Studies Directed Toward the Synthesis of the B-Type Amphidinolide Natural Products Using Nickel-Catalyzed Reductive Couplings of Enynes and Carbonyl Compounds

by

Andrew M. Lauer

B. S. Chemistry
Northern Kentucky University, 2004

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

January 2010
[June 2010]

Signature of Author _____
Department of Chemistry
January 18, 2010

Certified by _____
Timothy F. Jamison
Thesis Supervisor

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

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

Professor Rick L. Danheiser _____
Chairman

Professor Timothy F. Jamison _____
Thesis Supervisor

Professor Mohammad Movassaghi _____

To my beloved wife, Ana, and my parents

Studies Directed Toward the Synthesis of the B-Type Amphidinolide Natural Products Using Nickel-Catalyzed Reductive Couplings of Enynes and Carbonyl Compounds

by

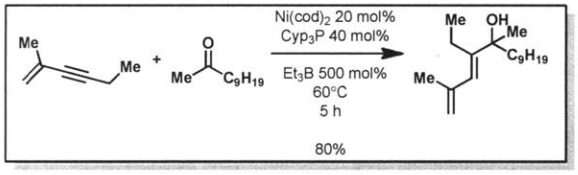
Andrew M. Lauer

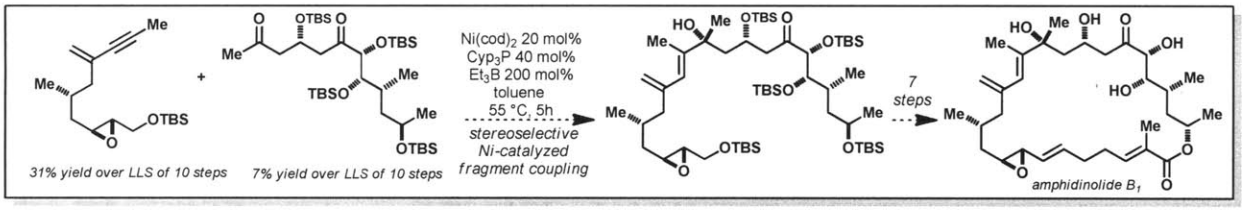
B. S. Chemistry
Northern Kentucky University, 2004

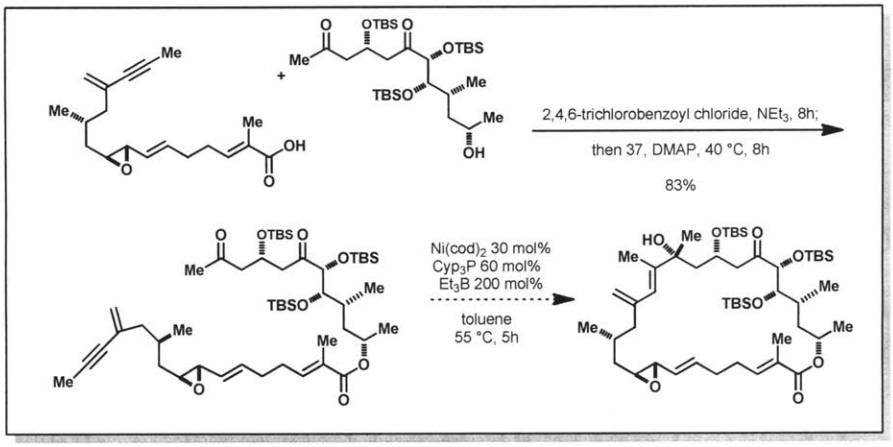
Submitted to the Department of Chemistry
In Partial Fulfillment of the Requirements for the Degree of
Doctor of Philosophy in Organic Chemistry

ABSTRACT

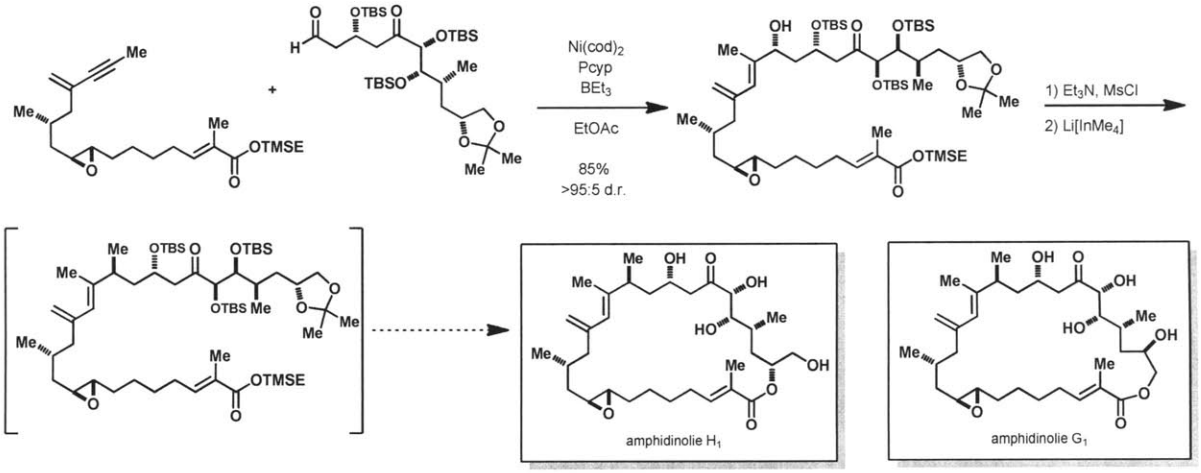
Progress toward the total synthesis of amphidinolide B_1 is described. The reductive coupling of 1,3-eynes and ketones was explored. It was found to work well with simple substrates, but failed to yield intermediates toward amphidinolide B_1.







The coupling of 1,3-enyne and aldehyde fragments toward the synthesis of amphidinolides G_3 and H_4 is also described. The entire carbon skeleton of these natural products has been prepared from this coupling and a subsequent installation of a methyl group using an indium based reagent.



Thesis Supervisor: Timothy F. Jamison

Title: Professor of Chemistry

Acknowledgments

There are many people I need to thank and acknowledge for their part in helping me through graduate school. First and foremost, I must thank my research advisor, Prof. Tim Jamison. Tim's advice and guidance motivated me through my projects from the beginning. If at any point I felt lost, Tim was always there to help and guide me along the way. No matter how difficult a problem was to solve, after discussing it with Tim, I was always encouraged to persevere. Tim does an excellent job of motivating his students, and I am grateful for the time I spent in his lab. While at MIT, a number of other faculty members were key in my development as a chemist. In particular, I would like to thank my committee chair, Prof. Rick Danheiser. The discussions I had with him always kept me focused on my projects and goals.

The chemistry department's instrumentation facilities and staff were necessary for the success of my work. I would like to especially thank Dr. Jeff Simpson, Instrumentation Facility Director, and Li Li, mass spectroscopy research specialist.

While at MIT, I had the pleasure of collaborating with a number of intelligent and motivated chemists. First among these was Dr. Chudi Ndubaku. During my first two years of graduate school, I worked with Chudi on the total synthesis of amphidinolide H_1 and amphidinolide H_4. During that time, I learned a great many synthetic techniques and had discussions that impacted my research greatly even after Chudi left the lab. Other than Tim, no one had a greater impact on my work than Chudi. I also had the opportunity to work with Prof. Hirohisa Ohmiya. His work ethic and love for chemistry was a great inspiration for me. While in the Jamison lab, I also had the opportunity to mentor a visiting student, Nikolas Huwyler, and an MIT undergraduate student, Ngan

Nguyen. While doing my best to teach them the synthetic techniques I had learned in the Jamison lab, I learned just as much from them. The conversations I had with Nikolas have had a lasting impact on my research. I worked with Ngan for almost two years, and it didn't take long for me to see that she was a brilliant and talented chemist. She came into the lab with very little experience and within two weeks she was almost working completely independent of me. And while I didn't have to invest much time training her, her hard work on our projects allowed me to investigate them further. I would also like to thank Ngan and Nikolas for my time interacting with and supervising them as this shaped my career goals. Working with them has made me realize that training undergraduate students, at a primarily undergraduate university, is what I would like to do.

There are many other scientists that I have had the pleasure to work alongside in the Jamison group. Far too many to name all of them; however, I would like to mention those that had the biggest effect on my growth as a chemist. When I first started in the lab Chudi, along with Dr. Elizabeth Colby, Dr. Tim Heffron, and Dr. Graham Simpson were instrumental in making me feel welcome and showing me what I needed to know to get started. For two years, I had the pleasure of working beside Dr. Neil Langille. Neil was always there to help me when I needed him, and my conversations with him were the backdrop for a great working environment. Discussions with Dr. Sze-Sze Ng and Dr. Chun-Yu Ho have also had a positive effect on my work. Another good friend I made while in the Jamison lab was Ivan Vilotijevic. It was evident to me from the first time I met Ivan that he was a brilliant and capable chemist, and his work on development of epoxide-opening cascade reactions served as an inspiration for my own

research. Conversations with Ivan on any topic in chemistry always resulted with positive influence on my work. I would like to also thank Dr. Jeffery Byers for contributions to my chemistry as well as to that of the group as a whole. Jeff has served as a great example of how a chemist should come to work every day and help his fellow lab mates while being very productive on his own projects. I would like to thank all the current and former members of the Jamison group including Dr. Adam Sniady, Dr. Denise Colby, Dr. Ryosuke Matsubara, Brian Underwood, Jessica Tanuwidjaja, Kurt Armbrust, Dr. Ryan Moslin, Chris Morten, Kristin Schleicher, Dr. Damien Webb, Dr. Andrew Leduc, and Dr. Aaron Van Dyke.

I would also, like to thank Prof. K. C. Russell, and the entire chemistry faculty at Northern Kentucky University. I first found my love for chemistry while working for Prof. Russell at NKU.

And lastly, I would be remiss if I did not thank my entire family. I would like to thank my parents David and Patricia Lauer for all their support throughout the years. I would also, like to thank my brother Matthew Lauer, who is also a graduate student in organic chemistry working at The Ohio State University. And last, but certainly not least, I would like to thank my beautiful wife, Ana. I met Ana while at MIT, and her support has greatly impacted my work. I would especially like to thank her for her understanding and patience during the times when I had to work very long hours to complete my work.

Andrew M. Lauer

Cambridge, MA January 2010

Table of Contents

Abbreviations

Ac	acetyl
Bn	benzyl
Bu	butyl
cod	cyclooctadiene
Cp	cyclopentadienyl
Cy	cyclohexyl
Cyp	cyclopentyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMF	*N,N'*-dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMP	Dess-Martin periodinane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
d.r.	diastereomer ratio
ee	enantiomer excess
EI	electron ionization
ESI	electron spray ionization
Et	ethyl
g	gram(s)
h	hour(s)
HKR	hydrolytic kinetic resolution
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectrometry
i-Pr	isopropyl
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
Me	methyl
m-CPBA	3-chloroperoxybenzoic acid

mg	milligram(s)
min	minute(s)
MOM	methoxymethyl
MS	molecular sieves
Ms	methanesulfonyl
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
Nu	nucleophile
Ph	phenyl
PMB	*p*-methyoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
PT	phenyl-1*H*-tetrazole
p-TsOH	*p*-toluenesulfonic acid
Py	pyridine
r.t.	room temperature
salen	*N*,*N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino
t-Bu	*tert*-butyl
TBS	*tert*-butyldimethylsilyl
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBHP	*tert*-butyl hydroperoxide
Tf	trifluoromethanesulfonyl
TMS	trimethylsilyl
TMSE	trimethylsilylethyl
THF	tetrahydrofuran
TPAP	tetrapropyl ammonium perruthenate
Ts	*p*-toluenesulfonyl

Chapter 1

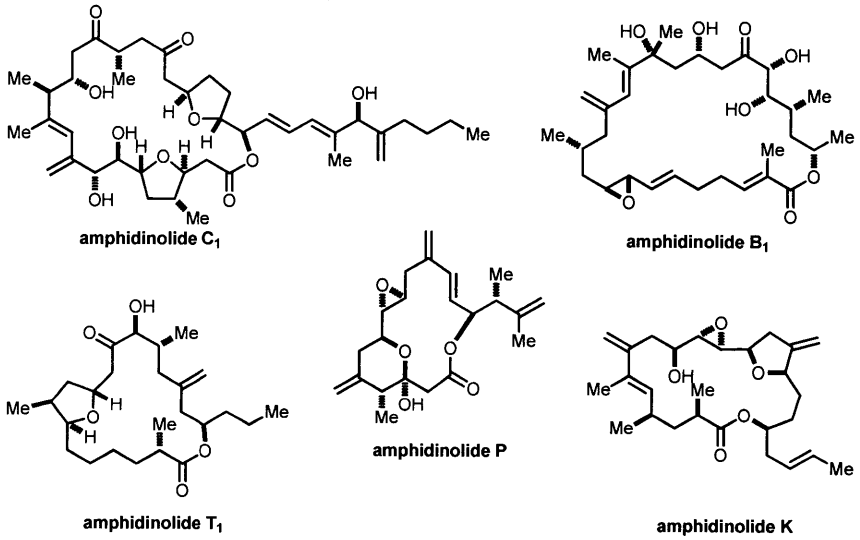
Ni-Catalyzed Reductive Coupling of 1,3-Enynes and Ketones, and Studies Directed Toward the Synthesis of Amphidinolide B_1

Introduction

A. Amphidinolide Natural Products

The amphidinolide natural products are secondary metabolites isolated from different strains of dinoflagellates, *Amphidinium sp.*, that reside within tissue of the marine flatworm *Amphiscolopes* sp. or other strains as free-swimming organisms off the coast of the US Virgin Islands.[1] Professor Jun'ichi Kobayshi isolated the first members of this class of natural products in 1986. Since that time many intriguing and biologically significant compounds (forty-one to date) from this class have been isolated (Figure 1).

Figure 1. Representative Amphidinolide Natural Products



B. Structure and Biological activity

The amphidinolide natural products share many characteristic functional groups. These features include multiple chiral centers, oxygen heterocycles including epoxides,

[1] (a) For reviews of the amphidinolides, see: Kobayashi J. *J. of Antibio.* **2008**, *61*, 271. (b) Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77. (c) Chakraborty, T. K.; Das, S. *Curr. Med. Chem.: Anti-Cancer Agents* **2001**, *1*, 131. (d) Kobayashi J.; Ishibashi M. in "*Comprehensive Natural Products Chemistry*", Vol. 8, pp. 619-649, K. Mori, Ed., Elsevier, New York, **1999**. (e) For a current website see: http://www2.onu.edu/~b-myers/amp/amphidinolides.html.

tetrahydrofurans, and tetrahydropyrans, as well as at least one *exo*-methylene group in all cases. In many, but not in all cases, the *exo*-methylene group is found to be part of a characteristic 1,3-diene system which makes the amphidinolides unique compared to other polyketide natural products. In addition, many of the amphidinolides have odd-numbered macrolactone rings and irregular oxygenation patterns, a feature that is uncommon in other polyketide natural products.

The amphidinolides have also been shown to possess *in vitro* antineoplastic activity against murine lymphoma L1210 and human epidermoid carcinoma KB cell lines (Table 1). Amphidinolides B_1, B_4, B_5, C_1, H_1, and N exhibit the greatest efficacy, with IC_{50} values as low as 50 pg/mL.

Table 1. Amphidinolide Cytotoxicity.[a]

amphidinolide	cytotoxicity (IC_{50} mg/mL)		amphidinolide	cytotoxicity (IC_{50} mg/mL)		amphidinolide	cytotoxicity (IC_{50} mg/mL)	
	L1210	KB		L1210	KB		L1210	KB
A	2.0	5.7	G_2	0.3	0.8	Q	6.4	>10
B_1	0.00014	0.0042	G_3	0.72	1.3	R	1.4	0.67
B_3	--	--	H_1	0.00048	0.00052	S	4	6.5
B_4	0.00012	0.001	H_2	0.06	0.06	T_1	18	35
B_5	0.0014	0.004	H_3	0.002	0.022	T_2	10	11.5
B_6	--	--	H_4	0.18	0.23	T_3	7.0	10
B_7	--	--	H_5	0.2	0.6	T_4	11	18
C_1	0.0058	0.0046	J	2.7	3.9	T_5	15	20
C_2	0.8	3	L	0.092	0.1	U	12	20
D (B_2)	0.019	0.08	M	1.1	0.44	V	3.2	7
E	2.0	10	N	0.00005	0.00006	W	3.9	--
F	1.5	3.2	O	1.7	3.6	X	0.6	7.5
G_1	0.0054	0.0046	P	1.6	5.8	Y	0.8	8.0

[a] Data compiled and reported in ref. 1e.

The unique structure paired with the striking biological activity; make the amphidinolides attractive targets for chemical synthesis. Much effort has been put

toward this end and has resulted in the total synthesis of eighteen members of this class of natural products.[2]

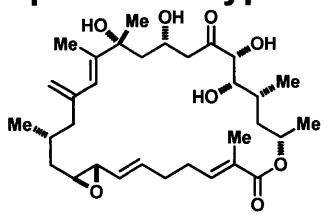
C. The B-Type Amphidinolides

There are sixteen members of the amphidinolide class of natural products that are collectively termed the "B-type" amphidinolides. They are so-called due to their closeness in structure to Amphidinolide B_1 (the first compound of this subclass to be isolated). The B subclass of the amphidinolide natural products comprise those amphidinolides from the B-series, G-series, and H-series (Figure 2).

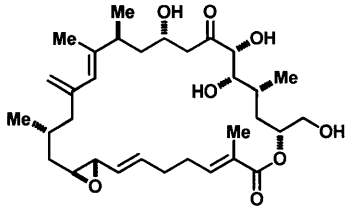
---

[2] Proposed structure of amphidinolide A: (a) Lam, H. W.; Pattenden, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 508. (b) Maleczka, R. E., Jr.; Terrell, L. R.; Geng, F.; Ward, J. S., III.; *Org. Lett.* **2002**, *4*, 2841. (c) Trost, B. M.; Chisholm, J. D.; Wrobleski, S. T.; Jung, M. *J. Am. Chem. Soc.* **2002**, *124*, 12420. Structural revision and total synthesis of amphidinolide A: (d) Trost, B. M.; Harrington, P. E.; Chisholm, J. D.; Wrobleski, S. T. *J. Am. Chem. Soc.* **2005**, *127*, 13598. Amphidinolide B1 and the proposed structure of amphidinolide B_2/D: (e) Lu, L.; Zhang, W.; Carter, R. G. *J. Am. Chem. Soc.* **2008**, *130*, 7253. Amphidinolide E: (f) Va, P.; Roush, W. R. *J. Am. Chem. Soc.* **2006**, *128*, 15960. (g) Kim, C. H.; An, A. H.; Shin, W. K.; Yu, W.; Woo, S. K.; Jung, S. K.; Lee, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 8019. Amphidinolide H_1 and G_1: (h) Fürstner, A.; Bouchez, L. C.; Funel, J.; Liepins, V.; Porrée, F.; Gilmour, R.; Beaufils, F.; Laurich, D.; Tamiya, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 9265. Amphidinolide J: (i) Williams, D. R.; Kissel, W. S.; *J. Am. Chem. Soc.* **1998**, *120*, 11198. Amphidinolide K: (j) Williams, D. R.; Meyer, K. G. *J. Am. Chem. Soc.* **2001**, *123*, 765. Amphidinolide P: (k) Williams, D. R.; Myers, B. J.; Mi, L. *Org. Lett.* **2000**, *2*, 945. (l) Trost, B. M.; Papillon, J. P. N. *J. Am. Chem. Soc.* **2004**, *126*, 13618. (m) Trost, B. M.; Papillon, J. P. N.; Nussbaumer, T. *J. Am. Chem. Soc.* **2005**, *127*, 17921. Amphidinolide Q: (n) Hangyou, M.; Ishiyama, H.; Takahashi, Y.; Kobayashi, J. *Org. Lett.* **2009**, *11*, 5046. Amphidinolide R: (o) Kissel W. S. in "*The Asymmetric Total Synthesis of Amphidinolides J and R*", Ph. D. Thesis, Indiana University, **1998**. Amphidinolide T_1: (p) Gosh, A. K.; Liu, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2374. (q) Colby, E. A.; O'Brian, K. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 998. Amphidinolide T_4: (r) Fürstner, A.; Aïssa, C.; Riveiros, R.; Ragot, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4763. (s) Colby, E. A.; O'Brian, K. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2005**, *127*, 4297. Amphidinolides T_1, T_3, T_4, and T_5: (t) Aïssa, C.; Riveiros, R.; Ragot, J.; Fürstner, A. *J. Am. Chem. Soc.* **2003**, *125*, 15512. Proposed structure of amphidinolide V: (u) Fürstner, A.; Larionov, O.; Flügge, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5545. Amphidinolide W: (v) Gosh, A. K.; Gong, G. *J. Am. Chem. Soc.* **2004**, *126*, 3704. (w) Gosh, A. K.; Gong, G. *J. Org. Chem.* **2006**, *71*, 1085. Amphidinolide X: (x) Lepage, O.; Kattnig, E.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 15970. Amphidinolides X and Y: (y) Fürstner, A.; Kattnig, E.; Lepage, O. *J. Am. Chem. Soc.* **2006**, *128*, 9194.

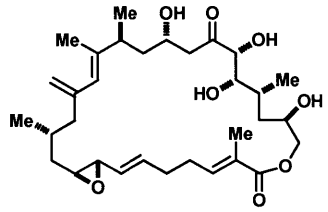
Figure 2. Examples of B-Type Amphidinolides.



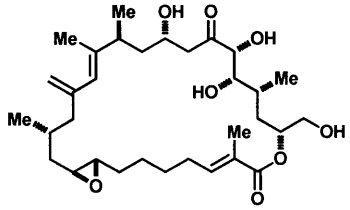
amphidinolide B_1



amphidinolide H_1



amphidinolide G_1



amphidinolide H_4

All members of the G-series form 27-membered macrolactones instead of the usually encountered 26-membered ring scaffold, but other than that correspond closely to the H-series. In fact, it could be shown that by treatment with potassium carbonate in ethanol amphidinolide G_1 or H_1 can be converted to a 1:1 mixture of the two compounds underscoring the relationship of these two series (Figure 3).[3]

The structures of the B-type amphidinolides were elucidated by extensive 1D- and 2D-NMR experiments in course of their isolation. The relative stereochemistry of amphidinolide B_1 and H_1 could be derived from X-ray crystallography and the absolute configuration was assigned on the basis of degradation studies combined with chiral HPLC-analyses.[3, 4, 5] Biosynthetic studies on amphidinolide B_1 with ^{13}C-labeled

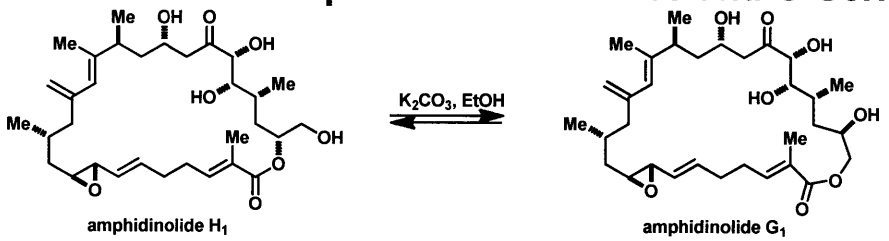
---

[3] Kobayashi, J.; Shimbo, K.; Kubota, T.; Tsuda, M. *Pure Appl. Chem.* **2003**, *75*, 337.

[4] Isolation of B_1 and B_3: (a) Ishibashi, M.; Ohizumi, Y.; Hanashima, M.; Nakamura, H.; Hirata, Y.; Sasaki, T. ; Kobayashi, J. *J. Chem. Soc., Chem. Commun.* **1987**, 1127. (b) Ishibashi, M.; Ishiyama, H.; Kobayashi, J. *Tetrahedron Lett.* **1994**, *35,* 8241. Isolation of B_4 and B_5: (c) Tsuda, M.; Kariya, Y.; Iwamoto, R.; Fukushi, E.; Kawabata, J.; Kobayashi, J.; *Marine Drugs* **2005**, *3,* 1. Isolation of D: (d) Kobayashi, J.; Ishibashi, M.; Nakamura, H.; Ohizumi, Y.;

acetates revealed that this macrolide is most likely generated through non-successive mixed polyketides.[6]

Figure 3. Relation between Amphidinolide H-Series and G-Series.



A few of the challenges posed by the B-type amphidinolides include, but are not limited to: (i) nine stereogenic centers (three of which are contiguous); (ii) an α-hydroxy ketone; (iii) a 1,3-diene with adjacent stereocenter; (iv) and, in most cases, a labile alkenyl epoxide; (v) which are all contained within a 26-membered (or 27-membered) macrocyclic lactone ring. These highlighted challenges along with the biological activity have made the B-type amphidinolides the focus of much synthetic work, and many fragments have been prepared.[7] However, despite these numerous attempts it was not

---

Yamasu, T.; Hirata, Y.; Sasaki, T.; Otha, T.; Nozoe, S. J. *J. Nat. Prod.* **1989**, *52*, 1036. Isolation of G_1 and H_1: (e) Kobayashi, J.; Shigemori, H.; Ishibashi, M.; Yamasu, T.; Hirota, H.; Sasaki, T. *J. Org. Chem.* **1991**, *56*, 5221. Isolation of G_2, G_3 and H_2-H_5: (f) Kobayashi, J.; Shimbo, K.; Sato, M.; Tsuda, M. *J. Org. Chem.* **2002**, *67*, 6585. Isolation of L: (g) Tsuda, M.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1994**, *59*, 3734.

[5] X-ray crystallography: (a) Bauer, I.; Maranda, L.; Shimizu, Y.; Peterson, R. W.; Cornell, L.; Steiner, J. R.; Clardy, J. *J. Am. Chem. Soc.* **1994**, *116*, 2657. (b) Kobayashi, J.; Shimbo, K.; Sato, M.; Shiro, M.; Tsuda, M. *Org. Lett.* **2000**, *2*, 2805-2807.

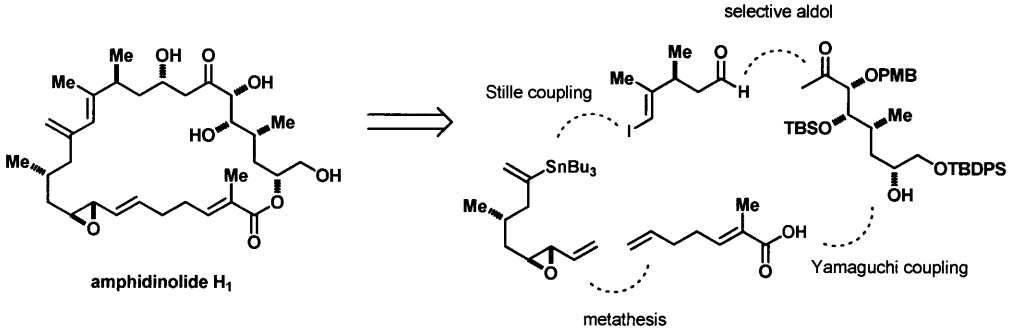
[6] Tsuda, M.; Kubota, T.; Sakuma, Y.; Kobayshi, J. *Chem. Pharm. Bull.* **2001**, *49*, 1366.

[7] Fragment syntheses of B-type amphidinolides: (a) Eshelby, J. J.; Parsons, P. J.; Sillars, N. C.; Crowley, P. J. *Chem. Commun.* **1995**, 1497. (b) Lee, D.-H.; Lee, S.-W. *Tetrahedron Lett.* **1997**, *38*, 7909. (c) Chakraborty, T. K.; Suresh, V. R. *Chem. Lett.* **1997**, 565. (d) Chakraborty, T. K.; Thippeswamy, D.; Suresh, V. R.; Jayaprakash, S. *Chem. Lett.* **1997**, 563. (e) Ohi, K.; Shima, K.; Hamada, K.; Saito, Y.; Yamada, N.; Ohba, S.; Nishiyama, S. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2433. (f) Lee, D.-H.; Rho, M.-D. *Bull. Kor. Chem. Soc.* **1998**, *19*, 386. (g) Cid, B. M.;

until recently that the first total synthesis of any of the B-type amphidinolides was realized. Fürstner reported the first total synthesis of amphidinolide H_1 and its acid catalyzed conversion to amphidinolide G_1 in 2007.[2h] The total synthesis of amphidinolide B_1 and of the proposed structure of amphidinolide B_2 (now referred to as amphidinolide D) was then reported by Carter shortly after.[2e] The key disconnections for Fürstner's synthesis of amphidinolide H_1 are shown in Figure 4. The ester was prepared from carboxylic acid and alcohol fragments through a Yamaguchi coupling. Another key step toward amphidinolide H_1 was a selective aldol reaction where the PMB ether group exerted strong 1,4-anti induction. The 1,3-diene was formed *via* a difficult Stille coupling which required 0.70 equivalents of $Pd(PPh_3)_4$. This was quite an accomplishment as previously cross-couplings were shown to be problematic.[7o] The ring was then closed by making use of ring closing metathesis, and the silyl groups were removed using TASF to give amphidinolide H_1.

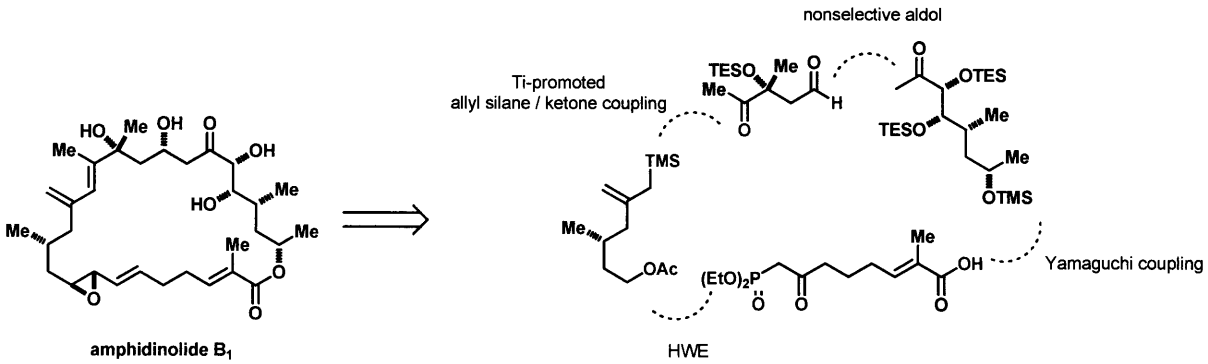
Pattenden, G. *Synlett* **1998**, 540. (h) Ohi, K.; Nishiyama, S. *Synlett* **1999**, 571. (i) Ishiyama, H.; Takemura, T.; Tsuda, M.; Kobayashi, J. *Tetrahedron* **1999**, *55*, 4583. (j) Ishiyama, H.; Takemura, T.; Tsuda, M.; Kobayashi, J. *J. Chem. Soc. Perkin Trans. I* **1999**, 1163. (k) Eng, H. M.; Myles, D. C. *Tetrahedron Lett.* **1999**, *40*, 2279. (l) Eng, H. M.; Myles, D. C. *Tetrahedron Lett.* **1999**, *40*, 2275. (m) Chakraborty, T. K.; Thippeswamy, D. *Synlett* **1999**, 150. (n) Lee, D.-H.; Rho, M.-D. *Tetrahedron Lett.* **2000**, *41*, 2573. (o) Cid, M. B.; Pattenden, G. *Tetrahedron Lett.* **2000**, *41*, 7373. (p) Zhang, W.; Carter, R. G.; Yokochi, A. F. T. *J. Org. Chem.* **2004**, *69*, 2569. (q) Mandal, A. K.; Schneekloth, J. S.; Crews, C. M. *Org. Lett.* **2005**, *7*, 3645. (r) Zhang, W.; Carter, R. G. *Org. Lett.* **2005**, *7*, 4209. (s) Gopalarathnam, A.; Nelson, S. G. *Org. Lett.* **2006**, *8*, 7. Amphidinolides G_1 and H_1: (t) Chakraborty, T. K.; Suresh, V. R. *Tetrahedron Lett.* **1998**, *39*, 9109. (u) Chakraborty, T. K.; Suresh, V. R. *Tetrahedron Lett.* **1998**, *39*, 7775. Amphidinolide L: (v) Tsuda, M.; Hatakeyama, A.; Kobayashi, J. *J. Chem. Soc. Perkin Trans. I* **1998**, 149. (w) Kobayashi, J.; Hatakeyama, A.; Tsuda, M. *Tetrahedron* **1998**, *54*, 697.

Figure 4. The Key Disconnections in Fürstner's Synthesis of Amphidinolide H_1.



The key disconnections for Carter's synthesis are presented in Figure 5. The 1,3-diene was prepared *via* a Ti-promoted allyl silane and ketone coupling followed by elimination. Carter also used an aldol reaction as a key step; however, due to the lack ot the PMB ether, it was not stereoselective. The synthesis also employed a Yamaguchi coupling, and in this case it was performed with the 1,3-diene unit present. The ring was closed with the Horner-Wadsworth-Emmons (HWE) olefination. The product of the HWE was then further elaborated to give the alkenyl epoxide and the silyl groups were deprotected using TASF to give the first total synthesis of amphidinolide B_1.

Figure 5. The Key Disconnections in Carter's Synthesis of Amphidinolide B_1.



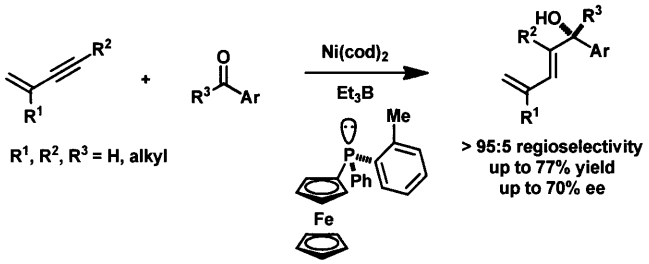
Assembly of the sensitive 1,3-diene has been the biggest challenge for chemists and has prevented more synthesis of these natural products. In addition, if the diene could be assembled, the chemist was often limited by the types of transformations that could take place in the presence of the diene. The 1,3-diene has been shown to be incompatible to basic and acid conditions because of the *exo*-methylene unit which isomerizes to the more stable internal olefin.[2h] Our laboratory recently described the Ni-catalyzed reductive coupling reactions of 1,3-enynes with aldehydes and ketones that generate dienyl alcohols.[8, 9] These reactions give us access to the difficult to prepare 1,3-dienes with the same arrangement found in the B-type amphidinolides. Although, when we embarked on developing this unified strategy to the 1,3-dienes contained within the B-type amphidinolides, the only known reductive coupling between 1,3-enynes and ketones were described for 1,3-enynes and aryl ketones (Figure 6).[9] However, we envisioned access to the amphidinolides in the B-series via reductive coupling of a 1,3-enyne and methyl ketone. In addition, we could access the amphidinolides in the G-series and H-series via reductive coupling of a 1,3-enyne and aldehyde, followed by displacement of the newly formed alcohol with a methyl nucleophile.

---

[8] (a) Ni-catalyzed reductive coupling of 1,3-enynes and aldehydes: Miller, K. M.; Luanphaisarnnont, T.; Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 4130. For a mechanistic discussion see: (b) McCarren, P. R. Liu, P.; Cheong, P. H.-Y.; Jamison, T. F.; Houk, K. N. *J. Am. Chem. Soc.* **2009**, *131*, 6654. (c) Liu, P.; McCarren, P. R.; Cheong, P.H-Y.; Jamison, T. F.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, ASAP Article, **DOI:** 10.1021/ja909562y.

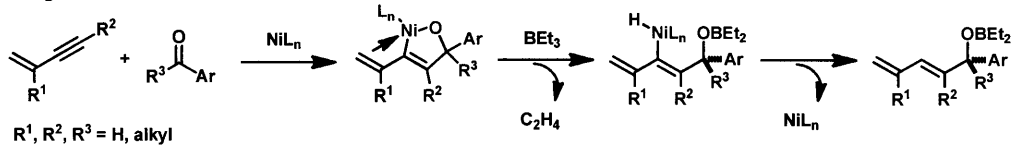
[9] Ni-catalyzed reductive coupling of 1,3-enynes and ketones: Miller, K. M.; Jamison, T. F. *Org. Lett.* **2005**, *7*, 3077. For a review see: Moslin, R. M.; Moslin, K. M.; Jamison, T. F. *Chem. Commun.* **2007**, 4441.

Figure 6. Ni-Catalyzed Reductive Coupling of 1,3-Enynes and Ketones.



The mechanism for the Nickel-catalyzed reductive coupling of 1,3-enynes and ketones is believed to proceed *via* a nickel matallacycle (Figure 7).[8b, 8c] In this case the alkene acts as a directing group, and we believe there is a bonding interaction between Nickel and the olefin which imparts high levels of regioselectivity. From there β-hydride elimination followed by reductive elimination gives the desired coupled product.

Figure 7. Proposed Mechanism for Ni-Catalyzed Reductive Coupling of 1,3-Enynes and Ketones.



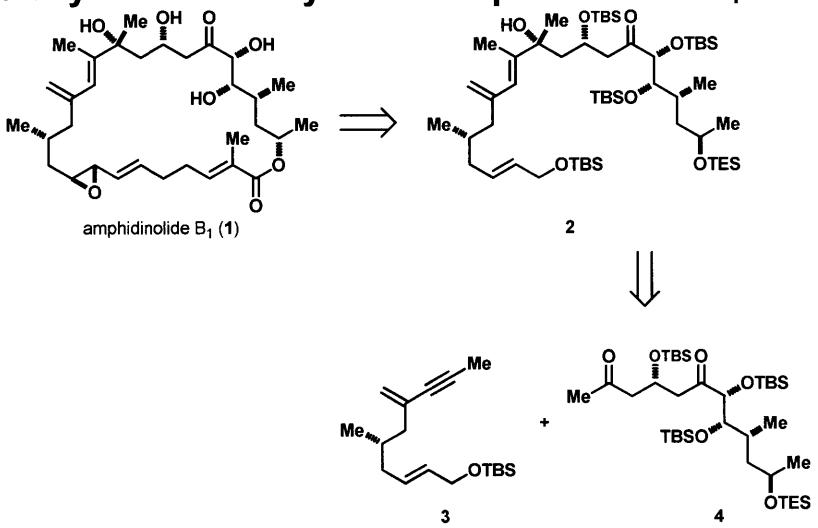
Synthetic Strategy Towards Amphidinolide B_1

Our strategy toward amphidinolide B_1 involves a convergent Ni-catalyzed reductive coupling of 1,3-enyne **3** and methyl ketone **4** to generate the tertiary alcohol **2** (Figure 8). The alcohol **2** can in turn be transformed into amphidinolide B_1 (**1**) with the thought that the ring can be formed via Mitsunobu cyclization.[10] The key coupling reaction for this sequence would require us to first investigate the viability of methyl ketones as

[10] a) Mitsunobu, O.; Yamada, Y. *Bull. Chem. Soc. Japan* **1967**, *40*, 2380. b) Review of the Mitsunobu Reaction: Hughes, D. L. *Org. React.* **1992**, *42*, 335.

coupling partners with 1,3-enynes. Another key requirement for this strategy would be for the reductive coupling to proceed with a high degree of diastereoselectivity. We anticipated that a chiral phosphine ligand would be necessary to influence the stereoselectivity during the fragment coupling step. After investigating the fragment coupling step we would prepare the 1,3-enyne **3** and the ketone **4**.

Figure 8. Retrosynthetic Analysis of Amphidinolide B_1.



Results and Discussion

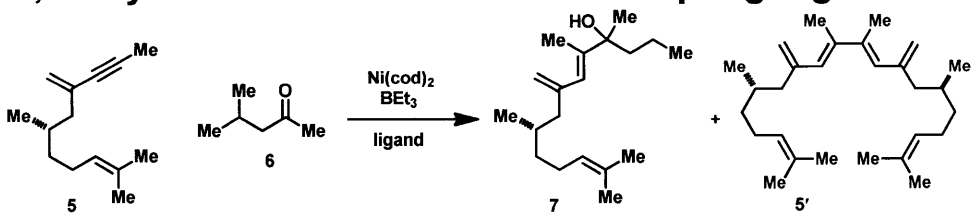
A. 1,3-Enyne and Ketone Reductive Coupling

The key step for the proposed synthesis of amphidinolide B_1 involves an enyne and ketone reductive coupling. To date the only catalytic intermolecular reductive coupling of ketones and enynes reported uses chiral monodentate ferrocenyl phosphines to achieve the coupling of 1,3-enynes and aromatic ketones.[9] The proposed synthesis of amphidinolide B_1 would require a di-alkylketone to be coupled with an enyne.

To achieve this we set out to find conditions that would give the desired coupling. We envisioned using $Ni(cod)_2$, Et_3B as a stoichiometric reducing agent, and a tertiary

phosphine ligand. Initially, several ligands were investigated for the coupling of 1,3-enyne **5** and ketone **6** (Table 2). Many ligands were screened that gave little to no product including *i*-Pr_3P, Ph_3P, (*o*-anisyl)$_3$P, (2,4,6-trimethoxy-phenyl)$_3$P, and (*t*-$Bu_3)_2$MeP (Table 2, entries 2-6). The best result was observed when Cyp_3P was used as the ligand at 35 °C, and 22% of the desired alcohol **7** was obtained (entry 1). Adding a solvent such as toluene decreased the yield significantly when Cyp_3P was used as the ligand, and further investigations using solvents during the ligand screening were not performed. Using *t*-Bu_3P also gave product, but the reaction produced many uncharacterized products that were difficult to separate from the desired alcohol **7** (entry 7). With the exception of using *t*-Bu_3P as the ligand, all other reactions gave varying amounts of starting materials **5** and **6**, the desired alcohol **7** as a 1:1 mixture of diastereomers, and another compound believed to be the reductive self-coupling (**5'**) of enyne **5**.

Table 2. 1,3-Enyne and Ketone Reductive Coupling Ligand Screening.

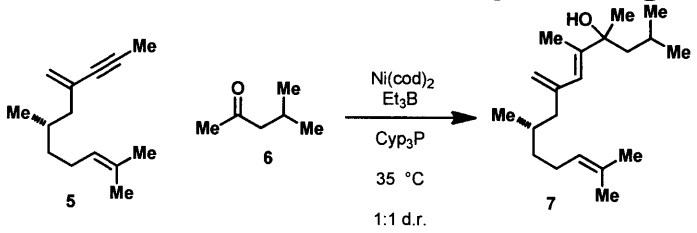


entry[a]	Ligand	yield (%)[b]
1	Cyp_3P	22
2	$i\text{-}Pr_3P$	<5
3	Ph_3P	<5
4	$(o\text{-anisyl})_3P$	0
5	$(2,4,6\text{-trimethoxy-phenyl})_3P$	0
6	$(t\text{-Bu})_2MeP$	<5
7	$t\text{-Bu}_3P$	21[c]

[a] All reactions were performed on 0.131 mmol scale at 35 °C with 250 mol% of ketone **6** and 100 mol% of enyne **5** added at once to a catalyst mixture containing 250 mol% BEt_3, 10 mol% $Ni(cod)_2$, and 20 mol% ligand. [b] All yields are isolated yields. [c] The product could not be seperated from decomposition products that were not seen in previous cases.

Further investigations showed that the yield could be further optimized while using Cyp_3P as the ligand (Table 3). Increasing the catalyst loading or amount of Et_3B did not increase the yield in a significant manner (entries 2 and 3). However, increasing both the catalyst loading and the amount of Et_3B in conjunction with prolonging the addition time of the enyne did serve to increase the yield to 36%; a full 63% increase compared to 22% seen previously (entries 1, 4).

Table 3. Further Enyne and Ketone Coupling Investigations.

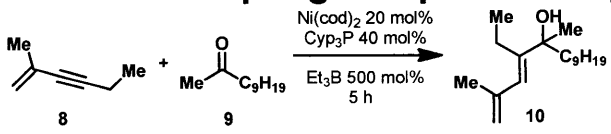


entry[a]	$Ni(cod)_2$:Cyp_3P (mol%)	Et_3B (mol%)	**5** addition time (min)	yield (%)[b]
1	10:20	250	1	22
2	20:40	250	1	26
3	10:20	1000	1	26
4	20:40	500	105	36

[a] All reactions were performed on 0.131 mmol scale at 35 °C with 250 mol% of ketone **6** added to a catalyst mixture containing Et_3B, $Ni(cod)_2$, and Cyp_3P. Then 100 mol% of enyne **5** was added while stirring, and the reaction was stirred for an additional 2 hours. [b] All yields are isolated yields.

We found that we could further improve the yield for the 1,3-enyne and ketone coupling by increasing the temperature and using a 2:1 ratio of enyne **8** to ketone **9**, 20 mol% $Ni(cod)_2$, 40 mol% Cyp_3P, and 500 mol% Et_3B (Table 4). The yield increased as the reaction temperature increased, and the best yield (80%) was observed when the reaction was performed at 60 °C (entries 1-5). Increasing the temperature of the reaction beyond 60 °C gave a decrease in yield for alcohol **10** compared to when the reaction was performed at 60 °C (entry 6). In all cases the remaining ketone **9**, which did not couple with the enyne **8**, was reisolated nearly quantitatively even at 65 °C. The enyne that did not couple with the ketone underwent a reaction to give cyclotrimer product. We also extended the reaction time and the enyne addition time; however, no noticeable increase in yield was observed.

Table 4. Enyne and Ketone Coupling Temperature Optimization.



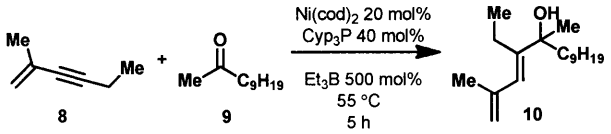
8 9 10

entry[a]	temperature (°C)	yield (%)[b]	recovered **9** (%)[b]
1	35	35	65
2	45	56	43
3	50	67	22
4	55	73	27
5	60	80	15
6	65	68	32

[a] All reactions were performed on 0.350 mmol scale with 100 mol% of ketone **9** added to a catalyst mixture containing Et_3B, $Ni(cod)_2$, and Cyp_3P. Then 200 mol% of enyne **8** was added over 3 hours while stirring, and the reaction was stirred for an additional 2 hours. [b] All yields are isolated yields.

Further optimization was done to investigate what effect the enyne and ketone ratio had on the reaction (Table 5). It was found that a 2.5:1 ratio of enyne:ketone gave the best result with a yield of 77% for the desired alcohol **10** and 20% yield of recovered ketone **9** (entry 2). In addition, the yield did not substantially decrease for 1.5:1 and 1:1 ratios respectively (entries 3 and 4). However, one troubling result was that a significant decrease in yield was seen when the coupling was performed on a smaller scale (entry 5). When the 1,3-enyne and ketone coupling was performed on a 0.131 mmol scale, a yield of 36% was observed compared to 51% yield under identical conditions on a 0.350 mmol scale. It is hypothesized that the decrease in yield is seen because on small scale, in the absence of a solvent, the Et_3B evaporates off when the reaction is performed at 55 °C.

Table 5. Reductive Coupling Optimization for Enyne Equivalents.

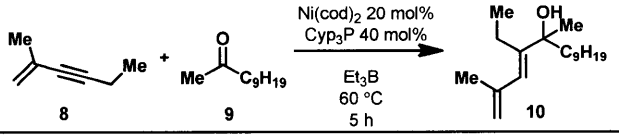


entry[a]	8 (mol%)	yield (%)[b]	recovered 9 (%)[b]
1	300	74	25
2	250	77	20
3	150	66	32
4	100	51	43
5[c]	100	36	64

[a] Unless otherwise noted all reactions were performed on 0.350 mmol scale with 100 mol% of ketone **9** added to a catalyst mixture containing Et_3B, $Ni(cod)_2$, and Cyp_3P. Then the enyne **8** was added over 3 hours while stirring, and the reaction was stirred for an additional 2 hours. [b] All yields are isolated yields. [c] Reaction performed on 0.131 mmol scale.

We believed that use of a solvent would address this problem, and to that end the reductive coupling of enyne **8** and ketone **9** was performed in the presence of solvents. However, a decrease in yield was seen when compared to the neat conditions for a reaction performed on a 0.350 mmol scale (Table 6, entry 1). In this case the yield was 50% for the desired alcohol **10** compared to 77% when performed in the absence of solvent. This loss in yield was offset slightly when the amount of Et_3B was reduced from 500 mol% to 200 mol% (entry 2). Toluene proved to be a better solvent for the coupling when compared to EtOAc (entry 3). When the enyne was dissolved in toluene and added over three hours the yield was increased from 60% to 70%, and both conditions allowed for complete recovery of the ketone (entries 2, 6). Reducing the amount of Et_3B below 200 mol% decreased the yield of the reaction (entry 5). The advantage of using the solvent was realized when the coupling reaction was able to be performed in good yields for scales of 0.131 and 0.066 mmol respectively. We now had conditions that worked well on a variety of scales, and we could add a solvent to achieve reliable results on particularly small scales.

Table 6. Reductive Coupling Optimization with use of Solvent.



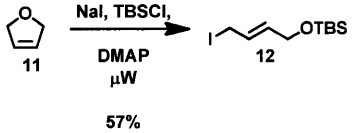
entry[a]	solvent	Et_3B (mol%)	yield (%)[f]	recovered **9** (%)[f]
1[b]	toluene	500	50	46
2[b]	toluene	200	60	34
3[b]	EtOAc	200	51	48
4[c]	toluene	500	61	39
5[c]	toluene	150	60	39
6[c]	toluene	200	71	29
7[c, d]	toluene	200	66	33
8[c, e]	toluene	200	51	48

[a] Unless otherwise noted reactions were performed using 0.350 mmol **9.** 250 mol% of Enyne **8** was added over 3 hours and the reaction was carried out for an additional 2 h. [b] Ketone **9** added as 2 M solution in solvent. [c] Enyne **8** added as 6 M solution in toluene. [d] The scale for this reaction was 0.131 mmol. [e] The scale for this reaction was 0.066 mmol. [f] All yields are isolated yields.

B. Synthesis of the 1,3-Enyne Fragment[11]

The synthesis of the 1,3-enyne **3** commenced by forming the *trans* allylic ether region. To that end the allylic iodide **12** could be prepared efficiently by the ring opening of 2,5-dihydrofuran (**11**) in the presence of TBSCl, DMAP, and NaI at reflux for 48 hours.[12] We found that the long reaction time could be averted by heating in a microwave at 150 °C for 20 min (Scheme 1). This method could be used to prepare 50 g of the allylic iodide in short order and with great cost efficiency.

Scheme 1

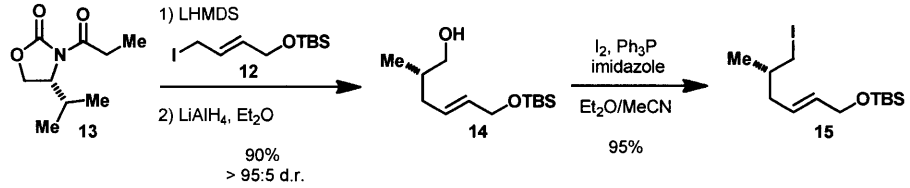


[11] The author collaborated closely with Dr. Chudi Ndubaku during this stage of work and portions have been reported in: . Ndubaku, C. O. "*Diastereoselective Nickel-Catalyzed Reductive Coupling of Alkynes and Aldehydes and Application Toward the B-Type Amphidinolides*", Ph. D. Thesis, Massachusetts Institute of Technology, **2005**.

[12] Sun, M.; Deng, Y.; Batyreva, E.; Sha, W.; Salomon, R. G. *J. Org. Chem.* **2002**, *67*, 3575.

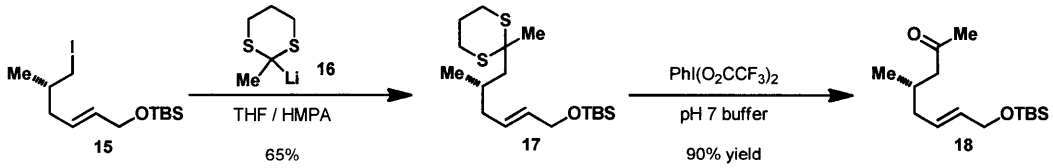
Asymmetric alkylation of the Evans *N*-acyl oxazolidinone auxiliary **13**,[13] with allylic iodide **12**, proceeded with excellent selectivity and yield (Scheme 2). The auxiliary was then cleaved reductively with $LiAlH_4$ in excellent yield to give the alcohol **14**. The alcohol was then in turn converted to the iodide **15** in 95% yield.

Scheme 2



We had initially envisioned reaction with a lithiated dithiane **16** to give compound **17** (Scheme 3). Subsequent deprotection of the dithiane **17** provided the desired methyl ketone **18**. [14]

Scheme 3



Although the route to the methyl ketone was adequate, we found a more direct and cost effective route by metal-halogen exchange with iodide **15**. This was followed by addition of Weinreb amide **19** (Table 7). However, the lithium-iodide exchange was met with difficulty. Generally lithium-iodide exchange takes place within minutes at -78 °C

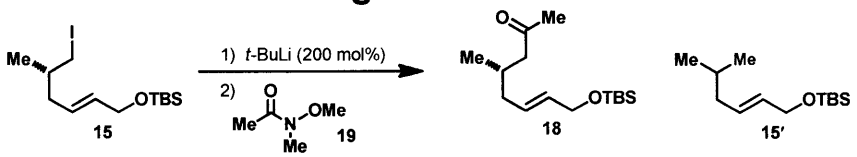
---

[13] Original report: (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737. For an excellent review, see: (b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichim. Acta* **1997**, *30*, 3.

[14] (a) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287. (b) Nicolaou, K. C.; Li, Y.; Sugita, K.; Monenschein, H.; Guntupalli, P.; Mitchell, H. J.; Fylaktakidou, K. C.; Vourloumis, D.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2003**, *125*, 15443.

and then the reaction is warmed to room temperature for two hours, in order to convert the tertiary iodide that is formed to an alkene *via* elimination. However, when performed under these conditions, various decomposition pathways prevailed, and none of the ketone **18** was isolated (entry 1). Instead of warming to r.t. the reaction was warmed to 0 °C for two hours, but once again only decomposition resulted (entry 2). Shorter amounts of time at 0 °C also resulted in the same decomposition products (entry 3). If the reaction was warmed to -40 °C for one hour, decomposition resulted once again, but 30% of the desired ketone **18** was also observed along with **15'** resulting from reaction with H^+ (entry 4). Finally, keeping the reaction at -78 °C for 2 hours allowed for the ketone **18** to be isolated in 65% yield along with **15'** (entry 5). In an attempt to prevent the undesired product one equivalent of $CeCl_3$ was added; however the yield was not further improved and **15'** was still obtained.

Table 7. Lithium-Iodide Exchange.



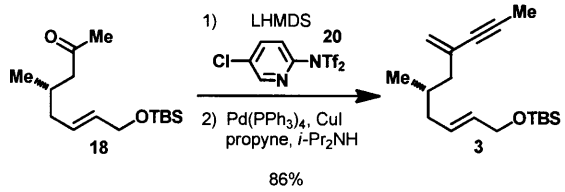
entry	temperature[a]	yield (%) **18**	comment
1	-78 °C → rt 2 h → -78 °C	0	decomposition
2	-78 °C → 0 °C 2 h → -78 °C	0	decomposition
3	-78 °C → 0 °C 0.5 h → -78 °C	0	decomposition
4	-78 °C → -40 °C 1 h → -78 °C	30	decomposition was also observed
5	-78 °C 2 h	65	ketone **18** and **15'** were observed

[a] Temperature of reaction after addition of *t*-BuLi but before Weinreb amide addition.

Making use of Comins's reagent (**20**) allowed for the clean conversion of the methyl ketone **18** to the corresponding kinetic enol triflate, and without the use of HMPA

(Scheme 4).[15] With the triflate in hand, Sonogashira cross-coupling with propyne provided the desired 1,3-enyne fragment **3**. [16] Overall the enyne fragment was prepared in 48% yield over five steps from the Evans *N*-acyl oxazolidinone auxiliary **13**. The synthesis is very scalable and has been used to make 4 g of the enyne **3** at once.

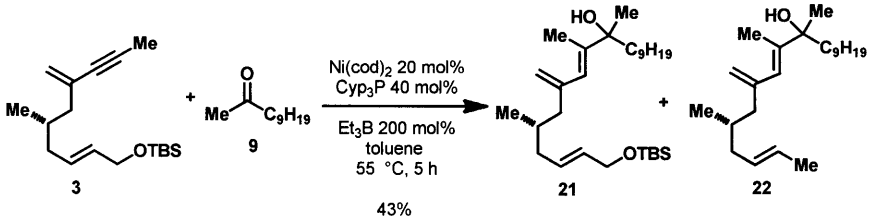
Scheme 4



C. Ni-Catalyzed 1,3-Enyne and Model Ketone Fragment Coupling

Before setting out to prepare the ketone fragment, we investigated the reductive coupling between the 1,3-enyne fragment **3** and 2-undecanone (**9**). Initially, we attempted the coupling using the conditions we had previously found to be successful for our model compounds (Scheme 5). However, despite numerous attempts and variations, we observed an inseparable mixture of the desired alcohol **21** and alcohol **22** (which resulted from the reduction of the TBS ether).

Scheme 5



[15] Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.

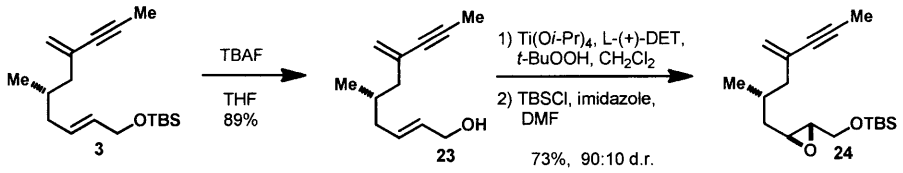
[16] (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Ch. 5.

At room temperature the reduction of the TBS ether did not occur, but the coupling also did not take place.

D. Synthesis of Modified 1,3-Enyne Fragment

Due to the difficulties associated with having the allylic TBS ether present during the reductive coupling, we decided a modification to our approach was necessary. The change we decided to implement was installing the epoxide functional group before the coupling instead of after. Enyne **3** was TBS deprotected using TBAF to give allylic alcohol **23**, which was converted to the epoxide using the Sharpless method for asymmetric epoxidation (Scheme 6).[17] The epoxide was then protected once again to give the TBS ether **24** in good yield.

Scheme 6



E. Ni-Catalyzed Reductive Coupling with new 1,3-Enyne and Model Ketone

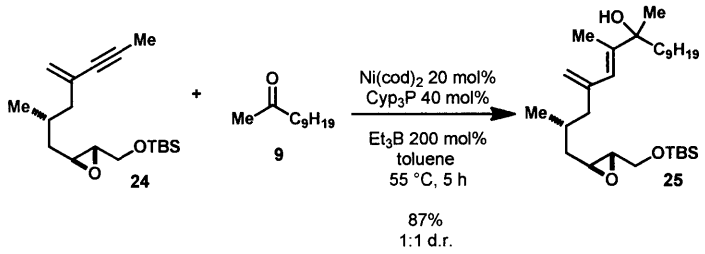
Gratifyingly, with use of the newly synthesized 1,3-enyne **24**, the Ni-catalyzed reductive coupling was successful to give the alcohol **25** as 1:1 mixture of diastereomers (Scheme 7). The preparation of alcohol **25** resulted from exclusive *cis* addition across the alkyne. Noteworthy is that no TBS ether reduction was observed for the reaction to give the desired alcohol **25** in 87% yield; which was a higher yield than any observed in our previous 1,3-enyne and ketone reductive coupling investigations.

---

[17] (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974-5976. (b) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

We were also happy to see that internal epoxides were tolerated under the reaction conditions.

Scheme 7



F. Synthetic Strategies for the Ketone Fragment

There are several strategies that could be employed to tackle the ketone fragment. Before setting out to synthesize ketone **4** we developed two such strategies. The first strategy involves Horner-Wadsworth-Emmons (HWE) olefination between advanced intermediates, ketophosphonate **28** and aldehyde **29**, to give the *E*-α,β-unsaturated ketone **27** (Figure 9).[18] Subsequently we anticipated a selective ozonolysis would give diketone **26**, which in turn could be used to give the desired ketone fragment **4** after Sharpless asymmetric dihydroxylation.[19, 20] This strategy would allow for the installation of all five stereogenic centers in ketone **4** with control of relative and absolute stereochemistry.

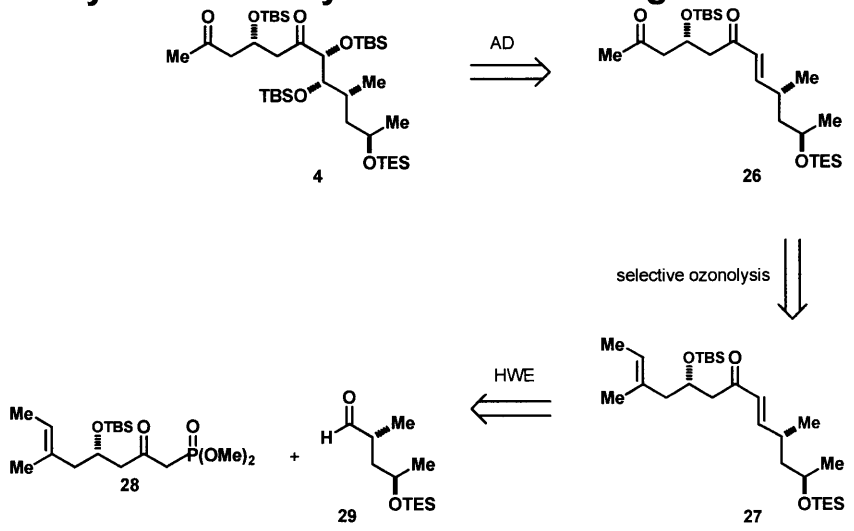
---

[18] Reviews: (a) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73-253. (b) Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, pp 729. (c) Walker, B. J. In *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic Press: New York, 1979; pp 155.

[19] Review of the Sharpless Asymmetric Dihydroxylation (AD): Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; 2nd ed.; pp 357.

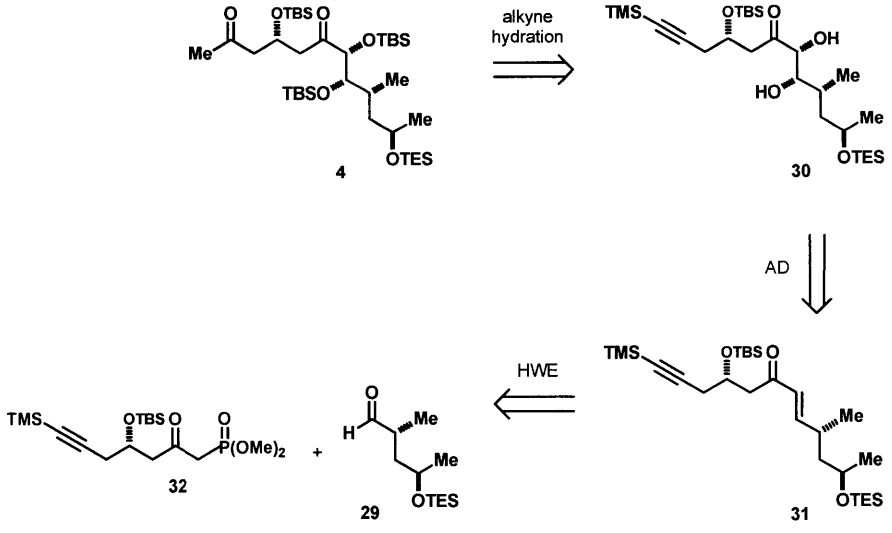
[20] An asymmetric dihydroxylation strategy has been used previously on a substrate related to compound related to **27**: (a) Lee, D.-H.; Rho, M.-D. *Tetrahedron Lett.* **2000**, *41,* 2573. (b) Eng, H. M.; Myles, D. C. *Tetrahedron Lett.* **1999**, *40*, 2279.

Figure 9. Retrosynthetic Analysis of Ketone Fragment.



An alternative strategy involves HWE olefination with ketophosphonate **32** and aldehyde **29** to once again give the *E*-α,β-unsaturated ketone (Figure 10). However, this strategy would call for asymmetric dihydroxylation at this stage, followed by alkyne hydration to give the desired ketone **4** and the five stereocenters contained within. We were confident that one or both of these strategies would suffice to give ketone **4**.

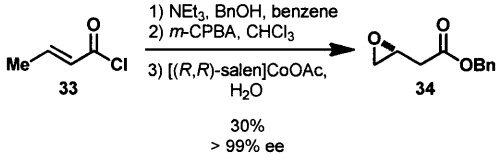
Figure 10. Alternative Retrosynthetic Analysis of Ketone Fragment.



G. Selective Ozonolysis / Asymmetric Dihydroxylation Approach

In our first strategic approach we anticipated installing the β-hydroxy ketone moiety by making use of the novel Ni-catalyzed reductive coupling of alkynes and mono-substituted epoxides developed in our lab.[21] And indeed this strategy had been successfully employed in our earlier studies toward amphidinolide H_1.[22] In order to implement this strategy we first prepared the enantiomerically enriched epoxide **34** according to the literature precedent.[23] Reacting *trans*-crotonyl chloride (**33**) in the presence of triethylamine and benzyl alcohol gave the alkene transposed benzyl ester, via a ketene intermediate, in quantitative yield (Scheme 8). The ester then underwent epoxidation and Jacobsen hydrolytic kinetic resolution to give the desired epoxide **34**.[24]

Scheme 8



With the desired enantiomerically enriched epoxide **34** in hand we explored the use of the Ni-catalyzed reductive coupling described earlier with 2-butyne (**35**). We were

---

[21] (a) Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 8076. For an application in total synthesis, see: (b) Colby, E. A.; O'Brien, K. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 998.

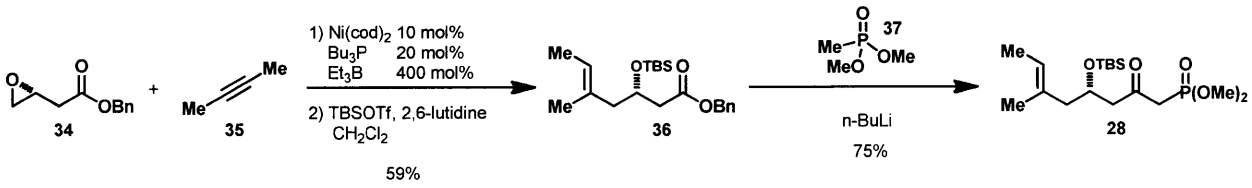
[22] Ndubaku, C. O. "*Diastereoselective Nickel-Catalyzed Reductive Coupling of Alkynes and Aldehydes and Application Toward the B-Type Amphidinolides*", Ph. D. Thesis, Massachusetts Institute of Technology, **2005**.

[23] Liu, P; Panek, J. S. "Total Synthesis of (–)-Mycalolide." *J. Am. Chem. Soc.* **2000**, *122*, 1235.

[24] (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (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.

pleased to see that under standard conditions the coupling worked in moderate yield to give the desired homoallylic alcohol (Scheme 9).[21a] However, we were able to increase the yield slightly by performing the reaction at 0 °C. Carrying out the reaction at this colder temperature helped with the volatility of the 2-butyne without negatively effecting the reactivity of the catalyst system. The newly formed homoallylic alcohol was then protected to deliver the TBS ether **36**. Addition of the lithiated dimethyl methylphosphonate gave the desired ketophosphonate fragment **28** for the HWE olefination.

Scheme 9



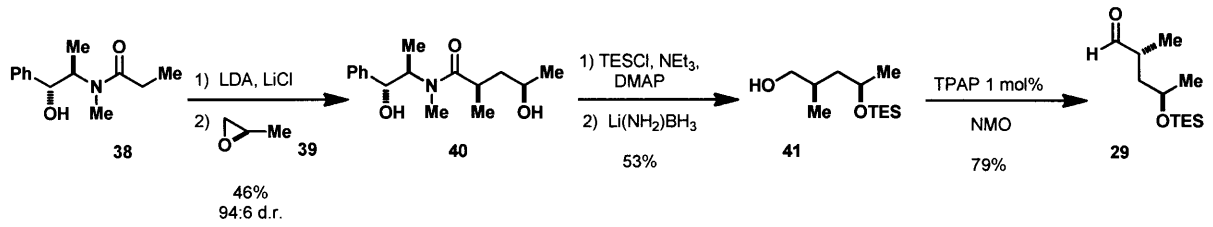
The aldehyde fragment for the HWE coupling was prepared according to literature precedent (Scheme 10).[7p] Myers auxiliary **38** was alkylated with (*R*)-propylene oxide (**39**) to give the diol **40**.[25] The diol was subsequently TES protected and reduced with lithium amidotrihydridoborate to deliver alcohol **41**. Ley oxidation then gave the desired aldehyde **29**.[26]

---

[25] Myers, A. G.; McKinstry, L. *J. Org. Chem.* **1996**, *61*, 2428.

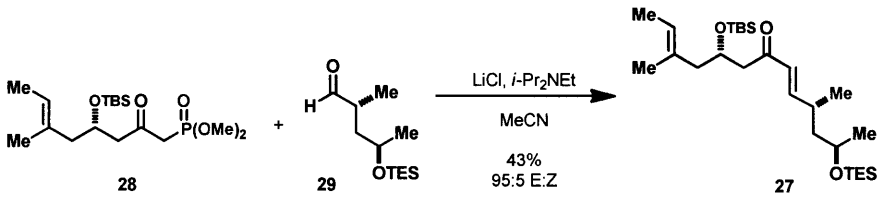
[26] a) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625. b) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

Scheme 10



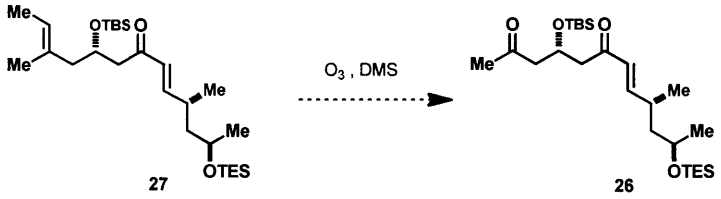
With the ketophosphonate **28** and aldehyde **29** prepared, the HWE olefination was performed under the conditions reported by Masamune and Roush (Scheme 11).[27] The conditions provided the desired *E*-α,β-unsaturated ketone **27** in a non optimized yield of 43%, but with high E/Z selectivity.

Scheme 11



Subjection of *E*-α,β-unsaturated ketone **27** to ozonolysis under a variety of conditions did not lead to selective ozonolysis of the desired trisubstituted olefin (Scheme 12).

Scheme 12

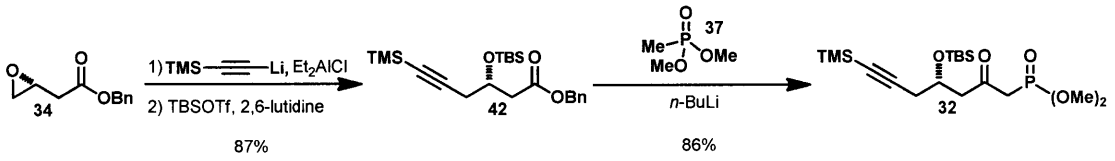


[27] Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T.; *Tetrahedron Lett.* **1984**, *25*, 2183.

H. Asymmetric Dihydroxylation / Alkyne Hydration Approach

Due to the problems with the ozonolysis approach, we turned to alkyne hydration as an alternative approach to the ketone fragment **4**. To install the alkyne moiety, lithiated TMS-acetylene was added into the epoxide **34**, followed by TBS protection to deliver the ester **42** efficiently (Scheme 13). Once again, addition of the lithiated dimethyl methylphosphonate gave the desired ketophosphonate fragment **32** for the HWE olefination.

Scheme 13

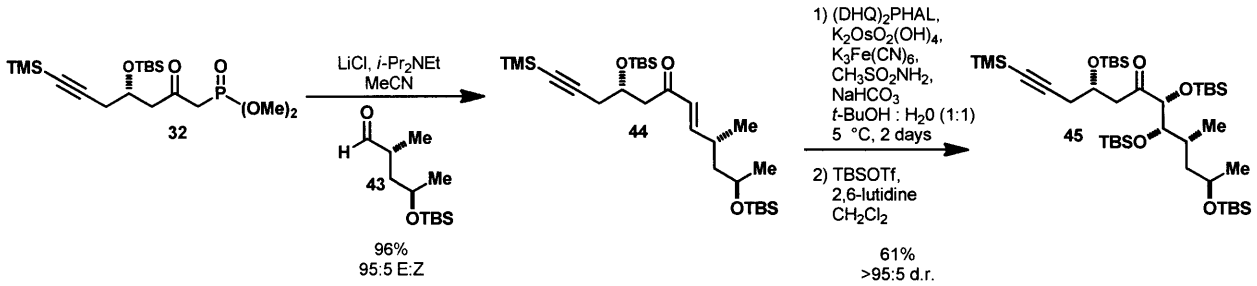


Another change that was made to our strategy was to use the known TBS protected aldehyde **43**, because the TBS group would be more stable to a wider variety of reaction conditions. The aldehyde **43** could be prepared using the same strategy as used to prepare aldehyde **29**.[7p] The HWE reaction went efficiently and with high selectivity to give the *E*-α,β-unsaturated ketone **44** (Scheme 14). The introduction of the *syn*-1,2-diol moiety was achieved by using the asymmetric dihydroxylation method reported by Sharpless in adequate yield and excellent diastereoselectivity.[19, 28] The diol was then protected as the *bis*-TBS ether **45**.

---

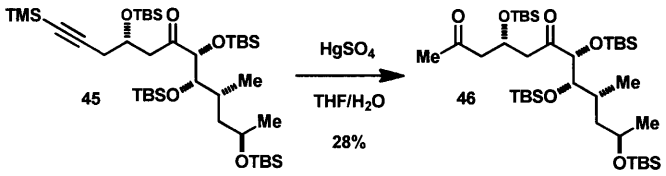
[28] Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.

Scheme 14



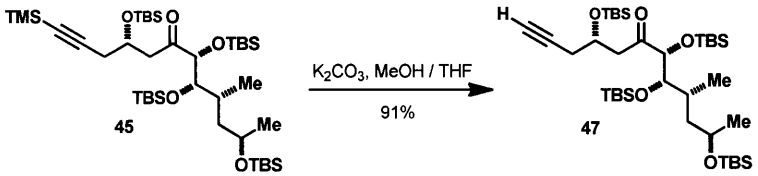
Only two transformations were needed to access the desired ketone **46**. We anticipated that the TMS group could be deprotected and the alkyne hydrated in a single step by using $HgSO_4$ to give the ketone fragment. And indeed such a transformation was possible; however, the process was inconsistent, sluggish, and low yielding (Scheme 15). The best yield was obtained at 28% after 24 h of reaction time.

Scheme 15



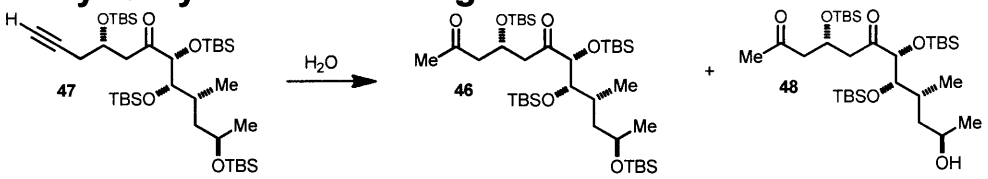
We believed that removing the TMS protecting group before the alkyne hydration would improve the yield (Scheme 16). The initial conditions of excess K_2CO_3 in a solvent system of THF / H_2O / MeOH failed to remove the TMS group. However, after using 20 equivalents K_2CO_3 in MeOH / THF the deprotection proceeded in 91% yield to give alkyne **47**.

Scheme 16



The conversion of alkyne **47** to ketone **46** was met with great difficulty (Table 8). No hydration of alkyne **47** was seen when $[Ph_3PAu]Cl$ was used as the catalyst (entry 1). Use of mercury salts did lead to the desired ketone **46** as well as the undesired ketone **48** (with removal of the least hindered TBS group). Use of $Hg(COOCF_3)_2$ for the hydration was sluggish and gave inconsistent yields, so further investigations were done using $HgSO_4$ (entry 2). Using $HgSO_4$ as the reagent for hydration also proved to give inconsistent results particularly on larger scale (entries 3- 7). Performing the hydration with 20 mol% $HgSO_4$ allowed the reaction to proceed much faster compared to 10 mol% $HgSO_4$, but a significant amount of ketone **48** was isolated along with the desired ketone **46**.

Table 8. Alkyne Hydration Investigation.

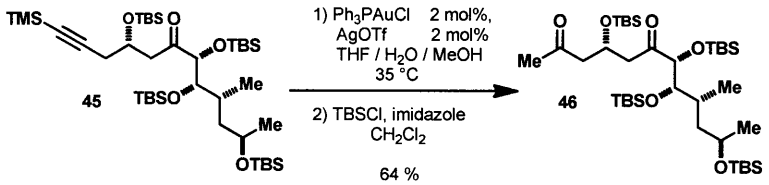


entry	**47** (mol%)	reagent	time	result
1[a]	0.28	5 mol% $[Ph_3PAu]Cl$	48 h	No reaction
2	0.48	20 mol% $Hg(COOCF_3)_2$	24 h	12% **46**; 55% **47**; <5% **48**
3	0.28	20 mol% $HgSO_4$	12 h	78% **46**; 10% **48**
4[b]	0.48	20 mol% $HgSO_4$	12 h	36% **46**; 37% **47**; <5% **48**
5	0.56	10 mol% $HgSO_4$	12 h	<5% **46**; 73% **47**; <5% **48**
6	0.56	10 mol% $HgSO_4$	24 h	29% **46**; 29% **47**; <5% **48**
7	0.112	20 mol% $HgSO_4$	12 h	39% **46**; 24% **48**

[a] An additive of AgOTf was used. [b] Average of 5 trials with results that were inconsistent.

After investigating the hydration as well as looking into other methods to synthesize the ketone **46,** we found that using 2% $[Ph_3PAu]Cl$ with 2% AgOTf at 35 °C in MeOH / THF / H_2O gave a mixture of the desired ketone **46** and undesired ketone **48**. However, the reaction was otherwise fairly clean and the crude material could be subjected to TBS protection conditions to give the ketone **46** in 64% yield (Scheme 17).

Scheme 17

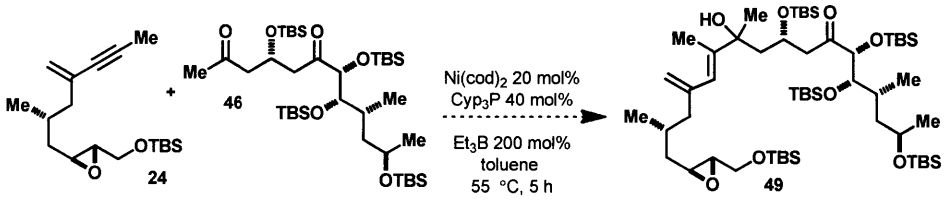


In summary we prepared the ketone fragment, and the five stereogenic centers contained within, in 23% yield over seven steps from the known enantiomerically enriched epoxide **34**. This was accomplished by making use of the HWE olefination, followed by Sharpless asymmetric dihydroxylation, and alkyne hydration.

I. Investigation of the Ni-Catalyzed 1,3-Enyne and Ketone Coupling

The Ni-catalyzed coupling between 1,3-enyne fragment **24** and ketone **46** was initially performed on a small scale of 0.054 mmol, so the use of toluene as a solvent was needed (Scheme 18). We also decided to use 200 mol% of the 1,3-enyne **24**, which was added over three hours as a 6 M solution in toluene. However, despite the fact that these conditions had worked well for 1,3-enyne **24** and 2-undecanone, we observed none of the desired dienol **49** when the conditions were applied to the coupling of enyne **24** and ketone **46**. We also investigated several small modifications to no avail. In all cases the enyne could not be recovered and gave primarily the reductive dimerization product. The ketone could be recovered; although, it often contained impurities which were difficult to separate.

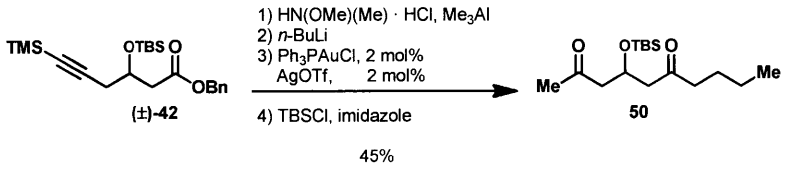
Scheme 18



J. Synthesis of Model Ketone

We hypothesized that the problem with the coupling of 1,3-enyne **24** and ketone **46** may be due to steric hindrance from the β-TBS ether. Previously this enyne and ketone coupling had been optimized using the sterically unencumbered 2-undecanone. In order to test the viability of the coupling reaction on more hindered substrates we set out to synthesize racemic ketone **50** which would provide a model for ketone **46**. The enantiomerically enriched Benzyl ester **42** is an intermediate toward the ketone **46** (Scheme 13). We prepared the (±)-**42** in the same manner, and addition of *n*-BuLi after preparation of the Weinreb amide gave the ketone product. The diketone **50** was prepared via subsequent alkyne hydration, and the TMS and TBS groups were deprotected during this process as well (Scheme 19). The crude alcohol was then protected as the TBS ether once again under standard conditions.

Scheme 19

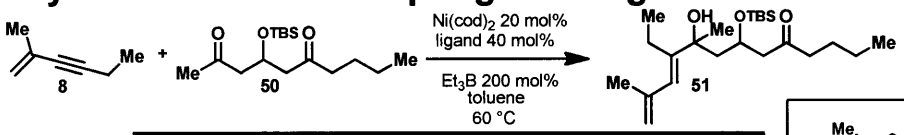


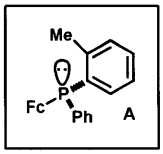
K. Investigation of the Model 1,3-Enyne and Ketone Coupling

Under our previously optimized conditions the coupling of model ketone **50** and enyne **8** went in modest yield to give the dienol **51**, (as a mixture of all four possible diastereomers) when the enyne was added over one, three, and five hours with Cyp_3P as the ligand (Table 9, entries 1-3). Other ligands were investigated as well but failed to give product (entries 4 and 5). While the yield was modest at best for the coupling of 1,3-enyne **8** and ketone **50**, we were pleased to see that the coupling was at least

viable for the model ketone. Also, we did not observe coupling between enyne **8** and the butyl ketone moiety. Further attempts at optimization were met with difficulty, and indeed a yield of 35% was the best yield obtained for the coupling.

Table 9. Enyne and Ketone Coupling Investigations.



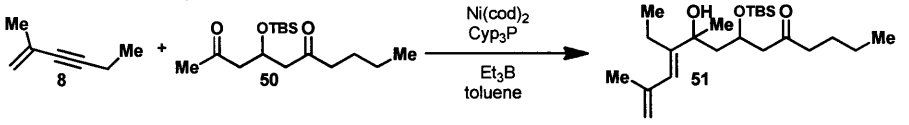


entry[a]	ligand	enyne addition time (h)[b]	yield (%)[c]
1	Cyp_3P	3	35
2	Cyp_3P	1	35
3	Cyp_3P	5	30
4	Bu_3P	3	0
5	A	3	0

[a] Reactions were performed using 0.131 mmol of **50** with 250 mol% of Enyne **8** added. [b] Enyne **8** added as a 6M solution in toluene, and the reactions were performed for an additional 2 hours after the enyne was completely added. [c] Yields are approximate, as **51** was not isolated cleanly.

Doubling the catalyst loading gave better overall conversion for the coupling of enyne **8** and ketone **50**, but the yield of product **51** was approximately the same (Table 10, entry 2). On smaller scale; however, the reaction did not work very well at all. Even doubling the catalyst loading and amount of Et_3B gave less than 5% yield (entry 5).

Table 10. Further Enyne and Hindered Ketone Coupling Optimization.

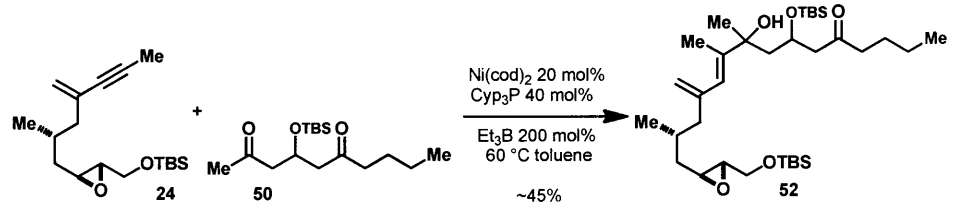


entry[a]	**50** (mmol)	$Ni(cod)_2$:Cyp_3P:Et_3B (mol%)	temperature (°C)	yield (%)[b]
1	0.131	20:40:200	65	35
2	0.131	40:80:200	65	35
3	0.066	20:40:200	65	0
4	0.066	20:40:200	55	<5
5	0.066	40:80:400	55	<5

[a] Reactions were performed using 250 mol% of Enyne **8** added as a 6M solution in toluene, and the reactions were performed for an additional 2 hours. [b] Yields are approximate, as **51** was not isolated cleanly.

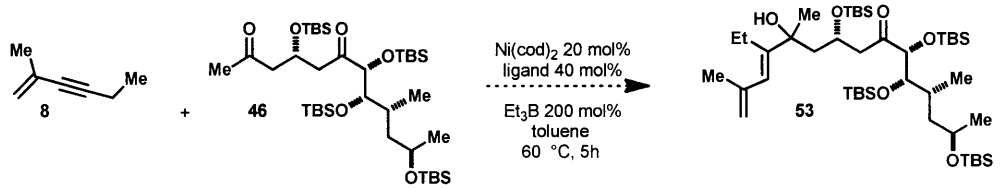
Given that the coupling between enyne **8** and ketone **50** did not work on 0.066 mmol scale, but did work on 0.131 mmol scale, gave us reason to believe that the coupling between enyne **24** and ketone **46** failed because it was carried out on a 0.064 mmol scale or smaller (Scheme 18). To test this hypothesis the coupling of 1,3-enyne fragment **24** and ketone **50** was investigated (Scheme 20). To our delight when the reaction was performed on a scale of 0.131 mmol the reaction did work in adequate yield to give the dienol **52** as a mixture of diastereomers.

Scheme 20



With these results in hand, the coupling of 1,3-enyne **24** and methyl ketone **46** was once again investigated, but this time on scales of 0.131 or larger (Scheme 18). However, to our dismay the coupling reaction still failed to give the desired product. We investigated several modifications of the reaction conditions, but found the coupling was not viable. The ketone **46** appeared to be particularly hindered toward the Ni-catalyzed coupling reaction, and the ketone also would not undergo coupling with enyne **8** (Scheme 21).

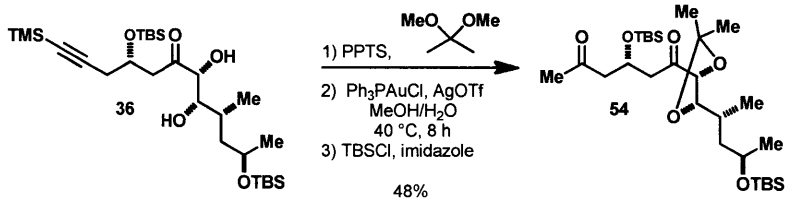
Scheme 21



L. Synthesis of New Ketone Fragment

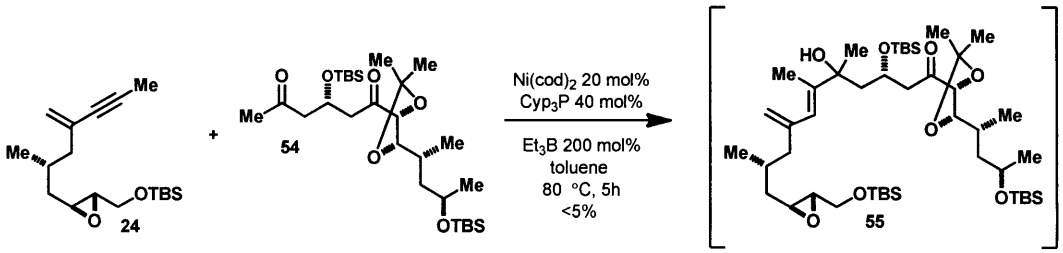
Due to the fact that ketone **46** was particularly unreactive to our ketone coupling conditions, we set out to prepare a less sterically hindered ketone. This would be realized by preparing ketone **54** which would have the *cis*-diol protected as the acetonide instead of *bis*-TBS protected diol. The diol **36** was protected as the acetonide and subsequent alkyne hydration and TBS protection gave the desired ketone **54** (Scheme 22). The acetonide group held up well to the alkyne hydration; however, either one or both of the TBS groups were cleaved and hence the crude product was subjected to standard TBS protection conditions.

Scheme 22



Attempts at coupling the newly prepared ketone **54** and enyne **24** were once again largely unsuccessful. If the reaction was heated to 80 °C we did observe a reductive coupling product which has tentatively been assigned as the desired **55** (Scheme 23). However, the compound was not isolated cleanly and could not be fully characterized.

Scheme 23



M. Ni-Catalyzed Cyclization Strategy Toward Amphidinolide B_1

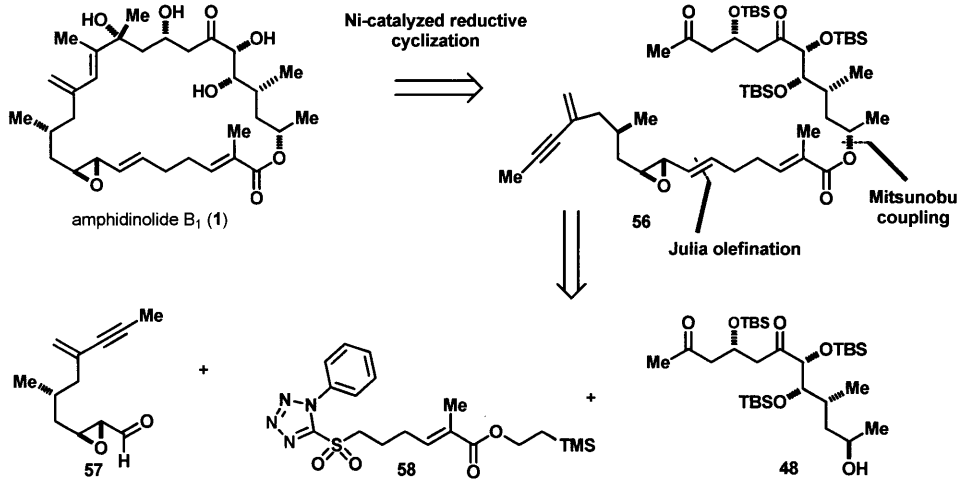
Due to the difficulties associated with the intermolecular Ni-catalyzed coupling of the enyne **24** and ketone **54** we decided that a different approach was needed to complete the synthesis of amphidinolide B_1. We decided to keep the same basic strategy toward the natural product. Our new strategy would entail a Mitsunobu coupling to join the fragments and Ni-catalyzed reductive cyclization to close the ring (Figure 11). This would be the opposite of the previous strategy, which would have joined the fragments via Ni-catalyzed reductive coupling and followed by cyclization through Mitsunobu reaction. Our new strategy also has several advantages over our previous strategy. First it would require fewer steps. The ketone **56** can be formed from the enyne **57**, ester **58**, and ketone **48** through a Kocienski-modified Julia olefination[29, 30] and Mitsunobu coupling.[10] The enyne **57**, and ketone **48** could be easily accessed in one step from intermediates from our previous strategy. In addition, the ester **58** is a known compound that can be easily prepared.[7o] Another technical advantage of the Ni-catalyzed cyclization strategy is that the enyne would not need to be added dropwise, and thus the reaction could in principle be performed on small scale more easily. Lastly, the highly unstable diene that is formed during the coupling would not have to survive many transformations, with removal of the three TBS protecting groups as the only remaining step.

---

[29] For original report see: Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, *14*, 4833.

[30] For Kocienski modified version see: Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.

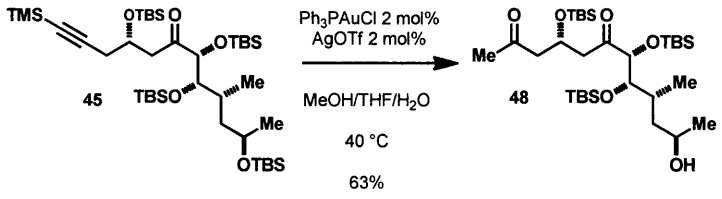
Figure 11. Modified Retrosynthetic Analysis of Amphidinolide B_1.



N. Second Generation Ketone Fragment Synthesis

Previously when attempting to synthesize ketone **46**, we had inadvertently prepared ketone **48**. However, the synthesis had not yet been optimized for yield, and to optimize the yield of the synthesis of ketone **48** from alkyne **45,** a few reactions were performed. Use of either MeCN or MeOH as solvent gave ketone **48** as the major product after five hours at 35 °C; however, with MeCN, a significant amount other products were formed. In THF the reaction proceeded very slowly. In MeOH / THF at 40 °C the reaction was complete within four hours and gave ketone **48** in 63% yield (Scheme 24).

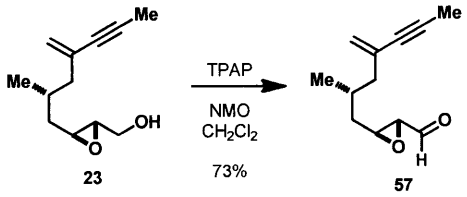
Scheme 24



O. Second Generation 1,3-Eyne Fragment Synthesis

The 1,3-enyne **57** was prepared in one step from the 1,3-enyne **23**, an intermediate from our previous strategy, via Ley oxidation of the alcohol to the corresponding aldehyde (Scheme 25).[26]

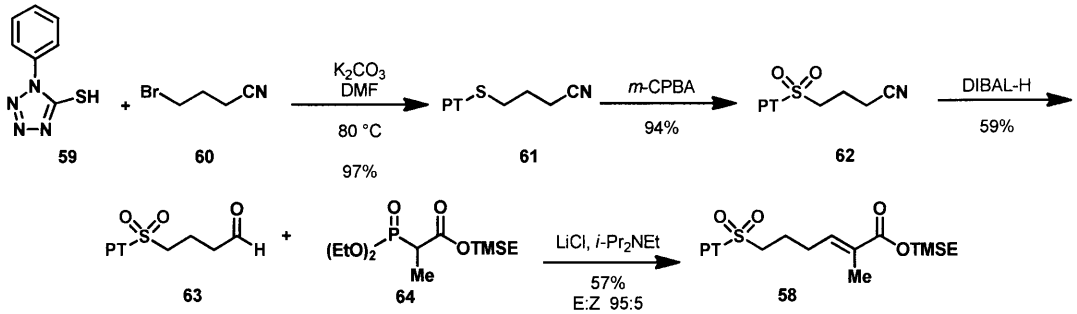
Scheme 25



P. Synthesis of Ester Fragment

The previously reported ester **58** was prepared according to the literature (Scheme 26).[7o] The 1-phenyl-1*H*-tetrazole-5-thiol (**59**) was first alkylated with bromide **60** to give sulfide **61**, which in turn was oxidized to sulfone **62** with *m*-CPBA. Reduction of the nitrile group to the aldehyde **63**, followed by a Horner-Wadsworth-Emmons olefination with phosphonate 64,[27] gave the ester fragment **58** in 31% yield over 4 steps. The trimethylethylsilyl (TMSE) ester was chosen because the group could be cleaved using TBAF instead of harsh basic conditions that would have been problematic for the labile alkenyl epoxide.

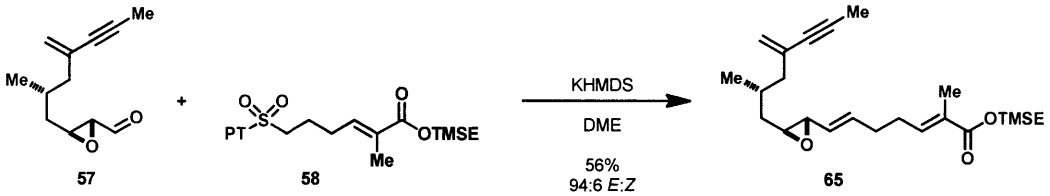
Scheme 26



Q. Synthesis of Ni-Catalyzed Cyclization Precursor

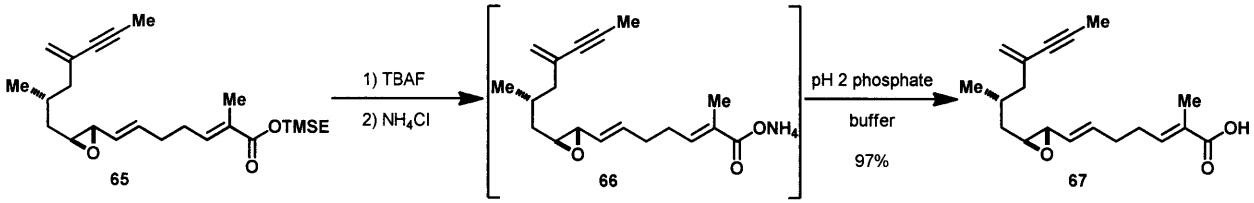
The Kocienski-modified Julia olefination worked well in 56% yield to give the 1,3-enyne **65** (Scheme 27). The fragment coupling was highly selective for the desired alkenyl epoxide, and gave a 94:6 *E*:*Z* ratio of isomers.

Scheme 27



The trimethylethylsilyl group could be deprotected with TBAF (Scheme 28). After deprotection acidification of the corresponding carboxylate salt was met with difficulties due to the labile alkenyl epoxide moiety present. Dilute HCl caused decomposition under all conditions investigated. When AcOH was used the acid was slow to form and decomposition eventually resulted. Finally quenching with NH_4Cl, diluting with THF, and treating with a pH 2 phosphate buffer solution, produced the desired 1,3-enyne fragment **67**, which was now set up for Mitsunobu coupling.

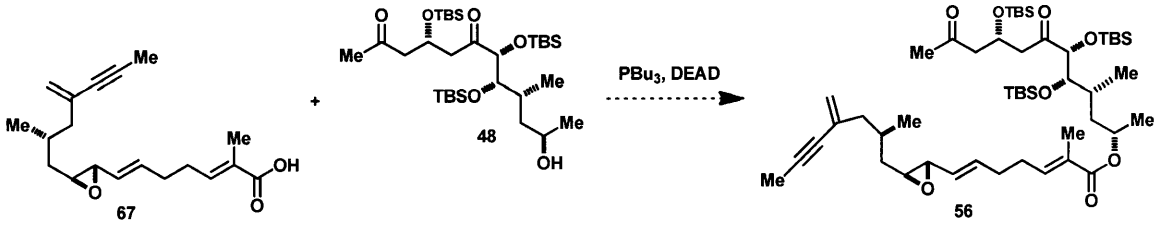
Scheme 28



Unfortunately, the Mitsunobu reaction did not work with acid **67** and alcohol **48** under various reaction conditions (Scheme 29). Both DEAD and DIAD as well as PPh_3 and PBu_3 were used as reagents for the coupling, but to no avail. The reaction was also

performed at several different temperatures, but in all cases the desired ester **56** was not formed.

Scheme 29

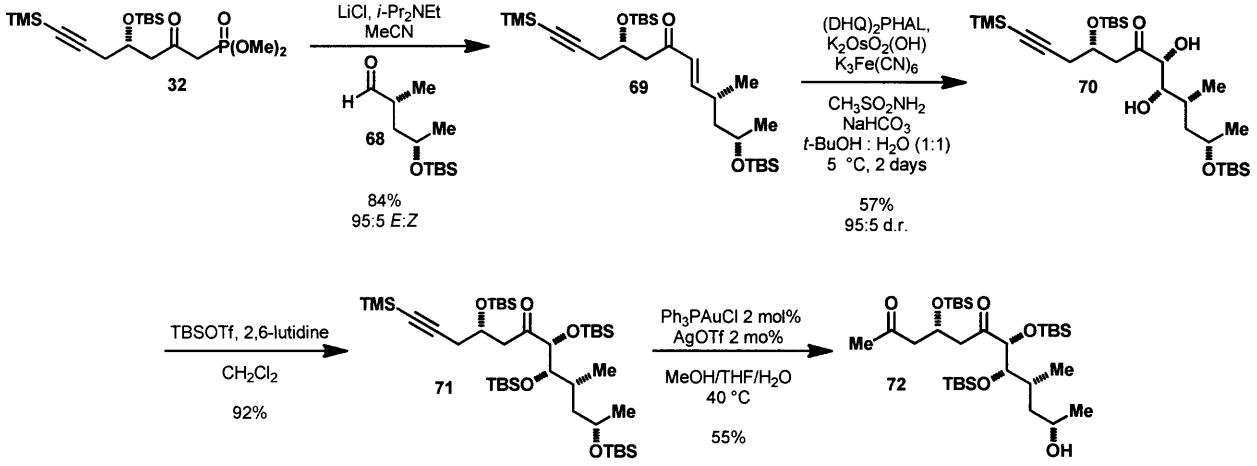


R. Yamaguchi Coupling Approach

Given that the investigations into the Mitsunobu coupling were not met with success we decided to investigate a Yamaguchi coupling approach.[31] Since the Mitsunobu reaction proceeds with inversion of stereochemistry and the Yamaguchi reaction does not, we needed to invert the stereocenter of the alcohol moiety of ketone **48**. To accomplish this we decided to synthesize the known aldehyde **68** in a similar manner to that shown in Scheme 10. Then as before HWE olefination with ketophosphonate **32** gave the enone **69** in good yield and selectivity (Scheme 30).[27] The Sharpless asymmetric dihydroxylation[19, 28] gave **70**, which was followed by *bis*-TBS protection to give alkyne **71**. Once again the alcohol **72** could be prepared using catalytic Ph_3AuCl and AgOTf.

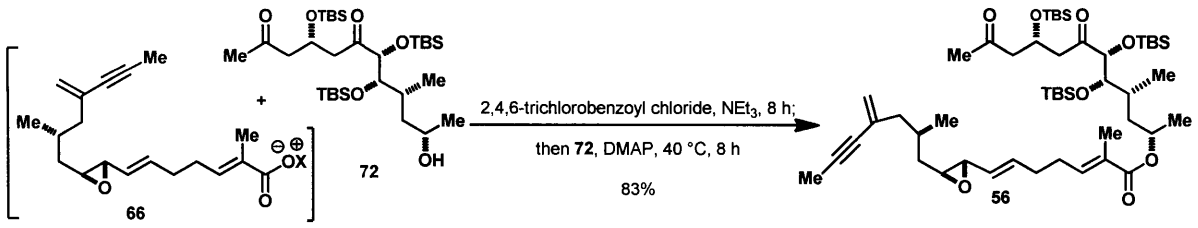
[31] (a) A Yamaguchi coupling has since been shown to be successful toward the synthesis of B-type amphidinolide natural products. See ref: 2a. (b) Inanaga, J. ; Hirata, K.; Saeki, H. ; Katsuki, T. ; Yamaguchi, M. A. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

Scheme 30



We were pleased to see that the Yamaguchi coupling between carboxylate salt **66** and alcohol **72** gave the desired ketone **56** in 83% yield (Scheme 31). It is also noteworthy that **56** contains all of the carbon atoms found in amphidinolide B_1. With **56** in hand, all that remained for the synthesis of amphidinolide B_1 was Ni-catalyzed cyclization and removal of the three TBS protecting groups.

Scheme 31

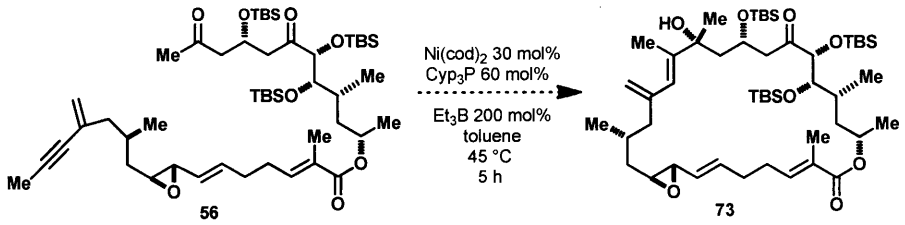


S. Investigations of the Ni-Catalyzed Cyclization

Multiple attempts at reductive cyclization of **56** have as of yet not afforded the desired compound **73** (Scheme 32). For example the reaction was carried out using 30 mol% $Ni(cod)_2$, 60 mol% Cyp_3P, and 200 mol% Et_3B at 45 °C as a 0.08 M solution in toluene. While it is not clear what products had formed; the alkenyl epoxide was not present in any of the products isolated. The cyclization reaction was also carried out at lower and

higher temperatures; though unfortunately, these attempts as well as many others with minor modifications were not successful. It is noteworthy that the α,β-unsaturated ester moiety was present in the uncharacterized compounds that were isolated. Previously these functional groups were shown to undergo coupling under similar conditions.[32]

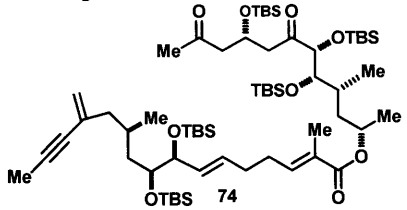
Scheme 32



T. Second Generation Ni-Catalyzed Cyclization Approach

Due to the failed attempts at reductive cyclization of enyne **56**, our strategy was modified to target enyne **74** (Figure 12). It was our aim that enyne **74** would more readily cyclize under the Ni-catalyzed conditions, and be of greater stability because it lacked the labile alkenyl epoxide present in enyne **56**. The cyclization product could then be converted to amphidinolide B_1 after deprotection, and use of the Sharpless method for conversion of 1,2-diols into epoxides.[33]

Figure 12. New Reductive Cyclization Substrate.



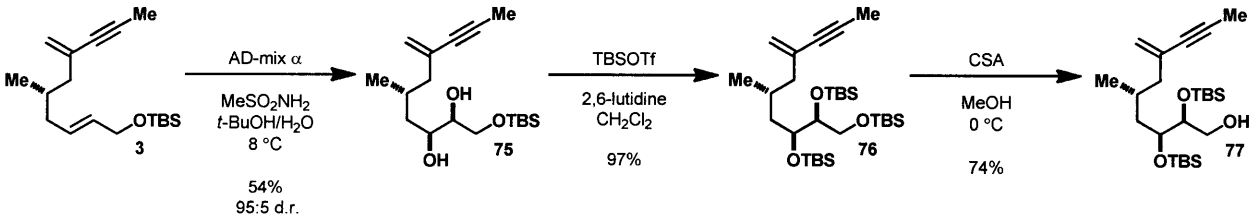
[32] For a review see: Montgomery, J. *Angew. Chem. Int. Ed.* **2004**, *43*, 3890.

[33] Kolb H. C.; Sharpless K. B. *Tetrahedron*, **1992**, *48*, 10515.

U. Synthesis of a Protected Diol for Ni-Catalyzed Cyclization

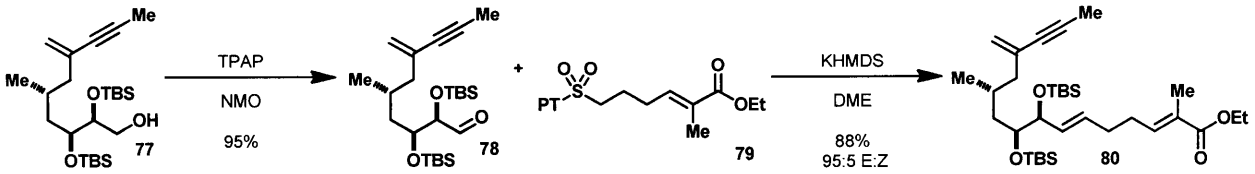
Synthesis of the Ni-catalyzed cyclization precursor **74** commences with selective Sharpless asymmetric dihydroxylation of allylic TBS ether **3** (Scheme 33).[28] When the reaction was carried out at 0 °C, it was near completion after 24 hours and gave diol **75** in 49% yield, with 29% of recovered enyne **3**. Warming the reaction to 8 °C gave a yield of 54% for diol **75** with a d.r. of 95:5. Protection of the diol using TBSOTf and 2,6-lutidine yielded enyne **76**. Selective deprotection of the primary TBS ether was accomplished using CSA in MeOH to give the alcohol **77** in good yield, even though secondary TBS ethers were cleaved to some degree. Nevertheless, these byproducts could be subsequently protected again to give enyne **76**, and resubjected to the CSA in MeOH reaction conditions.

Scheme 33



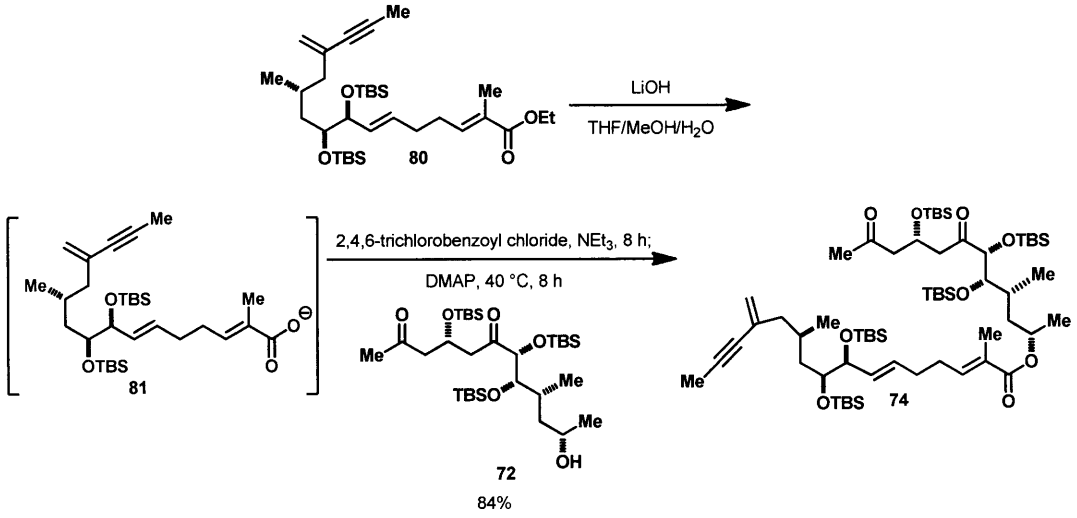
The alcohol **77** was transformed to the aldehyde **78** via Ley oxidation in excellent yield (Scheme 34).[26] The ester **79** was prepared using the same strategy as previously described in Scheme 26. However, for this strategy the ethyl ester was desired instead of the trimethylethylsilyl ester because we required the carboxylate salt, and because removal of the TMSE group would be difficult in the presence of the TBS groups. The Kocienski-modified Julia olefination went with excellent selectivity and yield to give the desired enyne **80**.

Scheme 34



The successful saponification of ethyl ester **80** was realized when using excess LiOH in a solvent mixture of THF, MeOH, and H_2O (Scheme 35). The carboxylate salt **81** subsequently underwent Yamaguchi coupling with alcohol **72** to give the reductive cyclization precursor **74**.

Scheme 35

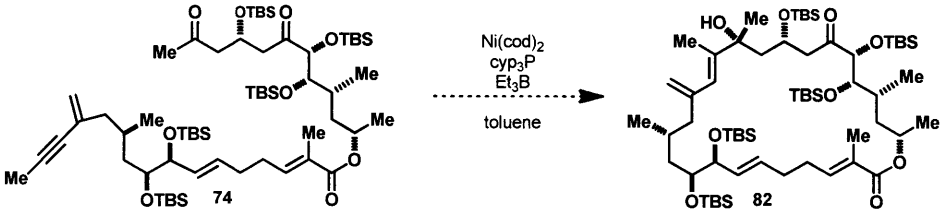


V. Investigations of the Second Generation Ni-Catalyzed Cyclization

Our investigations into the Ni-catalyzed cyclization of **74** to dienol **82** proved to be unsuccessful (Scheme 36). When carried out under dilute conditions (<0.02 M) and using 40 mol% $Ni(cod)_2$ and 80 mol% Cyp_3P most of the enyne **74** was recovered. When performing the cyclization reaction under more concentrated conditions in the presence of excess Et_3B, the enyne **74** underwent decomposition to what appeared to

be a single product. When the reaction was carried out under even more concentrated conditions the decomposition product was once again primarily isolated. The primary decomposition product isolated in all cases is believed to be diketone **83**[34], shown as the product in Table 11, which resulted from a surprising fragmentation process.

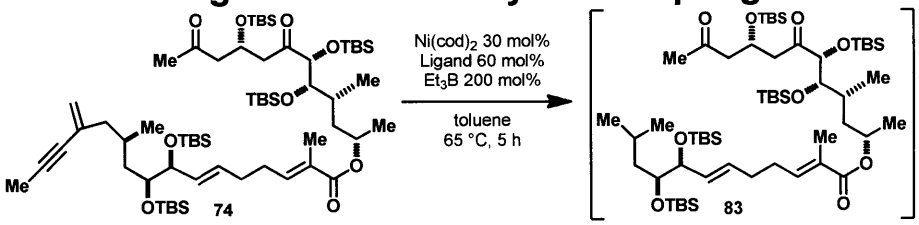
Scheme 36



It should be noted that the production of diketone **83** seemed to be dependent on the ligand used for the Ni-catalyzed reaction (Table 11). If Cyp_3P was chosen as the ligand none of the enyne **74** was recovered; however, the fragmentation product **83** was isolated in 54% yield (entry 2). When NMDPP, (*o*-anisyl)$_3$P, or Me_2PPh were used as the ligand some of the diketone **83** was isolated while a portion of the enyne **74** was recovered (entries 4-6). Surprisingly, if $FcPPh_2$ or Bu_3P were chosen for the ligand none of the diketone **83** was isolated, and the enyne **74** was isolated almost quantitatively even at 65 °C (entries 1 and 3). While there does not seem to be any obvious correlation between ligands and product, it is likely not a coincidence that Cyp_3P (which is generally the best ligand for Ni-catalyzed reductive couplings of enynes and carbonyl compounds) gives the diketone product in the highest yield. The pathway for the synthesis of **83** is currently unknown.

[34] Diketone **83** has been characterized by ^{1}H NMR and HRMS.

Table 11. Effect of Ligand on Ni-Catalyzed Coupling Product.



entry	ligand	recovered **74** (%)	**83** (%)
1	$FcPPh_2$	80	0
2	Cyp_3P	0	54
3	Bu_3P	90	0
4	NMDPP	30	35
5	$(o\text{-anisyl})_3P$	39	37
6	Me_2PPh	30	30

Conclusion

We had envisioned preparing amphidinolide B_1 via a convergent fragment coupling of a ketone and enyne, and thus developed a method for Ni-catalyzed reductive coupling of enynes and dialkyl ketones. However, application of this method to the synthesis of amphidinolide B_1 proved unsuccessful under a variety of conditions. We also looked into different ketone coupling partners to no avail.

We investigated an alternative Ni-catalyzed cyclization approach to amphidinolide B_1 that would have allowed for a more convergent and simpler synthesis. While we were able to prepare the cyclization substrate, which would have required only two synthetic steps thereafter to prepare amphidinolide B_1, the Ni-catalyzed cyclization suffered from undesired side reactions.

Nevertheless, during the course of these studies we learned a great deal about Ni-catalyzed enyne and ketone reductive couplings. We also found that internal epoxides were tolerated under the enyne and ketone reductive coupling conditions. Also, we found that the α,β-unsaturated ester moiety present in the B-type amphidinolides could

be tolerated under the reductive coupling conditions. What we learned from our studies toward amphidinolide B_1 will subsequently put to use in our work toward assembling amphidinolides from the G-series and H-series.

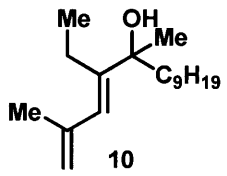
Experimental Section

General Information. All non-aqueous reactions were performed under an inert atmosphere of dry nitrogen in flame-dried glassware, sealed with a rubber septum. Argon was passed over Drierite® ($CaSO_4$) and supplied through a glass manifold. Dichloromethane, diethyl ether, THF, toluene, and triethylamine were purified by distillation and dried by passage over activated alumina under an argon atmosphere (H_2O content < 30 ppm, *Karl-Fischer* titration).[35] Ethyl acetate was pre-dried over anhydrous $MgSO_4$, distilled from CaH_2, degassed by the freeze-pump-thaw procedure and stored over activated 4 Å molecular sieve. Diisopropylamine was distilled from CaH_2 and stored over KOH. Ti(O*i*-Pr)$_4$ was distilled from CaH_2. Magnesium bromide was dried under high vacuum at 150 °C for 2 days. Ozonolysis was performed using a CLEARWATER TECHNOLOGIES CD1500 Ozone Generator supported by a pressurized oxygen gas source. Microwave reactions were performed using a BIOTAGE Initiator Eight Microwave Synthesizer (400W maximum power). Reactions were stirred magnetically unless indicated otherwise and monitored by thin layer chromatography (TLC). Analytical thin layer chromatography was performed using MERCK Silica Gel F^{254} glass plates and visualized by ultraviolet light. Additionally, TLC

[35] Pangborn, A. B.; Giradello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

plates were stained with ethanolic phosphomolybdic acid (PMA), aqueous potassium permanganate ($KMnO_4$) or cerium molybdate (CAM). Chromatographic purification was performed as flash chromatography on SILICYCLE SiliaFlash® F60 (230-400 mesh) silica gel using a forced flow of eluant at 0.3 - 0.5 bar over-pressure. Concentration under reduced pressure was performed by rotator evaporation at 40 °C at the appropriate pressure. Purified compounds were dried further under high vacuum (0.01 to 0.25 Torr). Yields refer to the isolated compound unless stated otherwise. ^1H and ^{13}C NMR spectra were recorded in deuterochloroform ($CDCl_3$), unless otherwise noted, on a Bruker Avance 400 MHz, a Varian Inova 500 MHz or a Bruker Avance 600 MHz spectrometer. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent and br = broad), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.2 ppm) on the δ scale. Infrared (IR) spectra were recorded on a Perkin-Elmer 2000 FT-IR. High Resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by Dr. Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 589 nm. Data are reported as follows: $[\alpha]_{\lambda}^{temp}$, concentration (*c* g/100 mL), and solvent. All chemicals were purchased from ACROS, ALDRICH, FLUKA, MERCK, STREM or LANCASTER and were used as supplied by the commercial manufacturer without any further purification unless specifically noted. Deuterated solvents were purchased from

CAMBRIDGE ISOTOPE LABORATORIES, Inc., Andover MA, USA and stored in a sealed secondary containment over Drierite® ($CaSO_4$) under absence of light. The Dess-Martin periodinane was prepeared according to the reported procedures in literature and the reports cited therein.[36]

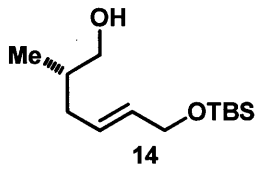


10

(*E*)-4-ethyl-2,5-dimethyltetradeca-1,3-dien-5-ol (10): $Ni(cod)_2$ (0.07 mmol, 19.3 mg) and Cyp_3P (0.14 mmol, 39.2 µL) were placed in a 8 mL vial inside a glove box. After the flask was removed from the glove box and placed under an argon atmosphere, triethylborane (1.75 mmol, 253 µL) was added at ambient temperature. The mixture was then stirred for 5 min. before the addition of ketone **9** (0.350 mmol, 72 µL) followed by placing in a 60 °C oil bath. After 1 min, dropwise addition of the enyne **8** (0.700 mmol, 88 µL) was begun and continued for 3 h at 60 °C. After all of the enyne was added the resultant reaction mixture was stirred at 60 °C for 2 h. After that time the mixture was diluted with EtOAc and the septum seal was removed, and the reaction allowed to air-oxidize for 1 h. The solution was concentrated in vacuo and purified the residue by flash column chromatography (5% EtOAc/hexane) to give the title compound

[36] For the synthesis of IBX see: Frigerio, M.; Santagostino, M.; Sputore, S.; *J. Org. Chem.* **1999**, *64*, 4537. For the acetylation of IBX to DMP see: Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(**10**, >95:5 regio, >95:5 *Z/E*) as a clear oil (93 mg, 80% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.99 (s, 1H); 4.98 (s, 1H), 4.90 (s, *1*H), 2.34-2.18 (*m*, 2H), 1.89 (s, 3H), 1.65-1.57 (m, 2H), 1.40 (s, 1H), 1.28 (s, 3H), 1.27-1.21 (m, 14H), 1.09 (t, J = 6.5 Hz, 3H), 0.90 (t, *J* = 7.2, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.2, 142.6, 125.8, 113.7, 76.5, 41.5, 32.1, 30.2, 29.8, 29.5, 28.7, 28.6, 24.1, 24.0, 22.9, 21.3, 15.7, 14.3; IR (film) 3447, 2927, 2854, 1684, 1576, 1457, 1374, 892, 668 cm^{-1}; HRMS ESI (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{34}O$, 267.2682; found 267.2695.

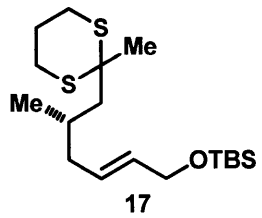


14

(2*S*,4*E*)-6-(*tert*-Butyldimethylsilanyloxy)-2-methylhex-4-en-1-ol (14). The oxazolidinone **13** (142 mmol, 26.4 g) was dissolved in THF (441 mL) and cooled to -78 °C. To the stirring solution was added LHMDS (1.0 M in THF, 150 mmol, 150 mL) dropwise slowly. The reaction was subsequently stirred for 30 min. at -78 °C. A solution of iodide **12** (190 mmol, 60 g) in THF (87 mL) was added dropwise and stirred for 30 min. at -78 °C for 30 min., 0 °C for 15 min., and r.t. for 15 min. The solution was then quenched with saturated aq. NH_4Cl soln (140 mL). The solution was diluted with Et_2O (300 mL) and H_2O (185 mL), partitioned the phases and then extracted the aqueous layer with Et_2O (2 x 200 mL). The organic layers were combined and dried with $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by FCC

(20% EtOAc/hexanes) to give the oxazolidinone as a yellow oil (48.8 g, 93%). $[\alpha]_D$ –18.3 (*c* = 6.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.63-5.58 (m, 2H); 4.46 (ddd, *J* = 8.5, 3.0, 1.0 Hz, 1H), 4.27 (t, *J* = 9.0 Hz, 2H), 4.20 (dd, *J* = 9.0, 3.0 Hz, 1H), 4.11 (br d, *J* = 3.0 Hz, 2H), 3.85 (*app.* sextet, *J* = 7.0 Hz, 1H), 2.53-2.46 (m, 1H), 2.36-2.27 (m, 1H), 2.23-2.15 (m, 1H), 1.14 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 5.5 Hz, 3H), 0.90 (s, 9H), 0.87 (d, *J* = 7.0), 0.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 154.4, 132.8, 127.8, 64.3, 63.8, 59.1, 38.2, 37.3, 29.1, 26.7, 18.7, 16.9, 15.4, –4.5; IR (film) 2959, 2931, 2857, 1783, 1702, 1463, 1387, 1301, 1238, 1205, 1120, 1056, 967, 837, 776 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{19}H_{35}NO_4SiNa$, 392.2228; found 392.2226. The alkylated oxazolidinone (139 mmol, 51.5 g) was dissolved in Et_2O (518 mL) and cooled to 0 °C. $LiAlH_4$ (418 mmol, 15.5 g) was added slowly in portions. The solution was stirred at cold temperature for 1 h and quenched by pouring the reaction mixture into H_2O (750 mL). The solution was diluted with Et_2O (1 L) and saturated aq. Rochelle's salt soln (750 mL) and stirred very vigorously for 12 h. The phases were separated and extracted the aqueous layer with EtOAc (2 x 500 mL). Dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (20% EtOAc/hexanes) to give the 1° alcohol **14** as a colorless oil (33.1 g, 97% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 5.70-5.55 (m, 2H), 4.13 (d, *J* = 7.0 Hz, 2H), 3.56-3.42 (m, 2 H), 2.15 (dt, *J* = 14.7, 7.5 Hz, 1H), 1.93 (dt, *J* = 14.0, 6.5 Hz, 1H), 1.73 (sextet, *J* = 6.0 Hz, 1H), 1.36 (t, *J* = 5.3 Hz, 1H), 0.93 (d, *J* = 7.3 Hz, 3H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.2, 129.3, 68.2, 64.1, 36.4, 36.1, 26.2, 18.7, 16.7, –4.9; IR (film) 3356, 2956, 2930, 2858, 1472, 1378, 1255, 1100, 1053, 971, 837, 776 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{13}H_{28}O_2SiNa$, 267.1751; found 267.1747. $[\alpha]_D$

+2.27 (*c* 8.8, $CHCl_3$).[37]



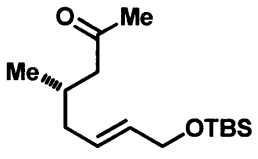
17

(2*S*,4*E*)-6-(*tert*-Butyldimethylsilanyloxy)-2-methyl-1-(2-methyl-[1,3]dithian-2-yl)hex-4-ene (17). Alcohol **14** (110 mmol, 27 g) was taken up in Et_2O:MeCN (3:1, 644 mL) and to the stirring solution at r.t. were added imidazole (248 mmol, 16.8 g), triphenylphosphine (165 mmol, 43 g), and iodine (165 mmol, 42 g) sequentially. The resulting yellow reaction mixture was stirred 1.5 h and quenched with H_2O (200 mL). At that point, the solution went clear. The aqueous layer was extracted with Et_2O (3 x 150 mL). Dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash column chromatography (2% EtOAc/hexanes) to give the iodide **15** as a clear oil (37 g, 95%). 2-Methyl-1,3-dithiane (**16**) (0.86 mmol, 103 µL) was dissolved in THF (4 mL) and cooled to –78 °C and *n*-butyl lithium (2.5 M in hexanes, 0.86 mmol, 0.34 mL) was added. The solution was warmed to 0 °C and stirred for 30 min then re-cooled to –78 °C and added the iodide (0.77 mmol, 275 mg) in a solution of THF (1 mL). The solution was allowed to gradually warm to r.t. while stirring 12 h. The solution was

---

[37] Adapted from . Ndubaku, C. O. "*Diastereoselective Nickel-Catalyzed Reductive Coupling of Alkynes and Aldehydes and Application Toward the B-Type Amphidinolides*", Ph. D. Thesis, Massachusetts Institute of Technology, **2005**.

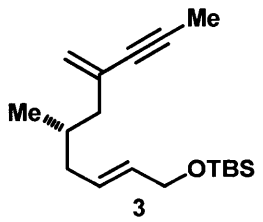
quenched with saturated aq. NH_4Cl soln (5 mL) and diluted with Et_2O (20 mL) and H_2O (15 mL). The phases were separated and the aqueous layer was extracted with Et_2O (2 x 15 mL) and dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by gradient silica gel chromatography (1% to 3% EtOAc/hexanes) to give the title compound **17** as a colorless oil (181 mg, 65% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 5.67-5.53 (m, 2H), 4.13 (d, *J* = 4.0 Hz, 2H), 2.87-2.81 (m, 4H), 2.17-2.09 (m, 1H), 2.06-1.92 (m, 4H), 1.88-1.80 (m, 1H), 1.72 (dd, *J* = 14.5, 6.0 Hz, 1H), 1.65 (s, 3H), 1.03 (d, *J* = 6.5 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.5, 129.5, 64.2, 49.8, 48.0, 41.8, 31.0, 30.1, 28.6, 26.9, 26.9, 26.2, 25.5, 22.5, 18.7, –4.9; IR (film) 2954, 2929, 2856, 1472, 1462, 1423, 1255, 1132, 1097, 1054, 1006, 972, 908, 837, 776 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{36}OS_2SiNa$, 383.1869; found 383.1865. $[\alpha]_D$ +4.2 (*c* 4.8, $CHCl_3$).[37]



18

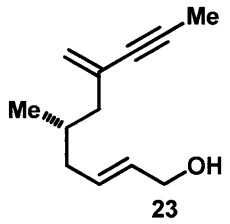
(4*S*,6*E*)-8-(*tert*-Butyldimethylsilanyloxy)-4-methyloct-6-en-2-one (**18**). The iodide **15** (22.1 mmol, 7.82 g) was dissolved in Et_2O (87 mL) and cooled to –78 °C. To the stirring solution was added *t*-BuLi (1.7 M in pentanes, 48.6 mmol, 28.6 mL) dropwise. The solution was stirred for 1.5 h at –78 °C and *N*-methoxy-*N*-methyl-acetamide (66.3

mmol, 9.4 mL) was added. The solution was then warmed to r.t. and stirred for 3 h. The solution was quenched with H_2O (70 mL) and diluted with Et_2O (100 mL). An extraction with Et_2O (2 x 150 mL) was performed and then dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (5% EtOAc/hexanes) to give **18** as a colorless oil (3.88 g, 65% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 5.63-5.49 (m, 2H), 4.12 (d, *J* = 4.5 Hz, 2H), 2.44 (dd, *J* = 16.0, 5.5 Hz, 1H), 2.20 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.14-2.05 (m, 1H), 2.12 (s, 3H), 2.03-1.91 (m, 2H), 0.93-0.88 (m, 15H,), 0.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.1, 131.7, 128.9, 64.0, 50.6, 39.7, 30.7, 29.5, 26.2, 24.5, 20.0, 18.7, –4.9; IR (film) 2956, 2930, 2857, 1717, 1463, 1362, 1255, 1099, 1054, 972, 837, 776 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{15}H_{30}O_2SiNa$, 293.1907; found 293.1926. $[\alpha]_D$ –6.0 (*c* 11.6, $CHCl_3$).[37]



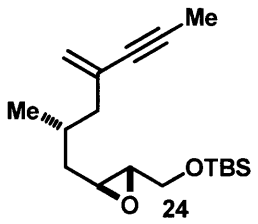
(6*S*,8*E*)-10-(*tert*-Butyldimethylsilanyloxy)-6-methyl-4-methylene-8-decen-2-yne (3). A solution of the ketone **18** (24.4 mmol, 6.59 g) in THF (79 mL) was cooled to –78 °C. To the stirring solution was added LHMDS (1.0 M in THF, 31.8 mmol, 31.8 mL) dropwise. The solution was stirred at –78 °C for 1 h and *N*-(5-chloro-2-pyridyl) triflimide (27.3 mmol, 10.73 g) was added dissolved in THF (24 mL). The resultant reaction

mixture was stirred for 0.5 h at –78 °C and warmed to 0 °C and continued stirring for another 0.5 h. The mixture was partitioned between Et_2O (100 mL) and saturated aq. $NaHCO_3$ solution (100 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was then taken up in diisopropylamine (77 mL) and palladium tetrakistriphenylphosphine (2.64 mmol, 3 g) and copper iodide (2.64 mmol, 696 mg) were added. Propyne was subsequently bubbled through the reaction mixture at –78 °C until an amount determined to be in excess was added. The reaction mixture was then stirred at –78 °C for 15 min and r.t. for 1 h. The residue was filtered through a short pad of silica and concentrated in vacuo. The crude residue was purified by flash column chromatography (2% EtOAc/hexanes) to give the enyne **3** as a yellow oil (6.14 g, 86% yield from **18**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68-5.51 (m, 2H), 5.26 (s, 1H), 5.11 (s, 1H), 4.14 (d, J = 4.5 Hz, 2H), 2.18-2.05 (m, 2H), 1.95 (s, 3H), 1.94-1.81 (m, 3H), 0.92 (s, 9H), 0.88 (d, J = 6.0 Hz, 3H), 0.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.0, 129.7, 121.2, 98.9, 64.3, 45.0, 39.3, 31.8, 26.2, 24.5, 24.5, 19.2, 18.7, 4.5, –4.9; IR (film) 2955, 2928, 2857, 1611, 1472, 1463, 1437, 1377, 1361, 1297, 1255, 1122, 1097, 1053, 1006, 971, 894, 836, 814, 776 cm^{-1}; HRMS ESI (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{33}OSi$, 293.2295; found 293.2294. $[\alpha]_D$ –10.7 (*c* = 2.8, $CHCl_3$).[37]



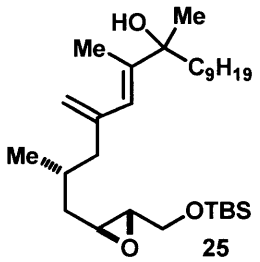
23

2*E*-(5*S*)-5-methyl-7-methylenedec-2-en-8-yn-1-ol (23): To a flame-dried 50 mL round-bottom flask equipped with a magnetic stir bar and set under an argon atmosphere was added enyne **3** (41 mmol, 12 g) in THF (129 mL). The flask was cooled to 0 °C and tetrabutylammonium fluoride (1.0 M in THF, 129 mmol, 129 mL) was added and the resulting solution was stirred 1 h at 0 °C. The solution was quenched by adding H_2O (100 mL), diluting with brine (50 mL) and EtOAc (250 mL). The aqueous layer was extracted with EtOAc (3 x 250 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by flash column chromatography (25% EtOAc/hexane) to give the allylic alcohol (**23**) as a yellow oil (6.5 g, 89% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73-5.65 (m, 2H), 5.26 (s, 1H), 5.13 (s, 1H), 4.10 (d, *J* = 5.5 Hz, 2H), 2.17-2.11 (m, 2H), 1.94 (s, 3H), 1.93-1.82 (m, 2H), 0.84 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.2, 131.7, 131.2, 121.8, 86.2, 80.8, 64.5, 45.4, 39.8, 32.1, 19.7, 4.9; IR (film) 3323, 2955, 2918, 2870, 2229, 1670, 1610, 1456, 1437, 1377, 1297, 1085, 1001, 972, 896, 801 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{12}H_{18}ONa$, 201.1250; found 201.1257. $[\alpha]_D$ –9.7 (*c* 7.2, $CHCl_3$).



***tert*-butyldimethyl(((2*S*,3*S*)-3-((*R*)-2-methyl-4-methylenehept-5-yn-1-yl)oxiran-2-yl)methoxy)silane (24):** To a suspension of flame-dried 4 ÅMS (660 mg) in CH_2Cl_2 (3.7 mL) at -23 °C was added $Ti(O^iPr)_4$ (83 µL, 0.277 mmol), L-(+)-DET (0.76 mL, 0.442 mmol), and TBHP (221 µL, 1.11 mmol) in that order. Diluted with additional CH_2Cl_2 (3.7 mL) and stirred the resulting mixture for 20 min before added allyl alcohol **23** (98.6 mg, 0.553 mmol) dissolved in CH_2Cl_2 (5.5 mL). The reaction mixture was stirred at -23 °C for 16 hours before it was quenched with a solution of $FeSO_4$ (74 mg) and citric acid (22 mg) dissolved in water (1.9 mL). Allowed the quenched reaction mixture to warm to ambient temperature and filtered through a short pad of silica gel eluting with Et_2O. The mixture was concentrated to approximately 100 mL and water (20 mL) was added. The organic phase was separated and the aqueous phase was extracted with Et_2O (3 × 75 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purified the residue by FCC (30% EtOAc/hexanes) and concentrated the product containing fractions *in vacuo*. The residue was re-dissolved in Et_2O (50 mL), washed with water (6 × 10 mL) to remove remaining diethyl tartrate and concentrated in vacuo to afford the title epoxy alcohol **41** as a clear oil (97 mg, 90%). The epoxy alcohol (0.741 mmol, 144 mg) was then taken up in anhydrous *N*,*N*-dimethylformamide (750 µL) and to the stirring solution was added imidazole (1.93 mmol, 131 mg) and TBSCl (0.965 mmol, 146 mg). The reaction mixture was allowed to

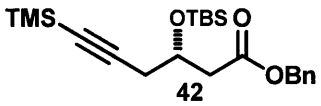
stir at r.t. for 16 h. The solution was then quenched with H_2O (20 mL) and diluted with Et_2O (100 mL), partitioned the phases and then extracted the aqueous layer with Et_2O (2 x 75 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified the crude residue by FCC (2% EtOAc/hexanes) to give compound **7** as a clear oil (185 mg, 81%). ^1H NMR (600 MHz, $CDCl_3$) δ 5.28 (s, 1H), 5.14 (s, 1H), 3.80-3.70 (m, 2H), 2.92-2.81 (m, 2H), 2.19 (dd, J = 12.0, 6.0 Hz, 1H), 2.08-1.97 (m, 2H), 1.96 (s, 3H), 1.74-1.68 (m, 1H), 1.34-1.27 (m, 1H), 0.95 (d, *J* = 7.5 Hz, 3H), 0.90 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 131.8, 121.3, 85.9, 80.2, 63.9, 59.3, 55.5 45.5, 38.6, 29.7, 26.2, 19.4, 18.5, 4.4, -5.1, -5.2; IR (film) 3093, 2928, 2857, 2341, 2229, 1653, 1472, 1253, 1108, 1089, 1006, 939, 837, 814 cm^{-1}; HRMS ESI (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{32}O_2Si$, 309.2244; found 309.2253. $[\alpha]_D$ –9.7 (*c* 1.9, $CHCl_3$).



25

(2*R*,*E*)-1-((2*S*,3*S*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)oxiran-2-yl)-2,6,7-trimethyl-4-methylenehexadec-5-en-7-ol (25): $Ni(cod)_2$ (0.026 mmol, 7.2 mg) and Cyp_3P (0.052 mmol, 14 μL) were placed in a 8 mL vial inside a glove box. After the

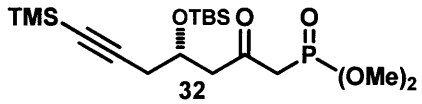
flask was removed from the glove box and placed under an argon atmosphere, triethylborane (0.262 mmol, 38 µL) was added at ambient temperature. The mixture was then stirred for 5 min. before the addition of ketone **9** (0.131 mmol, 27 µL) followed by placing in a 55 °C oil bath. After 1 min., dropwise addition of the enyne **24** (0.262 mmol, 88 µL) dissolved in toluene (60 µL) was begun and continued for 3 h at 55 °C. After all of the enyne was added the resultant reaction mixture was stirred at 60 °C for 2 h. After that time the mixture was diluted with EtOAc and the septum seal was removed and the reaction allowed to air-oxidize for 1 h. The solution was concentrated in vacuo and purified the residue by flash column chromatography (5% EtOAc/hexane) to give the title compound (**25**, as a mixture of diastereomers) as a yellow oil (55 mg, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (s, 1H), 5.05 (s, 1H), 4.84 (s, 1H), 3.80-3.65 (m, 2H), 2.92-2.81 (m, 2H), 2.20-2.18 (m, 1H), 2.1-1.90 (m, 1H), 1.66 (s, 3H), 1.60-1.45 (m, 5H), 1.40 (s, 3H), 1.34-1.20 (m, 16H), 0.95 (d, *J* = 7.5 Hz, 3H), 0.90 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 144.6, 143.0, 124.0, 114.6, 76.9, 76.6, 75.8, 75.3, 63.6, 59.1, 59.0, 55.1, 45.9, 40.4, 38.6, 38.4, 31.8, 30.0, 29.7, 29.6, 29.3, 27.9, 27.8, 25.8, 23.8, 22.6, 19.5, 19.4, 18.3, 14.8, 14.1, -5.3, -5.4.



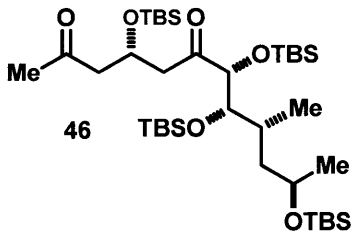
(*S*)-benzyl 3-((*tert*-butyldimethylsilyl)oxy)-6-(trimethylsilyl)hex-5-ynoate (42): A solution of TMS-acetylene (20.8 mmol, 2.94 mL) in toluene (20.1 mL) was cooled to -40

°C. To the solution was added *n*-BuLi (2.4 M in hexanes, 20.8 mmol, 8.7 mL) and stirred at -40 °C for 15 min. The solution was then warmed to 0 °C and Et_2AlCl (1.0 M in hexanes, 20.8 mmol, 20.8 mL) was added and then stirred for 1 h. The enantiomerically enriched epoxide **34** (10.4 mmol, 2.0 g) was dissolved in toluene (6 mL) and added. The solution was stirred for 2 h at 0 °C before quenching with sat. aq. NH_4Cl (6 mL and 1 N HCl (8 mL). The mixture was stirred for 30 min at r.t. and then filtered through celite with EtOAC and washed with brine (50 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by FCC (20% EtOAc/hexanes) to give the alcohol as a clear oil (2.66 g, 88%). A portion of the alcohol (8.6 mmol, 2.5 g) was dissolved in CH_2Cl_2 (47.2 mL), and at 0 °C 2,6-lutidine (25.83 mmol, 3.0 mL) was added all at once followed by the dropwise addition of TBSOTf (12.92 mmol, 3.02 mL) over 5 min. The reaction mixture was stirred at 0 °C for 30 min and subsequently warmed to ambient temperature and stirred for 30 min. The reaction mixture was quenched with water (50 mL) and diluted with CH_2Cl_2 (100 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by FCC (2% EtOAc/hexanes) to give the title benzyl ester **42** as a clear oil (3.45 g, 99%). ^1H NMR (600 MHz, $CDCl_3$) δ 7.41-7.35 (m, 5H), 5.17 (q *J* = 12 Hz, 2H), 4.30 (m, 1H), 2.77 (dd, *J* = 15.0, 4.2 Hz, 1H), 2.62 (dd, *J* = 15.1, 7.8 Hz, 1H), 2.49-2.45 (m, 2H), 0.84 (s, 9H), 0.16 (s, 9H), 0.11 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 136.1, 128.7, 128.5, 128.4, 103.8, 87.5, 68.2, 66.1, 42.3, 29.1, 26.0, 18.2, 0.3, -4.3, -4.8; IR (film) 3035, 2912, 2930, 2178, 1732, 1472, 1252, 799 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$

calcd for $C_{22}H_{36}O_3Si_2$, 405.2276; found 405.2285. $[\alpha]_D$ +19.3 (*c* 8.4, $CHCl_3$).



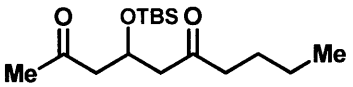
(*S*)-dimethyl (4-((*tert*-butyldimethylsilyl)oxy)-2-oxo-7-(trimethylsilyl)hept-6-yn-1-yl)phosphonate (32). Dimethyl methylphosphonate (15.57 mmol, 1.66 mL) was dissolved in THF (168 mL) and cooled to –78 °C. To the stirring solution was added *n*-BuLi (2.3 M in hexanes, 15.57 mmol, 6.77 mL) dropwise. The solution was stirred for 50 min at –78 °C and a solution of benzyl ester **42** (5.19 mmol, 2.1 g) in THF (66 mL) was added. The solution was then stirred at –78 °C for 1 h. The solution was quenched cold with sat. aq. $NaHCO_3$ (60 mL) and diluted with EtOAc (100 mL). The aqueous layer was extracted with EtOAC (2 x 100 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (20% EtOAc/hexanes to EtOAc gradient) to give **32** as a colorless oil (1.87 mg, 86% yield) ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.19 (quintet, J = 5.9 Hz, 1H), 3.71- 3.68 (m, 6H), 3.07-2.98 (m, 2H), 2.78 (d, *J* =6.0 Hz, 2H), 2.30 (d, J = 6 Hz, 2H), 0.82 (s, 9H), 0.11 (s, 9H), 0.08 (s, 3H), -0.05 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.1, 103.1, 87.4, 67.2, 53.1, 50.9, 43.5, 42.3, 28.9, 25.9, 18.0, 0.3, -4.4, -4.8; IR (film) 3629, 2959, 2361, 2178, 1717, 1473, 1035, 839 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{37}O_5PSi_2$, 421.1990; found 421.1991. $[\alpha]_D$ +30.5 (*c* 8.3, $CHCl_3$).



(4*S*,7*R*,8*S*,9*R*,11*R*)-4,7,8,11-tetrakis((*tert*-butyldimethylsilyl)oxy)-9-methyldodecane-2,6-dione (46). To a vigorously stirred suspension of vacuum-dried LiCl (2.1 mmol, 90 mg) in MeCN (12 mL) was added the ketophosphonate **32** (1.75 mmol, 735 mg). Diisopropylethylamine (2.1 mmol, 366 µL) was added followed by the aldehyde **43** (1.65 mmol, 403 mg). The reaction mixture was then stirred 16 h at ambient temperature. The mixture was quenched with saturated aq. NH_4Cl (1.8 mL) and diluted with Et_2O (25 mL) and H_2O (25 mL). The phases were partitioned and extracted the aqueous with Et_2O (3 x 20 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (5% EtOAc/hexanes) to give the enone **44** (95:5 *E:Z*) as an off-color oil (887 mg, 96%). A portion of the enone **44** was placed into a flask and cooled. In a separate flask was placed AD-mix-α (1.4 mmol, 1.9 g), potassium osmate (0.14 mmol, 47 mg), $(DHQ)_2PHAL$ (0.07 mmol, 55 mg), and $NaHCO_3$ (4.2 mmol, 353 mg) were combined in a 20-mL dram vial equipped with a stir bar and dissolved in *t*-BuOH/H_2O (1:1, 15.4 mL). The mixture was stirred vigorously until all the solids were dissolved then added $MeSO_2NH_2$ (133 mg, 1.4 mmol). This solution was then stirred for 10 min and transferred by a Pasteur pipet into a cooled (5 °C) flask containing the enone **28** (1.4 mmol, 735 mg). The mixture was then stirred 36 h while maintaining the temperature between 0–5 °C in a refrigerator. The mixture was quenched at cold temperature after

this time with saturated aq. Na_2SO_3 (1.18 mL) and stirring was continued for 30 min. Finally, the brown-colored mixture was diluted with EtOAc (15 mL) and H_2O (3 mL). The phases were seperated and extracted the aqueous layer with EtOAc (2 x 10 mL). The combined organic phases were dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (20% EtOAc/hexanes) to give the diol (>95:5 d.r.) as a clear oil (479 mg, 61%). A portion of the diol (0.44 mmol, 248 mg) was dissolved in CH_2Cl_2 (4.4 mL) and cooled to 0 °C. Added 2,6-lutidine (3.55 mmol, 412 µL) all at once and TBSOTf (1.78 mmol, 408 µL) dropwise over 3 min. The solution was stirred 30 min at 0 °C and subsequently warmed to r.t. and stirred 60 min. The solution was diluted with H_2O (10 mL), partitioned the phases, and extracted the aqueous with Et_2O (15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude was purified by flash column chromatography (2% EtOAc/hexanes) to give the alkyne **45** as a clear oil (347 mg, 99%). A portion of the alkyne **45** (0.038 mmol, 30 mg) was dissolved in MeOH (400 µL) and placed in a flask and then added THF (50 µL) and H_2O (50 µL). This was followed by the addition of PPh_3AuCl (0.004 mmol, 2 mg) and AgOTf (0.004, 1 mg). The reaction mixture was heated to 35 °C and stirred for 10 h. The mixture was diluted with H_2O (10 mL) and Et_2O (10 mL), partitioned the phases and extracted the aqueous with Et_2O (2 x 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude material was then dissolved in anhydrous *N*,*N*-dimethylformamide (120 µL) and to the stirring solution was added imidazole (0.618 mmol, 42 mg) and TBSCl (0.309 mmol, 47 mg). The reaction mixture was allowed to stir at r.t. for 16 h. The solution was then

quenched with H_2O (10 mL), diluted with Et_2O (60 mL), partitioned the phases, and then extracted the aqueous layer with Et_2O (2 x 75 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by FCC (2% EtOAc/hexanes) to give compound **7** as a clear oil (18 mg, 64%). ^1H NMR (400 MHz, $CDCl_3$) δ 4.58-4.51 (m, 1H), 4.10 (d, J = 4.9 Hz 1H), 3.80-3.72 (m, 1H), 3.59-3.56 (m, 1H), 2.92-2.87 (m, 1H), 2.78-2.65 (m, 2H), 2.49-2.43 (m, 1H), 2.14 (s, 3H), 1.74-1.68 (m, 1H), 1.48-1.40 (m, 2H), 1.06 (d, *J* = 6.7 Hz, 3H), 0.92 (s, 9H), 0.90 (s, 9H), 0.85 (s, 9H), 0.83 (s, 9H), 0.72 (d, *J* = 6.3 Hz, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.05 (s, 6H), 0.04 (s, 3H) 0.03 (s, 3H), 0.02 (s, 6H), 0.00 (s, 3H); HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{37}H_{80}O_6Si_4Na$, 755.4998; found 732.4973 $[\alpha]_D$ –12.3 (*c* 8.9, $CHCl_3$).

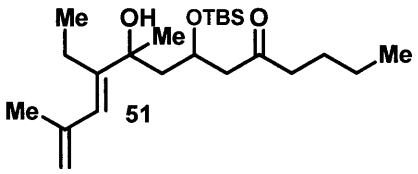


50

4-((tert-butyldimethylsilyl)oxy)decane-2,6-dione (50): *N,O*-dimethylhydroxylamine hydrochloride (32.12 mmol, 3.12 g) was dissolved in CH_2Cl_2 (32.5 mL) and cooled to 0 °C. $AlMe_3$ (2.0 M in hexane, 32.12 mmol, 16.05 mL) was added slowly and stirred at 0 °C for 10 min. The reaction mixture was then warmed to r.t. and stirred for 20 min before adding a solution of ester **(±)-42** in 19.5 mL CH_2Cl_2. The mixture was stirred for 5 h and quenched with H_2O (16 mL) and diluted with Et_2O (100 mL) and saturated aq.

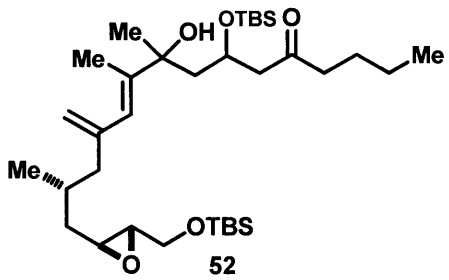
Rochelle's salt soln (75 mL). The mixture was stirred very vigorously for 2 h. The phases were separated and extracted the aqueous with Et_2O (2 x 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (20% EtOAc/hexanes) to give the Weinreb amide as a colorless oil (2.16 g, 76% yield). A portion of the amide (1.10 mmol, 392 mg) was dissolved in Et_2O (1.5 mL) and cooled to 0 °C. *n*-BuLi (2.4 M in hexane, 1.43 mmol, 594 µL) was added slowly. The reaction was then warmed to r.t. and stirred for 1.5 h and quenched with a sol. aq. NH_4Cl (10 mL). Diluted with Et_2O (10 mL). The phases were seperated and extracted the aqueous with Et_2O (2 x 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (5% EtOAc/hexanes) to give the ketone as a colorless oil (274 mg, 70% yield). A portion of the ketone (0.677 mmol, 191 mg) was dissolved in MeOH (1.2 mL) and placed in a flask and then added H_2O (120 µL). This was followed by the addition of PPh_3AuCl (0.034 mmol, 16.7 mg) and AgOTf (0.034, 8.7 mg). The reaction mixture was heated to 35 °C and stirred for 10 h. The mixture was diluted with H_2O (10 mL) and Et_2O (10 mL), partitioned the phases and extracted the aqueous with Et_2O (2 x 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude material was then dissolved in anhydrous *N*,*N*-dimethylformamide (960 µL) and to the stirring solution was added imidazole (4.9 mmol, 336 mg) and TBSCl (2.5 mmol, 376 mg). The reaction mixture was allowed to stir at r.t. for 16 h. The solution was then quenched with H_2O (10 mL), diluted with Et_2O (60 mL), partitioned the phases, and then extracted the aqueous layer with Et_2O (2 x 75 mL). The

combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by FCC (2% EtOAc/hexanes) to give compound **50** as a clear oil (106 mg, 85%). ^1H NMR (600 MHz, $CDCl_3$) δ 4.58 (quintet, J = 6.0 Hz, 1H), 2.66- 2.54 (m, 4H), 2.46-2.36 (m, 2H), 2.15 (s, 3H), 1.53 (dquintet, J = 7.2, 1.8 Hz, 2H), 1.30 (quintet, J = 7.2 Hz, 2H), 0.89 (t, J = 7.8, 3H), 0.85 (s, 9H), 0.11 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.5, 207.5, 65.58, 50.9, 49.8, 44.3, 31.7, 26.0, 25.7, 22.5, 18.1, 14.1, -4.62, -4.65.



(*E*)-7-((*tert*-butyldimethylsilyl)oxy)-10-ethyl-9-hydroxy-9,12-dimethyltrideca-10,12-dien-5-one (51): $Ni(cod)_2$ (0.027 mmol, 7.3 mg) and Cyp_3P (0.54 mmol, 14 µL) were placed in a 8 mL vial containing ketone **50** (0.133 mmol, 40 mg) inside a glove box. After the flask was removed from the glove box and placed under an argon atmosphere, triethylborane (0.266 mmol, 38.5 µL) was added at ambient temperature. The mixture was then placed in a 60 °C oil bath. After 1 min., dropwise addition of the enyne **8** (0.333 mmol, 41 µL) as a solution in toluene (80 µL) was begun and continued for 3 h at 60 °C. After all of the enyne was added the resultant reaction mixture was stirred at 60 °C for 2 h. After that time the mixture was diluted with EtOAc and the septum seal was removed and the reaction allowed to air-oxidize for 1 h. The solution was concentrated

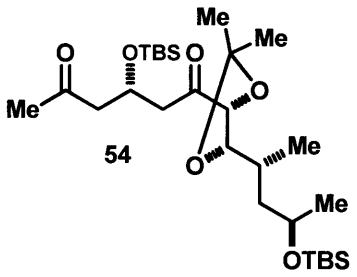
in vacuo and purified the residue by flash column chromatography (5% EtOAc/hexane) to give the title compound **51** as a mixture of diastereomers (18 mg, 35% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (s, 1H), 6.03 (s, 1H), 4.92-4.89 (m, 2H), 4.88-4.82 (m, 3H), 4.40-4.29 (m, 2H), 4.07 (s, 1H) 3.87 (s, 1H), 2.68 (t, J = 6.4, 3H), 2.61-2.59 (m, 3H), 2.56-2.55 (m, 1H), 2.39-2.33 (m, 8H), 2.13 (s, 1H), 2.04-1.92 (m, 6H), 1.87-1.86 (m, 4 H) 1,84-1.82 (m, 4H), 1.79-1.77 (m, 3H), 1.57 (s, 2H), 1.53-1.43 (m, 8H), 1.33 (s, 4H), 1.32-1.21 (m, 16H), 0.90-0.80 (m, 40H), 0.10 (s, 4H), 0.06 (s, 4H), 0.05 (s, 4H), 0.04 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.5, 209.2, 207.5, 148.3, 147.4, 142.7, 126.5, 125.8, 113.9, 113.6, 75.6, 68.4, 68.1, 65.6, 51.5, 50.9, 50.3, 49.8, 46.4, 44.5, 44.3, 44.0, 31.8, 29.6, 29.2, 26.1, 26.0, 25.9, 25.8, 25.7, 24.1, 24.0, 22.5, 21.5, 21.4, 18.0, 15.8, 15.4, 14.3, 14.0, -3.4, -4.1, -4.4, -4.5, -4.6. $[M+Na]^+$ calcd for $C_{37}H_{80}O_6Si_4Na$, 755.4998; found 732.4973.



52

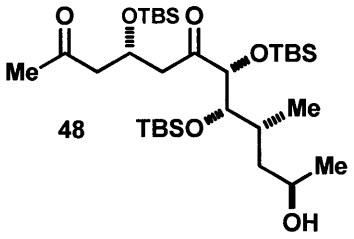
(14*R*,*E*)-7-((*tert*-butyldimethylsilyl)oxy)-15-((2*S*,3*S*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)oxiran-2-yl)-9-hydroxy-9,10,14-trimethyl-12-methylenepentadec-10-en-5-one (52): $Ni(cod)_2$ (0.027 mmol, 7.3 mg) and Cyp_3P (0.54

mmol, 14 μL) were placed in a 8 mL vial containing ketone **50** (0.133 mmol, 40 mg) inside a glove box. After the flask was removed from the glove box and placed under an argon atmosphere, triethylborane (0.266 mmol, 38.5 μL) was added at ambient temperature. The mixture was then placed in a 60 °C oil bath. After 1 min., dropwise addition of the enyne **24** (0.266 mmol, 82 mg) as a solution in toluene (80 μL) was begun and continued for 3 h at 60 °C. After all of the enyne was added the resultant reaction mixture was stirred at 60 °C for 2 h. After that time the mixture was diluted with EtOAc and the septum seal was removed and the reaction allowed to air-oxidize for 1 h. The solution was concentrated in vacuo and purified the residue by flash column chromatography (5% EtOAc/hexane) to give the title compound **51** as a mixture of diastereomers (37 mg, 45% yield). ^{1}H NMR (400 MHz, C_6D_6) δ 6.60 (s, 2H), 6.45 (s, 1H), 6.40 (s, 1H), 5.13 (brs, 4 H), 5.08 (brs, 2H), 5.01 (brs, 3H), 4.62-4.59 (m, 1H), 3.76-3.56 (m, 13H), 2.91-2.79 (m, 18H), 2.44-2.38 (m, 16H), 2.30-1.90 (m, 22H), 1.86 (s, 8H), 1.87-1.86 (m, 4 H), 1.60-1.45 (m, 19H), 1.42-1.18 (m, 40H), 1.06-0.85 (m, 85H), 0.19-0.11 (m, 60H); ^{13}C NMR (100 MHz, C_6D_6) δ 209.7, 209.5, 207.4, 205.1, 145.4, 143.5, 143.4, 142.6, 142.5, 125.5, 125.0, 114.9, 114.7, 76.0, 74.7, 74.6, 68.4, 68.3, 68.0, 65.6, 59.1, 59.0, 54.7, 51.4, 50.6, 49.9, 49.8, 49.7, 46.5, 46.4, 45.9, 44.7, 44.6, 43.8, 43.6, 39.3, 38.8, 31.9, 30.9, 30.0, 29.9, 29.3, 26.1, 26.0, 25.8, 25.7, 25.6, 25.0, 23.0, 22.6, 22.5, 19.8, 19.7, 19.6, 19.5, 18.5, 18.1, 18.0, 15.4, 15.3, 14.3, 14.1, 14.0, -3.7, -4.3, -4.4, -4.6, -4.7, -5.1, -5.2.



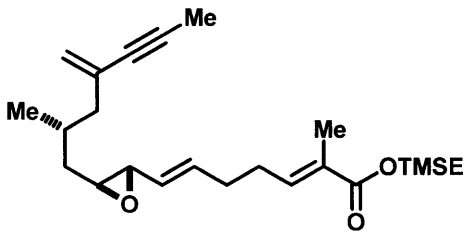
(S)-3-((tert-butyldimethylsilyl)oxy)-1-((4R,5S)-5-((2R,4R)-4-((tert-butyldimethylsilyl)oxy)pentan-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)hexane-1,5-dione (54): Alkyne **36** (0.207 mmol, 116 mg) was dissolved in acetone (1.5 mL) and treated with 2,2-dimethoxypropane (15.53 mmol, 191 mL) and PPTS (0.082 mmol, 21 mg). The reaction was stirred for 12 h and the solvent was evaporated and the crude product was dissolved in EtOAc (50 mL) and washed with a sol. aq. $NaHCO_3$ (20 mL) and brine (20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (2% EtOAc/hexanes) to give the acetonide as a colorless oil (106 mg, 85% yield). The acetonide (0.177 mmol, 106 mg) was dissolved in MeOH (1 mL) and placed in a flask and then added H_2O (100 µL). This was followed by the addition of PPh_3AuCl (0.019 mmol, 9.5 mg) and AgOTf (0.019, 4.9 mg). The reaction mixture was heated to 35 °C and stirred for 10 h. Diluted with H_2O (10 mL) and Et_2O (10 mL), partitioned the phases and extracted the aqueous with Et_2O (2 x 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude material was then dissolved in anhydrous *N,N*-dimethylformamide (300 µL) and to the stirring solution was added imidazole (1.94 mmol, 132 mg) and TBSCl (0.97 mmol, 146.2 mg). The reaction mixture was allowed to stir at r.t. for 16 h. The solution

was then quenched with H_2O (10 mL), and diluted with Et_2O (60 mL), partitioned the phases, and then extracted the aqueous layer with Et_2O (2 x 75 mL). The organic layers were combined and dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by FCC (2% EtOAc/hexanes) to give compound **54** as a clear oil (57 mg, 56%). ^1H NMR (400 MHz, C_6D_6) δ 4.89 (quintet, J = 6.0 Hz, 1H), 4.35 (dd, J = 7.2, 4 Hz, 1H), 4.21 (d, J = 7.6, 1H), 4.01 (q, J = 6.4, 1H) 3.17 (dd, J = 16.0, 6.4 Hz, 1H), 2.93 (dd, J = 17.2, 6.0 Hz, 1H), 2.46 (dq, J = 16.0, 6.0 Hz, 2H), 2.13-2.04 (m, 1H), 1.77 (s, 3H), 1.68-1.64 (m, 1H), 1.42 (s, 3H), 1.35 (s, 3H), 1.17 (d, *J* = 6.0 Hz, 3H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.07 (s, 9H), 1.01 (s, 9H), 0.23 (s, 3H), 0.19 (brs, 6H), 0.15 (s, 3H); HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{28}H_{56}O_6Si_2Na$, 567.3589; found 567.3548.



(4*S*,7*R*,8*S*,9*R*,11*R*)-4,7,8-*tris*((*tert*-butyldimethylsilyl)oxy)-11-hydroxy-9-methyldodecane-2,6-dione (48): The alkyne **45** (0.094 mmol, 74 mg) was dissolved in MeOH (0.960 mL) and placed in a flask and then added THF (120 µL) and H_2O (120 µL). This was followed by the addition of PPh_3AuCl (0.0094 mmol, 4.67 mg) and AgOTf (0.0094, 2.42 mg). The reaction mixture was heated to 35 °C and stirred for 5 h. The mixture was diluted with H_2O (10 mL) and Et_2O (10 mL), partitioned the phases and

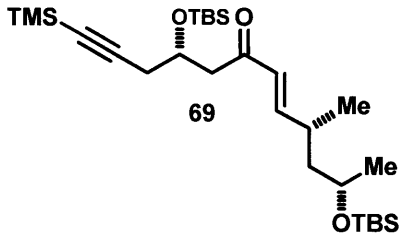
extracted the aqueous layer with Et_2O (2 x 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by FCC (20% EtOAc/hexanes) to give compound **48** as a clear oil (33 mg, 63%). ^1H NMR (600 MHz, $CDCl_3$) δ 4.60-4.55 (m, 1H), 4.19 (d, J = 4.8 Hz, 1H), 3.88-3.82 (m, 1H), 3.78 (t, J = 4.2 Hz, 1H), 2.95 (dd, J = 18.6, 4.2 Hz, 1H), 2.78-2.67 (m, 2H), 2.50 (dd, J = 14.4, 5.4 Hz, 1H), 2.17 (s, 3H), 1.86-1.79 (m, 2H), 1.51-1.46 (m, 1H), 1.39-1.32 (m, 1H), 1.15 (d, *J* = 6.2 Hz, 3H), 0.93 (s, 9H), 0.90 (s, 9H), 0.84 (s, 9H), 0.81 (d, *J* = 6.8 Hz, 3H), 0.14 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.01 (s, 3H); $[\alpha]_D$ –15.2 (*c* 9.0, $CHCl_3$).



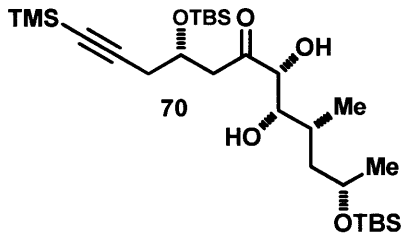
65

(2E,6E)-2-(trimethylsilyl)ethyl 2-methyl-7-((2S,3S)-3-((R)-2-methyl-4-methylenehept-5-yn-1-yl)oxiran-2-yl)hepta-2,6-dienoate (65): The alcohol **23** (0.180 mmol, 35 mg) was dissolved in CH_2Cl_2 (1.8 mL) and placed in a flask containing activated 4 Å ms. This was followed by the addition of NMO (0.27 mmol, 33 mg) and TPAP (0.0094, 3.2 mg). The reaction was then stirred for 4 h and filtered through celite (eluting with 30% Et_2O in petane) and concentrated in vacuo. The crude aldehyde **57**

was carried forward without further purification. In a separate flask sulfone **58** (0.1 mmol, 32 mg) was dissolved in DME (1 mL) and cooled to -78 °C. A solution of KHMDS (0.12 mmol, 24 mg) in DME (1 mL) was added and the solution was stirred for 30 min. A solution of the aldehyde **57** (0.1 mmol, 19 mg) in DME (1 mL) was then added and the solution was warmed to r.t. and stirred for 8 h. The solution was quenched with H_2O (10 mL) and diluted with Et_2O (100 mL). The aqueous layer was extracted with Et_2O (2 x 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (5% EtOAc/hexanes) to give **65** as a colorless oil (23 mg, 56% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (t, *J* = 6.0 Hz, 1H), 5.20 (s, 1H), 5.22-5.16 (m, 2H), 5.07 (s, 1H), 4.19 (t, J = 8.4 Hz, 2H), 3.01 (dd, *J* = 8, 2.0 Hz, 1H), 2.81 (dt, *J* = 6.0, 2.0 Hz, 1H), 2.33-2.25 (m, 5H), 2.04-1.94 (m, 1H), 1.89 (s, 3H), 1.82-1.74 (m, 1H), 1.78 (brs, 3H), 1.68-1.60 (m, 1H), 1.29-1.21 (m, 2H), 0.99 (t, 8.4 Hz, 2H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 140.9, 135.0, 130.8, 128.7, 128.4, 121.4, 85.9, 80.1, 62.9, 59.3, 59.2, 45.5, 38.8, 31.4, 29.6, 28.3, 26.9, 19.5, 17.5, 12.7, 4.4, –1.2; IR (film) 2955, 2919, 1709, 1653, 1457, 1379, 1251 1115, 1075, 893, 860, 838, 746, 695 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{24}H_{38}O_3SiNa$, 425.2482; found 425.2470. $[\alpha]_D$ –12.8 (*c* 3.8, $CHCl_3$).

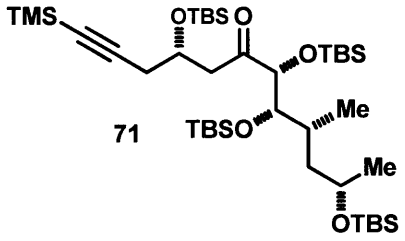


(5*S*,10*R*,12*R*,*E*)-2,2,3,3,10,12,14,14,15,15-decamethyl-5-(3-(trimethylsilyl)prop-2-yn-1-yl)-4,13-dioxa-3,14-disilahexadec-8-en-7-one (69): To a vigorously stirred suspension of vacuum-dried LiCl (2.6 mmol, 115 mg) in MeCN (13 mL) was added the ketophosphonate **32** (2.2 mmol, 924 mg). Diisopropylethylamine (2.1 mmol, 461 µL) was added followed by the aldehyde **68** (2.01 mmol, 508 mg). The reaction mixture was then stirred 16 h at ambient temperature. The mixture was quenched with saturated aq. NH_4Cl (1.8 mL) and diluted with Et_2O (25 mL) and H_2O (25 mL). The phases were partitioned and extracted the aqueous with Et_2O (3 x 20 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (5% EtOAc/hexanes) to give the enone **69** (95:5 *E:Z*) as an off-color oil (970 mg, 84%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.72 (dd, J = 17.6, 7.2 Hz, 1H), 6.02 (dd, J = 15.6, 0.8 Hz 1H), 4.31-4.28 (m, 1H), 3.81-3.77 (m, 1H), 2.75 (dq, J = 15.2, 7.6 Hz, 2H), 2.45 (quintet, J = 6.8 Hz, 1H), 2.37 (d, J = 6.0 Hz, 2H), 1.60-1.53 (m, 1H), 1.29-1.24 (m, 1H), 1.09 (d, *J* = 6.0 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.84 (s, 9H), 0.80 (s, 9H), 0.10 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H) -0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 153.6, 129.2, 103.6, 86.9, 68.1, 66.0, 46.7, 45.8, 33.1, 29.2, 25.9, 25.8, 24.1, 18.9, 18.0, 0.1, -4.1, -4.6, -4.8,; IR (film) 2958, 2858, 1697, 1626, 1473, 1361, 1215 1099, 1006, 840, 776, 699, 643, 576 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{28}H_{56}O_3Si_3Na$, 547.3429; found 547.3523; $[\alpha]_D$ 19.1 (*c* 7.6, $CHCl_3$).



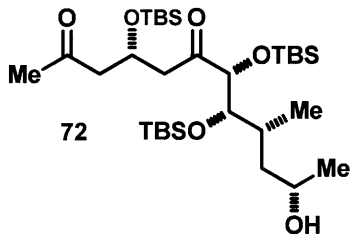
(5S,8R,9S,10R,12S)-8,9-dihydroxy-2,2,3,3,10,12,14,14,15,15-decamethyl-5-(3-(trimethylsilyl)prop-2-yn-1-yl)-4,13-dioxa-3,14-disilahexadecan-7-one (70): The enone **69** was placed into a flask and cooled. In a separate flask was placed AD-mix-α (1.4 mmol, 1.9 g), potassium osmate (0.14 mmol, 47 mg), $(DHQ)_2PHAL$ (0.07 mmol, 55 mg), and $NaHCO_3$ (4.2 mmol, 353 mg) and dissolved in *t*-BuOH/H_2O (1:1, 15.4 mL). The mixture stirred vigorously until all the solids were dissolved then added $MeSO_2NH_2$ (133 mg, 1.4 mmol). This solution was then stirred for 10 min and transferred by a Pasteur pipet into a cooled (5 °C) flask containing the enone **28** (1.4 mmol, 735 mg). The mixture was then stirred 36 h while maintaining the temperature between 0–5 °C in a refrigerator. Quenched at cold temperature after this time with saturated aq. Na_2SO_3 (1.18 mL) and stirring was continued for 30 min. Finally, the brown-colored mixture was diluted with EtOAc (15 mL) and H_2O (3 mL). Separated the phases and extracted the aqueous layer with EtOAc (2 x 10 mL). The combined organic phases were dried with Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (20% EtOAc/hexanes) to give the diol **70** (>95:5 d.r.) as a clear oil (319 mg, 57%). ^1H NMR (400 MHz, $CDCl_3$) δ 4.34-4.29 (m, 1H), 4.19 (brs, 1H), 3.90-3.84 (m, 1H), 3.62 (brs, 3H), 2.80 (dd, J = 5.6, 1.2 Hz, 2H), 2.39 (dd, J = 5.2, 2.4 Hz, 2H), 2.06-2.04 (m, 1H), 1.99-1.93 (m, 1H), 1.63-1.56 (m, 1H), 1.12 (d, *J* = 6.0 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.84 (s, 9H), 0.83 (s, 9H), 0.10 (s, 9H), 0.07 (s, 3H), 0.03

(s, 3H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.5, 102.8, 87.6, 77.5, 75.1, 67.5, 66.2, 45.0, 43.3, 33.7, 28.9, 25.9, 25.8, 24.8, 18.1, 18.0, 15.4, 0.4, -3.9, -4.7, -4.8,; IR (film) 3463, 2958, 1718, 1653, 1472, 1374, 1251 1076, 1006, 838, 667, 643, cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{28}H_{58}O_5Si_3Na$, 581.3484; found 581.3467; $[\alpha]_D$ 15.3 (*c* 4.9, $CHCl_3$).



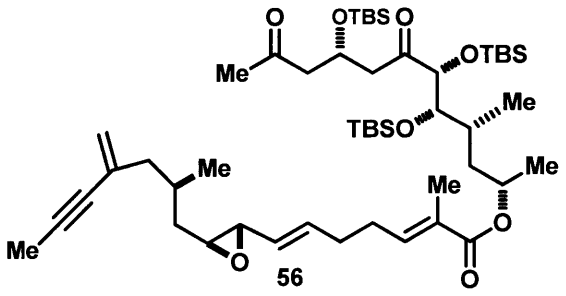
(5*S*,8*R*,9*S*,10*R*,12*R*)-8,9-*bis*((*tert*-butyldimethylsilyl)oxy)-2,2,3,3,10,12,14,14,15,15-decamethyl-5-(3-(trimethylsilyl)prop-2-yn-1-yl)-4,13-dioxa-3,14-disilahexadecan-7-one (71): The diol **70** (1.209 mmol, 676 mg) was dissolved in CH_2Cl_2 (12 mL) and cooled to 0 °C. Then 2,6-lutidine (9.68 mmol, 1.12 mL) was added all at once and TBSOTf (4.85 mmol, 1.11 mL) dropwise over 3 min. The solution was stirred 30 min at 0 °C and subsequently warmed to r.t. and stirred 60 min. The solution was diluted with H_2O (10 mL), partitioned the phases, and extracted the aqueous with Et_2O (15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (2% EtOAc/hexanes) to give the alkyne **71** as a clear oil (876 mg, 92%). ^1H NMR (400 MHz, $CDCl_3$) δ 4.27-4.21 (m, 1H), 4.03 (d, J = 4.8 Hz, 1H), 3.82-

3.75 (m, 1H), 3.62 (dd, J = 5.2, 3.2 Hz, 1H), 3.03 (dd, J = 18.8, 5.2 Hz, 1H), 2.71 (dd, J = 19.2, 7.2 Hz, 1H), 2.37 (dq, J = 16.4, 4.8 Hz, 2H), 1.99-1.93 (m, 1H), 1.49-1.43 (m, 1H), 1.22-1.15 (m, 1H), 1.07 (d, *J* = 6.0 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.83 (s, 9H), 0.82 (s, 9H), 0.71 (d, *J* = 6.8 Hz, 3H), 0.09 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H) -0.01 (s, 3H), -0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8, 104.0, 86.3, 80.9, 79.1, 65.9, 47.8 45.3, 30.5, 28.6, 25.7, 24.7, 18.3, 18.2, 18.1, 18.0, 14.1, 0.4, -2.9, -3.8, -4.1, -4.5, -4.7, -5.0; IR (film) 2957, 2179, 1718, 1653, 1473, 1362, 1252, 1083, 938, 836, 774, 668 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{40}H_{96}O_5Si_5Na$, 809.5214; found 809.5226; $[\alpha]_D$ -7.2 (*c* 7.2, $CHCl_3$).



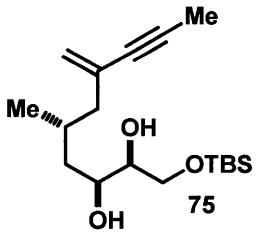
(4*S*,7*R*,8*S*,9*R*,11*S*)-4,7,8-*tris*((*tert*-butyldimethylsilyl)oxy)-11-hydroxy-9-methyldodecane-2,6-dione (72): The alkyne **71** (0.094 mmol, 74 mg) was dissolved in MeOH (0.960 mL) and placed in a flask and then added THF (120 µL) and H_2O (120 µL). This was followed by the addition of PPh_3AuCl (0.0094 mmol, 4.67 mg) and AgOTf (0.0094, 2.42 mg). The reaction mixture was heated to 35 °C and stirred for 5 h. The mixture was diluted with H_2O (10 mL) and Et_2O (10 mL), partitioned the phases, and

extracted the aqueous with Et_2O (2 x 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by FCC (20% EtOAc/hexanes) to give compound **72** as a clear oil (32 mg, 55%). ^1H NMR (600 MHz, $CDCl_3$) δ 4.59-4.55 (m, 1H), 4.20 (d, J = 4.8 Hz, 1H), 3.88-3.82 (m, 1H), 3.62 (t, J = 4.2 Hz, 1H), 2.98 (dd, J = 18.6, 4.2 Hz, 1H), 2.81-2.72 (m, 2H), 2.54 (dd, J = 14.4, 5.4 Hz, 1H), 2.20 (s, 3H), 1.90-1.80 (m, 1H), 1.79-1.71 (m, 1H), 1.59-1.57 (m, 1H), 1.20 (d, *J* = 6.2 Hz, 3H), 1.19-1.15 (m, 1H), 0.96 (s, 9H), 0.94 (s, 9H), 0.86 (s, 12H), 0.18 (s, 3H), 0.14 (s, 3H), 0.09 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2, 208.2, 104.0, 81.9, 79.1, 65.9, 64.8, 50.8 48.1, 43.9, 32.8, 32.0, 26.3, 26.1, 26.0, 24.7, 18.3, 18.2, 18.1, 18.0, 15.9, -3.8, -4.1, -4.5, -4.7; IR (film) 3482, 2930, 2340, 1717, 1653, 1473, 1362, 1256, 1079, 939, 836, 776, 668 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{31}H_{66}O_6Si_3Na$, 641.4059; found 641.4075; $[\alpha]_D$ -21 (*c* 2.0, $CHCl_3$).



(2*E*,6*E*)-(2*R*,4*R*,5*S*,6*R*,9*S*)-5,6,9-*tris*((*tert*-butyldimethylsilyl)oxy)-4-methyl-7,11-dioxododecan-2-yl 2-methyl-7-((2S,3S)-3-((R)-2-methyl-4-methylenehept-5-yn-1-yl)oxiran-2-yl)hepta-2,6-dienoate (56): Enyne **65** (0.085 mmol, 34 mg) was dissolved in THF (1 mL) and cooled to 0 °C. Then TBAF (1.0 M in THF, 0.425 mmol, 0.425 mL) was added and the resulting solution was stirred 30 min at 0 °C. After that time the solution was warmed to r.t. and stirred for 4 h before being quenched by adding a sol. aq. NH_4Cl (10 mL) and diluting with brine (5 mL) and EtOAc (25 mL). The aqueous layer was extracted with EtOAc (3 x 25 mL), dried over Na_2SO_4, filtered, and concentrated. A portion of the crude carboxylate salt (0.013 mmol, 4 mg) was dissolved in toluene (300 µL). While stirring NEt_3 (0.065 mmol, 9 µL) and 2,4,6-trichlorobenzoyl chloride (0.033 mmol, 5 µL) were added. The mixture was stirred for 8 h and then filtered through celite and evaporated. The resulting residue was dissolved in toluene (300 µL) along with alcohol **72** (0.013 mmol, 8 mg) and DMAP (0.039 mmol, 4.5 mg). The resulting mixture was heated to 40 °C for 8 h. After that reaction time the mixture was filtered through celite and evaporated. The residue was purified by flash column chromatography (10:90 EtOAc:hexanes) to give the enyne **56** as a colorless oil (9 mg, 82%). ^1H NMR (600 MHz, $CDCl_3$) δ 6.74-6.70 (m, 1H), 5.85-5.80 (m, 1H), 5.23 (s, 1H), 5.22-5.20 (m, 1H), 5.08 (s, 1H), 5.03-4.97 (m, 1H), 4.53-4.48 (m, 1H), 4.12 (d, J = 6.6 Hz, 1H), 3.62-

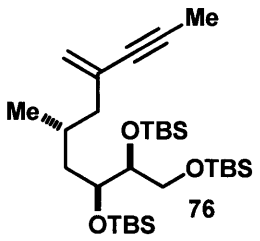
3.60 (m, 1H), 3.02 (dd, J = 12.0, 3.0 Hz, 1H), 2.89-2.82 (m, 2H), 2.73-2.62 (m, 2H), 2.45 (dd, J = 22.2, 9.6 Hz, 1H), 2.28-2.15 (m, 4H), 2.13 (s, 3H), 2.04-1.93 (m, 2H), 1.90 (s, 3H), 1.77 (brs, 3H), 1.68-1.61 (m, 1H), 1.31-1.21 (m, 3H), 1.18 (d, *J* = 9.0 Hz, 3H), 0.92 (d, *J* = 9.6 Hz, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.86 (s, 12H), 0.76 (d, *J* = 10.2 Hz, 3H), 0.18 (s, 3H), 0.15 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H), -0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4, 207.7, 167.9, 140.8, 135.2, 130.8, 128.8, 128.6, 121.4, 85.9, 81.3, 78.6, 77.2, 76.8, 68.7, 65.3, 59.3, 50.4, 48.1, 45.5, 40.8, 40.6, 38.9, 32.1, 31.8, 31.5, 29.6, 28.4, 26.2, 26.0, 21.1, 19.5, 18.4, 18.1, 15.1, 12.8, 12.7, 4.4, -3.8, -4.3, -4.4, -4.6, -4.8; IR (film) 2956, 2930, 2857, 1718, 1653, 1472, 1362, 1257, 1081, 939, 837, 777, 668 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{50}H_{90}O_8Si_3Na$, 925.5836; found 925.58325 $[\alpha]_D$ -21.9 (*c* 3.2, $CHCl_3$).



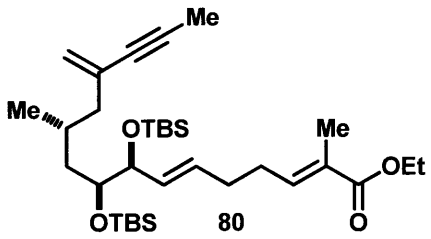
75

(2*S*,3*S*,5*R*)-1-((*tert*-butyldimethylsilyl)oxy)-5-methyl-7-methylenedec-8-yne-2,3-diol (75): The enyne **3** was placed into a flask and cooled. In a separate flask was placed AD-mix-α (0.766 mmol, 1.085 g) dissolved in *t*-BuOH/H_2O (1:1, 7.66 mL). The mixture was stirred vigorously until all the solids were dissolved then added $MeSO_2NH_2$ (0.766 mmol, 72 mg). This solution was then stirred for 10 min and transferred by a Pasteur

pipet into a cooled (5 °C) flask containing the enone **28** (1.4 mmol, 735 mg). The mixture was then stirred 24 h while maintaining the temperature between 0–5 °C in a refrigerator. The mixture was quenched at cold temperature after this time with saturated aq. Na_2SO_3 (0.65 mL) and stirring was continued for 30 min. Finally, the brown-colored mixture was diluted with EtOAc (15 mL) and H_2O (3 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic phases were dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (20% EtOAc/hexanes) to give the diol **75** (95:5 d.r.) as a clear oil (135 mg, 54%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.26 (s, 1H), 5.16 (s, 1H), 3.81-3.70 (m, 2H), 3.69-3.63 (m, 1H), 3.50-3.40 (m, 1H), 2.80-2.69 (brs, 2H), 2.18-2.10 (m, 1H), 2.08-2.02 (m, 1H), 1.95-1.91 (m, 1H), 1.90 (s, 3H), 1.70-1.66 (m, 1H), 1.15-1.11 (m, 1H), 0.94 (d, J = 7.5 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 131.1, 121.3, 85.9, 80.2, 74.3, 70.1, 65.9, 46.1, 40.6, 28.7, 26.2, 19.4, 18.5, 4.4, -5.1, -5.2; IR (film) 3419, 2931, 2739, 2361, 2046, 1611, 1472, 1256, 1113, 837, 778 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{34}O_3SiNa$, 349.2169; found 349.2179. $[\alpha]_D$ –17.8 (*c* 7.6, $CHCl_3$).

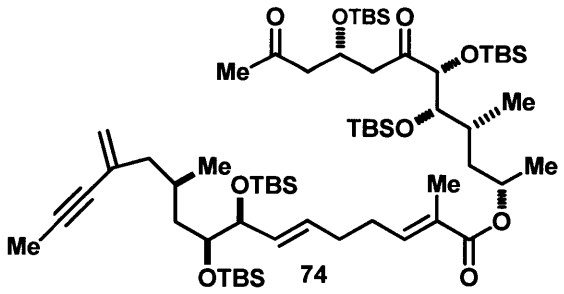


(5*S*,6*S*)-6-((*tert*-butyldimethylsilyl)oxy)-2,2,3,3,9,9,10,10-octamethyl-5-((*R*)-2-methyl-4-methylenehept-5-yn-1-yl)-4,8-dioxa-3,9-disilaundecane (76): The diol **75** (0.704 mmol, 230 mg) was dissolved in CH_2Cl_2 (4.56 mL) and cooled to 0 °C. Then added 2,6-lutidine (5.66 mmol, 0.65 mL) all at once and TBSOTf (2.84 mmol, 0.65 mL) dropwise over 3 min. The solution was stirred 30 min at 0 °C and subsequently warmed to r.t. and stirred 60 min. The solution was diluted with H_2O (10 mL), partitioned the phases, and extracted the aqueous with Et_2O (15 mL). The combined organic extracts were dried over anhydrous over $MgSO_4$, filtered, and concentrated in vacuo. The crude was purified by flash column chromatography (2% EtOAc/hexanes) to give the alkyne **76** as a clear oil (379 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 (s, 1H), 5.07 (s, 1H), 3.81-3.77 (m, 1H), 3.69-3.63 (m, 2H), 3.43-3.38 (m, 1H), 2.09-2.00 (m, 1H), 1.89-1.87 (m, 4H), 1.66-1.60 (m, 1H), 1.35-1.30 (m, 1H), 1.25-1.19 (m, 1H), 0.87 (s, 9H), 0.86 (s, 9H), 0.85 (s, 9H), 0.78 (d, *J* = 6 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.4, 120.9, 85.5, 80.4, 76.9, 72.0, 64.1, 46.7, 37.9, 27.6, 26.2, 26.0, 18.6, 18.3, 18.2, 4.4, -3.9, -4.0, -4.5, -4.7, -5.0, -5.2; IR (film) 3094, 2962, 2739, 2361, 1923, 1613, 1472, 1253, 1107, 842, 668 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{30}H_{62}O_3Si_3Na$, 577.3899; found 577.3898. $[\alpha]_D$ –31.4 (*c* 9.7, $CHCl_3$).



(2*E*,6*E*,8*S*,9*S*,11*R*)-ethyl 8,9-*bis*((*tert*-butyldimethylsilyl)oxy)-2,11-dimethyl-13-methylenehexadeca-2,6-dien-14-ynoate (80): The enyne **76** (0.683 mmol, 379 mg) was dissolved in MeOH (1 mL) and cooled to 0 °C. CSA (0.14 mmol, 32 mg) was added all at once and stirred 30 min at 0 °C. The mixture is diluted with H_2O (10 mL), partitioned the phases, and extracted the aqueous with Et_2O (15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude was purified by flash column chromatography (10% EtOAc/hexanes) to give the alcohol **77** as a clear oil (221 mg, 74%). The alcohol **77** (0.502 mmol, 221 mg) was dissolved in CH_2Cl_2 (4.5 mL) and placed in a flask containing activated 4 Å ms (276.25 mg). This was followed by the addition of NMO (0.753 mmol, 100 mg) and TPAP (0.028, 10.3 mg). The reaction was then stirred for 4 h and filtered through celite (eluting with 30% Et_2O in petane) and concentrated in vacuo. The crude aldehyde **78** was carried forward without further purification. In a separate flask sulfone **79** (0.502 mmol, 182 mg) was dissolved in DME (5 mL) and cooled to -78 °C. A solution of KHMDS (0.602 mmol, 210 mg) in DME (5 mL) was added and the solution was stirred for 30 min. A solution of the aldehyde **78** in DME (5 mL) was then added and the solution was warmed to r.t. and stirred for 8 h. The solution was quenched with H_2O (10 mL) and diluted with Et_2O (100 mL). The aqueous layer was extracted with Et_2O (2 x 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and

concentrated in vacuo. The crude residue was purified by flash column chromatography (5% EtOAc/hexanes) to give **80** as a colorless oil (255 mg, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (t, *J* = 5.6 Hz, 1H), 5.58-5.55 (m, 2H), 5.18 (s, 1H), 5.05 (s, 1H), 4.14 (q, J = 7.2 Hz, 2H), 4.08-4.05 (m, 1H), 3.63 (quintet, *J* = 4.0 Hz, 1H), 2.25-2.19 (m, 5H), 2.04-1.99 (m, 1H), 1.88-1.82 (m, 5H), 1.80 (brs, 3H), 1.25 (t, 7.2 Hz, 3H), 1.24-1.21 (m, 1H), 0.99 (t, 8.4 Hz, 2H), 0.86 (s, 18H), 0.77 (d, *J* = 6.0 Hz, 3H), 0.04 (s, 6H), 0.00 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 141.8, 131.4, 129.8, 129.6, 128.2, 120.7, 85.3, 80.4, 74.7, 73.3, 60.5, 46.8, 38.0, 31.4, 28.9, 27.3, 26.1, 18.5, 18.3, 18.2, 14.5, 12.6, 4.3, -3.9, -4.4, -4.5, -4.7; IR (film) 2930, 2361, 1717, 1653, 1473, 1258, 1102, 836, 668 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{33}H_{60}O_4Si_2Na$, 599.3922; found 599.3943. $[\alpha]_D$ –31.3 (*c* 7.2, $CHCl_3$).

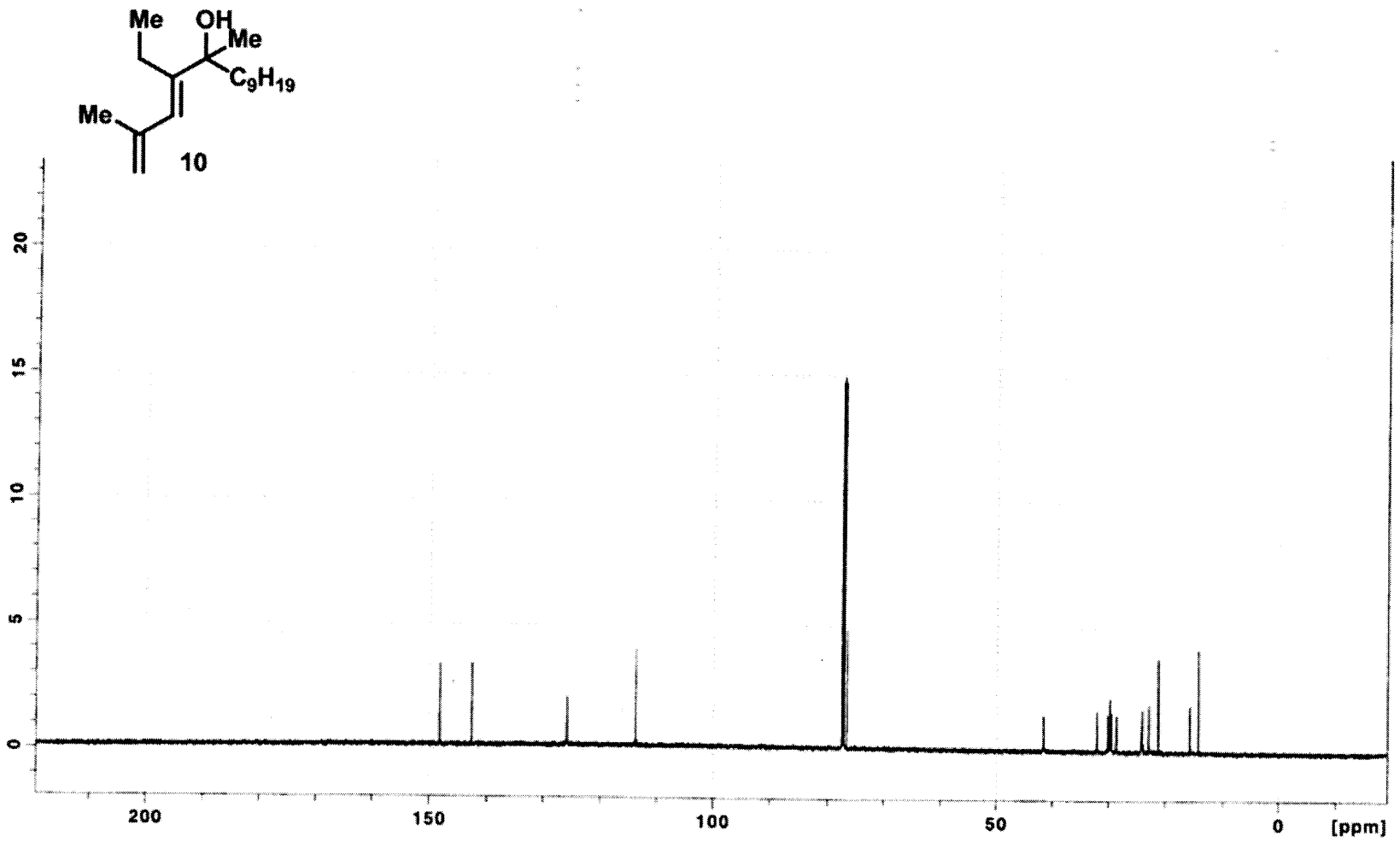


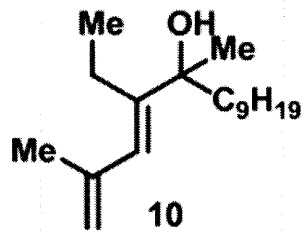
(2*E*,6*E*,8*S*,9*S*,11*R*)-(2*S*,4*R*,5*S*,6*R*,9*S*)-5,6,9-*tris*((*tert*-butyldimethylsilyl)oxy)-4-methyl-7,11-dioxododecan-2-yl 8,9-*bis*((*tert*-butyldimethylsilyl)oxy)-2,11-dimethyl-13-methylenehexadeca-2,6-dien-14-ynoate (74): Enyne **80** (0.124 mmol, 72 mg) was dissolved in THF (3.8 mL), MeOH (1.75 mL), and H_2O (1.75 mL) and added LiOH (4.34

mmol, 104 mg). The resulting solution was stirred at r.t. for 15 h. The solution was quenched by adding a sol. aq. NH_4Cl (20 mL), diluting with brine with Et_2O (25 mL). The aqueous layer was extracted with Et_2O (3 x 25 mL), dried over Na_2SO_4, filtered, and concentrated. A portion of the crude carboxylate salt **81** (0.043 mmol, 24 mg) was dissolved in toluene (992 µL). While stirring NEt_3 (0.22 mmol, 30 µL) and 2,4,6-trichlorobenzoyl chloride (0.11 mmol, 17 µL) were added. The mixture was stirred for 8 h and then filtered through celite and evaporated. The resulting residue was dissolved in toluene (992 µL) along with alcohol **72** (0.043 mmol, 27 mg) and DMAP (0.130 mmol, 15 mg). The resulting mixture was heated to 40 °C for 8 h. After that reaction time the mixture was filtered through celite and evaporated. The residue was purified by flash column chromatography (15:95 EtOAc:hexanes) to give the enyne **74** as a colorless oil (42 mg, 84%). ^1H NMR (600 MHz, $CDCl_3$) δ 6.71-6.68 (m, 1H), 5.58-5.48 (m, 2H), 5.18 (s, 1H), 5.04 (s, 1H), 5.03-4.97 (m, 1H), 4.53-4.48 (m, 1H), 4.12 (d, J = 6.6 Hz, 1H), 4.06-4.05 (m, 1H), 3.65-3.61 (m, 2H), 2.86 (dd, J = 12, 3 Hz, 1H), 2.73-2.62 (m, 2H), 2.45 (dd, J = 22.2, 9.6 Hz, 1H), 2.28-2.13 (m, 5H), 2.12 (s, 3H), 2.11-2.03 (m, 1H), 1.86 (s, 3H), 1.85-1.79 (m, 2H), 1.78 (brs, 3H), 1.37-1.19 (m, 4H), 1.17 (d, *J* = 9.0 Hz, 3H), 0.92 (d, *J* = 9.6 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.85 (s, 9H), 0.78 (s, 15H), 0.08 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H), 0.00 (s, 6H), -0.02 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.5, 207.7, 167.9, 141.6, 131.5, 130.0, 128.4, 128.1, 120.8, 85.4, 81.3, 80.4, 78.5, 77.5, 77.4, 74.9, 73.3, 68.6, 65.3, 50.4, 48.1, 46.8, 40.8, 38.0, 32.0, 31.8, 31.6, 29.1, 27.3, 26.2, 26.1, 25.9, 21.0, 18.5, 18.4, 18.3, 18.2, 18.1, 15.1, 12.7, 4.4, -3.8, -4.3, -4.4, -4.5, -4.6, -4.7, -4.8; IR (film) 2929, 22361, 1720, 1717, 1715 1653, 1472, 1256, 1081, 835, 777 cm^{-1}; HRMS ESI

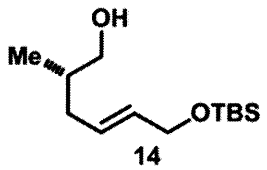
(*m/z*): $[M+Na]^+$ calcd for $C_{62}H_{120}O_9Si_5Na$, 1171.7671; found 1171.7631 $[\alpha]_D$ -27.2 (*c* 5.4, $CHCl_3$).

Chapter 1: Spectra

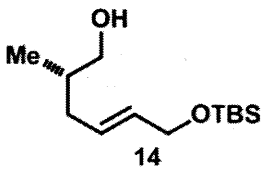

Me
OH
Me
C_9H_{19}
Me
10
20
15
10
5
0
200
150
100
50
0
[ppm]



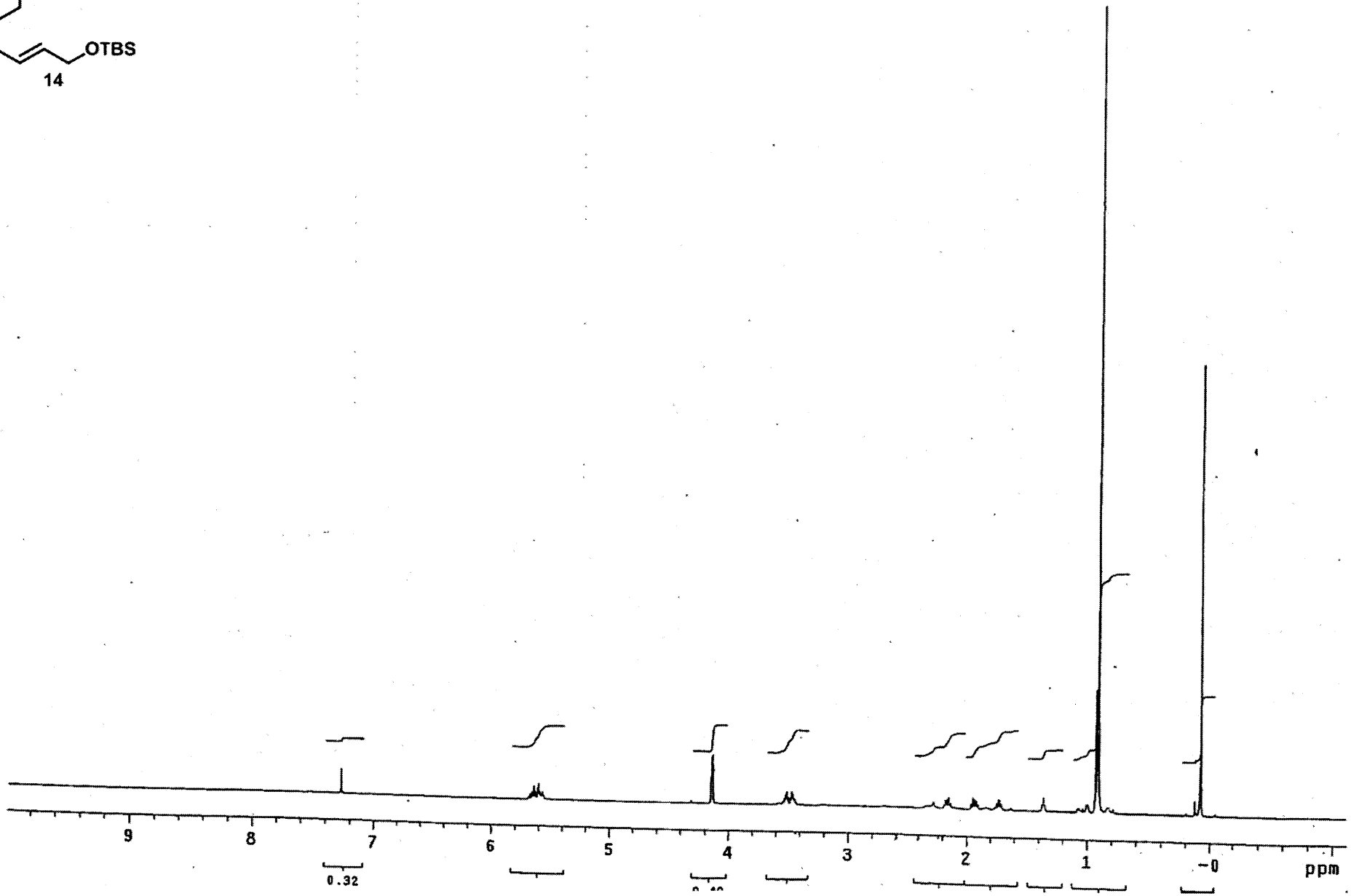
10

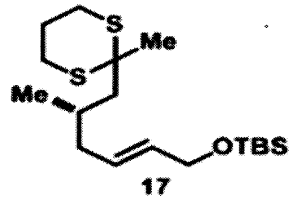


14

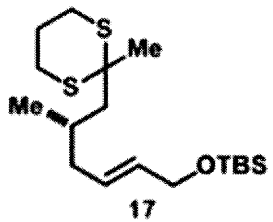


14

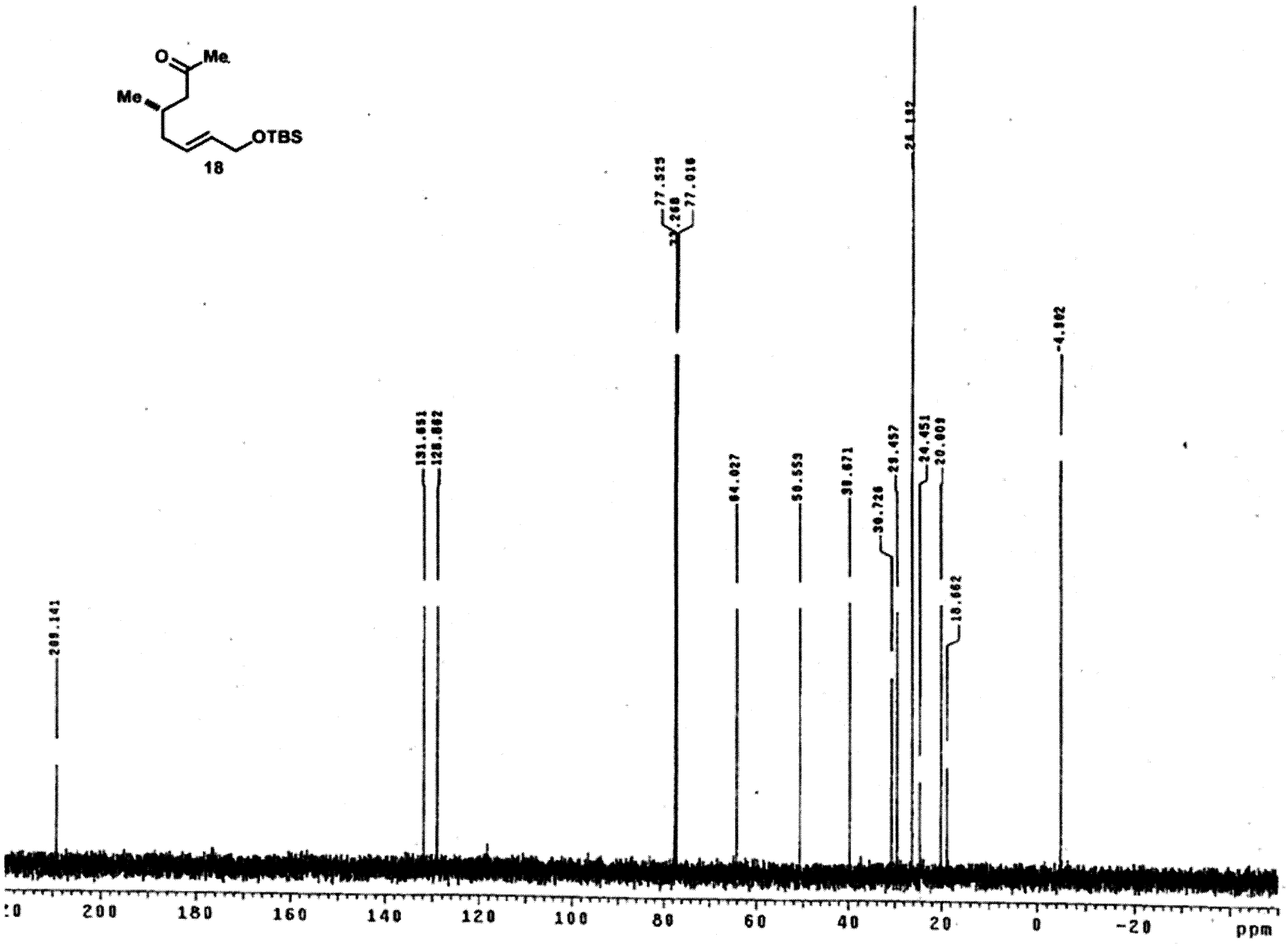


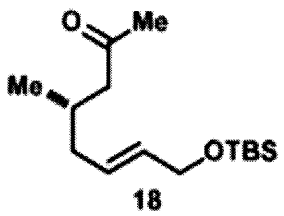

S
Me
S
Me
OTBS
17

200
180
160
140
120
100
80
60
40
20
0
-20
ppm

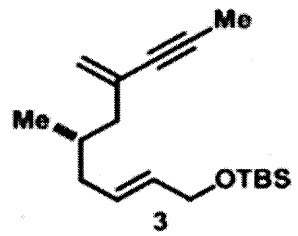


17

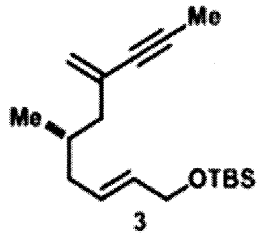

O
Me
Me
OTBS
18
209.141
131.651
128.882
77.525
77.268
77.010
64.027
50.553
39.871
30.728
28.457
26.182
24.451
20.003
18.462
-4.882
200
180
160
140
120
100
80
60
40
20
0
-20
ppm



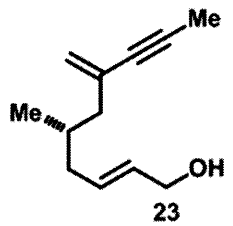
18



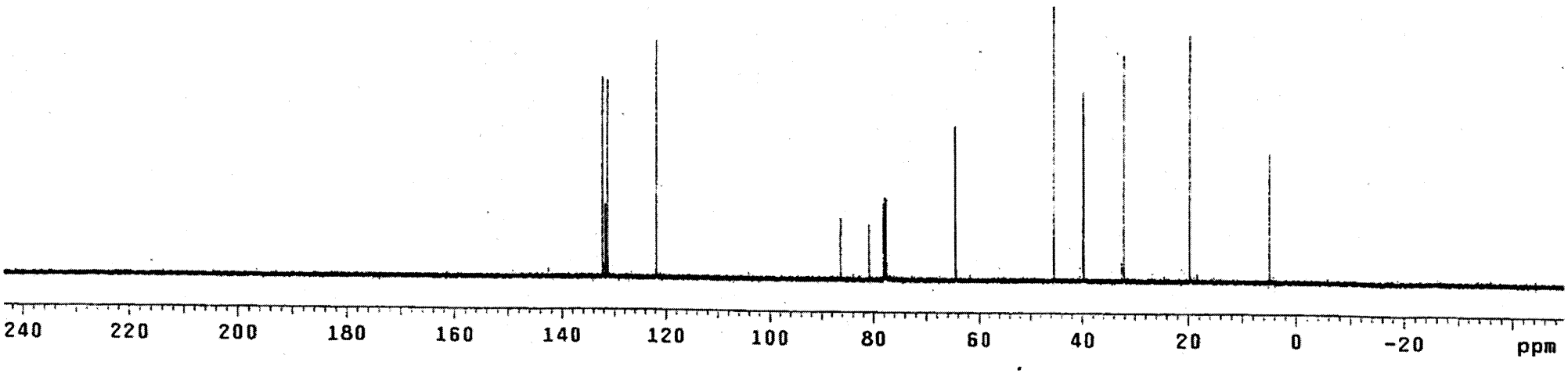
3

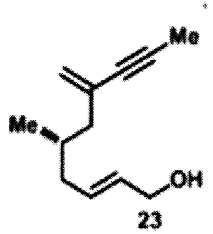


3

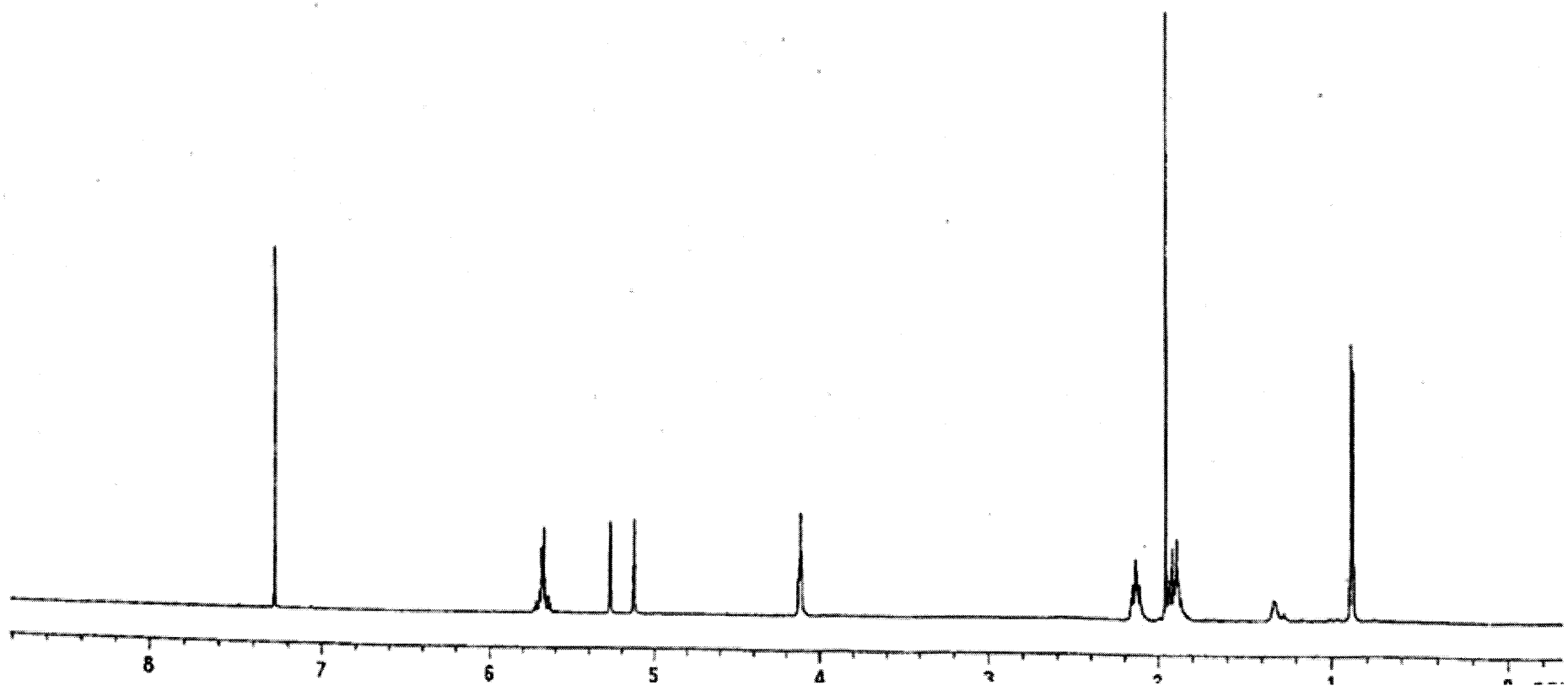


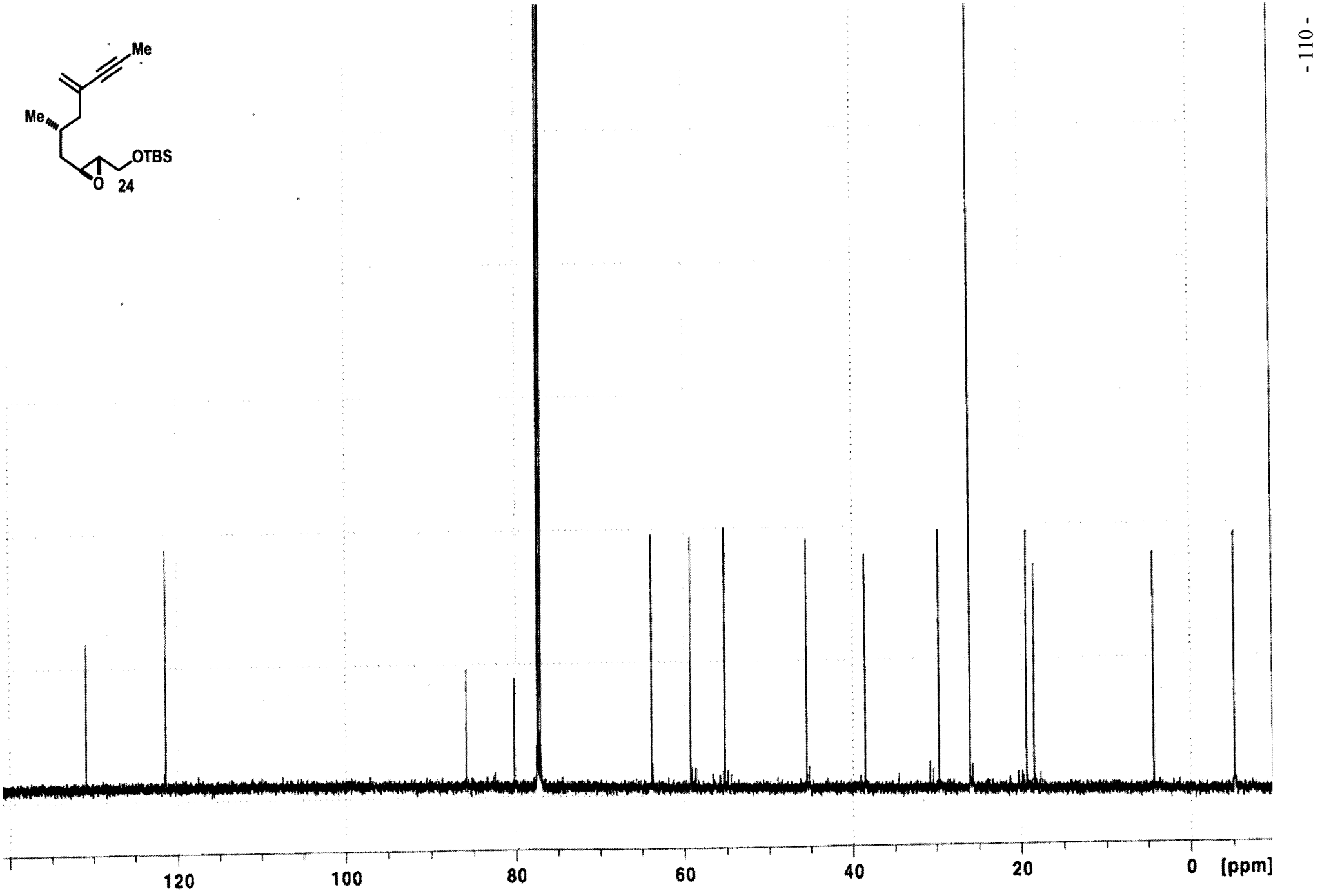
23

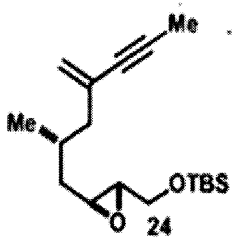




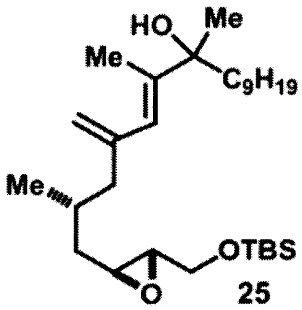
23




Me
Me
OTBS
O
24
120
100
80
60
40
20
0
[ppm]

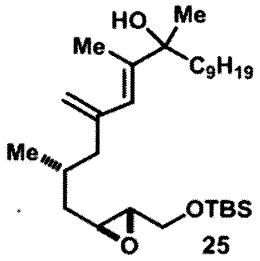

Me
Me
OTBS
O
24

5
4
3
2
1
– 0
[ppm]

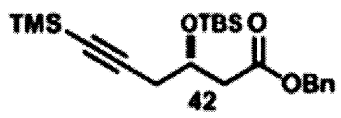

HO
Me
Me
C_9H_{19}
Me
OTBS
O

25

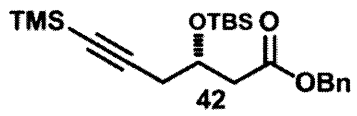
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0



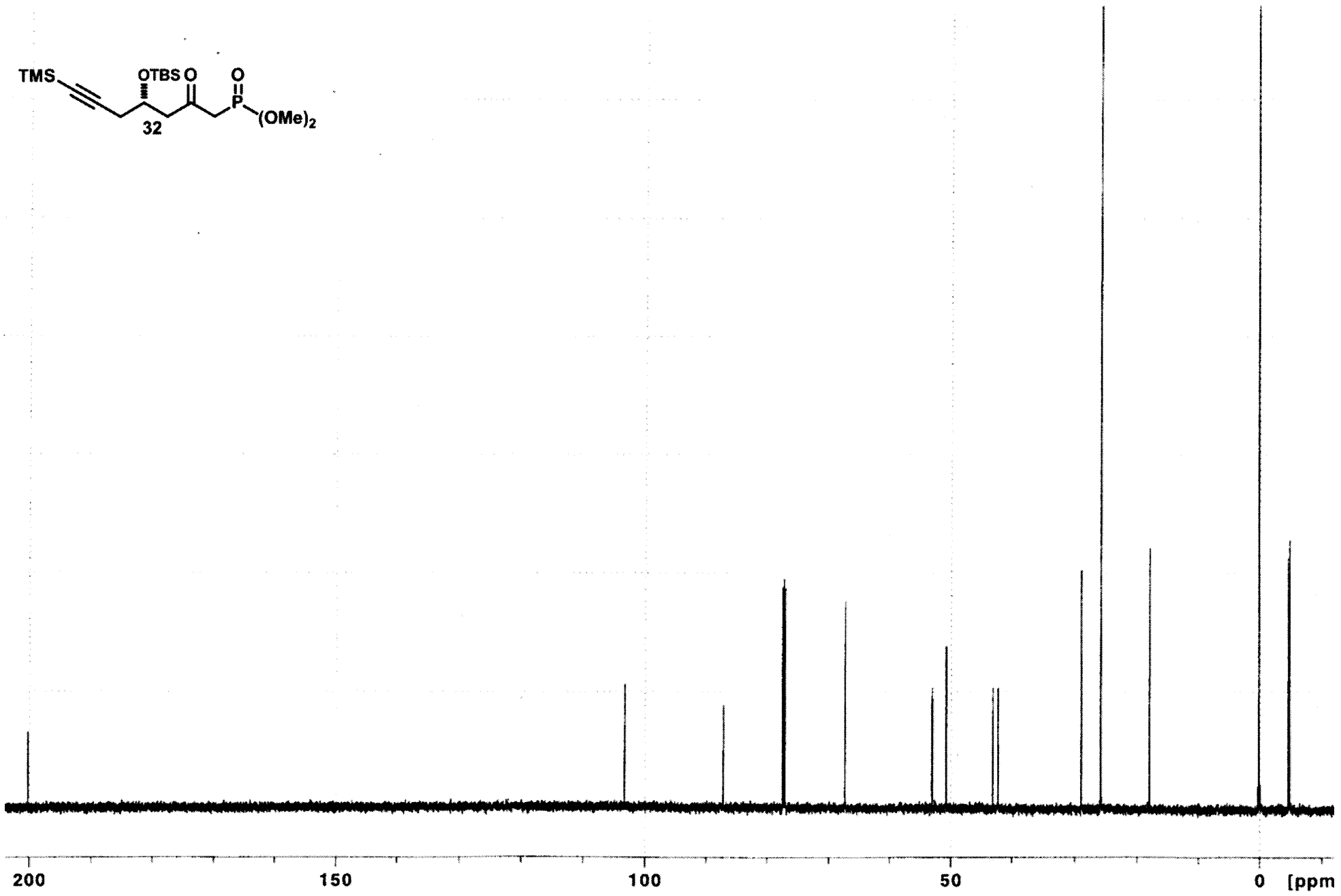
25

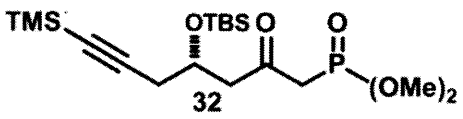

TMS
OTBS
O
OBn
42

150
100
50
0
(ppm)

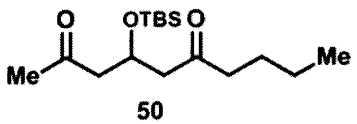

TMS
OTBS
O
OBn
42

8
6
4
2
0
[ppm

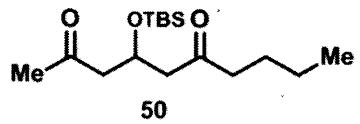

TMS
OTBS
O
O
P
(OMe)2
32
200
150
100
50
0
[ppm


TMS
OTBS
O
O
P
(OMe)2
32

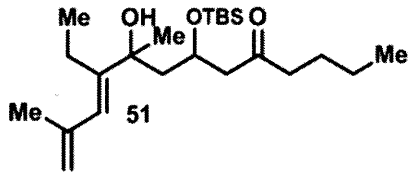
6
4
2
0 [ppm



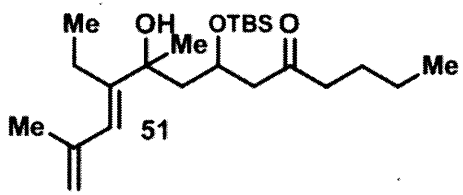
50



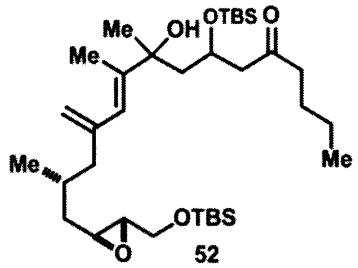
50


Me
OH
Me
OTBS
O
Me
Me
51

ppm 200
180
160
140
120
100
80
60
40
20
0

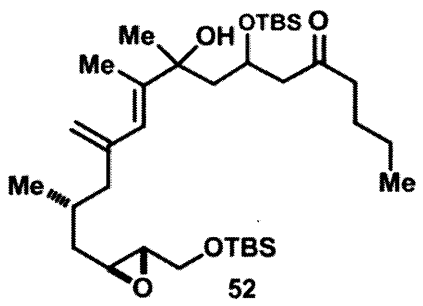

Me
OH
Me
OTBS
O
Me
Me
51

ppm 8
7
6
5
4
3
2
1
0

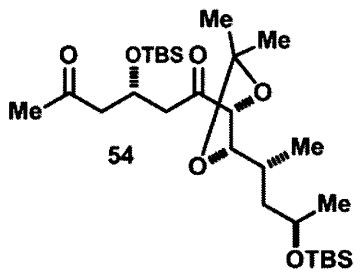

Me
OH
OTBS
O
Me
Me
Me
OTBS
O

52

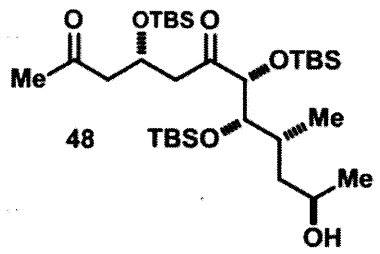
ppm 200
180
160
140
120
100
80
60
40
20
0



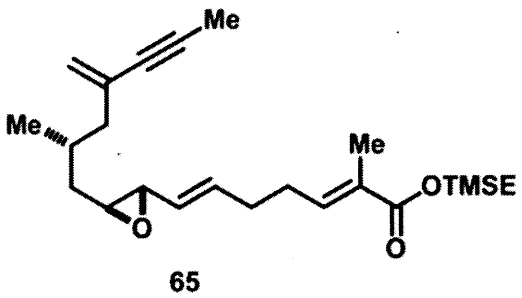
52


Me
Me
O
OTBS
O
O
Me
54
O
Me
Me
OTBS

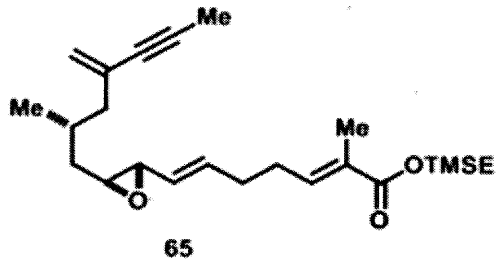
ppm 7
6
5
4
3
2
1
0


O
OTBS
O
Me
OTBS
48
TBSO
Me
Me
OH

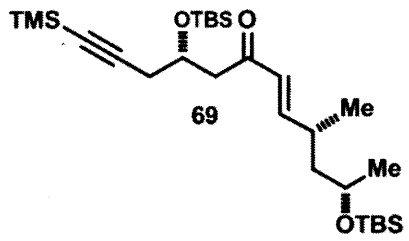
1
– 0
[ppm]



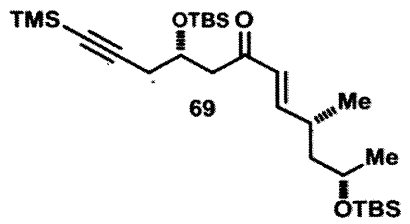
65

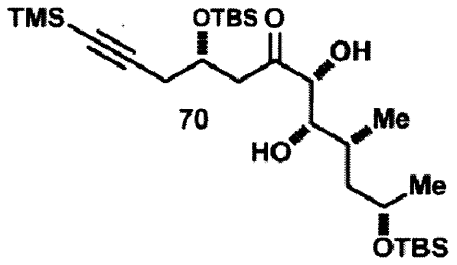


65

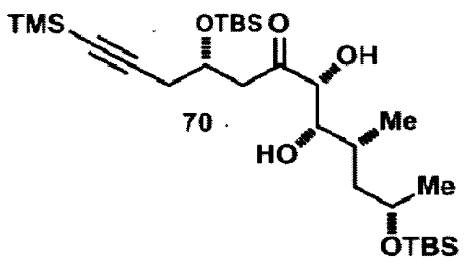


69

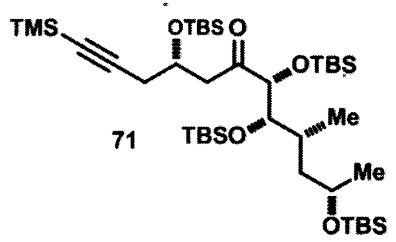

TMS
OTBS
O
69
Me
Me
OTBS


TMS
OTBS
O
OH
70
HO
Me
Me
OTBS

ppm 200
180
160
140
120
100
80
60
40
20
0

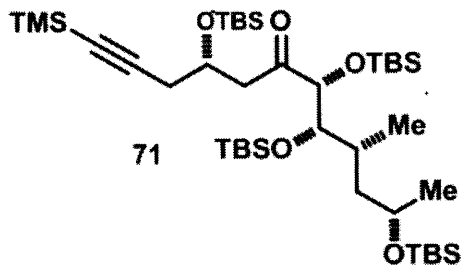

TMS
OTBS
O
OH
70
Me
HO
Me
OTBS

7
6
5
4
3
2
1
0

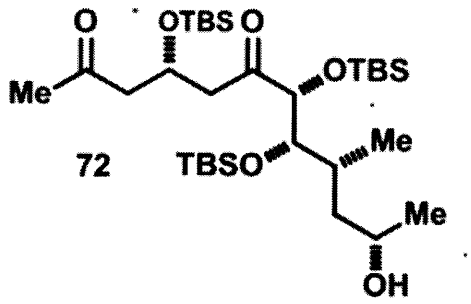

TMS
OTBS
O
OTBS
TBSO
Me
Me
OTBS

71

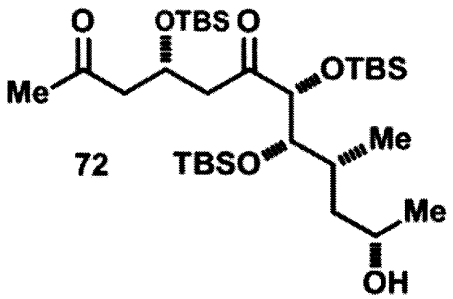
ppm 200
180
160
140
120
100
80
60
40
20
0



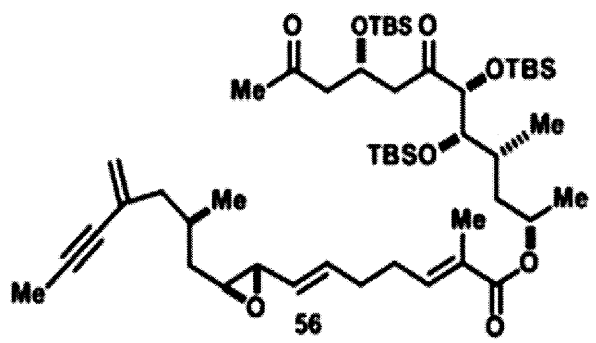
71



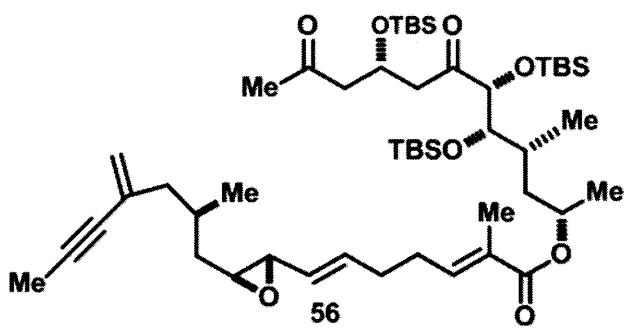
72



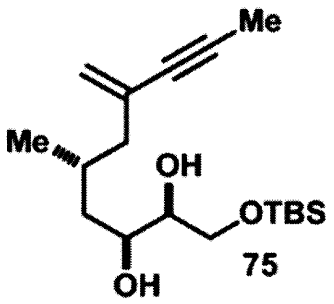
72


O
OTBS
O
Me
OTBS
TBSO
Me
Me
Me
Me
Me
O
O
O
56

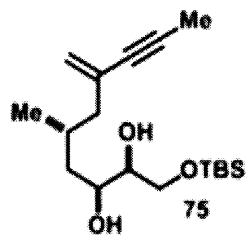
ppm 200
180
160
140
120
100
80
60
40
20
0


O
OTBS
O
Me
OTBS
TBSO
Me
Me
Me
Me
Me
O
O
O
56

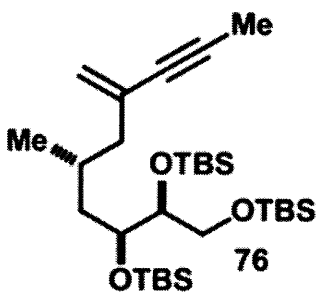
ppm 7
6
5
4
3
2
1
0



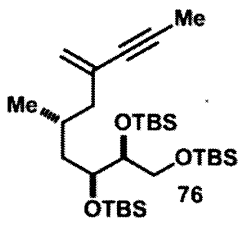
75



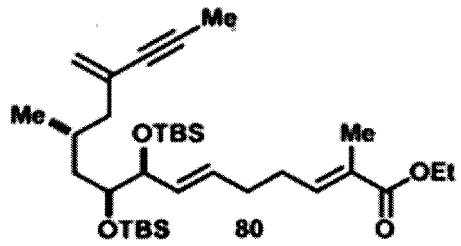
75



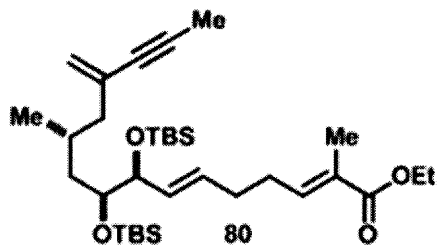
76


Me
Me
OTBS
OTBS
OTBS
76

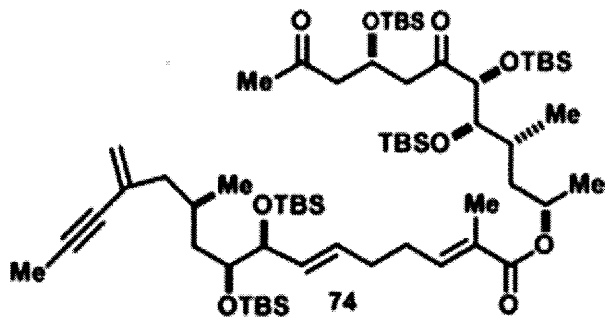
ppm 7
6
5
4
3
2
1
0


Me
Me
OTBS
Me
OEt
OTBS
80
O

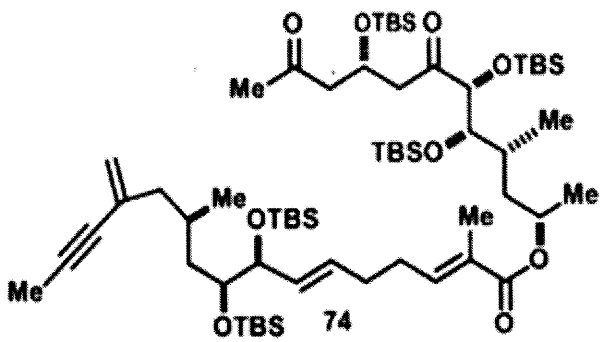
180
160
140
120
100
80
60
40
20
0


Me
Me
OTBS
Me
OEt
OTBS
80
O

ppm 7
6
5
4
3
2
1
0


O
OTBS
O
OTBS
Me
Me
TBSO
Me
Me
OTBS
Me
O
Me
O
OTBS
74

ppm 200
180
160
140
120
100
80
60
40
20
0


O
OTBS
O
Me
OTBS
TBSO
Me
Me
Me
OTBS
Me
O
Me
OTBS
74
O

7
6
5
4
3
2
1
0

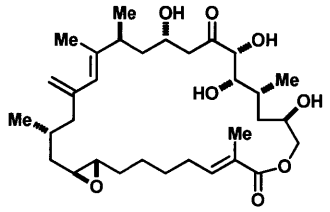
Chapter 2

Studies Directed Toward the Synthesis of Amphidinolide G_3 and H_4

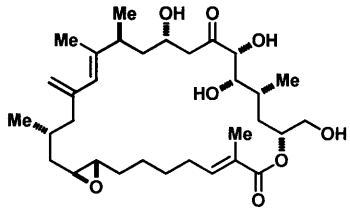
Introduction

The structures of amphidinolides G_3 and H_4 provide a number of synthetic challenges (Figure 1),[1] including a 26- or 27-membered macrocyclic lactone ring, nine stereogenic centers (three of which are consecutive), an α-hydroxy ketone, and 1,3-diene that has been shown to be very sensitive to various reaction conditions.[1, 2]

Figure 1. Targeted Amphidinolides G_3 and H_4



amphidinolide G_3



amphidinolide H_4

We envisioned tackling the problem of the 1,3-diene via the Ni-catalyzed reductive coupling of a 1,3-enyne and aldehyde developed in our lab (Figure 2).[3] After the reductive coupling, displacement of the activated alcohol with a nucleophilic methyl group would yield the desired 1,3-diene moiety.

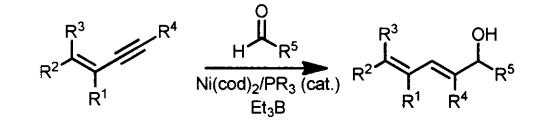
---

[1] (a) For reviews of the amphidinolides, see: Kobayashi J. *J. of Antibio.* **2008**, *61,* 271. (b) Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77. (c) Chakraborty, T. K.; Das, S. *Curr. Med. Chem.: Anti-Cancer Agents* **2001**, *1*, 131. (d) Kobayashi J.; Ishibashi M. in "*Comprehensive Natural Products Chemistry*", Vol. 8, pp. 619-649, K. Mori, Ed., Elsevier, New York, **1999**. (e) For a current website see: http://www2.onu.edu/~b-myers/amp/amphidinolides.html.

[2] Fürstner, A.; Bouchez, L. C.; Funel, J.; Liepins, V.; Porrée, F.; Gilmour, R.; Beaufils, F.; Laurich, D.; Tamiya, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 9265.

[3] Original report: (a) Miller, K. M.; Luanphaisarnnont, T.; Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 4130. (b) For a review see: Moslin, R. M.; Moslin, K. M.; Jamison, T. F. *Chem. Commun.* **2007**, 4441.

Figure 2. Ni-catalyzed coupling of 1,3-enynes with aldehydes.



R^1, R^2, R^3 = H, alkyl;
R^4 = aryl, alkyl (1°, 2°, 3°)

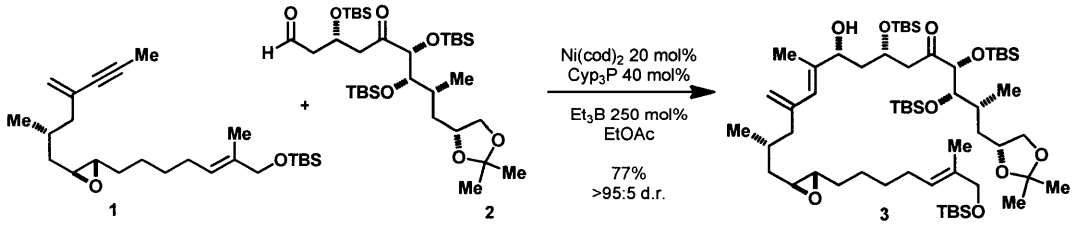
90:10 regioselectivity

Previously Reported Work Toward Amphidinolide H_4[4]

A. Ni-Catalyzed Reductive Coupling[5]

In our previous work toward amphidinolide H_4 we prepared enyne **1** and aldehyde **2** and successfully coupled them in excellent yield and diastereoselectivity to give dienol **3** (Scheme 1).[4] Even though an achiral ligand was used for the coupling, we nevertheless observed excellent diastereoselectivity. Our current hypothesis is that this diastereoselectivity was due to one or more of the stereocenters from the aldehyde fragment.

Scheme 1



---

[4] Ndubaku, C. O. "*Diastereoselective Nickel-Catalyzed Reductive Coupling of Alkynes and Aldehydes and Application Toward the B-Type Amphidinolides*", Ph. D. Thesis, Massachusetts Institute of Technology, **2005**.

[5] The author collaborated with Dr. Chudi O. Ndubaku during this stage of work. The work in this section was performed by Dr. Chudi O. Ndubaku and is reported in ref. 4.

B. Installation of the Methyl Substituent[6]

Initial studies directed toward methyl group installation to displace the activated alcohol **3** were not met with success. Thus we turned our attention to less complex model systems that resembled alcohol **3**, but would be simpler and more efficient to synthesize. To that end the model dienols **4** and **5** were prepared to carry out the S_N2 displacement studies.[4]

Figure 3. Model Dienols for the Methyl Group Installation Studies.

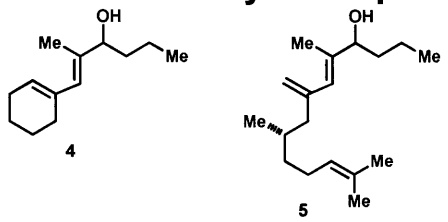


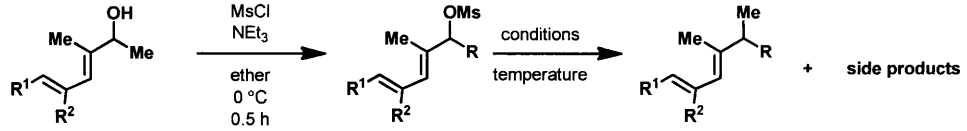
Table 1 provides a summary of an exhaustive investigation into the ideal conditions for stereospecific and site-selective installation of the methyl group. We investigated many groups to activate the hydroxyl group including acetic anhydride, tosyl chloride, mesyl chloride, isopropylsulfonyl chloride, and *n*-butylsulfonyl chloride among others. We found that only mesyl chloride gave the desired activated alcohol followed by displacement products (Table 1). Other activators either failed to activate the dienol or gave elimination products, rather than the desired S_N2 displacement product. We started our studies by focusing on the displacement of the mesylate with $Me_2Cu(CN)Li_2$. However, with $Me_2Cu(CN)Li_2$ as the nucleophile, primarily S_N2' and S_N2'' products were observed although a trace amount of the S_N2 product could be seen in the ^1H NMR spectra of the unpurified reaction mixture (entries 1-4). Use of Me_3In or Me_3Ga derived

[6] The author collaborated with Dr. Chudi O. Ndubaku during this stage of work. The work performed in this section is that of the author and portions are reported in ref. 4.

from InI_3, GaI_3, or $GaCl_3$ and three equivalents of MeLi, respectively, gave what appeared to be elimination and various rearrangement products that could not be separated (entries 5-7). A similar result was seen with $AlMe_3$ as the reagent (entry 8). We did find limited success with Me_3In (derived from $InCl_3$ and three equivalents of MeLi) in a solvent system of 1:1 Et_2O/hexane (entry 9). The regioselectivity for the S_N2 product under these conditions appeared to be good; however, it was difficult to tell the exact amount of the desired product that had formed due to impurities that could not be separated. We were prompted to investigate these conditions based on a report by Hirashita on regioselective displacement of primary allylic bromides.[7] Performing the reaction at colder temperatures did not noticeably increase the yield or selectivity for the desired S_N2 product (entries 10 and 11). We also investigated other solvent systems, but in the absence of hexane as a co-solvent the S_N2' and S_N2'' products began to dominate again (entries 12 and 13).

[7] Hirashita, T.; Hayashi, Y.; Mitsui, K.; Araki, S. *Tetrahedron Lett.* **2004**, *45*, 3225.

Table 1. Summary of Methyl Group Installation Investigations.



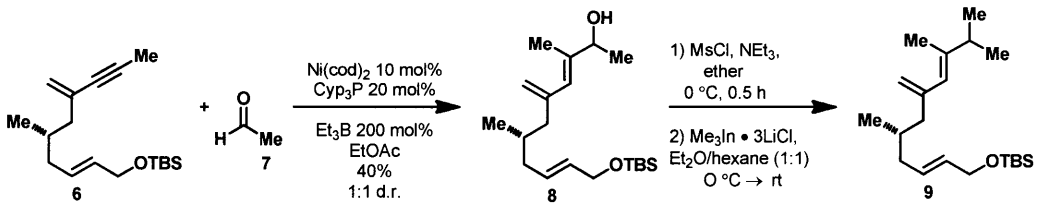
dienol mesylate S_N2

entry	dienol	conditions	temperature	results[a]
1	**4**	$Me_2Cu(CN)Li_2$, Et_2O	O °C → rt	S_N2' and S_N2'' major + S_N2 minor
2	**4**	$Me_2Cu(CN)Li_2$, Et_2O/THF (2:1)	O °C → rt	S_N2' and S_N2'' major + S_N2 minor
3	**4**	$Me_2Cu(CN)Li_2$, Et_2O/THF (1:1)	-78 °C → O °C	S_N2' and S_N2'' major + S_N2 minor
4	**4**	$Me_2Cu(CN)Li_2$, Et_2O/hexane (1:1)	O °C → rt	S_N2' and S_N2'' major + S_N2 minor
5	**5**	Me_3In • 3LiI, Et_2O/hexane (1:1)	O °C → rt	many unidentified products
6	**5**	Me_3Ga • 3LiI, Et_2O/hexane (1:1)	O °C → rt	many unidentified products
7	**5**	Me_3Ga • 3LiCl, Et_2O/hexane (1:1)	O °C → rt	many unidentified products
8	**5**	$AlMe_3$, Et_2O/toluene (1:1)	O °C → rt	many unidentified products
9	**5**	Me_3In • 3LiCl, Et_2O/hexane (1:1)	O °C → rt	> 50% S_N2
10	**5**	Me_3In • 3LiCl, Et_2O/hexane (1:1)	-78 °C	> 50% S_N2
11	**5**	Me_3In • 3LiCl, Et_2O/hexane (1:1)	-130 °C	> 50% S_N2
12	**5**	Me_3In • 3LiCl, Et_2O	O °C → rt	40% S_N2
13	**5**	Me_3In • 3LiCl, Et_2O/THF (2:1)	O °C → rt	S_N2' and S_N2'' major + S_N2 minor

[a] Compounds characterized by crude ^1H NMR.

The compounds identified in Table 1 were not rigorously characterized due to difficulty with the separation of the compounds. Therefore we prepared a model system that would be easier to characterize. To that end we carried out the Ni-catalyzed reductive coupling of enyne **6** and acetaldehyde (**7**) to give dienol **8**. We then subjected the alcohol to mesylation conditions followed by the addition of the prepared $InMe_3$ reagent, which gave what has been identified as diene **9**, as the major product.[8]

Scheme 2



[8] The diene **9** could not be separated from other minor products, but could be characterized by ^1H NMR because of the characteristic *i*-Pr group contained within the framework of diene **9**. The *i*-Pr group would not be present if S_N2' and S_N2'' products were formed. The S_N2 product was estimated to be formed in about 65% yield.

While we were confident that we had indeed formed the S_N2 product diene **9**, the reaction received further investigation. In order to determine that S_N2 displacement was favored over S_N2' and S_N2'', we used a ^{13}C-labeled methyl group (after preparing alcohol **11** as a 1:1 mixture of diastereomers). Experiments using $(^{13}CH_3)_2Cu(CN)Li_2$ and $(^{13}CH_3)_3In(LiCl)_3$ as reagents were thus performed (Scheme 3). When $(^{13}CH_3)_2Cu(CN)Li_2$ was used as the nucleophile, the ^{13}C NMR spectrum showed six major peaks, as well as a few minor peaks, each corresponding to a methyl group having been installed on the different products (and their corresponding diastereomers, Figure 4). When $(^{13}CH_3)_3In(LiCl)_3$ was used as the nucleophile, one major product was obtained (as a mixture of diastereomers) with suppressed formation of the two other compounds (Figure 5). The major peak (20.2 ppm) in the ^{13}C NMR spectrum for the $(^{13}CH_3)_3In(LiCl)_3$ case correlated well to the same chemical shift as the corresponding methyl group in the amphidinolide H_4.

Scheme 3

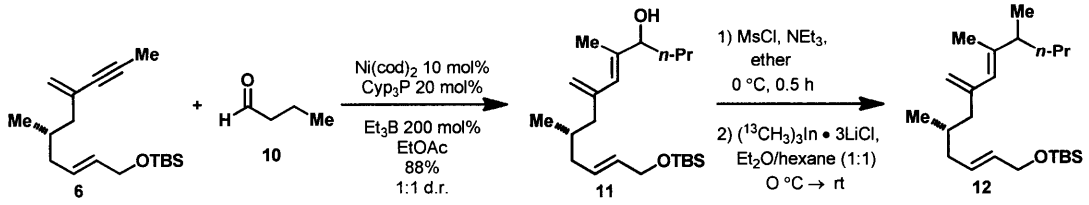


Figure 4. ^{13}C NMR Spectrum of Reaction with $(^{13}CH_3)_2Cu(CN)Li_2$.

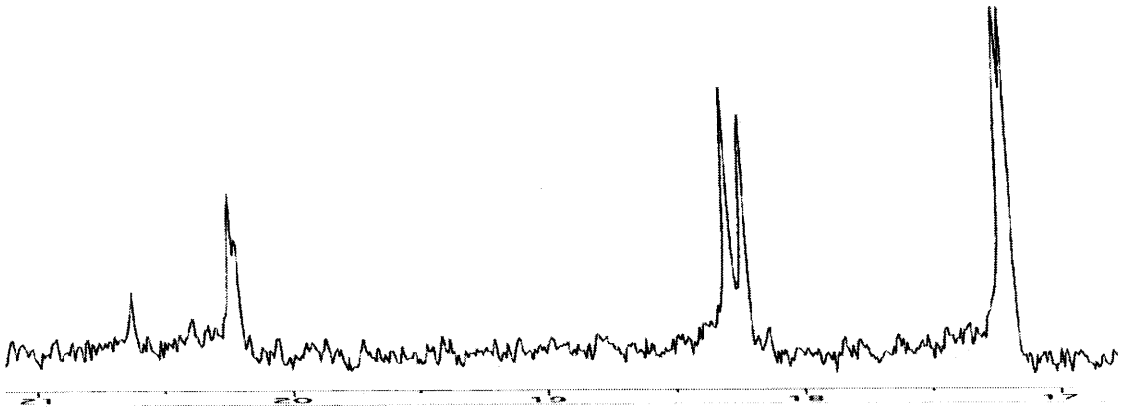
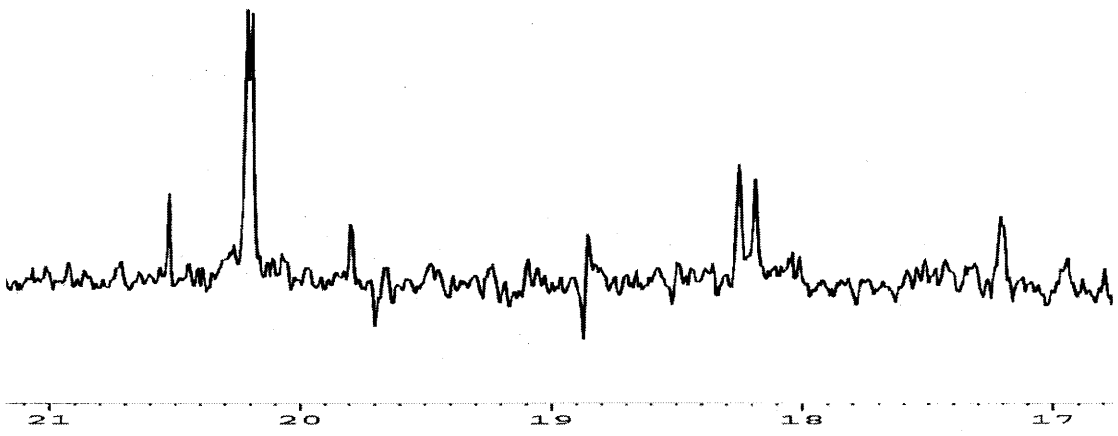


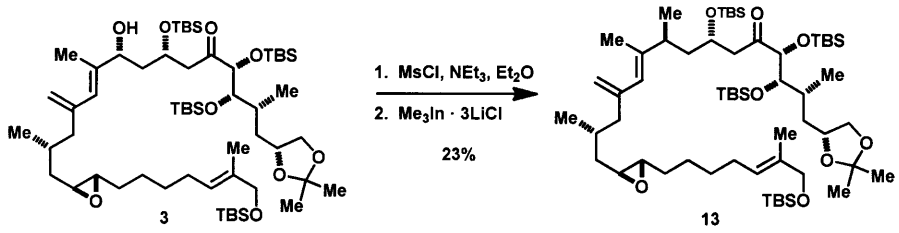
Figure 5. ^{13}C NMR Spectrum of Reaction with $(^{13}CH_3)_3In$.



C. Application of the Trimethylindium Method to the Amphidinolide H_4[5]

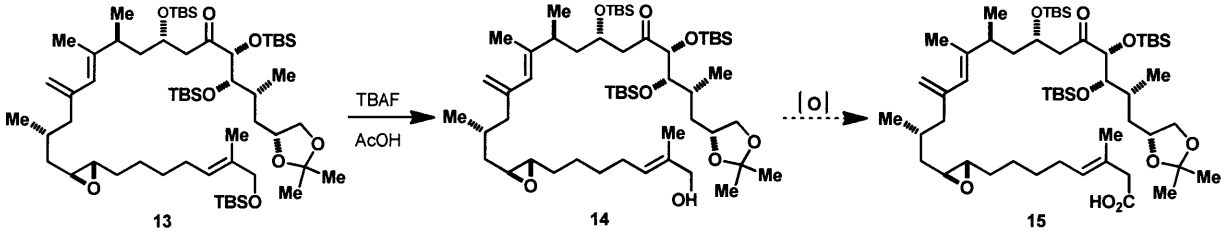
We were able to apply our results from the model system to the amphidinolide system to give the diene **13** in modest yield (Scheme 4).

Scheme 4



Although we able to prepare diene **13**, we found that after TBS deprotection, we were unable to oxidize alcohol **14** to desired carboxylic acid **15**. Many oxidation conditions were investigated, but all resulted in decomposition of the diene (Scheme 5).

Scheme 5



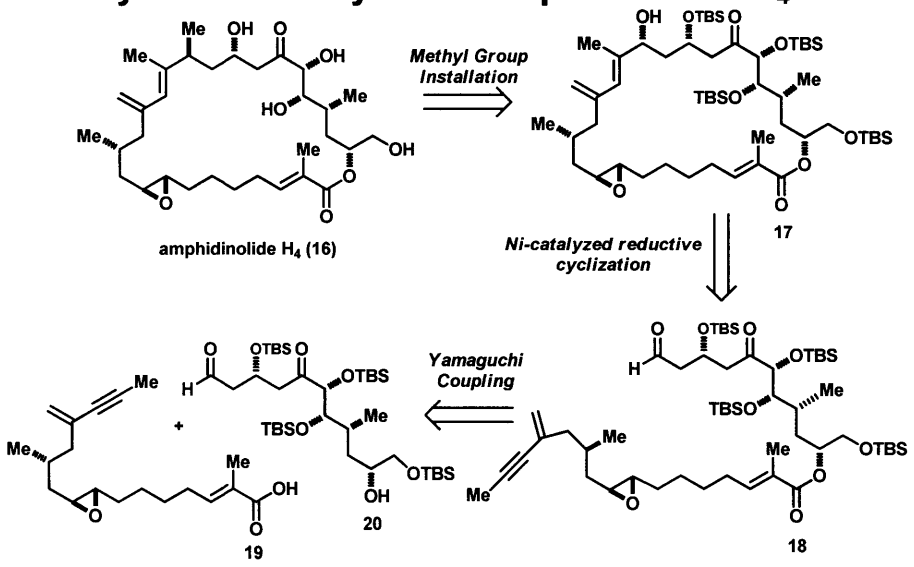
Synthetic Strategy Toward Amphidinolides H_4

Based on our work toward amphidinolide B_1 we reasoned that we could apply an intramolecular Ni-catalyzed reductive cyclization approach to amphidinolide H_4. This would provide several advantages over our previous intermolecular Ni-catalyzed reductive coupling approach. First, this strategy would provide a route in which the ester moiety was in place prior to diene formation. This would be beneficial because the diene does not tolerate a wide variety of reaction conditions. Secondly, it would allow us to install the methyl group at a later stage, and only four TBS groups would need to be removed after the methyl group was installed.

To this end we envisioned preparing amphidinolide H_4 (**16**) after methyl group installation and TBS deprotection of alcohol **17** (Figure 6). We intended to prepare alcohol **17** via Ni-catalyzed reductive cyclization of substrate **18**, which can be readily simplified further by cleavage of the ester C-O bond to give the two relatively evenly sized fragments enyne **19** and aldehyde **20**, respectively. The two fragments can be joined together via a Yamaguchi coupling reaction which had previously been successful for us in studies toward amphidinolide B_1.[9] Our approach would hinge on the stability of the α,β-unsaturated ester under the cyclization conditions, and based on our previous studies toward amphidinolide B_1 we did not envision any problems. Also, the Ni-catalyzed cyclization product would need to be obtained with high diastereoselectivity. In our previous attempt to amphidinolide H_4 we observed high diastereoselectivity without the use of a chiral phosphine ligand, and we hoped to see similar results with a similar substrate, the only difference being the intramolecular cyclization instead of the Ni-catalyzed coupling (Scheme 1).[4]

[9] Inanaga, J. ; Hirata, K.; Saeki, H. ; Katsuki, T. ; Yamaguchi, M. A. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

Figure 6. Retrosynthetic Analysis of Amphidinolide H_4.



Results and Discussion

A. Synthesis of the Aldehyde Fragment[10]

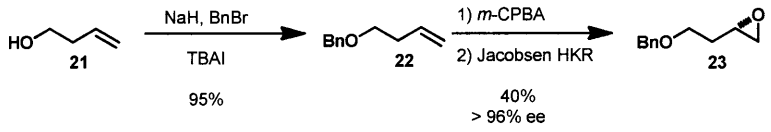
For the synthesis of the aldehyde fragment **20**, we envisioned making use of novel Ni-catalyzed reductive coupling of alkynes and mono-substituted epoxides.[11] Therefore, implementation of this strategy required the formation of the enantiomerically enriched epoxide **23**. Benzyl protection of 3-buten-1-ol (**21**) gave benzyl ether **22**, and epoxidation generated the racemic epoxide. Then Jacobsen hydrolytic kinetic

[10] The author collaborated with Dr. Chudi O. Ndubaku during this stage of work. The work in this section was first performed by Dr. Chudi O. Ndubaku and is reported in ref. 4. The author worked on scaling up the process.

[11] (a) Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 8076. For an application in total synthesis, see: (b) Colby, E. A.; O'Brien, K. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 998.

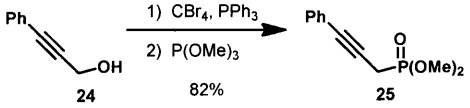
resolution (HKR) was employed to resolve the racemic epoxide to enantiomeric purity which gave epoxide **23** (Scheme 6).[12]

Scheme 6



The alkyne coupling partner **25**, meanwhile, was readily synthesized in two steps by the conversion of the commercially available 3-phenyl-2-propyn-1-ol (**24)** into the corresponding propargyl bromide followed by an Arbuzov reaction to give alkynylphosphonate **25** in good yield over the two steps (Scheme 7).[13]

Scheme 7



We also planned to make use of a Horner–Wadsworth–Emmons coupling (HWE)[14] with aldehyde **29**. The aldehyde fragment was derived from the highly diastereoselective

---

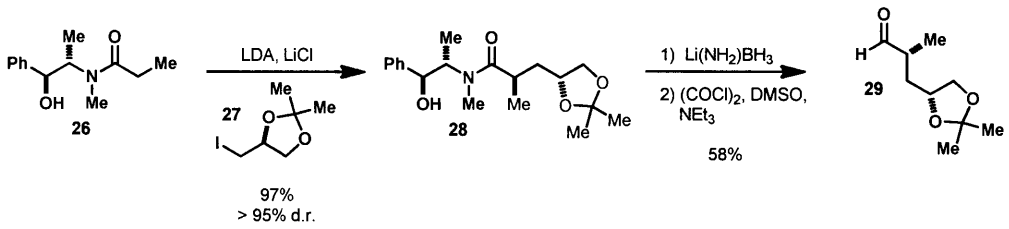
[12] (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307.

[13] For an excellent review on the Arbuzov reaction: Bhattacharya, A. K.; Thayagarajan, G. *Chem. Rev.* **1981,** *81*, 415.

[14] Reviews: (a) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73. (b) Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, pp 729. (c) Walker, B. J. In *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic Press: New York, 1979; pp 155.

alkylation of the Myers pseudoephedrine chiral auxiliary (**26**)[15] with the iodide **27** (Scheme 8). Reduction of the amide **28** with lithium amidotrihydridoborate provided the corresponding alcohol that was directly subjected to the Swern oxidation conditions[16] to generate the desired aldehyde **29**.

Scheme 8



With these three simple fragments in hand we were prepared to begin to couple them. We used the previously described Ni-catalyzed reaction to unite the alkyne **25** and epoxide **23** to give alcohol **30** (Scheme 9). This was followed by TBS protection of the hydroxyl group under standard conditions to give phosphonate **31**. Ozonolysis of the alkene moiety of phosphonate **31** and subsequent reductive work-up with dimethylsulfide gave access to phosphonate **32** in good yield. The HWE olefination of the phosphonate **32** and the aldehyde **29** was accomplished under the Roush–Masamune conditions to provide the *E*-α,β-unsaturated ketone **33**.[17] The olefination reaction was highly selective and gave the desired ketone in 95:5 *E:Z* ratio.

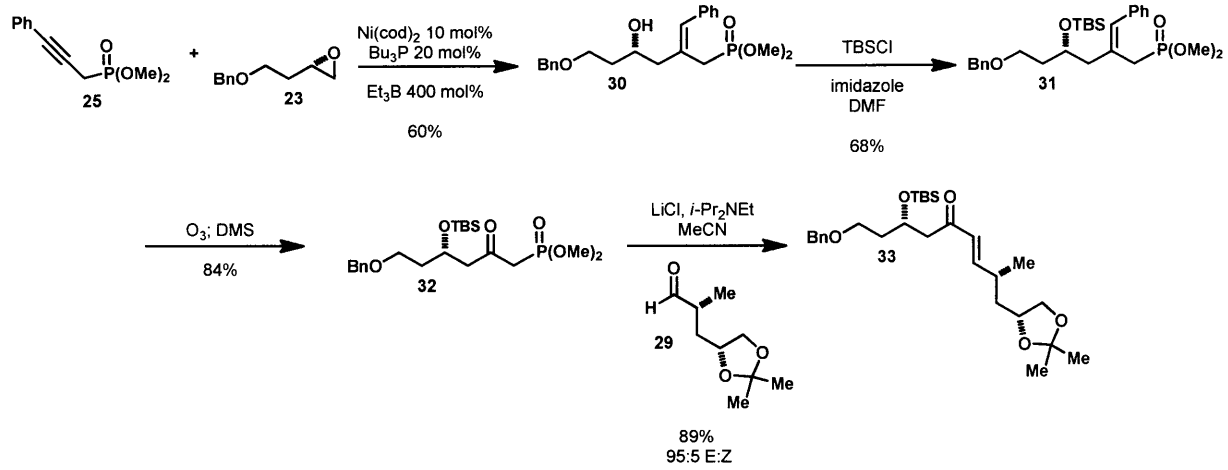
---

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

[16] (a) Tidwell, T. T. *Org. React.* **1990**, *39*, 297-572. (b) Tidwell, T. T. *Synthesis* **1990**, 857-870. (c) Haines, A. H. *Methods for the Oxidation of Organic Compounds*; Academic: New York, 1988. (d) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165. (e) Moffatt, J. G. In *Oxidation*; Augustine, R. L., Trecker, D. J., Eds.; Dekker: New York, 1971; Vol. 2, Ch. 1, pp 1-64.

[17] Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T.; *Tetrahedron Lett.* **1984**, *25*, 2183.

Scheme 9



Introduction of the *syn*-1,2-diol moiety was achieved by utilizing the Sharpless Asymmetric Dihydroxylation (SAD) procedure (Scheme 10).[18] Due to the electron-deficient nature of the alkene portion of enone **33** the commercial AD-mix in this reaction was supplemented with additional potassium osmate and $(DHQ)_2PHAL$ (sometimes referred to as *super AD-mix*) in order to proceed more efficiently and delivered the 1,2-diol **34** in good yield and diastereoselectivity. *Bis*-protection of the hydroxyl groups of diol **34** as TBS ethers, followed by hydrogenolysis of the benzyl ether using Pearlman's catalyst,[19] and subsequent Dess-Martin oxidation[20] of the resulting alcohol, afforded the desired acetonide **2** in excellent overall yield.

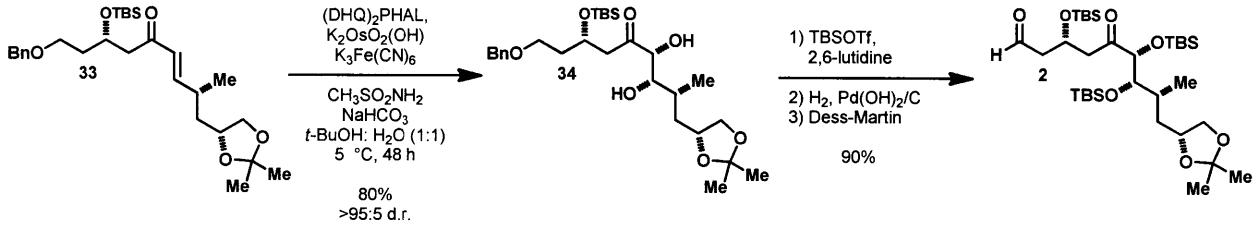
---

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

[19] Pearlman, W. M. *Tetrahedron Lett.* **1967**, *8* (17), 1663.

[20] (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155-4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277-7287. (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

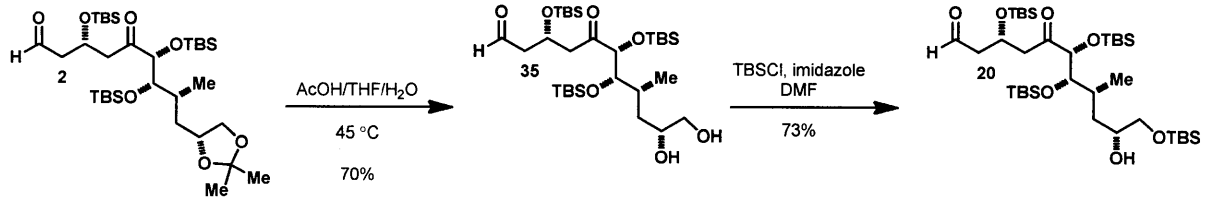
Scheme 10



B. Completion of the Synthesis of the Aldehyde Fragment

Completion of the synthesis of the aldehyde fragment began with cleavage of acetonide protecting group (Scheme 11). The optimized conditions for the acetonide removal were 2:1:1 AcOH:THF:H_2O at 45 °C for two hours. The reaction could also be performed in a microwave at 90 °C for six minutes and gave a better yield (70% – 80%). The primary alcohol could then be protected selectively as the silyl ether in moderate yield to complete the synthesis of the desired aldehyde **20**.

Scheme 11

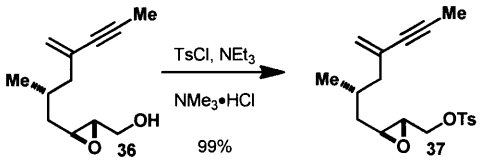


C. Synthesis of the Enyne Fragment[21]

The synthesis of the enyne fragment commences with intermediate **36** from our synthesis of amphidinolide B_1. The tosylate **37** could be prepared in excellent yield under standard conditions (Scheme 12).

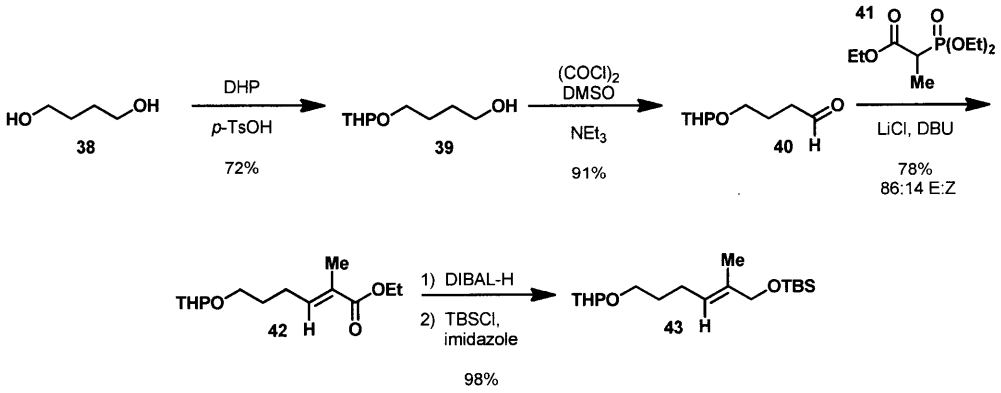
[21] The author collaborated with Dr. Chudi O. Ndubaku during this stage of work and portions have been reported in ref. 4.

Scheme 12



The tosylate (**37**) was formed in order to employ it in a cuprate mediated displacement[22] by an appropriate nucleophile in order to complete the synthesis of the enyne fragment. The cuprate was constructed from commercially available 1,4-butanediol (**38**) (Scheme 13). Formation of the mono-THP ether **39** and subsequent Swern oxidation provided access to the known aldehyde **40**.[23] This aldehyde was converted to the corresponding α,β-unsaturated ester **42** by HWE olefination with phosphonate **41** under Roush–Masamune conditions.[17] While the E:Z selectivity was only modest, we were able to separate the isomers during the purification process. Reduction of the ester **42** followed by TBS protection provided the TBS ether **43** in excellent yield.

Scheme 13



[22] Tsuboi, S.; Yamafuji, N.; Utaka, M. *Tetrahedron Asymm.* **1997**, *8*, 375.

[23] Uesato, S.; Kobayashi, K.; Inouye, H. *Chem. Pharm. Bull.* **1982**, *30*, 927.

We were able to optimize the formation of alcohol **44**, with a process to remove the THP protecting group in the presence of the TBS protecting group. The use of $MgBr_2$ gave modest yields of 58 – 60% (Table 1, Entry 1).[24] However, on larger scale the yield was generally decreased even further. Dimethylaluminum chloride, which has been reported to selectively cleave acetonide protecting groups in the presence of primary TBS groups, did not perform the desired transformation (Entry 2).[25] In order to expand the scope of possible conditions for this transformation, it was decided to also examine Brønsted acids. It was found that the rate of solvolysis of TBS ethers is quite solvent-dependent and therefore useful for the selective cleavage of groups such as THP ethers.[26] It was reported that dilute methanolic HCl in anhydrous THF (<0.5 vol% MeOH) cleaved THP ethers; whereas, TBS groups remained intact even at elevated temperatures. However, if the amount of methanol was increased (50 vol% MeOH) both THP and TBS ethers were efficiently cleaved at 0 °C. These findings were successfully translated to the present case, and after some optimization, it was possible to ascertain conditions that allowed for production of **44** in acceptable yield (Entries 3 – 5).

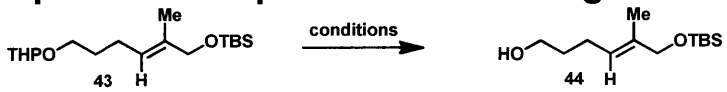
---

[24] Kim, S.; Park, J.-H. *Tetrahedron Lett.* **1987**, *28*, 439.

[25] Wovkulich, P. M.; Shankaran, K.; Kiegiel, J.; Uskokovic, M. R. *J. Org. Chem.* **1993**, *58*, 832.

[26] (a) Zimmermann, K. *Synth. Commun.* **1995**, *25*, 2959. (b) Gössinger, E.; Graupe, M.; Kratky, C.; Zimmermann, K. *Tetrahedron* **1997**, *53*, 3083.

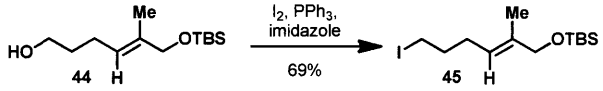
Table 2. THP Deprotection Optimization Investigation.



entry	Reagent	equivalent.	concentration (M)	solvent (vol%)	t (h)	T (° C)	product (%)
1	$MgBr_2$ (anhydrous)	3.00	-	Et_2O	16	25	58 – 60
2	Me_2AlCl	4.00	-	DCM	2	-20	Decomposition
3	HCl (2.0 N in Et_2O)	1.30	0.052	THF/MeOH (99.6:0.4)	7	67	67
4	HCl (2.0 N in Et_2O)	0.32	0.013	THF/MeOH (99.6:0.4)	7	67	70
5	HCl (2.0 N in Et_2O)	0.32	0.013	THF/MeOH (99:1)	20	67	77
6	HCl (2.0 N in Et_2O)	0.32	0.013	THF/MeOH (95:5)	20	25	Decomposition

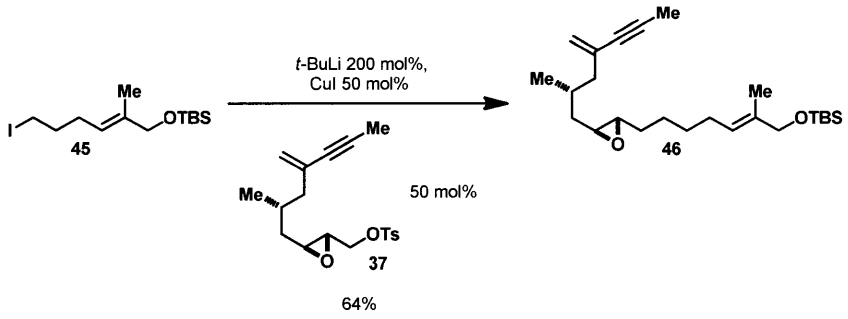
The desired iodide could then be prepared from alcohol **44** in good yield (Scheme 14).

Scheme 14



With the iodide and tosylate in place, formation of the dialkyl cuprate (generated by metal–halogen exchange[27] with **45** and mixing with one-half molar equivalent of CuI at cold temperatures) and subsequent addition of the tosylate **37** furnished the long-sought 1,3-enyne **46** (Scheme 15).

Scheme 15

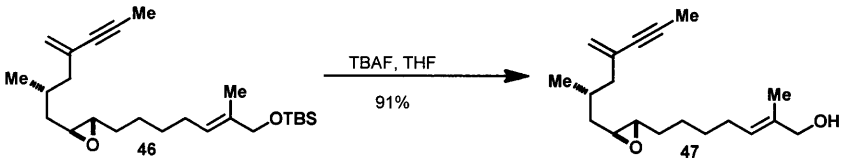


[27] Negishi, E.; Swanson, D. R.; Roussert, C. J. *J. Org. Chem.* **1990**, *55*, 5406.

D. Completion of the Synthesis of the Enyne Fragment and Yamaguchi Coupling

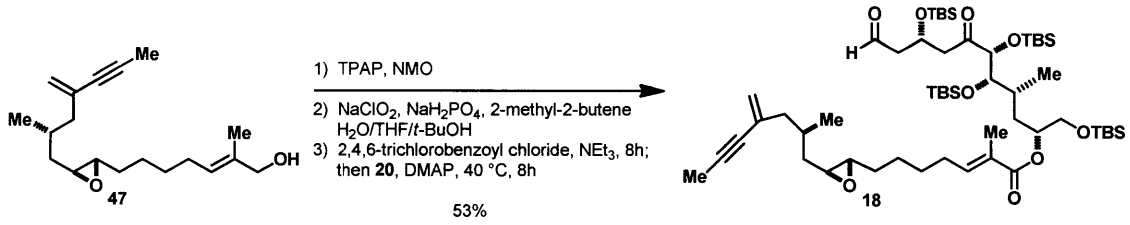
The synthesis of the enyne fragment culminated with TBAF deprotection of the TBS-ether **46** to giving allylic alcohol **47** (Scheme 16).

Scheme 16



Ley oxidation[28] of alcohol **47**, followed by oxidation of the corresponding aldehyde using $NaClO_2$ gave the corresponding carboxylic acid (Scheme 17). Yamaguchi coupling of the acid with alcohol **20** provided the desired reductive coupling precursor **18**. These results are obtained using 300 mol% DMAP. A higher yield of 79% over the three steps is obtained when 600 mol% DMAP is used, but a considerable amount of the alkene portion of the α,β-unsaturated ester is scrambled in that case.

Scheme 17



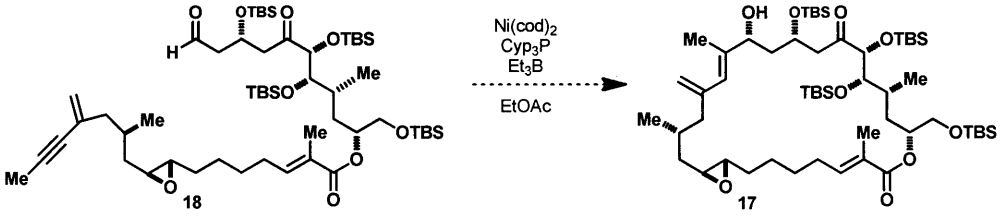
E. Ni-Catalyzed Cyclization Investigation

Our investigations into the Ni-catalyzed cyclization are summarized in Table 2. Thus far the Ni-catalyzed cyclization of compound **18** has been unsuccessful. Various conditions have been investigated but to no avail. The reaction goes to completion

[28] a) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625. b) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

quickly when 30 mol% $Ni(cod)_2$ is used at 0.05 M in EtOAc (Entries 2 and 4). However, many products that could not be separated are obtained. Nevertheless, HRMS analysis of the mixture correlates to the desired alcohol **17**. Similar results are seen when 10 mol% $Ni(cod)_2$ is used (Entry 5). When the reaction is performed at 0 °C very little conversion of the enyne **18** is observed (entry 6).

Table 3. Ni-Catalyzed Cyclization Investigation.

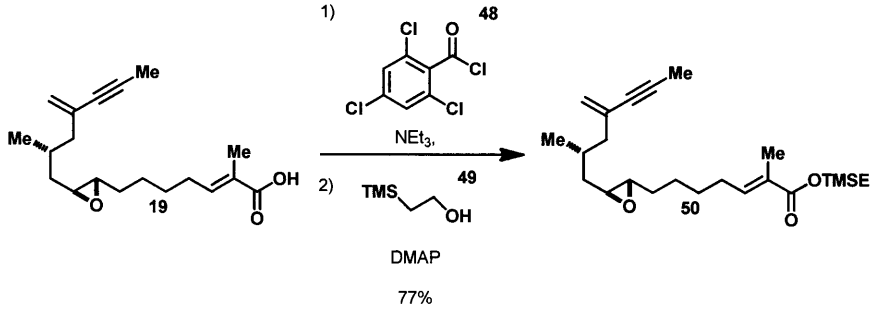


entry	$Ni(cod)_2$ / Cyp_3P / Et_3B (mol%)	conditions	results
1	20 / 40 / 400	0.08 M, 16h, rt	many products
2	30 / 60 / 400	0.05 M, 16h, rt	many products
3	30 / 60 / 400	0.02 M, 16h, rt	No reaction
4	30 / 60 / 200	0.05 M, 3.5h, rt	many products
5	10 / 20 / 200	0.05 M, 10h, rt	many products
6	10 / 20 / 200	0.05 M, 6h, 0 °C	No reaction
7	100 / 200 / 200	0.01 M, 10h, rt	many products

F. Revised Synthetic Strategy Toward Amphidinolides G_3 and H_4

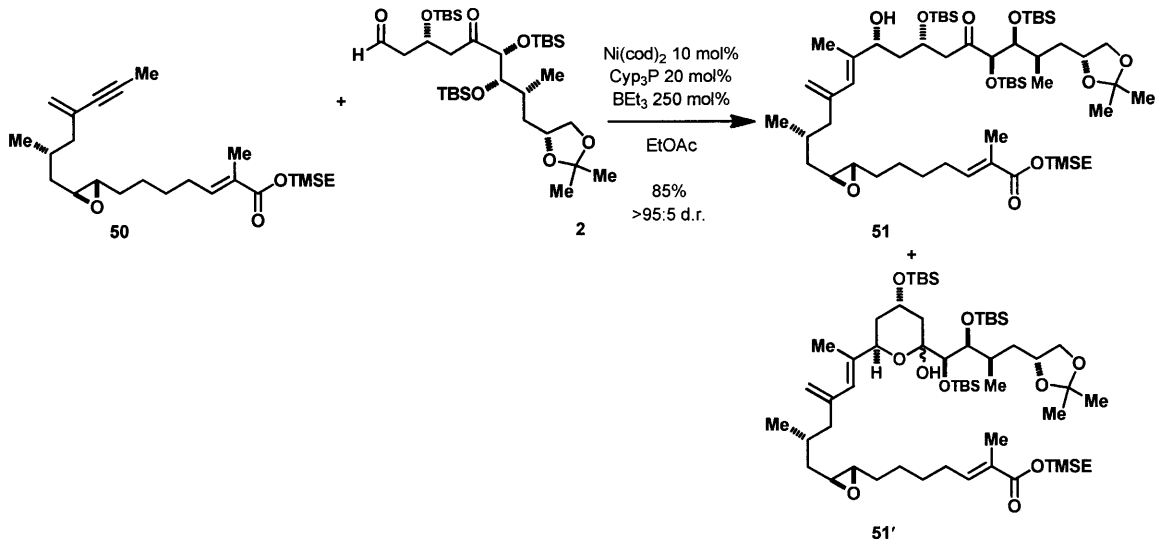
Because of the difficulties of the Ni-catalyzed cyclization we were prepared to investigate a new Ni-catalyzed coupling approach. This approach would focus on the coupling of an advanced enyne fragment with the α,β-unsaturated ester in place. To that end the enyne **50** can be prepared from enyne **19** via a Yamaguchi coupling with 2-(trimethylsilyl)ethanol in 77% yield (Scheme 18).

Scheme 18



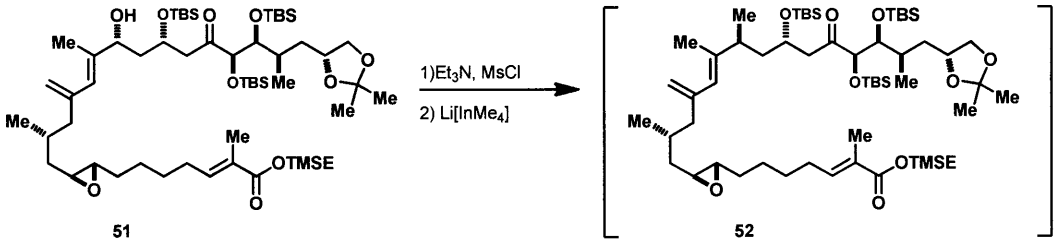
To our delight the coupling of enyne **50** and aldehyde **2** was executed in the presence of 20 mol% $Ni(cod)_2$, 40 mol% Cyp_3P, and 250 mol% Et_3B to give the dienol **51** (Scheme 19). Notably, the reaction was tolerant of the α,β-unsaturated ester. In addition to the good yield, we once again observed excellent diastereoselectivity in correlation with our previous studies.[4] We relied on Mosher ester analysis once again to determine the carbinol configuration. Based on our studies we found the carbinol to be of the *S* configuration. This configuration was assigned because of the observed upfield shift (δ 5.98) of the vinyl proton from the ester derived from *S* acid, and conversely, the downfield shift (δ 6.04) of the vinyl proton of the ester derived from the *R* acid. This was a fortuitous find, as it was required for the carbinol to be of the *S* configuration in order to obtain the correct methyl configuration found in the natural products, after S_N2 inversion with a methyl nucleophile. We also obtained 13% of the hemiketal product **51'** along with the desired dienol **51**. The prepared dienol was not stable and began to form the hemiketal **51'** after one hour. Thus it was imperative that we use the dienol once it was formed.

Scheme 19



After a lot of investigation into the displacement we found that use of the indate complex $Li[InMe_4]$ gave the desired diene **52**, albeit in low yield (Scheme 20).[29]

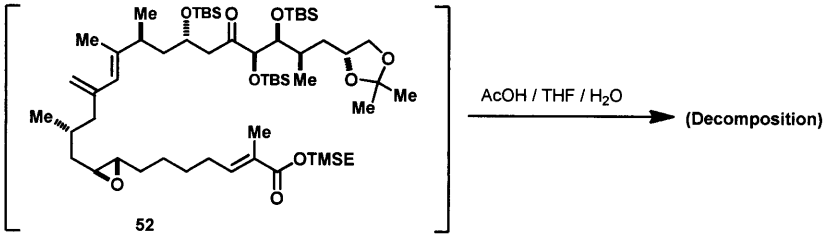
Scheme 20



We then subjected **52** to conditions we believed would deprotect the acetonide (Scheme 21). The acetonide was deprotected but during the process a portion of the diene moiety underwent isomerization to the more stable internal olefin.

[29] The yield of approximately 20% has been obtained. The structure of compound **52** has been tentatively assigned by HRMS and ^1H NMR.

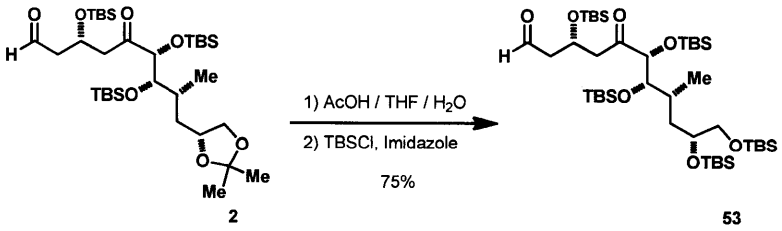
Scheme 21



G. Modified Protecting Group Strategy

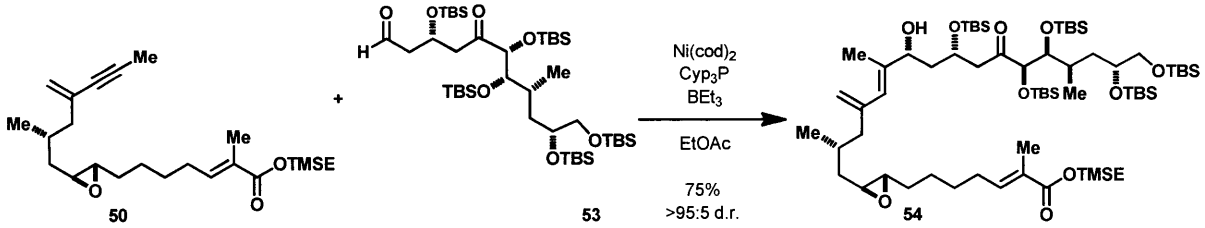
Our studies have shown that removal of protecting groups, other than silyl groups, are very difficult once the diene has been formed, and other groups have reported similar findings.[1, 2] We accordingly adjusted our strategy to have only TBS protecting groups present after installation of the diene. Therefore, we prepared aldehyde **53** in one pot by first removing the acetonide portion of aldehyde **2** and subsequent TBS protection of the crude material (Scheme 22).

Scheme 22



We carried out the reductive coupling with the new aldehyde fragment **53** and the enyne fragment **50**. Once again the coupling reaction went with good yield and diastereoselectivity (Scheme 23).

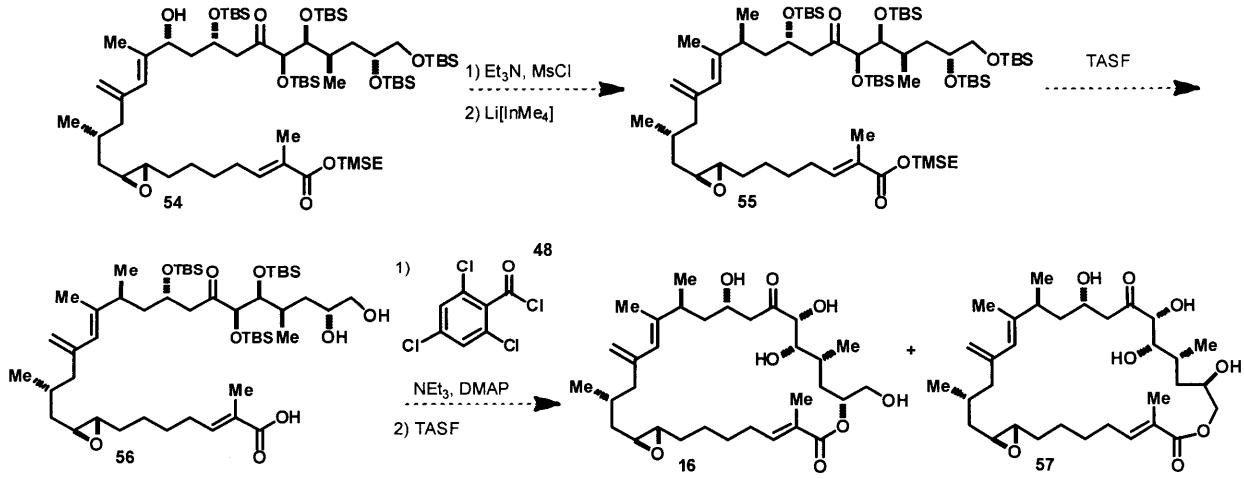
Scheme 23



H. Future Experiments

With a convergent and concise route to dienol **54** the proposed remaining steps toward amphidinolide H_4 and G_3 are shown in Scheme 24. We propose using the indate Li[$InMe_4$] to displace alcohol **54**, after mesylation, to give **55**. Removal of the TBS groups along with the TMSE group using TASF[2] would yield acid **56**.[30] A non-selective Yamaguchi cyclization would then give rise to amphidinolide H_4 (**16**) and G_3 (**57**).

Scheme 24



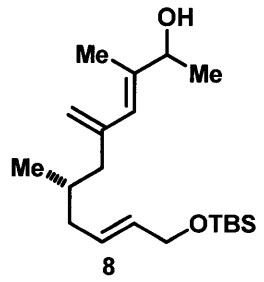
[30] We are aware that the other TBS groups could be removed during this process and complicate the Yamaguchi cyclization reaction. The plan would be to separate the undesired Yamaguchi cyclization products from amphidinolide G_3 and H_4.

Conclusion

We were able to assemble an advanced intermediate toward amphidinolides G_3 and H_4 *via* a Ni-catalyzed reductive coupling of 1,3-enyne and aldehyde. This coupling reaction gave rise to the difficult to obtain 1,3-diene moiety common to all B-type amphidinolides. We also found that Me_3In and $Li[InMe_4]$ could be employed to displace the activated dienol formed during the coupling. Future work is being directed toward completing the synthesis of amphidinolide G_3 and H_4.

Experimental Section

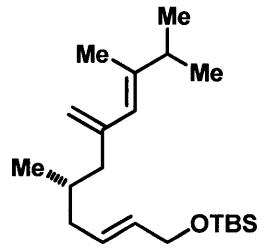
For General Information, see Experimental Section in Ch. 1.



8

(3*E*,7*S*,9*E*)-11-((tert-butyldimethylsilyl)oxy)-3,7-dimethyl-5-methyleneundeca-3,9-dien-2-ol (8). In the glovebox, $Ni(cod)_2$ (0.014 mmol, 3.76 mg) and tricyclopentylphosphine (0.028 mmol, 8 μL) were combined. Set under an argon atmosphere and outside the glovebox, Et_3B (0.274 mmol, 40 μL) was added and the mixture was cooled to 0 °C. The orange mixture was stirred at that temperature for 10 min before the addition of acetaldehyde (1.37 mmol, 77 μL). Then a solution containing

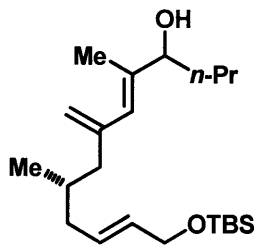
the enyne **6** (0.137 mmol, 40 mg) in EtOAc (0.25 mL) was added. The resulting light yellow reaction mixture was stirred 14 h while warming to r.t. The mixture was diluted with EtOAc (2 mL) and stirred open to air to allow for aerobic oxidation of the catalyst evident by the slow conversion of the color to pale green. The mixtudre was filtered through a short pad of silica gel (eluting with EtOAc), concentrated in vacuo, and purified by flash column chromatography (5% EtOAc/hexane). This provided the dienol (**8**) as a colorless oil (18 mg, 40% yield) as a 1:1 mixture of diastereomers. ^{1}H NMR (400 MHz, C_6D_6) δ 5.97-5.65 (m, 6H), 5.21-5.15 (m, 2H), 5.07-5.02 (m, 2H), 4.21-4.05 (m, 6H), 2.50-1.80 (m, 10H), 1.65 (s, 6H), 1.38-1.22 (m, 4H) 1.12 (s, 18H), 1.05-0.96 (m, 6H), 0.18 (s, 12H).



9

***tert*-butyldimethyl(((*S*,2*E*,8*E*)-5,9,10-trimethyl-7-methyleneundeca-2,8-dien-1-yl)oxy)silane (9).** To the dienol (**8**) (0.05 mmol, 17 mg) in anhydrous Et_2O (0.300 mL) cooled to 0 °C was added Et_3N (0.151 mmol, 21 µL) and subsequently treated with MsCl (0.19 mmol, 12 µL). The resulting reaction mixture was stirred 30 min at 0 °C. Meanwhile in a different flask, $InCl_3$ (0.201 mmol, 44.5 mg) was treated with MeLi (1.4 M

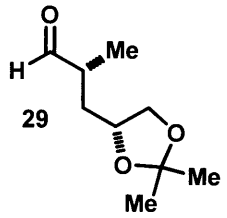
in Et_2O, 0.602 mmol, 430 µL) at 0 °C. Warmed to r.t. and stirred 15 min. The flask containing the trimethylindium reagent was diluted with anhydrous hexane (1.0 mL) and syringe transferred to the 0 °C flask of the mesylate. The resulting mixture was allowed to warm to r.t after 5 min and stirred for another 10 min. At this point, the reaction mixture was observed to change to a bright yellow color. The mixture was filtered through a plug of silica, concentrated in vacuo, and purified by silica gel chromatography (10% EtOAc/hexane) to give the displacement compound (**9**) as a colorless oil (isolated as a mixture of displacement products with the title compound **9** indentified to be the major compound by ^1H NMR). ^1H NMR (400 MHz, C_6D_6) δ 5.69-5.45 (m, 3H), 4.95 (s, 1H), 4.65 (s, 1H), 4.21-4.05 (m, 2H), 2.15-2.00 (m, 2H), 1.89-1.81 (m, 2H), 1.72 (s, 3H), 1.04 (d, J = 6.8 Hz, 6H), 1.03-0.96 (m, 1H), 0.92 (s, 9H), 0.84 (d, J = 6.4 Hz, 3H), 0.08 (s, 6H).



11

(5*E*,9*S*,11*E*)-13-((*tert*-butyldimethylsilyl)oxy)-5,9-dimethyl-7-methylenetrideca-5,11-dien-4-ol (11). In the glovebox, $Ni(cod)_2$ (0.032 mmol, 8.8 mg) and tricyclopentylphosphine (0.064 mmol, 19.2 µL) were combined. Set under an argon

atmosphere and outside the glovebox, Et_3B (0.642 mmol, 94 μL) was added. The orange mixture was stirred at r.t. for 10 min before the addition of a solution containing the enyne **6** (0.321 mmol, 94 mg) and butyraldehyde (1.12 mmol, 100 μL) in EtOAc (0.500 mL). The resulting red reaction mixture was stirred 14 h while warming to r.t. The mixture was then diluted with EtOAc (2 mL), and it was stirred open to air to allow for aerobic oxidation of the catalyst evident by the slow conversion of the color to pale green. The mixture was filtered through a short pad of silica gel (eluting with EtOAc), concentrated in vacuo, and purified by flash column chromatography (5% EtOAc/hexane). This provided the dienol (**11**) as a colorless oil (104 mg, 88% yield) as a 1:1 mixture of diastereomers. ^1H NMR (500 MHz, C_6D_6) δ 5.77-5.76 (m, 1H), 5.69-5.63 (m, 2H), 5.01 (s, 1H), 4.93 (s, 1H), 4.07-4.05 (m, 2H), 3.79 (t, J = 6.3 Hz, 1H), 2.13 (dd, J = 13.6, 6.3 Hz, 1H), 2.06-2.01 (m, 1H), 1.87-1.78 (m, 2H), 1.72-1.71 (m, 3H), 1.67-1.60 (m, 1H), 1.49-1.38 (m, 2H), 1.37-1.29 (m, 1H), 1.29-1.08 (m, 1H), 0.96 (s, 9H), 0.87-0.82 (m, 6H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 144.9, 141.2, 141.1, 131.7,129.4,126.5, 126.4, 115.3, 77.7, 64.2, 45.7, 39.9, 37.9, 32.3, 26.3, 19.7, 19.6, 18.7, 14.5, 13.7, 13.6, -4.8.

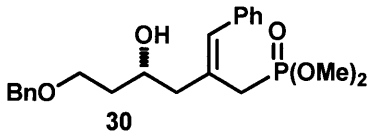


(2*R*)-3-((4*R*)-2,2-Dimethyl-[1,3]dioxolan-4-yl)-2-methyl-propionaldehyde (29). *n*-BuLi (2.5 M in hexane, 16.4 mmol, 6.6 mL) was added to a suspension of LiCl (52.1 mmol, 2.2 g) and diisopropylamine (17.6 mmol, 2.5 mL) in THF (12 mL) at –78 °C. The resulting reaction mixture was warmed to 0 °C and stirred 30 min. The mixture was re-cooled to –78 °C for the slow addition of the amide (**26**)[33] (8.6 mmol, 1.9 g) in THF (25 mL) over 5 min. The mixture was stirred 1 h at –78 °C, warmed to 0 °C and stirred 30 min and again to r.t. for 5 min. The mixture was re-cooled to 0 °C and added the iodide (**27**) all at once. The reaction mixture was stirred while warming to r.t. over a 40 h period. Then the mixture was quenched with saturated aq. NH_4Cl (20 mL). The mixtrure was diluted with H_2O (50 mL) and EtOAc (100 mL). The aqueous layer was extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (100% EtOAc) to furnish the amide (**28**) as an off-color viscous oil (1.31 g, 95% yield). Diisopropylamine (12.9 mmol, 1.8 mL) was dissolved in THF (14 mL) and cooled to –78 °C. Treated with *n*-BuLi (2.5 M in hexane, 12.0 mmol, 4.8 mL) and then warmed to 0 °C and stirred 30 min. Added bBorane–ammonia complex (tech 90%, 12.3 mmol, 380 mg) was added and stirred 15 min, and warmed to r.t. for 15 min. The mixture was then cooled to 0 °C and added a solution of the amide (**28**) (3.07 mmol, 1.03 g) in THF (14 mL). The mixture was warmed to r.t. and stirred for a 16 h period. C, and then cooled to 0 °C and quenched with a 3 M HCl soln

(2.5 mL) slowly as not to cause a violent reaction. The mixture was diluted immediately with H_2O (50 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (3 x 15 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by slow gradient chromatography (30% to 60% EtOAc/hexane) to provide a primary alcohol[31] (455 mg, 85% yield). Oxalyl chloride (3.87 mmol, 338 µL) was dissolved in CH_2Cl_2 (8.6 mL) and cooled to –78 °C. Added DMSO (5.18 mmol, 369 µL) and stirred 15 min. A solution of the alcohol (2.58 mmol, 455 mg) dissolved in CH_2Cl_2 (4.5 mL) was added dropwise and stirred 45 min at –78 °C. Subsequently added Et_3N (7.74 mmol, 1.08 mL). The reaction mixture was stirred 1 h while warming to r.t. before being quenched with saturated aq. NH_4Cl soln (5 mL). Diluted and extracted with Et_2O. The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (20% EtOAc/hexanes) to give the aldehyde **29** (306 mg, 68% yield). R_f = 0.28 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.66 (d, *J* = 1.5 Hz, 1H), 4.20-4.14 (m, 1H), 4.08 (dd, *J* = 8.2, 6.1 Hz, 1H), 3.55 (dd, *J* = 7.9, 6.7 Hz, 1H), 2.62-2.53 (m, 1H), 2.03 (ddd, *J* = 15.3, 9.2, 6.1 Hz, 1H), 1.48 (ddd, *J* = 11.9, 7.9, 4.0 Hz, 1H), 1.40 (s, 3H), 1.34 (s, 3H), 1.15 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 109.4, 73.8, 69.8, 44.0, 34.9, 27.2, 25.9, 13.8; IR (film) 2986, 2878, 2718, 1726, 1585, 1458, 1380, 1215, 1160, 1059, 932, 879, 827, 788, 746 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_9H_{16}O_3$, 195.0992; found 195.0999. $[\alpha]_D$ –4.2 (*c* 4.8, $CHCl_3$).[32]

---

[31] For previous syntheses of this alcohol (in eight steps), see: (a) Tsuda, M.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1994**, *59,* 3734-3737. (b) Horita, K.; Tanaka, K.; Yonemitsu, O. *Chem. Pharm. Bull.* **1993**, *41*, 2044-2046 and references cited therein.



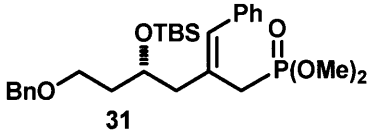
30

[(2*Z*)-2-((2*R*)-4-Benzyloxy-2-hydroxy-butyl)-3-phenyl-allyl]phosphonic acid dimethyl ester (30). $Ni(cod)_2$ (0.85 mmol, 234 mg) was placed in a 25-mL flask inside a glove box. After the flask was removed from the glove box and placed under an argon atmosphere, tributylphosphine (1.7 mmol, 425 μL) and triethylborane (34.0 mmol, 5 mL) were added at ambient temperature. The mixture was then stirred for 5 min before the addition of epoxide **23** (>96% ee, 17.9 mmol, 3.2 g) followed by the syringe pump addition of the alkynylphosphonate **25** (8.5 mmol, 1.9 g) dissolved in EtOAc (3.3 mL) over 4 h. The resultant reaction mixture was stirred at r.t. for 12 h, before the septum seal was removed and the reaction allowed to air-oxidize for 1 h. The solution was concentrated in vacuo and purified the residue by gradient flash column chromatography (EtOAc → 5% MeOH/EtOAc) to give the title compound (**30**, >95:5 regio, >95:5 *Z*/*E*) as a yellow oil (2.31 g, 68% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72-7.66 (m, 1H), 7.59-7.46 (m, 1H), 7.39-7.22 (m, 10H), 6.60 (d, *J* = 5.2 Hz, 1H), 4.56 (s, 2H), 4.13-4.11 (m, 1H), 3.79-3.66 (m, 2H), 3.69 (d, *J* = 11.0 Hz, 3H), 3.66 (d, *J* = 11.0 Hz, 3H), 3.32 (d, *J* = 3.1 Hz, 1H), 2.98 (dt, *J* = 22.5, 15.0, Hz, 2H), 2.63 (dt, *J* = 13.7, 3.1 Hz, 1H), 2.50 (dd, *J* = 13.4, 8.9 Hz, 1H), 1.84 (app q, *J* = 6.1, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 132.9, 132.8, 132.6, 132.6, 132.5, 130.5, 129.3, 129.3, 129.3, 129.2, 129.1, 128.4, 128.4, 127.6, 74.0, 69.8, 69.8, 69.4, 53.4, 53.3, 46.7, 46.7, 37.4, 29.5,

---

[32] Adapted from Ndubaku, C. O. "*Diastereoselective Nickel-Catalyzed Reductive Coupling of Alkynes and Aldehydes and Application Toward the B-Type Amphidinolides*", Ph. D. Thesis, Massachusetts Institute of Technology, **2005**.

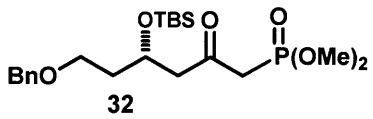
28.4; IR (film) 3391, 2950, 2851, 1495, 1453, 1438, 1251, 1182, 1054, 1028, 867, 699 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{22}H_{29}O_5PNa$, 427.1645; found 427.1659. $[\alpha]_D$ –12.5 (*c* 0.8, $CHCl_3$).[32]



31

{(2*Z*)-2-[(2*R*)-4-Benzyloxy-2-(*tert*-butyl-dimethyl-silanyloxy)-butyl]-3-phenyl-allyl}-phosphonic acid dimethyl ester (31). Alcohol **30** (3.5 mmol, 1.4 g) was dissolved in anhydrous *N*,*N*-dimethylformamide (1.4 mL) and to the stirring solution was added imidazole (14.0 mmol, 0.95 g) and TBSCl 7.0 mmol, 1.06 g). The reaction mixture was allowed to stir at r.t. for 16 h. The mixture was then loaded directly onto a silica column and purified by flash column chromatography (3:2 EtOAc/hexanes) to give the TBS-ether **31** as a colorless oil (1.1 g, 60% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.20 (m, 10H), 6.52 (d, *J* = 5.5, 1H), 4.55-4.41 (m, 2H), 4.12-4.04 (m, 1H), 3.67 (d, *J* = 2.8, 3H), 3.64 (d, *J* = 2.8, 3H), 3.59 (app. t. *J* = 6.5, 2H), 2.89 (dt, *J* = 25.1, 14.6 Hz, 2H), 2.56-2.52 (m, 2H), 1.91-1.76 (m, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 137.4, 132.2, 130.0, 128.8, 128.7, 128.6, 127.8, 127.7, 126.9, 73.2, 68.8, 68.8, 67.1, 56.7, 56.7, 52.6, 45.7, 37.4, 29.4, 28.0, 26.1, 18.2, –4.2, –4.5; IR (film) 2952, 2855, 1495, 1454, 1361, 1255, 1182, 1096, 1057, 1030, 938, 836, 776, 699 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{28}H_{43}O_5PSiNa$, 541.2510; found

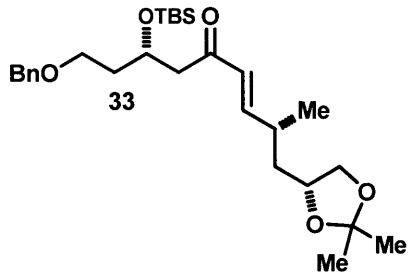
541.2537. $[\alpha]_D$ –7.1 (*c* 2.8, $CHCl_3$).[32]



32

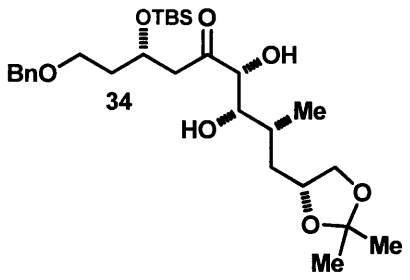
[(4*S*)-6-Benzyloxy-4-(*tert*-butyl-dimethyl-silanyloxy)-2-oxo-hexyl] phosphonic acid dimethyl ester (32). The olefin **31** (3.45 mmol, 1.79 g) was dissolved in a solvent composition of CH_2Cl_2/MeOH (9:1, 35 mL) and cooled to –78 °C while purging with O_2. An ozone stream was introduced and bubbled through the reaction mixture until the solution turned blue in color. At this point, ozone treatment was discontinued and the reaction mixture was re-purged with O_2. Methylsulfide (35.0 mmol, 2.5 mL) was added and the resulting mixture was stirred, warming to r.t. for 6 h. The solution was concentrated in vacuo and the residue was purified by flash column chromatography (3:2 EtOAc/hexanes) to give the ketophosphonate **32** as a colorless oil (1.19 g, 78% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.27 (m, 5H), 4.62 (ABq, *J* = 11.8, 5.8 Hz, 2H), 4.45-3.81 (m, 1H), 3.78 (d, *J* = 2.1 Hz, 3H), 3.76 (d, *J* = 2.1 Hz, 3H), 3.56-3.52 (m, 2H), 3.11 (d, *J* = 1.5 Hz, 1H), 3.07 (d, *J* = 1.5 Hz, 1H), 2.80 (d, *J* = 7.0 Hz, 2H), 1.82-1.77 (m, 2H), 0.86 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.5, 139.1, 130.2, 129.1, 129.1, 128.3, 128.3, 73.6, 67.1, 67.0, 53.7, 53.7, 53.7, 53.6, 52.1, 52.1, 43.7, 42.7, 37.9, 26.5, 18.7, –4.0, –4.1; IR (film) 2955, 2856, 1717, 1471, 1361, 1257, 1184, 1031, 937, 836, 777, 698 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for

$C_{21}H_{37}O_6PSiNa$, 467.1989; found 467.1984. $[\alpha]_D$ +2.1 (*c* 4.8, $CHCl_3$).[32]



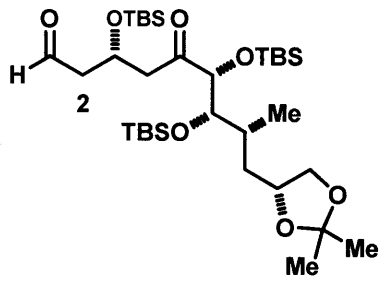
(2*R*,3*E*,7*S*)-9-Benzyloxy-7-(*tert*-butyl-dimethyl-silanyloxy)-1-((4*R*)-2,2-dimethyl-[1,3] dioxolan-4-yl)-2-methyl-non-3-en-5-one (33). To a vigorously stirred suspension of vacuum-dried LiCl (1.4 mmol, 59 mg) in MeCN (8 mL) was added the ketophosphonate **32** (1.15 mmol, 511 mg). Diisopropylethylamine (1.4 mmol, 240 µL) was added followed by the aldehyde **29** (1.09 mmol, 187 mg). The reaction mixture was then stirred 40 h at ambient temperature. The mixture was quenched with saturated aq. NH_4Cl (1.3 mL) and diluted with Et_2O (25 mL) and H_2O (25 mL). Partitioned the phases and extracted the aqueous with Et_2O (3 x 20 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (10% EtOAc/hexanes) to give the enone **33** (>9:1 *E/Z*) as an off-color oil (475 mg, 89%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.27 (m, 5H), 6.74 (dd, *J* = 15.9, 7.6 Hz), 6.07 (d, *J* = 15.9), 4.49 (ABq, *J* = 19.2, 12.2 Hz, 2H), 4.42-4.36 (m, 1H), 4.14-4.08 (m, 1H), 4.04 (dd, *J* = 7.6, 5.8 Hz, 1H), 3.60-3.52 (m, 2H), 3.50 (dd, *J* = 7.6, 7.0 Hz, 1H), 2.78 (dd, *J* = 15.3, 7.0 Hz, 1H), 2.64 (dd, *J* = 15.3, 7.0 Hz, 1H), 2.49-2.43 (m, 1H), 1.86-1.78 (m, 2H), 1.81-1.74 (m, 1H), 1.50-1.45 (m, 1H), 1.41 (s, 3H), 1.35 (s,

3H), 1.09 (d, J = 7.0 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0, 152.7, 139.2, 130.1, 129.1, 128.3, 128.2, 128.2, 109.6, 74.4, 73.6, 70.3, 67.7, 67.3, 48.6, 40.5, 38.3, 34.4, 27.8, 26.6, 26.5, 19.8, 18.7, –3.9, –4.0; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{28}H_{46}O_5SiNa$, 513.3007; found 513.2997. $[\alpha]_D$ –5.9 (*c* 6.8, $CHCl_3$).[32]



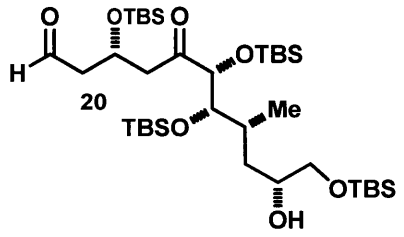
(2*R*,3*S*,4*R*,7*S*)-9-Benzyloxy-7-(*tert*-butyl-dimethyl-silanyloxy)-1-((4*R*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-3,4-dihydroxy-2-methyl-nonan-5-one (34). AD-mix α (2.94 g, 2.10 mmol), $K_2OsO_2(OH)_4$ (67 mg, 0.182 mmol), $(DHQ)_2PHAL$ (67 mg, 0.086 mmol) and $NaHCO_3$ (529 mg, 6.30 mmol) were combined in a 25 mL Erlenmeyer flask equipped with a stir bar and dissolved in ^{t}BuOH/water (1:1, 23.2 mL). The mixture was stirred vigorously until all the solids were dissolved before adding $MeSO_2NH_2$ (232 mg, 2.44 mmol). The mixture was stirred for an additional 10 min before the solution was transferred *via* Pasteur pipette into a cooled round bottom flask containing enone **33** (1.03 g, 2.10 mmol) at 0 °C. The resulting reaction mixture was stirred at 0 °C - 5 °C for 40 hours in a refrigerator. The mixture was quenched at 0 °C with saturated aqueous

Na_2SO_3 (1.8 mL) and stirred for another 30 min before the mixture was diluted with water (5 mL) and EtOAc (50 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with saturated aqueous NaCl (1 × 80 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification was performed by column chromatography (EtOAc/hexanes 30:70) afforded the title diol **34** as a clear oil (0.908 g, 86%).; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H), 4.45 (ABq, *J* = 20.5, 12.0, 2H), 4.43-4.39 (m, 1H), 4.19-4.14 (m, 1H), 4.12 (dd, *J* = 4.0, 1.5 Hz, 1H), 4.05 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.74 (d, *J* = 4.0, 1H), 3.73-3.70 (m, 1H), 3.60-3.56 (m, 1H), 3.52-3.48 (m, 1H), 2.78 (dt, *J* = 16.0, 7.0 Hz, 2H), 2.25 (d, *J* = 9.5 Hz, 1H), 1.99-1.94 (m, 1H), 1.84-1.75 (m, 3H), 1.41 (s, 3H), 1.35 (s, 3H), 1.34-1.29 (m, 1H), 1.03 (d, *J* = 6.5 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.4, 138.9, 129.1, 128.4, 128.3, 109.6, 78.4, 75.4, 75.1, 73.7, 70.6, 67.3, 67.0, 46.4, 37.7, 37.6, 35.6, 27.7, 26.5, 18.7, 16.4, –4.0, –4.1; IR (film) 3454, 2954, 2931, 2858, 1715, 1455, 1371, 1253, 1217, 1080, 837, 777, 698 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{28}H_{48}O_7SiNa$, 547.3061; found 547.3079. $[\alpha]_D$ –10.2 (*c* 6.4, $CHCl_3$).[32]



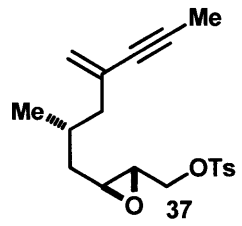
(3*S*,6*R*,7*S*)-3,6,7-Tris-(*tert*-butyl-dimethyl-silanyloxy)-9-((4*R*)-2,2-dimethyl-[1,3]dioxo-lan-4-yl)-8-methyl-5-oxo-nonanal (2). The diol **34** (0.78 mmol, 408 mg) was dissolved in CH_2Cl_2 (8 mL) and cooled to 0 °C. Added 2,6-lutidine (4.7 mmol, 0.54 mL) all at once and TBSOTf (2.3 mmol, 0.54 mL) dropwise over 3 min. Stirred 30 min at 0 °C and subsequently warmed to r.t. and stirred 30 min. The solution was diluted with H_2O (10 mL), partitioned the phases, and extracted the aqueous with Et_2O (15 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (5% EtOAc/hexanes) to give the benzyl ether as a clear oil (577 mg, 92%). A portion of this benzyl ether (0.14 mmol, 108 mg) was dissolved in EtOH (10 mL) and $Pd(OH)_2/C$ (14 mg) was added. The reaction flask was evacuated and re-cycled with H_2 from a balloon source. This process was repeated two more times. The suspension was then allowed to stir 6 h at r.t. The mixture was filtered through a short pad of silica gel eluting with Et_2O. The filtrate was concentrated in vacuo. This compound was then dissolved in anhydrous CH_2Cl_2 (50 mL), and at r.t. treated with the Dess-Martin periodinane (0.21 mmol, 89 mg). The mixture was stirred 1 h and concentrated in vacuo. The crude residue was purified by flash column chromatography (5% EtOAc/hexanes) to give the title compound **2** as a clear oil (92 mg, 98%). ^1H NMR (500 MHz, $CDCl_3$) δ 9.81 (q, *J* =

1.8 Hz, 1H), 4.71-4.65 (m, 1H), 4.13-4.08 (m, 1H), 4.04 (t, *J* = 6.1 Hz, 1H), 3.74 (t, *J* = 4.3 Hz, 1H), 3.45 (t, *J* = 7.6 Hz, 1H), 3.11 (dd, *J* = 18.9, 4.0 Hz, 1H), 2.76 (dd, *J* = 18.9, 8.5 Hz, 1H), 2.70 (ddd, *J* = 15.6, 4.3, 1.6 Hz, 1H), 2.45 (ddd, *J* = 15.6, 6.7, 3.7 Hz, 1H), 2.02-1.93 (m, 1H), 1.80-1.75 (m, 1H), 1.39 (s, 3H), 1.34 (s, 3H), 1.32-1.27 (m, 1H), 0.95 (s, 9H), 0.92 (s, 9H), 0.85 (s, 9H), 0.83 (d, *J* = 6.7, 3H), 0.14 (s, 3H), 0.12 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.2, 202.6, 109.5, 81.8, 78.9, 74.9, 70.7, 64.7, 51.5, 49.3, 39.1, 33.0, 27.7, 26.7, 26.7, 26.6, 26.5, 26.5, 26.4, 26.4, 18.9, 18.5, 16.0, –3.3, –3.9, –3.9, –4.2, –4.3; IR (film) 2955, 2931, 2858, 1723, 1473, 1369, 1254, 1068, 1005, 836, 776 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{33}H_{68}O_7Si_3Na$, 683.4165; found 683.4182. $[\alpha]_D$ –12.4 (*c* 6.8, $CHCl_3$).[32]

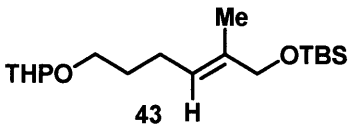


(3S,6R,7S,8R,10R)-3,6,7,11-tetrakis(tert-butyldimethylsilyloxy)-10-hydroxy-8-methyl-5-oxoundecanal (20). The acetonide **2** (0.529 mmol, 350 mg) was dissolved in THF:H_2O:AcOH (1:1:2, 64 mL) and stirred vigorously for 2 h at 45 °C. Quenched with saturated aq. $NaHCO_3$ solution (20 mL) and diluted with Et_2O (30 mL). The organic

layer was washed with saturated aq. $NaHCO_3$ solution (5 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (3:7 EtOAc:hexanes) to give the the diol **35** as a colorless oil (187 mg, 57%), which was immediately taken up in DMF (1.1 mL) and added to a 10 mL round bottom flask. While stirring imidazole (0.784 mmol, 53.0mg) and TBSCl (0.392 mmol, 59.0 mg) were added. The solution was stirred 12h at ambient temperature and quenched with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (5:95 EtOAc:hexanes) to give the the alcohol **20** as a colorless oil (161 mg, 73%). ^1H NMR (600 MHz, $CDCl_3$) δ 9.71 (bs, 1H), 4.61-4.55 (m, 1H), 4.10 (d, *J* = 4.5 Hz, 1H), 3.70 (t, *J* = 6.1 Hz, 1H), 3.68-362 (m, 1H), 3.56 (dd, *J* = 9.8, 3.8 Hz, 1H), 3.40 (dd, *J* = 9.8, 7.0 Hz, 1H), 3.14 (dd, *J* = 19.0, 4.4 Hz, 1H), 2.76-2.60 (m, 2H), 2.47 (dd, *J* = 6.4, 3.5 Hz, 1H), 2.45 (dd, *J* = 6.7, 3.7 Hz, 1H), 2.10-2.03 (m, 1H), 1.92-1.87 (m, 1H), 1.66-1.61 (m, 1H), 1.22-1.17 (m, 1H), 0.95 (s, 9H), 0.92 (s, 9H), 0.85 (s, 9H), 0.83 (s, 12H), 0.14 (s, 3H), 0.12 (s, 3H), 0.09 (s, 3H), 0.07 (bs, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.9, 202.1, 81.8, 78.7, 74.9, 68.9, 64.2, 50.9, 48.8, 37.3, 32.0, 26.2, 26.1, 26.0, 25.8, 18.5, 18.4, 18.3, 15.5, –3.7, –4.3, -4.4, -4.5, -4.7, -4.8, -5.2, -5.3; IR (film) 2930, 2858, 1724, 1473, 1362, 1256, 1005, 939, 836, 776 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{33}H_{68}O_7Si_4Na$, 757.4717; found 757.4733. $[\alpha]_D$ –14.0 (*c* 3.2, $CHCl_3$).



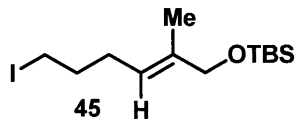
((2*S*,3*S*)-3-((*R*)-2-methyl-4-methylenehept-5-ynyl)oxiran-2-yl)methyl 4-methylbenzene-sulfonate (37): The alcohol **36** (1.5 g, 7.85 mmol) was taken up in CH_2Cl_2 (52 mL) and Et_3N (23.23 mmol, 3.23 mL) was added and followed by TsCl (13.9 mmol, 2.66 g). Then finally $Me_3N{\cdot}HCl$ (7.85 mmol, 751 mg) was added. The mixture was stirred for 2 h at 0 °C. The mixture was then quenched with saturated aq. $NaHCO_3$ soln (40 mL), diluted with H_2O (100 mL), and extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by silica gel chromatography (10% EtOAc/hexane) to give the tosylate **37** as a yellow oil (2.7 g, 99% yield).; ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 5.27 (s, 1H), 5.11 (s, 1H), 4.20 (dd, *J* = 7.3, 3.6 Hz, 1H), 4.02 (dd, *J* = 7.5, 3.6 Hz, 1H), 2.98-2.94 (m, 1H), 2.86-2.82 (m, 1H), 2.47 (s, 3H), 2.14-2.08 (m, 1H), 2.05-1.96 (m, 2H), 2.00 (s, 3H), 1.65-1.58 (m, 1H), 1.34-1.26 (m, 1H), 0.94 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.8, 131.4, 130.6, 129.2, 128.7, 122.2, 86.6, 80.5, 70.8, 56.4, 55.7, 45.8, 38.7, 30.1, 22.3, 20.0, 4.9; IR (film) 2959, 2920, 2227, 1726, 1598, 1454, 1365, 1190, 1178, 1097, 966, 815, 666 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{19}H_{24}OSNa$, 371.1288; found 371.1271. $[\alpha]_D$ –15.1 (*c* 2.0, $CHCl_3$).[32]



(*E*)-*tert*-butyldimethyl(2-methyl-6-(tetrahydro-2*H*-pyran-2-yloxy)hex-2-enyloxy)silane (43): Ester **42**[33] (9.75 mmol, 2.5 g) was dissolved in CH_2Cl_2 (95 mL) and cooled to –78 °C. Then a solution of diisobutylaluminum hydride (1.0 M in hexane, 19.5 mmol, 19.5 mL) was added. The mixture was warmed to r.t. after 15 min and stirred an additional 45 min. The mixture was poured directly into a biphasic mixture of saturated aq. Rochelle's salt solution (200 mL) and Et_2O (350 mL) and stirred vigorously until the phases partitioned. They layers were separated and extracted the aqueous layer with Et_2O (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The crude residue was dissolved in DMF (9.8 mL) and to the stirring solution was added imidazole (29.3 mmol, 2 g) and TBSCl (14.6 mmol, 2.2 g). The solution was stirred 1 h at r.t. and loaded directly onto a silica gel column and purified by flash column chromatography (20% EtOAc/hexane) to give the title compound **43** as a clear oil (3.14 g, 98% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.41 (t, *J* = 7.2 Hz, 1H), 4.58 (t, *J* = 2.8 Hz, 1H), 3.90 (s, 2H), 3.88 (dt, *J* = 7.6, 2.9 Hz, 1H), 3.75 (dt, *J* = 9.6, 2.9 Hz, 1H), 3.53-3.48 (m, 1H), 3.39 (dt, *J* = 13.3, 6.6 Hz, 1H), 2.18-2.06 (m, 2H), 1.89-1.80 (m, 1H), 1.75-1.64 (m, 2H), 1.61 (s, 3H), 0.92 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.5, 124.7, 99.6, 77.9, 69.3, 67.8, 62.9, 31.5, 30.3, 26.7, 26.4, 26.2, 24.9, 20.4, 14.1, –4.5; IR (film) 2938, 2857, 1713, 1463, 1361, 1253, 1201, 1121, 1076, 1035, 837, 775, 666 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for

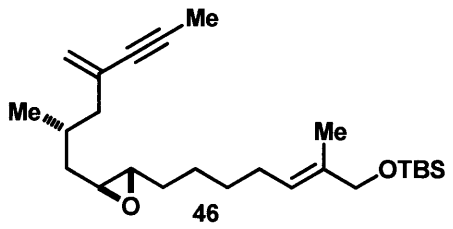
[33] Uesato, S.; Kobayashi, K.; Inouye, H. *Chem. Pharm. Bull.* **1982**, *30*, 927-940.

$C_{18}H_{36}O_3SiNa$, 351.2326; found 351.2333.[32]



(*E*)-*tert*-butyl((6-iodo-2-methylhex-2-en-1-yl)oxy)dimethylsilane (45). To a solution of THP ether **43** (329 mg, 1.00 mmol) dissolved in THF (24.6 mL) was added MeOH (0.25 mL, 1 vol%) followed by HCl (2.0 M in Et_2O, 0.16 mL, 0.32 mmol). The resulting reaction mixture was heated at reflux (67 °C) for 20 hours. The mixture was then cooled to ambient temperature, quenched with saturated aqueous $NaHCO_3$ (30 mL) and diluted with saturated aqueous NaCl (20 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification was done by column chromatography (EtOAc/hexanes 25:75) to afford alcohol **44** as a clear oil (189 mg, 77%). Due to the occurrence of TBS scrambling this compound should be taken further to the next step without intermediate storage. The alcohol **44** (4.66 mmol, 1.14 g) was dissolved in MeCN/Et_2O (1:3, 30 mL) and imidazole (10.7 mmol, 750 mg), triphenylphosphine (7.0 mmol, 1.82 g), and iodine (7.0 mmol, 1.78 g) were added in that order. Stirred the resulting yellow reaction mixture 1 h at r.t. Diluted with H_2O (50 mL) and Et_2O (100 mL) and extracted with Et_2O. The combined organic layers were washed with saturated $Na_2S_2O_3$ solution. The combined organic extracts were dried over

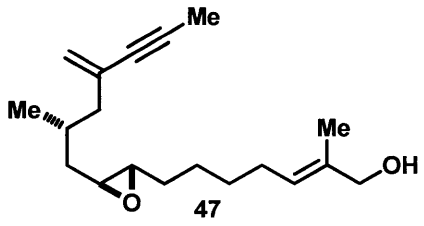
anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (5% EtOAc/hexane) to give the iodide (**45**) as a clear, colorless oil (1.47 g, 89% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 5.38 (t, *J* = 5.9 Hz, 1H), 4.02 (s, 2H), 3.21 (t, *J* = 7.0 Hz, 2H), 2.19-2.13 (m, 2H), 1.95-1.87 (m, 2H), 1.64 (s, 3H), 0.92 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.7, 122.7, 69.0, 34.3, 34.1, 29.0, 26.7, 21.9, 19.1, 14.4, 7.5, –4.5; IR (film) 2955, 2929, 2856, 1674, 1472, 1462, 1361, 1252, 1206, 1164, 1111, 1072, 1006, 939, 837, 776, 666 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{13}H_{27}IOSiNa$, 377.0768; found 377.0759.



46

***tert*-butyldimethyl((*E*)-2-methyl-7-((2*S*,3*S*)-3-((*R*)-2-methyl-4-methylenehept-5-ynyl)oxi-ran-2-yl)hept-2-enyloxy)silane (46):** The iodide **45** (2.44 mmol, 870 mg) was dissolved in Et_2O (10 mL) and cooled to –78 °C. The solution was treated slowly with *t*-BuLi and stirred 1 h while maintaining the same temperature. The solution was subsequently warmed to r.t. and stirred 30 min. The solution was then syringe transferred to a flask containing a suspension of CuI (1.22 mmol, 233 mg) in Et_2O (5 mL) at –30 °C and stirred 30 min. A solution of the tosylate **37** (0.61 mmol, 211 mg) in Et_2O (6 mL) was added and the resulting dark grey reaction mixture was stirred an

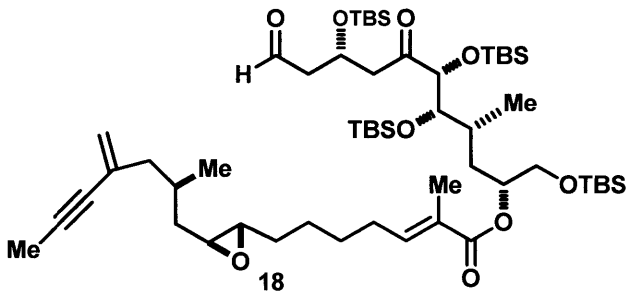
additional 30 min at –30 °C. The mixture was filtered through a plug of silica (ca. 1 cm), concentrated in vacuo, and purified by silica gel chromatography (3% EtOAc/hexane) to give **46** as a light yellow oil (158 mg, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 (t, *J* = 5.8 Hz, 1H), 5.29 (s, 1H), 5.13 (s, 1H), 4.03 (s, 2H), 2.73 (dt, *J* = 6, 2.1 Hz, 1H), 2.68 (dt, *J* = 5.3, 2.3 Hz, 1H), 2.22-2.13 (m, 1H), 2.09-1.94 (m, 3H), 1.96 (s, 3H), 1.82-1.74 (m, 1H), 1.69-1.58 (m, 2H), 1.61 (s, 3H), 1.60-1.51 (m, 2H), 1.49-1.35 (m, 1H), 1.32-1.25 (m, 2H), 0.98 (d, *J* = 5.1 Hz, 3H), 0.93 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.2, 131.4, 125.1, 121.9, 86.4, 80.7, 69.4, 59.9, 58.2, 46.1, 39.6, 32.8, 30.2, 28.1, 27.5, 27.1, 26.7, 26.4, 23.5, 20.0, 19.2, 14.6, 14.1, 4.9, –4.5; IR (film) 2956, 2929, 2857, 1611, 1463, 1361, 1252, 1111, 1069, 1006, 894, 837, 775, 667 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{25}H_{44}O_2SiNa$, 427.3003; found 427.2983. $[\alpha]_D$ –8.3 (*c* 2.4, $CHCl_3$).



47

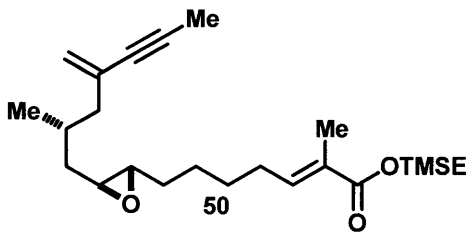
(E)-2-methyl-7-((2S,3S)-3-((R)-2-methyl-4-methylenehept-5-yn-1-yl)oxiran-2-yl)hept-2-en-1-ol (47): To a flame-dried 50 mL round-bottom flask equipped with a magnetic stir bar and set under an argon atmosphere was added **46** (1 mmol, 405 mg) in THF (3 mL). The flask was cooled to 0 °C and tetrabutylammonium fluoride (1.0 M in

THF, 3 mmol, 3 mL) was added and the resulting solution was stirred 2 h at 0 °C. The solution was quenched by adding H_2O (100 mL), diluting with brine (50 mL) and EtOAc (250 mL). The layer was extracted with EtOAc (3 x 250 mL), dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by flash column chromatography (25% EtOAc/hexane) to give the allylic alcohol (**47**) as a yellow oil (264 mg, 91% yield). ^1H NMR (600 MHz, $CDCl_3$) δ 5.33 (t, J = 5.8 Hz, 1H), 5.18 (s, 1H), 5.04 (s, 1H), 3.90 (s, 2H), 2.65 (dt, J = 6, 2.1 Hz, 1H), 2.60-2.58 (m, 1H), 2.38 (bs, 1H), 2.11-2.08 (m, 1H), 2.00-1.89 (m, 3H), 1.86 (s, 3H), 1.72-1.68 (m, 1H), 1.58 (s, 3H), 1.55-1.30 (m, 5H), 1.24-1.17 (m, 1H), 0.95-0.91 (m, 1H), 0.89 (d, J = 5.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.2, 131.8, 125.8, 122.2, 85.7, 80.1, 68.7, 59.4, 57.7, 46.1, 38.6, 32.2, 29.6, 29.4, 27.5, 26.7, 19.2, 14.1, 4.9,; IR (film) 3421, 2856, 1653, 1457, 1378, 1295, 1012, 1069, 896, 667 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{19}H_{30}O_2Na$, 313.2138; found 313.2143. $[\alpha]_D$ –13.5 (*c* 13.7, $CHCl_3$).

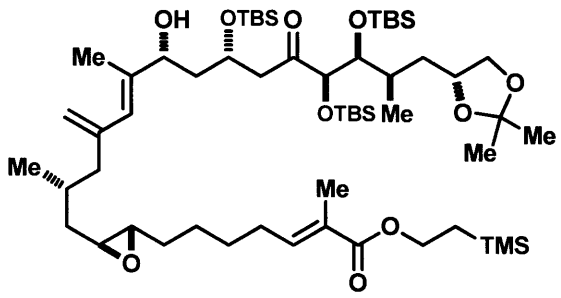


(E)-((6R,8R,9S,10R,13S)-9,10-bis(tert-butyldimethylsilyloxy)-2,2,3,3,8,15,15,16,16-nonamethyl-11-oxo-13-(2-oxoethyl)-4,14-dioxa-3,15-disilaheptadecan-6-yl) 2-methyl-7-((2S,3S)-3-((R)-2-methyl-4-methylenehept-5-ynyl)oxiran-2-yl)hept-2-enoate (18). The Allylic alcohol **47** (0.12 mmol, 35 mg) was dissolved in CH_2Cl_2 (1.07 mL) and added to a 10 mL round bottom flask containing 4 Å molecular sieves. The solution was stirred and NMO (0.18 mmol, 21 mg) and TPAP (0.0012 mmol, 0.43 mg) were added. The reaction mixture was then stirred 4 h at ambient temperature. The reaction mixture was filtered through a short pad of silica, eluting with Et_2O:pentane (30:70), and concentrated in vacuo. The crude product was then taken up in THF (0.715 mL) and added to a 10 mL round bottom flask. To the solution was added *t*-BuOH (1.43 mL), 2-methyl-2-butene (0.715 mL), H_2O (1.43 mL), $NaClO_2$ (1.19 mmol, 108 mg), and NaH_2PO_4 (0.690 mmol, 108 mg). The reaction mixture was stirred at ambient temperature for 7 h. The mixture was quenched with saturated aq. NH_4Cl (5 mL) solution, extracted with ether (10 mL), and concentrated in vacuo. The crude product was dissolved in EtOAc (10 mL) and washed with H_2O (10 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated to give the carboxylate salt (39 mg, 100%) as an oil that was approximately 90% pure and carried on without further purification. A portion of the salt

(0.1 mmol, 32 mg) was dissolved in toluene (1.3 mL). While stirring NEt_3 (0.5 mmol, 70 μL) and 2,4,6-trichlorobenzoyl chloride (0.125 mmol, 33 μL) were added. The mixture was stirred for 8 h and then filtered through celite and evaporated. The resulting residue was dissolved in toluene along with alcohol **20** (0.05 mmol, 37 mg) and DMAP (0.15 mmol, 18 mg). The resulting mixture was heated to 45 °C for 8 h. After that reaction time the mixture was filtered through celite and evaporated. The residue was purified by flash column chromatography (5:95 EtOAc:hexanes) to give the enyne **18** as a colorless oil (28 mg, 53%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.81 (s, 1H), 6.78-6.75 (m, 1H), 5.28 (bs, 1H), 5.13 (bs, 1H), 5.05-5.01 (m, 1H), 4.66-4.62 (m, 1H), 4.12 (d, J = 6.6 Hz, 1H), 3.68-3.58 (m, 3H), 3.10 (dd, J = 19.2, 4.2 Hz, 1H), 2.75-2.68 (m, 4H), 2.45-2.40 (m, 1H), 2.20-2.17 (m, 3H), 2.05-1.97 (m, 2H), 1.96 (s, 3H), 1.83 (s, 3H), 1.65-1.55 (m, 2H), 1.55-1.45 (m, 4H), 1.32-1.21 (m, 4H), 1.03 (d, *J* = 3.0 Hz, 1H), 0.98 (d, *J* = 9.6 Hz, 3H), 0.94 (s, 9H), 0.92 (s, 9H), 0.87 (s, 9H), 0.85 (s, 12H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.12 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H), 0.05 (s, 6H), 0.03 (s, 6H), 0.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.5, 202.1, 167.9, 142.2, 130.8, 128.0, 121.4, 85.9, 81.1, 78.9, 72.1, 65.0, 64.2, 59.3, 57.6, 50.9, 48.8, 45.6, 39.0, 35.8, 32.2, 31.3, 29.7, 28.8, 28.7, 26.2, 26.1, 26.0, 25.9, 25.8, 20.5, 19.5, 18.4, 18.0, 14.8, 12.7, 4.5, -3.8, -4.4, -4.5, -4.8,-5.2; IR (film) 2929, 1736, 1718, 1653, 1457, 1256, 1111, 837, 777, 668 cm^{-1}; HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{55}H_{104}O_9Si_4Na$, 1043.6650; found 1043.6646 $[\alpha]_D$ -9.77 (*c* 2.4, $CHCl_3$).



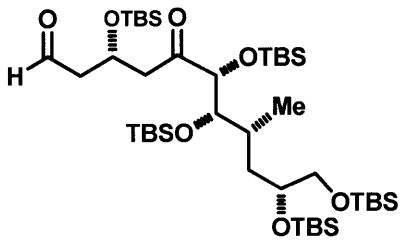
(E)-2-(trimethylsilyl)ethyl 2-methyl-7-((2S,3S)-3-((R)-2-methyl-4-methylenehept-5-ynyl)oxiran-2-yl)hept-2-enoate (50). The enyne **19** (0.94 mmol, 30 mg) was dissolved in toluene (1.88 mL). While stirring NEt_3 (0.47 mmol, 65 µL) and 2,4,6-trichlorobenzoyl chloride (0.116 mmol, 31 µL) were added. The mixture was stirred for 3 h and then filtered through celite and evaporated. The resulting residue was dissolved in toluene along with 2-(trimethylsilyl)ethanol (0.2 mmol, 29 µL) and DMAP (0.14 mmol, 17 mg). The resulting mixture was stirred for 10 h. After that reaction time the mixture was filtered through celite and evaporated. The residue was purified by flash column chromatography (5:95 EtOAc:hexanes) to give the enyne 50 as a colorless oil (29 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66-6.63 (m, *J* = 1H), 5.20 (s, 1H), 5.07 (s, 1H), 4.13 (t, J = 8.4 Hz, 2H), 2.74-2.71 (m, 1H), 2.63-2.59 (m, 1H), 2.33-2.20 (m, 4H), 2.10-2.00 (m, 1H), 1.89 (s, 3H), 1.78 (bs, 3H), 1.68-1.60 (m, 2H), 1.60-1.50 (m, 5H), 1.29-1.21 (m, 1H), 1.01 (t, 8.4 Hz, 2H), 0.98 (d, *J* = 6.4 Hz, 3H), 0.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 141.7, 130.8, 128.2, 121.2, 85.8, 80.1, 65.2, 62.7, 59.1, 57.4, 45.5, 38.9, 32.1 29.6, 28.7, 28.6, 25.9, 19.4, 17.4, 12.5, 4.3, –1.4; IR (film) 2954, 2859, 1708, 1651, 1457, 1376, 1269 1119, 1060, 895, 838, 762, 696 cm^{-1}; HRMS ESI (*m/z*): $[M+H]^+$ calcd for $C_{24}H_{40}O_3SiNa$, 427.2639; found 427.2635. $[\alpha]_D$ –9.5 (*c* 4.0, $CHCl_3$).



51

(E)-2-(trimethylsilyl)ethyl 2-methyl-7-((2S,3S)-3-((2R,7R,9S,12R,13S,14R,E)-9,12,13-tris((tert-butyldimethylsilyl)oxy)-15-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-7-hydroxy-2,6,14-trimethyl-4-methylene-11-oxopentadec-5-en-1-yl)oxiran-2-yl)hept-2-enoate (51). In the glovebox, $Ni(cod)_2$ (0.032 mmol, 3.4 mg) and tricyclopentylphosphine (0.064 mmol, 7.4 μL) were combined. Set under an argon atmosphere and outside the glovebox, Et_3B (0.155 mmol, 22.7 μL) was added. The orange mixture was stirred at r.t. for 10 min before the addition of a solution containing the enyne **50** (0.062 mmol, 25 mg) and aldehyde **2** (0.062 mmol, 41 mg) in EtOAc (0.900 mL). The resulting red reaction mixture was stirred 14 h while warming to r.t. The mixture was then diluted with EtOAc (2 mL), and it was stirred open to air to allow for aerobic oxidation of the catalyst evident by the slow conversion of the color to pale green. The mixture was filtered through a short pad of silica gel (eluting with EtOAc), concentrated in vacuo, and purified by flash column chromatography (10% EtOAc/hexane). This provided the dienol (**51**) as a colorless oil (56 mg, 85% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 6.70 (t, J = 6.3 Hz, 1H), 5.80 (brs, 1H), 4.94 (s, 1H), 4.83 (s, 1H), 4.40-4.34 (m, 1H), 4.21-4.14 (m, 3H), 4.10 (d, J = 4.4 Hz, 1H), 4.08-4.02 (m, 1H), 4.01-3.97 (m, 1H), 3.69 (t, J = 4.4 Hz, 1H), 3.40 (t, J = 7.5 Hz, 1H), 3.00 (s, 1H), 2.85 (app d, J = 6.4 Hz, 2H), 2.64-2.57 (m, 3H), 2.18-2.08 (m, 4H), 2.00-1.84 (m, 2H), 1.79 (s, 3H), 1.77-1.70 (m, 6H), 1.60-1.50 (m,

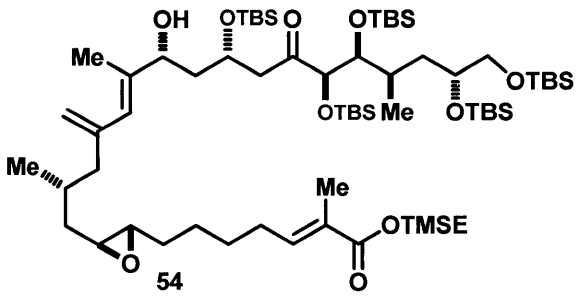
2H), 1.50-1.40 (m, 5H), 1.34 (s, 3H), 1.28 (s, 3H), 1.26-1.22 (m, 2H), 1.01 (t, J = 3.9 Hz, 1H), 0.91 (s, 9H), 0.87 (s, 9H), 0.85 (s, 12H), 0.79 (d, J = 6.6 Hz, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.04 (s, 3H), 0.01 (s, 12H), -0.04 (s, 3H); ; HRMS ESI (*m/z*): $[M+H]^+$ calcd for $C_{42}H_{92}O_7Si_5$, 1089.7276; found 1089.7264.



53

(3*S*,6*R*,7*S*,8*R*,10*R*) - 3,6,7-tris(*tert*-butyldimethylsilyloxy) -10,11 - dihydroxy - 8 - methyl - 5 - oxoundecanal (53). Acetonide **2** (169 mg, 0.256 mmol) was dissolved in a solvent composition of THF/H_2O/AcOH (1:1:2, 12 mL) under stirring before it was heated to 90 °C for 6 min in a microwave oven. Quenched the reaction mixture after cooling to ambient temperature with saturated aqueous $NaHCO_3$ (50 mL) and diluted with Et_2O (200 mL). The organic phase was separated and washed with $NaHCO_3$ (2 × 50 mL) and with saturated aqueous NaCl (1 × 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The product was immediately dissolved in DMF (0.40 mL) and imidazole (174 mg, 2.56 mmol) and TBSCl (193 mg, 1.28 mmol) were added. Stirred at r.t. for 16h. The mixture was loaded directly on to silica gel and

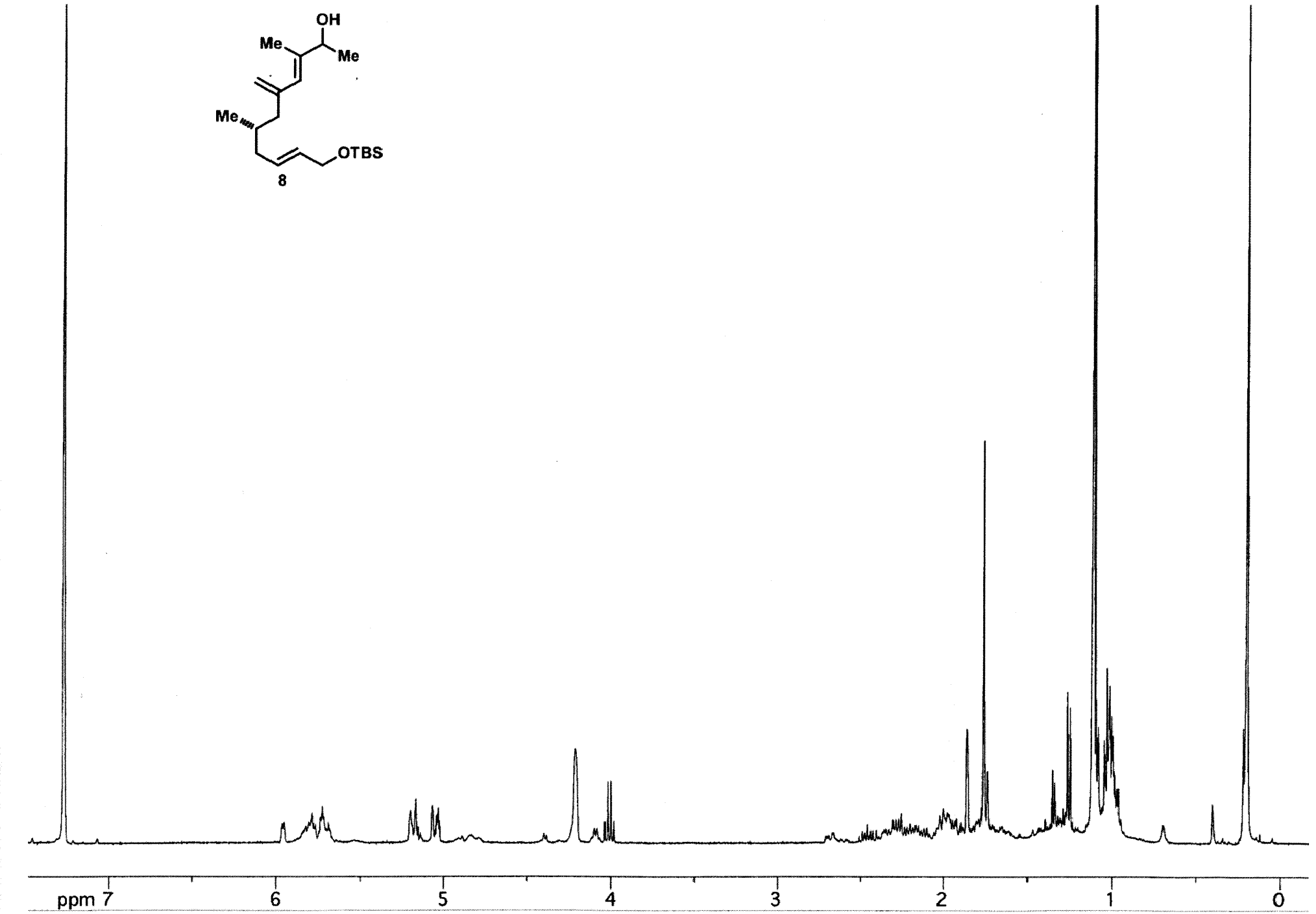
purified by flash column chromatography (95:5 hexanes:EtOAc) to give the aldehyde **53** as a colorless oil (217 mg ,75%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.61 (bs, 1H), 4.61-4.55 (m, 1H), 4.13 (d, *J* = 4.5 Hz, 1H), 3.63-358 (m, 2H), 3.57-3.54 (m, 1H), 3.31-3.24 (m, 1H), 3.14 (dd, *J* = 19.0, 4.4 Hz, 1H), 2.76-2.62 (m, 2H), 2.41-2.35 (m, 1H), 2.10-2.03 (m, 1H), 1.58-1.44 (m, 1H), 1.22-1.17 (m, 1H), 0.90 (s, 9H), 0.86 (s, 9H), 0.85 (s, 9H), 0.83 (s, 9H), 0.80 (s, 9H), 0.69 (d, J = 6.0 Hz, 1H), 0.09 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.02 (bs, 9H), 0.01 (bs, 9H), -0.04 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.7, 202.1, 81.3, 80.1, 70.9, 68.2, 64.2, 50.9, 48.8, 40.8, 29.9, 29.8, 26.2, 26.1, 25.9, 18.5, 18.4, 18.3, 18.0, 13.7, –3.7, -3.9, –4.3, -4.4, -4.7, -4.8, -5.1, -5.2; IR (film) 3567, 2930, 2858, 1718, 1473, 1362, 1256, 1095, 939, 836, 776 cm^{-1}; HRMS ESI (*m/z*): $[M+H]^+$ calcd for $C_{42}H_{92}O_7Si_5$, 849.7562; found 849.7562. $[\alpha]_D$ –8.0 (*c* 4.0, $CHCl_3$).

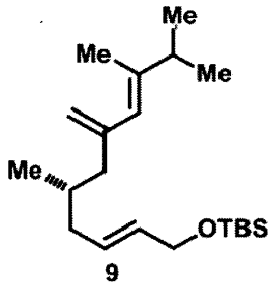


(*E*)-2-(trimethylsilyl)ethyl 2-methyl-7-((2*S*,3*S*)-3-((2*R*,7*R*,9*S*,12*R*,13*S*,14*R*,16*R*,*E*)-9,12,13,16,17-pentakis((tert-butyldimethylsilyl)oxy)-7-hydroxy-2,6,14-trimethyl-4-methylene-11-oxoheptadec-5-en-1-yl)oxiran-2-yl)hept-2-enoate (54). In the glovebox, $Ni(cod)_2$ (0.032 mmol, 3.4 mg) and tricyclopentylphosphine (0.064 mmol, 7.4 µL) were combined. Set under an argon atmosphere and outside the glovebox, Et_3B (0.155 mmol, 22.7 µL) was added. The orange mixture was stirred at r.t. for 10 min before the addition of a solution containing the enyne **50** (0.062 mmol, 25 mg) and aldehyde **53** (0.062 mmol, 52 mg) in EtOAc (0.900 mL). The resulting red reaction mixture was stirred 14 h while warming to r.t. The mixture was then diluted with EtOAc (2 mL), and it was stirred open to air to allow for aerobic oxidation of the catalyst evident by the slow conversion of the color to pale green. The mixture was filtered through a short pad of silica gel (eluting with EtOAc), concentrated in vacuo, and purified by flash column chromatography (10% EtOAc/hexane). This provided the dienol (**54**) as a colorless oil (58 mg, 75% yield) along with the hemiketal. ^1H NMR (400 MHz, $CDCl_3$) δ 6.68 (t, *J* = 6.8 Hz, 1H), 5.80 (brs, 1H), 4.94 (s, 1H), 4.85 (s, 1H), 4.40-4.34 (m, 1H), 4.21-4.09 (m, 3H), 4.07-4.04 (m, 1H), 3.71-3.53 (m, 2H), 3.51-3.47 (m, 1H), 3.35 (t, *J* = 7.5 Hz, 1H), 3.10 (s, 1H), 2.82-2.75 (m, 2H), 2.64-2.57 (m, 3H), 2.18-2.08 (m, 4H), 2.00-

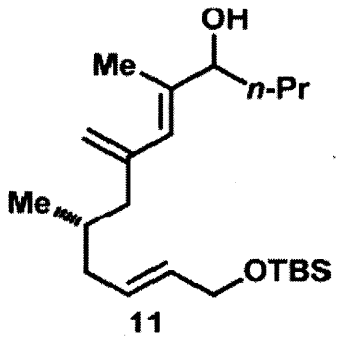
1.84 (m, 2H), 1.79 (s, 3H), 1.77-1.70 (m, 6H), 1.60-1.50 (m, 2H), 1.50-1.40 (m, 5H), 1.26-1.22 (m, 2H), 1.01 (t, J = 4.2 Hz, 1H), 0.91 (s, 9H), 0.87 (s, 18H), 0.85 (s, 21H), 0.79 (d, J = 6.6 Hz, 3H), 0.11 (s, 3H), 0.09 (s, 6H), 0.08 (s, 6H), 0.04 (s, 3H), 0.01 (s, 18H), -0.04 (s, 3H); $[\alpha]_D$ –13.9 (*c* 7.0, $CHCl_3$).

Chapter 2: Spectra

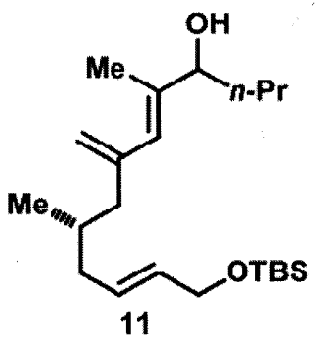

OH
Me
Me
Me
OTBS
8
ppm 7
6
5
4
3
2
1
0



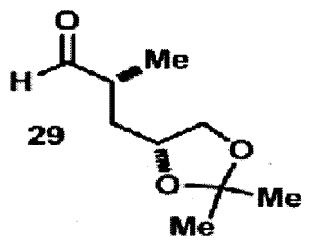
9

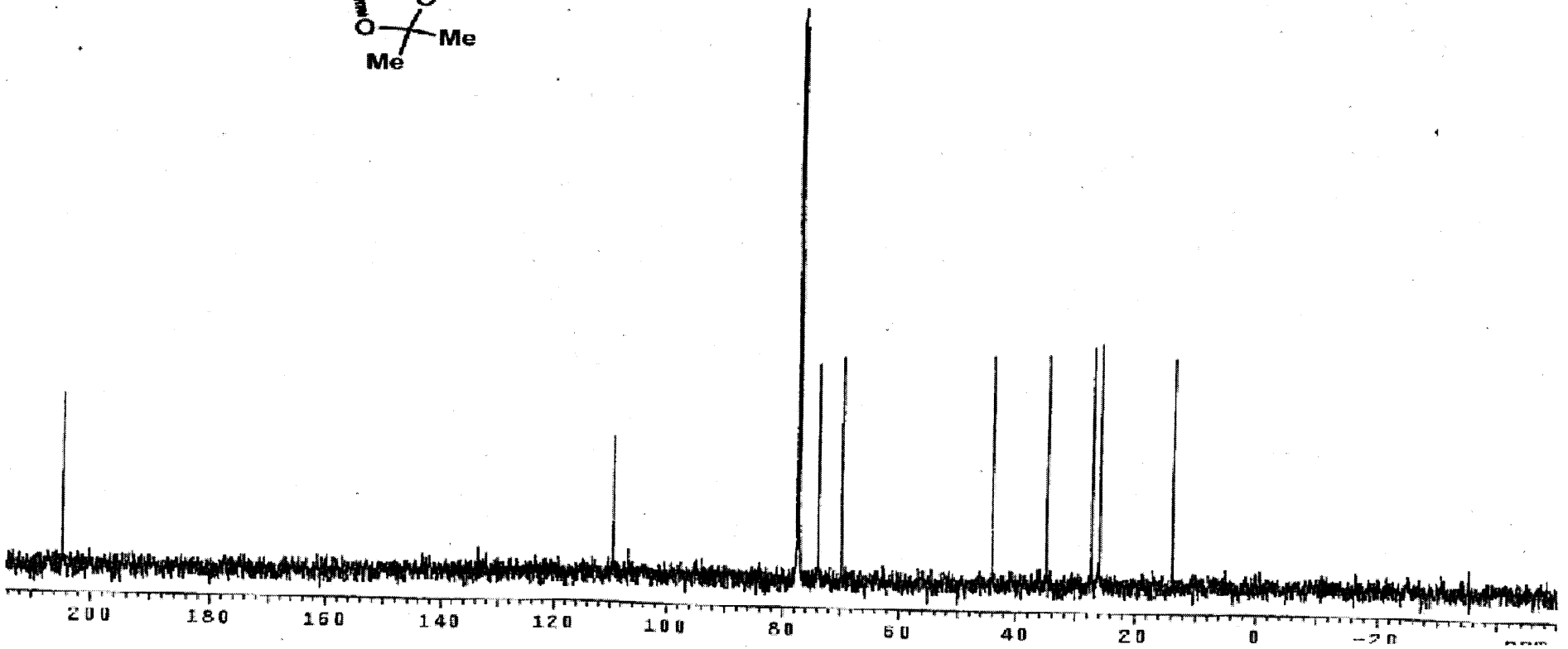


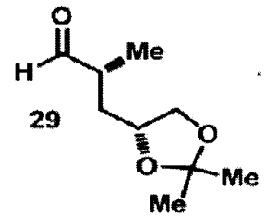
11

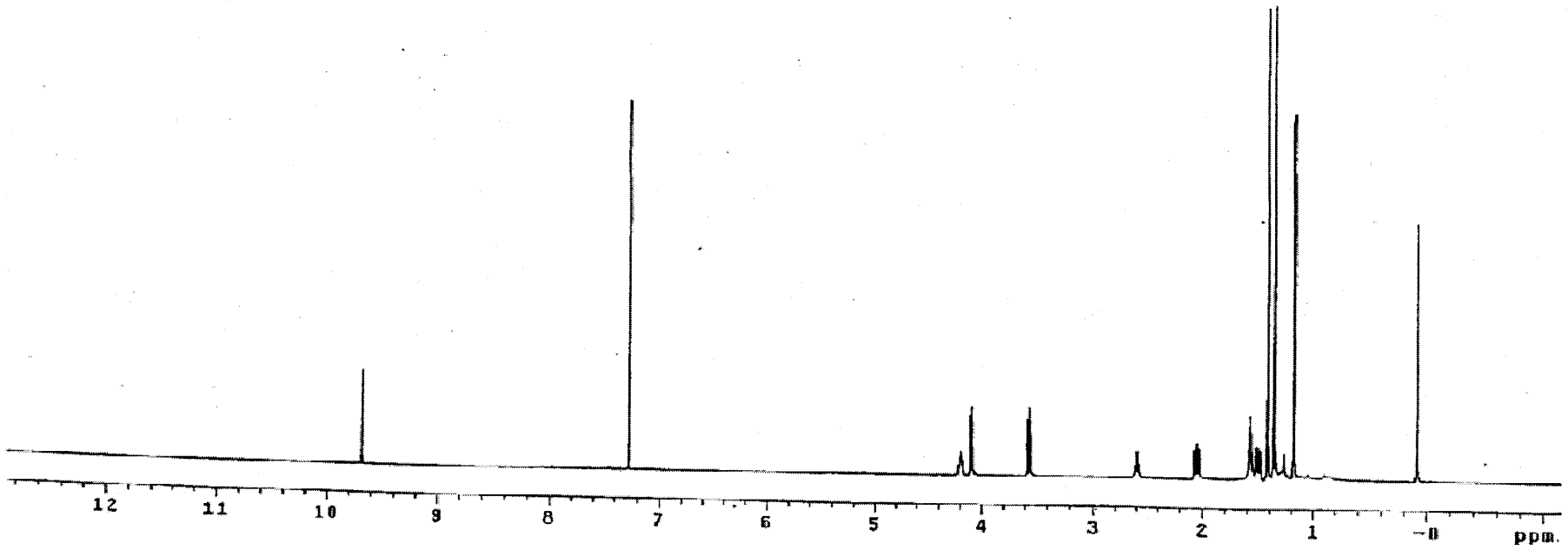


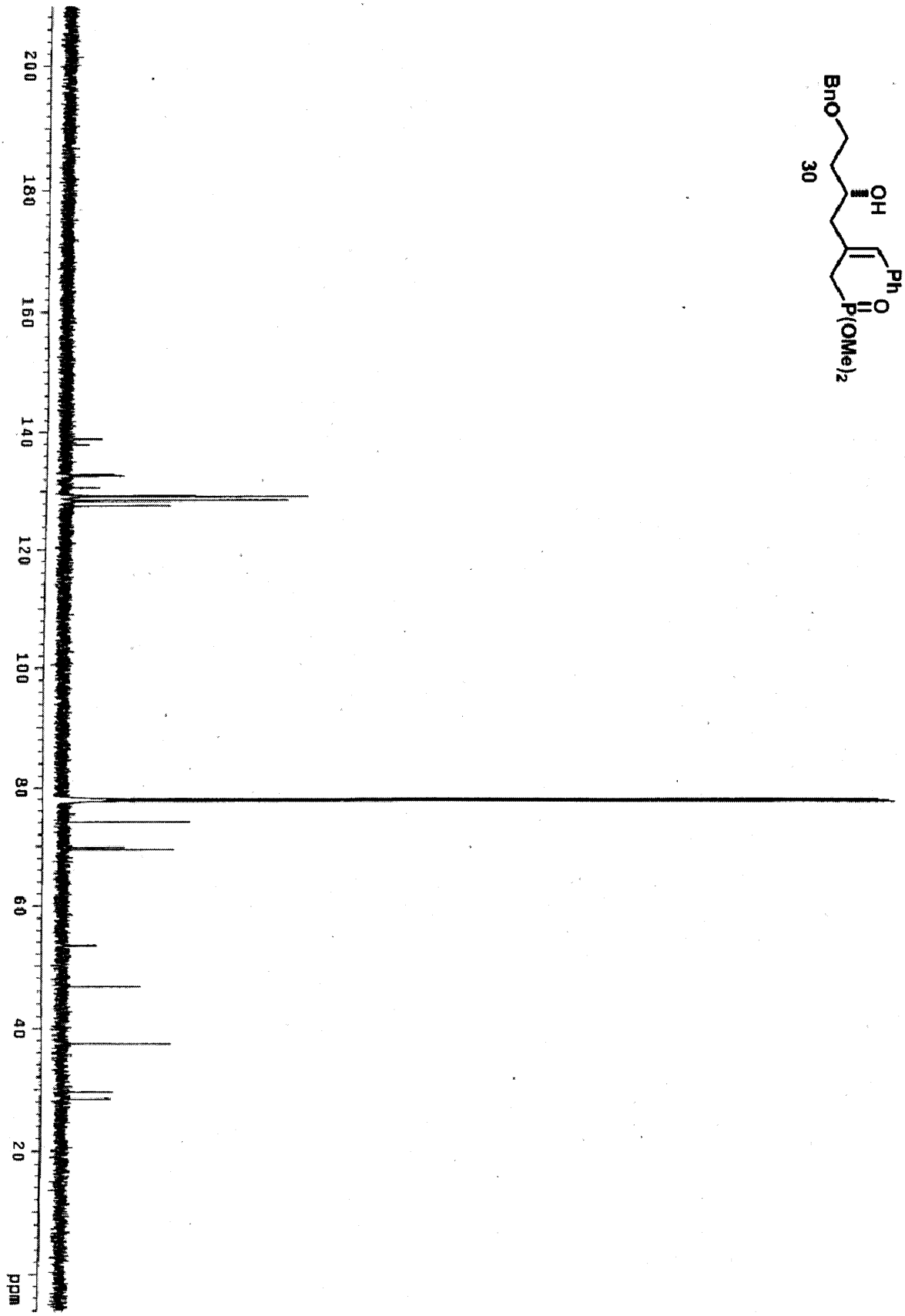
11

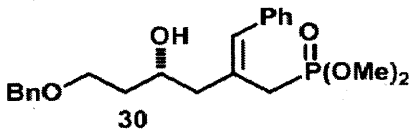

O
H
Me
29
O
O
Me
Me


200
180
160
140
120
100
80
60
40
20
0
-20

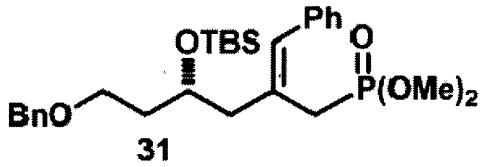

O
H
Me
29
O
O
Me
Me


12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

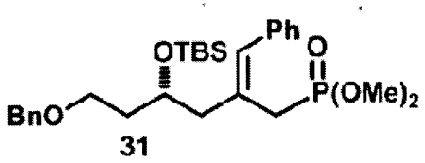

BnO
OH
30
Ph
O
P(OMe)2
200
180
160
140
120
100
80
60
40
20
ppm



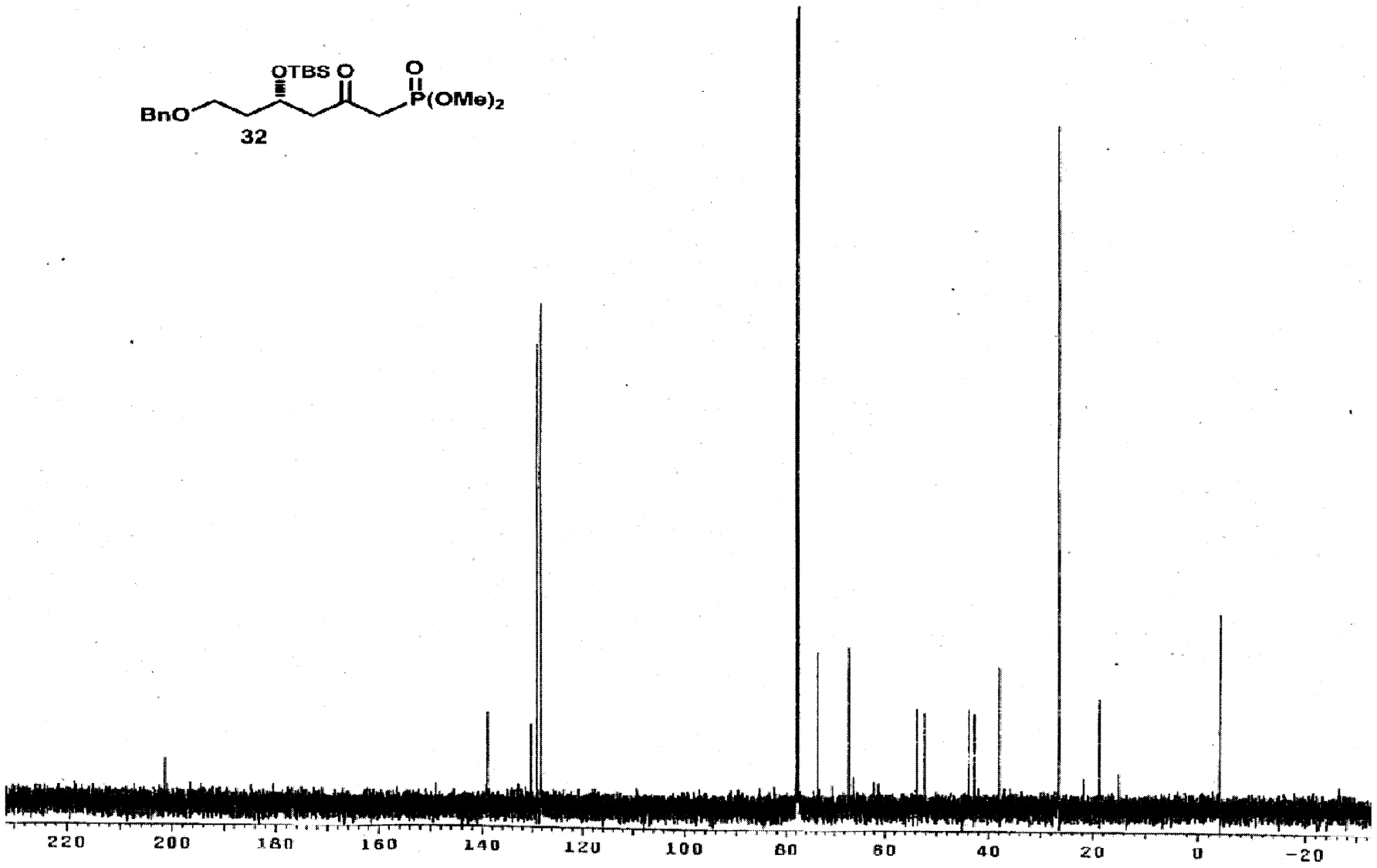
30

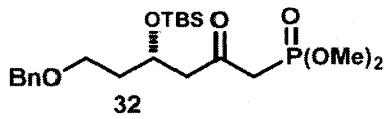


31

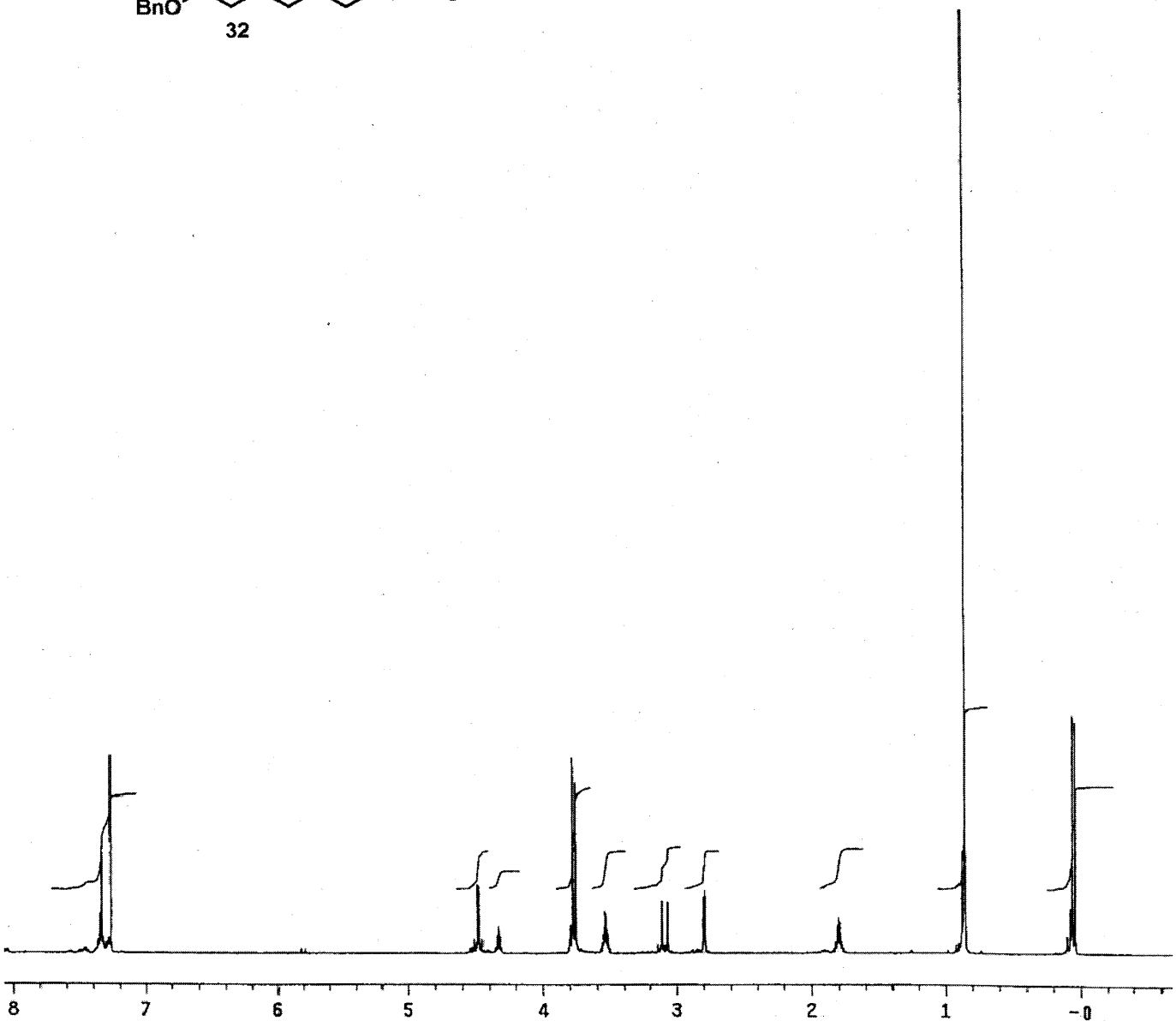


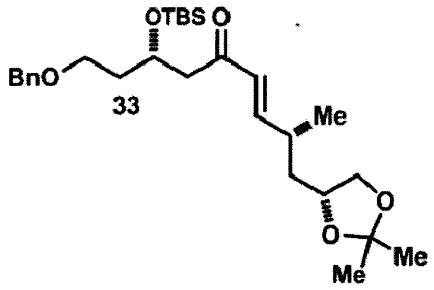
31

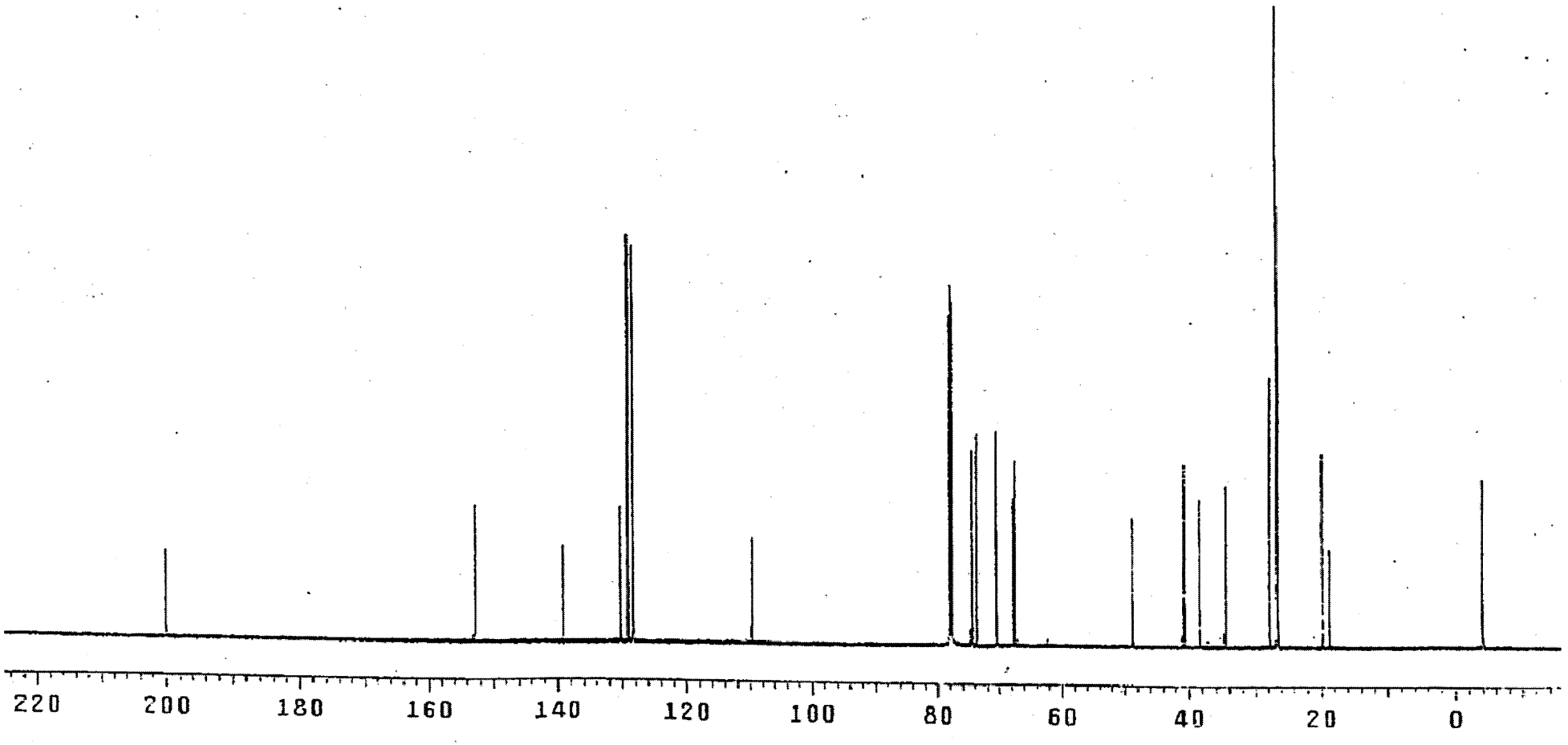

OTBS
O
O
P(OMe)2
BnO
32
220
200
180
160
140
120
100
80
60
40
20
0
-20

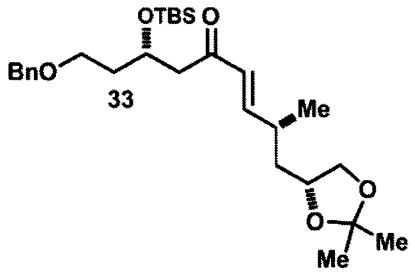


32

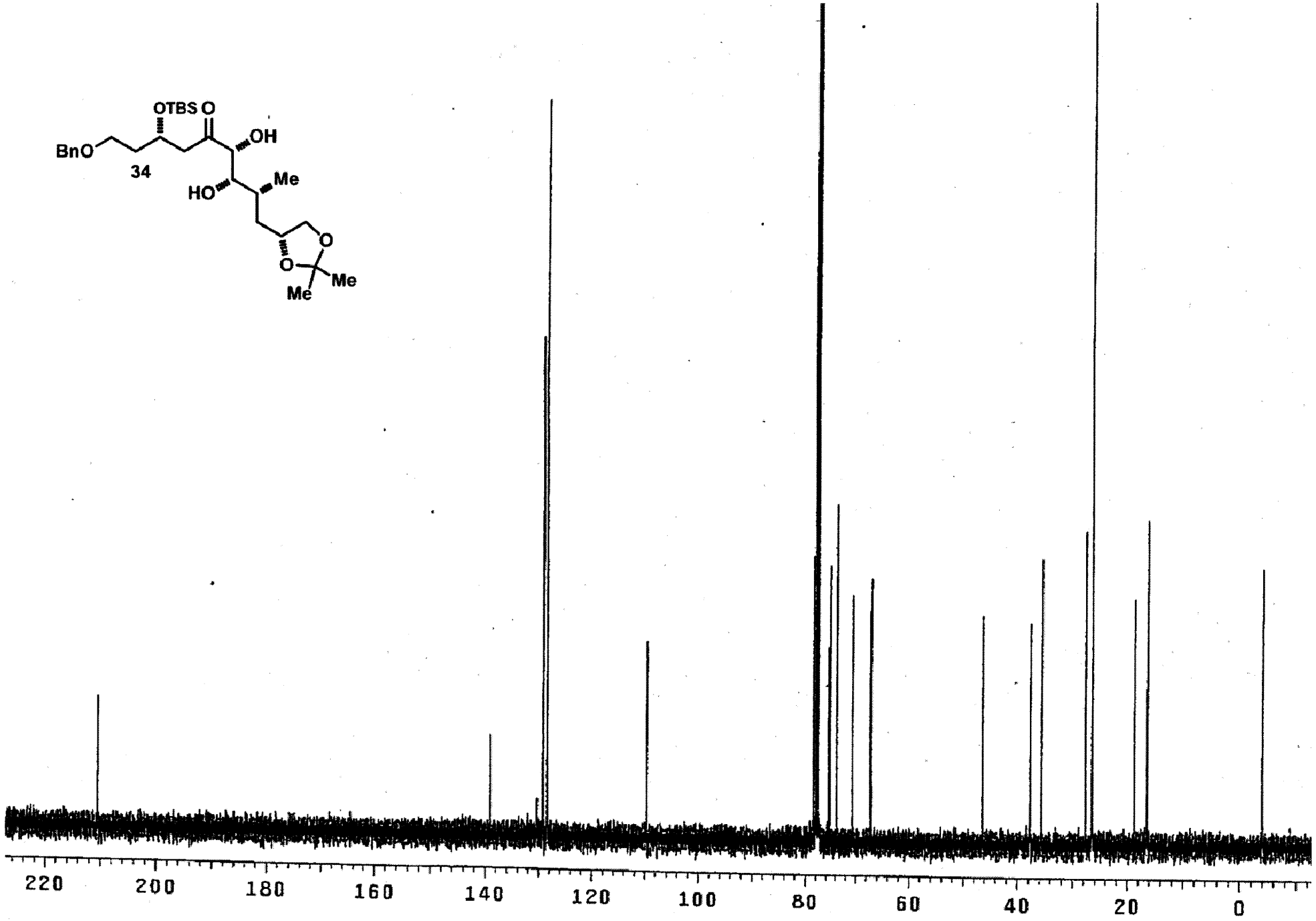


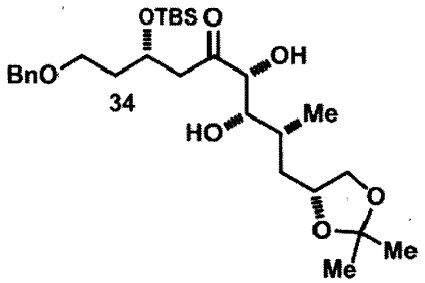

OTBS
O
BnO
33
Me
O
O
Me
Me


220
200
180
160
140
120
100
80
60
40
20
0

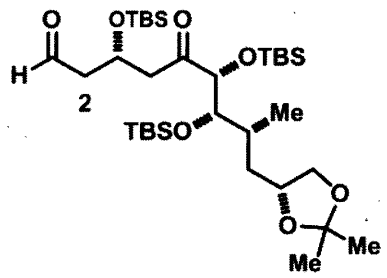

OTBS O
BnO
33
Me
O
O
Me
Me

8
7
6
5
4
3
2
1
0

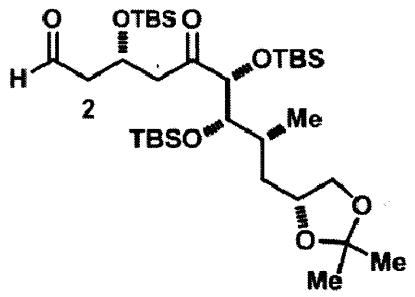

OTBS O
OH
BnO
34
HO
Me
O
O
Me
Me
220
200
180
160
140
120
100
80
60
40
20
0


OTBS O
OH
BnO
34
HO
Me
O
O
Me
Me

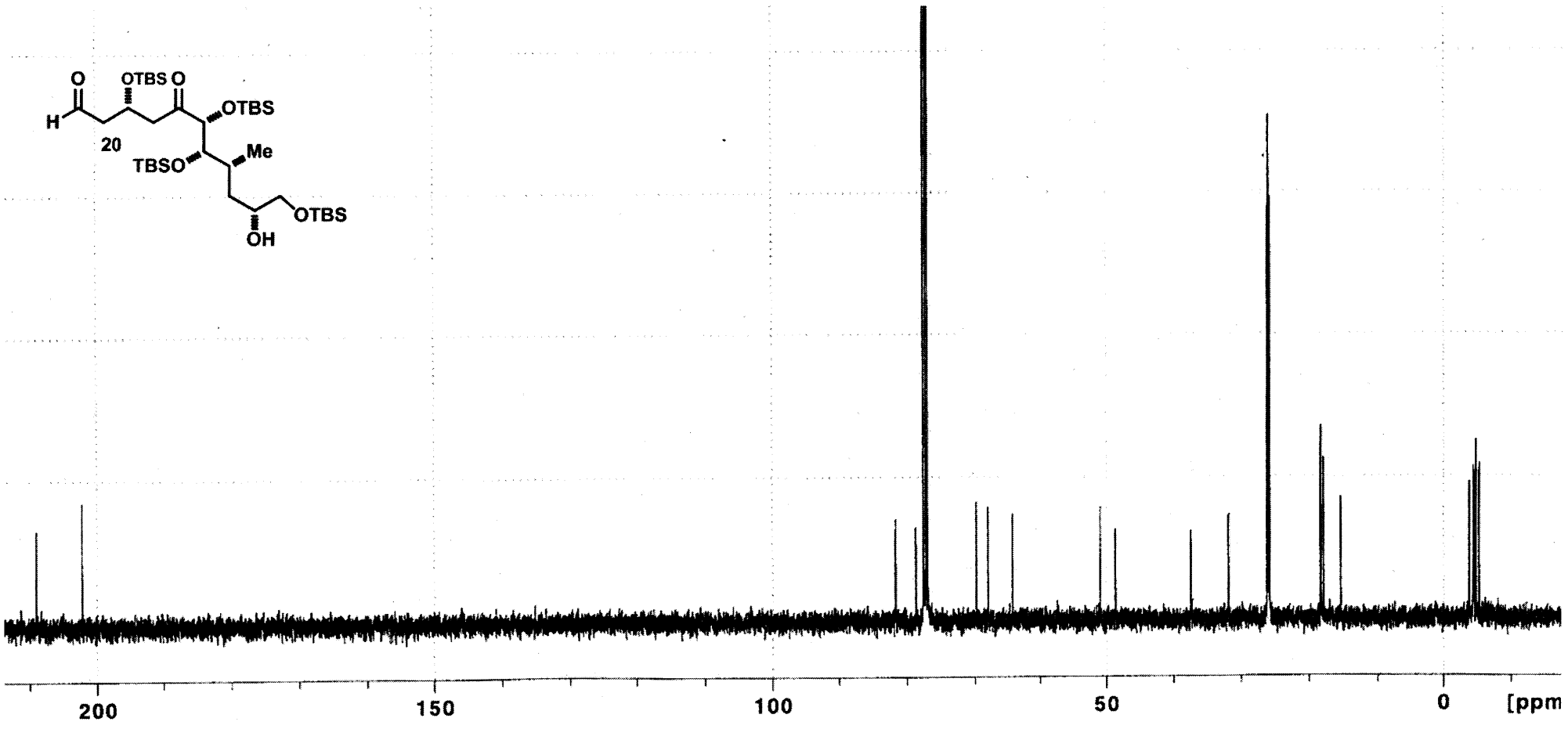
7
6
5
4
3
2
1
-0

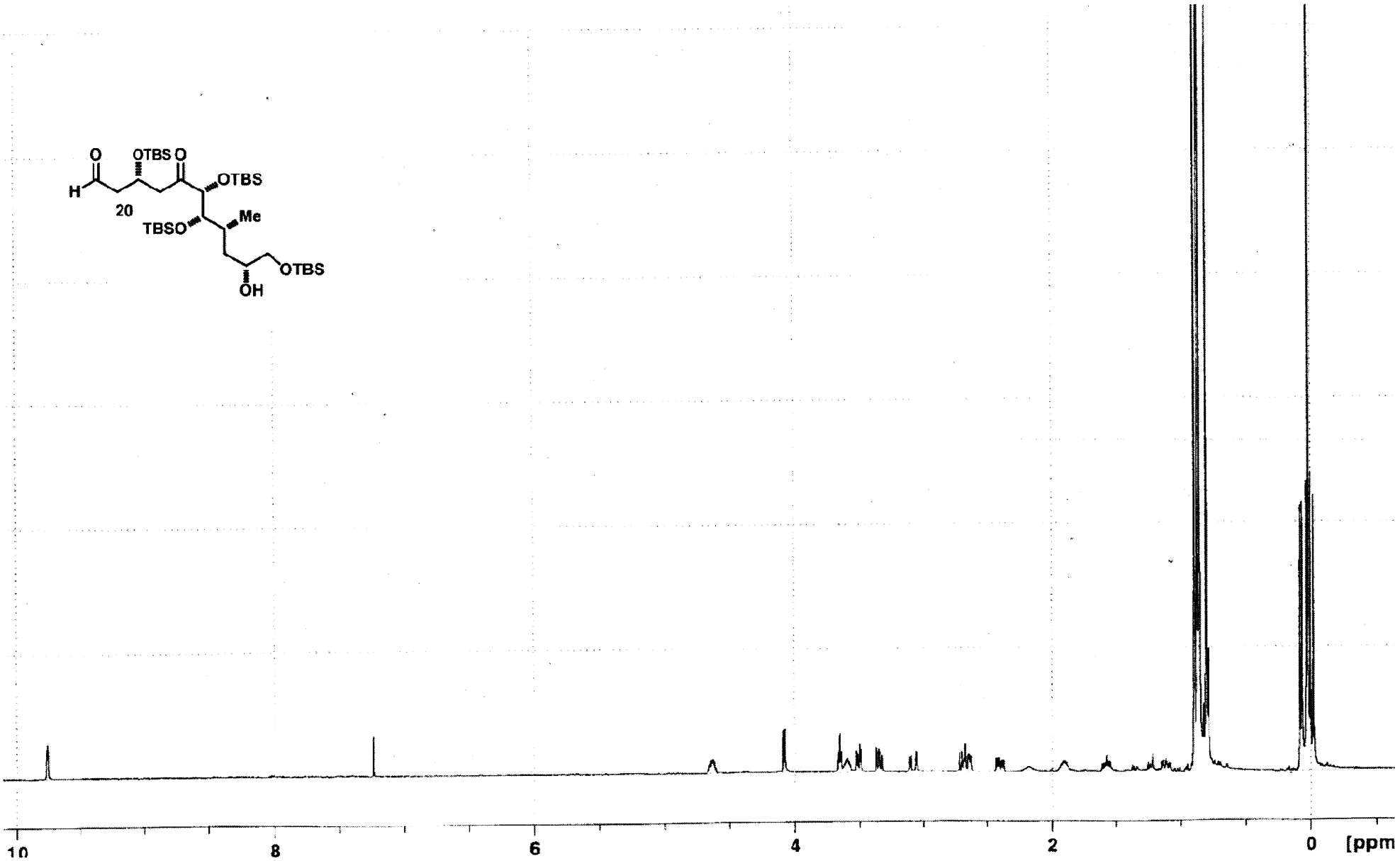

O
OTBS
O
H
OTBS
2
TBSO
Me
O
O
Me
Me

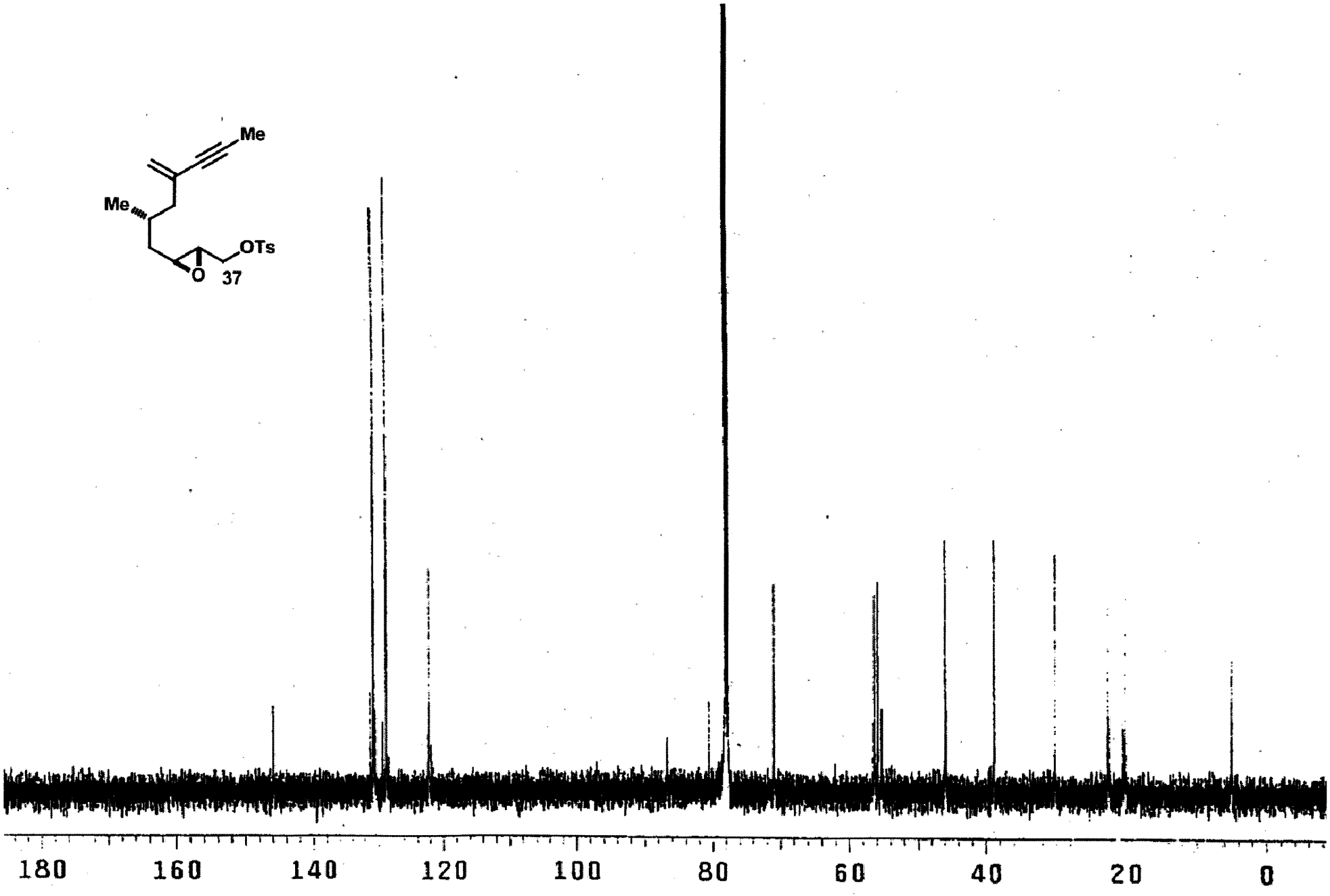
200
180
160
140
120
100
80
60
40
20
0

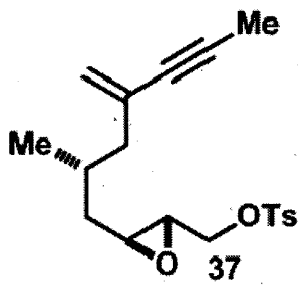

O
OTBS
O
H
OTBS
2
TBSO
Me
O
O
Me
Me

10
9
8
7
6
5
4
3
2
1
-0
ppm

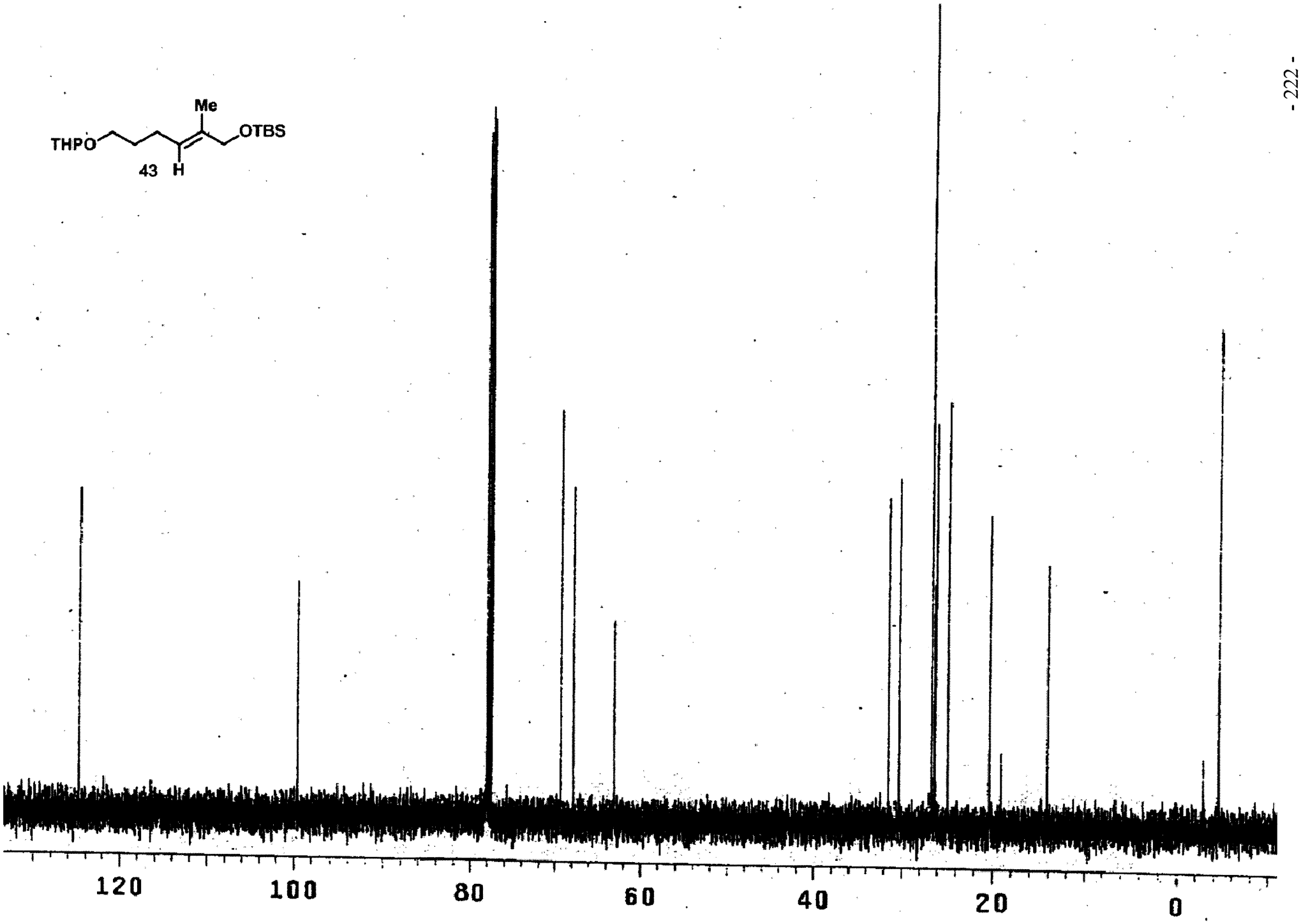

O
OTBS
O
H
OTBS
20
TBSO
Me
OTBS
OH
200
150
100
50
0
[ppm

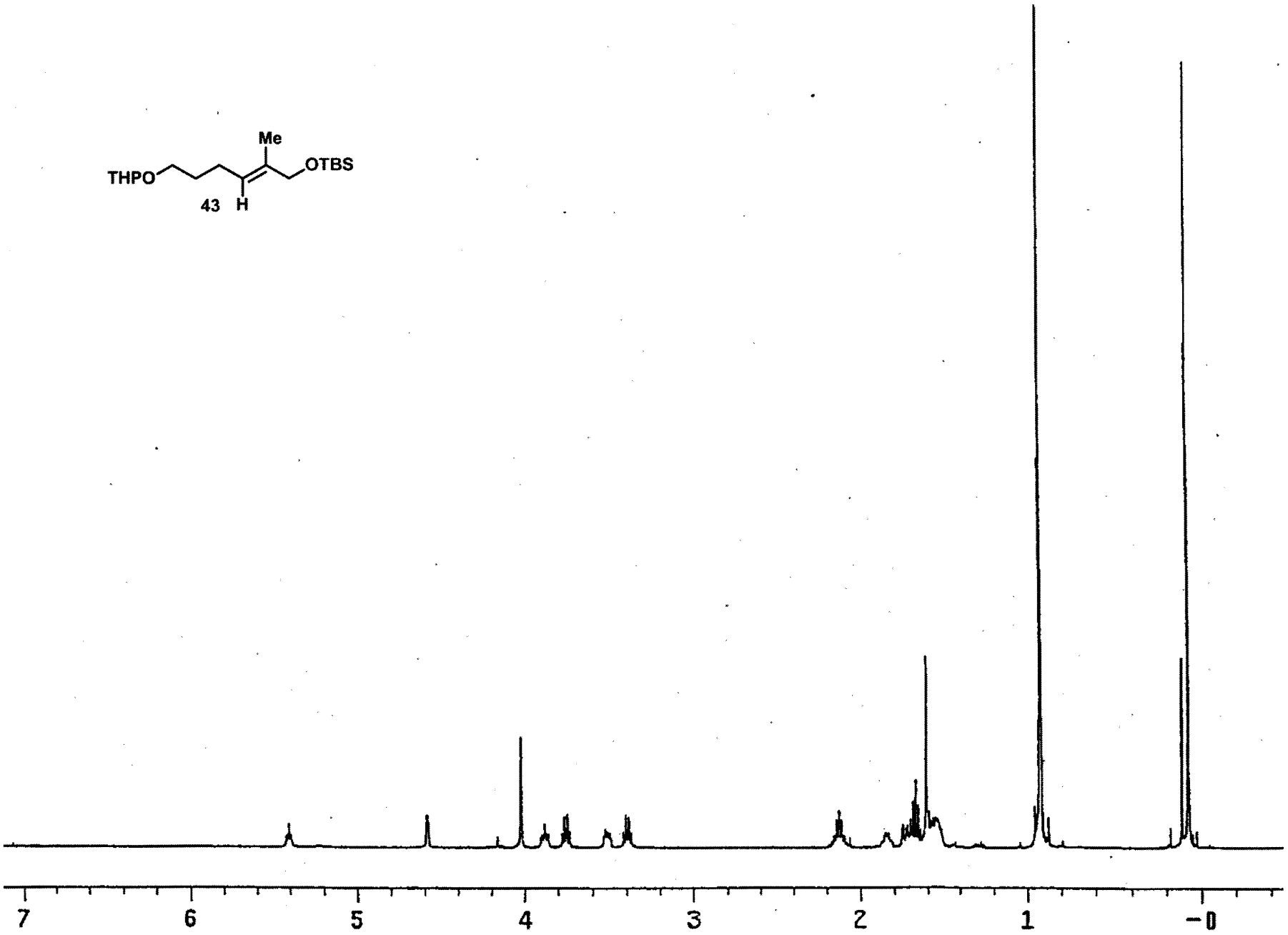

O
OTBS
O
H
OTBS
20
TBSO
Me
OTBS
OH
10
8
6
4
2
0
[ppm

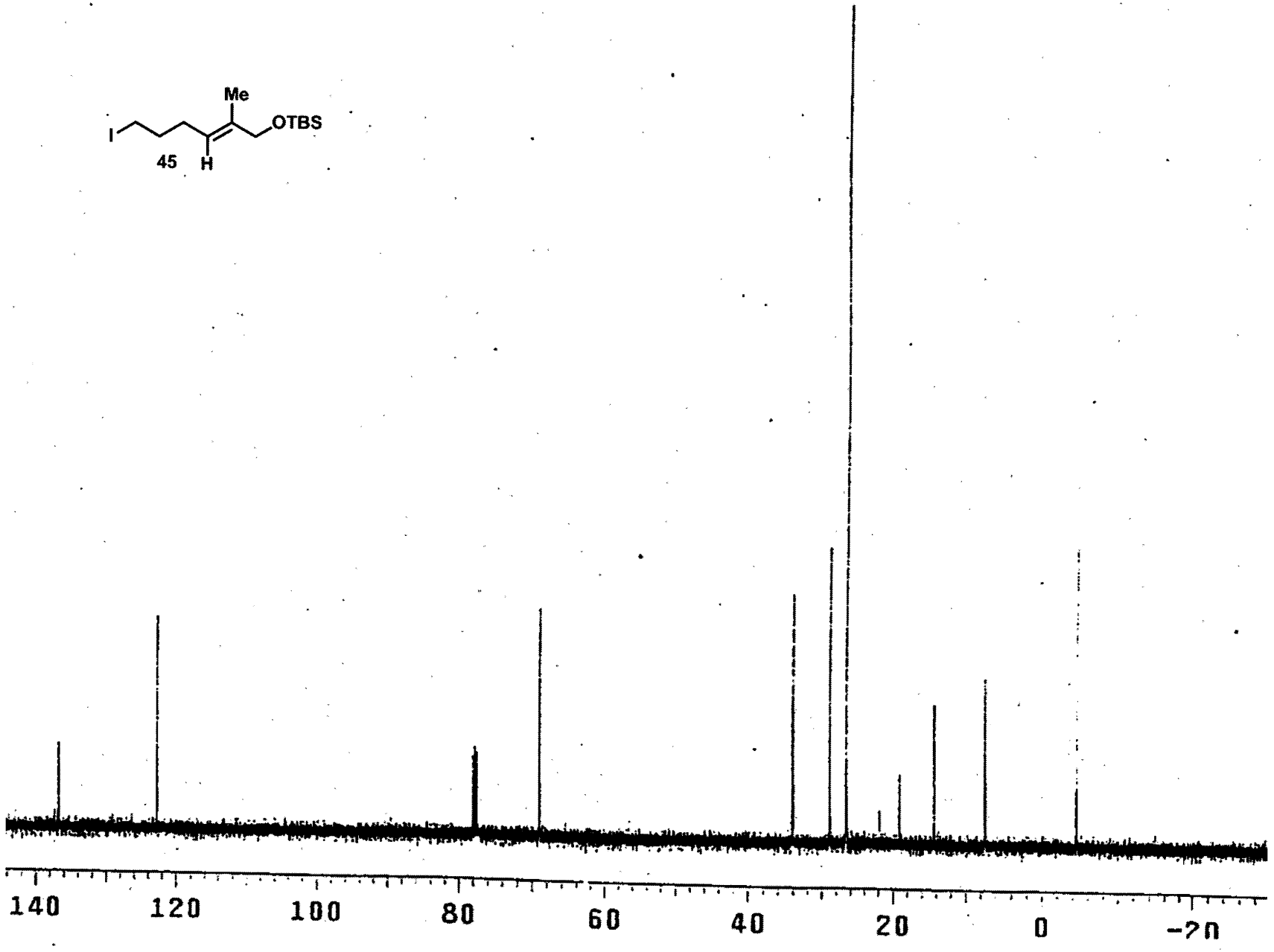

Me
Me
OTs
O
37
180
160
140
120
100
80
60
40
20
0

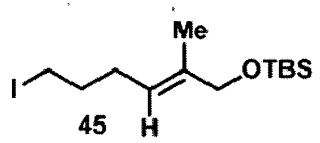

Me
Me
OTs
O
37

8
7
6
5
4
3
2
1

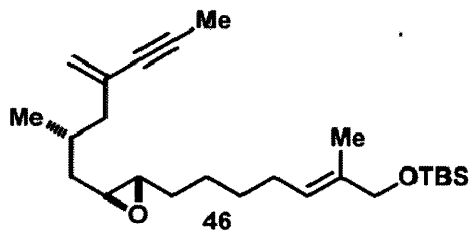

Me
THPO
OTBS
43
H
120
100
80
60
40
20
0


Me
THPO
OTBS
43 H
7
6
5
4
3
2
1
-0

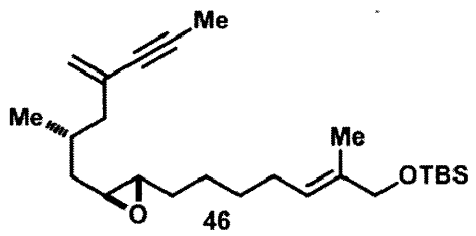

Me
OTBS
I
45
H
140
120
100
80
60
40
20
0
-20


Me
OTBS
I
45
H

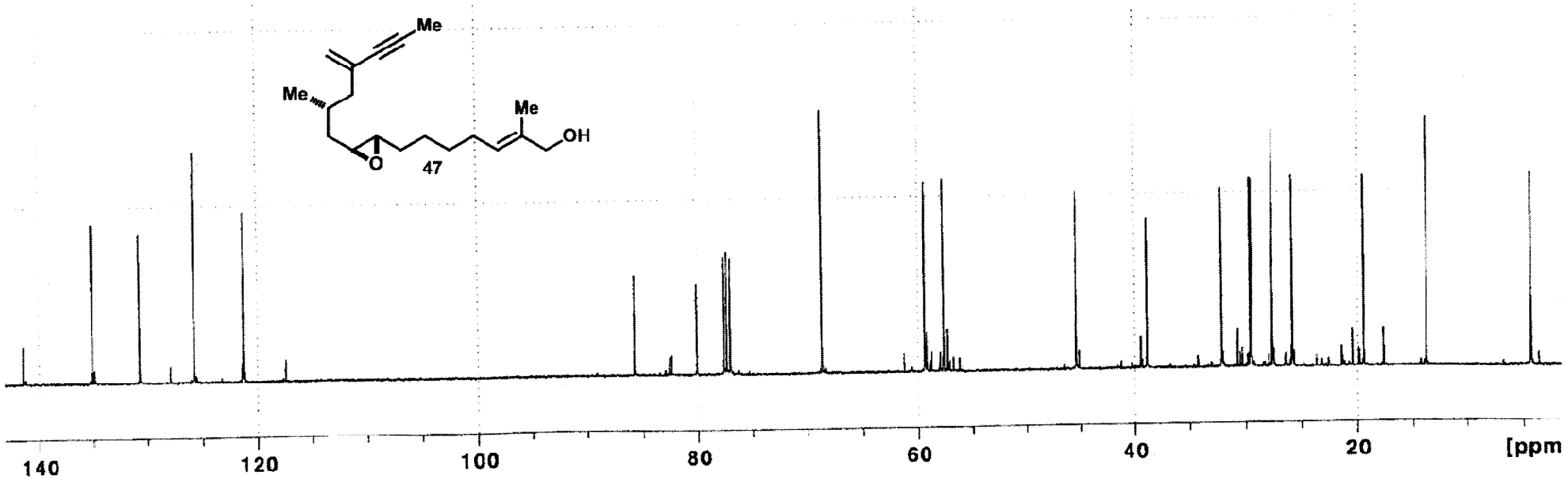
7
6
5
4
3
2
1
0

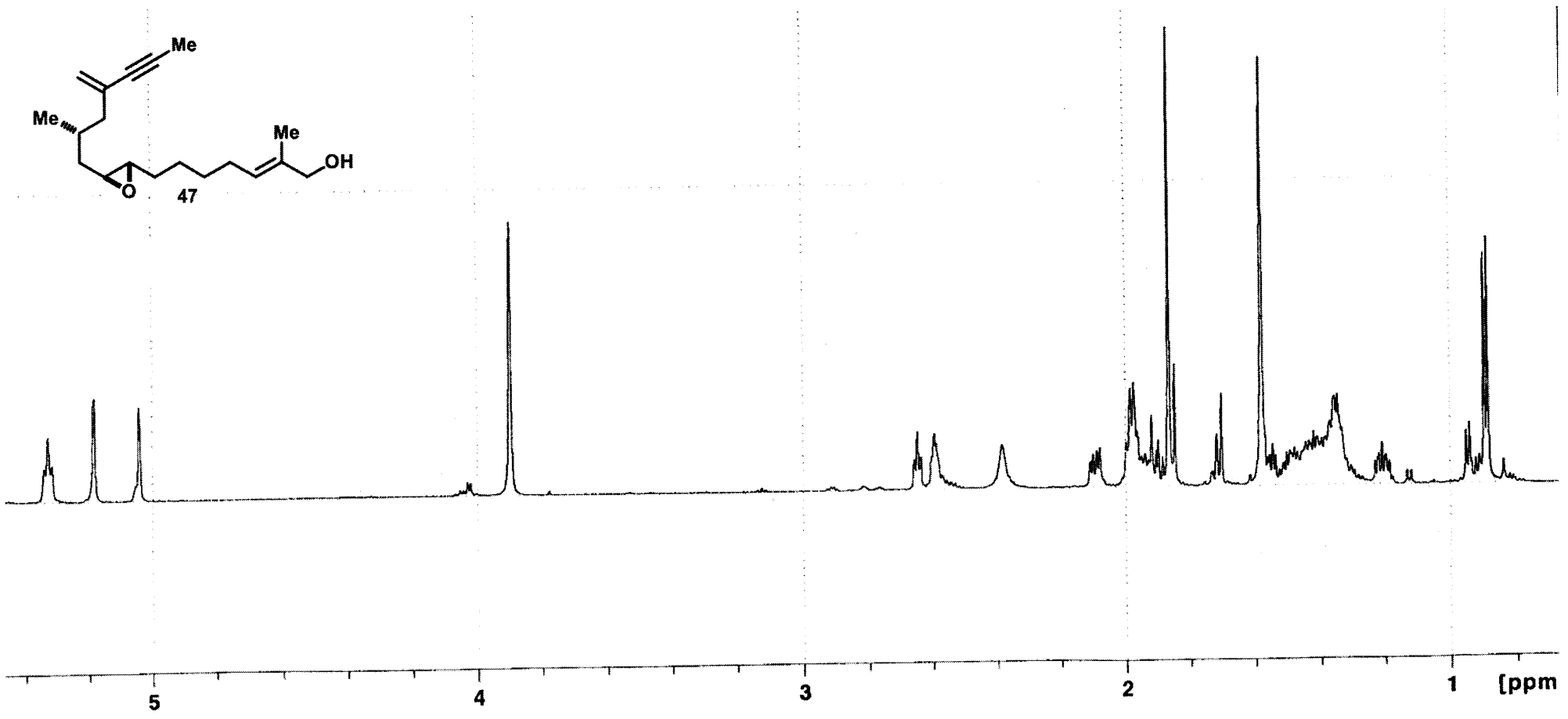

Me
Me
Me
OTBS
O
46

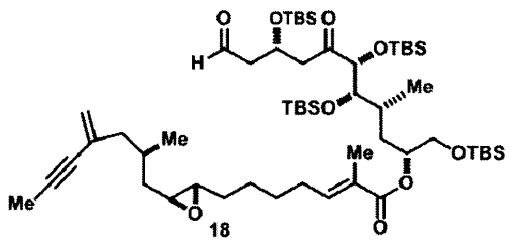
160
140
120
100
80
60
40
20
0


Me
Me
Me
OTBS
O
46

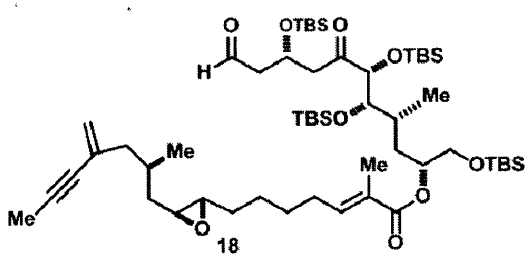
7
6
5
4
3
2
1
0


Me
Me
Me
OH
O
47
140
120
100
80
60
40
20
[ppm

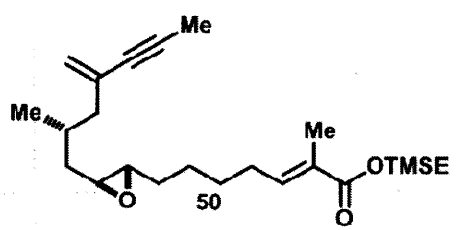

Me
Me
Me
OH
O
47
5
4
3
2
1
[ppm

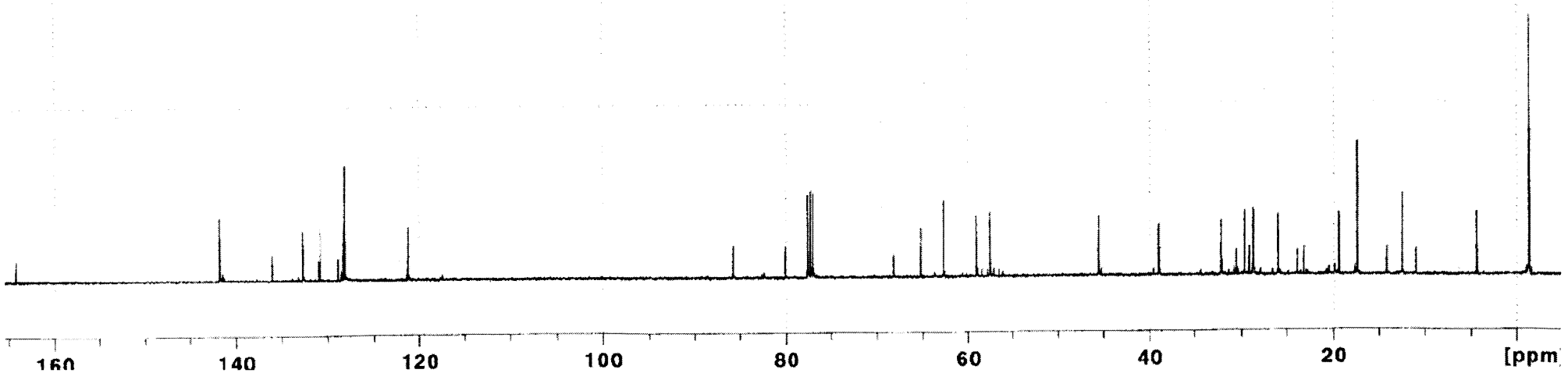

O
OTBS
O
H
OTBS
Me
TBSO
Me
Me
Me
OTBS
O
O
O
18

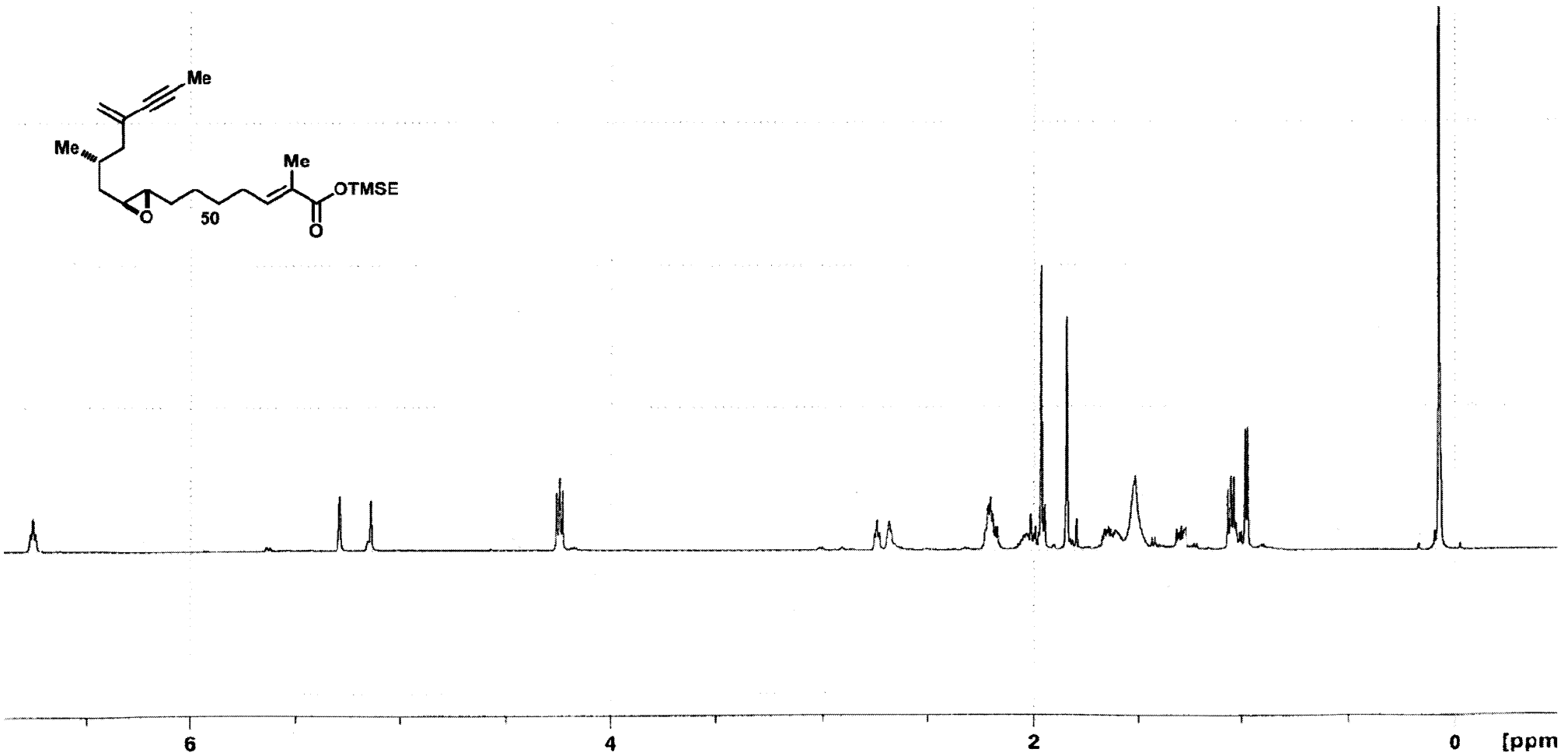
ppm 200
180
160
140
120
100
80
60
40
20
0

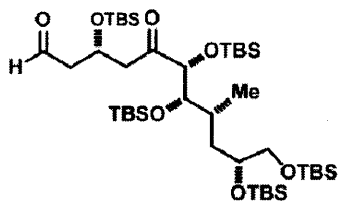

O
OTBS
O
H
OTBS
TBSO
Me
Me
Me
OTBS
Me
O
O
O
18

10
9
8
7
6
5
4
3
2
1
0


Me
Me
Me
OTMSE
O
50
O

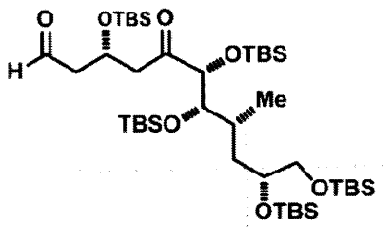

160
140
120
100
80
60
40
20
[ppm]


Me
Me
Me
OTMSE
O
50
O
6
4
2
0
[ppm

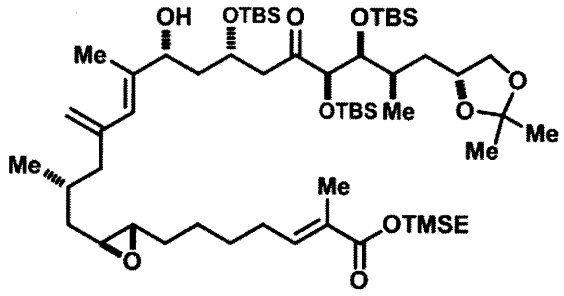

O
OTBS
O
H
OTBS
Me
TBSO
OTBS
OTBS

53

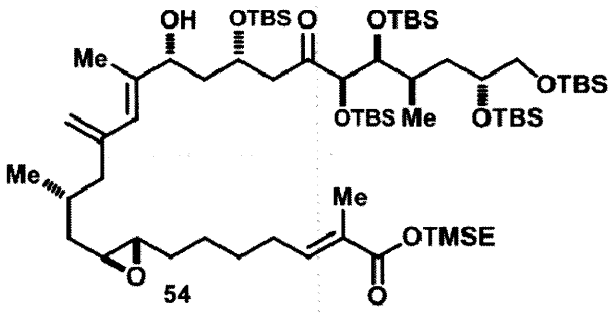
ppm 200
180
160
140
120
100
80
60
40
20
0



53



51


OH
OTBS
O
OTBS
Me
OTBS
Me
OTBS
OTBS
Me
Me
OTMSE
O
54
O

8
6
4
2
0
[ppm

Curriculum Vitae

Education

Massachusetts Institute of Technology, Cambridge, MA
Candidate for Ph.D degree in Organic Chemistry **January 2010**
GPA: 4.6/5.0
Research advisor: Prof. Timothy F. Jamison

Northern Kentucky University, Highland Heights, KY
B.S. in Chemistry **May 2004**
Minor: Mathematics
GPA: 3.95/4.0
Chemistry GPA: 4.0/4.0
Research advisor: Prof. K. C. Russell

Research Experience

Massachusetts Institute of Technology
Research with Prof. Timothy F. Jamison **January 2005 – Present**
I am working on the development of nickel catalyzed enyne / ketone reductive couplings and their application toward amphidinolide natural product synthesis.

Northern Kentucky University
Research with Prof. K. C. Russell **May 2002 – August 2004**
I worked on the synthesis of ten membered ring enediynes, and the Bergman cyclization of enediynes using a modulated differential scanning calorimeter.

Teaching Experience

Massachusetts Institute of Technology, Department of Chemistry
Grader **fall 2008**
Course: 5.511 (Organic Synthesis I)
Duties: I helped prepare and grade problem sets and exams.

Massachusetts Institute of Technology, Department of Chemistry
Teaching Assistant **fall 2004**

Course: 5.13 (Organic Chemistry II lecture)
Duties: I led four recitation sections a week, held office hours, and graded homework.

Northern Kentucky University, Department of Chemistry
Faculty Member **summer 2004**

Title: Level 1 instructor
Course: CHE-311L (Organic Chemistry II laboratory)
Duties: I instructed students in lab, prepared and graded quizzes and exams, and assigned term grades.

Northern Kentucky University
Tutor, Chemistry **August 2001 – May 2004**

Northern Kentucky University, Department of Chemistry
Teaching Assistant **spring 2003**

Course: CHE-311L (Organic Chemistry II lab)
Duties: I prepared and graded weekly quizzes, supervised experiments, and obtained NMR spectra for students.

Northern Kentucky University, Department of Chemistry
Teaching Assistant **fall 2002**

Course: CHE-120L (General Chemistry I lab)
Duties: I supervised experiments and assisted students with lab equipment.

Northern Kentucky University, Department of Chemistry
Tutor, Mathematics **fall 2001**

Conference Presentations

Poster:

Kentucky Academy of Science Poster Competition,
Highland Heights, KY **November 2003**
Towards Synthesis of Ten-Membered Enediynes with DNA Cleaving Activity.

National American Chemical Society Meeting,
New Orleans, LA **March 2003**
Lauer, A. M.; Machado, L.; Mousseau, K.; Trout, A.; Gabbard, J.; Russell, K. C. *Electronic Control of Bergman Cyclization.*

Oral:

Undergraduate Research Symposium,
MIT, Cambridge, MA **April 2009**
Nguyen, N.; Lauer, A. M.; Jamison, T. F. *Work Toward the Total Synthesis of B-Type Amphidinolide Natural Products.*

Graduate Research Symposium,
MIT, Cambridge, MA **May 2008**
Lauer, A. M.; Jamison, T. F. *Toward the Total Synthesis of B-Type Amphidinolides via Ni-Catalyzed Couplings of Enynes and Carbonyl Groups.*

National American Chemical Society Meeting,
Boston, MA **August 2007**
Ndubaku, C. O.; **Lauer, A. M.**; Jamison, T. F. *Toward the Total Synthesis of Amphidinolide H4 via Diastereoselective Ni-Catalyzed Coupling of an Enyne and Aldehyde Fragment.*

Invited lecture for NSF-REU program,
Highland Heights, KY **July 2006**
Work Toward the Total Synthesis of Amphidinolide H1.

Northern Kentucky University Celebration of Student Research,
Highland Heights, KY **April 2004**
Gaining Insight into Anti-Cancer Drugs Through the Synthesis of Enediynes.

Greaves Scholarship Banquet, student quest speaker,
Highland Heights, KY **September 2003**
NKU Anti-Cancer Research.

Trinity College, NSF-REU program,
Hartford, CT **August 2003**
Synthesis of Novel Enediynes.

Publications

Lauer, A. M.; Mousseau, K.; Russell K. C.; *Towards Synthesis of Novel Enediyne Anti-Cancer Drugs*, Norse Scientist, **2004**, 67. (Publication of Northern Kentucky University).

Grants and Fellowships Received

NSF Graduate Research Fellowship **June 2005 – May 2008**

DuPont/MIT First Year Graduate Student Fellowship **September 2004 – May 2005**

Grant of $500 for research supplies from NKU **Septemeber 2003**

NSF-REU Grant **May 2003**

Greaves Summer Fellowship for research in chemistry **May 2002**
Title of grant -*Novel Nucleic Acid Enediynes: Tautomeric Effect on Bergman Cyclization and Development of Anti-Cancer Drugs*

Honors and Awards

Northern Kentucky University Outstanding Senior Scholarship **May 2004**

NKU Outstanding Senior Chemistry Student Book Scholarship Award **May 2004**

American Chemical Society Travel Award **March 2003**
For travel to national meeting in New Orleans, LA for poster presentation

Greaves Scholarship Award **February 2000**
Full scholarship to Northern Kentucky University

Professional Memberships

American Chemical Society **February 2003 – Present**