Nickel-Catalyzed Reductive Coupling Reactions: Application to the Total Syntheses of Pumiliotoxins 209F and 251D

by

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B.S., Chemistry
University of New Hampshire, 2004

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

MASTER OF SCIENCE
IN ORGANIC CHEMISTRY

at the

Massachusetts Institute of Technology
[February 2007]
January 2007

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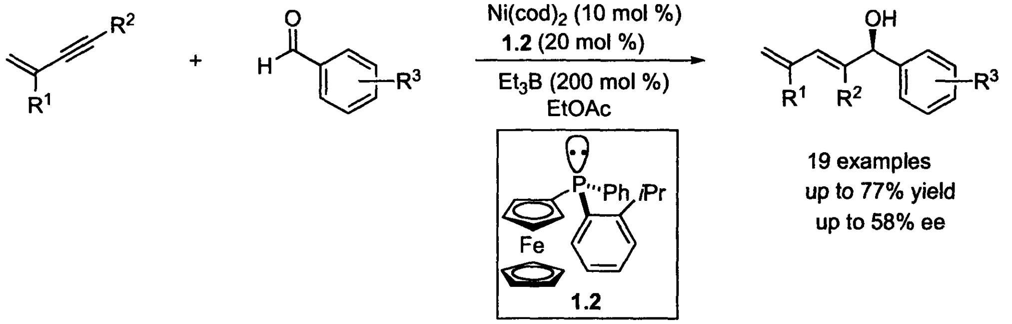
Robert W. Field
Chairman, Department Committee on Graduate Students

To my beloved Matthew

Abstract

Catalytic Asymmetric Reductive Coupling of 1,3-Enynes and Aromatic Aldehydes

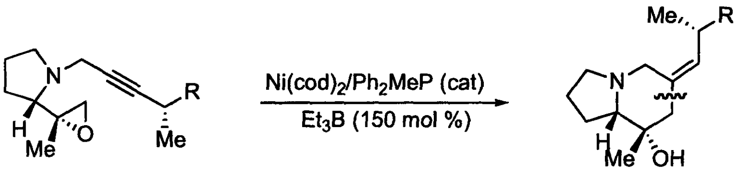
Nickel-catalyzed reductive coupling reactions of 1,3-enynes and aromatic aldehydes efficiently afford conjugated dienols in excellent regioselectivity and modest enantioselectivity. These reactions were conducted in the presence of a catalytic ligand (*R*)-ferrocenyl(2-isopropylphenyl)phenylphosphine, whose overall synthesis was improved during the course of this investigation. 1-(Trimethylsilyl)-substituted enynes are shown to be efficient coupling partners in these reactions, and the dienol products formed readily undergo protiodesilylation under mild conditions.



19 examples
up to 77% yield
up to 58% ee

Catalytic, Asymmetric, Intramolecular Reductive Coupling of 1,1-Disubstituted Epoxides and Alkynes: Total Synthesis of Pumiliotoxin 209F and 251D

Pumiliotoxins 209F and 251 D were prepared using a novel nickel-catalyzed intramolecular cyclizations between alkynes and 1,1-disubstituted epoxides. These cyclizations formed exclusively *endo* products without the use of a directing group on the alkyne. The synthesis of the reductive coupling precursors involved a diastereoselective sulfur ylide epoxidation of a proline-derived methyl ketone, where the choice of sulfonium salt conferred a major effect on the diastereoselectivity.



R = Me, pumiliotoxin 209F
R = *n*Bu, pumiliotoxin 251D

Thesis Supervisor: Timothy F. Jamison

Title: Associate Professor of Chemistry

Preface

Portions of this thesis have appeared in the following articles that were co-written by the author:

Asymmetric Catalytic Reductive Coupling of 1,3-Enynes and Aromatic Aldehydes. Miller, K. M.; Colby, E. A.; Woodin, K. S.; Jamison, T. F. *Adv. Synth. Catal.* **2005**, *347*, 1533-1536.

Total Syntheses of Pumiliotoxins 209F and 251D via Late-Stage, Nickel-Catalyzed Epoxide-Alkyne Reductive Cyclization. Woodin, K. S.; Jamison, T. F. *Manuscript in Preparation.*

Acknowledgements

The pursuit of this degree has been a challenging and rewarding experience. It has given me perspective I would have gained no where else. I would never have gotten this far if it were not for the support of many.

I would like to first thank my research advisor, Dr. Timothy Jamison, for accepting me into his group and shaping me into the organic chemist I am today. I will look back at my time in his lab very fondly. I would also like to thank my thesis chair Dr. Gregory Fu, whose knowledge of chemistry is only outweighed by his ability to teach it to others. I owe much appreciation to Dr. Mo Movassaghi, who always had an open door to give advice on chemistry and my career; I will never forget his support.

I am especially grateful to Tim for attracting some of the greatest scientists I've ever known to the group. I owe my deepest gratitude to my dearest friend and mentor, Dr. Chudi Ndubaku, who has given me unyielding support throughout. Chudi is the kind of person I strive to be; his kind nature, enthusiasm, determination, and humility are matched by few, and I am honored to be his friend. I also want to thank the very patient Dr. Neil Langille, who always seemed to have an answer for my unending stream of questions, as he taught me to be a better chemist. I also value his friendship greatly and look forward to having him as a colleague at Amgen. Thank you to Victor "paperless hater" Gehling, whose intellect, ambition, and kindness are a source of inspiration. I also want to thank Dr. Karen Miller-Moslin who showed me how to be an organic chemist from day one; I enjoyed our collaboration on the asymmetric enyne project.

My bay-mates, Dr. Graham Simpson, Dr. Tim Heffron, Dr. Chudi Ndubaku, Brian Sparling, Brian "sucks to be you" Underwood, Ivan Vilotijevic, and Chris Morten have kept me laughing constantly and I could not imagine a better environment for cutting edge research. I also want to thank my other great lab-mates, Dr. Elizabeth Colby, Dr. Stephan Kaiser, Dr. Jason Ho, Dr. Ryan Moslin, Jim Trenkle, CiCi Ng, Andrew Lauer, Aaron Van Dyke, and Kristin Scheleicher. I have also appreciated the meals out with my year-mates Dustin Siegel and Meiliana Tjandra. Thank you to all my other friends in the department, especially Bin Chen, Matthew Hill, Elvedin Lukovic, Laura Jennings, and Mathew Tantama, for countless good times.

My family has supported me throughout, even when they may not have agreed with every decision I made. My father continues to inspire me to be the best scientist I can, and to love what I do. My mother is the strongest woman I've ever met, and I truly aspire to have her courage, will, and sense of humor. I'm lucky to have the most loving, fun, and supportive parents anyone could have. My brother and sister have also always been there for late-night conversations, and I wish them both the best in their own careers.

Finally to my fiancé, Matthew, I love you. I don't think any person has supported me more than you have. Whether it be making food for us on late nights or early mornings, listening to my late night rants, sacrificing your weekends when I was in the lab, you have always been there keeping me sane throughout this experience. You make me a better person, and I feel so lucky to have you. I look forward to many more adventures as we spend our lives together.

Table of Contents

Abbreviations

Å	angstrom(s), 10^{-8} centimeter(s)
[α]	specific rotation
Ac	acetyl
Alloc	allyl carbamate
aq.	aqueous
Ar	aryl
Bn	benzyl
BRSM	based on recovered starting material
Bu	butyl
°C	degree (Celsius)
calcd	calculated
Cbz	benzyl carbamate
cod	cyclooctadiene
cm	centimeter
Cy	cyclohexyl
Cyp	cyclopentyl
δ	chemical shift in parts per million
dba	dibenzylideneacetone
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DMSO	dimethylsulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dr	diastereomeric ratio
ee	enantiomeric excess
Et	ethyl
Et_3B	triethylborane
EtOAc	ethyl acetate
Fc	ferrocenyl
Fmoc	9-fluorenylmethyl carbamate
g	gram
GC	gas chromatography
h	hours
hex	hexyl
HOAc	acetic acid
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
i	*iso-*
IR	infrared spectroscopy
J	coupling constant
L	liters
LDA	lithium diisopropylamide
m	milli
m	*meta-*

μ	micro
M	molar
*m*CPBA	metachloroperoxybenzoic acid
Me	methyl
MeOH	methanol
MeCN	acetonitrile
MHz	megahertz
min	minutes
mol	mole
Ms	mesyl
n	*normal-*
NMDPP	neomenthyldiphenylphosphine
NMO	morpholine-*N*-oxide
NMR	nuclear magnetic resonance
Nvoc	6-nitroveratryl carbamate
o	*ortho-*
[O]	oxidation
p	*para-*
Pd/C	palladium on carbon graphite
Ph	phenyl
Ppm	parts per million
PPTS	pyridinium-*para*-toluenesulfonate
Pr	propyl
py	pyridine
R_F	retention factor
rt	room temperature
sat.	saturated
t	*tert-*
t_R	retention time
TBAF	tetrabutylammonium fluoride
Teoc	2-trimethylsilylethyl carbamate
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*para*-toluenesulfonate
wt	weight

Chapter 1

Catalytic Asymmetric Reductive Coupling of 1,3-Enynes and Aromatic Aldehydes

Introduction

1,3-Dienes are important synthetic intermediates in a variety of chemical transformations. These include many cycloadditions, such as the Diels-Alder reaction.[1,2,3] There are a variety of methods for synthesizing 1,3-dienes[4] including cross-couplings,[5,6] olefination reactions,[7] and enyne metathesis.[8] Another strategy for the synthesis of 1,3-dienes has been developed in our laboratory[9] and others,[10] utilizing transition metal-catalyzed reductive coupling reactions of 1,3-enynes and aldehydes. Chiral 1,3-dien-5-ol substructures are formed in these reactions, which are present in a

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[1] Fringuelli, F.; Taticchi, A. *Dienes in the Diels-Alder Reaction;* Wiley: New York, **1990**.

[2] Fringuelli, F.; Taticchi, A. *The Diels-Alder Reaction: Selected Practical Methods*; Wiley: New York, **2002**.

[3] Wasserman, A. *Diels-Alder Reactions*; Elsevier: Amsterdam, 1965.

[4] Mehta, G.; Rao, S. P. in *The Chemistry of Dienes and Polyenes*; Rappoport, Z., Ed. Wiley: Chicester, U. K., 1997, Chapter 9.

[5] Reviews: (a) Stille, J. K. *Angew. Chem., Int. Ed.* **1986**, *25*, 508-524. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, 147-168.

[6] (a) Scott, W. J.; Pena, M. R.; Swared, K.; Stoessel, S. J.; Stille, J. K. *J. Org. Chem.* **1985**, *50*, 2302-2308. (b) Lyapkato, I. M.; Webel, M.; Reissig, H. U. *Eur. J. Org. Chem.* **2002**, 3646-3658. (c) Molander, G. A.; Felix, L. A. *J. Org. Chem.* **2005**, *70*, 3950-3956.

[7] (a) Wang, Y.; West, F. G. *Synthesis* **2002**, 99-103, and references therein. (b) Keck, G. E.; Romer, D. R. *J. Org. Chem.* **1993**, *58*, 6083-6089. (c) Trost, B. M.; Brandi, A. *J. Org. Chem.* **1984**, *49*, 4811-4816.

[8] Recent Reviews: (a) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317-1382. (b) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900-1923.

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

[10] (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.

variety of natural products.[11] Chiral 1,3-dienes have also been widely employed in diastereoselective Diels Alder reactions.[12,13]

Previous work from our laboratory has shown that nickel-catalyzed reductive couplings of terminal alkynes (H-C≡C-R), trimethylsilyl alkynes (TMS-C≡C-R), and aryl-substituted alkynes (Ar-C≡C-R) all proceed with high regioselectivity to form the carbon-carbon bond proximal relative to the proton or TMS and distal relative to the aryl group for the alkynes, respectively.[14] High enantioselectivity can also be imparted on these reactions when either (+)-neomenthyldiphenylphosphine (NMDPP)[14b] or a chiral ferrocenyl phosphine is used as a chiral ligand (Scheme 1).[15]

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[11] Several examples of natural products include: (a) Amphidinolide C: Kobayashi, J.; Ishibashi, M.; Walchli, M. R.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Ohizumi, Y. *J. Am. Chem. Soc.* **1998**, *110*, 490-494. (b) Galbonolides: Sakoh, H.; Jona, H.; Sugimoto, Y.; Imamura, H.; Sakuraba, S.; Yamada, K.; Morishima, H. *Chem. Pharm. Bull.* **2004**, *53*, 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.

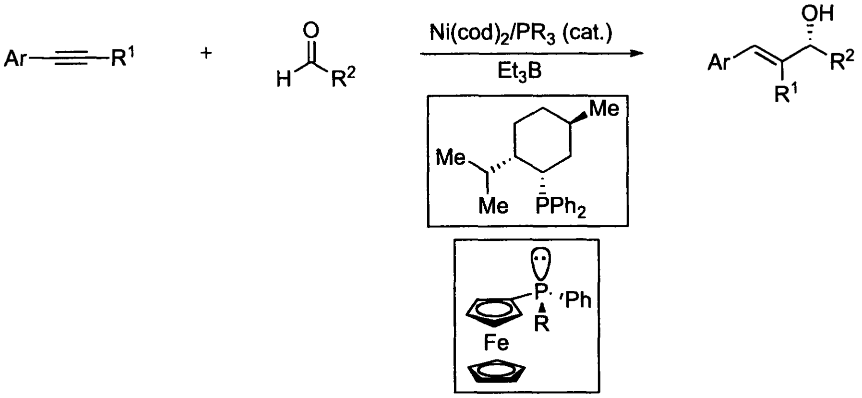
[12] In intermolecular Diels-Alder reactions: (a) Barriault, L.; Thomas, J. D. O.; Clement, R. *J. Org. Chem.* **2003**, *68*, 2317-2323. (b) Adam, W.; Glaser, J.; Peters, K.; Prein, M. *J. Am. Chem. Soc.* **1995**, *117*, 9190-9193. (c) Datta, S. C.; Franck, R. W.; Tripathy, R.; Quigley, G. J.; Huang, L.; Chan, S.; Sihaed, A. *J. Am. Chem. Soc.* **1990**, 8472-8478. (d) Fisher, M. J.; 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.

[13] (a) Shiiina, J.; Nishiyama, S. *Tetrahedron* **2003**, *59*, 6039-6044. (b) Bols, M.; Skrystrup, T. *Chem. Rev.* **1995**, *95*, 1253-1277.

[14] (a) Huang, W. S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221-4223. (b) Miller, K. M.; Huang, W. S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442-3443.

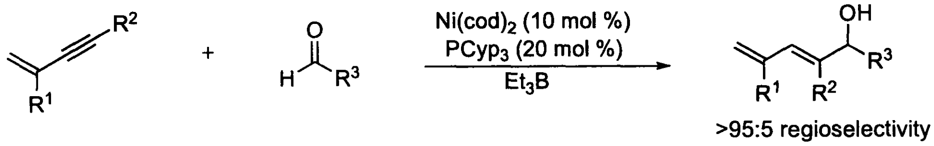
[15] Colby, E. A.; Jamison, T. F. *J. Org. Chem.* **2003**, *68*; 156-166.

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



However, when alkyl-alkyl alkynes are employed in the couplings, the regioselectivity is influenced by steric effects, but can be as low as a one to one mixture of the two regioisomers. When a 1,3-enyne is employed in the reductive coupling, the regioselectivity is high, and favors formation of the carbon-carbon bond distal to the alkene substituent, regardless of the substituent on the alkyne (Scheme 2).[9] The Montgomery laboratory also observed high regioselectivity with intermolecular aldehyde-enyne couplings, but instead observed the opposite regioselectivity with intramolecular aldehyde-enyne couplings to form 6-membered rings.[10a,16]

Scheme 2. Nickel-catalyzed reductive coupling of enynes and aldehydes.



We proposed that a transient interaction between a conjugated alkene and the nickel center dramatically enhances the reactivity and imparts the high regioselectivity

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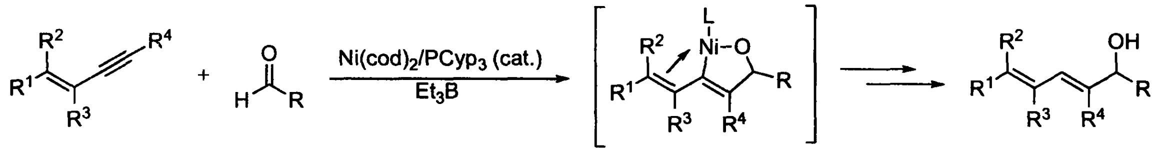
[16] (a) Lozanov, M.; Montgomery, J. *J. Am. Chem. Soc.* **2002**, *124*, 2106-2107. (b) Ni, Y.; Amarsinghe, K. K. D.; Montgomery, J. *Org. Lett.* **2002**, *4*, 1743-1745.

(Scheme 3).[17] A catalytic site-selective hydrogenation of the dienol alcohol products utilizing Wilkinson's catalyst[18] was also developed.[9] This provided the corresponding allylic alcohols, representing a strategy of circumventing the poor regioselectivity observed during the reductive coupling of dialkyl-substituted alkynes.

Scheme 3. Proposed nickel-bound alkene intermediate.



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

The utility of 1,3-enynes in the highly regioselective coupling reaction led to the development of the first catalytic asymmetric reductive coupling of 1,3-enynes and aromatic aldehydes. For the enantioselective reductive coupling of the various enynes with aldehydes, NMDPP, ferrocenyl phosphine **1.1** and **1.2** were surveyed (Table 1, entries 1-3). In these experiments, the *ortho*-isopropylphenyl substituted ferrocenyl phosphine **1.2** produced the highest yields and enantioselectivities (Figure 1). This is consistent with a hypothesis that the steric bulk at the *ortho* position of the aryl group increases the enantioselectivity of the reductive coupling.[20]

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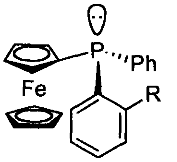
[17] Crystallographic evidence for a similar interacted in a related group 10 Pt complex: Benyunes, S. A.; Brandt, L.; Fries, A.; Green, M.; Mahon, M. F.; Papworth, T. M.; *J. Chem. Soc. Dalton. Trans.* **1993**, 3785-3793.

[18] (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.

[19] This portion of work was done in collaboration with Dr. Karen M. Miller and Dr. Elizabeth A. Colby. This work also appears in Miller, K. M., Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, Massachusetts, 2005, pp 83-90, 97-114.

[20] Increased enantioselectivity in alkyne-imine reductive couplings: Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 3941-3944.

Figure 1. Ferrocenyl Phosphine Ligands.



1.1 R = Me
1.2 R = *i*Pr

The synthesis of (*R*)-ferrocenyl(2-isopropylphenyl)phenylphosphine **1.2** was improved from the original route employing a modification of Jugé's ephedrine-based method (Scheme 4).[21] Compound **1.5** was available from dichlorophenyl phosphine **1.3** and (+)-ephedrine **1.4**. Addition of *ortho*-lithiated isopropyl benzene occurred in a highly diastereoselective fashion to provide **1.6**. It is proposed that the addition occurs through an associative pathway, which terminates in the cleavage of the O-P bond.[22] Notably, the reactivity of this step was improved by employing *s*-butyllithium instead of *t*-butyllithium. Methanolysis of **1.6**, although slow, proceeded in good yield with inversion of stereochemistry to yield compound **1.7**. Direct lithiation of ferrocene with *t*-BuLi was employed to give ferrocenyl lithium; addition of this compound to **1.7** yielded the borane-protected **1.8**. Finally, ligand **1.2** was produced by removing the borane protecting group with refluxing diethylamine.[23] The improved synthesis, employing *s*-BuLi in the metal-halogen exchange, as well as direct deprotonation of ferrocene, yielded ligand **1.2** in 25% overall yield with >98% ee,[24] which represents an eight-fold increase in yield to that previously reported.[20]

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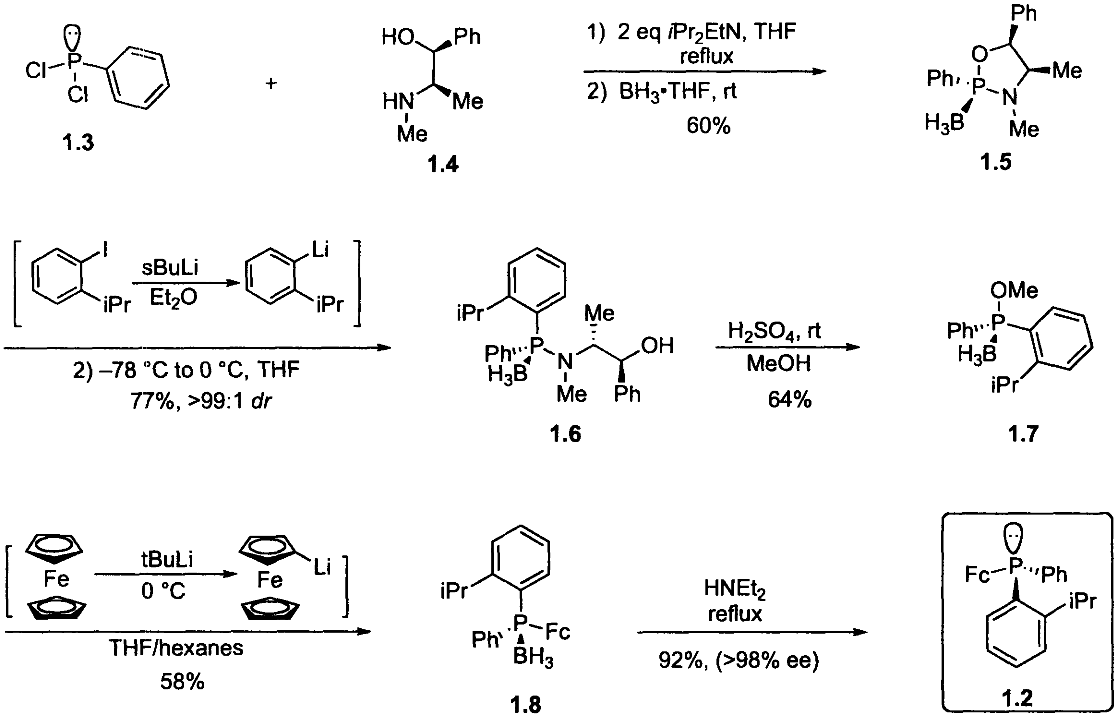
[21] Jugé, S.; Stephan, M.; Merdès, R.; Genêt, J. P. *Tetrahedron Lett.* **1990**, *31*, 6357-6360.

[22] Jugé, S.; Stephan, M.; Merdès, R.; Genêt, J. P.; Halut-Desportes, S. *J. Chem. Soc., Chem. Comm.* **1993**, 531-533.

[23] The BH_3 group allows the phosphine to be air stable, and also helps with chromatography.

[24] The enantioselectivity was determined by HPLC (chiracel OJ).

Scheme 4. Synthesis of chiral ligand **1.2**.



A variety of aromatic aldehydes underwent reductive coupling with 2-methyl-1-hexen-3-yne in an enantioselective fashion employing Ni(cod)$_2$ with ligand **1.2** as a catalyst system (Table 1).[25] The reactions gave modest yields and enantioselectivities, and all occurred with high regioselectivity to give dienol alcohols **1.9-1.12**. Electron-donating groups on the aromatic aldehyde (entries 4-6, 11-2) as well as aromatic ketones and esters (entries 9 and 10) are tolerated. However, when an electron-withdrawing group was present on the aldehyde (entries 7-10), a small amount of allene side-product was observed.[26] This mode of reactivity was suppressed by heating the reaction mixture.

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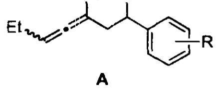
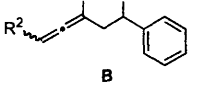
[25] Miller, K. M.; Colby, E. A.; Woodin, K. S.; Jamison, T. F. *Adv. Synth. Catal.* **2005**, *347*, 1533-1536.

[26] Allene by-products of general form **A** (Table 1) or **B** (Table 2):



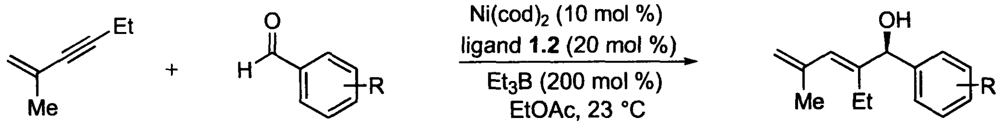
A



B

Interestingly, Sato and coworkers also reported related allene products in the addition reaction of 1,3-enyne-titanium complexes to aldehydes.[27]

Table 1. Catalytic, asymmetric reductive coupling of 2-methyl-1-hexen-3-yne and aromatic aldehydes.[a]



entry	R	Dienol	% yield[b] (regioselectivity)[c]	% ee[d]
1[e]	Ph	**1.9**	16 (>95:5)	8
2[f]	"	"	61 (>95:5)	36
3	"	"	66 (>95:5)	56[g]
4	*o*-Me	**1.10**	71 (>95:5)	54
5	*p*-Me	**1.11**	73 (>95:5)	56
6	*p*-OMe	**1.12**	66 (>95:5)	56
7[h]	*p*-Cl	**1.13**	54 (>95:5)	55
8[h]	*p*-CF_3	**1.14**	62 (>95:5)	50
9[h]	*p*-(COMe)	**1.15**	55 (>95:5)	56
10[h]	*p*-(CO_2Me)	**1.16**	65 (>95:5)	53
11	1-naphthyl	**1.17**	52 (>95:5)	48
12	2-naphthyl	**1.18**	47 (>95:5)	58

[a] Experimental conditions: To $Ni(cod)_2$ (0.05 mmol) and ligand **1.2** (0.1 mmol) at room temperature were added EtOAc (0.5 mL), Et_3B (1.0 mmol), the aldehyde (1.0 mmol), and 2-methyl-1-hexen-3-yne (0.5 mmol). The reaction was stirred 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 or Chiralpak AD-H column. [e] (+)-Neomenthyldiphenylphosphine (NMDPP) was used in place of **1.2**. [f] **1.1** was used in place of **1.2**. [g] Absolute configuration of the major enantiomer determined to be (*R*) via Mosher's ester analysis. [h] Reaction was conducted at 35 °C.

The coupling of 1,3-enynes was previously determined to proceed with high regioselectivity, regardless of the alkene substitution and the nature of the alkyne substituent.[9] This was also the case with the ferrocenyl phosphine **1.2** promoted reactions,

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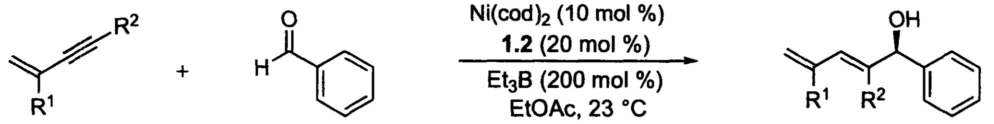
[27] Hamada, T.; Mizojiri, R.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2000**, *122*, 7138-7139.

where a variety of substituted 1,3-enynes[28] were coupled with benzaldehyde to yield a single dienol regioisomer with moderate yields and enantioselectivities (Table 2, entries 1-5). The C-C bond even formed proximal to the sterically-demanding *tert*-butyl and trimethylsilyl groups (entries 4 and 5), revealing the strong directing ability of the pendant alkene substituent. A series of isopropenyl-substituted enynes were also synthesized and coupled for the first time with the aldehyde (entries 6-9). Interestingly, the reactions occurred with excellent regioselectivity and higher enantioselectivities than the corresponding vinyl-substituted enynes (entries 2-5).

Table 2. Catalytic, asymmetric reductive coupling reactions of 1,3-enynes with benzaldehyde



Entry	R^1	R^2	Dienol	Yield [%],[b] Regioselectivity[c]	ee [%][d]
1[e]	H	*n*-hex	**1.19**	66 (>95:5)	32
2	"	Cy	**1.20**	70 (>95:5)	42
3	"	Ph	**1.21**	58 (>95:5)	44
4[f]	"	*t*-Bu	**1.22**	66 (>95:5)	33
5[e]	"	$SiMe_3$	**1.23**	53 (>95:5)	14
6[g]	Me	Cy	**1.24**	77 (>95:5)	55[h]
7	"	Ph	**1.25**	42 (>95:5)	54
8[f]	"	*t*-Bu	**1.26**	64 (>95:5)	52
9	"	$SiMe_3$	**1.27**	69 (>95:5)	28

(a) Experimental conditions: see Table 1. (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. (g) Reaction was conducted at 38 °C. (h) Absolute configuration of the major enantiomer determined to be (*R*) via Mosher's ester analysis.

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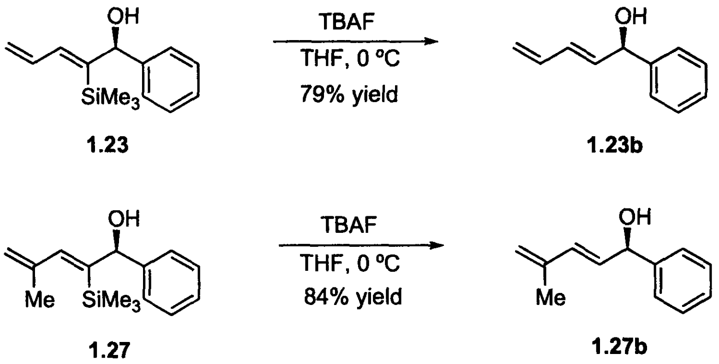
[28] 1,3-Enynes were either commercially available, prepared from Negishi coupling of the corresponding vinyl bromide, or prepared through acylation and elimination of corresponding propargylic alcohol, see experimental section for details.

Although the 1-(trimethylsilyl)-substituted enynes (Table 2, entries 5 and 9) underwent coupling in low enantioselectivity, they do provide access to synthetically-versatile, silyl-substituted conjugated dienes. These alkenyl silanes, **1.23** and **1.27**, undergo efficient protiodesilylation under mild conditions to afford dienols **1.23b** and **1.27b** (Scheme 5). The functionalized dienol products of these reactions are the expected products from reductive coupling reactions of terminal enynes (H-C≡C-CR_2=CR_2) which are not typically effective coupling partners.

Scheme 5. Protiodesilylation of alkenyl silanes.



Conclusion

In conclusion, the first method for the catalytic, enantioselective reductive coupling of various 1,3 enynes and aldehydes has been described. The reaction is promoted by a P-chiral ferrocenyl monophosphine ligand to afford conjugated dienols in high regioselectivity and modest enantioselectivity. Numerous aromatic aldehydes coupled efficiently with the 1,3-enynes, and a variety of novel substituted enynes were synthesized and coupled effectively with benzaldehyde. The 1-(trimethylsilyl)-substituted dienols obtained via reductive coupling undergo protiodesilylation under mild conditions, providing access to a number of synthetically useful disubstituted 1,3-dienes. Finally, during the course of this investigation, the efficiency of the synthesis of (*R*)-ferrocenyl(2-isopropylphenyl)phenylphosphine (**1.2**) was greatly improved.

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(cyclooctadienyl)-nickel(0) (Ni(cod)$_2$) and (+)-neomenthyldiphenylphosphine (NMDPP) were purchased from Strem Chemicals, Inc. and used without further purification. (*R*)-Ferrocenyl(2-methylphenyl)phenylphosphine (**1.1**) and (*R*)-Ferrocenyl(2-isopropylphenyl)-phenylphosphine (**1.2**) were prepared in five steps from (+)-ephedrine as previously reported.[1,2] Triethylborane (Et$_3$B, 98%), and 2-methyl-1-hexen-3-yne were purchased from Aldrich Chemical Co. and used as received. Benzaldehyde was purchased from Aldrich Chemical Co. and distilled prior to use. All other aldehydes were purchased from either Alfa Aesar or Aldrich Chemical Co. and used as received. Ethyl acetate was freshly distilled over MgSO$_4$ and was purged 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), cerium molybdate (CAM), or aqueous potassium permanganate (KMnO$_4$). Liquid chromatography was performed using a forced flow (flash chromatography)[3] 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$_3$) (unless otherwise noted) 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-

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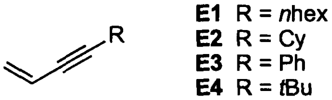
[1] Colby, E. A.; Jamison, T. F. *J. Org. Chem.* **2003**, *68*, 156-166.

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

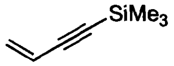
[3] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

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. Gas chromatography was performed on a Varian Cp-3800 chromatograph equipped with a Chiraldex B-OA column. Optical rotations were measured on a Jasco P-1010 polarimeter.

Preparation of Starting Materials[4]



Enynes **E1-E4** were prepared as previously described.[5]



E5

3-Buten-1-ynyl-trimethyl silane (E5): As reported by Mayr,[6] 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)[7] 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 E6, E8, and E9:[8,5] 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

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[4] Compounds designated as E# refer compounds appearing only in the experimental section.

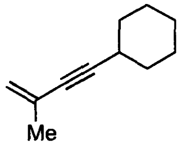
[5] Miller, K. M.; Luanphaisarnnont, T.; Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 4130-4131.

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

[7] 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.

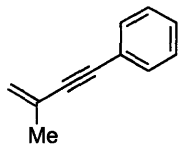
[8] Negishi, E.-I.; Okukado, M.; Lovich, S. F.; Luo, F.-T. *J. Org. Chem.* **1984**, *49*, 2629-2632.

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.



E6

(3-Methyl-3-buten-1-ynyl)-cyclohexane (E6): 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 5.17-5.16 (m, 1H), 4.96-4.95 (m, 1H), 2.33-2.30 (m, 1H), 1.74-1.73 (m, 3H), 1.70-1.63 (m, 2H), 1.60-1.51 (m, 2H), 1.39-1.27 (m, 3H), 1.16-1.05 (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].



E7

(3-Methyl-3-buten-1-ynyl)-benzene (E7): 2-Methyl-4-phenyl-3-butyn-2-ol[9] (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 $MgSO_4$,

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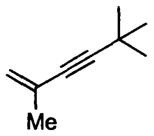
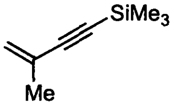
[9] Prepared according to: Yu, W.-Y.; Alper, H. *J. Org. Chem.* **1997**, *62*, 5684-5687.

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.[10]



E8

2,5,5-Trimethyl-1-hexen-3-yne (E8): Prepared according to the general procedure (30 mmol scale, 1.59 g, 43% yield). Spectral data were consistent with those previously reported.[11]



E9

Trimethyl-(3-methyl-3-buten-1-ynyl)-silane (E9)[12]: Prepared according to the general procedure (30 mmol scale, 2.30 g, 55% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.35-5.34 (m, 1H), 5.25-5.24 (m, 1H), 1.89-1.88 (m, 3H), 0.19 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 127.1, 123.1, 106.6, 93.1, 23.5, 0.2 (3C).

Standard Experimental Procedures for Catalytic, Asymmetric Reductive Coupling of 1,3-Enynes and Aldehydes (Table 1 and 2).

Procedure A (liquid aldehydes): In a glovebox, Ni(cod)$_2$ (14 mg, 0.5 mmol) and **1.2**^{2} (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_3B (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

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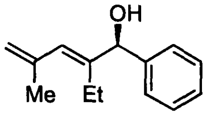
[10] Krijnen, E. S.; Zuilhof, H.; Lodder, G. *J. Org. Chem.* **1994**, *59*, 8139-8150.

[11] (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.

[12] 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.

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.

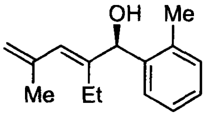
Procedure B (solid aldehydes): In a glovebox, Ni(cod)$_2$ (14 mg, 0.5 mmol), **1.2**[2] (42 mg, 0.1 mmol), and the aldehyde (1.0 mmol) were placed into a 10 mL oven-dried, single-necked round-bottom flask, which was then sealed with a rubber septum. The flask was removed from the glovebox, placed under 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.



1.9

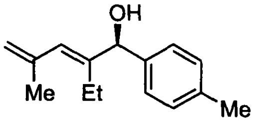
(2*E*)-2-Ethyl-4-methyl-1-phenyl-penta-2,4-dien-1-ol (1.9, Table 1, entry 3): In the reductive coupling of 2-methyl-1-hexen-3-yne (47 mg, 0.5 mmol, 63 μL) and benzaldehyde (106 mg, 1.0 mmol, 101 μL), Procedure A was used. Silica gel chromatography afforded the title compound as a clear oil (62 mg, 66% yield, 56% 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 7.41-7.34 (m, 4H); 7.31-7.27 (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. $[\alpha]_D$ = + 32.0 (23 °C, 589 nm, 1.03 g/100 mL, $CHCl_3$).



1.10

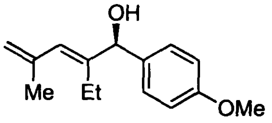
(2*E*)-2-Ethyl-4-methyl-1-*o*-tolyl-penta-2,4-dien-1-ol (1.10, Table 1, entry 4): In the reductive coupling of 2-methyl-1-hexen-3-yne (47 mg, 0.5 mmol, 63 μL) and *o*-tolualdehyde (120 mg, 1.0 mmol, 116 μL), Procedure A was used. Silica gel chromatography afforded the title compound as a clear oil (77 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); 7.26-7.14 (m, 3H); 6.03 (s, 1H); 5.42 (s, 1H); 5.00-4.97 (m, 1H); 4.89 (t, J = 1 Hz, 1H); 2.39-2.30 (m, 4H); 2.09-2.00 (m, 1H); 1.89 (s, 3H); 1.78-1.74 (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. $[\alpha]_D$ = + 12.0 (23 °C, 589 nm, 1.00 g/100 mL, $CHCl_3$).



1.11

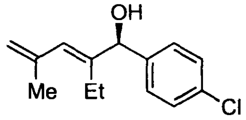
(2*E*)-2-Ethyl-4-methyl-1-*p*-tolyl-penta-2,4-dien-1-ol (1.11, Table 1, entry 5): In the reductive coupling of 2-methyl-1-hexen-3-yne (47 mg, 0.5 mmol, 63 μL) and *p*-tolualdehyde (120 mg, 1.0 mmol, 118 μL), Procedure A was used. Silica gel chromatography afforded the title compound as a clear oil (79 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); 4.99-4.98 (m, 1H); 4.91 (d, *J* = 1 Hz, 1H); 2.36 (s, 3H); 2.34-

2.26 (m, 1H); 2.01-1.92 (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, $CHCl_3$).



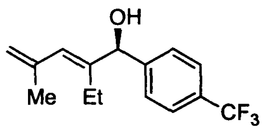
1.12

(2*E*)-2-Ethyl-1-(4-methoxy-phenyl)-4-methyl-penta-2,4-dien-1-ol (1.12, Table 1, entry 6): In the reductive coupling of 2-methyl-1-hexen-3-yne (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 7.34-7.28 (m, 2H); 6.92-6.86 (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); 2.35-2.26 (m, 1H); 1.99-1.92 (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, $CHCl_3$).



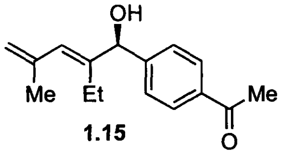
1.13

(2*E*)-1-(4-Chloro-phenyl)-2-ethyl-4-methyl-penta-2,4-dien-1-ol (1.13, Table 1, entry 7): In the reductive coupling of 2-methyl-1-hexen-3-yne (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 7.35-7.30 (m, 4H); 6.13 (s, 1H); 5.20 (s, 1H); 5.01-5.00 (m, 1H); 4.91 (t, J = 1 Hz, 1H); 2.30-2.21 (m, 1H); 2.05-1.96 (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, $CHCl_3$).



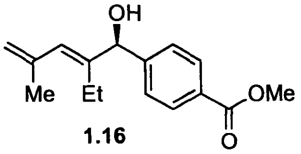
1.14

(2*E*)-2-Ethyl-4-methyl-1-(4-trifluoromethyl-phenyl)-penta-2,4-dien-1-ol (1.14, Table 1, entry 8): In the reductive coupling of 2-methyl-1-hexen-3-yne (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); 2.26-2.22 (m, 1H); 2.07-2.02 (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, $CHCl_3$).



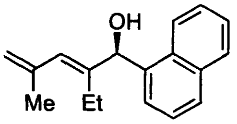
1.15

(2*E*)-1-[4-(2-Ethyl-1-hydroxy-4-methyl-penta-2,4-dienyl)-phenyl]-ethanone (1.15, Table 1, entry 9): In the reductive coupling of 2-methyl-1-hexen-3-yne (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); 2.25-2.22 (m, 1H); 2.05-2.02 (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, $CHCl_3$).



1.16

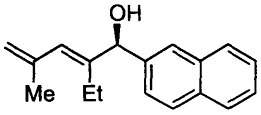
(2*E*)-4-(2-Ethyl-1-hydroxy-4-methyl-penta-2,4-dienyl)-benzoic acid methyl ester (1.16, Table 1, entry 10): In the reductive coupling of 2-methyl-1-hexen-3-yne (47 mg, 0.5 mmol, 63 μL) and methyl 4-formylbenzoate (164 mg, 1.0 mmol), Procedure B was used, except that the reaction was conducted at 35 °C (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); 2.26-2.12 (m, 1H), 2.07-2.02 (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. $[\alpha]_D$ = +1.9 (23 °C, 589 nm, 1.6 g/100 mL, $CHCl_3$).



1.17

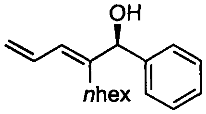
(2*E*)-2-Ethyl-4-methyl-1-naphthalen-1-yl-penta-2,4-dien-1-ol (1.17, Table 1, entry 11): In the reductive coupling of 2-methyl-1-hexen-3-yne (47 mg, 0.5 mmol, 63 μL) and 1-naphthaldehyde (156 mg, 1.0 mmol, 136 μL), Procedure A was used. Silica gel chromatography (use of a 3:1 toluene:hexanes to toluene 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 8.20-8.17 (m, 1H); 7.90-7.87 (m, 1H); 7.82 (d, *J* = 8.5 Hz, 1H); 7.67 (d, *J* = 7.5 Hz, 1H); 7.55-7.47 (m, 3H); 6.23 (s, 1H); 5.97 (d, *J* = 4 Hz, 1H); 5.02-4.99 (m, 1H); 4.92 (t, *J* = 1 Hz, 1H); 2.44-2.36 (m, 1H); 2.09-2.01 (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. $[\alpha]_D$ = +26.0 (23 °C, 589 nm, 1.00 g/100 mL, $CHCl_3$).



1.18

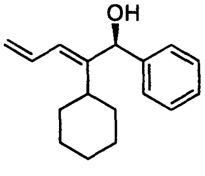
(2*E*)-2-Ethyl-4-methyl-1-naphthalen-2-yl-penta-2,4-dien-1-ol (1.18, Table 1, entry 12): In the reductive coupling of 2-methyl-1-hexen-3-yne (47 mg, 0.5 mmol, 63 µL) and 2-naphthaldehyde (156 mg, 1.0 mmol), Procedure B was used. Silica gel chromatography (use of a 3:1 toluene:hexanes to toluene gradient 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 7.90-7.80 (m, 4H); 7.52-7.46 (m, 3H); 6.24 (s, 1H); 5.40 (d, *J* = 3.5 Hz, 1H); 5.01 (m, 1H); 4.94 (s, 1H); 2.36-2.28 (m, 1H); 2.09-2.01 (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, $CHCl_3$).



1.19

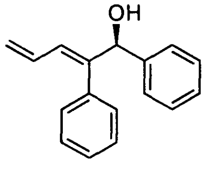
(2*E*)-2-Hexyl-1-phenyl-penta-2,4-dien-1-ol (1.19, Table 2, entry 1): In the reductive coupling of enyne **E1** (64 mg, 0.5 mmol) and benzaldehyde (106 mg, 1.0 mmol, 101 µL), Procedure A was used, except that the reaction was conducted at 0 °C (i.e. the reaction flask was placed in a 0 °C ice bath prior 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 7.38-7.33 (m, 3H); 7.30-7.27 (m, 2H); 6.65-6.57 (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); 2.18-2.13 (m, 1 H); 1.92-1.1.97 (m, 1 H); 1.94 (d, *J* = 3.5 Hz, 1H); 1.31-1.19 (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, $CHCl_3$).



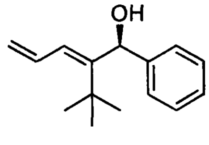
1.20

(+)-(2*E*)-2-Cyclohexyl-1-phenyl-penta-2,4-dien-1-ol (1.20, Table 2, entry 2): In the reductive coupling of enyne **E2** (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 7.39-7.26 (m, 5H); 6.82-6.74 (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); 2.46-2.41 (m, 1H), 1.81 (d, *J* = 3.7 Hz, 1H), 1.76-1.72 (m, 1H), 1.66-1.48 (m, 4H), 1.35-1.33 (m, 1H), 1.28-1.07 (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. $[\alpha]_D = +2.5$ (23 °C, 589 nm, 0.80 g/100 mL, $CHCl_3$).



1.21

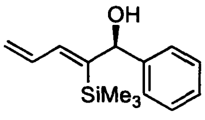
(+)-(2*E*)-1,2-Diphenyl-penta-2,4-dien-1-ol (1.21, Table 2, entry 3): In the reductive coupling of enyne **E3** (64 mg, 0.5 mmol, 68 μL) and benzaldehyde (106 mg, 1.0 mmol, 101 μL), Procedure A was used. Silica gel chromatography afforded the title compound as a clear yellow oil (69 mg, 58% yield, 44% 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 7.34-7.20 (m, 7H); 7.05-7.01 (m, 3H), 6.54 (d, *J* = 11.0 Hz, 1H), 6.34-6.26 (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. $[\alpha]_D = +2.5$ (23 °C, 589 nm, 1.6 g/100 mL, $CHCl_3$).



1.22

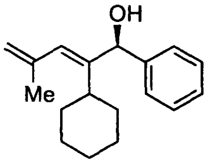
(+)-(2*E*)-2-tert-Butyl-1-phenyl-penta-2,4-dien-1-ol (1.22, Table 2, entry 4): In the reductive coupling of enyne **E4** (54 mg, 0.5 mmol, 73 μL) and benzaldehyde (106 mg, 1.0 mmol, 101 μL), Procedure A was used except that the reaction was conducted at 65 °C in the following manner: a solution of $Ni(cod)_2$, **1.2**, 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 7.40-7.34 (m, 4H), 7.30-7.28 (m, 1H), 7.08-7.00 (m, 1H), 6.35 (d, *J* = 11.6 Hz, 1H), 5.47 (d, *J* = 4.6 Hz, 1H), 5.22-5.17 (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$_3$).



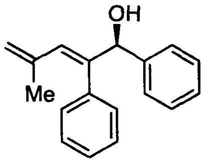
1.23

(2*E*)-1-Phenyl-2-(trimethyl-silanyl)-penta-2,4-dien-1-ol (1.23, Table 2, entry 5): In the reductive coupling of enyne **E5** (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 7.37-7.26 (m, 5 H); 6.94 (d, *J* = 11.5 Hz, 1H); 6.81-6.74 (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). ^{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. 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$_3$).



1.24

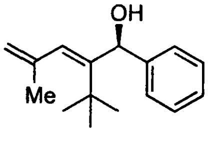
(+)-(2*E*)-2-Cyclohexyl-4-methyl-1-phenyl-penta-2,4-dien-1-ol (1.24, Table 2, entry 6): In the reductive coupling of enyne **E6** (74 mg, 0.5 mmol, 80 μL) and benzaldehyde (106 mg, 1.0 mmol, 101 μL), Procedure A was used except that the reaction was conducted at 38 °C in the following manner: a solution of Ni(cod)$_2$, **1.2**, EtOAc and Et$_3$B was prepared at ambient temperature as described in the general procedure, then heated to 38 °C in an oil bath for 5 min 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). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.41-7.37 (m, 2H); 7.36-7.30 (m, 2H); 7.29-7.26 (m, 1H), 6.03 (s, 1H); 5.35 (d, *J* = 4.0 Hz, 1H); 5.00-4.99 (m, 1H); 4.80-4.79 (m, 1H); 2.83-2.77 (m, 1H), 1.87-1.86 (m, 3H); 1.79-1.67 (m, 2H); 1.64-1.61 (m, 3H), 1.55 (qd, *J* = 12.5, 3.4 Hz, 1H), 1.34-1.07 (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$_3$).



1.25

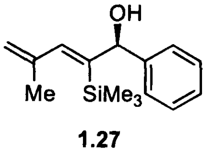
(+)-(2*E*)-4-Methyl-1,2-diphenyl-penta-2,4-dien-1-ol (1.25, Table 2, entry 7): In the reductive coupling of enyne **E7** (71 mg, 0.5 mmol, 76 μL) and benzaldehyde (106 mg, 1.0 mmol, 101 μL), Procedure A was used. Silica gel chromatography afforded the title compound as a clear yellow oil (53 mg, 42% 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 7.32-7.25 (m, 5H); 7.23-7.19 (m, 3H); 6.93-6.91 (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, $CHCl_3$).



1.26

(+)-(2*E*)-2-*tert*-Butyl-4-methyl-1-phenyl-penta-2,4-dien-1-ol (1.26, Table 2, entry 8): In the reductive coupling of enyne **E8** (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 $Ni(cod)_2$, **1.2**, EtOAc and Et_3B was prepared at ambient temperature as described in the general procedure, then heated to 65 °C in an oil bath for 5 min before simultaneous addition of enyne and aldehyde. Silica gel chromatography (toluene: hexanes; 3:1) 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 7.43-7.41 (m, 2H); 7.37-7.34 (m, 2H); 7.30-7.27 (m, 1H), 6.12-6.11 (m, 1H), 5.42 (d, *J* = 4.6 Hz, 1H), 4.91-4.90 (m, 1H); 4.80-4.79 (m, 1H), 1.87-1.86 (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, $CHCl_3$).

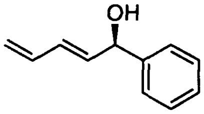


1.27

(+)-(2*Z*)-4-Methyl-1-phenyl-2-trimethylsilanyl-penta-2,4-dien-1-ol (1.27, Table 2, entry 9): In the reductive coupling of enyne **E9** (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,

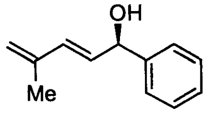
>95:5 *E*/*Z*). R_f = 0.21 (9:1 hexanes: ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.28 (m, 4H); 7.27-7.26 (m, 1H); 6.81 (s, 1H); 5.34 (d, *J* = 1.4 Hz, 1H); 4.93-4.92 (m, 1H); 4.90-4.89 (m, 1H); 1.86-1.85 (m, 3H); 1.79 (s, 1H); 0.01 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 143.7, 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 1.23 and 1.27.



1.23b

1-Phenyl-penta-2,4-dien-1-ol (1.23b): A solution of **1.23** (0.37 mg, 0.16 mmol) in THF (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.[13] ^{1}H NMR (500 MHz, $CDCl_3$) δ7.41-7.23 (m, 5H); 6.43-6.29 (m, 2H); 5.94-5.89 (m, 1H); 5.32-5.12 (m, 3H); 1.98 (d, *J* = 6 Hz, 1H).



1.27b

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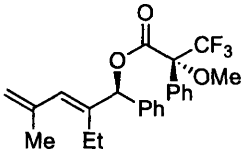
[13] Carreño, M. C.; García-Cerrada, S.; Urbano, A.; Di Vitta, C. *J. Org. Chem.* **2000**, 65, 4355-4363.

(–)-(2*E*)-4-Methyl-1-phenyl-penta-2,4-dien-1-ol (1.27b): A solution of **1.27** (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). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.36 (m, 4H), 7.32-7.29 (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 1.3 via Mosher's Ester Analysis.[14]



major diastereomer

Alcohol **1.9** (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

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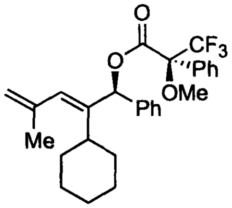
[14] (a) Mosher, H. S.; Dale, J. A. *J. Am. Chem. Soc.* **1973**, *95*, 512-519. (b) Dale, J. A.; Dull, D. L.; Mosher, H. S.; *J. Org. Chem.* 1969, **34**, 2543-2449.

the alkenyl peaks of the major diastereomer to be upfield (shielded) relative to the minor diastereomer indicating the *R* absolute configuration of **1.9**. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.45-7.25 (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); 2.26-2.21 (m, 1.4H); 2.14-2.05 (m, 0.4H); 1.97-1.93 (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).

Absolute Configuration Determination of 1.14 via Mosher Ester Analysis.

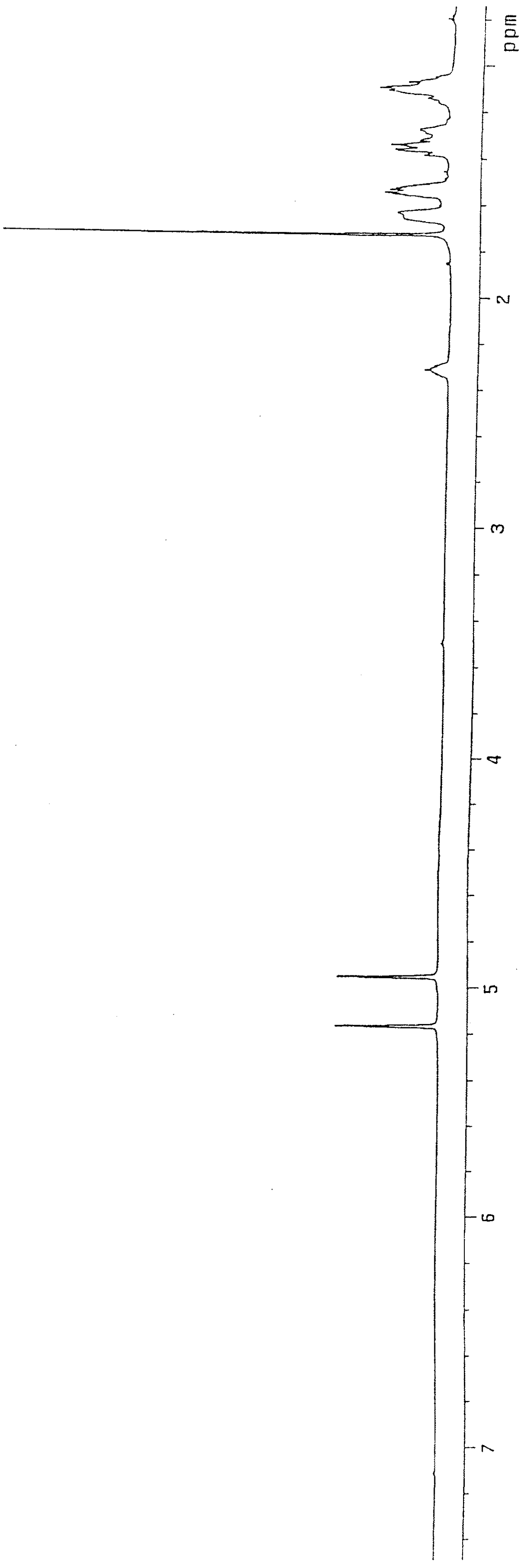


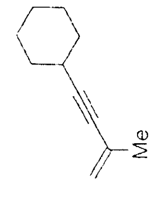
major diastereomer

Alcohol **1.24** was dissolved in 0.6 ml CH$_2$Cl$_2$. 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, then the solvent was removed *in vacuo*. The crude residue was purified via gradient silica gel chromatography (50:1 hexanes: EtOAc to 9:1 hexanes: EtOAc) 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 **1.24**. ^{1}H NMR (500 MHz, C$_6$D$_6$) δ 7.44-7.29 (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), 2.83-2.77 (m, 1H), 1.85 (s, 3H, major), 1.77 (s, 3H, minor), 1.76-1.74 (m, 1H), 1.67-1.54 (m, 4H), 1.31-1.23 (m, 2H), 1.20-1.10 (m, 2H), 1.08-0.98 (m, 1H, major), 0.96-0.85 (m, 1H, minor).

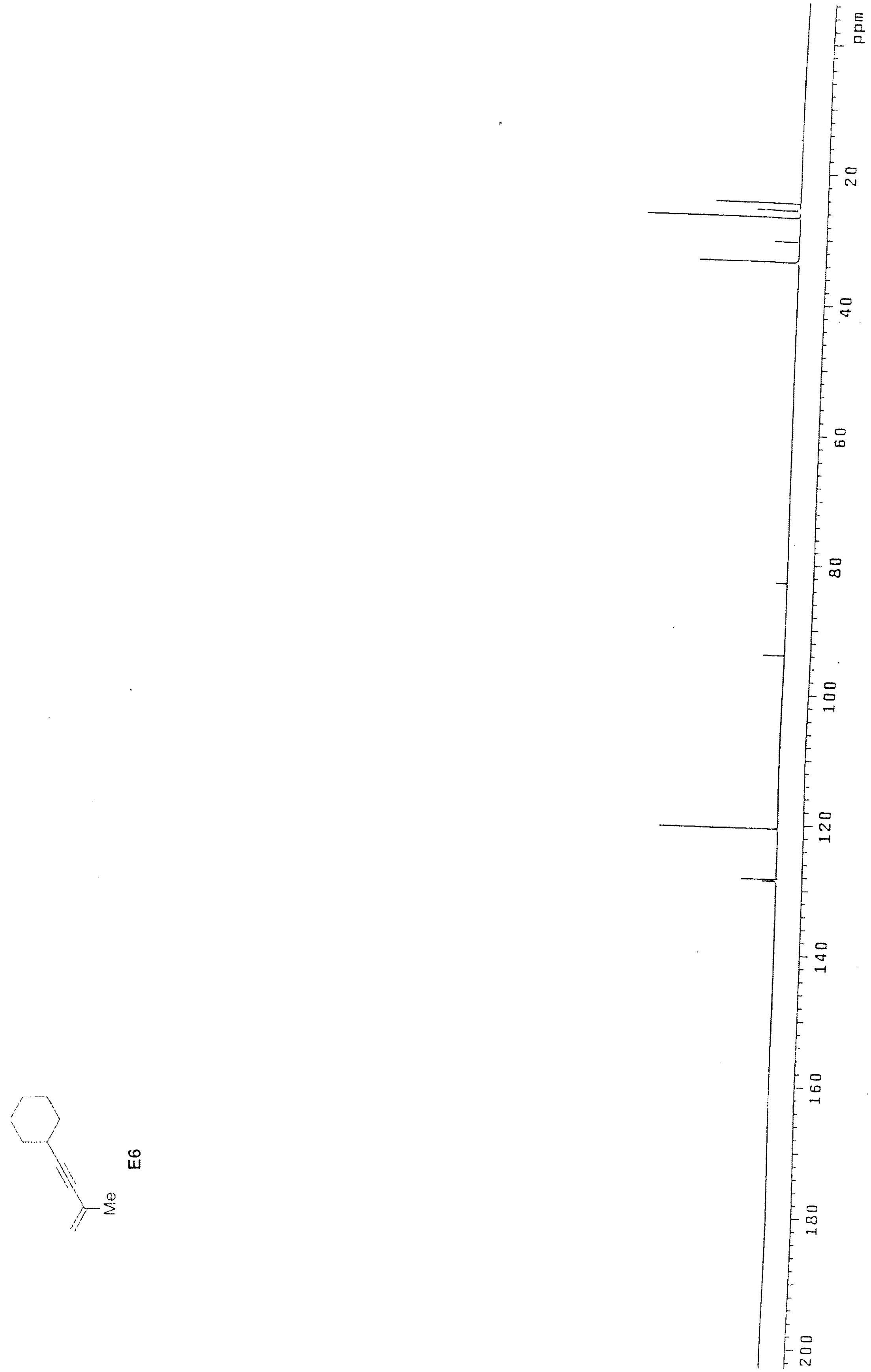
Chapter 1

Spectral Data





E6



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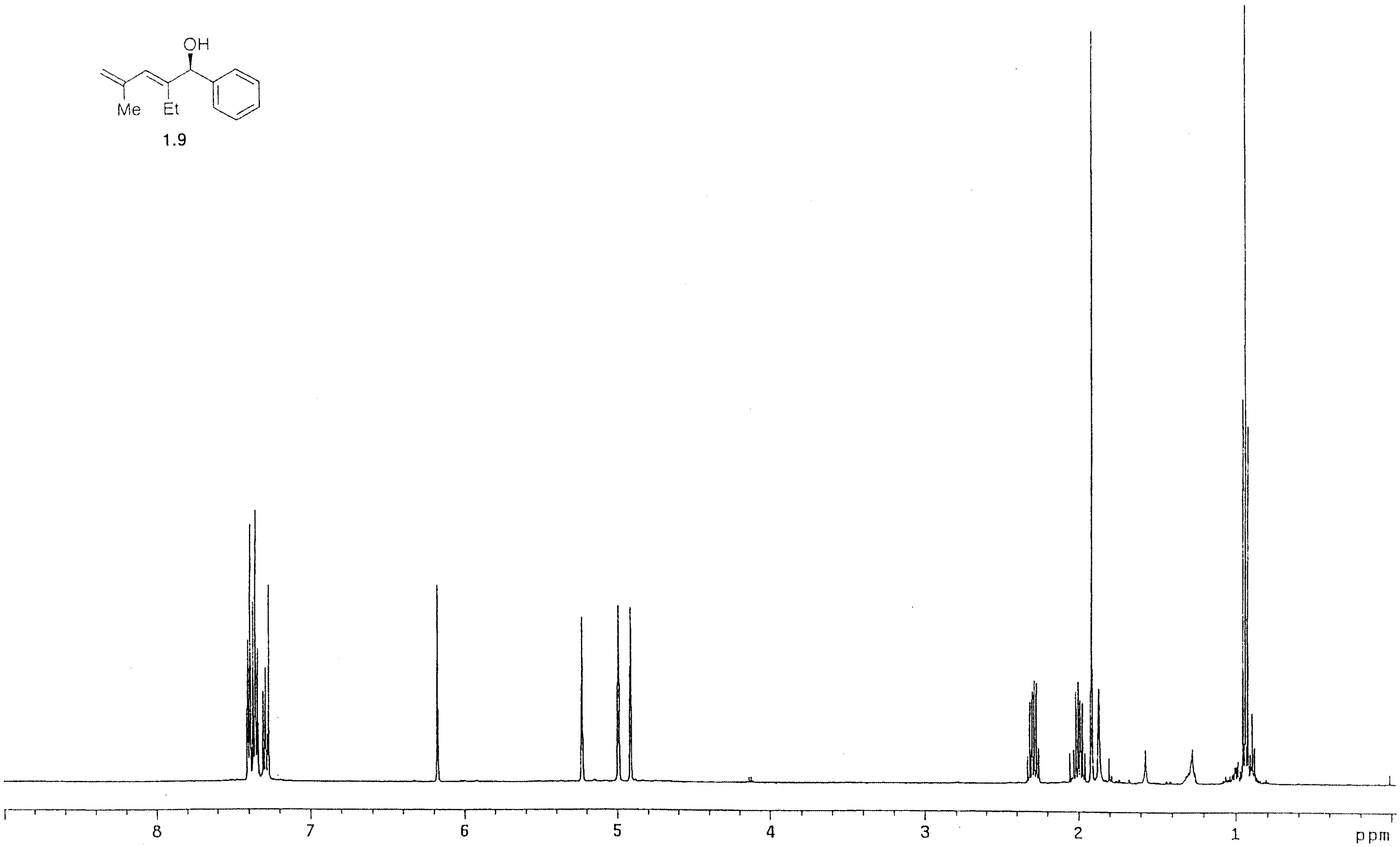

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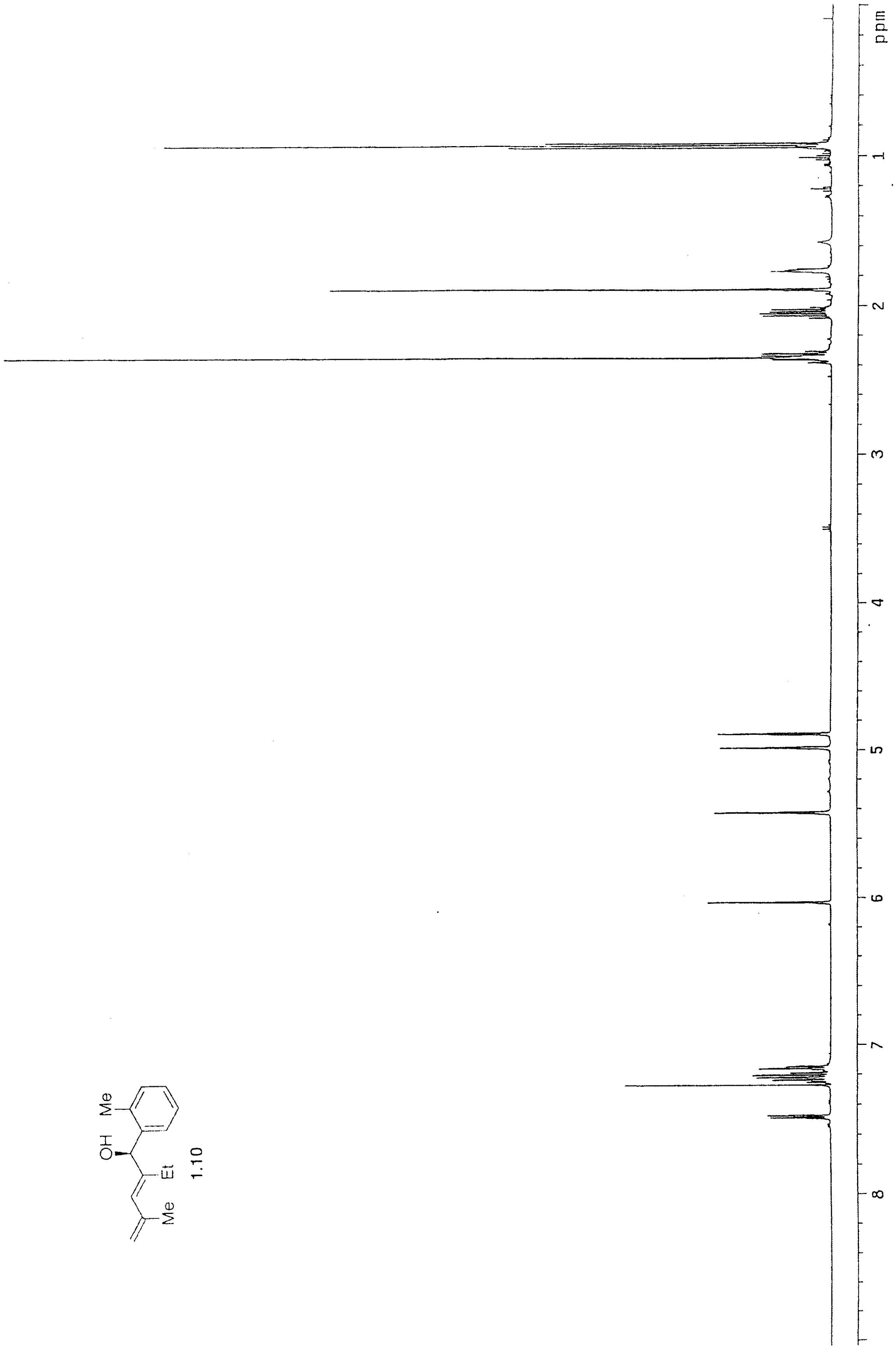
1.9



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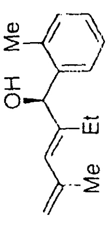

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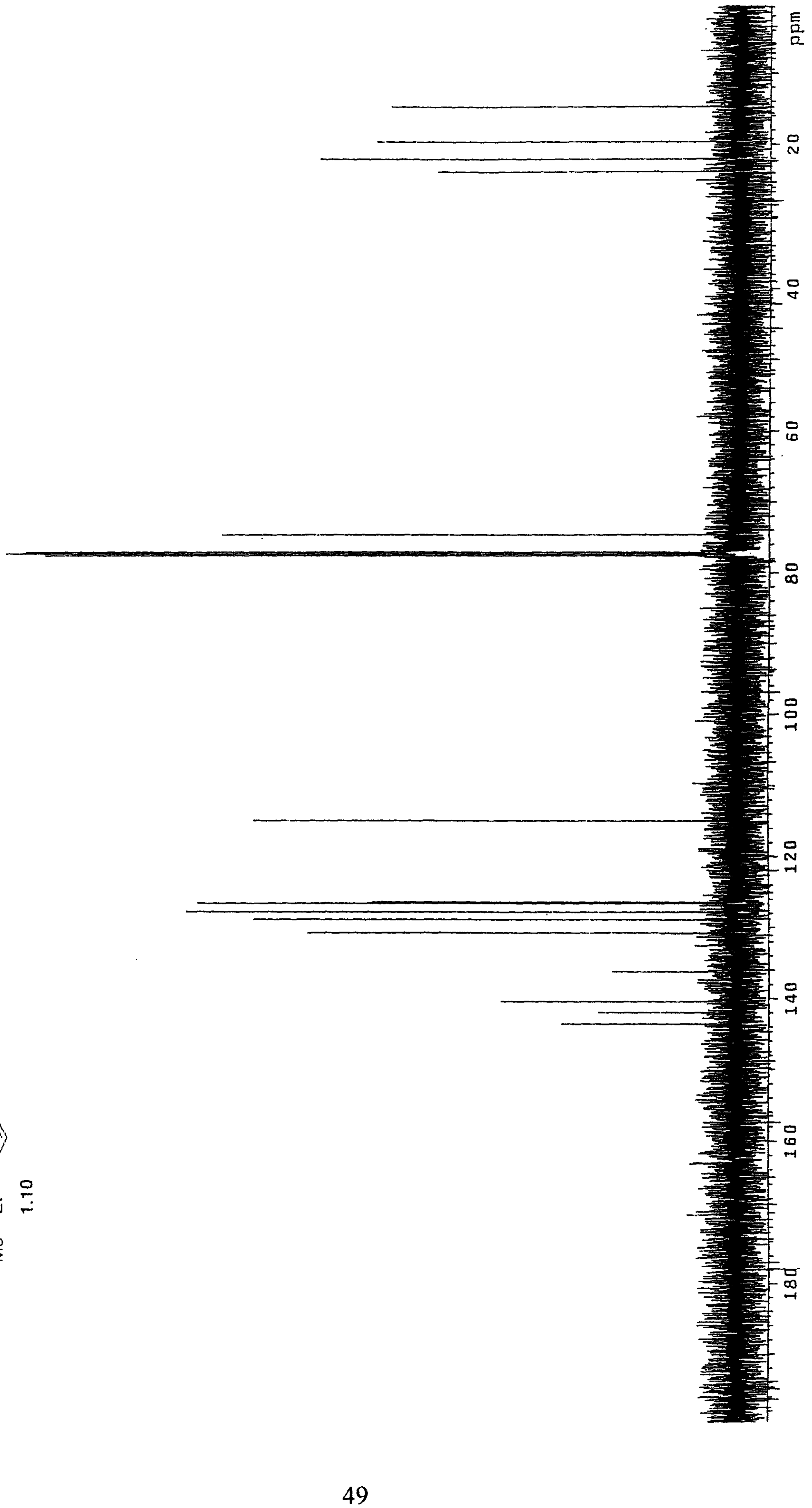

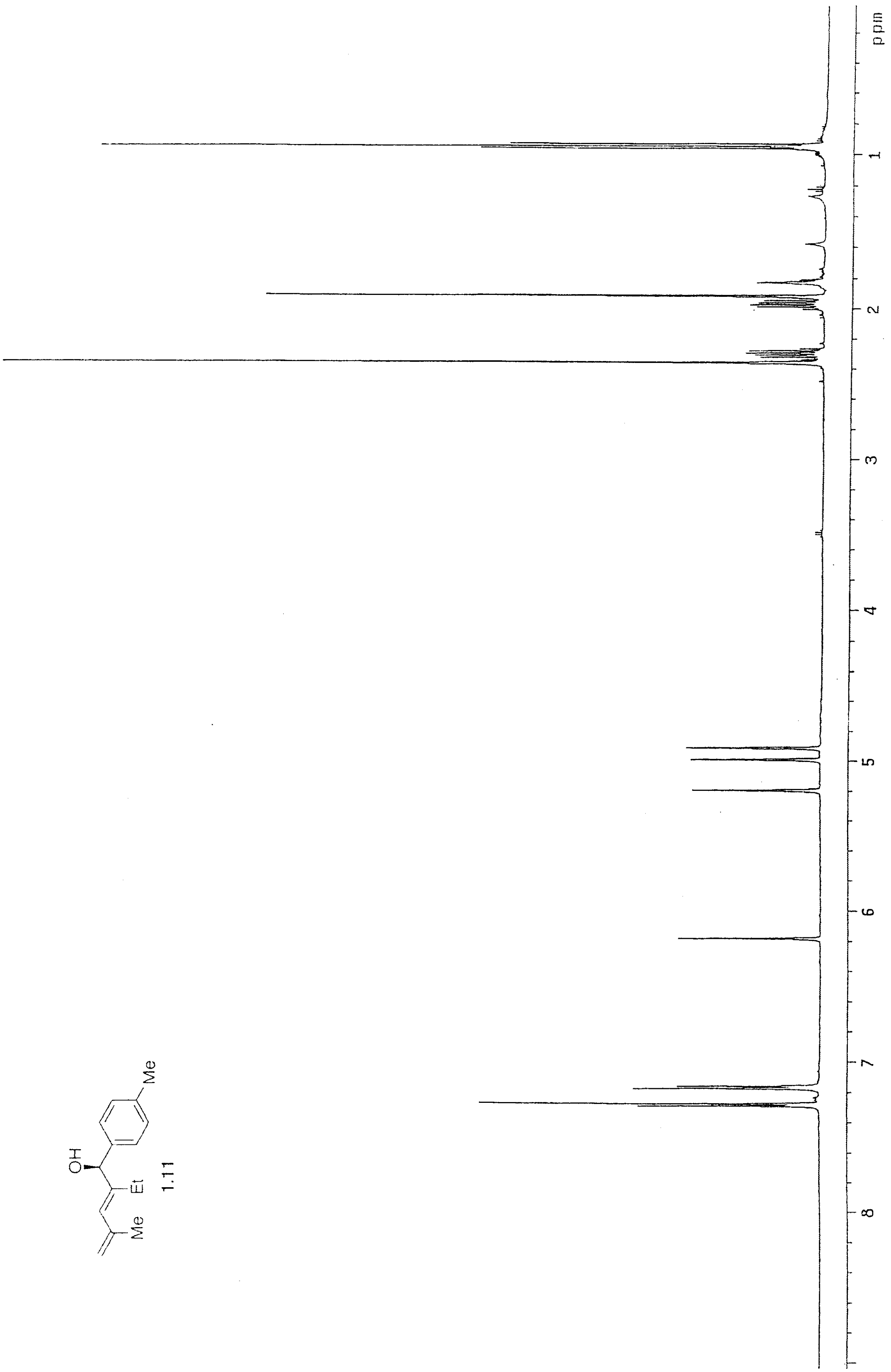

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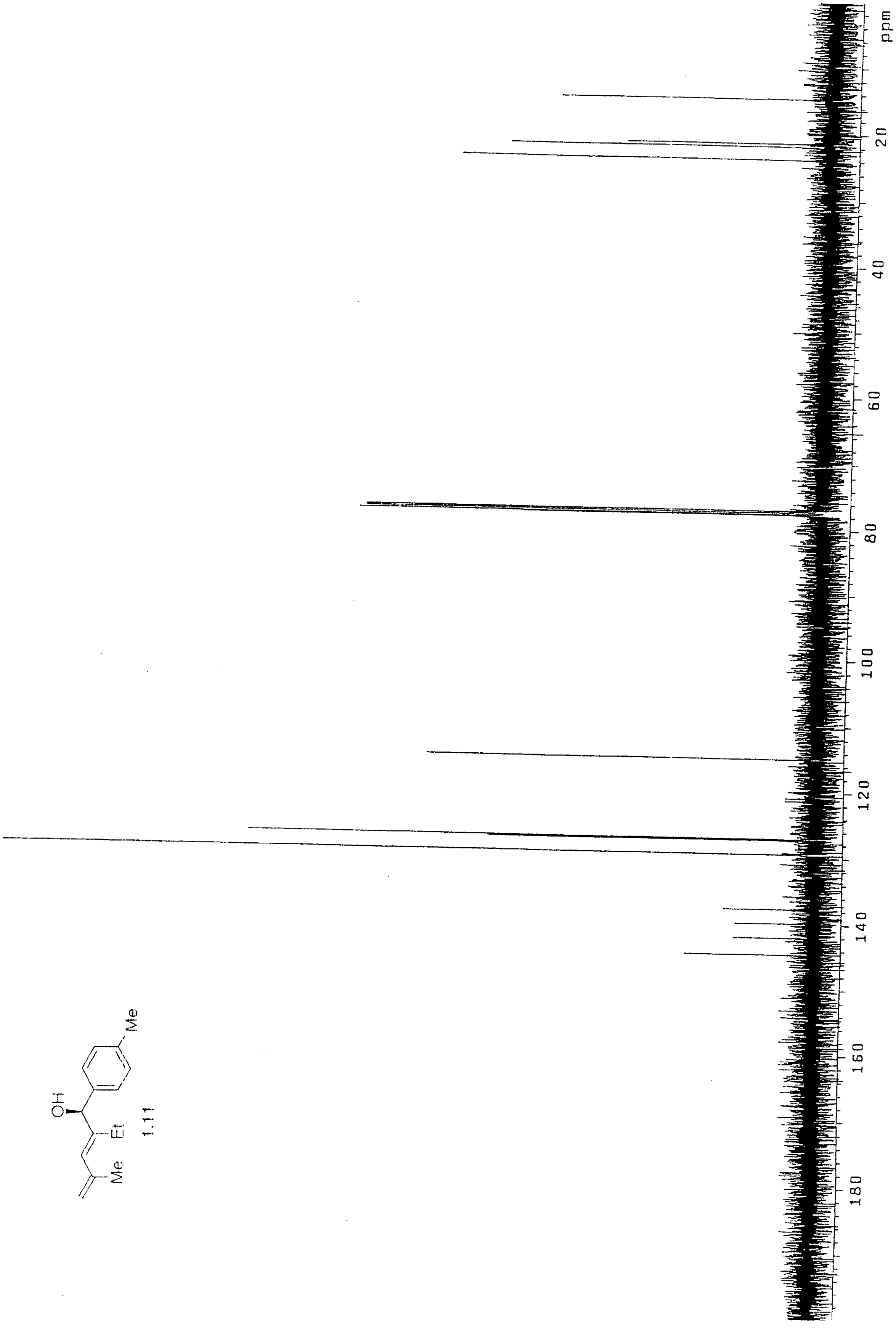

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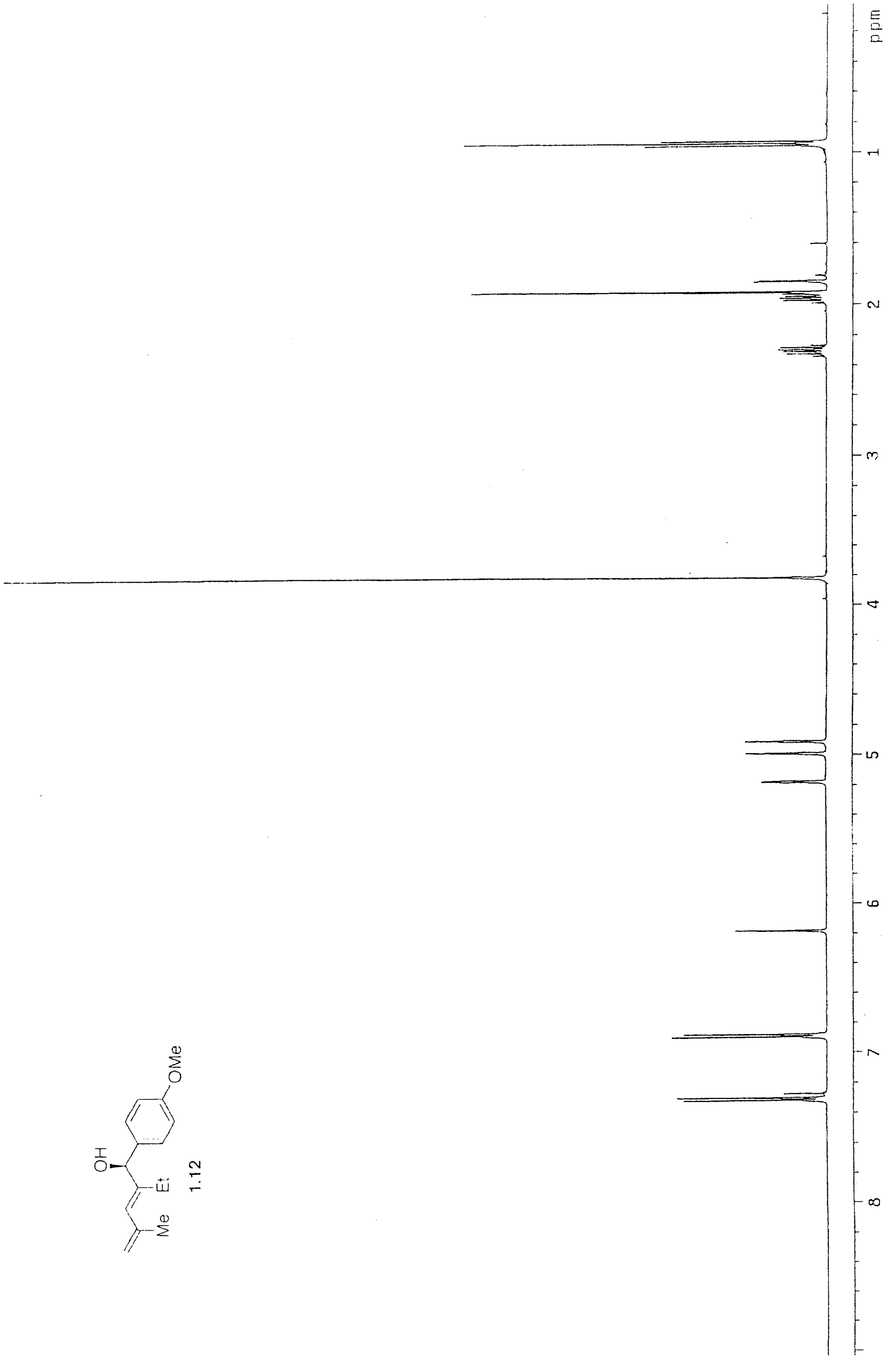

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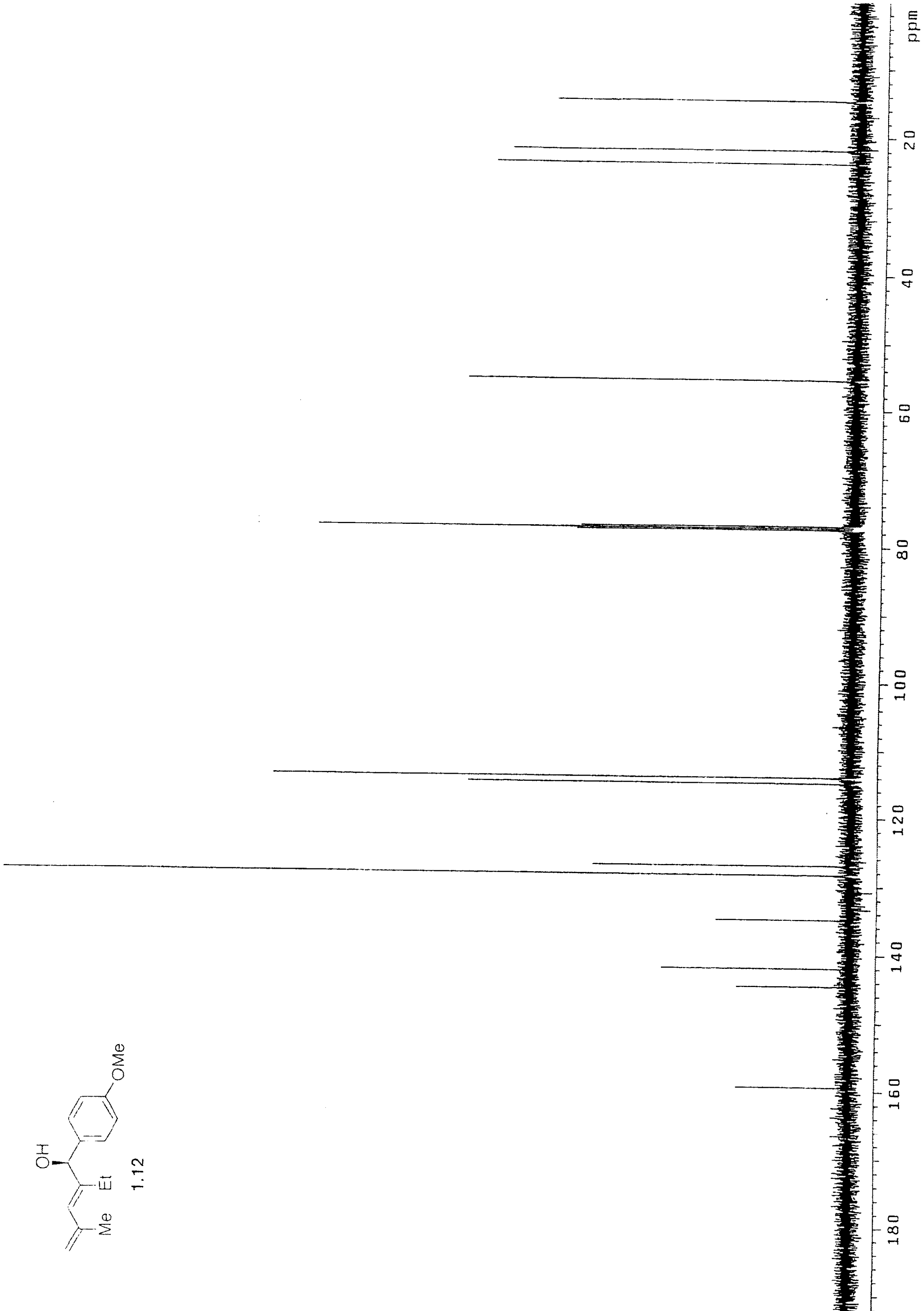

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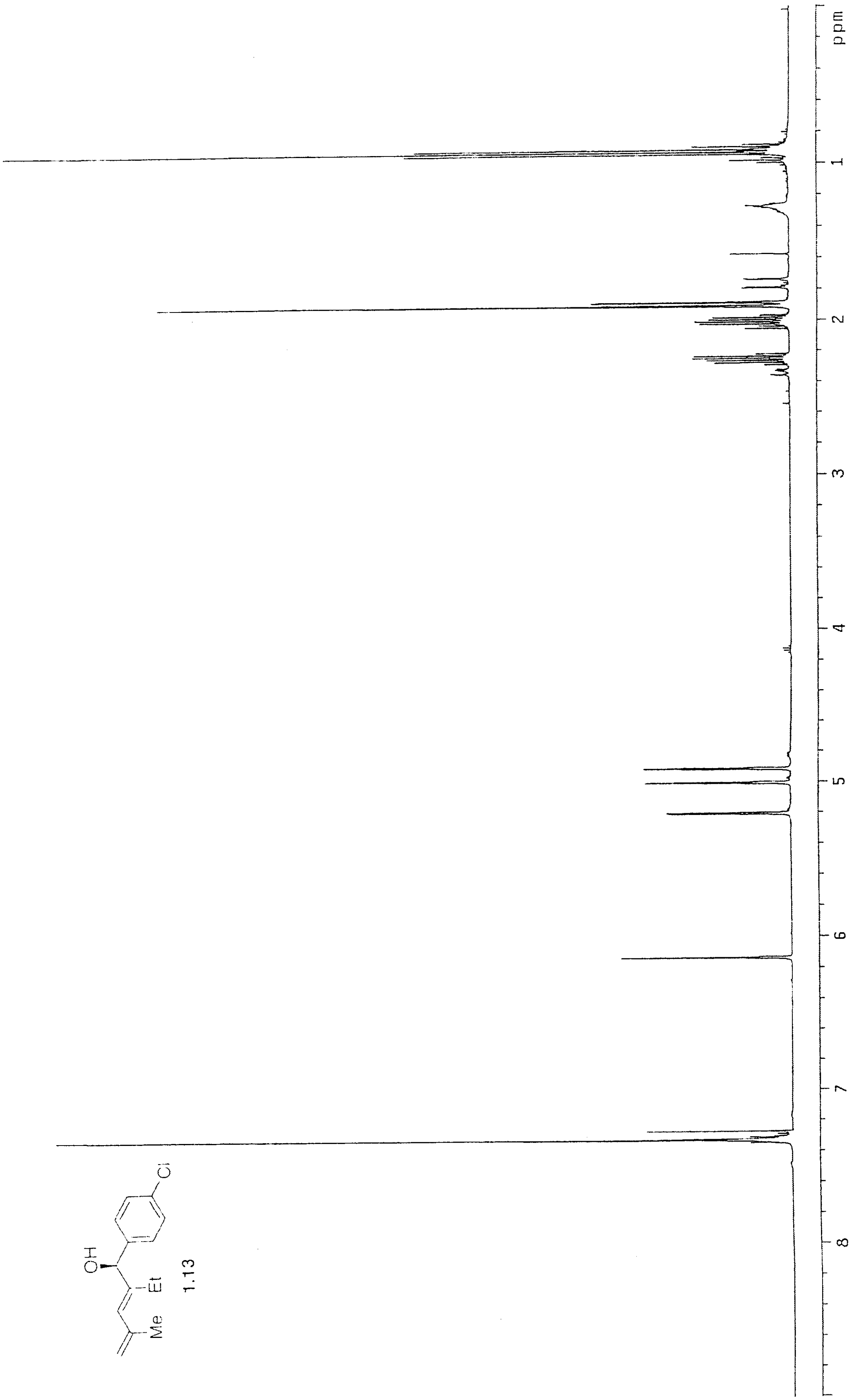

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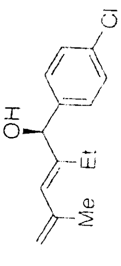

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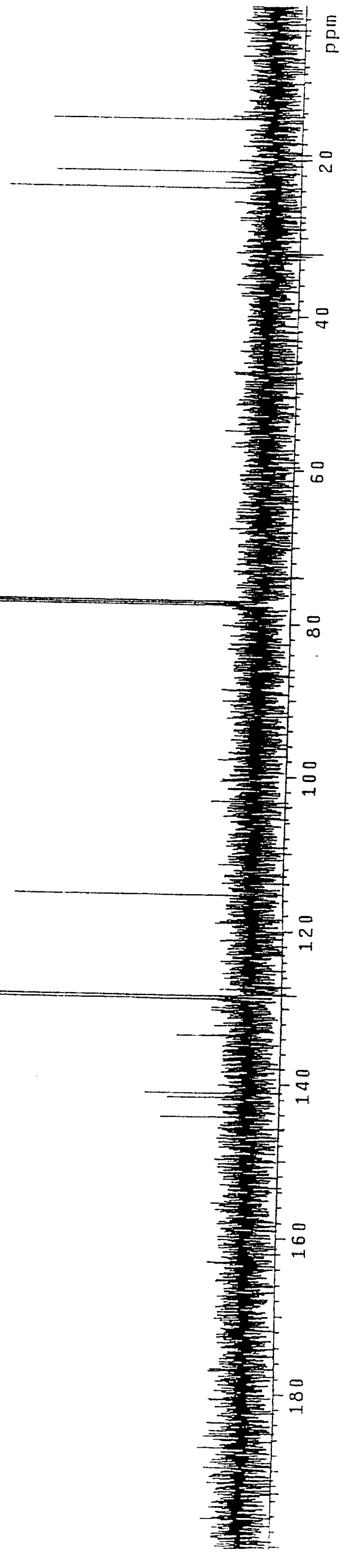

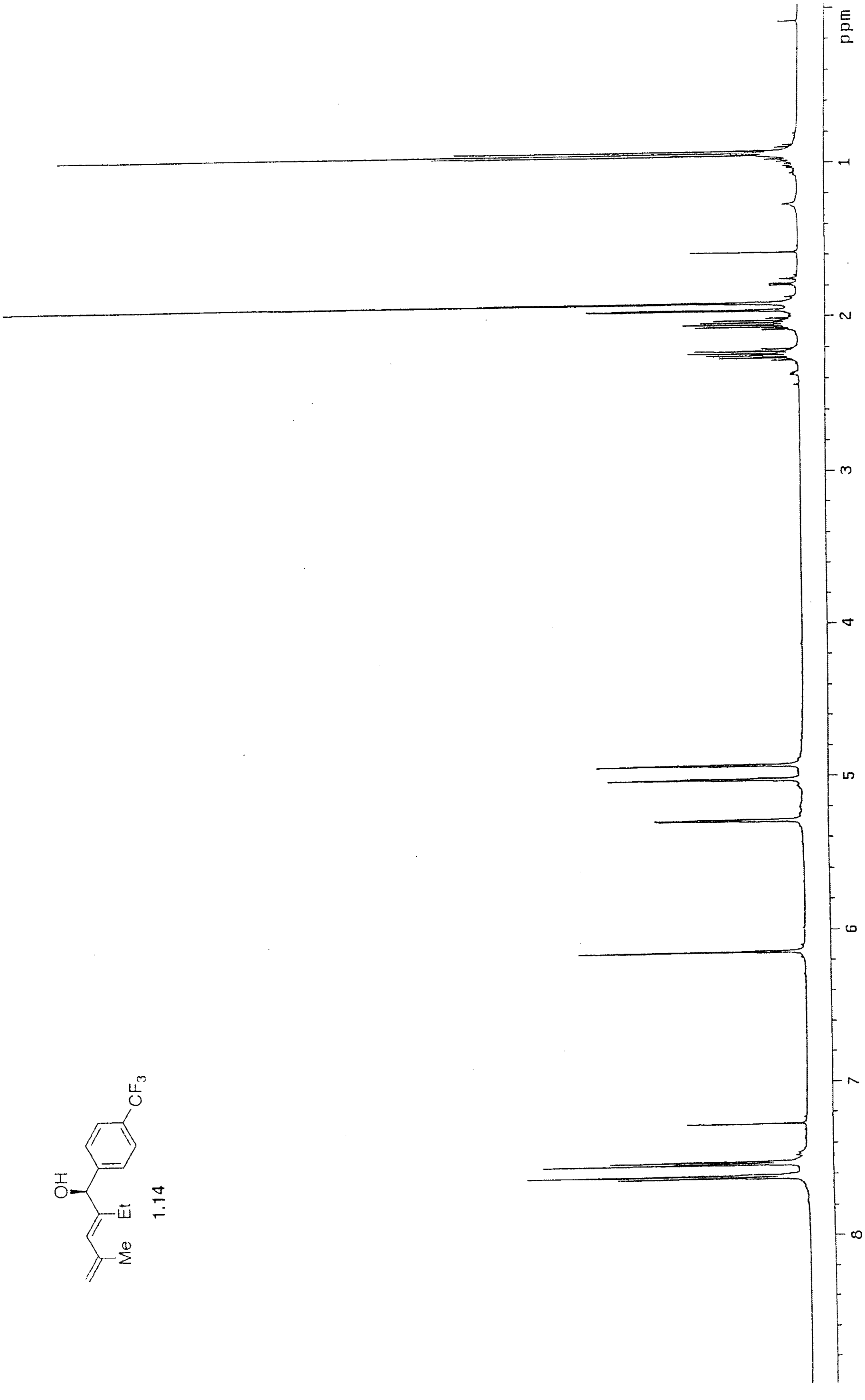

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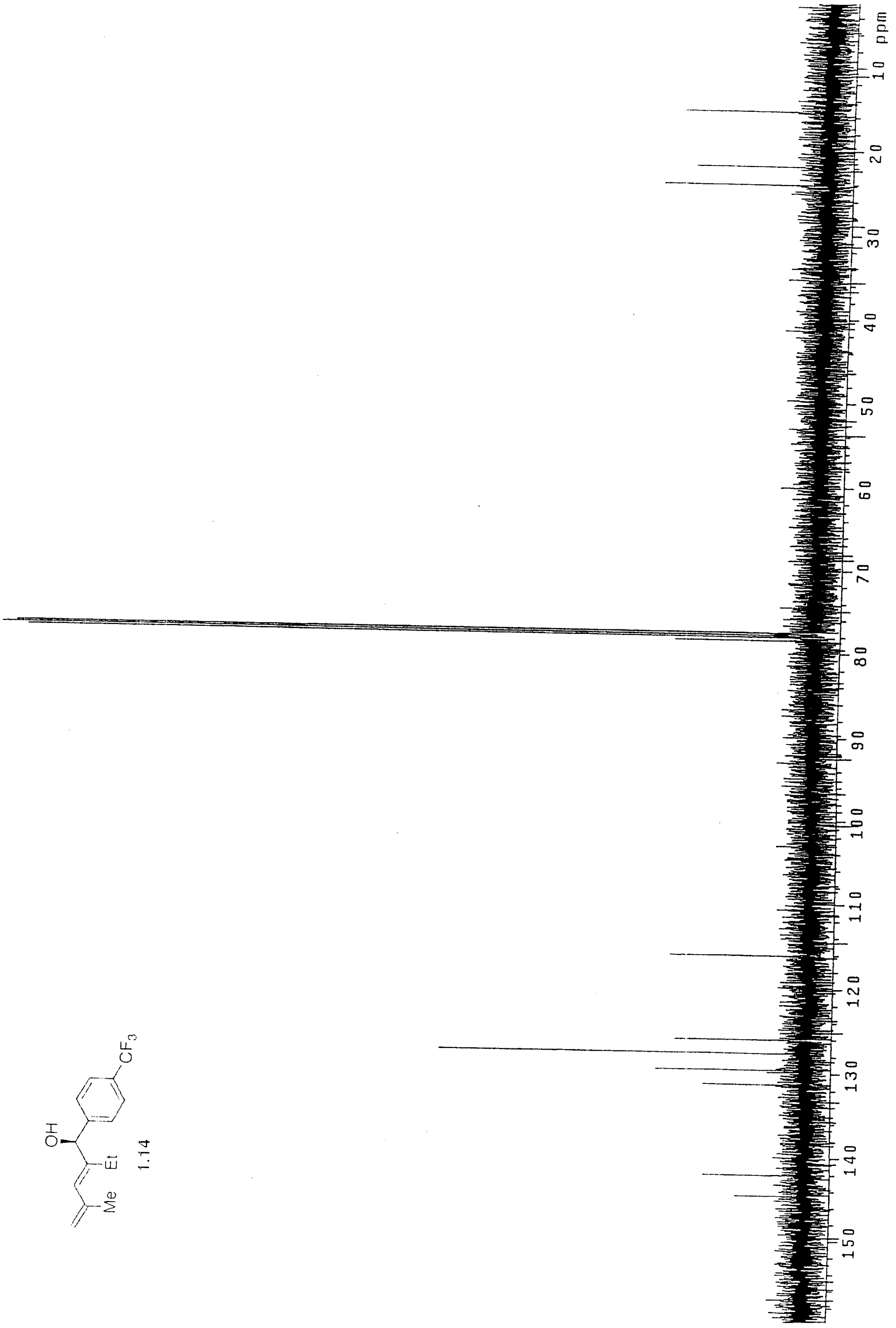

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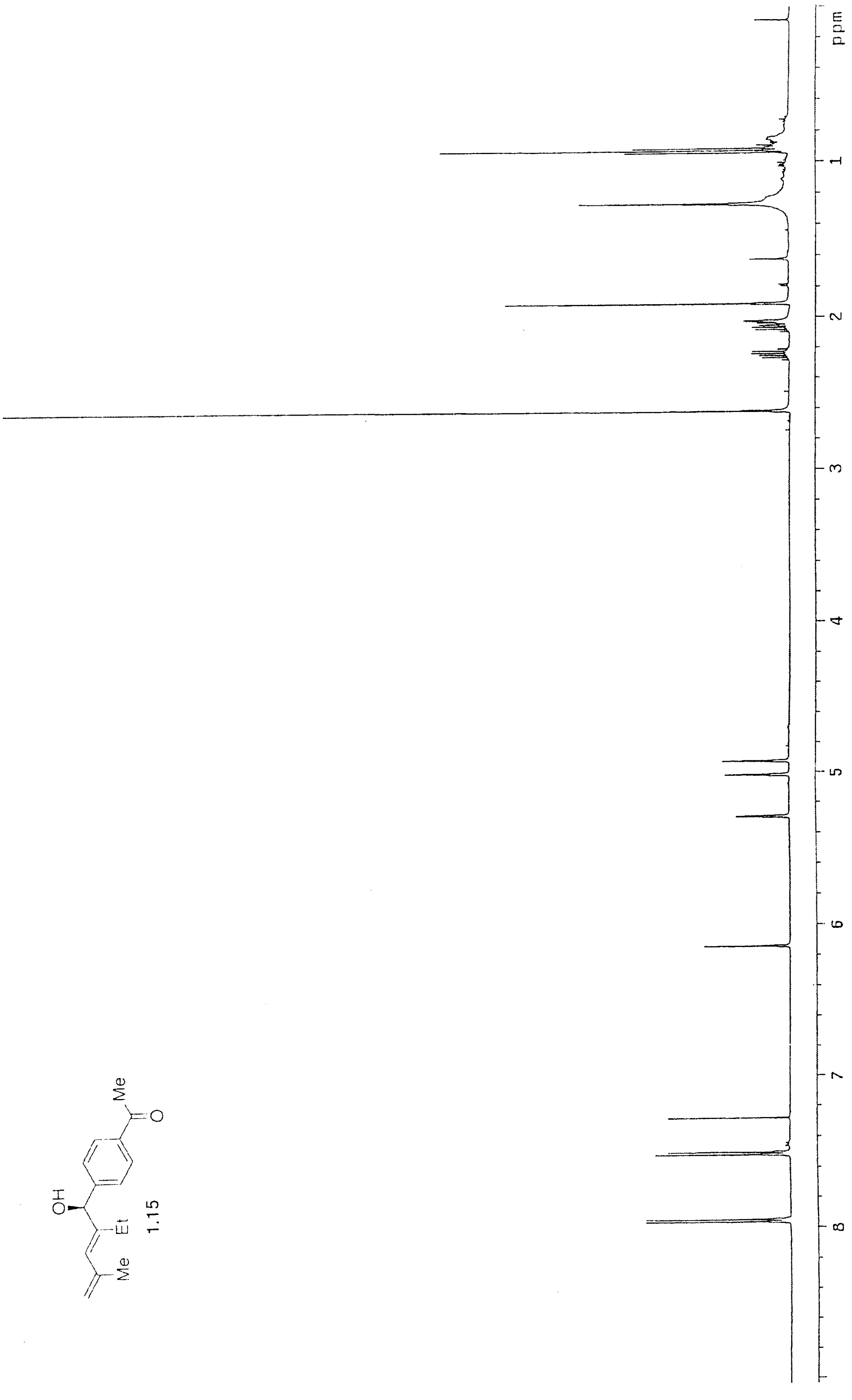

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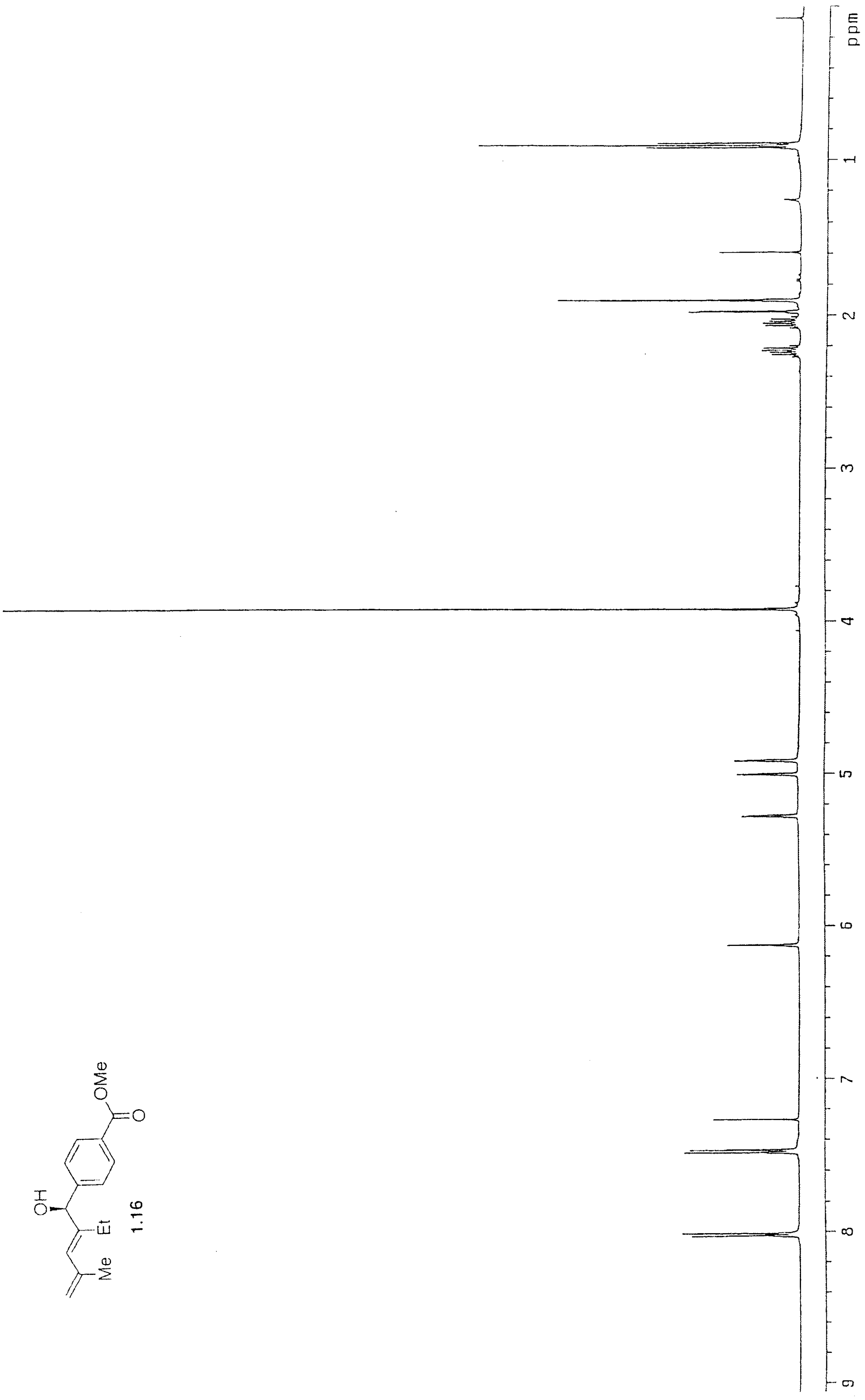

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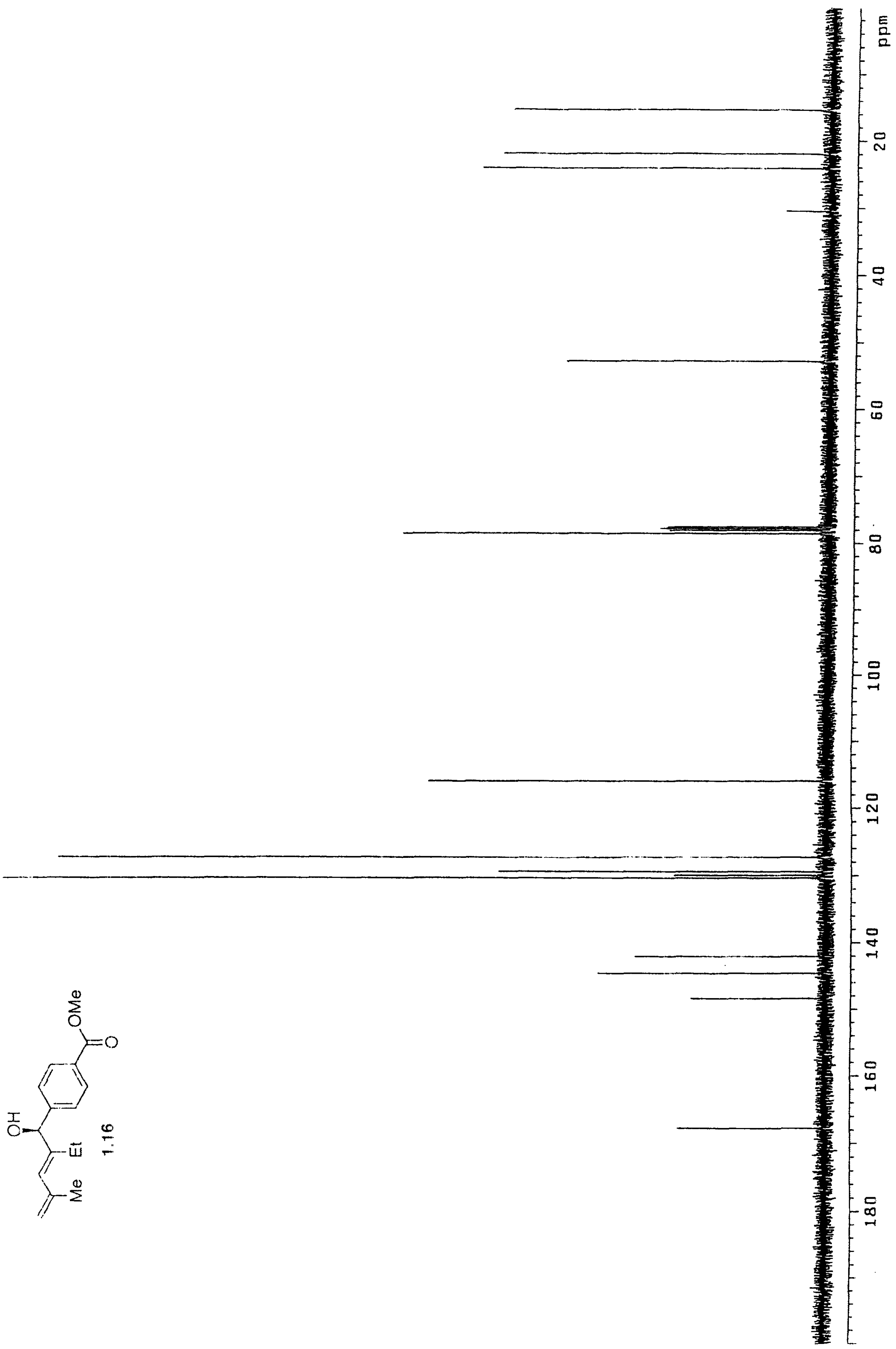
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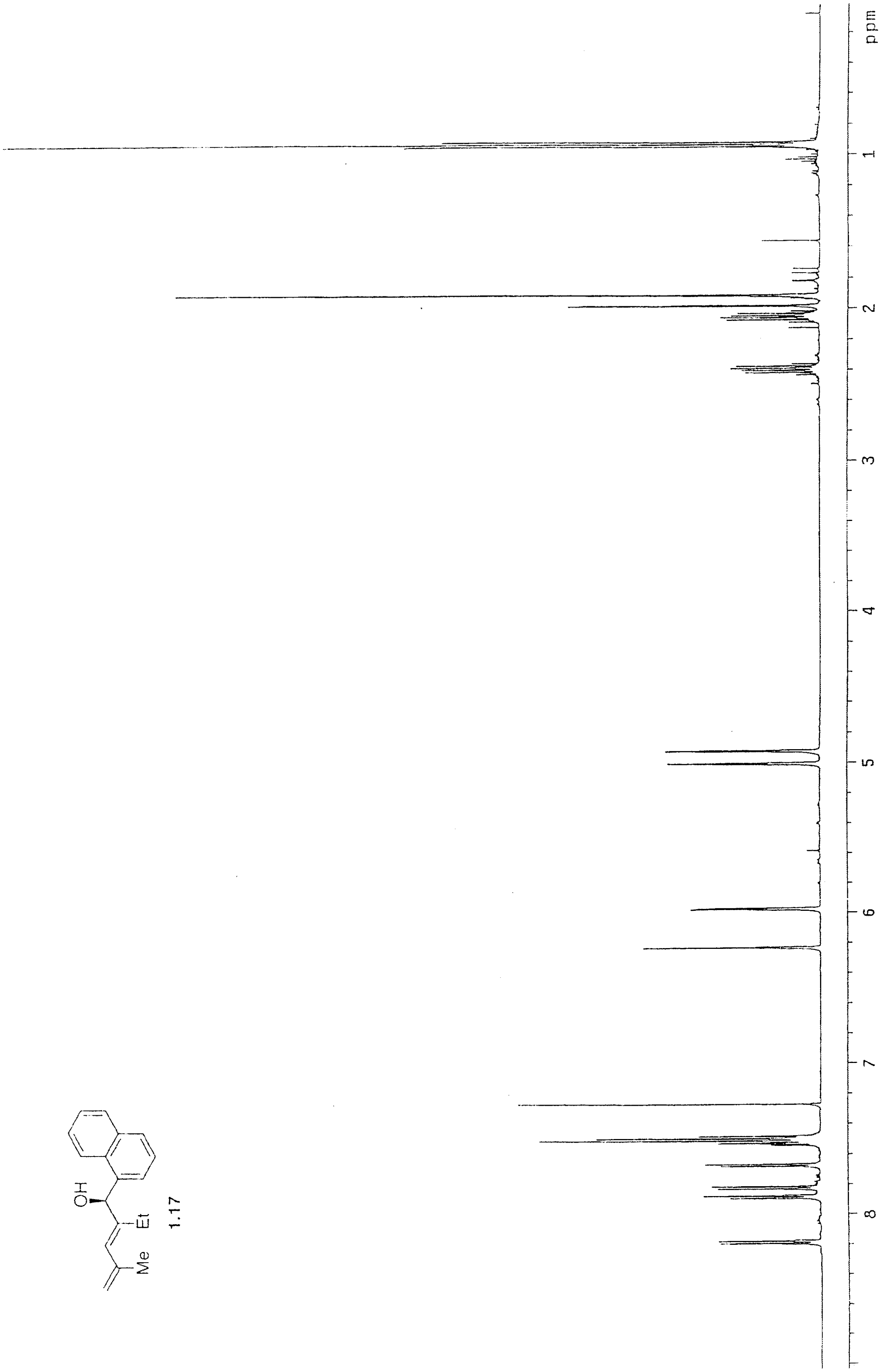

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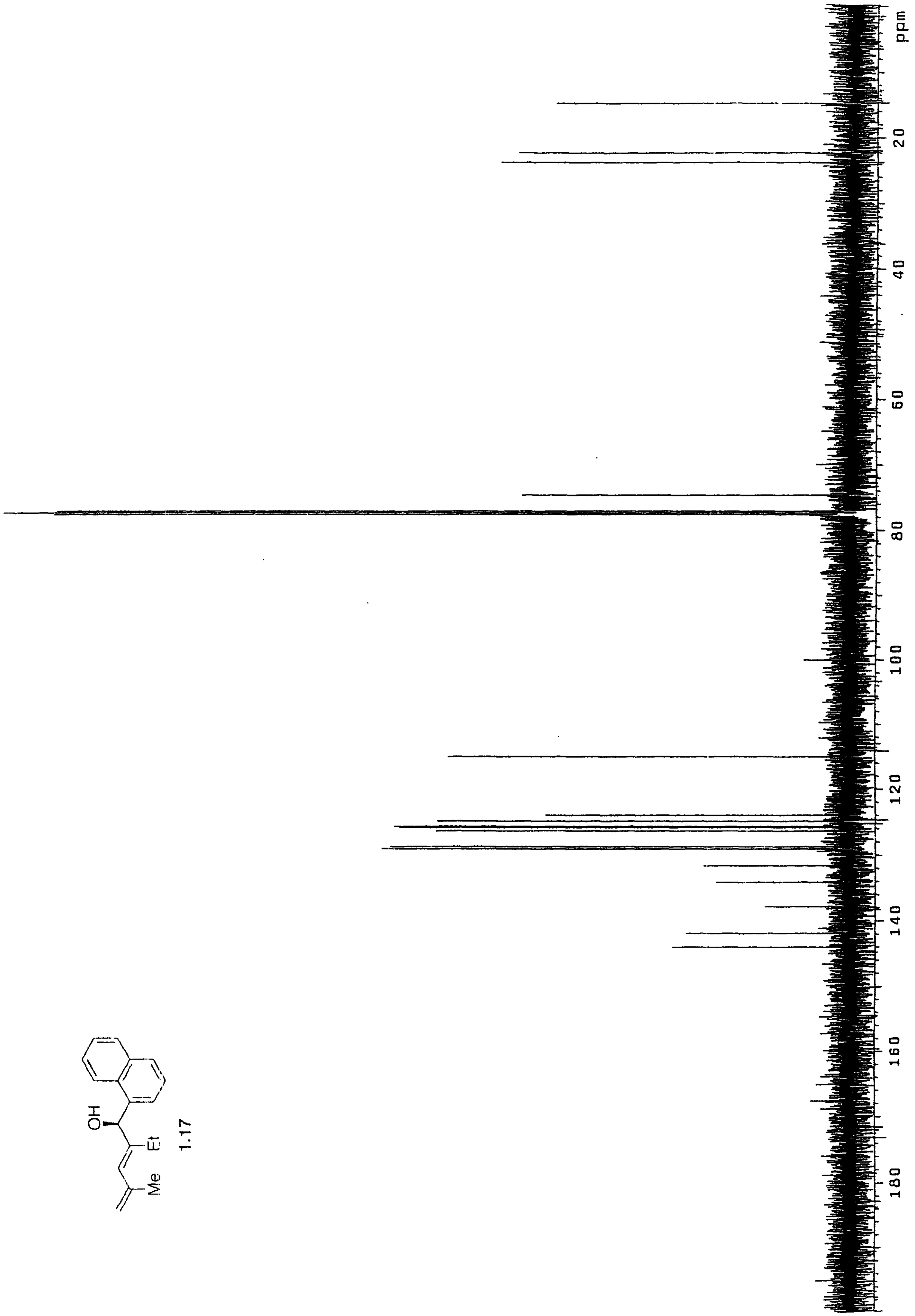

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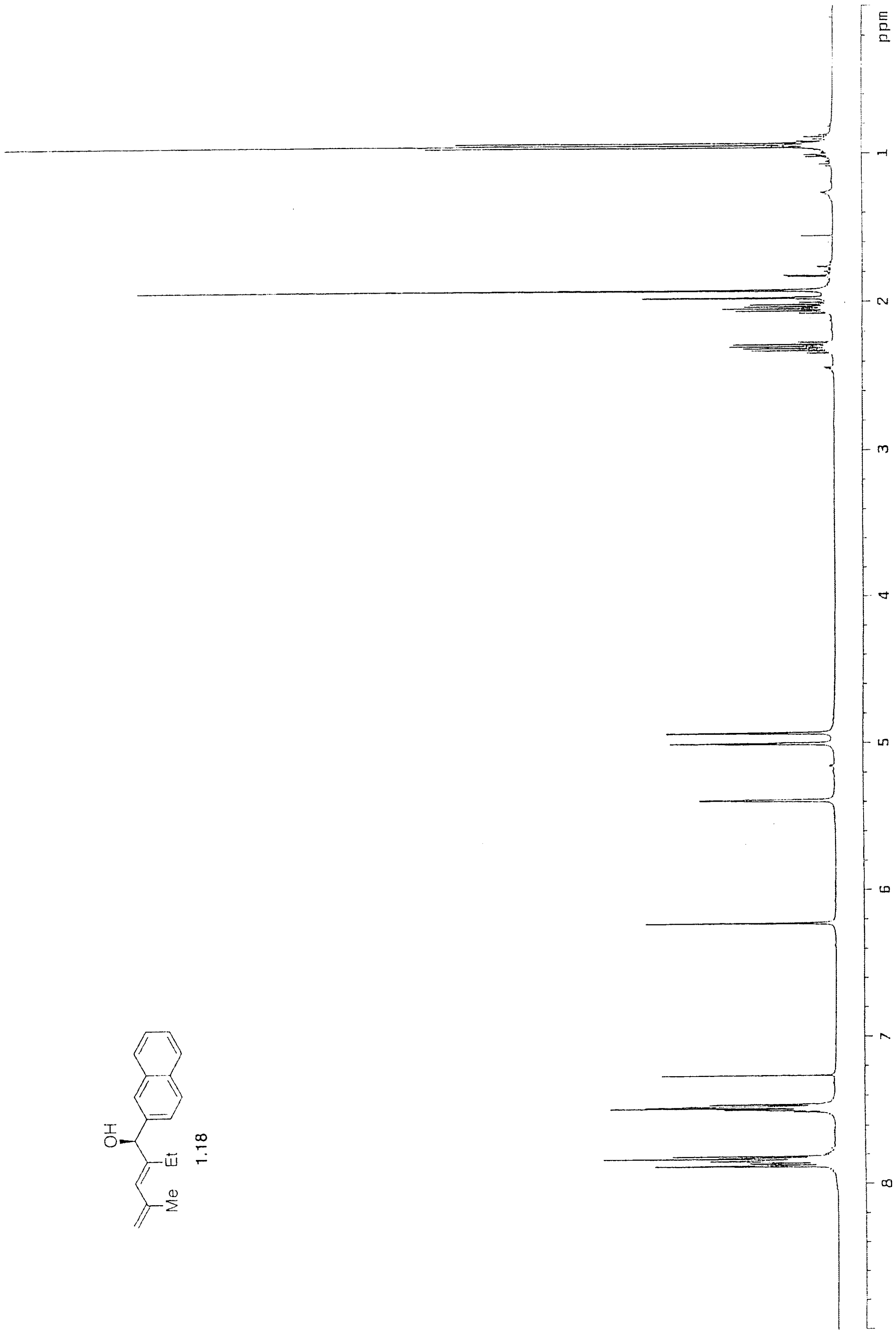
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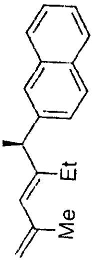

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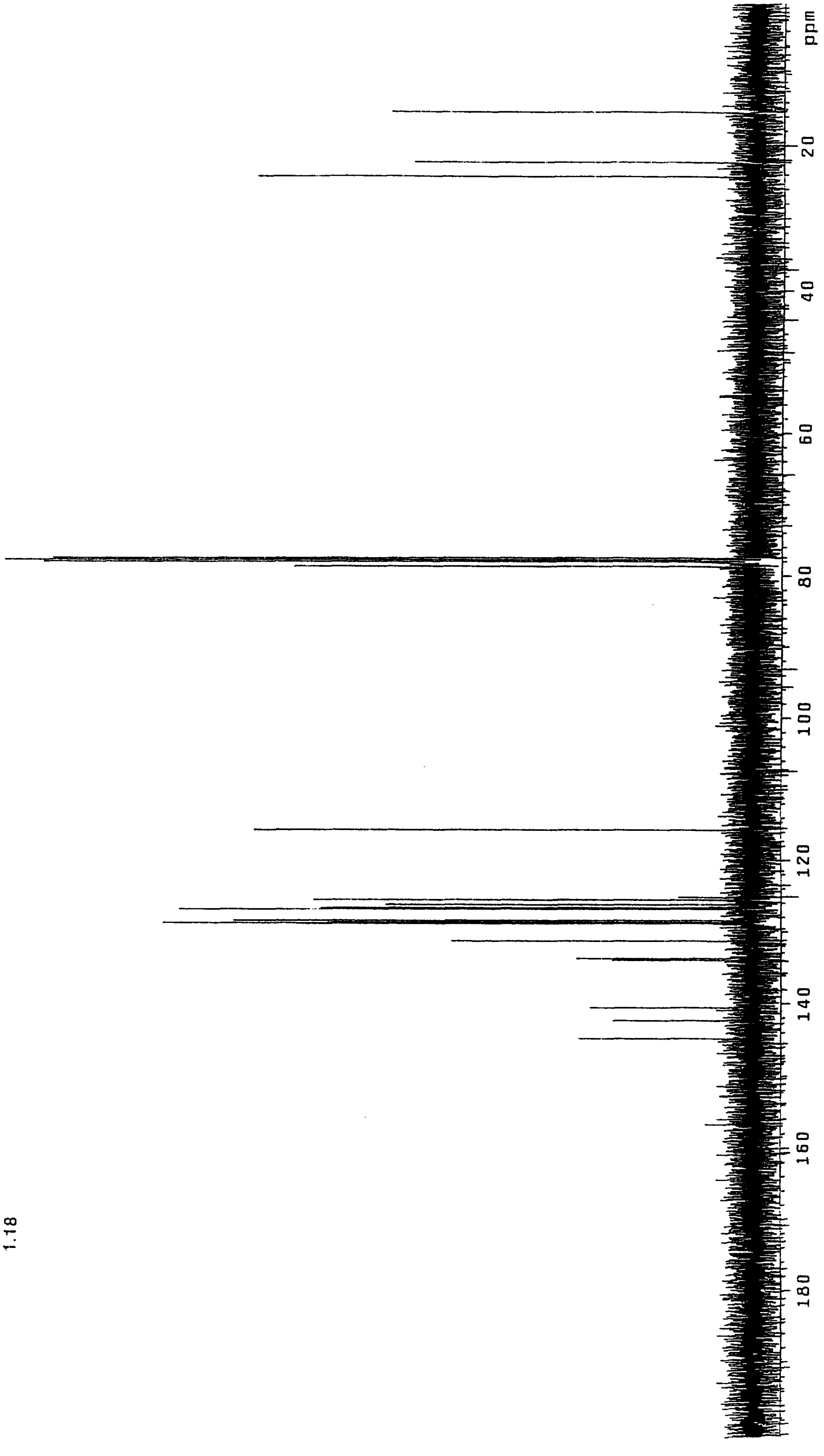

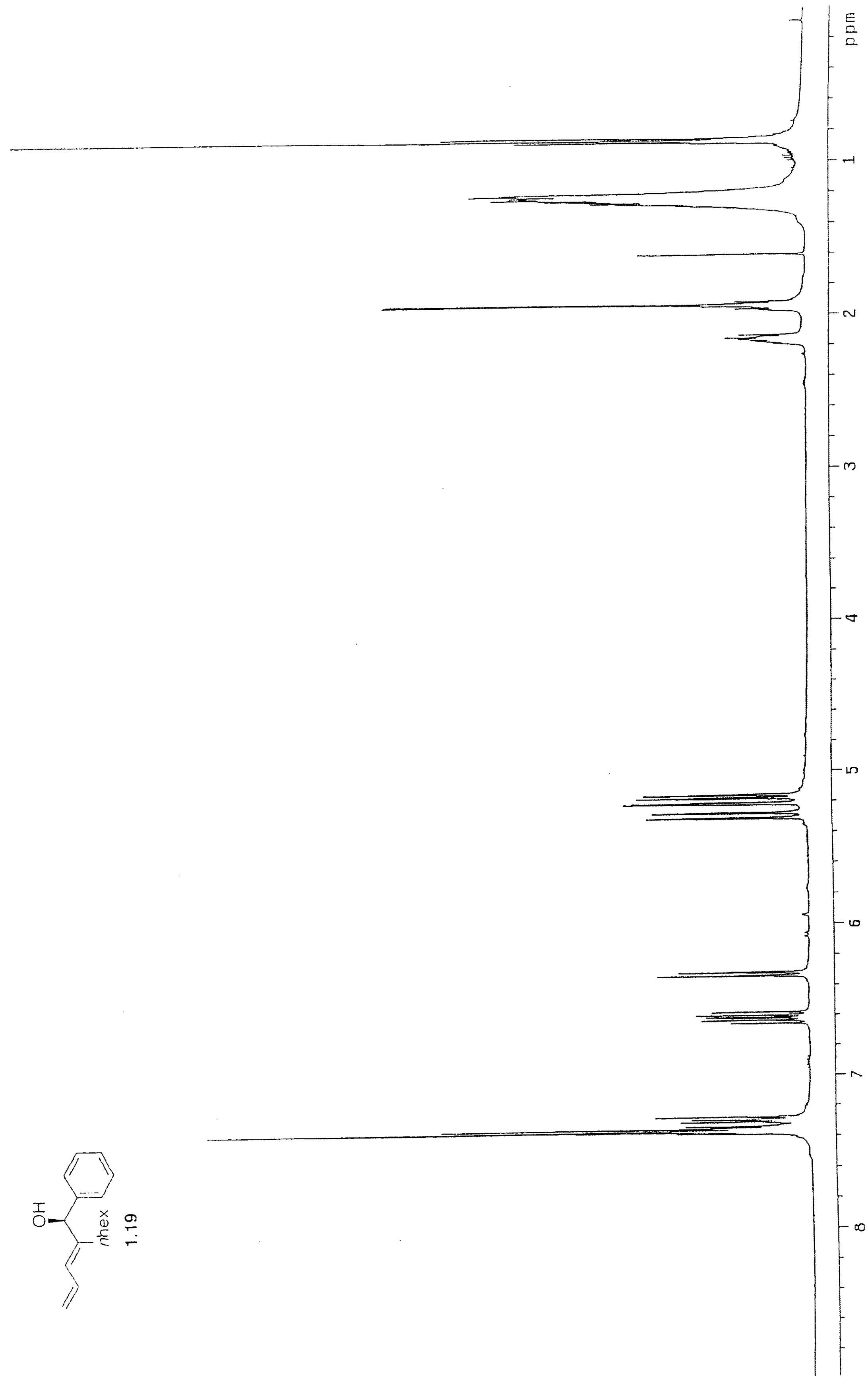
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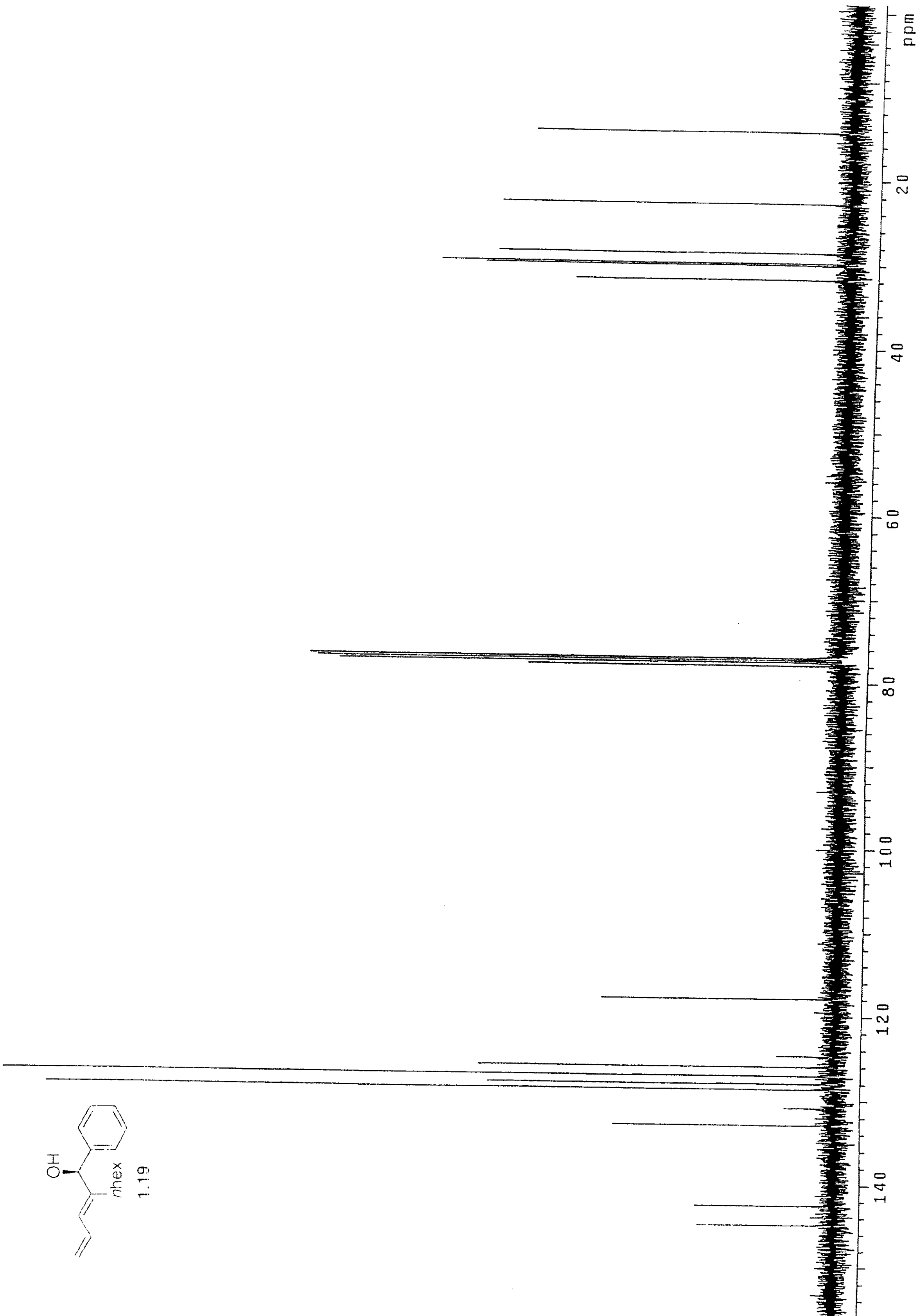

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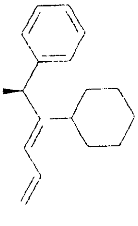

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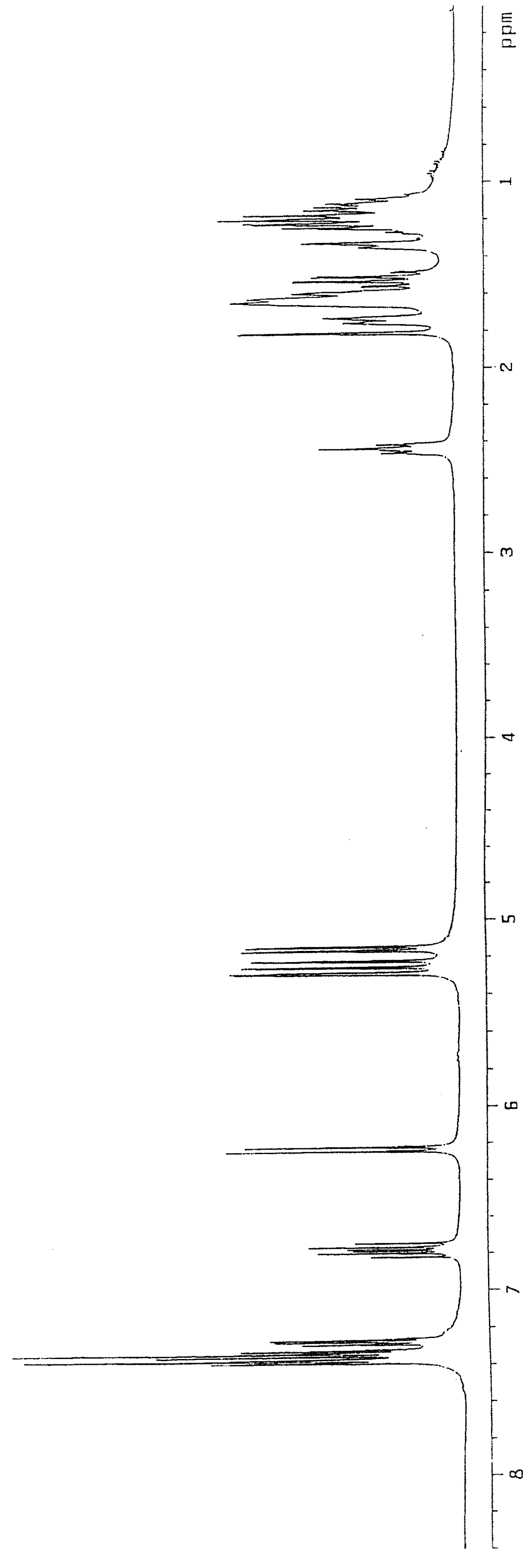

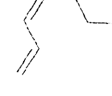

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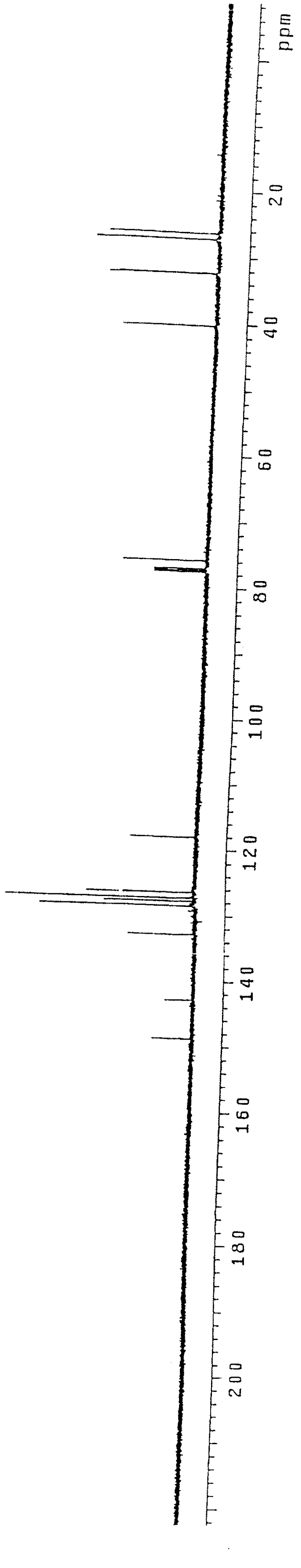

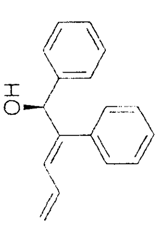

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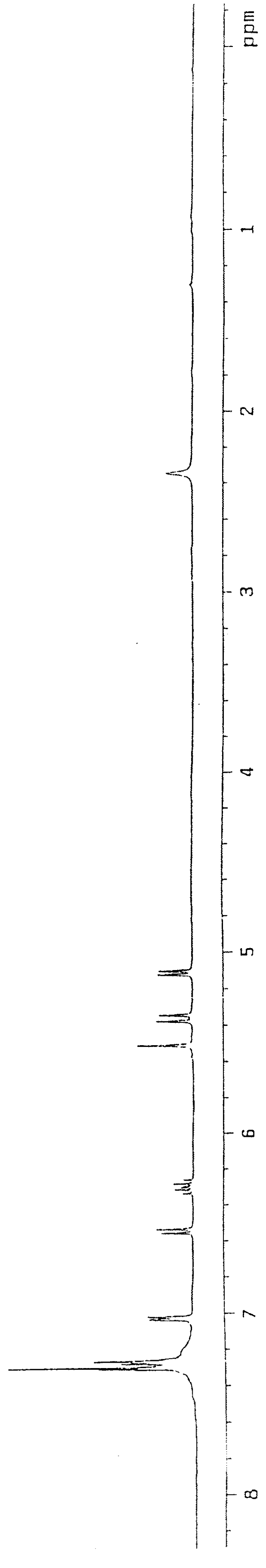

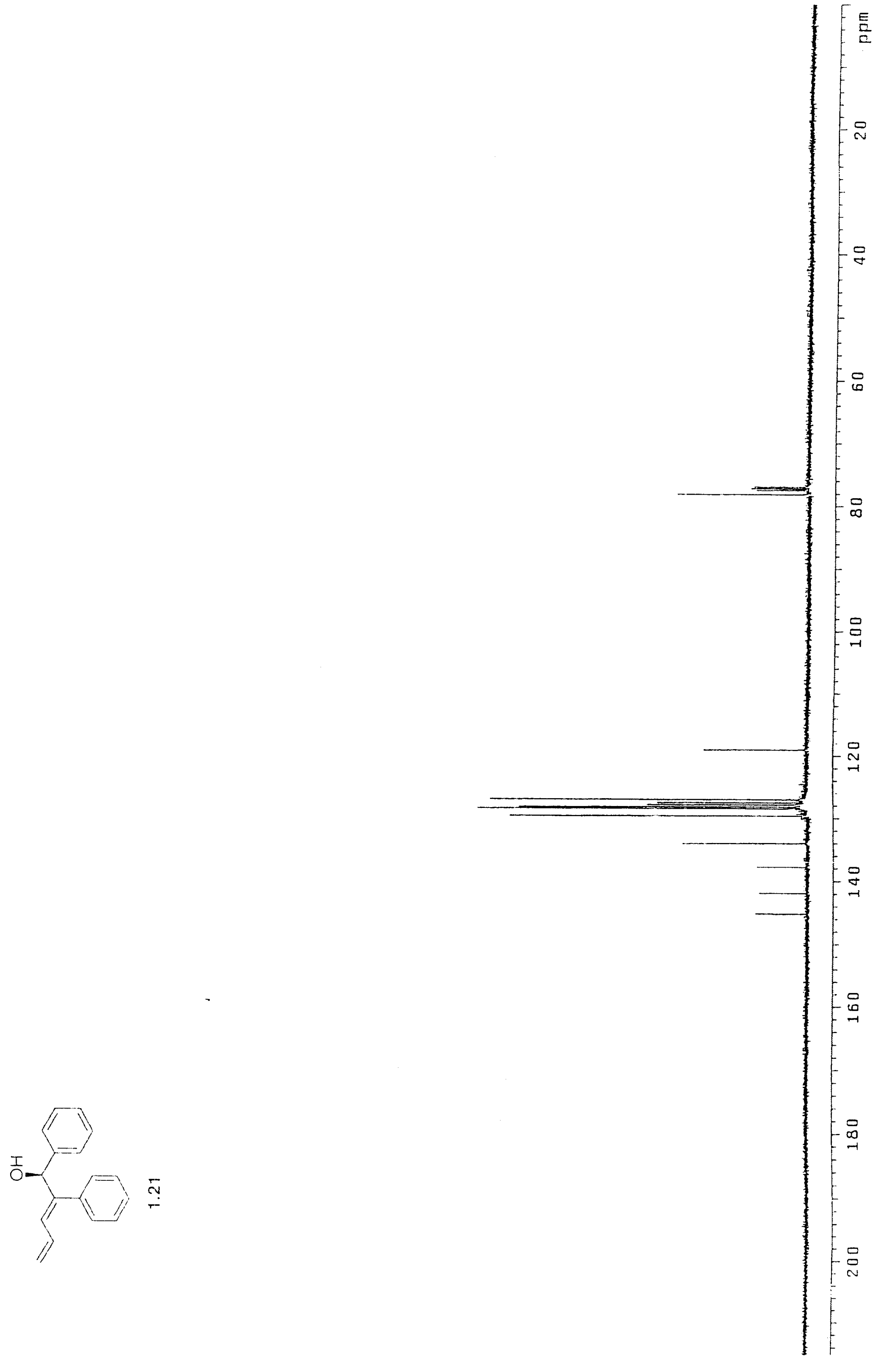

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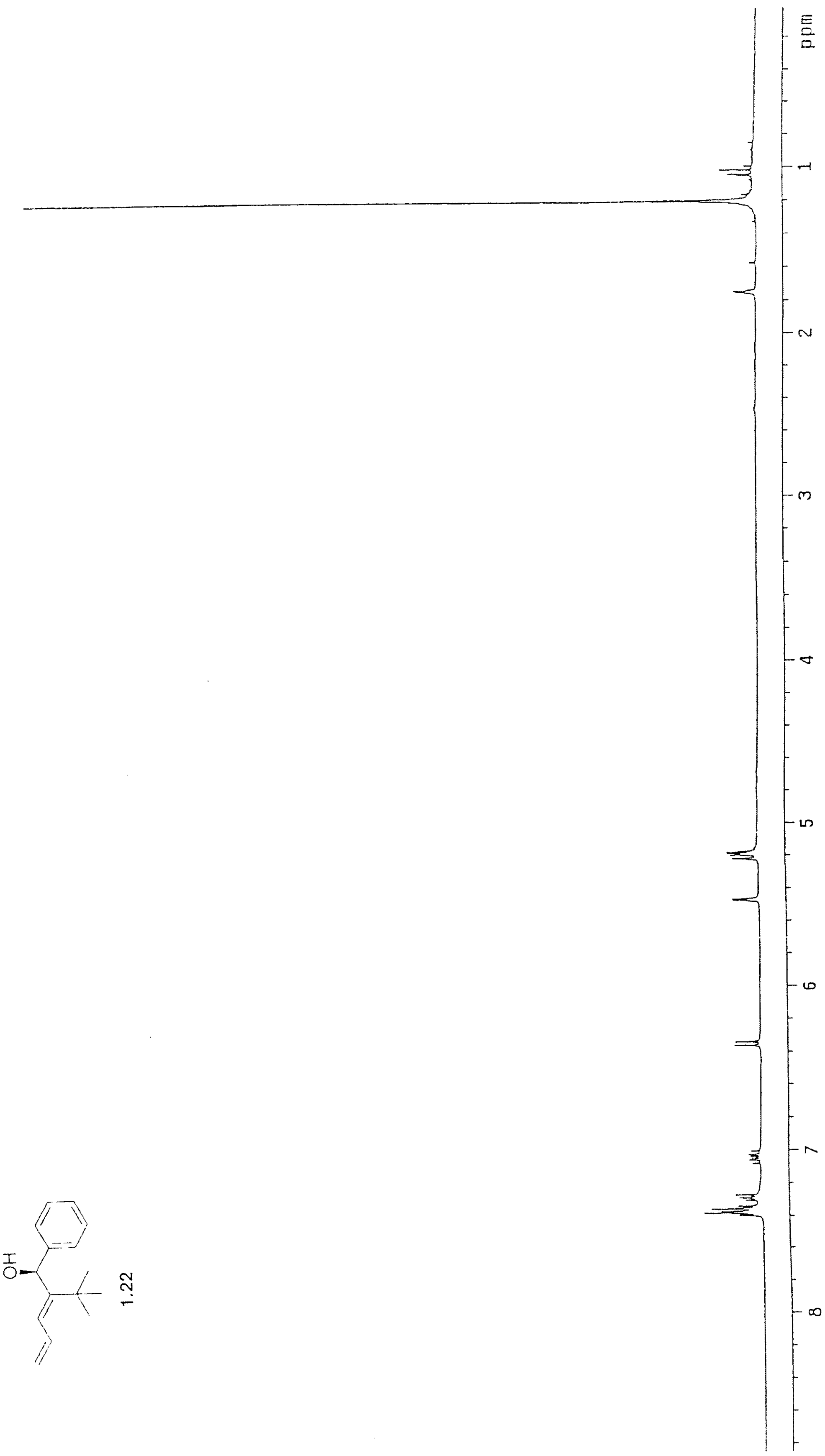

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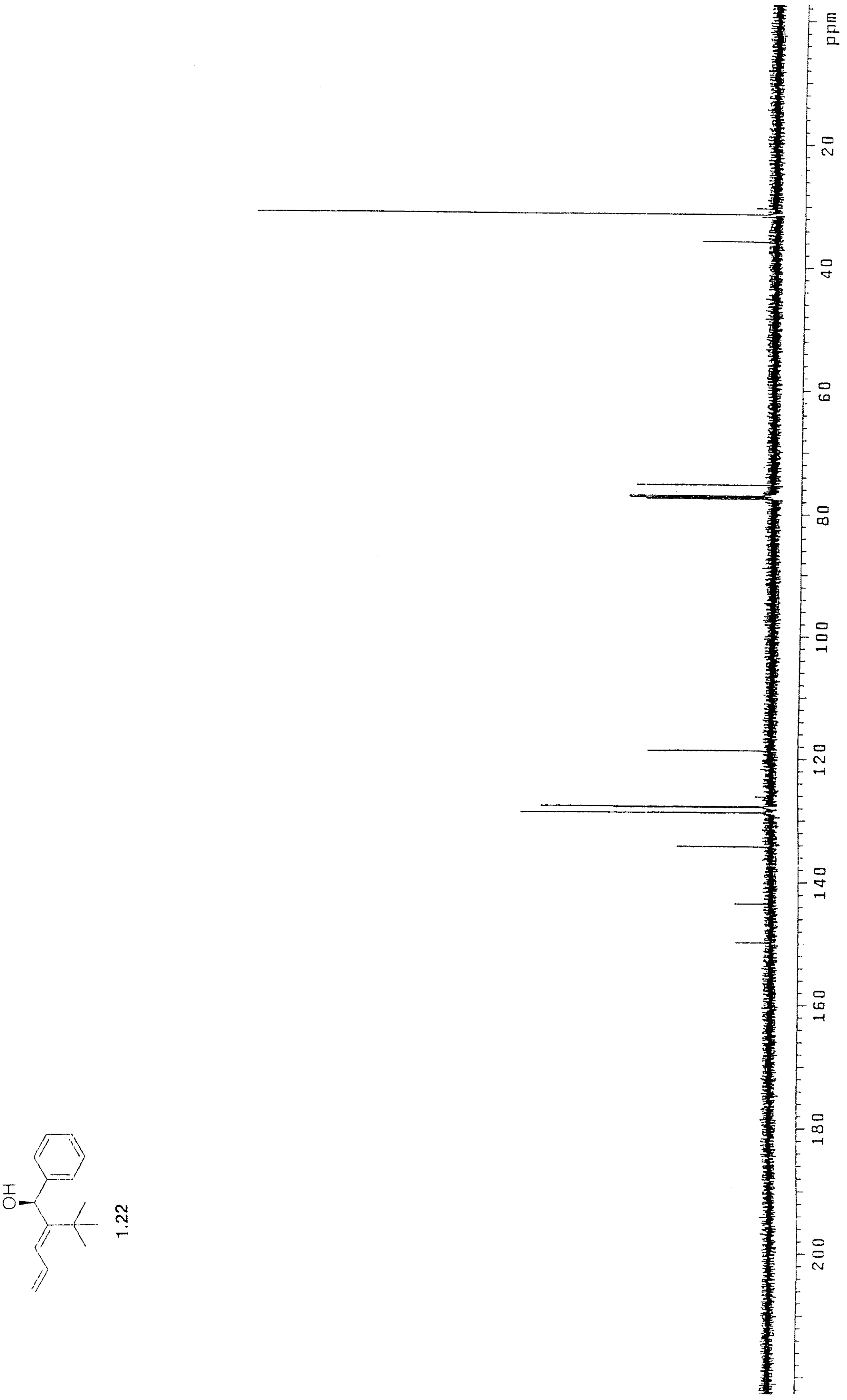

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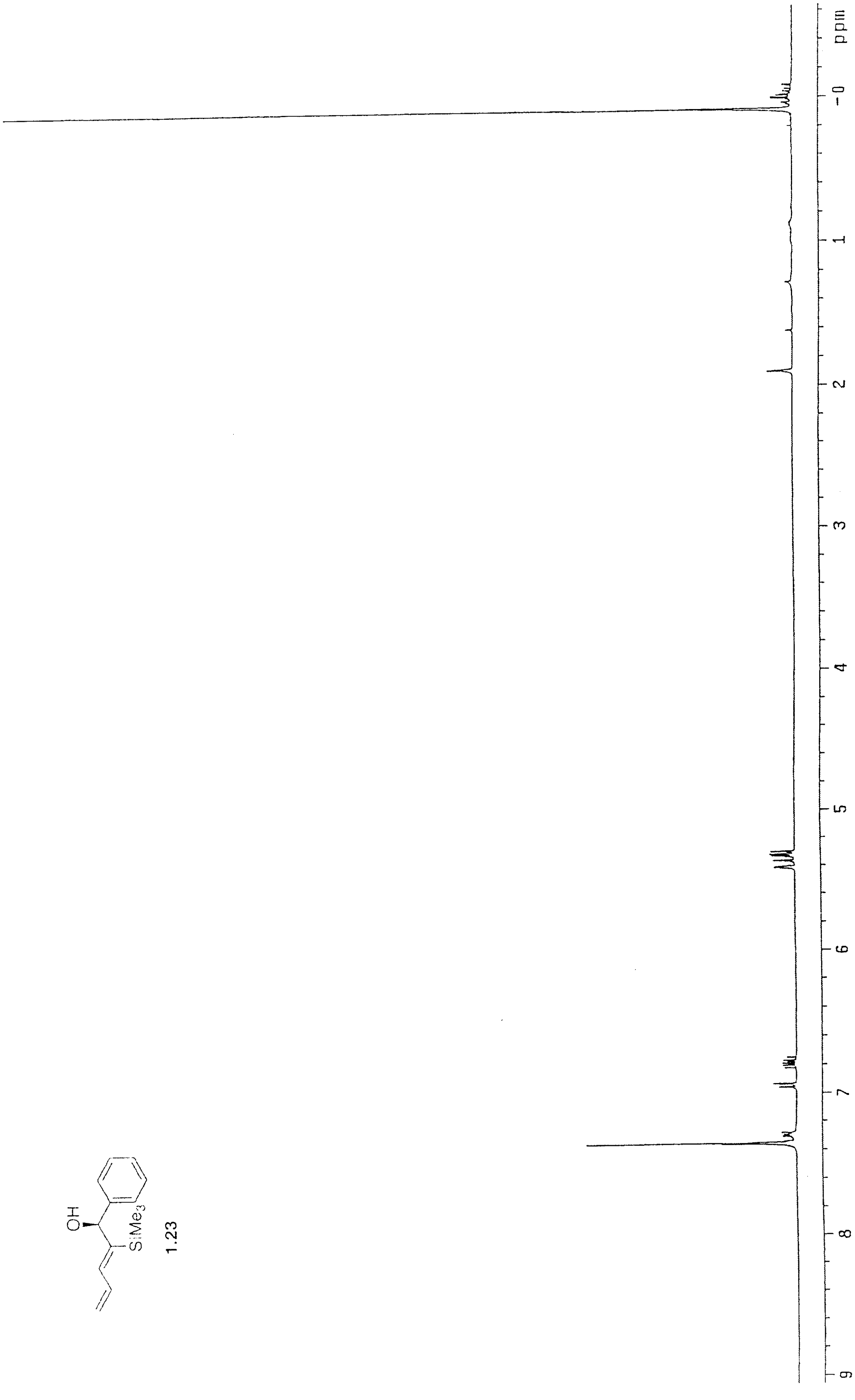

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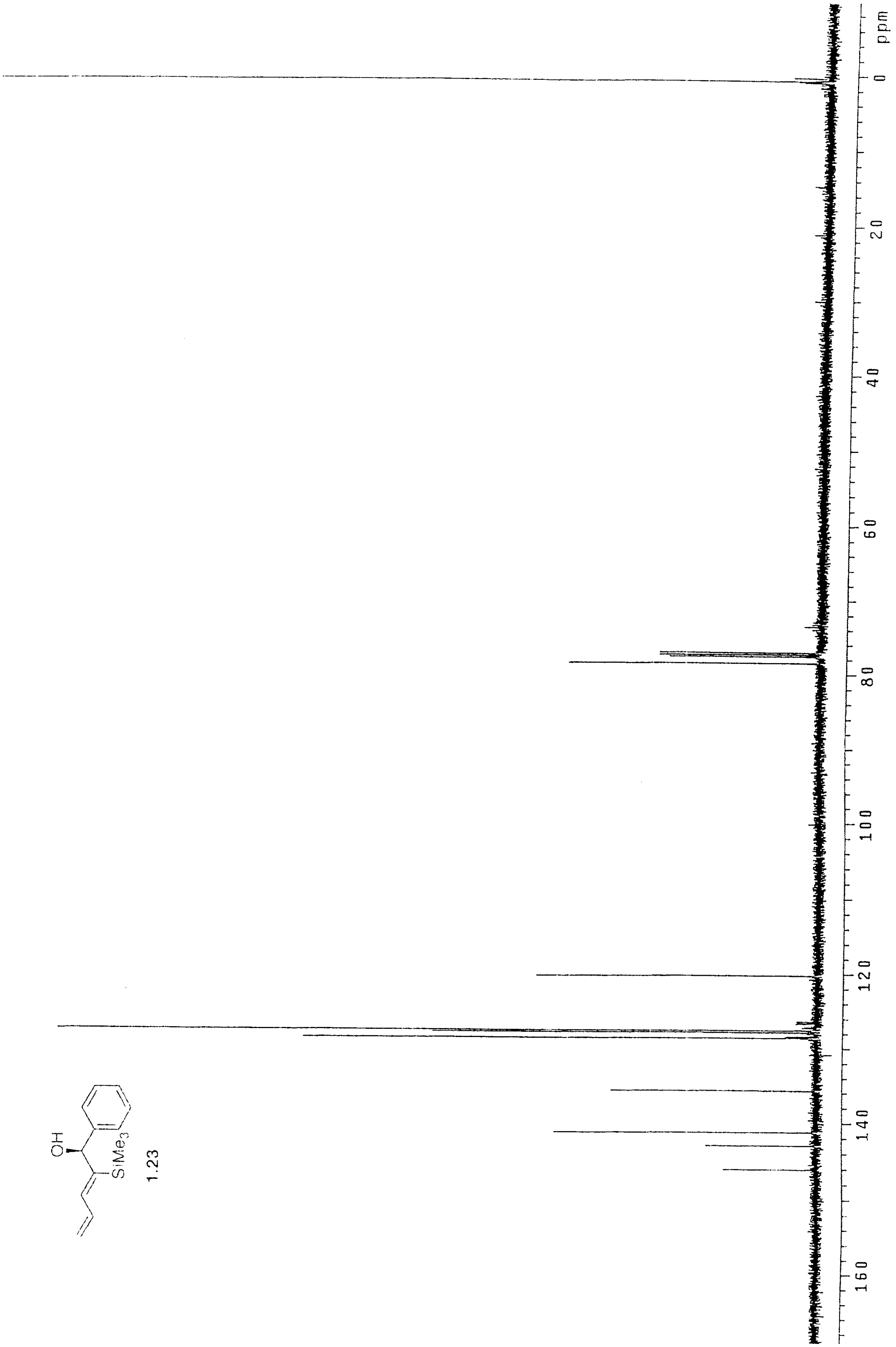

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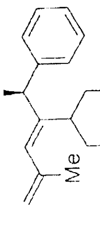

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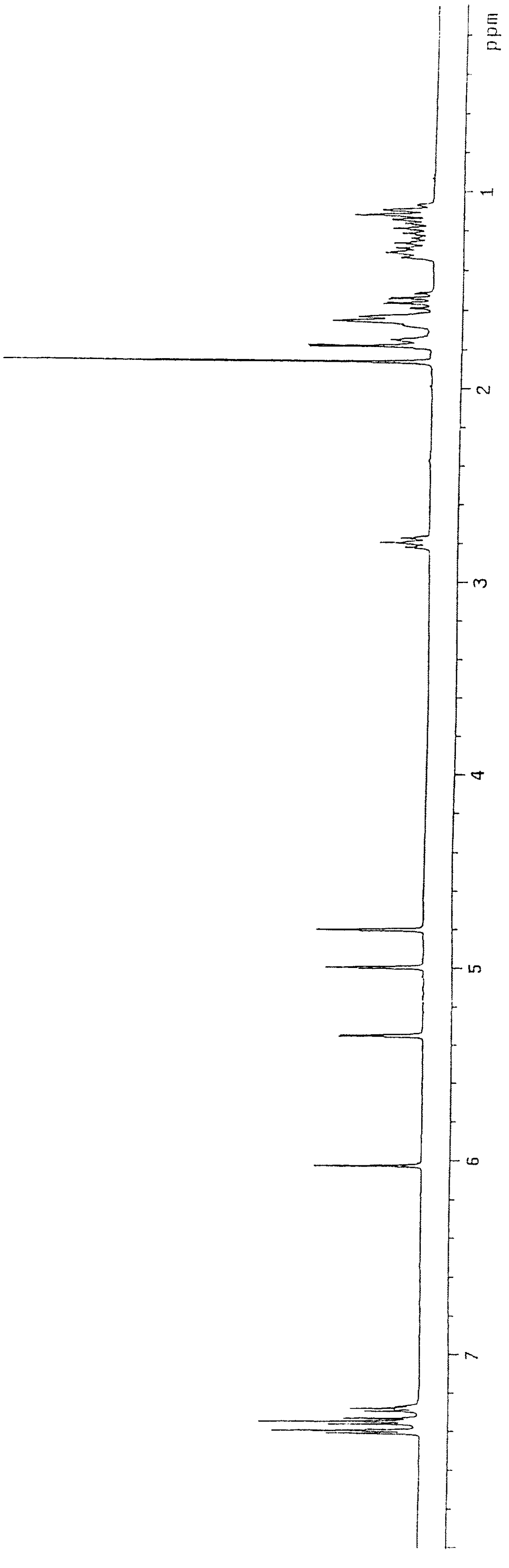

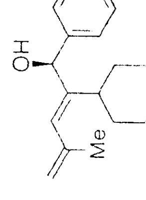

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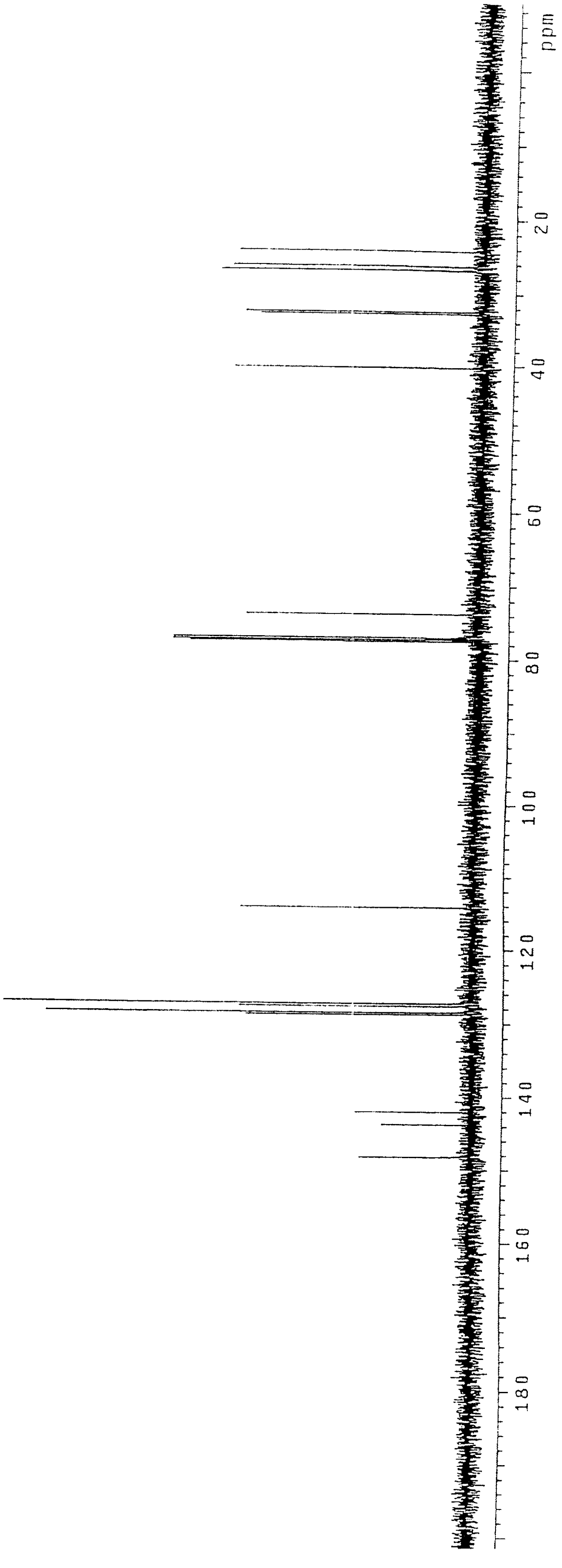

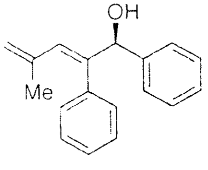

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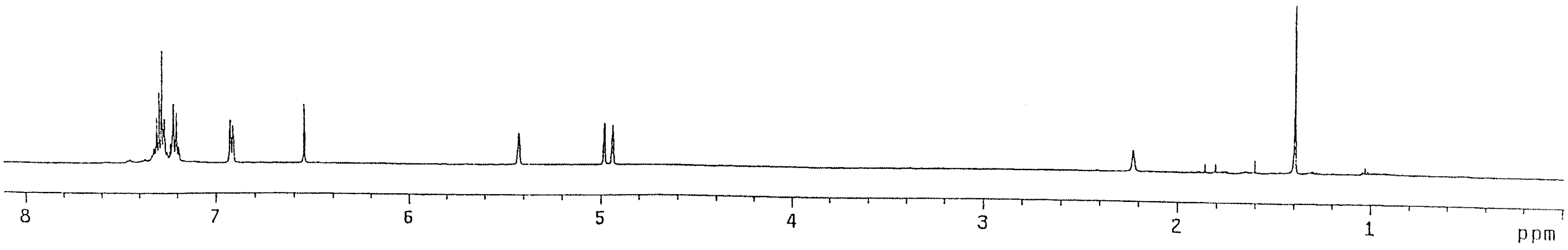

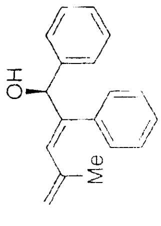

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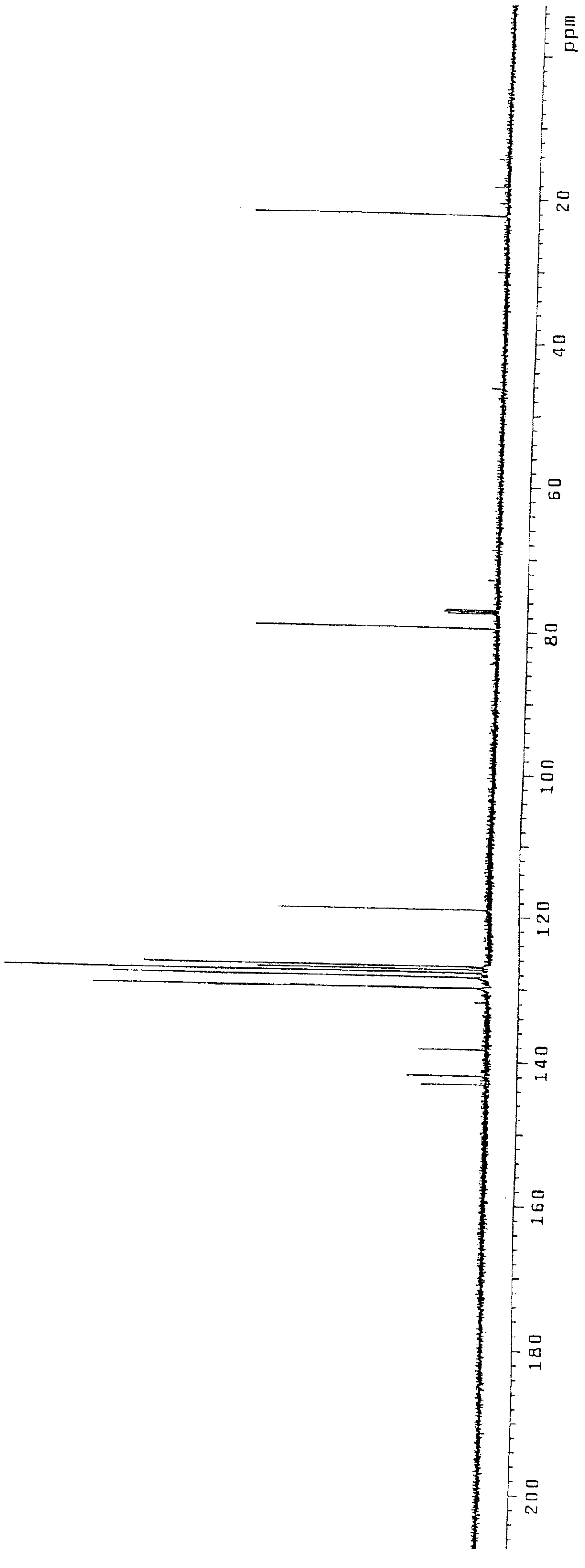

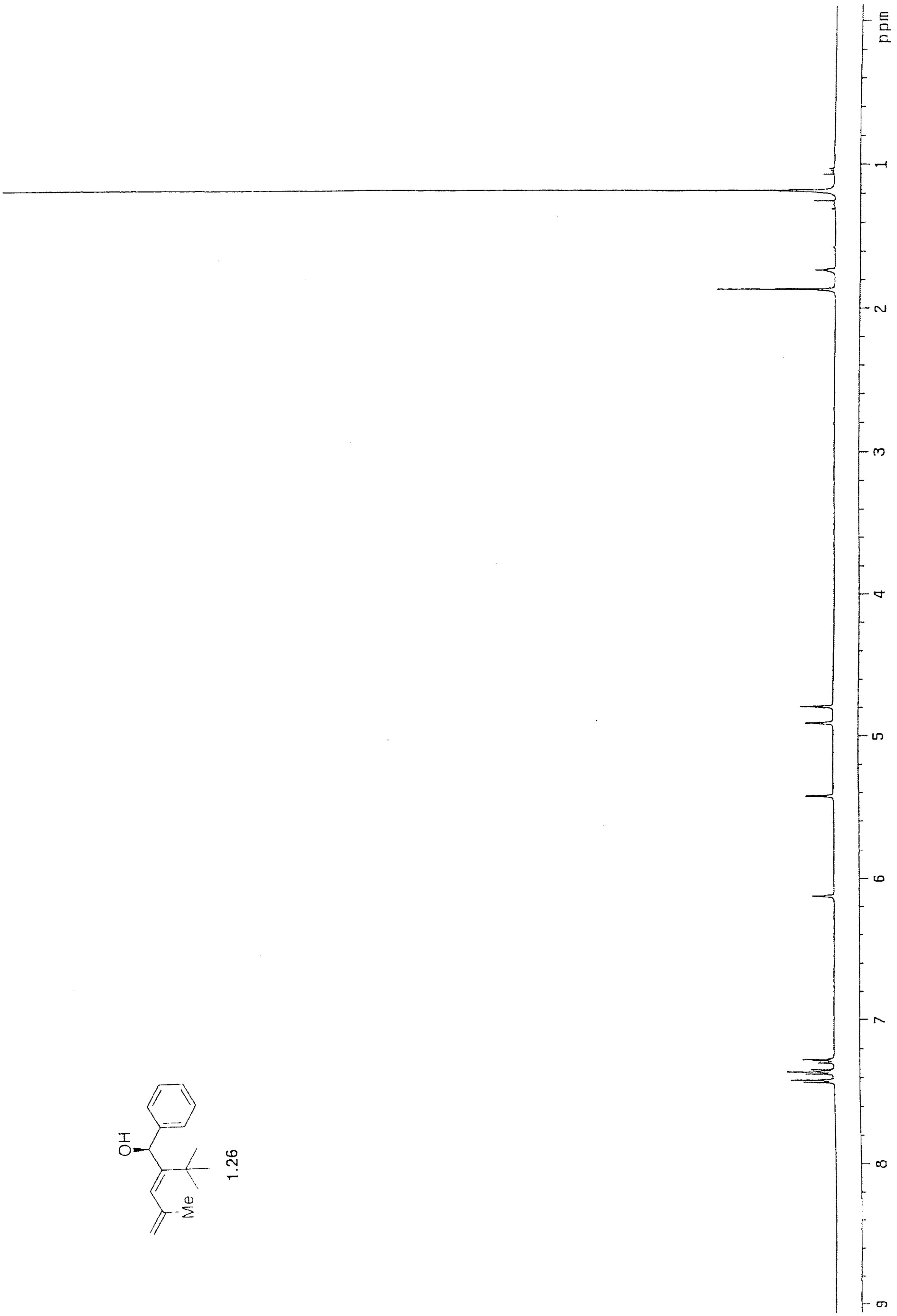

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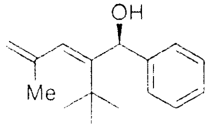

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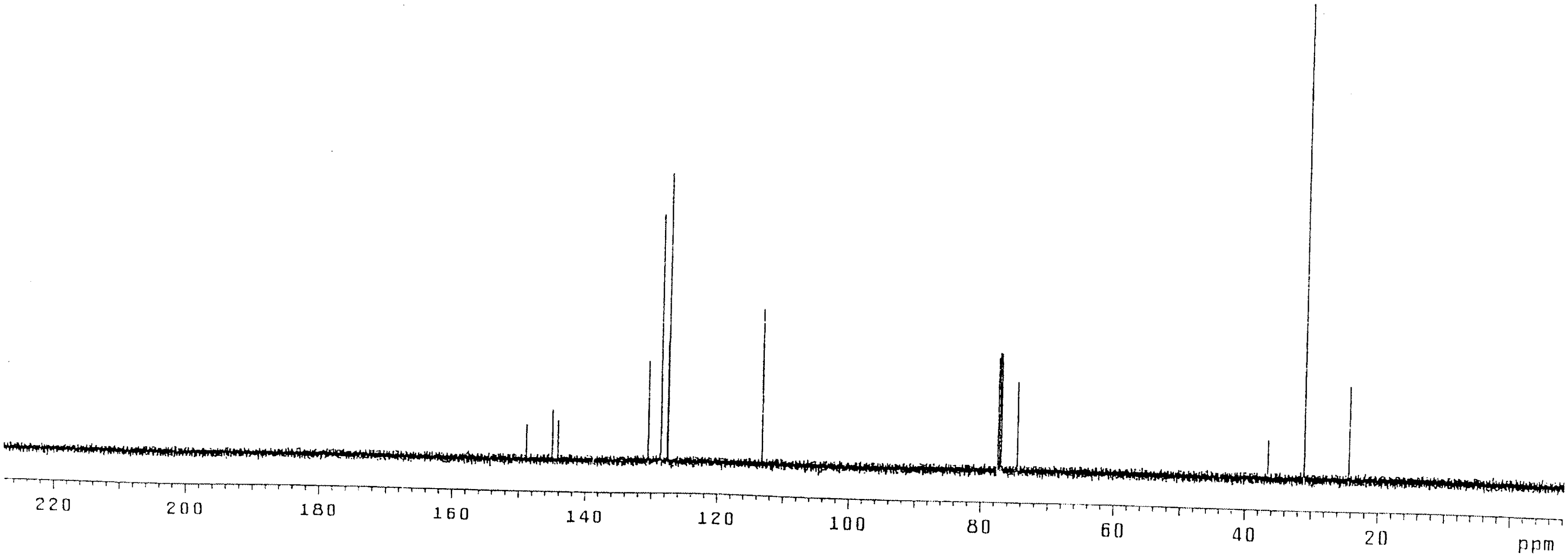

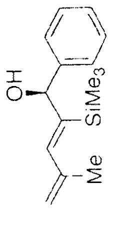

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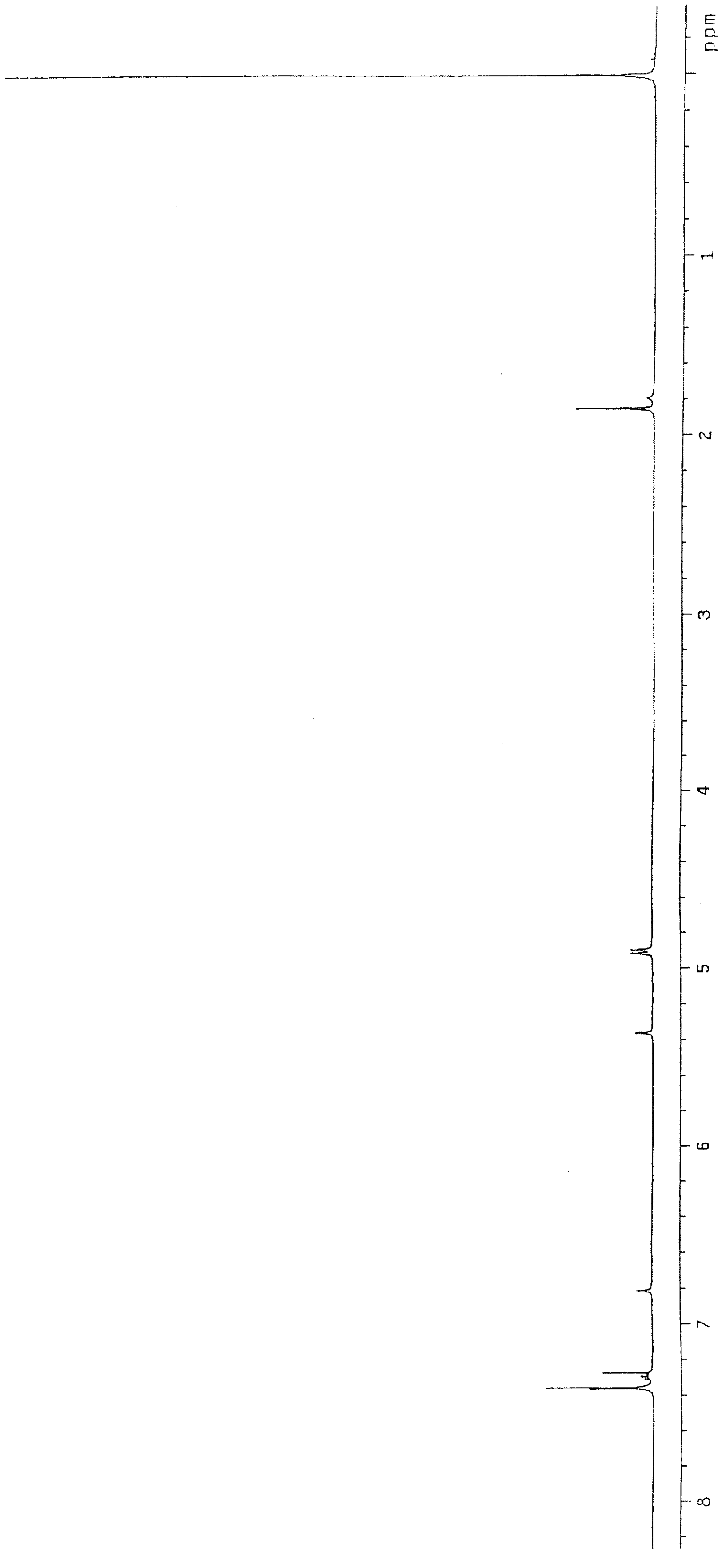

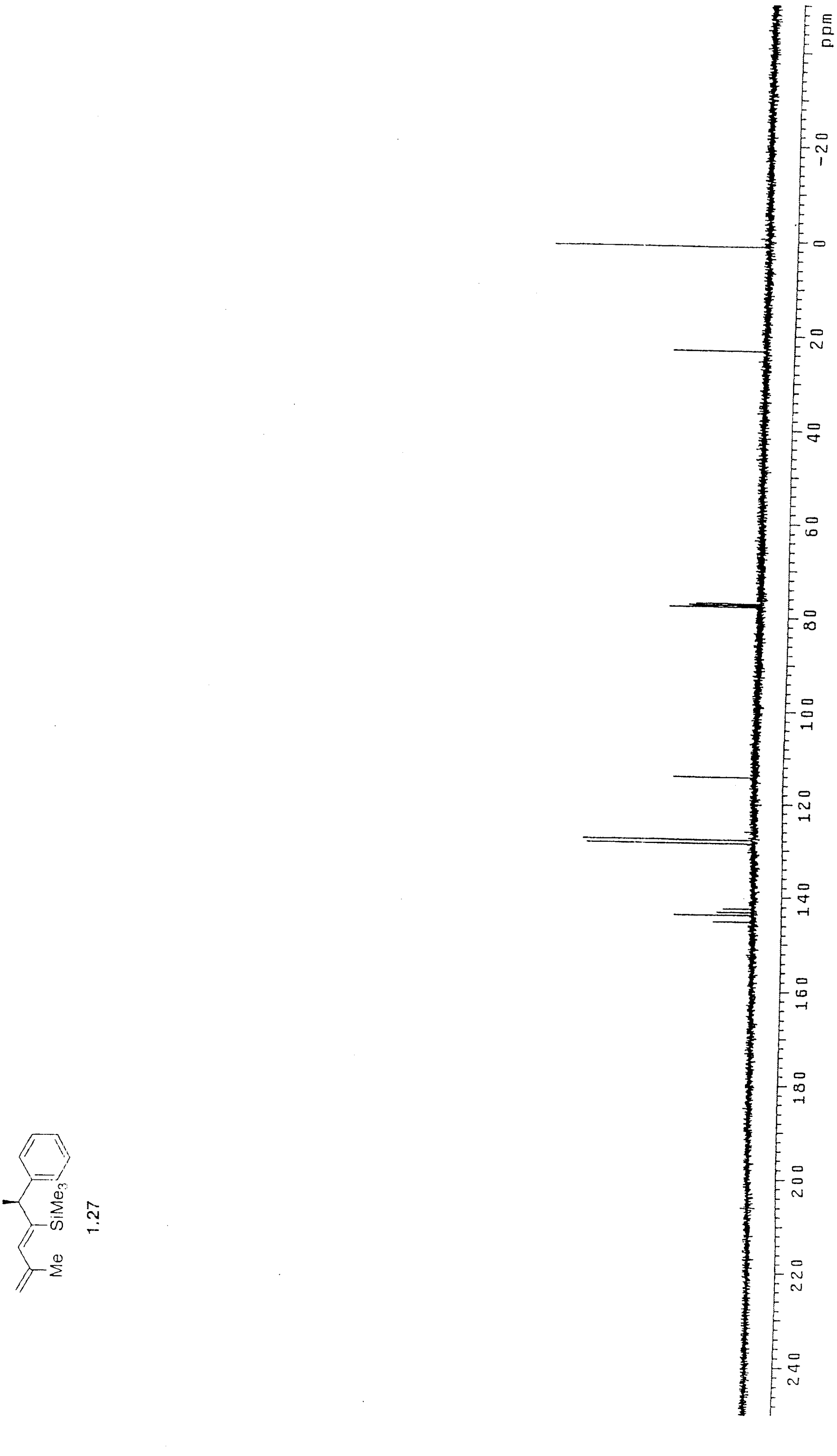

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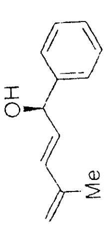

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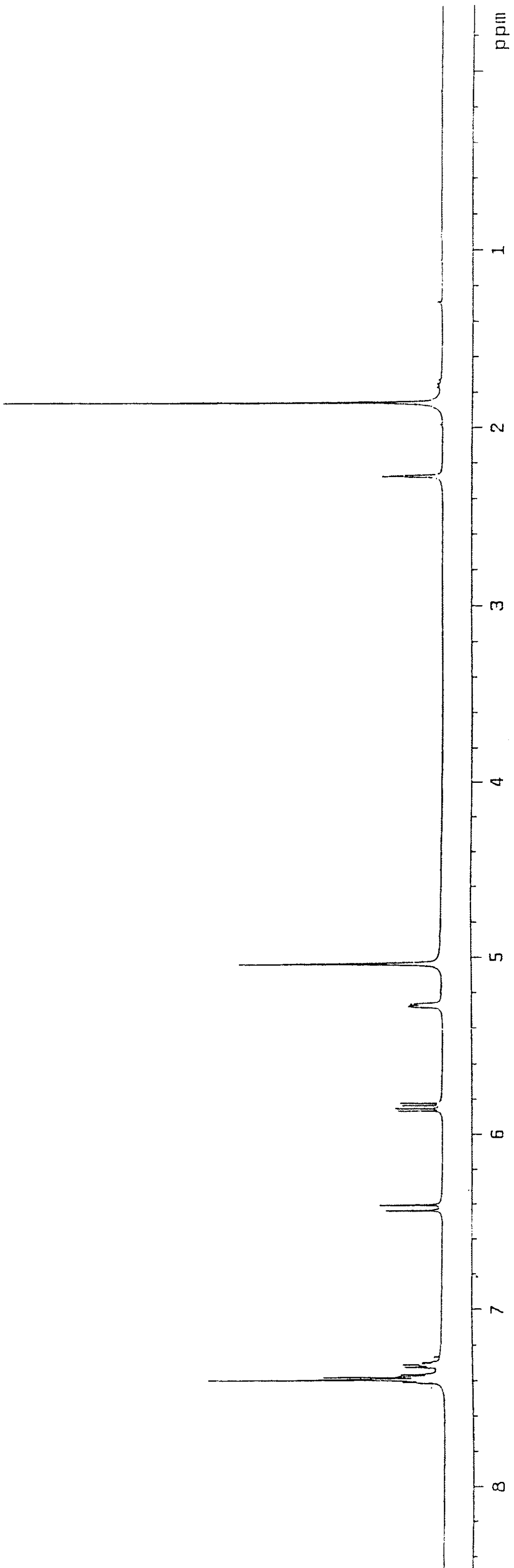

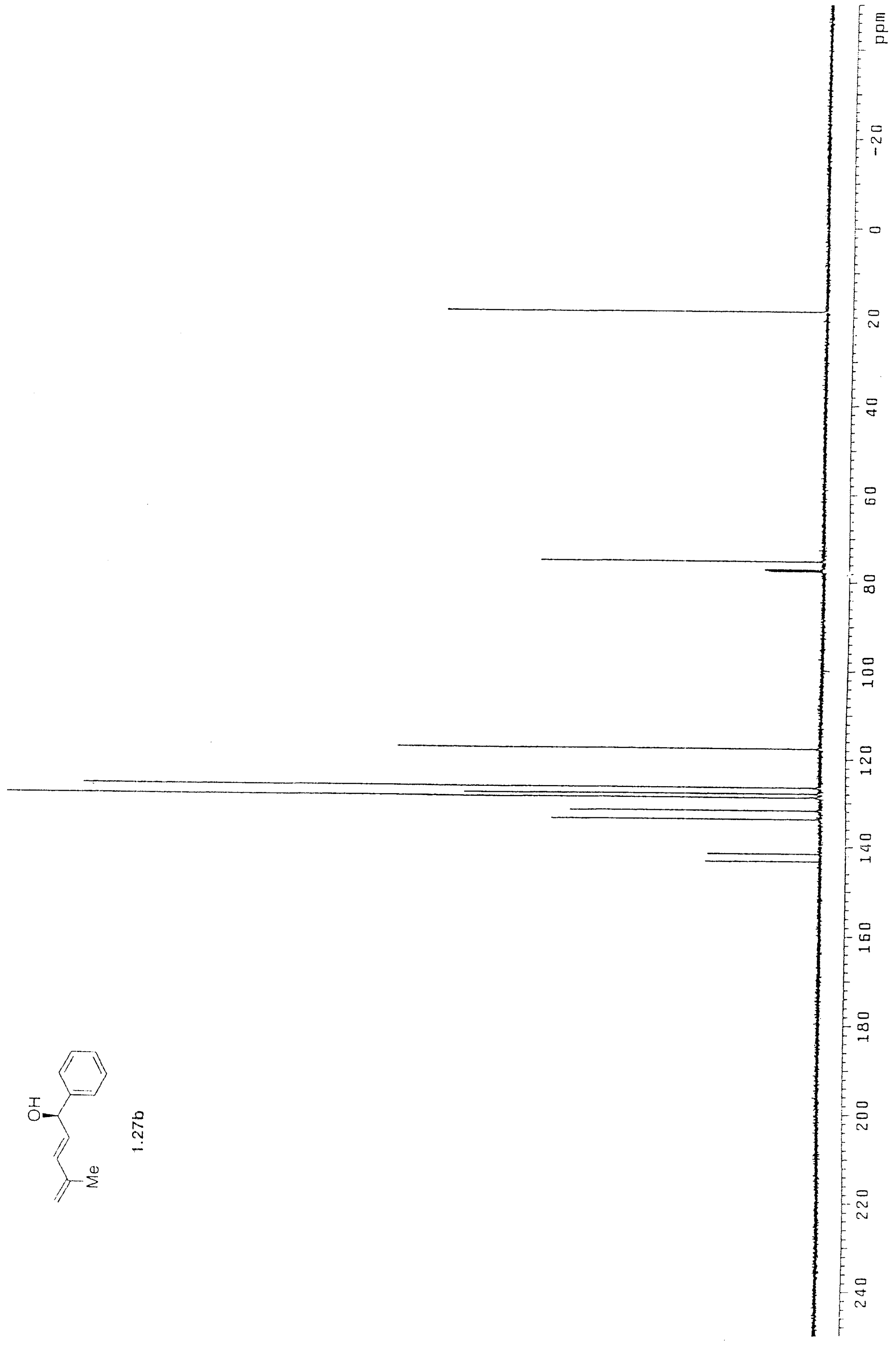
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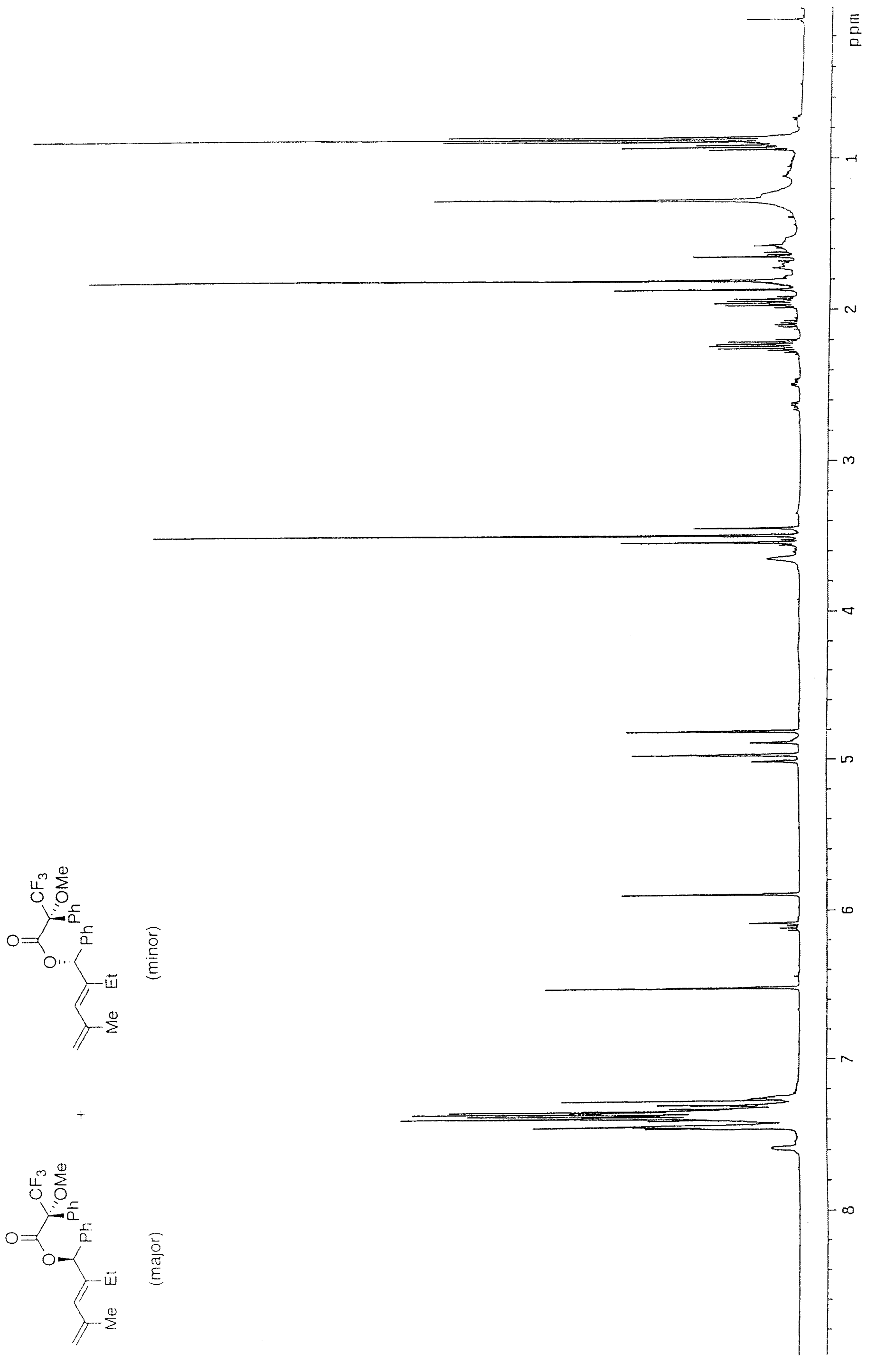

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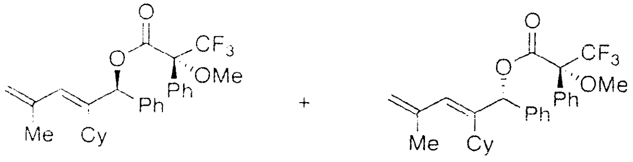

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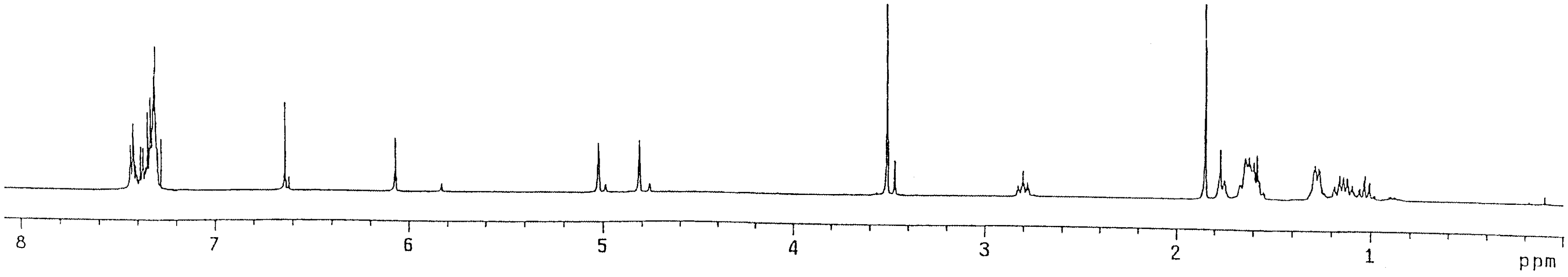


Chapter 2

Catalytic, Asymmetric, Intramolecular Reductive Coupling of 1,1-Disubstituted Epoxides and Alkynes: Total Syntheses of Pumiliotoxins 209F and 251D.

Introduction

The pumiliotoxins were first isolated in the 1970's from the *Dendrobates pumilio* frogs in South America.[1,2] These molecules are potent cardiotonics and cause increased chronotopic and inotropic effects,[3] with the most potent of the class being pumiliotoxin B (pumiliotoxin 323A). There are over thirty known pumiliotoxins, and all consist of a common indolizidine framework, displaying a tertiary alcohol at C8, and an *exo*-cyclic double bond (representative pumiliotoxins are shown in Figure 1). Interestingly, the only variance in the pumiliotoxin family occurs at the alkylidene appendage. This consistency enables the possibility of developing a concise method for the synthesis of the indolizidine core and for subsequent diversification to generate the entire family. As such, several total and partial syntheses of the pumiliotoxin molecules have been reported.[4,5,6,7]

---

[1] (a) Daly, J. W.; Myers, C. W. *Science* **1967**, *156*, 970-973. (b) Daly, J. W.; Tokuyama, T.; Fujiwara, T.; Highet, R. J.; Karle, I. L. *J. Am. Chem. Soc.* **1980**, *102*, 830-836.

[2] For a review on pumiliotoxins: Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556-1575.

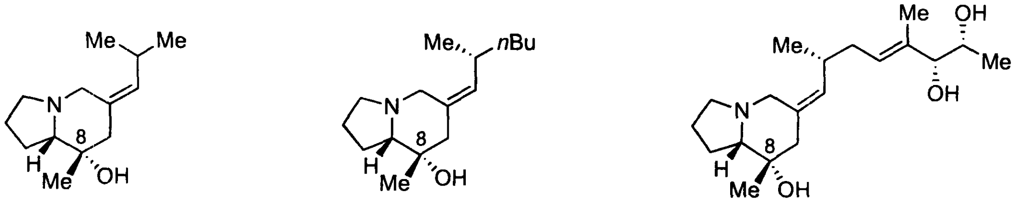
[3] (a) Daly, J. W.; McNeal, E.; Ito, F.; Overman, L. E. *J. Med. Chem.* **1988**, *31*, 477-480. (b) Bargar, T. M., Lett, R. M.; Johnson, P. L.; Hunter, J. E.; Chang, C. P.; Pernich, D. J.; Sabol, M. R.; Dick, M. R *J. Agric. Food. Chem.* **1995**, *43*, 1044-1051.

[4] Total syntheses of 209F: (a) Overman, L. E.; Lesuisse, D. *Tetrahedron Lett.* **1985**, *26*, 4167-4170. (b) Kibayashi, C,; Aoyagi, S. *Synth. Org. Chem., Jpn.* **1999**, *57*, 981-992. (c) Sudau, A.; Münch, W.; Bats, J.-W.; Nubbemeyer, U. *Eur. J. Org. Chem.* **2002**, 3315-3325.

[5] Total syntheses of 251D: (a) Overman, L. E.; Bell, K. L. *J. Am. Chem. Soc.* **1981**, *103*, 1851-1853. (b) Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. *J. Am. Chem. Soc.* **1991**, *113*, 2652-2656; (c) Bargar, T. M.; Lett, R. M.; Johnson, P. L.; Hunter, J. E.; Chang, C. P.; Pernich, D. J.; Sabol, M. R.; Dick, M. R. *J. Agric. Food Chem.* **1995**, *43*, 1044-1051. (d) see ref 4c.

[6] Formal syntheses of pumiliotoxin class: (a) Honda, T.; Hoshi, M.; Kanai, K.; Tsubuki, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2091-2101. (b) Cossy, J.; Cases, M.; Pardo, D. G. *Synlett* **1996**, 909-910; (c) Barrett, A. G. M. Damiani, F. *J. Org. Chem.* **1999**, *64*, 1410-1411. (d) Martin, S. F.; Bur, S. K. *Tetrahedron* **1999**, *55*, 8905-8914. (e) Ni, Y.;

Figure 1. Representative pumiliotoxins.



209F **251D** **323A**

We became attracted to these compounds due to the tertiary homoallylic alcohol moiety common to these natural products. Previous work in the Jamison group has shown that nickel-catalyzed reductive coupling of alkynes with epoxides produces homoallylic alcohols, and more importantly, this methodology was most efficient for intramolecular couplings (Scheme 1).[8] This reaction proceeds with high regioselectivity when an aryl group is present on the alkyne and with *endo* opening of the epoxide.[9] Of equal significance, the configuration of the epoxide is retained in the homoallylic alcohol product.

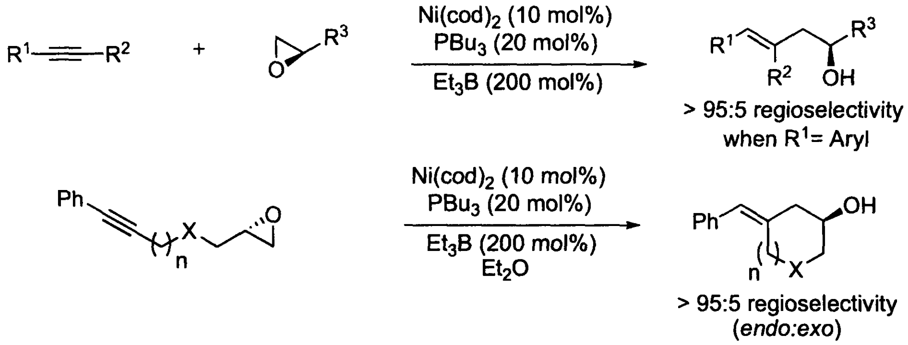
Zhao, G.; Ding, Y. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3264-3266. (f) Wang, B.; Fang, K.; Lin, G.-Q. *Tetrahedron Lett.* **2003**, *44*, 7981-7984.

[7] For a review on other pumiliotoxin syntheses: Franklin, A. S.; Overman, L. E. *Chem. Rev.* **1996**, *96*, 505-522.

[8] Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 8076-8077.

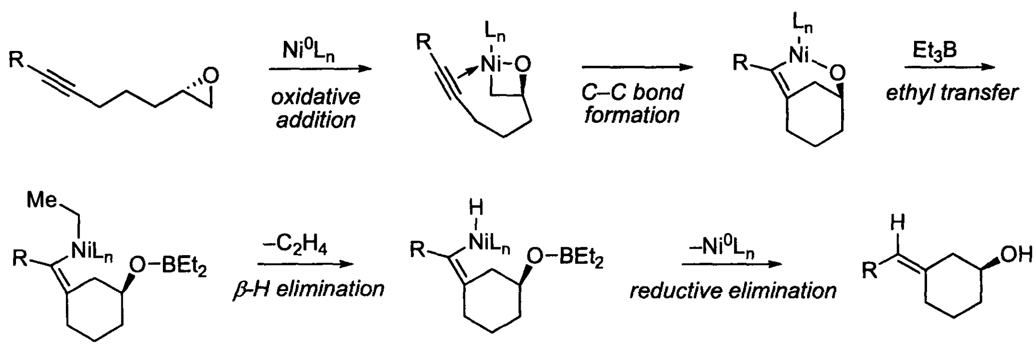
[9] *Exo* opening of epoxides is typically favored and the existing alkyne-epoxide reductive cyclizations follow this trend: (a) Mellor, M.; Santos, A.; Scovell, E. G.; Sutherland, J. K. *J. Chem. Soc., Chem. Commun.* **1978**, 528-529. (b) Amupitan, J. A.; Scovell, E. G.; Sutherland, J. K. *J. Chem. Soc., Perkin Trans. 1* **1983**, 755-757. (c) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986-997. (d) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849-12859. (e) Gansäuer, A.; Pierobon, M.; Bluhm, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 101-103.

Scheme 1. Inter- and intramolecular coupling of epoxides and alkynes.



A new mechanism was proposed to help support the *endo* regioselectivity observed during cyclizations.[8] It was suggested that the epoxide could oxidatively insert into the phosphine-nickel(0) complex regioselectively on the less hindered side of the C-O bond of the epoxide, thereby forming a metallaoxetane (Scheme 2). An exo-dig cyclization, followed by the transfer of an ethyl group from Et_3B, allows for the subsequent β-H elimination to form a nickel hydride species. Finally, reductive elimination would recycle the nickel catalyst, producing the observed product where the newly formed bonds add *syn* across the alkyne.

Scheme 2. Proposed mechanism for the reductive cyclization.



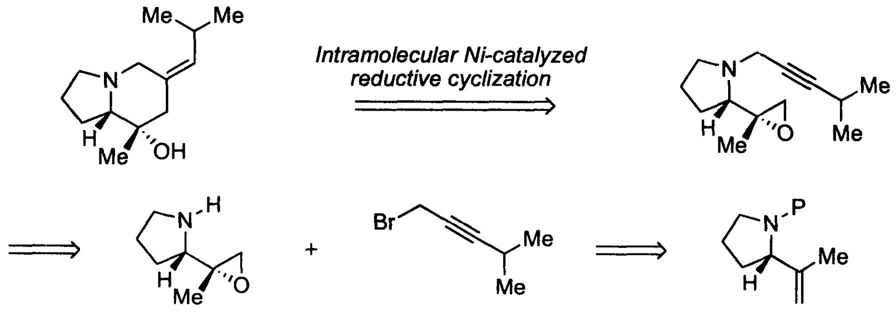
Similarly, we envisioned that the reductive coupling of alkynes and 1,1-disubstituted epoxides, would generate tertiary homoallylic alcohols for the synthesis of the members of the pumiliotoxins (Scheme 3). The main challenge with implementing this strategy was to overcome the poor reactivity anticipated for these 1,1-disubstituted epoxides. In fact, it has been found that sterically hindered epoxides, such as α-branched terminal epoxides, react very poorly under standard intermolecular reaction conditions.[10] Despite this limitation, this method would be valuable for installing the tertiary allylic alcohol present in all naturally occurring members of the pumiliotoxin family. Previously established methods of catalytic intramolecular coupling of 1,1-disubsituted epoxides with alkynes include Lewis acid-based[9a,b] or titanium-mediated conditions.[9d,e]

Catalytic, Asymmetric, Intramolecular Reductive Coupling of 1,1-Disubstituted Epoxides and Alkynes: Total Syntheses of Pumiliotoxins 209F and 251D.

Synthesis of the Reductive Coupling Precursor of Pumiliotoxin 209F

The retrosynthetic analysis of the pumiliotoxin core (shown for pumiliotoxin 209F) involves an intramolecular reductive cyclization of a proline-derived epoxy-alkyne in the penultimate step (Scheme 3). The first approach involved assembly of the epoxy-alkyne through an early stage epoxidation, followed by a late-stage propargylation. This approach would facilitate convergent synthesis of various members of this natural product class from a common intermediate.

Scheme 3. Retrosynthetic analysis for pumiliotoxin 209F.



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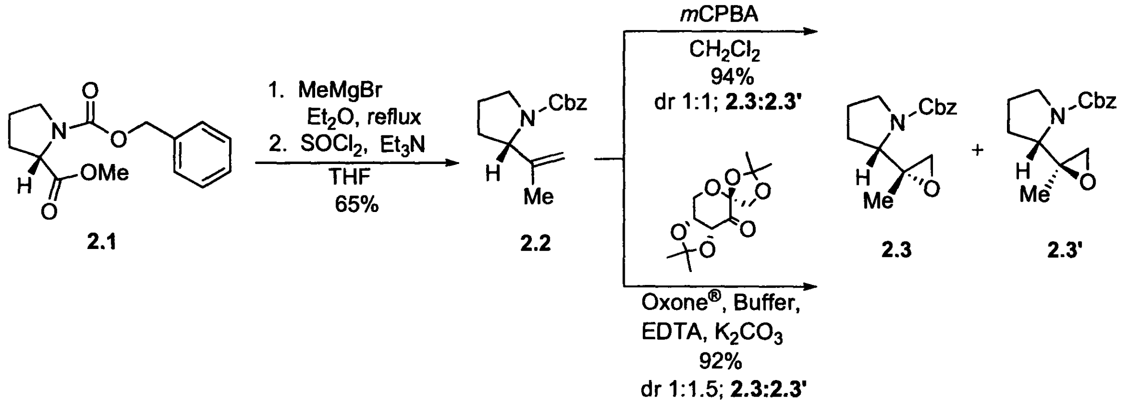
[10] Sparling, B. A.; Simpson, G. L.; Jamison, T. F. Unpublished results.

The synthesis of the reductive coupling precursor was based on a route previously described by Overman (Scheme 4).[11] Commercially available Cbz-protected proline methyl ester **2.1** was treated with a Grignard reagent, and the resulting tertiary alcohol product was subsequently treated with thionyl chloride to force an elimination reaction to provide alkene **2.2** in 65% yield over the two steps. Next, epoxidation of the alkene via treatment with *m*CPBA produced **2.3/2.3'** in 94% yield, but as a 1:1 mixture of diastereomers.[12] When Shi ketone epoxidation conditions were applied,[13] the diastereomeric epoxides **2.3/2.3'** were obtained in 92% yield, providing a 1:1.5 mixture, favoring the undesired epoxide isomer **2.3'**.

Scheme 4. Synthesis of Cbz-protected epoxides.



Alternatively, alkene **2.2** was dihydroxylated[14] with AD-mix-α or -β to provide diols **2.4/2.4'** in 49% yield (100% BRSM) but in 1:4 d.r. favoring the *epi* isomer **2.6** (Scheme 5). Epoxides **2.3** and **2.3'** were then synthesized by a straightforward epoxidation via the mesylate in a combined yield of 89%, again favoring epoxide **2.3'**.

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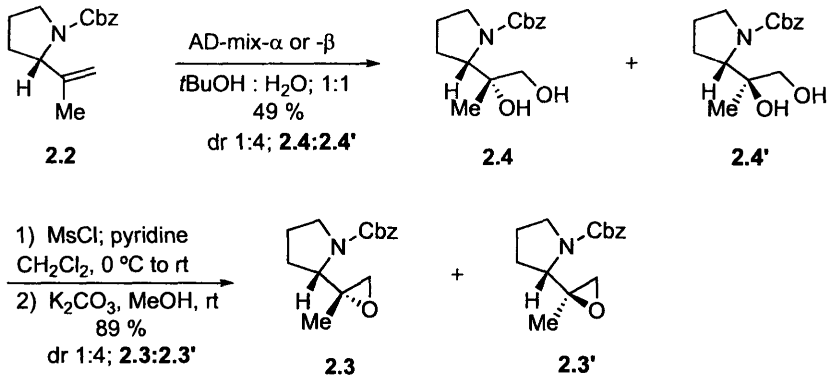
[11] Overman, L. E.; Bell, K. L. *J. Am. Chem. Soc.* **1981**, *103*, 1851-1853.

[12] The stereochemical identities of the product epoxides were established by comparing them to literature values, see ref. 5a.

[13] Warren, J. D.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7675-7677.

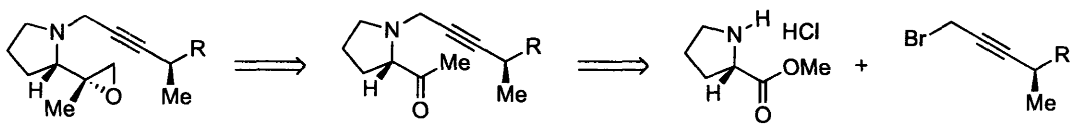
[14] Jacobsen, E. N.; Marko, I.; Mungall, G. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968-1970.

Scheme 5. Alternative route to the Cbz-protected epoxides.



Since these methods either failed to impart diastereoselectivity or favored the wrong diastereomer of the epoxide, the approach was revised to include an early stage propargylation, followed by a late stage epoxidation, which would potentially be selective to favor the desired diastereomer (Scheme 6).

Scheme 6. Revised retrosynthetic analysis for pumiliotoxin 209F.



The first step in this new sequence was the propargylation of the proline methyl ester **2.5** with bromide **2.6**[15] to form substrate **2.7** (Scheme 7). A variety of bases (*i*Pr$_2$EtN, Et$_3$N, NaH, K$_2$CO$_3$, Na$_2$CO$_3$, NaHCO$_3$), solvents (THF, Et$_2$O, DCM, DMF), reaction times, temperatures and reagent stoichiometries were screened, and the best yield obtained was 72% employing *i*Pr$_2$EtN as the base in THF for eight hours (Scheme 7). Reductive amination was also investigated but was unsuccessful due to the unproductive side reactions observed with the aldehyde (not shown).

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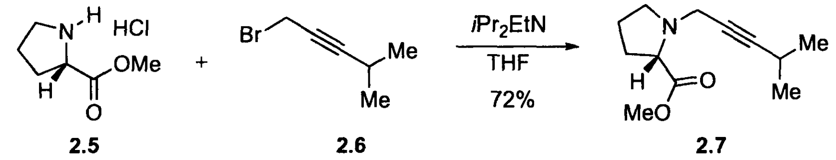
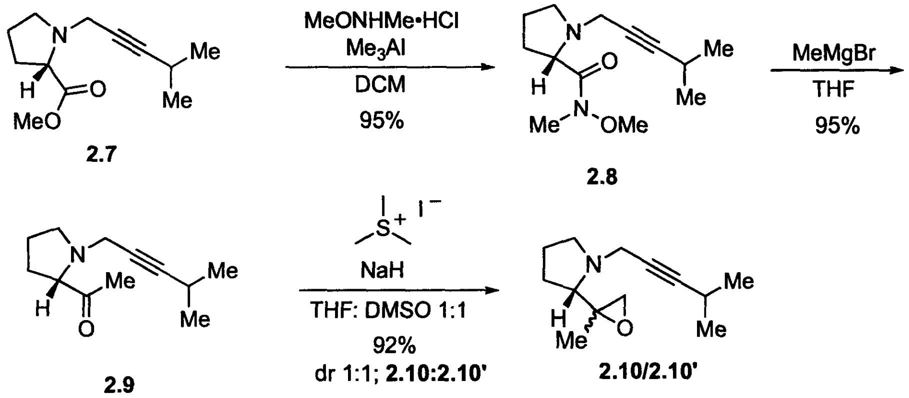
[15] Propargyl bromide **2.6** was prepared by treatment of a propargyl alcohol with CBr$_4$ and PPh$_3$ in CH$_2$Cl$_2$. Alcohol was prepared from 2-methylpropyne and paraformaldehyde; see experimental section for more detail.

Scheme 7. Coupling of proline methyl ester and propargyl bromide.



The next steps involved formation of the Weinreb amide **2.8**, followed by treatment with a Grignard reagent to give the desired ketone **2.9** in 90% yield over the two steps (Scheme 8). Applying Corey-Chaykovsky sulfur ylide conditions[16] to the epoxidation of ketone **2.9** yielded 92% of epoxide **2.10/2.10'**, albeit as a 1:1 mixture of diastereomers. Nevertheless, the reductive coupling precursor was synthesized in 51% overall yield and in only six steps from commercially available materials.

Scheme 8. Synthesis of a diastereomeric mixture of the reductive coupling precursor.



A final strategy was then evaluated for the synthesis of the reductive coupling precursor. Instead of epoxidizing the propargyl-proline structure, epoxidation of the carbamate-protected proline-derived ketone followed by deprotection and propargylation

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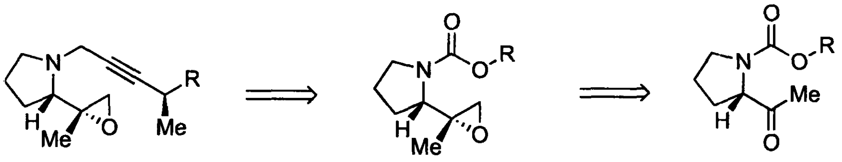
[16] Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353-1364.

was considered. Indeed, previous results from the Thomas laboratory suggested that a substrate of this type may be more amenable to diastereoselective epoxide formation.[17]

Scheme 9. Final strategy for pumiliotoxin 209F.



The Weinreb amide **2.12** was formed initially from a protected proline methyl ester **2.11.**[18] Treatment with methylmagnesium bromide as before formed methyl ketone **2.13**. Various carbamate protecting groups were surveyed (Table 1), and it was observed that Weinreb amide formed in moderate to excellent yields for all cases. Notably, trimethyl aluminum, typically used for the formation of the Weinreb amide, led to decomposition of the Teoc protected substrate **2.11d**. However, this problem was circumvented by using isopropylmagnesium bromide to generate the Weinreb amide substrate instead leading to the desired **2.12d** in 82% yield. Formation of the ketone proceeded uneventfully for Cbz, Teoc, and Alloc protected substrates. However, both Fmoc and Nvoc proved too base-labile under a variety of conditions to warrant further investigation.

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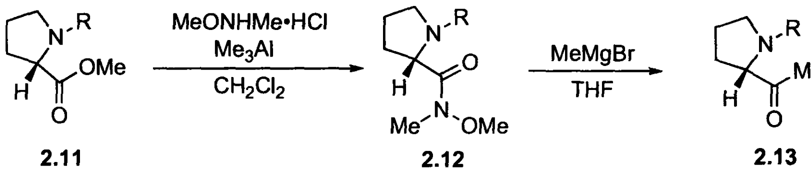
[17] Fray, M. J.; Thomas, E. J.; Wallis, J. D. *J. Chem. Soc.; Perkin Trans. I* **1983**, 395-401.

[18] Carbamate methyl esters were either commercially available or made in one step in quantitative yield in all cases.

Table 1.



R	% Yield (2.12)	% Yield (2.13)
Cbz (**2.11a**)	75 (**2.12a**)	47 (**2.13a**)
Fmoc (**2.11b**)	60 (**2.12b**)	20 (**2.13b**)[b]
Nvoc (**2.11c**)	60 (**2.12c**)	0 (**2.13c**)[b]
Teoc (**2.11d**)	82 (**2.12d**)[a]	65 (**2.13d**)
Alloc (**2.11e**)	95 (**2.12e**)	70 (**2.13e**)

(a) *i*PrMgBr used instead of Me$_3$Al during amide formation. (b) Product proved unstable to base.

Next, we addressed the formation of the protected epoxides via Corey-Chaykovsky sulfur ylide conditions (Table 2). When ketone **2.13a** was subjected to dimethylsulfonium methylide, the undesired diastereomer of the epoxide **2.14a'** was formed in 80% yield (94:6 dr). Remarkably, when ketone **2.13a** was subjected to *dimethyloxosulfonium methylide*, the desired diastereomer of the epoxide **2.14a** formed in 75% yield (>10:1 dr).[16,19] Similarly, both the Teoc and Alloc protected ketone formed the desired epoxide in excellent yield when exposed to optimized dimethyloxosulfonium methylide conditions. Again, the Fmoc protected substrate was too base-labile under the reaction conditions.

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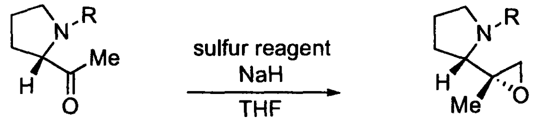
[19] dr determined by ^{1}H NMR integration.

Table 2.



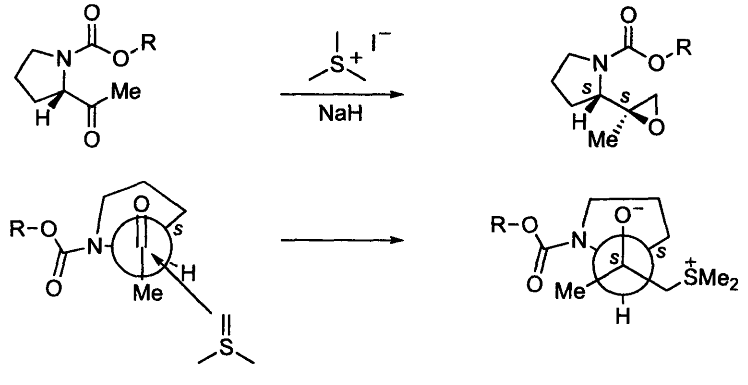
2.13 **2.14**

entry	sulfur reagent	R	% Yield (**2.14**)[a]
1	Me_3SI	Cbz (**2.13a**)	80, 6:96 dr (**2.14a'**)
2	$Me_3S(=O)Cl$	Cbz (**2.13a**)	75, >10:1 dr (**2.14a**)
3	"	Fmoc (**2.13b**)	0 (**2.14b**)
4	"	Teoc (**2.13d**)	95, >10:1 dr (**2.14d**)
5	"	Alloc (**2.13e**)	95, >10:1 dr (**2.14e**)

(a) Yield and dr reflect product distribution of desired:undesired diastereomer.

The complete turnover in diastereoselectivity demonstrated the sensitivity of these pyrrolidines to the reagent employed and deserves some comment. It is well understood that the dimethylsulfonium methylide reacts under kinetic control.[20] Drawing on this analysis, one can invoke a Felkin-Ahn transition state (Scheme 10), whereby the nucleophile approaches *anti* to the carbamate group, forming an *S*-centered betaine. The betaine then rapidly cyclizes to form the observed *S*-centered epoxide.

Scheme 10. Epoxidation under kinetic control.



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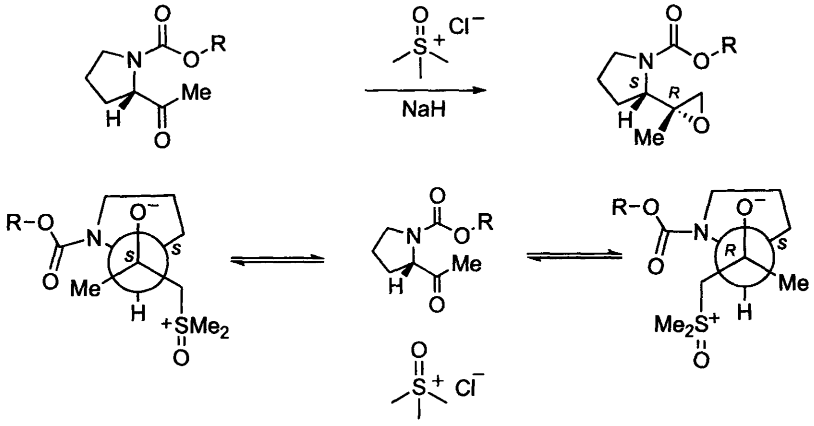
[20] Kinetic vs. thermodynamic control with sulfur ylides: Johnson, C. R.; Schroeck, C. W.; Shanklin, J. R. *J. Am. Chem. Soc.* **1973**, *95*, 7424-7431.

Conversely, dimethylsulfoxonium methylide reagent reacts under thermodynamic control. The formation of the desired *R*-centered epoxide is favored under these conditions due to possible developing stereoelectronic interactions (Scheme 11).[21]

Scheme 11. Epoxidation under thermodynamic control.



However, a major concern was that during the epoxidation the ketone could racemize before forming the epoxide due to the basic nature of the ylide.[22] It was later discovered that this was in fact the case, and although the reaction proceeded with high yield and high dr, a racemic mixture of two epoxides was produced (Table 3, entry 1).[23] When only one equivalent of base was utilized, and using a slight excess of Me_3SOCl, the enantiomeric excess was improved (entry 2). By lowering the temperature to 0 °C, ee of the product was further improved (entries 3-4) at the expense of reactivity and chemical yield. Further lowering of the temperature to -20 °C was successful in preventing racemization (entries 5-7), and the highest yield of 38% was obtained after

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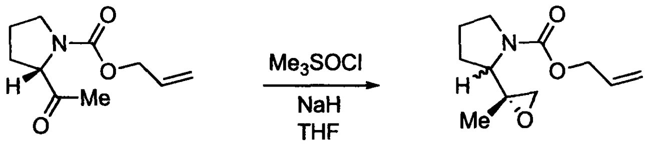
[21] For a discussion of thermodynamic epoxidation of pyrrolidines see ref. 17.

[22] pKa of diemethylsulfoxonium methylide is 18.2 in DMSO.

[23] % ee of ketone determined by chiral GC to be >98% before epoxidation. % ee of epoxide determined by chiral GC; see experimental for more detail.

40h.[24] Increasing the reaction concentration improved yields, but led to a decrease in the ee (entry 8).

Table 3: Various epoxidation conditions and effect on racemization.[25]



>10:1 dr

2.13e **2.14e**

entry^a	temperature	rxn time	mol % NaH	mol % Me$_3$SOCl	yield (%)^b	ee (%)^c
1	0 °C to rt	16h	300	300	95	0
2	0 °C to rt	16h	100	150	20	40
3	0 °C	32h	200	250	29	40
4	0 °C	16h	100	150	19	67
5	-20 °C	24h	"	"	12	>98
6	-20 °C	32h	150	200	32	>98
7	-20 °C	40h	"	"	38	>98
8^d	-20 °C	40h	"	"	91	61

(a) The ylide was pre-formed by refluxing Me$_3$SOCl and NaH for 4.5 hr, and cooling to indicated temperature using a cryogenically cooled bath. The ketone was dissolved in THF in a separate flask and also cooled, then the ylide was transferred to the ketone by dropwise addition via cannula. The reaction was quenched at the reaction temperature with 0.1M NaHSO$_4$. See Experimental Section for more details. (b) Isolated yield after column chromatography. (c) Determined by chiral GC, using a Chiraldex B-OA column. (d) Reaction was on a 0.1M concentration instead of 0.05 M.

It was further discovered that employing *n*butyllithium as a base instead of NaH also prevented racemization of the ketone at lowered temperature (Scheme 12). This reaction was higher yielding, and this base was much more easily quantified in the reaction.[26]

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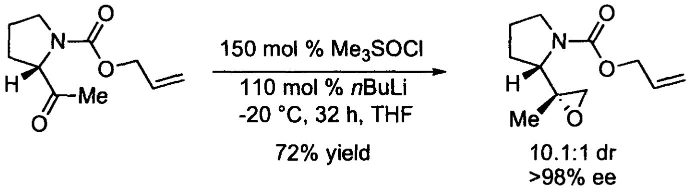
[24] When the reaction was allowed to proceed for longer time periods (i.e. >48 h) the product began to racemize.

[25] Reaction conditions were surveyed on the alloc-protected substrate.

[26] Reaction was ran identically to those in Table 3, see Experimental section for more detail.

Scheme 12. Epoxidation of ketone using *n*BuLi as base to form the ylide.



2.13e

2.14e

The next challenge that was encountered was the deprotection of the Cbz protecting group in the presence of the epoxide. Subjection of epoxide **2.14a** to standard hydrogenation conditions with either Pd/C or $Pd(OH)_2/C$ led to simultaneous reduction to the tertiary alcohol **2.15** (Scheme 13). Attempts to deprotect with $Ba(OH)_2$ were also unsuccessful.[27] Upon treatment with Et_3SiH, Et_3N and $PdCl_2$, the desired deprotection was finally realized.[28] However, this was compounded by the facile replacement with TES, leading to the TES carbamate **2.16**. Treatment of this intermediate with TBAF finally revealed the long sought after free amine **2.17**. This compound was difficult to isolate due to its extreme polarity and rapid decomposition upon exposure to silica gel. Ultimately, coupling of the free amine with the propargyl bromide **2.6** was also difficult and low yielding, forming the desired reductive coupling precursor **2.10** in only 20% yield over the three steps. It is possible that the low yield observed was due to impurities that were not separated from the deprotection step complicated the coupling reaction.

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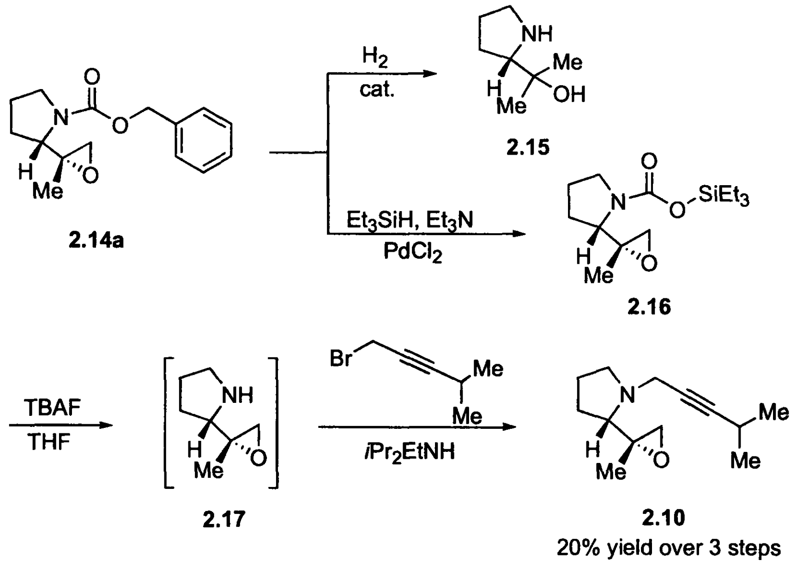
[27] Overman, L. E.; Sharp, M. J. *Tetrahedron Lett.* **1988,** *29,* 901-904.

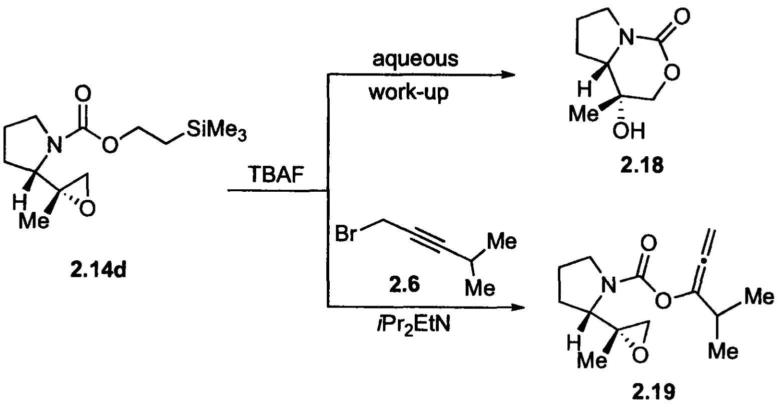
[28] (a) Birkofer, L.; Bierwirth, E.; Ritter, A. *Chem. Ber.* **1961,** *94,* 821-823. (b) Coleman, R.; Carpenter, A. J. *J. Org. Chem.* **1992,** *57,* 5813-5815.

Scheme 13. Deprotection of Cbz and formation of reductive coupling precursor.



In an alternate series, deprotection of the Teoc protecting group also proved challenging. Upon treatment of **2.14d** with TBAF,[29] and after an aqueous work-up, only the cyclic-carbamate product **2.18** was isolated (Scheme 14). Further attempts to trap the intermediate in situ with the propargyl bromide **2.6** were also unsuccessful, and produced the S_N2' product **2.19**.

Scheme 14. Deprotection of the Teoc substrate.



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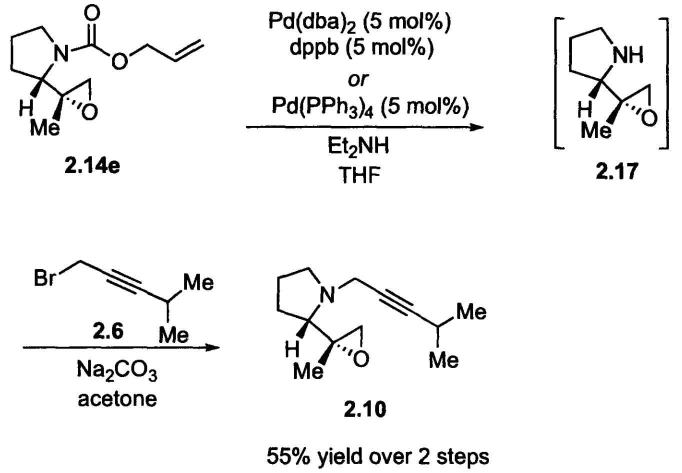
[29] Carpino, L. A.; Sau, A. C. *J. Chem. Soc., Chem. Commun.* **1979**, 514-515.

The Alloc protecting group was also initially difficult to remove and under conditions utilizing a variety of palladium catalysts, the substrate either was not reactive or formed undesired tertiary alcohol side-product **2.15**. However, upon treatment with $Pd(dba)_2$ and dppb or $Pd(PPh_3)_4$[30] in the presence of excess diethyl amine,[31] the free amine **2.17** was produced (Scheme 15). This was subsequently treated with propargyl bromide **2.6** to form the reductive coupling precursor **2.10** in 55% yield over the two steps. Thus in 6 steps and 34% overall yield, the reductive coupling precursor was obtained.

Scheme 15. Deprotection of Alloc and formation of reductive coupling precursor **2.10**.



Intramolecular Nickel-Catalyzed Reductive Coupling to Form Pumiliotoxin 209F

Initial screening for the intramolecular nickel-catalyzed reductive coupling of the 1,1-disubstituted epoxide and alkyne was performed on the 1:1 mixture of diastereomers **2.10/2.10'** due to availability. Various conditions were initially screened, and representative examples are shown in Table 4. It was immediately realized that carrying

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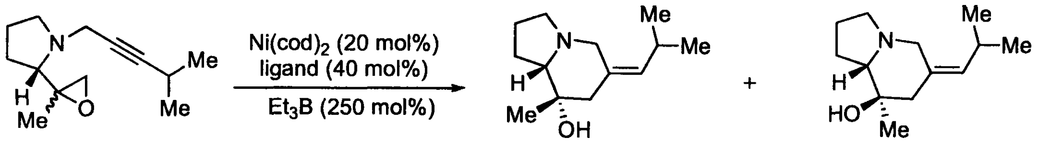
[30] $Pd(PPh_3)_4$ could be used in place of $Pd(dba)_2$ to make purification simpler.

[31] Genêt, J. P.; Blart, E.; Savignac, M.; Lemeune, S.; Lemaire-Audoire, S.; Bernard, J. M. *Synlett*, **1993**, 680-682.

out the reaction in the absence of solvent had a dramatic effect on reactivity to produce **2.20** (corresponding to pumiliotoxin 209 F) and the undesired stereoisomer **2.20'**.[32] Heating the reductive coupling reaction promoted a further increase in the yield of the desired products, with 65 °C representing the maximum improvement. Other ligands were screened (entries 6 and 7), but proved less productive than PBu_3. Interestingly for entries 3-6, the product ratio was ~7:3 **2:20:2.20'**, showing that the desired epoxide was faster to react than the undesired.[33]

Table 4. Initial reductive coupling conditions with diastereomeric mixture.



2.10
1:1 dr

2.20, pumiliotoxin 209 F

2.20', 8-*epi*-pumiliotoxin 209 F

entry[a]	ligand	solvent	temperature	% yield 2.20/2.20'[b]
1	PBu_3	Et_2O	23 °C	0
2	"	neat	"	9[c]
3	"	"	35 °C	13
4	"	"	55 °C	30
5	"	"	65 °C	53
6	P(*n*-octyl)$_3$	"	55 °C	23[c]
7	P(*o*-anisyl)$_3$	"	"	0

(a) Experimental conditions: To $Ni(cod)_2$ and ligand at indicated temperature were added Et_3B and **2.10** in a sealed tube. The reaction was stirred for 16 h, unless otherwise noted. Work-up involved aerobic oxidation and filtration through silica gel. (b) Isolated yield of diastereomers after column chromatography. (c) Not isolated, combined yield of **2.20** and **2.20'** based on ^1H NMR external standard of $MeNO_2$ (500 MHz).

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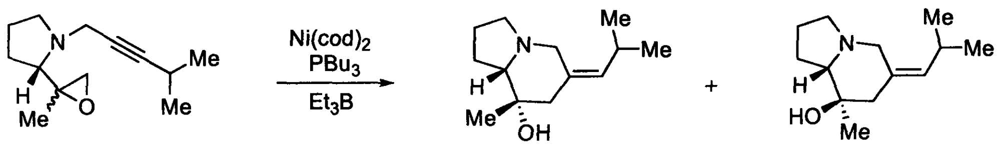
[32] Both isomers were characterized by ^1H NMR, ^{13}C NMR, HRMS, and IR and compared to literature values. **2.20**: (a) Overman, L. E.; Lesuisse, D. *Tetrahedron Lett.* **1985**, *26*, 4167-4170; and **2.20'**: (b) Sudau, A.; Münch, W.; Bats, J.-W.; Nubbemeyer, U. *Eur. J. Org. Chem.* **2002**, 3304-3314.

[33] Also, recovered starting material favored **2.10'** in a ratio of ~7:3 **2.10':2.10**.

Additional conditions were surveyed by changing the stoichiometry of the reagents (Table 5). Lowering the catalyst loadings (entries 1-2) resulted in decreased reactivity. When the catalyst loading was increased (entry 3-5), there was no significant increase in reactivity. Shorter reaction times led to lower yields (4-5), but those greater than 16 hours did not result in significant improvement. Slow addition of Et_3B over 16 hours did not increase the yield appreciably, as the reactivity was hampered by Et_3B evaporation from the reaction because a sealed vessel could not be used.

Table 5. Stoichiometric screening of reductive coupling with diastereomeric mixture.



2.10
1:1 dr

2.20, pumiliotoxin 209 F

2.20', 8-*epi*-pumiliotoxin 209 F

entry[a]	mol % Ni	mol % PBu_3	mol % Et_3B	% yield 2.20/2.21[b]
1	10	20	250	29
2[c]	"	"	"	15
3	50	100	"	32
4[e]	"	"	"	13[d]
5[f]	"	"	"	40
6[g]	"	"	500	41

(a) Experimental conditions: same as Table 4 at 65 °C. (b) Isolated yield of each diastereomer after column chromatography. (c) Reaction conducted at 55 °C. (d) Not isolated, combined yield of **2.20** and **2.21** based on ^1H NMR external standard of $MeNO_2$ (500 MHz). (e) Reaction time of 2 h. (f) Reaction time of 6 h. (g) Slow addition of additional 250 mol % Et_3B over 16 hrs in a test tube with septum (not a sealed tube).

With the positive initial results on the diastereomeric mixture, the reaction was optimized with the diastereomerically-enriched precursor[34] **2.10** (Table 6). Under the optimum conditions given in Table 4, enriched **2.10** cyclized to form the desired

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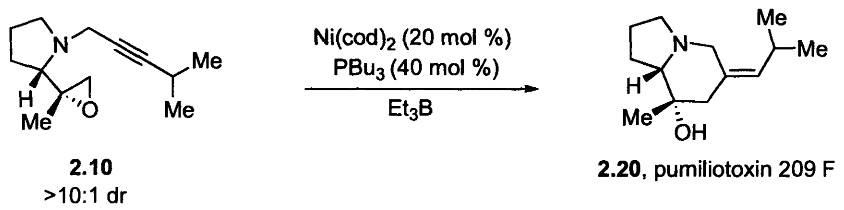
[34] All screening was performed on presumably racemic material; best conditions were repeated on the single diastereomer obtained from lower temperature epoxidation method.

pumiliotoxin 209F in 40% yield as a single diastereomer (entry 1). Lowering the amount of ligand in the reaction led to very little conversion to product. Longer reaction time, as well as addition of more Et_3B, did not improve yield. However, by decreasing the amount of Et_3B (and thus increasing the substrate concentration), the yield of product was increased to 61%.

Table 6. Reductive coupling conditions to form pumiliotoxin 209F.



entry[a]	mol % Et_3B	% yield[b]
1	250	40
2[c]	"	<10
3[d]	"	35
4	500	35
5	150	61

a) Experimental conditions: To $Ni(cod)_2$ and PBu_3 were added Et_3B and **2.10** at 65 °C in a sealed tube. The reaction was stirred for 16 hrs, unless otherwise noted. Work-up involved aerobic oxidation and filtration through silica gel. (b) Isolated yield of 2.21 after column chromatography. (c) Used 1:1 Ni:PBu_3, 20 mol % of each. (d) Reaction time of 44 hrs

A variety of phosphine ligands were also screened for reactivity (Table 7). All phosphinite and phosphite ligands were unsuccessful (entries 2-4). Ligands with larger cone angles than PBu_3 also did not produce any desired product (entry 1). However, when PMe_2Ph was employed the reactivity increased, perhaps due to the small cone angle of the ligand.[35]

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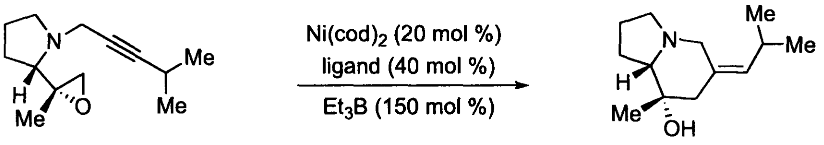
[35] Cone angle of PBu_3 is 132°, whereas the cone angle of PMe_2Ph is 122°; ref: Rahman, M. M.; Liu, H.-Y.; Eriks, K.; Prock, A.; Giering, W. P. *Organometallics* **1989**, *8*, 1-7.

Table 7. Reductive coupling screen of phosphorous-based ligands.



2.10
>10:1 dr

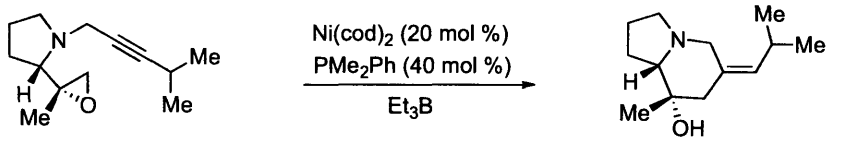
2.20, pumiliotoxin 209 F

entry[a]	ligand	% yield[b]
1	P(Cyc)$_3$	no reaction
2	PPh$_2$OEt	"
3	PPh(OEt)$_2$	"
4	P(OEt)$_3$	"
5	P(CNEt)$_3$	"
6	PMe$_2$Ph	70

a) Experimental conditions: same as Table 6 with indicated ligand and 150 mol % Et$_3$B. (b) Isolated yield of 2.21 after column chromatography.

Finally, employing the PMe$_2$Ph ligand, it was again observed that increasing the amount of Et$_3$B to 250 mol % decreased the reactivity (Table 8, entry 1). Also, decreasing the amount of Et$_3$B to 110 mol % led to decreased reactivity (entry 2), as much of the nickel catalyst remained undissolved in highly concentrated reaction mixture. Increasing the temperature further to 75 °C also led to decreased reactivity. Thus the best condition for the reductive cyclization were obtained by employing 20 mol% Ni(cod)$_2$, 40 mol % PMe$_2$Ph, 150 mol % Et$_3$B, at 65 °C for 16 hours (Table 7, entry 6).

Table 8. Triethylborane screen in the reductive cyclization to form pumiliotoxin 209F.



2.10
>10:1 dr

2.20, pumiliotoxin 209 F

entry[a]	mol % Et_3B	% yield[b]
1	250%	47
2	110%	62
3[c]	150%	55

a) Experimental conditions: same as Table 6 with PMe_2Ph. (b) Isolated yield of 2.21 after column chromatography. (c) Ran reaction at 75 °C.

The spectral data for the synthesis of pumiliotoxin 209F corresponded to natural product isolated from the *Dendrobates pumilio* frogs. The ^1H NMR for pumiliotoxin 209F is somewhat limited (Table 9), but shifts that were previously reported from isolation and from synthetic material correlate well with our synthetic material.[36] The ^{13}C NMR data also correlates well (Table 10).

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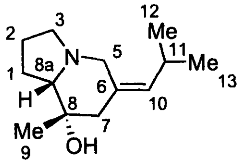
[36] Spectral data found in: (a) Naturally isolated: see ref. 1b. (b) Synthetic: see ref. 4a.

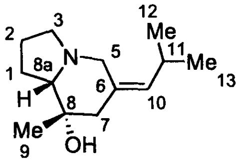
Table 9. ^{1}H NMR data for pumiliotoxin 209F.



2.20, pumiliotoxin 209F

Carbon #	Natural Product 209F	Synthetic 209F	Overman's Synthetic 209F
1	not reported	1.79-1.65 (m, 2H)	not reported
2	"	1.79-1.65 (m, 2H)	"
3	"	3.07 (t, J = 8.3 Hz, 1H)	"
3'	"	2.24-2.20 (m, 1H)	"
5	"	3.80 (d, J = 11.9 Hz, 1H)	3.79 (d, J = 12 Hz, 1H)
5'	"	2.36 (d, J = 11.9 Hz, 1H)	2.32 (d, J = 11.9 Hz, 1H)
7	"	2.12 (d, J = 13.8 Hz, 1H)	not reported
7'	"	2.09 (d, J = 13.8 Hz, 1H)	"
8a	"	1.98 (t, J = 5.0 Hz, 1H)	"
9	"	1.14 (s, 3H)	"
10	"	5.11 (d, J = 9.2 Hz, 1H)	5.10 (d, J = 9.8 Hz, 1H)
11	"	2.60-2.55 (m, 1H	not reported
12	0.99	0.99 (d, J = 6.7 Hz, 3H)	"
13	0.91	0.92 (d, J = 6.7 Hz, 3H)	"
OH	not reported	2.67	"

Table 10. ^{13}C NMR data for pumiliotoxin 209F.



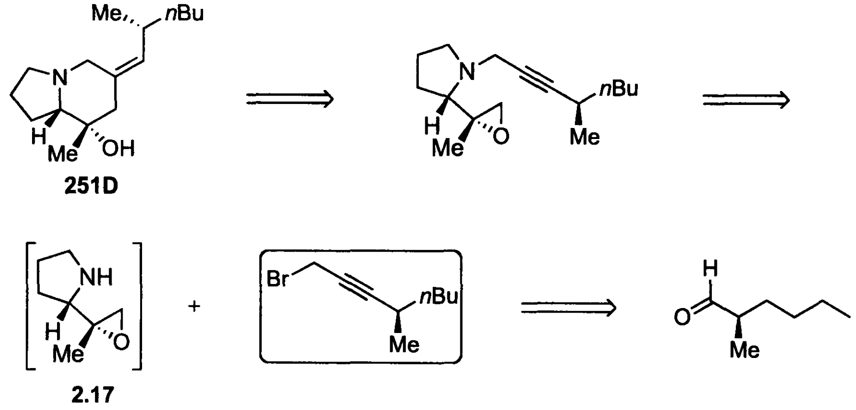
2.20, pumiliotoxin 209F

Carbon #	Natural Product 209F	Synthetic 209F
1	23.3	23.4
2	21.2	21.3
3	54.6	54.6
5	53.0	53.1
6	129.4	129.4
7	48.8	48.9
8	68.4	68.6
8a	71.8	71.9
9	24.3	24.5
10	135.7	135.8
11	26.8	26.9
12	23.4	23.4
13	23.5	23.7

Synthesis of the Reductive Coupling Precursor of Pumiliotoxin 251D

In order to demonstrate the usefulness of our newly developed methodology, another member of the pumiliotoxin family, pumiliotoxin 251D, was synthesized. Our retrosynthetic analysis of the pumiliotoxin 251D also involves an intramolecular reductive cyclization of a proline-derived epoxy-alkyne in the final step (Scheme 16). Since the free amine **2.17** had already been synthesized, the primary challenge was to synthesize a different propargyl bromide[37] from a known aldehyde.[38]

Scheme 16. Retrosynthetic analysis for pumiliotoxin 251D.



The synthesis of the aldehyde followed a method previously reported by Overman.[27a] Coupling of Evans' oxazolidinone-based chiral auxiliary **2.21** with hexanoyl chloride **2.22** proceeded with an excellent yield to form intermediate **2.23**

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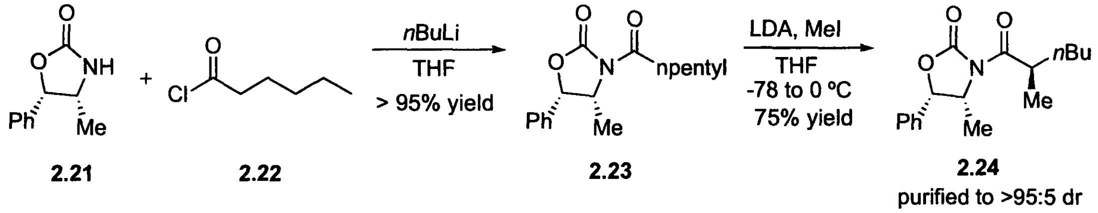
[37] This bromide has been made previously, but the variation in this report is shorter and more efficient. Reference for previous route: Okamoto, S.; Iwakubo, M.; Kobayashi, K.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 6984-6990.

[38] Previous synthesis of aldehyde **2.26** include: (a) Goldstein, S. W.; Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem.* **1992**, *57*, 1179-1190. (b) see ref. 5b; (c) for synthesis of alcohol precursor (*R*)-2-methylhexanol: Kato, M.; Mori, K. *Agric. Biol. Chem.* **1985**, *49*, 2479-2480.

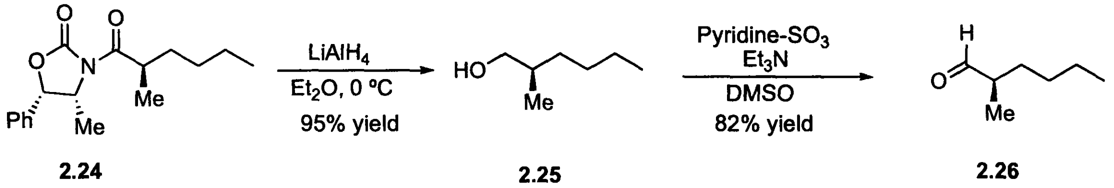
(Scheme 17).[39] Treatment with LDA followed by methyl iodide formed the desired compound **2.24**, which could be purified to >95:5 dr by silica-based chromatography.

Scheme 17. Synthesis of the stereocenter on the side-chain of pumiliotoxin 251D.



Reduction of the auxiliary with $LiAlH_4$ proceeded smoothly to form alcohol **2.25** (Scheme 18). This alcohol was then subsequently oxidized with using the Parikh-Doering method[40] to form aldehyde **2.26** in 82% yield.[41]

Scheme 18. Synthesis of the aldehyde for the side-chain of pumiliotoxin 251D.



The aldehyde was then subsequently exposed to Corey-Fuchs[42] methodology to form the dibromide **2.27** in 90% yield (Scheme 19). This intermediate was then treated with *n*BuLi and trapped with paraformaldahyde to form alcohol **2.28**[43] in excellent yield.

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[39] Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982,** *104,* 1737-1739.

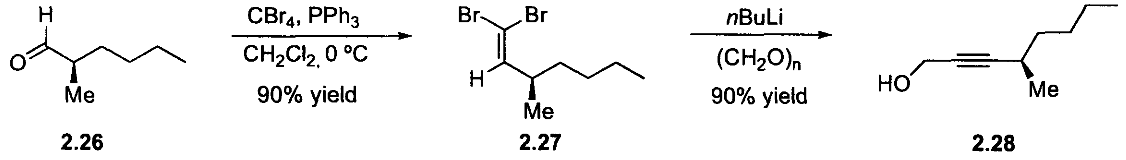
[40] Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967,** *89,* 5505-5507.

[41] See ref. 38a for procedure for determining final enantiomeric excess of the aldehyde. Product **2.26** corresponded to previous reported characterization data, including four optical rotations at various wavelengths.

[42] Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972,** *13,* 3769-3772.

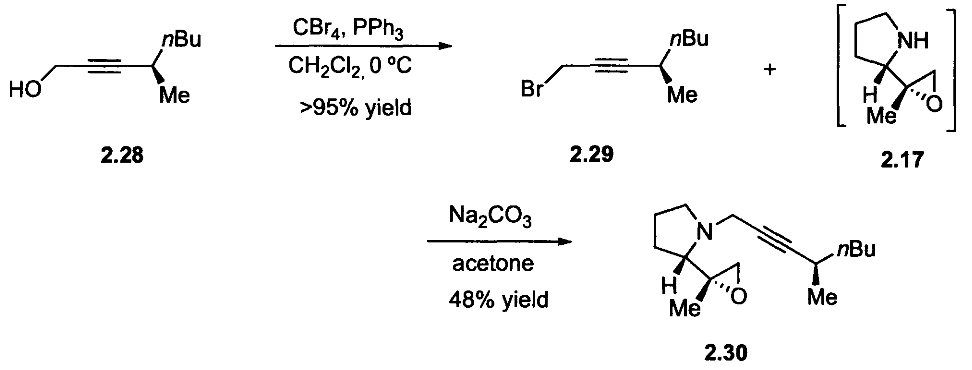
[43] Alcohol synthesized by another route and reported it: Aoyagi, S.; Wang, T.-C.; Kibayashi, C. *J. Am. Chem. Soc.* **1993,** *115,* 11393-11409.

Scheme 19. Synthesis of the alcohol for the side-chain of pumiliotoxin 251D.



The alcohol was then converted to the propargyl bromide **2.29** by treatment with CBr_4 and PPh_3 (Scheme 20).[44] This propargyl bromide was coupled with the free amine **2.17** (obtained from deprotection of alloc-substrate) to form the reductive coupling precursor **2.30**.

Scheme 20. Synthesis of the reductive coupling precursor of pumiliotoxin 251D.



Intramolecular Nickel-Catalyzed Reductive Coupling to Form Pumiliotoxin 251D

The final step in the synthesis involved the intramolecular nickel-catalyzed reductive cyclization to form the indolizidine ring of pumiliotoxin 251D (Scheme 21). Under optimum conditions developed for pumiliotoxin 209F, **2.30** cyclized to form **2.31**, pumiliotoxin 251D, as single diastereomer in 82% yield.

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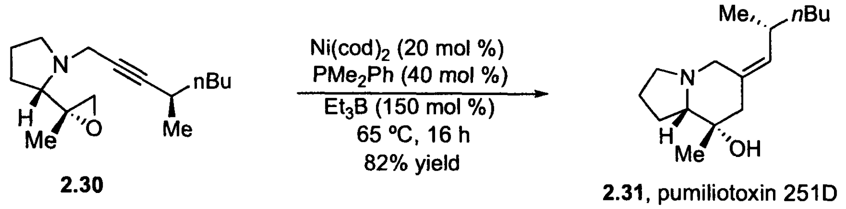
[44] See ref. 37.

Scheme 21. Reductive coupling to form pumiliotoxin 251D.



Again, the spectral data for the synthesis of pumiliotoxin 251D corresponded to natural product isolated from the *Dendrobates pumilio* frogs.[45] The ^{1}H NMR for pumiliotoxin 251D is (Table 11) correlate well with both natural and synthetic materials.[46] The ^{13}C NMR data also correlates well (Table 12) with the naturally isolated material.

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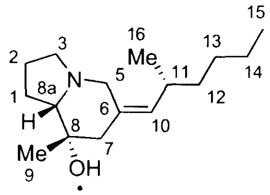
[45] Spectral data found in: (a) Naturally isolated: see ref. 1b. (b) Synthetic: see ref. 5.

[46] See Spectral Data section, Figure E1 for comparison of the ^{1}H NMR spectra.

Table 11. ^{1}H NMR data for pumiliotoxin 251D.

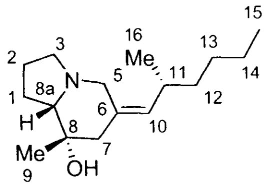


2.31, pumiliotoxin 251D

Carbon #	Natural Product 251D	Synthetic 251D	Overman's Synthetic 251D	Nubbemeyers's Synthetic 251D
1	1.73	1.78-1.60 (m, 1H)	not reported	1.78-1.60 (m, 1H)
1'^{a}	2.36	1.78-1.60 (m, 1H)	not reported	1.78-1.60 (m, 1H)
2	1.73	1.78-1.60 (m, 2H)	not reported	1.78-1.60 (m, 2H)
3	3.09	3.07-3.03 (m, 1H)	3.07 (m, 1H)	3.07-3.00 (m, 1H)
3'	2.24	2.25-2.15 (m, 1H)	2.1-2.3 (m, 1H)	2.25-2.15 (m, 1H)
5	not reported	3.78 (d, J = 12.0 Hz, 1H)	3.78 (d, J = 12.1Hz, 1H)	3.78-3.73 (d, J = 12.0Hz, 1H)
5'	not reported	2.34 (d, J = 12.0 Hz, 1H)	2.34 (d, J = 12.1Hz, 1H)	2.35-2.29 (d, J = 12.0 Hz, 1H)
7	2.16	2.15-2.12 (m, 2H)	2.17 (br app. s, 2H)	2.15-2.12 (s, 2H)
8a^{a}	3.82	2.00-1.90	2.0-1.9 (m, 1H)	1.99-1.92 (m, 1H)
9	1.16	1.14 (s, 3H)	1.16 (s, 3H)	1.11 (s, 3H)
10	5.07	5.04 (d, J = 9.5 Hz, 1H)	5.05 (d, J = 9.5 Hz, 1H)	5.04-4.97 (d, J = 9.5 Hz, 1H)
11	2.37	2.42-2.30 (m, 1H)	2.3-2.5 (m, 1H)	2.43-2.40 (m, 1H)
12	not reported	1.32-1.10 (m, 2H)	1.4-1.1 (m, 2H)	1.30-1.10 (m, 2H)
13	1.16	1.32-1.10 (m, 2H)	1.4-1.1 (m, 2H)	1.30-1.10 (m, 2H)
14	1.16	1.32-1.10 (m, 2H)	1.4-1.1 (m, 2H)	1.30-1.10 (m, 2H)
15	0.89	0.87 (t, J = 6.9 Hz, 3H)	0.87 (app. t, J = 6.8 Hz, 3H)	0.87-0.80 (t, J = 6.5 Hz, 3H)
16	0.98	0.97 (d, J = 6.5 Hz, 3H)	0.98 (d, J = 6.2 Hz, 3H)	0.96-0.93 (d, J = 6.5 Hz, 3H)
OH	not reported	2.67 (s, 1H)	2.6 (br s, 1H)	2.65 (s, 1H)

(a) Our assignments of the C5 and C5' protons are consistent with Overman's and Nubbeymeyer's observations and inconsistent with Daly's nomenclature. Similar discrepancies exist for C1 and C8a.

Table 12. ^{13}C NMR data for pumiliotoxin 251D.



2.31, pumiliotoxin 251D

Carbon #	Natural Product 251D	Synthetic 251D
1	23.4	23.3
2	21.2	21.2
3	54.7	54.7
5	53.0	53.3
6	130.0	130.0
7	49.0	48.9
8	68.4	68.4
8a	71.8	71.8
9	24.3	24.4
10	134.7	134.7
11	32.1	32.2
12	37.6	37.6
13	29.8	29.8
14	22.9	22.9
15	14.2	14.2
16	21.8	21.8

Conclusion

A novel methodology was successfully developed involving the intramolecular nickel-catalyzed reductive cyclization of 1,1-disubstituted epoxides and alkynes to form tertiary homoallylic alcohol products. These were also the first examples of a nickel-catalyzed cyclization resulting in exclusive C-C bond formation at the *endo* position on the alkyne without the use of a directing group on the alkyne.[47] A divergent strategy was developed involving this methodology that was applied to the total syntheses of pumiliotoxins 209F and 251D. The synthesis of pumiliotoxin 209F was accomplished in only seven steps in the longest linear sequence and in 34% overall chemical yield. Pumiliotoxin 251D was synthesized in nine steps in the longest linear sequence and 18% overall yield.

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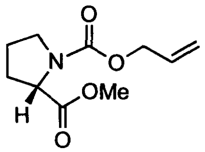
[47] See ref. 8, typically an aromatic substituent is used to direct the cyclization.

Experimental Section

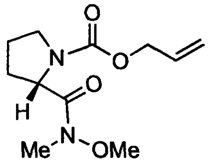
For General Methods, see Experimental Section in Ch. 1.

All commercially available materials were used as is, unless otherwise noted. Pyridine was distilled from CaH_2, and stored over 4Å molecular sieves. Acetone was distilled from K_2CO_3 and stored over 4Å molecular sieves. Na_2CO_3 was stored in an oven to keep dry prior to use.



2.11e

(*S*)-1-Allyl 2-methyl pyrrolidine-1,2-dicarboxylate (2.11e). L-proline methyl ester (0.664 g, 4 mmol) was dissolved in CH_2Cl_2 (16 mL) and cooled to 0 °C. To the stirring solution was added pyridine (0.808 mL, 10 mmol) and allyl chloroformate (0.638 mL, 6 mmol), and the solution was allowed to stir for 20 min as a white precipitate formed. The solution was allowed to warm to rt and was diluted with $CHCl_3$ (10 mL) which dissolved the precipitate. The solution was washed with sat. $NaHCO_3$ (2 × 20 mL), brine (2 × 20 mL) and dried over Na_2SO_4. The solution was filtered and concentrated in vacuo, and was purified by flash column chromatography (3:7 EtOAc:hexanes) to give alloc-protected ester **2.11e** as a colorless oil (848 mg, 99% yield). R_f 0.53 (1:1 EtOAc:hexanes). ^1H NMR (500 MHz, $CDCl_3$) (reported as ~1:1 mixture of rotamers) δ 5.98-5.82 (m, 2H), 5.30 (t, J = 15.9 Hz, 2H), 5.27-5.16 (m, 2H), 4.64-4.56 (m, 2H), 4.53 (d, J = 5.3, Hz, 1H), 4.51 (d, J = 5.3, Hz, 1H), 4.38 (dd, J = 8.7, 3.8 Hz, 1H), 4.35 (dd, J = 8.7, 3.8 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.64-3.57 (m, 2H), 3.55-3.45 (m, 2H), 2.28-2.18 (m, 2H), 2.06-1.88 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) (reported as ~1:1 mixture of rotamers) δ 173.5, 173.3, 154.9, 154.3, 133.1, 133.0, 117.5, 117.1, 66.1, 66.0, 59.3, 59.0, 52.4, 52.3, 47.0, 46.5, 31.1, 30.1, 24.5, 23.7. IR (thin film NaCl) 2955, 2883, 1750, 1708, 1408, 1350, 1202, 1174, 1129, 1089 cm^{-1}. HRMS (ESI) *m/z* 236.090 [M+Na; calcd for $C_{10}H_{15}NO_4$: 236.089]. $[\alpha]_D = -51.0$ (23 °C, 589 nm, 75.76 g/100 mL, $CHCl_3$).



2.12e

(*S*)-Allyl 2-(methoxy(methyl)carbamoyl)pyrrolidine-1-carboxylate (2.12e). *N-O*-dimethylhydroxylamine hydrochloride (9.95g, 102 mmol) was dissolved in CH_2Cl_2 (250 mL) and cooled to 0 °C. Trimethylaluminium (51 mL, 102 mmol) was added and the reaction was allowed to stir 10 min at 0 °C, then warmed to rt and stirred for 20 min. The ester **2.11e** was added (7.26 g, 34 mmol), and the reaction stirred for an additional 5 h at rt. The reaction was quenched with ether (200 mL) and Rochelle's salt (300 mL) and stirred for 2 h. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 200 mL). The combined organics were washed with brine (500 mL) and dried over Na_2SO_4. The solution was filtered and concentrated in vacuo, and was purified by flash column chromatography (1:19 MeOH:EtOAc) to give alloc-protected Weinreb amide **2.12e** as a colorless oil (7.84 g, 95% yield). R_f 0.41 (1:9 MeOH:EtOAc). ^1H NMR (500 MHz, $CDCl_3$) (1:0.6 mixture of rotamers, asterisk denotes minor rotamer peaks[1]) δ 5.97-5.82 (m, 1H), 5.30 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.25* (dd, *J* = 17.2, 1.4 Hz, 0.6H), 5.19 (dd, *J* = 10.5, 1.4, 1H), 5.15* (dd, *J* = 10.5, 1.4, 0.6H), 4.76-4.65 (m, 1H), 4.63-4.53 (m, 2H), 3.78 (s, 3H), 3.71* (s, 1.8H), 3.66-3.61 (m,

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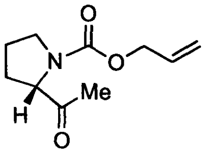
[1] When minor rotamer overlaps with major, no asterisk is indicated.

1H), 3.57-3.46 (m, 1H), 3.20 (s, 3H), 3.19* (s, 1.8H), 2.27-2.15 (m, 1H), 2.08-1.97 (m, 1H), 1.96-1.82 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) (1.6:1 mixture of rotamers) δ 173.3, 172.8, 154.7, 154.1, 133.1, 133.0, 117.1, 117.0, 65.7, 65.6, 61.3, 56.9, 56.5, 47.1, 46.6, 32.3, 32.1, 30.6, 26.6, 24.2, 23.3. IR (thin film NaCl) 2979, 2882, 1737, 1707, 1676, 1409, 1354, 1243, 1175, 1122, 997 cm^{-1}. HRMS (ESI) *m/z* 243.134 [M+H; calcd for $C_{11}H_{18}N_2O_4$: 243.134]. $[\alpha]_D = -13.7$ (23 °C, 589 nm, 39.59 g/100 mL, $CHCl_3$).



2.13e

(*S*)-Allyl 2-ethanoylpyrrolidine-1-carboxylate (2.13e). The Weinreb amide **2.12e** (5.33 g, 22 mmol) was dissolved in ether (280 mL) and cooled to 0 °C. Methylmagnesium bromide (18 mL, 54 mmol) in ether (50 mL) was added to the flask with vigorous stirring, and was allowed to warm to rt over 2 h. The reaction was quenched with sat. NH_4Cl (200 mL), the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 200 mL). The combined organics were washed with brine (500 mL) and dried over Na_2SO_4. The solution was filtered and concentrated in vacuo, and was purified by flash column chromatography (3:7 EtOAc:hexanes) to give alloc-protected ketone **2.13e** as a pale yellow oil (4.12 g, 95% yield).[2] R_f 0.26 (1:1 EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) (reported as ~1:1 mixture of rotamers) δ 5.95-5.81 (m, 2H), 5.30 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.23 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.19 (dd, *J* = 10.4, 1.1 Hz, 1H), 5.16 (dd, *J* = 10.4, 1.1 Hz, 1H), 4.59-4.49 (m, 4H), 4.38 (dd, *J*

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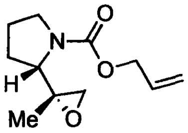
[2] >98% ee of ketone determined by chiral GC (cyclodex column): 50-180 °C, at 0.2 °C/min, at 1 mL/min. Retention time of desired ketone is 294 min (undesired retention time is 292 min).

= 8.5, 4.5 Hz, 1H), 4.29 (dd, *J* = 8.5, 4.5 Hz, 1H), 3.61-3.46 (m, 4H), 2.25-2.11 (m, 2H), 2.17 (s, 3H), 2.12 (s, 3H), 1.91-1.82 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) (reported as ~1:1 mixture of rotamers) δ 208.1, 207.7, 155.1, 154.5, 133.1, 132.8, 117.9, 117.6, 66.2, 65.7, 47.4, 46.8, 30.0, 28.9, 27.0, 26.1, 24.6, 23.8. IR (thin film NaCl) 2980, 2956, 2883, 1703, 1649, 1409, 1354, 1190, 1165, 1125, 1092, 988, 769 cm^{-1}. HRMS (ESI) *m/z* 220.095 [M+Na; calcd for $C_{10}H_{15}NO_3$: 220.094]. $[\alpha]_D$ = –72.3 (23 °C, 589 nm, 0.65 g/100 mL, $CHCl_3$).



2.14e

(*S*)-Allyl 2-((*R*)-2-methyloxiran-2-yl)pyrrolidine-1-carboxylate (2.14e).

Using NaH as base: NaH (0.030 g, 0.75 mmol) and Me_3SOCl (0.129 g, 1 mmol) were dissolved in THF (7 mL) and refluxed for 4.5 h. The reaction was cooled to –20 °C and the slurry was then added to the ketone **2.13e** (0.099 g, 0.5 mmol), which was dissolved in THF (2 mL), dropwise via cannula over 20 min. The reaction was allowed to stir at –20 °C for 40 h and was quenched 0.1 M $NaHSO_4$ (10 mL).[3] The aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the organic extracts were washed with brine (50 mL), and dried over Na_2SO_4. The solution was filtered and concentrated in vacuo, and was purified by flash column chromatography (3:7 EtOAc:hexanes) to give alloc-

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[3] Added enough acid until the pH of the aqueous layer was neutral.

protected epoxide **2.14e** as a light yellow oil (0.040 g, 38% yield, 11:1 dr favoring desired diastereomer, >98%, as determined by chiral GC[4]).

Using *n*BuLi as base: Me_3SOCl (0.096 g, 0.75 mmol) was dissolved in THF (7 mL) and *n*BuLi (0.22 mL, 0.55 mmol, 2.5M in hexanes) was added dropwise at rt. The reaction was stirred at rt for 4.5 h, then cooled to –20 °C and the slurry was added to the ketone **2.13e** (0.099 g, 0.5 mmol), dissolved in THF (2 mL), dropwise via cannula over 20 min. The reaction was stirred at –20 °C for 32 h and quenched with 0.1 M $NaHSO_4$ (10 mL).[3] The aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the organic extracts were washed with brine (50 mL), and dried over Na_2SO_4. The solution was filtered and concentrated in vacuo, and was purified by flash column chromatography (3:7 EtOAc:hexanes) to give alloc-protected epoxide **2.14e** (0.076 g, 72% yield, 91:9 dr favoring desired diastereomer, >98% ee, as determined by chiral GC[4]).

R_f 0.41 (1:1 EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) (reported as ~1:1 mixture of rotamers)[5] δ 5.97-5.90 (m, 2H), 5.31 (dd, *J* = 10.4, 1.1 Hz, 2H), 5.20 (dd, *J* = 10.4, 1.1 Hz, 2H), 4.68-4.52 (m, 4H), 4.06 (d, *J* = 6.4 Hz, 1H), 3.94 (d, *J* = 6.4 Hz, 1H), 3.62-3.28 (m, 4H), 2.63 (d, *J* = 4.6 Hz, 2H), 2.53 (d, *J* = 4.6 Hz, 2H), 2.10-1.67 (m, 8H), 1.35 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) (reported as ~1:1 mixture of rotamers) δ 155.6, 155.3, 133.3, 117.5, 117.4, 65.9, 59.5, 59.0, 52.6, 52.4, 47.7, 47.2, 29.0, 27.8, 24.6, 23.9, 19.9, 19.6. IR (thin film NaCl) 3057, 2980, 2882, 1702, 1648, 1405, 1350,

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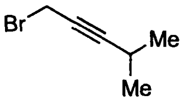
[4] Determined by chiral GC, using a Chiraldex B-OA column; ran from 60-170 °C, at 0.2 °C/min, at 1 mL/min. Retention time of desired epoxide is 220 min (undesired retention time is 222 min).

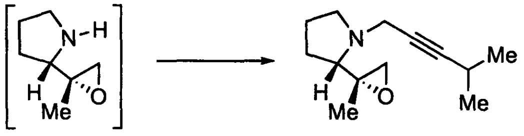
[5] Minor diastereomer not reported as it overlaps with the rotamers of the major diastereomer. Minor ^{1}H NMR peaks do not overlap at: δ 2.92, 2.81, 2.76, 2.71, 2.46, 2.36, 1.25. Determined dr from integration of methyl groups for each diastereomer. Confirmed dr in subsequent step, when the two diastereomers are more distinguished due to lack of rotamers.

1335, 1277, 1186, 1121, 1098, 919, 774 cm^{-1}. HRMS (ESI) *m/z* 234.111 [M+Na; calcd for $C_{11}H_{17}NO_3$: 234.110]. $[\alpha]_D = -80.8$ (23 °C, 589 nm, 0.45 g/100 mL, $CHCl_3$).



2.6

1-Bromo-4-methylpent-2-yne (2.6). 4-Methylpent-2-yn-1-ol[6] (1.96 g, 20 mmol) was dissolved in dichloromethane (60 mL) and cooled to 0 °C. Carbon tetrabromide (7.96 g, 24 mmol) and triphenylphosphine (6.29 g, 24 mmol) were added and the reaction was stirred at 0 °C for 1 h. The reaction was quenched with sat. $NaHCO_3$ solution (60 mL) and was further diluted with ether (120 mL) and water (60 mL). Separated the organic layer and washed with water (3 × 120 mL), brine (120 mL), dried over $MgSO_4$, filtered and concentrated. The residue was then purified by flash column chromatography (hexanes to 1:49 EtOAc:hexanes) to give propargyl bromide **2.6** as a colorless liquid (3.03 g. 94% yield). R_f 0.58 (1:9 EtOAc:hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 3.94 (d, *J* = 2.1 Hz, 2H), 2.62 (m, 1H), 1.17 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 93.6, 74.8, 22.8, 20.9, 16.0. IR (thin film NaCl) 2972, 2935, 2872, 2228, 1466, 1320, 1210 cm^{-1}.



2.17 **2.10**

(*S*)-2-((*R*)-2-methyloxiran-2-yl)-1-(4-methylpent-2-ynyl)pyrrolidine (2.10). $Pd(dba)_2$ (0.086 g, 0.15 mmol) and dppb (0.064 g, 0.15 mmol) were combined in a glove box.

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[6] Formation of alcohol from 3-methylbut-1-yne and paraformaldehyde: Hatch, L. F.; Li, T. P. *J. Org. Chem.* **1963**, *28*, 2400-2403.

Alloc-protected epoxide **2.14e** (0.317 g, 1.5 mmol) in THF (4 mL) was added followed by addition of diethylamine (2.3 mL, 22.5 mmol). The reaction was stirred at rt for 2 h, then filtered through a plug of celite with ether (10 mL) to removed the palladium catalyst and was concentrated in vacuo[7] to form free amine **2.17**. Amine **2.17** was dissolved in acetone (15 mL) and Na_2CO_3 (0.398 g, 3.75 mmol) and propargyl bromide **2.6** (0.290 g, 1.8 mmol) were added, and the reaction was allowed to stir at rt for 16 h. The solvent was removed in vacuo, and the compound was purified by flash column chromatography using a solvent gradient (1:19 to 3:7 EtOAc:hexanes) to give amine **2.10** as a pale yellow oil (0.17 g, 55% yield over the two steps, 91:9 dr retained). R_f 0.51 (1:1 EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) (reported as a 10:1 mixture of diastereomers, asterisk denotes minor diastereomer)[8]: δ 3.60 (dd, J = 16.7, 1.9 Hz, 1H), 3.49* (dd, J = 16.7, 1.9 Hz, 0.1H), 3.41* (dd, J = 16.7, 1.9 Hz, 0.1H), 3.31 (dd, J = 16.7, 1.9 Hz, 1H), 3.08 (t, J = 7.3 Hz, 1H), 2.96* (t, J = 7.3 Hz, 0.1H), 2.77* (d, J = 5.3 Hz, 0.1H), 2.62-2.48 (m, 4H), 2.27 (t, J = 7.33 Hz, 1H), 1.89-1.70 (m, 4H), 1.33 (s, 3H), 1.29* (s, 0.3H), 1.60 (d, J = 6.9 Hz, 6H) 1.15* (d, J = 6.9 Hz, 0.6H). ^{13}C NMR (125 MHz, $CDCl_3$) (major and minor peaks reported) δ 91.2, 90.4, 74.7, 73.9, 66.8, 65.4, 58.1, 57.4, 54.0, 53.5, 53.2, 51.0, 42.6, 41.8, 28.4, 27.8, 23.6, 23.5, 23.3, 23.1, 20.8, 20.7, 16.8, 16.7. IR (thin film NaCl) 3035, 2969, 2873, 2813, 2242, 1462, 1444, 1400, 1368, 1319, 1180, 1123, 1095, 1067, 909 cm^{-1}. HRMS (ESI) *m/z* 208.170 [M+H; calcd for $C_{13}H_{21}NO$: 208.170]. $[\alpha]_D = -40.4$ (23 °C, 589 nm, 0.2 g/100 mL, $CHCl_3$).

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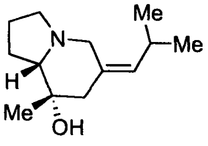
[7] Free amine may be volatile, and precaution was used when concentrating solvent.

[8] When minor overlaps with major diastereomer, no asterisk is indicated.



2.20

Pumiliotoxin 209F (2.20). In a glovebox, Ni(cod)$_2$ (5.6 mg, 0.02 mmol) and Me$_2$PhP (5.7 μL, 0.04 mmol) were placed into an oven-dried, sealed tube, which was sealed with a rubber septum and teflon cap. The tube was removed from the glovebox, placed under argon, and triethylborane (22 μL, 0.15 mmol) was added via syringe. The resulting solution was stirred 5 min, and the epoxy-alkyne **2.10** (21 mg, 0.10 mmol) was added dropwise via microsyringe.[9] The reaction was heated to 65 °C and allowed to stir 16 h. The solution was then cooled to rt, and ether (2 mL) was added to dilute the solution at which point the septum 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 (1:49 to 1:19 MeOH:CHCl$_3$) to give pumiliotoxin 209F as a colorless oil (14.6 mg, 70% yield, 1 diastereomer).[10] R_f 0.33 (1:9 MeOH:CHCl$_3$) ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.11 (d, J = 9.2 Hz, 1H), 3.80 (d, J = 11.9 Hz, 1H), 3.07 (t, J = 8.3 Hz, 1H), 2.67 (s, 1H), 2.60-2.55 (m, 1H), 2.36 (d, J = 11.9 Hz, 1H), 2.24-2.20 (m, 1H), 2.12 (d, J = 13.8 Hz, 1H), 2.09 (d, J = 13.8 Hz, 1H), 1.98 (t, J = 5.0 Hz, 1H), 1.79-1.65 (m, 4H), 1.14 (s, 3H), 0.99 (d, J = 6.7 Hz, 3H), 0.92 (d, J = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 135.8, 129.4, 71.9, 68.6, 54.6, 53.1, 48.9, 26.96, 24.5, 23.7, 23.6, 23.4, 21.3. IR (thin film NaCl) 3512, 2959, 2874, 2785, 2743, 1464, 1445, 1424, 1396, 1376, 1321, 1309, 1297, 1275, 1216, 1175, 1150, 1098, 967 cm^{-1}.

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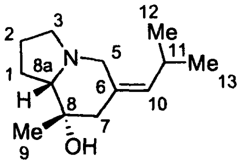
[9] Order of addition of substrate or Et$_3$B did not affect chemical yield.

[10] Spectral data is in accord with literature values: (a) Tokuyama, T.; Tsujita, T.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Tetrahedron* **1991**, *47*, 5415-5424. (b) Overman, L. E.; Lesuisse, D. *Tetrahedron Lett.* **1985**, *26*, 4167-4170. See Tables E1 and E2 for comparison.

HRMS (ESI) *m/z* 210.185 [M+H; calcd for $C_{13}H_{23}NO$: 210.185]. $[\alpha]_D$ = −12.8 (23 °C, 589 nm, 0.3 g/100 mL, $CHCl_3$).[11]

Table E1. ^1H NMR data for pumiliotoxin 209F.



2.20, pumiliotoxin 209F

Carbon #	Natural Product 209F	Synthetic 209F	Overman's Synthetic 209F
1	not reported	1.79-1.65 (m, 2H)	not reported
2	"	1.79-1.65 (m, 2H)	"
3	"	3.07 (t, *J* = 8.3 Hz, 1H)	"
3'	"	2.24-2.20 (m, 1H)	"
5	"	3.80 (d, *J* = 11.9 Hz, 1H)	3.79 (d, *J* = 12 Hz, 1H)
5'	"	2.36 (d, *J* = 11.9 Hz, 1H)	2.32 (d, *J* = 11.9 Hz, 1H)
7	"	2.12 (d, *J* = 13.8 Hz, 1H)	not reported
7'	"	2.09 (d, *J* = 13.8 Hz, 1H)	"
8a	"	1.98 (t, *J* = 5.0 Hz, 1H)	"
9	"	1.14 (s, 3H)	"
10	"	5.11 (d, *J* = 9.2 Hz, 1H)	5.10 (d, *J* = 9.8 Hz, 1H)
11	"	2.60-2.55 (m, 1H	not reported
12	0.99	0.99 (d, *J* = 6.7 Hz, 3H)	"
13	0.91	0.92 (d, *J* = 6.7 Hz, 3H)	"
OH	not reported	2.67	"

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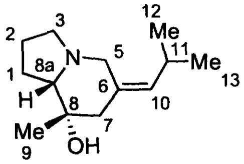
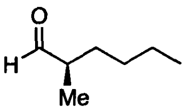
[11] $[\alpha]_D$ reported to be −11.6 (589 nm, 0.1 g/100 mL, $CHCl_3$), see ref 9a.

Table E2. ^{13}C NMR data for pumiliotoxin 209F.



2.20, pumiliotoxin 209F

Carbon #	Natural Product 209F	Synthetic 209F
1	23.3	23.4
2	21.2	21.3
3	54.6	54.6
5	53.0	53.1
6	129.4	129.4
7	48.8	48.9
8	68.4	68.6
8a	71.8	71.9
9	24.3	24.5
10	135.7	135.8
11	26.8	26.9
12	23.4	23.4
13	23.5	23.7



2.26

(R)-2-Methylhexanal (2.26). Followed previously reported procedure to synthesize aldehyde **2.26** in 56% yield over 4 steps from commercially available materials.[12] Spectral data, including optical rotation to confirm ee (>98%), were consistent with those previously reported.

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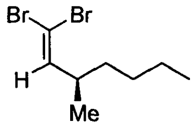
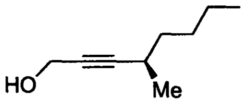
[12] Goldstein, S. W.; Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem.* **1992**, *57*, 1179-1190.



2.27

(R)-1,1-Dibromo-3-methylheptene (2.27). Dibromide **2.27** was prepared according to Overman's procedure,[13] in 90% yield. Spectral data were consistent with those previously reported.



2.28

(R)-4-Methyl-2-octyn-1-ol (2.28). Dibromide **2.27** (0.184 g, 0.68 mmol) was dissolved in THF (2.1 mL) and cooled to –78 °C. *n*BuLi (0.54 mL, 1.4 mmol; 2.5 M solution in hexanes) was then added and the reaction was stirred at –78 °C for 30 min. To this cooled solution was added a suspension of paraformaldehyde (0.245 g, 2.7 mmol) in THF (1.4 mL) and the mixture was allowed to warm to rt over 1 h. The mixture was filtered through celite, brine was added (2 mL) and the organic layer was separated. The aqueous layer was extracted with ether (3 × 2 mL), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on silica gel (1:9 EtOAc:hexanes) to give **2.28** as a colorless liquid (86 mg, 90% yield). Spectral data were consistent with those previously reported.[14]

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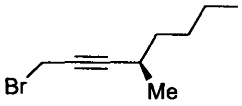
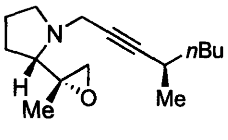
[13] Caderas, C.; Lett, R.; Overman, L. E.; Rabinowitz, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, *118*, 9073-9082.

[14] Aoyagi, S.; Wang, T.-C.; Kibayashi, C. *J. Am. Chem. Soc.* **1993**, *115*, 11393-11409.



2.29

(*R*)-1-Bromo-4-methyloct-2-yne (2.29).[15] This procedure is similar to that for propargyl bromide **2.6**. Propargyl alcohol **2.28** (42 mg, 0.3 mmol,) was dissolved in dichloromethane (0.9 mL) and cooled to 0 °C. Carbon tetrabromide (0.119 g, 0.36 mmol) and triphenylphosphine (0.094 g, 0.36 mmol) were added and the reaction was stirred at 0 °C for 1 h. The reaction was quenched with sat. $NaHCO_3$ solution (1 mL) and was further diluted with ether (2 mL) and water (1 mL). Separated the organic layer and washed with water (3 × 2 mL), brine (2 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography using a solvent gradient (hexanes to 1:49 EtOAc:hexanes) to give propargyl bromide **2.29** as a colorless liquid (59 mg, 96% yield). R_f 0.47 (1:9 EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.94 (d, *J* = 2.2 Hz, 2H), 2.49-2.41 (m, 1H), 1.44-1.22 (m, 6H), 1.13 (d, *J* = 7.0 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 92.9, 75.6, 36.6, 29.7, 29.3, 22.7, 20.9, 16.1, 14.3. IR (thin film NaCl) 2959, 2931, 2872, 2858, 2231, 1458, 1376, 1333, 1208, 7660 cm^{-1}. $[\alpha]_D$ = -19.8 (23 °C, 589 nm, 0.45 g/100 mL, $CHCl_3$).



2.30

(*S*)-1-((*R*)-4-methyloct-2-ynyl)-2-((*R*)-2-methyloxiran-2-yl)pyrrolidine (2.30). $Pd(PPh_3)_4$ (7 mg, 0.006 mmol) was weighed into a vial and to this was added a solution

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[15] Spectral data for **2.29** is in accord with literature values: Okamoto, S.; Iwakubo, M.; Kobayashi, K.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 6984-6990.

of the alloc-protected epoxide **2.14e** (0.026 g, 0.12 mmol) in THF (0.28 mL) followed by diethylamine (0.20 mL, 1.8 mmol). The reaction was stirred at rt for 2 h, then filtered through a plug of celite with ether (5 mL) to remove the palladium catalyst, and was subsequently concentrated in vacuo to form the free amine **2.17**.[16] Amine **2.17** was dissolved in acetone (1 mL) and Na_2CO_3 (0.064 g, 0.6 mmol) and propargyl bromide **2.29** (0.024 g, 0.12 mmol) were added, and the reaction was allowed to stir at rt for 16 h. The solvent was removed in vacuo, and the compound was purified by flash column chromatography using a solvent gradient (1:19 to 3:7 EtOAc:hexanes) to give amine **2.30** as a colorless oil (0.14 g, 48% yield over the two steps, 91:9 dr retained). R_f 0.58 (1:1 EtOAc:hexanes) ^{1}H NMR (500 MHz, $CDCl_3$) (reported as a 10:1 mixture of diastereomers, asterisk denotes minor diastereomer)[17]: δ 3.61 (dd, J = 16.7, 1.9 Hz, 1H), 3.50* (dd, J = 16.7, 1.9 Hz, 0.1H), 3.44* (dd, J = 16.7, 1.9 Hz, 0.1H), 3.36 (dd, J = 16.7, 1.9 Hz, 1H), 3.06 (t, J = 7.3 Hz, 1H), 2.95* (t, J = 7.3 Hz, 0.1H), 2.77* (d, J = 5.3 Hz, 0.1H), 2.62* (d, J = 5.3 Hz, 0.1H), 2.56 (d, J = 5.0 Hz, 1H), 2.54 (d, J = 5.0 Hz, 1H), 2.42 (br. dd, J = 13.4, 6.8 Hz, 1H), 2.32 (t, J = 7.3 Hz, 1H), 1.89-1.70 (m, 4H), 1.45-1.26 (m, 7H), 1.31 (s, 3H), 1.14 (d, J = 6.9 Hz, 3H), 0.90 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) (major and minor peaks reported[18]) δ 89.5, 75.6, 66.5, 65.2, 58.1, 53.9, 53.4, 53.0, 51.1, 42.5, 41.7, 29.9, 28.4, 27.8, 26.1, 23.4, 23.1, 22.8, 22.4, 21.6, 18.9, 16.9, 16.7, 14.3, 12.1. IR (thin film NaCl) 3034, 2963, 2930, 2873, 2860, 2814, 2243, 1460, 1401, 1373, 1327, 1280, 1123, 1096, 1068, 908 cm^{-1}. HRMS (ESI) *m/z* 250.217 [M+H; calcd for $C_{16}H_{27}NO$: 250.217]. $[\alpha]_D = -66.1$ (23 °C, 589 nm, 0.22 g/100 mL, $CHCl_3$).

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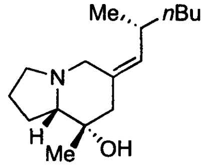
[16] $Pd(PPh_3)_4$ was utilized due to ease of purification (relative to $Pd(dba)_2$).

[17] Not all protons for minor diastereomer are reported, as they overlap with major diastereomers or are not well resolved.

[18] Not all minor diastereomer carbon peaks are resolved, or overlap with major diastereomer.



2.31

Pumiliotoxin 251 D (2.31). Epoxy-alkyne **2.31** (15 mg, 0.06 mmol) was added to a sealed tube which was brought into a glovebox.[19] In the glove box, Ni(cod)$_2$ (3.3 mg, 0.012 mmol) and 1.2 (3.4 μL, 0.024 mmol) were added to the sealed tube, which was sealed with a rubber septum and teflon cap. The tube was removed from the glovebox, placed under argon, and triethylborane (13 μL, 0.09 mmol) was added via syringe. The reaction was heated to 65 °C and allowed to stir 16 h. The solution was cooled to rt, and ether (2 mL) was added to dilute the solution at which point the septum 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 (1:49 to 1:19 MeOH:CHCl$_3$) to give pumiliotoxin 251D as a colorless solid (12.4 mg, 82% yield, 1 diastereomer).[20] R_f 0.30 (1:9 MeOH:CHCl$_3$). ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.04 (d, J = 9.5 Hz, 1H), 3.78 (d, J = 12.0 Hz, 1H), 3.07-3.03 (m, 1H), 2.67 (s, 1H), 2.42-2.30 (m, 1H), 2.34 (d, J = 12.0 Hz, 1H), 2.25-2.15 (m, 1H), 2.15-2.12 (m, 2H), 2.00-1.90 (m, 1H), 1.78-1.60 (m, 4H), 1.32-1.10 (m, 6H), 1.14 (s, 3H), 0.97 (d, J = 6.5 Hz, 3H), 0.87 (t, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 134.7, 130.0, 71.8, 68.4,

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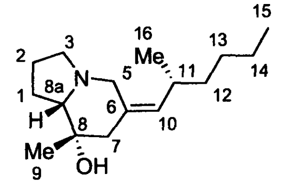
[19] Due to small scale, the substrate was dissolved in ether, place in sealed tube, and solvent was removed via vacuum pump.

[20] Spectral data is in accord with literature values: (a) see Ref. 9a. (b) Daly, J. W.; Tokuyama, T.; Fujiwara, T.; Highet, R. J; Karle, I. L. *J. Am. Chem. Soc.* **1980**, *102*, 830-836. (b) Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, *106*, 4192-4201. (c) Sudau, A.; Münch, W.; Bats, J.-W.; Nubbemeyer, U. *Eur. J. Org. Chem.* **2002**, 3315-3325. See Tables E3 and E4 for a comparison. Also see Figure E1 for comparison of the ^{1}H NMR spectra.

54.7, 53.3, 48.9, 37.6, 32.2, 29.8, 24.4, 23.3, 22.9, 21.8, 21.2, 14.2. IR (thin film NaCl) 3418, 2982, 2909, 2872, 1660, 1465, 1420, 1324, 1305, 1291, 1176, 1121, 1072, 939, 913, 871 cm^{-1}. HRMS (ESI) *m/z* 252.232 [M+H; calcd for $C_{16}H_{29}NO$: 252.232]. $[\alpha]_D$ = –9.3 (23 °C, 589 nm, 0.05 g/100 mL, $CHCl_3$).

Table E3. ^{1}H NMR data for pumiliotoxin 251D.

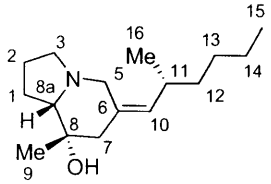


2.31, pumiliotoxin 251D

Carbon #	Natural Product 251D	Synthetic 251D	Overman's Synthetic 251D	Nubbemeyers's Synthetic 251D
1	1.73	1.78-1.60 (m, 1H)	not reported	1.78-1.60 (m, 1H)
1'[a]	2.36	1.78-1.60 (m, 1H)	not reported	1.78-1.60 (m, 1H)
2	1.73	1.78-1.60 (m, 2H)	not reported	1.78-1.60 (m, 2H)
3	3.09	3.07-3.03 (m, 1H)	3.07 (m, 1H)	3.07-3.00 (m, 1H)
3'	2.24	2.25-2.15 (m, 1H)	2.1-2.3 (m, 1H)	2.25-2.15 (m, 1H)
5	not reported	3.78 (d, *J* = 12.0 Hz, 1H)	3.78 (d, *J* = 12.1Hz, 1H)	3.78-3.73 (d, *J* = 12.0Hz, 1H)
5'	not reported	2.34 (d, *J* = 12.0 Hz, 1H)	2.34 (d, *J* = 12.1Hz, 1H)	2.35-2.29 (d, *J* = 12.0 Hz, 1H)
7	2.16	2.15-2.12 (m, 2H)	2.17 (br app. s, 2H)	2.15-2.12 (s, 2H)
8a[a]	3.82	2.00-1.90	2.0-1.9 (m, 1H)	1.99-1.92 (m, 1H)
9	1.16	1.14 (s, 3H)	1.16 (s, 3H)	1.11 (s, 3H)
10	5.07	5.04 (d, *J* = 9.5 Hz, 1H)	5.05 (d, *J* = 9.5 Hz, 1H)	5.04-4.97 (d, *J* = 9.5 Hz, 1H)
11	2.37	2.42-2.30 (m, 1H)	2.3-2.5 (m, 1H)	2.43-2.40 (m, 1H)
12	not reported	1.32-1.10 (m, 2H)	1.4-1.1 (m, 2H)	1.30-1.10 (m, 2H)
13	1.16	1.32-1.10 (m, 2H)	1.4-1.1 (m, 2H)	1.30-1.10 (m, 2H)
14	1.16	1.32-1.10 (m, 2H)	1.4-1.1 (m, 2H)	1.30-1.10 (m, 2H)
15	0.89	0.87 (t, J = 6.9 Hz, 3H)	0.87 (app. t, *J* = 6.8 Hz, 3H)	0.87-0.80 (t, *J* = 6.5 Hz, 3H)
16	0.98	0.97 (d, *J* = 6.5 Hz, 3H)	0.98 (d, *J* = 6.2 Hz, 3H)	0.96-0.93 (d, *J* = 6.5 Hz, 3H)
OH	not reported	2.67 (s, 1H)	2.6 (br s, 1H)	2.65 (s, 1H)

(a) Our assignments of the C5 and C5' protons are consistent with Overman's and Nubbeymeyer's observations and inconsistent with Daly's nomenclature. Similar discrepancies exist for C1 and C8a.

Table E4. ^{13}C NMR data for pumiliotoxin 251D.

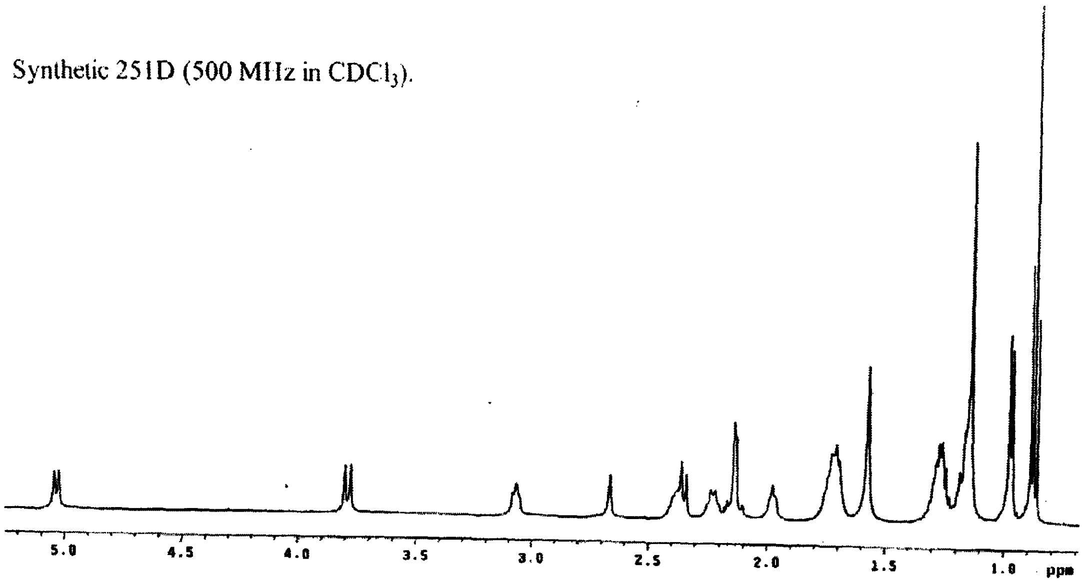


2.31, pumiliotoxin 251D

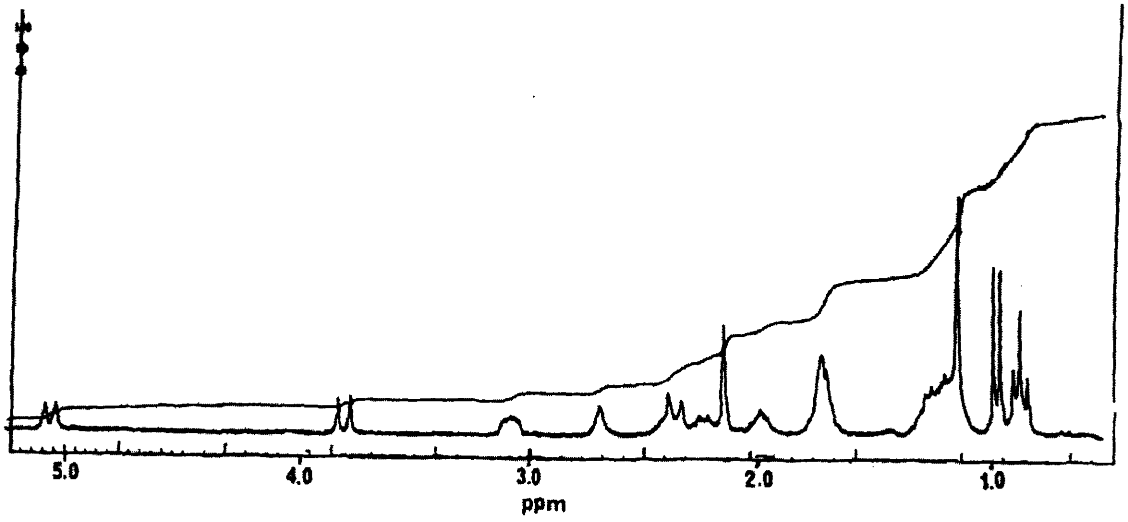
Carbon #	Natural Product 251D	Synthetic 251D
1	23.4	23.3
2	21.2	21.2
3	54.7	54.7
5	53.0	53.3
6	130.0	130.0
7	49.0	48.9
8	68.4	68.4
8a	71.8	71.8
9	24.3	24.4
10	134.7	134.7
11	32.1	32.2
12	37.6	37.6
13	29.8	29.8
14	22.9	22.9
15	14.2	14.2
16	21.8	21.8

Figure E1. Pumiliotoxin 251D.

Synthetic 251D (500 MHz in $CDCl_3$).

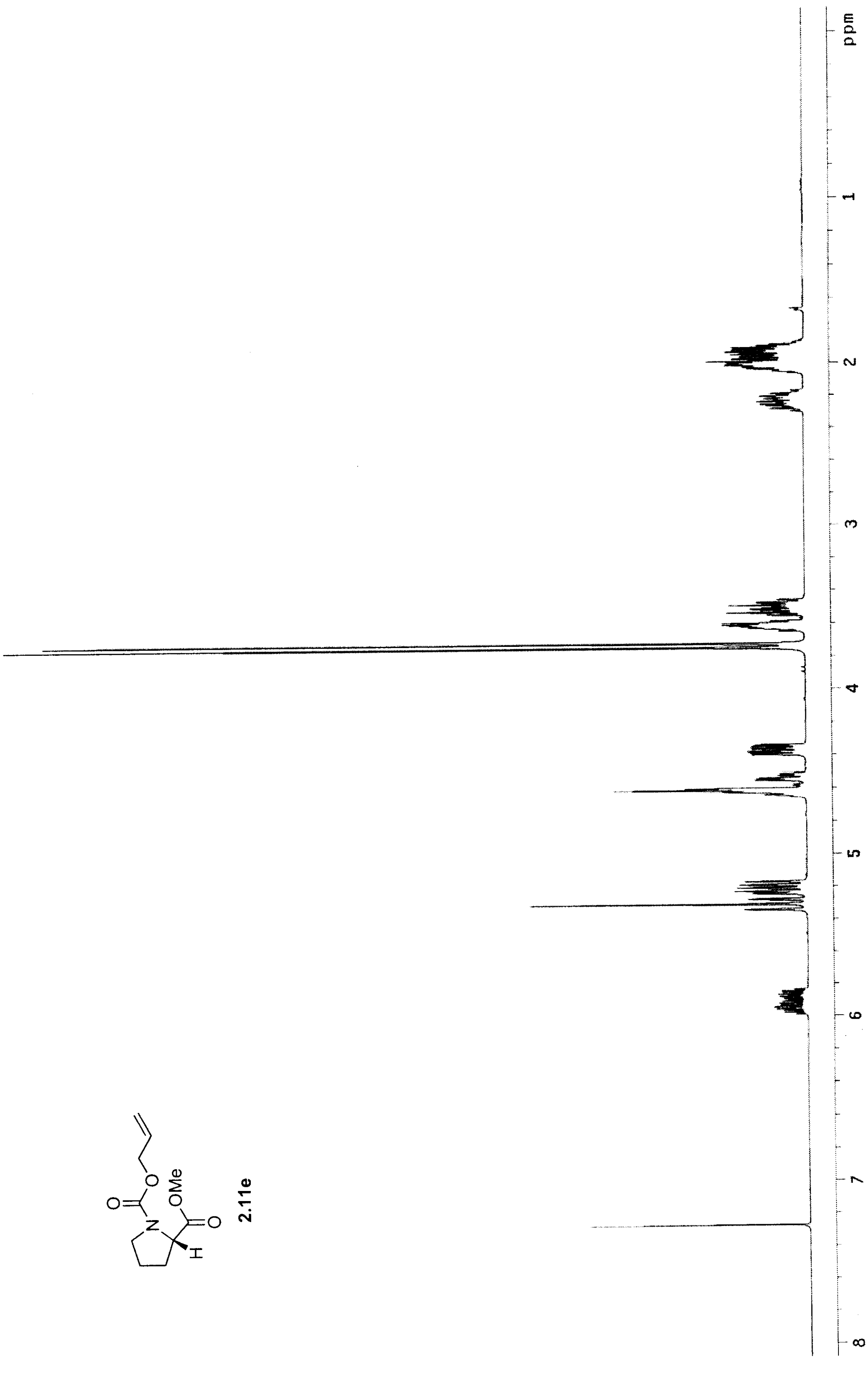


Natural 251D (220 MHz in $CDCl_3$).

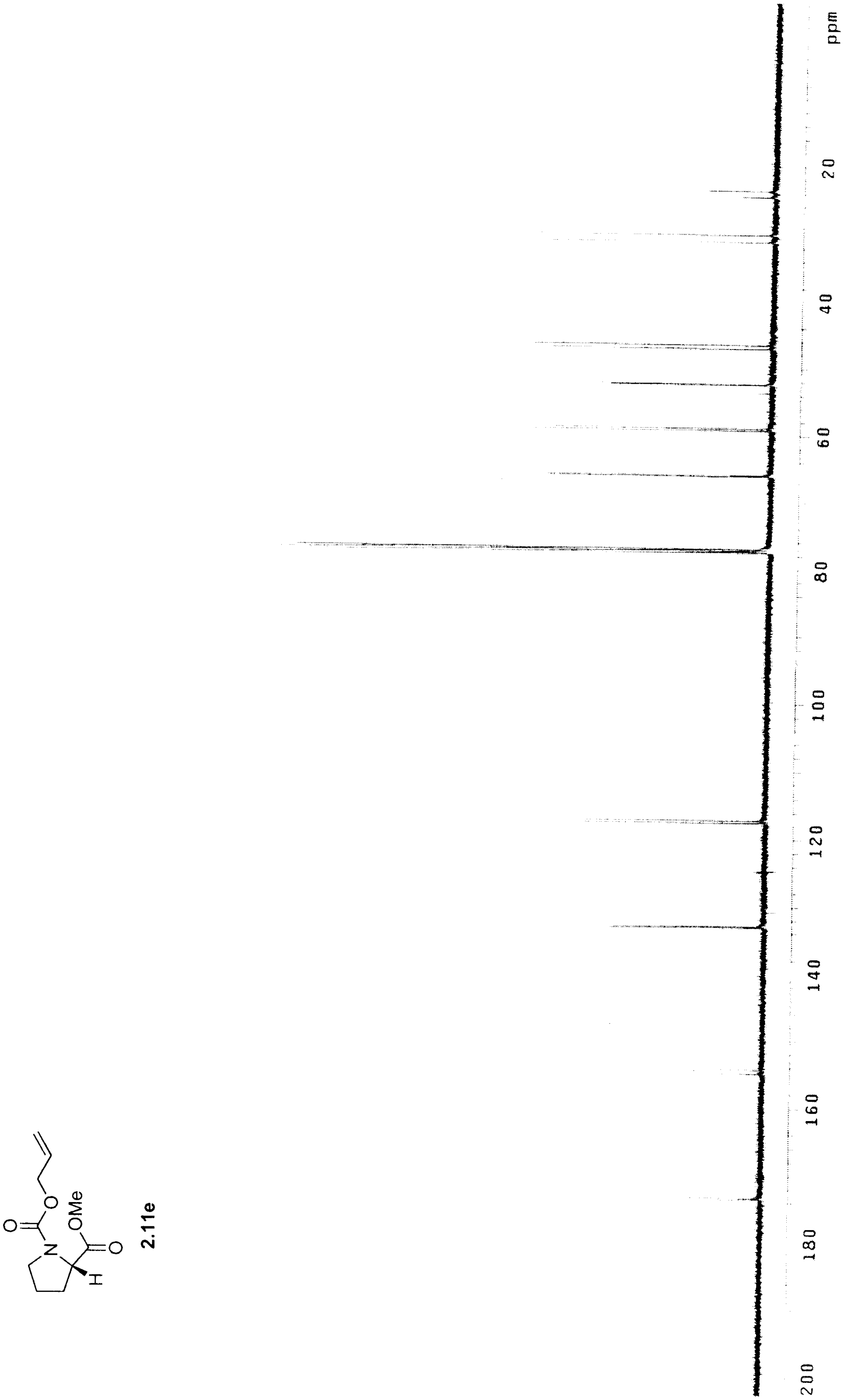


Chapter 2

Spectral Data



2.11e



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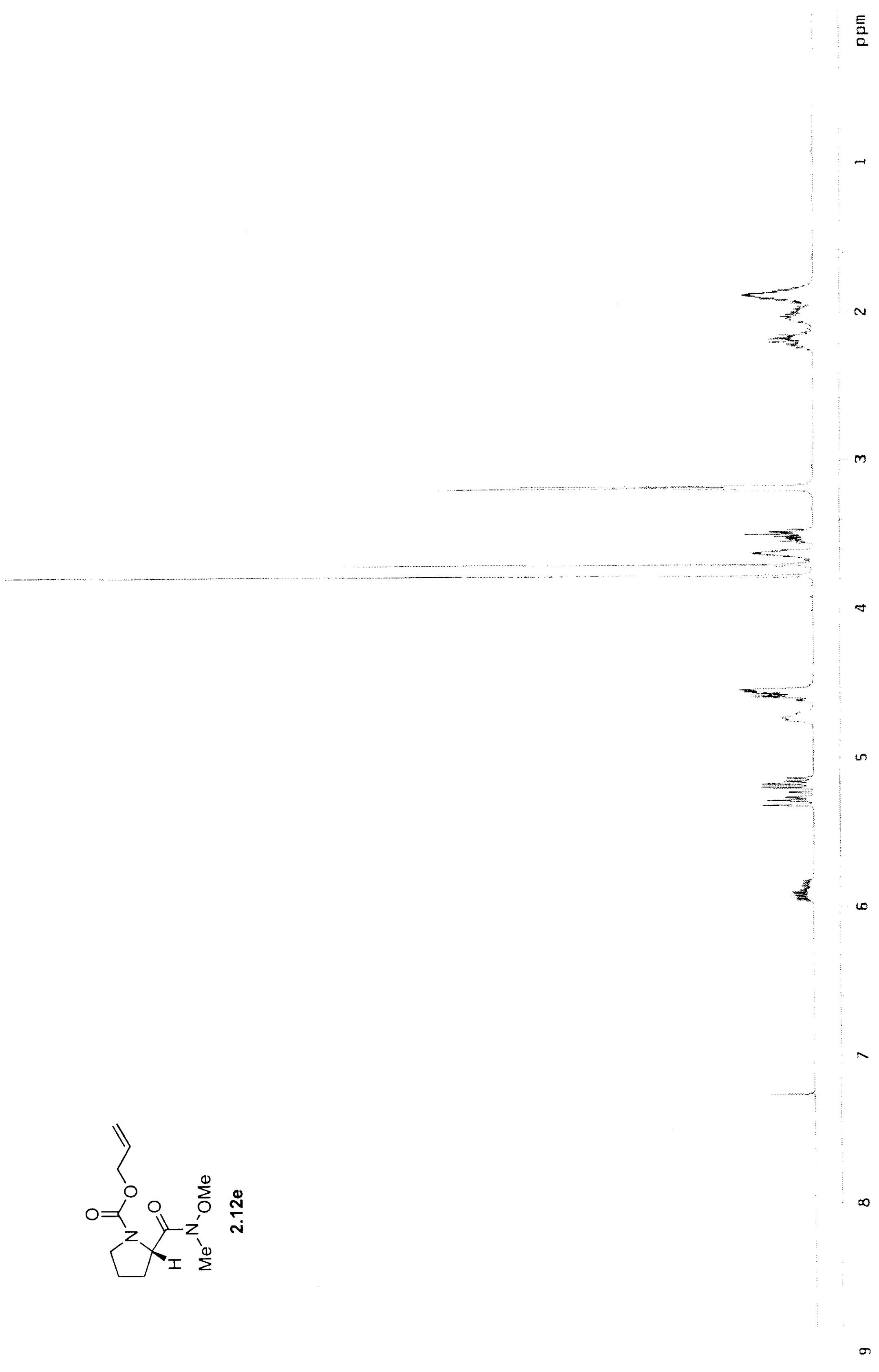

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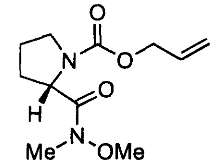

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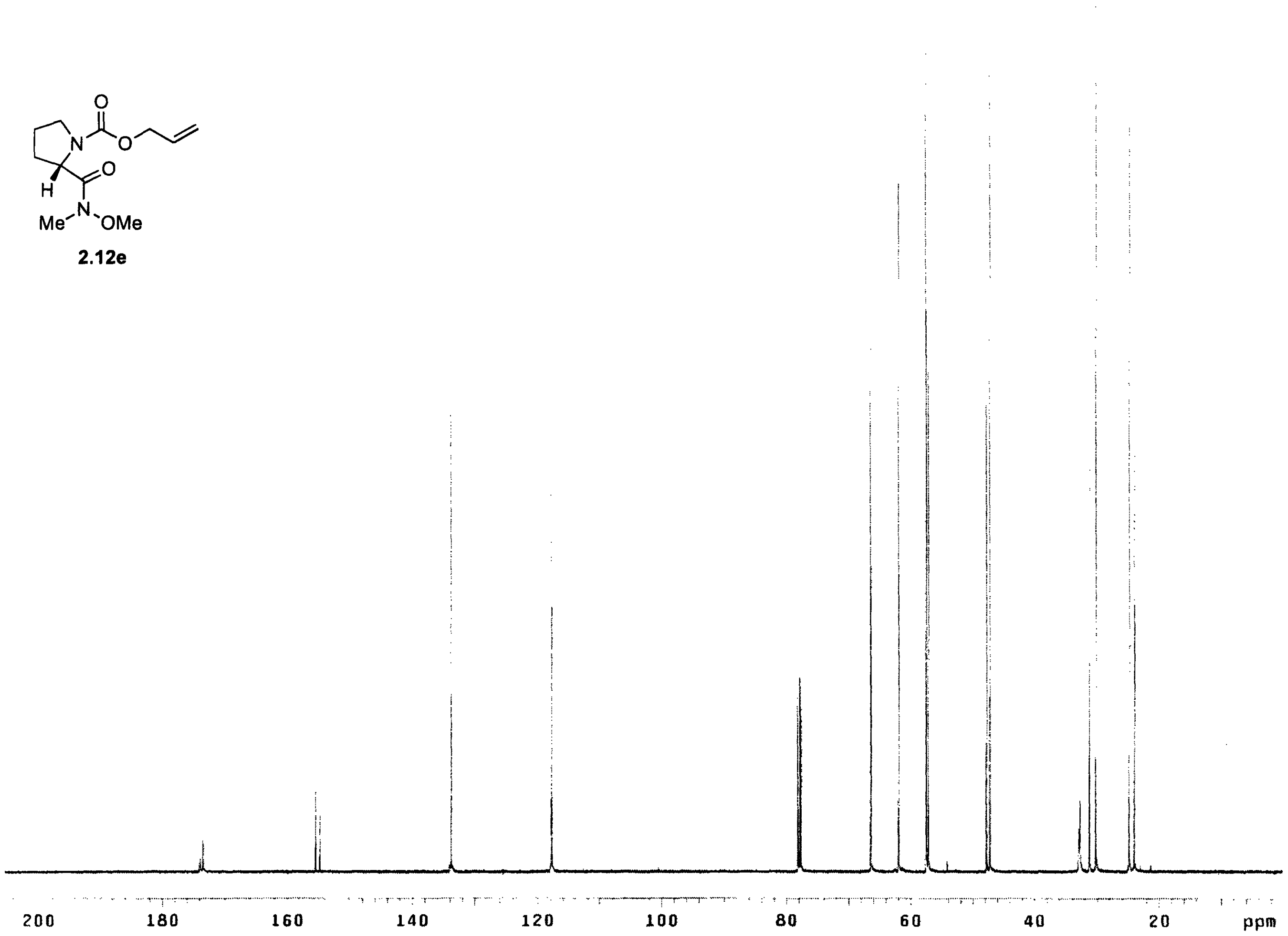

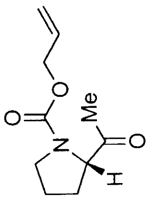

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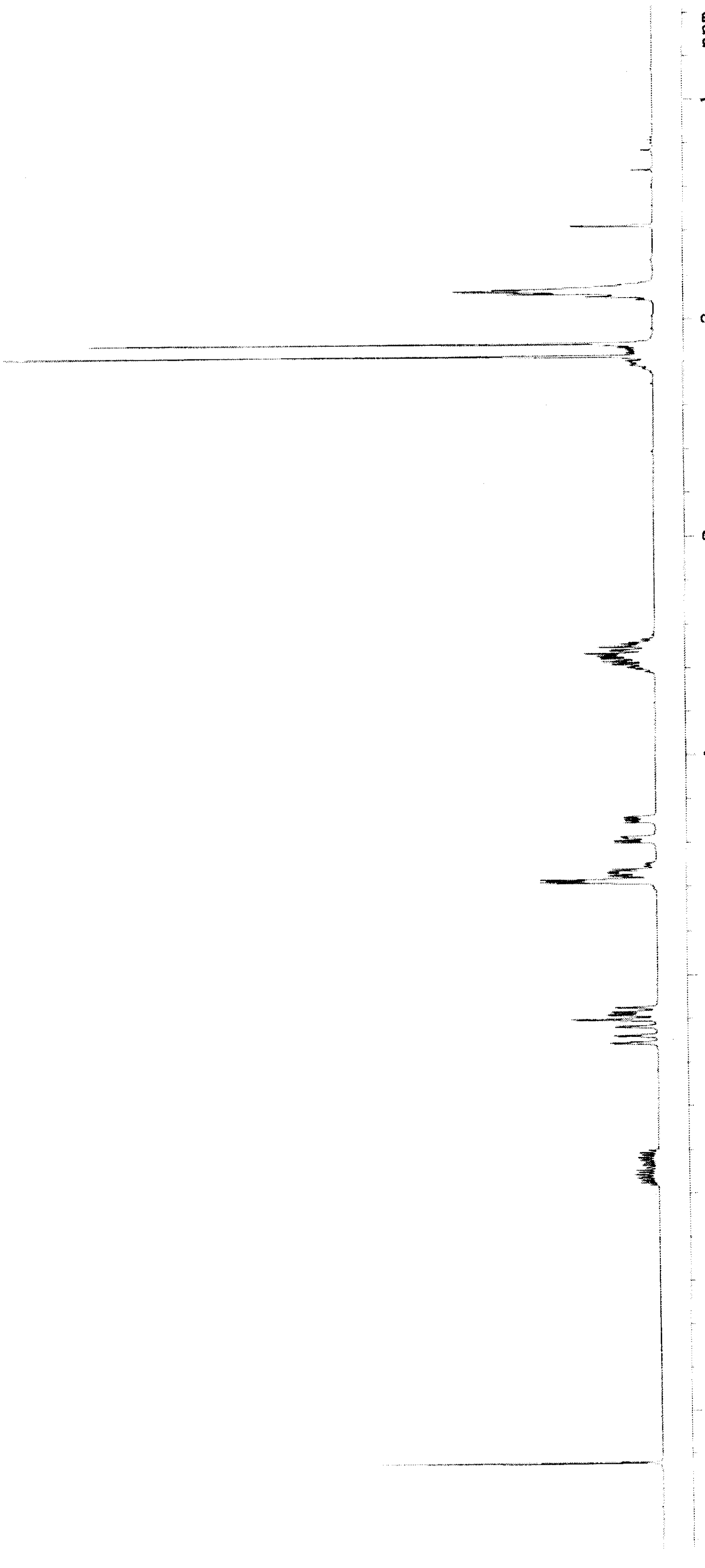

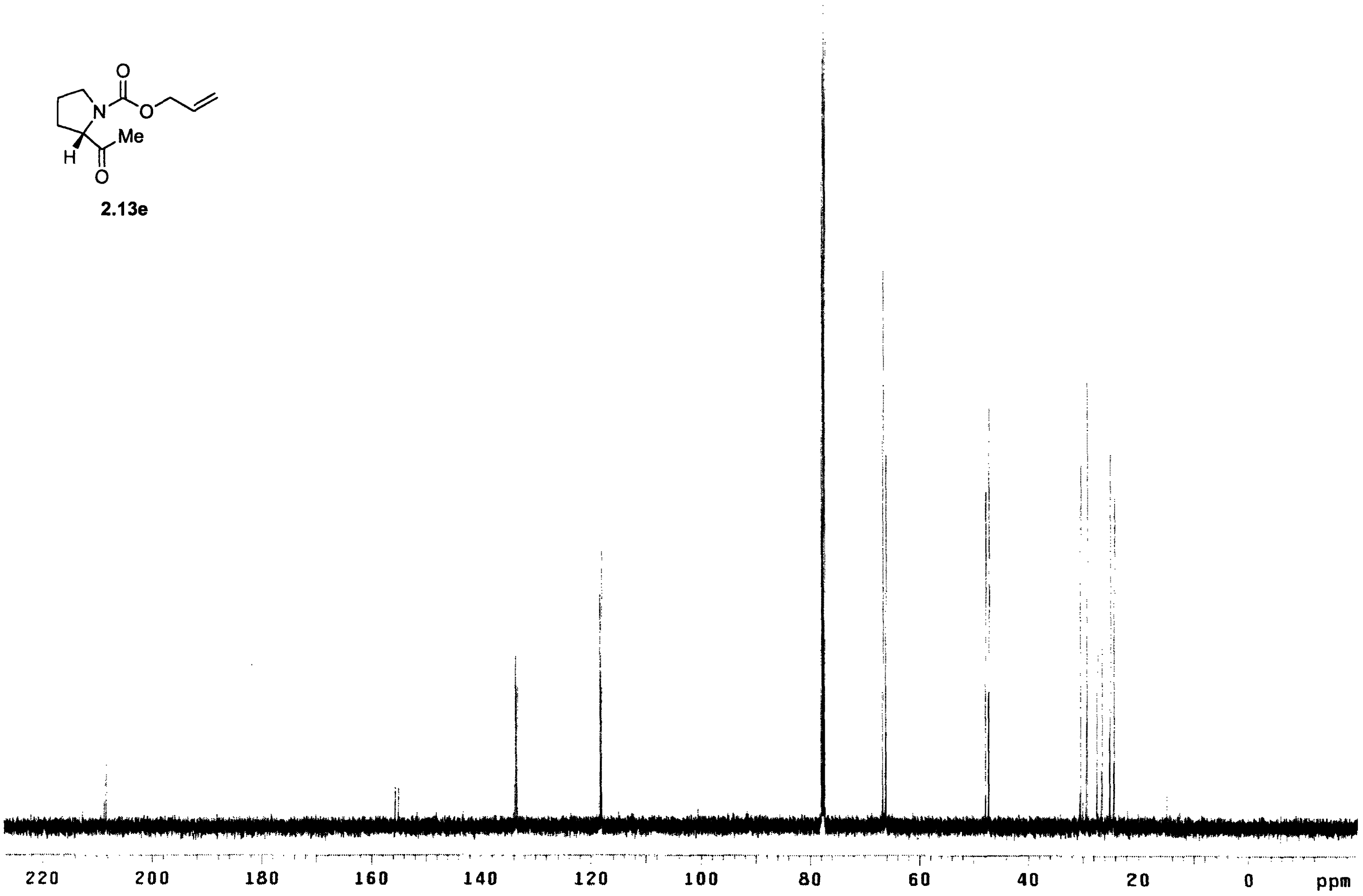

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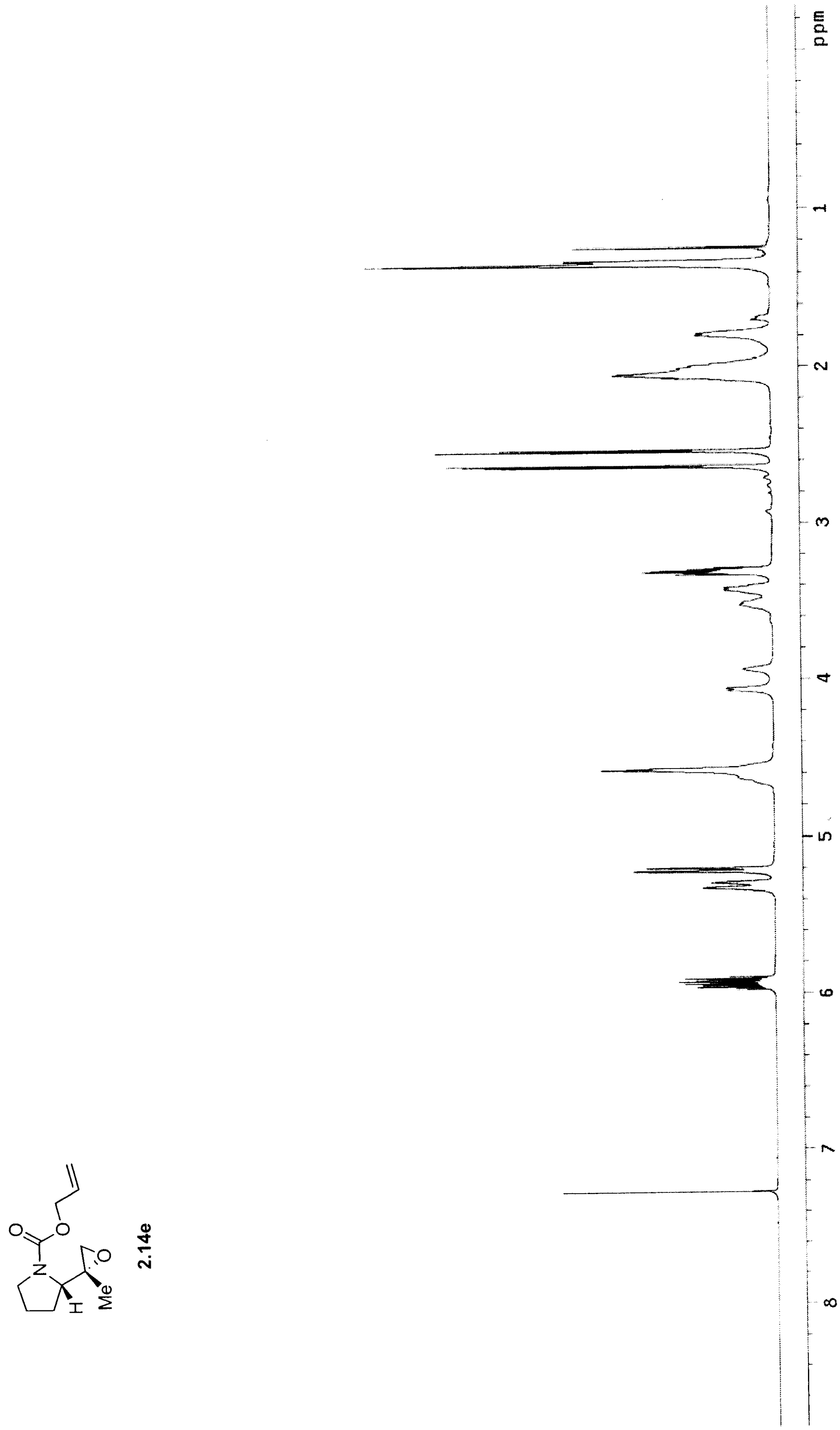

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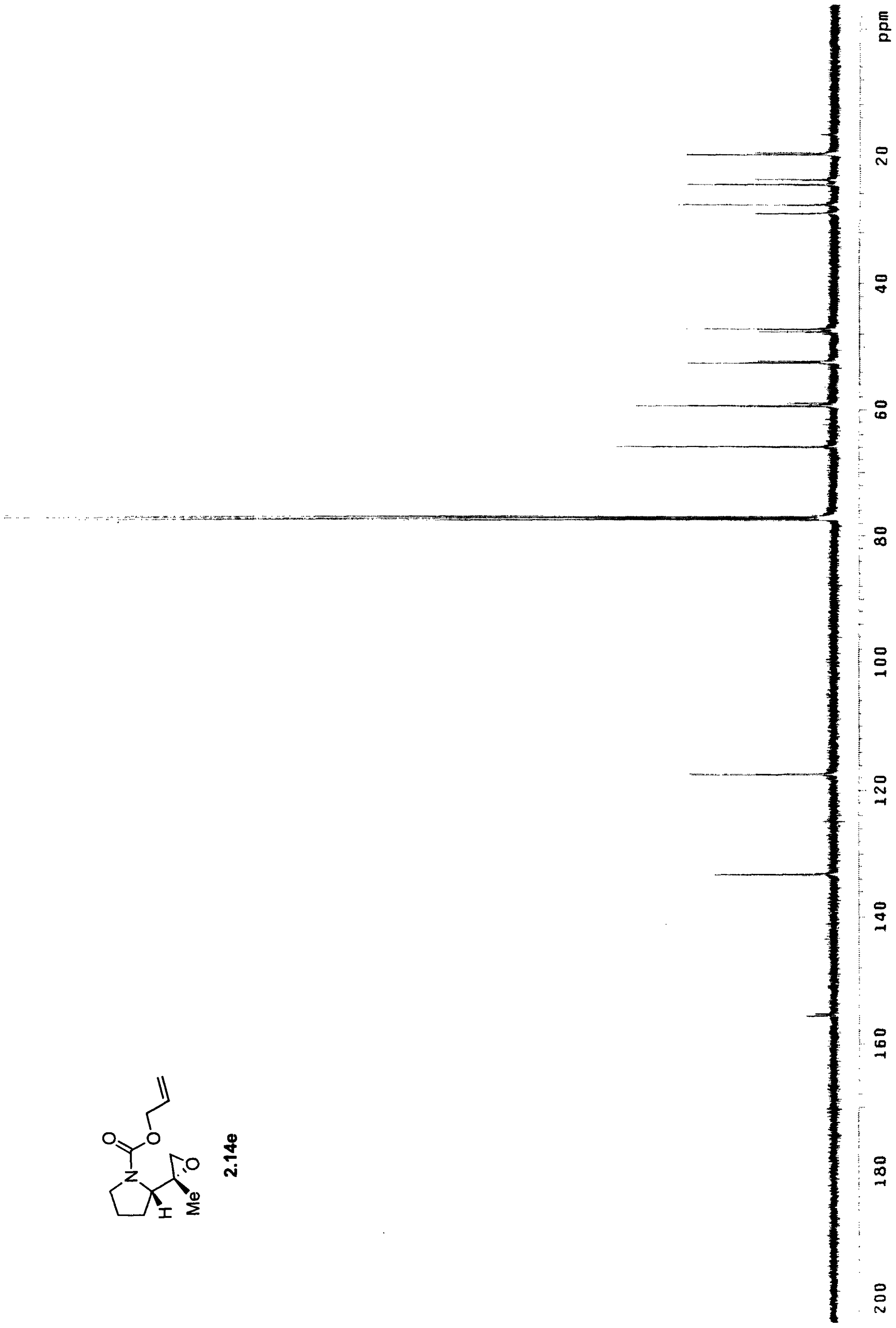

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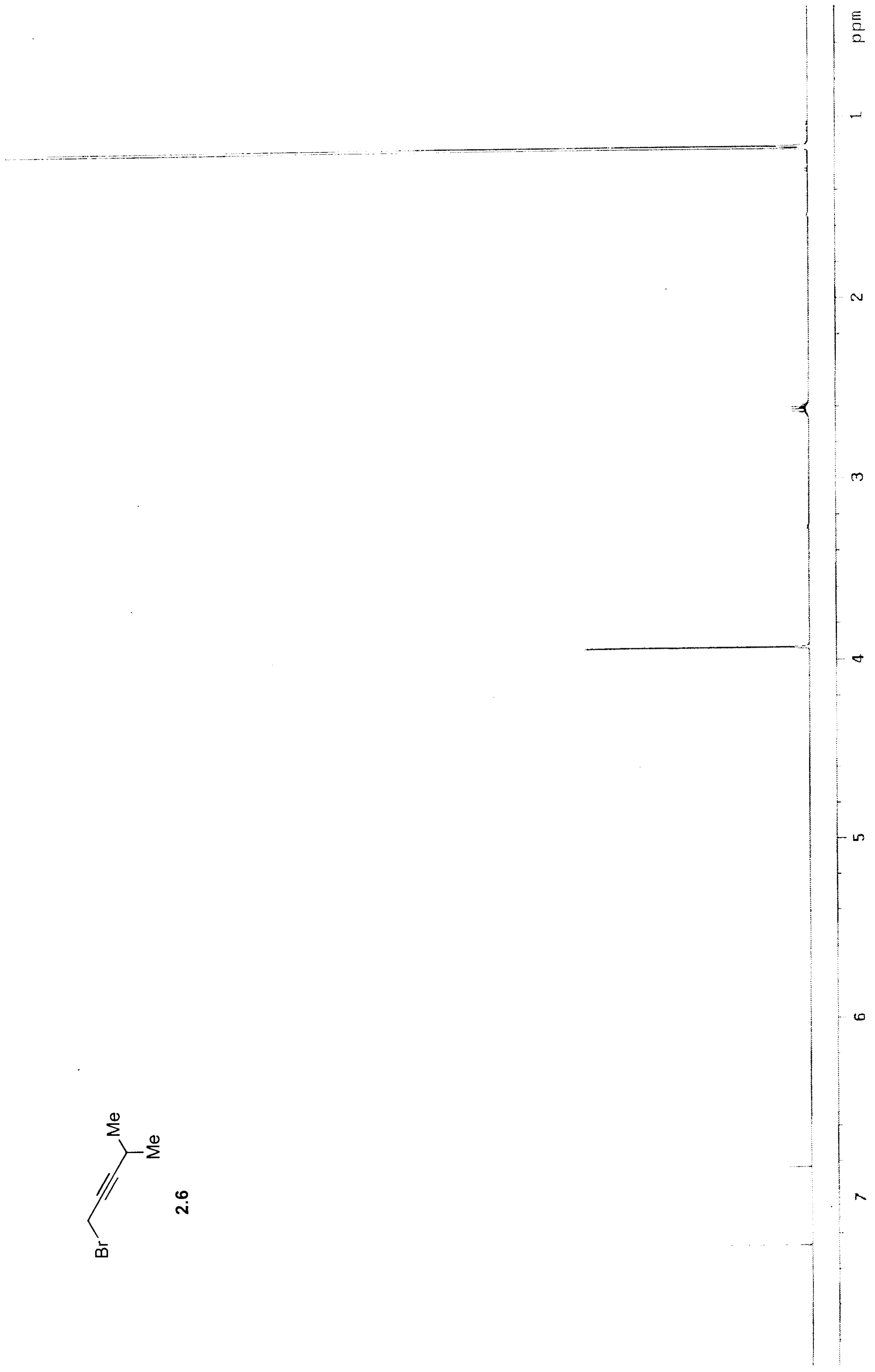

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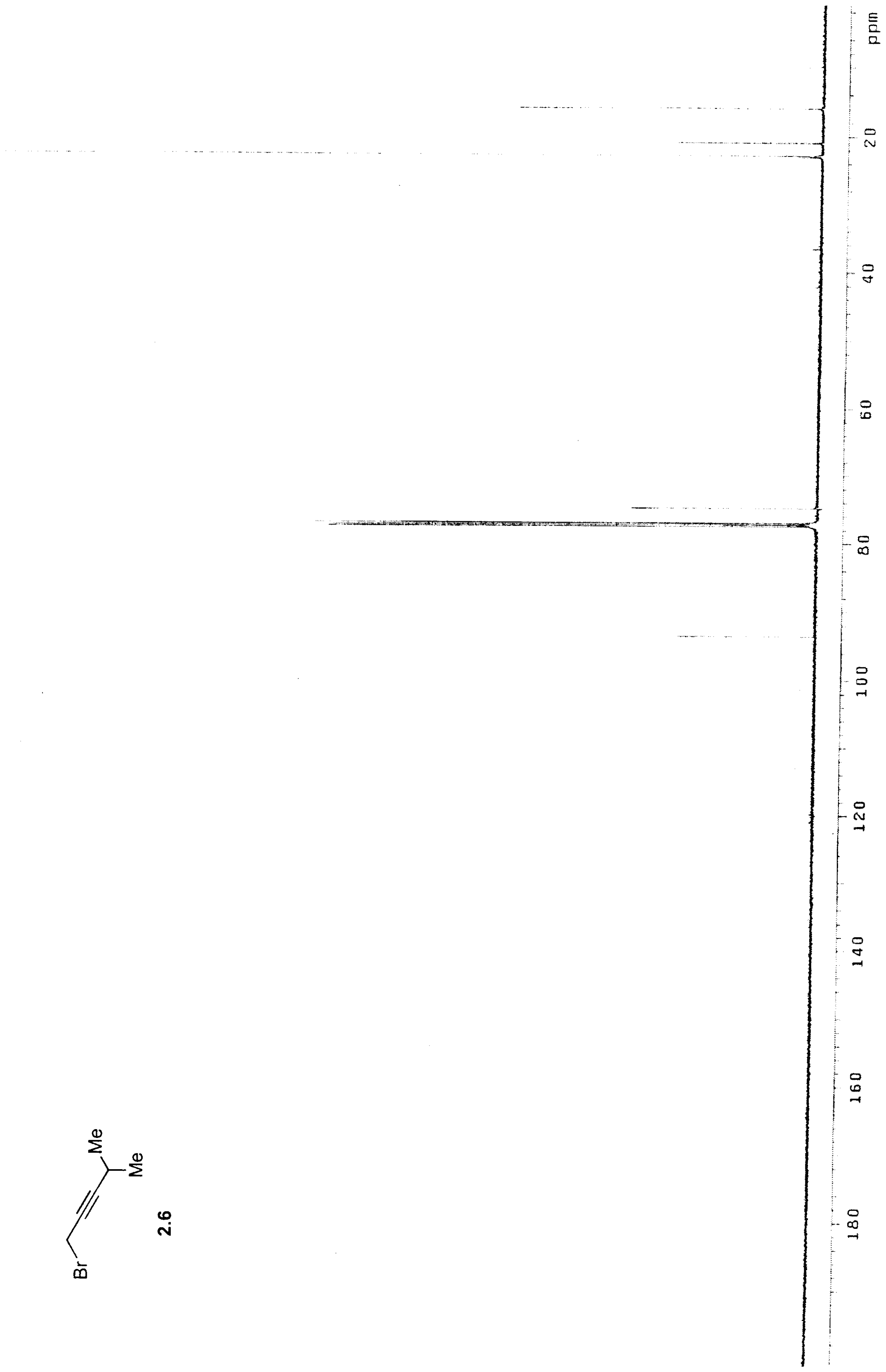

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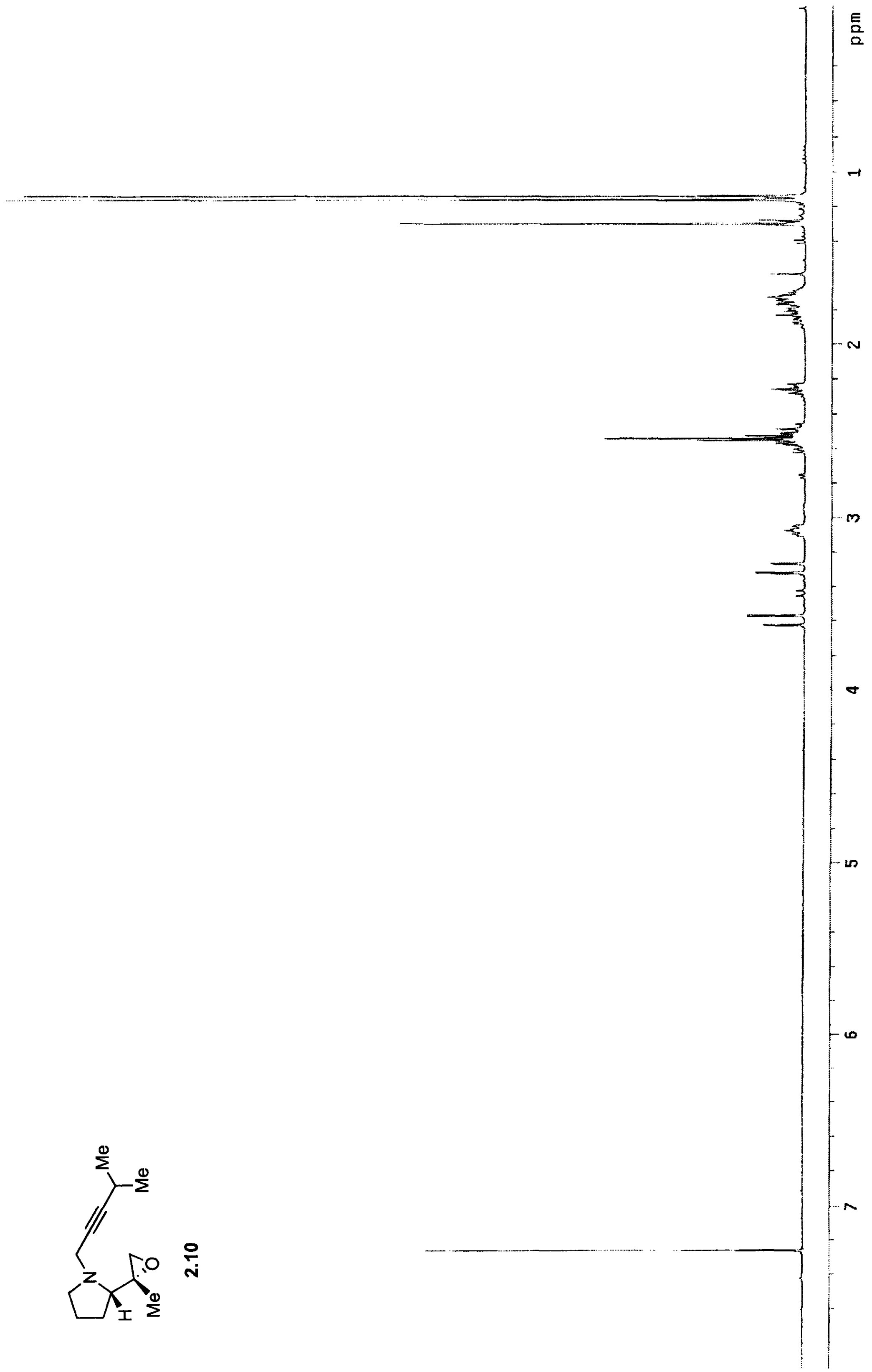

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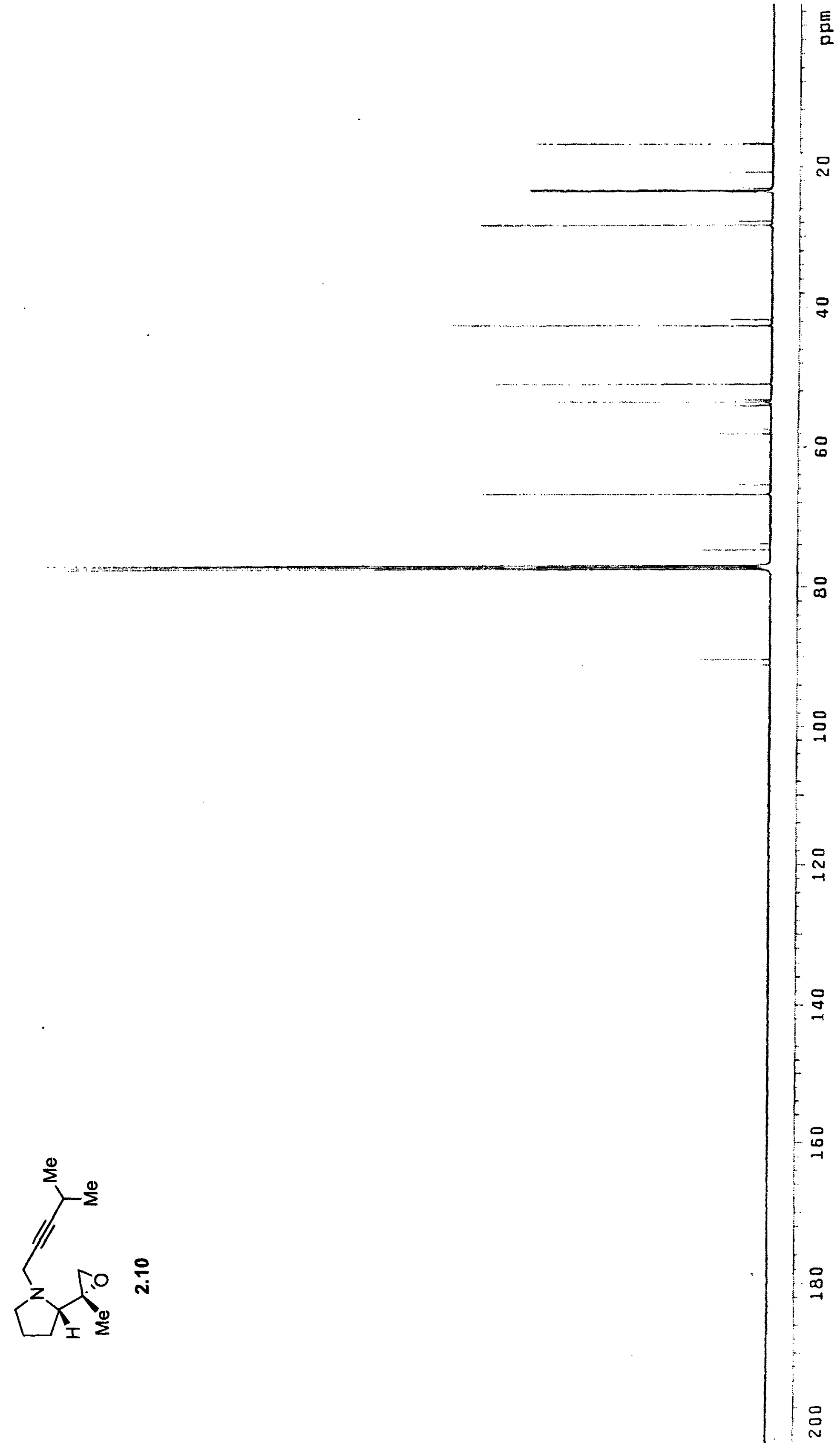
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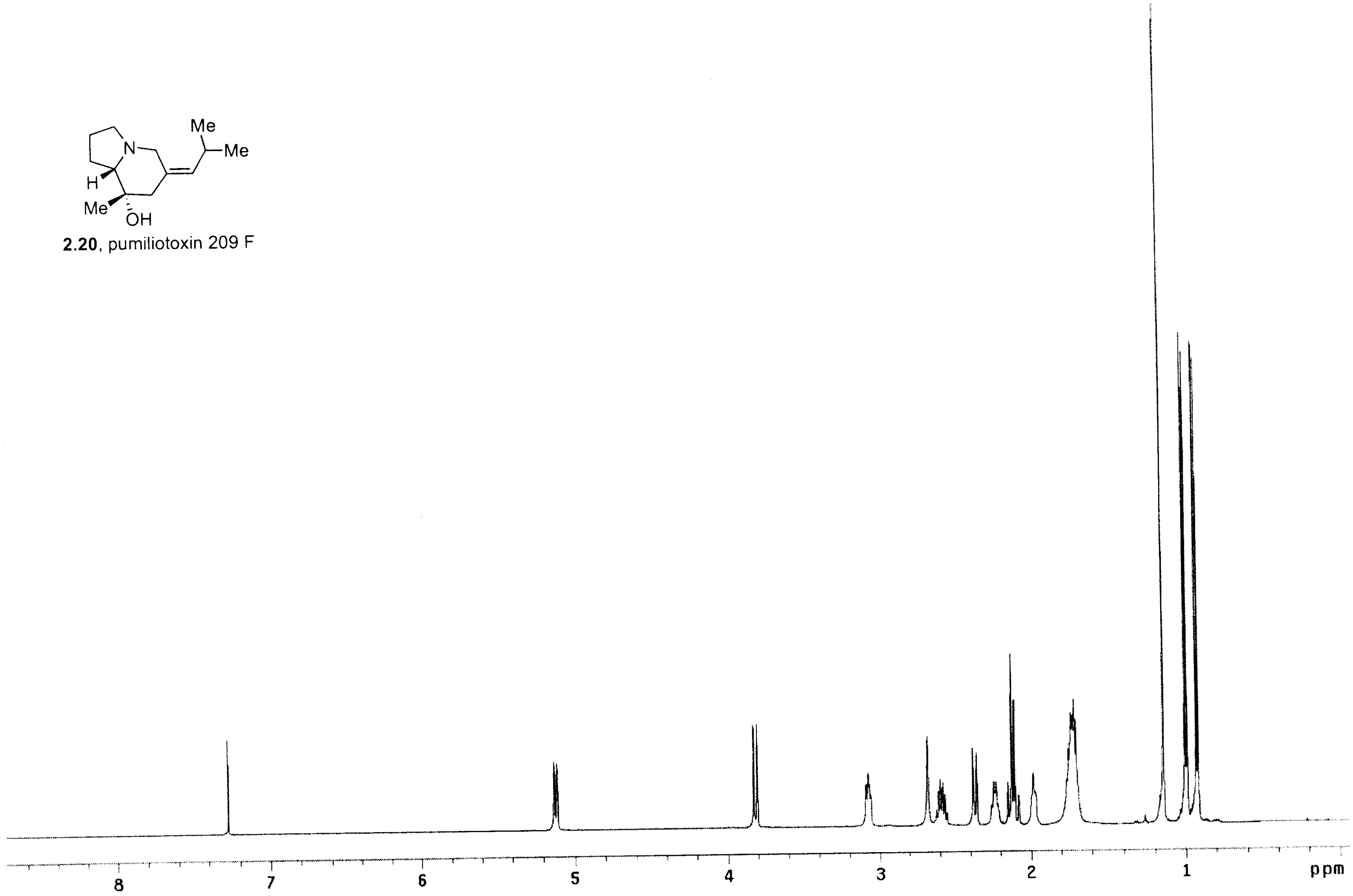
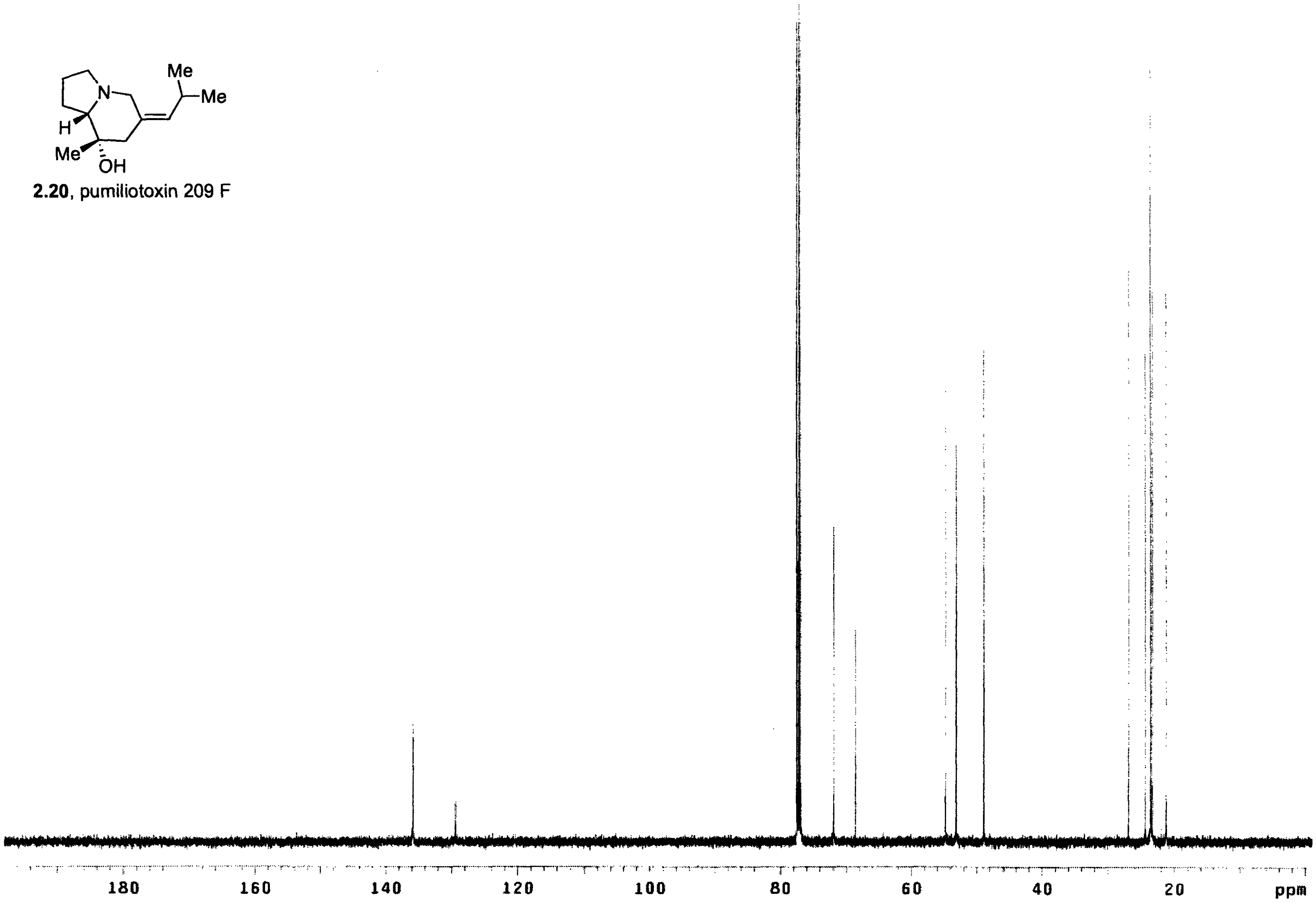
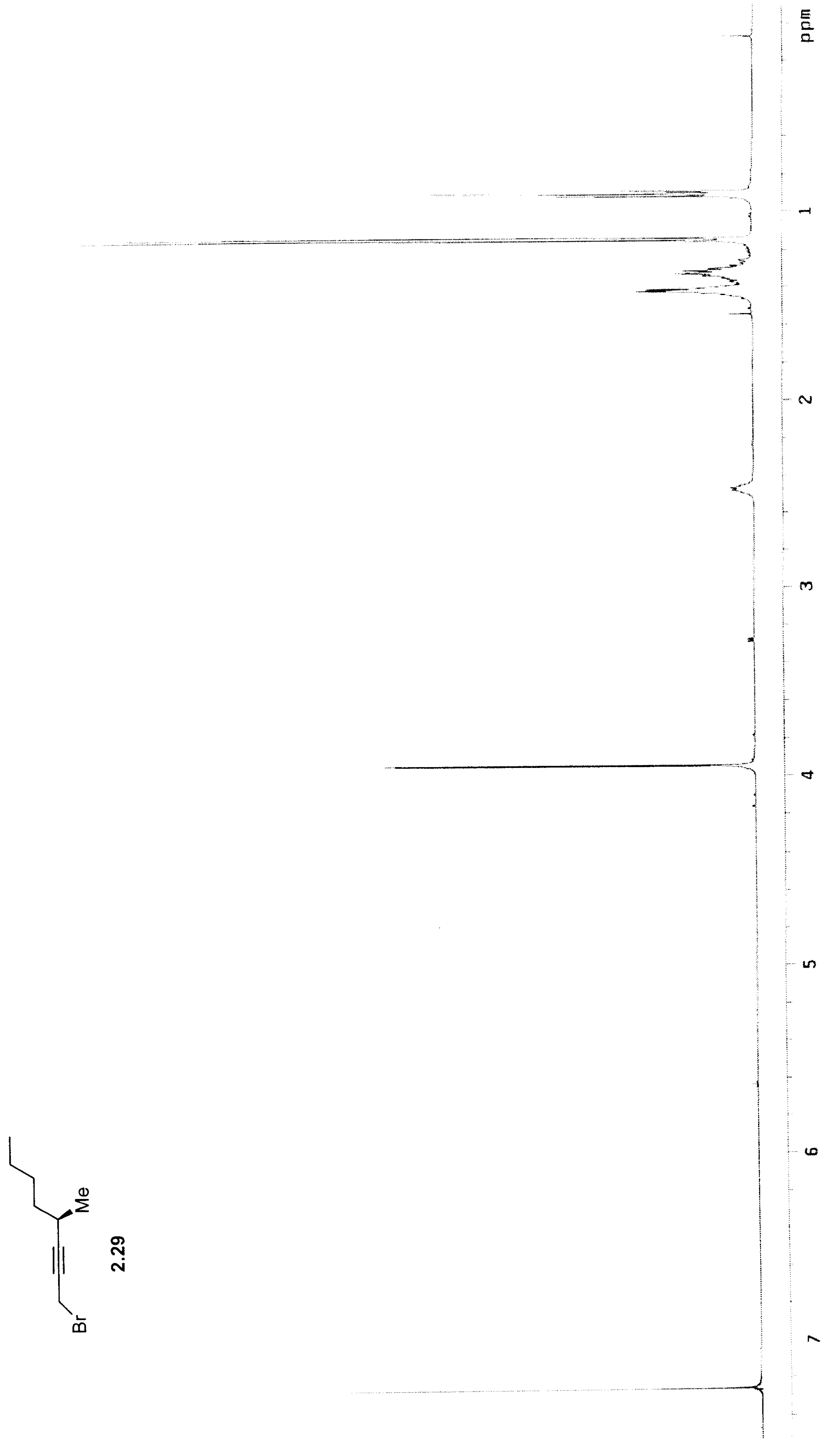
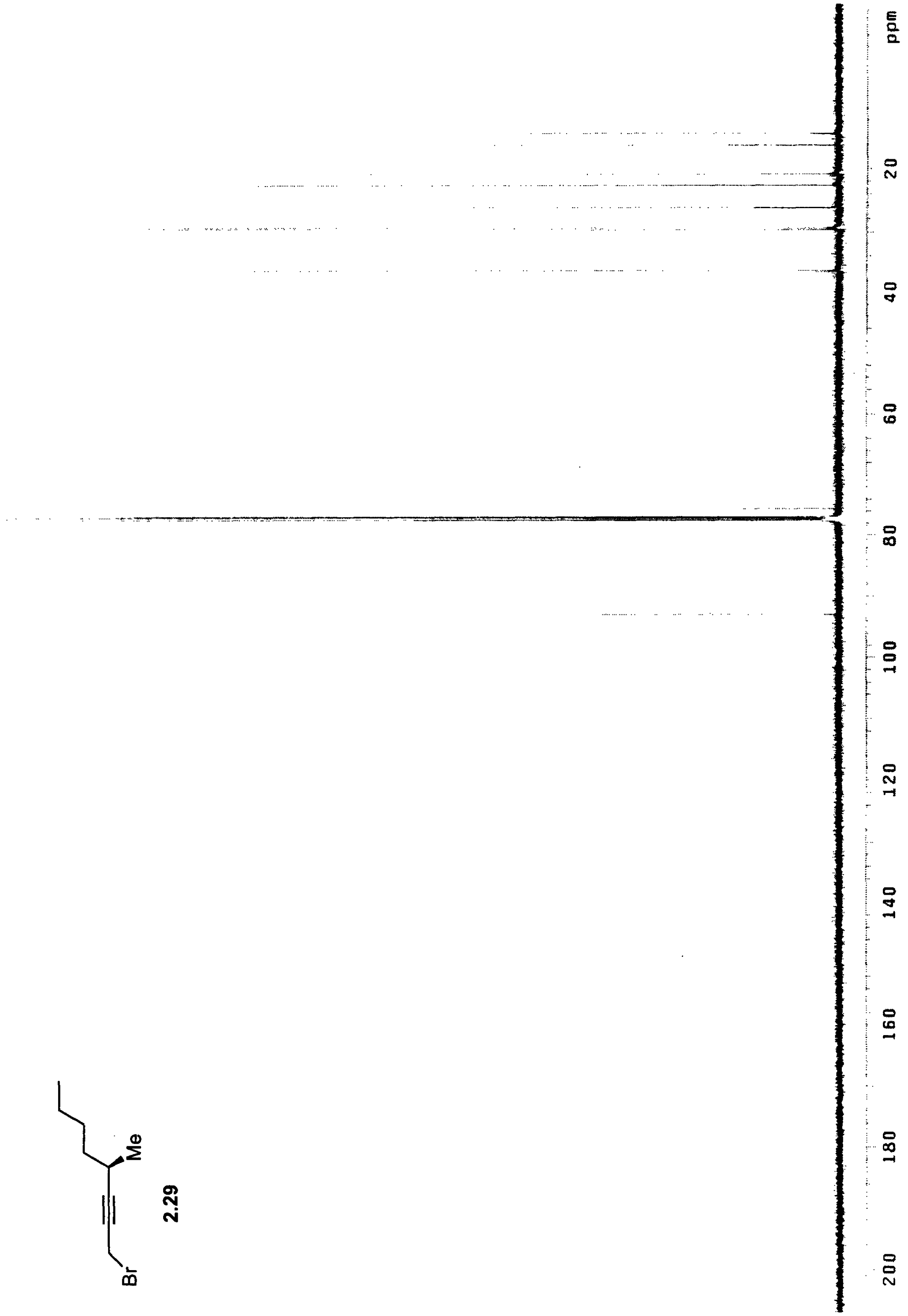


2.20, pumiliotoxin 209 F



2.20, pumiliotoxin 209 F


Br
Me
2.29
ppm
1
2
3
4
5
6
7



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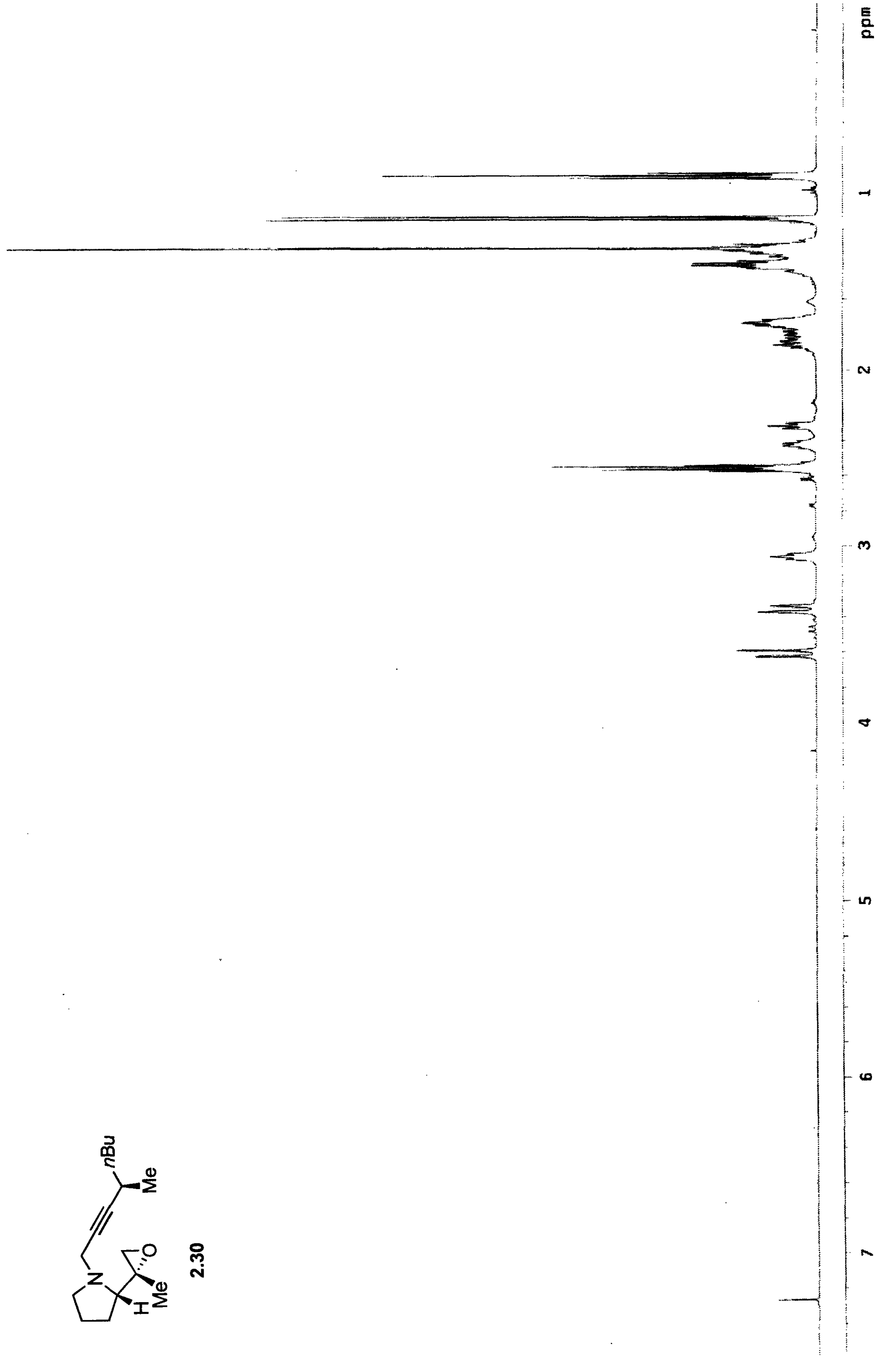
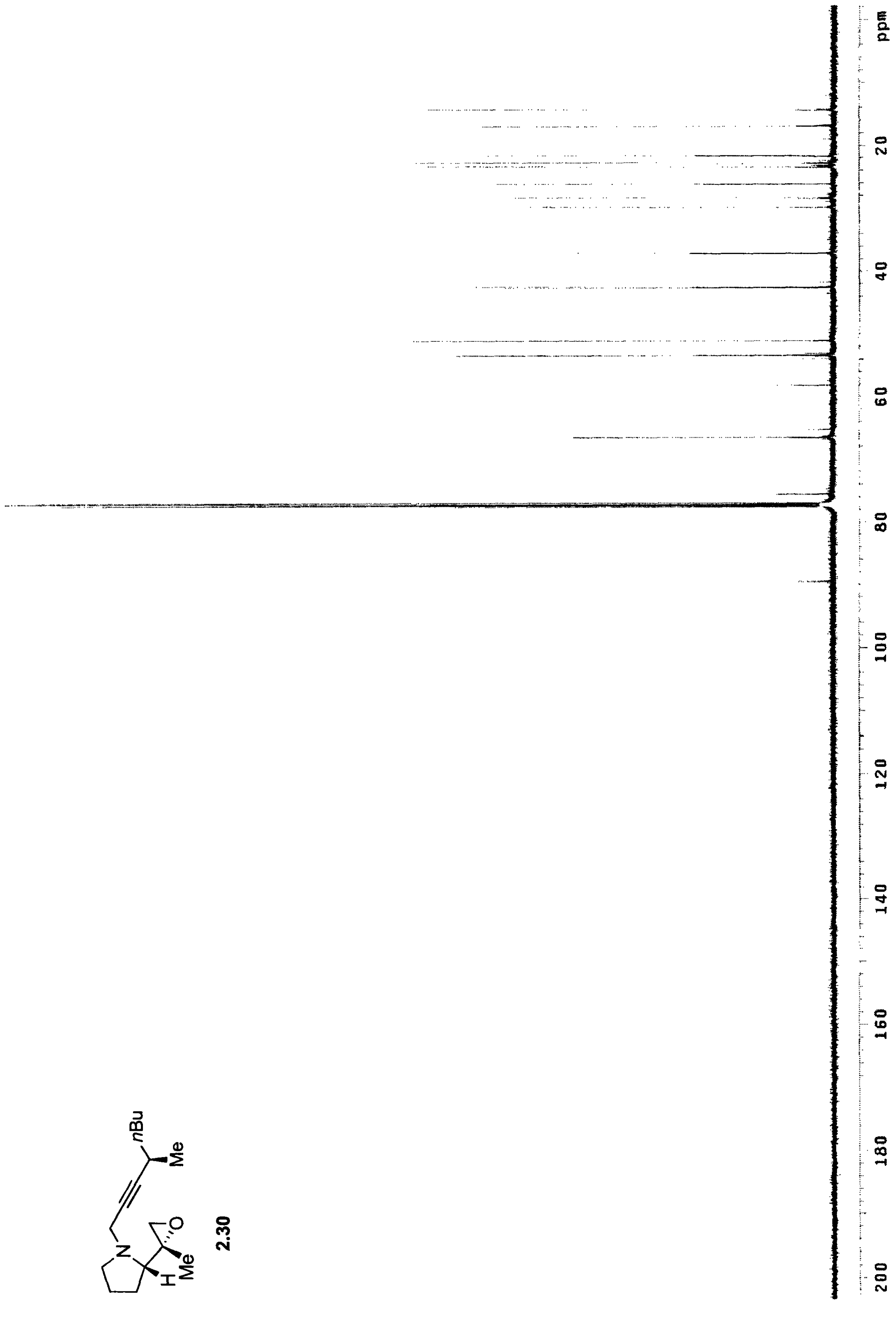
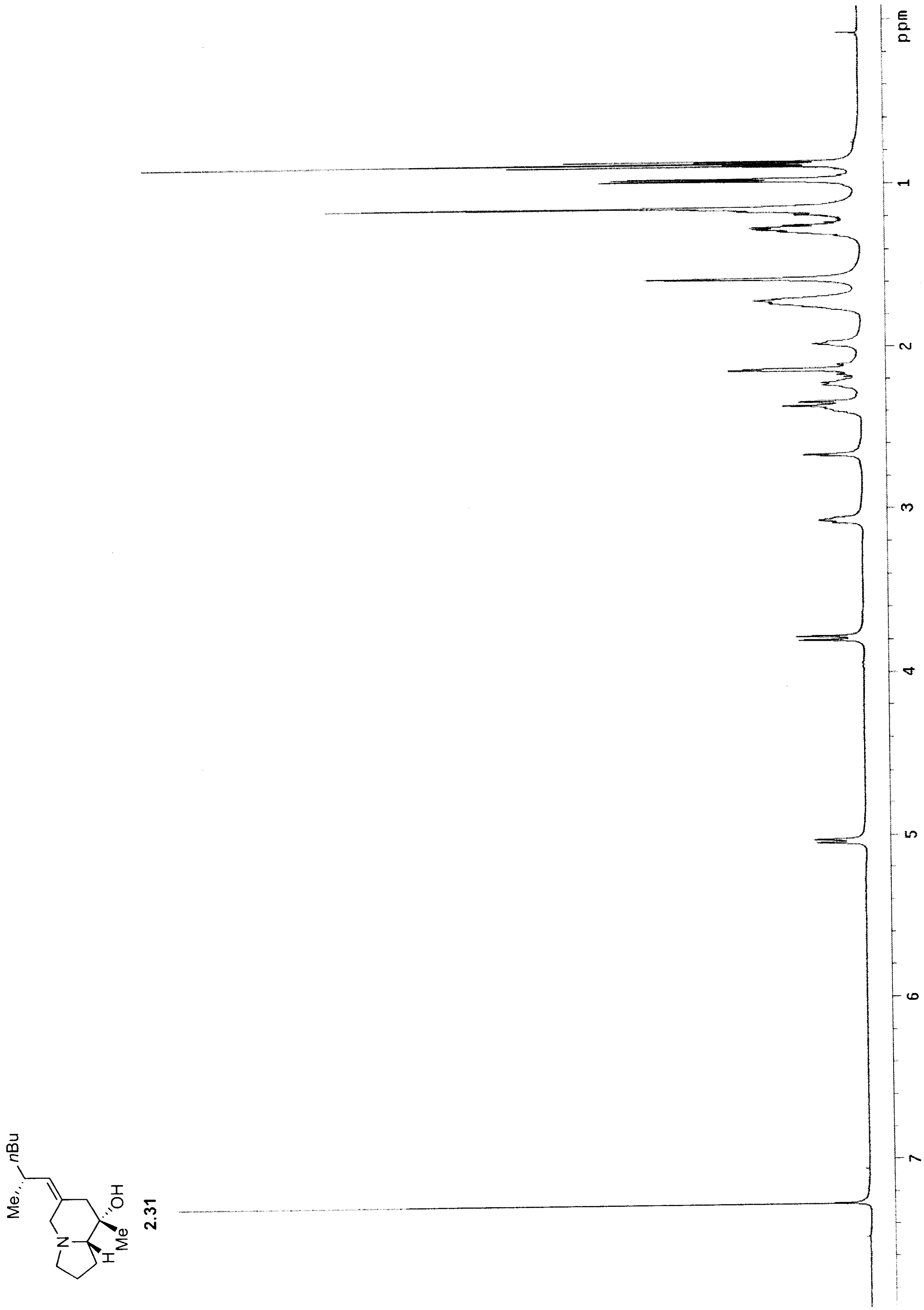


2.30

2.30





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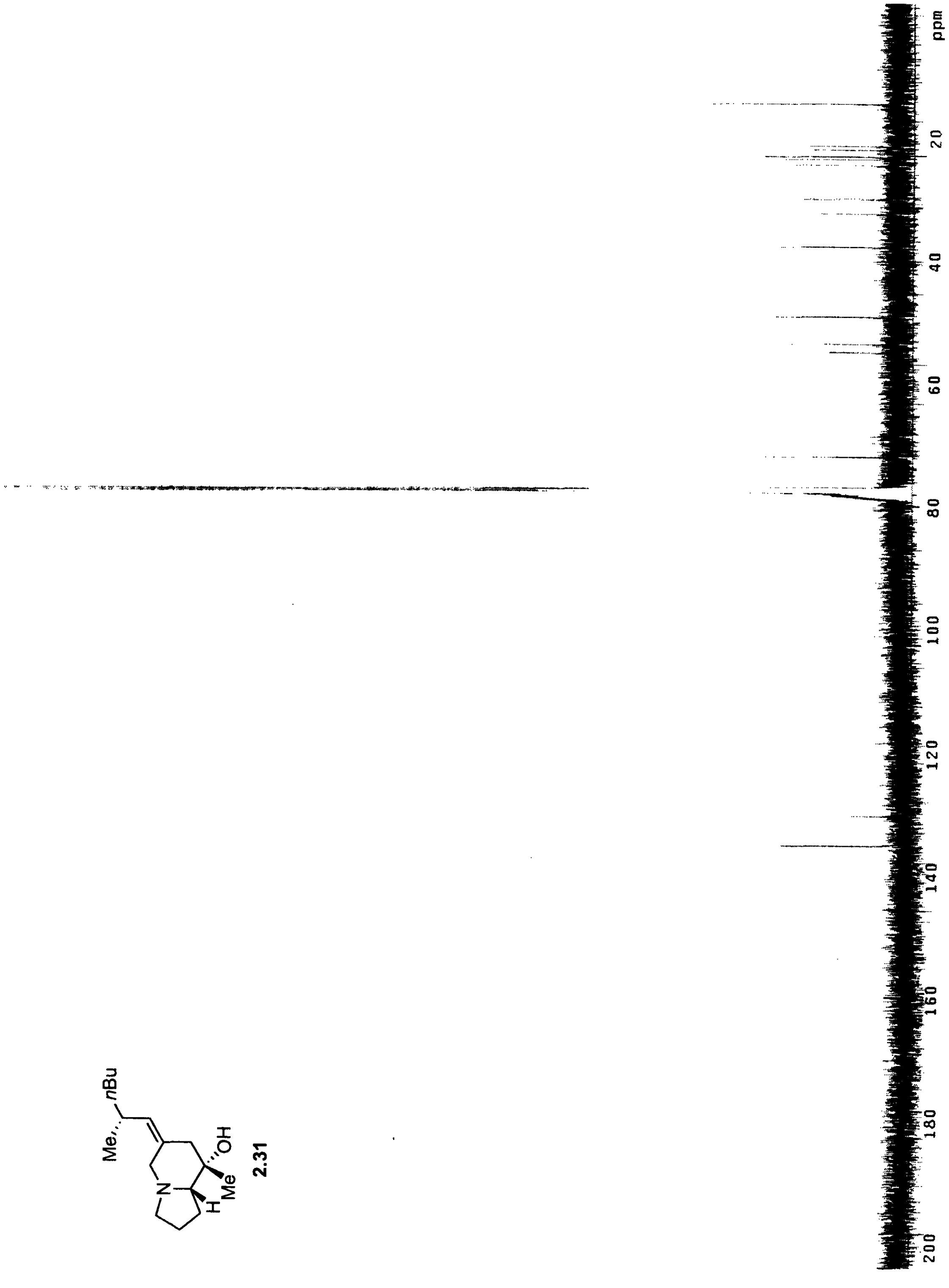

2.31

Curriculum Vitae

Education

2007	M.S., Organic Chemistry, Massachusetts Institute of Technology Thesis Title: "Nickel-Catalyzed Reductive Coupling Reactions: Application to the Total Syntheses of Pumiliotoxins 209F and 251D" Thesis Advisor: Professor Timothy F. Jamison
2004	B.S., Chemistry, University of New Hampshire Thesis Title: "Spectral, Structural, and Kinetic Studies of Copper(II) Complexes of Pendant-Armed Cross-Bridged Tetraamines" Undergraduate Thesis Advisor: Dr. Edward H. Wong

Research and Professional Experience

2004-2007	Graduate Research Fellow, Massachusetts Institute of Technology
2004-2006	Recitation Instructor, Massachusetts Institute of Technology One semester Principles of Chemical Science (5.112) One semester Organic Chemistry (5.12)
2003-2004	Undergraduate Research Fellow, University of New Hampshire
2001	Associates of Cape Cod, Summer Laboratory Technician

Publications and Presentations

Woodin, K. S.; Jamison, T. F. "Total Syntheses of Pumiliotoxins 209F and 251D via Late-Stage, Nickel-Catalyzed Epoxide-Alkyne Reductive Cyclization." *Manuscript in Preparation.*

Miller, K. M.; Colby, E. A.; **Woodin, K. S.**; Jamison, T. F. "Asymmetric Catalytic Reductive Coupling of 1,3-Enynes and Aromatic Aldehydes." *Adv. Synth. Catal.* **2005**, *347*, 1533-1536.

Woodin, K. S.; Heroux, K. J.; Boswell, C. A.; Wong, E. H.; Weisman, G. R.; Niu, W.; Tomellini, S. A.; Anderson, C. J.; Zakharov, L. N.; Rheingold, A. L. "Kinetic Inertness and Electrochemical Behavior of Copper (II) Tetraazamacrocyclic Complexes: Possible Implications for in Vivo Stability." *Euro. J. Inorg. Chem.* **2005**, *23*, 4829-4833.

Woodin, K. S.; Niu, W.; Wong, E. H.; Weisman, G. R.; Tomellini, S. A.; Anderson, C. J.; Zakharov, L. N.; Rheingold, A. L. "Acid Decomplexation, Solution Spectral, and X-ray Studies of Copper (II) Complexes of Carboxylate-armed Cross-bridged Tetraamines." 227th ACS National Meeting, Anaheim, CA, March 2004.

Honors and Awards

2004-2005	• Donald O'Brien Fellowship Recipient
2000-2004	• Dean's List Highest Honors • Dean's Scholarship (College of Engineering and Physical Sciences, CEPS) • Henry Herbert Smythe Scholarship • Cape Cod Association Scholarship • UNH Scholarship
2003-2004	• Summer Undergraduate Research Fellowship (UNH) • A. Fredrick Daggett Scholarship • Fogg Scholarship (highest ranking analytical chemistry student) • Helmut M. Haendler Award (highest ranking inorganic chemistry student) • Ford Memorial Award • Marie Louise Langelier Scholarship (CEPS) • Elmer F. and Marien Mitchell Cutts 1916 Scholarship (CEPS) • Merck Index Award
2002-2003	• Robert T. Hart Scholarship • Basset Scholarship (CEPS)
2001-2002	• Edna O. Brown Memorial Scholarship • John H. Smith Scholarship (CEPS) • UNH Study Abroad Scholarship • AustraLearn Scholarship
2001-2002	• CRC Award (highest ranking chemistry freshman) • Arthur Hennessey Scholarship • Cancer Society Scholarship • Elks Scholarship