

Phosphine-Promoted Cross-Coupling Reactions of Propargylcopper Reagents and Alkenyl Iodides and the Total Synthesis of (-)-Gloeosporone via Nickel-Catalyzed Epoxide-Alkyne Reductive Macrocyclization

by

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University of Michigan, Ann Arbor, 2002

Submitted to the Department of Chemistry
in Partial Fulfillment of the Requirements
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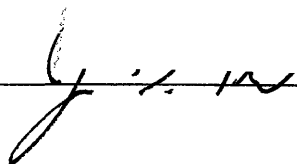
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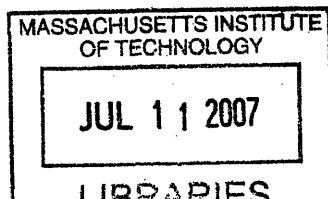
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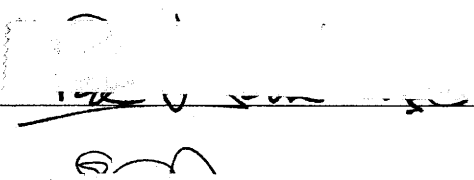
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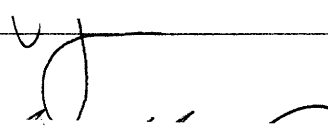
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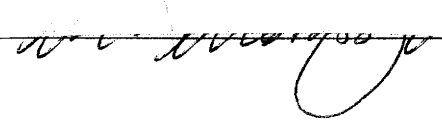
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Thesis Supervisor

Professor Mohammad Movassaghi



*To my family
and to my dearest Deniska*

Phosphine-Promoted Cross-Coupling Reactions of Propargylcopper Reagents and Alkenyl Iodides and the Total Synthesis of (-)-Gloeosporone via Nickel-Catalyzed Epoxide-Alkyne Reductive Macrocyclization

by

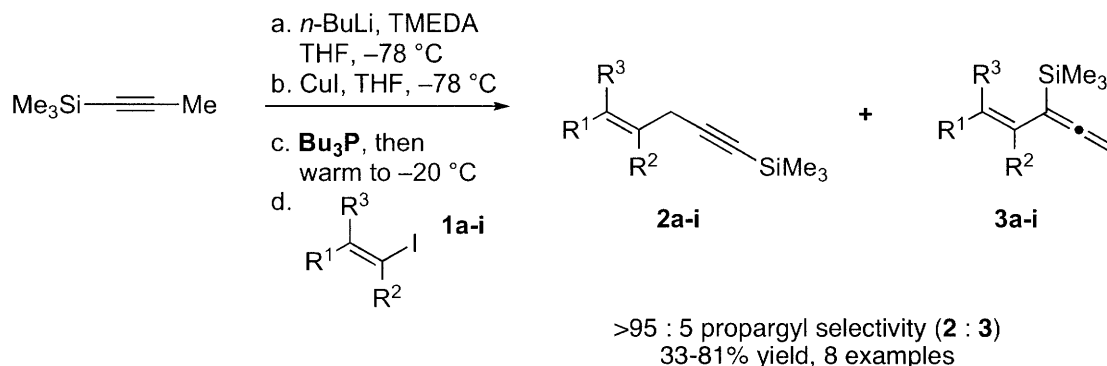
James D. Trenkle

Submitted to the Department of Chemistry on May 3rd, 2007
in Partial Fulfillment of the Requirements for the Degree of
Doctor of Philosophy in Organic Chemistry

Abstract

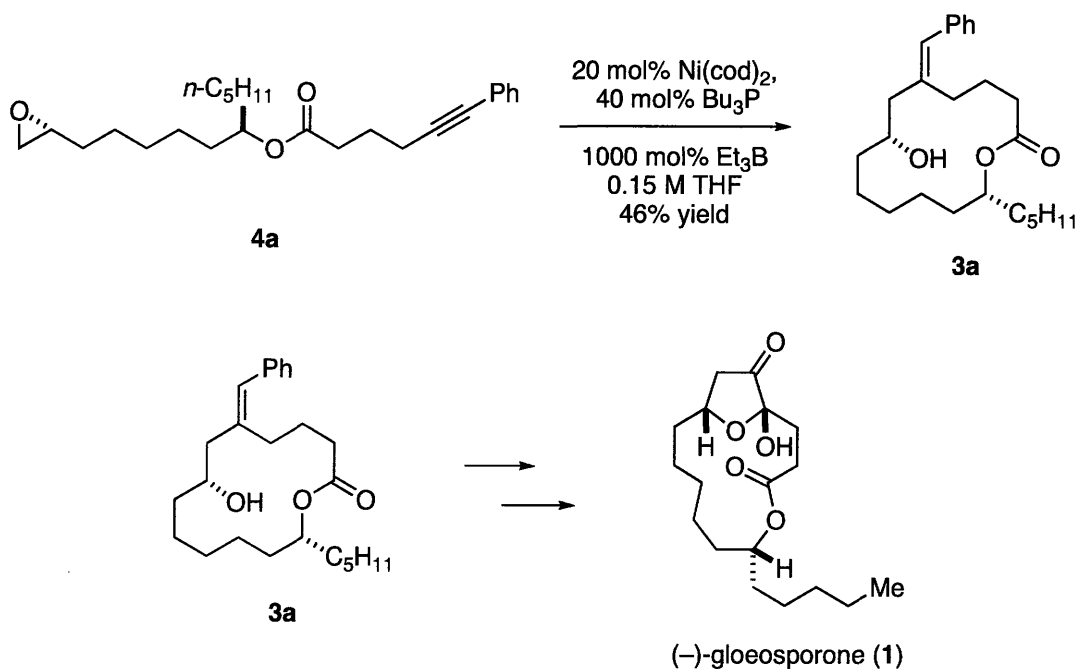
I. Phosphine-Promoted Cross-Coupling Reactions of Propargylcopper Reagents and Alkenyl Iodides

An electron-rich phosphine additive is critical and sufficient for propargyl-selective couplings of propargylcopper reagents and alkenyl iodides. This method is complementary to those previously described, in which high allenyl selectivity is observed in analogous coupling reactions. While the basis of the phosphine effect requires further investigation, the information gained in these studies enables the synthesis of complex molecules by way of skipped enyne intermediates.



II. Total Synthesis of (-)-Gloeosporone via Nickel-Catalyzed Epoxide-Alkyne Reductive Macrocyclization

The total synthesis of macrolide natural product (-)-gloeosporone **1** is described in 10 steps (LLS) and 5.2% overall yield. The key macrocyclization was performed via nickel-catalyzed reductive macrocyclization of an alkyne and an epoxide to give the 14-membered ring in 46% yield (**4a** → **3a**; up to 67% yield could be achieved with stoichiometric nickel). This transformation differs from previous strategies in closing the macrocycle of **1** using more traditional approaches such as macrolactonization and ring-closing metathesis.



Additional nickel-catalyzed macrocyclization studies of alkynes and epoxides were undertaken with other alkynylepoxides. With these studies we were able to recognize an important structural pattern (a δ,ϵ -unsaturated ynoate) which might be necessary for efficient cyclization. Using this information, the nickel-catalyzed reductive cyclization of alkynes and epoxides was extended to the formation of 12- and 15-membered rings.

Preface

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

Synthesis of skipped enynes via phosphine-promoted couplings of propargylcopper reagents

Tetrahedron **2003**, *Symposium-In-Print, New Synthetic Methods VII*, 59, 8913–8917.

Heffron, T. P.; Trenkle, J. D.; Jamison, T. F.

Acknowledgments

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I must also thank those whose work have provided important groundwork for my own. Thus, my gratitude goes to Tim Heffron for his key role in the discovery of the propargylation chemistry, to Dr. Carmela Molinaro for her seminal efforts on nickel-catalyzed alkyne-epoxide reductive coupling, and to the other members of the Jamison group whose efforts we have all built upon.

There are many other coworkers who have been instrumental in not only the academic aspects of my growth, but my personal path as well. In both regards, I am extremely lucky to have excellent lab mates in Victor Gehling, Aaron Van Dyke, Chudi Ndubaku, Graham Simpson, Brian Sparling, and Ryan Moslin. Victor "bald guy on my right" Gehling has been a fun bay mate and a good friend. Aaron has been a caring part of my life, and an important confidant. I must also thank Aaron for being an excellent editor, and often helping me organize my thoughts into near coherence. Dr. Graham "Gee-money" Simpson was a breath of fresh air when he swept into the lab, and I believe his wit, charm, enthusiasm, and outgoing nature still evident themselves in those who remember him. Chudi, Brian, and Ryan have been good friends and coworkers, and I wish each of them very well in their coming endeavors. In particular, I

look forward to seeing Chudi often in the coming year. I would also like to thank my other lab mates, Neil Langille and Andrew Lauer, for helpful discussions and meaningful conversations, and the rest of the students from my year, especially Joseph Martinelli, for all our good times.

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These words do poor justice to these fine individuals in my life. To those of you in my life, past and present, bless you. May your days be filled with happiness, abundance, and peace.

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Abbreviations

Ac	acetyl
Bn	benzyl
Bu	butyl
Bz	benzoyl
cod	cyclooctadiene
Cp	cyclopentadiene
Cy	cyclohexyl
DIBAL	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	N,N'-dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
EI	electron ionization
er	enantiomeric ratio
ESI	electron spray ionization
Et	ethyl
g	gram(s)
h	hour(s)
HKR	hydrolytic kinetic resolution
HMBC	heteronuclear multiple bond correlation
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
<i>i</i> -Pr	isopropyl

LA	Lewis acid
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
<i>m</i> -CPBA	3-chloroperoxybenzoic acid
Me	methyl
mg	milligram(s)
min	minute(s)
MS	molecular sieves
<i>n</i> -Bu	<i>n</i> -butyl
<i>n</i> -Hex	<i>n</i> -hexyl
nm	nanometer
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
<i>n</i> Oe	nuclear Overhauser effect
Nu	nucleophile
Ph	phenyl
PPTS	pyridine <i>p</i> -toluenesulfonate
Pr	propyl
salen	<i>N,N'</i> -bis(3,5-di- <i>tert</i> -butylsalicylidene)-1,2-cyclohexanediamino
<i>s</i> -Bu	<i>sec</i> -butyl
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
<i>t</i> -Bu	<i>tert</i> -butyl
TES	triethylsilyl
THF	tetrahydrofuran
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TLC	thin layer chromatography
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	<i>p</i> -toluenesulfonyl

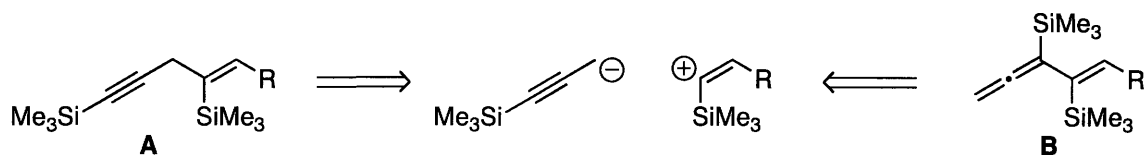
Chapter 1

Phosphine-Promoted Cross-Coupling Reactions of Propargyl Copper Reagents and Alkenyl Iodides

Introduction

1,4 or “skipped”-enynes are important intermediates in organic synthesis.¹ In order to obtain these starting materials, we sought to join together a propargyl nucleophile with an alkenyl electrophile (Scheme 1). The simple joining of these two partners, however, is complicated by the possibility of obtaining the corresponding allenyl isomers.

Scheme 1. Divergent products from addition of propargyl nucleophiles



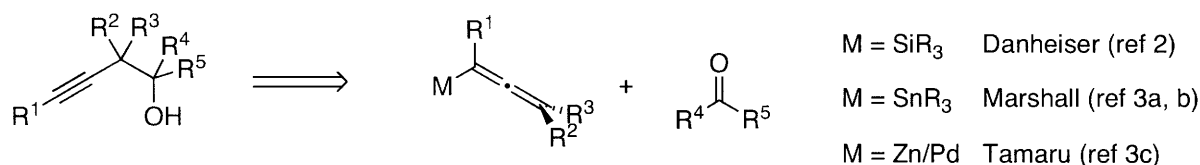
The development of carbon-carbon bond forming reactions that favor propargyl-coupled products where allenyl-derived adducts are also possible has received much attention. Danheiser demonstrated that high propargyl selectivity is obtained in additions of allenylsilane reagents to carbonyl groups and oxocarbenium ions,² and Marshall found that chiral, enantiomerically enriched allenylstannanes also undergo propargyl-selective carbonyl addition reactions (Scheme 2). In related work, chiral allenylzinc species can be prepared in high enantiomeric excess from

¹ For the use of silylated 1,4-enynes as important intermediates in the synthesis of ladder polyether fragments, see: (a) Heffron, T. P.; Jamison, T. F. *Org. Lett.* **2003**, *5*, 2339–2342. (b) Simpson, G.; Heffron, T. P.; Estibaliz, M.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 1056–1057.

² (a) Danheiser, R. L.; Carini, D. J. *J. Org. Chem.* **1980**, *45*, 3925–3927. (b) Danheiser, R. L.; Carini, D. J.; Kwasigroch, C. A. *J. Org. Chem.* **1986**, *51*, 3870–3878.

chiral propargyl mesylates, and subsequent 1,2-addition to achiral and chiral aldehydes can be effected with high diastereoselectivity.³

Scheme 2. Propargyl-selective addition to carbonyl groups



Prior to these carbonyl addition processes, Corey pioneered propargyl-selective alkylation and allylation of propargylcopper reagents,⁴ and Ganem later reported the first propargyl-selective conjugate additions of these species.⁵ Danheiser's allenylsilane reagents generally favor (trimethylsilyl)cyclopentene annulation in analogous reactions,⁶ whereas Haruta showed that certain allenylstannanes were selective for 1,4-S_E2' addition, affording 4-alkynylcarbonyl compounds.⁷

The development of propargyl-selective cross-coupling methods, however, has received much less attention. In a series of investigations, Ma observed that Pd-catalyzed cross-coupling

³ (a) Marshall, J. A.; *Chem. Rev.* **1996**, *96*, 31–47. (b) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163–3185. See also: (c) Tamaru, Y.; Goto, S.; Tanaka, A.; Shimizu, M.; Kimura, M. *Angew. Chem. Int. Ed.* **1996**, *35*, 878–880.

⁴ Corey, E. J.; Kirst, H. A. *Tetrahedron Lett.* **1968**, *9*, 5041–5043.

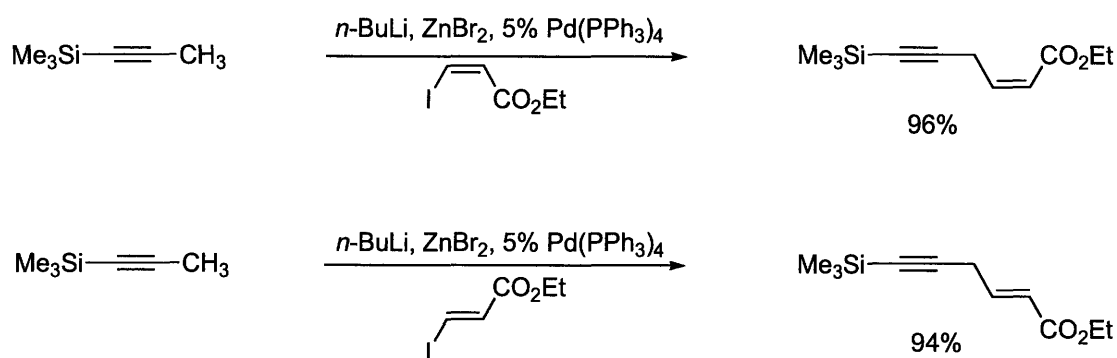
⁵ Ganem, B. *Tetrahedron Lett.* **1974**, *15*, 4467–4470.

⁶ (a) Danheiser, R. L.; Carini, D. J.; Basak, A. *J. Am. Chem. Soc.* **1981**, *103*, 1604–1606. (b) Danheiser, R. L.; Carini, D. J.; Fink, D. M.; Basak, A. *Tetrahedron*, **1983**, *39*, 935–947. See also: (c) Danheiser, R. L.; Dixon, B. R.; Gleason, R. W. *J. Org. Chem.* **1992**, *57*, 6094–6097.

⁷ (a) Haruta, J.; Nishi, K.; Matsuda, S.; Tamura, Y.; Kita, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 1065–1066. (b) Haruta, J.; Nishi, K.; Matsuda, S.; Akai, S.; Tamura, Y.; Kita, Y. *J. Org. Chem.* **1990**, *55*, 4853–4859.

of allenylzinc reagents and alkenyl iodides favored the propargyl regioisomer when the electrophile contained an electron-withdrawing group (Scheme 3).^{8, 9}

Scheme 3. Examples of Pd-catalyzed cross-coupling of allenylzinc reagents with electron deficient alkenyl iodides (ref 8).



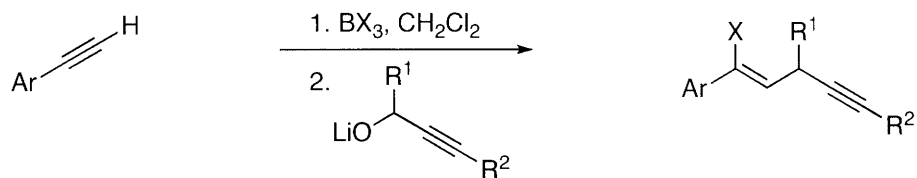
Also noteworthy is recent work by Kabalka on the halopropargylation of alkynes with boron trihalides and propargyl alkoxides (Scheme 4).¹⁰ Terminal aryl alkynes, after haloboration, couple with propargyl alkoxides to give (*Z*)-1-halo-1,4-enynes.

⁸ (a) Ma, S.; Zhang, A. *J. Org. Chem.* **1998**, *63*, 9601–9604. (b) Ma, S.; Zhang, A.; Yu, Y.; Xia, W. *J. Org. Chem.* **2000**, *65*, 2287–2291. (c) Ma, S.; Zhang, A. *J. Org. Chem.* **2002**, *67*, 2287–2294.

⁹ For related work on palladium-catalyzed coupling an alkenyl zinc reagent bearing an electron-withdrawing group with a propargyl mesylate to give 1,4-enyne products, see: Ma, S.; Wang, G. *Angew. Chem. Int. Ed.* **2003**, *42*, 4215–4217.

¹⁰ Kabalka, G. W.; Wu, Z.; Ju, Y. *Org. Lett.* **2004**, *6*, 3929–3931.

Scheme 4. Halopropargylation of aromatic alkynes to give (Z)-1-halo-1,4-enynes (Ref 10)

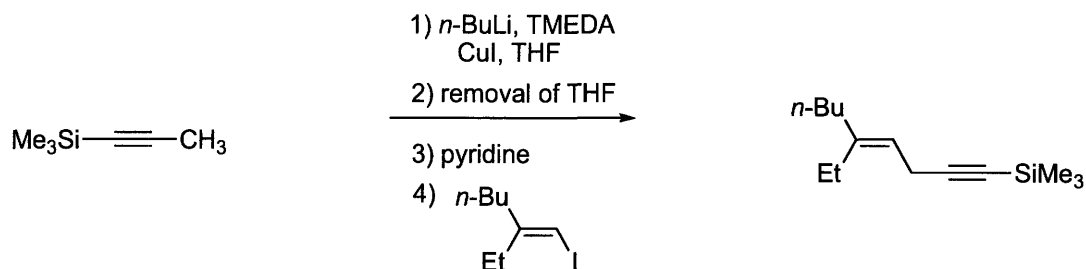


As we required products lacking aryl groups or electron-withdrawing functionalities,¹¹ the starting point for our investigations was a singular example of selective propargyl- sp^2 coupling described by Normant in 1975 (Scheme 5).¹² Preparation of the organocopper reagent involved deprotonation of 1-(trimethylsilyl)-1-propyne with *n*-BuLi in TMEDA/THF, addition of CuI, removal of the THF *in vacuo*, and addition of pyridine. An explanation for the solvent switch was not provided, but we reasoned that modification of the organocopper species by interaction with pyridine might be necessary for maximum yield of the propargyl-coupled product. Due to our desire to develop a general, scalable method for the synthesis of 1,4-enynes, we sought a method that would obviate the need for the solvent exchange.¹¹ We therefore examined a variety of additives with the aim of duplicating this high propargyl selectivity while simultaneously eliminating the solvent exchange.

¹¹ 1,4-enyne products were needed for studies directed towards the synthesis of ladder polyether fragments (ref 1).

¹² Commercon, A.; Normant, J.; Villieras, J. *J. Organomet. Chem.* **1975**, *93*, 415–421.

Scheme 5. Coupling reaction of a propargyl copper reagent and an alkenyl iodide (ref 12).



Results and Discussion

As summarized in Scheme 6 and Table 1, we found that several additives had dramatic effects upon both yield and propargyl/allenyl selectivity in our initial investigations with alkenyl iodide **1a**.¹³ Although propargyl selectivity was high in reactions conducted in THF, they were not of preparative utility (entry 2). Nitrogen- and sulfur-containing additives were either efficacious or selective, but not both (entries 3-6). Organophosphines on the other hand (entries 7-9) displayed very high levels of propargyl selectivity, and of these, tributylphosphine (Bu₃P) also gave the desired product in good yield.

Several explanations for the higher yield and selectivity imparted by Bu₃P are possible, including increased solubility and/or thermal stability of the organocopper species, or a change in

¹³ The initial studies on the use of DMAP as an additive/promoter for the coupling of propargyl copper reagents and alkenyl iodides were completed by Mr. Timothy Paul Heffron (see ref 8).

Scheme 6

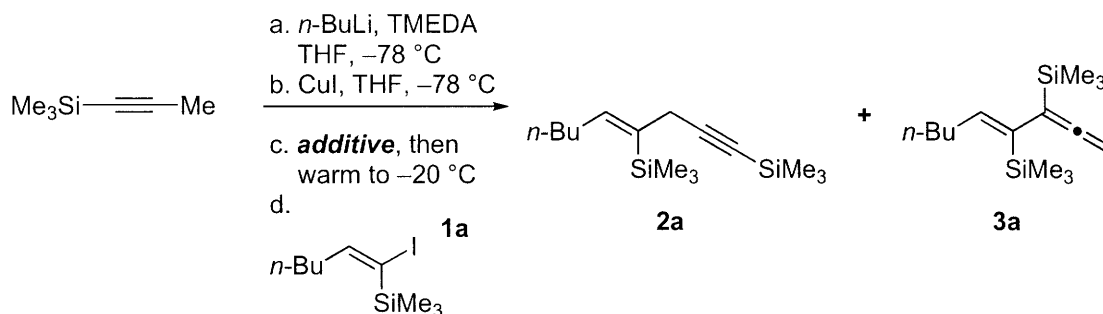


Table 1. Effects of additives upon yield and selectivity in coupling reactions of alkenyl iodide.^a

Entry	Solvent	Additive	2a : 3a ^b	Isolated Yield of 2a (%)
1	ether	none	n.d.	< 5
2	THF	none	>20:1	37
3	THF	pyridine	10:1	47
4	THF	DMAP	7:1	69
5	THF	Et ₃ N	10:1	39
6	THF	Me ₂ S	20:1	33
7	THF	Ph ₃ P	>20:1	41
8	THF	Bu ₃ P	>20:1	81
9	THF	Cy ₃ P	>20:1	41

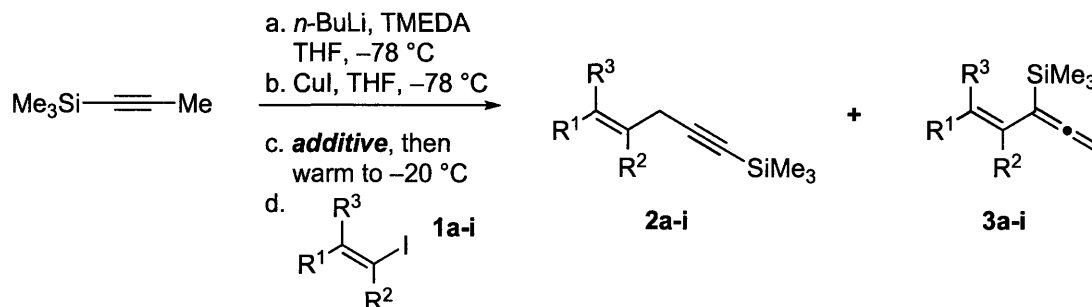
^a Performed on 2.0-gram scale (7.1 mmol of iodide **1a**). See Scheme 6 and Experimental Section for details.

^b Determined by ¹H NMR analysis of unpurified product mixture.

its aggregation state.^{14, 15} Since higher yields are observed with the more electron-rich Bu₃P than with Ph₃P (entries 7 and 8), it is possible that oxidative addition into the carbon-iodine bond is accelerated by the former. Nevertheless, the results with Cy₃P (entry 9) might suggest otherwise, unless the increased steric demand of this phosphine is responsible for the reduction in yield.

The scope of this transformation with respect to the substitution pattern and nature of the alkenyl iodide was also evaluated (Scheme 7 and Table 2). In all cases, the desired propargyl-coupled product is formed exclusively (>20:1, ¹H NMR). Protected (entry 2) and free hydroxyl groups (entries 3 and 4) are tolerated, and significantly, no π -bond isomerization is observed in entry 4 with skipped diene **1d**. A trimethylsilyl group geminal to the iodine atom is not required for efficacy or selectivity, as shown by entries 6-9. In one case, substitution *cis* to the iodide significantly reduces the efficiency of coupling (entry 5). Nevertheless, conjugated alkenyl iodides couple smoothly, as demonstrated by (*E*)-1-iodo-2-phenylpropene (entry 7). Finally, the coupling is stereospecific with respect to olefin geometry (entries 8 and 9).

Scheme 7



¹⁴ Whitesides, G. W.; Casey, C. P.; Krieger, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1379–1389.

¹⁵ Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210–7211.

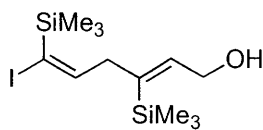
Table 2. Propargyl-selective coupling of alkenyl iodides **1a-i**.^a

Entry	Iodide	R ¹	R ²	R ³	2 : 3 ^b	Yield (%)
1	1a	<i>n</i> -Bu	Me ₃ Si	H	>20:1	81
2	1b	TBSOCH ₂	Me ₃ Si	H	>20:1	45
3	1c	HO(CH ₂) ₃	Me ₃ Si	H	>20:1	67
4	1d	(see below)	Me ₃ Si	H	>20:1	67
5	1e	H	<i>n</i> -Pr	<i>n</i> -Pr	n.d.	< 5
6	1f	<i>n</i> -Pr	<i>n</i> -Pr	H	>20:1	33 ^c
7	1g	Ph	H	Me	>20:1	80
8	1h	<i>n</i> -Bu	H	H	>20:1	38
9	1i	H	H	<i>n</i> -Bu	>20:1	52

^a See Scheme 1 and Experimental Section for details.

^b Determined by ¹H NMR analysis of unpurified product mixture.

^c NMR analysis of the unpurified product mixture indicated a 2:1 mixture of iodide **1f** and product **2f**, i.e. conversion was approximately 33%. The yield reported (33%) is the isolated yield based on a theoretical 100% and therefore is nearly quantitative based on conversion.

**1d**

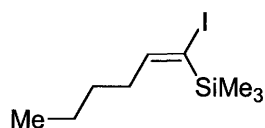
Conclusion

In summary, an electron-rich phosphine additive (Bu_3P) is critical and sufficient for propargyl-selective couplings of propargylcopper reagents derived from 1-trimethylsilyl-1-propyne with a variety of alkenyl iodides. In all cases examined, complete selectivity was observed for the desired 1,4-enyne products. The products thus obtained are complementary to those reported by Ma, who observed efficient propargyl coupling with electron-deficient alkenyl halides. The discoveries reported herein represent a useful entry into the selective synthesis of 1,4-enyne products.

Experimental Section

General Information. Unless otherwise noted, all non-aqueous reactions were performed under an oxygen-free atmosphere of argon with rigid exclusion of moisture from reagents and glassware. Dichloromethane was distilled from calcium hydride. Tetrahydrofuran (THF) and Et₂O were distilled from a blue solution of benzophenone ketyl. Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F₂₅₄ plates. The developed chromatogram was analyzed by UV lamp (254 nm) and ethanolic phosphomolybdic acid (PMA) or aqueous potassium permanganate (KMnO₄). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230-400 mesh).¹⁶ ¹H and ¹³C NMR spectra were recorded in CDCl₃, unless otherwise noted, on a Varian Inova 500 MHz spectrometer. Chemical shifts in ¹H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent, and br = broad), coupling constant in hertz (Hz), and integration. Chemical shifts of ¹³C NMR spectra are reported in ppm from the central peak of CDCl₃ (77.2 ppm), C₆D₆ (128.4 ppm), or CD₂Cl₂ (54.0 ppm) on the δ scale. Infrared (IR) spectra were recorded on a Perkin-Elmer 2000 FT-IR. High resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by Ms. Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 589 nm.

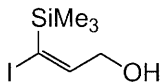
¹⁶ Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.



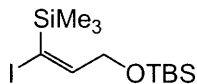
(E)-1-Iodo-hex-1-enyl-trimethyl-silane (1a): To a solution of 1-trimethylsilyl-1-hexyne (10 g, 65 mmol) in Et₂O (32 mL) in a water bath was added a 1.0 M solution of DIBAL in hexane (71 mL, 71 mmol). The reaction mixture was brought to reflux and maintained for 1 h. The solution was cooled to -78 °C and was diluted with Et₂O (38 mL). A solution of I₂ (21 g, 84 mmol) in Et₂O (140 mL) was added over 2 h via additional funnel. The resulting mixture was stirred 1 h at -78 °C. The reaction mixture was warmed to 0 °C and stirred 30 min before pouring into 1 M HCl (250 mL) and ice (65 g). This mixture was stirred until complete dissolution of the precipitate and was then extracted with hexane (3 × 200 mL). The combined organic layers were washed with 1 N NaOH, saturated Na₂S₂O₃, brine, dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (hexane) to provide **1a** (16 g, 89%). NMR spectral data were consistent with reported values.^{17, 18}

¹⁷ Zweifel, G.; Lewis, W. *J. Org. Chem.* **1978**, *43*, 2739–2744.

¹⁸ Zweifel, G.; Murray, R. E. *J. Org. Chem.* **1981**, *46*, 1292–1295.



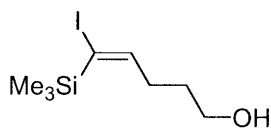
(E)-3-Iodo-3-trimethylsilylprop-2-en-1-ol (4): To a solution of 3-trimethylsilylprop-2-yn-1-ol¹⁹ (8.0 g, 63 mmol) in Et₂O (160 mL) was added a 1 M solution of DIBAL in hexane (156 mL). The resulting solution was heated 24 h at reflux. This solution was then cooled to -78 °C, diluted with Et₂O (60 mL), and a solution of I₂ (63.5 g, 250 mmol) in Et₂O (200 mL) was added. After stirring 2 h at -78 °C the reaction was quenched by pouring into 1 M HCl (100 mL) and ice (50 g). The organic layer was separated, and the aqueous layer was extracted with Et₂O (3 × 150 mL). The combined organic layers were washed with saturated Na₂S₂O₃, brine, dried over MgSO₄, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to yield alkenyl iodide **4** (10.7 g, 67% yield, >95% *E*): R_f = 0.35 (20% EtOAc in hexane); IR (thin film, NaCl) 3312, 2955, 1250, 1018, 842 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.35 (t, *J* = 7.0 Hz, 1H), 4.09 (dd, *J* = 7.0, 6.1 Hz, 2H), 0.29 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 154.3, 111.6, 63.6, 1.2; HRMS (ESI) Calcd for C₆H₁₃NaIOSi [M + Na]⁺ 278.9673, found 278.9673.



(E)-3-(tert-Butyl-dimethylsilyloxy)-1-iodo-1-trimethylsilylpropene (1b): To a solution of alkenyl iodide **4** (5.1 g, 20 mmol) in DMF (20 mL) were added imidazole (1.9 g, 28 mmol)

¹⁹ Danheiser, R. L.; Carini, D. J.; Fink, D. M.; Basak, A. *Tetrahedron* **1983**, *39*, 935–948.

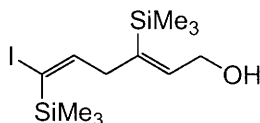
and TBSCl (4.2 g, 28 mmol). The reaction mixture stirred overnight at room temperature then was quenched with water. The aqueous layer was extracted with Et₂O (3 × 50 mL). The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo* to yield silyl ether **1b** without the need for further purification (6.8 g, 92%): *R_f* = 0.45 (5% EtOAc in hexane); IR (thin film, NaCl) 3853, 2955, 2929, 2857, 1251, 1098, 838, 776 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.25 (t, *J* = 6.0 Hz, 1H), 4.11 (d, *J* = 6.5 Hz, 2H), 0.90 (s, 9H), 0.27 (s, 9H), 0.07 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 156.2, 109.0, 64.6, 26.6, 19.0, 1.6, -4.4; HRMS (ESI) Calcd for C₁₂H₂₇NaIOSi₂ [M + Na]⁺ 393.0537, found 393.0534.



(E)-5-Iodo-5-trimethylsilyl-pent-4-en-1-ol (1c): To a solution of 5-trimethylsilyl-pent-4-yn-1-ol²⁰ (12.2 g, 77.8 mmol) in Et₂O (190 mL) at 0 °C was added a 1 M solution of DIBAL in hexane (190 mL). The resulting solution was heated 24 h at reflux. This solution was then cooled to -78 °C, diluted with Et₂O (60 mL), and a solution of I₂ (79.0 g, 310 mmol) in Et₂O (175 mL) was added. After stirring 2 h at -78 °C, the reaction was warmed to 0 °C and stirred 1 h before the reaction was quenched by pouring into 1 M HCl (200 mL) and ice (40 g). The organic layer was separated and the aqueous layer was extracted with Et₂O (3 × 200 mL). The combined organic layers were washed with saturated Na₂S₂O₃, brine, dried over MgSO₄, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc

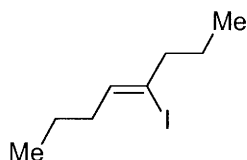
²⁰ Cruciani, P.; Stammler, R.; Aubert, C.; Malacria, M. *J. Org. Chem.* **1996**, *61*, 2699–2708.

in hexane) to yield alkenyl iodide **1c** (20.1 g, 91%, >95% *E*): $R_f = 0.20$ (20% EtOAc in hexane); IR (thin film, NaCl) 3335, 2952, 1588, 1407, 1249, 1059, 841 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.18 (t, $J = 7.9$ Hz, 1H), 3.66 (t, $J = 6.4$ Hz, 2H), 2.18 (dt, $J = 7.7, 7.6$ Hz, 2H), 1.67 (m, 2H), 0.28 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.7, 107.6, 62.2, 32.2, 31.7, 1.4; HRMS (ESI) Calcd for $\text{C}_8\text{H}_{17}\text{IOSi}$ $[\text{M}]^+$ 284.0088, found 284.0091.

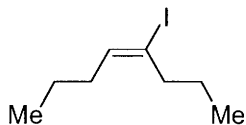


(2Z,5E)-6-Iodo-3,6-bis-trimethylsilyl-hexa-2,5-dien-1-ol (1d): To a solution of **2b** (see below; 9.6 g, 25 mmol) in Et_2O (60 mL) was added a 1 M solution of DIBAL in hexane (60 mL). The resulting solution was heated 24 h at reflux. This solution was then cooled to -78 $^\circ\text{C}$, diluted with Et_2O (50 mL), and a solution of I_2 (25 g, 98 mmol) in Et_2O (150 mL) was added. After stirring 2 h at -78 $^\circ\text{C}$, the reaction mixture was warmed to 0 $^\circ\text{C}$ and stirred 1 h, then warmed to room temperature and stirred 40 min before the reaction was quenched by pouring into 1 M HCl (200 mL) and ice (70 g). The organic layer was separated and the aqueous layer was extracted with Et_2O (3×250 mL). The combined organic layers were washed with saturated $\text{Na}_2\text{S}_2\text{O}_3$, brine, dried over MgSO_4 , and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to yield alkenyl iodide **1d** (5.6 g, 55%, >95% *E*): $R_f = 0.28$ (20% EtOAc in hexane); IR (thin film, NaCl) 3324, 2954, 1250, 839 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.10 (t, $J = 7.6$ Hz, 1H), 6.14 (tt, $J = 7.0, 1.5$ Hz, 1H), 4.23 (dd, $J = 6.7, 5.8$ Hz, 2H), 2.87 (dd, $J = 7.6, 1.5$ Hz, 2H), 0.27 (s, 9H), 0.17 (s, 9H); ^{13}C NMR

(125 MHz, CDCl₃) δ 154.4, 141.5, 141.4, 108.0, 62.3, 41.9, 1.2, 0.3; HRMS (ESI) Calcd for C₁₂H₂₉INaOSi₂ [M + Na]⁺ 391.0381, found 391.0394.



(Z)-4-Iodo-oct-4-ene (1e): Synthesized according to a reported procedure.²¹ NMR spectral data were consistent with reported values.²²

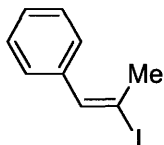


(E)-4-Iodo-oct-4-ene (1f): To a solution of Cp₂ZrHCl (22.0 g, 87.1 mmol) in CH₂Cl₂ (360 mL) was added 4-octyne (8.0 g, 73 mmol) and the reaction mixture stirred overnight. The mixture was cooled to 0 °C, I₂ (20 g, 80 mmol) was added and the reaction was warmed to room temperature, stirred 1 h, then was quenched by pouring into 1 M HCl (200 mL) and ice (50 g). The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (3 × 150 mL). The combined organic layers were washed with saturated Na₂S₂O₃, brine, dried over MgSO₄, and

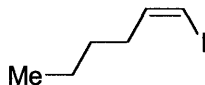
²¹ Ma, S.; Lu, X.; Li, Z. *J. Org. Chem.* **1992**, *57*, 709–713.

²² Kropp, P. J.; Crawford, S. D. *J. Org. Chem.* **1994**, *59*, 3102–3112.

concentrated *in vacuo*. The crude product was purified by column chromatography (hexane) to yield **1f** (9.3 g, 54%, >95% *E*). NMR spectral data were consistent with reported values.²²



[(*E*)-2-Iodo-1-methyl-vinyl]-benzene (1g): Synthesized according to a reported procedure.²³ NMR spectral data were consistent with reported values.

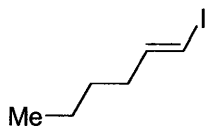


(*Z*)-1-Iodo-hex-1-ene (1h): Synthesized according to a reported procedure.²⁴ NMR spectral data were consistent with reported values.²⁵

²³ Negishi, E.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639–6647.

²⁴ (a) Larock, R. C.; Varaprath, S.; Lau, H. H.; Fellows, C. A. *J. Am. Chem. Soc.* **1984**, *106*, 5274–5284. (b) Brown, H. C.; Blue, C. D.; Nelson, D. J.; Bhat, N. G. *J. Org. Chem.* **1989**, *54*, 6064–6067.

²⁵ Dieck, H. A.; Heck, F. R. *J. Org. Chem.* **1975**, *40*, 1083–1090.

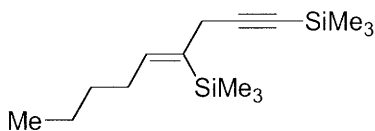


(E)-1-Iodo-hex-1-ene (1i): Synthesized according to a reported procedure.²⁶ NMR spectral data were consistent with reported values.

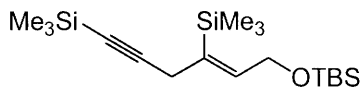
Representative Procedure for the Propargyl/Allenyl Coupling of Alkenyl Iodides 1a-b, 1e-i.

To a solution of 1-trimethylsilyl-1-propyne (1.5 mL, 10 mmol) in THF (21 mL) at $-78\text{ }^{\circ}\text{C}$ were added a 2.5 M solution of *n*-BuLi in hexane (4.6 mL) and TMEDA (1.7 mL, 11 mmol). The solution was warmed to $0\text{ }^{\circ}\text{C}$ and stirred 45 min. The solution was then transferred *via* cannula to a $-78\text{ }^{\circ}\text{C}$ slurry of CuI (2.3 g, 12 mmol) and Bu₃P (10 mmol) in THF (29 mL). The solution was warmed to $-20\text{ }^{\circ}\text{C}$. The alkenyl iodide (7.1 mmol) was added and the reaction mixture was allowed to warm to room temperature gradually and stirred overnight. The reaction was quenched with 1 M HCl and the organic layer was separated. The aqueous layer was extracted with Et₂O (3 × 200 mL). The combined organic layers were washed with water, brine, dried over MgSO₄, and concentrated *in vacuo*. The allenyl/propargyl ratio of the coupled products was determined by ¹H NMR analysis of the unpurified reaction mixture. The crude product was then purified by column chromatography.

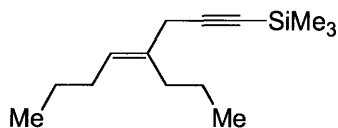
²⁶ Stille, J. K.; Simpson, J. H. *J. Am. Chem. Soc.* **1987**, *109*, 2138–2152.



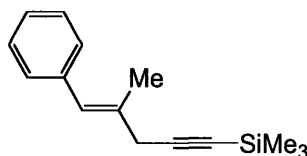
(Z)-1,4-Bis-trimethylsilyl-non-4-en-1-yne (2a): $R_f = 0.31$ (hexane); IR (thin film, NaCl) 2958, 2859, 2174, 1618, 1466, 1420, 1250, 1054, 1010, 841, 759, 695, 642 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.24 (t, $J = 7.6$ Hz, 1H), 2.98 (s, 2H), 2.14 (app q, $J = 13.7, 6.4$ Hz, 2H), 1.36 (m, 4H), 0.92 (t, $J = 6.7$ Hz, 3H), 0.18 (s, 9H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 144.4, 132.7, 106.3, 87.6, 32.3, 31.8, 28.9, 22.7, 14.3, 0.4, 0.3; HRMS (ESI) Calcd for $\text{C}_{15}\text{H}_{30}\text{NaSi}_2$ $[\text{M} + \text{Na}]^+$ 289.1778, found 289.1773.



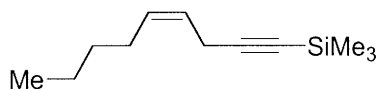
(Z)-6-(*tert*-Butyl-dimethyl-silyloxy)-1,4-bis-trimethylsilyl-hex-4-en-1-yne (2b): $R_f = 0.41$ (5% EtOAc in hexane); IR (thin film, NaCl) 2957, 2857, 1645, 1472, 1250, 839, 759 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.36 (tt, $J = 6.4, 1.5$ Hz, 1H), 4.27 (tt, $J = 6.2, 1.2$ Hz, 2H), 3.02 (br d, $J = 1.5$ Hz, 2H), 0.91 (s, 9H), 0.17 (s, 9H), 0.16 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 143.8, 135.2, 105.7, 88.7, 63.3, 29.1, 26.7, 19.1, 0.8, 0.6, -4.3; HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{38}\text{NaOSi}_3$ $[\text{M} + \text{Na}]^+$ 377.2123, found 377.2124.



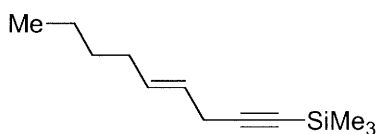
Trimethyl-[(*E*)-4-propyl-oct-4-en-1-ynyl]-silane (2f): $R_f = 0.39$ (hexane); IR (thin film, NaCl) 2960, 2932, 2873, 2176, 1250, 843, 760 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.46 (br t, $J = 7.3$ Hz, 1H), 2.94 (d, $J = 1.2$ Hz, 2H), 2.07 (t, $J = 7.6$ Hz, 2H), 2.01 (app q, $J = 7.3$ Hz, 2H), 1.45-1.34 (m, 4H), 0.91 (app q, $J = 7.6$ Hz, 6H), 0.17 (s, 9H) ^{13}C NMR (125 MHz, CDCl_3) δ 133.7, 126.9, 105.3, 87.0, 32.6, 30.1, 27.9, 23.2, 21.6, 14.3, 14.1, 0.3; HRMS (EI) Calcd for $\text{C}_{14}\text{H}_{26}\text{Si}$ $[\text{M}]^+$ 222.1798, found 222.1801.



Trimethyl-[(*E*)-5-phenyl-hex-4-en-1-ynyl]-silane (2g): $R_f = 0.41$ (5% EtOAc in hexane); IR (thin film, NaCl) 2960, 2931, 2873, 2176, 1249, 842, 759 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.41-7.24 (m, 5H), 5.80 (tq, $J = 6.1, 1.2$ Hz, 1H), 3.17 (d, $J = 6.7$ Hz, 2H), 2.05 (br s, 3H), 0.17 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 143.3, 136.9, 128.5, 127.2, 126.0, 122.5, 105.3, 84.7, 26.6, 20.1, 0.4; HRMS (ESI) Calcd for $\text{C}_{15}\text{H}_{21}\text{Si}$ $[\text{M} + \text{H}]^+$ 229.1407, found 229.1407.



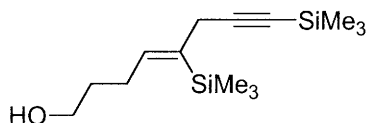
(Z)-Trimethyl-non-4-en-1-ynyl-silane (2h): $R_f = 0.32$ (hexane); IR (thin film, NaCl) 2959, 2929, 2177, 1250, 842, 760 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.51-5.38 (m, 2H), 2.99 (d, $J = 6.4$ Hz, 2H), 2.05 (app q, $J = 6.4$ Hz, 2H), 1.38-1.28 (m, 4H), 0.89 (t, $J = 7.0$ Hz, 3H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 132.2, 124.0, 105.7, 84.2, 31.7, 27.1, 22.6, 18.6, 14.2, 0.3; HRMS (EI) Calcd for $\text{C}_{11}\text{H}_{19}\text{Si}$ $[\text{M} - \text{CH}_3]^+$ 179.1251, found 179.1252.



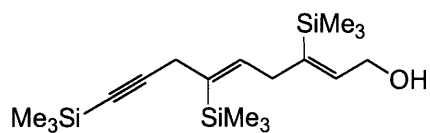
(E)-Trimethyl-non-4-en-1-ynyl-silane (2i): $R_f = 0.24$ (hexane); IR (thin film, NaCl) 2959, 2927, 1250, 842, 760 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.68 (dt, $J = 15.3, 7.0$ Hz, 1H), 5.39 (dt, $J = 15.0, 5.5$ Hz, 1H), 2.95 (d, $J = 5.5$ Hz, 2H), 2.03 (app q, $J = 6.1$ Hz, 2H), 1.39-1.29 (m, 4H), 0.90 (t, $J = 7.0$ Hz, 3H), 0.17 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 132.2, 124.0, 105.7, 84.2, 31.7, 27.1, 22.6, 18.6, 14.2, 0.3; HRMS (EI) Calcd for $\text{C}_{12}\text{H}_{22}\text{Si}$ $[\text{M}]^+$ 194.1485, found 194.1491.

Representative Procedure for the Propargyl/Allenyl Coupling of Alkenyl Iodides 1c-d. To a solution of 1-trimethylsilyl-1-propyne (1.0 mL, 6.5 mmol) in THF (4.3 mL) at -78 °C were

added a 2.5 M solution of *n*-BuLi in hexane (2.7 mL) and TMEDA (1.0 mL, 6.7 mmol). The solution was warmed to 0 °C and stirred 45 min. The solution was then transferred *via* cannula to a slurry of CuI (1.4 g, 7.2 mmol) and Bu₃P (1.6 mL, 6.5 mmol) in THF (5.7 mL) at -78 °C. The solution was warmed to -20 °C and the alkenyl iodide (1.4 mmol) was added. The reaction mixture was allowed to warm to room temperature gradually and stirred overnight. The reaction was quenched with 1 M HCl and the organic layer was separated. The aqueous layer was extracted with Et₂O (3 × 20 mL). The combined organic layers were washed with water, brine, dried over MgSO₄, and concentrated *in vacuo*. The crude product was purified by column chromatography.

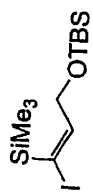


(Z)-5,8-Bis-trimethylsilyl-oct-4-en-7-yn-1-ol (2c): $R_f = 0.41$ (20% EtOAc in hexane); IR (thin film, NaCl) 3314, 2956, 2898, 2173, 1618, 1420, 1249, 1053, 841, 759 cm^{-1} ; ¹H NMR (500 MHz, CDCl₃) δ 6.24 (t, $J = 7.6$ Hz, 1H), 3.68 (t, $J = 6.4$ Hz, 2H), 2.99 (s, 2H), 2.24 (dt, $J = 7.6, 7.3$ Hz, 2H), 1.68 (m, 2H), 0.19 (s, 9H), 0.16 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 143.6, 134.5, 106.5, 88.3, 63.3, 33.5, 29.4, 28.9, 0.8, 0.7; HRMS (ESI) Calcd for C₁₄H₂₈NaOSi₂ [M + Na]⁺ 291.1571, found 291.1577.

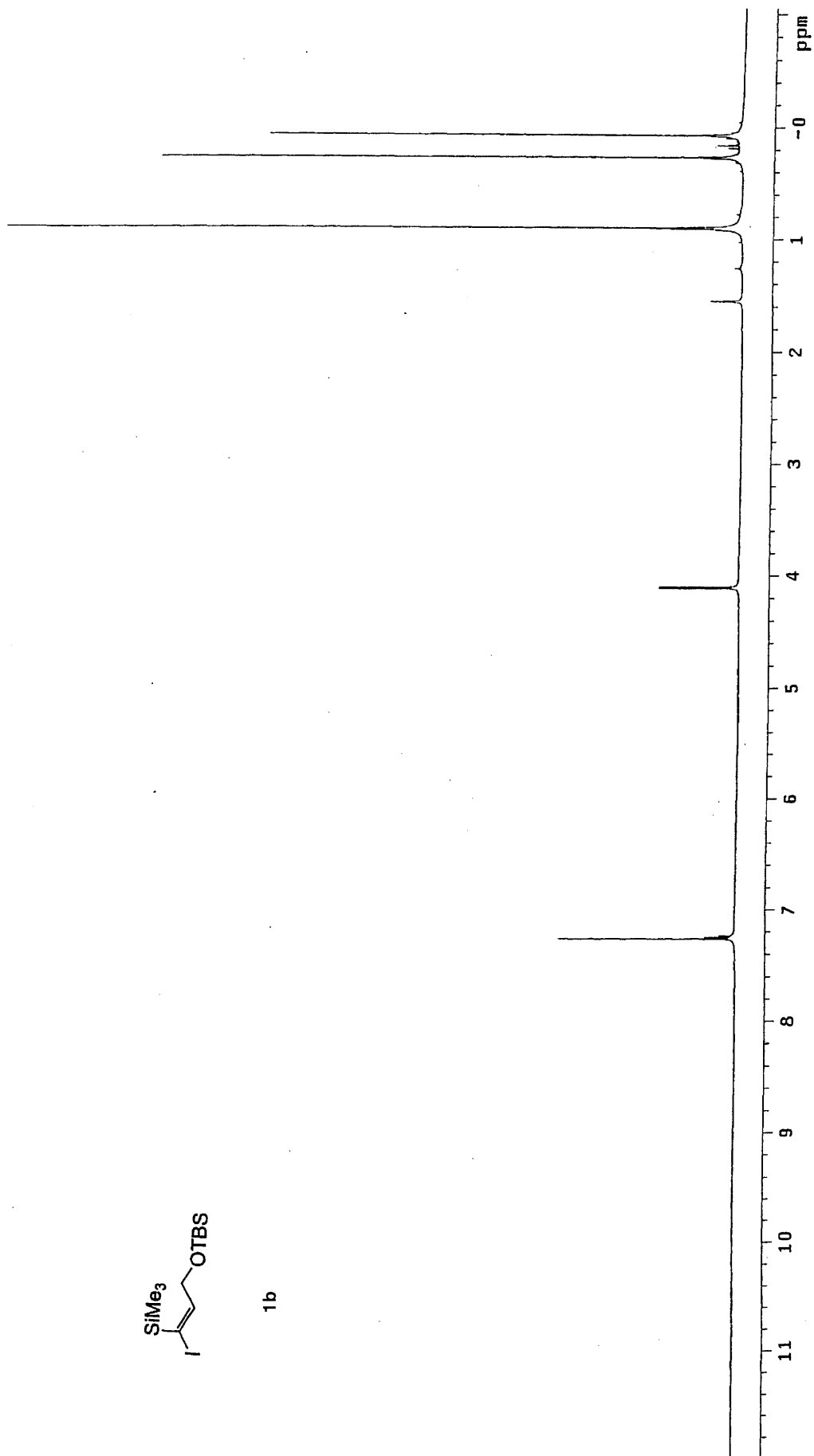


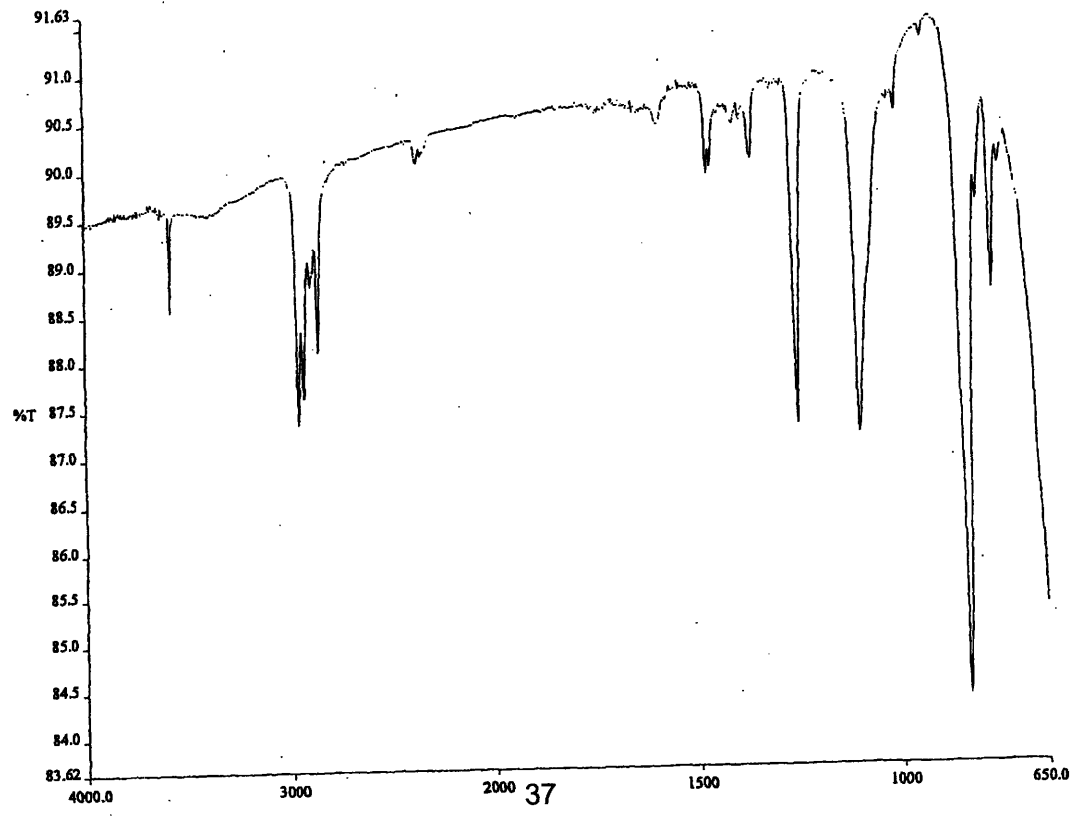
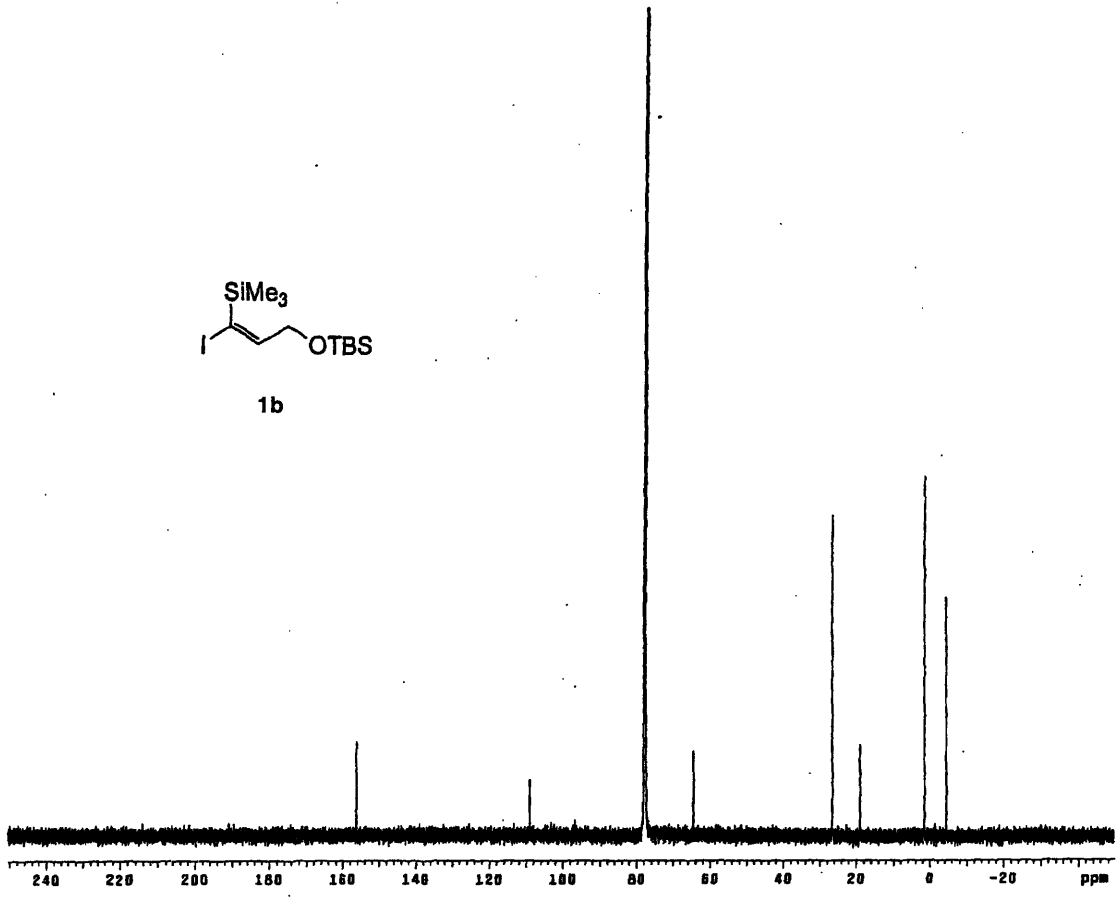
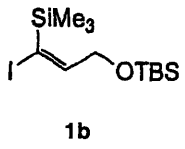
(2Z,5Z)-3,6,9-Tris-trimethylsilyl-nona-2,5-dien-8-yn-ol (2d): $R_f = 0.42$ (20% EtOAc in hexane); IR (thin film, NaCl) 3313, 2956, 2898, 2173, 1249, 839 758 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.23 (tt, $J = 7.3, 1.5$ Hz, 1H), 6.13 (tt, $J = 7.0, 1.5$ Hz, 1H), 4.22 (d, $J = 7.0$ Hz, 2H), 3.02 (d, $J = 1.2$ Hz, 2H), 2.96 (dd, $J = 7.3, 1.2$ Hz, 2H), 0.19 (s, 9H), 0.17 (s, 9H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 143.1, 141.9, 140.9, 134.5, 105.8, 87.9, 62.4, 39.1, 28.8, 0.49, 0.43, 0.20; HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{36}\text{NaOSi}_3$ $[\text{M} + \text{Na}]^+$ 375.1966, found 375.1964.

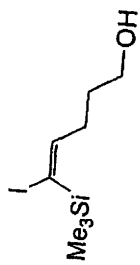
Chapter 1: Spectra



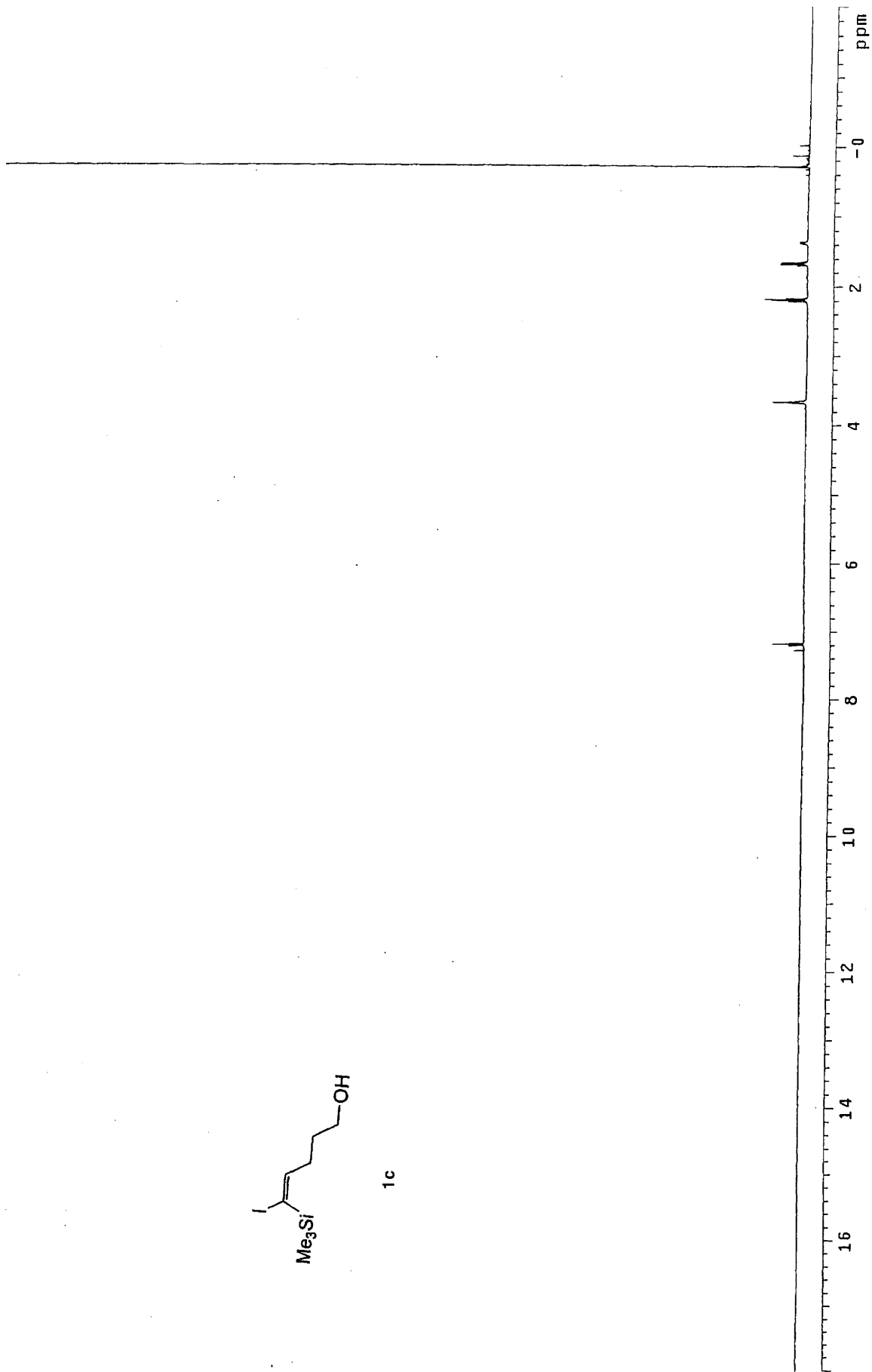
1b

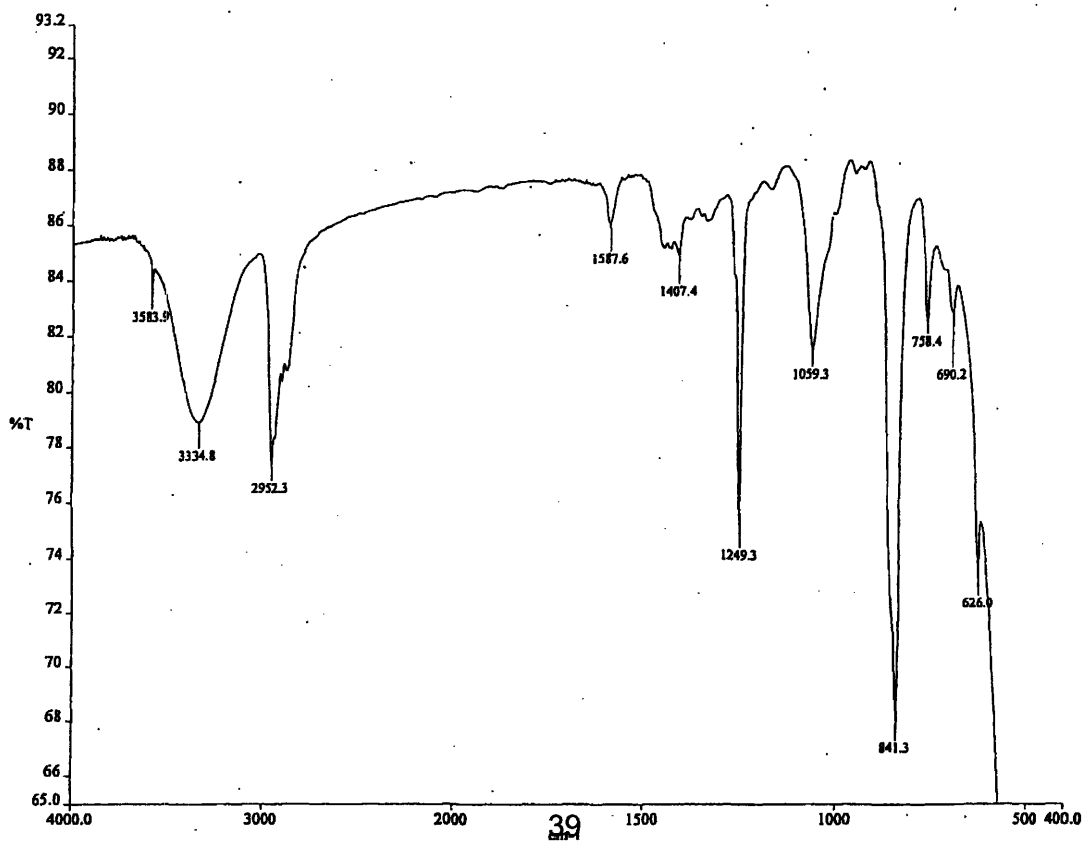
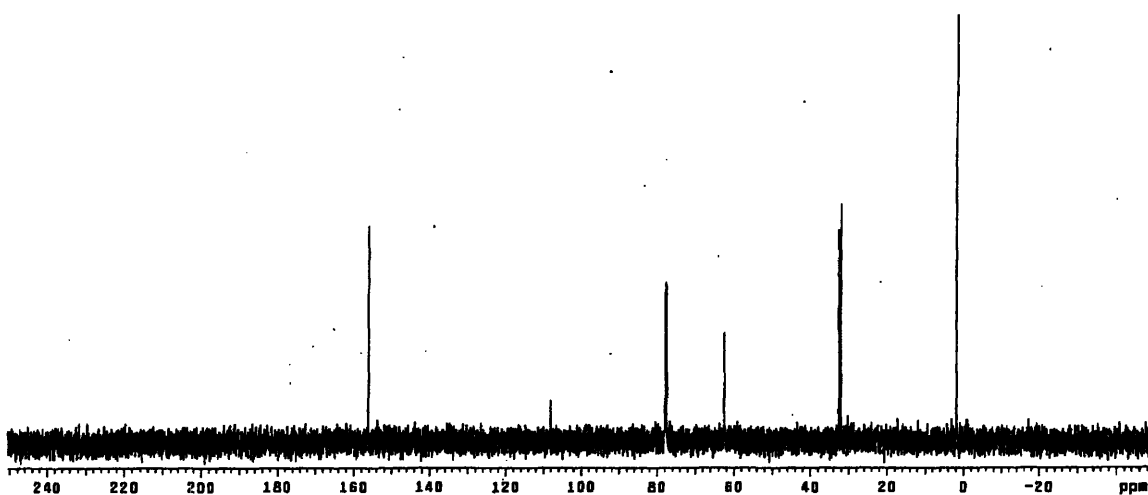
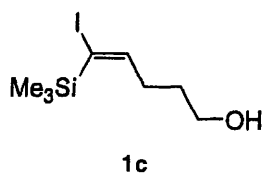


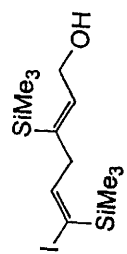




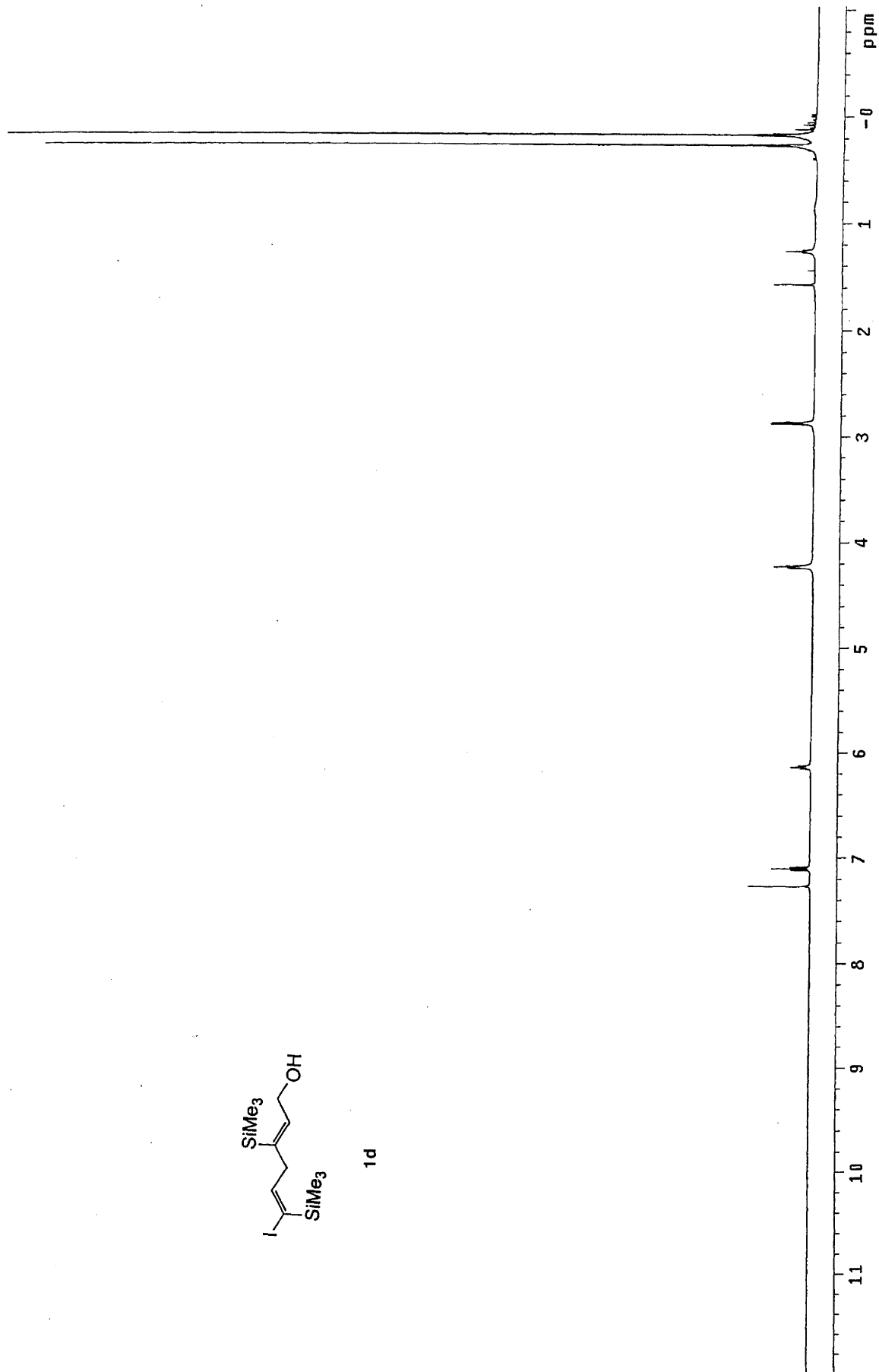
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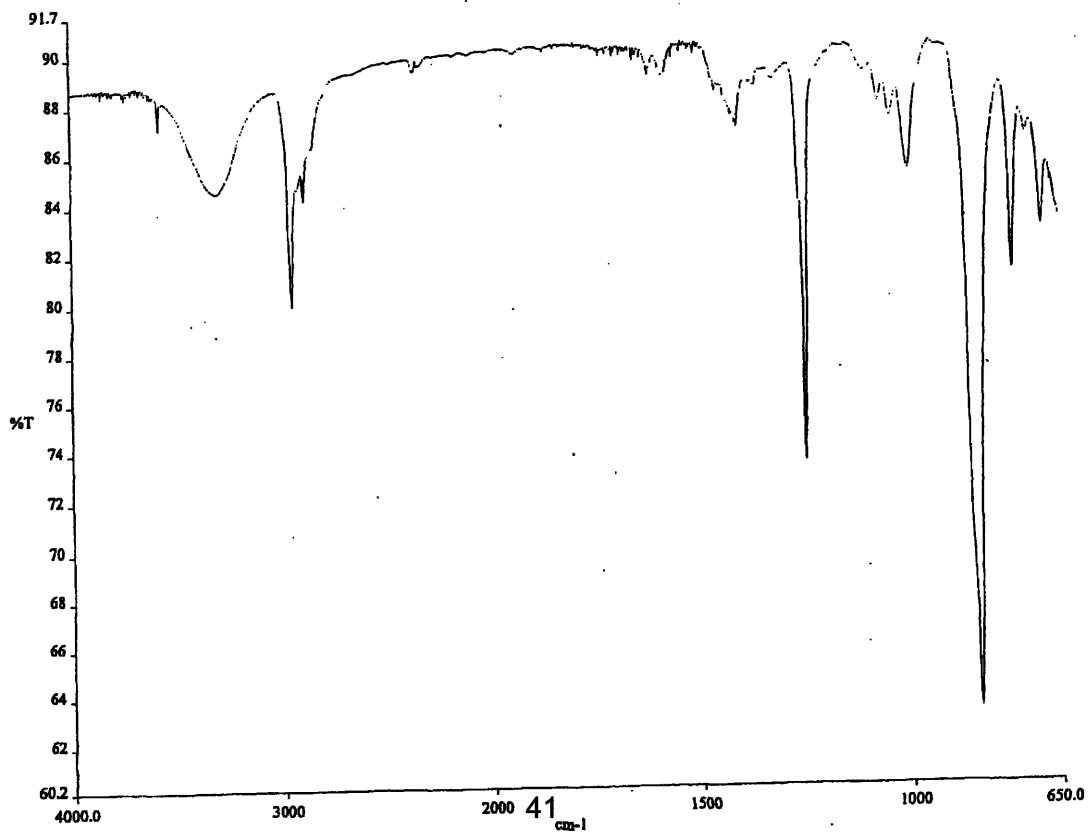
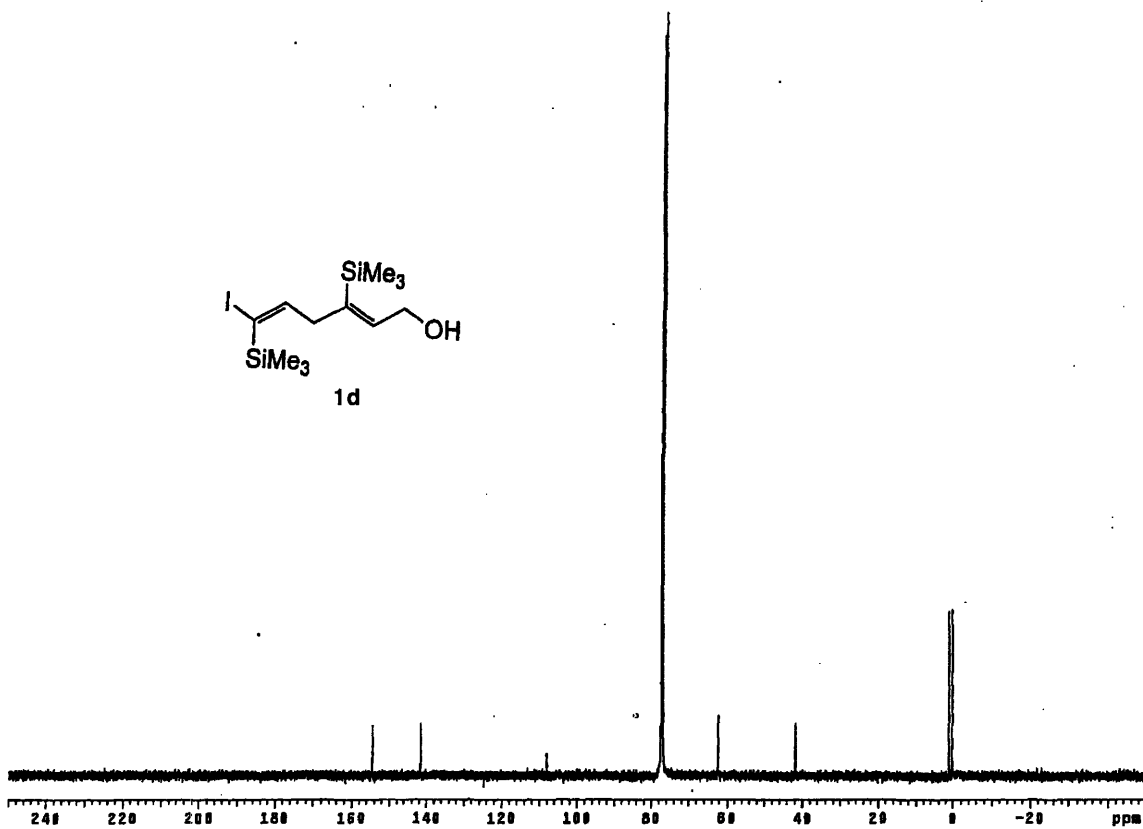
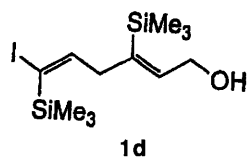


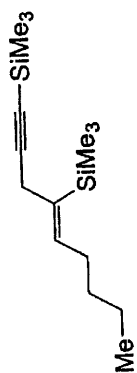




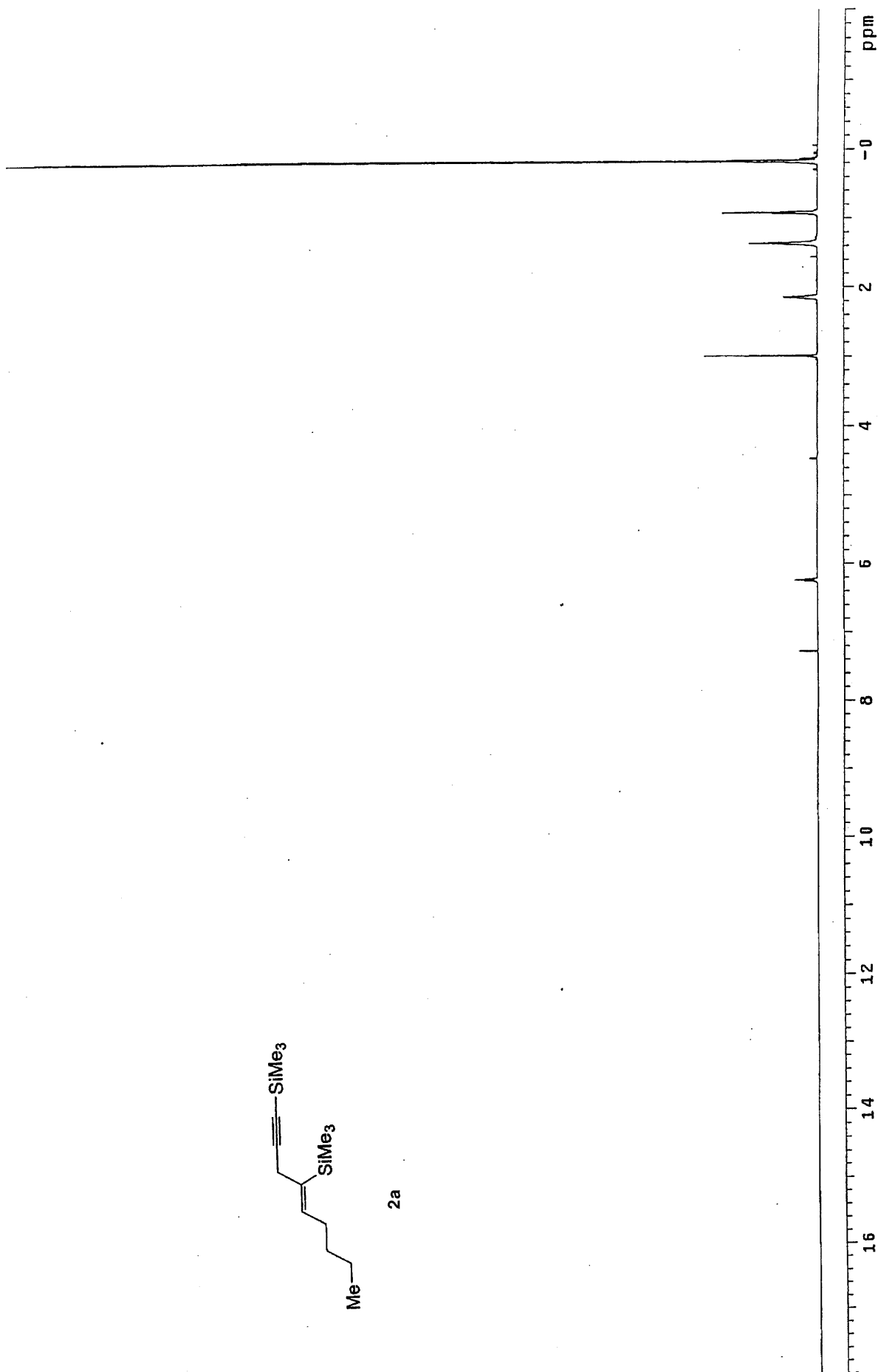
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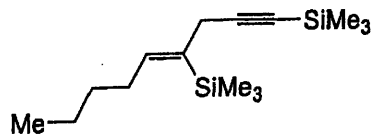




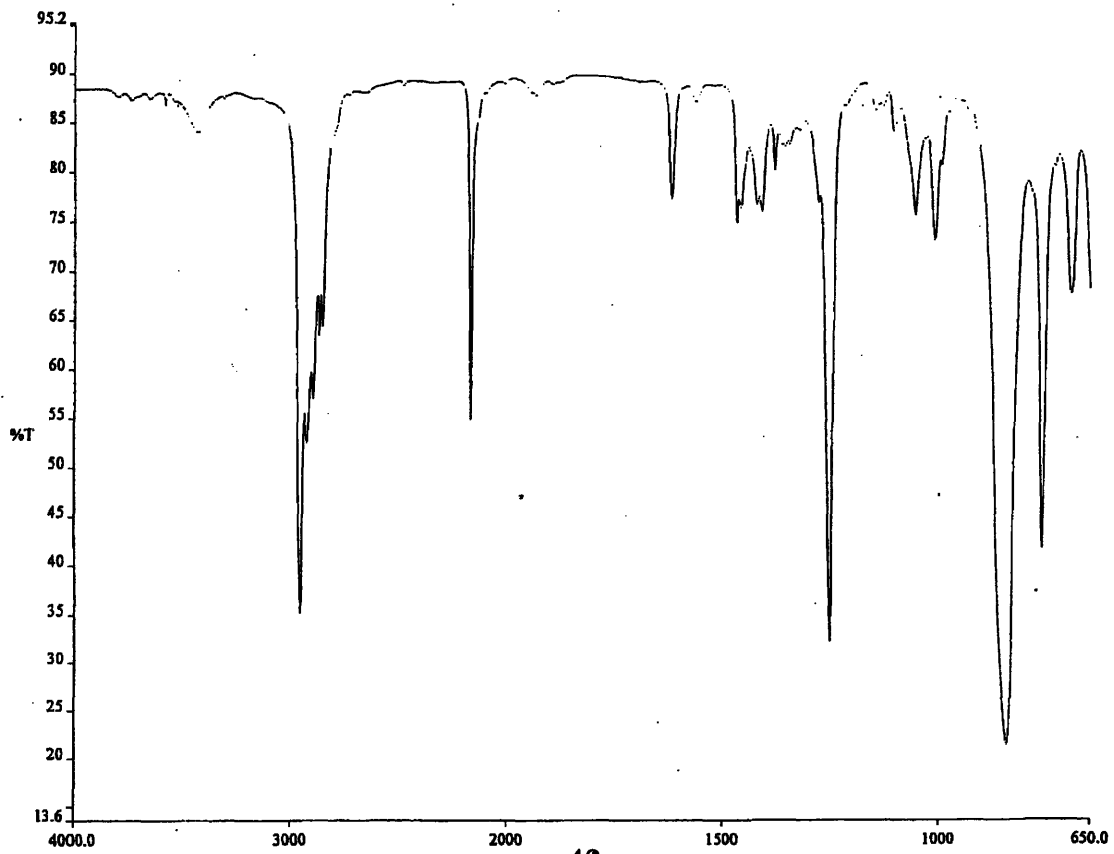
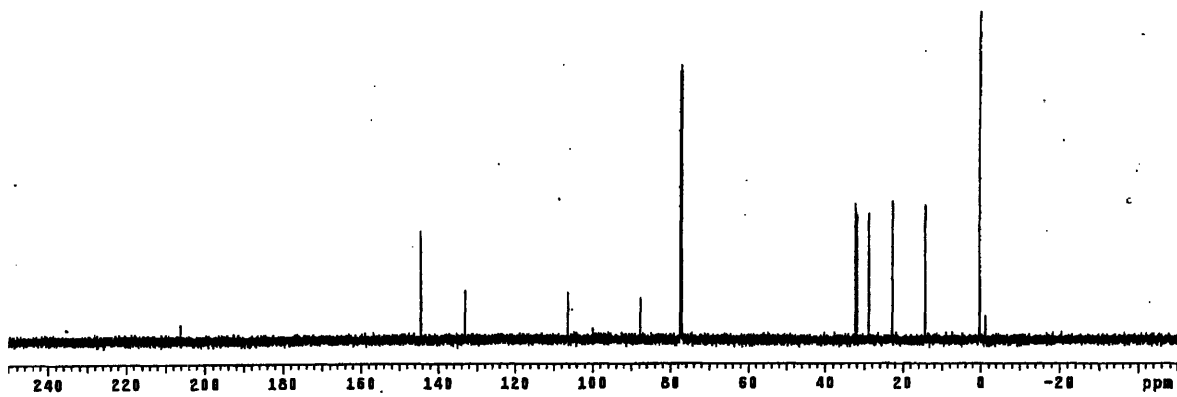


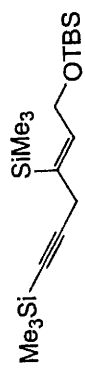
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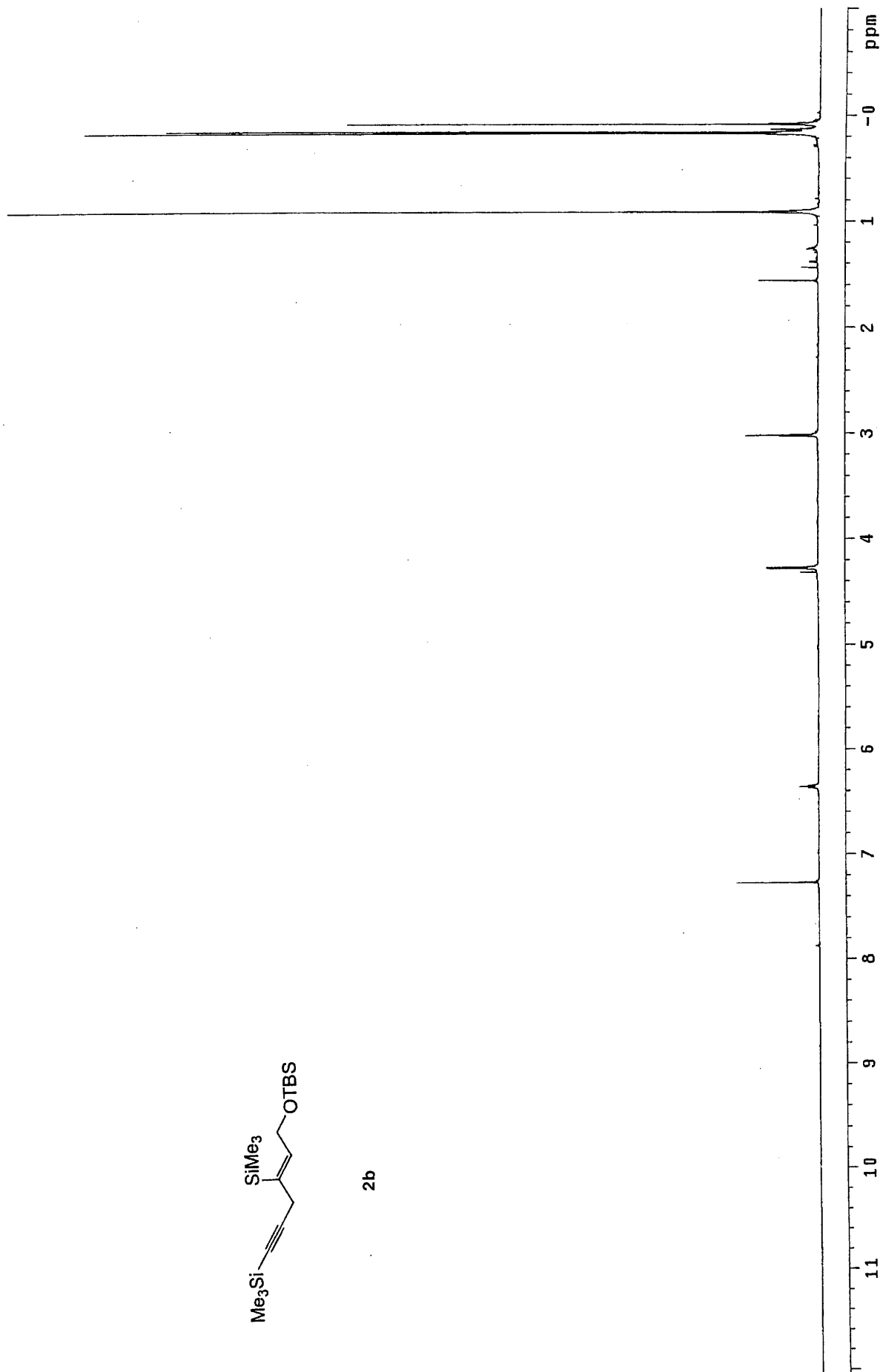


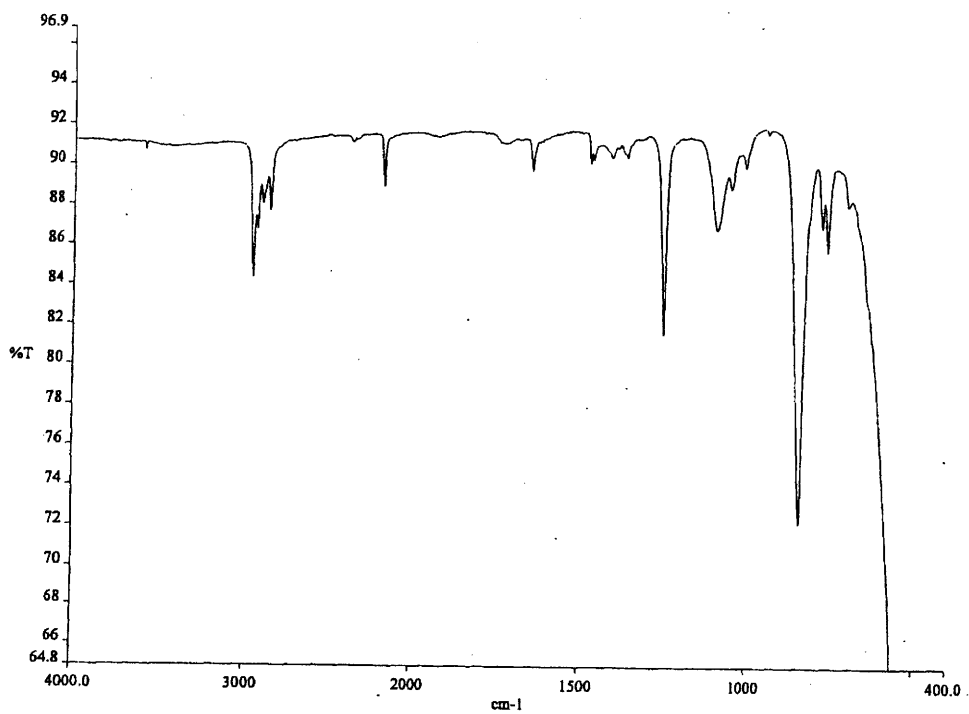
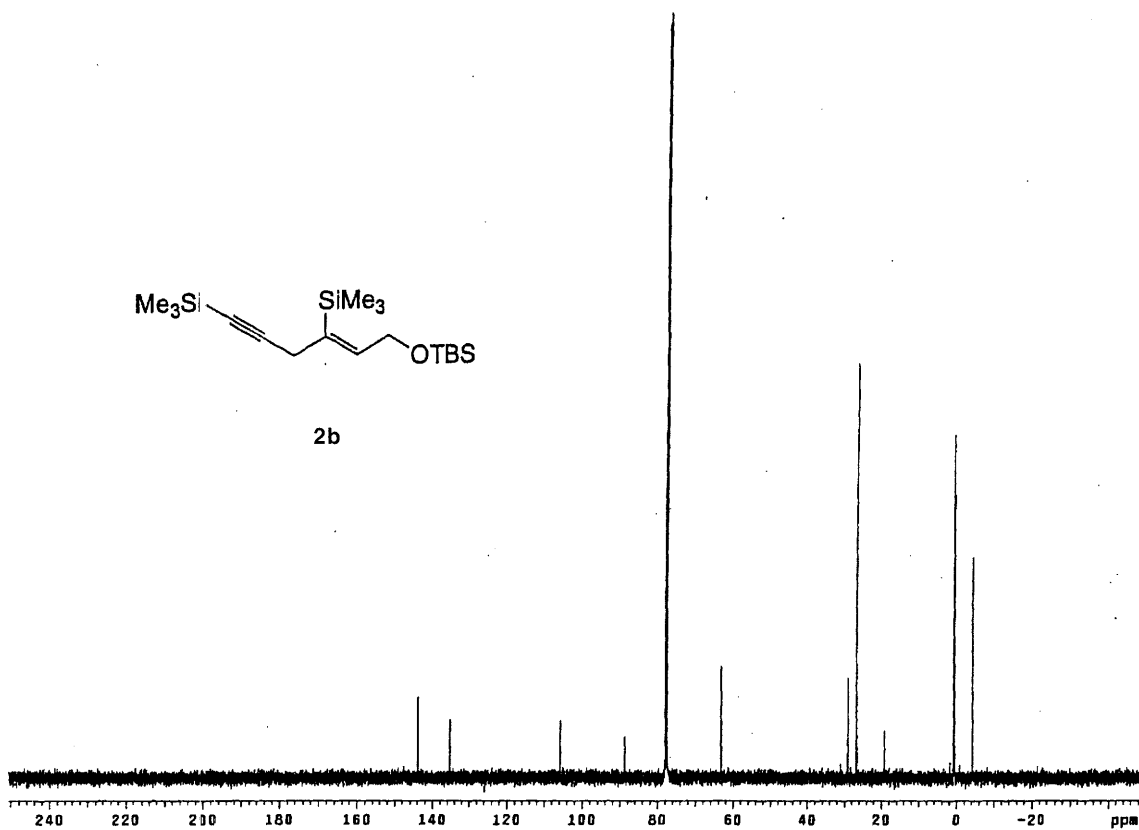
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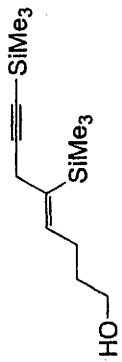




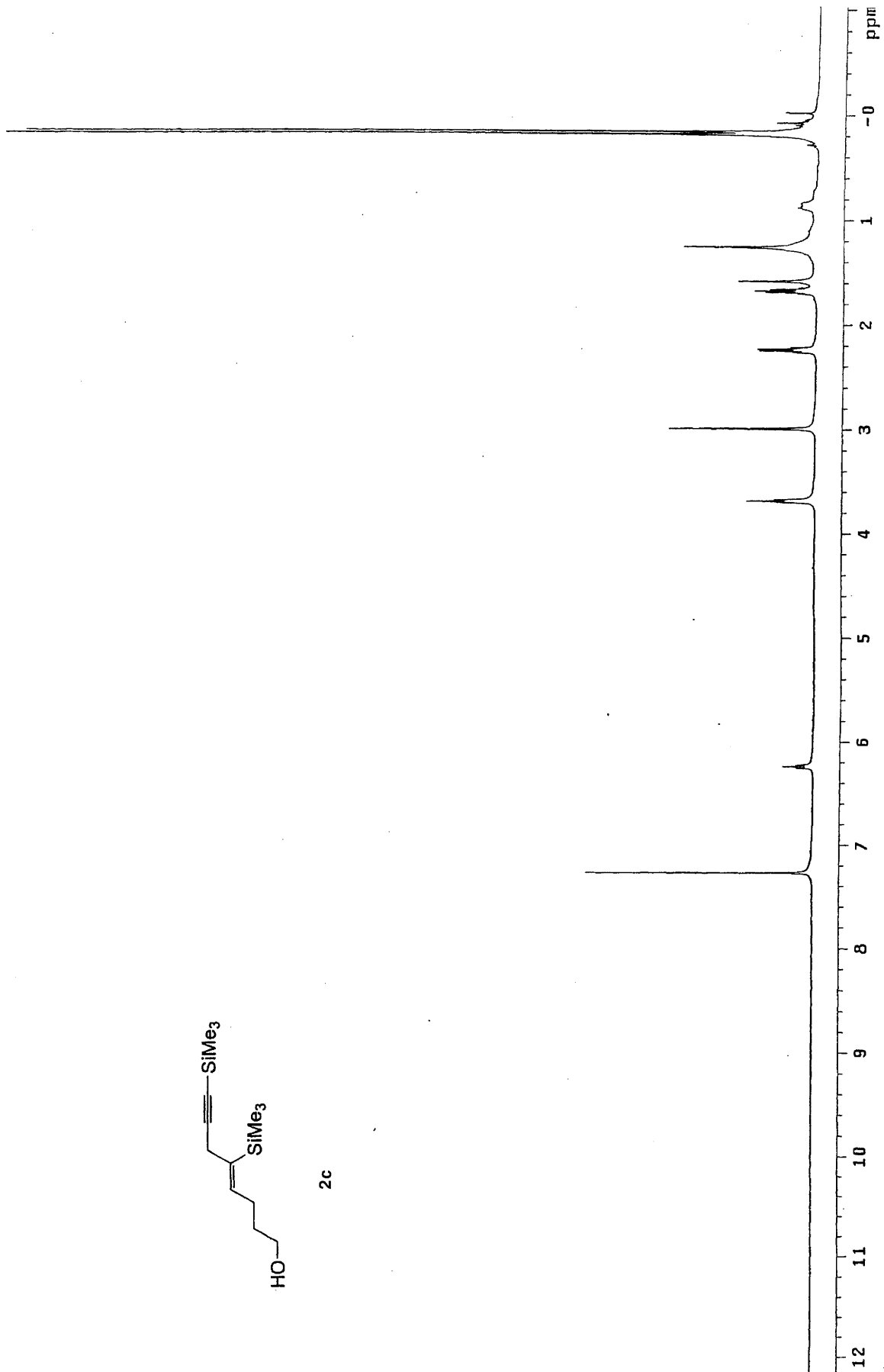
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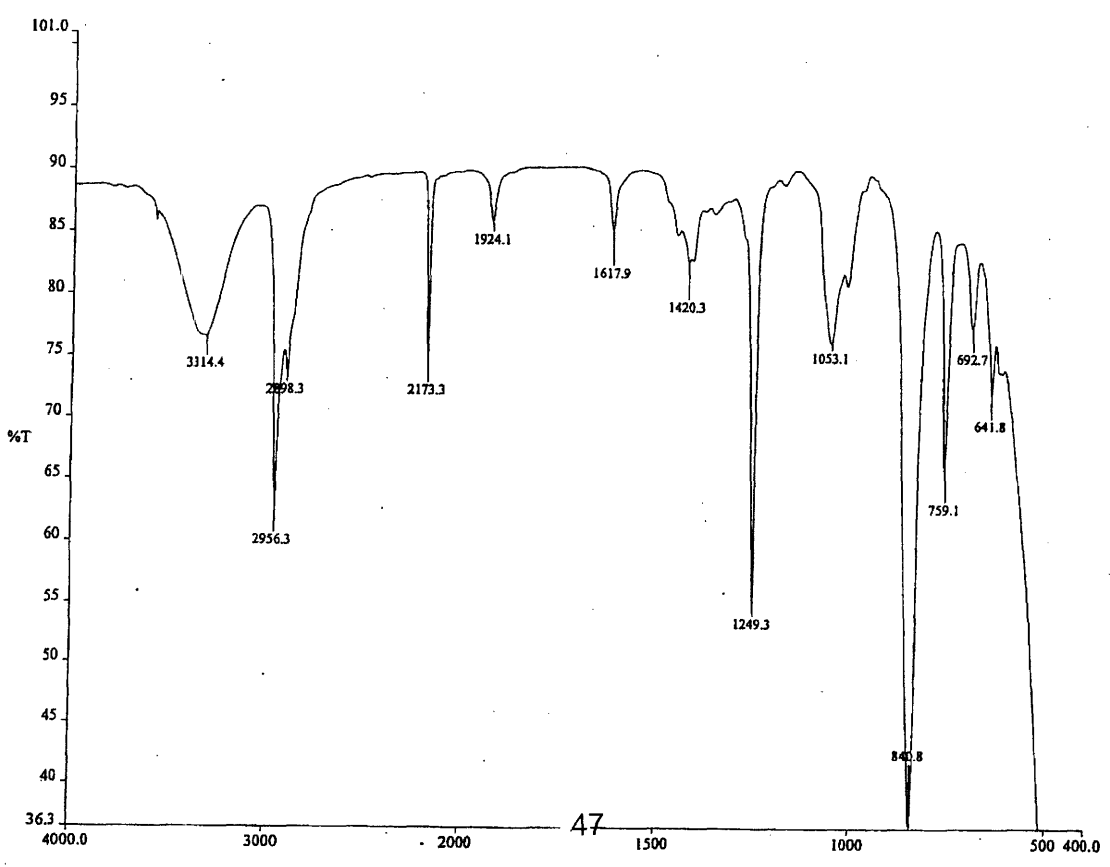
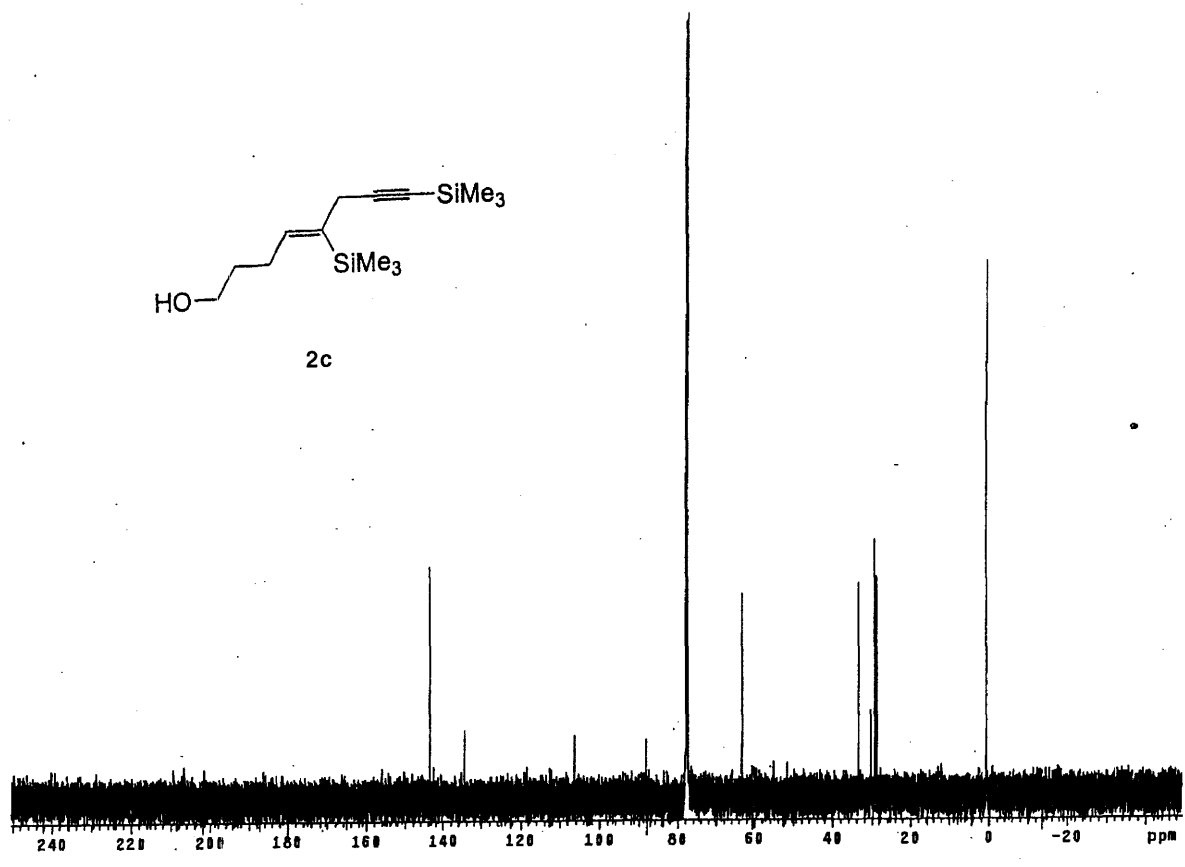


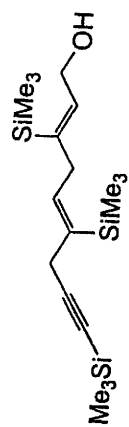




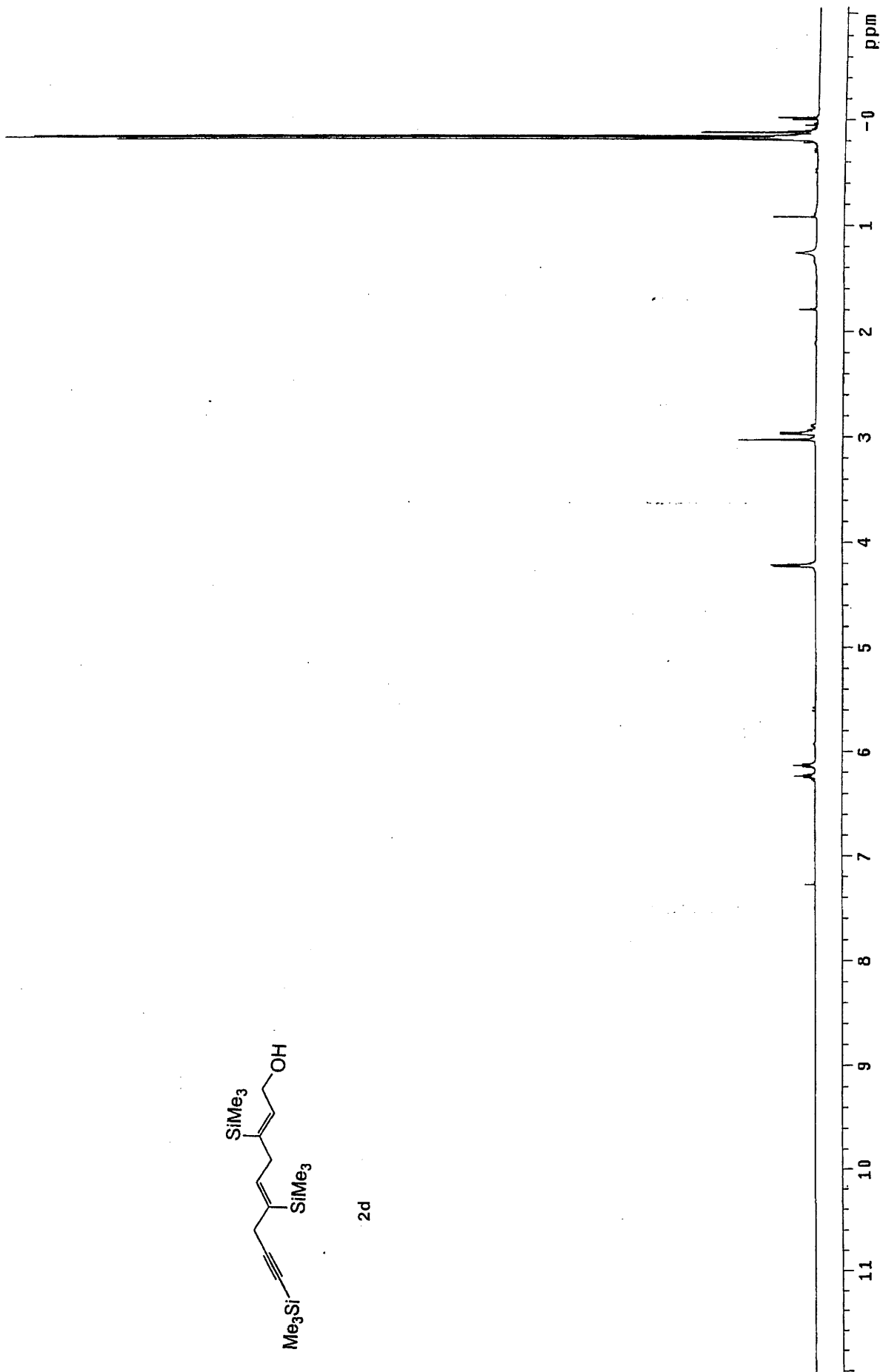
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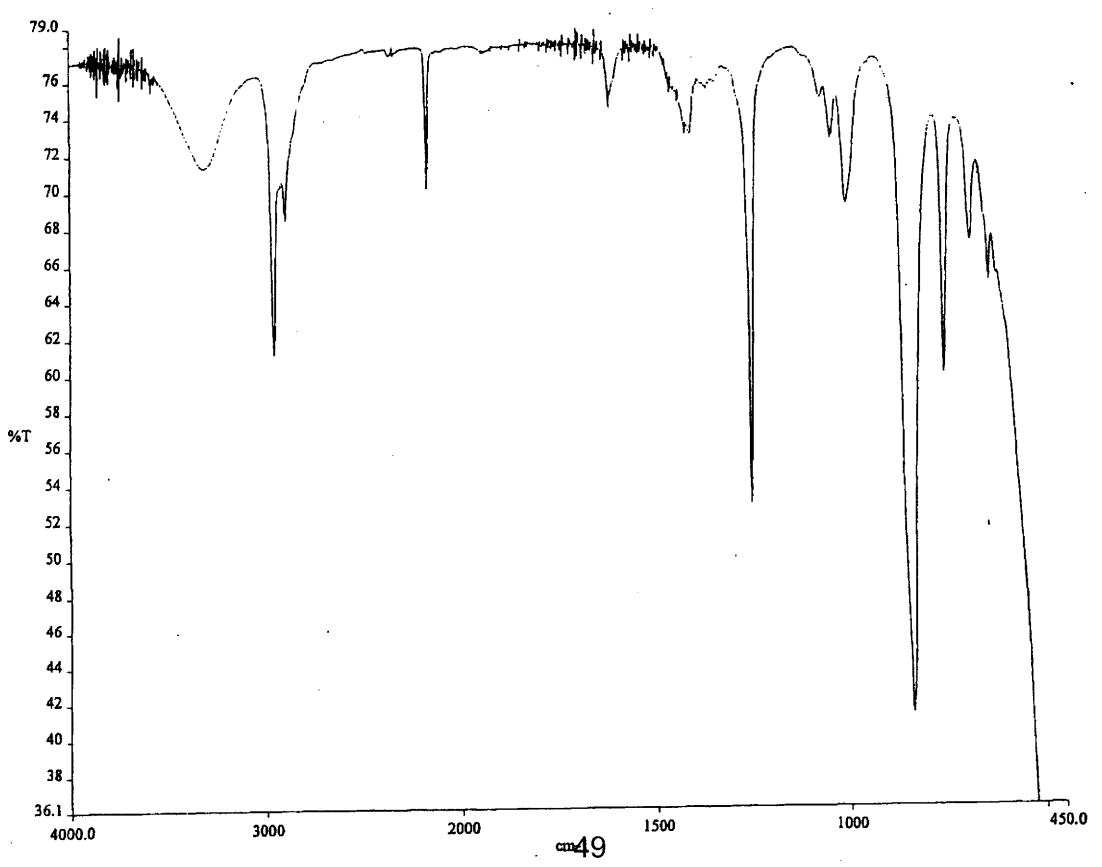
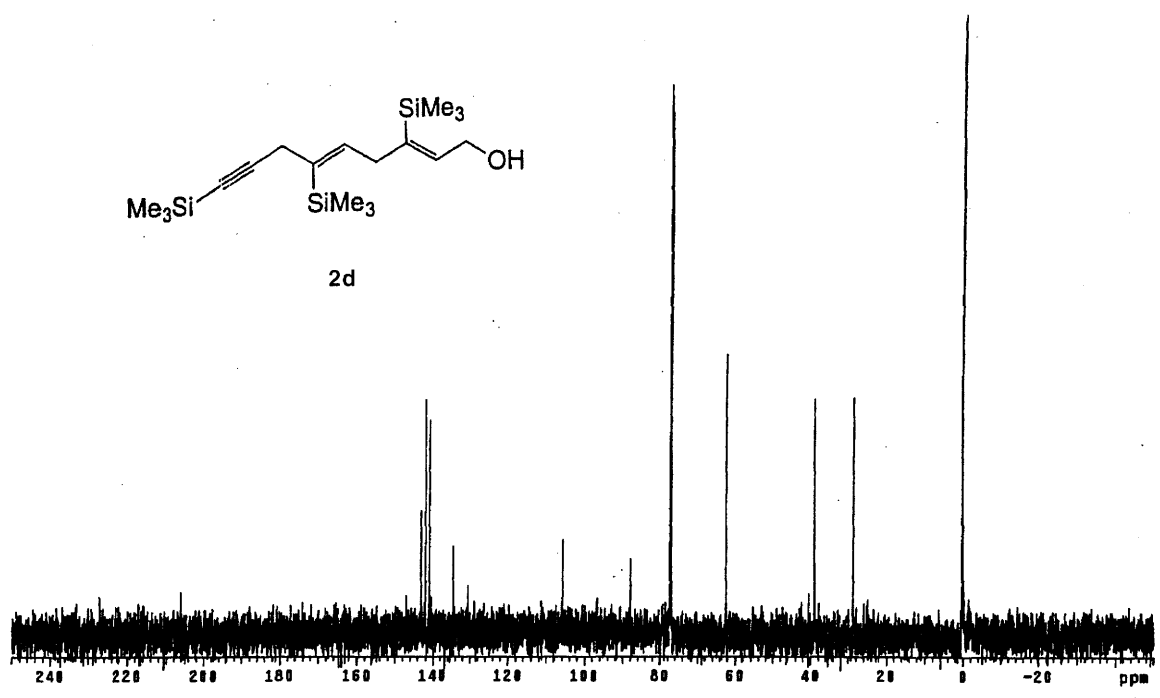
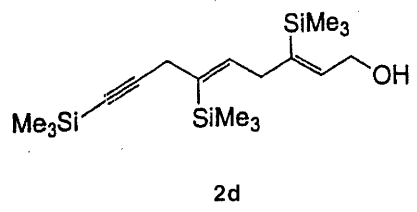


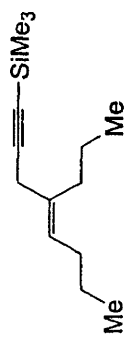




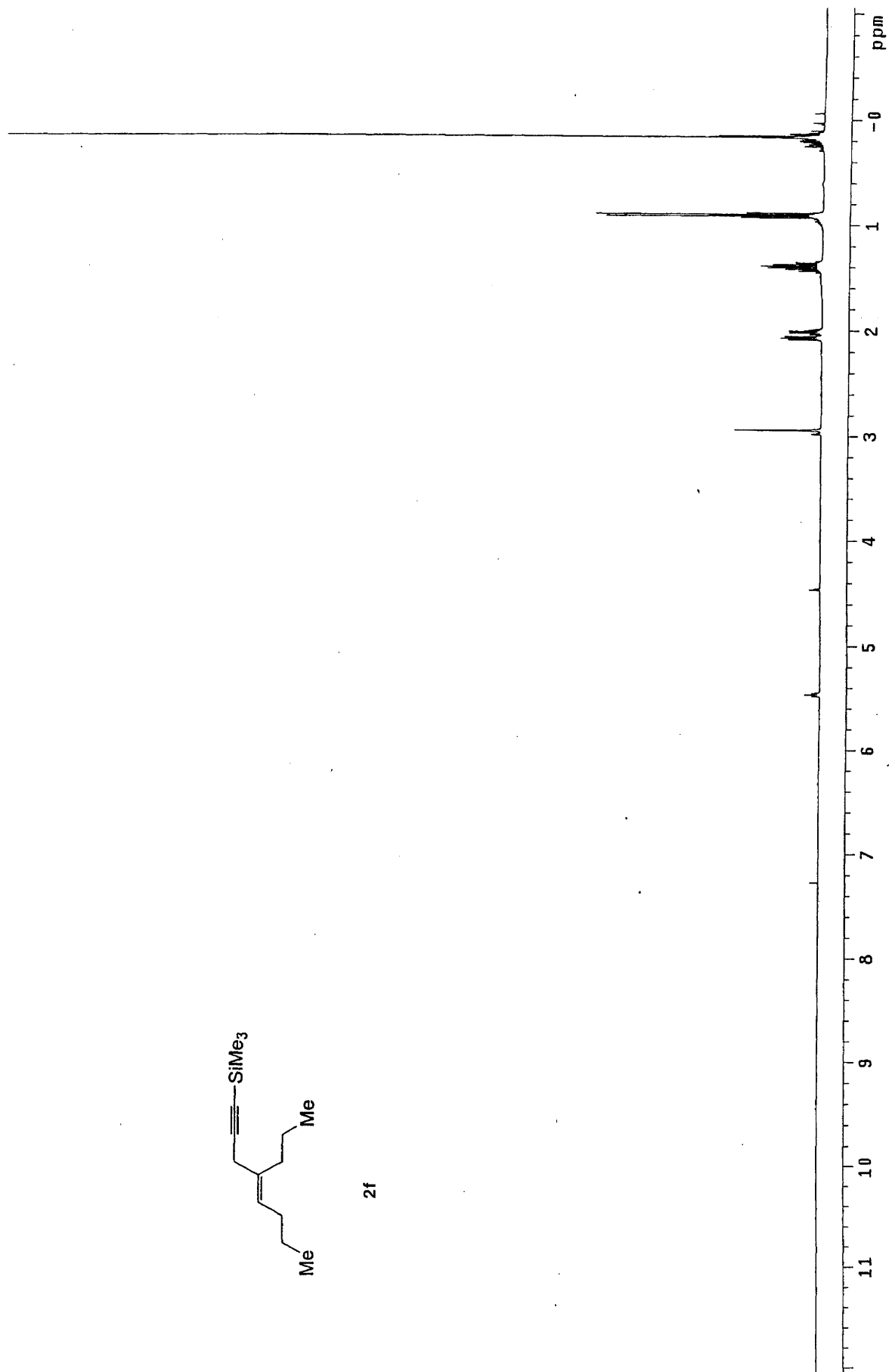
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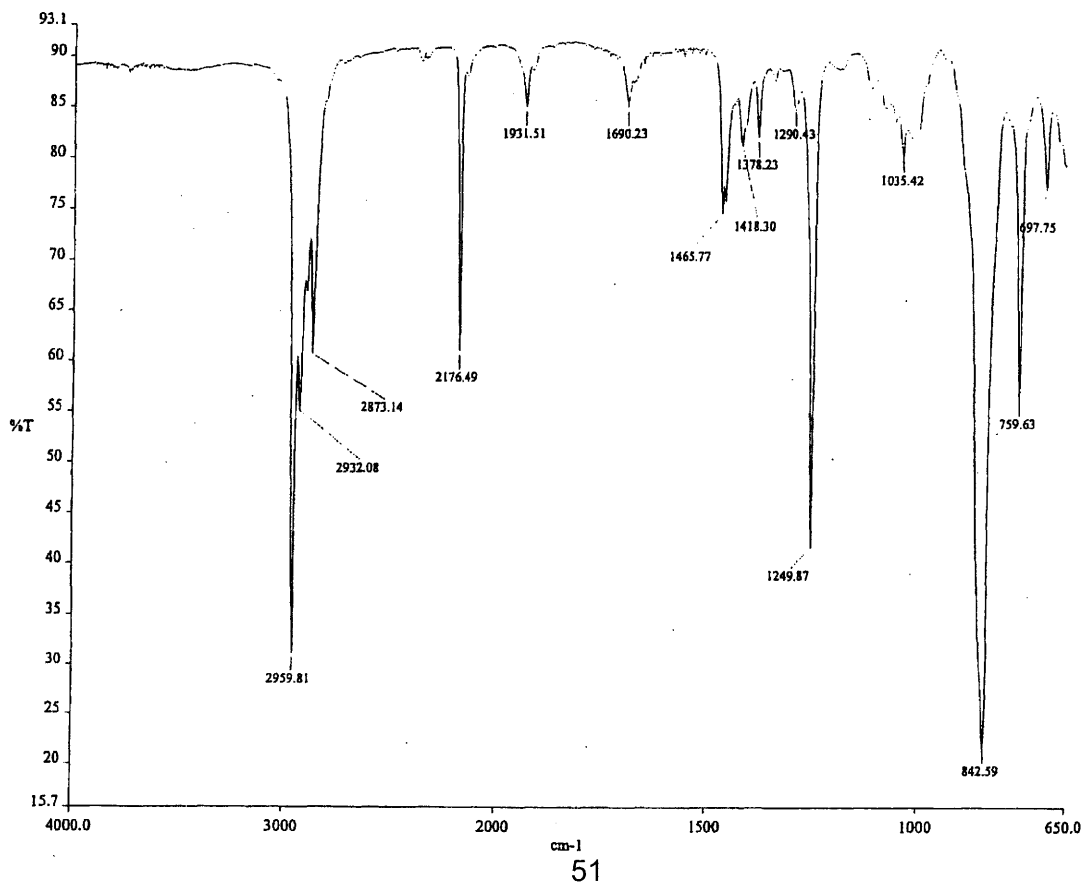
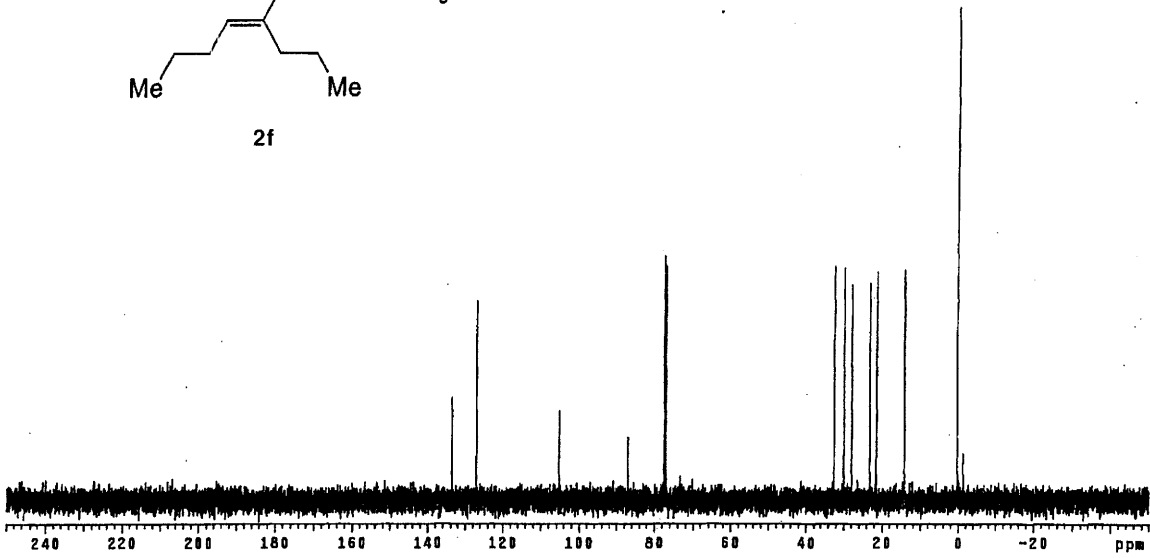
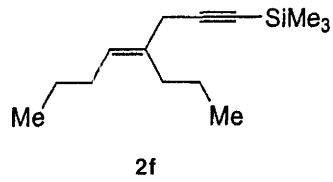


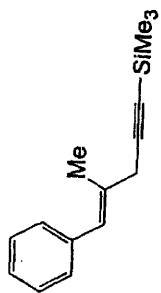




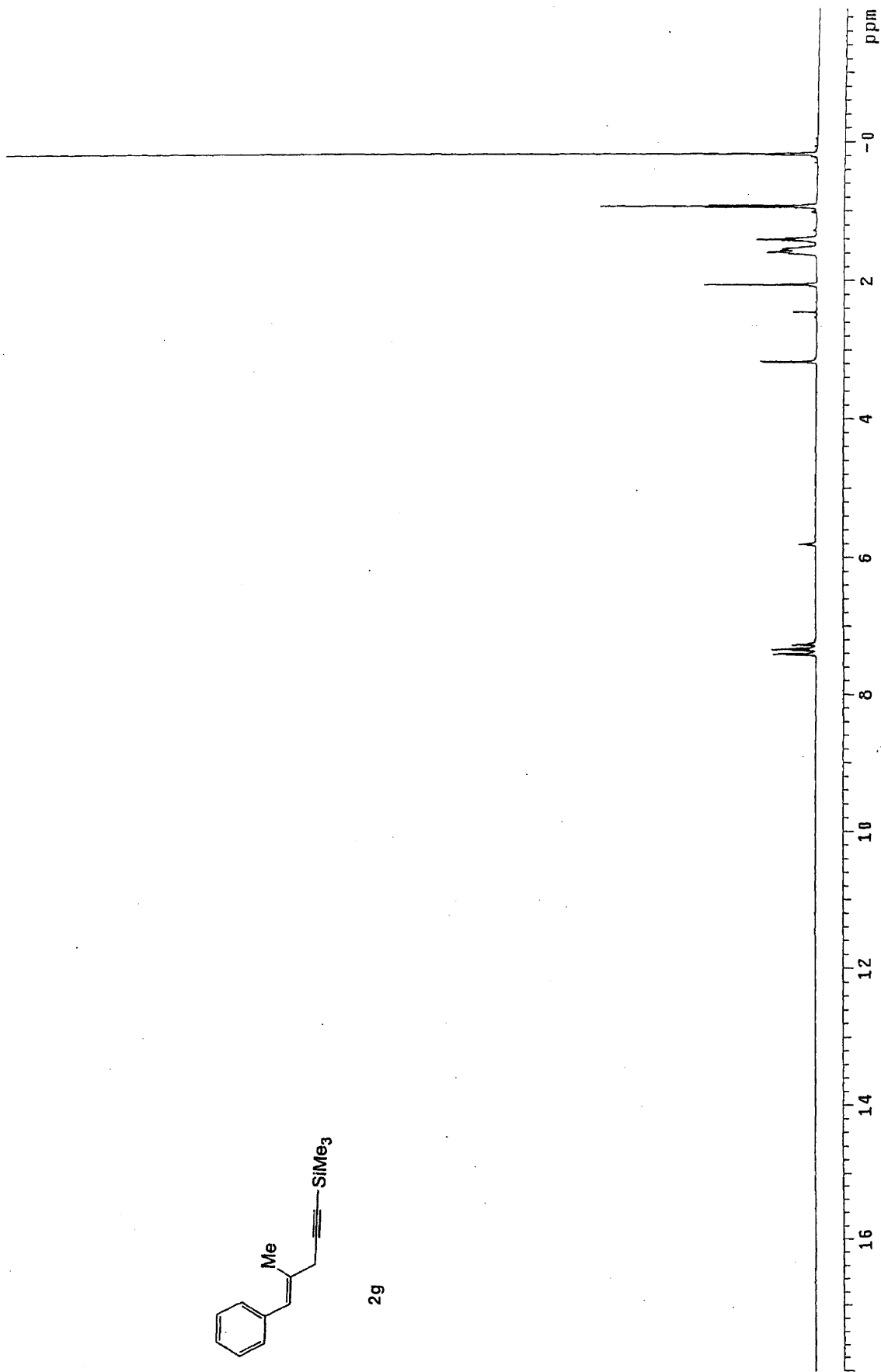
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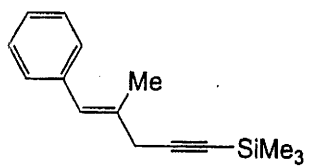




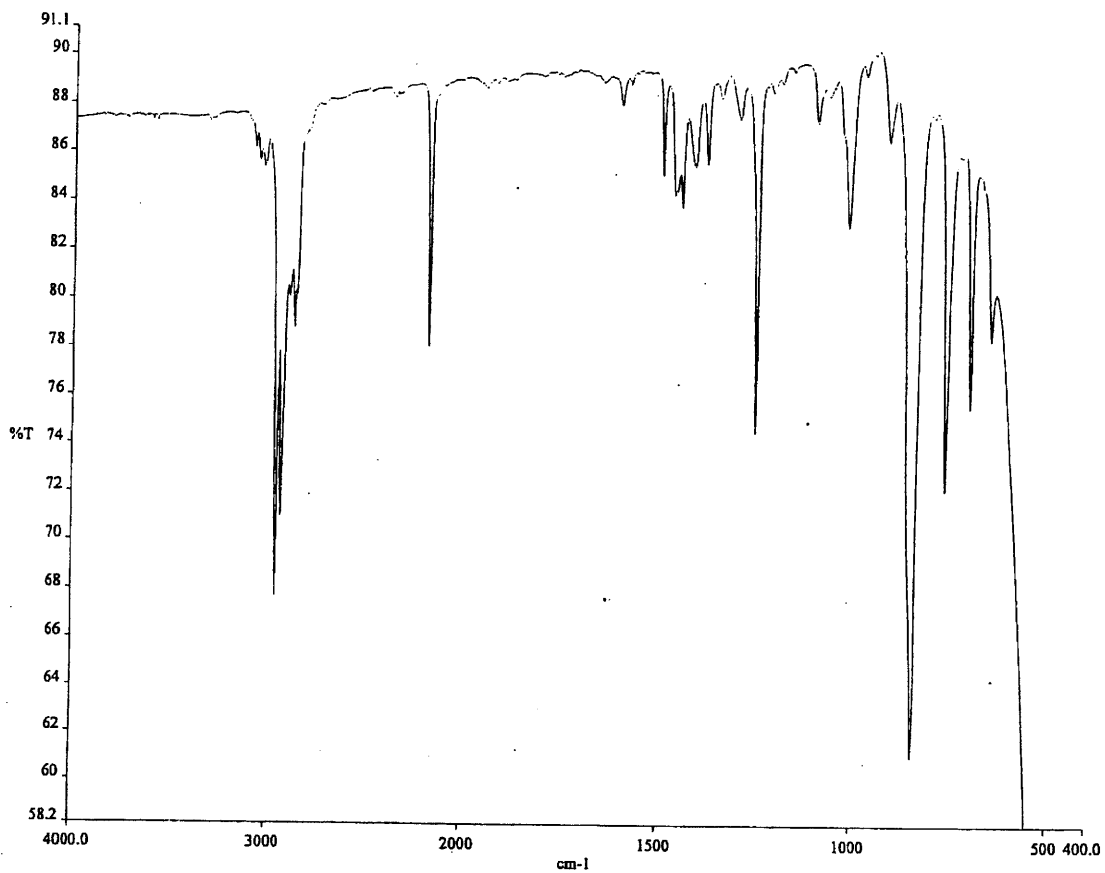
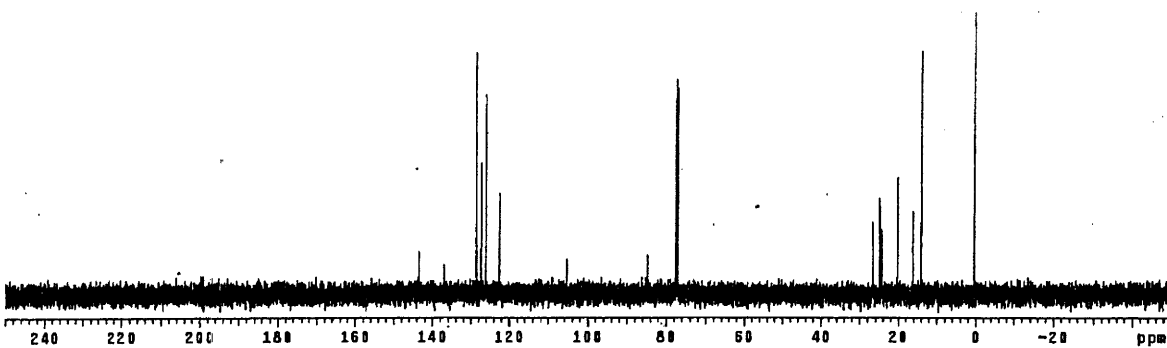


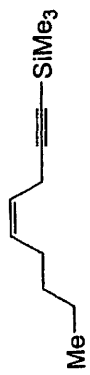
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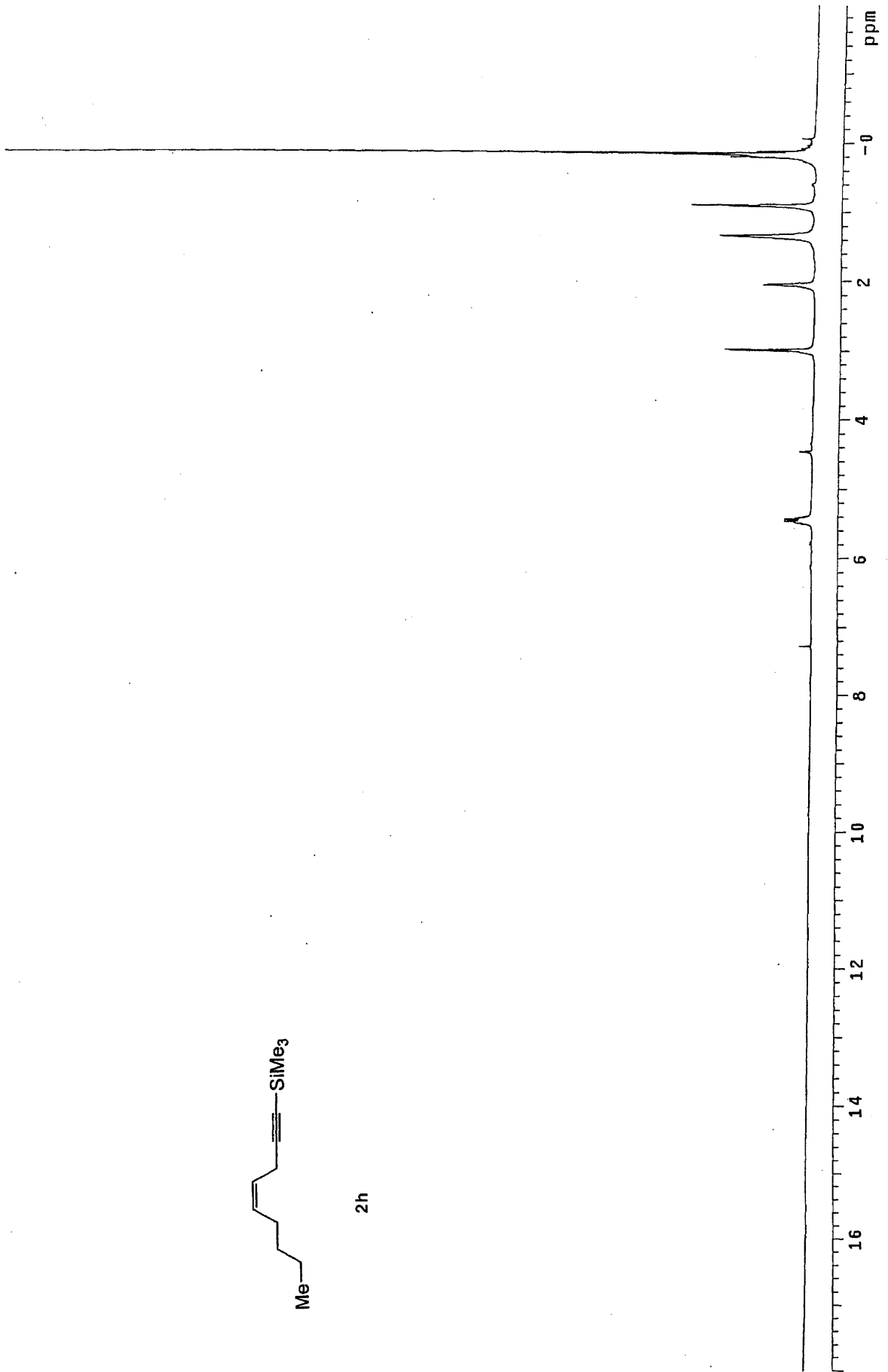


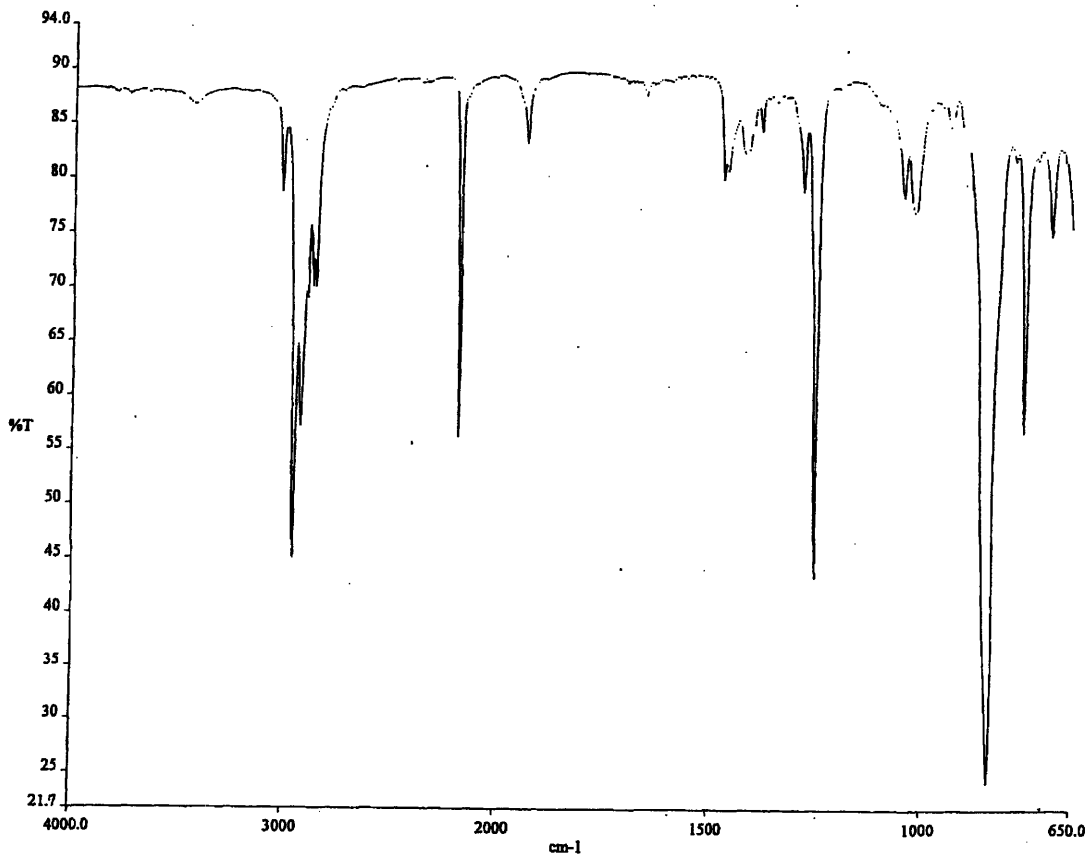
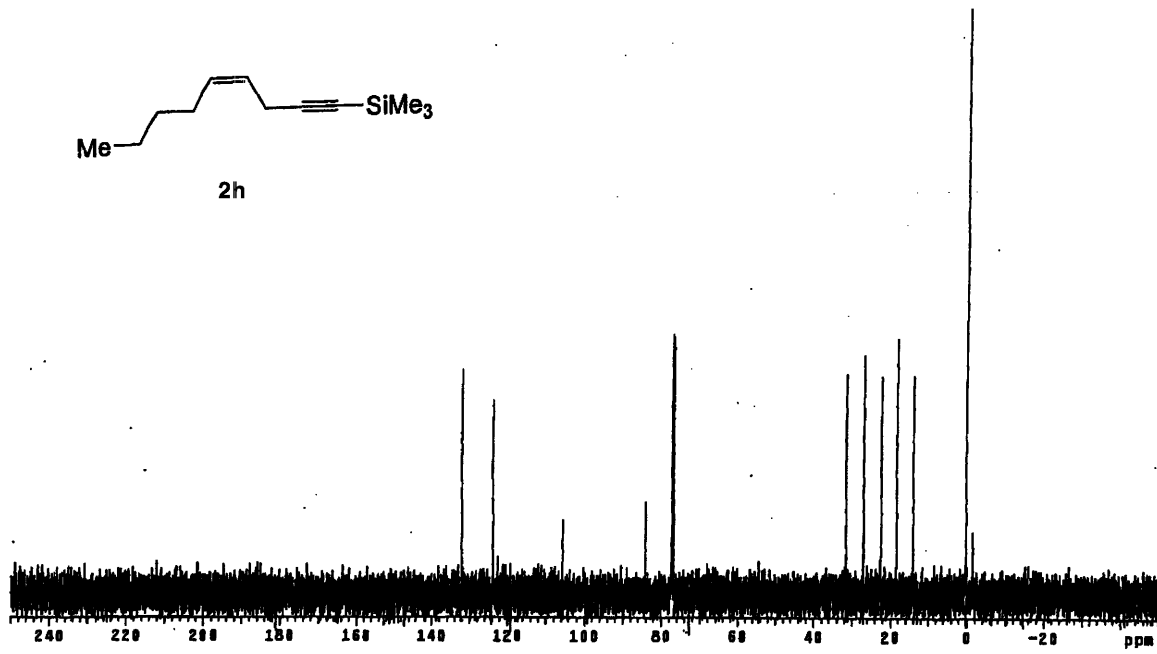
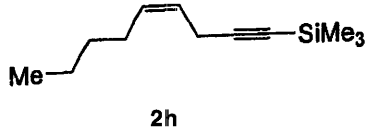
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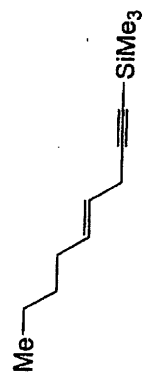




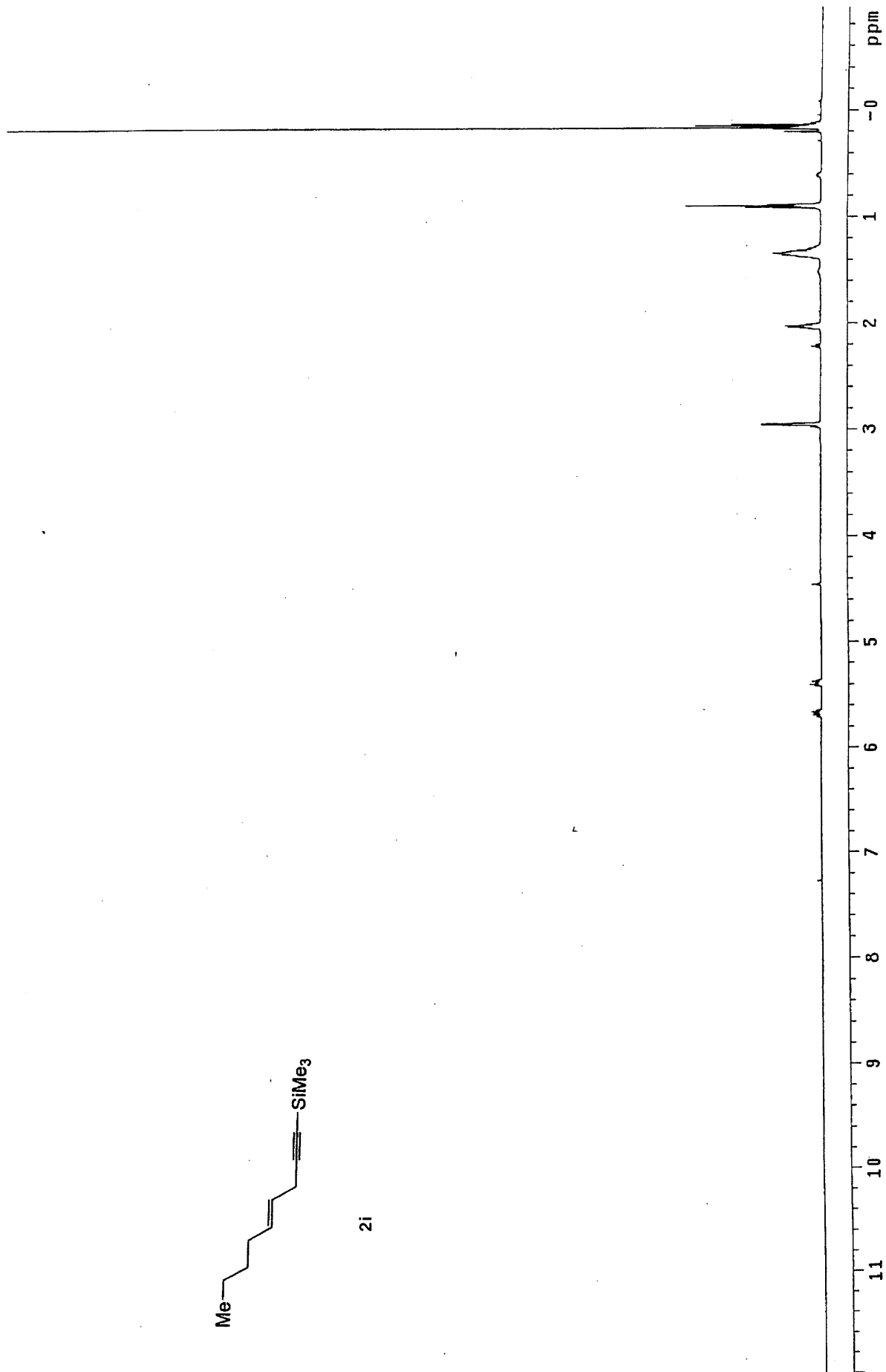
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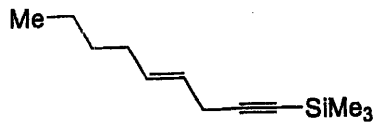




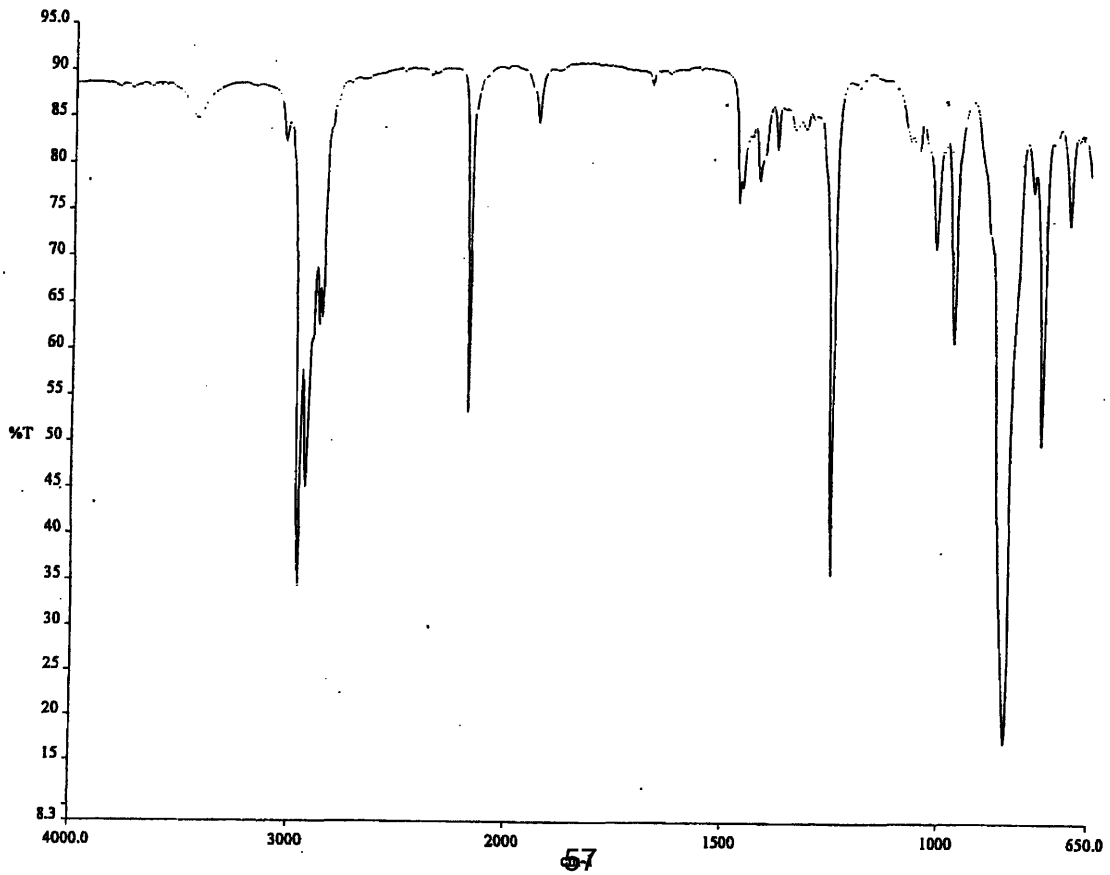
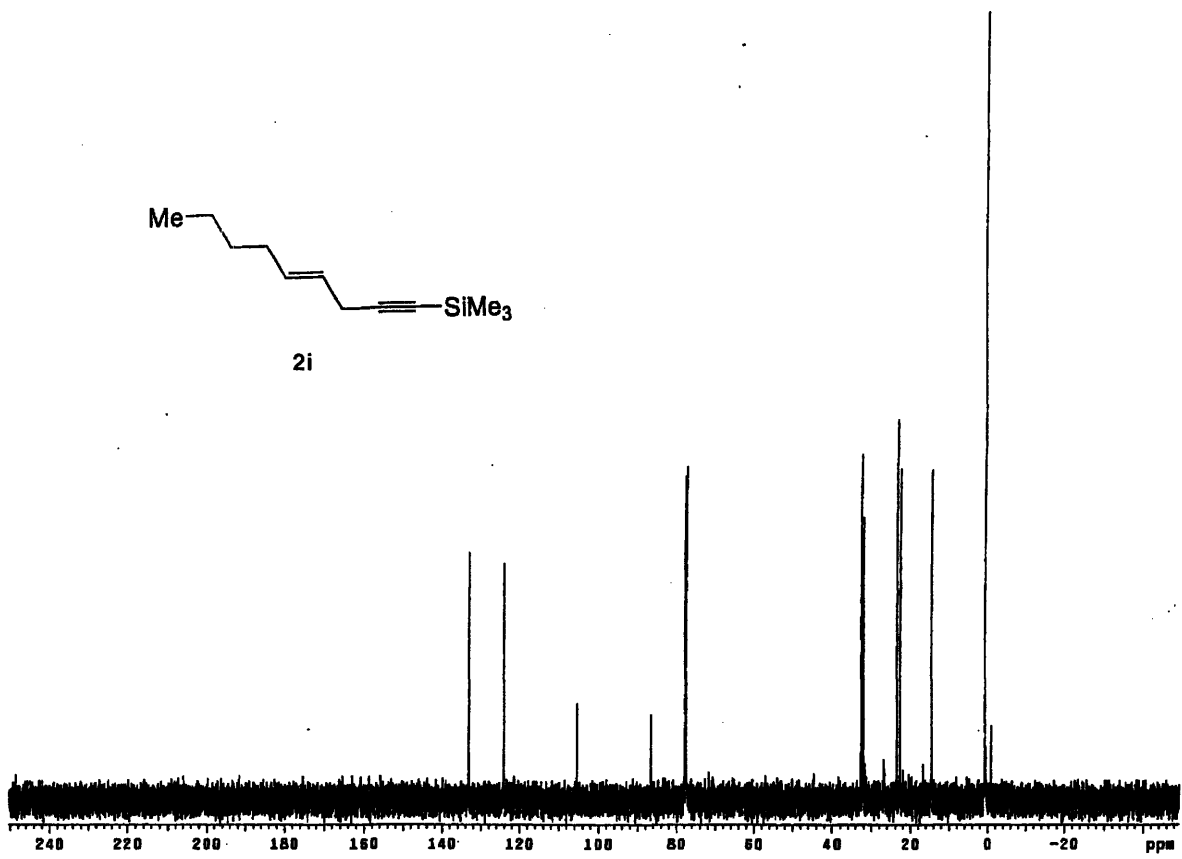


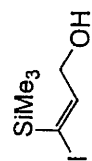
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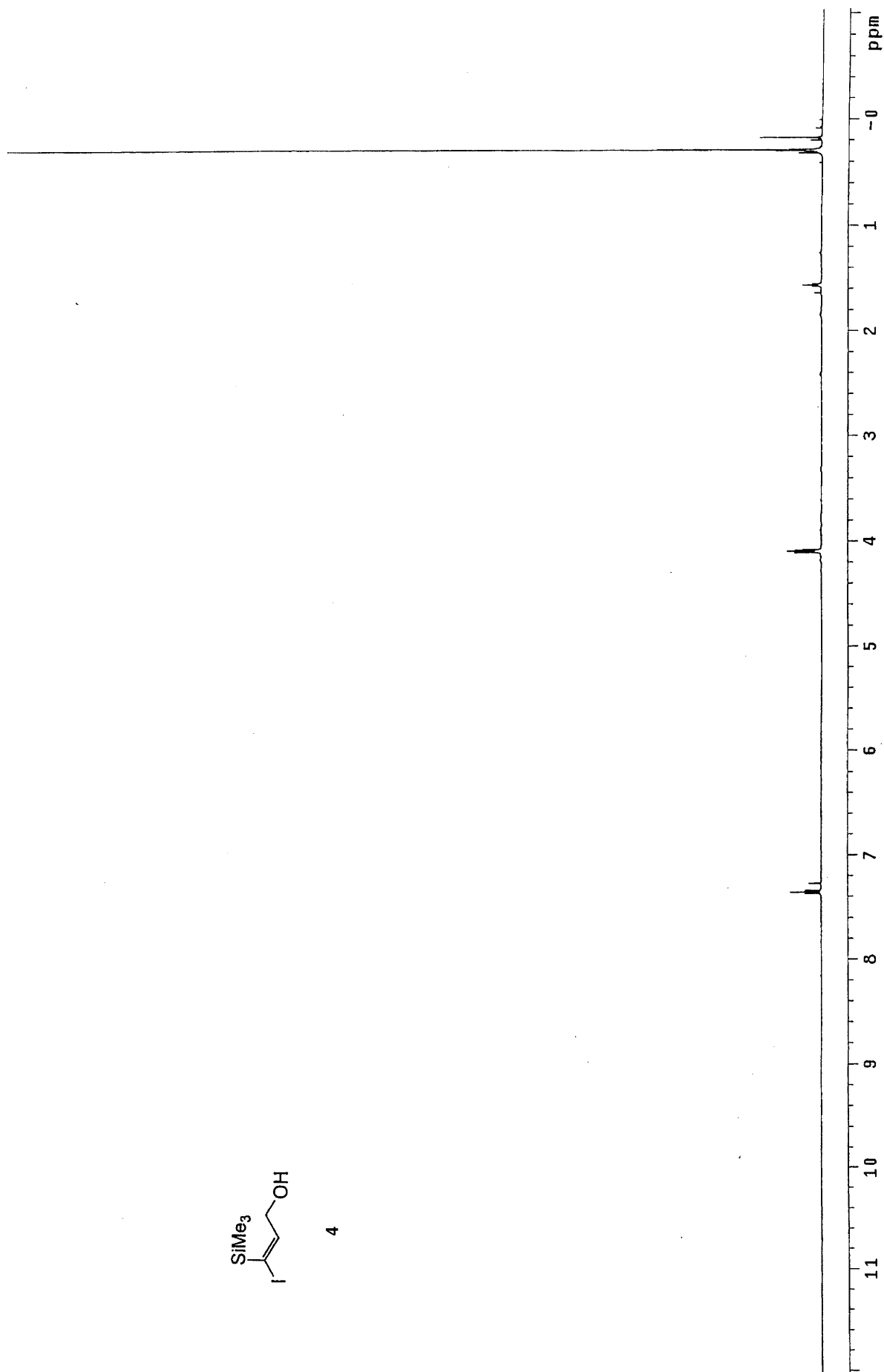


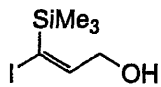
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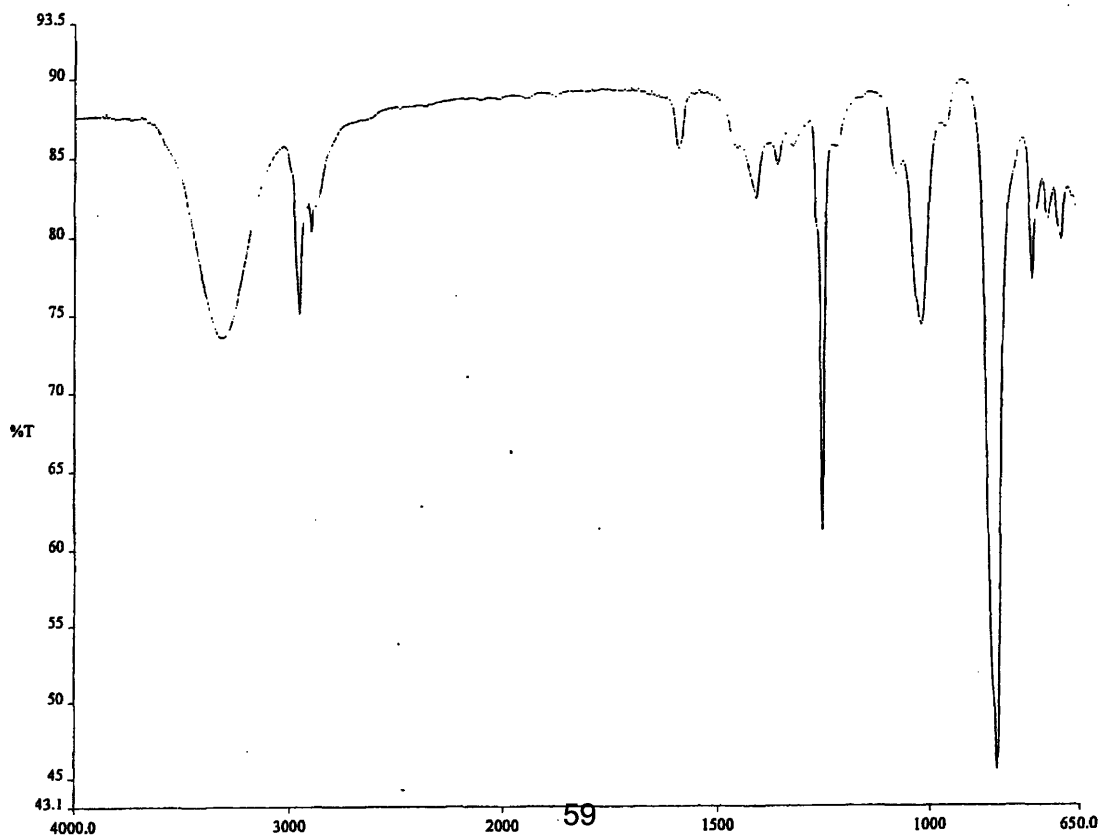
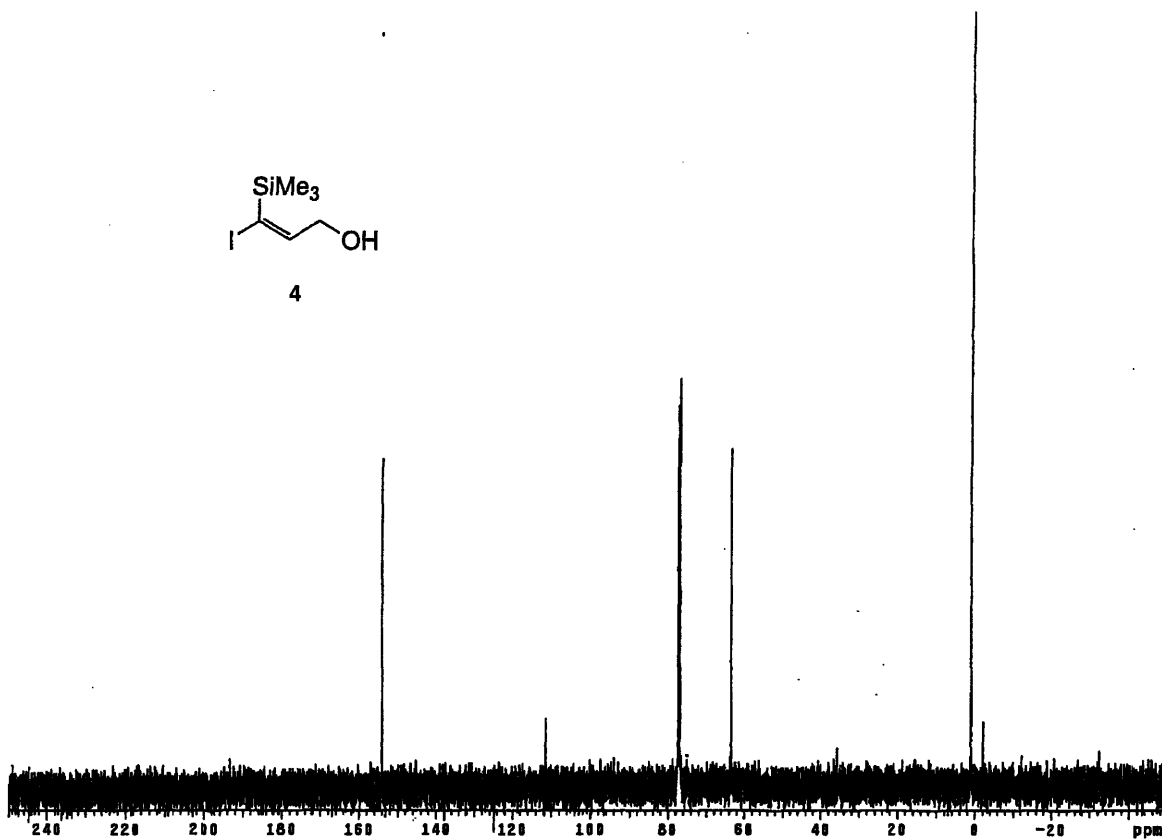


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Chapter 2

Total Synthesis of (-)-Gloeosporone via Nickel-Catalyzed Epoxide-Alkyne Reductive Macrocyclization

Introduction

Macrocycles are found in diverse classes of important molecules including naturally-occurring peptides (e.g., cyclosporine), oligosaccharides (e.g., cyclodextrins), polyketides (e.g., erythromycin), and synthetic compounds such as crown ethers and polyenes.¹ The most common strategy to prepare macrocyclic lactones (macrolides) is by intramolecular C–O bond formation to provide the lactone functional group itself.² Though often successful and high-yielding, this approach is also highly context-dependent and in some cases provides little to none of the desired macrocycle.² Accordingly, the development of methods for macrocyclization have received much attention.³ Herein we report a new C–C bond-forming strategy for macrocyclization, nickel-catalyzed epoxide-alkyne reductive coupling, and illustrate its use in the total synthesis of the macrolide natural product (–)-gloeosporone (**1**).

The development of nickel(0)-catalyzed multi-component coupling reactions has been a focus of research in the Jamison laboratories and in others.⁴ In 2003, we reported the reductive coupling of alkynes and epoxides by a nickel(0)-trialkylphosphine complex to give homoallylic alcohols in generally good yields (Scheme 1).⁵ Through use of an aryl or alkenyl directing group

¹ Bielawski, C. W.; Benitez, D.; Grubbs, R. H. *Science* **2002**, *297*, 2041–2044.

² Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911–939.

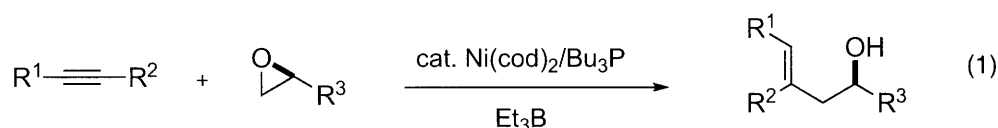
³ Gradillas, A.; Pérez-Castells, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6086–6101. (b) Dieters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238.

⁴ (a) For a recent issue of *Tetrahedron* dedicated to the subject of *Recent Advances in Organonickel Chemistry*, see: (preface) Jamison, T. F. *Tetrahedron* **2006**, *62*, 7503. (b) For a recent review on nickel-catalyzed reductive cyclizations, see: Montgomery, J. *Angew. Chem. Int. Ed.* **2004**, *43*, 3890–3908.

⁵ (a) Molinaro, C. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 8076–8077. For extension to the use of 1,3-enyne coupling partners, see: (b) Miller, K. M.; Luanphaisarnont, T.; Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *126*, 4130–4131.

on the alkyne (R^1 , Scheme 1, eq 1), excellent regioselectivity was attained with a variety of epoxide partners.⁶ For epoxides that were enantiomerically enriched, the sense of chirality and degree of enantiopurity were preserved in the reaction, providing homoallylic alcohol products in high enantiopurity. These products could also be treated with ozone to oxidatively cleave the olefin, providing important β -hydroxy ketone moieties (Scheme 1, eq 2). The β -hydroxy ketones thus obtained offer a complement to acetate aldol disconnections.

Scheme 1

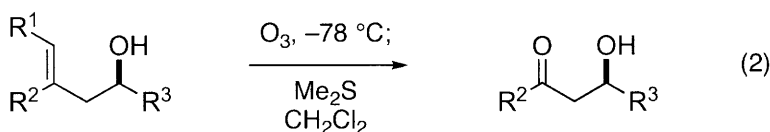


35 - 71% yield, 6 examples

R^1 = aryl, alkenyl, > 95:5 regioselectivity for epoxide and alkyne

R^2 = alkyl

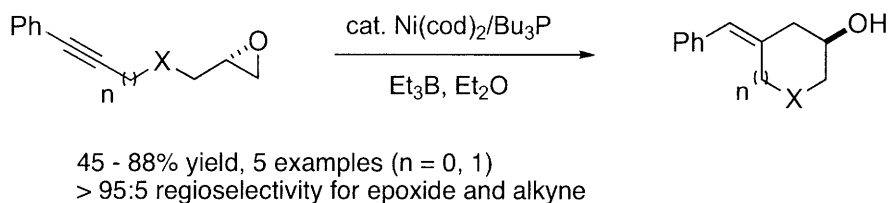
R^3 = alkyl, aryl



The original report also described the nickel-catalyzed reductive cyclizations of alkynes and epoxides to give 5- and 6-membered rings (Scheme 2).^{5a} In these cases, regioselectivity for the resulting alkene was again controlled by the presence of an aryl directing group on the alkyne. The epoxide, in all examples, opened solely at the terminal position providing the *endo* product.⁶

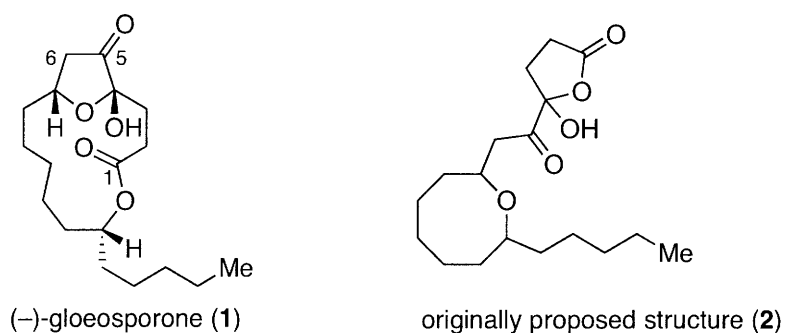
⁶ The coupling of 1-phenyl-1-propyne with styrene oxide showed decreased regioselectivity for both partners (~9:1).

Scheme 2



We were interested in extending the nickel-catalyzed reductive cyclization of epoxides and alkynes to the formation of large rings. As an interesting target, containing a macrocyclic core with a β -hydroxy ketone moiety, we became intrigued by the possibility of constructing (-)-gloeosporone **1** through nickel-catalyzed reductive macrocyclization of an alkyne and epoxide.

Figure 1. Originally proposed (**2**) and revised (**1**) structures of (-)-gloeosporone



In 1982, a biologically active component of *Colletotrichum gloeosporioides* was isolated by Meyer *et al.* and given the trivial name gloeosporone.^{7a} The following year a structure was

⁷ (a) Lax, A. R.; Templeton, G. E.; Meyer, W. L. *Phytopathology* **1982**, *74*, 503. (b) Meyer, W. L.; Lax, A. R.; Templeton, G. E.; Brannon, M. J. *Tetrahedron Lett.* **1983**, *24*, 5059–5062.

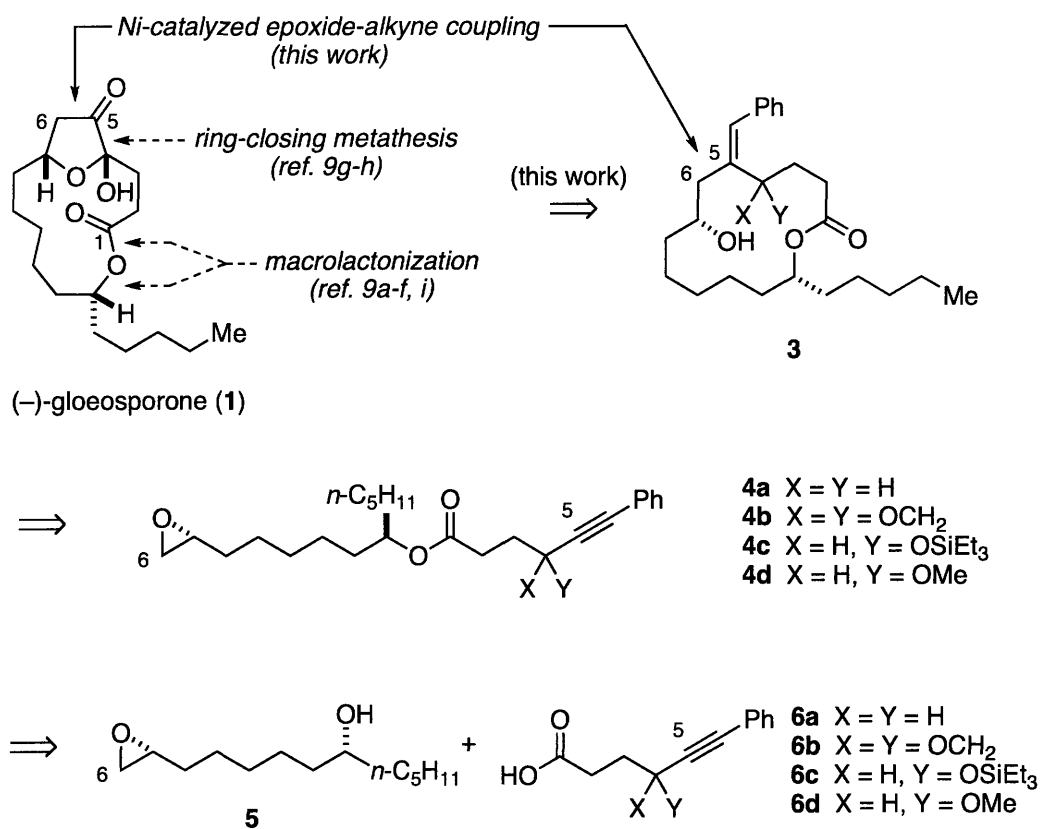
proposed for this spore germination inhibitor as oxocane **2** (Figure 1).^{7b} Subsequent independent synthesis of **2**, however, revealed that this was not the structure of the natural product.^{8a} A collaborative effort, aided by single crystal X-ray analysis, then led to structural revision of (-)-gloeosporone as **1**.^{8b}

In the eight reported syntheses of gloeosporone, the 14-membered ring was constructed by either well established macrolactonization methods or by the powerful ring-closing metathesis (Scheme 3).⁹ The nickel-catalyzed epoxide-alkyne reductive macrocyclization strategy described herein represents a departure from these strategies, and for the first time in all gloeosporone syntheses uses the C5–C6 bond as the site of macrocyclization whereby the homoallylic alcohol product **3** of an epoxide-alkyne reductive coupling reaction corresponds to the β -hydroxy ketone pattern in gloeosporone **1**.

⁸ (a) Carling, R. W.; Holmes, A. B. *Tetrahedron Lett.* **1986**, *27*, 6133–6136. (b) Meyer, W. L.; Seebach, D.; Schreiber, S. L. *Helv. Chim. Acta* **1987**, *70*, 281–291.

⁹ (a) Adam, G.; Zibuck, R.; Seebach, D. *J. Am. Chem. Soc.* **1987**, *109*, 6176–6177. (b) Schreiber, S. L.; Kelly, S. E.; Porco, J. A.; Sammakia, T.; Suh, E. M.; *J. Am. Chem. Soc.* **1988**, *110*, 6210–6218. (c) Takano, S.; Shimazaki, Y.; Takashi, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1004–1005. (d) Seebach, D.; Adam, G.; Zibuck, R.; Simon, W.; Rouilly, M.; Meyer, W. L.; Hinton, J. F.; Privett, T. A.; Templeton, G. E.; Heiny, D. K.; Gisi, U.; Binder, H. *Liebigs Ann. Chem.* **1989**, 1233–1240. (e) Curtis, N. R.; Holmes, A. B.; Looney, M. G.; Pearson, N. D.; Slim, G. C. *Tetrahedron Lett.* **1991**, *32*, 537–540. (f) Matsushita, M.; Yoshida, M.; Zhang, Y.; Miyashita, M.; Irie, H.; Ueno, T.; Tsurushima, T. *Chem. Pharm. Bull.* **1992**, *40*, 524–527. (g) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130–9136. (h) Ley, S. V.; Cleator, E.; Harter, J.; Hollowood, C. *J. Org. Biomol. Chem.* **2003**, *1*, 3263–3264. (i) Sharma, A.; Gamre, S.; Chattopadhyay, S. *Lett. Org. Chem.* **2005**, *2*, 547–549.

Scheme 3



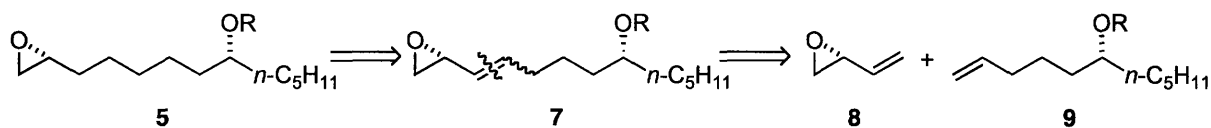
The original retrosynthetic plan called for oxidative cleavage of the styrenyl olefin of **3**, which would be derived by cyclization of alkynyl epoxide **4** containing at C4 the requisite oxidation state (e.g., **4b**) or a functional group handle for oxidation state manipulation (e.g., **4c**, **d**). The reductive macrocyclization precursor **4** could be constructed by dehydrative coupling of epoxy alcohol **5** and ynoic acid **6**.

Results and Discussion

A. Synthesis of Epoxy Alcohol Intermediate 5

Several routes were envisioned for the synthesis of epoxy alcohol intermediate **5**. For convergence considerations, we sought to disconnect **5** in a manner that would separate the two stereogenic centers. We therefore desired a selective manner to bring together two pieces of similar complexity. Cross metathesis was investigated as a means to meet these criteria (Scheme 4). Thus, epoxy alcohol **5** could be derived by reduction of vinyl epoxide **7**, which could then be derived by union of butadiene monoxide **8** and alkenyl alcohol **9**.

Scheme 4



Cross metathesis has found recent resurgence in utility for the synthetic chemist, due to the development of defined and highly active catalysts by Schrock or Grubbs, Hoveyda, and others.¹⁰ The prerequisite for selective cross metathesis is use of two olefins of different “type

¹⁰ For recent reviews on metathesis, see: (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043. (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29. (c) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.*, **2003**, *42*, 4592–4633. (d) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900–1923. For development of Grubbs 2nd generation catalyst and Hoveyda's modification, see: (d) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956. (e) Hoveyda, A.; Garber, S.; Kingsbury, J.; Gray, B. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179. (f) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973–9976.

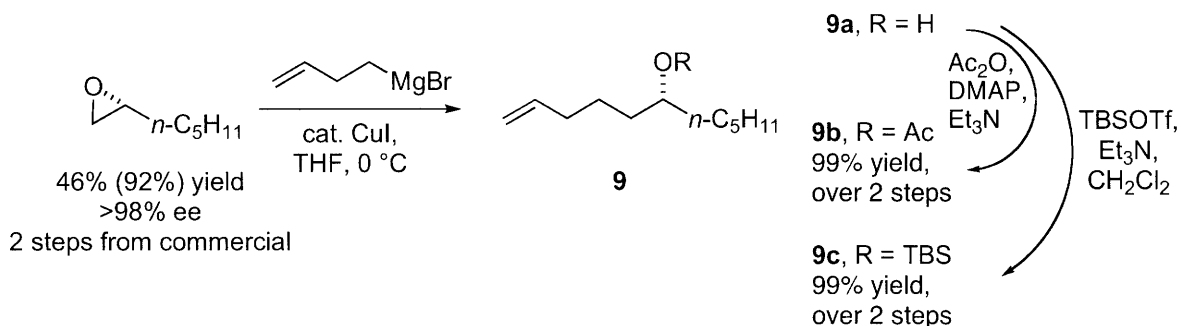
numbers” for a given catalyst system, following Grubbs’ nomenclature.¹¹ Higher type numbers correspond to less reactive olefins which thus are slower to insert into the catalyst, resulting in slower homo-coupling and stabilizing the olefin metathesis products to further reaction. Generally, more electron-deficient or sterically-encumbered olefins correspond to higher type numbers (lower reactivity) for a given catalyst system. Thus, for selective cross metathesis one must combine a more reactive olefin (lower type number) with a less reactive one.

A mono-substituted vinyl epoxide (e.g., butadiene monoxide) is classified as type II with use of Grubbs’ second-generation catalyst and has shown selective cross metathesis with type I olefins.^{11, 12} A type II olefin is described as an olefin whose metathesis products are slow to undergo further reaction and which is slow to undergo self-metathesis. Therefore, designing the cross metathesis disconnection such that one partner is a vinyl epoxide (e.g., **8**) was anticipated to provide a successful route to selective cross metathesis (Scheme 4). The other partner **9** was expected to be classified as type I with Grubbs’ second-generation catalyst (where its self-metathesis products readily undergo subsequent metathesis processes).

¹¹ Chatterjee, A.; Choi, T.-L.; Sanders, D.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

¹² Grubbs, R.; Chatterjee, A.; Morgan, J.; Scholl, M. *J. Am. Chem. Soc.* **2000**, *122*, 3783–3784.

Scheme 5

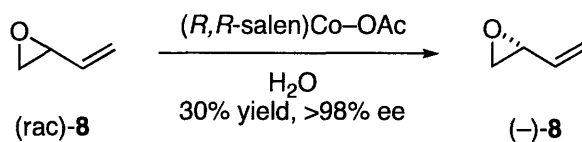


The preparation of the desired olefins was straightforward (Schemes 5 and 6). (*R*)-1,2-Epoxyheptane (prepared in two steps, 46% yield, and in >99% ee from 1-heptene)^{13, 14} was opened with homoallylmagnesium bromide, in the presence of catalytic copper, to provide alkenyl alcohol **9a** (Scheme 5). The crude residue could be directly treated with either acetic anhydride and triethylamine or *tert*-butyldimethylsilyl triflate and triethylamine to provide **9b** (R = Ac) or **9c** (R = TBS), respectively, in 99% yield over the two steps. Enantiomerically pure olefin **8** was prepared in one step starting from commercially available butadiene monoxide using Jacobsen's (salen)Co(III)-catalyzed hydrolytic kinetic resolution (HKR) method (Scheme 6).¹⁴

¹³ Moslin, R.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 15106–15107.

¹⁴ (a) Tokunaga, M.; Larrow, J. F.; Kakuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936–938. (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307–1315.

Scheme 6



With both olefins in hand, we next investigated the desired cross metathesis (Scheme 7 and Table 1). The system proved remarkably unreactive in the presence of several different ruthenium catalysts (**A**, **B**, and **C**), with a high percentage of **9** recovered in each case. This observation is in contrast to our expectation that **9** would rapidly undergo self-metathesis condensation.¹⁵ A number of conditions were investigated to improve the reactivity of the system, including changing addition time of each olefin partner, changing protecting group on **9** (Ac, Bn, TBS, and free hydroxy tested), and changing catalyst systems and loading. The protecting group did not seem to have an effect on the reactivity (compare entries 7, 12, and 13), although free alcohols were not tolerated (entries 10 and 11). The biggest effect on conversion was found to depend on the catalyst choice (**A** is less reactive than **B**, and **B** is less reactive than **C** – compare entries 1, 2 and 7). Finally, changing the addition time of **8** from 5 seconds to 4 hours (entries 4 and 5) did increase the conversion; however, doing so also increased dimerization of **9**. This result suggested to us that the butadiene monoxide partner **8** might be

¹⁵ In the absence of **8**, **9** would slowly undergo self-metathesis utilizing catalyst **C**. Other catalysts were not tested under conditions lacking the presence of **8**.

decomposing the catalyst under the conditions.¹⁶ Considering this possibility, dropwise addition of **C** to a solution of **8** and **9** was attempted (entries 15 and 17), a modification that provided a significant increase in conversion, allowing for synthetically useful amounts of **7** to be isolated. Notably, the yields based on recovered starting material of the desired product **7** are very high – up to 91% yield based on recovered **9**.

¹⁶ Though no decomposed ruthenium species have been isolated, significant amounts (up to 5 mol %) of *o*-*i*PrO styrene have been isolated in metathesis reactions with catalyst D. This would be consistent with catalyst destruction under the reaction conditions.

Scheme 7

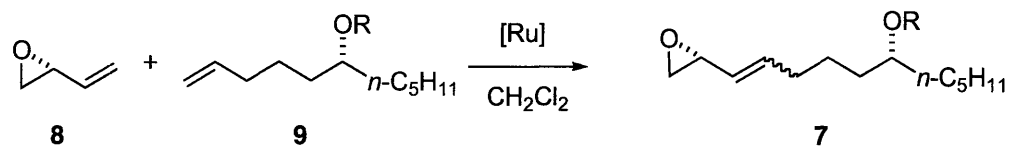


Table 1. Condition screen for cross metathesis

Entry	R	mol % [Ru]	conditions	addn time (8)	homodimer of 9	recovered 9	yield (7)
1	Ac	5 (A)	reflux, 12h	<5s	1%	53%	9%
2	Ac	5 (B)	reflux, 12h	<5s	<1%	57%	17%
3	Ac	10 (B)	reflux, 36h	<5s	3%	70%	16%
4	Ac	5 (B)	reflux, 12h	4h	36%	34%	24%
5	Ac	5 (B)	reflux, 12h	10h	41%	n.d.	0%
6	Ac	5 (B)	reflux, 12h	(a)	<1%	80%	8%
7	Ac	5 (C)	RT, 10 min.	<5s	<1%	60%	30%
8	Ac	2.5 (C)	RT, 72h	<5s	<1%	50%	24%
9	Ac	5 (C)	RT, 60h	(b)	1%	47%	14%
10	H	5 (B)	reflux, 12h	<5s	<1%	n.d.	<2%
11	H	5 (C)	RT, 12h	<5s	<1%	41%	<5%
12	Bn	5 (C)	RT, 12h	<5s	<1%	44%	30%
13	TBS	5 (C)	RT, 12h	<5s	<1%	49%	32%
14	TBS	5 (C)	RT, 12h	1h	<1%	45%	40%
15	Ac	5 (C) ^e	RT, 12h	<5s	<1%	56%	40% ^e
16	Ac	10 (C) ^d	RT, 24h	<5s	<1%	53%	30%
17	TBS	5 (C) ^e	RT, 12h	<5s	<1%	36%	49% ^e

Homodimer of 8 was isolated for each entry.

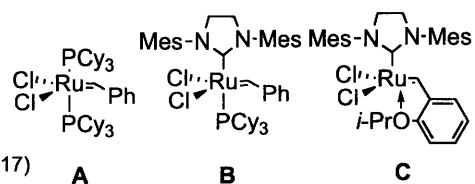
^a Both alkenes were added concurrently to over 4h

^b Added 200 mol% in 4 aliquots, at 12h intervals.

^c Catalyst added dropwise as a solution in CH₂Cl₂ over 8 hours

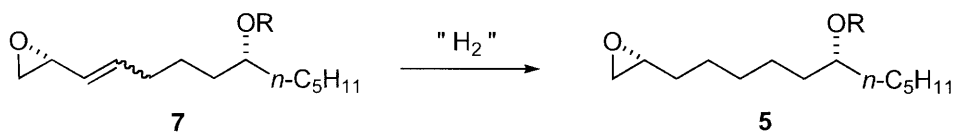
^d Catalyst added dropwise as a solution in CH₂Cl₂ over 16 hours

^e Based on recovered 9, yields are 91% (entry 15) and 77% (entry 17)



With a viable route to bring the two olefin fragments together, we next needed a means to reduce vinyl epoxide **7**. Vinyl epoxides can react in a variety of manifolds.¹⁷ Despite the sensitive nature of this functional group pattern, a number of reduction conditions have been employed successfully for vinyl epoxides where the epoxide is di- or trisubstituted.¹⁸ However, to the best of our knowledge, the reduction of a terminal epoxide bearing an α -vinyl substituent was unknown. A screen of the known conditions for di- or trisubstituted vinyl epoxides¹⁸ showed that the reactivity of **7** depends greatly upon the choice of conditions (Scheme 8 and Table 2).

Scheme 8



Utilizing heterogeneous catalysts such as rhodium on alumina or palladium on carbon led to over-reduction (**10**) and rearrangement (**11**) products as inseparable mixtures with desired **5** (entries 1-3, Table 2). Diimide reduction did provide access to the desired product after some optimization (entries 4-9), however the bulk of the material in each case was an unidentified

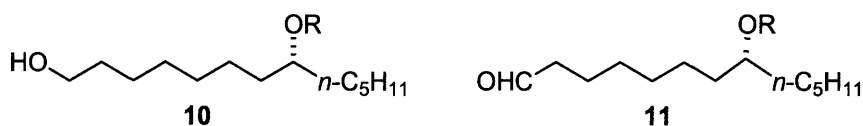
¹⁷ Marshall, J. *Chem. Rev.* **1989**, *89*, 1503–1511.

¹⁸ For the use of dimide, see: (a) McDonald, F. E.; Wei, X. *Org. Lett.* **2002**, *4*, 593–595. (b) Pasto, D. J.; Taylor, R. T. *Org. Reactions* **1991**, *40*, 91. (c) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330–5334. (d) Corey, E. J.; Mock, W. L.; Pasto, D. J. *Tetrahedron Letters*. **1961**, *2*, 347–352. (e) Corey, E. J.; Pasto, D. J.; Mock, W. L. *J. Am. Chem. Soc.* **1961**, *83*, 2957–2958. For the use of Rh/Al₂O₃, see: (f) Corey, E. J.; Ha, D.-C. *Tetrahedron Lett.* **1988**, *26*, 3171–3174. For the use of Wilkinson's catalyst, see: (g) Marschall, H.; Penninger, J.; Weyerstahl, P. *Liebigs Ann. Chem.* **1982**, 49–67. For the use of Pd/C, see: (h) Narayan, R. S.; Sivakumar, M.; Bouhlel, E.; Borhan, B. *Org. Lett.* **2001**, *3*, 2489–2492.

highly polar byproduct (possibly due to epoxide ring opening by hydrazine). Wilkinson's catalyst, however, provided clean reactivity to the desired product (entry 11). An interesting

Table 2. Condition screen for the reduction of vinyl epoxide **7**

Conditions	5:10:11 ^c (isolated 5) ^d	
R = Ac (7a)	1. cat. Rh/Al ₂ O ₃ , H ₂ (3 atm), pyr, THF	33:33:33
	2. cat. Pd/C (dry), H ₂ (1 atm), EtOAc	0:100:0
	3. cat. Pd/C (wet), H ₂ (1 atm), EtOAc	33:33:33
	4. H ₂ NNH ₂ •H ₂ O, H ₂ O ₂ , EtOH	– ^a
	5. KO ₂ CN=NCO ₂ K, AcOH, MeOH	0:0:100
	6. KO ₂ CN=NCO ₂ K, AcOH, pyr	100:0:0 (10%)
	7. KO ₂ CN=NCO ₂ K, AcOH, MeOH/pyr (1:1)	100:0:0 (22%)
	8. KO ₂ CN=NCO ₂ K, AcOH, MeOH/pyr (1:3)	100:0:0 (31%)
R = TBS (7b)	9. KO ₂ CN=NCO ₂ K, AcOH, MeOH/pyr (1:3)	100:0:0 (32%)
	10. 10 mol% RhCl(PPh ₃) ₃ , C ₆ H ₆ , 1 atm H ₂	100:0:0 (52%)
	11. 5 mol% RhCl(PPh ₃) ₃ , C ₆ H ₆ , 1 atm H ₂	100:0:0 (85%)
	12. 5 mol% RhCl(PPh ₃) ₃ , C ₆ H ₆ , 4 atm H ₂	15:85:0
	13. 2.5 mol% RhCl(PPh ₃) ₃ , C ₆ H ₆ , 1 atm H ₂	– ^b



^a formation of a very polar unidentified product was observed

^b rearrangement to the allylic alcohol was observed

^c determined by ¹H NMR spectral analysis of the crude mixture

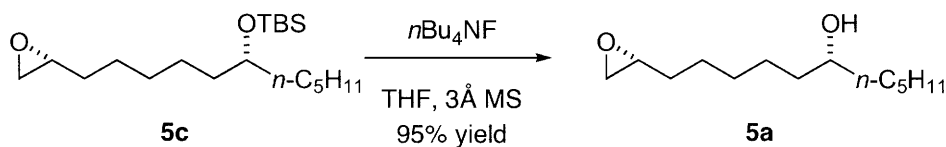
^d percent isolated yield of desired **5**

dependence on catalyst loading was observed, such that at lower catalyst loading (2.5 mol %, entry 13) a rearrangement product, rather than one of reduction, was isolated. We postulate that poisoning of the catalyst (due to impurities present in samples of **7**) might be responsible for this

result – if reduction is stemmed, the Lewis acid-catalyzed rearrangement pathway might take prevalence.¹⁹

Finally, to obtain the desired free epoxy alcohol **5a**, deprotection was necessary (Scheme 9). Initial investigations in deprotecting **5b** (R = Ac) were unpromising, as significant amounts of epoxide ring-opening were observed. Accordingly, further studies were undertaken with silyl ether **5c**. Treatment of silyl ether **5c** with TBAF in the presence of molecular sieves smoothly gave the desired epoxy alcohol **5a** in excellent yield.

Scheme 9



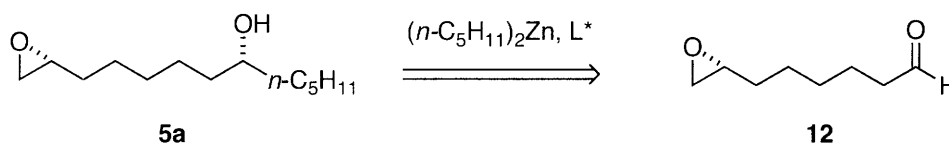
Starting from commercially available 1-heptene, the synthesis of epoxy alcohol **5a** required 7 steps (longest linear sequence). Notable aspects of the sequence were the use of Jacobsen's hydrolytic kinetic resolution to set both stereocenters, selective cross metathesis to bring the two fragments together, and successful reduction of a sensitive vinyl epoxide intermediate. Epoxy alcohol **5a** was prepared as a single enantiomer and diastereomer in 17% overall yield from 1-heptene (77% per step), with 50% overall yield being the theoretical yield because of the hydrolytic kinetic resolution.

¹⁹ Due to the sensitive nature of **7**, complete purification was difficult and required the presence of triethylamine-doped silica gel for reasonable recovery of material during flash column chromatography. It is possible triethylamine, or another impurity, present in samples of **7** were responsible for the catalyst-loading dependence of the reduction.

B. Revised Route to Epoxy Alcohol 5a

Despite the successes outlined above, we postulated that **5a** could be obtained in fewer steps and higher yield through a revision in strategy. Thus, an additional approach was investigated utilizing an asymmetric alkyl metal addition to set the alcohol stereocenter (Scheme 10). For the high level of reagent control we desired, we turned our attention to asymmetric addition of an organozinc reagent to an aldehyde.

Scheme 10. Revision of approach to epoxy alcohol **5a**



A large body of work has explored the asymmetric addition of organozinc reagents to aldehydes.²⁰ The seminal work on asymmetric addition of organozinc reagents to an aldehyde was reported by Oguni and Omi in 1984 utilizing (*S*)-leucinol.²¹ Then, in 1986, Noyori reported the first highly enantioselective organozinc addition to aromatic aldehydes, utilizing (-)-3-exo-dimethylaminoisobornenol [(-)-DAIB].²² In 1989, Yoshioka and Ohno introduced the use of *bis*-

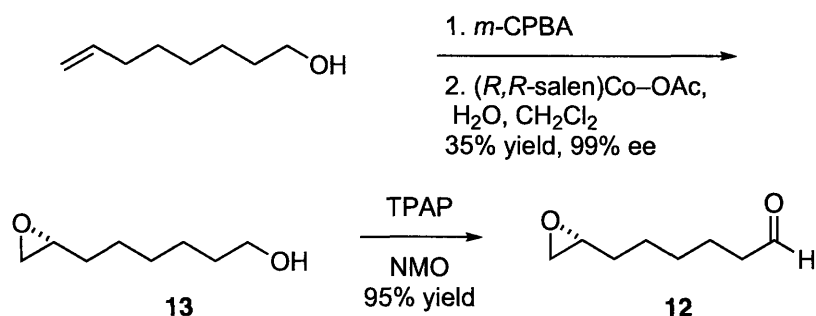
²⁰ For recent reviews on titanium's role in asymmetric organozinc addition reactions to carbonyl compounds, among other reactions, see: (a) Ramón, D. J.; Yus, M. *Chem. Rev.* **2006**, *106*, 2126–2208. (b) Walsh, P. J. *Acc. Chem. Res.* **2003**, *36*, 739–749. For a recent review on asymmetric additions of organozincs to carbonyl compounds, see: (c) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824. For a review on the preparation of functionalized organozinc reagents, see: (d) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117–2188.

²¹ (a) Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823–2824. (b) Oguni, N.; Omi, T.; Yamamoto, Y.; Nakamura, A. *Chem. Lett.* **1983**, 841–842.

²² Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071–6072.

sulfamide ligands for the highly enantioselective addition of organozinc reagents to aldehydes. Importantly, their work showed that the addition of titanium was crucial for high levels of turnover and enantioselectivity.²³ Following in the footsteps of these works, a wide variety of ligand classes have been shown to be useful in asymmetric organozinc additions to aldehydes.²¹ Indeed, this reaction has become a bar by which many new ligands are measured.

Scheme 11



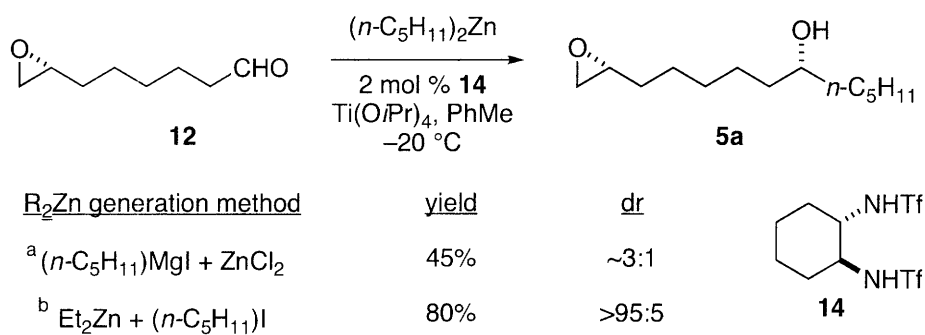
In order to test the efficacy for our proposed system, we first needed a route to aldehyde **12**. Synthesis of **12** started from commercially available 7-octen-1-ol (Scheme 11). Epoxidation with *m*-chloroperbenzoic acid (*m*-CPBA), followed by Jacobsen's hydrolytic kinetic resolution,¹⁴ gave epoxy alcohol **13** in 35% yield and excellent enantioselectivity. Oxidation using tetra-*n*-propylammonium peruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) gave the desired epoxyaldehyde **12** in high yield over the three steps.^{24, 25}

²³ (a) Yoshioka, M.; Kawakita, T.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 1657-1660. (b) Takahashi, H.; Kawakita, T.; Yoshioka, M.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 7095-7098. (c) Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S.; *Tetrahedron* **1992**, *48*, 5691. (d) Knochel, P.; Perea, J.; Almena, J.; Jones, P. *Tetrahedron* **1998**, 8275. (e) Knochel, P. *Synlett* **1995**, 393.

²⁴ Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem Commun.* **1987**, 1625.

With the requisite intermediate **12** in hand, reagent-controlled addition to the aldehyde was next investigated (Scheme 12). Utilizing Yoshioka and Ohno's *bis*-triflamide ligand **14** under standard conditions,²³ high diastereoselectivity was gratifyingly observed (>95:5 dr).²⁶ Interestingly, the method for generation of the organozinc species was important to selectivity of the addition reaction, with the presence of magnesium or zinc salts degrading the diastereoselectivity.²⁷

Scheme 12



^a organozinc generated *in situ*, and used without purification

^b organozinc generated separately, and purified by removal of EtI under reduced pressure (ref 27)

The revised sequence to epoxy alcohol **5a** represents a significant improvement over the previous cross metathesis route (*vide supra*). Starting from 7-octen-1-ol, **5a** was available in 4

²⁵ Other oxidation protocols investigated, including Swern and Dess-Martin periodinane, gave significantly lower yields, with cyclization of the aldehyde onto the epoxide decomposing the product under the reaction conditions.

²⁶ Diastereoselectivities were determined by TLC and purification, with the two diastereomers being readily separable by silica gel chromatography. The two compounds ¹H NMR spectra were indistinguishable.

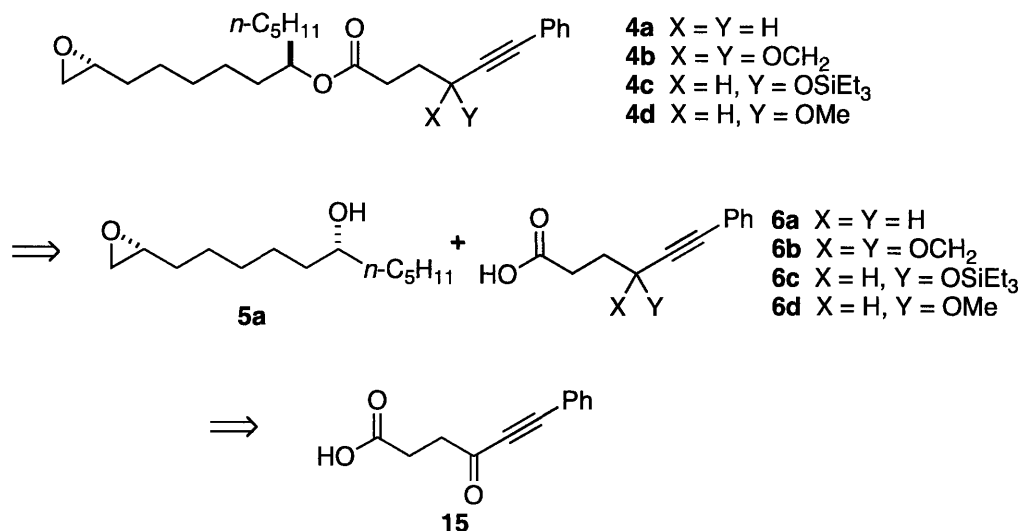
²⁷ Rozema, M. J.; Sidduri, A.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 1956–1958.

steps and 27% yield as a single diastereomer and enantiomer. This route proved highly scalable, with multi-gram quantities of **5a** being available in a single iteration.

C. Synthesis of Ynoic Acid Fragment 6 and Fragment Coupling

For the synthesis of ynoic acid fragment **6** we desired a modular route, which would provide access to multiple derivatives. The availability of various derivatives was important as the effect of substitution proximal to the alkyne was anticipated to have important effects on the key reductive cyclization. It was expected that protection of common intermediate **15** as a ketal, or reduction then alcohol protection would provide ready access to **6a-d** (Scheme 13).

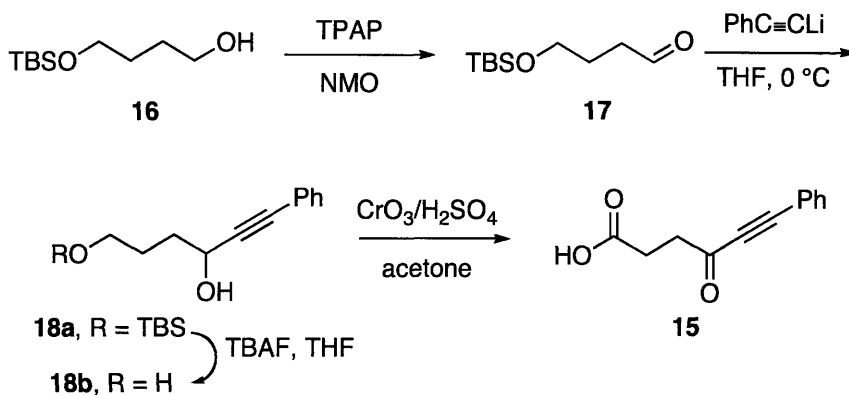
Scheme 13



The first-generation synthesis of **15** started from 4-(*t*-butyldimethylsilyloxy)-1-butanol **16** (Scheme 14). Ley oxidation²⁴ provided aldehyde **17**, which was reacted with lithiated

phenylacetylene to provide **18a**. Silyl group deprotection under standard conditions was followed by Jones oxidation²⁹ to give keto acid **15**.

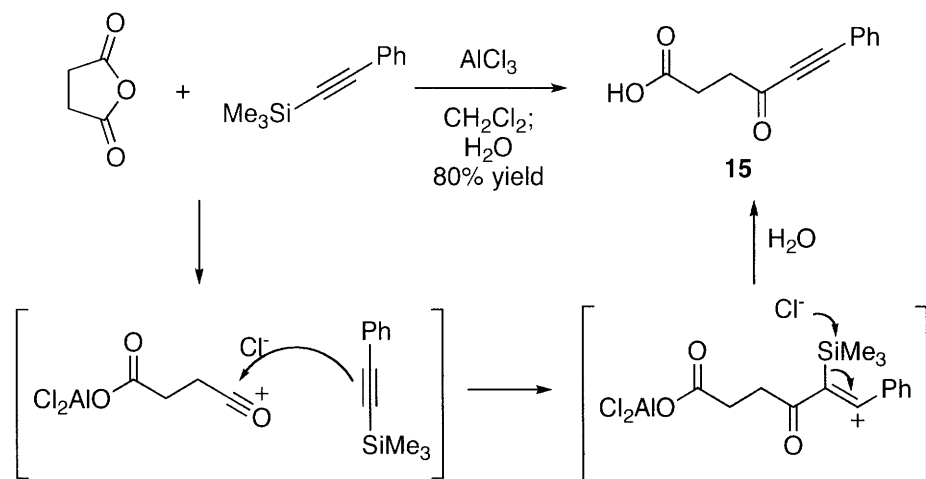
Scheme 14



During the course of these studies, it was recognized that a more convenient and concise route to **15** might be devised. Indeed, a one step protocol was developed that started from the inexpensive succinic anhydride and trimethyl(phenylethynyl)silane. Addition of aluminum trichloride effects the formation of the acylium ion derived from succinic anhydride (Scheme 15).²⁸ The alkynylsilane then acts as the nucleophile to give a β -carbocation, followed by elimination of the silyl group to give **15** in 80% yield.

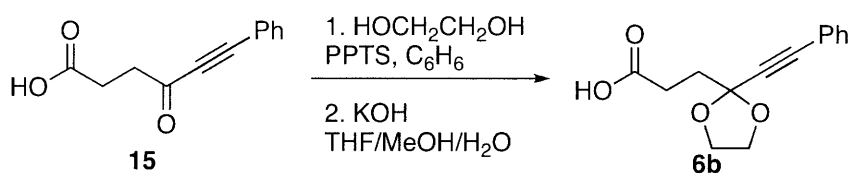
²⁸ For the use of alkynylsilanes to make α , β -unsaturated yrones, see: Birkofer, L.; Ritter, A.; Uhlenbrauck, H. *Chem. Ber.* **1963**, *96*, 3280.

Scheme 15

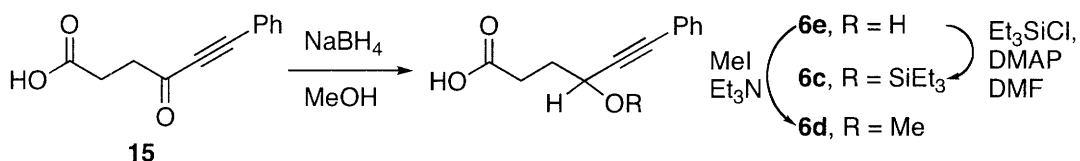


With **15** in hand, a number of derivatives were prepared. The ketone could be protected as an ethylene glycol acetal under standard conditions, followed by hydrolysis of the ester under basic work-up to provide **6b** (Scheme 16). Ynone **15** could also be reduced with sodium borohydride to provide **6e** (Scheme 17). Use of aluminum-based reductants, such as lithium aluminum hydride or diisobutylaluminum hydride, provided over-reduction or cyclization to the γ -lactone respectively. The propargyl alcohol **6e** could then be protected under standard conditions to provide triethylsilyl ether **6c** or methyl ether **6d** (Scheme 17), albeit in poor yields due to competing cyclization to the γ -lactone under the reaction conditions.

Scheme 16



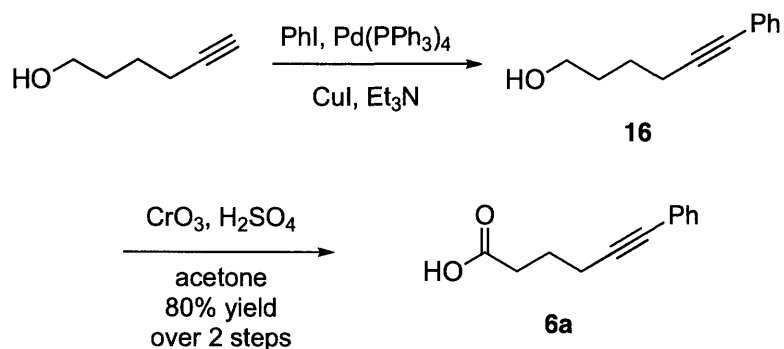
Scheme 17



Finally, we were interested in generating **6a**, which lacks propargyl substitution, as steric bulk proximal to the alkyne was expected to attenuate reactivity in the nickel-catalyzed reductive macrocyclization. Starting from 5-hexyn-1-ol, Sonogashira coupling gave **16**, which was carried onward without need for purification (Scheme 18). Jones oxidation²⁹ of **16** gave **6a** in 80% yield for the two steps.

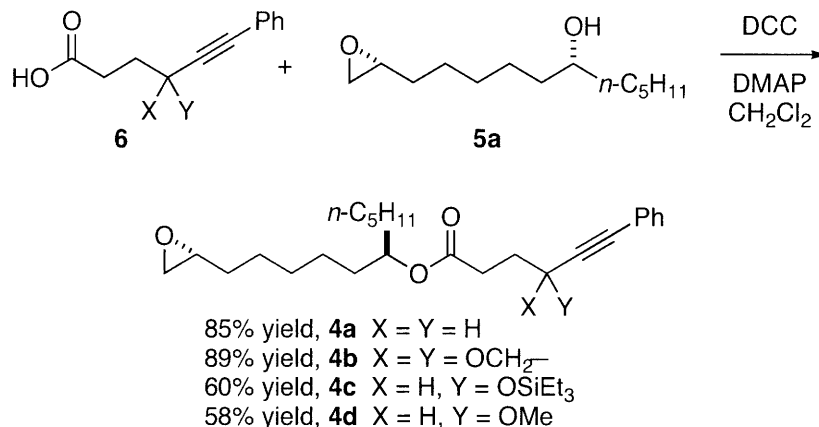
²⁹ (a) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39–45. (b) Bowers, A.; Halsall, T. G.; Jones, E. R. H.; Lemin, A. J. *J. Chem. Soc., Abstracts* **1953**, 2548–2560.

Scheme 18



With a variety of ynoic acids **6** in hand, we were able to join them with **5a** (Scheme 19). Each ynoic acid **6** was coupled with **5a** in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) to smoothly give epoxy alkynes **4** in good yield. In each case, “spot-to-spot” reactions were observed. Improved yields were obtained by purification without work-up (i.e. direct addition of silica gel to the reaction mixture, see the Experimental Section for details). In the case of **4c** and **4d**, aqueous work-ups were investigated, but decreased yields were observed.

Scheme 19



D. Reductive Cyclization Studies of Epoxy alkynes **4**

The application of nickel-catalyzed reductive cyclization of alkynes and aldehydes to the formation of macrocyclic allylic alcohols has been reported by Jamison³⁰ and Montgomery³¹. However, the application of nickel-catalyzed reduction cyclization of alkynes and *epoxides* to the formation of macrocyclic homoallylic alcohols has not. With the novelty of this approach in mind, we took a broad approach to the choice of cyclization substrates and conditions.

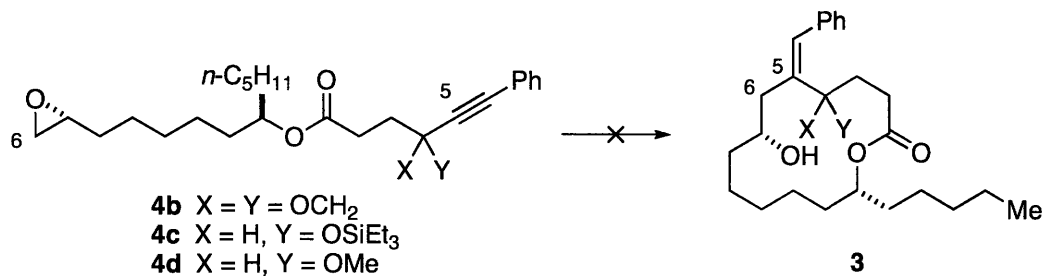
As they would allow for the key reductive cyclization to be used at a later stage in the synthesis, we were most interested in studying substrates containing a functional group handle for oxidation state manipulation at the propargylic position (e.g., cyclizations of **4b-d**, Scheme 20). Unfortunately, upon exposure of **4b-d** to a wide variety of nickel-catalyzed conditions the

³⁰ *Towards the synthesis of terpestatin*: (a) Chan, J. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 10682–10691. *In the synthesis of amphidinolide T1 and T4*: (b) Colby, E. A.; O'Brien, K. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 998–999. (c) Colby, E. A.; O'Brien, K. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2005**, *127*, 4297–4307.

³¹ Knapp-Reed, B.; Mahandru, G. M.; Montgomery, J. *J. Am. Chem. Soc.* **2005**, *127*, 13156–13157.

alkyne of **4** proved highly unreactive. Reisolated starting material or decomposition of the epoxide moiety were observed in all cases.³² This lack of desired reactivity is somewhat unsurprising, as other studies in our laboratories have shown that α -branching on the alkyne greatly attenuates its reactivity in nickel-catalyzed processes. However, the stability of alkynes **4b-d** were still noteworthy, particularly the lack of alkyne decomposition products.³³

Scheme 20

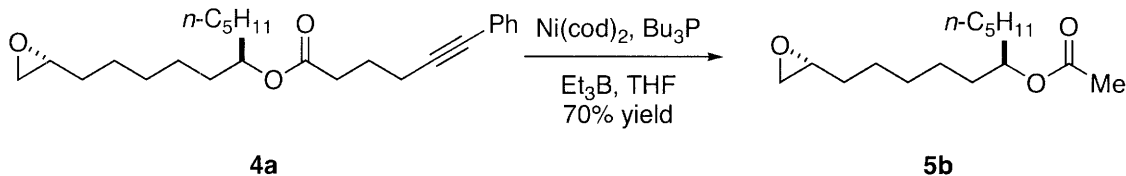


Due to the lack of alkyne reactivity of **4b-d**, we turned our attention to the less sterically encumbered **4a**, with the hope that the lack of propargylic substitution might increase its propensity to react. Upon exposure to standard reductive coupling conditions, we were surprised to isolate product **5b**, corresponding to bond cleavage of the α,β -bond of the ester of **4a** (Scheme 21).

³² These byproducts were tentatively assigned as the corresponding methyl ketone by ¹H NMR spectroscopy. This corresponds to byproducts observed in the initial studies (see ref 5a and unpublished results by Dr. Carmela Molinaro).

³³ Alkynes of similar structure studied in our lab have decomposed (cyclotrimerization and reductive dimerization) under very similar conditions. This, along with other results discussed later, suggests to us that the alkyne of **4** possesses unique attributes due to the ester functionality present.

Scheme 21



Consideration of the nature of this transformation led us to propose the following hypothesis for formation of **5b** from **4a** (Scheme 22). Triethylborane is well preceded to form ethyl radicals in the presence of trace oxygen.³⁴ An ethyl radical could abstract a hydrogen from the propargylic position of **4a**, possibly aided by nickel coordination to the alkyne, to give **17**.³⁵ The intermediate **17** could undergo radical fragmentation to give the enolate radical **18** and 1,3-enyne **19**.³⁶ Subsequent hydrogen abstraction by **18** would provide **5b** and propagate the radical process.

Considering this decomposition product, and potential pathway, we sought means to rigorously exclude oxygen from the reaction. Standard benchtop techniques were employed,

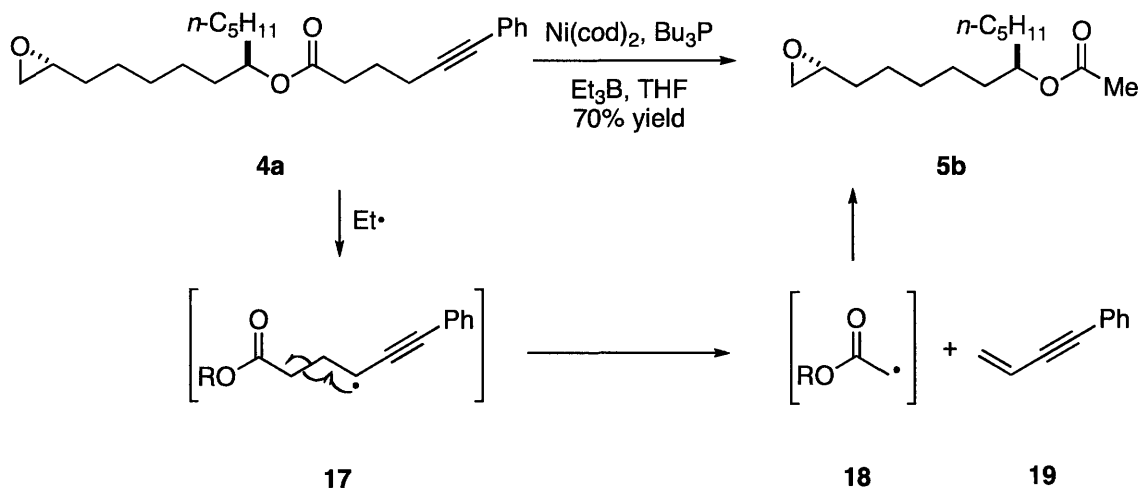
³⁴ Ichinose, Y.; Nozaki, K.; Wakamatsu, K.; Oshima, K. *Tetrahedron Lett.* **1987**, 28, 3709–3712. (b) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, 109, 2547–2549.

³⁵ Postulation of nickel assistance is supported by control studies, where exposure of **4a** to Bu_3P , Et_3B , THF and air (but no $\text{Ni}(\text{cod})_2$) led to reisolated **4a** and no formation of **5a**.

³⁶ **19** was not isolated or observed in the crude reaction mixture, however previous studies in our laboratories with **19** shows that it undergoes rapid decomposition under similar reaction conditions (unpublished results by Karen Miller).

including use of Schlenck technique and “freeze-pump-thawing” of solvents, however **5b** was still observed as the major byproduct. The use of other reductants such as Et_2Zn ³⁷ and Et_3SiH

Scheme 22



prevented formation of **5b**, but no desired product was formed and starting material was reisolated. Interestingly, the addition of radical traps to the reaction mixture, such as 2,6-di-*tert*-butyl-4-methyl phenol (BHT), suppressed formation of **5b**, but doing so was not sufficient to provide a well-behaved reaction.³⁸ After much effort and experimentation it was finally discovered that by setting the reaction up in a glove box under nitrogen atmosphere, followed by sealing the tube and running the reaction on the bench, it was possible to prevent radical

³⁷ Successful intermolecular reductive coupling of alkynes and epoxides has been observed with diethylzinc as the stoichiometric reductant (Carmela Molinaro, unpublished work), albeit in diminished efficiency relative to triethylborane.

³⁸ Desired cyclization product **3a** could be formed under conditions employing BHT and running the reaction on the benchtop, however the results were irreproducible providing highly varied outcomes from each attempt at reproduction.

decomposition of **4a**. Thus, with a means of suppressing undesired reactivity in the formation of **5b**, a screen of conditions was undertaken (Scheme 23 and Table 3).³⁹

³⁹ Initial studies in the glove box were marred by irreproducibility. Reproducible results required several additional precautions (i.e. titration of the solvent with sodium benzophenone ketyl). See the experimental section for details.

Scheme 23

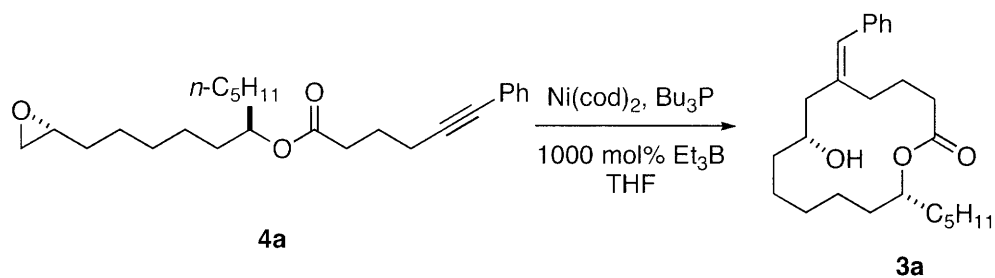


Table 3. Condition screen for the reductive cyclization of **4a**

Entry	[4a] ₀ mM	[Ni] ₀ mM	cat. loading	isolated 3a (%)	conversion of 4a (%)
1	150.0	15.0	10%	32	50
2	500.0	100.0	20%	42	85
3	250.0	50.0	20%	43	80
4	150.0	30.0	20%	46	68
5	75.0	15.0	20%	42	55
6	40.0	8.0	20%	31	34
7	20.0	4.0	20%	21	66
8	150.0	75.0	50%	47	97
9	75.0	37.5	50%	49	79
10	40.0	20.0	50%	55	66
11	20.0	10.0	50%	42	54
12	150.0	150.0	100%	60	92
13	75.0	75.0	100%	67	80
14	40.0	40.0	100%	63	70

After an initial screen of reductants, solvent, temperature, and reaction time, it was determined that the best conditions employed triethylborane (1000 mol %) as the reductant in THF at room temperature for 2 days. These standard conditions were then employed for the remainder of the studies, where catalyst loading and concentration were varied.⁴⁰ Several interesting results were observed. Surprisingly, at no point were alkyne oligomerization products observed (e.g. products resulting from alkyne-alkyne dimerization or trimerization). This is in contrast to previous study in our lab and others where, under like conditions, alkynes of similar structure undergo facile oligomerization.⁴¹ As expected,⁴² at increased concentrations increased conversion was observed, but led to increased amounts of intermolecular reductive coupling products. Continued dilution, then, required a balance with reactivity, as at lower concentrations conversion was lower (while selectivity for monomeric cyclization was improved). Thus, one could find an optimal concentration at each catalyst loading as a balance of selectivity and conversion (e.g., 0.15M⁴³ at 20 mol % Ni(cod)₂, entry 4).

To further improve the efficiency of the reaction, higher catalyst loadings were also employed. These higher catalyst loadings were found to have a reactivity profile such that lower concentrations could be employed for optimal conversion, thereby increasing selectivity for the desired product. For instance, the best conditions at 20 mol % Ni(cod)₂ were 0.15M⁴³ in THF

⁴⁰ Standard conditions involved setting the reaction up in a glove box under nitrogen atmosphere (*vide supra*), using a 2:1 ratio of phosphine to nickel (e.g., 20 mol % Ni(cod)₂ with 40 mol % Bu₃P) with 1000 mol % Et₃B in THF (various concentrations) and working up with air in the presence of BHT. See the experimental section for further details.

⁴¹ Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49–92.

⁴² The original report of alkyne epoxide reductive coupling showed that the best conditions employed neat conditions (no additional solvent added beyond the stoichiometric reductant, Et₃B).

⁴³ Refers to the starting concentration of **4a** (not catalyst concentration).

(46% yield, entry 4), while with 100 mol % Ni optimum yields were observed at 0.075M⁴³ (67% yield, entry 13).⁴³ The optimized conditions provided efficient formation of the 14-membered ring, giving comparable yields to previously reported macrocyclization approaches towards the gloeosporone scaffold.⁴⁴ These results were in contrast to the previous studies with propargyl-substituted **4b-d**, suggesting that the decrease in steric encumbrance proximal to the alkyne in **4a** relative to **4b-d** was important in increasing the reactivity of the system.

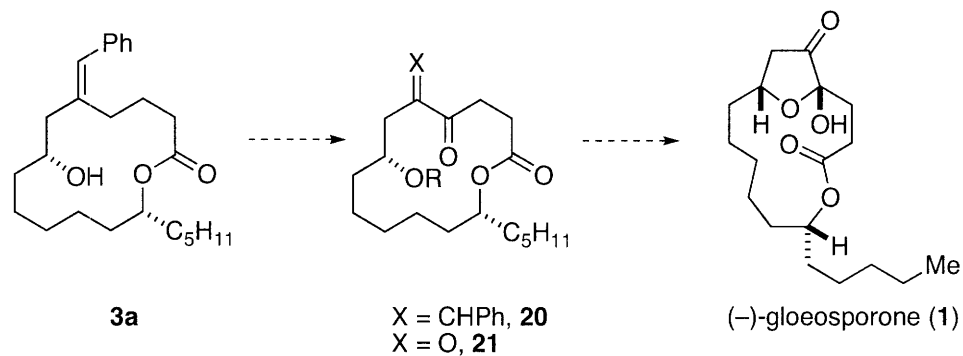
E. Final Steps Towards (–)-Gloeosporone

While pleased with the successful catalytic macrocyclization, we nevertheless were presented with some additional challenges related to our choice of cyclization substrate (**4a**). Despite having the complete carbon framework and both stereocenters installed, the product of this cyclization (**3a**) required oxidation state manipulation to provide (–)-gloeosporone (**1**) (Scheme 24). This challenge was necessitated by the lack of reactivity of **4b-d** in nickel-catalyzed reductive macrocyclization (*vide supra*). Cyclization precursors **4b-d** had functional group handles, but also additional steric bulk, in the propargylic position for oxidation state manipulation post-cyclization. However, these functional group handles were also seemingly responsible for the lack of reactivity of the alkynes of **4b-d**. Thus, to carry onward, **3a** required not only oxidative cleavage of the styrenyl olefin, but also regioselective oxidation of one allylic methylene group. Two strategies were envisioned for regioselective oxidation state manipulation

⁴⁴ Previous macrocyclizations en route to **1** using macrolactonization gave yields between 44 and 62%. Previous macrocyclizations en route to **1** using ring-closing metathesis gave yields between 79 and 99%. See reference 9 for further details.

of **3a** (Scheme 24): Allylic oxidation and α -oxidation of a ketone. Allylic oxidation was investigated first (**3a** \rightarrow **20**).

Scheme 24



Attempts at allylic oxidation of **3a** or its TBS ether or acetate-protected derivative led to no desired reactivity across a broad range of conditions. In each case, **3a** and its derivatives led to recovered starting material or unidentifiable byproducts, with one exception. Selenium dioxide (super-stoichiometric,⁴⁵ or catalytic with TBHP⁴⁶) in alcoholic solvents (ethanol or methanol) led to clean oxidation of **3a**. However, closer examination of its ¹H and ¹³C NMR spectra and due to the products stability to ozone, led us to assign this product as *epoxidation* of **3a**.⁴⁷ Other oxidants or conditions that failed to give allylic functionalization of **3a** or its

⁴⁵ Guillemonat, A. *Ann. Chim. (Paris)*, **1939**, *11*, 143.

⁴⁶ Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526–5528.

⁴⁷ This structure assignment is supported by HRMS.

alcohol-protected derivatives include Pd(OAc)₂,⁴⁸ Pd(OH)₂,⁴⁹ CrO₃, PCC,⁵⁰ CuBr₂/*t*-BuOOBz,⁵¹ Hg(OAc)₂,⁵² Rh₂cap₄/TBHP,⁵³ TEMPO,⁵⁴ BiCl₃/TBHP,⁵⁵ and allylic deprotonation/silylation.

With allylic oxidation proving difficult, attention was turned to α -oxidation of a ketone to a 1,2-diketone. Oxidative cleavage of **3a** with ozone, followed by reductive work-up, proceeded smoothly providing **22a** in 90% yield (Scheme 25). The solvent system (5:1 methylene chloride to methanol) was chosen as increased amounts of methanol (e.g., 1:1 CH₂Cl₂/MeOH) led to isolation of a second product,⁵⁶ and conditions lacking methanol led to decreased mass recovery (possibly due to incomplete reduction of the ozonide under the conditions). The use of triphenylphosphine as a reductant also led to decreased yields, due to the necessity of longer exposure of **22a** to silica gel during purification (which led to isolation of the retro-aldol product, *vide supra*) to remove the triphenylphosphine oxide and excess triphenylphosphine.

⁴⁸ Kitching, W.; Rappoport, Z.; Winstein, S.; Young, W. G. *J. Am. Chem. Soc.* **1966**, *88*, 2054–2055.

⁴⁹ (a) Yu, J.-Q.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 3232–3233. (b) Yu, J.-Q.; Corey, E. J. *Org. Lett.* **2002**, *4*, 2727–2730.

⁵⁰ (a) Parish, E. J.; Wei, T. Y. *Synth. Commun.* **1987**, *17*, 1227–1228. (b) Rathore, R.; Saxena, N.; Chadrasekaran *Synth. Commun.* **1986**, *16*, 1493–1494.

⁵¹ Rawlingon, D. J.; Sosnovsky, G. *Synthesis* **1972**, 1–28.

⁵² Rappoport, Z.; Winstein, S.; Young, W. G. *J. Am. Chem. Soc.* **1972**, *94*, 2320–2329.

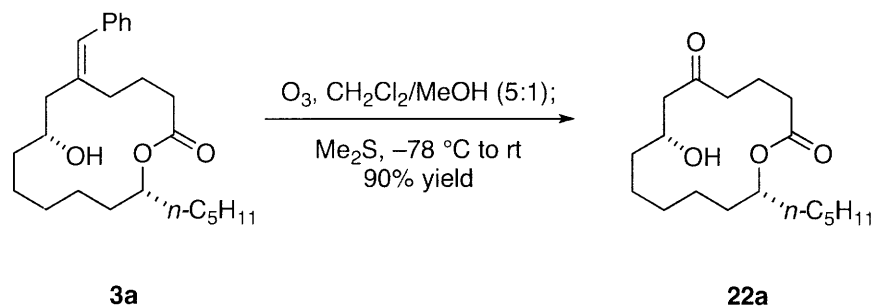
⁵³ Catino, A. J.; Forslund, R. E.; Doyle, M. P. *J. Am. Chem. Soc.* **2004**, *126*, 13622–13633.

⁵⁴ Breton, T.; Liaigre, D.; Belgsir, E. M. *Tetrahedron Lett.* **2005**, *46*, 2487–2490.

⁵⁵ Salvador, J. A. R.; Silvestre, S. M. *Tetrahedron Lett.* **2005**, *46*, 2581–2584.

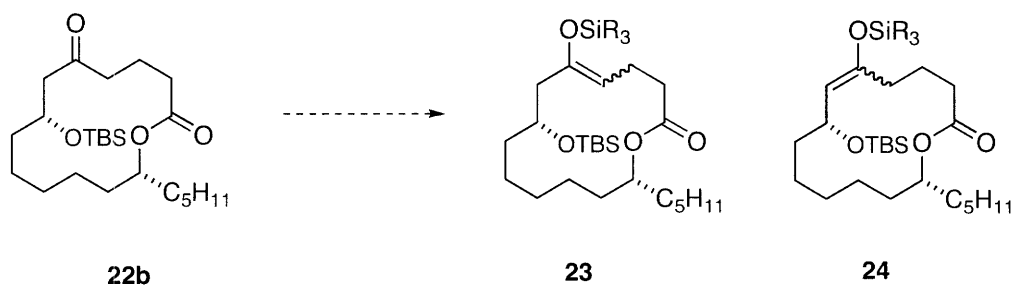
⁵⁶ Tentatively assigned as the straight-chain retro-aldol product of **22** [Me-C(=O)-CH₂-CH₂-CH₂-C(=O)-O-CH₂-CH₂-CH₂-CH₂-CH₂-CHO] based on ¹H NMR spectroscopy and HRMS.

Scheme 25



After a number of conditions proved unsuccessful in providing direct α -oxidation of **22** or its alcohol-protected derivatives, a two step protocol was investigated: silyl enol ether formation, followed by oxidation (i.e. Rubottom-type oxidations). As regioselectivity could be problematic, initial investigations were performed with TBS-protected derivative **22b**. The bulky TBS group was hoped to block deprotonation of one methylene unit, potentially through steric effects or through conformational bias. Thus **22b** was exposed to a number of bases and silicon sources in order to test the feasibility of this approach (Scheme 26).

Scheme 26



Unfortunately, exposure of **22b** to a wide variety of conditions, including either enolate formation (with LDA or LHMDS) followed by silyl chloride trapping or soft enolization with silyl triflate (Me_3SiOTf or TBSOTf) and amine bases (Et_3N , 2,6-lutidine), gave only recovered starting material. Considering that the presence of the bulky TBS group might be attenuating the reactivity of **22b** overmuch, other approaches to **23** were explored.

Scheme 27

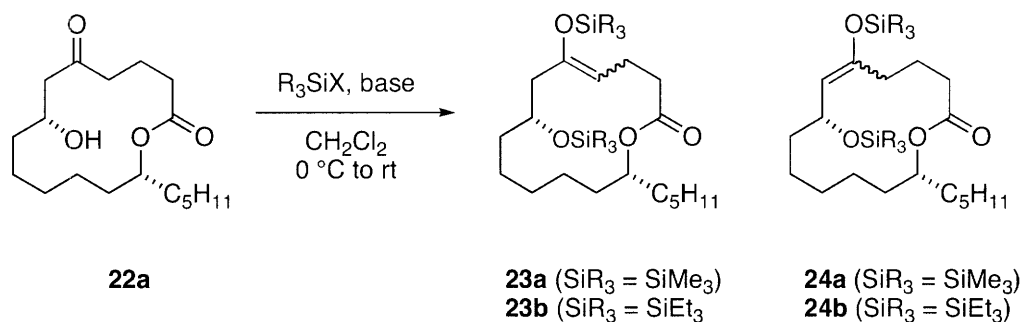


Table 4. Condition screen for silyl enol ether formation

Entry	R_3SiX	base	23:24	yield 23
1	TBSOTf	2,6-lutidine	–	– ^a
2	Et_3SiOTf	2,6-lutidine	–	– ^a
3	Me_3SiOTf	2,6-lutidine	–	– ^a
4	Me_3SiOTf	Et_3N	>95:5	>95% (23a , NMR) ^b
5	Et_3SiOTf	Et_3N	>95:5	90% (23b , isolated) ^c

^a **22** was reisolated as the corresponding alcohol-protected silyl ether.

^b Due to the lability of the trimethylsilyl enol ether, product ratios and yield were assigned by crude 1H NMR.

^c Complete purification was not possible, as the triethylsilyl enol ether slowly degrades on exposure to silica gel. Product ratios were determined by crude 1H NMR

Starting from unprotected β -hydroxyketone **22a**, several silyl triflate and amine base combinations were tested (Scheme 27 and Table 4). As anticipated from the previous studies,

the bulky TBSOTf failed to react with the ketone, providing instead only alcohol protection (entry 1). With 2,6-lutidine as the base, neither Et₃SiOTf nor Me₃SiOTf gave any desired reaction (entries 2 and 3). Switching to a more basic amine (Et₃N) allowed silyl enol ether formation with both Et₃SiOTf and Me₃SiOTf (entries 4 and 5) providing, surprisingly, a single regioisomer of the desired **23**.⁵⁷ Trimethylsilyl enol ether **23a** proved too sensitive to chromatograph, so further studies were conducted with **23b** (triethylsilyl derivative). Thus, **23b** could be obtained as a single regioisomer in 90% isolated yield and as a single regioisomer (entry 5).

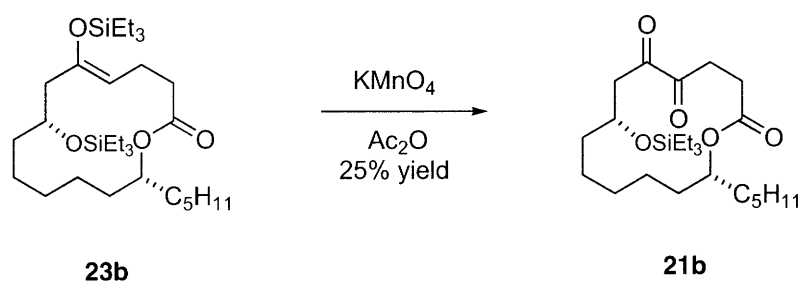
In considering the origin of the high regioselectivity observed in the silyl enol ether formation, several explanations are possible. Steric bulk from the nearby silyl ether could be disfavoring deprotonation of the undesired α -proton. It is also possible that stereoelectronic effects could be at play. Conformational bias from the nearby stereocenter, or possibly from the transannular pentyl group, could place one proton more appropriately aligned for deprotonation (i.e. orthogonal to the carbonyl). In an effort to better understand the origin of this regioselectivity, computational studies at various calculation levels were undertaken of the ground state energy conformation of **22c** (SiEt₃ ether, *vide infra*) with the aid of Jean Bouffard.⁵⁸ These calculations, while inconclusive, suggested stereoelectronic effects were most likely responsible for the high regioselectivity observed.

⁵⁷ Regioselectivities were determined by crude ¹H NMR spectra analysis.

⁵⁸ Calculations were performed at several levels (molecular mechanics, semi-empirical – pm3 and am1 – and with density functional theory calculations – STO-3G* and 3-21G*), providing low energy conformations for **22c** at its *ground state*. These calculations, particularly the semi-empirical and DFT sets, suggested stereoelectronic factors were most important in effecting regioselectivity of silyl enol ether formation. However, the ground state conformation does not necessarily suggest the relative energies of the *reactive* conformations, and thus must be treated only as a cursory explanation of the outcome.

With a regioselective means of α -functionalization of **22**, our efforts turned to oxidation of silyl enol ether **23**. Attempts at Rubottom oxidation of **23a** or **23b** were complicated by the lability of the silyl group. Cleavage (of the silyl enol ether) occurred upon treatment with *m*-CPBA. Alternatively, treatment with DMDO gave an oxidation product with concomitant silyl group migration and deprotection. These complications led to investigation of a one step oxidation to the desired oxidation state.

Scheme 28



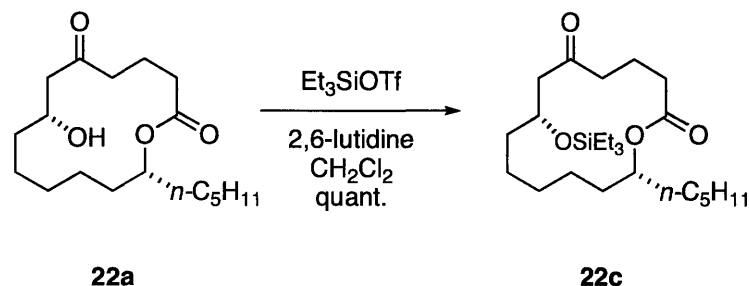
After some experimentation, it was found that potassium permanganate in acetic anhydride provided the desired 1,2-diketone **21b** in moderate yield, with the remainder of the material isolated as a mixture of apparent α -acetoxy ketones (Scheme 28). These conditions were originally reported by Sharpless for the oxidation of 1,2-dialkylsubstituted olefins to 1,2-diketones,⁵⁹ however they proved amenable to silyl enol ether oxidation as well (albeit in low yields). Use of this procedure allowed us to isolate, for the first time, the direct precursor to (-)-gloeosporone, with **21b** possessing all the attributes of the natural product and requiring only silyl group deprotection.

⁵⁹ Sharpless, K. B.; Lauer, R. F.; Repic, O.; Teranishi, A. Y.; Williams, D. R. *J. Am. Chem. Soc.* **1971**, *93*, 3303–3304.

F. Revised Approach to Diketone 21b

In spite of our excitement, we felt the moderate yields obtained by the silyl enol ether oxidation were unsatisfactory and merited further optimization. It was reasoned that other processes with silyl ether **22c** might display similarly high levels of regioselectivity as the silyl enol ether formation described above. Therefore, additional approaches to the 1,2-diketone **21b** were explored, starting from silyl ether **22c**.

Scheme 29



Treatment of **22a** with Et₃SiOTf in presence of 2,6-lutidine provided monosilylated **22c** in excellent yield (Scheme 29). Silyl enol ether **23b** was the major product when Et₃N was the base (Scheme 27 and Table 4). In the 1960s, Bredereck, *et al.*, reported the use of aminal ester **25** (Scheme 30, commonly known as Bredereck's reagent) as an aminomethylenating reagent for CH₂-acidic compounds.⁶⁰ Subsequent to Bredereck's report, Wasserman reported transformation

⁶⁰ (a) Bredereck, H.; Effenberger, F.; Botsch, H. J. *Chem. Ber.* **1964**, *97*, 3397. (b) Bredereck, H.; Simchen, G.; Rebsdats, S.; Kantlehner, W.; Horn, P.; Wahl, R.; Hoffmann, H.; Grieshaber, P. *Chem. Ber.* **1968**, *101*, 41.

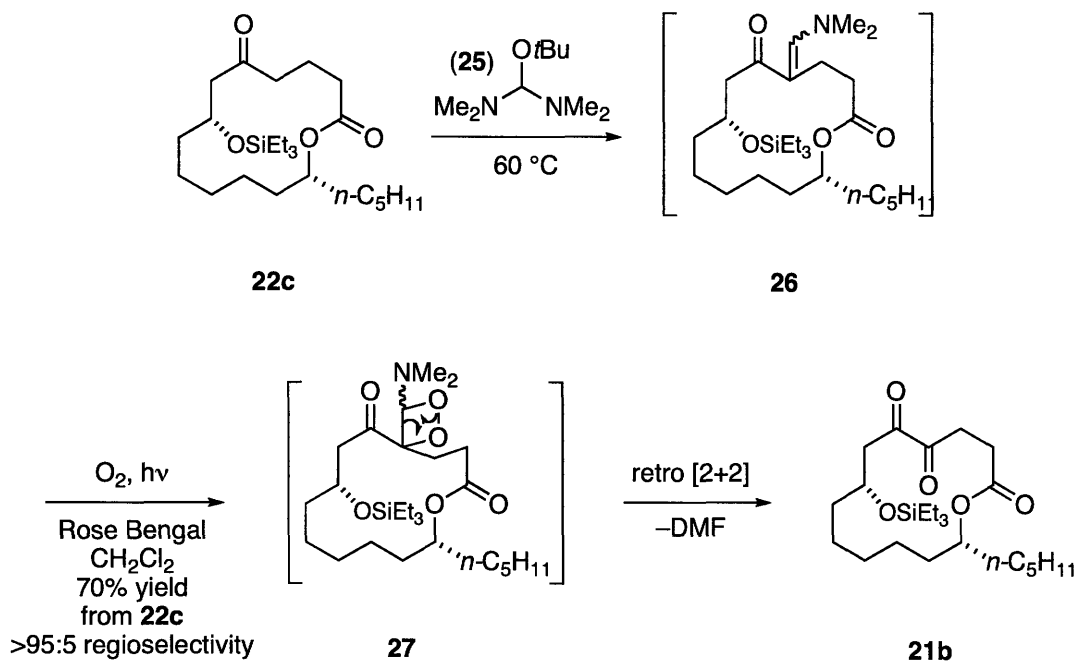
of enaminoketones to 1,2-diketones by treatment with singlet oxygen.⁶¹ Intrigued by the possibility of transforming **22c** directly to the desired oxidation state in one pot, we investigated use of these protocols.

Upon heating neat with **25**, we were extremely pleased to find that **22c** retained the sense and degree of regioselectivity enjoyed in the silyl enol ether formation (>95:5 regioselectivity, Scheme 30) to provide **26** as interpreted by crude ¹H NMR analysis. Direct treatment of crude **26** in the same pot with singlet oxygen in dichloromethane provided **21b** as the only detectable product. The oxidation presumably goes through the intermediacy of dioxetane **27** by formal [2+2] cycloaddition with singlet oxygen, followed by retro [2+2], as proposed by Wasserman.⁶¹ Use of this protocol allowed access to **21b** in 70% yield as a single regioisomer.⁶²

⁶¹ (a) Wasserman, H. H.; Terao, S. *Tetrahedron Lett.* **1975**, *21*, 1735–1738. (b) Wasserman, H. H.; Ives, J. L. *J. Am. Chem. Soc.* **1976**, *98*, 7868–7869. (c) Wasserman, H. H.; Ives, J. L. *J. Org. Chem.* **1985**, *50*, 3573–3580.

⁶² The remainder of the mass is attributed to decomposition of **21b** with water as careful avoidance of moisture was important to reproducible yields and NMR yields were close to quantitative.

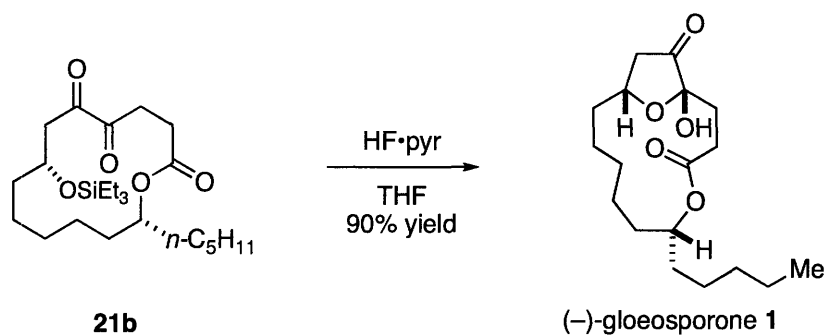
Scheme 30



Having facile access to **21b**, we were poised for the ultimate deprotection/cyclization to provide the hemiketal natural product **1**. Gratifyingly, treatment of **21b** with HF·pyr in THF protidesilylated the triethylsilyl ether, followed by cyclization of the incipient alcohol, to give (–)-gloeosporone **1** in 90% yield (Scheme 31). Our samples of synthetic (–)-**1** matched in all manners with previous reports of synthetic **1** by ^1H and ^{13}C NMR spectroscopy, as well as high resolution mass spectrometry, optical rotation, and infrared spectroscopy (figure 2).^{9, 63}

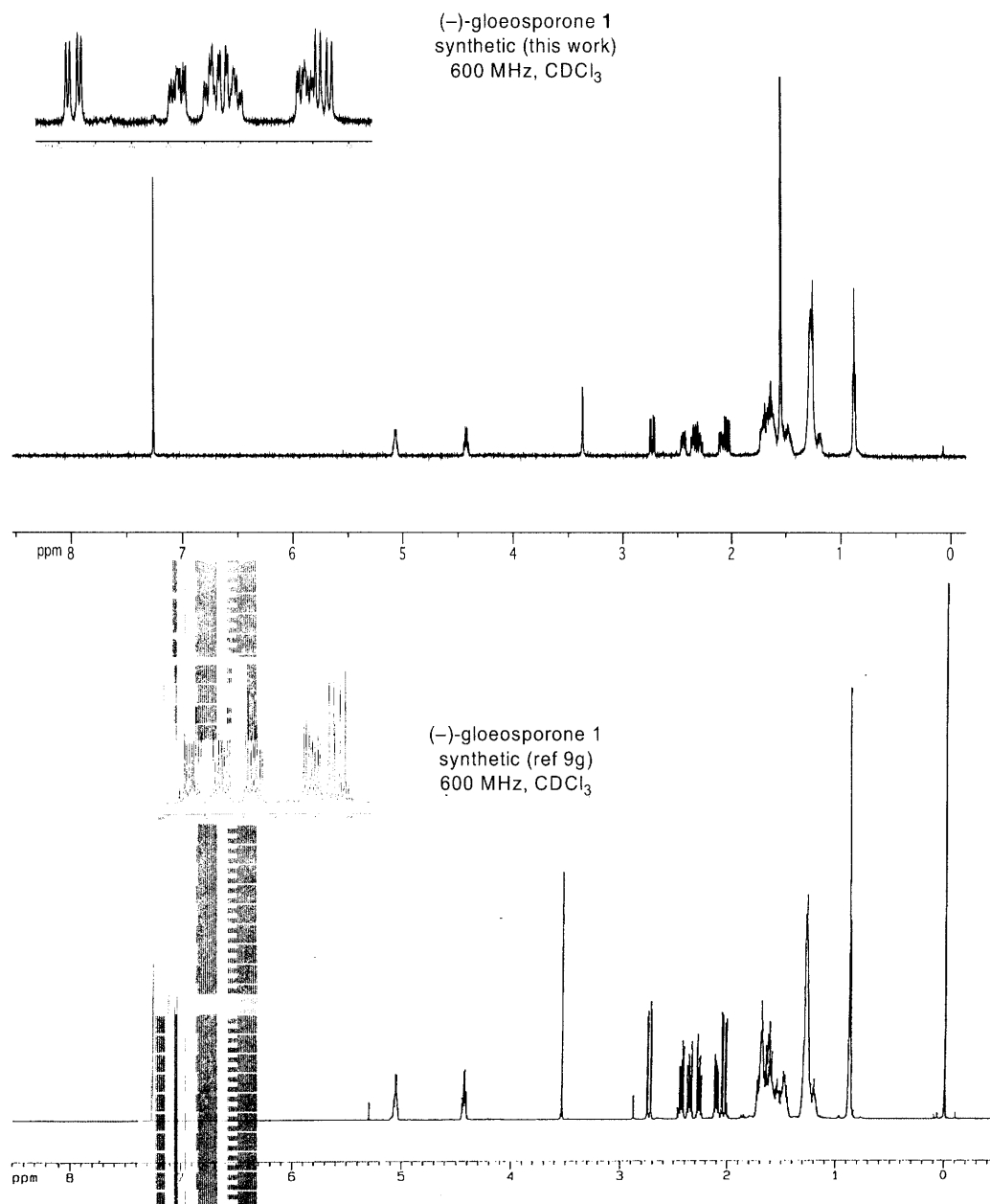
⁶³ The slight discrepancy of the spectral regions of δ 2.0 – 2.5 are attributed to concentration effects (hydrogen bonding).

Scheme 31



Overall, the synthesis of **1** starting from commercially available 7-octen-1-ol required 10 steps (LLS, 12 total operations) and 5.9% overall yield. This yield is calculated using results with 20 mol % Ni(cod)₂ in the reductive macrocyclization. The overall yield is 8.6% overall yield when 100 mol % Ni(cod)₂ is employed in the reductive macrocyclization. Noteworthy aspects of this synthesis are the nickel-catalyzed reductive macrocyclization to provide the 14-membered homoallylic alcohol **3a**, which allows ready access to the 1,2-dicarbonyl moiety found in the natural product through a 4-step sequence involving oxidative cleavage of the double bond, followed by condensation to the enaminoketone and oxidation with singlet oxygen.

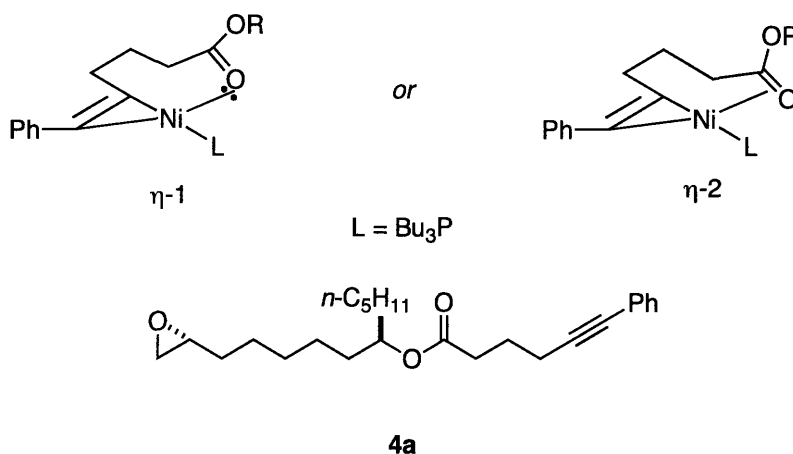
Figure 2. Comparison of reported (ref 9g) and synthetic (this work) (-)-gloeosporone **1**



G. Scope of Nickel-Catalyzed Reductive Macrocyclization Studies

Having completed the total synthesis of (-)-gloeosporone (**1**) via a reductive nickel-catalyzed 14-membered-ring macrocyclization, we sought to better understand the generality of this transformation. As during our reductive macrocyclization studies with **4a**, the alkyne moiety had behaved quite differently than anticipated (radical cleavage, less reactive than anticipated, *vide supra*), we suspected that **4a** might possess unique structural attributes which contributed to these observations. We postulated that perhaps the ester could be playing a key role in the cyclization, potentially by chelation with a nickel-alkyne complex – a role that other remote functionality had played in similar transformations in our laboratories.⁶⁴

Figure 3. Postulated modes of chelation between nickel, alkyne, and ester of **4a**



⁶⁴ Tethered alkenes at the same distance from the alkyne as in **4a** (i.e. 1,6-enynes) have been shown to act as ligands to nickel, changing the course of the reaction. See: (a) Miller, K. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 15342–15343. (b) Moslin, R. M.; Jamison, T. F. *Org. Lett.* **2006**, *8*, 455–458. (c) Moslin, R. M.; Miller, K. M.; Jamison, T. F. *Tetrahedron* **2006**, *62*, 7598–7610.

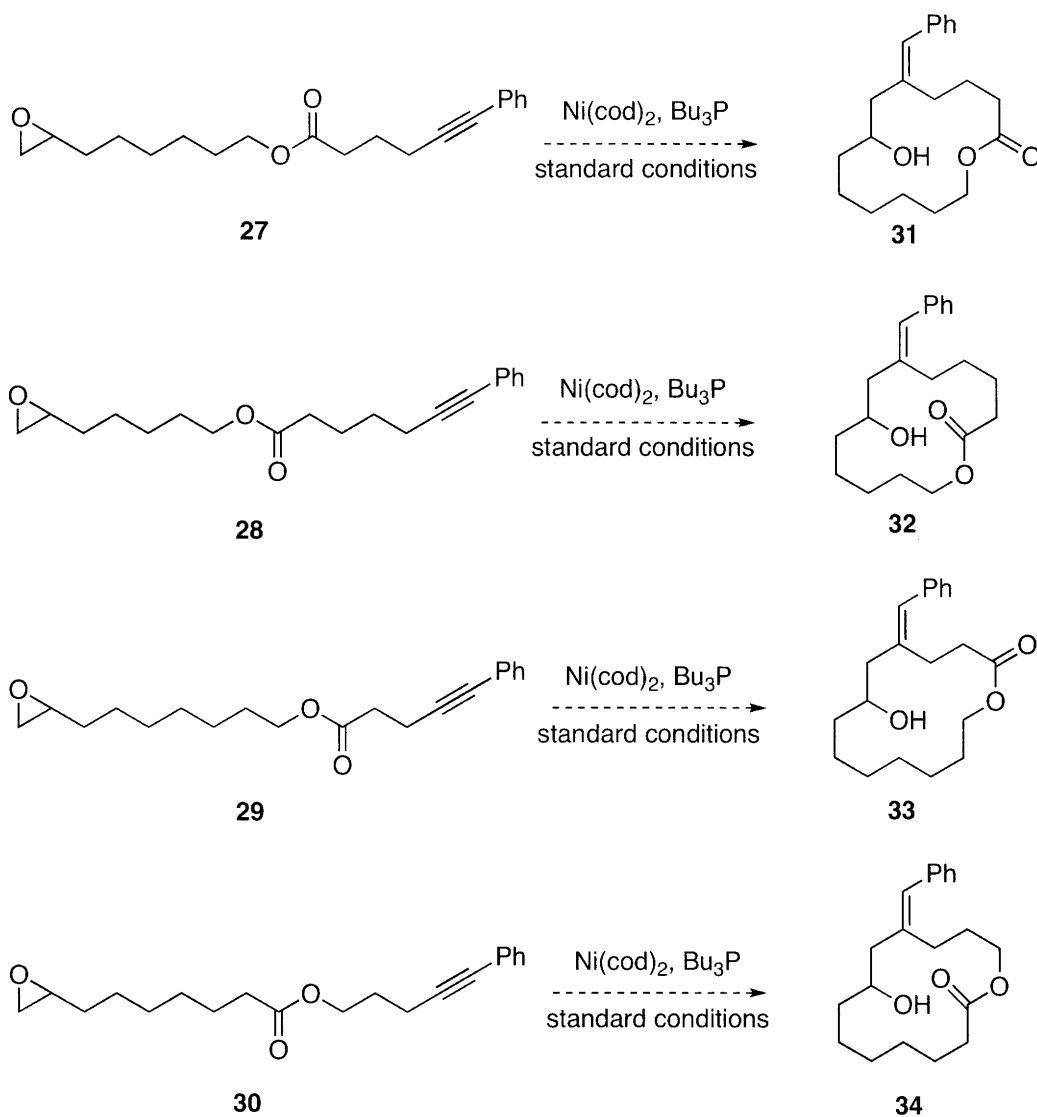
In our nickel-catalyzed reductive macrocyclization studies of **4a** we had observed no oligomerization of the alkyne. Due to this observation, we postulate that the ester's role in these cyclizations might be one of alkyne "protection" through chelation, whereby chelation of the ester prevents undesired dimerization or oligomerization of the alkyne – processes that would require two alkynes to ligate to nickel simultaneously.⁴¹ Ester complexes of nickel are known via lone-pair interactions from either oxygen, and most typically from the carbonyl oxygen,⁶⁵ but to the best of our knowledge have not been reported as π -complexes with nickel. However, other remote π -systems at the same tether length had affected the course of nickel-catalyzed reductive coupling reactions of alkynes and aldehydes.⁶⁴ We therefore considered two modes of chelation of the ester and alkyne of **4a** with nickel (Figure 3). We assume a d^8 , approximately square planar Ni^0 center, with the ester acting as a two electron donor either through an η -1 interaction with the oxygen lone pair or through an η -2 interaction with the carbonyl π -bond to make a seven or six-membered ring chelate respectively. In both cases, L is assumed to be Bu_3P , but is omitted for clarity. Considering these possibilities, we set out to test a number of ester positions on the ring to evaluate the structural features necessary for cyclization. To limit the changes in the system, we chose substrates whose macrocyclization products would each be 14-membered macrolactones.

As a preliminary means of testing the effect of the ester on the cyclization, we conducted the cyclizations of four similar substrates **27**, **28**, **29**, and **30** (Scheme 32). These substrates

⁶⁵ For examples of ester's acting as ligands to nickel, see: (a) Tang, X.; Sun, W.-H.; Gao, T.; Hou, J.; Chen, J.; Chen, W. *J. Organomet. Chem.* **2005**, 1570–1580. (b) William, S. B.; Leatherman, M. D.; White, P. S.; Brookhart, M. *J. Am. Chem. Soc.* **2005**, 127, 5132–5146. (c) Guicher, N.; Stoeckli-Evans, H.; Bernauer, K. *Chimia* **2003**, 57, 581–585. (d) Giorgi, G.; Savini, L.; Chiasserini, L.; Necini, C.; Pellerano, C. *Polyhedron* **1998**, 17, 3851–3858. (e) Ecke, A.; Keim, W.; Bonnet, M. C.; Tkatchenko, I.; Dahan, F. *Organometallics* **1995**, 14, 5302–5307. (f) Van de Kuil, L. A.; Veldhuizen, Y. S. J.; Grove, D. M.; Zwikker, J. W.; Jenneskens, L. W.; Drenth, W.; Smeets, W. J. J.; Spek, A. L.; Van Koten, G. *J. Organomet. Chem.* **1995**, 191–197. (g) Bianchini, C.; Innocenti, P.; Masi, D.; Meli, A.; Sabat, M. *Organometallics* **1986**, 5, 72–78.

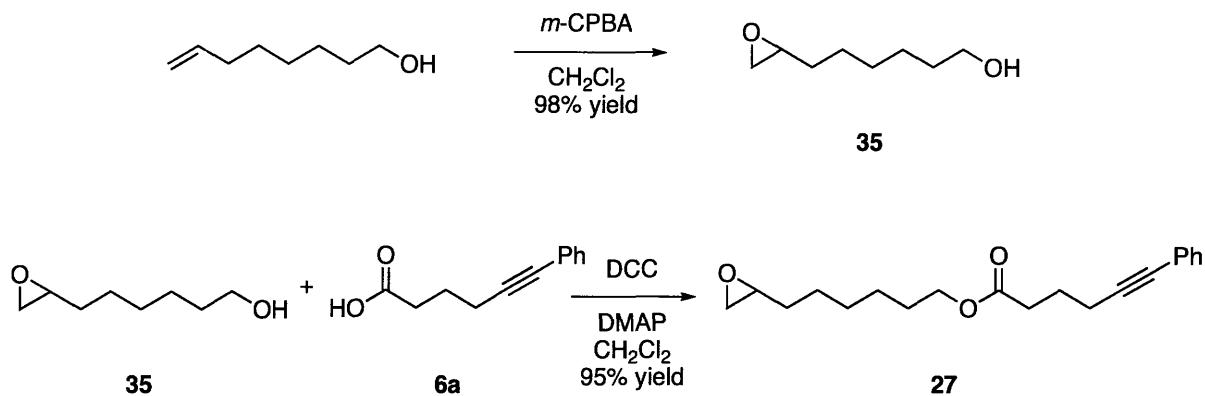
differ from each other in the position of the ester and differ from **4a** (which leads to (-)-gloeosporone **1**) as they lack an amyl side chain. All would afford 14-membered rings upon macrocyclization (as does **4a**, *vide supra*). Epoxy alkyne **27** was prepared as a control, to confirm that the amyl group is not significantly influencing the cyclization. Therefore, if ester ligation is important, **27** was expected to cyclize in a similar manner and efficiency as **4a**. Epoxy alkynes **28** and **29** lengthen and shorten, respectively, the ester tether to the alkyne by one methylene unit, which was anticipated to have an effect on any hypothetical chelation to the metal. Finally, **30** has the ester's oxygen-carbonyl order reversed, which might provide further insight into the binding mode of the ester with nickel. Any and all of these conclusions will, of course, be complicated by conformational changes effected by the movement of the ester. Nevertheless, we hoped they would provide us with some valuable insight into these cyclizations.

Scheme 32



The synthesis of **27** started with commercially available 7-octen-1-ol. Epoxidation with *m*-CPBA gave **35** (Scheme 33). The epoxy alcohol **35** was dehydratively coupled with **6a** in the presence of dicyclohexyl carbodiimide (DCC) to give **27** in excellent yield over 2 steps.

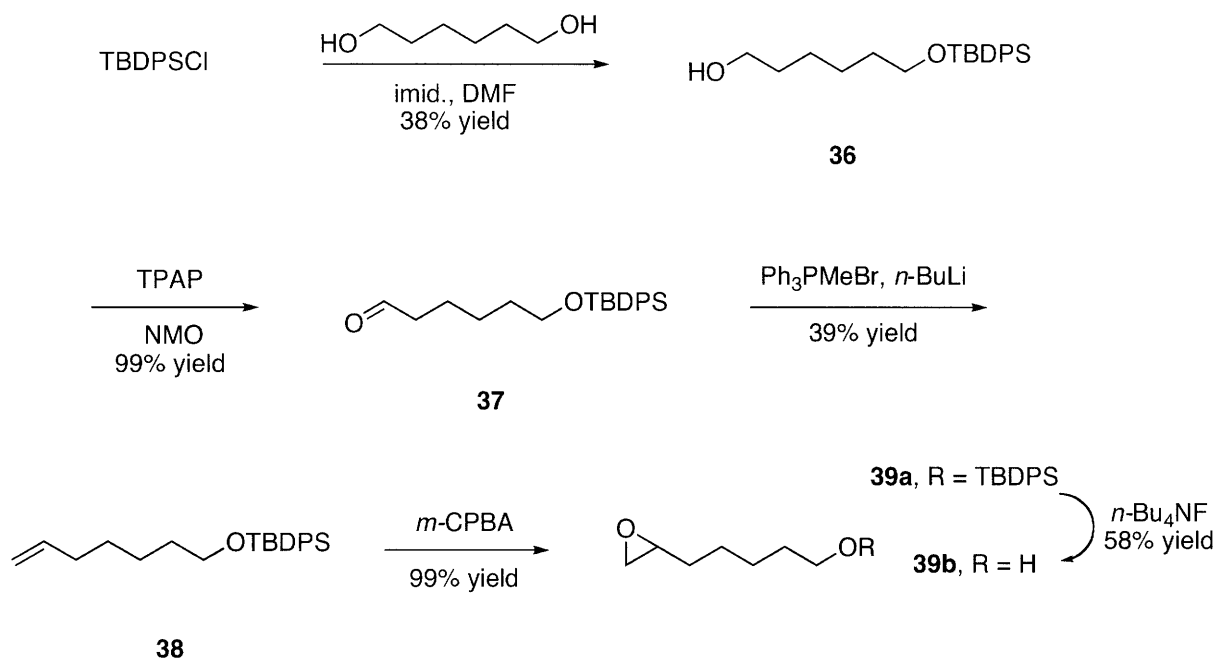
Scheme 33



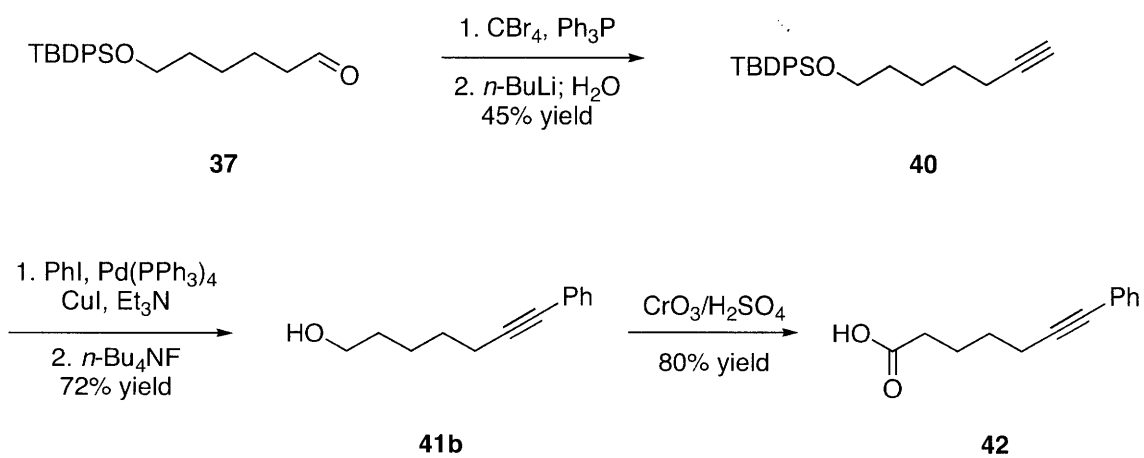
The synthesis of **28** required seven steps (LLS). Starting from *tert*-butyldiphenylsilyl chloride (TBDPSCl) and 1,6-hexane diol, monosilylation gave **36** in moderate yield (Scheme 34). The primary alcohol was subsequently oxidized to **37** in excellent yield using Ley's conditions.²⁴ One step epoxidation protocols (e.g., Corey's sulfur ylide chemistry)⁶⁶ failed to provide **39a**, instead giving polar byproducts (presumably via aldol condensation of **37**). Instead, a two step protocol via methylenation and epoxidation with *m*-CPBA provided **39a** in moderate yield. Silyl ether deprotection with tetrabutylammonium fluoride gave epoxy alcohol **39b** in a straightforward fashion.

⁶⁶ Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353–1364.

Scheme 34

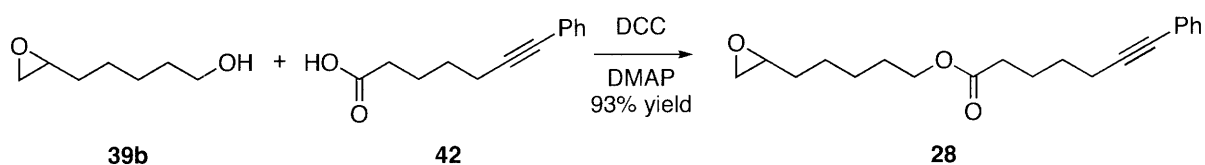


Scheme 35



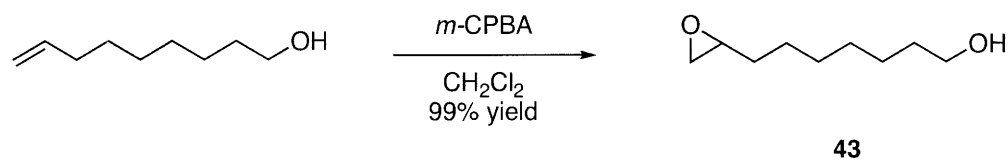
The ynoic acid fragment of **28** started from aldehyde **37**, which was subjected to the Corey-Fuchs protocol to give **40** in moderate yield (Scheme 35).⁶⁷ Arylation of the alkyne via Sonogashira coupling, followed by protidesilylation of the crude silyl ether gave **41b** in 71% yield over 2 steps. Jones oxidation of **41b** then provided **42** in good yield.²⁹ The ynoic acid and **39b** were next coupled in the presence of DCC to give **28** in excellent yield (Scheme 36).

Scheme 36

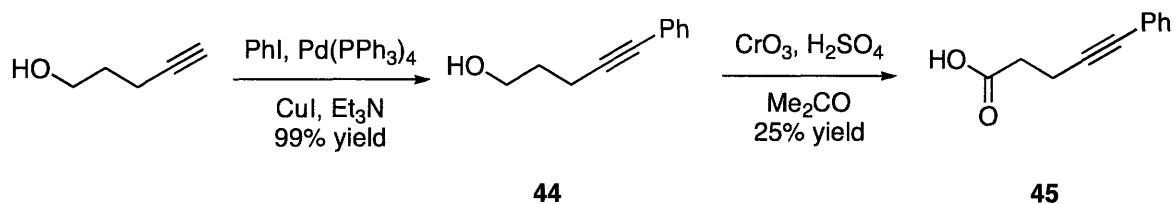
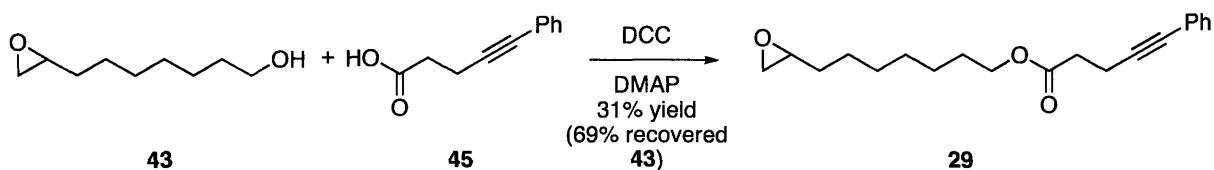


The synthesis of **29** started from 8-nonen-1-ol and 4-pentyn-1-ol (Schemes 37 and 38). Epoxidation of 8-nonen-1-ol with *m*-CPBA gave **43** in excellent yield (Scheme 37). Arylation of 4-pentyn-1-ol, followed by Jones oxidation²⁹ gave **45** in low yield (Scheme 38). The epoxy alcohol **43** and **45** were then dehydratively coupled in the presence of DCC to give **29**, albeit with low conversion (Scheme 39).

Scheme 37

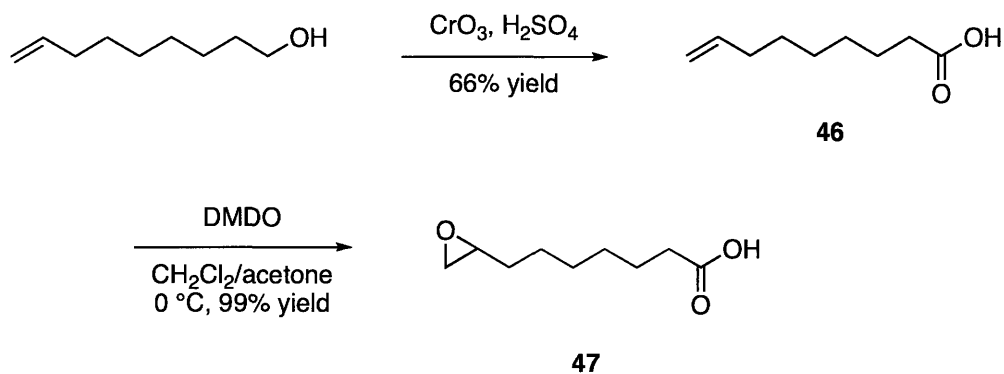


⁶⁷ Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769–3772.

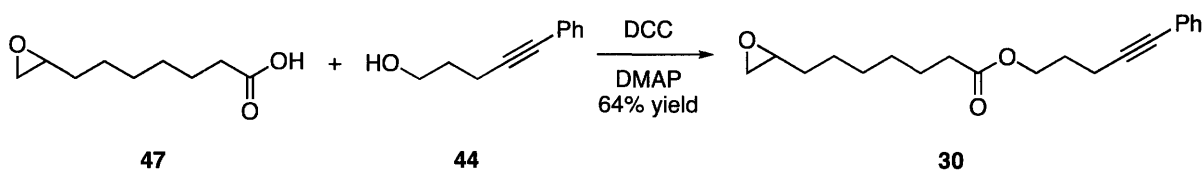
Scheme 38**Scheme 39**

The synthesis of **30** started from 8-nonen-1-ol (Scheme 40). Jones oxidation²⁹ to acid **46** followed by epoxidation with dimethyldioxirane (DMDO, freshly prepared) gave **47** in 66% yield over two steps. Dehydrative coupling of **47** and **44** in the presence of DCC gave **30** in 64% yield (Scheme 41).

Scheme 40



Scheme 41



With epoxy alkynes **27**, **28**, **29**, and **30** in hand we investigated the nickel-catalyzed reductive cyclizations of these compounds. We selected the optimized conditions from cyclization studies of related compound **4a** (*vide supra*), testing both 20 mol % and 100 mol % $\text{Ni}(\text{cod})_2$ catalyst loading conditions (Scheme 32 and Table 5).

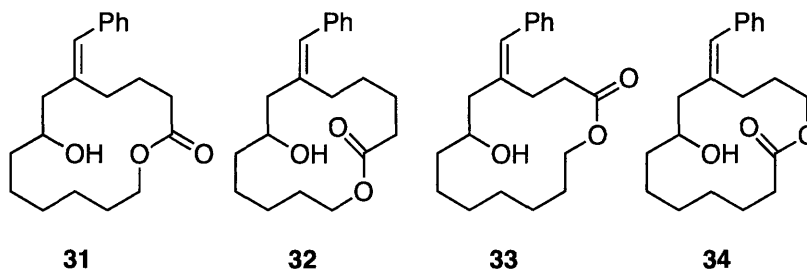
Table 5. Reductive macrocyclization screen of **27**, **28**, **29**, and **30** under standard conditions⁶⁸

substrate	conditions	yield (product)
27	A	40 (31)
27	B	50 (31)
28	A	5% (32)
28	B	18% (32)
29	A	< 5% (33)
29	B	< 5% (33)
30	A	< 5% (34)
30	B	< 5% (34)

conditions:

A: 20mol% Ni(cod)₂, 40mol% Bu₃P
1000mol% Et₃B, 0.15M THF

B: 100mol% Ni(cod)₂, 200mol% Bu₃P
1000mol% Et₃B, 0.075M THF

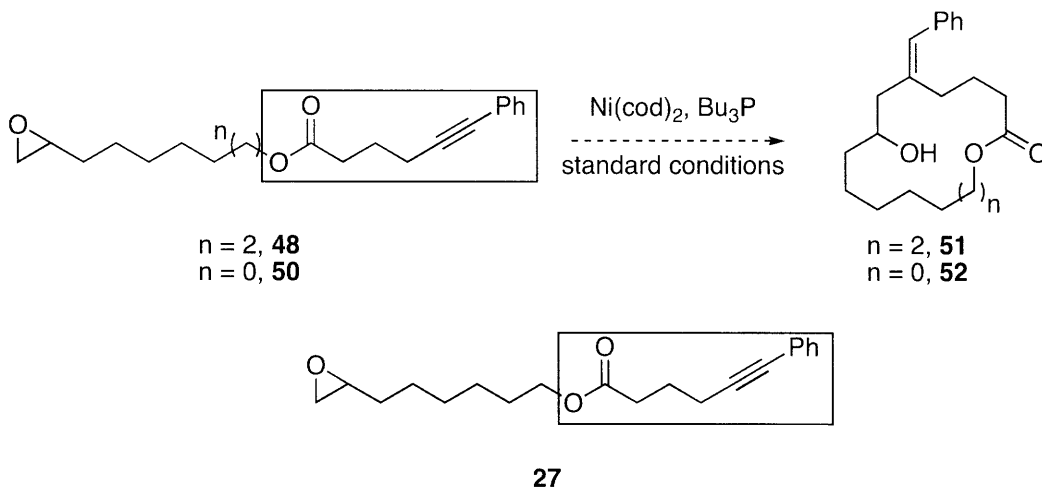


⁶⁸ Standard conditions developed during studies on the nickel-catalyzed reductive macrocyclization of **4a** (see Table 3).

Several interesting trends were observed during this study. As originally postulated, **27** was the most competent in macrocyclization, with only a slight decrease in efficiency seen relative to cyclizations with **4a** (40% yield with **27** versus 46% yield with **4a** under the same conditions). The other substrates, however, failed to cyclize competently, with only **28** providing appreciable amounts of the 14-membered ring. The lack of cyclization of **29** is significant, which may suggest that the tether is too short to accommodate the necessary chelation. Similarly, epoxy alkyne **30** failed to provide the 14-membered ring, which when compared to **28** implies that both the orientation and position of the ester is important. While conformational effects may be playing a role in these differences, the singular efficacy of **27** suggests that the ester may be important as a ligand to nickel during the course of the reaction.

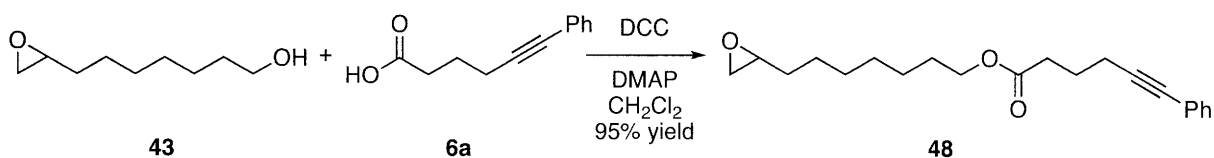
With the nickel-catalyzed reductive macrocyclization studies of epoxy alkynes **27-30**, we were able to recognize that only the substrate possessing a δ,ϵ -unsaturated ynoate (**27**) was able to cyclize competently. With this information, two additional macrocyclizations were investigated, with the alkynylester moiety of **27** kept constant, but the epoxide tether lengthened and shortened by one methylene unit. In this manner, we hoped to test if presence of a δ,ϵ -unsaturated ynoate might be sufficient to promote macrocyclizations of epoxy alkynes to form a variety of large ring sizes (Figure 4).

Figure 4. Nickel-catalyzed reductive macrocyclizations of epoxides and δ,γ -ynoates



Synthesis of the substrate containing one additional methylene (**48**) was straightforward (Scheme 42). Epoxy alkyne **43**, previously prepared, was dehydratively coupled with **6a** under standard conditions to give **48** in excellent yield.

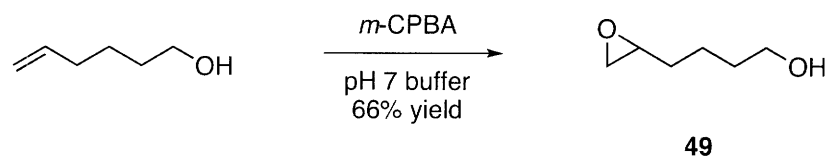
Scheme 42



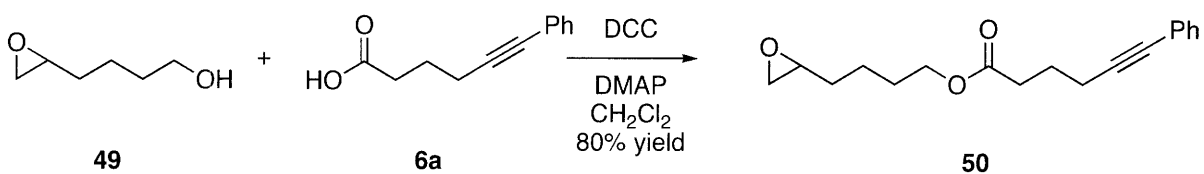
Access to the additional substrate, corresponding to two methylene units shorter, was similarly straightforward. Starting from commercially available 5-hexen-1-ol, epoxidation in

aqueous phosphate buffer gave **49** (Scheme 43).⁶⁹ Epoxy alcohol **49** and **6a** were then coupled under standard conditions to provide **50** in good yield (Scheme 44).

Scheme 43



Scheme 44



With **48** and **50**, we were ready to investigate nickel-catalyzed reductive macrocyclizations of these two substrates to give 15- and 12-membered rings respectively. Thus, each epoxy alkyne was subjected to the standard conditions developed with 20 mol % and 100 mol % Ni(cod)₂ (Scheme 45 and Table 6).

⁶⁹ The buffer was necessary to prevent cyclization under the conditions.

Scheme 45

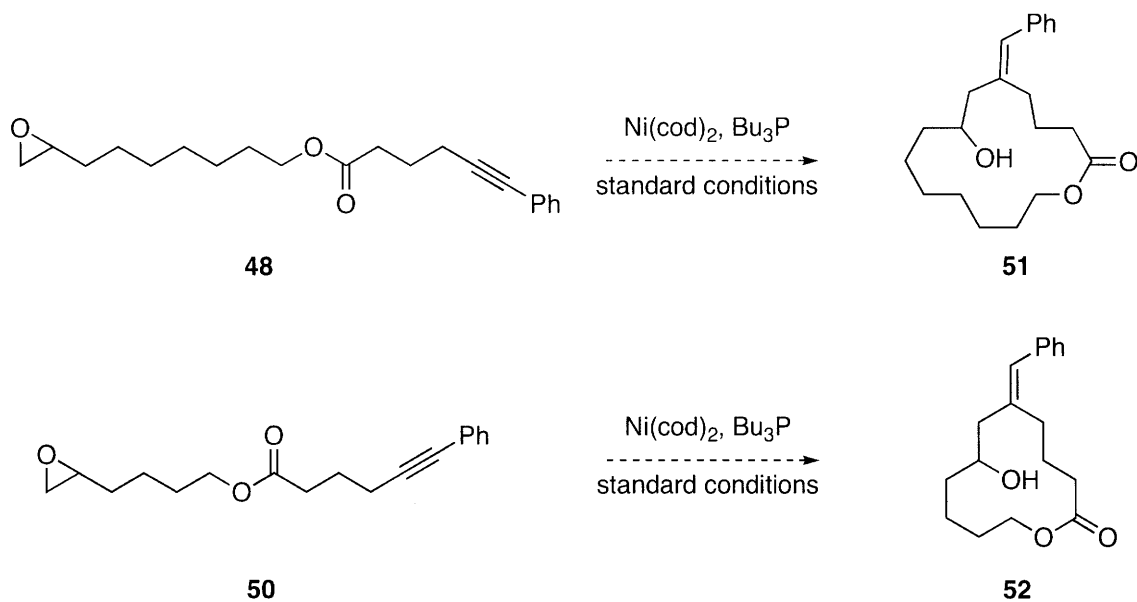


Table 6. Cyclization studies of **48** and **50** under standard conditions

substrate	conditions	yield (product)
48	A	28% (51)
48	B	53% (51)
50	A	12% (52) ^a
50	B	26% (52) ^a

conditions:

A: 20 mol% Ni(cod)₂, 40mol% Bu₃P, 1000mol% Et₃B, 0.15M THF

B: 100 mol% Ni(cod)₂, 200mol% Bu₃P, 1000mol% Et₃B, 0.075M THF

^a Complete purification was not possible as uncharacterized impurities coeluted with **52**. Product assigned and yield estimated by ¹H NMR spectral analysis (~70% purity) and HRMS.

Under the conditions we had employed in the previous cases, we were pleased to find that both **48** and **50** gave 15- and 12-membered ring **51** and **52** respectively. A strong difference between conditions A and B was seen, with B giving approximately twice the desired product in both cases. The 12-membered ring **52** was formed in both cases with much lower efficiency, regardless of catalyst loading. However, **51** was obtained in up to 53% yield. While these results are not conclusive, combined with the previous findings, it is possible that nickel-catalyzed or -mediated macrocyclizations of epoxy alkynes containing an ester in the proper position (δ,ϵ -unsaturated ynoates) may provide a general strategy for the formation of macrolactones.

Conclusion

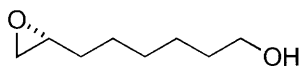
The total synthesis of (-)-gloeosporone **1** was described in 10 steps (LLS) and 5.9% overall yield, with a 14-membered ring formed via nickel-catalyzed reductive macrocyclization of an alkyne and an epoxide in 46% yield. Up to 67% yield could be achieved for the reductive macrocyclization with stoichiometric nickel (calculation of the overall yield, based on these cyclization conditions was 8.6%). This transformation differs from previous strategies in closing the macrocycle of **1** using more traditional approaches such as macrolactonization and ring-closing metathesis.⁹ Interested in the generality of this reaction, and surprised by its efficacy at high concentrations, additional studies were undertaken with related alkynyl esters. With these studies we were able to recognize an important structural pattern (a δ,ϵ -unsaturated ynoate) that might be necessary for efficient cyclization. Using this information, the nickel-catalyzed

reductive cyclization of alkynes and epoxides was extended to the formation of 12- and 15-membered rings.

Experimental

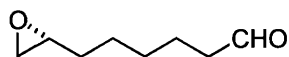
General Information. Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of argon with rigid exclusion of moisture from reagents and glassware. Dichloromethane was distilled from calcium hydride. Triethylamine and 2,6-lutidine were distilled over calcium hydride and stored over potassium hydroxide. Tetrahydrofuran (THF) and diethylether (Et₂O) were distilled from a blue solution of sodium benzophenone ketyl. Dimethylformamide (DMF) was used as supplied by Aldrich (99.8% anhydrous; stored over molecular sieves). Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F254 plates. The developed chromatogram was analyzed by UV lamp (254 nm) ethanolic phosphomolybdic acid (PMA), aqueous cerium molybdate (CAM) or aqueous potassium permanganate (KMnO₄). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230–400 mesh). ¹H and ¹³C NMR spectra were recorded in CDCl₃, unless otherwise noted, on a Bruker Avance 400 MHz, Varian Inova 500 MHz, or a Bruker Avance 600 MHz spectrometer. Chemical shifts in ¹H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, qt=quintet, m=multiplet, app=apparent, and br=broad), coupling constant in hertz (Hz), and integration. Chemical shifts of ¹³C NMR spectra are reported in ppm from the central peak of CDCl₃ (77.2 ppm) on the δ scale. Infrared (IR) spectra were recorded on a Perkin–Elmer 2000 FT-IR. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 589 nm with 0.1 dm cell length. Data are reported as follows: $[\alpha]_{\lambda}^{\text{temp}}$, concentration (*c* g/100 mL), and solvent. High-resolution mass spectra (HRMS) were

obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by Ms Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility.

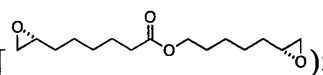


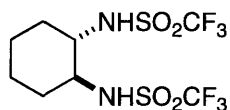
(R)-6-(oxiran-2-yl)hexan-1-ol, 13: A solution of *m*-chloroperbenzoic acid (77 wt %, 8.9 g, 40 mmol) in CH₂Cl₂ (130 mL) was cooled to 0 °C. To this solution was added 7-octen-1-ol (4 mL, 26.5 mmol) over 5 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 3 hours. The reaction was quenched by pouring into a chilled solution of sodium hydroxide (1M in water), and subsequently extracted with diethylether. The organic extracts were then washed with 1M NaOH, water, and brine, and dried over sodium sulfate. Concentration *in vacuo* provided pure racemic epoxide. The product was then added to (salen)₂Co-OAc (480 mg, 0.80 mmol).¹⁴ The mixture was cooled to 0 °C and deionized water was added (22 mmol, 4.0 mL). The mixture was stirred overnight. Vacuum distillation (76 °C, 0.3 torr), followed by drying over magnesium sulfate, provided pure **13** (1.34 g, 9.28 mmol, 35% yield): $R_f = 0.095$ (30% EtOAc/hexanes); $[\alpha]_D +9.0^\circ$ (c 0.19, CHCl₃, 23 °C); >99% e.e., as determined by chiral HPLC analysis (OD-H column, 9:1 hexane:*i*PrOH, 1mL/min of 2-naphylenethiol addition product) t_R (*S*) = 24.2 min, t_R (*R*) = 28.6 min; IR (thin film, NaCl) 3397, 2931, 2858, 1463, 1056 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.66 (q, $J = 6.5$ Hz, 2H), 2.92 (m, 1H), 2.76 (dd, $J = 5.0, 4.1$ Hz, 1H), 2.48 (dd, $J = 5.0, 2.7$ Hz, 1H), 1.63-1.35 (m, 9H), 1.27-

1.23 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 63.6, 53.1, 47.8, 33.3, 33.1, 29.9, 26.7, 26.3; HRMS (ESI) calcd for $\text{C}_8\text{H}_{16}\text{O}_2$ $[\text{M} + \text{Na}]^+$ 167.1043, found 167.1048.

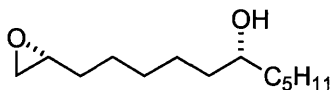


(R)-6-(oxiran-2-yl)hexanal, 12: A mixture of 3 Å molecular sieves (1 g), N-methylmorpholine N-oxide (10.2 mmol, 1.2 g), and tetra-*n*-propylammonium perruthenate (0.21 mmol, 73 mg) and dichloromethane (50 mL) was stirred at room temperature. To this mixture was added a solution of **13** (6.9 mmol, 1 g) in dichloromethane (5 mL) over 5 minutes. The reaction was stirred for 2 h at room temperature, until TLC showed complete consumption of **13**. The crude reaction mixture was poured through a short pad of silica gel and flushed with dichloromethane (100 mL) and 30% EtOAc/hexanes (200 mL). Concentration and purification by flash column chromatography (10% EtOAc/hexanes) gave **12** (6.6 mmol, 927 mg, 95% yield; contaminated

with ~2% of the corresponding ester []: $R_f = 0.34$ (30% EtOAc in hexane); $[\alpha]_D +13.2^\circ$ (c 0.17, CHCl_3 , 23 °C); IR (thin film, NaCl) 2936, 1709, 1411, 1260, 912 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.78 (s, 1H), 2.94-2.89 (m, 1H), 2.76 (app t, $J = 4.5$ Hz, 1H), 2.49-2.43 (m, 3H), 1.66 (q, $J = 7.4$ Hz, 1H), 1.6-1.36 (m, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 202.9, 52.5, 47.3, 44.0, 32.5, 29.1, 26.0, 22.1; HRMS (ESI) calcd for $\text{C}_8\text{H}_{14}\text{O}_2$ $[\text{M} + \text{Na}]^+$ 165.0886, found 165.0891.



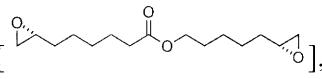
N,N'-((1*S*,2*S*)-cyclohexane-1,2-diyl)*bis*(1,1,1-trifluoromethanesulfonamide), **14**: Synthesized according to a known procedure.⁷⁰ NMR spectral and optical rotation data were consistent with that reported.

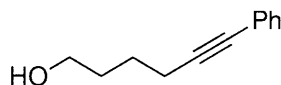


(R)-1-((*R*)-oxiran-2-yl)undecan-6-ol, **5a**: A mixture of titanium isopropoxide (5.35 mmol, 1.6 mL), **14** (*bis*-triflamide ligand, 0.18 mmol, 68 mg), and toluene (4.5 mL) were heated to 40 °C for 30 minutes, giving a clear solution. This solution was cooled to –78 °C followed by addition of diamyl zinc⁷¹ (5.35 mmol, 1.11 g) and **12** (aldehyde, 4.46 mmol, 634 mg). The reaction was then allowed to warm to –20 °C and stirred thus for 14 additional hours. The reaction was directly poured into a mixture of EtOAc (25 mL), 1M NaHSO₄ (25 mL) and ice and stirred until clear (15 minutes). The organic layer was separated and the aqueous layer was extracted (2 x 25 mL EtOAc). The combined organic layers were washed (25 mL water, 25 mL 1M NaHCO₃, 25 mL water, and brine) and dried over sodium sulfate. Flash column chromatography of the concentrated crude residue (10% EtOAc/hexanes) gave **5a** (80% yield 3.57 mmol, 850 mg,

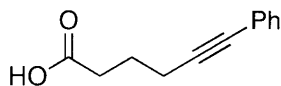
⁷⁰ Ostwald, R.; Chavant, P.-Y.; Stadtmüller, H.; Knochel, P. *J. Org. Chem.* **1994**, *59*, 4143–4153.

⁷¹ Prepared according to the method of Knochel, see: Rozema, M. J.; Sidduri, A.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 1956–1958.

contaminated with ~5% of [], which was present in the starting material): $R_f(S) = 0.33$ (30% EtOAc/hexanes); $R_f(R) = 0.22$ (30% EtOAc/hexanes); $[\alpha]_D +5.6^\circ$ (c 0.29, CHCl_3 , 23°C); IR (thin film, NaCl) 3425, 2930, 1465, 1259, 1130, 915, 836 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.64-3.55 (m, 1H), 2.93-2.83 (m, 1H), 2.75 (dd, $J = 5.0, 4.1$ Hz, 1H), 2.46 (dd, $J = 5.0, 2.8$ Hz, 1H), 1.6-1.21 (m, 18H), 0.89 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 72.5, 53.1, 47.8, 38.2, 38.0, 33.1, 32.6, 30.1, 26.7, 26.2, 26.0, 23.3, 14.8; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{26}\text{O}_2$ $[\text{M} + \text{Na}]^+$ 237.1830, found 237.1830.



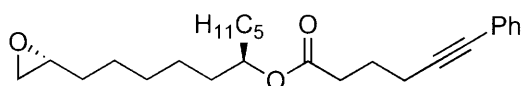
6-phenylhex-5-yn-1-ol, 16: Synthesized according to known procedure.⁷² ^1H and ^{13}C NMR spectral data were consistent with those reported.



6-phenylhex-5-ynoic acid, 6a: A solution of **16** (8.9 g) in acetone (250 mL) was cooled to 0°C . To this solution was added dropwise Jones reagent²⁹ (110 mL, 0.5 M CrO_3 in 2:3 conc. $\text{H}_2\text{SO}_4/\text{H}_2\text{O}$) over 30 minutes. The reaction was stirred at 0°C for 30 minutes, then *i*PrOH (5

⁷² Molinaro, C. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *123*, 8076–8077.

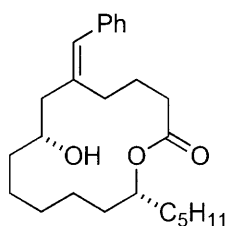
mL) was added dropwise over 5 minutes to quench. The solution was poured into 1M HCl and extracted with Et₂O (3 x 100 mL). The Et₂O was extracted with 1M NaOH (3 x 50 mL). The combined basic aqueous extracts were acidified with 3M HCl and subsequently extracted with Et₂O (3 x 100 mL). The combined extracts were washed with water and brine and dried over sodium sulfate. Concentration *in vacuo* gave the title compound (7.7 g, 80% yield), without need for further purification. ¹H and ¹³C NMR spectral data were consistent with those reported.⁷³



(R)-1-((R)-oxiran-2-yl)undecan-6-yl 6-phenylhex-5-ynoate, 4a: To a 250 mL round-bottom flask were added dicyclohexylcarbodiimide (1.2 g), 4-dimethylaminopyridine (76 mg), and dichloromethane (54 mL). After cooling to 0 °C, a solution of epoxy alcohol **5a** (1.4 g) and ynoic acid **6a** (1.0 g) in dichloromethane (5 mL) was added to the mixture. The reaction was allowed to warm to rt and stirred for 14 h. To the mixture was directly added silica gel (5 g), and the mixture concentrated *in vacuo*. Purification by flash column chromatography (2% to 5% EtOAc in hexanes) gave **4a** (1.7 g, 85% yield) as a colorless oil: $R_f = 0.52$ (30% EtOAc/hexanes); $[\alpha]_D +0.19^\circ$ (c 2.1, CHCl₃, 23 °C); IR (thin film, NaCl) 2931, 2858, 1728, 1490, 1457, 1214, 1160, 1020, 756 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.43-7.38 (m, 2H), 7.31-7.27 (m, 3H), 4.91 (q, $J = 5.7$ Hz, 1H), 2.93-2.87 (m, 1H), 2.75 (dd, $J = 4.6, 4.4$ Hz, 1H),

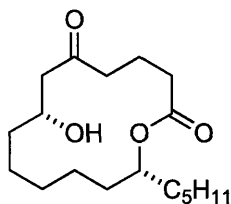
⁷³ Du, W.; Curran, D. P. *Org. Lett.* **2003**, *10*, 1765–1768.

2.53-2.48 (m, 4H), 2.47 (dd, $J = 5.0, 2.7$ Hz, 1H), 1.94 (q, $J = 7.2$ Hz, 2H), 1.60-1.22 (m, 18H), 0.89 (dd, $J = 6.9, 6.7$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.2, 131.8, 128.4, 127.9, 124.0, 89.1, 81.6, 74.5, 52.6, 47.3, 34.3, 34.3, 33.7, 32.6, 31.9, 29.6, 26.1, 25.5, 25.2, 24.3, 22.8, 19.1, 14.3; HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{36}\text{O}_3$ $[\text{M} + \text{Na}]^+$ 407.2557, found 407.2550.



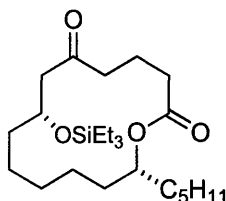
(8R,14R,E)-6-benzylidene-8-hydroxy-14-pentyloxacyclotetradecan-2-one, 3a: To a 25 mL sealed tube in a glove box under nitrogen atmosphere was added $\text{Ni}(\text{cod})_2$ (22 mg for 20 mol %, 108 mg for 100 mol %; supplied by Strem; if not bright yellow, or if powdered, *do not use*), Bu_3P (40 μL for 40 mol %, 200 μL for 100 mol %; stored in the glove box in a vial fitted with a Teflon® cap; if not completely clear and colorless, *do not use*), and Et_3B (190 μL , 1000 mol %). To the yellow mixture was added THF (2.9 mL for 0.15M, 5.9 mL for 0.075M; titrated with sodium benzophenone ketyl/THF solution to have < 5 ppm H_2O or O_2). To the reaction mixture was added **4a** (150 mg) upon which the reaction should turn red – other colors, e.g., brown, indicate that the reaction has been improperly set up (see above). The tube was sealed, removed from the glove box, and stirred for 36 hours. The tube was then opened and a solution of BHT (150 mg) in ethyl acetate (5 mL) was added and stirred open to air until yellow (approximately 1 hour). Concentration *in vacuo*, followed by purification by flash column chromatography (crude mixture loaded on the column by dissolution in toluene, then eluted with 5% EtOAc in hexanes)

gave the title compound (69 mg, 46% yield for 20 mol % Ni(cod)₂/40 mol % Bu₃P; 100 mg, 67% yield for 100 mol % Ni(cod)₂/200 mol % Bu₃P): IR (thin film, NaCl) 3438, 2930, 1727, 1459, 1248, 1027 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.35-7.2 (m, 5H), 6.4 (s, 1H), 4.92-4.87 (m, 1H), 3.95-3.87 (m, 1H), 2.51-2.26 (m, 5H), 2.22 (dd, *J* = 13.6, 8.3 Hz, 1H), 1.93-1.83 (m, 1H), 1.81-1.73 (m, 1H), 1.71-1.21 (m, 19H), 0.89-0.84 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 174.1, 139.5, 138.2, 130.2, 129.2, 129.0, 127.2, 75.8, 68.7, 46.4, 36.5, 36.1, 35.5, 34.0, 32.4, 31.2, 28.9, 25.7, 25.7, 25.0, 23.2, 23.2, 14.7; HRMS (ESI) calcd for C₂₅H₃₈O₃ [M + Na]⁺ 409.2713, found 409.2734; [α]_D +10.8 ° (*c* 0.12, CHCl₃, 23 °C).



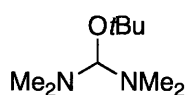
(8*R*,14*R*)-8-hydroxy-14-pentyloxacyclotetradecane-2,6-dione, 22a: A solution of **3a** (210 mg) in dichloromethane and methanol (50 mL, 5:1 CH₂Cl₂/MeOH) was cooled to -78 °C. Ozone was bubbled through the solution until a pale blue color persisted and TLC showed complete disappearance of starting material. Argon was then bubbled through the solution until colorless. Dimethylsulfide was added (3 mL) and the reaction was allowed to warm to room temperature over fourteen hours. Concentration *in vacuo* was followed by flash column chromatography of the crude oil (10% to 30% EtOAc in hexanes) to give **22a** as a colorless oil (160 mg, 94% yield): *R_f* = 0.32 (50% EtOAc/hexanes); IR (thin film, NaCl) 3442, 2931, 2854, 1725, 1694, 1432, 1222, 986 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.98-4.92 (m, 1H), 4.12-4.07 (m, 1H), 2.79 (ddd, *J* =

18.6, 9.5, 5.5 Hz, 1H), 2.72 (dd, $J = 14.3, 7.6$ Hz, 1H), 2.59 (dd, $J = 18.9, 5.2$ Hz, 1H), 2.46-2.41 (m, 2H), 2.0-1.82 (m, 2H), 1.66-1.20 (m, 22H), 0.86-0.84 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 211.1, 173.8, 75.0, 69.1, 49.6, 42.7, 35.5, 34.5, 33.3, 32.9, 32.3, 27.8, 25.9, 23.6, 23.2, 23.1, 18.9, 14.7; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{32}\text{O}_4$ $[\text{M} + \text{Na}]^+$ 335.2193, found 335.2206; $[\alpha]_{\text{D}} -6.7^\circ$ (c 0.28, CHCl_3 , 23 °C).

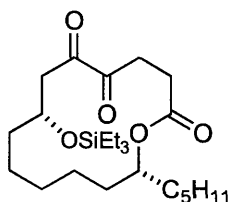


(8R,14R)-14-pentyl-8-(triethylsilyloxy)oxacyclotetradecane-2,6-dione, 22c: A solution of **22a** (160 mg) in dichloromethane (10 mL) was cooled to 0 °C for the addition of 2,6-lutidine (0.84 mL) and triethylsilyltriflate (0.14 mL). The reaction was warmed to rt and stirred for 4 h, or until TLC showed complete consumption of starting material. The reaction was then poured into a mixture of ice and sodium hydrogen sulfate (1 M, 50 mL). This mixture was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with NaHSO_4 , water, and brine, to give **22c** (230 mg, 100% yield) without need for further purification: $R_f = 0.35$ (10% EtOAc /hexanes); IR (thin film, NaCl) 2935, 2875, 1729, 1711, 1458, 1377, 1213, 1162, 1006, 726 cm^{-1} ; ^1H NMR (600 MHz, C_6D_6) δ 5.13-5.05 (m, 1H), 4.34-4.26 (m, 1H), 2.69 (ddd, $J = 19.4, 10.7, 4.5$ Hz, 1H), 2.63-2.60 (m, 1H), 2.57 (dd, $J = 14.3, 9.9$ Hz, 1H), 2.28 (dd, $J = 14.4, 4.2$ Hz, 1H), 2.18 (ddd, $J = 16.8, 5.5, 3.9$ Hz, 1H), 1.98 (dt, $J = 19.4, 4.6$ Hz, 1H), 1.90-1.82 (m, 1H), 1.77-1.69 (m, 1H), 1.58-1.44 (m, 3H), 1.43-1.10 (m, 15H), 1.00 (t, $J = 8.0$ Hz, 9H),

0.89 (t, $J = 6.9$ Hz, 3H), 0.59 (q, $J = 8.0$ Hz, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 208.1, 172.9, 73.8, 69.7, 50.5, 42.2, 35.6, 33.9, 32.6, 32.4, 32.4, 28.0, 26.2, 23.3, 22.4, 22.2, 18.6, 14.6, 7.6, 5.6; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{46}\text{O}_4\text{Si}$ $[\text{M} + \text{Na}]^+$ 449.3058, found 449.3075; $[\alpha]_{\text{D}} +5.3^\circ$ (c 4.1, CHCl_3 , 23°C).



***t*-butoxy-*bis*(dimethylamino)methane (Bredereck's reagent), 25:** Prepared from DMF as previously reported.⁶⁰ ^1H NMR spectral data matched those reported. Chemistry described below required prepared **25** for reproducible results, which could be stored in a sealed round bottom flask in a refrigerated desiccator for several months without apparent decomposition. Material supplied from Aldrich was of inconsistent purity, and did not prove amenable to purification.

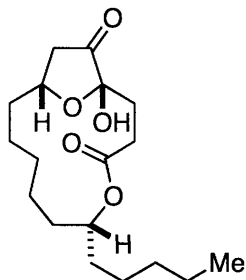


Diketone intermediate, 21b: To a 1 mL conical vial fitted with a rubber septum were added silyl ether **22c** (41 mg, 0.096 mmol) and *t*-butoxy-*bis*(dimethylamino)methane (Bredereck's

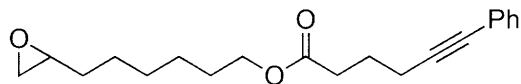
reagent, **25**, 0.27 mL). The vial was heated to 60 °C for 4 h under a stream of argon. The septum was then punctured with an additional needle, and argon was blown over the reaction mixture while continued to be heated for an additional hour. Any additional volatiles were then removed (0.1 torr, 60 °C), and the crude mixture was analyzed by ¹H NMR spectroscopy. In the event that incomplete conversion was observed, the crude residue (obtained by concentration of the NMR sample *in vacuo*) was resubjected to the above conditions. Upon complete disappearance of starting material, the crude residue (obtained by concentration of the NMR sample *in vacuo*) was dissolved in dichloromethane (13 mL). Rose Bengal was added (6.7 mg) and stirred until completely dissolved. The pink solution was cooled to -78 °C and oxygen was bubbled through. A 600 W halogen lamp was used to irradiate the reaction for 15 minutes, upon which TLC showed complete consumption of starting material. The crude reaction mixture was filtered directly through a pad of silica gel,⁷⁴ which was washed with Et₂O (100 mL). Concentration *in vacuo* provided the title compound (30 mg, 70% yield), which was carried onward without further purification.⁷⁵

⁷⁴ Filtration through silica gel directly after the reaction (without concentration) was crucial to the overall yield, as moisture had condensed during the reaction. Decomposition products of diketone **21b** were observed upon exposure to water. The silica gel acted not only to remove the Rose Bengal and other very polar byproducts, but also as a drying agent.

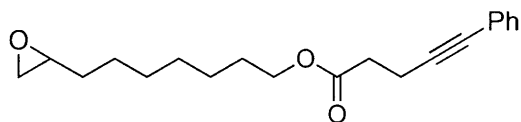
⁷⁵ Diketone **21b** proved unstable prolonged exposure to silica gel, as evidenced by decreased purity and mass recovery after attempted silica gel chromatography. The structure was assigned by ¹H NMR of the crude mixture, and by chemical transformation to (-)-gloeosporone **1**.



(-)-gloeosporone, 1: To a plastic 5 mL conical vial were added **21b** (30 mg) and THF (2 mL). To the reaction mixture was then added HF•pyr in aliquots (50 μ L) every five minutes until starting material was consumed (total necessary, 200 μ L). The reaction mixture was then poured into an 150 mL Erlenmeyer flask containing saturated sodium bicarbonate (20 mL). The reaction was extracted with Et₂O (3 x 50 mL). The combined organic extracts were washed with saturated sodium bicarbonate, water, and brine, then dried over sodium sulfate. Concentration *in vacuo* gave the crude residue, which was purified by flash column chromatography (5% EtOAc in hexanes) to give the title compound (20 mg, 90% yield): $R_f = 0.19$ (30% EtOAc/hexanes); IR (thin film, NaCl) 3330, 2932, 2850, 1749, 1714, 1462, 1421, 1150, 1069, 1038 cm^{-1} ; ¹H NMR (600 MHz, CDCl₃) δ 5.09-5.03 (m, 1H), 4.45-4.41 (m, 1H), 3.54 (br s, 1H), 2.74 (dd, $J = 18.7, 6.2$ Hz, 1H), 2.44 (ddd, $J = 16.5, 8.5, 3.9$ Hz, 1H), 2.35 (ddd, $J = 14.3, 9.0, 3.8$ Hz, 1H), 2.28 (ddd, $J = 15.2, 8.9, 3.6$ Hz, 1H), 2.10 (ddd, $J = 14.3, 8.3, 3.5$ Hz, 1H), 2.04 (dd, $J = 18.8, 8.3$ Hz, 1H), 1.71-1.43 (m, 10H), 1.34-1.16 (m, 8H), 0.89 (br t, $J = 6.8$ Hz, 3H); ¹³C NMR (125 MHz, C₆D₆) δ 209.2, 174.7, 99.1, 74.7, 73.5, 40.7, 34.9, 32.4, 32.3, 31.9, 30.3, 29.7, 26.0, 25.4, 22.7, 21.3, 14.2; HRMS (ESI) calcd for C₁₈H₃₀O₅ [M + Na]⁺ 349.1985, found 349.1997; [α]_D -46.8° (c 0.16, CHCl₃, 23 °C).

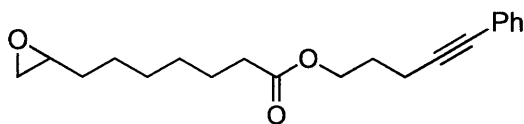


6-(oxiran-2-yl)hexyl 6-phenylhex-5-ynoate, 27: To a 100 mL round bottom flask were added DCC (860 mg), DMAP (100 mg), and dichloromethane (35 mL). The reaction was cooled to 0 °C, and **35** (500 mg) and **6a** (780 mg) were added concurrently. After stirring for 30 minutes, TLC showed complete disappearance of **35**. Silica gel (2 g) was added directly and the volatiles removed *in vacuo*. Flash column chromatography (5% EtOAc in hexanes) gave the title compound as a colorless oil (1.05 g, 95% yield): IR (thin film, NaCl) 2932, 1733 1490, 1157, 1070 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.42-7.38 (m, 2H), 7.32-7.27 (m, 3H), 4.04 (t, $J = 6.6$ Hz, 2H), 2.85 (m, 1H), 2.76 (dd, $J = 5.0, 4.8$ Hz, 1H), 2.50 (app q, $J = 7.6$ Hz, 4H), 2.46 (dd, $J = 5.0, 2.8$ Hz, 1H), 1.94 (qt, $J = 7.1$ Hz, 2H), 1.70-1.60 (m, 2H), 1.60-1.31 (m, 8H); ^{13}C NMR (125 MHz, CDCl_3) δ 174.0, 132.3, 128.9, 128.4, 124.4, 89.6, 82.1, 65.2, 53.0, 47.8, 33.9, 33.1, 29.8, 29.2, 26.6, 26.5, 24.6, 19.6; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{26}\text{O}_3$ $[\text{M} + \text{Na}]^+$ 337.1774, found 337.1785.



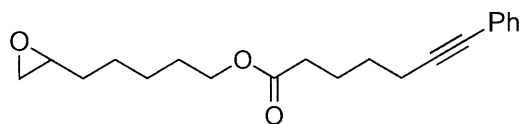
7-(oxiran-2-yl)heptyl 5-phenylpent-4-ynoate, 29: To a 100 mL round bottom flask were added DCC (1.15 g), DMAP (72 mg), and dichloromethane (50 mL). The reaction was cooled to 0 °C, and **43** (800 mg) and **45** (880 mg) were added concurrently. After stirring for 30 minutes, silica

gel (2 g) was added directly and the volatiles removed *in vacuo*. Flash column chromatography (5% EtOAc in hexanes, then 30% EtOAc in hexanes) gave the title compound as a colorless oil (490 mg, 31% yield; with 620 mg recovered **43**): IR (thin film, NaCl) 2930, 2857, 1735, 1492, 1442, 1255, 1167 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.42-7.37 (m, 2H), 7.32-7.27 (m, 3H), 4.13 (t, $J = 6.7$ Hz, 2H), 2.94-2.89 (m, 1H), 2.79-2.72 (m, 3H), 2.68-2.62 (m, 2H), 2.48 (dd, $J = 5.0, 2.7$ Hz, 1H), 1.7-1.61 (m, 2H), 1.57-1.29 (m, 10H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.7, 132.3, 128.9, 128.5, 124.2, 88.8, 81.8, 65.5, 53.1, 47.8, 34.4, 33.1, 30.0, 29.9, 29.3, 26.6, 26.5, 16.1; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{26}\text{O}_3$ $[\text{M} + \text{Na}]^+$ 337.1774, found 337.1762.



5-phenylpent-4-ynyl 7-(oxiran-2-yl)heptanoate, 30: To a 50 mL round bottom flask were added DCC (230 mg), DMAP (15 mg), and dichloromethane (10 mL). The reaction was cooled to 0 °C, and **47** (172 mg) and **44** (249 mg) were added concurrently. After stirring for 30 minutes, TLC showed complete disappearance of **47**. Silica gel (500 mg) was added directly and the volatiles removed *in vacuo*. Flash column chromatography (5% EtOAc in hexanes) gave the title compound as a colorless oil (200 mg, 64% yield): IR (thin film, NaCl) 2928, 2914, 1734, 1490, 1457, 1165 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.43-7.37 (m, 2H), 7.32-7.25 (m, 3H), 4.24 (t, $J = 6.3$ Hz, 2H), 2.93-2.88 (m, 1H), 2.75 (dd, $J = 4.9, 4.1$ Hz, 1H), 2.53 (t, $J = 7.0$ Hz, 2H), 2.47 (dd, $J = 4.9, 2.7$ Hz, 1H), 2.33 (t, $J = 7.5$ Hz, 2H), 1.93 (app qt, $J = 6.7$ Hz, 2H), 1.62 (app br qt, $J = 7.5$ Hz, 2H), 1.56-1.31 (m, 8H); ^{13}C NMR (125 MHz, CDCl_3) δ 174.5, 132.3,

128.9, 128.4, 124.3, 89.3, 82.0, 63.7, 53.0, 47.8, 35.0, 33.1, 29.8, 29.7, 28.5, 26.5, 25.6, 16.9; HRMS (ESI) calcd for C₂₀H₂₆O₃ [M + Na]⁺ 337.1774, found 337.1782.

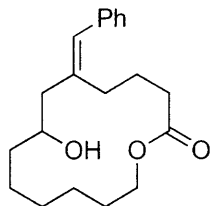


5-(oxiran-2-yl)pentyl 7-phenylhept-6-ynoate, 28: To a 25 mL round bottom flask were added DCC (155 mg), DMAP (7 mg), and dichloromethane (5 mL). The reaction was cooled to 0 °C, and **39b** (65 mg) and **42** (140 mg) were added concurrently. After stirring for 30 minutes, TLC showed complete disappearance of **39b**. Silica gel (300 mg) was added directly and the volatiles removed *in vacuo*. Flash column chromatography (5% EtOAc in hexanes) gave the title compound as a colorless oil (146 mg, 93% yield): IR (thin film, NaCl) 2936, 2861, 1733, 1490, 1442, 1260, 1176, 1071 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.42-7.36 (m, 2H), 7.31-7.24 (m, 3H), 4.08 (t, *J* = 6.7 Hz, 2H), 2.92-2.87 (m, 1H), 2.75 (dd, *J* = 4.8, 4.2 Hz, 1H), 2.47-2.45 (m, 1H), 2.44 (t, *J* = 6.8 Hz, 1H), 2.37 (t, *J* = 7.4 Hz, 2H), 1.81 (app qt, *J* = 7.6 Hz, 2H), 1.69-1.61 (m, 4H), 1.61-1.34 (m, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 174.3, 132.2, 128.9, 128.3, 124.6, 90.3, 81.6, 65.0, 52.9, 47.8, 34.6, 33.1, 29.3, 28.9, 26.5, 26.4, 24.9, 19.8; HRMS (ESI) calcd for C₂₀H₂₆O₃ [M + Na]⁺ 337.1774, found 337.1774.

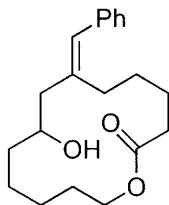
General procedure for the reductive cyclization of epoxy alkynes 27-30 with 20 mol % Ni(cod)₂: A flame-dried 25 mL Schlenk tube was brought into a glove box under nitrogen atmosphere. Ni(cod)₂ (22 mg), Bu₃P (38 μL), Et₃B (0.57 mL), and THF (rigorously

deoxygenated, 2.6 mL, 0.15M) were then added to the tube and stirred for 5 minutes. To the bright yellow reaction mixture was then added the alkyne (0.39 mmol). The tube was sealed, removed from the glove box, and stirred for 36 h. A solution of BHT (butylated hydroxytoluene or 2,6-di-*tert*-butyl-4-methylphenol, 430 mg, 1.95 mmol) in EtOAc (5 mL) was added for work-up. The reaction was stirred open to air until yellow (1-3 h), concentrated *in vacuo*, and purified by flash column chromatography.

General procedure for the reductive cyclization of epoxy alkynes 27-30 with 100 mol % Ni(cod)₂: A flame-dried 25 mL Schlenk tube was brought into a glove box under nitrogen atmosphere. Ni(cod)₂ (107 mg, 0.39 mmol), Bu₃P (0.19 mL, 0.78 mmol), Et₃B (0.57 mL, 3.9 mmol), and THF (rigorously deoxygenated, 5.2 mL, 0.075M) were then added to the tube and stirred for 5 minutes. To the bright yellow reaction mixture was then added the alkyne (0.39 mmol). The tube was then sealed, removed from the glove box, and stirred for 36 h. A solution of BHT (butylated hydroxytoluene or 2,6-di-*tert*-butyl-4-methylphenol, 430 mg, 1.95 mmol) in EtOAc (5 mL) was added for work-up. The reaction was stirred open to air until yellow (1-3 h), concentrated *in vacuo*, and purified by flash column chromatography.

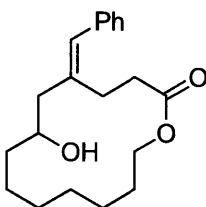


(E)-6-benzylidene-8-hydroxyoxacyclotetradecan-2-one, 31: IR (thin film, NaCl) 3439, 2930, 1729, 1443, 1248, 1048 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.35-7.30 (m, 2H), 7.26-7.18 (m, 3H), 6.44 (s, 1H), 4.23 (app dt, $J = 10.9, 2.4$ Hz, 1H), 4.12-4.07 (m, 1H), 3.94-3.87 (m, 1H), 2.60-2.54 (m, 1H), 2.54-2.46 (m, 3H), 2.28 (ddd, $J = 14.5, 10.7, 3.5$ Hz, 1H), 2.18-1.91 (m, 1H), 1.90-1.80 (m, 1H), 1.76-1.30 (m, 10H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.9, 139.4, 138.2, 130.1, 129.3, 129.0, 127.2, 66.8, 64.3, 45.8, 35.9, 34.8, 29.8, 27.7, 25.4, 25.0, 24.6, 23.9; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{28}\text{O}_3$ $[\text{M} + \text{Na}]^+$ 339.1931, found 339.1939.

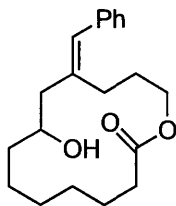


(E)-7-benzylidene-9-hydroxyoxacyclotetradecan-2-one, 32: IR (thin film, NaCl) 3282, 2923, 2862, 1723, 1460, 1333, 1270, 1243, 1030 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.36-7.31 (m, 2H), 7.25-7.18 (m, 3H), 6.43 (s, 1H), 4.44-4.37 (m, 1H), 4.02-3.95 (m, 1H), 3.94-3.86 (m, 1H), 2.65 (d, $J = 14.0$ Hz, 1H), 2.54-2.42 (m, 2H), 2.35 (ddd, $J = 14.8, 7.9, 3.5$ Hz, 1H), 2.13 (app dt, $J = 12.7, 3.2$ Hz, 1H), 1.94 (dd, $J = 13.9, 10.0$ Hz, 1H), 1.87-1.72 (m, 4H), 1.71-1.32 (m, 9H);

^{13}C NMR (125 MHz, CDCl_3) δ 174.3, 140.0, 138.3, 129.6, 129.4, 128.9, 127.1, 67.7, 63.5, 44.1, 35.3, 34.3, 29.8, 28.3, 27.2, 25.7, 24.0, 23.6; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{28}\text{O}_3$ $[\text{M} + \text{Na}]^+$ 339.1931, found 339.1947.

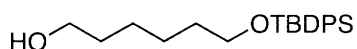


(E)-5-benzylidene-7-hydroxyoxacyclotetradecan-2-one, 33: Coeluted with unidentified side product(s), making complete purification not feasible. Structure tentatively assigned based on HRMS, IR, and analogy of impure ^1H NMR spectra to related compounds: $R_f = 0.26$ (30% EtOAc/hexanes); IR (thin film, NaCl) 3298, 2922, 2854, 1736, 1456, 1270, 1098, 1039 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{28}\text{O}_3$ $[\text{M} + \text{Na}]^+$ 339.1931, found 339.1944.

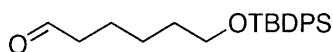


(E)-11-benzylidene-9-hydroxyoxacyclotetradecan-2-one, 34: IR (thin film, NaCl) 3440, 2930, 2860, 1733, 1446, 1256, 1178, 1142, 1088, 1027, 747, 699 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.37-7.31 (m, 2H), 7.25-7.19 (m, 3H), 6.43 (s, 1H), 4.61 (ddd, $J = 11.0, 5.8, 3.0$ Hz, 1H), 3.94-

3.87 (m, 1H), 3.77 (ddd, $J = 11.0, 9.2, 2.5$ Hz, 1H), 2.53-2.44 (m, 2H), 2.42 (dd, $J = 10.7, 3.7$ Hz, 1H), 2.38 (dd, $J = 6.8, 4.0$ Hz, 1H), 2.36-2.28 (m, 1H), 2.12 (dd, $J = 13.9, 9.1$ Hz, 1H), 1.93-1.23 (m, 13H); ^{13}C NMR (125 MHz, CDCl_3) δ 174.4, 139.4, 138.2, 130.3, 129.2, 129.0, 127.2, 67.2, 64.1, 45.5, 34.9, 33.6, 28.6, 27.7, 26.9, 26.0, 25.0, 24.5; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{28}\text{O}_3$ [$\text{M} + \text{Na}$] $^+$ 339.1931, found 339.1923.



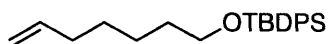
6-(tert-butyldiphenylsilyloxy)hexan-1-ol, 36: Synthesized according to a reported procedure.⁷⁶ NMR spectral data were consistent with reported values.



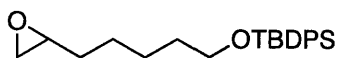
6-(tert-butyldiphenylsilyloxy)hexanal: To a flame-dried 500 mL round-bottom flask were added 3Å molecular sieves (2 g), N-methylmorpholine N-oxide (1.12 g), tetrapropylammonium peruthenate (84 mg), and dichloromethane (168 mL). To this mixture was added **36** (3.0 g) over 5 minutes. After stirring for 4 h, the reaction mixture was filtered through a plug of silica gel, which was washed with 1:3 EtOAc/hexanes (500 mL). Concentration *in vacuo* gave aldehyde **37**

⁷⁶ Chen, M.-Y.; Lee, A. S.-Y. *J. Org. Chem.* **2002**, *67*, 1384-1387.

(3.0 g, 100% yield) without need for further purification. NMR spectral data were consistent with reported values.⁷⁷



tert-butyl(hept-6-enyloxy)diphenylsilane, 38: To a 100 mL flame-dried round-bottom flask was added triphenylphosphonium methyl bromide (1.2 g) and THF (28 mL). After cooling to 0 °C, *n*-BuLi (1.34 mL, 2.5 M solution in hexanes) was added. The reaction was warmed to rt, stirred for 1 h, and then cooled to –78 °C. Aldehyde **37** (1 g) was then added, and the reaction was allowed to slowly warm to rt over 3h. The reaction was quenched by pouring into water (50 mL), and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with water, brine, and dried over sodium sulfate. Concentration *in vacuo* gave the crude residue, which was purified by flash column chromatography (1% EtOAc in hexanes), to give **38** (390 mg, 39% yield) as a colorless oil. NMR spectral data were consistent with reported values.⁷⁸

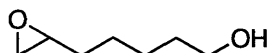


tert-butyl(5-(oxiran-2-yl)pentyloxy)diphenylsilane, 39a: To a 25 mL round bottom flask were added *m*-CPBA (340 mg, 77 wt%) and dichloromethane (10 mL). The mixture was cooled to 0

⁷⁷ Sono, M.; Nakashiba, Y.; Nakashima, K.; Tori, M. *J. Org. Chem.* **2000**, *65*, 3099-3106.

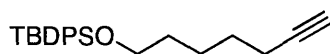
⁷⁸ Clive, D. L. J.; Yeh, V. S. C. *Synth. Commun.* **2000**, *30*, 3267-3274.

°C and **38** (360 mg) was added with a small amount (1 mL) of dichloromethane. The reaction was warmed to rt and stirred 1 h, then poured into 1 M NaOH (20 mL, precooled to 0 °C). Extraction with Et₂O (3 x 25 mL) was followed by washing the combined organic extracts with 1 M NaOH, water, and brine. The solution was dried with sodium sulfate and concentrated *in vacuo* to give **39a** (373 mg, 100% yield) without need for further purification. The NMR spectral data were consistent with reported values.⁷⁹



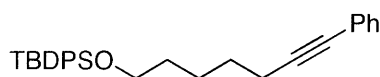
5-(oxiran-2-yl)pentan-1-ol, 39b: To a solution of **39a** (360 mg) in THF (10 mL) was added tetrabutylammonium fluoride (1.2 mL, 1M in THF). The reaction was stirred 2 h, then poured into water (50 mL) and extracted with Et₂O (3 x 25 mL). The combined organics were washed with water and brine and dried over sodium sulfate. Concentration *in vacuo* gave the crude oil, which was purified by flash column chromatography (1:3 EtOAc/hexanes) to give **39b** (76 mg, 58% yield) as a pale yellow oil: *R_f* = 0.24 (1:1 EtOAc/hexanes); IR (thin film, NaCl) 3387, 2933, 2860, 1458, 1410, 1259, 1054, 829 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.66 (br t, *J* = 6.4 Hz, 2H), 2.94-2.89 (m, 1H), 2.76 (dd, *J* = 4.9, 4.1 Hz, 1H), 2.47 (dd, *J* = 5.0, 2.7 Hz, 1H), 1.63-1.39 (m, 8H), 1.34 (br s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 63.5, 53.0, 47.8, 33.3, 33.1, 26.5, 26.3; HRMS (ESI) calcd for C₇H₁₄O₂ [M + Na]⁺ 153.0886, found 153.0882.

⁷⁹ Solladie, G.; Ziani-Chérif, C. *J. Org. Chem.* **1993**, *58*, 2181-2185.

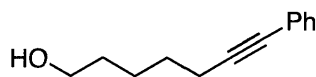


tert-butyl(hept-6-ynoxy)diphenylsilane, 40: To a flame dried 100 mL round-bottom flask were added CBr_4 (3.7 g) and dichloromethane (30 mL). After cooling to 0 °C, Ph_3P (5.8 g) was added and stirred for 5 minutes, followed by addition of Et_3N (7.8 mL) and 5 more minutes of stirring. The aldehyde **37** was then added in a small amount of dichloromethane (2 mL) and stirred at 0 °C for 3 h. The reaction mixture was then added to hexanes (60 mL) and the precipitated was filtered off via filtration through a short plug of silica gel (washed with 1:3 Et_2O /hexanes, 250 mL). Concentration *in vacuo* gave the dibromoolefin (1.0 g, 69% yield) as a pale yellow oil, which was carried onward without further purification: $R_f = 0.80$ (10% EtOAc in hexanes); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.71-7.65 (m, 4H), 7.46-7.36 (m, 6H), 6.38 (t, $J = 7.3$ Hz, 1H), 3.66 (t, $J = 6.4$ Hz, 2H), 2.07 (app t, $J = 7.1$ Hz, 2H), 1.69-1.21 (m, 6H), 1.06 (s, 9H). To a 50 mL flame-dried round-bottom flask were added the dibromoolefin (1.0 g) and THF (20 mL). The mixture was cooled to -78 °C and *n*-BuLi (1.96 mL, 2.5M in hexanes) was added. The reaction was stirred 1 h at -78 °C, then placed in a ice/water bath for 1 additional hour, then poured into ice/water/hexanes. The mixture was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with water and brine, dried over sodium sulfate, and concentrated *in vacuo*. Purification by flash column chromatography (5% EtOAc in hexanes) gave **40** (450 mg, 65% yield) as a colorless oil: $R_f = 0.33$ (5% EtOAc in hexanes); IR (thin film, NaCl) 3309, 3071, 2932, 2858, 1473, 1428, 1111, 823 cm^{-1} ; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.72-7.65 (m, 4H), 7.47-7.36 (m, 6H), 3.68 (t, $J = 6.3$ Hz, 2H), 2.18 (dt, $J = 6.8, 2.6$ Hz, 2H), 1.95 (t, $J = 2.6$ Hz, 1H), 1.62-1.45 (m, 6H), 1.06 (s, 9H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 135.8,

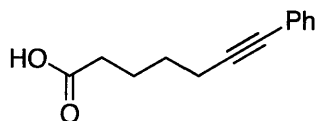
134.2, 129.7, 127.8, 84.8, 68.4, 63.9, 32.2, 28.4, 27.0, 25.2, 19.4, 18.6; HRMS (ESI) calcd for $C_{23}H_{30}OSi$ $[M + Na]^+$ 373.1958, found 373.1959.



tert-butyl diphenyl(7-phenylhept-6-ynoxy)silane, 41a: To a 10 mL round bottom flask was added copper iodide (4.6 mg), $Pd(PPh_3)_4$ (14 mg), and Et_3N (5 mL). Iodobenzene (130 μ L) was added and stirred for 30 min. To the reaction mixture was then added **40** in THF (1 mL). The reaction was heated to 60 $^{\circ}C$ and stirred for 12 h, then cooled to rt, and poured onto 1M HCl (50 mL, precooled to 0 $^{\circ}C$). The quenched mixture was extracted with Et_2O (3 x 50 mL). The combined organics were then washed with 1M HCl (50 mL), water (50 mL), and brine (50 mL), then dried over sodium sulfate. Concentration *in vacuo* gave the title compound (527 mg, 100% yield) as a colorless oil: $R_f = 0.54$ (5% EtOAc in hexanes); IR (thin film, NaCl) 2931, 2857, 2000, 1490, 1472, 1428, 1111 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 7.72-7.65 (m, 6H), 7.45-7.35 (m, 9H), 3.69 (t, $J = 6.1$ Hz, 2H), 2.41 (t, $J = 6.7$ Hz, 2H), 1.66-1.50 (m, 6H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 134.8, 132.2, 130.2, 128.9, 128.3, 128.2, 124.7, 91.0, 81.4, 64.5, 32.8, 29.2, 27.6, 25.9, 20.1, 19.9, 14.9, 1.7; HRMS (ESI) calcd for $C_{29}H_{34}OSi$ $[M + Na]^+$ 449.2271, found 449.2275.



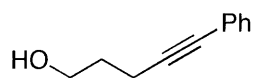
7-phenylhept-6-yn-1-ol, 41a: To a solution of **41a** (527 mg) in THF (12 mL) was added tetrabutylammonium fluoride (1.5 mL, 1 M in THF). After stirring 2 h, the reaction was poured into water and extracted with Et₂O (3 x 25 mL). The combined extracts were washed with water and brine, and dried over sodium sulfate. Purification by flash column chromatography (30% EtOAc in hexanes) gave **41b** (163 mg, 72% yield) as a pale yellow oil. NMR spectral data were consistent with reported values.⁸⁰



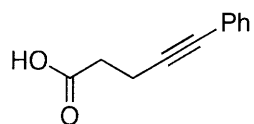
7-phenylhept-6-ynoic acid, 42: To a solution of alcohol **41b** (163 mg) in acetone (10 mL) was added Jones reagent²⁹ (0.5M CrO₃ in 2:3 conc. sulfuric acid/water, 2 mL) dropwise over 15 minutes. The reaction was stirred an additional 30 min at 0 °C, then *i*-PrOH (3 mL) was added dropwise to quench over 10 minutes. After stirring for 15 additional min, the mixture was poured into 1 M HCl (100 mL) and extracted with Et₂O (3 x 50 mL). The combined organic extracts were washed with 1 M HCl (50 mL), water, and brine, and dried over sodium sulfate.

⁸⁰ Patil, N. T.; Lutete, L. M.; Wu, H.; Pahadi, N. K.; Gridnev, I. D.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 4270-4279.

After concentration, ynoic acid **42** was used without further purification. NMR spectral data were consistent with reported values.⁸¹



5-phenylpent-4-yn-1-ol, 44: Synthesized according to a reported procedure.⁸² NMR spectral data were consistent with reported values.

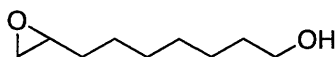


5-phenylpent-4-ynoic acid, 45: To a solution of alcohol **44** (1.3 g) in acetone (200 mL) was added Jones reagent²⁹ (0.5M CrO₃ in 2:3 conc. sulfuric acid/water, 20 mL) dropwise over 15 minutes. The reaction was stirred an additional 30 min at 0 °C, then *i*-PrOH (10 mL) was added dropwise to quench over 10 minutes. After stirring for 15 additional min, the mixture was poured into 1 M HCl (100 mL) and extracted with Et₂O (3 x 50 mL). The combined organic extracts were washed with 1 M HCl (50 mL), water, and brine, and dried over sodium sulfate. After concentration, purification by flash column chromatography (30% EtOAc in hexanes) gave

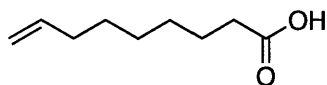
⁸¹ Curran, D. P.; Yu, H.; Liu, H. *Tetrahedron*, **1994**, *50*, 7343-7366.

⁸² Molinaro, C. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 8076-8077.

45 as a yellow sticky solid (830 mg, 65% yield). NMR spectral data were consistent with reported values.⁸³



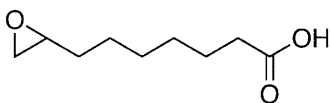
7-(oxiran-2-yl)heptan-1-ol, 43: To a solution of *m*-CPBA (2.4 g) in dichloromethane (35 mL) at 0 °C was added 8-nonen-1-ol (1 mL, 890 mg). The reaction was allowed to warm to rt over 2 h, then poured into 1 M NaOH (100 mL). The quenched mixture was extracted with Et₂O (3 x 100 mL), followed by washing the combined organic extracts with 1 M NaOH, water, and brine. Drying over sodium sulfate, followed by concentration *in vacuo* gave **43** (892 mg, 90% yield) as a colorless oil, without need for further purification: *R_f* = 0.35 (50% EtOAc in hexanes); IR (thin film, NaCl) 3421, 2929, 2856, 1457, 1058 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.66 (t, *J* = 6.6 Hz, 2H), 2.93-2.89 (m, 1H), 2.76 (dd, *J* = 5.0, 4.0 Hz, 1H), 2.46 (dd, *J* = 5.0, 2.8 Hz, 1H), 1.62-1.30 (m, 12H), 1.27 (br s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 63.7, 53.1, 47.9, 33.4, 33.2, 30.1, 30.0, 26.6, 26.3; HRMS (ESI) calcd for C₉H₁₈O₂ [M + Na]⁺ 181.1199, found 181.1196.



non-8-enoic acid, 46: To a solution of 8-nonen-1-ol (1.0 g, TCI America) in acetone (70 mL) was added Jones reagent²⁹ (0.5M CrO₃ in 2:3 conc. sulfuric acid/water, 14 mL) dropwise over 30

⁸³ O'Neal, W. G.; Roberts, W. P.; Ghosh, I.; Jacobi, P. A. *J Org. Chem.* **2005**, *70*, 7243–7251.

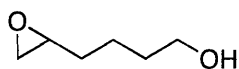
minutes. The reaction was stirred an additional 1 h at 0 °C, then *i*-PrOH (10 mL) was added dropwise to quench over 10 minutes. After stirring for 15 additional min, the mixture was poured into 1 M HCl (100 mL) and extracted with Et₂O (3 x 50 mL). The combined organic extracts were washed with 1 M HCl (50 mL), water, and brine, and dried over sodium sulfate. After concentration, **46** was obtained as a yellow sticky solid (730 mg, 66% yield), which was used without further purification. NMR spectral data were consistent with reported values.⁸⁴



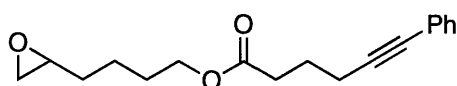
7-(oxiran-2-yl)heptanoic acid, 47: To a solution of **46** (360 mg) in dichloromethane (69 mL) at 0 °C was added freshly prepared dimethyldioxirane⁸⁵ (69 mL, 0.08M in acetone). The reaction was stirred 30 min at 0 °C, then concentrated to give **47** (392 mg, 100% yield), without need for further purification: IR (thin film, NaCl) 2933, 2859, 1734, 1709, 1464, 1411, 1256, 1181, 1108, 914, 834 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 11.3 (br s, 1H), 2.93-2.89 (m, 1H), 2.76 (dd, *J* = 4.8, 4.1 Hz, 1H), 2.47 (dd, *J* = 5.0, 2.8 Hz, 1H), 2.36 (t, *J* = 7.4 Hz, 2H), 1.62 (app qt, *J* = 7.4 Hz, 2H), 1.57-1.26 (m, 8H); ¹³C NMR (125 MHz, CDCl₃) δ 180.5, 53.1, 47.9, 34.6, 33.0, 29.7, 29.6, 26.5, 25.2; HRMS (ESI) calcd for C₉H₁₆O₃ [M + Na]⁺ 195.0992, found 195.0988.

⁸⁴ Goudreau, N.; Brochu, C.; Cameron, D.R.; Duceppe, J.-S.; Faucher, A.-M.; Ferland, J.-M.; Grand-Maitre, C.; Poirier, M.; Simoneau, B.; Tsantrizos, Y. S. *J. Org. Chem.* **2004**, *69*, 6185-6201.

⁸⁵ Murray, R. W.; Singh, M. *Org. Synth.* **1997**, *74*, 91-97.

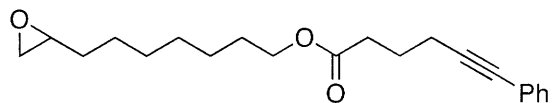


4-(oxiran-2-yl)butan-1-ol, 49: Synthesized according to a reported procedure.⁸⁶ NMR spectral data were consistent with reported values.

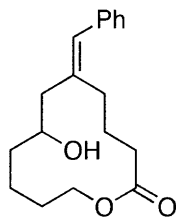


4-(oxiran-2-yl)butyl 6-phenylhex-5-ynoate, 50: To a 25 mL round bottom flask were added DCC (578 mg), DMAP (40 mg), and dichloromethane (14 mL). The reaction mixture was cooled to 0 °C. Alcohol **49** (330 mg) and ynoic acid **6a** (540 mg) were added concurrently. After stirring for 30 minutes, TLC showed complete disappearance of **49**. Silica gel (500 mg) was added directly and the volatiles removed *in vacuo*. Flash column chromatography (5% EtOAc in hexanes) gave the title compound as a colorless oil (520 mg, 65% yield): $R_f = 0.44$ (30% EtOAc in hexanes); IR (thin film, NaCl) 2918, 1996, 1731, 1490, 1156, 757 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.38-7.32 (m, 2H), 7.27-7.21 (m, 3H), 4.07 (t, $J = 6.5$ Hz, 2H), 2.89-2.84 (m, 1H), 2.71 (dd, $J = 5.0, 4.0$ Hz, 1H), 2.47 (t, $J = 7.4$ Hz, 2H), 2.45 (t, $J = 7.3$ Hz, 2H), 2.43 (dd, $J = 5.0, 2.7$ Hz, 1H), 1.89 (app qt, $J = 7.3$ Hz, 2H), 1.70-1.42 (m, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 174.0, 132.3, 128.9, 128.4, 124.4, 89.5, 82.1, 64.9, 52.8, 47.7, 33.8, 32.8, 29.1, 24.6, 23.2, 19.6; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{22}\text{O}_3$ $[\text{M} + \text{Na}]^+$ 309.1461, found 309.1459.

⁸⁶ Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *J. Org. Chem.* **2003**, *68*, 8248–8251.

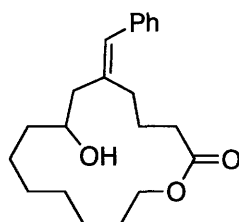


7-(oxiran-2-yl)heptyl 6-phenylhex-5-ynoate, 48: To a 25 mL round bottom flask were added DCC (312 mg), DMAP (19 mg), and dichloromethane (13 mL). The reaction mixture was cooled to 0 °C. Alcohol **43** (200 mg) and ynoic acid **6a** (285 mg) were added concurrently. After stirring for 30 minutes, TLC showed complete disappearance of **43**. Silica gel (250 mg) was added directly and the volatiles removed *in vacuo*. Flash column chromatography (5% EtOAc in hexanes) gave the title compound as a colorless oil (172 mg, 42% yield): $R_f = 0.55$ (30% EtOAc in hexanes); IR (thin film, NaCl) 2926, 2856, 1733, 1490, 1457, 1158 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.43-7.37 (m, 2H), 7.32-7.25 (m, 3H), 4.09 (t, $J = 6.8$ Hz, 2H), 2.94-2.88 (m, 1H), 2.75 (dd, $J = 5.0, 4.0$ Hz, 1H), 2.52 (t, $J = 7.3$, 2H), 2.49 (t, $J = 7.1$ Hz, 2H), 2.47 (dd, $J = 5.0, 2.8$ Hz, 1H), 1.94 (app qt, $J = 7.2$ Hz, 2H), 1.68-1.28 (m, 12H); ^{13}C NMR (125 MHz, CDCl_3) δ 174.0, 132.3, 128.9, 128.4, 124.4, 89.6, 82.1, 65.3, 53.1, 47.8, 33.9, 33.2, 30.0, 29.9, 29.3, 26.6, 26.5, 24.6, 19.6; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{28}\text{O}_3$ $[\text{M} + \text{Na}]^+$ 351.1931, found 351.1929.

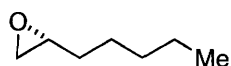


(E)-6-benzylidene-8-hydroxyoxacyclododecan-2-one, 51: Complete purification was not feasible, due to the presence of impurities that coeluted during flash column chromatography.

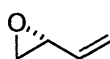
Structure assigned based on ^{13}C NMR spectral data, HRMS, IR, and comparison of impure ^1H NMR spectral data to ^1H NMR data of structurally similar compounds: $R_f = 0.16$ (30% EtOAc in hexanes), $R_f = 0.38$ (60% EtOAc in hexanes); IR (thin film, NaCl) 3433, 2921, 1728, 1456, 1240, 1153, 1072, 1047, 750, 699 cm^{-1} ; ^{13}C NMR (125 MHz, CDCl_3) δ 173.6, 139.6, 138.3, 130.1, 129.20, 129.18, 129.0, 68.7, 65.0, 43.5, 35.8, 35.5, 29.1, 27.1, 24.1, 21.5; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{24}\text{O}_3$ $[\text{M} + \text{Na}]^+$ 311.1618, found 311.1621.



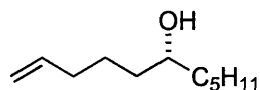
(E)-6-benzylidene-8-hydroxyoxacyclo-pentadecan-2-one, 52: $R_f = 0.34$ (30% EtOAc in hexanes); IR (thin film, NaCl) 3433, 2930, 2857, 1730, 1492, 1459, 1247, 1126, 1048, 748, 699 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.37-7.30 (m, 2H), 7.26-7.18 (m, 3H), 6.43 (s, 1H), 4.34 (ddd, $J = 11.0, 6.7, 3.1$ Hz, 1H), 3.99 (ddd, $J = 11.0, 8.2, 2.8$ Hz, 1H), 3.81-3.75 (m, 1H), 2.59 (dd, $J = 13.5, 2.8$ Hz, 1H), 2.51-2.41 (m, 1H), 2.28 (ddd, $J = 14.7, 9.5, 5.2$ Hz, 1H), 2.10 (ddd, $J = 13.2, 12.2, 5.2$ Hz, 1H), 2.10 (dd, $J = 13.5, 9.0$ Hz, 1H), 2.10-1.90 (m, 1H), 1.87-1.15 (m, 14H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.8, 139.9, 138.1, 130.3, 129.2, 129.0, 127.3, 69.0, 65.4, 45.6, 36.2, 35.8, 30.7, 28.8, 28.0, 27.8, 26.2, 25.2, 23.9; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{30}\text{O}_3$ $[\text{M} + \text{Na}]^+$ 353.2087, found 353.2085.



(R)-1,2-epoxyheptane: Prepared in 46% yield and >99% e.e. according to a reported procedure.^{13, 14} NMR spectral and chiral HPLC data were consistent with reported values.¹³



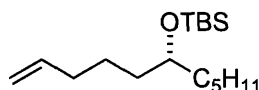
(R)-butadiene monoxide, 8: Prepared in 32% yield and >99% e.e. according to a reported procedure.¹⁴ NMR spectral and chiral HPLC data were consistent with reported values.



(R)-undec-1-en-6-ol, 9a: A 500 mL flame-dried round bottom flask was charged with THF (285 mL), magnesium metal (2.0 g), and 1-bromo-3-butene (8.1 mL). After refluxing for 30 min, the reaction mixture was cooled to 0 °C and copper iodide (1.1 g) and (R)-1,2-heptene-oxide (6.7 g) in THF (60 mL) was added. The reaction was warmed to rt and stirred for 2 h, upon which TLC showed complete consumption of starting material. The reaction was poured onto ice. Water (200 mL) and 1 M HCl (200 mL) were added, and the mixture was extracted with Et₂O (3 x 200 mL). The combined organic extracts were washed with water and brine and dried over magnesium sulfate. After concentration *in vacuo*, the copper salts were removed by filtration

through a plug of silica gel (30% EtOAc in hexanes used as eluent) to give **9a** (9.6 g, 99% yield).

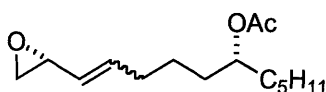
NMR spectral data were consistent with reported values.⁸⁷



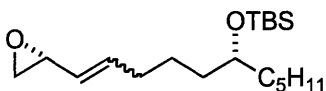
(R)-tert-butyltrimethyl(undec-1-en-6-yloxy)silane, 9c: A 250 mL round bottom flask was charged with alcohol **9a** (3.5 g), 2,6-lutidine (4.8 mL), and dichloromethane (100 mL) and cooled to 0 °C. To the reaction mixture was then added *t*-BuMe₂SiOTf (6 mL) dropwise over 5 min. The reaction was allowed to warm to rt and stirred overnight. The reaction was poured into ice water (200 mL) to quench. The dichloromethane layer was separated, and the aqueous layer was extracted with Et₂O (3 x 100 mL). The combined organics were washed with brine and dried over magnesium sulfate. Flash column chromatography (1% EtOAc in hexanes) of the concentrated crude residue gave **9c** (5.95 g, 100% yield) as a clear oil: IR (thin film, NaCl) 2930, 2858, 1462, 1377, 1073, 835, 773 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.86 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H), 5.02 (ddt, *J* = 17.1, 2.1, 1.6 Hz, 1H), 4.98-4.94 (m, 1H), 3.86 (app qt, *J* = 5.7 Hz, 1H), 2.04 (m, 2H), 1.5-1.22 (m, 12H), 0.91 (s, 9H), 0.91 (t, *J* = 7.1 Hz, 3H), 0.06 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 139.2, 114.5, 37.4, 36.7, 34.2, 32.3, 26.2, 25.2, 24.9, 22.9, 18.4, 14.3, -4.19, -4.18; HRMS (ESI) calcd for C₁₇H₃₆OSi [M + Na]⁺ 307.2433, found 307.2432.

⁸⁷ Fürstner, A.; Mueller, T. *J. Org. Chem.* **1998**, *63*, 424–425.

Representative procedure for cross metathesis of 8 and 9 to make 7: A 250 mL round bottom flask was charged with **8b** (1.7 g, 6 mmol), **9** (1.93 mL) and dichloromethane (55 mL). A solution of second generation Hoveyda-Grubbs catalyst (185 mg, Aldrich) in dichloromethane (5 mL) was then added dropwise over 8 hours via syringe pump. The reaction was stirred an additional 6 hours, then Et₃N (1 mL) and silica (4 g) were added and the mixture was concentrated *in vacuo*. Flash column chromatography (gradient solvent system: 1% EtOAc and 1% Et₃N in hexanes to 2.5% EtOAc and 1% Et₃N in hexanes) gave **7b** as a pale yellow oil (970 mg, 49% yield) and **8b** (recovered starting material, 680 mg).



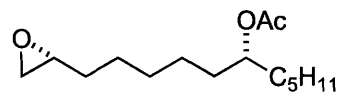
(R)-1-((R)-oxiran-2-yl)undec-1-en-6-yl ethanoate, 7a: Due to the sensitivity of this compound to silica gel chromatography, the impure mixture obtained after flash column chromatography was tentatively assigned as ~5:1 mixture of olefin diastereomers by ¹H NMR spectral analysis (with ~5% of a corresponding aldehyde present in spectrum). The mixture was carried onward without complete purification.



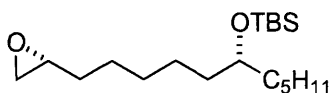
tert-butyl dimethyl((R)-1-((R)-oxiran-2-yl)undec-1-en-6-yl)oxy silane, 7b: Due to the sensitivity of this compound to silica gel chromatography, the impure mixture obtained after

flash column chromatography was tentatively assigned as ~4:1 mixture of olefin diastereomers by ^1H NMR spectral analysis (with ~5% of a corresponding aldehyde present in spectrum). The mixture was carried onward without complete purification.

Representative procedure for the reduction of 7 to 5: A 100 mL round bottom flask was charged with Wilkinson's catalyst (290 mg, Strem) and benzene (20 mL). Nitrogen was bubbled through the mixture for 10 minutes. Hydrogen was then bubbled through the mixture for 10 minutes, and **7b** (2.02 g) was added. The reaction was stirred under a balloon of hydrogen for 12 hours, then flushed with nitrogen and concentrated *in vacuo*. Purification by flash column chromatography (5% EtOAc in hexanes) gave **5b** (1.65 g, 82% yield) as a colorless oil.

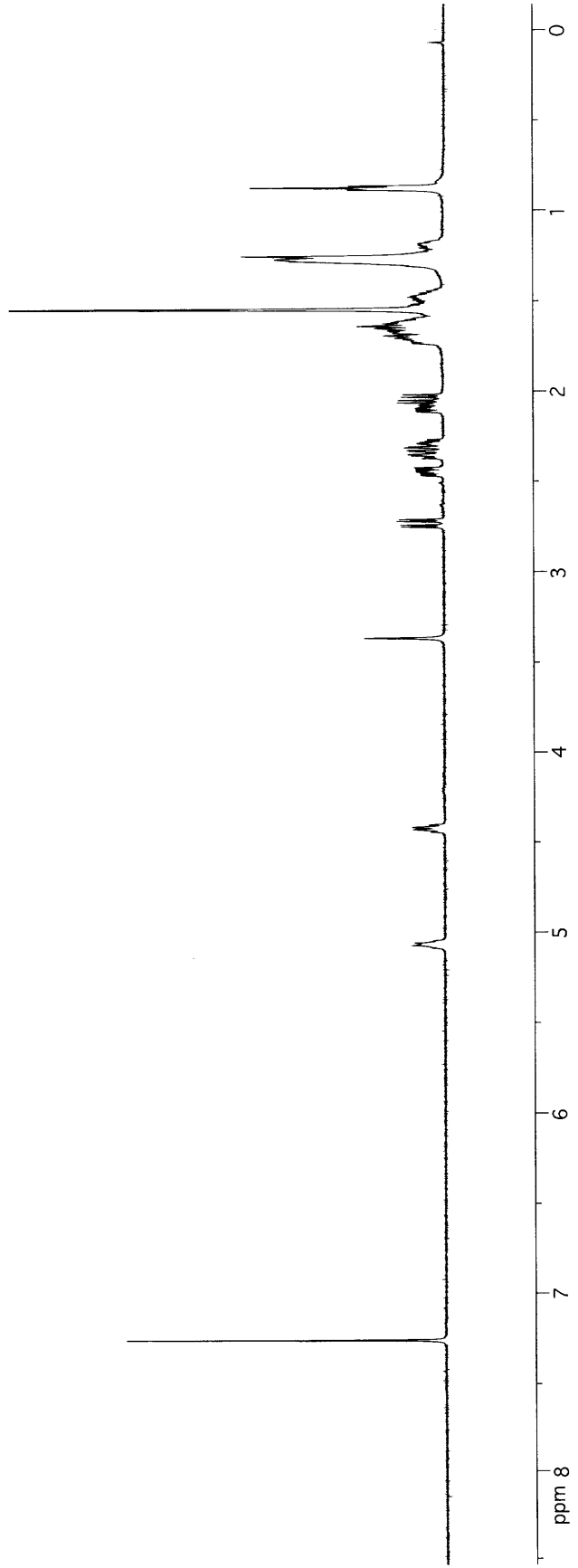
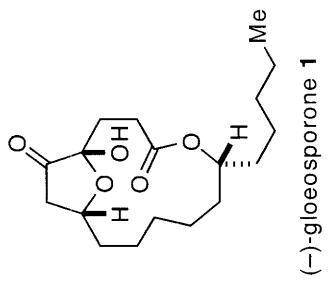


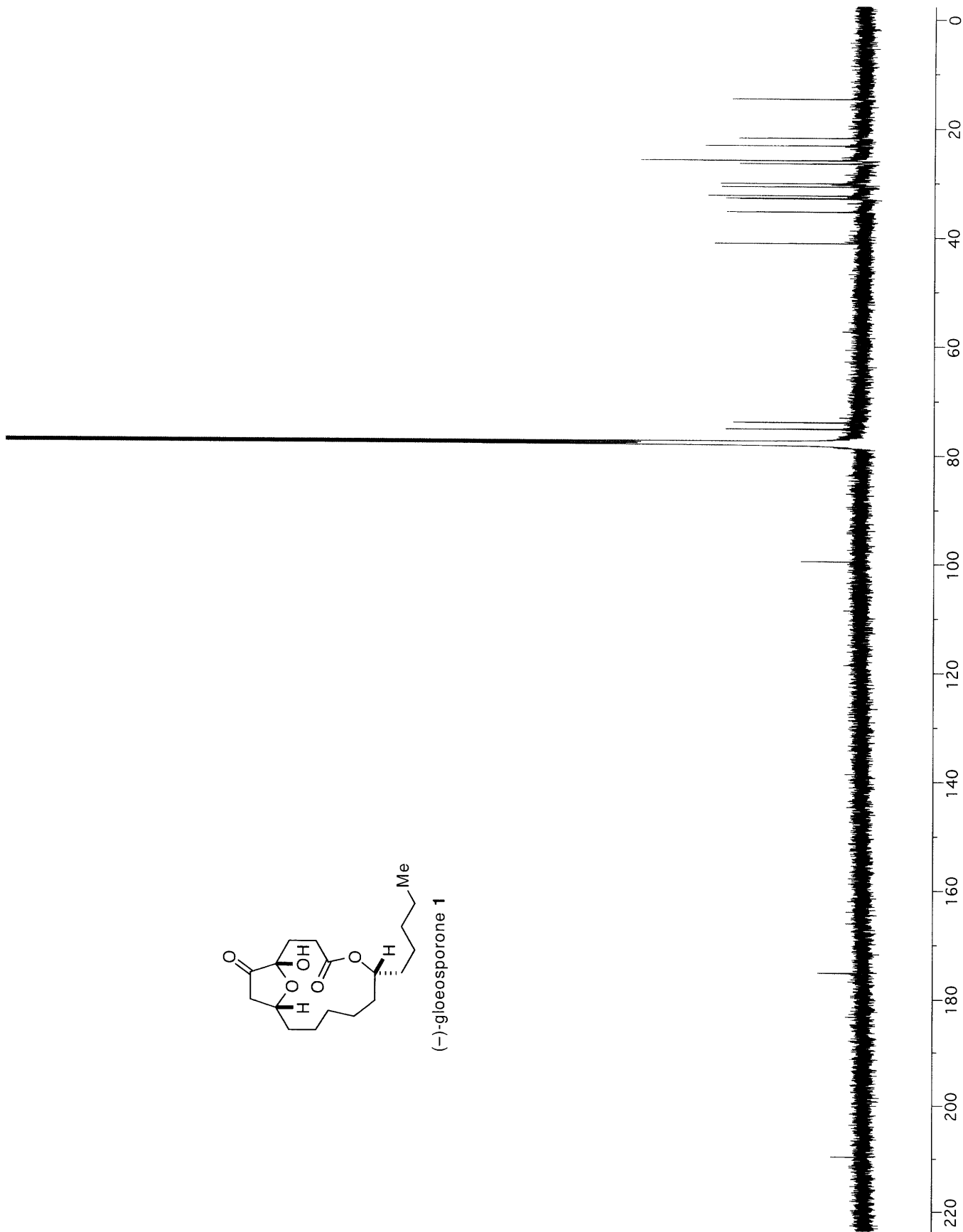
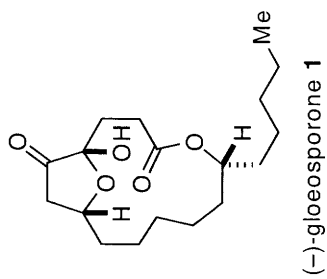
(R)-1-((R)-oxiran-2-yl)undecan-6-yl ethanoate, 5b: $R_f = 0.30$ (10% EtOAc in hexanes); IR (thin film, NaCl) 2932, 2860, 1736, 1465, 1373, 1243, 1021 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.87 (app qt, $J = 6.2$ Hz, 1H), 2.93-2.88 (m, 1H), 2.76 (dd, $J = 5.2, 4.3$ Hz, 1H), 2.47 (dd, $J = 5.2, 2.7$ Hz, 1H), 2.05 (s, 3H), 1.57-1.2 (m, 18H), 0.89 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.7, 75.0, 47.8, 34.8, 34.7, 33.1, 32.4, 30.0, 26.6, 25.9, 25.7, 23.2, 22.0, 14.7; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{28}\text{O}_3$ $[\text{M} + \text{Na}]^+$ 279.1931, found 279.1934.

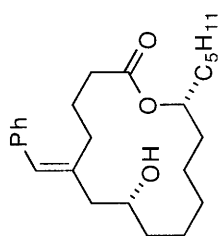


***tert*-butyldimethyl((*R*)-1-((*R*)-oxiran-2-yl)undecan-6-yloxy)silane, 5c:** $R_f = 0.52$ (10% EtOAc/hexanes); IR (thin film, NaCl) 2930, 2857, 1733, 1463, 1376, 1255, 1129, 1058, 835, 773 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.63 (app qt, $J = 5.7$ Hz, 1H), 2.94-2.90 (m, 1H), 2.76 (dd, $J = 5.0, 4.0$ Hz, 1H), 2.48 (dd, $J = 5.0, 2.8$ Hz, 1H), 1.57-1.21 (m, 18H), 0.91-0.88 (m, 12H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 73.0, 53.1, 47.9, 37.8, 37.7, 33.2, 32.8, 30.4, 26.7, 26.6, 26.0, 25.7, 23.4, 14.8, -3.70, -3.71; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{40}\text{O}_2\text{Si}$ $[\text{M} + \text{Na}]^+$ 351.2690, found 351.2692.

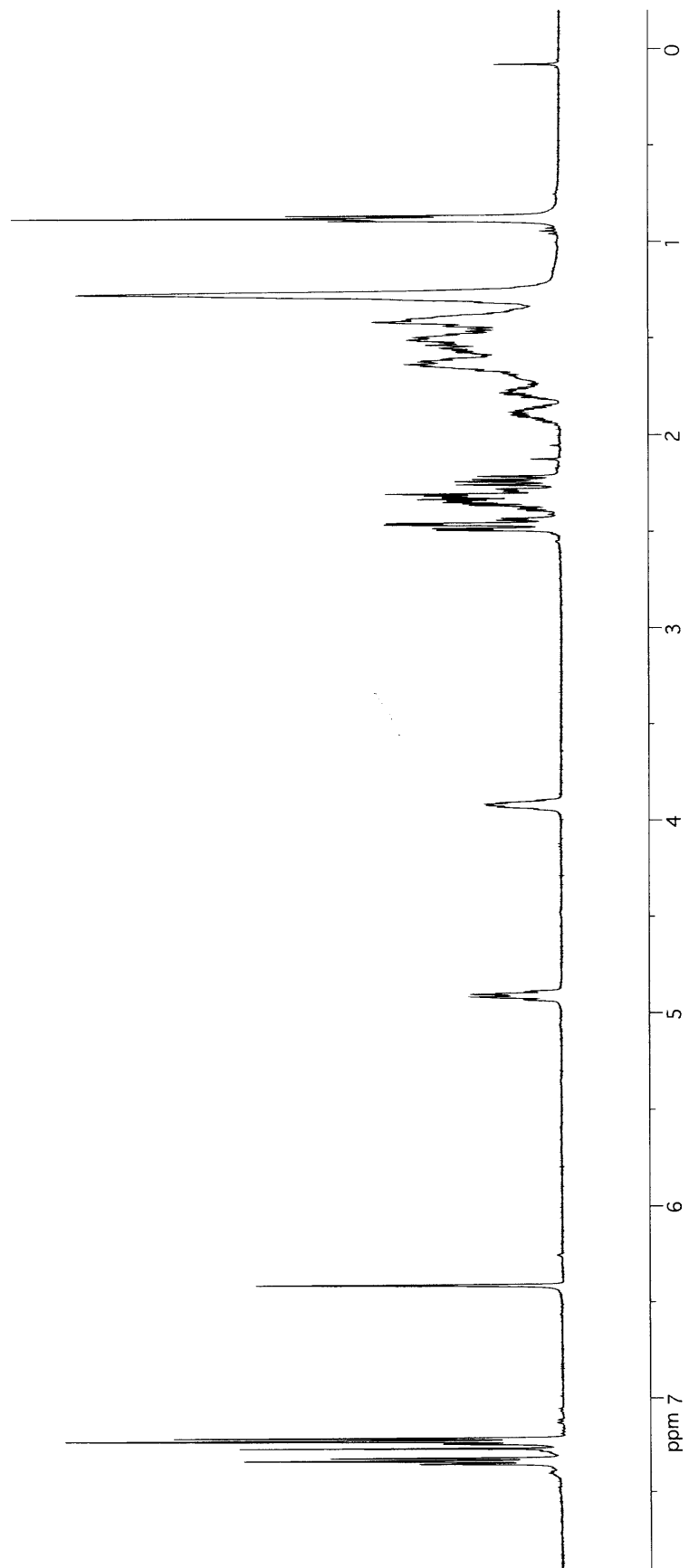
Chapter 2: Spectra

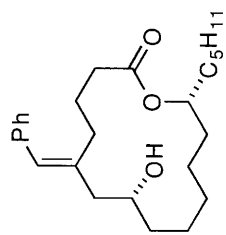




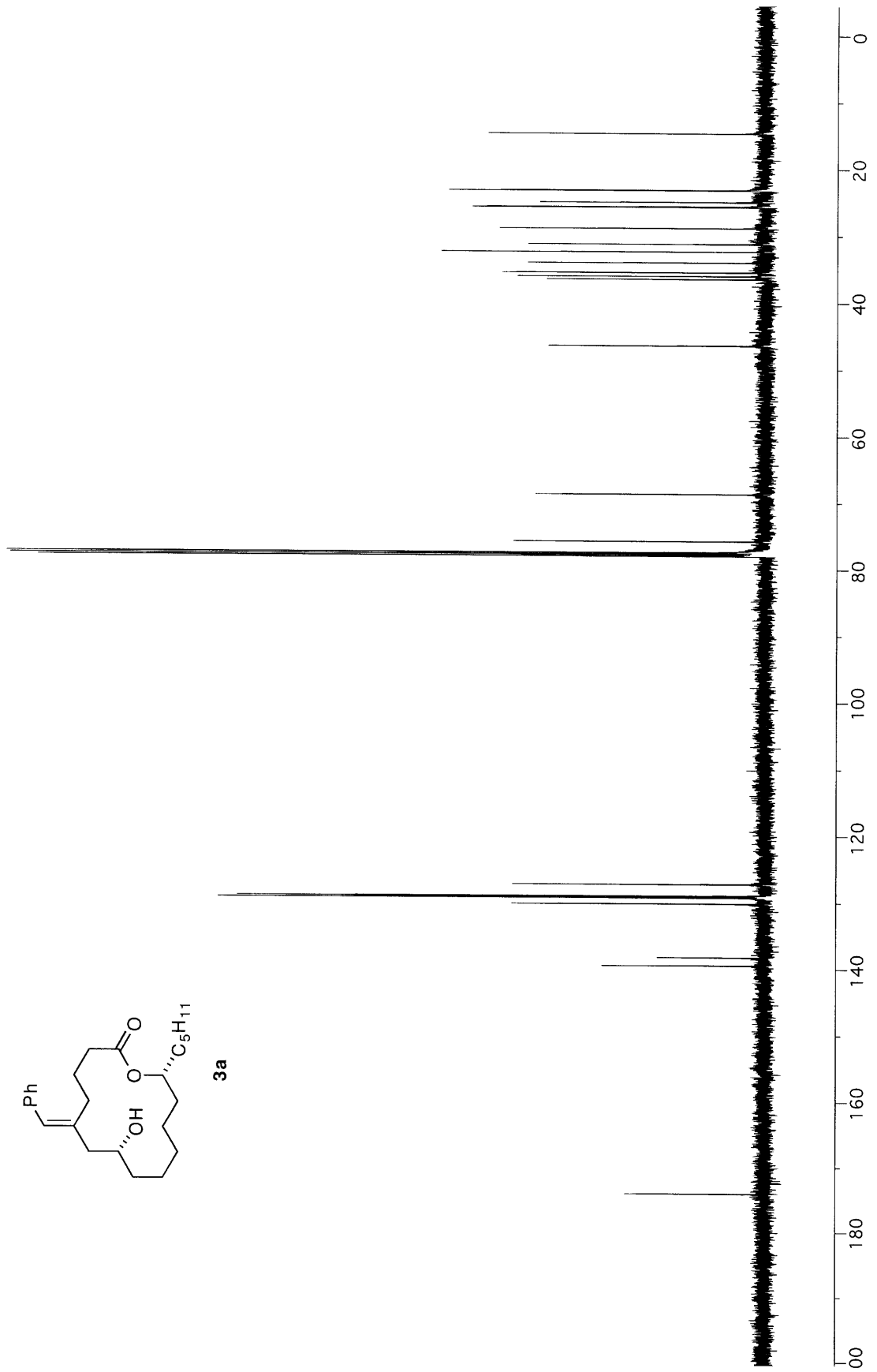


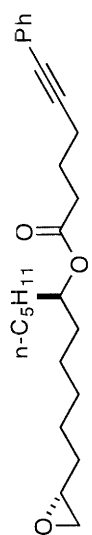
3a



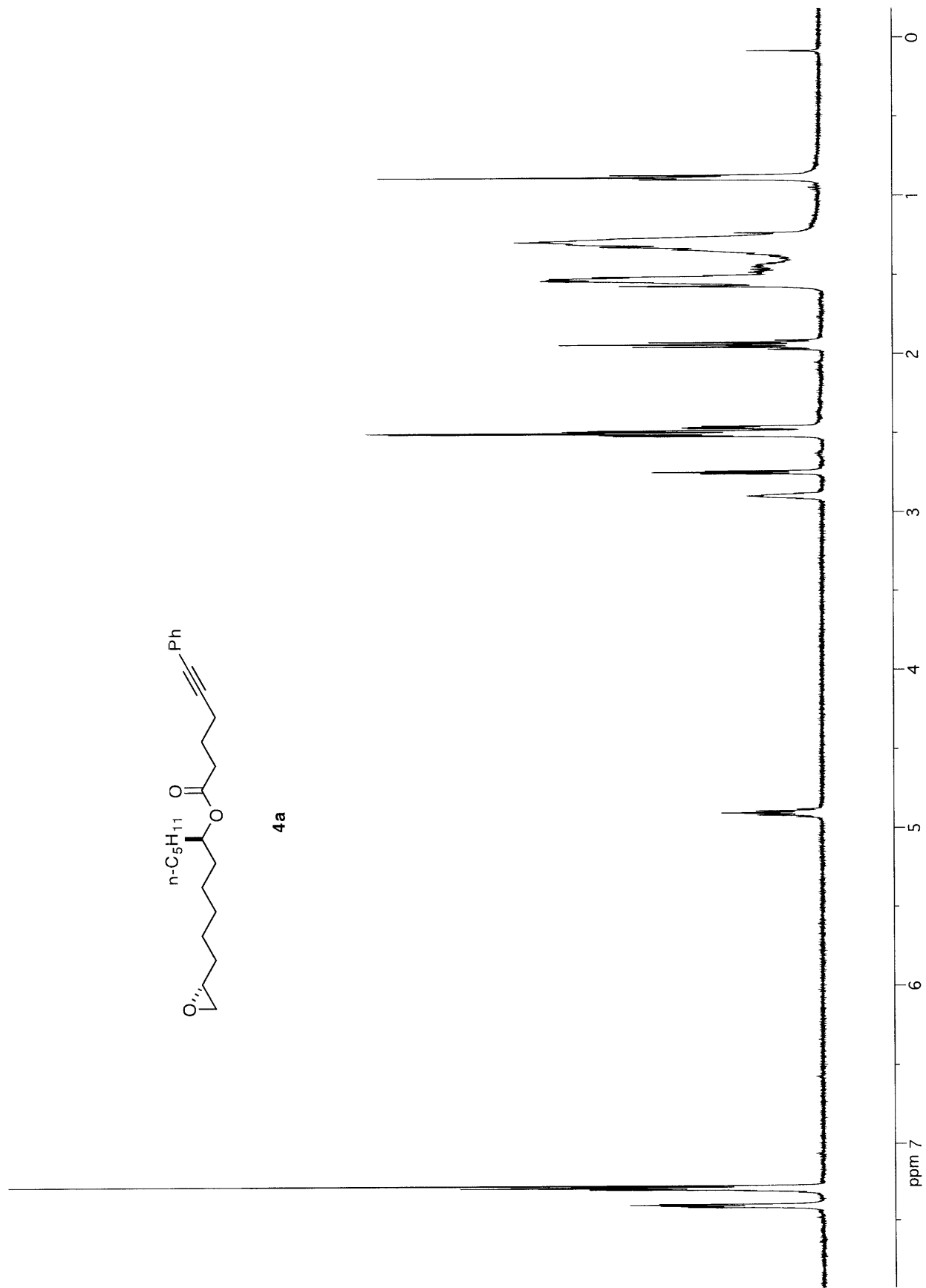


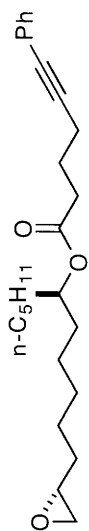
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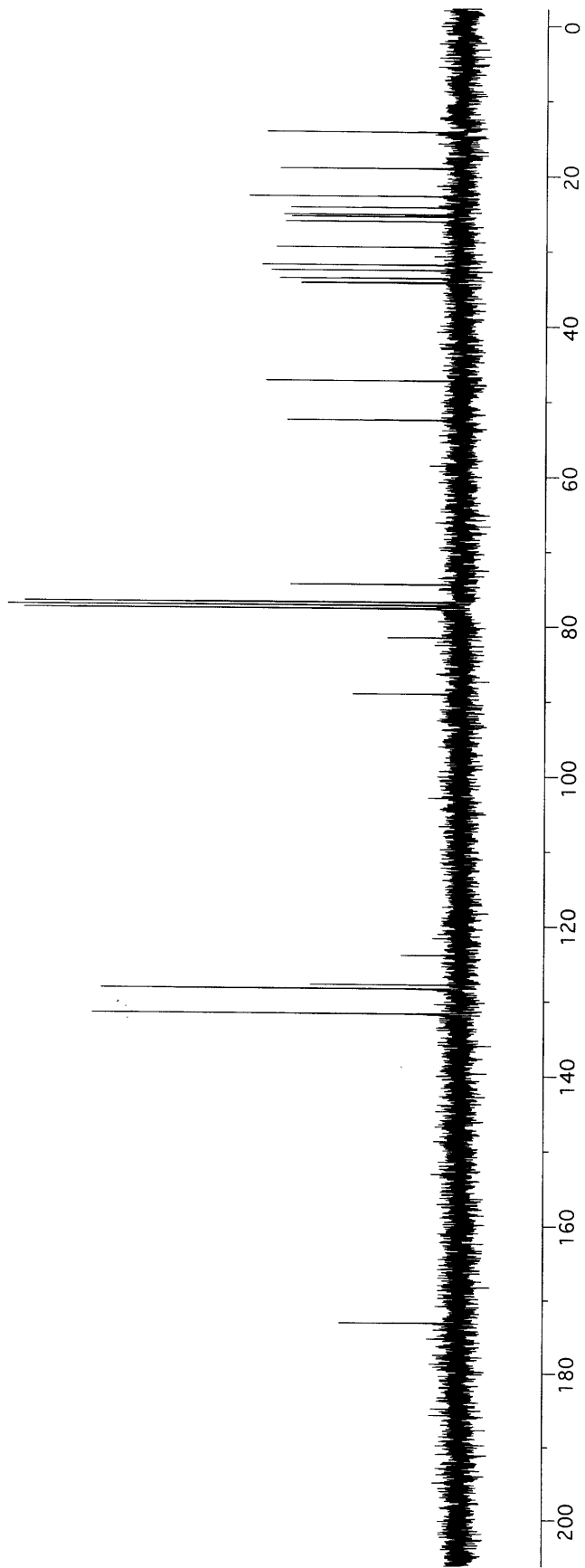


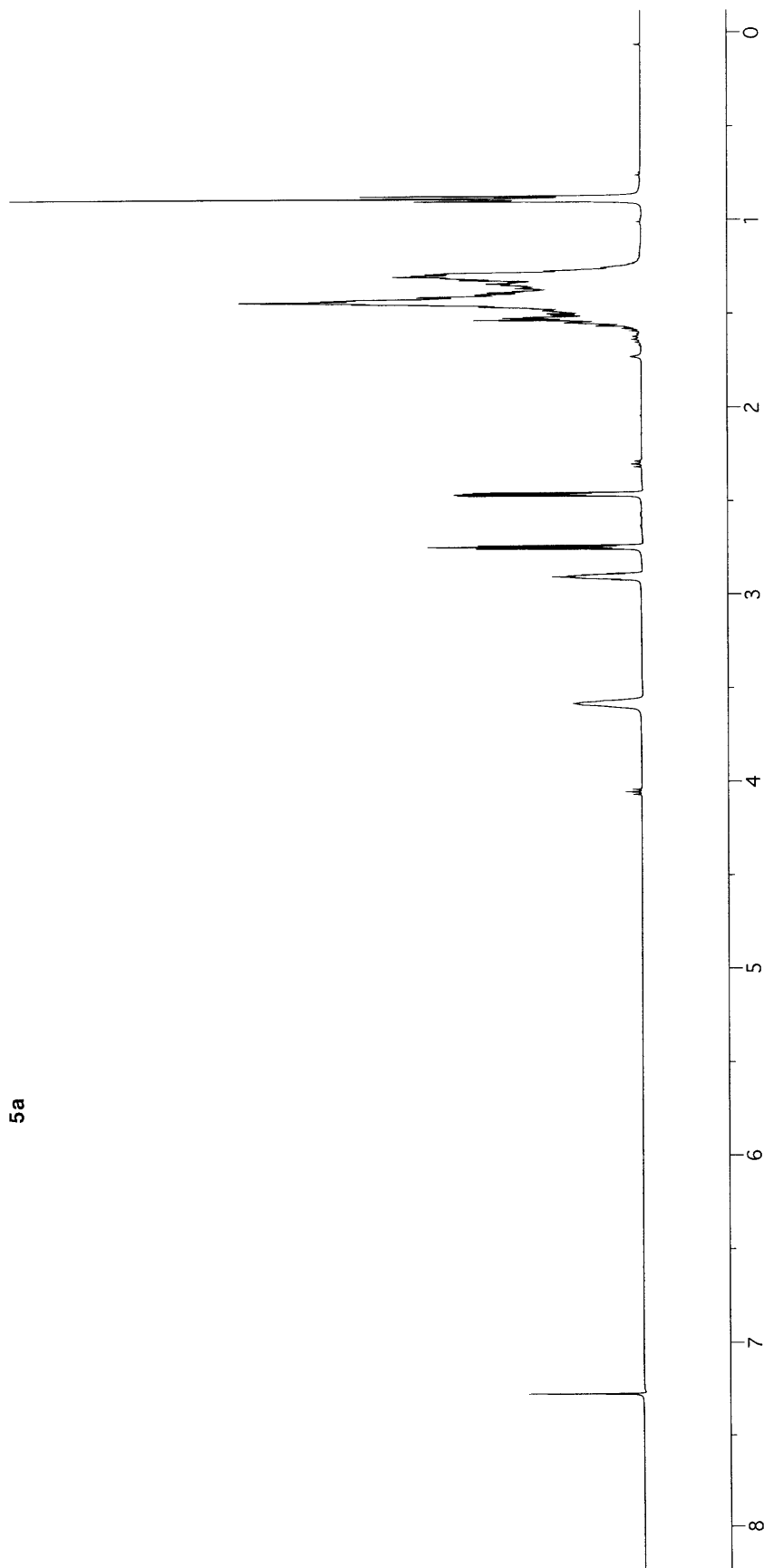
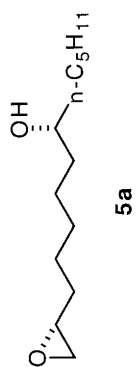
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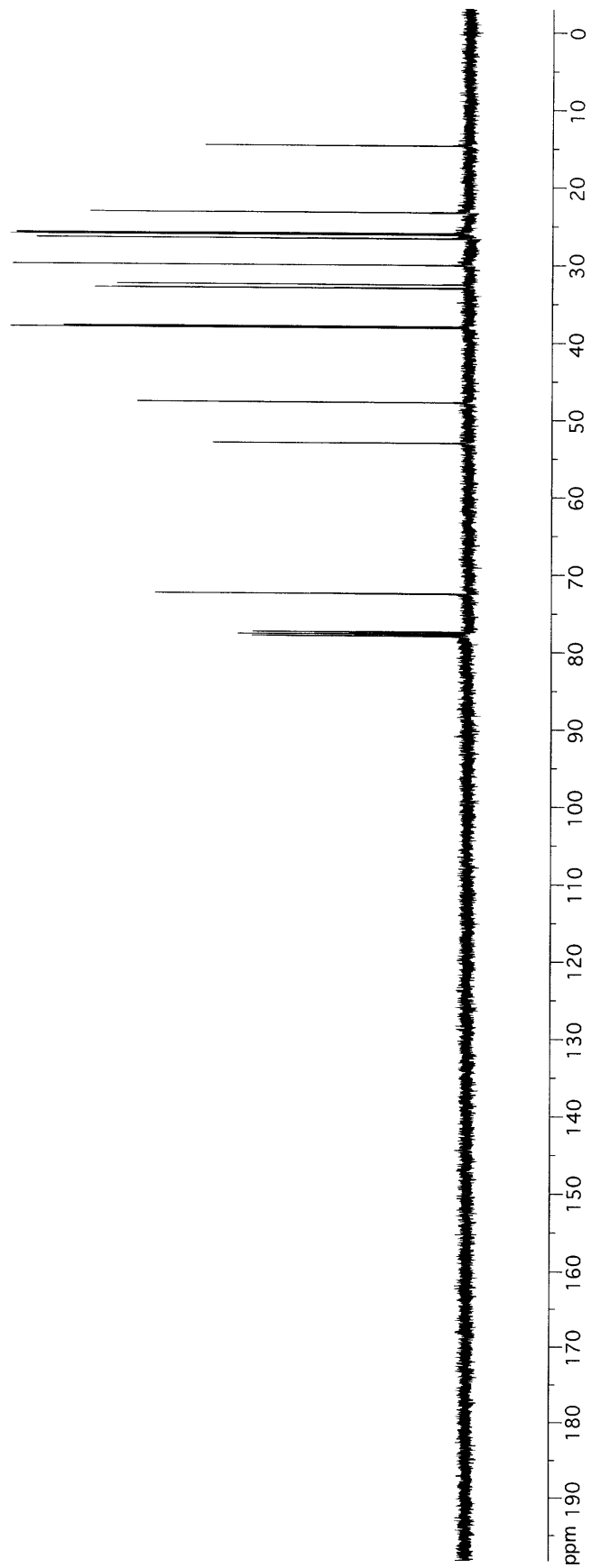
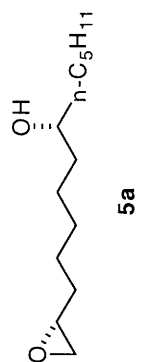


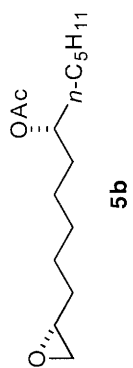


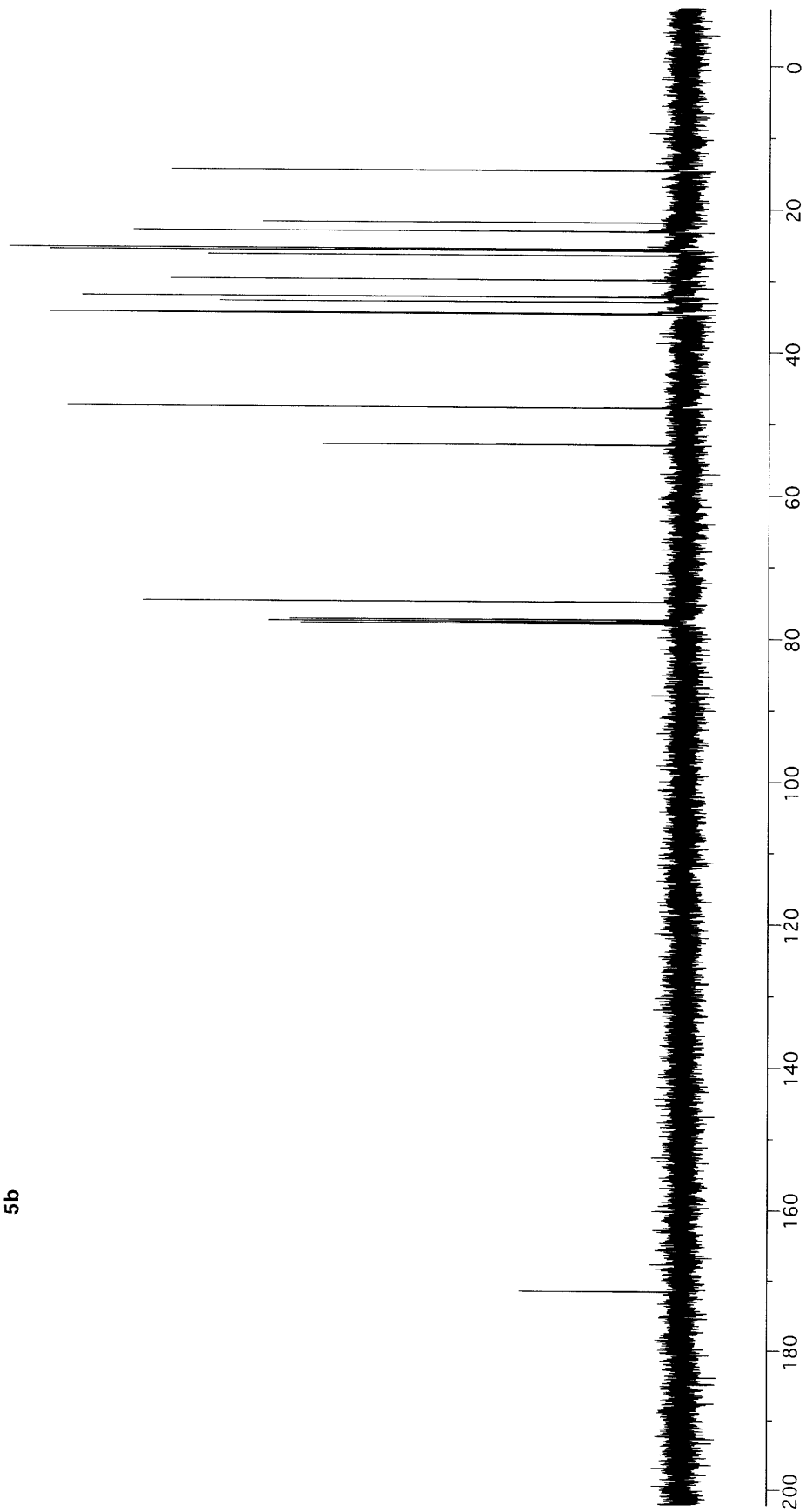
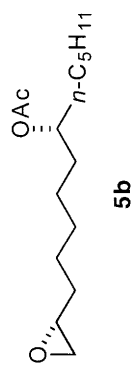
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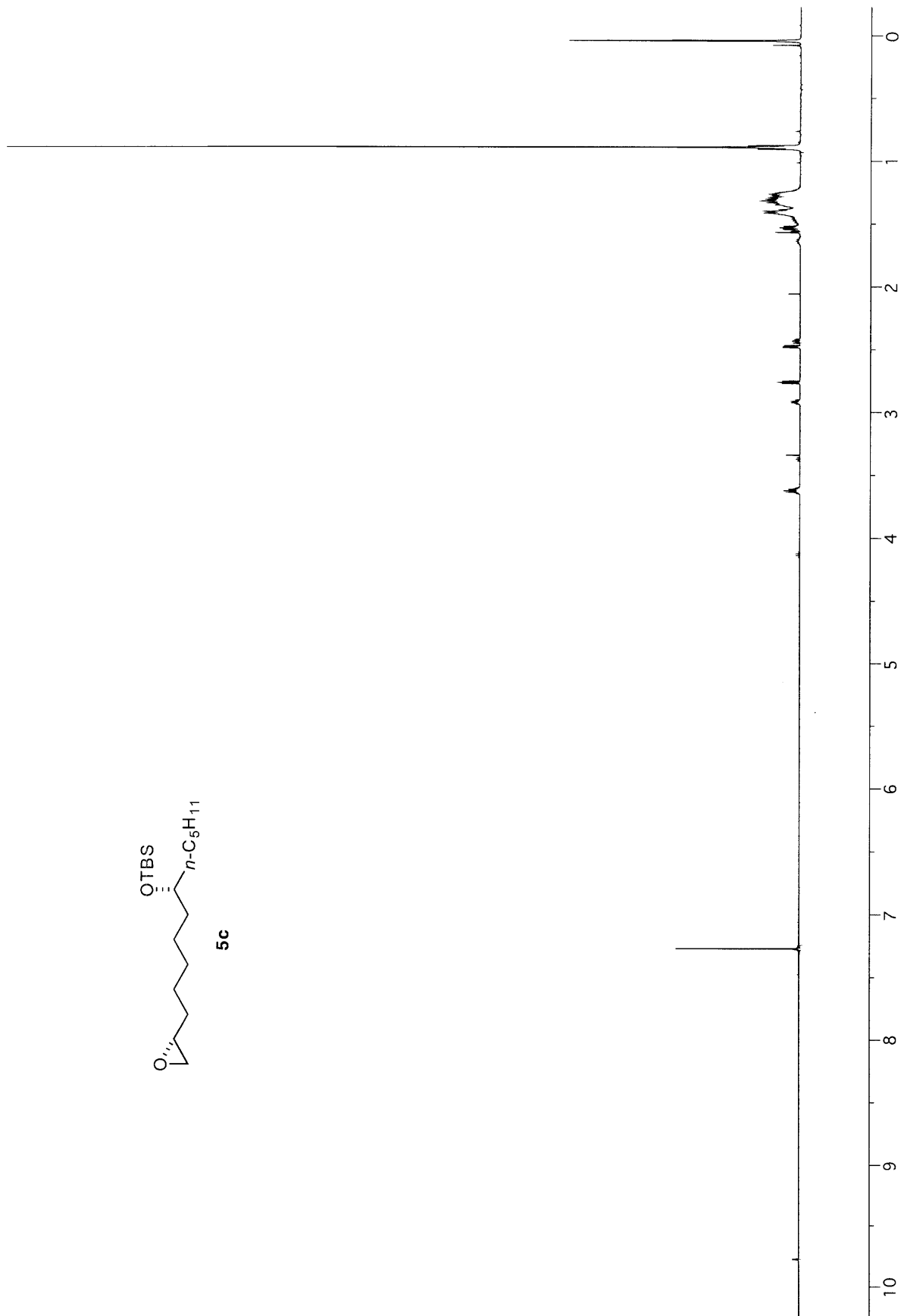
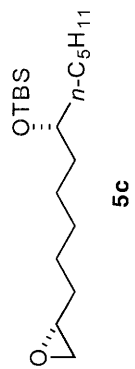


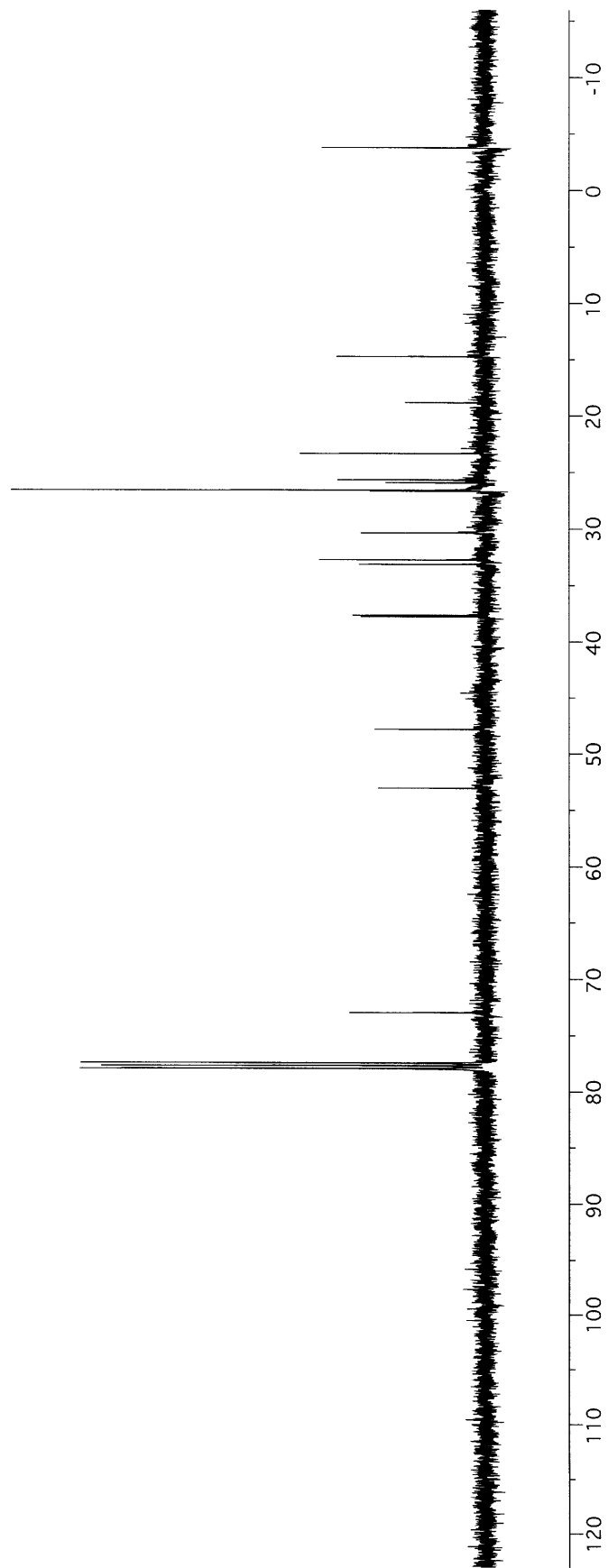
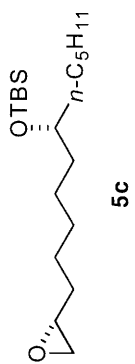


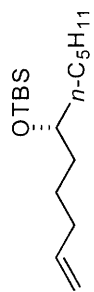




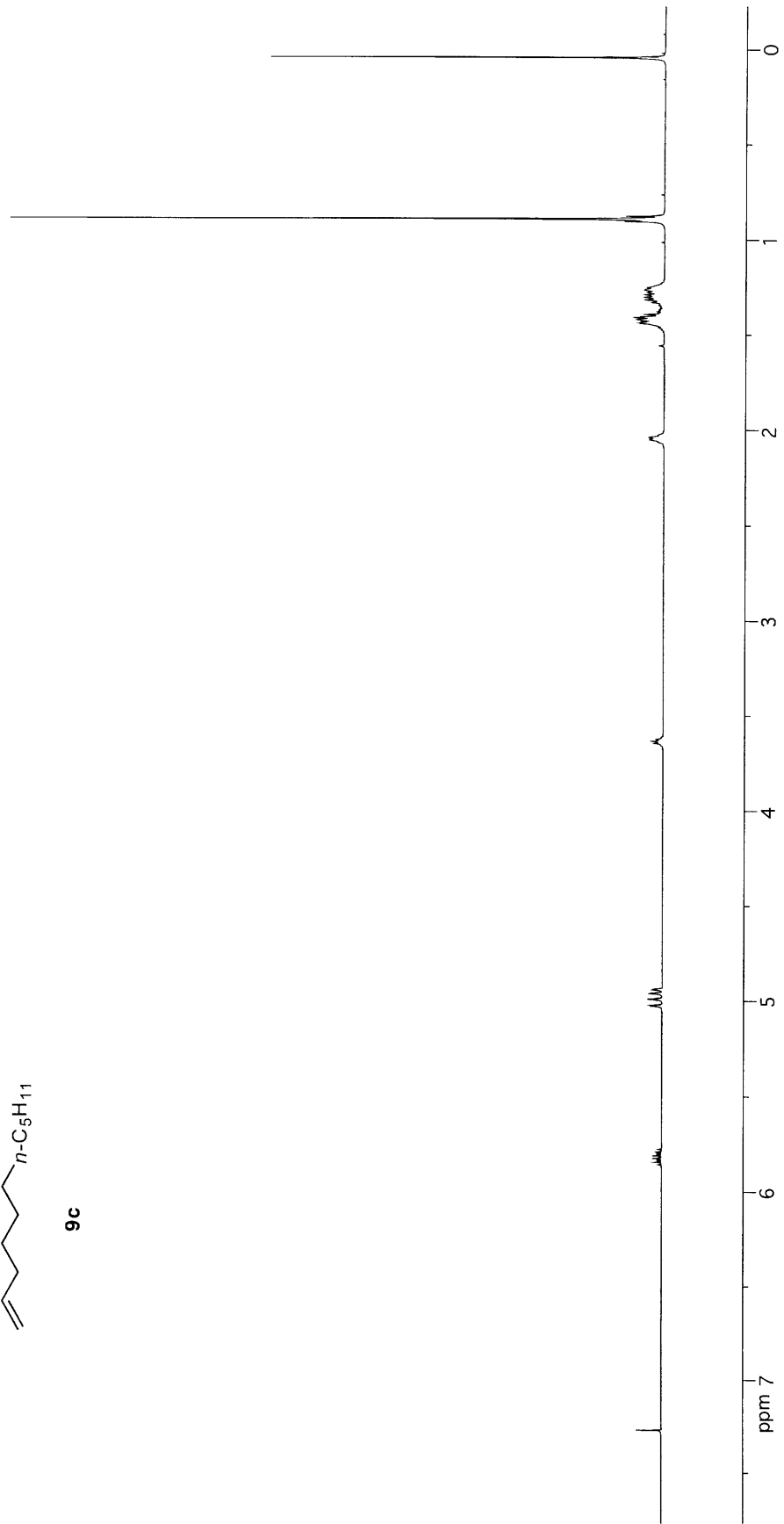


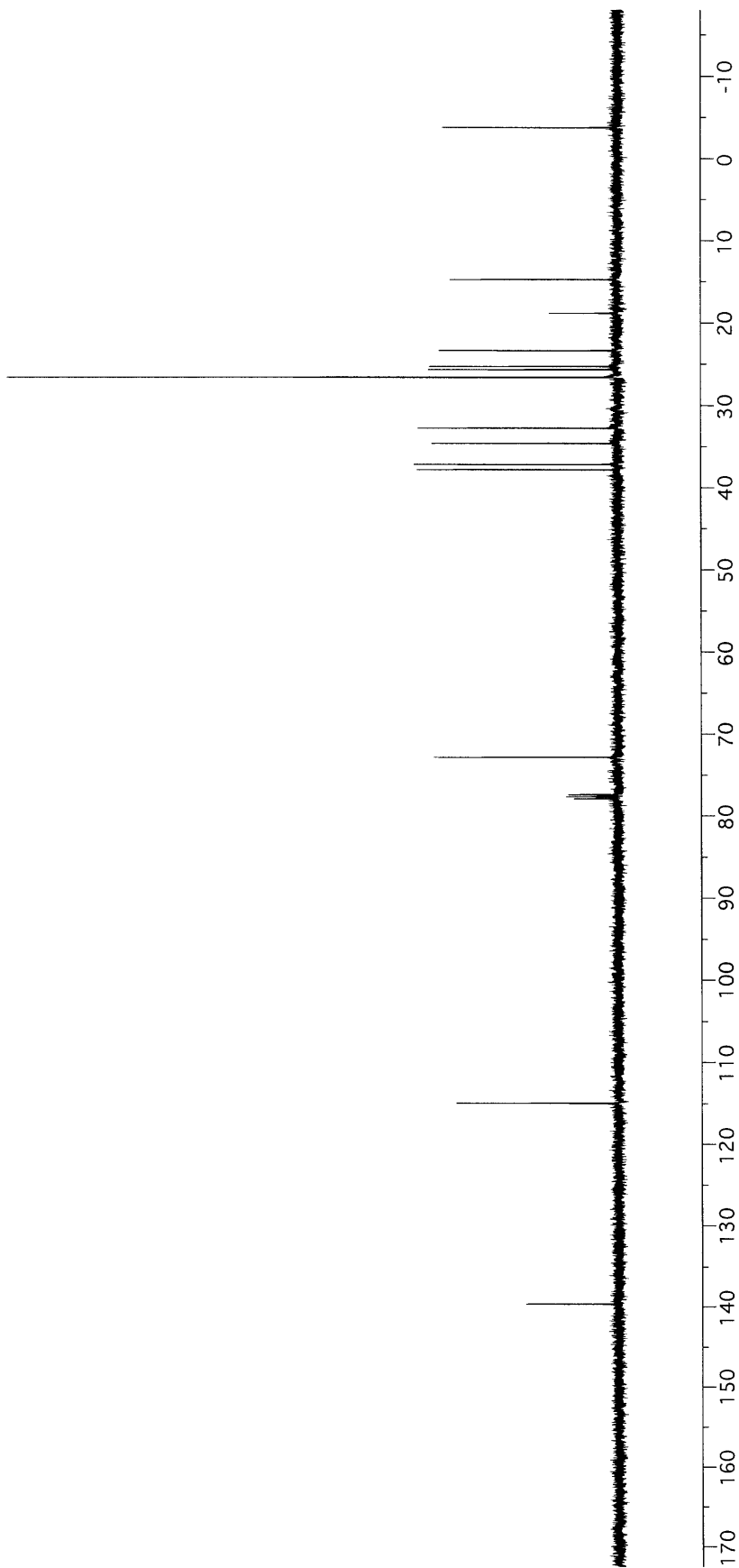
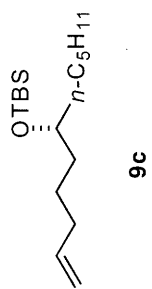






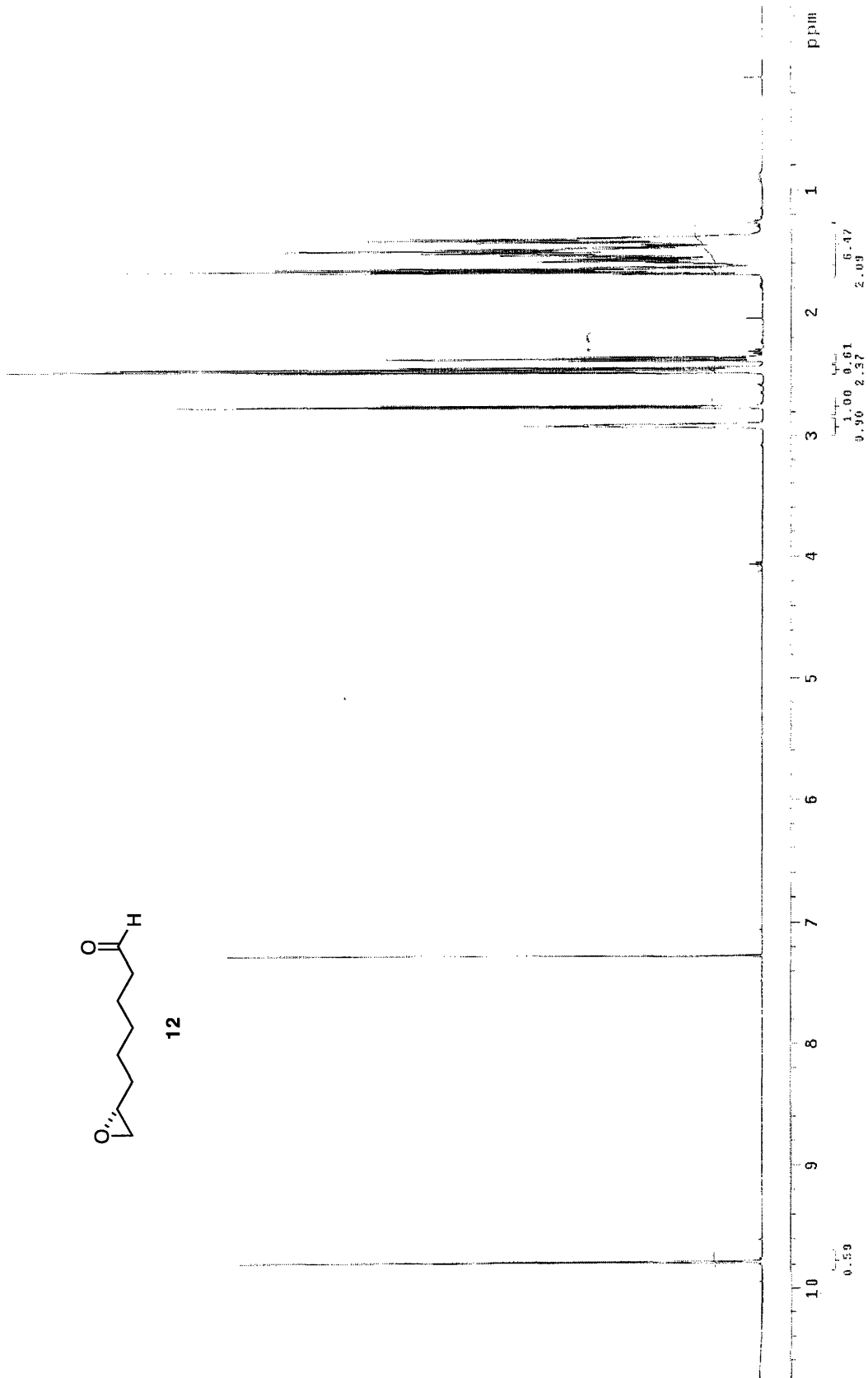
9c





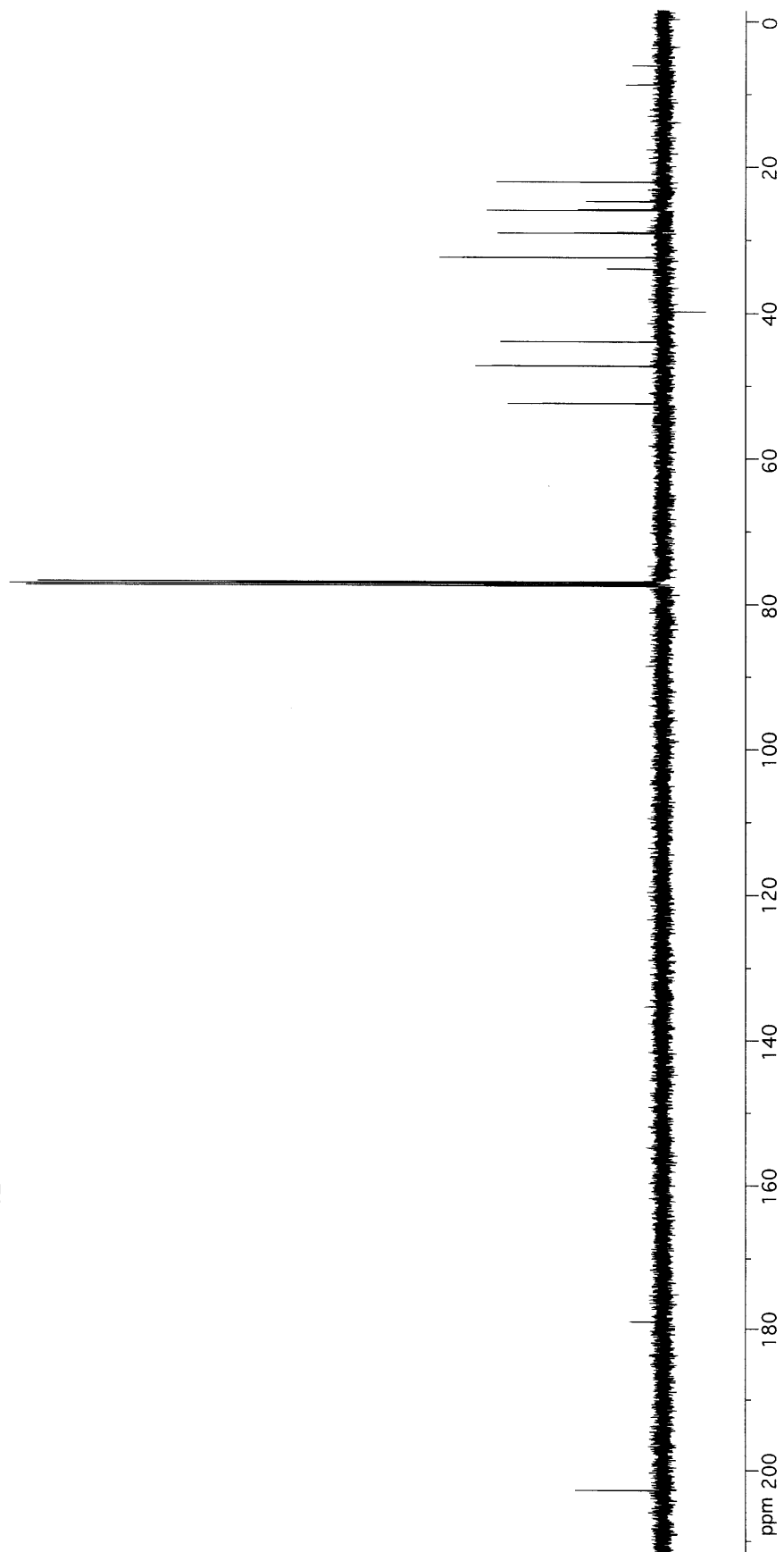


12



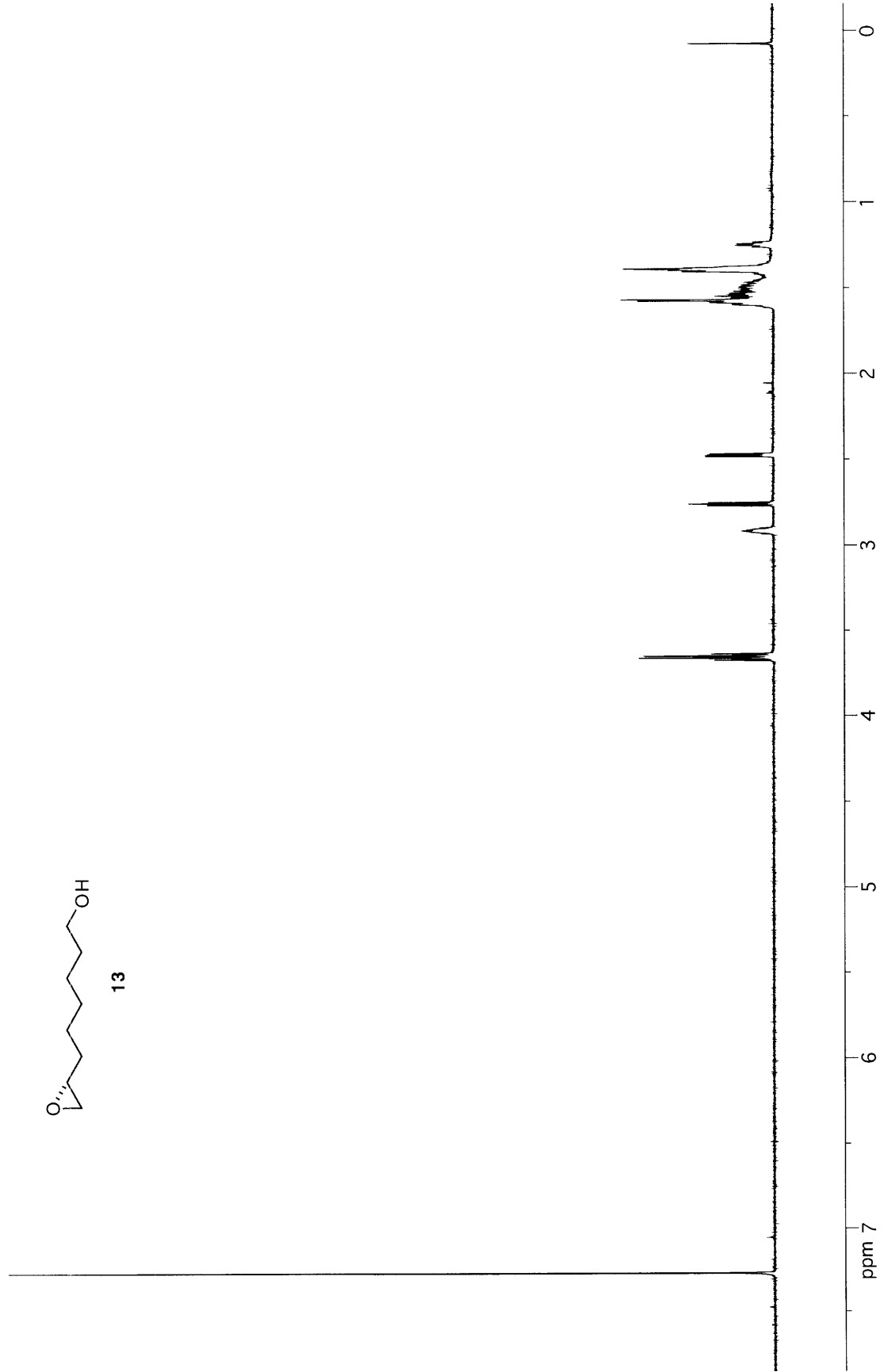


12



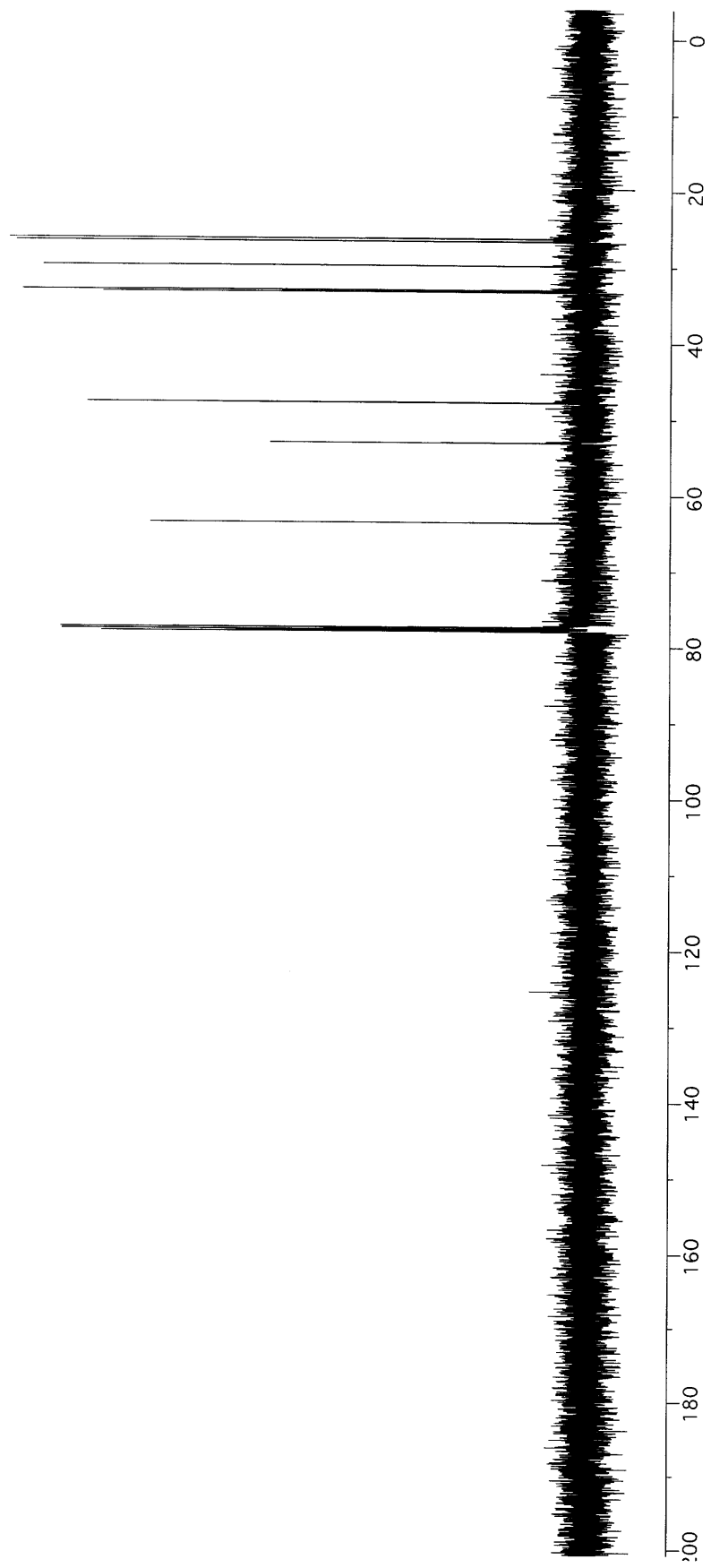


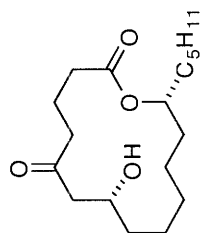
13



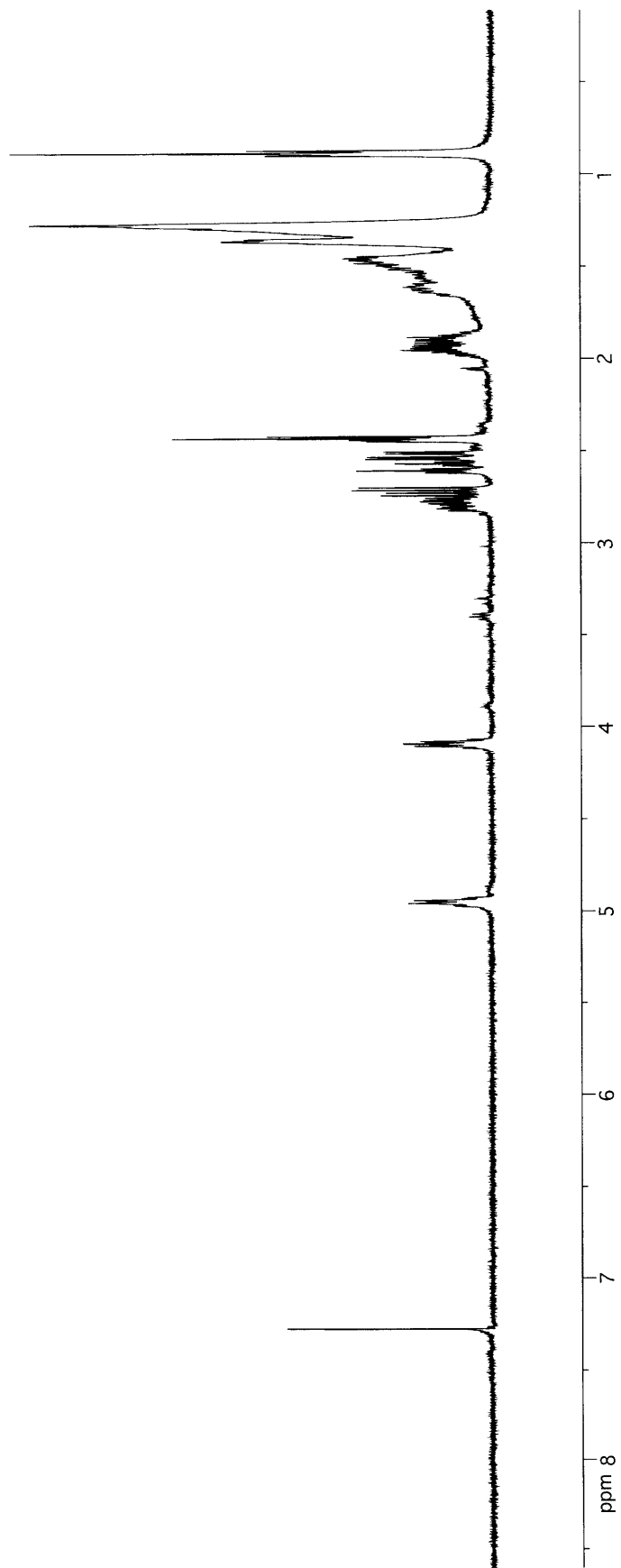


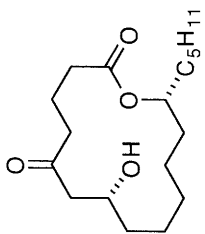
13



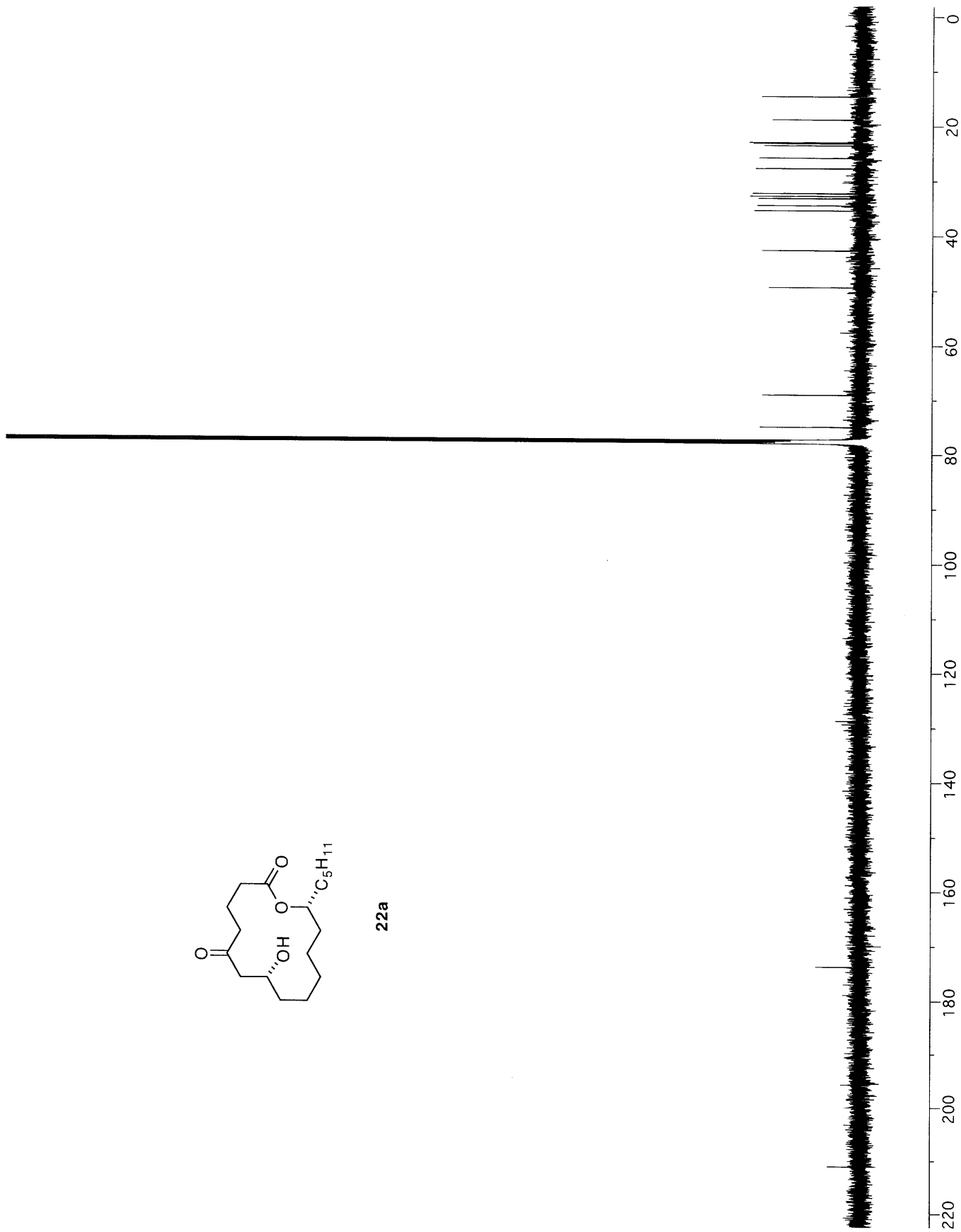


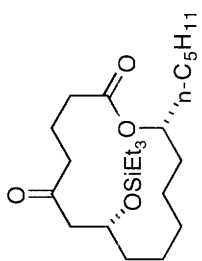
22a



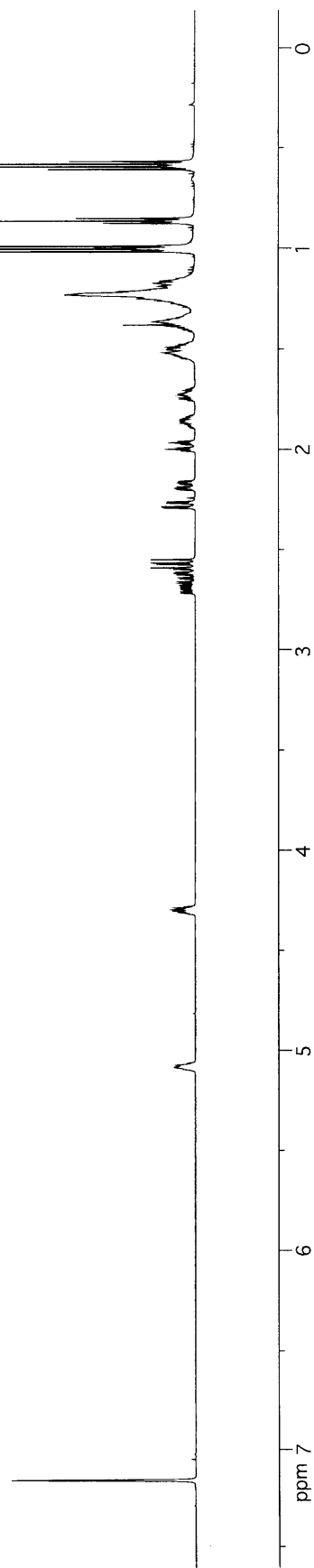


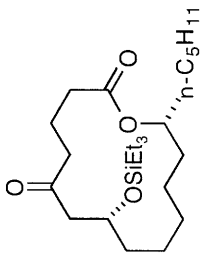
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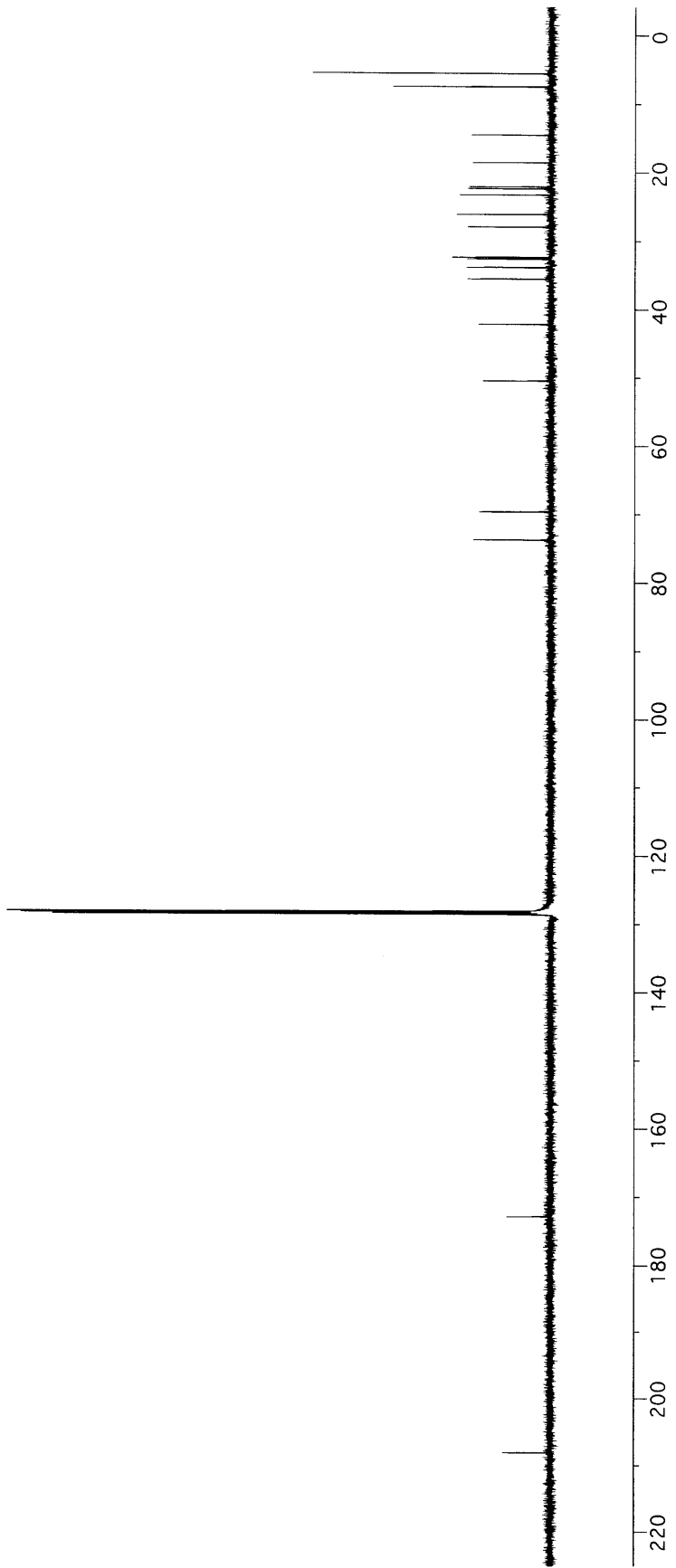


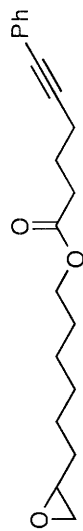
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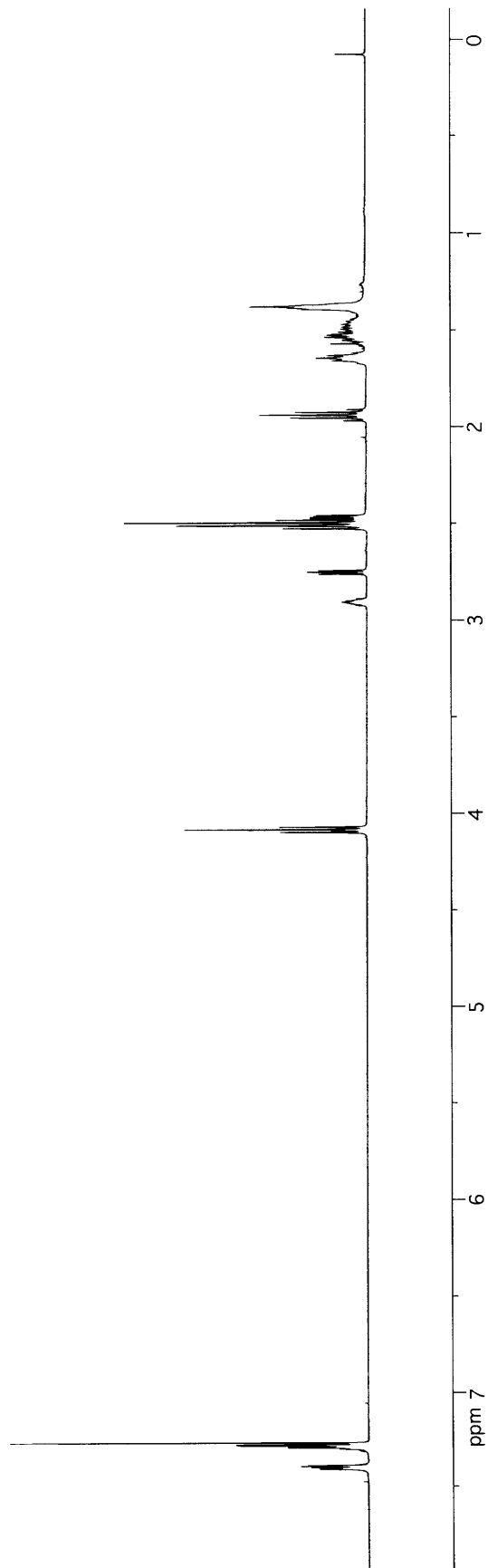


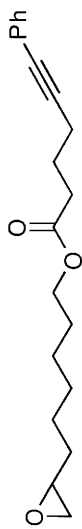
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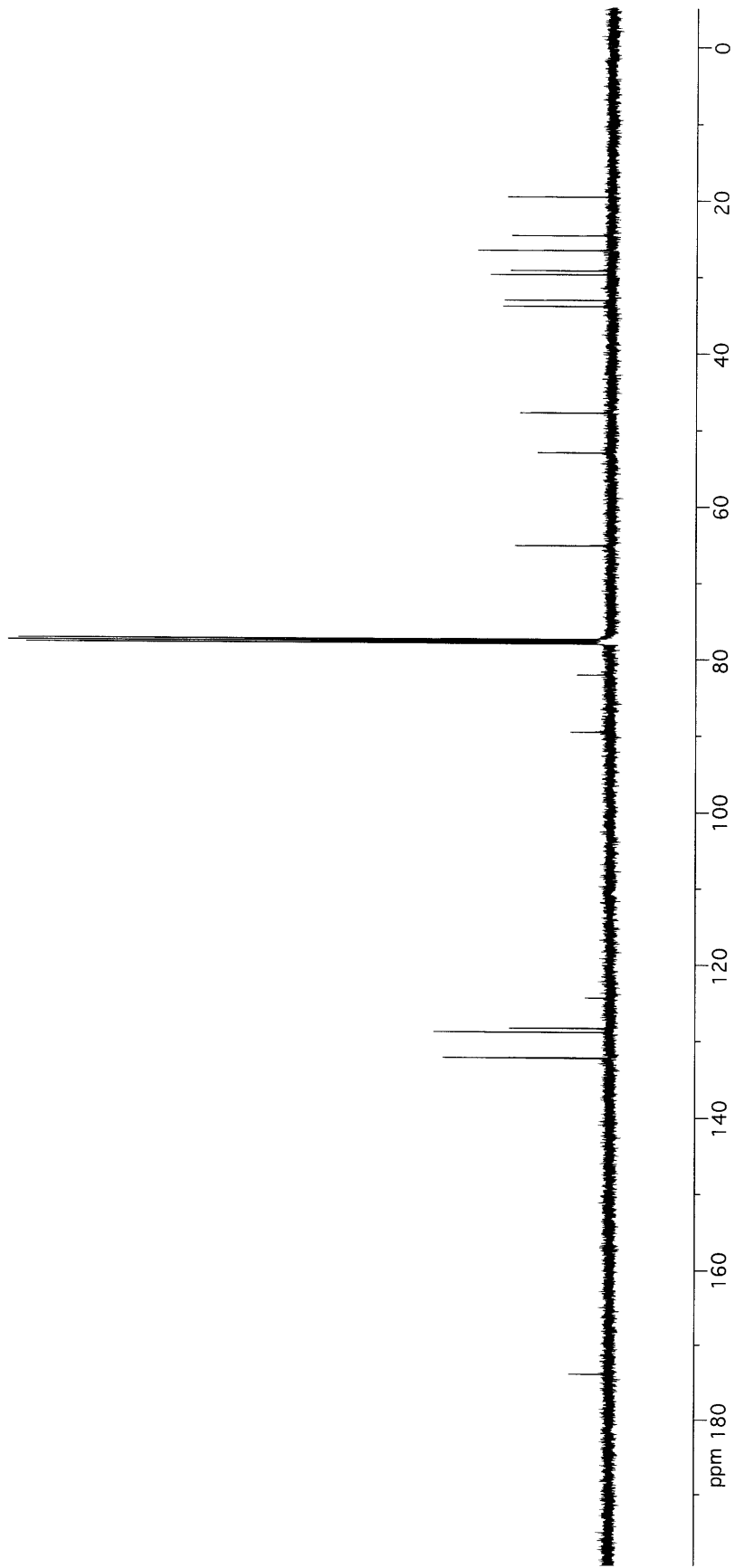


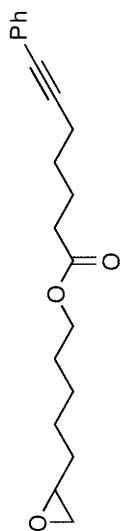
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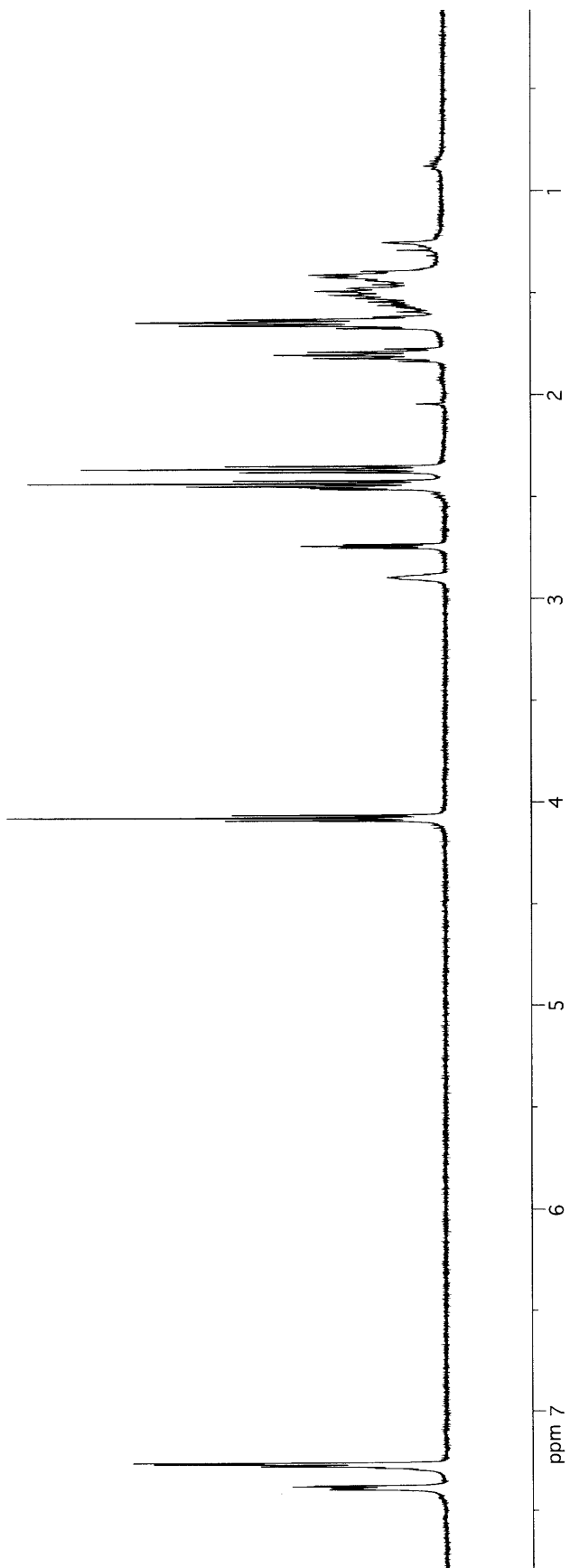


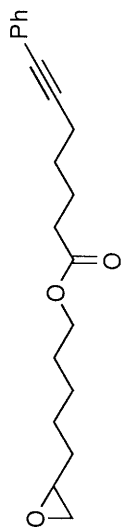
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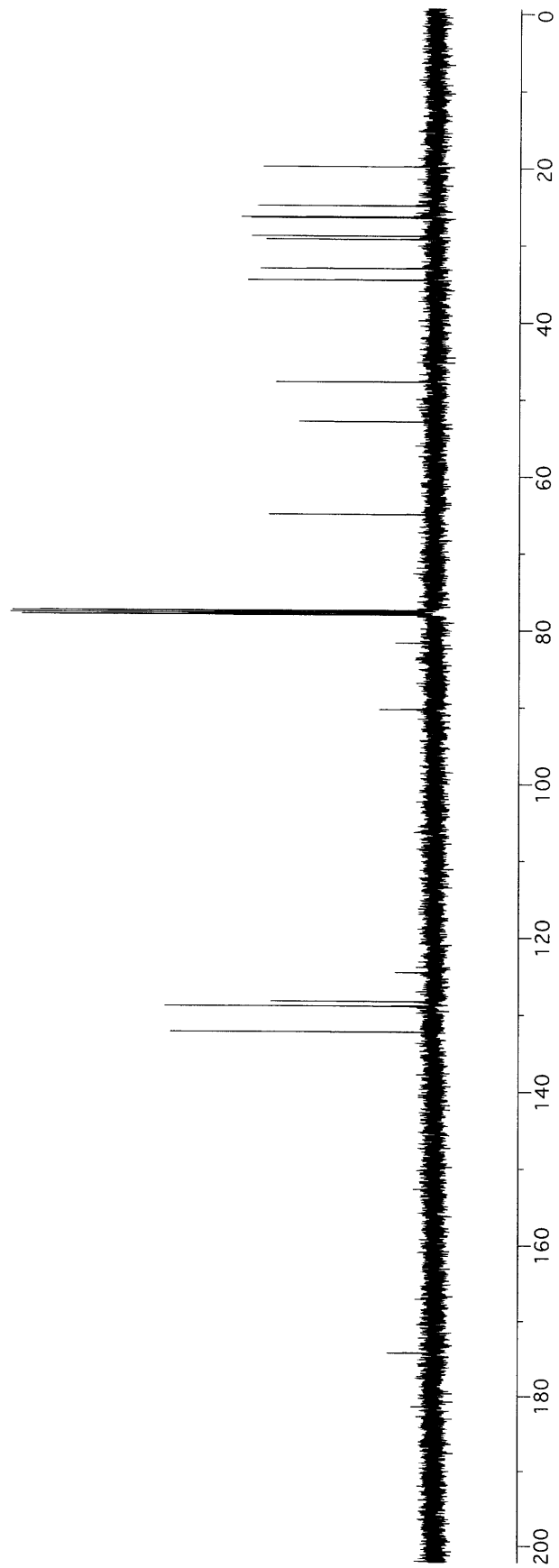


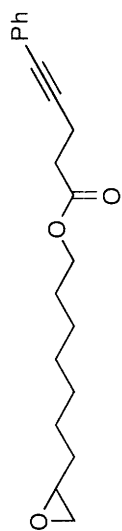
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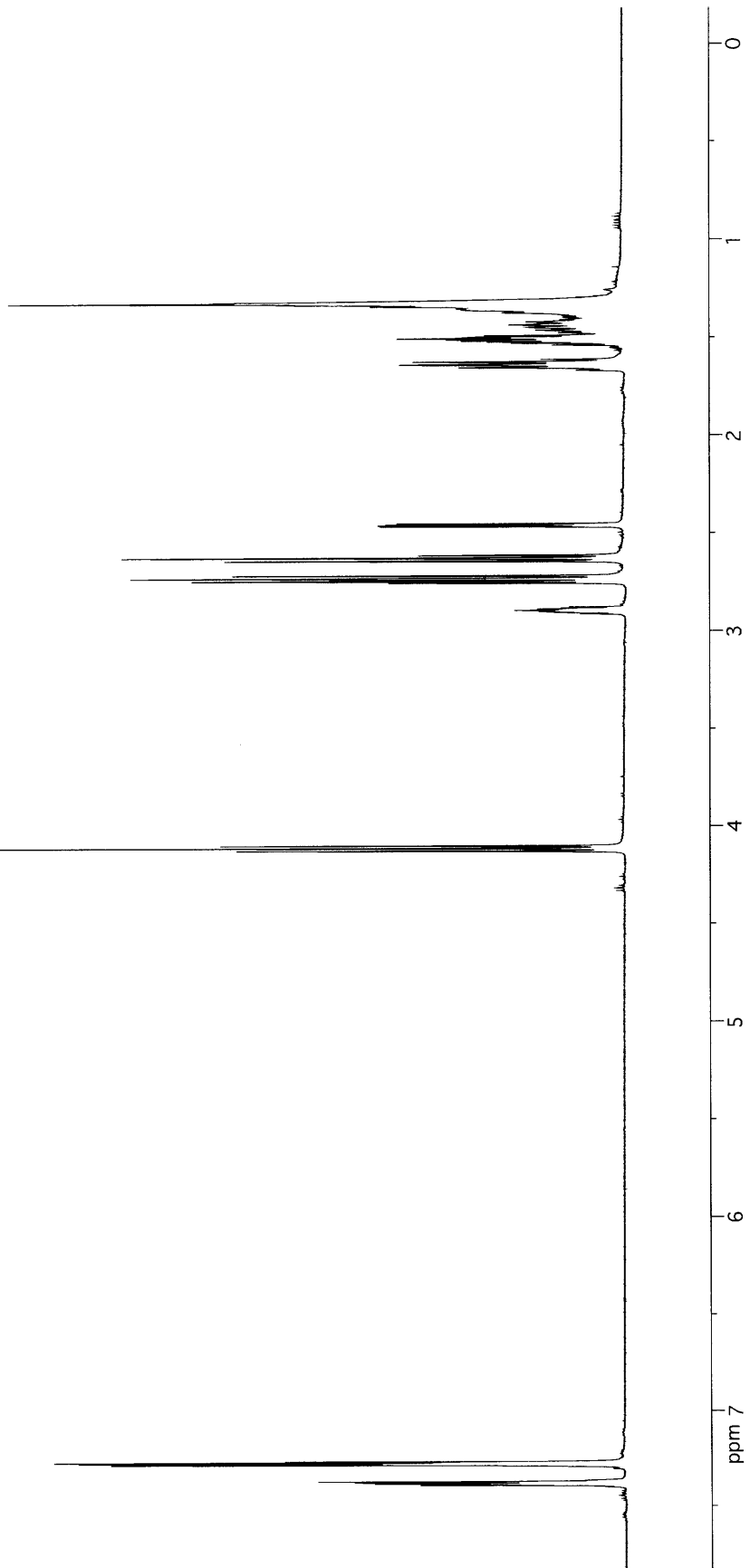


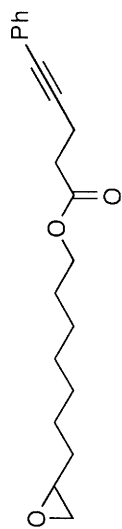
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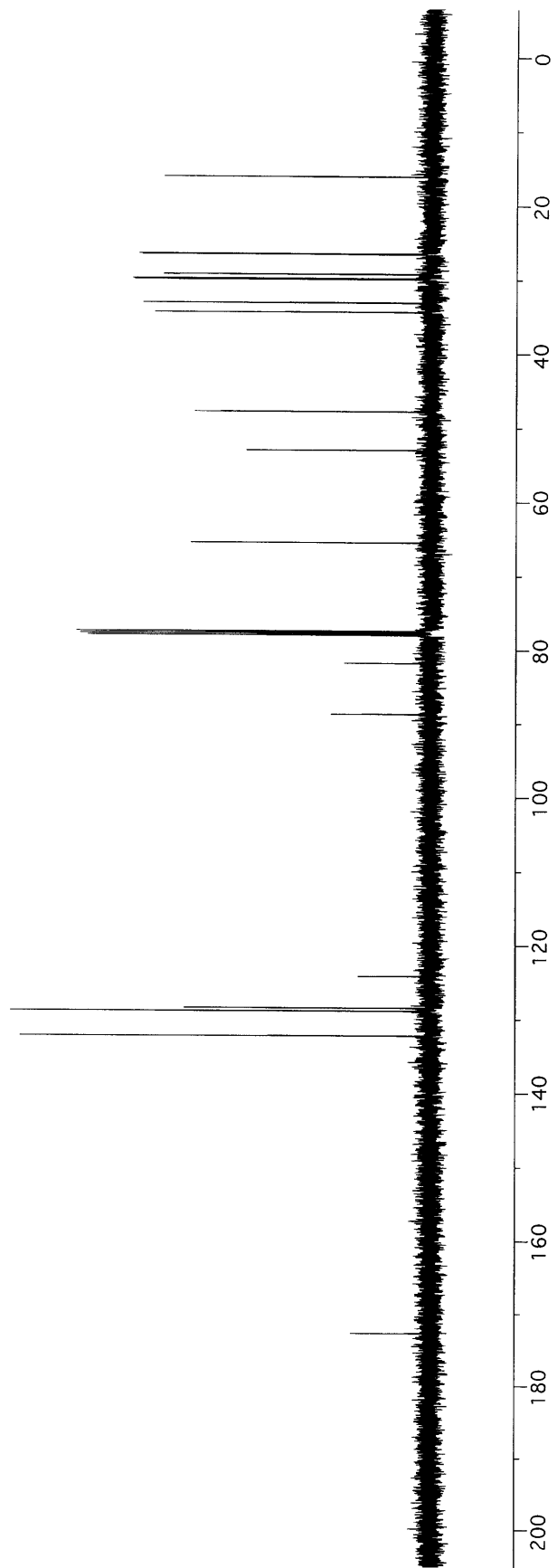


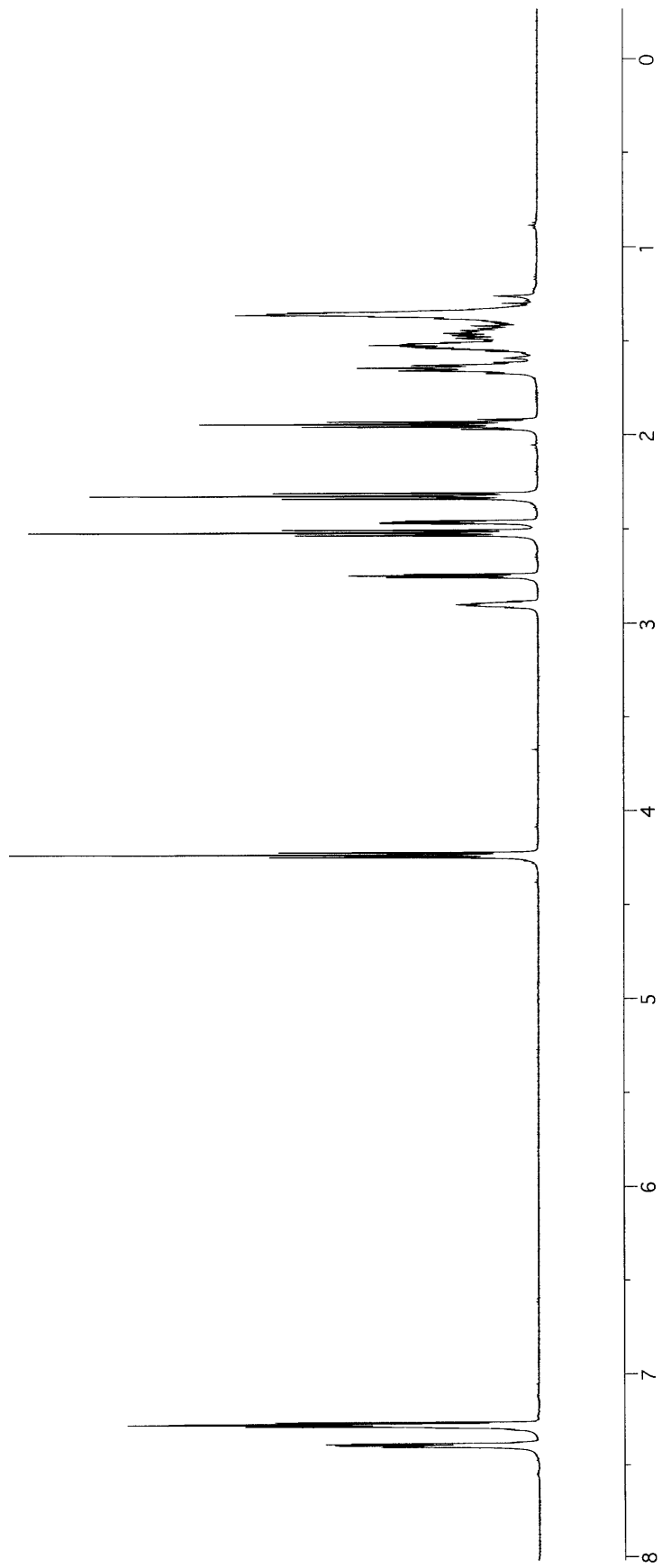
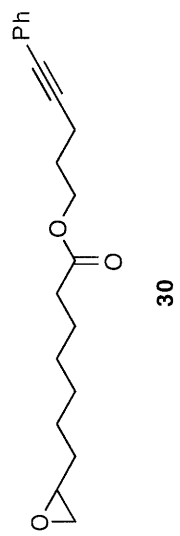
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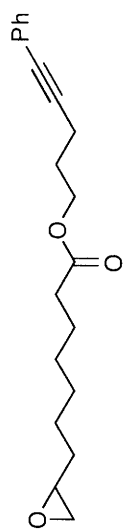




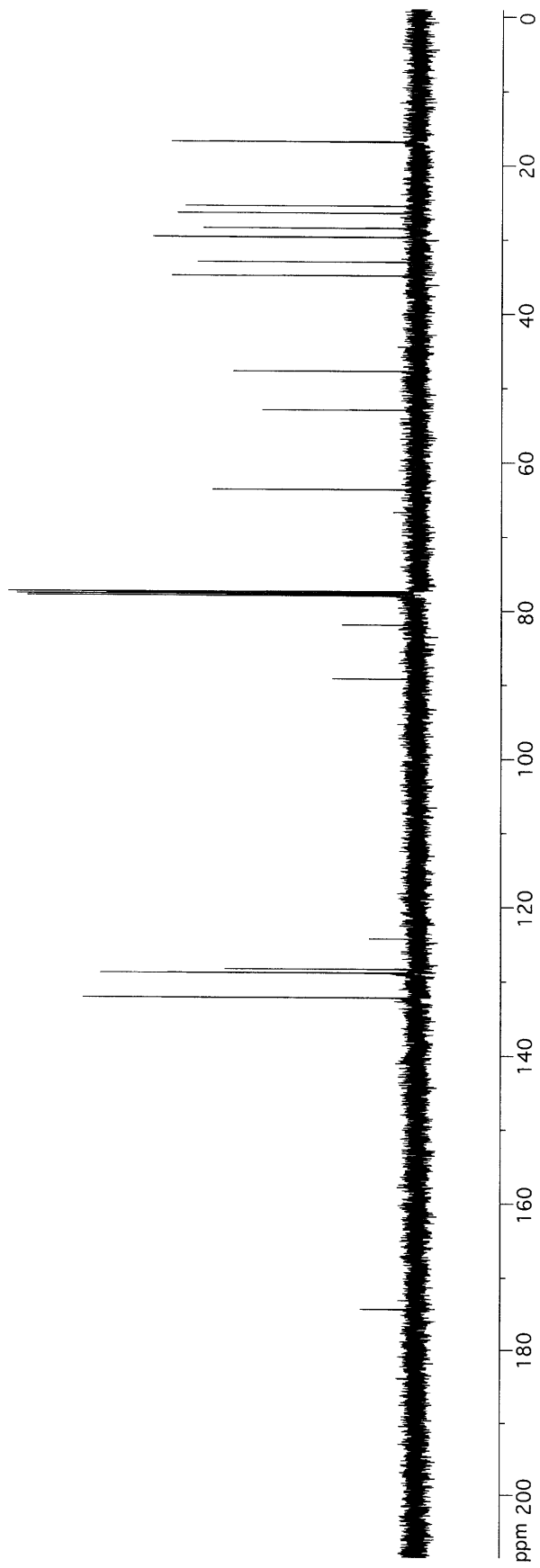
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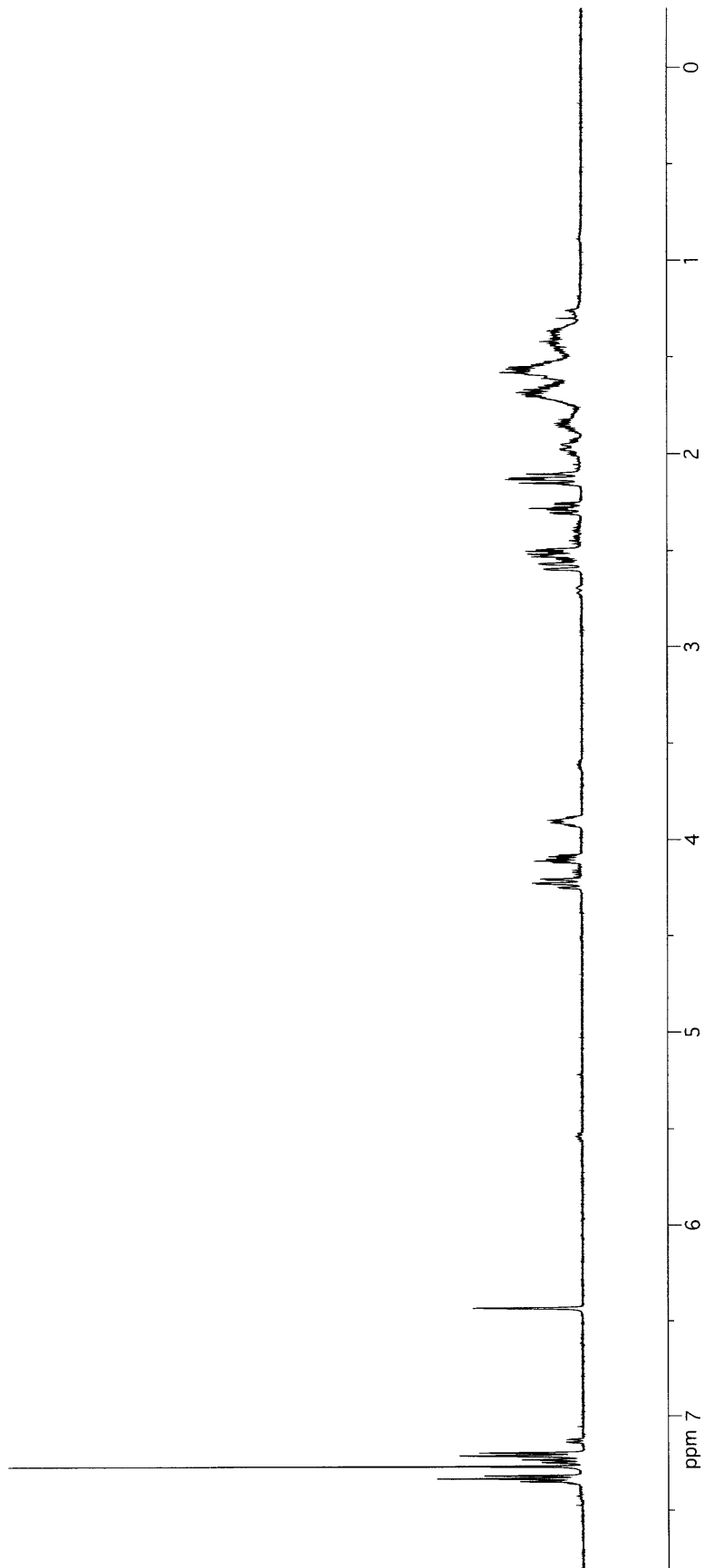
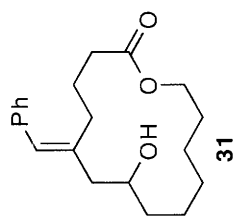


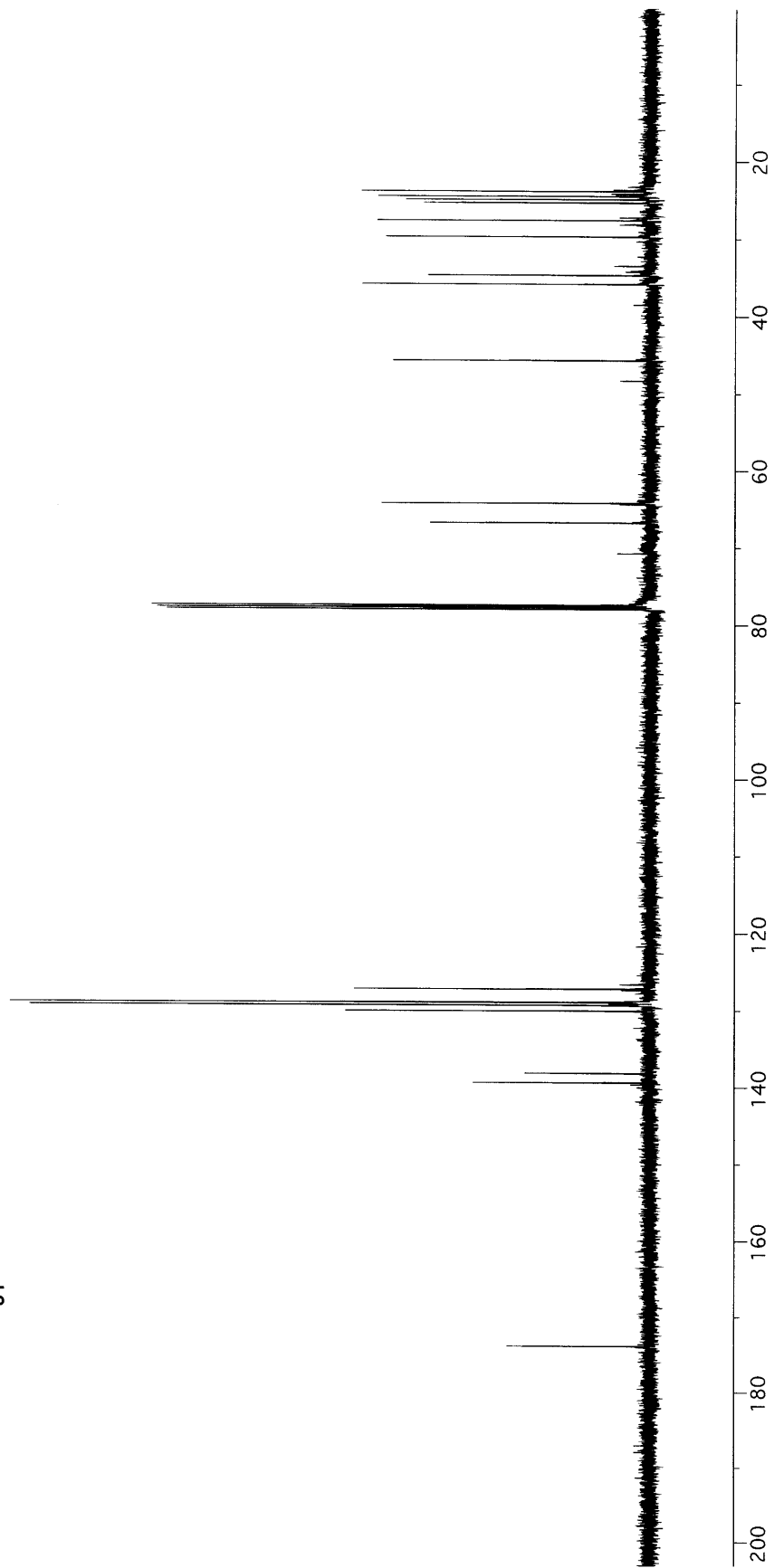
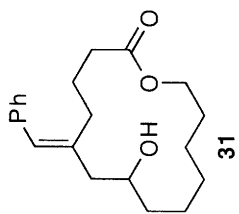


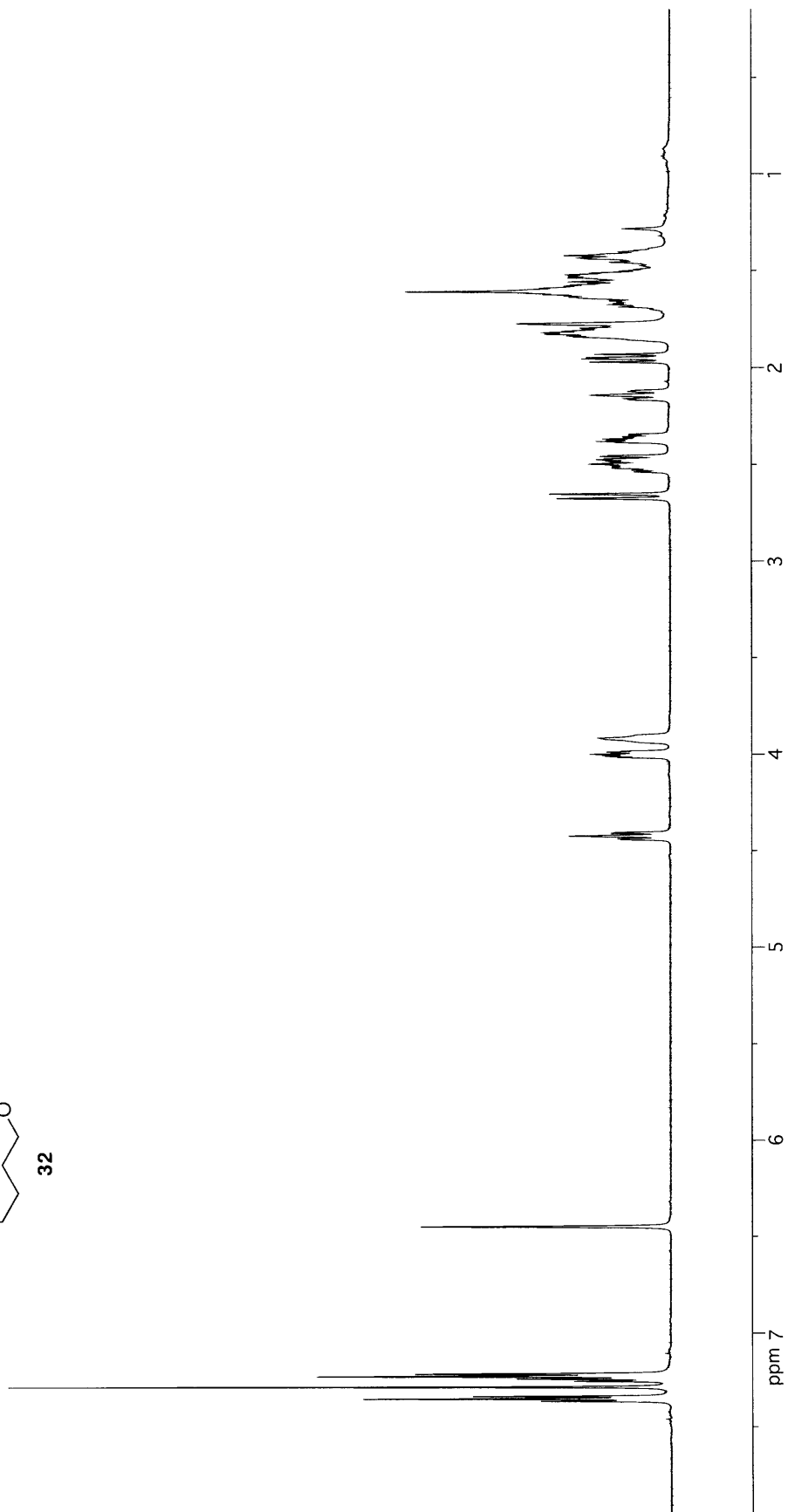
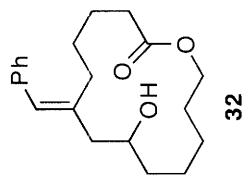


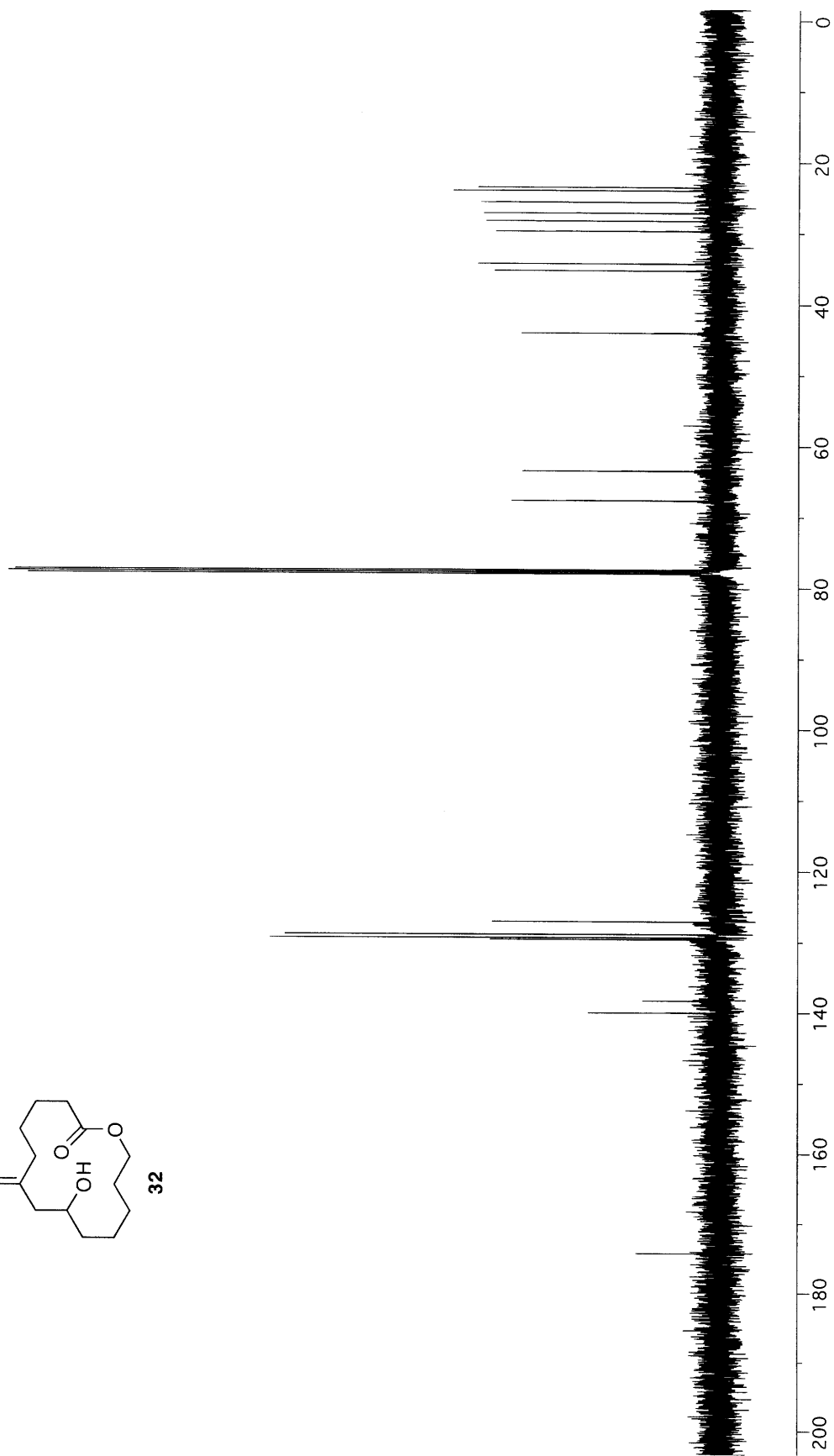
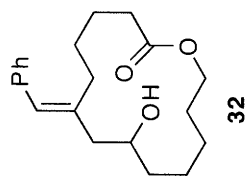
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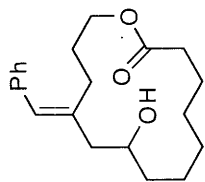




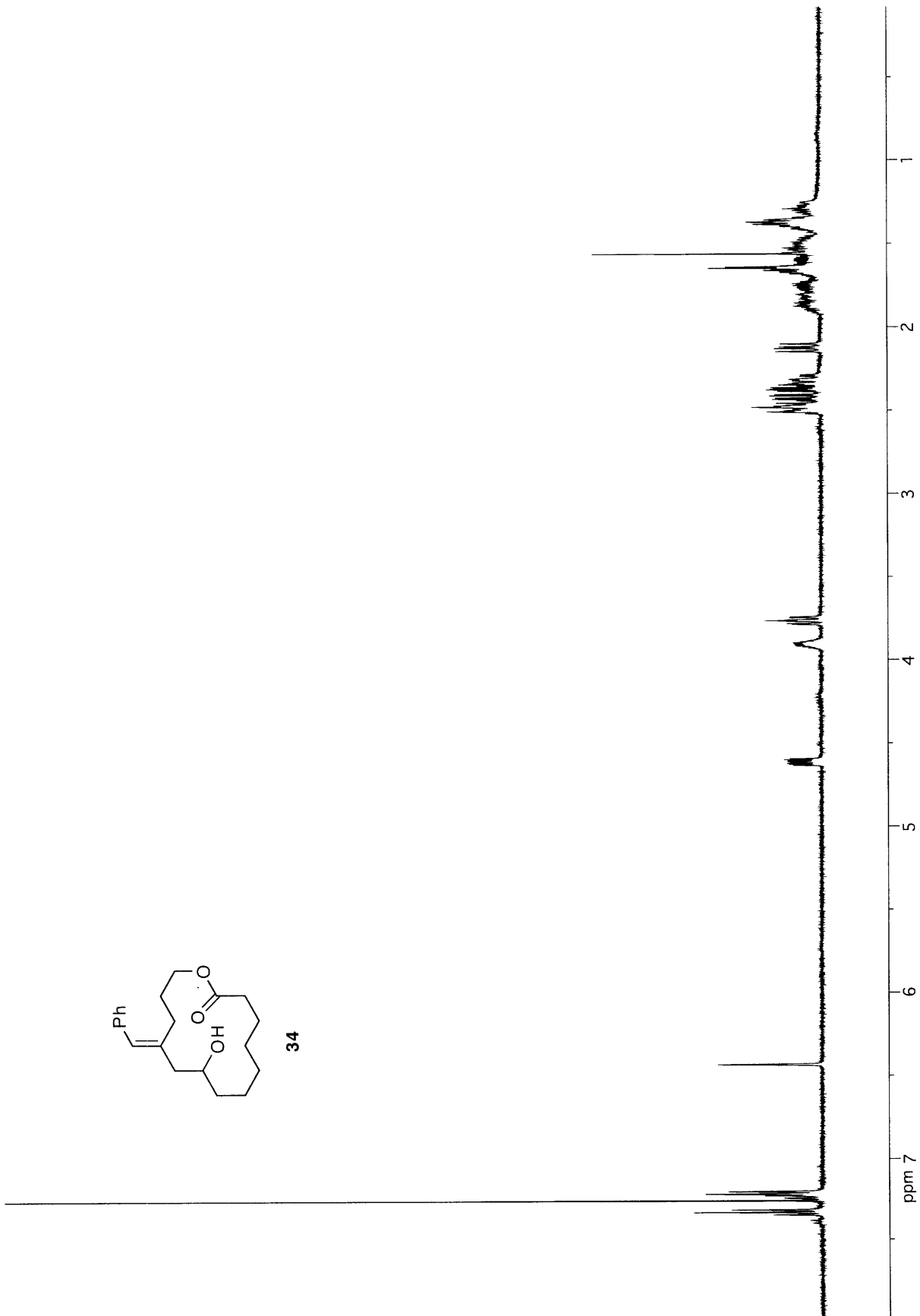


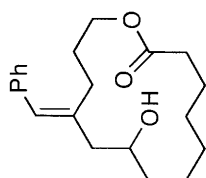




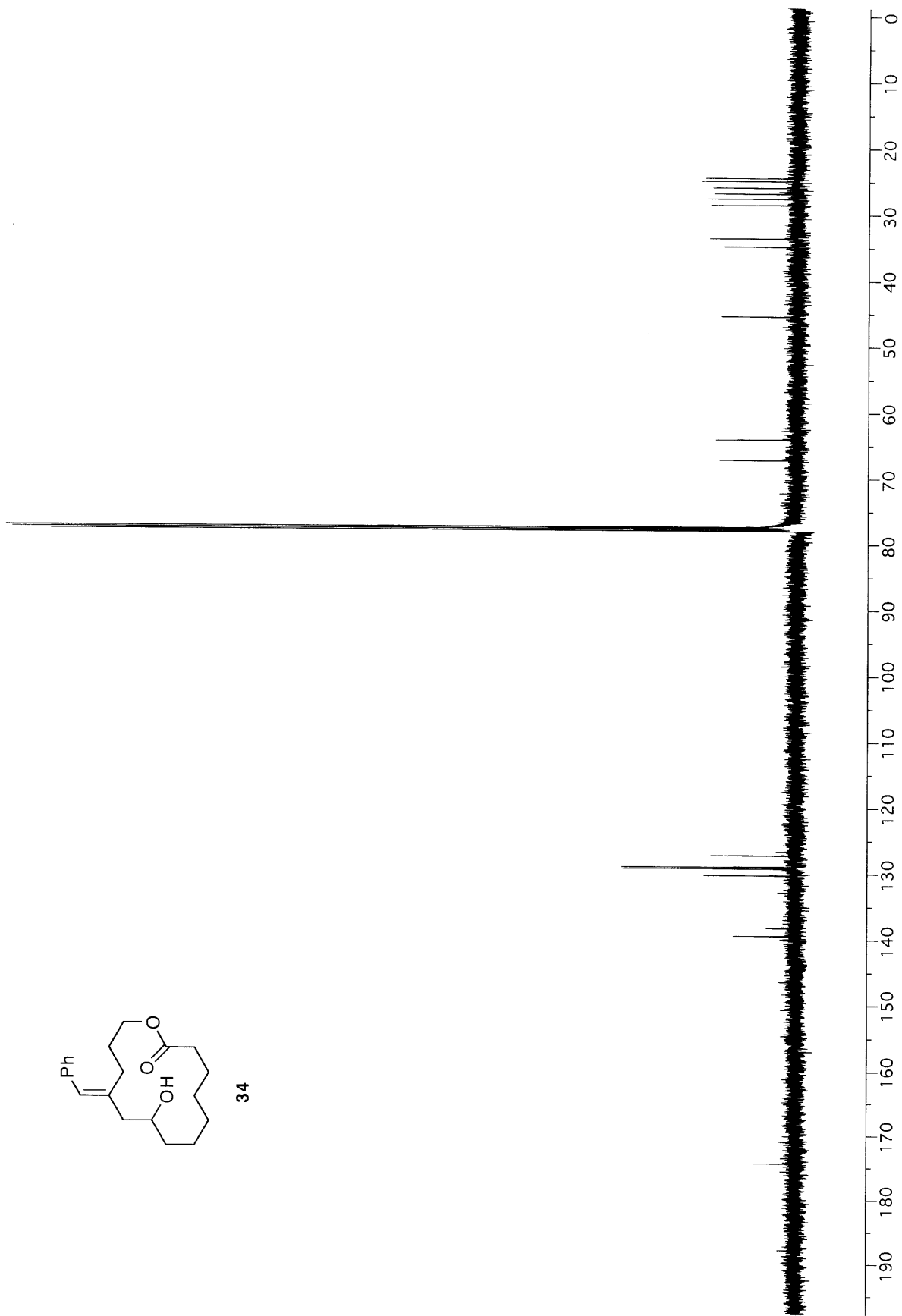


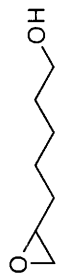
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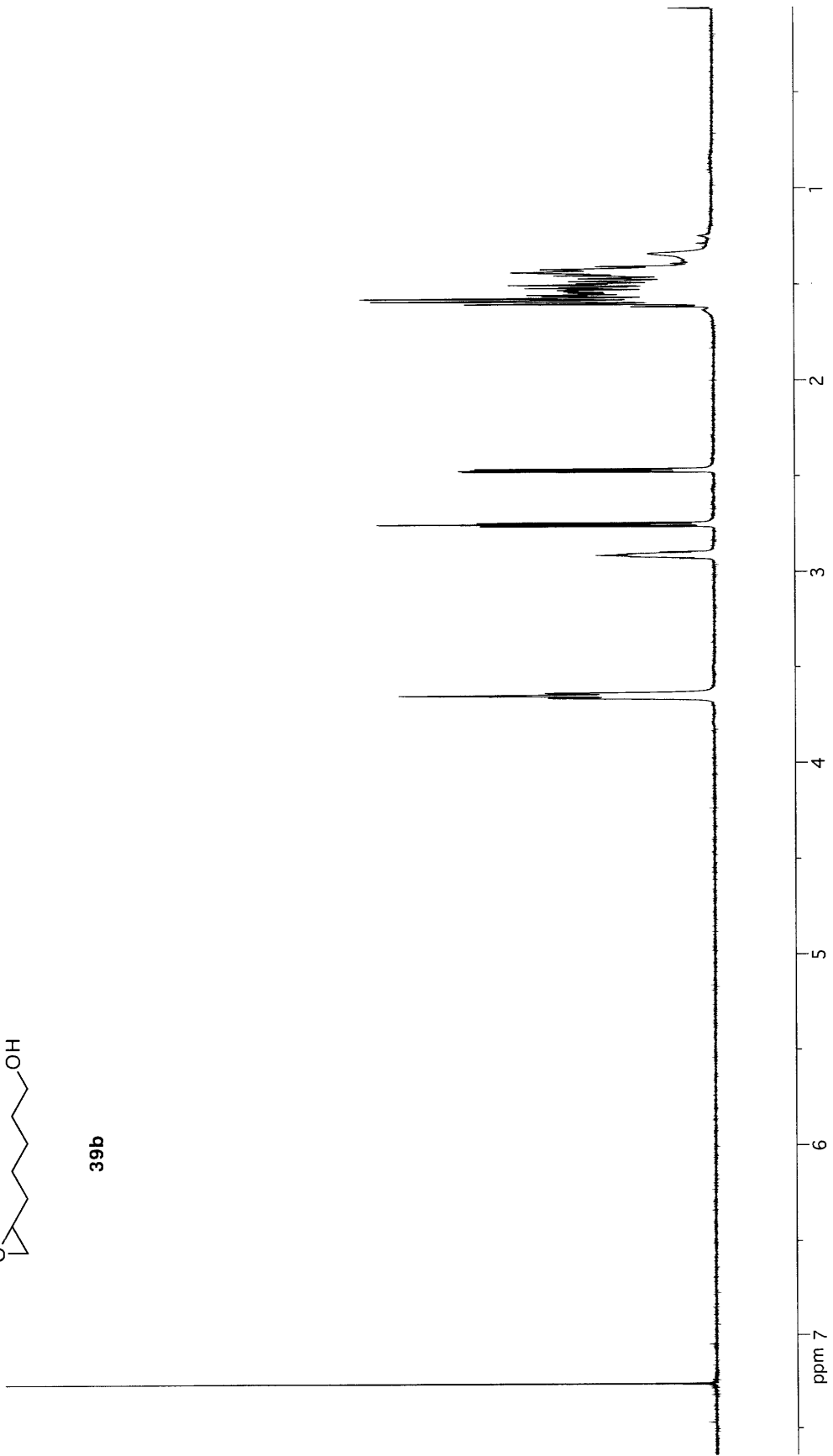


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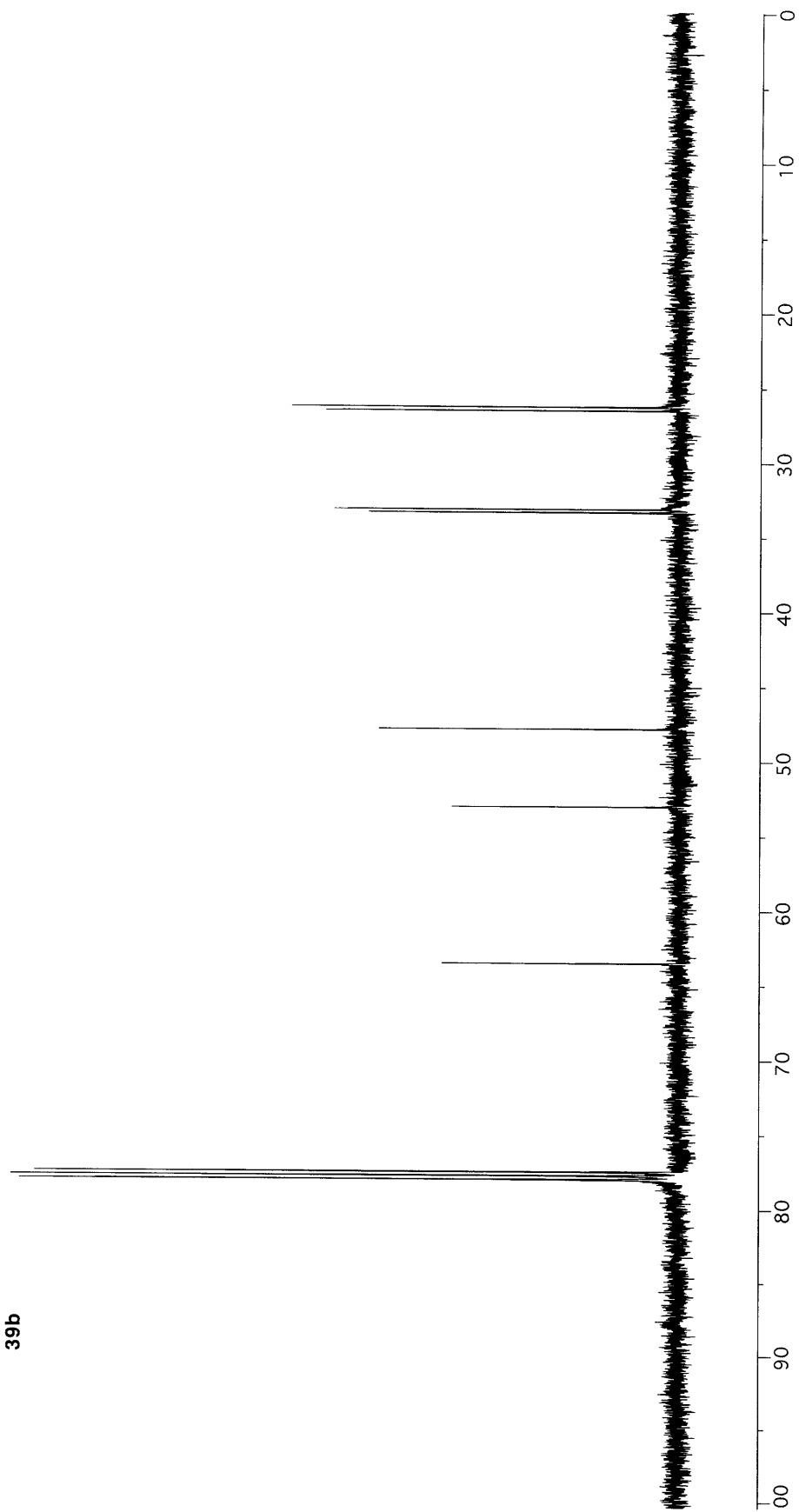


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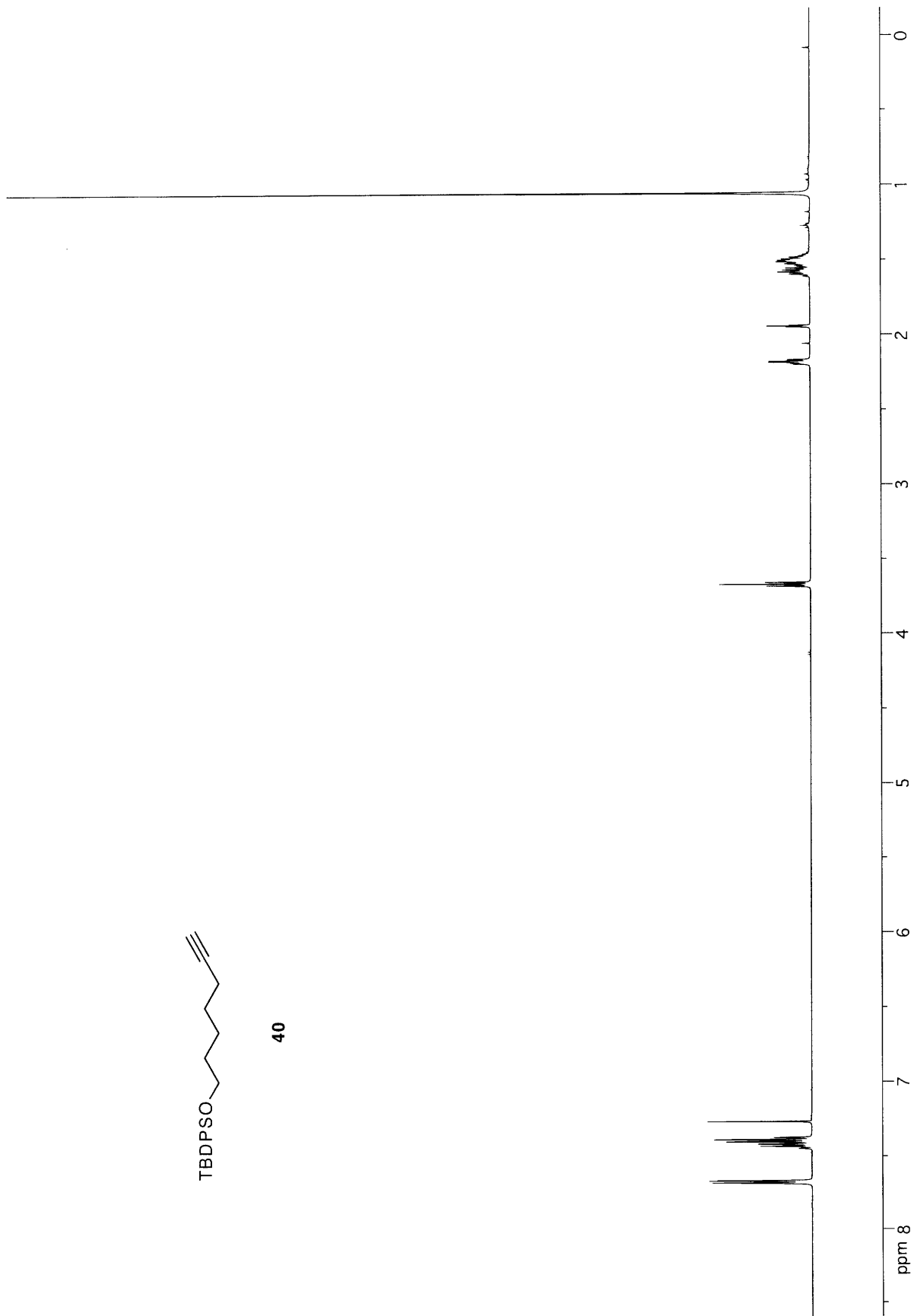


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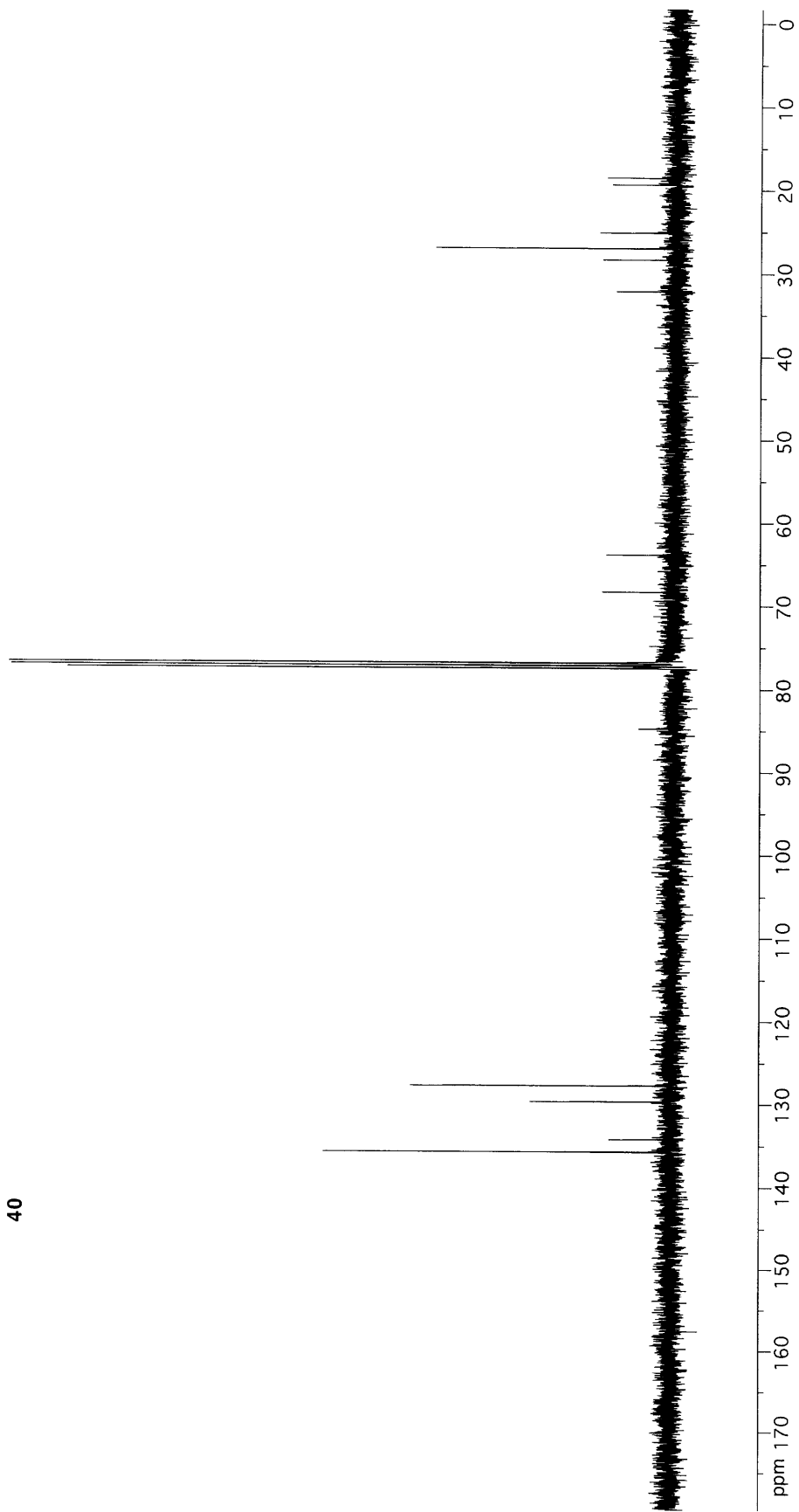


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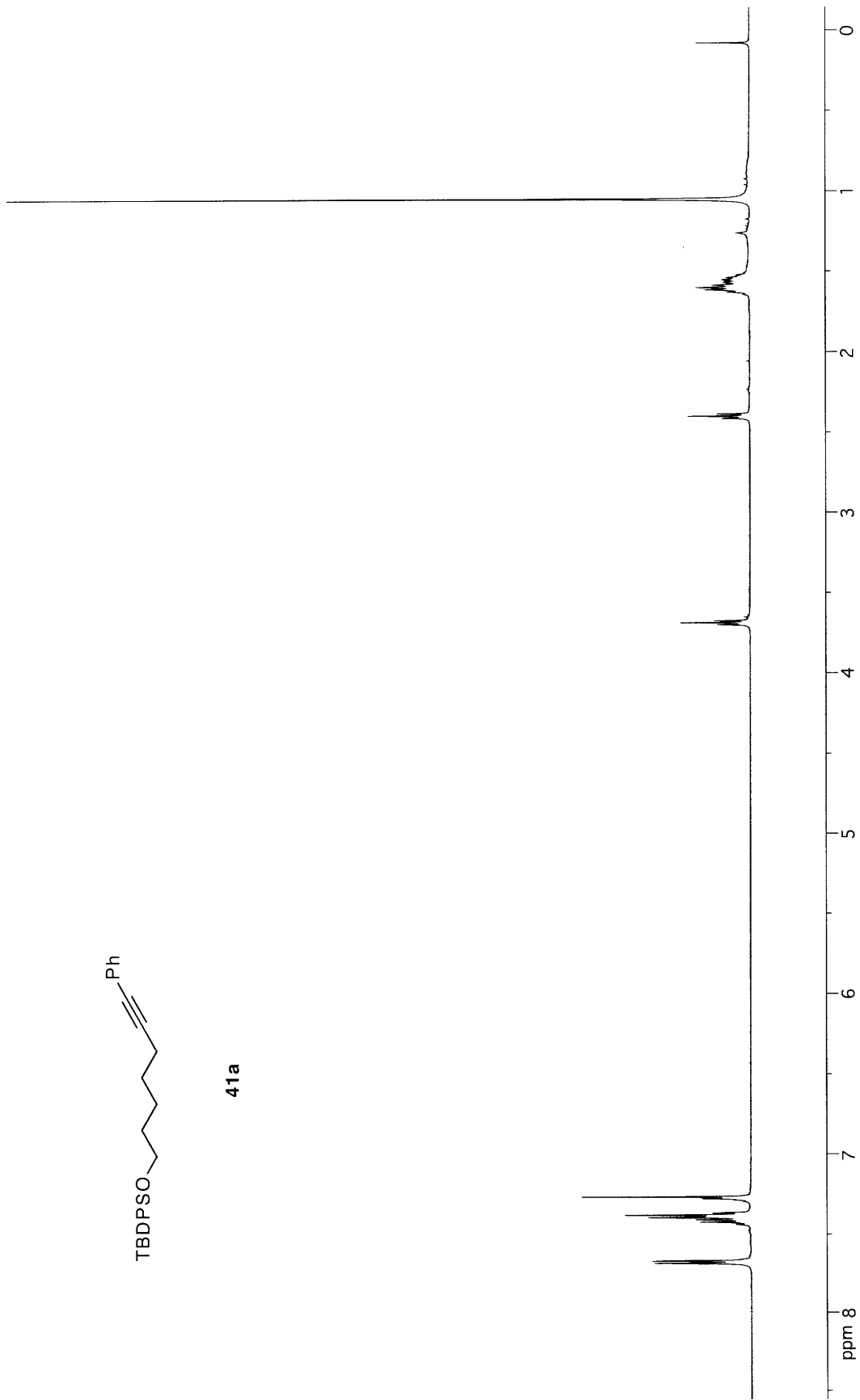


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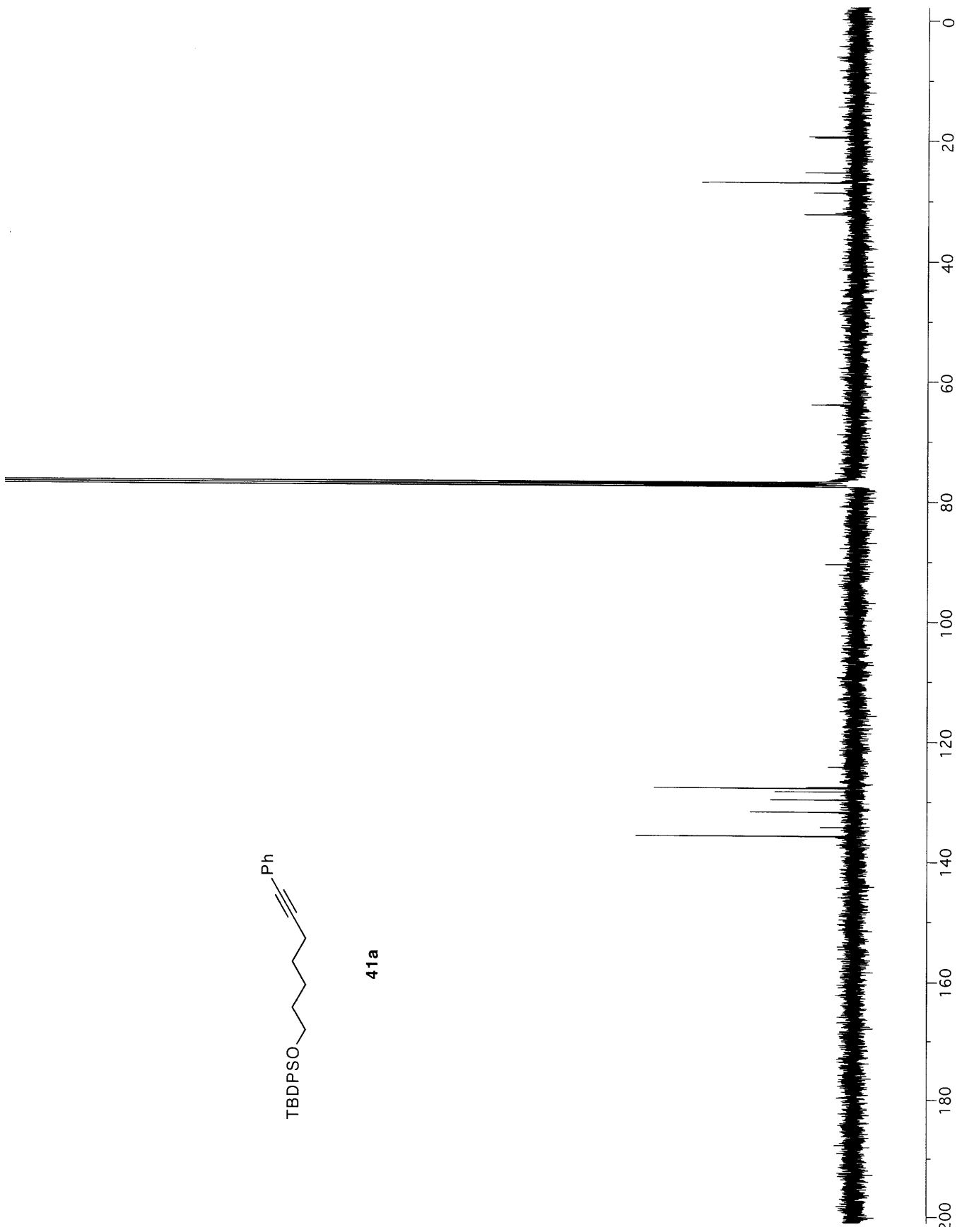


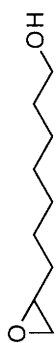
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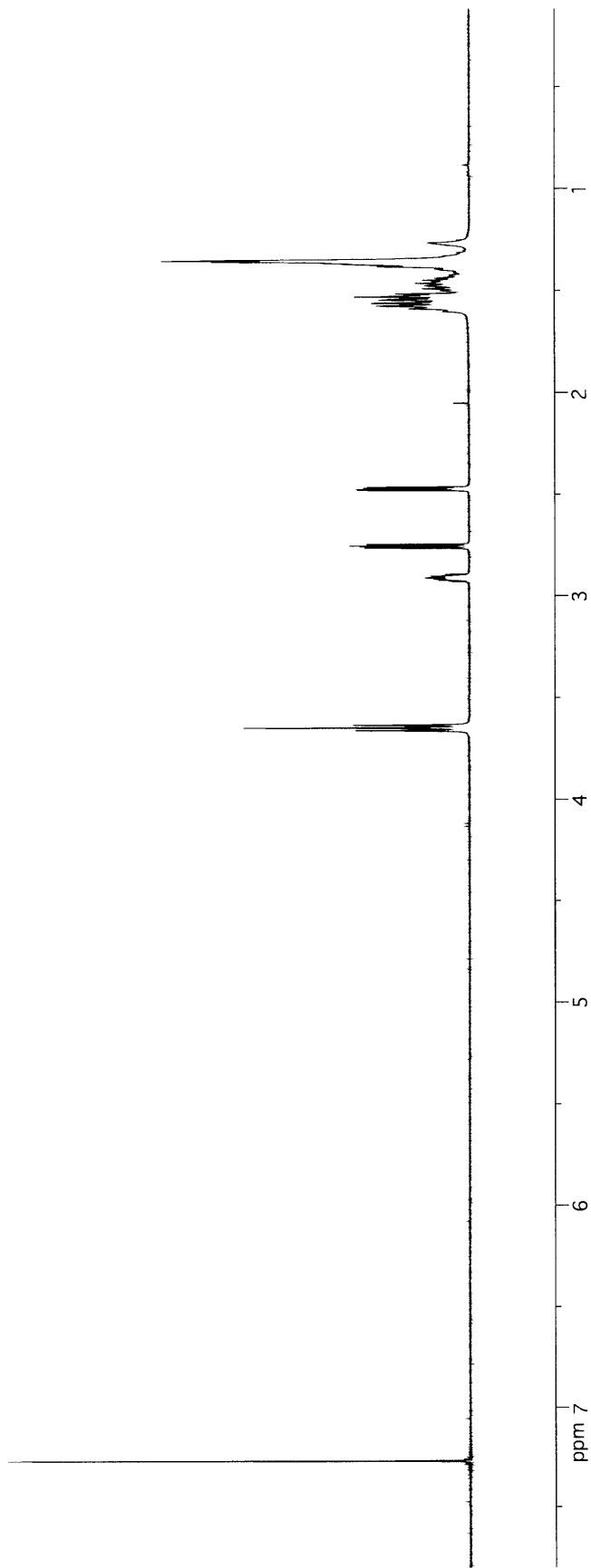


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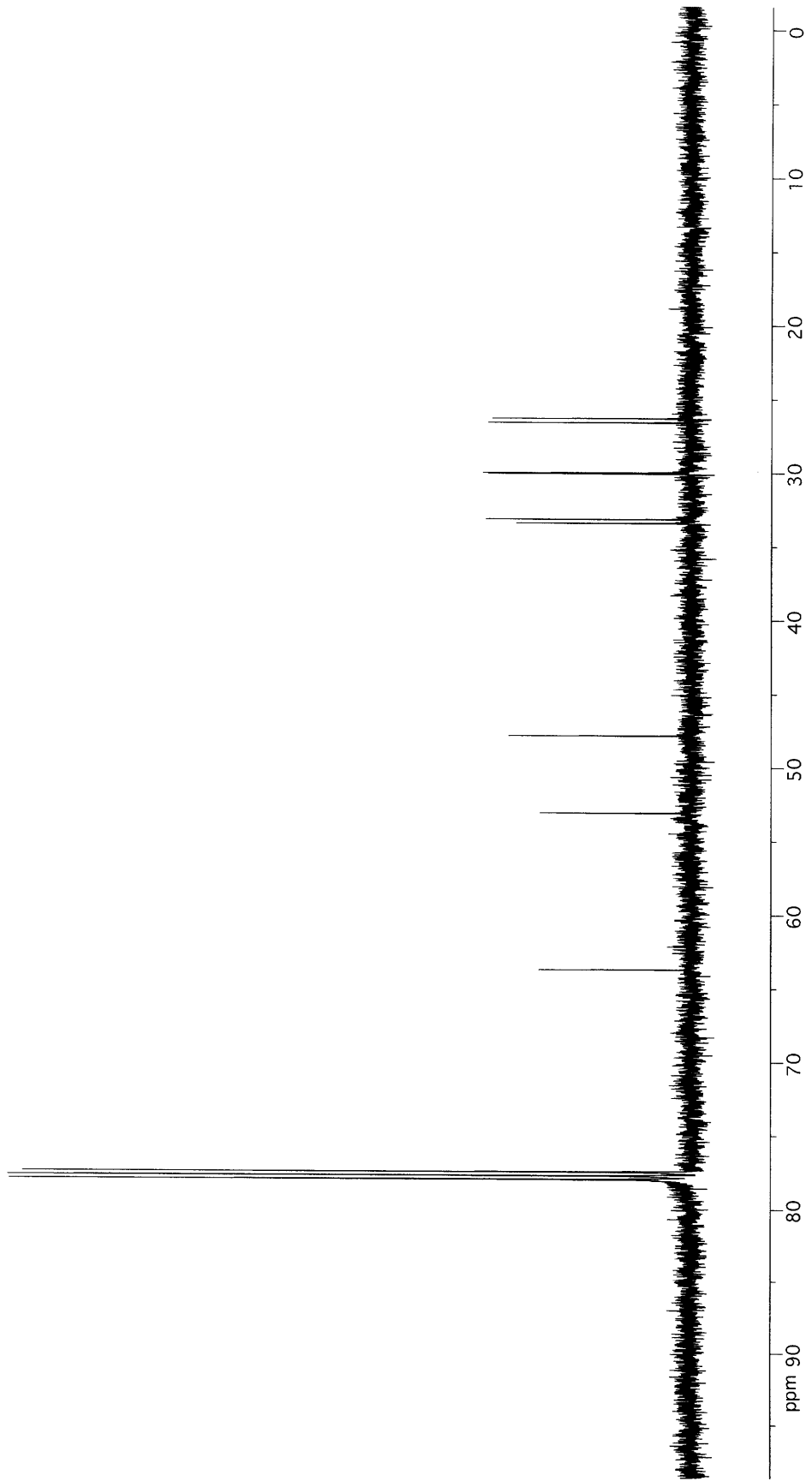


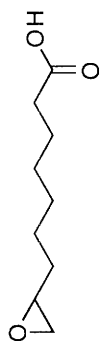
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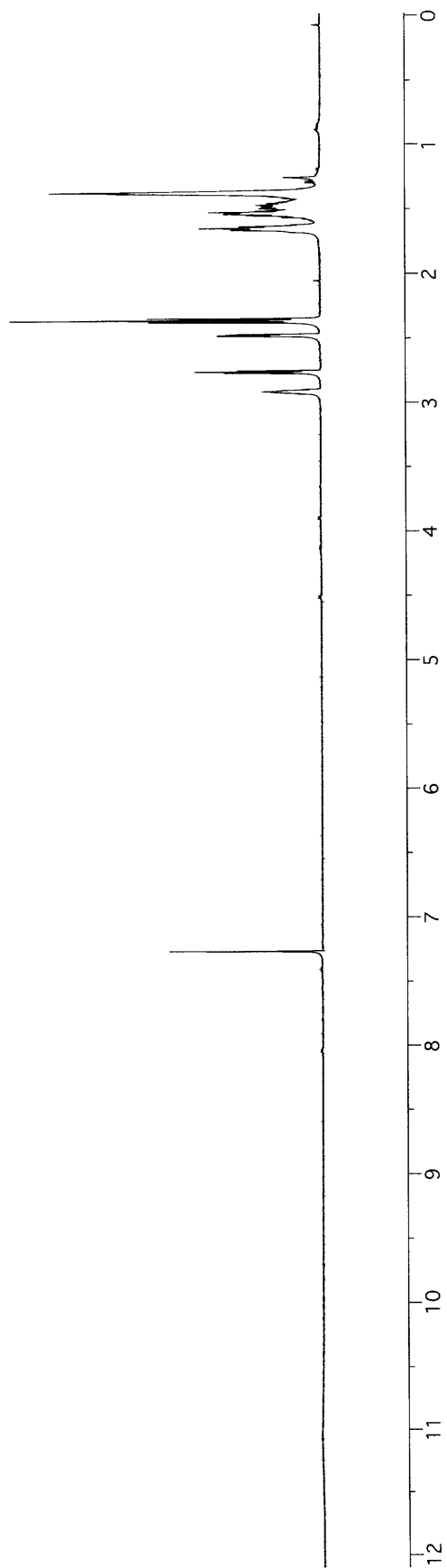


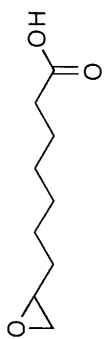
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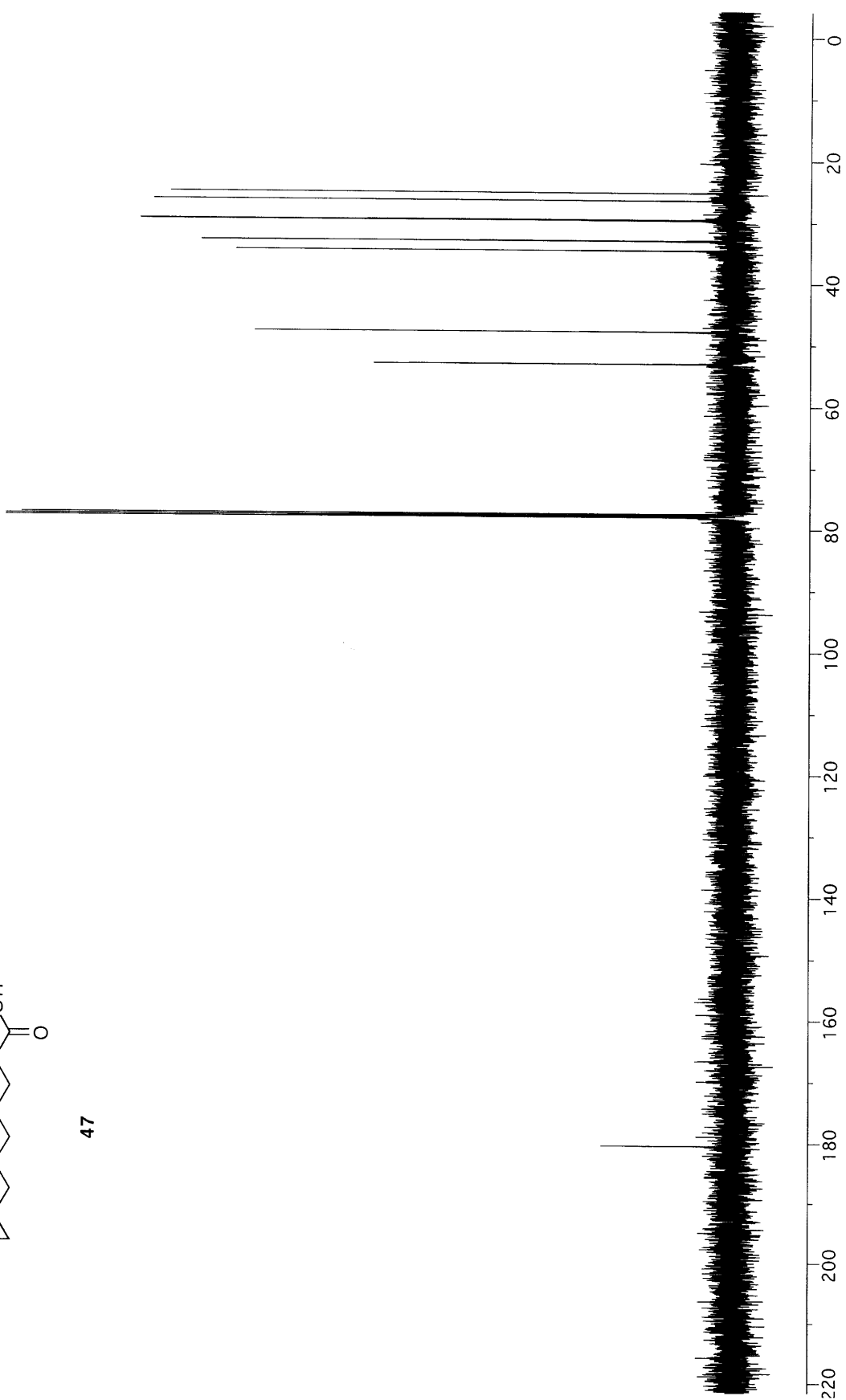


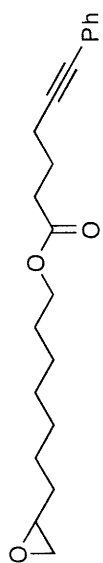
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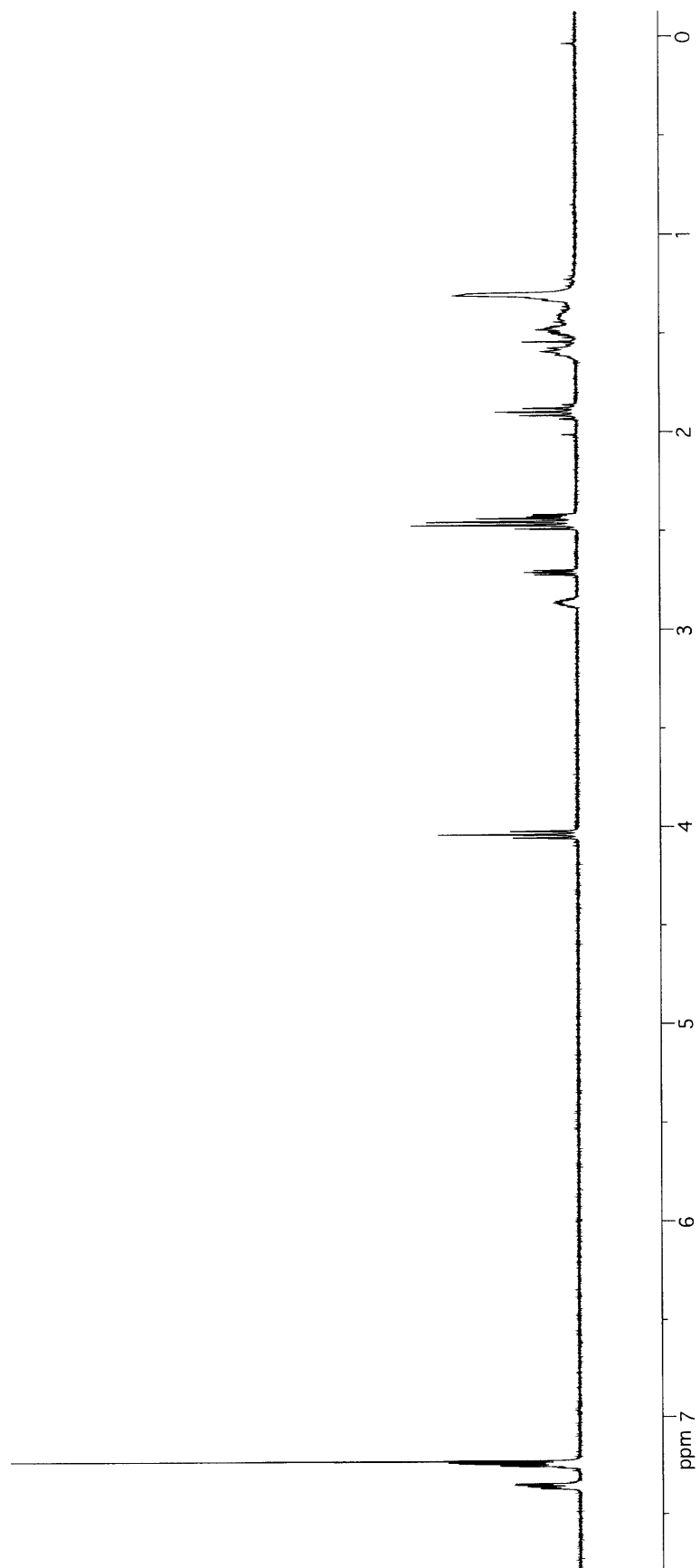


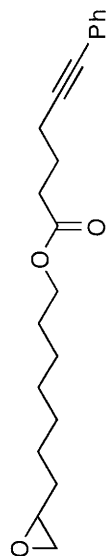
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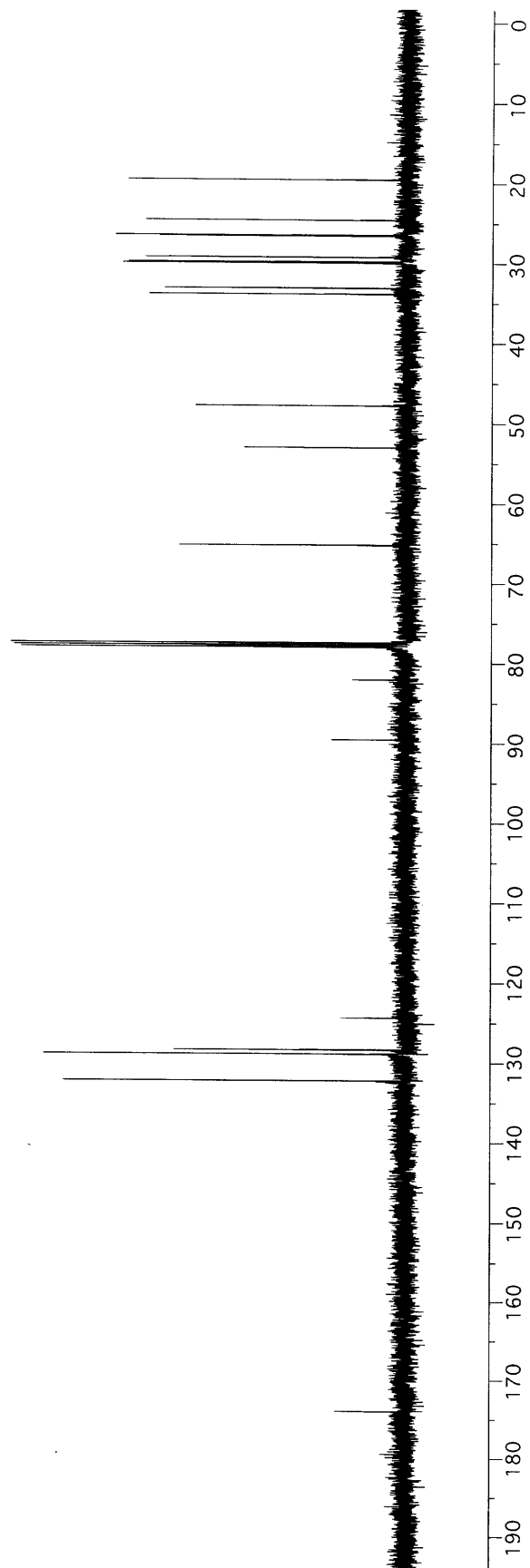


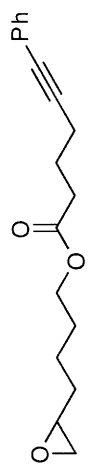
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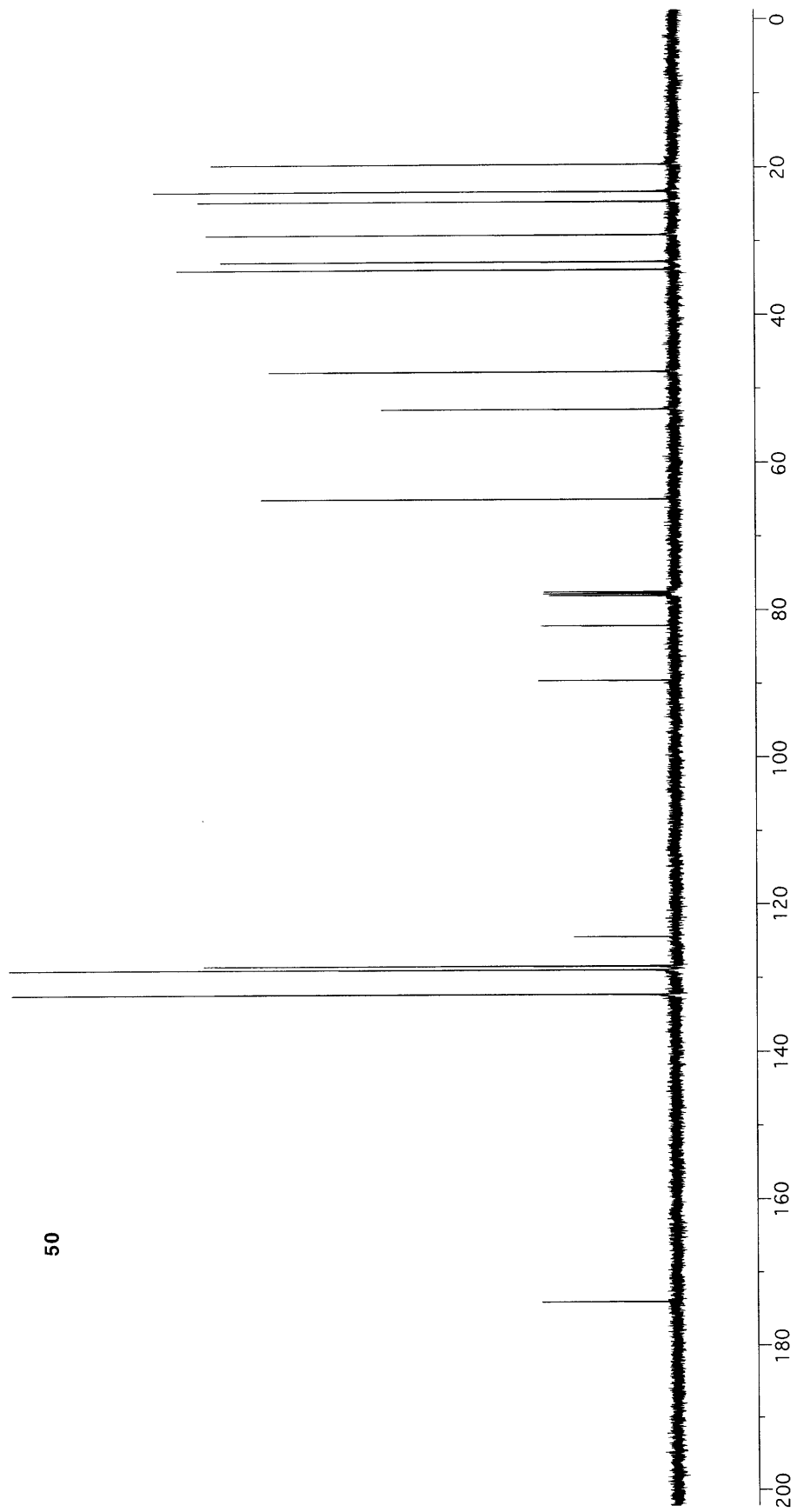


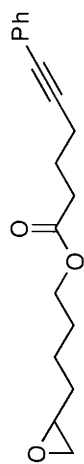
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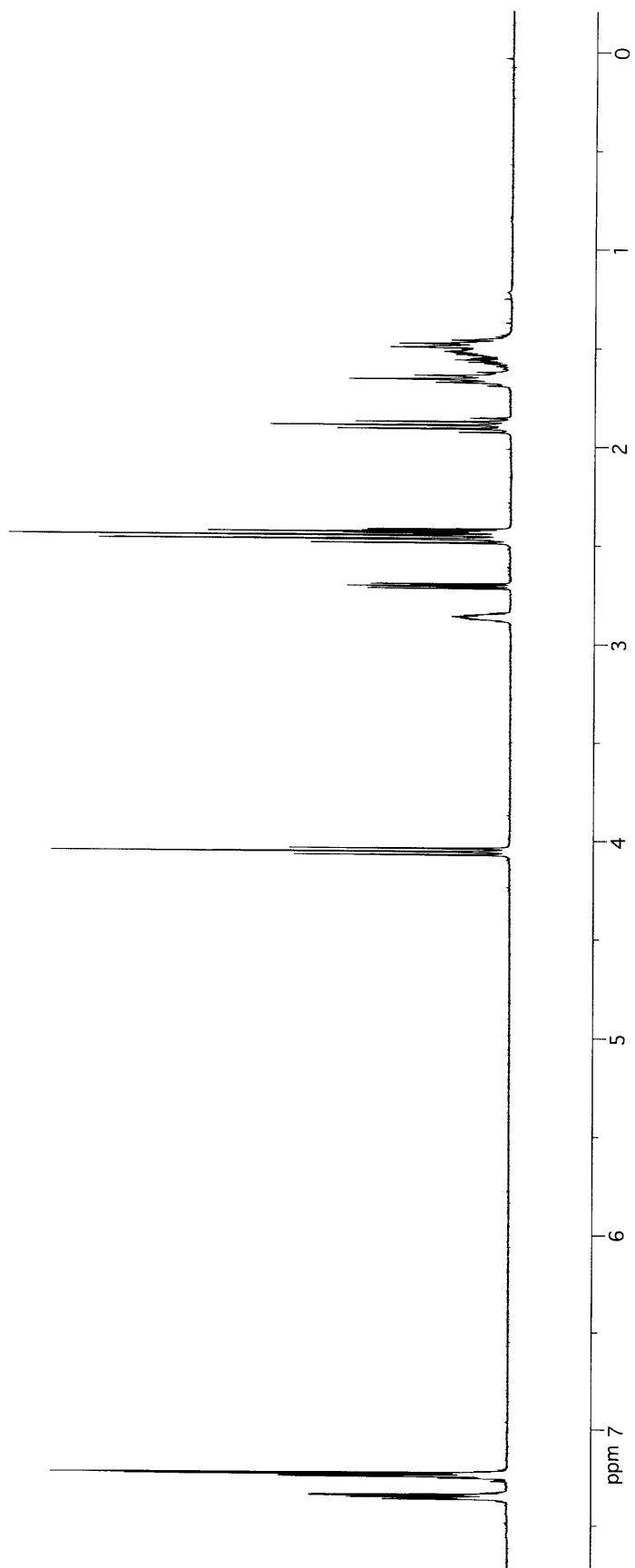


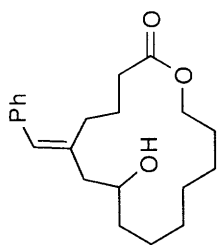
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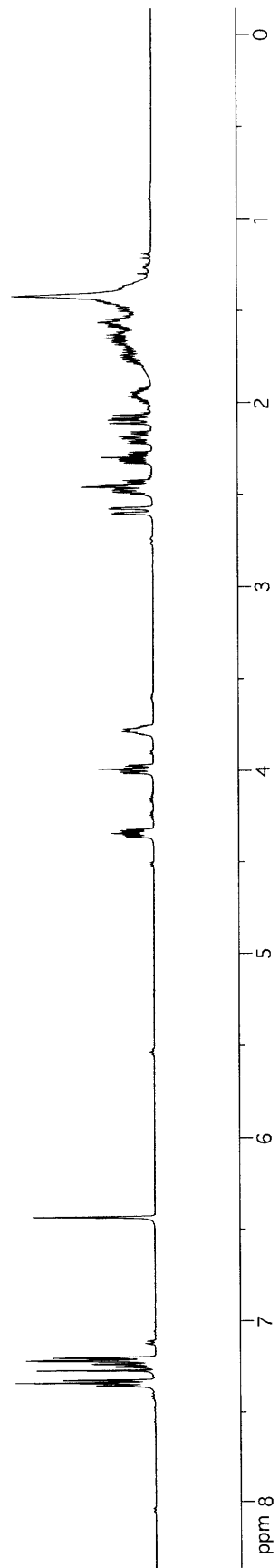


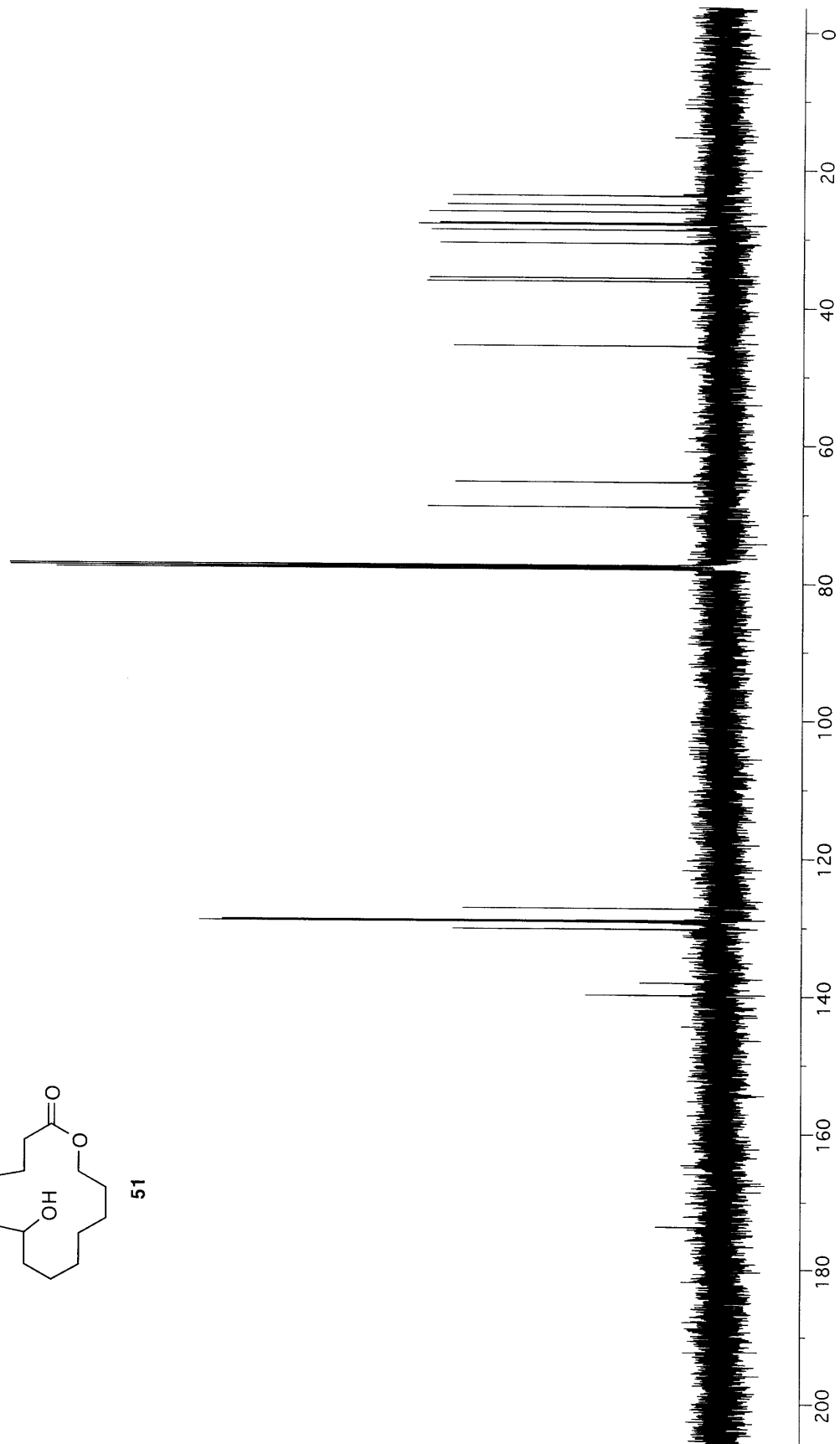
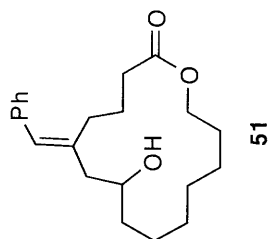
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Curriculum Vitae

Education:

- 2002-2007 Ph. D. candidate
Department of Chemistry
Massachusetts Institute of Technology, Cambridge, MA
Research Advisor: Professor Timothy F. Jamison
- Methodology: Phosphine-promoted cross-coupling reactions of propargylcopper reagents and alkenyl iodides
- Synthesis: Total synthesis of (-)-gloeosporone via nickel-catalyzed epoxide-alkyne reductive macrocyclization
- 2002 B.S. (Honors Chemistry), University of Michigan, Ann Arbor
Honors Thesis: "Studies on the Rate of Double Allylboration Reactions"
Research Advisor: William R. Roush.

Research and Teaching Experience:

- 2002-2007 Graduate Research Fellow with Professor Timothy F. Jamison
Massachusetts Institute of Technology
- 2003 Teaching Assistant, Chemistry 5.311 (Undergraduate Laboratory)
- 2002 Teaching Assistant, Chemistry 5.12 (Undergraduate Organic Chemistry)
- 2002 Teaching Assistant, Chemistry 5.311 (Undergraduate Laboratory)
- 2002 Research Intern
Pfizer Global Research and Development, Ann Arbor
- 2000-2002 Undergraduate Research Assistant with Professor William R. Roush
University of Michigan, Ann Arbor
- 2000 Kelley Tutor, Electricity and Magnetism
University of Michigan, 2000

Honors and Awards:

- 2006 Morse Travel Grant for the 55th Gordon Research Conference on Natural Products
2005 Pfizer Travel Award for Pfizer Green Chemistry Student Workshop

2005 President, Chemistry Graduate Student Committee, Mass. Inst. of Technology
2002 Merck Index Award for Outstanding Organic Chemistry Senior
2001 Intramural Tennis Champion, Men's Doubles, University of Michigan
1998 Eagle Scout

Publications:

Heffron, T. P.; Trenkle, J. D.; Jamison, T. F. "Synthesis of Skipped Enynes via Phosphine-Promoted Coupling Reactions of Propargylcopper Reagents," *Tetrahedron* **2003**, Symposium-In-Print, *New Synthetic Methods VII*, 8913-8917.

Presentations:

Trenkle, J. D.; Jamison, T. F. "Total Synthesis of (-)-Gloeosporone: Nickel Catalyzed Reductive Macrocyclization of Alkynes and Epoxides." The 55th Gordon Research Conference on Natural Products, Tilton School, Tilton, NH, July **2006**. Poster given.