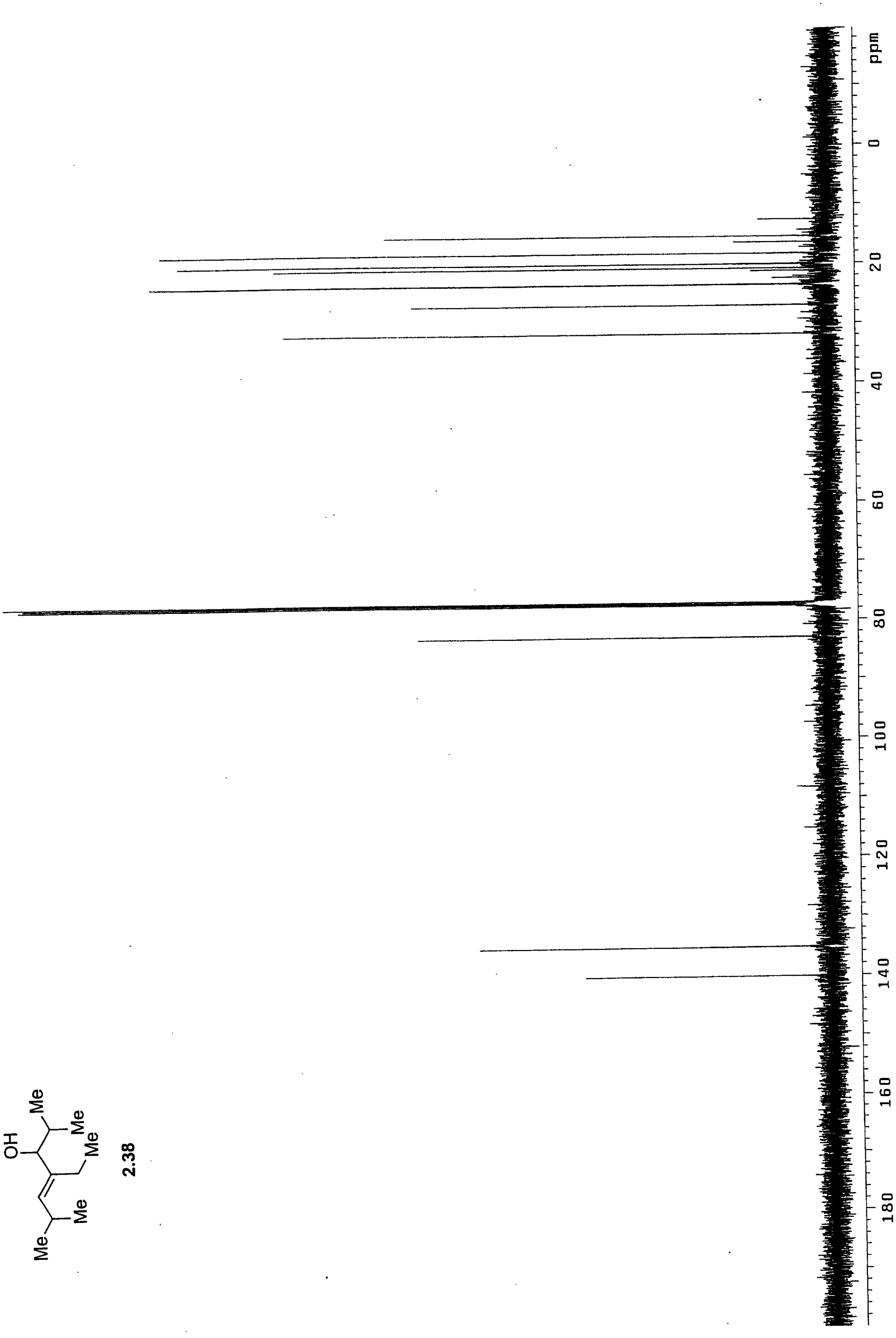

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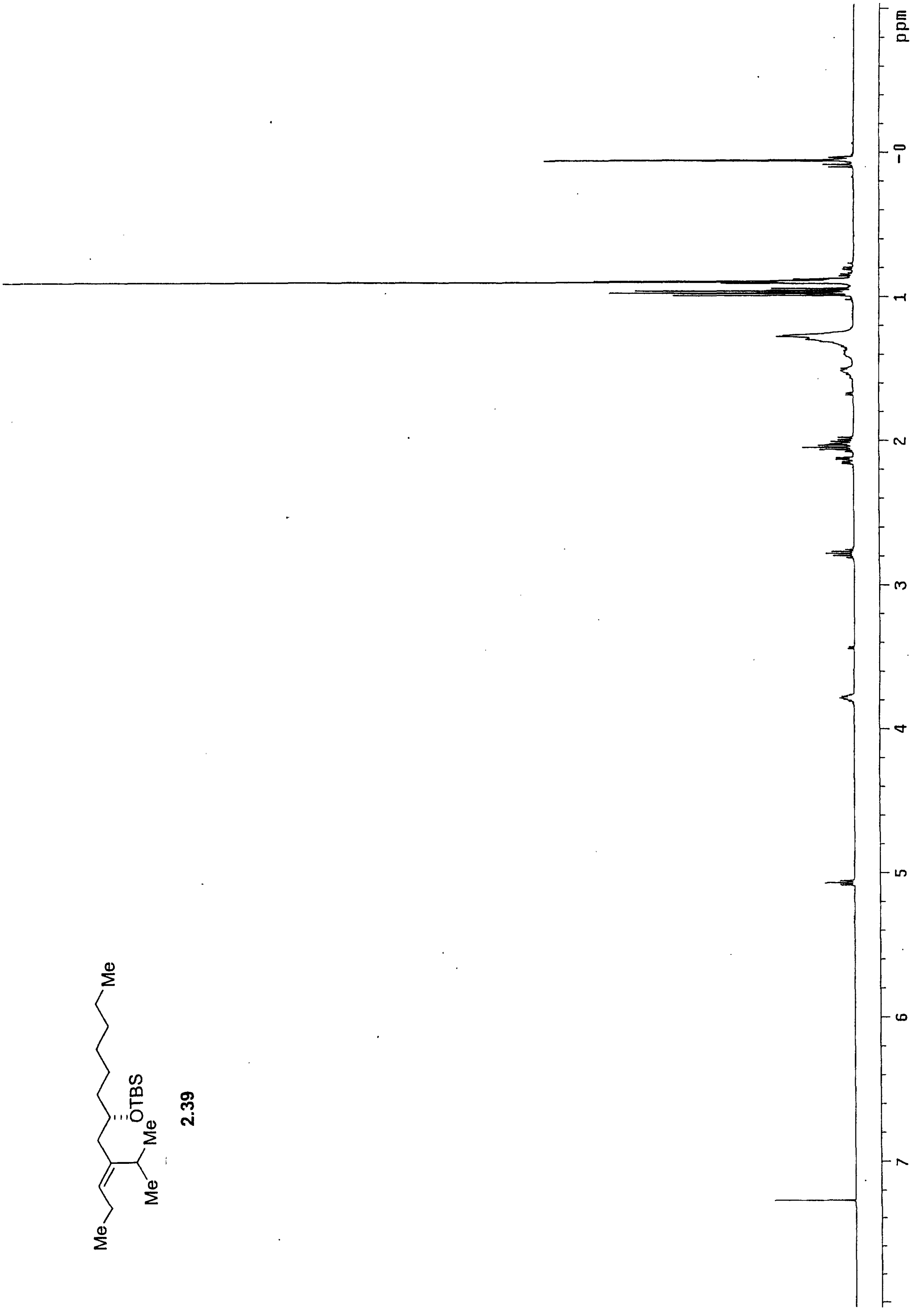

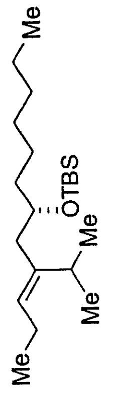

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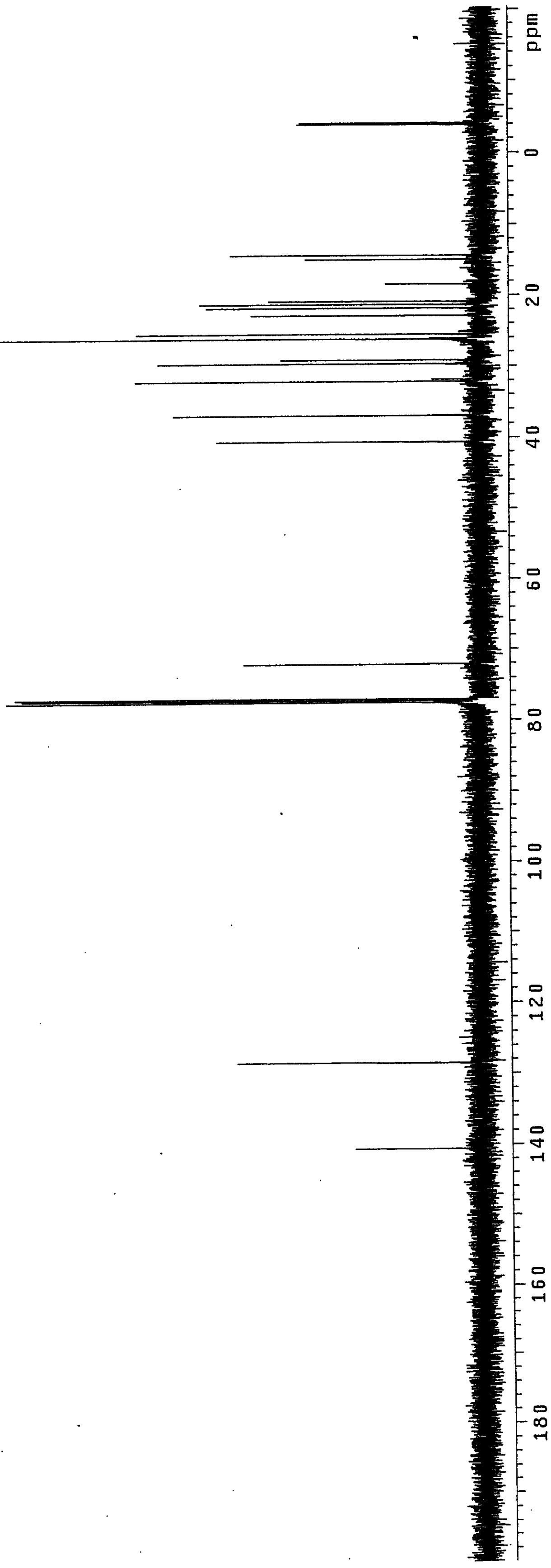

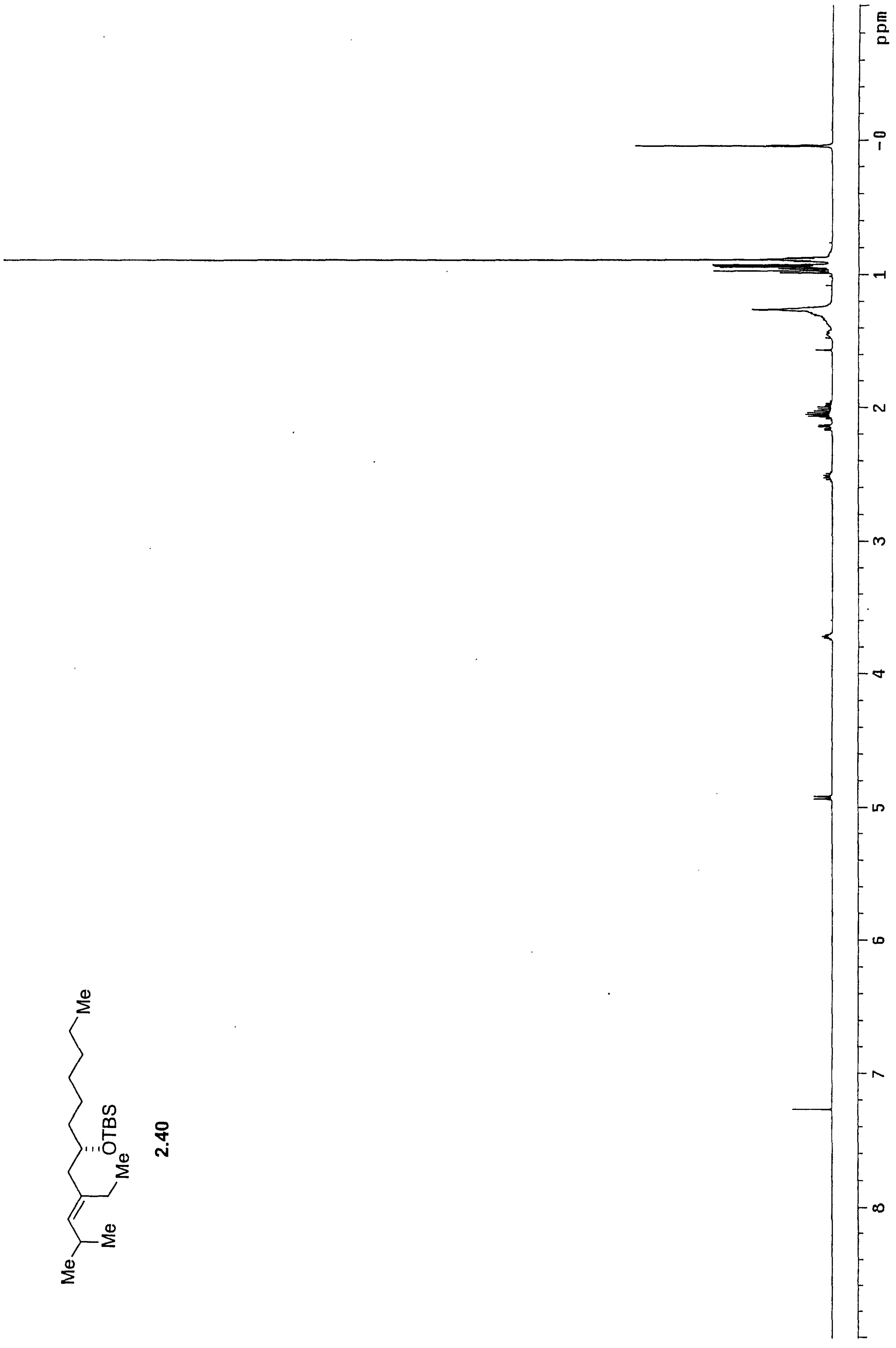

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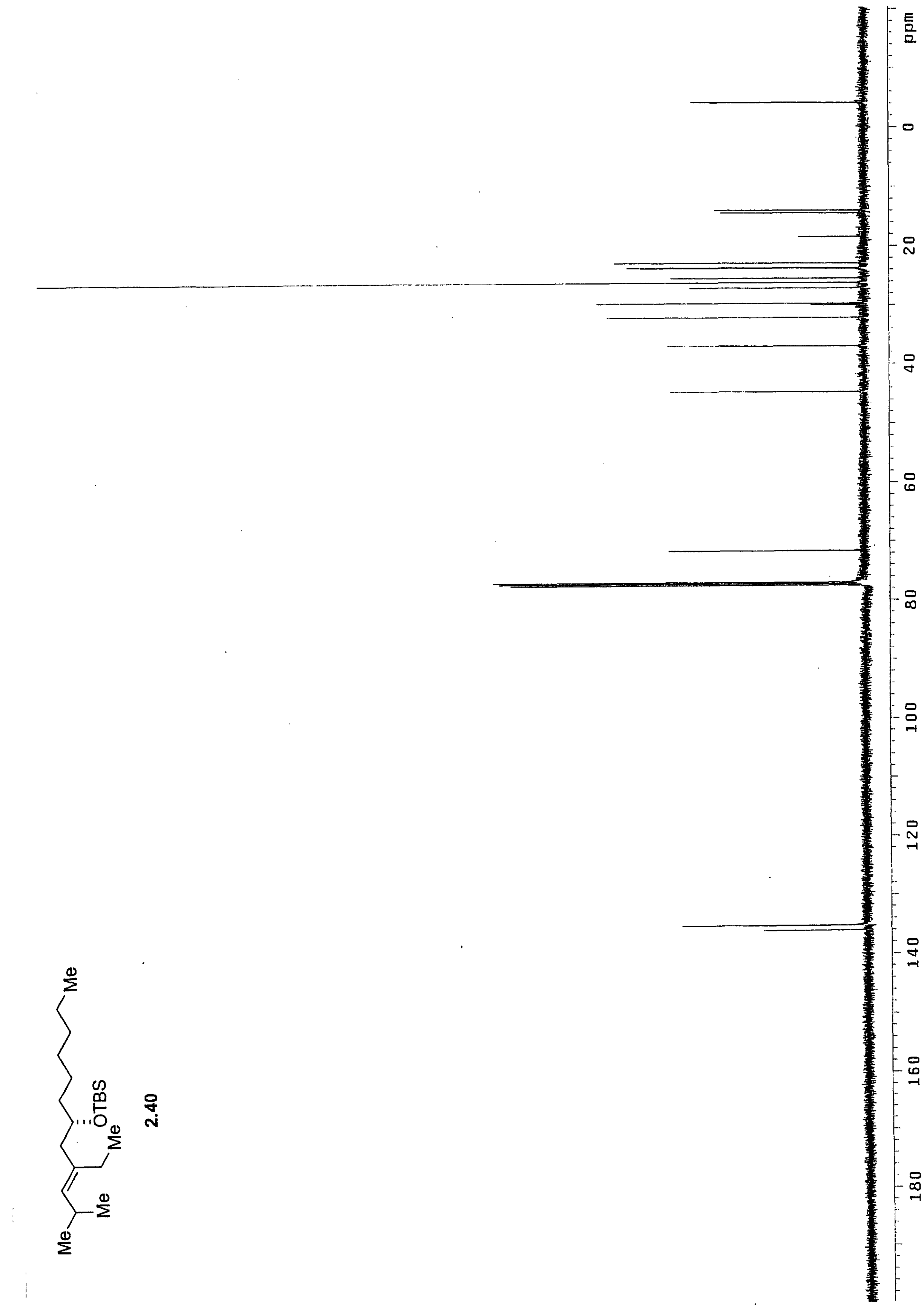

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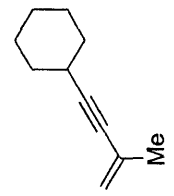
Appendix C.

^{1}H and ^{13}C NMR Spectra (Chapter 3)



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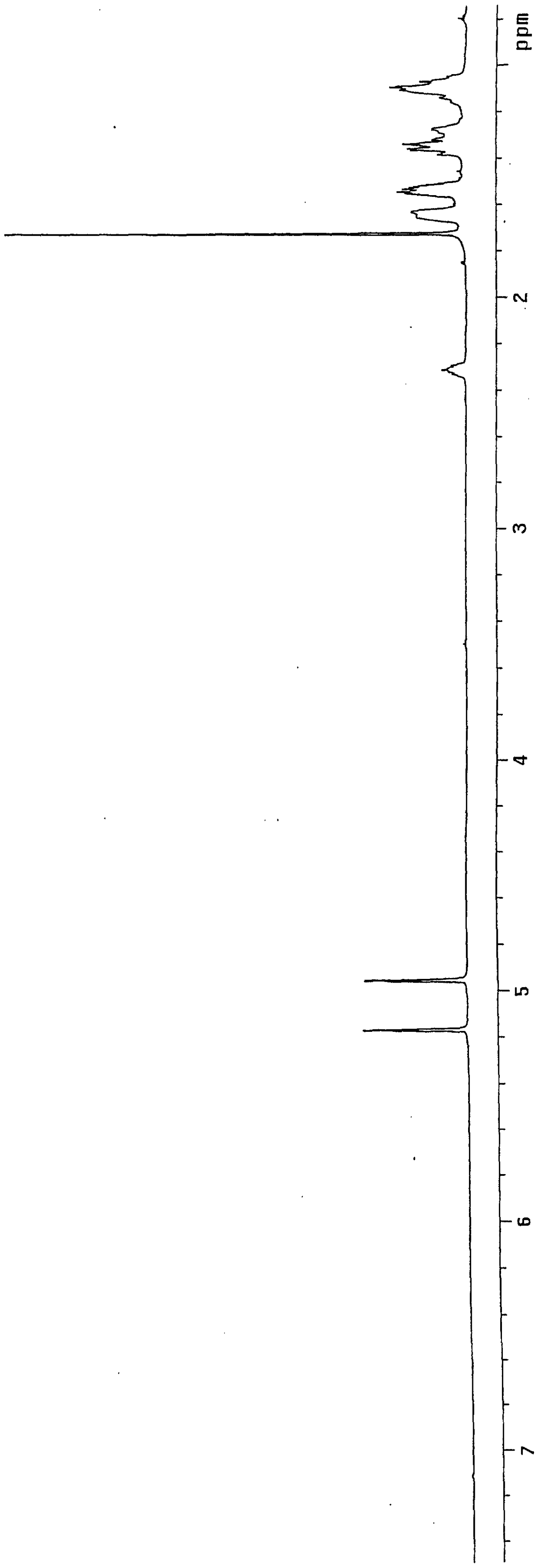

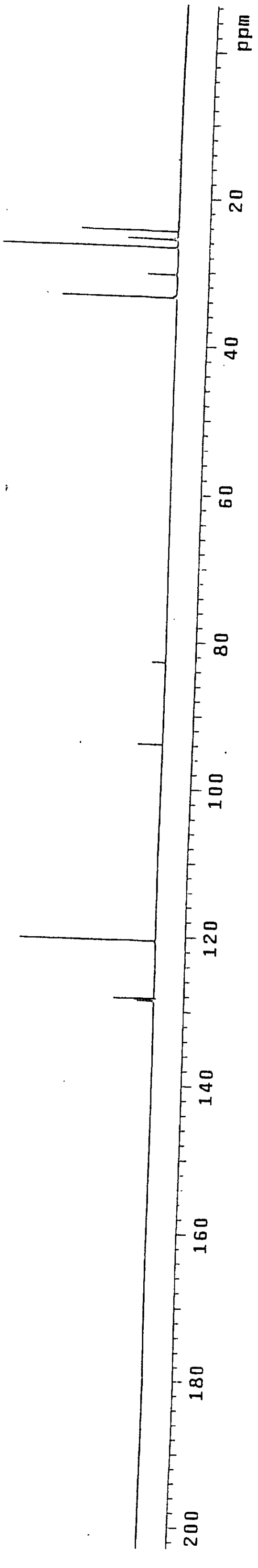

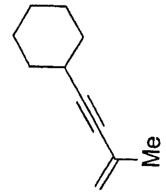

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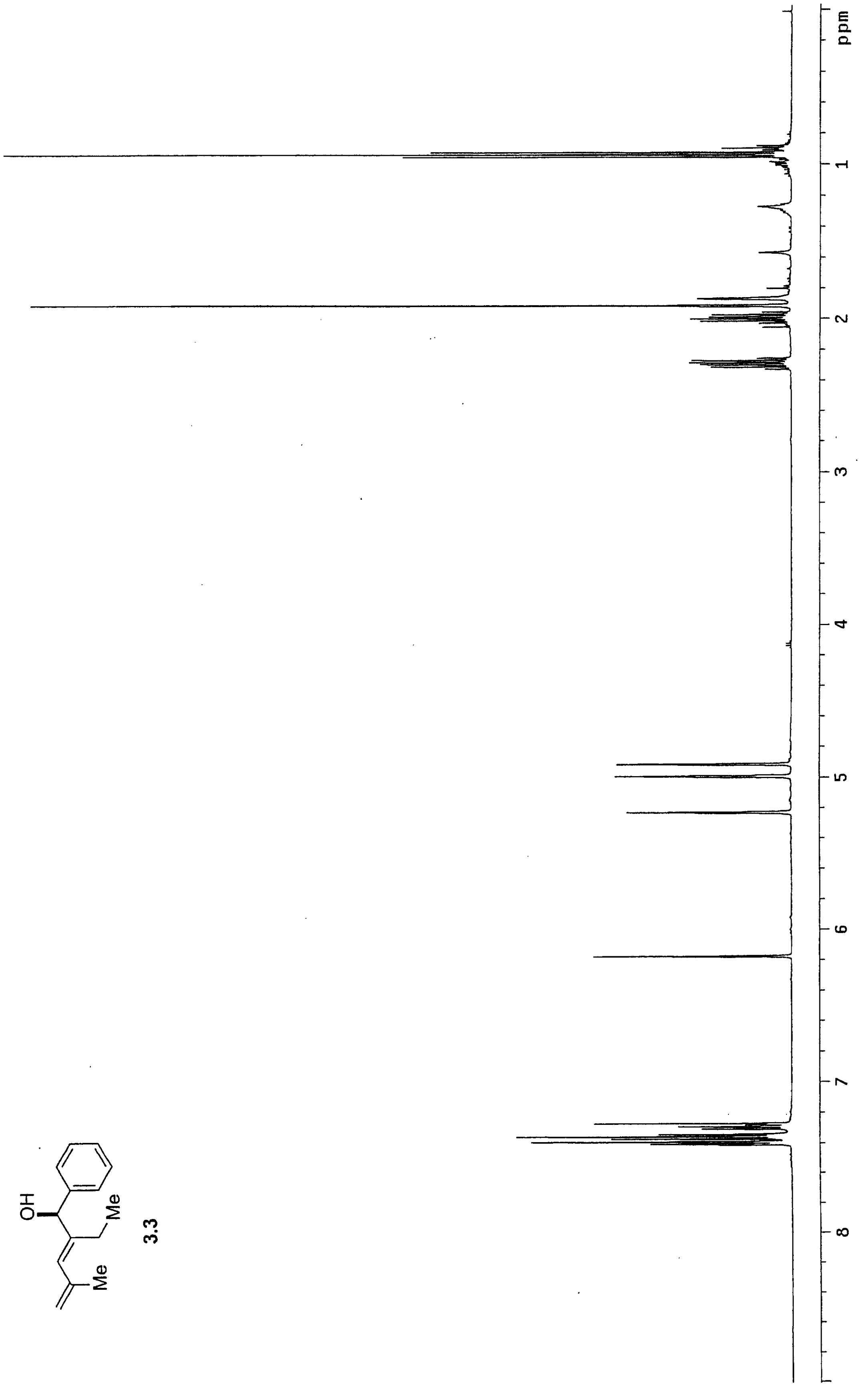

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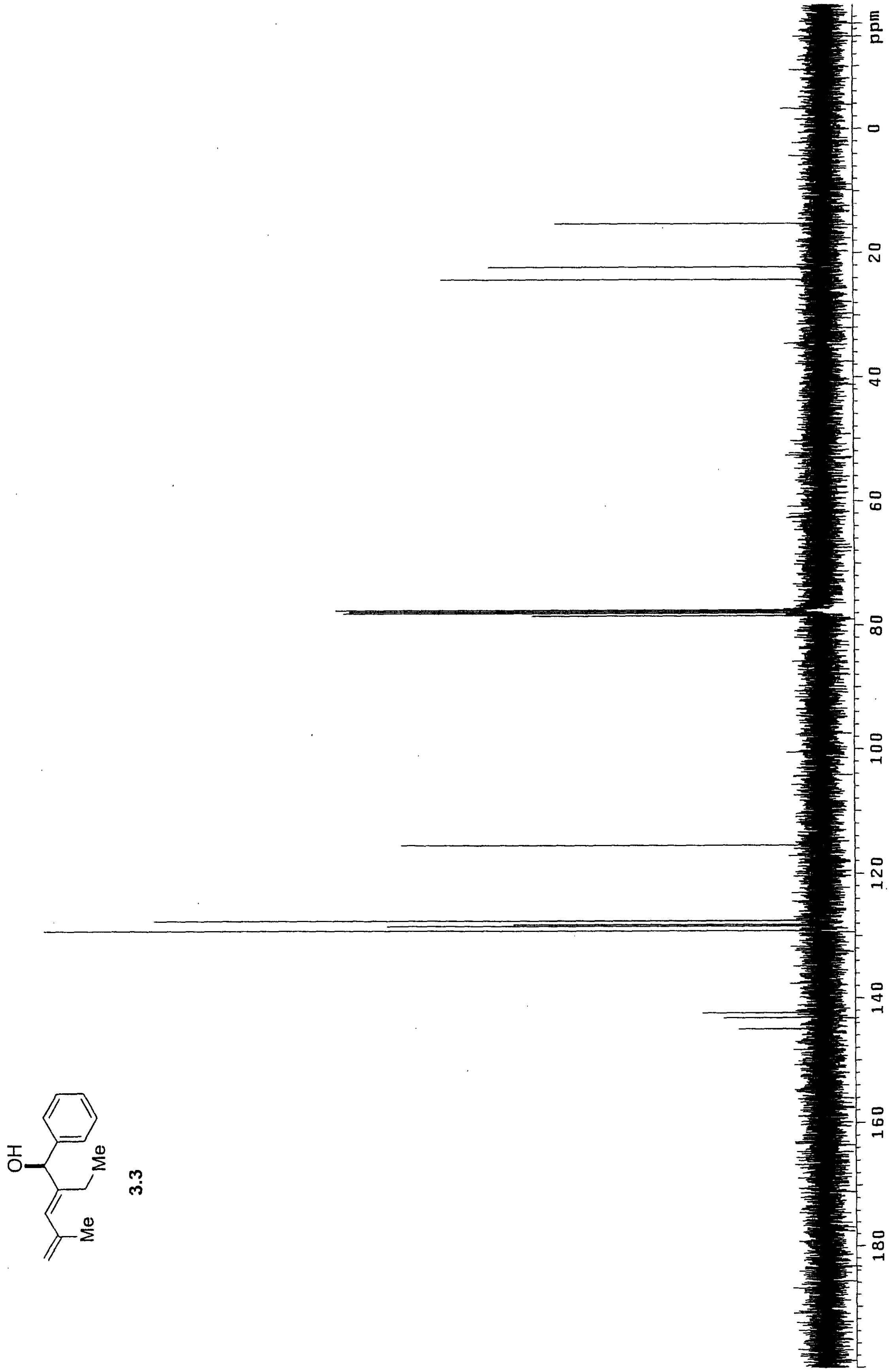

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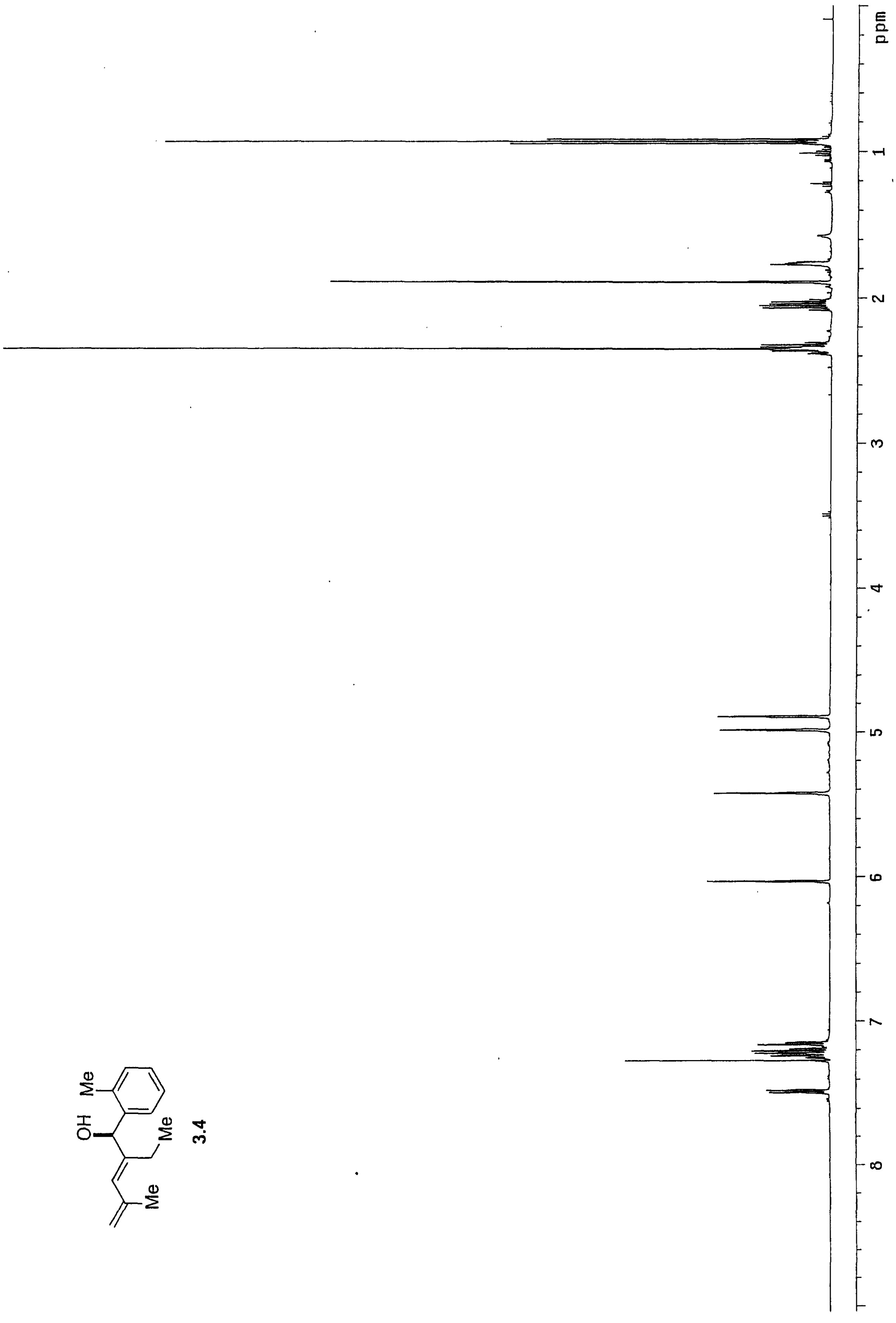

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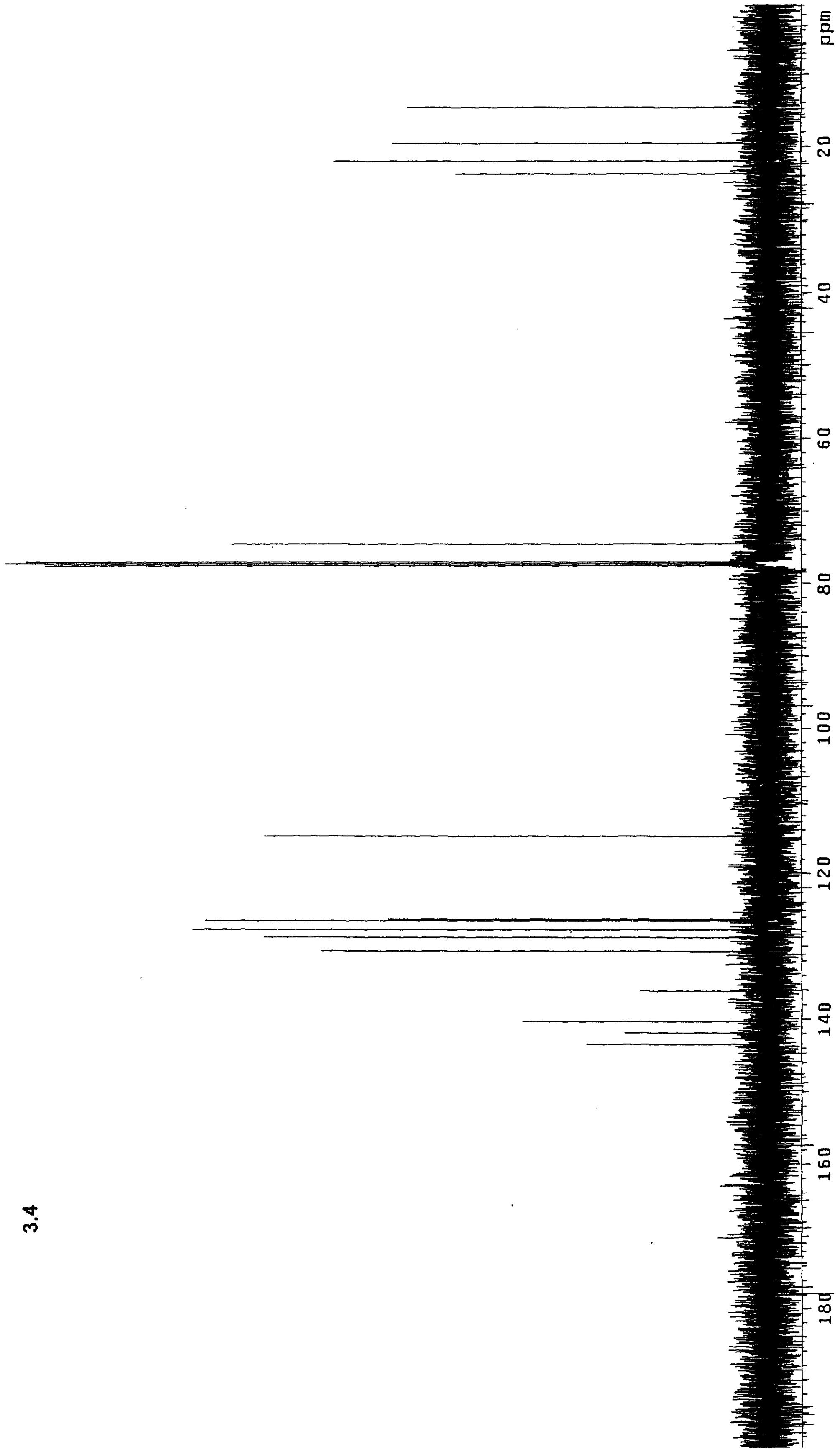

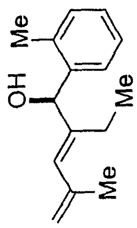

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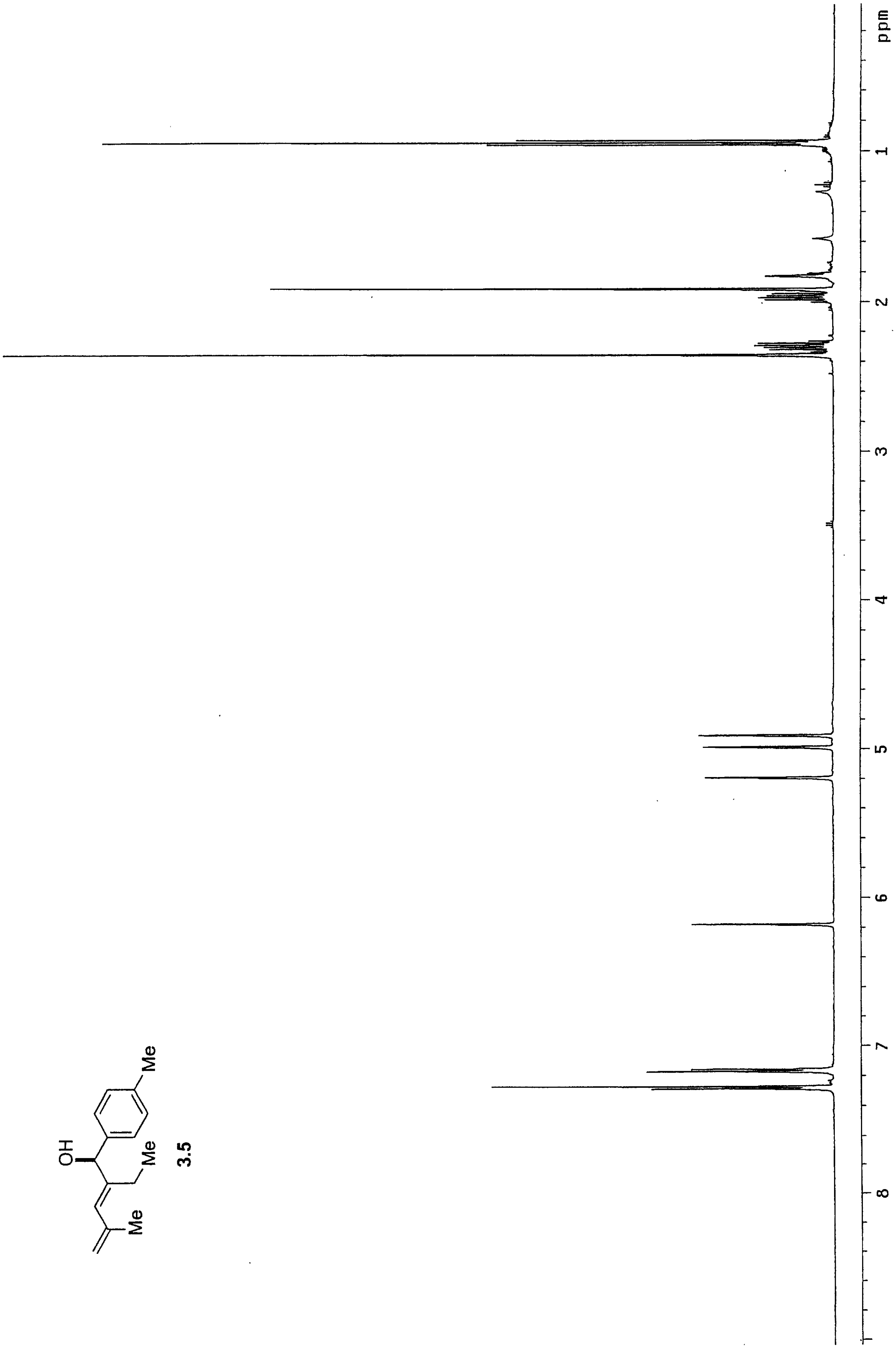

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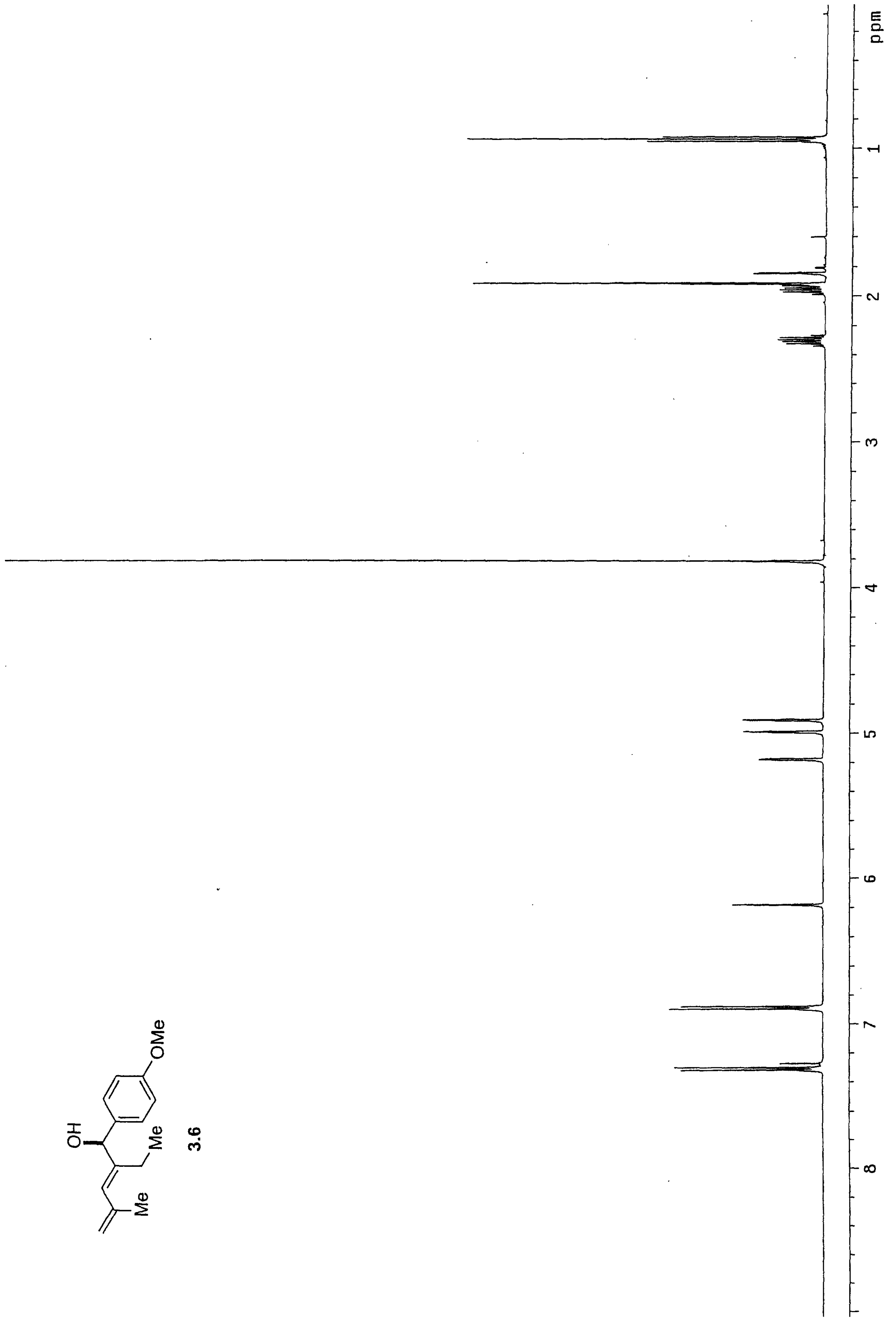

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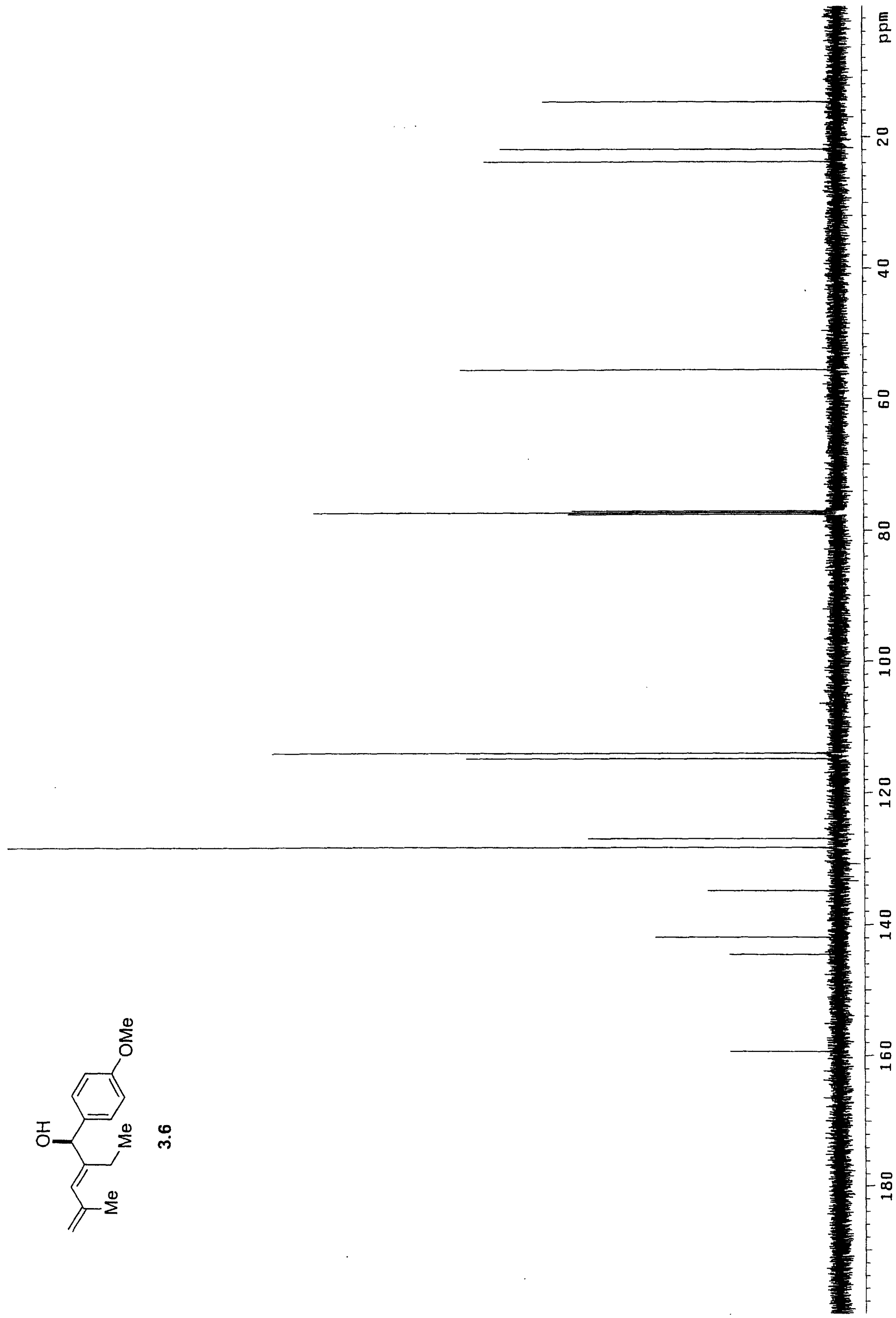

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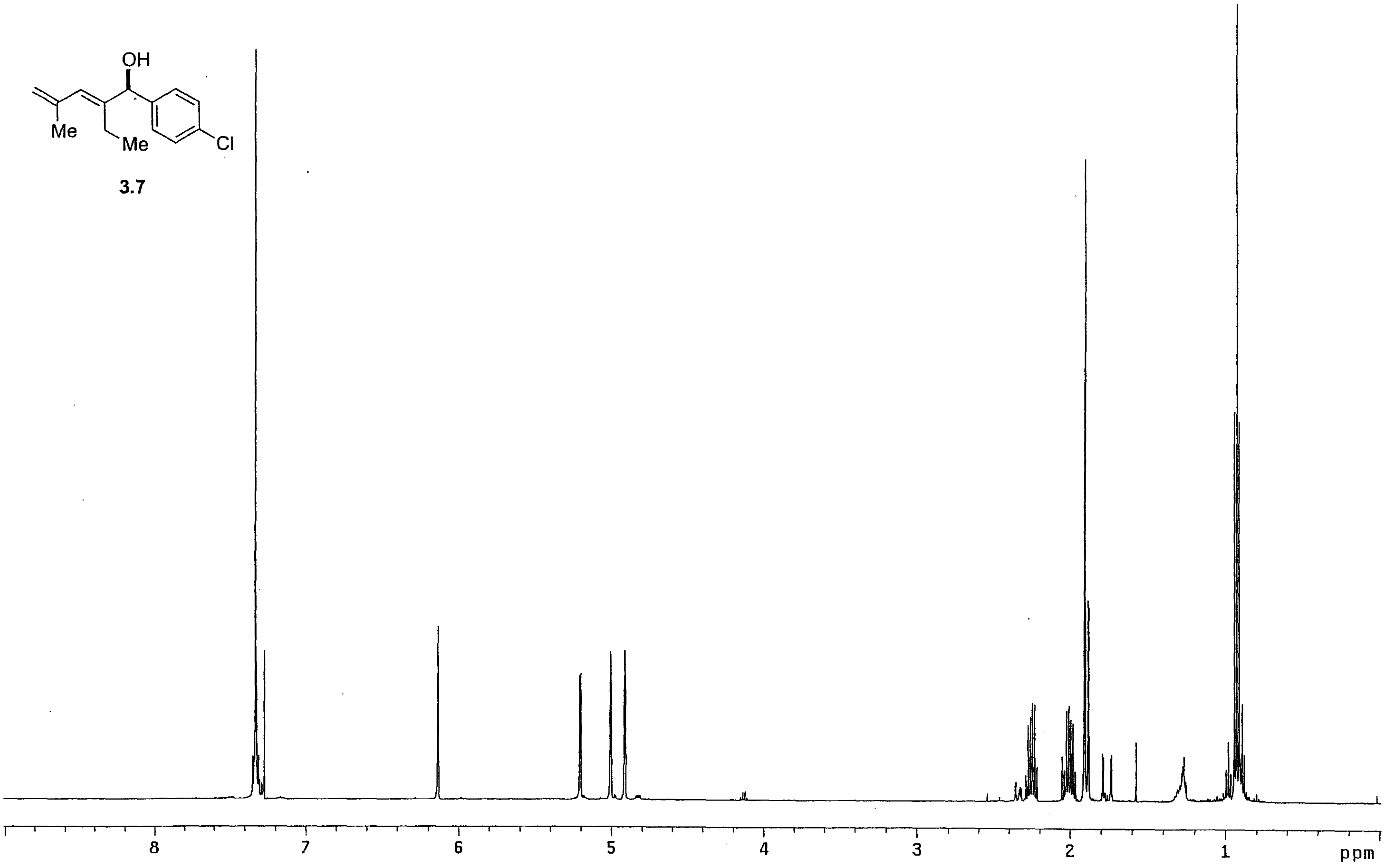

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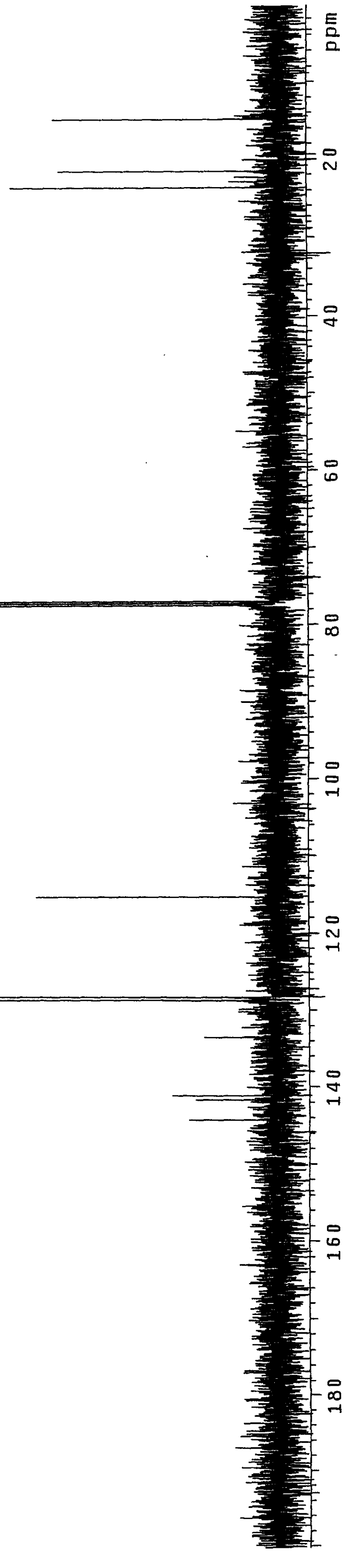

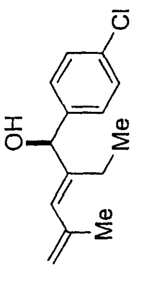

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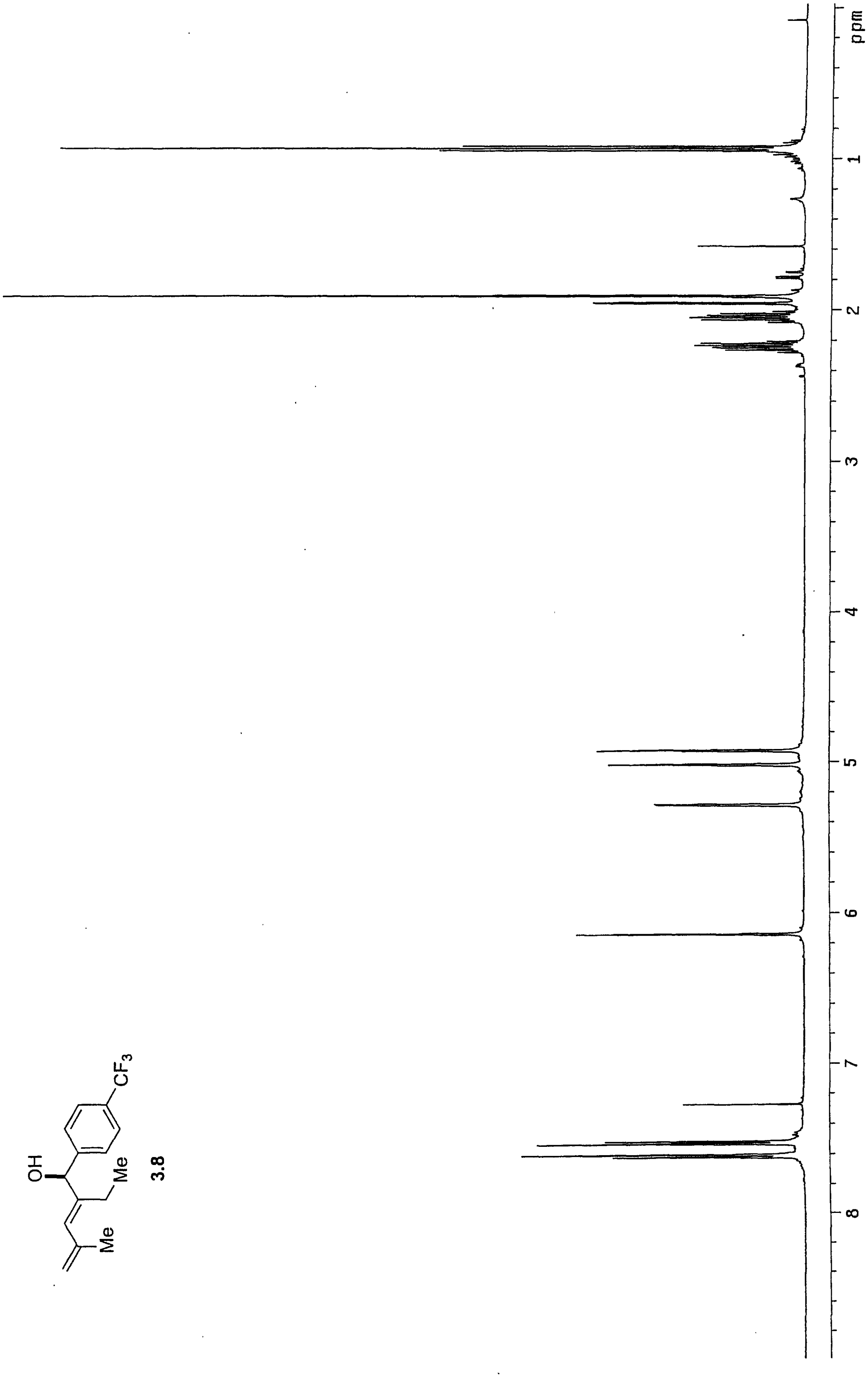

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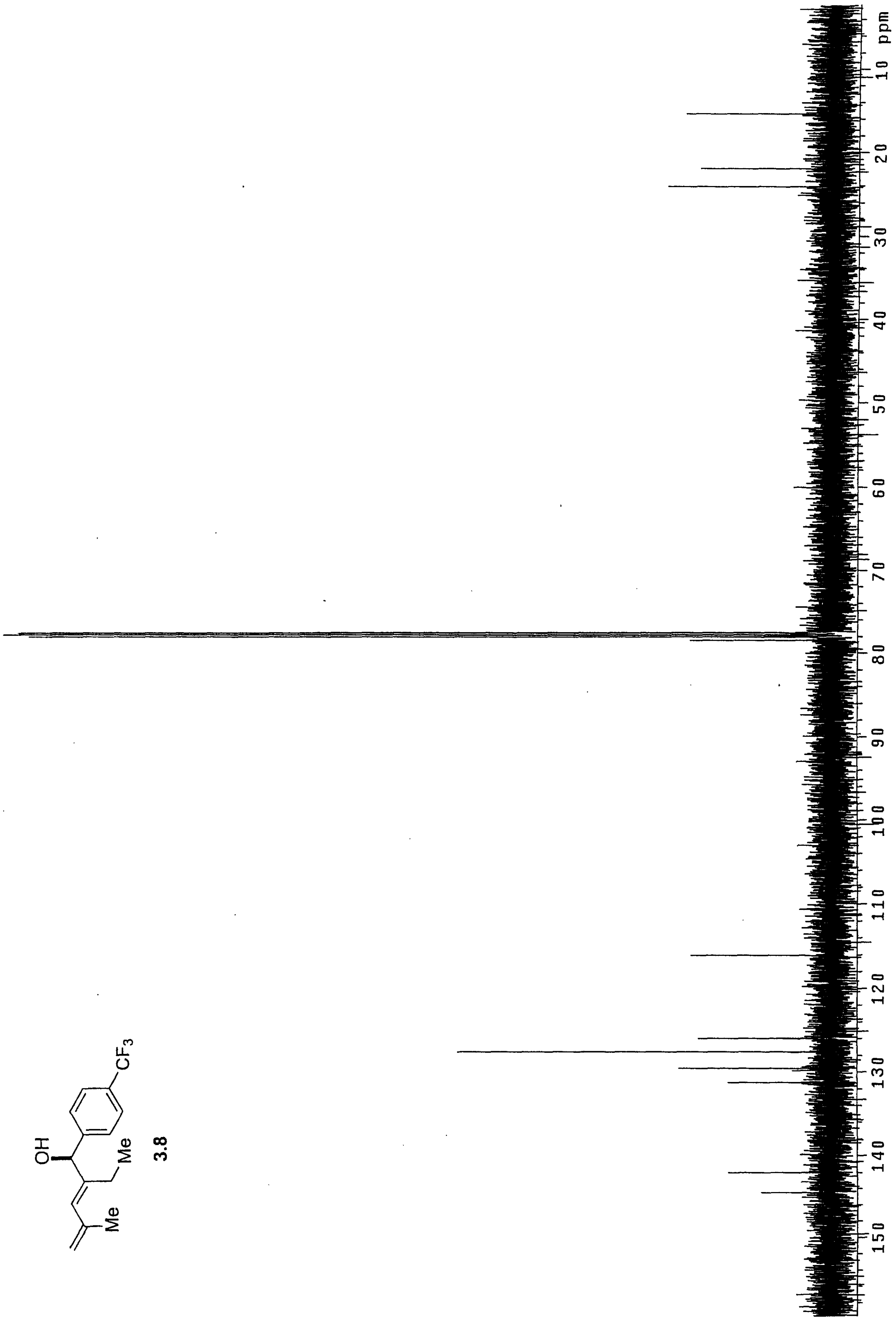

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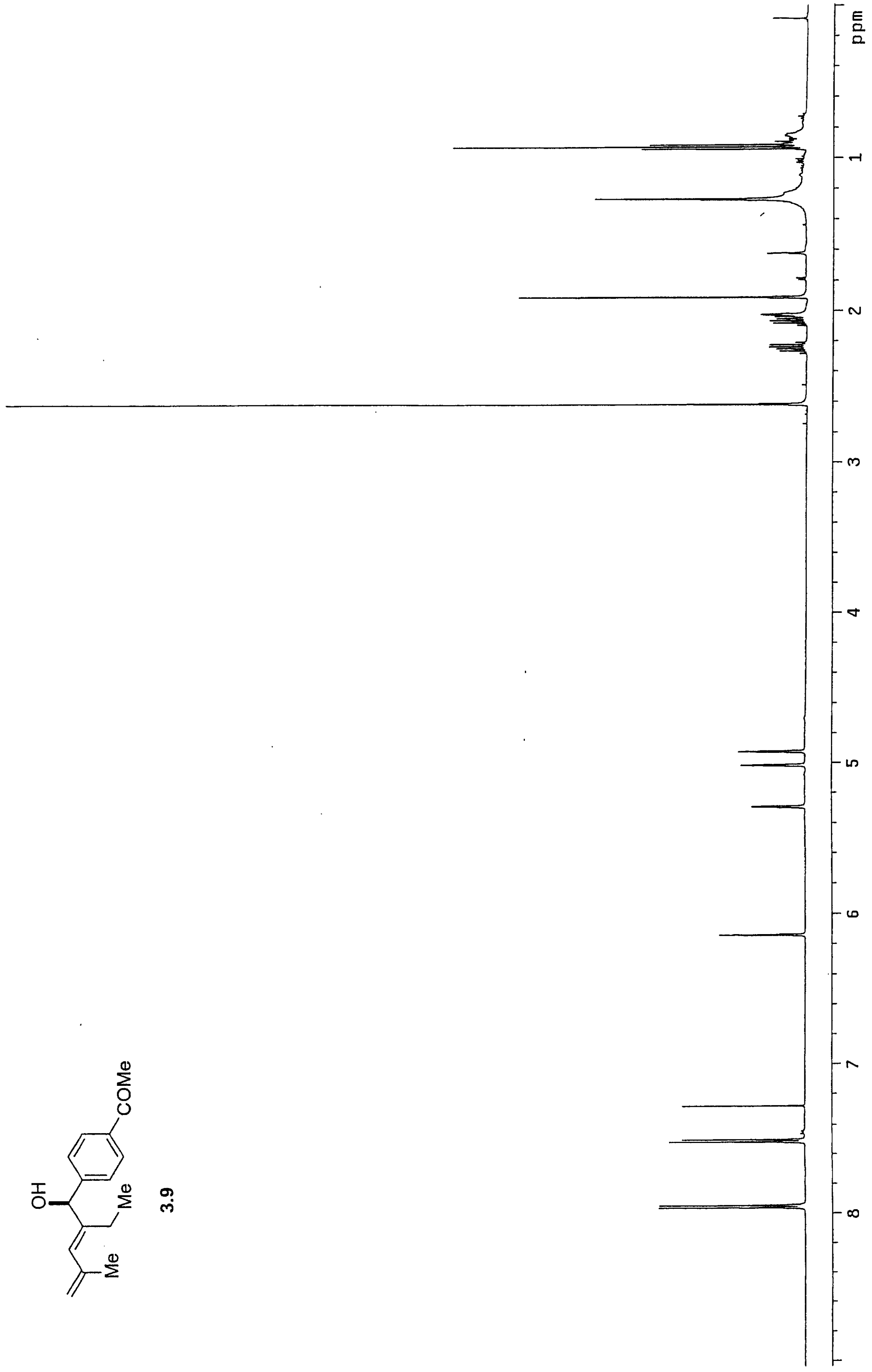

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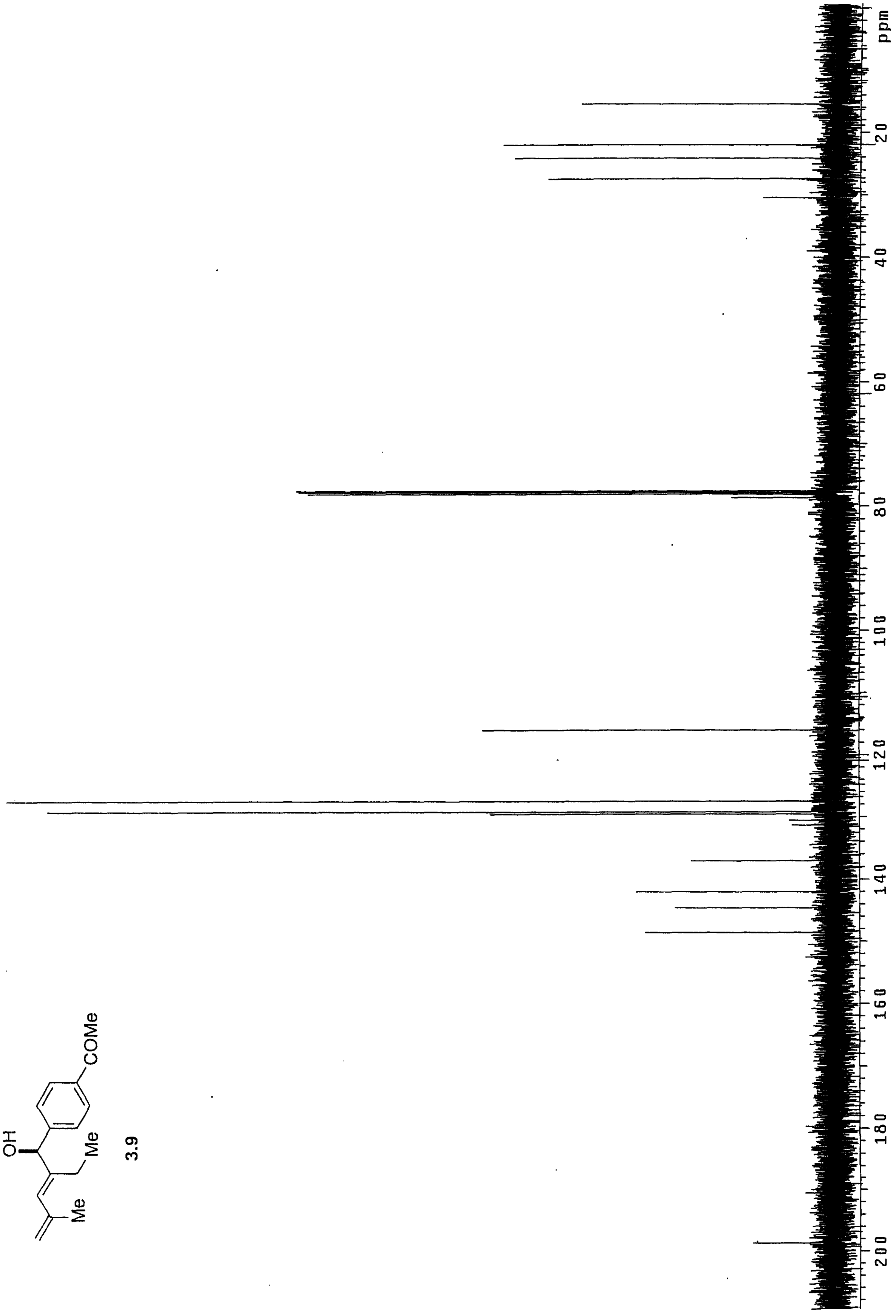
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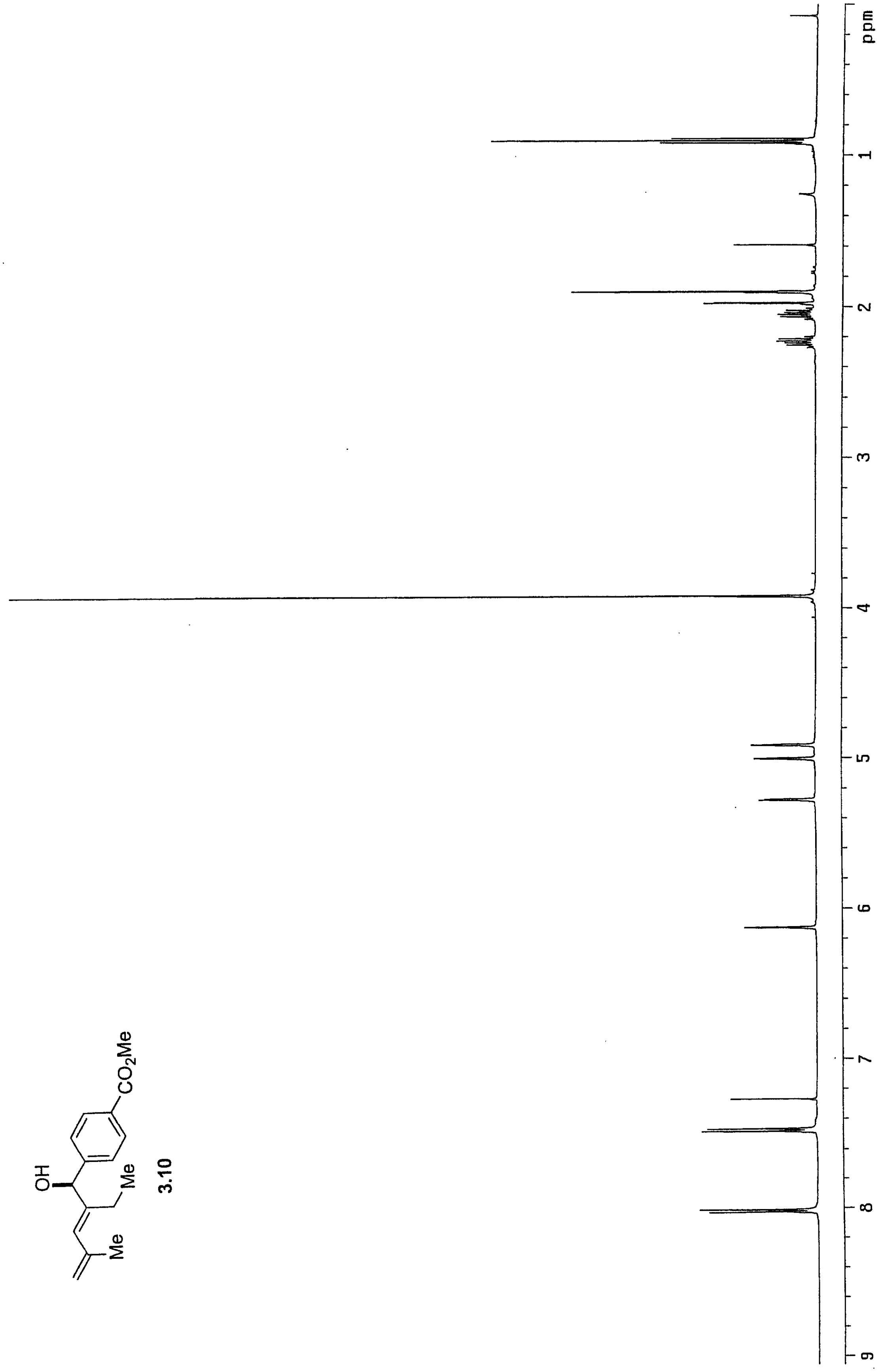
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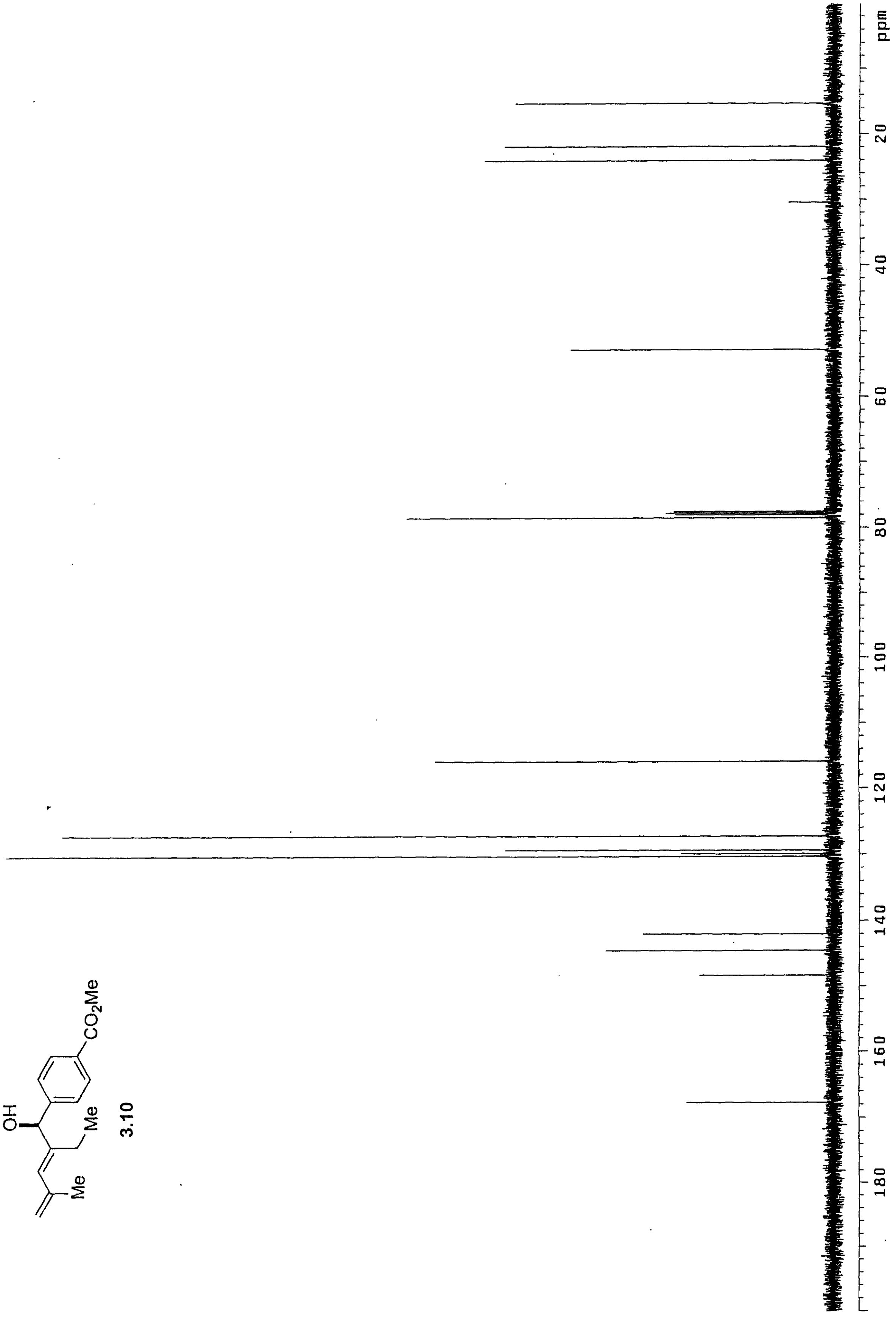

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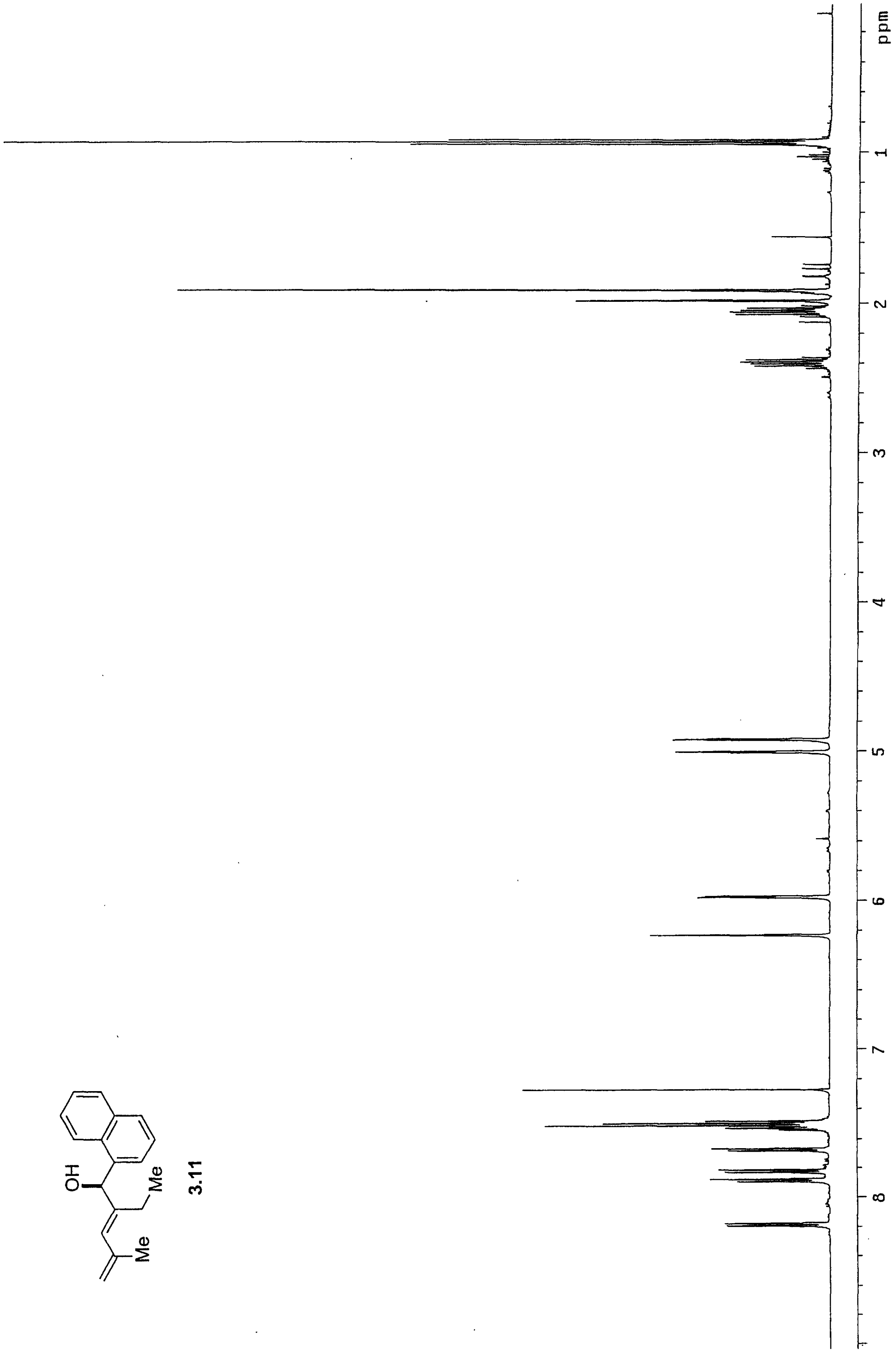

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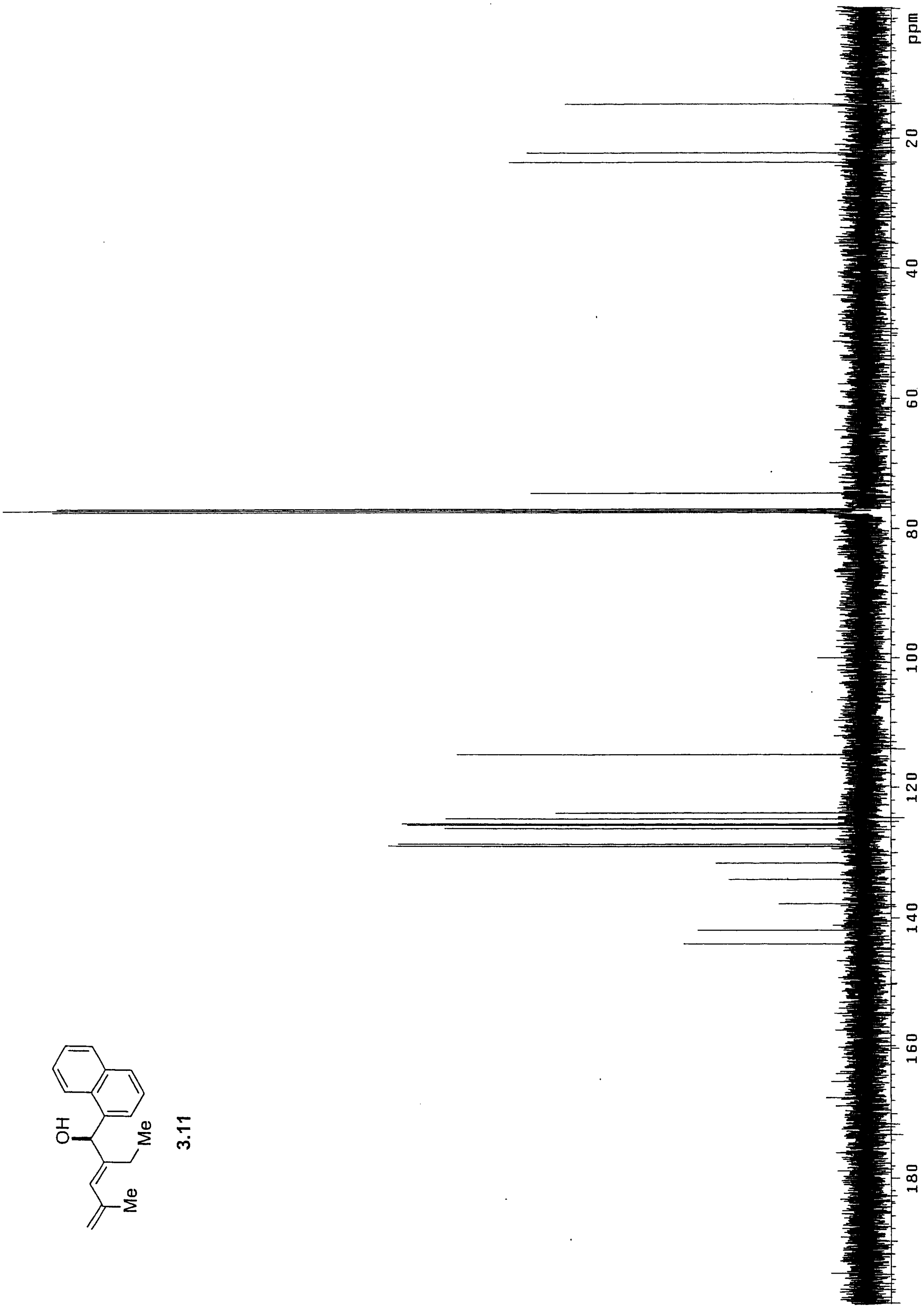

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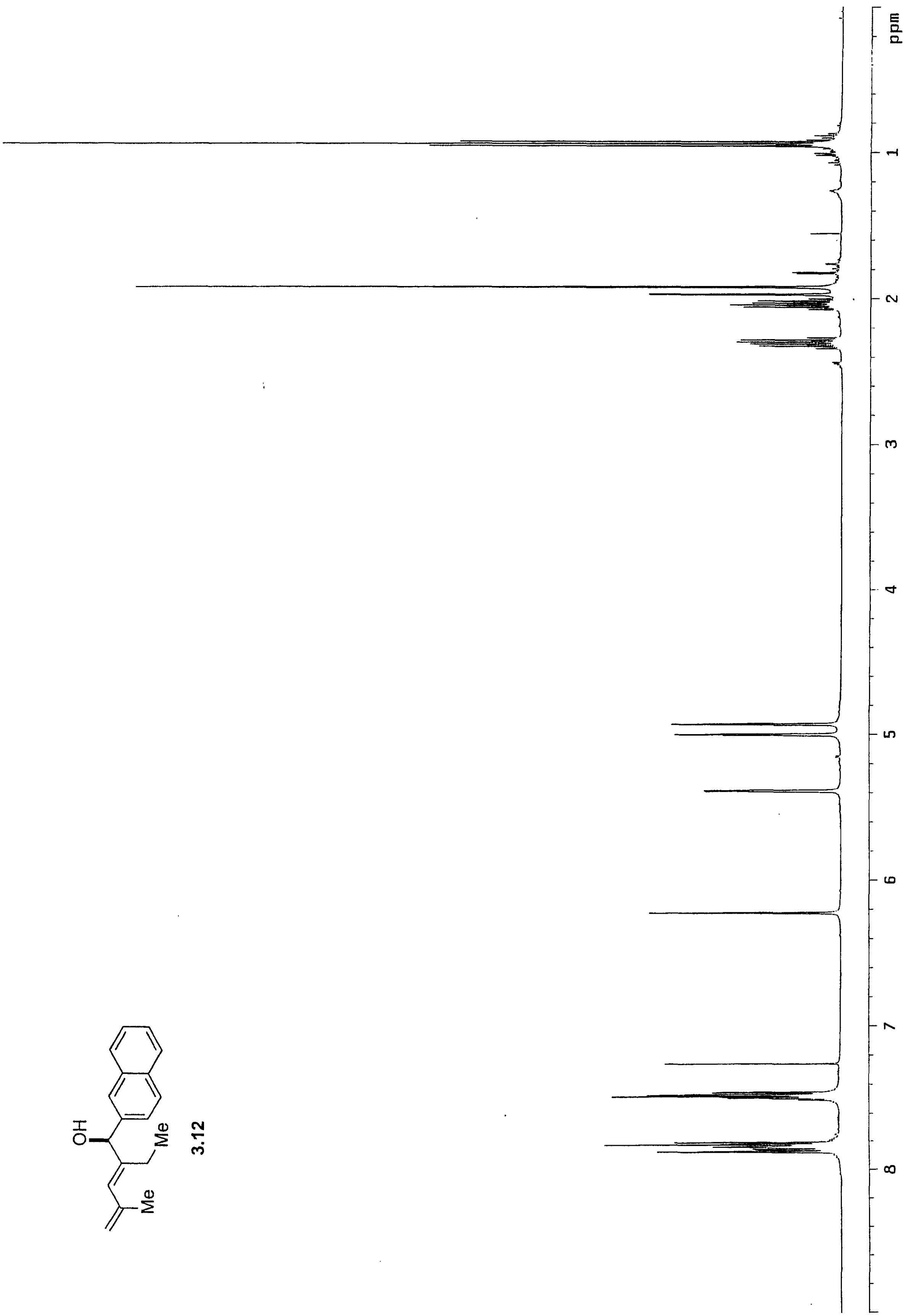

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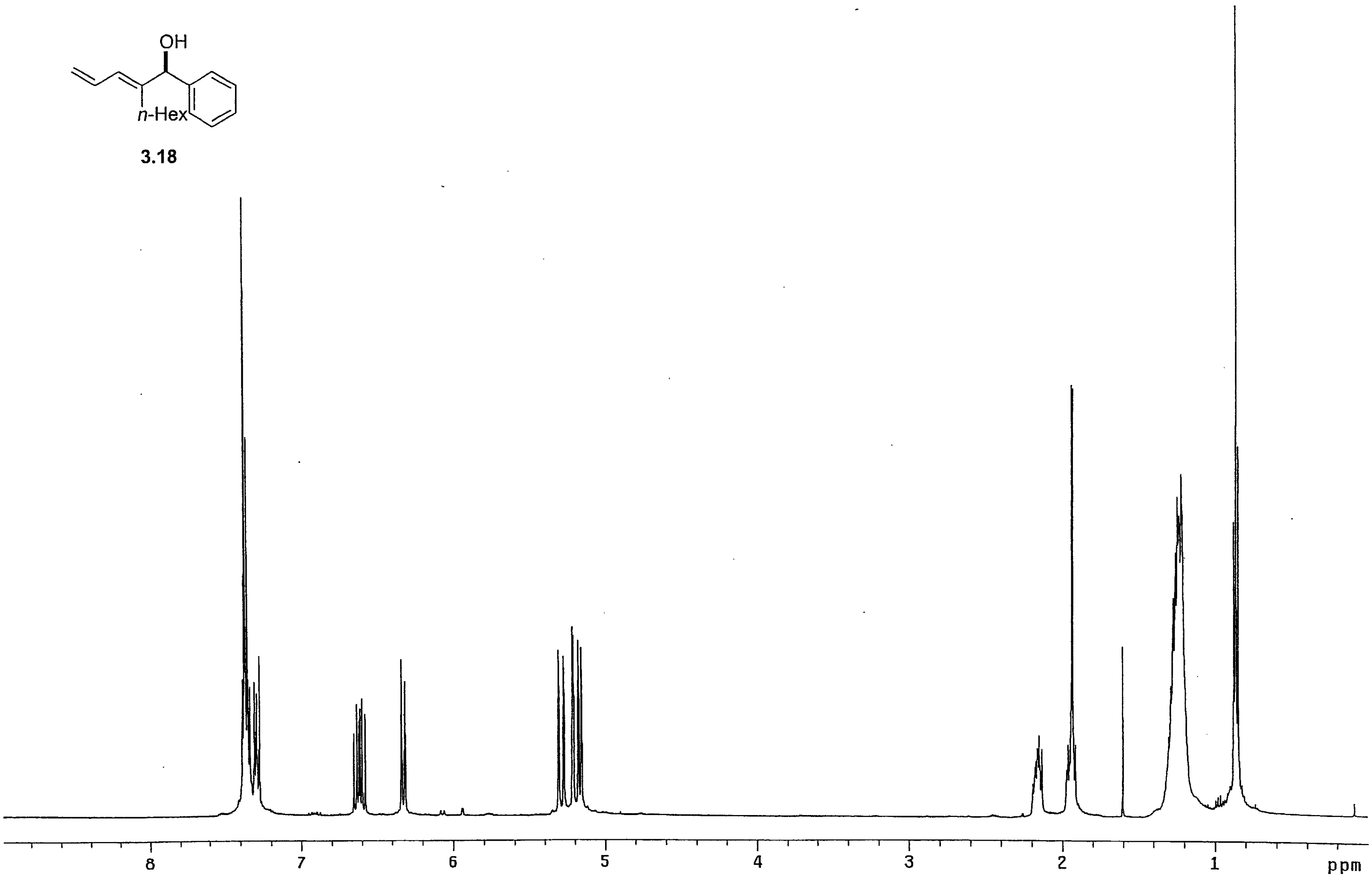

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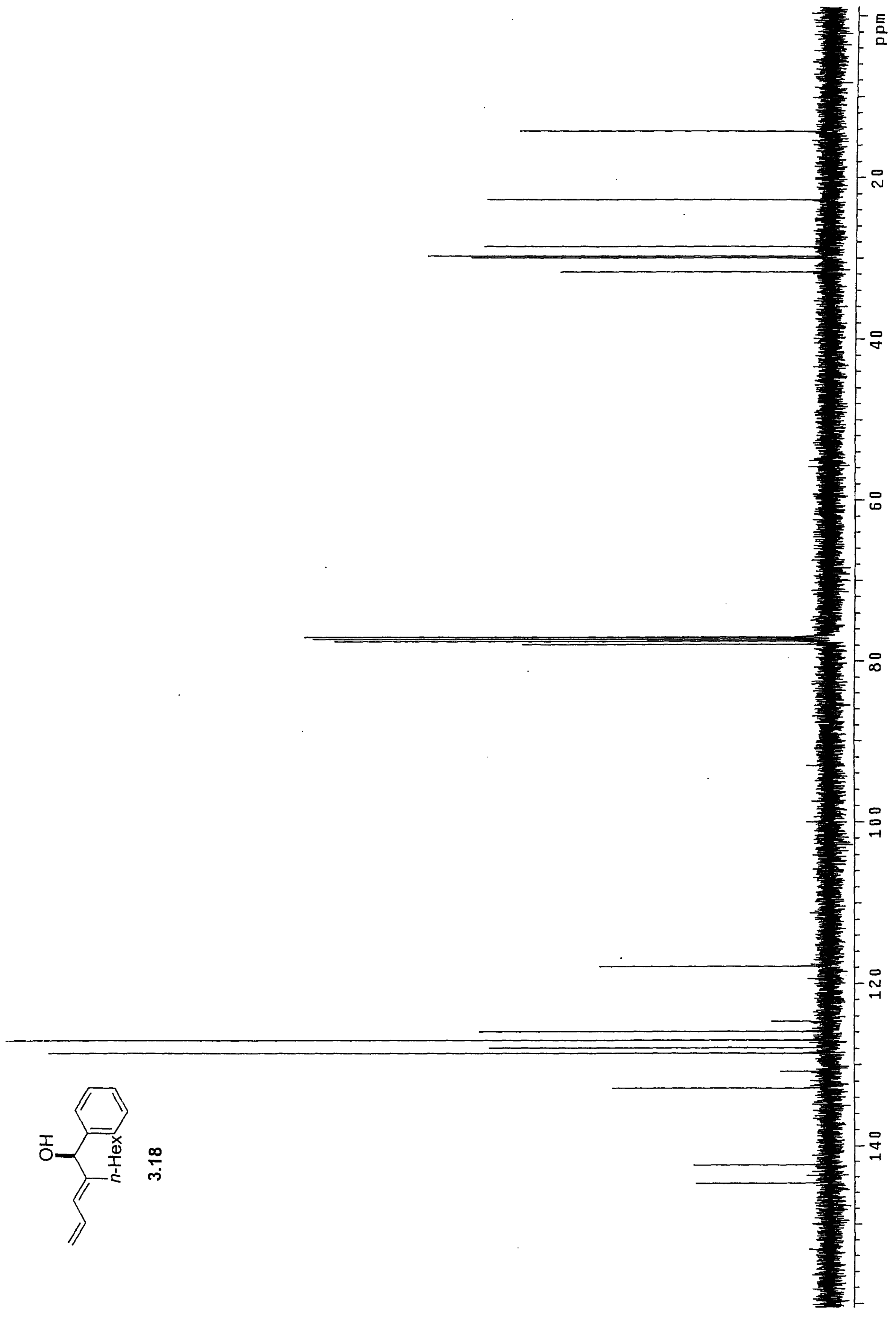

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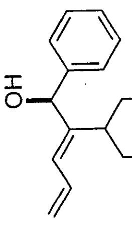

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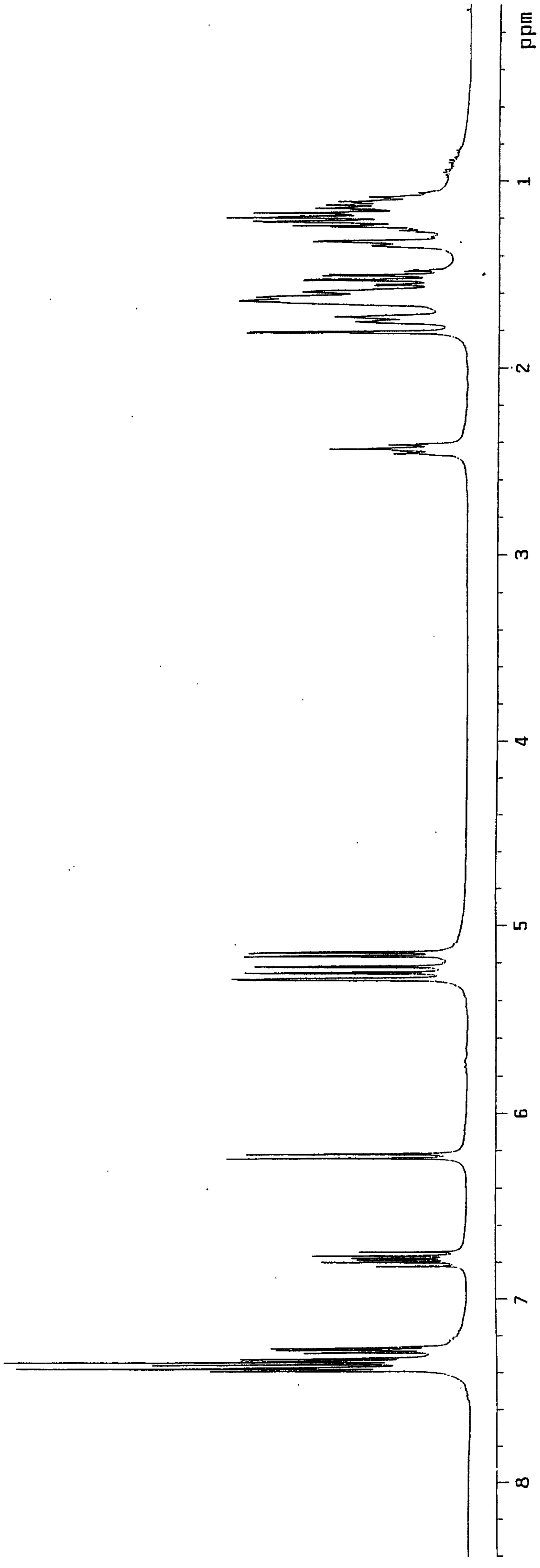

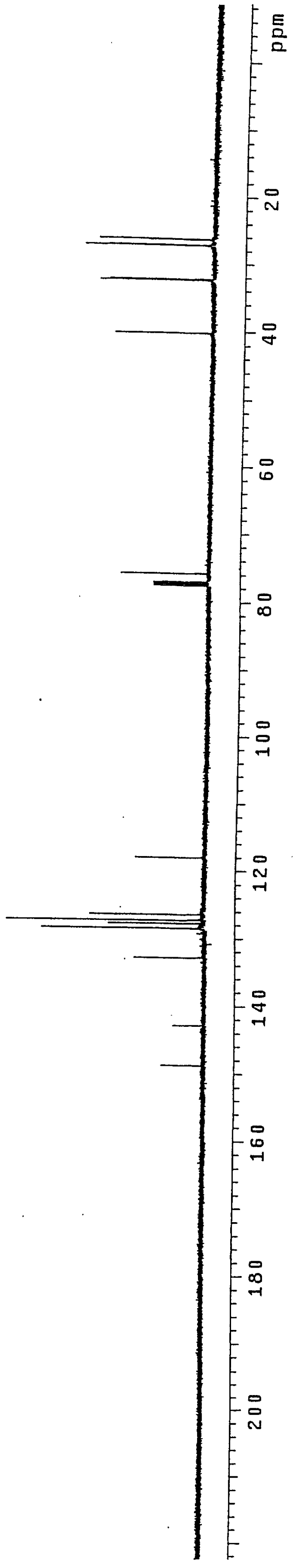

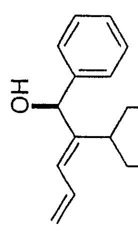

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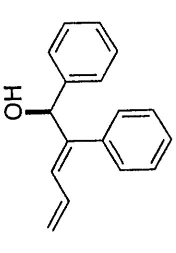

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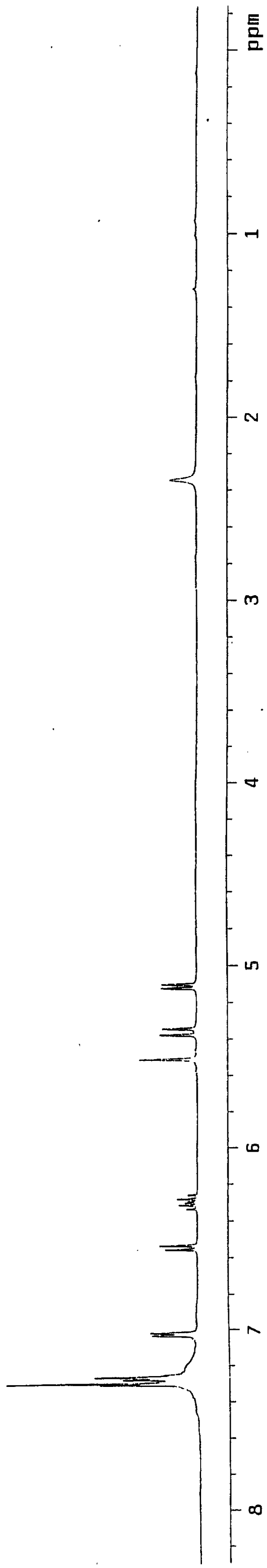

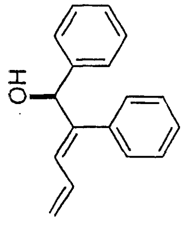

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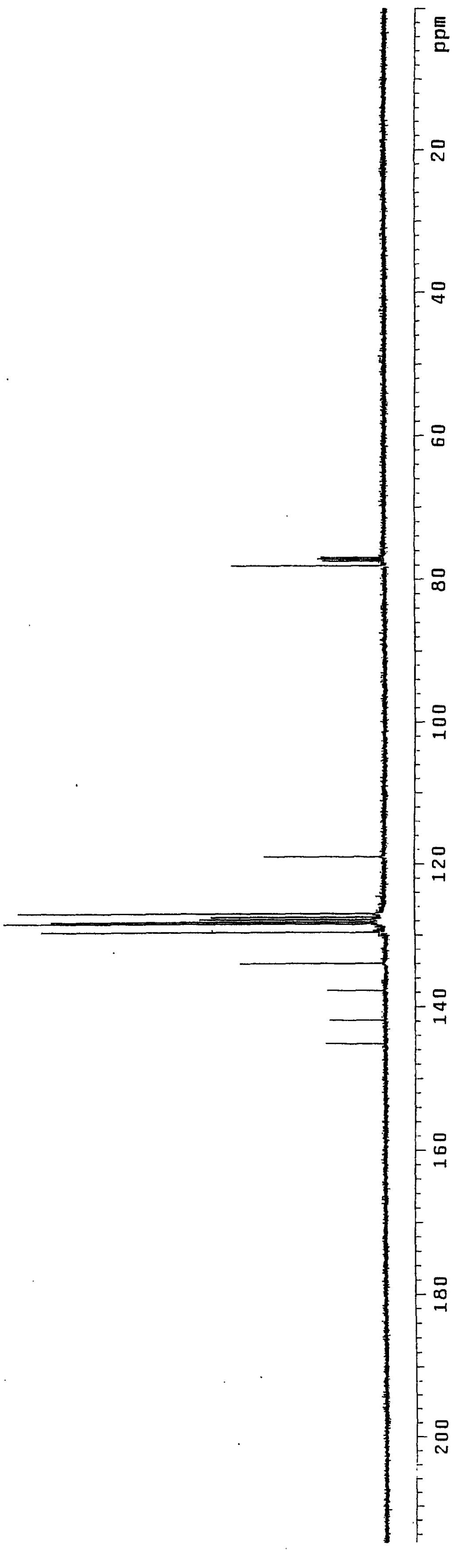

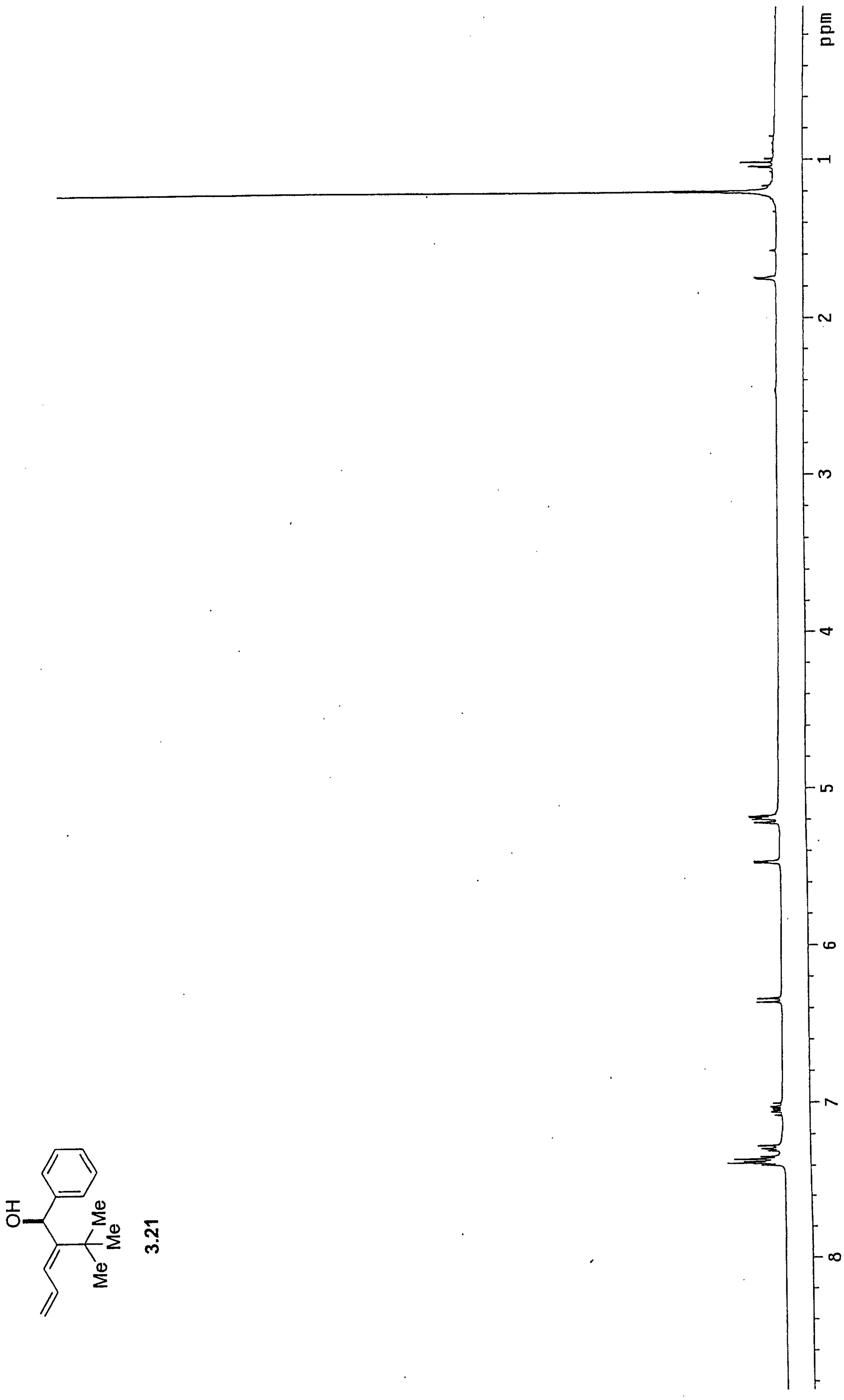

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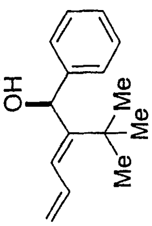

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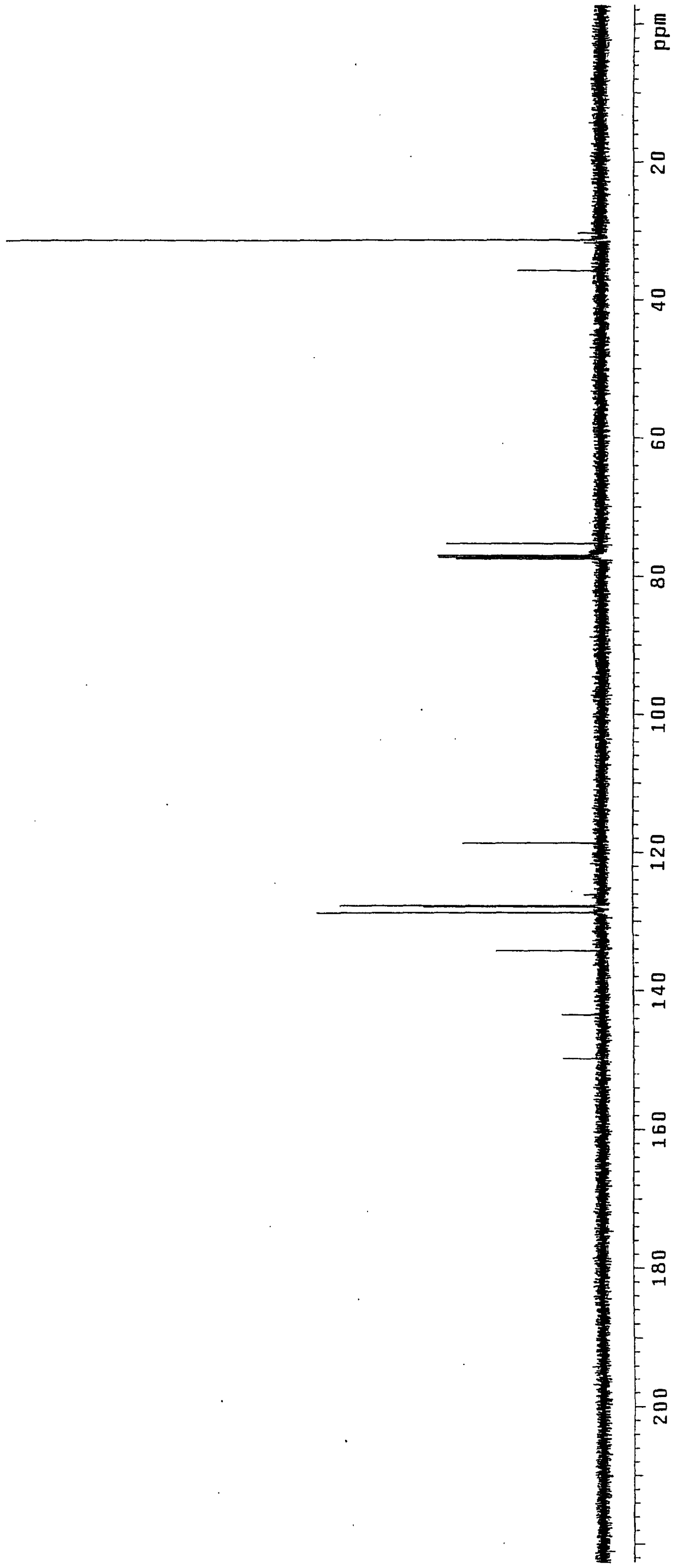

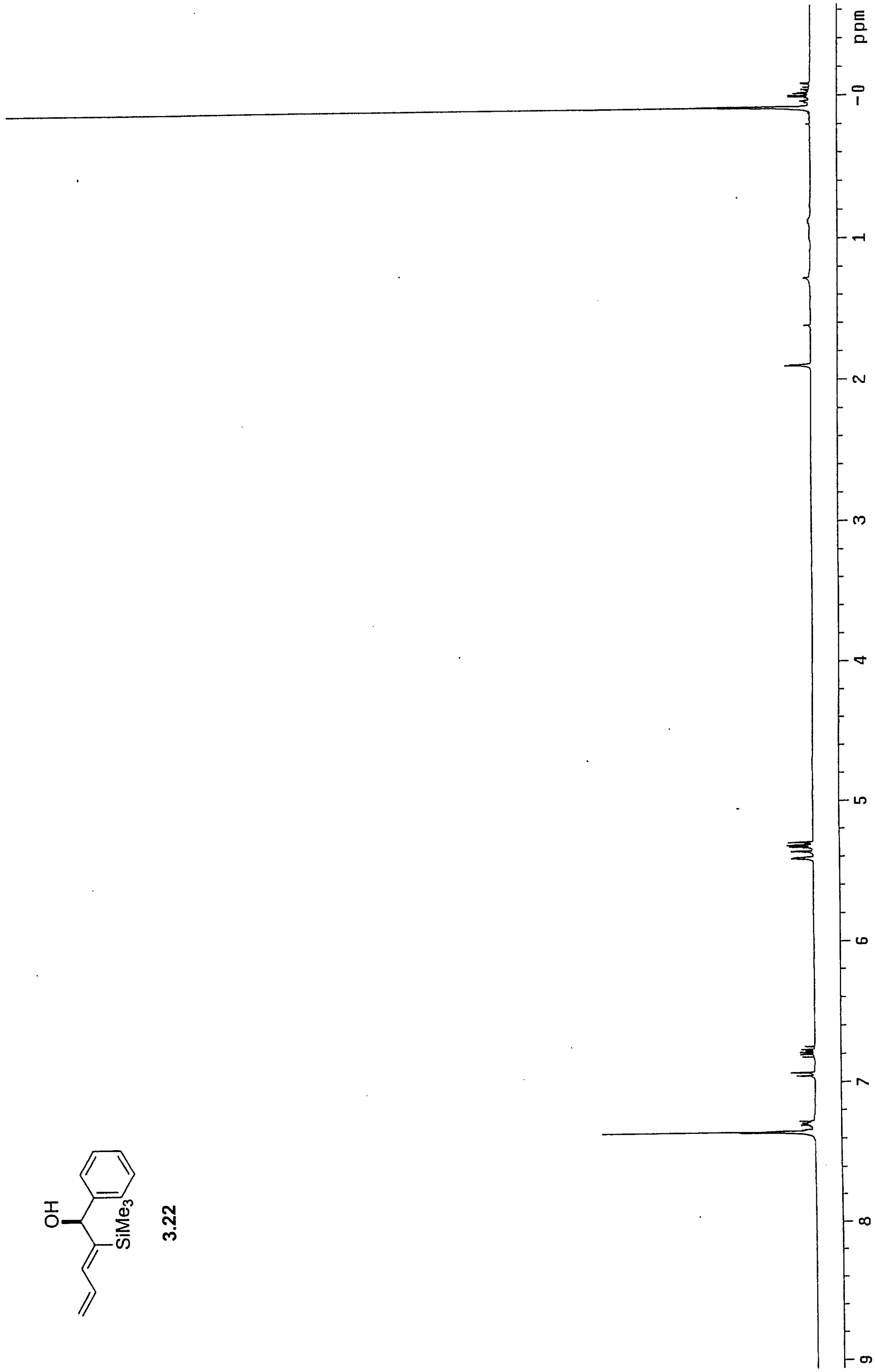

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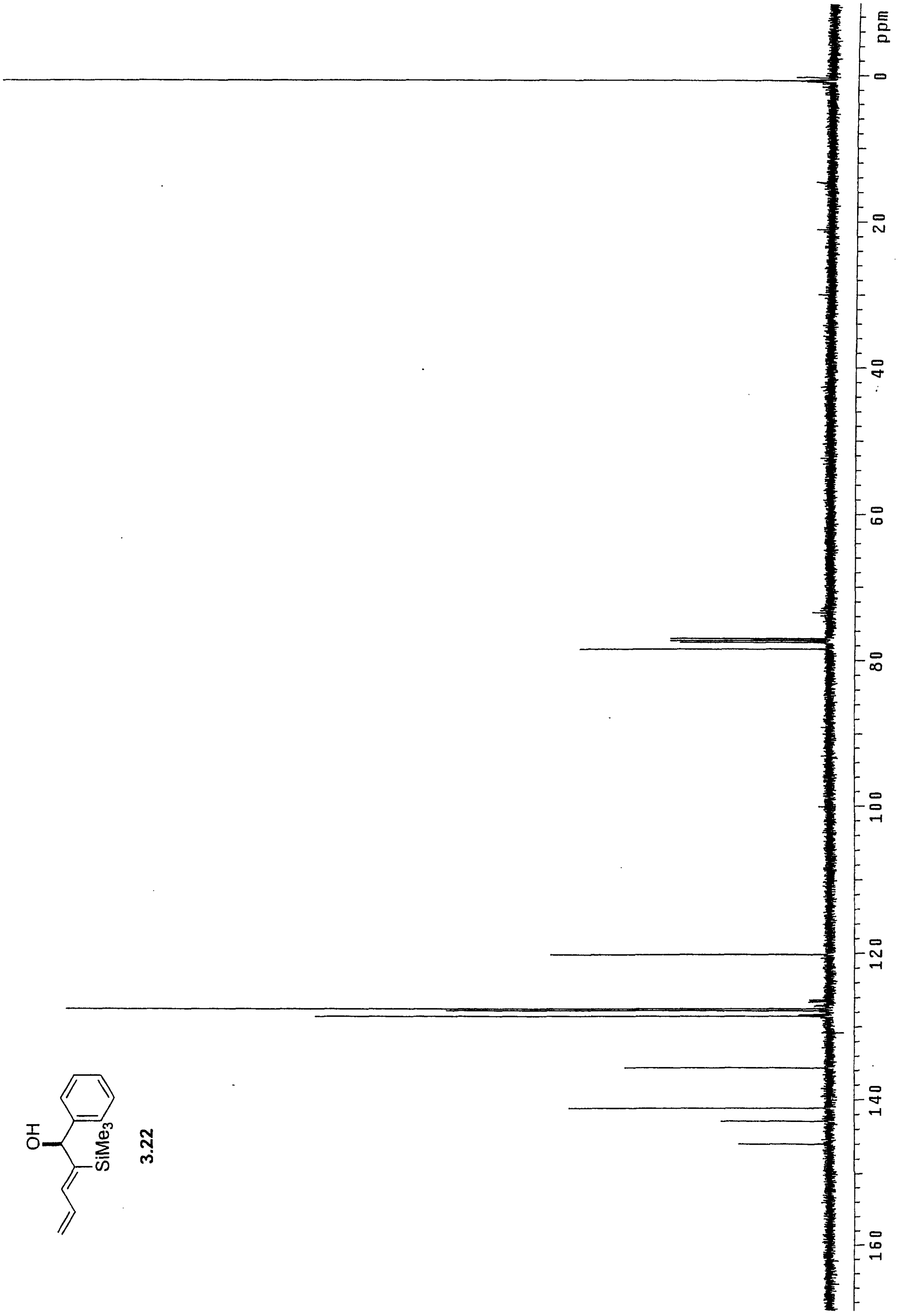

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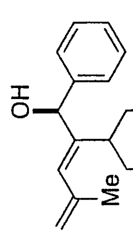

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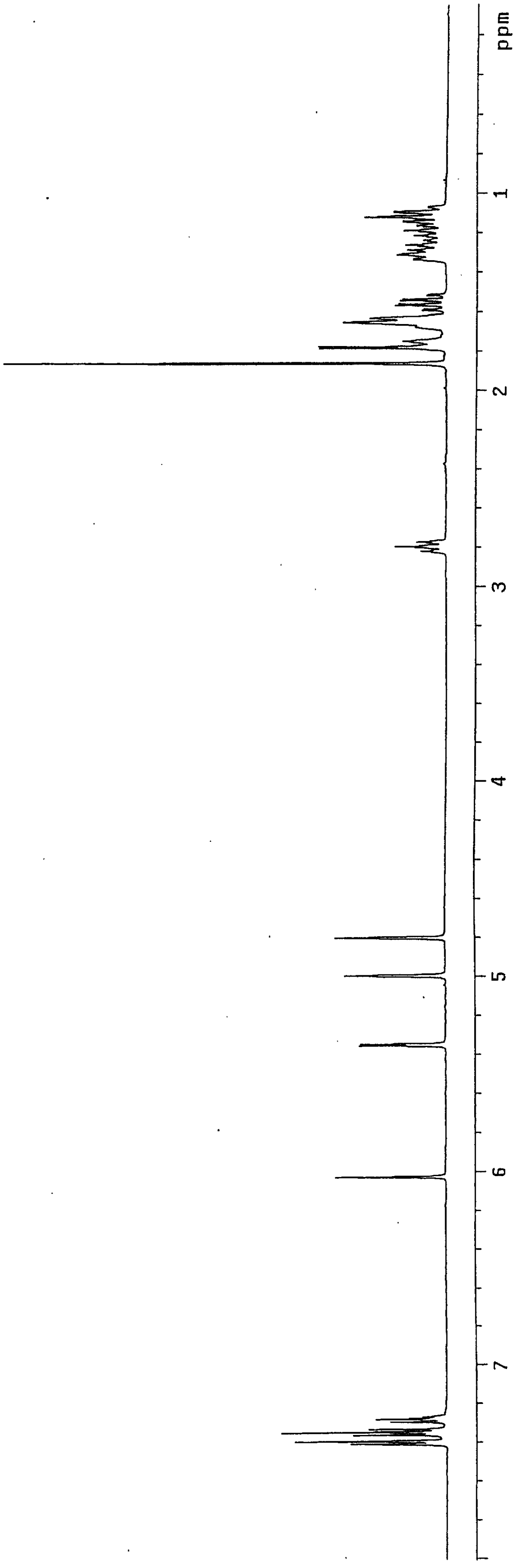

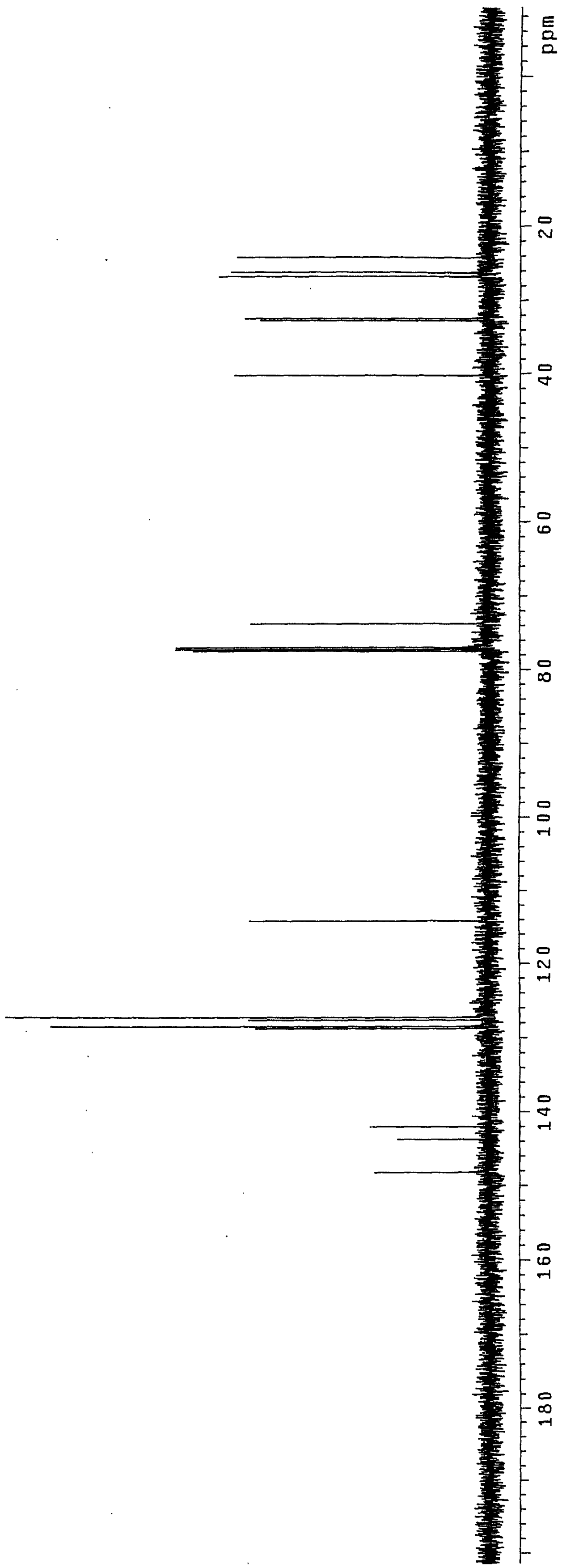

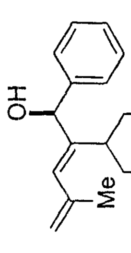

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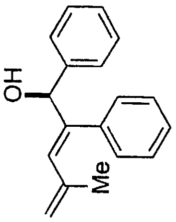

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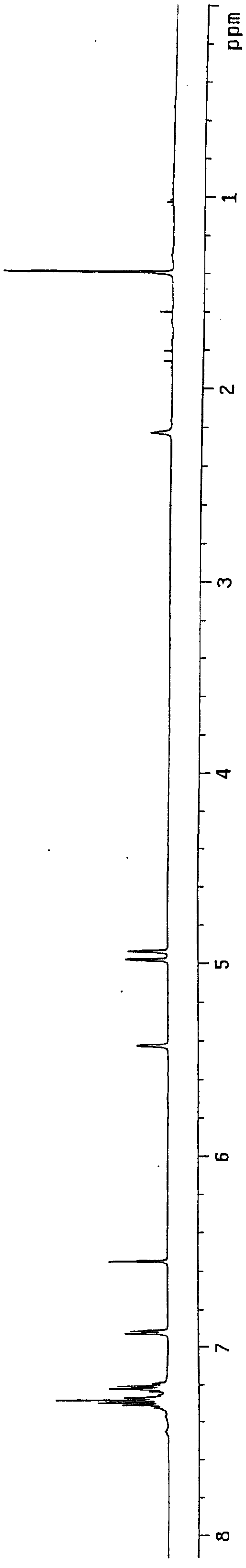

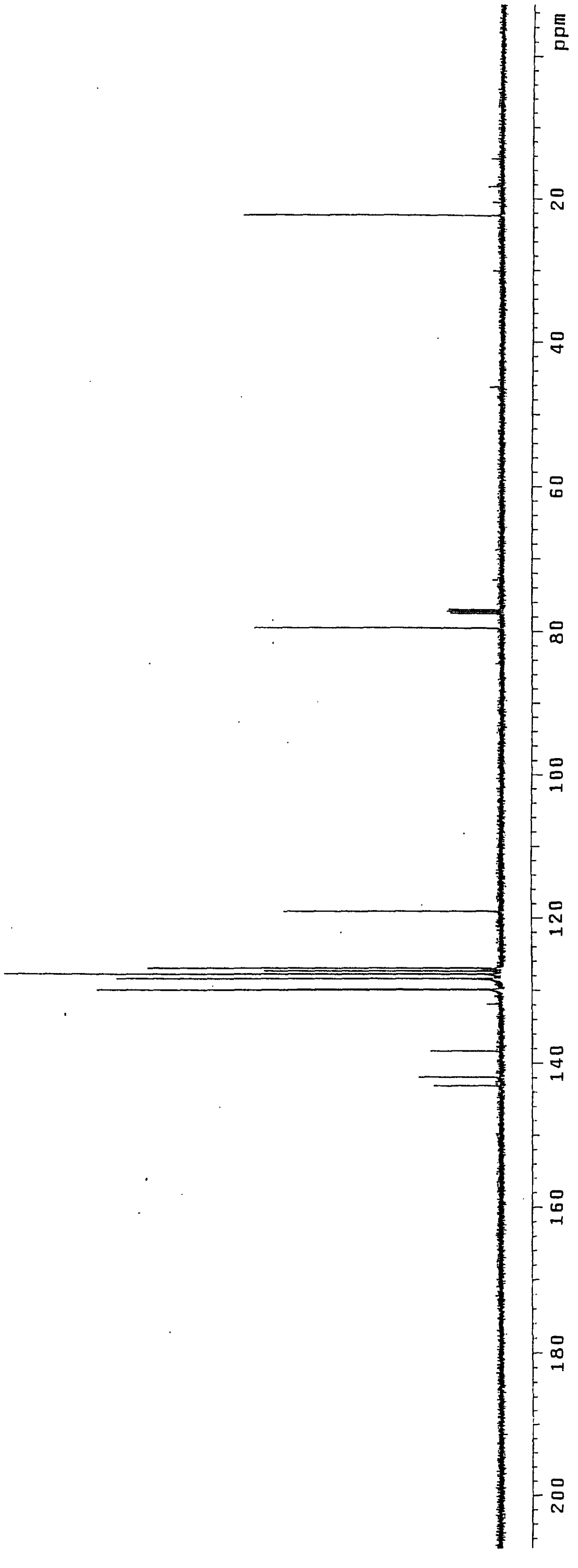

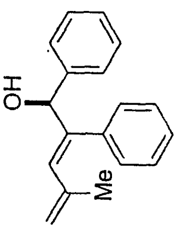

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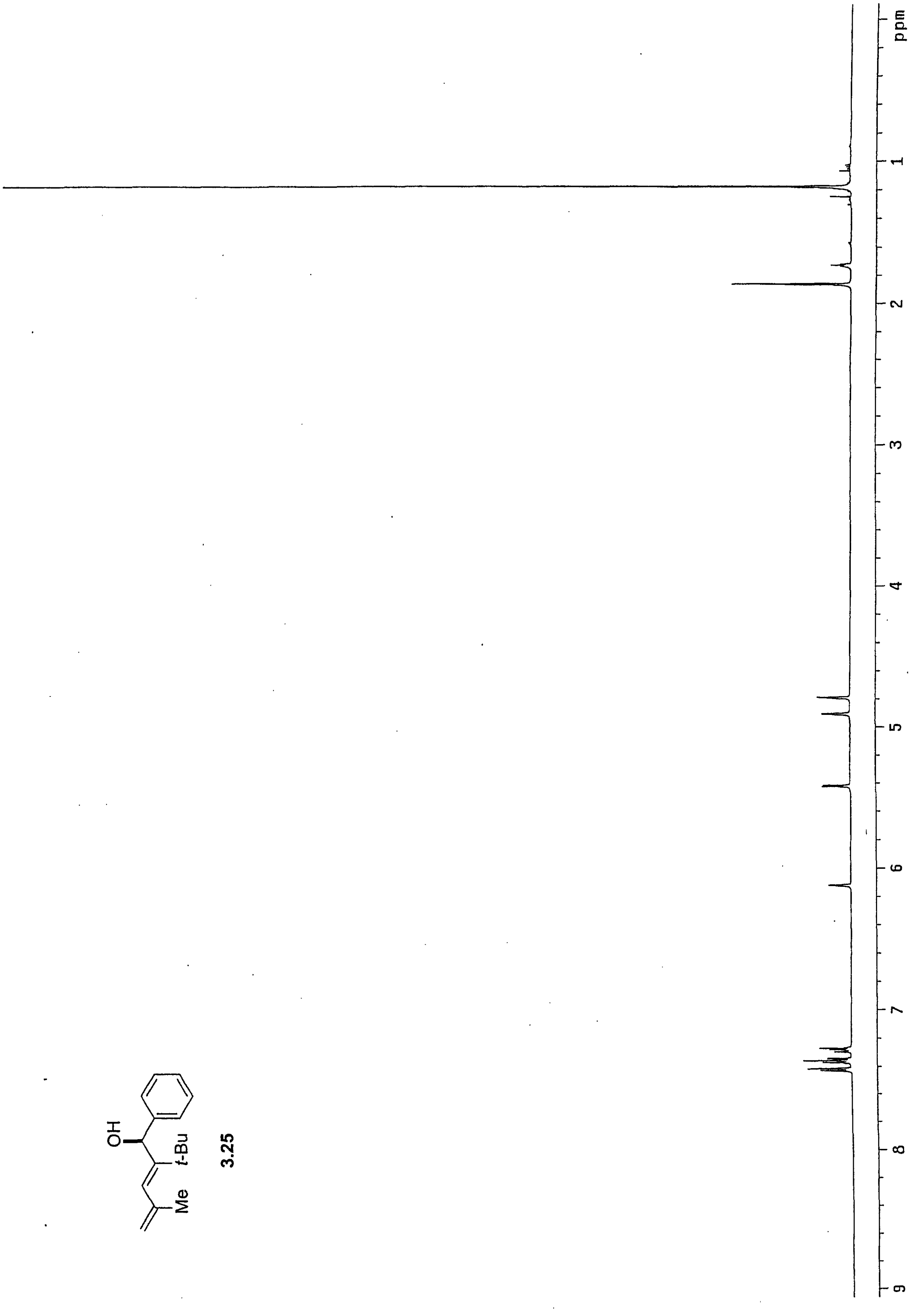

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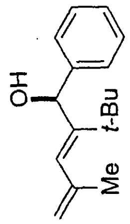

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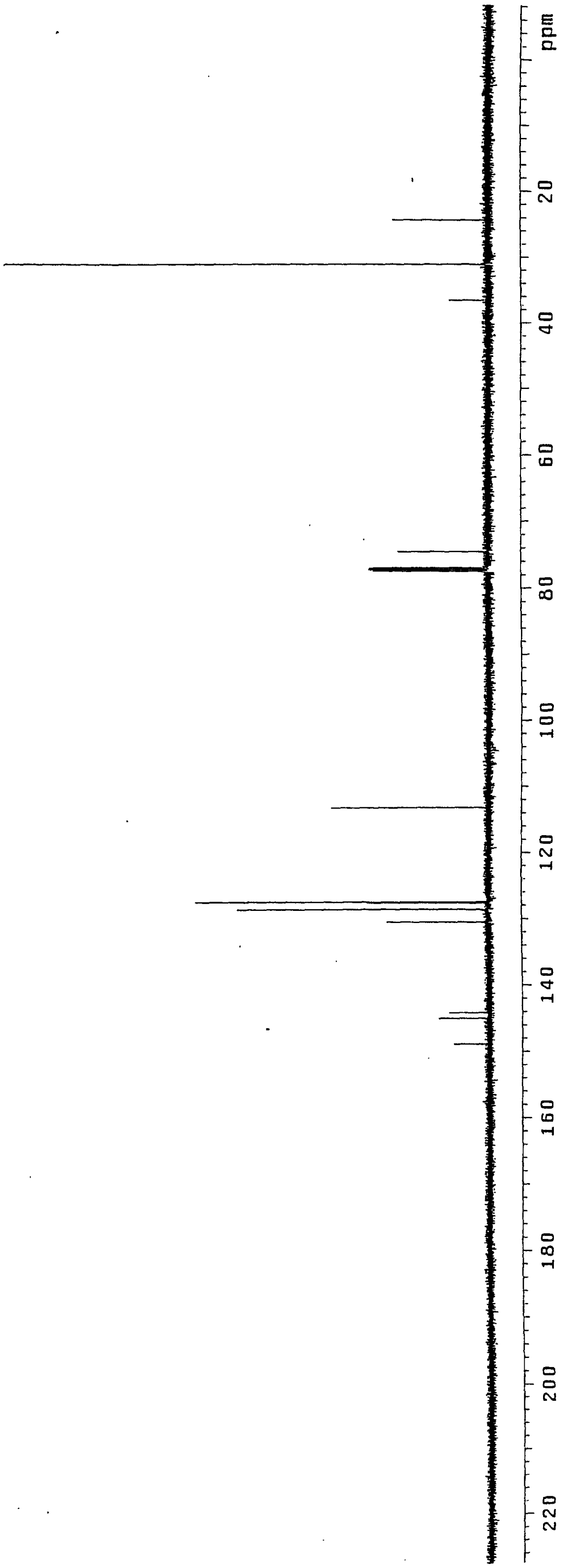

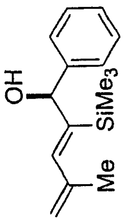

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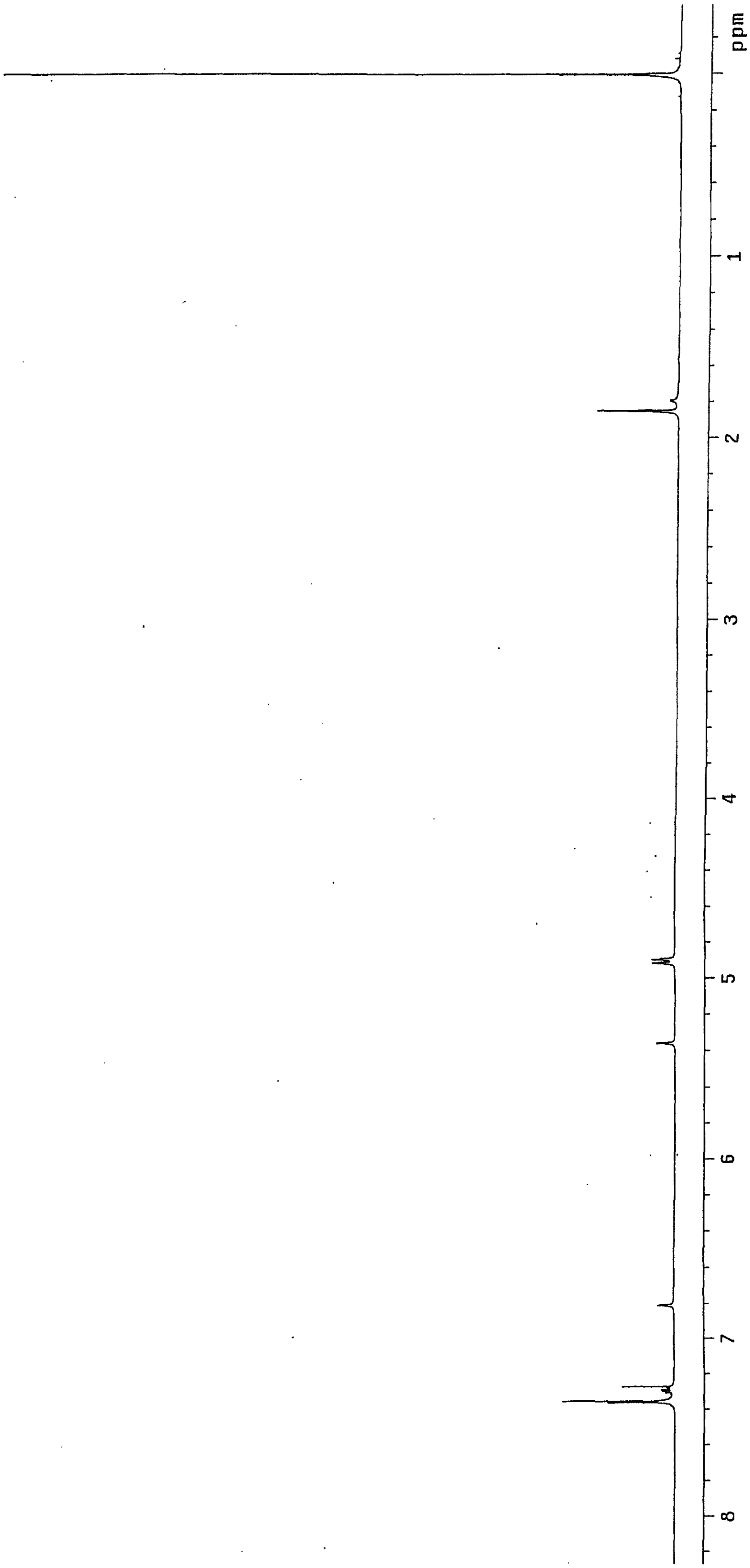

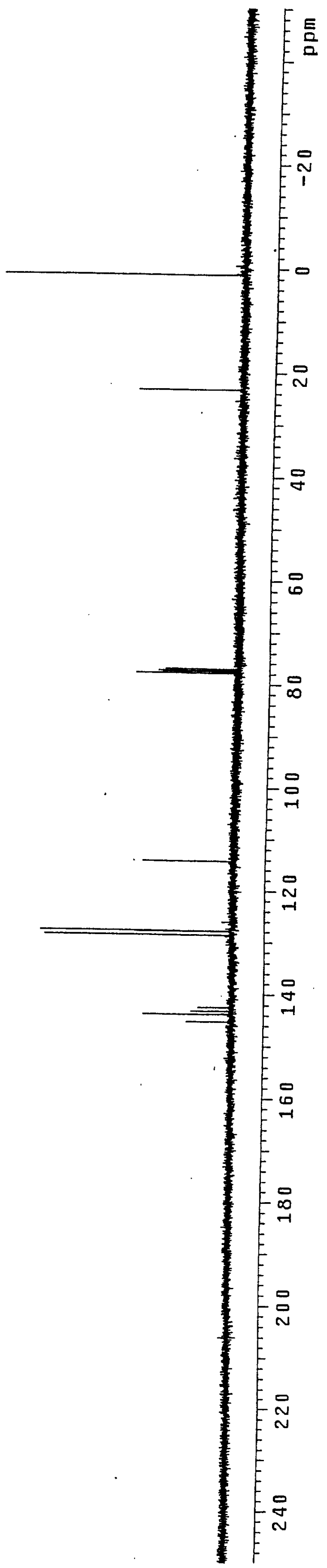

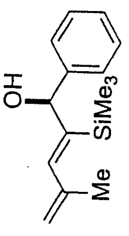

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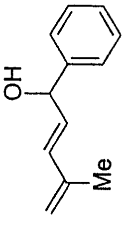

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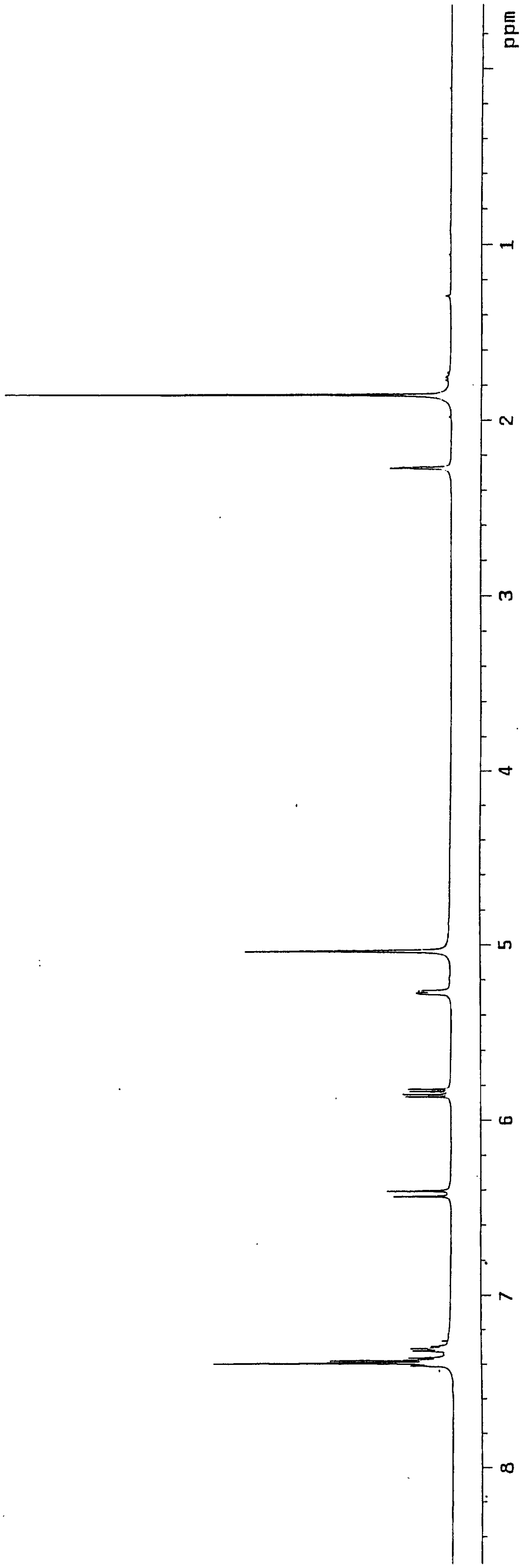

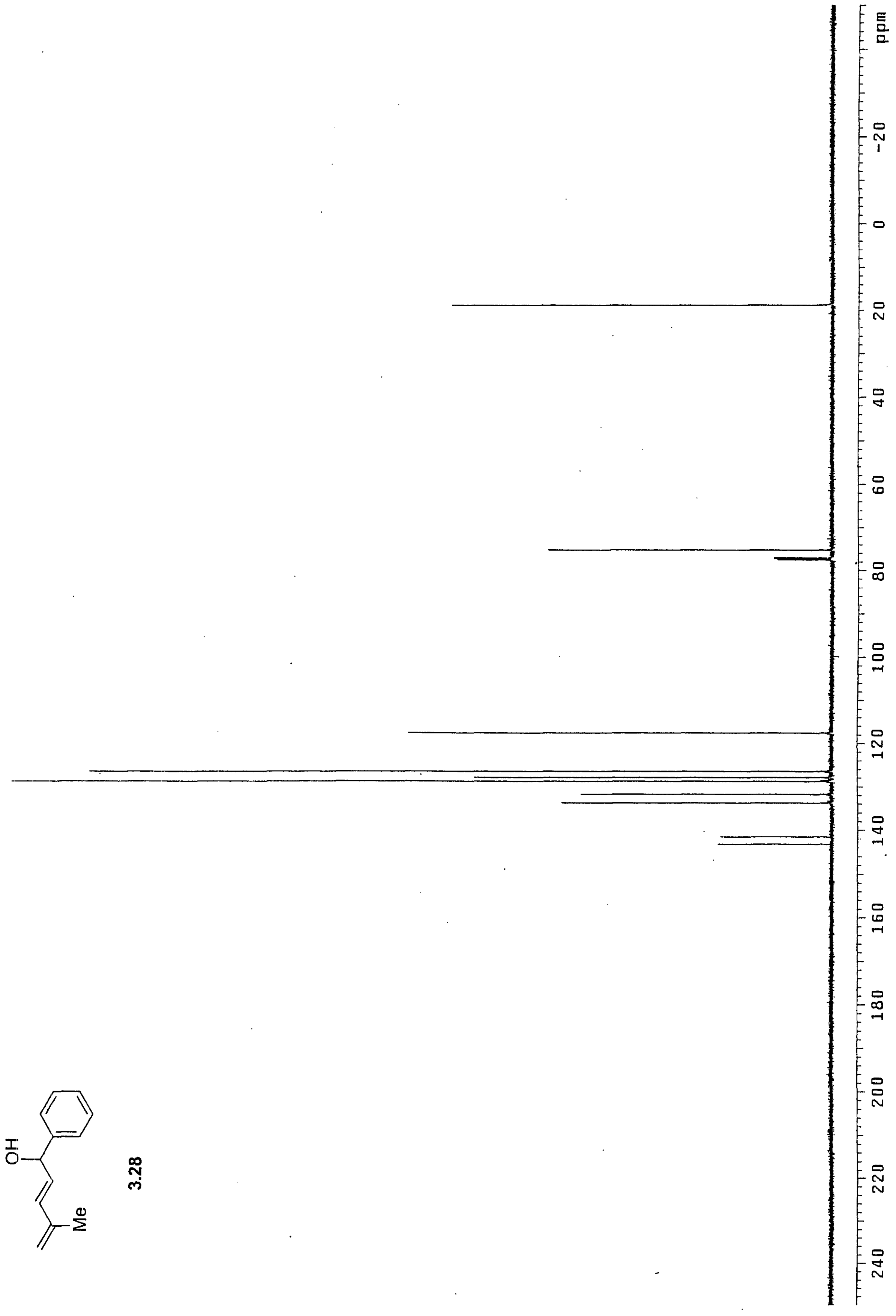

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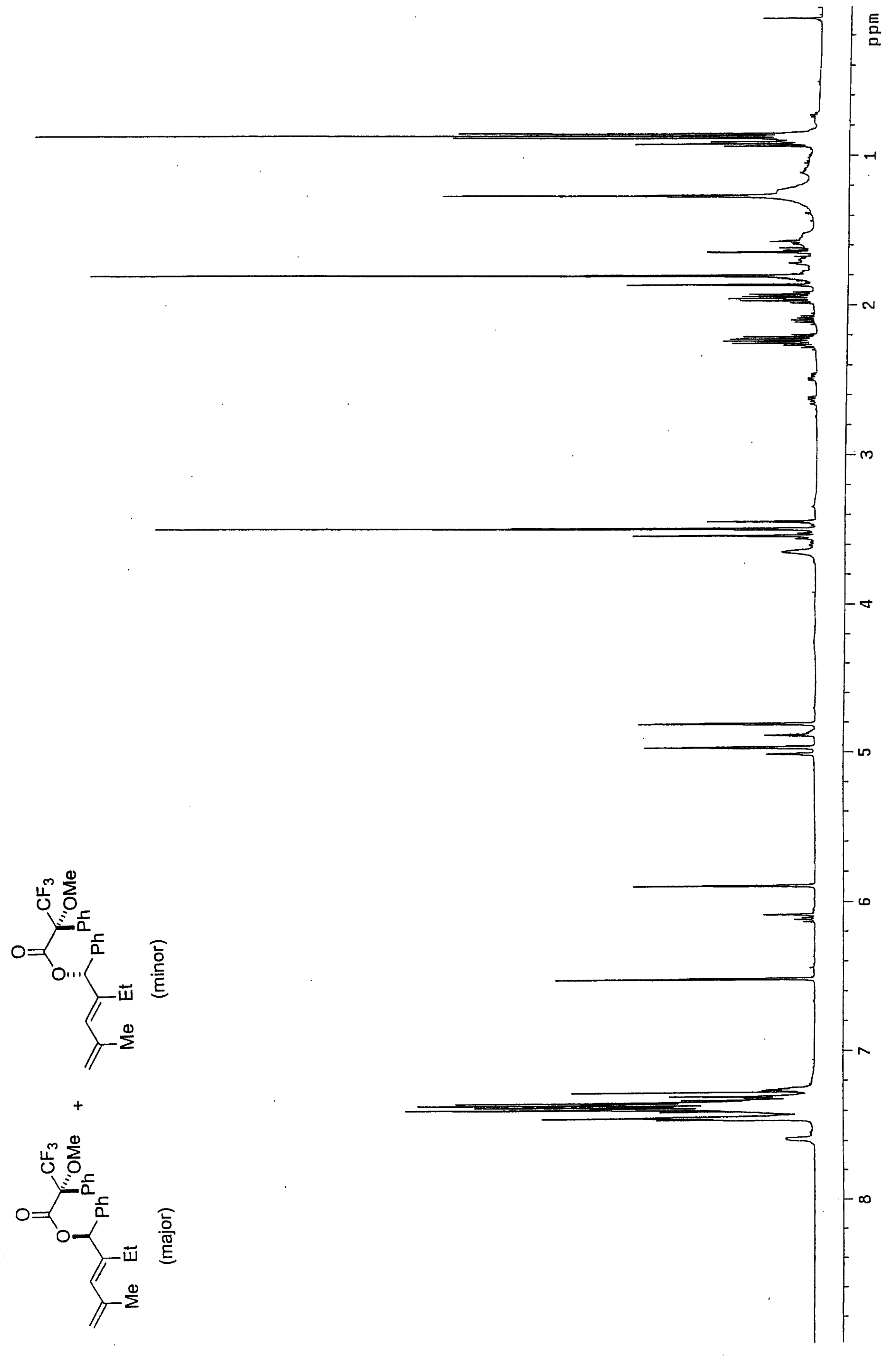

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(major)
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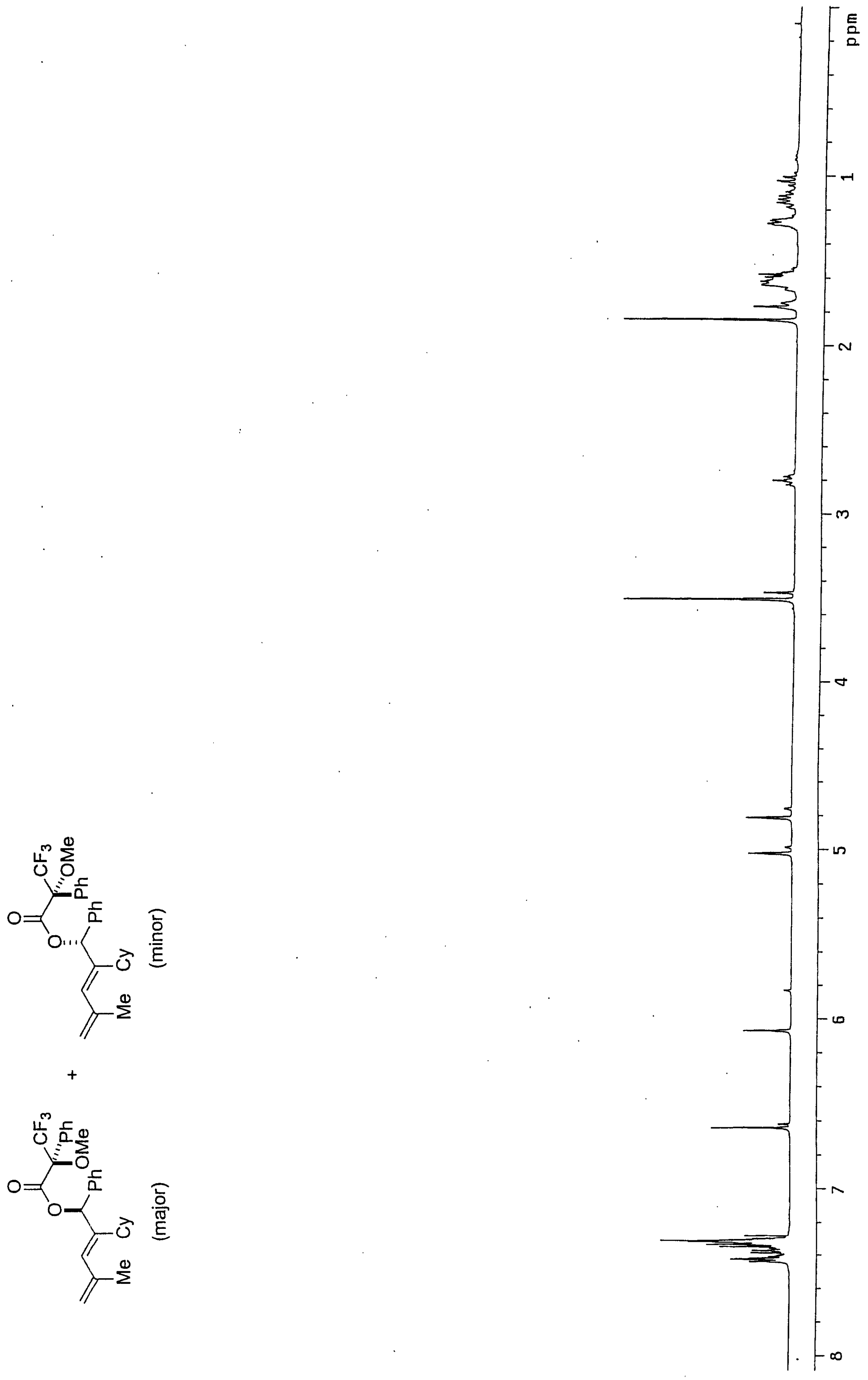

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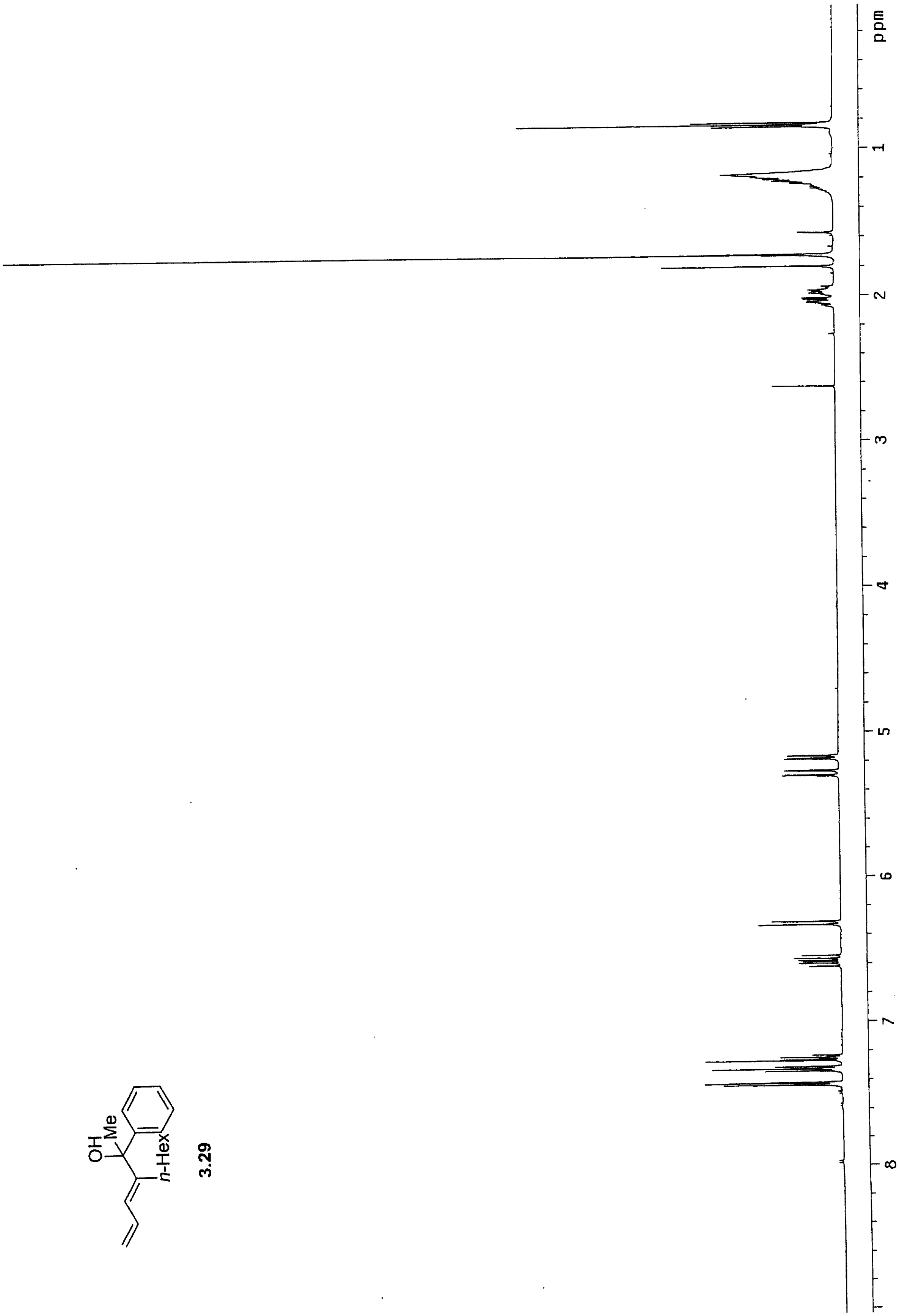
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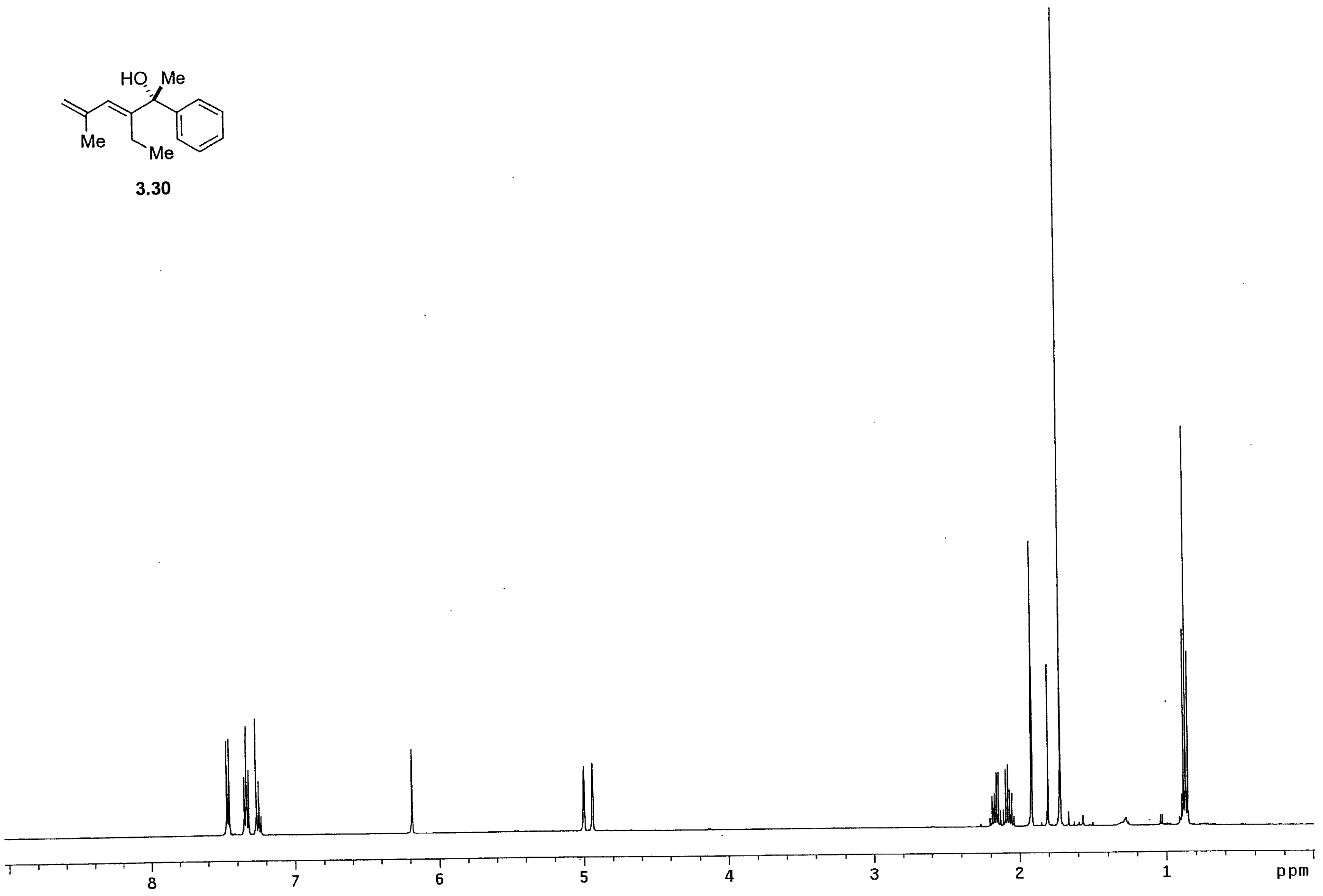

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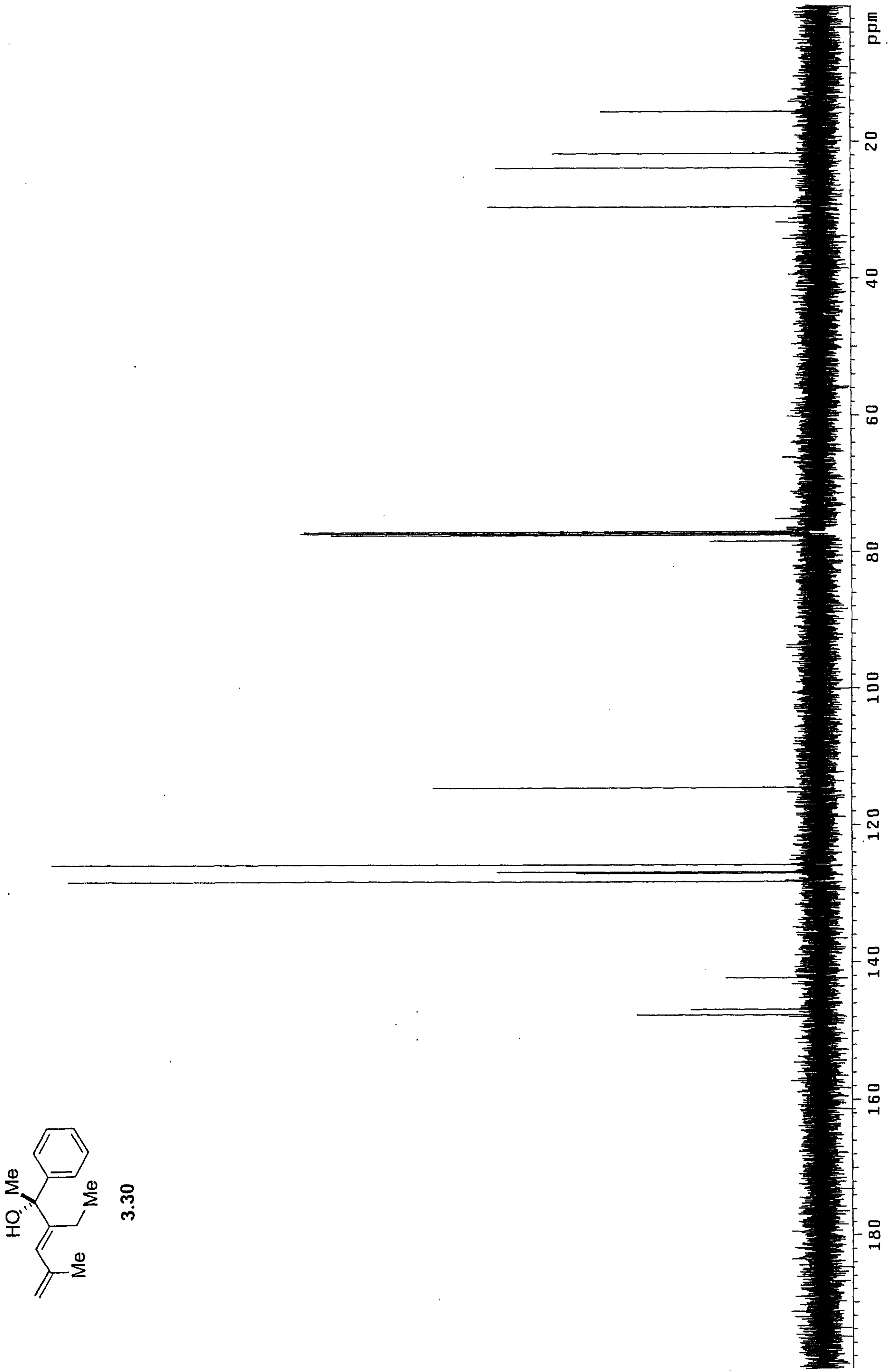

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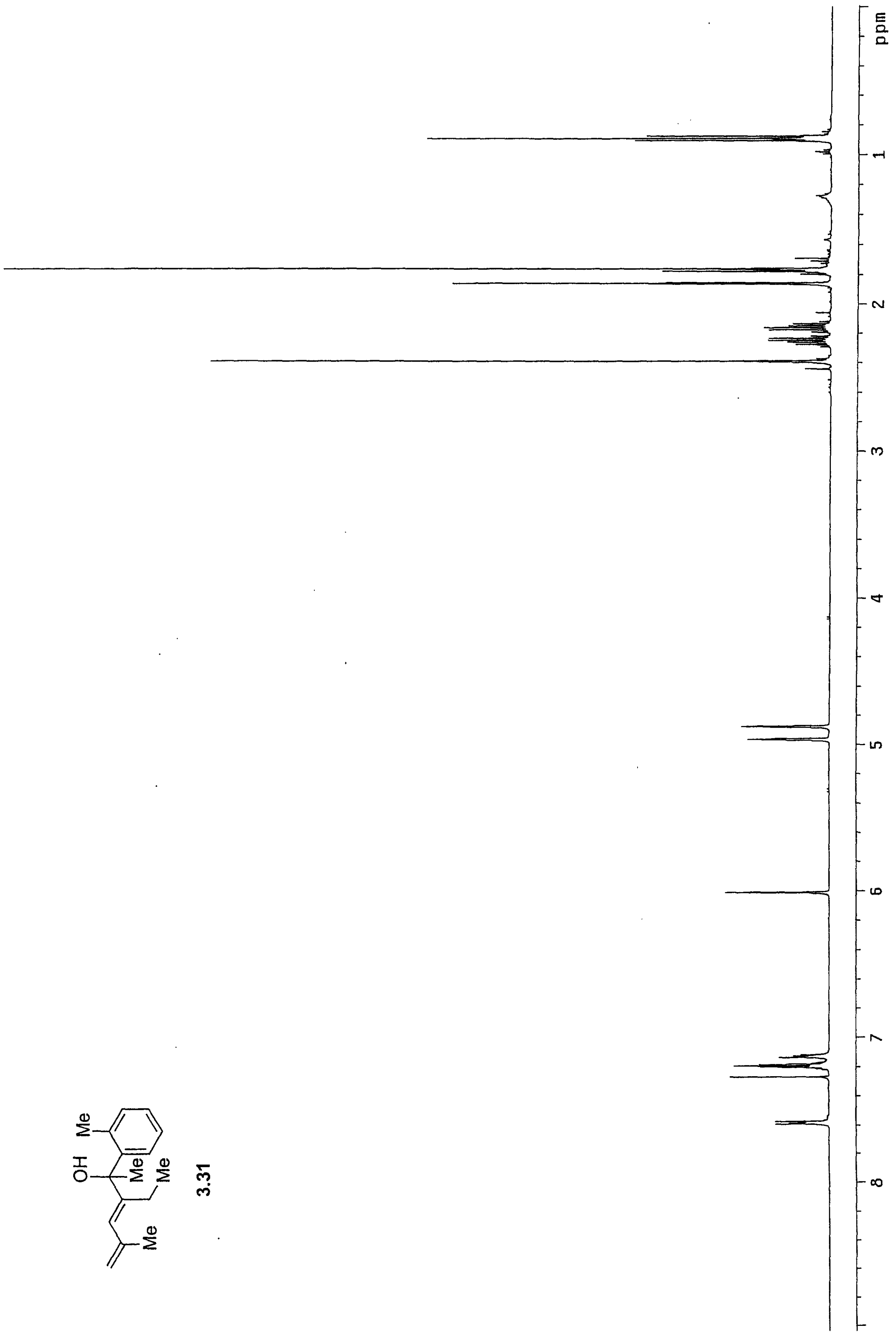

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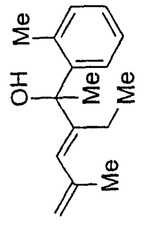

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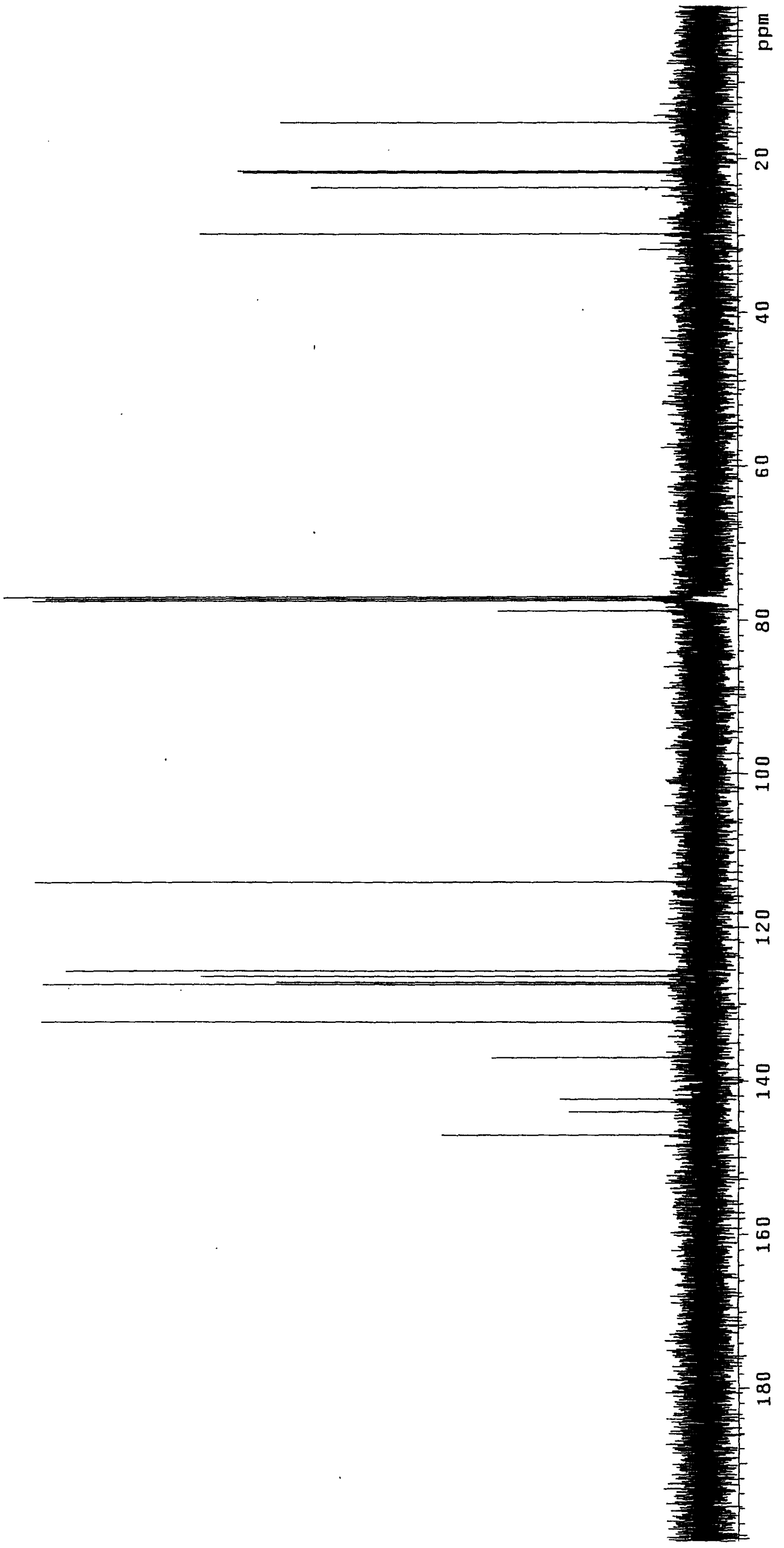

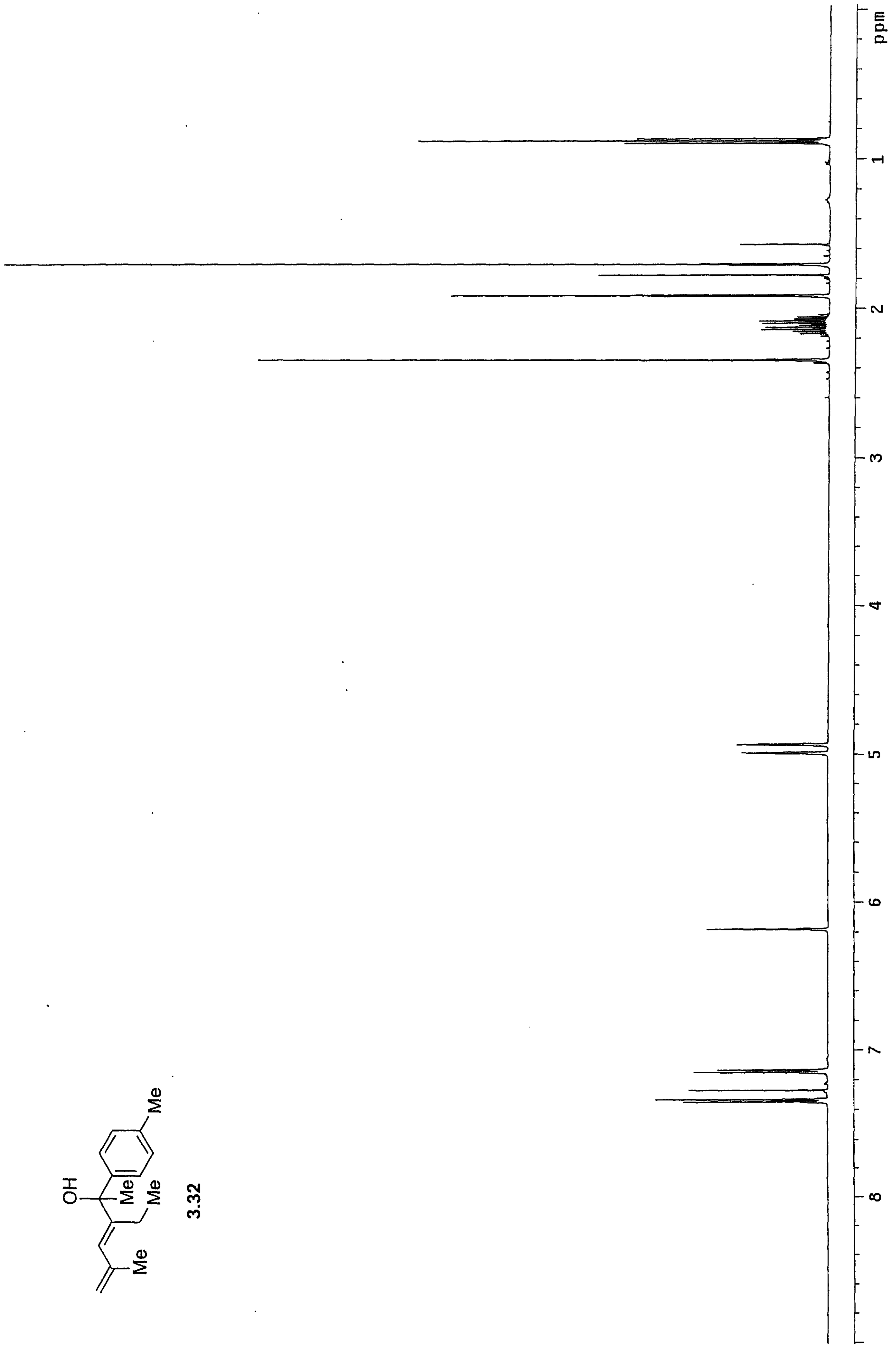

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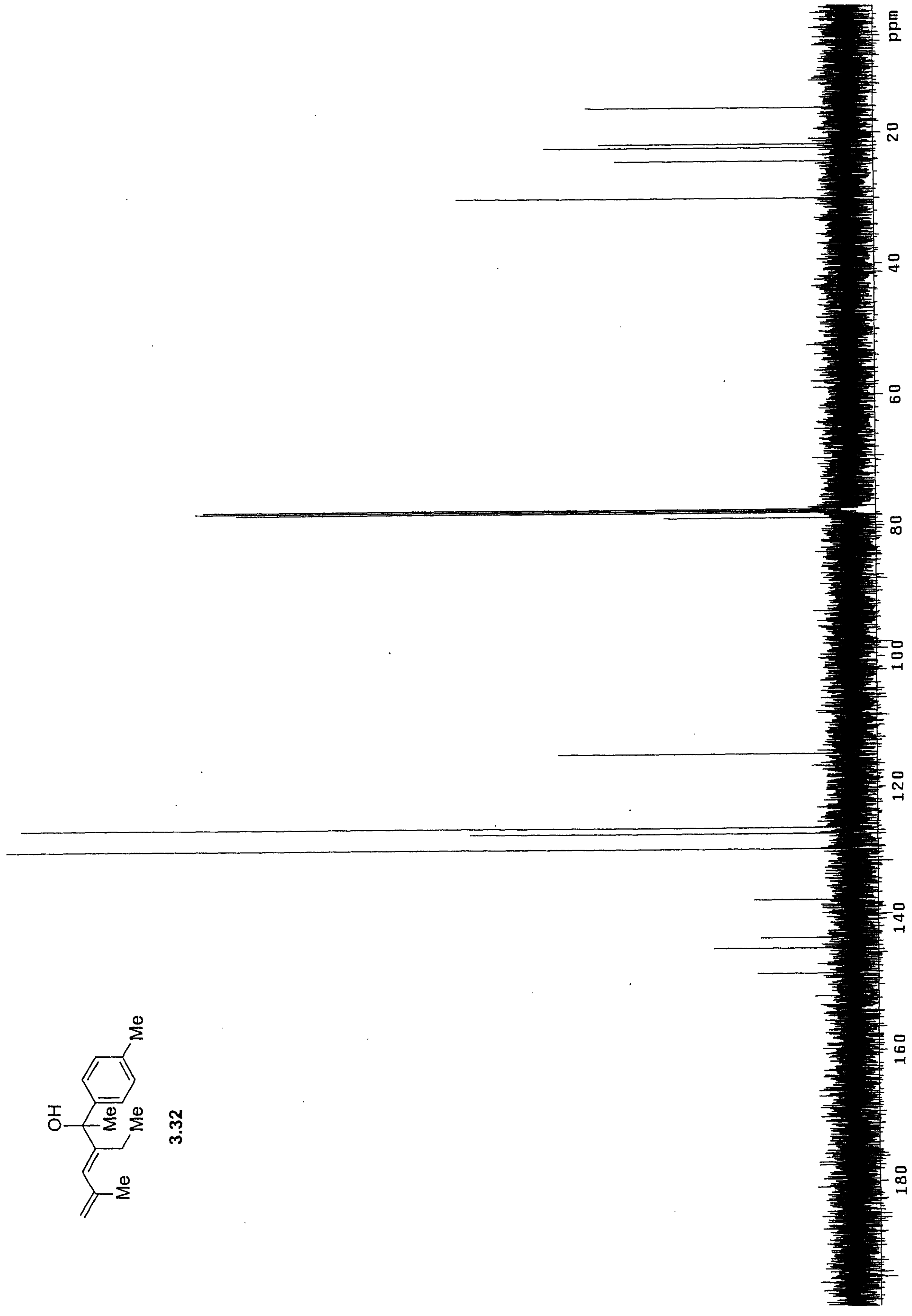

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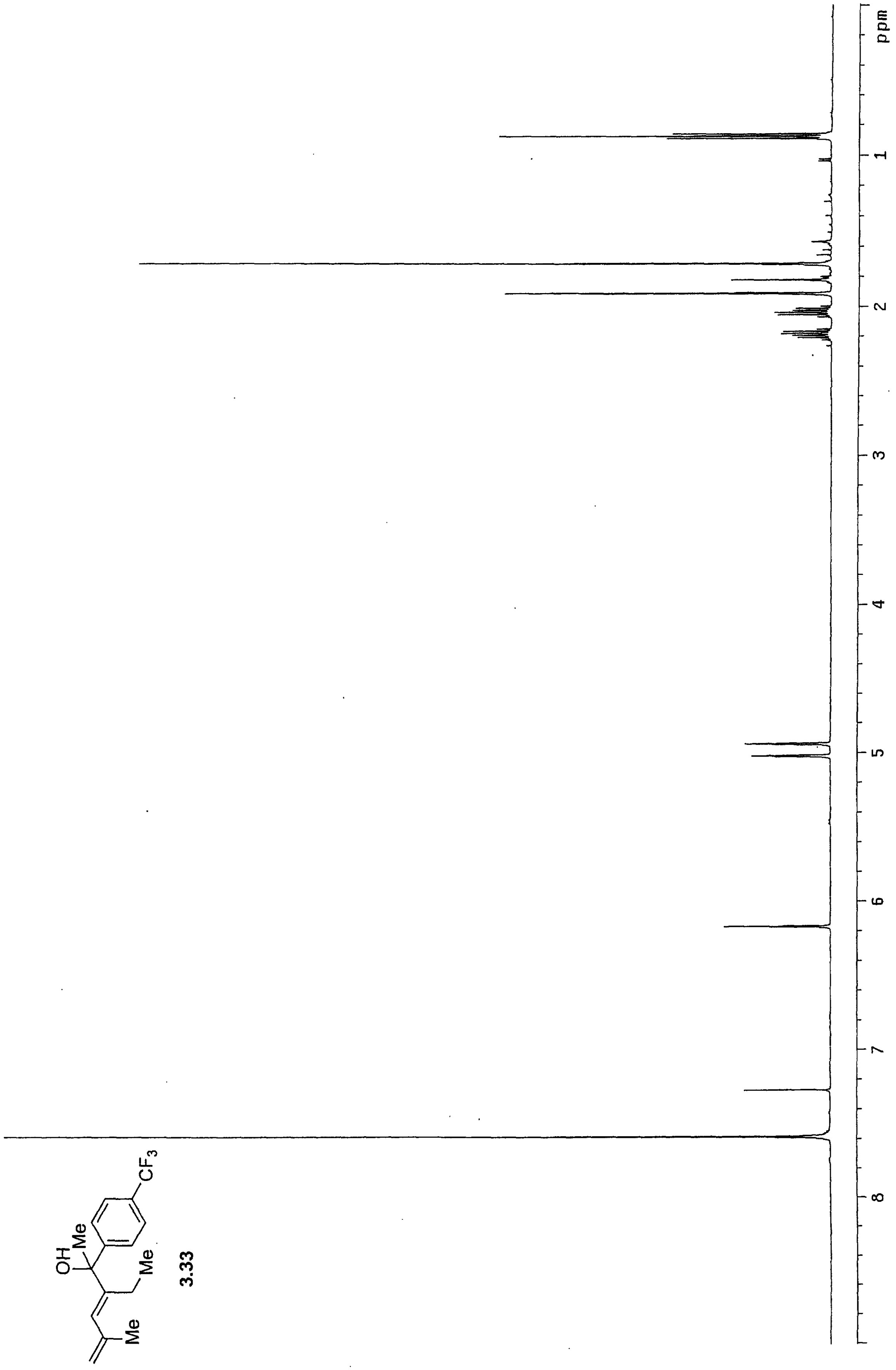

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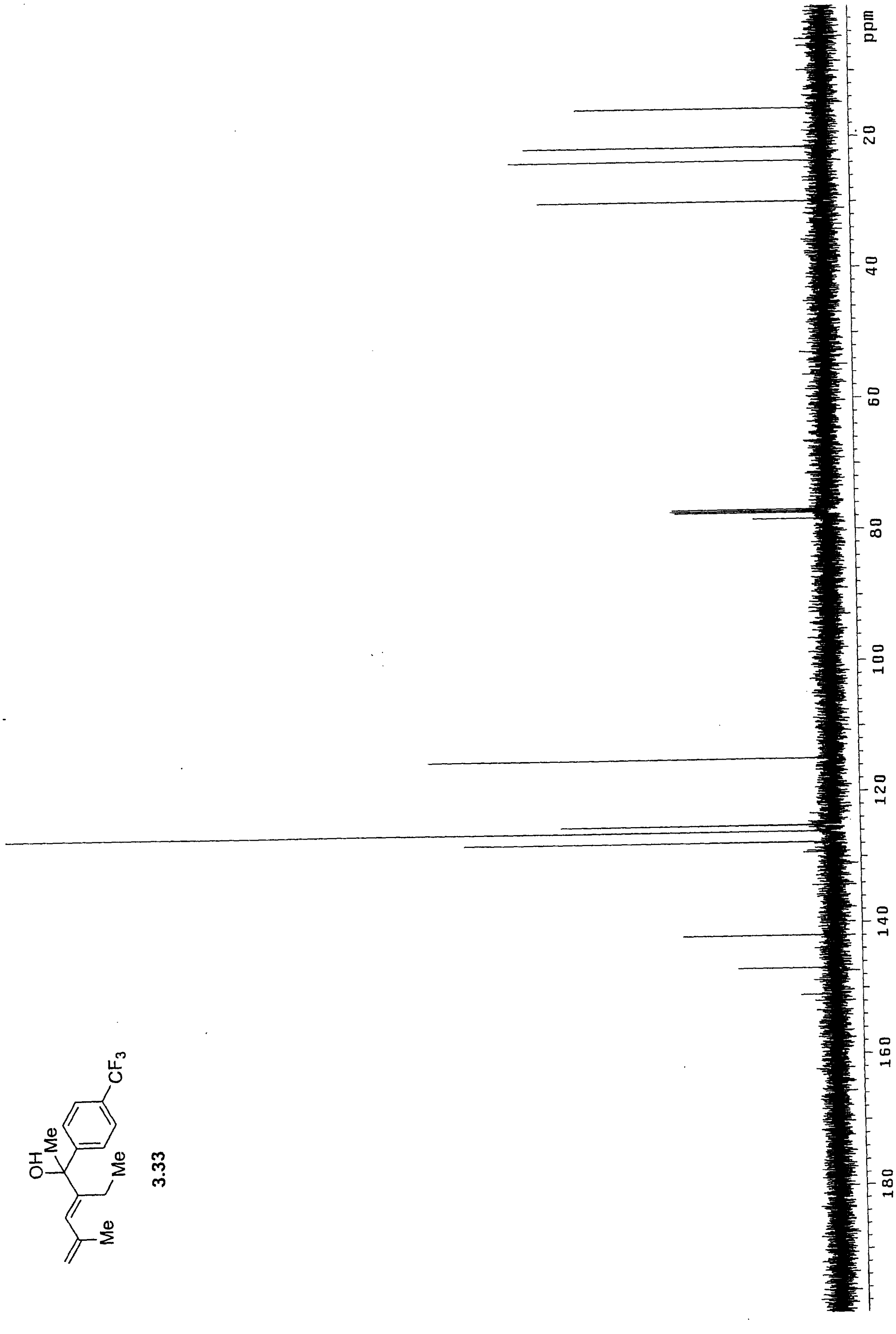

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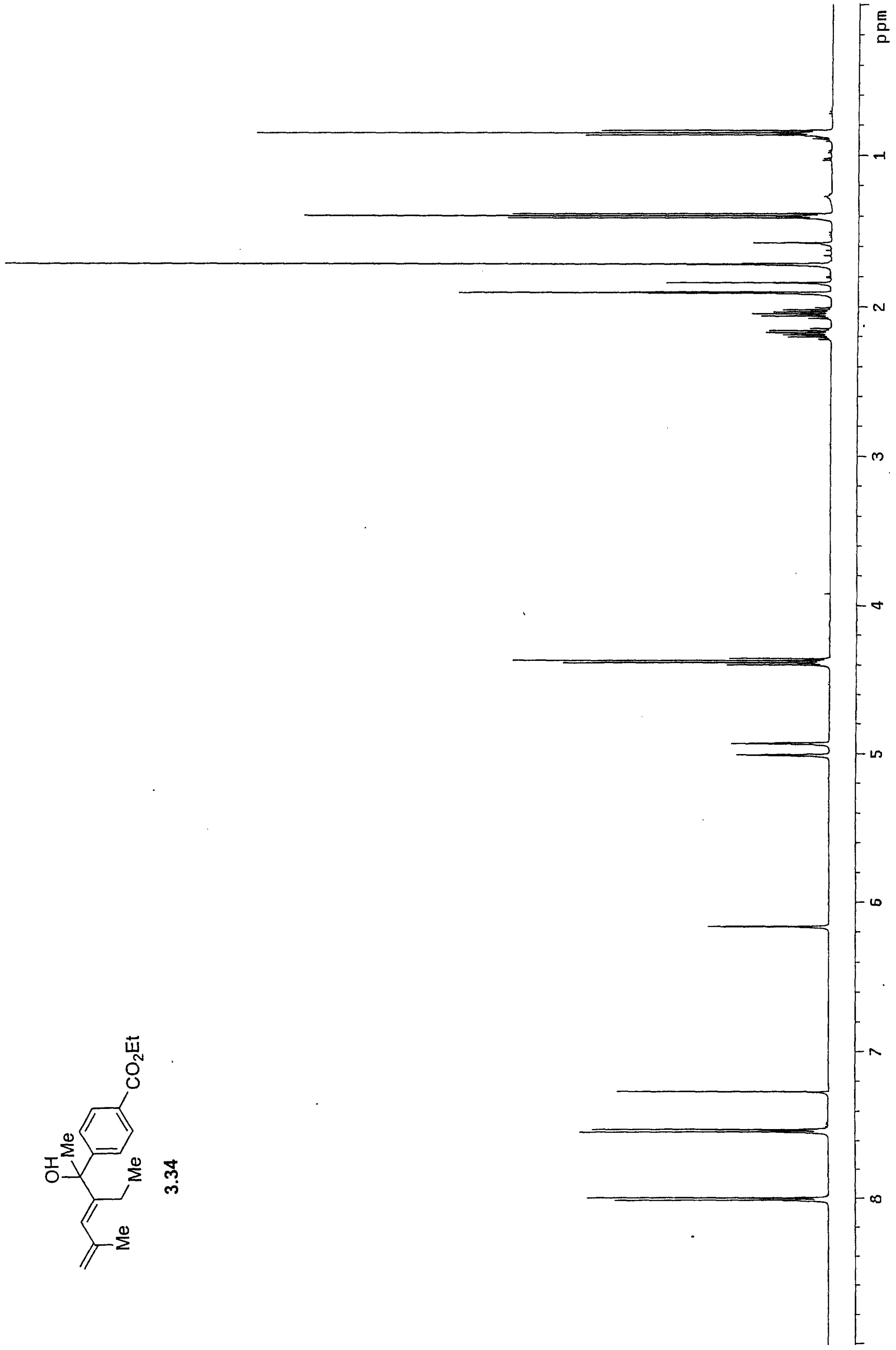

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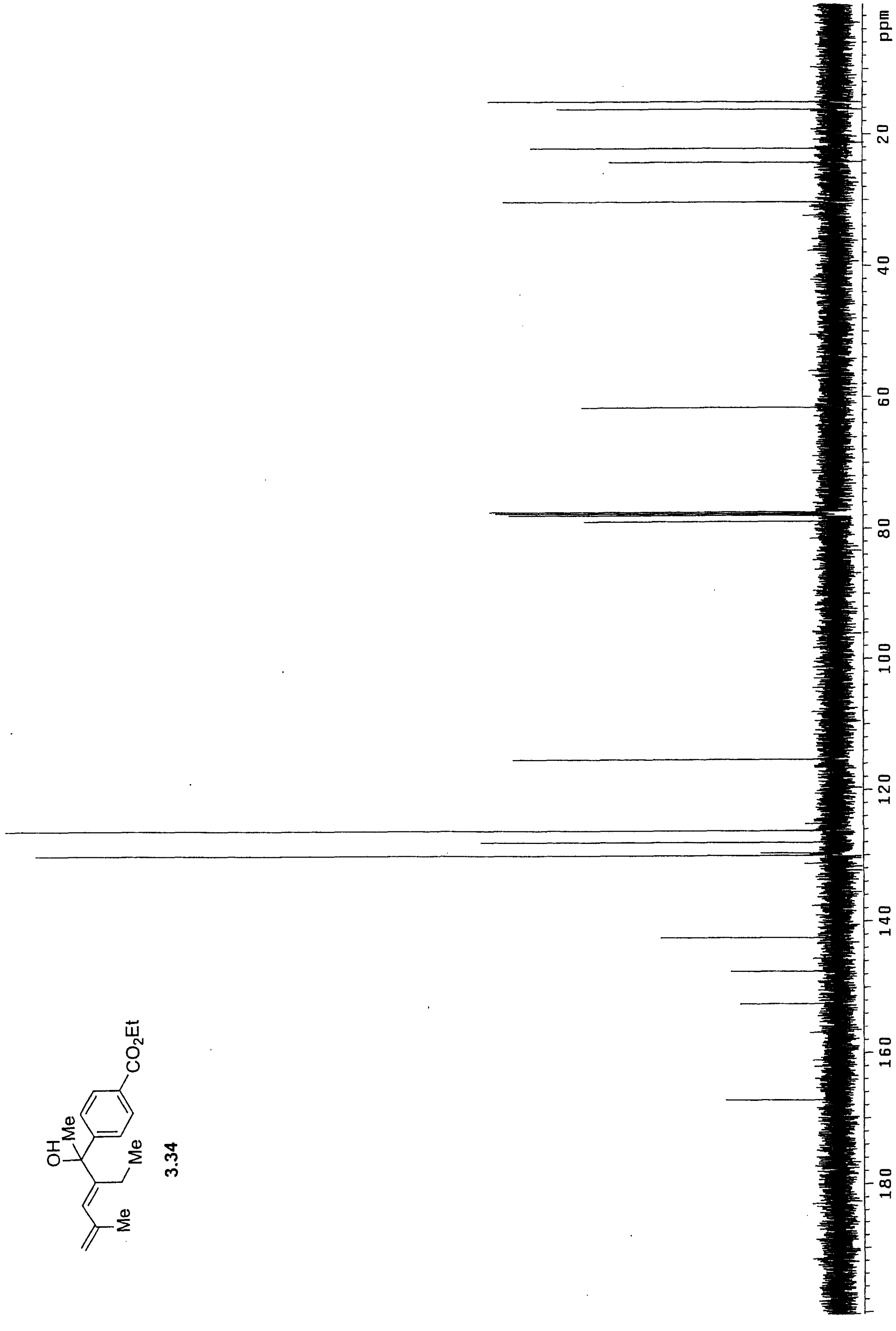

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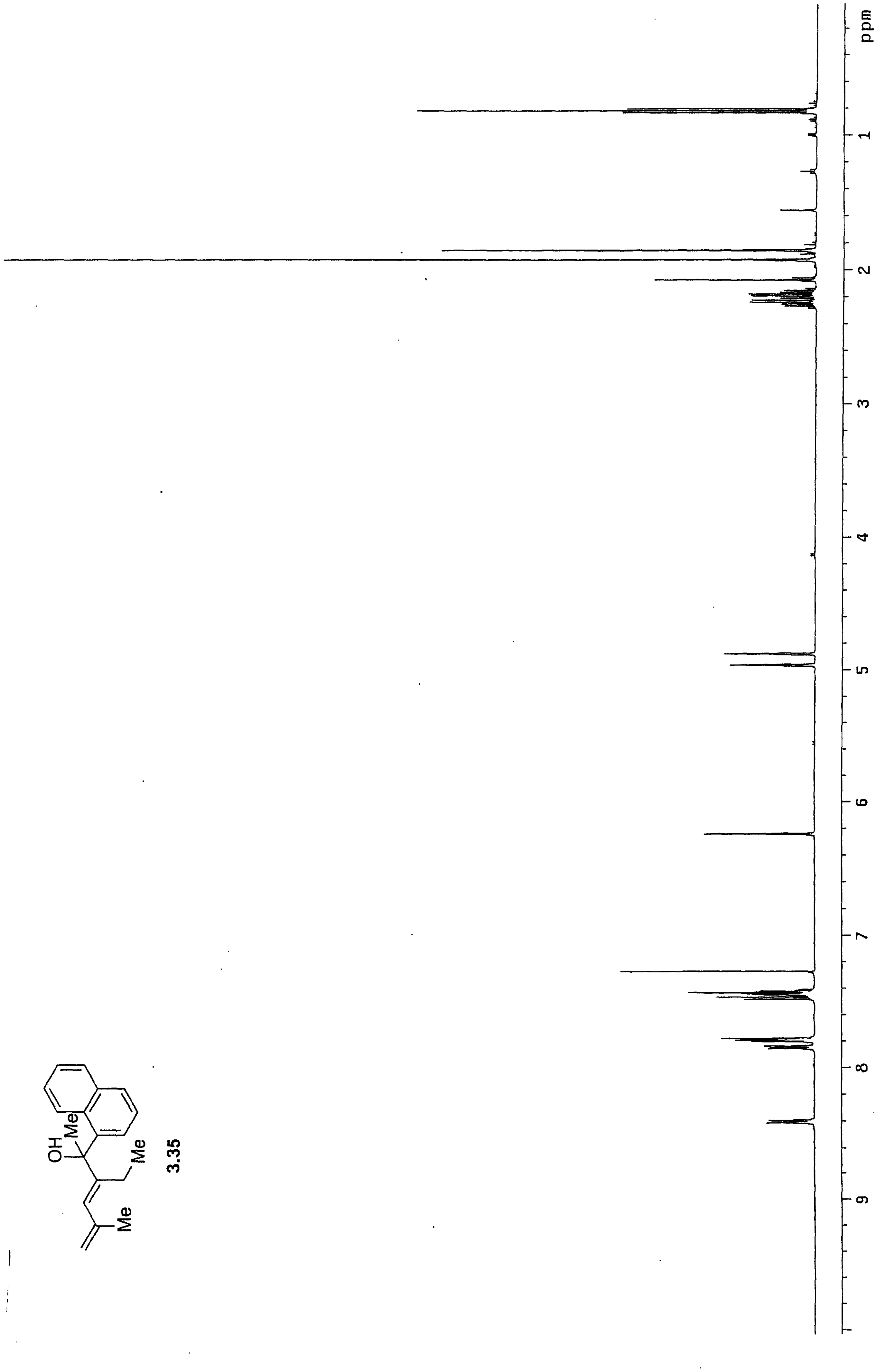

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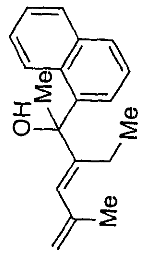

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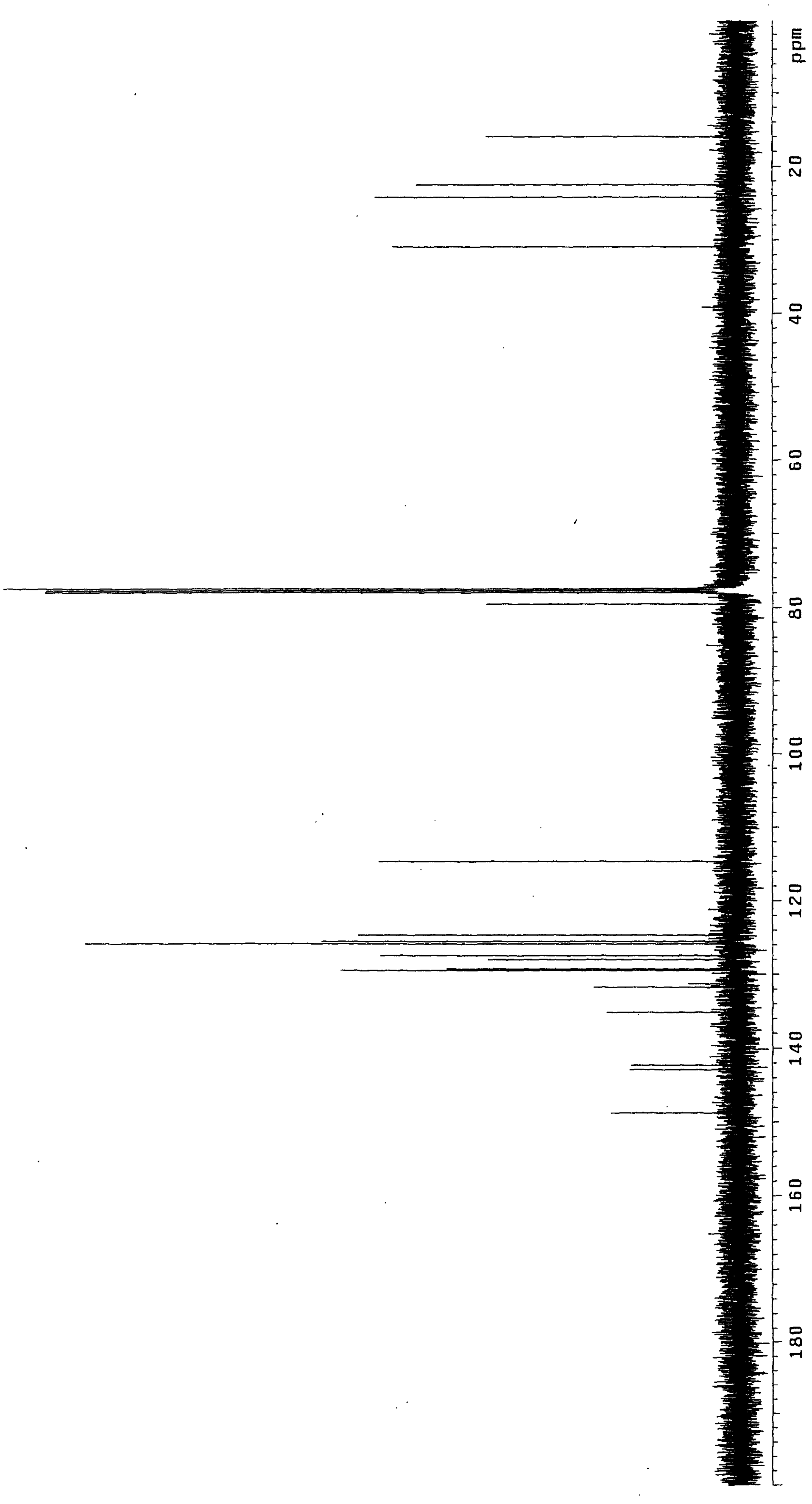

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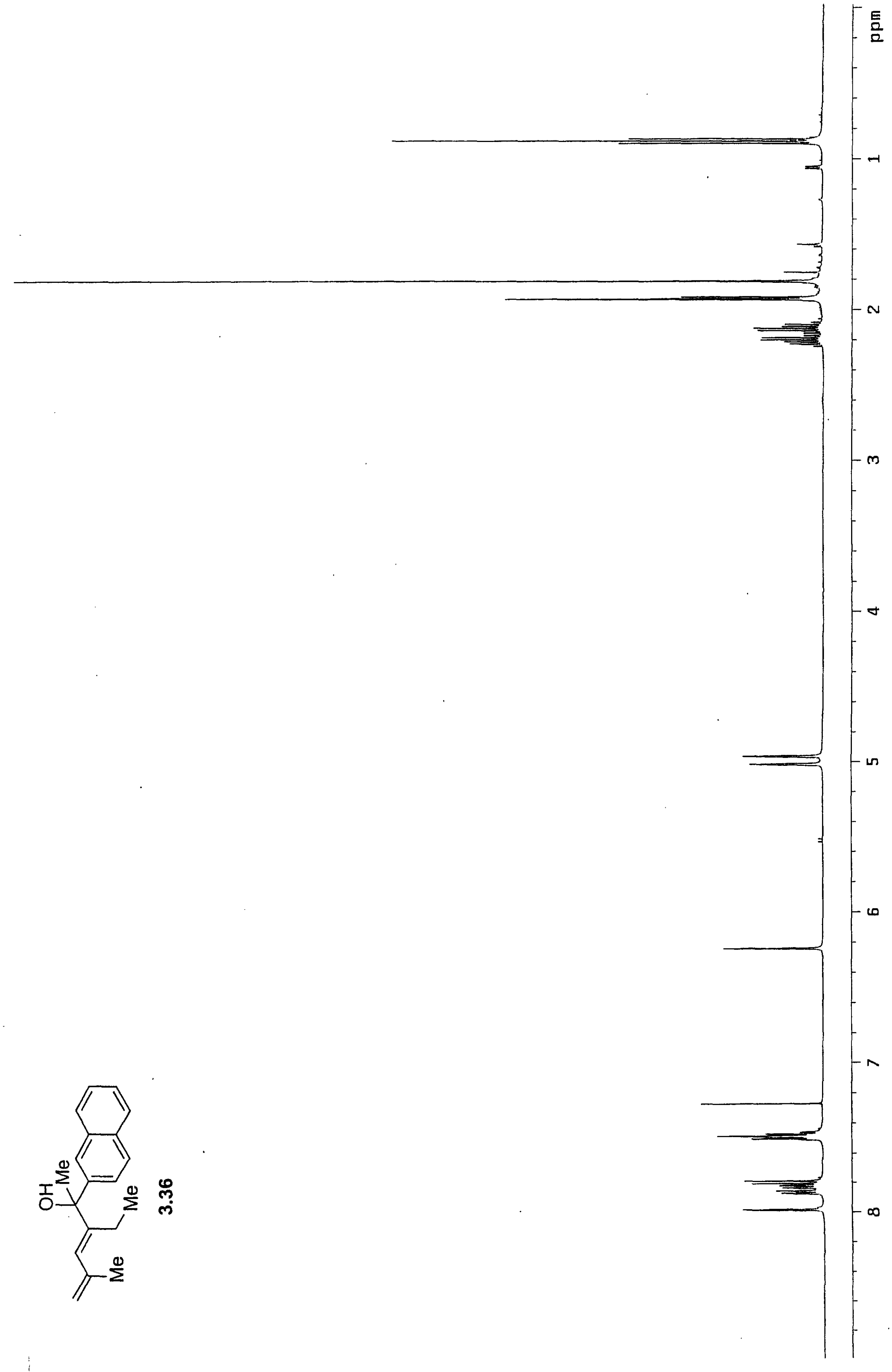

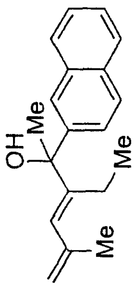

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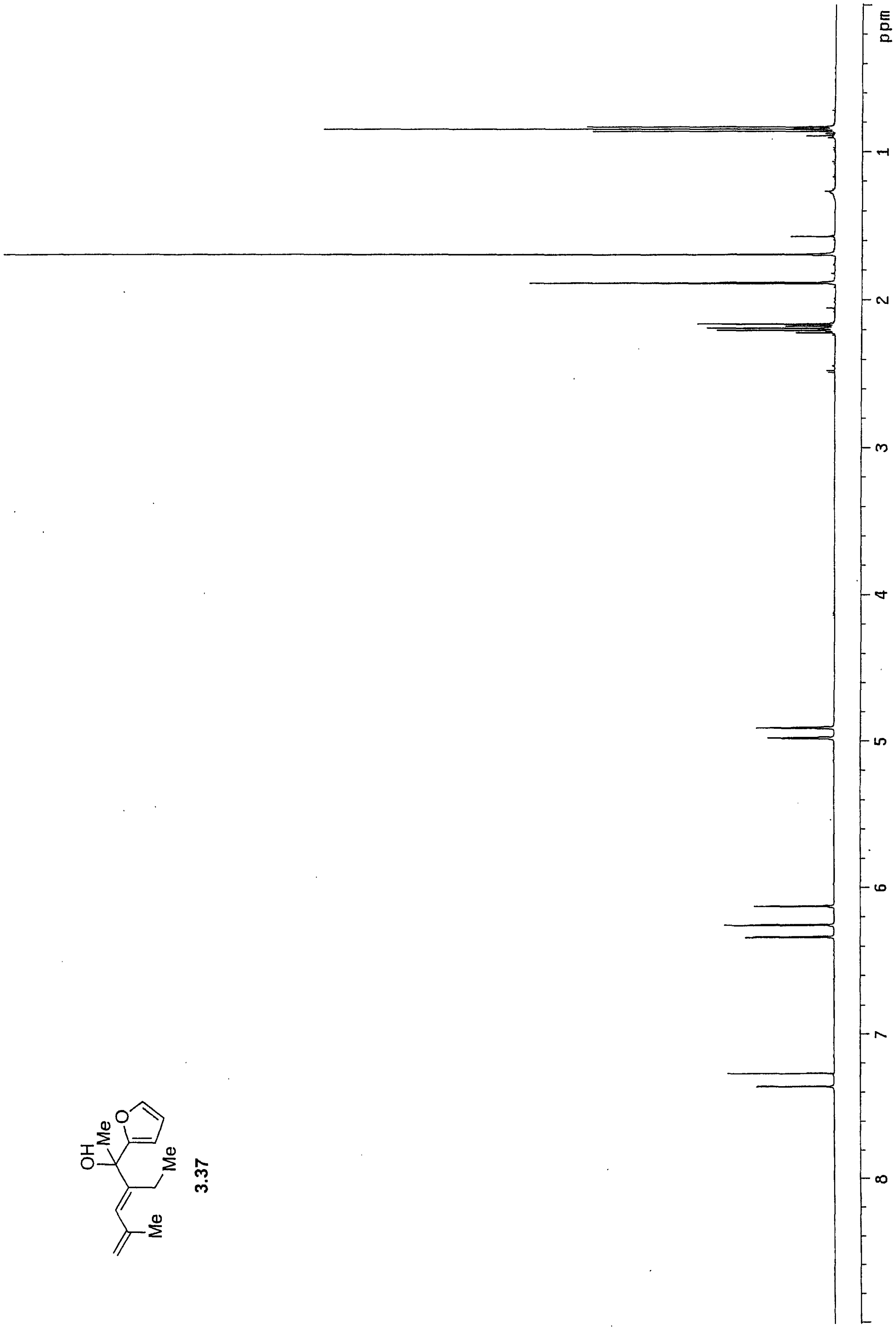

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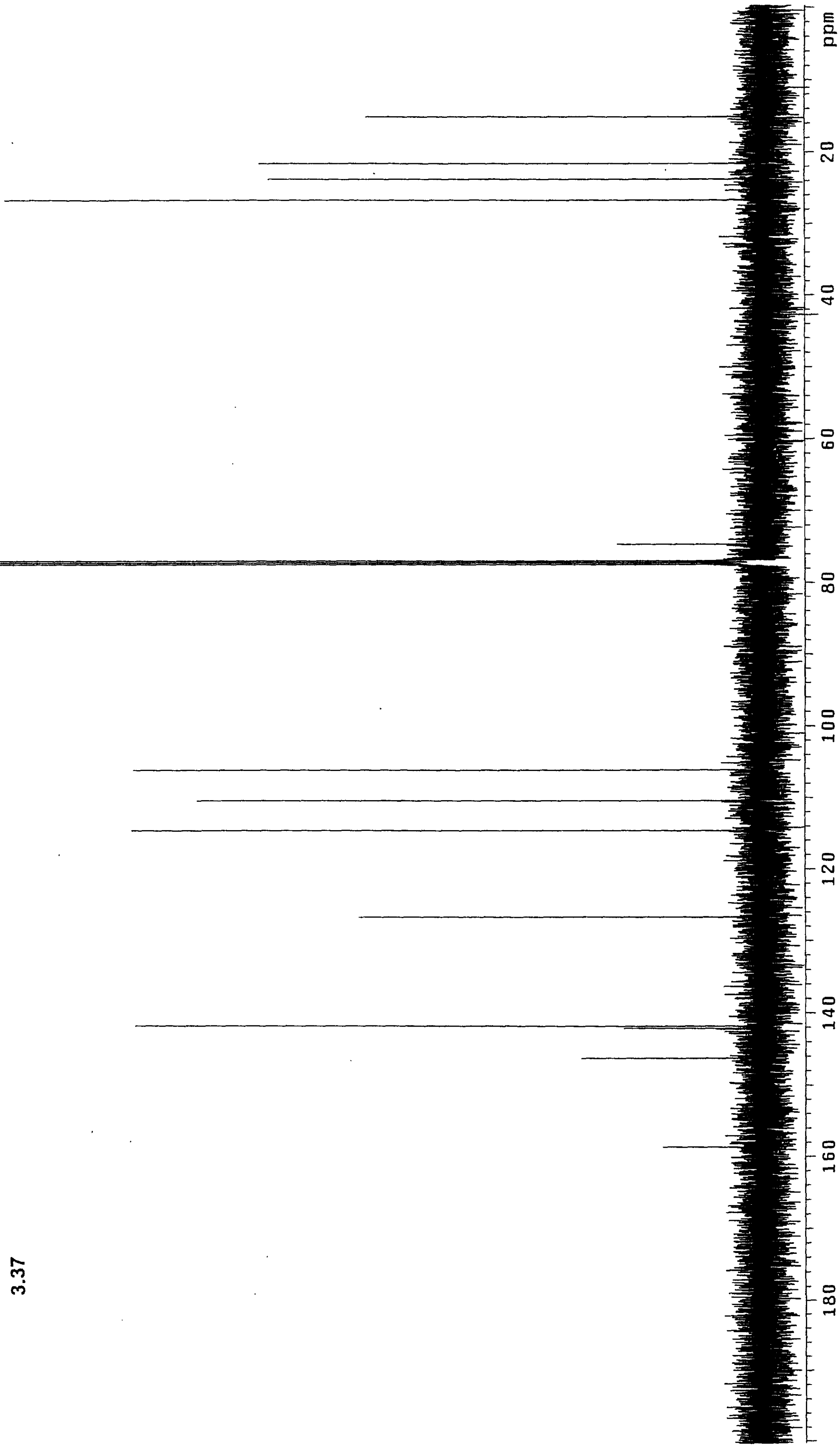

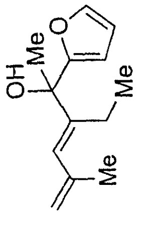

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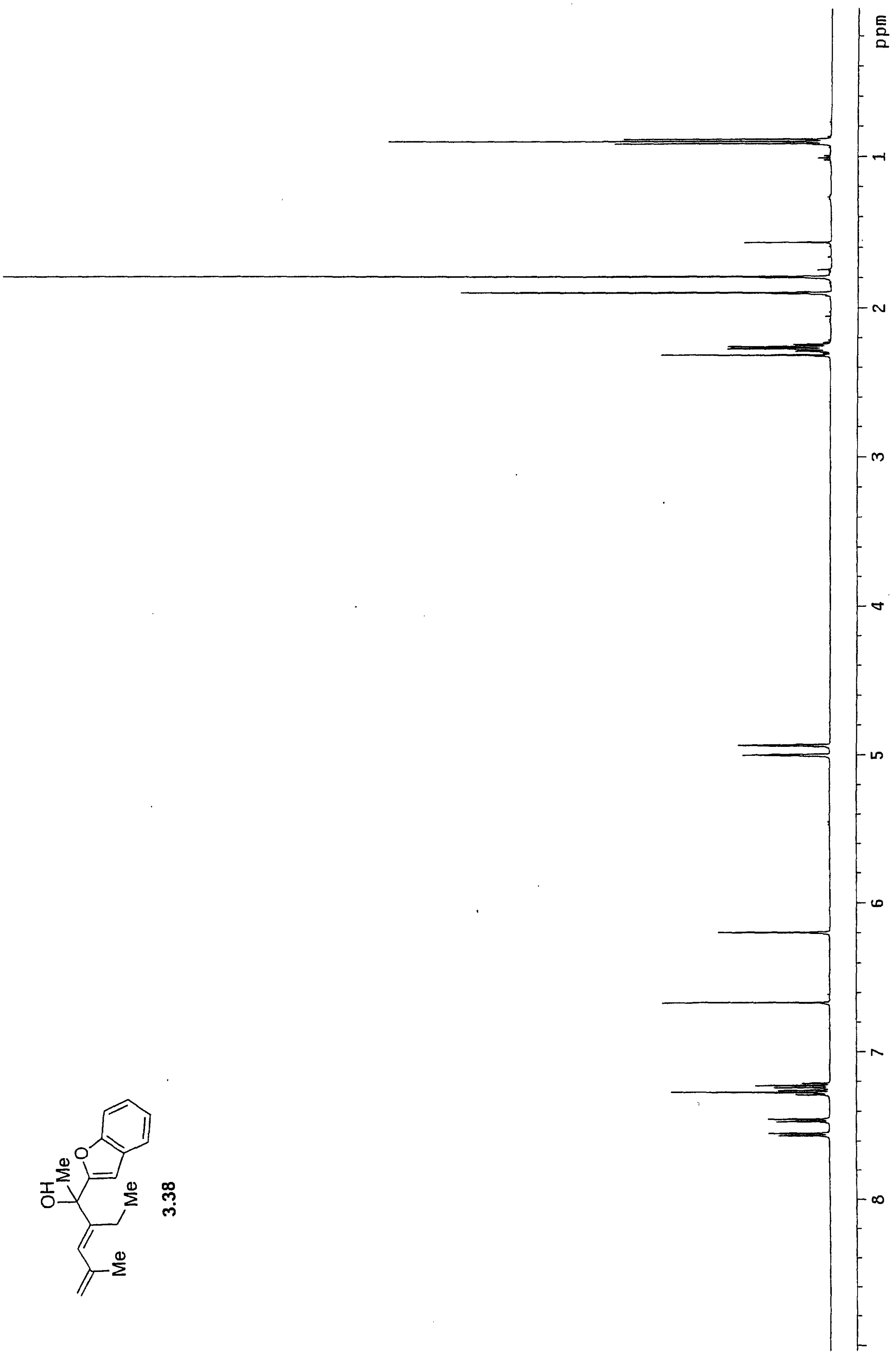

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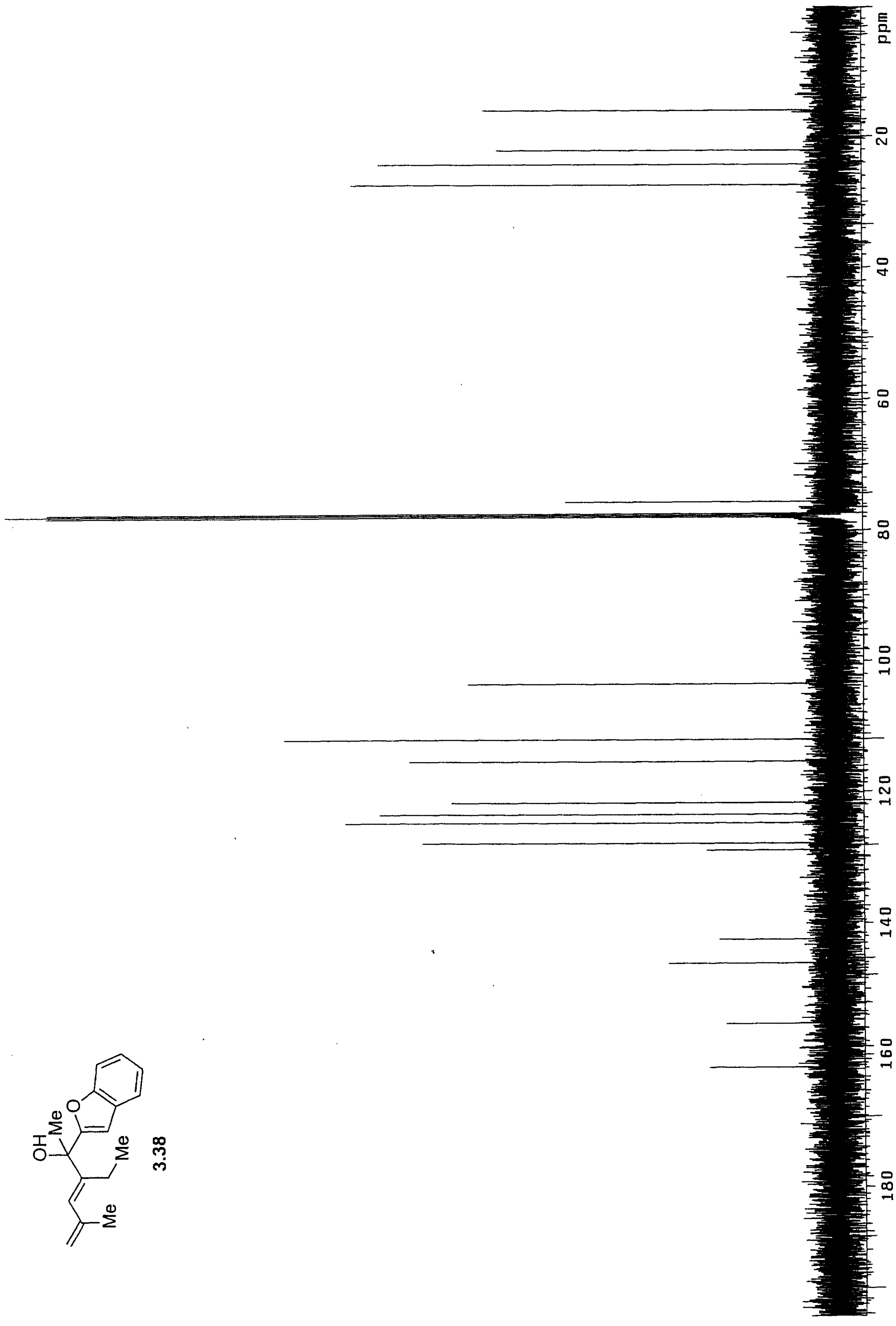

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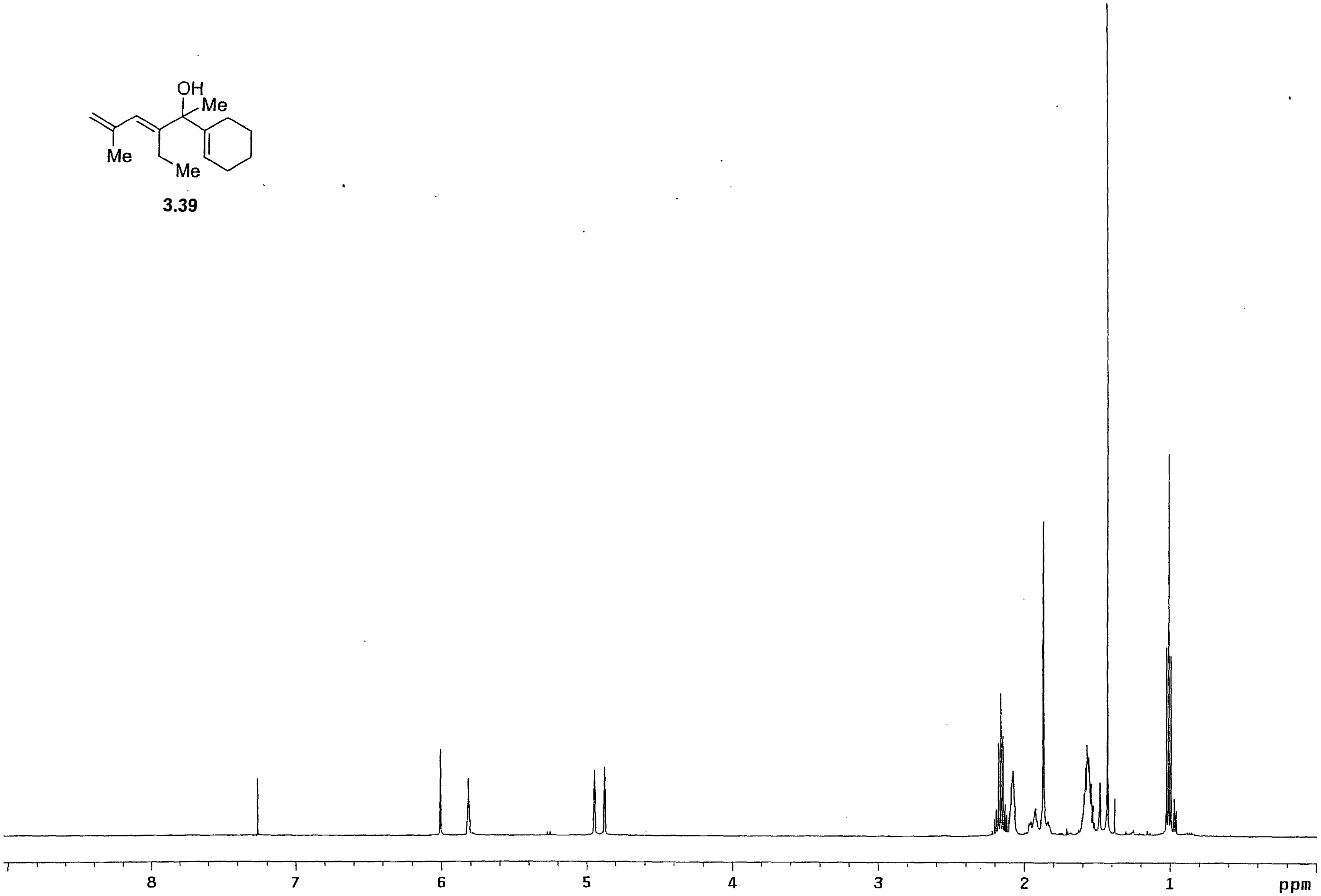

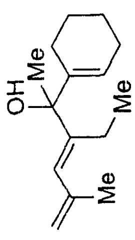

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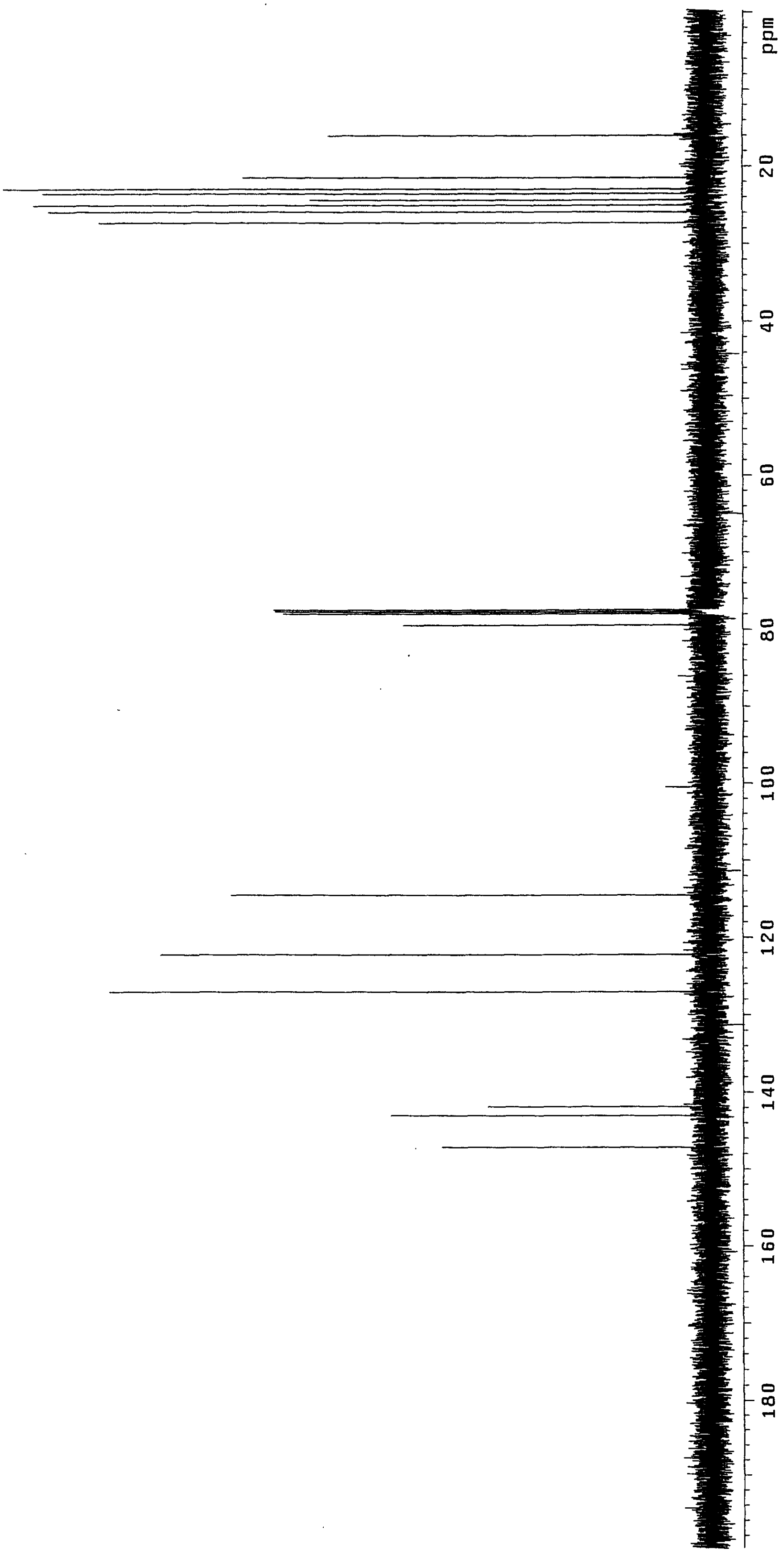

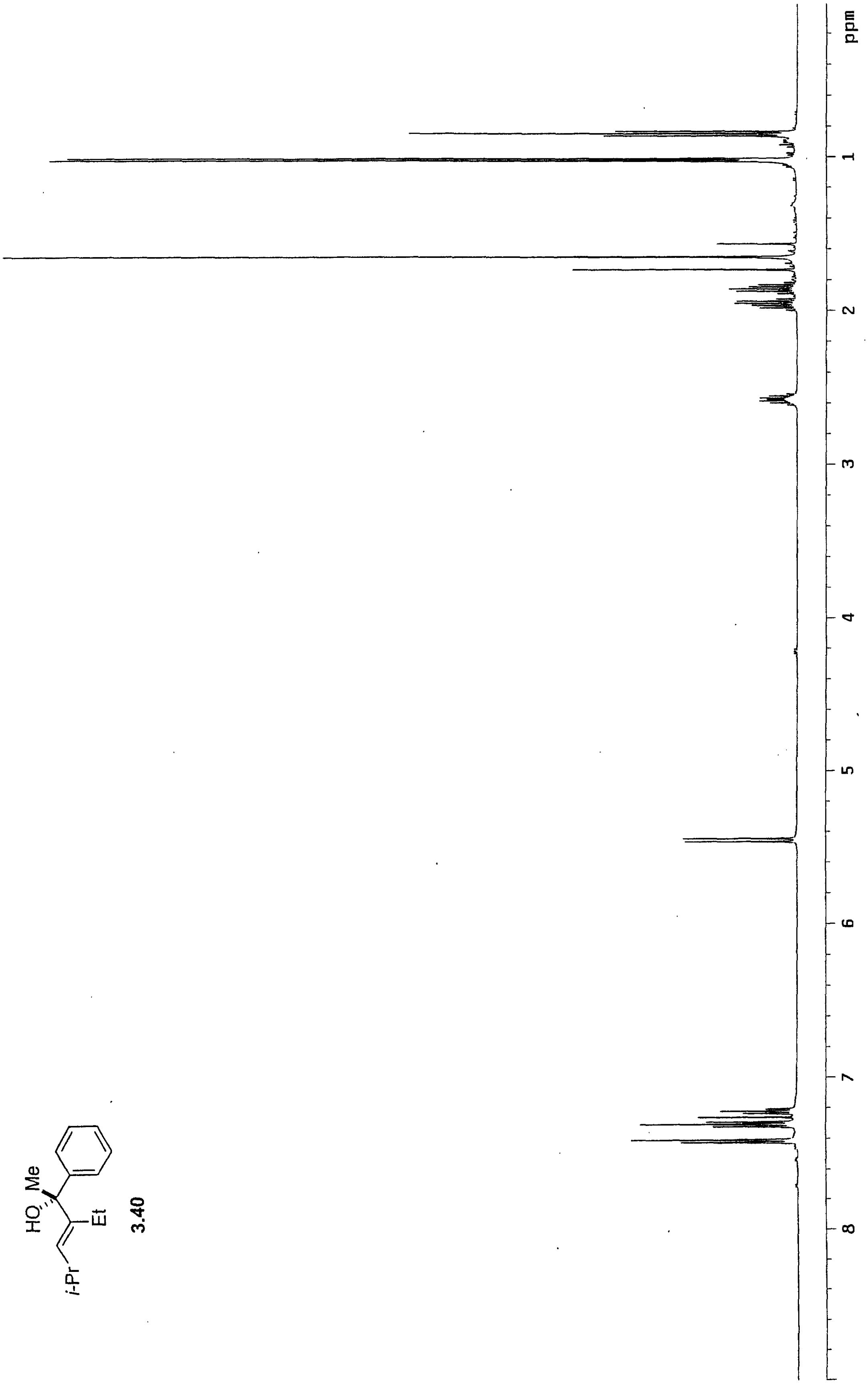

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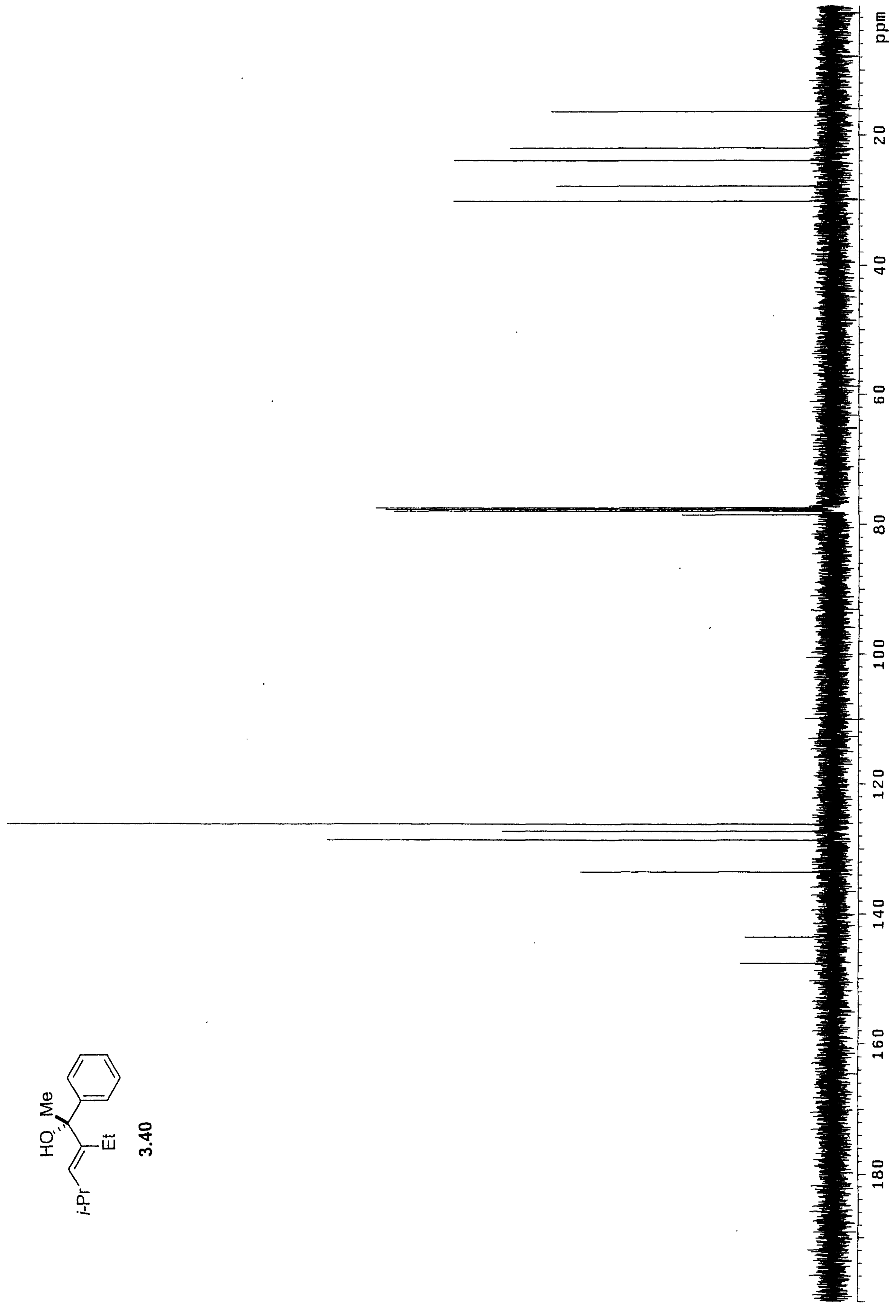

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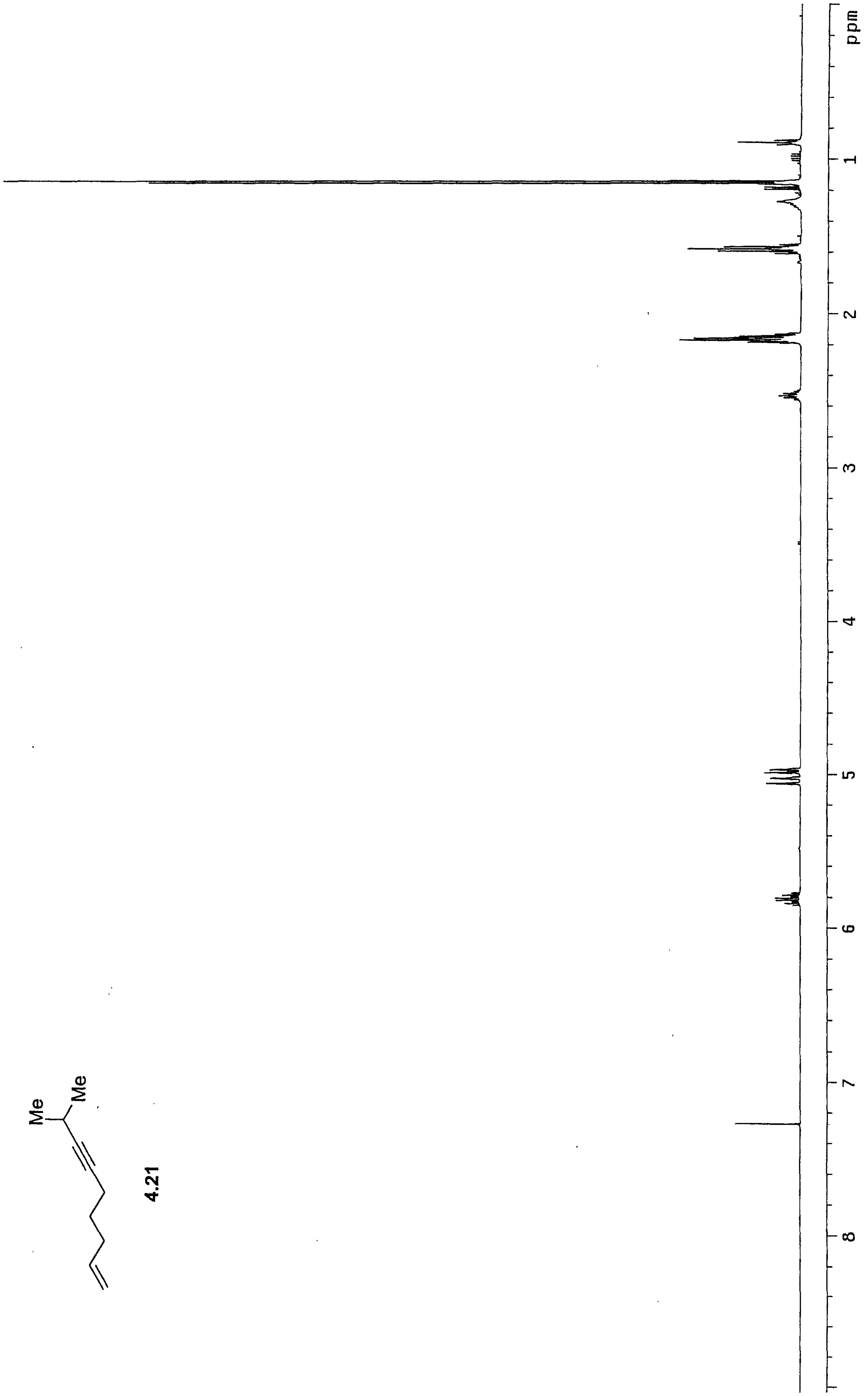
Appendix D.

^{1}H and ^{13}C NMR Spectra (Chapter 4)



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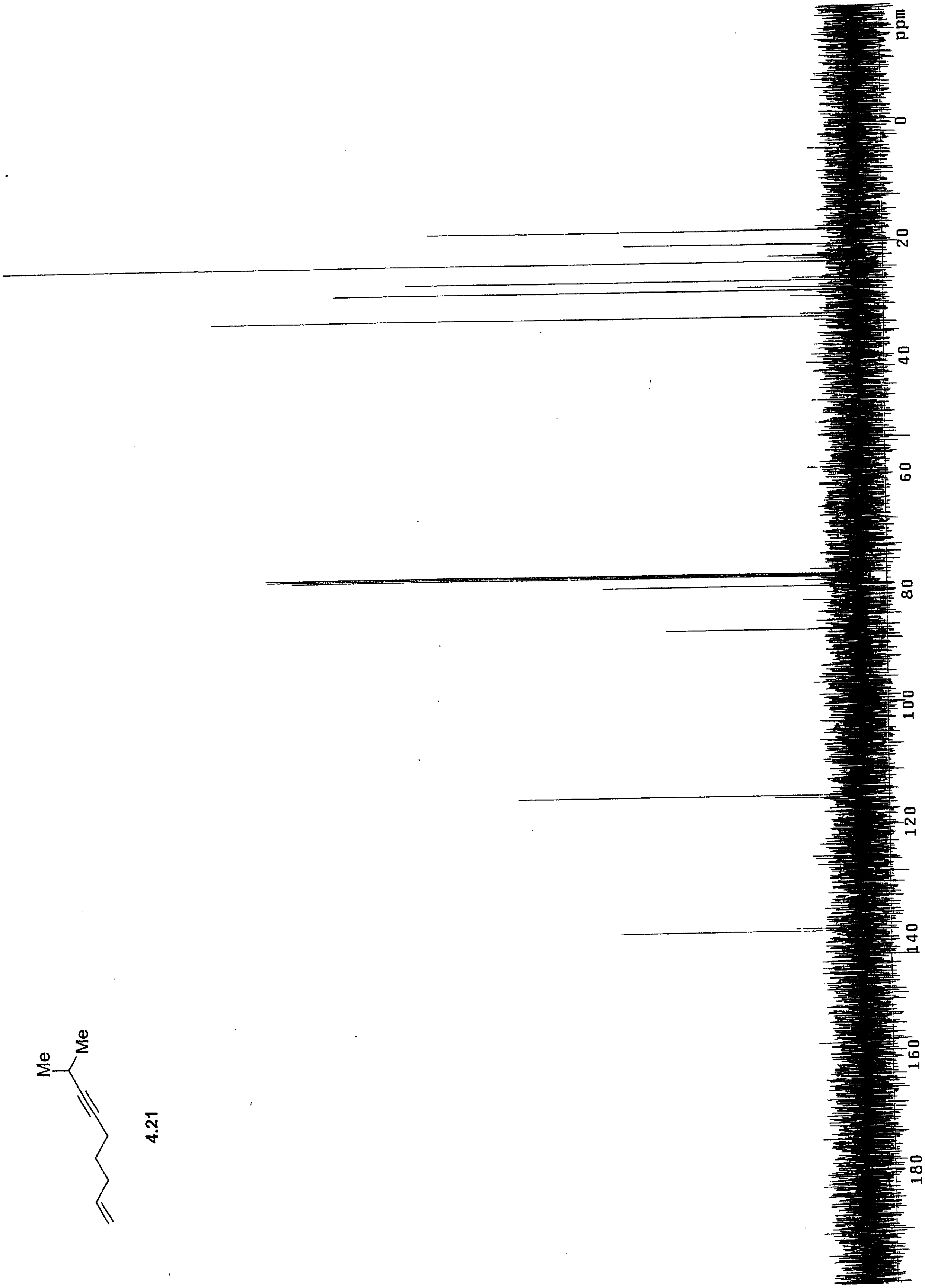

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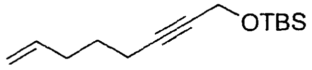

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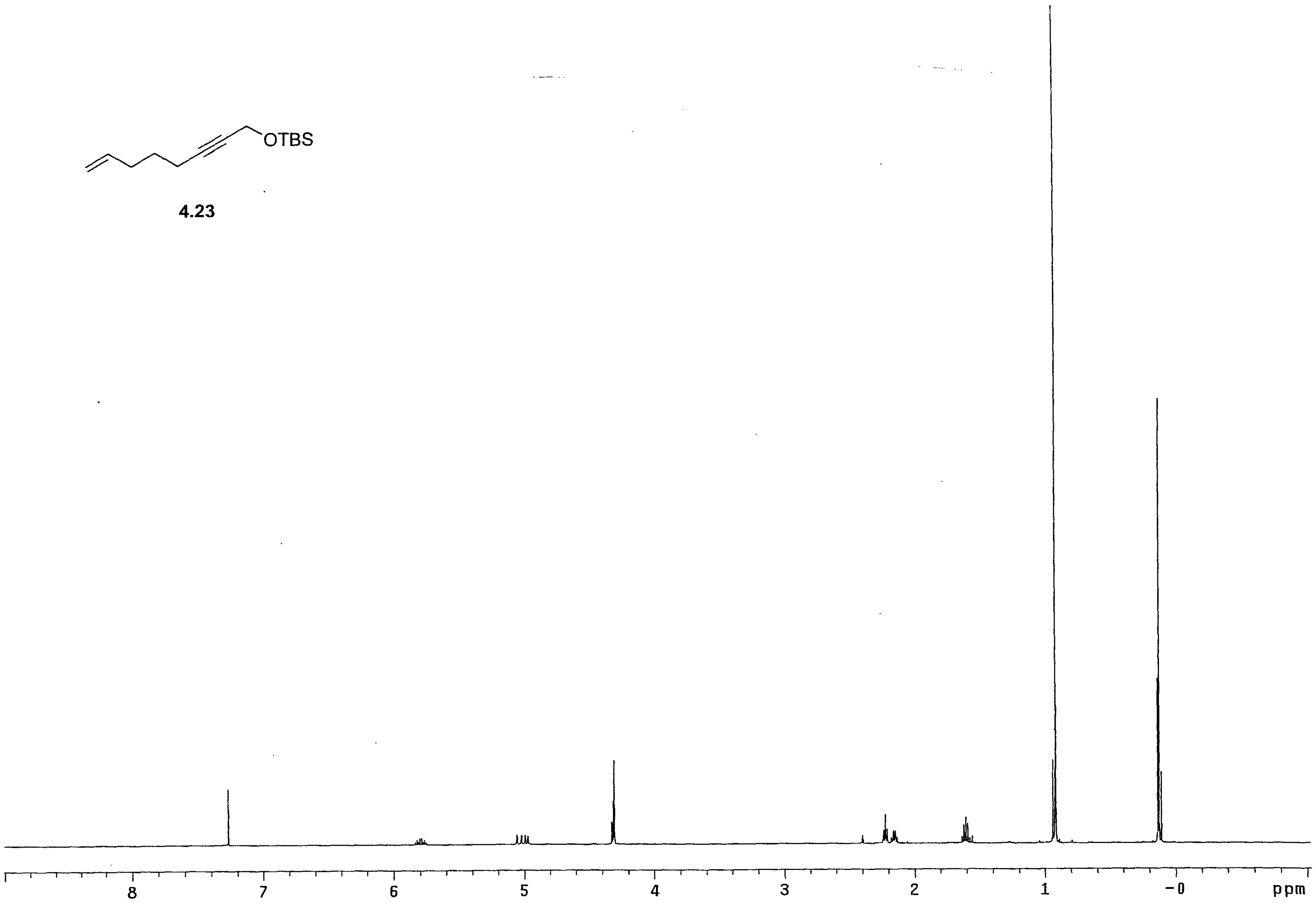

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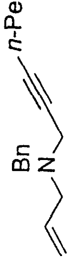

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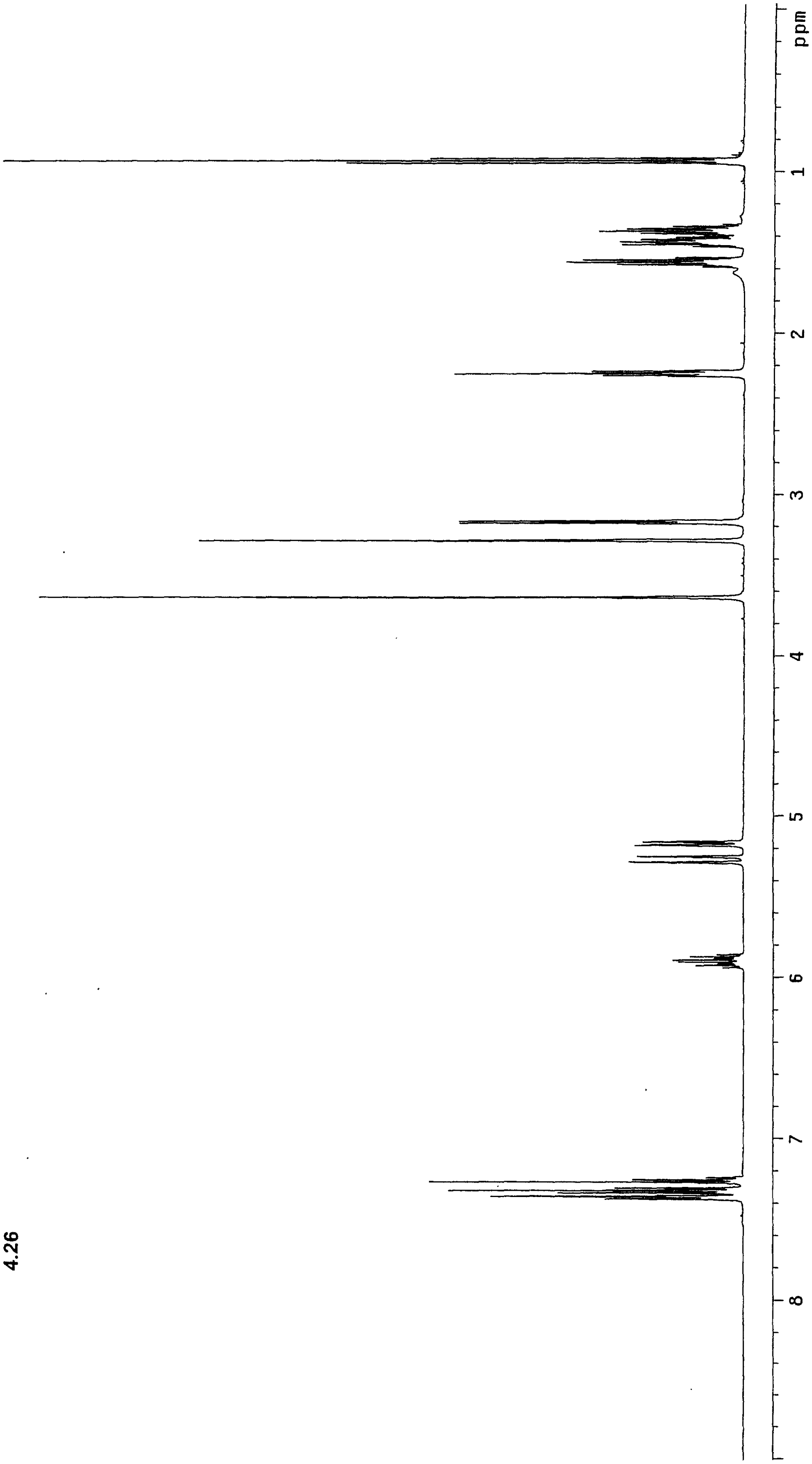

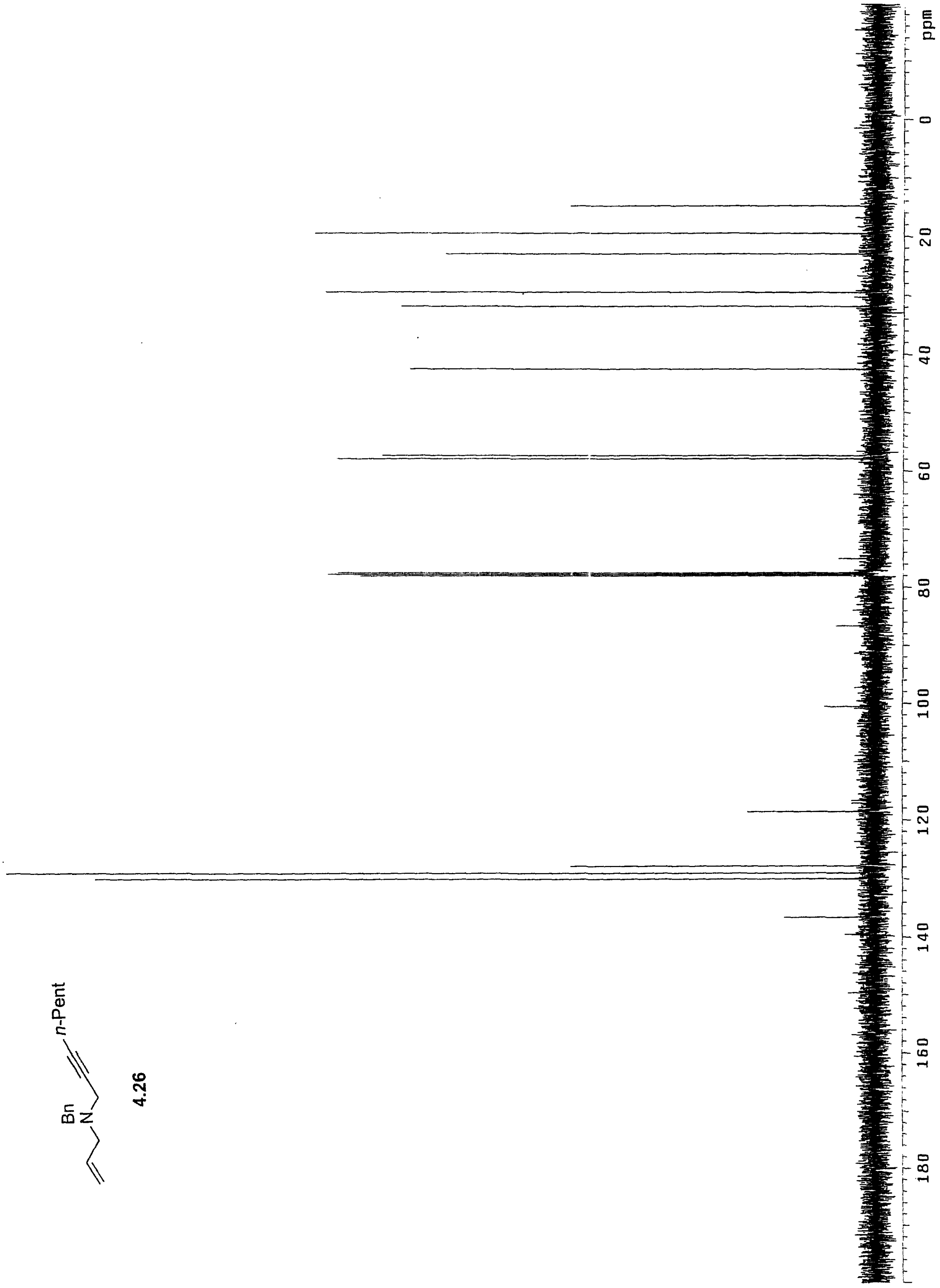

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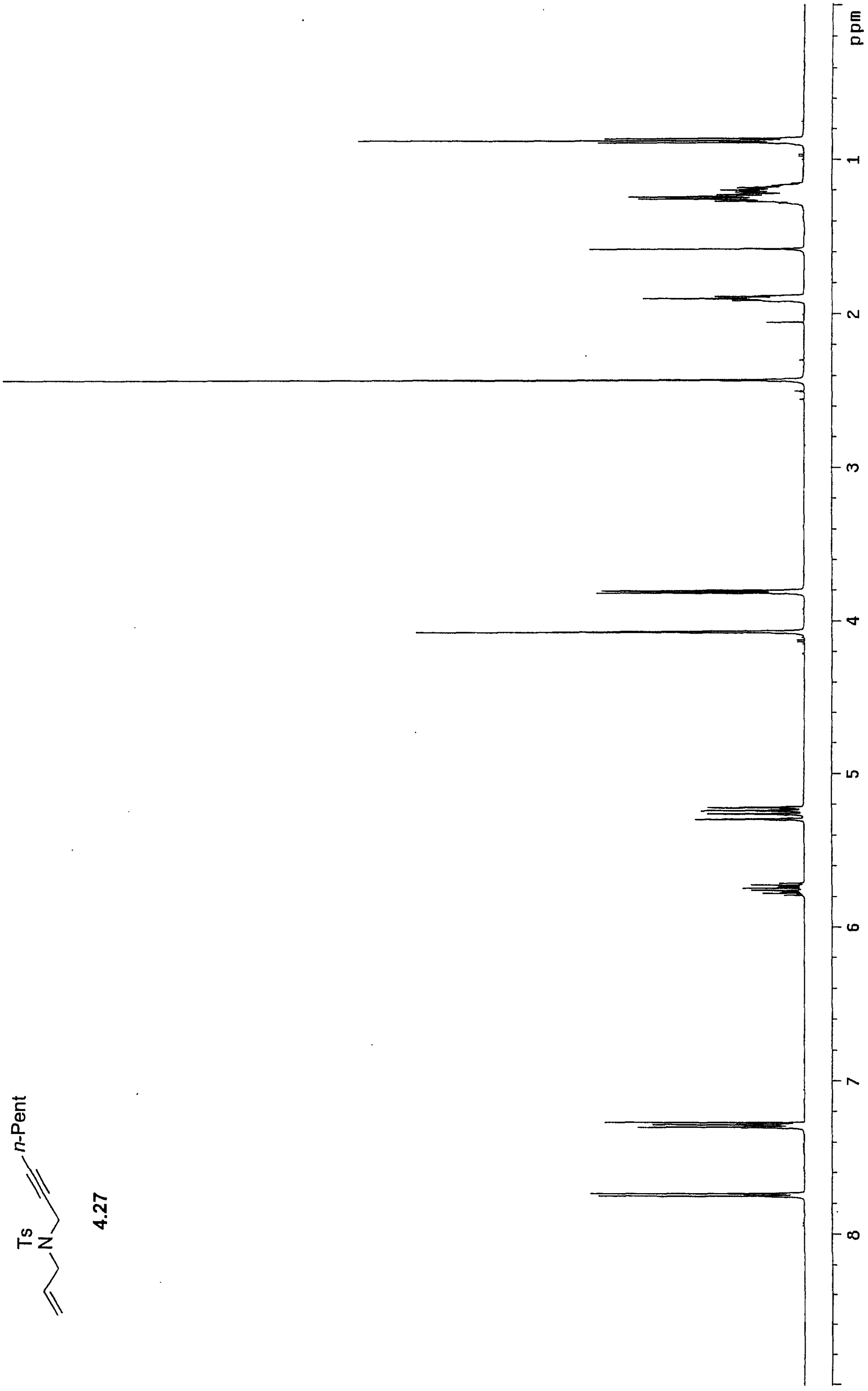

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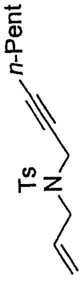

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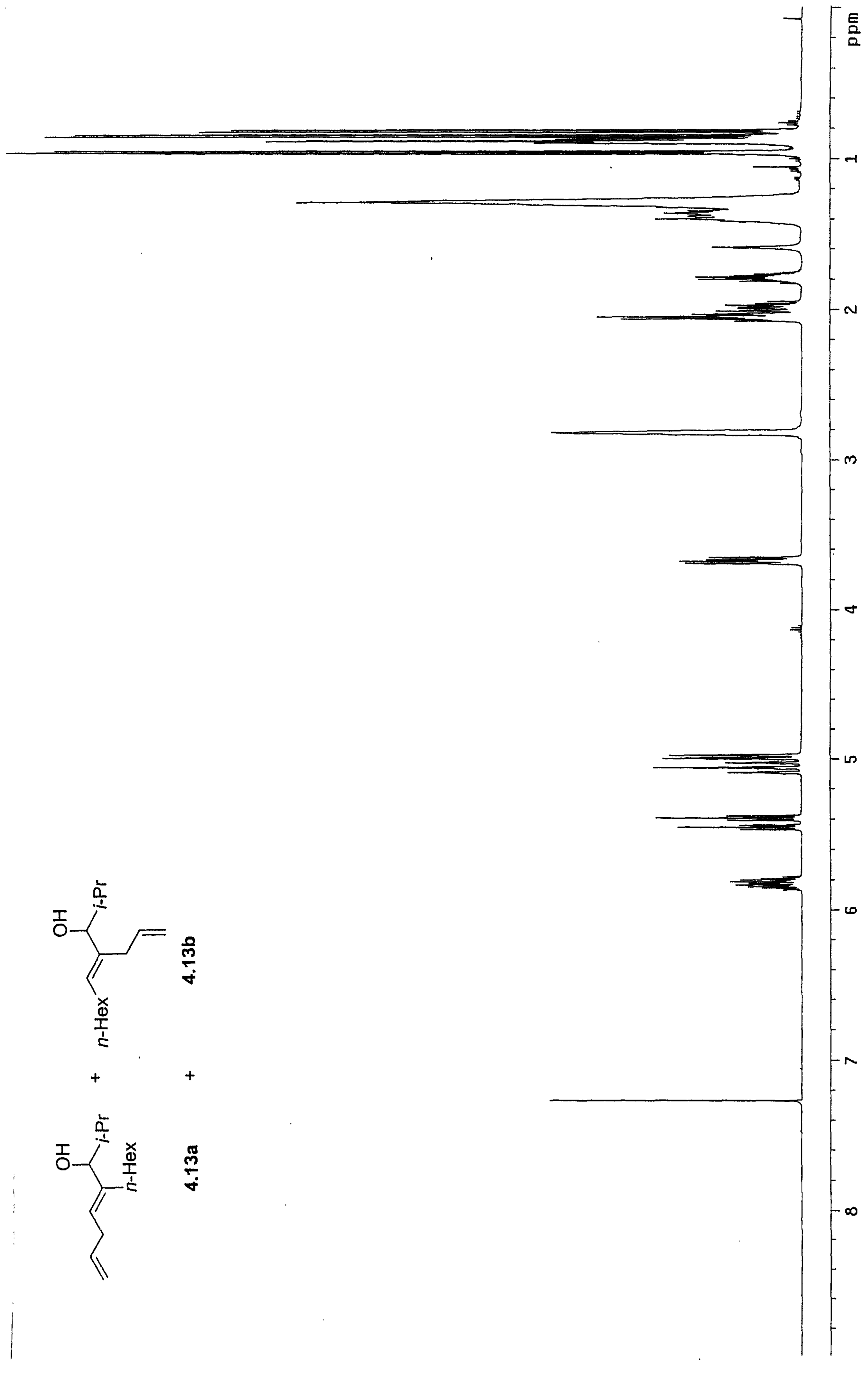
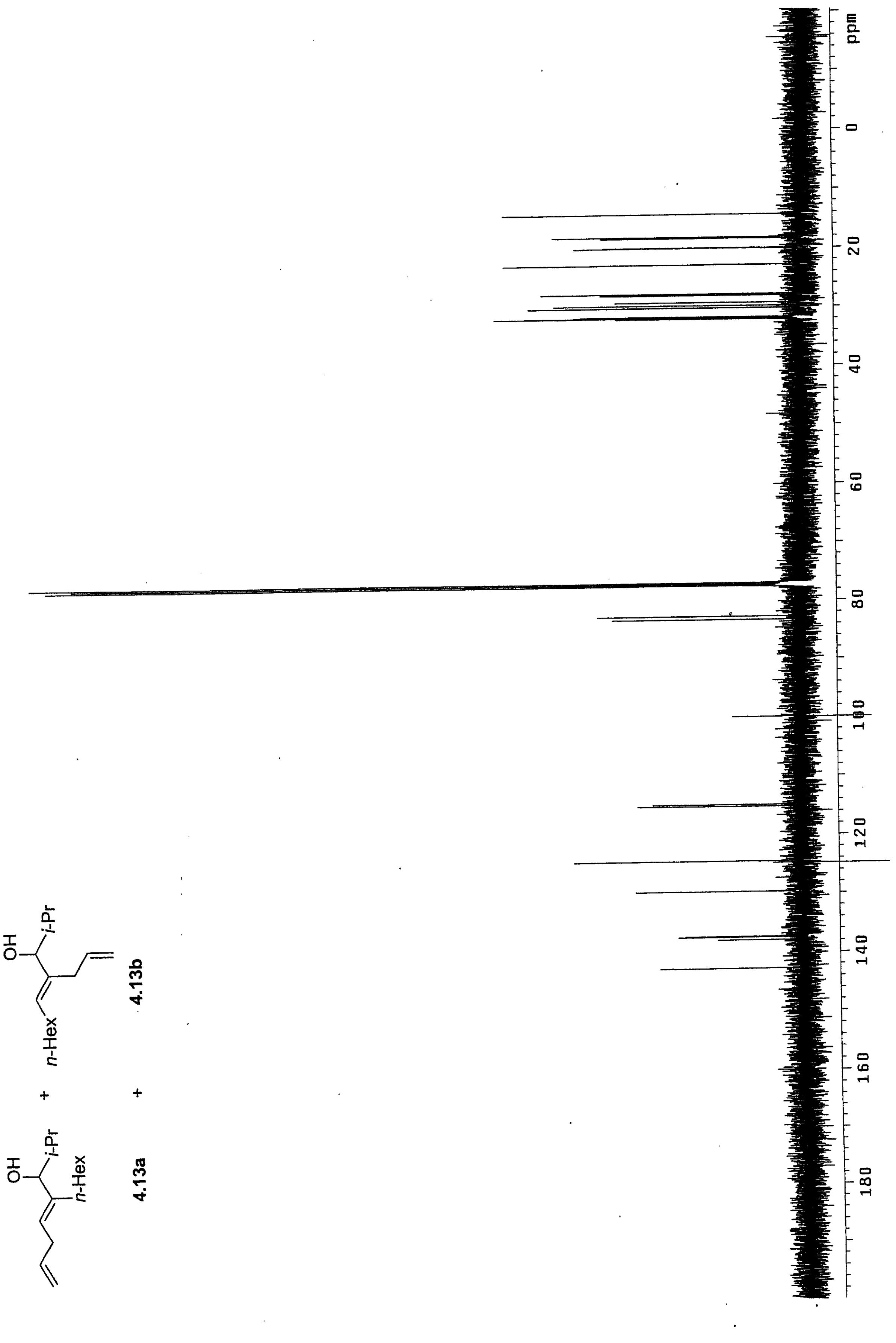

4.13a + 4.13b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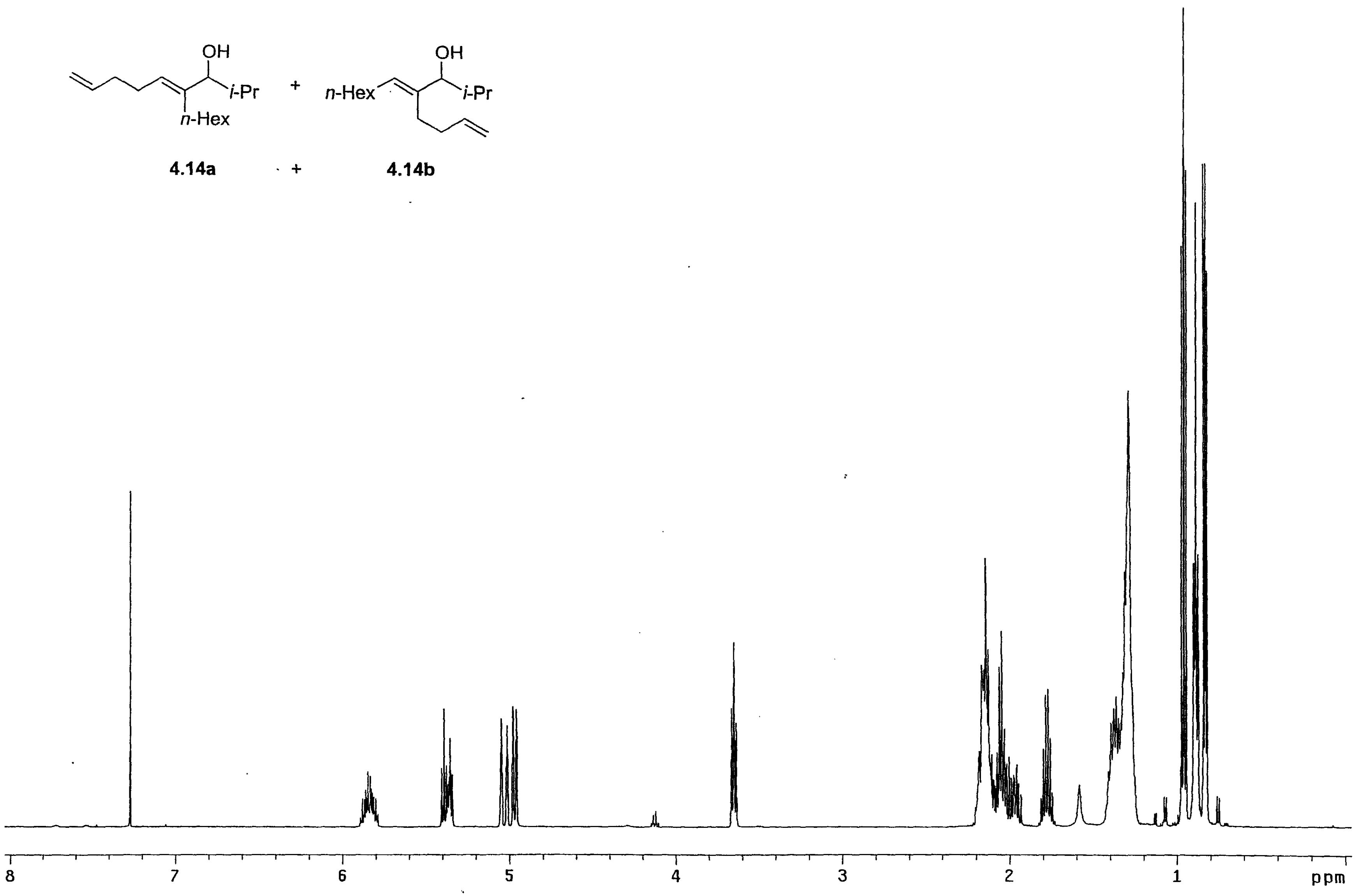

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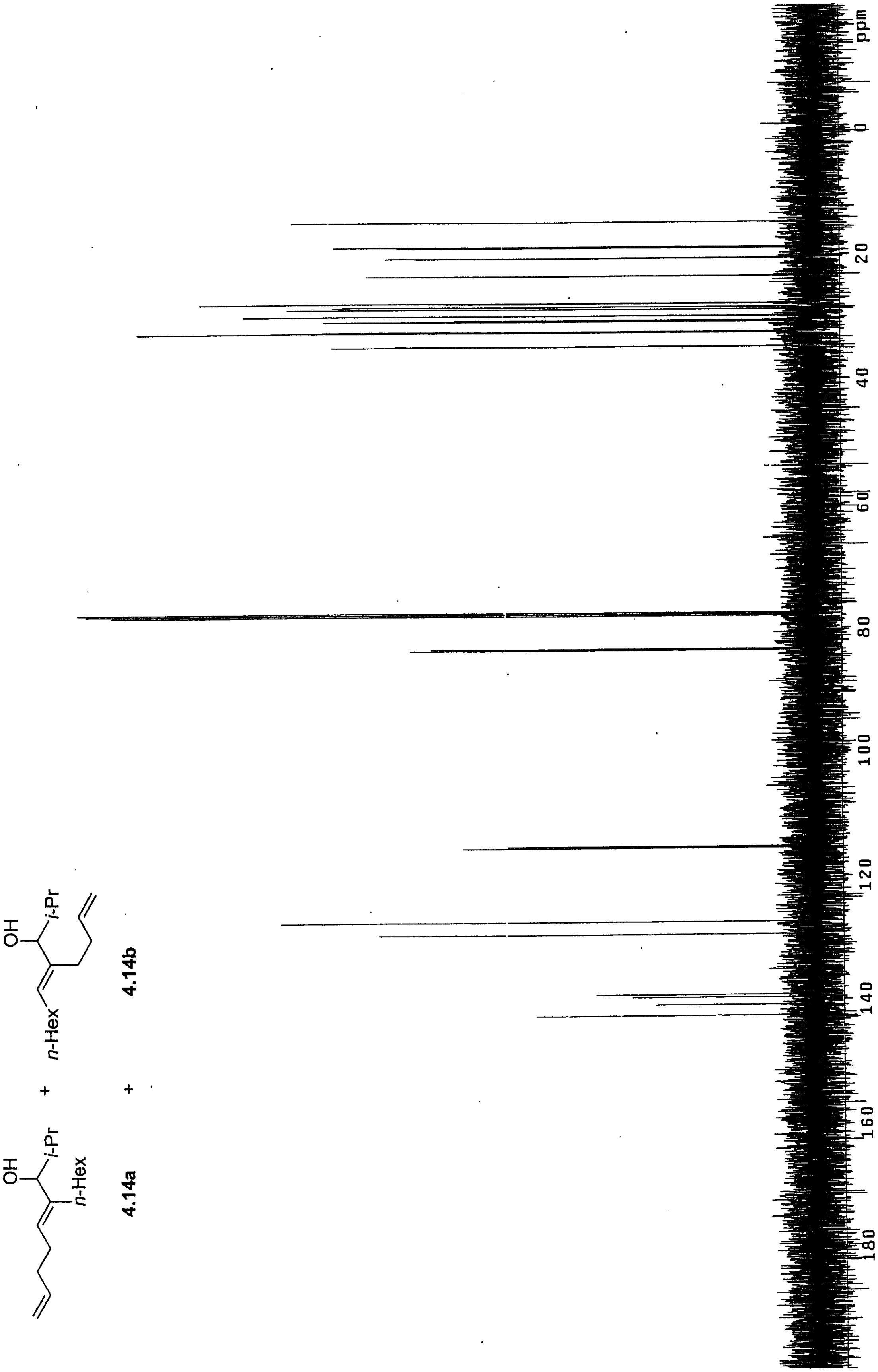
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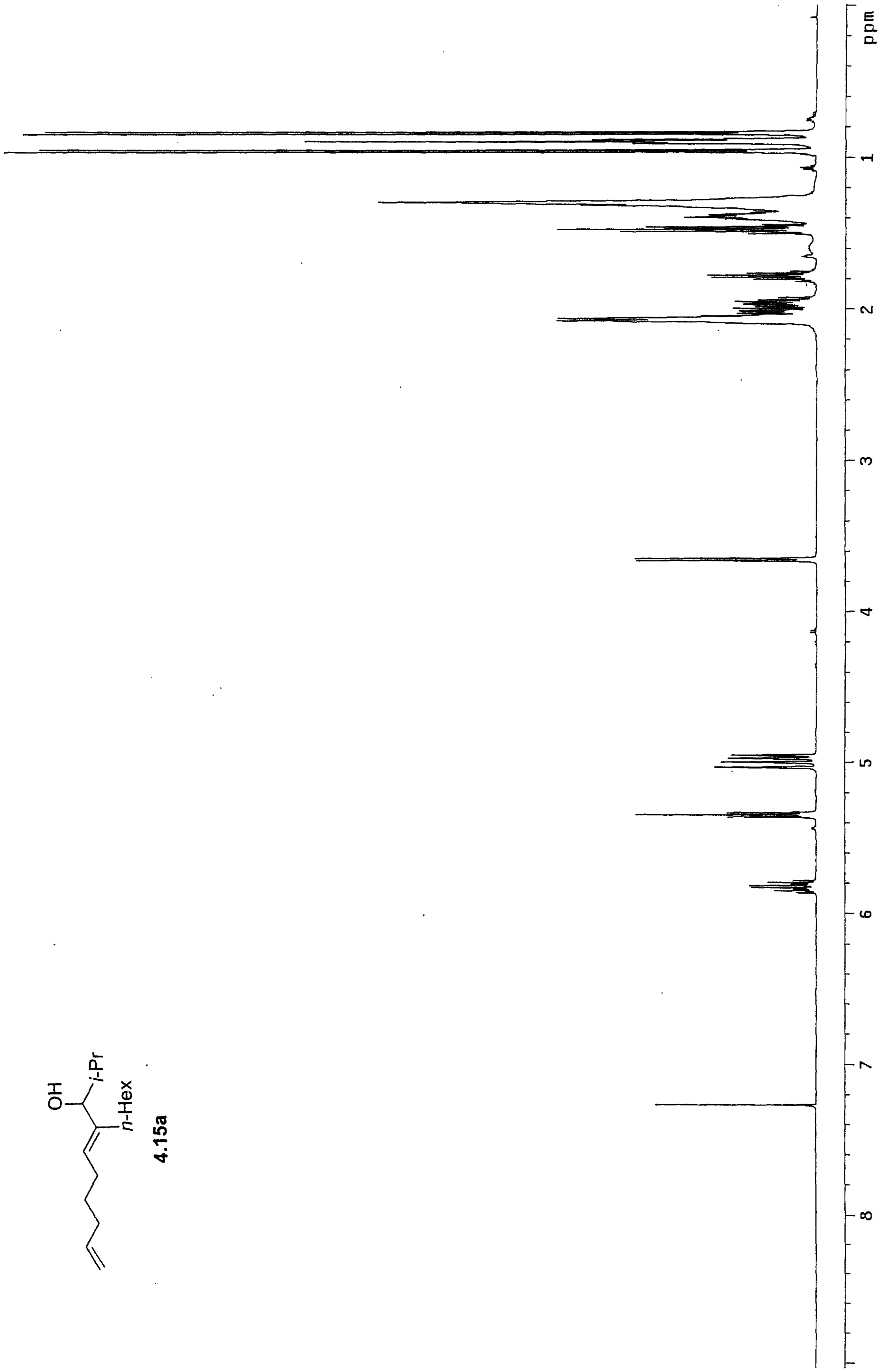
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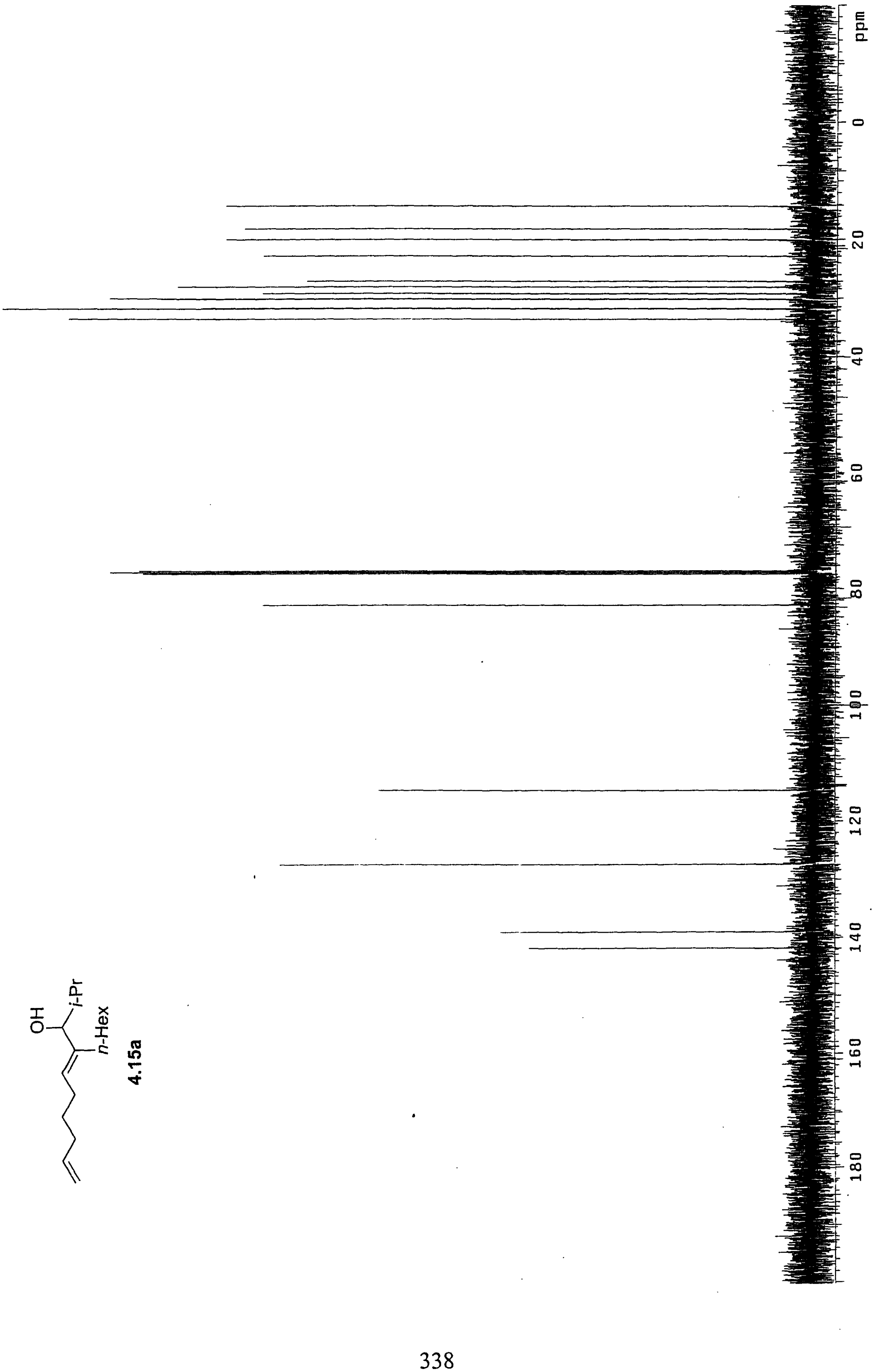

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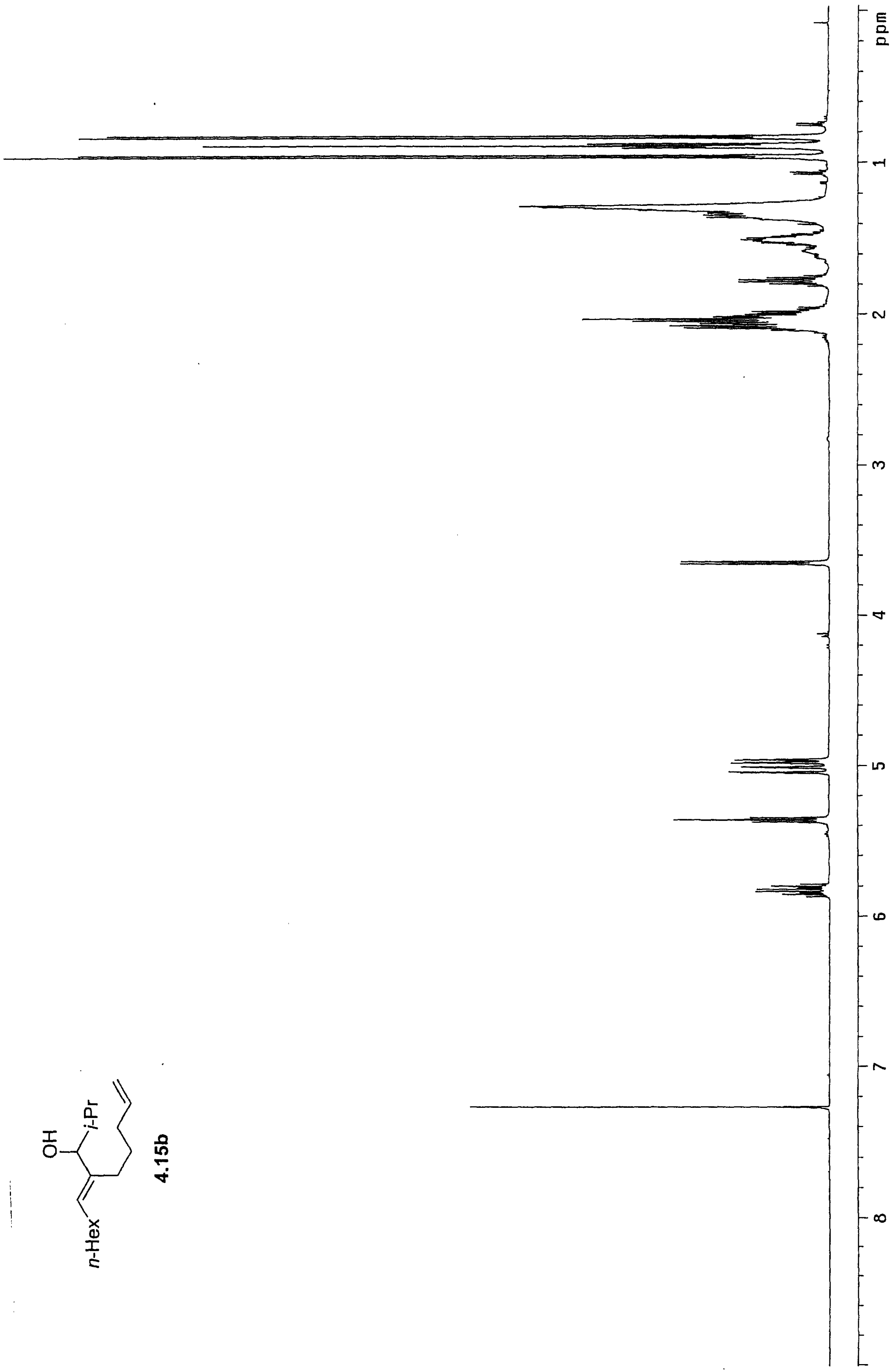

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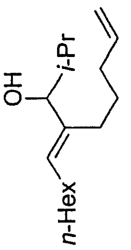

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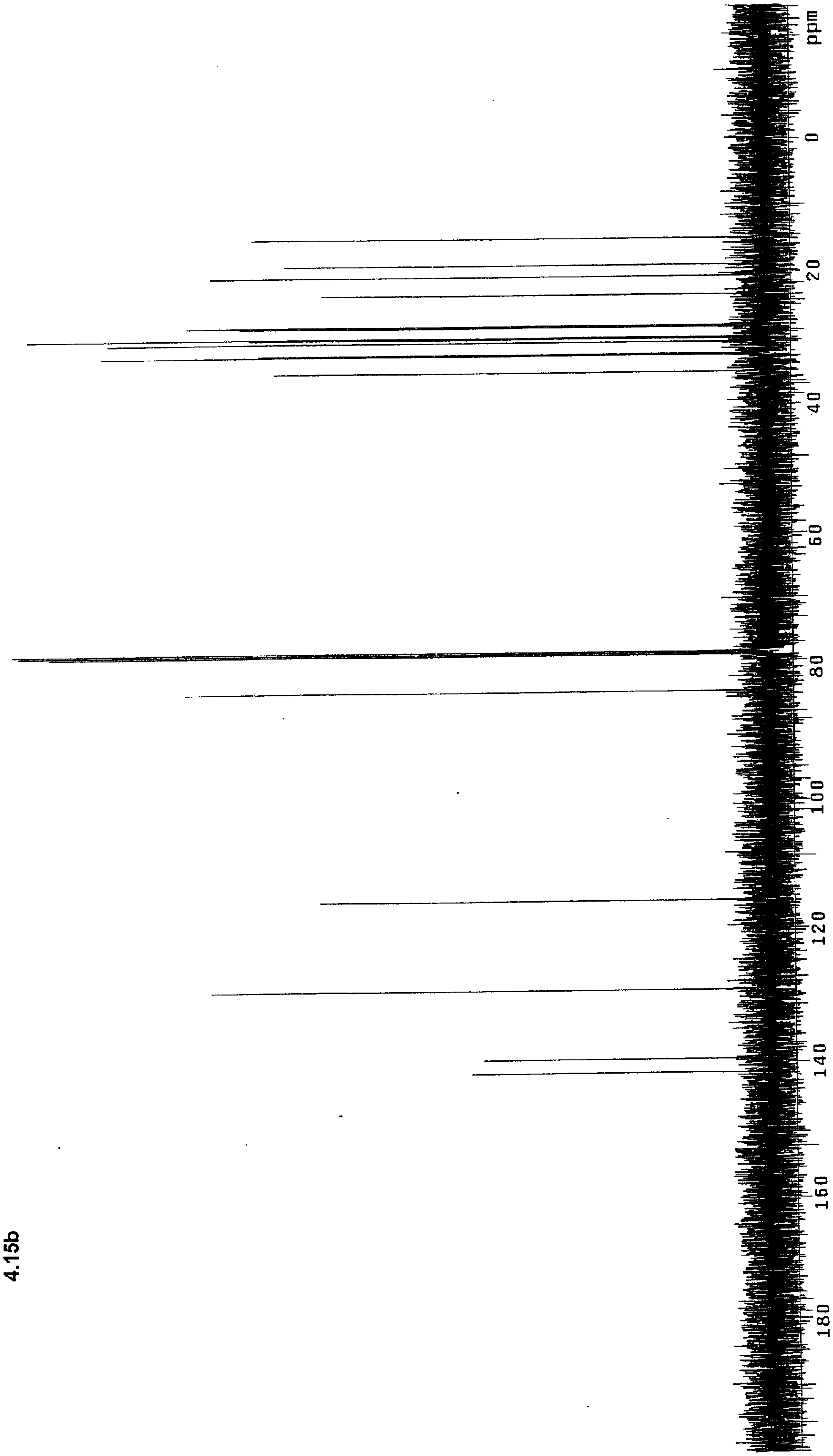

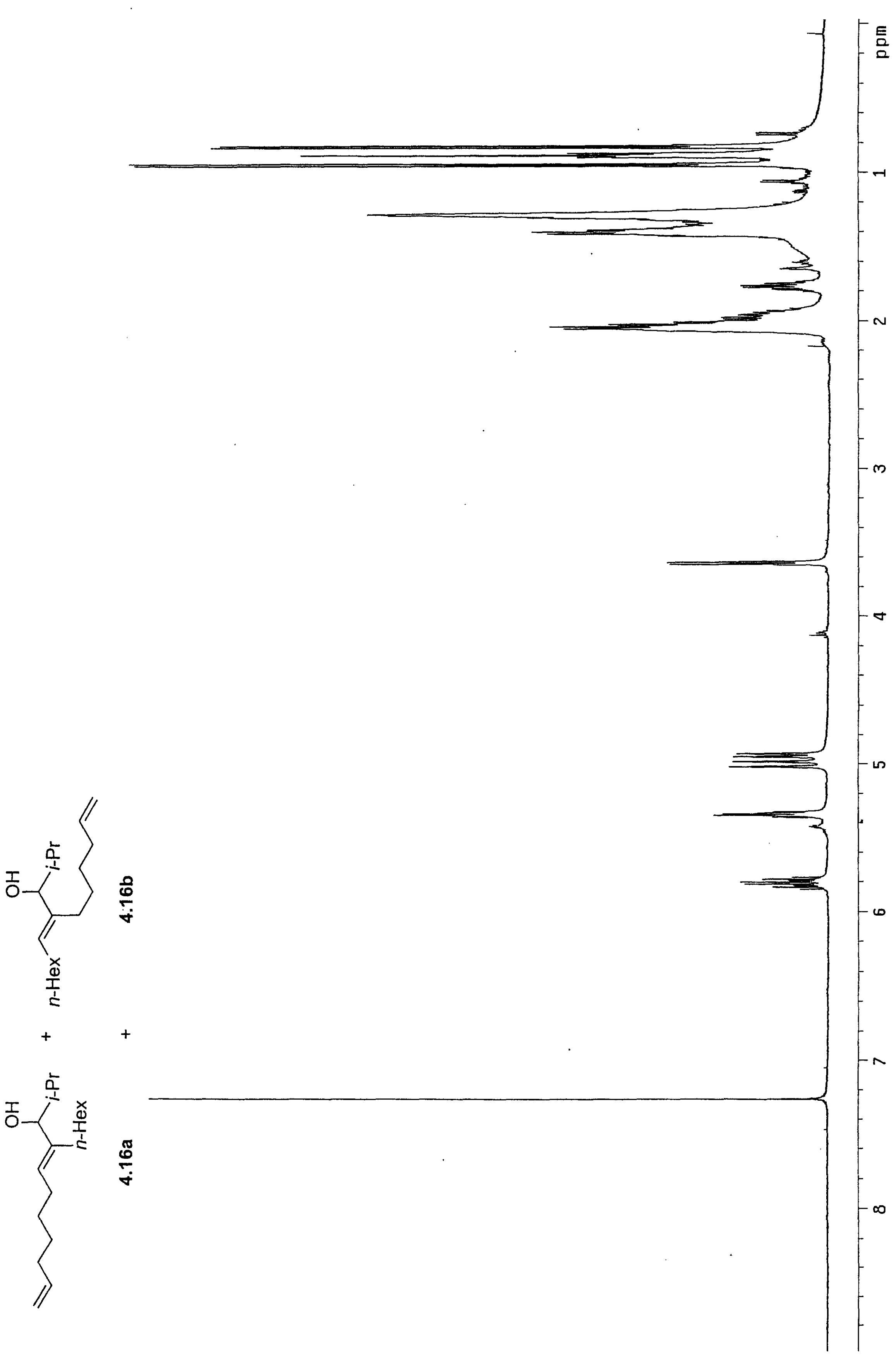

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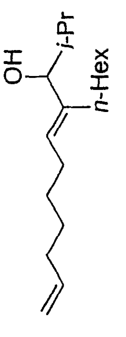

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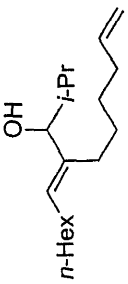

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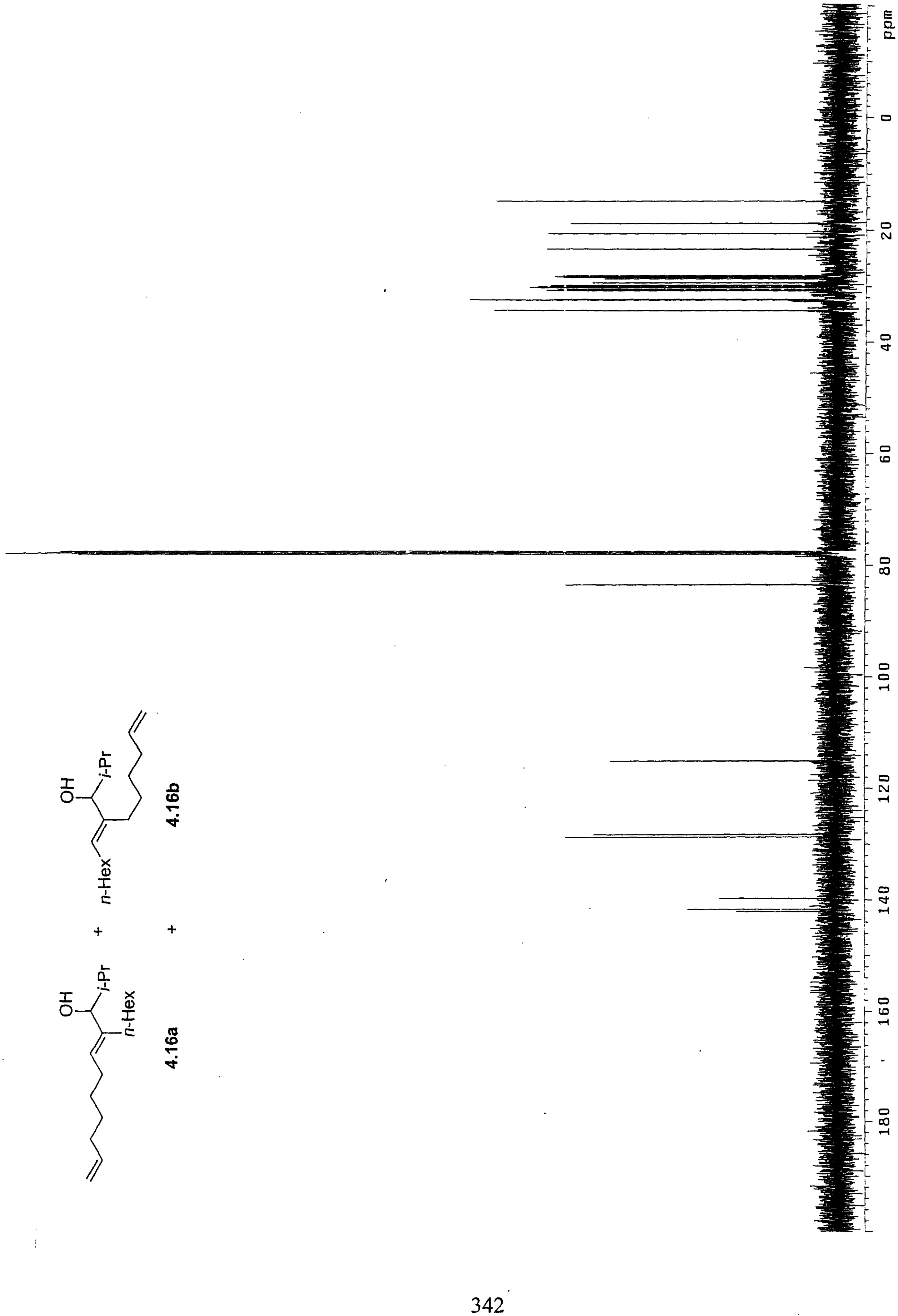

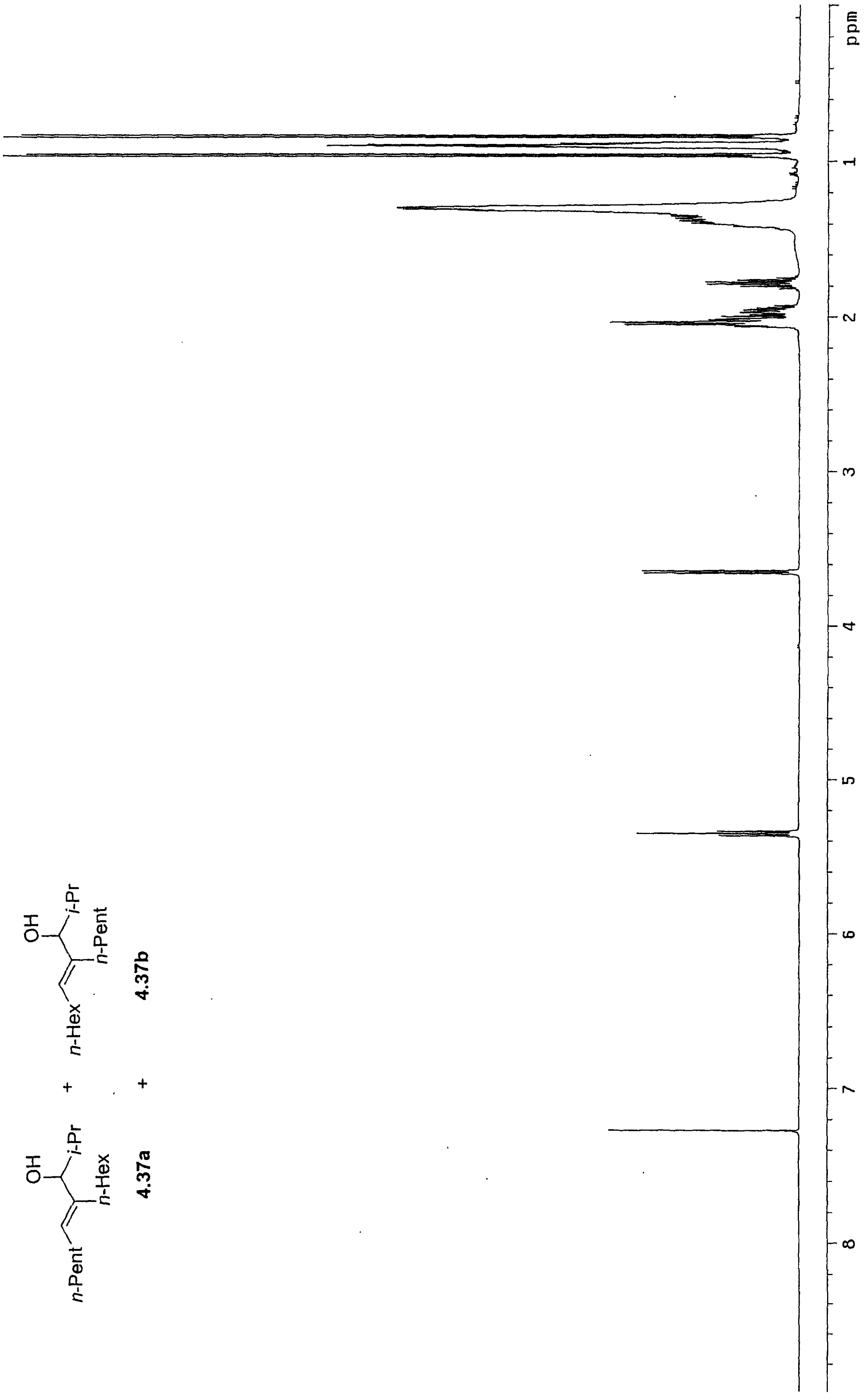

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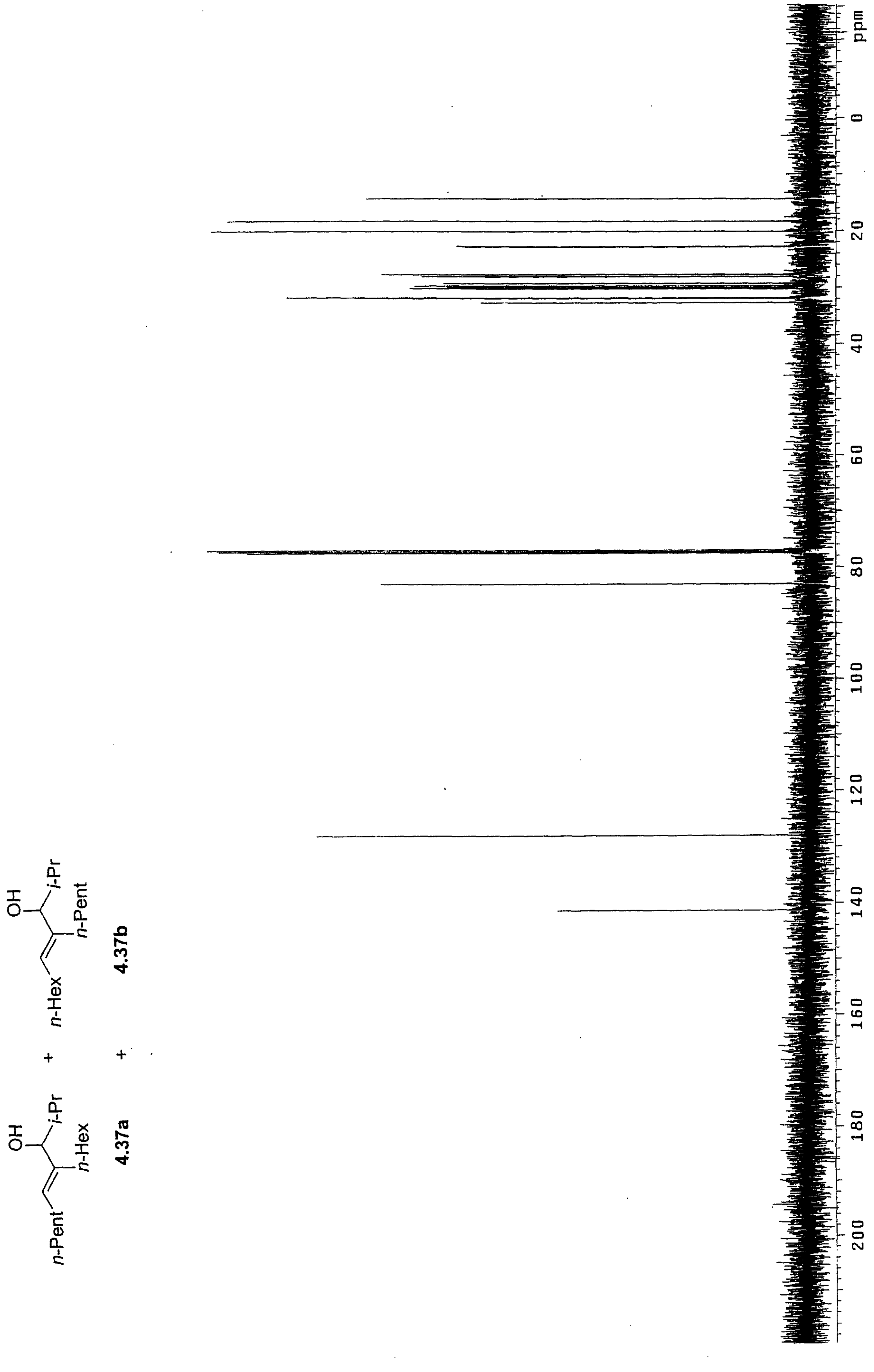

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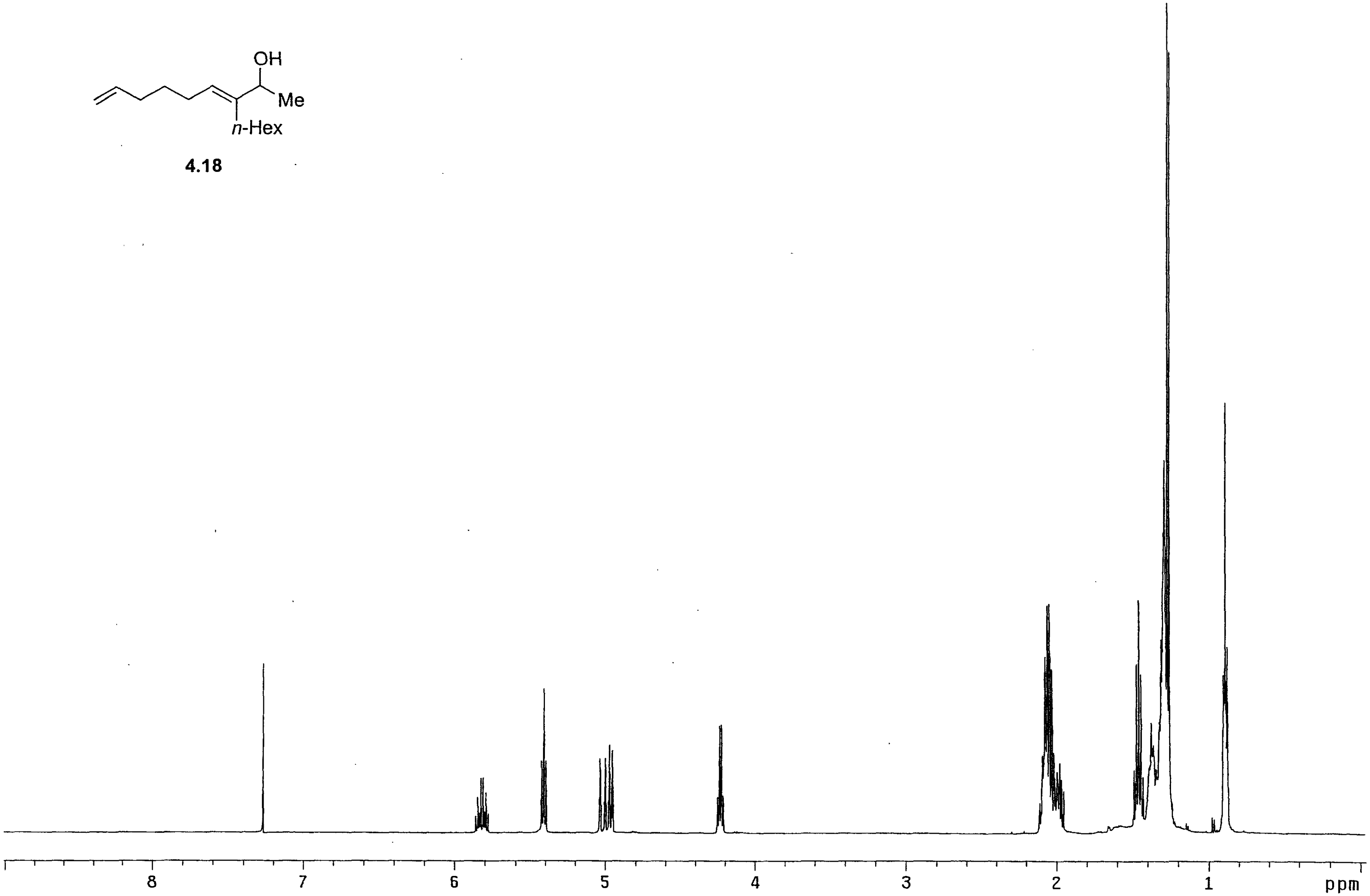

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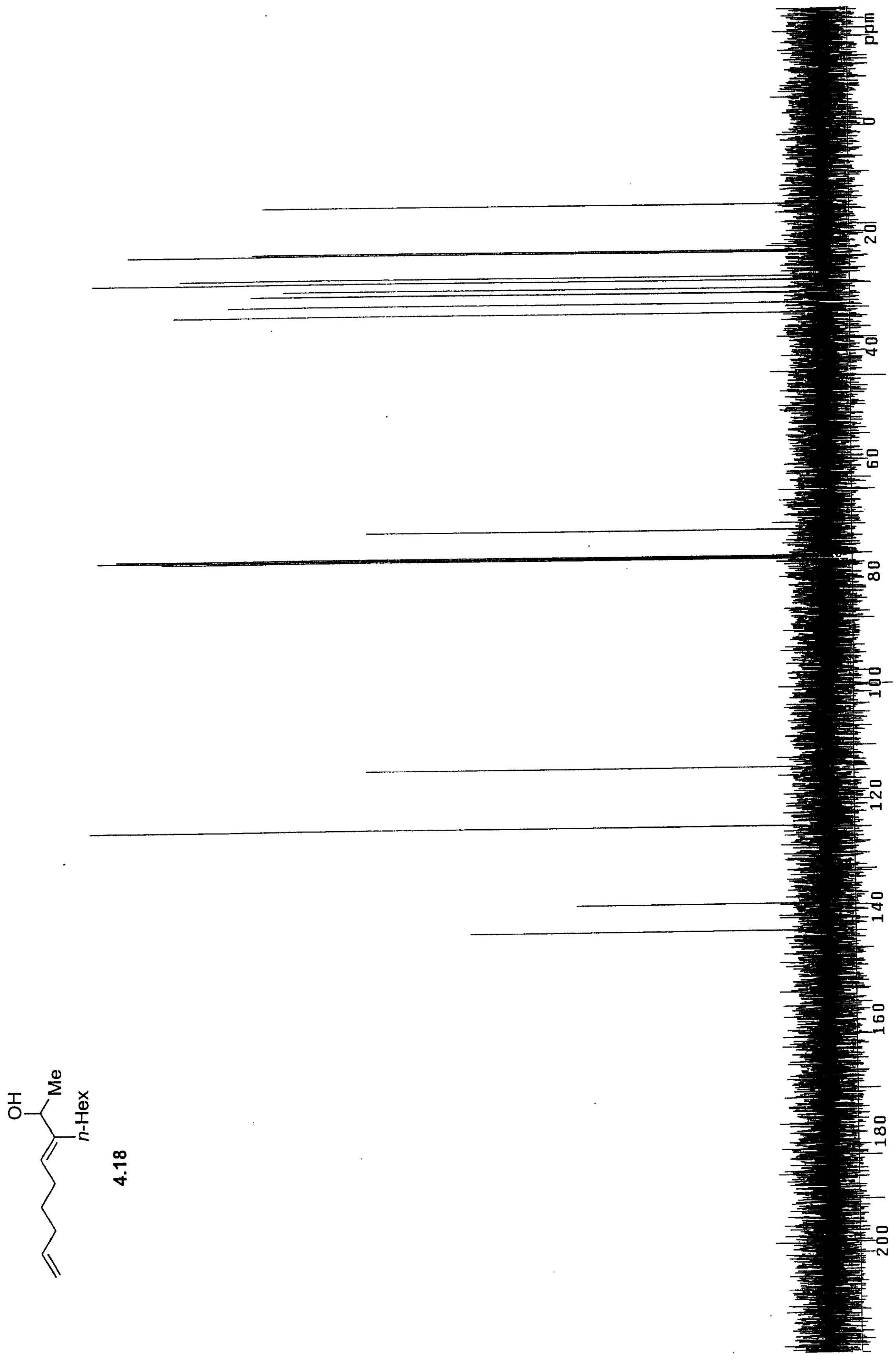

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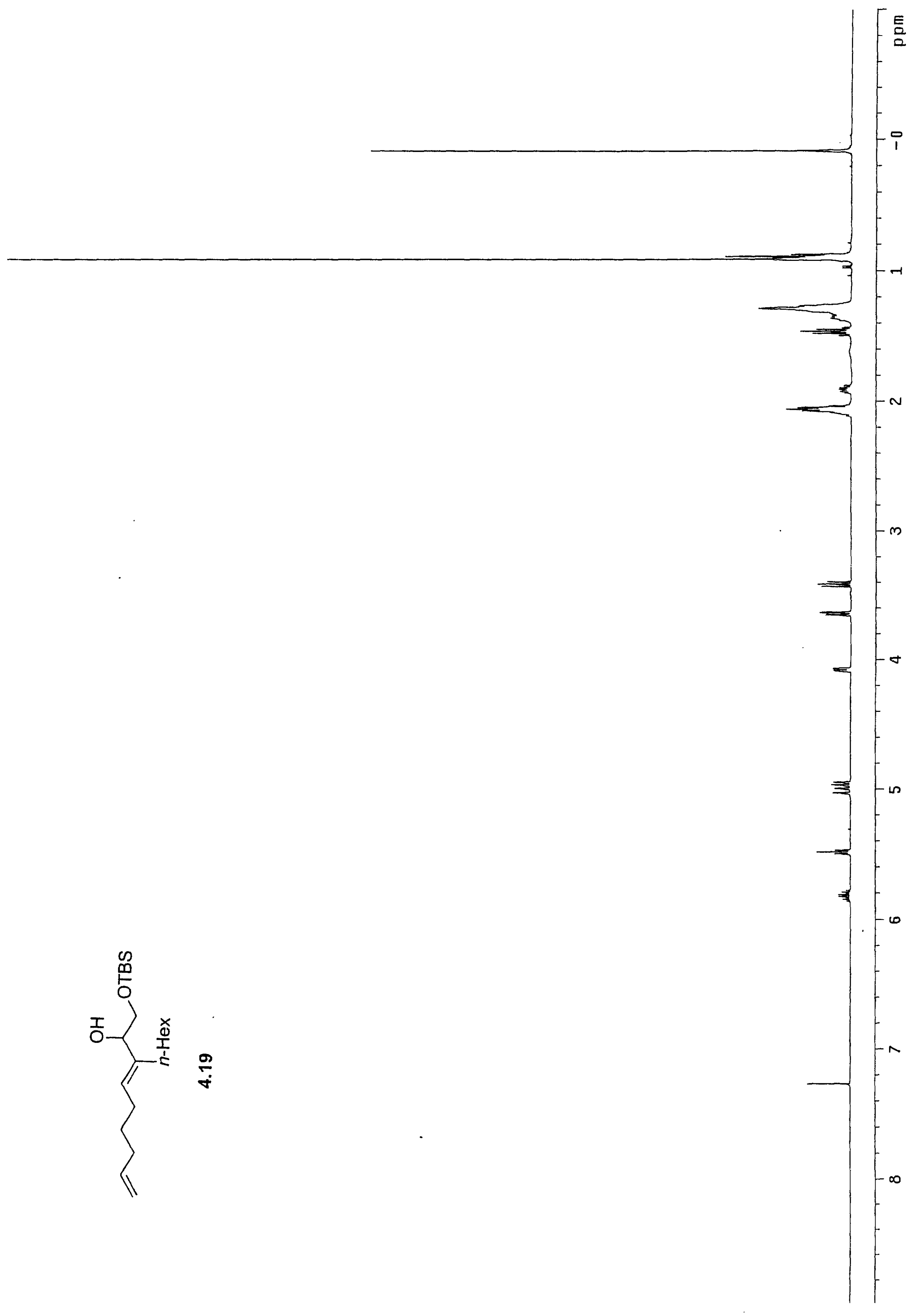

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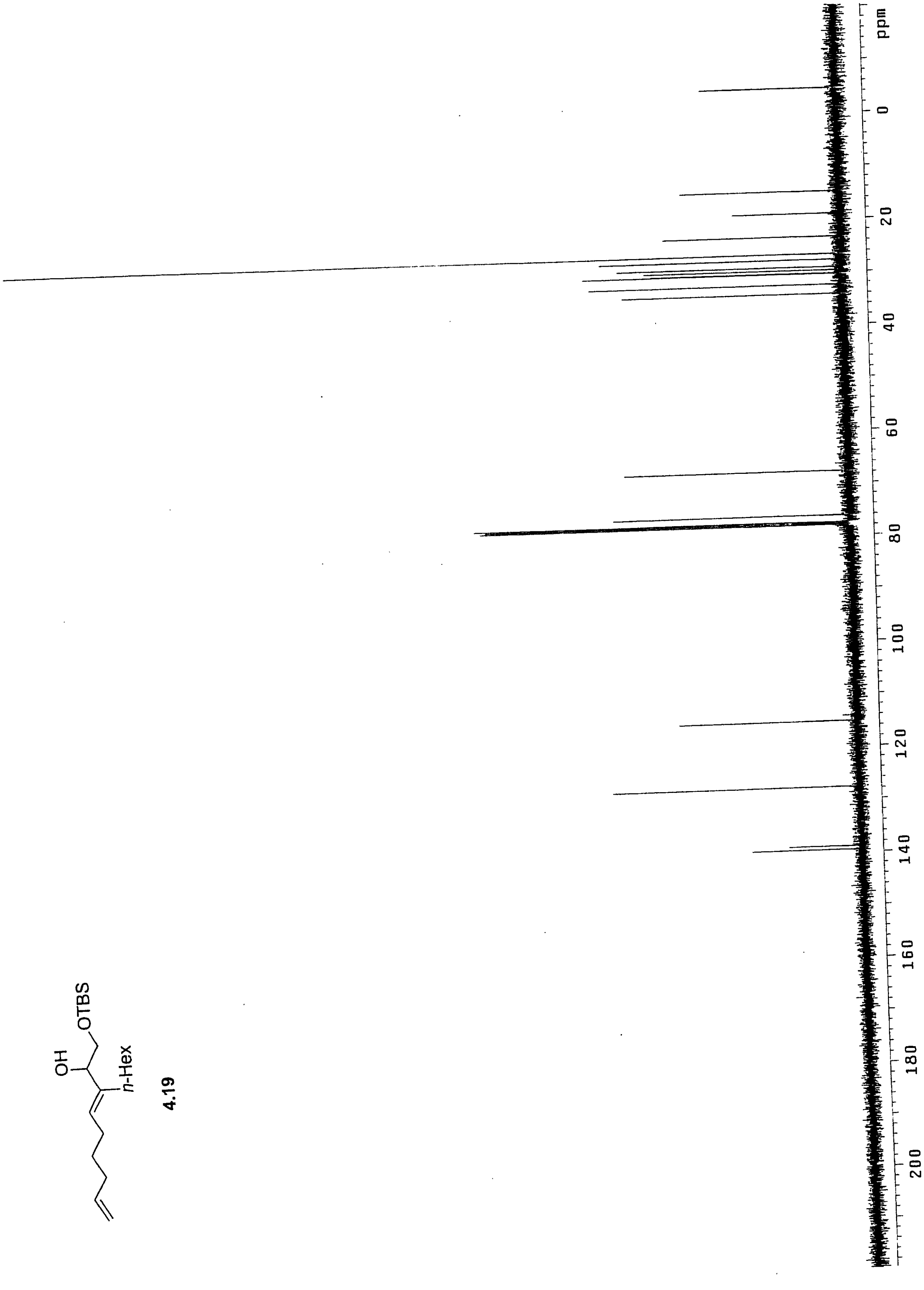
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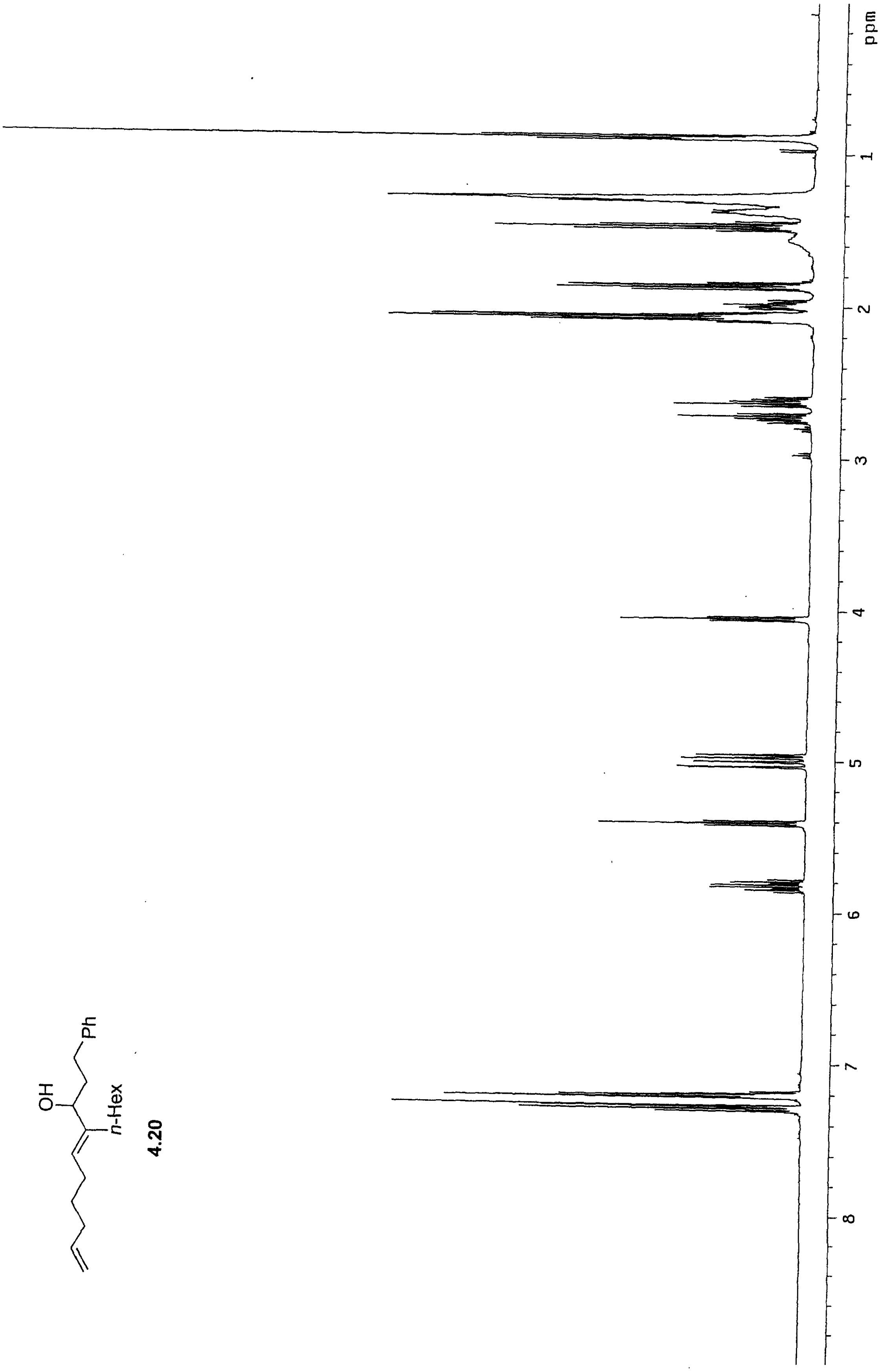

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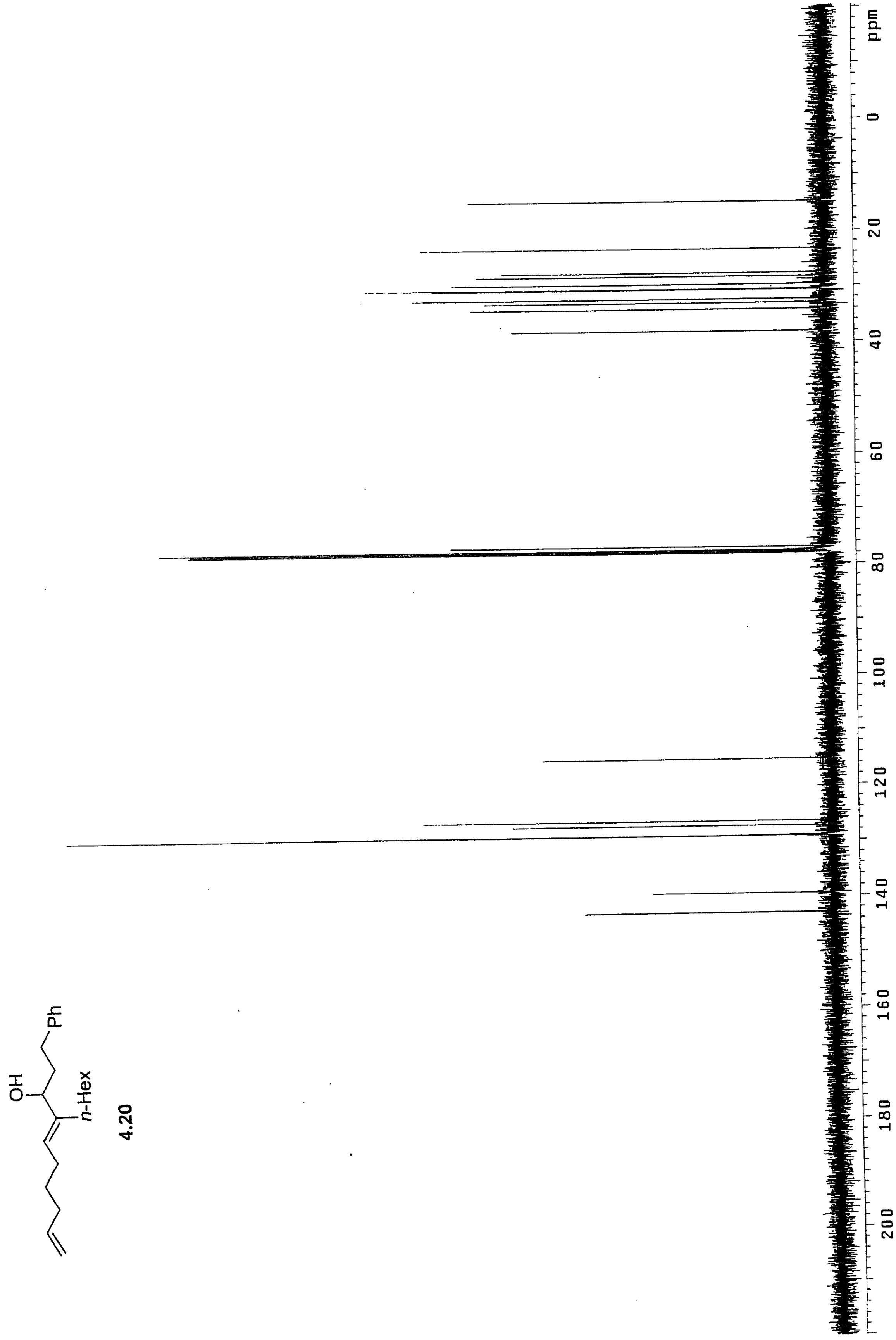

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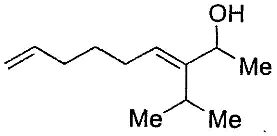

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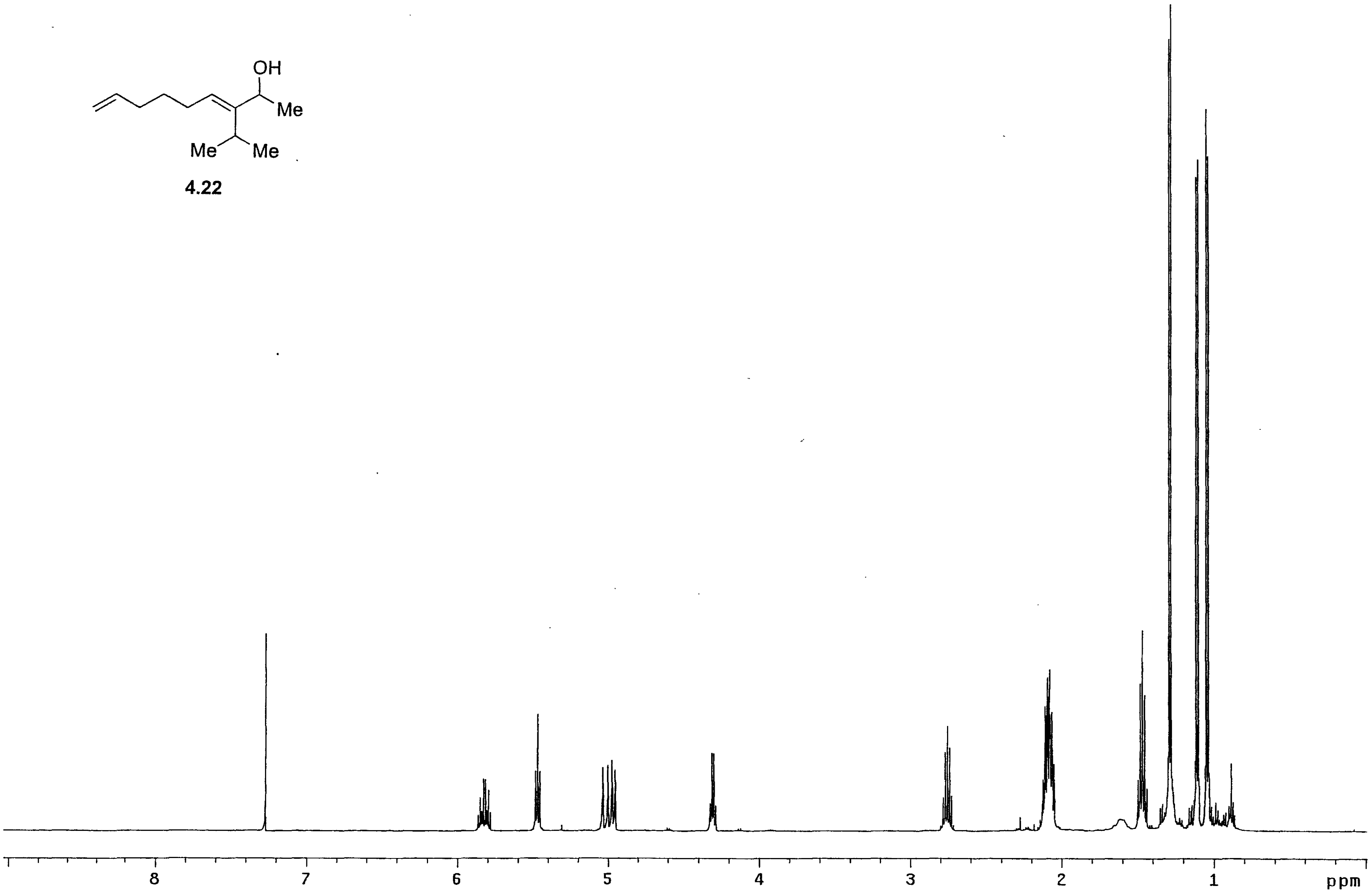

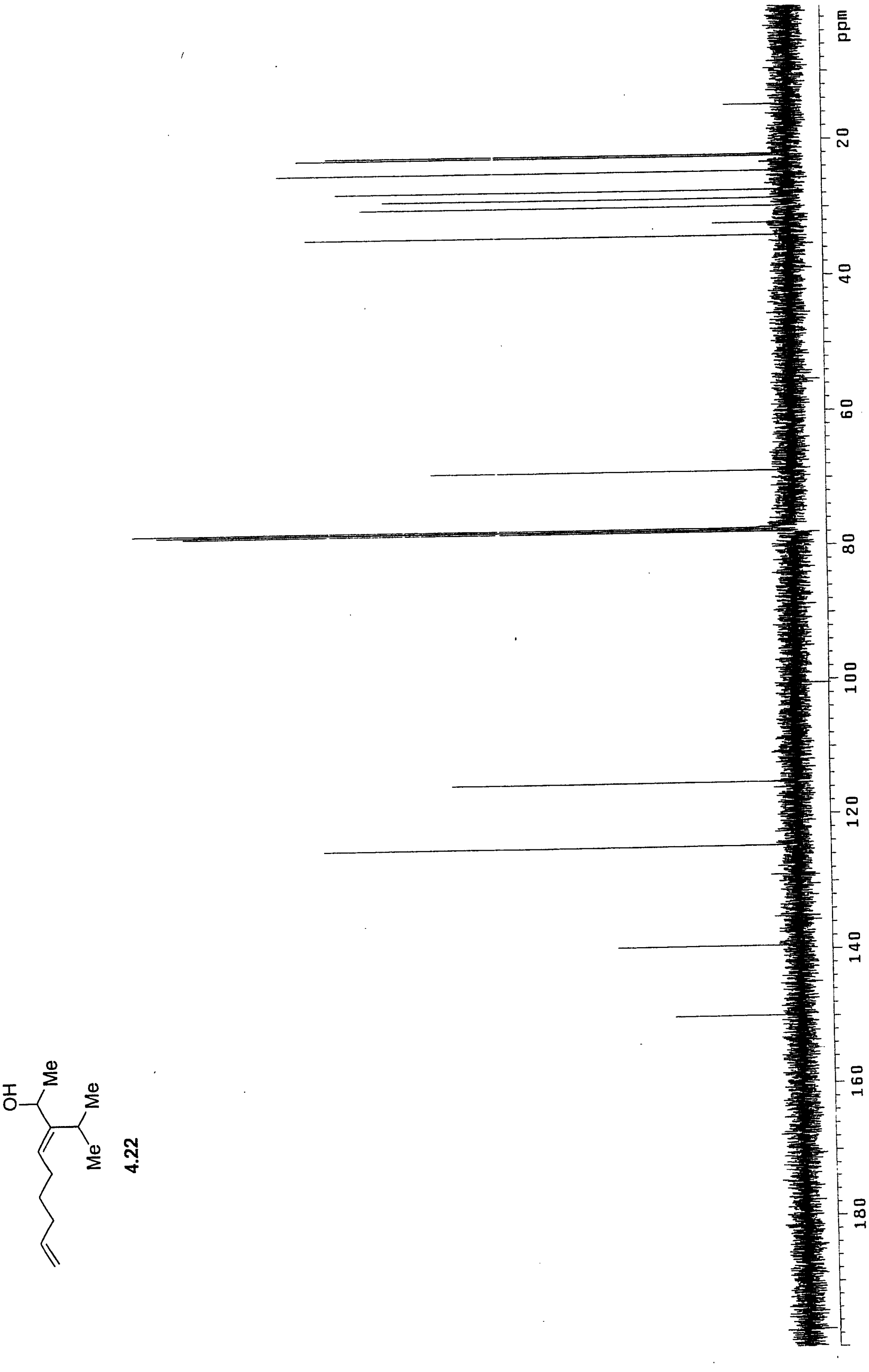

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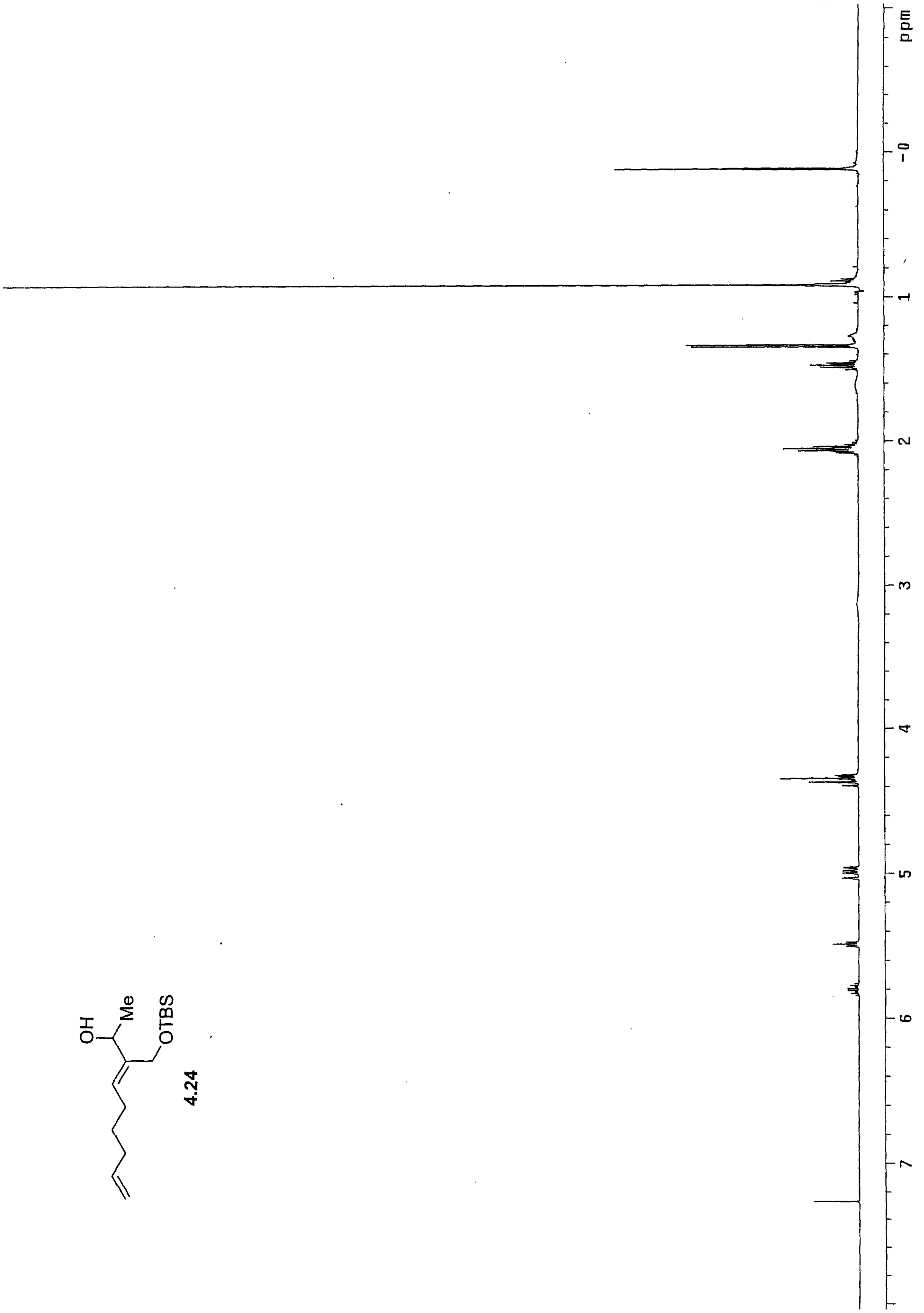

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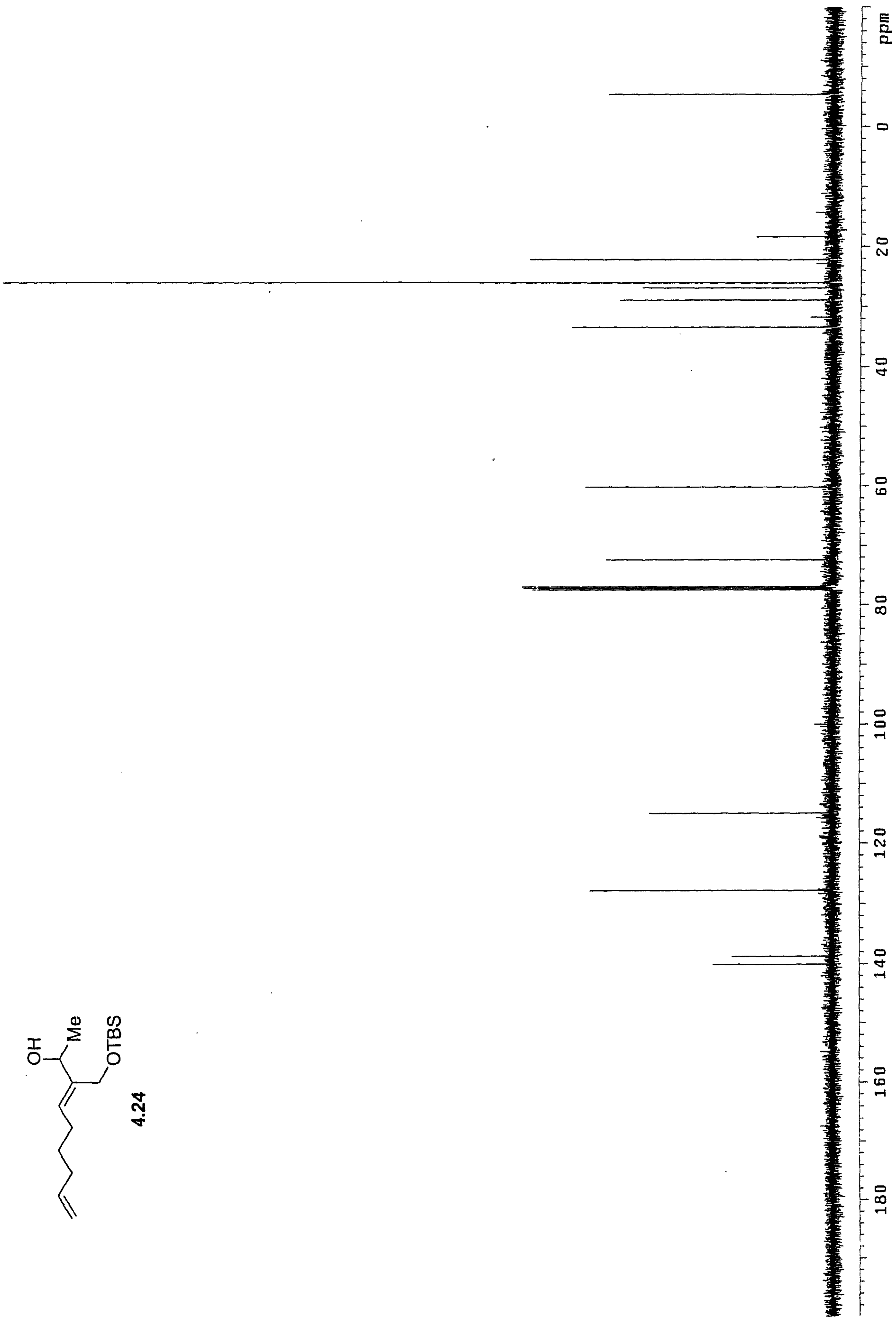

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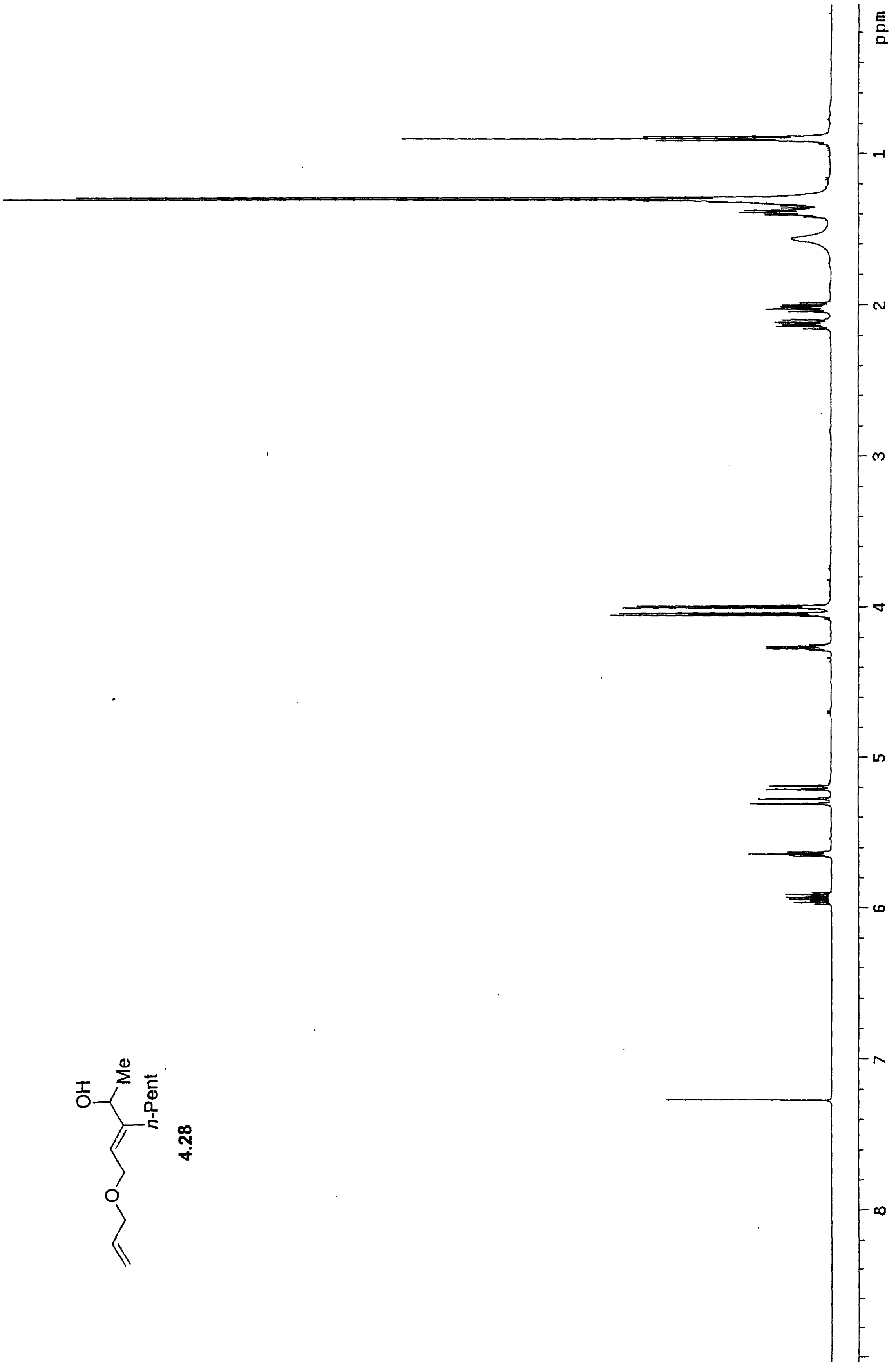

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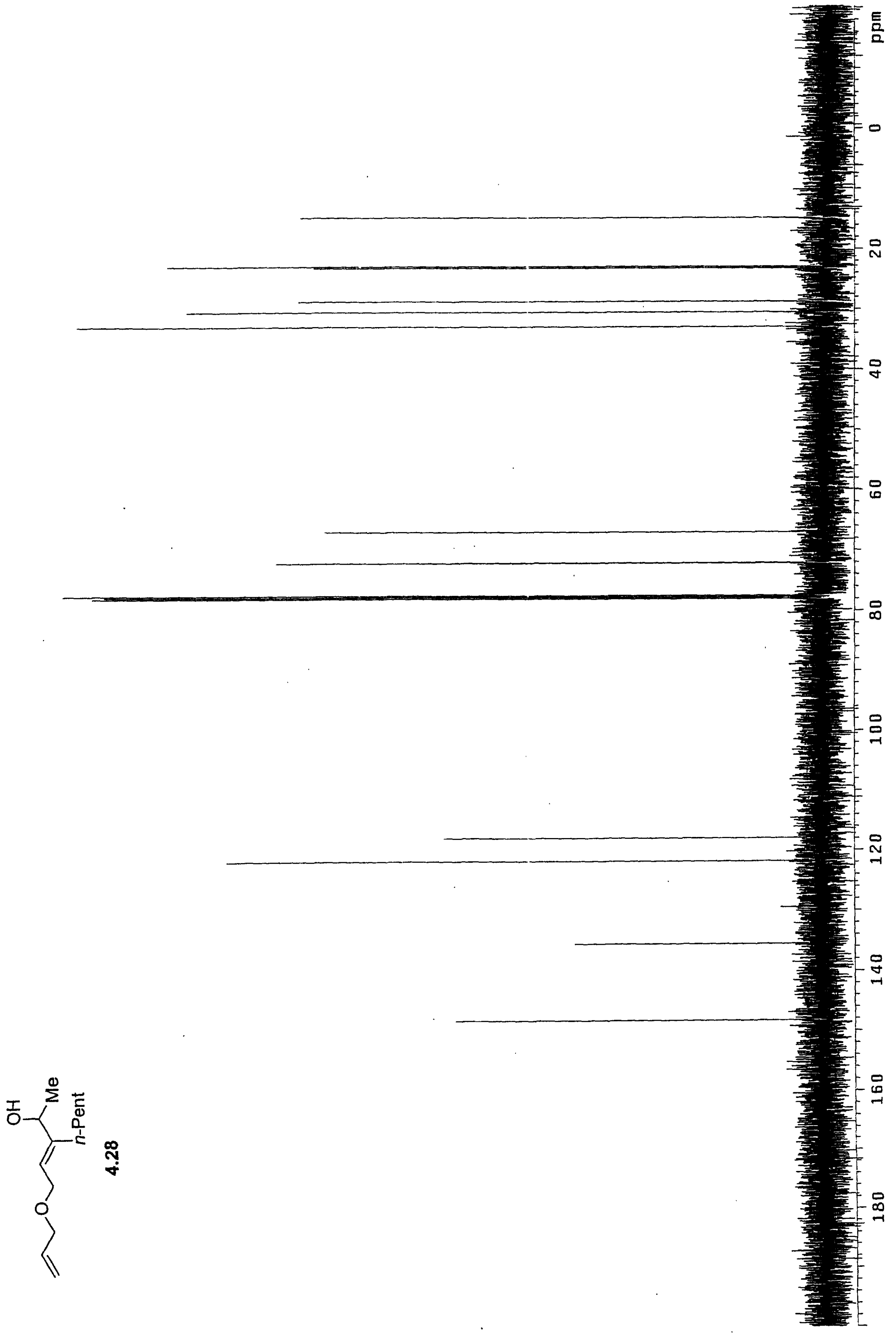

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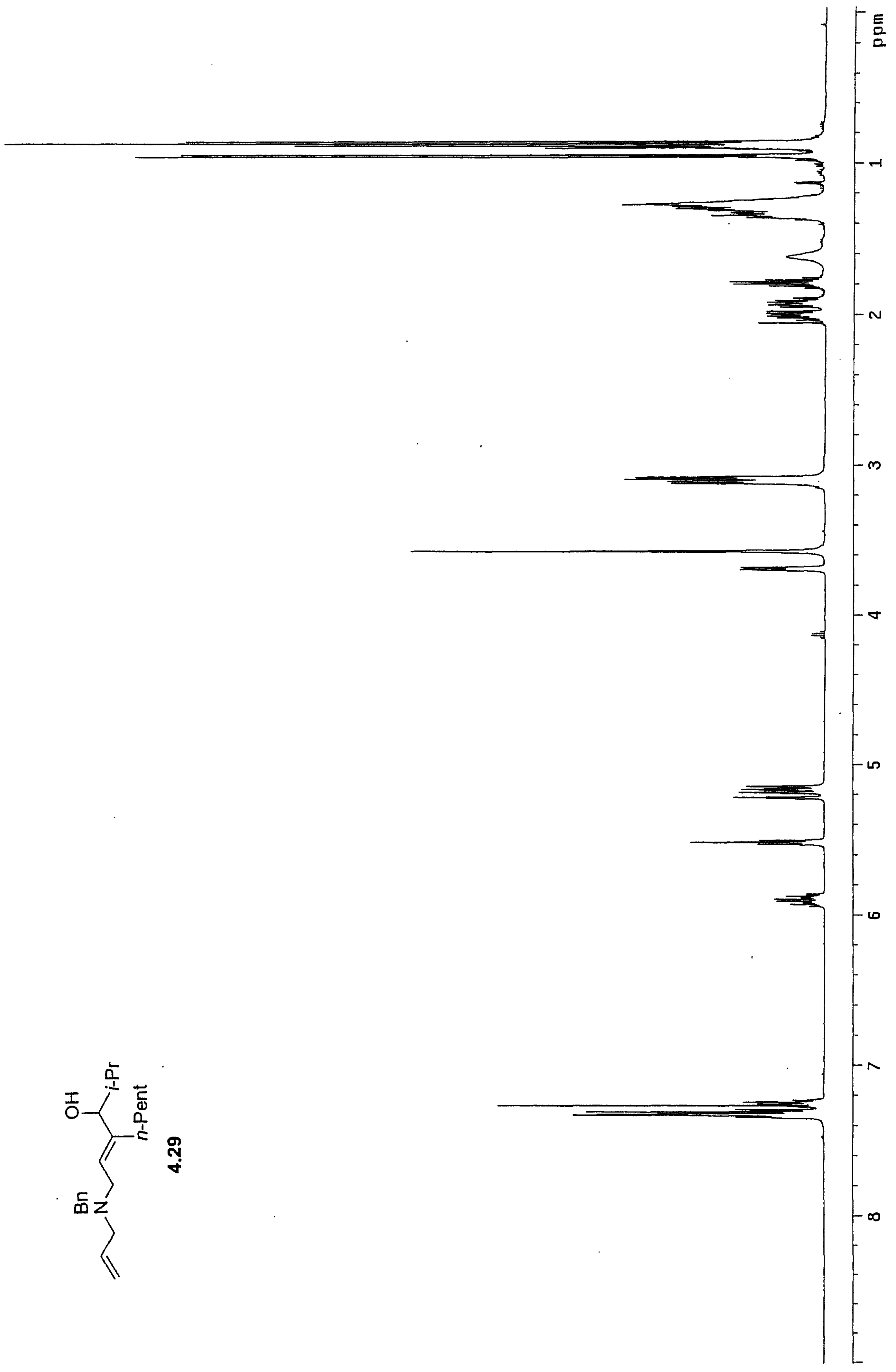

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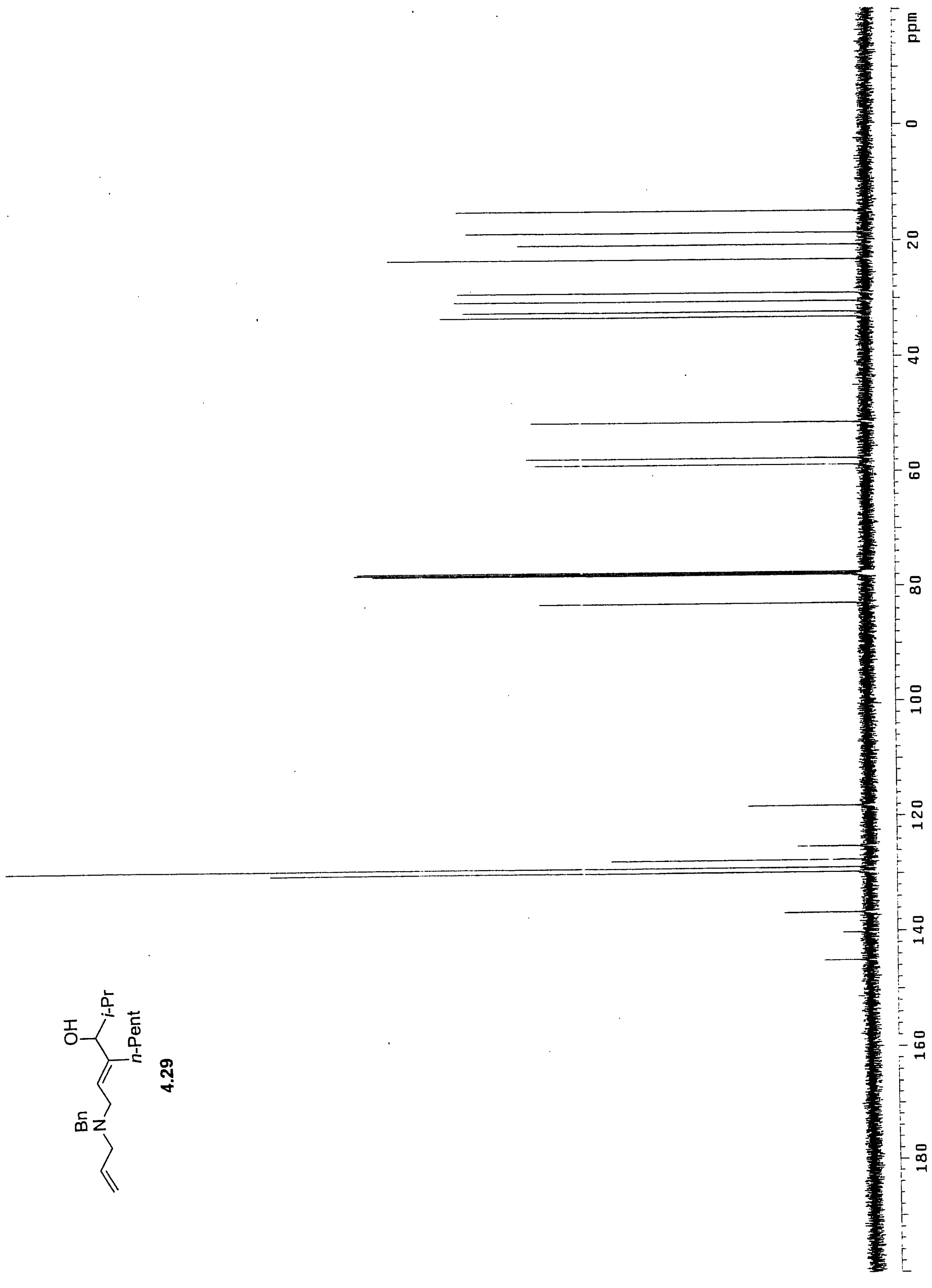

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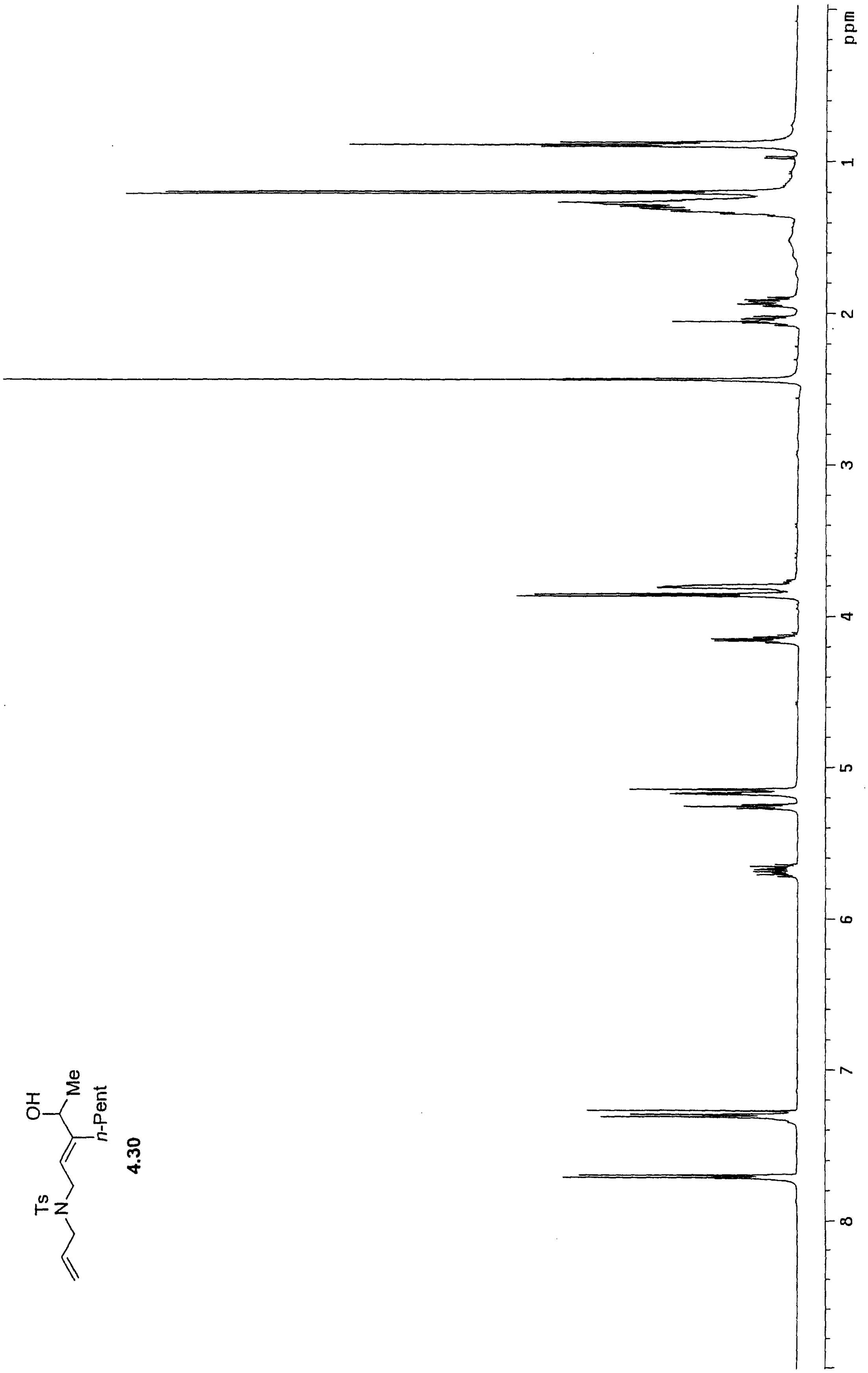

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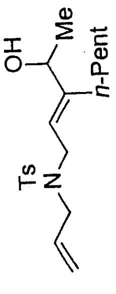

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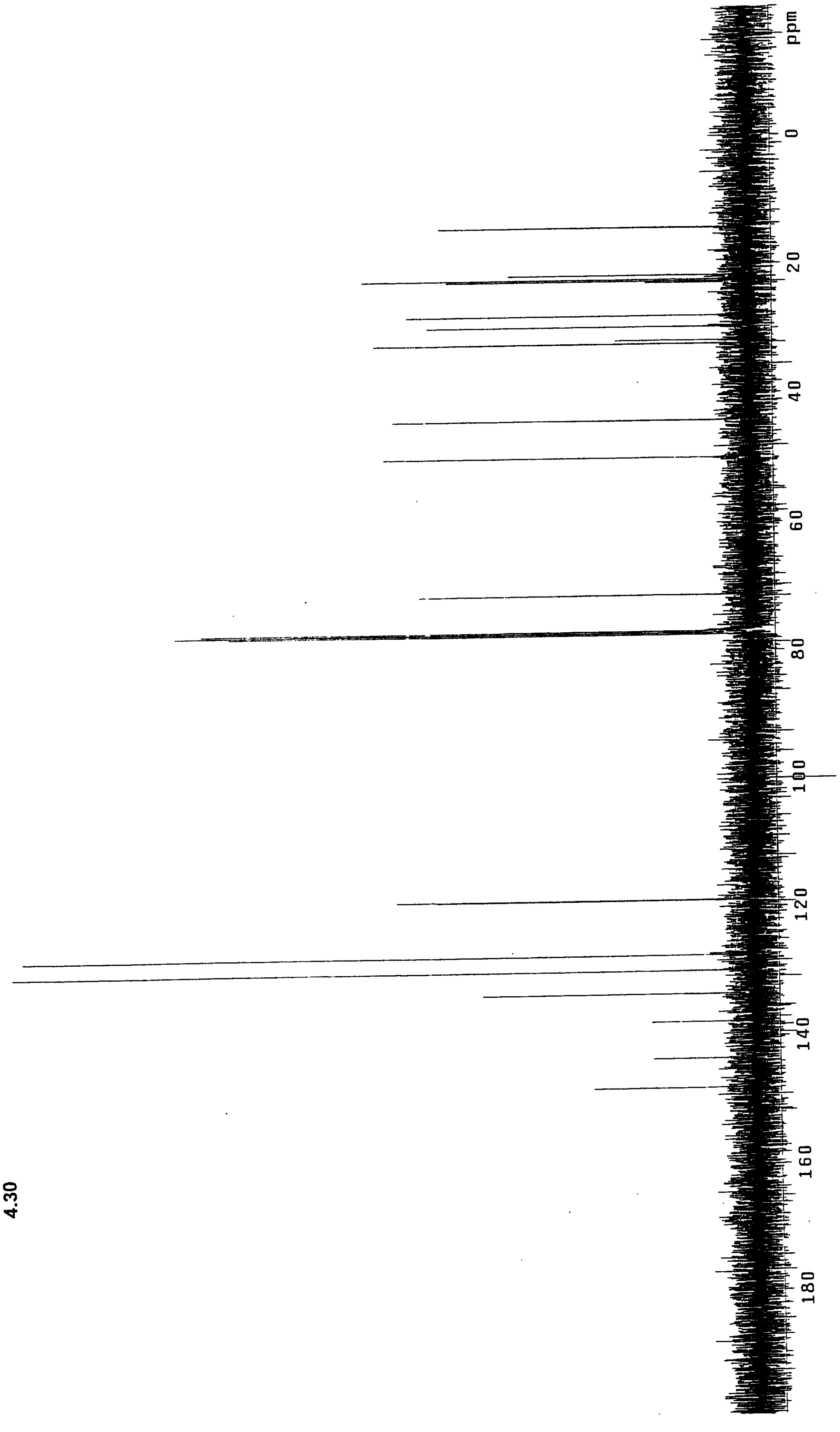

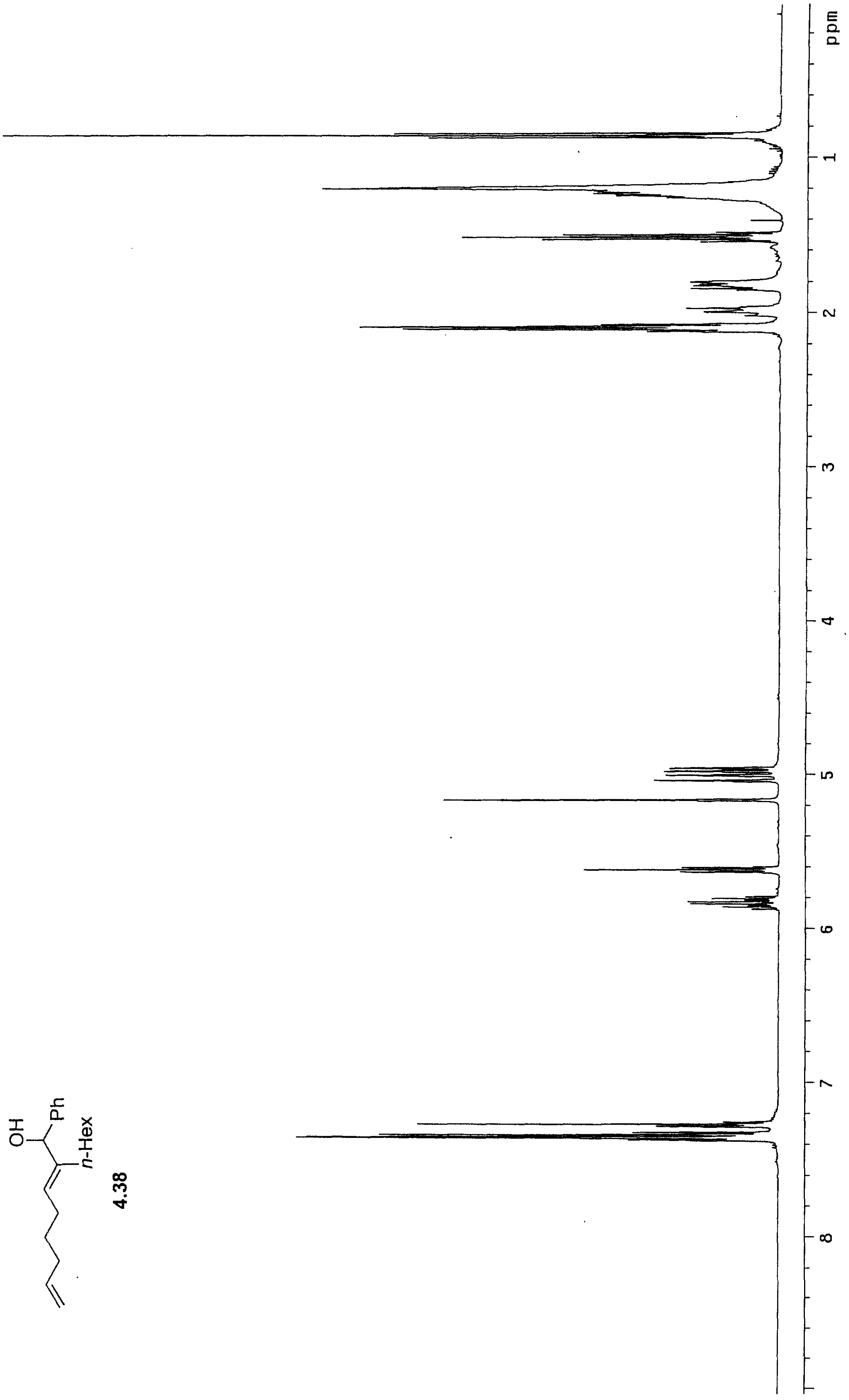
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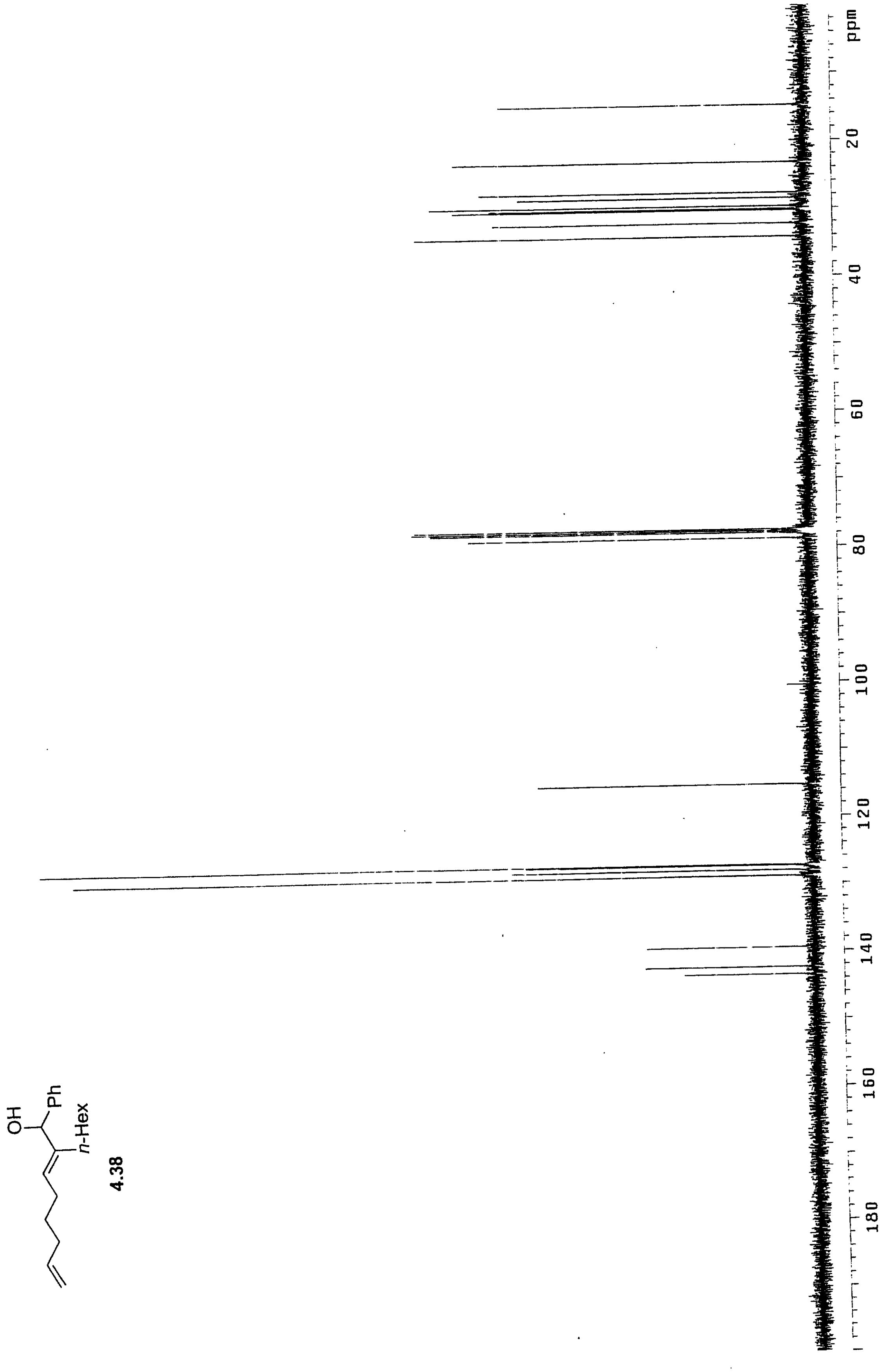

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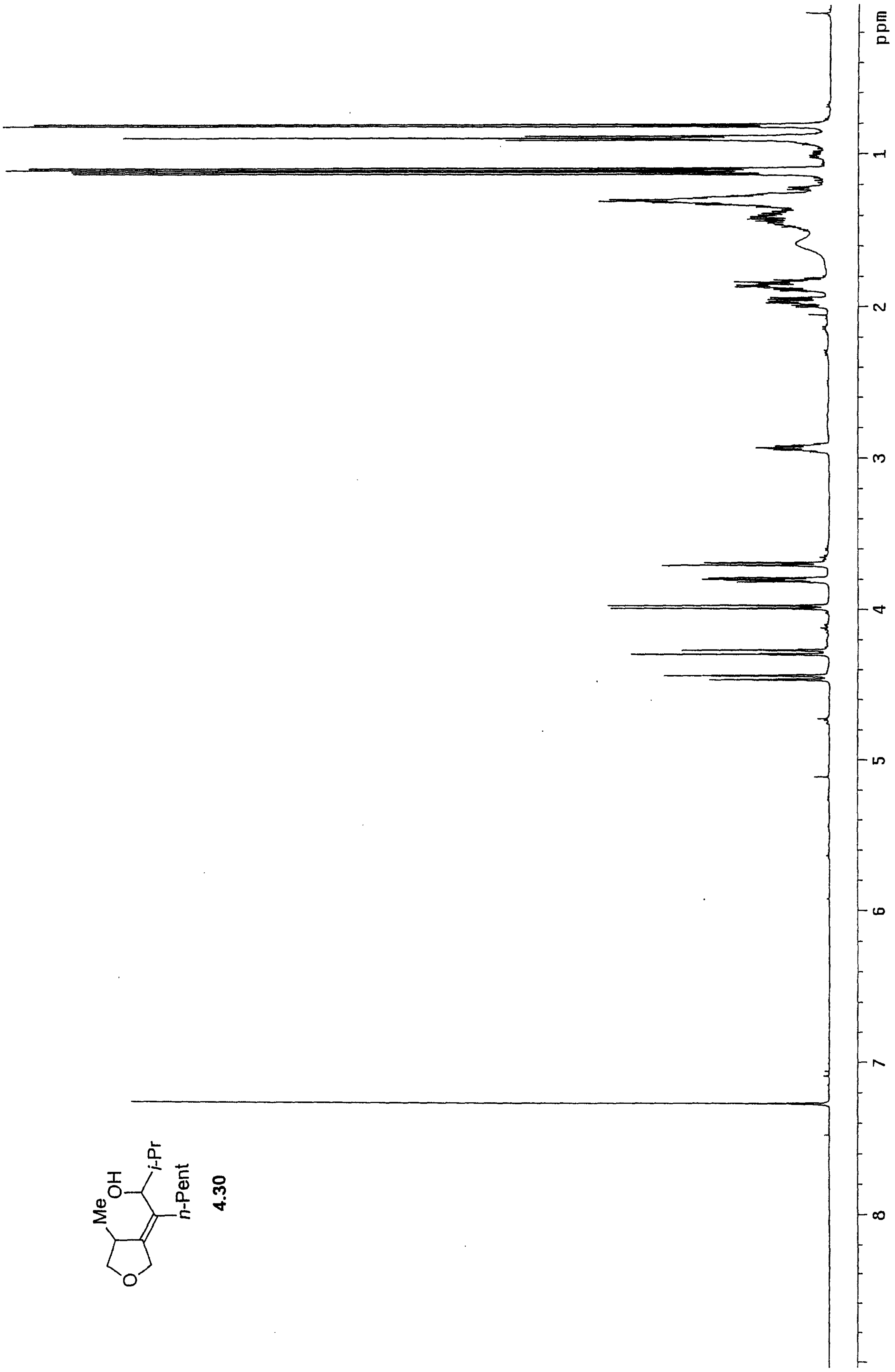

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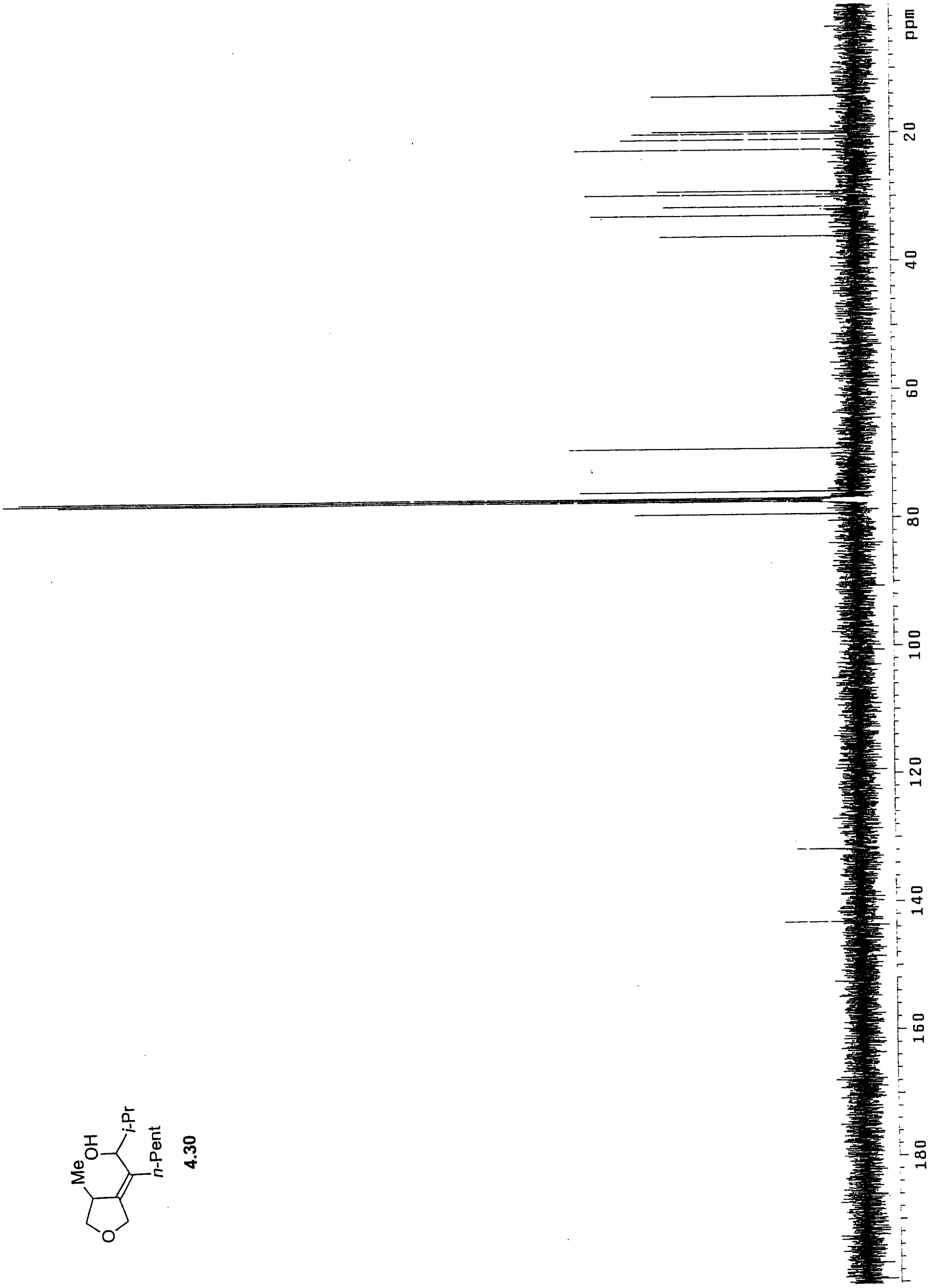

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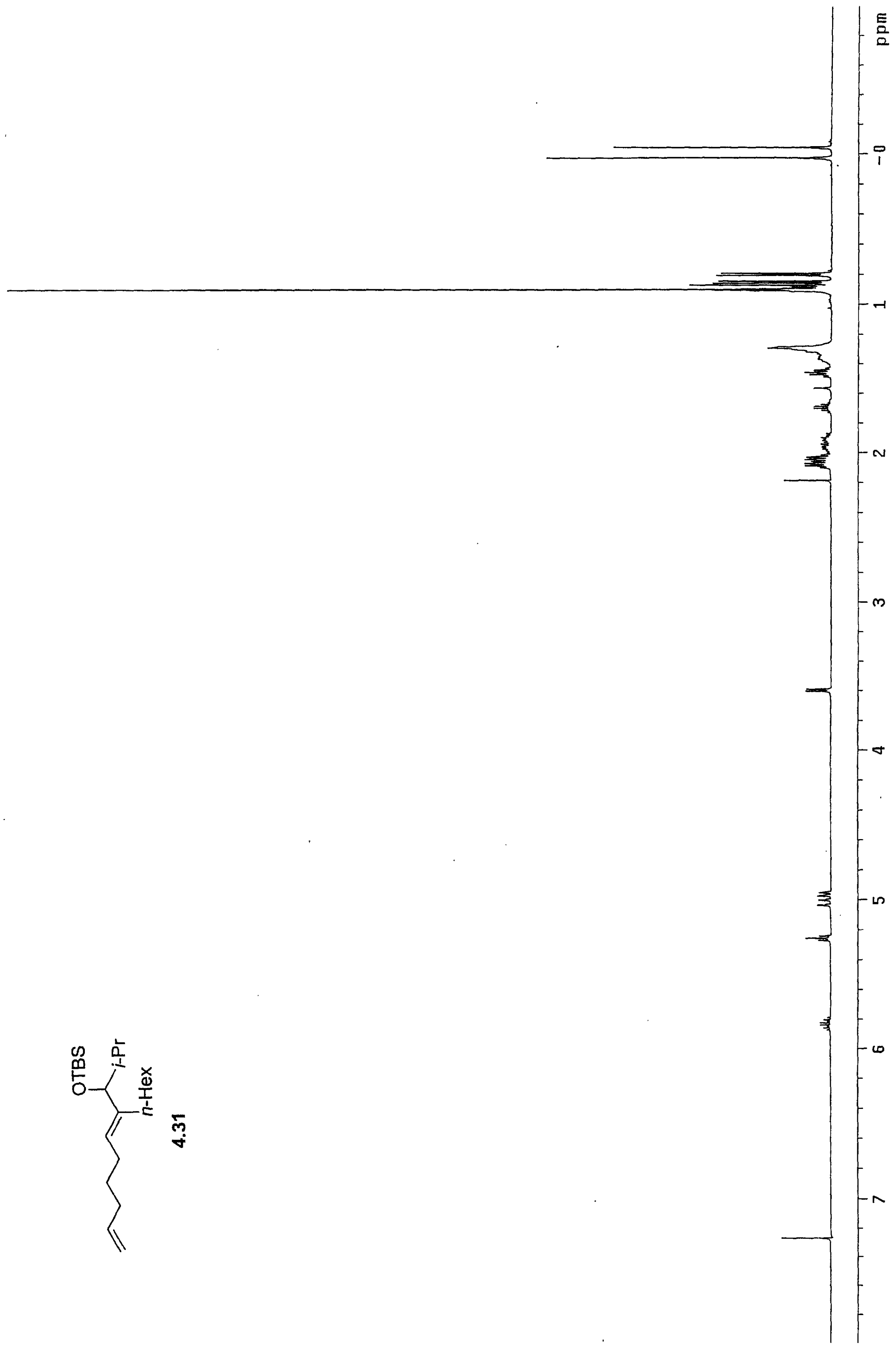

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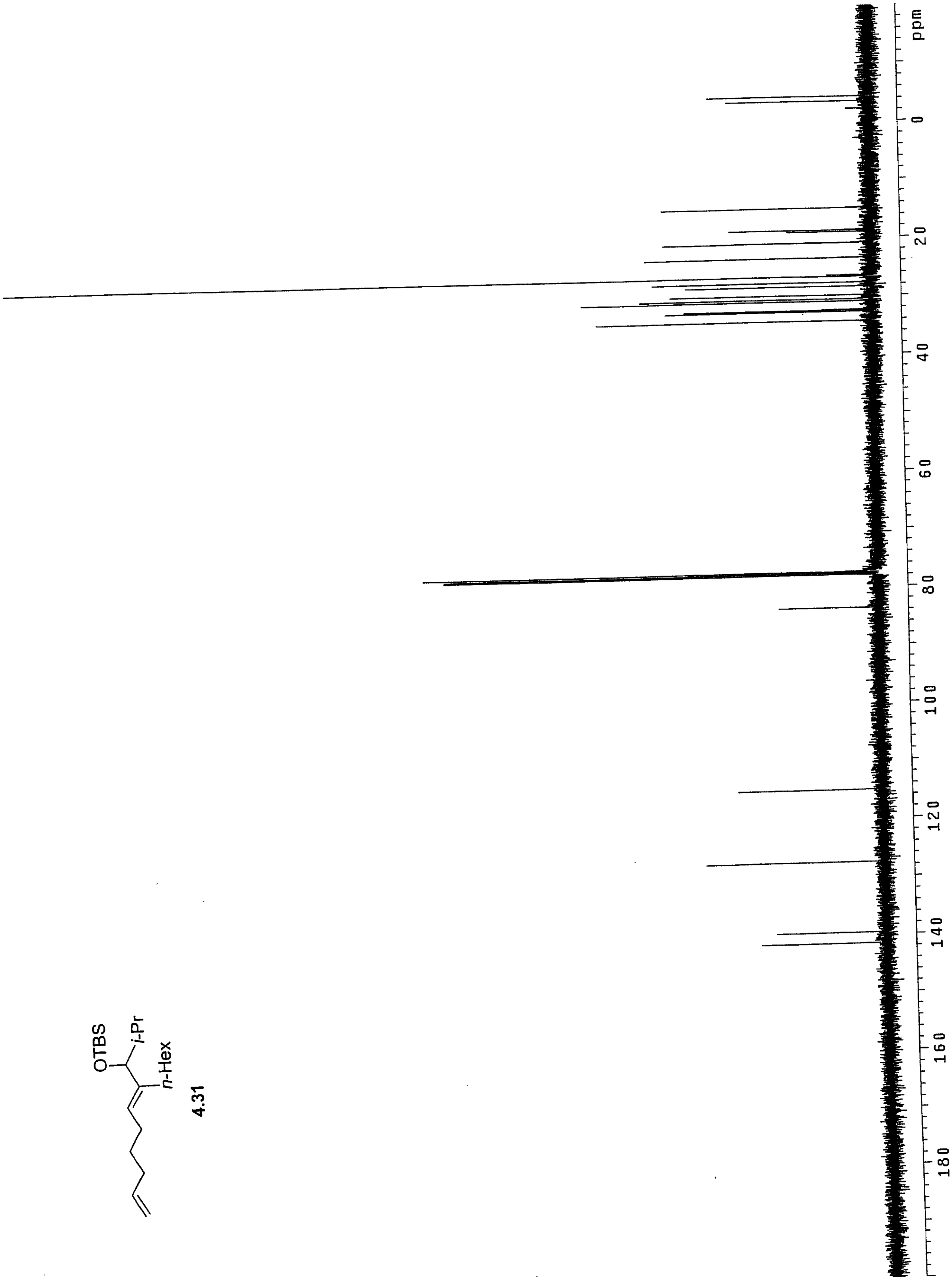

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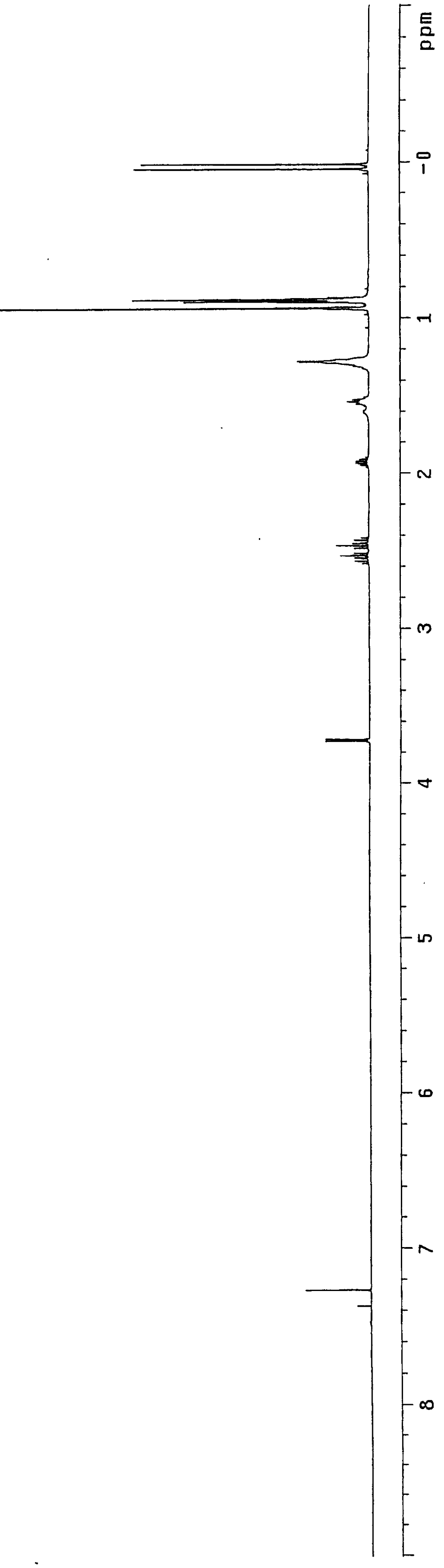

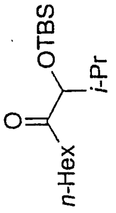

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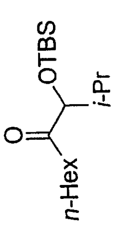

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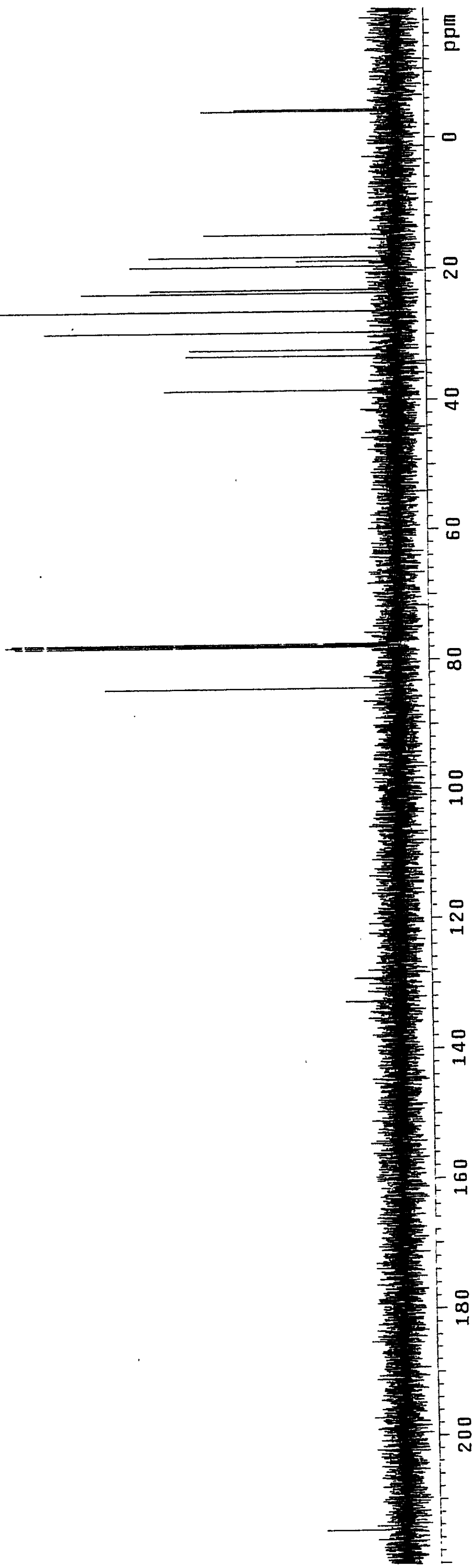

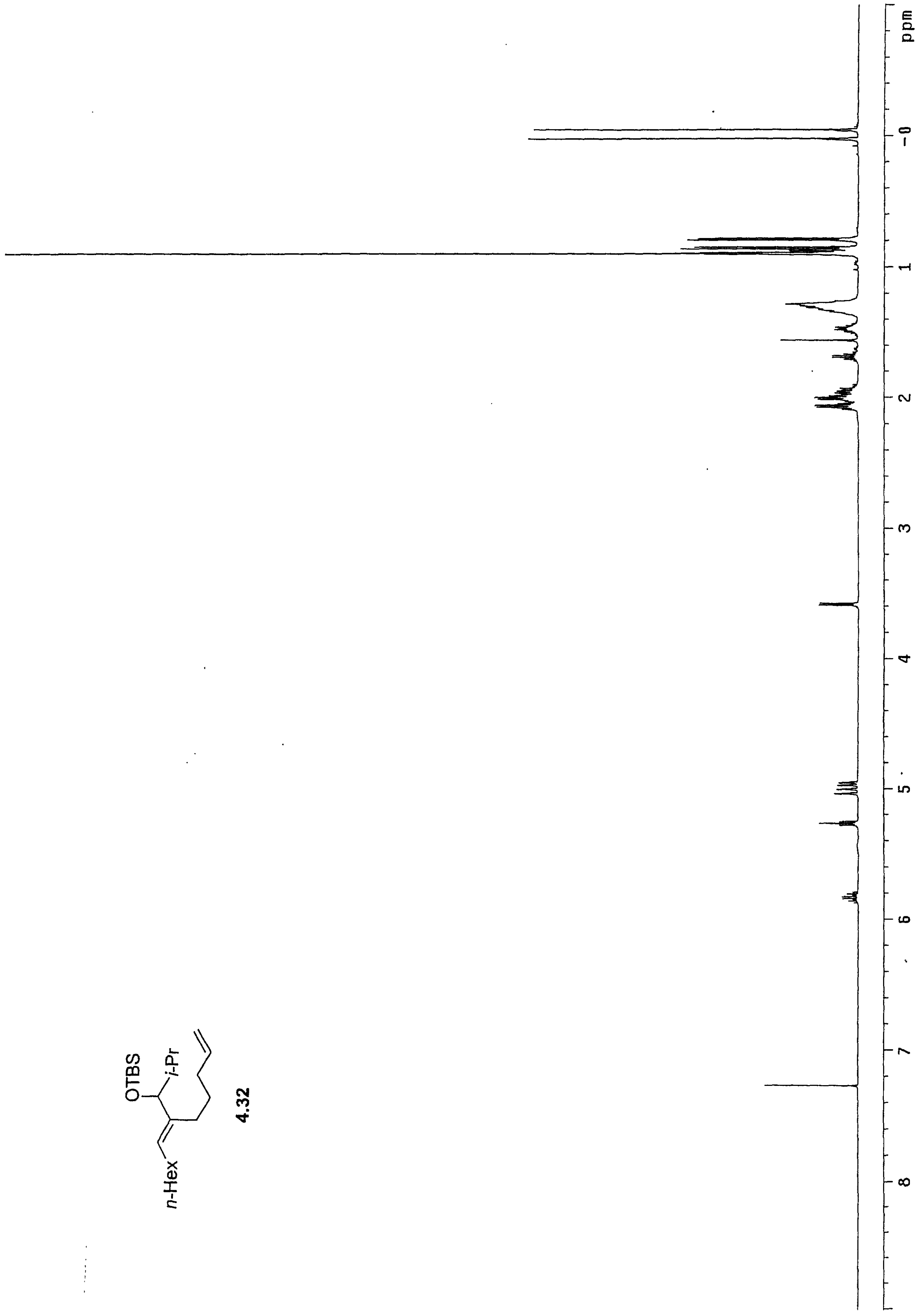

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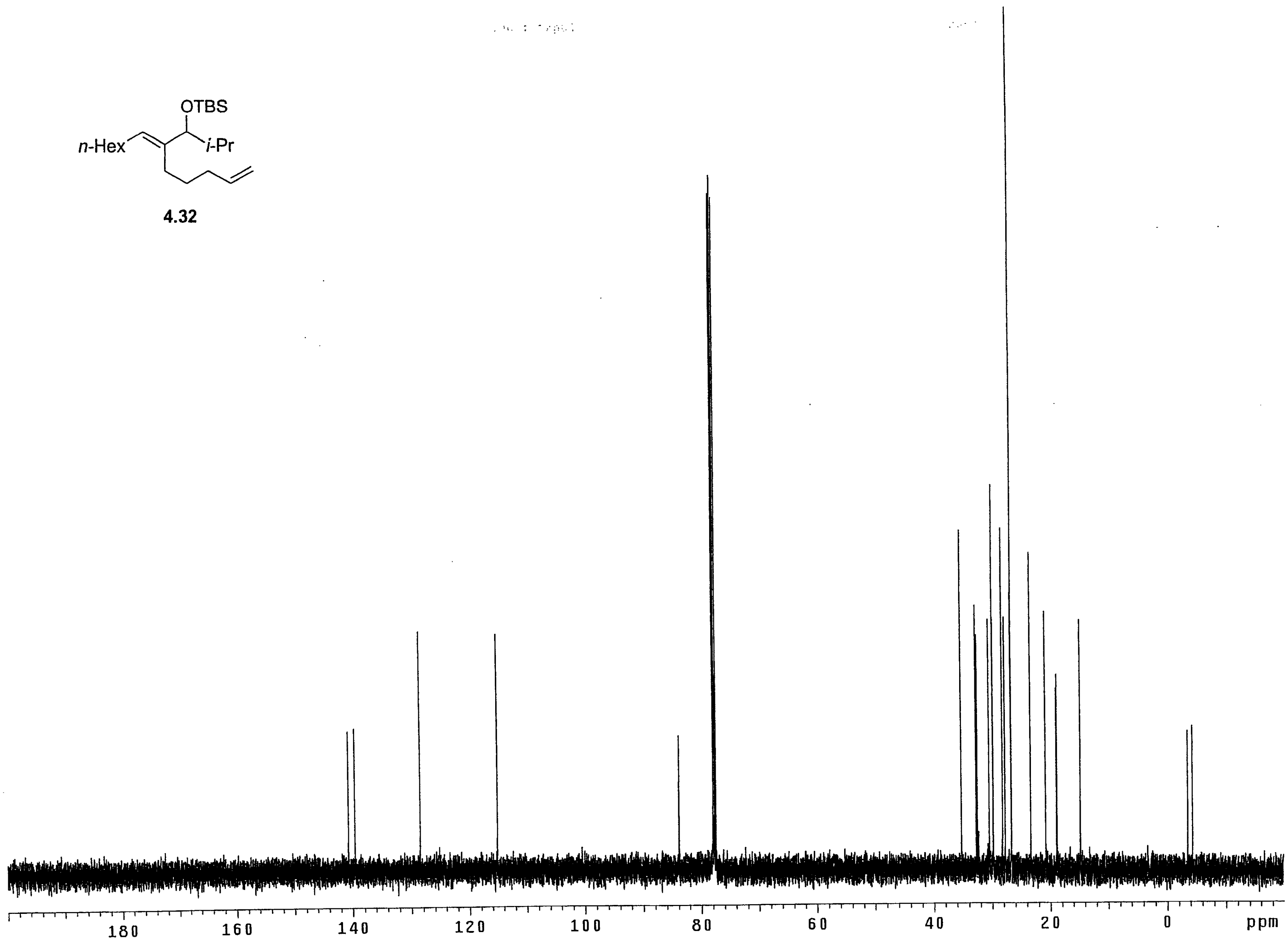

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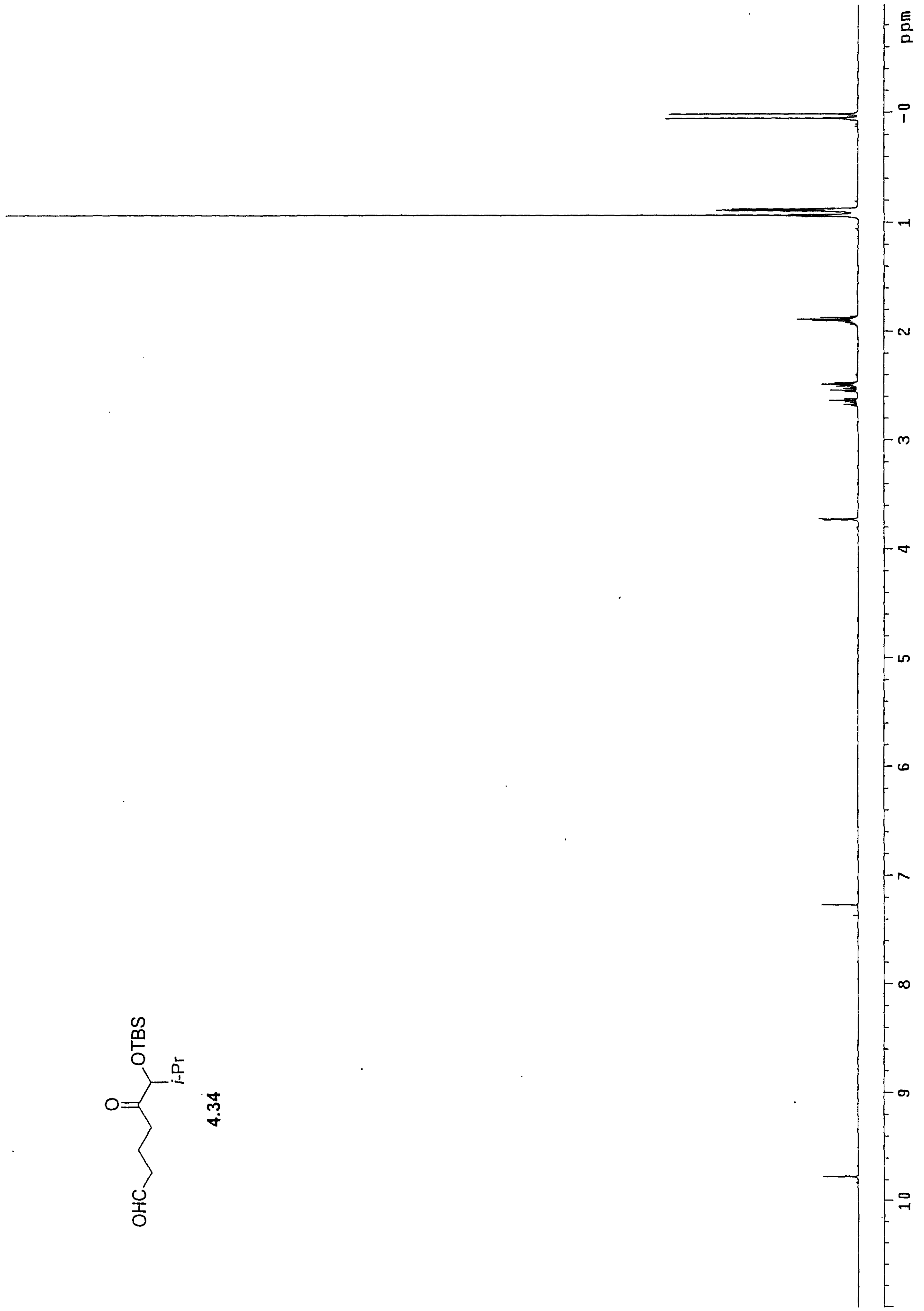

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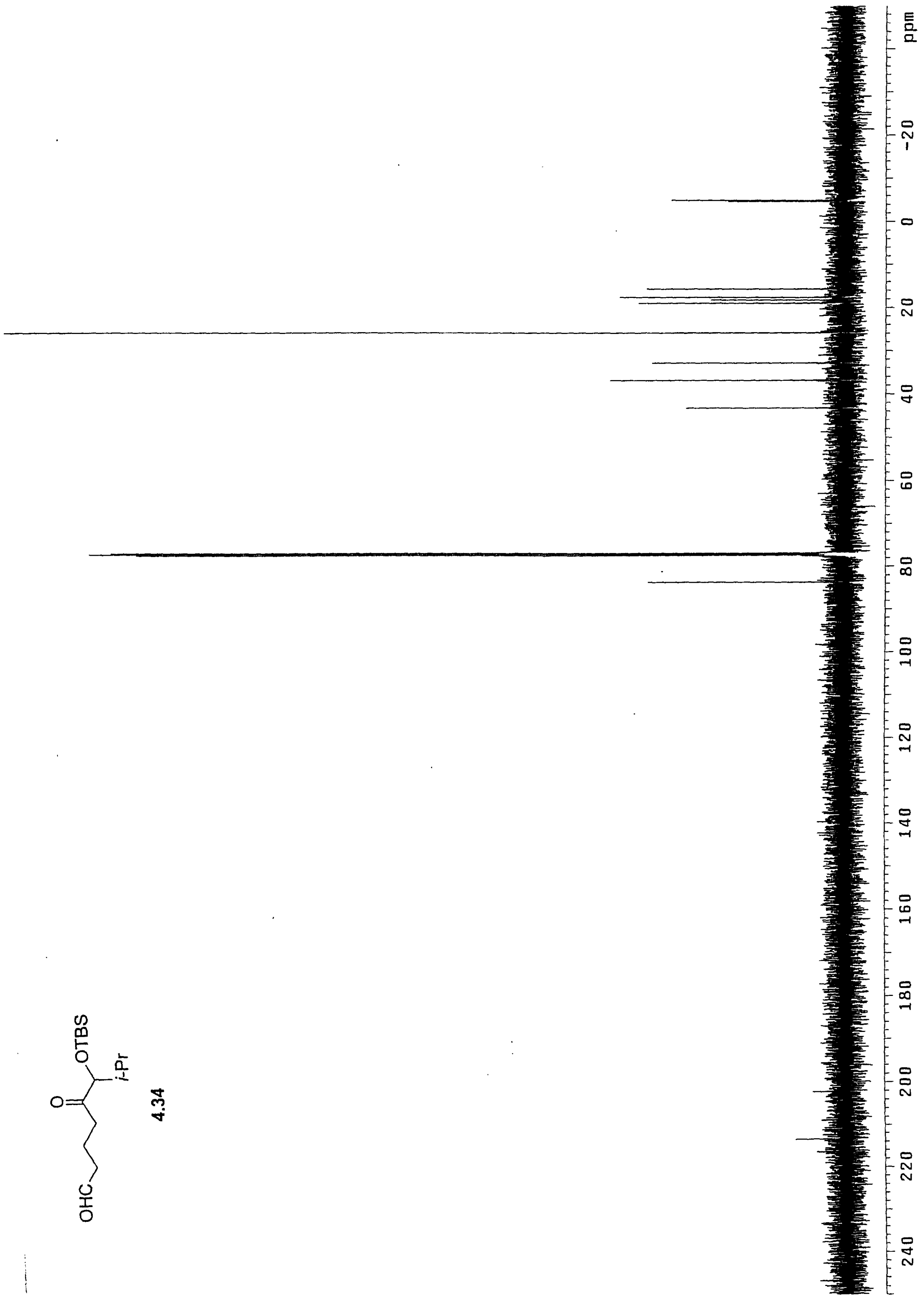

CURRICULUM VITAE

Karen M. Miller

Education:

2005 Ph.D. (Organic Chemistry), Massachusetts Institute of Technology
Thesis Title: *"Selective, Nickel-Catalyzed Carbon-Carbon Bond-Forming Reactions"*
Thesis Advisor: Professor Timothy F. Jamison

2000 A.B. (Chemistry), Dartmouth College
Thesis Title: *"Progress Toward the Synthesis of 1,2-Difluorocyclobutadiene"*
Undergraduate Thesis Advisor: Professor David M. Lemal

Research and Professional Experience:

1998-2000 Undergraduate Research Assistant, Dartmouth College

1999 Intern, Chemical and Screening Sciences, Wyeth Research, Pearl River, NY

2000-2001 Recitation Instructor, Massachusetts Institute of Technology
One semester Principles of Chemical Science (5.111)
One semester Organic Chemistry I (5.12)

2001-2005 Graduate Research Assistant, Massachusetts Institute of Technology

Awards and Honors:

- MIT Wyeth Scholar Travel Award for outstanding research accomplishments – *June 2004*
- First Prize Graduate Student Poster – *2003 Northeastern Student Chemistry Research Conference, Boston University*
- Henry Bromfield Rogers Fellowship, MIT – *Fall 2002*
- Graduated Cum Laude, with Honors (Chemistry), Dartmouth College – *June 2000*
- Presidential Scholar, Dartmouth College – *June 2000*
- Merck Index Award – *June 2000*
- Class of 1964 Dartmouth College Alumni Association Scholarship – *'99-'00 academic year*

Publications:

Miller, Karen M.; Jamison, Timothy F. "Highly Regioselective, Catalytic Asymmetric Reductive Coupling of 1,3-Enynes and Ketones," *manuscript submitted.*

Miller, Karen M.; Colby, Elizabeth A.; Woodin, Katrina S.; Jamison, Timothy F. "Catalytic Asymmetric Reductive Coupling of 1,3-Enynes and Aromatic Aldehydes," *manuscript submitted.*

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Presentations:

Miller, Karen M.; Luanphaisarnnont, Torsak; Molinaro, Carmela; Jamison, Timothy F. "Alkene-Directed, Nickel-Catalyzed Coupling Reactions," 228th National Meeting, American Chemical Society, Philadelphia, PA, August 2004.

Miller, Karen M.; Jamison, Timothy F. "Asymmetric Catalytic Reductive Coupling of Alkynes and Aldehydes," 224th National Meeting, American Chemical Society, Boston, MA, August 2002.

Miller, Karen M.; Jamison, Timothy F. "Asymmetric Catalytic Reductive Coupling of Alkynes and Aldehydes," 2003 Northeastern Student Chemistry Research Conference, Boston University.