I. **Enantioselective Nickel-Catalyzed Reductive Coupling Reactions of Alkynes and Aldehydes**

II. **Syntheses of Amphidinolides T1 and T4 via Catalytic, Stereoselective Macrocyclizations**

by

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B. A., Chemistry
Macalester College, 2000

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

DOCTOR OF PHILOSOPHY
IN ORGANIC CHEMISTRY

at the

Massachusetts Institute of Technology

May 2005 [June 2005]

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Professor Rick L. Danheiser _____

To my parents, Dwight and Nancy Colby

and

my husband, Chris

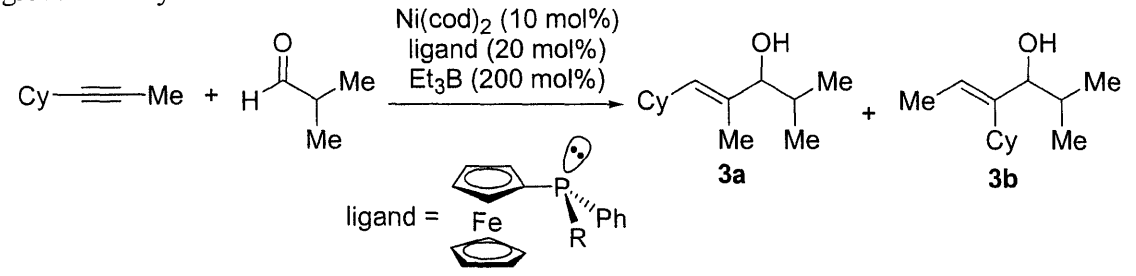
"The pursuit of truth and beauty is a sphere of activity in which we are able to remain children all our lives."

-Albert Einstein

Abstract

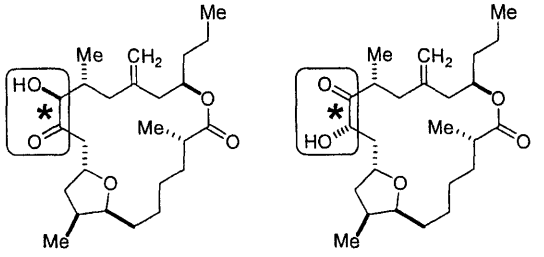
I. Enantioselective Nickel-Catalyzed Reductive Couplings of Alkynes and Aldehydes

Allylic alcohol synthesis via a nickel-catalyzed reductive coupling reaction of alkyl-substituted alkynes and aldehydes was studied for ligand effects with respect to the regioselectivity and enantioselectivity of the coupling process. A class of *P*-chiral, ferrocenyl phosphines was designed, synthesized, and evaluated for efficacy. Ultimately, these phosphines were found to be the most effective chiral ligands for coupling reactions of this class of alkynes, providing (*E*)-allylic alcohols in up to 67% ee and 85:15 regioselectivity.



II. Total Syntheses of Amphidinolides T1 and T4 via Catalytic, Stereoselective Reductive Macrocyclizations

Total syntheses of amphidinolides T1 and T4 were achieved using two nickel-catalyzed reductive coupling reactions of alkynes, with an epoxide in one case (intermolecular) and with an aldehyde in another (intramolecular). The latter was used to effect a macrocyclization, form a C-C bond and install a stereogenic center with >10:1 selectivity in both natural product syntheses. Alternative approaches in which intermolecular alkyne-aldehyde reductive coupling reactions would serve to join key fragments were investigated and are also discussed; it was found that macrocyclization was superior in several respects (diastereoselectivity, yield, and length of syntheses). Alkyne-epoxide couplings were instrumental in the construction of key fragments corresponding to approximately half of the molecule of both natural products. In one case (T4 series), the alkyne-epoxide coupling exhibited very high site selectivity in a coupling of a diyne. A model for the stereoselectivity observed in the macrocyclizations is also proposed.



amphidinolide T1 **amphidinolide T4**

* site of catalytic, stereoselective macrocyclization

Thesis Supervisor: Timothy F. Jamison
Title: Paul M. Cook Development Associate Professor of Chemistry

Preface

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

Colby, Elizabeth A.; Jamison, Timothy F.
***P*-Chiral, Monodentate Ferrocenyl Phosphines, Novel Ligands for Asymmetric Catalysis**.
J. Org. Chem. **2003**, *68*, 156-166. Copyright 2003 American Chemical Society.

Colby, Elizabeth A.; O'Brien, Karen. C.; Jamison, Timothy F.
Synthesis of Amphidinolide T1 via Catalytic, Stereoselective Macrocyclization.
J. Am. Chem. Soc. **2004**, *126*, 998-999. Copyright 2004 American Chemical Society.

Colby, Elizabeth A.; O'Brien, Karen. C.; Jamison, Timothy F.
Total Syntheses of Amphidinolides T1 and T4 via Catalytic, Stereoselective, Reductive Macrocyclizations
J. Am. Chem. Soc. **2005**, *127*, 4297-4307. Copyright 2005 American Chemical Society.

Acknowledgments

I'd like to begin by thanking my advisor, Tim Jamison, for providing a stimulating atmosphere in which to conduct research. I have enjoyed and learned a great deal from the projects that comprise this thesis. I am indebted to Tim for numerous productive suggestions and countless helpful discussions along the way; it's been quite a ride the past five years. I'm looking forward to seeing many more publications from the Jamison lab in the future.

I'm grateful to all past and present members of the Jamison lab for contributing to a dynamic research environment, for sharing insights during group meetings and daily discussions, and for the generous spirit in which time and material is shared throughout the lab. Thanks to Dr. Johann Chan, Dr. Sejal Patel, Dr. Aaron Skaggs, and Robert Jackson for showing me the ropes first year, giving advice over the years, and providing ligands to screen. It was a pleasure to approach the various milestones of graduate school with my classmates Tim Heffron, Karen Miller, Andrew Knox and David Goeddel. I particularly thank Karen for a productive collaboration this past year. Newer members of the lab have made many important and sometimes colorful contributions- my thanks and the best of luck to Ryan Moslin, Chudi Ndubaku, Jim Trenkle, Victor Gehling, Cici Ng, Andrew Lauer, Kate Woodin, and Aaron Van Dyke. Further thanks to postdocs Dr. Wei-Sheng Huang, Dr. Carmela Molinaro, Dr. Graham Simpson, and Dr. Neil Langille for sharing their experience. Additionally, I have been very privileged to work with several talented undergraduate students. I wish all the best to Valer Jeso and thank him for his work on the methylenation of sterically-hindered ketones. I am particularly grateful to Karen C. O'Brien (KC) for reaction optimization efforts, for providing copious quantities of starting materials, and a fruitful overall collaboration. I also thank Anna Hirsch who was also a wonderful coworker and made significant contributions of starting material.

A number of people have made my experience at MIT more positive through their special efforts. Susan Brighton is an amazing woman who keeps up the spirits of countless grad students and I thank her for personal encouragement. I am particularly grateful to my thesis committee chair, Professor Gregory C. Fu, for constructive annual meetings and for his advice and support both with respect to chemistry and career-planning. Many thanks are due to Dr. David Bray, Dr. Mark Wall, Dr. Li Li and Dr. Jeff Simpson for keeping the DCIF up and running on a daily basis and meeting the numerous needs of the department. I especially thank Li Li for going out of her way to help me out on a number of occasions by completing last-minute HRMS analysis.

I would like to thank several mentors from my years at Macalester College. Professor A. Truman Schwartz inspired me as a first-year student by his gifted teaching and personally encouraged me to pursue a major in chemistry. Professor Thomas D. Varberg is a wonderful lecturer and patient lab instructor; I appreciate the support that he offered despite my interest in organic chemistry. I am grateful to Professor Thomas R. Hoye for the opportunity to spend a summer in his lab at the University of Minnesota and the exciting synthetic project that I was able to continue at Macalester.

Importantly, I would like to thank my undergraduate advisor Professor Rebecca C. Hoye for her rigorous lectures in introductory organic chemistry and challenging coursework. She captured my interest and respect from the first day through her energy, intellect, and integrity. I am grateful for the two years I worked in her lab during which time

she patiently introduced me to the techniques of research-level synthetic chemistry. I cannot adequately express my deep appreciation for Professor Hoye's constant encouragement and continued mentorship.

Several of my classmates at MIT have become true friends. Thanks to Diana Hunt for study groups, get-togethers, and encouraging me to run! Thanks to Touch (Charnsak Thongsornkleeb) for memorable Davis Square races, ACS trip, barbeques, and movies. Can't wait for a reunion in Thailand!

Joshua Dunetz is a true "life" friend. We met during TA training the first week here and developed an instant bond that saw us through grad school. I'll never forget the times we've shared, whether we were learning the transition metals, memorizing sugar structures, laughing about nonsense, stressing about oral exams, practicing presentations, watching stupid movies or talking about important stuff. I cannot thank you enough for your support, good humor, and generosity. I wish you the absolute best in future endeavors, but you better believe I'm not losing track of you!

I am incredibly thankful to have an amazing, supportive and loving family. Many thanks to my brother Dave for encouraging me to continually reach higher in any effort and to consider the things that really matter. My sister Julie has been a constant source of support and friendship; I am at a loss to describe how important it was to have her in the Boston area for several years. Throughout my life, my parents Nancy and Dwight have made countless selfless sacrifices to give me the best chances at success. Along the way, they have been extraordinary examples of responsible and caring parents and human beings. I cannot thank them enough for the opportunities they have provided, especially with respect to education. It's been difficult to be separated by more than a thousand miles during my graduate school years, but their endless encouragement and support have been close to my heart and have sustained me.

Finally, it is a great joy to thank my friend and husband Chris Davie. Your kindness, support, and love mean the world to me. Thanks for always being there, sharing your thoughts and advice, and yes, being willing to listen to the same chemistry frustrations for the hundredth time. While we close this chapter of our life together, I very much look forward to the next- whatever it may hold and wherever we may be, we'll have each other. I do believe the best is yet to come!

Table of Contents

Abbreviations

Ac	acetyl
Bn	benzyl
Bu	butyl
cod	cyclooctadiene
Cp	cyclopentadienyl
Cy	cyclohexyl
dba	dibenzylideneacetone
DCC	*N,N'*-dicyclohexylcarbodiimide
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DMAP	4-dimethylaminopyridine
DMF	*N,N'*-dimethylformamide
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et	ethyl
Fc	ferrocenyl
g	grams
h	hours
Hex	hexyl
HKR	hydrolytic kinetic resolution
HMDS	hexamethyldisilamide
HMPA	hexamethylphosphoramide
i-Pr	isopropyl
LDA	lithium diisopropylamide
Me	methyl
mg	milligram
MOM	methoxymethyl
NBS	*N*-bromosuccinimide
NHK	Nozaki-Hiyama-Kishi
NMDPP	neomenthyldiphenylphosphine
NMO	*N*-methylmorpholine-*N*-oxide
nOe	nuclear Overhauser effect
Oct	octyl
OTf	trifluoromethanesulfonate
PAMP	phenyl(*o*-anisyl)(methyl)phosphine
Ph	phenyl
Py	pyridine
t-Bu	*tert*-butyl
TBS	*tert*-butyldimethylsilyl
TBAF	tetrabutylammonium fluoride
TMS	trimethylsilyl
THF	tetrahydrofuran
TPAP	tetrapropyl ammonium perruthenate
Ts	*p*-toluenesulfonyl

Chapter 1

Enantioselective Nickel-Catalyzed Reductive Coupling Reactions of Alkynes and Aldehydes

Introduction

Chiral allylic alcohols[1] are found in many natural products with potential therapeutic applications[2] and, importantly, provide a means for stereoselective functionalization in organic synthesis.[3] Accordingly, several catalytic enantioselective methods of allylic alcohol preparation have been described and can be divided into three types – additions of organometallic reagents to carbonyls, carbonyl reduction,[4] and kinetic resolution[5] of racemic allylic alcohols. Significantly, the first of these forms a carbon-carbon bond in the course of the reaction, rendering the process amenable to fragment coupling within the context of total synthesis. This potential has attracted a considerable amount of interest in the chemical community and has resulted in the development of a number of enantioselective methods that fall within this subgroup of allylic alcohol assembly strategies.

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[1] For reviews of useful reactions of allylic alcohols: (a) Brückner, R., in *Comprehensive Organic Synthesis*, Trost, B. M., Ed.; Pergamon, New York, 1991; vol. 6, Ch. 4.6, 873-908. (b) Hill, R. K., *ibid.*, vol. 5, Ch. 7.1, 785-826. (c) Wipf, P., *ibid.*, vol. 5, Ch. 7.2, 827-873.

[2] Terpestacin: (a) Iimura, S.; Oka, M.; Narita, Y.; Konishi, M.; Kakisawa, H.; Gao, Q.; Oki, T. *Tetrahedron Lett.* **1993**, *34* 493-496. (b) Oka, M.; Iimura, S.; Tenmyo, O.; Sawada, Y.; Sugawara, M.; Ohkusa, N.; Yamamoto, H.; Kawano, K.; Hu, S.-L.; Fukagawa, Y.; Oki, T. *J. Antibiotics* **1993**, *46*, 367-373. (c) Oka, M.; Iimura, S.; Narita, Y.; Furumai, T.; Konishi, M.; Oki, T.; Gao, Q.; Kakisawa, H. *J. Org. Chem.* **1993**, *58*, 1875-1881. Acutiphycin: (d) Moore, R. E.; Patterson, G. M. L. *J. Am. Chem. Soc.* **1984**, *106*, 8193-8197. Epothilones: (e) Bollag, D. M.; McQueney, P. A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazarides, E.; Woods, C. M. *Cancer Research* **1995**, *55*, 2325-2333. Chondropsins: (f) Cantrell, C. L.; Gustafson, K. R.; Cecere, M. R.; Pannell, L. K.; Boyd, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 8825-8829. (g) Rashid, M. A.; Gustafson, K. R.; Boyd, M. R. *Tetrahedron Lett.* **2001**, *42*, 1623-1626. (h) Rashid, M. A.; Cantrell, C. L.; Gustafson, K. R.; Boyd, M. R. *J. Nat. Prod.* **2001**, *64*, 1341-1344. (i) Bowman, E. J.; Gustafson, K. R.; Bowman, B. J.; Boyd, M. R. *J. Biol. Chem.* **2003**, *278*, 44147-44152.

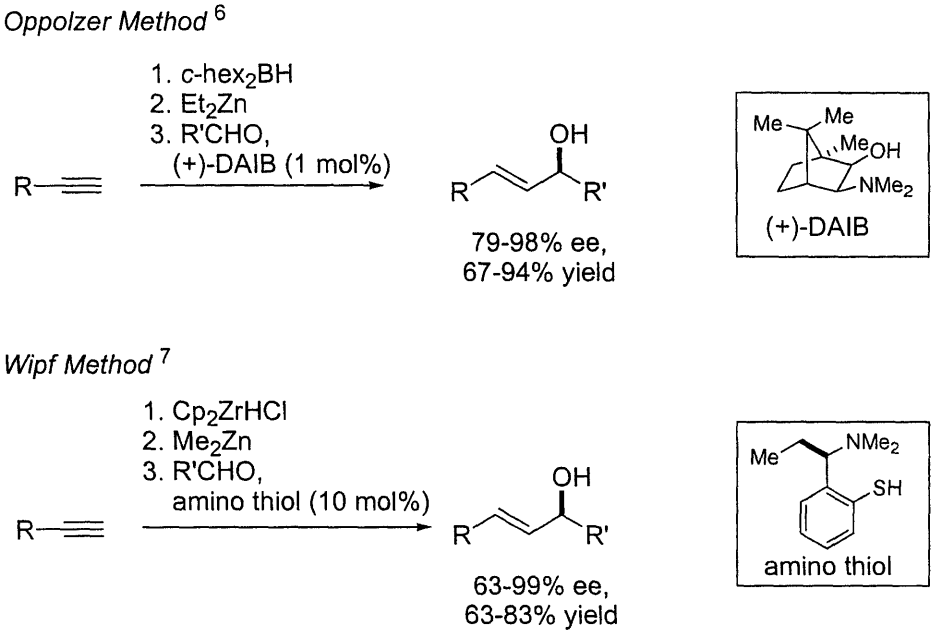
[3] Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307-1370.

[4] Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13529-13530.

[5] Martin, V.S.; Woodard, S.S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K.B. *J. Am. Chem. Soc.* **1981**, *103*, 6237-6240.

The methods of Oppolzer[6] and Wipf[7] form a carbon-carbon bond using different transition metals, by first preparing organometallic reagents by way of hydrometalation of a terminal alkyne (hydroboration and hydrozirconation, respectively). In each case, transmetalation with a dialkylzinc reagent precedes addition of a chiral ligand (amino alcohol and amino thiol, respectively) and an aldehyde (Scheme 1). The (*E*)-disubstituted allylic alcohol products are obtained in good to high yields and, in many cases, in very high enantiomeric excess. These procedures are not as effective with internal acetylenes (e.g., Et-C≡C-Et) as interconversion of the *(E)* and *(Z)* isomers has been reported to occur upon transmetalation with the organozinc reagent.[8]

Scheme 1



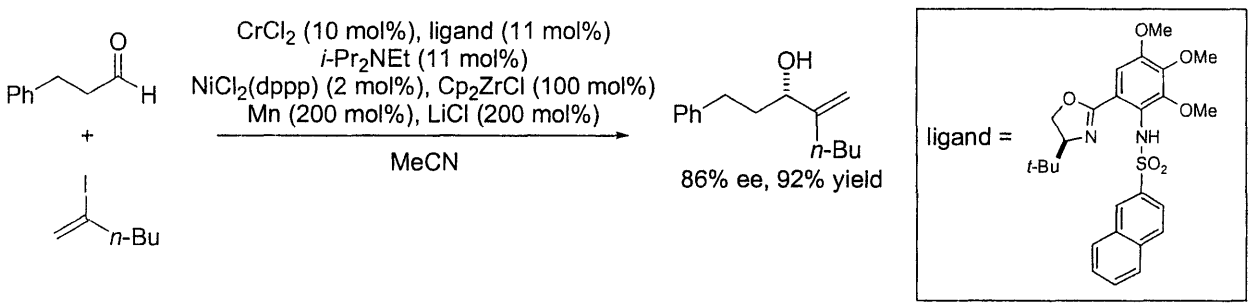
[6] (a) Oppolzer, W.; Radinov, R. N. *Helv. Chim. Acta*, **1992**, *75*, 170-173. (b) Oppolzer, W.; Radinov, R. N. *J. Am. Chem. Soc.* **1993**, *115*, 1593-1594. (c) Oppolzer, W.; Radinov, R. N.; El-Sayed, E. *J. Org. Chem.* **2001**, *66*, 4766-4770.

[7] (a) Wipf, P.; Ribe, S. *J. Org. Chem.* **1998**, *63*, 6454-6455. (b) Wipf, P.; Xu, W. *Org. Synth.* **1997**, *74*, 205-211.

[8] (a) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197-5200. In later work Wipf has reported the reductive coupling of aldehydes and imines and internal alkynes without *E/Z*- isomerization. Aldehydes: (b) Wipf, P.; Kendall, C. *Chem. Eur. J.* **2002**, *8*, 1778-1784. Imines: (c) Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2003**, *125*, 761-768. (b) Wipf, P.; Stephenson, C. R. J.; Okumura, K. *J. Am. Chem. Soc.* **2003**, *125*, 14694-14695.

Another well-known method for chiral allylic alcohol synthesis, the Nozaki-Hiyama-Kishi (NHK) reaction,[9] involves a chromium-mediated coupling of an alkenyl halide with an aldehyde. While several catalytic, enantioselective methods have been developed for related NHK couplings involving allylic halides (resulting in the asymmetric synthesis of homoallylic alcohols),[10] there are few reports of the use alkenyl halides in such an enantioselective manner. The method of Kishi using a chromium/nickel/zirconium/manganese system generates 1,1-disubstituted allylic alcohols in up to 86% ee when a chiral sulfonamide ligand is employed (Scheme 2).[11] Contemporaneously with this work, Paterson developed enantioselective couplings of alkenyl iodides and triflates with aldehydes exploiting the efficacy of chiral salen ligands in combination with a chromium/nickel/manganese/chlorotrimethylsilane system (Scheme 3).[12] To date, however, there are no reports of catalytic, enantioselective NHK reactions that generate a trisubstituted allylic alcohol moeity.

Scheme 2. Kishi's Enantioselective NHK Method.[11b]



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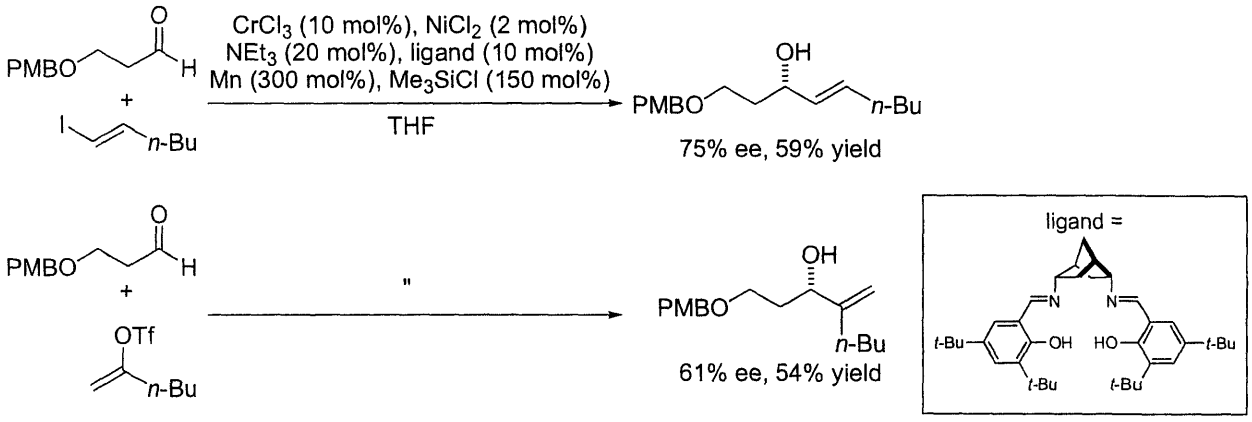
[9] (a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179-3181. (b) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644-5646. (c) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048-6050. (d) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 2533-2534. (e) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349-12357.

[10] (a) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umani-Ronchi, A. *Angew. Chem. Int. Ed.* **1999**, *38*, 3357-3359. (b) Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Polyhedron* **2000**, *19*, 537-539. (c) Inoue, M.; Suzuki, T.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 1140-1141. (d) Kurosu, M.; Lin, M.-H.; Kishi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 12248-12249.

[11] (a) Choi, H.; Nakajima, K.; Demeke, D.; Kang, F.-A.; Jun, H.-S.; Wan, Z.-K.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4435-4438. (b) Namba, K.; Kishi, Y. *Org. Lett.* **2004**, *6*, 5031-5033.

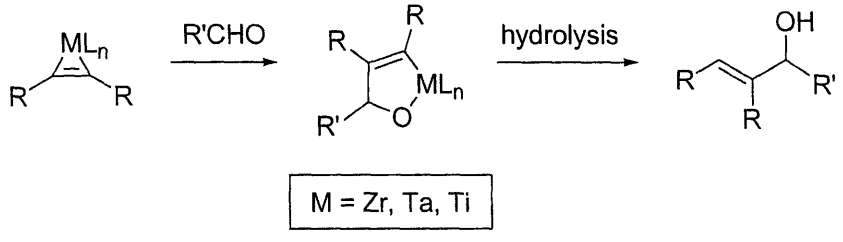
[12] Berkessel, A.; Menche, D.; Sklorz, C. A.; Schröder, M.; Paterson, I. *Angew. Chem. Int. Ed.* **2003**, *42*, 1032-1035.

Scheme 3. Paterson's Enantioselective NHK Method.[12]



Chiral allylic alcohols can also be obtained by way of in situ reductive coupling of an alkyne and an aldehyde. Several methods that involve stoichiometric use of early transition metals have been described. Buchwald,[13] Livinghouse,[14] and Negishi[15] have found that zirconocene-alkyne complexes may be coupled with aldehydes and ketones to form oxametallacyclopentenes which, upon hydrolysis, produce allylic alcohols (Scheme 4).

Scheme 4. Reductive Coupling of Aldehydes with Metal-Alkyne Complexes.[13-15]



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[13] Buchwald, S. L.; Watson, B. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1987**, *10*, 2544-2546.

[14] Van Wagenen, B. C.; Livinghouse, T. *Tetrahedron Lett.* **1989**, *30*, 3495-3498.

[15] Takagi, K.; Rousset, C. J.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 1440-1442.

Comparable reactivity has been found for other early transition metals. Takai and Utimoto[16] have demonstrated that tantalum-alkyne complexes add to aldehydes to form allylic alcohols. Sato[17] has shown an analogous transformation using titanium-alkyne complexes. A subsequent report by the same group has shown that optically enriched allylic alcohols can be obtained via stoichiometric use of chiral titanium-alkyne complexes derived from menthol.[18]

Recent advances in the reductive coupling of alkynes and aldehydes have included *catalytic* methods for the reductive coupling of alkynes and aldehydes. The first intramolecular variant[19] was reported by Crowe using a titanium catalyst. Montgomery[20] later developed reductive cyclizations of alkynals employing diethylzinc as a reducing agent and a nickel catalyst derived from $Ni(cod)_2$ and tributylphosphine. Despite the success of this catalyst system in an intramolecular fashion, Montgomery reported that it is not an effective promoter of *inter*molecular reductive coupling although intermolecular three-component coupling can be achieved in the absence of tributylphosphine (Scheme 5).[20a] The first such intermolecular reductive coupling of alkynes and aldehydes was reported by our group[21] using a nickel catalyst system composed of $Ni(cod)_2$, trialkylphosphine, and triethylborane providing (*E*)-trisubstituted allylic alcohols in good yield (Scheme 6).[22]

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[16] (a) Takai, K.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1990**, *55*, 1707-1708. (b) Kataoka, Y.; Miyai, J.; Oshima, K.; Takai, K. Utimoto, K. *J. Org. Chem.* **1992**, *57*, 1973-1981.

[17] Harada, K.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3203-3206.

[18] Takayanagi, Y.; Yamashita, K.; Yoshida, Y.; Sato, F. *Chem. Commun.* **1996**, 1725-1726.

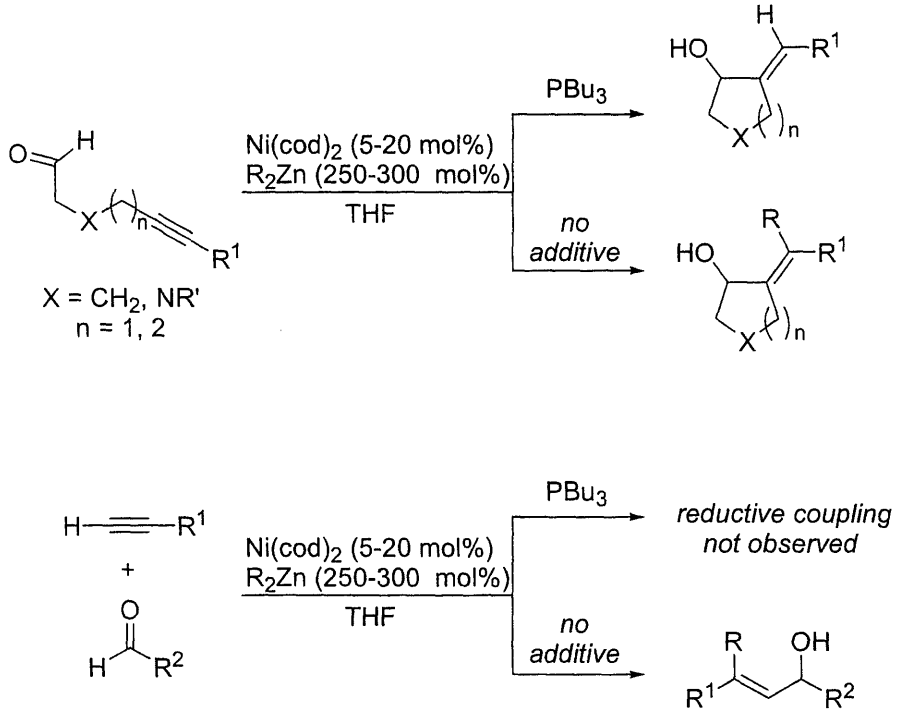
[19] Crowe, W. E.; Rachita, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 6787-6788.

[20] (a) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065-9066. (b) Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 6098-6099. (c) Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **2000**, *122*, 6950-6954. (d) Review: Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467-473.

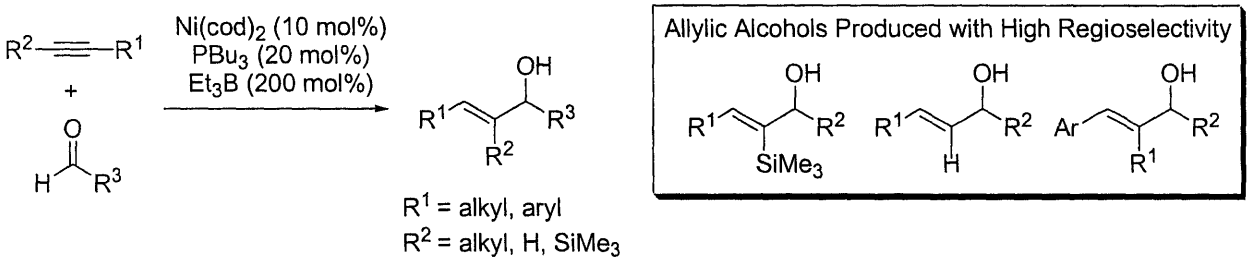
[21] Huang, W.-S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221-4223.

[22] After the work discussed in this thesis was published, Montgomery reported the intermolecular reductive coupling of alkynes and aldehydes catalyzed by $Ni(cod)_2$ and an imidazolium carbene ligand in the presence of triethylsilane, affording allylic triethylsilyl ethers. Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698-3699.

Scheme 5. Montgomery's Ni-Catalyzed Couplings of Alkynes and Aldehydes.[20]



Scheme 6. Jamison's Intermolecular Reductive Coupling of Alkynes and Aldehydes.[21]



Several intra- and intermolecular variants of nickel-catalyzed alkyne-carbonyl reductive and alkylative coupling reactions have been described in the literature.[23] While mechanistic proposals are essentially speculative, there are two predominant mechanistic frameworks that have been suggested to account for the observed reactivity. Generally, the first involves the oxidative cyclization of a nickel (0) complex, alkyne and carbonyl compound to form an oxanickelacyclopentene intermediate.[24,25,26] Transmetalation of an alkyl-metal containing β-hydrogen substituents generates an alkenyl-nickel species. Subsequent β-hydride elimination produces a nickel hydride complex which may then undergo reductive elimination to afford the final product. In the context of the reaction that we have developed (mechanism **I** in Scheme 7), triethylborane is utilized as the alkyl-metal reagent and, importantly, may play a dual role as reducing agent and aldehyde activator[26a] in the promotion of the oxidative cyclization event.

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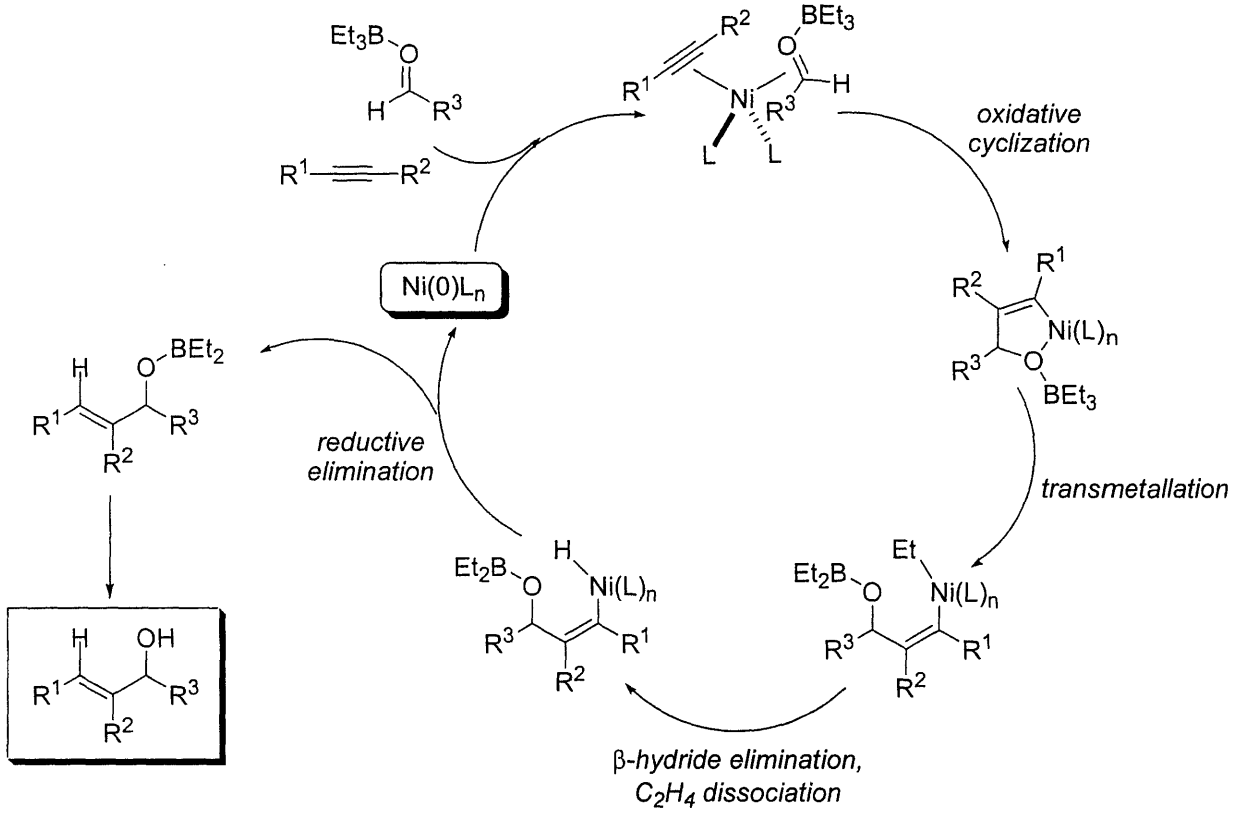
[23] Reviews: (a) Montgomery, J. *Angew. Chem. Int. Ed.* **2004**, *43*, 3890-3908. (b) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467-473. (c) Ikeda, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 5120-5122. (d) Miller, K. M.; Molinaro, C.; Jamison, T. F. *Tetrahedron: Asymmetry* **2003**, *14*, 3619-3625.

[24] For mechanistic proposals of nickel-catalyzed alkyne-aldehyde coupling reactions that invoke an oxametallacyclopentene intermediate, see: (a) Tsuda and Saegusa, reference 36. (b) Montgomery, references 20a, 20b, and 22. (c) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442-3443. (d) Chan, J.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 10682-10691. (e) Miller, K. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 15342-15343.

[25] For x-ray crystal structures of oxanickelacyclopentene structures, see: (a) Walther, D.; Bräunlich, G.; Kempe, R.; Sieler, J. *J. Organomet. Chem.* **1992**, *436*, 109-120. (b) Bennett, M. A.; Hockless, D. C. R.; Wenger, E. *Organometallics* **1995**, *14*, 2091-2101. (c) Cámpura, J.; Maya, C. M.; Palma, P.; Carmona, E.; Graiff, C.; Tirpicchio, A. *Chem. Commun.* **2003**, 1742-1743.

[26] For mechanistic proposals invoking related nickelacycles resulting from the oxidative cyclization of alkynes and alkenes, see: (a) Kimura, M.; Fujimatsu, H.; Ezoe, A.; Shibata, K.; Shimizu, M.; Matsumoto, S.; Tamaru, Y. *Angew. Chem. Int. Ed.* **1999**, *38*, 397-400. (b) Chowdhury, S. K.; Amarasinghe, K. K. D.; Heeg, M. J.; Montgomery, J. *J. Am. Chem. Soc.* **2000**, *122*, 6775-6776. (c) Including a crystal structure: Amarasinghe, K. K. D.; Chowdhury, S. K.; Heeg, M. J.; Montgomery, J. *Organometallics* **2001**, *20*, 370-372. (d) Sato, Y.; Takanashi, T.; Mori, M. *Organometallics* **1999**, *18*, 4891-4893. (e) Sato, Y.; Saito, N.; Mori, M. *J. Am. Chem. Soc.* **2000**, *122*, 2371-2372.

Scheme 7. Proposed Mechanism (**I**) Proceeding via an Oxanickelacyclopentene Intermediate.



Another possible mechanism for the nickel-catalyzed reductive coupling of alkynes and carbonyl compounds involves a hydrometalation event.[27,28] For the reaction in Scheme 6, this type of mechanism can be envisioned to proceed first by oxidative addition of a nickel (0) complex into a carbon-boron bond of triethylborane (proposed mechanism **II**, Scheme 8). Elimination of a β-hydride would form a nickel-hydride species that could undergo migratory insertion into an alkyne. Subsequent association of the aldehyde and migratory insertion would

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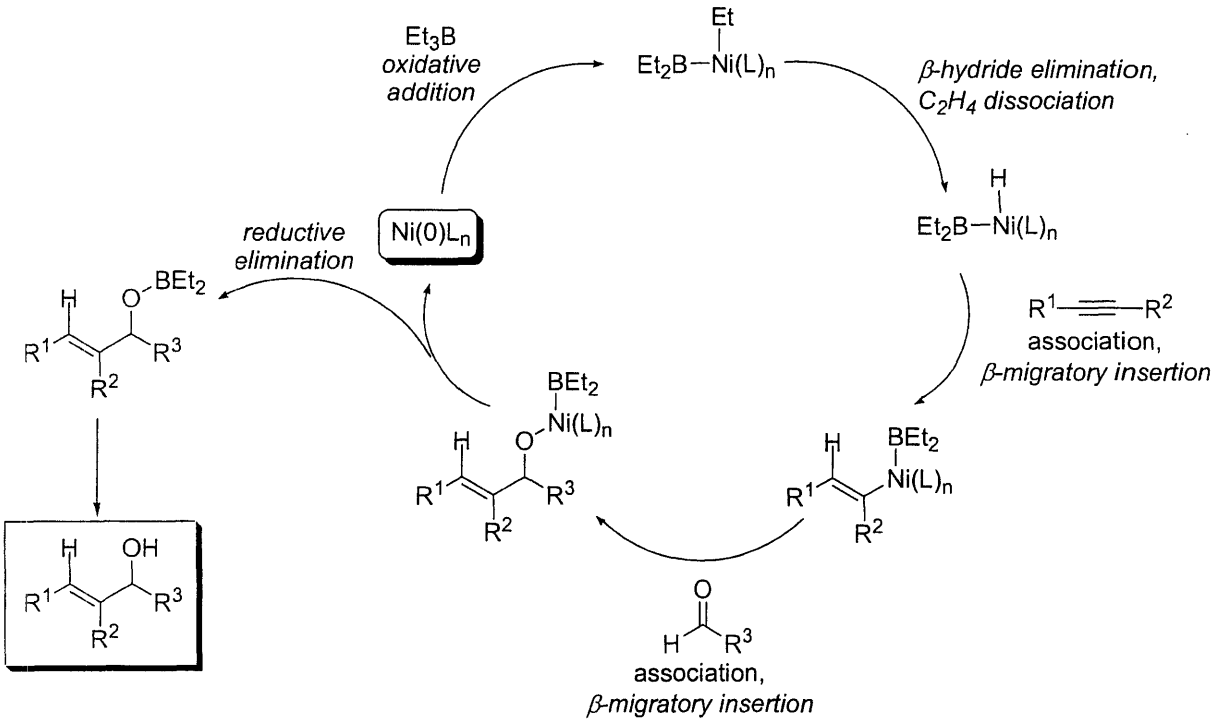
[27] For nickel-catalyzed alkyne-aldehyde reductive coupling reactions that propose a hydrometalation pathway, see: (a) Montgomery, reference 22. (b) Jamison, reference 24e.

[28] For related nickel-catalyzed coupling reactions of alkynes and alkenes that suggest a hydrometalation event as part of the operating mechanism, see: (a) Sato, Y.; Takimoto, M.; Hayashi, K.; Katsuhara, T.; Takagi, K.; Mori, M. *J. Am. Chem. Soc.* **1994**, *116*, 9771-9772. (b) Sato, Y.; Takimoto, M.; Mori, M. *J. Am. Chem. Soc.* **2000**, *122*, 1624-1634.

generate an alkoxy-nickel complex. Finally, reductive elimination would liberate the allylic diethylboryl ether, which would be cleaved to the allylic alcohol upon air workup.

Scheme 8. Proposed Hydrometalation Mechanistic Pathway (**II**).



At the outset of this work, examples of *asymmetric* catalytic reductive or alkylative coupling of alkynes and aldehydes not involving an initial stoichiometric hydrometalation of the alkyne had not been described in the literature.[29] As a variety of chiral phosphines have proven to be effective and highly selective ligands for an array of enantioselective transition metal-catalyzed reactions,[30] it was anticipated that the use of a chiral phosphine ligand might induce enantioselectivity in the transformation depicted in Scheme 6. Since the introduction of DIOP in

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[29] Krische has since reported Rh-catalyzed catalytic, enantioselective reductive coupling reactions of 1,3-diynes and glyoxals. Huddleston, R. R.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 11488-11489.

[30] (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley & Sons: New York, 1994; Chapter 2. (b) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*; VCH Publishers: Weinheim, 1993; Chapter 1. (c) Pietrusiewicz, K. M.; Zablocka, M. *Chem. Rev.* **1994**, *94*, 1375-1411. (d) Ohff, M.; Holz, J.; Quirmbach, M.; Börner, A. *Synthesis* **1998**, 1391-1415. (e) Yamanoi, Y.; Imamoto, T. *Rev. Heteroatom Chem.* **1999**, *20*, 227-248. (f) Brunel, J. M. and Buono, G., In "Topics in Current Chemistry", Springer-Verlag: New York, **2002**, *220*, pp. 79-105.

the early 1970's by Kagan,[31] bidentate phosphines have been the center of considerable attention. The exceptional enantioselectivities observed with chiral bisphosphines have often overshadowed the utility of chiral monophosphine ligands. Certain metal-catalyzed reactions, however, are inhibited or completely suppressed by bisphosphine ligands yet proceed smoothly and with high enantioselectivity when monophosphines are used.[32] Examples include rhodium-catalyzed hydrogenation of olefins and carbonyls, palladium-catalyzed hydrosilylation of olefins, rhodium-catalyzed hydrosilylation of carbonyls, nickel-catalyzed cross-coupling reactions, and palladium-catalyzed allylic substitution reactions.[33] The reaction shown in Scheme 6 appears to fall into this second category with respect to reactivity as several achiral monophosphine ligands form competent catalysts with $Ni(cod)_2$ but bisphosphines are ineffective.[21] Therefore, we set our sights on the use of chiral monophosphines. In the event that employment of chiral phosphines was feasible, the readily accessible functional groups of alkynes and aldehydes could be joined in a single catalytic operation to provide enantiomerically enriched, chiral allylic alcohols.

Since allylic alcohols corresponding to catalytic reductive couplings between aldehydes and "alkyl-alkyl" alkynes (alkyl-C≡C-alkyl') are commonly found in natural products and related molecules,[2] such an enantioselective transformation would constitute an efficient and rapid entry into these important functional group assemblies. A significant consideration in such coupling reactions is control over the regioselectivity of the process. In a number of transition metal-catalyzed reductive coupling reactions of internal alkynes, selective functionalization can be difficult to achieve when the alkyne is substituted with groups of similar electronic and steric demand as shown in the summary of aldehyde-alkyne coupling reactions in Table 1 (reductive couplings (entries 1-3) and hydroacylation (entry 4)).[34,35,36] For these cases in which the

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[31] (a) Dang, T. P.; Kagan, H. B. *J. Chem. Soc., Chem. Comm.* **1971**, 481. (b) Kagan, H. B.; Dang, T. P. *J. Am. Chem. Soc.* **1972**, *94*, 6429-6433.

[32] (a) Komarov, I. V.; Börner, A. *Angew. Chem. Int. Ed.* **2001**. *40*, 1197-1200. (b) Van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741-2769.

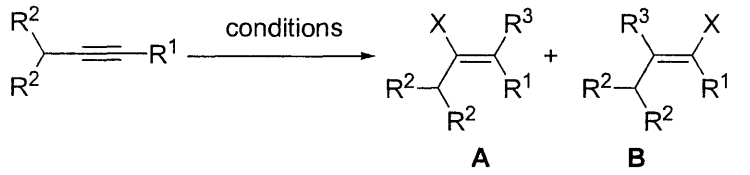
[33] Recent reviews: (a) Lagasse, F.; Kagan, H. B. *Chem. Pharm. Bull.* **2000**, *48*, 315-324. (b) Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354-362.

[34] Maier, M. E.; Oost, T. *J. Organomet. Chem.* **1995**, *505*, 95-107.

[35] Bahadoor, A. B.; Flyer, A. Micalizio, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 3694-3695.

differentiation is between a primary and secondary alkyl group, product ratios are commonly 2:1 or 3:1, with higher selectivity achieved with functionalized alkynes and aldehydes (entry 3).

Table 1. Transition Metal-Mediated Coupling Reactions of Internal Alkynes and Aldehydes.



R^1 = Me or primary alkyl
R^2 = alkyl

entry	conditions	products	reference
1	1. $TaCl_5$ (200 mol%), Zn (300 mol%) 2. pyridine, RCHO, 3. NaOH, H_2O	X = H, R^3 = CH(OH)R **A**:**B**, 65:35 to 74:36	Takai and Utimoto (ref 16b)
2	1. $Cp_2ZrH(Cl)$ (100 mol%) 2. MeLi 3. RCHO 4. MeOH	X = H, R^3 = CH(OH)R **A**:**B**, 65:35	Maier (ref 34) Buchwald (ref 13)
3	1. BuLi (*R^2 contains free OH*) 2. $ClTi(O\textit{i}\text{-}Pr)_3$; C_5H_9MgCl 3. $BF_3 \cdot OEt_2$, RCHO	X = H, R^3 = CH(OH)R **A**:**B**, 75:25 to 95:5	Micalizio (ref 35)
4	$Ni(cod)_2$ (10 mol%) $P(\textit{n}\text{-}oct)_3$ (20 mol%) RCHO (100 mol%)	X = H, R^3 = COR **A**:**B**, 78:22	Tsuda and Saegusa (ref 36)

In contrast to these examples, there are some hydrometalation reactions of this class of alkynes in which very high selectivity is realized. Hydroboration[37] and hydrozirconation[38]

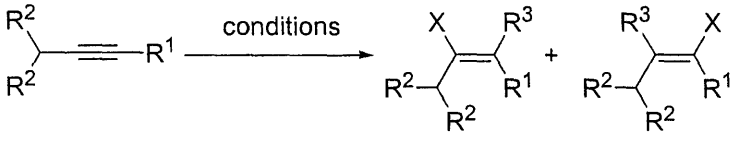
[36] Tsuda, T.; Kiyoi, T.; Saegusa, T. *J. Org. Chem.* **1990**, *55*, 2554-2558.

[37] Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370-4371.

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

reactions that are conducted under conditions in which thermodynamic equilibration of the initial alkenyl-metal species is possible result in selective functionalization adjacent to the less-hindered alkyl group of an alkyne (Table 2, entries 1 and 2). In the case of hydrozirconation, this equilibration is only possible when superstoichiometric zirconium reagent is utilized. When the reaction is performed under kinetically-controlled conditions (100 mol% zirconium), selectivity is not as high (entry 3). Wipf has recently capitalized on the high selectivity and speed of hydrozirconation under microwave conditions in a two-step reductive coupling of alkynes and imines in the selective synthesis of (*E*)-allylic amines (entry 4).[39]

Table 2. Highly Selective Hydrometalations of Alkynes.



R^1 = Me or primary alkyl
R^2 = alkyl

entry	conditions	products	reference
1	catecholborane (100 mol%)	X = H, R^3 = BOR_2 **A**:**B**, 92:8	Brown (ref 37)
2	1. $Cp_2ZrH(Cl)$ (200 mol%) 2. I_2	X = H, R^3 = I **A**:**B**, >98:2	Schwartz (ref 38)
3	1. $Cp_2ZrH(Cl)$ (100 mol%) 2. I_2	X = H, R^3 = I **A**:**B**, 89:16	Schwartz (ref 38)
4	1. $Cp_2ZrH(Cl)$ (200 mol%, μW) 2. Me_2Zn 3. $ArCHNP(O)Ph_2$	X = H, R^3 = $CArH(NH)P(O)Ph_2$ **A**:**B**, >99:1	Wipf (ref 39)

[39] Wipf, P.; Janjic, J.; Stephenson, C. R. J. *Org. Biomol. Chem.* **2004**, *2*, 443-445.

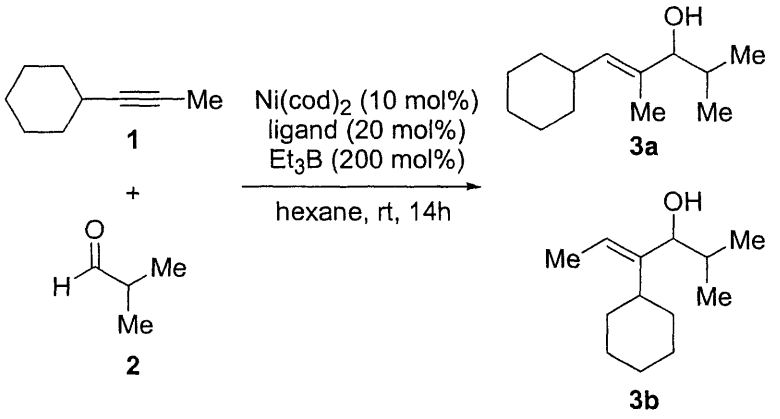
Results and Discussion

At the outset of our studies directed toward the development of nickel-catalyzed enantioselective reductive couplings of aldehydes and "alkyl-alkyl" alkynes, it was clearly necessary not only to consider how an appropriate chiral ligand might control the formation of the stereogenic center, but also how the use of such a ligand might achieve high regioselectivity in the formation of allylic alcohol products. Accordingly, we launched our investigations by probing the second of these considerations, regioselectivity, by examining achiral catalyst systems. We planned to apply our findings regarding ligand structure and regioselectivity to related chiral catalyst systems in an effort to develop an enantioselective reductive coupling reaction.

Initial Regioselectivity Investigations

In the original report of intermolecular reductive coupling of alkynes and aldehydes using achiral phosphine ligands,[21] several notable observations with respect to regioselectivity of the transformation are included. That is, allylic alcohols formed via couplings of terminal alkynes and alkynes containing one aromatic substituent or a trimethylsilyl group (or both) were obtained in high regioselectivity (see Scheme 6). We sought to study the effect of ligand structure on the regiochemical outcome of couplings in which there was a small difference in electronic and steric demand between the two groups bonded to the alkyne. To this end, 1-cyclohexyl-1-propyne (**1**) was chosen as a test alkyne with isobutyraldehyde (**2**) as the coupling partner (eq 1). Tributylphosphine was effective in this catalytic reaction although allylic alcohols **3a** and **3b** were afforded in low regioselectivity (Table 3, entries 1-2). Similar low levels of selectivity were also observed with other achiral phosphines (entries 3-6), with ferrocenyldiphenylphosphine (entry 6) emerging as the most selective ligand. Performing the reaction in hexane or toluene had a minimal effect on yield and regioselectivity (entries 1-2 and 6-7), while reducing the temperature to 0 °C failed to increase selectivity.

Table 3. Representative Achiral Ligand Effects on Regioselectivity.



(1)

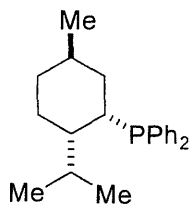
entry[a]	ligand	yield **3**[b]	**3a** : **3b**[c]
1	PBu_3	55%	67:33
2[d]	PBu_3	52%	63:37
3	$Ph_2P(n\text{-Bu})$	56%	65:35
4[d]	$Ph_2P(Cy)$	62%	67:33
5	PBn_3	19%	43:57
6	Ph_2PFc	52%	75:25
7[d]	Ph_2PFc	60%	75:25
8[d,e]	Ph_2PFc	55%	70:30

[a] Reaction conducted in hexane unless noted. [b] Combined isolated yield of **3a** and **3b**. [c] Determined by integration of the alkenyl H signals in the ^1H NMR spectrum (doublet and quartet, **3a** and **3b**). [d] Reaction conducted in toluene. [e] Reaction conducted at 0 °C.

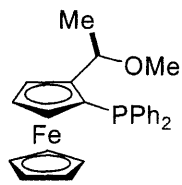
Initial Investigations with Known Chiral Ligands

Upon conclusion of the initial achiral ligand screen, an investigation of chiral ligands was conducted. Disappointingly, (neomenthyl)diphenylphosphine (NMDPP, **4**),[40] a ligand that induces a high degree of enantioselectivity in couplings of aryl alkynes and branched aldehydes,[41] provided both low regioselectivity and enantioselectivity in the test coupling reaction of 1-cyclohexyl-1-propyne (**1**) and isobutyraldehyde (**2**) (entry 1). Likewise, Hayashi's chiral ferrocenyl phosphine ligands[42] (eg **5**, Table 4, entry 2) did not deliver the allylic alcohol with promising levels of regio- or enantioselectivity. Finally, proline-derived alkyldiphenylphosphine **6**[43] also provided products with disappointing selectivity (entry 3).

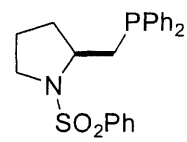
Table 4. Effects of Representative Known Chiral Ligands.



4



5



6

entry[a]	ligand	yield **3**[b]	**3a** : **3b**[c]	ee (**3a**)[d]
1[e]	**4**	50%	67:33	35%
2[e]	**5**	40%	50:50	20%
3[f]	**6**	20%	55:45	35%

[a] Reaction as performed in Eq 1. [b] Combined isolated yield of **3a** and **3b**. [c] Determined by integration of ^{1}H NMR spectrum. [d] Measured by chiral GC analysis, B-PH column. [e] Conducted in toluene. [f] Conducted in hexane.

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[40] Morrison, J. D.; Burnett, R. E.; Aguiar, A. M.; Morrow, C. J.; Philips, C. *J. Am. Chem. Soc.* **1971**, *93*, 1301-1303.

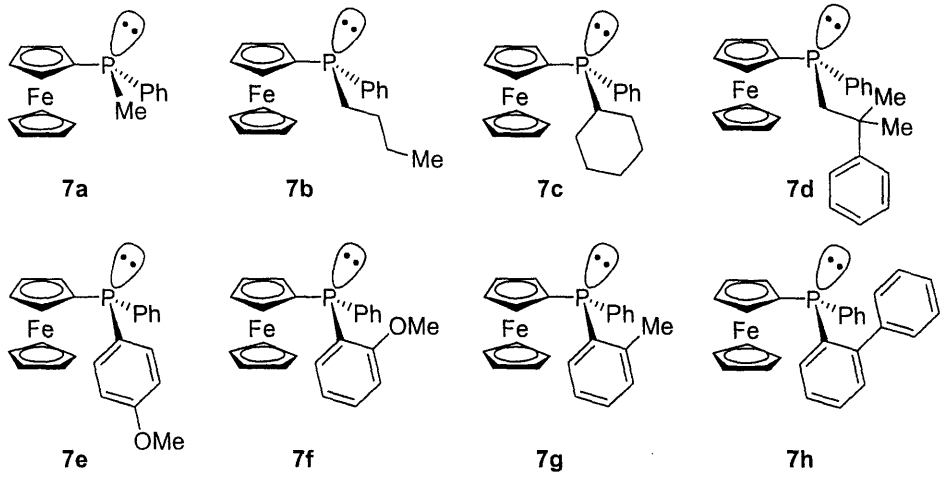
[41] See reference 24c.

[42] Prepared by Dr. Johann Chan as reported by: (a) Hayashi, T.; Konishi, M.; Fukushima, M.; Mise, T.; Kagotani, M.; Tajika, M.; Kumada, M.; *J. Am. Chem. Soc.* **1982**, *104*, 180-186. (b) Hayashi, T.; Hayashizaki, K.; Kiyoi, T.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8153-8156.

[43] Prepared by Dr. Sejal Patel as reported by: Hiroi, K.; Hidaka, A.; Sezaki, R.; Imamura, Y. *Chem. Pharm. Bull.* **1997**, *45*, 769-777.

Encouraged both by the precedent that monophosphines containing a ferrocenyl moiety have been particularly effective ligands for several catalytic, asymmetric metal-catalyzed reactions[44,45,46] and by the original screening of achiral ligands for regioselectivity (Table 3), $FcPPh_2$ was taken as a lead structure. Because ferrocenyl phosphines containing *C*-chiral substituents did not selectively deliver allylic alcohols, we targeted several *P*-chiral ferrocenyl phosphines. Compounds **7a-h** (Chart 1) are representative members of a class of *P*-chiral monodentate phosphines that has not been thoroughly explored to date and were prepared in order to investigate their steric and electronic effects on these and other catalytic reactions.[47]

Chart 1



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[44] Reviews: (a) Colacot, T. J. *Chem. Rev.* **2003**, *103*, 3101-3118. (b) Togni, A.; Hayashi, T, eds. *Ferrocenes. Homogeneous Catalysis, Organic Synthesis, Materials Science;* VCH Publishers: Weinheim, 1995. (c) Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377-2407.

[45] Asymmetric, catalytic reactions using planar-chiral phosphaferrocene ligands: (a) Qiao, S.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *63*, 4168-4169. (b) Tanaka, K.; Qiao, S.; Tobisu, M.; Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 9870-9871. (c) Shintani, R.; Lo, M. M-C.; Fu, G. C. *Org. Lett.* **2000**, *2*, 3695-3697. (d) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542-547.

[46] Both achiral and chiral (racemic) ferrocenyl monophosphines are highly effective for Pd-catalyzed arylation and cross-coupling reactions, see: (a) Stambuli, J. P.; Stauffer, S. R.; Shaughnessy, K. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 2677-2678. (b) Stauffer, S. R.; Beare, N. A.; Stambuli, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4641-4642. (c) Beare, N. A.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 541-555. (d) Kataoka, N.; Shelby, Q.; Stambuli, J. P; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553-5566.

[47] The *o*-anisyl derivative **7e** has been previously reported (92% ee): (a) Brown, J. M.; Laing, J. C. P. *J. Organomet. Chem.* **1997**, *529*, 435-444. Racemic **7a** and **7b** have also been synthesized previously, but not in enantiomerically enriched form (b) (+/-) **7a**: Seyferth, D.; Withers, Jr., H. P. *Organometallics* **1982**, *1*, 1275-1282. (c) (+/-) **7b**: Chacon, S. T.; Cullen, W. R.; Bruce, M. I.; Shawkataly, O. B. *Can. J. Chem.* **1990**, *68*, 2001-2010.

Synthesis of *P*-Chiral Monodentate Ferrocenyl Phosphines

The van Leeuwen[48] and Mezzetti[49] laboratories recently described procedures for preparing related bidentate *P*-chiral ferrocenyl bisphosphines using Jugé's method[50] for the enantioselective synthesis of PAMP[51] and other *P*-chiral phosphines using ephedrine-based oxazaphospholidine borane **8** (prepared in one step from dichlorophenylphosphine, ephedrine, diethylisopropylamine and borane-tetrahydrofuran, see Experimental Section). This method is based upon a highly diastereoselective addition of an organolithium species to **8** (shown using ferrocenyllithium in Scheme 9). The addition is believed to proceed through an associative mechanism, culminating in the cleavage of the O-P bond.[52] Specifically, the organolithium approaches **8** opposite nitrogen to form a pentacoordinate intermediate which undergoes pseudorotation to relieve eclipsing steric interactions between the phenyl and *N*-methyl groups. Cleavage of the O-P bond generates phosphinamide boranes (**9**) with overall retention of configuration. Substitution reactions from this point forward in the sequence proceed via S_N2-type displacements with inversion of stereochemistry. Finally, removal of the borane protecting group proceeds with retention at phosphorus as diethylamine attacks at boron.

Our initial investigations began with one of van Leeuwen's intermediates, (*R*)-methyl (ferrocenylphenyl)phosphinite borane (**10i**).[48c] Using this strategy (Scheme 9), the ferrocenyl and phenyl groups of all the ligands would be installed first to allow for straightforward variation of the third group from a common intermediate. Phosphinamide borane **9i** ((*R*$_p$, 1*R*, 2*S*)-*N*-methyl-*N*-(1-hydroxy-1-phenyl)prop-2-yl-*P*-(ferrocenyl)-*P*-(phenyl)-phosphinamide borane) was prepared by addition of ferrocenyllithium (generated from bromoferrocene, vide infra) to **8**.

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[48] (a) Nettekoven, U.; Widhalm, M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron: Asymmetry* **1997**, *8*, 3185-3188. (b) Nettekoven, U.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Widhalm, M.; Spek, A. L.; Lutz, M. *J. Org. Chem.* **1999**, *64*, 3996-4004. (c) Nettekoven, U.; Widhalm, M.; Kalchhauser, H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Lutz, M.; Spek, A. L. *J. Org. Chem.* **2001**, *66*, 759-770.

[49] Maienza, F.; Wörle, M.; Steffanut, P.; Mezzetti, A.; Spindler, F. *Organometallics* **1999**, *18*, 1041- 1049.

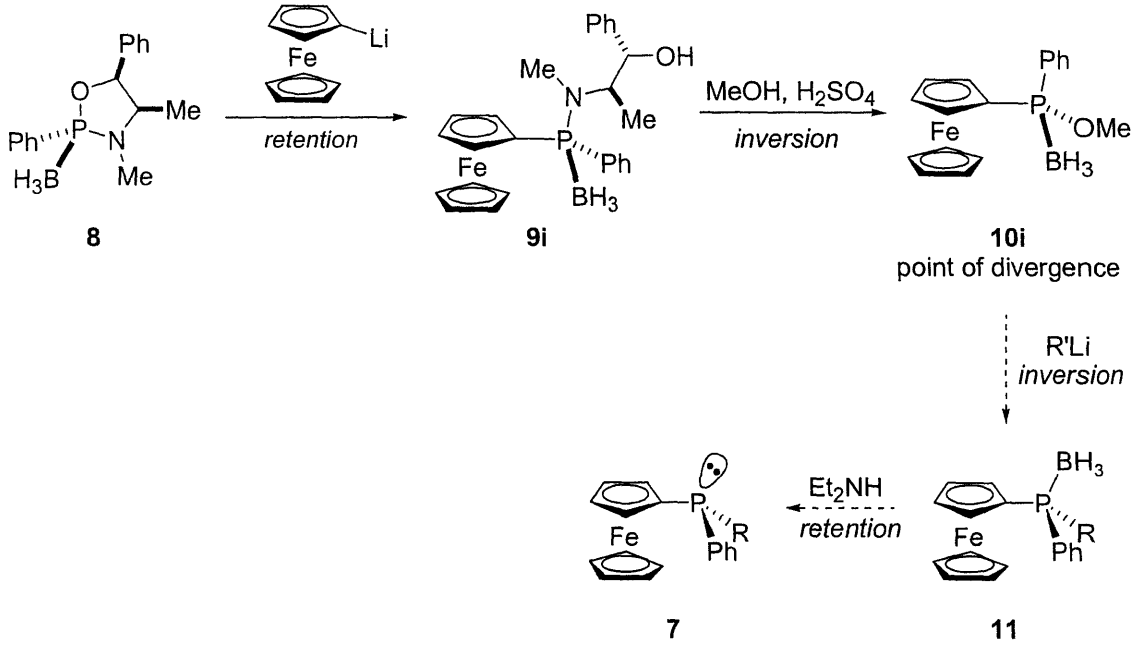
[50] Jugé, S.; Stephan, M.; Laffitte, J. A.; Genêt, J. P. *Tetrahedron Lett.* **1990**, *31*, 6357-6360.

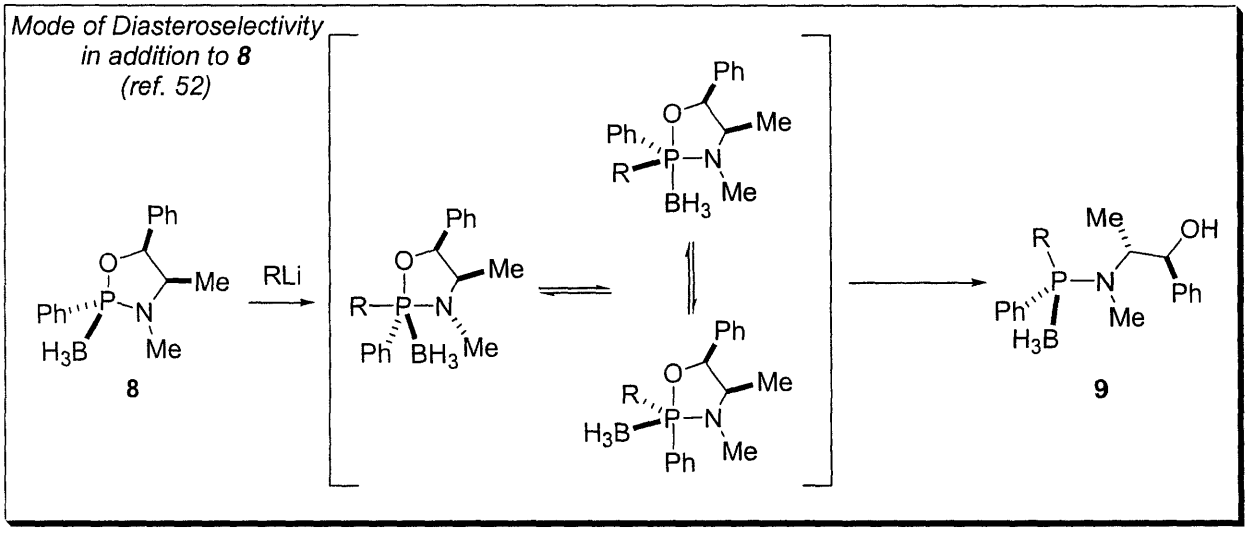
[51] PAMP was first synthesized by Knowles using a strategy developed by Mislow, by way of an enantiomerically-enriched menthyl phosphinate. (a) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D. *J. Chem. Soc., Chem. Comm.* **1972**, 10-11. (b) Korpiun, O.; Lewis, R. A.; Chickos, J.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4842-4846.

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

However, as observed by van Leeuwen, we found that the acid-promoted methanolysis to key intermediate **10i** was sluggish and low yielding (approximately 30% yield of **10i**, 35% recovered **9i**).

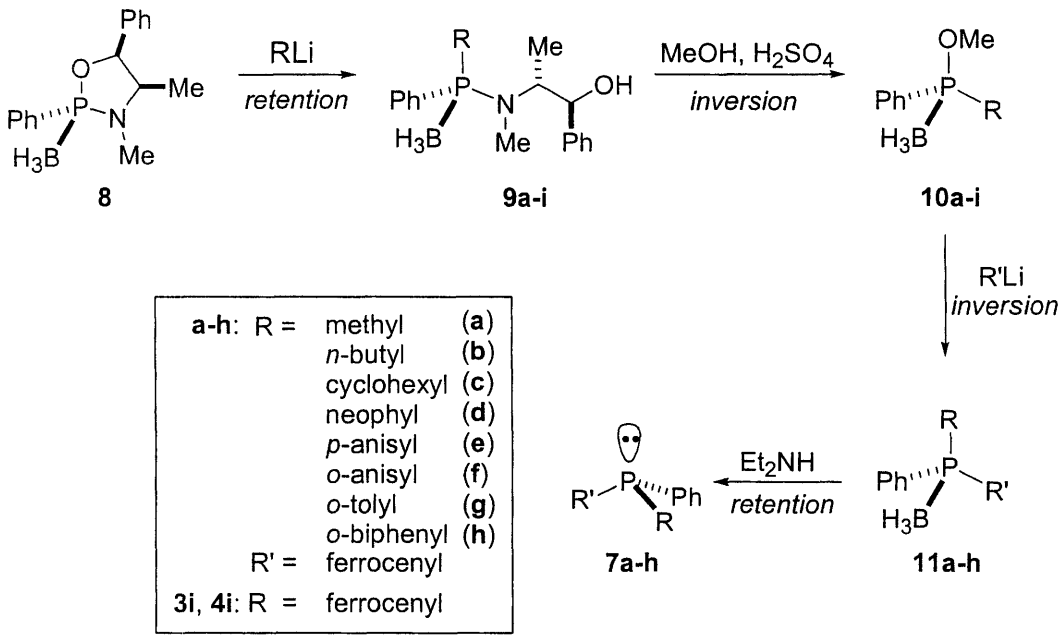
Scheme 9. Strategy for the Synthesis of **7a-h** from a Common Intermediate.





Accordingly, in order to prepare the ligands in a quantity suitable for thorough study, we investigated an alternative strategy that installs the sterically bulky (and acid-sensitive) ferrocenyl group later in the synthesis.[53] As shown in Scheme 10, treatment of oxazaphospholidine borane **8** with the appropriate organolithium reagent (retention of stereochemistry) was followed by acid-promoted methanolysis of the resulting phosphinamide borane product **9** (inversion). It should be noted that preparation of cyclohexyllithium and 2-methyl-2-phenyl-1-propyllithium (neophyllithium) was accomplished using a naphthalene-catalyzed oxidative addition of lithium metal[54] to chlorocyclohexane and 1-chloro-2-methyl-2-phenylpropane, respectively. Methanolysis of aryl and primary alkyl substituted phosphinamide boranes **9a-b** and **9d-h** proceeded smoothly, but formation of methyl-cyclohexylphenylphosphinite borane **10c** was lower yielding. Secondary and tertiary alkyl substituted phosphinamide boranes are notoriously difficult to convert to phosphinite boranes, and usually require heating to obtain the desired product, often in low yield.[55]

Scheme 10. Higher-Yielding Route to **7a-h**.



[53] Brown used a similar approach to prepare **1e** in 92% ee. See reference 47a.

[54] Yus, M.; Ramón, D. J. *J. Chem. Soc., Chem. Comm.* **1991**, 398-400.

[55] Rippert, A. J.; Linden, A.; Hansen, H.-J. *Helv. Chim. Acta* **2000**, *83*, 311-321.

Completion of the phosphine syntheses required installation of the ferrocenyl substituent. Although methods of direct deprotonation of ferrocene with *s*-butyllithium or *t*-butyllithium are commonly used to generate ferrocenyllithium (FcLi), we found that FcLi prepared via metal-halogen exchange of commercially-available bromoferrocene and *t*-butyllithium provided the desired substitution products (inversion of configuration) in superior yields.[56,57] The metal-halogen exchange can also be performed with *n*-butyllithium, but in the case of ferrocenylmethylphenylphosphine (**7a**), we observed significant amounts (>30%) of an *n*-pentyl-containing product, which likely arose from ferrocenyl substitution, deprotonation of one of the methyl protons, and alkylation of the resulting organolithium compound by *n*-butyl bromide.[58]

In all cases, the BH_3 group facilitates chromatographic purification, providing the corresponding complexes of the phosphines as orange, air-stable compounds. Removal of the BH_3 group by heating in the presence of diethylamine proceeds in good to excellent yield in all cases, providing the free phosphines. The enantiomeric purities of **7a-h** were determined by re-protection with BH_3 (retention) and subsequent measurement via chiral HPLC. As shown in Scheme 11, comparison of the enantiomeric excesses of **11a-h** before and after the deprotection-reprotection sequence confirmed the preservation of stereochemical integrity during the diethylamine-mediated BH_3 removal.

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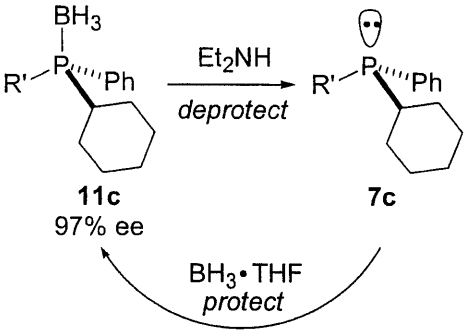
[56] For other selective methods of FcLi generation, see: (a) Sanders, R.; Mueller-Westerhoff, U. T. *J. Organomet. Chem.* **1996**, *512*, 219-224. (b) Chieffi, A.; Comasseto, J. V.; Snieckus, V. *Synlett* **2000**, *2*, 269-271. (c) Guillaneux, D.; Kagan, H. B. *J. Org. Chem.* **1995**, *60*, 2502-2505.

[57] Bromoferrocene was recently discontinued by Aldrich. In subsequent ligand syntheses, Kagan's procedure (reference 56c) was used to generate FcLi from ferrocene, using 200 mol% *t*-BuLi in THF/hexane at 0 °C. This method produced the desired compounds of structure **11** in yields that are typically 10-20% lower than the yields obtained using FcLi generated from bromoferrocene.

[58] (a) Imamoto, T.; Kusumoto, T.; Suzuki, N.; Sato, K. *J. Am Chem. Soc.* **1985**, *107*, 5301-5303. (b) Imamoto, T.; Oshiki, T.; Onozawa, T.; Kusumoto, T.; Sato, K. *J. Am. Chem. Soc.* **1990**, *112*, 5244-5252.

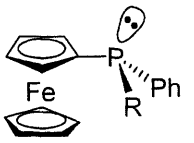
Scheme 11. Determination of the Enantiomeric Purity of **7a-h**.



Summarized in Table 5 are the results obtained for the synthesis leading to *P*–chiral phosphines **7a-h**. The average yield for the 4-step sequences range from 75-86% per step in all but one case (R = *c*–C_6H_{11}, **7c**), and **7b** is the only ligand of the eight described that was not afforded in ≥ 94% ee at the end of the sequence. Several of these ligands are moderately air-stable, and the corresponding BH_3 complexes (**11a-h**) are convenient for long-term storage of these novel *P*–chiral phosphines (Scheme 9).[59]

[59] In two cases shown in Table 5, the diastereoselectivity of RLi addition (for **9b** and **9g**) does not agree with the enantiomeric excess of the corresponding phosphine-borane complexes (**11b** and **11g**). It is possible that racemization may occur during the methanolysis step (giving **10b** and **10g**) in these cases. For similar observations, see: Moulin, D.; Bago, S.; Bauduin, C.; Darcel, C.; Jugé, S. *Tetrahedron: Asymmetry* **2000**, *11*, 3939-3956.

Table 5. Summary of Synthetic Operations in the Preparation of **7a-h**.[a]



7a-h

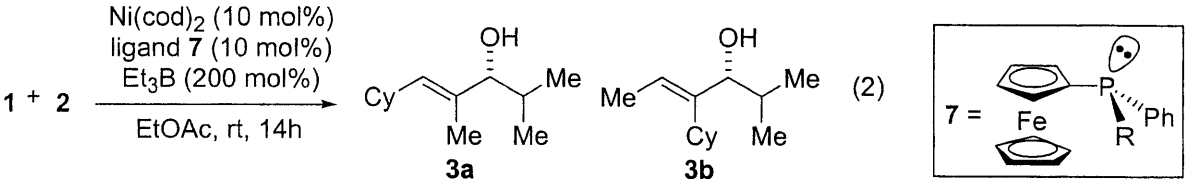
	RLi addition			Methanolysis		FcLi addition			BH_3 removal			Overall Yield (4 steps)
R	Cpd	Yield	d.r.[b]	Cpd	Yield	Cpd	Yield	ee[c]	Cpd	Yield	**ee**[c]	
Me	**9a**	79%	9:1	**10a**	75%	**11a**	58%	83%	**7a**	93%	**>95%**[d]	**32%**
n-Bu	**9b**	80%	16:1	**10b**	62%	**11b**	90%	77%	**7b**	88%	**80%**	**39%**
Cy	**9c**	88%	>98:2	**10c**	29%	**11c**	66%	97%	**7c**	83%	**98%**	**14%**
Neophyl	**9d**	72%	>98:2	**10d**	65%	**11d**	79%	98%	**7d**	>99%	**96%**	**37%**
p-anisyl	**9e**	80%	>98:2	**10e**	77%	**11e**	85%	95%	**7e**	95%	**94%**	**50%**
o-anisyl	**9f**	93%	>98:2	**10f**	77%	**11f**	92%	>98%	**7f**	83%	**>98%**	**55%**
o-tolyl	**9g**	80%	>98:2	**10g**	87%	**11g**	70%	83%	**7g**	>99%	**>98%**[e]	**48%**
o-biphenyl	**9h**	81%	>98:2	**10h**	77%	**11h**	69%	98%	**7h**	94%	**96%**	**40%**

[a] See Scheme 10. [b] Determined by ^{1}H NMR. [c] Determined by HPLC. [d] Recrystallized from hexane. [e] Crystallized from diethylamine upon standing after BH_3 removal.

Enantioselective Reductive Coupling Reactions of Alkynes and Aldehydes

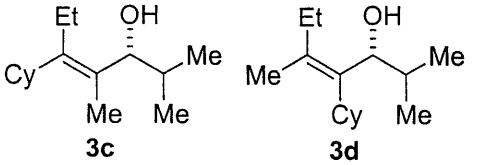
With the target ligands **7a-h** in hand, they were tested for efficacy in the nickel-catalyzed reductive coupling of **1** and **2**.[60] As shown in Table 6, all of the ligands were found to be competent promoters of the desired reaction. In these studies of **7a–7h**, we found *o*-tolyl ligand **7g** to be superior with respect to regio- and enantioselectivity, giving an 85:15 mixture of **3a** (55% ee) and **3b** (entry 7). Phosphines **7a** (R = Me, entry 1) and **7f** (R = *o*-anisyl, entry 6) displayed nearly the same degrees of selectivity, with **7a** (entry 1) providing the best combination of yield and selectivity among these three ligands.

Table 6. Catalytic, Enantioselective Reductive Couplings with *P*-Chiral Ferrocenyl Ligands.



entry	ligand	R	yield **3**[a]	**3a** : **3b**[b]	ee (**3a**)[c]	ee (**3b**)[c]
1	**7a**	Me	65%	70:30	46%	45%
2	**7b**	*n*-Bu	27%	65:35	8%	12%
3	**7c**	Cy	53%	62:38	– 34%[d]	– 28%[d]
4	**7d**	neophyl	33%	50:50	– 44%[d]	– 10%[d]
5	**7e**	*p*-anisyl	71%	71:29	2%	4%
6	**7f**	*o*-anisyl	60%	79:21	– 28%[d]	– 17%[d]
7	**7g**	*o*-tolyl	46%[e]	85:15	– 55%[d]	– 19%[d]
8	**7h**	*o*-biphenyl	33%[e]	50:50	– 52%[d]	– 37%[d]

[a] Combined isolated yield of **3a** and **3b**. [b] Determined by integration of ^{1}H NMR spectrum. [c] Measured by chiral GC analysis, B-PH column. Absolute configuration assigned by Mosher ester analysis. [d] Opposite enantiomer favored (*ent*-**3a**/**3b**). [e] Byproducts include significant quantities of alkylative coupling (Et addition instead of H addition to the alkyne, **3c** and **3d**).



[60] In the course of screening, it was found that a 1:1 ratio of $Ni(cod)_2$ and phosphine ligand was instrumental in reducing the amount of side products resulting from aldol reactions of **2**.

Of significance is that the reaction is quite sensitive to the size of the R group bound to phosphorus (FcP(Ph)R). When R is an alkyl group (**7a-7d**, entries 1-4), less sterically demanding R groups promote higher regioselectivity. This observation is consistent with the hypothesis that the level of differentiation between the groups bound to phosphorus (Fc vs. Ph vs R) is greatest when R is small. When R is an aryl group (**7e-7h**, entries 5-8), the size of the group at the *ortho* position of that aryl group appears to influence regioselectivity. As the *ortho* substituent is changed from hydrogen to methoxy to methyl (**7e-7g**, entries 5-7), allylic alcohol **3a** is increasingly favored. Again, this corresponds to greater differentiation between the substituents on phosphorus. Interestingly, the placement of a phenyl group at this position erodes regioselectivity indicating an important balance of steric demand. A related observation also highlights the sensitivity of the reaction to ligand size- larger ligands also catalyze addition of an ethyl group to the alkyne ("alkylative" coupling, products **3c** and **3d**) which begins to compete with the desired reductive coupling (entries 7-8). This phenomenon is probably attributable to an acceleration of reductive elimination,[61] that is, reductive elimination of the ethyl group before the requisite β-hydride elimination and subsequent reductive elimination of a hydride can occur (see discussion of mechanism, pages 9-10).

Ligand **7a** was chosen to examine the effect of solvent and temperature on selectivity in formation of **3** via the coupling of **1** and **2**. As shown in Table 7, temperature appears to play a minor role in both the regioselectivity and enantioselectivity of the reaction (entries 1-3) although reduced temperatures attenuated the overall reactivity of the system. Similarly, selectivity was largely unaffected by the choice of solvent (entries 1, 4-6).

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[61] There are many reports of bulky phosphine ligands accelerating reductive elimination from transition metals. (a) Jones, W. D.; Kuykendall, V. L. *Inorg. Chem.* **1991**, *30*, 2615-2622. (b) Hartwig, J. F.; Richards, S.; Barañano, D.; Paul, F. *J. Am. Chem. Soc.* **1996**, *118*, 3626-3633. (c) Mann, G.; Shelby, Q.; Roy, A. H.; Hartwig, J. F. *Organometallics* **2003**, *22*, 2775. (d) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369-4378.

Table 7. Temperature and Solvent Effects.

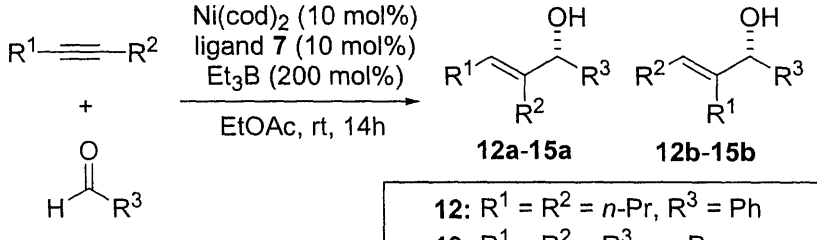
entry[a]	solvent	temp (°C)	yield **3**[b]	(**3a** : **3b**)[c]	ee (**3a**)[d]
1	EtOAc	23	65%	70:30	46%
2	EtOAc	0	40%	74:26	51%
3	EtOAc	−22	21%	68:32	48%
4	toluene	23	76%	70:30	43%
5	THF	23	65%	75:25	46%
6	acetone	23	40%	75:25	47%

[a] Reaction as performed in Eq 2 with **7a**. [b] Combined isolated yield of **3a** and **3b**. [c] Determined by integration of ^{1}H NMR spectrum. [d] Measured by chiral GC analysis, B-PH column.

Finally, the scope of aldehyde and alkyne in nickel-catalyzed couplings of alkyl-alkyl alkynes was examined (Table 8). Benzaldehyde was found to be an excellent substrate for the reaction (entries 1-5); ligand **7a** once again proved to be superior in couplings of 4-octyne and benzaldehyde providing the allylic alcohol in good yield and modest enantioselectivity. Both straight-chain and branched aliphatic aldehydes were efficient coupling partners, undergoing smooth coupling with 4-octyne in 55% ee (entries 6 and 7). Finally, unsymmetrical alkyne **1** was found to couple to *n*-butyraldehyde (albeit in lower yield than *i*-butyraldehyde) with a slight increase in enantioselectivity and modest preference for allylic alcohol **15a** (entry 8).[62]

[62] The above results appear in the following report: Colby, E. A.; Jamison, T. F. *J. Org. Chem.* **2003**, *68*, 156-166.

Table 8. Scope of Alkyne and Aldehyde Coupling Partners.



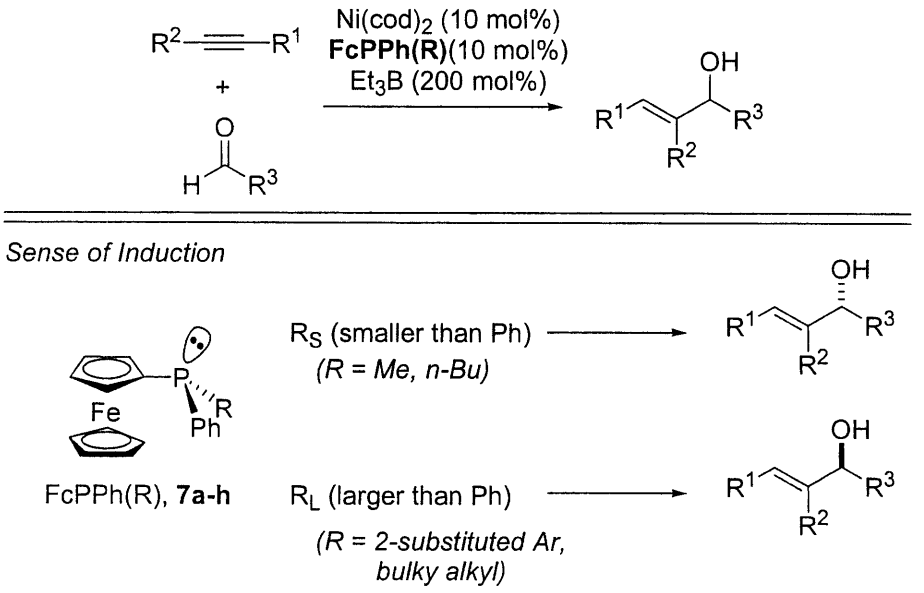
12: $R^1 = R^2 = n\text{-Pr}$, $R^3 = Ph$
13: $R^1 = R^2 = R^3 = n\text{-Pr}$
14: $R^1 = R^2 = n\text{-Pr}$, $R^3 = i\text{-Pr}$
15a,b: $R^1 = Cy$, $R^2 = Me$, $R^3 = n\text{-Pr}$

entry	ligand	R^1	R^2	R^3	yield (product)[a]	(**a** : **b**)[b]	ee (**a**)[c]	ee (**b**)[c]
1	**7a**	*n*-Pr	*n*-Pr	Ph	85% (**12**)	na	49%	na
2	**7c**	*n*-Pr	*n*-Pr	Ph	80% (**12**)	na	− 4%[d]	na
3	**7f**	*n*-Pr	*n*-Pr	Ph	81% (**12**)	na	12%	na
4	**7g**	*n*-Pr	*n*-Pr	Ph	79% (**12**)	na	− 28%[d]	na
5	**7h**	*n*-Pr	*n*-Pr	Ph	87% (**12**)	na	− 36%[d]	na
6	**7a**	*n*-Pr	*n*-Pr	*n*-Pr	80% (**13**)	na	55%	na
7	**7a**	*n*-Pr	*n*-Pr	*i*-Pr	80% (**14**)	na	55%	na
8	**7a**	Cy	Me	*n*-Pr	30% (**15**)	69:31	67%	68%

[a] Combined isolated yield of **a** and **b**. [b] Determined by integration of ^1H NMR spectrum. [c] Measured by chiral GC analysis, B-PH column. Absolute configuration assigned by analogy to **3**. [d] Opposite enantiomer favored.

To date, we do not have direct evidence that unambiguously establishes which mechanism (**I**, **II**, or other variant) is in operation for the reductive couplings of simple alkyl-alkyl alkynes. On a basic level, the observations of enantioselectivity using chiral ligands and changes in regioselectivity when different ligands are employed indicate that at least one phosphine is bound to the nickel center upon union of the aldehyde and alkyne. A simple predictive mnemonic is provided for the stereochemical outcome of Ni-catalyzed reductive coupling reactions of alkyl-alkyl alkynes and aldehydes using *P*-chiral ferrocenyl phosphines (Scheme 12).

Scheme 12. Asymmetric Induction with *P*-Chiral Ferrocenyl Phosphines.



The modest levels of regioselectivity may be explained in the context of either proposed mechanism. With respect to the mechanism **I** invoking an oxanickelacyclopentene intermediate, the C-C bond-forming step of oxidative cyclization may be irreversible. Therefore, equilibration to the more energetically-favored isomer would be impossible and the ratio of regioisomers reflects the initial kinetic differentiation of the alkyne substituents. Similar limitations of selectivity may exist if a hydrometalation mechanism is in operation (mechanism **II**). In the event that β-hydride elimination from the alkenyl-nickel species (reversion to an alkyne-nickel

complex) is slower than addition to the aldehyde, equilibration of the alkenyl-nickel species would not be possible.

Conclusions and Further Utility of *P*-Chiral Ferrocenyl Phosphines

Enantioselective nickel-catalyzed, reductive coupling of alkyl-substituted alkynes and aldehydes was accomplished using a class of *P*-chiral ferrocenyl phosphines. Expedient access to these phosphine ligands was achieved by way of a four-step route from oxazaphospholidine-borane **8**. This synthetic sequence was amenable to variation of the steric and electronic demand of the substituents on phosphorus. While such tuning of the phosphine structure successfully allowed for an increase in both enantioselectivity and regioselectivity, total control over these variables has yet to be realized. Despite the moderate levels of regioselectivity and enantioselectivity of these coupling reactions, ligands **7a-h** are the most efficacious ligands of those that have been screened to date for this particular class of alkyne couplings.

Ligands of structure **7** have recently demonstrated utility in other projects completed within the Jamison group and remain an ongoing area of research. Importantly, they have been employed in total synthesis endeavors involving the reductive coupling of alkyl-substituted alkynes and aldehydes. Phosphine **7a** in particular has proved its superiority in a number of coupling reactions, most notably promoting a key fragment coupling reaction in the synthesis of terpestacin accomplished by former group member Dr. Johann Chan.[63] Efforts to optimize this coupling reaction led to synthesis of related phosphines of the structure (FcP(Ph)Ar) in which the varied aryl group is 2- or 2,6-substituted (Scheme 13).

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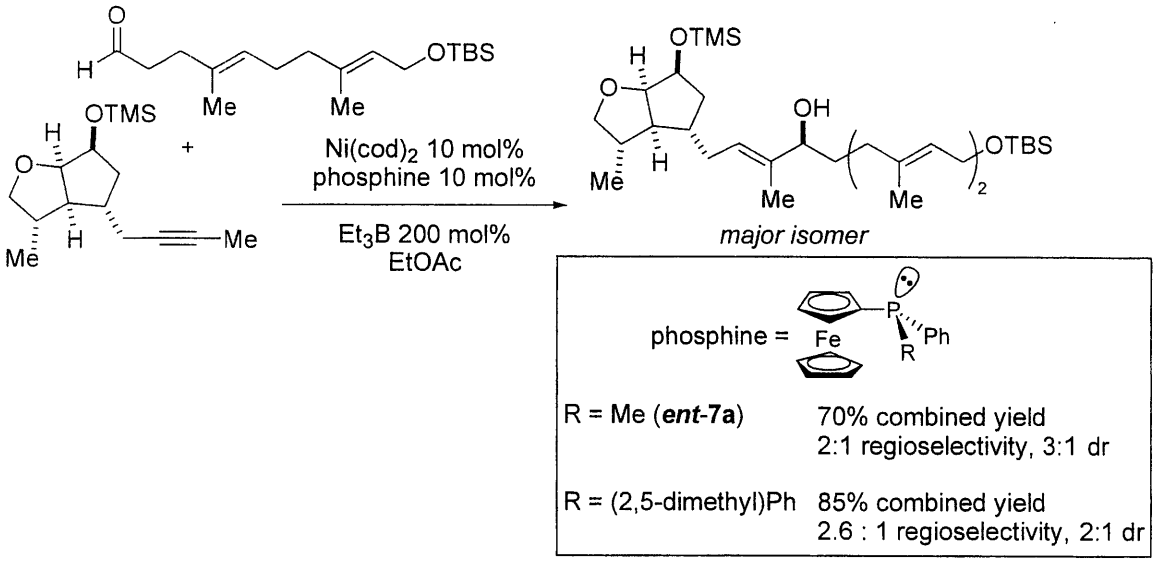
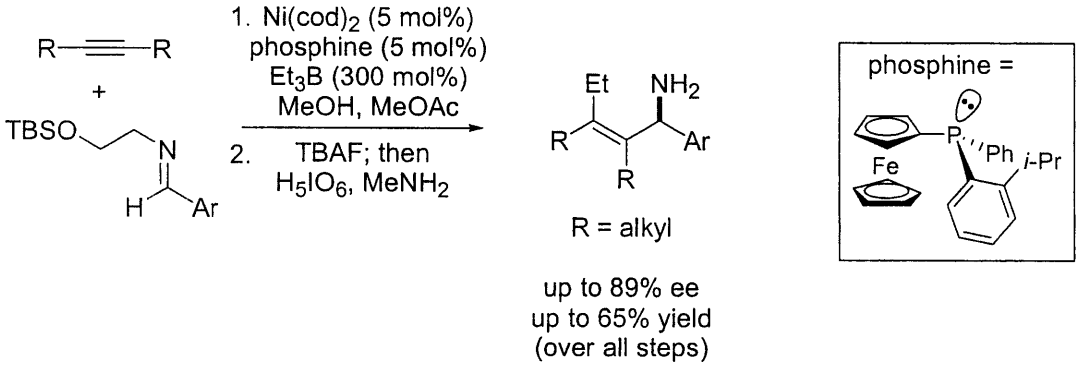
[63] Reactions and ligand synthesis performed by Dr. Johann Chan. First report: (a) Chan, J.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 11514-11515. Full disclosure of optimization efforts: (b) Chan and Jamison, reference 24d.

Scheme 13. Use of Ligand **7a** and Analogs in the Total Synthesis of Terpestacin.[24d]



Ligands related to **7a-h** have also been used in nickel-catalyzed, enantioselective three-component coupling reactions of alkynes and imines[64] by former group member Dr. Sejal Patel. As shown in Scheme 14, allylic amines are assembled in good yield and high enantiomeric purity via the coupling of alkynes with imines and organoboranes. Again, phosphines of the structure (FcP(Ph)Ar) in which the aryl group bears an *ortho* substituent proved to be efficient in promoting enantioselective coupling.

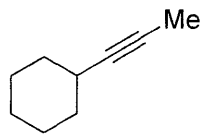
Scheme 14. Catalytic, Enantioselective Assembly of Allylic Amines Mediated by *P*-Chiral Monodentate Ferrocenyl Phosphines.



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

Experimental Section

General Information. Unless otherwise noted, all reactions performed in organic solvents were conducted under an atmosphere of argon with rigorous exclusion of moisture from reagents and glassware. THF and Et_2O were distilled from a blue solution of sodium benzophenone ketyl. CH_2Cl_2 was distilled from calcium hydride. Toluene was distilled from sodium metal. Diethylamine and methanol were purchased in 99.5% purity, and were degassed before use by bubbling argon through for 20 min. EtOAc was distilled from $CaSO_4$ and degassed before use by bubbling argon through for 20 min. Isobutyraldehyde, *n*-butyraldehyde, and benzaldehyde were distilled under argon before use. 4-octyne was purchased from Aldrich and used without further purification. Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F_{254} plates and UV light, 12-molybdophosphoric acid (PMA stain), or potassium permanganate ($KMnO_4$ stain) for analysis of the developed plates. Flash chromatography was performed using silica gel 60 (40-63 μm) from Silicycle. NMR spectra were recorded on a Varian 300 or 500 MHz spectrometer. IR spectra were recorded on a Perkin-Elmer 2000 FT-IR using NaCl plates. High resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by Dr. Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. Melting points were measured on a Thomas Hoover capillary melting point apparatus. Analysis by chiral GC was performed on a Hewlett-Packard 5890 Series II chromatograph equipped with a Chiradex B-PH column. HPLC was performed on a Hewlett-Packard 1100 chromatograph equipped with a variable wavelength detector and Chiralcel OD, AD, or OJ column (0.46 cm x 25 cm). Specific rotations ($[\alpha]_D$) values for chiral compounds were measured on a Perkin-Elmer 241 polarimeter at 589 nm.



1-Cyclohexyl-1-propyne (1).[65,66] Carbon tetrabromide (26.6 g, 80.4 mmol) was dissolved in 120 mL CH_2Cl_2 and cooled to 0 °C. Triphenylphosphine (42.0 g, 161 mmol) was added in one portion and the bright orange solution was stirred 30 min. Cyclohexanecarboxaldehyde was added via syringe (4.90 mL, 40.2 mmol) and the heterogeneous mixture was stirred at ambient temperature 4 h. Hexane was added (200 mL) and the mixture was filtered through Celite. The filtrate was partially concentrated, then passed through filter paper to remove triphenylphosphine oxide. After concentration, the crude residue was purified via column chromatography (hexane) to afford 2,2-dibromovinylcyclohexane (9.80 g, 91% yield). This dibromide was dissolved in THF (90 mL) and cooled to −78 °C. Methyllithium (57.0 mL, 1.6 M, 91.2 mmol) was added slowly via syringe and the resulting yellow solution was stirred 75 min at −78 °C. Methyl iodide (6.3 mL, 100.4 mmol) was filtered through activated basic alumina and added via syringe. The mixture was allowed to warm to ambient temperature over 5 h, then stirred 11 h at this temperature. The reaction was quenched with saturated NH_4Cl (15 mL) and H_2O (15 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 x 40 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified via column chromatography (hexanes) to afford the title compound as a clear, colorless oil (3.86 g, 87% yield).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.24-2.32 (m, 1H), 1.80 (d, J = 2.4 Hz, 1H), 1.74-1.80 (m, 2H), 1.65-1.73 (m, 2H), 1.47-1.57 (m, 1H), 1.32-1.42 (m, 2H), 1.21-1.31 (m, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 84.5, 75.8, 33.8 (2C), 29.9, 26.6 (2C), 25.8, 4.2.

General Procedure for the Reductive Coupling of Alkynes and Aldehydes.

In a glovebox, $Ni(cod)_2$ (14 mg, 0.05 mmol) and solid ligand (0.05 mmol) were placed into a flask which was then sealed with a rubber septum and removed from the glovebox. If a liquid phosphine was employed, it was added via syringe immediately after removal from the glovebox. A 2.0 M solution of Et_3B in EtOAc was added (0.5 mL, 1.0 mmol) and the mixture was stirred 10 min at ambient temperature. The aldehyde (1.0 mmol) and alkyne (0.5 mmol) were added via syringe in succession, and the reaction was stirred 14 h at ambient temperature. After this time, the solution was allowed to stir open to the air for 1 h. The solvent was evaporated and the crude residue was purified via gradient column chromatography (50:1 hexanes-EtOAc, polarity gradually increased to 9:1) to afford the desired alcohol as a clear, colorless oil.

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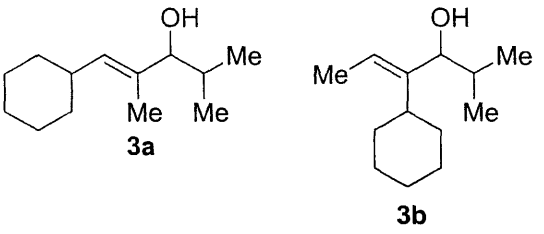
[65] Performed in analogy to the preparation of cyclohexylacetylene (with methyl iodide quench instead of proton quench in the second step) as reported by: Harrity, J. P. A.; Kerr, W. J.; Middlemiss, D.; Scott, J. S. *J. Organomet. Chem.* **1997**, *532*, 219-227.

[66] 1 is commercially available from GFS Chemicals.



3a **3b**

(*E*)-1-Cyclohexyl-2,4-dimethyl-pent-1-en-3-ol (3a) and (*E*)-4-Cyclohexyl-2-methyl-hex-4-en-3-ol (3b). Prepared according to the general procedure. R_f(90:10 hexane-EtOAc) = 0.38.

Enantiomeric excess determined by chiral GC analysis (B-PH, isothermal, 140 °C, t_R [(*R*)-**3b**] = 6.85 min, t_R [(*S*)-**3b**] = 7.04 min, t_R [(*R*)-**3a**] = 9.36 min, t_R [(*S*)-**3a**] = 9.64 min).

IR (thin film): 3383, 2925, 2852, 1448, 1010 cm^{-1}.

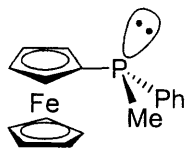
^1H NMR ($CDCl_3$, 500 MHz): δ 5.46 (q, 1H, **3b,** *J* = 7.0 Hz), 5.18 (d, 1H, **3a**, *J* = 9.2 Hz), 3.65 (d, 1H, **3b,** *J* = 7.6 Hz), 3.29 (d, 1H, **3a**, *J* = 8.2 Hz), 2.34-2.28 (m, 1H, **3b**), 2.23-2.16 (m, 1H, **3a**), 1.87-0.99 (m, 18H, **3a, 3b**), 0.83 (d, 1H, **3b**, *J* = 6.7 Hz), 0.77 (d, 1H, **3a**, *J* = 6.7 Hz).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.7, 134.6, 134.1, 120.6, 84.4, 80.0, 39.1, 36.7, 33.2, 32.2, 31.6, 31.3, 31.2, 27.20, 27.19, 26.4, 26.3, 26.17, 26.14, 20.5, 19.6, 18.9, 18.2, 13.7, 11.4.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{13}H_{24}NaO$ 219.1719, obsd 219.1723.

General Procedure for the Preparation of Phosphines 7a-h.

Diethylamine was degassed and a 0.1 M solution of **11** was prepared (1 mmol in 10 mL diethylamine). The solution was heated at reflux 14 h, cooled to ambient temperature, and the diethylamine was removed by evaporation by rotary evaporation (after concentration was complete, the rotovap was backfilled with N_2). The crude orange residue was taken up in a solution of 95:5 hexane-EtOAc (degassed by bubbling Ar through for 10 min) and passed through a short column of silica gel eluting, under argon, with 95:5 hexane:EtOAc (also degassed) to yield an orange solid (unless otherwise noted). The enantiomeric excess was determined by reprotection with BH_3·THF and analysis by chiral HPLC.



(*S*)-Ferrocenylmethylphenylphosphine (7a). Yield: 93% (343 mg, 1.1 mmol). R_f (95:5 hexane-EtOAc) = 0.42. Mp: 84-85 °C.

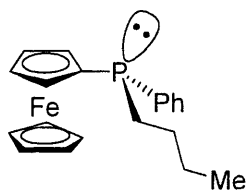
Enantiomeric excess: 87% ee determined by chiral HPLC (Chiracel OJ, isocratic, hexane:2-propanol = 95:5, t_R [(*R*)-**11a**] = 16.8 min, t_R [(*S*)-**11a**] = 24.7 min). Recrystallization from hexane (90% yield) provided **7a** in 96% ee.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.40-7.34 (m, 3H), 7.31-7.25 (m, 2H), 4.39-4.30 (m, 4H), 4.22-4.21 (s, 5H), 1.64 (d, 3H, J = 3.0 Hz).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 131.3 (d, J = 18.4 Hz, 2C), 130.2 (d, J = 9.2 Hz), 128.5 (d, J = 11.5 Hz), 128.3 (d, J = 6.7 Hz, 2C), 74.5 (d, J = 28.5 Hz), 71.2, 69.8, 12.6 (d, J = 8.1 Hz).

^{31}P NMR ($CDCl_3$, 121 MHz): δ −37.4.

HRMS (EI) $[M]^+$: *m/z* calcd for $C_{17}H_{17}FeP$ 308.0412, obsd 308.0422.



(*S*)-*n*-Butylferrocenylphenylphosphine (7b). Yield: 88% (350 mg, 1 mmol), isolated as an orange oil. R_f(90:10 hexane-EtOAc) = 0.48.

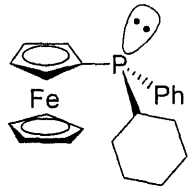
Enantiomeric excess: 80% ee determined by chiral HPLC (Chiracel OJ, isocratic, hexane:2-propanol = 97.5:2.5, t_R [(*R*)-**11b**] = 10.0 min, t_R [(*S*)-**11b**] = 12.0 min).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.53-7.50 (m, 2H), 7.34-7.33 (m, 3H), 4.40-4.38 (m, 2H), 4.33 (br s, 1H), 4.18 (br s, 1H), 4.16 (s, 5H), 2.03-1.96 (m, 2H), 1.55-1.40 (m, 4H), 0.92 (t, J = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 140.2 (d, J = 13.8 Hz), 132.8 (d, J = 19.6 Hz, 2C), 128.7, 128.2 (d, J = 6.9 Hz, 2C), 77.6 (d, J = 8.1 Hz), 73.2 (d, J = 20.1 Hz), 70.7 (d, J = 4.6 Hz), 70.4 (d, J = 8.1 Hz), 70.1 (d, J = 2.3 Hz), 69.2 (s, 5C), 28.8 (d, J = 11.5 Hz), 28.7 (d, J = 2.3 Hz), 24.5 (d, J = 13.2 Hz), 14.0.

^{31}P NMR ($CDCl_3$, 121.5 MHz): δ −27.1.

HRMS (EI) $[M]^+$: *m/z* calcd for $C_{20}H_{23}FeP$ 350.0881, obsd 350.0880.



(*S*)-Cyclohexylferrocenylphenylphosphine (7c). Yield: 84% (350 mg, 0.90 mmol). R_f (90:10 hexane-EtOAc) = 0.49. Mp: 99-101 °C.

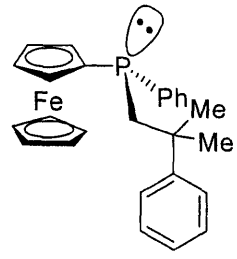
Enantiomeric excess: 98% ee by chiral HPLC (Chiracel OJ, isocratic, hexane:2-propanol = 97.5:2.5, t_R [(*R*)-**11c**] = 8.3 min, t_R [(*S*)-**11c**] = 10.0 min).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.67-7.63 (m, 2H), 7.42-7.39 (m, 3H), 4.37-4.36 (m, 1H), 4.34-4.43 (m, 1H) 4.28-4.26 (m, 1H), 4.03-4.02 (m, 1H), 4.00 (s, 5H), 1.96-1.93 (m, 1H), 1.86-1.84 (m, 1H), 1.79-1.78 (m, 1H), 1.68-1.66 (m, 2H), 1.48-1.45 (m, 1H), 1.29-1.17 (m, 4H), 1.09-1.05 (m, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.4 (d, J = 10.9 Hz), 134.5 (d, J = 20.7 Hz, 2C), 129.2, 128.2 (d, J = 8.1 Hz, 2C), 76.6 (d, J = 11.5 Hz), 74.1 (d, J = 24.8 Hz), 71.1 (d, J = 2.9 Hz), 70.5 (d, J = 1.7 Hz), 70.0 (d, J = 6.3 Hz), 69.2 (s, 5C), 38.1 (d, J = 6.3 Hz), 30.3, 30.2, 27.0 (d, J = 12.1 Hz), 26.9, 26.6.

^{31}P NMR ($CDCl_3$, 121.5 MHz): δ −12.0.

HRMS (EI) $[M]^+$: *m/z* calcd for $C_{22}H_{25}FeP$ 376.1038, obsd 376.1030.



(*S*)-Ferrocenylphenyl(2-methyl-2-phenyl-1-propyl)phosphine (7d). Yield: >99% (0.40 g, 0.94 mmol), isolated as an orange oil. R_f (90:10 hexane-EtOAc) = 0.47.

Enantiomeric excess: 96% ee by chiral HPLC analysis (Chiracel AD, isocratic, hexane:2-propanol = 98:2, t_R [(*R*)-**11d**] = 7.3 min, t_R [(*S*)-**11d**] = 7.8 min).

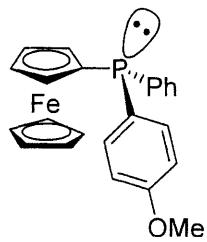
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.46-7.43 (m, 2H), 7.35-7.33 (m, 2H), 7.27-7.23 (m, 5H), 7.17-7.16 (m, 1H), 4.28-4.27 (m, 1H), 4.25-4.23 (m, 2H), 4.09-4.06 (m, 1H), 4.05 (s, 5H), 2.57 (dd, J = 6.3, 13.9 Hz, 1H), 2.43 (d, J = 13.7 Hz, 1H), 1.46 (s, 3H), 1.43 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.5 (d, J = 3.4 Hz), 133.6 (d, J = 21.3 Hz, 2C), 128.8, 128.2 (d, J = 7.5 Hz, 2C), 128.0 (d, J = 1.2 Hz, 2C), 126.0, 72.8 (d, J = 19.0 Hz), 70.9 (d, J = 11.5 Hz),

70.6 (d, J = 5.2 Hz), 70.0 (d, J = 2.9 Hz), 69.1 (s, 5C), 46.3 (d, J = 12.1 Hz), 38.2 (d, J = 15.5 Hz), 30.3, 30.2.

^{31}P NMR ($CDCl_3$, 121.5 MHz): δ −36.3.

HRMS (EI) $[M]^+$: *m/z* calcd for $C_{26}H_{27}FeP$ 426.1194, obsd 426.1197.



(*R*)-Ferrocenyl(4-methoxyphenyl)phenylphosphine (7e). Yield: 95% (86 mg, 0.21 mmol), isolated as an orange oil. R_f(95:5 hexane:EtOAc) = 0.25.

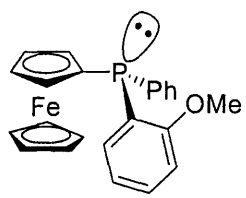
Enantiomeric excess: 94% ee by chiral HPLC (Chiracel OJ, isocratic, hexane:2-propanol = 90:10, t_R [(*S*)-**11e**] = 22.8 min, t_R [(*R*)-**11e**] = 30.3 min).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40-7.30 (m, 7H), 6.91 (d, J = 7.9 Hz, 2H), 4.40-4.39 (m, 1H), 4.38-4.37 (m, 1H), 4.18-4.17 (m, 1H), 4.11 (s, 5H), 4.10-4.07 (m, 1H), 3.83 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.4, 135.5 (d, J = 21.3 Hz, 2C), 133.0 (d, J = 19.0 Hz, 2C), 128.3, 128.2 (d, J = 6.3 Hz, 2C), 114.0 (d, J = 8.1 Hz, 2C), 73.4 (d, J = 18.4 Hz, 1C), 72.4 (d, J = 10.9 Hz, 1C), 70.9 (d, J = 4.0 Hz, 2C), 69.3 (s, 5C), 55.3.

^{31}P NMR ($CDCl_3$, 121 MHz): δ −17.7.

HRMS (EI) $[M]^+$: *m/z* calcd for $C_{23}H_{21}FeOP$ 400.0674, obsd 400.0672.



(*R*)-Ferrocenyl(2-methoxyphenyl)phenylphosphine (7f).[47] Yield: 83% (261 mg, 0.65 mmol). R_f(90:10 hexane-EtOAc) = 0.31. Mp: 128-130 °C.

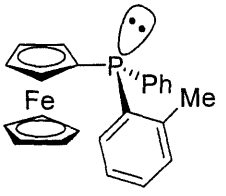
Enantiomeric excess: >98% e.e. by chiral HPLC analysis (Chiracel OJ, isocratic, hexane:2-propanol = 99:1, t_R [(*R*)-**11f**] = 43.8 min, t_R [(*S*)-**11f**] = 56.9 min).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.50-7.46 (m, 2H), 7.35-7.29 (m, 4H), 6.94-6.91 (m, 1H), 6.89-6.87 (m, 1H), 6.85-6.83 (m, 1H), 4.41-4.40 (m, 1H), 4.35-4.34 (m, 1H), 4.30-4.29 (m, 1H), 4.12 (s, 5H), 3.85-3.84 (m, 1H), 3.73 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.9 (d, J = 15.5 Hz), 138.0, 133.8 (d, J = 20.1 Hz, 2C), 130.2, 128.6, 128.0 (d, J = 7.5 Hz, 2C), 120.9, 110.3 (d, J = 1.7 Hz), 74.1 (d, J = 24.7 Hz), 72.3 (d, J = 4.6 Hz), 71.1 (d, J = 5.8 Hz), 70.6 (s, 1C), 69.3 (s, 5C), 55.8.

^{31}P NMR ($CDCl_3$, 121 MHz): δ −28.8.

HRMS (EI) $[M]^+$: *m/z* calcd for $C_{23}H_{21}FeOP$ 400.0674, obsd 400.0672.



(*R*)-Ferrocenyl(2-methylphenyl)phenylphosphine (7g). Yield: >99% (0.42 g, 1.1 mmol), crystallized from diethylamine upon cooling and standing. The crystals were purified via column chromatography. R_f(90:10 hexane-EtOAc) = 0.42. Mp: 116-117 °C.

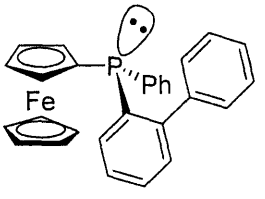
Enantiomeric excess: >98% e.e. by chiral HPLC analysis (Chiracel OJ, isocratic, hexane:2-propanol = 99:1, t_R [(*R*)-**11g**] = 14.0 min, t_R [(*S*)-**11g**] = 20.3 min).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.54-7.51 (m, 2H), 7.40-7.38 (m, 3H), 7.25-7.21 (m, 1H), 7.15-7.11 (m, 2H), 6.99-6.97 (m, 1H), 4.48-4.47 (m, 1H), 4.41-4.38 (m, 2H), 4.14 (s, 5H), 3.80-3.79 (m, 1H), 2.31(s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 141.1 (d, J = 23.6 Hz), 138.8 (d, J = 11.5 Hz), 136.8 (d, J = 7.5 Hz), 134.5 (d, J = 19.6 Hz, 2C), 132.1, 130.0 (d, J = 4.0 Hz), 129.1, 128.4, 128.3 (d, J = 7.5 Hz, 2C), 125.7, 75.8 (d, J = 4.0 Hz), 74.7 (d, J = 30.5 Hz), 71.9, 71.4 (d, J = 6.9 Hz), 70.7, 69.3 (s, 5C), 24.2 (d, J = 20.1 Hz).

^{31}P NMR ($CDCl_3$, 121 MHz): δ −23.4.

HRMS (EI) $[M]^+$: *m/z* calcd for $C_{23}H_{21}FeP$ 384.0725, obsd 384.0735.



(*R*)-Ferrocenyl(2-biphenylyl)phenylphosphine (7h). Yield: 94% (0.30 g, 0.7 mmol). R_f(90:10 hexane-EtOAc) = 0.40. Mp: 63-65 °C.

Enantiomeric excess: 96% e.e. by chiral HPLC analysis (Chiracel AD, isocratic, hexane:2-propanol = 99.4:0.6, t_R [(*R*)-**11h**] = 13.2 min, t_R [(*S*)-**11h**] = 14.3 min).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38-7.23 (m, 11H), 7.21-7.18 (m, 1H), 7.13-7.12 (m, 2H), 4.43-4.43 (m, 1H), 4.37-4.36 (m, 1H), 4.34-4.33 (m, 1H), 4.0 (s, 5H), 3.86-3.85 (m, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.9 (d, J = 24.4 Hz), 141.9 (d, J = 5.2 Hz), 139.1 (d, J = 15.0 Hz), 138.3 (d, J = 8.1 Hz), 134.5 (d, J = 20.1 Hz, 2C), 132.9, 130.0 (d, J = 3.5. Hz), 129.8 (d, J = 3.5 Hz, 2C), 128.7, 128.2, 128.0 (d, J = 8.1 Hz, 2C), 127.7 (s, 2C), 127.1 (s, 2C), 76.6 (d, J = 7.5 Hz), 74.9 (d, J = 31.9 Hz), 72.0, 71.2 (d, J = 6.9 Hz), 70.7, 69.2 (s, 5C).

^{31}P NMR ($CDCl_3$, 121 MHz): δ −22.0.

HRMS (EI) $[M]^+$: *m/z* calcd for $C_{28}H_{23}FeP$ 446.0887, obsd 446.0871.

($2S_p$, 4*R*, 5*S*)-(-)-3,4-Dimethyl-2,5-diphenyl-1,3,2-oxazaphospholidine borane (2).[50] A solution of (+)-ephedrine (14.2 g, 85.6 mmol) in 400 mL tetrahydrofuran was cooled to 0 °C. Diisopropylethylamine (30.0 mL, 171 mmol) was added via syringe; then dichlorophenylphosphine (11.8 mL, 85.6 mmol) was added slowly via syringe. The heterogeneous mixture was allowed to warm to ambient temperature, then refluxed 24 h (white precipitate never fully dissolved). After cooling to ambient temperature, BH_3·THF was added (63.0 mL, 1.5 M in THF, 94.5 mmol) and the heterogeneous mixture was stirred 18 h. H_2O was added and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with saturated aqueous NaCl, dried with $MgSO_4$, filtered, and concentrated in vacuo. Recrystallization from methanol provided the title compound (14.6 g, 51.2 mmol, 59% yield) as a white crystalline solid. R_f (80:20 hexane-EtOAc) = 0.23. Mp: 103-104 °C.

IR (thin film): 3428, 3062, 2977, 2935, 2381, 1644, 1497, 1454, 1436, 1207, 1177, 1113, 1057, 965, 878, 851, 748 700 cm^{-1}.

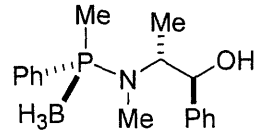
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.84-7.81 (m, 2H), 7.55-7.50 (m, 3H), 7.40-7.28 (m, 5H), 5.60 (dd, J = 3.1, 6.0 Hz, 1H), 3.71-3.67 (m, 1H), 2.69 (d, J = 11.0 Hz, 3H), 0.84 (d, J = 6.7 Hz, 3H), 1.3-0.7 (br m, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 136.4 (d, J = 5.4 Hz), 132.6 (d, J = 2.2 Hz), 131.1 (d, J = 12.1 Hz, 2C), 128.8 (d, J = 9.8 Hz, 2C), 128.54 (s, 2C), 125.52, 126.8 (s, 2C), 84.5 (d, J = 7.6 Hz), 59.3 (d, J = 1.9 Hz), 29.9 (d, J = 8.1 Hz), 14.0 (d, J = 3.6 Hz).

^{31}P NMR ($CDCl_3$, 121 MHz): δ 132.8 (br q, J = 87 Hz).

General Procedure for the Synthesis of Phosphinamides 9a-h (Typical Procedure).

A 1.0 M solution of **8** (20 mmol) in tetrahydrofuran was cooled to -78 °C before addition of a solution of alkyl- or aryllithium (40 mmol, commercially available unless noted). The mixture was allowed to stir 3 h, warming slowly to 0 °C. Water was added, and the aqueous phase was extracted with diethyl ether. The combined organic layers were washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified via column chromatography.



(S_p, 1*S*, 2*R*)- *N*-Methyl-*N*-(1-hydroxy-1-phenyl)prop-2-yl-*P*-(methyl)-*P*-(phenyl)-phosphinamide borane (3a).[50]** Purification: column chromatography (elution with 95:5 toluene-EtOAc). Small scale yield: 79% (0.10 g, 0.33 mmol), prepared and purified for spectral analysis. Large scale crude yield: >99% (6.0 g, 20 mmol), used without purification. The diastereomeric ratio of the isolated material was determined to be 9:1 by ^{1}H NMR integration. R_f (95:5 toluene-EtOAc) = 0.17. Mp: 108-109 °C.

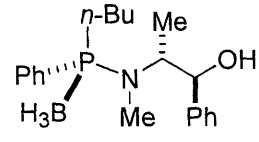
IR (NaCl): 3446, 2968, 2369 cm $^{-1}$.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.46-7.26 (m, 8H), 7.11-7.07 (m, 2H), 4.74 (dd, 1H, J = 3.4, 7.2 Hz), 4.06-4.01 (m, 1H), 2.47 (d, 3H, J = 8.5 Hz), 1.94 (d, 1H, J = 3.7 Hz), 1.52 (d, 3H, J = 9.0 Hz), 1.24 (d, 3H, J = 6.7 Hz), 1.1-0.4 (br m, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.3, 133.5 (d, J = 65.6 Hz), 131.3, 131.2, 131.0, 130.9, 129.3, 129.2, 129.1, 129.1, 128.7, 127.5, 78.5 (d, J = 6.3 Hz), 58.7 (d, J = 8.6 Hz), 29.7, 14.8, 12.0 (d, J = 41.5 Hz).

^{31}P NMR ($CDCl_3$, 121 MHz): δ 66.1 (br q, J = 77 Hz).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{17}H_{25}BNNaOP$ 324.1659, obsd 324.1652.



(*S*p, 1*S*, 2*R*)-*N*-Methyl-*N*-(1-hydroxy-1-phenyl)prop-2-yl-*P*-(*n*-butyl)-*P*-(phenyl)-phosphinamide borane (9b).[50]

Purification: column chromatography (95:5 toluene-EtOAc). Yield: 80% (1.67 g, 4.9 mmol), isolated as a colorless oil. The diastereomeric ratio of the isolated material was determined to be 16:1 by ^{1}H NMR integration. R_f (95:5 toluene-EtOAc) = 0.25.

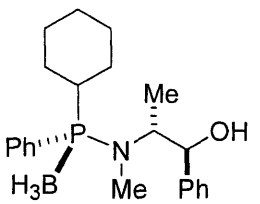
IR (thin film): 3503, 2957, 2872, 2379, 1455, 1436, 1025 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.44-7.42 (m, 2H), 7.36-7.28 (m, 8H), 4.87 (dd, J = 3.7, 5.5 Hz, 1H), 4.07-4.02 (m, 1H), 2.57 (d, J = 7.6 Hz, 3H), 2.00-1.96 (m, 1H), 1.88-1.84 (m, 1H), 1.83 (d, J = 3.6 Hz, 1H), 1.69-1.62 (m, 1H), 1.47-1.38 (m, 3H), 1.19 (d, J = 6.7 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H), 1.05-0.4 (br m, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.2, 133.0 (d, J = 60.9 Hz), 131.2, 131.11, 131.10, 129.22, 129.19, 129.14, 126.7, 127.1 (2C), 79.4 (d, J = 4.0 Hz), 58.8 (d, J = 8.6), 30.0 (d, J = 2.9 Hz), 25.8 (d, J = 42.0 Hz), 25.5, 25.0 (d, J = 15.6 Hz), 14.4, 13.6 (d, J = 2.8 Hz).

^{31}P NMR ($CDCl_3$, 121.5 MHz): δ 70.3 (br q, J = 73 Hz).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{20}H_{31}BNNaOP$ 366.2129, obsd 366.2123.



(*Sp*, 1*S*, 2*R*)-*N*-Methyl-*N*-(1-hydroxy-1-phenyl)prop-2-yl-*P*-(cyclohexyl)-*P*-(phenyl)-phosphinamide borane (9c). Cyclohexyllithium was prepared from chlorocyclohexane and lithium-naphthalenide.[54] Lithium (35 mmol) and naphthalene (0.35 mmol) were combined in 7 mL tetrahydrofuran. The mixture was vigorously stirred at ambient temperature until it turned dark green, at which point the mixture was cooled to −78 °C. Chlorocyclohexane was added dropwise via syringe (3.5 mmol) and the mixture was stirred 3 h at −78 °C to generate cyclohexyllithium which was added to a solution of **8** (1.7 mmol) at −78 °C. Purification: gradient silica gel chromatography (90:10 hexane:EtOAc, polarity gradually increased to 50:50 hexane-EtOAc). Yield: 88% (0.57 g, 1.5 mmol), isolated as a white foam. Only one diastereomer was detected by ^1H NMR integration. R_f (80:20 hexane-EtOAc) = 0.24.

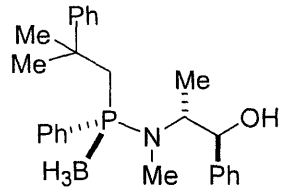
IR (NaCl): 3495, 2934, 2854, 2382, 1480, 1435, 1023 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.56-7.52 (m, 2H), 7.43-7.33 (m, 5H), 7.27-7.18 (m, 3H), 4.74 (d, J = 4.6 Hz, 1H), 4.09-4.04 (m, 1H), 2.60 (d, J = 7.0 Hz, 3H), 2.35 (dd, J = 2.6, 12.4 Hz, 1H), 2.0 (br s, 1H), 2.00-1.88 (m, 1H), 1.75 (m, 3H), 1.58-1.50 (m, 2H), 1.45-1.38 (m, 1H), 1.33-1.23 (m, 3H), 1.12 (d, J = 7.0 Hz, 3H), 1.1-0.5 (br m, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 142.7, 131.4 (d, J = 9.2 Hz), 131.1 (d, J = 40.1 Hz), 130.7 (d, J = 1.7 Hz), 128.5 (d, J = 9.2 Hz), 128.4 (s, 2C), 127.6, 126.3 (s, 2C), 78.8, 58.5 (d, J = 8.6 Hz), 32.7 (d, J = 43.7 Hz), 29.5 (d, J = 3.5 Hz), 27.2 (d, J = 12.1 Hz), 26.93 (d, J = 8.6 Hz), 26.86, 26.2, 26.1, 12.4 (d, J = 4.0 Hz).

^{31}P NMR ($CDCl_3$, 121.5 MHz): δ 72.2 (br q, J = 66 Hz).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{22}H_{33}BNNaOP$ 392.2285, obsd 392.2290.



(*S*p, 1*S*, 2*R*)-*N*-Methyl-*N*-(1-hydroxy-1-phenyl)prop-2-yl-*P*-(2-methyl-2-phenyl-1-propyl)-*P*-(phenyl)-phosphinamide borane (9d). Neophyllithium was prepared from 1-chloro-2-methyl-2-phenylpropane (neophyl chloride) and lithium-naphthalenide as described for **9c**. Purification: gradient silica gel chromatography (90:10 hexane-EtOAc, polarity gradually increased to 50:50 hexane-EtOAc). Yield: 72% (1.53 g, 3.7 mmol), isolated as a white foam. Only one diastereomer was detected by ^{1}H NMR integration. R_f (90:10 hexane-EtOAc) = 0.12.

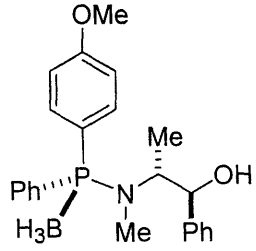
IR (NaCl): 3511, 2968, 2389, 1601, 1496, 1450, 1435 cm $^{-1}$.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.67-7.63 (m, 2H), 7.46-7.40 (m, 6H), 7.36-7.31 (m, 4H), 7.27-7.21 (m, 3H) , 5.12 (br s, 1H), 4.09-4.07 (m, 1H), 2.70 (t, J = 16.3 Hz, 1H), 2.65 (d, J = 7.0 Hz, 3H), 2.25 (dd, J = 2.1, 15.3 Hz, 1H), 1.87 (d, J = 2.1 Hz, 1H), 1.67 (s, 3H), 1.64 (s, 3H), 0.95 (d, J = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 150.9 (d, J = 7.5 Hz), 142.8, 135.4 (d, J = 59.9 Hz), 130.5 (d, J = 8.6 Hz, 2C), 130.3 (d, J = 1.7 Hz), 128.7 (d, J = 9.2 HZ, 2C), 128.4 (d, J = 4.0 Hz, 2C), 127.4, 126.2, 125.9 (s, 2C), 125.6 (s, 2C), 79.8, 58.2 (d, J = 10.4 Hz), 41.1 (d, J = 36.3 Hz), 38.0, 31.2 (d, J = 5.2 Hz), 31.1 (d, J = 3.5 Hz), 28.4 (d, J = 4.6 Hz), 10.4 (d, J = 5.2 Hz).

^{31}P NMR ($CDCl_3$, 121.5 MHz): δ 67.4 (br q, J = 53 Hz).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{26}H_{35}BNNaOP$ 442.2442, obsd 442.2464.



(*R*p, 1*S*, 2*R*)-*N*-Methyl-*N*-(1-hydroxy-1-phenyl)prop-2-yl-*P*-(4-methoxyphenyl)-*P*-(phenyl)-phosphinamide borane (9e). A 1.0 M solution of 4-bromoanisole (10 mmol) in diethyl ether was cooled to −78 °C and treated with a solution of *t*-butyllithium (20 mmol). The solution was allowed to stir 15 min at -78 °C, warmed to 0 °C and stirred an additional 30 min producing a clear, yellow solution of *p*-anisyllithium. The aryllithium reagent was transferred via cannula to a 1.0 M solution of **8** in tetrahydrofuran (5.0 mmol) at −78 °C. The mixture was allowed to stir 30 min at −78 °C, warmed to 0 °C to increase the solubility of salts, and stirred for an additional 2 h. Water and diethyl ether were added, and the solution was warmed to ambient temperature. Purification: gradient silica gel chromatography (90:10 hexane-EtOAc, polarity gradually increased to 50:50 hexane-EtOAc). Yield: 80% (1.6 g, 4.0 mmol), isolated as a white solid. Only

one diastereomer was detected by ^{1}H NMR integration. R_f (80:20 hexane-EtOAc) = 0.14. Mp: 51-52 °C.

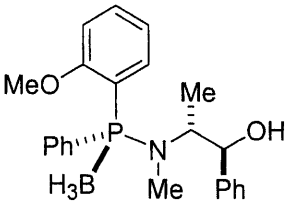
IR (thin film): 3457, 2969, 2384, 1596, 1501, 1255 cm $^{-1}$.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.55-7.46 (m, 4H), 7.41-7.25 (m, 6H), 7.14-7.10 (m, 2H), 6.95 (dd, J = 1.7, 8.7 Hz, 2H), 4.82 (dd, J = 4.0, 6.3 Hz, 1H), 4.33-4.28 (m, 1H), 3.85 (s, 3H), 2.46 (d, J = 7.9 Hz, 3H), 1.85 (d, J = 4.0 Hz, 1H), 1.24 (d, J = 6.7 Hz, 3H), 1.3-0.7 (br m, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 162.0, 142.7, 134.5 (d, J = 11.5 Hz, 2C), 132.1 (d, J = 9.8 Hz, 2C), 130.7, 128.8 (s, 2C), 128.4 (d J = 10.9 Hz, 2C), 128.1, 127.0 (s, 2C), 122.0 (d, J = 63.9 Hz), 114.2 (d, J = 10.9, 2C), 78.9 (d, J = 6.3 Hz), 58.2 (d, J = 10.4 Hz), 55.5, 30.4 (d, J = 4.0 Hz), 13.8.

^{31}P NMR ($CDCl_3$, 121.5 MHz): δ 69.2 (br q, J = 95 Hz).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{23}H_{29}BNNaO_2P$ 416.1921, obsd 416.1918.



(*R*p, 1*S*, 2*R*)-*N*-Methyl-*N*-(1-hydroxy-1-phenyl)prop-2-yl-*P*-(2-methoxyphenyl)-*P*-(phenyl)-phosphinamide borane (9f). [47a, 48a-b, 50] *o*-Anisyllithium was prepared from the corresponding bromide and the reaction was carried out as described for **9e**. Purification: gradient silica gel chromatography (90:10 hexane-EtOAc, polarity gradually increased to 50:50 hexane-EtOAc). Yield: 93% (1.46 g, 3.7 mmol), isolated as a white solid. Only one diastereomer was detected by ^{1}H NMR integration. R_f (80:20 hexane-EtOAc) = 0.18. Mp: 108 °C.

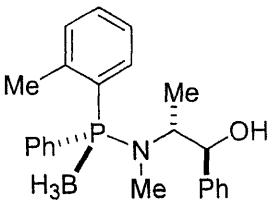
IR (thin film): 3416, 3060, 2940, 2376, 1589, 1477, 1431, 1276, 1251 cm $^{-1}$.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.57 (ddd, J = 1.8, 7.6, 12.7 Hz), 7.50-7.46 (m, 3H), 7.39-7.23 (m, 8H), 7.03 (tdd, J = 0.9, 1.5, 7.5 Hz, 1H), 6.92 (dd, J = 4.1, 7.8 Hz), 4.91 (d, J = 5.2 Hz, 1H), 4.37-4.32 (m, 1H), 3.59 (s, 3H), 2.56 (d, J = 7.9 Hz), 1.91 (br s, 1H), 1.23 (d, J = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 135.10 (d, J = 10.4 Hz), 133.4, 132.4 (d, J = 71.4), 131.0 (d, J = 10.4, 2C), 130.1, 128.5 (s, 2C), 128.1 (d, J = 10.9, 2C), 127.8, 126.8 (s, 2C), 121.0 (d, J = 10.9 Hz), 118.7 (d, J = 57 Hz), 111.7 (d, J = 4.6 Hz), 79.0 (d, J = 5.2 Hz), 58.3 (d, J = 10.4 Hz), 55.2 , 31.1 (d, J = 4.0), 12.7.

^{31}P NMR ($CDCl_3$, 121.5 MHz): δ 68.5 (br q, J = 84 Hz).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{23}H_{29}BNNaO_2P$ 416.1921, obsd 416.1920.



(*R*p, 1*S*, 2*R*)-*N*-Methyl-*N*-(1-hydroxy-1-phenyl)prop-2-yl-*P*-(2-methylphenyl)-*P*-(phenyl)-phosphinamide borane (9g).[67] *o*-Tolyllithium was prepared from the corresponding iodide and the reaction was carried out as described for **9e**. Purification: gradient silica gel chromatography (90:10 hexane-EtOAc, polarity gradually increased to 50:50 hexane-EtOAc). Yield: 80% (1.2 g, 3.2 mmol). Only one diastereomer was detected by ^{1}H NMR integration. R_f (90:10 hexane-EtOAc) = 0.09. Mp: 118 °C.

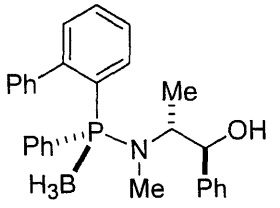
IR (NaCl, thin film): 3507, 3059, 2979, 2391, 1451, 1436, 1384, 1069, 1024 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.64-7.60 (m, 2H), 7.51-7.47 (m, 1H), 7.44-7.21 (m, 11H), 4.95 (t, J = 3.7 Hz, 1H), 4.39-4.35 (m, 1H), 2.65 (d, *J* = 7.3 Hz, 3H), 2.33 (s, 1H), 1.77 (d, *J* = 3.7 Hz, 1H), 1.26 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 142.7, 142.4 (d, *J* = 12.7 Hz), 132.8 (d, *J* = 8.1 Hz), 132.5, 132.4 (d, *J* = 9.2 Hz), 132.0 (d, *J* = 9.8 Hz, 2C), 131.1 (d, *J* = 2.3 Hz), 131.0 (d, *J* = 2.3 Hz), 129.1, 128.6 (d, *J* = 10.4 Hz, 2C), 128.4 (s, 2C), 127.6, 126.2 (s, 2C), 125.8 (d, *J* = 9.8 Hz), 79.1 (d, *J* = 2.3 Hz), 58.2 (d, *J* = 9.8 Hz), 31.5 (d, *J* = 3.5 Hz), 22.2 (d, *J* = 3.5 Hz), 11.7 (d, *J* = 4.6 Hz).

^{31}P NMR ($CDCl_3$, 121.5 MHz): δ 69.9 (br q, *J* = 78 Hz).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{23}H_{29}BNNaOP$ 400.1972, obsd 400.1962.



(*R*p, 1*S*, 2*R*)-*N*-Methyl-*N*-(1-hydroxy-1-phenyl)prop-2-yl-*P*-(2-biphenylyl)-*P*-(phenyl)-phosphinamide borane (9h).[48b] *o*-Biphenyllithium was prepared from the corresponding bromide and the reaction was carried out as described for **3e**. Purification: gradient silica gel chromatography (90:10 hexane-EtOAc, polarity gradually increased to 80:20 hexane-EtOAc). Yield: 81% (1.8 g, 4.1 mmol). R_f (80:20 hexane-EtOAc) = 0.24. Mp: 110 °C.

IR (thin film): 3566, 3058, 2983, 2366, 1465, 1445, 1436 cm^{-1}.

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[67] Moulin, D.; Bago, S.; Bauduin, C.; Darcel, C.; Jugé, S. *Tetrahedron: Asymmetry* **2000**, *11*, 3939-3956.

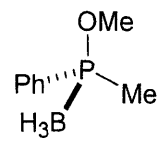
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.72-7.68 (m, 2H), 7.51-7.47 (m, 1H), 7.44-7.18 (m, 16H), 4.88-4.87 (m, 1H), 3.97-3.93 (m, 1H), 2.57 (d, J = 7.3 Hz, 3H), 1.50 (d, J = 3.1 Hz, 1H), 1.4-0.8 (br m, 3H), 0.69 (d, J = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 147.6 (d, J = 9.8 Hz), 142.7, 141.6 (d, J = 2.9 Hz), 134.3 (d, J = 9.8 Hz), 133.6 (d, J = 58.2 Hz), 132.9 (d, J = 8.6 Hz), 132.4 (d, J = 9.8 Hz, 2C), 130.74 (d, J = 2.3 Hz), 130.70 (d, J = 2.3 Hz), 129.8, 129.0 (d, J = 66.2 Hz), 128.4, 128.31 (s, 2C), 128.29, 127.6 (s, 2C), 127.5, 127.3, 127.0 (d, J = 9.8 Hz), 125.8 (s, 2C), 79.0, 58.2 (d, J = 10.4 Hz), 32.0 (d, J = 4.0 Hz), 10.0 (d, J = 6.9 Hz).

^{31}P NMR ($CDCl_3$, 121.5 MHz): δ 70.1 (br q, J = 55 Hz).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{28}H_{31}BNNaOP$ 462.2129, obsd 462.2127.

Synthesis of Phosphinite Boranes 10a-h (Typical Procedure). Concentrated sulfuric acid (120 mol%) was added slowly to a solution of phosphinamide borane **9** in methanol (0.1 M) at ambient temperature. The solution was allowed to stir 18 h, partitioned between dichloromethane and water, and the aqueous phase was extracted with dichloromethane. The combined dichloromethane layers were washed with saturated, aqueous sodium bicarbonate, dried with $MgSO_4$, and concentrated. The crude residue was purified via column chromatography (elution with 90:10 hexane-EtOAc) to give clear, colorless oils (unless otherwise specified).



(*R*)-Methyl-(methylphenyl)phosphinite borane (10a).[50] The general procedure was followed except **9a** was used without purification. Yield over two steps: 75% (2.52 g, 15 mmol). R_f (95:5 hexane-EtOAc) = 0.42.

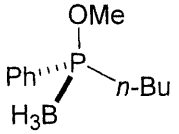
IR (neat): 3058, 2988, 2944, 2842, 2382, 1037 cm $^{-1}$.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.82-7.78 (m, 2H), 7.58-7.49 (m, 3H), 3.58 (d, 3H, J = 12.2 Hz), 1.71 (d, 3H, J = 9.2 Hz), 1.1-0.5 (br m, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 132.9 (d, J = 65.6 Hz), 131.5, 131.4, 129.53, 129.45, 54.4 (d, J = 2.9 Hz), 16.8 (d, J = 47.2 Hz).

^{31}P NMR ($CDCl_3$, 121 MHz): δ 113 (br q, J = 72 Hz).

HRMS (EI) [M-H+]: *m/z* calcd for $C_8H_{13}BOP$ 167.0792, obsd 167.0794.



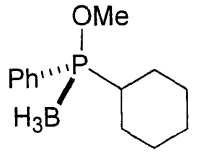
(*R*)-Methyl-(*n*-butylphenyl)phosphinite borane (10b).[50] Yield: 62% (0.6 g, 2.9 mmol). R_f (90:10 hexane-EtOAc) = 0.32.

IR (thin film): 2958, 2872, 2375, 1437, 1033 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ 7.79-7.73 (m, 2H), 7.55-7.45 (m, 3H), 3.60 (d, J = 11.9 Hz, 3H), 2.00-1.86 (m, 2H), 1.52-1.32 (m, 4H), 0.88 (t, J = 7.2 Hz, 3H), 1.2-0.3 (br m, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 132.1 (d, J = 2.3 Hz), 131.5, 131.1 (d, J = 10.4 Hz, 2C), 128.9 (d, J = 9.8 Hz, 2C), 54.0 (d, J = 2.9 Hz), 30.4 (d, J = 45.5 Hz), 24.14, 24.11 (d, J = 13.8 Hz), 13.7. ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ 116.6 (br q, J = 72 Hz).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{11}H_{20}BNaOP$ 233.1237, obsd 233.1235.



(*R*)-Methyl-(cyclohexylphenyl)phosphinite borane (10c). The general procedure was followed except that the reaction was heated to 45 °C after addition of sulfuric acid. Yield: 29% (0.2 g, 0.9 mmol). R_f(90:10 hexane-EtOAc) = 0.38.

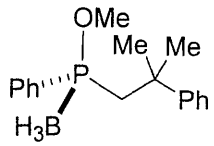
IR (NaCl, thin film): 2933, 2855, 2383, 1728, 1450, 1437 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.72-7.68 (m, 2H), 7.54-7.46 (m, 3H), 3.61 (d, J = 12.1 Hz), 1.93-1.86 (m, 2H), 1.81-1.78 (m, 1H), 1.73 (br s, 1H), 1.66-1.61 (m, 2H), 1.34-1.30 (m, 1H), 1.26-1.13 (m, 4H), 1.1-0.4 (br m, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 131.9 (d, J = 2.3 Hz), 131.5 (d, J = 10.4 Hz, 2C), 130.3 (d, J = 51.2 Hz), 128.7 (d, J = 9.8 Hz, 2C), 54.3 (d, J = 3.5 Hz), 39.2 (d, J = 45.5 Hz), 26.5 (d, J = 4.5 Hz), 26.4 (d, J = 5.2 Hz), 26.0, 25.6, 25.2.

^{31}P NMR ($CDCl_3$, 121.5 MHz): δ 119.5 (br q, J = 75 Hz).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{13}H_{22}BNaOP$ 259.1394, obsd 259.1384.



(*R*)-Methyl-[(2-methyl-2-phenyl-1-propyl)phenyl]phosphinite borane (10d). Yield: 65% (0.67 g, 2.3 mmol). R_f (90:10 hexane-EtOAc) = 0.29.

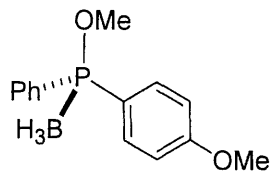
IR (NaCl): 3058, 2967, 2945, 2384, 1496, 1437 cm $^{-1}$.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.62-7.58 (m, 2H), 7.47-7.44 (m, 1H), 7.40-7.7.37 (m, 2H), 7.31-7.29 (m, 2H), 7.24-7.21 (m, 2H), 7.16-7.13 (m, 1H), 3.42 (d, J = 11.9 Hz, 3H), 2.51 (t, J = 14.8Hz, 1H), 2.31 (dd, J = 5.2, 15.2 Hz, 1H), 1.55 (s, 3H), 1.50 (s, 3H), 1.2-0.5 (br m, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 148.6, 133.1 (d, J = 55.8 Hz), 131.6 (d, J = 2.9 Hz), 130.6 (d, J = 10.4 Hz, 2C), 128.7 (d, J = 9.8 Hz, 2C), 128.2 (s, 2C), 126.1, 125.8 (s, 2C), 53.7, 47.3 (d, J = 38.6 Hz), 37.7, 30.4 (d, J = 5.2 Hz), 30.2 (d, J = 5.8 Hz).

^{31}P NMR ($CDCl_3$, 121.5 MHz): δ 114.5 (br q, J = 69 Hz).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{17}H_{24}BNaOP$ 309.1550, obsd 309.1551.



(*S*)-Methyl-[(4-methoxyphenyl)phenyl]phosphinite borane (10e). Yield: 77% (0.7 g, 2.7 mmol). R_f (80:20 hexane-EtOAc) = 0.31.

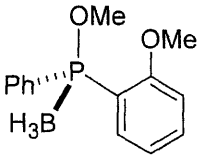
IR (thin film): 3059, 3008, 2944, 2840, 2383, 1595, 1503 cm $^{-1}$.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.74-7.67 (m, 4H), 7.52-7.45 (m, 3H), 7.0-6.96 (m, 2H), 3.85 (s, 3H), 3.72 (d, J = 12.2 Hz, 3H), 1.3-0.7 (br m, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 162.6 (d, J = 2.2 Hz), 133.5 (d, J = 12.6, 2C), 131.8 (d, J = 2.4 Hz), 132.1 (d, J = 65.6 Hz), 131.1 (d, J = 11.2 Hz, 2C), 128.7 (d, J = 10.5 Hz, 2C), 122.3 (d, J = 67.7 Hz), 114.4 (d, J = 11.4 Hz), 55.6, 54.1.

^{31}P NMR ($CDCl_3$, 121.5 MHz): δ 105.9 (br q, J = 76 Hz).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{14}H_{18}BNNaO_2P$ 283.1030, obsd 283.1024.



(*S*)-Methyl-[(2-methoxyphenyl)phenyl]phosphinite borane (10f).[47a, 48a-b, 50] Yield: 76% (0.53 g, 2.0 mmol). R_f (10:90 hexane-EtOAc) = 0.18.

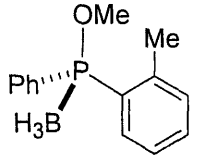
IR (thin film): 3060, 2943, 2840, 2382, 1590, 1478, 1432, 1278, 1252, 1064, 1033 cm $^{-1}$.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.81 (ddd, J = 1.7, 7.6, 12.4, 1H) 7.77-7.73 (m, 2H), 7.53-7.47 (m, 2H), 7.45-7.42 (m, 2H), 7.08 (tdd, J = 0.9, 1.8, 7.5, 1H), 6.88 (dd, J = 4.3, 8.2 Hz, 1H), 3.75 (d, J = 12.2 Hz, 3H), 3.64 (s, 3H), 1.3-0.7 (br m, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 161.2 (d, J = 3.5 Hz), 134.13 (d, J = 1.7 Hz), 134.13 (d, J = 10.9 Hz), 132.2 (d, J = 66.2 Hz), 131.5 (d, J = 2.3 Hz), 131.3 (d, J = 11.5 Hz, 2C), 128.3 (d, J = 10.9 Hz, 2C), 121.0 (d, J = 10.9 Hz), 119.5 (d, J = 63.3 Hz), 111.8 (d, J = 5.2 Hz), 55.7, 54.1 (d,J = 2.9 Hz).

^{31}P NMR ($CDCl_3$, 121.5 MHz): δ 105.8 (br q, J = 76 Hz).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{14}H_{18}BNNaO_2P$ 283.1030, obsd 283.1026.



(*S*)-Methyl-[(2-methylphenyl)phenyl]phosphinite borane (10g). Yield: 87% (0.62 g, 2.5 mmol). R_f (10:90 hexane-EtOAc) = 0.37.

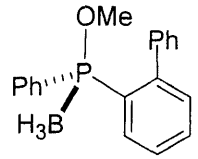
IR (thin film): 3058, 2944, 2385, 1438, 1137, 1067, 1033 cm $^{-1}$.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.90 (dd, J = 7.6, 12.8, 1H, 7.68-7.64 (m, 2H), 7.54-7.51 (m, 1H), 7.47-7.44 (m, 3H), 7.34 (t, J = 7.3, 1H), 6.22 (dd, J = 3.7, 7.3 Hz, 1H), 3.76 (d, J = 12.2 Hz, 3H), 2.25 (s, 3H), 1.3-0.7 (br m, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 142.1 (d, J = 8.1 Hz), 133.9 (d, J = 15.0 Hz), 132.5 (d, J = 2.3 Hz), 132.0 (d, J = 64.5 Hz), 131.9 (d, J = 2.3 Hz), 131.8 (d, J = 8.6 Hz), 131.4 (d, J = 11.5, 2C Hz), 129.2 (d, J = 60.4 Hz), 128.8 (d, J = 10.4 Hz, 2C), 125.9 (d, J = 11.5 Hz), 54.0 , 21.4 (d, J = 4.0 Hz).

^{31}P NMR ($CDCl_3$, 121.5 MHz): δ 109.5 (br q, J = 72 Hz).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{14}H_{18}BNaOP$ 267.1081, obsd 267.1089.



(*S*)-Methyl-[(2-biphenylyl)phenyl]phosphinite borane (10h).[48b] Yield: 77% (0.95 g, 3.1 mmol), isolated as a white solid. R_f (90:10 hexane-EtOAc) = 0.34. Mp: 62-63 °C.

IR (thin film): 3056, 2943, 2383, 1465, 1438, 1131, 1114, 1064, 1033 cm^{-1}.

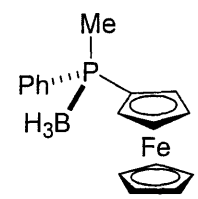
^1H NMR ($CDCl_3$, 500 MHz): δ 8.10-8.06 (m, 1H), 7.57-7.50 (m, 2H), 7.39-7.31 (m, 3H), 7.27-7.21 (m, 4H), 7.14-7.11 (m, 2H), 6.94-6.92 (m, 2H), 3.58 (d, J = 12.2 Hz, 3H), 1.2-0.8 (br m, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.8 (d, J = 7.5 Hz), 140.5 (d, J = 2.9 Hz), 133.7 (d, J = 5.0 Hz), 132.4 (d, J = 67.3 Hz), 131.8 (d, J = 7.4 Hz), 131.7 (d, J = 2.3 Hz), 131.3 (d, J = 2.3 Hz), 131.1 (d, J = 10.9 Hz, 2C), 130.3 (d, J = 60.4 Hz), 129.7 (s, 2C), 128.3 (d, J = 10.9 Hz, 2C), 127.4, 127.35 (s, 2C), 127.2 (d, J = 11.5 Hz), 53.8.

^{31}P NMR ($CDCl_3$, 121.5 MHz): δ 108.6 (br q, J = 69 Hz).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{19}H_{20}BNaOP$ 329.1237, obsd 329.1251.

Synthesis of Phosphine Boranes 11a-h (Typical Procedure). A 0.075 M solution of bromoferrocene (8 mmol) in diethyl ether was prepared and cooled to −78 °C. *t*-Butyllithium (16 mmol) was slowly added and the solution was stirred 10 min at −78 °C. The solution was warmed to 0 °C and stirred an additional 15 min to generate FcLi. A 1.0 M solution of **4** (4 mmol) in THF was cooled to −78 °C, and the FcLi solution was transferred to it via cannula over 10 min. The solution was allowed to warm to ambient temperature and stirred 14 h. Water was added, and the aqueous phase was extracted with diethyl ether. The combined organic layers were washed with saturated, aqueous NaCl, dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified via gradient column chromatography (elution with 80:20 hexane-CH_2Cl_2, polarity gradually increased to 50:50).



(*S*)-Ferrocenylmethylphenylphosphine borane (11a). Yield: 58% (0.75 g, 2.3 mmol), isolated as an orange oil that was crystallized from hexane. R_f (50:50 hexane-CH_2Cl_2) = 0.35. Mp: 73-74 °C.

Enantiomeric excess: 83% ee by HPLC analysis (Chiracel OJ, isocratic, hexane:2-propanol = 95:5, t_R [(*R*)-**11a**] = 16.8 min, t_R [(*S*)-**11a**] = 24.7 min).

IR (thin film): 3096, 2919, 2379 cm^{-1}.

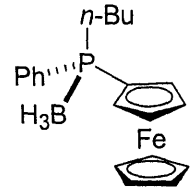
^1H NMR ($CDCl_3$, 500 MHz): δ 7.67-7.63 (m, 2H), 7.44-7.40 (m, 3H), 4.51-4.48 (m, 3H), 4.45 (m, 1H), 4.29-4.28 (s, 5H), 1.80 (d, 3H, J = 10.4 Hz), 1.2-0.7(br m, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 133.1 (d, J = 56 Hz), 131.8 (d, 2C, J = 6.3 Hz), 131.5 (d, 1C, J = 2.8 Hz), 129.3 (d, 2C, J = 13.8 Hz), 72.5 (d, 1C, J = 8.6 Hz), 72.2 (d, 1C, J = 6.9 Hz), 71.1 (d, 1C, J = 6.3 Hz), 70.5 (5C), 13.9 (d, J = 42 Hz).

^{31}P NMR δ ($CDCl_3$, 121 MHz): 6.2 (br q, J = 76 Hz).

HRMS (EI): *m/z* calcd for $C_{17}H_{20}BFeP$ 322.0740, obsd 322.0750.

$[\alpha]^{20}_D = -32.3$ (c = 0.60; CH_2Cl_2).



(*S*)-*n*-Butylferrocenylphenylphosphine-borane (11b). Yield: 90% (0.7 g, 1.8 mmol), isolated as an orange oil. R_f(50:50 hexane-CH_2Cl_2) = 0.36.

Enantiomeric excess: 77% ee by HPLC analysis (Chiracel OJ, isocratic, hexane:2-propanol = 97.5:2.5, t_R [(*R*)-**11b**] = 10.0 min, t_R [(*S*)-**11b**] = 12.0 min).

IR (NaCl): 3386, 3097, 2957, 2870, 2380, 1436, 1172, 1107, 1065 cm^{-1}.

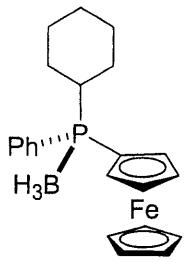
^1H NMR ($CDCl_3$, 500 MHz): δ 7.79-7.75 (m, 2H), 7.49-7.44 (m, 3H), 4.56-4.55 (m, 1H), 4.47-4.46 (m, 1H), 4.44-4.42 (m, 1H), 4.37-4.36 (m, 1H), 4.18 (s, 5H), 2.09-2.03 (m, 2H), 1.60-1.57 (m, 1H), 1.40-1.30 (m, 3H), 0.88 (t, J = 7.2 Hz, 3H), 1.3-0.7 (br m, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 132.2 (d, J = 8.6 Hz, 2C), 131.1 (d, J = 2.3 Hz), 130.6 (d, J = 2.9 Hz), 128.7 (d, J = 9.8 Hz, 2C), 71.9 (d, J = 9.8 Hz), 71.8 (d, J = 3.5 Hz), 71.7, 71.3 (d, J = 7.5 Hz), 69.9 (s, 5C), 27.7 (d, J = 39.1 Hz), 25.5, 24.5 (d, J = 14.4 Hz), 13.8.

^{31}P NMR ($CDCl_3$, 121.5 MHz): δ 11.9 (br q, J = 75 Hz).

HRMS (EI): *m/z* calcd for $C_{20}H_{26}BFeP$ 364.1209, obsd 364.1194.

$[\alpha]^{20}_D = -48.4$ (c = 1.10; CH_2Cl_2).



(*S*)-Cyclohexylferrocenylphenylphosphine borane (11c). Yield: 66% (1.0 g, 2.6 mmol), isolated as an orange solid. R_f(50:50 hexane-CH_2Cl_2) = 0.33. Mp: 95-96 °C.

Enantiomeric excess: 97% ee by chiral HPLC analysis (Chiracel OJ, isocratic, hexane:2-propanol = 97.5:2.5, t_R [(*R*)-**11c**] = 8.3 min, t_R [(*S*)-**11c**] = 10.0 min).

IR (NaCl): 2931, 2854, 2381 cm^{-1}.

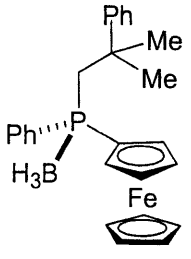
^1H NMR ($CDCl_3$, 500 MHz): δ 7.95-7.91 (m, 2H), 7.54-7.53 (m, 3H), 4.66 (br s, 1H), 4.43 (br s, 1H), 4.40 (br s, 1H), 4.24 (br s, 1H), 3.97 (s, 5H), 2.03 (dd, J = 12.4, 26 Hz, 1H), 1.77-1.76 (m, 1H), 1.70-1.62 (m, 3H), 1.44-1.23 (m, 3H), 1.20-1.12 (m, 3H), 1.1-0.6 (br m, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 132.8 (d, J = 8.6 Hz, 2C), 131.3 (d, J = 2.9 Hz), 129.3 (d, J = 55.9 Hz), 128.7 (d, J = 9.2 Hz, 2C), 74.6 (d, J = 15.0 Hz), 71.8 (d, J = 6.3 Hz), 70.9 (d, J = 8.6 Hz), 70.6 (d, J = 4.0 Hz), 69.8 (s, 5C), 69.2 (d, J = 62.8 Hz), 37.2 (d, J = 37.4 Hz), 27.1, 26.9 (d, J = 4.6 Hz), 26.9 (d, J = 19.6 Hz), 26.7, 26.0 (d, J = 1.2 Hz).

^{31}P NMR ($CDCl_3$, 121.5 MHz): δ 19.3 (br q, J = 67 Hz).

HRMS (EI): *m/z* calcd for $C_{22}H_{28}BFeP$ 390.1366, obsd 390.1351.

$[\alpha]^{20}_D = -281.8$ (c = 0.55; CH_2Cl_2).



(*S*)-Ferrocenylphenyl(2-methyl-2-phenyl-1-propyl)phosphine borane (11d). Yield: 79% (0.66 g, 1.5 mmol), isolated as an orange oil. R_f(80:20 hexane-CH_2Cl_2) = 0.06.

Enantiomeric excess: 98% ee by chiral HPLC analysis (Chiracel AD, isocratic, hexane:2-propanol = 98:2, t_R [(*R*)-**11d**] = 7.3 min, t_R [(*S*)-**11d**] = 7.8 min).

IR (NaCl): 3088, 3057, 2965, 2389, 1496, 1437, 1387, 1171, 1107, 1063 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.74-7.70 (m, 2H), 7.41-7.40 (m, 1H), 7.36-7.33 (m, 2H), 7.26-7.24 (m, 2H), 7.20-7.16 (m, 2H), 7.13-7.11 (m, 1H), 4.55-4.54 (m, 1H), 4.41-4.40 (m, 1H), 4.37

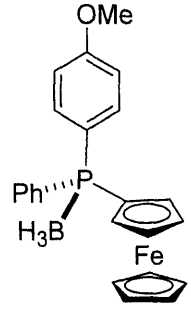
(m, 2H), 4.10 (s, 5H), 2.72 (t, J = 14.2 Hz, 1H), 2.63 (dd, J = 9.2, 14.6 Hz, 1H), 1.54 (s, 3H), 1.43 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 148.8 (d, J = 6.9 Hz), 132.0 (d, J = 11.4 Hz, 2C), 131.6, 130.7 (d, J = 2.3 Hz), 128.4 (d, J = 9.8 Hz, 2C), 128.2 (s, 2C), 126.1, 125.7 (s, 2C), 72.6 (d, J = 66.2 Hz), 71.9 (d, J = 10.4 Hz), 71.6 (d, J = 7.5 Hz), 71.5 (d, J = 9.2 Hz), 70.9 (d, J = 7.5 Hz), 69.8 (s, 5C), 43.6 (d, J = 32.2 Hz), 38.3, 31.0 (d, J = 5.2 Hz), 29.2 (d, J = 4.6 Hz).

^{31}P NMR ($CDCl_3$, 121.5 MHz): δ 6.3 (br q, J = 70 Hz).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{26}H_{30}BFeNaP$ 463.1420, obsd 463.1418.

$[\alpha]^{20}_D$ = −72.3 (c = 0.90; CH_2Cl_2).



(*R*)-Ferrocenyl(4-methoxyphenyl)phenylphosphine borane (11e). Yield: 85% (0.56 g, 1.4 mmol), isolated as an orange oil. R_f(50:50 hexane-CH_2Cl_2) = 0.30.

Enantiomeric excess: 95% ee by chiral HPLC analysis (Chiracel OJ, isocratic, hexane:2-propanol = 90:10, t_R [(*S*)-**11e**] = 22.8 min, t_R [(*R*)-**11e**] = 30.3 min).

IR (thin film): 3056, 2960, 2838, 2384, 1596, 1570, 1501, 1293, 1256, 1181, 1109, 1062 cm^{-1}.

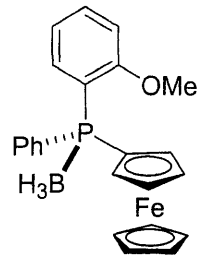
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.58-7.53 (m, 4H), 7.45-7.43 (m, 1H), 7.41-7.38 (m, 2H), 6.95 (dd, J = 1.8, 8.9 Hz, 2H), 4.52-4.50 (m, 2H), 4.46-4.45 (m, 1H), 4.37 (m, 1H), 4.13 (s, 5H), 3.84 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 161.9, 134.6 (d, J = 10.9 Hz, 2C), 132.5 (d, J = 9.2 Hz, 2C), 132.2 (d, J = 59.9 Hz), 130.8, 128.5 (d, J = 9.8 Hz, 2C), 121.9 (d, J = 64.5 Hz), 114.2 (d, J = 10.9 Hz, 2C), 73.1 (d, J = 10.9 Hz), 72.6 (d, J = 9.2 Hz), 72.0, 71.9, 71.84, 69.9 (s, 5C), 55.5.

^{31}P NMR ($CDCl_3$, 121.5 MHz): δ 14.8 (br q, J = 65 Hz).

HRMS (EI): *m/z* calcd for $C_{23}H_{24}BFeOP$ 414.1002, obsd 414.0999.

$[\alpha]^{20}_D$ = +20.0 (c = 0.25; CH_2Cl_2).



(*R*)-Ferrocenyl(2-methoxyphenyl)phenylphosphine borane (11f).[47a] Yield: 92% (0.38 g, 0.9 mmol). R_f(90:10 hexane-EtOAc) = 0.18. Mp: 140 °C.

Enantiomeric excess: >98% e.e. by chiral HPLC analysis (Chiracel OJ, isocratic, hexane:2-propanol = 99:1, t_R [(*R*)-**11f**] = 43.8 min, t_R [(*S*)-**11f**] = 56.9 min).

IR (thin film): 3434, 3074, 2938, 2382, 1736, 1589, 1574, 1478, 1432, 1277, 1251, 1170, 1107, 1061 cm^{-1}.

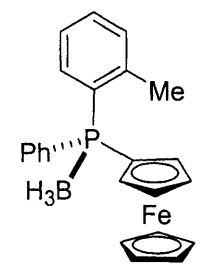
^1H NMR ($CDCl_3$, 500 MHz): δ 7.82-7.77 (m, 1H), 7.55-7.48 (m, 3H), 7.40-7.33 (m, 3H), 7.09-7.06 (m, 1H), 6.89 (dd, J = 3.8, 8.1 Hz, 1H), 4.70-4.69 (m, 1H), 4.54 (br s, 1H), 4.51-4.49 (m, 2H), 4.04 (s, 5H), 3.47 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 135.6, 133.5, 131.5 (d, J = 9.8 Hz, 2C), 130.1, 128.0 (d, J = 10.9 Hz, 2C), 121.0 (d, J = 10.9 Hz, 1C), 112.0, 74.1 (d, J = 12.1 Hz), 73.6 (d, J = 8.6 Hz), 71.8 (d, J = 7.5 Hz), 71.6 (d, J = 8.1 Hz), 69.9 (s, 5C), 55.5.

^{31}P NMR ($CDCl_3$, 121 MHz): δ 14.1 (br q, J = 55 Hz).

HRMS (EI): *m/z* calcd for $C_{23}H_{24}BFeOP$ 414.1002, obsd 414.1004.

$[\alpha]^{20}_D$ = +60.0 (c = 0.25; CH_2Cl_2).



(*R*)-Ferrocenyl(2-methylphenyl)phenylphosphine borane (11g). Yield: 70% (0.50 g, 1.3 mmol). R_f(80:20 hexane-EtOAc) = 0.50. Mp: 168-169 °C.

Enantiomeric excess: 83% e.e. by chiral HPLC analysis (Chiracel OJ, isocratic, hexane:2-propanol = 99:1, t_R [(*R*)-**11g**] = 14.0 min, t_R [(*S*)-**11g**] = 20.3 min).

IR (thin film): 3055, 2393, 1437, 1171, 1107, 1063 cm^{-1}.

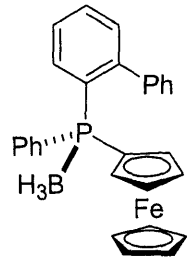
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.80-7.76 (m, 2H), 7.58-7.54 (m, 1H), 7.52-7.49 (m, 2H), 7.33-7.11 (m, 2H), 7.08-7.04 (m, 1H), 4.77-4.76 (m, 1H), 4.59-4.58 (m, 1H), 4.50-4.49 (m, 1H), 4.08-4.07 (m, 1H), 4.07 (s, 5H), 2.09 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 141.8 (d, J = 10.4 Hz), 133.4 (d, J = 8.1 Hz), 132.8 (d, J = 9.8 Hz, 2C), 131.7 (d, J = 9.2 Hz), 131.3, 130.9, 130.8, 130.4 (d, J = 16.1 Hz), 128.8 (d, J = 9.8 Hz, 2C), 125.7 (d, J = 9.8 Hz), 72.2 (d, J = 6.3 Hz), 72.0 (d, J = 10.4 Hz), 71.8, 70.1 (d, J = 70.2 Hz), 70.0 (s, 5C), 22.2 (d, J = 4.6 Hz).

^{31}P NMR ($CDCl_3$, 121 MHz): δ 17.1 (br q, J = 60 Hz).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{23}H_{24}BFeNaP$ 421.0950, obsd 421.0952.

$[\alpha]^{20}_D = -269.3$ (c = 0.15; CH_2Cl_2).



(*R*)-Ferrocenyl(2-biphenylyl)phenylphosphine borane (11h). Yield: 69% (0.54 g, 1.2 mmol). R_f(50:50 hexane-CH_2Cl_2) = 0.34. Mp: 135-137 °C.

Enantiomeric excess: 98% e.e. by chiral HPLC analysis (Chiracel AD, isocratic, hexane:2-propanol = 99.4:0.6, t_R [(*R*)-**11h**] = 13.2 min, t_R [(*S*)-**11h**] = 14.3 min).

IR (thin film): 3055, 2385, 1464, 1438, 1169, 1108, 1060 cm^{-1}.

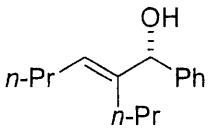
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.64-7.60 (m, 2H), 7.46-7.40 (m, 2H), 7.36-7.33 (m, 2H), 7.31-7.26 (m, 2H), 7.18-7.15 (m, 1H), 7.13-7.10 (m, 1H), 7.04-7.01 (m, 2H), 6.94 (br s, 2H), 4.75 (br s, 1H), 4.49 (br s, 1H), 4.43 (br s, 1H), 4.10 (br s, 1H), 3.90 (s, 5H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.7 (d, J = 9.2 Hz), 140.5 (d, J = 3.5 Hz), 133.5 (d, J = 8.6 Hz), 133.0 (d, J = 9.2 Hz, 2C), 131.80 (d, J = 8.1 Hz), 131.79, 131.3 (d, J = 18.4 Hz), 130.9 (d, J = 2.3 Hz), 130.7, 130.15, 130.1 (d, J = 2.3 Hz), 128.1 (d, J = 10.4 Hz, 2C), 127.1 (s, 2C), 127.0, 126.9 (d, J = 9.2 Hz).

^{31}P NMR ($CDCl_3$, 121 MHz): δ 18.1 (br s).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{28}H_{26}BFeNaP$ 483.1107, obsd 483.1107.

$[\alpha]^{20}_D = -180.8$ (c = 0.40; CH_2Cl_2).



(*E*)-1-Phenyl-2-propyl-hex-2-en-1-ol (12).[68] Prepared according to the general procedure for the reductive coupling of alkynes and aldehydes (Table 8, entries 1-5). R_f (90:10 hexane-EtOAc) = 0.28.

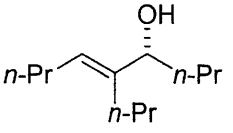
Enantiomeric excess determined by chiral HPLC analysis (Chiracel OD, isocratic, 99:1 hexane:isopropanol, 0.8 mL/min, t_R [(*R*)-**12**] = 15.7 min, t_R [(*S*)-**12**] = 17.4 min).

IR (thin film): 3365, 2958, 2930, 2871, 1493, 1453, 1377, 1035 cm $^{-1}$.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38-7.31 (m, 4H), 7.29-7.25 (m, 1H), 5.64 (5, 1H, J = 7.3 Hz), 5.17 (d, 1H, J = 3.1 Hz), 2.09-2.05 (m, 2H), 2.01-1.96 (m, 1H), 1.86-1.81 (m, 1H), 1.81 (d, 1H, J = 3.1 Hz), 1.48-1.40 (m, 2H), 1.34-1.19 (m, 3H), 0.94 (t, 3H, J = 7.3 Hz), 0.83 (t, 3H, J = 7.3 Hz).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.0, 141.4, 128.4, 127.54, 127.49, 126.8, 78.4, 30.2, 29.9, 23.2, 23.0, 14.7, 14.2.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{15}H_{22}NaO$ 241.1564, obsd 241.1564.



(*E*)-5-Propyl-non-5-en-4-ol (13). Prepared according to the general procedure for the reductive coupling of alkynes and aldehydes (Table 8, entry 6). R_f (90:10 hexane-EtOAc) = 0.25.

Enantiomeric excess determined from the chloroacetate derivative by chiral GC analysis (B-PH, isothermal, 120 °C, t_R [(*S*)-**13**] = 21.2 min, t_R [(*R*)-**13**] = 21.9 min).

IR (thin film): 3357, 2958, 2872, 1465, 1378, 1017 cm $^{-1}$.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.39 (t, 1H, J = 7.3 Hz), 4.03 (td, 1H, J = 2.5, 6.5 Hz), 2.07-1.94 (m, 4H), 1.54-1.50 (m, 2H), 1.46-1.53 (m, 5H) 1.33-1.26 (m, 2H), 0.95-0.90 (m, 9H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 142.2, 127.0, 76.9, 38.2, 29.9, 29.8, 23.5, 23.2, 19.4, 14.9, 14.3, 14.1.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{12}H_{24}NaO$ 207.1719, obsd 207.1723.

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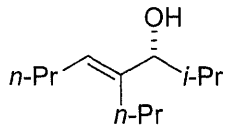
[68] Srebnik, M. *Tetrahedron Lett.* **1991**, *32*, 2449-2452.



(*E*)-2-Methyl-4-propyl-oct-4-en-3-ol (14). Prepared according to the general procedure for the reductive coupling of alkynes and aldehydes (Table 8, entry 7). R_f (90:10 hexane-EtOAc) = 0.34.

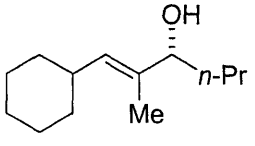
Enantiomeric excess determined from the chloroacetate derivative by chiral GC analysis (B-PH, 90 °C for 30 min then 140 °C for 15 min, t_R [(*S*)-**14**] = 38.4 min, t_R [(*R*)-**14**] = 38.9 min).

IR (thin film): 3409, 2958, 2931, 2872, 1466, 1379, 1005 cm $^{-1}$.

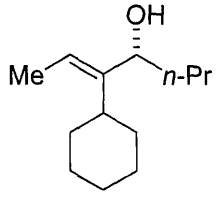
^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.35 (t, 1H, J = 7.3 Hz), 3.65 (d, 1H, J = 7.3 Hz), 2.05-1.92 (m, 4H), 1.81-1.75 (m, 1H), 1.47-1.35 (m, 5H) 0.98-0.89 (m, 9H), 0.83 (t, 3H, J = 7.0 Hz).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 141.4, 127.9, 83.0, 31.8, 30.3, 29.8, 23.5, 20.1, 18.3, 14.9, 14.1.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{12}H_{24}NaO$ 207.1719, obsd 207.1716.



15a



15b

(*E*)-1-Cyclohexyl-2-methyl-hex-1-en-3-ol (15a) and (*E*)-3-cyclohexyl-hept-2-en-4-ol (15b). R_f(90:10 hexane:EtOAc) = 0.33.

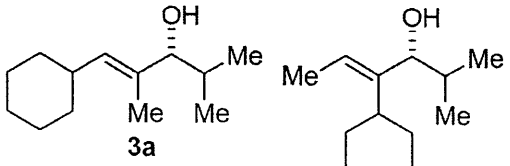
Enantiomeric excess determined by chiral GC analysis (B-PH, isothermal, 140 °C, t_R [(*R*)-**15b**] = 7.86 min, t_R [(*S*)-**15b**] = 8.03 min, t_R [(*R*)-**15a**] = 11.40 min, t_R [(*S*)-**15a**] = 11.66 min).

IR (thin film): 3348, 2926, 2852, 1448 cm $^{-1}$.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.51 (q, 1H, **15b,** J = 7.0 Hz), 5.20 (d, 1H, **15a**, J = 8.8 Hz), 4.05 (t, 1H, **15b**, J = 5.5 Hz), 3.96 (t, 1H, **15a,** J = 6.7 Hz), 2.37-2.33 (m, 1H, **15b**), 2.21-2.15 (m, 1H, **15a**), 1.78-0.87 (m, 21H, **15a, 15b**).

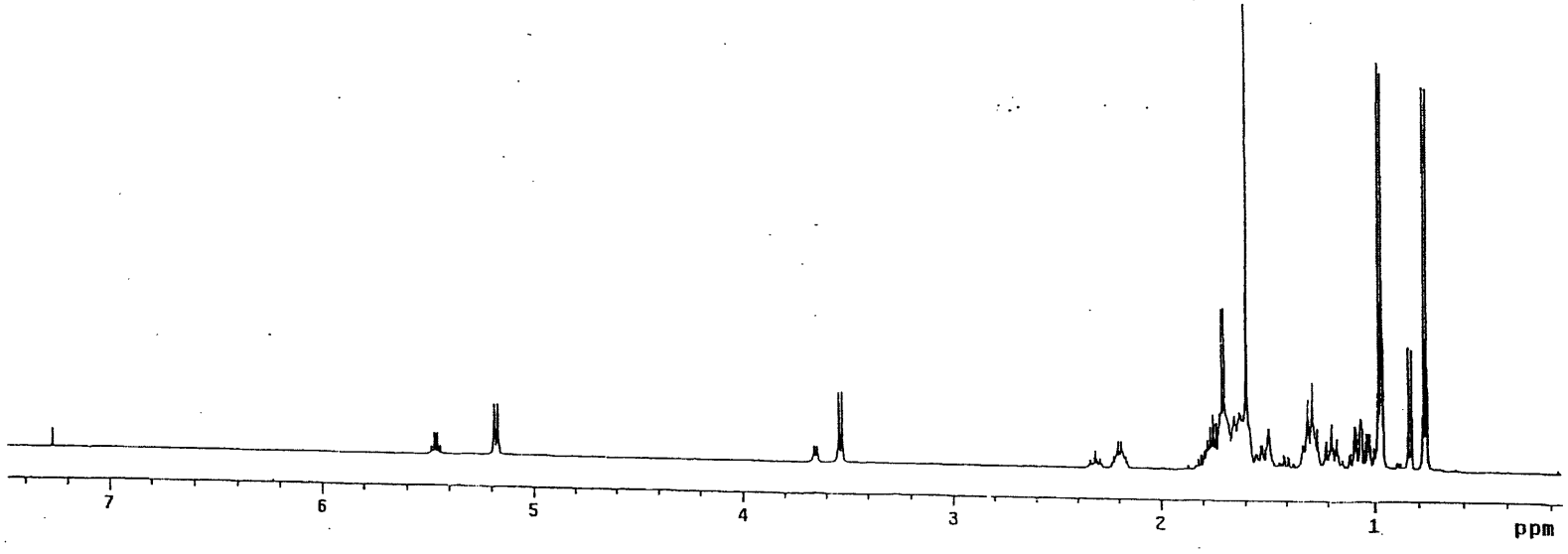
^{13}C NMR ($CDCl_3$, 125 MHz): δ 148.0, 135.4, 133.1, 119.6, 78.0, 73.6, 39.4, 38.9, 37.2, 36.7, 33.3, 33.2, 31.6, 31.4, 27.2, 26.4, 26.3, 26.18, 26.17, 19.7, 19.2, 14.28, 14.25, 13.5, 12.8, 11.3.

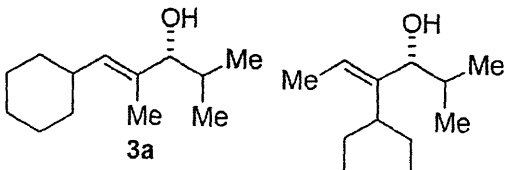
HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{13}H_{24}NaO$ 219.1719, obsd 219.1724.



3a

3b

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Me
Me
Me

3a

OH
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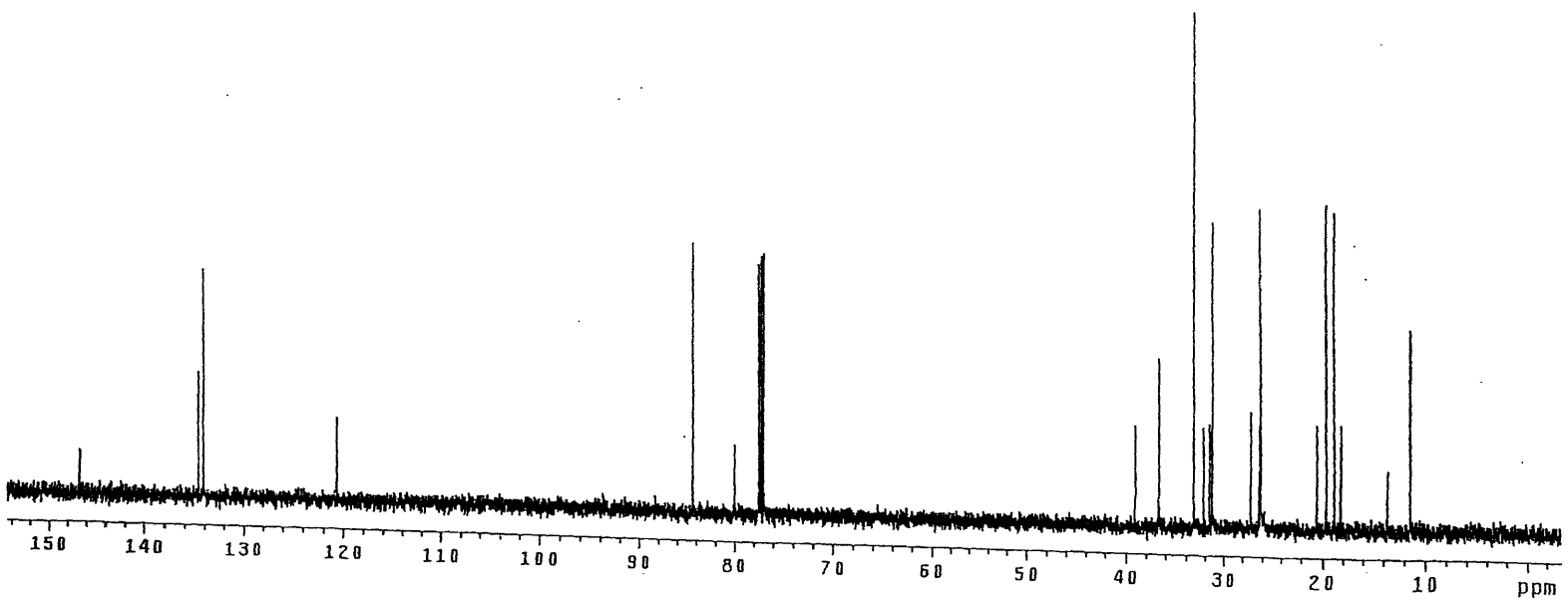
Me
Me

3b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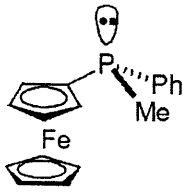
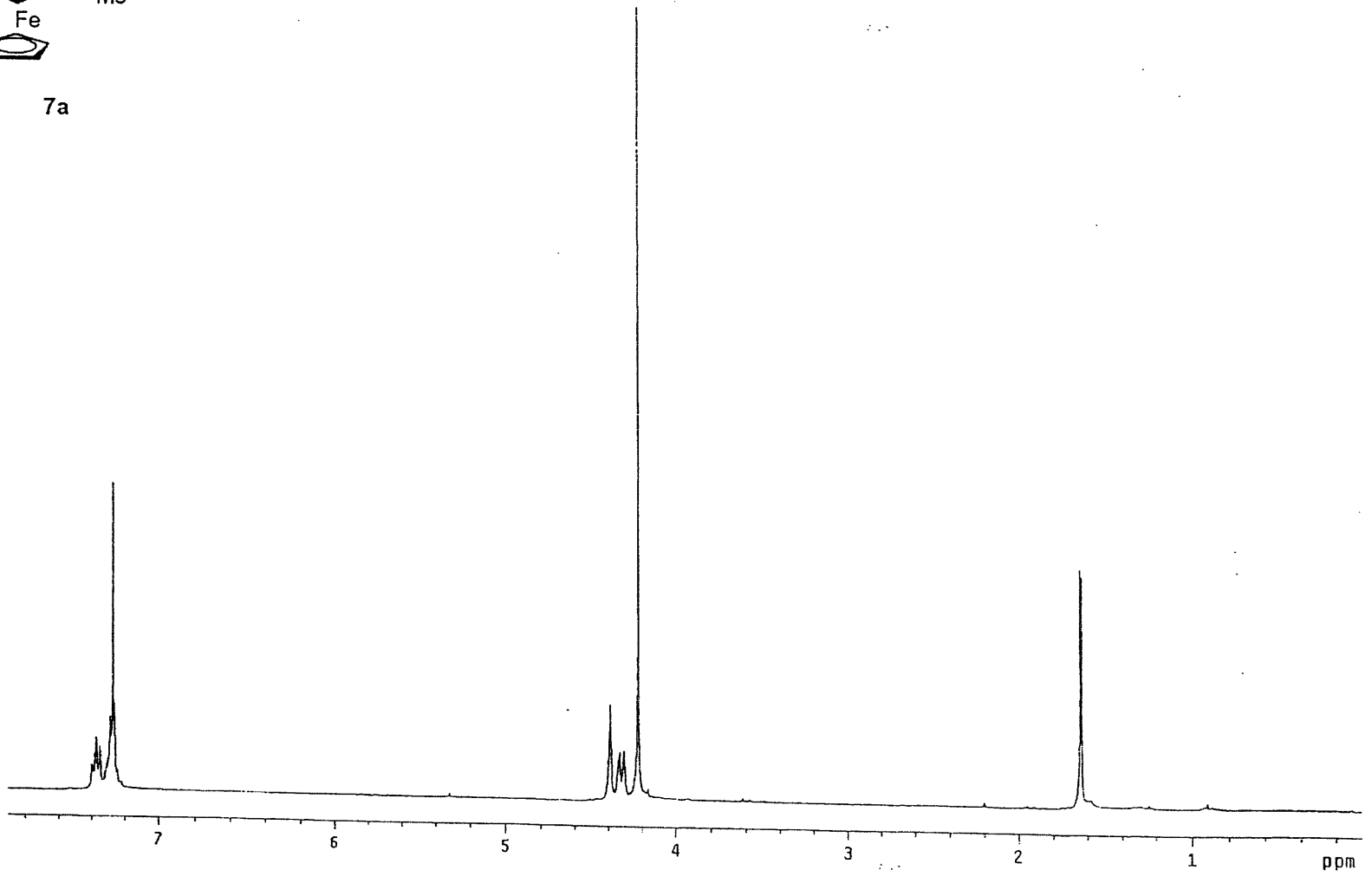
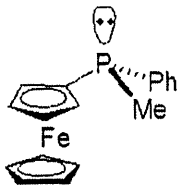


7a

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Fe

7a

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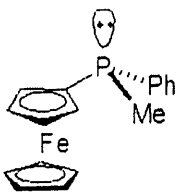
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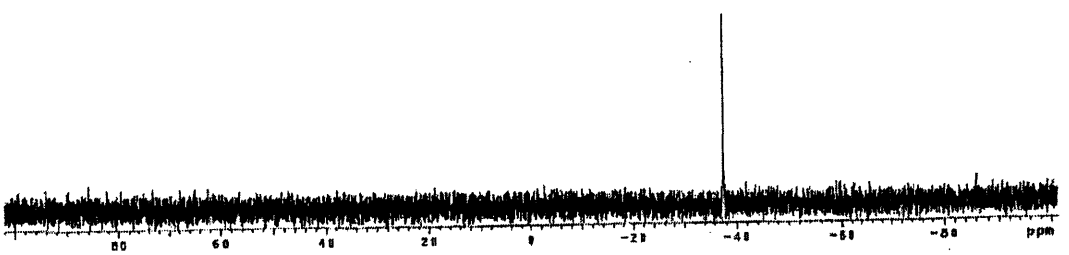
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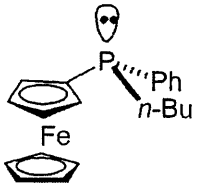
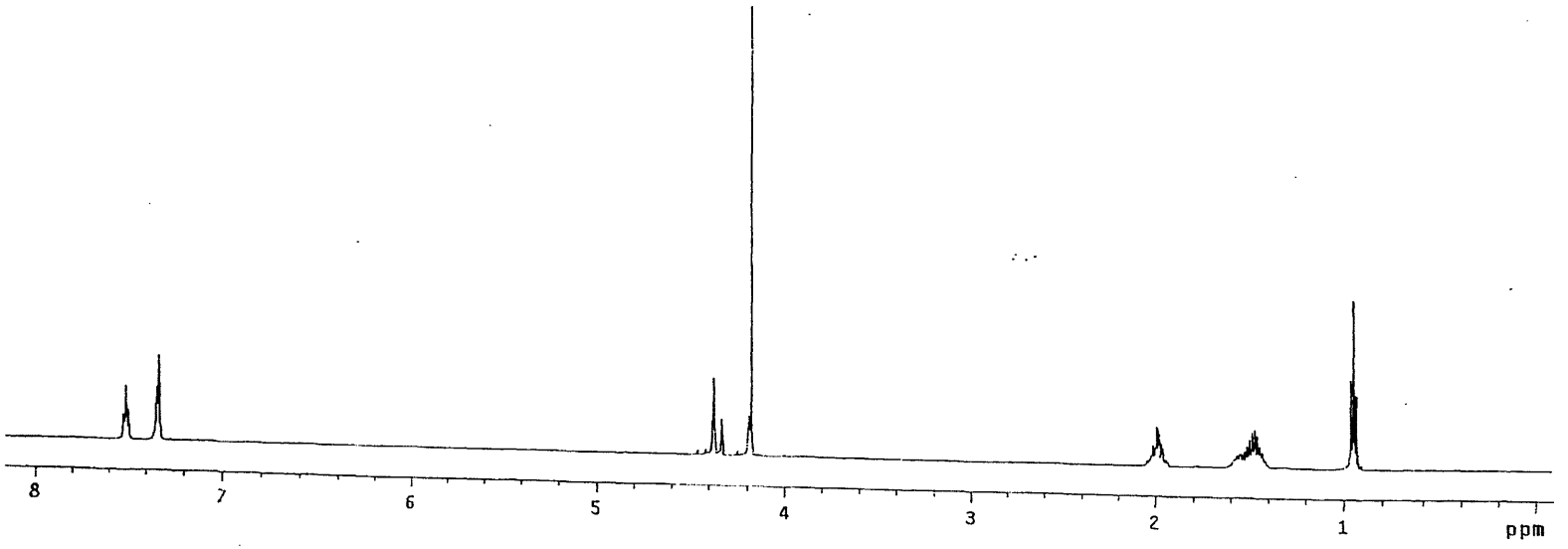
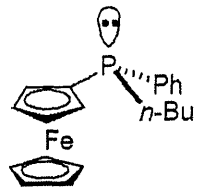


7b




P
Ph
n-Bu
Fe

7b

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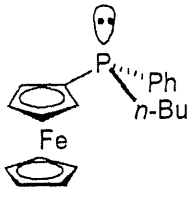
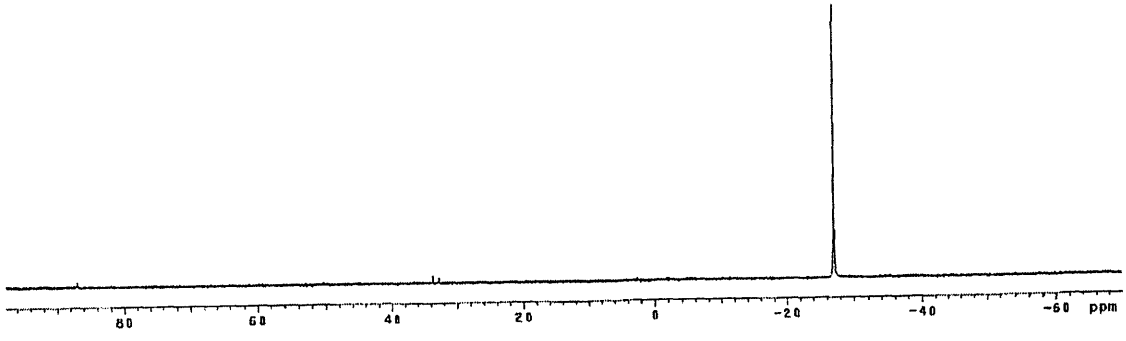
ppm


P
Ph
n-Bu
Fe

7b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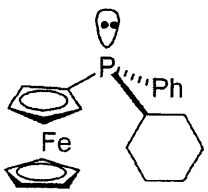

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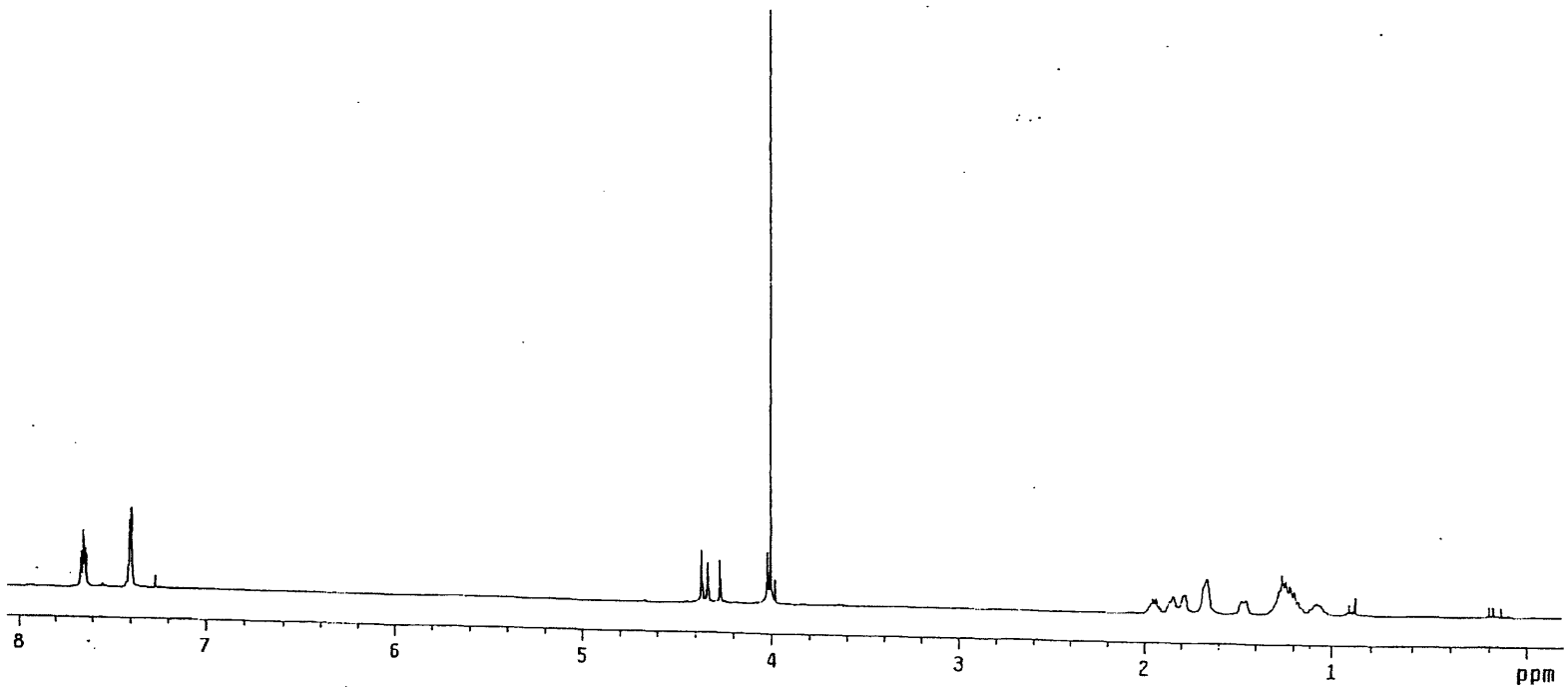

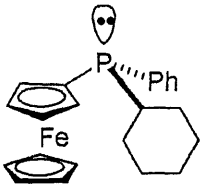
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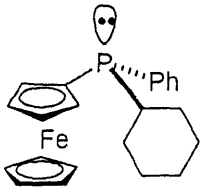
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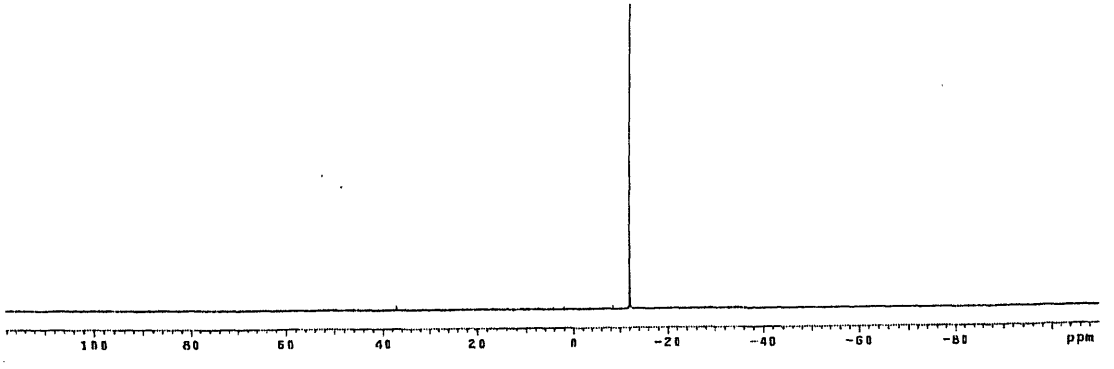
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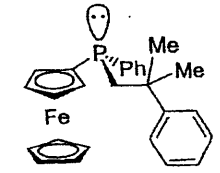

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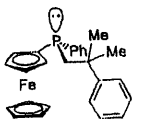
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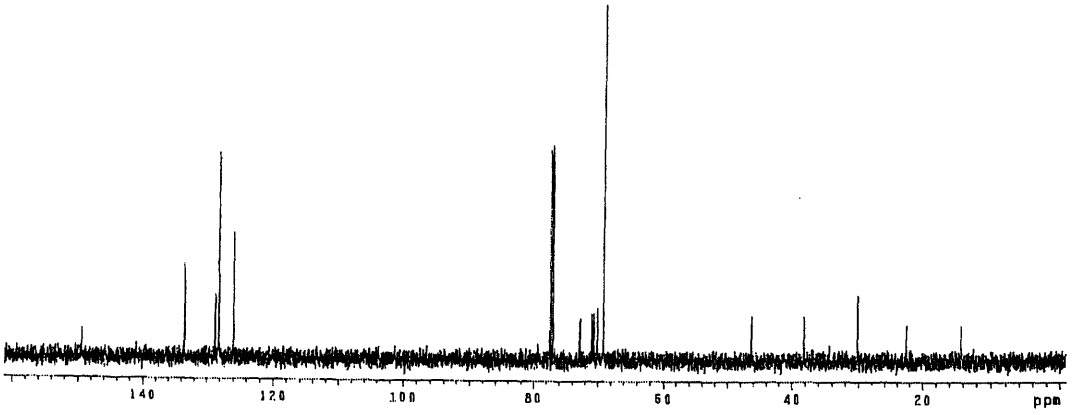
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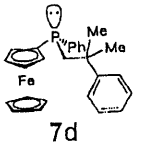
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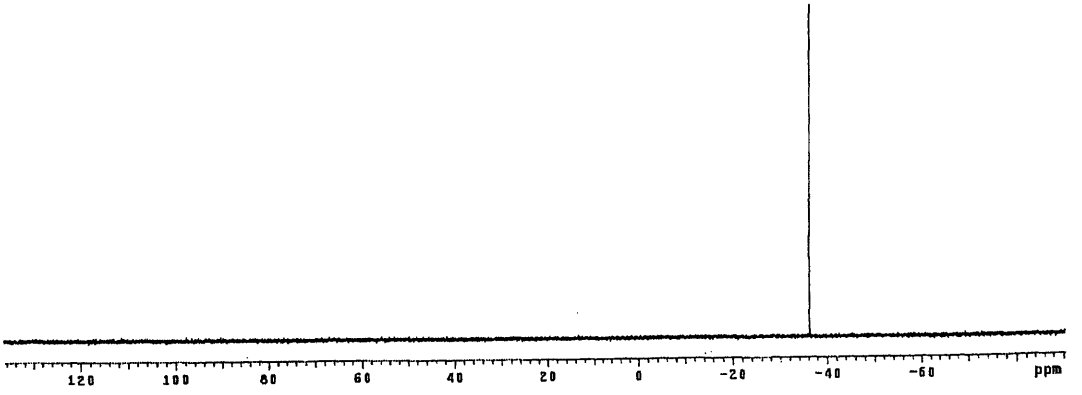
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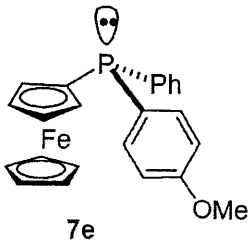

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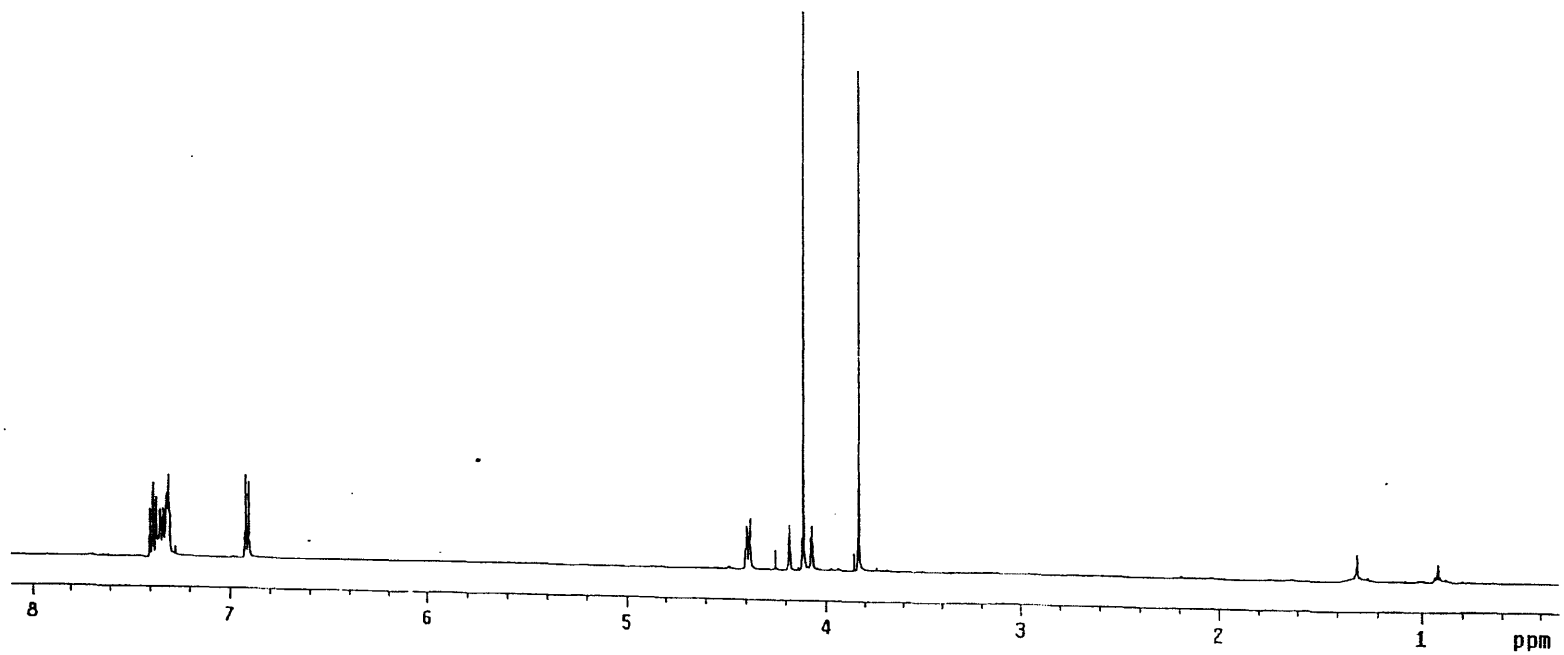

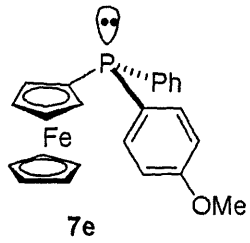
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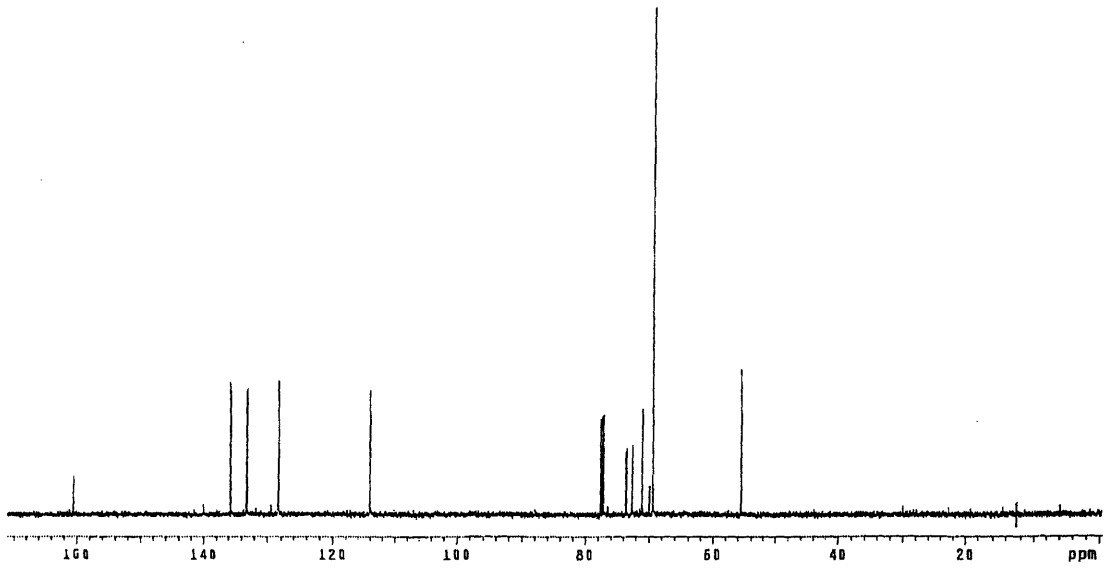
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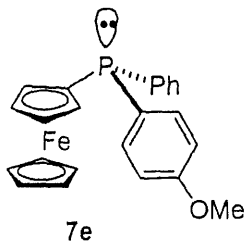
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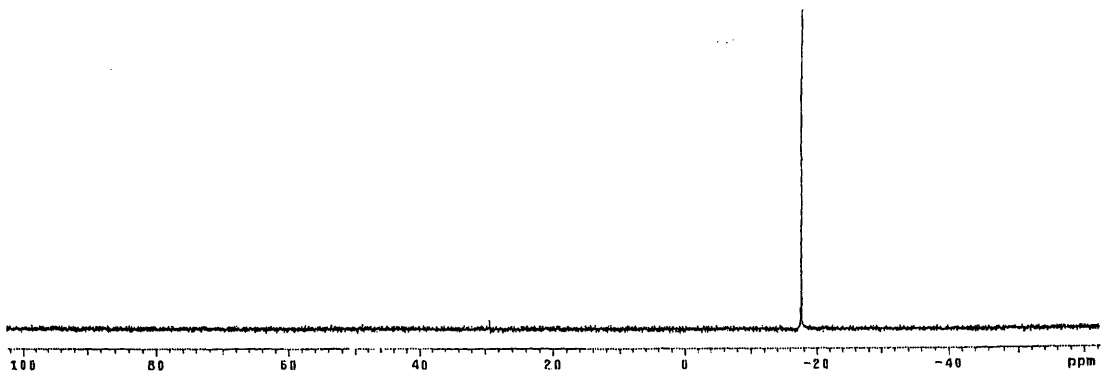
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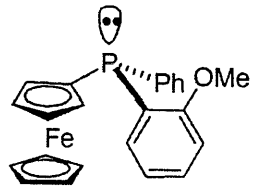

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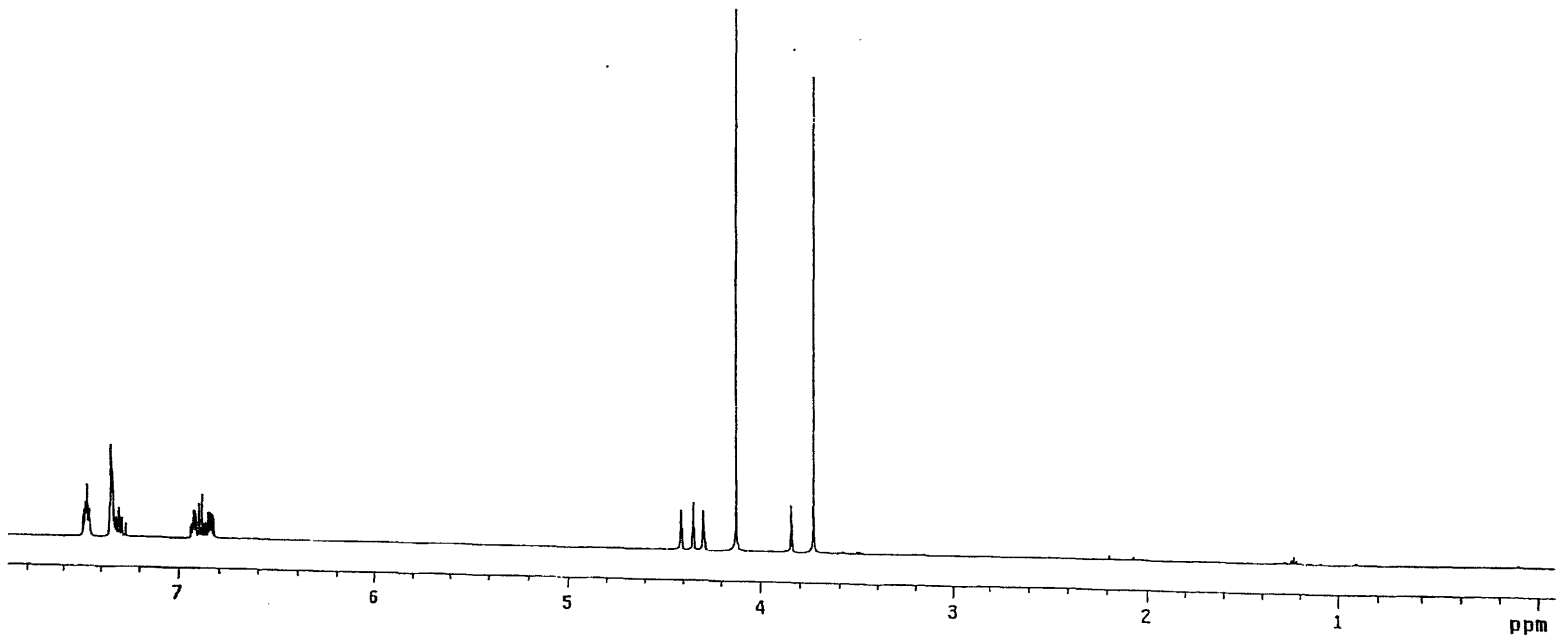

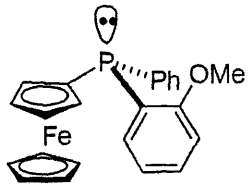
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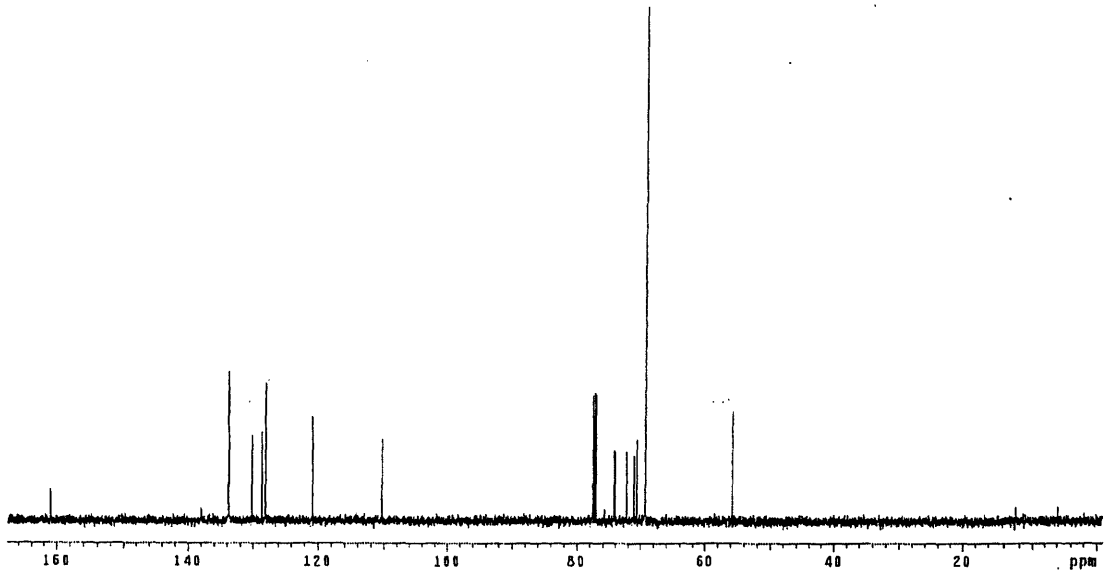
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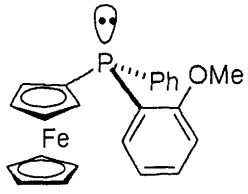
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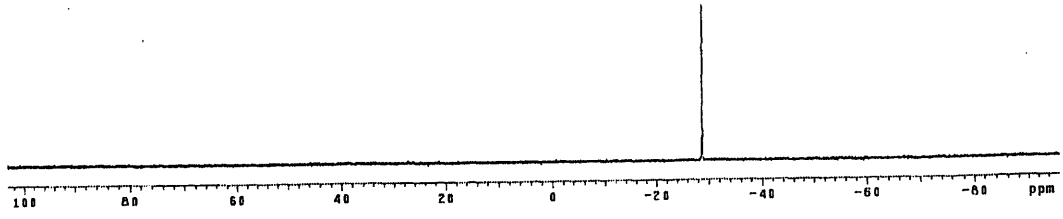
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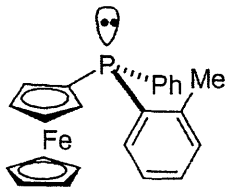

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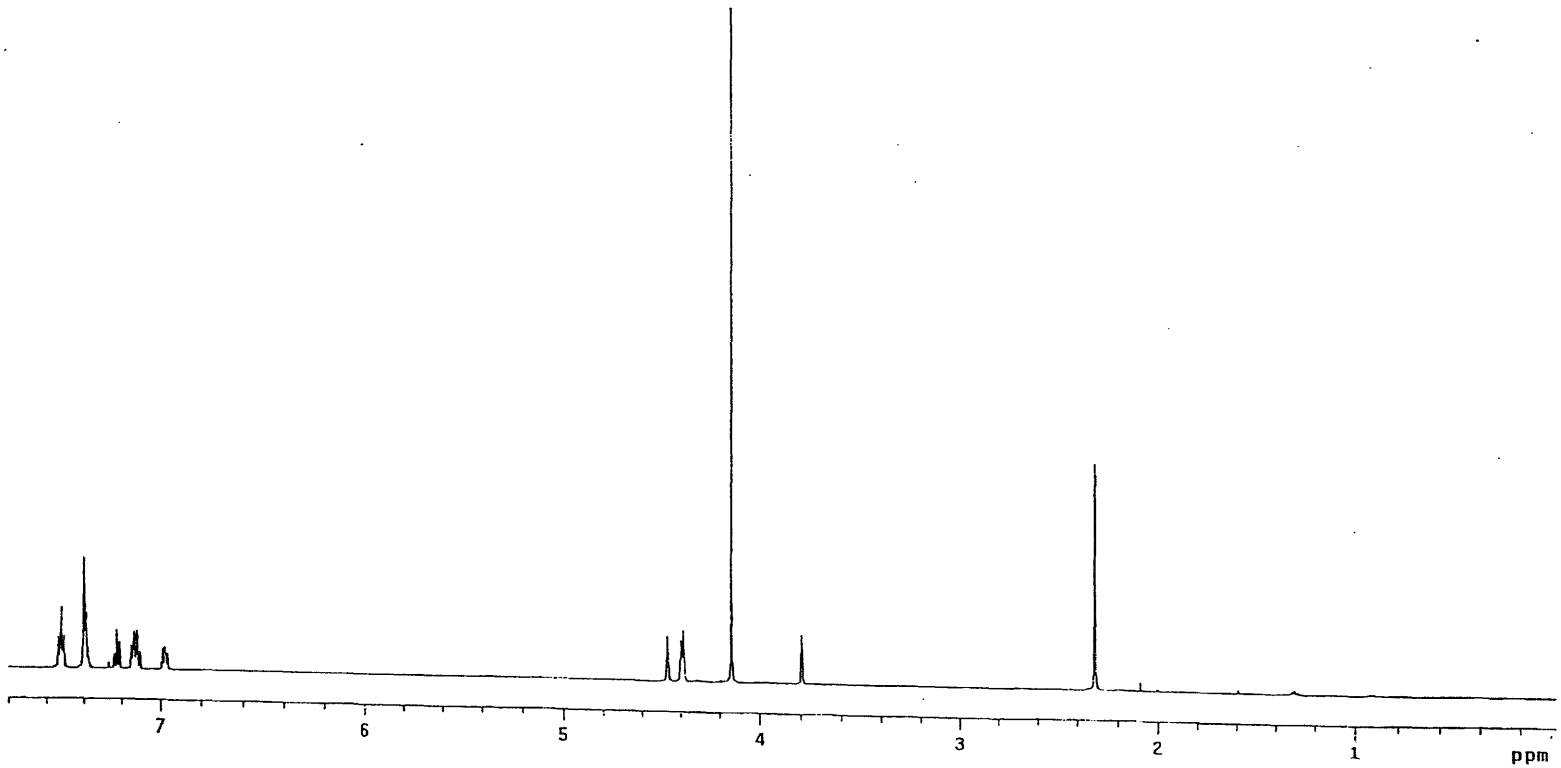

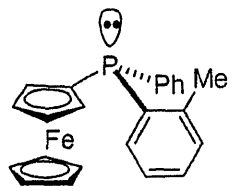
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7g

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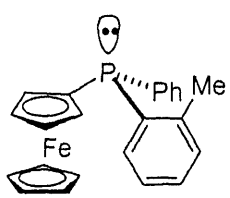
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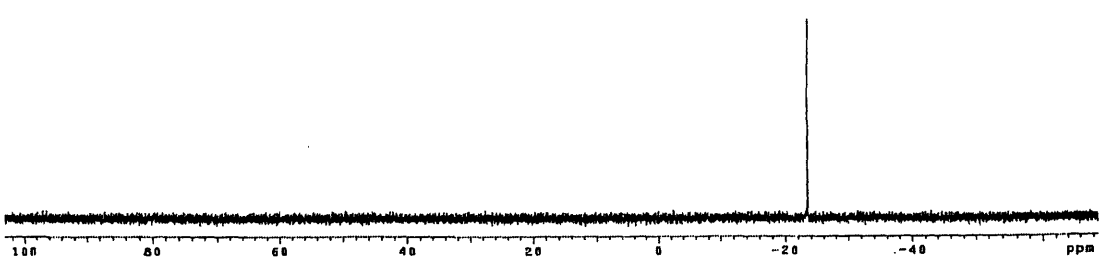
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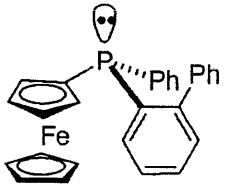

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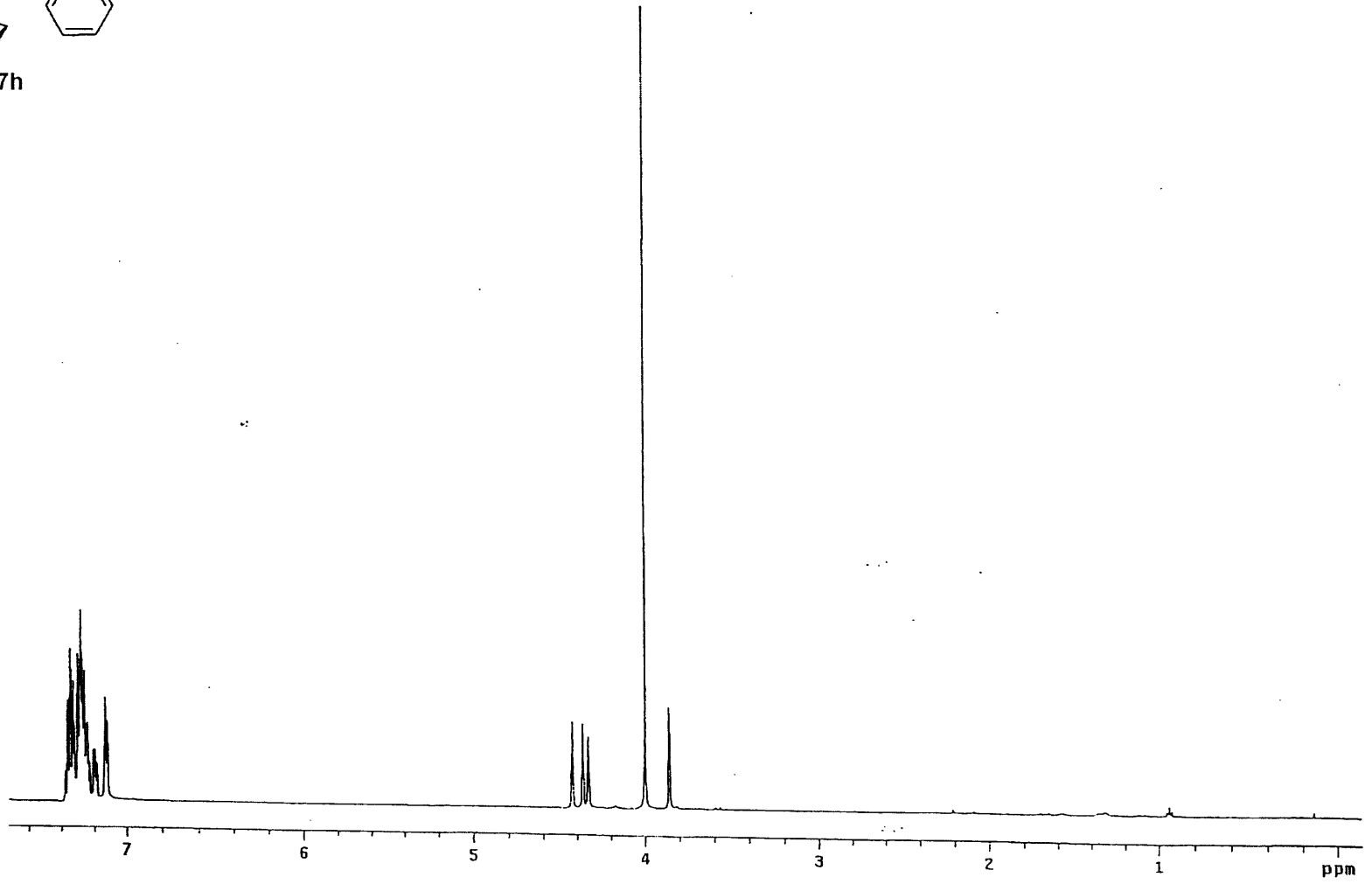

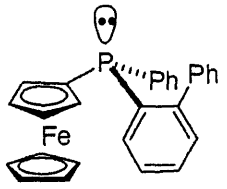
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Ph
Fe

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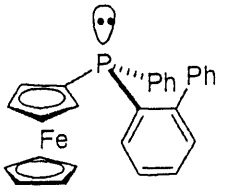
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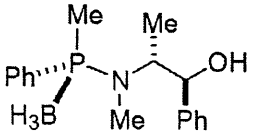

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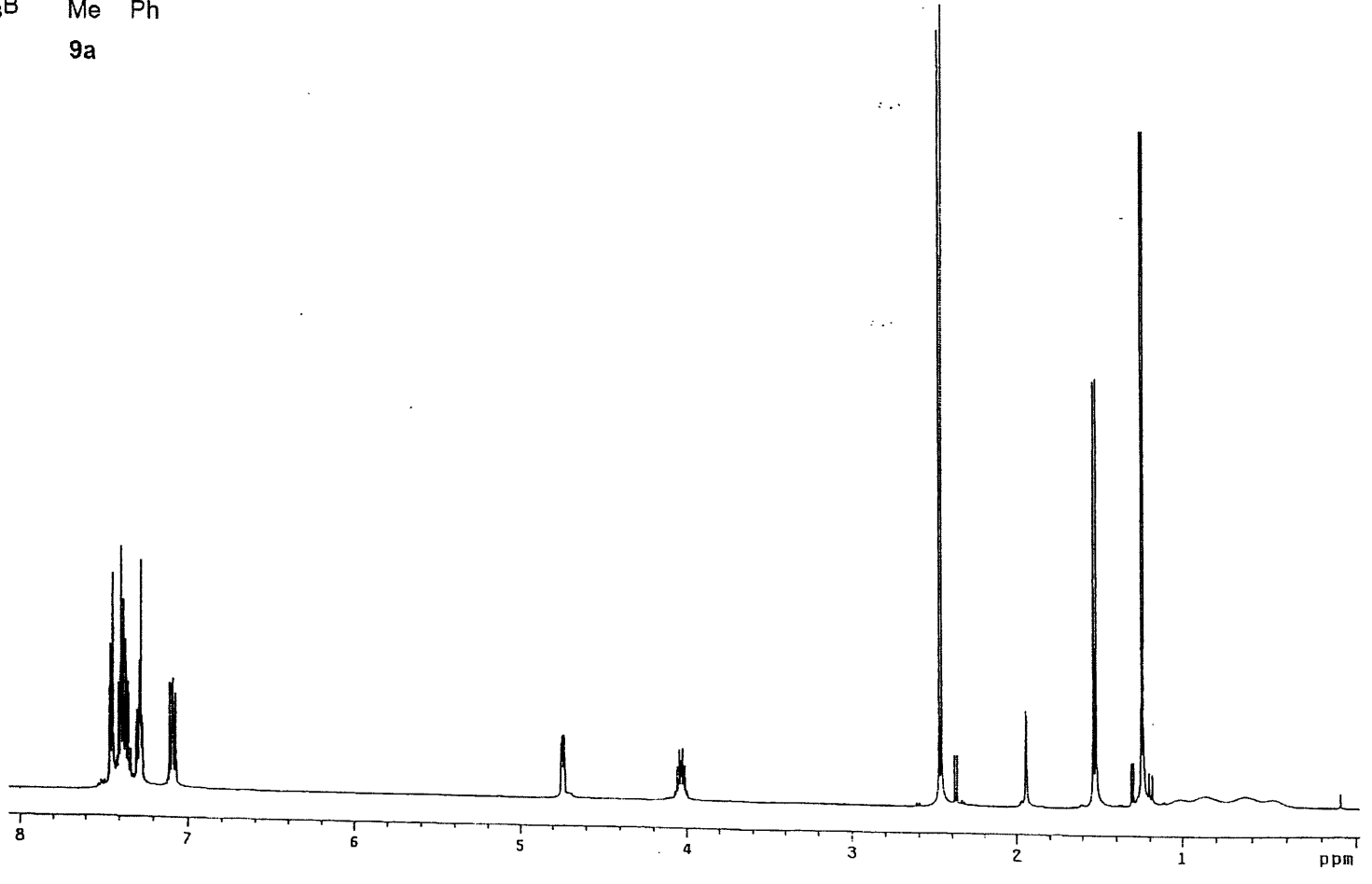

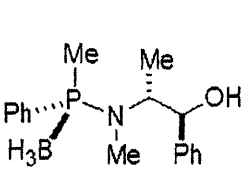
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Me
Ph

9a

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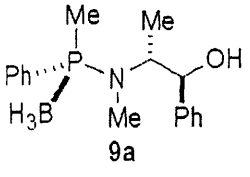
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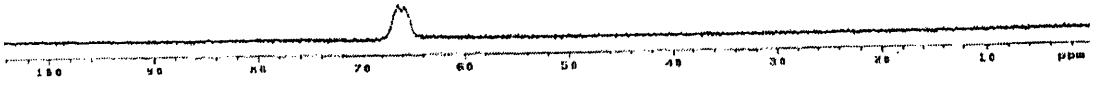
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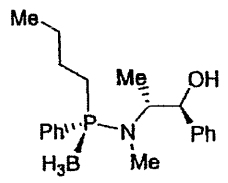

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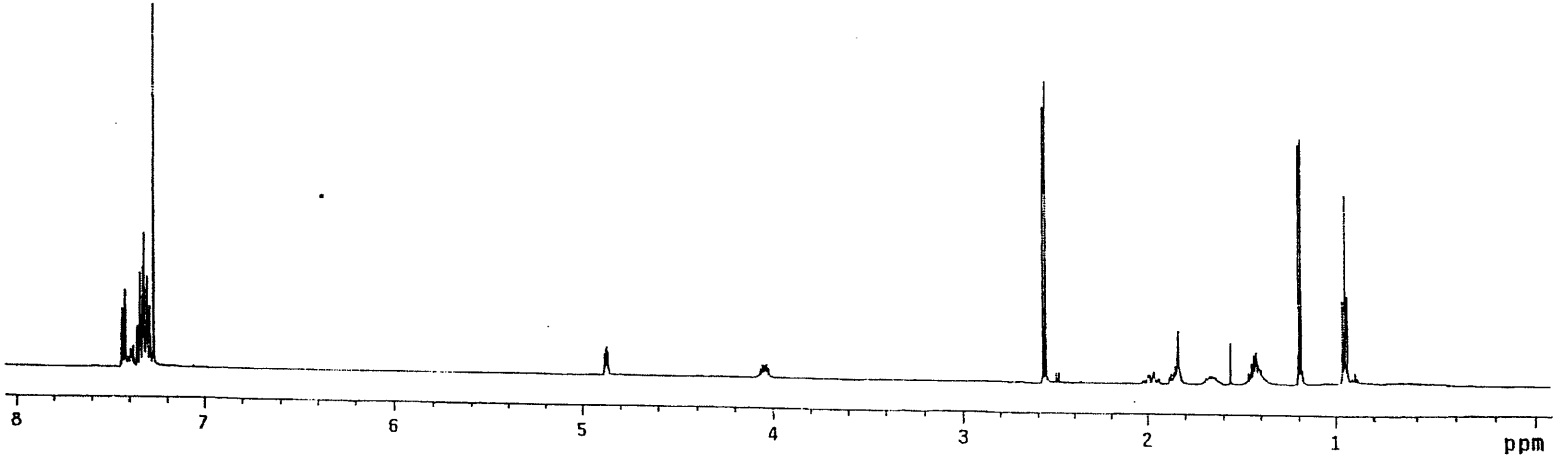

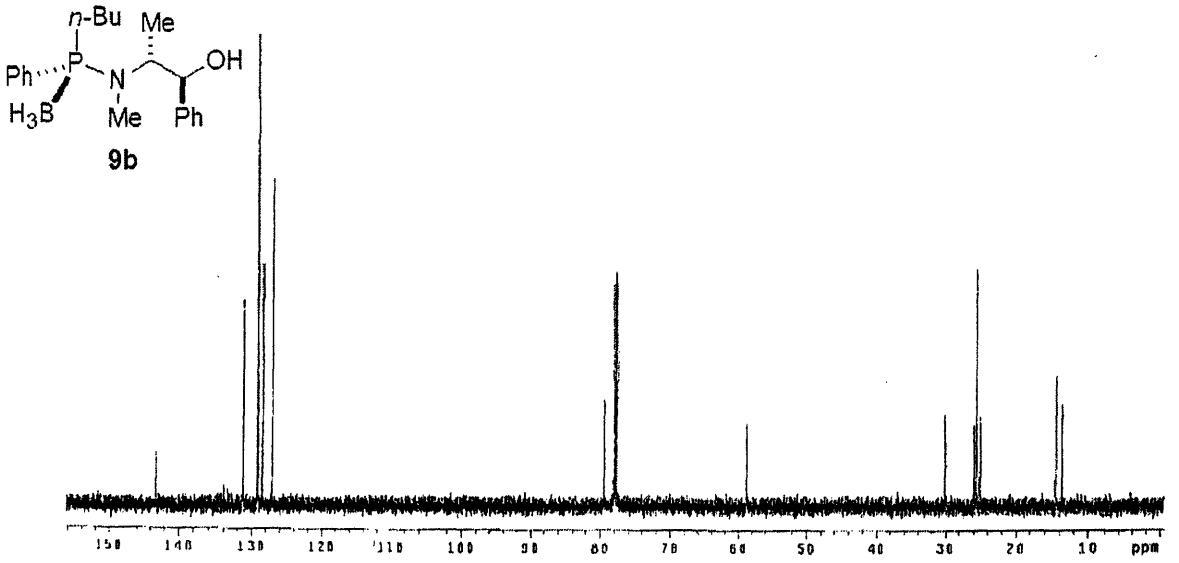
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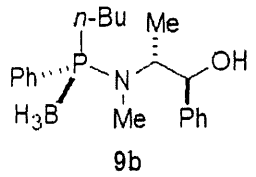
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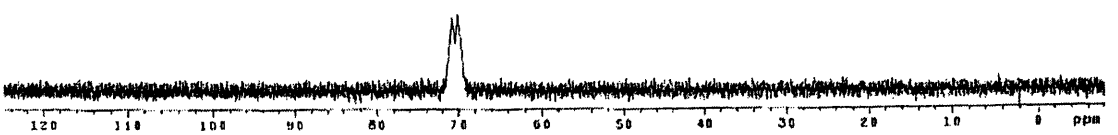
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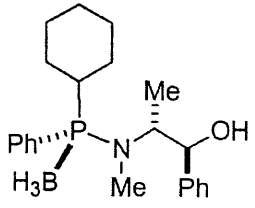

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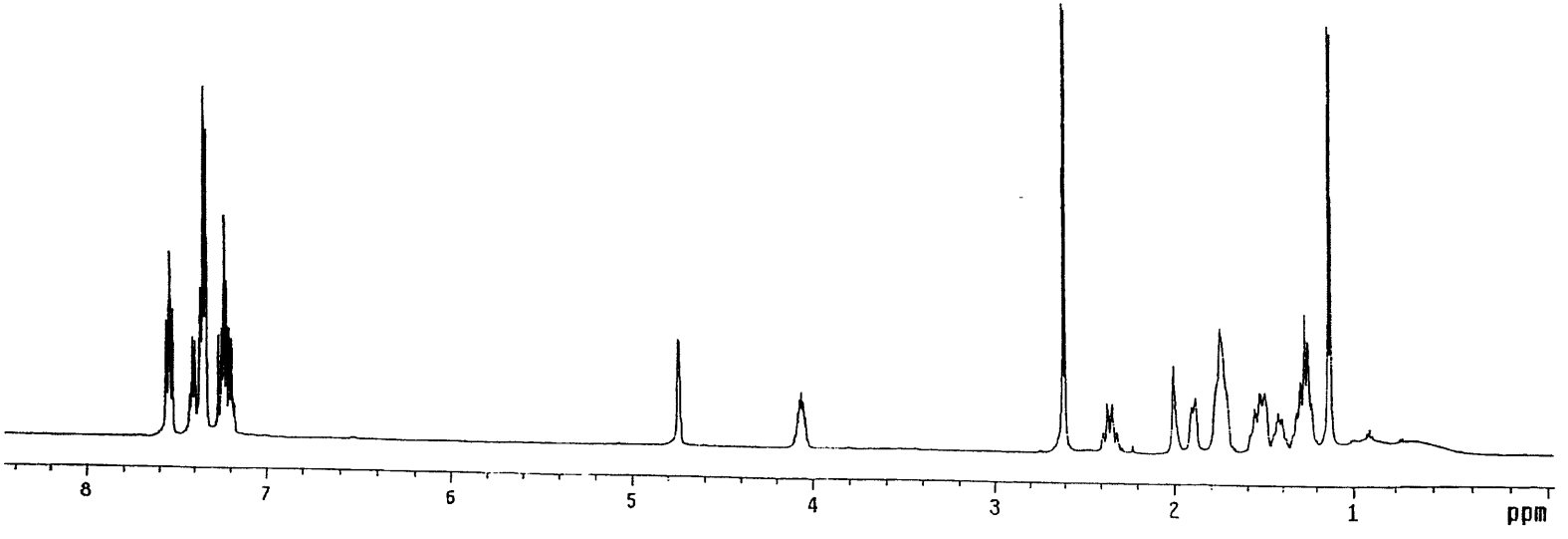

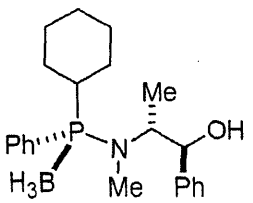
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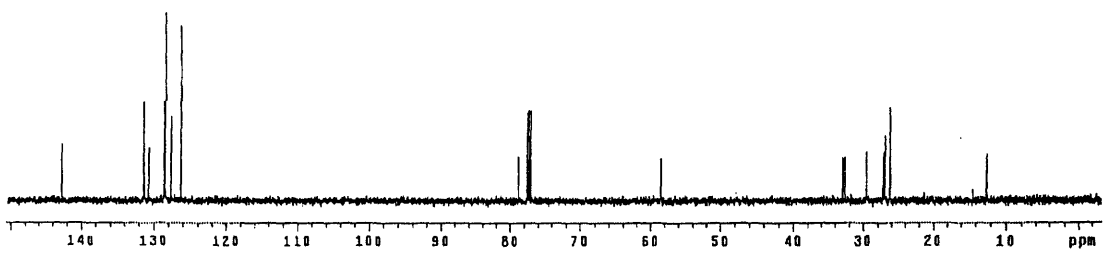
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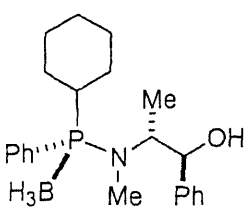
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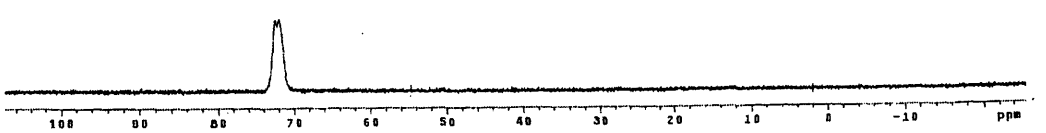
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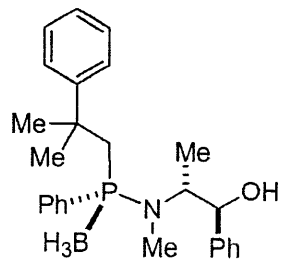

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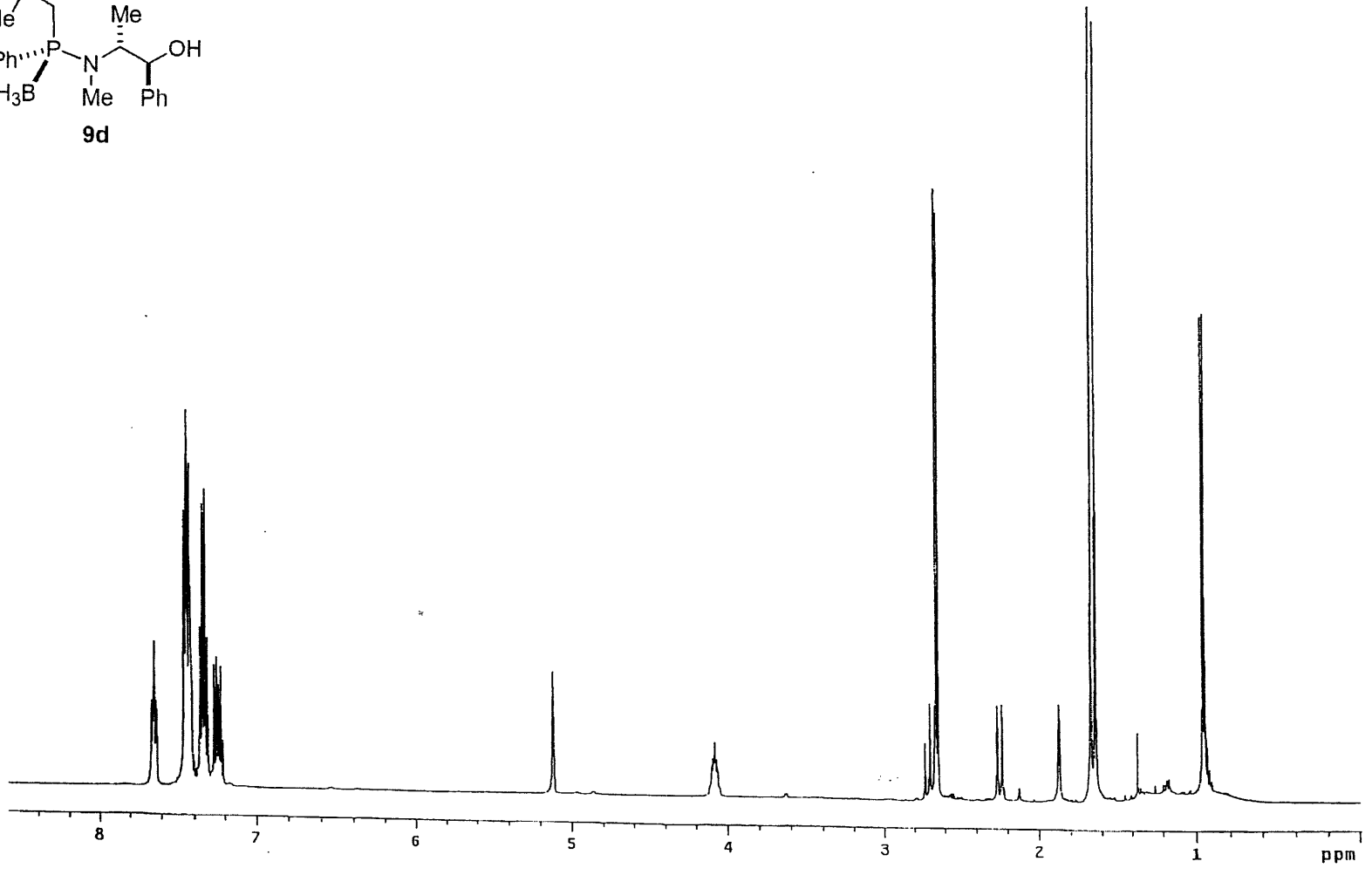

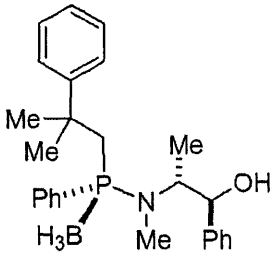
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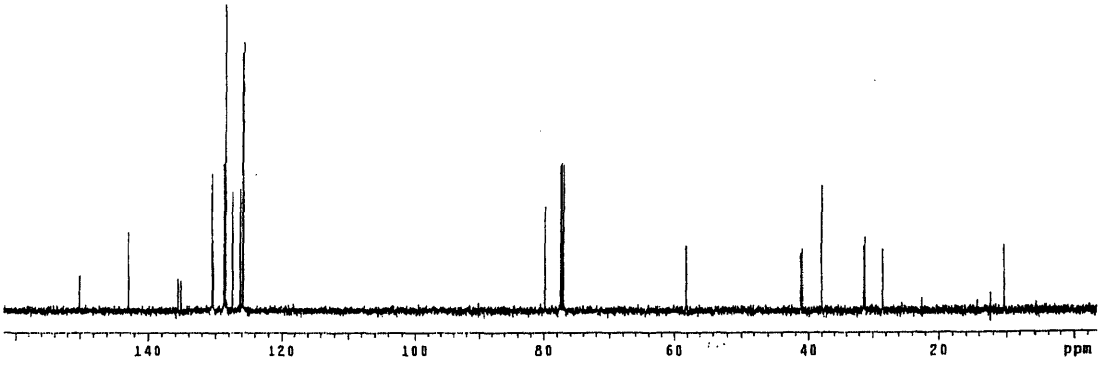
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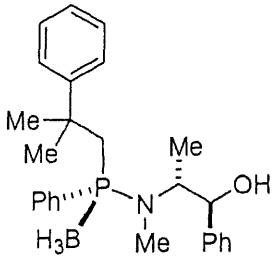
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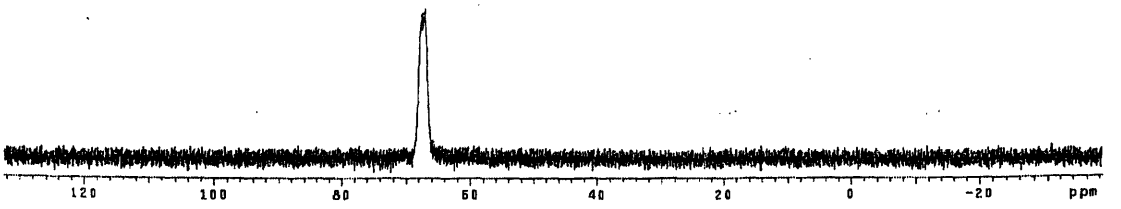
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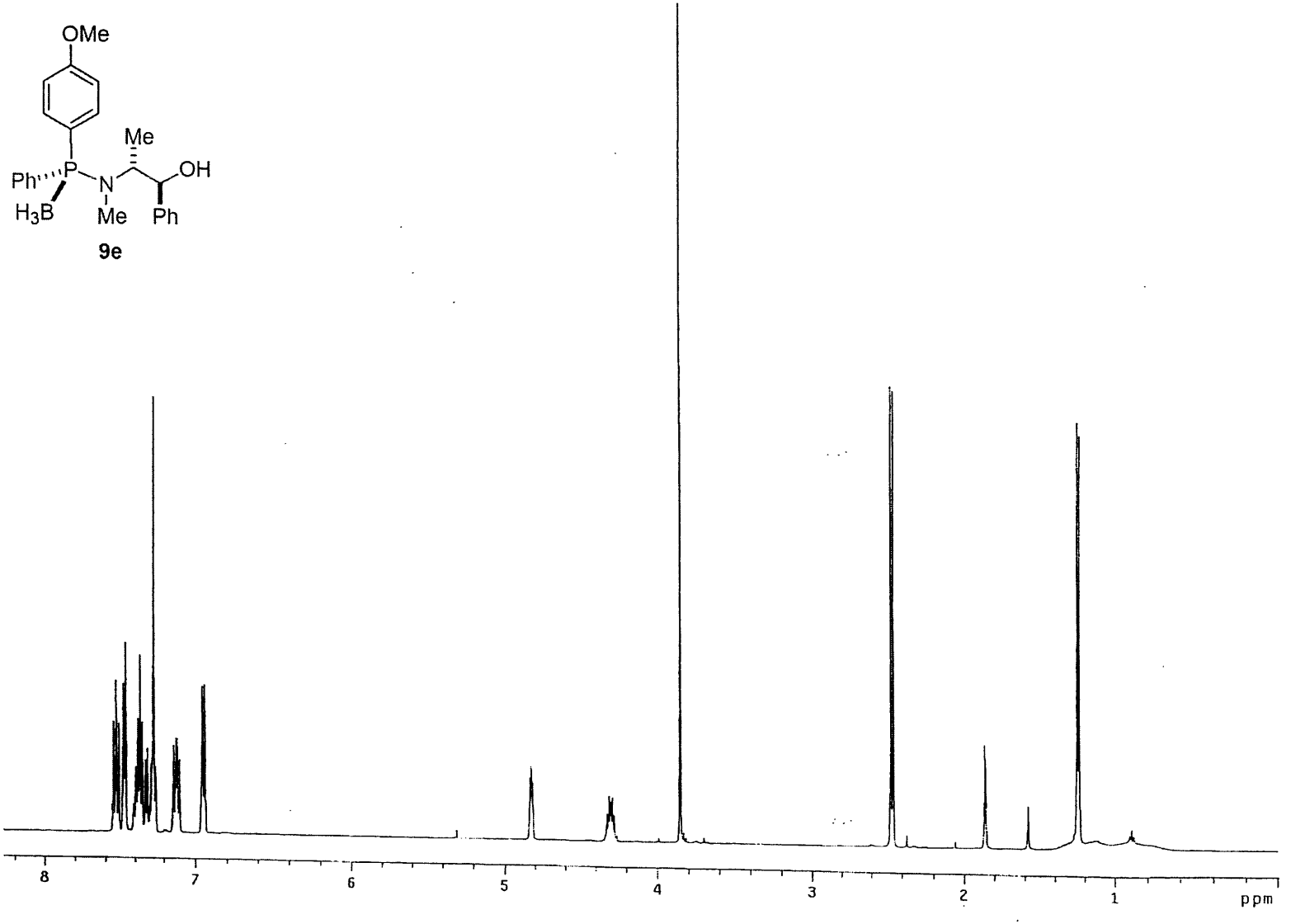
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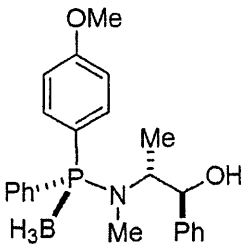
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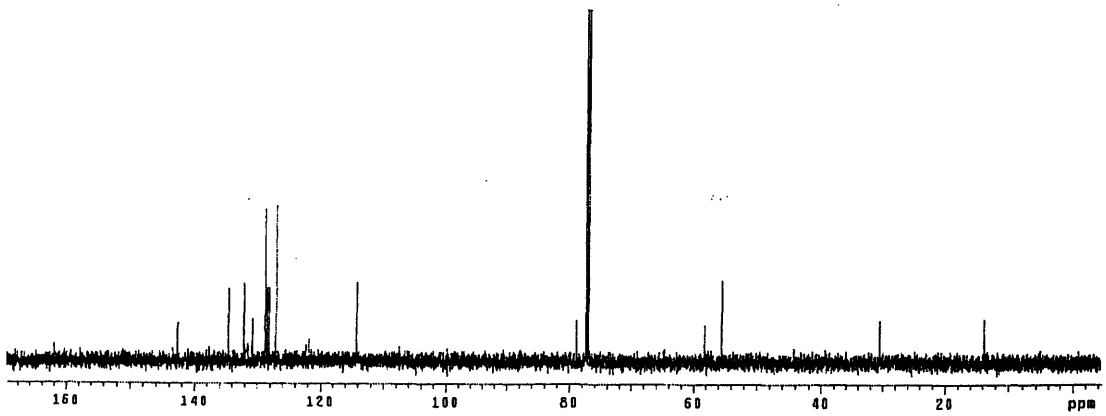
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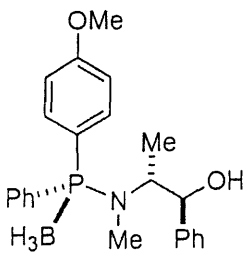
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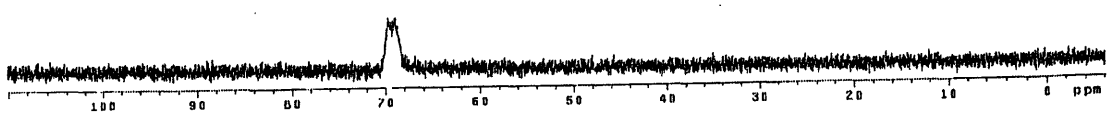
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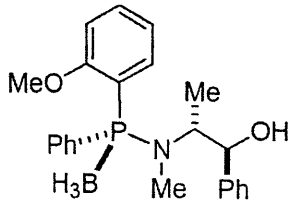

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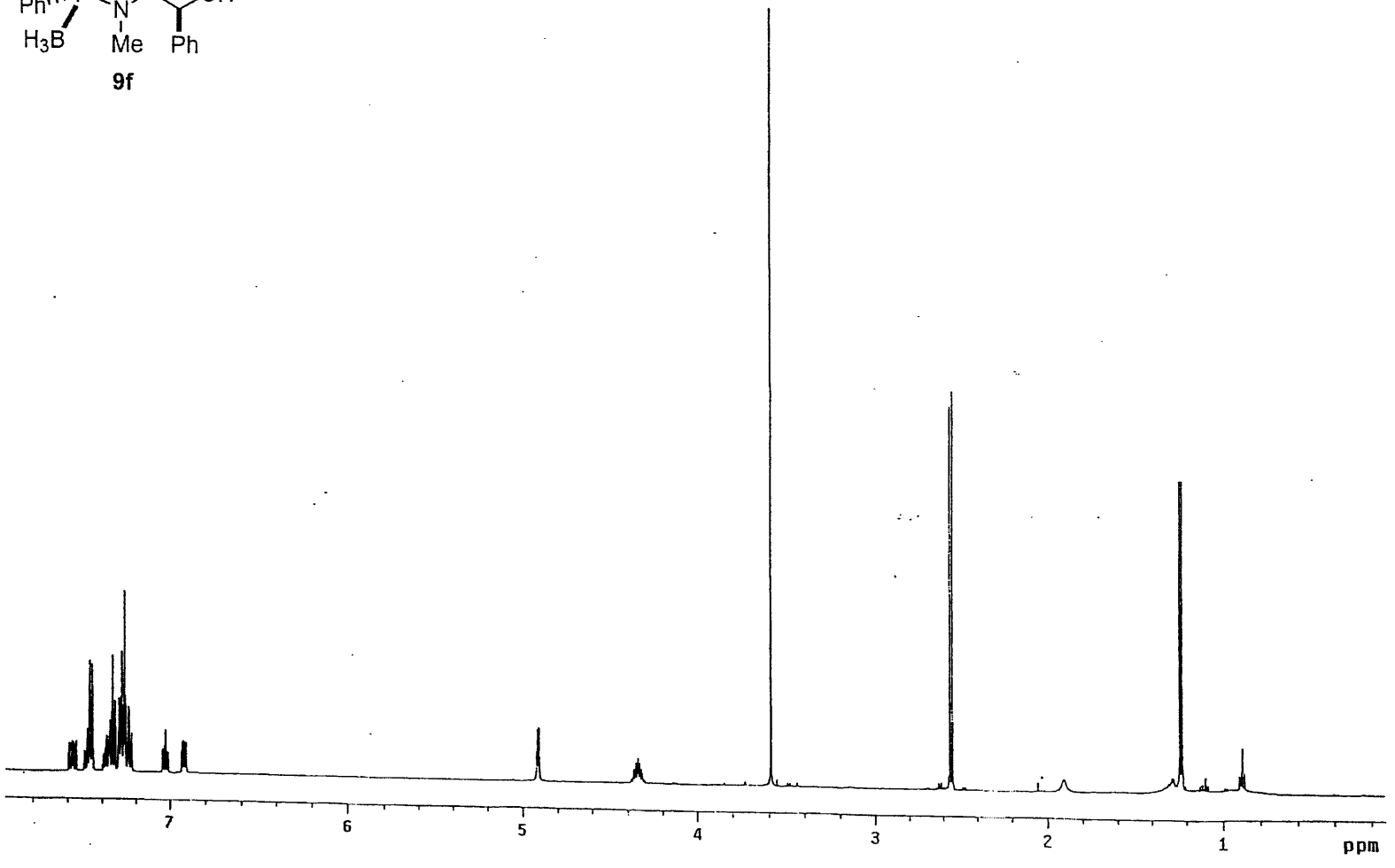

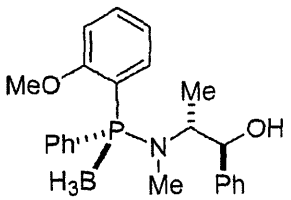
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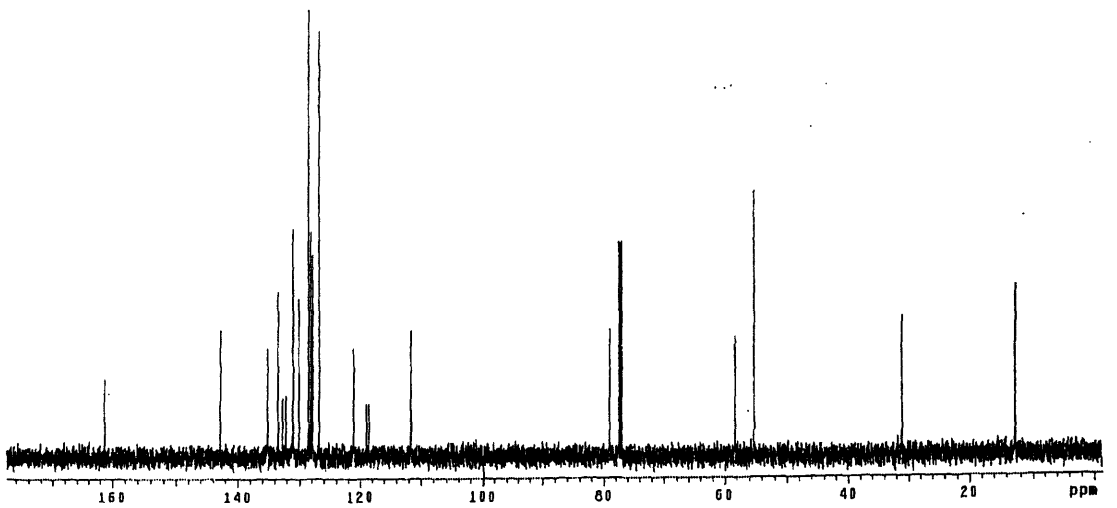
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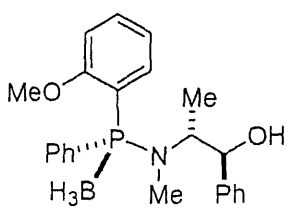
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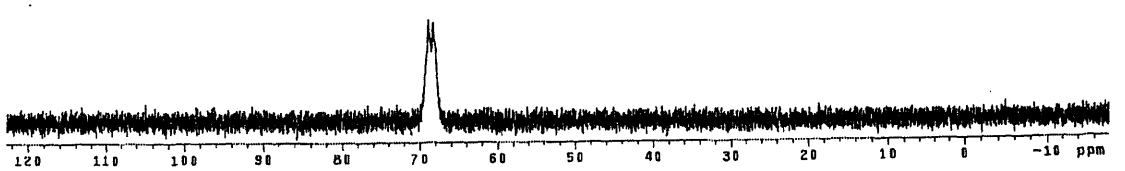
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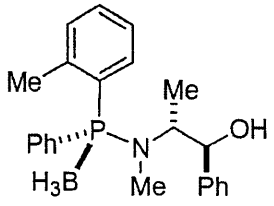

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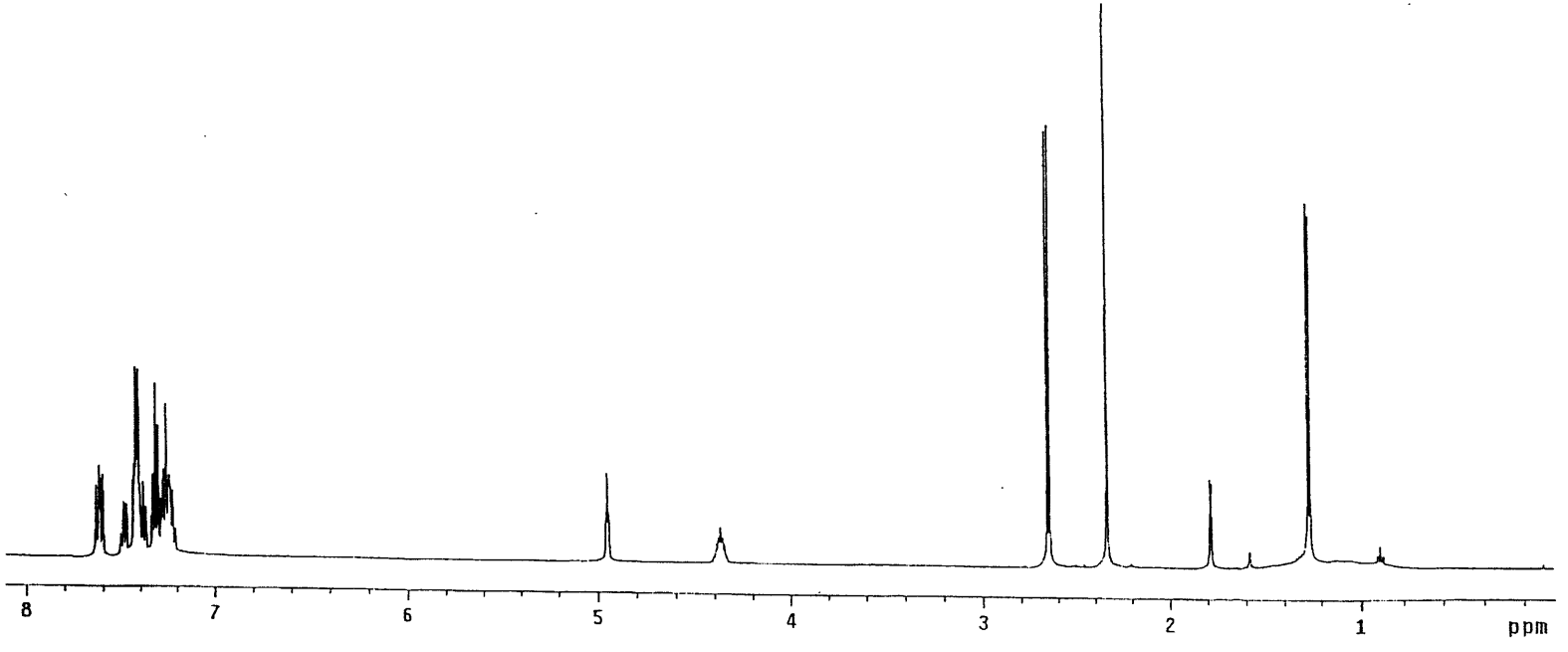

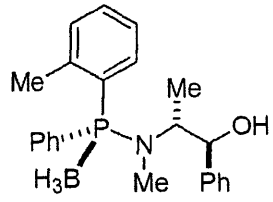
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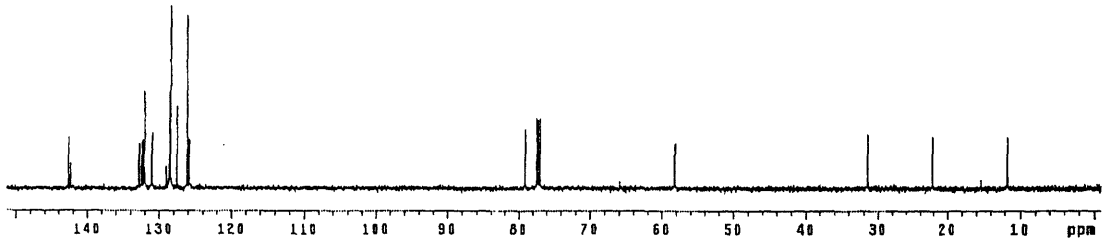
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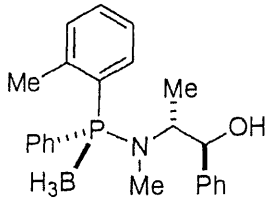
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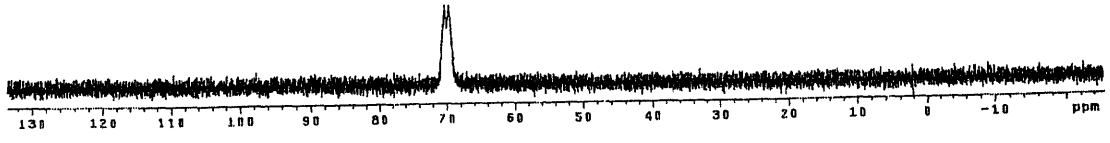
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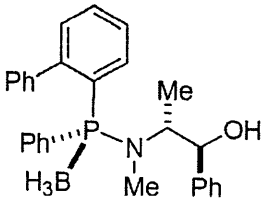

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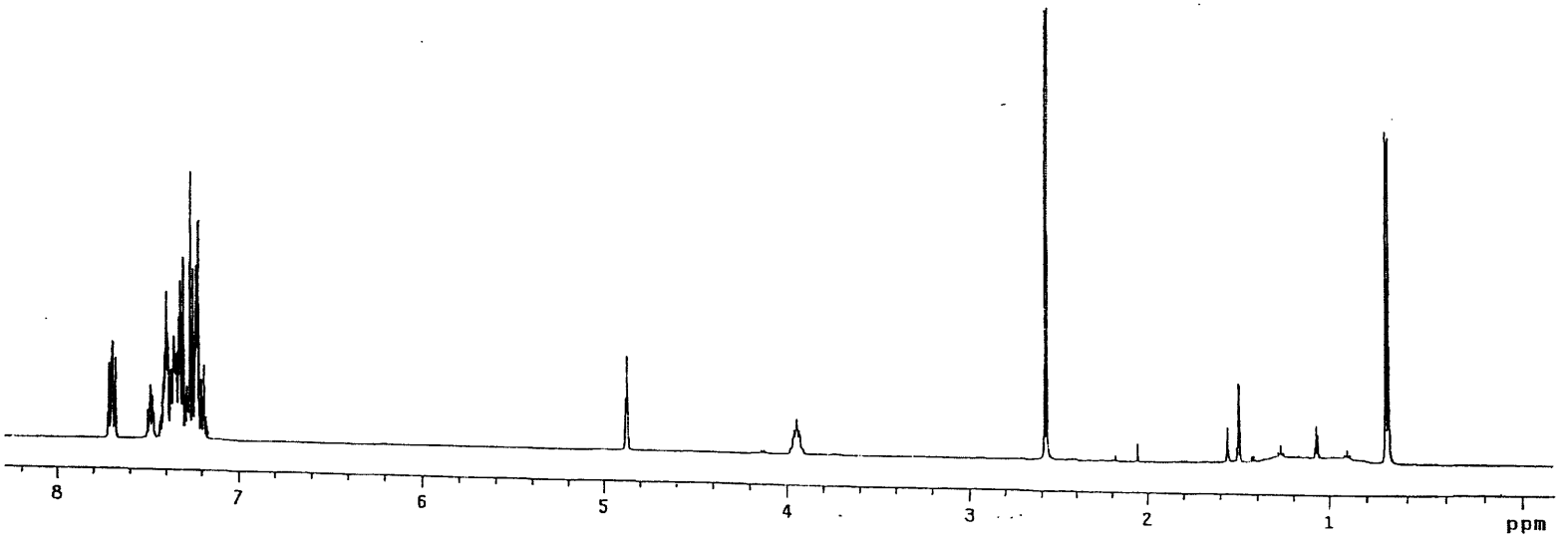

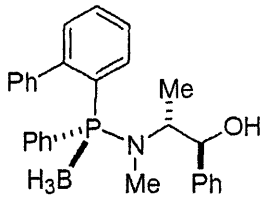
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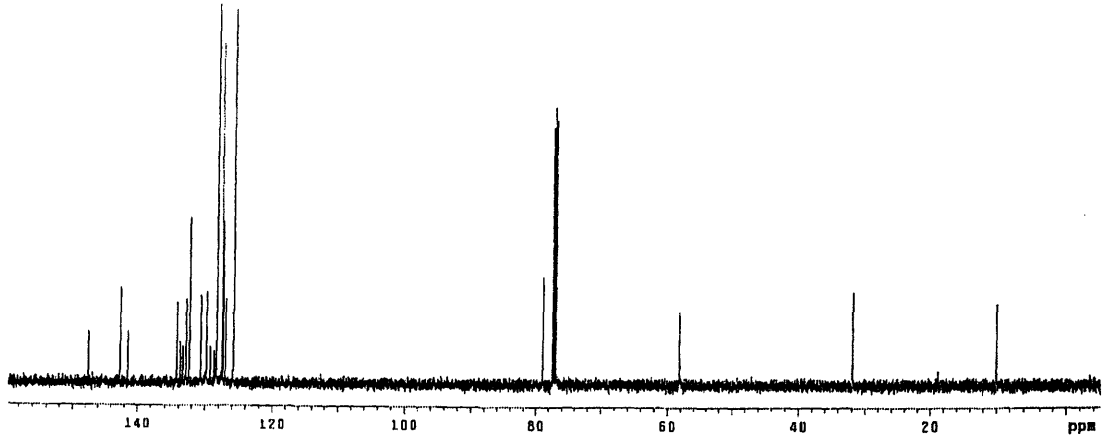
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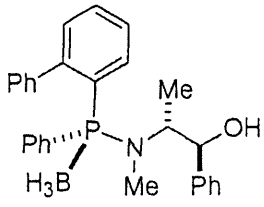
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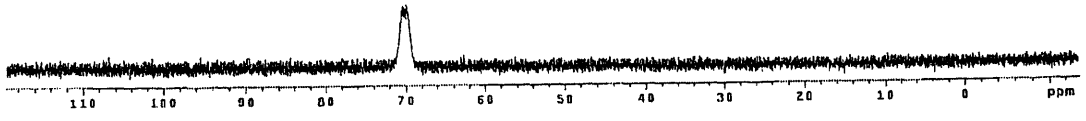
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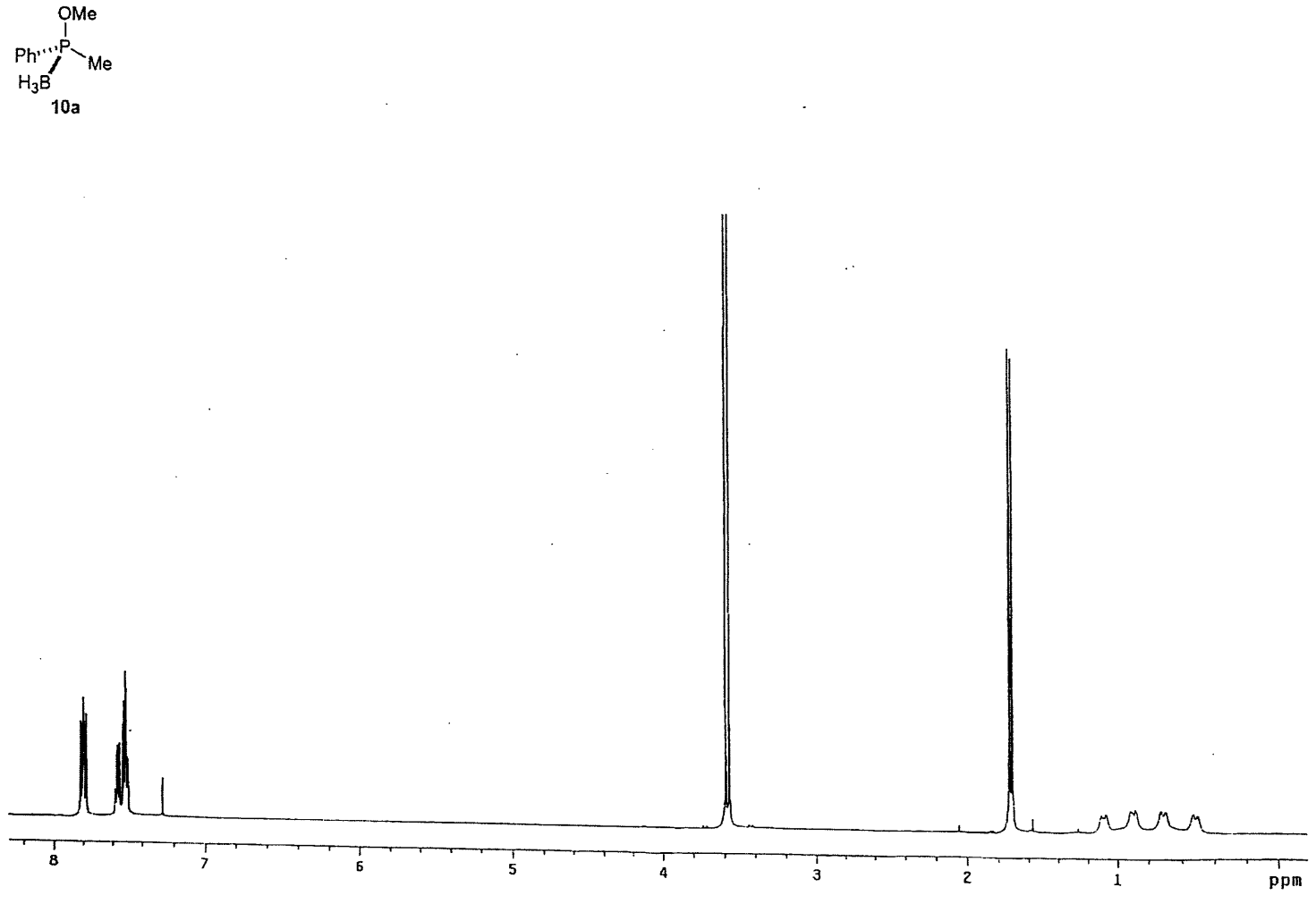
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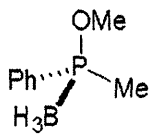
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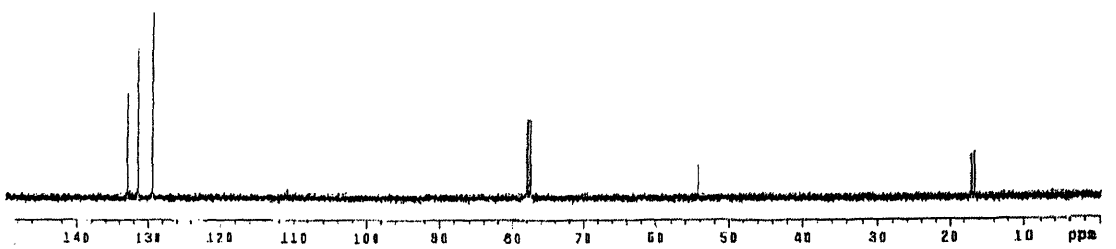
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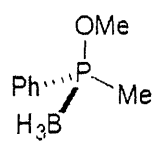
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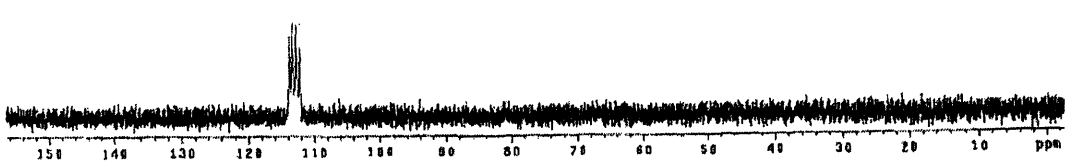
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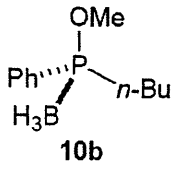

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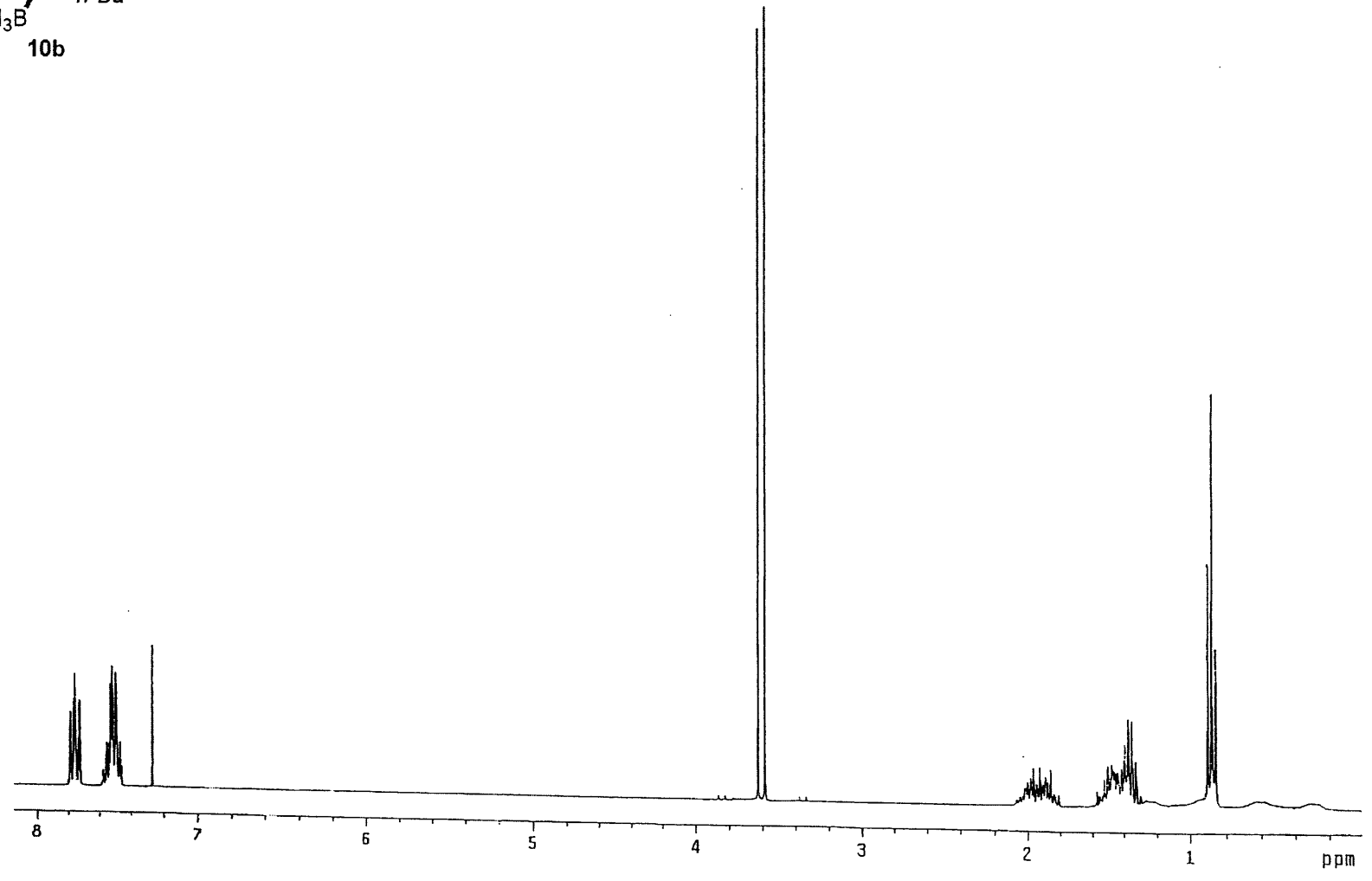

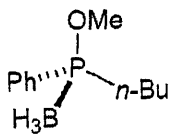
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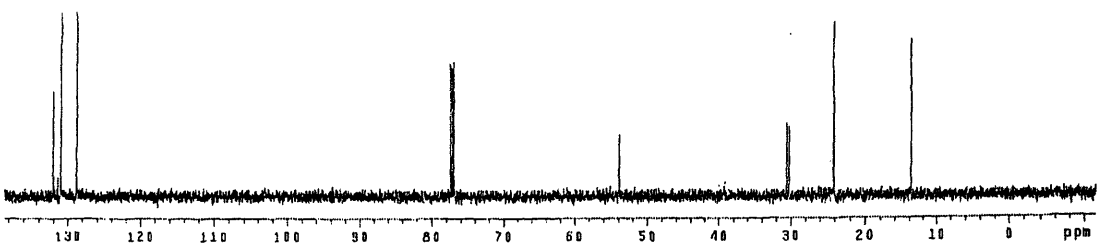
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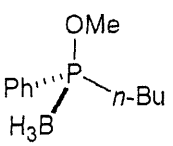
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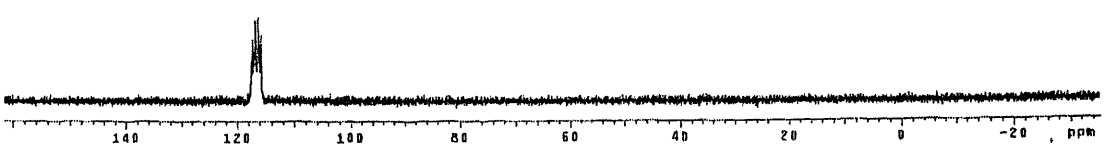
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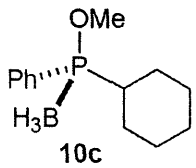

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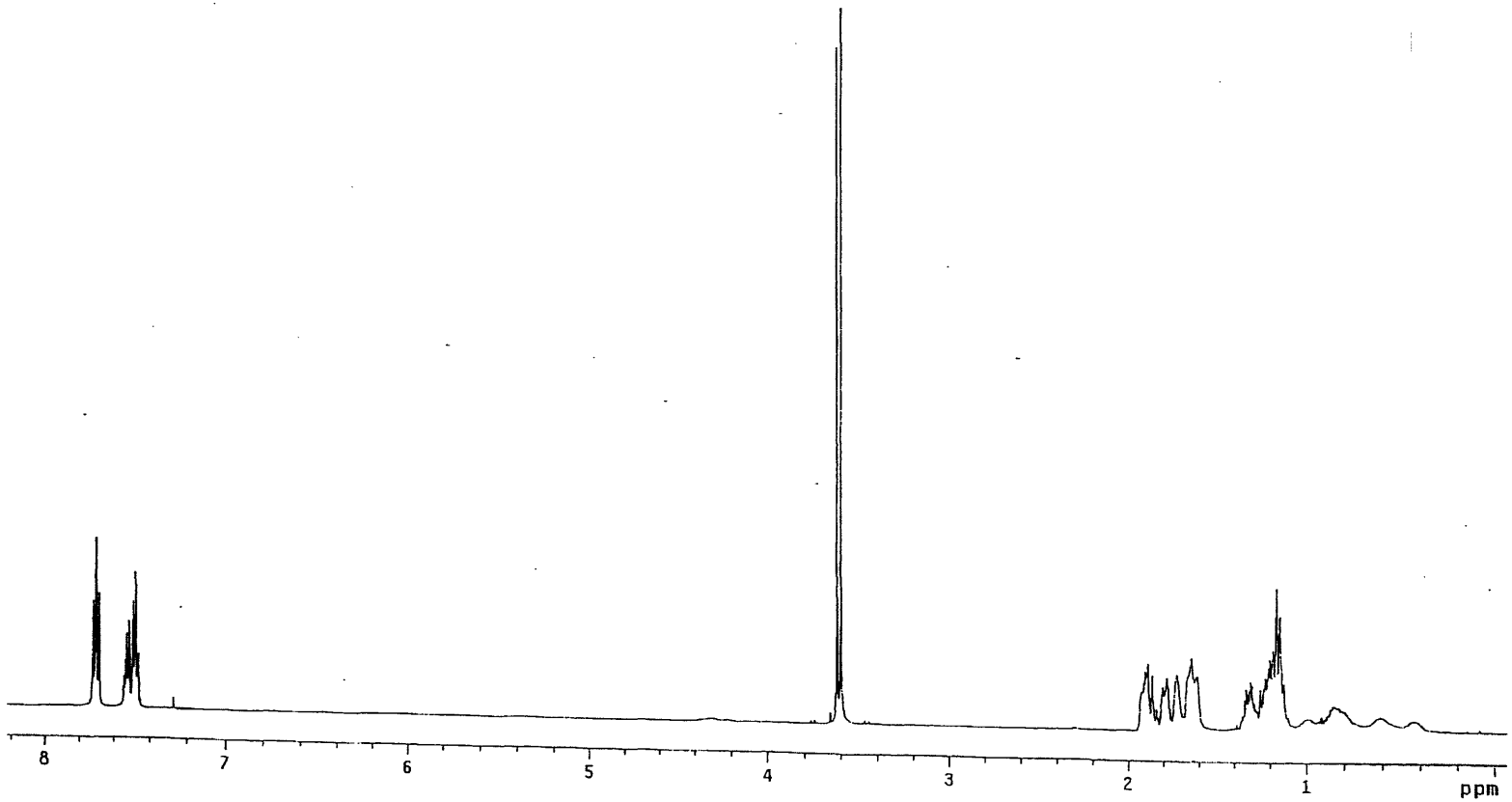

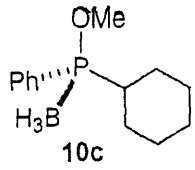
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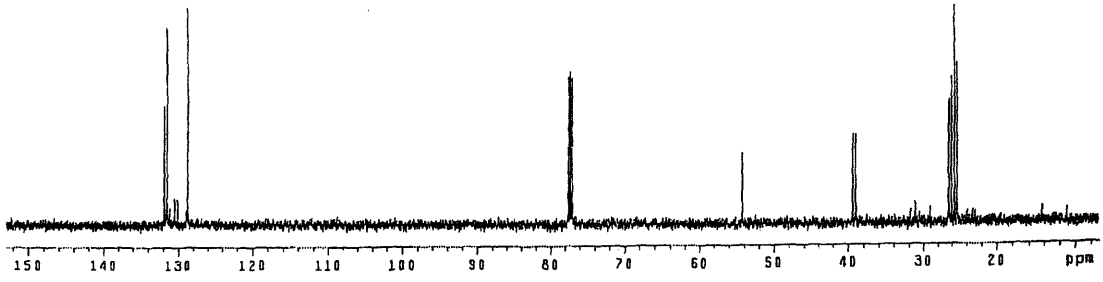
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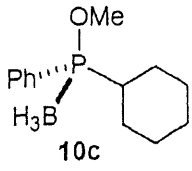
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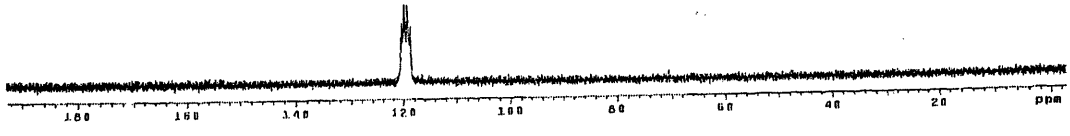
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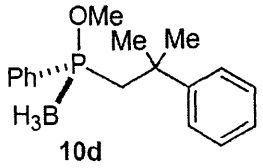

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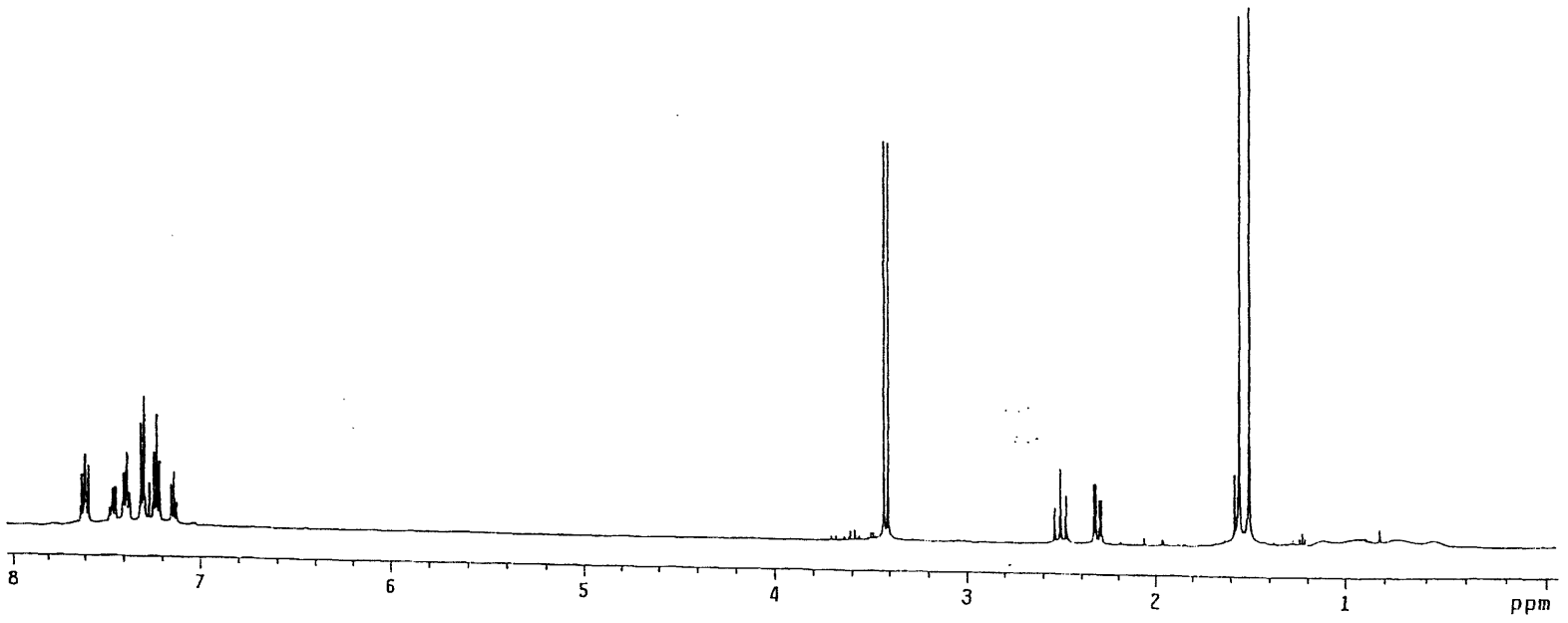

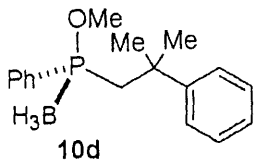
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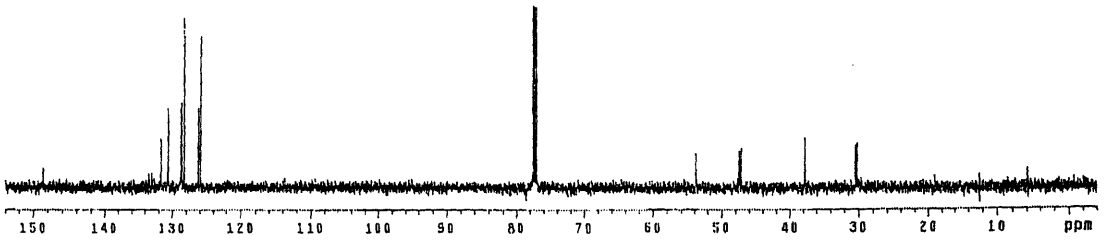
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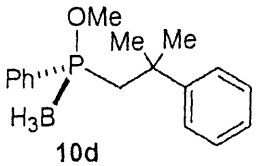
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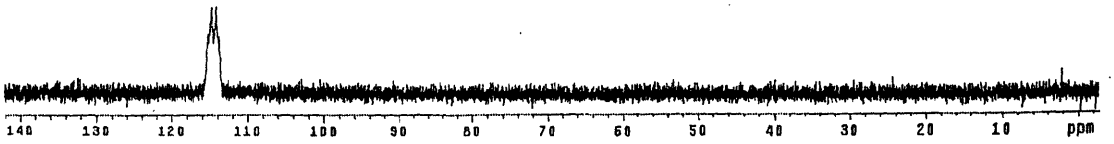
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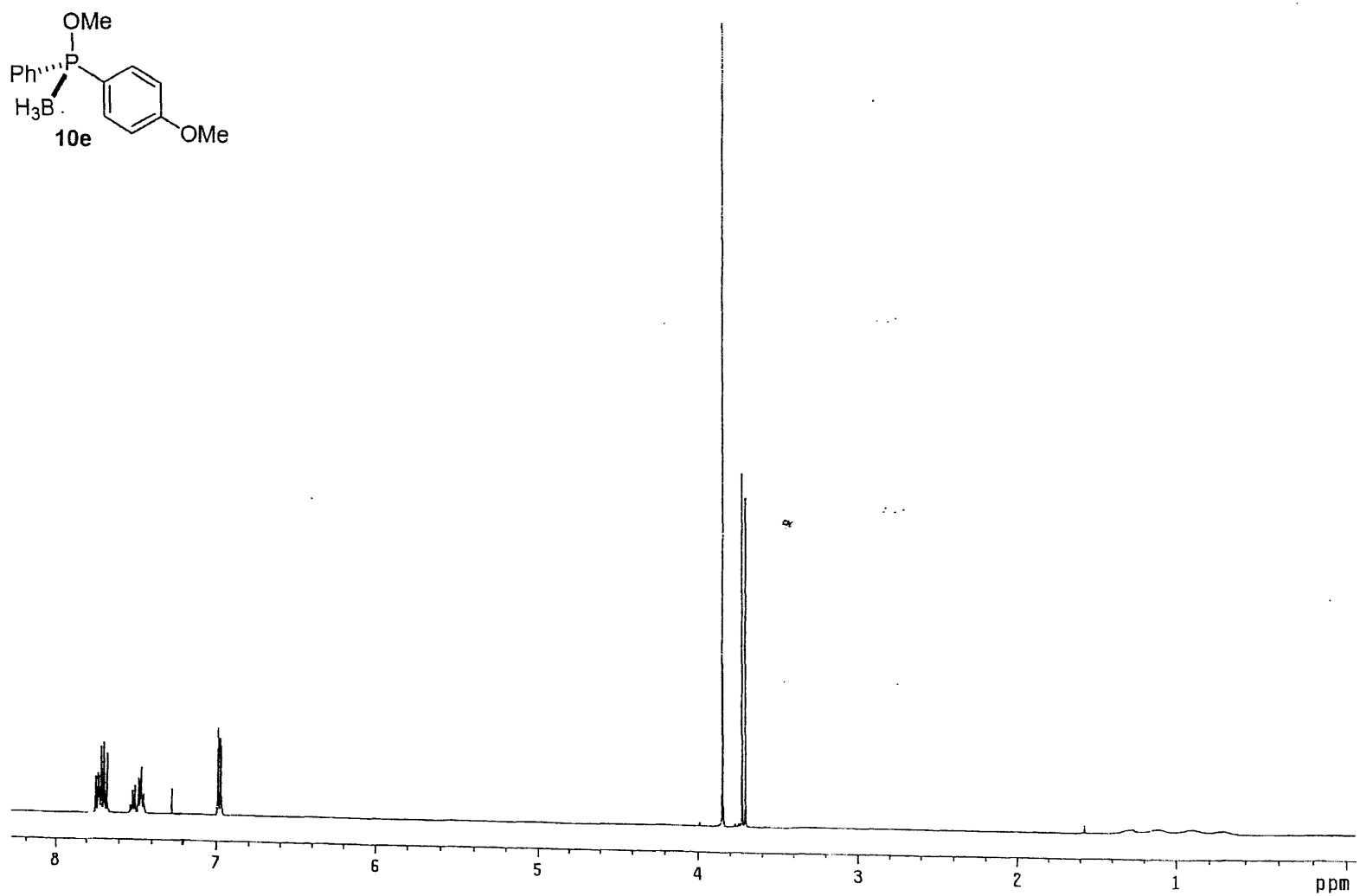
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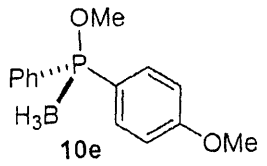
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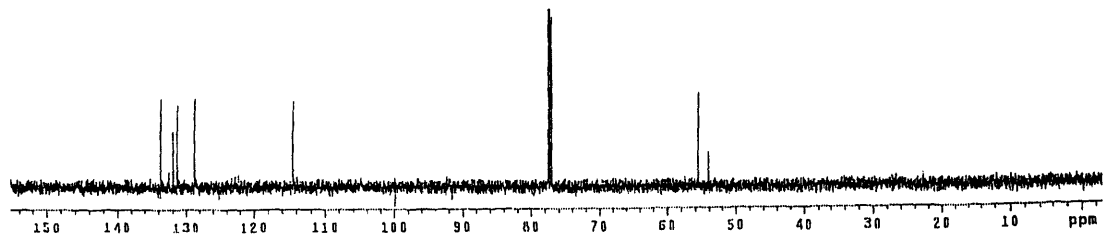
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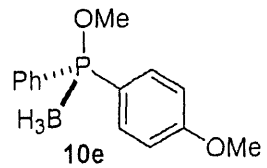
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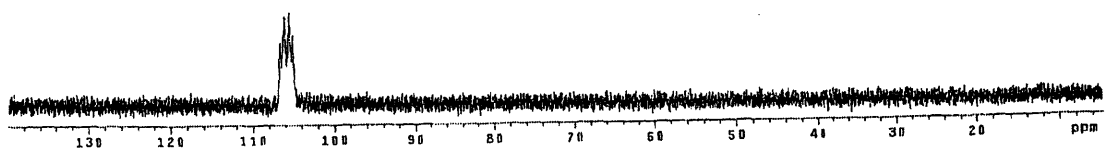
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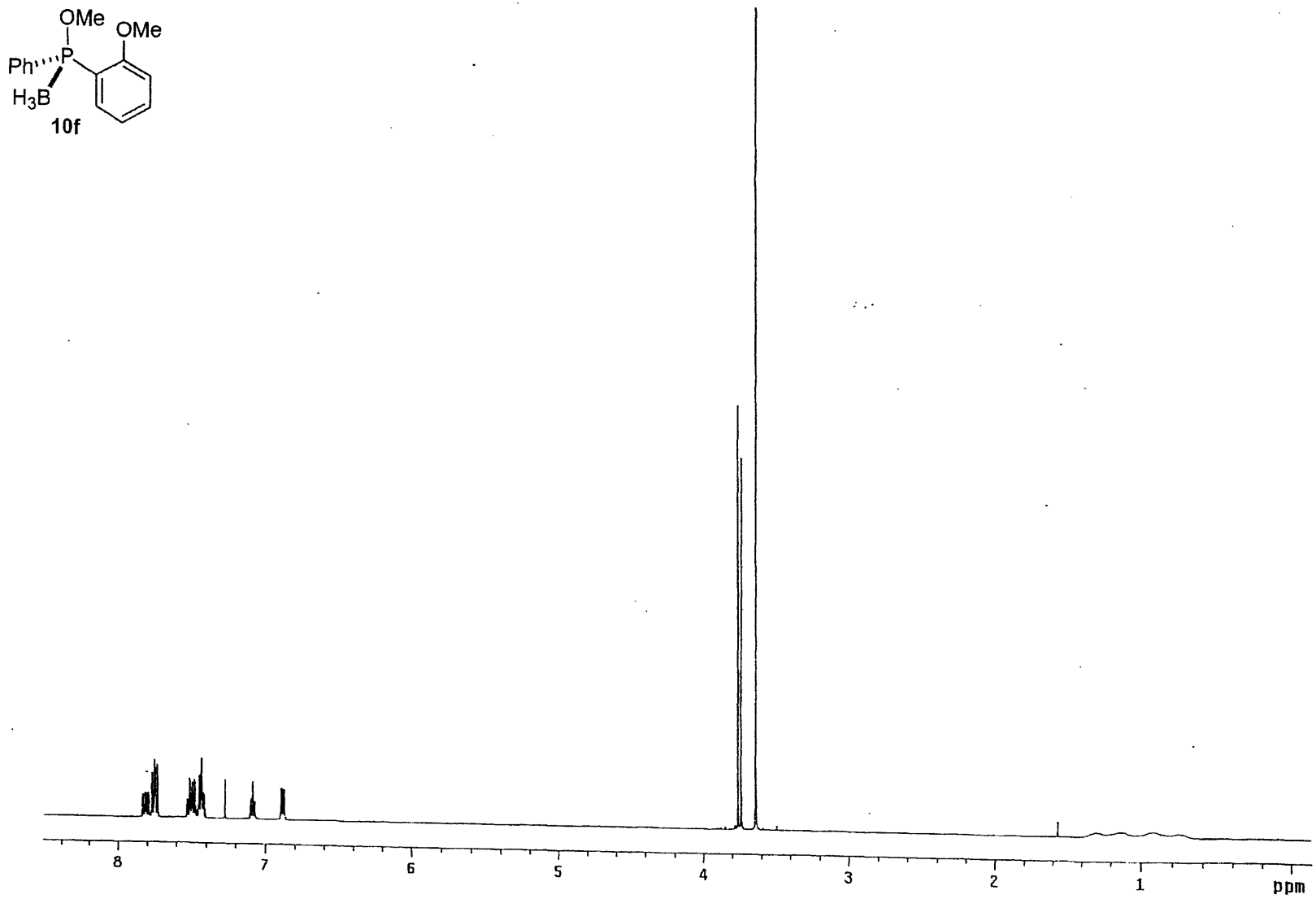
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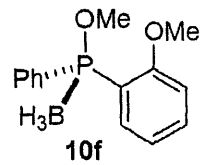
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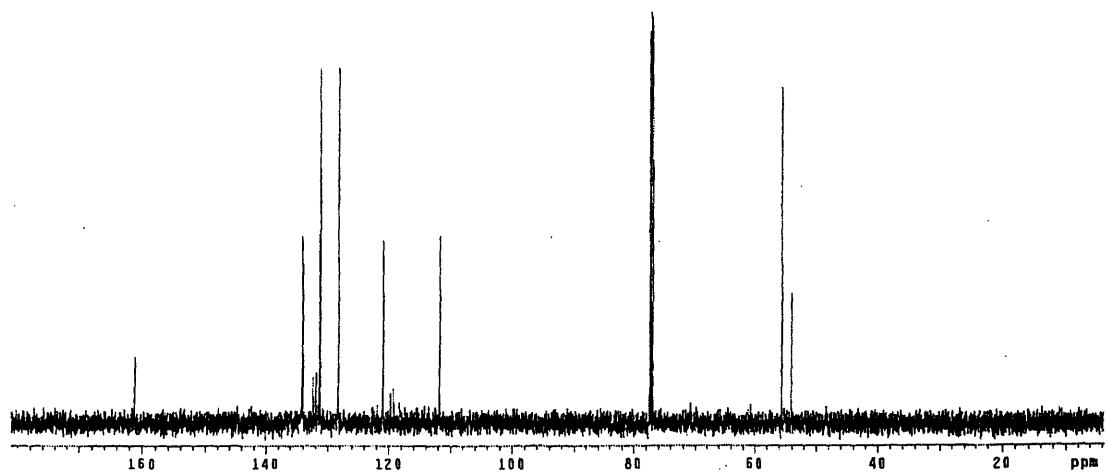
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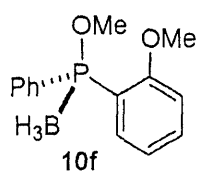
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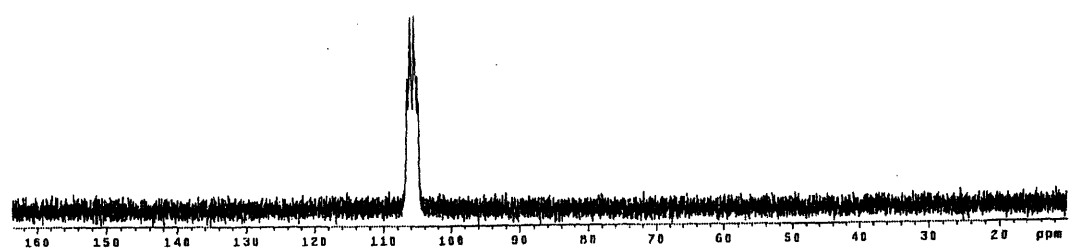
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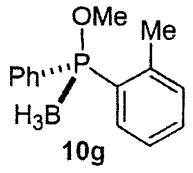

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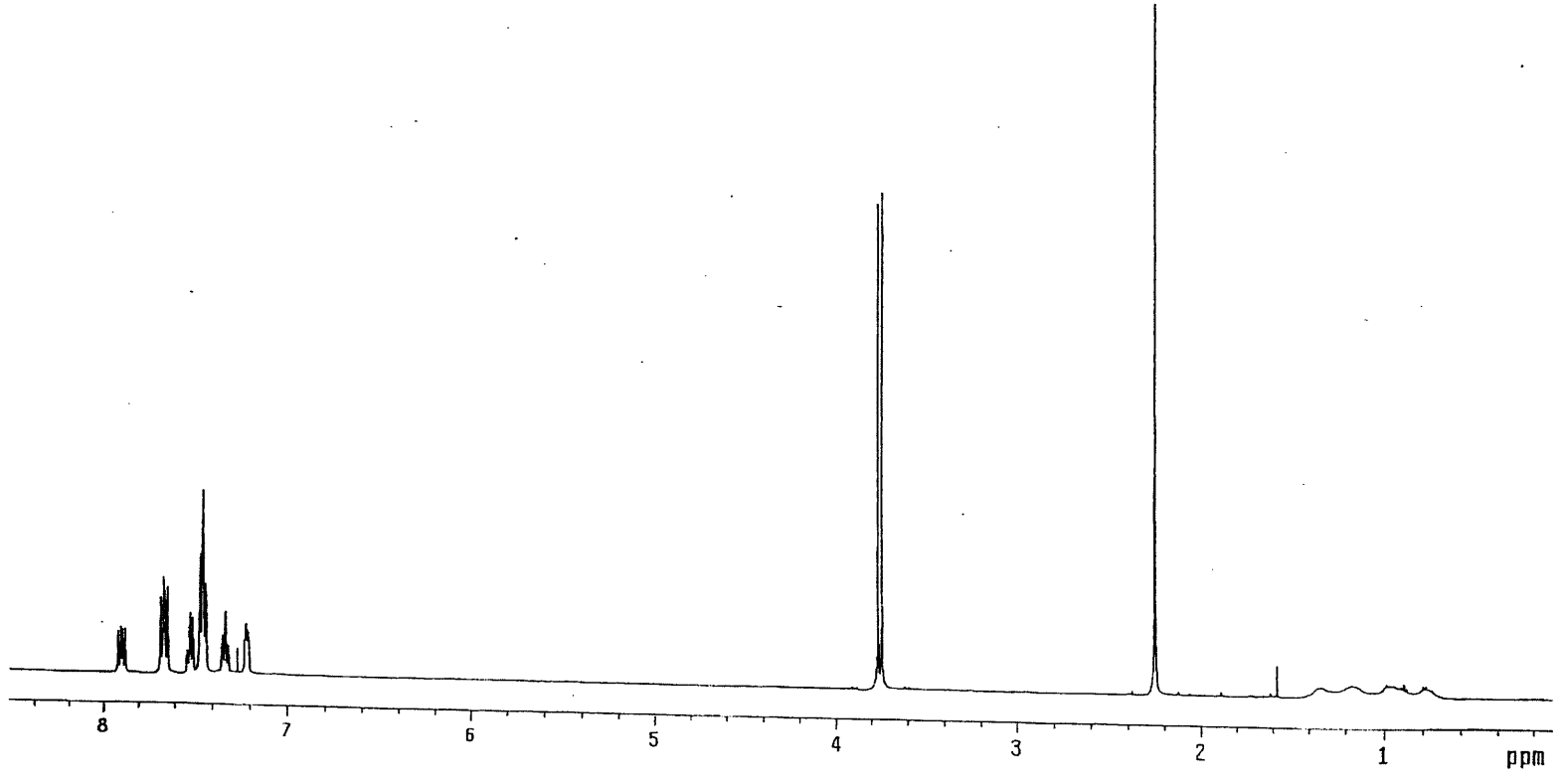

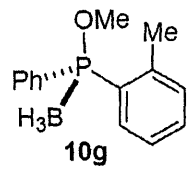
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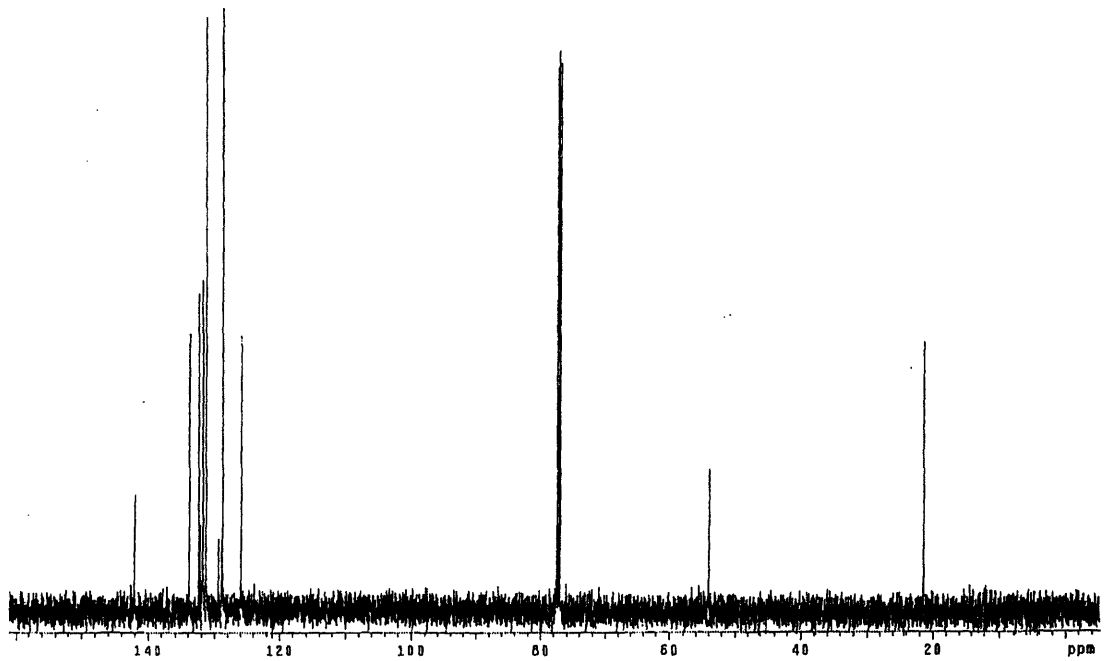
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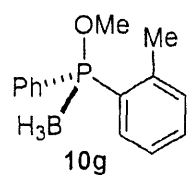
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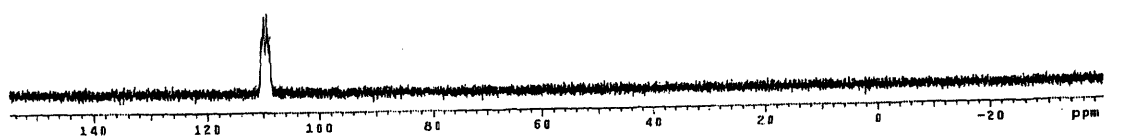
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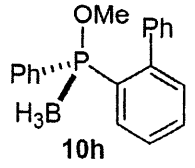

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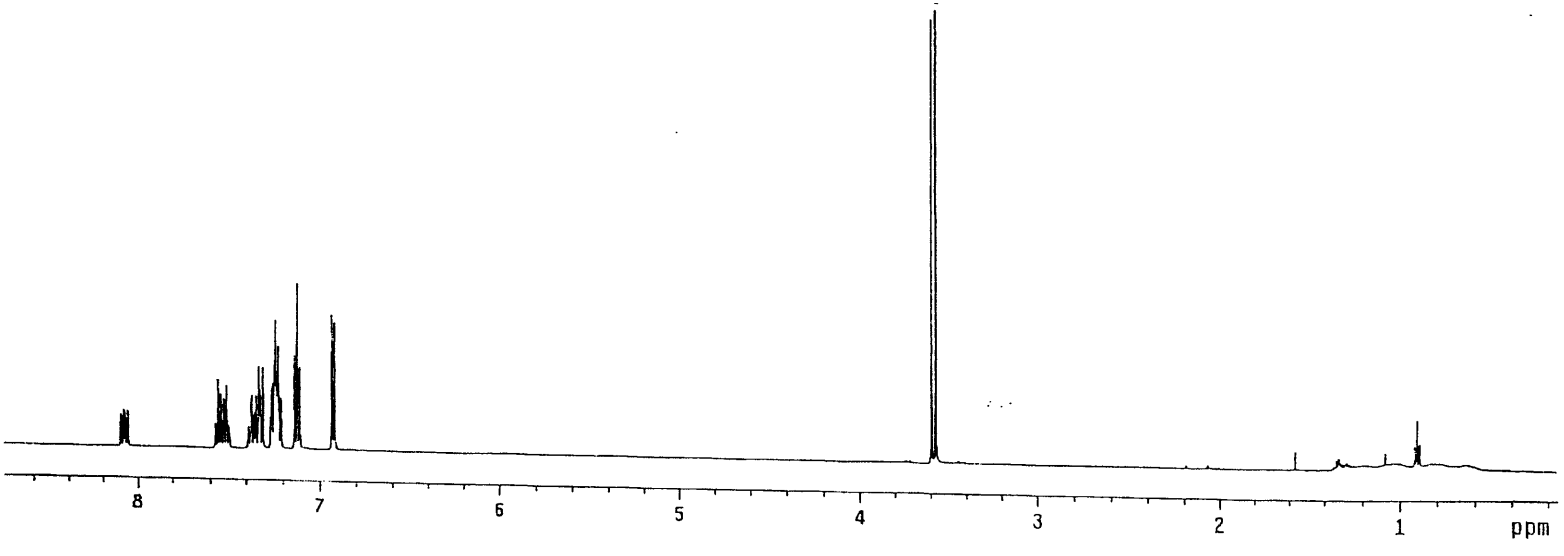

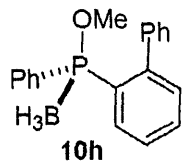
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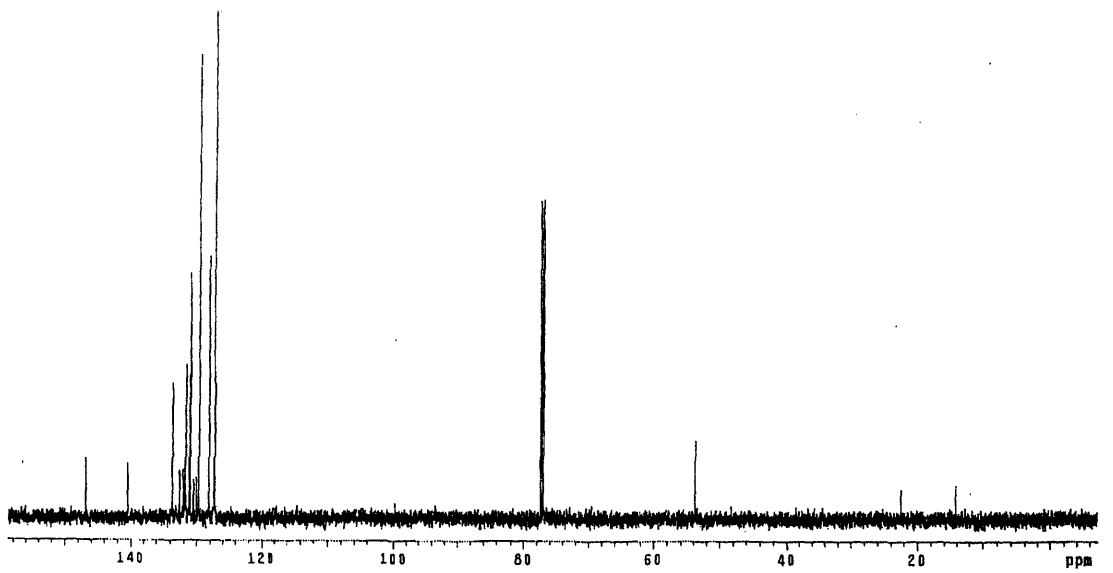
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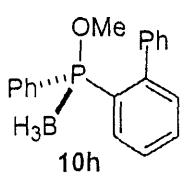
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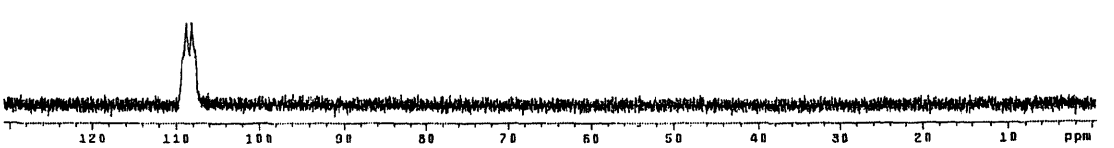
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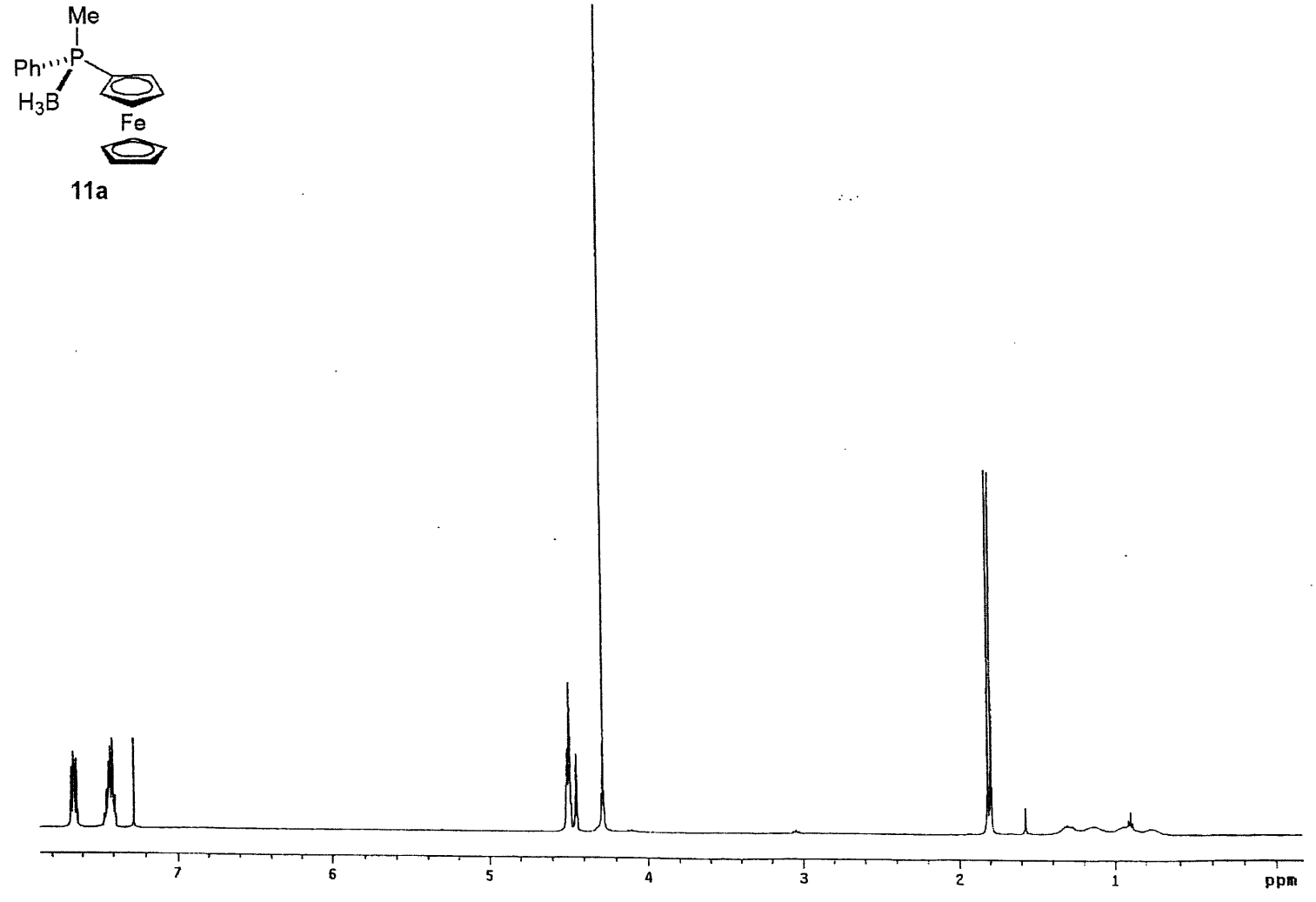
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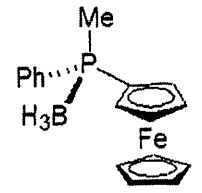
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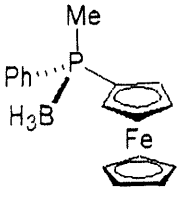
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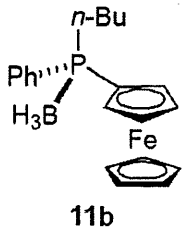

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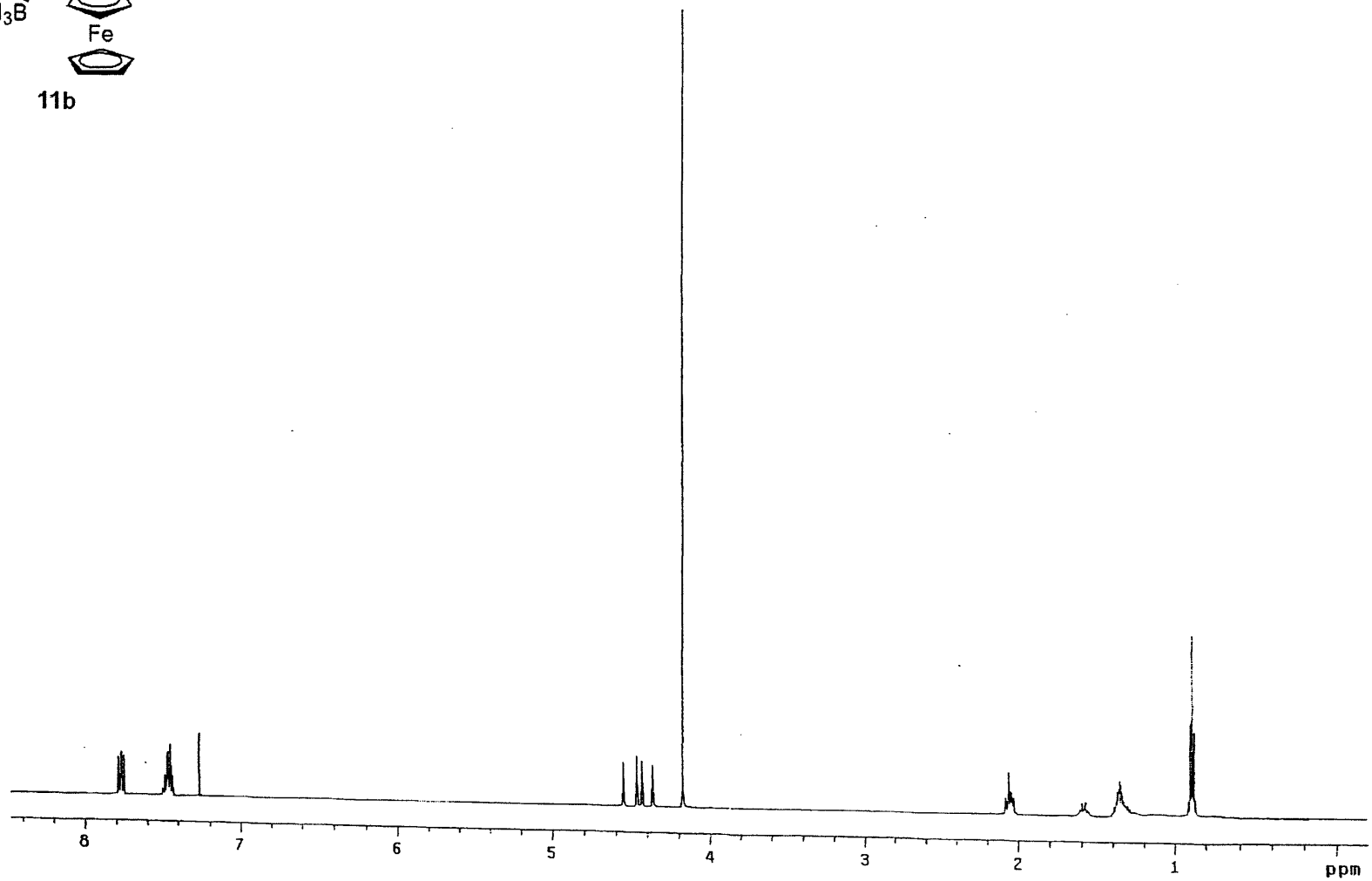

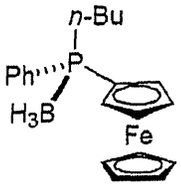
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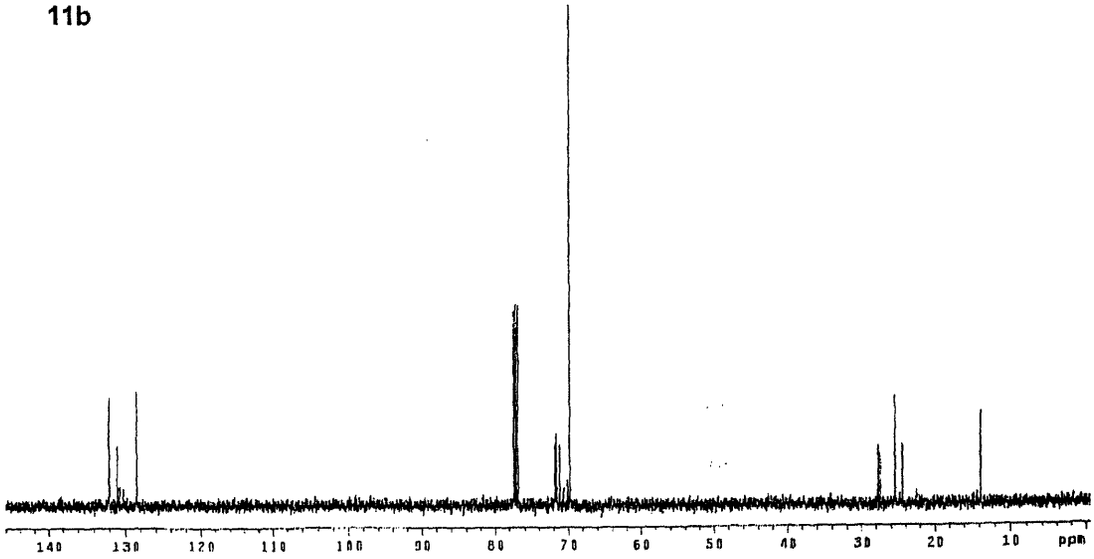
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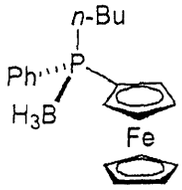
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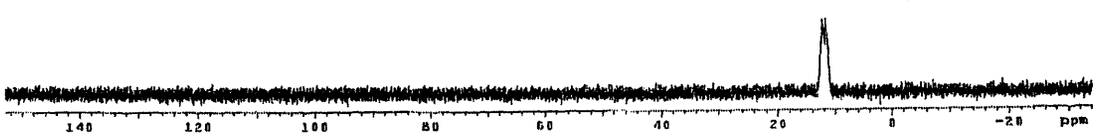
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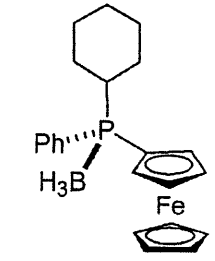

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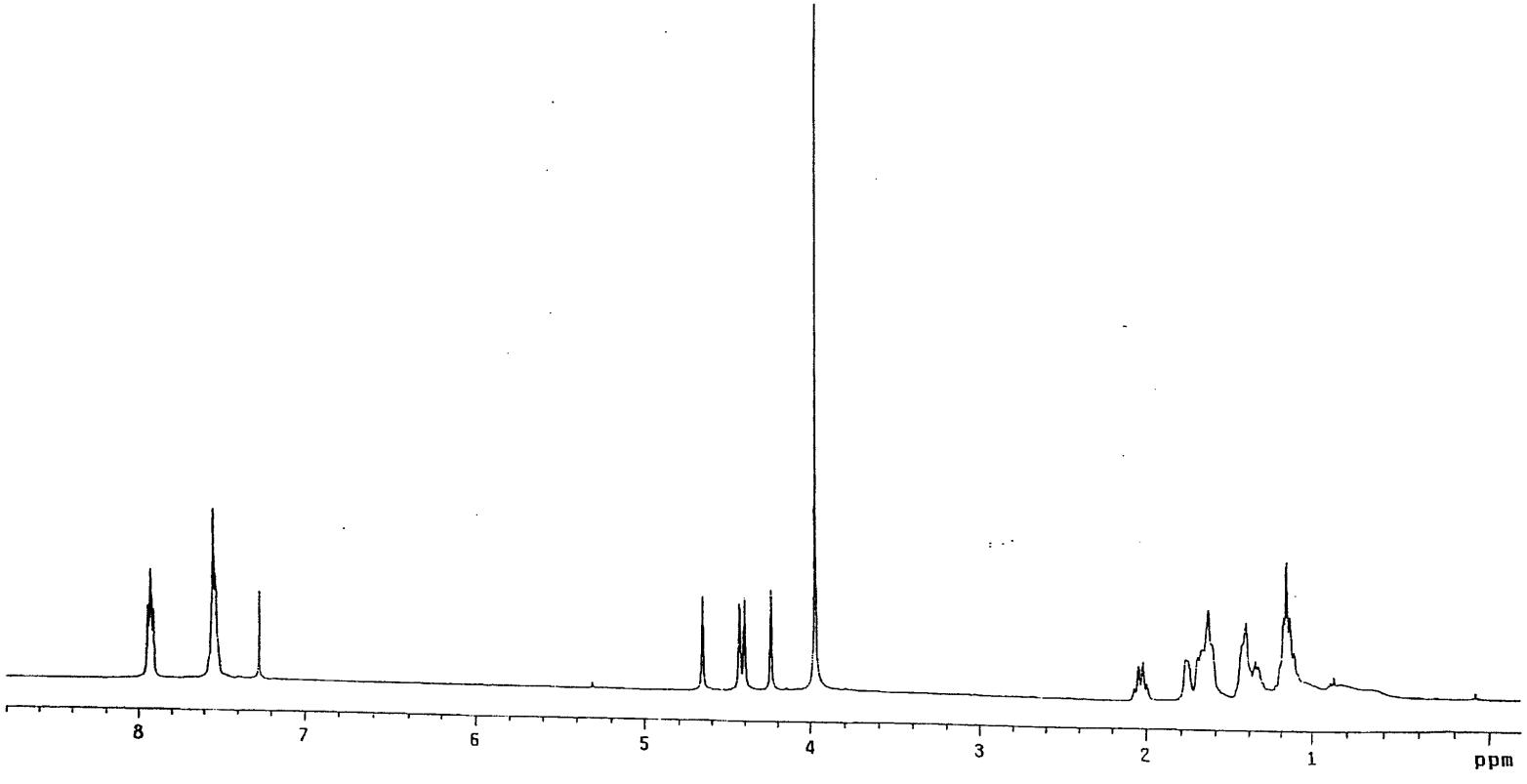

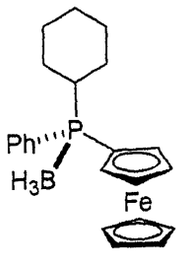
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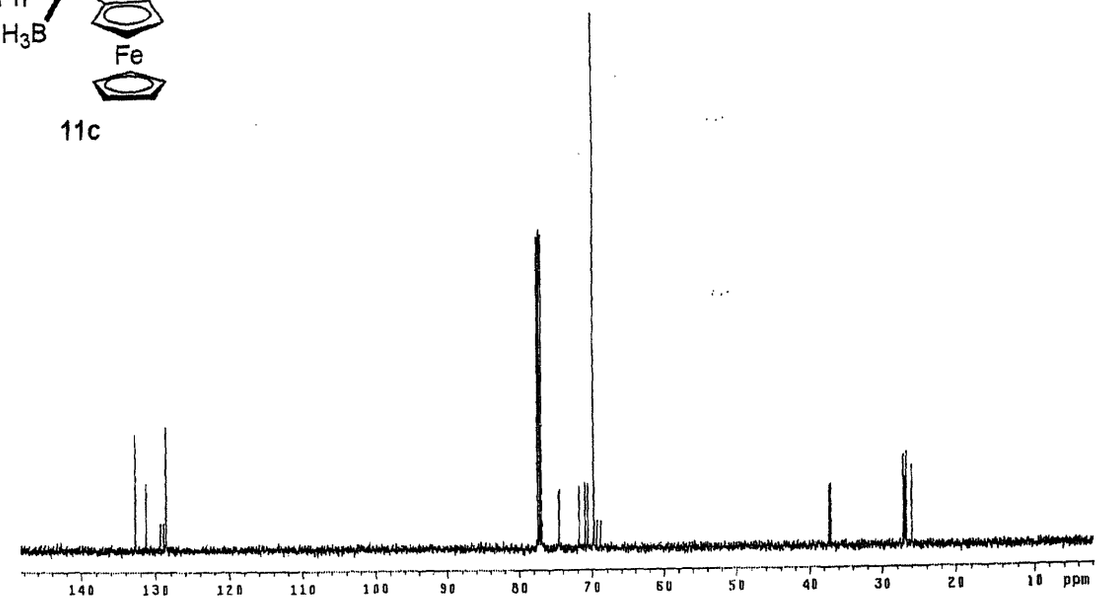
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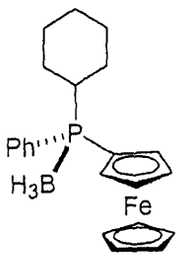
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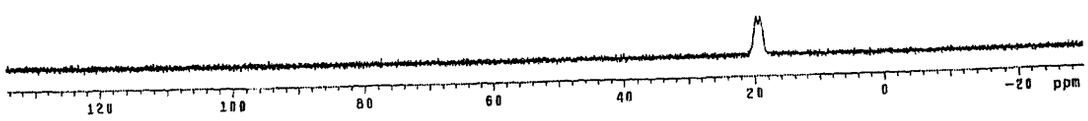
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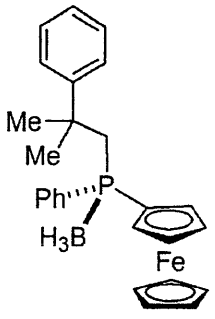

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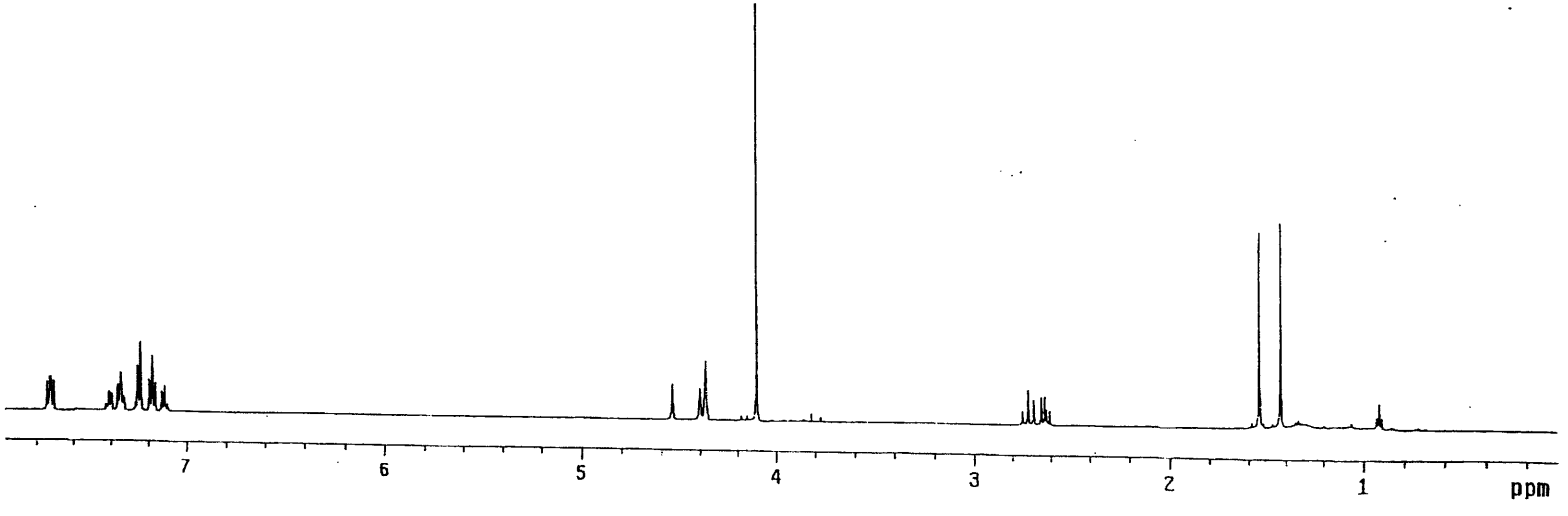

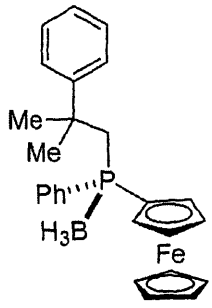
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P
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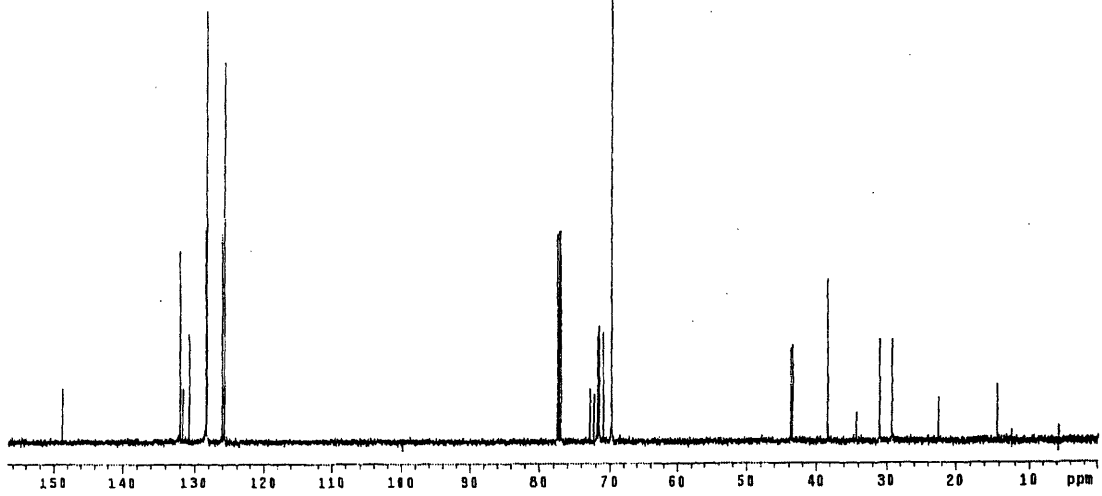
Fe

11d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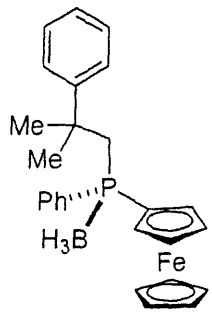
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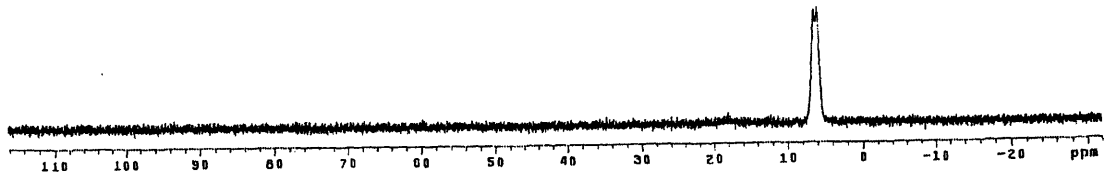
11d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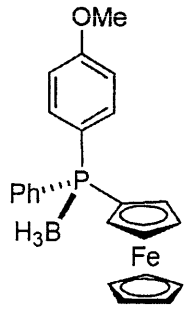

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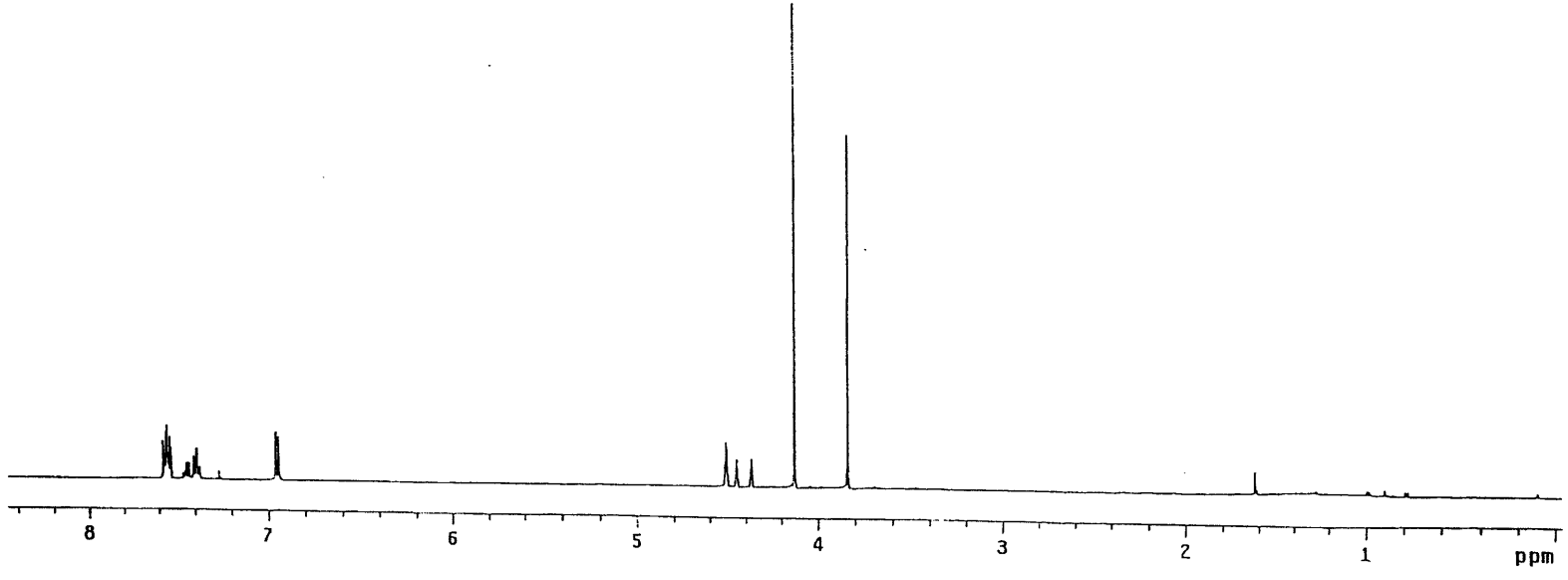

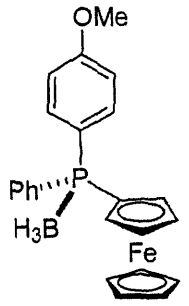
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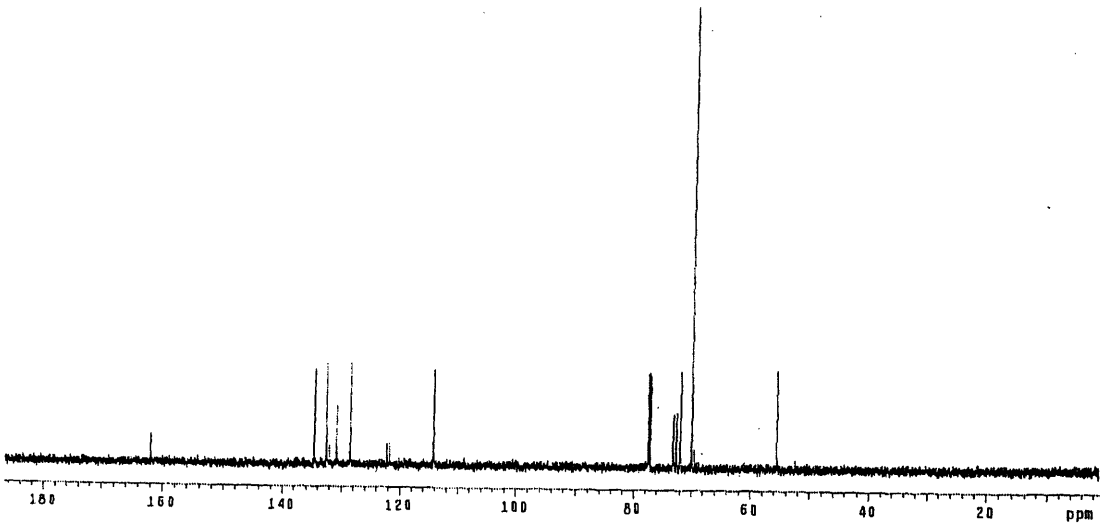
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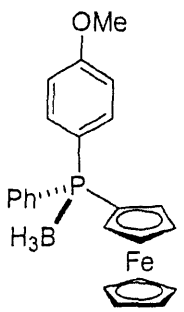
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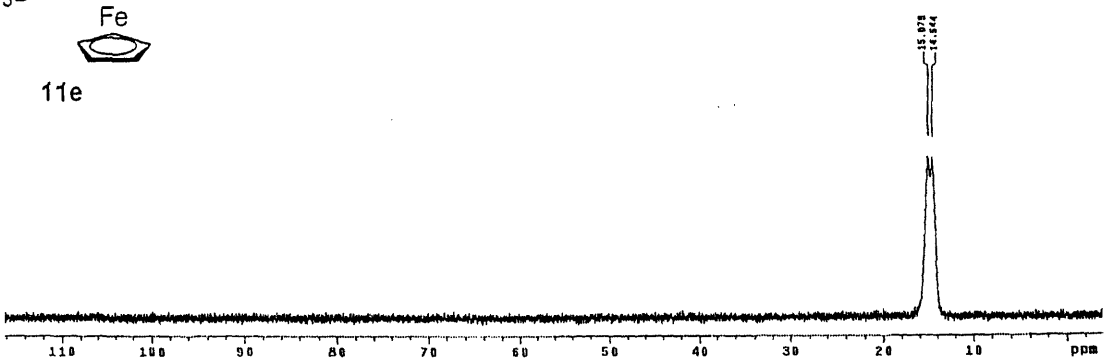
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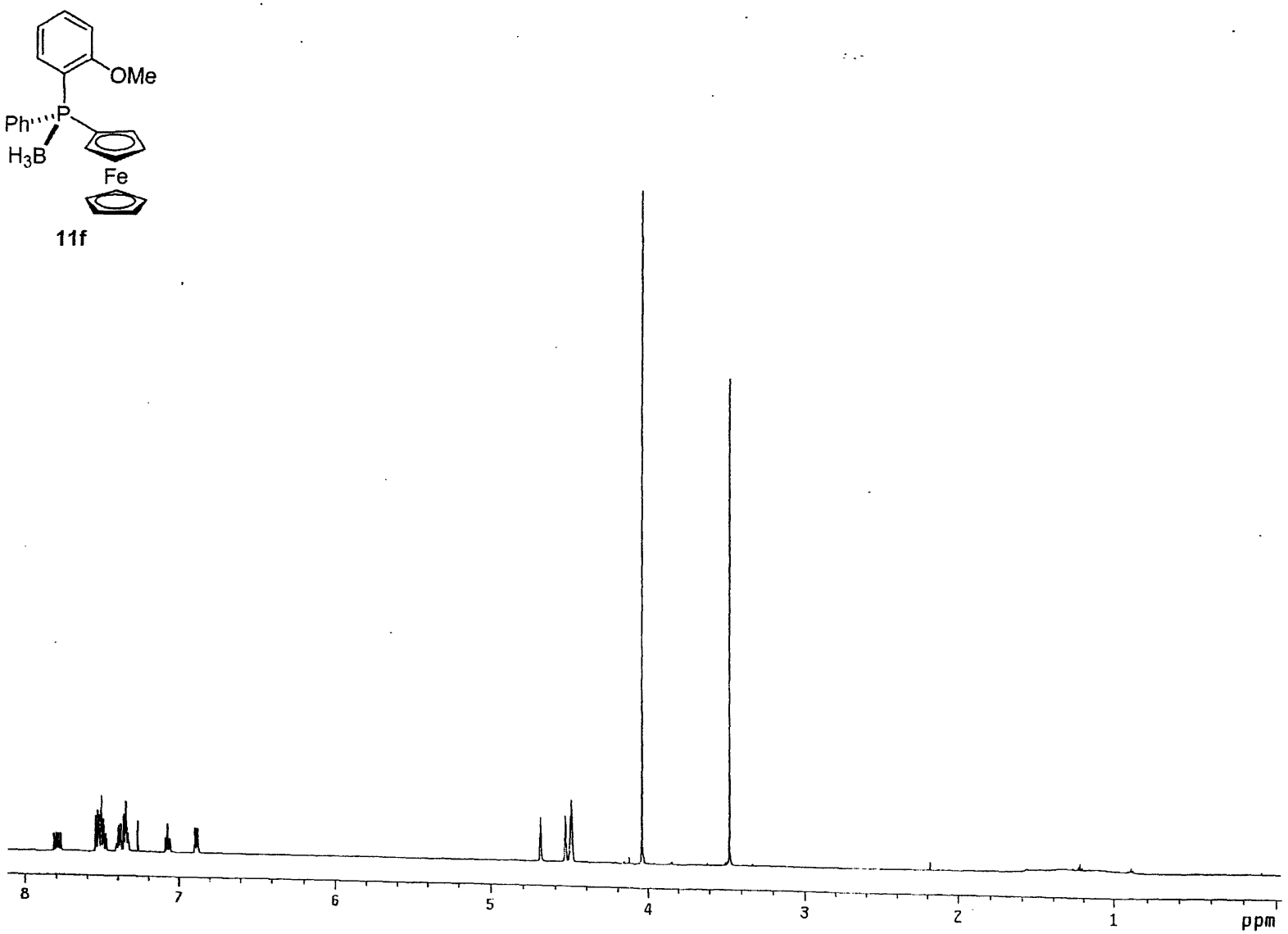
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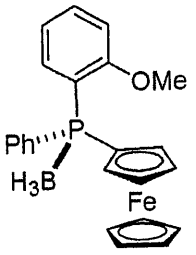
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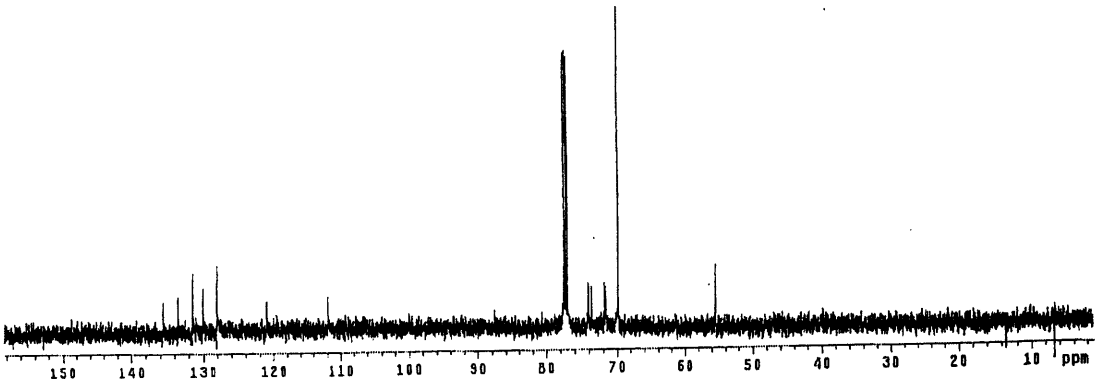
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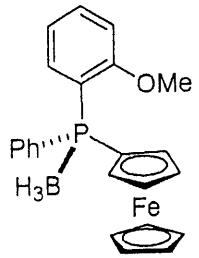
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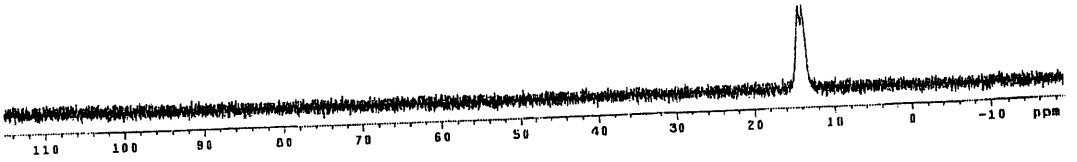
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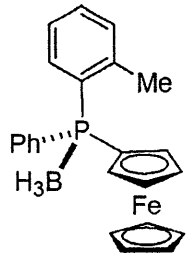

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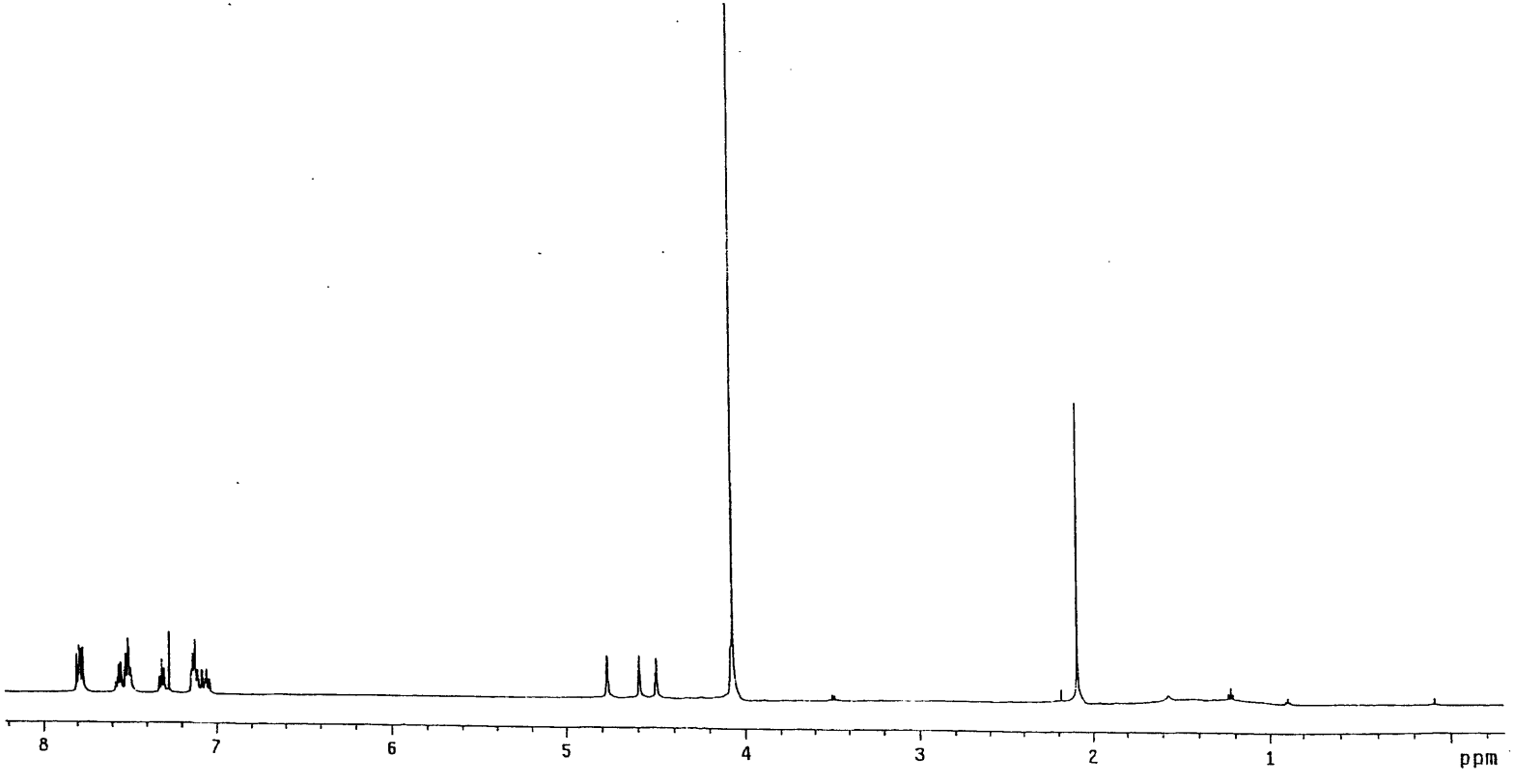

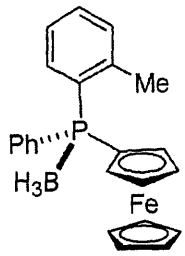
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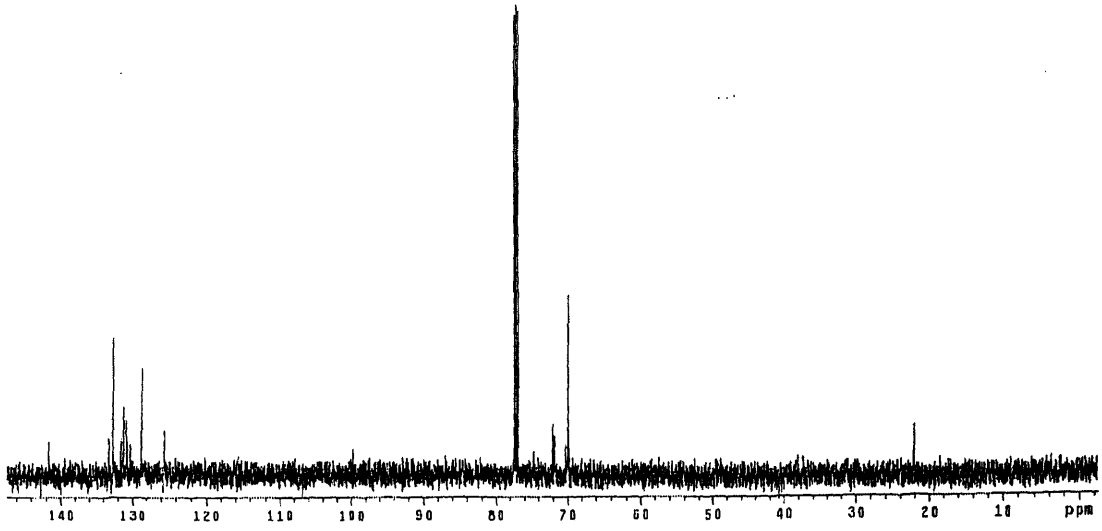
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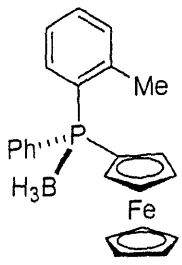
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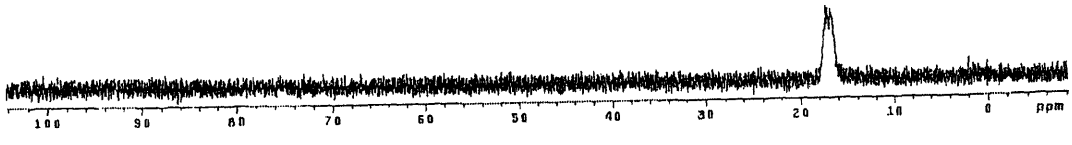
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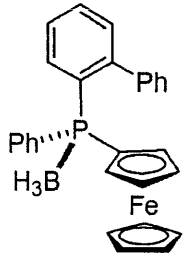

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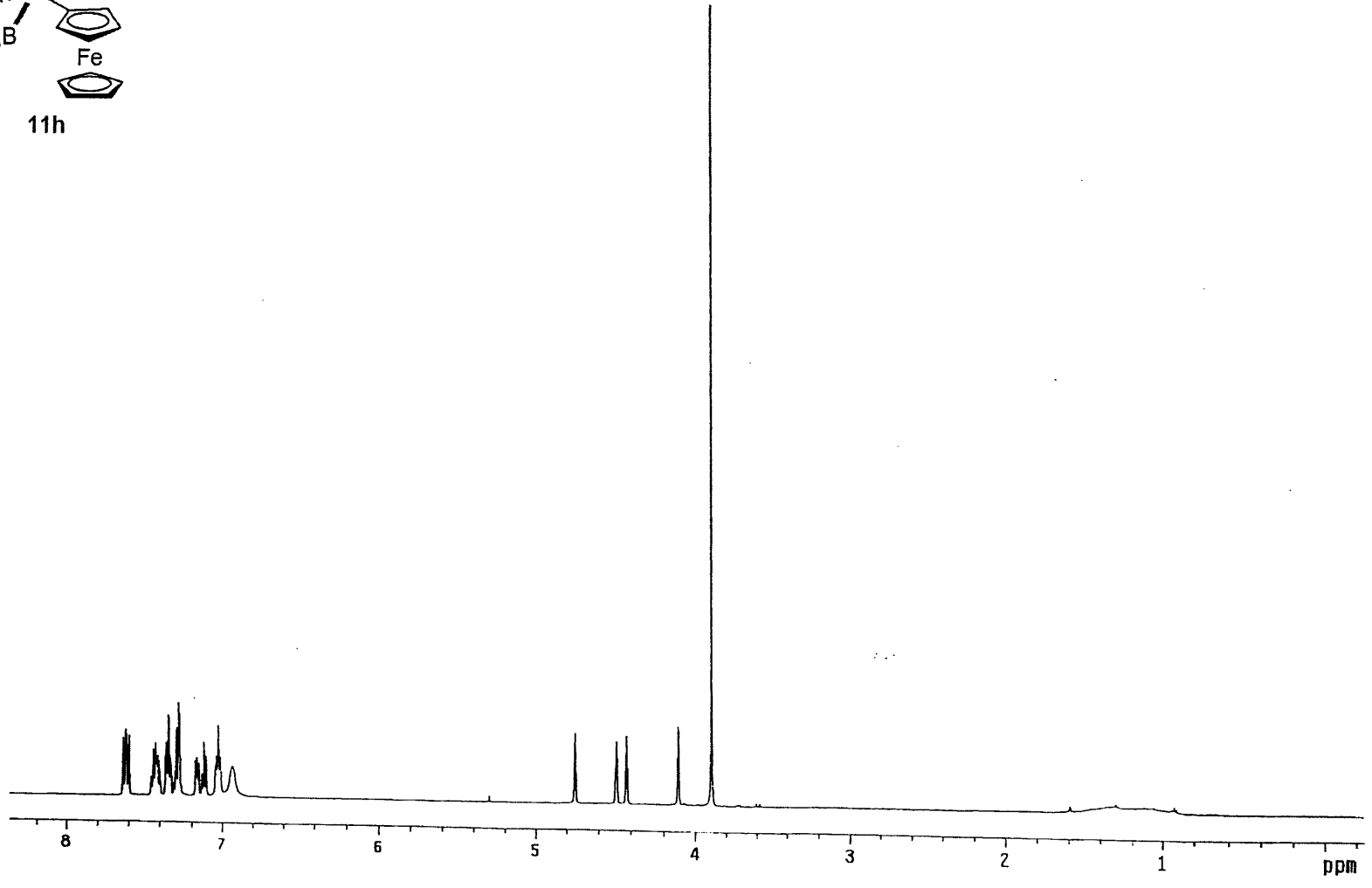

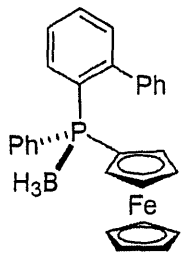
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11h

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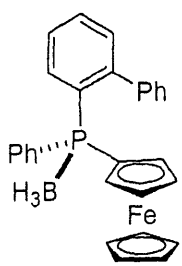
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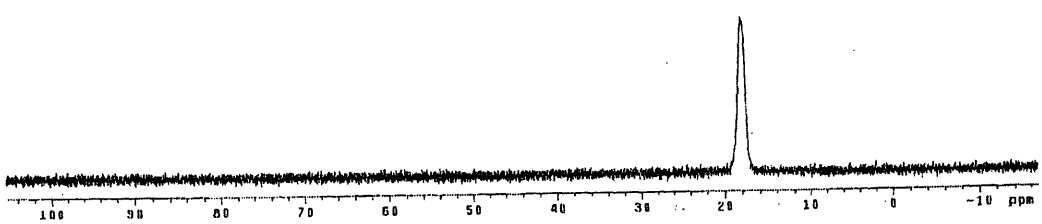
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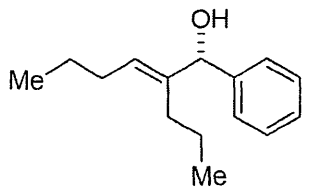

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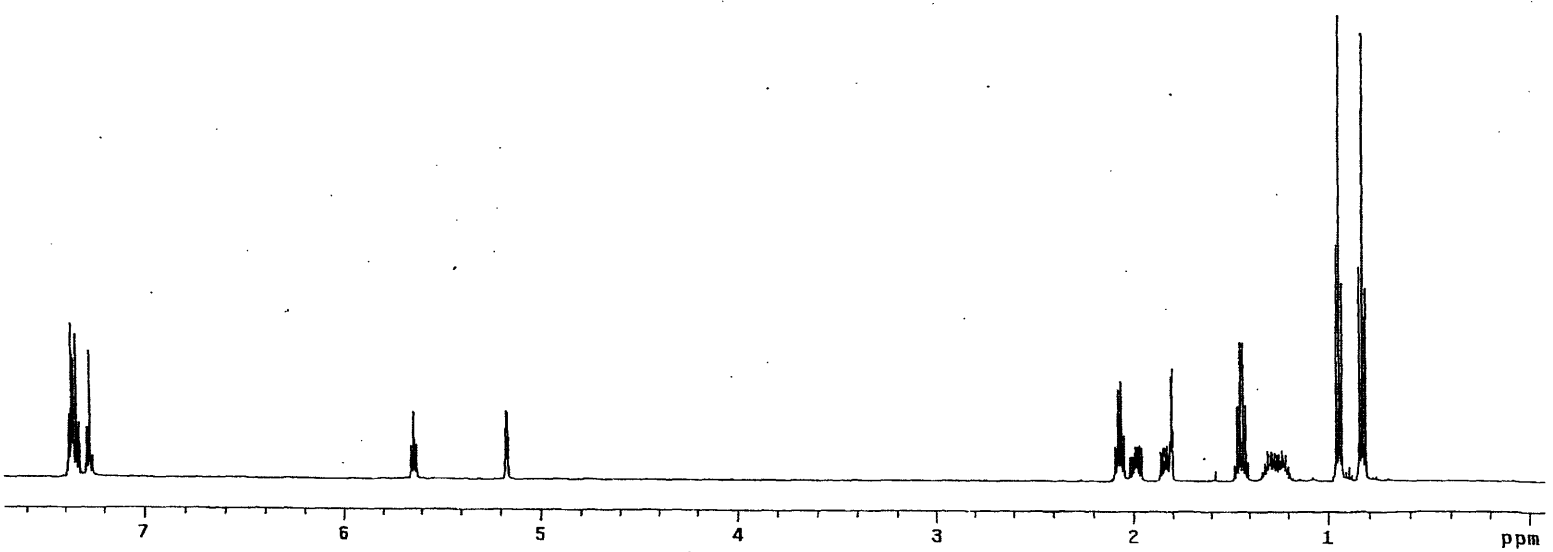

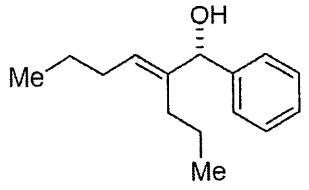

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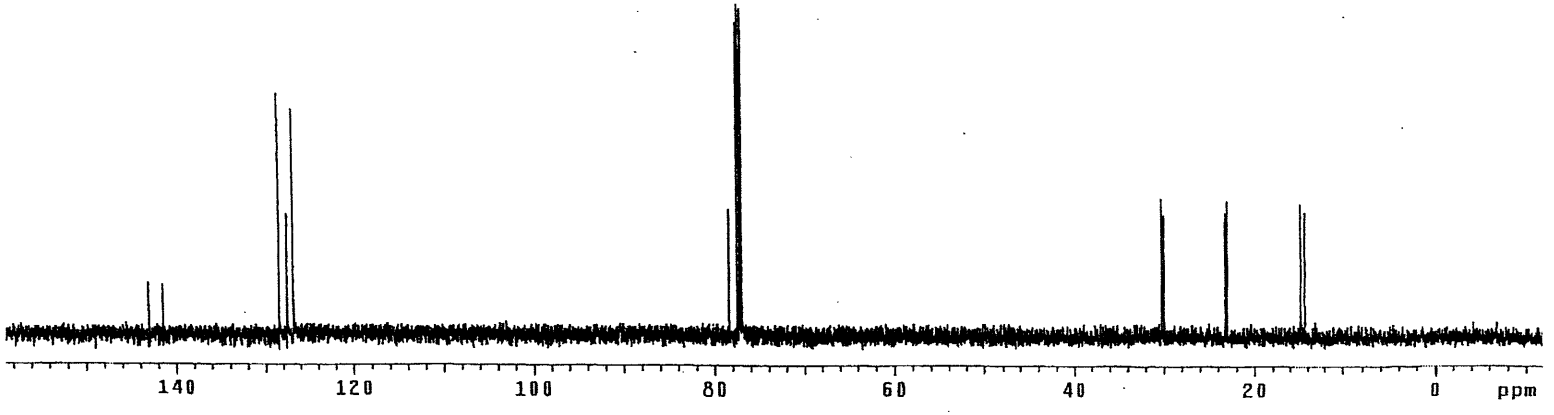

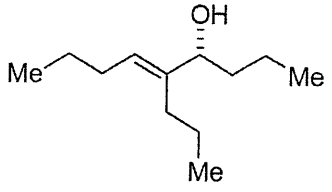

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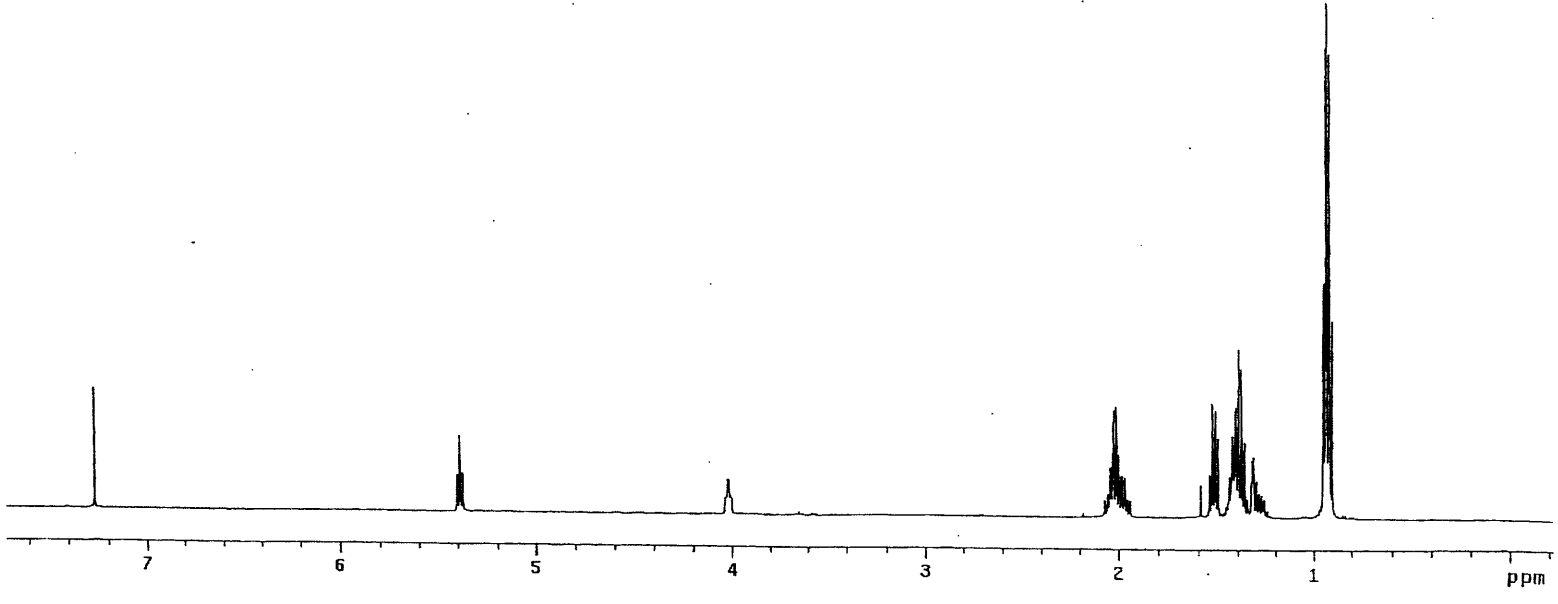

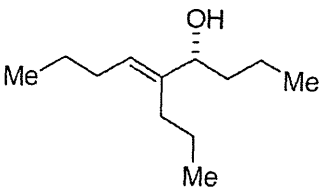

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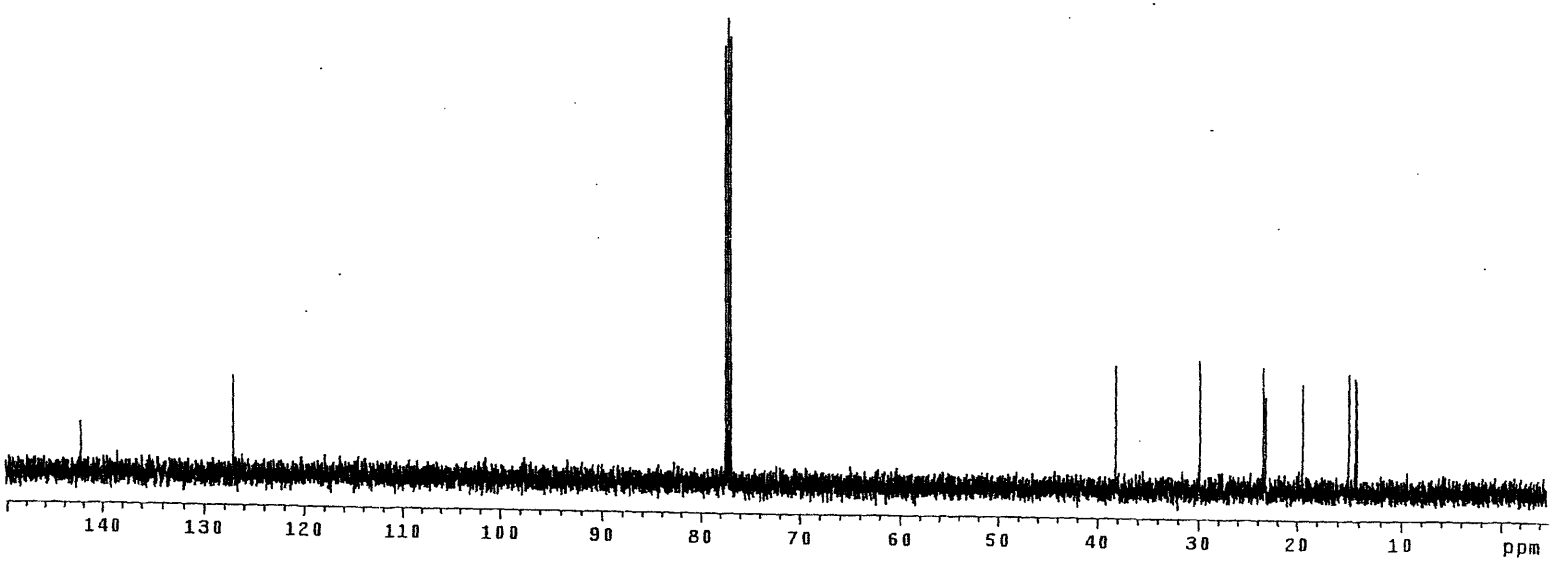

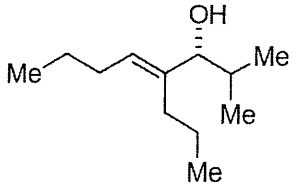

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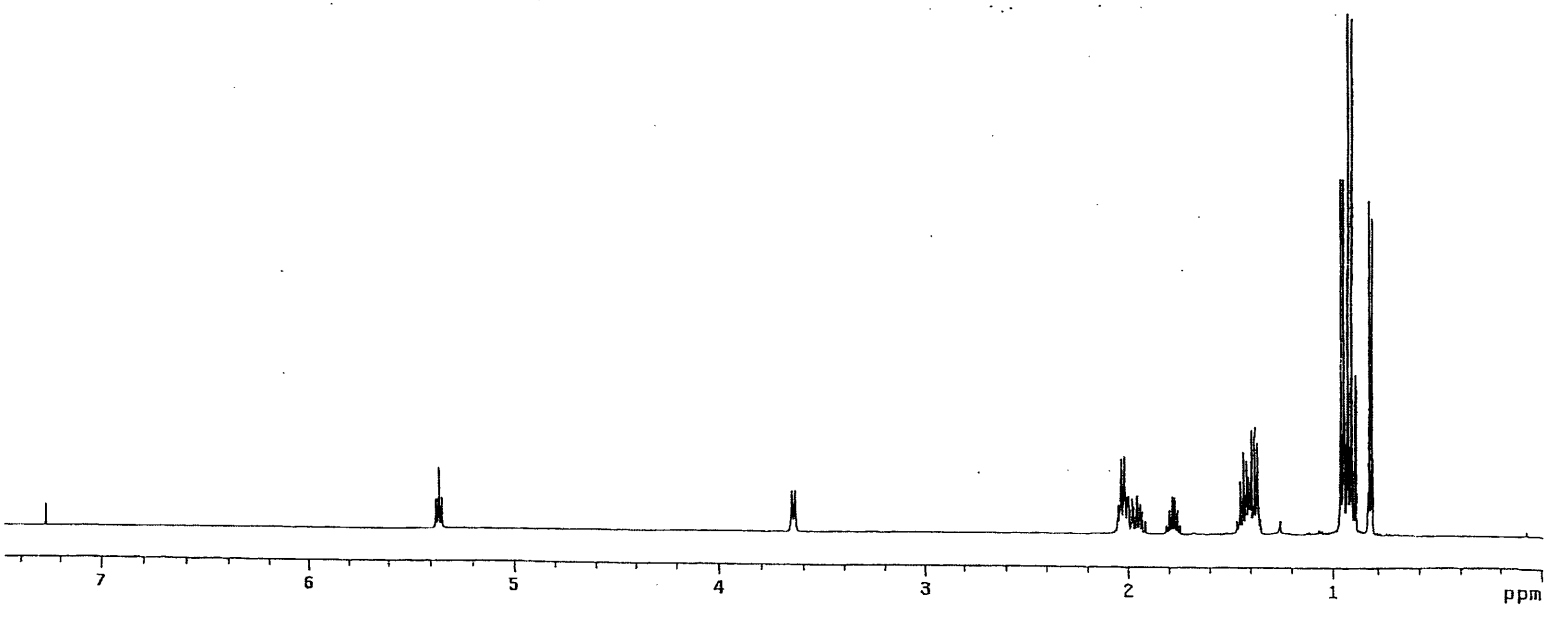

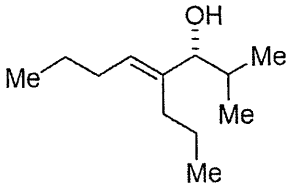

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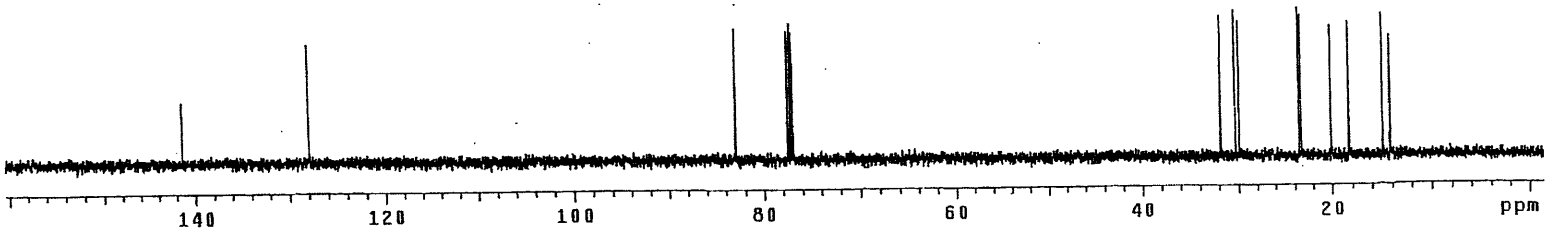

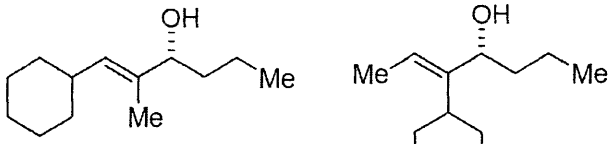

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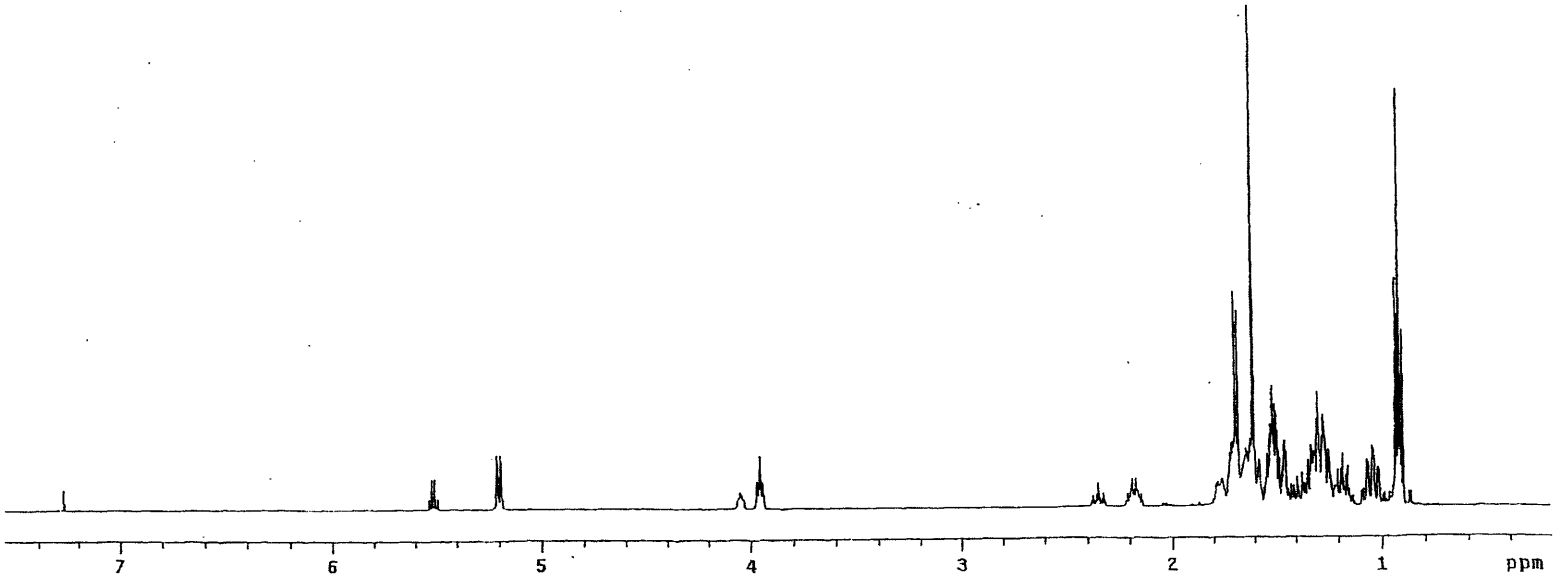

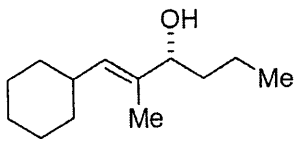

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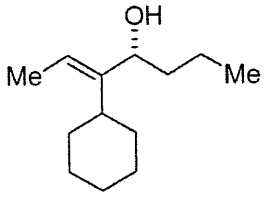

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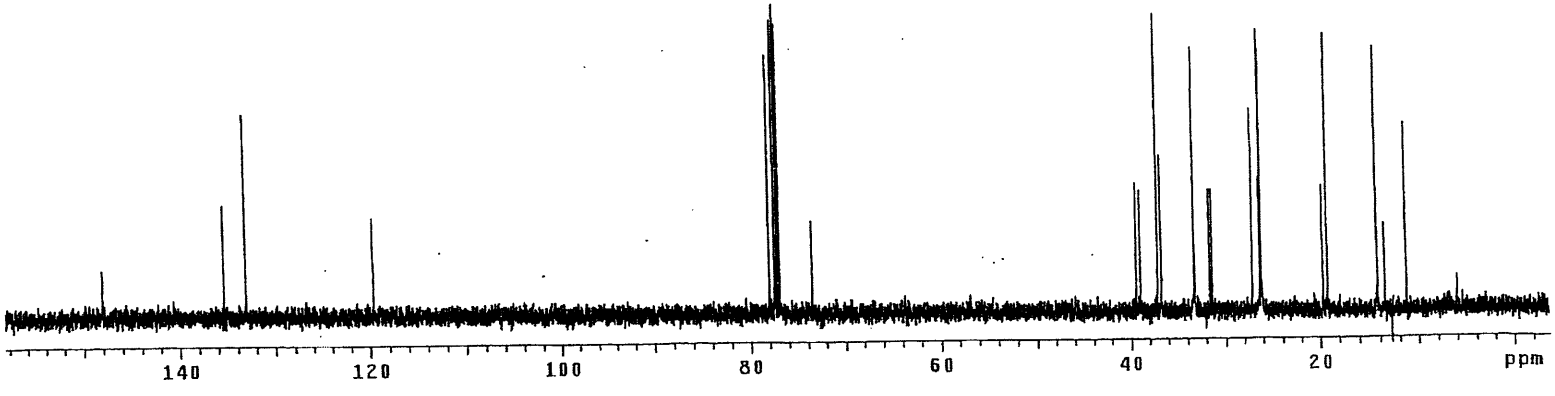


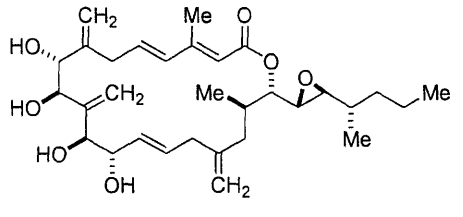
Chapter 2

Total Syntheses of Amphidinolides T1 and T4 via Catalytic, Stereoselective Reductive Macrocyclizations

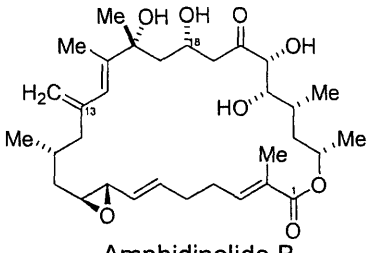
Introduction- Amphidinolides

In the search for novel bioactive compounds, natural products isolated from marine organisms have shown a wealth of pharmacological and structural diversity.[1] Unfortunately, the sources of the active compounds (sponges in particular) contain very small amounts of the desired products, limiting the quantities that may be isolated and studied. During the 1980s, Jun'ichi Kobayashi and co-workers undertook the isolation of natural products originating from marine *symbiotic* microorganisms (such as bacteria, fungi, and microalgae) with the intent to cultivate the microorganisms and subsequently isolate larger amount of active compounds.[1a] Early on, Kobayashi focused on a marine microalga dinoflagellate from the genus *Amphidinium*, found in the inner tissue of the Okinawan flatworm *Amphiscolops*. Four novel bioactive macrolides were originally isolated, amphidinolides A-D[2] (Chart 1), exhibiting cytotoxicity against murine lymphoma cells (L1210) and human epidermoid carcinoma KB cells.

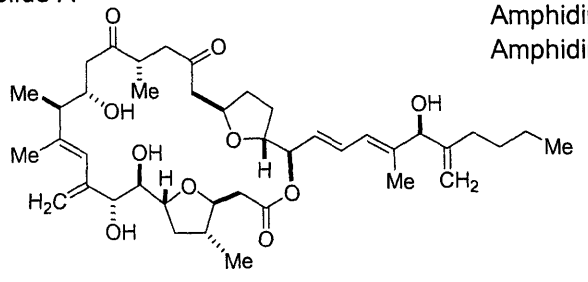
Chart 1



Amphidinolide A



Amphidinolide B
Amphidinolide D (epi-C_{18})



Amphidinolide C

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[1] (a) Kobayshi, J. *J. Nat. Prod.* **1989**, *52*, 225-238. For a review of marine natural products, see: (b) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2005**, *22*, 15-61. For a review of natural products in drug development, see: (c) Newman, D. J.; Cragg, G. M.; Snader, K. M. *J. Nat. Prod.* **2003**, *66*, 1022-1037.

[2] Original report: (a) Kobayashi, J.; Ishibashi, M.; Nakamura, H.; Ohizumi, Y.; Yamasu, T.; Hirata, Y.; Sasaki, T.; Ohta, T.; Nozoe, S. *J. Nat. Prod.* **1989**, *52*, 1036-1041. Structure elucidation: (b) A: Trost, B. M.; Harrington, P. E.

Additional species of *Amphidinium* were subjected to the extraction procedure, leading to the discovery of amphidinolides E-H. During the process of isolation, several fractions were found to exhibit cytotoxicity of greater potency than any of the amphidinolides A-H. Further investigation of these cultures led to the discovery of related macrolides, amphidinolides J-Y.[3] Table 1 summarizes the notable anticancer activity of the amphidinolides, highlighting the activity of B, C, G, H, and N which display the greatest potency.

Table 1.[a] Summary of the Cytotoxicity of the Amphidinolides.

Amphidinolide	Cytotoxicity (IC_{50} μg/ml)		Amphidinolide	Cytotoxicity (IC_{50} μg/ml)	
	L1210	KB		L1210	KB
A	2	5.7	M	1.1	0.44
B	0.00014	0.0042	N	0.00005	0.00006
C	0.0058	0.0046	O	1.7	3.6
D	0.019	0.08	P	1.6	5.8
E	2	10	Q	6.4	>10
F	1.5	3.2	R	1.4	0.67
G1	0.0054	0.0059	S	4	6.5
G2[b]	0.3	0.8	T1[c]	18	35
G3[b]	0.72	1.3	T2[c]	10	11.5
H1	0.00048	0.00052	T3[c]	7	10
H2[b]	0.06	0.06	T4[c]	11	18
H3[b]	0.002	0.022	T5[d]	15	20
H4[b]	0.18	0.23	U	12	20
H5[b]	0.2	0.6	V	3.2	7
J	2.7	3.9	W[e]	3.9	-
K	1.65	2.9	X[f]	0.6	7.5
L	0.092	0.1	Y[g]	0.8	8

(*a*) Data compiled and reported by Chakraborty, T. K.; Das, S. *Curr. Med. Chem.-Anti-Cancer Agents* **2001**, *1*, 131-149. (*b*) Kobayashi, J.; Shimbo, K.; Sato, M.; Tsuda, M. *J. Org. Chem.* **2002**, *67*, 6585-6592. (*c*) Kobayashi, J.; Kubota, T.; Endo, T.; Tsuda, M. *J. Org. Chem.* **2001**, *66*, 134-142. (*d*) Kubota, T.; Endo, T.; Tsuda, M.; Kobayashi, J. *Tetrahedron* **2001**, *57*, 6175-6179. (*e*) Shimbo, K.; Tsuda, M.; Izui, N.; Kobayashi, J. *J. Org. Chem.* **2002**, *67*, 1020-1023. (*f*) Tsuda, M.; Izui, N.; Shimbo, K.; Sato, M.; Fukushi, E.; Kawabata, J.; Katsumata, K.; Horiguchi, T.; Kobayashi, J. *J. Org. Chem.* **2003**, *68*, 5339-5345. (g) Tsuda, M.; Izui, N.; Shimbo, K.; Sato, M.; Fukushi, E.; Kawabata, J.; Kobayashi, J. *J. Org. Chem.* **2003**, *68*, 9109-9112.

J. Am. Chem. Soc. **2004**, *126*, 5028-5029. (c) B: Ishibashi, M.; Ishiyama, H.; Kobayashi, J. *Tetrahedron Lett.* **1994**, *34*, 8241-8242. (d) C: Kubota, T.; Tsuda, M.; Kobayachi, J. *Org. Lett.* **2001**, *3*, 1363-1366.

[3] For reviews of the amphidinolides, see (a) Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77-93. (b) Chakraborty, T. K.; Das, S. *Curr. Med. Chem.-Anti-Cancer Agents* **2001**, *1*, 131-149. (c) Kobayashi, J.; Ishibashi, M. In *Comprehensive Natural Products Chemistry*. Mori, K., Ed.; Elsevier; New York, **1999**; Vol. 8, 619-649.

In addition to the striking biological activity of the amphidinolides, they possess several interesting structural features. This family of macrolides shows diversity in size, including lactones of odd-numbered ring size, and display an abundance of stereogenic centers, exo- and endocyclic double bonds, and oxygen-containing substituents (including epoxides, THF and TFP rings, hydroxyl groups, and ketones). Due to their remarkable biological activity and structural functionality, the amphidinolides are ideal and challenging synthetic targets. Since the first reports of the amphidinolide family, considerable effort has been focused on synthesizing these macrolides, resulting in several innovative and efficient total syntheses.[4]

In particular, the amphidinolide T class (Chart 2) has garnered significant attention since its discovery in 2000.[5] Members of this subclass, amphidinolides T1-5 (**1-5**), contain a 19-membered macrocycle, a trisubstituted tetrahydrofuran moiety, α-hydroxy ketone, exocyclic methylene group, and a homoallylic ester linkage. T3-T5 are the most closely related molecules, all containing a ketone at C13, hydroxyl group at C12, and methyl group at C14, and they differ only in their configuration at C12 and C14. Amphidinolide T2 (**2**) displays the same functionality at C12-C14 as **3-5**, but contains an additional hydroxymethyl substituent at C18 where the other four members have an *n*-propyl group. Amphidinolide T1 (**1**) differs from **3-5** in the oxidation states at C12 and C13, possessing the reversed hydroxy ketone moiety.

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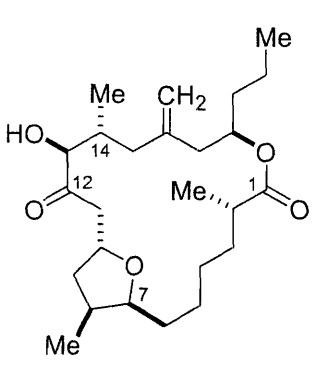
[4] Proposed structure of A: (a) Lam, H. W.; Pattendon, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 508-511. (b) Maleczka, R. E., Jr.; Terrell, L. R.; Geng, F.; Ward, J. S., III. *Org. Lett.* **2002**, *4*, 2841-2844. (c) Trost, B. M.; Chisholm, J. D.; Wrobleski, S. T.; Jung, M. *J. Am. Chem. Soc.* **2002**, *124*, 12420-12421. Structural revision and synthesis of Amphidinolide A: (d) Trost, B. M.; Harrington, P. E. *J. Am. Chem. Soc.* **2004**, *126*, 5028-5029. Amphidinolide J: (e) Williams, D. R.; Kissel, W. S. *J. Am. Chem. Soc.* **1998**, *120*, 11198-11199. Amphidinolide K: (f) Williams, D. R.; Meyer, K. G. *J. Am. Chem. Soc.* **2001**, *123*, 765-766. Amphidinolide P: (g) Williams, D. R.; Myers, B. J.; Mi, L. *Org. Lett.* **2000**, *2*, 945-948. (h) Trost, B. M.; Papillon, J. P. N. *J. Am. Chem. Soc.* **2004**, *126*, 13618-13619. Amphidinolide R: (i) Kissel, W. S. "The Asymmetric Total Syntheses of Amphidinolides J and R," Ph.D. Thesis, Indiana University, 1998. Amphidinolide T1: (j) Ghosh, A. K.; Liu, C. *J. Am. Chem. Soc.* **2003**, *125*, 2374-2375. Amphidinolide T1, T3, T4, T5: (k) Fürstner, A.; Aïssa, C.; Riveiros, R.; Ragot, J. *Angew.Chem. Int. Ed.* **2002**, *41*, 4763-4766. (l) Aïssa, C.; Riveiros, R.; Ragot, J.; Fürstner, A. *J. Am. Chem. Soc.* **2003**, *125*, 15512-15520. Amphidinolide W: (m) Ghosh, A. K.; Gong, G. *J. Am. Chem. Soc.* **2004**, *126*, 3704-3705. Amphidinolide X: (n) Lepage, O.; Kattnig, E.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 15970-15971.

[5] For the isolation, structure determination, and biological studies of Amphidinolides T1-5, see: (a) Tsuda, M.; Endo, T; Kobayashi, J. *J. Org. Chem.* **2000**, *65*, 1349-1352. (b) Kobayashi, J.; Kubota, T.; Endo, T.; Tsuda, M. *J. Org. Chem.* **2001**, *66*, 134-142. (c) Kubota, T.; Endo, T.; Tsuda, M.; Shiro, M.; Kobayashi, J. *Tetrahedron* **2001**, *57*, 6175-6179.

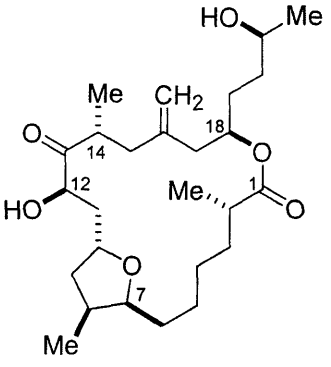
Previous Syntheses of Amphidinolides T1 and T3-T5

Total syntheses of **1** and **3-5** were reported shortly after this work was begun. Amphidinolide T4 was synthesized in 2002 by Fürstner and coworkers by taking advantage of an efficient ring closing metathesis to form the macrocycle.[4k] Related strategies were applied by the same group to the syntheses of T1, T3, and T5 reported in 2003.[4l] Amphidinolide T1 was first synthesized by Ghosh and Liu in 2003, utilizing a macrolactonization reaction to form the 19-membered ring.[4j]

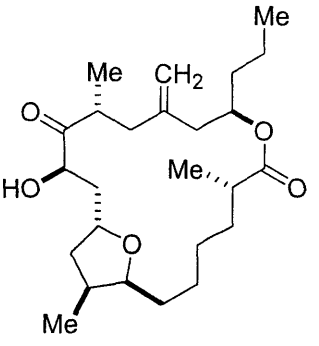
Chart 2. Amphidinolide T Family of Natural Products.



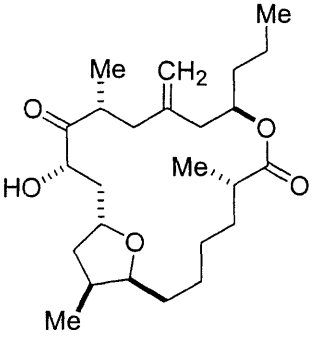
1 amphidinolide T1



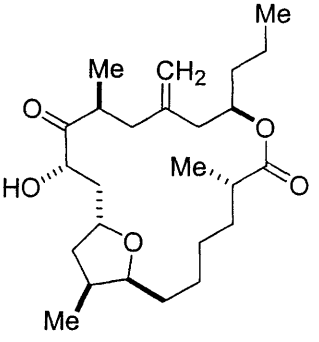
2 amphidinolide T2



3 amphidinolide T3



4 amphidinolide T4

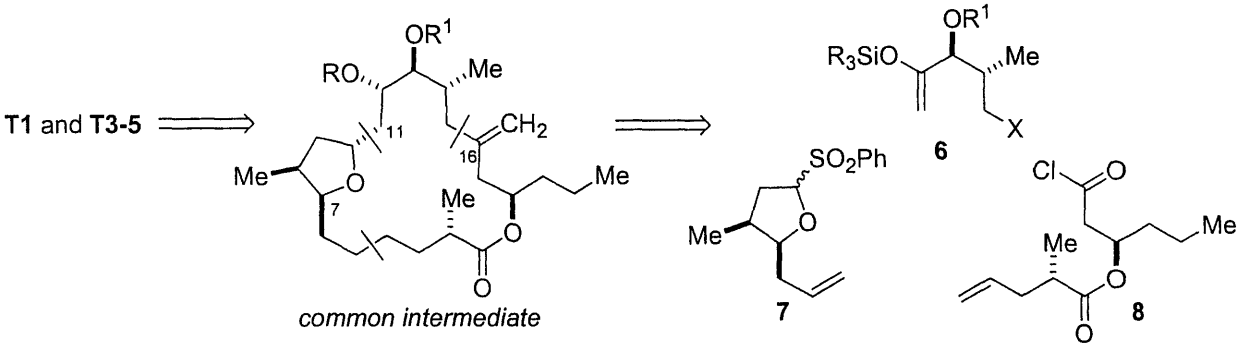


5 amphidinolide T5

Fürstner's Syntheses of Amphidinolides T1 and T3-T5.

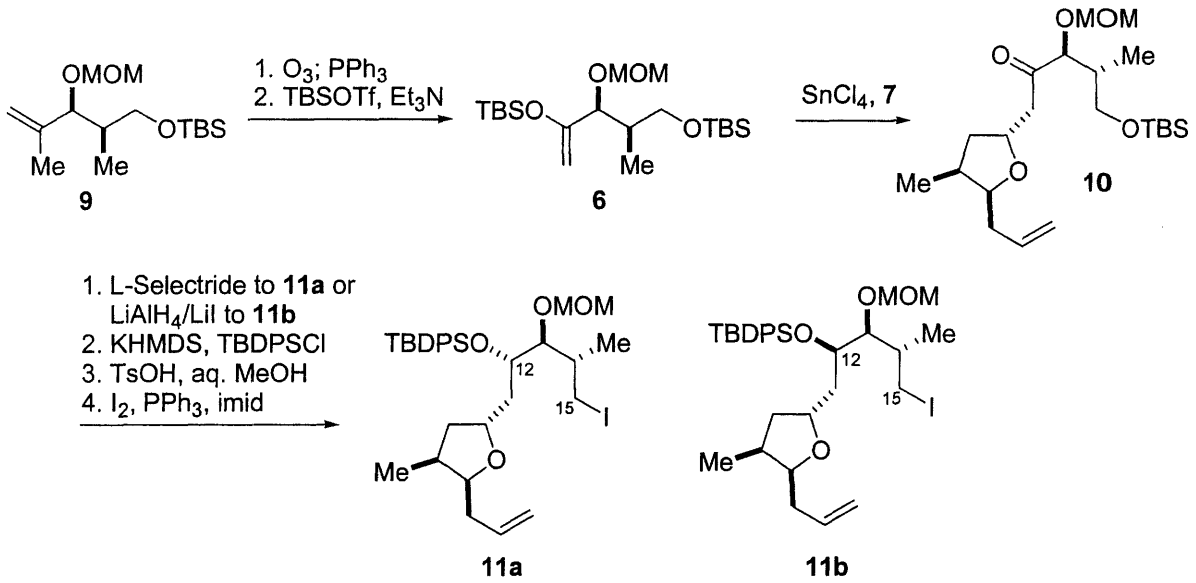
It was clear from Fürstner's initial T4 communication[4k] and delineated in the later full account[4l] that an ultimate synthetic strategy hinged upon a late-stage intermediate that would provide a point of divergence to both the T1 and T3-5 frameworks (Scheme 1). This key intermediate bears hydroxyl groups at both C12 and C13; ostensibly simple deprotection and oxidation state adjustment was predicted to provide access to **1** and **3-5**. The common intermediate was envisioned to be rapidly assembled from three simpler fragments (**6**, **7**, and **8**).

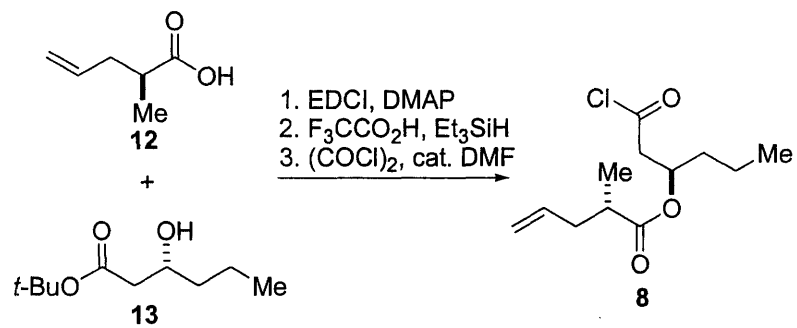
Scheme 1. Fürstner's Retrosynthetic Disconnections.



In the forward direction (Scheme 2), alkene **9** (easily prepared using an auxiliary-based diastereoselective aldol reaction) was ozonolyzed to the ketone and silylated under basic conditions to produce fragment **6**. Lewis acid-mediated coupling with sulfone **7** proceeded smoothly and in very high diastereoselectivity, affording ketone **10**. Selective reduction using L-Selectride produced the C12 *S* diastereomer (24:1 dr), while reduction with $LiAlH_4$/LiI afforded the *R* configuration at C12 (7:1 dr). The newly-formed secondary alcohol was protected as a TBDPS ether, allowing for selective deprotection of the primary alcohol and subsequent iodination, giving **11a** or **11b** depending on the protocol used for reduction of ketone **10**. Fragment **8** was synthesized through the esterification of carboxylic acid **12** with alcohol **13**, deprotection of the *t*-Bu ester and conversion to an acid chloride. (Coupling partners **12** and **13** were readily prepared through an auxiliary-based, diastereoselective alkylation and catalytic enantioselective reduction, respectively).

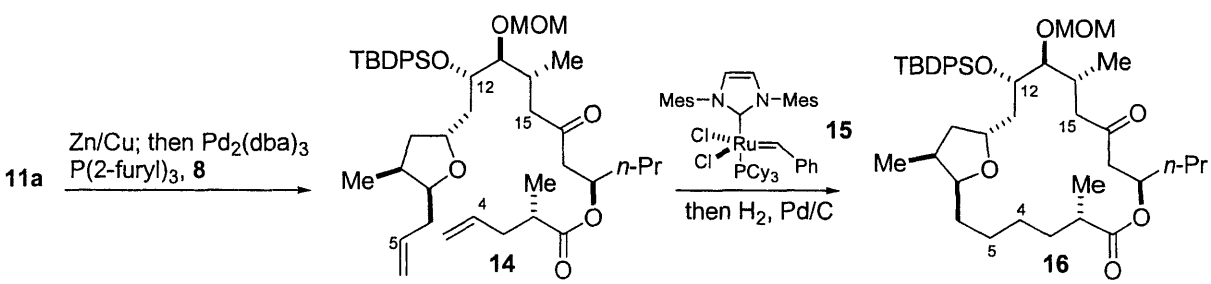
Scheme 2





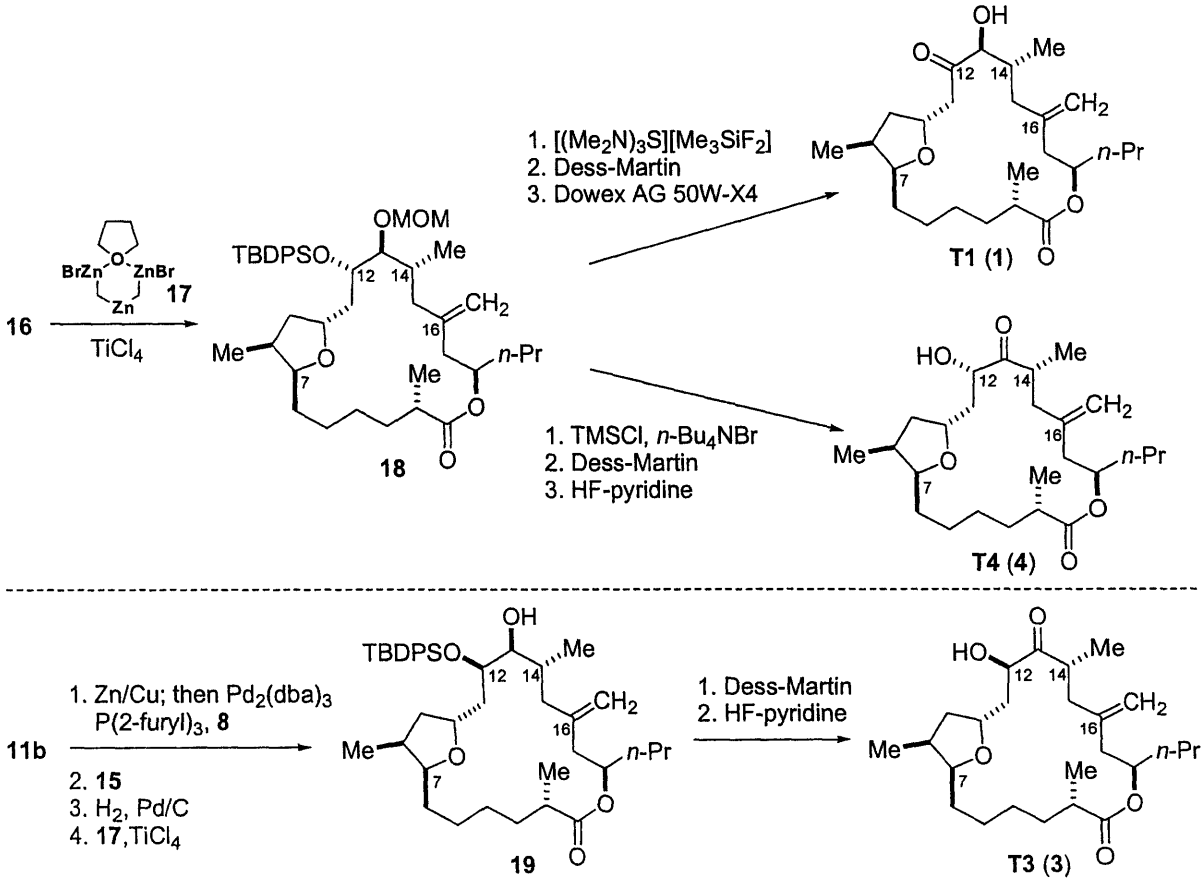
Union of alkyl halide **11a** and acid chloride **8** was accomplished by a palladium-catalyzed acylation (Scheme 3). Macrocycle formation via ring closing metathesis proceeded smoothly and in high yield (86%); subsequent hydrogenation delivered macrolactone **16**.

Scheme 3



Methylenation of ketone **16** using Nysted's reagent (**17**, Scheme 4) produced alkene **18**, which was intended to be the key common intermediate in syntheses of **1** and **3**-**5**. To this end, a sequence of steps from **18** indeed resulted in the synthesis of **1**. The silyl protective group was selectively removed by treatment with a fluorosilicate reagent, and the alcohol was oxidized to the C12 ketone. Deprotection of the MOM ether by exposure to acidic Dowex resin produced amphidinolide T1. Complementing this sequence and leading to the reversed hydroxy ketone array of **3**-**5**, the order of deprotection was reversed so that the MOM ether was first removed from **18** to liberate the C13 hydroxyl group. Oxidation and desilylation produced amphidinolide T4 (**4**). As **4** is known to be partially epimerized to **5** when treated with K_2CO_3/MeOH,[5c] a formal synthesis of amphidinolide T5 was also achieved. Attempts to access T3 from **18** via removal of the C13 MOM group, oxidation to the ketone, and C12 epimerization failed. However, elaboration of iodide **11b** and elaboration in analogy to the sequence used for **11a** culminated in the successful synthesis of **3**.

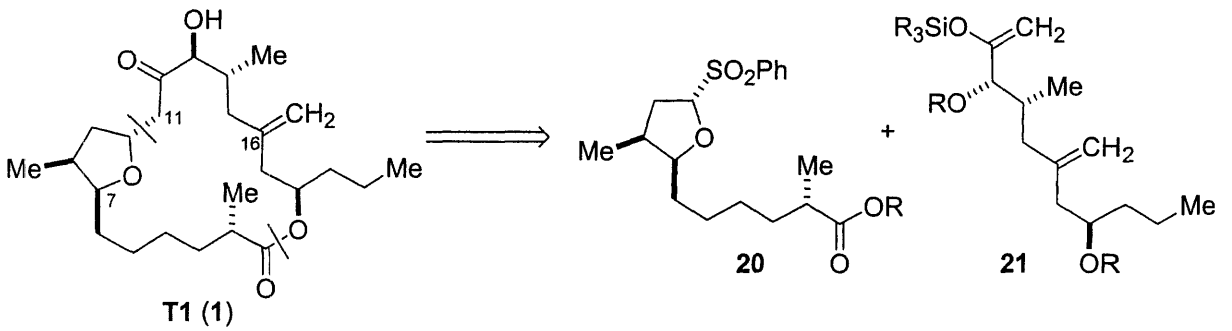
Scheme 4



Ghosh's Synthesis of Amphidinolide T1.

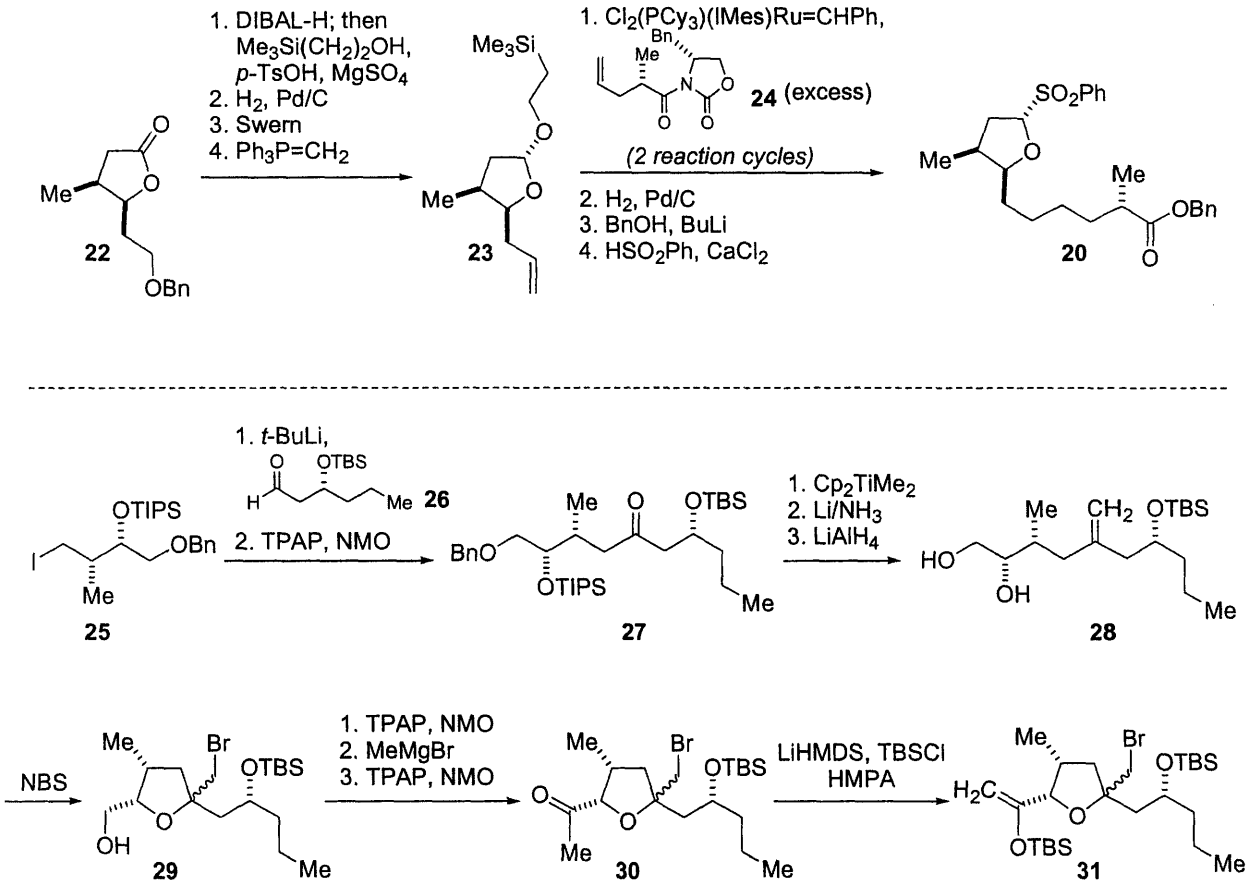
Shortly after Fürstner's synthesis of T4 was published, Ghosh reported the first total synthesis of amphidinolide T1. The target was dissected into two fragments of approximately the same complexity, sulfone **20** and silyl enol ether **21** (Scheme 5). Fragment coupling via oxocarbenium ion alkylation and later macrolactonization were envisioned to give access to **1**.

Scheme 5. Key Disconnections in Ghosh's Synthesis of **1**.



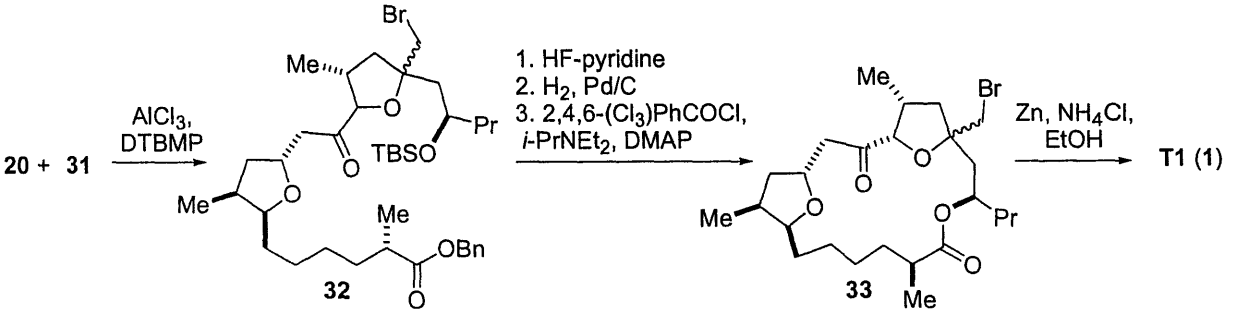
In the forward direction (Scheme 6), lactone **22** was partially reduced, and a mixed acetal with trimethylsilylethanol was formed. Subsequent removal of the benzyl protecting group, oxidation and methylenation produced acetal **23**. Cross-metathesis with alkene **24** and hydrogenation of the newly-formed alkene proceeded in 94% yield. Cleavage of the auxiliary and exchange of the 2-trimethylsilylethoxy substituent with phenylsulfinic acid provided the target sulfone **20**. The other key fragment was produced starting from intermediate iodide **25** (prepared using an auxiliary-based diastereoselective aldol reaction). Lithiation, addition to aldehyde **26** (derived from (*S*)-glycidol), and oxidation provided ketone **27**. Subsequent methylenation and deprotection furnished diol **28**. Treatment of **28** with *N*-bromosuccinimide promoted cyclization to bromotetrahydrofuran **29**. Oxidation of the primary alcohol, methyl addition and re-oxidation furnished ketone **30**, which was converted to a silyl enol ether (**31**).

Scheme 6



Fragment coupling was achieved by a Lewis acid-mediated alkylation reaction of **20** and **31** (Scheme 7). Removal of the TBS and benzyl groups was followed by macrolactonization, affording macrocycle **33**. Finally, reductive cleavage of the bromotetrahydrofuran moiety by treatment with Zn unveiled amphidinolide T1 (**1**).

Scheme 7



Summary and Comparison of Amphidinolide T Synthetic Strategies.

Our interest in the amphidinolide T natural products stemmed from the presence of the α-hydroxy ketone and homoallylic ester moieties, both of which are patterns of functional groups that we have prepared using nickel-catalyzed, alkyne-electrophile reductive coupling reactions developed in our laboratory.[6,7,8] From the inception of our investigations, we planned to form the 19-membered macrocycle using an intramolecular variant of our alkyne-aldehyde coupling reaction. Additionally, we intended to utilize an alkyne-epoxide coupling reaction to join key fragments en route to the open-chain alkynal needed for the anticipated macrocyclization. This synthetic strategy represents a novel approach to the T natural products, based on an alternate ring-closing method (Scheme 8).[9] In contrast to all previously reported syntheses of amphidinolide natural products (i.e., T1 or otherwise), this approach features the installation of a stereogenic center during the macrocyclization event.

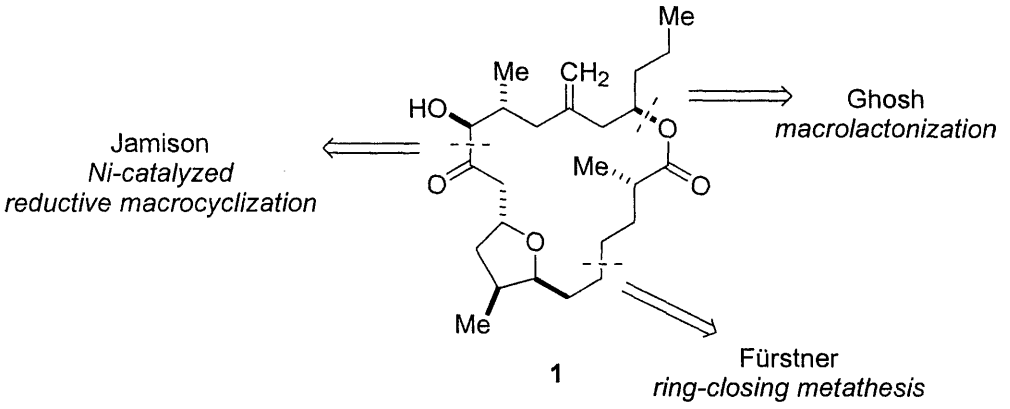
---

[6] (a) Huang, W.-S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221-4223. (b) Colby, E. A.; Jamison, T. F. *J. Org. Chem.* **2003**, *68*, 156-166. (c) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442-3443. (d) Chan, J.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 11514-11515.

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

[8] Several other nickel-catalyzed carbon-carbon bond-forming reactions of alkynes have been developed by Montgomery: (a) Montgomery, J. *Angew. Chem. Int. Ed.* **2004**, *43*, 3890-3908. (b) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698-3699. (c) Lozanov, M.; Montgomery, J. *J. Am. Chem. Soc.* **2002**, *124*, 2106-2107. (d) Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 6098-6099. (e) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065-9066.

Scheme 8. Macrocyclization Bond Disconnections for Reported Syntheses of **1**.



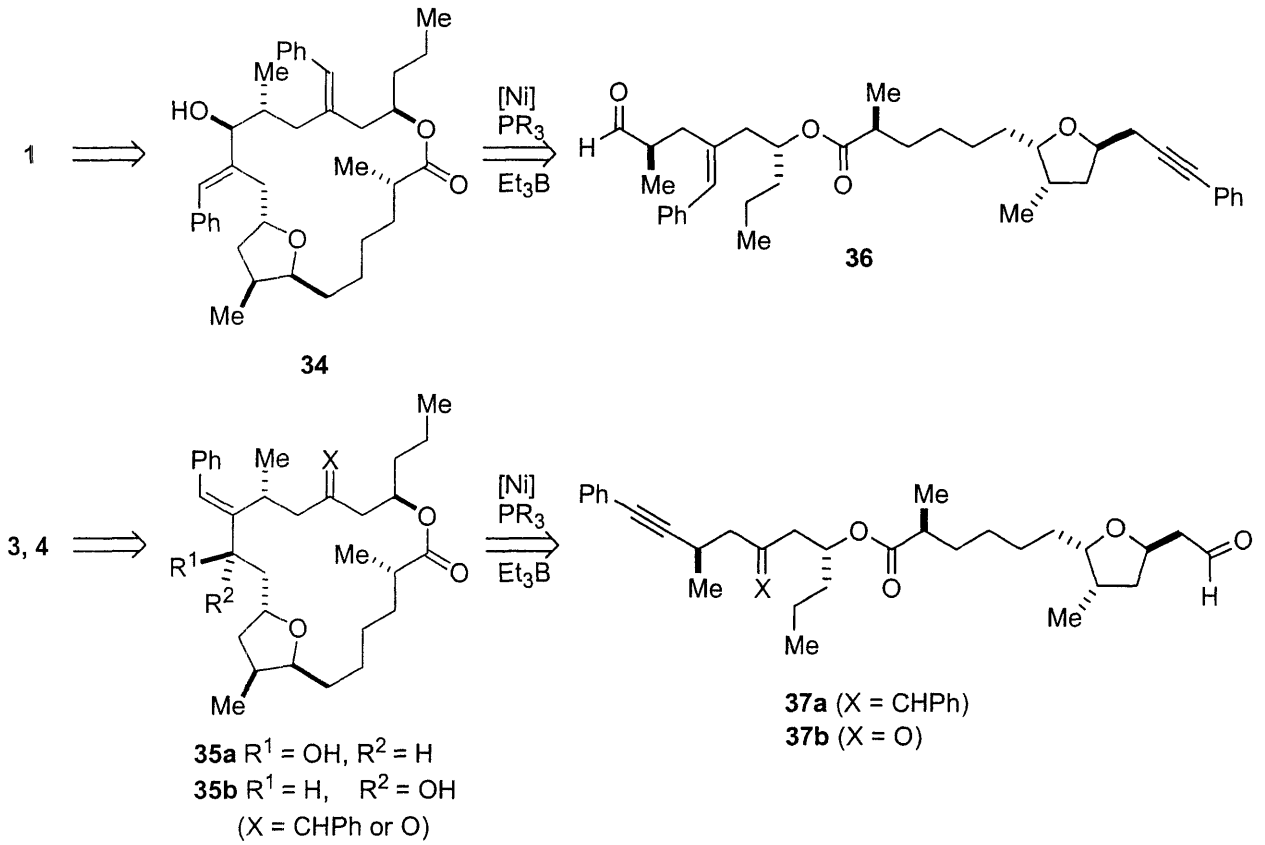
Retrosynthetic Analysis

The foundation of our strategy for the synthesis of both amphidinolide T frameworks (the hydroxy ketone array found in **1** and its reversed positioning in **2**-**5**) is the use of nickel-catalyzed reductive coupling reactions of alkynes, the aforementioned intramolecular alkyne-aldehyde coupling reaction, as well as an intermolecular reductive coupling of an alkyne and epoxide. As shown in Scheme 9, the product of the former, an allylic alcohol, would serve as a latent α-hydroxy ketone moiety.

---

[9] Colby, E. A.; O'Brien, K. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 998-999.

Scheme 9. Intramolecular Nickel-Catalyzed α,ω-Alkynal Reductive Coupling Strategies.



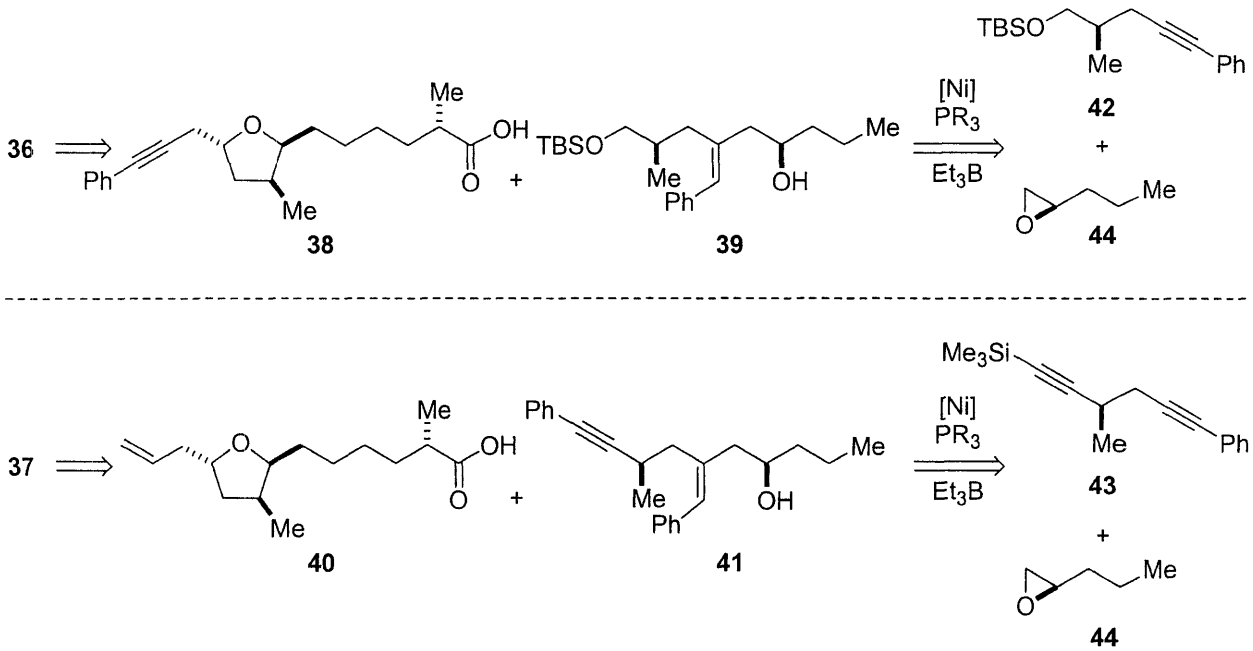
Our plan for installing the hydroxy ketone of **1** and the "reversed" hydroxy ketone of **4** hinged upon analogous nickel-catalyzed reductive cyclizations of alkynals **36** and **37** to form the requisite macrocyclic allylic alcohols **34** and **35**. As noted above, this process would not only close the 19-membered ring, but also concomitantly install a stereogenic center. Control over the configuration of this center would thus be critical to the syntheses.

Although the positions of the alkyne and aldehyde portion of the corresponding alkynal cyclization substrates **36** and **37** are inverted relative to one another, earlier synthetic intermediates nevertheless share many structural and stereochemical features (Scheme 10). The synthesis of amphidinolide T1 necessitates alkynyl acid **38** and homoallylic alcohol **39**, while amphidinolide T4 requires alkenyl acid **40** and hydroxyenyne **41**.

Both homoallylic alcohols (**39** and **41**) were predicted to be available from intermolecular nickel-catalyzed reductive coupling reactions of alkynes and epoxides.[7] Alcohol **39**, for example, would be the product of the reaction between alkyne **42** and (*R*)-*n*-propyloxirane (**44**). While aryl alkynes couple with epoxides with excellent regioselectivity and good yield, in preliminary investigations of alkynylsilanes as coupling partners, the homoallylic alcohol product is not formed under the same conditions, returning only recovered alkyne and epoxide.[10] We planned to exploit this difference in reactivity of alkynes in a group-selective coupling of diyne **43** with epoxide **44** to form a hydroxyenyne, which would be elaborated to **41**.

[10] Molinaro, C.; Jamison, T. F. Unpublished results.

Scheme 10. Intermolecular Alkyne-Epoxide Coupling Strategies.



Results and Discussion

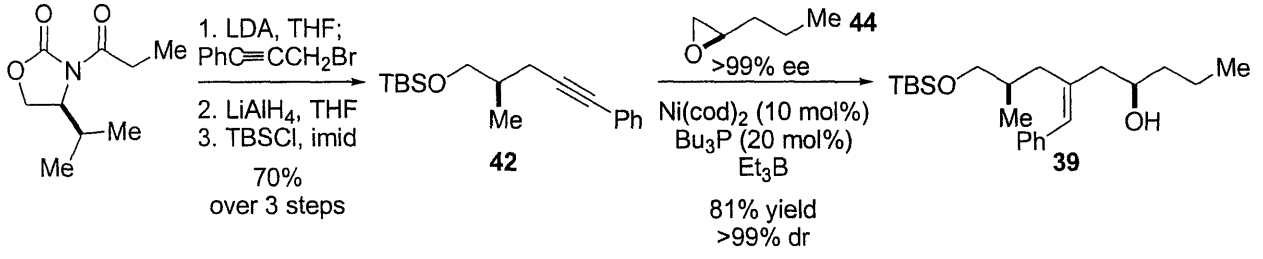
Synthesis of Amphidinolide T1: Construction of C13-C21 Fragment via Intermolecular Alkyne-Epoxide Reductive Coupling.

We commenced our studies by targeting α,ω-alkynal **36** in order to investigate catalytic, stereoselective reductive macrocyclization *en route* to amphidinolide T1 (**1**). Chiral alkyne **42** was synthesized in a three-step sequence (Scheme 11), beginning with alkylation of an Evans oxazolidinone with 3-bromo-1-phenyl-1-propyne.[11] Cleavage of the auxiliary with lithium aluminum hydride followed by TBS protection furnished **42** in 70% yield and 98% ee. The requisite enantiomerically enriched epoxide **44** was easily prepared by way of Jacobsen's

[11] Prepared from commercially available 3-phenyl-2-propyn-1-ol via treatment with MsCl/Et3N, then LiBr as reported by (a) Yi, X.-H.; Meng, Y.; Hua, X.-G.; Li, C.-J. *J. Org. Chem.* **1998**, *63*, 7472-7480. Alkylation: (b) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737-1739. Alkylation with propargyl bromides: (c) Savignac, M.; Durand, J.-O.; Genêt, J.-P. *Tetrahedron: Asymmetry* **1994**, *5*, 717-722.

hydrolytic kinetic resolution (HKR).[12] Nickel-catalyzed union of these fragments proceeded smoothly, delivering homoallylic alcohol **39** in very good yield in >95:5 dr and with >95:5 regioselectivity with respect to both addition across the alkyne and opening of the epoxide. Optimal conditions were found when excess epoxide was employed (700 mol% relative to the alkyne) and the reaction was conducted without additional solvent. As enantiomerically pure **44** is readily available in one step from commercial racemic *n*-propyloxirane via Jacobsen's HKR, this transformation constitutes an efficient fragment coupling reaction providing rapid access to the C13-C21 portion of amphidinolide T1 in just four steps.

Scheme 11.



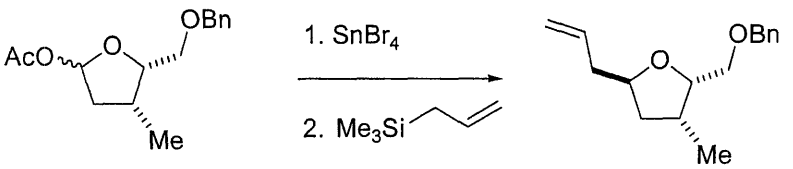
Synthesis of Amphidinolide T1: Assembly of C1-C12 Fragment.

We next turned our attention to the synthesis of alkynyl acid **38**. The key issues to address would be the installation of a highly substituted tetrahydrofuran ring as well as a remote carboxylic acid moiety with a stereogenic center at the α-position. We predicted that the first of these problems could be solved by a Lewis acid-mediated addition of a propargyl equivalent to a five-membered cyclic oxocarbenium ion. This type of reaction has been well-studied by Reißig, who demonstrated that substituted five-membered lactols undergo smooth addition reactions with a variety of nucleophiles when treated with a Lewis acid, presumably through an

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

oxocarbenium ion intermediate.[13] Woerpel and coworkers have also conducted extensive studies regarding the stereochemical course of similar transformations (Scheme 12).[14] It has been established that 2-acetoxy-4,5-*cis*-disubstituted tetrahydrofuran derivatives such as **45** undergo allylation with a very high degree of stereocontrol when treated with allyltrimethylsilane and stannic bromide, delivering products possessing a 2,4,5-*trans-cis* relationship across the tetrahydrofuran ring (**46**, Scheme 12).

Scheme 12. Woerpel's Study of Nucleophilic Addition to Oxocarbenium Ions (ref. 14).



45 **46**, 93 : 7 dr

Encouraged by this stereochemical precedent, we needed to choose an appropriate propargyl nucleophile equivalent to effect the desired addition reaction. As shown in Scheme 13, propargylmagnesium bromide has been reported to react with cyclic oxocarbenium ions derived from **47**, but the propargyl-allenyl selectivity is low (68:32, **48**:**49**).[15] The use of a propargyl aluminum species has been reported as a means to avoid allenyl-derived products in the Lewis acid-mediated reaction of **50**, delivering pure alkyne **51**.[16] Finally, Danheiser's reports of allenylsilanes as effective propargyl nucleophiles in related additions to acyclic acetals, aldehydes and ketones also served as an important starting point for our investigations.[17] Specifically, treatment of allenylsilane **52** with a mixture of acyclic acetal **53** and titanium tetrachloride afforded the corresponding homopropargyl alcohol **54** in 75% yield with complete selectivity for the propargyl product and bond formation at the carbon distal to the silicon

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[13] Schmitt, A.; Reißig, H.-U. *Synlett* **1990**, 40-42.

[14] Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208-12209.

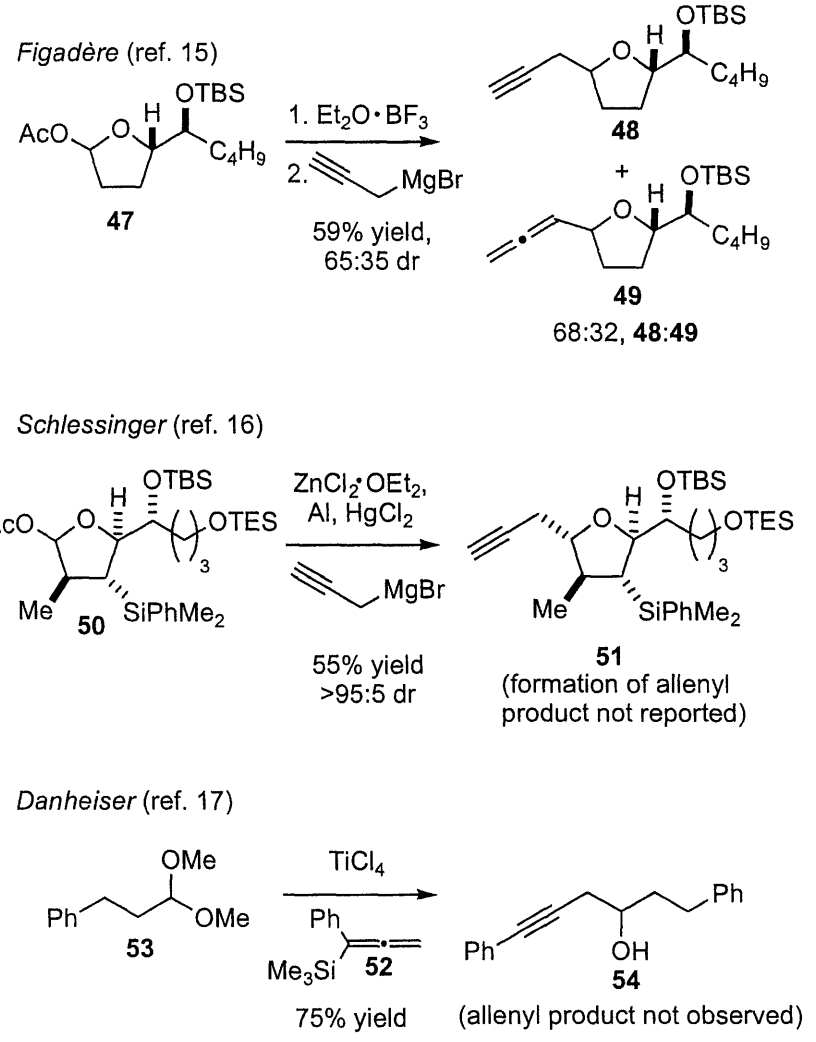
[15] Franck, X.; Hocquemiller, R.; Figadère, B. *Chem. Commun.* **2002**, 160-161.

[16] Dankwardt, S. M.; Dankwardt, J. W.; Schlessinger, R. H. *Tetrahedron Lett.* **1998**, *39*, 4975-4978.

[17] Danheiser, R. L.; Carini, D. J. *J. Org. Chem.* **1980**, *45*, 3925-3927.

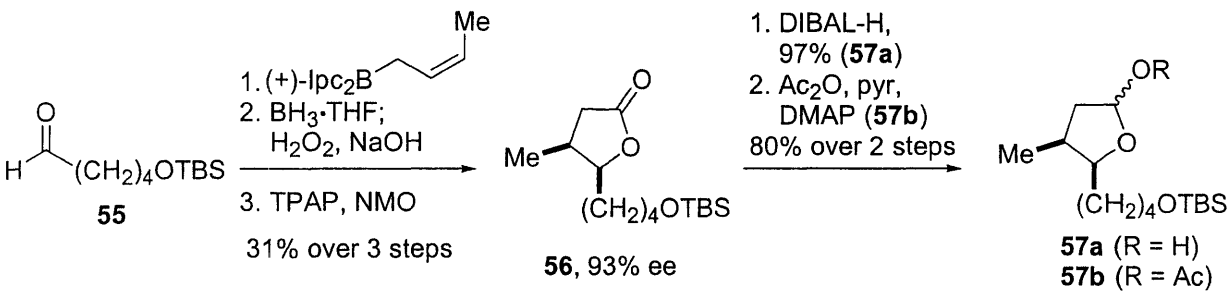
substituent. Prompted by the high reactivity of the allenylsilanes toward oxocarbenium ions, we therefore began our studies using a *cyclic* oxocarbenium ion and trimethyl(1-phenyl-1,2-propadienyl)silane (**52**).

Scheme 13. Lewis Acid-Mediated Propargylation Precedents.



Synthesis of the target oxocarbenium ion precursors began with an enantioselective addition of a chiral (*Z*)-crotylborane developed by Brown[18] to aldehyde **55**,[19] ultimately setting the C7-C8 syn relationship (Scheme 14). Hydroboration-oxidation of the crotylation product furnished a diol which was oxidatively cyclized, delivering lactone **56** in good yield over the three step sequence.[20] Reduction of the lactone furnished lactol **57a** (2.3-2.6:1 dr), while direct acetate protection of this reduction product provided acetoxy acetal **57b** (2.3-2.6:1 dr). Allenylsilane **52** was prepared according to Vermeer.[21]

Scheme 14.



With lactol **57a**, acetal **57b**, and allenylsilane **52** in hand, an investigation of propargylation conditions was conducted. Initial experiments were conducted following Danheiser's conditions for allenylsilane additions using acetal **57b** as the oxocarbenium ion precursor. Treatment of **57b** with $TiCl_4$ at −78 °C followed by addition of allenylsilane **52** gave no desired product. Disappointingly, variation of reaction temperature and time failed to effect propargylation and resulted only in decomposition of the starting acetal. The reaction conditions were consequently modified to emulate Woerpel's method; the acetal and allenylsilane were

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[18] Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919-5923.

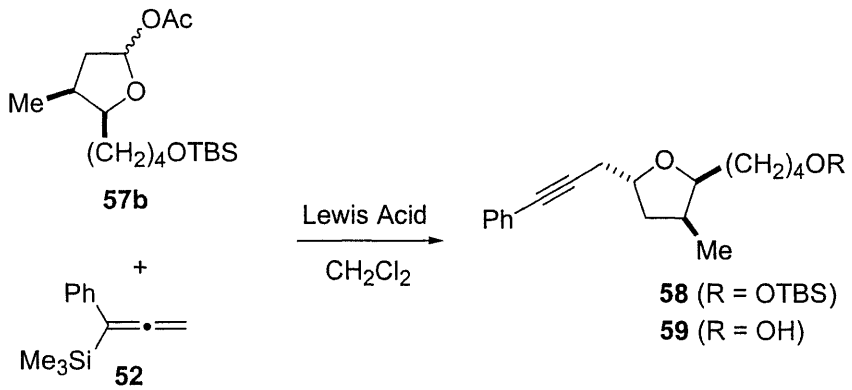
[19] Marshall, J. A.; Shearer, B. G.; Crooks, S. L. *J. Org. Chem.* **1987**, *52*, 1236-1245.

[20] This sequence of functional group manipulations was performed as reported in reference 14.

[21] Westmijze, H.; Vermeer, P. *Synthesis* **1979**, 390-392.

premixed and cooled to −78 °C, Lewis acid was added and the mixture was warmed to ambient temperature.

Table 2. Nucleophilic Addition of Allenylsilane **52** to Acetal **57b**.[a]



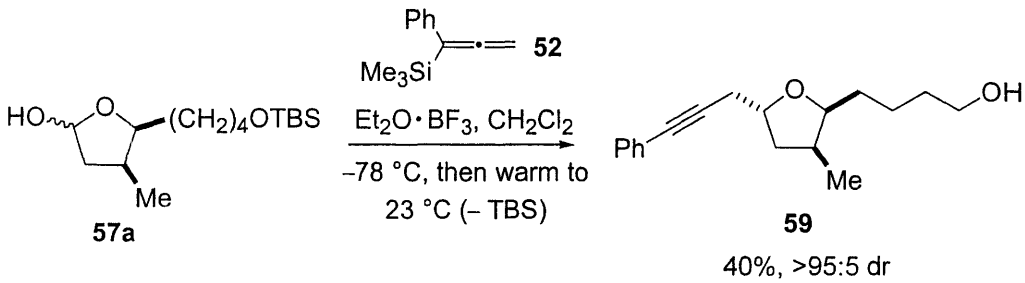
Entry	Lewis Acid	[**57b**] M	temperature	Product(s)[b]
1	$TiCl_4$	0.05	− 78 °C to 23 °C	**58** not observed
2	$SnBr_4$	0.05	− 78 °C to 23 °C	**58** < 5%[c]
3	TBDMS-OTf	0.05	− 78 °C to 23 °C	**58** 17%[d] + **59** 11%[d]
4	$BF_3{\cdot}OEt_2$	0.05	− 78 °C to 23 °C	**59** 13%[d]
5	$BF_3{\cdot}OEt_2$	0.50	− 78 °C to 23 °C	**59** 14%[d]
6	$BF_3{\cdot}OEt_2$	0.05	− 78 °C to 0 °C	**58** 13%[d]
7	$BF_3{\cdot}OEt_2$	0.25	− 78 °C	**58** not observed

a) 400 mol% **52** and 100 mol% **57b** were combined in CH_2Cl_2 and cooled to -78 °C before addition of 120 mol% Lewis acid. b) Characterized by ^1H NMR, ^{13}C NMR, and nOe experiments. c) Observed by ^1H NMR. d) Isolated yield.

We were pleased to find that **57b** did indeed undergo the desired propargylation reaction when treated with Lewis acids other than $TiCl_4$. As shown in Table 2, stannic bromide afforded traces of the propargylated TBS-ether **58** while boron trifluoride diethyl etherate promoted nucleophilic addition as well as removal of the TBS protective group, giving free alcohol **59**. Utilization of *t*-butyldimethylsilyltrifluoromethane sulfonate (TBSOTf) also caused addition and, counterintuitively, protiodesilylation, but the latter process was incomplete, as both **58** and **59**

were isolated. In an effort to optimize this process with $BF_3{\cdot}OEt_2$, both concentration and temperature parameters were varied. Surprisingly, increasing the concentration by a factor of ten did not influence the outcome of the reaction (entries 4 and 5). Reducing the final temperature to 0 °C prevented loss of TBS (entry 6) but did not enhance the yield of **58**, while further reduction of the temperature to -78 °C (entry 7) completely suppressed propargylation. We next explored the character of the oxocarbenium ion precursor, replacing **57b** with lactol **57a** (more closely following Reißig's conditions). Gratifyingly, the lactol proved to be a much better substrate, providing the desired alcohol **59** in 41% yield and in >95:5 dr when treated with boron trifluoride diethyl etherate and **52** (Scheme 15).

Scheme 15. Allenylsilane Addition to Lactol **57a**.



The use of different Lewis acids, concentration, temperature, and addition rate of Lewis acid were all parameters investigated in an endeavor to improve the yield of the reaction, but no such efforts were fruitful in this regard. Accordingly, we concentrated on the nucleophilic component, aiming to increase the nucleophilicity[22] of the allene toward the oxocarbenium ion by using allenyl*stannane* **60**[23] in place of allenyl*silane* **52**. To our satisfaction, the addition

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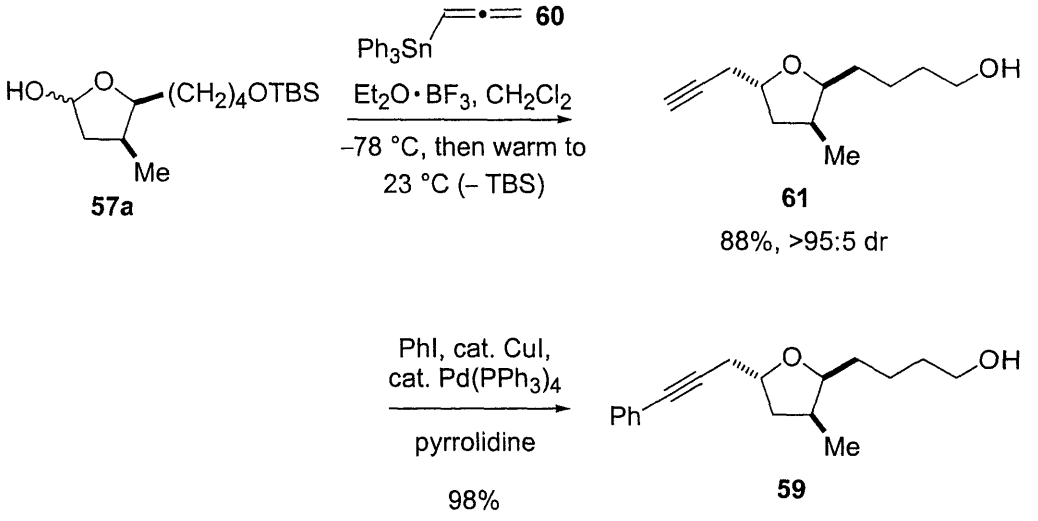
[22] Allylstannanes are reported to be much more nucleophilic compared to corresponding allylsilanes: (a) Denmark, S. E.; Weber, E. J. *J. Am. Chem. Soc.* **1984**, *106*, 7970-7971. (b) Yamamoto, Y.; Nishii, S.; Yamada, J. *J. Am. Chem. Soc.* **1986**, *108*, 7116-7117. (c) Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.* **1990**, *55*, 6116-6121. Allenylstannanes have also been shown to add to thioacetals under Lewis acidic conditions: (d) Sato, T.; Okura, S.; Otera, J. Nozaki, H. *Tetrahedron Lett.* **1987**, *28*, 6299-6302. (e) Takeda, T.; Ohshima, H.; Inoue, M.; Togo, A.; Fujiwara, T. *Chem. Lett.* **1987**, 1345-1348.

[23] Reported to propargylate enones in a 1,4-addition mode under Lewis acidic conditions: Haruta, J.; Nishi, K.; Matsuda, S.; Akai, S.; Tamura, Y.; Kita, Y. *J. Org. Chem.* **1990**, *55*, 4853-4859.

proceeded very smoothly with concomitant complete protiodesilylation, delivering terminal alkyne **61** in excellent yield and diastereoselectivity (Scheme 16). Subsequent Sonogashira coupling with iodobenzene furnished target alcohol **59** in near quantitative yield, constituting a vast improvement over the one-step propargylation with allenylsilane **52** that we had reported previously.[9]

Scheme 16. Allenylstannane Addition to Lactol **57a**.

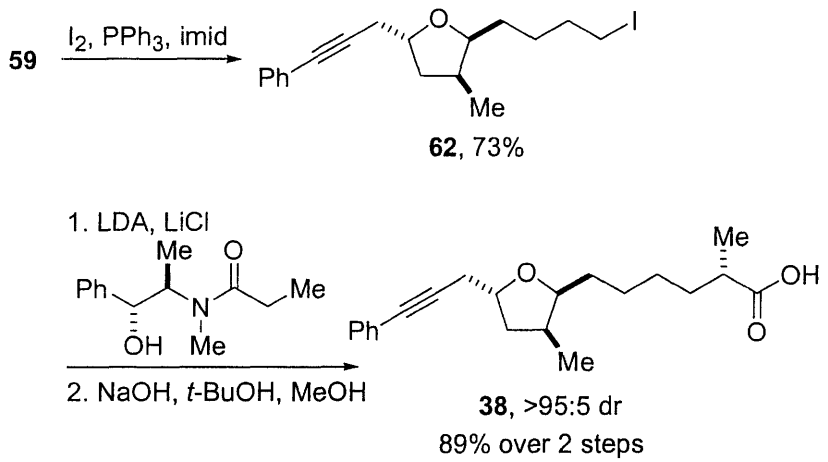


With the installation of the substituted tetrahydrofuran ring achieved by the allenylstannane addition, introduction of the remaining stereogenic center of carboxylic acid **38** was the next challenge to address. This was accomplished using an auxiliary-controlled, diastereoselective alkylation reaction. The pseudoephedrine-based method developed by Myers was selected as it displays very high diastereoselectivity, allows for use of the iodide as the limiting reagent, and is well-suited for the alkylation of unactivated primary alkyl electrophiles.[24] Alcohol **59** was converted to alkyl iodide **62** which was an effective electrophile for the desired alkylation reaction, proceeding in near quantitative yield and in excellent diastereoselectivity

[24] Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am Chem. Soc.* **1997**, *119*, 6496-6511.

(Scheme 17). The alkylated amide underwent base-promoted hydrolysis to furnish alkynyl acid **38** in excellent yield and in >95:5 dr.

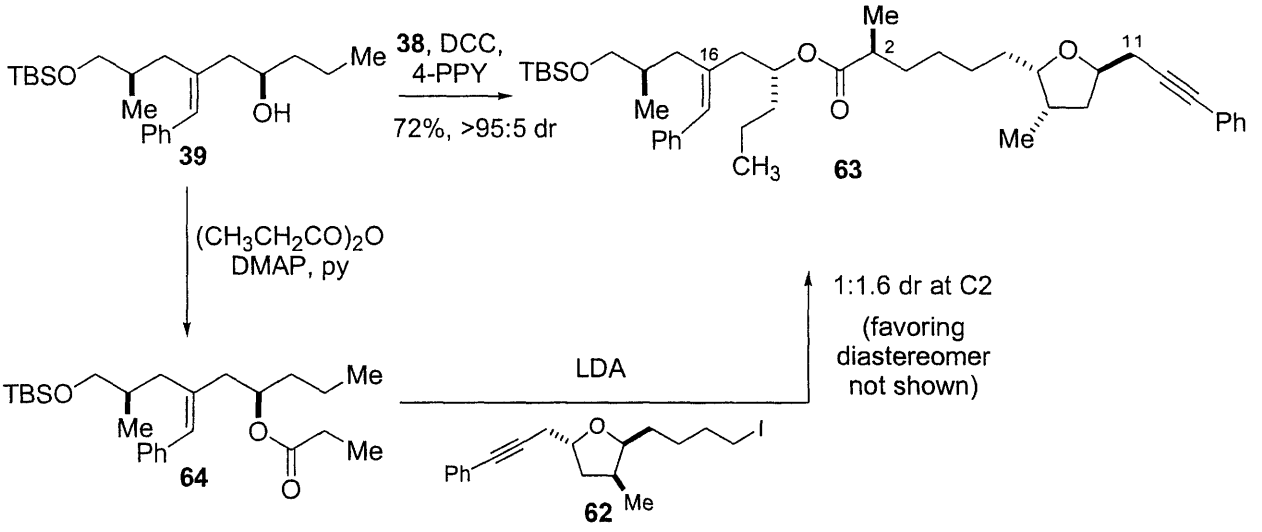
Scheme 17. Synthesis of Alkynyl Acid **38**.



Synthesis of Amphidinolide T1: Fragment Coupling and Reductive Macrocyclization.

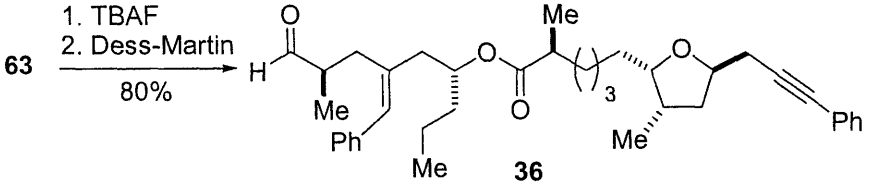
Enantiomerically pure homoallylic alcohol **39** and enantiomerically pure alkynyl acid **38** were joined in a DCC-mediated ester formation, affording **63** in 72% yield (Scheme 18). While this C-O bond formation was certainly satisfactory, we investigated an alternative, stereoselective fragment coupling via alkylation of an enolate derived from the propionate ester of alcohol **39**. This approach would indeed save one step relative to the route described above, but it would nevertheless have to surpass the very high efficiency and complete stereocontrol provided by the Myers' asymmetric alkylation method. Treatment of ester **64** with LDA and iodide **62** did indeed afford **63** (converging with the original route), but this process was nearly nonselective (1.6:1 dr, favoring the undesired diastereomer). Clearly, therefore, this strategy modification did not result in any improvement in the preparation of ester **63**.

Scheme 18. Contrasting Fragment Coupling Strategies.



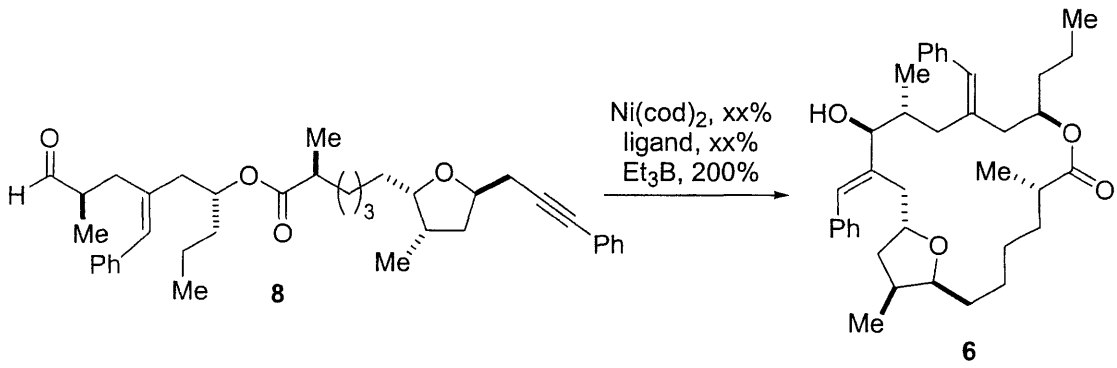
After two functional group manipulations (TBS removal with TBAF and oxidation with the Dess-Martin periodinane reagent), we were poised to investigate conditions to form the 19-membered ring via an intramolecular alkyne-aldehyde reductive coupling reaction (Scheme 19). We began our studies with an achiral catalyst consisting of $Ni(cod)_2$ and tributylphosphine (see Table 3), which had been very successful in other alkyne-aldehyde intramolecular reductive coupling reactions in our group.[25] In these cases, 14- and 15-membered rings containing three (*E*)-trisubstituted double bonds were successfully formed via reductive macrocyclization of alkynals. The alkynal needed for the T1 synthesis (**36**) differs from these previously studied substrates in that it contains only one trisubstituted double bond (probably more flexible) and would form a 19-membered ring upon cyclization.

Scheme 19



[25] Chan, J.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 10682-10691.

Table 3. Summary of Macrocyclization Optimization Experiments.



entry	ligand	mol% $Ni(cod)_2$/ligand	solvent	conc.	temp.	product(s)[a]
1	PBu_3	10/20	toluene	0.05 M	23 °C	**8** only
2	PBu_3	10/20	toluene	0.10 M	23 °C	**8** only
3	(*R*)-NMDPP	10/20	EtOAc	0.02 M	23 °C	**8** only
4	(*R*)-NMDPP	10/20	EtOAc	0.06 M	23 °C	**8** only
5	(*R*)-NMDPP	10/20	EtOAc	0.12 M	23 °C	**8** only
6	(*S*)-FcP(Ph)Me	10/20	EtOAc	0.10 M	23 °C	**8** only
7	(*R*)-FcP(Ph)(*o*-anisyl)	10/20	EtOAc	0.10 M	23 °C	**8** and <5% **6**
8	PBu_3	10/20	toluene	0.10 M	60 °C	**6**, 30% >10:1 dr
9	(*R*)-NMDPP	10/20	EtOAc	0.08 M	55 °C	decomposition
10	PBu_3	20/40	toluene	0.10 M	60 °C	**6**, 44% >10:1 dr

[a] When **8** was observed to be the only product by TLC and ^1H NMR, it could be recovered in 60-80% yield (indicated by "**8** only"). Yield and dr were determined by ^1H NMR of purified product.

A dilute solution of alkynal **36** (0.05 M in toluene), 10 mol% $Ni(cod)_2$, 20 mol% phosphine and triethylborane was stirred at ambient temperature, but no reaction was observed (only **36** was isolated, entry 1). Screening of phosphine ligands and concentrations was conducted, but the desired cyclization was not observed in any case (entries 2-7). We next explored the use of elevated temperature and were pleased to find that tributylphosphine/$Ni(cod)_2$

promoted cyclization when the reaction mixture was heated to 60 °C, albeit in low yield (25-30%, entry 8). Nevertheless, the stereoselectivity of the cyclization was outstanding; macrocyclic allylic alcohol **34** was isolated in greater than 10:1 diastereoselectivity possessing the (*S*)-carbinol configuration, corresponding to that found in the natural product, amphidinolide T1 (**1**).[26] Further optimization efforts revealed that an NMDPP-derived catalyst was unstable toward heating (entry 9). Returning to tributylphosphine as a ligand, we were pleased to find that higher catalyst loading improved the yield; the best conditions proved to be a 20 mol% $Ni(cod)_2$/40 mol% tributylphosphine combination, giving **34** in 44% yield and in >10:1 dr (entry 10).[27]

Two features of the macrocyclization are noteworthy. First, the complete diastereocontrol observed in the reductive macrocyclization was quite surprising as *inter*molecular couplings of aldehyde **65** and alkyne **58** were virtually nonselective (Scheme 20), affording allylic alcohol **66** in 1.5:1 dr. Moreover, we observed that the sense of induction matches the Felkin-Anh product[28] of nucleophilic addition to chiral aldehydes, and we therefore hypothesized that the configuration at C14 of the alkynal is largely responsible for the sense of stereoinduction in the intramolecular coupling (macrocyclization). Second, the *intra*molecular alkyne-aldehyde reductive coupling reaction used in Table 3 shortens the overall synthesis by several steps relative to an intermolecular coupling strategy that would require protection of both alkynyl acid **38** and alcohol **39** (and subsequent deprotection (prior to macrolactonization)).

Scheme 20. Intermolecular Reductive Coupling Strategy.

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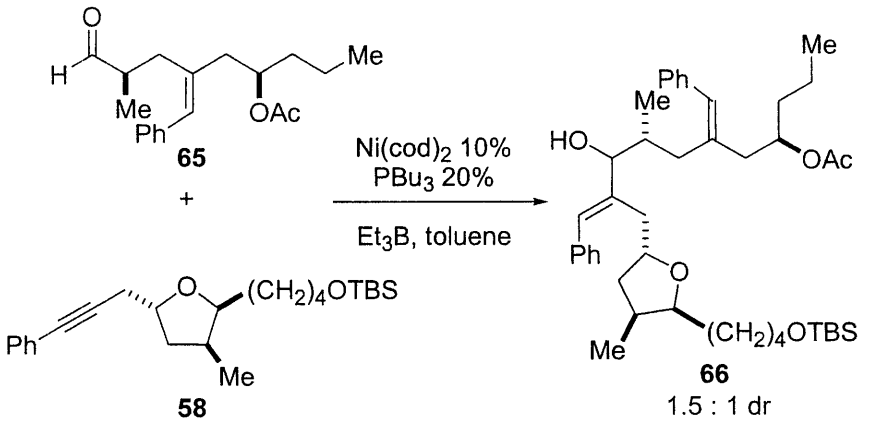
[26] Determined by Mosher ester analysis and ultimate conversion to **1**.

[27] Remaining material appeared to be a number of decomposition products of the alkynal that could not be identified. The dr was measured by ^{1}H NMR on purified material as crude NMR data was distorted by the presence of nickel. None of the side products were identified to be the minor diastereomer; in subsequent cyclizations of epimeric alkynals, the minor diastereomer of the allylic alcohol product co-eluted with the major diastereomer and could be detected by NMR (vide supra).

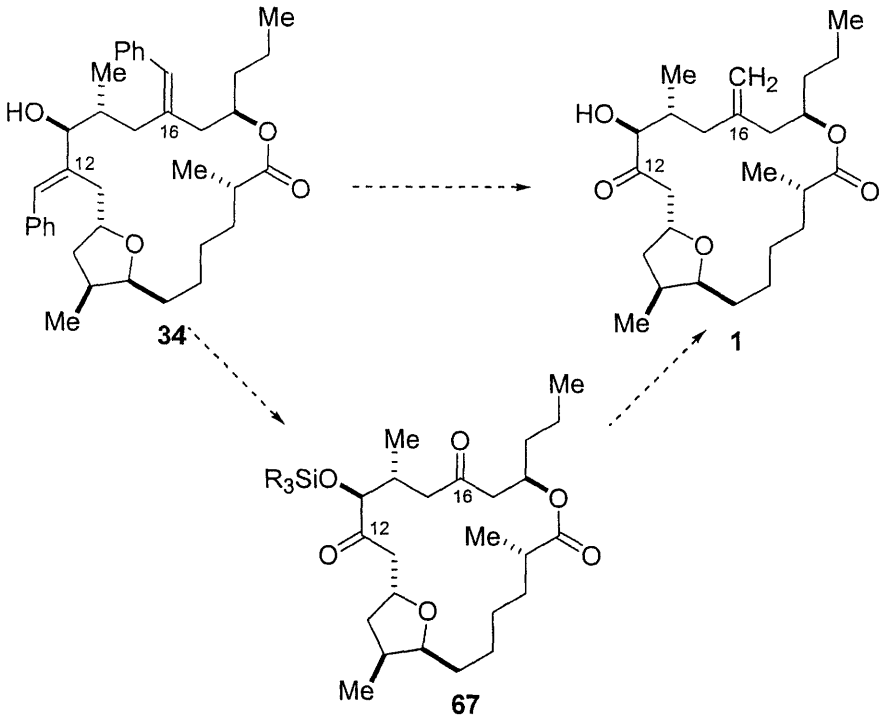
[28] (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 2199-2204. (b) Chérest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, *18*, 2204-2208. (c) Anh, N. T.; Eisenstein, O. *Nouv. J. Chimie.* **1977**, *1*, 61-70. (d) Anh, N. T. *Topics in Current Chemistry* **1980**, *88*, 145-162.



Synthesis of Amphidinolide T1: Endgame.

Macrocyclization of alkynal **36** overcame a significant hurdle in the synthesis of **1**; all of the stereogenic centers of **1** had been set, and all of the carbon atoms within the ring framework of **1** were present in **34**. The remaining challenge was differentiation of the two benzylidene groups at C12 and C16. Specifically, oxidative cleavage of the C12 benzylidene to a ketone and conversion of the C16 benzylidene to an *exo*-methylidene group were required (Scheme 21). We decided to exploit the difference in steric congestion around the carbon atoms at issue and accordingly protected the allylic hydroxyl group at C13 with a silyl group of an appropriate size. Subsequent global ozonolysis would thus afford a diketone with very different environments around the two carbonyl groups. We predicted that the resultant C16 carbonyl (flanked by two CH_2 groups) would be more susceptible to nucleophilic attack than the C12 carbonyl (flanked by a bulky silyl ether and a tetrahydrofuran β to C12), and treatment with a methylenating reagent would lead to the functional group pattern present in **1**.

Scheme 21. Strategy for C12-C16 Differentiation.



Moving forward with this plan, we chose to protect alcohol **34** with a TBS group, smoothly effected by treatment of **34** with TBSOTf and 2,6-lutidine. Ozonolysis indeed produced diketone **67** in moderate yield (43%). As we set our sights upon selective methylenation, we took into account that both carbonyl groups possessed β-oxygen substituents that might act as leaving groups under strongly basic conditions. We first investigated the Oshima reagent (Zn, CH_2Br_2, $TiCl_4$),[29] as well as the Lombardo-modified reagent "low-temperature aged",[30] but in both cases only diketone was recovered. Standard Takai conditions (Zn, CH_2I_2, $TiCl_4$)[31] were also unsuccessful, but replacement of $TiCl_4$ by $ZrCl_4$ and the addition of lead (II) chloride[32] resulted in clean methylenation at the C16 carbonyl furnishing the desired

---

[29] Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, *19*, 2417-2420.

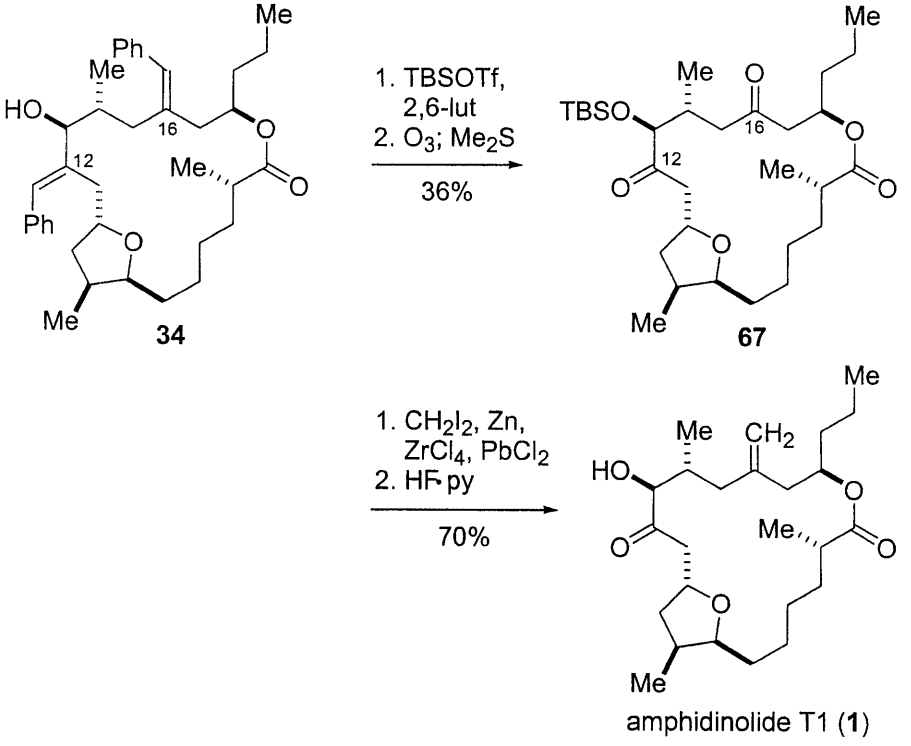
[30] Lombardo, L. *Org. Syn.* **1987**, *65*, 81.

[31] Hibino, J.; Okazoe, T.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5579-5580.

[32] Lead effects: (a) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668-2670. Zirconium alkylidene reagents: (b) Hartner, F. W., Jr.; Schwartz, J.; Clift, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 640-641. (c) Tucker, C. E.; Knochel, P. *J. Am. Chem. Soc.* **1991**, *113*, 9888-9890.

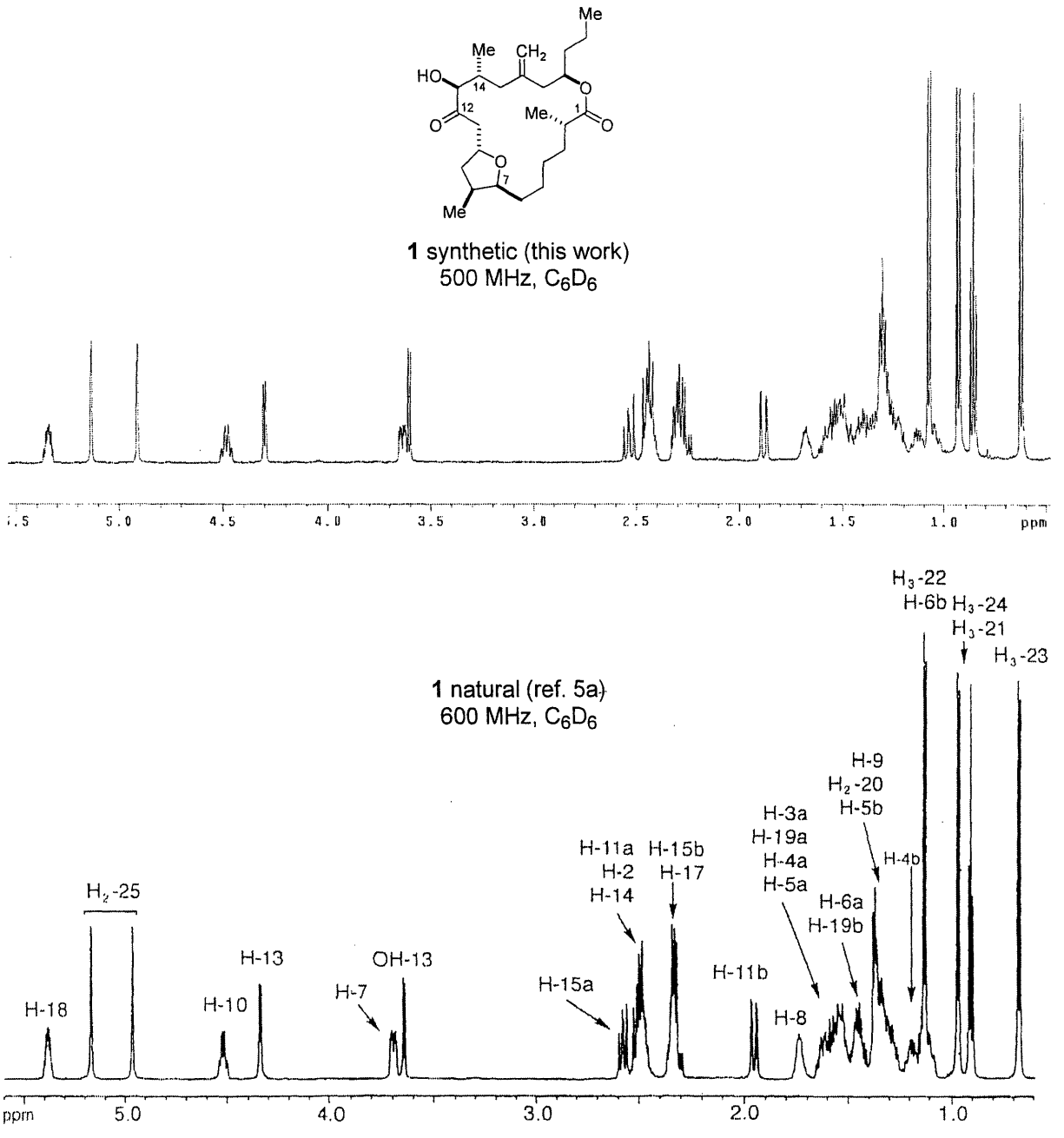
monoketone in 65-75% yield.[33] Finally, treatment of this product with HF-pyridine promoted clean conversion (>90% yield) to amphidinolide T1 (Scheme 22), whose spectroscopic, spectrometric, and physical properties matched those reported for natural product **1** (Figure 1).

Scheme 22. Synthesis of **1** via Selective Methylenation.



[33] Work in our laboratory has shown that this system is effective for the methylenation of sterically hindered ketones. Jeso, V.; Jamison, T. F. Unpublished results.

Figure 1. Comparison of ^{1}H NMR spectra of synthetic and natural **1**.



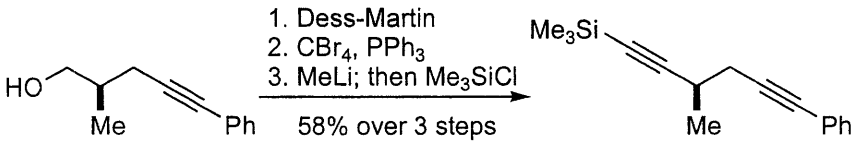
Synthesis of Amphidinolide T4 Framework.

Completion of the total synthesis of **1** indicated that our strategy of reductive macrocyclization was indeed a viable route to amphidinolide T1. Nevertheless, a critical issue in using this strategy for the synthesis of other members (T2-5) was the reversed hydroxy ketone pattern at C12 and C13 (see Chart 2, p. 143). In our next synthetic undertaking, we set out to address this issue by studying the reductive cyclization of alkynal **37**, and whether it would exert a high degree of substrate diastereocontrol in a cyclization using an achiral catalyst system as it contains β-branching with respect to the aldehyde instead of α-branching (Scheme 11).

Synthesis of Amphidinolide T4 Framework: Construction of C13-C21 Fragment via Site-Selective, Intermolecular Diyne-Epoxide Reductive Coupling.

Synthesis of the requisite alkynal **37** began with an investigation of the viability of a site-selective alkyne-epoxide reductive coupling of diyne **43**. Alcohol **68** (previously synthesized in the T1 synthesis, Scheme 11) was oxidized to the aldehyde, converted to the dibromo olefin and finally exposed to methyllithium and chlorotrimethylsilane to arrive at diyne **43** (Scheme 23).

Scheme 23.

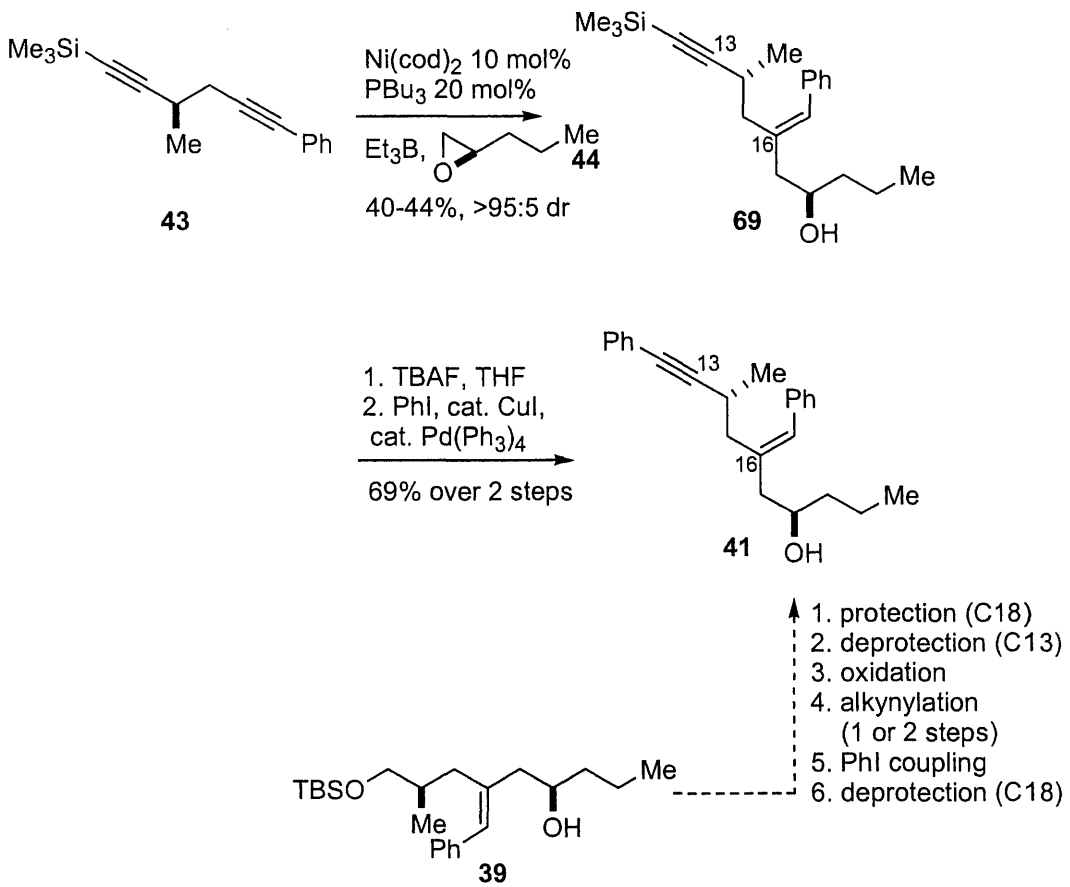


68 **43**

We found that **43** did indeed undergo coupling with (*R*)-propyloxirane to give the desired hydroxyenyne **69** with >95:5 regioselectivity and >95:5 diastereoselectivity (Scheme 24). While the crude product mixture was contaminated with products of polymerization of the alkyne, there was no evidence of epoxide coupling at the alkynylsilane. Coupling product **69** was converted to the target homoallylic alcohol **41** by treatment with TBAF and subsequent Sonogashira coupling

with iodobenzene. The chemoselective epoxide coupling streamlined the synthesis of the C13-C21 fragment by directly introducing the necessary alkyne at C13 rather than starting from T1 coupling product **39** and elaborating to the alkyne. The former route saves several steps, thus compensating for the moderate yield of the diyne coupling reaction.

Scheme 24. Site-Selective Diyne-Epoxide Reductive Coupling.

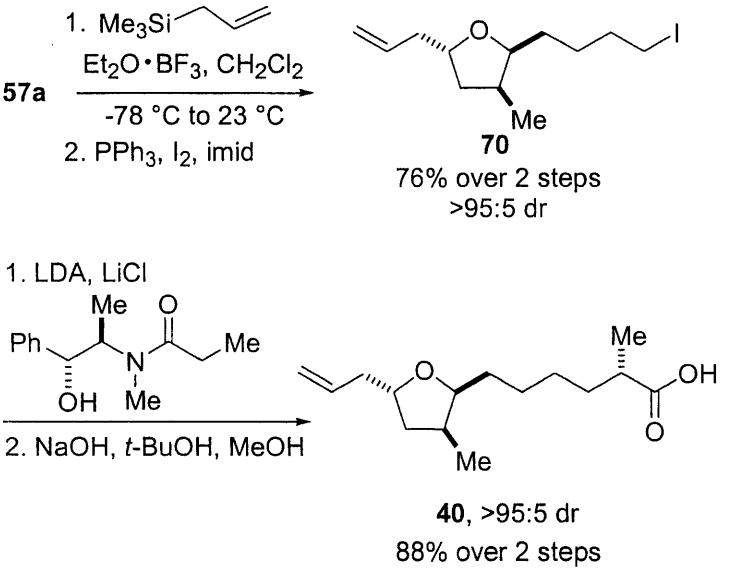


Synthesis of Amphidinolide T4 Framework: Construction of C1-C12 Alkenyl Acid, Fragment Coupling and Alkynal Synthesis.

Alkenyl acid **40** was targeted next to advance the investigation of the T3/T4 synthesis. This acid was synthesized in a route similar to alkynyl acid **38** (Scheme 25). Lewis acid-mediated allylation of lactol **57a** by allyltrimethylsilane proceeded in excellent yield to deliver

the primary alcohol, which underwent smooth iodination to afford iodide **70**. The iodide was incorporated into an asymmetric Myers' alkylation-hydrolysis sequence similar to that used in the T1 synthesis affording acid **40** in 88% yield over two steps and in >95:5 dr.

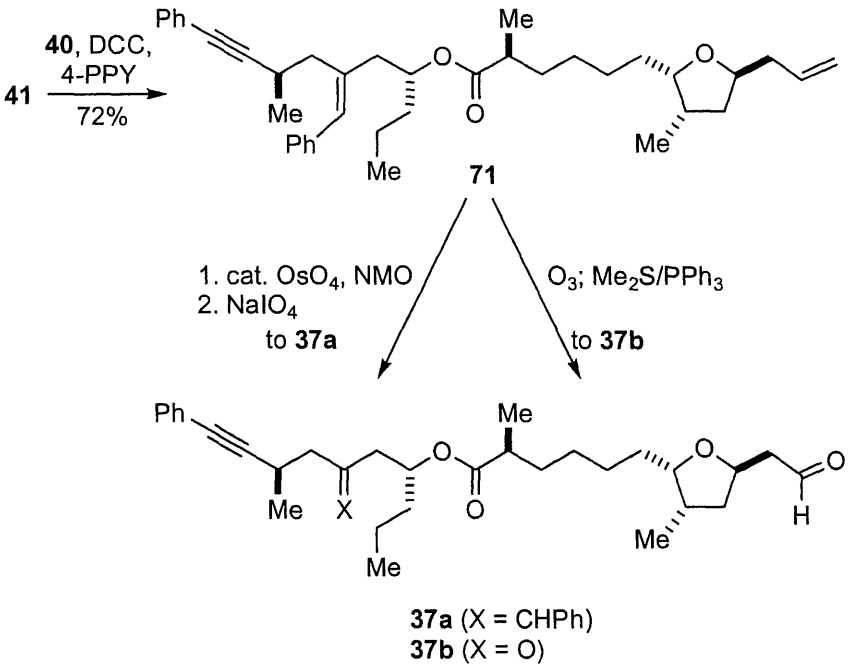
Scheme 25. Synthesis of Alkenyl Acid **40**.



Fragment coupling was carried out by way of a DCC-mediated esterification, affording **71** in good yield (Scheme 26). As we sought to study ring-closing reductive cyclizations, we examined methods of selective, oxidative cleavage of the terminal alkene in **71**, which would afford alkynal **37a**. This target compound (with the benzylidene group at C16 intact) was the logical starting point for the "reversed" reductive coupling strategy as the T1 alkynal also possessed a benzylidene at this position and underwent cyclization successfully. We found that **37a** could indeed be prepared by a dihydroxylation-periodate cleavage sequence, but over-oxidation produced **37b**, and moreover, the overall mass recovery of the process was low (< 20% yield on 10 mg scale, 3:2 ratio of **37a** to **37b**). Given these difficulties, we reconsidered our tactics and realized that a ketone might possibly be tolerated at C16 as ketones are much less reactive than aldehydes under our nickel-catalyzed reductive coupling conditions and, in most

cases, inert.[34] This alternative oxidation was accomplished via double ozonolysis of **71**, cleaving both alkenes while leaving the alkyne intact to deliver **37b** in very good yield.[35]

Scheme 26. Routes to Alkynals **37a-b**.



[34] Many alkyne-aldehyde couplings may be conducted in acetone without a decrease in yield. Nevertheless, a notable exception exists, that being an intramolecular, Ni-catalyzed alkyne-ketone coupling observed during studies directed toward the synthesis of terpestacin, reference 25.

[35] Ozonolysis was followed by exposure to dimethyl sulfide affording **37b** and another product, determined to be the ozonide at terminal position. Treatment of the ozonide with triphenylphosphine promoted clean conversion to **37b** giving an 80% combined yield of **37b**. Direct reductive work-up with triphenylphosphine resulted in much lower yields. See experimental section for more detail. While most ozonolysis reactions are safely conducted using MeOH as a cosolvent, the use of MeOH promoted the formation of undesired methyl acetal and hemiacetal products.

Synthesis of Amphidinolide T4 Framework: Reductive Macrocyclization and Elaboration to T4.

Both **37a** and **37b** were subjected to the nickel-catalyzed reductive coupling conditions found to promote macrocyclization in our earlier synthesis of **1**. Upon addition to a warm solution of $Ni(cod)_2$, tributylphosphine and triethylborane, **37a** and **37b** underwent reductive cyclization to afford the desired macrocyclic allylic alcohols (Scheme 27). In both cases, the diastereoselectivity was very high (>10:1 dr) and in the case of **37b**, the yield was 58%. TBS protection and ozonolysis of the two alcohols led to diketone **72** which was selectively methylenated and deprotected with HF-pyridine. The ^1H NMR data of the final product matched that of amphidinolide T4 (**4**) and differed significantly from its C12 diastereomer T3 (**3**), revealing the stereochemical outcome of the reductive cyclization. A comparison of the diagnostic region of the ^1H NMR spectra of natural **3**, natural **4**, and synthetic **4** is shown in Figure 2.

Scheme 27. Reductive Macrocyclizations of **37a-b** and Synthesis of **4**.

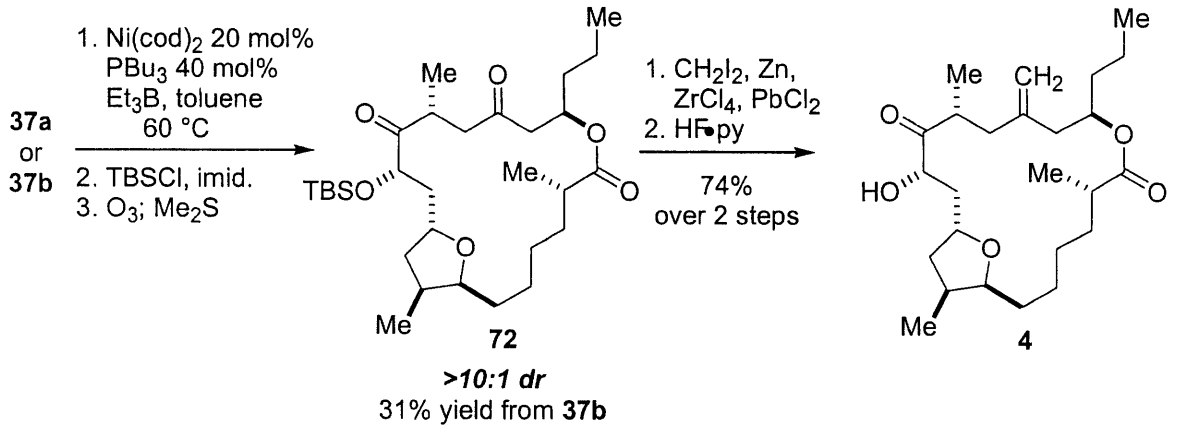
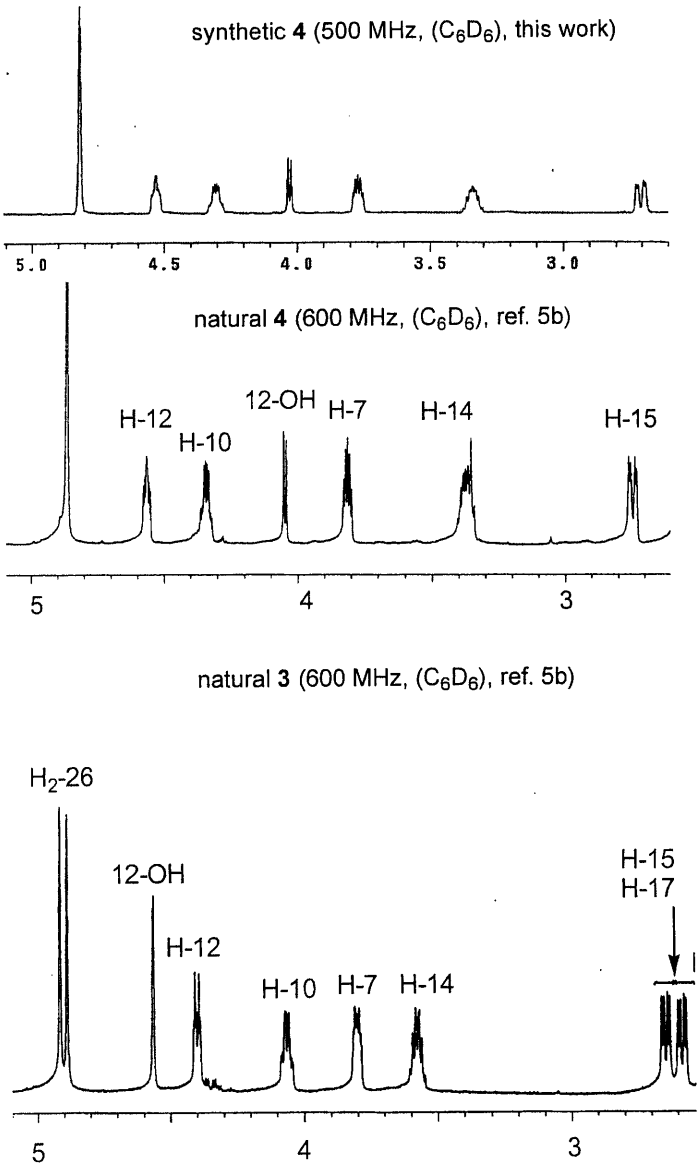
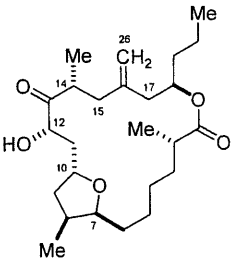
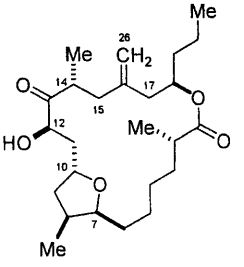


Figure 2. Diagnostic Region of the ^{1}H NMR spectra of **3** and **4**.





amphidinolide T4 (**4**)

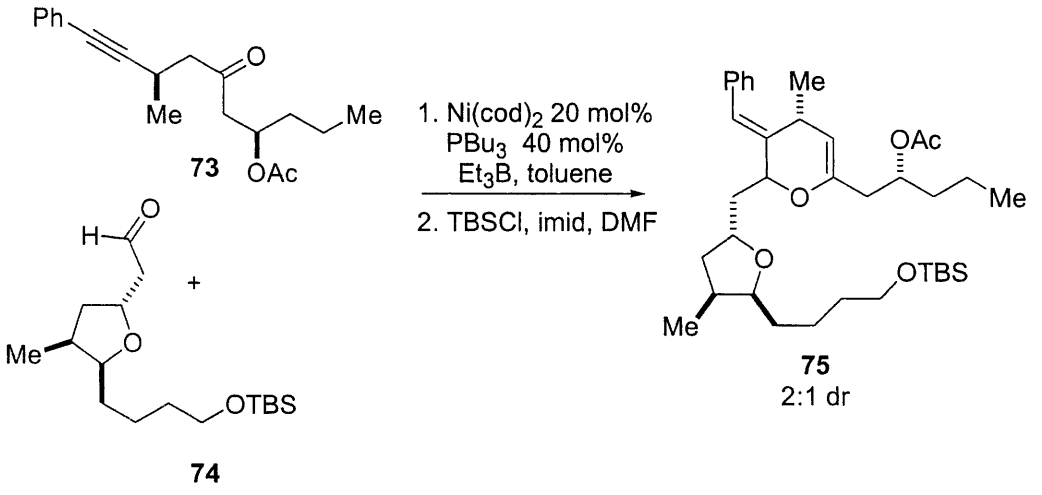


amphidinolide T3 (**3**)

Synthesis of Amphidinolide T4 Framework: Comparison of Inter- and Intramolecular Reductive Coupling Strategies.

As we had done in the T1 series (Scheme 20), we sought to compare the corresponding intermolecular alkyne-aldehyde reductive coupling for the **3-4** framework. Interestingly, nickel-catalyzed coupling of ketoalkyne **73** and tetrahydrofuranyl aldehyde **74** resulted in a mixture of products that have been tentatively assigned as various elimination products and the intramolecular hemiketal of the desired allylic alcohol. In attempt to identify reaction products with certainty, the coupling was repeated with immediate silyl protection of the crude product mixture. As shown in Scheme 28, the isolated product was dihydropyran **75** as a 2:1 mixture of diastereomers, confirming our hypothesis that the coupling product was undergoing hemiketal formation and dehydration upon treatment with TBSCl. Not only did this result once again point to a strong conformational bias in the cyclization process that does not exist in the intermolecular process, but also that the macrocycle prevents formation of undesired byproducts such as dihydropyrans related to **75**.

Scheme 28. Intermolecular Coupling Study.

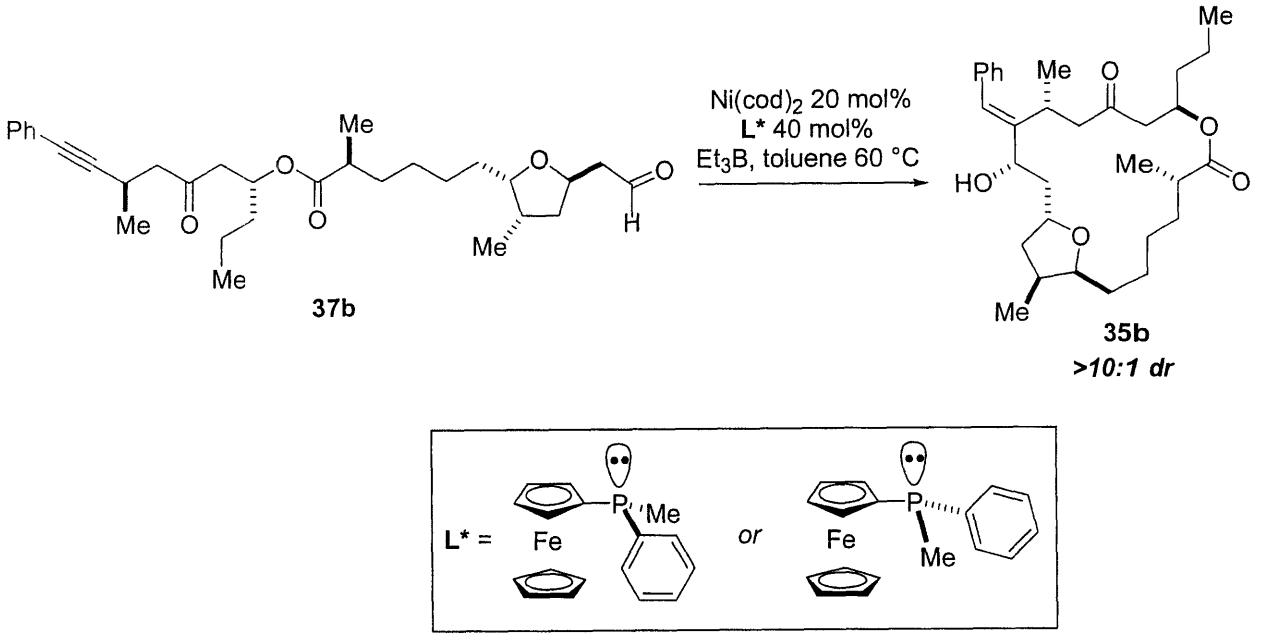


Investigation of Substrate Control in Reductive Macrocyclizations and Development of a Stereoselectivity Model.

With the successful nickel-catalyzed macrocyclization of **37b** using an achiral catalyst system, we endeavored to employ a chiral catalyst to overcome the inherent bias for the (*S*)-carbinol configuration of T4 (**4**) which, if successful, would provide an entry into the T3 stereochemical pattern. We first examined the ligand (*S*)-neomenthyldiphenylphosphine (NMDPP)[36] in combination with $Ni(cod)_2$ and triethylborane, but were disappointed to find that the catalyst system was not stable toward heating and cyclization did not occur. We next turned to *P*-chiral ferrocenyl ligands developed in our laboratory.[6c] We were pleased to find that **37b** did indeed undergo cyclization when heated with a catalytic amount of $Ni(cod)_2$ and (*S*)-ferrocenylmethylphenylphosphine and stoichiometric triethylborane, producing allylic alcohol **35b** in 30% yield and >10:1 dr. Interestingly, when the opposite enantiomer of the ligand was utilized, **35b** was also afforded in >10:1 dr (and 25% yield) with the *same* configuration at C12 (T4 configuration, Scheme 29).

[36] During intermolecular reductive coupling studies of aldehydes and aryl alkynes in our laboratory (reference 6c), NMDPP emerged as a uniquely powerful promoter of asymmetric Ni-catalyzed coupling reactions.

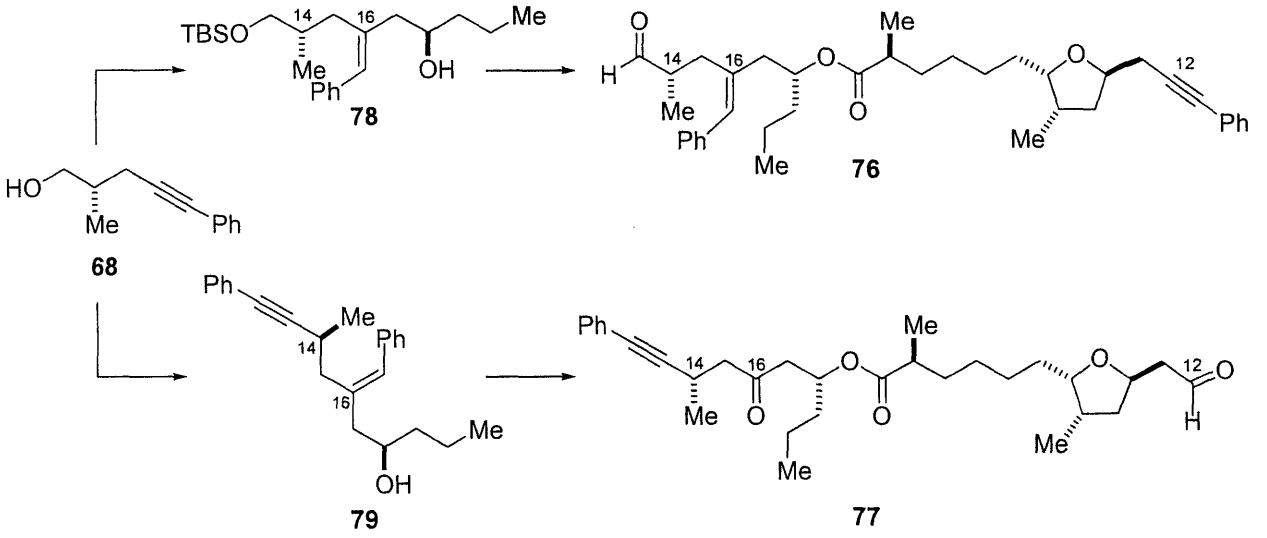
Scheme 29. Reductive Cyclizations of **37b** with *P*-Chiral Ferrocenyl Ligands.



This result demonstrated that these stereoselective macrocyclizations are under *complete* substrate control, and are consistent with our growing hypothesis that both alkynals **36** and **37b** are highly conformationally constrained during the reductive macrocyclization process. As noted above, we initially suspected that the configuration of the C14 methyl group in both cases (adjacent to the aldehyde group in **36** and adjacent to the alkyne in **37**) played a significant role in inducing this bias.

To probe this hypothesis, we synthesized alkynals **76** and **77** with the opposite configuration at C14 (Scheme 30). Syntheses of both *epi*-C14 alkynals commenced with *ent*-**68** (prepared using the *R* enantiomer of the Evans auxiliary) and followed the respective T1 and T4 syntheses exactly. The inverted methyl configuration did not affect either of the alkyne-epoxide or selective diyne-epoxide reductive coupling reactions and subsequent elaboration afforded the alkynals (details included in the Experimental Section).

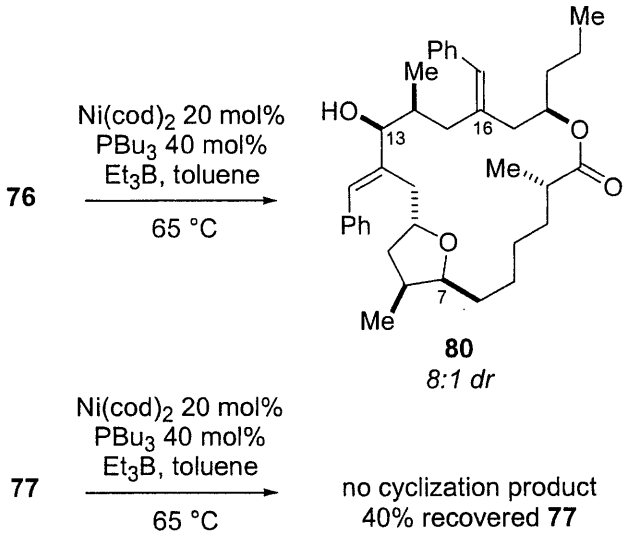
Scheme 30. Synthesis of *Epi*-C14 Alkynals.



With the alkynals in hand, we were poised to examine reductive macrocyclization conditions. We found that the alkynal **76** underwent cyclization when heated in the presence of 20 mol% $Ni(cod)_2$, 40 mol% tributylphosphine and excess triethylborane in 35% yield with high diastereoselectivity (8:1 dr). Analysis of macrocyclic alcohol **80** using the Mosher method[37] revealed that the major diastereomer possessed the *S* configuration at the carbinol center (Scheme 31). Interestingly, under the same conditions, alkynal **77** did not undergo cyclization (the only recovered compound was unreacted **77**).

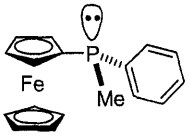
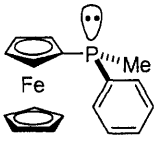
[37] Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512-519.

Scheme 31. Inverted C14 Methyl Effect on Reductive Macrocyclizations.



The results of this set of coupling reactions are summarized in Table 4 and required significant revision of our model of stereoinduction in the catalytic macrocyclizations. Contrary to our original hypothesis and as evidenced by entries 1 and 2, the Felkin-Anh model clearly does not apply in the case of the T1 series. That is, the configuration of the stereogenic center adjacent to the aldehyde undergoing reductive coupling with the alkyne has *no* effect whatsoever on the sense of induction. A minimum of 8:1 diastereoselectivity favoring the (*S*) configuration was observed in both cases.

Table 4. Macrocyclization Experiments.

entry	macrocyclization experiment	ligand	dr	configuration of major diastereomer
1	T1 (**36**, Table 3 entry 10)	PBu_3	>10:1	(*S*) C13
2	14-*epi*-T1 (**76**, Scheme 31)	PBu_3	8:1	(*S*) C13
3	T4 (**37a**, Scheme 27)	PBu_3	>10:1	(*S*) C12
4	T4 (**37b**, Scheme 27)	PBu_3	>10:1	(*S*) C12
5	T4 (**37b**, Scheme 29)		>10:1	(*S*) C12
6	T4 (**37b**, Scheme 29)		>10:1	(*S*) C12
7	14-*epi*-T4 (**77**, Scheme 31)	PBu_3	n.a.	(macrocyclization not observed)

The results of the T4 series of macrocyclizations (entries 3-6) are especially striking since the same sense *and* degree of stereoselectivity are observed for two different alkynals (**37a** (benzylidine at C16) and **37b** (ketone at C16)) and, in the case of **37b**, for three very different ligands (achiral, (*R*), or (*S*)). That the analogous "*epi*-methyl" (entry 7) experiment did not afford the desired product unfortunately prevents direct analysis of the effect of this stereogenic center upon the sense and degree of induction in the reductive macrocyclizations.

While we hesitate to infer too much information from a direct comparison of the T1 and T4 series of macrocyclizations, in which the positions of the alkyne and aldehyde have been reversed, we nevertheless propose a simple model of stereoinduction that is applicable to both of these cases (Figure 3). The elements of the analysis that led to this rationale are as follows:

(1) We have invoked an oxanickelacyclopentene[6c,25,38] as an approximation of the transition state of the reductive coupling. (2) Although clearly an oversimplification, the primary consideration in our conformational analysis was strain (torsional and steric) developing in the vicinity of the site of reactivity.

Both possible product diastereomers were subjected to the same analysis, and a rough comparison was made between the two. Figure 3a represents our proposed model that minimizes the unfavorable interactions in the transition state of the catalytic macrocyclization used to prepare amphidinolide T1. For clarity, three key 1,3-interactions are highlighted although many more are incorporated into the proposed model. The conformation shown possesses the fewest number of *gauche*$^{+}$–*gauche*$^{-}$ ("syn-pentane"),[39] $A^{1,3}$ strain[40] and related 1,3-interactions for this diastereomer. For example, orienting the bonds highlighted (in bold) in the same direction generates no syn-pentane-like interactions in any of these three cases. (Not emphasized in this drawing is the fact that several other 1,3-interactions are also avoided.) On the contrary, all other possible conformations induce at least one syn-pentane-like interaction.

The net effect of this arrangement is that the carbon-carbon bonds connected by the loop representing the rest of the macrocycle are pointed in the same direction (see asterisked bonds). The remaining 12 atoms in the macrocycle are thus easily accommodated without inducing severe steric and/or torsional interactions.

When the same analysis was applied to the diastereomer not observed in this cyclization, the structure in Figure 3b was generated. As can be seen, the bonds that are connected by the loop are now pointed in different directions, approximately 120° relative to one another. Moreover, the loop in this case represents only 9 additional atoms, and model building suggests

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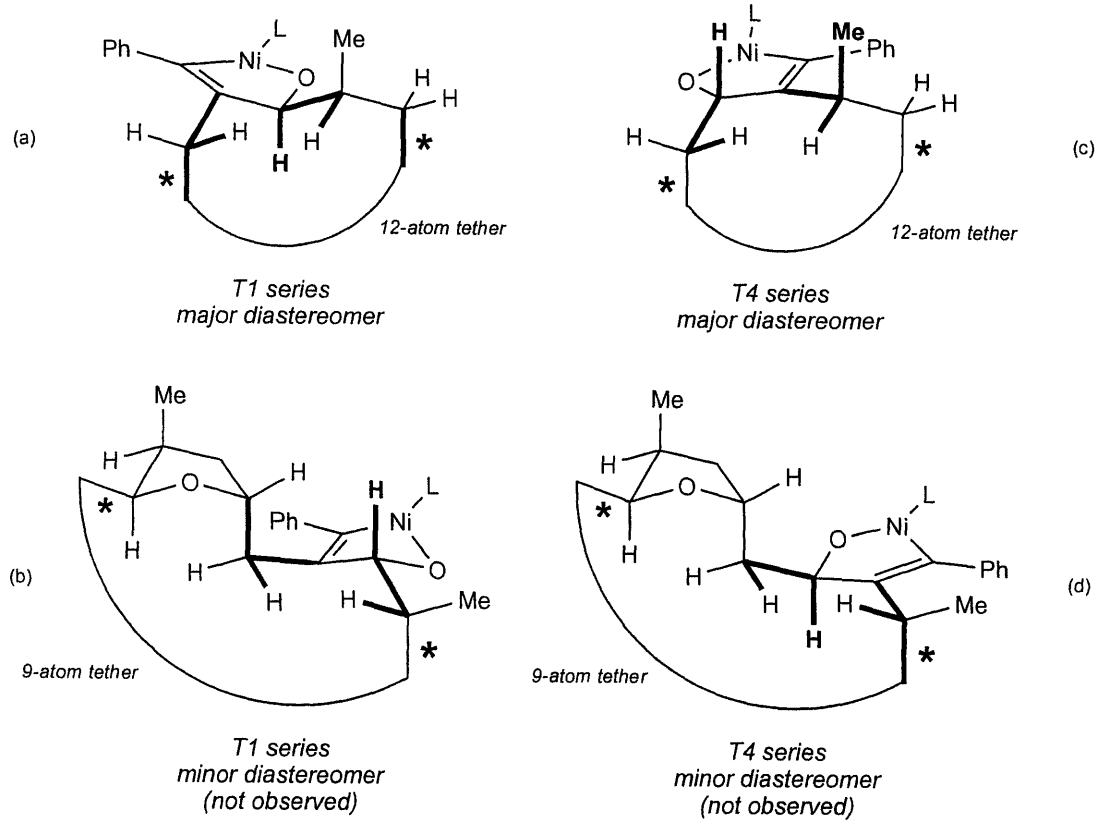
[38] (a) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065-9066. (b) Miller, K. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 15342-15343.

[39] Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841-1860.

[40] Wiberg, K. B.; Murcko, M. A. *J. Am. Chem. Soc.* **1988**, *110*, 8029-8038.

that requiring this shorter chain to span the required distance is not nearly as straightforward as was the case in the other diastereomer (Figure 3a).

Figure 3.

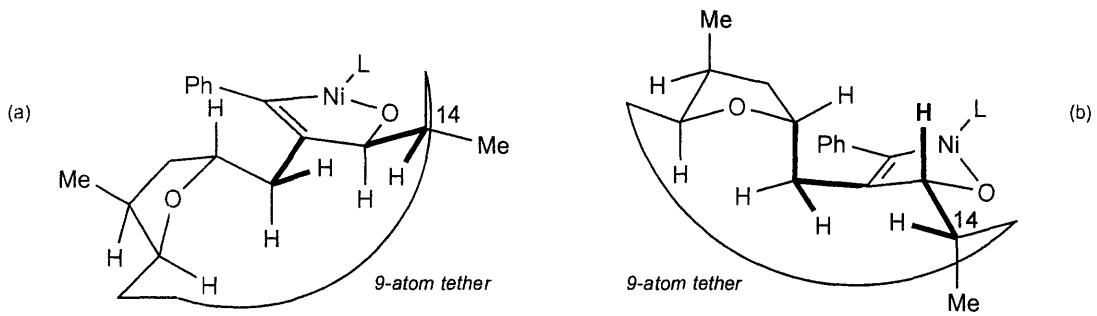


A particularly satisfying feature of this model is that it can in fact be used to explain the observed stereochemical outcomes of the macrocyclizations that were used in the synthesis of amphidinolide T4. In other words, despite the fact that the "ends are reversed" so to speak, minimization of a very similar set of developing steric interactions accounts for the sense of induction in *both* the T1 *and* T4 series. As shown in Figure 3c and 3d, the net effect of this analysis for the T4 series is also strikingly similar to that in the T1 series. In Figures 3a (T1) and 3c (T4), 12 atoms are available to join the two ends (which are pointed in the same direction), whereas Figures 3b and 3d suggest that a much greater demand would be required of the 9 atoms in the chain.

A comparison of the results of the T1 series of macrocyclizations and of the 14-*epi*-T1 series is also worthy of comment (Figures 3a-b, 4, and 5). The goal of these exercises was to account for the initially counterintuitive observation that the stereogenic center adjacent to the site of the aldehyde had no effect on the sense of induction. One must be careful, however, in drawing too much from this comparison, especially since the diastereoselectivity in the 14-*epi*-T1 series was not "complete", as it was in the T1 and T4 series. To a first approximation, 8:1 dr at 60 °C represents a difference in energy of the two transition states of about 1.4 kcal•mol^{-1}, a rather small value when compared to all the possible interactions in these complex systems.

Nevertheless, as shown in Figure 4, low energy conformations for the diastereomers observed in the macrocyclizations in the "*epi*-methyl-T1" series were generated using the criteria in the other cases, and they are reminiscent of those for the corresponding diastereomers in the T1 series (Figures 3a and 3b). The essence of this comparison is summarized in Figure 5.

Figure 4.



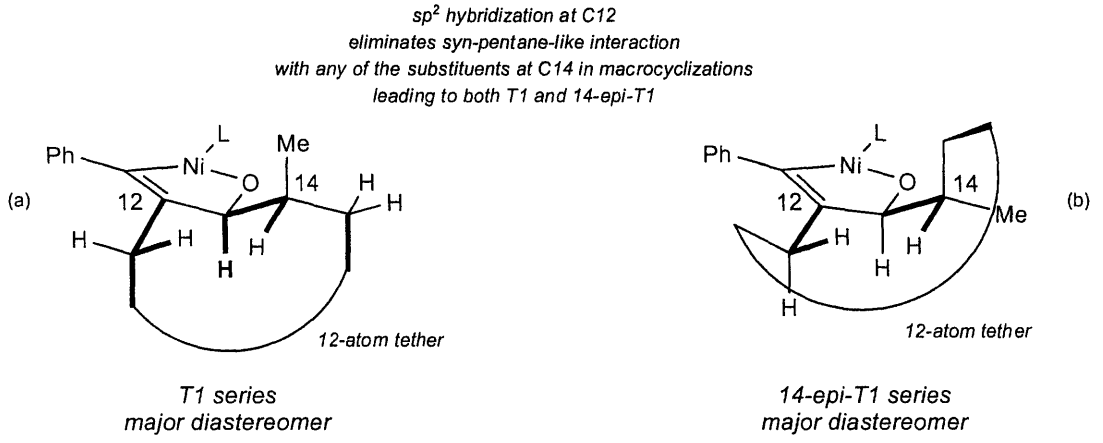
14-epi-T1 series
major diastereomer

14-epi-T1 series
minor diastereomer

To summarize, our conclusion from these analyses is that the strongest effect upon the sense of induction is minimization of 1,3-interactions near the site of reactivity in the transition state. Moreover, branching (i.e., 2 substituents that are not hydrogen) at the carbon adjacent to the aldehyde (C14 in these cases) can be accommodated without energetic penalty since C12 is sp^2 hybridized. That is, because of the *absence* of a substituent at C12, there are no 1,3-interactions with the substituents at C14, and thus the effect on stereoselectivity of branching

adjacent to the aldehyde is dramatically attenuated. In other words, as long as the remainder of the nascent macrocycle can be accommodated without inducing severe unfavorable interactions, the configuration adjacent to the reacting aldehyde is of no consequence in determining the stereochemical outcome. Rather, it is the minimization of other interactions around the site of reaction that has the greatest effect. This hypothesis is not new in its own right of course,[41] but it does suggest a unifying strategy that might be exploited in related stereoselective macrocyclizations.

Figure 5.



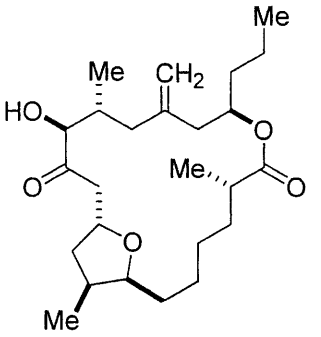
[41] For an in-depth study of situations in which developing 1,3-interactions (syn-pentane-like) better account for the observed sense of stereoinduction in additions to chiral aldehydes than the Felkin-Anh model, see: Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151-4157.

Conclusion

In summary, we have found that intramolecular alkyne-aldehyde couplings are efficient methods for closing the 19-membered ring present in the amphidinolide T framework. The simultaneous installation of the carbinol stereogenic center found in **1** and **4** occurred with complete disastereocontrol. Our strategy presents a very different approach from the previous syntheses of amphidinolides T1 and T4 by Ghosh and Fürstner as the ring closing process not only formed a carbon-carbon bond, but also set a stereogenic center. This reductive macrocyclization approach proved to be far superior to the corresponding intermolecular reductive coupling strategy not only with respect to stereoselectivity, but also in the overall number of steps necessary to synthesize the natural products (seventeen linear steps in the case of amphidinolide T1 and fifteen linear steps for T4 from aldehyde **55**). Additionally, intermolecular alkyne-epoxide reductive fragment couplings provided facile access to key intermediates, streamlining the total syntheses and reducing the number of total synthetic operations to twenty-one for T1 and twenty-four for T4.

Experimental Section

General Information. The experimental procedures are in order of compound number (lowest to higher). Unless otherwise noted, all reactions performed in organic solvents were conducted under an atmosphere of argon with rigorous exclusion of moisture from reagents and glassware. THF and Et_2O were distilled from a blue solution of sodium benzophenone ketyl. CH_2Cl_2 was distilled from calcium hydride. Toluene was distilled from sodium metal. Anhydrous DMF and CH_3CN were purchased from Aldrich and used without purification. Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F_{254} plates and UV light, 12-molybdophosphoric acid (PMA stain), or potassium permanganate ($KMnO_4$ stain) for analysis of the developed plates. Flash chromatography was performed using silica gel 60 (40-63 μm) from Silicycle. NMR spectra were recorded on a Varian 500 MHz spectrometer in $CDCl_3$ or C_6D_6. 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 Dr. Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. GC analysis was performed on a Varian CP-3800 gas chromatograph fitted with Chiraldex B-PH, B-DA, and G-TA capillary columns. HPLC was performed on a Hewlett-Packard 1100 chromatograph equipped with a variable wavelength detector and Chiralcel OD, AD, or OJ column. Specific rotations ($[\alpha]_D$) values for chiral compounds were measured on a Perkin-Elmer 241 polarimeter at 589 nm.



(+)-Amphidinolide T1 (1). A 2 mL plastic Eppendorf tube was charged with a solution of **59** (2.2 mg, 0.004 mmol) in CH_3CN (0.70 ml) and a Teflon-coated stirbar. Anhydrous HF-pyridine was added via syringe (0.10 ml), and the reaction was stirred 72 h at ambient temperature. After this time, the mixture was partitioned between H_2O and EtOAc (1 mL each), and the layers were separated. The aqueous phase was extracted with EtOAc (5 x 1 mL) and the combined organic layers were washed with brine (1 x 2 mL), dried over Na_2SO_4, filtered and concentrated. The crude residue was purified via Pasteur pipet column chromatography (9:1 hexane-EtOAc) to give the title compound as a clear, colorless oil (1.6 mg, 94% yield). R_f (80:20, hexane-EtOAc) = 0.32.

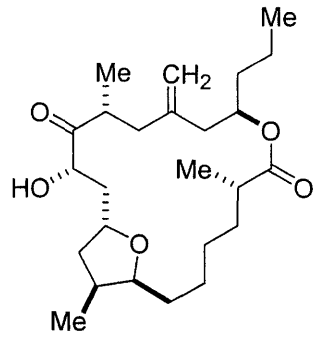
IR (thin film/NaCl): 3485, 2925, 2854, 1727 cm^{-1}.

^1H NMR (C_6D_6, 500 MHz): δ 5.37-5.32 (m, 1H), 5.13 (s, 1H), 4.92 (s, 1H), 4.51-4.46 (m, 1H), 4.30 (dd, J = 1.5, 5.8 Hz, 1H), 3.64 (ddd, J = 2.5, 4.4, 10.8 Hz, 1H), 3.60 (d, J = 5.8 Hz, 1H), 2.53 (dd, J = 10.4, 13.4 Hz, 1H), 2.47-2.41 (m, 3H), 2.33-2.23 (m, 3H), 1.88 (dd, J = 2.7, 14.3 Hz, 1H), 1.70-1.65 (m, 1H), 1.62-1.48 (m, 5H), 1.46-1.20 (m, 7H), 1.19-1.11 (m 1H), 1.07 (d, J = 7.0 Hz, 3H), 1.05-1.02 (m, 1H), 0.93 (d, J = 6.4 Hz, 3H), 0.86 (t, J = 7.3 Hz, 3H), 0.62 (d, J = 7.0 Hz, 3H).

^{13}C NMR (C_6D_6, 125 MHz): δ 212.5, 175.4, 144.0, 116.7, 78.9, 78.6, 74.1, 72.2, 45.5, 42.3, 41.7, 40.5, 40.2, 37.0, 36.1, 35.6, 32.4, 30.2, 27.3, 26.7, 19.6, 18.6, 14.6, 14.5, 14.3.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{25}H_{42}NaO_5$ 445.2924, obsd 445.2938.

$[\alpha]_D$ = +6.7 (23 °C, c = 0.3, $CHCl_3$)



(−)-Amphidinolide T4 (4). A 2 mL plastic Eppendorf tube was charged with a solution of **68** (3.0 mg, 0.0055 mmol) in CH_3CN (0.70 ml) and a Teflon-coated stirbar. Anhydrous HF-pyridine was added via syringe (0.10 ml), and the reaction was stirred 17 h at ambient temperature. After this time, the mixture was partitioned between H_2O and EtOAc (5 mL each), and the layers were separated. The aqueous phase was extracted with EtOAc (5 x 3 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated. The crude residue was purified via Pasteur pipet column chromatography (9:1 hexane-EtOAc) to give the title compound as a clear, colorless oil (2.0 mg, 87% yield). R_f (80:20 hexane-EtOAc) = 0.17.

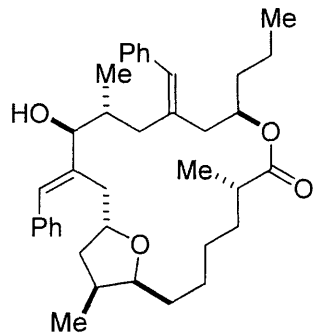
IR (thin film/NaCl): 3465, 2960, 2873, 1725, 1071 cm^{-1}.

^1H NMR (C_6D_6, 500 MHz): δ 5.23-5.18 (m, 1H), 4.83 (s, 2H), 4.56-4.53 (m, 1H), 4.33-4.29 (m, 1H), 4.03 (d, J = 6.7 Hz, 1H), 3.79-3.75 (m, 1H), 3.36-3.32 (m, 1H), 2.73 (dd, J = 4.0, 14.0 Hz, 1H), 2.54 (dd, J = 4.9, 13.4 Hz, 1H), 2.42-2.40 (m, 1H), 2.10 (dd, J = 8.7, 13.6 Hz, 1H), 2.02 (dd, J = 10.1, 14.0 Hz, 1H), 1.99-1.94 (m, 1H), 1.88-1.86 (m, 1H), 1.71-1.66 (m, 1H), 1.63-1.26 (br m, 13H), 1.19-1.13 (m, 1H), 1.10 (d, J = 7.0 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H), 0.85 (t, J = 7.3 Hz, 3H), 0.70 (d, J = 7.3 Hz, 3H).

^{13}C NMR (C_6D_6, 125 MHz): δ 216.2, 176.0, 143.5, 116.0, 79.7, 75.4, 75.0, 72.3, 41.5, 41.2, 40.64, 40.57, 39.9, 38.8, 36.5, 35.9, 34.3, 29.1, 27.1, 26.4, 19.2, 18.5, 16.4, 14.6, 14.4.

HRMS (ESI)$[M+Na]^+$: *m/z* calcd for $C_{25}H_{42}NaO_5$ 445.2924, obsd 445.2929.

$[\alpha]_D$ = − 7.5 (23 °C, c = 0.8, $CHCl_3$)



(−)-11,15-Dibenzylidene-(14*S*)-hydroxy-(6*S*,13*R*,19*R*)-trimethyl-(9*R*)-propyl-8,20-dioxa-bicyclo[15.2.1]icosan-7-one (34). A stock solution of catalyst was prepared in the following manner: in a glovebox, $Ni(cod)_2$ (26 mg, 0.095 mmol) was placed in a flask containing a stirbar. The flask was sealed with a rubber septum, removed from the glovebox, and immediately placed under argon. Tributylphosphine (26 μL, 0.19 mmol), toluene (4.74 ml, previously degassed by bubbling argon through for 10 minutes), and triethylborane (0.26 ml, 1.8 mmol) were added sequentially, producing a clear yellow catalyst solution. A 2 ml Woodward reaction tube equipped with a stirbar, rubber septum, and septum screw cap on the side-arm was purged with argon. Stock catalyst solution was added to the tube (500 μL), and the tube was immediately placed in an oil bath at 60 °C for 3 min. A solution of **36** in degassed toluene (27 mg, 0.047 mmol in 500 μL) was added to the tube dropwise, causing the solution to turn red-brown. The reaction was allowed to stir at 60 °C for 14 h. After this time, the solution was cooled to ambient temperature, diluted with 1.5 ml EtOAc, and stirred open to the air 1 h; then concentrated. The crude residue was purified via Pasteur pipet column chromatography (90:10 hexane-EtOAc) to give the title compound as a clear, yellow oil (12 mg, 44% yield). R_f (90:10, hexane-EtOAc) = 0.20.

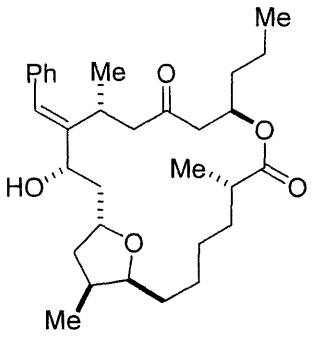
IR (thin film/NaCl): 3377, 2959, 2932, 2872, 1726, 1599, 1462, 1453 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.32-7.13 (m, 10H), 6.49 (s, 1H), 6.45 (s, 1H), 5.29-5.27 (m, 1H), 4.15-4.08 (m, 2H), 3.98 (d, J = 4.6 Hz, 1H), 3.90-3.87 (m, 1H), 2.73 (dd, J = 5.8, 13.7 Hz, 1H), 2.53-2.42 (m, 3H), 2.37 (dd, J = 7.5, 13.9 Hz, 1H), 2.21 (dd, J = 7.3, 13.4 Hz, 1H), 2.14-2.10 (m, 2H), 2.06-1.98 (m, 1H), 1.75-1.69 (m, 1H), 1.68-1.28 (br m, 13H), 1.20 (d, J = 7.0 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H), 0.91 (d, J = 6.1 Hz, 3H), 0.83 (d, J = 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.2, 142.7, 139.1, 138.5, 138.1, 129.01, 128.98 (2C), 128.96 (2C), 128.5 (2C), 128.4 (2C), 128.0, 126.5 (2C), 79.3, 77.3, 72.7, 42.9, 41.7, 40.4, 38.5, 36.5, 36.3, 35.0, 34.8, 34.1, 30.2, 27.5, 25.9, 18.64, 18.62, 14.9, 14.5, 14.3 (missing one C under $CDCl_3$ signal; when spectrum taken in C_6D_6 there are four signals in the 70-80 ppm region: δ 79.7, 77.6, 76.8, 72.5).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{38}H_{52}NaO_4$ 595.3758, obsd 595.3746.

$[\alpha]_D = -67.8$ (23 °C, c = 1.8, C_6D_6)



(−)-14-Benzylidene-(15*S*)-hydroxy-(6*S*,13*R*,19*S*)-trimethyl-(9*R*)-propyl-8,20-dioxa-bicyclo[15.2.1]icosane-7,11-dione (35b). A stock solution of catalyst was prepared in the following manner: in a glovebox, $Ni(cod)_2$ (26 mg, 0.095 mmol) was placed in a flask containing a stirbar. The flask was sealed with a rubber septum, removed from the glovebox, and immediately placed under argon. Tributylphosphine (26 μL, 0.19 mmol), toluene (4.74 ml, previously degassed by bubbling argon through for 10 minutes), and triethylborane (0.26 ml, 1.8 mmol) were added sequentially, producing a clear yellow catalyst solution. A 2 ml Woodward reaction tube equipped with a stirbar, rubber septum, and septum screw cap on the side-arm was purged with argon. Stock catalyst solution was added to the tube (240 μL), and the tube was immediately placed in an oil bath at 60 °C for 3 min. A solution of **37b** in degassed toluene (12 mg, 0.024 mmol in 760 μL) was added to the tube dropwise, causing the solution to turn red-brown. The reaction was allowed to stir at 60 °C for 14 h. After this time, the solution was cooled to ambient temperature, diluted with 1.5 ml EtOAc, and stirred open to the air 1 h; then concentrated. The crude residue was purified via gradient Pasteur pipet column chromatography (85:15 hexane-EtOAc polarity increased to 73:30 hexane-EtOAc) to give the title compound as a clear, yellow oil (7.0 mg, 58% yield). R_f (50:50 hexane-EtOAc) = 0.41.

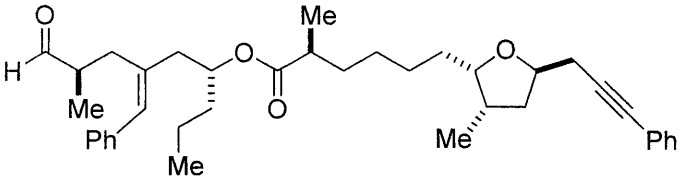
IR (thin film/NaCl): 3432 (br), 2960, 2935, 2873, 1780, 1732, 1458 cm^{-1}.

^1H NMR (C_6D_6, 500 MHz): δ 7.33-7.31 (m, 2H), 7.18 (app t, J = 7.6 Hz, 2H), 7.03 (app t, J = 7.3 Hz, 1H), 6.86 (s, 1H), 5.36-5.31 (m, 1H), 4.58 (d, J = 8.9 Hz, 1H), 4.44-4.39 (m, 1H), 3.71-3.63 (m, 2H), 2.52-2.46 (m, 2H), 2.41 (dd, J = 7.9, 17.1 Hz, 1H), 2.37-2.33 (m, 1H), 2.11 (dd, J = 5.0, 14.5 Hz, 1H), 2.05 (br s, 1H), 1.83-1.79 (m, 1H), 1.74-1.60 (m, 3H), 1.57-1.37 (m, 7H), 1.33-1.24 (m, 2H), 1.23-1.09 (m, 4H), 1.08-1.05 (m, 6H), 0.78-0.74 (m, 6H).

^{13}C NMR (C_6D_6, 125 MHz): δ 206.9, 175.1, 150.4, 138.9, 130.4, 127.2 (2C), 125.2 (2C), 122.0, 79.2, 74.4, 71.9, 69.0, 50.0, 47.8, 46.0, 40.72, 40.70, 37.3, 37.0, 35.3, 30.7, 30.6, 27.6, 27.3, 21.1, 18.9, 17.1, 14.9, 14.4.

HRMS (ESI)$[M+Na]^+$: *m/z* calcd for $C_{31}H_{44}O_5Na$ 519.3081, obsd 519.3077.

$[\alpha]_D$ = −2.5 (23 °C, c = 2.4, C_6H_6)



(+)-(2*S*)-Methyl-6-[(3*S*)-methyl-(5*R*)-(3-phenyl-prop-2-ynyl)-tetrahydro-furan-(2*S*)-yl]-hexanoic acid 3-benzylidene-(5*R*)-methyl-6-oxo-(1*R*)-propyl-hexyl ester (36). Dess-Martin periodinane was dissolved in CH_2Cl_2 (124 mg, 0.30 mmol, 2.4 mL) and a solution of **84** in CH_2Cl_2 was added dropwise via syringe (80 mg, 0.14 mmol, 1.2 mL). The resulting solution was stirred at ambient temperature for 75 min, diluted with Et_2O (15 ml), and poured into 10 ml saturated $NaHCO_3$ containing 2.5 g $Na_2S_2O_3$. When the organic layer cleared, the layers were separated. The organic phase was washed with saturated $NaHCO_3$ (1 x 15 ml), H_2O (1 x 15 ml), and brine (1 x 15 ml), then dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified via column chromatography (90:10 hexane-EtOAc) to give the title compound as a clear, colorless oil (67 mg, 84% yield). R_f (70:30, hexane-EtOAc) = 0.55.

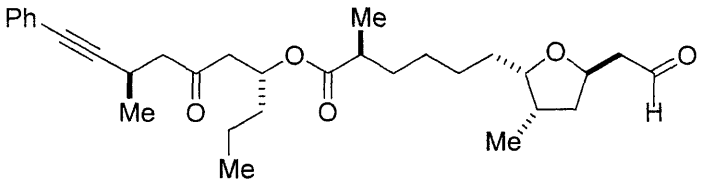
IR (thin film/NaCl): 2961, 2934, 2873, 1726, 1599, 1491, 1460 cm^{-1}.

^1H NMR (C_6D_6, 500 MHz): δ 9.21 (d, J = 1.8 Hz, 1H), 7.50-7.48 (m, 2H), 7.16-7.13 (m, 5H), 7.05-6.97 (m, 3H), 6.40 (s, 1H), 5.28-5.23 (m, 1H), 4.24-4.19 (m, 1H), 3.88-3.85 (m, 1H), 2.79-2.73 (m, 1H), 2.60 (dd, J = 4.9, 16.5 Hz, 1H), 2.51 (dd, J = 7.0, 16.5 Hz, 1H), 2.43-2.30 (m, 4H), 2.22 (dd, J = 4.9, 14.0 Hz, 1H), 2.03-1.98 (m, 1H), 1.88 (ddd, J = 7.0, 9.0, 10.8 Hz, 1H), 1.79-1.74 (m, 1H), 1.63-1.58 (m, 1H), 1.55-1.42 (m, 4H), 1.40-1.21 (m, 6H), 1.11 (d, J = 7.0 Hz, 3H), 0.88 (d, J = 7.3 Hz, 3H), 0.75 (d, J = 7.0 Hz, 3H), 0.71 (d, J = 6.7 Hz, 3H).

^{13}C NMR (C_6D_6, 125 MHz): δ 203.4, 176.5, 138.3, 136.7, 132.3 (2C), 131.0, 129.5 (2C), 128.95 (2C), 128.92 (2C), 128.7, 127.2, 125.0, 88.2, 82.7, 82.2, 75.6, 71.5, 45.1, 43.3, 40.4, 39.9, 37.2, 36.7, 34.6, 31.7, 31.2, 28.2, 27.8, 27.4, 19.5, 17.9, 14.49, 14.47, 13.8.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{38}H_{50}NaO_4$ 593.3601, obsd 593.3601.

$[\alpha]_D$ = +0.60 (23 °C, c = 3.4, CH_2Cl_2)



(−)-(2*S*)-Methyl-6-[(3*S*)-methyl-(5*R*)-(2-oxo-ethyl)-tetrahydro-furan-(2*S*)-yl]-hexanoic acid (5*R*)-methyl-3-oxo-7-phenyl-(1*R*)-propyl-hept-6-ynyl ester (37b). A solution of **71** in CH_2Cl_2 (91 mg, 0.16 mmol in 50 mL) was cooled to −78 °C. Ozone was bubbled through the solution until a blue color persisted. Argon was immediately bubbled through until the solution was colorless. Dimethylsulfide was added (0.80 ml) and the solution was allowed to slowly warm to ambient temperature over 3 h. The solution was concentrated and immediately purified by gradient column chromatography (85:15 hexane-EtOAc, polarity increased to 70:30 hexane-EtOAc). Two products were isolated: a diastereomeric ketoalkynyl-ozonide (less polar) and the desired ketoalkynal **37b** (more polar). The ozonide was dissolved in 10 ml CH_2Cl_2 and stirred with triphenylphosphine (256 mg) for 40 min. Concentration and purification on a silica gel column (elution with 80:20 hexane-EtOAc) afforded pure ketoynal which was combined with the original portion (combined: 63 mg, 80% overall yield). R_f (50:50 hexane-EtOAc) = 0.46.

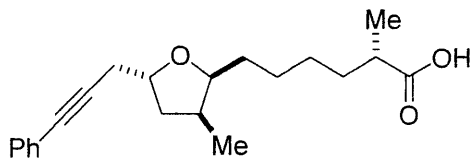
IR (thin film/NaCl): 2962, 2935, 2874, 1727 (br) cm^{-1}.

^1H NMR (C_6D_6, 500 MHz): δ 9.51 (dd, J = 1.8, 2.8 Hz), 7.48-7.46 (m, 2H), 7.16-6.97 (m, 3H), 5.50-5.45 (m, 1H), 4.23-4.18 (m, 1H), 3.66-3.63 (m, 1H), 3.25-3.21 (m, 1H), 2.52-2.46 (m, 2H), 2.41-2.37 (m, 1H), 2.27-2.21 (m, 2H), 2.16 (dd, J = 7.0, 16.5 Hz, 1H), 1.96 (ddd, J = 1.7, 5.3, 15.9 Hz, 1H), 1.85-1.81 (m, 1H), 1.77-1.72 (m, 1H), 1.58-1.38 (m, 5H), 1.36-1.19 (m, 8H), 1.16 (d, J = 6.7 Hz, 3H), 1.13 (d, J = 7.0 Hz, 3H), 0.82 (t, J = 7.3 Hz, 3H), 0.69 (d, J = 7.3 Hz, 3H).

^{13}C NMR (C_6D_6, 125 MHz): δ 205.8, 201.9, 176.4, 131. 8 (2C), 128.4 (2C), 128.0, 123.7, 93.2, 81.7, 81.2, 71.7, 69.9, 50.7, 50.1, 47.9, 40.2, 39.8, 36.5, 36.0, 33.8, 30.4, 27.6, 26.7, 22.4, 21.0, 18.7, 17.2, 14.06, 14.04.

HRMS (ESI)$[M+Na]^+$: *m/z* calcd for $C_{31}H_{44}O_5Na$ 519.3081, obsd 519.3077.

$[\alpha]_D$ = −2.5 (23 °C, c = 2.4, C_6H_6)



(+)-(2*S*)-Methyl-6-[(3*S*)-methyl-(5*R*)-(3-phenyl-prop-2-ynyl)-tetrahydro-furan-(2*S*)-yl]-hexanoic acid (38).[42] A flask containing lithium chloride (549 mg, 13.0 mmol) was flame-dried under a stream of Ar for five minutes, cooled to ambient temperature, and charged with THF (2.5 mL) and diisopropylamine (0.62 mL, 4.4 mmol). The heterogenous mixture was cooled to −78 °C and *n*-butyllithium was added (1.63 mL, 2.5M in hexane, 4.1 mmol). The mixture was stirred 5 min at −78 °C, warmed to 0 °C for 30 min, then re-cooled to −78 °C. An ice-cooled solution of *N*-(2-hydroxy-1-methyl-2-phenyl-ethyl)-*N*-methyl-propionamide in THF (474 mg, 2.14 mmol in 4.6 mL) was added slowly via cannula, followed by a 1.0 mL wash portion of THF. The mixture was allowed to stir 60 min at −78 °C, 15 min at 0 °C, and 5 min at ambient temperature before re-cooling to 0 °C. An ice-cooled solution of **62** in THF (391 mg, 1.02 mmol, in 1.8 mL) was added, followed by a 1.0 ml wash portion of THF. The mixture was stirred at 0 °C for 5h, at which point the reaction was quenched with saturated NH_4Cl (5 ml). H_2O and EtOAc were added (5 ml each), the layers were separated, and the aqueous phase extracted with EtOAc (3 x 10ml). The combined organic phases were dried over Na_2SO_4, filtered and concentrated to give a crude orange oil. The crude oil was purified by gradient column chromatography (90:10 CH_2Cl_2-EtOAc, polarity increased to 50:50) to afford the alkylated amide (R_f 50:50 CH_2Cl_2-EtOAc = 0.47). The amide was taken up in a 1:1 mixture of *t*-BuOH and CH_3OH (3.4 mL) and transferred to a sealable reaction tube equipped with a magnetic stirbar. NaOH was added (3.3 mL, 3.22N aqueous solution), the tube was sealed, and the mixture was heated to refluxed 48h. After cooling to ambient temperature, the volatile organic components were removed in vacuo. The remaining residue was stirred in CH_2Cl_2 and H_2O (20 ml each), forming an emulsion which was carefully acidified to pH < 2 by the addition of 6 N H_2SO_4. The resulting layers (now clearly distinct) were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 ml). The combined organic phases were dried over Na_2SO_4, filtered and concentrated to give a clear, pale yellow oil which was >95:5 dr by ^1H NMR (298 mg, 89% yield over two steps). R_f (EtOAc) = 0.30.

IR (thin film/NaCl): 3055 (br), 2936, 2860, 2241, 1950, 1705 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.41-7.39 (m, 2H), 7.29-7.27 (m, 3H), 4.33-4.28 (m, 1H), 4.00-3.97 (m, 1H), 2.68 (dd, J = 4.6, 16.6 Hz, 1H), 2.60 (dd, J = 7.0, 16.6 Hz, 1H), 2.50-2.43 (m, 1H), 2.35-2.28 (m, 1H), 2.09-2.03 (m, 1H), 1.87 (ddd, J = 3.7, 7.0, 12.5, 1H), 1.75-1.68 (m, 1H), 1.52-1.25 (m, 7H), 1.18 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 182.7, 131.8 (2C), 128.4 (2C), 127.9, 124.0, 87.1, 82.3, 82.0, 75.2, 39.44, 39.37, 36.1, 33.7, 30.4, 27.6, 27.2, 26.7, 17.0, 14.2.

HRMS (ESI)[M-H]$^-$: *m/z* calcd for $C_{21}H_{27}O_3$ 327.1966, obsd 327.1963.

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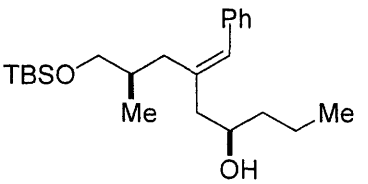
[42] Followed procedure for asymmetric alkylation according to reference 24.

$[\alpha]_D$ = +2.9 (23 °C, c = 4.1, $CDCl_3$)



(+)-2-[3-(tert-Butyldimethylsilanyloxy)-(2*R*)-methylpropyl]-1-phenyl-hept-1-en-(4*R*)-ol (39). In a glovebox, $Ni(cod)_2$ (28 mg, 0.10 mmol) was placed in a 10 ml flask which was then sealed with a rubber septum. The flask was removed from the glovebox and placed under Ar. To this flask was added tributylphosphine (28 μL, 0.20 mmol), (*R*)-*n*-propyloxirane (**44**) (degassed by bubbling Ar through for 10 min, 0.70 ml, 6.8 mmol), triethylborane (0.30 mL, 2.0 mmol), and **42** (290 mg, 1.00 mmol). The resulting dark brown solution was stirred at ambient temperature 14 h, then opened to the air for 1 h. Volatile organics were evaporated, and the crude residue was purified via gradient column chromatography (50:1 hexane-EtOAc, polarity gradually increased to 9:1) to afford the title compound as a clear, colorless oil (304 mg, 81% yield, 1 diastereomer by ^{1}H NMR). R_f (90:10, hexane-EtOAc) = 0.22.

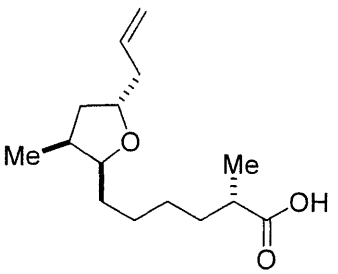
IR (thin film/NaCl): 3376, 2956, 2930, 2857, 1463 cm $^{-1}$.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33-7.30 (m, 2H), 7.27-7.26 (m, 2H), 7.22-7.19 (m, 1H), 6.44 (s, 1H), 3.85-3.82 (m, 1H), 3.40 (dd, J = 6.0, 9.7 Hz, 1H), 3.32 (dd, J = 6.2, 9.9 Hz, 1H), 2.50 (dd, J = 6.4, 13.7 Hz, 1H), 2.42 (dd, J = 4.3, 13.7 Hz, 1H), 2.28-2.23 (m, 1H), 2.09-1.90 (m, 1H), 1.85 (s, 1H), 1.58-1.50 (m, 3H), 1.46-1.40 (m, 1H), 0.98 (t, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.85 (d, J = 6.7 Hz, 3H), 0.02 (s, 3H), 0.01 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.1, 138.0, 129.5, 129.1 (2C), 128.3 (2C), 126.4, 69.4, 68.2, 46.5, 39.5, 34.5, 34.3, 26.1 (3C), 19.2, 18.5, 17.1, 14.4, -5.21, -5.23.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{23}H_{40}NaO_2Si$ 399.2690, obsd 399.2675.

$[\alpha]_D$ = +10.5 (23 °C, c = 15.2, CH_2Cl_2).



(+)-6-[(5*R*)-Allyl-(3*S*)-methyl-tetrahydro-furan-(2*S*)-yl]-(2*S*)-methyl-hexanoic acid (40). A flask containing lithium chloride (490 mg, 11.6 mmol) was flame-dried under a stream of Ar for five minutes, cooled to ambient temperature, and charged with THF (2.0 mL) and diisopropylamine (0.48 mL, 3.4 mmol). The heterogenous mixture was cooled to −78 °C and n-butyllithium was added (1.26 mL, 2.5M in hexane, 3.2 mmol). The mixture was stirred 5 min at −78 °C, warmed to 0 °C for 30 min, then re-cooled to −78 °C. An ice-cooled solution of *N*-(2-hydroxy-1-methyl-2-phenyl-ethyl)-*N*-methyl-propionamide in THF (350 mg, 1.58 mmol in 3.3 mL) was added slowly via cannula, followed by a 1.0 mL wash portion of THF. The mixture was allowed to stir 60 min at −78 °C, 15 min at 0 °C, and 5 min at ambient temperature before re-cooling to 0 °C. An ice-cooled solution of iodide **70** in THF (262 mg, 0.85 mmol, in 1.2 mL) was added, followed by a 1.0 ml wash portion of THF. The mixture was stirred at 0 °C for 3h, at which point the reaction was quenched with saturated NH_4Cl (5 ml). H_2O and EtOAc were added (5 ml each), the layers were separated, and the aqueous phase extracted with EtOAc (3 x 10ml). The combined organic phases were dried over Na_2SO_4, filtered and concentrated to give a crude yellow oil. The crude oil was purified by gradient column chromatography (90:10 CH_2Cl_2-EtOAc, polarity increased to 50:50) to afford the alkylated amide (R_f 50:50 CH_2Cl_2-EtOAc = 0.35). The amide was taken up in a 1:1 mixture of *t*-BuOH and CH_3OH (2.64 mL) and transferred to a 25 mL flask equipped with a magnetic stirbar. NaOH was added (2.64 mL, 3.22N aqueous solution), the flask was equipped with a reflux condensor, and the mixture was heated to reflux 48h. After cooling to ambient temperature, CH_2Cl_2 and H_2O were added (20 ml each). Acidification to pH < 2 was effected by the addition of 6 N H_2SO_4. The resulting layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 ml). The combined organic phases were dried over Na_2SO_4, filtered and concentrated to give a clear, pale yellow oil which was diastereomerically pure by ^{1}H NMR (191 mg, 88% yield over two steps). R_f(EtOAc) = 0.85.

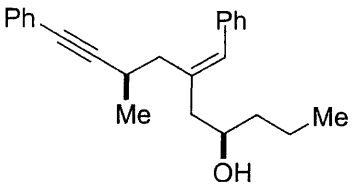
IR (thin film/NaCl): 3077 (br), 2965, 2937, 2862, 1706, 1642 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.8 (br s, 1H), 5.83-5.75 (m, 1H), 5.09-5.02 (m, 2H), 4.15-4.09 (m, 1H), 3.87-3.83 (m, 1H), 2.48-2.41 (m, 1H), 2.36-2.30 (m, 1H), 2.25-2.16 (m, 2H), 1.79-1.65 (m, 3H), 1.52-1.33 (m, 6H), 1.32-1.25 (m, 1H), 1.16 (d, J = 7.0 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 183.0, 135.2, 117.0, 81.5, 76.2, 41.2, 39.5, 39.4, 36.0, 33.7, 30.4, 27.6, 26.7, 17.0, 14.2.

HRMS (ESI)[M-H]$^-$: *m/z* calcd for $C_{15}H_{25}O_3$ 253.1798, obsd 253.1801.

$[\alpha]_D$ = +8.4 (23 °C, c = 4.5, CH_2Cl_2)



(+)-6-Benzylidene-(8*R*)-methyl-10-phenyl-dec-9-yn-(4*R*)-ol (41). Copper (I) iodide (100 mg, 0.54 mmol) and palladium tetrakis(triphenylphosphine) (39 mg, 0.033 mmol) were combined in a round bottom flask. The flask was evacuated and back-filled with Ar three times. Pyrrolidine (3.0 mL), alkyne **91** (132 mg, 0.51 mmol in 0.5 ml pyrrolidine), and iodobenzene (200 μL, 1.79 mmol) were added sequentially and the mixture was stirred at ambient temperature 16 h. Et_2O was added (20 mL) and the mixture was filtered through a plug of silica gel. Solvent was evaporated, and the crude residue was purified via column chromatography (9:1 hexane-EtOAc) to afford the title compound as a clear, yellow oil (147 mg, 86% yield). R_f (90:10, hexane-EtOAc) = 0.15.

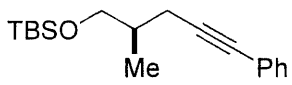
IR (thin film/NaCl): 3417, 2958, 2930, 2871, 1598, 1491, 1442 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.40-7.32 (m, 6H), 7.28-7.22 (m, 4H), 6.56 (s, 1H), 3.90-3.86 (m, 1H), 2.99-2.93 (m, 1H), 2.74 (dd, J = 9.8, 13.7 Hz, 1H), 2.68-2.56 (m, 1H), 2.35 (dd, J = 5.8, 13.7 Hz, 1H), 2.26 (dd, J = 9.8, 13.8 Hz, 1H), 1.87 (br s, 1H), 1.57-1.39 (m, 4H), 1.27 (d, J = 6.7 Hz, 3H), 0.96 (t, J = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.9, 137.7, 131.7 (2C), 130.7, 129.1, 128.39 (2C), 128.36 (2C), 127.8 (2C), 126.7, 123.8, 93.8, 81.9, 69.3, 45.6, 39.5, 37.4, 25.3, 21.5, 19.2, 14.4.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{24}H_{28}ONa$ 355.2032, obsd 355.2021.

$[\alpha]_D$ = +12 (23 °C, c = 3.2, $CDCl_3$)



(+)-1-(*t*-butyldimethylsiloxy)-(2*R*)-methyl-5-phenyl-4-pentyne (42). A 50 mL round bottom flask was charged with **68** (1.10 g, 6.3 mmol), imidazole (0.79 g, 11.6 mmol), *t*-butyldimethylsilylchloride (1.60 g, 10.6 mmol) and DMF (6.3 ml). The solution was stirred 20 h at ambient temperature, then partitioned between H_2O and Et_2O (80 mL each). The ethereal layer was washed with H_2O (3 x 100 mL), brine (3 x 100 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified via gradient column chromatography (50:1 hexane-EtOAc, polarity gradually increased to 19:1) to afford the title compound as a clear, colorless oil (1.74 g, 96% yield). R_f (hexane) = 0.21.

IR (thin film/NaCl): 2956, 2929, 2857, 1490, 1471 cm^{-1}.

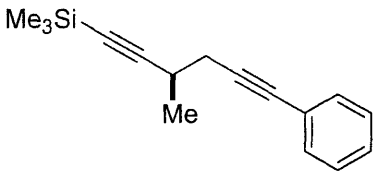
^1H NMR ($CDCl_3$, 500 MHz): δ 7.42-7.40 (m, 2H), 7.32-7.27 (m, 3H), 3.60-3.54 (m, 2H), 2.52 (dd, J = 5.8, 16.5 Hz, 1H), 2.37 (dd, J = 7.0, 16.7 Hz, 1H), 1.97-1.93 (m, 1H), 1.05 (d, J = 6.7 Hz, 3H), 0.93 (s, 9H), 0.09 (s, 6H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 131.7 (2C), 128.4 (2C), 127.7, 124.3, 89.1, 81.7, 67.1, 35.7, 26.2, 26.1, 23.2, 18.6, 16.4, -5.13, -5.15, -5.18.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{18}H_{28}NaOSi$ 311.1802, obsd 311.1806.

$[\alpha]_D$ = +1.2 (23 °C, *c* = 10.7, CH_2Cl_2).

ent-**42**: $[\alpha]_D$ = −15 (23 °C, *c* = 4.1, CH_2Cl_2).



(−)-Trimethyl-[(3*R*)-methyl-6-phenyl-hexa-1,5-diynyl]-silane (43). A solution of dibromide **89** in THF (421 mg, 1.29 mmol in 3.5 mL) was cooled to −78 °C. A 1.6 M solution of methyllithium in Et_2O was added dropwise (2.0 mL, 3.2 mmol) and the solution was stirred 1.5 h at −78 °C. Chlorotrimethylsilane was filtered through basic alumina and immediately added dropwise (0.49 ml, 3.9 mmol) to the reaction. The solution was stirred 14 h, warming to ambient temperature slowly. Saturated NH_4Cl was added (1 mL), and the mixture was diluted with Et_2O and H_2O (2 ml each). The aqueous phase was extracted with Et_2O (3 x 5 mL), and the combined organic layers were washed with brine (3 x 15 ml), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified via gradient column chromatography (50:1 hexanes:EtOAc, polarity gradually increased to 19:1) to afford the product as a clear, colorless oil (284 mg, 92% yield). R_f (90:10, hexane:EtOAc) =0.62.

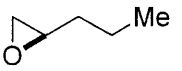
IR (thin film/NaCl): 2962, 2932, 2907, 2170, 1491, 1280 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.43-7.41 (m, 2H), 7.30-7.29 (m, 3H), 2.80-2.73 (m, 1H), 2.67 (dd, J = 5.5, 16.8 Hz, 1H), 2.52 (dd, J = 7.9, 16.8 Hz, 1H), 1.34 (d, J = 7.0 Hz, 3H), 0.17 (s, 9H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 131.8 (2C), 128.4 (2C), 127.9, 123.9, 110.3, 87.7, 85.2, 82.4, 27.5, 27.0, 20.4, 0.4 (3C).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{16}H_{20}NaSi$ 263.1226, obsd 263.1227.

$[\alpha]_D$ = − 3.0 (23 °C, c = 5.4, CH_2Cl_2).



(+)-(*R*)-1,2-epoxypentane (44). Prepared according to Jacobsen's HKR protocol; yields are best using at least 2 mol% catalyst.[12] A flask was charged with (+/−)-1,2-epoxypentane (20.8 mL, 200 mmol) and (*R*,*R*)-*N*,*N*'-bis(3,5-di-*t*-butylsalicylidene)-1,2-cyclohexanediamino cobalt (III) acetate (4.0 g, 6.0 mmol). The mixture was cooled to 0 °C and H_2O (1.98 mL) was added over 5 min. The mixture was allowed to warm to ambient temperature and stirred 21 h. Separation of the volatile epoxide and H_2O from the 1,2-diol was accomplished by distillation (essentially vacuum transfer). Residual H_2O was removed by treatment with $MgSO_4$ and subsequent filtration to afford the resolved epoxide (4.5 g, 26% yield, >98% ee). Spectral data matched those previously reported.[43]

Determination of ee: Derivitization was necessary. The epoxide was opened by PhLi in the presence of $BF_3{\cdot}OEt_2$, followed by acetate protection by treatment with acetic anhydride, DMAP and pyridine. Chiral GC analysis of the acetate: (B-PH, 60 °C for 4 min, then increase by 2 °C per min until 130 °C, t_R [(*S*)] = 34.56 min, t_R [(*R*)] = 34.80 min).

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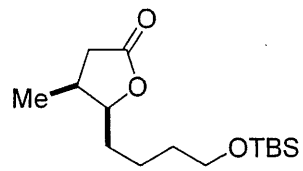
[43] Prepared from (*R*)-1,2-pentanediol by treatment *p*-toluenesulfonyl chloride and pyridine. MacMillan, J. B.; Molinski, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 9944-9945.



(−)-(5*S*)-[4-(tert-Butyldimethylsilanyloxy)-butyl]-(4*S*)-methyl-dihydro-furan-2-one (56).[44] A 100 mL flask was charged with 3Ä powdered molecular sieves (8.1 g) and 4-*N*-methylmorpholine-*N*-oxide (5.70 g, 49.1 mmol). A solution of **82** in dry CH_3CN (4.75 g, 16.4 mmol in 160 mL) was added via cannula and the mixture was stirred 5 min. Tetrapropylammonium perruthenate was added slowly (0.86 g, 2.5 mmol), and the mixture was stirred 14h. Silica gel was added, and the solvent was evaporated. The dry silica gel was loaded onto a slurry-packed column (70:30 hexanes-EtOAc), eluted and concentrated to give the title compound as a clear, colorless oil (3.35 g, 71% yield, 93% ee). R_f (70:30, hexane-EtOAc) = 0.34.

IR (thin film/NaCl): 2930, 2858, 1780 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 4.45-4.41 (m, 1H), 3.64-3.59 (m, 2H), 2.69 (dd, J = 7.9, 17.0 Hz, 1H), 2.60-2.55 (m, 1H), 2.19 (dd, J = 3.8, 17.0 Hz, 1H), 1.70-1.59 (m, 1H), 1.58-1.47 (m, 4H), 1.45-1.40 (m, 1H), 1.00 (d, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.1, 83.8, 63.0, 37.7, 33.1, 32.7, 29.9, 26.1 (3C), 22.5, 18.5, 14.0, -5.1 (2C).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{15}H_{30}NaO_3Si$ 309.1856, obsd 309.1840.

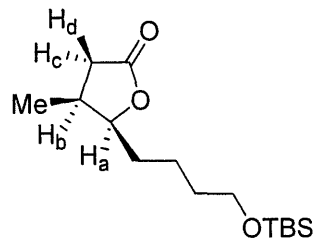
$[\alpha]_D = -37.0$ (23 °C, c = 10.6, CH_2Cl_2).

Chiral GC analysis was performed on the acetate derivative (OAc instead of OTBS): (G-TA, isothermal, column = 150 °C, injector = 200 °C, flow (H_2) = 1.5 ml/min): $t_R[(S,S)]$ = 21.32 min; $t_R[(R,R)]$ = 21.86 min).

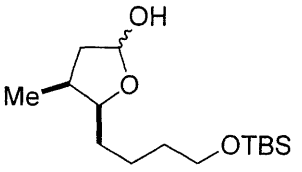
Relative configuration confirmed by nOe studies:

Summary of nOe data:

$H_{a(irradiated)}$-H_b: 5.7%
$H_{a(irradiated)}$-H_c: 1.8%
$H_{Me(irradiated)}$-H_b: 2.0%
$H_{Me(irradiated)}$-H_d: 2.3%



[44] Prepared in analogy to lactones and tetrahydrofuran acetates reported in reference 14.



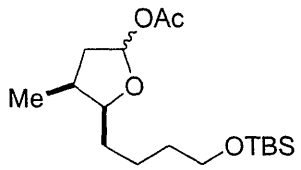
(5*S*)-[4-(tert-Butyldimethylsilanyloxy)-butyl]-(4*S*)-methyl-tetrahydro-furan-2-ol (57a).[44] Diisobutylaluminum hydride (4.3 ml, 1.0 M in hexane, 4.3 mmol) was added to a cooled solution (−78 °C) of **56** in CH_2Cl_2 (1.02 g, 3.60 mmol, in 70 ml CH_2Cl_2). The solution was stirred 1 h, then quenched with saturated NH_4Cl (5 ml) and allowed to warm to ambient temperature. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 ml), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give the title compound as a clear, colorless oil that was used without purification (1.00 g, 97% yield, 2.4:1 d.r.). R_f (70:30, hexane-EtOAc) = 0.29

IR (thin film/NaCl): 3411, 2935, 2858 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ major 5.52-5.51(m, 1H), minor 5.43 (m, 1H), major 4.13-4.10 (m, 1H), 3.92 (s, 1H, OH) minor 3.88-3.86 (m, 1H), 3.61-3.58 (m, 2H), major 2.40-2.33 (m, 1H), minor 2.23-2.21 (m, 1H), 2.00-1.96 (m, 1H), 1.79-1.75 (m, 1H), 1.61-1.52 (m, 2H), 1.50-1.30 (m, 4H), minor 1.03 (d, J = 6.9 Hz, 3H), 0.87-0.83 (m, 9H + 3H from major diastereomer), 0.03 (s, 6H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 98.4 (minor 97.4), 82.9 (minor 80.7), 63.3 (minor 63.2), 42.1 (minor 41.3), 34.5 (minor 35.0), 33.1 (minor 33.0), 30.3 (minor 31.0), 26.1, 22.89 (minor 22.93), 18.5, 14.6 (minor 14.8), -5.1.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{15}H_{32}NaO_3Si$ 311.2013, obsd 311.2004.



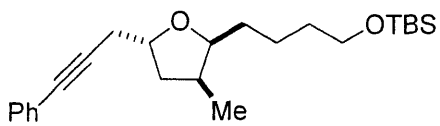
Acetic acid (5*S*)-[4-(tert-butyldimethylsilanyloxy)-butyl]-(4*S*)-methyl-tetrahydro-furan-2-yl ester (57b). A solution of **56** in CH_2Cl_2 was cooled to -78 °C (0.86 g, 3.0 mmol, in 60 mL). DIBAL-H was added via syringe (3.6 mL, 1.0 M in CH_2Cl_2, 3.6 mmol) and the solution was stirred at -78 °C for 2h. 4-Dimethylaminopyridine (0.44 g, 3.6 mmol), acetic anhydride (2.8 mL, 30 mmol), and pyridine (1.9 mL, 24 mmol) were added sequentially. The mixture was stirred at −78 °C for 15 min, then allowed to warm to ambient temperature and stir 18h. The reaction was quenched by addition of saturated NH_4Cl (30 mL), and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (5 x 30 mL) and concentrated. The crude residue was partitioned between Et_2O and H_2O (50 mL each). The ethereal layer was washed with saturated NH_4Cl (2 x 25 mL) and brine (2 x 50 mL), dried over $MgSO_4$, filtered and concentrated. The crude oil was purified via column chromatography (90:10 hexanes:EtOAc) to afford the title compound as a clear, slightly yellow oil (0.79 g, 80% yield, 1.3:1 d.r.). R_f (95:5, EtOAc:hexane) = 0.14.

IR (NaCl): 2931, 2858, 1749, 1250 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ major 6.24 (dd, J = 2.3, 5.6 Hz, 1H), minor 6.16 (dd, J = 1.8, 6.1 Hz, 1H), major 4.12-4.08 (m, 1H), minor 3.98-3.96 (m, 1H), 3.61-3.57 (m, 2H), 2.43-2.36 (m, 1H), major 2.10 (ddd, J = 2.4, 7.3, 13.7 Hz, 1H), 2.02 (s, 3H), major 1.88 (dt, J = 5.8, 13.7 Hz, 1H), minor 1.75 (ddd, J = 2.0, 4.3, 13.6 Hz, 1H), 1.57-1.32 (m, 6H), minor 1.02 (d, J = 7.0 Hz, 3H), major 0.91 (d, J = 7.0 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.8 (minor 170.7), 98.3 (minor 98.8), 82.6 (minor 84.4), 63.2, 40.6 (minor 40.1), 33.9 (minor 34.3), 33.0, 30.2 (minor 30.7), 26.1, 22.7 (minor 22.8), 21.60 (minor 21.64), 18.5, 14.4 (minor 14.3), -5.1.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{17}H_{34}NaO_4Si$ 353.2119, obsd 353.2108.



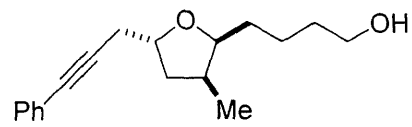
***tert*-Butyldimethyl-{4-[(3*S*)-methyl-(5*R*)-(3-phenyl-prop-2-ynyl)-tetrahydro-furan-2-yl]-butoxy}-silane (58).** Obtained in some reactions following the procedure described in Table 2 (see also the following procedure for **59**). R_f (90:10, hexane-EtOAc) = 0.34.

IR (thin film/NaCl): 2956, 2930, 2857, 1254 cm $^{-1}$.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.41-7.39 (m, 2H), 7.29-7.28 (m, 3H), 4.30 (d^4, J = 4.9, 7.0, 7.0, 7.0 Hz, 1H), 3.99 (m, 1H), 3.65-3.60 (m, 2H), 2.68 (dd, J = 4.7, 16.6 Hz, 1H), 2.60 (dd, J = 7.2, 16.6 Hz, 1H), 2.34-2.28 (m, 1H), 2.06 (ddd, J = 7.3, 9.0, 10.8 Hz, 1H), 1.87 (ddd, J = 3.4, 7.0, 12.5 Hz, 1H), 1.60-1.32 (m, 6H), 0.94 (d, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.05 (s, 6H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 131.8 (2C), 128.4 (2C), 127.9, 124.0, 87.1, 82.3, 81.9, 75.2, 63.3, 39.4, 36.1, 33.2, 30.4, 27.2, 26.20, 26.19 (3C), 22.9, 14.2, -5.0 (2C).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{24}H_{38}NaO_2Si$ 409.2535, obsd 409.2529.



(+)-4-[(3*S*)-Methyl-(5*R*)-(3-phenyl-prop-2-ynyl)-tetrahydro-furan-(2*S*)-yl]-butan-1-ol (59). A solution of **57a** (480 mg, 1.65 mmol) and trimethyl-(1-phenyl-propa-1,2-dienyl)-silane (**52**)[45] (1.39mL, 0.89 g/mL, 6.6 mmol) in 3.3 mL CH_2Cl_2 was cooled to −78 °C. $BF_3{\cdot}OEt_2$ (0.63 mL, 4.9 mmol) was added dropwise via syringe, and the mixture was stirred for 2 h, then allowed to warm to ambient temperature slowly over 14 h. The reaction was quenched by dropwise addition of saturated $NaHCO_3$ (2 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 4 mL), dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by gradient column chromatography (90:10 CH_2Cl_2-EtOAc, polarity increased to 50:50) to afford the title compound as a clear, yellow oil (180 mg, 41% yield). R_f (50:50, EtOAc-CH_2Cl_2) = 0.47.

Also prepared from terminal alkyne **61**: Copper (I) iodide (83 mg, 0.44 mmol) and palladium tetrakis(triphenylphosphine) (170 mg, 0.15 mmol) were combined in a round bottom flask with alkyne **61** (296 mg, 1.48 mmol). The flask was evacuated and back-filled with Ar three times. Pyrrolidine (5.0 mL) and iodobenzene (0.50 mL, 4.5 mmol) were added sequentially and the mixture was stirred at ambient temperature 3.5 h. Et_2O was added (10 mL) and the mixture was filtered through a plug of silica gel. Solvent was evaporated, and the crude residue was purified via column chromatography (70:30 hexane-EtOAc, polarity gradually increased to 50:50 hexane-EtOAc) to afford the title compound as a clear, yellow oil (395 mg, 98% yield).

IR (thin film/NaCl): 3395, 2936, 2870, 2361 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.41-7.39 (m, 2H), 7.29-7.28 (m, 3H), 4.33-4.28 (m, 1H), 4.02-3.98 (m, 1H), 3.67 (t, J = 6.6 Hz, 2H), 2.67 (dd, J = 4.8, 16.6 Hz, 1H), 2.60 (dd, J = 7.0, 16.6 Hz, 1H), 2.34-2.32 (m, 1H), 2.07 (ddd, J = 7.0, 9.0, 10.8 Hz, 1H), 1.89 (ddd, J = 3.7, 7.0, 12.5 Hz, 1H), 1.65-1.61 (m, 2H), 1.54-1.50 (m, 2H), 1.46-1.41 (m, 2H), 0.94 (d, J = 7.0 Hz, 3H).

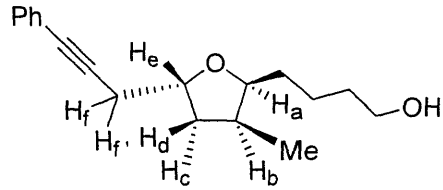
^{13}C NMR ($CDCl_3$, 125 MHz): δ 131.8 (2C), 128.4 (2C), 127.9, 124.0, 87.1, 82.3, 82.0, 75.3, 63.1, 39.4, 36.2, 33.0, 30.3, 27.2, 23.0, 14.2.

HRMS (ESI) $[M+H]^+$: *m/z* calcd for $C_{18}H_{25}O_2$ 273.1849, obsd 273.1856.

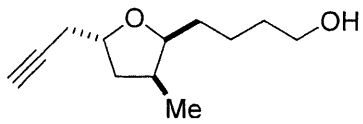
$[\alpha]_D$ = +1.0 (23 °C, c = 7.8, CH_2Cl_2).

Relative configuration confirmed by nOe studies:
Summary of nOe data:

$H_{a(irradiated)}$-H_b: 3.4%; $H_{a(irradiated)}$-H_c: 0.3%
$H_{e(irradiated)}$-H_d: 2.9%; $H_{e(irradiated)}$-H_f/H_f': 2.9%



[45] Prepared as reported in reference 21.



(−)-4-[(3*S*)-Methyl-(5*R*)-(prop-2-ynyl)-tetrahydro-furan-(2*S*)-yl]-butan-1-ol (61). A solution of **57a** (340 mg, 1.20 mmol) and triphenyl-propa-1,2-dienyl-stannane (**60**)[46] (930 mg, 2.39 mmol) in 3.6 mL CH_2Cl_2 was cooled to −78 °C. $BF_3{\cdot}OEt_2$ (0.46 mL, 3.6 mmol) was added dropwise via syringe, and the mixture was stirred for 2 h, then allowed to warm to ambient temperature slowly over 14 h. The reaction was quenched by dropwise addition of saturated $NaHCO_3$ (2 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL), dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by gradient column chromatography (90:10 hexane-EtOAc, polarity increased to 50:50) to afford the title compound as a clear, colorless oil (207 mg, 88% yield). R_f (50:50, EtOAc-hexane) = 0.26.

IR (thin film/NaCl): 3384, 3294, 2934, 2870, 2119 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 4.25-4.19 (m, 1H), 3.97-3.93 (m, 1H), 3.65 (t, J = 6.7 Hz, 2H), 2.44 (ddd, J = 2.6, 5.2, 16.6 Hz, 1H), 2.37 (ddd, J = 2.7, 6.8, 16.6 Hz, 1H), 2.32-2.27 (m, 1H), 1.99-1.93 (m, 1H), 1.82 (ddd, J = 3.7, 7.0, 12.5 Hz, 1H), 1.64-1.58 (m, 2H), 1.55-1.46 (m, 2H), 1.43-1.35 (m, 2H), 0.92 (d, J = 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 82.2, 81.5, 75.0, 69.8, 63.0, 39.3, 36.1, 33.0, 30.2, 26.2, 22.9, 14.1.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{12}H_{20}NaO_2$ 219.1356, obsd 219.1351.

$[\alpha]_D$ = −1.0 (23 °C, c = 3.0, CH_2Cl_2)

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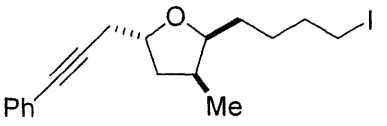
[46] Victor Gehling generously donated **60** which he had previously prepared according to reference 23.



(+)-(2*S*)-(4-Iodo-butyl)-(3*S*)-methyl-(5*R*)-(3-phenyl-prop-2-ynyl)-tetrahydro-furan (62). A solution of **59** in a 2:3 mixture of CH_3CN-Et_2O (383 mg, 1.40 mmol, in 4.2 mL) was cooled to 0 °C. Imidazole (124 mg, 1.82 mmol), triphenylphosphine (440 mg, 1.68 mmol), and iodine (497 mg, 1.96 mmol) were added sequentially, and the brown heterogeneous mixture was stirred at 0 °C for 3.5 h. Silica gel was added, and the solvents were removed in vacuo. The dry silica gel was loaded onto a slurry-packed column (95:5 hexane-EtOAc), the title compound was eluted and concentrated to give a clear, pale yellow oil (391 mg, 73% yield). R_f (90:10 hexane-EtOAc) = 0.30.

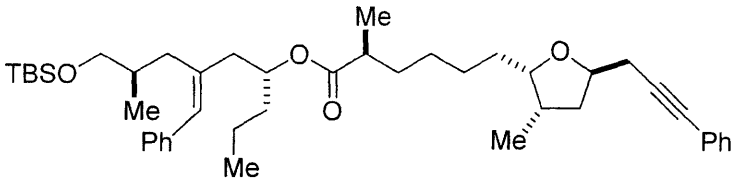
IR (thin film/NaCl): 3055, 2960, 2934, 2872, 1598 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ 7.43-7.38 (m, 2H), 7.33-7.26 (m, 3H), 4.31 (ddd, J = 5.0, 6.8, 14.0 Hz, 1H), 4.03-3.97 (m, 1H), 3.22 (t, J = 6.9 Hz, 2H), 2.70 (dd, J = 5.0, 16.5 Hz, 1H), 2.62 (dd, J = 6.9, 16.5 Hz, 1H), 2.39-2.31 (m, 1H), 2.13-2.04 (m, 1H), 1.95-1.85 (m, 3H), 1.61-1.39 (m, 5H), 0.97 (d, J = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 131.6 (2C), 128.2 (2C), 127.7, 123.8, 87.0, 81.92, 81.89, 75.2, 39.4, 36.2, 33.9, 29.6, 27.8, 27.3, 14.3, 7.3.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{18}H_{23}INaO$ 405.0763, obsd 405.0679.

$[\alpha]_D$ = +16 (23 °C, c = 7.5, $CHCl_3$)



(+)-(2*S*)-Methyl-6-[(3*S*)-methyl-(5*R*)-(3-phenyl-prop-2-ynyl)-tetrahydro-furan-(2*S*)-yl]-hexanoic acid 3-benzylidene-6-(tert-butyl-dimethyl-silanyloxy)-(5*R*)-methyl-(1*R*)-propyl-hexyl ester (63). A flask containing **38** (21 mg, 0.064 mmol) was charged with **39** (31 mg, 0.083 mmol), dicyclohexylcarbodiimide (21 mg, 0.10 mmol), 4-pyrrolidinopyridine (15 mg, 0.10 mmol), and CH_2Cl_2 (0.42 ml). The mixture was stirred 24 h at ambient temperature. Silica gel was added, and the solvents were removed in vacuo. The dry silica gel was loaded onto a slurry-packed column (90:10 hexane-EtOAc) and the title compound was eluted to give a clear, colorless oil (28 mg, 72% yield) upon concentration. R_f (90:10, hexane-EtOAc) = 0.39.

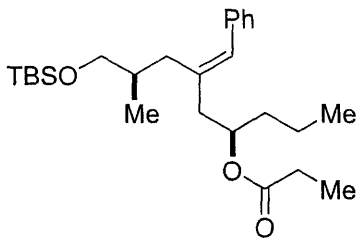
IR (thin film/NaCl): 2933, 2857, 1730, 1463 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.41-7.39 (m, 2H), 7.31-7.28 (m, 5H), 7.19-7.16 (m, 3H), 6.36 (s, 1H), 5.14-5.11 (m, 1H), 4.31-4.26 (m, 1H), 3.96-3.92 (m, 1H), 3.40 (dd, *J* = 5.5, 9.8 Hz, 1H), 3.23 (dd, *J* = 6.6, 9.8 Hz, 1H), 2.68 (dd, *J* = 4.9, 16.5 Hz, 1H), 2.59 (dd, *J* = 7.0, 16.5 Hz, 1H), 2.44-2.34 (m, 3H), 2.32-2.27 (m, 1H), 2.14 (dd, *J* = 8.2, 14.0 Hz, 1H), 2.05 (ddd, *J* = 7.0, 9.0, 10.8 Hz, 1H), 1.92-1.84 (m, 2H), 1.69-1.63 (m, 1H), 1.60-1.56 (m, 2H), 1.51-1.22 (m, 10H), 1.09 (d, *J* = 6.7 Hz, 3H), 0.93 (t, *J* = 7.3 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.86 (s, 9H), 0.82 (d, *J* = 6.7 Hz, 3H), -0.01 (s, 3H), -0.02 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.7, 138.3, 138.0, 131.8 (2C), 129.3, 129.1 (2C), 128.4 (2C), 128.2 (2C), 127.9, 126.3, 124.0, 87.1, 82.3, 81.9, 75.2, 71.9, 68.2, 42.8, 40.0, 39.4, 36.6, 36.1, 34.3, 34.01, 33.95, 30.5, 27.7, 27.2, 26.7, 26.1 (3C), 18.9, 18.5, 17.4, 17.1, 14.23, 14.19, -5.20, -5.22.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{44}H_{66}NaO_4Si$ 709.4623, obsd 709.4611.

$[\alpha]_D$ = +1.0 (23 °C, *c* = 4.9, $CDCl_3$)



(+)-Propionic acid 3-benzylidene-6-(tert-butyl-dimethyl-silanyloxy)-(5*R*)-methyl-(1*R*)-propyl-hexyl ester (64). To a solution of alcohol **39** in CH_2Cl_2 (96 mg, 0.25 mmol, in 1.5 mL) was added propionic anhydride (50 μL, 0.38 mmol), pyridine (31 μL, 0.38 mmol), and 4-dimethylaminopyridine (3 mg, 0.025 mmol). The solution was allowed to stir at ambient temperature 16h. After concentration, the crude residue was taken up in 30 mL Et_2O, washed with saturated NH_4Cl (3 x 15ml) and brine (3 x 15 mL), dried over $MgSO_4$, filtered and concentrated. Purification via column chromatography (50:1 hexanes-EtOAc) afforded the title compound as a colorless oil (110 mg, >99% yield). R_f (95:5, hexane-EtOAc) = 0.28.

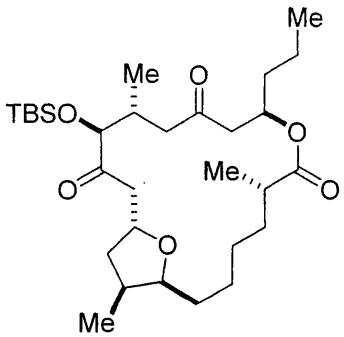
IR (thin film/NaCl): 2958, 2930, 2857, 1735, 1463 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.30-7.28 (m, 2H), 7.20-7.16 (m, 2H), 7.06-7.03 (m, 1H), 6.46 (s, 1H), 5.40-5.35 (m, 1H), 3.40 (dd, J = 5.5, 9.8 Hz, 1H), 3.27 (dd, J = 6.1, 9.8 Hz, 1H), 2.61 (dd, J = 6.4, 14.0 Hz, 1H), 2.47 (dd, J = 7.9, 13.5 Hz, 1H), 2.38-2.31 (m, 2H), 2.15-2.12 (m, 2H), 2.09-2.04 (m, 1H), 1.65-1.46 (m, 2H), 1.43-1.32 (m, 2H), 1.00 (t, J = 7.6 Hz, 3H), 0.96 (s, 9H), 0.91-0.87 (m, 6H), 0.034 (s, 3H), 0.028 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.8, 139.0, 138.7, 130.0, 129.6 (2C), 128.8 (2C), 126.9, 72.1, 68.6, 43.7, 37.1, 35.0, 34.6, 28.3, 26.5 (3C), 19.5, 18.9, 17.4, 14.5, 9.8, -4.9 (2C).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{26}H_{44}NaO_3Si$ 433.3132, obsd 433.3123.

$[\alpha]_D$ = +0.77 (23 °C, c = 2.6, CH_2Cl_2).



(−)-(14*S*)-(tert-Butyl-dimethyl-silanyloxy)-(6*S*,13*R*,19*R*)-trimethyl-(9*R*)-propyl-8,20-dioxa-bicyclo[15.2.1]icosane-7,11,15-trione (67). A solution of **86** in CH_2Cl_2 was prepared (9.1 mg, 0.013 mmol in 2.0 ml) and cooled to −78 °C. Ozone was bubbled through the solution until a persistent blue color was observed. The ozone source was removed, and the saturated solution was stirred 15 min. After this time, Ar was bubbled through the solution until it was colorless. Methyl sulfide (0.10 ml) was added via syringe. The solution was allowed to warm to ambient temperature over 6 h; then concentrated. The crude residue was purified via Pasteur pipet gradient column chromatography (50:1 hexane-EtOAc, polarity gradually increased to 9:1 hexane-EtOAc) to give the title compound as a clear, yellow oil (3.0 mg, 43% yield). R_f (90:10, hexane-EtOAc) = 0.21.

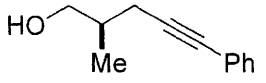
IR (thin film/NaCl): 2960, 2932, 2857, 1730, 1728, 1713, 1259 cm^{-1}.

^1H NMR (C_6D_6, 500 MHz): δ 5.64-5.59 (m, 1H), 4.71-4.66 (m, 1H), 4.47 (d, J = 1.5 Hz, 1H), 3.82-3.80 (m, 1H), 3.08-3.03 (m, 1H), 3.05 (dd, J = 10.7, 14.0 Hz, 1H), 2.67 (dd, J = 10.1, 19.2 Hz, 1H), 2.43-2.37 (m, 2H), 2.17 (dd, J = 2.4, 19.2 Hz, 1H), 1.97 (dd, J = 2.4, 14.8 Hz, 1H), 1.83 (dd, J = 1.7 Hz, 14.2 Hz, 1H), 1.67-1.62 (m, 1H), 1.61-1.53 (m, 2H), 1.50-1.43 (m, 2H), 1.41-1.35 (m, 3H), 1.31-1.20 (m, 3H), 1.18-1.09 (m, 4H), 1.08-1.07 (m, 12H), 1.01 (d, J = 7.0 Hz, 3H), 0.80 (t, J = 7.0 Hz, 3H), 0.65 (d, J = 7.0 Hz, 3H), 0.25 (s, 3H), 0.03 (s, 3H).

^{13}C NMR (C_6D_6, 125 MHz): δ 208.7, 208.2, 174.3, 81.1, 77.7, 74.6, 71.2, 50.1, 46.5, 46.3, 43.2, 40.8, 37.3, 37.1, 37.0, 31.4, 28.2, 27.6, 27.3, 26.5 (3C), 26.3, 18.9, 18.8, 14.6, 14.5, 14.2, -3.8, -4.9.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{30}H_{54}NaO_6Si$ 561.3582, obsd 561.3587.

$[\alpha]_D$ = −5 (23 °C, *c* = 0.8, $CDCl_3$)



(+)-(2*R*)-methyl-5-phenyl-pent-4-yn-1-ol (68). A solution of **81** (0.69 g, 2.3 mmol in 8 mL THF) was cooled to 0 °C. $LiAlH_4$ was added slowly in one portion (0.26 g, 6.9 mmol). The slurry was stirred 1 h at 0 °C, then quenched with 0.75 mL H_2O. Saturated Rochelle's salt solution (10 mL) and Et_2O (15 mL) were added, and the mixture was stirred 30 min to aid in disrupting the emulsion. After this time, the opaque aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 40 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified via column chromatography (95:5 CH_2Cl_2-EtOAc) to afford the title compound as a pale yellow oil (0.32 g, 79% yield, 98% ee). R_f (95:5, CH_2Cl_2-EtOAc) = 0.35.

IR (thin film/NaCl): 3330, 2958, 2924, 2873, 1490 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.42-7.39 (m, 2H), 7.32-7.28 (m, 3H), 3.68-3.64 (m, 2H), 2.51 (dd, J = 6.1, 16.8 Hz, 1H), 2.45 (dd, J = 6.4, 16.8 Hz, 1H), 2.02-1.96 (m, 1H), 1.65 (br s, 1H), 1.08 (d, J = 6.7 Hz, 3H).

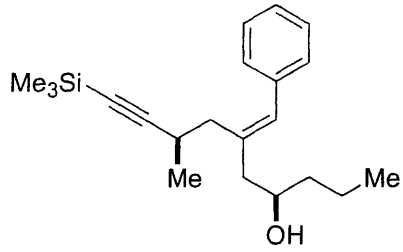
^{13}C NMR ($CDCl_3$, 125 MHz): δ 131.7 (2C), 128.4 (2C), 127.9, 123.9, 88.3, 82.2, 67.3, 35.5, 23.4, 16.5.

HRMS (EI) $[M^+]$: *m/z* calcd for $C_{12}H_{14}O$ 174.1039, obsd 174.1035.

$[\alpha]_D$ = +2.0 (23 °C, *c* = 3.0, CH_2Cl_2).

ent-**68**: $[\alpha]_D$ = −12 (23 °C, *c* = 7.2, CH_2Cl_2).

Chiral HPLC analysis was performed on the Mosher ester derivative[37] (alcohol was coupled with *R*-MTPA using DCC/DMAP conditions): (OD, isocratic, 98:2 hexane:*i*-propanol, 1 ml/min): $t_R[(R,R)]$ = 9.23 min; $t_R[(R,S)]$ = 11.86 min).



(+)-6-Benzylidene-(8*R*)-methyl-10-trimethylsilanyl-dec-9-yn-(4*R*)-ol (69). In a glovebox, $Ni(cod)_2$ (36 mg, 0.13 mmol) was placed in a 10 ml flask which was then sealed with a rubber septum. The flask was removed from the glovebox and placed under Ar. To this flask was added tributylphosphine (36 μL, 0.26 mmol), **44** (degassed by bubbling Ar through for 10 min, 0.70 ml, 6.7 mmol), triethylborane (0.36 mL, 2.3 mmol), and diyne **43** (267 mg, 1.11 mmol). The resulting dark brown solution was stirred at ambient temperature 14 h, then opened to the air for 1 h. Volatile organics were evaporated, and the crude residue was purified via gradient column chromatography (50:1 hexane-EtOAc, polarity gradually increased to 9:1) to afford the title compound as a clear, yellow oil (158 mg, 45% yield). R_f (90:10, hexane-EtOAc) = 0.23.

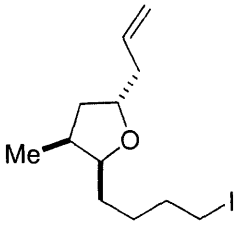
IR (thin film/NaCl): 3416 (br), 2959, 2931, 2873, 2162, 1599 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.36-7.30 (m, 3H), 7.25-7.21 (m, 2H), 6.53 (s, 1H), 3.85-3.83 (m, 1H), 2.79-2.74 (m, 1H), 2.61 (dd, J = 9.8, 13.7 Hz, 1H), 2.53-2.50 (m, 1H), 2.27-2.19 (m, 2H), 1.95 (d, J = 2.4 Hz, 1H), 1.58-1.42 (m, 4H), 1.17 (d, J = 7.0 Hz, 3H), 0.98 (t, J = 7.0 Hz, 3H), 0.12 (s, 9H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.9, 137.6, 130.5, 129.1 (2C), 128.3 (2C), 126.6, 111.2, 85.7, 69.3, 45.5, 39.5, 37.4, 25.5, 21.4, 19.2, 14.4, 0.3 (3C).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{21}H_{32}ONa$ 351.2115, obsd 351.2128.

$[\alpha]_D$ = + 116 (23 °C, c = 4.1, CH_2Cl_2)



(−)-(5*R*)-Allyl-(2*S*)-(4-iodo-butyl)-(3*S*)-methyl-tetrahydro-furan (70). A solution of **93** in a 2:3 mixture of CH_3CN-Et_2O (220 mg, 1.11 mmol, in 3.2 mL) was cooled to 0 °C. Imidazole (98 mg, 1.44 mmol), triphenylphosphine (350 mg, 1.33 mmol), and iodine (398 mg, 1.57 mmol) were added sequentially, and the brown heterogeneous mixture was stirred at 0 °C for 4 h. Silica gel was added, and the solvents were removed in vacuo. The dry silica gel was loaded onto a slurry-packed column (95:5 hexane-EtOAc), the title compound was eluted and concentrated to give a clear, pale yellow oil (295 mg, 86% yield). R_f (90:10 hexane-EtOAc) = 0.31.

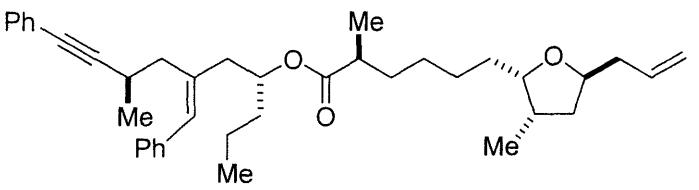
IR (thin film/NaCl): 3074, 2960, 2935, 2873, 1641 cm^{-1}.

^1H NMR (C_6D_6, 500 MHz): δ 5.91-5.83 (m, 1H), 5.10-5.04 (m, 2H), 4.04-3.98 (m, 1H), 3.65-3.62 (m, 1H), 2.72 (t, J = 7.0 Hz, 2H), 2.34-2.28 (m, 1H), 2.15-2.10 (m, 1H), 1.91-1.86 (m, 1H), 1.54-1.48 (m, 3H), 1.42-1.36 (m, 2H), 1.35-1.28 (m, 1H), 1.27-1.15 (m, 1H), 1.10-1.03 (m, 1H), 0.70 (d, J = 7.0 Hz, 3H).

^{13}C NMR (C_6D_6, 125 MHz): δ 136.1, 117.0, 81.2, 76.5, 41.9, 39.9, 36.6, 34.2, 30.0, 28.2, 14.5, 7.2.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{12}H_{21}IONa$ 331.0529, obsd 331.0521.

$[\alpha]_D$ = −1.1 (23 °C, c = 4.5, C_6H_6)



(+)-6-[(5*R*)-Allyl-(3*S*)-methyl-tetrahydro-furan-(2*S*)-yl]-(2*S*)-methyl-hexanoic acid 3-benzylidene-(5*R*)-methyl-7-phenyl-(1*R*)-propyl-hept-6-ynyl ester (71). Acid **40** (48 mg, 0.19 mmol) and alcohol **41** (31 mg, 0.093 mmol) were dissolved in 0.95 mL CH_2Cl_2. Dicyclohexylcarbodiimide (40 mg, 0.19 mmol) and 4-pyrrolidinopyridine (30 mg, 0.20 mmol) were added and the heterogeneous mixture was stirred at ambient temperature 14h. Silica gel was added, and the solvent was removed in vacuo. The dry silica gel was loaded onto a slurry-packed column (93:7 hexane-EtOAc) and the title compound was eluted and concentrated to give a clear, pale yellow oil (38 mg, 72% yield). R_f (90:10 hexane-EtOAc) = 0.23.

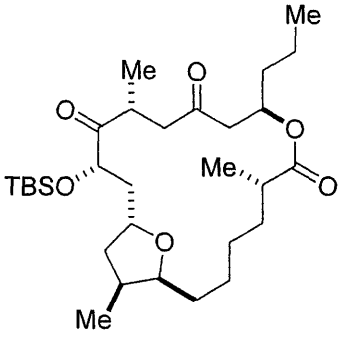
IR (thin film/NaCl): 2961, 2933, 2872, 2229, 1727, 1641, 1598 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.36-7.29 (m, 10H), 6.45 (s, 1H), 5.85-5.77 (m, 1H), 5.20-5.15 (m, 1H), 5.10-5.04 (m, 2H), 4.13-4.08 (m, 1H), 3.84-3.80 (m, 1H), 2.99-2.94 (m, 1H), 2.70 (dd, *J* = 9.5, 13.7 Hz, 1H), 2.59-2.52 (m, 1H), 2.48-2.39 (m, 2H), 2.37-2.32 (m, 1H), 2.23-2.17 (m, 2H), 1.79-1.72 (m, 1H), 1.71-1.66 (m, 2H), 1.63-1.58 (m, 2H), 1.47-1.26 (m, 10H), 1.24 (d, *J* = 6.7 Hz, 3H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.8, 138.1, 136.8, 135.3, 131.7 (2C), 130.4, 129.1 (2C), 128.32, 128.28 (3C), 127.7, 126.4, 124.0, 117.0, 94.1, 81.4, 76.1, 71.7, 42.6, 41.2, 39.9, 39.4, 37.1, 36.8, 36.0, 33.9, 30.5, 27.7, 26.7, 25.2, 21.3, 19.0, 17.4, 14.2 (2C).

HRMS (ESI)$[M+Na]^+$: *m/z* calcd for $C_{39}H_{52}O_3Na$ 591.3809, obsd 591.3814.

$[\alpha]_D$ = +11 (23 °C, *c* = 6.3, $CDCl_3$)



(+)-(15*S*)-(tert-Butyl-dimethyl-silanyloxy)-(6*S*,13*R*,19*S*)-trimethyl-(9*R*)-propyl-8,20-dioxa-bicyclo[15.2.1]icosane-7,11,14-trione (72). A solution of **95** in CH_2Cl_2 (6.7 mg, 0.011 mmol in 35 mL) was cooled to −78 °C. Ozone was bubbled through the solution until a blue color persisted. Argon was immediately bubbled through until the solution was colorless. Dimethylsulfide was added (0.80 ml) and the solution was allowed to slowly warm to ambient temperature over 3 h. The solution was concentrated and purified by gradient column chromatography (50:1 hexane-EtOAc, polarity increased to 93:7 hexane-EtOAc) to give the title compound as a clear oil (4.5 mg, 78% yield). R_f (80:20 hexane-EtOAc) = 0.45.

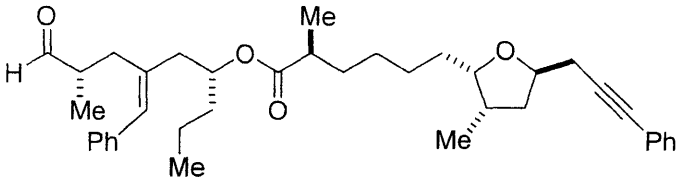
IR (thin film/NaCl): 2932, 2858, 1732, 1717 (br) cm^{-1}.

^1H NMR (C_6D_6, 500 MHz): δ 5.40-5.34 (m, 1H), 4.92 (t, J = 4.3 Hz, 1H), 4.43-4.38 (m, 1H), 4.02-4.00 (m, 1H), 3.60-3.56 (m, 1H), 3.09 (dd, J = 9.6, 18.8 Hz, 1H), 2.83-2.78 (m, 1H), 2.42-2.38 (m, 1H), 2.27 (dd, J = 11.1, 14.8 Hz, 1H), 2.09 (dd, J = 3.0, 18.8 Hz, 1H), 1.82 (dd, J = 2.6, 14.8 Hz, 1H), 1.77-1.66 (m, 3H), 1.59-1.43 (m, 6H), 1.36-1.28 (m, 3H), 1.26-1.15 (m, 4H), 1.07-1.04 (m, 15H), 0.77-0.74 (m, 6H), 0.26 (s, 3H), 0.14 (s, 3H).

^{13}C NMR (C_6D_6, 125 MHz): δ 211.8, 207.0, 174.3, 77.1, 76.5, 76.1, 71.4, 48.0, 45.9, 42.71, 42.67, 40.8, 37.5, 36.9, 36.7, 36.2, 30.5, 27.8, 27.2, 26.5 (3C), 19.0, 18.7, 18.6, 18.1, 14.8, 14.4, -3.6, -4.2.

HRMS (ESI)$[M+Na]^+$: *m/z* calcd for $C_{30}H_{54}O_6NaSi$ 561.3582, obsd 561.3576.

$[\alpha]_D$ = +3.3 (23 °C, c = 0.9, C_6D_6)



(−)-(2*S*)-Methyl-6-[(3*S*)-methyl-(5*R*)-(3-phenyl-prop-2-ynyl)-tetrahydro-furan-(2*S*)-yl]-hexanoic acid 3-benzylidene-(5*S*)-methyl-6-oxo-(1*R*)-propyl-hexyl ester (76). Dess-Martin periodinane (56 mg, 0.13 mmol) was added to a solution of **85** in CH_2Cl_2 (21 mg, 0.037 mmol, 1.2 mL). The resulting solution was stirred at ambient temperature for 90 min, then partially concentrated and purified via column chromatography (90:10 hexane-EtOAc) to give the title compound as a clear, colorless oil (17 mg, 81% yield). R_f (90:10, hexane-EtOAc) = 0.11.

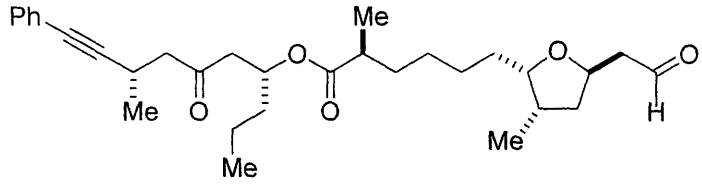
IR (thin film/NaCl): 2960, 2932, 2871, 1724, 1597, 1490 cm^{-1}.

^1H NMR (C_6D_6, 500 MHz): δ 9.22 (d, J = 1.8 Hz, 1H), 7.51-7.48 (m, 2H), 7.18-7.13 (m, 5H), 7.04-6.95 (m, 3H), 6.41 (s, 1H), 5.32-5.27 (m, 1H), 4.25-4.19 (m, 1H), 3.89-3.85 (m, 1H), 2.66 (dd, J = 6.4, 14.3 Hz, 1H), 2.60 (dd, J = 4.6, 16.5 Hz, 1H), 2.52 (dd, J = 7.3, 16.5 Hz, 1H), 2.46 (dd, J = 8.5, 14.3 Hz, 1H), 2.43-2.40 (m, 1H), 2.28-2.20 (m, 3H), 2.03-1.98 (m, 1H), 1.89 (ddd, J = 7.0, 8.8, 10.7 Hz, 1H), 1.80-1.75 (m, 1H), 1.63-1.58 (m, 1H), 1.57-1.50 (m, 1H), 1.49-1.45 (m, 2H), 1.43-1.38 (m, 2H), 1.37-1.30 (m, 4H), 1.29-1.20 (m, 2H), 1.11 (d, J = 7.0 Hz, 3H), 0.89 (t, J = 7.0 Hz, 3H), 0.75 (d, J = 7.0 Hz, 3H), 0.68 (d, J = 7.0 Hz, 3H).

^{13}C NMR (C_6D_6, 125 MHz): δ 203.1, 176.3, 138.4, 136.8, 132.3 (2C), 131.0, 129.9, 129.5 (2C), 128.92 (2C), 128.89 (2C), 128.7, 127.2, 125.0, 88.2, 82.7, 82.2, 75.6, 71.4, 45.3, 43.3, 40.4, 39.9, 37.4, 36.7, 34.6, 31.4, 31.2, 28.2, 27.8, 27.4, 19.5, 17.9, 14.5, 13.6.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{38}H_{50}NaO_4$ 593.3601, obsd 593.3602.

$[\alpha]_D$ = −7.8 (23 °C, c = 6.8, CH_2Cl_2)



(+)-(2*S*)-Methyl-6-[(3*S*)-methyl-(5*R*)-(2-oxo-ethyl)-tetrahydro-furan-(2*S*)-yl]-hexanoic acid (5*S*)-methyl-3-oxo-7-phenyl-(1*R*)-propyl-hept-6-ynyl ester (77). A solution of **94** in CH_2Cl_2 (35 mg, 0.062 mmol in 20 mL) was cooled to −78 °C. Ozone was bubbled through the solution until a blue color persisted. Argon was immediately bubbled through until the solution was colorless. Dimethylsulfide was added (0.4 ml) and the solution was allowed to slowly warm to ambient temperature over 3 h. The solution was concentrated and immediately purified by gradient column chromatography (85:15 hexane-EtOAc, polarity increased to 70:30 hexane-EtOAc). Two products were isolated: a diastereomeric ketoalkynyl-ozonide (less polar) and the desired ketoalkynal **77** (more polar). The ozonide was dissolved in 5 ml CH_2Cl_2 and stirred with triphenylphosphine (90 mg) for 40 min. Concentration and purification on a silica gel column (elution with 80:20 hexane-EtOAc) afforded pure ketoynal which was combined with the original portion (combined: 19 mg, 63% overall yield). R_f (80:20 hexane-EtOAc) = 0.26.

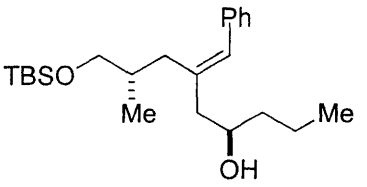
IR (thin film/NaCl): 2963, 2935, 2874, 2729, 2234, 1728 (br) cm^{-1}.

^1H NMR (C_6D_6, 500 MHz): δ 9.51 (dd, J = 1.7, 2.6 Hz, 1H), 7.48-7.46 (m, 2H), 7.02-6.95 (m, 3H), 5.48-5.43 (m, 1H), 4.23-4.18 (m, 1H), 3.66-3.63 (m, 1H), 3.23-3.19 (m, 1H), 2.53-2.44 (m, 2H), 2.40-2.36 (m, 1H), 2.27-2.18 (m, 3H), 1.96 (ddd, J = 1.8, 5.2, 15.9 Hz, 1H), 1.86-1.82 (m, 1H), 1.76-1.69 (m, 2H), 1.52-1.35 (m, 5H), 1.34-1.19 (m, 7H), 1.17 (d, J = 6.7 Hz, 3H), 1.12 (d, J = 7.0 Hz, 3H), 0.81 (t, J = 7.3 Hz, 3H), 0.69 (d, J = 7.0 Hz, 3H).

^{13}C NMR (C_6D_6, 125 MHz): δ 204.6, 200.4, 176.0, 132.3 (2C), 128.9 (2C), 128.6, 124.7, 94.1, 81.9, 81.7, 72.0, 70.0, 50.9, 50.0, 48.1, 40.42, 40.39, 37.1, 36.4, 34.5, 31.0, 28.2, 27.3, 22.8, 21.3, 19.2, 17.8, 14.4, 14.3.

HRMS (ESI)$[M+Na]^+$: *m/z* calcd for $C_{31}H_{44}O_5Na$ 519.3081, obsd 519.3086.

$[\alpha]_D$ = +4.8 (23 °C, c = 4.8, C_6D_6)



(−)-2-[3-(tert-Butyldimethylsilanyloxy)-(2*S*)-methylpropyl]-1-phenyl-hept-1-en-(4*R*)-ol (78). Prepared as described above (same scale) except *ent*-**42** was used: (264 mg, 70% yield, >95:5 dr by ^{1}H NMR). R_f (90:10, hexane-EtOAc) = 0.22.

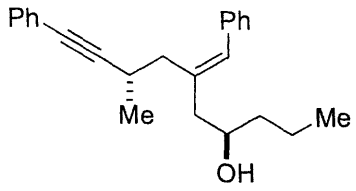
IR (thin film/NaCl): 3403, 2956, 2930, 2857, 1600, 1463 cm $^{-1}$.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34-7.31 (m, 2H), 7.27-7.20 (m, 3H), 6.49 (s, 1H), 3.82-3.80 (m, 1H), 3.41 (dd, J = 5.8, 9.8 Hz, 1H), 3.37 (dd, J = 6.2, 9.9 Hz, 1H), 2.51-2.48 (m, 1H), 2.34-2.27 (m, 2H), 2.12 (dd, J = 9.8, 13.6 Hz, 1H), 1.88-1.85 (m, 2H), 1.58-1.41 (m, 4H), 0.98 (t, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.77 (d, J = 6.7 Hz, 3H), 0.03 (s, 6H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.0, 138.0, 130.1, 129.1 (2C), 128.3 (2C), 126.5, 68.8, 68.4, 45.8, 39.6, 34.7, 33.3, 26.1 (3C), 19.2, 18.5, 16.3, 14.4, -5.19, -5.21.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{23}H_{40}NaO_2Si$ 399.2690, obsd 399.2693.

$[\alpha]_D$ = −55 (23 °C, c = 2.2, CH_2Cl_2).



(−)-6-Benzylidene-(8*S*)-methyl-10-phenyl-dec-9-yn-(4*R*)-ol (79). Copper (I) iodide (4 mg, 0.02 mmol) and palladium tetrakis(triphenylphosphine) (12 mg, 0.01 mmol) were combined in a round bottom flask. The flask was evacuated and back-filled with Ar three times. Pyrrolidine (1.2 mL), alkyne **92** (52 mg, 0.20 mmol in 0.3 ml pyrrolidine), and iodobenzene (85 μL, 0.76 mmol) were added sequentially and the mixture was stirred at ambient temperature 16 h. Et_2O was added (10 mL) and the mixture was filtered through a plug of silica gel. Solvent was evaporated, and the crude residue was purified via column chromatography (9:1 hexane-EtOAc) to afford the title compound as a clear, yellow oil (51 mg, 77% yield). R_f (90:10, hexane-EtOAc) = 0.14.

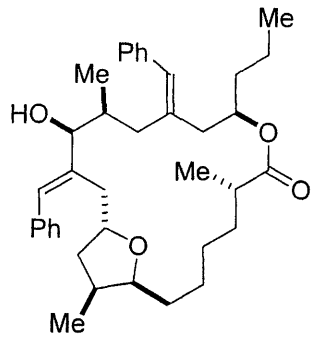
IR (thin film/NaCl): 3408, 2957, 2929, 2870, 1598, 1490 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.38-7.25 (m, 6H), 7.24-7.20 (m, 4H), 6.54 (s, 1H), 3.93-3.89 (m, 1H), 2.95-2.90 (m, 1H), 2.63-2.51 (m, 3H), 2.28 (dd, J = 9.5, 13.9 Hz, 1H), 1.88 (s, 1H), 1.59-1.52 (m, 3H), 1.50-1.39 (m, 1H), 1.25 (d, J = 6.9 Hz, 3H), 0.96 (t, J = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.9, 137.8, 131.7 (2C), 130.7, 129.0, 128.4 (2C), 128.4 (2C), 127.8, 126.7, 123.8, 94.2, 81.8, 69.4, 45.9, 39.6, 37.7, 25.7, 21.3, 19.2, 14.4.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{24}H_{28}ONa$ 355.2032, obsd 355.2035.

$[\alpha]_D$ = −14 (23 °C, c = 7.3, $CDCl_3$).



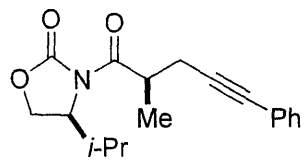
11,15-Dibenzylidene-(14*S*)-hydroxy-(6*S*,13*S*,19*R*)-trimethyl-(9*R*)-propyl-8,20-dioxa-bicyclo[15.2.1]icosan-7-one (80). A stock solution of catalyst was prepared in the following manner: in a glovebox, $Ni(cod)_2$ (26 mg, 0.095 mmol) was placed in a flask containing a stirbar. The flask was sealed with a rubber septum, removed from the glovebox, and immediately placed under argon. Tributylphosphine (26 μL, 0.19 mmol), toluene (4.74 ml, previously degassed by bubbling argon through for 10 minutes), and triethylborane (0.26 ml, 1.80 mmol) were added sequentially, producing a clear yellow catalyst solution. A 2 ml Woodward reaction tube equipped with a stirbar, rubber septum, and septum screw cap on the side-arm was purged with argon. Stock catalyst solution was added to the tube (500 μL), and the tube was immediately placed in an oil bath at 60 °C for 3 min. A solution of **76** in degassed toluene (15 mg, 0.026 mmol in 500 μL) was added to the tube dropwise, causing the solution to turn red-brown. The reaction was allowed to stir at 60 °C for 14 h. After this time, the solution was cooled to ambient temperature, diluted with 1.0 ml EtOAc, and stirred open to the air 1 h; then concentrated. The crude residue was purified via Pasteur pipet column chromatography (93:7 hexane-EtOAc) to give the title compound as a clear, colorless oil (6.0 mg, 35% yield, 8:1 dr 14*S*:14*R*). R_f (90:10, hexane-EtOAc) = 0.21.

IR (thin film/NaCl): 3377, 2959, 2932, 2872, 1726, 1599, 1462, 1453 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz, major diastereomer): δ 7.37-7.33 (m, 2H), 7.30-7.20 (3H), 7.14-7.11 (m, 2H), 7.08-7.06 (m, 2H), 7.03-7.00 (m, 1H), 6.56 (s, 1H), 6.33 (s, 1H), 5.51-5.47 (m, 1H), 5.08 (d, J = 7.5 Hz, 1H), 4.18-4.14 (m, 1H), 3.75-3.71 (m, 1H), 3.65 (dd, J = 7.9, 9.5 Hz, 1H), 3.14 (dd, J = 2.4, 15.3 Hz, 1H), 2.81 (dd, J = 9.5, 13.1 Hz, 1H), 2.73-2.64 (m, 2H), 2.55-2.52 (m, 3H), 1.97-1.88 (3H), 1.86-1.80 (m, 2H), 1.75-1.67 (m, 2H), 1.64-1.58 (m, 2H), 1.54-1.25 (m, 6H), 1.23 (d, J = 6.8 Hz, 3H), 0.90 (t, J = 7.3 Hz, 3H), 0.67 (d, J = 6.7 Hz, 3H), 0.56 (d, J = 7.0 Hz, 3H).

^{13}C NMR (C_6D_6, 125 MHz, major diastereomer): δ 175.5, 142.3, 139.6, 139.5, 138.4, 131.6, 130.4, 129.9 (2C), 129.5 (2C), 128.9 (2C), 127.5 (2C), 127.2, 126.8, 84.3, 79.3, 78.0, 74.0, 42.8, 41.0, 40.6, 38.8, 36.9, 36.6, 35.6, 35.2, 34.7, 30.4, 30.3, 27.8, 26.2, 19.8, 18.8, 16.8, 14.5.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{38}H_{52}NaO_4$ 595.3758, obsd 595.3762.



(+)-(4*S*)-Isopropyl-3-[(2*R*)-methyl-5-phenyl-pent-4-ynoyl]-oxazolidin-2-one (81).[47] A solution of diisopropylamine in THF (0.51 g, 5.0 mmol amine in 7.0 mL THF) was cooled to 0 °C. A solution of *n*-butyllithium in hexane was added (2.1 mL, 2.5 M, 5.2 mmol), and the resulting solution was stirred 30 min at 0 °C. After this time, the solution was cooled to −78 °C and stirred 10 min. A separate solution of (*S*)-4-isopropyl-3-propionyl-oxazolidin-2-one[47] in THF (0.87 g, 4.7 mmol, in 1.5 mL THF) was slowly added via syringe down the side of the reaction flask. The mixture was stirred 30 min at −78 °C. A solution of 3-bromo-1-propynylbenzene[48] in THF (2.50 g, 12.8 mmol, in 1.3 mL) was added via syringe down the side of the reaction flask. The mixture was stirred 15 min at −78 °C, then 2 h at 0 °C. The reaction was quenched at 0 °C with saturated NH_4Cl (5 mL), diluted with H_2O (5 mL) and Et_2O (10ml). The aqueous phase was extracted with Et_2O (3 x 25 mL), washed with brine (3 x 25 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified via column chromatography (70:30 CH_2Cl_2-hexane, a second column was necessary to separate diastereomers) to afford the title compound as a yellow oil (1.30 g, 92% yield, >95:5 dr). R_f (80:20, hexane-EtOAc) = 0.19.

IR (thin film/NaCl): 2966, 2877, 1779, 1703, 1387 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.38-7.34 (m, 2H), 7.28-7.25 (m, 3H), 4.51-4.47 (m, 1H), 4.29 (app t, J = 8.9 Hz, 1H), 4.20 (dd, J = 3.2, 9.2 Hz, 1H), 4.10-4.03 (m, 1H), 2.80 (dd, J = 6.9, 16.8 Hz, 1H), 2.70 (dd, J = 6.4, 16.8 Hz, 1H), 2.40-2.34 (m, 1H), 1.31 (d, J = 6.9 Hz, 3H), 0.89 (d, J = 7.2 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 175.4, 153.9, 131.8 (2C), 128.3 (2C), 127.9, 123.7, 87.0, 82.4, 63.5, 58.7, 37.9, 28.6, 24.1, 18.1, 16.8, 14.8.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{18}H_{21}NaNO_3$ 322.1414, obsd 322.1415.

$[\alpha]_D$ = +37 (23 °C, c = 4.8, CH_2Cl_2).

ent-**81**: $[\alpha]_D$ = −43 (23 °C, c = 6.3, CH_2Cl_2).

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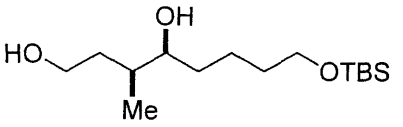
[47] For the general asymmetric alkylation procedure, see reference 11b. For asymmetric alkylation with a propargylic bromide, see 11c.

[48] Prepared using the procedure reported in reference 11a.



(−)-8-(tert-Butyl-dimethyl-silanyloxy)-(3*S*)-methyl-octane-(1,4*S*)-diol (82).[49] Gaseous *cis*-2-butene was condensed (15 ml, 150 mmol) and transferred via cannula to a cooled suspension (−78 °C) of potassium *t*-butoxide in THF (4.21 g, 37.6 mmol in 15 ml THF). A solution of *n*-butyllithium was added via syringe (15 mL, 2.5 M in hexane, 37.6 mmol), causing the mixture to turn bright yellow. The mixture was stirred 5 min at −78 °C, warmed to −45 °C for 20 min, then re-cooled to −78 °C. A solution of (+)-Ipc_2BOMe in Et_2O was prepared (14.2 g, 45.0 mmol in 45 ml) and transferred to the reaction via cannula. After stirring 30 min at −78 °C, $BF_3{\cdot}OEt_2$ (7.6 ml, 60 mmol) was added via syringe and the mixture was stirred 5 min. Aldehyde **55**[19] was added (9.75 g, 45.0 mmol), and the viscous mixture was allowed to stir 3 h at −78 °C. A mixture of 3N NaOH and 30% H_2O_2 (27.0 mL NaOH, 11.0 mL H_2O_2) was added, and the reaction was allowed to warm to ambient temperature with stirring for 3 h. H_2O and Et_2O were added (50 mL each) and the phases were separated. The organic phase was washed with H_2O (2 x 50 mL) and brine (3 x 50 mL), dried over $MgSO_4$, filtered and concentrated. The crude oil was then taken up in 300 ml THF and cooled to 0 °C. $BH_3{\cdot}THF$ was added via syringe (150 mL, 1 M in THF, 150 mmol) and the solution was stirred 14 h, warming to ambient temperature. The solution was re-cooled to 0 °C and methanol was added slowly (50 mL). After bubbling ceased, a mixture of 1.8 N NaOH and 30% H_2O_2 was added (30 mL NaOH, 12 mL H_2O_2) and the mixture was stirred at ambient temperature 3 h. Brine and Et_2O were added (150 mL each), the layers were separated, and the aqueous phase was extracted with 80:20 EtOAc:Et_2O (3 x 150 mL). The combined organic phases were washed with brine (3 x 150 mL), dried over Na_2SO_4, filtered and concentrated. The crude residue was purified via gradient column chromatography (70:30 hexane-EtOAc, polarity increased to 50:50) to afford the title compound as a viscous, clear oil (4.75 g, 43% yield over two steps). R_f (80:20, EtOAc-hexane) = 0.25.

IR (thin film/NaCl): 3321, 2928, 2855 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.9 (br s, 1H, OH), 3.81-3.76 (m, 1H), 3.70-3.60 (m, 4H), 2.3 (br s, 1H, OH), 1.80-1.70 (m, 2H), 1.60-1.37 (m, 7H), 0.91 (d, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 74.9, 63.4, 60.6, 36.28, 36.26, 33.4, 32.9, 26.1 (3C), 22.9, 18.5, 14.1, -5.1 (2C).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{15}H_{34}NaO_3Si$ 313.2169, obsd 313.2169.

$[\alpha]_D$ = −8.9 (23 °C, c = 10.0, CH_2Cl_2).

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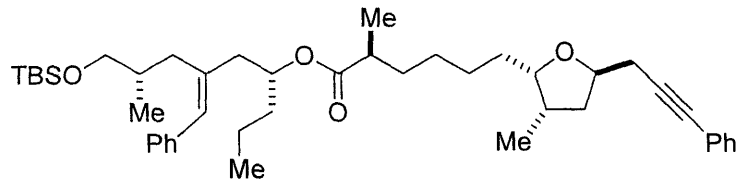
[49] Prepared according to the general procedure reported in reference 18.



(−)-(2*S*)-Methyl-6-[(3*S*)-methyl-(5*R*)-(3-phenyl-prop-2-ynyl)-tetrahydro-furan-(2*S*)-yl]-hexanoic acid 3-benzylidene-6-(tert-butyl-dimethyl-silanyloxy)-(5*S*)-methyl-(1*R*)-propyl-hexyl ester (83). A flask containing acid **38** (110 mg, 0.33 mmol) was charged with alcohol **78** (200 mg, 0.53 mmol), dicyclohexylcarbodiimide (120 mg, 0.58 mmol), 4-pyrrolidinopyridine (90 mg, 0.61 mmol), and CH_2Cl_2 (5.5 ml). The mixture was stirred 24 h at ambient temperature. Silica gel was added, and the solvents were removed in vacuo. The dry silica gel was loaded onto a slurry-packed column (90:10 hexane-EtOAc) and the title compound was eluted to give a clear, colorless oil (120 mg, 53% yield) upon concentration. R_f (90:10, hexane-EtOAc) = 0.32.

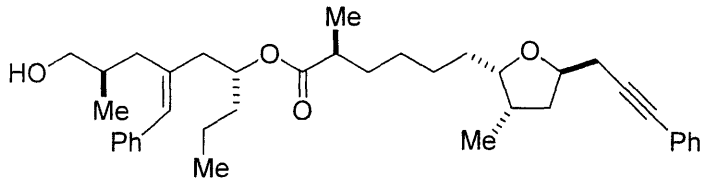
IR (thin film/NaCl): 2957, 2933, 2857, 1729, 1599, 1462 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.41-7.39 (m, 2H), 7.30-7.24 (m, 5H), 7.19-7.16 (m, 3H), 6.36 (s, 1H), 5.16-5.12 (m, 1H), 4.31-4.26 (m, 1H), 3.96-3.92 (m, 1H), 3.41 (dd, J = 5.5, 9.8 Hz, 1H), 3.32 (dd, J = 6.4, 9.8 Hz, 1H), 2.68 (dd, J = 4.6, 16.5 Hz, 1H), 2.59 (dd, J = 7.3, 16.5 Hz, 1H), 2.41-2.28 (m, 4H), 2.23-2.19 (m, 1H), 2.08-2.02 (m, 1H), 1.88-1.81 (m, 2H), 1.69-1.62 (m, 1H), 1.60-1.55 (m, 2H), 1.48-1.25 (m, 10H), 1.08 (d, J = 7.0 Hz, 3H), 0.95-0.91 (m, 6H), 0.88 (s, 9H), 0.74 (d, J = 6.7 Hz, 3H), 0.02 (s, 3H), 0.01 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.7, 138.4, 137.9, 131.8 (2C), 129.4, 129.1 (2C), 128.4 (2C), 128.2 (2C), 127.9, 126.2, 124.0, 87.1, 82.3, 81.9, 75.2, 71.6, 68.4, 42.8, 40.0, 39.4, 37.0, 36.0, 34.5, 33.9, 33.4, 30.5, 27.7, 27.2, 26.7, 26.1 (3C), 19.0, 18.5, 17.4, 16.5, 14.20, 14. 18, -5.2 (2C).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{44}H_{66}NaO_4Si$ 709.4623, obsd 709.4643.

$[\alpha]_D$ = −23 (23 °C, c = 1.0, CH_2Cl_2)



(+)-(2*S*)-Methyl-6-[(3*S*)-methyl-(5*R*)-(3-phenyl-prop-2-ynyl)-tetrahydro-furan-(2*S*)-yl]-hexanoic acid 3-benzylidene-6-hydroxy-(5*R*)-methyl-(1*R*)-propyl-hexyl ester (84). A solution of tetrabutylammonium fluoride (0.33 mL, 1.0 M in THF, 0.33 mmol) was added to a stirred solution of **63** in THF (150 mg, 0.22 mmol in 1.8 mL). The mixture was allowed to stir 2 h, then EtOAc and saturated NaCl (aqueous) were added (5 ml each). The layers were separated, the aqueous phase was extracted with EtOAc (3 x 5 ml), and the combined organic phases were concentrated. The crude residue was purified via column chromatography (70:30 hexane-EtOAc) to give the title compound as a clear, colorless oil (122 mg, 97% yield). R_f (70:30, hexane-EtOAc) = 0.31.

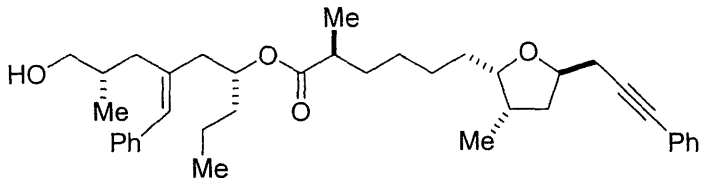
IR (thin film/NaCl): 3447, 2959, 2934, 2872, 2360, 1727, 1458 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.41-7.39 (m, 2H), 7.32-7.28 (m, 5H), 7.22-7.17 (m, 3H), 6.40 (s, 1H), 5.14-5.09 (m, 1H), 4.32-4.26 (m, 1H), 3.97-3.93 (m, 1H), 3.36 (t, J = 5.8 Hz, 2H), 2.68 (dd, J = 4.6, 16.5 Hz, 1H), 2.59 (dd, J = 7.0, 16.5 Hz, 1H), 2.49-2.40 (m, 3H), 2.39-2.34 (m, 1H), 2.32-2.28 (m, 1H), 2.15 (dd, J = 7.3, 14.0 Hz, 1H), 2.05 (ddd, J = 7.0, 9.0, 10.8 Hz, 1H), 1.91-1.84 (m, 2H), 1.70-1.64 (m, 1H), 1.61-1.57 (m, 2H), 1.49-1.26 (m, 10H), 1.10 (d, J = 6.7 Hz, 3H), 0.94 (t, J = 7.3 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H), 0.85 (d, J = 6.7 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.9, 138.0, 137.9, 131.8 (2C), 129.6, 129.0 (2C), 128.37 (2C), 128.35 (2C), 127.9, 126.5, 123.9, 87.0, 82.2, 81.9, 75.2, 71.8, 67.8, 42.7, 39.9, 39.3, 36.5, 36.1, 34.3, 33.9, 33.6, 30.4, 27.6, 27.2, 26.6, 18.9, 17.4, 17.1, 14.2 (2C).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{38}H_{52}NaO_4$ 595.3758, obsd 595.3748.

$[\alpha]_D$ = +0.16 (23 °C, c = 12.6, CH_2Cl_2)



(−)-(2*S*)-Methyl-6-[(3*S*)-methyl-(5*R*)-(3-phenyl-prop-2-ynyl)-tetrahydro-furan-(2*S*)-yl]-hexanoic acid 3-benzylidene-6-hydroxy-(5*S*)-methyl-(1*R*)-propyl-hexyl ester (85). A solution of tetrabutylammonium fluoride (0.050 mL, 1.0 M in THF, 0.050 mmol) was added to a stirred solution of **83** in THF (27 mg, 0.039 mmol in 0.6 mL). The mixture was allowed to stir 1 h, then EtOAc and saturated NaCl (aqueous) were added (1 ml each). The layers were separated, the aqueous phase was extracted with EtOAc (3 x 1 ml), and the combined organic phases were concentrated. The crude residue was purified via column chromatography (70:30 hexane-EtOAc) to give the title compound as a clear, colorless oil (23 mg, 95% yield). R_f (70:30, hexane-EtOAc) = 0.29.

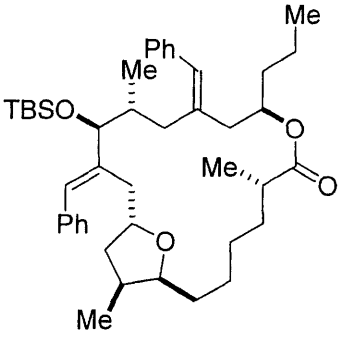
IR (thin film/NaCl): 3439, 2932, 2869, 1725, 1490 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.41-7.39 (m, 2H), 7.31-7.27 (m, 5H), 7.21-7.16 (m, 3H), 6.40 (s, 1H), 5.15-5.13 (m, 1H), 4.30-4.27 (m, 1H), 3.96-3.93 (m, 1H), 3.44-3.41 (m, 1H), 3.37-3.34 (m, 1H), 2.67 (dd, J = 4.8, 16.6 Hz, 1H), 2.59 (dd, J = 7.2, 16.6 Hz, 1H), 2.43-2.35 (m, 4H), 2.30-2.27 (m, 1H), 2.22-2.18 (m, 1H), 2.08-2.02 (m, 1H), 1.90-1.83 (m, 2H), 1.69-1.65 (m, 1H), 1.62-1.56 (m 2H), 1.48-1.25 (m, 10H), 1.10 (d, J = 7.0 Hz, 3H), 0.95-0.91 (m, 6H), 0.79 (d, J = 6.7 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.8, 138.1, 137.6, 131.8 (2C), 129.8, 129.0 (2C), 128.4 (2C), 128.3 (2C), 127.9, 126.4, 123.9, 87.1, 82.2, 81.9, 75.2, 71.7, 68.2, 42.6, 39.9, 39.4, 36.8, 36.1, 34.3, 33.9, 33.5, 30.4, 27.7, 27.2, 26.6, 18.9, 17.4, 16.6, 14.19, 14.17.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{38}H_{52}NaO_4$ 595.3758, obsd 595.3749.

$[\alpha]_D$ = −0.16 (23 °C, c = 3.0, $CDCl_3$)



(+)-11,15-Dibenzylidene-(14*S*)-(tert-butyl-dimethyl-silanyloxy)-(6*S*,13*R*,19*R*)-trimethyl-(9*R*)-propyl-8,20-dioxa-bicyclo[15.2.1]icosan-7-one (86). A solution of **34** in CH_2Cl_2 was prepared (9.0 mg, 0.016 mmol in 2.0 ml) and cooled to −78 °C. 2,6-Lutidine (30 μL, 0.24 mmol) and *t*-butyldimethylsilyl trifluoromethanesulfonate (30 μL, 0.13 mmol) were added via microliter syringe, and the resulting solution was stirred 2 h at −78 °C. A minimal amount of MeOH was added to quench the reaction (5 drops); then the solution was warmed to ambient temperature and concentrated. The crude residue was purified via Pasteur pipet column chromatography (50:1 hexane-EtOAc) to give the title compound as a clear, yellow oil (9.1 mg, 84% yield). R_f (90:10, hexane-EtOAc) = 0.44.

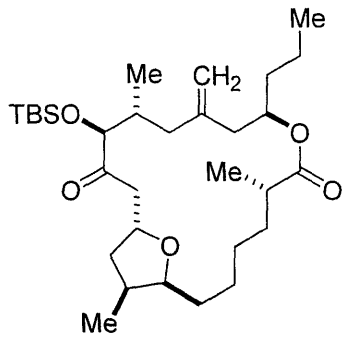
IR (thin film/NaCl): 2958, 2931, 2856, 1728, 1599, 1461 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.39-7.35 (m, 3H), 7.24-7.19 (m, 5H), 7.09-7.06 (m, 2H), 6.81 (br s, 1H), 6.57 (s, 1H), 5.38-5.36 (m, 1H), 4.37-4.31 (m, 2H), 3.87-3.70 (m, 1H), 2.93 (app t, J = 12.4 Hz, 1H), 2.71 (dd, J = 8.0, 14.6 Hz, 1H), 2.64-2.59 (m, 2H), 2.53 (dd, J = 4.1, 14.6 Hz, 1H), 2.46-2.44 (m, 2H), 2.27 (dd, J = 5.8, 13.6 Hz, 1H), 1.96-1.91 (m, 1H), 1.83-1.72 (m, 2H), 1.71-1.62 (m, 2H), 1.60-1.29 (br m, 10H), 1.17 (d, J = 6.7 Hz, 3H), 1.03 (d, J = 6.4 Hz, 3H), 1.01 (s, 9H), 0.91 (t, J = 7.3 Hz, 3H), 0.70 (d, J = 7.0 Hz, 3H), 0.15 (s, 3H), 0.13 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.7, 140.6, 139.0, 138.7, 138.4, 129.4, 129.2 (2C), 129.0 (2C), 128.4, 128.3 (2C), 128.2 (2C), 126.3, 126.2, 80.0, 74.8, 74.5, 40.2, 39.7, 39.0, 36.8, 36.5, 36.2, 36.0, 34.8, 33.2, 29.9, 28.6, 26.4, 26.2 (3C), 24.7, 18.7, 18.4, 17.5, 14.6, 14.3, -3.9, -4.7 (missing one C under $CDCl_3$ signal; when spectrum taken in C_6D_6 there are three signals in the 70-80 ppm region: δ 80.8, 75.0 (2C), 74.8).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{44}H_{66}NaO_4Si$ 709.4623, obsd 709.4615.

$[\alpha]_D$ = +2.1 (23 °C, c = 3.8, C_6D_6)



(+)-(14*S*)-(tert-Butyl-dimethyl-silanyloxy)-(6*S*,13*R*,19*R*)-trimethyl-11-methylene-(9*R*)-propyl-8,20-dioxa-bicyclo[15.2.1]icosane-7,15-dione (87). A stock solution of methylenating reagent was prepared in the following manner: a 50 ml flask was charged with activated zinc[50] (0.51 g, 7.8 mmol), lead (II) chloride (0.093 g, 0.33 mmol), and THF (4.0 ml); then cooled to 0 °C. Diiodomethane (0.21 mL, 2.6 mmol) was added via syringe, and the mixture was stirred 30 min at 0 °C. During this time, a suspension of zirconium (IV) chloride in THF (0.25 g, 1.1 mmol in 3.0 mL) was prepared by stirring together 20 min at ambient temperature. The suspension of zirconium (IV) chloride transferred to the $Zn/PbCl_2/CH_2I_2$ mixture via cannula. The resulting heterogeneous mixture was stirred 30 minutes at 0 °C. (During this time, the mixture assumed a green color, which indicated the generation of the active methylenation reagent.) A solution of diketone **67** in THF (3.0 mg in 0.5 mL) was cooled to 0 °C. Methylenating reagent was transferred to the diketone solution via syringe (0.4 mL), and the reaction was stirred for 3.5 h at 0 °C. Water (0.5 mL) and Et_2O (5 mL) were added; then the cold bath was removed. The layers were separated, and the aqueous phase was extracted with Et_2O (5 x 5 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated. The crude residue was purified via Pasteur pipet gradient column chromatography (50:1 hexane-EtOAc, polarity gradually increased to 13:1 hexane-EtOAc) to give the title compound as a clear, yellow oil (2.2 mg, 75% yield). R_f (90:10, hexane-EtOAc) = 0.37.

IR (thin film/NaCl): 2928, 2856, 1728, 1458 cm^{-1}.

^1H NMR (C_6D_6, 500 MHz): δ 5.37-5.33 (m, 1H), 5.04 (s, 1H), 4.90 (s, 1H), 4.61-4.55 (m, 1H), 4.25 (d, J = 2.1 Hz, 1H), 3.77 (ddd, J = 3.5, 6.0, 8.2 Hz, 1H), 2.49-2.40 (m, 3H), 2.30 (app d, J = 5.5 Hz, 2H), 2.12 (dd, J = 3.4, 15.3 Hz, 1H), 1.86-1.80 (m, 1H), 1.61-1.43 (m, 7H), 1.39-1.29 (m, 5H), 1.26-1.16 (m 2H), 1.15-1.07 (m, 13H), 1.05 (d, J = 6.1 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H), 0.69 (d, J = 7.0 Hz, 3H), 0.30 (s, 3H), 0.11 (s, 3H).

^{13}C NMR (C_6D_6, 125 MHz): δ 208.9, 175.5, 144.4, 116.2, 81.5, 78.8, 73.6, 72.3, 45.8, 42.1, 42.0, 40.5, 40.0, 36.9, 36.1, 35.3, 32.6, 30.6, 29.8, 27.1, 26.6 (3C), 26.2, 19.6, 18.5, 14.7, 14.6, 14.5, -3.3, -4.3.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{31}H_{56}NaO_5Si$ 559.3789, obsd 559.3781.

$[\alpha]_D$ = +5.7 (23 °C, c = 0.7, $CHCl_3$)

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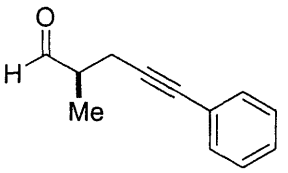
[50] Zinc was activated according to the procedure reported by Fieser and Fieser: Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967, Vol. 1, p. 1276.



(+)-(2*R*)-Methyl-5-phenyl-pent-4-ynal (88). Dess-Martin periodinane (0.85 g, 2.0 mmol) was added carefully to a solution of **68** in CH_2Cl_2 (174 mg, 1.0 mmol in 25 mL) and the mixture was stirred at ambient temperature 2.5 h. The volume of the solution was reduced to approximately 2 ml by concentration in vacuo and loaded onto a slurry-packed column (90:10 hexane-EtOAc) and the title compound was eluted to give a clear, colorless oil (160 mg, 92% yield) upon concentration. R_f (90:10, hexane-EtOAc) =0.22.

IR (thin film/NaCl): 2972, 1728, 1490 cm^{-1}.

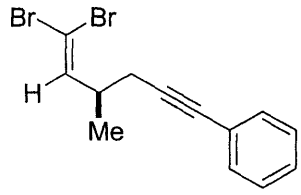
^1H NMR ($CDCl_3$, 500 MHz): δ 9.78 (d, J = 0.9 Hz, 1H), 7.41-7.39 (m, 2H), 7.31-7.29 (m, 3H), 2.77 (dd, J = 5.1, 15.9 Hz, 1H), 2.69-2.60 (m, 2H), 1.30 (d, J = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 203.6, 131.82, 131.78 (2C), 128.4 (2C), 123.5, 86.6, 82.8, 45.6, 21.0, 13.4.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{12}H_{12}NaO$ 195.0780, obsd 195. 0785.

$[\alpha]_D$ = +7.1 (23 °C, c = 3.1, CH_2Cl_2)

ent-**88**: $[\alpha]_D$ = −6.9 (23 °C, c = 1.6, CH_2Cl_2)



(+)-[6,6-Dibromo-(4*R*)-methyl-hex-5-en-1-ynyl]-benzene (89). A solution of carbon tetrabromide in CH_2Cl_2 (1.26 g, 3.8 mmol in 5.0 ml) was cooled to 0 °C. Triphenylphosphine was added (1.99 g, 7.6 mmol) and the bright orange solution was stirred 40 min. Aldehyde **88** was added as a solution in CH_2Cl_2 (0.32 g, 1.9 mmol in 2.0 ml) and the mixture was stirred 16 h, warming slowing to ambient temperature. The heterogeneous mixture was diluted with hexane, filtered through Celite and concentrated. The residue was taken up in hexane, filtered to remove solid triphenylphosphine oxide, and re-concentrated. The crude residue was purified via column chromatography (19:1 hexane-EtOAc) to give the title compound as a clear, light yellow oil (0.42 g, 69% yield). R_f (90:10, hexane-EtOAc) =0.47.

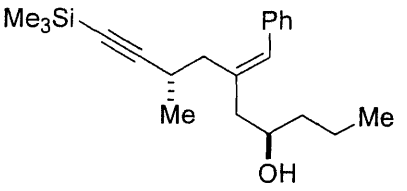
IR (thin film/NaCl): 2966, 2927, 1598 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.46-7.43 (m, 2H), 7.35-7.30 (m, 3H), 6.42 (d, J = 9.2 Hz, 1H), 2.85-2.79 (m, 1H), 2.50 (dd, J = 1.2, 6.1 Hz, 2H), 1.21 (d, J = 6.7 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 142.3, 131.8 (2C), 128.4 (2C), 128.0, 123.7, 88.9, 87.1, 82.7, 37.8, 25.8, 18.6.

HRMS (EI) M^+: *m/z* calcd for $C_{13}H_{12}Br_2$ 325.9300, obsd 325.9303.

$[\alpha]_D$ = +5.1 (23 °C, c = 6.3, CH_2Cl_2).



(−)-6-Benzylidene-(8*S*)-methyl-10-trimethylsilanyl-dec-9-yn-(4*R*)-ol (90). Procedure and scale exactly as described above except the opposite enantiomer of the diyne was used (*ent*-**43**). The title compound was isolated as a colorless oil (120 mg, 33% yield). R_f (90:10, hexane-EtOAc) = 0.16.

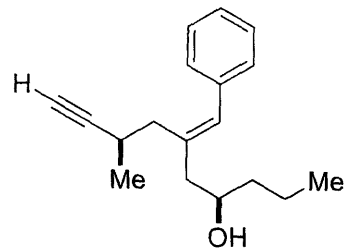
IR (thin film/NaCl): 3419 (br), 2959, 2932, 2873, 2163, 1599 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.35-7.29 (m, 4H), 7.25-7.22 (m, 1H), 6.51 (s, 1H), 3.88-3.84 (m, 1H), 2.76-2.71 (m, 1H), 2.56 (dd, J = 3.0, 13.7 Hz, 1H), 2.48 (dd, J = 9.2, 13.4 Hz, 1H), 2.39 (dd, J = 6.4, 13.4 Hz, 1H), 2.22 (dd, J = 9.5, 13.7 Hz, 1H), 1.90 (d, J = 2.7 Hz, 1H), 1.58-1.49 (m, 3H), 1.48-1.42 (m, 1H), 1.15 (d, J = 7.0 Hz, 3H), 0.98 (t, J = 7.3 Hz, 3H), 0.14 (s, 9H).

^{13}C NMR (C_6D_6, 125 MHz): δ 138.6, 138.4, 131.2, 129.7 (2C), 128.8 (2C), 127.1, 112.2, 86.0, 69.8, 46.6, 40.5, 38.4, 26.5, 21.6, 19.8, 14.8, 0.6 (3C).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{21}H_{32}ONa$ 351.2115, obsd 351.2122.

$[\alpha]_D$ = − 105 (23 °C, c = 2.4, CH_2Cl_2)



(+)-6-Benzylidene-(8*R*)-methyl-dec-9-yn-(4*R*)-ol (91). A solution of alkyne **69** in THF (200 mg, 0.61 mmol in 6.0 mL) was cooled to 0 °C. A solution of tetrabutylammonium fluoride in THF was added dropwise (0.75 ml, 1.0 M, 0.75 mmol). The solution was stirred 1 h at 0 °C, then partitioned between EtOAc and brine (6 mL each). The aqueous phase was extracted with EtOAc (3 x 6 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by column chromatography (85:15 hexane-EtOAc) to afford the title compound as a clear, light yellow oil (132 mg, 80% yield). R_f (80:20, hexane-EtOAc) = 0.25.

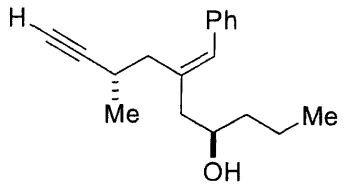
IR (thin film/NaCl): 3420, 3307, 2960, 2931, 2872, 2170, 1599 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.35-7.26 (m, 3H), 7.25-7.22 (m, 2H), 6.54 (s, 1H), 3.85-3.83 (br m, 1H), 2.75-2.71 (m, 1H), 2.63 (dd, J = 9.5, 13.7 Hz, 1H), 2.53-2.47 (m, 2H), 2.30 (dd, J = 6.1, 13.7 Hz, 1H), 2.26-2.21 (m, 1H), 2.08 (d, J = 2.4 Hz, 1H), 1.85 (br s, 1H), 1.56-1.42 (m, 4H), 1.18 (d, J = 6.7 Hz, 3H), 0.97 (t, J = 6.7 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.8, 137.4, 130.7, 129.0 (2C), 128.4 (2C), 126.7, 88.4, 69.4, 69.2, 45.6, 39.5, 37.2, 24.3, 21.2, 19.2, 14.4.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{18}H_{24}ONa$ 279.1719, obsd 279.1710.

$[\alpha]_D$ = +7.8 (23 °C, c = 3.6, $CDCl_3$)



(−)-6-Benzylidene-(8*S*)-methyl-dec-9-yn-(4*R*)-ol (92). A solution of alkyne **90** in THF (120 mg, 0.37 mmol in 3.7 mL) was cooled to 0 °C. A solution of tetrabutylammonium fluoride in THF was added dropwise (0.46 ml, 1.0 M). The solution was stirred 1 h at 0 °C, then partitioned between EtOAc and brine (4 mL each). The aqueous phase was extracted with EtOAc (3 x 4 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by column chromatography (85:15 hexane-EtOAc) to afford the title compound as a clear, light yellow oil (53 mg, 52% yield). R_f (80:20, hexane-EtOAc) = 0.28.

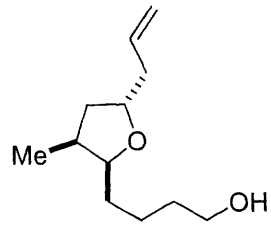
IR (thin film/NaCl): 3411, 3306, 2959, 2932, 2872, 2111, 1598 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.35-7.32 (m, 2H), 7.29-7.25 (m, 2H), 7.24-7.22 (m, 1H), 6.52 (s, 1H), 3.88-3.84 (m, 1H), 2.72-2.67 (m, 1H), 2.55 (dd, J = 3.5, 13.8 Hz, 1H), 2.48 (d, J = 7.9 Hz, 2H), 2.22 (dd, J = 9.5, 14.6 Hz, 1H), 2.09 (d, J = 2.4 Hz, 1H), 1.88 (br s, 1H), 1.58-1.50 (m, 3H), 1.48-1.41 (m, 1H), 1.15 (d, J = 7.0 Hz, 3H), 0.98 (t, J = 6.7 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.7, 137.6, 130.8, 129.0 (2C), 128.4 (2C), 88.7, 69.4, 69.3, 45.8, 39.6, 37.4, 24.7, 21.0, 19.2, 14.4.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{18}H_{24}ONa$ 279.1719, obsd 279.1718.

$[\alpha]_D$ = −7.8 (23 °C, c = 1.8, CH_2Cl_2)



(−)-4-[(5*R*)-Allyl-(3*S*)-methyl-tetrahydro-furan-(2*S*)-yl]-butan-1-ol (93). A solution of lactol **57a** (0.29 g, 1.0 mmol) and allyltrimethylsilane (0.64 mL, 4.0 mmol) in 20 mL CH_2Cl_2 was cooled to −78 °C. Distilled boron trifluoride diethyl etherate was added dropwise (0.38 mL, 3.0 mmol), and the solution was allowed to stir, coming to ambient temperature, for 16 h. Saturated $NaHCO_3$ and H_2O were added (5 mL each), the layers were separated, and the organic phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude residue was purified via gradient column chromatography (70:30 hex-EtOAc, polarity gradually increased to 50:50) to afford the title compound as a clear, colorless oil (0.18 g, 88% yield). R_f (50:50, hexane-EtOAc) = 0.25.

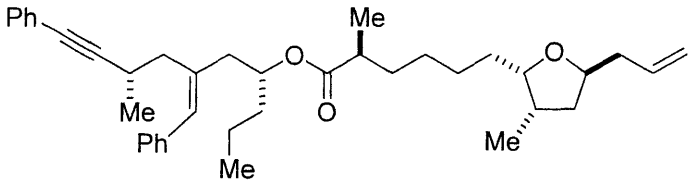
IR (thin film/NaCl): 3379, 3076, 2936, 2868, 1641 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 5.85-5.76 (m, 1H), 5.10-5.04 (m, 2H), 4.15-4.09 (m, 1H), 3.89-3.85 (m, 1H), 3.66 (t, J = 6.4 Hz, 2H), 2.36-2.31 (m, 1H), 2.26-2.17 (m, 2H), 1.80-1.65 (m, 2H), 1.64-1.46 (m, 4H), 1.43-1.37 (m, 2H), 0.89 (d, J = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 135.2, 117.0, 81.5, 76.3, 63.0, 41.2, 39.5, 36.1, 33.0, 30.3, 23.0, 14.2.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{12}H_{22}O_2Na$ 221.1521, obsd 221.1515.

$[\alpha]_D$ = −1.3 (23 °C, c = 4.8, CH_2Cl_2)



(−)-6-[(5*R*)-Allyl-(3*S*)-methyl-tetrahydro-furan-(2*S*)-yl]-(2*S*)-methyl-hexanoic acid 3-be26nzylidene-(5*S*)-methyl-7-phenyl-(1*R*)-propyl-hept-6-ynyl ester (94). Acid **40** (83 mg, 0.3 mmol) and alcohol **79** (50 mg, 0.15 mmol) were dissolved in 2.0 mL CH_2Cl_2. Dicyclohexylcarbodiimide (61 mg, 0.30 mmol) and 4-pyrrolidinopyridine (44 mg, 0.30 mmol) were added and the heterogeneous mixture was stirred at ambient temperature 14h. Silica gel was added, and the solvent was removed in vacuo. The dry silica gel was loaded onto a slurry-packed column (93:7 hexane-EtOAc) and the title compound was eluted and concentrated to give a clear, pale yellow oil (71 mg, 84% yield). R_f (90:10 hexane-EtOAc) = 0.32.

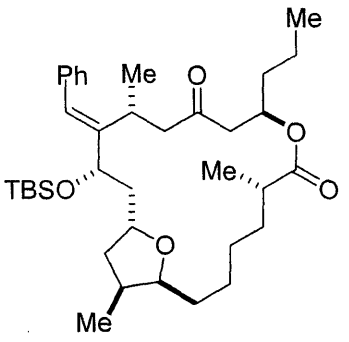
IR (thin film/NaCl): 2962, 2934, 2873, 2231, 1728, 1598, 1491 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.38-7.35 (m, 2H), 7.34-7.29 (m, 2H), 7.28-7.26 (m, 4H), 7.25-7.21 (m, 2H), 6.45 (s, 1H), 5.87-5.78 (m, 1H), 5.22-5.17 (m, 1H), 5.12-5.05 (m, 2H), 4.14-4.09 (m, 1H), 3.85-3.81 (m, 1H), 2.93-2.89 (m, 1H), 2.64-2.58 (m, 2H), 2.54-2.42 (m, 3H), 2.40-2.33 (m, 1H), 2.24-2.18 (m, 2H), 1.80-1.67 (m, 3H), 1.64-1.58 (m, 2H), 1.48-1.41 (m, 4H), 1.40-1.24 (m, 5H), 1.22 (d, J = 6.7 Hz, 3H), 1.12 (d, J = 7.0 Hz, 3H), 0.94-0.89 (m, 6H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.8, 138.0, 137.2, 135.3, 131.7 (2C), 130.0, 129.0 (2C), 128.3 (4C), 127.7, 126.5, 124.0, 116.9, 94.4, 81.4, 76.1, 71.7, 42.7, 41.2, 40.0, 39.4, 37.1, 36.7, 36.0, 33.9, 30.5, 27.7, 26.7, 25.5, 21.3, 19.0, 17.4, 14.2.

HRMS (ESI)$[M+Na]^+$: *m/z* calcd for $C_{39}H_{52}O_3Na$ 591.3809, obsd 591.3800.

$[\alpha]_D$ = −7.8 (23 °C, c = 6.8, CH_2Cl_2)



(−)-14-Benzylidene-(15*S*)-(tert-butyl-dimethyl-silanyloxy)-(6*S*,13*R*,19*S*)-trimethyl-(9*R*)-propyl-8,20-dioxa-bicyclo[15.2.1]icosane-7,11-dione (95). Macrocyclic alcohol **35b** was dissolved in anhydrous DMF (21 mg, 0.042 mmol in 1.0 mL) and *t*-butyldimethylchlorosilane (46 mg, 0.31 mmol), imidazole (36 mg, 0.53 mmol), and *N,N*-dimethylaminopyridine (1 mg, 0.008 mmol) were added sequentially. The mixture was stirred at ambient temperature 20 h, then partitioned between 15 mL Et_2O and 10 ml H_2O. The organic phase was washed with H_2O (3 x 5 mL) and brine (3 x 10 mL), dried over Na_2SO_4, filtered and concentrated. The crude residue was purified via column chromatography (96:4 hexane-EtOAc) to afford the title compound as a clear, colorless oil (17 mg, 68% yield). R_f (90:10 hexane-EtOAc) = 0.29.

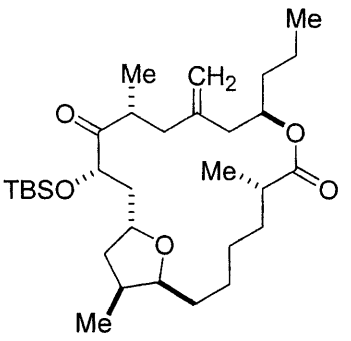
IR (thin film/NaCl): 2959, 2932, 2857, 1733 (br), 1463 cm^{-1}.

^1H NMR (C_6D_6, 500 MHz): δ 7.35 (app d, J = 7.6 Hz, 2H), 7.19-7.16 (m, 2H), 7.07 (s, 1H), 7.05-7.02 (m, 1H), 5.35-5.32 (m, 1H), 4.64 (d, J = 8.8 Hz, 1H), 4.46-4.41 (m, 1H), 3.78-3.75 (m, 1H), 3.67-3.62 (m, 1H), 2.58 (dd, J = 5.8, 17.4 Hz, 1H), 2.48-2.41 (m, 2H), 2.37-2.30 (m, 1H), 2.03-1.96 (m, 2H), 1.86-1.79 (m, 1H), 1.67-1.53 (m, 5H), 1.52-1.44 (m, 3H), 1.42-1.31 (m, 3H), 1.30-1.24 (m, 2H), 1.17 (d, J = 7.0 Hz, 3H), 1.14-1.08 (m, 2H), 1.07-1.04 (m, 12H), 0.78 (d, J = 7.0 Hz, 3H), 0.75 (t, J = 7.3 Hz, 3H), 0.29 (s, 3H), 0.24 (s, 3H).

^{13}C NMR (C_6D_6, 125 MHz): δ 206.3, 175.0, 149.8, 139.5, 129.4 (2C), 129.0 (2C), 127.0, 124.9, 78.3, 73.9, 71.6, 71.4, 50.0, 48.2, 47.9, 41.3, 41.0, 37.4, 37.0, 35.4, 30.7, 30.5, 27.7, 27.5, 26.6 (3C), 21.6, 18.90, 18.87, 17.5, 15.1, 14.4, -3.5, -4.1.

HRMS (ESI)$[M+Na]^+$: *m/z* calcd for $C_{31}H_{44}O_5Na$ 635.4102, obsd 635.4094.

$[\alpha]_D$ = −2.6 (23 °C, c = 2.3, CH_2Cl_2)



(+)-(15*S*)-(tert-Butyl-dimethyl-silanyloxy)-(6*S*,13*R*,19*S*)-trimethyl-11-methylene-(9*R*)-propyl-8,20-dioxa-bicyclo[15.2.1]icosane-7,14-dione (96). A stock solution of methylenating reagent was prepared as described for **87**. Methylenating reagent was transferred to the diketone solution (4.2 mg, 0.0078 mmol, in 1.0 mL THF) via syringe (0.80 mL), and the reaction was stirred for 1 h at 0 °C. Water (0.5 mL) and Et_2O (5 mL) were added; then the cold bath was removed. The layers were separated, and the aqueous phase was extracted with Et_2O (5 x 5 mL). The combined organic phase was washed with saturated NaS_2O_3 (1 x 10 ml), dried over Na_2SO_4, filtered and concentrated. The crude residue was purified via Pasteur pipet gradient column chromatography (50:1 hexane-EtOAc, polarity gradually increased to 13:1 hexane-EtOAc) to give the title compound as a clear, colorless oil (3.6 mg, 85% yield). R_f (90:10 hexane-EtOAc) = 0.47.

IR (thin film/NaCl): 2933, 2857, 1725, 1461 cm^{-1}.

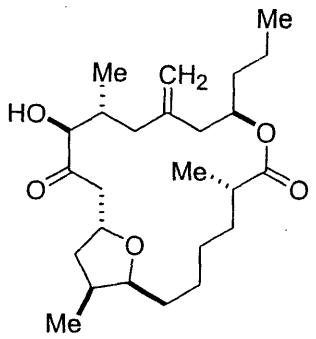
^1H NMR (C_6D_6, 500 MHz): δ 5.09-5.04 (m, 1H), 4.88 (s, 1H), 4.83 (s, 1H), 4.80 (dd, J = 2.1, 9.0 Hz, 1H), 4.46 (ddd, J = 2.4, 7.2, 15.8 Hz, 1H), 3.87 (ddd, J = 4.8, 4.8, 7.9 Hz, 1H), 3.27-3.23 (m, 1H), 2.57-2.50 (m, 2H), 2.41-2.36 (m, 1H), 2.21 (dd, J = 9.6, 14.3 Hz, 1H), 2.08 (app dd, J = 8.2, 13.4 Hz, 2H), 1.97-1.93 (m, 1H), 1.77-1.68 (m, 2H), 1.66-1.57 (m, 3H), 1.49-1.18 (br m, 10H), 1.10-1.05 (m, 15H), 0.83 (t, J = 7.3 Hz, 3H), 0.80 (d, J = 7.0 Hz, 3H), 0.27 (s, 3H), 0.14 (s, 3H).

^{13}C NMR (C_6D_6, 125 MHz): δ 212.8, 176.2, 143.4, 116.3, 78.4, 76.4, 73.7, 72.4, 41.4, 41.3, 41.2, 41.0, 40.4, 38.9, 36.3, 35.8, 33.8, 28.3, 26.54 (3C), 26.53, 26.0, 19.3, 19.1, 18.5, 17.5, 14.9, 14.3, −3.8, −4.5.

HRMS (ESI)$[M+Na]^+$: *m/z* calcd for $C_{31}H_{56}O_5NaSi$ 559.3789, obsd 559.3780.

$[\alpha]_D$ = + 0.7 (23 °C, c = 1.4, $CHCl_3$)

Spectra for Chapter 2



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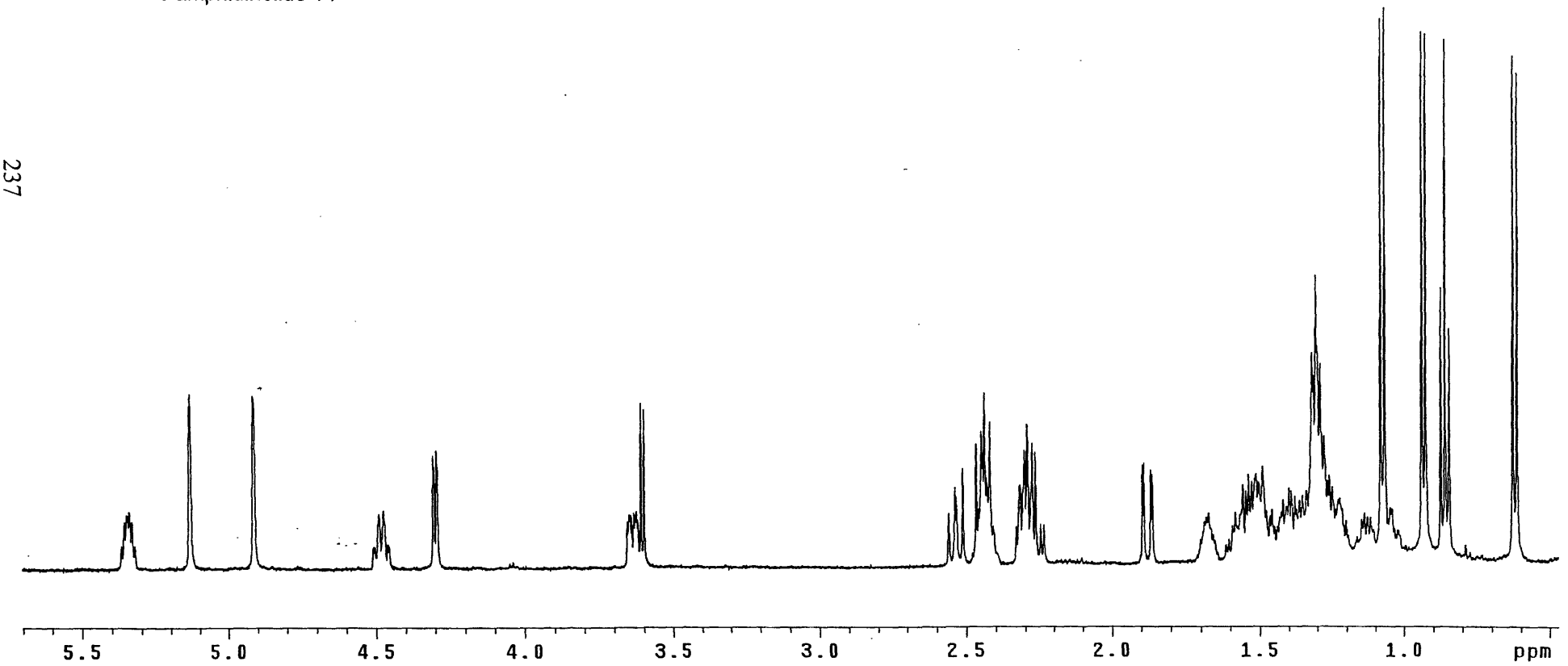

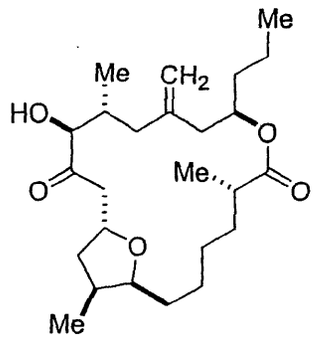

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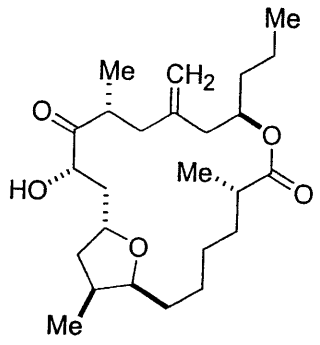

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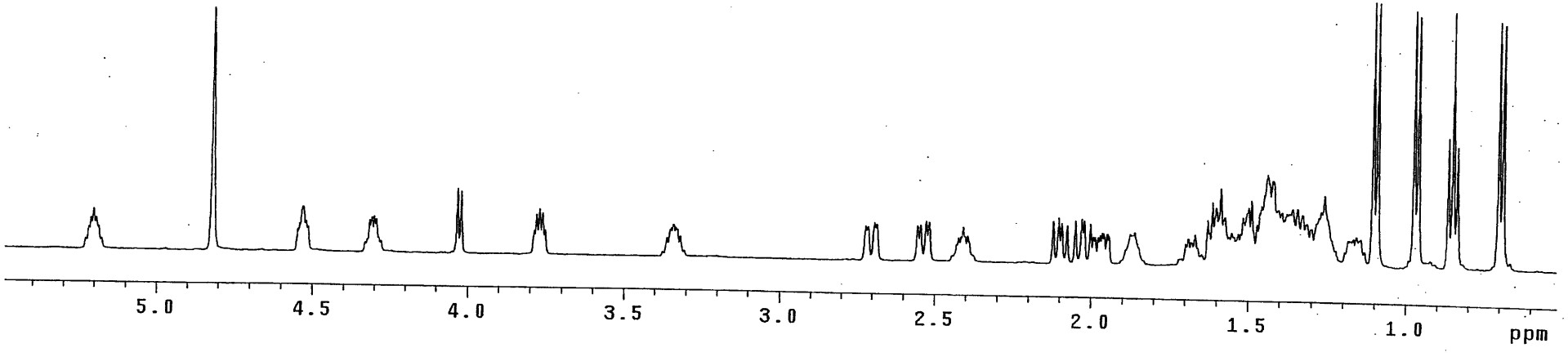

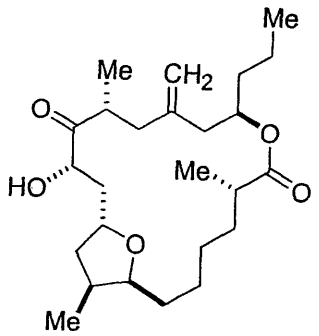

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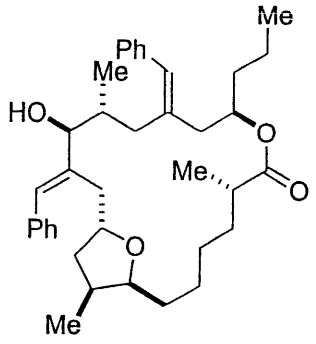

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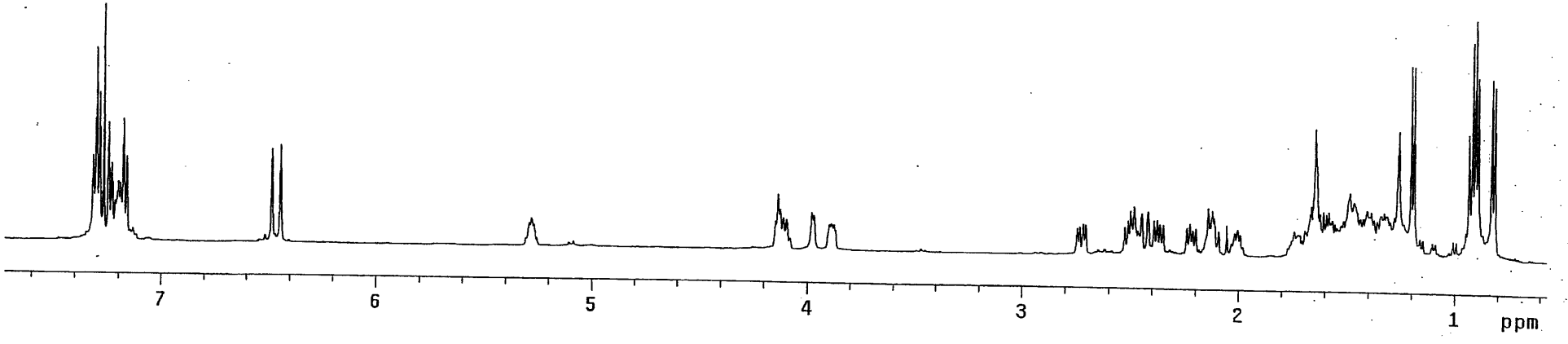

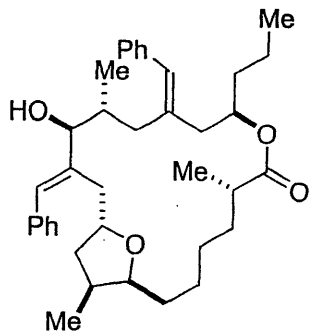

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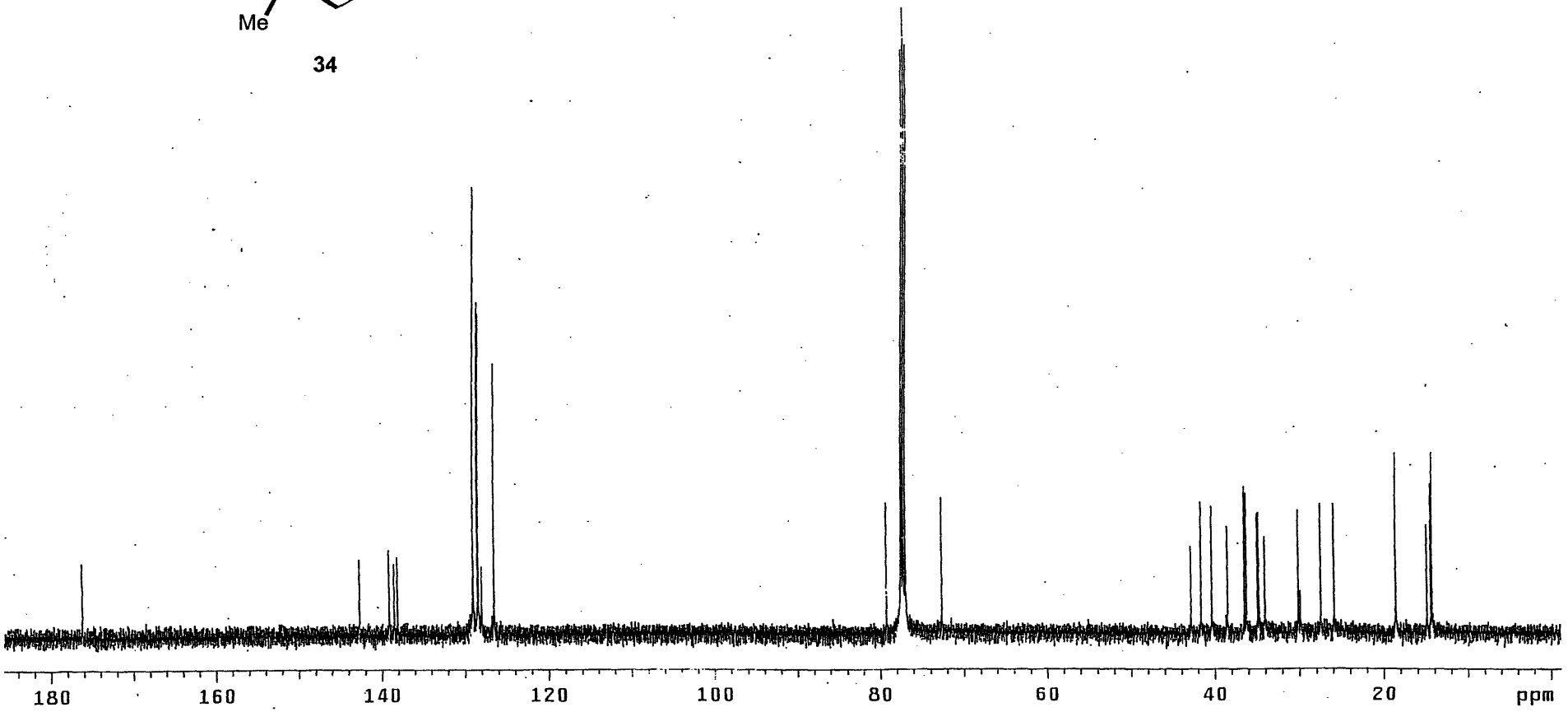

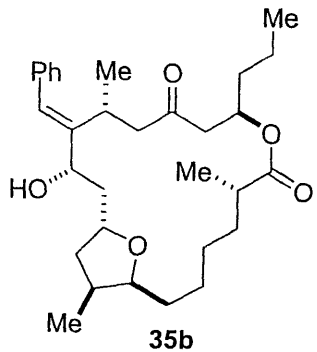

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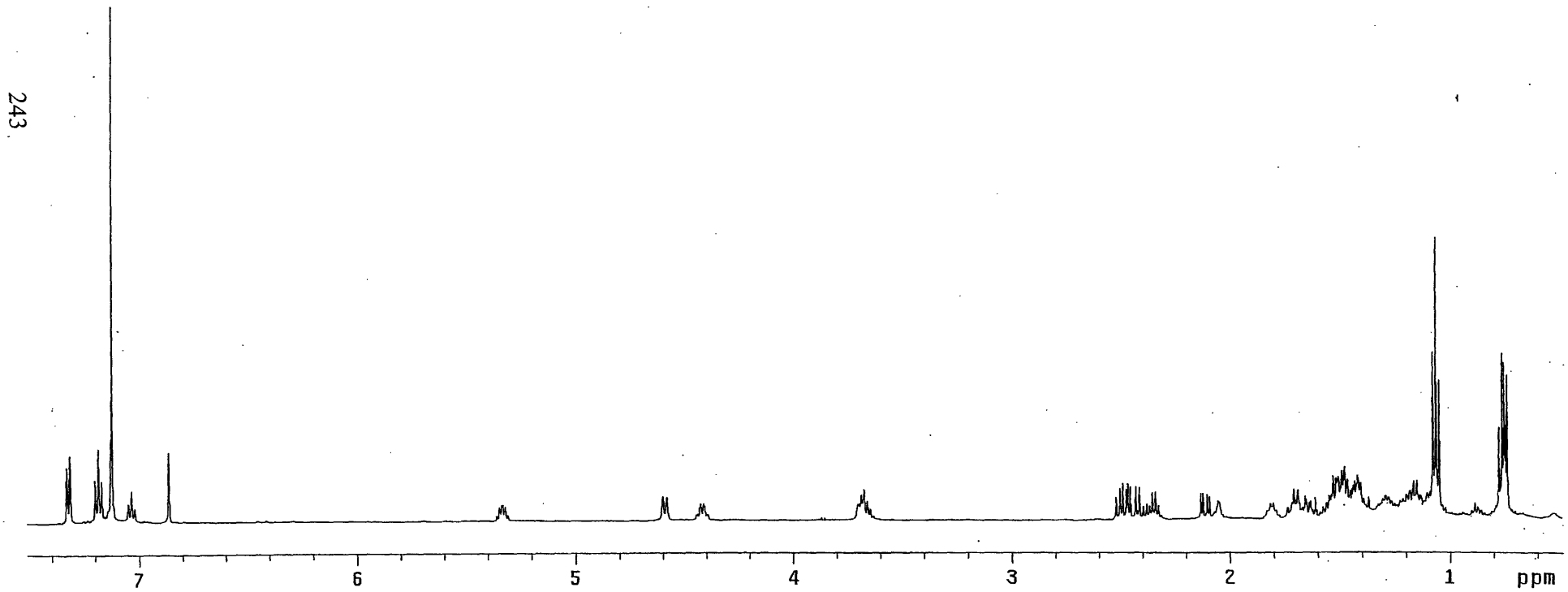

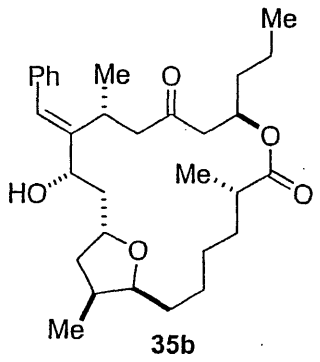

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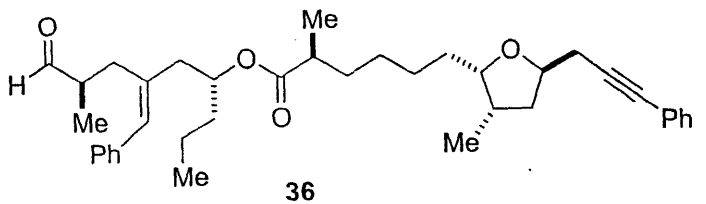

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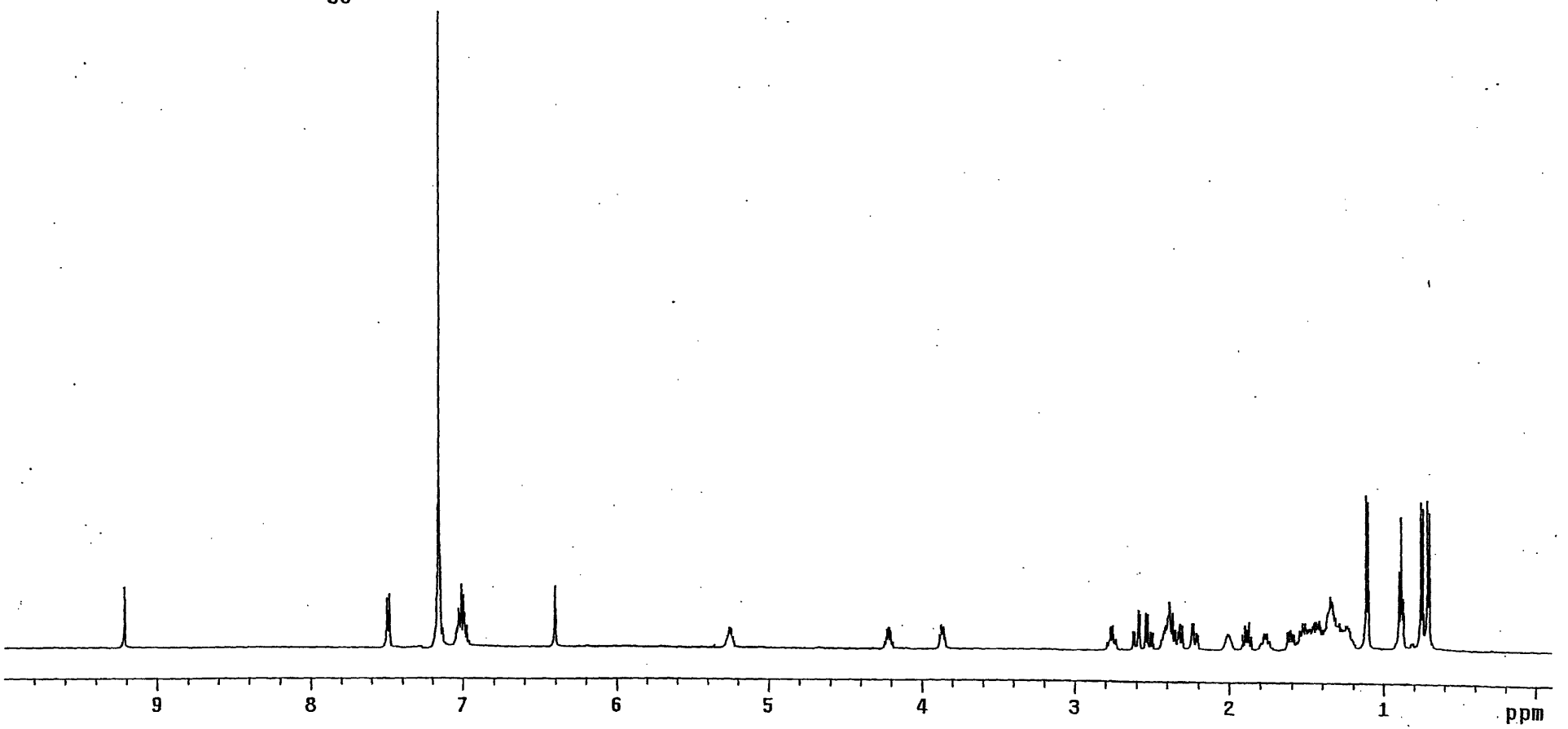

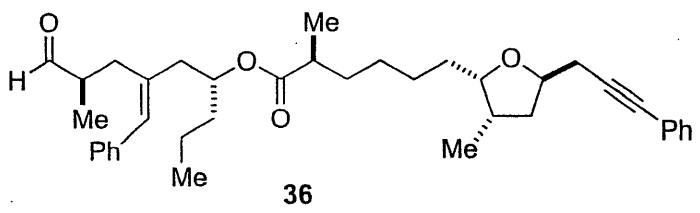
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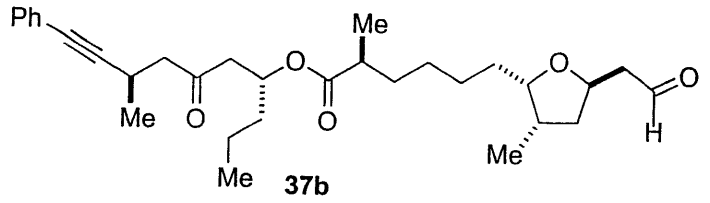

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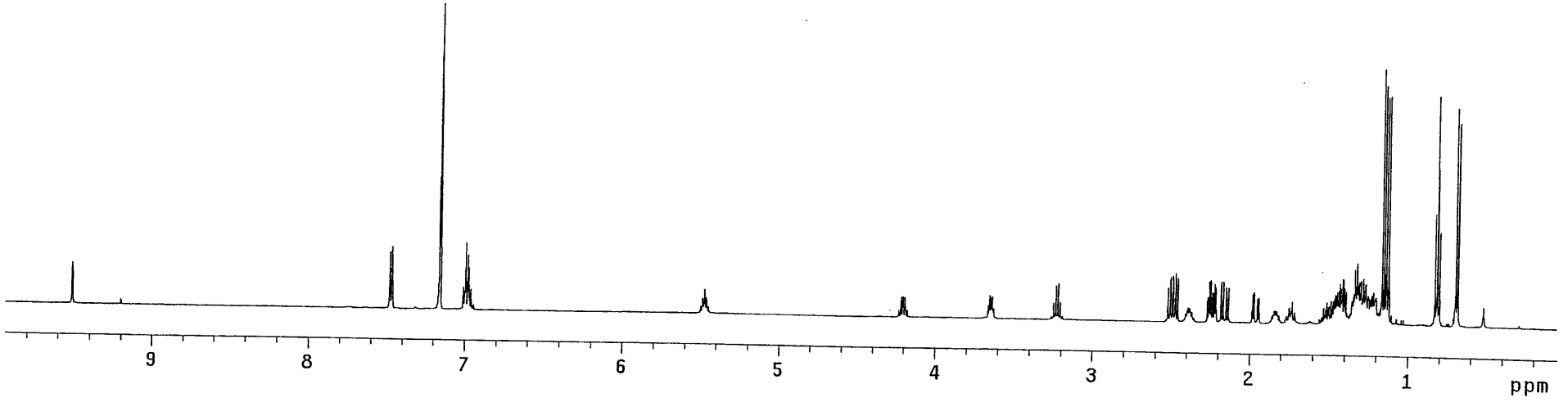

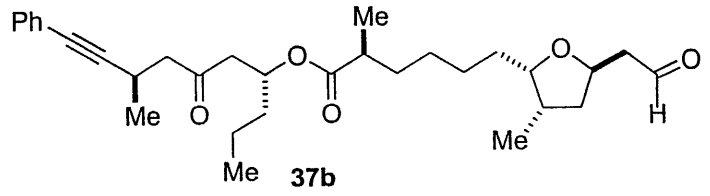

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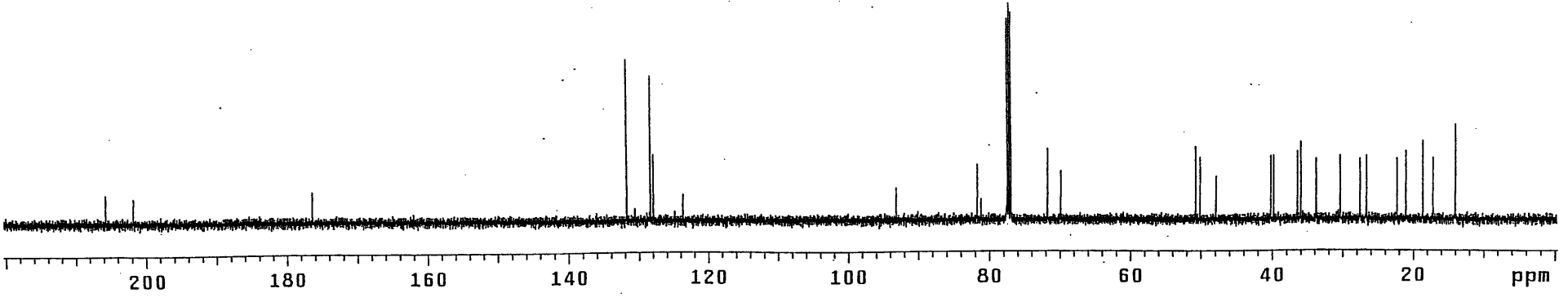

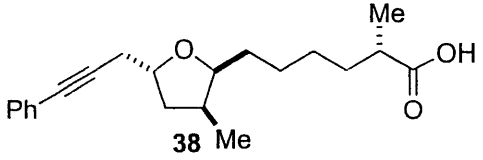
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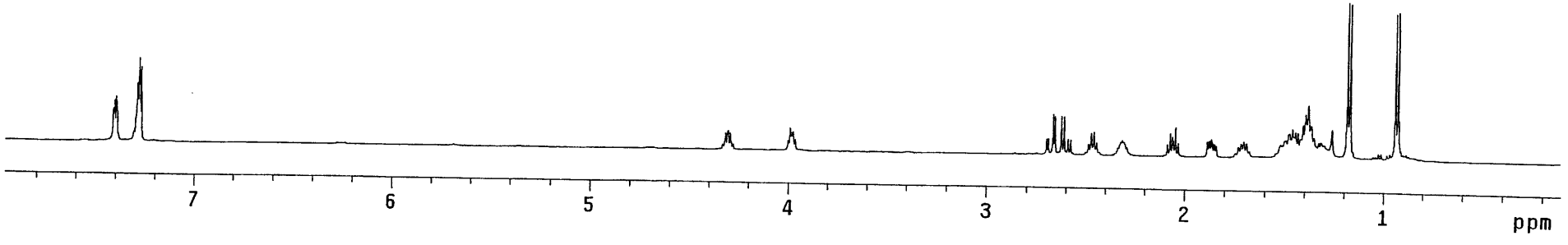
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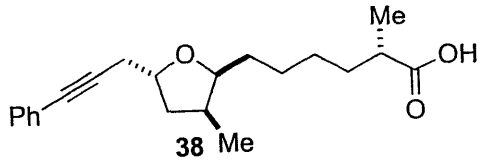
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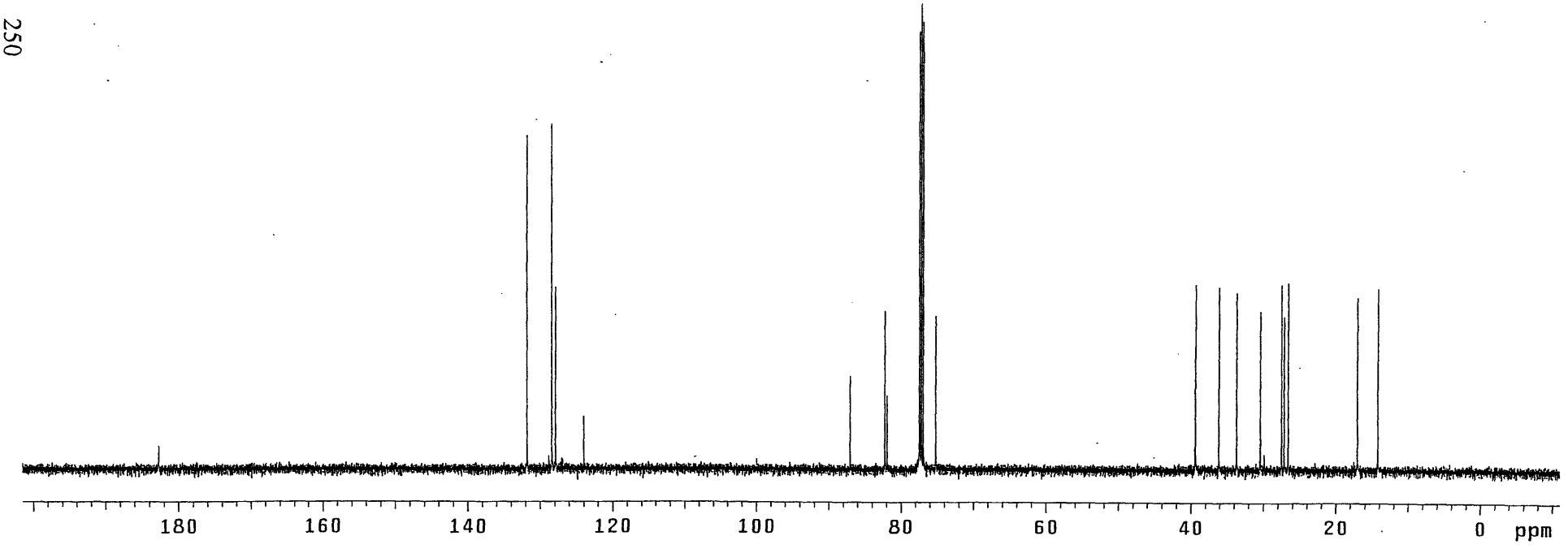
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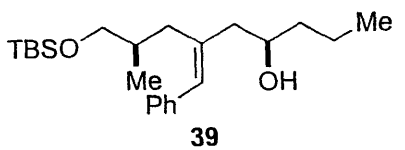

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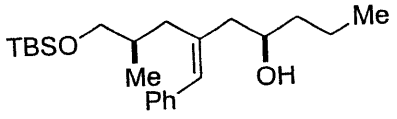

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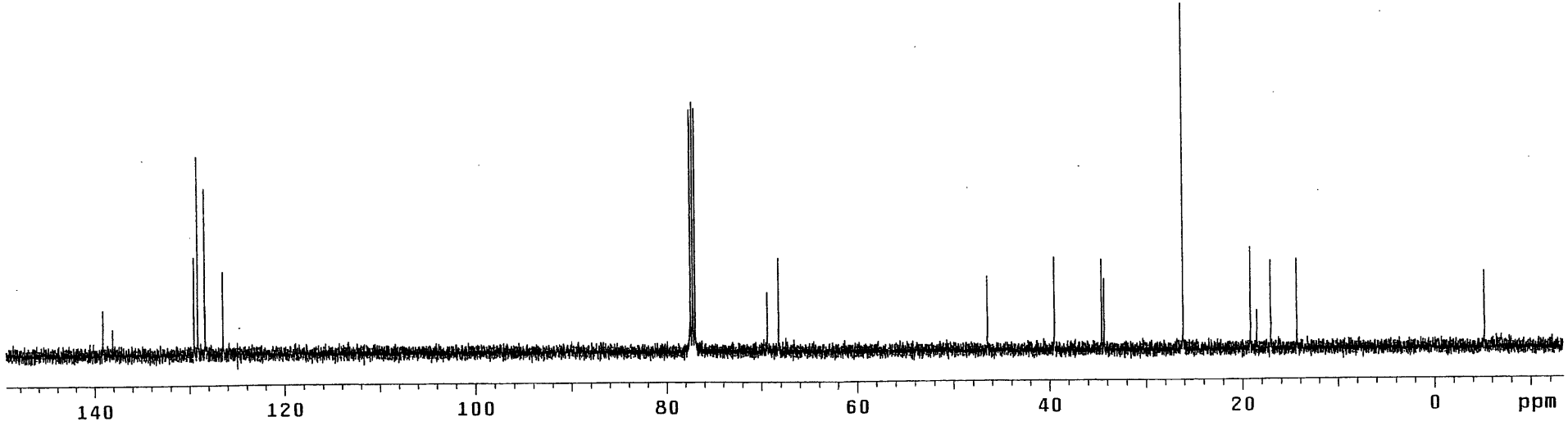

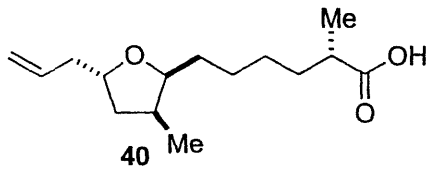

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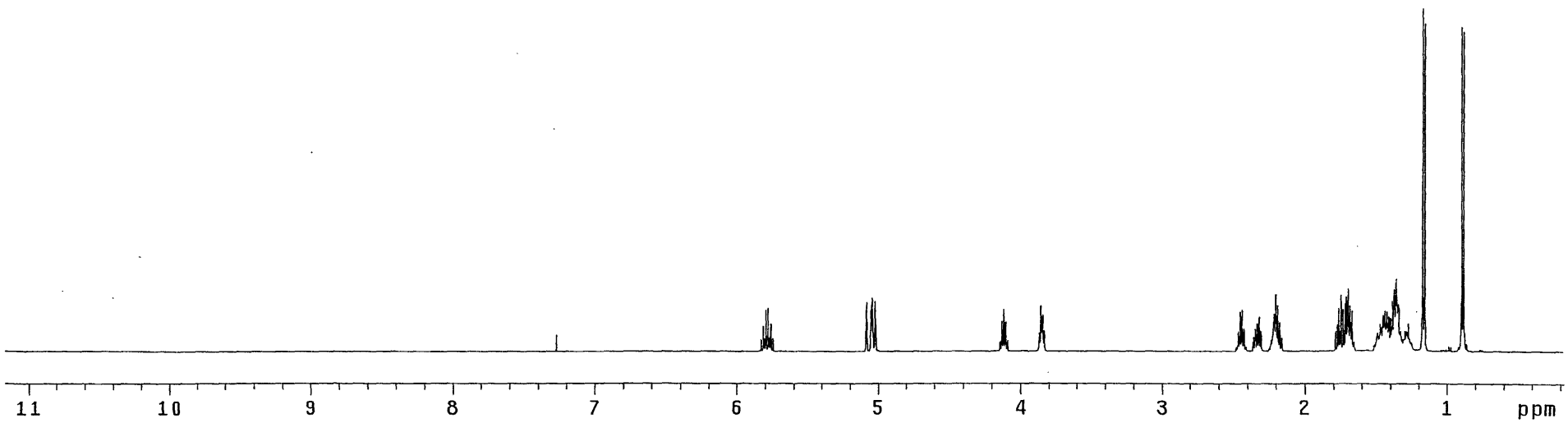

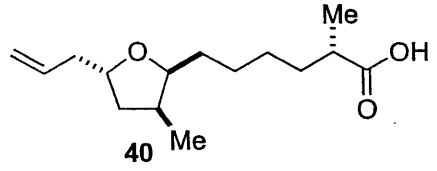

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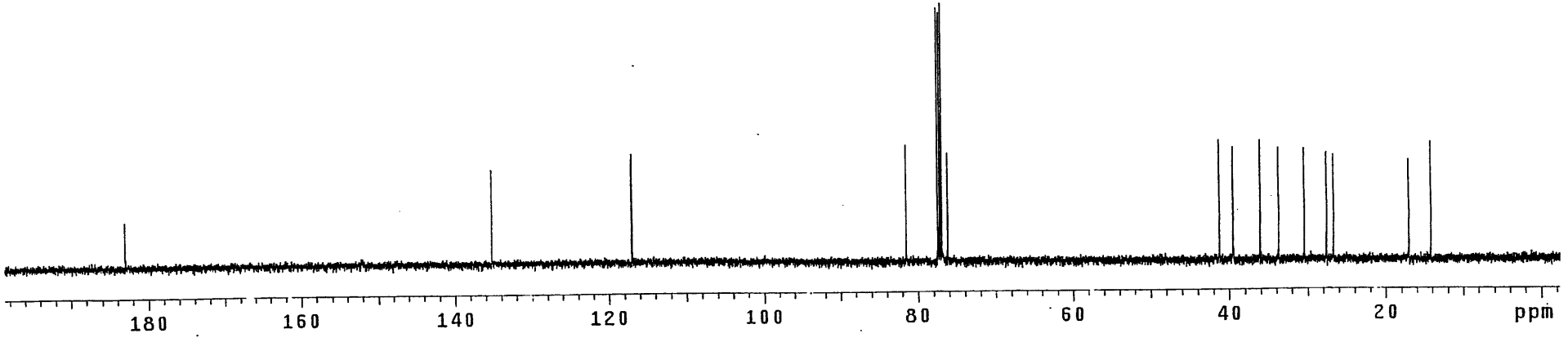

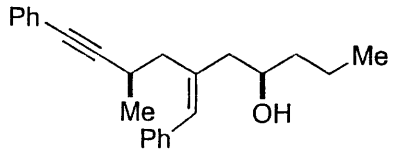

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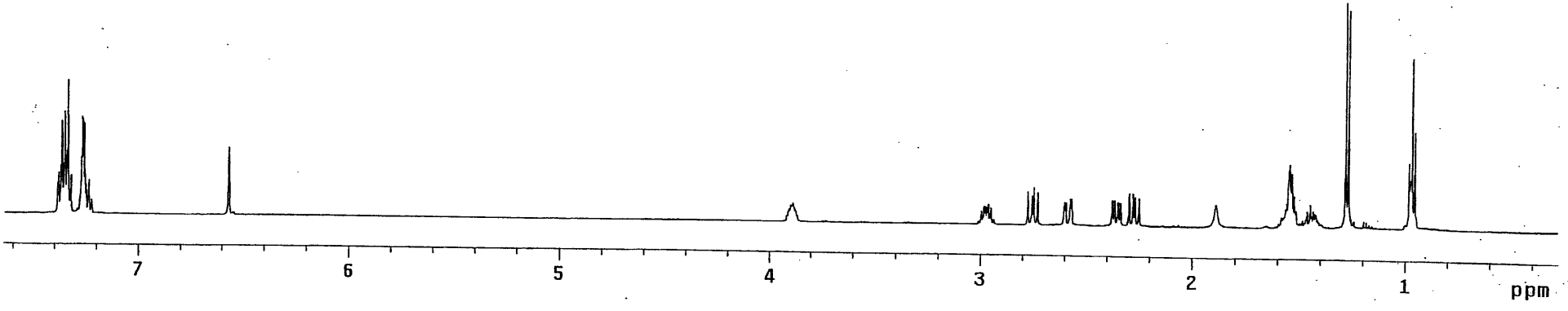

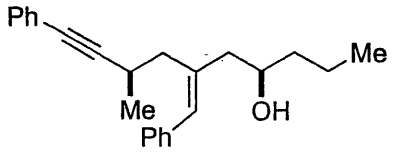

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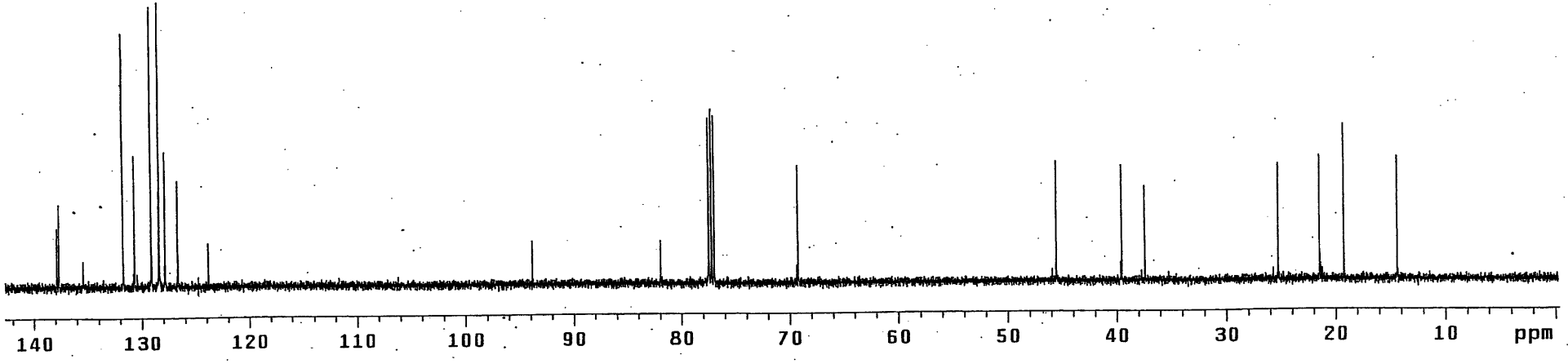

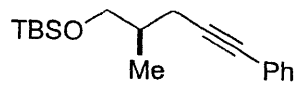

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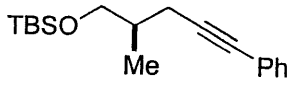

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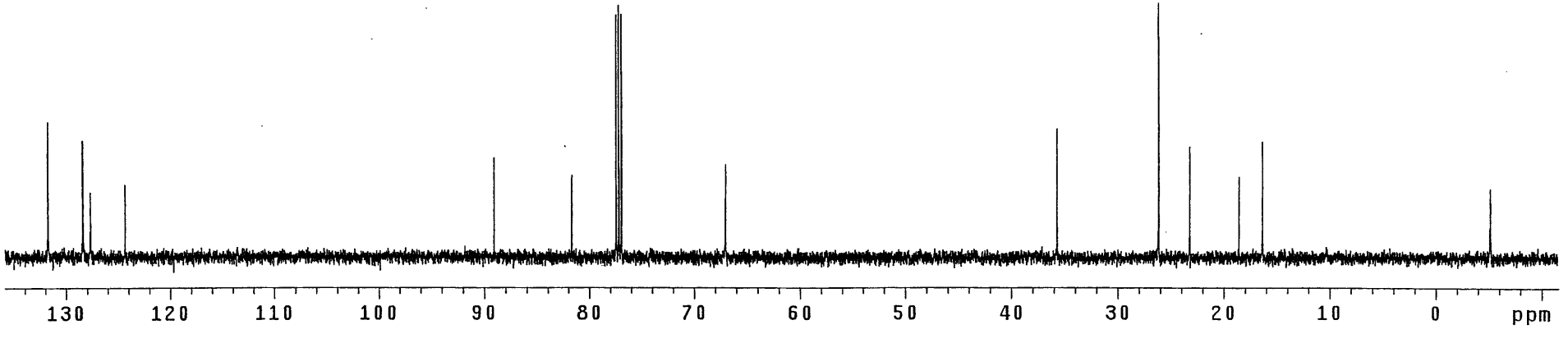

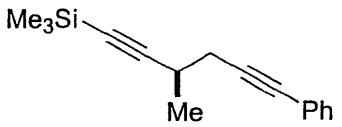

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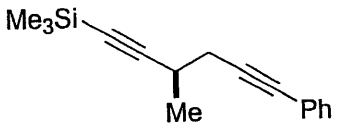

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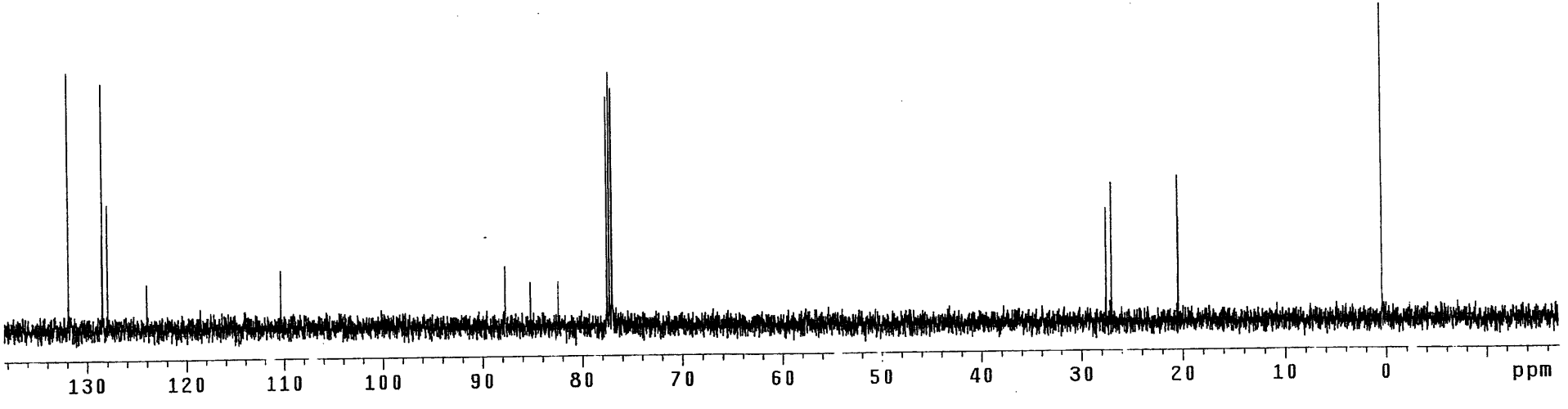

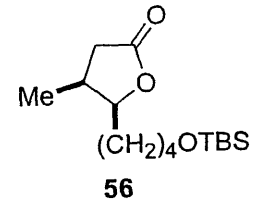

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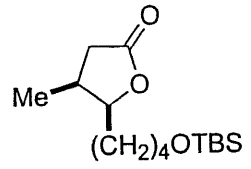

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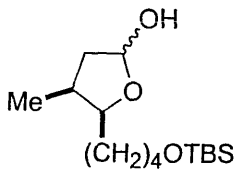

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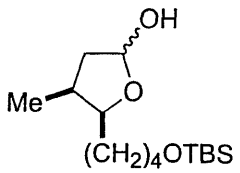

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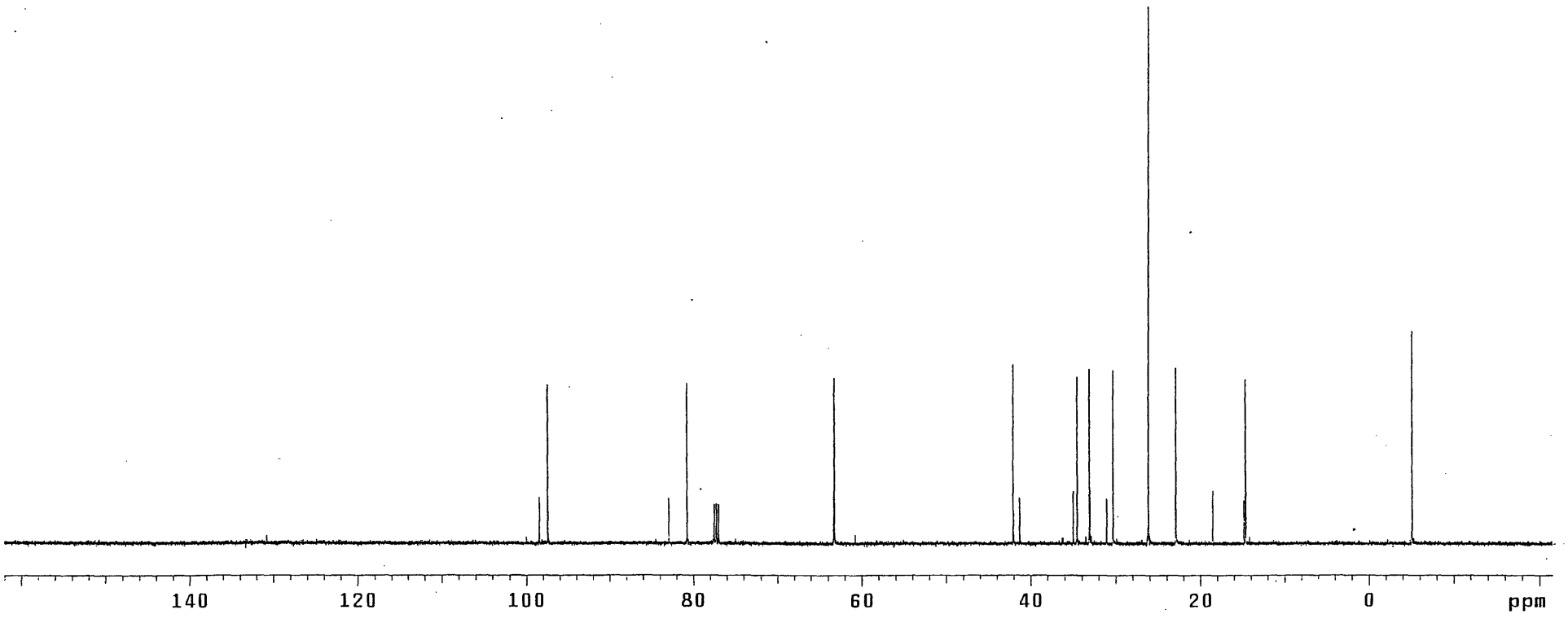

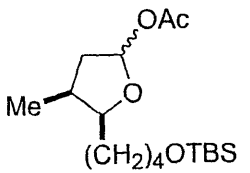

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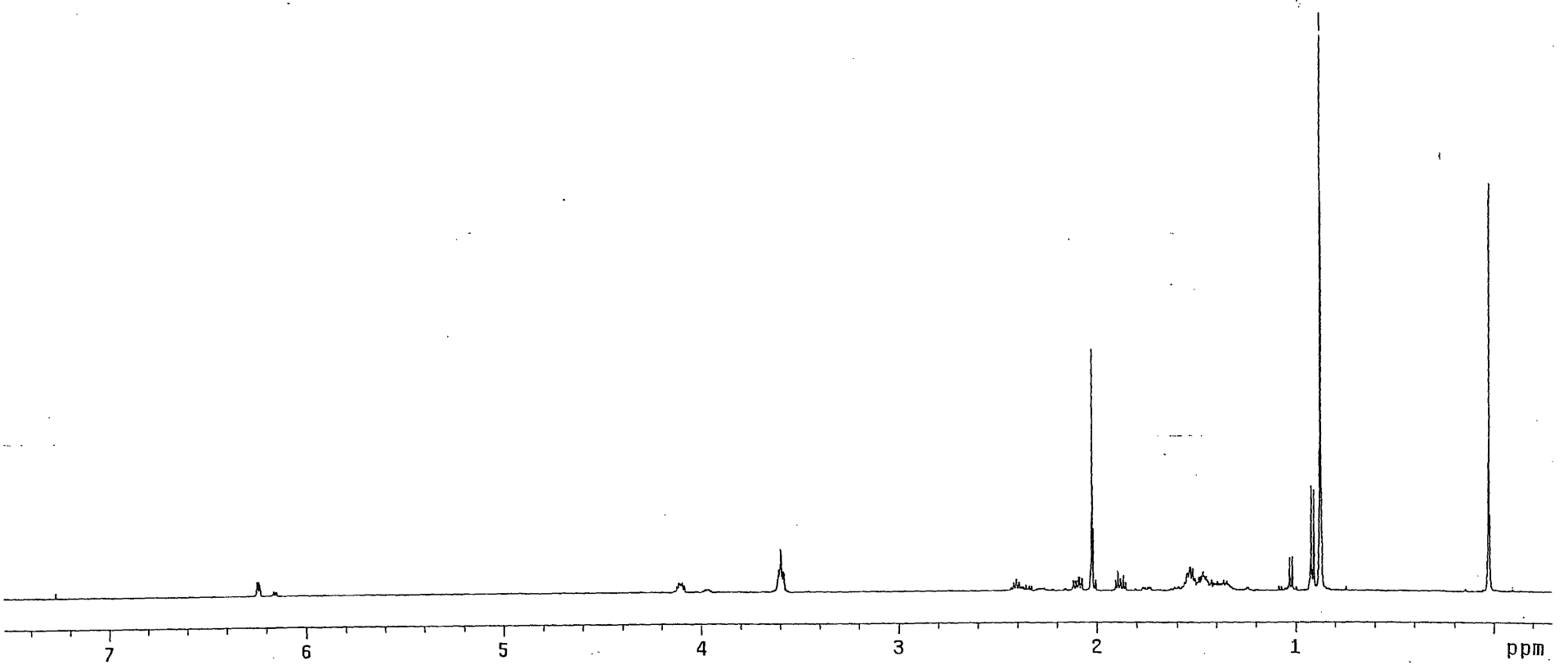

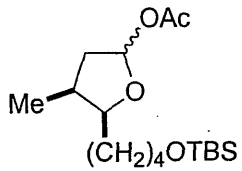

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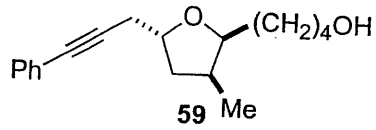

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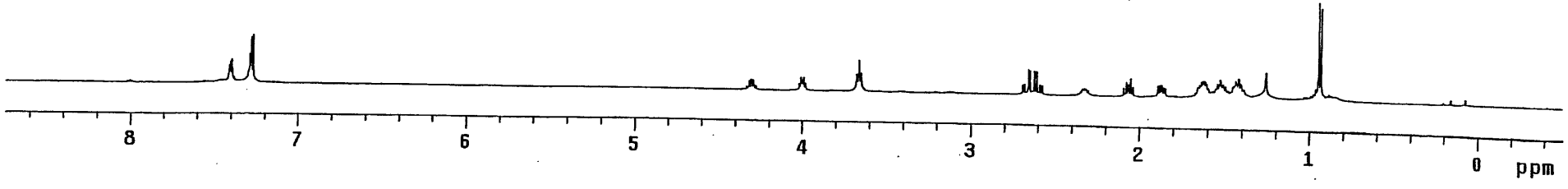

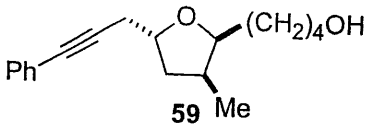

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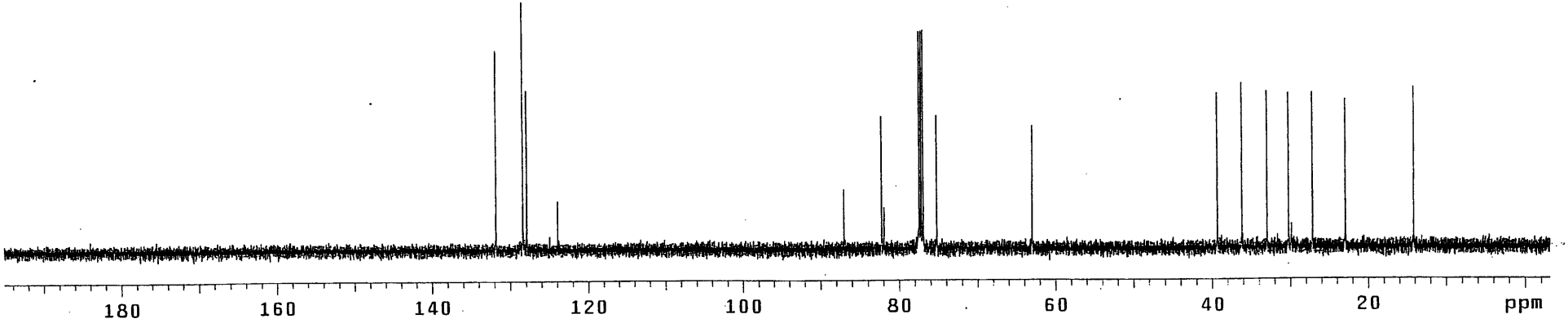

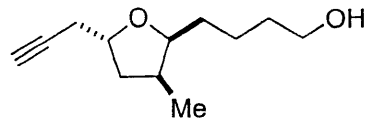

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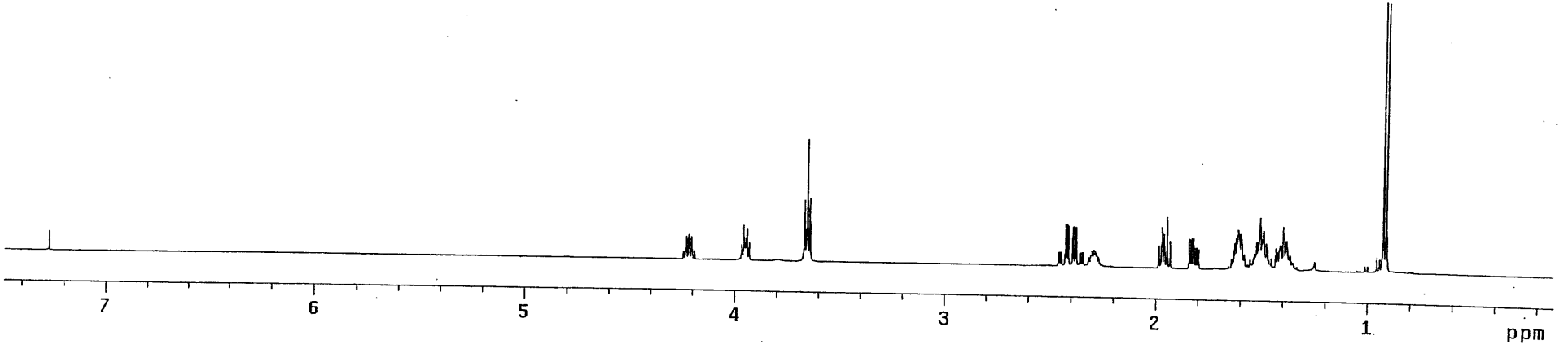

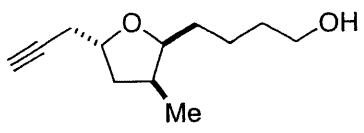

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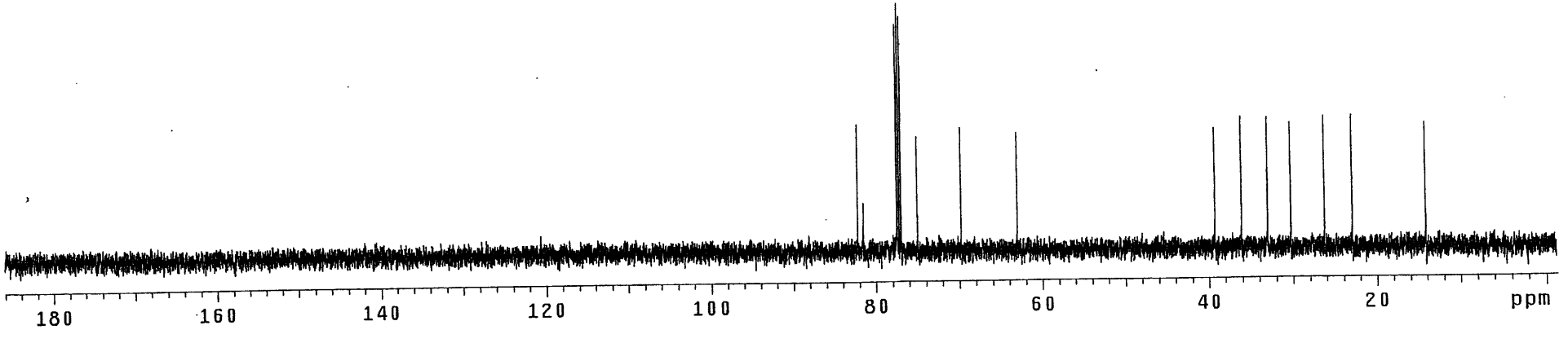

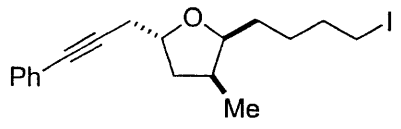

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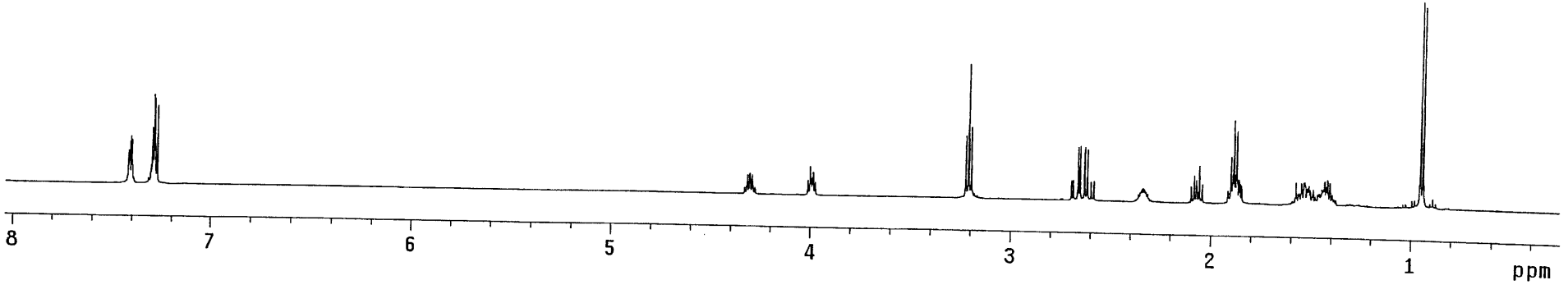

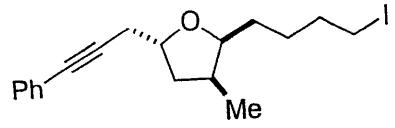

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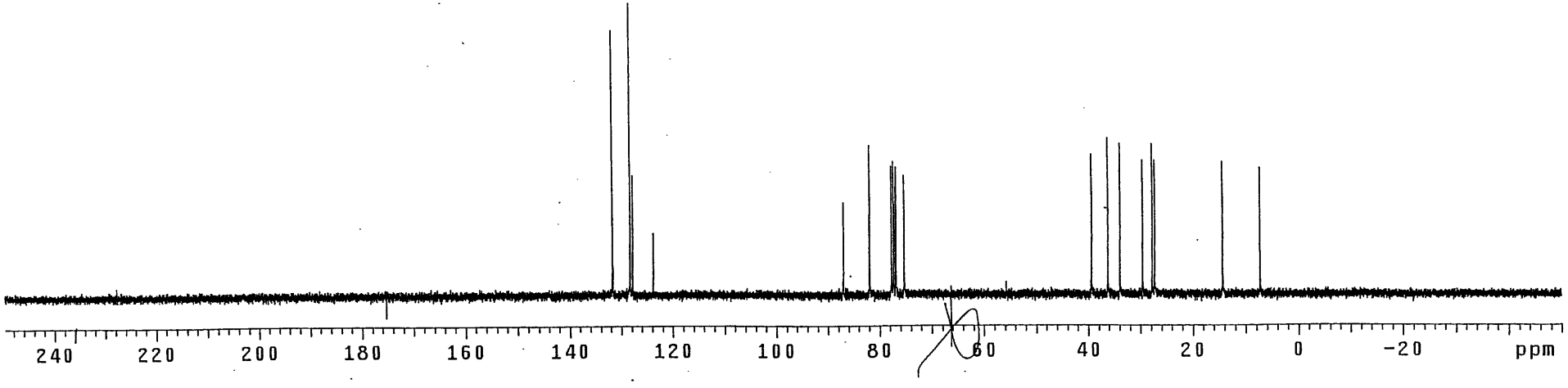

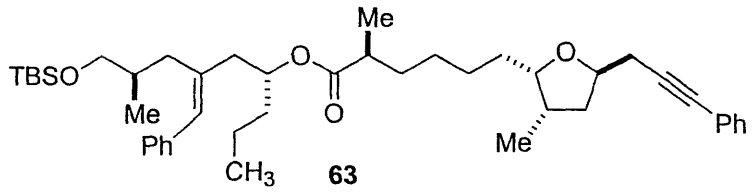

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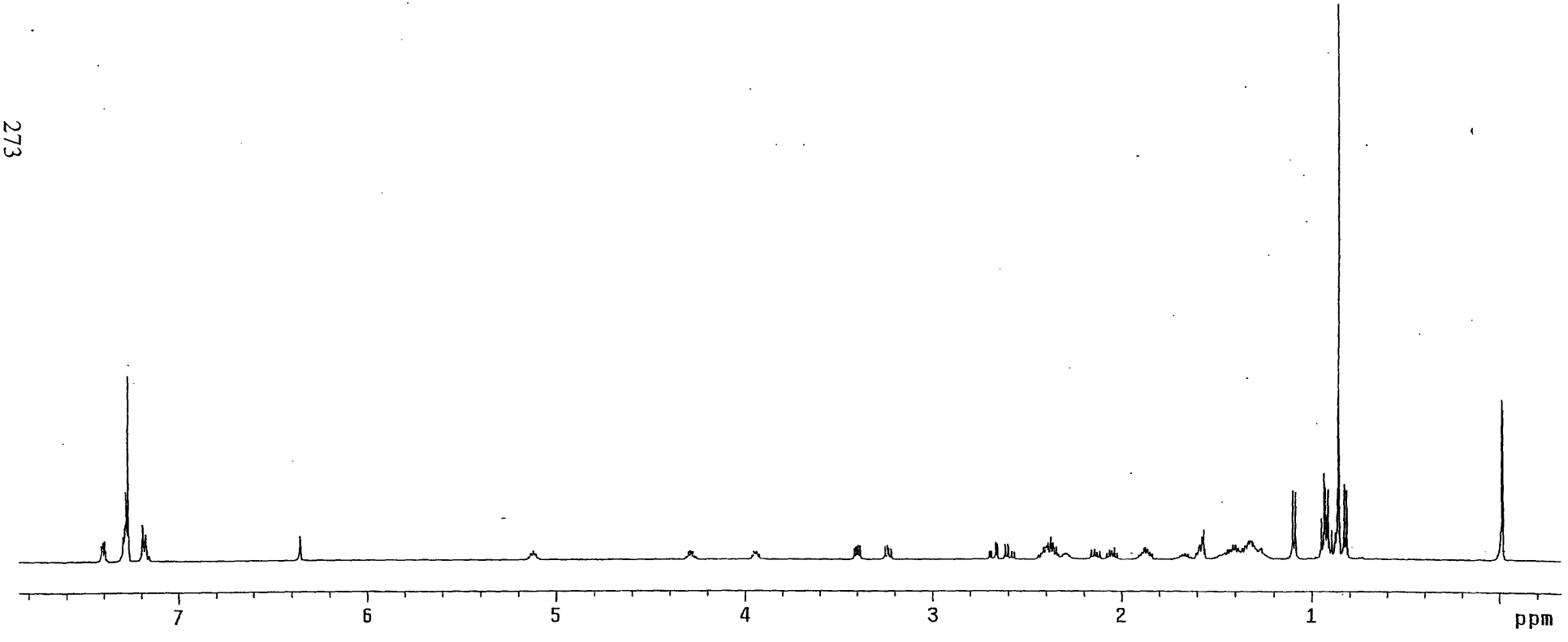

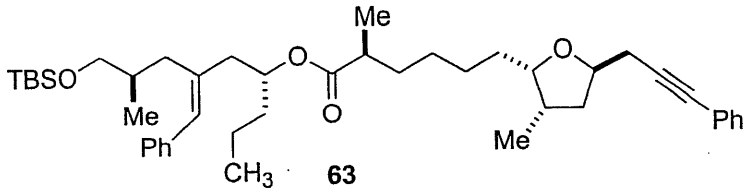

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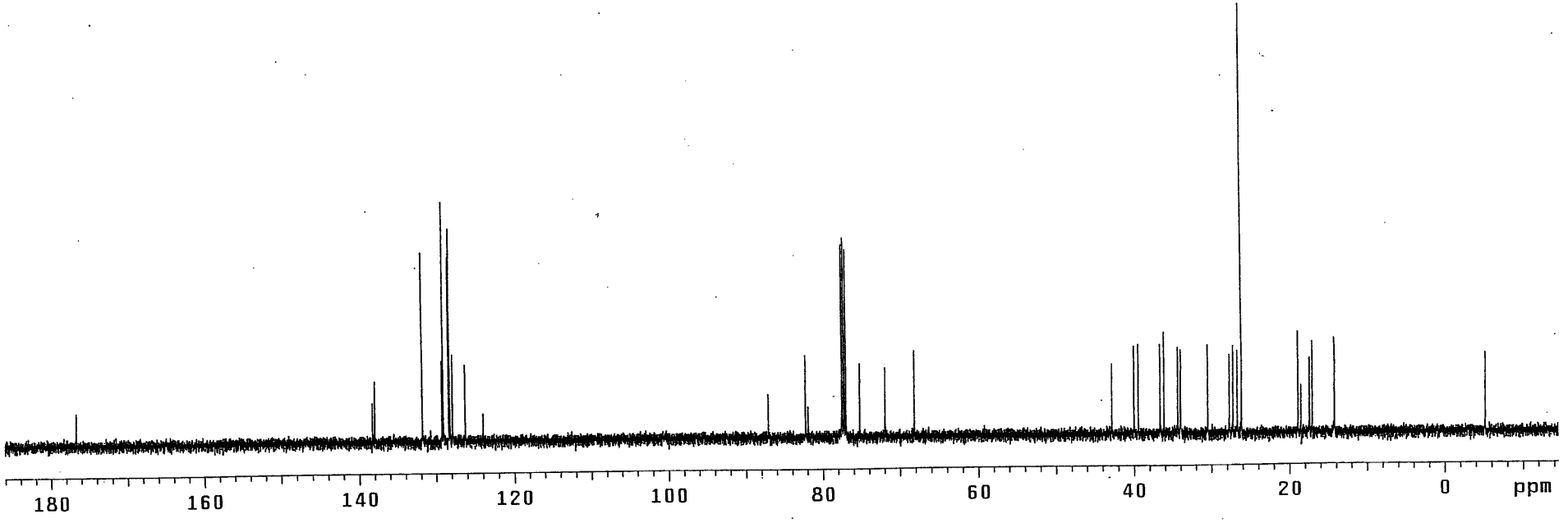

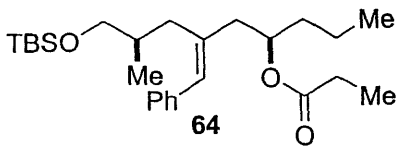

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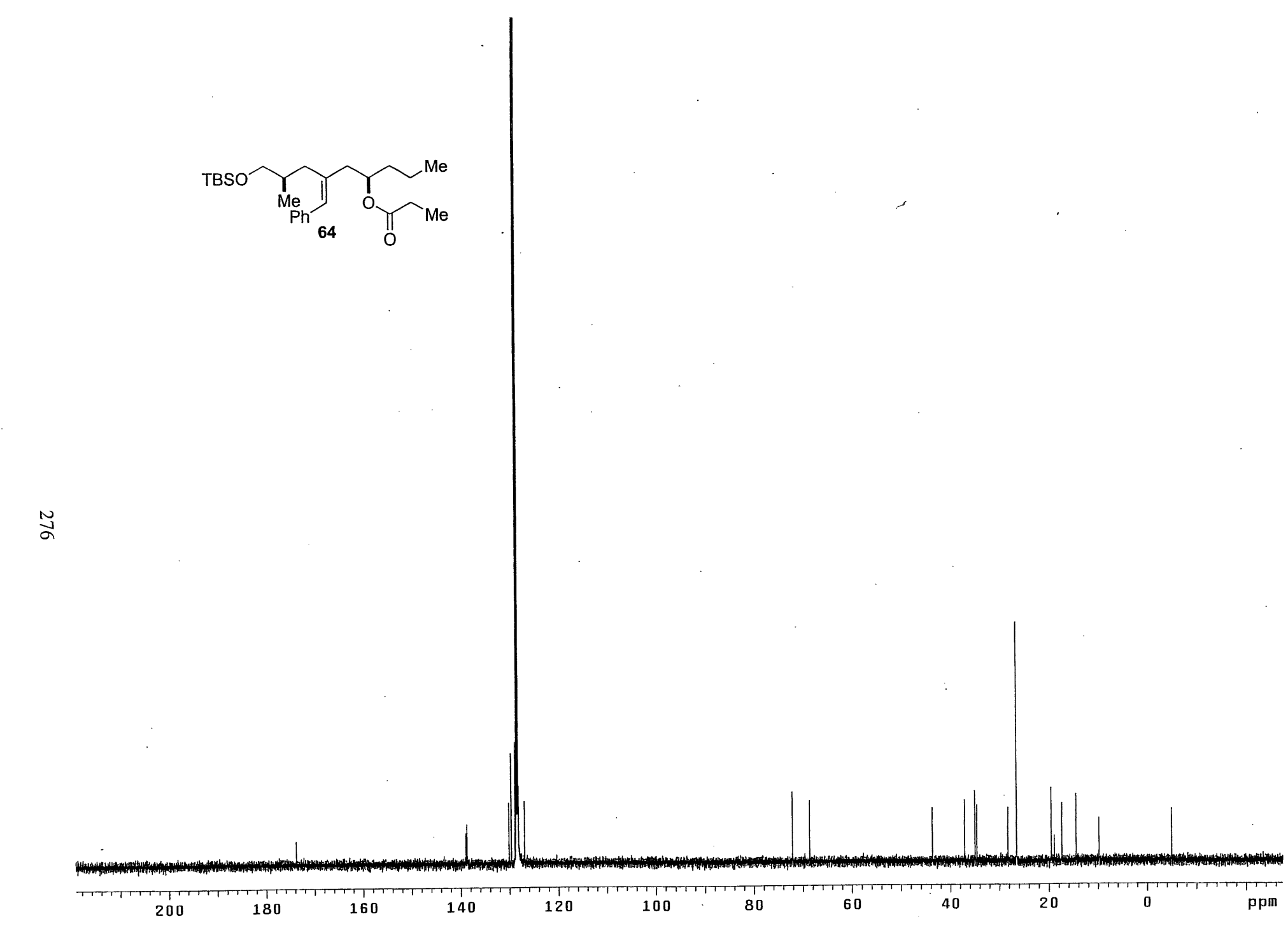
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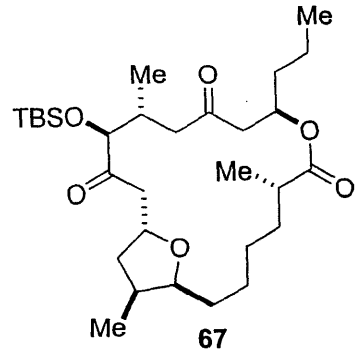
ppm



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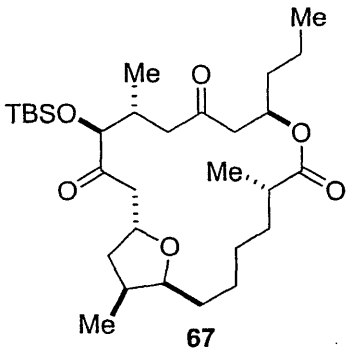

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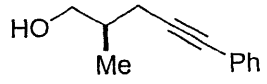

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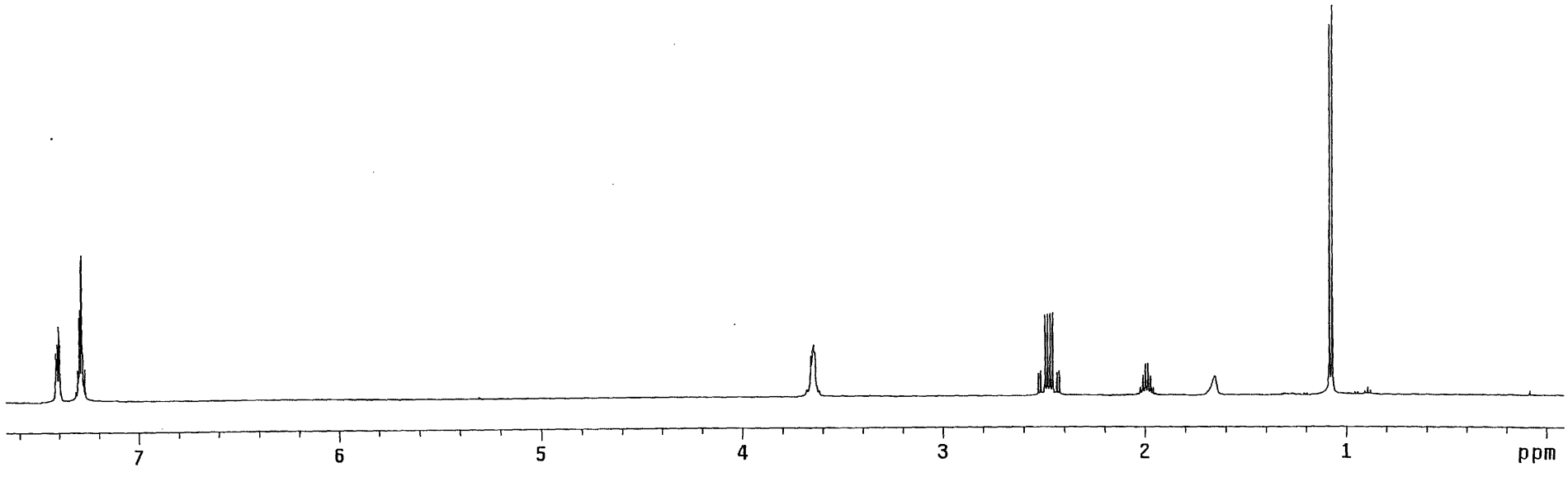

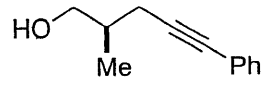

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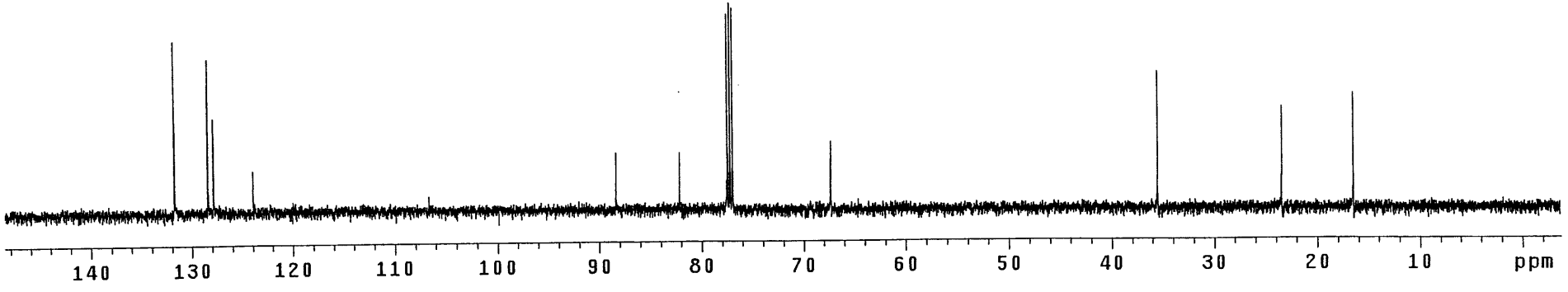

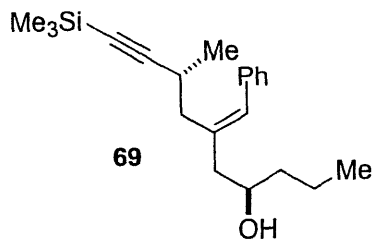

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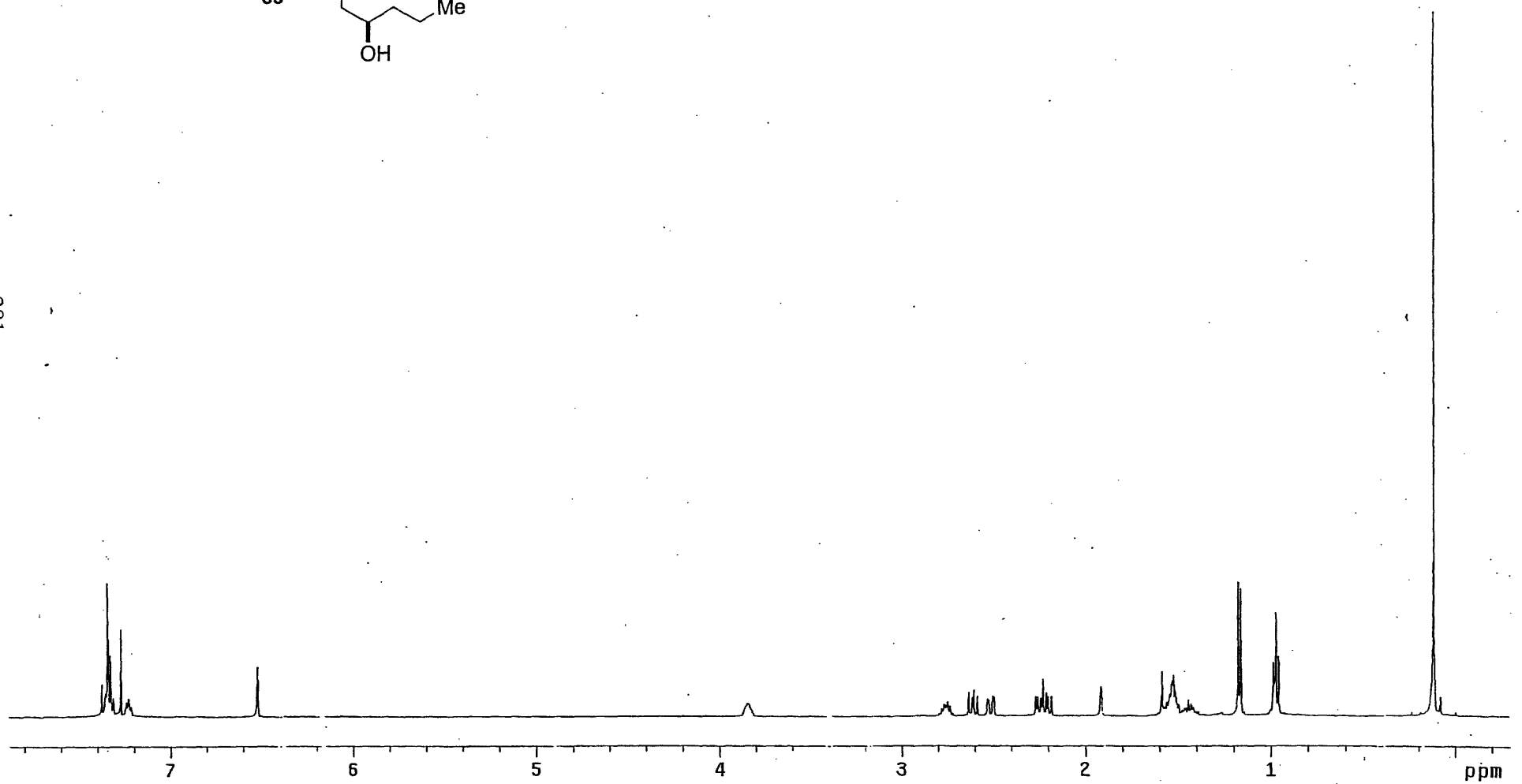

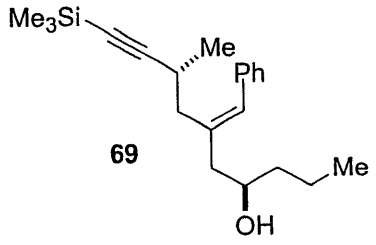
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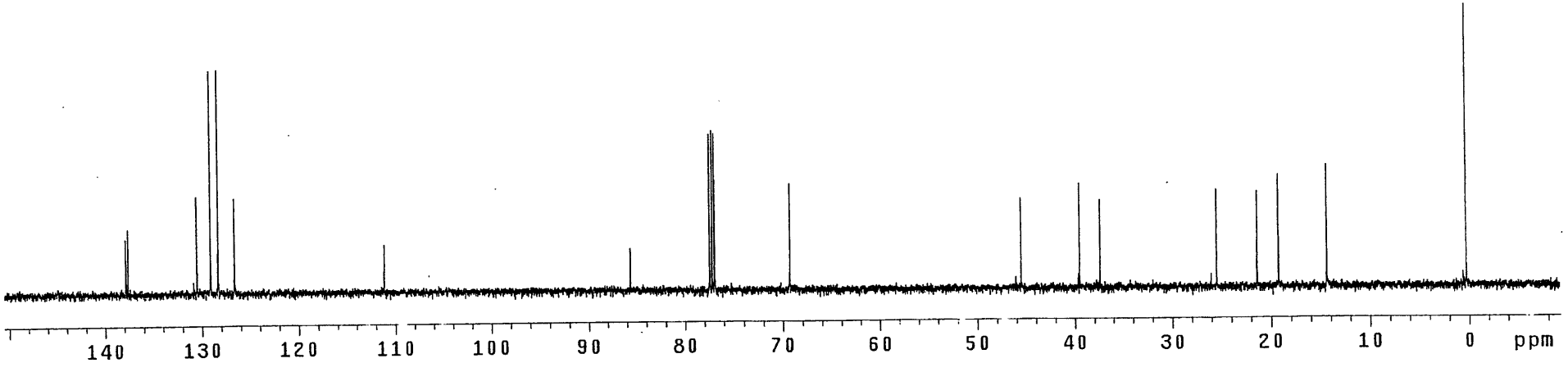
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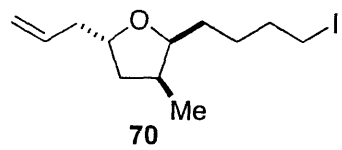
ppm



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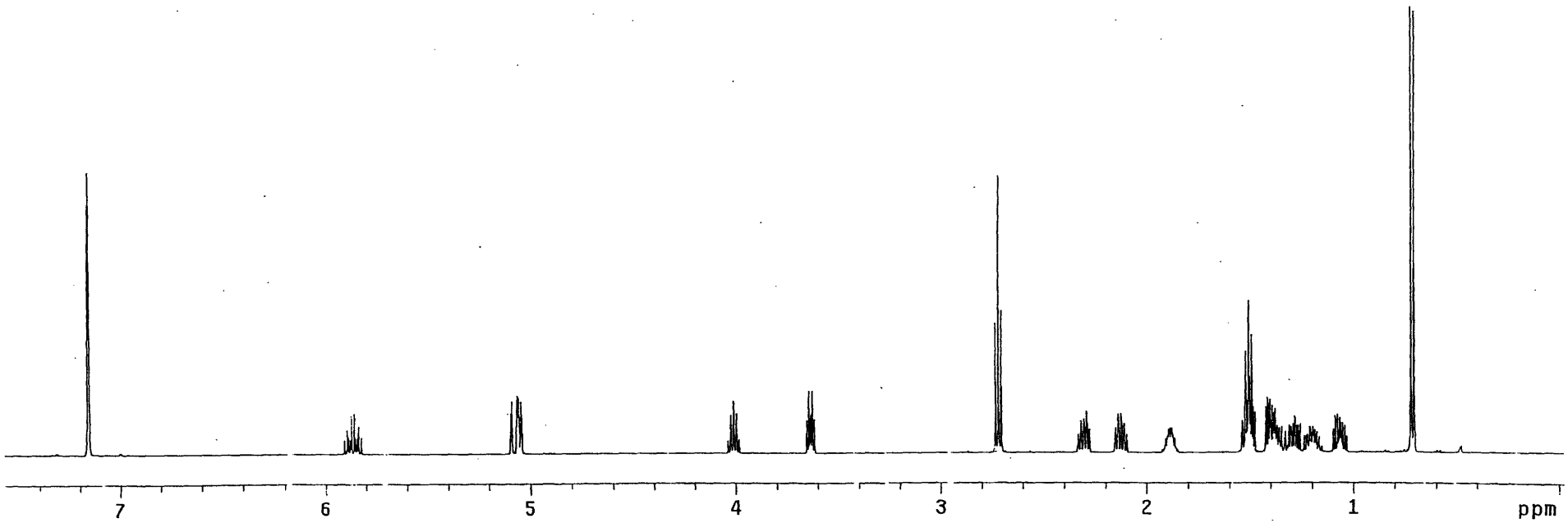

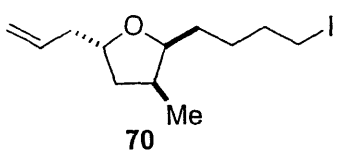

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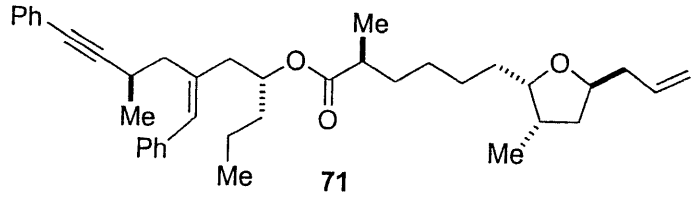

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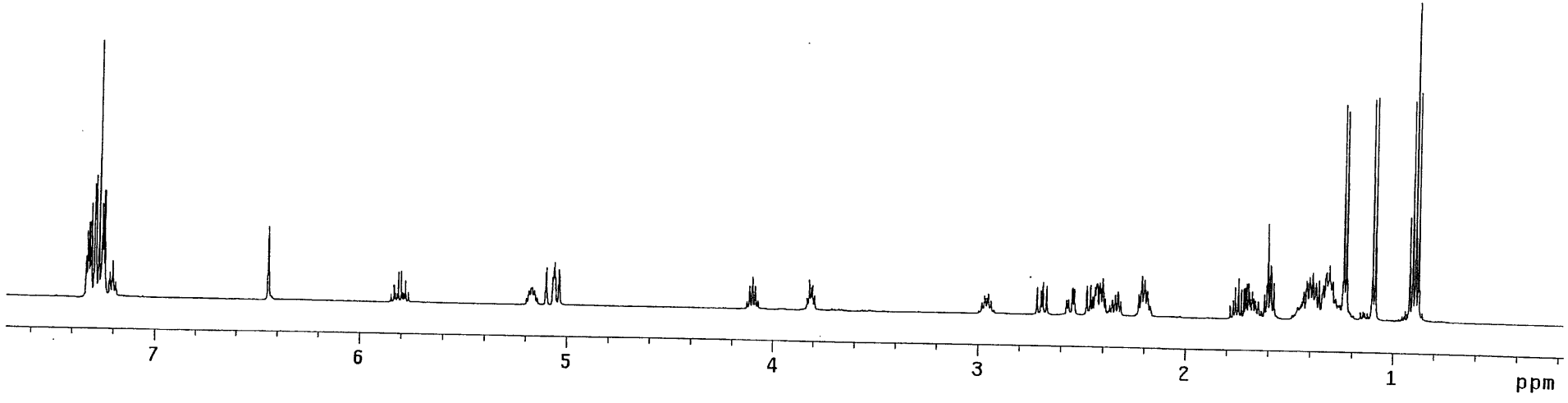

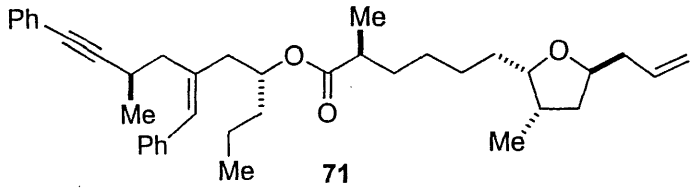

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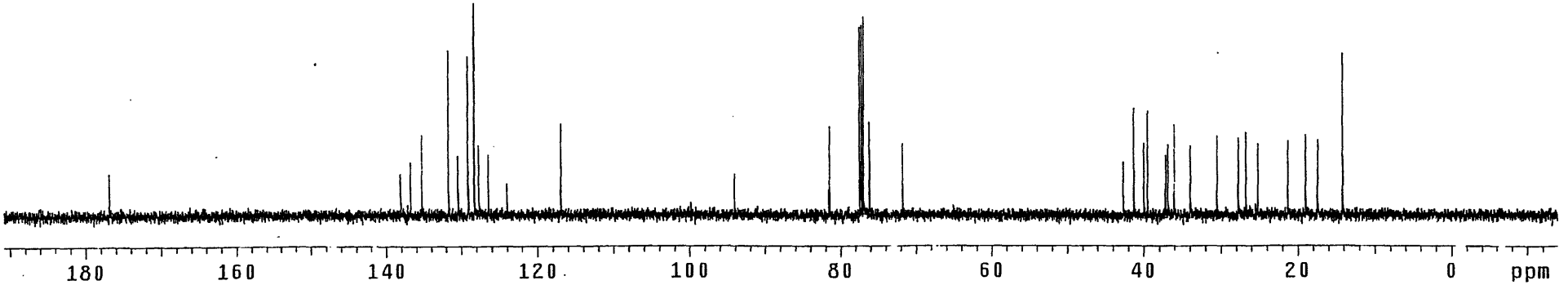

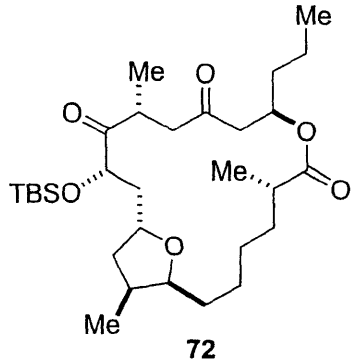

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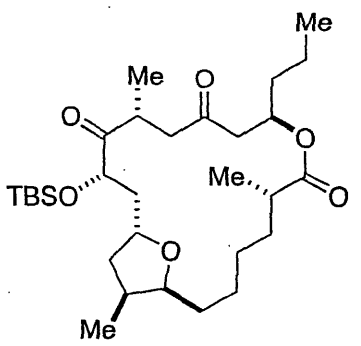
Me
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TBSO
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72

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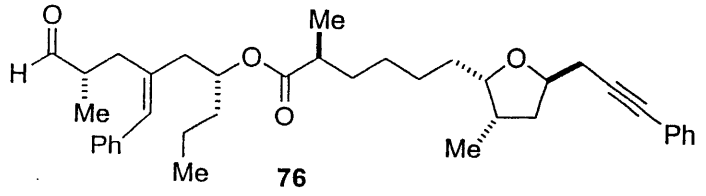

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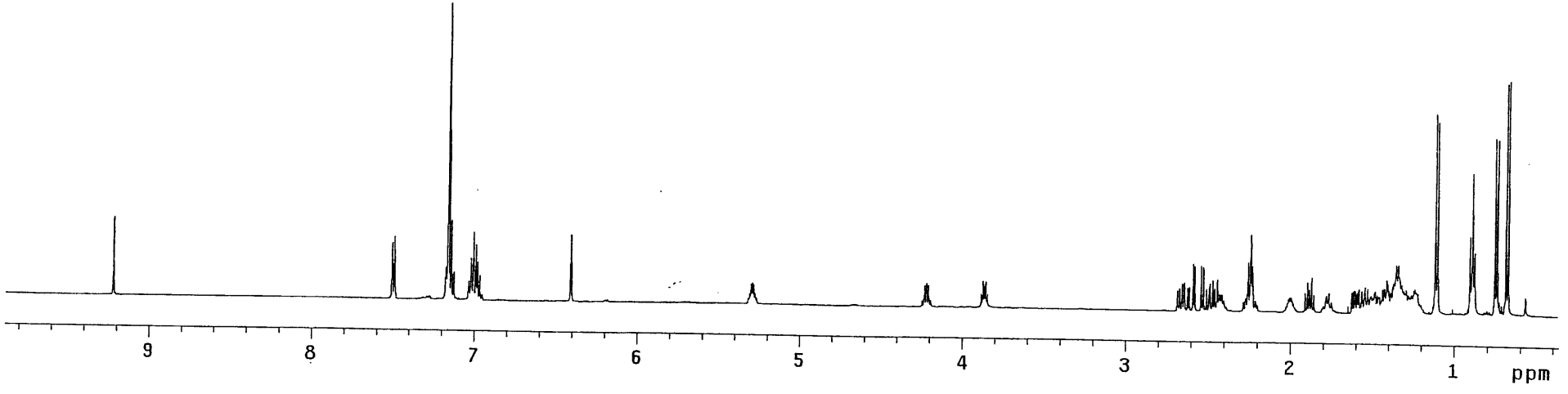

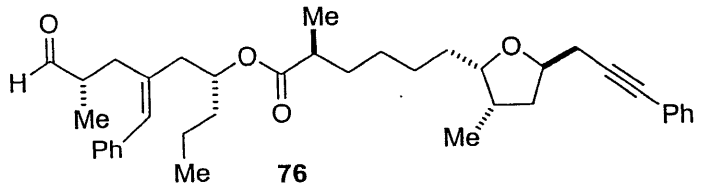

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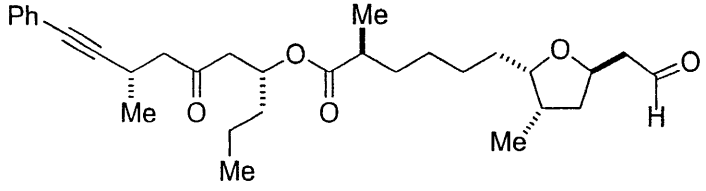

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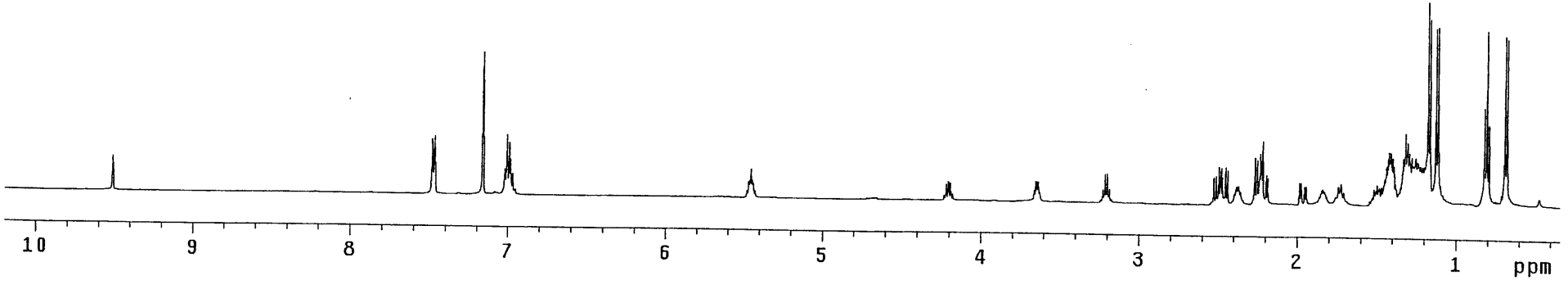

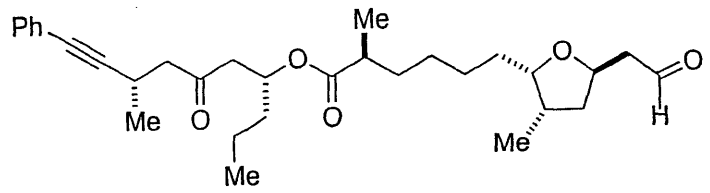

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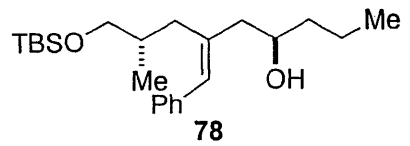

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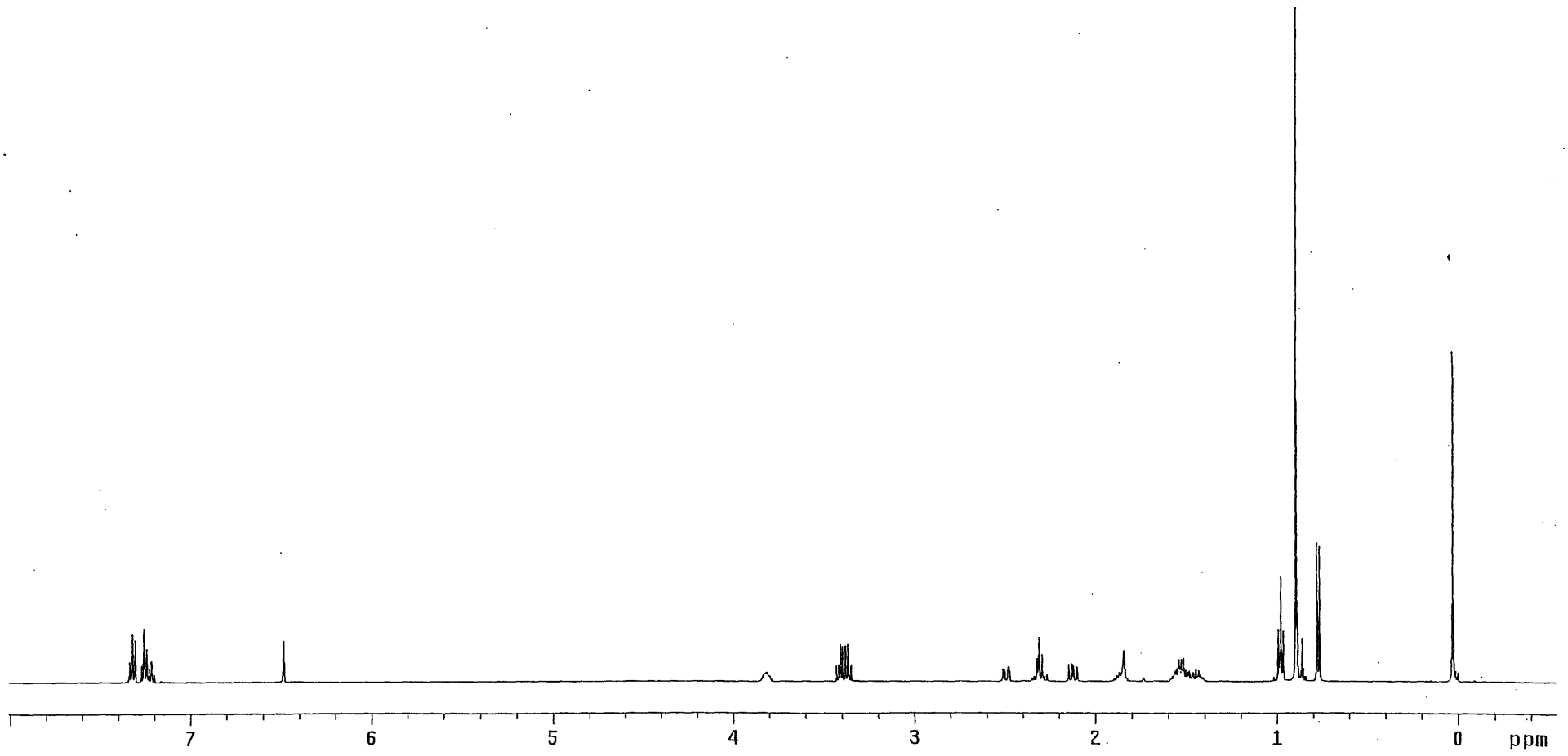

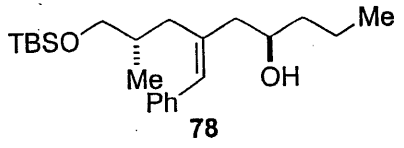

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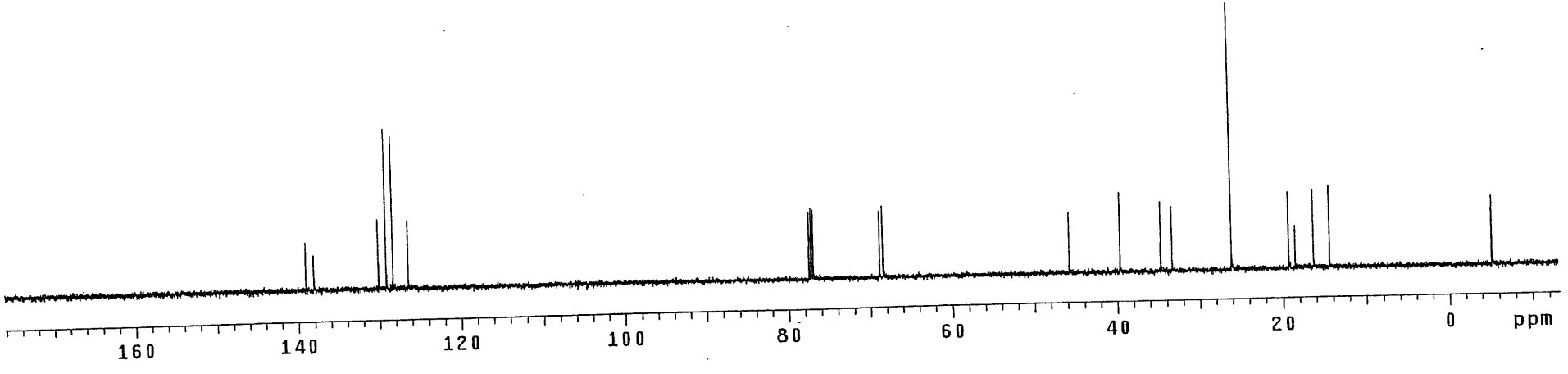

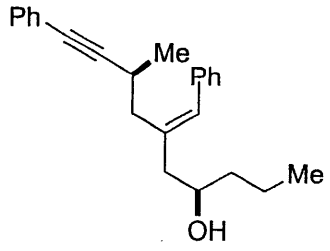

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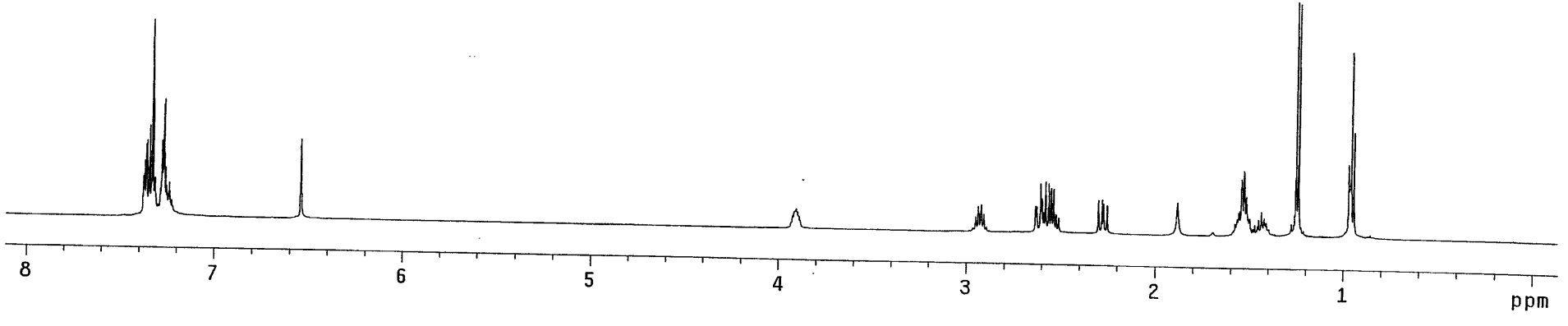

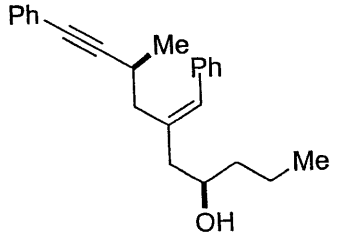

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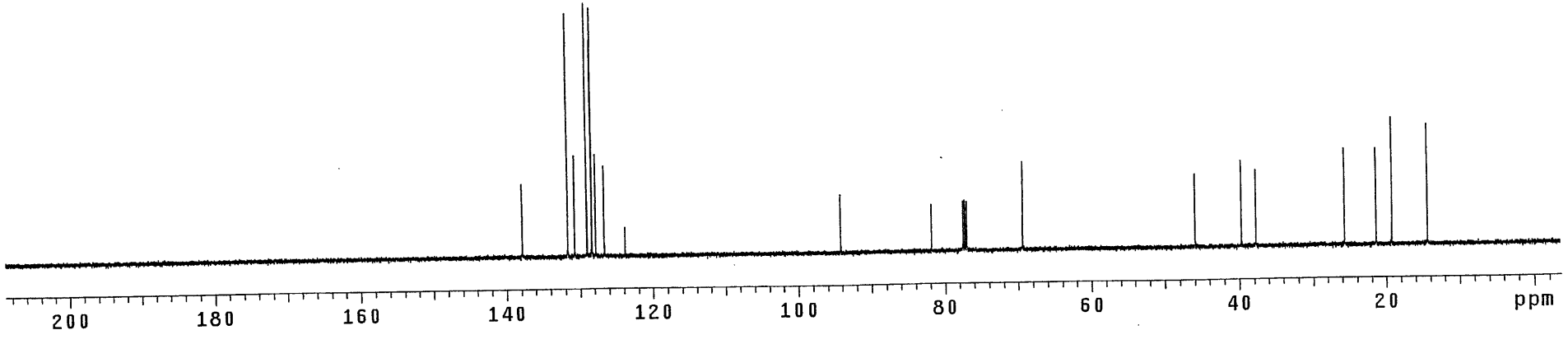

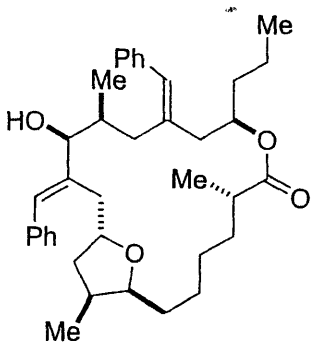

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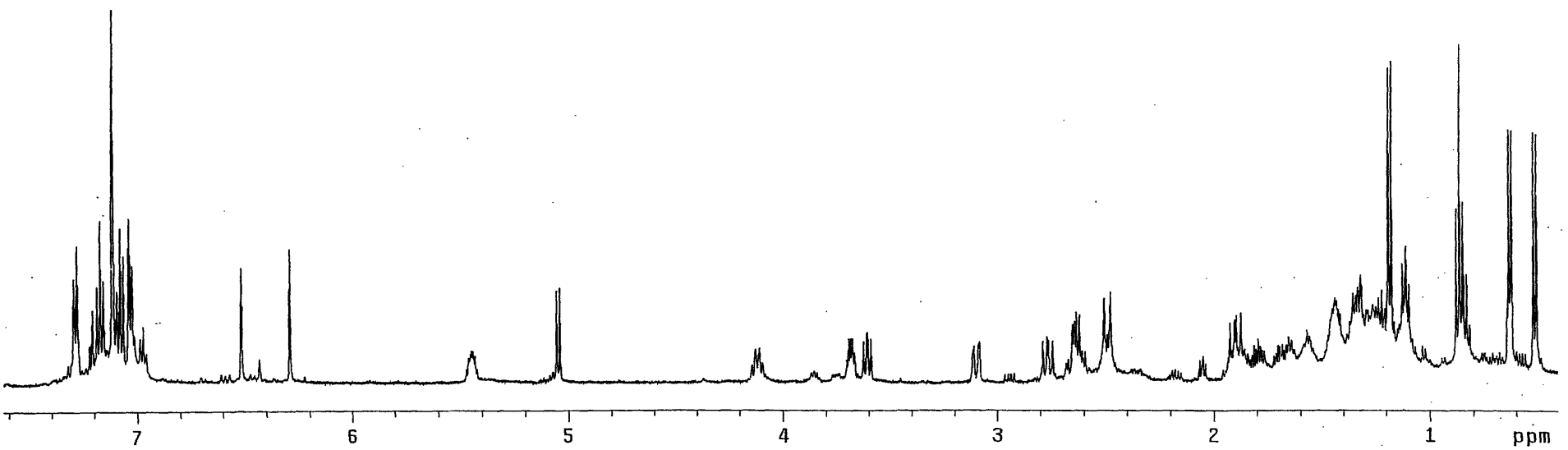

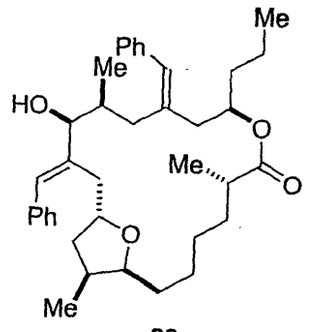

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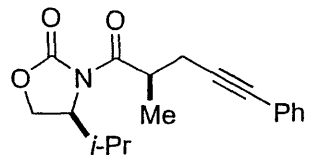

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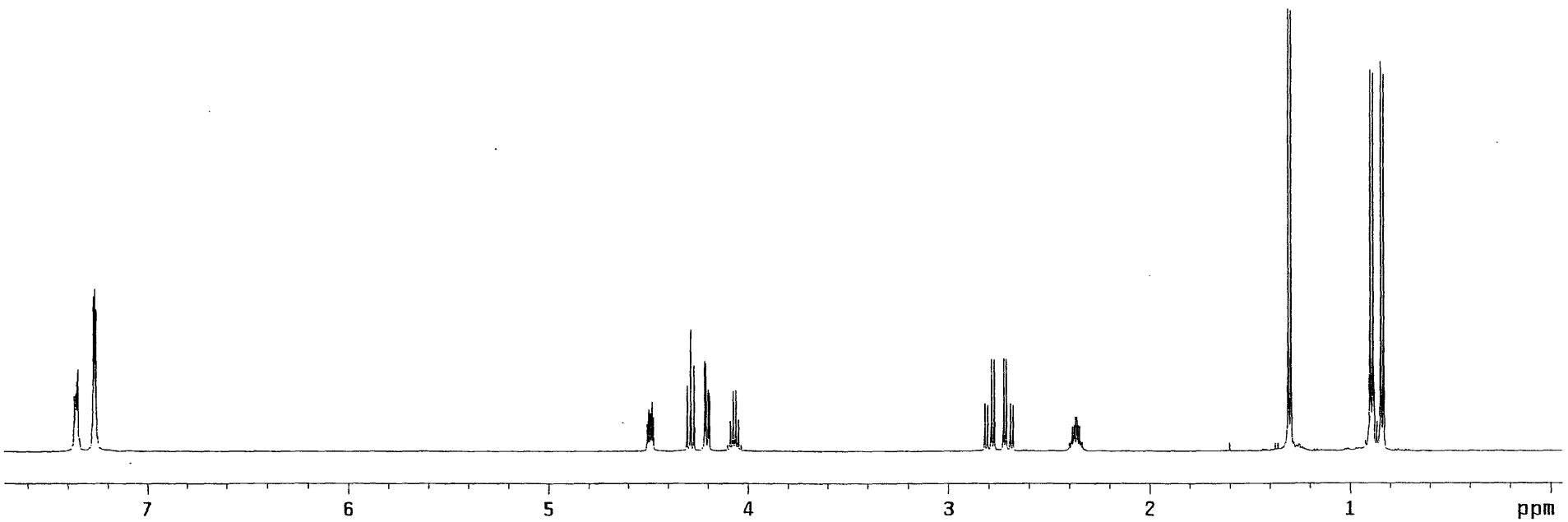

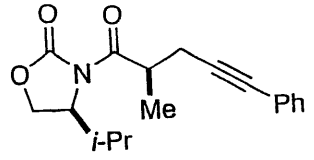

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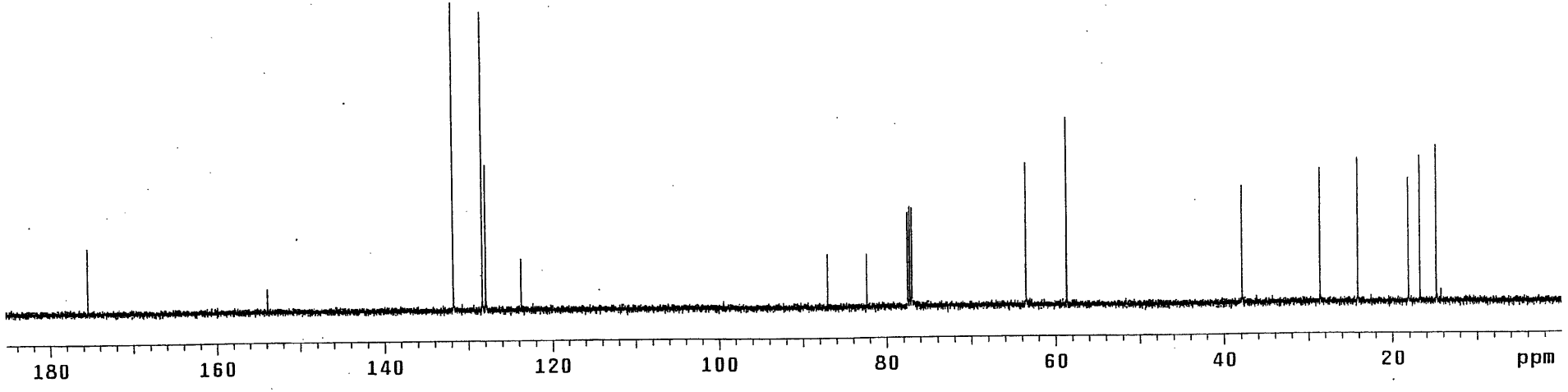

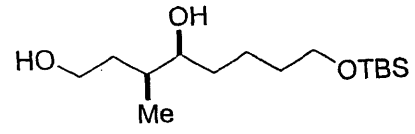

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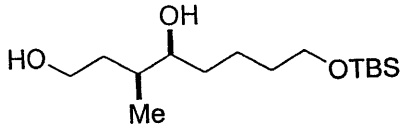

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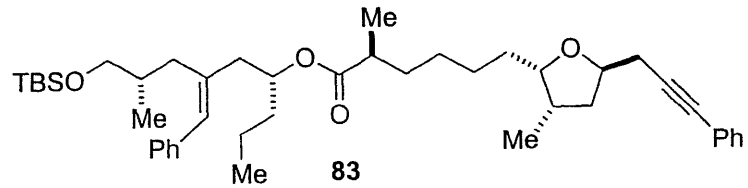

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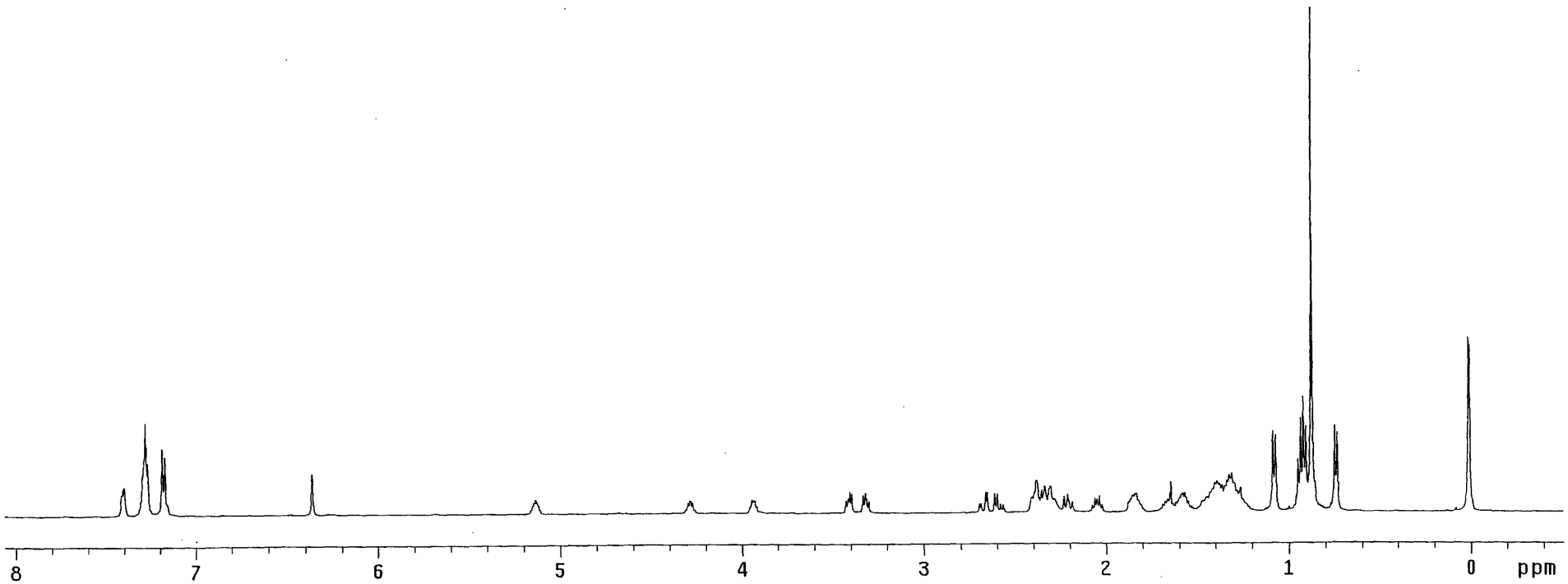

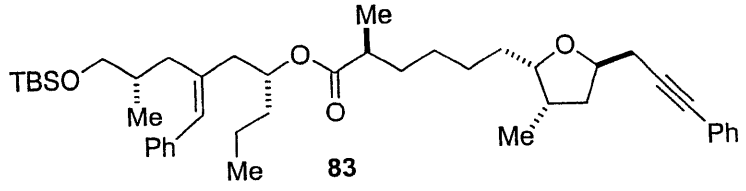

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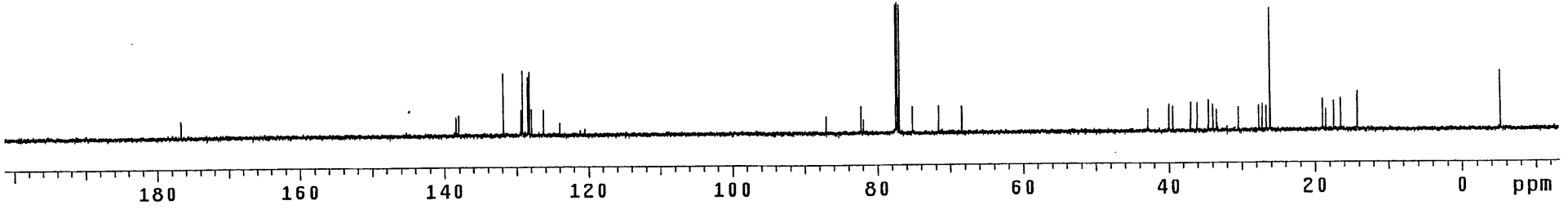

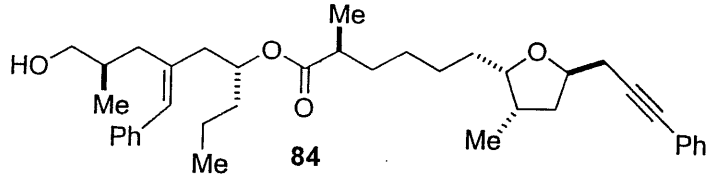

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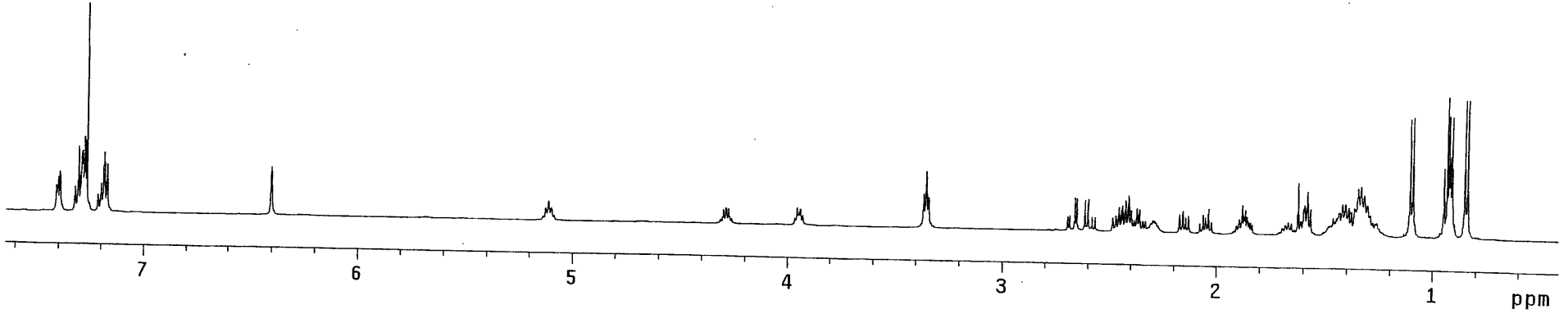

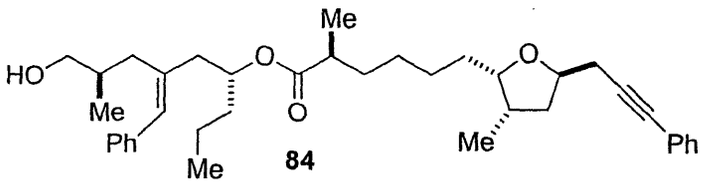

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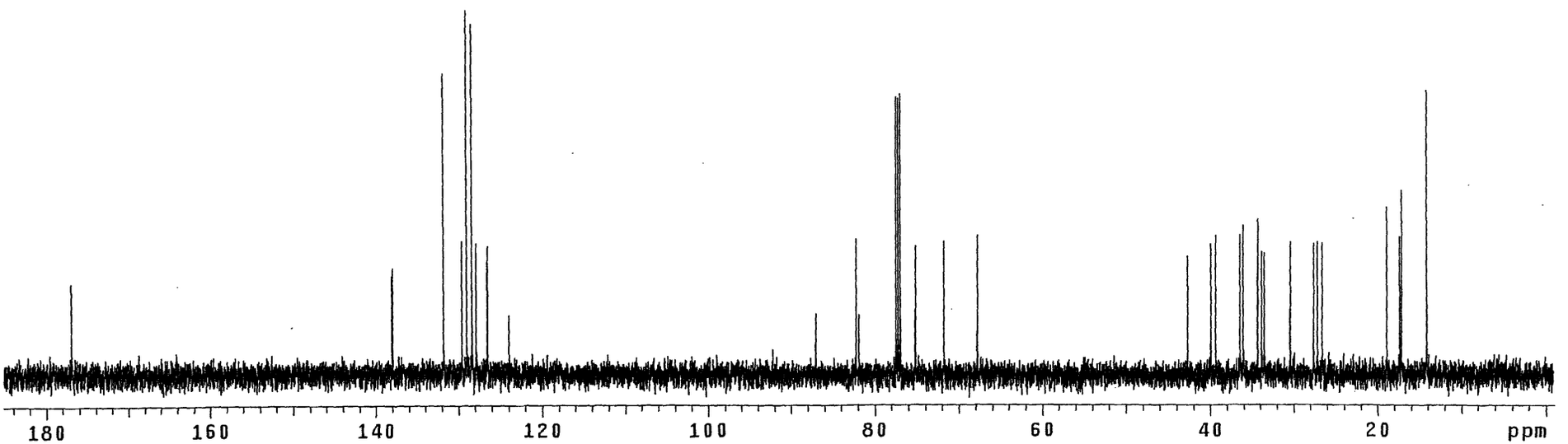

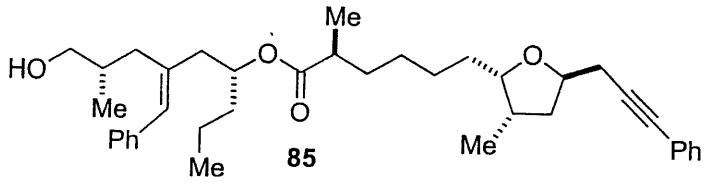

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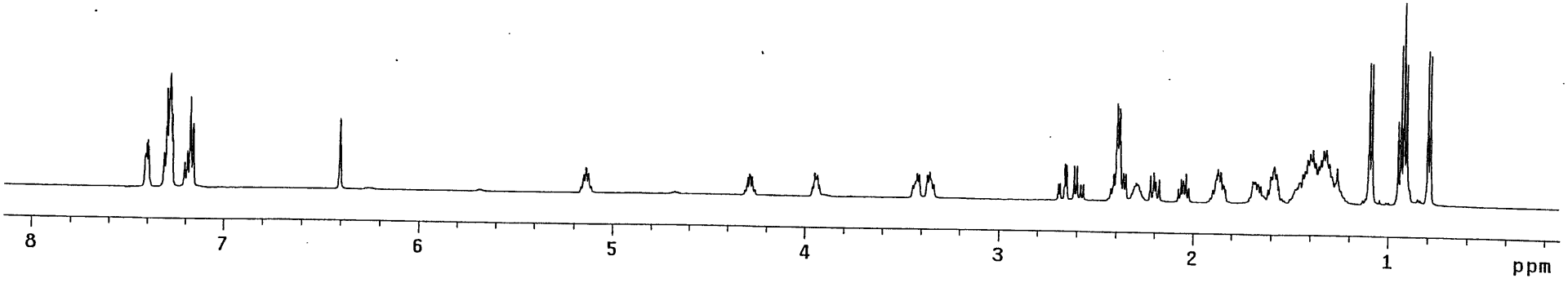

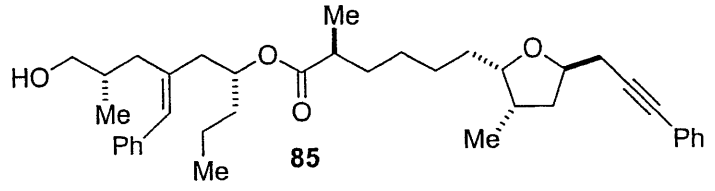

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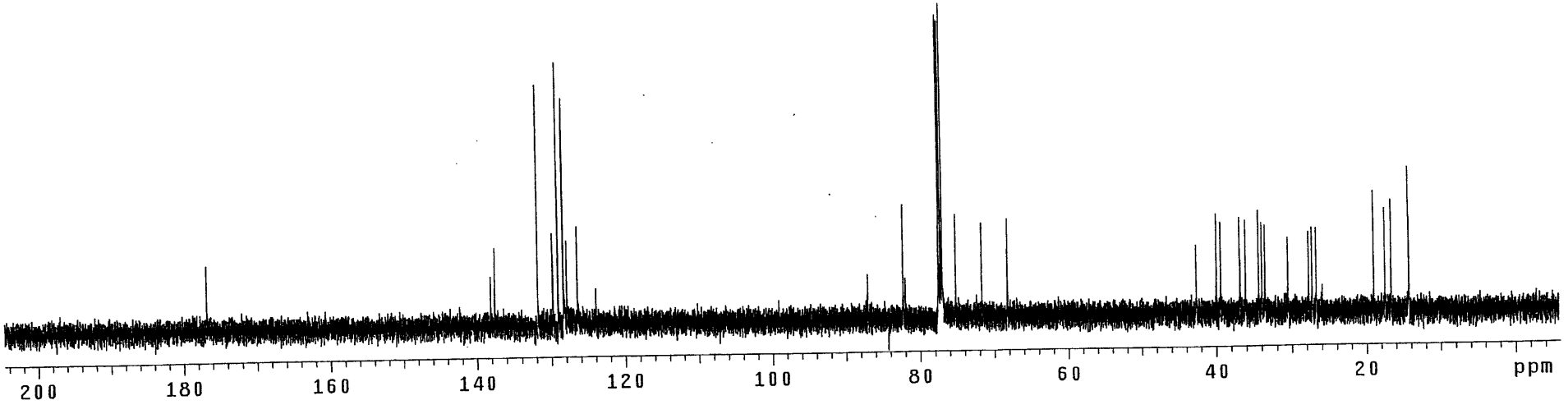

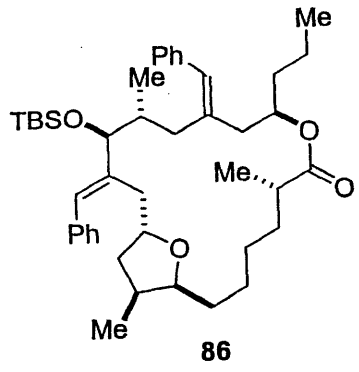

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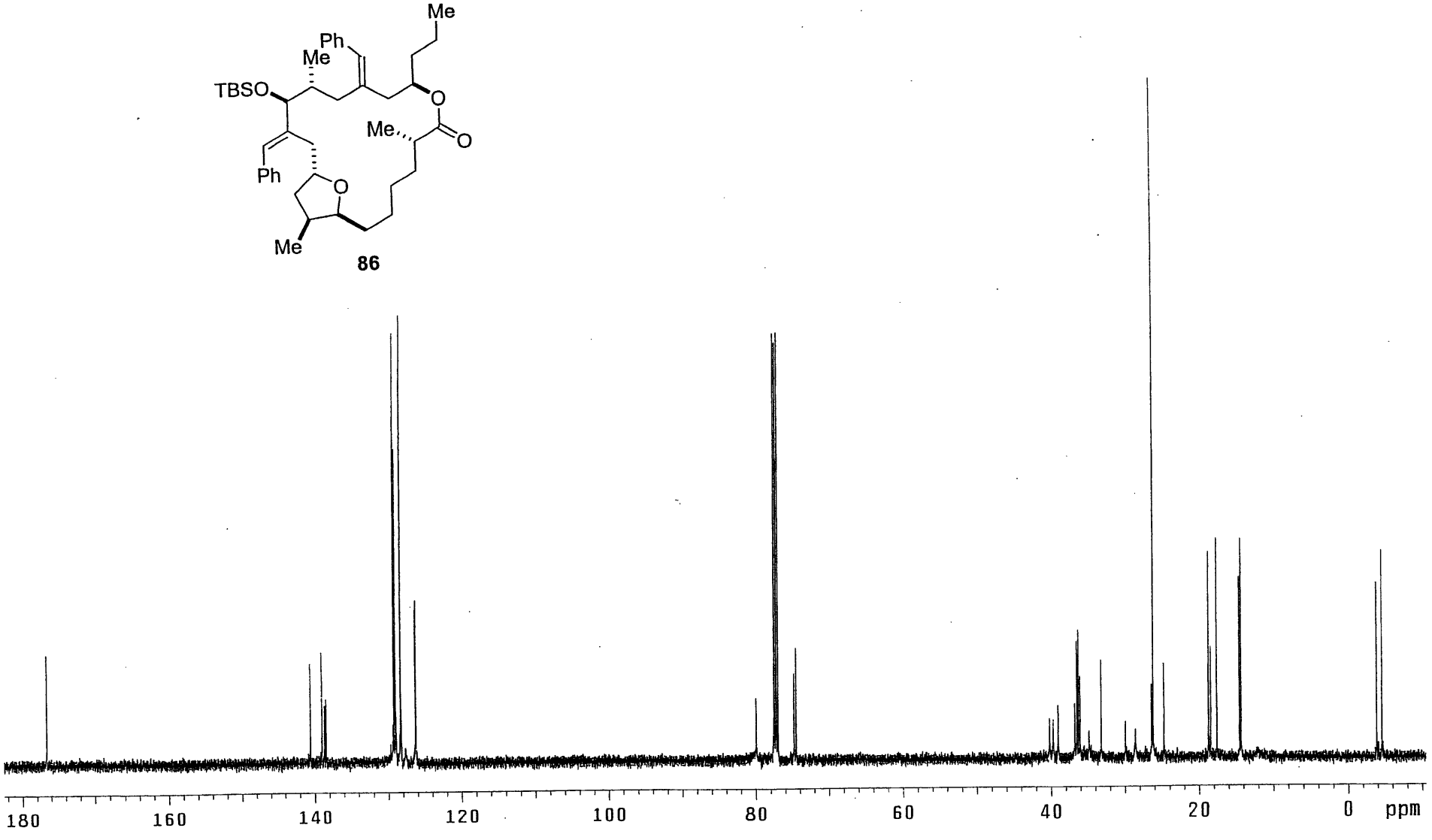

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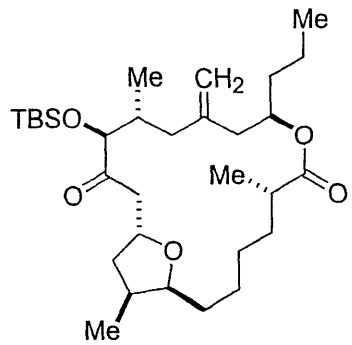

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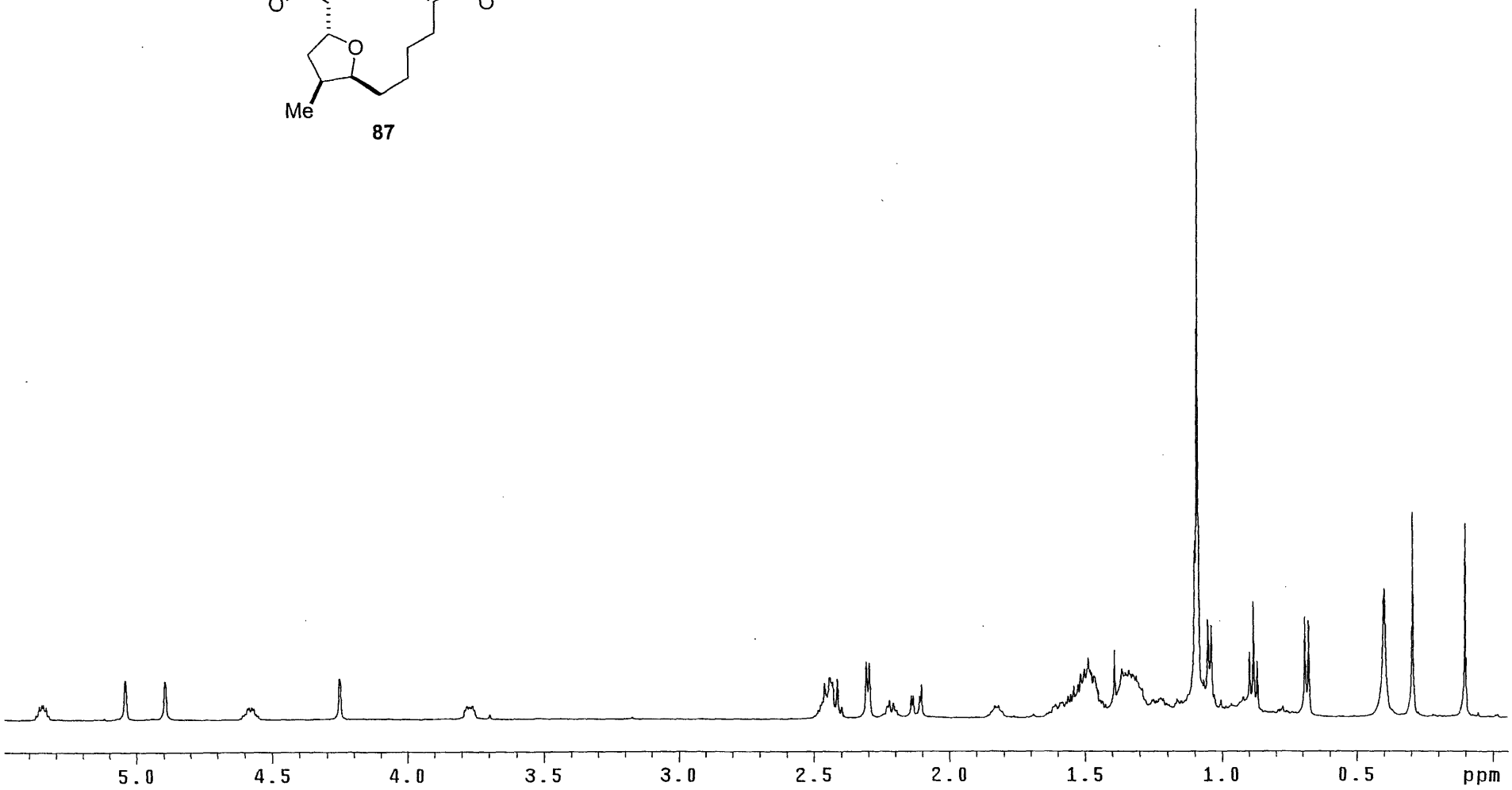

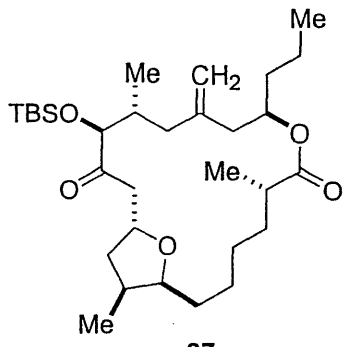

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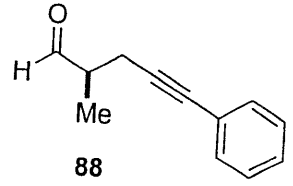

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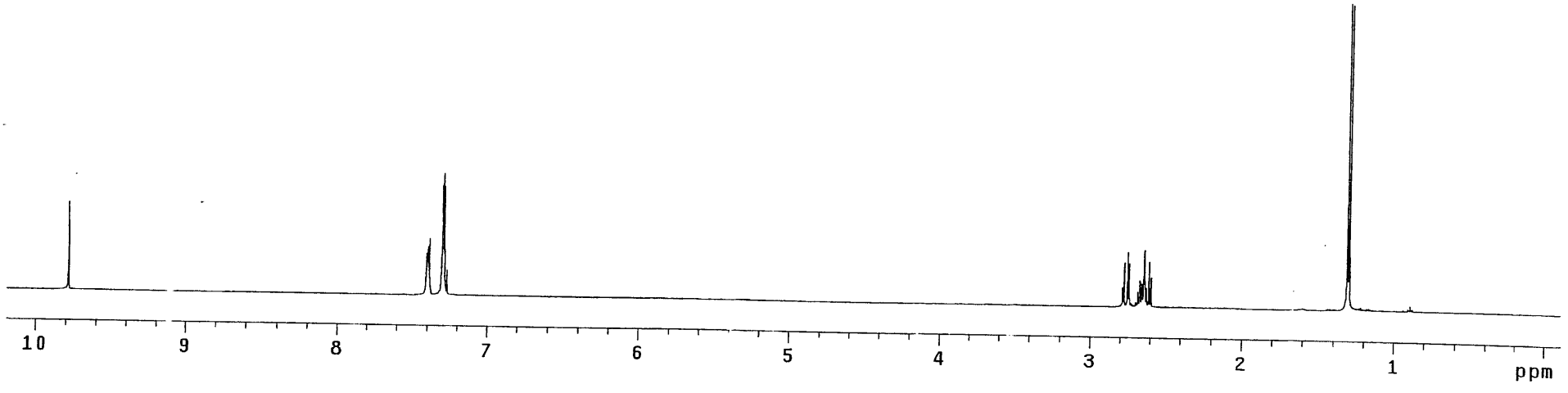

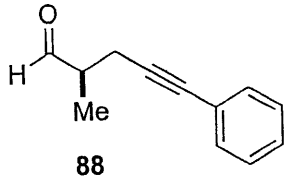

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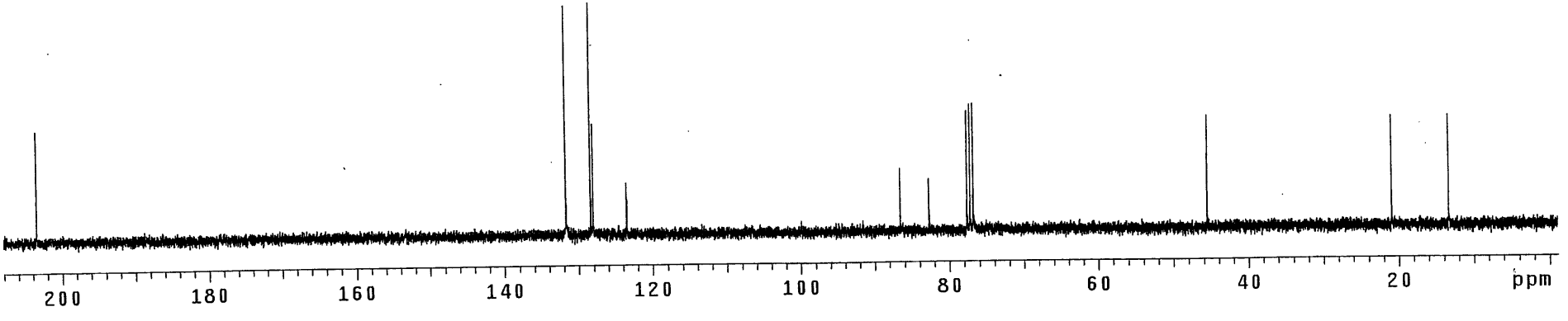

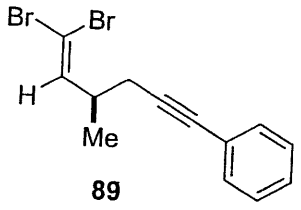

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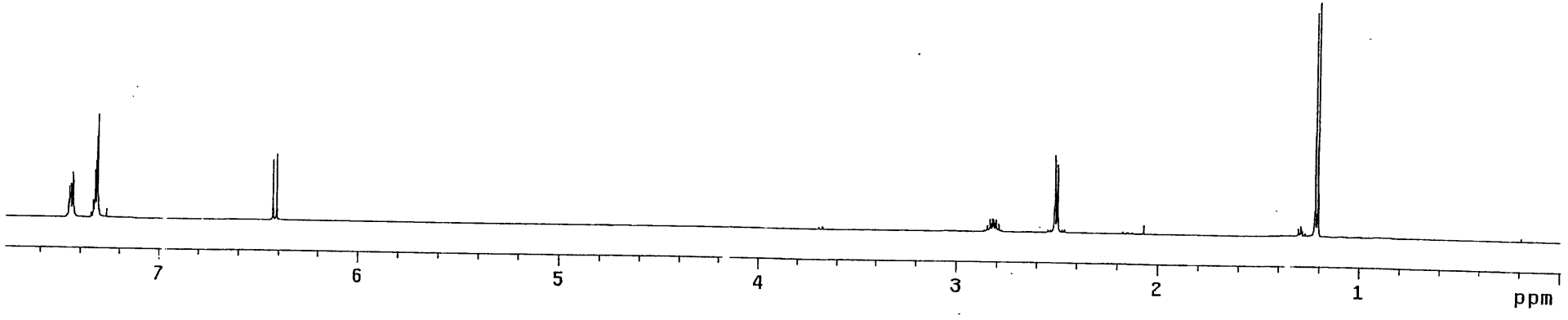

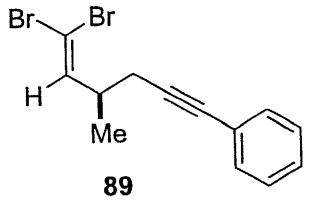

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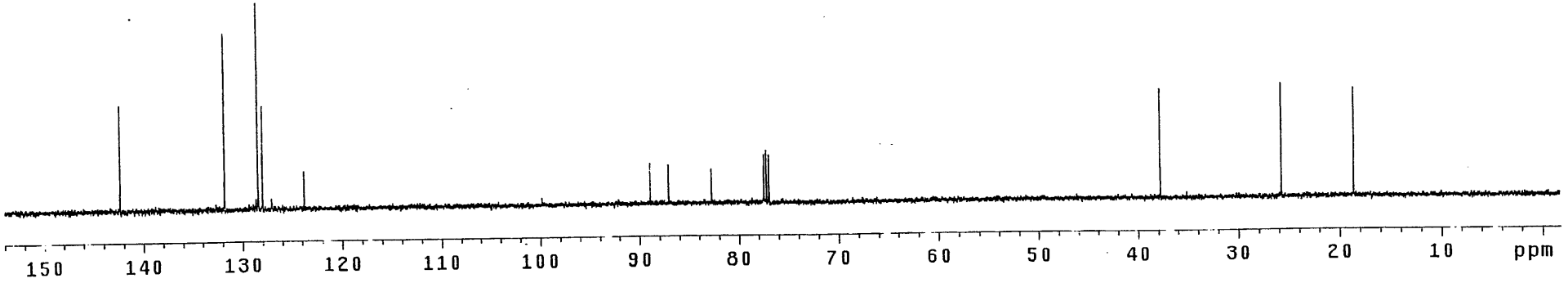

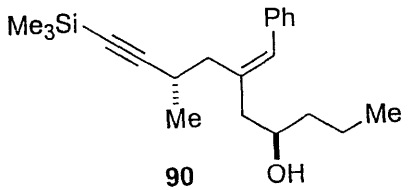

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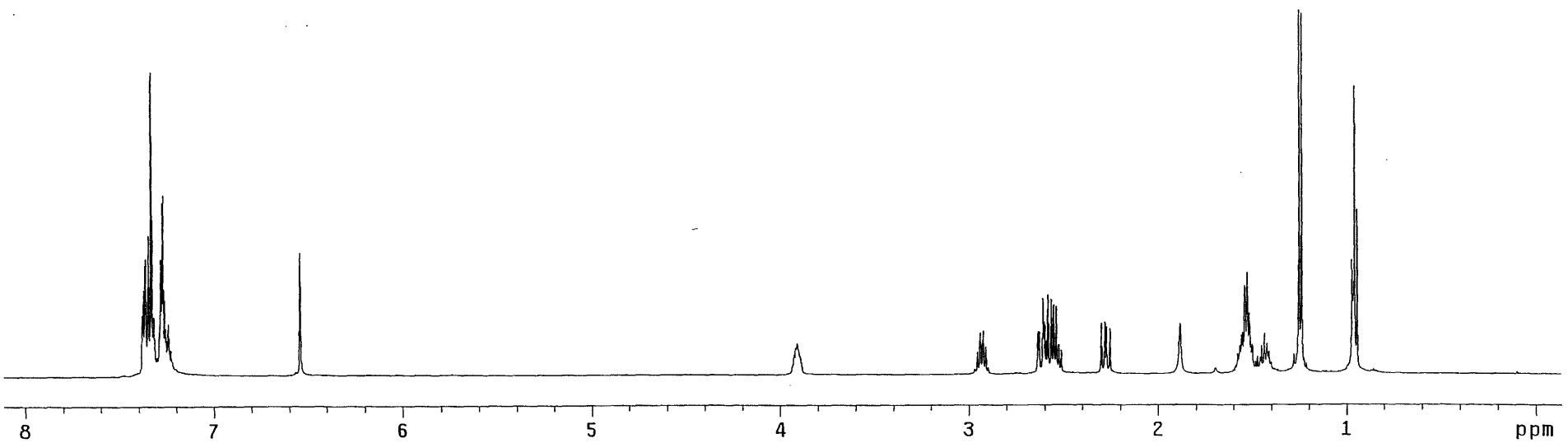

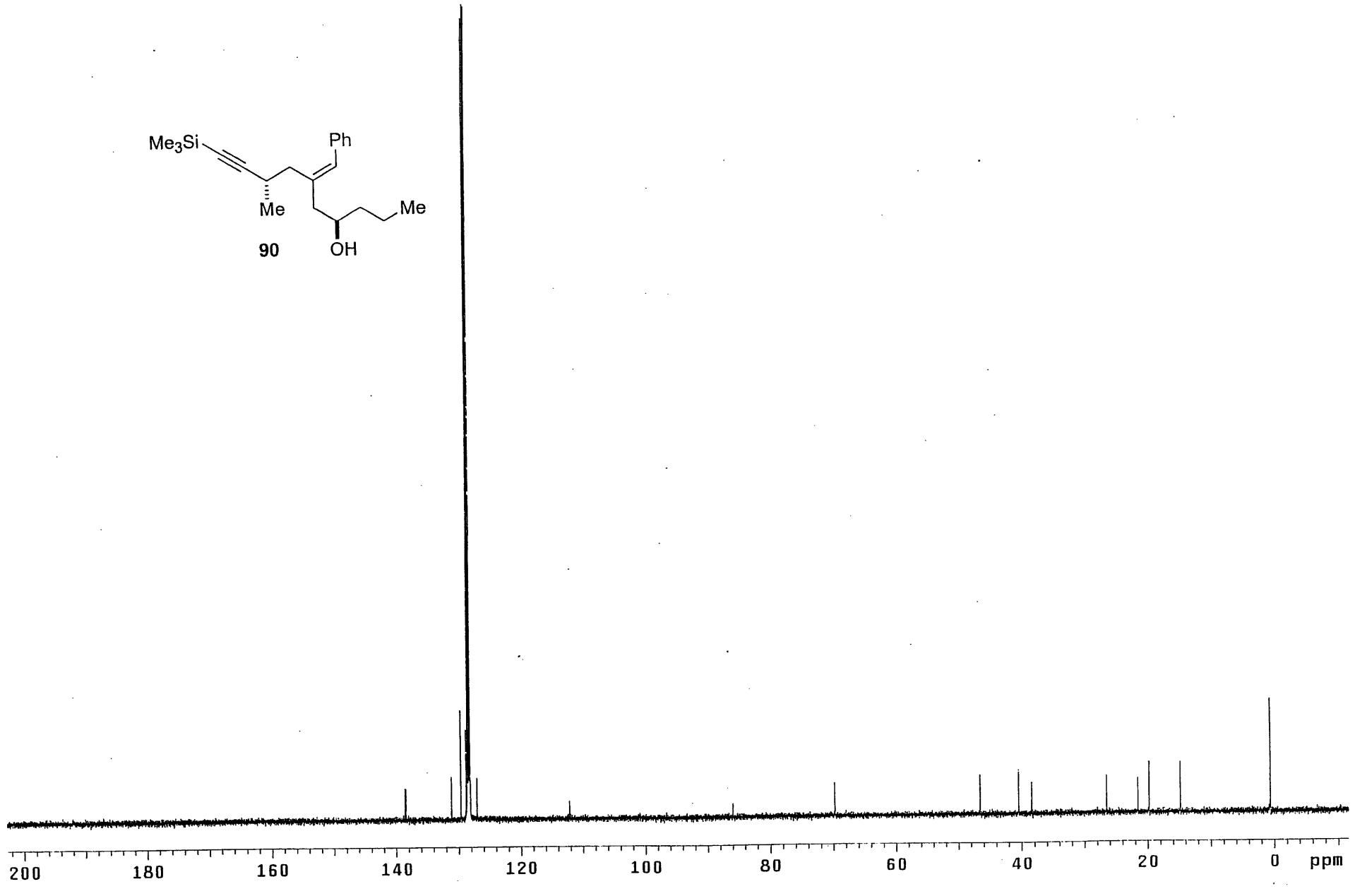
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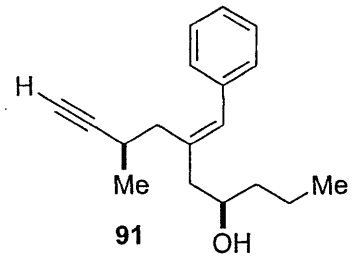

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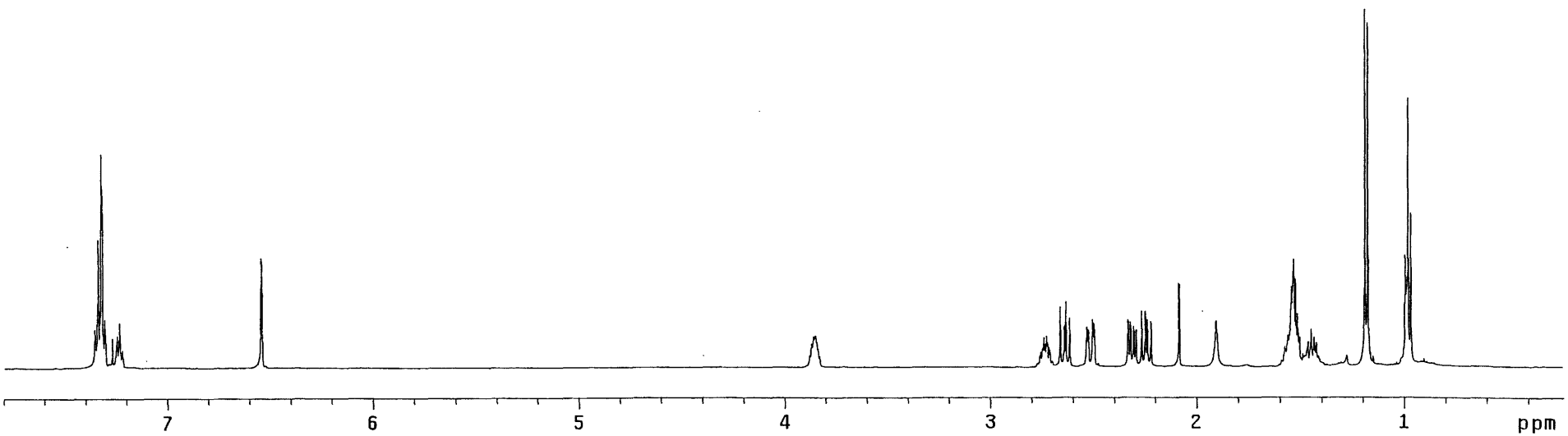

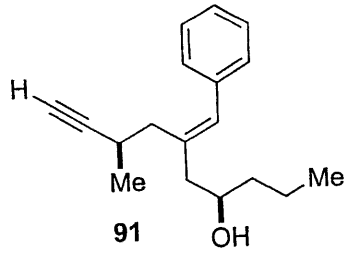

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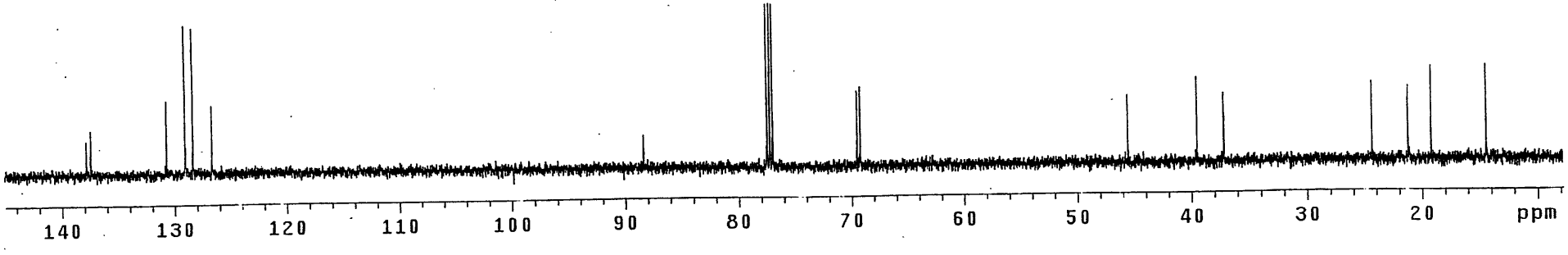

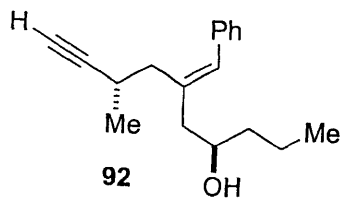

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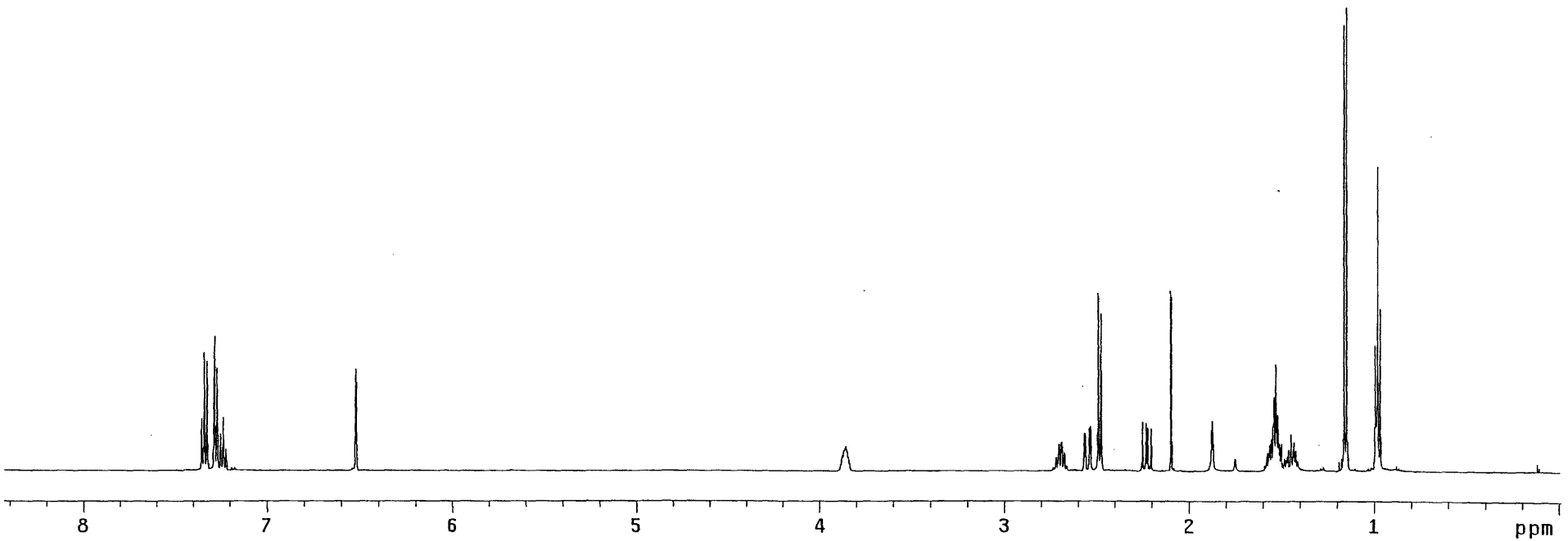

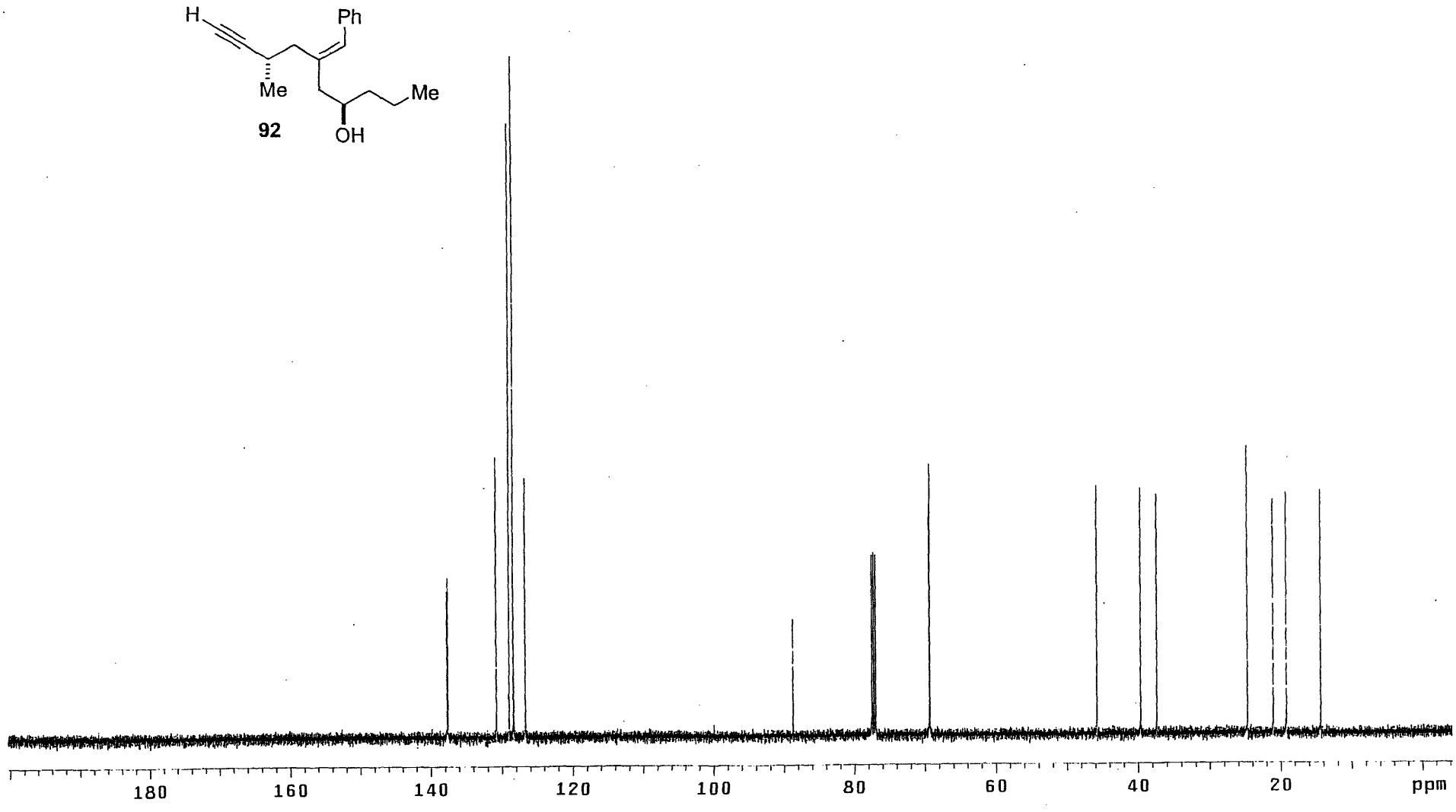
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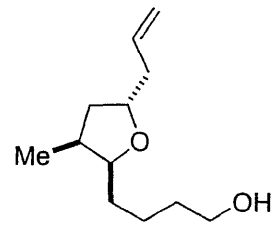

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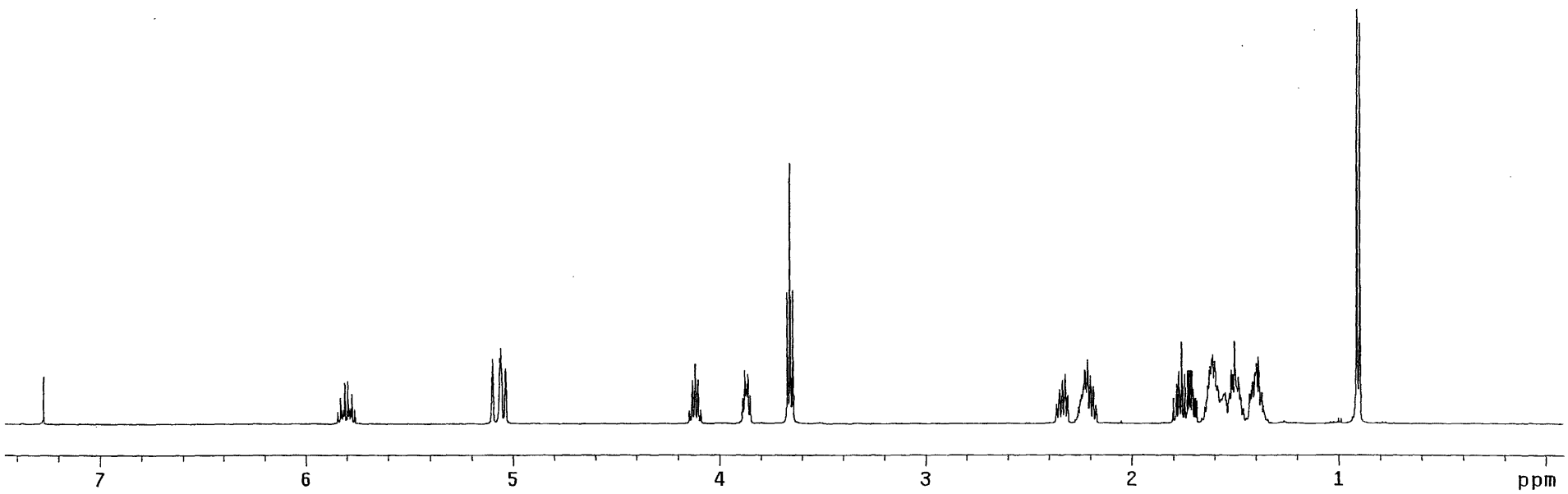

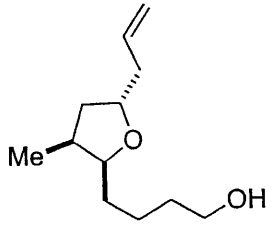

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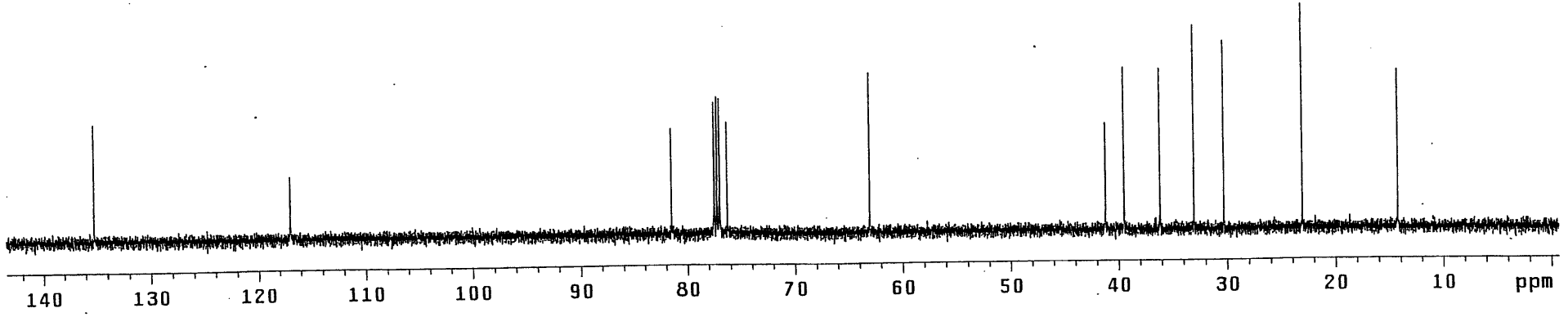

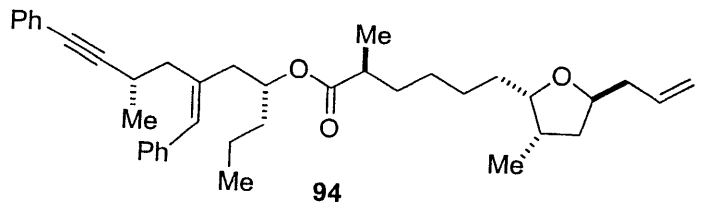

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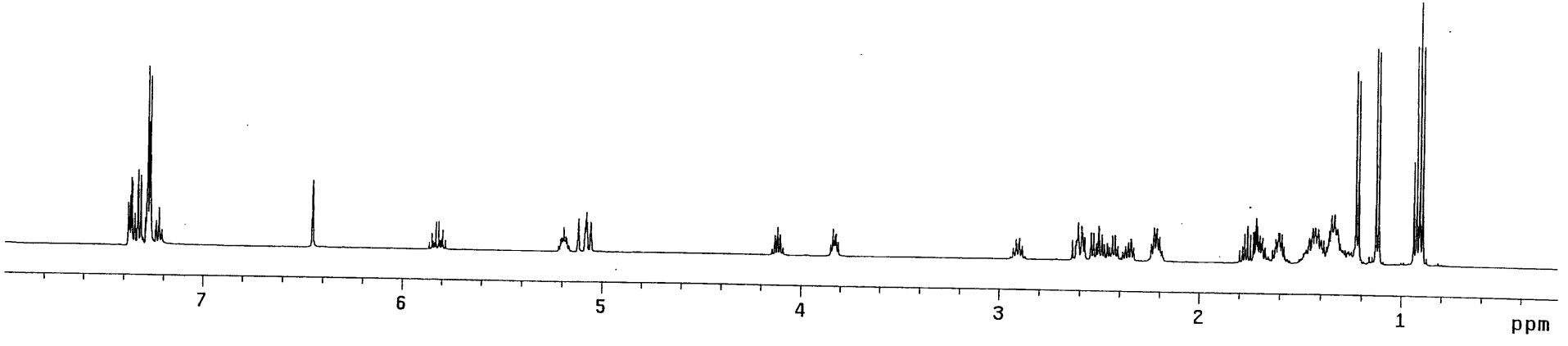

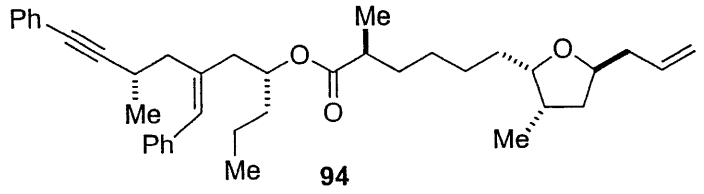

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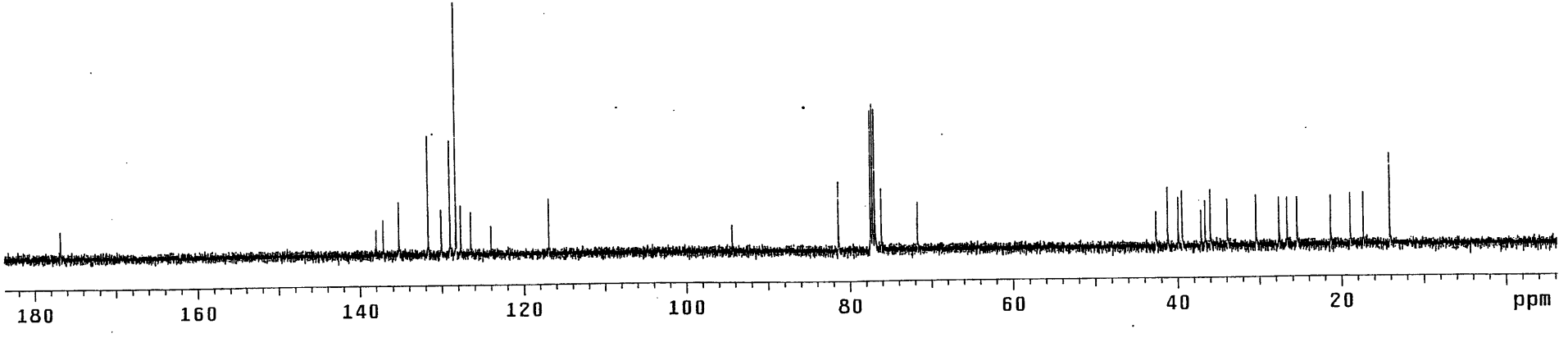

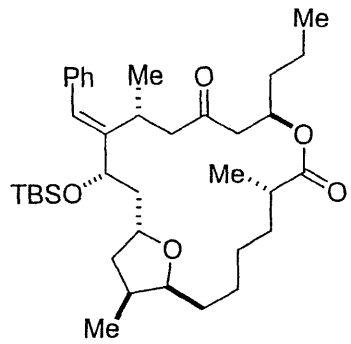

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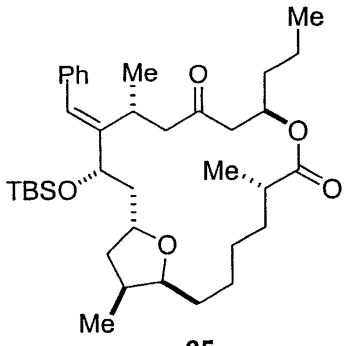

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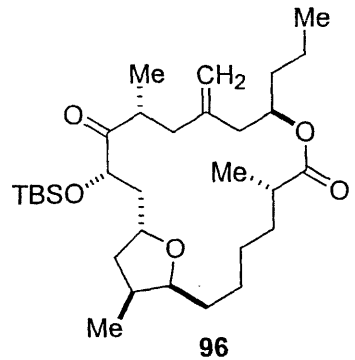

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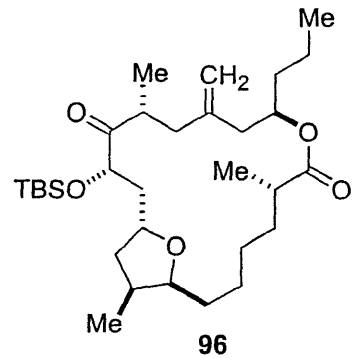
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40
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ppm

Curriculum Vitae

Education:

2000-2005 Ph. D. candidate
Department of Chemistry
Massachusetts Institute of Technology, Cambridge, MA
Research Advisor: Professor Timothy F. Jamison

Methodology: Synthesis and investigation of *P*-chiral ferrocenyl phosphines in the asymmetric catalytic reductive coupling of alkynes and aldehydes.

Synthesis: Total synthesis of amphidinolide T1 and T4 via catalytic reductive coupling reactions. Synthetic studies of related natural product amphidinolide T2.

2000 B.A. (Chemistry) *summa cum laude*, Macalester College, St. Paul, MN

Honors Thesis: "Efforts Toward the Synthesis of Simplified Acetogenins"

Research and Teaching Experience:

2001-2005 Graduate Research Fellow with Professor Timothy F. Jamison
Massachusetts Institute of Technology

2001 Teaching Assistant, Chemistry 5.511 (Graduate-Level Organic Synthesis, 1 semester)

2000 Teaching Assistant, Chemistry 5.12 and 5.13 (Undergraduate Introductory Organic Chemistry, 2 semesters)

1999 Summer Lando Undergraduate Research Fellow
University of Minnesota, with Professor Thomas R. Hoye

1998 Summer Howard Hughes Undergraduate Research Fellow
Macalester College, with Professor Rebecca C. Hoye

Honors and Awards:

2004-2005 Bristol-Myers Squibb Graduate Fellowship in Synthetic Organic Chemistry
2001-2004 National Defense Science and Engineering Graduate Research Fellowship
2001 Massachusetts Institute of Technology Outstanding Teaching Assistant
2000 Macalester College Outstanding Research in Chemistry Award
2000 Macalester College Outstanding Senior Student in Chemistry award
2000 Macalester College Presidential Leadership Award

2000	Macalester College Outstanding Scholar-Athlete
2000	Academic All-American Athlete
1999	Elected to Phi Beta Kappa, Pi Mu Epsilon, and Iota Sigma Pi
1999	Macalester College Outstanding Junior Student in Chemistry award
1997	Macalester College Outstanding First Year Student in Chemistry Award

Publications:

Colby, E. A.; O'Brien, K. C.; Jamison, T. F. Total Syntheses of Amphidinolides T1 and T4 via Catalytic, Stereoselective Reductive Macrocyclizations. *J. Am. Chem. Soc.* **2005**, *127*, 4297-4307.

Colby, E. A.; O'Brien, K. C.; Jamison, T. F. Synthesis of Amphidinolide T1 via Catalytic, Stereoselective Macrocyclization. *J. Am. Chem. Soc.* **2004**, *126*, 998-999.

Colby, E. A.; Jamison, T. F. *P*-Chiral, Monodentate Ferrocenyl Phosphines, Novel Ligands for Asymmetric Catalysis. *J. Org. Chem.* **2003**, *68*, 156-166.

O'Brien, K. C.; Colby, E. A.; Jamison, T. F. Synthesis of C13-C22 of Amphidinolide T2 via Nickel-Catalyzed Reductive Coupling of an Alkyne and a Terminal Epoxide. *Tetrahedron* **2005**, *Symposium-in-Print, Applications of Catalysis in Industry and Academia* (in press).

Miller, K. M.; Colby, E. A.; Woodin, K. S.; Jamison, T. F. Asymmetric Catalytic Reductive Couplings of 1,3-Enynes and Aromatic Aldehydes. *Submitted for Publication, April 2005.*

Presentations:

Oral presentation at the 226th National Meeting of the American Chemical Society, September 10, 2003. "Application of Asymmetric Nickel-Catalyzed Reductive Coupling Reactions to the Total Synthesis of Amphidinolide T1."

Oral presentation at the 224th National Meeting of the American Chemical Society, August 20, 2002. "Novel *P*-Chiral Ferrocenyl Phosphines for Nickel-Catalyzed Reductive Coupling of Alkynes and Aldehydes.