Synthesis and Determination of the Absolute Configuration of Armatol A Through a Polyepoxide Cyclization Cascade. Revision of the Proposed Structures of Armatols A-F.

by

Brian Saxton Underwood

B. S. with Honors, Chemistry and Electrical Engineering
California Institute of Technology, 2005

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

February 2011

Signature of Author _____
Department of Chemistry
October 8, 2010

Certified by _____
Timothy F. Jamison
Professor of Chemistry
Thesis Supervisor

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

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

Professor Mohammad Movassaghi ___ _____
Chairman

Professor Timothy F. Jamison _____ _____
Thesis Supervisor

Professor Stephen L. Buchwald __ _____

Synthesis and Determination of the Absolute Configuration of Armatol A Through a Polyepoxide Cyclization Cascade. Revision of the Proposed Structures of Armatols A-F.

by

Brian Saxton Underwood

Submitted to the Department of Chemistry on October 8, 2010
in Partial Fulfillment of the Requirements for the Degree of
Doctor of Philosophy in Organic Chemistry

ABSTRACT

Cyclization Cascades Leading to the Tricyclic Fragment of Armatol A

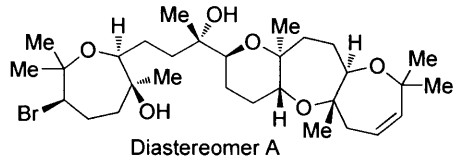
The synthesis of the fused 6,7,7-tricycle of armatol A was investigated. Fragments containing both a ketone and an aldehyde for subsequent fragment coupling were generated via a triepoxide cascade. Elimination of the secondary alcohol in the oxepane ring proved challenging; however, employing the Shapiro reaction successfully provided the desired oxepene. Ketone and aldehyde tricycles were synthesized in 11 and 7 steps, respectively, and both enantiomers of aldehyde fragment were synthesized. These short routes enable the preparation of sufficient quantities of these tricycles for fragment coupling studies.

Fragment Coupling, Synthesis, and Determination of the Absolute Configuration of Armatol A

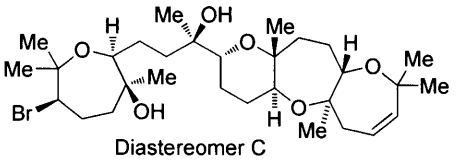
A stereoselective synthesis of a bromooxepane ring via a bromonium-initiated epoxide-opening cyclization was explored. Functionalization of the primary alcohol formed from this cascade allowed for a variety of coupling strategies to be explored to form the carbon framework of armatol A. Difficulties reducing a cis alkene adjacent to a tertiary alcohol forced a strategic revision; an analogous trans alkene was easily reduced to form the acyclic alkyl chain connecting the ring-containing fragments of armatol A.

Stereoselective installation of the tertiary alcohol allowed for a detailed investigation of the absolute structure of armatol A. At the outset, four diastereomers were consistent with the published data for the natural product. After determining that this tertiary alcohol must be syn to the adjacent THP ring stereocenter, the syntheses of the two remaining possible diastereomers of armatol A were completed. Of the four diastereomers shown in the figure, diastereomer B was confirmed by synthesis to be the correct structure of armatol A. Using this information, structural revisions of the entire family of armatols were proposed, as was a new biogenesis of these natural products.

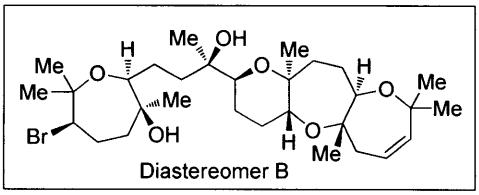
Four possible diastereomers of armatol A based on reported data



Diastereomer A

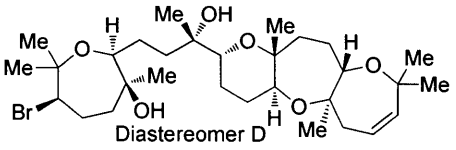


Diastereomer C



Diastereomer B

Confirmed structure of armatol by chemical synthesis



Diastereomer D

Thesis Supervisor: Timothy F. Jamison

Title: Professor of Chemistry

ACKNOWLEDGMENTS

Working in the Jamison lab has been an enjoyable and exciting experience in my life. From the very beginning working with a relatively small group of highly motivated graduate students and post-docs to a lab that has doubled in size since my arrival and included students from around the world who have influenced my growth as an organic chemist.

Professor Brian Stoltz and Jeremy May helped shape my undergraduate appreciation for organic chemistry as I got started in the midst of a burgeoning new organic laboratory at Caltech. Watching new graduate students and a new professor quickly develop prepared me for what to expect when heading off to my own graduate school experience.

Professor Timothy Jamison has provided me with a graduate school experience that allowed me to freely modify my own research and envision new pathways to pursue on my own accord. The free-rein allowed me to develop as an independent researcher while still having someone to rely on for suggestions and course-corrections where appropriate to keep the overall goal of the project moving forward. Tim was always there to provide new ideas when the research seemed to stall allowing me to realize that a dead-end was really just an opportunity to explore outside the traditional organic toolbox a bit more.

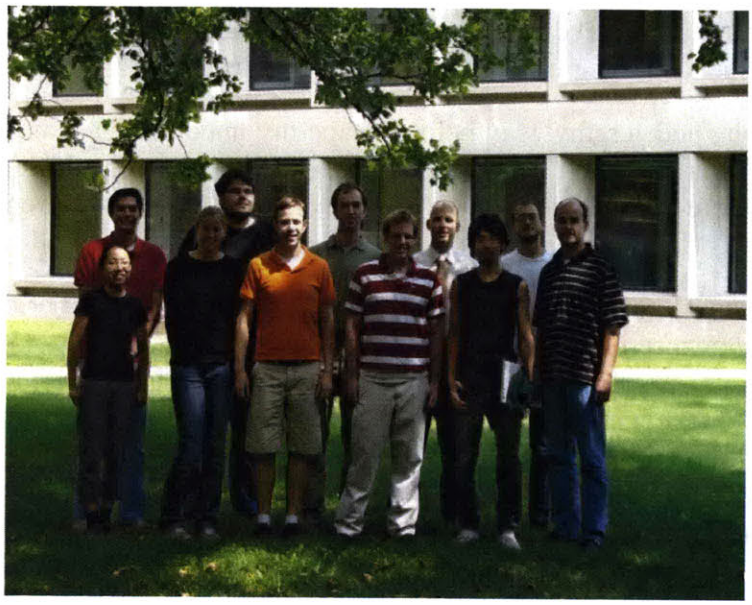
Professor Mohammad Movassaghi was insightful and provided honest opinions and suggestions for my thesis over the years while always encouraging me to move forward with my graduate school experience and my project. Professor Stephen Buchwald provided useful feedback and guided a few discussions to help clarify my research.

In Tim's lab I got to learn directly from many senior chemists including Dr. Victor Gehling, Dr. Jason Chun-Yu Ho, Dr. Ryan Moslin, Dr. Chudi Ndubaku, Dr. Graham Simpson, Dr. Jim Trenkle, Dr. Aaron Van Dyke, and others. Without a direct mentor in my early days in the Jamison group, the ability to learn from those around me helped tremendously in learning the "tricks of the trade" and fitting in the group and at MIT.

I would like to especially thank Katrina Woodin, Dr. Neil Langille, and Dr. Sze-Sze-Ng for not only provided an endless amount of intellectual knowledge, but also a dose of humorous adventures in the laboratory. Throughout long days in the lab, the personal interactions with those around me proved to be the basis of what kept me going day after day even in the face of synthetic difficulties. Kate taught me that even a little bit of fire in the hood was no reason to panic, just an opportunity to ask for some sand from those around you and keep a smile on your face the whole time. As dangerous as some of the activities are around the lab, learning to quickly keep them under control was a very important lesson to learn early on.

While we had quite a few undergraduate students work in the Jamison group over my time, Brian Sparling ("Sparkles") had the "privilege" of sharing a hood with me for a few months when I first joined the lab. I still remember the Monday morning I came into lab and found a suspicious 250 mL Erlenmeyer flask sitting in the middle of the hood between our shared spaces. I saw a colorless liquid inside and assumed I had left an aqueous layer out from earlier in the weekend and quickly rushed to dispose of my waste. Sparkles came back into lab from the NMR facility looking for his intermediate that he had just synthesized in order to carry it forward before his next class. Luckily it was a very early compound in his synthesis, but I still regret my decision

to clean up random glassware today. I wish Sparkles all the best as he pursues his own independent graduate school career at Harvard and I know Chris Morten and I miss having our very own Yoda within our bay.



While working in the bay, one of the biggest influences on my graduate career was Dr. Ivan Vilotijevic. Always there as a friend and a cheerful influence, he provided countless hours of not only academic discussions, but also endless hours of fun and entertainment. He was the only person I could count on in my early years in graduate school to escort me to McDonald's for a little escape from the stresses of lab. He was always highly supportive of my project and was willing to provide useful feedback whenever it was needed.

The two of us worked next to the wonder that is the "Sea Monkey" (Chris Morten). While he tried to keep a serious tone as the safety officer for the lab, he was probably the most entertaining person in the entire group. His way of leading discussions not only about chemistry but about every other topic under the sun filled the long days in lab with plenty of conversations to keep the time moving along.

Dr. Denise Colby joined the lab in my fourth year when things really started getting stressful and was a wonderful calming influence and friend during the last two years of my PhD. I wish her all the luck in her future endeavors in California as she finally gets to pursue her own career.

To those that worked with me on a daily basis, Kurt Armbrust, Dr. Matthew G. Beaver, Dr. Jeffery Byers, Dr. Megan Foley, Dr. Alicia Gutierrez, Dr. Andrew Lauer, Dr. Ryosuke Matsubara, Dr. Kristin Diann Schleicher, Satapanawat Sittihan, Dr. Adam Sniady, Jessica Tanuwidjaja, and many others I thank you for your patience and all your help over the years. Between suggestions, criticisms, and general knowledge the lab has always been a wealth of talent and skill sets that always provide someone useful to talk with about my research.

As a special thanks I need to acknowledge Chris Morten, Dr. Denise Colby, Jessica Tanuwidjaja, Kurt Armbrust, Satapanawat Sittihan, Dr. Alicia Gutierrez, and Dr. Matthew G. Beaver for

graciously offering to edit and revise my thesis. There is no way it would be in shape it is in without their help and support.

To my family, the patience and support that they have provided over the last 27 years has been amazing. Even for these last few weeks when I have been finalizing my research and this thesis, they have supported me with their thoughts while letting me finish my project on my own.

I have to acknowledge "The Uncle" who has provided me with over two years of joy and excitement outside of lab. She has been a constant source of encouragement and an understanding ear to listen to all my concerns and problems. She is a talented synthetic chemist who has already started her own successful career and makes me proud every day of the achievements that she has brought to her work.

TABLE OF CONTENTS

ABBREVIATIONS

Ac	acetyl
Acac	acetoacetate
Anis	anisyl (methoxy-phenyl)
Ar	aryl
atm	atmospheres
Bn	benzyl
Boc	tert-butoxy carbonyl
BRSM	based on recovered starting material
BHT	2,6-di-*tert*-butyl-4-methylphenol
Bu	butyl
°C	degree (Celsius)
cat.	catalytic
COSY	correlated spectroscopy
CSA	camphorsulfonic acid
δ	chemical shift in parts per million
DBU	1,8-diazabicyclo[5.4.0]-7-undecene
DCM	dichloromethane
DEAD	diethylazodicarboxylate
DET	diethyltartrate
DIBAL	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMF	*N,N'*-dimethylformamide
DMM	dimethoxymethane
DMP	Dess–Martin periodinane
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
ESI	electron spray ionization
Et	ethyl
Et_2O	diethylether
EtOAc	ethyl acetate
eq	equation
g	grams
GC	gas chromatography
h	hours
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
i-Pr	isopropyl
IR	infrared
L	liters
LHMDS	lithium hexamethyldisilazide
m	milli
μ	micro

M	molar
Me	methyl
MeO	methoxy
MeOH	methanol
MHz	megahertz
MIB	3-*exo*-morpholinoisoborneol
min	minutes
mol	moles
n	normal
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
n.d.	not determined
nOe	nuclear Overhauser effect
NOSEY	nuclear Overhauser effect spectroscopy
Ph	phenyl
PPTS	pyridinium *para*-tolulenesulfonate
Pr	propyl
Pyr	pyridine
R	any substituents
R_f	retardation factor
SiO_2	silica gel
t_R	retention time
t-Bu	*tert*-butyl
temp	temperature
TMS	trimethylsilyl
TBS	*tert*-butyl dimethylsilyl
TBAF	tetrabutylammonium fluoride
TBHP	tert-butyl hydroperoxide
TES	triethylsilyl
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TPAP	Tetrapropylammonium perruthenate
Ts	tosyl
TsOH	*para*-toluenesulfonic acid
wt	weight

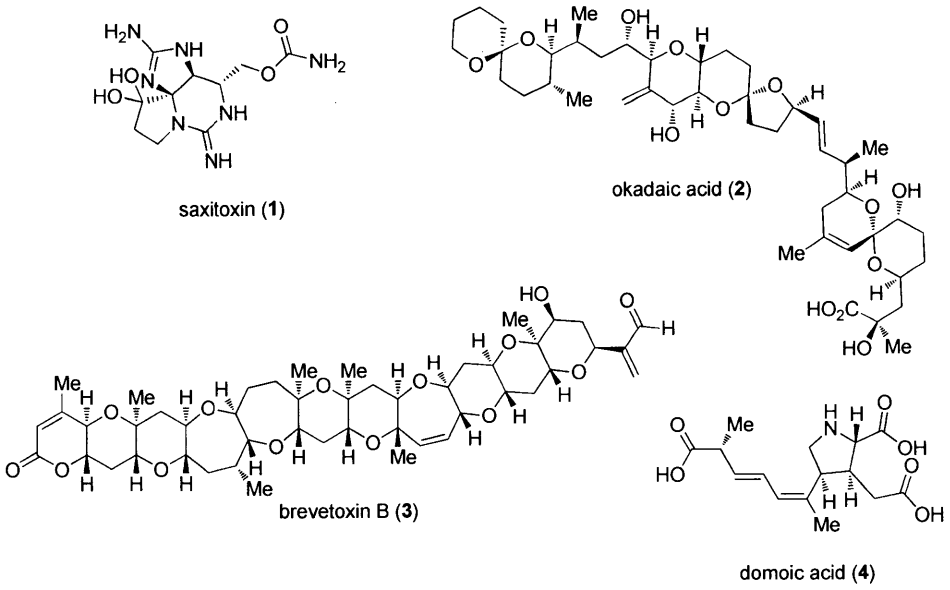
Chapter 1

Cyclization Cascades Leading to the Tricyclic Fragment of Armatol A

Background

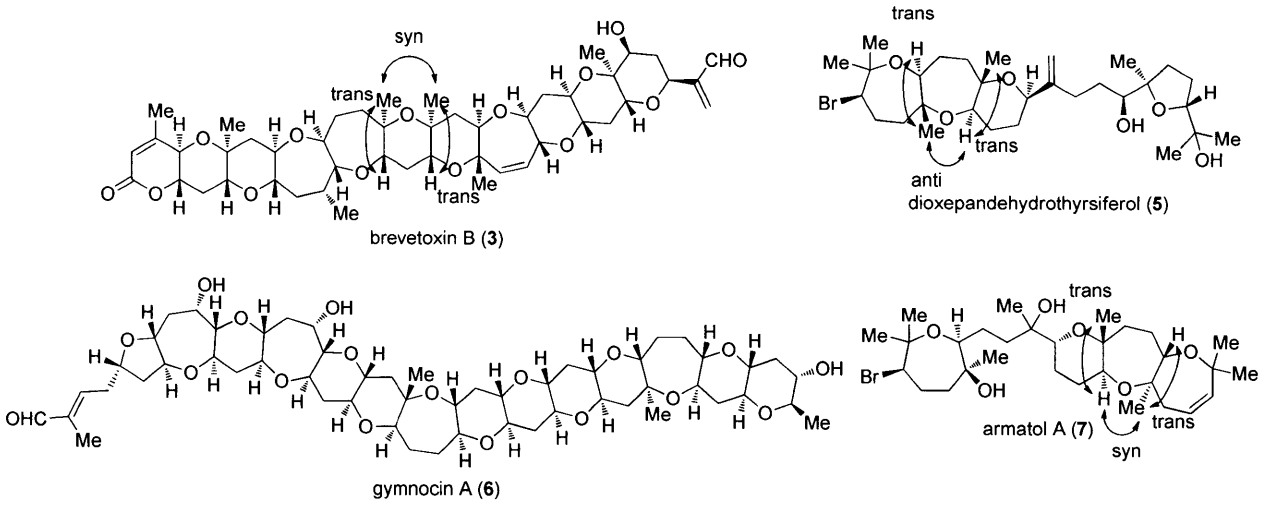
Marine natural products are a diverse set of complex molecules. The ocean provides vast biodiversity with an array of organisms forming structurally distinct and biologically active natural products. Harmful algal blooms, also known as red tide events, occur throughout the world in both temperate and tropical climates and are characterized by their intense colors resulting from a rapid growth of these microbes.[1] Many of the complex molecules produced by those microbes are known for their potent toxicity toward other organisms. Ingestion of large quantities of the harmful algae by shellfish and fish results in an accumulation of the toxic chemicals in higher organisms and can cause severe poisoning upon human consumption. Four distinct classes of shellfish poisonings result from the consumption of structurally unique marine toxins: paralytic shellfish poisoning (PSP) is caused by saxitoxin (**1**, Figure 1-1), diarrheal shellfish poisoning (DSP) results from high molecular weight polyethers including okadaic acid (**2**) and yessotoxin, neurotoxic shellfish poisoning (NSP) is associated with the brevetoxins including brevetoxin B (**3**), and amnesic shellfish poisoning (ASP) comes from the unusual amino acid, domoic acid (**4**).

Figure 1-1. Marine toxins responsible for shellfish poisoning



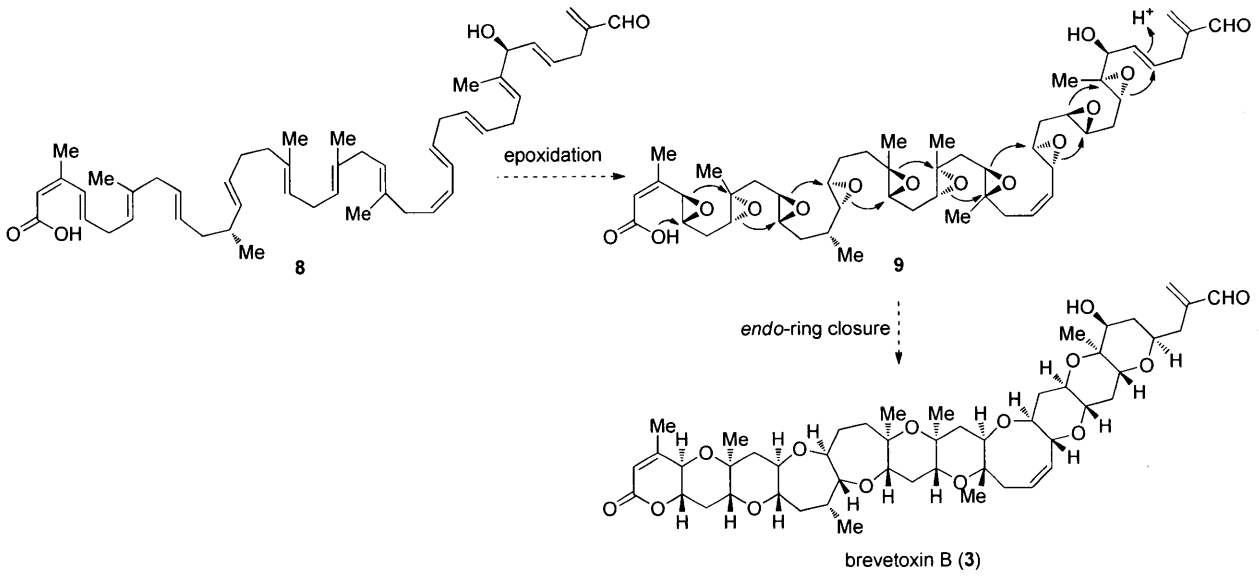
The biological activity of some of these marine polyethers derives from their effects on sodium and potassium ion channels.[2] Although hundreds of polyethers exist, the unique scaffolds can be divided into three categories: polyether ionophores,[3] ladder polyethers,[4] and squalene-derived polyethers.[5] The Jamison group has focused on the synthesis of ladder polyethers (e.g., **3** and **6**, Figure 1-2) and squalene-derived polyethers (e.g., **5** and **7**) to examine the scope and utility of epoxide-opening cascades that have been developed in our laboratory.

Figure 1-2. Representative ladder and squalene-derived polyethers



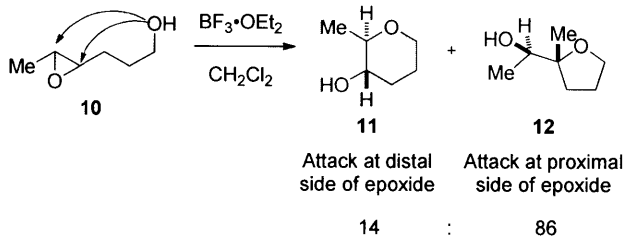
One of the unique structural features of marine polyethers is the relative configurations at the ring junctions, appearing as *trans-syn-trans* in almost all cases in the ladder polyethers and as a mixture of other configurations, with *trans-anti-trans*, for example, found in the squalene-derived polyethers. These scaffolds present an interesting structural challenge for chemical synthesis. The earliest report in the general scientific literature for a biosynthetic model that accounts for the *trans-syn-trans* configurations found in the ladder polyethers was by Nakanishi in 1985.[6] However, Nakanishi in turn acknowledges Robert Thomas as the inspiration for his model.[7] Furthermore, around the same time, Shimizu[8] and Nicolaou[9] conceived of similar biosyntheses. All of these authors hypothesized that the distinctive *trans-syn-trans* stereochemistry could be derived from a series of *endo*-selective epoxide-opening cyclizations (Scheme 1-1).

Scheme 1-1. Nakanishi's biosynthetic proposal for ladder polyethers



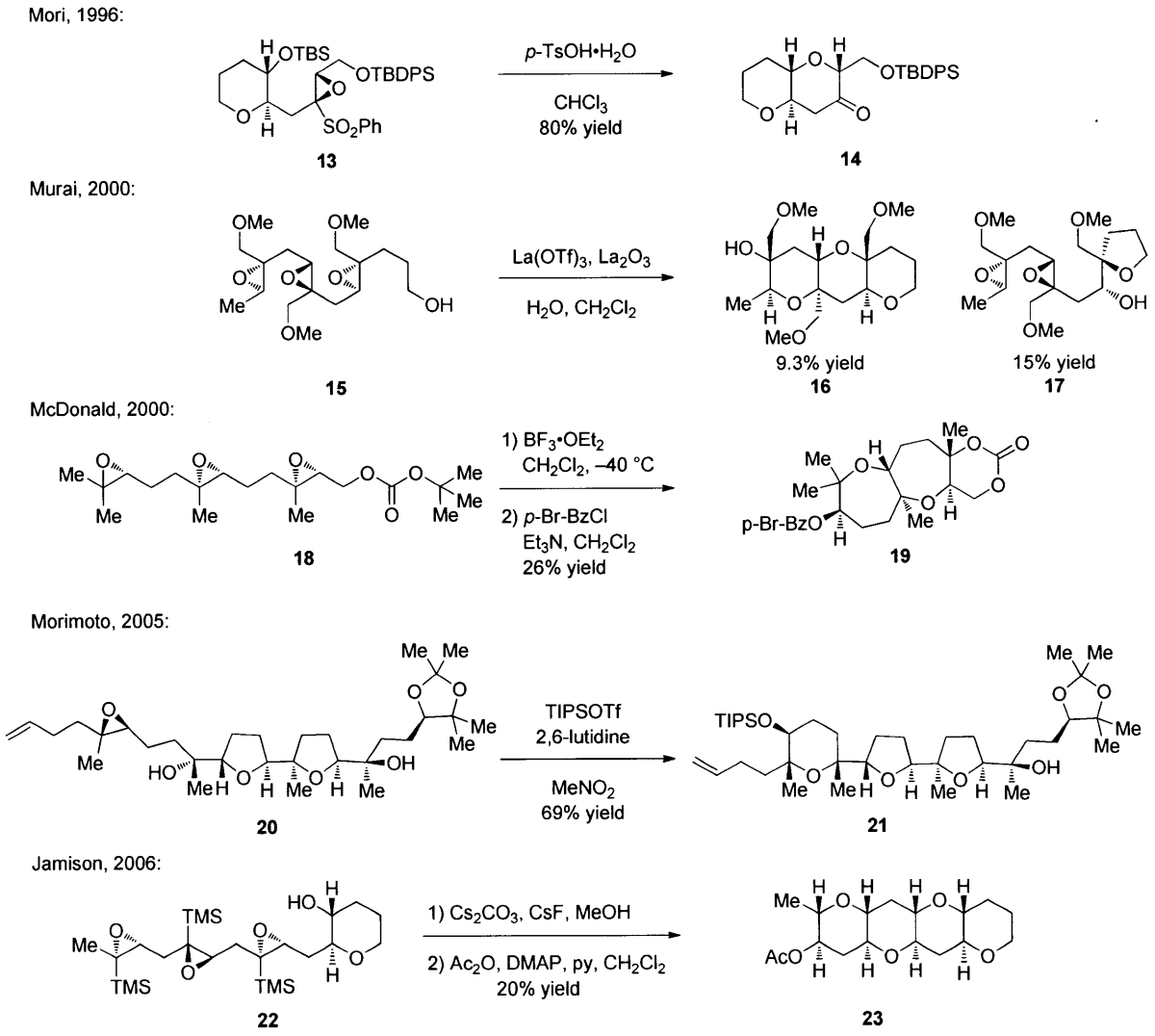
Research in the Jamison group has focused on methods for epoxide-opening cascade reactions to form ladder polyether structures similar to those found in marine environments.[10] The intrinsic bias of epoxide-opening of the simple epoxy alcohol **10**, as demonstrated by Coxon (Scheme 1-2),[11] tends towards nucleophilic substitution at the proximal site of the epoxide by the alcohol, resulting in *exo*-opening to favor formation of the THF **12**. While the terms *exo* and *endo* originate from Baldwin's rules[12] for cyclizations, they do not apply directly to epoxide opening since the bond breaking occurs outside the ring in both cases. Baldwin does discuss opening three-membered rings in a general context based on epoxynitrile cyclizations and concludes that the geometry of three-membered rings seems to lie between tetrahedral and trigonal and that their cyclizations generally prefer the *exo* mode.[13] These terms, nevertheless, are commonly used, convenient, and well known identifiers of the two cyclization products, the larger (*endo*, e.g., **11**) and smaller (*exo*, e.g., **12**) rings.

Scheme 1-2



Many groups have investigated approaches towards overcoming this selectivity trend by using directing groups to promote *endo*-selective ring opening; examples are shown in Scheme 1-3.[14] These directing groups modulate the reactivity of an epoxide by either activation of the distal site of an epoxide or deactivating the proximal site. Mori relies on an electron-withdrawing sulfone to deactivate addition to the proximal site and favor tetrahydropyran (THP) formation,[15] while Murai proposes that chelation of a Lewis acid by the epoxide and a methoxymethyl group favors the desired product.[16] McDonald has employed Lewis acids to promote opening of trisubstituted epoxides in cascades that provide a trans-fused bisoxepane motif. In this approach the methyl groups attached to the epoxide serve as the directing groups.[17] Jamison and co-workers used a silyl group to stabilize positive charge on the distal side of the epoxide leading to 6-*endo* epoxide-opening.[10d] They extended this methodology to a cascade with the silyl group acting as a disappearing directing group due to protiodesilylation during the reaction. Morimoto has used the steric bulk of triisopropylsilyl triflate to activate a trisubstituted epoxide towards *endo* attack by a tertiary alcohol nucleophile in his synthesis of aurilol.[18]

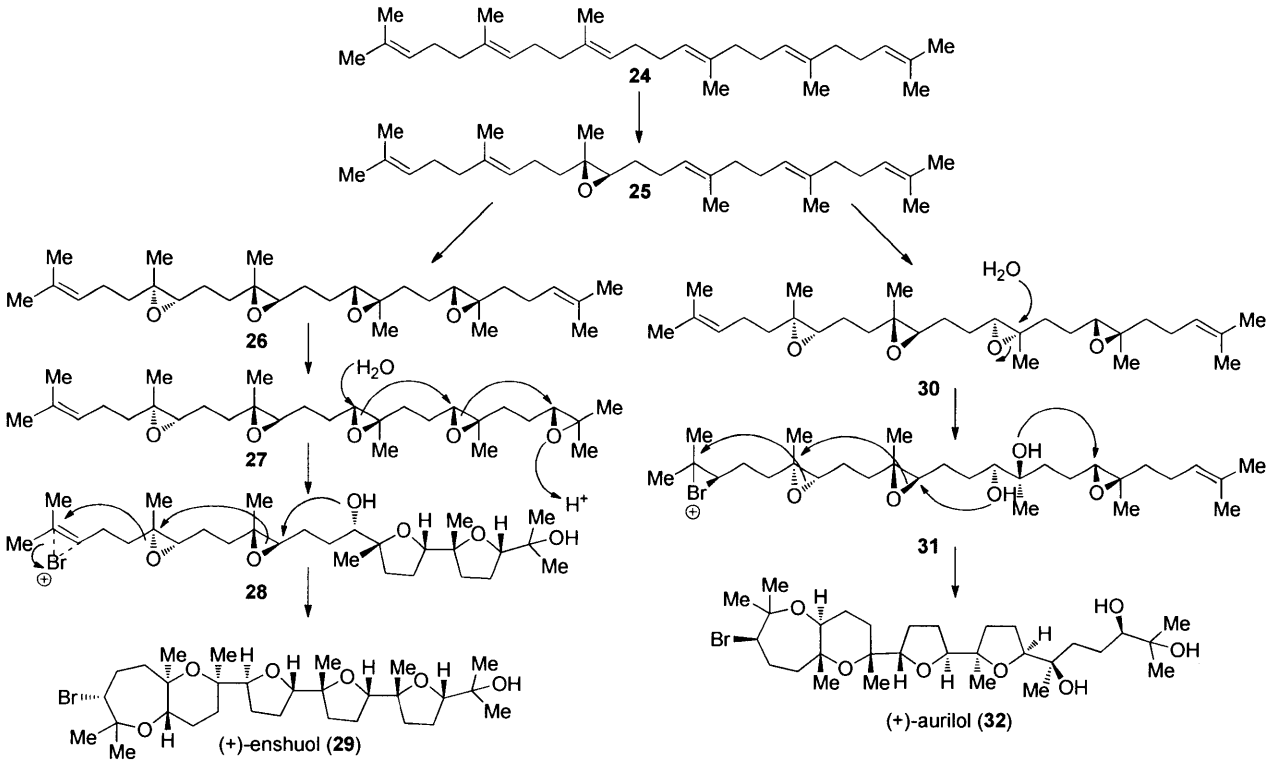
Scheme 1-3. Use of directing groups to bias epoxide-openings



Terpenoid polyethers, also known as oxasqualenoids (e.g., **5** and **7**, Figure 1-2) are derived from squalene and contain methyl groups at each ring junction. The isolation of a monoepoxide, (10*R*,11*R*)-squalene 10,11-epoxide (**25**), from the *Laurencia* family of marine algae led to a series of proposals for the biosynthesis of a large class of natural products.[5,19] For example, Suzuki proposed (6*S*,7*S*,10*R*,11*R*,14*R*,15*R*,18*S*,19*S*)-squalene tetraepoxide as a common intermediate towards enshuol (**29**) in which methyl groups direct the regioselectivity of epoxide cyclizations.[20] Morimoto's total synthesis of this molecule led to the structural

reassignment of (+)-enshuol (**29**).[18,21] The revised structure of enshuol suggests that tetraepoxide **26** might be a biosynthetic intermediate for enshuol (**29**), instead of (6*S*,7*S*,10*R*,11*R*,14*R*,15*R*,18*S*,19*S*)-squalene tetraepoxide that had previously been invoked as a common intermediate in *Laurencia* triterpenoids (Scheme 1-4). A different tetraepoxide (**30**) may also be invoked to account for a biosynthetic pathway to aurilol (**32**).

Scheme 1-4. Proposed biosynthetic hypothesis for enshuol and aurilol (Suzuki, 1995)

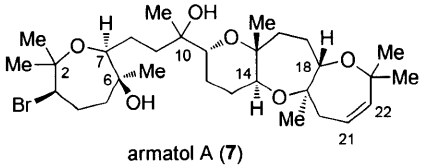


As the methyl groups present in squalene were used by Morimoto to direct single epoxide-opening events in a stepwise fashion, it appeared feasible to install many of the stereogenic centers in these natural products through a series of epoxidations followed by a methyl group-directed epoxide-opening cyclization.[22]

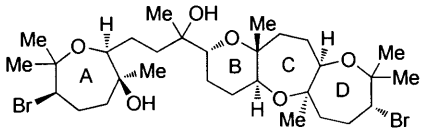
Armatol family of natural products

As an avenue to explore the use of methyl groups to control the regioselectivity of epoxide-opening events, the armatol family (Figure 1-3) presented itself as intriguing targets.[23] All six of the armatol natural products were isolated in 2000 from *Chrondria armata* by Ciavatta and coworkers. Since that time, no total syntheses have been disclosed, with the only reports published being by the Fujiwara group on their progress towards the ABC rings of armatol F (**37**).[24] Of particular interest to the Jamison group was that armatol A is the only natural product in this family that, to our knowledge, contains a 6,7,7-fused system in which one of the 7-membered rings is an oxepene. The other armatol natural products contain a bromine atom at C22, suggesting that armatol A might be an elimination product of armatols B or D, and furthermore, that bromination of armatol A could provide access to two other members of the armatol family.

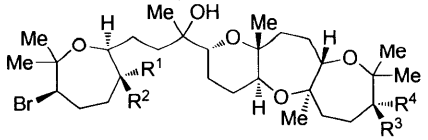
Figure 1-3. Armatol family of marine polyethers isolated by Ciavatta



armatol A (**7**)



armatol F (**37**)

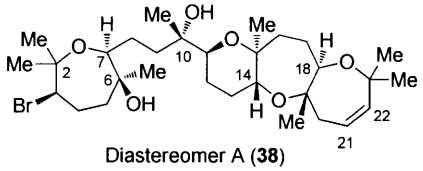


armatol B (**33**): R^1=Me, R^2=OH, R^3=H, R^4=Br
armatol C (**34**): R^1=OH, R^2=Me, R^3=H, R^4=Br
armatol D (**35**): R^1=Me, R^2=OH, R^3=Br, R^4=H
armatol E (**36**): R^1=OH, R^2=Me, R^3=Br, R^4=H

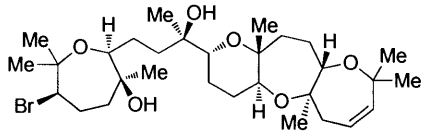
Despite extensive spectroscopic analysis, the absolute structure of any of the members of the armatol family has yet to be fully elucidated. While NOESY and HMBC techniques allowed assignment of the relative configuration of the tricycle, the stereochemical relationship between

this tricycle and the tertiary alcohol at C10 allows for four possible diastereomers of the natural product (**38-41**, Figure 1-4). Although the relative and absolute configuration of the natural product is not known, the absolute configuration of the bromooxepane has been confirmed by Mosher ester analysis of the resultant C7 secondary alcohol formed after treatment with zinc and ammonium chloride.[25] Based on the structural similarities within the family, it stands to reason that once the absolute structure of one member of the family has been resolved, the absolute structures of the remaining five armatol products could be proposed with some confidence.

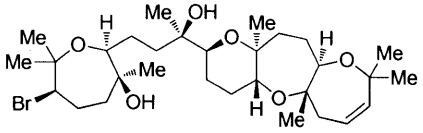
Figure 1-4. Four possible diastereomers for armatol A



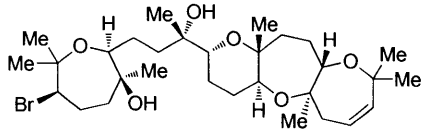
Diastereomer A (**38**)



Diastereomer C (**40**)



Diastereomer B (**39**)



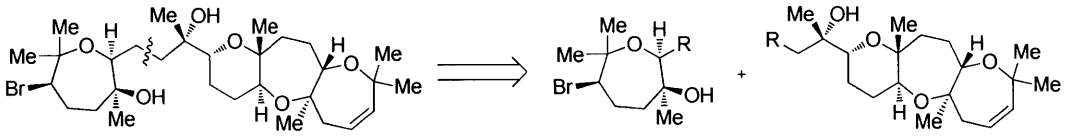
Diastereomer D (**41**)

Retrosynthetic analysis of armatol A

Ciavatta and co-workers put forth a biosynthetic hypothesis that all of the armatol natural products could arise from the common precursor to the *Laurencia* family (6*S*,7*S*,10*R*,11*R*,14*R*,15*R*,18*S*,19*S*)-squalene tetraepoxide. However, they note that due to the stereochemical inconsistencies at C6, C18, and C22, the biosynthesis of the armatol natural products may proceed in a stepwise manner. Without a confirmed biosynthetic proposal and in order to determine the absolute and relative configuration of armatol A, we devised a convergent

synthesis, as shown in Scheme 1-5. This chapter will focus on the challenges in forming the fused tricycle of armatol A (**43**), while Chapter 2 will discuss the bromooxepane (**42**) synthesis and the coupling strategies explored to prepare the four possible diastereomers of armatol A. Our detailed analysis and assignment of the absolute configuration of the natural product will also be presented.

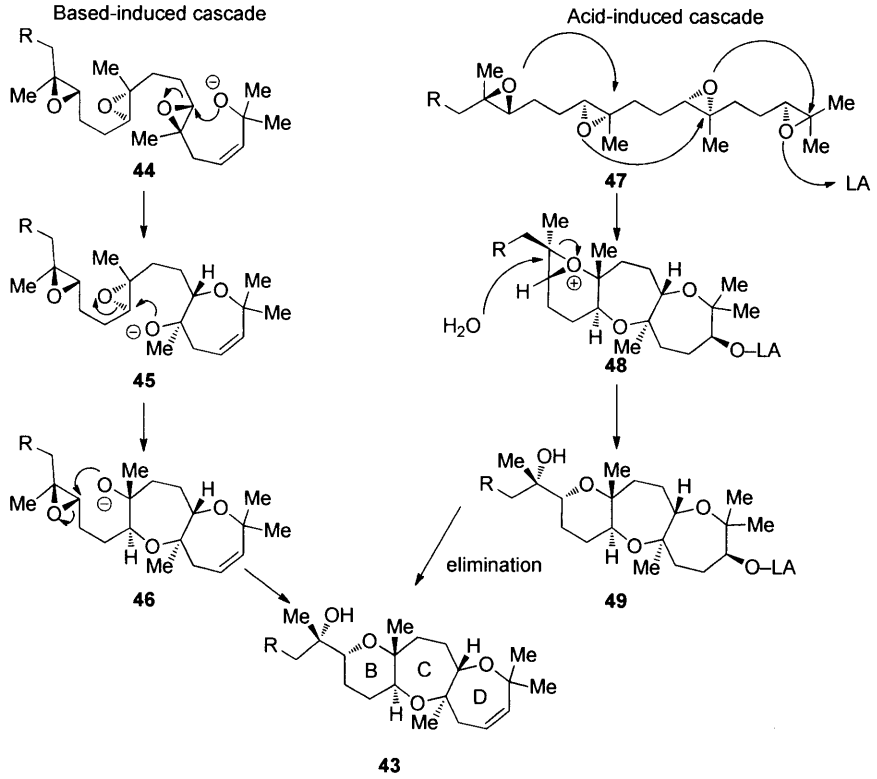
Scheme 1-5. Retrosynthetic analysis of diastereomer D of armatol A



41 Bromooxepane (**42**) Fused tricycle (**43**)

We envisioned two possible synthetic precursors that would lead to the relative stereochemistry found in the fused tricycle of armatol A (Scheme 1-6). A base-induced pathway could be used with a tertiary allylic alcohol as the initiating nucleophile leading to a 7-*endo* cyclization onto a trisubstituted epoxide. This strategy would allow the exploration of the use of steric interactions to control regioselectivity in Brønsted base-induced epoxide-openings.[14,26] The sterically demanding resulting tertiary alcohol (**45**) could favor the same *endo* selectivity in opening of the second epoxide, i.e., at the less substituted carbon of the epoxide, to provide the C and D rings of armatol A (**46**). The third tertiary alcohol, again guided by steric interactions, could react in a 6-*exo* manner to form the THP ring and the tertiary alcohol at C10. This proposed synthetic route would lead to the same stereochemical configuration as diastereomer D (**41**) and was the first stereoisomer we investigated. While the use of THP rings as templates for *endo*-selective opening of epoxides has been extensively explored by our group,[10] the use of oxepanes or oxepenes as templates for forming additional oxepane rings has not.[27]

Scheme 1-6. Possible mechanisms to form the 6,7,7-tricycle of armatol A



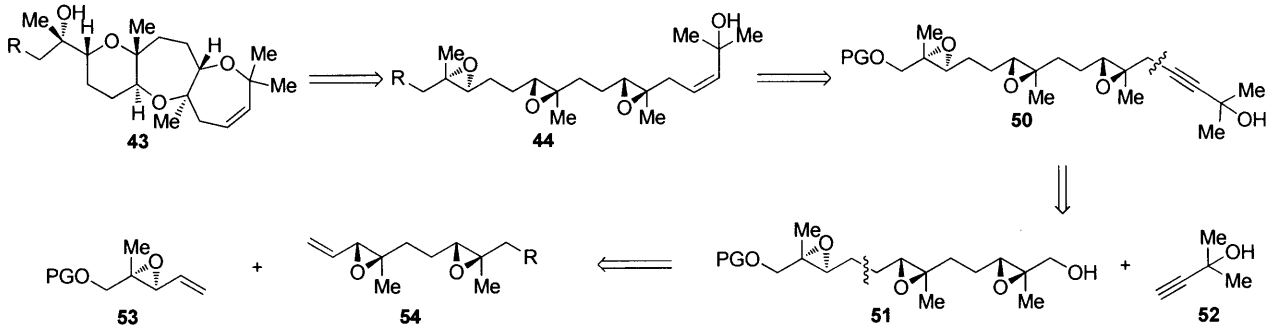
A Lewis-acid initiated cascade[17] could also be employed on tetraepoxide **47** with the methyl groups directing epoxide-opening to the more substituted position (Scheme 1-6). Consecutive *endo*-opening of the first three epoxides followed by trapping with water could lead to a secondary alcohol such as **49**. Further synthetic manipulations would then form the oxepene in armatol A.

Synthetic studies towards armatol A

Prior to attempting the proposed base-initiated cascade, a synthesis of the triepoxide **44** was needed. The cis alkene of triepoxide **44** could be formed by partial hydrogenation of alkyne

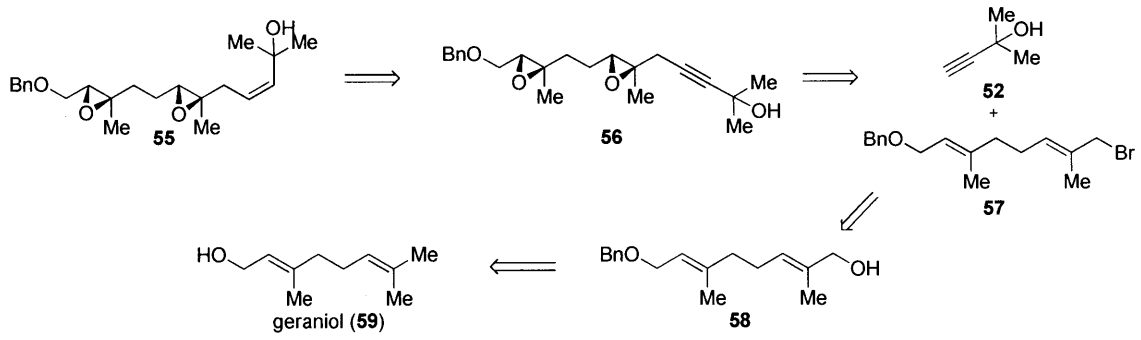
50, which itself could be derived from fragments **51** and **52** (Scheme 1-7).[28] A cross-metathesis between vinyl epoxide **53** and geraniol-derived fragment **54** would provide triepoxide **51**.[29]

Scheme 1-7. Retrosynthetic analysis of the tricycle fragment



Based on the assumption that the final ring may be formed by an *exo*-cyclization, we designed a simpler model system (**55**) to investigate the regioselectivity of the first two epoxide-opening steps (Scheme 1-8). A copper-mediated coupling of allylic bromide **57** and alkyne **52**,[30] followed by epoxide installation would lead to diepoxide **56**. Fragment **57** could be assembled from geraniol (**59**) via allylic alcohol **58**.

Scheme 1-8. Diepoxide model system **55**



The preparation of **55** began with protection of the hydroxyl group of geraniol followed by a chemoselective SeO_2–catalyzed oxidation to afford allylic alcohol **58** (Scheme 1-9).[31]

Conversion of alcohol **58** to the allylic bromide with phosphorous tribromide, followed by a copper-mediated coupling with alkyne **52**, provided the skipped diene-yne **61** in 60% yield as a mixture of the S_N2 and the S_N2' displacement products.[32] Shi epoxidation[33] of the diene provided diepoxide **56**,[†] which was then reduced with hydrogen in the presence of Lindlar's catalyst[34] to provide model system **55**.

Scheme 1-9. Synthesis of model system **55**

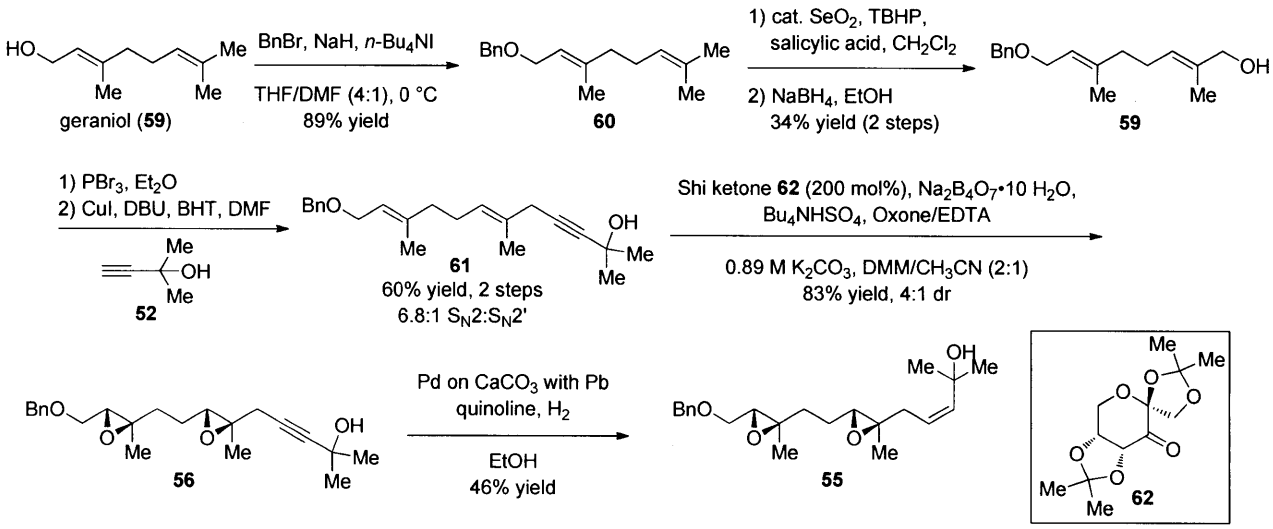
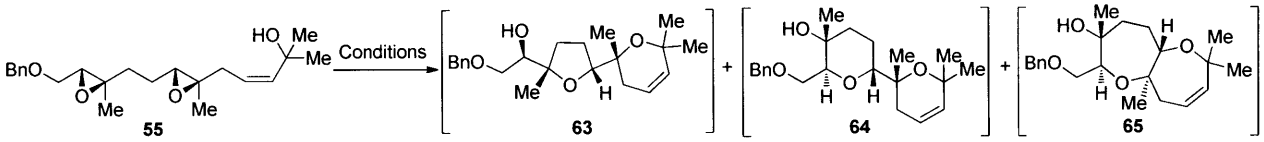


Table 1-1 depicts a summary of the conditions attempted to achieve the *endo*-selective opening of both epoxide rings. Unfortunately, in all cases where reactivity was observed, a mixture of the 6,5-*exo*,*exo* product (**63**) and the 6,6-*exo*,*endo* product (**64**) was obtained, with the first ring consistently opening with undesired *exo*-selectivity. The modest *endo*-selectivity (~2:1) observed in the second ring, slightly favoring the THP ring over the THF, may support the proposed steric basis of regioselectivity in base-mediated cyclizations. In many cases, complex

[†]Diastereomeric ratio for all Shi epoxidations were determined by ^{1}H-NMR analysis. The given ratio is the amount of the major diastereomer relative to the sum of all other diastereomers that were detected in the reaction. The yields for all Shi epoxidations represent the sum of all epoxide diastereomers.

product mixtures were generated that were difficult to analyze by proton NMR. In light of this challenge, the analysis of a simpler monoepoxide model system was undertaken.

Table 1-1. Cyclization Screen of **55**



Entry	Base	Equiv	Solvent	Temperature	Time	Conversion	**63**:**64**	Comments
1	Cs_2CO_3	5	H_2O (0.1 M)	55 °C	16 h	<5%	n.d.	-
2	Li_2CO_3	5	H_2O (0.1 M)	55 °C	14 d	<5%	n.d.	-
3	K_2CO_3	5	MeOH (0.1 M)	60 °C	16 h	100%	n.d.	-
4	Rb_2CO_3	5	MeOH (0.1 M)	60 °C	16 h	100%	1:3.1	-
5	Cs_2CO_3	30	MeOH (0.06 M)	60 °C	16 h	100%	1:2.1	-
6	Cs_2CO_3	5	MeCN (0.1 M)	60 °C	16 h	100%	n.d.	-
7	K_3PO_4	5	MeOH (0.1 M)	60 °C	16 h	100%	1:1.8	-
8	NaOH	138	MeOH (0.1 M)	60 °C	3 d	100%	1:2.8	-
9	*t*-BuOK	7	THF (0.1 M)	rt	16 h	100%	n.d.	Decomposition
10	DBU	5	THF (0.1 M)	rt to reflux	16 h	0%	n.d.	-
11	KCH_2SOCH_3	5	THF (0.1 M)	rt	16 h	100%	n.d.	Decomposition
12	$NaCH_2SOCH_3$	5	THF (0.1 M)	rt	16 h	100%	n.d.	Decomposition
13	$LiCH_2SOCH_3$	5	THF (0.1 M)	rt	16 h	0%	n.d.	-
14	$BF_3{\cdot}OEt_2$	1	CH_2Cl_2 (0.03 M)	0 °C	30 min	100%	n.d.	-
15	$BF_3{\cdot}OEt_2$	1	CH_2Cl_2 (0.03 M)	–78 °C	30 min	n.d.	n.d.	Some SM remained (**55**)

A phenyl group was incorporated in monoepoxide **69** was chosen to provide an UV-active chromophore and to minimize the volatility of synthetic intermediates. The desired allylic alcohol **69** was synthesized starting with a Wittig homologation of hydrocinnamaldehyde (**66**) and phosphorane **67**, followed by reduction using lithium aluminum hydride to provide allylic alcohol **65** in good yield (Scheme 1-10). Treatment of this alcohol with phosphorous tribromide led to the corresponding allylic bromide, which was then coupled with 2-methyl-3-butyn-2-ol

(**52**) in the presence of copper iodide to provide the propargylic alcohol. Shi epoxidation followed by Lindlar reduction provided the desired cis-alkene **69**.

Scheme 1-10. Synthesis of monoepoxide model system **69**

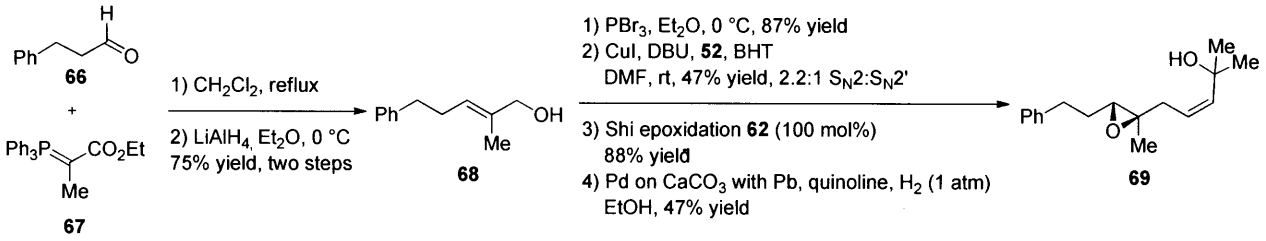


Table 1-2 summarizes the conditions used in an attempt to select for *endo*-opening of the epoxide. Both basic conditions, which did not prove fruitful, and Lewis acids were screened. A possible mechanism for a Lewis acid-mediated pathway is shown in Scheme 1-11 and involves ionization of the tertiary allylic alcohol with subsequent epoxide attack on the allylic cation to form intermediate epoxonium ion **72**. The epoxonium ring could then undergo ring-opening with water upon quenching.

Scheme 1-11. Possible mechanism for oxepene formation via an allylic carbocation

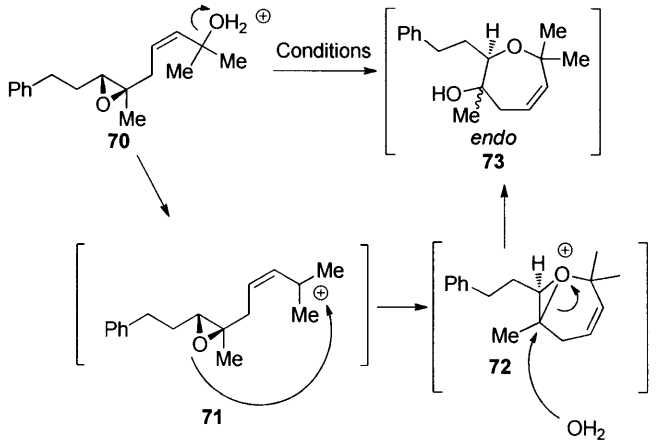
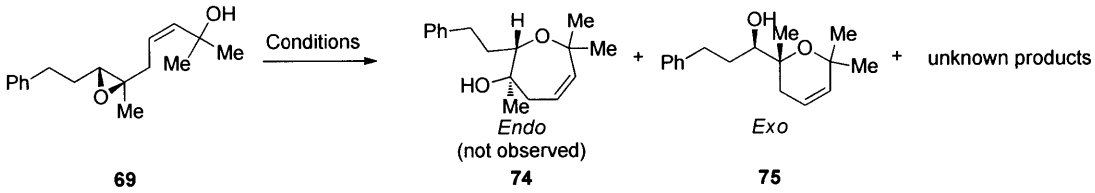


Table 1-2. Cyclization screens on monoepoxide **69**



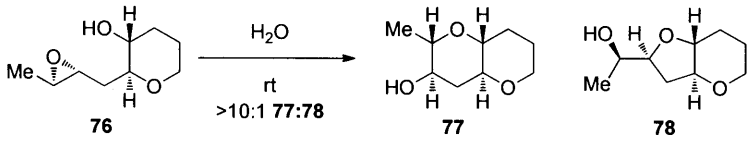
69 **74** **75**

Entry	Conditions	Temperature	Time	Ratio of **75:69**[a]	Byproducts?
1	Cs_2CO_3, MeOH	60 °C	16 h	>20:1	N
2	Cs_2CO_3, H_2O	rt	16 h	<1:10	N
3	H_2O	rt	9 d	<1:10	N
4	CH_2Cl_2	rt	9 d	>20:1	N
5	BF_3•OEt_2, CH_2Cl_2	–78 °C	15 min	>20:1	N
6	BF_3•OEt_2, CH_2Cl_2	–40 °C	15 min	>20:1	N
7	BF_3•OEt_2, CH_2Cl_2	0 °C	15 min	-	Y
8	BF_3•OEt_2, CH_2Cl_2	rt	15 min	-	Y
9	$Yb(OTf)_3$, CH_2Cl_2	rt	15 min	>20:1	N
10	$Gd(OTf)_3$, CH_2Cl_2	rt	15 min	>20:1	N
11	PBr_3, Et_2O	0 °C	30 min		Y
12	$MgBr_2$•OEt_2	0 °C	30 min	1.5:1	Y
13	$TiCl_4$, CH_2Cl_2	rt	16 h	-	Y
14	$SnCl_4$, CH_2Cl_2	rt	16 h	-	Y
15	$SbCl_5$, CH_2Cl_2	rt	16 h	-	Y
16	$Ti(O\textit{i}\text{-}Pr)_4$, CH_2Cl_2	rt	16 h	1.5:1	N

a) Conversion determined by ^{1}H NMR analysis

Concurrent with the investigations into acid- and base-mediated cyclization reactions of **69** other members of the Jamison discovered that aqueous conditions gave high selectivity for *endo*-selective epoxide openings to form THP rings when using an alcohol nucleophile on a THP template (Scheme 1-12).[10a] In light of this discovery, epoxy alcohol **69** was subjected to a range of phosphate buffers where the pH varied from 2-12. Unfortunately, the desired phenomenon was not observed in this case; none of the oxepane product was observed. As expected, a faster cyclization was observed at lower pH, with the *exo* product formed exclusively.

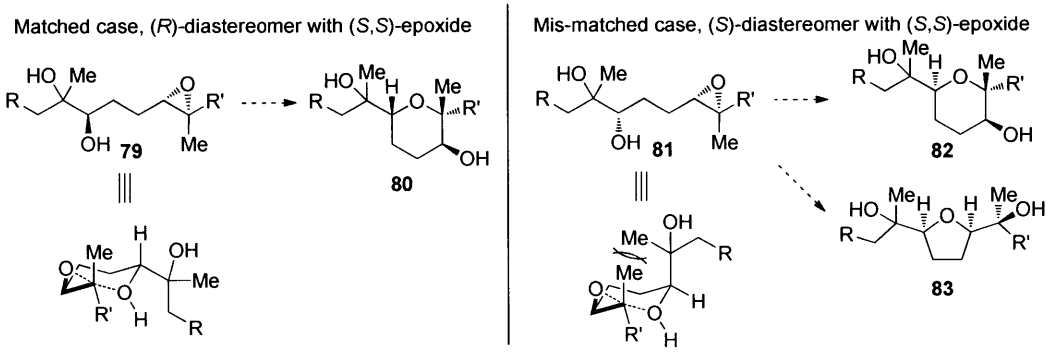
Scheme 1-12. Template effect directing *endo*-opening of an epoxide in an aqueous environment (Vilotijevic, Jamison, 2007)



Lewis acid-mediated approach towards armatol A

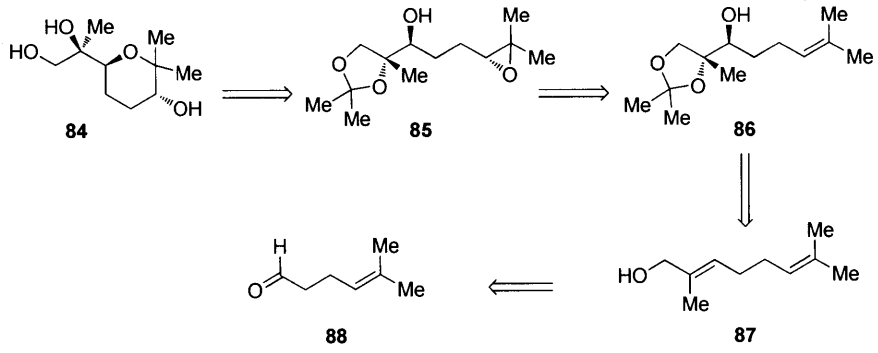
Due to the failure of a Brønsted base-mediated cascade, an alternative strategy was formulated based on the Lewis acid-mediated pathway[17] proposed in Scheme 1-6. Earlier experiments by Dr. Sze-Sze Ng with a monoepoxide and an allylic secondary alcohol nucleophile showed that the yield for the THP ring formation was dependent on the relative configuration of the epoxide and the alcohol nucleophile.[35] In light of this trend, we reasoned that a stereodefined, intramolecular alcohol nucleophile might serve as a trapping nucleophile in an epoxide-opening cascade. Structural analysis of a monoepoxide related to our system is shown in Scheme 1-13. A matched case involving an (*R*)-secondary alcohol nucleophile with an (*S,S*)-epoxide may be predicted to favor a transition state geometry in which the tertiary alcohol side chain lies in a pseudo-equatorial position. This configuration should favor THP formation. In the mismatched case, the tertiary alcohol side chain is expected to reside in a pseudo-axial orientation, generating 1,3-diaxial interactions with the incoming epoxide in the proposed transition state that would lead to the THP product. This mismatched case, therefore, would be expected to lead to the THF product **83** with high regioselectivity.

Scheme 1-13. Comparison of relative configuration of two epoxy alcohols



A possible model system (**84**) also contains a primary alcohol that may be used as a functional group handle for further elaboration after the cyclization (Scheme 1-14). An acetonide protecting group was selected to prevent these two hydroxyl groups from participating in the cyclization. In order to probe the stereochemistry of the natural product, the tertiary alcohol would have to be installed in a stereoselective manner. Alkene **86** was thus targeted, as it could be obtained from allylic alcohol **87** derived from known aldehyde **88**.[36] Developing a short synthetic route to this proposed epoxide would allow investigation of the feasibility of this cyclization strategy and, if successful, to extend it to a triepoxide system.

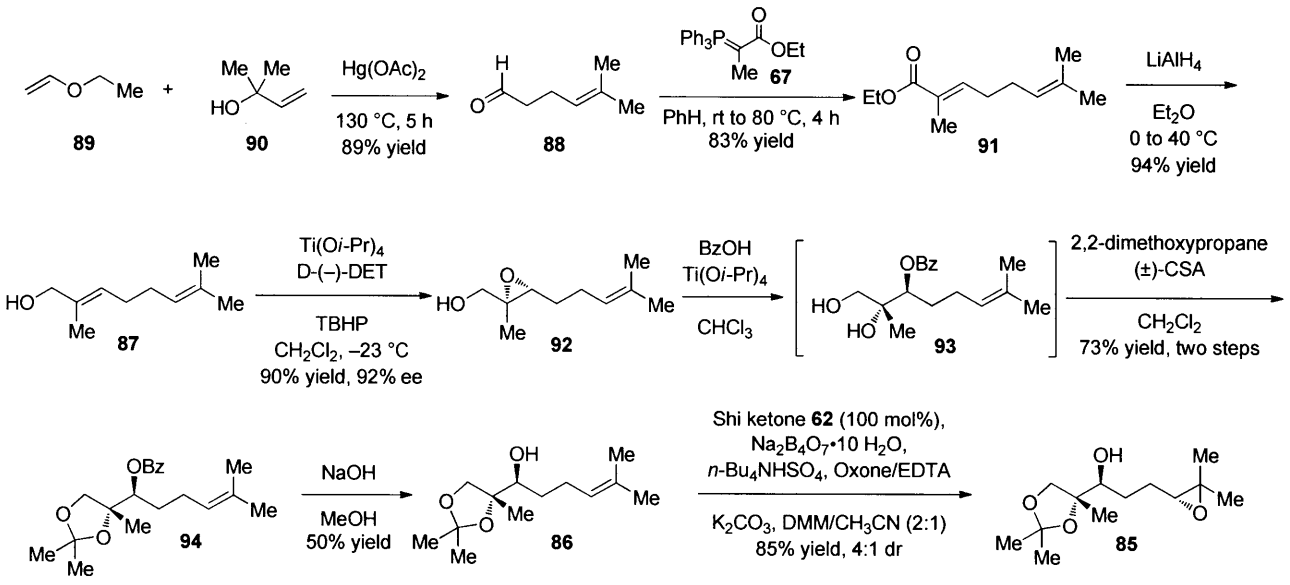
Scheme 1-14. Model THP ring retrosynthetic analysis



The synthesis of epoxy alcohol **85** commenced with a Claisen rearrangement between ethyl vinyl ether (**89**) and 2-methyl-3-buten-2-ol (**90**), to provide the aldehyde **88** in 89% yield

(Scheme 1-15).[36] A Horner–Wadsworth–Emmons reaction with (carbethoxyethylidene)-triphenylphosphorane (**67**) cleanly provided the *E*-olefin. Reduction to the allylic alcohol set the stage for a Sharpless asymmetric epoxidation.[37] Directed addition of benzoic acid, using a titanium-assisted epoxide opening,[38] provided diol **93**, which was then protected as an acetonide. Deprotection of the benzoate ester proceeded in modest yield to furnish **86**. Shi asymmetric epoxidation provided model system **85** in 85% yield with no cyclization detected under the basic conditions of the Shi epoxidation.[39]

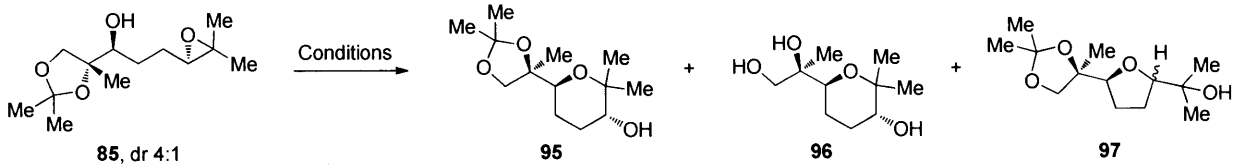
Scheme 1-15. Synthesis of epoxy alcohol **85**



With the model monoepoxide **85** in hand, a variety of cyclization conditions were examined (Table 1-3). As expected, basic conditions favored the *exo* product, while acidic conditions led predominately to the *endo* cyclization product. A pH screen in aqueous 0.1 M phosphate buffers also displayed this trend, with increasing THF formation at higher pH. Upon treatment with BF_3•OEt_2, the major epoxide diastereomer produced the *endo* product **95** and acetonide-cleaved product **96** almost exclusively, while the minor diastereomers led to *exo*

product **97**. This trend is in good agreement with the observations of Dr. Sze-Sze Ng (*vide supra*), discussed earlier in which the 1,3-diaxial interactions in the mismatched diastereomer disfavored *endo* opening, even under treatment with a Lewis acid.[35] The combined yield of *endo* cyclization products (**95** and **96**), with respect to the major diastereomer, was 88%.

Table 1-3. Cyclization of **85** to furnish the desired THP ring **95**



85, dr 4:1 **95** **96** **97**

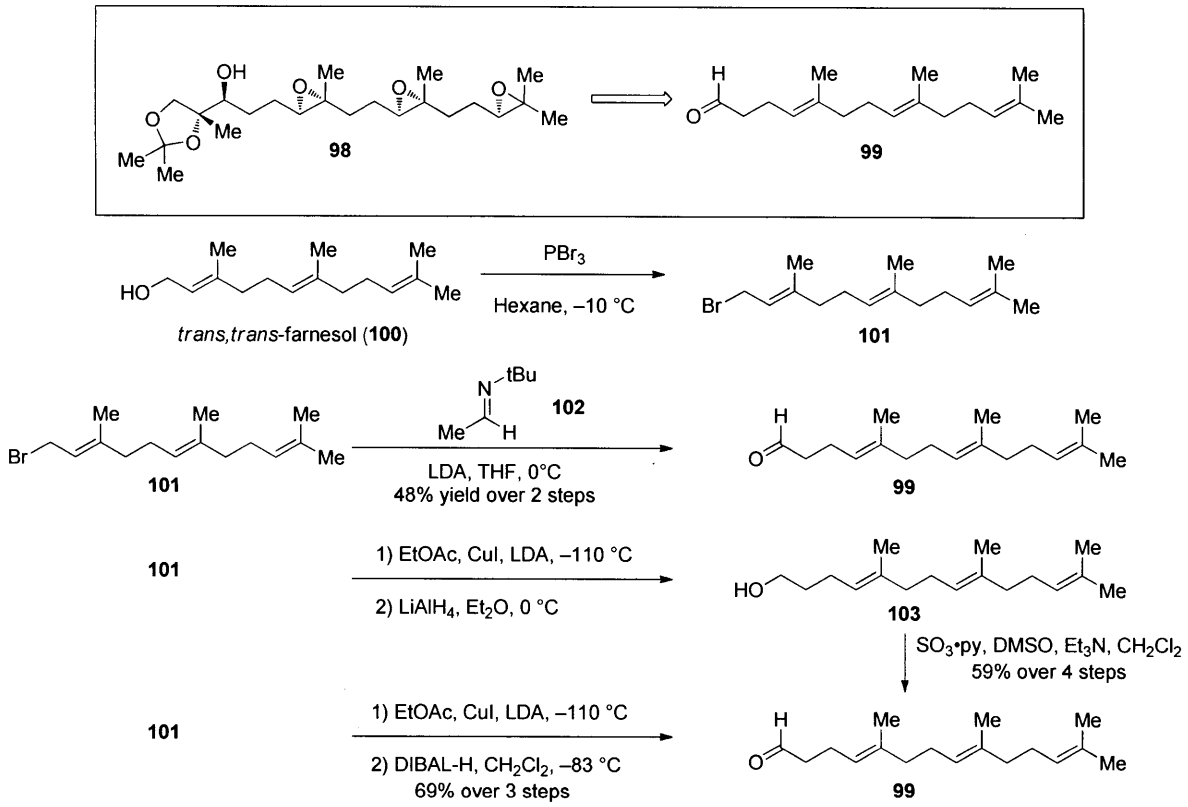
Entry	Condition	Time	Temperature	**95**:**97**[a] (yield)
1	Cs_2CO_3, MeOH	12 h	rt	0:1[b] (95 %)
2	pH 4.0, 0.1 M phosphate buffer	3 d	rt	1.1:1
3	pH 6.0, 0.1 M phosphate buffer	3 d	rt	1:1.4
4	pH 7.0, 0.1 M phosphate buffer	3 d	rt	1:2.8
5	pH 8.0, 0.1 M phosphate buffer	3 d	rt	1:3.5
6	pH 10.0, 0.1 M phosphate buffer	3 d	rt	1:4.1
7	BF_3•OEt_2, CH_2Cl_2	15 min	–78 °C	4.7[c]:1[d] (85%)

a) Ratio determined by ^{1}H NMR analysis b) **97** was isolated as 4:1 mixture of diastereomers c) The major product was a triol resulting from acetonide cleavage in a 6:1 ratio of **96**:**95**. d) **97** was isolated as a 10:1 ratio of diastereomers favoring reaction from the minor diastereomer

In order to test the epoxide-opening cascade on triepoxide **98** (Scheme 1-16), we would be able to use the same series of synthetic operations used in the synthesis from **88** to **85** (Scheme 1-15), provided we could prepare aldehyde **99**. Aldehyde **99** was synthesized from *trans,trans*-farnesol (**100**).[40] Although the aldehyde could in principle be formed in two steps using a metalloenamine derived from **102**, purification of the aldehyde proved difficult. Instead, the copper enolate of ethyl acetate was combined with allylic bromide **101** via an S_N2-type reaction. This operation provided a chromatographically stable intermediate that could be purified prior to reduction with $LiAlH_4$. Subsequent oxidation under Parikh–Doering conditions

gave aldehyde **99** in 59% yield. Alternatively, reduction with DIBAL-H also provided aldehyde **99** in 69% yield in three steps from farnesol.

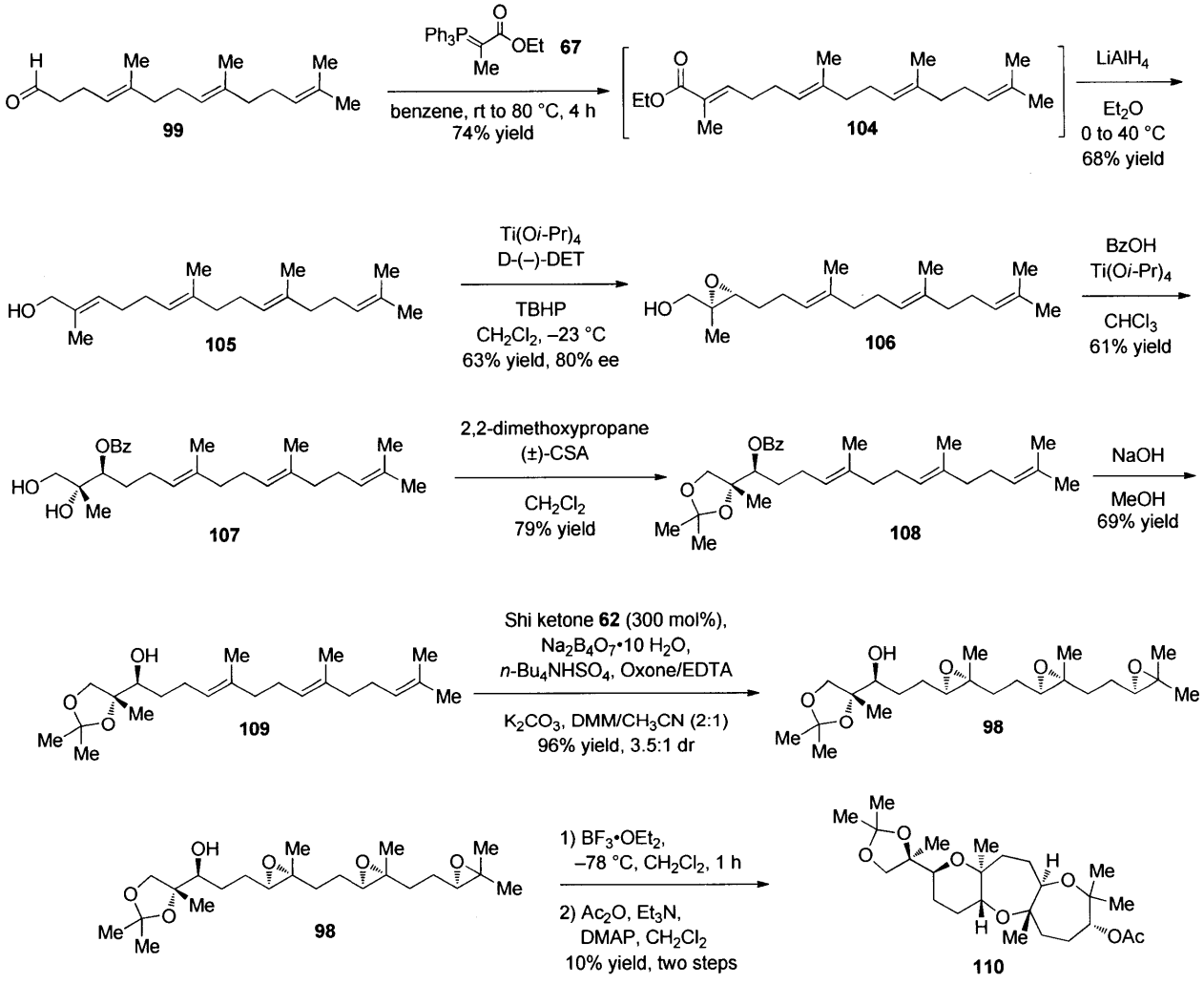
Scheme 1-16. Synthesis of aldehyde **99**



Scheme 1-17 shows a similar seven-step synthesis to that shown in Scheme 1-15 for the monoepoxide **85**, and the Shi epoxidation was the only reaction that required optimization in this series. Increasing the amount of Oxone to 300 mol% led to 96% yield of the desired triepoxide **98** with an overall diastereomeric ratio of 3.5:1. With the goal of preparing the tricyclic fragment in sight, triepoxide **98** was treated with BF_3•OEt_2 in dichloromethane. The desired tricycle was more easily purified as an acetate ester **110** and isolated in 10% yield. One of the reasons for the low yield could be due to the loss of the acetonide. Despite the low yield of tricycle **110**, this experiment demonstrated that the Lewis-acid mediated *endo*-selective

cyclization of a triepoxide was possible, and we therefore explored more robust protecting groups that could survive the cascade conditions. In addition, we desired a route that involved the late stage installation of the tertiary alcohol, as this stereogenic center would require varying in order to synthesize the four possible diastereomers of armatol A.

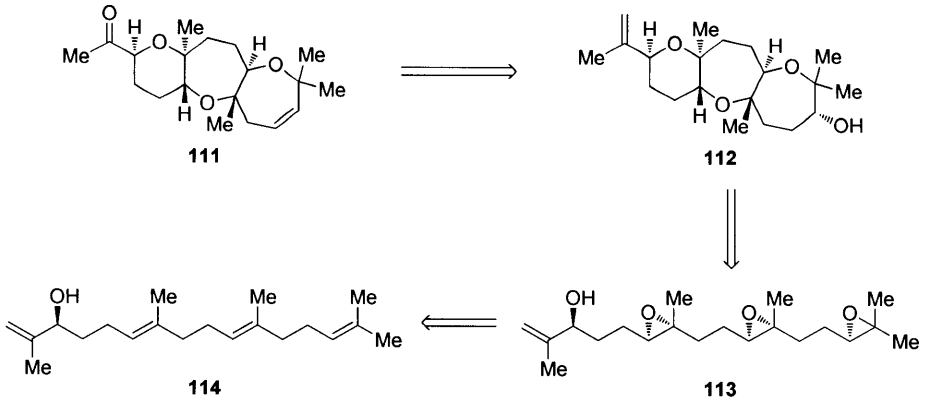
Scheme 1-17. Formation and cyclization of triepoxide **98**



Revised synthetic strategy toward the tricyclic fragment

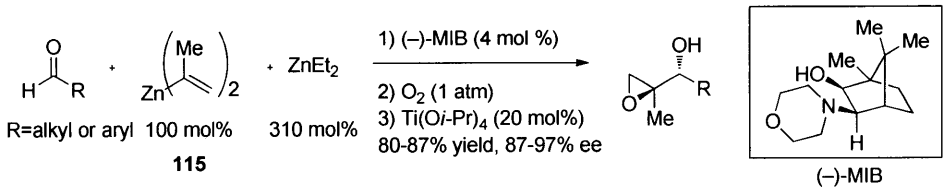
Based on the successful synthesis of **110**, we turned our attention to triepoxide **111** which contains an olefin as a masked carbonyl that could also serve as a functional group handle (Scheme 1-18). After forming the 6,7,7-tricycle, conversion of the isopropenyl group to the ketone **111** could provide a suitable electrophile site for fragment coupling. As the previous cascade precursor **98** did not cyclize before the cascade reaction, a similar secondary alcohol nucleophile was developed. The acetonide was replaced with an isoprenyl group for late-stage functionalization. Shi asymmetric epoxidation of **114** could provide triepoxide **113**, which could then cyclize to afford tricycle **112**.

Scheme 1-18. Revised retrosynthetic analysis



A direct approach to secondary alcohol **114** would involve an asymmetric addition of isopropenyl zinc into aldehyde **99**. A report from Walsh and co-workers on a related system demonstrated the viability of this approach using the chiral ligand (–)-3-*exo*-morpholinoisoborneol (MIB) (Scheme 1-19).[41] Significantly, the use of either (+) or (–)-MIB could provide either **114** or ***ent*-114** on route to both enantiomers of tricycle **111**.

Scheme 1-19. Enantioselective alkenyl zinc addition with *in situ* epoxidation (Walsh, 2004)



The *in situ* epoxidation would also prove useful once the configuration of the tertiary alcohol is determined; the enantioselective isopropenyl zinc addition would be sufficient to provide **114**. Use of (+)-MIB[42] as a catalyst for the enantioselective addition of isopropenyl zinc (**115**)[43] to aldehyde **99** gave allylic alcohol **114** in 84% yield and 79% ee (Scheme 1-20). Initial attempts at Shi epoxidation of allylic alcohol **114** gave substantial over-epoxidation, with tetraepoxide **116** as the major product. Even with fewer than 3 equivalents of Oxone, only 27% of the desired triepoxide **113** could be isolated. Fortunately, a good yield of the desired product was obtained by deactivating the allylic alcohol. Conversion of the alcohol to acetate ester **117** prevented epoxidation at this site, giving triepoxide **118** in 74% yield and 3.5:1 dr[†]. Selective acetate hydrolysis of **118** by LiOH in THF/MeOH/H_2O revealed the allylic alcohol in 69% isolated yield. Other deprotection conditions led to undesired cyclization of the first ring to a THF product, which further suggested that basic conditions should be avoided in the cascade reaction.

Scheme 1-20. Asymmetric synthesis of triepoxide **113**

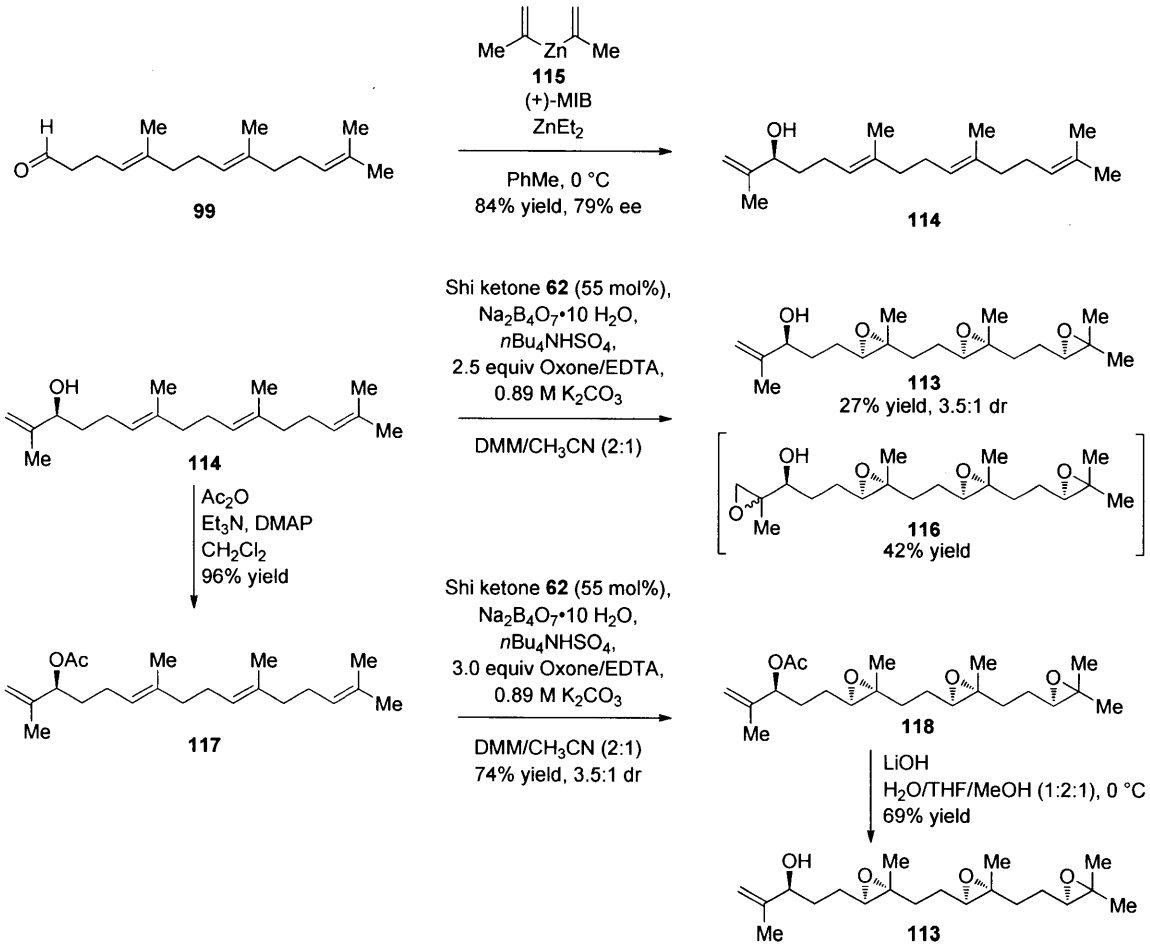
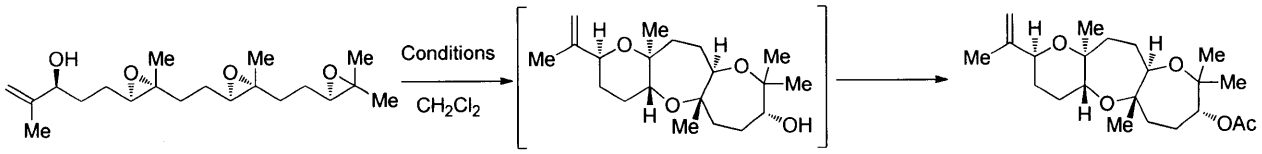


Table 1-4 shows a range of conditions investigated for the cyclization of triepoxide **113** to desired tricycle **112**. Treatment of epoxide of **113** with a Lewis acid, such as BF_3•OEt_2, led to a modest yield of the tricycle (isolated as acetate ester **119**). Using substoichiometric quantities of BF_3•OEt_2 or higher temperatures led to decreased yield. The desired tricycle was the major product of the cascade reaction, with the mass balance accounted for by other cyclization products from diastereomers obtained in the Shi epoxidation and from *exo* opening of the desired diastereomer.[44] Use of camphorsulfonic acid as an activator gave none of the desired product. The use of a bulky silylating reagent, such as TIPSOTf[18] led exclusively to epoxide

decomposition. Ultimately, $BF_3 \cdot OEt_2$ was determined to be the best activating agent for the cascade.

Table 1-4. Cyclization screens of triepoxide **113**



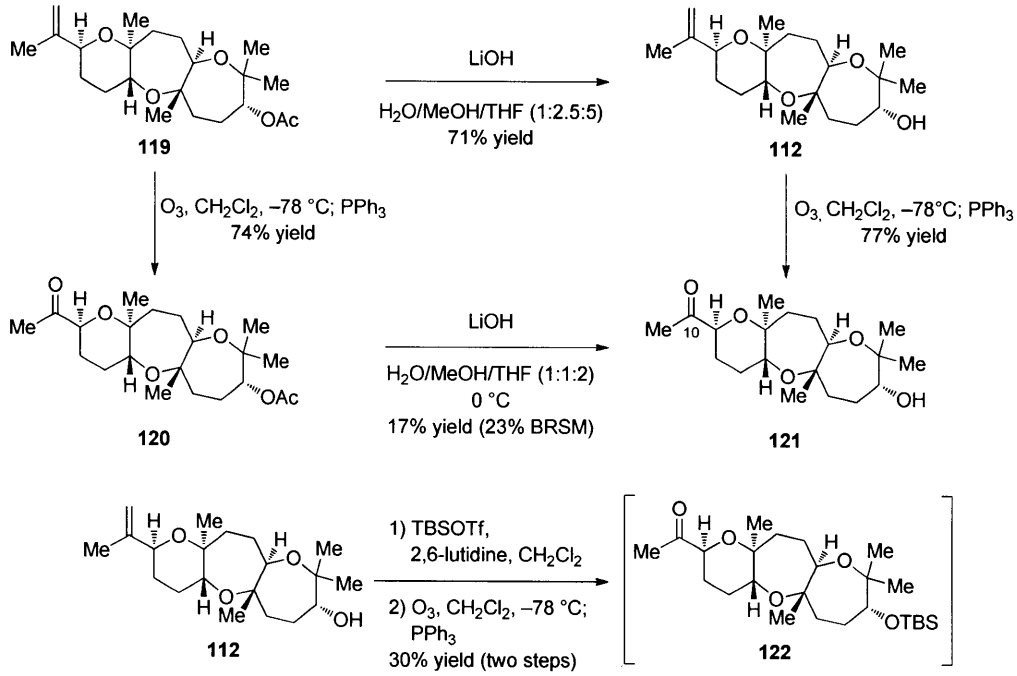
113 **112** **119**

Entry	Conditions	Time	Temperature	Yield
1	$BF_3 \cdot OEt_2$ (1 equiv)	15 min	–78 °C	23% **119**[a]
2	$BF_3 \cdot OEt_2$ (1 equiv)	15 min	–78 °C	15% **119**[b]
3	(±)-CSA (1 equiv)	16 h	0 °C	0%
4	TIPSOTf, 2,6-lutidine	1 h	–78 °C	0%

a) Crude reaction treated with Ac_2O, Et_3N, DMAP to provide acetate
b) Reaction quenched directly with Ac_2O

Subsequent studies were directed towards the elimination of the secondary alcohol and further functionalization of the ispropenyl group, and a variety of approaches were investigated. Formation of the ketone via ozonolysis of **119** proceeded smoothly to give **120** (Scheme 1-21). Removal of the acetate protecting group in **120** proved challenging as the reaction proceeded in just 23% yield (based on recovered starting material). Fortunately, the low yield could be improved by reversing the order of these synthetic operations. Acetate hydrolysis of **119** gave free alcohol **112** in 71% yield and subsequent ozonolysis furnished the desired ketone **121** in 77% yield. To accommodate the use of organometallic reagents in addition to the ketone, the secondary alcohol was protected using TBSOTf and ozonolysis gave **122** in moderate yield. Ketone **122** provided for the first time a coupling partner in which the key C10 quaternary center would be installed after the fragment coupling.

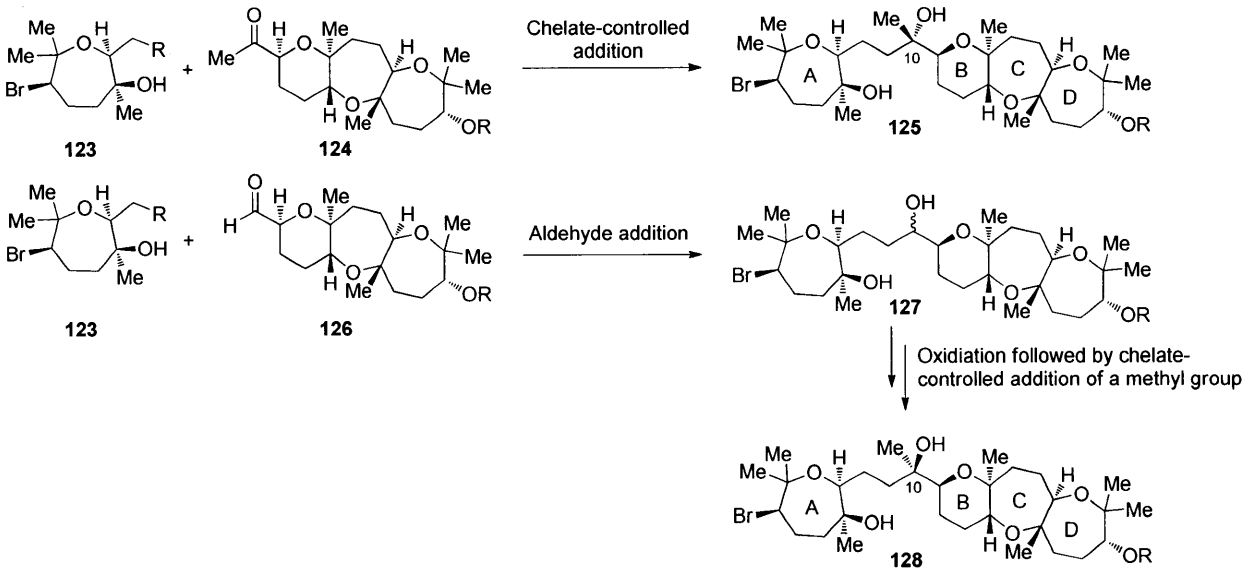
Scheme 1-21. Formation of coupling fragment **122**



Alternative coupling partner to probe absolute configuration of armatol A

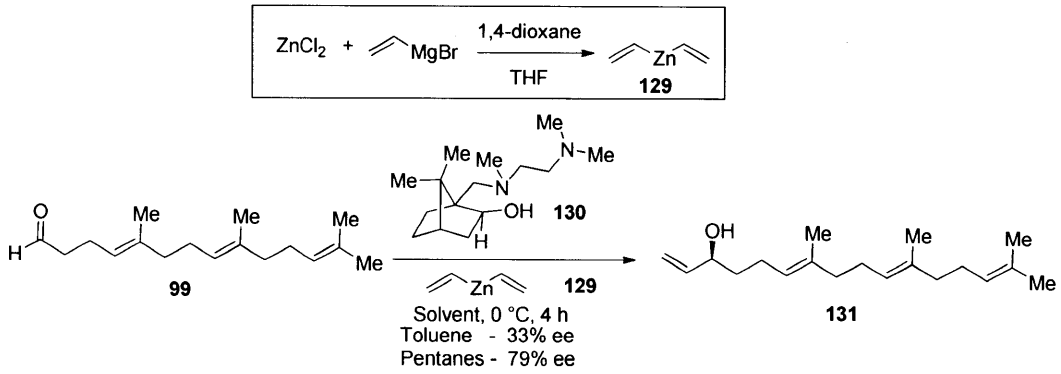
Ketone **122** was selected as a coupling partner because chelation-controlled addition of a suitable nucleophile would likely proceed with high stereoselectivity. In order to prepare the other configuration at this carbon, we pursued an aldehyde coupling partner. Chelate-controlled addition to **124** would lead exclusively to the (*S*)-configuration of the tertiary alcohol **125** (Scheme 1-22). In order to obtain the (*R*)-configuration with high selectivity secondary alcohol **127** would be prepared from aldehyde **126**, and a subsequent oxidation followed by chelation-controlled addition of methylmagnesium bromide would then form **128**.

Scheme 1-22. Chelation control strategies to establish the key C10 stereocenter



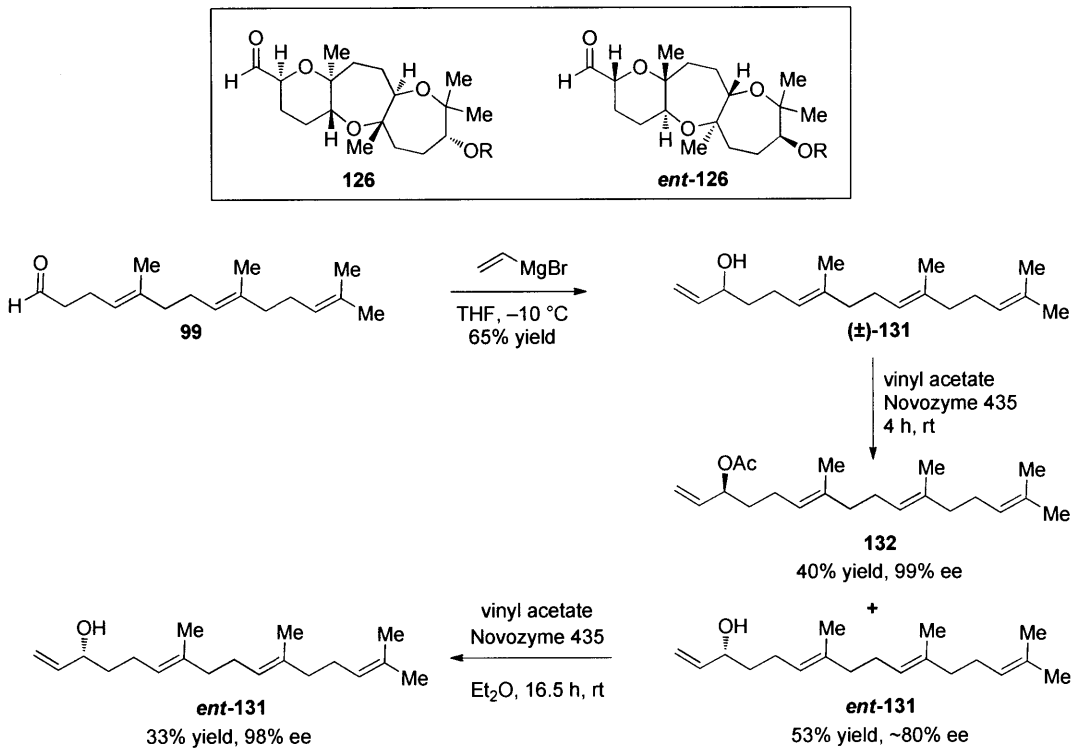
We pursued several variants of the tricycle containing a pendant aldehyde to test various coupling strategies. An added feature of the aldehyde electrophile would be the increased reactivity toward softer transition metals, thus requiring a less robust protecting group on the secondary alcohol. Modification of the synthetic route towards **112** involving an asymmetric vinyl addition into **99** could provide an aldehyde after ozonolysis, rather than a ketone. Based on our synthesis of triepoxide **113** (Scheme 1-20), asymmetric addition of a vinyl zinc to aldehyde **99** would ultimately lead to an aldehyde similar to **126** to test coupling strategies. Oppolzer reported that tridentate ligand ***ent*-130** gave greater than 96% enantioselectivity for the addition of divinyl zinc (**129**) in diethyl ether to 1-hexanal.[45] In this case, using toluene as the solvent and a solution of divinyl zinc in THF, tridentate ligand **130** gave an unacceptable 33% ee (Scheme 1-23).[46] Pentane as solvent provided higher enantioselectivity, but still not to the desired level of enantiocontrol. Before optimizing this enantioselective reaction further, we decided to investigate an enzymatic resolution of a racemic alcohol in order to quickly provide both enantiomers.

Scheme 1-23. Asymmetric addition of divinyl zinc into aldehyde **99**



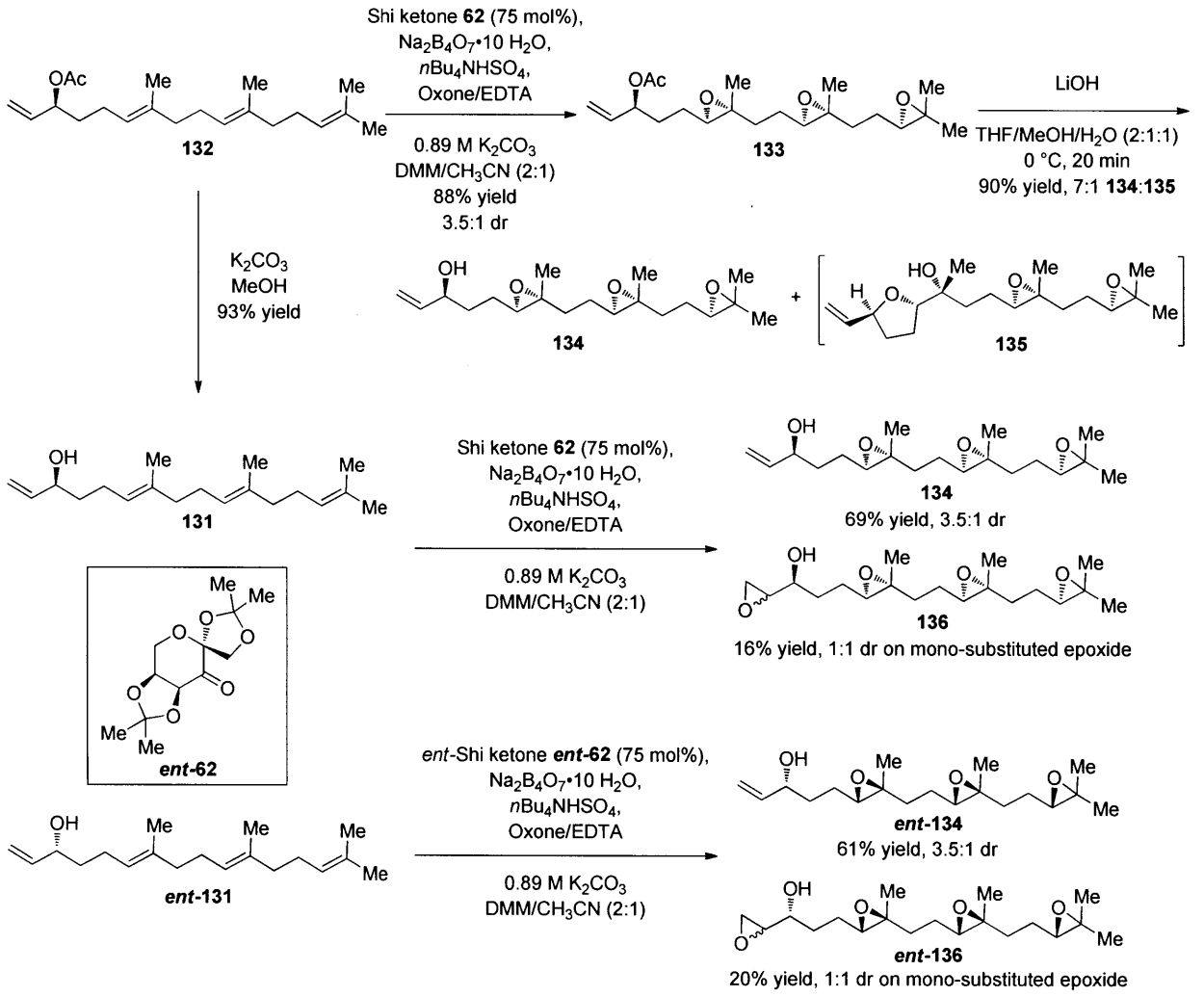
Because secondary allylic alcohols are amenable to enzymatic resolution,[47] both enantiomers of the tricyclic fragment could be prepared in high enantioselectivity (**126** and ***ent*-126**, Scheme 1-24). This strategy would thus provide a straightforward way to fully assign the absolute stereochemistry of armatol A. Enzymatic resolution (Novozyme 435) of racemic alcohol **131** facilitated the isolation of the (*S*)-acetate ester in high enantioselectivity. It was necessary to resubject the less reactive enantiomer (***ent*-131**) to slightly different reaction conditions to improve its optical purity.[48]

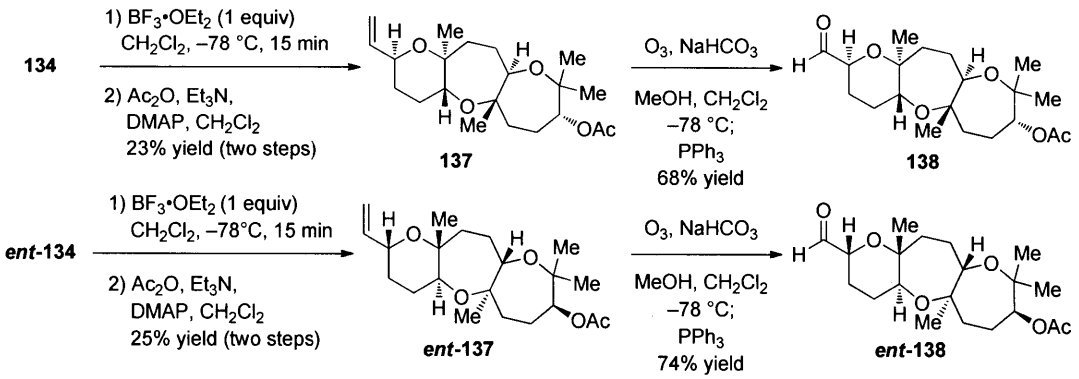
Scheme 1-24. Enzymatic resolution leading to both enantiomers of tricyclic fragment



Both enantiomers of **131** were carried forward, using opposite enantiomers of the Shi ketone **62** to install the correct absolute configuration of all the epoxides in each case. Shi epoxidation of the allylic ester **132** proceeded in an 88% yield, but subsequent base-induced cleavage of the acetate ester **133** induced a rapid cyclization of the allylic alcohol, producing **135** in considerable quantities. Deprotection of the acetate ester using potassium carbonate in MeOH, followed by direct Shi epoxidation on secondary alcohol **131** proceeded in 69% yield with only 16% of the over-epoxidized product obtained. Using *ent*-Shi ketone (***ent*-62**) the epoxidation of ***ent*-131** proceeded in a comparable 61% yield.[49] Cyclizations of both of these triepoxides proceeded in modest yields of 23% and 25% after acetylation, giving **137** and ***ent*-137**, respectively. Both alkenes were readily converted to the corresponding aldehydes upon treatment with ozone in about 70% yield for both substrates.

Scheme 1-25. Synthesis of both coupling fragments **138** and ***ent*-138**

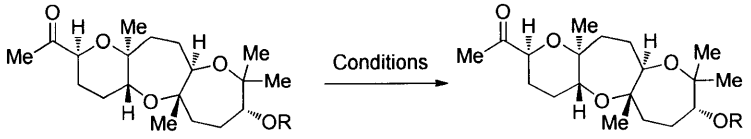




Elimination of secondary alcohol

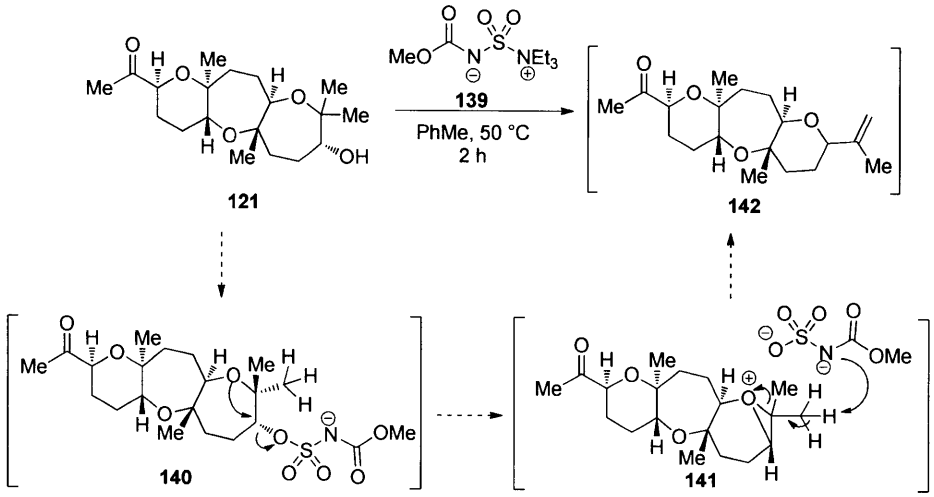
The final challenge in constructing the right-hand fragment of armatol A involves the elimination of the sterically encumbered secondary alcohol. Table 1-5 provides a summary of the methods investigated, via either direct elimination or by elimination of the acetate. Attempts to eliminate the acetate using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) lead to recovered starting material. The free alcohol was subjected to a variety of direct elimination conditions, including Martin's sulfurane,[50] Mitsunobu conditions, and the Grieco protocol,[51] which all failed to give the desired alkene. Burgess's reagent (**139**, Scheme 1-26)[52] did produce an interesting ring contraction product, **142**, resulting most likely from deprotonation of one of the geminal methyl groups, with displacement of the sulfate group by the oxepane oxygen. The exact mechanism of this elimination is uncertain, however, the formation of the *exo*-alkene exclusively suggests that the deprotonation may occur due to an ion pair interaction.

Table 1-5. Elimination attempts on ketone **120** and **121**



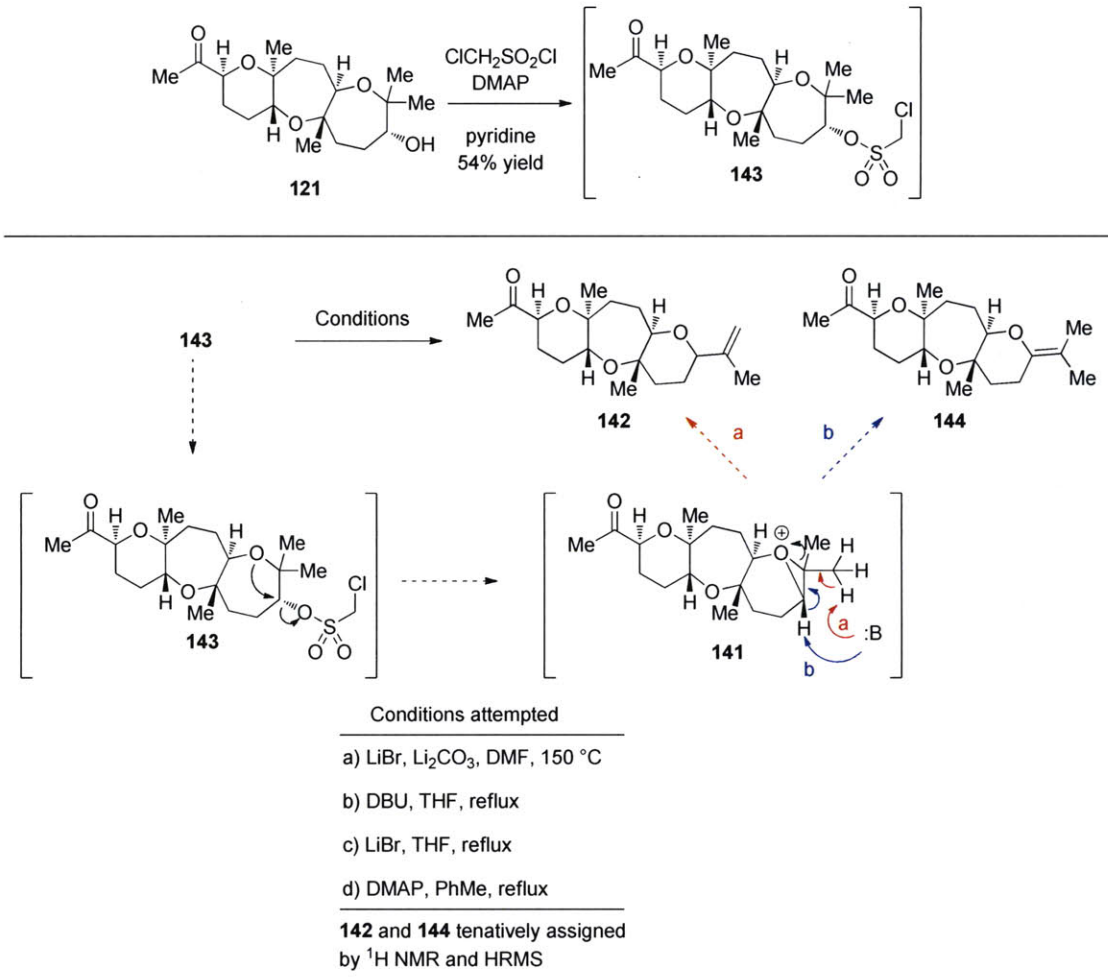
Entry	R	Conditions	Solvent	Temp	Time	Result
1	Ac, **120**	DBU	DMF	140 °C	24 h	No reaction
2	Ac, **120**	DBU	DMF	170 °C	60 h	No reaction
3	H, **121**	Martin sulfurane	CH_2Cl_2	rt to 40 °C	16 h	No reaction
4	H, **121**	PPh_3, DIAD, 4-nitrobenzoic acid	PhMe	rt to reflux	16 h	No reaction

Scheme 1-26. Proposed mechanism for ring contraction from Burgess's reagent



Our next approach involved converting **121** to chloromesylate **143**, which was then subjected to a variety of elimination and displacement conditions. However, ring contraction products (**142** and **144**, Scheme 1-27) were obtained exclusively,[53] most likely formed by a stepwise displacement of the mesylate with subsequent deprotonation via intermediate **141**. Models of the tricycle suggest that the *anti* proton to the secondary alcohol is not properly aligned for elimination. Attempts to invert the stereochemistry at the hydroxyl group via the ketone with both L-Selectride and sodium borohydride, which we proposed would provide a more favorable elimination substrate, were unsuccessful.

Scheme 1-27. Elimination products from chloromesylate **142**

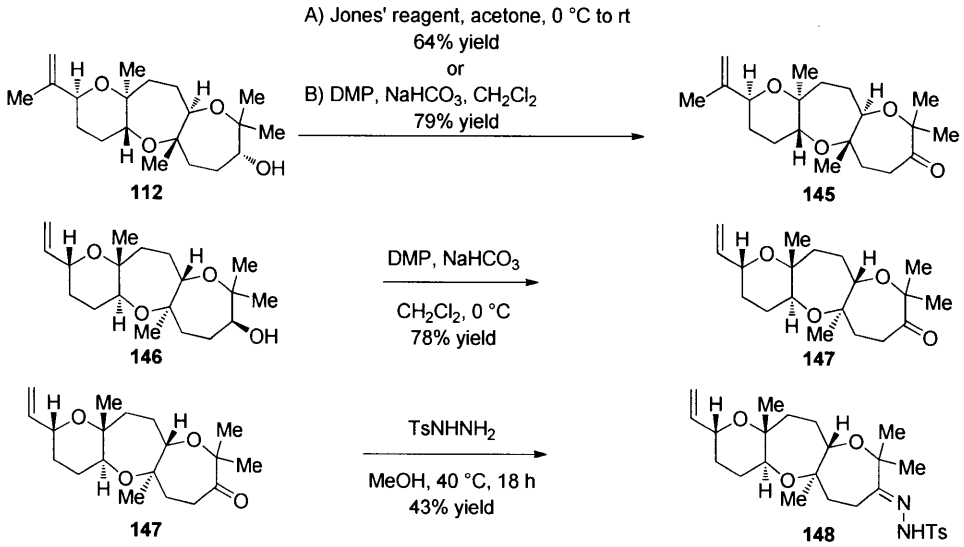


Conditions attempted
a) LiBr, Li_2CO_3, DMF, 150 °C
b) DBU, THF, reflux
c) LiBr, THF, reflux
d) DMAP, PhMe, reflux

142 and **144** tenatively assigned by ^{1}H NMR and HRMS

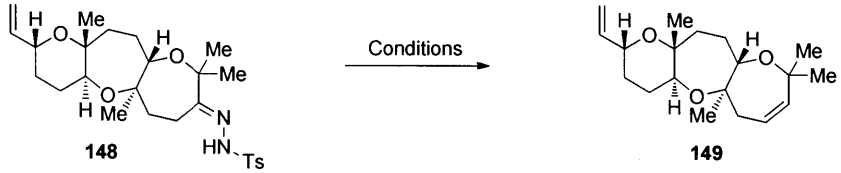
Our final attempt at the installation of the oxepene involved converting the secondary alcohols to a ketone, then to a corresponding hydrazone, followed by a subsequent Shapiro reaction. Oxidation of **112** can be performed with either Dess–Martin periodinane or even the harsher Jones' reagent demonstrating the robustness of the tricycle (Scheme 1-28). Dess–Martin periodinane also transformed the secondary alcohol to ketone **147** in 78% yield, and hydrazone **148** was formed by condensation with hydrazine. Compared to the difficult direct elimination of the secondary alcohol **121**, formation of the corresponding ketone **147** and the hydrazone **148** was rather facile.

Scheme 1-28. Oxidation and hydrazone formation attempts



The hydrazone **148** was subjected to an array of conditions reported for the Bamford–Stevens[54] reaction as shown in Table 1-6, but only sodium hydride in toluene or THF led to any of the desired olefin.[55] Many products were obtained, and 21% yield of the desired oxepane (**149**) was the highest observed case. Nevertheless, with a method to form the oxepene in hand, we looked forward to coupling the two fragments and establishing the absolute configuration of the natural product.

Table 1-6. Bamford–Stevens reaction on hydrazone **148**



Entry	Conditions	Solvent	Results
1	MeLi, –78 °C to rt	THF	No reaction
2	*n*-BuLi, –78 °C to rt	THF	Decomposition
3	LiHMDS, –78 °C to rt	THF	No reaction
4	NaH, reflux	THF	12% yield **149**
5	NaH, 90 °C	PhMe	21% yield **149**

Conclusion

The synthesis of the fused 6,7,7-tricycle of armatol A was investigated. Fragments containing both a ketone and an aldehyde were generated via a triepoxide cascade for subsequent fragment coupling (discussed in Chapter 2). Elimination of the secondary alcohol in the oxepane ring proved challenging; however, employing the Shapiro reaction successfully provided the desired oxepene, albeit in low yield. The ketone and aldehyde triads were synthesized in 11 and 7 steps, respectively, and both enantiomers could be obtained for the aldehyde system. These short synthetic routes enable the preparation of sufficient quantities of these triads for fragment coupling studies.

References

[1] Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897-1909.
[2] a) König, G. M.; Wright, A. D.; Sticher, O.; Angerhofer, C. K.; Pezzuto, J. M. *Planta Med.* **1994**, *60*, 532-537. b) Poli, M. A.; Mende, T. J.; Baden, D. G. *Mol. Pharmacol.* **1986**, *30*, 129-135. c) Cuypers, E.; Abdel-Mottaleb, Y.; Kopljar, I.; Rainier, J. D.; Raes, A. L.; Snyders, D. J.; Tytgat, J. *Toxicon* **2008**, *51*, 974-983.
[3] Dutton, C. J.; Banks, B. J.; Cooper, C. B. *Nat. Prod. Rep.* **1995**, *12*, 165-181.
[4] Rein, K. S.; Borrone, J. *Comp. Biochem. Physiol. Part B* **1999**, *124*, 117-131.
[5] Fernández, J. J.; Souto, M. L.; Norte, M. *Nat. Prod. Rep.* **2000**, *17*, 235-246.
[6] Nakanishi, K. *Toxicon* **1985**, *23*, 473-479.
[7] Based on a private communication from Professor Robert Thomas to Koji Nakanishi, 19 October 1983.
[8] Shimizu, Y. In *Natural Toxins: Animal, Plant and Microbial*; Harris, J. B., Ed.; Clarendon Press: Oxford, 1986; pp 115-125.
[9] a) NIH application GM31398-01 (submission date: February 24, 1982); b) K. C. Nicolaou, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 588-607.
[10] a) Vilotijevic, I.; Jamison, T. F. *Science* **2007**, *317*, 1189-1192. b) Morten, C. J.; Byers, J. A.; Van Dyke A. R.; Vilotijevic, I.; Jamison, T. F. *Chem. Soc. Rev.* **2009**, *38*, 3175-3192. c) Heffron, T. P.; Jamison, T. F. *Org. Lett.* **2003**, *5*, 2339-2342. d) Simpson, G. L.; Heffron, T. P.; Merino, E.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 1056-1057. e) Morten, C. J.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 6678-6679. f) Tanuwidjaja, J.; Ng, S. S.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 12084-12085. g) Van Dyke, A. R.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2009**, *48*, 4430-4432. h) Byers, J. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 6383-6385.
[11] Coxon, J. M.; Hartshorn, M. P.; Swallow, W. H. *Aust. J. Chem.* **1973**, *26*, 2521-2526.
[12] Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, 734-736.
[13] Stork, G.; Cohen, J. F. *J. Am. Chem. Soc.* **1974**, *96*, 5270-5272.
[14] Vilotijevic, I.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2009**, *48*, 5250-5281.
[15] Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1996**, *118*, 8158-8159.

[16] Tokiwano, T.; Fujiwara, K.; Murai, A. *Synlett* **2000**, 335-338.
[17] McDonald, F. E.; Wang, X.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2000**, *2*, 2917-2919.
[18] Morimoto, Y.; Nishikawa, Y.; Takaishi, M. *J. Am. Chem. Soc.* **2005**, *127*, 5806-5807.
[19] Kigoshi, H.; Ojika, M.; Shizuri, Y.; Niwa, H.; Yamada, K. *Tetrahedron Lett.* **1982**, *23*, 5413-5414.
[20] a) Suzuki, M.; Matsuo, Y.; Takeda, S.; Suzuki, T. *Phytochemistry* **1993**, *33*, 651-656. b) Matsuo, Y.; Suzuki, M.; Masuda, M. *Chem. Lett.* **1995**, 1043-1044.
[21] Morimoto, Y.; Yata, H.; Nishikawa, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 6481-6484.
[22] Vilotijevic, I.; Jamison, T. F. *Mar. Drugs* **2010**, *8*, 763-809.
[23] Ciavatta, M. L.; Wahidulla, S.; D'Souza, L.; Scognamiglio, G.; Cimino, G. *Tetrahedron Lett.* **2000**, *57*, 617-623.
[24] a) Fujiwara, K.; Tanaka, K.; Katagiri, Y.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2010**, *51*, 4543-4546. b) Fujiwara, K.; Hirose, Y.; Sato, D.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2010**, *51*, 4263-4266.
[25] Suenaga, K.; Shibata, T.; Takada, N.; Kigoshi, H.; Yamada, K. *J. Nat. Prod.* **1998**, *61*, 515-518.
[26] Inherent electronic bias for exo-opening in oxepane formation: Nicholaou, K. C.; Prasad, C. V.C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5335-5340.
[27] The use of an acidic promoter and a vinyl epoxide to direct *endo*-opening to form an oxepane ring was first investigated by Nicolaou (ref 26), but further reports using an oxepane to direct THP formation include a) Matsuo, G.; Kawamura, K.; Hori, N.; Matsukura, H.; Nakata, T. *J. Am. Chem. Soc.* **2004**, *126*, 14376-14378. b) Yoshikawa, K.; Inoue, M.; Hirama, M. *Tetrahedron Lett.* **2007**, *48*, 2177-2180.
[28] Wasserman, H. H.; Oku, T. *Tetrahedron Lett.* **1986**, *27*, 4913-4916.
[29] Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 4831-4832.
[30] a) Simpson, T. J.; Smith, R. W.; Westaway, S. M.; Willis, C. L. *Tetrahedron Lett.* **1997**, *38*, 5367-5370. b) Boland, W.; Mertes, K. *Synthesis* **1985**, 705-708.
[31] Fairlamb, I. J. S.; Dickinson, J. M.; Pegg, M. *Tetrahedron Lett.* **2001**, *42*, 2205-2208.
[32] a) Simpson, T. J.; Smith, R. W.; Westaway, S. M.; Willis, C. L. *Tetrahedron Lett.* **1997**, *38*, 5367-5370. b) Boland, W.; Mertes, K. *Synthesis* **1985**, 705-708.
[33] a) Tu, Y.; Wang, Z.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806-9807. b) Wong, O. A.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958-3987.
[34] Lindlar, H. *Helv. Chim. Acta* **1952**, *35*, 446-450.
[35] Ng, S.-S. Ph.D. Dissertation. Massachusetts Institute of Technology, 2008.
[36] a) Kraus, G. A.; Kim, J. *Org. Lett.* **2004**, *6*, 3115-3117. b) Wei, X.; Lorenz, J. C.; Kapadia, S.; Saha, A.; Haddad, N.; Busacca, C. A.; Senanayake, C. H. *J. Org. Chem.* **2007**, *72*, 4250-4253.
[37] Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526-5528.
[38] a) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557-1560. b) Morimoto, Y.; Muragaki, K.; Iwai, T.; Morishita, Y.; Kinoshita, T. *Angew. Chem. Int. Ed.* **2000**, *39*, 4082-4084.
[39] Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224-11235.
[40] a) Coates, R. M.; Ley, D. A.; Cavender, P. L. *J. Org. Chem.* **1978**, *43*, 4915-4922. b) Park, J.; Min, C.; Williams, H.; Scott, A. I. *Tetrahedron Lett.* **1995**, *36*, 5719-5722.
[41] a) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071-6072. b) Lurain, A. E.; Maestri, A.; Kelly, A. R.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 13608-13609.
[42] a) Nugent, W. A. *Chem. Commun.* **1999**, 1369-1370. b) Chen, Y. K.; Jeon, S.-J.; Walsh, P. J.; Nugent, W. A. *Org. Synth.* **2005**, *82*, 87-92.
[43] Shibata, T.; Nakatsui, K.; Soai, K. *Inorganica Chemica Acta*, **1999**, *296*, 33-36.
[44] The stereochemistry of the desired tricyle was confirmed by NOE analysis of the H-Me interactions across the ring junctions in addition to 1,4 diaxial interactions across the oxepane ring systems.
[45] Oppolzer, W.; Radinov, R. N. *Tet. Lett.* **1988**, *29*, 5645-5648.
[46] Tarwade, V.; Liu, X.; Yan, N.; Fox, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 5382-5383.
[47] a) Bornscheuer, U. T.; Kazlauskas, R. J. *Hydrolases in Organic Synthesis*; Wiley–VCH: Weinheim, 1999; b) Drauz, K.; Waldmann, H. *Enzyme catalysis in Organic Synthesis*; VCH: New York, 1995.

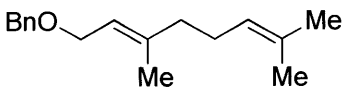
[48] Quirin, C.; Kazmaier, U. *Eur. J. Org. Chem.* **2009**, *3*, 371-377.
[49] A procedure to *ent*-Shi ketone was first reported in ref 39. This procedure was not amenable to large scale synthesis; Yutaka Ikeuchi provided a convenient new route that will be disclosed in due course.
[50] a) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003-5010. b) Martin, J. C.; Franz, J. A.; Arhart, R. J. *J. Am. Chem. Soc.* **1974**, *96*, 4604-4611.
[51] Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485-1486.
[52] Burgess, E. M.; Penton, Jr. H. R.; Taylor, E. A. *J. Am. Chem. Soc.* **1970**, *92*, 5224-5226.
[53] a) Urones, J. G.; Diez, D.; Marcos, I. S.; Basabe, P.; Lithgow, A. M.; Moro, R. F.; Garrido, N. M.; Escarcena, R. *Tetrahedron*, **1995**, *51*, 3691-3704. b) Miyashita, K.; Tanaka, A.; Shintaku, H.; Iwata, C. *Tetrahedron*, **1998**, *54*, 1395-1406.
[54] a) Bamford, W. R.; Stevens, T. S. *J. Chem. Soc.***1952**, 4735-4740. b) Shapiro, R. H.; Heath, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 5734-5735. c) Adlington, R. M.; Barrett, A. G. M. *Acc. Chem. Res.* **1983**, *16*, 55-59.
[55] a) Piers, E.; Abeysekera, B. F.; Herbert, D. J.; Suckling, I. D. *Can. J. Chem.* **1985**, *63*, 3418-3432. b) Sasaki, M.; Murae, T.; Takahashi, T. *J. Org. Chem.* **1990**, *55*, 528-540. c) Nan, F.; Liu, L.; Xiong, Z.; Chen, Y.; Li, T.; Li, Y. *Collect. Czech. Chem. Commun.* **1997**, *62*, 1089-1094. d) Maimone, T. J.; Shi, J.; Ashida, S.; Baran, P. S. *J. Am. Chem. Soc.* **2009**, *131*, 17066-17067.

Experimental Section

General Information

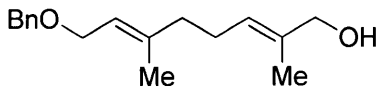
Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of argon or nitrogen with rigorous exclusion of moisture from reagents and glassware. Unless otherwise noted, all solvents and triethylamine used in the reactions were purified via a SG Water USA solvent column system. 4Å MS used in the Sharpless asymmetric epoxidations were activated by flame drying under high vacuum three times (with cooling in between) immediately before use. Analytical thin-layer chromatography was performed using EM Science silica gel 60 F254 plates. The developed chromatogram was visualized by UV lamp or stained using one of the following: aqueous potassium permanganate ($KMnO_4$), ethanolic phosphomolybdic acid (PMA), aqueous cerium ammonium molybdate (CAM, Hanessian's stain), or ethanolic vanillin. Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle silica gel (230-400 mesh).

^1H and ^{13}C NMR spectra were recorded on Varian 300 MHz, Varian 500 MHz, Bruker 400 MHz, or Bruker 600 MHz spectrometer in $CDCl_3$ or C_6D_6. 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) or residual benzene (7.16 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and bs = broad singlet), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.23 ppm) or C_6D_6 (128.37 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 Fourier Transform Mass Spectrometer by Ms. Li Li of the Massachusetts Institute of Technology, Department of Chemistry Instrumentation Facility. Chiral HPLC analysis was performed on a Hewlett-Packard 1100 chromatograph equipped with a variable wavelength detector and Chiralcel OD or OD-H, or AD-H columns. Specific Rotations ($[\alpha]^{24}_D$) were measured on a Perkin-Elmer 241 polarimeter at 589 nm.



60

Benzyl ether 60: To a 250 mL round-bottom flask equipped with a stir bar was added sodium hydride (1.705 g, 42.6 mmol, 60% in mineral oil) in 4:1 THF/DMF (125 mL). Geraniol (5.1 mL, 29.1 mmol) was added dropwise at 0 °C and stirred for 30 min. Benzyl bromide (4.2 mL, 35.4 mmol) and tetrabutylammonium iodide (261 mg, 0.718 mmol) were added and the reaction was allowed to warm to room temperature overnight. The reaction was quenched with saturated NH_4Cl and the aqeous layer was extracted 3x with Et_2O. The organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude oil was purified by column chromatography (5% EtOAc in hexanes) to furnish known benzyl ether **60** (6.336, 25.9 mmol, 89% yield)[1] as colorless oil.



59

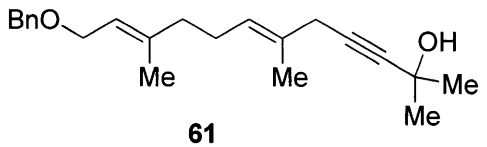
Allylic alcohol 59: To a 100 mL round-bottom flask equipped with a stir bar was added selenium dioxide (59 mg, 0.532 mmol), 4-hydroxybeonzoic acid (145 mg, 1.05 mmol), and a 5.5 M solution of TBHP in decanes (6.5 ml, 35.8 mmol) in 30 mL of CH_2Cl_2 and stirred for 1 h at room temperature. Benzyl ether **60** (2.673 g, 10.9 mmol) was added as a solution in 10 mL of CH_2Cl_2 over 5 min. The reaction was stirred for 24 h and then concentrated *in vacuo*. The crude was dissolved in Et_2O, washed 2x with saturated Na_2SO_3 and 1x with water. The organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was dissolved in 40 mL of EtOH in a 100 mL and then cooled to 0 °C. Sodium borohydride (369 mg, 9.75 mmol) was added in portions and stirred for 1 h. The reaction was quenched with saturated $NaHCO_3$ and then the aqueous layer was extracted 3x with Et_2O. The organic layers were combined and washed 2x with H_2O, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (20% EtOAc in hexanes) to furnish allylic alcohol **59** (877 mg, 3.37 mmol, 31% yield) as colorless oil.

^1H NMR (500 MHz; $CDCl_3$): δ 7.36 (d, J = 4.5, 4H), 7.30 (dd, J = 8.5, 4.3, 1H), 5.43-5.38 (m, 2H), 4.52 (s, 2H), 4.03 (d, J = 6.8, 2H), 3.99 (s, 2H), 2.18 (t, J = 7.5, 2H), 2.09 (t, J = 7.6, 2H), 1.67 (s, 3H), 1.66 (s, 3H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 140.1, 138.7, 135.3, 128.6, 128.0, 127.8, 125.8, 121.3, 72.3, 69.2, 66.7, 39.3, 26.0, 16.7, 13.9

IR (NaCl, thin film): 3369, 2919, 2851, 1996, 1454, 1068, 736

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{17}H_{24}O_2Na$, 283.1669; found, 283.1677.



61

Tertiary alcohol 61: To a 100 mL round-bottom flask equipped with a stir bar was added allylic alcohol **59** (877 mg, 3.37 mmol) in 30 mL of Et_2O and the reaction was cooled to 0 °C. Phosphorous tribromide (160 *u*L, 1.69 mmol) was added slowly and stirred for 1 h. The reaction was quenched with saturated $NaHCO_3$ and warmed to room temperature, shielded from light. The aqueous layer was extracted with Et_2O (3x) and the organic layers were washed with brine. The organic layers were then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude allylic bromide was used without further purification.

To a 100 mL round-bottom flask equipped with a stir bar in a glove box was added copper (I) iodide (615.2 mg, 3.23 mmol). The flask was sealed, removed from the glove box, and transferred to the hood where 24 mL of DMF was added. Upon addition of DBU (490 *u*L, 3.28 mmol), the color changed from light green to an olive-green, and the reaction was stirred for 15 min. Two cystals of BHT were added and 2-methyl-3-butyn-2-ol (310 *u*L, 3.2 mmol) was added and stirred for an additional 30 min at room temperature. The allylic bromide (632 mg, 1.95 mmol) was dissolved in 8 mL of DMF and added dropwise over 5 min. The reaction was stirred for 16 h under nitrogen. The crude reaction was poured into Et_2O and then washed with 1N HCl (2x) and with saturated NH_4Cl in NH_4OH (1x). The aqueous layer was extracted with Et_2O (3x) and then combined and dried over $MgSO_4$, filtered, and concentrated *in vauo*. The crude reaction was purified by column chromatography (3%) to furnish diene-yne **61** (655 mg, 2.01 mmol, 60% yield) as colorless oil.

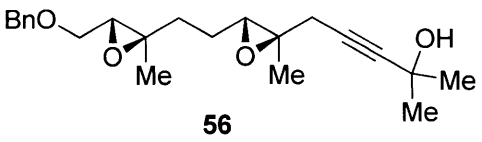
Data for major diastereomer:

^1H NMR (500 MHz; $CDCl_3$): δ 7.36 (d, J = 4.5, 4H), 7.31-7.28 (m, 1H), 5.42 (t, J = 7.3, 2H), 4.52 (s, 2H), 4.03 (d, J = 6.7, 2H), 2.87 (s, 2H), 2.16 (t, J = 7.2, 2H), 2.09 (dd, J = 15.5, 7.8, 2H), 1.67 (s, 3H), 1.65 (s, 3H), 1.51 (s, 6H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 140.2, 138.7, 130.3, 128.6, 128.1, 127.8, 125.4, 121.3, 112.2, 87.7, 72.2, 66.7, 39.4, 31.9, 28.8, 26.3, 16.7, 16.4

IR (NaCl, thin film): 3428, 2980, 2927, 2858, 1996, 1636, 1456, 1363, 1238, 1168, 1066, 948, 860, 737, 698

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{22}H_{39}O_2Na$, 349.2138; found, 349.2149.



56

Diepoxide 56: To a 100 mL round-bottom flask equipped with a stir bar was added a solution of diene-ye **61** (107 mg, 0.328 mmol) in 11.4 mL of 2:1 DMM/CH_3CN and 7.6 mL of EDTA buffer. $n$$Bu_4NHSO_4$ (5.7 mg, 0.0168 mmol) was added and the reaction was vigorously stirred followed by the addition of Shi ketone (173 mg, 0.670 mmol). A solution of Oxone (1.50 g, 2.44 mmol) in 10.7 mL of EDTA solution and a solution of 10.7 mL of 0.89 M K_2CO_3 were added dropwise side-by-side over 30 min. The reaction was allowed to stir for an additional 30 min before 60 mL of water was added and stirred for an additional 45 min. The reaction was extracted three times with CH_2Cl_2 and dried over Na_2SO_4. The reaction was filtered and evaporated *in vacuo* and subjected to column chromatography (50% EtOAc in hexanes) to provide colorless oil **56** (97 mg, 0.271 mmol, 83% yield, 3.5:1 dr).

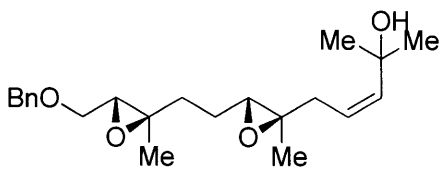
^{1}H NMR (500 MHz; $CDCl_3$): δ 7.37-7.35 (m, 4H), 7.32-7.29 (m, 1H), 4.64 (dd, J = 11.9, 1.1, 1H), 4.56-4.52 (m, 1H), 3.72 (ddd, J = 18.7, 11.1, 4.5, 1H), 3.57 (td, J = 10.9, 6.0, 1H), 3.06 (ddd, J = 15.1, 6.0, 4.6, 1H), 2.91-2.89 (m, 1H), 2.52 (dd, J = 17.0, 12.8, 1H), 2.36 (dd, J = 17.0, 11.3, 1H), 2.19 (bs, 1H), 1.82-1.79 (m, 1H), 1.72-1.62 (m, 3H), 1.50 (s, 6H), 1.35 (s, 3H), 1.28 (s, 3H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 138.0, 128.6, 128.0, 128.0, 87.9, 73.5, 68.9, 62.5, 61.7, 61.0, 59.7, 59.6, 34.9, 31.8, 28.9, 24.3, 17.1, 16.72, 16.72

$[\alpha]^{24}_D = -4.9$ (c 0.9, $CHCl_3$)

IR (NaCl, thin film): 3424, 2978, 2930, 2865, 1653, 1559, 1455, 1386, 1363, 1239, 1169, 1076, 950, 871, 740, 699

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{22}H_{30}O_4Na$, 381.2036; found, 381.2040.



55

Cis olefin 55: To a 10 mL round-bottom flask equipped with a stir bar was added Lindlar's catalyst (9 mg, 10% by weight palladium on calcium carbonate poisoned with lead) in 1.9 mL of EtOH followed by quinoline (3 *u*L, 0.0254 mmol). The reaction was stirred for 20 min under argon. Alkyne **56** (89 mg, 0.248 mmol) was added as a solution in 1.9 mL of EtOH and stirred under argon for 30 min. The flask was purged and subjected to hydrogen (1 atm) for 4 h. The reaction was filtered through Celite and washed with EtOAc. The solvents were removed *in vacuo*. The crude oil was purified by column chromatography (20 to 30% EtOAc in hexanes) to furnish allylic alcohol **55** (41.0 mg, 0.114 mmol, 46% yield) as colorless oil.

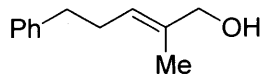
^{1}H NMR (500 MHz; $CDCl_3$): δ 7.36-7.35 (m, 4H), 7.30 (dt, J = 6.7, 3.4, 1H), 5.63 (d, J = 11.8, 1H), 5.35-5.30 (m, 1H), 4.63 (d, J = 11.9, 1H), 4.53 (dd, J = 11.9, 3.5, 1H), 3.69 (td, J = 11.0, 5.3, 1H), 3.58 (dd, J = 11.1, 5.9, 1H), 3.20 (s, 1H), 3.03 (ddd, J = 6.2, 4.4, 2.0, 1H), 2.91 (t, J = 5.9, 1H), 2.66-2.64 (m, 2H), 1.77-1.71 (m, 1H), 1.69-1.61 (m, 3H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 141.5, 128.6, 128.0, 128.0, 122.0, 73.5, 71.9, 68.9, 63.1, 61.6, 61.0, 34.9, 31.6, 31.1, 24.1, 17.2, 17.1, 59.8

$[\alpha]^{24}_D$ = +4.1 (c 0.8, $CHCl_3$)

IR (NaCl, thin film): 3445, 2968, 2926, 1718, 1653, 1559, 1457, 1386, 1094, 959, 738

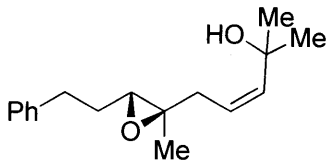
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{22}H_{33}O_4Na$, 383.2198; found, 383.2199.



68

Allylic alcohol 68: To a 25 mL round-bottom flask equipped with a stir bar was dissolved hydrocinnamaldehyde (100 *u*L, 0.759 mmol) in 10 mL of CH_2Cl_2. To the flask was added 1-carbethoxyethylidene triphenylphosphorane (288 mg, 0.795 mmol) in one portion at room temperature. The reaction was stirred for 24 h at room temperature then for 48 h at reflux. The solvent was removed *in vacuo* and then dissolved in Et_2O and filtered through a silca gel plug. The solvent was removed and to furnish a crude solution of allylic ester (171 mg) which was carried on without further purification.

Lithium aluminum hydride (25 mg, 0.66 mmol) was dissolved in 8 mL of Et_2O in a 25 mL round-bottom flask equipped with a stir bar and cooled to 0 °C. The allylic ester (171 mg) was added in a 1 mL of Et_2O. The reaction was heated to reflux for 30 min and then cooled to room temperature. The reaction was quenched with 25 *u*L of H_2O at 0 °C then 25 *u*L of a 15% solution of NaOH was added, followed to 75 *u*L of H_2O. The reaction was then stirred for 10 min and warmed to room temperature. $MgSO_4$ was added and the suspension was filtered through Celite to remove aluminum salts. The Celite was washed with Et_2O, and concentrated *in vacuo*. The crude oil was purified by column chromatography (20% EtOAc in hexanes) to provide known allylic alcohol **68** (83 mg, 0.545 mmol, 72% yield)[2] as colorless oil.



69

Tertiary allylic alcohol 69: To a 100 mL round-bottom flask equipped with a stir bar was added allylic alcohol **68** (795 mg, 4.51 mmol) in 50 mL of Et_2O and the reaction was cooled to 0 °C. Phosphorous tribromide (250 *u*L, 2.65 mmol) was added slowly and stirred for 45 min. The reaction was quenched with saturated $NaHCO_3$ and warmed to room temperature in the absence of light. The aqueous layer was extracted 3x with Et_2O and the organic layers were washed with brine. The organic layers were then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude allylic bromide was used without further purification.

To a 100 mL round-bottom flask equipped with a stir bar in a glove box was added copper (I) iodide (989 mg, 5.19 mmol). The flask was sealed, removed from the glove box, and transferred to the hood where 40 mL of DMF was added. Upon addition of DBU (780 *u*L, 5.22 mmol) the color changed from light green to an olive-green, and the reaction was stirred for 15 min. Two cystals of BHT were added and 2-methyl-3-butyn-2-ol (500 *u*L, 5.16 mmol) was added and stirred for an additional 30 min at room temperature. The allylic bromide (~5.2 mmol) was dissolved in 10 mL of DMF and added dropwise over 5 min. The reaction was stirred for 16 h under nitrogen. The crude reaction was poured into Et_2O and then washed with 1N HCl (2x) and with saturated NH_4Cl in NH_4OH (1x). The aqueous layer was extracted with Et_2O (3x) and then combined and dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction was purified by column chromatography (3%) to furnish a tertiary alcohol (517 mg, 2.13 mmol, 47% yield) as colorless oil. The alcohol was carried on to the next step without further purification.

To a 125 mL Erlenmyer equipped with a stir bar was added a solution of the tertiary alcohol (272 mg, 1.22 mmol) in 39 mL of 2:1 DMM/CH_3CN and 24.5 mL of EDTA buffer. $n$$Bu_4NHSO_4$ (171 mg, 0.504 mmol) was added and the reaction was vigorously stirred followed by the addition of Shi ketone (147 mg, 0.570 mmol). A solution of Oxone (1.377 g, 2.24 mmol) in 9.9 mL of EDTA solution and a solution of 9.9 mL of 0.89 M K_2CO_3 were added dropwise side-by-side over 30 min. The reaction was allowed to stir for an additional 30 min before 50 mL of water was added and stirred for an additional 45 min. The reaction was extracted three times with CH_2Cl_2 and dried over Na_2SO_4. The reaction was filtered and evaporated *in vacuo* and subjected to column chromatography (30% EtOAc in hexanes) to provide an epoxide (278 mg, 1.08 mmol, 88% yield) as colorless oil. The epoxide was carried onto the following reduction directly without further purification.

To a 10 mL round-bottom flask equipped with a stir bar was added Lindlar's catalyst (20 mg, 10% by weight palladium on calcium carbonate poisoned with lead) in 5 mL of EtOH followd by quinoline (7 *u*L, 0.059 mmol). The reaction was stirred for 20 min under argon. The previously synthesized alkyne (130 mg, 0.503 mmol) was added as a solution in EtOH and stirred under argon for 30 min. The flask was purged and subjected to hydrogen (1 atm) for 2 h. The reaction was filtered through Celite (eluting with EtOAc) and concentrated *in vacuo*. The crude oil was purified by column chromatography (20% EtOAc in hexanes) to furnish allylic alcohol **69** (62 mg, 0.238 mmol, 47% yield) as colorless oil.

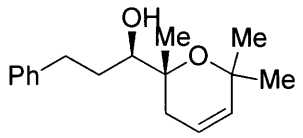
^{1}H NMR (500 MHz; $CDCl_3$): δ 7.32-7.20 (m, 5H), 5.75 (ddd, J = 10.3, 6.4, 2.1, 1H), 5.68 (ddd, J = 10.3, 2.9, 0.6, 1H), 3.47 (dd, J = 10.6, 1.9, 1H), 2.99 (ddd, J = 13.9, 9.7, 4.5, 1H), 2.68 (ddd, J = 13.7, 9.7, 7.0, 1H), 2.37 (dt, J = 16.7, 2.0, 1H), 1.74 (dddd, J = 13.5, 10.1, 7.0, 2.0, 1H), 1.67-1.59 (m, 2H), 1.29 (s, 3H), 1.24 (s, 3H), 1.16 (s, 3H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 142.6, 133.5, 128.7, 128.5, 125.9, 120.8, 76.8, 75.5, 72.3, 33.3, 32.2, 31.6, 29.1, 26.9, 22.9

$[\alpha]^{24}_D$ = +27.0 (c 1.9, $CHCl_3$)

IR (NaCl, thin film): 3470, 3029, 2974, 2928, 2864, 1742, 1604, 1496, 1454, 1372, 1205, 1128, 1072, 1007, 922, 749, 715, 700

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{17}H_{24}O_2Na$, 283.1669; found, 283.1677.



75

THP 75: To a 5 mL vial equipped with a stir bar was added allylic alcohol **69** (29 mg, 0.111 mmol) in 1.1 mL of MeOH. Cesium carbonate (182 mg, 0.559 mmol) was added the reaction was heated to 60 °C for 14 h. The reaction was cooled and concentrated *in vacuo*. The solid was dissolved in saturated NH_4Cl and Et_2O. The aqueous layer was extracted with Et_2O (5x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified by column chromatography (50% EtOAc in hexanes) to furnish secondary alcohol **75**.

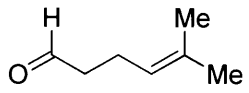
^{1}H NMR (500 MHz; C_6D_6): δ 7.21-7.17 (m, 4H), 7.10-7.07 (m, 1H), 5.55-5.51 (m, 1H), 5.42 (ddd, J = 10.2, 3.0, 0.9, 1H), 3.52 (dd, J = 9.6, 3.1, 1H), 3.11 (ddd, J = 13.8, 8.9, 5.1, 1H), 2.84 (s, 1H), 2.76 (ddd, J = 13.6, 9.2, 7.6, 1H), 2.37 (dt, J = 16.7, 2.2, 1H), 1.66-1.60 (m, 2H), 1.34 (ddd, J = 16.7, 6.6, 0.6, 2H), 1.14 (s, 3H), 1.06 (s, 3H), 0.99 (s, 3H)

^{13}C NMR (125 MHz; C_6D_6): δ 143.3, 133.9, 129.3, 129.0, 126.4, 121.4, 77.0, 75.9, 72.3, 33.8, 33.0, 31.8, 29.3, 27.7, 22.8

$[\alpha]^{24}_D$ = +26.2 (c 0.07, $CHCl_3$)

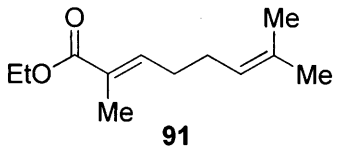
IR (NaCl, thin film): 3457, 3028, 2974, 2927, 1653, 1496, 1455, 1393, 1372, 1071, 1007

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{17}H_{24}O_2Na$, 283.1669; found, 283.1667.



88

Aldehyde 88: A 100 mL sealed tube equipped with a stir bar in a dry box was charged $Hg(OAc)_2$ (3.21 g, 10.1 mmol) and transferred under nitrogen to a hood. To the reaction vessel was added 2-methyl-3-buten-2-ol (5.3 mL, 50.7 mmol) and ethyl vinyl ether (14.5 mL, 151.4 mmol) and heated for 5 h under reflux. The reaction mixture was concentrated to remove volatiles and then purified via flash column chromatography (2% EtOAc in hexanes) to give rather volatile unsaturated aldehyde **88** (3.99 g, 70% yield) as a pale yellow oil. Spectral data matched previously reported.[3]



91

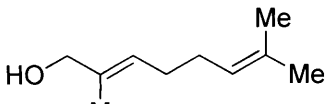
Ester 91: To a 500 mL round-bottom flame-dried flask equipped with a stir bar was added aldehyde **88** (3.99 g, 35.6 mmol) followed by benzene (300 mL). (1-Ethoxycarbonylethyldiene)triphenylphosphorane (12.9 g, 35.6 mmol) was added in one portion and the reaction was heated to 40 °C for 41 h. The reaction was cooled to room temperature and the volatiles were removed *in vacuo*. The remaining yellow solid was loaded with CH_2Cl_2 and purified via flash column chromatography (2% EtOAc in hexanes) to provide ester **91** (4.79 g, 69% yield) as colorless oil.

^1H (500 MHz, $CDCl_3$, δ): 6.75 (dq, *J*=7.2, 1.6 Hz, 1H), 5,11 (tqd, *J*=7.0, 1.5 Hz, 1H), 4.18 (q, *J*=7.2 Hz, 2H), 2.19 (m, 2H), 2.11 (m, 2H), 1.82 (m 3H), 1.69 (m, 3H), 1.60 (m, 3H), 1.29 (t, *J*=7.2 Hz, 3H).

^{13}C (125 MHz, $CDCl_3$, δ): 168.4, 142.0, 132.7, 128.1, 123.5, 50.5, 29.2, 27.2, 25.9, 17.9, 14.5, 12.5.

IR (NaCl, thin film): 2979, 2930, 1713, 1650, 1447, 1367, 1272, 1240, 1174, 1120, 1078, 1038.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{12}H_{24}O_3Na$, 219.1356; found, 219.1364.



87

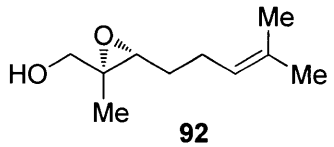
Alcohol 87: To a 200 mL round-bottom flame-dried flask equipped with a stir bar was dissolved ester **91** (4.79g, 24.4 mmol) in Et_2O (104 mL) and cooled to 0 °C. Lithium aluminum hydride (937 mg, 24.7 mmol) was added slowly in portions and the reaction was allowed to stir while warming to room temperature for 10 h. The reaction was returned to 0 °C and 937 *u*L of water was added, followed by 937 *u*L of 15% NaOH in brine, followed by 3 mL of water. The reaction was allowed to warm to room temperature while stirring for 45 min. $MgSO_4$ was added and stirred for an additional 30 min. The reaction was filtered through Celite washing with Et_2O and then concentrated *in vacuo* to provide colorless oil. The residue was purified via flash column chromatography (10% EtOAc in hexanes) to provide alcohol **87** (2.84g, 76% yield) as colorless oil.

^1H (500 MHz, $CDCl_3$, δ): 5.43 (m, 1H), 5.13(m, 1H), 4.00 (d, *J*=5.1 Hz, 2H), 2.06 (m, 5H), 1.70 (s, 3H), 1.67 (s, 3H), 1.61 (s, 3H).

^{13}C (125 MHz, $CDCl_3$, δ): 135.1, 132.1, 126.3, 124.3, 69.2, 28.2, 28.1, 25.9, 17.9, 13.9.

IR (NaCl, thin film): 3341, 2921, 1673, 1456, 1376, 1224, 1065, 1006.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{10}H_{18}ONa$, 177.1250; found, 177.1243.



92

Epoxy alcohol 92: To a 250 mL round-bottom flame-dried flask equipped with a stir bar was added 4 Å molecular sieves (3.07g) and heated under vacuum for 15 min. CH_2Cl_2 (108 mL) was added and the flask was cooled with a CryoCool to –20 °C. Titanium isopropoxide (725 *u*L, 2.4 mmol) and D-(–)-diethyl tartrate (505 *u*L, 2.95 mmol) were added and stirred for 35 min. A solution of *tert*-butyl hydrogen peroxide (5.5 M in decanes, 6.7 mL, 36.7 mmol) was added and stirred for 30 min. A solution of alcohol **87** (2.84 g, 18.4 mmol) in 10 mL of CH_2Cl_2 was added slowly over 20 min. The reaction was stirred at this temperature for 9.5 h. The reaction was quenched by adding 4.65 mL of a 40% solution of NaOH in brine (6.5 mL: 5.85 mL H_2O, 2.6 g NaOH, 325 mg NaCl) and then 11.2 mL of Et_2O and let warm while stirring for 30 min. 4.7 g of $MgSO_4$ was added along with 468 mg of Celite and stirred for 30 min at room temperature. The reaction was filtered through Celite washing with CH_2Cl_2 and concentrated *in vacuo*. The crude oil was purified via flash column chromatography (30% EtOAc in hexanes) to provide epoxy alcohol **92** (2.81g, 90% yield) as colorless oil. Enantiomeric excess determined to be 92% via chiral GC analysis of the acetonide product **90**.

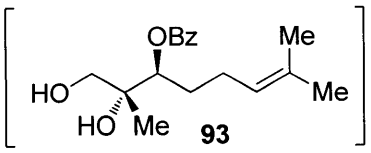
^1H (500 MHz, $CDCl_3$, δ): 5.12 (tqd, *J*=7.3, 1.4 Hz, 1H), 3.64 (d, *J*=12.2 Hz, 1H), 3.51 (d, *J*=12.2 Hz), 3.01 (t, *J*=6.2 Hz, 1H), 2.36 (bs, 1H), 2.12 (dt, *J*=8.0, 7.3 Hz , 2H), 1.67 (s, 3H), 1,62 (m, 1H), 1.55 (m, 1H), 1.25 (s, 3H).

^{13}C (125 MHz, $CDCl_3$, δ): 132.6, 123.3, 65.7, 61.3, 60.1, 28.5, 25.8, 25.0, 17.8, 14.3.

$[\alpha]^{24}_D$= +18.4 (c 1.5, $CHCl_3$).

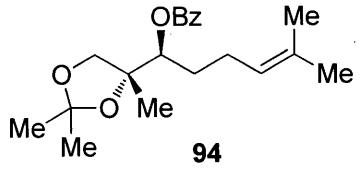
IR (NaCl, thin film): 3429, 2966, 2926, 2861, 1452, 1382, 1232, 1040.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{10}H_{18}O_2Na$, 193.1199; found, 193.1200.



93

Benzoate 93: To a 250 mL round-bottom flame-dried flask equipped with a stir bar was dissolved epoxy alcohol **92** (2.78 g, 16.3 mmol) in 108 mL of chloroform. 25.8 mL of a solution of benzoic acid and titanium isopropoxide in $CHCl_3$ was added (To a 50 mL round-bottom flask equipped with a stir bar was added (3.28 g, 26.9 mmol) followed by 24.4 mL of $CHCl_3$ and $Ti(O^iPr)_4$ (7.4 mL, 24.4 mmol). The flask was stirred for 30 min at room temperature and the dissolved solution added to the previous reaction.). The reaction was stirred at room temperature for 38 h before being concentrated *in vacuo*. Equal volumes of Et_2O and 10% citric acid solutions were added and stirred for 1 h. The aqueous layer was extracted with Et_2O (3x) and then washed with $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil was used without further purification.



94

Acetonide 94: To a 500 mL round-bottom flame-dried flask equipped with a stir bar was added benzoate **93** (5.42 g, 18.5 mmol) in CH_2Cl_2 (56 mL) and 2,2-dimethoxypropane (73 mL). (+/–)-CSA (430.9 mg, 1.85 mmol) was added and the reaction was stirred for 5 h at room temperature. Additional CH_2Cl_2 was added and then washed with saturated $NaHCO_3$. The organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil was purified via column chromatography (2 to 5% EtOAc in hexanes) to provide acetonide **94** (3.43 g, 73% yield for two steps) as colorless oil.

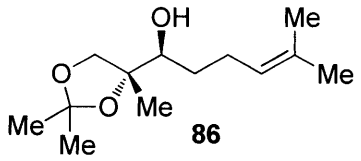
^1H (500 MHz, $CDCl_3$, δ): 8.06 (m, 2H), 7.57 (tt, *J*=7.4, 1.4 Hz, 1H), 7.45 (m, 2H), 5.25 (dd, *J*=10,3, 2.6 Hz, 1H), 5.11 (m, 1H), 4.01 (d, *J*=8.6 Hz, 1H), 3.71 (d, *J*=8.6 Hz, 1H), 2.06 (m, 2H), 1.85 (m, 1H), 1.70 (m, 1H), 1.61 (s, 3H), 1.53 (s, 3H), 1.41 (s, 3H), 1.38 (s, 3H), 1.34 (s, 3H).

^{13}C (125 MHz, $CDCl_3$, δ): 166.1, 133.2, 132.5, 130.4, 129.9, 128.6, 123.6, 110.1, 82.3, 76.7, 72.5, 30.1, 27.2, 26.9, 25.8, 24.8, 21.3, 17.8.

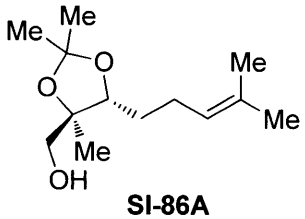
$[\alpha]^{24}_D = -10.9$ (c 10.9, $CHCl_3$).

IR (NaCl, thin film): 3427, 3063, 2984, 2934, 2873, 1722, 1602, 1451, 1378, 1272, 1214, 1060, 1026.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{20}H_{28}O_4Na$, 333.2060; found, 333.2046.



86



SI-86A

Acetonide 86: To a 200 mL round-bottom flame-dried flask equipped with a stir bar was added benzoate **94** (3.16 g, 9.5 mmol) in MeOH (48 mL) and THF (48 mL). Potassium carbonate (7.37 g, 53.3 mmol) was added and the reaction was stirred for 4 h at room temperature. The solvents were concentrated *in vacuo* and then the crude residue was dissolved in CH_2Cl_2 and sat. NH_4Cl was added to quench the remaining carbonate. The aqueous layer was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil was purified using a Biotage (100g column) to provide acetonide **86** (1.08 g, 50% yield) as colorless oil. Acetonide migration product **SI-86A** (484.6 mg, 22% yield) was obtained as well under the reaction conditions.

Acetonide **86**:

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.11-5.07 (m, 1H), 4.00 (d, J = 8.4, 1H), 3.62 (dd, J = 8.4, 0.5, 1H), 3.49 (dt, J = 10.6, 1.6, 1H), 2.38 (d, J = 3.4, 1H), 2.22-2.15 (m, 1H), 2.07 (dq, J = 14.7, 7.3, 1H), 1.65 (s, 3H), 1.60 (s, 3H), 1.55-1.47 (m, 1H), 1.40 (s, 3H), 1.34 (s, 3H), 1.29-1.23 (m, 1H), 1.22 (s, 3H)

^{13}C NMR (100 MHz; $CDCl_3$): δ 132.5, 124.0, 109.4, 83.9, 74.2, 70.4, 31.5, 27.6, 26.8, 25.9, 25.2, 21.7, 17.9

$[\alpha]^{24}_D$ = –9.8 (c 4.8, $CHCl_3$)

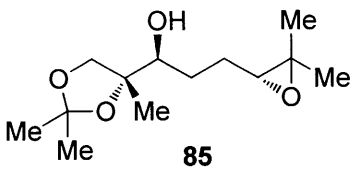
IR (NaCl, thin film): 3488, 2985, 2932, 2875, 1454, 1378, 1255, 1214, 1114, 1059, 1080, 984, 913, 856, 816

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{13}H_{24}O_3Na$, 251.1618; found, 251.1608.

SI-86A:

^{1}H NMR (600 MHz; $CDCl_3$): δ 5.12-5.09 (m, 1H), 3.81 (dd, J = 10.0, 3.2, 1H), 3.54 (dd, J = 10.9, 3.3, 1H), 3.32 (dd, J = 10.9, 9.1, 1H), 2.17 (t, J = 7.2, 1H), 2.08 (td, J = 11.2, 4.5, 2H), 1.69 (s, 3H), 1.62 (s, 3H), 1.64-1.57 (m, 1H), 1.44 (s, 3H), 1.46-1.41 (m, 1H), 1.37 (s, 3H), 1.26 (s, 3H)

^{13}C NMR (150 MHz; $CDCl_3$): δ 132.7, 123.5, 107.4, 82.4, 82.0, 65.4, 28.6, 28.1, 26.6, 25.9, 21.2, 17.9



85

Epoxide 85: To a 200 mL round-bottom flask equipped with a stir bar was added alkene **86** (987.5 mg, 4.32 mmol) in 37.8 mL of a 2:1 v/v solution of DMM:CH_3CN. A 0.05 M solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4 x 10^{-4} M Na_2EDTA (25 mL), $n$$Bu_4HSO_4$ (40.9 mg, 0.12 mmol), and chiral ketone **62** (347.7 mg, 0.1.35 mmol) were added. The biphasic mixture was stirred vigorously at room temperature. Two solutions (Oxone (2.85 g, 4.64 mmol) in 4x10^{-4} M Na_2EDTA (21.7 mL) and a 0.89 M solution of K_2CO_3 (21.7 mL)) were added simultaneously via syringe pump over 35 min. The reaction was stirred for an additional 30 min and then diluted with water and stirred for an additional 10 min. The aqueous layer was extracted with CH_2Cl_2 (3x) and then the organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil was purified by column chromatography (20 to 30% EtOAc in hexanes) to furnish epoxide **85** (894.5 mg, 0.3.66 mmol, 85% yield) as colorless oil.

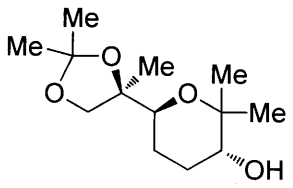
^{1}H NMR (400 MHz; $CDCl_3$): δ 4.03 (d, J = 8.5, 1H), 3.67 (d, J = 8.4, 1H), 3.59 (d, J = 10.8, 1H), 2.74 (dd, J = 7.8, 4.5, 1H), 2.52 (d, J = 2.1, 1H), 1.88 (ddt, J = 13.9, 9.4, 4.7, 1H), 1.73 (dddd, J = 12.8, 10.9, 6.1, 2.1, 1H), 1.57-1.48 (m, 1H), 1.42 (s, 3H), 1.37 (s, 3H), 1.40-1.34 (m, 1H), 1.30 (s, 3H), 1.27 (s, 3H), 1.26 (s, 3H)

^{13}C NMR (100 MHz; $CDCl_3$): δ 109.6, 83.8, 74.4, 70.6, 64.6, 58.7, 28.5, 27.6, 26.9, 26.2, 25.0, 21.7, 18.9

$[\alpha]^{24}_D$ = +3.8 (c 2.5, $CHCl_3$).

IR (NaCl, thin film): 3472, 2984, 2874, 1457, 1379, 1253, 1213, 1118, 1056.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{13}H_{24}O_4Na$, 267.1567; found, 267.1566.



95

Tetrahydropyran 95: To a 10 mL round-bottom flask equipped with a stir bar was added epoxy alcohol **85** (46.0 mg, 0.188 mmol) in 3.5 mL of CH_2Cl_2. The reaction was cooled to –78 °C and then BF_3•OEt_2 (23 *u*L, 0.186 mmol) was added dropwise and the reaction was stirred at this temperature for 1 h. The reaction was quenched with saturated NH_4Cl and extracted with CH_2Cl_2 (3x). The organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified by Biotage (10g column) to furnish acetonide **95** (4.6 mg, 0.019 mmol, 10% yield) along with diol **96** (27.6 mg, 0.113 mmol, 60% yield)

THF **95:**

^1H (500 MHz, $CDCl_3$, δ): 4.03 (d, 8.5 Hz, 1H), 3.67 (d, 8.4 Hz, 1H), 3.59 (d, 10.8 Hz, 1H), 2.75 (dd, 4.5, 7.8 Hz, 1H), 2.52 (bd, 2.1 Hz, 1H), 1.89 (m, 1H), 1.73 (m, 1H), 1.53 (m, 1H), 1.42 (s, 3H), 1.37 (m, 1H), 1.37 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H), 1.26 (s, 3H).

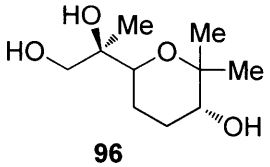
^{13}C (125 MHz, $CDCl_3$, δ): 109.6, 82.2, 75.4, 74.8, 73.8, 73.6, 28.6, 28.5, 27.4, 27.1, 25.5, 19.8, 16.7.

$[\alpha]^{24}_D$ = +18.3 (c 0.1, $CHCl_3$).

IR (NaCl, thin film): 3441, 2984, 2937, 2873, 1454, 1371, 1259, 1210, 1162, 1057.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{13}H_{24}O_4Na$, 267.1567; found, 267.1569.

Diol **96:**

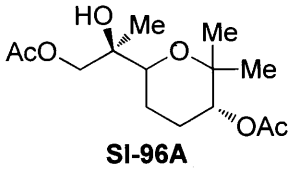


96

^1H NMR (600 MHz; $CDCl_3$): δ 3.79 (d, J = 11.2, 1H), 3.57 (dd, J = 12.1, 2.1, 1H), 3.43 (dd, J = 11.6, 4.7, 1H), 3.37-3.35 (m, 1H), 3.10 (s, 1H), 2.87-2.86 (m, 1H), 1.91 (td, J = 8.3, 4.2, 1H), 1.77-1.74 (m, 1H), 1.59 (ddd, J = 24.7, 12.9, 4.1, 1H), 1.46 (td, J = 12.7, 4.1, 1H), 1.28 (s, 3H), 1.18 (s, 3H), 1.08 (s, 3H)

^{13}C NMR (150 MHz; $CDCl_3$): δ 76.5, 74.3, 72.8, 72.2, 67.7, 28.5, 28.4, 26.3, 20.9, 16.4

Diol 96 also characterized as the diacetate (**SI-96A**) (Ac_2O, Et_3N, DMAP, CH_2Cl_2)

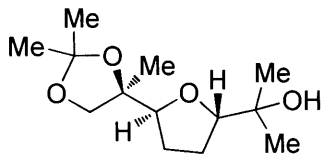


SI-96A

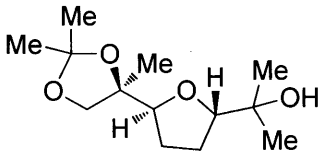
^1H NMR (600 MHz; $CDCl_3$): δ 4.58 (dt, J = 7.1, 3.1, 1H), 4.15 (d, J = 11.3, 1H), 3.99 (d, J = 11.3, 1H), 3.50 (d, J = 10.7, 1H), 2.49 (s, 1H), 2.10 (s, 3H), 2.04 (s, 3H), 1.98-1.96 (m, 1H), 1.75 (dd, J = 6.4, 2.8, 1H), 1.57 (q, J = 8.3, 2H), 1.20 (s, 3H), 1.16 (s, 3H), 1.16 (s, 3H)

^{13}C NMR (150 MHz; $CDCl_3$): δ 171.3, 170.6, 75.6, 74.3, 73.8, 72.8, 68.5, 28.3, 25.0, 24.8, 21.5, 21.2, 20.3, 17.7

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{14}H_{25}O_6$, 289.1646; found, 289.1655.



97a



97b

THF 97: Epoxy alcohol **85** (48.0 mg, 0.196 mmol) was dissolved in 2 mL of MeOH in a 20 mL vial with stir bar. Cesium carbonate (95.4 mg, 0.293 mmol) was added and the reaction was stirred at room temperature for 10 h. The solvent was removed *in vacuo* and the residue was dissolved in EtOAc and saturated NH_4Cl. The aqueous layer was extracted with EtOAc (3x) and then the organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil was purified by Biotage (10 g) to furnish a 4:1 mixture of THF **97a:97b** (45.6 mg, 0.187 mmol, 95% yield) as colorless oil.

NMR data for the major diastereomer **97a**:

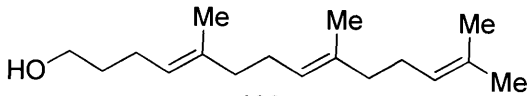
^1H (500 MHz, $CDCl_3$, δ): 4.03 (d, 8.5 Hz, 1H), 3.67 (d, 8.4 Hz, 1H), 3.59 (d, 10.8 Hz, 1H), 2.75 (dd, 4.5, 7.8 Hz, 1H), 2.52 (bd, 2.1 Hz, 1H), 1.89 (m, 1H), 1.73 (m, 1H), 1.53 (m, 1H), 1.42 (s, 3H), 1.37 (m, 1H), 1.37 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H), 1.26 (s, 3H).

^{13}C (125 MHz, $CDCl_3$, δ): 109.8, 86.9, 83.3, 83.0, 72.5, 72.3, 71.5, 28.1, 27.6, 27.2, 27.1, 27.0, 24.3, 21.1.

$[\alpha]^{24}_D = -3.7$ (c 1.3, $CHCl_3$).

IR (NaCl, thin film): 3473, 2980, 2874, 1460, 1371, 1257, 1210, 1072.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{13}H_{24}O_4Na$, 267.1572; found, 267.1578.



103

Primary alcohol 103: To a flame-dried 2 L flask with stir bar under N_2, *trans,trans*-farnesol (30.3518 g, 136.5 mmol) was dissolved in 1.2 L of hexane and cooled to 0°C. To this solution, phosphorus tribromide (6.5 mL, 68.9 mmol) was added dropwise and the reaction was stirred for 1 h at this temperature. The reaction was diluted with diethyl ether, washed with saturated $NaHCO_3$ and saturated NaCl, dried over $MgSO_4$ and concentrated *in vacuo* to provide known farnesyl bromide **101**[4] as a yellow oil. Product was carried forward without further purification.

To a flame-dried 500 mL flask with stir bar under N_2, diisopropylamine (32 mL, 227 mmol) was dissolved in 92 mL of THF. *n*BuLi (88 mL, 2.55 M in hexanes, 224 mmol) was added dropwise over 5 min and the reaction was stirred for 2 h at 0 °C then warmed to room temperature. To a flame-dried 1 L flask equipped with a stir bar under N_2, ethyl acetate (21.9 mL, 224 mmol) was dissolved in 400 mL of THF and cooled to –104°C. Copper iodide (85.65 g, 450 mmol) was added. A solution of lithium diisopropylamine (212 mL, 1.057 M solution in THF/hexane, 224 mmol) was added dropwise over 20 min and stirred for 10 min. The reaction was slowly warmed to –40°C and transferred to an acetonitrile bath. A solution of farnesyl bromide (~136 mmol) in 90 mL of THF was added by cannula. After stirring for 3 h at this temperature, the reaction was poured into 1 L of water and then 500 g of NH_4Cl was added until the solution turned dark blue. The reaction was extracted with hexanes (400 mL, 5x), dried over $MgSO_4$, filtered through Celite, and concentrated *in vacuo*. The product ester was obtained as colorless oil (35.5 g, 121 mmol, 89% yield) and used without further purification.

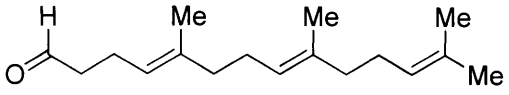
To a flame-dried 250 mL flask equipped with a stir bar under N_2 was added the previously synthesized ester (3.212g, 11.0 mmol) and dissolved in 100 mL of diethyl ether and cooled to 0°C. Lithium aluminum hydride (435.6 mg, 11.5 mmol) was added slowly in small portions to prevent vigorous heating over 5 min. The reaction was quenched with water (440 *u*L), 15% aq NaOH (440 *u*L), and then water (1.32 mL) and warmed to room temperature. $MgSO_4$ was added and the reaction mixture was filtered through Celite and concentrated *in vacuo* to provide a clear colorless oil of **103** (2.325g, 9.28 mmol, 84% yield).

^{1}H NMR (500 MHz; $CDCl_3$): δ 5.15 (ddd, J = 8.4, 6.0, 1.2, 1H), 5.12-5.08 (m, 2H), 3.65 (t, J = 6.4, 2H), 2.11-2.04 (m, 6H), 1.99 (dt, J = 13.9, 7.2, 5H), 1.69 (d, J = 1.1, 3H), 1.65-1.64 (m, 2H), 1.63 (s, 3H), 1.60 (s, 6H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 136.5, 135.7, 132.0, 125.1, 124.8, 124.4, 63.5, 40.4, 33.5, 27.4, 27, 3, 26.4, 25.0, 18.4, 16.7, 17.0.

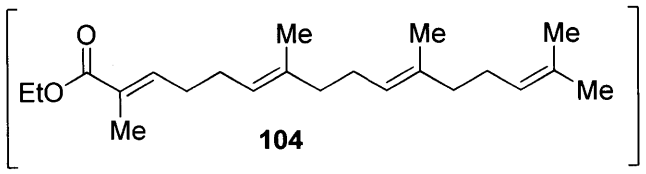
IR (NaCl, thin film): 3333, 2925, 1444, 1382, 1057.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{17}H_{30}ONa$, 273.2189; found, 273.2193.



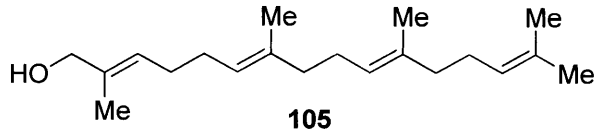
99

To a flame-dried 250 mL flask equipped with a stir bar under N_2 was added the previously synthesized alcohol **103** (2.325g, 9.28 mmol) and dissolved in 100 mL of CH_2Cl_2 and cooled to 0°C. Triethylamine (3.1 mL, 22.2 mmol) and DMSO (3.3 mL, 46.4 mmol) were both added followed by SO_3•pyridine (1.767g, 11.1 mmol) in small portions. The reaction was allowed to warm to room temperature overnight. The reaction was quenched with saturated NH_4Cl and extracted with CH_2Cl_2 (3x). The organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Column chromatography (10% EtOAc in hexanes) was used to purify the aldehyde (R_f=0.61 in 20% ethyl acetate/hexane) to give colorless oil **99** (1.832g, 73.7 mmol, 79% yield). Spectra matched previously reported data.[5]



104

Ester 104: To a 1 L round-bottom flame-dried flask equipped with a stir bar was added aldehyde **99** (2.75g, 11.1 mmol) followed by benzene (110 mL). (1-Ethoxycarbonylethyldiene)triphenylphosphorane (3.29 g, 9.1 mmol) was added in one portion and the reaction was heated to 40 °C for 10 h. The reaction was cooled to room temperature and the volatiles were removed *in vacuo*. The remaining yellow solid was loaded onto silica gel with CH_2Cl_2 and purified via flash column chromatography (2% to 5% EtOAc in hexanes) to provide **104** (2.86 g, 8.6 mmol, 74% yield) as colorless oil which was used without further purification.



105

Alcohol 105: To a 200 mL round-bottom flame-dried flask equipped with a stir bar was dissolved ester **104** (2.86 g, 8.6 mmol) in Et_2O (64 mL) and cooled to 0 °C. Lithium aluminum hydride (341.0 mg, 9.0 mmol) was added slowly in portions and the reaction was allowed to stir while warming to room temperature for 7.5 h. The reaction was returned to 0 °C and 340 *u*L of water was added, followed by 340 *u*L of 15% NaOH in brine, followed by 1 mL of water. The reaction was allowed to warm to room temperature while stirring for 30 min. $MgSO_4$ was added and stirred for an additional 30 min. The reaction was filtered through Celite (eluting with Et_2O) and then concentrated *in vacuo* to provide colorless oil. The residue was purified via flash

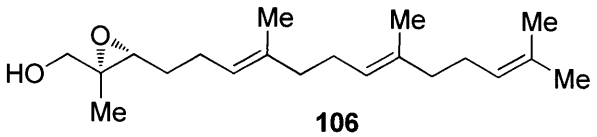
column chromatography (10% to 20% to 30% EtOAc in hexanes) to provide alcohol **105** (1.69 g, 5.82 mmol, 68% yield) as colorless oil.

^{1}H (500 MHz, $CDCl_3$, δ): 5.43 (m, 1H), 5.13 (m, 3H), 4.01 (d, *J*=3.3 Hz, 2H), 2.07 (m, 8H), 2.00 (m, 4H), 1.69 (s, 3H), 1.68 (s, 3H), 1.61 (s, 9H), 1.36 (bs, 1H).

^{13}C (125 MHz, $CDCl_3$, δ): 135.7, 135.2, 135.0, 131.5, 126.4, 124.6, 124.4, 124.1, 69.3, 39.9, 28.1, 27.0, 26.8, 25.9, 17.9, 16.3, 16.2, 13.9.

IR (NaCl, thin film): 3327, 2965, 2856, 2917, 1667, 1444, 1382, 1222, 1007.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{20}H_{34}ONa$, 313.2502; found, 313.2504.



106

Epoxy alcohol 106: To a 100 mL round-bottom flame-dried flask equipped with a stir bar was added 4 Å molecular sieves (1.06 g) and heated under vacuum for 15 min. CH_2Cl_2 (30 mL) was added and the flask was cooled with a CryoCool to –20 °C. Titanium isopropoxide (230 *u*L, 0.76 mmol) and D-(–)-diethyl tartrate (160 *u*L, 0.93 mmol) were added and stirred for 35 min. A solution of *tert*-butyl hydrogen peroxide (5.5 M in decanes, 2.1 mL, 11.5 mmol) was added and stirred for 30 min. A solution of alcohol **105** (1.67 g, 5.75 mmol) in 10 mL of CH_2Cl_2 was added slowly over 20 min. The reaction was stirred at this temperature for 9.5 h. The reaction was quenched by adding 1.45 mL of a 40% solution of NaOH in brine (6.5 mL: 5.85 mL H_2O, 2.6 g NaOH, 325 mg NaCl) and then 10 mL of Et_2O and let warm while stirring for 30 min. 1.5 g of $MgSO_4$ was added along with 150 mg of Celite and stirred for 30 min at room temperature. The reaction was filtered through Celite (eluting with CH_2Cl_2) and concentrated *in vacuo*. The crude oil was purified via flash column chromatography (20 to 30% EtOAc in hexanes) to provide epoxy alcohol **106** (1.10 g, 3.6 mmol, 63% yield) as colorless oil. Enantiomeric excess determined to be 80% via chiral HPLC analysis of the acetonide product **108**.

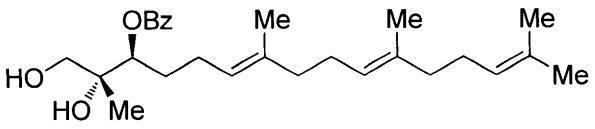
^{1}H (500 MHz, $CDCl_3$, δ): 5.16 (qt, *J*=7.2, 1.2 Hz, 1H), 5.10 (m, 2H), 3.68 (dd, *J*=12.1, 3.4 Hz, 1H), 3.56 (dd, *J*=12.1, 7.9 Hz), 3.05 (t, *J*=6.5 Hz, 1H), 1.94-2.24 (m, 10H), 1.91 (bs, 1H), 1.68 (s, 3H), 1.54-1.67 (m, 2H), 1.62 (s, 3H), 1.60 (s, 6H), 1.28 (s, 3H).

^{13}C (125 MHz, $CDCl_3$, δ): 136.4, 135.3, 131.5, 124.5, 124.2, 123.2, 65.6, 61.2, 60.1, 39.9, 28.6, 26.9, 26.8, 25.9, 25.0, 17.9, 16.2, 14.5.

$[\alpha]^{24}_D$ = +13.3 (c 1.0, $CHCl_3$).

IR (NaCl, thin film): 3425, 2918, 2854, 1441, 1380, 1033.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{20}H_{34}O_2Na$, 329.2451; found, 329.2437.



107

Benzoate 107: To a 100 mL round-bottom flame-dried flask equipped with a stir bar was dissolved epoxy alcohol **106** (1.08 g, 3.5 mmol) in 30 mL of chloroform. 5.6 mL of a solution of benzoic acid and titanium isopropoxide in $CHCl_3$ was added (To a 50 mL round-bottom flask equipped with a stir bar was added (3.28 g, 26.9 mmol) followed by 24.4 mL of $CHCl_3$ and $Ti(O^iPr)_4$ (7.4 mL, 24.4 mmol). The flask was stirred for 30 min at room temperature and the dissolved solution added to the previous reaction.). The reaction was stirred at room temperature for 42 h before concentrating *in vacuo*. Equal volumes of Et_2O and 10% citric acid solutions were added and stirred for 1 h. The aqueous layer was extracted with Et_2O (3x) and then washed with $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude white milky oil was purified via the Biotage (50 g column) to provide benzoate **107** (929 mg, 61% yield) as colorless oil.

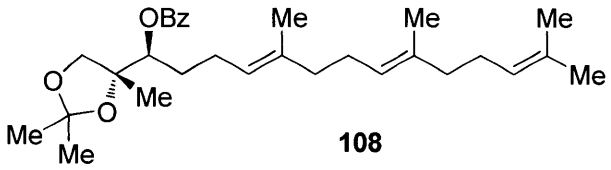
^1H NMR (400 MHz; $CDCl_3$): δ 8.07 (dd, J = 8.3, 1.4, 2H), 7.63-7.58 (m, 1H), 7.50-7.45 (m, 2H), 5.13-5.04 (m, 4H), 3.48 (dd, J = 11.8, 3.8, 1H), 3.37 (d, J = 4.1, 1H), 3.30-3.27 (m, 1H), 2.94 (s, 1H), 2.10-1.91 (m, 12H), 1.82 (t, J = 5.3, 1H), 1.68 (d, J = 1.1, 3H), 1.60 (d, J = 0.5, 3H), 1.58 (d, J = 1.0, 3H), 1.52 (d, J = 0.8, 3H), 1.15 (s, 3H)

^{13}C NMR (100 MHz; $CDCl_3$): δ 168.0, 136.4, 135.1, 133.7, 131.4, 130.0, 129.6, 128.7, 124.6, 124.3, 123.2, 76.0, 73.6, 67.0, 39.9, 39.8, 28.5, 26.9, 26.7, 25.9, 25.1, 17.9, 17.9, 16.2, 16.2

$[\alpha]^{24}_D = -34.6$ (c 3.4, $CHCl_3$)

IR (NaCl, thin film): 3436, 2966, 2926, 1721, 1700, 1602, 1585, 1451, 1377, 1278, 1177, 1118, 1026, 848, 711

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{27}H_{40}O_4Na$, 451.2819; found, 451.2807.



108

Acetonide 108: To a 25 mL round-bottom flame-dried flask equipped with a stir bar was added benzoate **107** (861.1 mg, 2.01 mmol) in CH_2Cl_2 (6.1 mL) and 2,2-dimethoxypropane (8 mL). (±)-CSA (55.1 mg, 0.24 mmol) was added and the reaction was stirred for 5 h at room temperature. Additional CH_2Cl_2 was added and then washed with saturated $NaHCO_3$. The organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil was purified via Biotage (50 g column) to provide acetonide **108** (743.2 mg, 79% yield) as colorless oil.

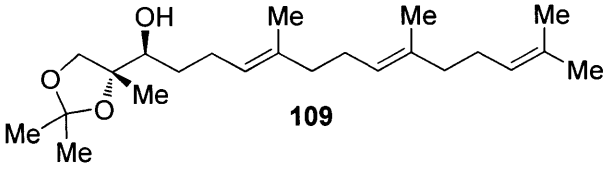
^{1}H NMR (400 MHz; $CDCl_3$): δ 8.08-8.06 (m, 2H), 7.60-7.56 (m, 1H), 7.48-7.44 (m, 2H), 5.26 (dd, J = 10.3, 2.6, 1H), 5.14-5.07 (m, 3H), 4.02 (d, J = 8.7, 1H), 3.72 (d, J = 8.6, 1H), 2.06 (dt, J = 11.0, 7.6, 6H), 2.01-1.92 (m, 5H), 1.68 (d, J = 1.1, 4H), 1.60 (d, J = 0.6, 3H), 1.58 (d, J = 1.0, 3H), 1.54 (d, J = 1.0, 3H), 1.41 (s, 3H), 1.39 (s, 3H), 1.34 (s, 3H)

^{13}C NMR (100 MHz; $CDCl_3$): δ 166.2, 136.3, 135.2, 133.2, 131.5, 130.4, 129.9, 128.6, 124.6, 124.4, 123.4, 110.2, 82.3, 72.6, 39.9, 39.88, 30.3, 27.3, 27.0, 27.0, 26.8, 25.9, 24.8, 21.4, 17.9, 16.3, 16.2

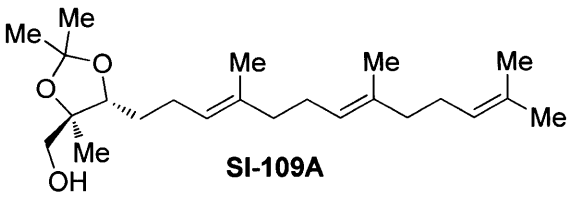
$[\alpha]^{24}_D = -8.9$ (c 6.0, $CHCl_3$).

IR (NaCl, thin film): 2983, 2931, 1724, 1603, 1451, 1378, 1271, 1110, 1068, 1027.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{30}H_{44}O_4Na$, 491.3132; found, 491.3121.



109



SI-109A

Acetonide 109: To a 50 mL round-bottom flame-dried flask equipped with a stir bar was added benzoate **108** (617.4 mg, 1.32 mmol) in MeOH (13 mL) and THF (5 mL). Potassium carbonate (237.5 mg, 1.72 mmol) was added and the reaction was stirred for 8 h at room temperature. The solvents were concentrated *in vacuo* and then the crude residue was dissolved in CH_2Cl_2 and saturated NH_4Cl was added to quench the remaining carbonate. The aqueous layer was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil was purified via the Biotage (50g column) to provide acetonide **109** (331.4 mg, 69% yield) as colorless oil. Acetonide migration product **SI-109A** (47.2 mg, 10% yield) was obtained as well under the reaction conditions.

Acetonide **109**:

^1H (500 MHz, $CDCl_3$, δ): 5.12 (m, 3H) , 4.04 (d, *J*=8.4 Hz, 1H), 3.66 (d, *J*=8.4 Hz, 1H), 3.55 (ddd, *J*=10.7, 2.9, 2.1, 1H), 2.23 (dd, *J*=3.0, 1.2 Hz, 1H), 2.30-1.94 (m, 11H), 1.68 (s, 3H), 1.64 (s, 3H), 1.60 (s, 6H), 1.56 (m, 1H), 1.45 (s, 3H), 1.39 (s, 3H), 1.26 (s, 3H).

^{13}C (125 MHz, $CDCl_3$, δ): 136.4, 135.3, 131.5, 124.6, 124.3, 123.9, 109.5, 84.0, 74.4, 70.4, 39.9, 31.5, 27.7, 27.0, 26.8, 25.9, 25.2, 21.9, 17.9, 16.3, 16.2.

$[\alpha]^{24}_D = -8.2$ (c 2.0, $CHCl_3$).

IR (NaCl, thin film): 3492, 2983, 2926, 1452, 1378, 1255, 1214, 1114, 1058.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{23}H_{40}O_3Na$, 387.2870; found, 387.2880.

SI-109A:

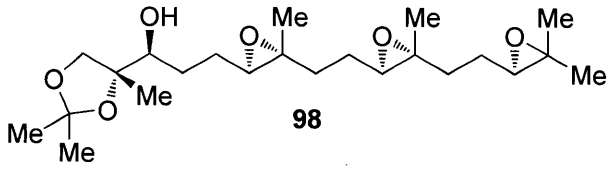
^1H (500 MHz, $CDCl_3$, δ): 5.11 (m, 3H), 3.83 (dd, *J*=10.0, 3.1 Hz, 1H), 3.57 (dd, *J*=10.9, 3.3 Hz, 1H), 3.32 (dd, *J*=10.9, 9.3 Hz, 1H), 2.25-1.87 (m, 12H), 1.68 (s, 3H), 1.65 (m, 1H), 1.63 (s, 3H), 1.60 (s, 6H), 1.45 (s, 3H), 1.38 (s, 3H), 1.27 (s, 3H).

^{13}C (125 MHz, $CDCl_3$, δ): 136.6, 135.3, 131.5, 124.5, 124.3, 123.4, 107.4, 82.3, 82.0, 65.5, 39.9, 28.6, 28.0, 27.0, 26.8, 26.6, 25.9, 25.5, 21.2, 17.9, 16.3, 16.2.

$[\alpha]^{24}_D = -1.6$ (c 2.4, $CHCl_3$).

IR (NaCl, thin film): 3477, 2983, 2930, 1446, 1378, 1247, 1216, 1108, 1053, 1002.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{23}H_{40}O_3Na$, 387.2870; found, 387.2886.



98

Triepoxide 98: To a 125 mL Erlenmeyer flask with stir bar was added triene **109** (292.4 mg, 0.802 mmol) in 21 mL of a 2:1 v/v solution of DMM:CH_3CN. A 0.05 M solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4 x 10^{-4} M Na_2EDTA (14 mL), $n$$Bu_4HSO_4$ (21 mg, 0.06 mmol), and chiral ketone **62** (178.7 mg, 0.692 mmol) were added. The biphasic mixture was stirred vigorously at room temperature. Two solutions (Oxone (1.6007 g, 2.60 mmol) in $4x10^{-4}$ M Na_2EDTA (11.9 mL) and a 0.89 M solution of K_2CO_3 (11.9 mL)) were added simultaneously via syringe pump over 35 min. The reaction was stirred for an additional 30 min and then diluted with 60 mL of water and stirred for 1 h. The aqueous layer was extacted with CH_2Cl_2 (3x) and then the organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil was purified by Biotage (50 g) to furnish triepoxide **98** (316.6 mg, 0.767 mmol, 96% yield) as colorless oil.

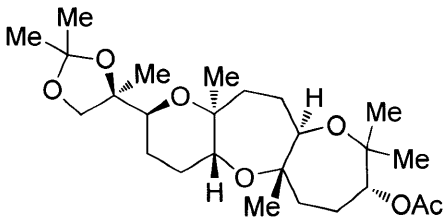
^1H NMR (400 MHz; $CDCl_3$): δ 4.01 (d, J = 8.5, 1H), 3.66 (d, J = 8.5, 1H), 3.56 (dd, J = 8.4, 2.4, 1H), 2.76-2.66 (m, 3H), 2.50 (d, J = 3.0, 1H), 1.86 (dt, J = 9.2, 4.6, 1H), 1.77-1.68 (m, 3H), 1.67-1.50 (m, 8H), 1.41 (s, 3H), 1.35 (s, 3H), 1.28 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H), 1.24 (s, 3H)

^{13}C NMR (100 MHz; $CDCl_3$): δ 109.6, 83.8, 74.4, 70.6, 64.0, 63.4, 62.8, 60.6, 60.5, 58.6, 35.3, 28.5, 27.6, 26.9, 26.1, 25.0, 24.7, 24.5, 21.6, 18.8, 16.9, 16.8

$[\alpha]^{24}_D$ = +15.1 (c 2.8, $CHCl_3$)

IR (NaCl, thin film): 3487, 2982, 2933, 2872, 1645, 1458, 1379, 1324, 1253, 1213, 1118, 1056, 984, 913, 857, 808, 677

HRMS-ESI (m / z): $[M + H]^+$ calcd for $C_{23}H_{41}O_6$, 413.2898; found, 413.2902.



110

Tricycle acetate 110: To a 100 mL round-bottom flask equipped with a stir bar was added triepoxide **98** (363.5 mg, 1.07 mmol) in 22 mL of CH_2Cl_2. The flask was cooled to –78 °C and then BF_3•OEt_2 (67 *u*L, 0.543 mmol) was added dropwise. The reaction was stirred for 1 h at this temperature and then allowed to warm to room temperature. The reaction was quenched by the addition of saturated NH_4Cl, and then the aqueous layers were extracted with CH_2Cl_2 (3x). The organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was used without purification for the acetate protection.

To a 50 mL round-bottom flask equipped with a stir bar was added crude alcohol (364 mg) in 11 mL of CH_2Cl_2. Triethyl amine (600 *u*L, 5.44 mmol) and acetic anhydride (205 *u*L, 2.17 mmol) were added followed by the addition of DMAP (10 mg, 0.082 mmol). The reaction was stirred at room temperature for 16 h and then quenched with saturated NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (3x) and then the organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (5 to 20% EtOAc in hexanes) to furnish acetate **110** (52.5 mg, 0.138 mmol, 13% yield) as colorless oil.

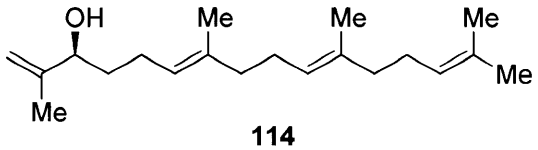
^{1}H NMR (600 MHz; $CDCl_3$): δ 4.91 (d, J = 6.7, 1H), 3.97 (d, J = 8.4, 1H), 3.67 (d, J = 8.3, 1H), 3.54 (dd, J = 11.4, 4.2, 1H), 3.46 (d, J = 11.5, 1H), 3.35 (d, J = 11.8, 1H), 2.12 (s, 3H), 2.07-2.01 (m, 2H), 1.88-1.79 (m, 3H), 1.79-1.63 (m, 5H), 1.52-1.47 (m, 2H), 1.38 (s, 3H), 1.37 (s, 3H), 1.25 (s, 3H), 1.22 (s, 6H), 1.15 (s, 3H), 1.14 (s, 3H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 170.3, 109.6, 82.3, 78.8, 78.7, 78.1, 77.3, 77.2, 73.8, 73.6, 70.6, 40.6, 36.8, 29.2, 28.9, 27.6, 27.4, 27.1, 25.7, 23.2, 21.8, 21.3, 20.2, 20.0, 16.5

$[\alpha]^{24}_D$ = +18.1 (c 0.34, $CHCl_3$)

IR (NaCl, thin film): 2982, 2937, 2872, 1741, 1453, 1371, 1241, 1211, 1085, 1029

HRMS-ESI (m / z): $[M + H]^+$ calcd for $C_{25}H_{43}O_7$, 455.3003; found, 455.3008.



114

Allylic alcohol 114: To a 25 mL round-bottom flask equipped with a stir bar was added (+)-MIB[6] (33.3 mg, 0.139 mmol) and transferred into a wet box. Added diisopropenyl zinc **115**[7] (573.5 mg, 0.3.89 mmol) and 10 mL of toluene and stirred for a few min. Added $ZnEt_2$ (1.1 mL, 10.5 mmol) and transferred out of a glove box and into a hood under N_2. The reaction was cooled in an ice bath to 0°C and then a solution of **99** (855.5 mg, 3.44 mmol) in 5 mL of toluene and added slowly to the reaction. The reaction was stirred at 0°C for 20 h. The reaction was quenched with 15 mL of saturated NH_4Cl and warmed to room temperature. The aqueous layer was extracted with Et_2O(3x, 40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The reaction mixture was purified by column chromatography (10% EtOAc in hexanes) to give **114** (809.3 mg, 2.79 mmol, 81% yield) as colorless oil.

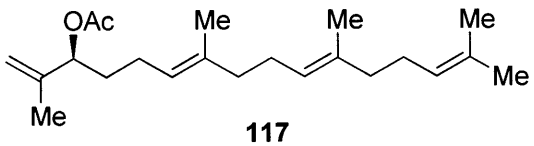
^1H NMR (500 MHz; $CDCl_3$): δ 5.16 (ddd, J = 8.4, 6.0, 1.2, 1H), 5.13-5.08 (m, 2H), 4.08 (td, J = 5.9, 4.4, 1H), 2.11-2.05 (m, 5H), 2.03-1.97 (m, 4H), 1.74 (t, J = 1.1, 3H), 1.69 (d, J = 1.2, 3H), 1.63 (d, J = 0.9, 3H), 1.61 (s, 6H), 1.62-1.57 (m, 1H), 1.52 (d, J = 3.9, 1H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 147.8, 136.0, 135.3, 131.5, 124.6, 124.3, 124.0, 111.2, 75.9, 39.9, 35.2, 27.0, 26.8, 25.9, 24.4, 17.9, 17.9, 16.3, 16.2

$[\alpha]^{24}_D = -2.6$ (c 0.23, $CHCl_3$)

IR (NaCl, thin film): 3368, 2926, 1653, 1559, 1540, 1457, 1057, 897

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{20}H_{34}ONa$, 313.2502; found, 313.2509.



117

Acetate 117: To a 20 mL vial equipped with a stir bar was added **114** (151 mg, 0.520 mmol) and dissolved in 5.2 mL of CH_2Cl_2. To the vessel was added Ac_2O (100 *u*L, 1.06 mmol) and Et_3N (290 *u*L, 2.08 mmol) followed by two crystals of DMAP. The reaction was stirred for two h before being quenched with saturated NH_4Cl and extracting with CH_2Cl_2 (3x). The organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The reaction mixture was purified by column chromatography to provide colorless oil of **117** (183 mg, 0.550 mmol, 95% yield).

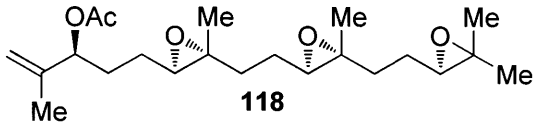
^{1}H NMR (500 MHz; $CDCl_3$): δ 5.16 (dd, J = 7.4, 6.1, 1H), 5.13-5.09 (m, 3H), 4.95 (t, J = 0.8, 1H), 4.89 (t, J = 1.6, 1H), 2.10-2.05 (m, 4H), 2.07 (s, 3H), 2.01-1.96 (m, 6H), 1.73 (t, J = 0.9, 3H), 1.69 (d, J = 0.8, 3H), 1.66-1.63 (m, 2H), 1.61 (s, 6H), 1.59 (s, 3H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 170.5, 143.4, 136.1, 135.2, 131.4, 124.6, 124.3, 123.4, 112.8, 77.2, 39.9, 39.9, 27.0, 26.8, 25.9, 24.1, 21.4, 18.3, 17.9, 16.2, 16.2

$[\alpha]^{24}_D$ = –6.6 (c 2.2, CDCl3) (77% ee)

IR (NaCl, thin film): 2967, 2922, 2956, 1742, 1653, 1437, 1370, 1238, 1021, 902, 834

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{22}H_{36}O_2Na$, 355.2608; found, 355.2613.



118

Triepoxide 118: To a 20 mL vial equipped with a stir bar was added a solution of acetate **117** (183 mg, 0.550 mmol) in 15 mL of 2:1 DMM/CH_3CN and 15 mL of EDTA buffer. nBu_4NHSO_4 (10 mg, 29.5 *u*mol) was added and the reaction was vigorously stirred followed by the addition of Shi ketone **62** (79 mg, 0.306 mmol). A solution of Oxone (1.002 g, 1.63 mmol) in 6.5 mL of EDTA solution and a solution of 9.5 mL of 0.89 M K_2CO_3 were added dropwise side-by-side over 25 min. The reaction was allowed to stir for an additional 30 min before equiv volume of water was added. The reaction was extracted with CH_2Cl_2 (3x) and dried over Na_2SO_4. The reaction was filtered and concentrated *in vacuo* and purified by column chromatography to provide colorless oil **118** (98 mg, 0.258 mmol, 47% yield).

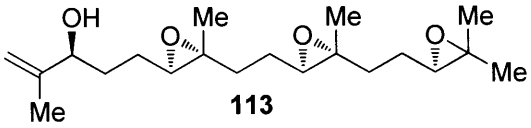
^1H NMR (400 MHz; $CDCl_3$): δ 5.18 (q, J = 7.1, 1H), 4.92 (dt, J = 18.6, 1.1, 2H), 2.75-2.68 (m, 3H), 2.06 (s, 3H), 1.72 (s, 3H), 1.90-1.42 (m, 12H), 1.30 (s, 3H), 1.27 (s, 3H), 1.27 (s, 3H), 1.26 (s, 3H)

^{13}C NMR (100 MHz; $CDCl_3$): δ 170.4, 142.9, 113.2, 64.0, 62.8, 62.76, 60.6, 60.5, 60.5, 58.6, 35.4, 35.3, 29.7, 25.0, 24.8, 24.78, 24.6, 21.4, 18.9, 18.4, 16.9, 16.8

$[\alpha]^{24}_D = +13.9$ (c 1.2, $CHCl_3$)

IR (NaCl, thin film): 2964, 2930, 1739, 1457, 1378, 1240, 1022, 900

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{22}H_{36}O_5Na$, 403.2455; found, 403.2437.



113

Allylic alcohol 113. To a 20 mL vial equipped with a stir bar was added **118** (99 mg, 0.240 mmol) and cooled to 0°C. Lithium hydroxide (36 mg, 0.250 mmol) in a 1:1:1 solution of THF/MeOH/H_2O (700 *u*L) was added and the reaction was stirred for 1.5 h and then quenched with saturated NH_4Cl. The reaction was extracted 3x with Et_2O and then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The reaction was purified by column chromatography to provide colorless oil **113** (45 mg, 0.133 mmol, 55% yield) along with **THF SI-113A**.

113:

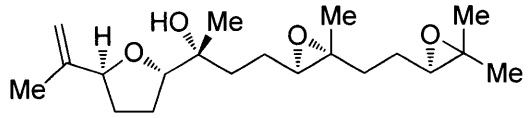
^1H NMR (500 MHz; $CDCl_3$): δ 4.96 (dt, J = 1.7, 0.9, 1H), 4.85 (d, J = 0.9, 1H), 4.13-4.11 (m, 1H), 2.81-2.68 (m, 3H), 1.73 (d, J = 0.5, 3H), 1.79-1.55 (m, 12H), 1.30 (s, 3H), 1.29 (s, 3H), 1.27 (s, 3H), 1.26 (s, 3H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 147.5, 111.2, 75.3, 64.0, 63.4, 62.8, 60.7, 60.6, 58.7, 35.4, 32.0, 25.0, 25.0, 24.8, 24.6, 18.9, 18.8, 18.1, 16.9, 16.8

$[\alpha]^{24}_D$ = +10.2 (c 0.73, $CHCl_3$)

IR (NaCl, thin film): 3452, 2966, 1653, 1559, 1457, 1386, 1251, 1068, 897

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{20}H_{34}O_4Na$, 361.2349; found, 361.2355.



SI-113A:

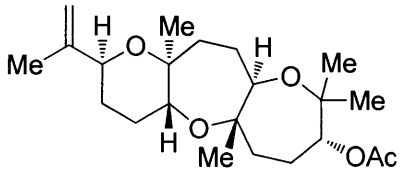
^1H NMR (500 MHz; $CDCl_3$): δ 4.99 (dd, J = 1.9, 1.0, 1H), 4.80 (dt, J = 1.4, 0.7, 1H), 4.38 (dd, J = 8.6, 6.4, 1H), 3.87 (dd, J = 9.2, 6.2, 1H), 2.77 (dd, J = 6.7, 5.8, 1H), 2.72 (t, J = 6.1, 1H), 2.15-2.06 (m, 2H), 1.92-1.84 (m, 2H), 1.82-1.67 (m, 3H), 1.71 (s, 3H), 1.66-1.52 (m, 5H), 1.32 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H), 1.23 (s, 3H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 146.2, 110.0, 86.1, 83.0, 73.1, 64.1, 63.5, 60.7, 58.7, 35.4, 33.8, 32.1, 27.0, 25.1, 24.8, 24.1, 23.2, 18.9, 18.1, 16.9

$[\alpha]^{24}_D$ = –2.6 (c 0.26, $CHCl_3$)

IR (NaCl, thin film): 3465, 2967, 2927, 1653, 1559, 1507, 1457, 1376, 1249, 1076, 955, 896

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{20}H_{34}O_4Na$, 361.2349; found, 361.2361.



119

Acetate 119: To a 100 mL round-bottom flask equipped with a stir bar was added triepoxide **113** (363.5 mg, 1.07 mmol) in 22 mL of CH_2Cl_2. The flask was cooled to –78 °C and then BF_3•OEt_2 (67 *u*L, 0.543 mmol) was added dropwise. The reaction was stirred for 1 h at this temperature and then allowed to warm to room temperature. The reaction was quenched by the addition of saturated NH_4Cl and then the aqueous layers were extracted with CH_2Cl_2 (3x). The organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was used without further purification for the acetate protection.

To a 50 mL round-bottom flask equipped with a stir bar was added crude alcohol **112** (364 mg) in 11 mL of CH_2Cl_2. Triethyl amine (600 *u*L, 5.44 mmol) and acetic anhydride (205 *u*L, 2.17 mmol) were added followed by the addition of DMAP (10 mg, 0.082 mmol). The reaction was stirred at room temperature for 16 h and then quenched with saturated NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (3x) and the organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (5 to 20% EtOAc in hexanes) to furnish acetate **119** (52.5 mg, 0.138 mmol, 13% yield) as colorless oil.

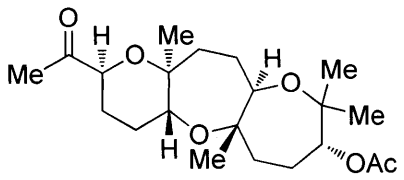
^{1}H NMR (500 MHz; $CDCl_3$): δ 4.96 (t, J = 0.9, 1H), 4.91 (d, J = 6.8, 1H), 4.81 (dd, J = 1.3, 0.6, 1H), 3.90-3.88 (dd, J = 11.8, 1.5, 1H), 3.61 (dd, J = 10.8, 5.3, 1H), 3.47 (dd, J = 11.4, 2.3, 1H), 2.12 (s, 3H), 2.07-2.04 (m, 1H), 1.95 (dq, J = 15.0, 4.5, 1H), 1.87 (ddt, J = 11.8, 6.9, 2.2, 2H), 1.79 (td, J = 13.8, 2.4, 2H), 1.73 (s, 3H), 1.71-1.64 (m, 2H), 1.54-1.42 (m, 4H), 1.29 (s, 3H), 1.26 (s, 3H), 1.16 (s, 3H), 1.14 (s, 3H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 170.8, 146.8, 111.1, 79.3, 79.1, 78.8, 77.8, 77.8, 73.5, 70.8, 41.3, 37.3, 31.4, 29.7, 29.4, 28.5, 23.7, 22.3, 21.8, 20.6, 19.6, 16.9

IR (NaCl, thin film): 2879, 2938, 1741, 1457, 1375, 1240, 1075

$[\alpha]^{24}_D$ = +13.3 (c 0.65, $CHCl_3$)

HRMS-ESI (m / z): $[M + H]^+$ calcd for $C_{22}H_{37}O_5$, 381.2636; found, 381.2642.



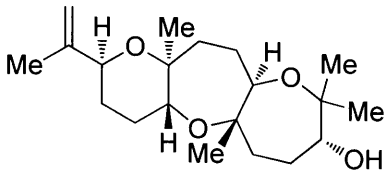
120

Ketone 120: To a 20 mL vial equipped with stir bar was added acetate **119** (67.7.6 mg, 0.178 mmol) in 2 mL of CH_2Cl_2. The reaction was cooled to –78 °C and subjected to ozone until the reaction turned light blue (~5 min). Oxygen was bubbled through the solution for 2 min, followed by nitrogen for 1 min. The reaction was quenched by the addition of triphenylphosphine (53.4 mg, 0.204 mmol) and allowing the reaction to warm to room temperature for 1 h. Reaction was concentrated *in vacuo* and the reaction was loaded directly onto a silica gel column. The crude reaction mixture was purified by column chromatography (20% EtOAc in hexanes) to furnish ketone **120** (50.5 mg, 0.132 mmol, 74% yield) as colorless oil.

^{1}H NMR (500 MHz; $CDCl_3$): δ 4.92 (d, J = 6.7, 1H), 3.92 (dd, J = 12.1, 2.8, 1H), 3.61 (t, J = 8.1, 1H), 3.46 (dd, J = 11.4, 2.4, 1H), 2.18 (s, 3H), 2.12 (s, 3H), 2.19-1.76 (m, 6H), 1.69-1.65 (m, 3H), 1.53-1.41 (m, 3H), 1.26 (s, 6H), 1.16 (s, 3H), 1.15 (s, 3H)

^{13}C NMR (100 MHz; $CDCl_3$): δ 209.9, 170.3, 78.9, 78.6, 78.2, 77.9, 77.4, 76.0, 69.7, 40.5, 36.7, 29.1, 28.9, 28.3, 27.4, 26.0, 23.2, 21.8, 21.3, 19.7, 16.4

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{21}H_{34}O_6Na$, 405.2248; found, 405.2251.



112

Secondary alcohol 112: To a 5 mL flask equipped with a stir bar was added acetate **119** (32.9 mg, 86.5 mmol) in 533 *u*L of MeOH and 1.1 mL of THF. A 1 M solution of LiOH was added (210 *u*L, 210 mmol) and the reaction was stirred at room temperature for 30 min. The reaction was quenched with saturated NH_4Cl and extracted with CH_2Cl_2 (3x). The organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil was purified by column chromatography (20 to 50% EtOAc in hexanes) to furnish alcohol **112** (17.9 mg, 52.9 mmol, 71% yield) as a colorless oil.

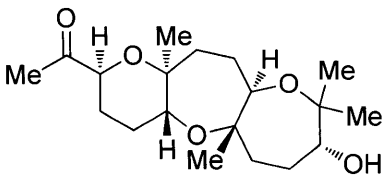
^{1}H NMR (500 MHz; $CDCl_3$): δ 4.96 (t, J = 1.0, 1H), 4.80 (t, J = 1.4, 1H), 3.89 (dd, J = 11.4, 1.3, 1H), 3.76 (ddd, J = 6.1, 4.0, 1.7, 1H), 3.62 (t, J = 3.1, 1H), 3.59 (dd, J = 7.0, 3.8, 1H), 2.08-2.01 (m, 1H), 2.00-1.91 (m, 2H), 1.89 (dd, J = 5.3, 3.7, 1H), 1.84-1.78 (m, 2H), 1.78-1.75 (m, 1H), 1.72 (s, 3H), 1.71-1.67 (m, 1H), 1.65 (dt, J = 5.1, 2.8, 1H), 1.50 (dt, J = 6.9, 3.4, 2H), 1.48-1.45 (m, 1H), 1.45-1.42 (m, 1H), 1.27 (s, 3H), 1.25 (s, 3H), 1.25 (s, 3H), 1.10 (s, 3H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 146.4, 110.6, 79.1, 78.0, 77.9, 77.4, 76.8, 73.0, 70.5, 40.5, 36.1, 30.9, 29.3, 29.1, 27.9, 25.9, 21.7, 19.7, 19.1, 16.6

$[\alpha]^{24}_D$ = +29.8 (c 0.5, $CHCl_3$)

IR (NaCl, thin film): 3432, 2935, 1653, 1559, 1540, 1507, 1457, 1375, 1074, 1034, 889

HRMS-ESI (m / z): $[M + H]^+$ calcd for $C_{20}H_{34}O_4$, 339.2530; found, 339.2526.

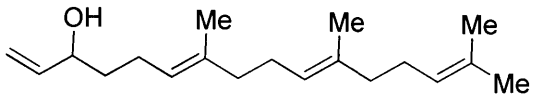


121

Ketone 121: To a 20 mL vial equipped with a stir bar was added alcohol **112** (13.6 mg, 40.2 mmol) in 2 mL of CH_2Cl_2. The reaction was cooled to –78 °C and subjected to ozone until the reaction turned light blue (~5 min). Oxygen was bubbled through the solution for 2 min, followed by nitrogen for 1 min. The reaction was quenched by the addition of triphenylphosphine (17.6 mg, 67.1 mmol) and allowing the reaction to warm to room temperature for 1 h. The reaction was concentrated *in vacuo* and then loaded directly onto a silica gel column. The crude was purified by column chromatography (50% EtOAc in hexanes) to furnish ketone **121** (10.5 mg, 30.8 mmol) as a colorless oil.

^{1}H NMR (500 MHz; $CDCl_3$): δ 3.92 (dd, J = 12.2, 2.9, 1H), 3.78-3.77 (m, 1H), 3.62 (dd, J = 11.5, 2.7, 1H), 3.60-3.58 (m, 1H), 2.18 (s, 3H), 2.07-1.91 (m, 4H), 1.86-1.79 (m, 3H), 1.68 (ddd, J = 11.4, 8.1, 3.6, 2H), 1.52-1.40 (m, 3H), 1.26 (s, 3H), 1.25 (s, 3H), 1.25 (s, 3H), 1.10 (s, 3H)

^{13}C NMR (100 MHz; $CDCl_3$): δ 210.0, 79.2, 78.0, 77.9, 77.4, 76.7, 75.9, 69.9, 40.2, 35.9, 29.2, 29.1, 28.4, 27.4, 26.0, 25.8, 21.7, 19.3, 16.5



(±)-131

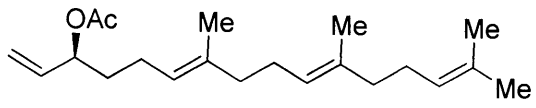
Allylic alcohol (128). Dissolved aldehyde (**99**) (5.85 g, 23.6 mmol) in 200 mL of THF in a 500 mL flame-dried round-bottom flask equipped with a stir bar. Cooled reaction to –10 °C in a acetone/dry ice bath and added solution of vinyl magnesium bromide in THF (50 mL, 1.0 M, 50 mmol) slowly over 5 min. The reaction was allowed to warm to room temperature over 1 h, then was quenched with saturated NH_4Cl and transferred into a separatory funnel. Extracted 3x with Et_2O, washed organic layers with brine, and then dried over $MgSO_4$. Filtered off solids and removed solvent *in vacuo*. Purified reaction by column chromatography (5 to 10% EtOAc/hexanes) to give **(±)-131** (4.73 g, 17.1 mmol, 73% yield) in 10% EtOAc/hexanes) as a colorless oil.

^{1}H NMR (500 MHz; $CDCl_3$): δ 5.88 (dddd, J = 17.0, 10.6, 6.3, 1.2, 1H), 5.23 (dd, J = 17.2, 1.4, 1H), 5.17-5.14 (m, 1H), 5.12-5.08 (m, 3H), 4.12 (d, J = 6.2, 1H), 2.12-2.04 (m, 6H), 1.99 (dt, J = 13.6, 7.0, 4H), 1.68 (s, 3H), 1.62 (s, 3H), 1.60 (s, 6H), 1.58-1.56 (m, 2H)

^{13}C NMR (100 MHz; $CDCl_3$): δ 141.4, 136.1, 135.2, 131.5, 124.6, 124.3, 124.0, 114.7, 73.1, 39.9, 37.2, 27.0, 26.8, 25.9, 24.1, 17.9, 16.3, 16.2

IR (NaCl, thin film): 3364, 2924, 2967, 2855, 1643, 1444, 1382, 1055, 990, 921, 835

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{19}H_{32}ONa$, 228.2345; found, 229.2340.



132

Allylic acetate (132). To a 20 mL vial equipped with a stir bar was added alcohol **131** (571.1 mg, 2.07 mmol) in 1 mL of Et_2O followed by vinyl acetate (950 *u*L, 10.3 mmol). Beads of Novozyme 435 enzyme (33 mg, Aldrich L4777 from Candida antartica) were added and the reaction was stirred for 2.5 h at room temperature and then 13.5 h at 4 °C in the fridge. The reaction was filtered through glass wool and washed with Et_2O (5x). The reaction was concentrated *in vacuo* and then purified by column chromatography (5 to 10% EtOAc/hexanes) to give **132** (263.5 mg, 0.827 mmol, 40% yield, 99% ee) in 10% EtOAc in hexanes) and ***ent*-131** (303.5 mg, 1.10 mmol, 53% yield, 29% ee). Resubjecting ***ent*-131** to the reaction conditions for an additional 16.5 h provided ***ent*-131** in 98% ee.

132:

Chiral HPLC analysis: (Chiralcel OD, hexanes:2-propanol, 210 nm): t_R (*R*) = 10.9 min; t_R (*S*) = 11.4 min. The enantiomeric excess was determined to be 98%.

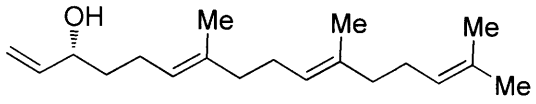
^{1}H NMR (500 MHz; $CDCl_3$): δ 5.78 (ddd, J = 17.1, 10.6, 6.5, 1H), 5.26-5.22 (m, 2H), 5.19-5.16 (m, 1H), 5.13-5.09 (m, 3H), 2.08 (s, 3H), 2.09-2.06 (m, 3H), 2.06-1.96 (m, 7H), 1.69 (d, J = 1.1, 3H), 1.68-1.62 (m, 2H), 1.61 (s, 3H), 1.60 (s, 3H), 1.59 (s, 3H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 170.6, 136.7, 136.2, 135.2, 131.5, 124.6, 124.3, 123.3, 116.8, 74.7, 39.93, 39.90, 34.5, 26.96, 26.78, 25.9, 23.8, 21.5, 17.9, 16.23, 16.20

$[\alpha]^{24}_D = -3.1$ (c 0.17, $CHCl_3$)

IR (NaCl, thin film): 2924, 1996, 1741, 1653, 1540, 1457, 1374, 1237

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{21}H_{34}O_2Na$, 341.2451; found, 341.2455.

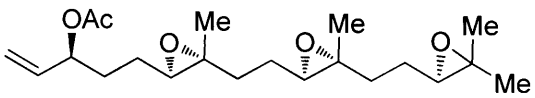


***ent*-131**

***ent*-131**:

Chiral HPLC analysis of the benzonate derivative (BzCl, Et_3N, DMAP, CH_2Cl_2): (Chiralcel OB-H, hexanes:2-propanol): t_R (*S*) = 7.5 min; t_R (*R*) = 8.4 min. The enantiomeric excess was determined to be 98%.

$[\alpha]^{24}_D = -3.4$ (c 1.3, $CHCl_3$)

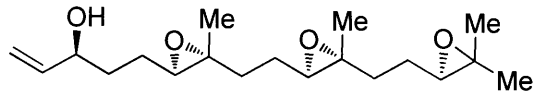


133

Triepoxide 133: To a 250 mL round-bottom flask equipped with a stir bar was added a solution of acetate **132** (260.1 mg, 0.817 mmol) in 37 mL of 2:1 DMM/CH_3CN and 25 mL of EDTA buffer. $n$$Bu_4NHSO_4$ (34.7 mg, 0.102 mmol) was added and the reaction was vigorously stirred followed by the addition of Shi ketone **62** (155.4 mg, 0.602 mmol). A solution of Oxone (2.78 g, 4.52 mmol) in 20.5 mL of EDTA solution and a solution of 20.5 mL of 0.89 M K_2CO_3 were added dropwise side-by-side over 30 min. The reaction was allowed to stir for an additional 30 min before 100 mL of water was added and stirred for an additional 45 min. The reaction was extracted with CH_2Cl_2 (3x) and dried over Na_2SO_4. The reaction was filtered and concentrated *in vacuo* and subjected to column chromatography (20 to 50% EtOAc in hexanes) to provide colorless oil **133** (263.2 mg, 0.718 mmol, 88% yield, 3.5:1 dr).

^1H NMR (500 MHz; $CDCl_3$): δ 5.78 (ddd, J = 17.2, 10.7, 6.4, 1H), 5.29-5.24 (m, 2H), 5.20 (dt, J = 10.5, 1.0, 1H), 2.76-2.69 (m, 3H), 2.08 (s, 3H), 1.84-1.52 (m, 12H), 1.31 (s, 3H), 1.28 (s, 3H), 1.27 (s, 3H), 1.26 (s, 3H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 170.5, 136.3, 117.3, 74.5, 64.20, 64.03, 63.6, 63.3, 62.8, 60.7, 35.80, 35.75, 35.4, 31.2, 29.9, 25.06, 24.98, 24.80, 21.4, 18.9, 16.6



134

Triepoxide 134: To a 20 ml vial equipped with a stir bar was added acetate **133** (259.1 mg, 0.707 mmol) in 1.5 mL of THF and cooled to 0 °C. 750 uL of MeOH was added followed by a 750 uL of a 1 M LiOH solution (prepared from 30.9 mg of LiOH in 815 uL of H_2O) added dropwise. The reaction was stirred for 30 min at which time TLC showed complete consumption of the starting material. The reaction was quenched with saturated NH_4Cl and extracted with Et_2O (3x). The organic layers were combined and dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Column chromatography provided the colorless oil **134** (213.1 mg, 0.657 mmol, 93% yield, 7:1 ratio with **136**).

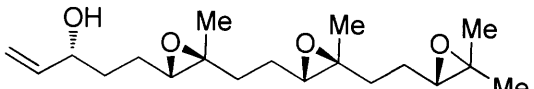
^1H NMR (500 MHz; $CDCl_3$): δ 5.92-5.84 (m, 1H), 5.25 (d, J = 17.2, 1H), 5.13 (d, J = 10.4, 1H), 4.20-4.17 (m, 1H), 2.82-2.77 (m, 1H), 2.76-2.69 (m, 2H), 1.81-1.53 (m, 14H), 1.31 (s, 3H), 1.30 (s, 2H), 1.28 (s, 4H), 1.27 (s, 3H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 141.0, 115.1, 72.6, 64.2, 64.0, 63.3, 63.1, 62.8, 60.8, 35.8, 35.4, 33.9, 25.0, 25.0, 24.8, 24.6, 18.9, 16.9, 16.8

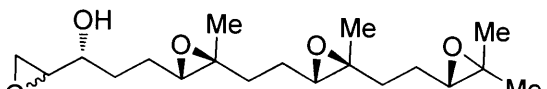
$[\alpha]^{24}_D$ = +17.5 (c 0.44, $CHCl_3$)

IR (NaCl, thin film): 3448, 2926, 1653, 1636, 1617, 1559, 1507, 1473, 1457, 1437, 1387, 1177

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{19}H_{32}O_4Na$, 347.2198; found, 347.2195.



***ent*-134**



***ent*-136**

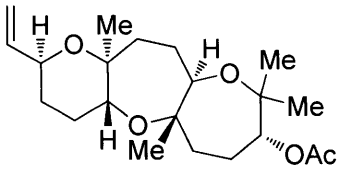
Triepoxide *ent*-134 and tetraepoxide *ent*-136: To a 250 mL round-bottom flask equipped with a stir bar was added a solution of allylic alcohol ***ent*-131** (260.1 mg, 0.817 mmol) in 37 mL of 2:1 DMM/CH_3CN and 25 mL of EDTA buffer. $n$$Bu_4NHSO_4$ (34.7 mg, 0.102 mmol) was added and the reaction was vigorously stirred followed by the addition of Shi ketone **62** (155.4 mg, 0.602 mmol). A solution of Oxone (2.78 g, 4.52 mmol) in 20.5 mL of EDTA solution and a solution of 20.5 mL of 0.89 M K_2CO_3 were added dropwise side-by-side over 30 min. The reaction was allowed to stir for an additional 30 min before 100 mL of water was added and stirred for an additional 45 min. The reaction was extracted with CH_2Cl_2 (3x) and dried over Na_2SO_4. The reaction was filtered and concentrated *in vacuo* and subjected to column chromatography (20 to 50% EtOAc/hexanes) to provide a colorless oil of triepoxide ***ent*-134** (263.2 mg, 0.718 mmol, 61% yield, 3.5:1 dr) and tetraepoxide ***ent*-136** (35 mg, 0.232 mmol, 20% yield, 1:1 dr).

***ent*-136:**

Data for a 1:1 mixture of diastereomers

^{1}H NMR (500 MHz; $CDCl_3$): δ 3.84 (dd, J = 7.9, 3.1, 1H), 3.53 (td, J = 4.3, 1.4, 1H), 3.02-2.98 (m, 2H), 2.82-2.76 (m, 4H), 2.75-2.68 (m, 6H), 1.85-1.52 (m, 24H), 1.30 (s, 6H), 1.29 (s, 6H), 1.27 (s, 6H), 1.26 (s, 6H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 71.2, 68.6, 64.2, 64.0, 63.3, 63.3, 62.8, 62.8, 60.7, 60.6, 58.7, 55.4, 55.4, 54.5, 54.5, 45.1, 43.8, 35.8, 35.4, 31.5, 30.5, 25.0, 24.8, 24.5, 18.8, 16.9



137

Acetate 137. To a flame-dried 100 ml round-bottom flask equipped with a stir bar was added triepoxide **134** (1.5594g, 4.81 mmol) in 100 mL of dichloromethane and cooled to -78 °C. BF_3•OEt_2 (210 *u*L, 1.70 mmol) was added dropwise and the reaction was stirred at the same temperature for 15 min. Saturated NH_4Cl was added to quench the reaction and it was warmed to room temperature. The reaction was poured into a seperatory funnel and extracted with CH_2Cl_2 (3x) from brine. The organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

The crude reaction mixture was dissolved in 50 mL of dichloromethane in a 100 mL flame-dried round-bottom flask equipped with a stir bar. Acetic anhydride (950 *u*L, 10.0 mmol), triethyl amine (2.8 mL, 20.1 mmol), and DMAP (59.8 mg, 0.490 mmol) were all added and reaction was stirred at room temperature overnight. Saturated NH_4Cl was added and the reaction was transferred to a separatory funnel and extracted with CH_2Cl_2 (3x). The organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Column chromatography provided colorless oil **137** (324.6 mg, 0.886 mmol, 18.4 % yield).

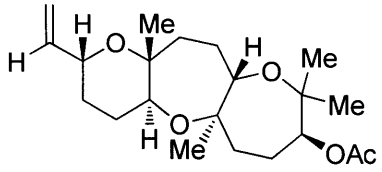
^{1}H NMR (500 MHz; $CDCl_3$): δ 5.84-5.77 (m, 1H), 5.21 (dt, J = 17.3, 1.4, 1H), 5.09 (ddd, J = 10.5, 1.6, 1.1, 1H), 4.92 (d, J = 6.7, 1H), 4.01-3.97 (m, 1H), 3.62 (dd, J = 11.1, 5.0, 1H), 3.46 (dd, J = 11.5, 2.5, 1H), 2.12 (s, 3H), 2.10-2.04 (m, 2H), 2.00-1.81 (m, 3H), 1.81-1.61 (m, 5H), 1.54-1.43 (m, 2H), 1.30 (s, 3H), 1.26 (s, 3H), 1.16 (s, 3H), 1.14 (s, 3H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 208.5, 139.6, 115.3, 78.8, 78.6, 78.4, 77.4, 77.1, 71.1, 70.2, 40.8, 36.8, 32.1, 29.2, 28.9, 27.8, 23.2, 21.8, 21.3, 20.1, 16.4

$[\alpha]^{24}_D$ = +22.9 (c 0.06, $CHCl_3$)

IR (NaCl, thin film): 2936, 2361, 2339, 1734, 1653, 1540, 1457, 1241, 1078

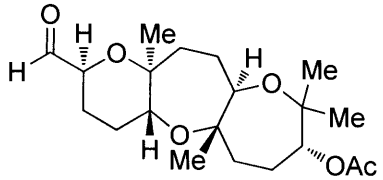
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{21}H_{34}O_5Na$, 389.2298; found, 389.2290.



***ent*-137**

***ent*-137**: An identical procedure as **137** was used to furnish the enantiomer from ***ent*-137**.

$[\alpha]^{24}_D$ = –18.2, (c 0.58, $CHCl_3$)



138

Aldehyde 138: To a 100 mL round-bottom flask equipped with a stir bar was added acetate **137** (324.6 mg, 0.886 mmol) in 44 mL of CH_2Cl_2. Sodium bicarbonate (20.2 mg, 0.240 mmol) and 8.9 mL of MeOH were added. The reaction was cooled to –78 °C and subjected to ozone until the reaction turned light blue (~10 min). Oxygen was bubbled through the solution for 2 min, followed by nitrogen for 1 min. The reaction was quenched by the addition of triphenylphosphine (256.5 mg, 0.978 mmol) and allowing the reaction to warm to room temperature for 1 h. The reaction was concentrated *in vacuo* and then loaded directly onto a silica gel column. The crude was purified by column chromatography (20% EtOAc in hexanes) to furnish aldehyde **138** (240.2 mg, 0.652 mmol, 65% yield) as a colorless oil.

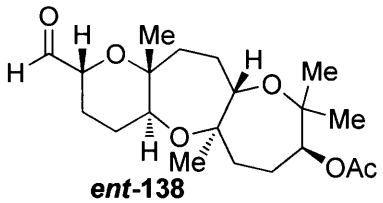
^{1}H NMR (500 MHz; $CDCl_3$): δ 9.59 (s, 1H), 4.92 (d, J = 6.4, 1H), 3.92 (dd, J = 12.2, 3.0, 1H), 3.62 (dd, J = 10.4, 5.8, 1H), 3.46 (dd, J = 11.3, 2.4, 1H), 2.12 (s, 3H), 2.07-2.00 (m, 2H), 1.94-1.90 (m, 1H), 1.86 (dtd, J = 11.9, 5.8, 3.0, 2H), 1.82-1.76 (m, 1H), 1.73-1.68 (m, 3H), 1.54-1.45 (m, 3H), 1.28 (s, 2H), 1.26 (s, 3H), 1.17 (s, 3H), 1.15 (s, 3H)

^{13}C NMR (100 MHz; $CDCl_3$): δ 202.3, 170.2, 79.0, 78.6, 78.3, 78.1, 77.4, 75.0, 69.7, 40.3, 36.7, 29.1, 28.92, 27.0, 26.7, 23.2, 21.8, 21.3, 19.5, 16.4

$[\alpha]^{24}_D$ = –4.6, (c 0.4, $CHCl_3$)

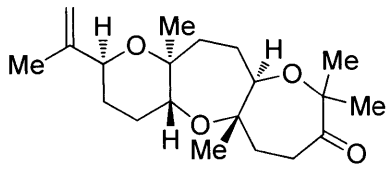
IR (NaCl, thin film): 2938, 1996, 1739, 1653, 1559, 1540, 1457, 1379, 1241, 1097, 1071, 981, 893

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{20}H_{32}O_6Na$, 391.2091; found, 391.2086.



***ent*-138**

***ent*-138**: An identical procedure as **138** was used to furnish the enantiomer from ***ent*-137.**



145

Ketone 145: To a 5 mL round-bottom flask equipped with a stir bar was added alcohol **112** (74.2 mg, 0.219 mmol) in 2.3 mL of CH_2Cl_2. Sodium bicarbonate (276.0 mg, 3.29 mmol) was added and the reaction was cooled to 0 °C. Dess-Martin periodinane (232 mg, 0.547 mmol) was added and the reaction was allowed to warm to room temperature and stir for 3 h. The reaction was quenched with a 1:1 solution of saturated $Na_2S_2O_3$ and $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (10% EtOAc in hexanes) to furnish **145** (58.0 mg, 0.172 mmol, 79% yield) as colorless oil.

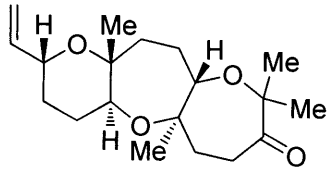
^{1}H NMR (500 MHz; $CDCl_3$): δ 4.96 (t, J = 0.8, 1H), 4.81 (t, J = 1.4, 1H), 3.89 (dd, J = 11.6, 1.7, 1H), 3.63 (dd, J = 11.1, 5.1, 1H), 2.99 (ddd, J = 14.4, 11.4, 3.1, 1H), 2.90 (dd, J = 11.3, 2.5, 1H), 2.23-2.18 (m, 1H), 1.98-1.93 (m, 1H), 1.87 (ddd, J = 13.8, 6.2, 3.1, 1H), 1.78-1.74 (m, 1H), 1.73 (s, 3H), 1.68-1.62 (m, 2H), 1.56-1.50 (m, 1H), 1.46 (qd, J = 12.3, 4.9, 1H), 1.39 (s, 3H), 1.34-1.33 (m, 1H), 1.31 (s, 3H), 1.26-1.25 (m, 1H), 1.24 (s, 3H), 1.22 (s, 3H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 217.6, 146.2, 110.7, 83.5, 82.9, 77.9, 77.1, 73.0, 70.8, 41.4, 40.5, 35.5, 30.8, 29.2, 27.8, 26.6, 20.9, 19.8, 19.2. 15.8

$[\alpha]^{24}_D = -10.2$ (c 0.26, $CHCl_3$)

IR (NaCl, thin film): 2927, 2853, 1717, 1559, 1457, 1377, 1074, 895

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{20}H_{32}O_4Na$, 359.2193; found, 359.2198.



147

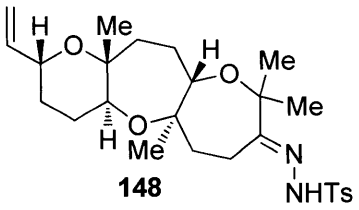
Ketone 147: To a 5 mL round-bottom flask equipped with a stir bar was added alcohol **146** (53.9 mg, 0.166 mmol) in 7.2 mL of CH_2Cl_2. Sodium bicarbonate (608.7 mg, 7.25 mmol) was added and the reaction was cooled to 0 °C. Dess-Martin periodinane (670.0 mg, 1.580 mmol) was added and the reaction was allowed to warm to room temperature and stir for 3 h. The reaction was quenched with a 1:1 solution of saturated $Na_2S_2O_3$ and $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (2 to 10% EtOAc in hexanes) to furnish **147** (34.4 mg, 0.107 mmol, 64% yield) as colorless oil.

^{1}H NMR (500 MHz; $CDCl_3$): δ 5.80 (ddd, J = 17.0, 10.7, 6.1, 1H), 5.21 (dd, J = 17.3, 1.3, 1H), 5.09 (dt, J = 10.4, 1.2, 1H), 4.01-3.97 (m, 1H), 3.64 (dd, J = 11.3, 4.8, 1H), 2.99 (ddd, J = 14.3, 11.3, 2.9, 1H), 2.88 (dd, J = 11.3, 2.4, 1H), 2.23-2.18 (m, 1H), 1.95 (ddd, J = 15.6, 5.2, 3.5, 1H), 1.87 (ddd, J = 13.8, 6.2, 3.1, 1H), 1.76-1.68 (m, 3H), 1.66-1.60 (m, 2H), 1.57-1.51 (m, 2H), 1.45-1.41 (m, 1H), 1.39 (s, 3H), 1.31 (s, 3H), 1.24 (s, 3H), 1.23 (s, 3H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 217.6, 139.5, 115.4, 83.0, 77.9, 77.4, 77.2, 71.0, 70.6, 41.3, 40.5, 35.5, 32.1, 29.2, 27.6, 26.6, 20.9, 19.7, 15.8

$[\alpha]^{24}_D$ = +1.7 (c 0.13, $CHCl_3$)

IR (NaCl, thin film): 2935, 1716, 1462, 1378, 1119, 1075, 1053, 922



148

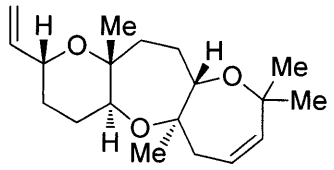
Hydrazone **148:** To a 5 mL round-bottom flask equipped with a stir bar was added ketone **147** (34.4 mg, 0.107 mmol) and tosyl hydrazide (37.8 mg, 0.203 mmol) in 1 mL of MeOH. The reaction was heated to 40 °C for 18 h. The reaction was cooled to room temperature and concentrated *in vacuo*. The crude white solid was purified by column chromatography (50 to 100% EtOAc in hexanes) to furnish hydrazone **148** (22.6 mg, 0.046 mmol, 43% yield).

^{1}H NMR (500 MHz; $CDCl_3$): δ 7.84 (d, J = 8.1, 2H), 7.33 (d, J = 8.2, 2H), 7.27 (d, J = 0.6, 1H), 5.81-5.74 (m, 1H), 5.19 (d, J = 17.3, 1H), 5.08 (d, J = 10.4, 1H), 3.98-3.94 (m, 1H), 3.52 (dd, J = 11.3, 4.6, 1H), 2.87-2.76 (m, 1H), 2.44 (s, 3H), 2.24 (dd, J = 10.4, 3.3, 1H), 2.05-2.02 (m, 1H), 1.84 (t, J = 1.9, 1H), 1.72-1.65 (m, 2H), 1.65-1.52 (m, 4H), 1.49-1.31 (m, 3H), 1.23 (s, 3H), 1.22 (s, 3H), 1.15 (s, 3H), 1.11 (s, 3H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 164.3, 144.3, 139.4, 129.7, 128.5, 128.3, 115.4, 80.6, 79.9, 77.6, 71.07, 70.90, 70.4, 40.45, 40.29, 32.0, 28.9, 27.5, 27.1, 22.9, 21.9, 20.7, 19.6, 15.9

$[\alpha]^{24}_D = -14.5$ (c 0.4, $CHCl_3$)

IR (NaCl, thin film): 3219, 2977, 2935, 1462, 1379, 1347, 1169, 1075, 1020.



149

Diene 149: To a 1 mL Schlenk flask equipped with stir bar was added 95% sodium hydride in mineral oil (2.0 mg, 0.079 mmol) from a dry box and transferred to a hood under nitrogen. A solution of hydrazone **148** (7.9 mg, 0.0161 mmol) in 500 *u*L of toluene was added and the flask was sealed and heated to 90 °C for 2.5 h. The flask was cooled and slowly quenched with saturated NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (3x) and the organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction was purified by column chromatography (5% EtOAc in hexanes) to furnish oxepene **149** (0.8 mg, 0.00261 mmol, 16% yield).

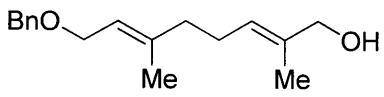
^{1}H NMR (500 MHz; $CDCl_3$): δ 5.84-5.77 (m, 1H), 5.47-5.42 (m, 1H), 5.38-5.35 (m, 1H), 5.24-5.19 (m, 1H), 5.10-5.06 (m, 1H), 4.02-3.97 (m, 1H), 3.73 (ddd, J = 11.4, 4.8, 2.8, 1H), 3.52-3.48 (m, 1H), 2.51-2.46 (m, 1H), 2.13-2.08 (m, 1H), 2.01-1.88 (m, 2H), 1.87-1.67 (m, 4H), 1.67-1.59 (m, 2H), 1.28 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H), 1.21 (s, 3H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 139.7, 136.7, 122.1, 115.2, 78.0, 76.8, 73.8, 73.2, 70.6, 70.4, 42.3, 38.8, 32.3, 29.7, 27.64, 27.50, 26.2, 18.2, 17.8

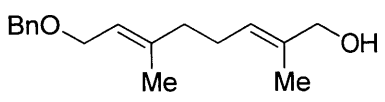
---

[1] Donohoe, T. J.; Butterworth, S. *Angew. Chem. Int. Ed.* **2005**, *44*, 4766-4768.
[2] Browder, C. C.; Marmsäter, F. P.; West, F. G. *Org. Lett.* **2001**, *3*, 3033-3035.
[3] a) Kraus, G. A.; Kim, J. *Org. Lett.* **2004**, *6*, 3115-3117. b) Wei, X.; Lorenz, J. C.; Kapadia, S.; Saha, A.; Haddad, N.; Busacca, C. A.; Senanayake, C. H. *J. Org. Chem.* **2007**, *72*, 4250-4253.
[4] Griffiths-Jones, C. M.; Knight, D. W. *Tetrahedron* **2010**, *66*, 4150-4166.
[5] Coates, R. M.; Ley, D. A.; Cavender, P. L. *J. Org. Chem.* **1978**, *43*, 4915-4922.
[6] Chen, Y. K.; Jeon, S.-J.; Walsh, P. J.; Nugent, W. A. *Org. Synth.* **2005**, *82*, 87-90.
[7] Lurain, A. E.; Maestri, A.; Kelly, A. R.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 13608-13609.

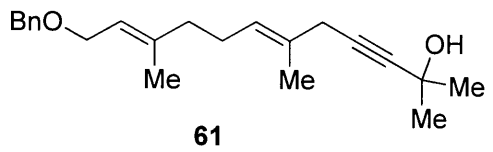
Chapter 1 ^{1}H NMR and ^{13}C NMR Spectra



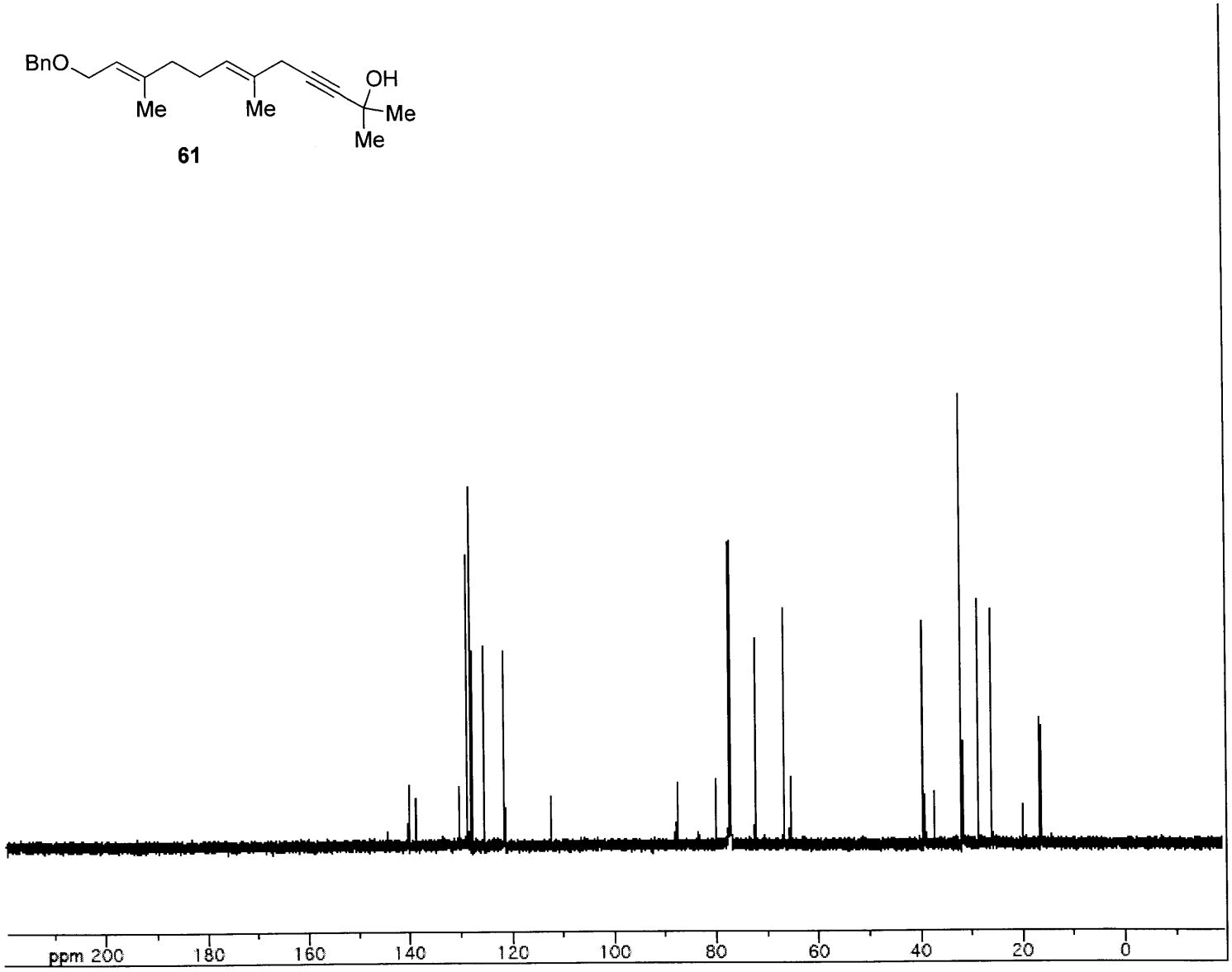
59

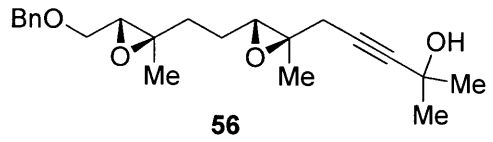


59

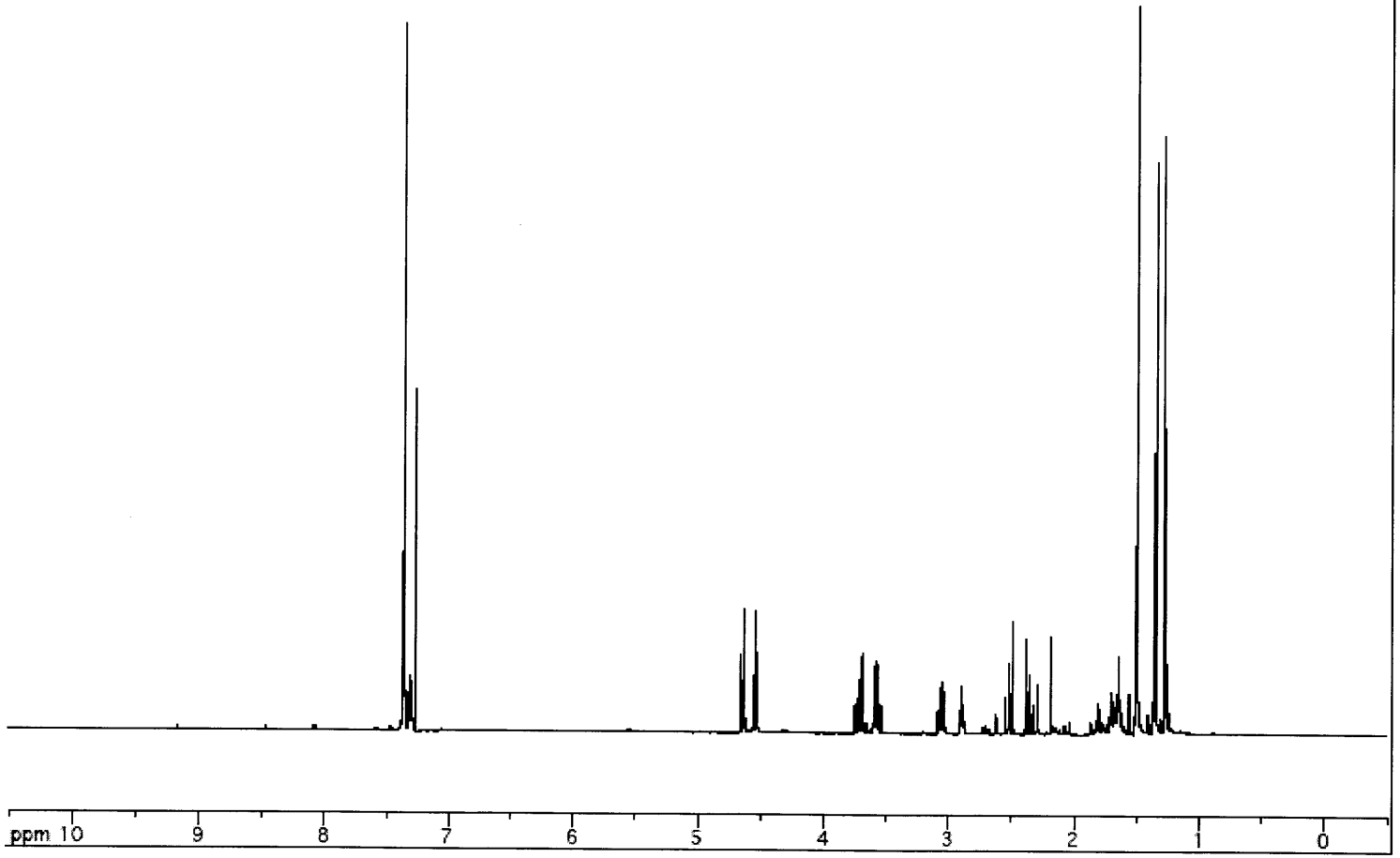


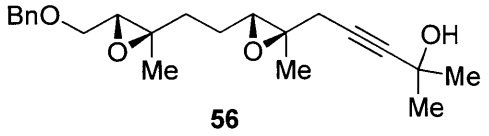
61


BnO
Me
Me
OH
Me
Me
61
ppm 200
180
160
140
120
100
80
60
40
20
0

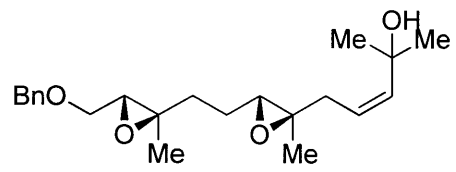


56

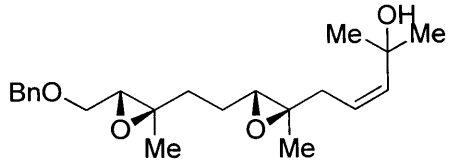




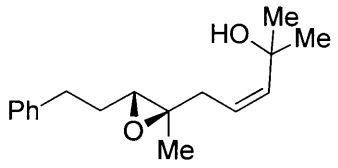
56



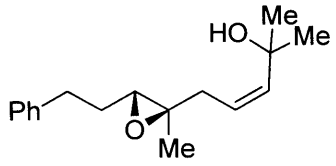
55



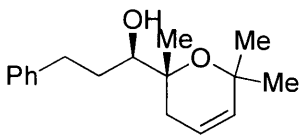
55



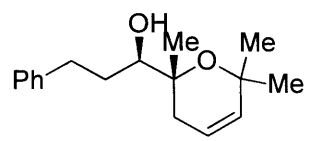
69



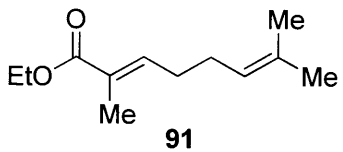
69



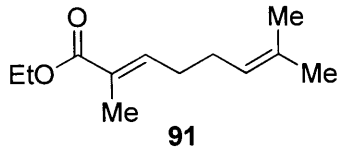
75



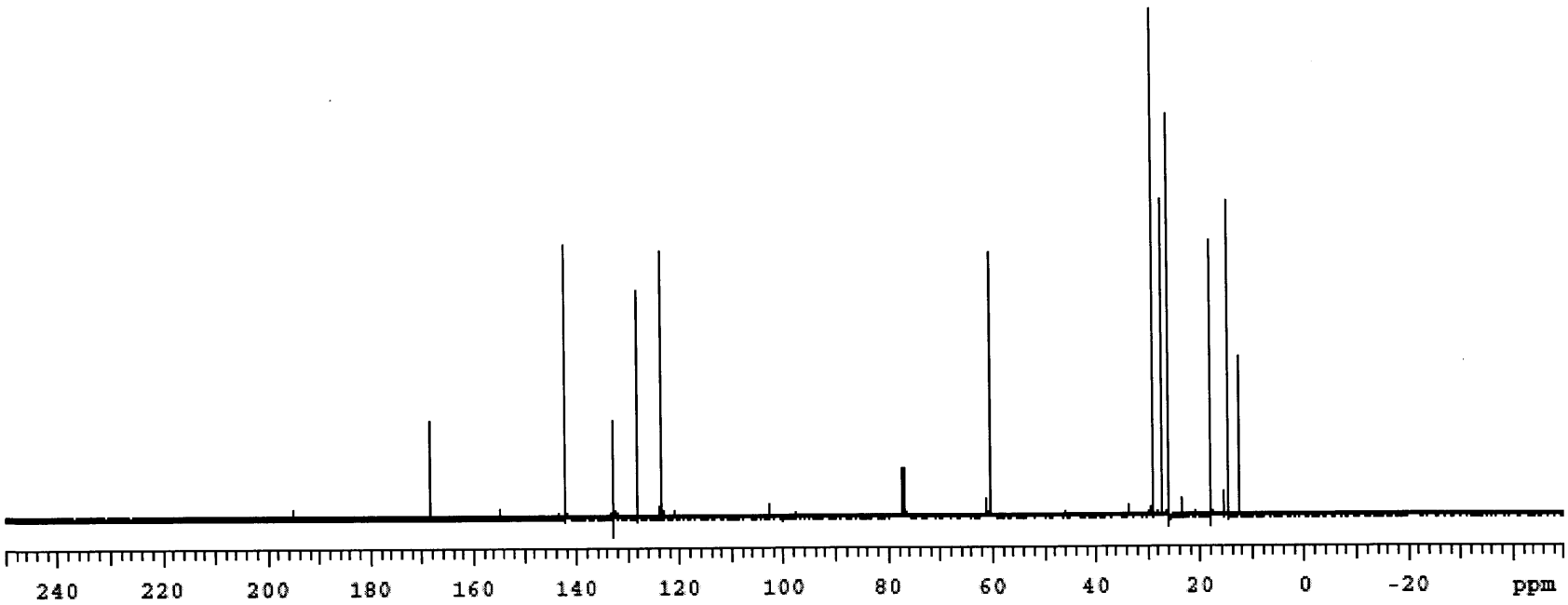
75

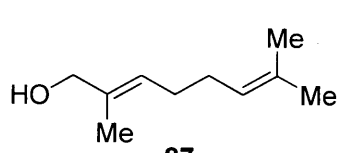


91

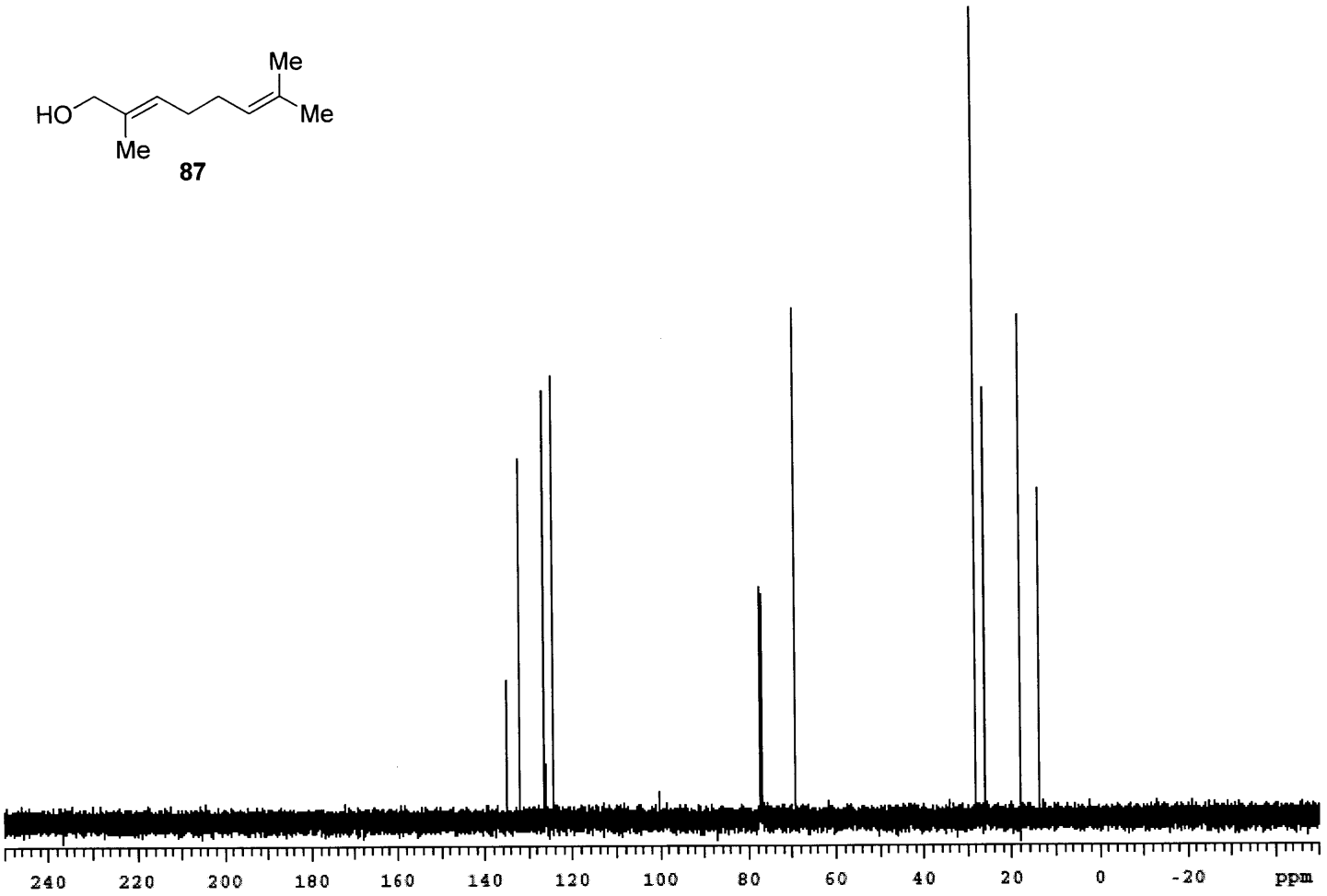


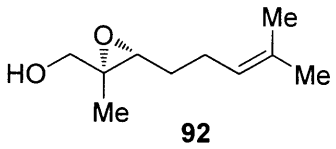
91



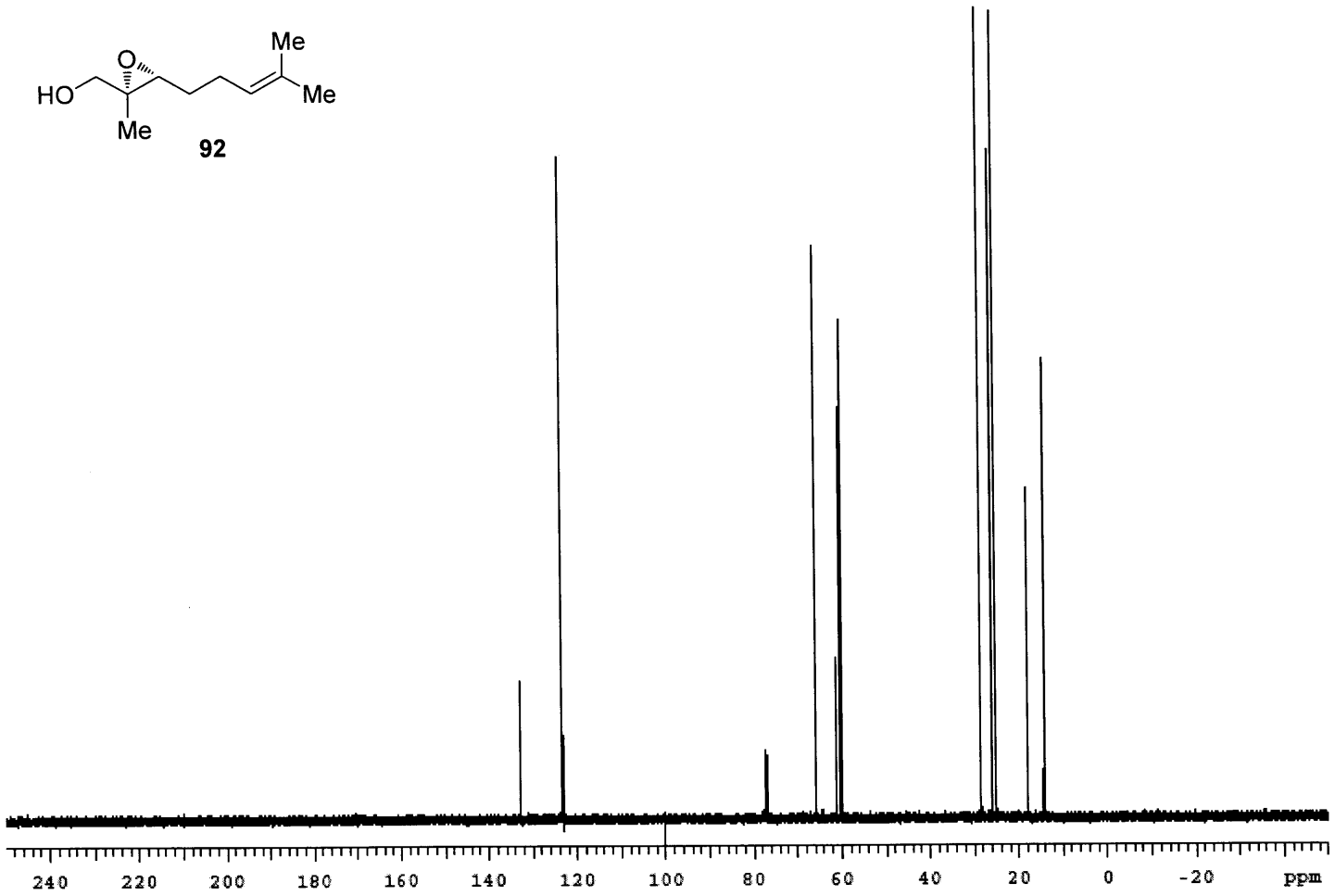


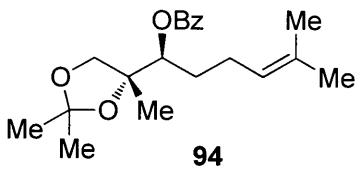
87


Me
HO
Me
Me
87
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

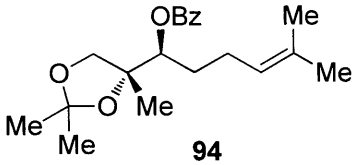


92

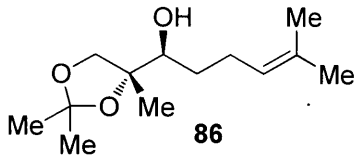

HO
O
Me
Me
Me
92
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm



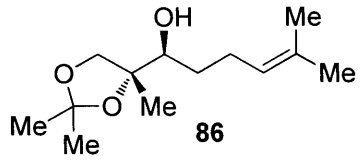
94



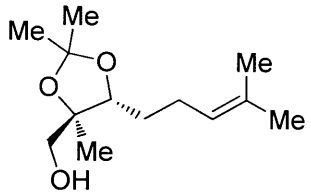
94



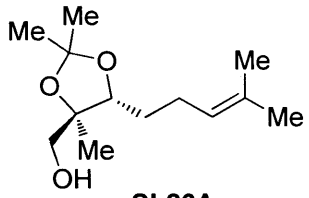
86



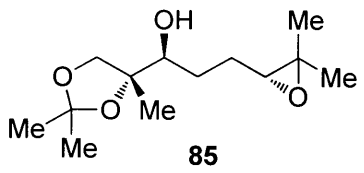
86



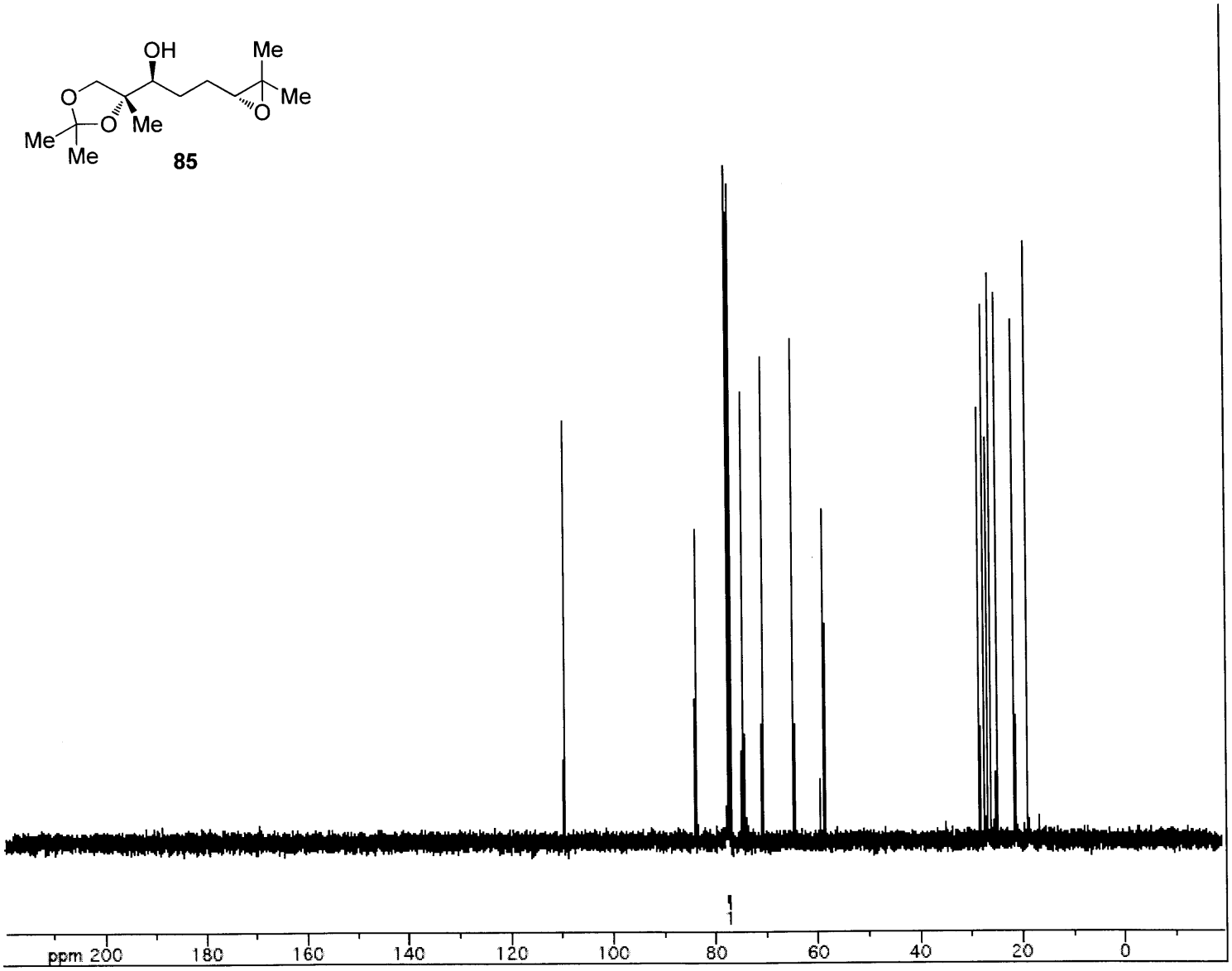
SI-86A

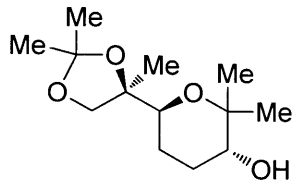


SI-86A

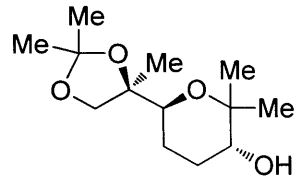


85

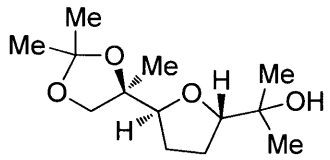

OH
Me
Me
O
O
Me
Me
Me
O
85
ppm 200
180
160
140
120
100
80
60
40
20
0



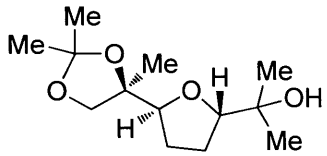
95



95

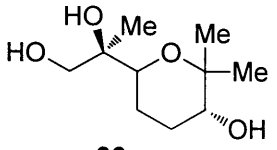


97a

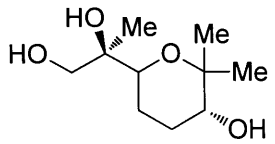

Me
Me
O
Me
O
H
Me
OH
H
Me

97a

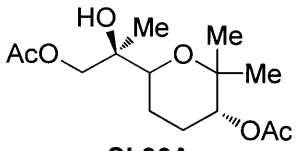
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40



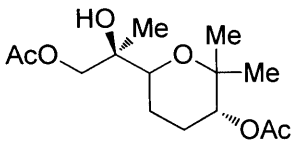
96



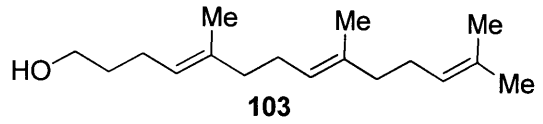
96



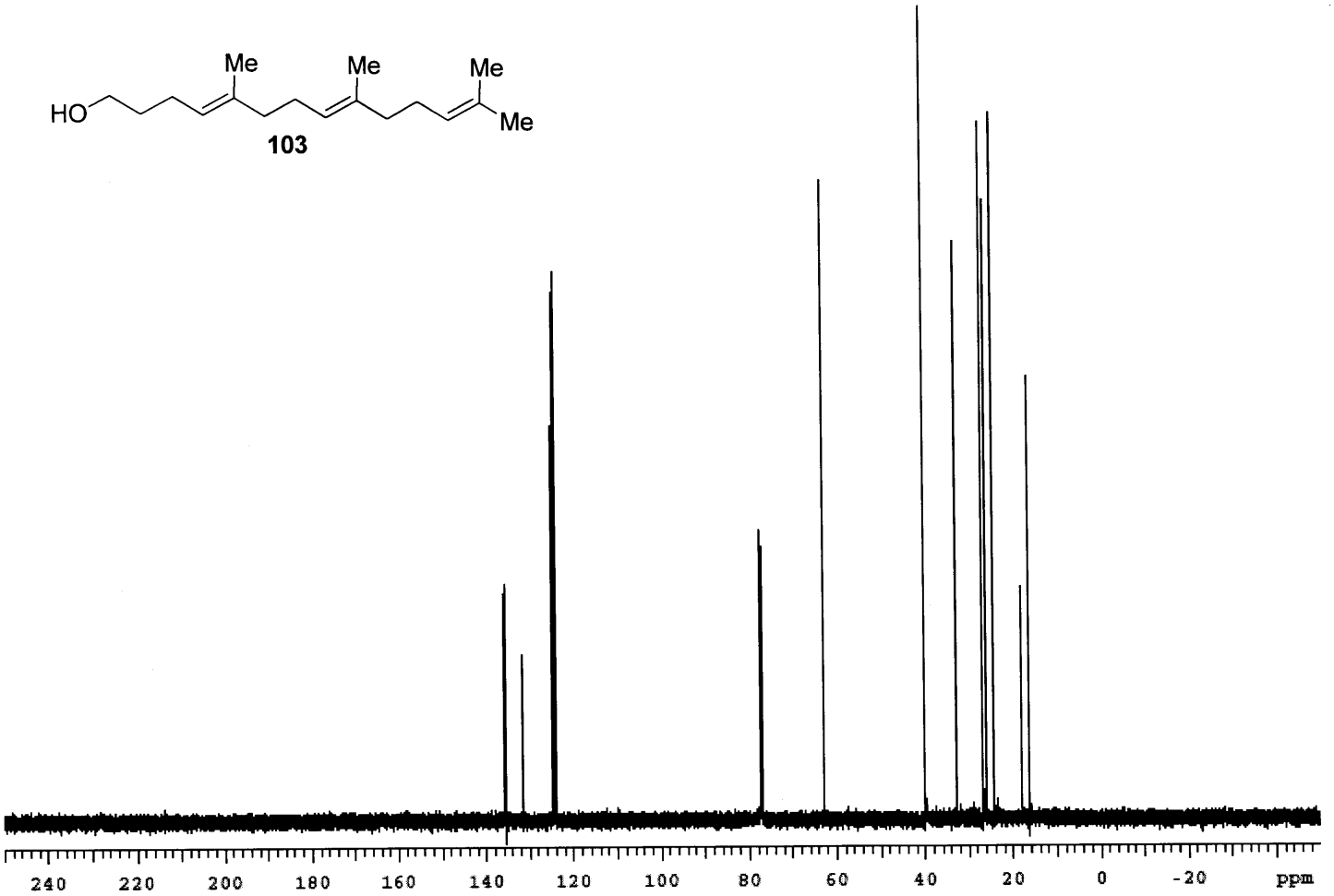
SI-96A



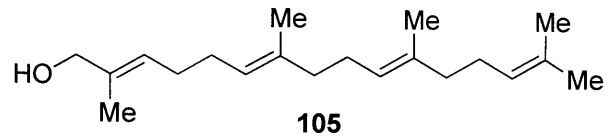
SI-96A



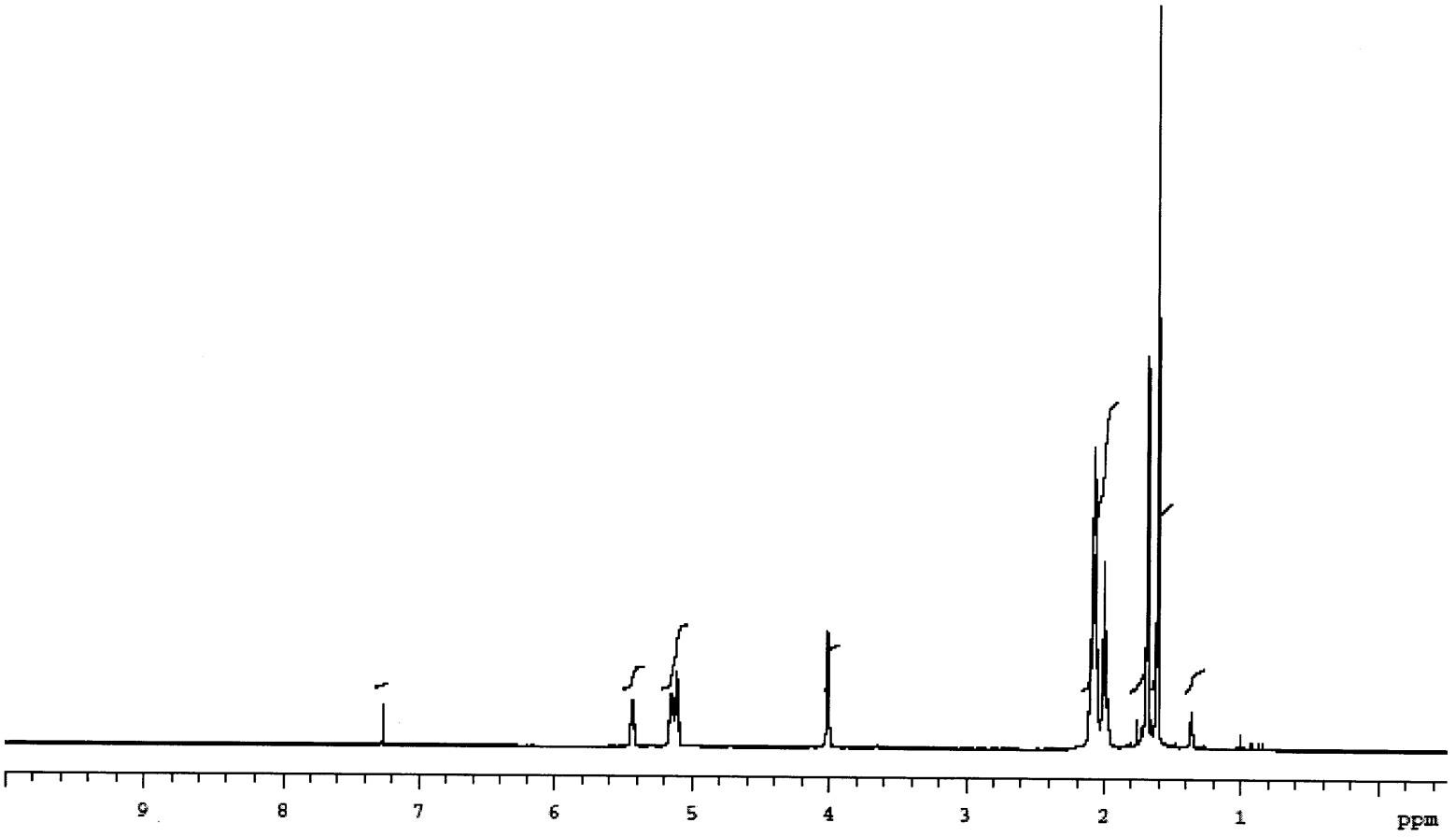
103

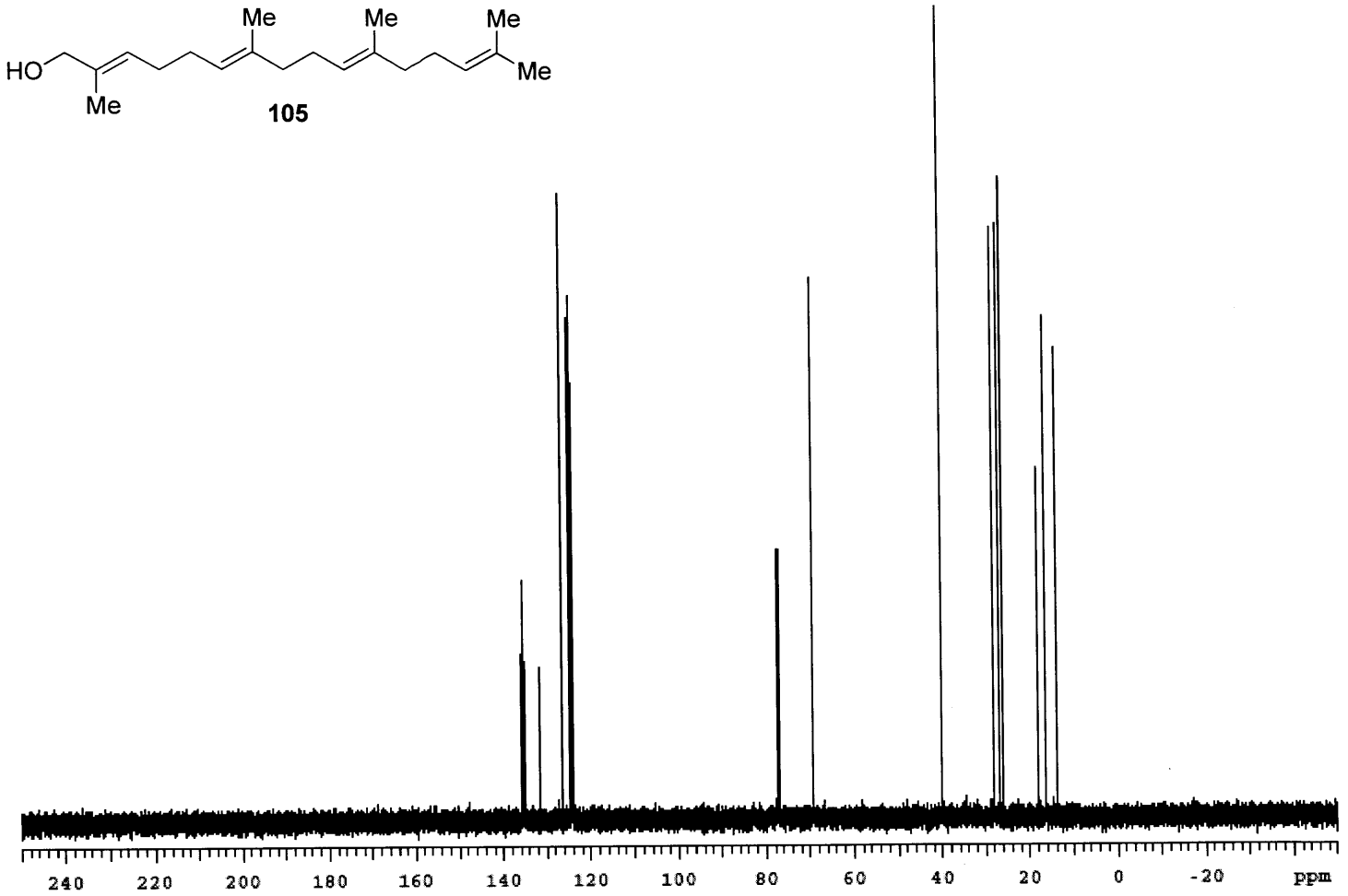


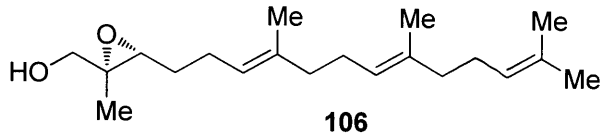
103



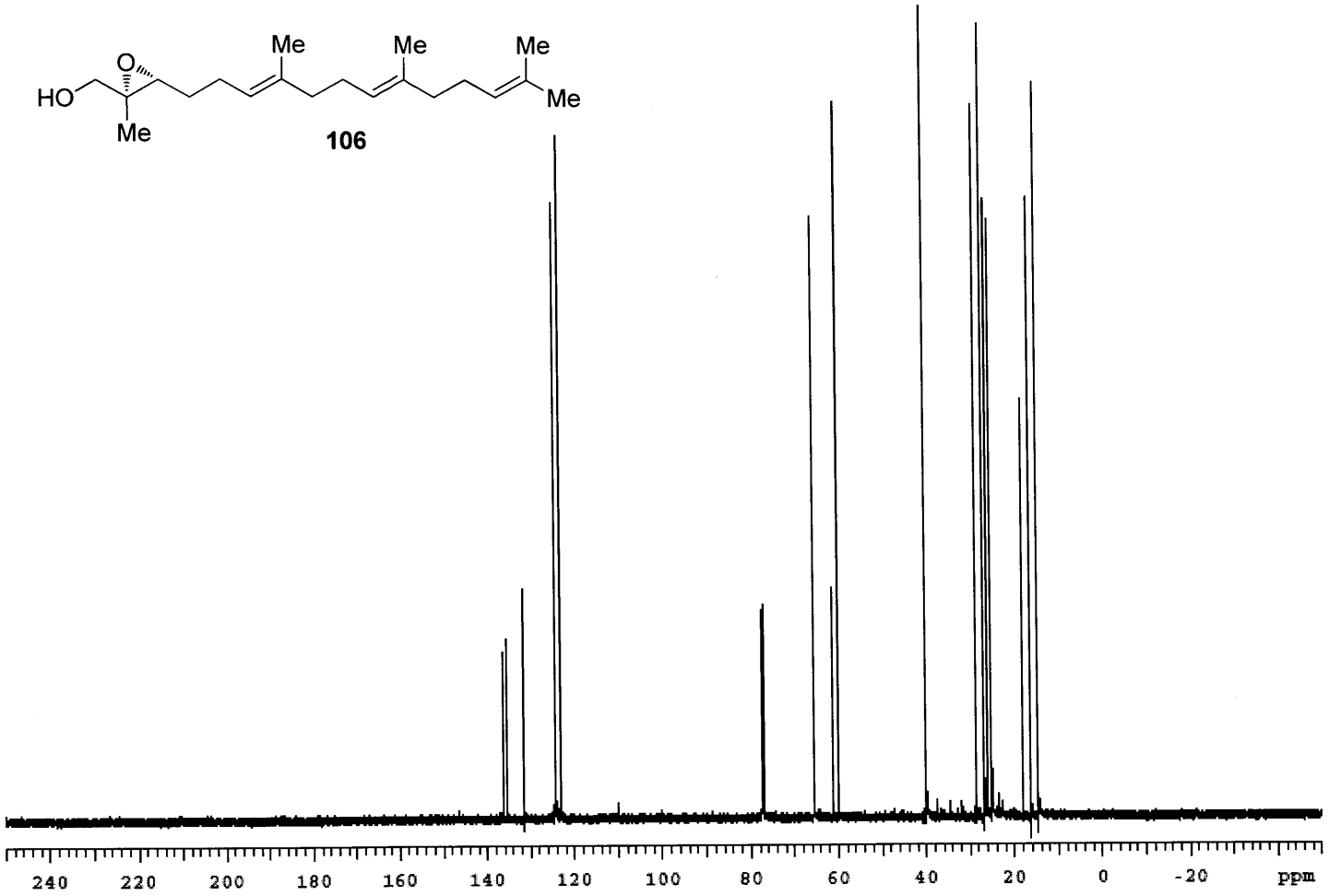
105

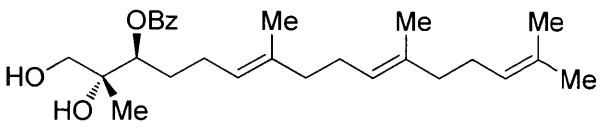



HO
Me
Me
Me
Me
Me
105
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

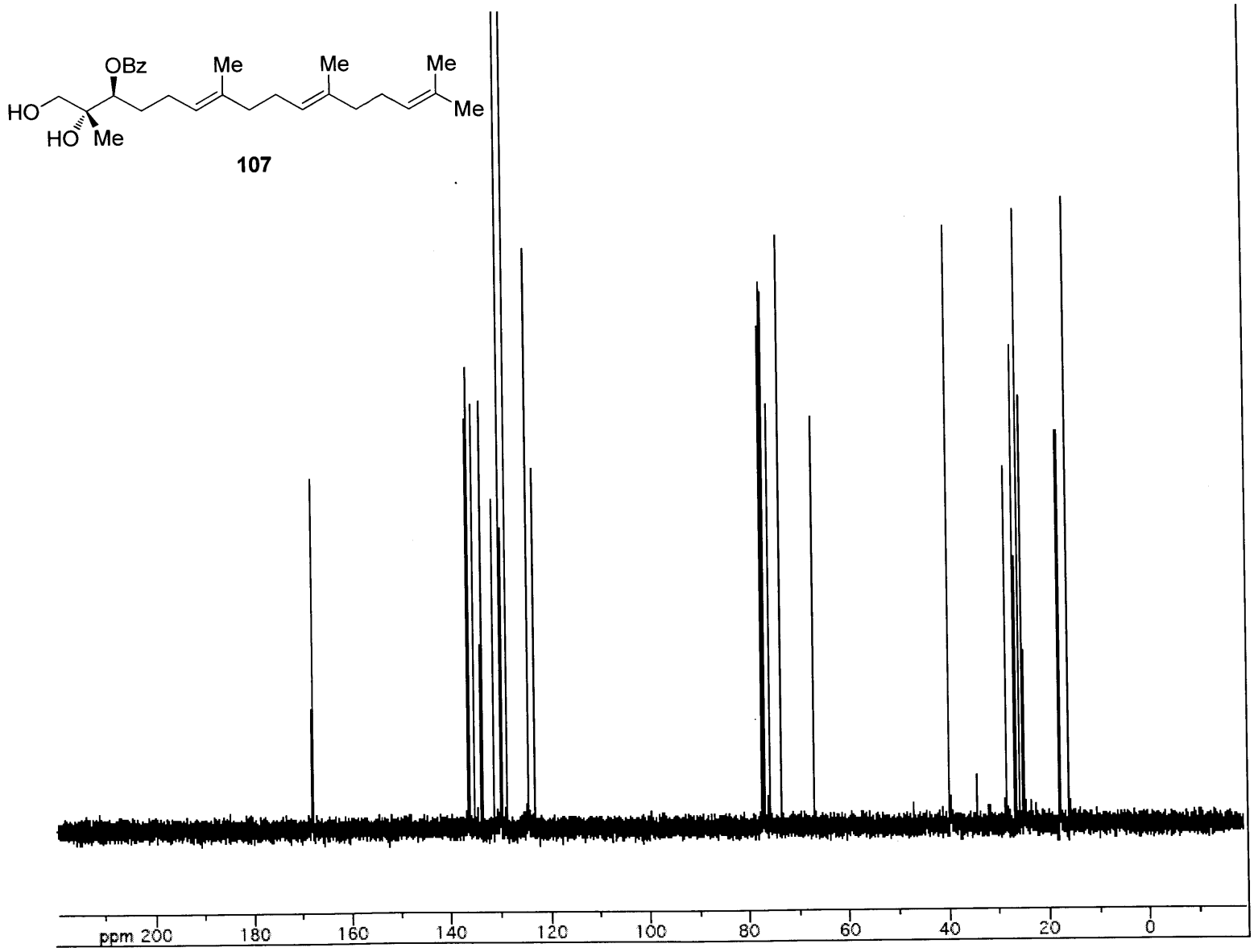


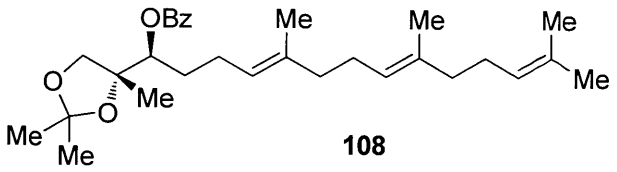
106


HO
O
Me
Me
Me
Me
Me
106
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

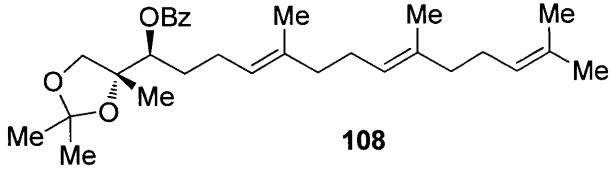


107

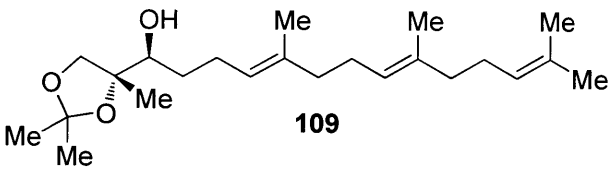

OBz
Me
Me
Me
HO
HO
Me
Me
107
ppm 200
180
160
140
120
100
80
60
40
20
0



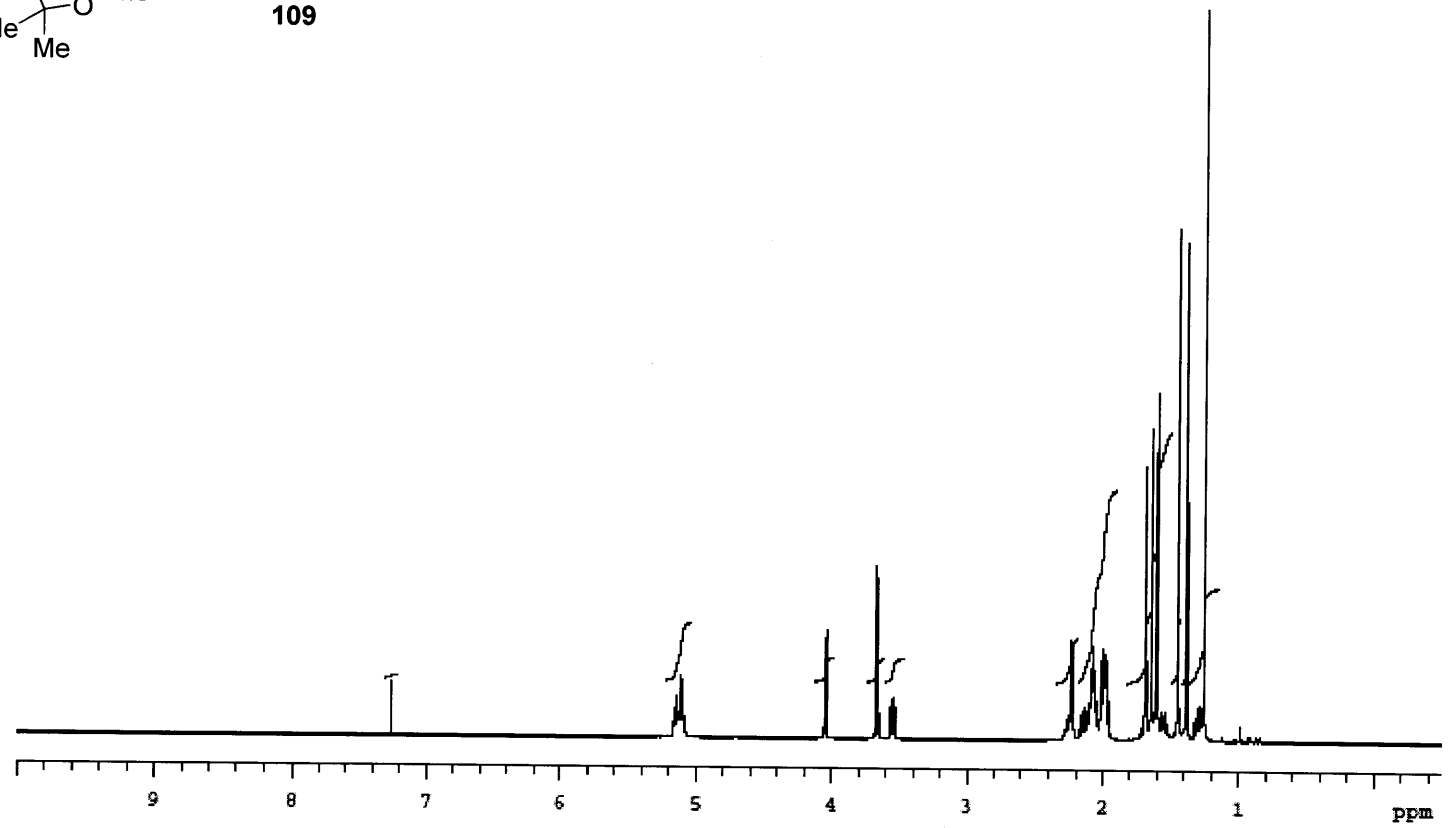
108

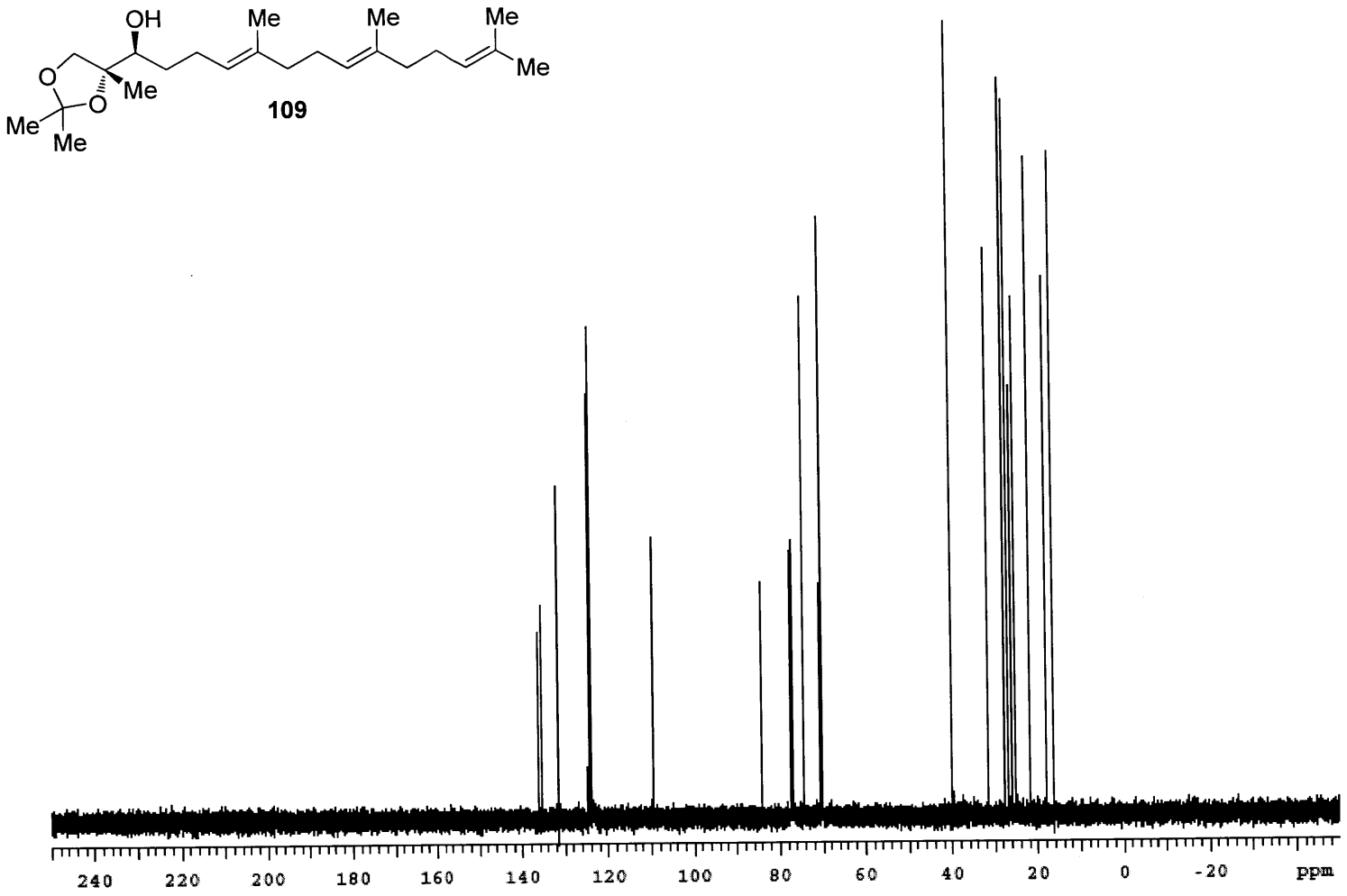


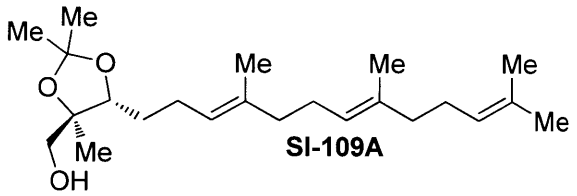
108



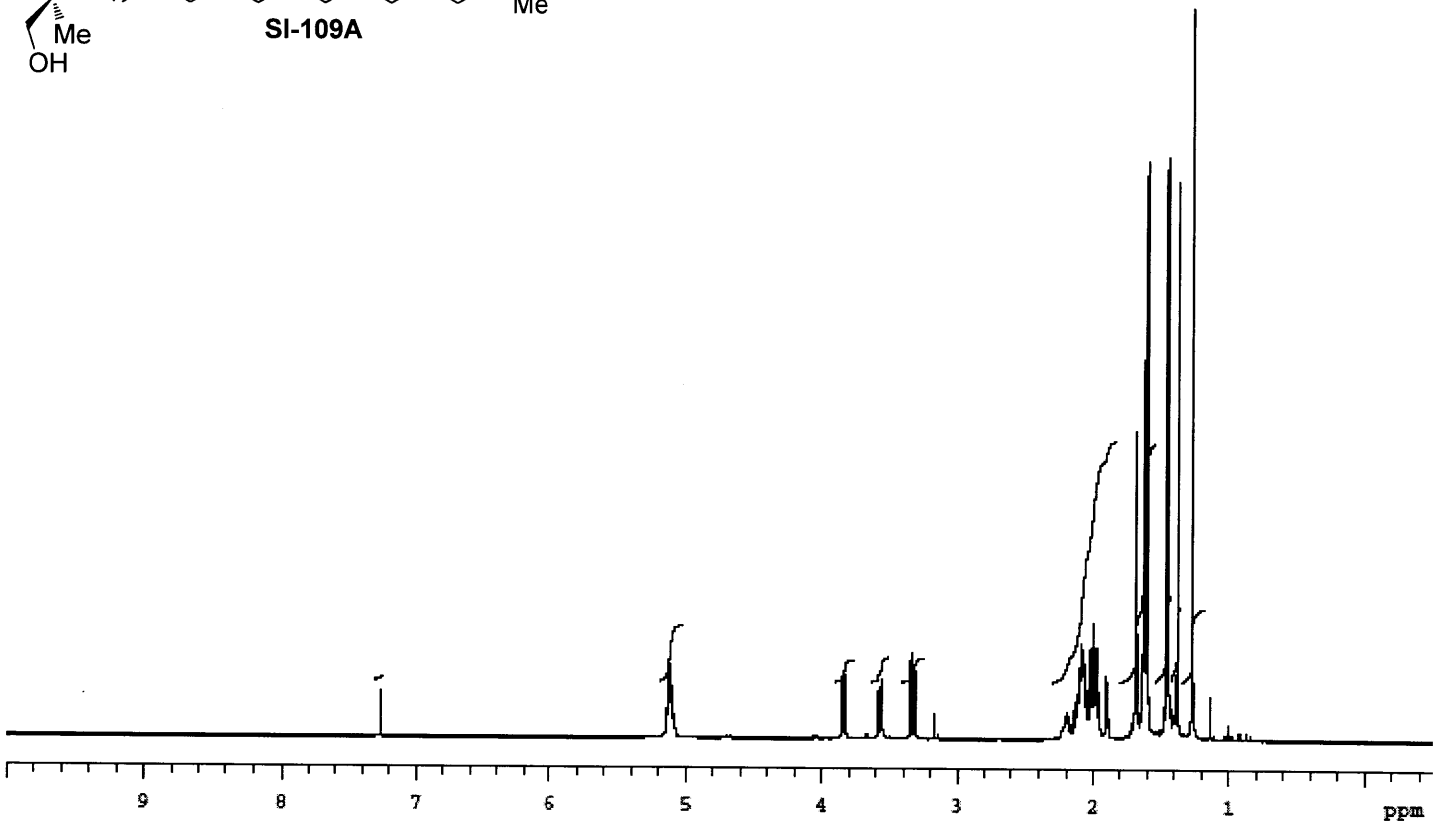
109

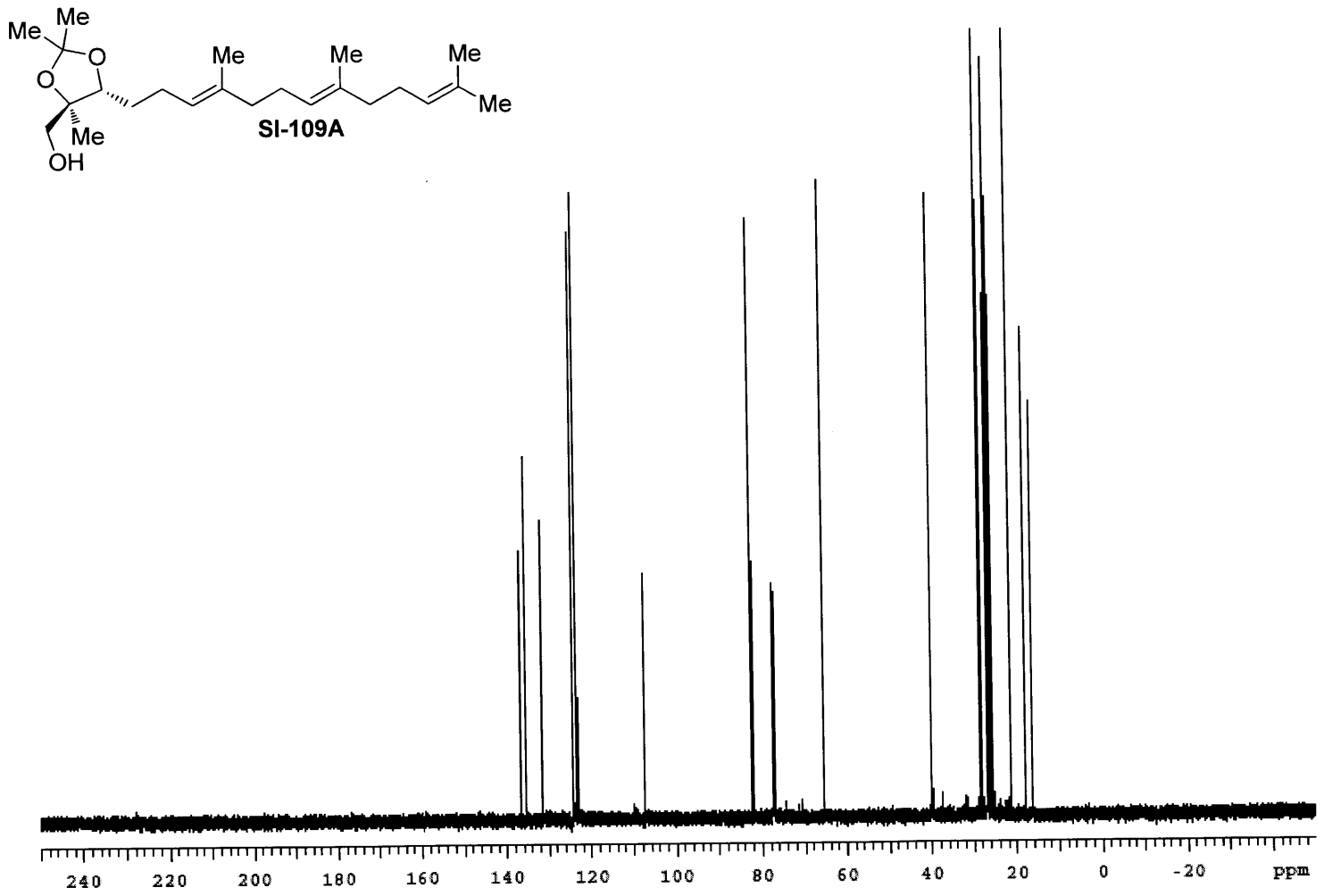


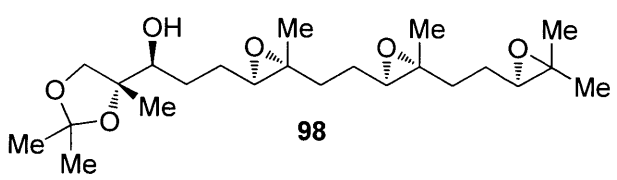

OH
Me
Me
Me
Me
O
Me
O
Me
Me
109
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm



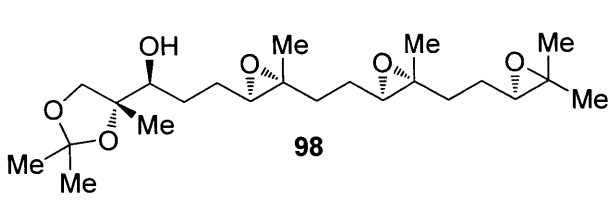
SI-109A




Me
Me
O
O
Me
Me
Me
Me
Me
OH
SI-109A
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

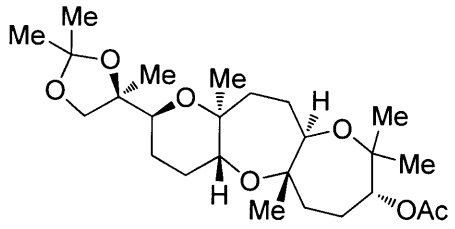


98

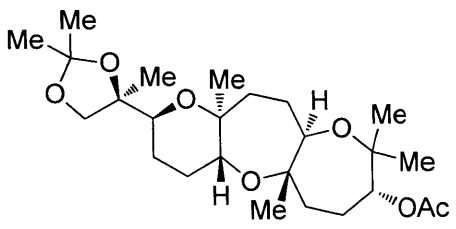

OH
Me
Me
Me
O
O
O
O
O
Me
Me
Me
Me

98

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

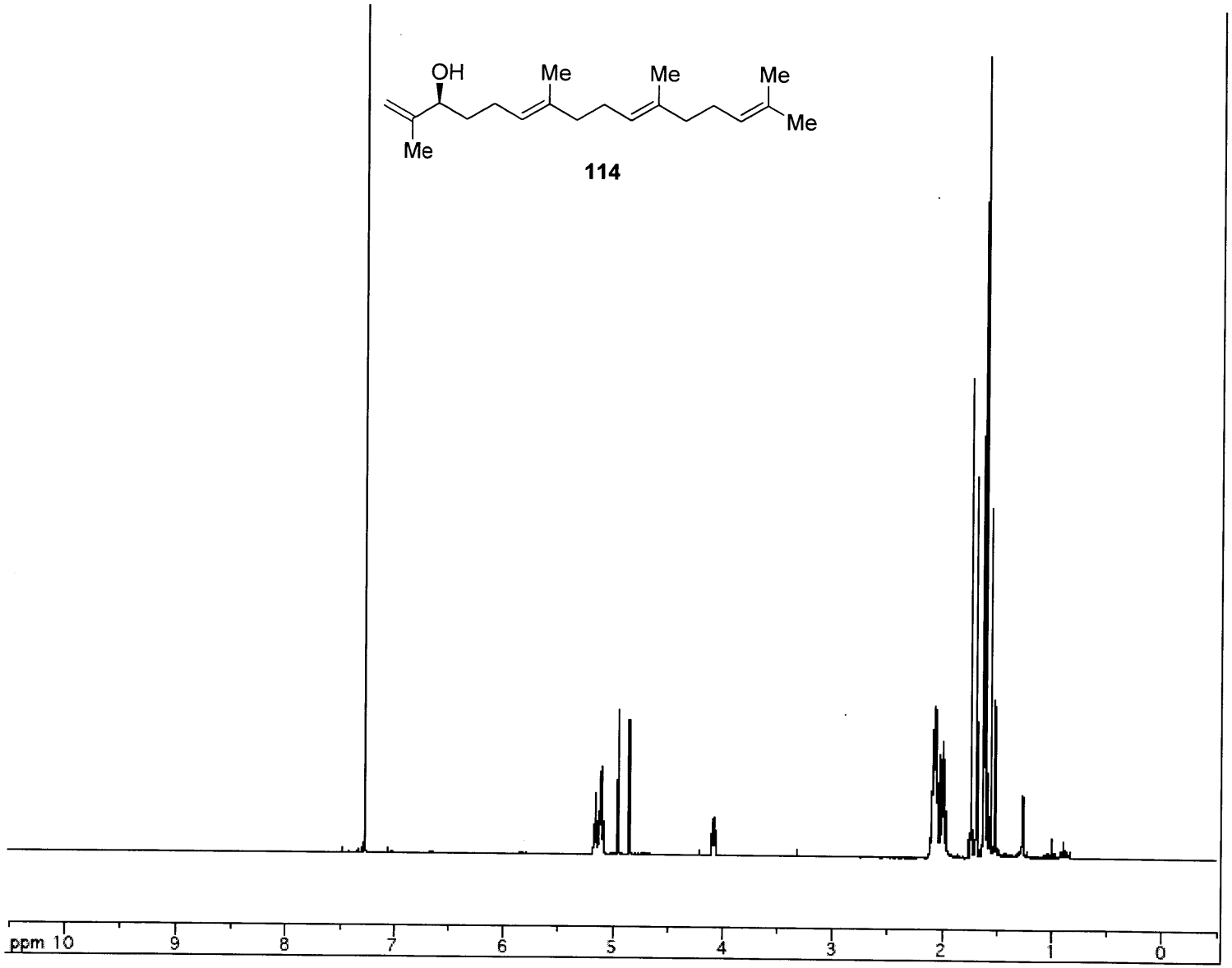


110

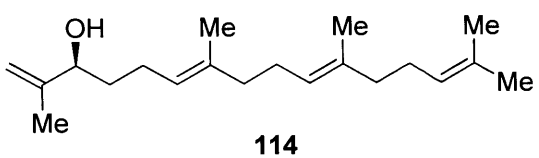

Me
Me
O
O
Me
O
Me
H
O
Me
Me
O
H
O
Me
OAc

110

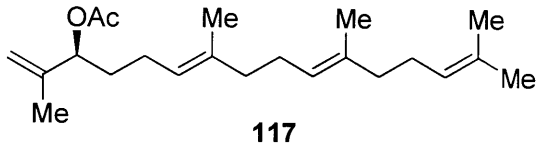
ppm 200
180
160
140
120
100
80
60
40
20
0



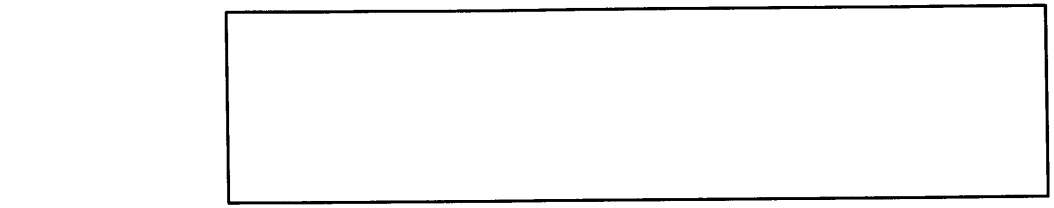
114

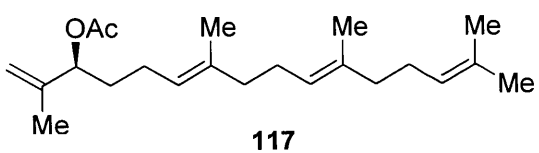


114

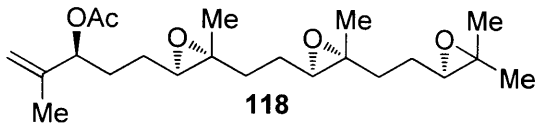


117

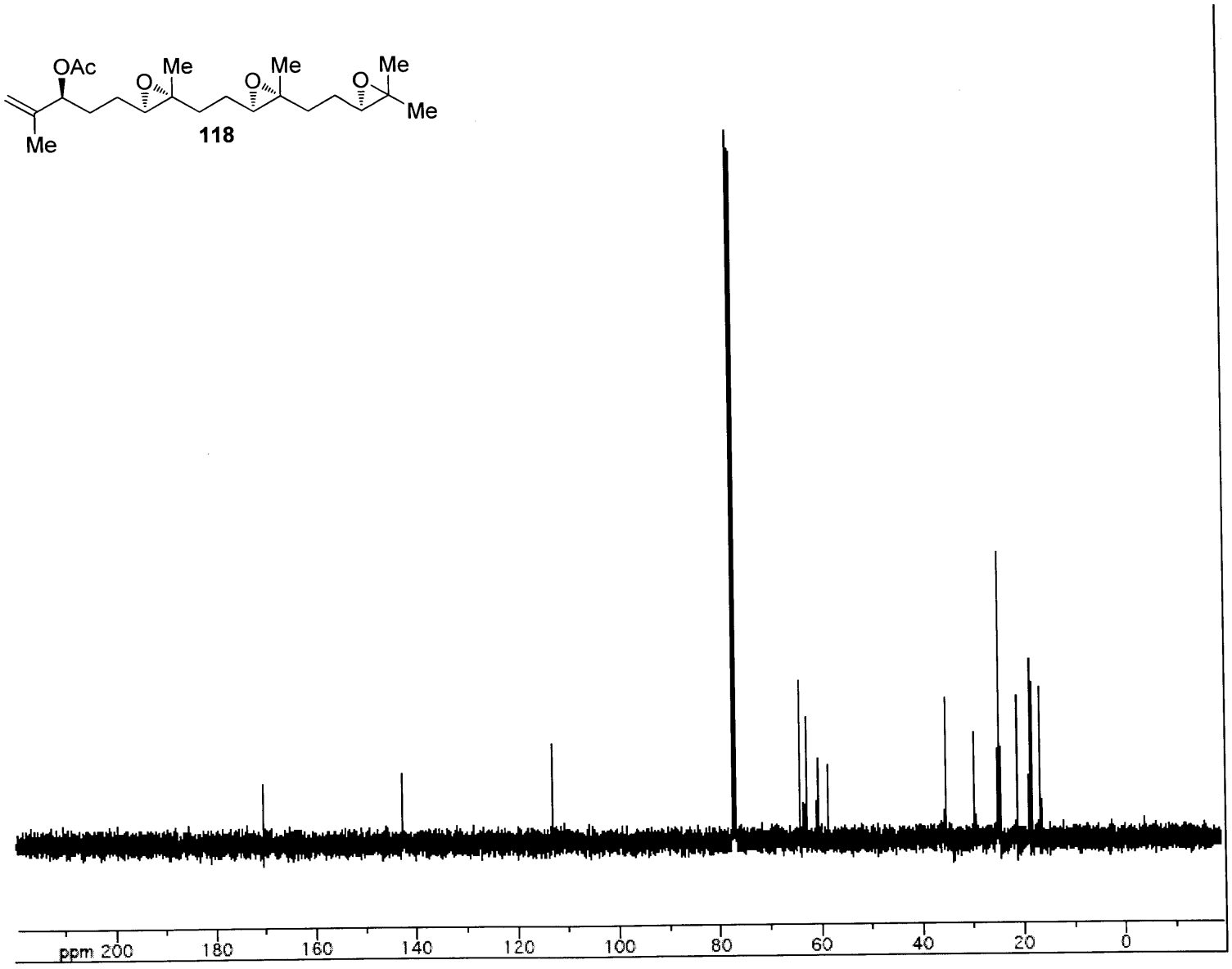


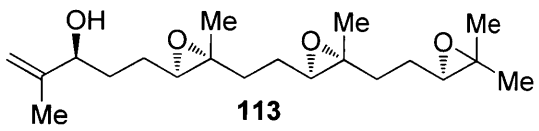


117

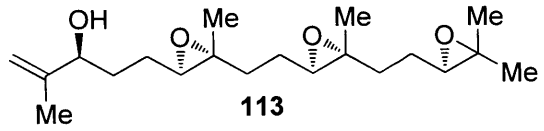


118

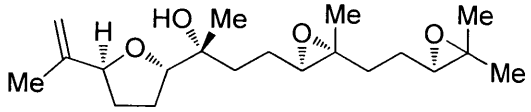

OAc
Me
Me
Me
Me
Me
O
O
O
118
ppm 200
180
160
140
120
100
80
60
40
20
0



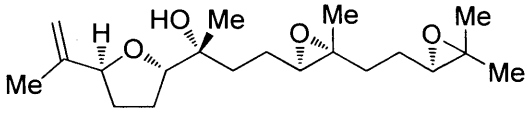
113



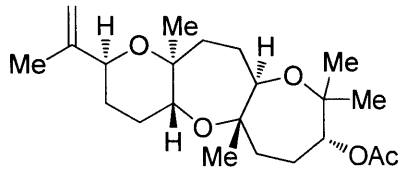
113



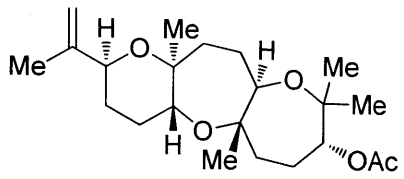
SI-113A



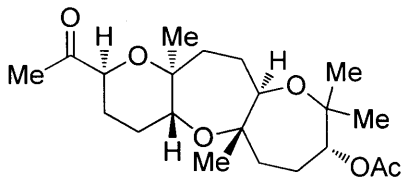
SI-113A



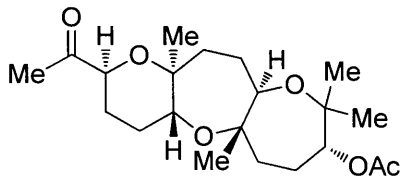
119



119

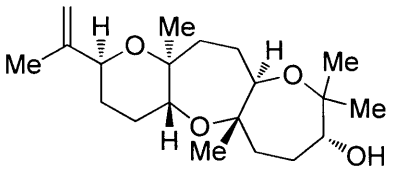


120

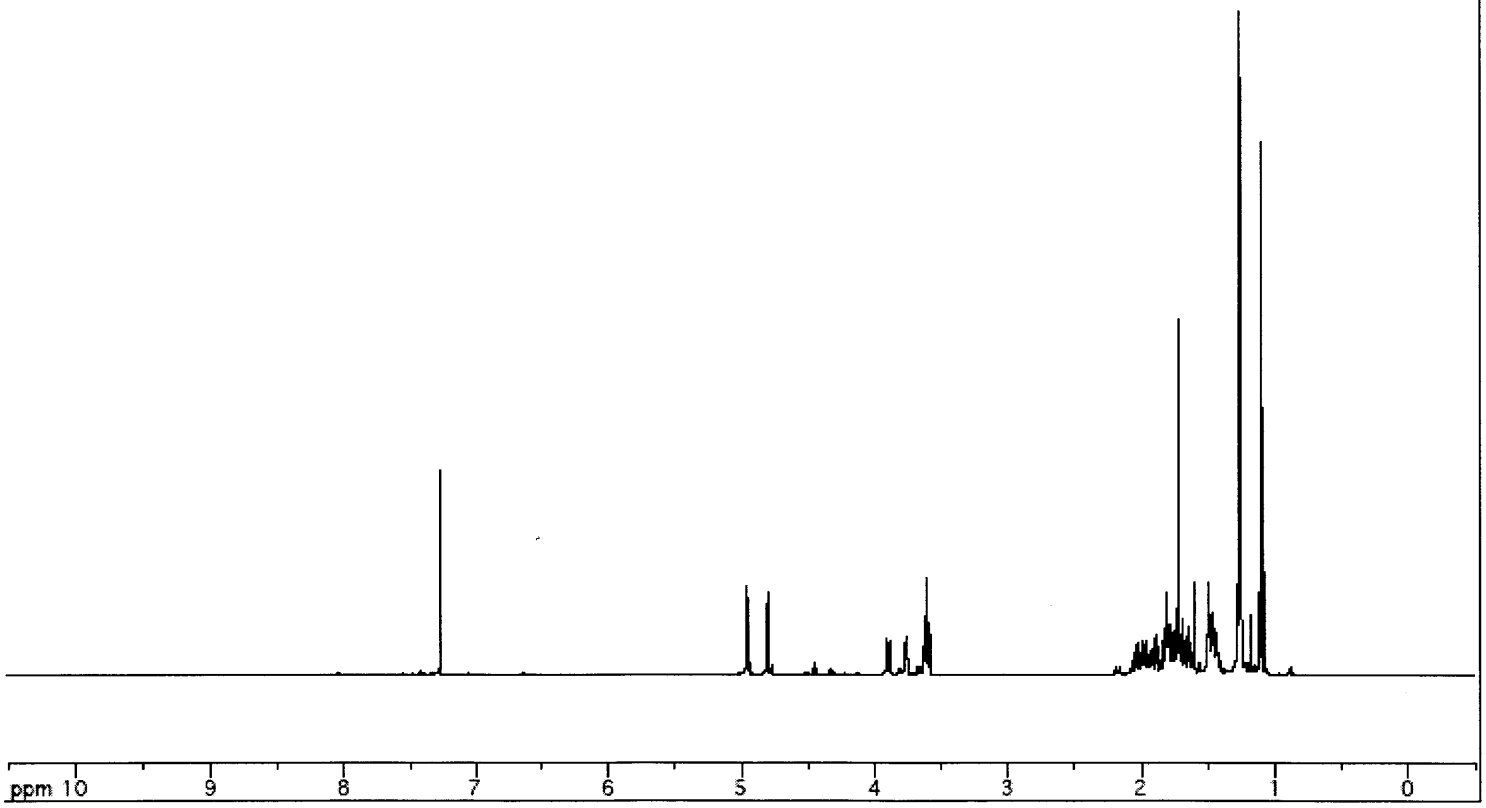

O
H
Me
O
Me
H
O
Me
Me
O
H
Me
OAc

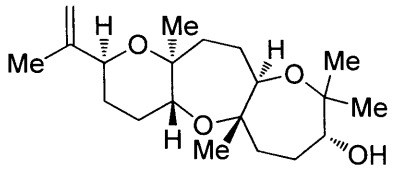
120

77.55
ppm 200
180
160
140
120
100
80
60
40
20
0

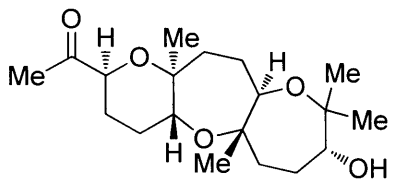


112

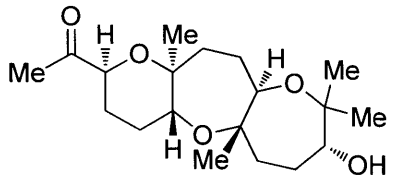




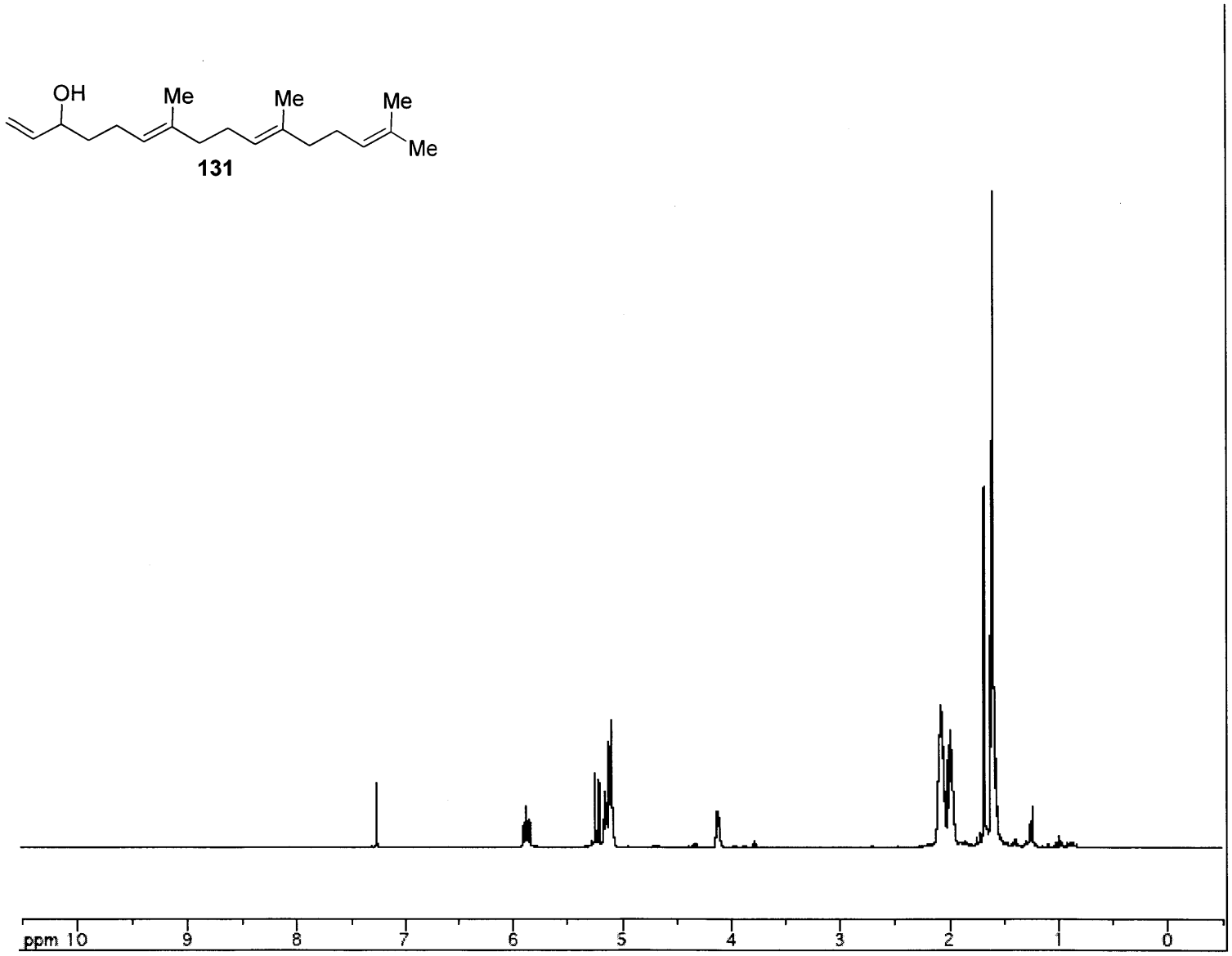
112



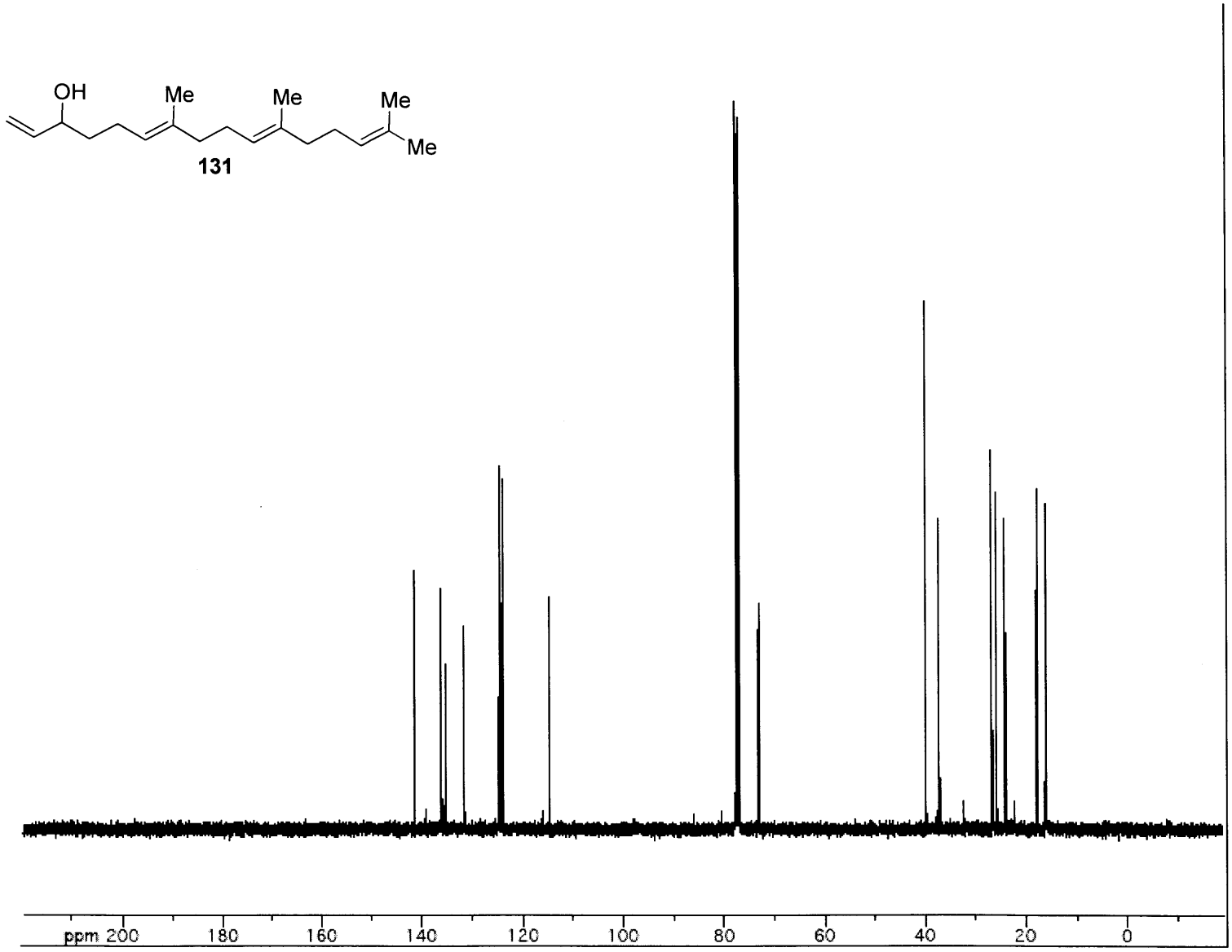
121

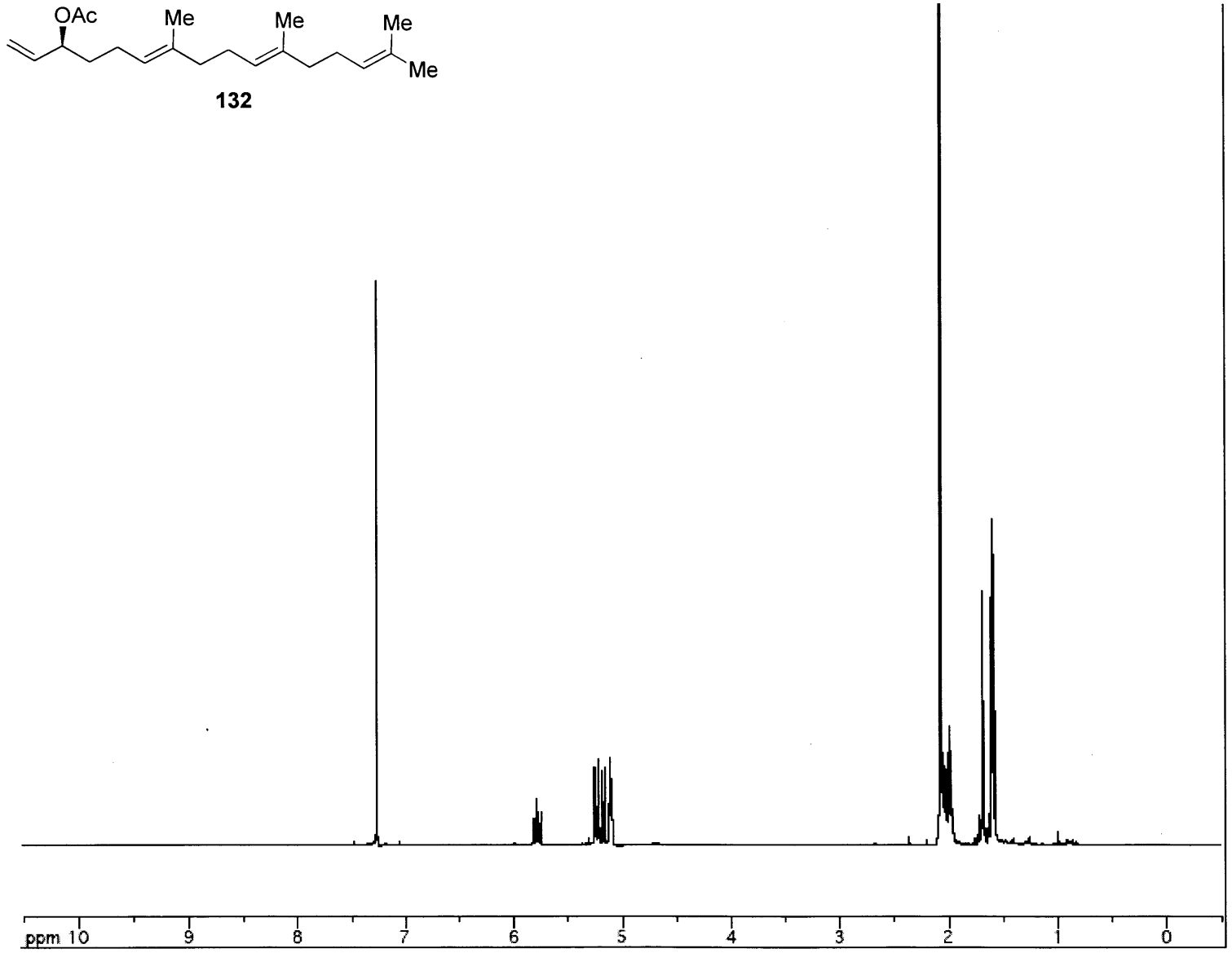


121

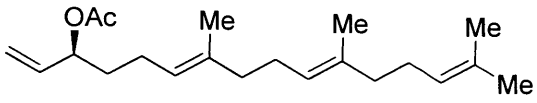


131

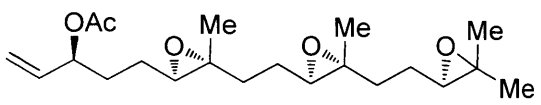

OH
Me
Me
Me
Me
131
ppm 200
180
160
140
120
100
80
60
40
20
0



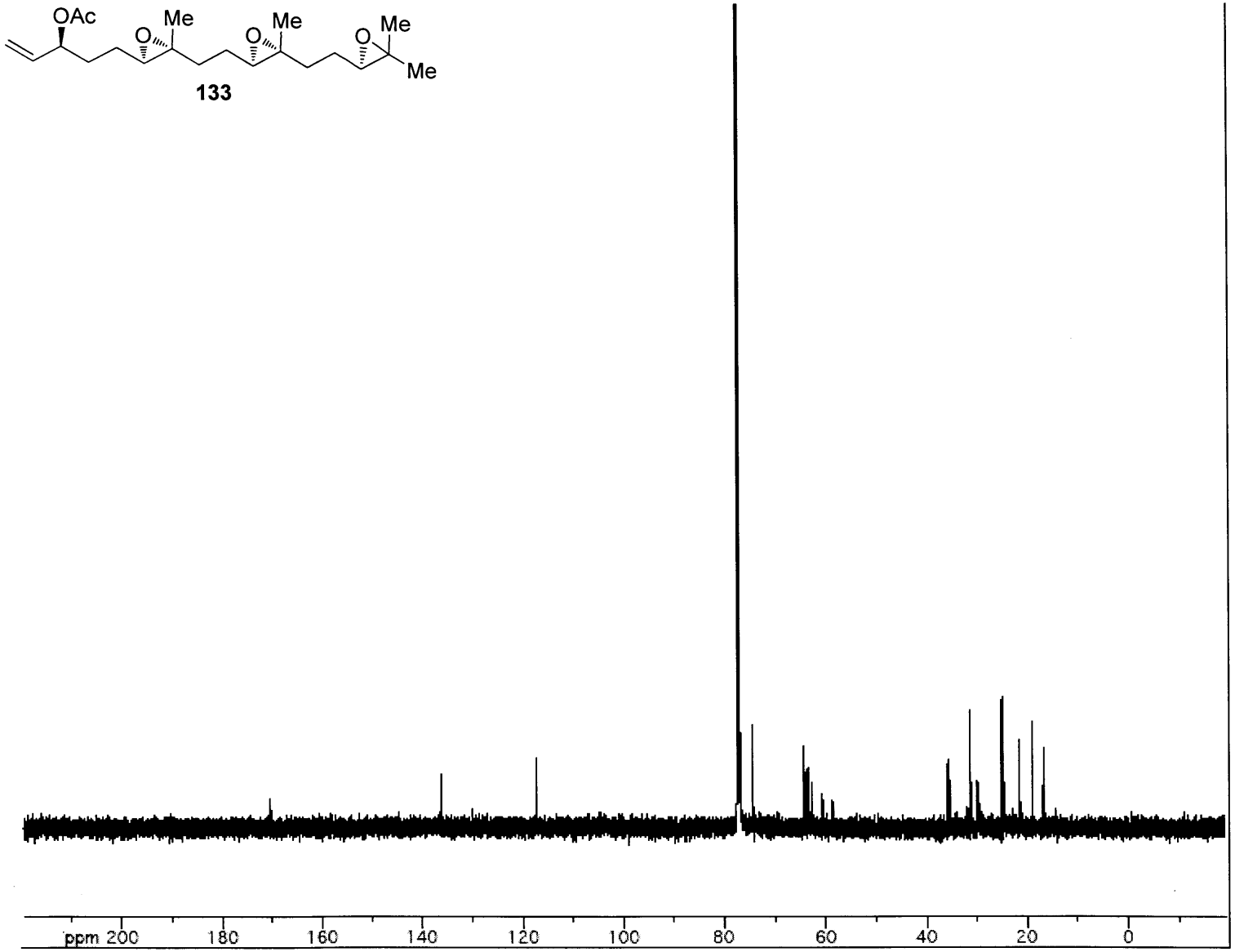
132

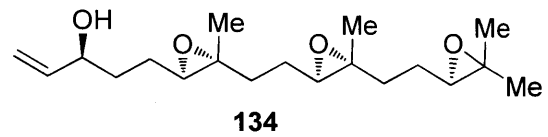


132

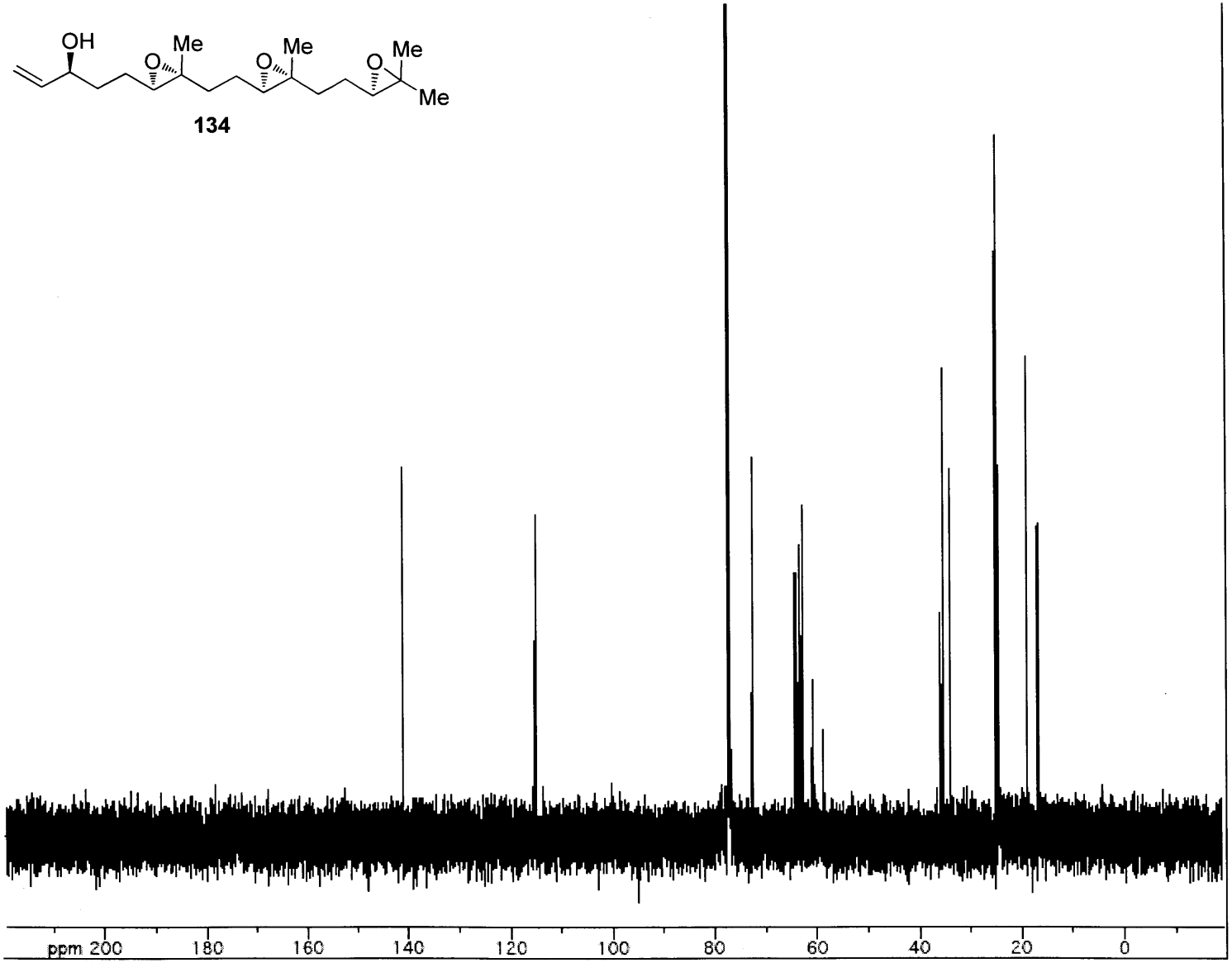


133

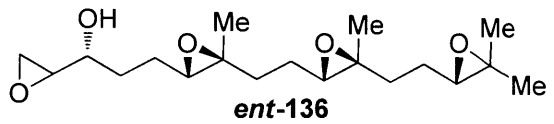

OAc
Me
Me
Me
Me
133
ppm 200
180
160
140
120
100
80
60
40
20
0



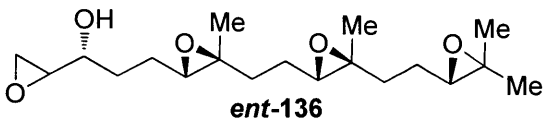
134



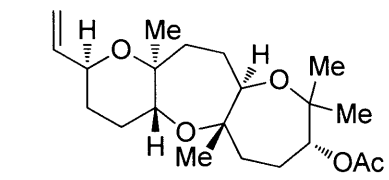
134



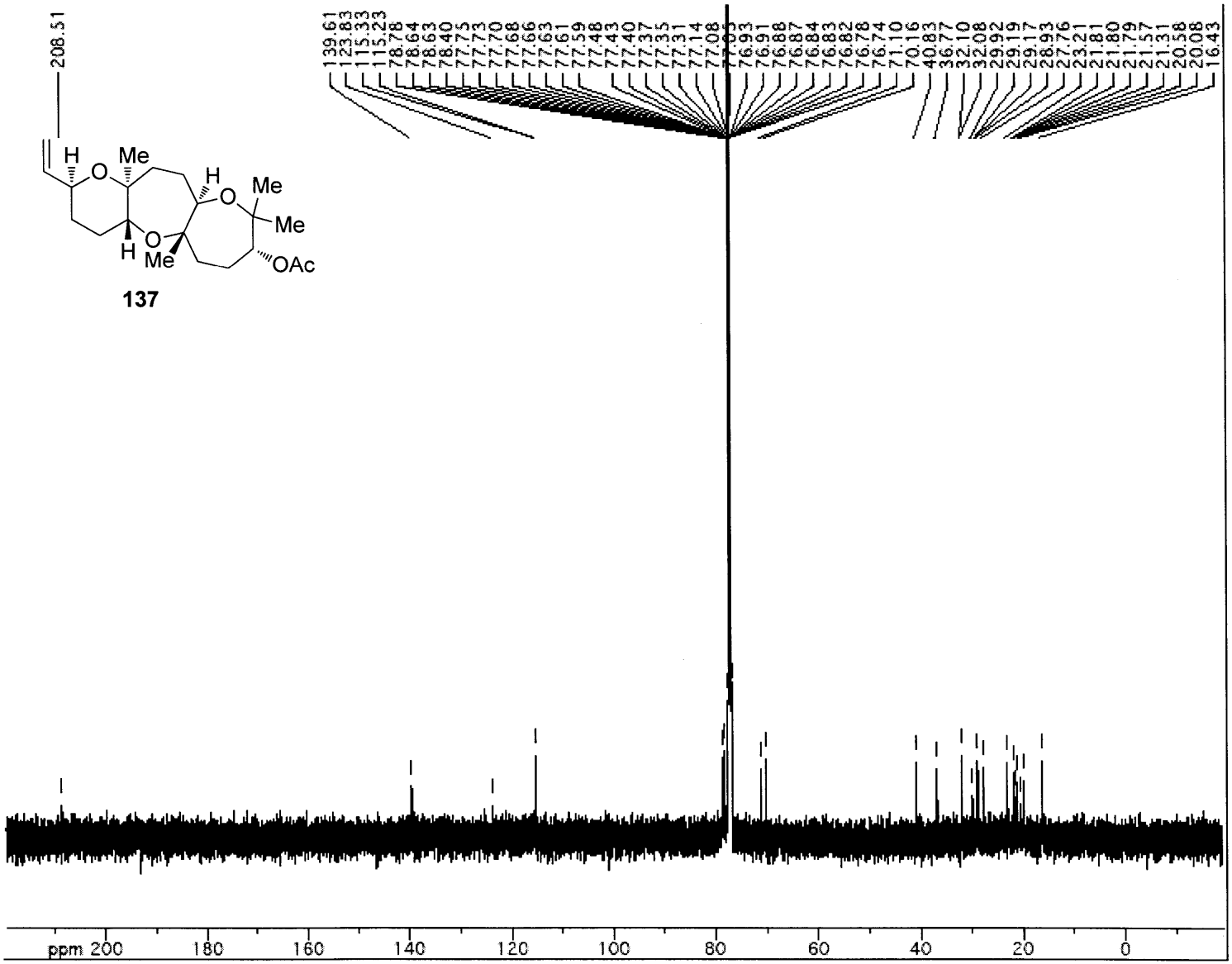
***ent*-136**

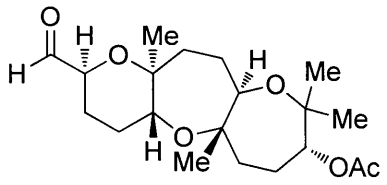


***ent*-136**

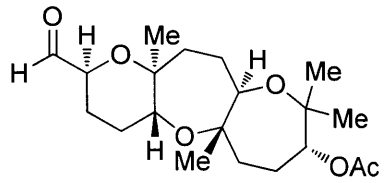


137

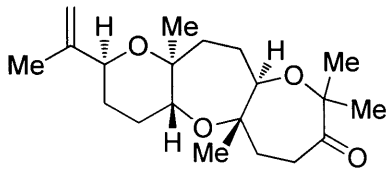

208.51
H
O
Me
H
O
Me
Me
O
H
Me
OAc
137
139.61
123.83
115.33
115.23
78.78
78.64
78.63
78.40
77.75
77.73
77.70
77.68
77.66
77.63
77.61
77.59
77.48
77.43
77.40
77.37
77.35
77.31
77.14
77.08
76.93
76.91
76.88
76.87
76.84
76.83
76.82
76.78
76.74
71.10
70.16
40.83
36.77
32.10
32.08
29.92
29.19
29.17
28.93
27.76
23.21
21.81
21.80
21.79
21.57
21.31
20.58
20.08
16.43
ppm 200
180
160
140
120
100
80
60
40
20
0



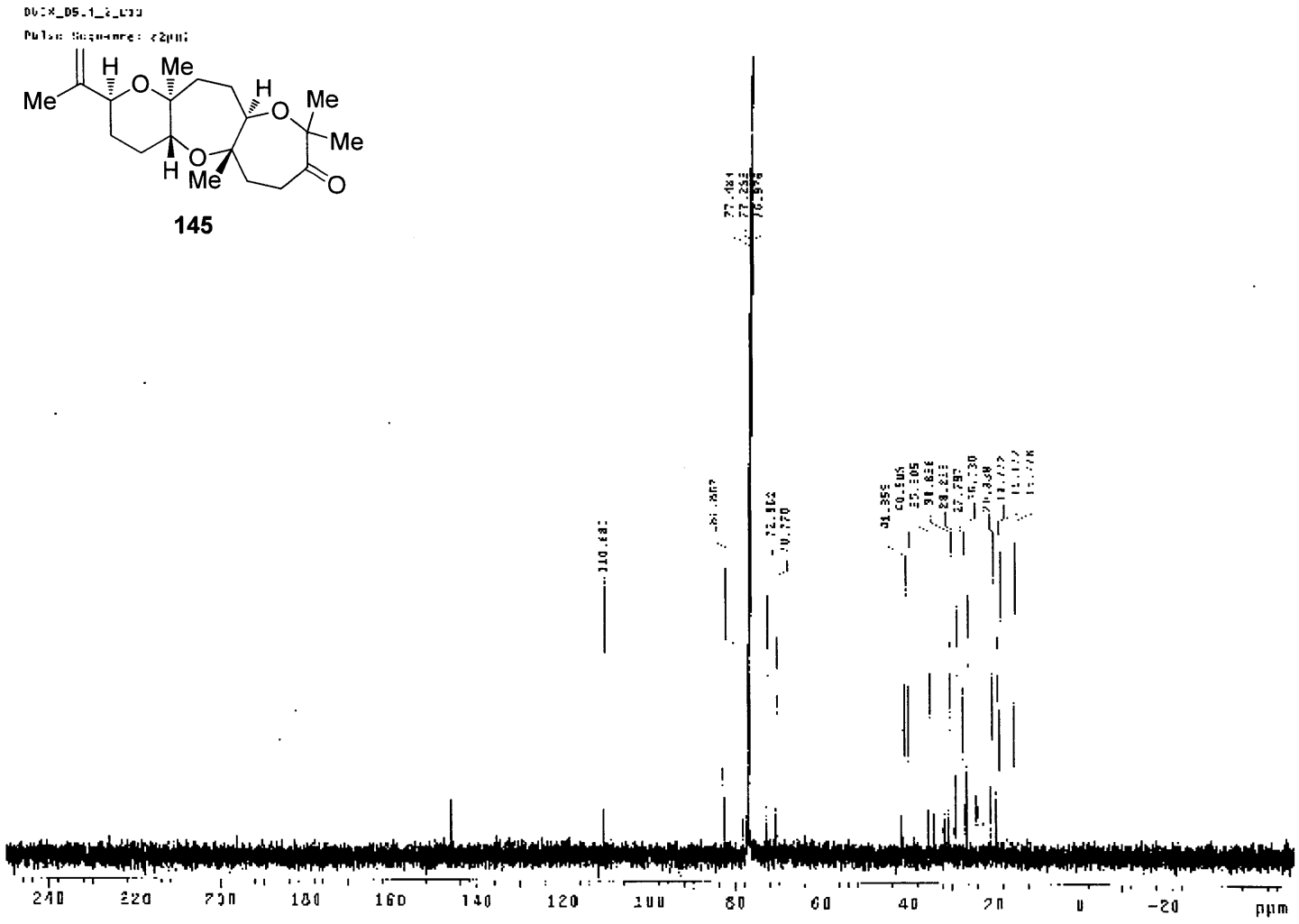
138

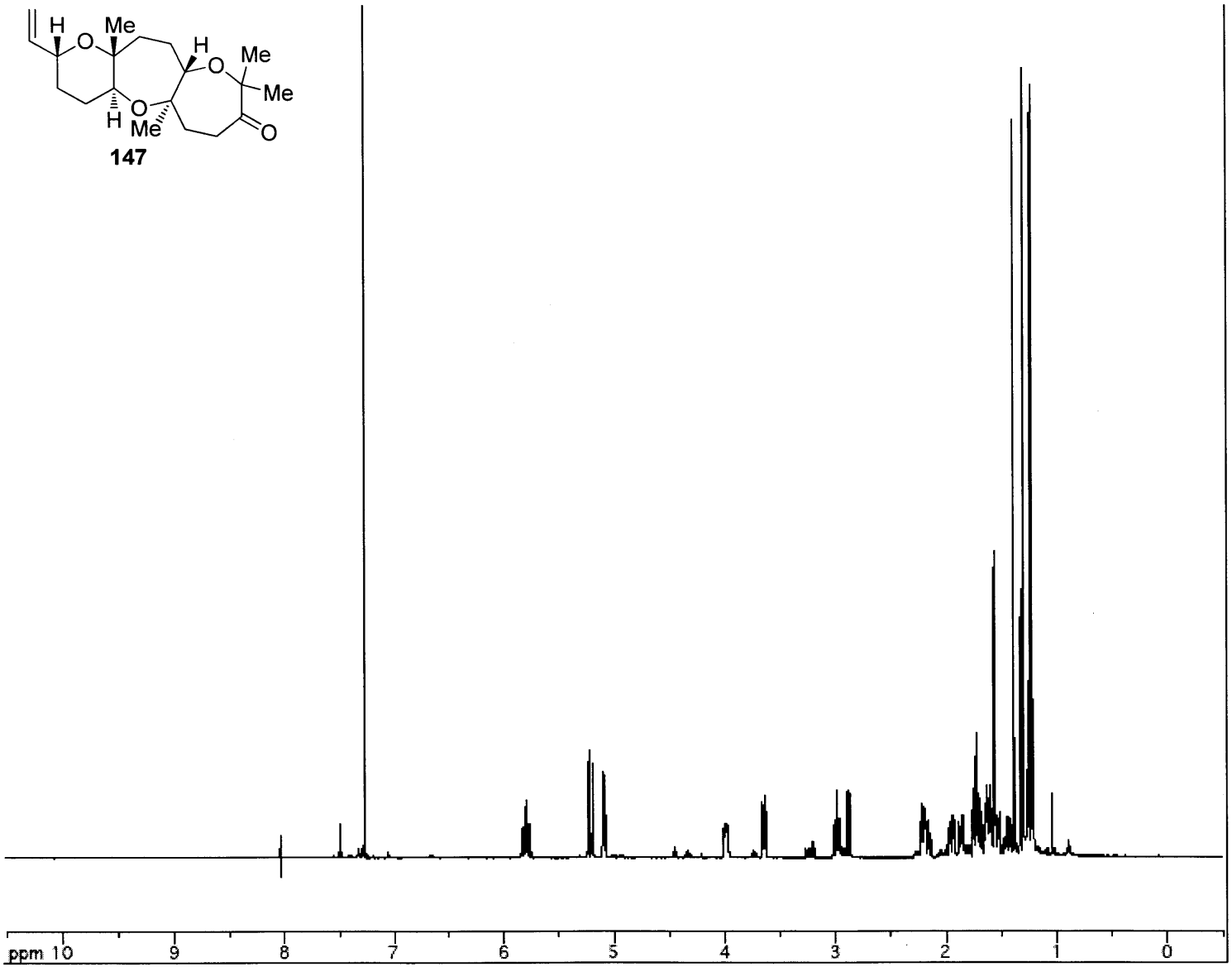


138

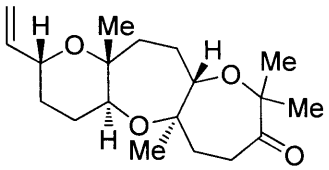


145

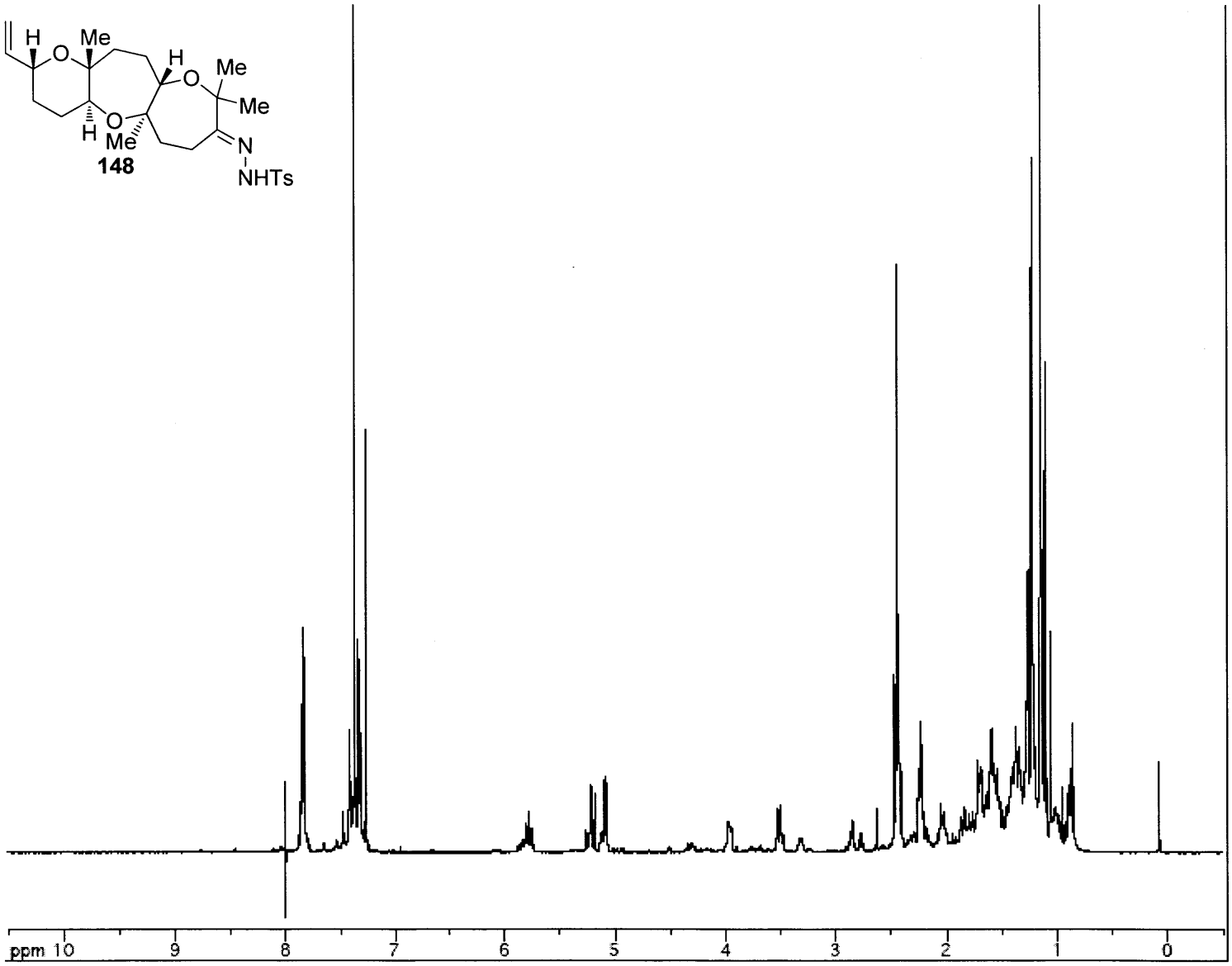

H
O
Me
Me
H
O
Me
Me
H
O
Me
O
145
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

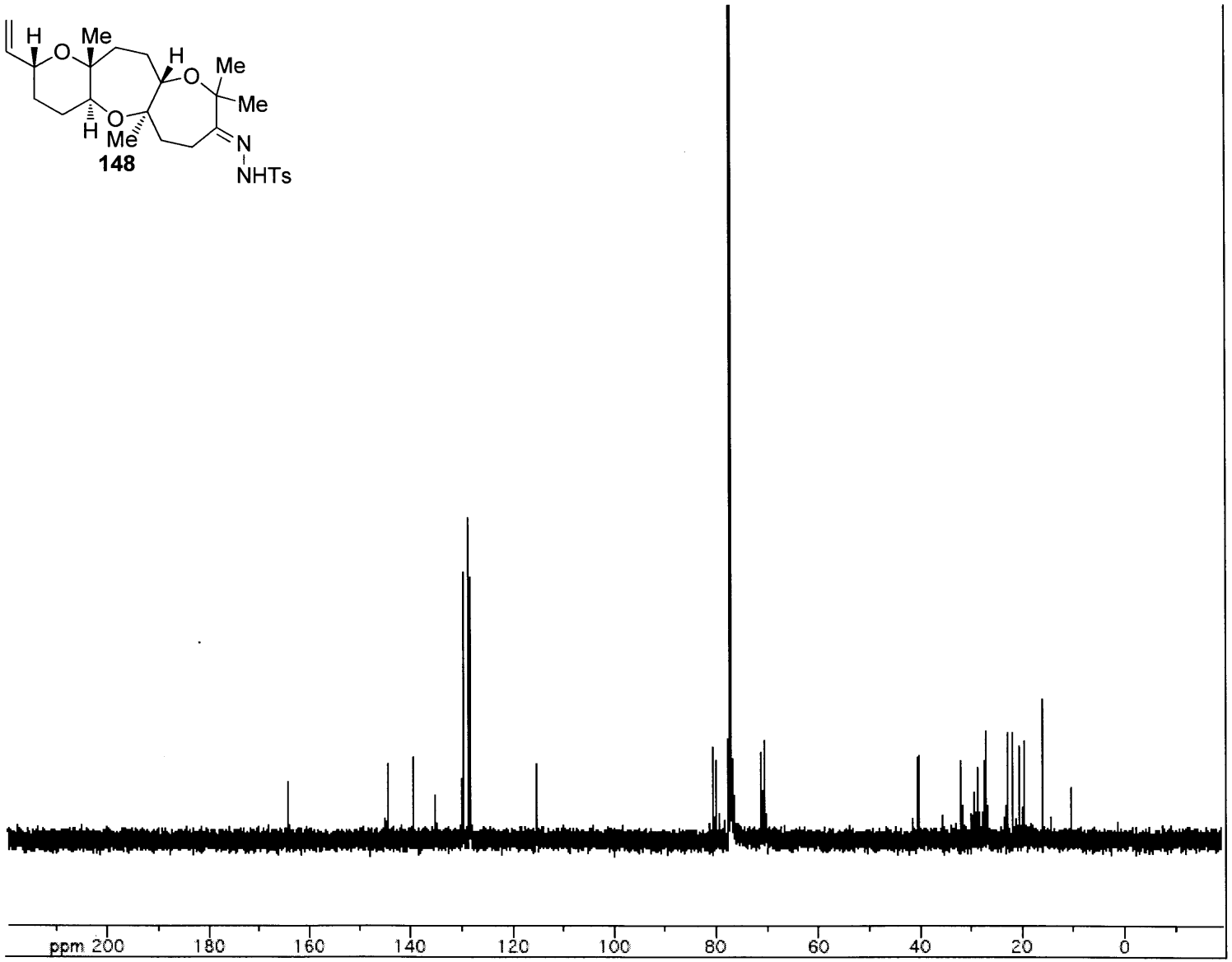


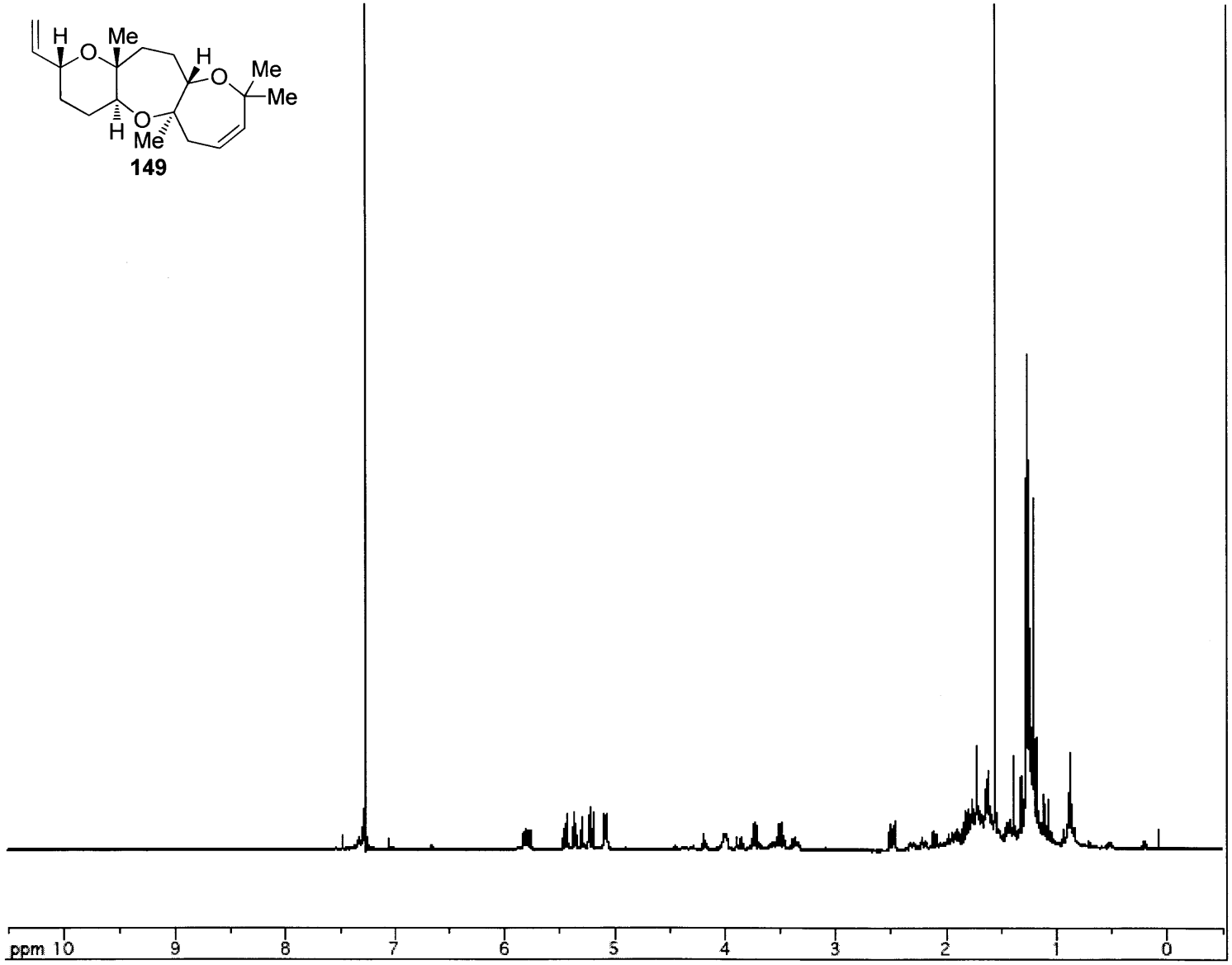
147



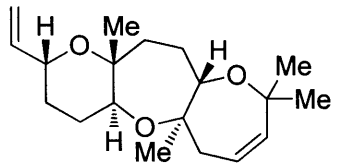
147


H
Me
O
H
O
Me
Me
H
O
Me
N
NHTs
148
ppm 10
9
8
7
6
5
4
3
2
1
0


H
Me
O
H
O
Me
Me
H
O
Me
N
NHTs
148
ppm 200
180
160
140
120
100
80
60
40
20
0



149



149

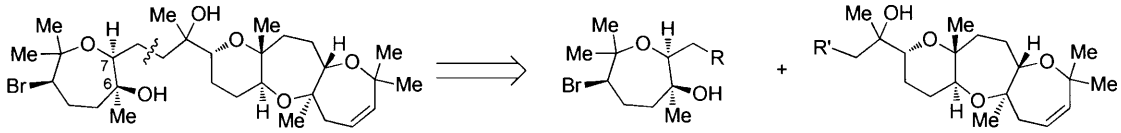
Chapter 2

Fragment Coupling, Synthesis, and Determination of the Absolute Configuration of Armatol A

Background

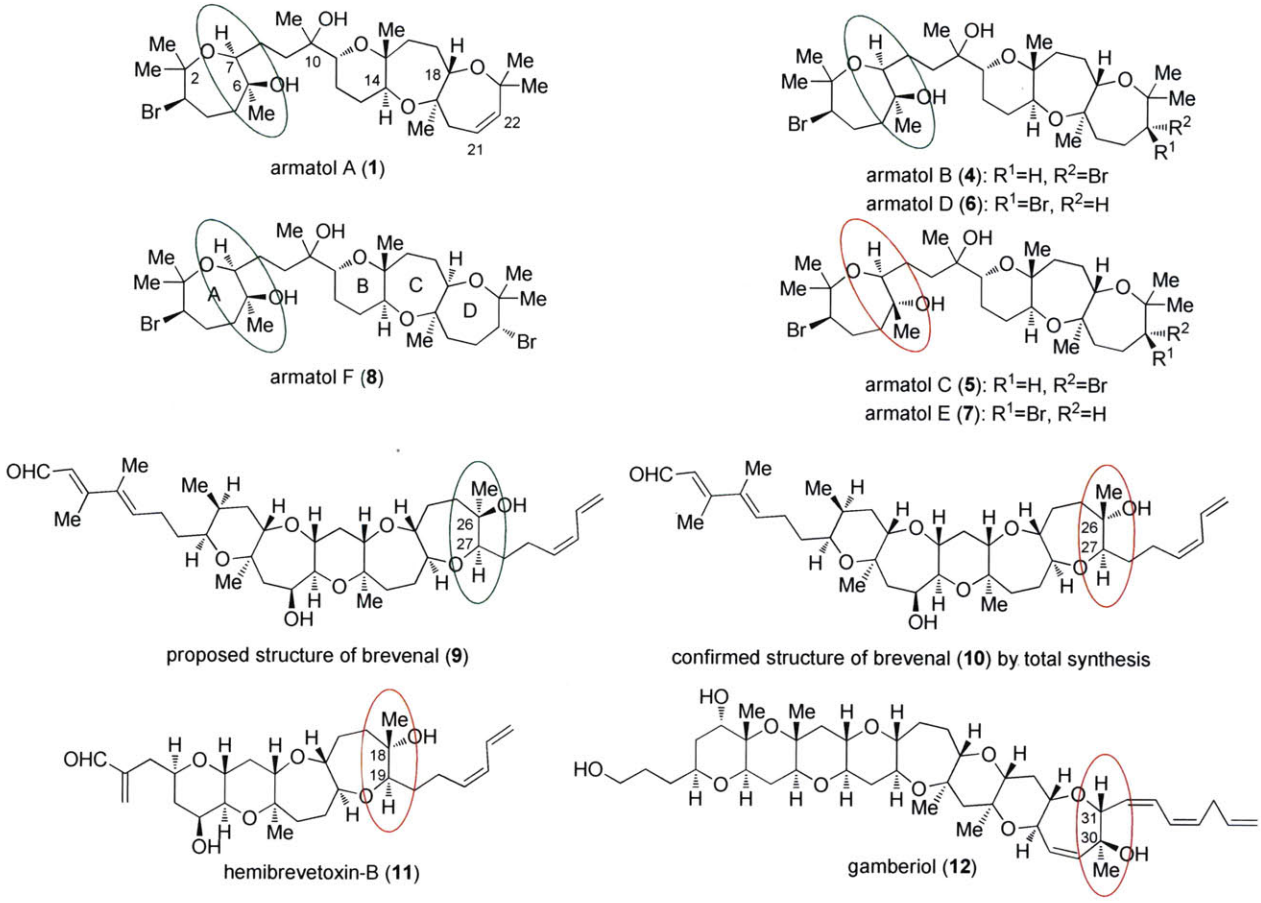
One of the key challenges in constructing a polyether natural product such as armatol A (**1**) is the installation of the bromooxepane ring, which is relatively rare in oxasqualenoids. Completion of this task is critical to the fragment coupling strategy shown in Scheme 2-1, in which oxepane **2** could be coupled with a suitably functionalized fragment such as tricycle **3**. As discussed in Chapter 1, this approach was also selected in order to determine the absolute and relative configuration of the natural product.

Scheme 2-1



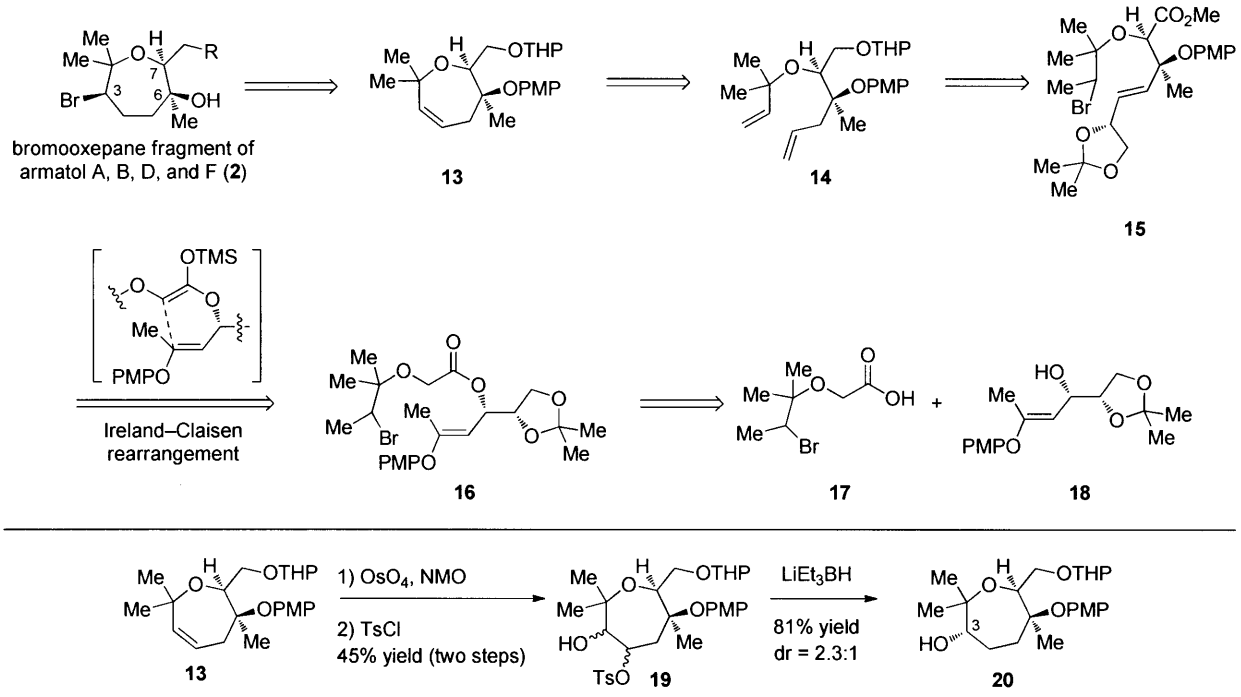
The cis-relationship between the hydroxyl group at C6 and the alkyl chain at C7 in **1** is unusual among polyether natural products, as many other related oxepanes found from marine sources have a trans-relationship of these groups (Figure 2-1).[1,2] Following the confirmation in 2006 of the correct structure of brevenal (**10**), the C6-C7 cis-relationship in the oxepane ring of armatols A (**1**), B (**4**), D (**6**), and F (**8**) are the only known marine polyethers with this stereochemical relationship. Since armatols C (**5**) and E (**7**) have a different trans-relationship within the same family of natural products, this family may arise from a different biogenesis than other oxasqualenoids leading to a different stereochemical relationship between C6 and C7.

Figure 2-1. Various marine natural products with cis or trans proton/methyl relationships



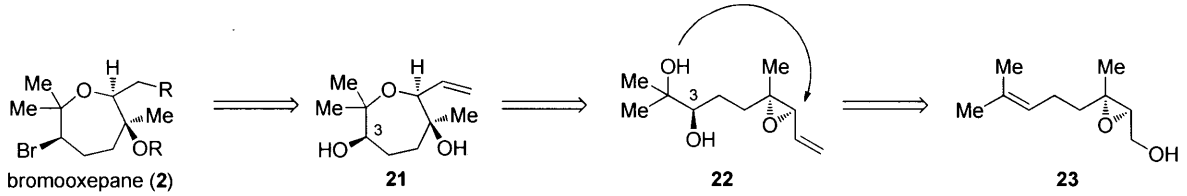
Recently, two reports by Fujiwara and co-workers described the first synthetic effort toward armatol F (**8**).[3] The total synthesis of armatol F has yet to be reported. Fujiwara's approach to bromooxepane **2**, also found in armatol A (**1**), B (**4**), and D (**6**) involves a stereoselective Ireland–Claisen rearrangement to form ether **15** and ring-closing metathesis to provide key intermediate **13** (Scheme 2-2). A three-step protocol (**13** to **20**) allowed for the installation of the hindered alcohol at C3, albeit in poor diastereomeric ratio. The synthesis of compounds bearing a bromine atom at this position was not discussed.

Scheme 2-2. Fujiwara's strategy for the synthesis of armatol F



Synthetic studies

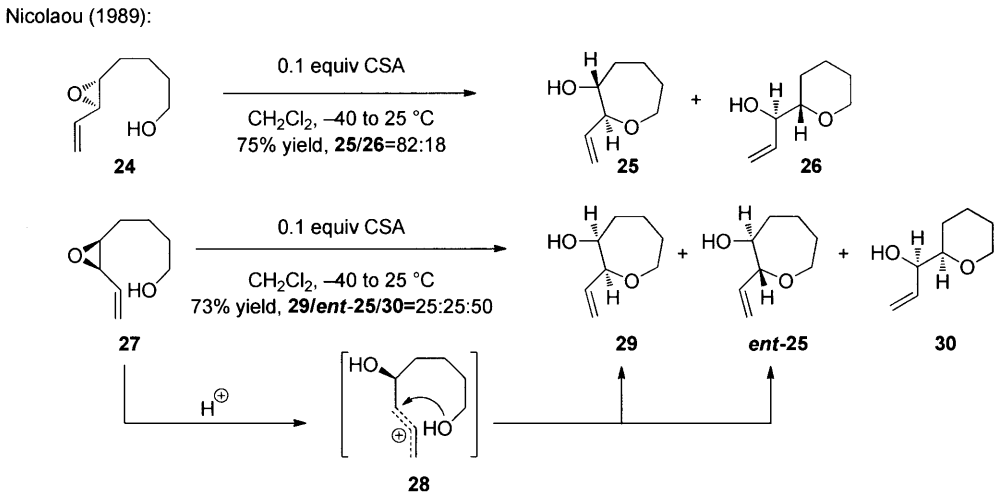
Scheme 2-3. Strategy for the construction of bromooxepane **2**



Our initial strategy to form bromooxepane **2** involved assembling alcohol **21** from epoxydiol **22** (Scheme 2-3). We planned to use a vinyl group[4] to affect an *endo*-selective epoxide-opening of substrate **22**. In two examples shown (Scheme 2-4), the nucleophile was a primary alcohol and acid-promoted conditions were used. Generally, stereochemical erosion occurs to some extent. In the first case, Nicolaou[4] prepared oxepane **29** from vinyl epoxide **27**,

and in the second, Nakata[5] observed that activation of styrenyl epoxide **31** with either PPTS or CSA gave 4:1 selectivity in favor of oxepane **33**, in which the hydroxyl group and the alkyl chain are cis.

Scheme 2-4. Previous synthetic efforts to form oxepane rings via alkene-directed, acid-promoted *endo*-selective cyclizations of epoxy alcohols

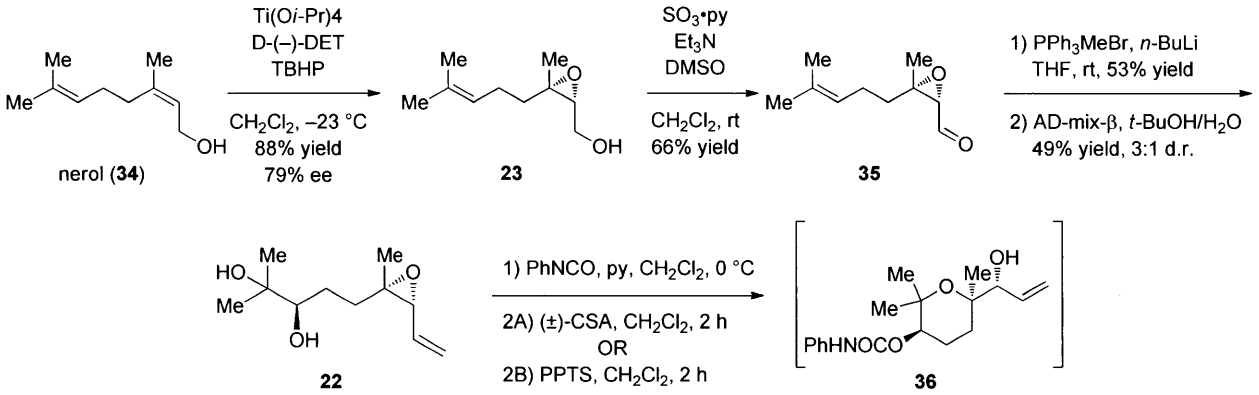


Promoter	Loading	Solvent	T	Time	Yield	(*E*)-*trans*-**32**		(*E*)-*cis*-**33**
PPTS	1.0 equiv	CH_2Cl_2	rt	19 h	80%	16	:	84
CSA	0.2 equiv	CH_2Cl_2	rt	10 min	83%	21	:	79

To investigate whether a tertiary alcohol might behave similarly under acidic conditions, diol **22** was constructed from nerol (**34**, Scheme 2-5). Sharpless asymmetric epoxidation proceeded smoothly with D-(–)-diethyl tartrate to give **20** in 79% ee. Parikh–Doering oxidation[6] provided epoxyaldehyde **35**. A Wittig methylenation followed by a Sharpless asymmetric dihydroxylation[7] proceeded in modest yield to provide a 3:1 mixture of diastereomers (**22**). To prevent cyclization initiated by the secondary alcohol (which has been observed in related

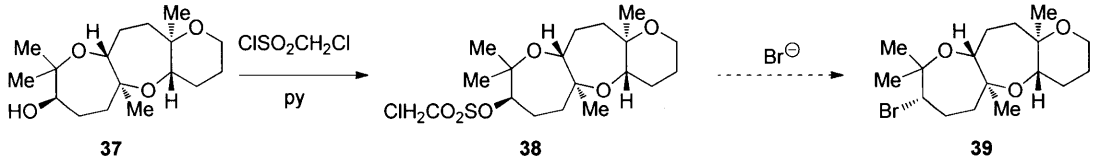
studies),[8] selective protection of the secondary alcohol was attempted. Unfortunately, under basic conditions using reagents such as TBSCl and TESCl, cyclization was observed. Vidari and co-workers reported an example of a selective protection with a carbamate group in a similar diol.[9] When **22** was treated with phenyl isocyanate the carbamate protected product was obtained, but treatment of this compound with both CSA and PPTS in dichloromethane led predominantly to THP **36**.

Scheme 2-5. Synthesis and cyclization of diol **22**



Similar studies in the Jamison group have also shown that the conversion of a similar, sterically hindered secondary alcohol to a bromide under S_N2 conditions was extremely difficult. Thus, we decided that pursuit of a route based on such a transformation should be reconsidered (Scheme 2-6).[10] The steric hindrance at this center prevented nucleophilic displacement. The only reaction observed was elimination to the oxepene.

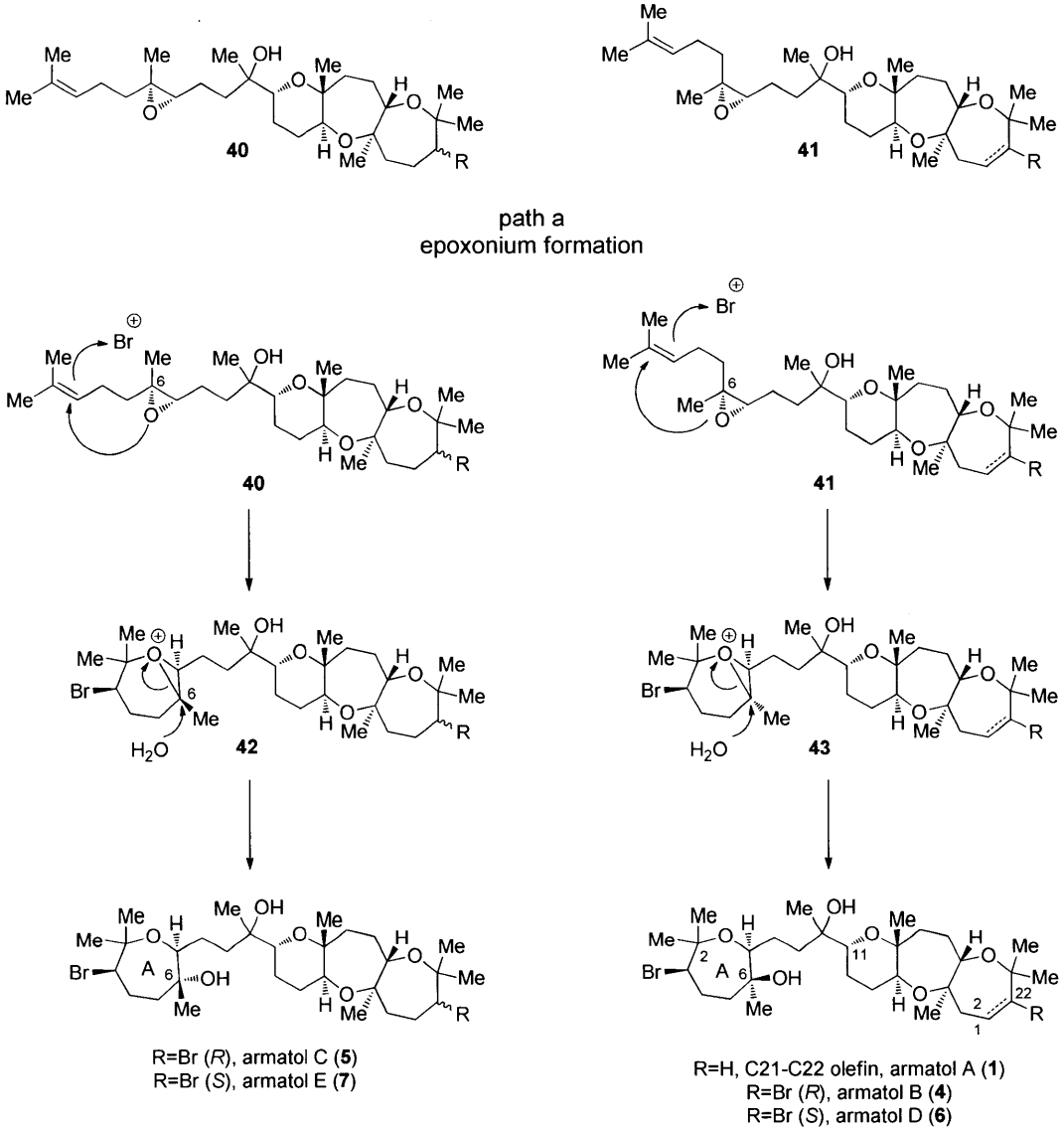
Scheme 2-6. Investigations of conversion of a hindered alcohol to a bromide.[10]



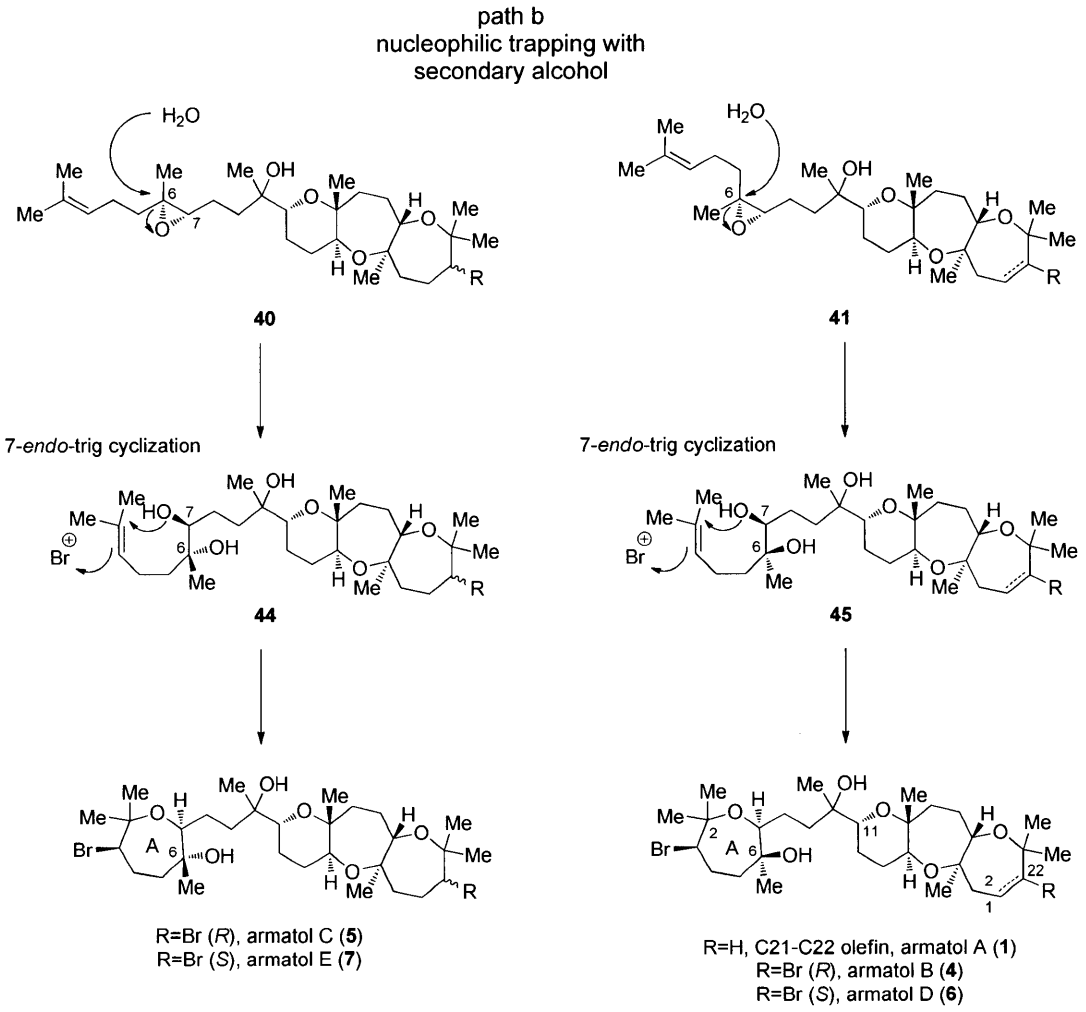
Bromonium-initiated cyclizations

In Chapter 1 we discussed the formation of the tricyclic fragment via an epoxide-opening cascade.[11] The configuration at C6 varies among the six members of the armatol family (Figure 2-1), and one way to account for this stereochemical difference would be a trans-to-cis isomerization of the squalene precursor, thus leading to tetraepoxides **40** and **41** (Schemes 2-7 and 2-8).[12] Isomers (**40** and **41**) could then react via two different pathways to form the A-ring of the armatol family. One possibility for the formation of the bromooxepane ring, path a, involves the attack of a bromonium intermediate by an epoxide to form an epoxonium ion (**42** and **43**, Scheme 2-7). Opening by water with inversion at C6 would lead to armatols A-E. Alternatively, in path b, acid-induced nucelophilic attack at the C6 carbon by a molecule of water would afford tertiary alcohols **44** and **45c** (Scheme 2-8). Bromoetherification with the C7 alcohol as a trapping nucleophile would then lead to armatols A-E. Further evidence to support that some of the armatol members are derived from a trans epoxide and some from a cis epoxide is the configuration of armatol F (**8**, Figure 2-1). It is epimeric to armatol B (**4**) at C18 which could be accounted for by another trans-to-cis isomerization. Therefore armatol F (**8**) could be formed from *cis,trans,trans,cis*-squalene while the remaining armatol family members are from either *trans,trans,trans,trans*-squalene (armatol A, B, and D) or *cis,trans,trans,trans*-squalene (armatol C and E). All previous successful synthetic efforts towards polyether natural products with bromooxepanes have used some type of bromonium-initiated cyclization.[13] Based on these investigations, it seemed that the best method for the challenging installation of the bromine atom in the bromooxepane would be a bromonium-initiated epoxide-opening cyclization.

Scheme 2-7. Epoxonium formation as a possible biosynthetic pathway to the bromooxepane ring of the armatols (path a)



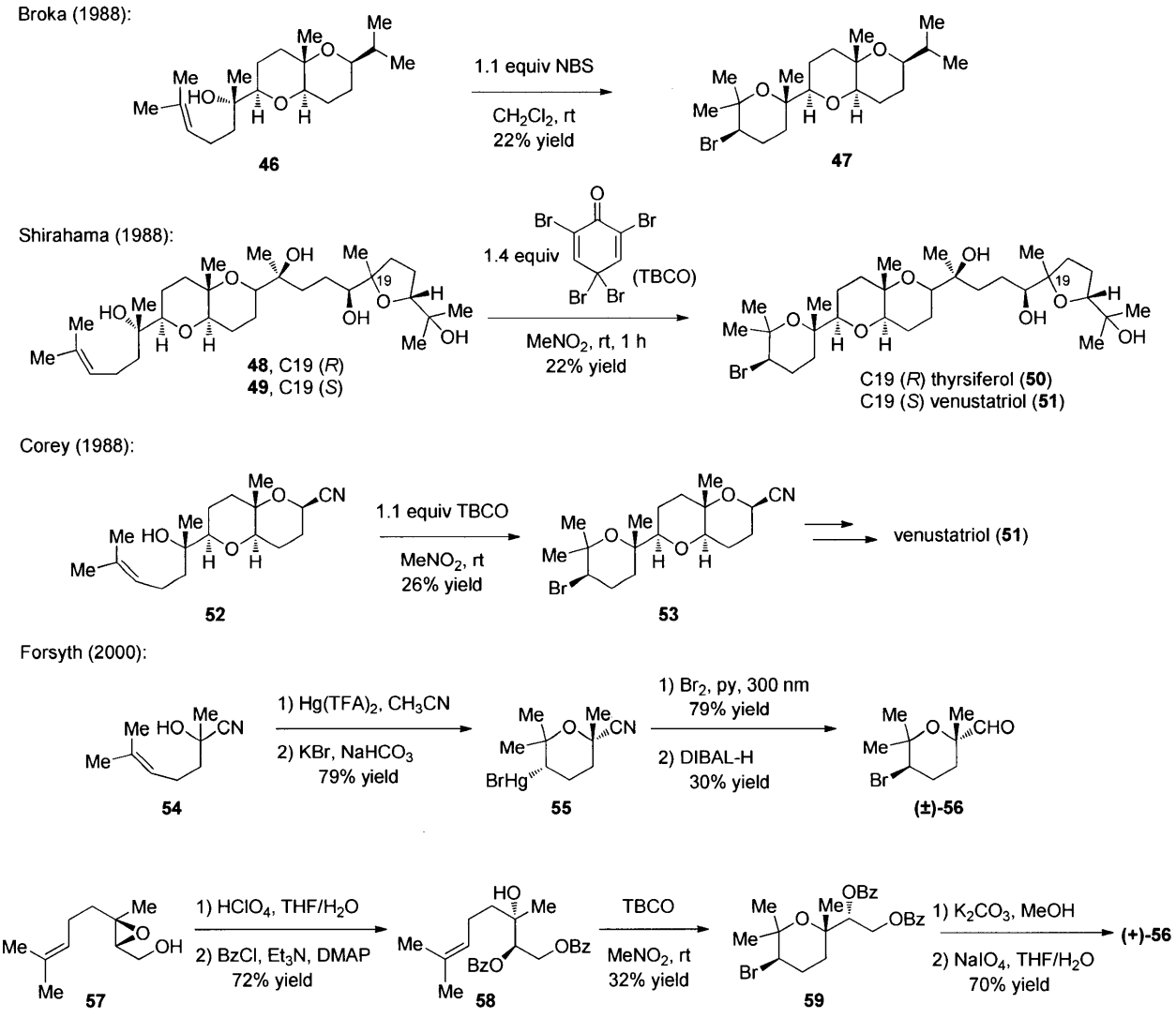
Scheme 2-8. Nucleophilic trapping of an epoxide with a secondary alcohol as a biosynthetic pathway to the bromooxepane ring of the armatols



Relative to bromooxepane synthesis, bromooxane synthesis has been more thoroughly investigated. The formation of THP rings with similarly hindered bromine-containing centers has been explored since the 1980s, especially in syntheses of venustatriol and thysiferol (Scheme 2-9).[14] Many of the strategies used either NBS or 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCO),[15] with a tertiary alcohol as the internal nucleophile. Because the methods were non-stereoselective, obtaining a particular diastereomer of the product was only possible via

purification. Forsyth's studies also demonstrated that this problem could be particularly challenging (Scheme 2-9).[14f]

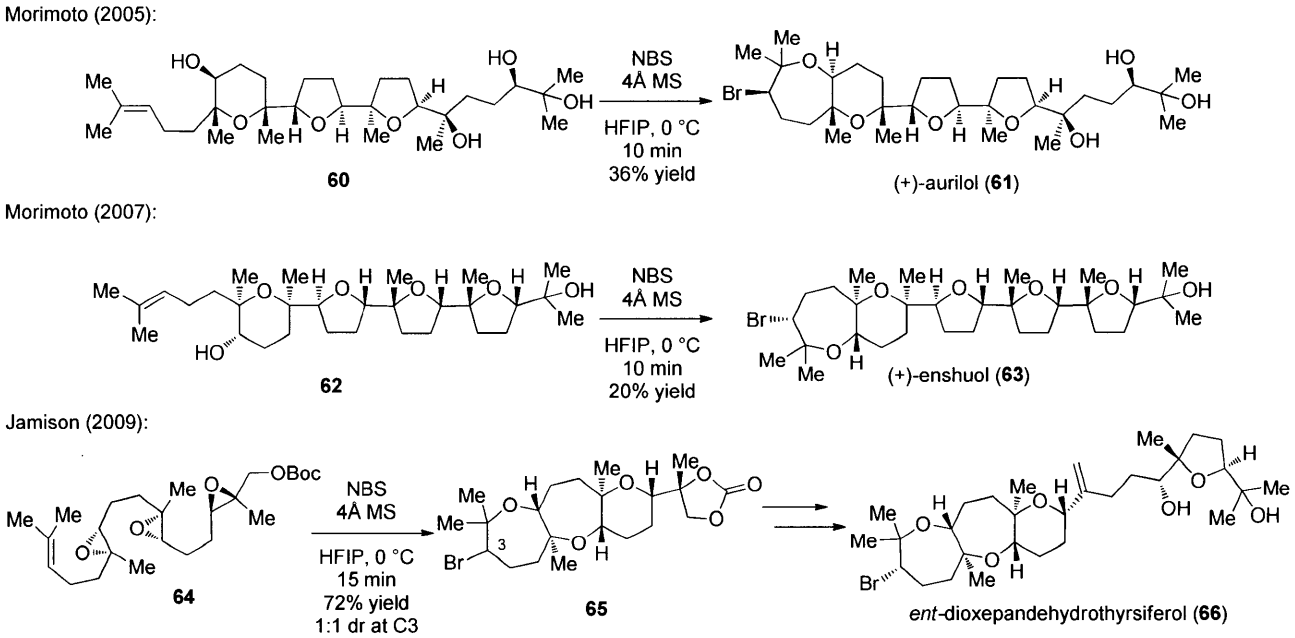
Scheme 2-9



(+)-Aurilol (**61**), (+)-enshuol (**63**), dioxepandehydrothyrsiferol (***ent*-66**), and the armatol family of natural products are the only members of the oxasqualenoids that display a secondary "neopentyl" stereogenic center in which one of the substituents is a bromine atom (Scheme 2-10). Morimoto and co-workers reported the 7-*endo*-trig cyclization of secondary alcohols **60** and

62 in the presence of NBS in hexafluoroisopropanol (HFIP) to form the bromooxepane rings **61** and **63** in 36% and 22% yields, respectively.[16] Tanuwidjaja, Ng, and Jamison recently reported the synthesis of *ent*-dioxepandehydrothyrsiferol (**66**).[17] A key step in the synthesis of **66** was the installation of the secondary bromide in **65** via a cascade event from triepoxide **64**, but no diastereoselectivity was observed. A recent report from Ishihara describes a method for enantioselective halocyclizations of polyprenoids in polyene cyclizations, while no methods for the analogous epoxide-opening cascades are known.[18]

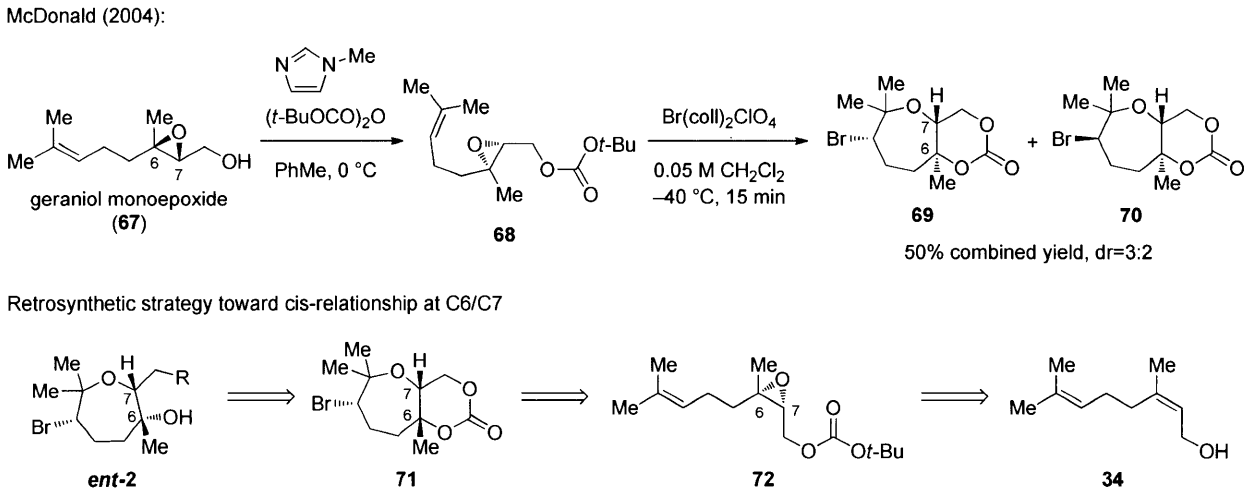
Scheme 2-10



McDonald reported the construction of bromooxepane rings as part of a study on regioselective polyepoxide oxacyclizations.[19] Treatment of Boc-protected epoxy alcohol **68** with bis(*sym*-collidine)bromonium perchlorate[20] furnished the desired bromooxepane as a 3:2 mixture of diastereomers (**69** and **70**, Scheme 2-11). Noted also was that these bromooxepanes are similar to subunits found in the armatol family of natural products. However, as discussed in Schemes 2-7 and 2-8, the trans epoxide of **68**, derived from geraniol, would lead only to armatols

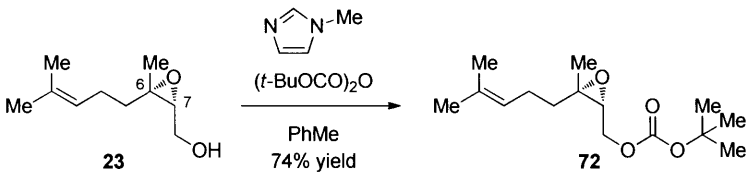
C and E, which possess a trans-fused C6-C7 junction. All other members of the armatol family bearing a cis-relationship in the analogous region of the molecule would need to arise from nerol (**34**) which would lead to **72**, epimeric to **68** at C6.

Scheme 2-11



Use of a bromonium-initiated cyclization toward armatol A

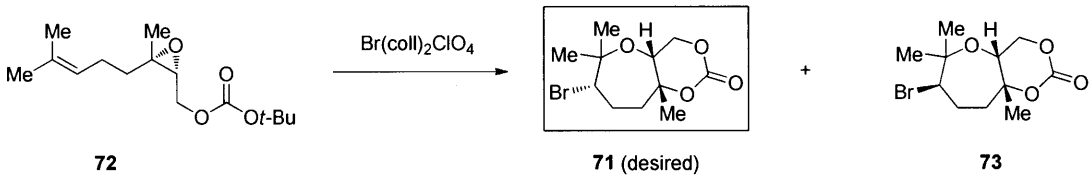
Scheme 2-12



The previously prepared epoxide **23** was treated with Boc anhydride to give the desired carbonate **72** (Scheme 2-12). Treatment of **72** with bis(*sym*-collidine)bromonium perchlorate, as in Scheme 2-11, in either acetonitrile or dichloromethane, led to about 25% total yield of a diastereomeric mixture of **71** and **73** (Table 2-1),[21] with a slight preference for the undesired

diastereomer (**73**). Other undesired side products, including bromohydrins and smaller rings, were formed concomitantly. It seems unlikely that the epoxide stereochemistry could affect the initial bromonium formation, given the distance between the epoxide and the olefin and the relatively high reactivity of this particular bromonium reagent.[22] An evaluation of reaction concentrations in dichloromethane showed concentration and yield to be inversely correlated (Table 2-1, entries 2-5).

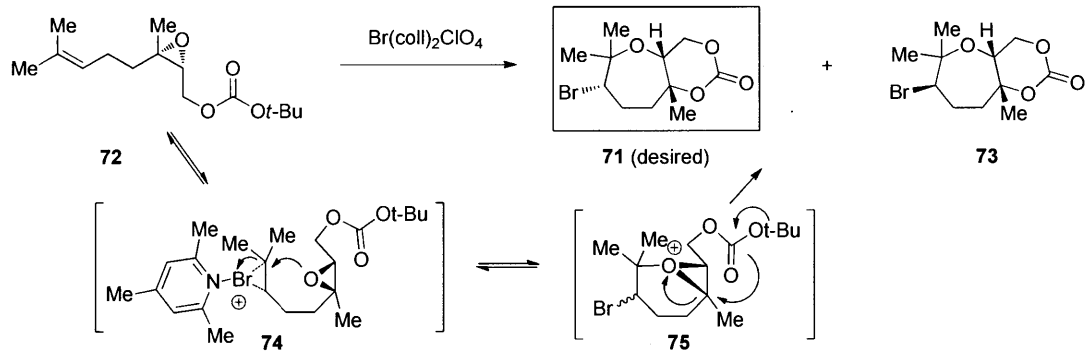
Table 2-1. Cyclization of **72** with $Br(coll)_2ClO_4$



72 **71** (desired) **73**

Entry	Solvent	Temperature (°C)	Conc. [M]	Scale (mmol)	Yield **71** (%)	Yield **73** (%)
1	CH_3CN	–40	0.05	0.37	10	n.d.
2	CH_2Cl_2	–40	0.09	1.23	7	19
3	CH_2Cl_2	–78	0.5	0.37	3	10
4	CH_2Cl_2	–78	0.05	0.37	10	13
5	CH_2Cl_2	–78	0.005	0.37	11	18
6	HFIP	0	0.05	0.37	19	28

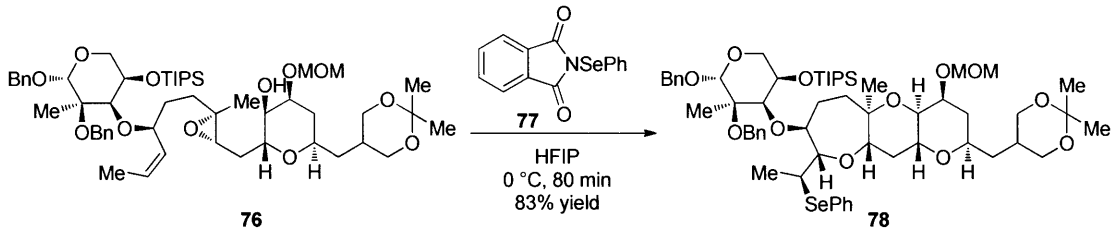
Scheme 2-13. Proposed mechanism for bromonium-initiated epoxide-opening cyclization



The reported ability of hexafluoroisopropanol (HFIP) to stabilize a more S_N1-type transition state in similar reactions led us to examine it as a solvent for this transformation.[23] The

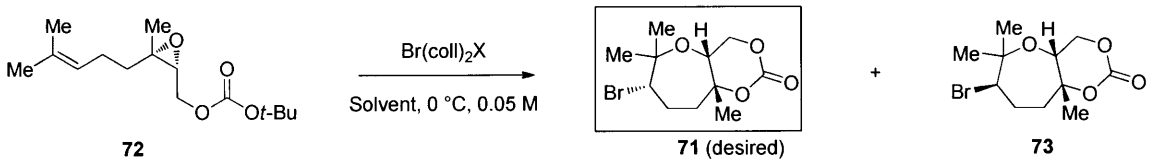
first use of this solvent in this context was described by Holton in a total synthesis of hemibrevetoxin B (Scheme 2-14).[24] *N*-(Phenylseleno)phthalimide proved to be the optimal electrophile to achieve a single diastereomer of the 6,6,7-fused tricycle **78** in which two ether rings were formed in a single operation. Use of HFIP improved the yield of both **71** and **73** to 19% and 28%, respectively (Table 2-1, entry 6). Due to the high price of HFIP and the improved reactivity observed at higher dilutions however, conducting the reactions at 0.05 M was considered an appropriate compromise of yield and cost.

Scheme 2-14. Use of HFIP in an electrophilic cascade for polyether synthesis (Holton)[24]



The requirement for low reaction concentrations may be attributed to a deleterious counterion effect (e.g., undesired ring-opening of the epoxide or product) and thus a screen of counterions was conducted (Table 2-2). However, no effect on yield was observed. Nitromethane, a highly polar, much less expensive solvent was also examined at this juncture. We were pleased to find that treatment of epoxide **72** with $Br(coll)_2BF_4$ in nitromethane (entries 5 and 6) gave results similar to HFIP.

Table 2-2. Evaluation of counterion effects in the cyclization of **72**

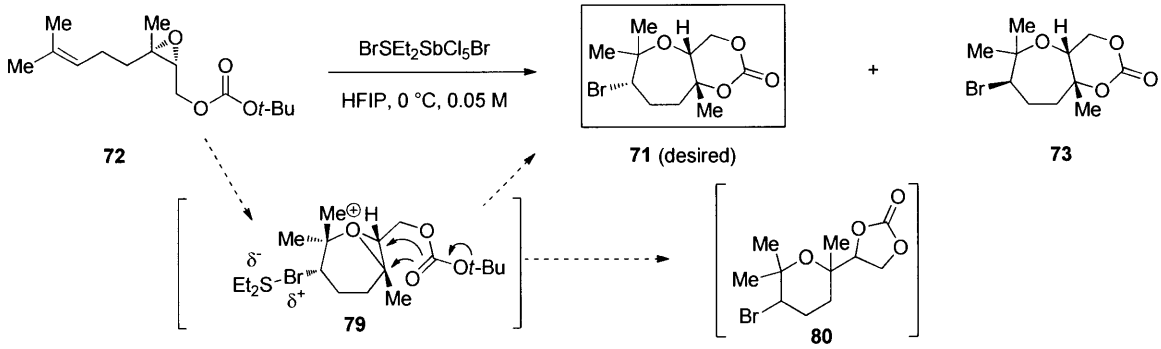


72 **71** (desired) **73**

Entry	X	Solvent	Scale (mmol)	Yield **71** (%)	Yield **73** (%)
1	$ClO_4^{\ominus}$	HFIP	0.37	19	28
2	$ClO_4^{\ominus}$	HFIP	2.27	18	32
3	$OTf^{\ominus}$	HFIP	0.37	17	30
4	$PF_6^{\ominus}$	HFIP	1.84	19	n.d.
5	$BF_4^{\ominus}$	HFIP	2.27	17	31
6	$BF_4^{\ominus}$	$MeNO_2$	0.37	18	28

We then examined bromodiethylsulfonium bromopentachloroantimonate (BDSB), a reagent recently reported by Snyder to have different reactivity towards alkenes than other reagents (Scheme 2-15).[25] While none of the previously observed side products with collidine-derived reagents formed with BDSB, other side products were formed including bromotetrahydropyran **80**.[26] Moreover, on larger scale, the poor solubility of BDSB gave lower yields than those found using collidine-based reagents despite the higher yields obtained on small scale (Table 2-3, entry 3).

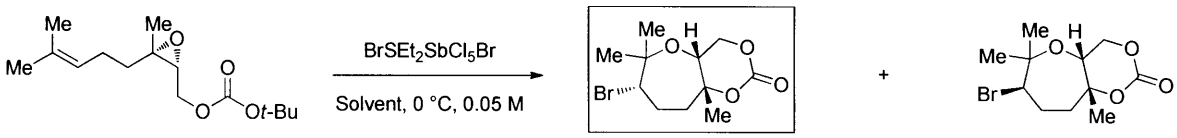
Scheme 2-15



72 **71** (desired) **73**

79 **80**

Table 2-3. Solvent screen for the cyclization of **72** using BDSB



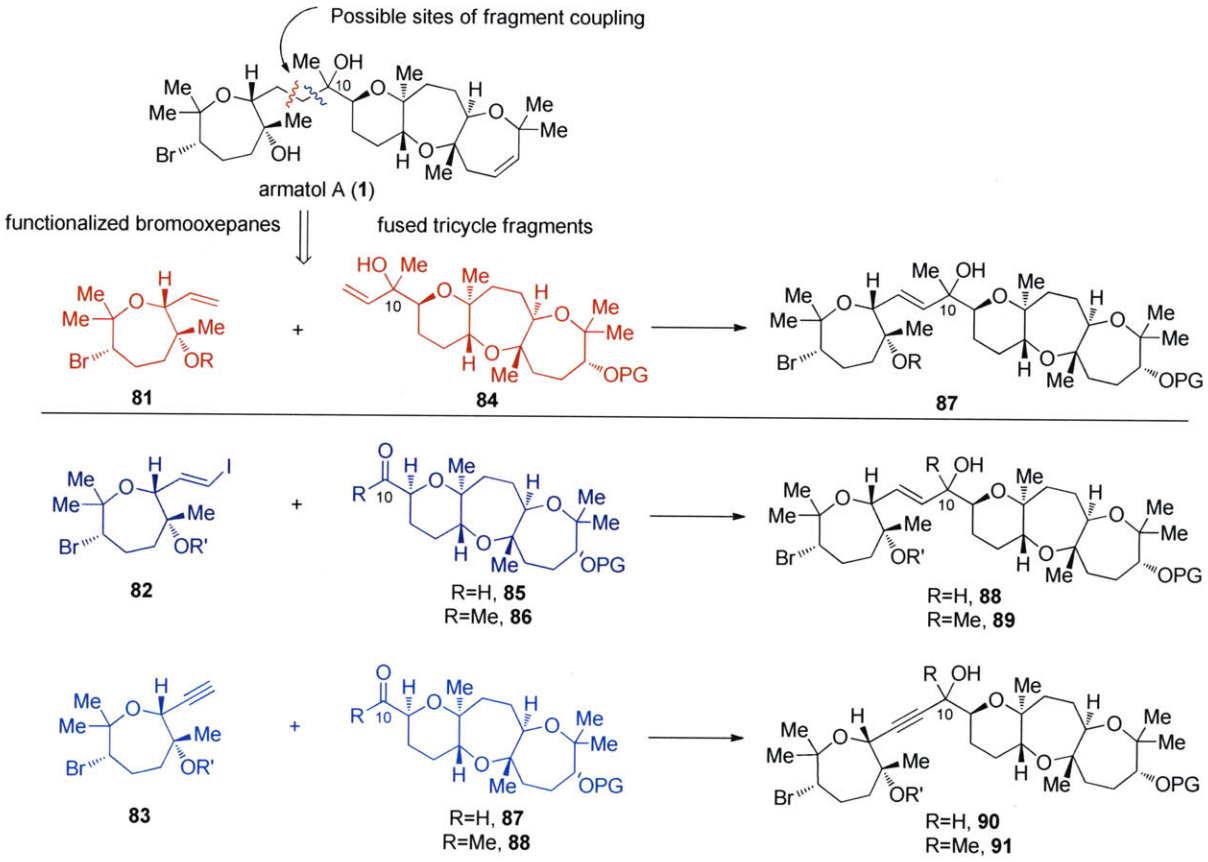
72 **71** (desired) **73**

Entry	Solvent	Scale (mmol)	Yield **71** (%)	Yield **73** (%)
1	$MeNO_2$	0.37	22	34
2	HFIP	0.37	23	36
3	HFIP	2.2	16	24

Initial coupling strategies – fragment synthesis

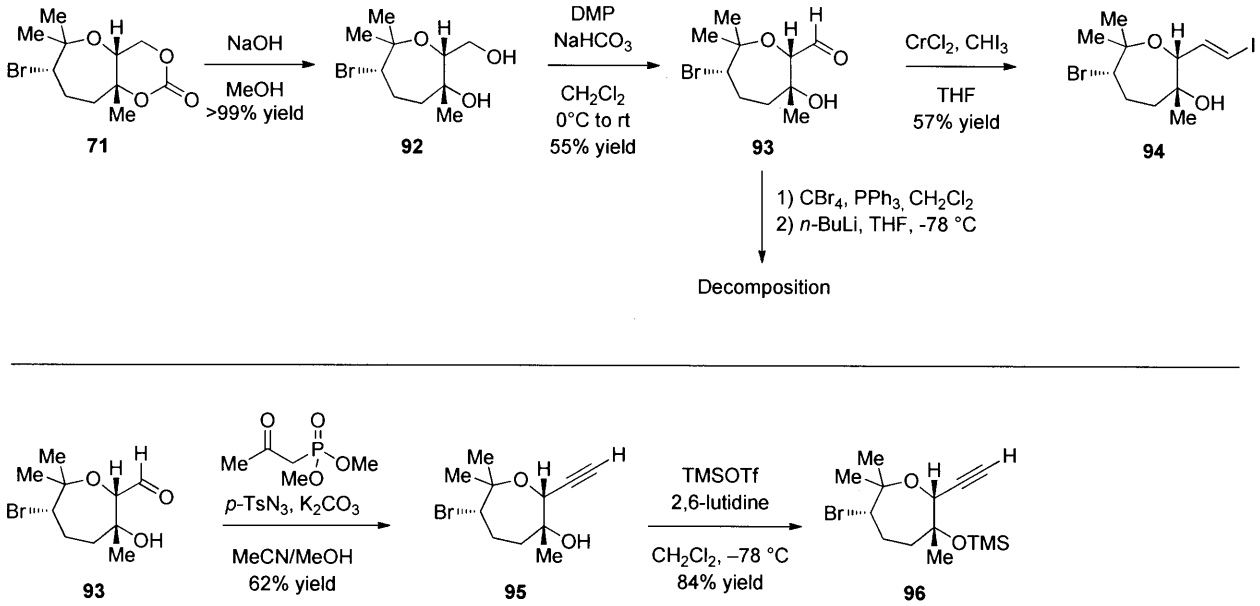
Despite the poor yield in which **71** was formed, the short, three-step route installed the challenging secondary bromide and gave rapid access to carbonate **71**. With all the stereocenters in the bromooxepane installed, we turned our attention toward suitable functional groups that would allow for coupling strategies to be investigated (Scheme 2-16). In Chapter 1, we examined the synthesis of tricycles **84**, **85**, and **86** as potential fragments in three different strategies: 1) cross-metathesis of an allylic alcohol and an allylic ether (**81** and **84** leading to **87**), 2) metal-halogen exchange of a vinyl iodide in the nucleophilic addition to an aldehyde or a ketone (**82** with **85** and **86** leading to **88** and **89**), and 3) alkyne addition to a ketone or an aldehyde (**83** with **87** and **88** leading to **90** and **91**). A cross-metathesis strategy between **81** and **84** would require all of the stereocenters to be installed before coupling, an inconvenient situation for determining the correct stereochemistry at C10 later in the synthesis. On the other hand, a vinyl iodide and an alkyne fragment would be more flexible in this regard, as the coupling reaction installs this key stereocenter at C10.

Scheme 2-16. Coupling strategies considered



The carbonate moiety of **71** allowed for elaboration into a variety of functional groups. Opening of the carbonate **71** using sodium hydroxide in methanol proceeded smoothly to give diol **92** (Scheme 2-17) and this diol could then be oxidized to the aldehyde (**93**) using Dess–Martin periodinane (55% yield). Takai olefination gave vinyl iodide **94**.[27] The Corey–Fuchs reaction on aldehyde **93** failed to form any of the desired alkyne **95** due to decomposition upon treatment of the *gem*-dibromoalkene with *n*-butyllithium. Gratifyingly, a Seyferth–Gilbert homologation[28] using Bestmann's reagent[29] successfully provided the desired alkyne (**95**) in 62% yield. Finally, a silyl protection furnished silyl ether **96** suitable for coupling studies.

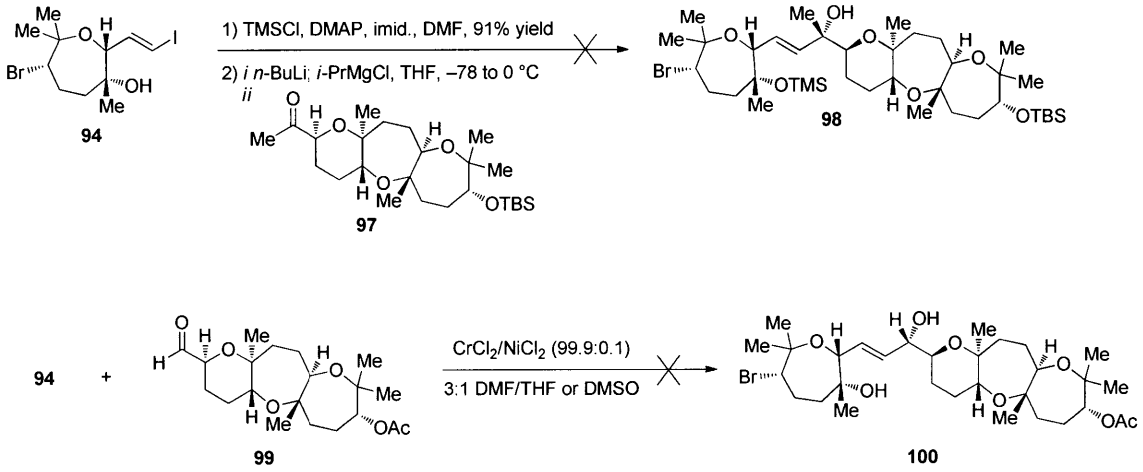
Scheme 2-17. Synthesis of coupling partners



Investigations of fragment coupling strategies

With a variety of coupling partners in hand, the first attempts to investigate the coupling of these two fragments of armatol A began with vinyl iodide **94**. Metal-halogen exchange and chelation-controlled addition into ketone **97** was predicted to provide allylic alcohol **98** (Scheme 2-16). Unfortunately, the vinyl iodide proved to be a capricious coupling partner. Attempts at a lithium-halogen exchange followed by transmetalation to magnesium led only to decomposition of the compound (Scheme 2-18). Nozaki-Hiyama-Kishi coupling[30] between vinyl iodide **94** and aldehyde **99** was attempted in both a 3:1 THF/DMF solution and in DMSO at room temperature.[31] In THF/DMF no reaction was observed, and both starting materials were recovered, while in DMSO no coupling was observed, but both starting materials had been consumed, possibly due to reduction of the aldehyde to the primary alcohol.

Scheme 2-18. Fragment coupling investigations with a vinyl iodide



Successful coupling strategies

Successful coupling occurred between alkyne **96** and ketone **97** by deprotonation of **96** with *n*-butyllithium and addition to ketone **97** (Scheme 2-20). Although the reaction proceeded with no diastereoselectivity, **102** and **103** were separable by column chromatography. It was found that use of an aprotic solvent in the hydrogenation was required to retain the silyl protecting group. The fact that the reduction stopped at the alkene instead of leading to the fully reduced alkane was surprising and required further investigation.

Scheme 2-19. Fragment coupling with alkyne **96**

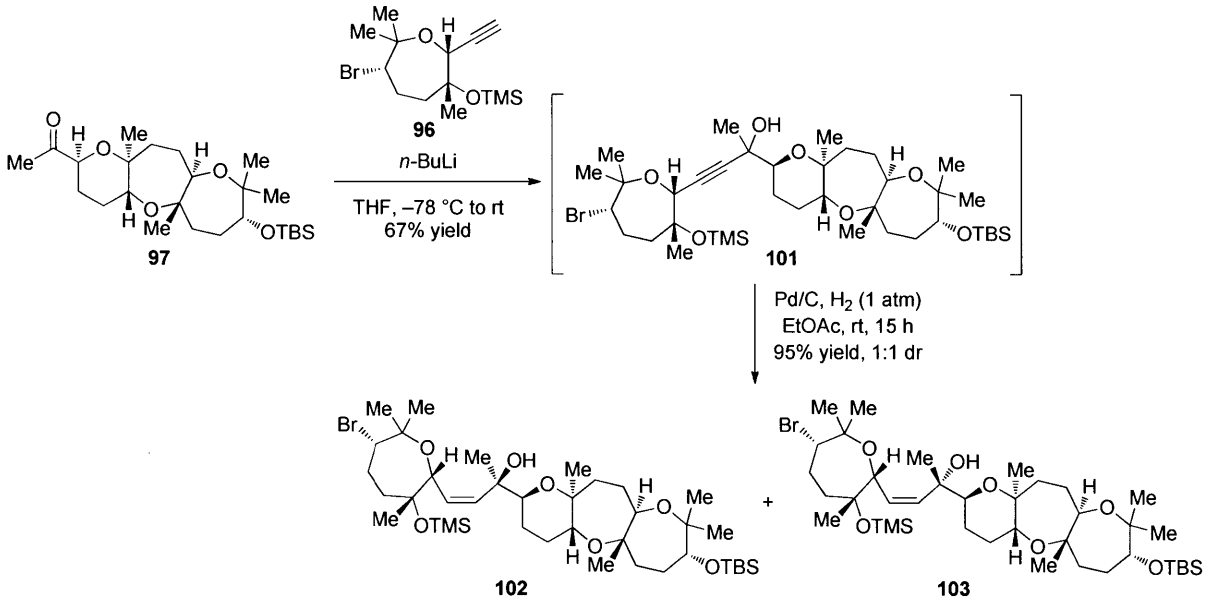
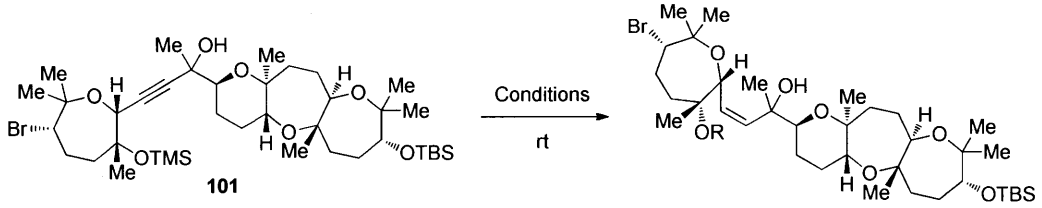


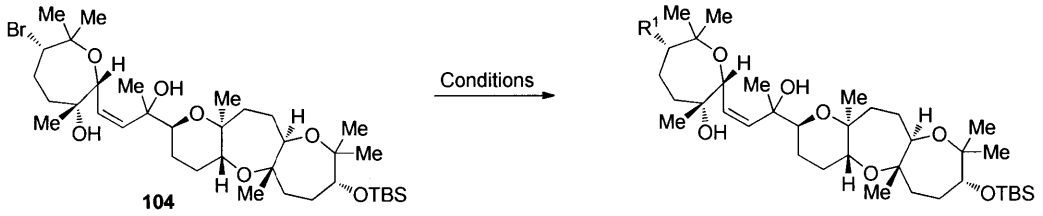
Table 2-4 shows a variety of conditions attempted for the reduction of alkyne **101**. Lindlar reduction and diimide reduction both left the silyl group intact and provided exclusively the cis-alkenes **102** and **103**. Using an alcoholic solvent such as methanol led to concomitant deprotection of the TMS group and reduction of the alkyne to alkene **104**, under higher pressure a small amount of the fully reduced alkane was detected. Table 2-5 shows attempts to reduce this double bond further. Pearlman's catalyst led to carbon–bromide bond reduction at high pressures, but did not reduce the alkene.[32] Harsher conditions for diimide reduction were not successful (entry 3).[33] Use of riboflavin tetraacetate (entry 4) to perform an aerobic hydrogenation also failed to provide any further reduction of the alkene.[34] Directed homogenous reduction using $Rh(dppb)(cod)BF_4$ (entry 5) just led to recovery of starting material and provided no desired reduction products.[35]

Table 2-4. Attempts to reduce alkyne **101**



Entry	Reagent(s)	Solvent	Time	Result
1	Pd/Pb/$CaCO_3$, Quinoline, H_2 (1 atm)	EtOH	3 h	R=TMS (**102** and **103**)
2	Trisyl hydrazine	MeOH	16 h	R=TMS (**102** and **103**)
3	Pd/C, H_2 (1 atm)	MeOH	3 h	R=H (**104**)
4	Pd/C, H_2 (900 psi)	MeOH	17 h	R=H (**104**) along with trace alkene reduction

Table 2-5. Attempts to reduce cis-alkene **104**



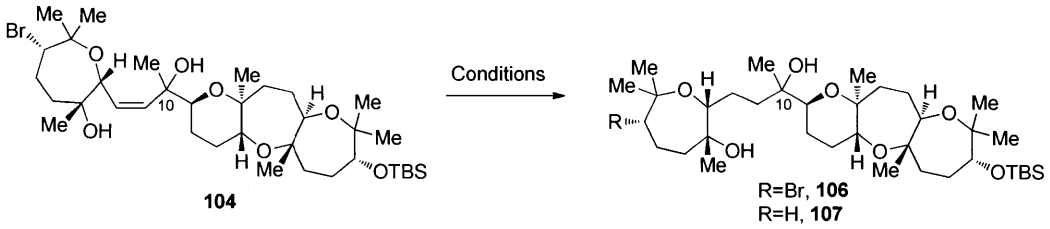
Entry	Reagent	Solvent	Temp, Time	Result
1	$Pd(OH)_2$, H_2 (1 atm)	EtOH	rt, 18 h	R=Br (**104**)
2	$Pd(OH)_2$, H_2 (1050 psi)	1:1 EtOH/THF	rt, 36 h	R=H (**105**), 54% yield
3	Trisyl hydrazine, $NaHCO_3$	2:1 THF/MeOH	rt, 3 d to 80 °C, 20 h	R=Br (**104**)
4	Riboflavin tetraacetate, $H_2NNH_2 \cdot H_2O$, O_2 (1 atm)	MeCN	30 °C, 2 d to 50 °C, 14 h	R=Br (**104**)
5	Rh(dppb)(cod)BF_4, H_2 (900 psi)	CH_2Cl_2	30 °C, 3 d	R=Br (**104**)

Note: Products were determined using ^{1}H NMR and HRMS analysis.

Even though the reduction of the carbon–bromide bond was observed with Pearlman's catalyst at high pressure, we reasoned that at higher pressures of H_2 and higher temperature, milder palladium and platinum catalysts might provide a selective olefin reduction (Table 2-6). Unfortunately, all conditions that reduced the olefin gave competitive reduction of the carbon–bromide bond, affording **107** and only traces of the desired product. In a ^{1}H NMR spectrum of **104**, the allylic proton was observed at approximately 5.2 ppm, suggesting that it lies in the plane

of the olefin due to allylic 1,3-strain.[36] The downfield shift can be attributed to an anisotropic, induced magnetic field around the olefin, inducing a local magnetic field around this hydrogen. This configuration of the olefin creates a congested environment that might prevent the molecule from interacting with the metal surface. The two adjacent allylic oxygens might also serve to deactivate the alkene towards hydrogenation.

Table 2-6

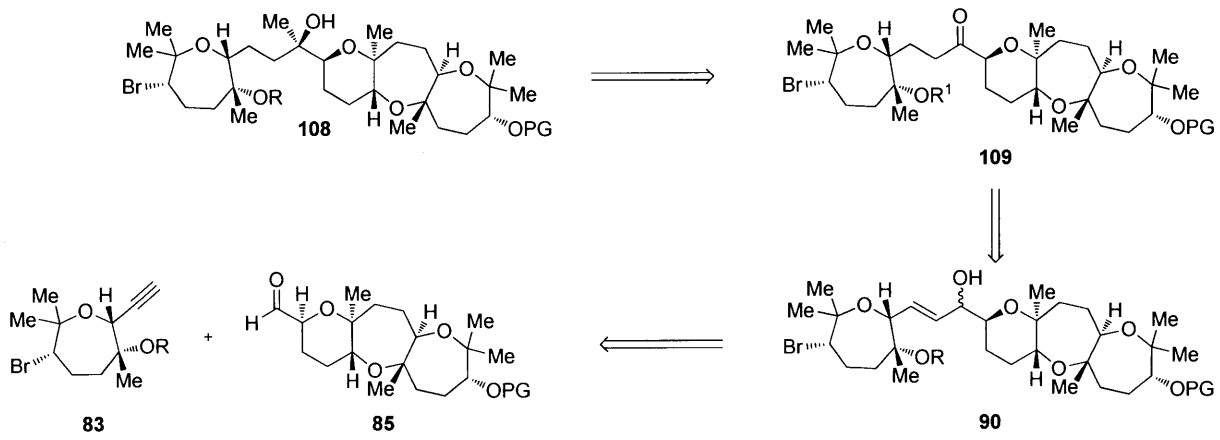


Entry	Conditions	SM	:	106	:	107
1	Pd/C, H_2 (875 psi) 1:1 MeOH/THF, 12 h, rt	100%	:	trace	:	trace
2	Pd/C, H_2 (890 psi) 1:1 MeOH/THF, rt, 89.5 h	50%	:	50%	:	trace
3	Pd/C, H_2 (890 psi) AcOH, 1:1 EtOH/THF, rt, 89.5 h	53%	:	24%	:	22%
4	Pt/C, H_2 (880 psi) EtOH, rt, 88 h	15%	:	31%	:	54%
5	Pd/C, H_2 (880 psi) EtOH, AcOH, 88 h	trace	:	9%	:	91%

Notes: Yield determined by ratios in NMR of crude product. No other products were observed and structures could be determined using ^{1}H NMR and HRMS.

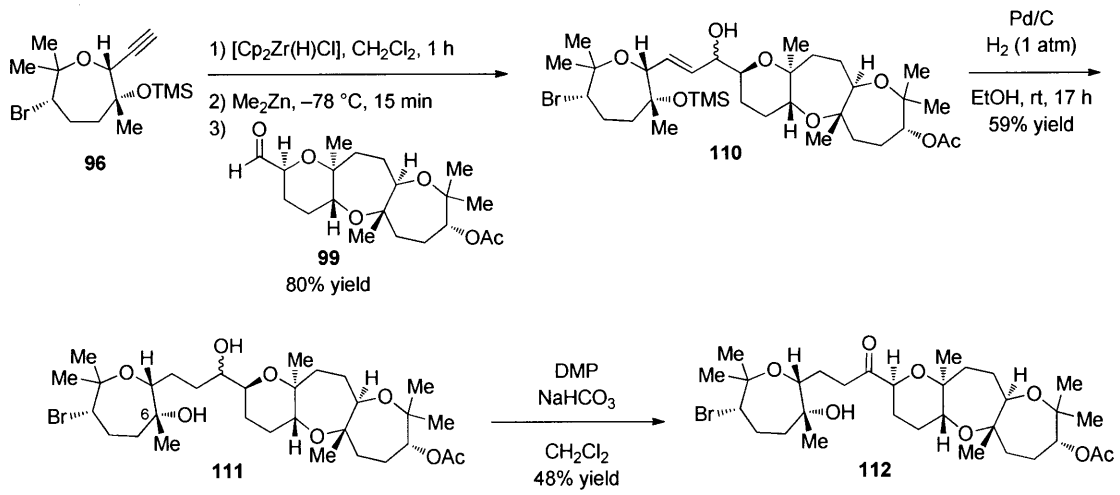
From these experiments it was concluded that the steric environment around the cis-olefin was likely inhibiting reduction of the C8-C9 bond. A strategy involving formation of the tertiary alcohol after reduction of the C8-C9 bond was then pursued (Scheme 2-20). In this approach, coupling of alkyne **83** and tricycle **85** would lead to allylic alcohol **90**. Reduction and oxidation would provide ketone **109** with subsequent addition of an organometallic methyl reagent, which would furnish tertiary alcohol **108**.

Scheme 2-20. Installation of key C10 tertiary alcohol after fragment coupling



This strategy proved to be effective. Alkyne **96** was treated with $Cp_2Zr(H)Cl$, transmetalated to zinc using Me_2Zn, and subsequently treated with aldehyde **99** to furnish allylic alcohol **110** in 66% yield (Scheme 2-21).[37] The acetate protecting group on **99** was originally employed to aid in purification of the tricycle cascade product and was stable to these coupling conditions.

Scheme 2-21. Successful coupling and formation of ketone **112**



Investigation of conditions for the reduction of alkyne **101** (Table 2-4) showed that using a protic solvent led to concomitant cleavage of the silyl protecting group. Similarly, treating

trans-alkene **110** with palladium on carbon at atmospheric pressure in ethanol led cleanly to the fully reduced alkane (**111**) in only a few hours and revealed the free tertiary alcohol present in the natural product at C6 in 73% yield. Oxidation of the secondary alcohol was sluggish with Dess-Martin periodinane and proceeded in 48% yield. With a method for successful installation of the alkyl chain in hand, we began optimization of the synthesis of the left-hand fragment with the absolute configuration found in armatol A (**1**).

Confirmation of the absolute and relative stereochemistry of armatol A

The optimized synthesis of alkyne **121**, with the correct stereochemistry in ring A, is shown in Scheme 2-22. Because of the modest enantioselectivity in the Sharpless asymmetric epoxidation of nerol, enzymatic resolution to enhance the enantioselectivity of epoxide **113** was required.[38] Slight modification of the procedure for the bromonium-initiated cyclization using nitromethane as the solvent gave 22% yield of the desired diastereomer **116** on large scale. Premixing the SO_3·py complex with DMSO in the oxidation of **117** and using the preformed α-diazo-β-ketophosphonate (**119**) for the synthesis of alkyne **120** led to increased yields of 80% and 75%, respectively. The protected alkyne (**121**) was now set for coupling with both enantiomers of the tricycle, in order to provide the four possible diastereomers of armatol A (Figure 2-2).

Scheme 2-22

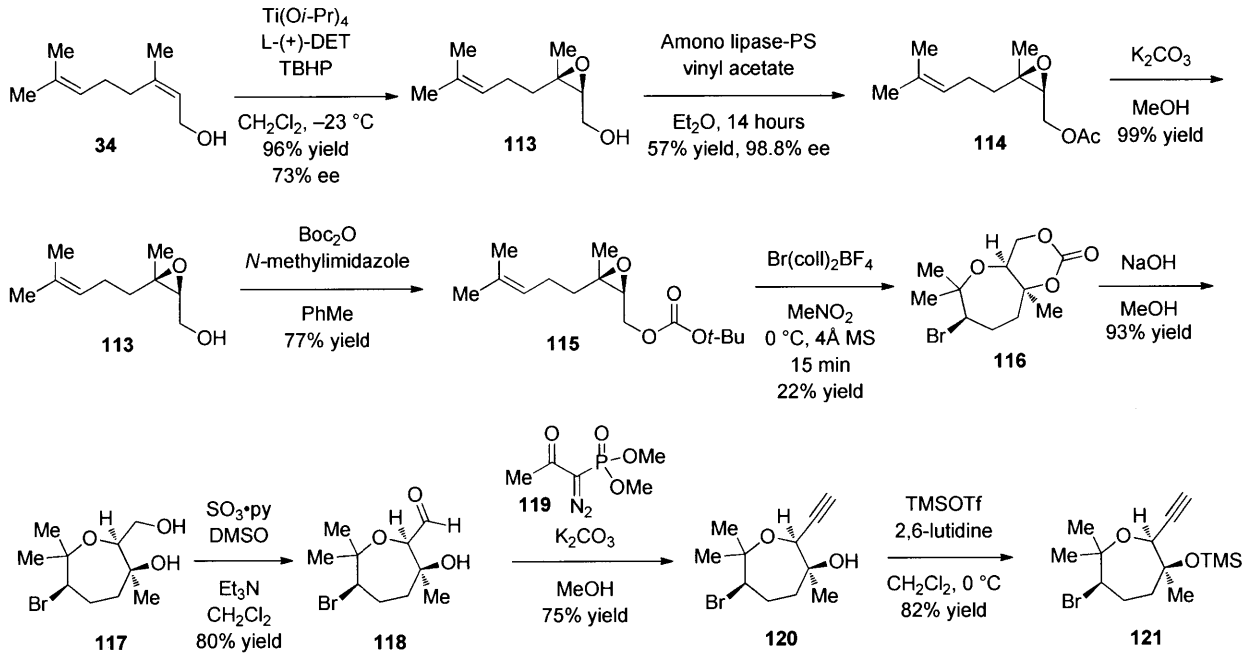
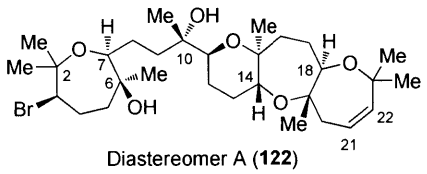
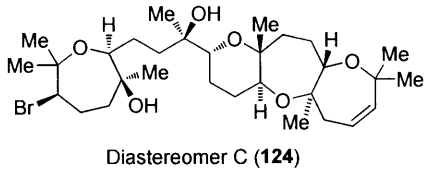


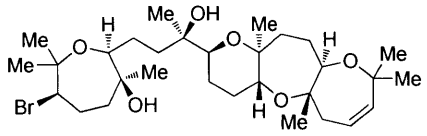
Figure 2-2. Four possible diastereomers of armatol A consistent with published data.



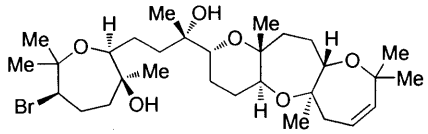
Diastereomer A (**122**)



Diastereomer C (**124**)



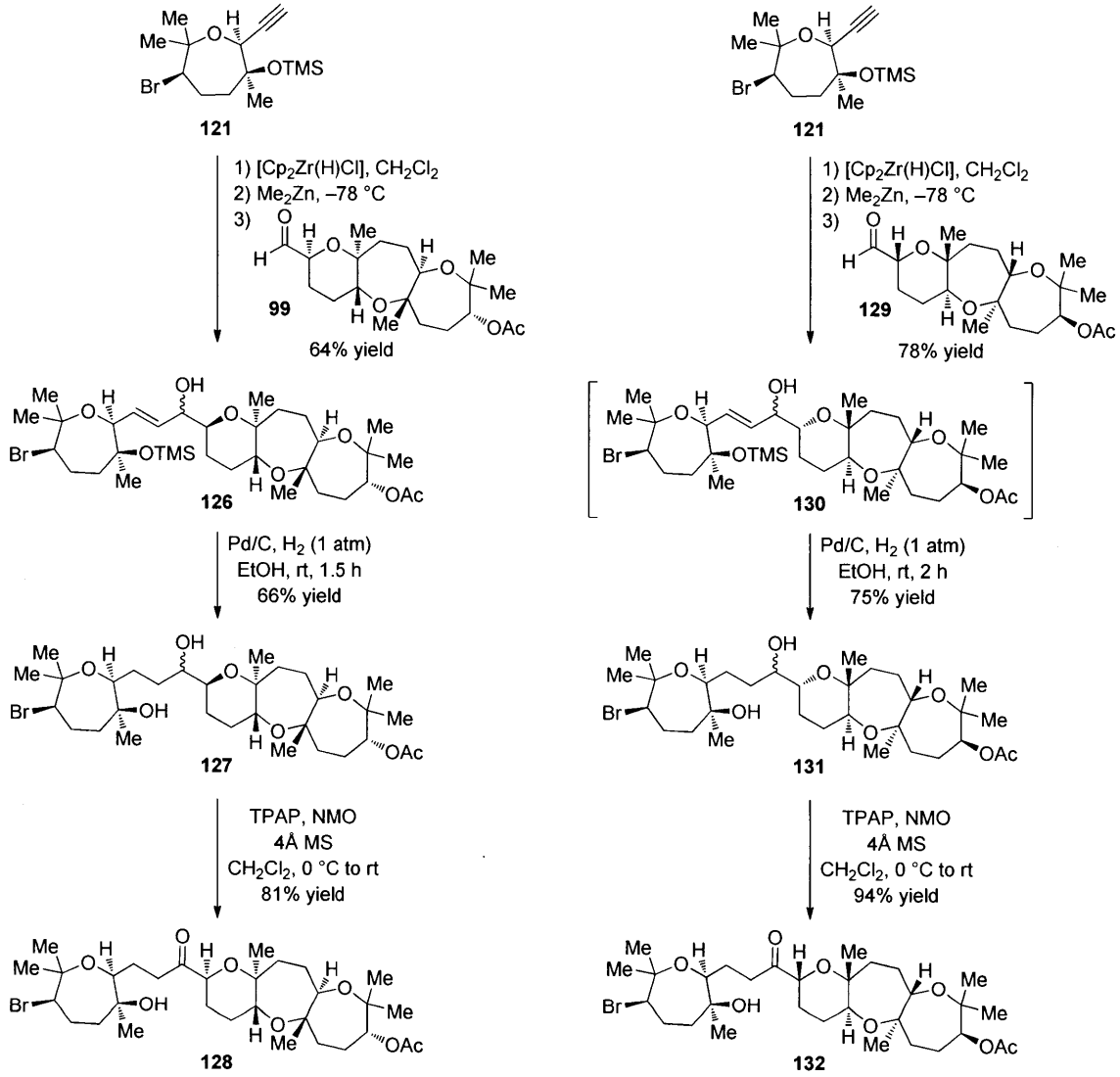
Diastereomer B (**123**)



Diastereomer D (**125**)

Coupling of **99** and **125** with alkyne **121** followed by reduction with palladium on carbon led to diastereomers **127** and **131**, respectively. Oxidation using TPAP/NMO increased the yield of oxidation which provided ketones **128** and **132** in good yield and avoided hemiketal formation, which had plagued the Parikh–Doering oxidation.[39]

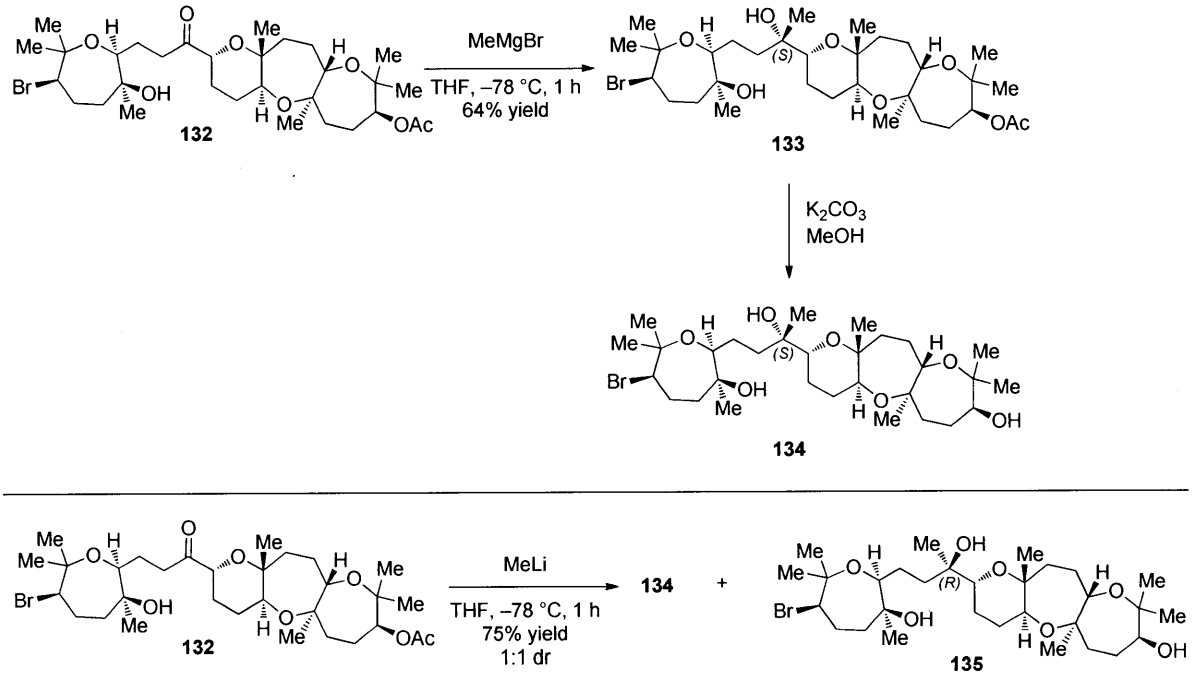
Scheme 2-23



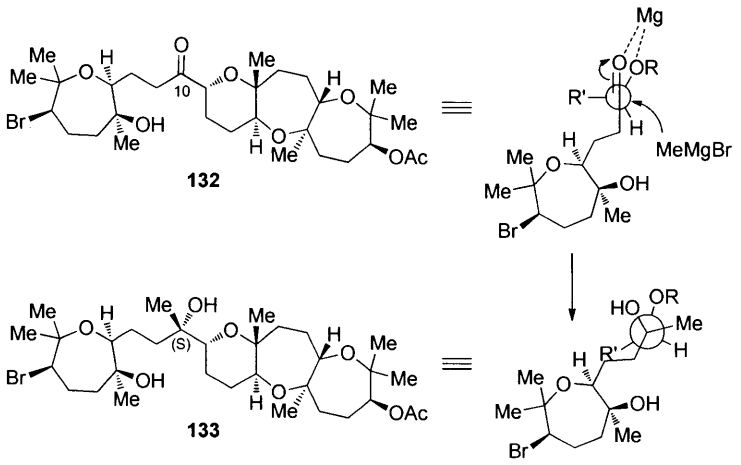
An acetate protecting group was chosen in the reaction of ketone **132** with organometallic methylating reagents due to the potentiality of concomitant deprotection under these conditions (Scheme 2-24). Treatment of ketone **132** with methyllithium at –78 °C in THF led to a 1:1 ratio of C10 epimers **134** and **135**. Treatment of the same ketone **132** with methylmagnesium bromide at –78 °C led only to the formation of protected alcohol **133** with high diastereoselectivity. Based on the model for a chelation-controlled addition (Scheme 2-25), the configuration of the key C10 tertiary alcohol **133** was assigned the (*S*)-configuration. In his seminal synthesis of

venustatriol, Corey used chelation-controlled addition of methyl magnesium bromide to **136** in order to install a similar tertiary alcohol in **137**.[14d,40] Hydrolysis of acetate **133** with potassium carbonate in MeOH gave exclusively one product, the spectrum of which matched perfectly with **134**. The other product observed from the methyl lithium addition (**135**) was then assigned as the opposite C10-epimer, with the (*R*)-configuration.

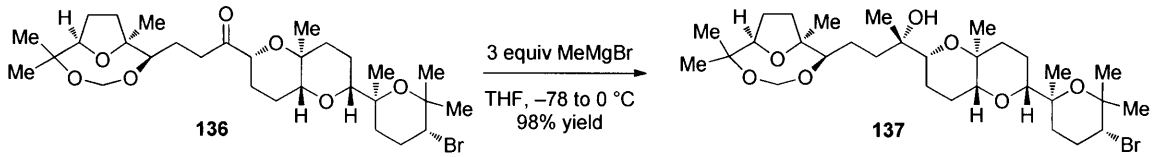
Scheme 2-24



Scheme 2-25

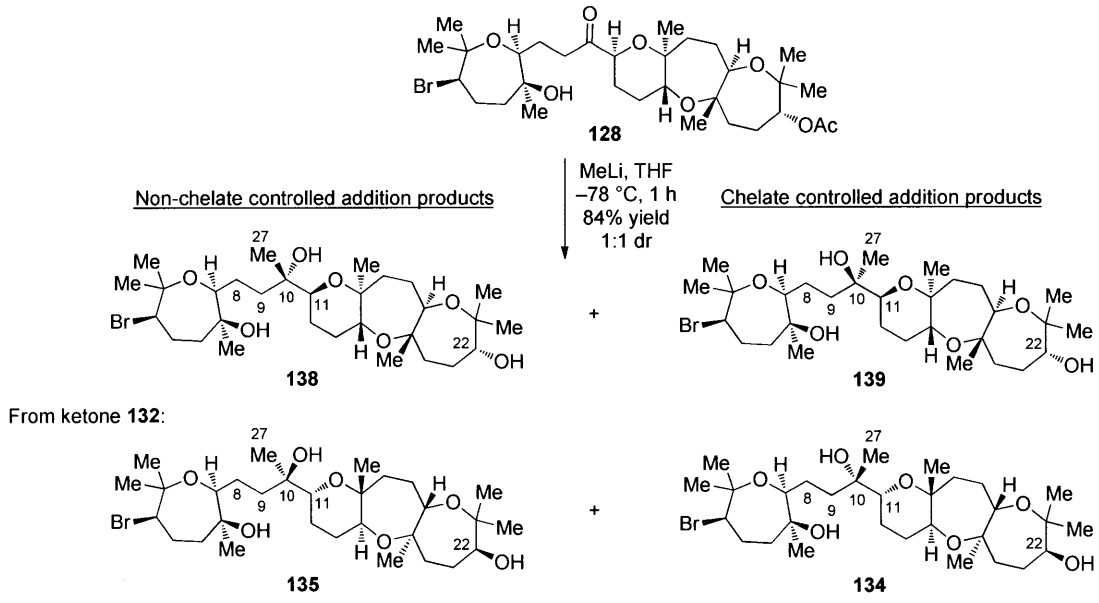


Corey (2000):

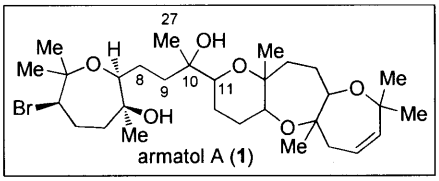


Using the same stereochemical model, methyllithium addition to ketone **128** furnished two diastereomeric products that were assigned as **138** and **139** (Scheme 2-26), giving us access to four diastereomers that would lead to the four possible diastereomers of armatol A (**134**, **135**, **138**, and **139**). We observed that the three carbons directly adjacent to the tertiary alcohol at C10 in two of the diastereomers were much closer to the assigned carbon shifts for armatol A (**1**). Diastereomers **134** and **139** (both derived from chelation-controlled addition into their corresponding ketones) are both within 0.4 ppm at every carbon of the left-hand side of the molecule up to the THP ring. On the other hand, diastereomers **135** and **138** (the two other diastereomers from methyllithium addition that did not correspond to the chelation products) differ by as much as 2.3 ppm from the reported data, especially at carbons 9, 11, and 27. It is reasonable that the chemical shifts of the bromoxepane are very similar for all four diastereomers because of the intervening flexible carbon chain.

Scheme 2-26



Carbon	138	139	135	134	1
8	24.7	24.1	24.6	24.4	24.1
9	36.8	34.4	36.8	34.7	34.5
10	73.4	73.3	73.4	73.3	73.4
11	74.4	76.3	75.4	76.3	76.1
27	23.0	24.0	21.7	24.3	23.9

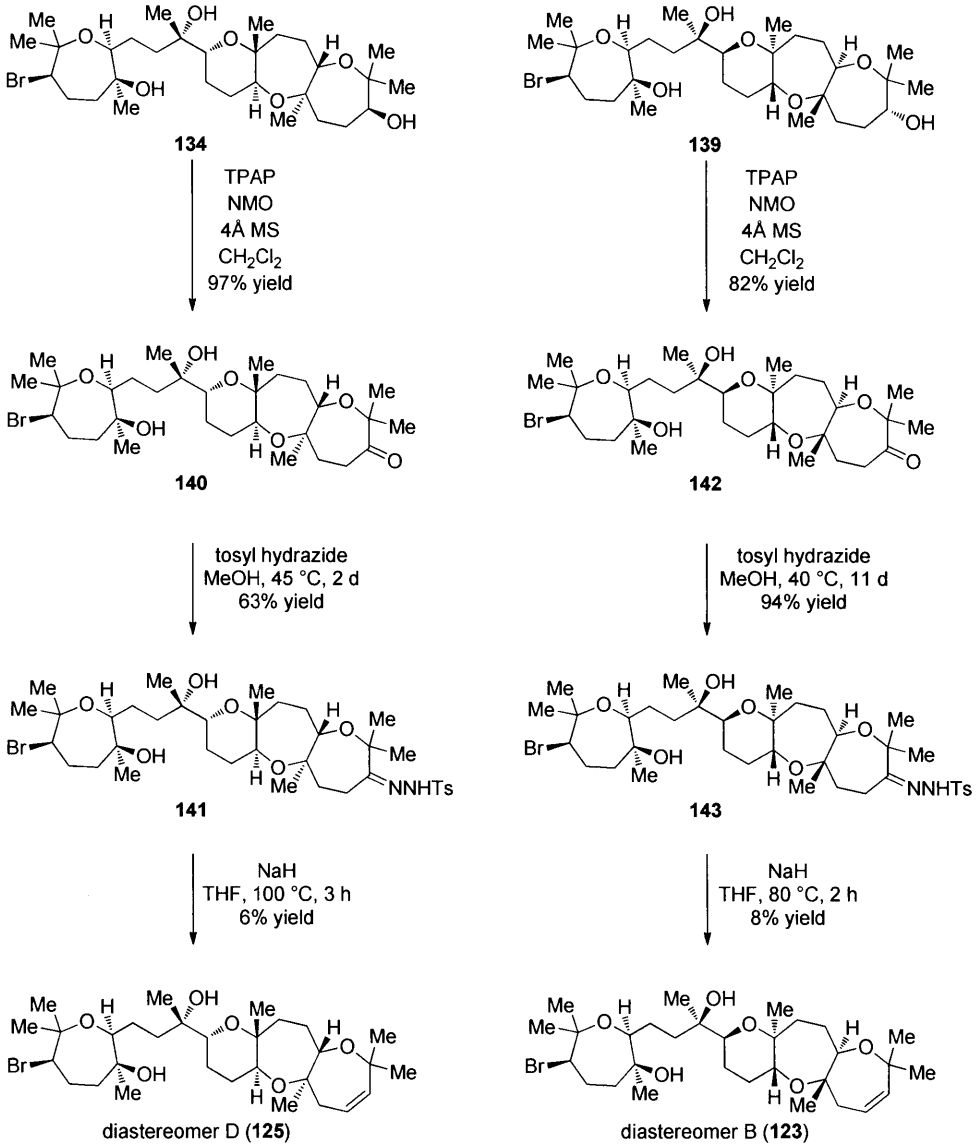


δ [ppm] in ^{13}C NMR (C_6D_6). The ^{13}C reference from the isolation paper of armatol A[2] in C_6D_6 was not reported and assumed to be 128.06 ppm. The carbon peaks in **1** reported above are adjusted to a reference peak of 128.37 ppm to match collected data for four possible diastereomers synthesized.

The much larger differences of the carbon resonances of **1** and those of diastereomers **135** and **138** suggest that they *do not* correspond to the correct configurations of armatol A. This analysis dramatically simplifies the problem, leaving only two possible diastereomers for the correct absolute configuration of armatol A. With these two alcohols in hand, all that remains is the elimination of the C22 secondary alcohol to form the two diastereomers of the natural product. As discussed in Chapter 1, model systems showed that the only successful strategy for the synthesis of the oxepene involved oxidation of the alcohol to a ketone, followed by hydrazone formation, and then elimination. Fortunately, this strategy also worked on late-stage intermediates **134** and **138**. Ley oxidation of both diastereomers **134** and **139** in

dichloromethane led cleanly to ketones **140** and **142**, respectively (Scheme 2-27). The limited solubility of these diols in methanol decelerated hydrazone formation significantly; however, forcing conditions and extension of the reaction time to 2-11 days led to complete conversion.

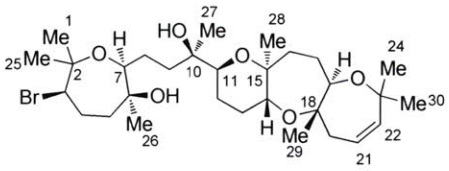
Scheme 2-27. Converting alcohols **134** and **139** to alkenes **125** and **123** via the Bamford–Stevens reaction



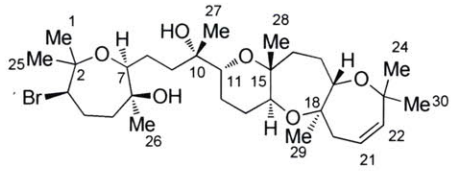
Treatment of hydrazones **141** and **143** with sodium hydride in toluene failed to give any of the desired elimination products, likely due to the insolubility of the hydrazone. However,

treating hydrazones **141** and **143** with sodium hydride in THF in a sealed tube at 80-100 °C for 2-3 hours led to the desired alkenes **125** and **123**, albeit in low yields. Table 2-7 shows the tabulation of the ^{13}C NMR data for the two possible diastereomers of armatol A. All signals in diastereomer B (**123**) are within 0.1 ppm of the data reported for the isolated natural product, with the exception of C11 (in C_6D_6) which differs by 0.2 ppm. Hydrogen bonding of the tertiary alcohol with the adjacent THP ring might account for this difference. On the other hand, the ^{13}C chemical shifts for diastereomer D (**125**) differ by at least 0.2 ppm in several cases, specifically the C8 to C13 portion of the molecule suggesting that it is not the correct structure of armatol A. Even more significantly, the optical rotation of diastereomer D (**125**) is -17.9, while diastereomer B (**123**) is +33.9. The reported optical rotation of armatol A in chloroform is +43.4. Taken together, these data confirm the correct structure of armatol A as **123**.

Table 2-7. Tabulation of ^{13}C NMR data of the possible diastereomers of armatol A



diastereomer B (**123**)



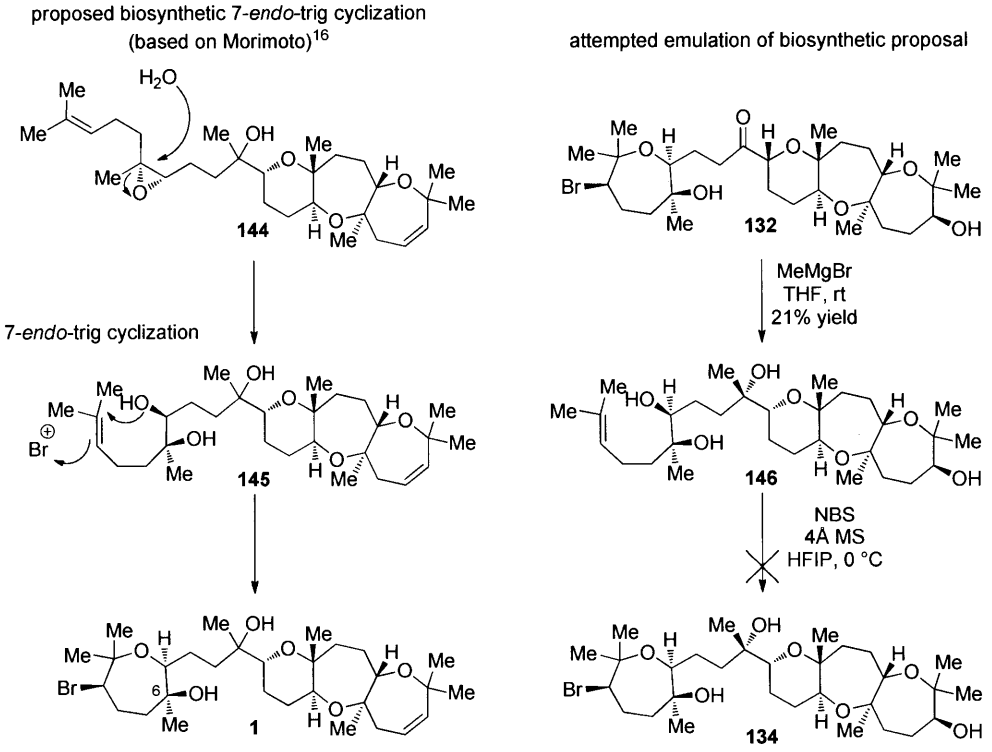
diastereomer D (**125**)

Ref: 77.0 ppm Solvent: $CDCl_3$	**123**	**125**	Natural (**1**)	Ref: 128.0 ppm Solvent: C_6D_6	**123**	**125**	Natural (**1**)
C1	25.3	25.2	25.3 (q)	C1	25.4	25.2	25.3
C2	77.7	77.9	77.7 (s)	C2	77.6	77.6	77.6
C3	59.2	59.2	59.1 (d)	C3	59.3	59.4	59.3
C4	30.4	30.4	30.4 (t)	C4	30.6	30.6	30.6
C5	44.3	44.4	44.3 (t)	C5	44.3	44.4	44.3
C6	72.3	72.2	72.3 (s)	C6	72.0	72.0	71.9
C7	76.4	76.0	76.4 (d)	C7	76.6	76.1	76.6
C8	23.4	23.7	23.4 (t)	C8	23.9	24.0	23.7
C9	33.4	33.4	33.4 (t)	C9	34.1	34.3	34.1
C10	73.1	73.0	73.1 (s)	C10	73.1	72.8	73.0
C11	74.9	75.0	74.9 (d)	C11	75.5	75.4	75.7
C12	27.0	27.1	26.9 (t)	C12	25.6	25.8	25.6
C13	27.2	27.2	27.3 (t)	C13	27.5	27.6	27.3
C14	73.5	73.5	73.5 (d)	C14	74.2	74.2	74.1
C15	77.2	77.2	77.2 (s)	C15	77.4	77.4	77.4
C16	38.4	38.4	38.4 (t)	C16	38.7	38.7	38.7
C17	27.3	27.2	27.3 (t)	C17	27.7	27.7	27.5
C18	76.4	76.4	76.4 (d)	C18	76.5	76.6	76.5
C19	80.1	80.1	80.1 (s)	C19	80.4	80.4	80.3
C20	41.9	41.7	41.8 (t)	C20	42.3	42.2	42.3
C21	121.9	121.9	121.9 (d)	C21	122.5	122.5	122.3
C22	136.4	136.4	136.4 (d)	C22	136.7	136.7	136.7
C23	77.8	77.8	77.8 (s)	C23	77.9	78.0	77.9
C24	26.0	25.9	25.9 (q)	C24	26.1	26.1	26.1
C25	25.7	25.7	25.7 (q)	C25	25.7	25.7	25.7
C26	26.0	25.5	25.9 (q)	C26	25.3	25.2	25.2
C27	23.4	23.8	23.4 (q)	C27	23.5	24.1	23.5
C28	26.0	25.0	25.9 (q)	C28	17.5	17.5	17.5
C29	18.0	18.0	18.0 (q)	C29	18.1	18.2	18.1
C30	29.4	29.4	29.3 (q)	C30	29.5	29.5	29.5

Attempted 7-endo-trig cyclization to form bromooxepane ring

Earlier in this chapter we discussed two bromonium-initiated cyclization pathways (Schemes 2-7 and 2-8) and then demonstrated that the first of these (involving an epoxonium intermediate trapped by a carbonate nucleophile) led to the desired bromooxepane ring for armatol A. An alternative pathway (shown again in Scheme 2-28 for armatol A), involves epoxide-opening by a molecule of water to give triol **145**, which would then undergo a 7-*endo*-trig cyclization to furnish **1**.

Scheme 2-28. Attempts to emulate proposed 7-*endo*-trig cyclization with **146**



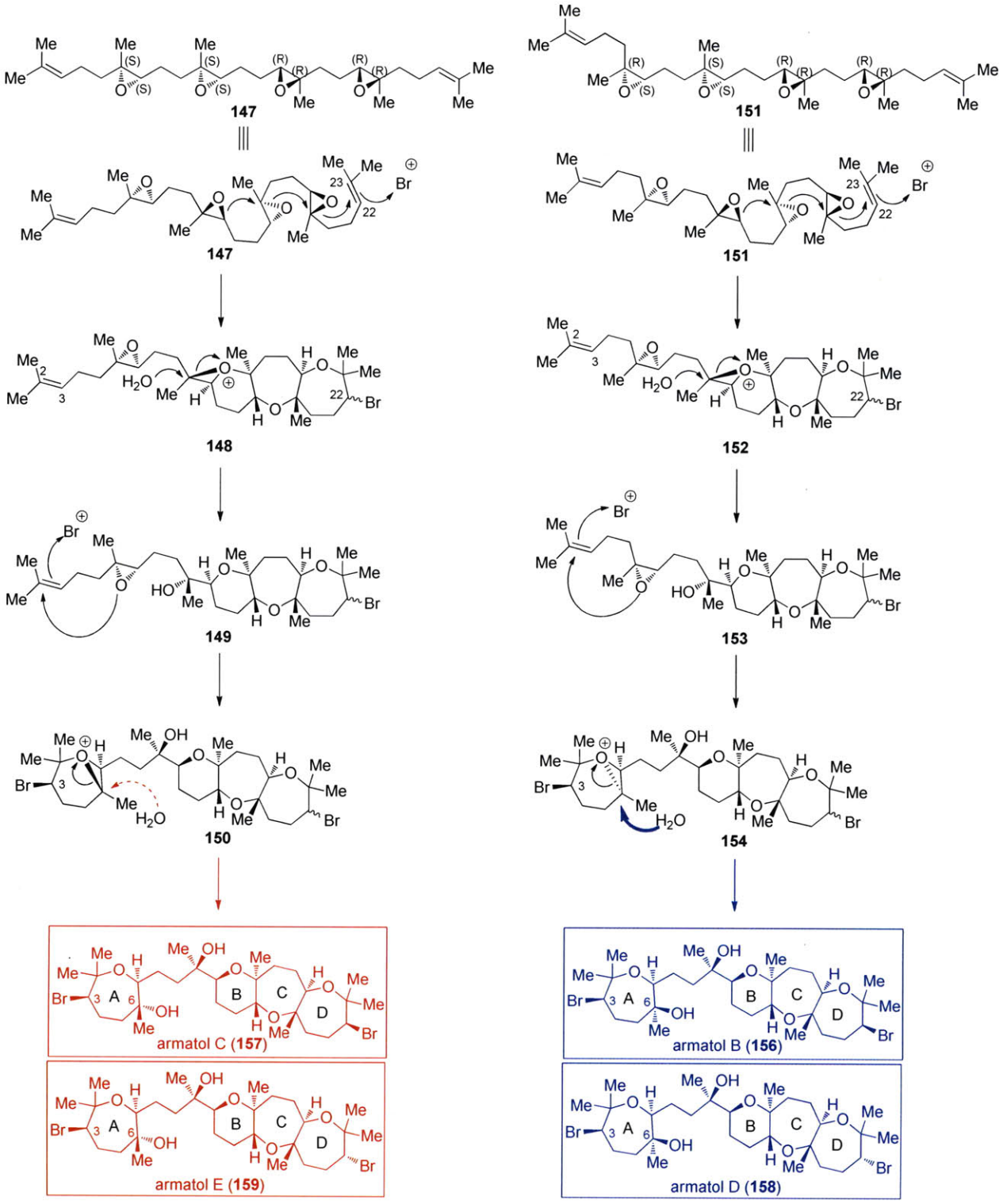
Because we had isolated **146** from a reductive dehalogenation of **132** as a side product, we could test this biogenetic hypothesis. Based on precedence from Morimoto,[16] treating this tetraol with NBS in HFIP should lead to **134**. Comparison of a ^{1}H NMR spectrum of the reaction mixture with that of an authentic sample of **134**, however, showed that no desired

product was obtained. While this result does not exclude epoxide-opening by water followed by a bromoetherification as a biosynthetic pathway, it does lend support in favor of a biosynthetic pathway in which a bromonium-initiated epoxide-opening cyclization occurs, similar to that used in the synthesis of armatol A described here.

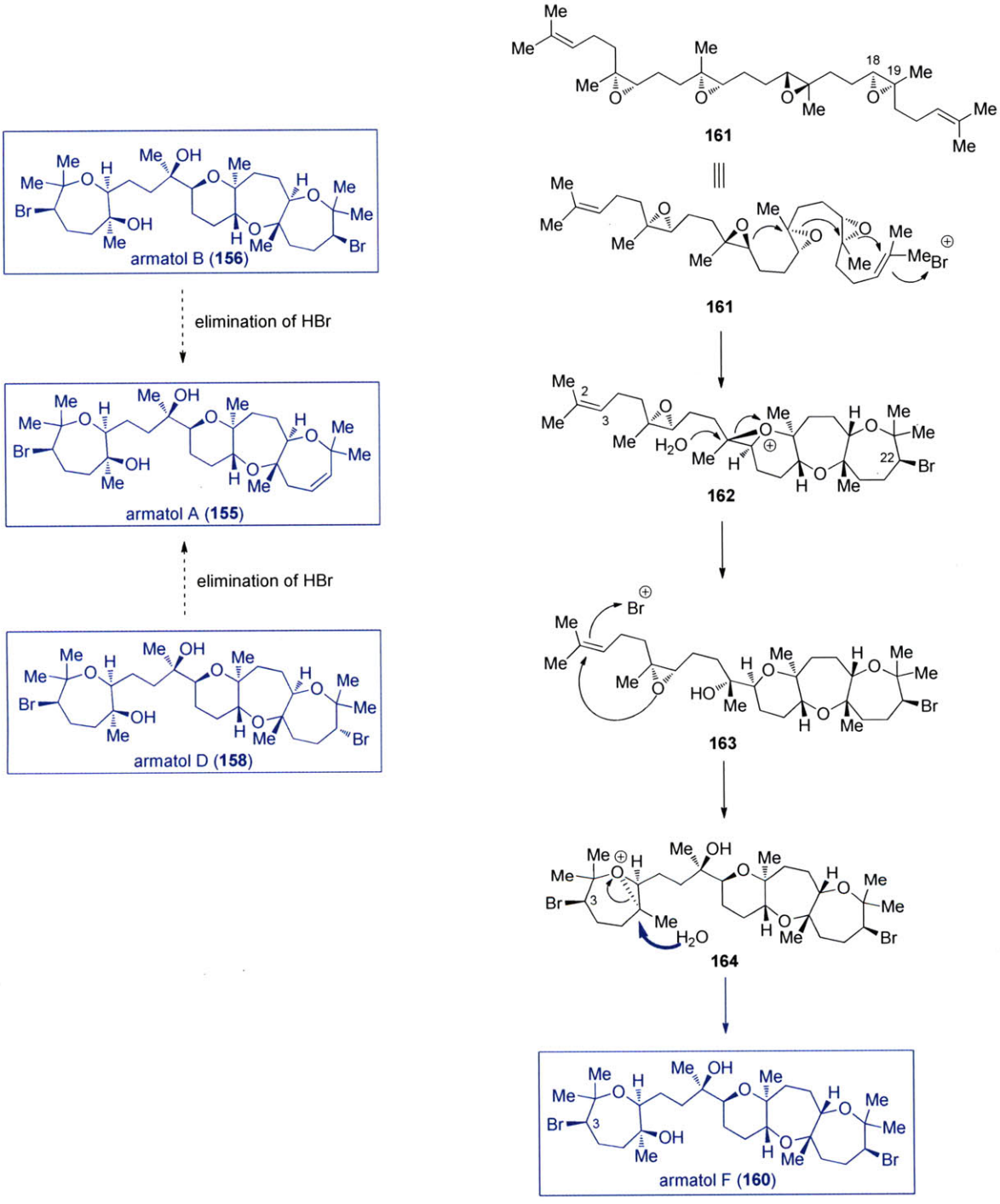
Revised biogenesis

In these investigations we have shown that a Lewis acid-mediated triepoxide cascade can be used to form the BCD rings of armatol A and that a bromonium-initiated epoxide-opening cyclization provides the bromooxepane ring (ring A). Therefore, we propose that a similar bromonium-initiated epoxide-opening cascade may be part of the biosynthetic pathway for the BCD rings of the armatol family.[41] Based on the relative stereochemistry observed in the six natural products, the requisite tetraepoxide biosynthetic precursors, **147**, **151**, and **161**, are proposed (Schemes 2-29 and 2-30). Applying our cascade hypothesis to the three tetraepoxides would lead to revised structures for the other members of the armatol family. For each proposed tetraepoxide, a bromonium-initiated epoxide-opening cascade to generate the tricycle leads to an epoxonium intermediate (**148**, **152**, and **162**). Opening by water with inversion then installs the C10 stereocenter. The bromonium formation at the C22-C23 alkene would not need to be stereoselective, as both diastereomers at C22 are found in the natural products. A bromonium-initiated epoxide-opening cyclization at the C2-C3 alkene would install the C3 bromide. The resulting epoxonium intermediate (**150**, **154**, and **164**) can also be opened with inversion by water leading to armatols B-F as shown. Armatol A (**155**) could then result from an elimination of either armatol B or D (Scheme 2-30).

Scheme 2-29. Revised biosynthetic proposal leading to armatols B-E



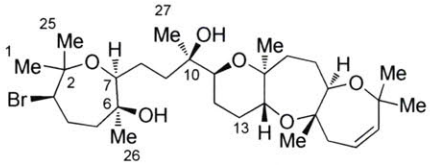
Scheme 2-30. Revised biosynthetic proposal leading to armatol A and F



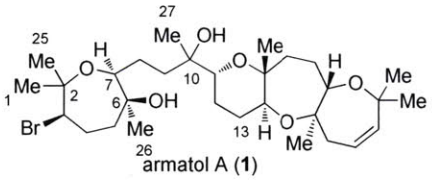
Further evidence for the newly assigned structures of the five other armatols is found by comparing the reported ^{1}H NMR data for the key tertiary alcohol at C27 and the ^{13}C NMR data

for the bromooxepane ring in the natural products (Table 2-8).[2] The tabulated data is consistent with the hypothesis that the stereochemistry at the C27 methyl group is identical to armatol A with the exception of armatol D (**6**). Since armatol D has been reported to share the same bromooxepane subunit with armatols A, B, and F, the large degree of inconsistency in the ^{13}C data for armatol D call into question the ability of this study to predict the correct structure for armatol D. We have now not only shown the correct absolute stereochemistry of armatol A, but we have strong support for the absolute configurations of four of the remaining five members of the armatol family (Figure 2-3).

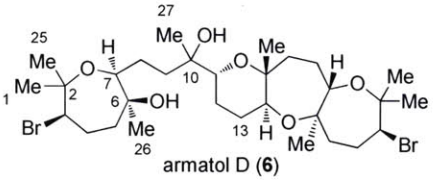
Table 2-8. NMR tabulation of the diastereomer B (**123**) to the reported armatol natural products



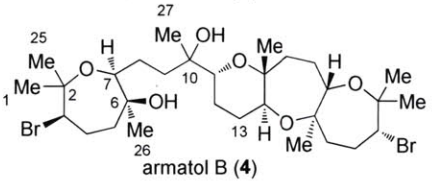
diasteromer B (**123**)



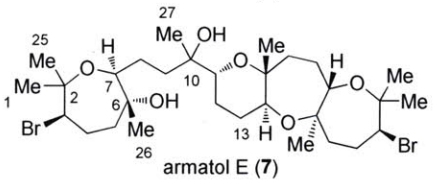
armatol A (**1**)



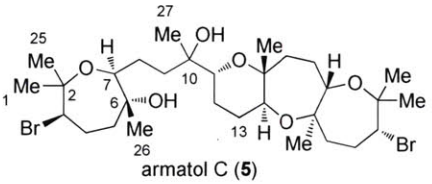
armatol D (**6**)



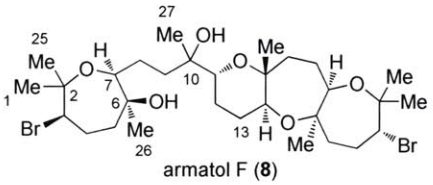
armatol B (**4**)



armatol E (**7**)



armatol C (**5**)



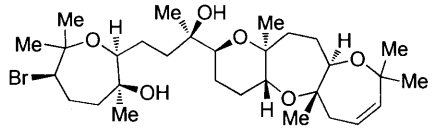
armatol F (**8**)

Position	**123**[a]	armatol A (**1**)[b]	armatol B (**4**)[b]	armatol C (**5**)[b]	armatol D (**6**)[b]	armatol E (**7**)[b]	armatol F (**8**)[b]
C1	25.3	25.3	25.3	25.5	25.8	25.8	25.3
C2	77.7	77.7	78.1	78.1	78.3	78.2	79.1
C3	59.2	59.1	59.2	60.1	59.7	60.4	59.2
C4	30.4	30.4	30.4	31.4	30.9	30.2	30.4
C5	44.3	44.3	44.3	44.3	44.9	45.5	44.3
C6	72.3	72.3	72.3	72.4	72.8	72.8	72.2
C7	76.4	76.4	76.5	76.5	76.9	78.8	79.5
C8	23.4	23.4	23.4	23.3	23.9	23.5	25.1
C9	33.4	33.4	33.5	33.4	34.0	33.7	33.1
C10	73.1	73.1	73.2	73.4	73.7	73.7	72.9
C11	74.9	74.9	75.4	75.5	75.7	75.3	76.6
C12	27.0	26.9	25.2	25.3	25.7	25.7	24.5
C13	27.2	27.3	27.1	27.3	27.8	27.5	23.3
C25	25.8	25.7	25.7	25.7	26.6	26.6	27.8
C26	26.0	25.9	25.0	21.3	24.0	21.3	24.9
C27	23.4	23.4	23.5	23.5	25.5	23.5	23.4
H27	1.09	1.08	1.09	1.09	1.09	1.10	1.10

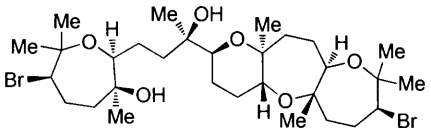
^{1}H NMR shifts in ppm referenced to 7.26 ppm, ^{13}C NMR shifts in ppm referenced to 77.0 ppm

a) Synthetic data for armatol A b) Reported data[2]

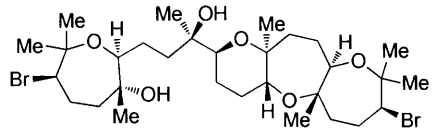
Figure 2-3. Revised structures of armatol A, B, C, E, and F



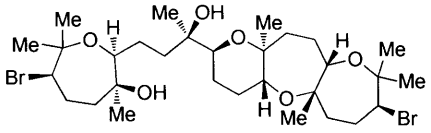
armatol A (**155**)



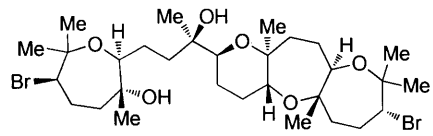
armatol B (**156**)



armatol C (**157**)



armatol F (**160**)



armatol E (**159**)

Conclusion

The completion of the synthesis of armatol A has allowed us to confirm the absolute structure and stereochemistry of not only armatol A, but also five of the six members of the natural product family. Additionally, the stereoselective synthesis of a bromooxepane ring via a bromonium-initiated epoxide-opening cascade was explored. Functionalization of the primary alcohol formed from this cascade (**92**) allowed for a variety of coupling strategies to form the carbon framework of armatol A to be investigated. Difficulties in reducing a cis alkene adjacent to a tertiary alcohol forced a strategic revision, where a trans alkene was easily reduced to form the acyclic alkyl chain connecting the two sides of armatol A. Formation of the key C10 tertiary alcohol allowed for complete analysis and determination of the absolute structure of armatol A. Synthesis of the two possible diastereomers of armatol A and comparison of the spectral data support a structure for armatol A with absolute configuration shown in **123**. Using this

information, structural revisions of the entire family of armatols and a new biogenesis of these natural products have been proposed.

References

[1] Hemibrevetoxin B: a) Prasad, A. V. K.; Shimizu, Y. *J. Am. Chem. Soc.* **1989**, *111*, 6476-6477. Gambierol: b) Satake, M.; Murata, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 361-362. c) Morohashi, A.; Satake, M.; Yasumoto, T. *Tetrahedron Lett.* **1999**, *40*, 97-100. Brevenal: d) Bourdelais, A. J.; Jacocks, H. M.; Wright, J. L. C.; Bigwarfe, P. M., Jr.; Baden, D. G. *J. Nat. Prod.* **2005**, *68*, 2-6. e) Fuwa, H.; Ebine, M.; Bourdelais, A. J.; Baden, D. G.; Sasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 16989-16999.

[2] Ciavatta, M. L.; Wahidulla, S.; D'Souza, L. D.; Scognamiglio, G.; Cimino, G. *Tetrahedron* **2000**, *57*, 617-623.

[3] a) Fujiwara, K.; Tanaka, K.; Katagiri, Y.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2010**, *51*, 4543-4546. b) Fujiwara, K.; Hirose, Y.; Sato, D.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2010**, *51*, 4263-4266.

[4] Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5335-5340.

[5] Matsukura, H.; Morimoto, M.; Koshino, H.; Nakara, T. *Tetrahedron Lett.***1997**, *38*, 5545-5548.

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

[7] Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768-2771.

[8] Van Dyke, A. R. Ph.D. Dissertation, Massachusetts Institute of Technology, 2009.

[9] Vidari, G.; Frazini, M.; Garlaschelli, L.; Maronati, A. *Tetrahedron Lett.* **1993**, *34*, 2685-2688.

[10] A) Ng, S.-S. Ph.D. Dissertation, Massachusetts Institute of Technology, 1998. b) Tanuwidjaja, J.; Jamison, T. F. Unpublished work.

[11] Proposed biogenesis for tricyclic fragment shown in Scheme 1-6 of Chapter 1

[12] Overton, K. H.; Roberts, F. M. *Biochem. J.* **1974**, *144*, 585-592.

[13] Fernández, J. J.; Souto, M. L.; Norte, M. *Nat. Prod. Rep.* **2000**, *17*, 235-246.

[14] a) Broka, C. A.; Lin, Y.-T. *J. Org. Chem.* **1988**, *53*, 5876-5885. b) Hashimoto M.; Kan, T.; Nozaki, K.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *J. Org. Chem.* **1990**, *55*, 5088-5107. c) Hashimoto, M.; Kan, T.; Nozaki, K.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1988**, *29*, 1143-1144. d) Corey, E. J.; Ha, D.-C. *Tetrahedron Lett.* **1988**, *29*, 3171-3174. e) Gonzalez, I. C.; Forsyth, C. J. *Org. Lett.* **1999**, *1*, 319-322. f) Gonzalez, I. C.; Forsyth, C. J. *J. Am. Chem. Soc.* **2000**, *122*, 9099-9108.

[15] Kato, T.; Ichinose, I.; Hosagi, T. *Chem. Lett.* **1976**, *5*, 1176-1190.

[16] a) Morimoto, Y.; Nishikawa, Y.; Takaishi, M. *J. Am. Chem. Soc.* **2005**, *127*, 5806-5807. b) Morimoto, Y.; Yata, H.; Nishikawa, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 6481-6484.

[17] Tanuwidjaja, J.; Ng, S. S.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 12084-12085.

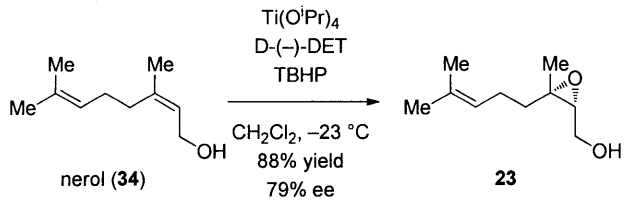
[18] Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900-903.
[19] Bravo, F.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *Org. Lett.* **2004**, *6*, 4478-4489.
[20] a) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2190-2197. b) Neverov, A. A.; Brown, R. S. *J. Org. Chem.* **1998**, *63*, 5977–5982. c) Roux, M.-C.; Paugam, R.; Rousseau, G. *J. Org. Chem.* **2001**, *66*, 4303-4310. d) Neverov, A. A.; Feng, H. X.; Hamilton, K.; Brown, R. S. *J. Org. Chem.* **2003**, *68*, 3802-3810.
[21] In the experimental for reference 19, McDonald reporting obtaining a 51% yield using acetonitrile instead of dichloromethane.
[22] a) Neverov, A. A.; Brown, R. S. *J. Org. Chem.* **1998**, *63*, 5977-5982. b) Neverov, A. A.; Feng, H. X.; Hamilton, K.; Brown, R. S. *J. Org. Chem.* **2003**, *68*, 3802-3810.
[23] a) Na, J.; Houk, K. N.; Shevin, C. G.; Janda, K. D.; Lerner, R. A. *J. Am. Chem. Soc.* **1993**, *115*, 8453-8454. b) Na, J.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, *118*, 9204-9205.
[24] Zakarian, A.; Batch, A.; Holton, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 7822-7824.
[25] Snyder, S. A.; Treitler, D. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 7899-7903.
[26] Structure found as mixture with the desired bromooxepane **71**, structure assignment found after deprotection of the carbonate and oxidation provided a ketone alpha to the ring.
[27] Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408-7410.
[28] a) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379-1386. b) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997-4998.
[29] Roth, G. J.; Liepold, B.; Müller, S. G.; Bestmann, H. J. *Synthesis* **2004**, 59-62.
[30] a) Jin, H.; Uenishi, J.-i.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644-5646. b) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048-6050.
[31] Precedence for NHK coupling in the presence of a alkyl bromide, albeit in only 37% yield: Nishiguchi, G. A.; Graham, J.; Bouraoui, A.; Jacobs, R. S.; Little, R. D. *J. Org. Chem.* **2006**, *71*, 5936-5941.
[32] Pearlman, W. M. *Tetrahedron Lett.* **1967**, *17*, 1663-1664.
[33] For reviews, see: a) Hünig, S.; Müller, H. R.; Thier, W. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 271-280. b) Pasto, D. J.; Taylor, R. T. *Org. React.* **1991**, *40*, 91-155.
[34] a) Imada, Y.; Kitagawa, T.; Ohno, T.; Iida, H.; Naota, T. *Org. Lett.* **2010**, *12*, 32-35. b) Imada, Y.; Iida, H.; Naota, T. *J. Am. Chem. Soc.* **2005**, *127*, 14544-14545.
[35] Brown, J. M. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 190-203.
[36] Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841-1860.
[37] a) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115-8116. b) Schwartz, J.; Labinger, J. A. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 333-340. c) Wipf, P.; Jahn, H. *Tetrahedron*, **1996**, *52*, 12853-12910.
[38] Tashiro, T.; Mori, K. *Tetrahedron: Asymmetry*, **2005**, *16*, 1801-1806.
[39] Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, *7*, 639-666.
[40] Little, R. D.; Nishiguchi, G. A. Synthetic efforts toward, and biological activity of, thyrsiferol and structurally-related analogues. In *Studies in Natural Products Chemistry;* Atta-ur-Rahman, FRS, Eds.; Elsevier: Amsterdam, 2008; Vol. 35, pp 3-56.
[41] A bromonium-initiated epoxide-opening cascade to support this biosynthetic proposal was demonstrated by Jamsion and co-workers in ref. 17.

Experimental Section

General Information

Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of argon or nitrogen with rigorous exclusion of moisture from reagents and glassware. Unless otherwise noted, all solvents and triethylamine used in the reactions were purified via a SG Water USA solvent column system. 4Å MS used in the Sharpless asymmetric epoxidations or the bromonium-initiated epoxide-opening cascades were activated by flame drying under high vacuum three times (with cooling in between) immediately before use. 1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP) (99%) was purchased from Aldrich® Chemical Company and was used without further purification. *N*-Bromosuccinimide (NBS) was recrystallized from H_2O before use and kept at 0 °C in the absence of light. Analytical thin-layer chromatography was performed using EM Science silica gel 60 F254 plates. The developed chromatogram was visualized by UV lamp or stained using one of the following: aqueous potassium permanganate ($KMnO_4$), ethanolic phosphomolybdic acid (PMA), aqueous cerium ammonium molybdate (CAM, Hanessian's stain), or ethanolic vanillin. Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle silica gel (230-400 mesh).

^1H and ^{13}C NMR spectra were recorded on Varian 300 MHz, Varian 500 MHz, Bruker 400 MHz, or Bruker 600 MHz spectrometer in $CDCl_3$ or C_6D_6. 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) or residual benzene (7.16 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and bs = broad singlet), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.23 ppm) or C_6D_6 (128.37 ppm) on the δ sc ale. 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 Fourier Transform Mass Spectrometer by Ms. Li Li of the Massachusetts Institute of Technology, Department of Chemistry Instrumentation Facility. Chiral HPLC analysis was performed on a Hewlett-Packard 1100 chromatograph equipped with a variable wavelength detector and Chiralcel OD or OD-H, or AD-H columns. Specific Rotations ($[\alpha]^{24}_D$) were measured on a Perkin-Elmer 241 polarimeter at 589 nm.

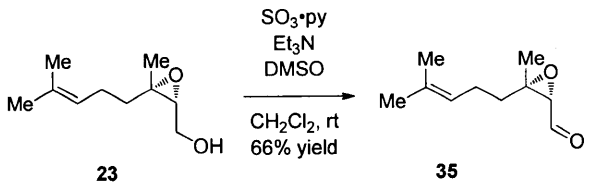


Epoxy alcohol 23: To a 1 L round-bottom flame-dried flask equipped with a stir bar was added 4 Å molecular sieves (1.005g) and heated under vacuum for 15 min. CH_2Cl_2 (40 mL) was added and the flask was cooled with a CryoCool to –23 °C. Titanium isopropoxide (0.62 mL, 2.1 mmol) and D-(–)-diethyl tartrate (0.49 mL, 2.8 mmol) were added and stirred for 30 min. A solution of *tert*-butyl hydrogen peroxide (5.5 M in decanes, 7.2 mL, 39.6 mol) was added and stirred for 30 min. Nerol (3.6 mL, 20.4 mmol) was added slowly over 15 min. The reaction was stirred at this temperature for 15 h. The reaction was quenched by adding of H_2O at 0 °C and stirring for 5 h. Added 74 mL of 22.1g of NaOH in 72 mL of H_2O followed by saturating with NaCl. The reaction mixture was filtered through Celite. Extracted with CH_2Cl_2 (3x) and the organic layers were dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The crude oil was purified by column chromatography (20% EtOAc in hexanes) to provide **23** (3.05 g, 17.9 mmol, 88% yield) as a colorless oil.

^{1}H NMR (500 MHz; $CDCl_3$): δ 5.09-5.05 (m, 1H), 3.79 (d, J = 12.0, 1H), 3.62 (dd, J = 12.0, 7.1, 1H), 2.95 (dd, J = 7.0, 4.2, 1H), 2.59 (s, 1H), 2.12-2.03 (m, 2H), 1.67 (s, 3H), 1.63 (dt, J = 9.6, 4.9, 1H), 1.59 (s, 3H), 1.46 (ddd, J = 13.7, 9.9, 7.0, 1H), 1.32 (s, 3H).

^{13}C NMR (125 MHz; $CDCl_3$): δ 132.6, 123.4, 64.6, 61.7, 61.4, 33.3, 25.8, 24.3, 22.3, 17.8.

Chiral HPLC analysis of the acetate (Ac_2O, Et_3N, DMAP, CH_2Cl_2): (Chiralcel OD, hexanes:2-propanol, 200:1, 1.0 mL/min): t_R(2*S*,3*S*) = 13.5 min; t_R(2*R*, 3*R*) = 14.7 min. The enantiomeric excess was determined to be 79%.



23 35

Epoxyaldehyde 35: To a 100 mL round-bottom flask equipped with a stir bar was added epoxyalcohol **23** (498 mg, 2.93 mmol) and dissolved in 30 mL of CH_2Cl_2. Et_3N (990 *u*L, 7.10 mmol) and DMSO (1.05 mL, 14.8 mmol) were added and the reaction was cooled to 0 °C. SO_3•py. (563 mg, 3.54 mmol) was added and the reaction was stirred for 2 h while warming to room temperature. The reaction was quenched with saturated NH_4Cl and then extracted with CH_2Cl_2 (3x). The organic layers were dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The crude oil was purified by column chromatography (10% EtOAc in hexanes) to provide epoxyaldehyde **35** (325 mg, 1.93 mmol, 66% yield) as a colorless oil.

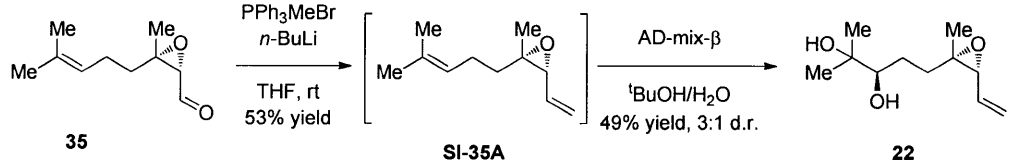
^{1}H NMR (500 MHz; $CDCl_3$): δ 9.42 (dd, J = 5.1, 1.1, 1H), 5.06-5.02 (m, 1H), 3.15 (d, J = 5.1, 1H), 2.23-2.16 (m, 1H), 2.12-2.04 (m, 1H), 1.86 (ddd, J = 14.1, 8.9, 5.3, 1H), 1.71 (dd, J = 2.4, 0.3, 1H), 1.67 (s, 3H), 1.64-1.60 (m, 1H), 1.59 (s, 3H), 1.43 (s, 3H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 199.1, 133.5, 122.6, 68.5, 64.8, 33.6, 25.8, 24.4, 22.3, 17.8

$[\alpha]^{24}_D$ = -66.9 (c 0.73, $CHCl_3$).

IR (NaCl, thin film): 3584, 2970, 2928, 2857, 1722, 1452, 1410, 1382, 1109, 1058.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{10}H_{16}O_2Na$, 191.1043; found, 191.1051.



Terminal alkene 22: To a 25 mL round-bottom flask equipped with a stir bar was added methyltriphenylphosphonium bromide (643 mg, 1.80 mmol) in 10 mL of THF. A 2.5 M of *n*-BuLi in hexanes (660 *u*L, 1.65 mmol) was added and the reaction was stirred for 30 min. A solution of aldehyde **35** (251 mg, 1.49 mmol) in 2 mL of THF was added and stirred for 15 h. The reaction was quenched with saturated NH_4Cl and extracted with Et_2O (3x). The organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (2% EtOAc in hexanes) to furnish alkene **SI-35A** (131 mg, 0.788 mmol, 53% yield) which was carried used without further purification.

To a 20 mL vial with stir bar was added alkene **SI-35A** (131 mg, 0.788 mmol) and 4 mL of *t*-BuOH. 4 mL of H_2O was cooled to 0 °C. AD-mix β (1.099 g) was added and the reaction was stirred at 4 °C for 24 h. The reaction was quenched with saturated Na_2SO_3 and warmed to room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction was purified by column chromatography (20% to 50% EtOAc in hexanes) to furnish **22** (72 mg, 0.382 mmol, 49% yield) as a colorless oil.

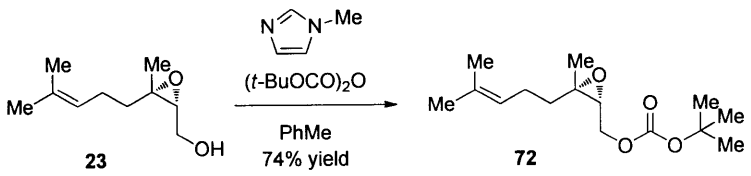
^{1}H NMR (500 MHz; $CDCl_3$): δ 5.84-5.77 (m, 1H), 5.50-5.45 (m, 1H), 5.38 (ddd, J = 10.5, 1.4, 0.7, 1H), 3.46 (d, J = 10.7, 1H), 3.26 (d, J = 7.2, 1H), 2.44 (d, J = 3.9, 1H), 1.98 (bs, 1H), 1.88-1.81 (m, 1H), 1.72-1.64 (m, 1H), 1.64-1.59 (m, 1H), 1.57 (s, 3H), 1.53-1.46 (m, 1H), 1.37 (s, 3H), 1.25 (s, 3H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 133.1, 120.7, 77.8, 77.4, 73.2, 65.0, 29.3, 27.0, 26.9, 23.5, 21.9

$[\alpha]^{24}_D$ = +11.5 (c 0.04, $CHCl_3$).

IR (NaCl, thin film): 3434, 2926, 1381.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{11}H_{20}O_3Na$, 223.1305; found, 223.1303.



Carbonate 72: To a 500 mL flame-dried round-bottom flask equipped with a stir bar was added epoxyalcohol **23** (6.7 g, 39 mmol) in toluene (130 mL). 1-methylimidazole (4.15 mL, 52.1 mmol) was added and the reaction was cooled to 0 °C. Liquid di-*tert*-butyl dicarbonate (9.72 g, 44.5 mmol) was added dropwise over 15 min and then stirred while warming to room temperature overnight. The reaction was poured into water and enough CH_2Cl_2 was added to separate into two layers. The aqueous layer was extracted with CH_2Cl_2 (3x) and then the organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (10% EtOAc in hexanes) to provide carbonate **72** (7.91 g, 29.3 mmol, 74% yield) as a colorless oil.

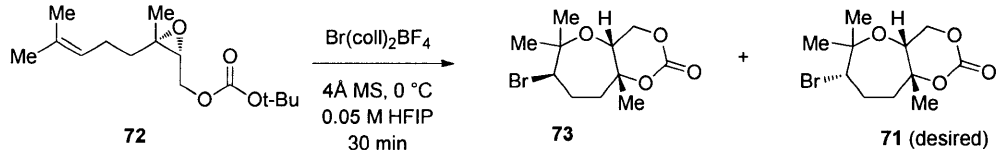
^{1}H NMR (500 MHz; $CDCl_3$): δ 5.11-5.08 (m, 1H), 4.24 (dd, J = 11.8, 4.7, 1H), 4.10 (dd, J = 11.8, 6.6, 1H), 3.02 (dd, J = 6.6, 4.7, 1H), 2.14-2.10 (m, 2H), 1.70 (s, 3H), 1.67-1.64 (m, 1H), 1.63 (s, 3H), 1.50 (s, 9H), 1.49-1.48 (m, 1H), 1.35 (s, 3H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 153.5, 132.6, 123.4, 82.7, 65.7, 61.0, 60.9, 33.4, 27.9, 25.9, 24.3, 22.1, 17.8

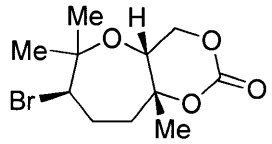
$[\alpha]^{24}_D$ = +5.8 (c 0.26, $CHCl_3$).

IR (NaCl, thin film): 3584, 2981, 2925, 1744, 1457, 1369, 1278, 1255, 1163, 1094.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{15}H_{26}O_4Na$, 293.1723; found, 293.1727.



Bromooxepanes 71 and 73: To a 500 mL round-bottom flask equipped with a stir bar was added 4Å molecular sieves (27 g) followed by carbonate **72** (3.87 g, 14.3 mmol) and 278 mL of HFIP. The reaction was cooled to 0 °C and $Br(coll)_2BF_4$ (17.6 g, 43.0 mmol) was added in one portion and the reaction was stirred for 30 min. The reaction was filtered through Celite and then added to 150 mL of brine and 150 mL of saturated $Na_2S_2O_3$. The aqueous layer was extracted with CH_2Cl_2 (3x) and then the organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude solid was purified by dry loading onto a silica gel column and performing column chromatography (20 to 50 to 100% EtOAc in hexanes) to furnish **73** (1.313g, 4.48 mmol, 31% yield) and **71** (693.1 mg, 2.36 mmol, 17% yield) as white solids.



73

Carbonate 73:

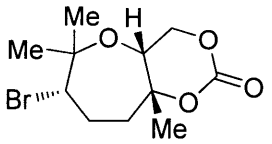
^1H NMR (600 MHz; $CDCl_3$): δ 4.46 (dd, J = 11.6, 2.8, 1H), 4.18 (dd, J = 11.6, 2.2, 1H), 4.13 (dd, J = 10.3, 2.5, 1H), 3.94 (t, J = 2.5, 1H), 2.35 (ddt, J = 14.9, 10.2, 2.2, 1H), 2.14 (ddd, J = 14.8, 10.1, 1.5, 1H), 2.03-1.99 (m, 1H), 1.86-1.80 (m, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 1.41 (s, 3H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 149.4, 86.6, 79.5, 70.4, 67.8, 61.9, 38.4, 30.4, 29.2, 25.8, 22.4

$[[\alpha]^{24}_D = -9.7$ (c 1.2, $CHCl_3$).

IR (NaCl, thin film): 2981, 1750, 1457, 1388, 1292, 1247, 1218, 1122, 1091, 1042..

HRMS-ESI (m / z): $[M + H]^+$ calcd for $C_{11}H_{18}O_4Br$, 293.0389; found, 293.0374.



71

Carbonate 71:

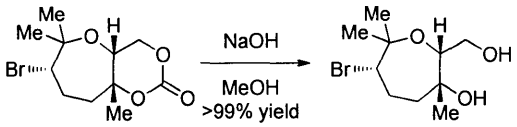
^1H NMR (600 MHz; $CDCl_3$): δ 4.52 (dd, J = 11.5, 2.9, 1H), 4.22 (dd, J = 11.4, 1.8, 1H), 3.88 (dd, J = 10.6, 1.9, 1H), 3.77 (dd, J = 2.7, 1.9, 1H), 2.50 (dtd, J = 14.5, 10.6, 3.6, 1H), 2.20 (ddd, J = 15.0, 6.9, 3.3, 1H), 2.03-1.99 (m, 1H), 1.72-1.67 (m, 1H), 1.43 (s, 3H), 1.42 (s, 3H), 1.39 (s, 3H)

^{13}C NMR (100 MHz; $CDCl_3$): δ 149.2, 83.7, 79.2, 71.2, 66.8, 57.1, 39.9, 30.3, 25.7, 25.5, 24.4

$[\alpha]^{24}_D = -23.0$ (c 0.1, $CHCl_3$).

IR (NaCl, thin film): 2937, 1732, 1159, 1540, 1457, 1298, 1208, 1120, 1086, 1040.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{11}H_{17}O_4BrNa$, 315.0202; found, 315.0214.

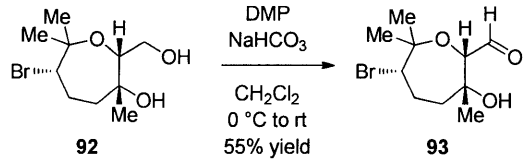


71 92

Diol 92: To a 100 mL round-bottom flask equipped with a stir bar was added **71** (693.1 mg, 2.36 mmol) in 24 mL of MeOH. NaOH (101.7 mg, 2.54 mmol) was added and the reaction was stirred for 45 min at room temperature. The reaction was concentrated *in vacuo* and then the remaining oil was redissolved in EtOAc and extracted with EtOAc (3x) from a saturated NH_4Cl solution followed by extraction with CH_2Cl_2 (3x). The organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide a colorless oil **92** (631.1 mg, 2.36 mmol, 100% yield) which was carried on without further purification.

^1H NMR (500 MHz; $CDCl_3$): δ 3.87 (ddd, J = 11.6, 7.2, 4.1, 1H), 3.81 (ddd, J = 11.8, 8.6, 3.2, 1H), 3.36 (dd, J = 6.9, 3.2, 1H), 3.30 (dd, J = 9.7, 3.7, 1H), 2.76 (s, 1H), 2.34 (dd, J = 8.5, 4.0, 1H), 1.86-1.80 (m, 3H), 1.79 (s, 3H), 1.76 (s, 3H), 1.61-1.54 (m, 1H), 1.18 (d, J = 10.3, 3H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 84.9, 83.6, 68.2, 67.6, 61.8, 37.3, 30.6, 24.6, 23.1, 30.3



92 93

Aldehyde 93: To a 100 mL round-bottom flask equipped with a stir bar was added diol **92** (631.1 mg, 2.36 mmol) followed by $NaHCO_3$ (1.89 g, 22.5 mmol) and 100 mL of CH_2Cl_2. Dess-martin periodinane[1] (1.16 g, 3.37 mmol) was added in portions and the reaction was stirred at 0 °C for 2 h then warmed to room temperature overnight. The reaction was quenched with saturated Na_2SO_3 and saturated $NaHCO_3$ and then extracted with CH_2Cl_2 (5x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction was purified by column chromatography (20 to 70% EtOAc in hexanes) to provide a **93** (343.8 mg, 1.30 mmol, 55% yield) as a colorless oil and some recovered diol **92** (115.1 mg, 0.43 mmol, 18% yield).

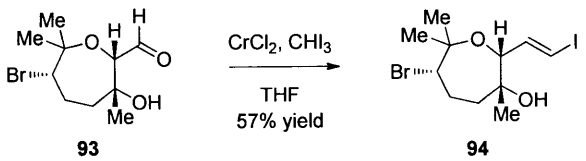
^{1}H NMR (500 MHz; $CDCl_3$): δ 9.52 (d, J = 3.0, 1H), 3.86 (dd, J = 11.0, 0.7, 1H), 3.59 (d, J = 3.0, 1H), 3.25 (s, 1H), 2.40 (dddd, J = 15.0, 13.0, 10.9, 2.2, 1H), 2.07 (dddd, J = 14.9, 5.3, 3.2, 0.9, 1H), 1.79 (ddd, J = 14.8, 5.4, 2.3, 1H), 1.63-1.55 (m, 1H), 1.52 (s, 3H), 1.37 (s, 3H), 1.20 (d, J = 0.9, 3H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 200.6, 80.1, 79.6, 72.5, 57.8, 44.3, 30.3, 25.6, 24.7, 23.7

$[\alpha]^{24}_D = -35.4$ (c 0.65, $CHCl_3$).

IR (NaCl, thin film): 3456, 2978, 2940, 1733, 1446, 1386, 1371, 1313, 1271, 1218, 1174, 1141, 1065.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{10}H_{17}BrO_3Na$, 287.0253; found, 287.0258.



Vinyl iodide 94: To an oven-dried 10 mL round-bottom flask equipped with a stir bar was added $CrCl_2$ (337.8 mg, 2.75 mmol) in the dry box and transferred into the hood under nitrogen. The solid was dissolved in 3 mL of THF and cooled to 0 °C. A solution of aldehyde **93** (80.6 mg, 0.304 mmol) and iodoform (384.7 mg, 0.977 mmol) dissolved in THF was slowly added to the flask and the solution turned from yellow to a shade of burgundy. The reaction was allowed to warm to room temperature overnight. The reaction was poured into water and extracted with Et_2O (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography (5% to 10% EtOAc in hexanes) to provide vinyl iodide **94** (29.9 mg, 0.077 mmol, 25% yield) as a colorless oil.

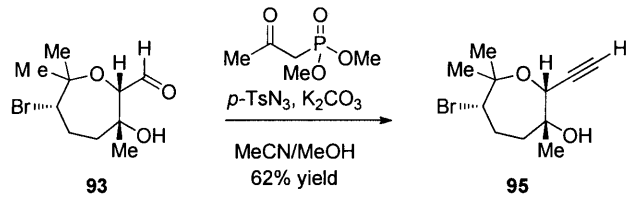
^1H NMR (500 MHz; $CDCl_3$): δ 6.63-6.59 (m, 1H), 6.33 (dd, J = 14.5, 1.1, 1H), 3.92 (d, J = 11.1, 1H), 3.76 (d, J = 6.8, 1H), 3.03 (s, 1H), 2.37-2.29 (m, 1H), 2.05-2.00 (m, 1H), 1.79 (ddd, J = 14.7, 5.3, 2.2, 1H), 1.57-1.51 (m, 1H), 1.43 (s, 3H), 1.37 (s, 3H), 1.09 (s, 3H)

^{13}C NMR (100 MHz; $CDCl_3$): δ 142.9, 79.2, 78.8, 78.5, 72.1, 58.5, 44.0, 30.5, 25.8, 25.0, 24.4

$[\alpha]^{24}_D = -20.8$ (c 1.5, $CHCl_3$).

IR (NaCl, thin film): 3546, 2970, 2933, 1607, 1446, 1384, 1369, 1269, 1169, 1140, 1095, 1038.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{11}H_{18}BrIO_2Na$, 410.9427; found, 410.9425.



Alkyne 95: To an oven-dried 50 mL round-bottom flask equipped with a stir bar was added *p*TsN_3 (417.5 mg, 2.12 mmol) and 26 mL of acetonitrile followed by potassium carbonate (743.0 mg, 5.38 mmol) and the solution was stirred. Dimethyl-(2-oxopropyl)-phosphate (290 *u*L, 2.12 mmol) was added and the reaction was stirred at room temperature for 2 h. Aldehyde **93** (462.6 mg, 1.74 mmol) was dissolved in 5.2 mL of MeOH and added as a solution. The reaction was allowed to stir for 15 h. The solvents were removed *in vacuo* and then 15 mL of H_2O and Et_2O were added. The aqueous layer was extracted with Et_2O (3x) and then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude solid was dry loaded onto silica gel and purified by column chromatography (10->20% EtOAc in hexanes) to provide **95** (283.0 mg, 1.08 mmol, 62% yield) as a colorless oil.

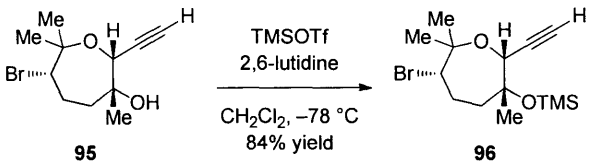
^{1}H NMR (600 MHz; $CDCl_3$): δ 4.15 (d, J = 2.1, 1H), 3.89 (d, J = 11.0, 1H), 3.10 (s, 1H), 2.50 (d, J = 2.1, 1H), 2.39-2.33 (m, 1H), 2.04 (ddd, J = 14.8, 5.3, 3.1, 1H), 1.88 (ddd, J = 14.8, 5.4, 2.1, 1H), 1.54 (td, J = 14.0, 2.6, 1H), 1.49 (s, 3H), 1.48 (s, 3H), 1.31 (s, 3H)

^{13}C NMR (100 MHz; $CDCl_3$): δ 80.5, 79.3, 74.5, 72.3, 68.2, 58.1, 43.0, 30.4, 25.7, 25.6, 24.5

$[\alpha]^{24}_D$ = –53.2 (c 1.1, $CHCl_3$).

IR (NaCl, thin film): 3541, 3293, 2972, 2937, 1447, 1385, 1371, 1319, 1286, 1172, 1141, 1090, 1048, 1032.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{11}H_{17}BrO_2Na$, 283.0304; found, 283.0284.



95 96

Silyl-protected alkyne 96: To a 20 mL vial with stir bar was added alkyne **95** (260.9 mg, 0.999 mmol) in 10 mL of CH_2Cl_2. The vial was cooled to 0 °C and 2,6-lutidine (350 *u*L, 3.02 mmol) and TMSOTf (275 *u*L, 1.52 mmol) were added and the reaction was tired at 0 °C for 90 min. The reaction was quenched with $NaHCO_3$ and then extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil was purified by column chromatography (2% EtOAc in hexanes) to furnish **96** (278.6 mg, 0.836 mmol, 84% yield) as a white solid.

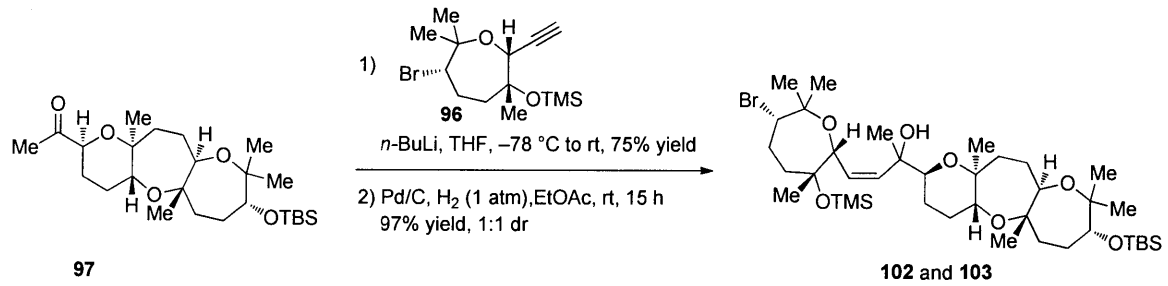
^1H NMR (500 MHz; $CDCl_3$): δ 3.99 (d, J = 2.3, 1H), 3.86 (d, J = 10.7, 1H), 2.59-2.51 (m, 1H), 2.42 (d, J = 2.3, 1H), 1.90 (s, 1H), 1.93-1.86 (m, 1H), 1.45 (s, 3H), 1.42 (s, 3H), 1.30 (s, 3H), 0.16 (s, 9H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 81.9, 78.5, 75.6, 73.8, 69.5, 60.0, 44.1, 30.7, 27.7, 25.9, 24.4, 2.8

$[\alpha]^{24}_D = -25.7$ (c 0.13, $CHCl_3$).

IR (NaCl, thin film): 2966, 1996, 1371, 1249, 1178, 1145, 1068, 1015.

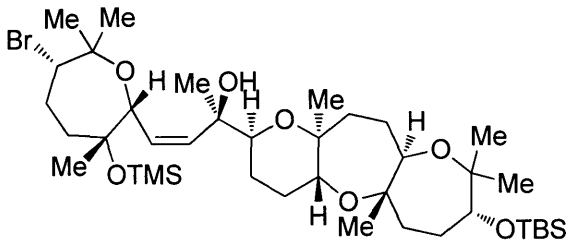
HRMS-ESI (m / z): $[M + H]^+$ calcd for $C_{14}H_{25}O_2BrSi$, 333.0880; found, 333.0874.

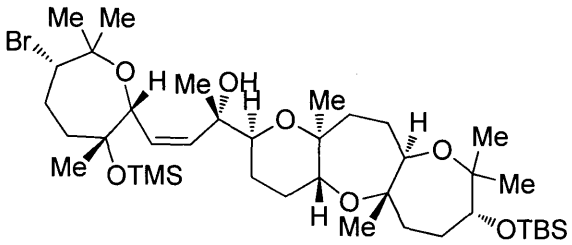


Allylic alcohols 102 and 103: To a 5 mL round-bottom flask equipped with a stir bar was added alkyne **96** (80.5 mg, 0.241 mmol) in 2.3 mL of THF and cooled to –78 °C. A 2.5 M of nBuLi in hexanes (95 *u*L, 0.238 mmol) was added slowly over 5 min and the reaction was stirred at this temperature for 20 min. The reaction was warmed to 0 °C for 10 min and then recooled to –78 °C. A solution of ketone **97** (50.9 mg, 0.115 mmol) in 700 *u*L of THF was added and the reaction was slowly warmed to room temperature over 4 h. The reaction was quenched with 1 mL of water and then saturated NH_4Cl was added. The reaction was extracted with EtOAc (3x) and with Et_2O (2x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil was purified by column chromatography (2 to 10% EtOAc in hexanes) to furnish alkyne **101** (60.1 mg, 0.077 mmol, 67% yield) as a colorless oil that was used without further purification.

To a 5 mL round-bottom flask equipped with a stir bar was added alkyne **101** (6.2 mg, 7.99 *u*mol) in 1 mL of EtOAc. The flask was placed under nitrogen and Pd/C (1.8 mg, 10% w/w) was added. The reaction was placed under hydrogen (1 atm) and stirred for 15 h. The reaction was filtered through Celite washing with EtOAc to remove the palladium. The solvent was removed *in vacuo* and then purified by column chromatography (2 to 5% EtOAc in hexanes) to furnish a mixture of alkenes **102** and **103** (6.0 mg, 7.59 *u*mol, 95% yield). Further purification in the same solvent system allowed for separation of the two alkenes **102** (0.52 R_f in 10% EtOAc in hexanes) and **103** (0.42 R_f in 10% EtOAc in hexanes).

Alkenes **102** and **103**:





Allylic alcohol higher R_f (102):

^{1}H NMR (500 MHz; $CDCl_3$): δ 5.46 (dd, J = 12.4, 9.7, 1H), 5.14 (dd, J = 12.5, 1.0, 1H), 5.03 (d, J = 9.8, 1H), 4.02 (d, J = 10.6, 1H), 3.75 (dd, J = 11.6, 2.4, 1H), 3.69 (d, J = 6.9, 1H), 3.52-3.49 (m, 1H), 3.26-3.23 (m, 1H), 2.60-2.52 (m, 1H), 2.48 (s, 1H), 2.06-1.95 (m, 3H), 1.94-1.70 (m, 6H), 1.62-1.59 (m, 5H), 1.46 (s, 3H), 1.45-1.40 (m, 1H), 1.39 (s, 3H), 1.25 (s, 3H), 1.23 (s, 3H), 1.20 (s, 3H), 1.16 (s, 3H), 1.08 (s, 3H), 1.07 (s, 3H), 0.96 (s, 9H), 0.11 (s, 9H), 0.03 (d, J = 1.6, 6H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 131.1, 127.4, 79.1, 78.6, 77.7, 77.6, 77.4, 76.5, 75.9, 75.5, 72.7, 72.2, 70.1, 61.4, 44.5, 40.8, 36.2, 31.2, 29.9, 29.1, 28.7, 28.4, 27.6, 26.6, 26.2, 26.0, 25.2, 23.1, 20.0, 18.4, 16.7, 2.8, -4.1, -5.3

$[\alpha]^{24}_D$ = +35.0 (c 0.14, $CHCl_3$).

IR (NaCl, thin film): 3425, 2927, 2855, 1462, 1454, 1377, 1249, 1138, 1075, 1009.

HRMS-ESI (m / z): $[M + H]^+$ calcd for $C_{39}H_{73}BrO_7Si_2$, 789.4151; found, 789.4138.

Allylic alcohol lower R_f (103):

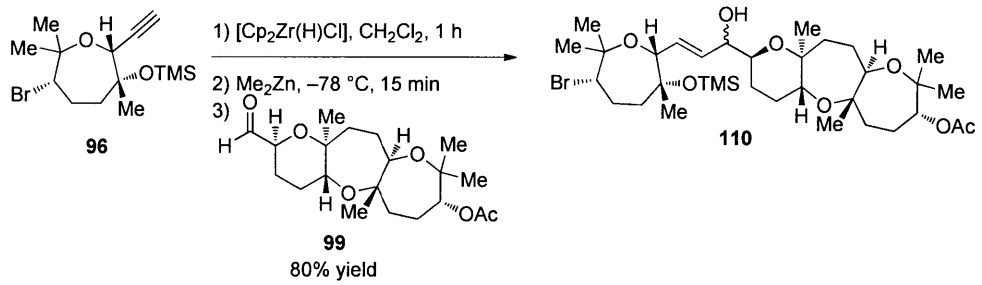
^{1}H NMR (500 MHz; $CDCl_3$): δ 5.46 (dd, J = 12.5, 9.5, 1H), 5.25 (d, J = 12.8, 1H), 5.01 (d, J = 9.2, 1H), 4.00 (d, J = 10.6, 1H), 3.76-3.73 (m, 1H), 3.68 (d, J = 6.7, 1H), 3.55-3.51 (m, 1H), 3.39-3.36 (m, 1H), 2.97 (d, J = 1.0, 1H), 2.59-2.50 (m, 1H), 2.06-1.61 (m, 10H), 1.54-1.45 (m, 2H), 1.41 (s, 3H), 1.40 (s, 3H), 1.26 (s, 3H), 1.23 (s, 3H), 1.16 (s, 3H), 1.15 (s, 3H), 1.12 (s, 3H), 1.07 (s, 3H), 0.96 (s, 6H), 0.11 (s, 9H), 0.03 (s, 9H).

^{13}C NMR (125 MHz; $CDCl_3$): δ 132.3, 128.3, 79.1, 78.6, 77.8, 77.7, 77.4, 76.4, 75.8, 72.5, 71.2, 70.3, 70.2, 61.4, 44.4, 40.8, 36.2, 29.9, 29.1, 28.7, 28.1, 27.6, 26.4, 26.2, 26.1, 25.9, 25.5, 24.1, 23.1, 19.9, 18.4, 16.7, 2.8, -4.1, -5.2

$[\alpha]^{24}_D$ = +3.0 (c 0.06, $CHCl_3$).

IR (NaCl, thin film): 3417, 2928, 2854, 1462, 1377, 1250, 1145, 1076.

HRMS-ESI (m / z): $[M + H]^+$ calcd for $C_{39}H_{73}BrO_7Si_2$, 789.4151; found, 789.4132.



Alcohol 110: To a 25 mL round-bottom flask equipped with a stir bar was added $[Cp_2Zr(H)Cl]$ (71.3 mg, 0.276 mmol) and alkyne **96** (92.3 mg, 0.277 mmol) and placed under nitrogen in the dark. 2.8 mL of CH_2Cl_2 was added and stirred for 1 h at room temperature. The flask was then cooled to –78 °C and Me_2Zn (2.0 M in toluene, 145 *u*L, 0.290 mmol) was added dropwise. After stirring for 15 min, a solution of aldehyde **99** (74.9 mg, 0.203 mmol) in 2 mL of CH_2Cl_2 was added and the reaction was allowed to slowly warm to room temperature overnight. A saturated solution of NH_4Cl was added and a white solid formed. The aqueous layer was extracted with CH_2Cl_2 (3x) and then the organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide a colorless oil. The crude reaction mixture was purified by column chromatography (10 to 20 to 30 to 50% EtOAc in hexanes) to provide allylic alcohol **110** (114.0 mg, 0.162 mmol, 80% yield) as a colorless oil.

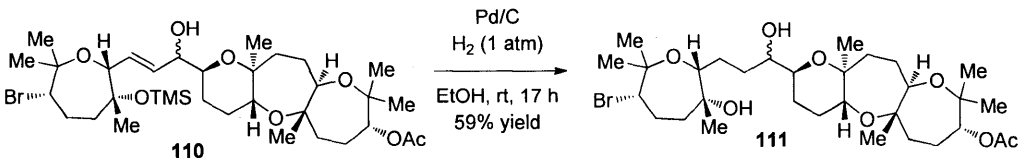
^{1}H NMR (500 MHz; $CDCl_3$): δ 5.827 (ddd, J = 15.53, 6.92, 0.72, 1H), 5.53-5.47 (m, 1H), 4.91 (d, J = 6.7, 1H), 3.95 (d, J = 10.4, 1H), 3.84 (q, J = 7.4, 1H), 3.63 (d, J = 6.4, 1H), 3.58 (dd, J = 16.1, 7.3, 1H), 3.45 (dd, J = 11.4, 2.3, 1H), 3.33 (ddd, J = 11.7, 7.2, 2.0, 1H), 2.76 (d, J = 1.3, 1H), 2.57-2.50 (m, 1H), 2.11 (s, 3H), 2.08-2.01 (m, 2H), 1.95-1.84 (m, 4H), 1.81-1.76 (m, 1H), 1.72-1.69 (m, 1H), 1.68-1.56 (m, 4H), 1.52-1.43 (m, 3H), 1.40 (s, 3H), 1.31 (s, 3H), 1.25 (s, 3H), 1.23 (s, 3H), 1.16 (s, 3H), 1.14 (s, 3H), 1.10 (s, 3H), 0.10 (s, 9H)

^{13}C NMR (125 MHz; $CDCl_3$): δ (Major diastereomer) 170.2, 132.1, 130.7, 78.8, 78.6, 78.3, 78.0, 77.7, 77.6, 77.4, 76.1, 72.9, 70.3, 60.7, 44.2, 40.6, 36.7, 31.1, 29.1, 28.9, 28.1, 28.0, 27.3, 26.2, 24.3, 23.2, 21.8, 21.3, 20.2, 16.4, 2.8

$[\alpha]^{24}_D$ = +6.2 (c 1.0, $CHCl_3$).

IR (NaCl, thin film): 3473, 2940, 2875, 1737, 1441, 1379, 1249, 1067, 840. 755.

HRMS-ESI (m / z): $[M + H]^+$ calcd for $C_{34}H_{59}BrO_8Si$, 725.3055; found, 725.3032.



Secondary alcohol 111: To a 10 mL round-bottom flask equipped with a stir bar was added allylic alcohol **110** (114.0 mg, 0.162 mmol) and 1.6 mL of EtOH. Palladium on carbon (9.1 mg, 10% by weight) was added and placed under vacuum. Hydrogen gas (1 atm) was added and the reaction was stirred at room temperature for 17 h. The solution was filtered through Celite washing with EtOAc to remove the palladium. The crude reaction mixture was purified by column chromatography (50% EtOAc in hexanes) to provide alcohol **111** (61.0 mg, 0.096 mmol, 59% yield) as a colorless oil.

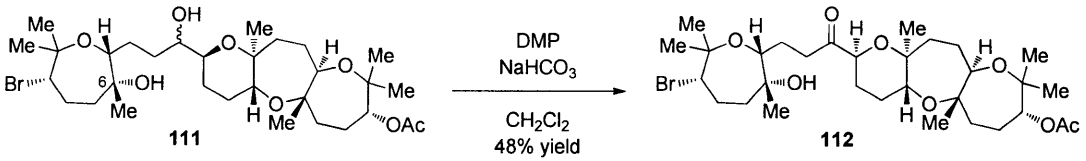
^{1}H NMR (500 MHz; $CDCl_3$): δ 4.92 (d, J = 6.6, 1H), 3.91 (d, J = 11.1, 1H), 3.58 (t, J = 7.9, 1H), 3.45 (dd, J = 11.4, 2.4, 1H), 3.34 (dd, J = 10.3, 2.9, 1H), 3.37-3.25 (m, 1H), 3.27 (d, J = 9.7, 1H), 3.01 (bs, 1H), 2.68 (bs, 1H), 2.38-2.30 (m, 1H), 2.12 (s, 3H), 2.08-1.99 (m, 2H), 1.91-1.84 (m, 2H), 1.83-1.69 (m, 5H), 1.68-1.56 (m, 6H), 1.53-1.46 (m, 4H), 1.42 (s, 3H), 1.36 (s, 3H), 1.26 (s, 3H), 1.24 (s, 3H), 1.16 (s, 3H), 1.14 (s, 3H), 1.12 (s, 3H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 170.3, 78.9, 78.6, 78.3, 78.0, 77.4, 77.4, 76.1, 75.0, 73.3, 72.4, 70.3, 59.4, 44.5, 40.6, 36.8, 30.6, 30.0, 29.1, 28.9, 28.0, 27.4, 26.5, 25.9, 25.5, 25.2, 23.2, 21.8, 21.3, 20.2, 16.4

$[\alpha]^{24}_D$ = +4.5 (c 0.25, $CHCl_3$).

IR (NaCl, thin film): 2937, 1734, 1684, 1636, 1559, 1540, 1507, 1457.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{31}H_{53}BrO_8$, 655.2816; found, 655.2812.



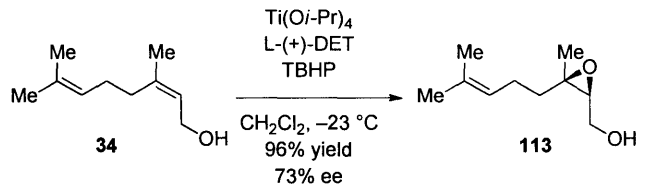
Ketone 112: To a 50 mL round-bottom flask equipped with a stir bar was added alcohol **111** (26.6 mg, 0.042 mmol) and sodium bicarbonate (34.6 mg, 0.412 mmol) in 1 mL of CH_2Cl_2. A 0.3 M solution of Dess-Martin periodinane (300 *u*L, 0.090 mmol) was added and the reaction was stirred for 13 hours at room temperature. The reaction was quenched with a 1:1 solution of saturated $NaHCO_3$ and Na_2SO_3. The aqueous layer was extracted with CH_2Cl_2 (3 x) and the organic layers were collected and dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography (20 to 30% EtOAc in hexanes) to furnish ketone **112** (12.5 mg, 0.0198 mmol, 47% yield) as a colorless oil.

^{1}H NMR (500 MHz; $CDCl_3$): δ 4.93 (d, J = 6.6, 1H), 3.92 (d, J = 2.9, 1H), 3.89 (d, J = 11.6, 1H), 3.58 (dd, J = 9.0, 7.2, 1H), 3.47 (dd, J = 11.4, 2.4, 1H), 3.40 (dd, J = 10.3, 2.8, 1H), 2.97 (s, 1H), 2.73-2.61 (m, 2H), 2.37-2.29 (m, 1H), 2.12 (s, 3H), 2.08-1.94 (m, 4H), 1.92-1.72 (m, 4H), 1.71-1.59 (m, 5H), 1.59-1.46 (m, 4H), 1.41 (s, 3H), 1.33 (s, 3H), 1.26 (s, 6H), 1.17 (s, 3H), 1.15 (s, 3H), 1.14 (s, 3H)

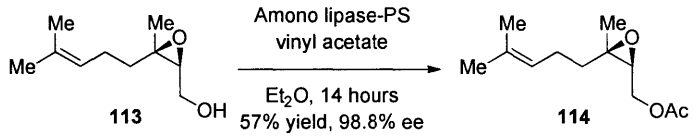
^{13}C NMR (125 MHz; $CDCl_3$): δ 211.8, 170.2, 79.0, 78.6, 78.3, 78.0, 77.9, 77.4, 75.5, 74.7, 72.3, 70.0, 59.1, 44.5, 40.5, 36.7, 34.4, 30.5, 29.0, 28.9, 28.4, 27.4, 25.9, 25.3, 25.0, 23.2, 23.2, 21.8, 21.3, 19.5, 16.4

$[\alpha]^{24}_D = -5.9$ (c 0.23, $CHCl_3$).

IR (NaCl, thin film): 2936, 1844, 1734, 1717, 1653, 1559, 1540, 1507, 1457, 1242.



Epoxy alcohol 113: To a 1 L round-bottom flame-dried flask equipped with a stir bar was added 4 Å molecular sieves (9.00 g) and heated under vacuum for 15 min. CH_2Cl_2 (500 mL) was added and the flask was cooled with a CryoCool to –23 °C. Titanium isopropoxide (19 mL, 64.8 mmol) and L-(+)-diethyl tartrate (14 mL, 81.8 mmol) were added and stirred for 30 min. A solution of *tert*-butyl hydrogen peroxide (5.5 M in decanes, 64 mL, 11.6 mol) was added and stirred for 30 min. Nerol (57 mL, 326 mmol) was added slowly over 49 min. The reaction was stirred at this temperature for 3 h. The reaction was quenched by adding 370 mL of H_2O at 0 °C and stirring for 5 h. Added 74 mL of 22.1g of NaOH in 72 mL of H_2O followed by saturating with NaCl. The reaction mixture was filtered through Celite. Extracted with CH_2Cl_2 (3x) and the organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to furnish **113** (40.1 g, 235.5 mmol). The reaction mixture was carried on directly to the enzymatic resolution.

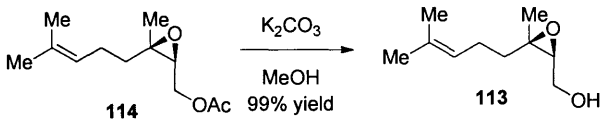


Acetate 114: To a 1 L flask with stir bar was loaded alcohol **113** (40.1 g, 235.5 mmol) in vinyl acetate (100 mL) and Et_2O (390 mL) and cooled to 0 °C in an ice bath. Amano lipase-PS (2.6096 g) was added and stirred at 0 °C for 14.25 h. The reaction mixture was filtered through Celite (eluted with Et_2O) and the solvent was removed *in vacuo*. The reaction mixture was purified by column chromatography (10 to 20 to 30% EtOAc in hexanes) to provide known acetate **114**[2] (28.59g, 134.7 mmol, 57% yield) as a colorless oil.

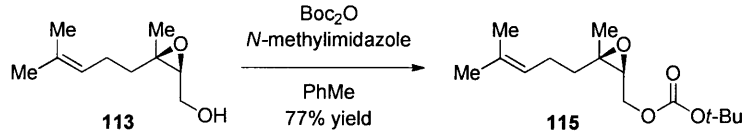
$[\alpha]^{24}_D$= –25.7 (c 5.9, $CHCl_3$) {lit.[2] $[\alpha]^{23}_D$ = –25.7 (c 0.58, $CHCl_3$)}

IR (NaCl, thin film): 2968, 2928, 2863, 1746, 1451, 1376, 1233, 1036, 887.

Chiral HPLC analysis: (Chiralcel OD, hexanes:2-propanol, 200:1, 1.0 mL/min): t_R(2*S*,3*S*) = 13.5 min; t_R(2*R*, 3*R*) = 14.7 min. The enantiomeric excess was determined to be 98.8%.

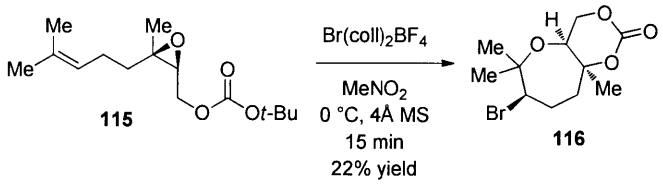


Epoxy alcohol 113: To a 1 L round-bottom flask equipped with a stir bar was added **114** (28.59 g, 134.7 mmol) in 340 mL of MeOH. K_2CO_3 (1.88 g, 13.6 mmol) was added and stirred for 4 h. The solvent was removed *in vacuo*, and the crude product was redissolved in Et_2O. The resulting suspension was filtered through Celite and concentrated *in vacuo* to provide epoxy alcohol **113** (22.66 g, 133 mmol, 99% yield) which was used without further purification.



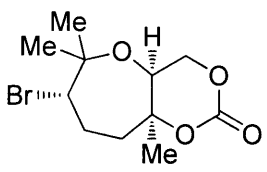
Carbonate 115: To a 1 L flame-dried round-bottom flask equipped with a stir bar was added epoxyalcohol **113** (22.66 g, 133.1 mmol) in toluene (620 mL). 1-methylimidazole (14 mL, 175.6 mmol) was added and the reaction was cooled to 0 °C. Liquid di-*tert*-butyl dicarbonate (117.3 g, 537 mmol) was added dropwise over 15 min and then stirred while warming to room temperature overnight. The reaction was poured into 1 L of water and enough CH_2Cl_2 was added to separate into two layers. The aqueous layer was extracted with CH_2Cl_2 (3x) and then the organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (10% EtOAc in hexanes) to provide carbonate **115** (27.73g, 103 mmol, 77 % yield) as a colorless oil.

$[\alpha]^{24}_D = -9.6$ (c 4.6, $CHCl_3$).



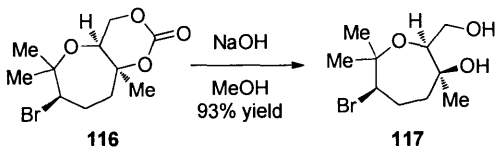
Bromooxepane 116: · To a 2 L round-bottom flask equipped with a stir bar was added 4Å molecular sieves (104.38 g) followed by 2:1 mixture of Boc_2O and carbonate **115** (13.86 g, 51.3 mmol) and 1 L of nitromethane. The reaction was cooled in an ice bath for 15 min with manual shaking. The reaction was covered with foil and $Br(coll)_2BF_4$ (51.55g, 126 mmol) was added in one portion and the reaction was swirled in an ice bath for 15 min. The reaction was filtered through Celite and the solvent was removed *in vacuo* at 40 °C. The reaction turned dark brown and was dissolved in CH_2Cl_2 and 1:1 $Na_2S_2O_3$/NaCl solutions. The aqueous layer was extracted with CH_2Cl_2 (3x) and then washed with 1N HCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude solid was purified by column chromatography (25% to 50% to 63% to 75% EtOAc in hexanes) to furnish **116** (3.3g, 11.3 mmol, 22% yield) as a white solid and a small amount of **SI-116A** for characterization purposes.

$[\alpha]^{24}_D = +33.6$ (c 0.66, $CHCl_3$).



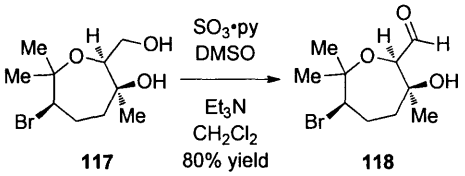
SI-116A

$[\alpha]^{24}_D = +19.1$ (c 1.1, $CHCl_3$).



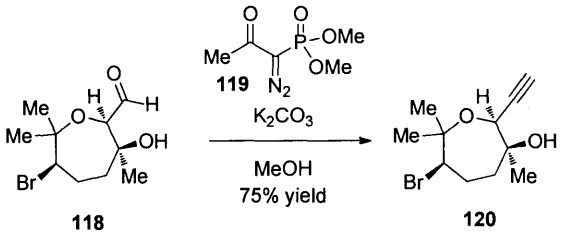
116 117

Diol 117: To a 200 mL round-bottom flask equipped with a stir bar was added **116** (3.3 g, 11.3 mmol) in 115 mL of MeOH. NaOH (536 mg, 13.4 mmol) was added and the reaction was stirred for 2 h at room temperature. The reaction was concentrated *in vacuo* and then the remaining oil was redissolved in EtOAc. A saturated NH_4Cl solution was added and was extracted with EtOAc (3x) followed by extraction with CH_2Cl_2 (3x). The organic layers were combined and dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide a colorless oil **117** (2.8 g, 10.5 mmol, 93% yield) which was used without further purification.



117 118

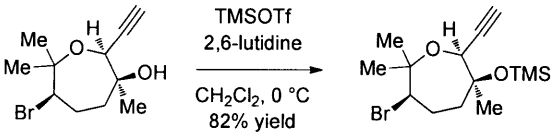
Aldehyde 118: To a 25 mL round-bottom flask equipped with a stir bar was added SO_3•py (3.654 g, 23.0 mmol) in 12 mL of DMSO and stirred for 15 min. To a separate 250 mL round-bottom flask equipped with a stir bar was added diol **117** (3.06 g, 11.5 mmol) in 120 mL of CH_2Cl_2. Triethyl amine (4.8 mL, 34.4 mmol) and 2 mL of DMSO was added and cooled to 0 °C. The SO_3•DMSO complex was added slowly and the reaction was stirred for 8 h while warming to room temperature. The reaction was poured into 100 mL of saturated NH_4Cl and extracted with CH_2Cl_2 (3x). The organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil was purified by Biotage column chromatography to furnish aldehyde **118** (2.42 g, 9.13 mmol, 80% yield) as a colorless oil.



118 120

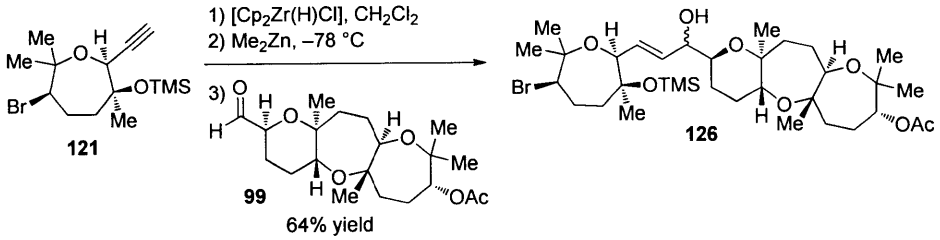
Alkyne 120: To a 200 mL round-bottom flask equipped with a stir bar was added aldehyde **118** (1.64g, 6.18 mmol) and dissolved in 86 mL of MeOH. Potassium carbonate (1.985 g, 14.4 mmol) was added followed by dropwise addition of dimethyl-1-diazo-2-oxopropylphosphate (1.3252 g, 6.90 mmol). The reaction was stirred for 16 h at room temperature, during which time the color the mixture changed from yellow to orange. 100 mL of Et_2O was added to the reaction

followed by 150 mL of saturated $NaHCO_3$. The aqueous layer was extracted with Et_2O (3x) and then dried over Na_2SO_4. The reaction was filtered and concentrated *in vacuo* to provide a milky light yellow solution. The crude was loaded directly onto the Biotage and alkyne **120** (1.2155 g, 4.65 mmol, 75% yield) was obtained a colorless oil.



120 **121**

Alkyne 121: To a 100 mL round-bottom flask equipped with a stir bar was added alkyne **120** (1.2155 g, 4.65 mmol) and dissolved in 47 mL of CH_2Cl_2. The reaction was cooled to 0 °C and 2,6-lutidine (1.62 mL, 14.0 mmol) was added followed by dropwise addition of TMSOTf (1.26 mL, 7.00 mmol). The reaction was stirred for 1 h at this temperature and then quenched with 30 mL of saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3x) and the organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil was purified by column chromatography (2% to 5% EtOAc in hexanes) to provide alkyne **121** (1.2095 g, 3.63 mmol, 78% yield) as a white solid.



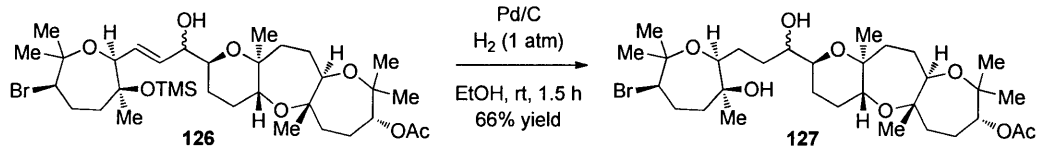
Alcohol 126: To a 25 mL round-bottom flask equipped with a stir bar was added $[Cp_2Zr(H)Cl]$ (256.0 mg, 0.99 mmol) and alkyne **121** (320.6 mg, 96 mmol) and placed under nitrogen in the dark. 9.6 mL of CH_2Cl_2 was added and stirred for 30 min at room temperature. The flask was then cooled to –78 °C and Me_2Zn (2.0 M in toluene, 505 *u*L, 1.01 mmol) was added dropwise. After stirring for 15 min, a solution of aldehyde **99** (306.3 mg, 0.83 mmol) in 8 mL of CH_2Cl_2 was added and the reaction was allowed to slowly warm to room temperature overnight. A saturated solution of NH_4Cl was added and a white solid formed. The aqueous layer was extracted with CH_2Cl_2 (3x) and then the organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide a colorless oil. The crude was purified by column chromatography (5 to 50% EtOAc in hexanes) to provide allylic alcohol **126** (373.2 mg, 0.53 mmol, 64% yield) as a colorless oil.

^{1}H NMR (600 MHz; $CDCl_3$): δ 5.85 (dd, J = 15.6, 7.5, 1H), 5.50 (dd, J = 15.6, 6.7, 1H), 4.91 (d, J = 6.8, 1H), 3.96 (d, J = 10.4, 1H), 3.86-3.84 (m, 1H), 3.63 (t, J = 6.8, 1H), 3.58 (dd, J = 9.7, 6.1, 1H), 3.45 (dd, J = 11.3, 2.0, 1H), 3.34 (ddd, J = 11.8, 7.2, 1.9, 1H), 2.69 (d, J = 2.4, 1H), 2.54 (td, J = 12.9, 10.1, 1H), 2.12 (s, 3H), 2.08-2.01 (m, 2H), 1.94-1.86 (m, 4H), 1.79 (dd, J = 14.4, 13.6, 2H), 1.70 (t, J = 14.0, 1H), 1.62 (dt, J = 6.8, 3.1, 2H), 1.52-1.44 (m, 4H), 1.41 (s, 3H), 1.33 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H), 1.16 (s, 3H), 1.15 (s, 3H), 1.06 (s, 3H), 0.11 (s, 9H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 170.3, 131.6, 131.0, 78.8, 78.6, 78.3, 78.3, 77.7, 77.6, 77.4, 75.9, 75.5, 73.2, 70.3, 60.8, 44.2, 40.6, 36.8, 31.0, 29.1, 28.9, 28.1, 27.8, 27.4, 26.2, 24.4, 23.2, 21.8, 21.3, 20.1, 16.4, 2.8

$[\alpha]^{24}_D$ = +28.2 (c 0.4, $CHCl_3$).

IR (NaCl, thin film): 3583, 2939, 1739, 1442, 1379, 1248, 1067, 840, 753.



Secondary alcohol 127: To a 25 mL round-bottom flask equipped with a stir bar was added allylic alcohol **126** (373.2 mg, 0.53 mmol) and 5.2 mL of EtOH. Palladium on carbon (218 mg, 10% by weight) was added and placed under vacuum. Hydrogen gas was added and the reaction was stirred at room temperature for 90 min. The solution was filtered through Celite (eluted with EtOAc) to remove the palladium. The crude reaction mixture was purified by Biotage (25 g column) to provide alcohol **127** (223.3 mg, 0.352 mmol, 66% yield) as a colorless oil.

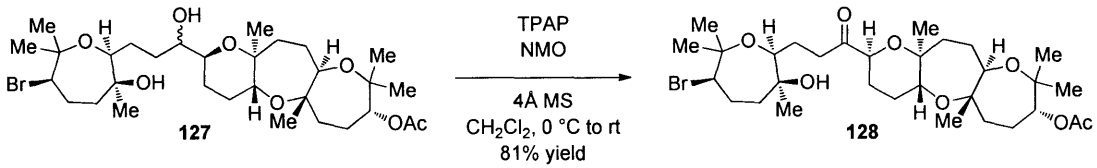
^{1}H NMR (400 MHz; $CDCl_3$): δ 4.92 (d, J = 6.3, 1H), 3.91 (d, J = 10.7, 1H), 3.57 (dd, J = 8.8, 7.0, 1H), 3.45 (dd, J = 11.4, 2.5, 1H), 3.38-3.31 (m, 3H), 3.03 (s, 1H), 2.64 (d, J = 2.8, 1H), 2.39-2.29 (m, 1H), 2.11 (s, 3H), 2.09-1.96 (m, 3H), 1.92-1.71 (m, 7H), 1.68-1.61 (m, 5H), 1.57-1.44 (m, 4H), 1.41 (s, 3H), 1.37 (s, 3H), 1.26 (s, 3H), 1.23 (s, 3H), 1.16 (s, 3H), 1.14 (s, 3H), 1.12 (s, 3H)

^{13}C NMR (100 MHz; $CDCl_3$): δ 170.3, 78.9, 78.6, 78.3, 78.0, 77.4, 77.4, 75.9, 74.1, 72.6, 72.4, 70.4, 59.4, 44.6, 40.6, 36.8, 30.6, 29.2, 29.1, 28.9, 27.8, 27.4, 25.9, 25.9, 25.6, 25.2, 23.2, 21.8, 21.3, 20.2, 16.4

$[\alpha]^{24}_D$ = +19.5 (c 0.25, $CHCl_3$).

IR (NaCl, thin film): 3542, 2977, 2938, 1732, 1446, 1380, 1243, 1137, 1076, 1029, 983.

HRMS-ESI (m / z): $[M + H]^+$ calcd for $C_{31}H_{54}BrO_8Na$, 633.2997; found, 633.3004.



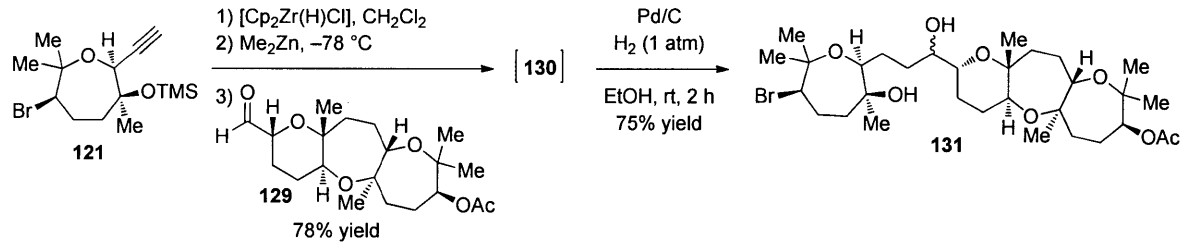
Ketone 128: To a 10 mL round-bottom flask equipped with a stir bar were added 4Å molecular sieves (193.8 mg) followed by alcohol **127** (223.3 mg, 0.352 mmol) in 3.5 mL of CH_2Cl_2. *N*-Methylmorpholine-*N*-oxide (131.0 mg, 1.12 mmol) was added and the reaction was cooled to 0 °C. Tetrapropylammonium perruthenate (29.0 mg, 82.5 mmol) was added and the reaction was allowed to warm to room temperature over 2 h. The crude reaction was filtered through Celite using a CH_2Cl_2 and EtOAc wash and concentrated *in vacuo*. The reaction was purified by Biotage (25 g column) to provide **128** (179.9 mg, 0.285 mmol, 81% yield) as a colorless oil.

^{1}H NMR (600 MHz; $CDCl_3$): δ 4.92 (d, J = 6.6, 1H), 3.89 (td, J = 7.5, 4.0, 2H), 3.60 (dd, J = 13.8, 7.0, 1H), 3.47 (dd, J = 11.4, 2.3, 1H), 3.41 (dd, J = 10.3, 2.8, 1H), 2.96 (s, 1H), 2.69-2.67 (m, 2H), 2.33 (qd, J = 13.0, 1.6, 1H), 2.12 (s, 3H), 2.04-1.60 (m, 13H), 1.53-1.46 (m, 4H), 1.41 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H), 1.25 (s, 3H), 1.17 (s, 3H), 1.15 (s, 3H), 1.14 (s, 3H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 212.1, 170.2, 78.9, 78.6, 78.2, 78.0, 77.8, 77.4, 75.8, 74.6, 72.3, 69.8, 68.1, 59.1, 44.5, 43.0, 40.5, 36.7, 34.1, 30.5, 30.4, 28.9, 25.8, 25.7, 25.6, 25.0, 24.5, 23.2, 21.8, 21.3, 19.6, 16.4

$[\alpha]^{24}_D$= –4.8 (c 0.24, $CHCl_3$).

IR (NaCl, thin film): 3584, 2976, 2938, 1736, 1445, 1379, 1243, 1138, 109, 1069, 1029.



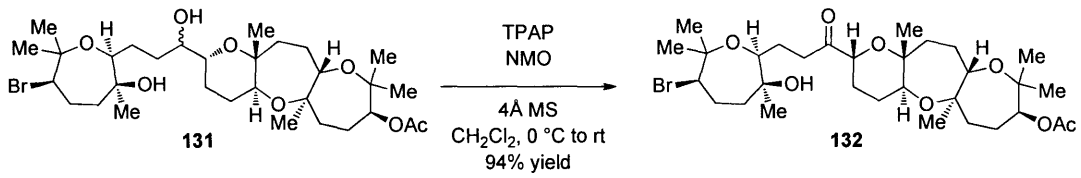
Secondary alcohol 131: To a 50 mL round-bottom flask equipped with a stir bar was added [$Cp_2Zr(H)Cl$] (387.2 mg, 1.50 mmol) and alkyne **121** (498.2 mg, 1.49 mmol) and placed under nitrogen in the dark. 15 mL of CH_2Cl_2 was added and stirred for 30 min at room temperature. The flask was then cooled to –78 °C and Me_2Zn (2.0 M in toluene, 780 *u*L, 1.56 mmol) was added dropwise. After stirring for 20 min, a solution of aldehyde **129** (450 mg, 1.22 mmol) in 12.5 mL of CH_2Cl_2 was added and the reaction was allowed to slowly warm to room temperature overnight. A saturated solution of NH_4Cl was added and a white solid formed. The aqueous layer was extracted with CH_2Cl_2 (3x) and then the organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide a colorless oil. The crude was purified by column chromatography (5 to 50% EtOAc in hexanes) to provide allylic alcohol **130** (667.2 mg, 0.948 mmol, 78% yield) as a colorless oil, which was used without further purification.

To a 25 mL round-bottom flask equipped with a stir bar was added allylic alcohol **130** (599.6 mg, 0.85 mmol) and 17 mL of EtOH. Palladium on carbon (235 mg, 10% by weight) was added and placed under vacuum. Hydrogen gas was added and the reaction was stirred at room temperature for 2 h. The solution was filtered through Celite (eluted with EtOAc) to remove the palladium. The crude reaction mixture was purified by Biotage (25 g column) to provide alcohol **131** (401.6 mg, 0.634 mmol, 75% yield) as a colorless oil.

^{1}H NMR (400 MHz; C_6D_6): δ 4.98 (d, J = 6.7, 1H), 3.63-3.53 (m, 3H), 3.34-3.23 (m, 2H), 2.92 (s, 1H), 2.88 (dd, J = 9.9, 3.1, 1H), 2.67 (d, J = 3.1, 1H), 2.23-2.12 (m, 2H), 1.98-1.90 (m, 3H), 1.86-1.74 (m, 4H), 1.68 (s, 3H), 1.67-1.41 (m, 8H), 1.36 (s, 3H), 1.28 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H), 1.23-1.10 (m, 3H), 1.07 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H)

^{13}C NMR (100 MHz; C_6D_6): δ 169.5, 79.2, 78.7, 78.7, 77.9, 77.7, 77.6, 76.4, 75.5, 74.0, 72.3, 70.9, 59.8, 44.7, 41.2, 37.5, 31.0, 30.6, 29.8, 29.1, 28.3, 28.1, 27.3, 26.2, 25.7, 25.6, 23.6, 22.0, 20.8, 20.5, 16.8

$[\alpha]^{24}_D$ = +5.1 (c 0.91, C_6H_6).

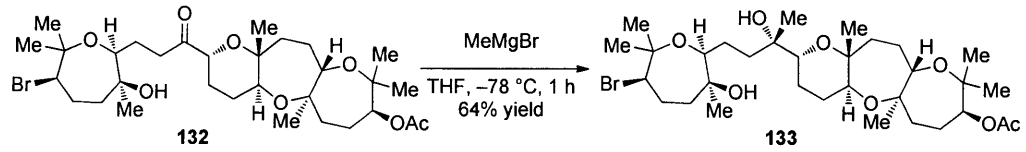


Ketone 132: To a 10 mL round-bottom flask equipped with a stir bar were added 4Å molecular sieves (360 mg) followed by alcohol **131** (382.9 mg, 0.604 mmol) in 3.5 mL of CH_2Cl_2. *N*-Methylmorpholine-*N*-oxide (230 mg, 1.96 mmol) was added and the reaction was cooled to 0 °C. Tetrapropylammonium perruthenate (30 mg, 0.085 mmol) was added and the reaction was allowed to warm to room temperature over 4 h. The crude reaction was filtered through Celite using a CH_2Cl_2 and EtOAc wash and concentrated *in vacuo*. The reaction was purified by Biotage (25 g column) to provide **132** (358.8 mg, 0.568 mmol, 94% yield) as a colorless oil.

^{1}H NMR (400 MHz; $CDCl_3$): δ 4.97 (d, J = 6.8, 1H), 3.67 (dd, J = 11.9, 2.9, 1H), 3.63-3.54 (m, 2H), 3.47 (d, J = 10.8, 1H), 2.98 (dd, J = 9.4, 3.7, 1H), 2.84 (s, 1H), 2.68-2.60 (m, 2H), 2.20-2.10 (m, 1H), 1.91-1.74 (m, 8H), 1.70 (s, 3H), 1.66-1.36 (m, 9H), 1.31 (s, 3H), 1.22 (s, 3H), 1.22 (s, 3H), 1.21 (s, 3H), 1.07 (s, 3H), 1.04 (s, 3H), 0.99 (s, 3H)

^{13}C NMR (100 MHz; $CDCl_3$): δ 210.5, 169.5, 79.3, 78.7, 78.6, 78.3, 78.0, 77.6, 75.8, 75.1, 72.3, 70.6, 59.6, 44.6, 41.1, 37.4, 34.8, 30.9, 29.7, 29.0, 28.7, 28.0, 26.0, 25.50, 25.5, 23.8, 23.6, 22.0, 20.8, 19.8, 16.8

$[\alpha]^{24}_D$ = +17.4 (c 1.6, $CHCl_3$).

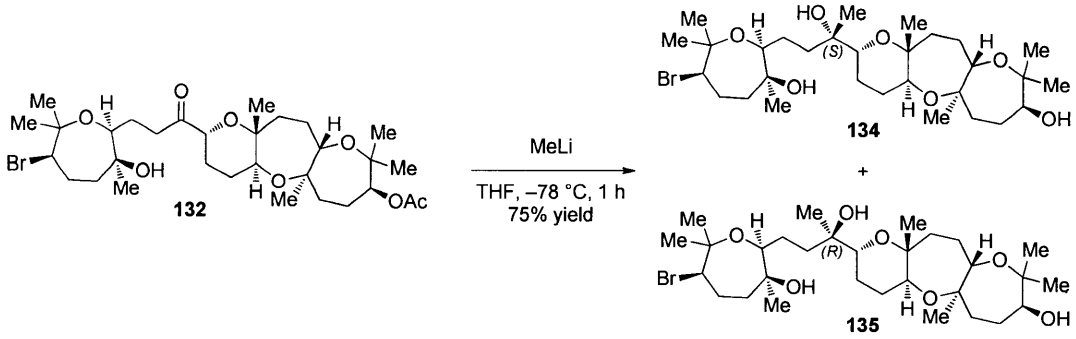


Tertiary alcohol 133: To a 20 mL vial with stir bar was added ketone **132** (11.7 mg, 18.5 mmol) in 1 mL of THF. The reaction was cooled to –78 °C and then a 3.0 M solution of methylmagnesium bromide in Et_2O (50 *u*L, 150 mmol) was added dropwise. The reaction was allowed to stir at this temperature for 1 h. The reaction was quenched with saturated NH_4Cl (1 mL) and then 5 mL of brine was added. The aqueous layer was extracted with Et_2O (5x) and then the organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil was purified by column chromatography to furnish starting material **132** (4.2 mg, 6.6 mmol) and acetate **133** (7.7 mg, 11.9 mmol, 64% yield, 100% BRSM).

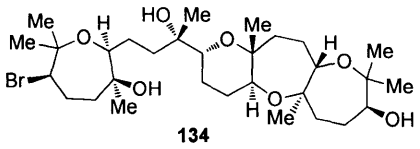
^{1}H NMR (500 MHz; $CDCl_3$): δ 4.92 (d, J = 6.8, 1H), 3.91 (d, J = 11.1, 1H), 3.55 (dd, J = 10.5, 5.7, 1H), 3.46 (dd, J = 11.4, 2.5, 1H), 3.31-3.27 (m, 2H), 3.04 (s, 1H), 2.37 (s, 1H), 2.39-2.34 (m, 1H), 2.12 (s, 3H), 2.07-2.00 (m, 3H), 1.90-1.85 (m, 2H), 1.82-1.70 (m, 5H), 1.70-1.60 (m, 5H), 1.52-1.46 (m, 4H), 1.42 (s, 3H), 1.37 (s, 3H), 1.26 (s, 3H), 1.23 (s, 3H), 1.16 (s, 3H), 1.15 (s, 3H), 1.12 (s, 3H), 1.11 (s, 3H)

^{13}C NMR (125 MHz; $CDCl_3$): δ 170.3, 78.8, 78.6, 78.3, 78.0, 77.4, 77.4, 76.2, 75.7, 73.2, 72.4, 70.5, 59.4, 44.6, 40.7, 36.8, 33.6, 30.6, 29.1, 28.9, 27.6, 25.9, 25.7, 25.4, 25.2, 24.0, 23.8, 23.2, 21.8, 21.3, 20.1, 16.4

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{32}H_{55}BrO_8Na$, 669.2973; found, 669.2979.



Alcohols 134 and 135: To a 20 mL vial equipped with a stir bar were added ketone **132** (192.0 mg, 0.304 mmol) and 6 mL of THF and the reaction was cooled to –78 °C. MeLi (2 mL, 1.6 M in Et_2O, 3.2 mmol) was added dropwise and the reaction was stirred for 2.5 h. Saturated NH_4Cl was added and the reaction was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by the Biotage (100g column) to provide clean alcohol **135** (56.2 mg, 0.0928 mmol, 31% yield) and the remaining material as a mixture of alcohol **134** and alcohol **135** (80.2 mg, 0.132 mmol, 44% yield).



134

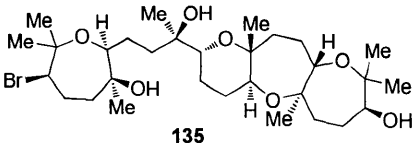
^{1}H NMR (400 MHz; C_6D_6): δ 3.82 (dd, J = 11.4, 2.6, 1H), 3.66 (dd, J = 10.1, 6.1, 1H), 3.54 (d, J = 11.1, 1H), 3.28-3.23 (m, 2H), 2.94 (s, 1H), 2.76 (dd, J = 9.3, 3.1, 1H), 2.25-2.15 (m, 4H), 1.92-1.80 (m, 5H), 1.72-1.44 (m, 13H), 1.34 (s, 3H), 1.33 (s, 3H), 1.28 (s, 3H), 1.24 (s, 3H), 1.16 (s, 3H), 1.15 (s, 3H), 1.00 (s, 3H), 0.98 (s, 3H).

^{13}C NMR (100 MHz; C_6D_6): δ 79.6, 78.2, 78.1, 78.0, 77.9, 76.7, 76.5, 76.3, 73.3, 72.4, 71.2, 59.8, 44.8, 41.1, 36.8, 34.7, 31.0, 30.0, 29.4, 28.4, 26.3, 26.1, 26.1, 25.6, 25.5, 24.4, 24.3, 22.1, 20.2, 17.1.

$[\alpha]^{24}_D$ = –15.0 (c 0.2, $CHCl_3$).

IR (NaCl, thin film): 3451, 2974, 2937, 1445, 1378, 1138, 1071, 801, 755.

HRMS-ESI (m / z): $[M + H]^+$ calcd for $C_{30}H_{53}BrO_7$, 605.3047; found, 605.3035.



135

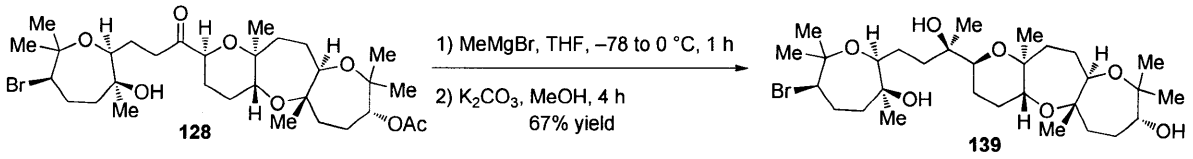
^{1}H NMR (400 MHz; C_6D_6): δ 3.82 (dd, J = 11.4, 2.6, 1H), 3.62 (t, J = 8.1, 1H), 3.55 (d, J = 10.9, 1H), 3.27-3.15 (m, 2H), 2.94 (bs, 1H), 2.80 (dd, J = 8.1, 4.3, 1H), 2.31 (bs, 1H), 2.27-2.11 (m, 3H), 1.96-1.79 (m, 4H), 1.73-1.40 (m, 13H), 1.36 (s, 3H), 1.34 (s, 3H), 1.28 (s, 3H), 1.25 (s, 3H), 1.14 (s, 3H), 1.04 (s, 3H), 1.02 (s, 3H), 0.98 (s, 3H).

13C-NMR (100 MHz, C_6D_6): δ 79.6, 78.1, 78.1, 77.9, 77.9, 76.7, 76.7, 75.4, 73.4, 72.4, 71.0, 59.8, 44.7, 41.0, 36.8, 36.8, 31.0, 30.0, 29.4, 28.4, 26.3, 26.1, 25.9, 25.7, 25.6, 24.6, 22.0, 21.7, 20.4, 17.1.

$[\alpha]^{24}_D$ = –22.1 (c 0.5, $CHCl_3$)

IR (NaCl, thin film): 3451, 2975, 2937, 1447, 1379, 1302, 1137, 1071, 1034, 995, 891, 754.

HRMS-ESI (m / z): $[M + H]^+$ calcd for $C_{30}H_{54}BrO_7$, 605.3047; found, 605.3029.



Alcohol 139: To a 5 mL round-bottom flask equipped with a stir bar was added ketone **128** (65.2 mg, 103.2 *u*mol) and 1.6 mL of THF. The reaction was cooled to -78 °C and MeMgBr (200 *u*L, 3.0 M in Et_2O, 600 *u*mol) was added and the reaction was allowed to warm to 0 °C over 1 h. The reaction was quenched with sat. NH_4Cl and the aqueous layer was extracted with Et_2O (3x). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil was purified by column chromatography (20->50% EtOAc in hexanes) to provide acetate **SI-139A** (19.6 mg, 30.3 *u*mol, 29% yield) and alcohol **139** (9.6 mg, 15.9 *u*mol, 15% yield) along with recovered ketone **128** (35.0 mg, 55.4 *u*mol, 54% yield).

The recovered starting material was redissolved in 3.2 mL of THF and MeMgBr (200 *u*L, 3.0 M in Et_2O, 600 umol) was added at –78 °C and allowed to stir for 1 h. The reaction was quenched with saturated NH_4Cl and extracted with Et_2O (3x). The organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue along with acetate **SI-139A** (19.6 mg, 30.3 umol) was dissolved in 3.4 mL of MeOH and K_2CO_3 (18.3 mg, 132.4 umol) was added and stirred at room temperature for 4 h. The reaction was then quenched with saturated NH_4Cl and extracted with Et_2O (5x). The organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (50% EtOAc in hexanes) to provide alcohol **139** (34.6 mg, 57.1 umol, 67% yield) as a colorless oil.

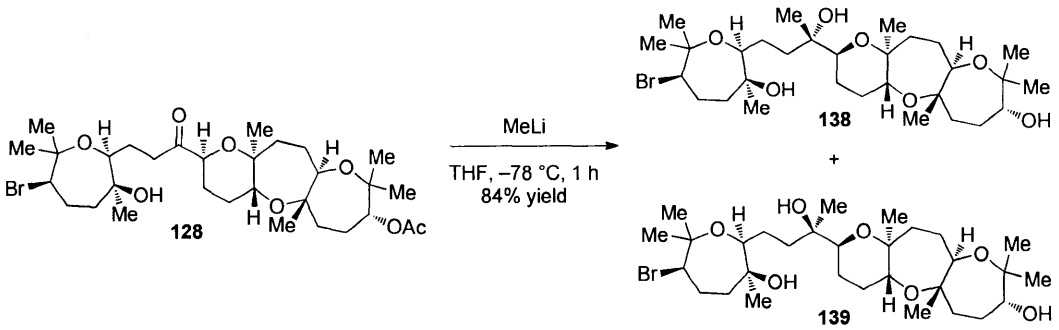
^{1}H NMR (500 MHz; C_6D_6): δ 3.81 (dd, J = 11.4, 2.4, 1H), 3.65 (dd, J = 10.6, 5.4, 1H), 3.51 (d, J = 11.1, 1H), 3.23 (td, J = 8.5, 3.5, 2H), 2.92 (s, 1H), 2.78 (dd, J = 9.9, 3.0, 1H), 2.24 (s, J = 5.2, 1H), 2.24-2.14 (m, 3H), 1.95-1.43 (m, 17H), 1.34 (s, 3H), 1.33 (s, 3H), 1.25 (s, 6H), 1.14 (s, 6H), 1.01 (s, 3H), 0.98 (s, 3H).

^{13}C NMR (125 MHz; C_6D_6): δ 79.6, 78.2, 78.1, 78.0, 77.9, 76.9, 76.7, 76.3, 73.4, 72.4, 71.2, 59.7, 44.7, 41.1, 36.8, 34.4, 31.0, 30.0, 29.4, 28.3, 26.3, 26.1, 26.0, 25.7, 25.6, 24.1, 24.0, 22.1, 20.2, 17.1.

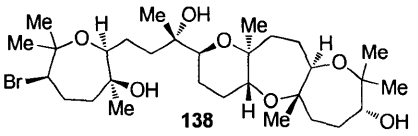
$[\alpha]^{24}_D$= +40.9 (c 0.2, $CHCl_3$). For reference, ***ent*-139:** $[\alpha]^{24}_D$ = –41.7 (c 0.1, $CHCl_3$)

IR (NaCl, thin film): 3583, 3452, 2932, 1659, 1641, 1462, 1451, 1378, 1137, 1071, 891.

HRMS-ESI (m / z): $[M + H]^+$ calcd for $C_{30}H_{54}BrO_7$, 605.3047; found, 605.3059.



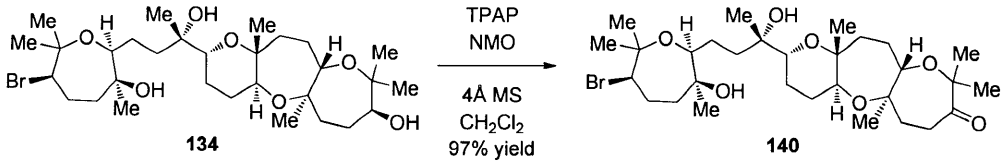
Alcohol 138: To a 20 mL vial with stir bar was added ketone **128** (179.9 mg, 0.285 mmol) and 3.5 mL of THF and the reaction was cooled to –78 °C. MeLi (950 *u*L, 1.6 M in Et_2O, 1.52 mmol) was added dropwise and the reaction was stirred for 1 h. The reaction solidified and eventually stirring ceased. Saturated NH_4Cl was added, and the reaction was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3x), dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The crude was redissolved in 10 mL of THF and cooled to –78 °C. MeLi (1 mL, 1.6 M in Et_2O, 1.6 mmol) was added dropwise and the reaction was stirred at this temperature for 1 h. The reaction stayed in solution and went to completion by TLC. Saturated NH_4Cl was added and allowed to warm to rt. The aqueous layer was extracted with Et_2O (3x) and then the organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by careful column chromatography (0.1% to 2% MeOH in Et_2O) on the Biotage (100g HP column) to provide clean alcohol **138** (29.7 mg, 49.3 mmol, 17% yield) and the remaining material as a mixture of alcohol **138** and alcohol **139** (116.5 mg, 0.192 mmol, 67% yield).



^{1}H NMR (400 MHz; C_6D_6): δ 3.80 (dd, J = 11.4, 2.3, 1H), 3.62 (dd, J = 10.2, 6.0, 1H), 3.50 (d, J = 11.0, 1H), 3.29-3.19 (m, 2H), 2.90 (bs, 1H), 2.78 (dd, J = 9.3, 3.2, 1H), 2.30 (bs, 1H), 2.27-2.12 (m, 3H), 1.92-1.75 (m, 4H), 1.72-1.53 (m, 8H), 1.53-1.40 (m, 5H), 1.33 (s, 6H), 1.25 (s, 3H), 1.24 (s, 3H), 1.13 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 0.97 (s, 3H)

13C-NMR (100 MHz, C_6D_6): δ 79.6, 78.1, 78.1, 77.9, 77.9, 76.7, 76.6, 74.4, 73.4, 72.4, 71.0, 59.8, 44.7, 41.1, 36.9, 36.8, 31.0, 30.1, 29.4, 28.3, 26.3, 26.1, 25.9, 25.6, 25.6, 24.7, 23.0, 22.0, 20.3, 17.1.

HRMS-ESI (m / z): $[M + H]^+$ calcd for $C_{30}H_{54}BrO_7$, 605.3047; found, 605.3051.



134 140

Ketone 140: To a 5 mL round-bottom flask equipped with a stir bar was added 30 mg of 4Å MS and heated under vacuum for 5 min. The flask was cooled to 0 °C and alcohol **134** (26.7 mg, 0.0441 mmol) was added in 2 mL of CH_2Cl_2. NMO (20 mg, 0.171 mmol) was added and then TPAP (~2 mg, 0.006 mmol) was added and the reaction was allowed to slowly warm to room temperature for 2 h. The crude material was loaded directly onto a Biotage column (10 g) to furnish ketone **140** (25.8 mg, 0.0427 mmol, 97% yield).

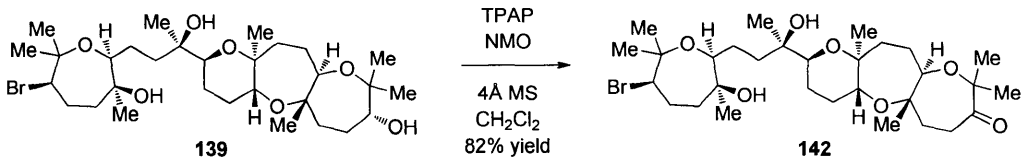
^{1}H NMR (400 MHz; C_6D_6): δ 3.57 (d, J=6.7, 1H), 3.56 (d, J = 10.7, 1H), 3.25 (dd, J = 11.3, 2.8, 1H), 2.90 (dd, J = 11.2, 2.5, 2H), 2.78 (dd, J = 9.2, 3.2, 1H), 2.68 (ddd, J = 13.1, 11.6, 4.3, 1H), 2.25-2.10 (m, 1H), 2.07 (ddd, J = 11.5, 5.7, 3.0, 1H), 1.93-1.81 (m, 4H), 1.75-1.70 (m, 2H), 1.69 (dd, J = 5.7, 2.0, 1H), 1.64-1.58 (m, 3H), 1.56-1.46 (m, 6H), 1.35 (s, 3H), 1.26 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H), 1.17 (s, 3H), 1.11 (s, 3H), 1.03 (s, 3H), 1.01 (s, 3H), 0.97-0.93 (m, 1H)

^{13}C NMR (100 MHz; C_6D_6): δ 215.7, 83.7, 83.1, 78.4, 78.0, 77.5, 76.4, 76.2, 73.2, 72.4, 71.4, 59.7, 44.8, 41.9, 40.7, 35.6, 34.8, 31.0, 29.7, 28.1, 26.7, 26.1, 26.0, 25.6, 25.5, 24.4, 24.4, 21.2, 20.0, 16.0

$[\alpha]^{24}_D$= +6.4 (c 1.3, C_6H_6).

IR (NaCl, thin film): 3583, 3457, 2976, 2937, 1714, 1462, 1445, 1379, 1261, 1137, 1088, 1053.

HRMS-ESI (m / z): $[M + H]^+$ calcd for $C_{30}H_{52}BrO_7$, 603.2891; found, 603.2873.



139 142

Ketone 142: To a 5 mL round-bottom flask equipped with a stir bar was added 15 mg of 4Å MS and heated under vacuum for 5 min. The flask was cooled to 0 °C and alcohol **139** (18.0 mg, 0.0298 mmol) was added in 2 mL of CH_2Cl_2. NMO (15 mg, 0.128 mmol) was added and then TPAP (~2 mg, 0.006 mmol) was added and the reaction was allowed to slowly warm to room temperature for 2 h. The crude material was loaded directly onto a Biotage column (10 g) to furnish ketone **142** (14.7 mg, 0.0244 mmol, 82% yield).

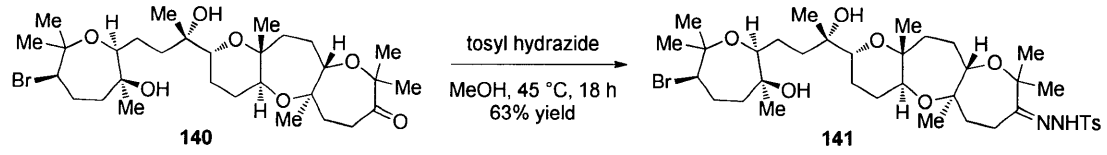
^{1}H NMR (400 MHz; C_6D_6): δ 3.57-3.54 (m, 1H), 3.52 (d, J = 11.2, 1H), 3.22 (dd, J = 10.4, 3.2, 1H), 2.91 (d, J = 2.3, 1H), 2.88 (d, J = 2.5, 1H), 2.79 (dd, J = 9.3, 3.4, 1H), 2.68 (td, J = 12.3, 3.7, 1H), 2.24-2.15 (m, 1H), 2.09-2.04 (m, 1H), 1.87-1.78 (m, 2H), 1.76-1.67 (m, 3H), 1.65-1.41 (m, 10H), 1.35 (s, 3H), 1.26 (s, 3H), 1.24 (s, 3H), 1.16 (s, 3H), 1.09 (s, 3H), 1.03 (s, 3H), 1.02 (s, 3H), 0.99-0.95 (m, 1H)

^{13}C NMR (100 MHz; C_6D_6): δ 215.7, 83.7, 83.1, 78.4, 78.0, 77.5, 76.9, 76.2, 73.4, 72.4, 71.4, 59.7, 44.7, 41.9, 40.7, 35.6, 34.6, 31.0, 29.7, 28.0, 26.7, 26.1, 25.9, 25.7, 25.6, 24.1, 24.0, 21.2, 20.1, 16.0

$[\alpha]^{24}_D$= +28.7 (c 0.44, C_6H_6).

IR (NaCl, thin film): 3583, 3453, 2976, 2938, 1714, 1462, 1444, 1379, 1137, 1087, 895.

HRMS-ESI (m / z): $[M - H]^+$ calcd for $C_{30}H_{50}BrO_7$, 601.2734; found, 601.2770.



140 141

Hydrazone 141: To a 5 mL flask equipped with a stir bar was added ketone **140** (25.8 mg, 42.7 *u*mol) and tosyl hydrazone (19.3 mg, 0.104 mmol) in 300 *u*L of MeOH. The reaction was heated to 45 °C with a reflux condenser for 18 h. The reaction was cooled to room temperature and concentrated *in vacuo* and loaded directly onto a silica gel column. The crude was purified by column chromatography (50 to 100% EtOAc in hexanes) to furnish hydrazone **141** (20.7 mg, 26.8 *u*mol, 63% yield) as a white solid.

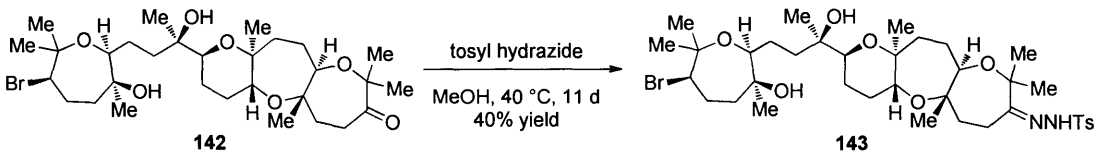
^{1}H NMR (600 MHz; C_6D_6): δ 8.02 (d, J = 8.2, 2H), 6.79 (d, J = 8.2, 2H), 3.54 (d, J = 11.1, 2H), 3.50 (t, J = 8.0, 2H), 3.28 (dd, J = 11.7, 2.2, 1H), 2.96 (s, 1H), 2.75 (dd, J = 9.4, 2.9, 1H), 2.54 (dd, J = 11.3, 2.1, 1H), 2.24-2.17 (m, 1H), 2.13-2.05 (m, 2H), 2.02-1.97 (m, 1H), 1.92 (s, 3H), 1.91-1.80 (m, 6H), 1.65-1.57 (m, 4H), 1.53-1.48 (m, 3H), 1.48-1.38 (m, 4H), 1.35 (s, 3H), 1.29 (s, 3H), 1.25 (s, 3H), 1.17 (s, 3H), 1.12 (s, 3H), 1.05 (s, 3H), 1.01 (s, 3H), 0.99 (s, 3H)

^{13}C NMR (150 MHz; C_6D_6): δ 164.1, 143.9, 136.8, 129.9, 128.8, 80.8, 80.2, 78.10, 77.95, 77.4, 76.33, 76.20, 73.3, 72.4, 71.1, 59.7, 44.7, 41.2, 40.8, 37.1, 34.7, 31.0, 29.5, 27.4, 26.10, 26.03, 25.56, 25.48, 24.36, 24.30, 23.3, 21.7, 20.0, 16.2

$[\alpha]^{24}_D = -15.4$ (c 1.0, $CHCl_3$)

IR (NaCl, thin film): 3535, 3220, 2977, 2937, 1644, 1598, 1463, 1381, 1342, 1262, 1169, 1088, 1031, 814, 756

HRMS-ESI (m / z): $[M + H]^+$ calcd for $C_{37}H_{60}BrSN_2O_9$, 771.3248; found, 771.3245.



142 143

Hydrazone 143: To a 5 mL flask equipped with a stir bar was added ketone **142** (2.5 mg, 4.1 *u*mol) and tosyl hydrazone (2.7 mg, 14.5 *u*mol) in 830 *u*L of MeOH. The reaction was heated to 40 °C with a reflux condenser for 11 d. The reaction was cooled to room temperature and concentrated *in vacuo* and loaded directly onto a silica gel column. The crude was purified with (50->100% EtOAc in hexanes) to furnish hydrazone **143** (3.0 mg, 3.89 *u*mol, 94% yield) as a white solid.

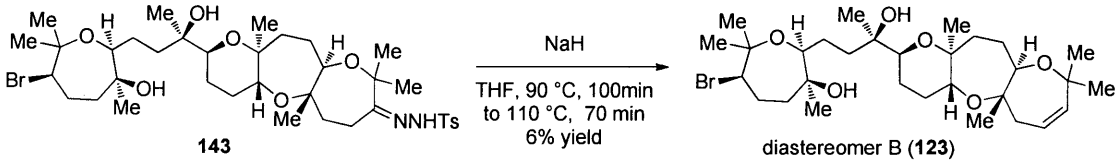
^{1}H NMR (500 MHz; C_6D_6): δ 8.00 (d, J = 8.2, 2H), 6.80 (d, J = 8.5, 2H), 3.51 (d, J = 10.9, 1H), 3.48 (d, J = 7.1, 1H), 3.25 (dd, J = 11.4, 2.2, 2H), 2.92 (bs, 1H), 2.78 (dd, J = 9.5, 3.3, 1H), 2.57-2.54 (m, 1H), 2.24-2.15 (m, 1H), 2.07-2.02 (m, 1H), 1.92 (s, 3H), 1.90-1.76 (m, 4H), 1.77-1.66 (m, 3H), 1.57 (dd, J = 12.1, 3.9, 4H), 1.55-1.39 (m, 6H), 1.35 (s, 3H), 1.29 (s, 3H), 1.25 (s, 3H), 1.15 (s, 3H), 1.12 (s, 3H), 1.03 (s, 3H), 1.02 (s, 3H), 0.98 (s, 3H)

^{13}C NMR (125 MHz; C_6D_6): δ 164.0, 143.9, 136.9, 129.9, 128.9, 80.8, 80.3, 78.11, 77.97, 77.5, 76.8, 76.3, 73.4, 72.4, 71.2, 59.6, 44.6, 41.1, 40.8, 34.6, 31.0, 29.5, 28.0, 27.4, 26.1, 25.87, 25.68, 25.62, 24.09, 23.95, 23.3, 21.6, 20.8, 20.1, 16.2

$[\alpha]^{24}_D$= +27.8 (c 1.4, $CHCl_3$).

IR (NaCl, thin film): 3534, 3219, 2976, 2935, 1598, 1462, 1380, 1345, 1169, 1138, 1088, 1031, 895.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{37}H_{59}BrSN_2O_9Na$, 793.3068; found, 793.3060.



Alkene 123: To a 500 *u*L sealed tube equipped with a stir bar was added sodium hydride (6.5 mg, 0.285 mmol, 95% in mineral oil) in the glove box and then transferred to the hood under nitrogen. The reaction was purged while a solution of hydrazone **143** (16.6 mg, 21.5 *u*mol) in 500 *u*L of THF was added by syringe. The reaction was sealed and heated to 90 °C for 100 min then to110 °C for 70 min. The reaction turned brown and was then cooled to room temperature. H_2O was added to quench remaining sodium hydride, followed by addition of 1 mL of saturated NH_4Cl. The aqueous layer was extracted with Et_2O (5x) and then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Careful column chromatography (20 to 50% HPLC-grade EtOAc in hexanes) provided a small amount of analytically clean **123** (0.8 mg, 1.3 *u*mol, 6% yield) as colorless oil.

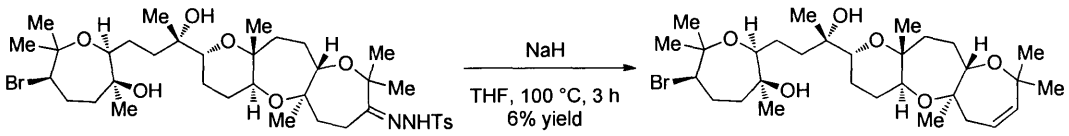
^{1}H NMR (600 MHz; C_6D_6): δ 5.46-5.42 (m, 4H), 5.21 (d, J = 11.7, 1H), 3.85 (dd, J = 11.4, 4.6, 1H), 3.53 (d, J = 11.0, 1H), 3.48 (dd, J = 11.5, 4.5, 1H), 3.26 (dd, J = 7.7, 4.3, 1H), 3.22 (dd, J = 10.9, 3.2, 1H), 2.89 (d, J = 0.5, 1H), 2.81 (dt, J = 6.4, 3.4, 1H), 2.58 (ddd, J = 15.4, 5.7, 1.7, 1H), 2.25-2.14 (m, 2H), 2.14-2.10 (m, 1H), 2.03 (t, J = 7.5, 1H), 2.01-1.95 (m, 1H), 1.84-1.67 (m, 5H), 1.65-1.46 (m, 6H), 1.34 (s, 3H), 1.29 (s, 3H), 1.25 (s, 6H), 1.22 (s, 3H), 1.15 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 0.96-0.90 (m, 1H)

^{13}C NMR (125 MHz; C_6D_6): δ 137.0, 122.8, 80.7, 78.3, 77.9, 77.8, 77.0, 76.9, 75.8, 74.5, 73.4, 72.4, 59.7, 44.7, 42.6, 39.1, 34.4, 31.0, 29.9, 28.1, 27.9, 26.5, 26.1, 26.0, 25.6, 25.4, 24.1, 23.9, 18.5, 17.9

$[\alpha]^{24}_D$ = +33.9 (c=0.04, $CHCl_3$)

IR (NaCl, thin film): 3432, 2922, 2851, 1727, 1463, 1378, 1261, 1088

HRMS-ESI (m / z): $[M + H]^+$ calcd for $C_{30}H_{52}O_6Br$, 587.2942; found, 587.2930.



141 diastereomer D (**125**)

Alkene 125: To a 500 *u*L sealed tube equipped with a stir bar was added sodium hydride (7.8 mg, 0.309 mmol, 95% in mineral oil) in the glove box and then transferred to the hood under nitrogen. The reaction was purged while a solution of hydrazone **141** (20.7 mg, 26.8 *u*mol) in 500 *u*L of THF was added by syringe. The reaction was sealed and heated to 100 °C for 3 h. The reaction turned brown and was then cooled to room temperature. H_2O was added to quench remaining sodium hydride, followed by addition of 1 mL of saturated NH_4Cl. The aqueous layer was extracted with Et_2O (5x) and then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Careful column chromatography (20->50% HPLC-grade EtOAc in hexanes) provided a small amount of analytically clean **125** (0.9 mg, 1.5 *u*mol, 6% yield) as colorless oil.

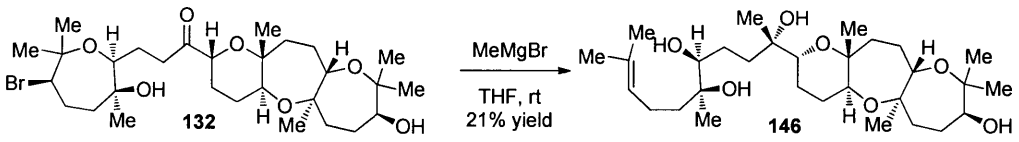
^{1}H NMR (600 MHz; C_6D_6): δ 5.46 (dt, J = 11.8, 6.0, 1H), 5.21 (d, J = 11.5, 1H), 3.88 (dt, J = 11.4, 6.4, 1H), 3.53 (d, J = 11.2, 1H), 3.48 (dd, J = 11.5, 4.3, 1H), 3.28-3.24 (m, 1H), 2.92 (bs, 1H), 2.75 (dd, J = 9.1, 2.7, 1H), 2.61 (ddd, J = 15.5, 5.6, 1.7, 1H), 2.25-2.17 (m, 2H), 2.11 (bs, 1H), 1.99-1.96 (m, 1H), 1.93-1.85 (m, 2H), 1.86-1.68 (m, 5H), 1.67-1.58 (m, 2H), 1.58-1.54 (m, 1H), 1.54-1.44 (m, 4H), 1.46 (td, J = 7.9, 3.9, 1H), 1.33 (s, 3H), 1.30 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H), 1.18 (s, 3H), 1.12 (s, 3H), 1.10 (s, 3H), 1.01 (s, 3H), 0.95-0.90 (m, 1H)

^{13}C NMR (125 MHz; C_6D_6): δ 137.1, 122.8, 78.3, 77.9, 77.8, 77.7, 76.9, 76.5, 75.8, 74.6, 73.2, 72.3, 59.8, 44.8, 42.6, 39.1, 34.6, 31.0, 29.9, 28.0, 28.0, 26.5, 26.2, 26.1, 25.6, 25.5, 24.4, 24.3, 18.5, 17.81

$[\alpha]^{24}_D = -17.9$ (c=0.05, $CHCl_3$)

IR (NaCl, thin film): 3428, 2926, 2852, 1726, 1464, 1377, 1262, 1139, 1084

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{30}H_{51}BrO_6Na$, 609.2761; found, 609.2770.



Alkene 146: To a 5 mL round-bottom flask equipped with a stir bar was added ketone **132** (59.1 mg, 93.6 *u*mol) in 1.6 mL of THF. The reaction was cooled to –78 °C and then 200 *u*L of methyl magnesium bromide (200 *u*L, 600 *u*mol, 3.0 M solution in Et_2O) was added dropwise. The reaction was stirred for 2 h at this temperature, during which time a precipitate had formed. An additional 1.6 mL of THF was added followed by more methyl magnesium bromide (300 *u*L, 900 *u*mol, 3.0 M solution in Et_2O) and the reaction was allowed to warm to 0 °C for 4 h and then room temperature overnight. The reaction was quenched with saturated NH_4Cl and then Et_2O was added. The reaction was extracted with Et_2O (3x), then the organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by Biotage (10 g column) to furnish **146** (10.2 mg, 19.4 *u*mol, 21% yield) as a colorless oil.

^{1}H NMR (500 MHz; C_6D_6): δ 5.27 (t, J = 7.1, 1H), 3.80 (dd, J = 11.4, 2.6, 1H), 3.59 (dd, J = 11.2, 5.1, 1H), 3.59 (dd, J = 11.2, 5.1, 1H), 3.44 (dd, J = 8.4, 2.7, 1H), 3.22 (d, J = 6.9, 1H), 3.10 (dd, J = 11.2, 2.9, 1H), 2.33-2.08 (m, 3H), 1.96-1.71 (m, 6H), 1.69 (s, 3H), 1.65 (dt, J = 7.6, 4.1, 2H), 1.62 (s, 3H), 1.61-1.45 (m, 8H), 1.34 (s, 3H), 1.23 (s, 3H), 1.20 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 0.98 (s, 3H), 0.97-0.91 (m, 1H)

^{13}C NMR (125 MHz; C_6D_6): δ 131.4, 126.0, 79.6, 78.7, 78.1, 78.1, 78.0, 76.7, 76.5, 74.8, 73.7, 71.0, 40.9, 39.8, 36.8, 35.3, 30.6, 30.0, 29.4, 28.3, 26.3, 26.3, 25.8, 23.6, 23.0, 22.0, 22.0, 20.3, 18.1, 17.1

$[\alpha]^{24}_D$ = –23.4 (c=0.51, $CHCl_3$)

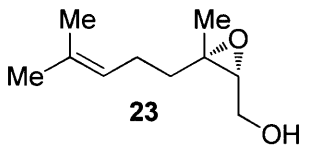
IR (NaCl, thin film): 3416, 2971, 2934, 2872, 1462, 1451, 1377, 1136, 1071, 1034, 891.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{30}H_{54}O_7Na$, 549.3762; found, 549.3773.

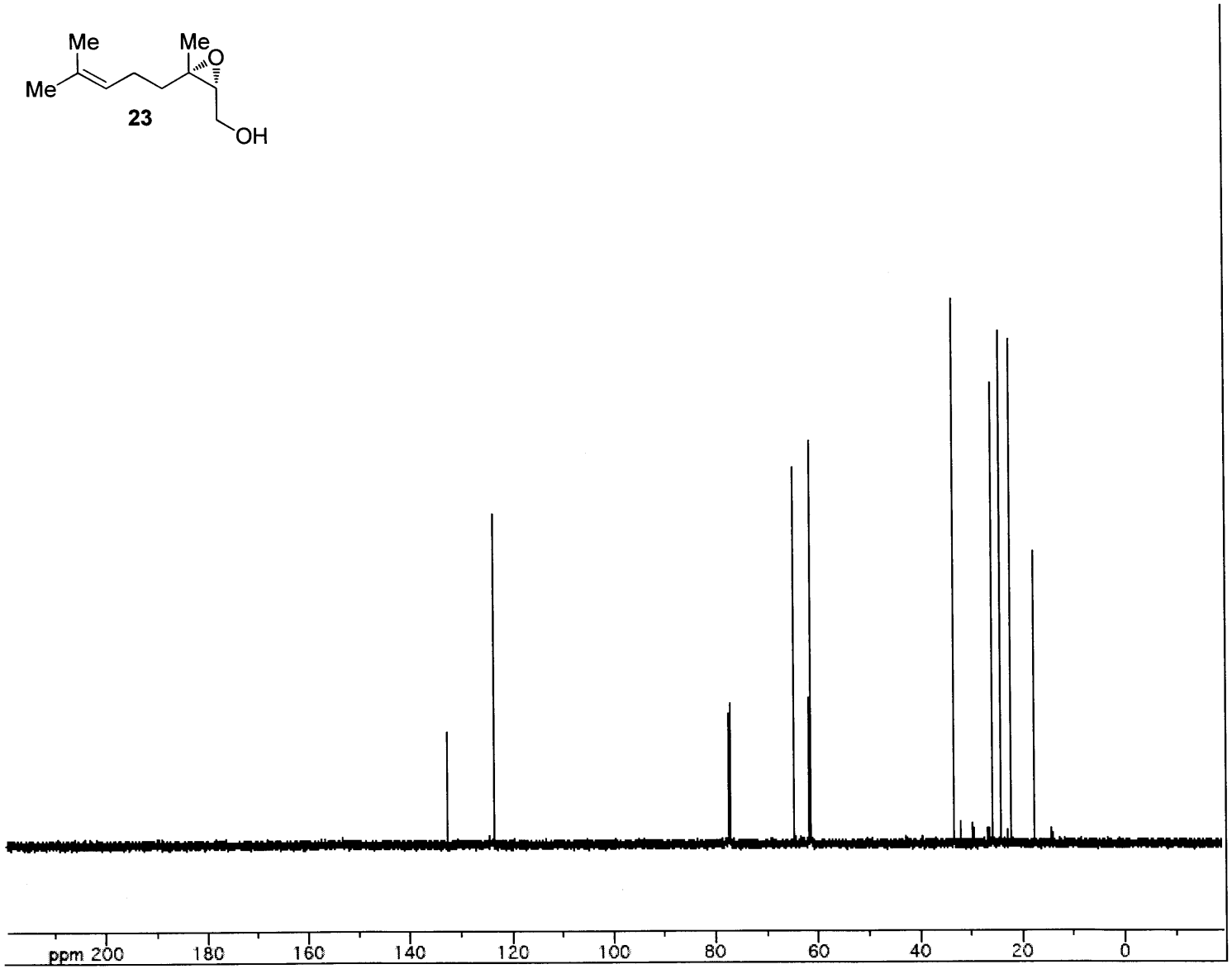
---

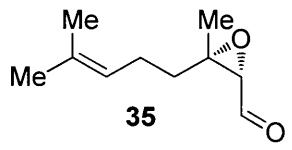
[1] Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155-4156.
[2] Tashiro, T.; Mori, K. *Tetrahedron: Asymmetry* **2005**, *16*, 1801-1806.

Chapter 2 ^{1}H NMR and ^{13}C NMR Spectra

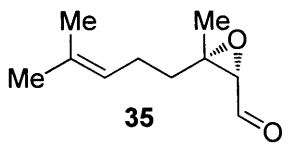


23

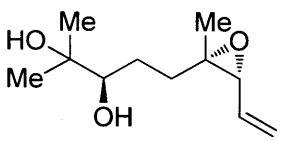

Me
Me
Me
O
OH
23
ppm 200
180
160
140
120
100
80
60
40
20
0



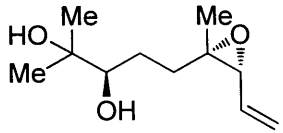
35



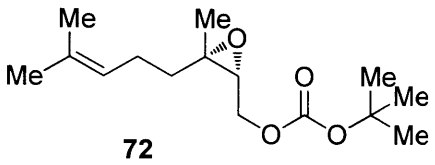
35



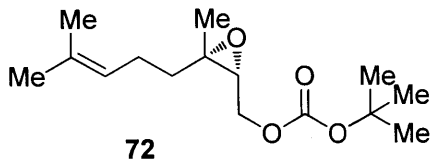
22



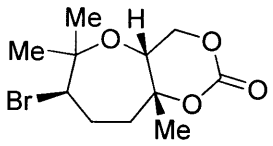
22



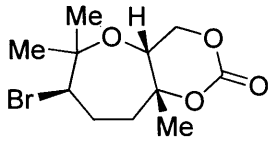
72



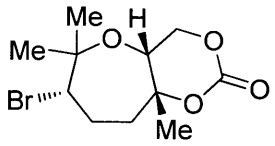
72



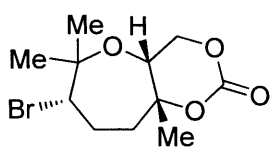
73



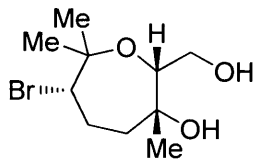
73



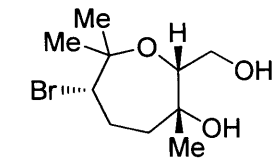
71



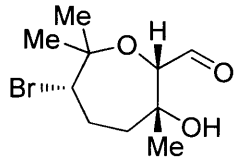
71



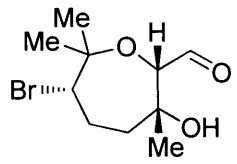
92



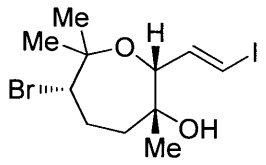
92



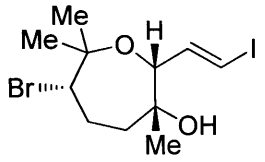
93



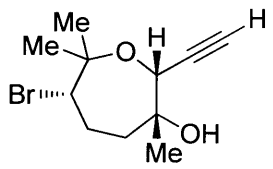
93



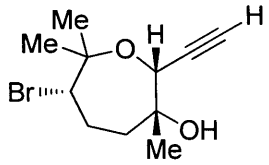
94



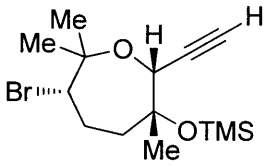
94



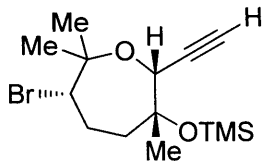
95



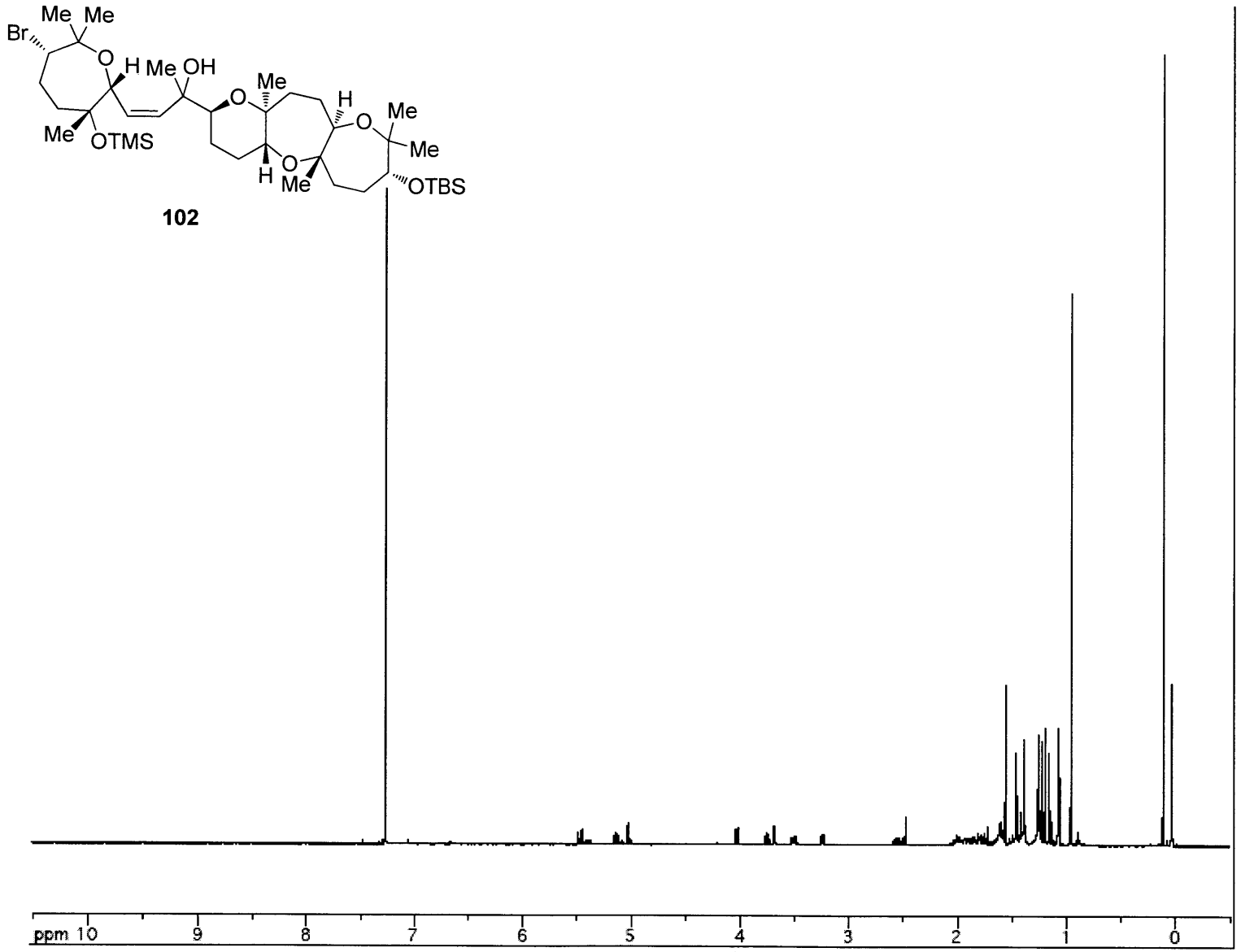
95



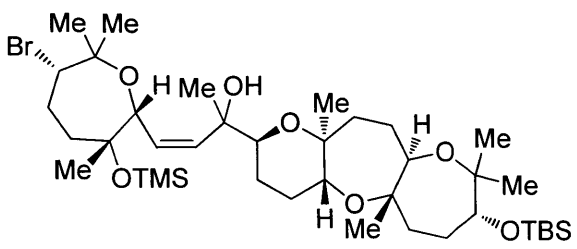
96



96

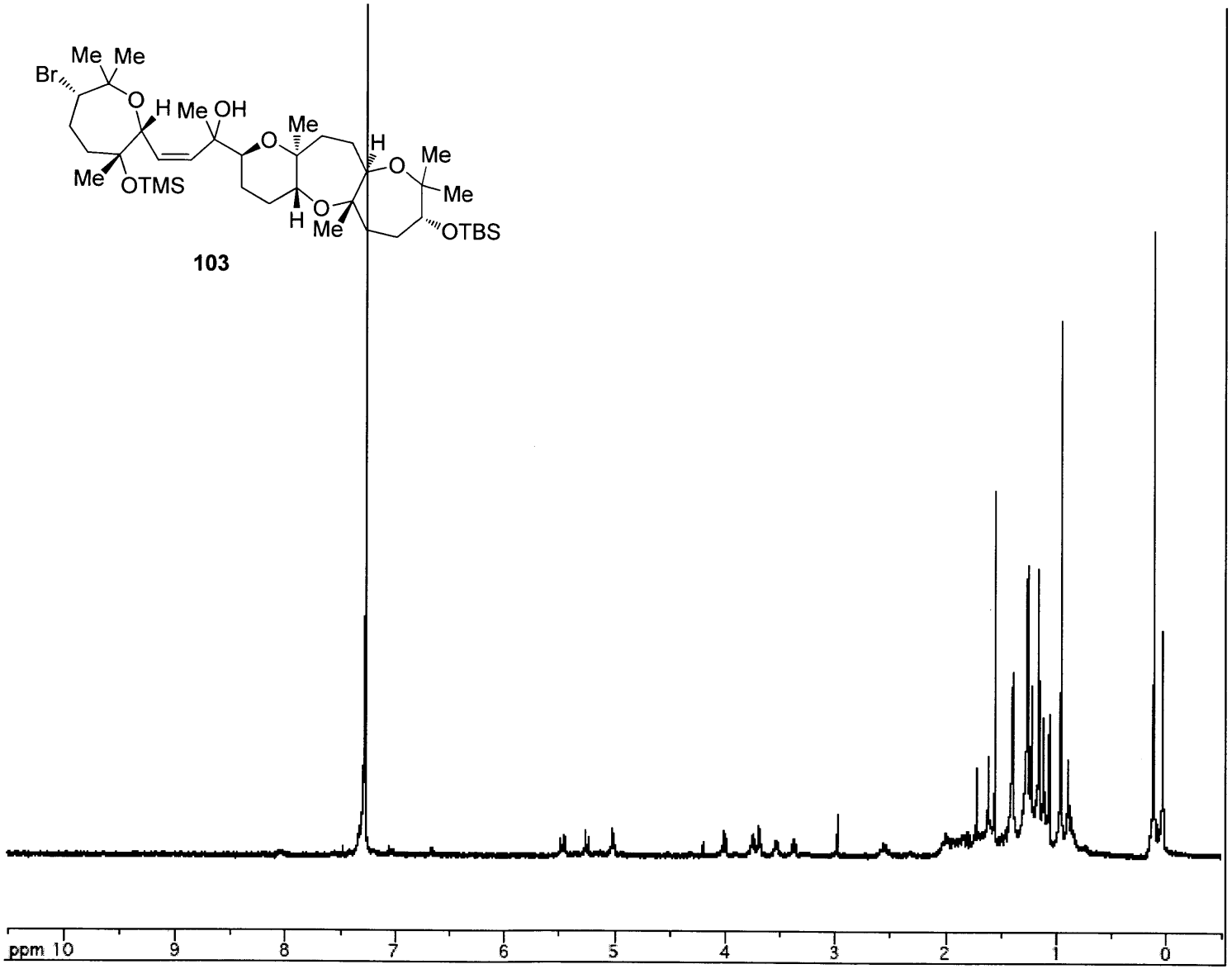

Me Me
Br
O
H Me OH
Me
O
H
O
Me
Me
Me OTMS
O
H
Me
OTBS
ppm 10
9
8
7
6
5
4
3
2
1
0

102

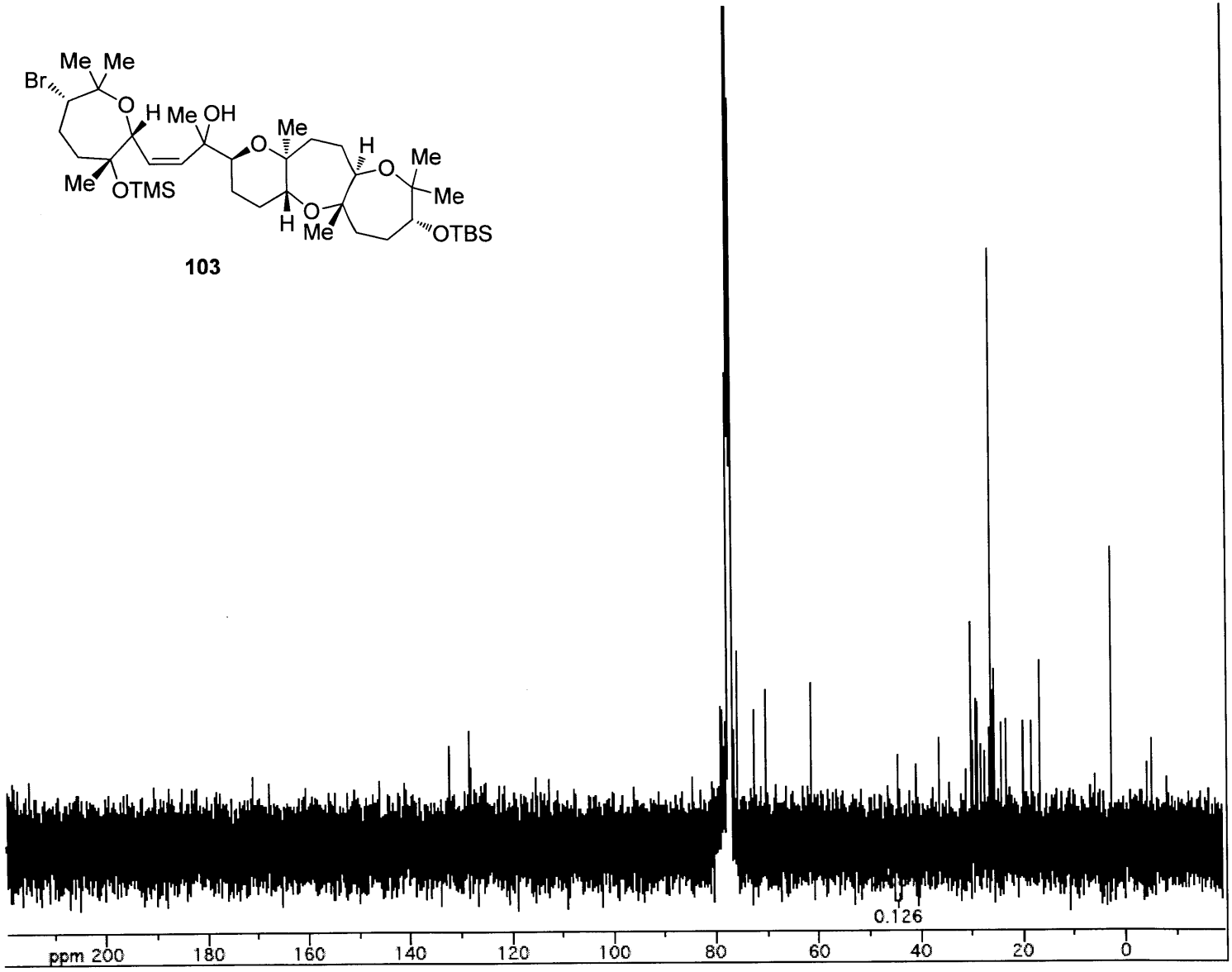

Me Me
Br
O
H Me OH
Me
O
H
O
Me
Me
Me OTMS
H
O
Me
Me
OTBS

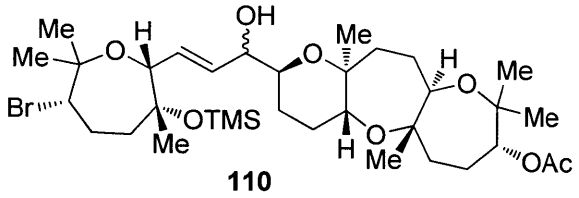
102

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

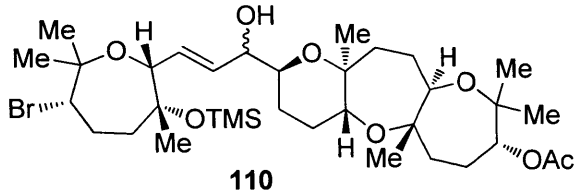

Me Me
Br
O
H Me OH
Me
O
H
O
Me
Me
Me OTMS
H
O
Me
Me
OTBS
ppm 10
9
8
7
6
5
4
3
2
1
0

103


Me Me
Br
O
H Me OH
Me
O
H
O
Me
Me
Me
OTMS
O
H
Me
Me
OTBS
103
0.126
ppm 200
180
160
140
120
100
80
60
40
20
0

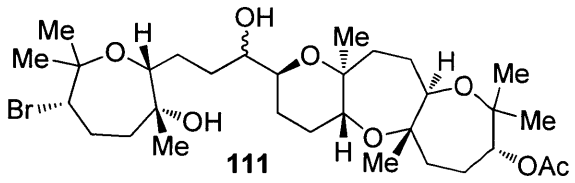


110

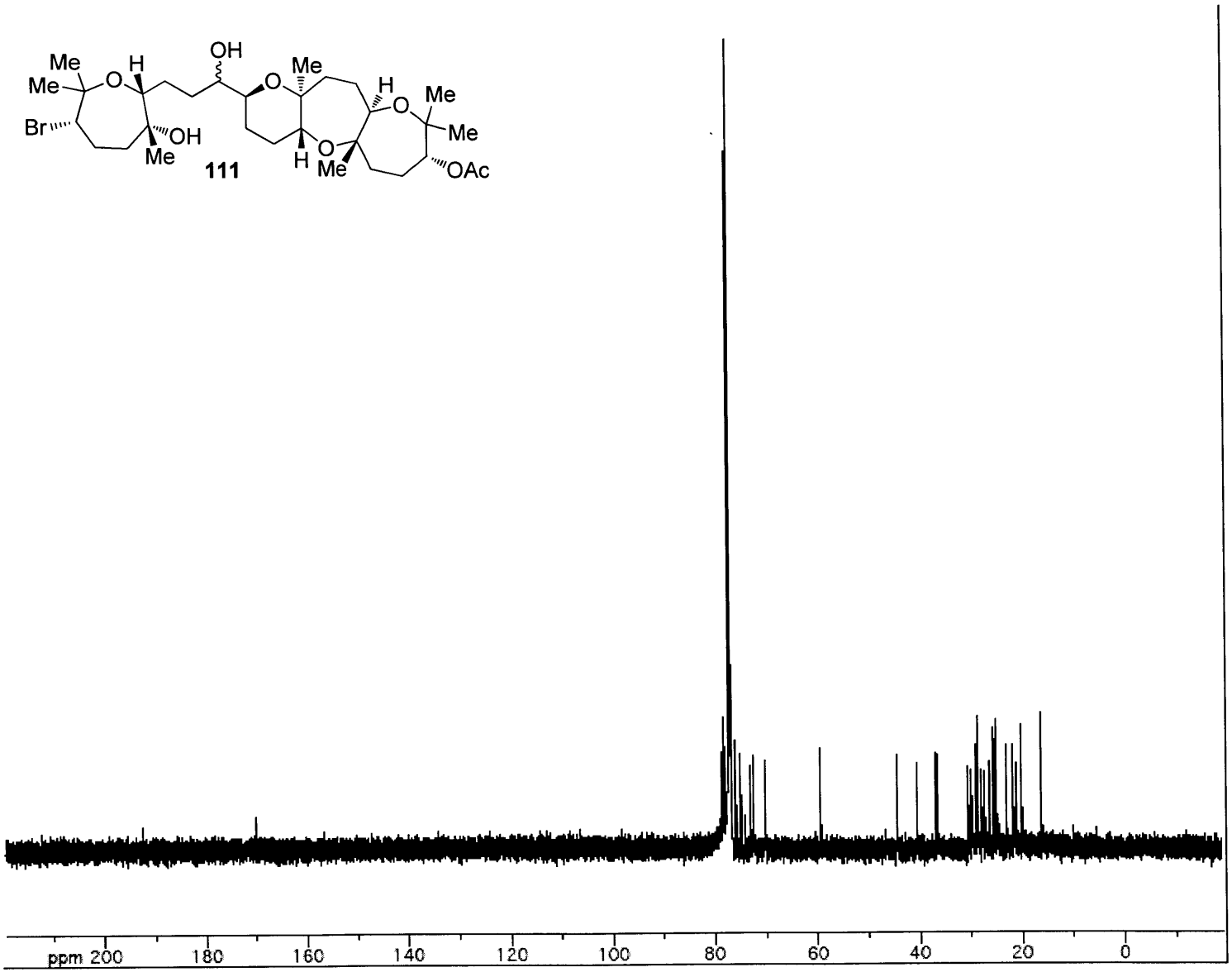

Me
Me
H
OH
Me
H
Me
Br
OTMS
Me
H
Me
Me
OAc

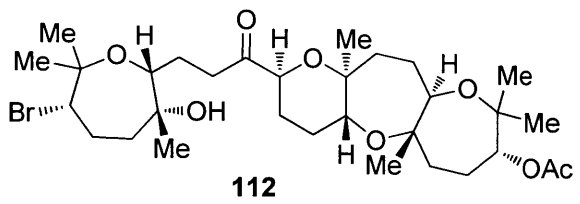
110

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

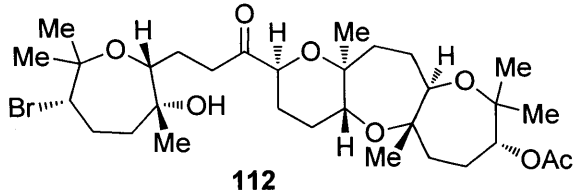

Me
Me
Br
H
O
OH
Me
OH
Me
111
Me
O
H
O
Me
H
O
Me
Me
Me
OAc

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


Me
Me
O
H
OH
Br
OH
Me
111
Me
O
O
Me
H
O
Me
Me
H
O
Me
OAc
ppm 200
180
160
140
120
100
80
60
40
20
0

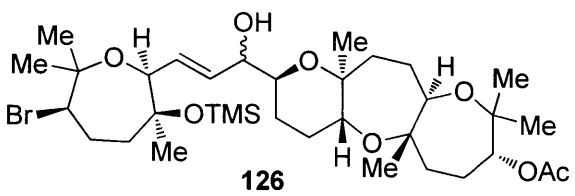


112

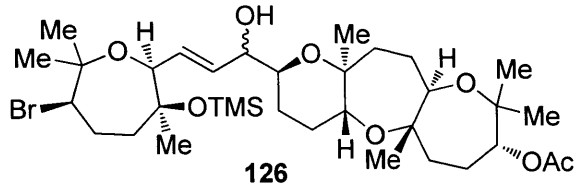

Me
Me
O
H
O
H
Me
H
O
Me
Me
Br
OH
Me
H
O
Me
OAc

112

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

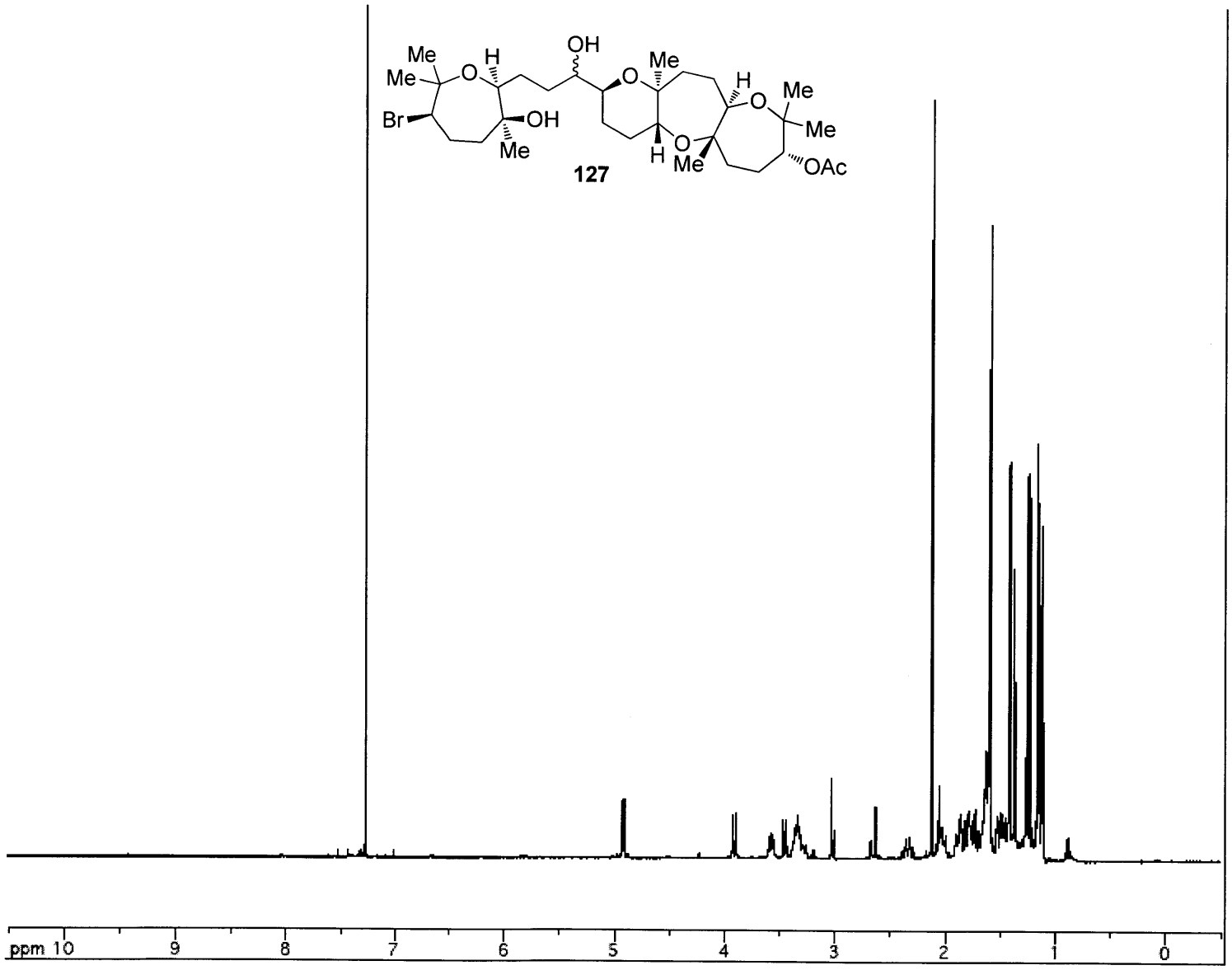


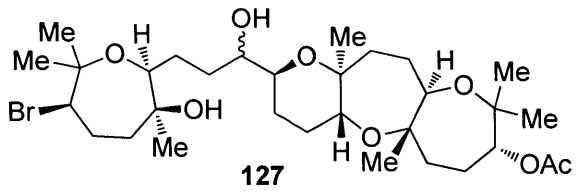
126


Me
Me
O
H
OH
Me
O
H
O
Me
Me
Br
OTMS
Me
H
O
Me
Me
OAc

126

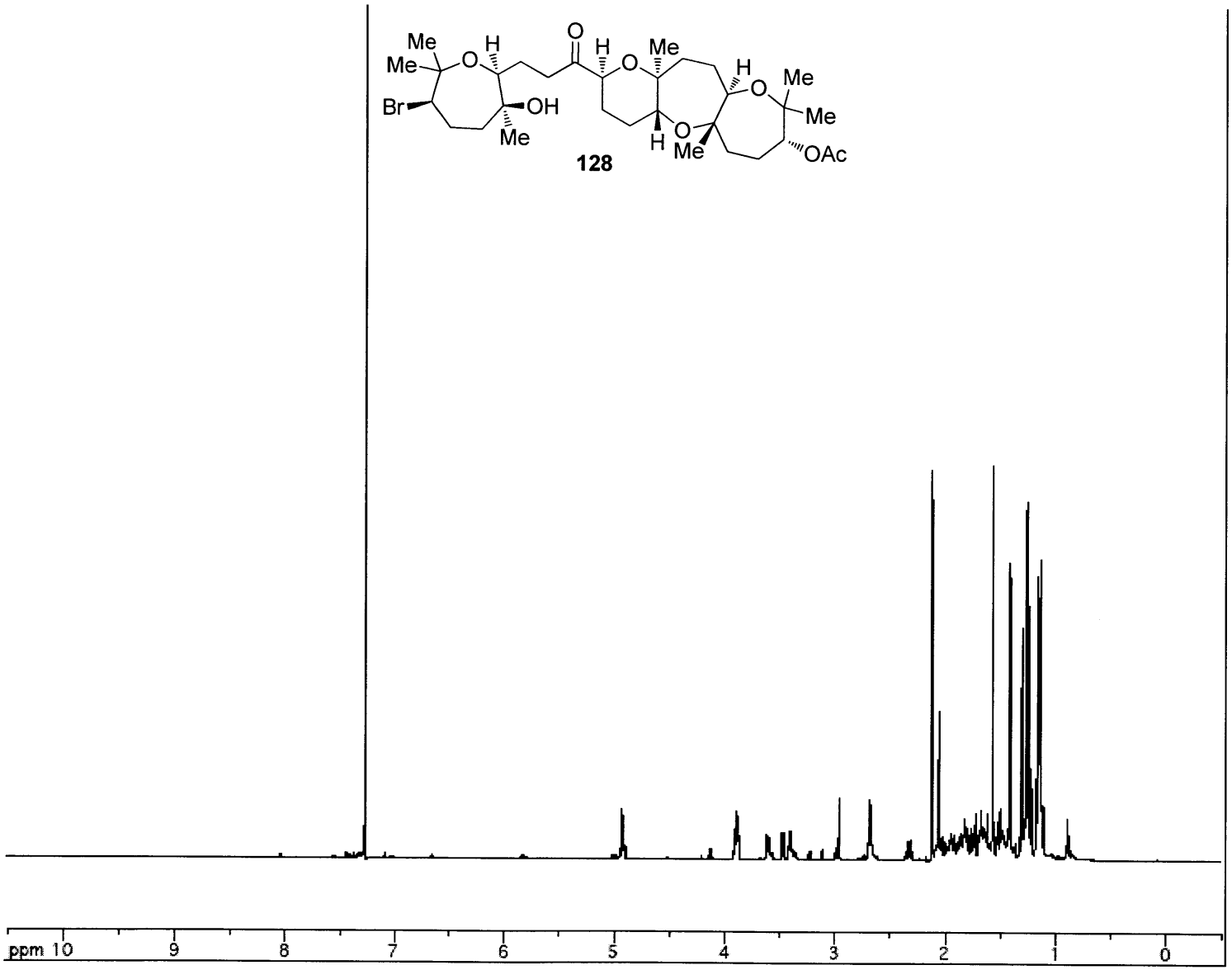
ppm 200
180
160
140
120
100
80
60
40
20
0


Me
Me
O
H
OH
Me
O
H
O
Me
Me
Br
OH
Me
H
O
Me
Me
OAc
127
ppm 10
9
8
7
6
5
4
3
2
1
0

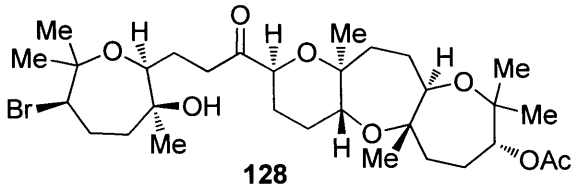

Me
Me
O
H
OH
O
Me
H
O
Me
Me
Br
OH
Me
H
O
Me
OAc

127

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

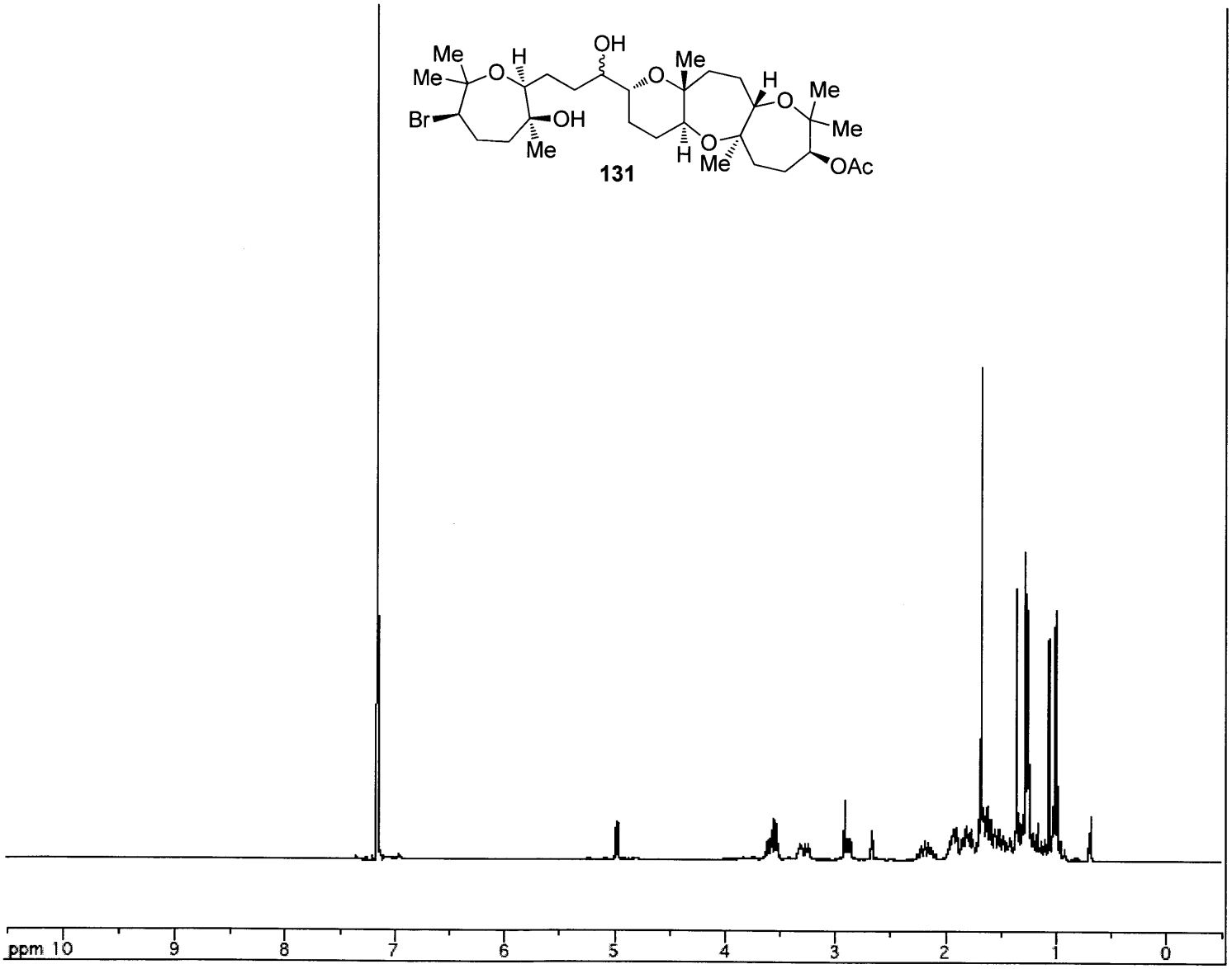


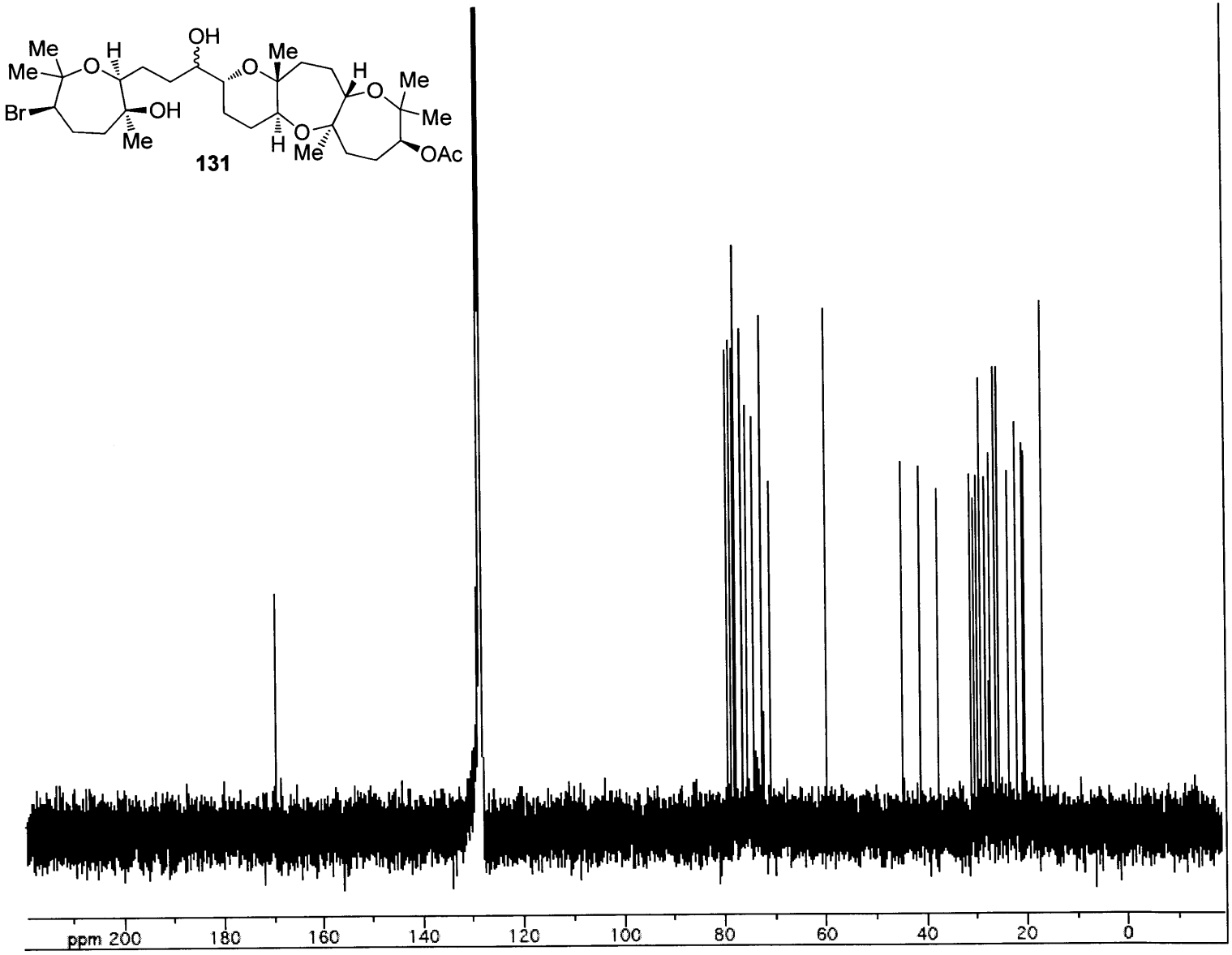
128

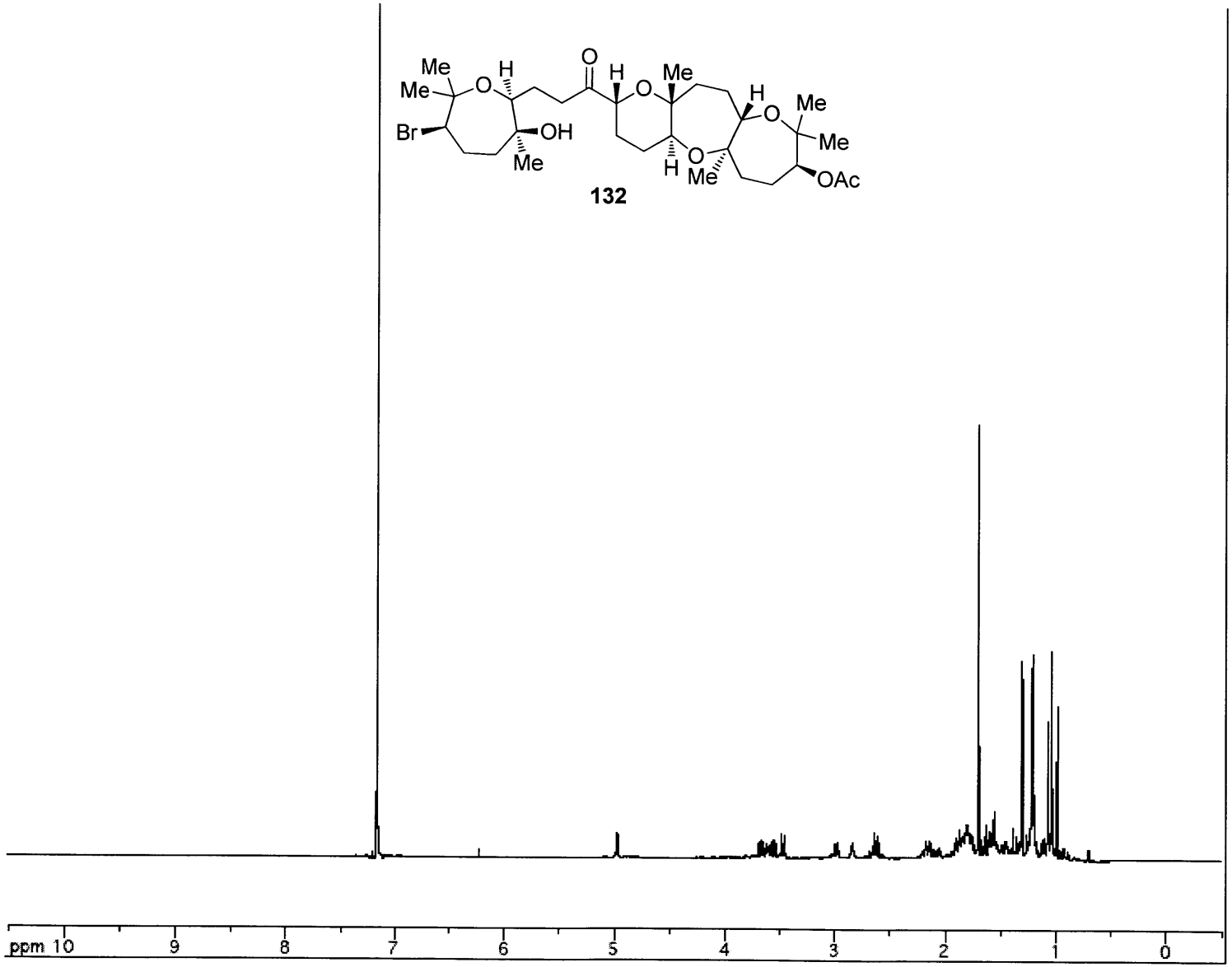

Me
Me
O
H
O
H
Me
H
O
Me
Me
Br
OH
Me
O
H
Me
OAc

128

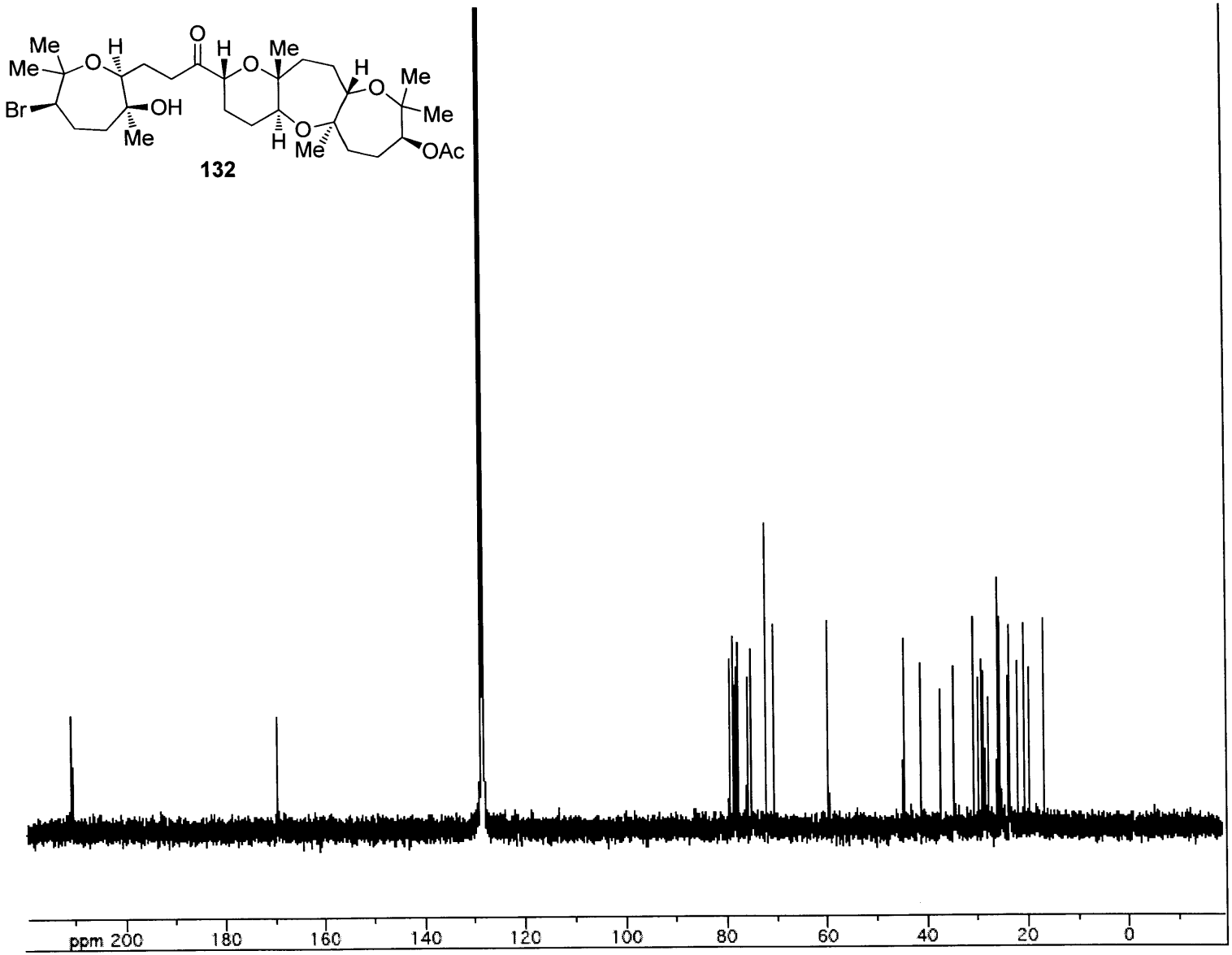
ppm 200
180
160
140
120
100
80
60
40
20
0

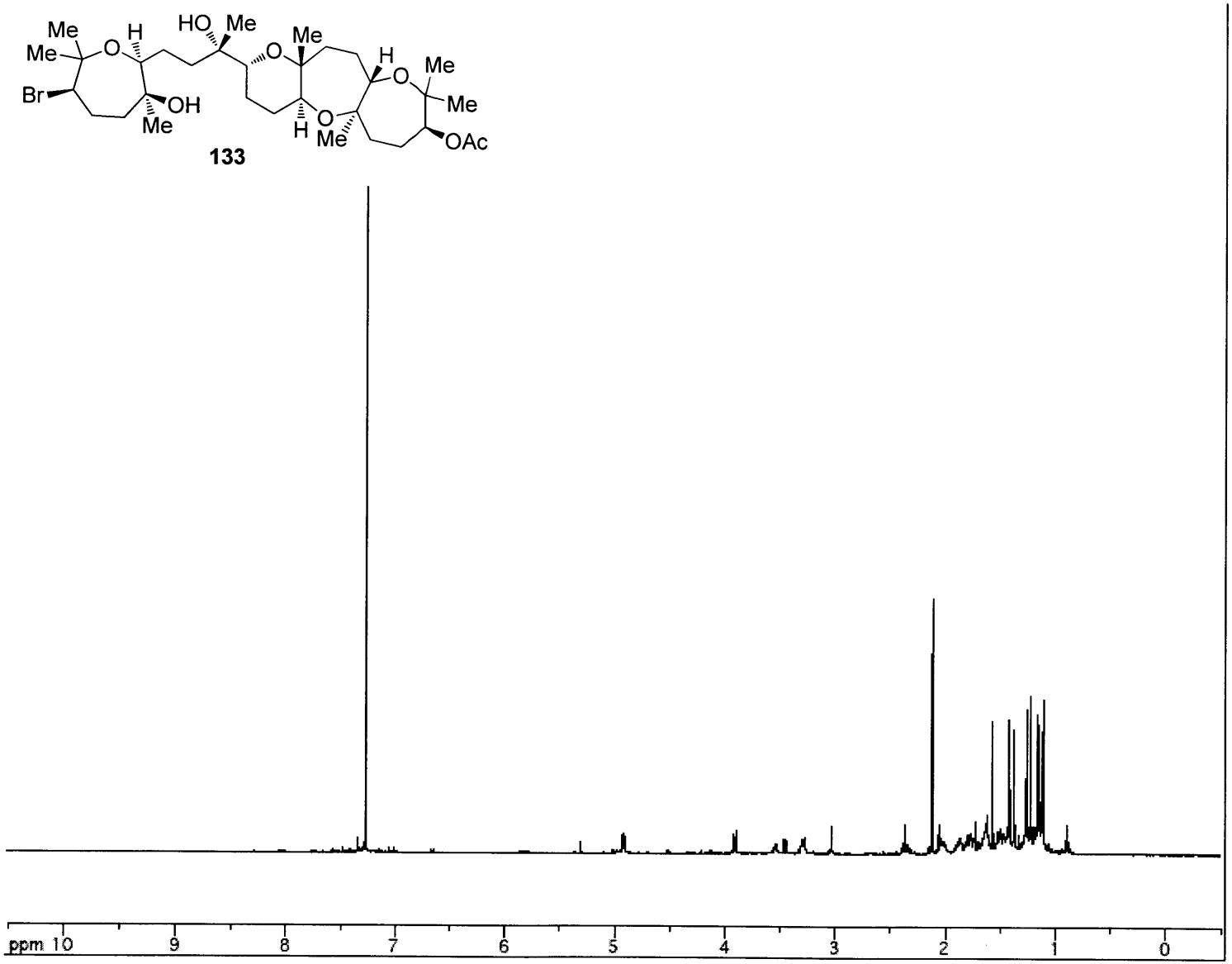

Me
Me
O
H
OH
O
Me
H
O
Me
Me
Br
OH
Me
H
O
Me
OAc
131
ppm 10
9
8
7
6
5
4
3
2
1
0


Me
Me
O
H
OH
Br
OH
Me
O
Me
H
O
Me
Me
H
O
Me
OAc
131
ppm 200
180
160
140
120
100
80
60
40
20
0

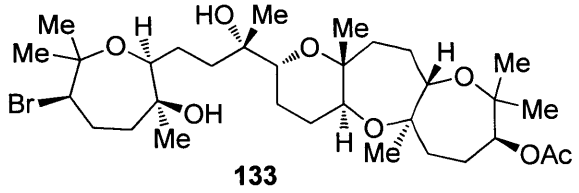


132


Me
Me
O
H
O
H
Me
H
O
Me
Br
OH
Me
Me
O
H
Me
O
Me
OAc
132
ppm 200
180
160
140
120
100
80
60
40
20
0

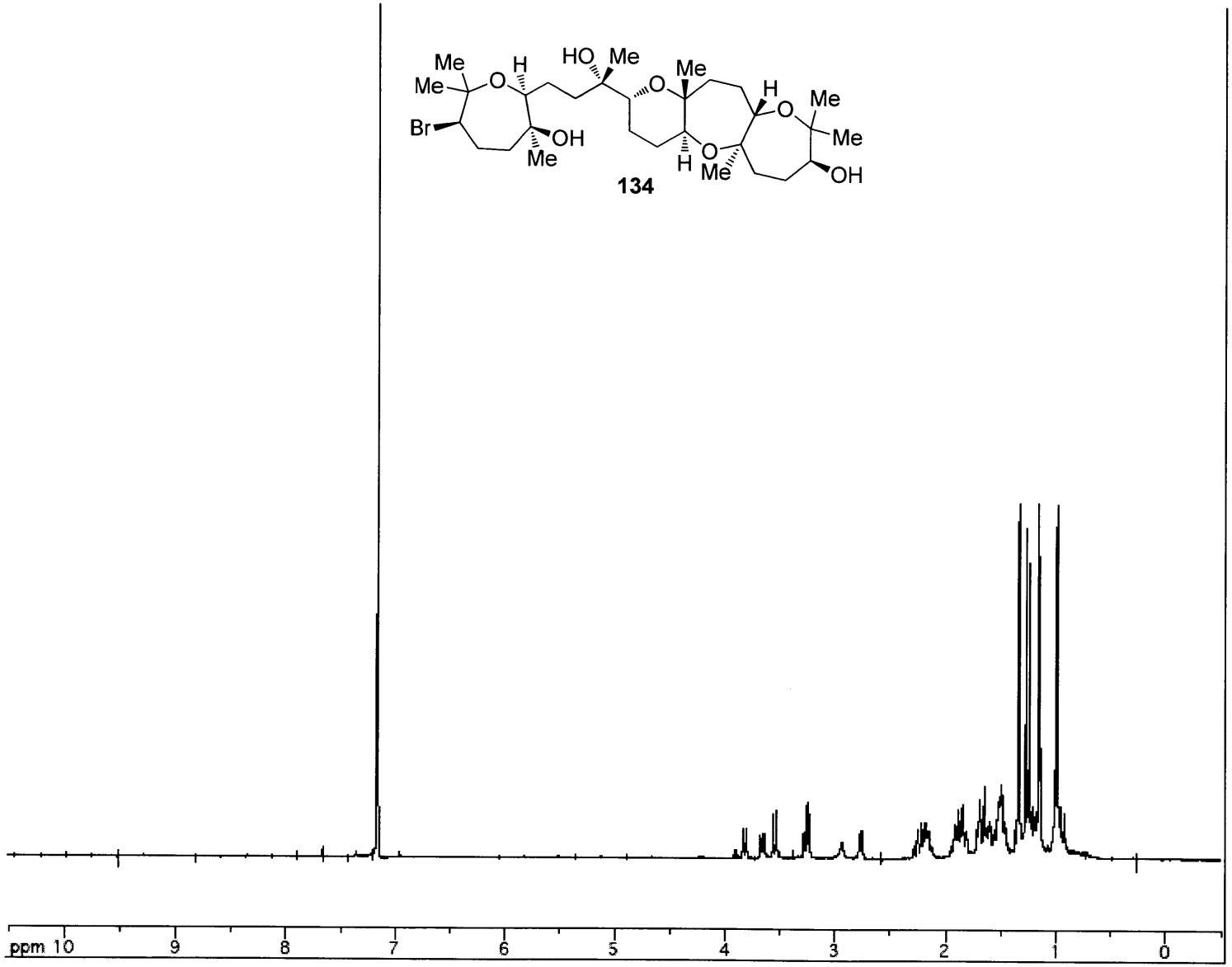


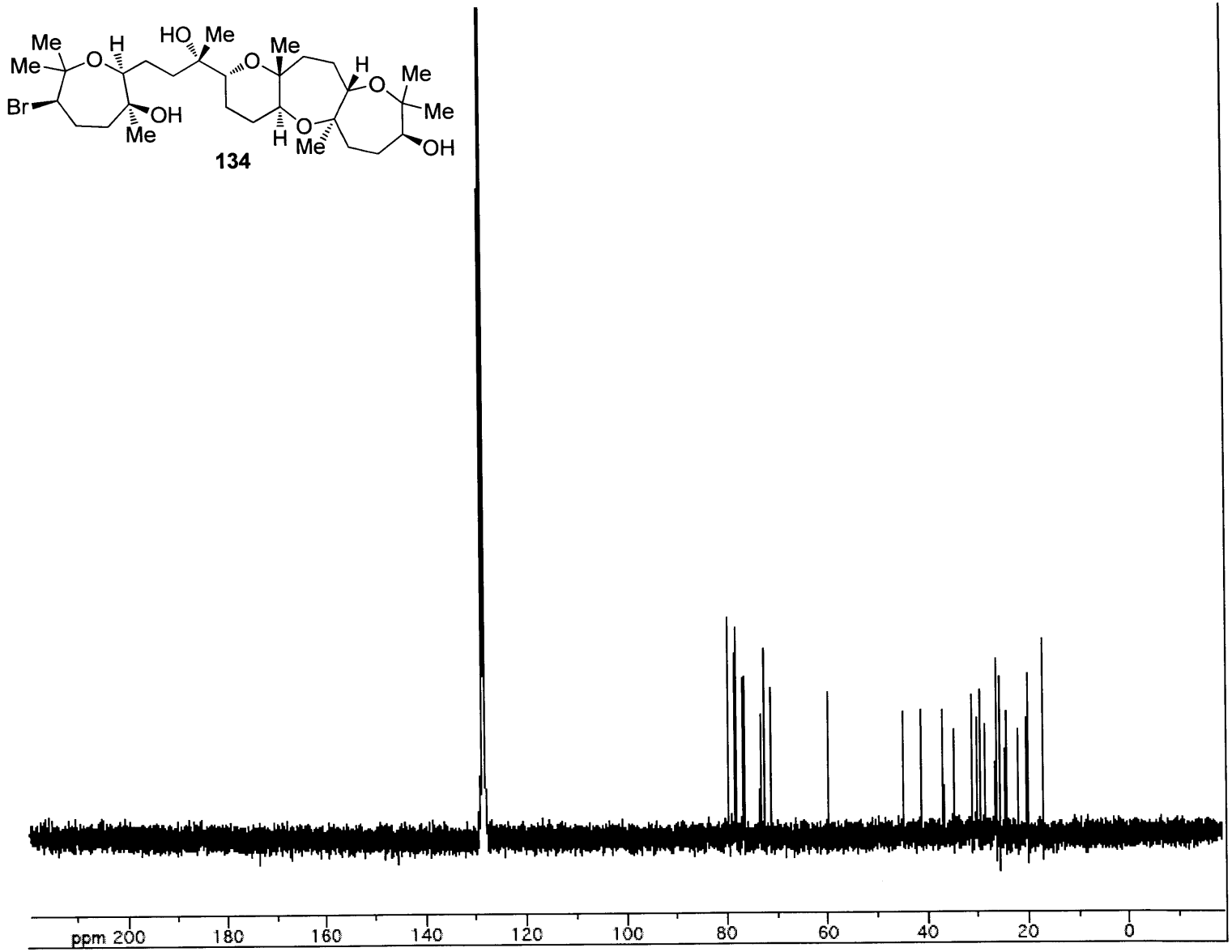
133

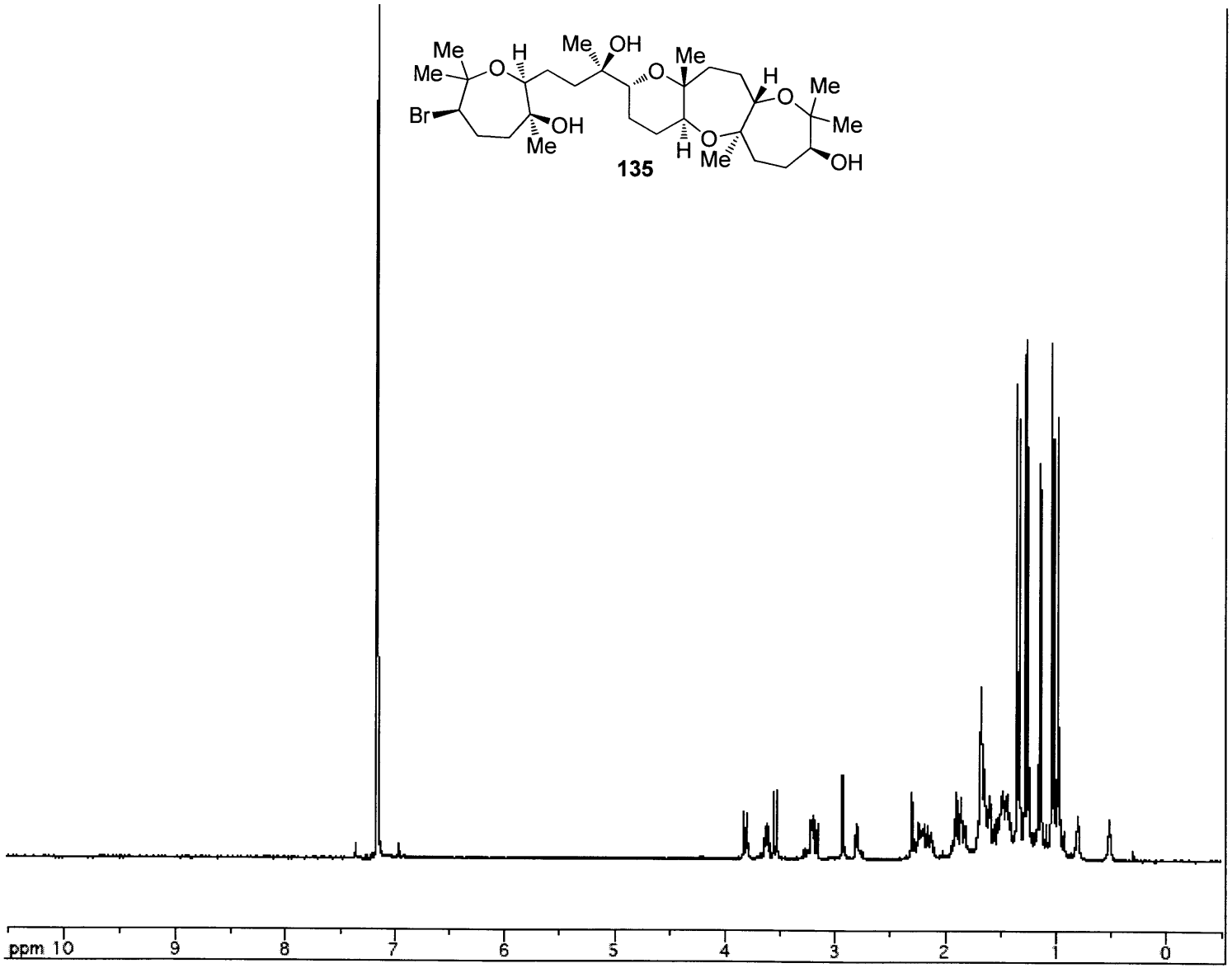

Me
Me
O
H
HO
Me
Me
O
H
O
Me
Br
OH
Me
H
O
Me
Me
OAc

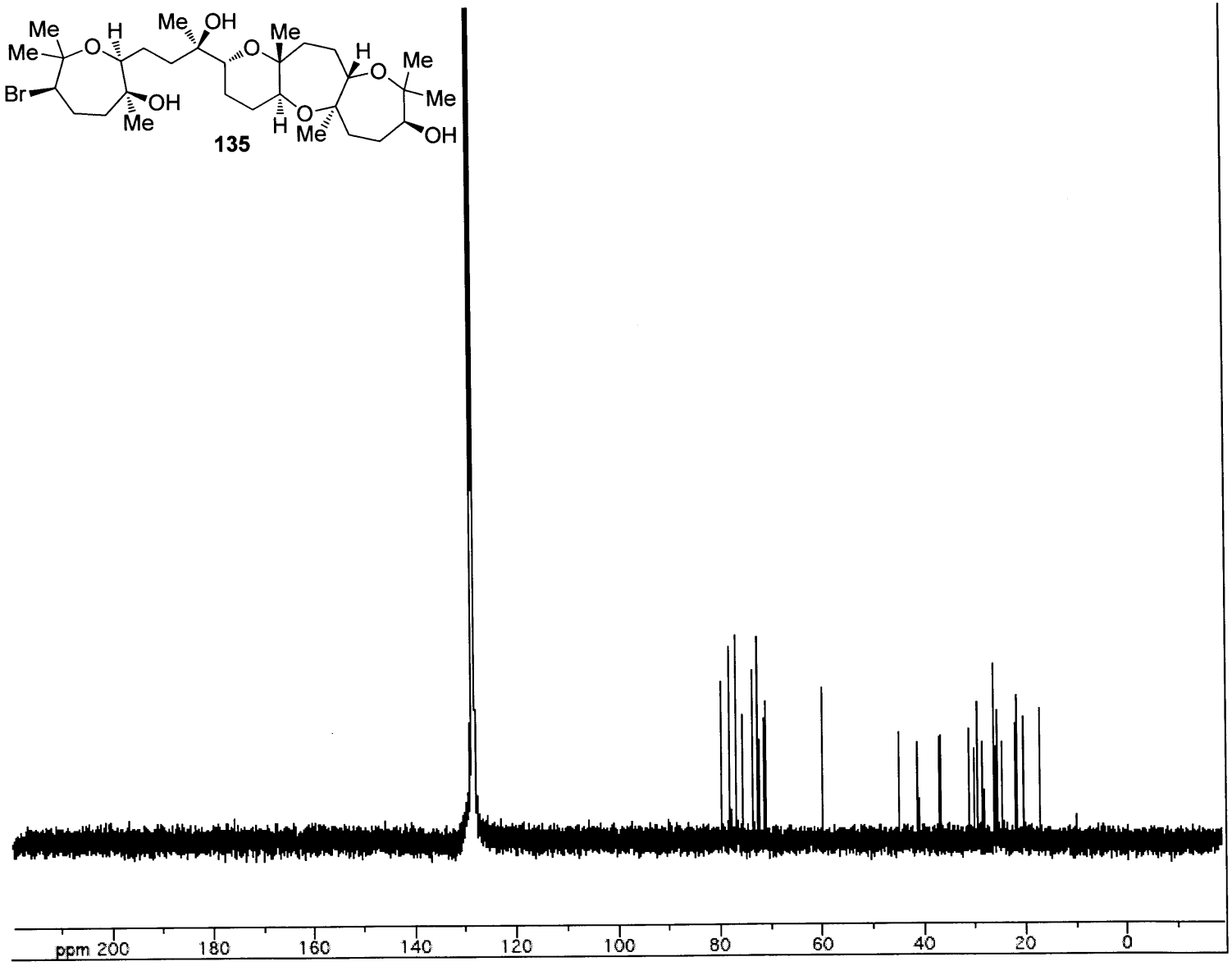
133

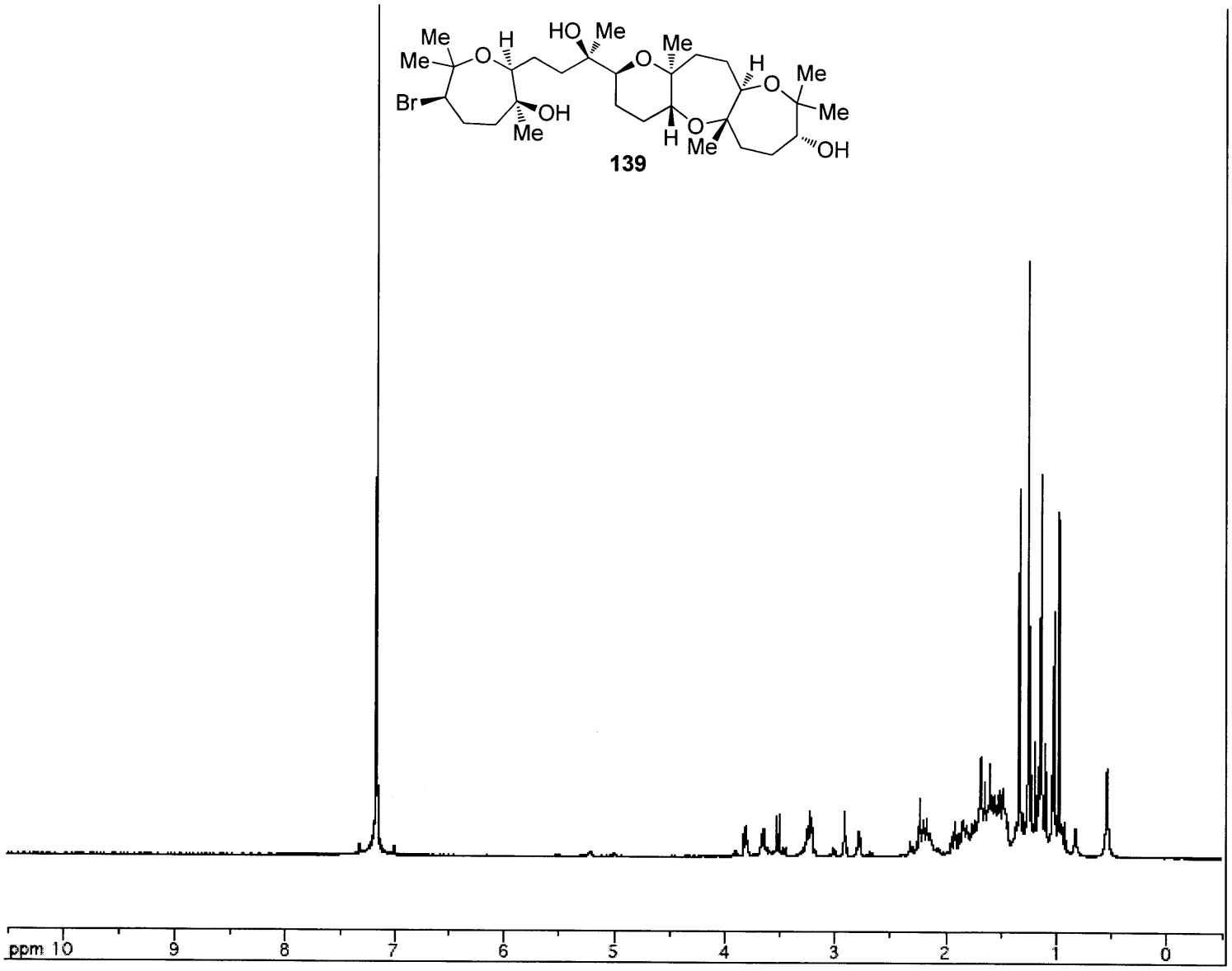
ppm 200
180
160
140
120
100
80
60
40
20
0

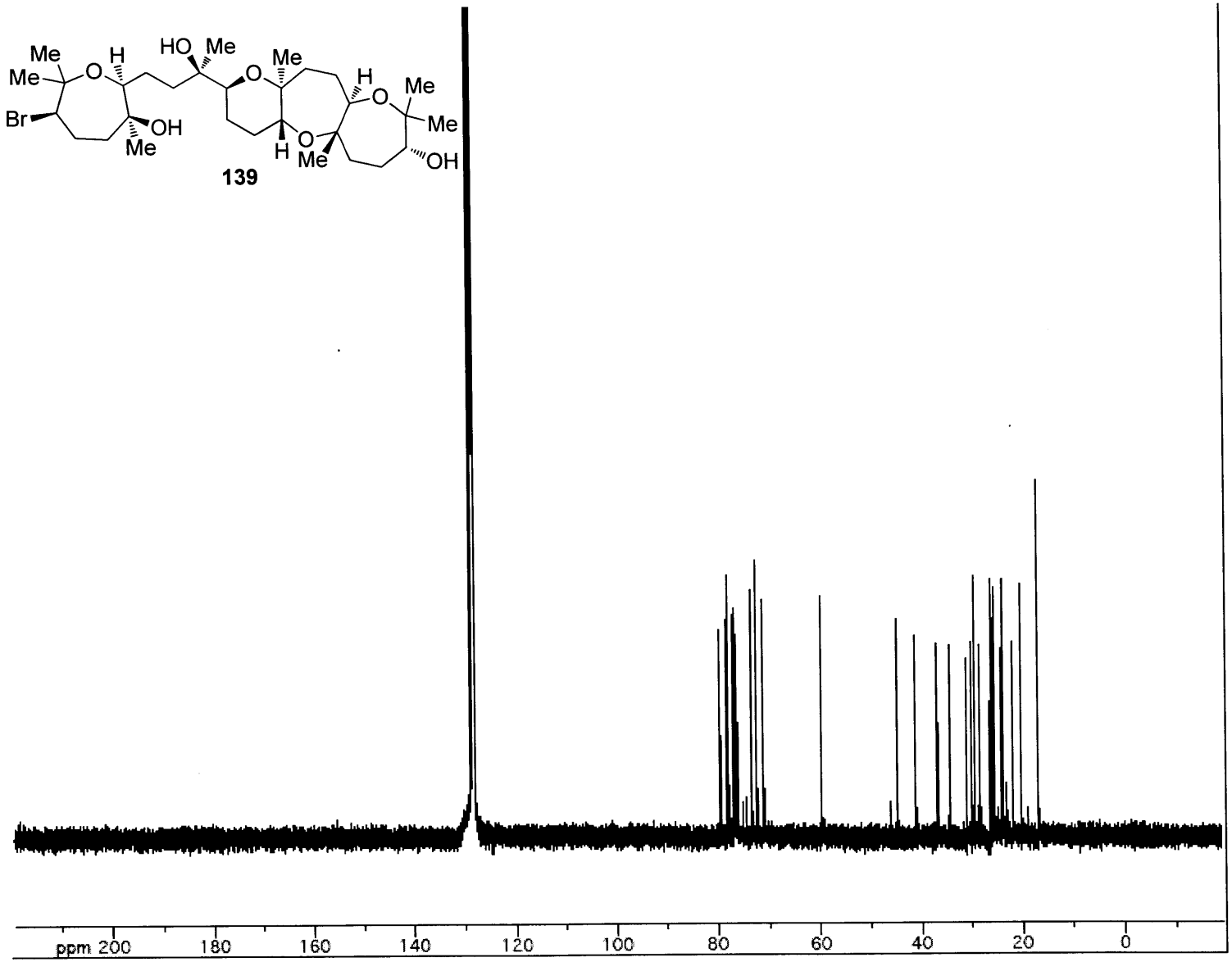

Me
Me
O
H
HO
Me
Me
O
H
O
Me
Br
OH
Me
H
O
Me
Me
OH
134
ppm 10
9
8
7
6
5
4
3
2
1
0

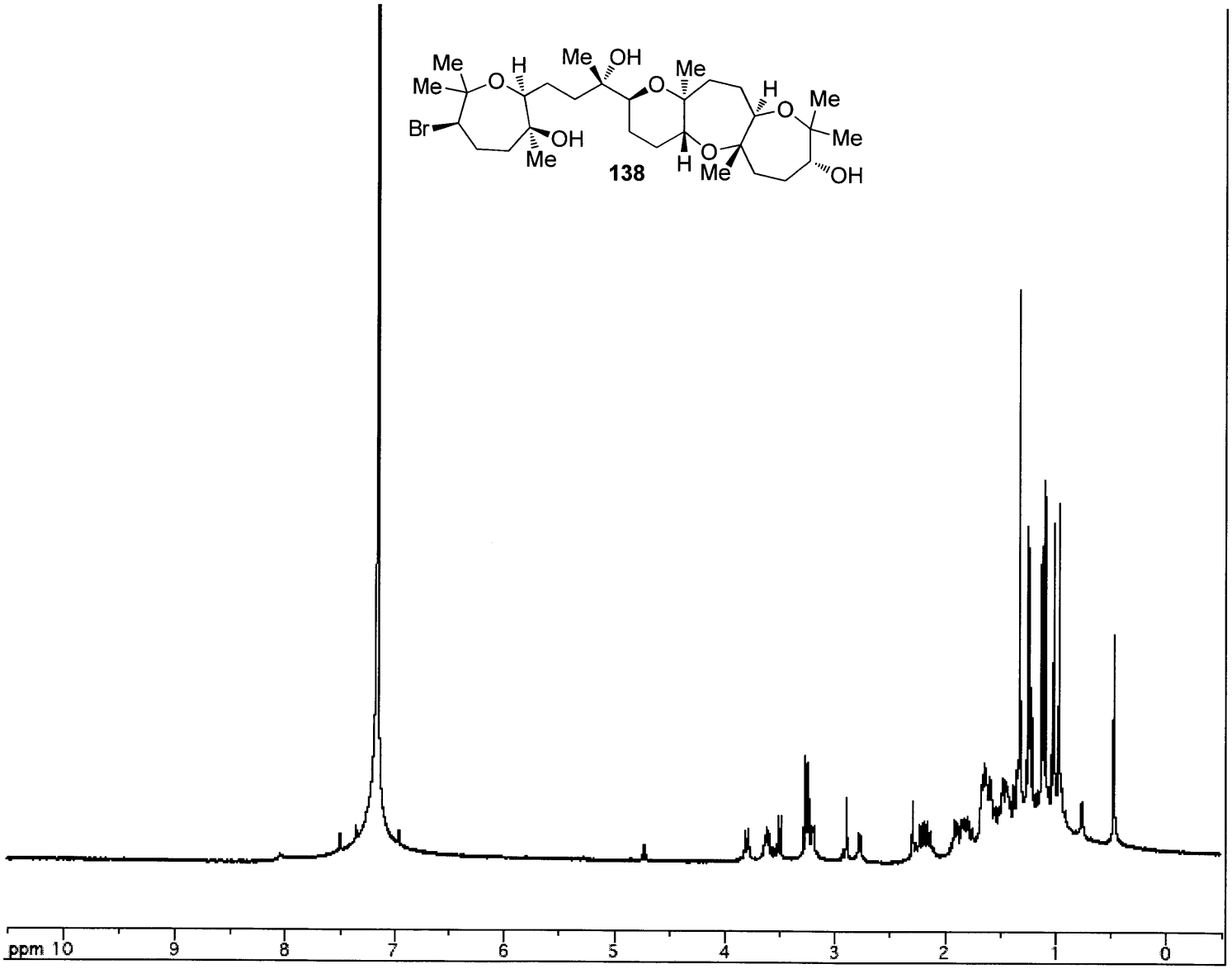

Me
Me
O
H
HO
Me
Me
O
H
O
Me
Br
OH
Me
Me
H
O
Me
OH
134
ppm 200
180
160
140
120
100
80
60
40
20
0

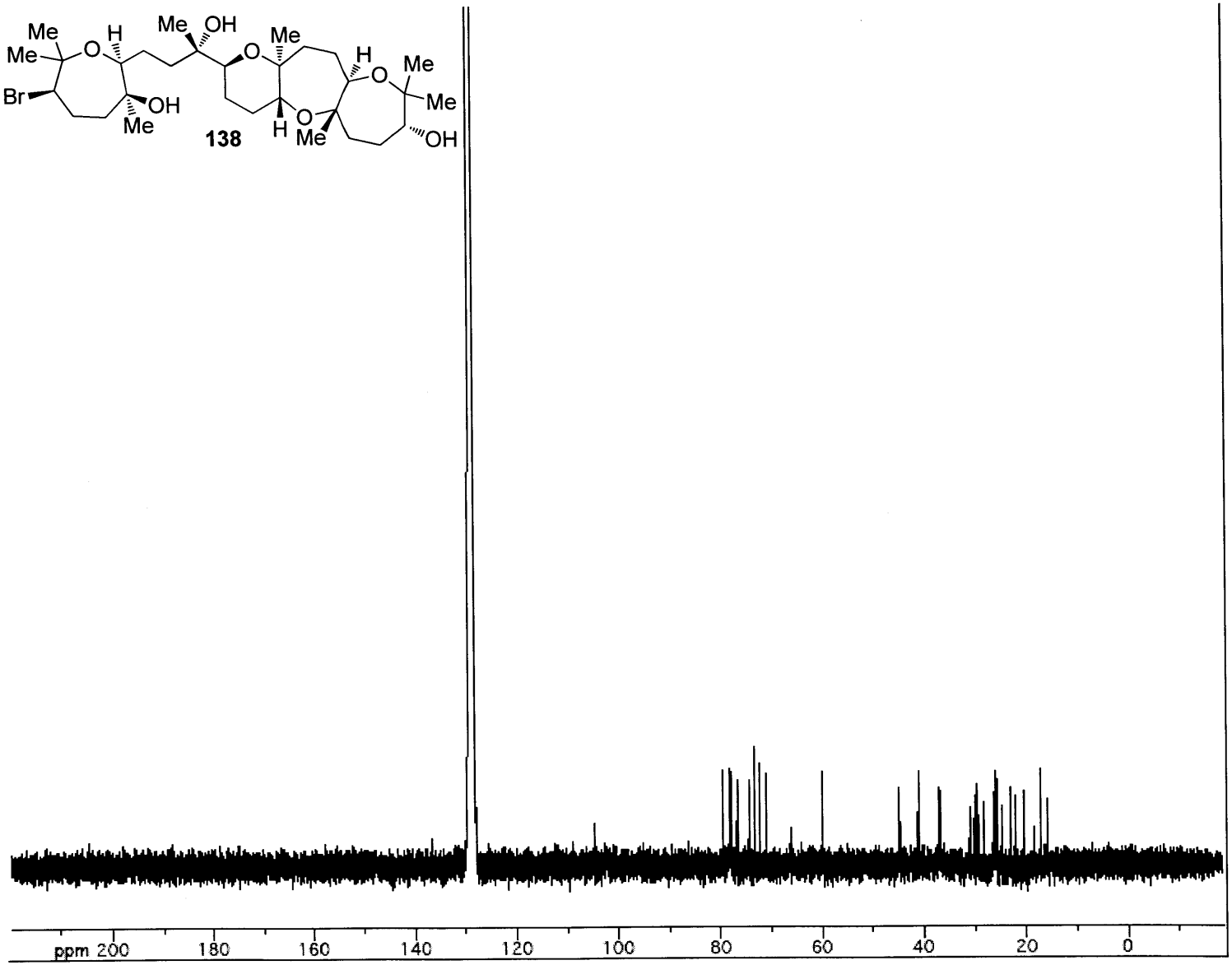

Me
Me
Br
O
H
OH
Me
Me
OH
O
Me
H
O
Me
Me
H
O
Me
OH
135
ppm 10
9
8
7
6
5
4
3
2
1
0

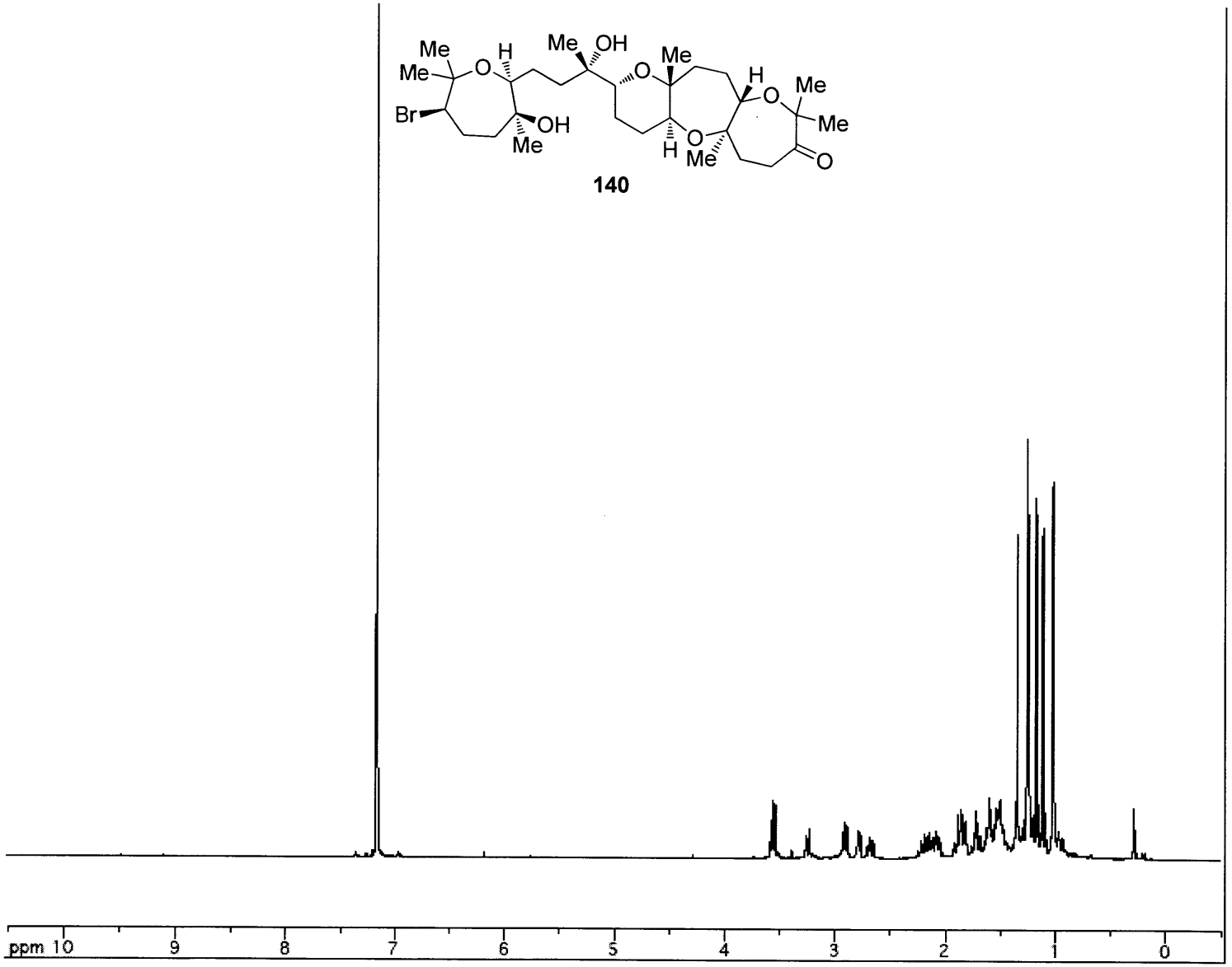

Me
Me
H
O
Me
OH
Br
OH
Me
135
O
Me
H
O
Me
Me
O
Me
OH
ppm 200
180
160
140
120
100
80
60
40
20
0


Me
Me
O
H
HO
Me
Me
O
H
O
Me
Br
OH
Me
H
O
Me
Me
OH
139
ppm 10
9
8
7
6
5
4
3
2
1
0

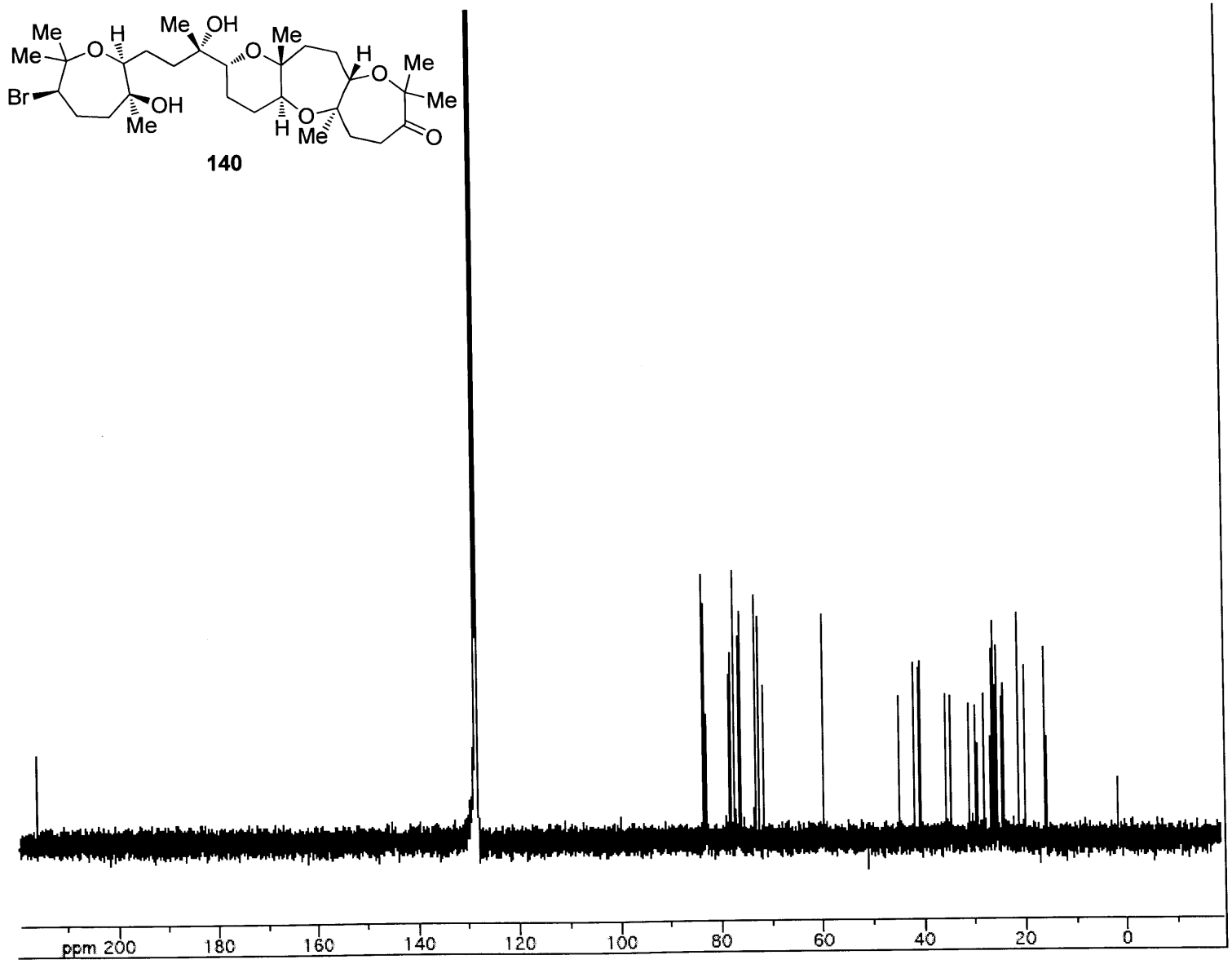

Me
Me
O
H
HO
Me
Me
O
H
O
Me
Br
OH
Me
H
O
Me
Me
OH
139
ppm 200
180
160
140
120
100
80
60
40
20
0


Me
Me
Br
O
H
OH
Me
Me
OH
Me
O
Me
H
O
Me
Me
H
O
Me
OH
138
ppm 10
9
8
7
6
5
4
3
2
1
0

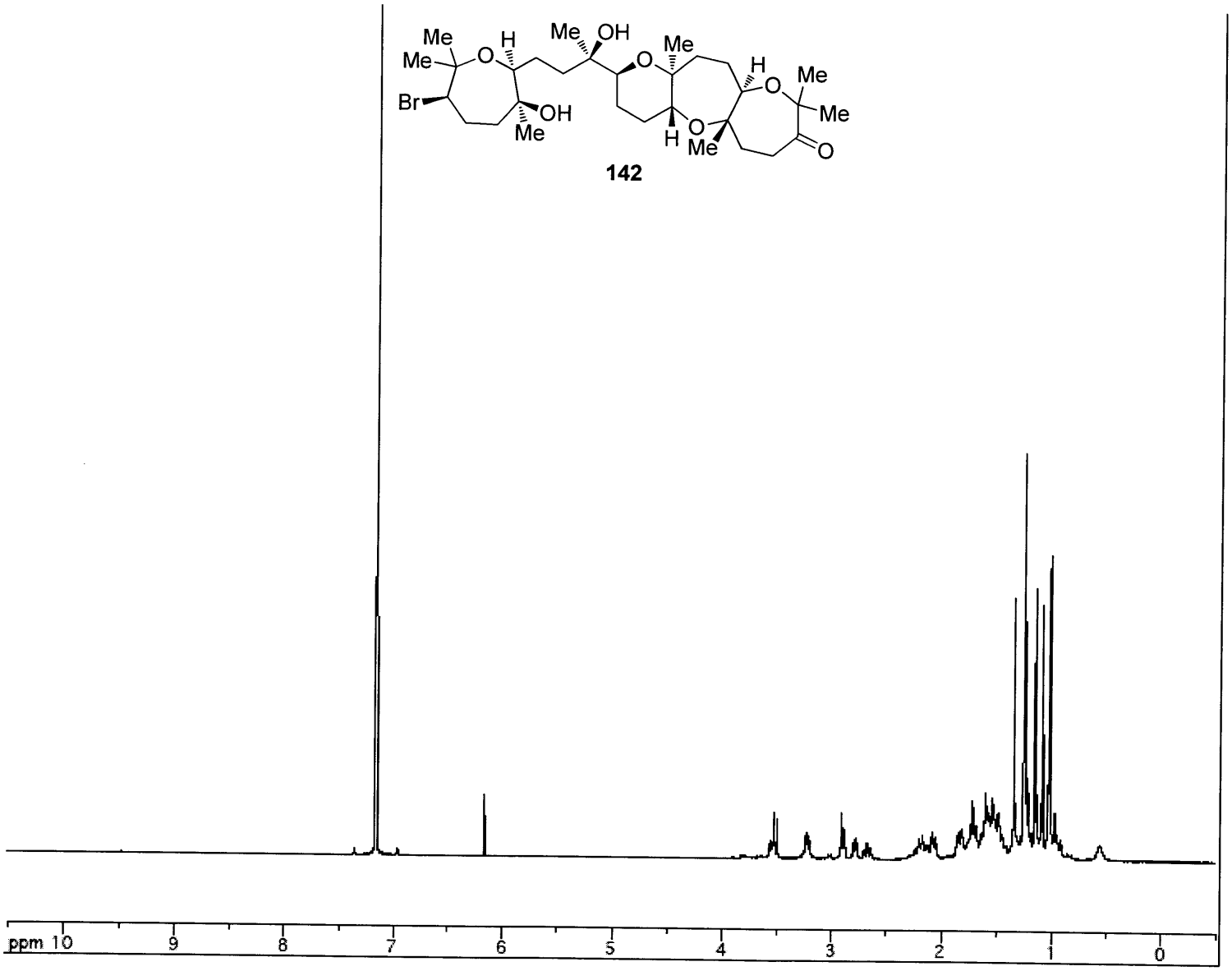

Me
Me
O
H
Me
OH
Br
OH
Me
138
Me
O
H
O
Me
Me
O
H
Me
OH
ppm 200
180
160
140
120
100
80
60
40
20
0

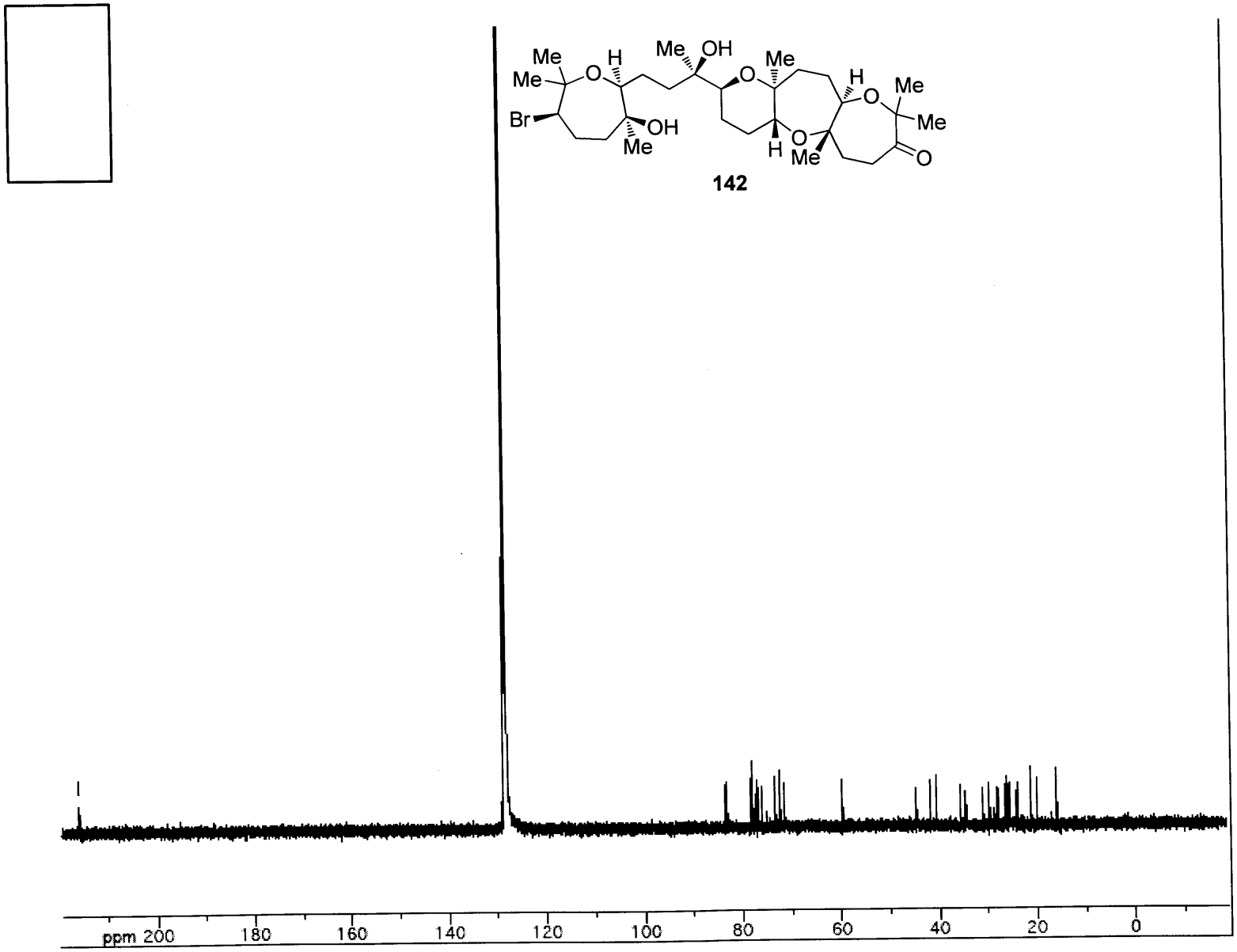


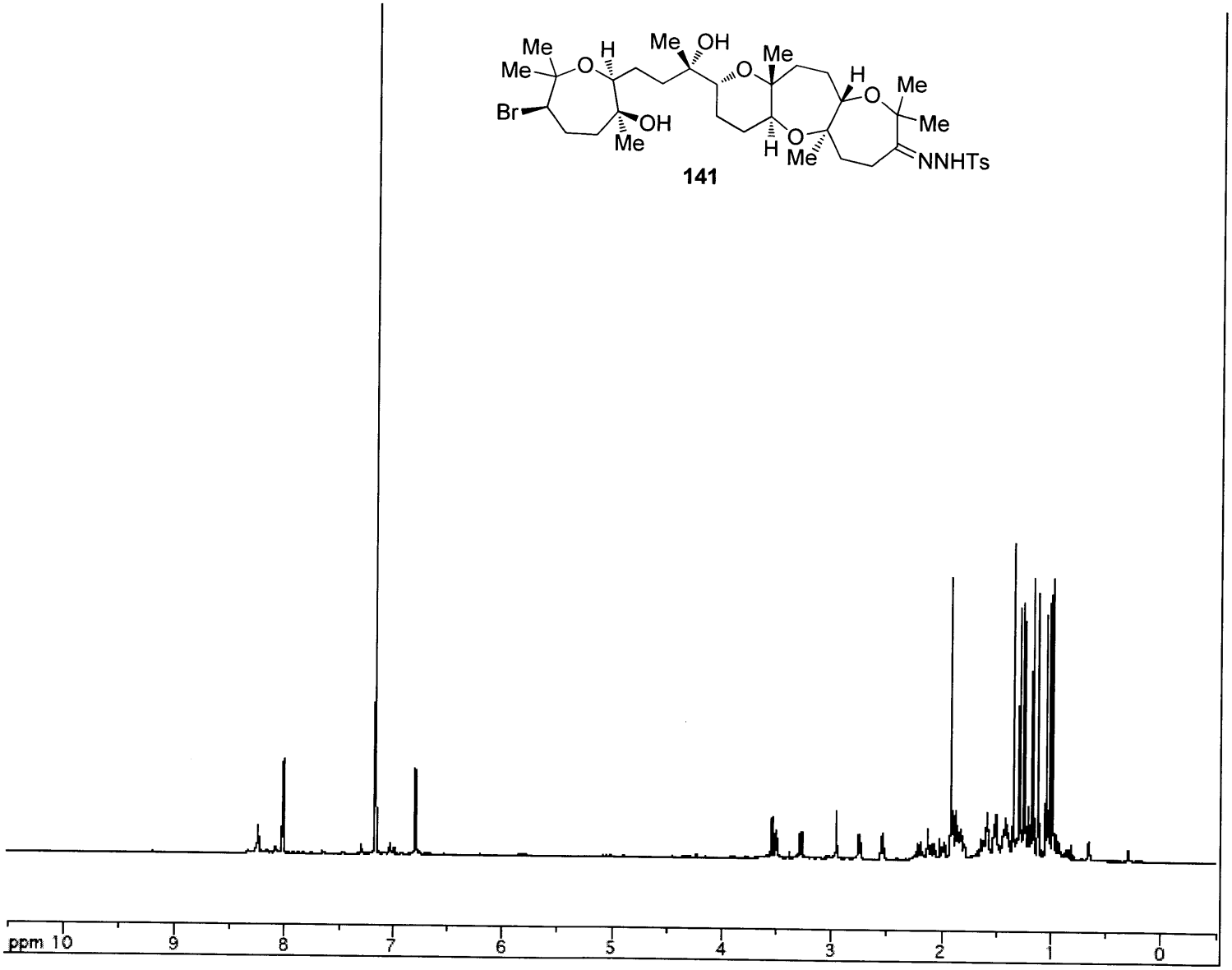
140


Me
Me
O
H
Me
OH
Me
O
Me
H
O
Me
Me
Br
OH
Me
H
O
Me
O
ppm 200
180
160
140
120
100
80
60
40
20
0

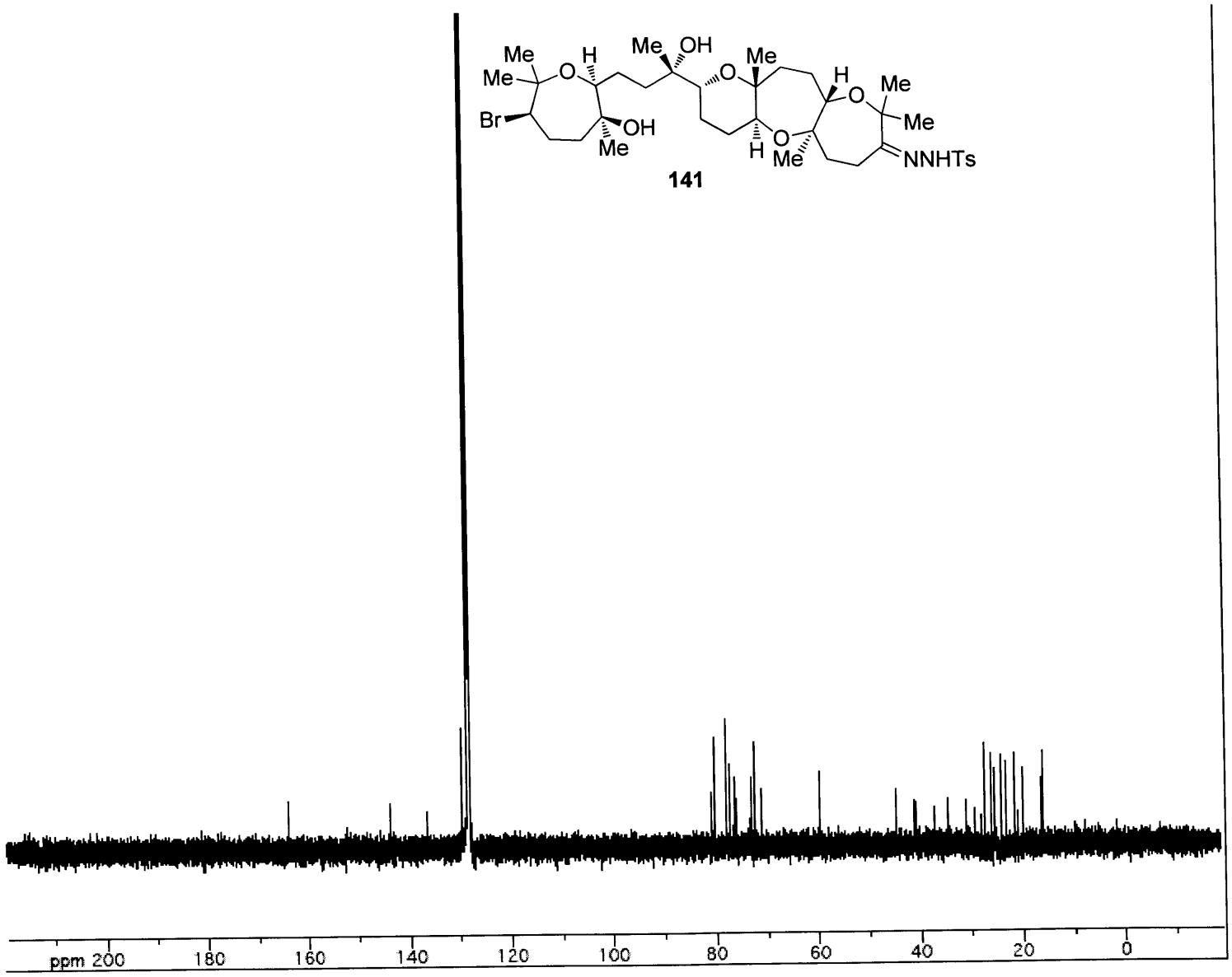
140

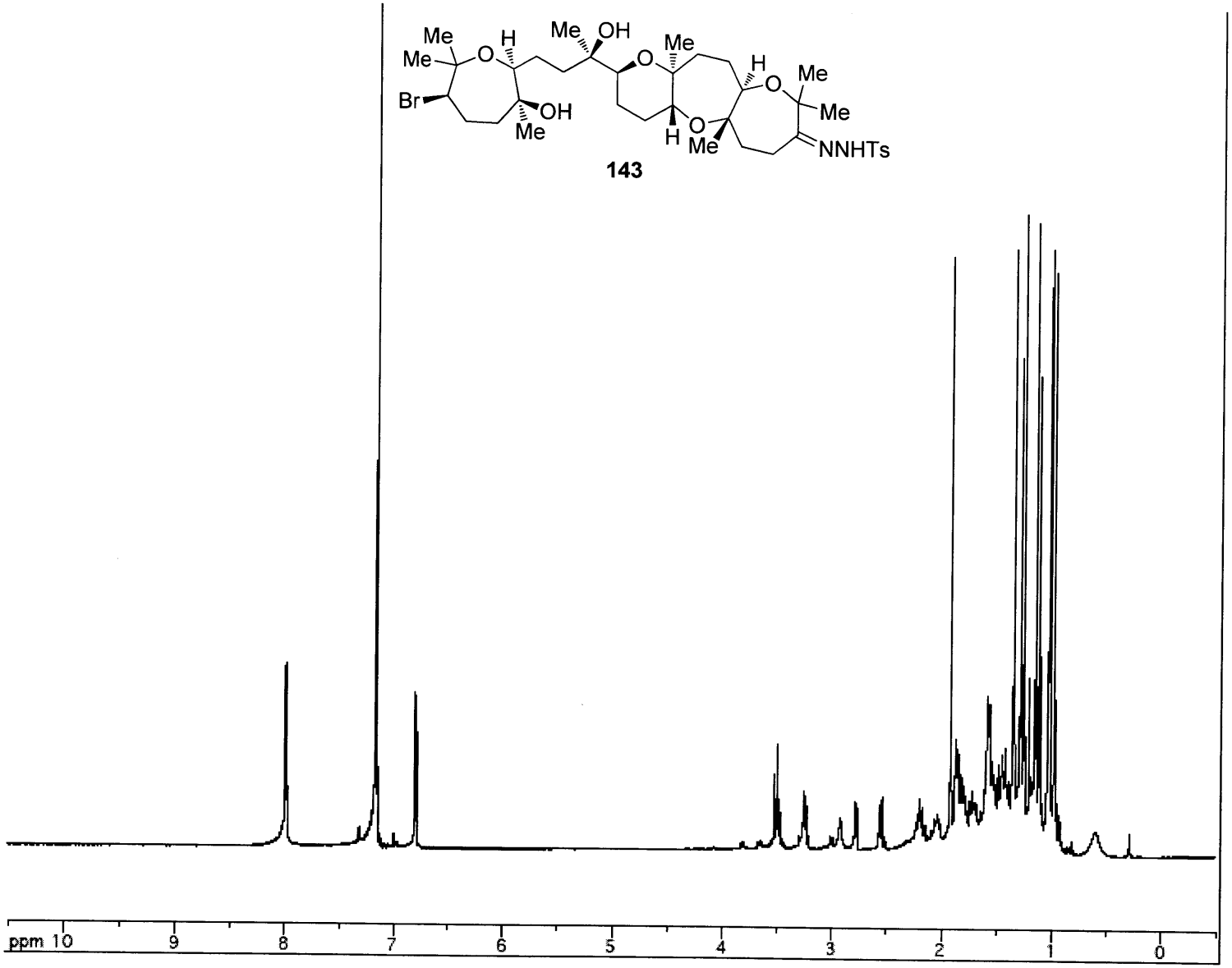

Me
Me
O
H
Me
OH
Me
O
Me
H
O
Me
Me
Br
OH
Me
H
O
Me
O
142
ppm 10
9
8
7
6
5
4
3
2
1
0

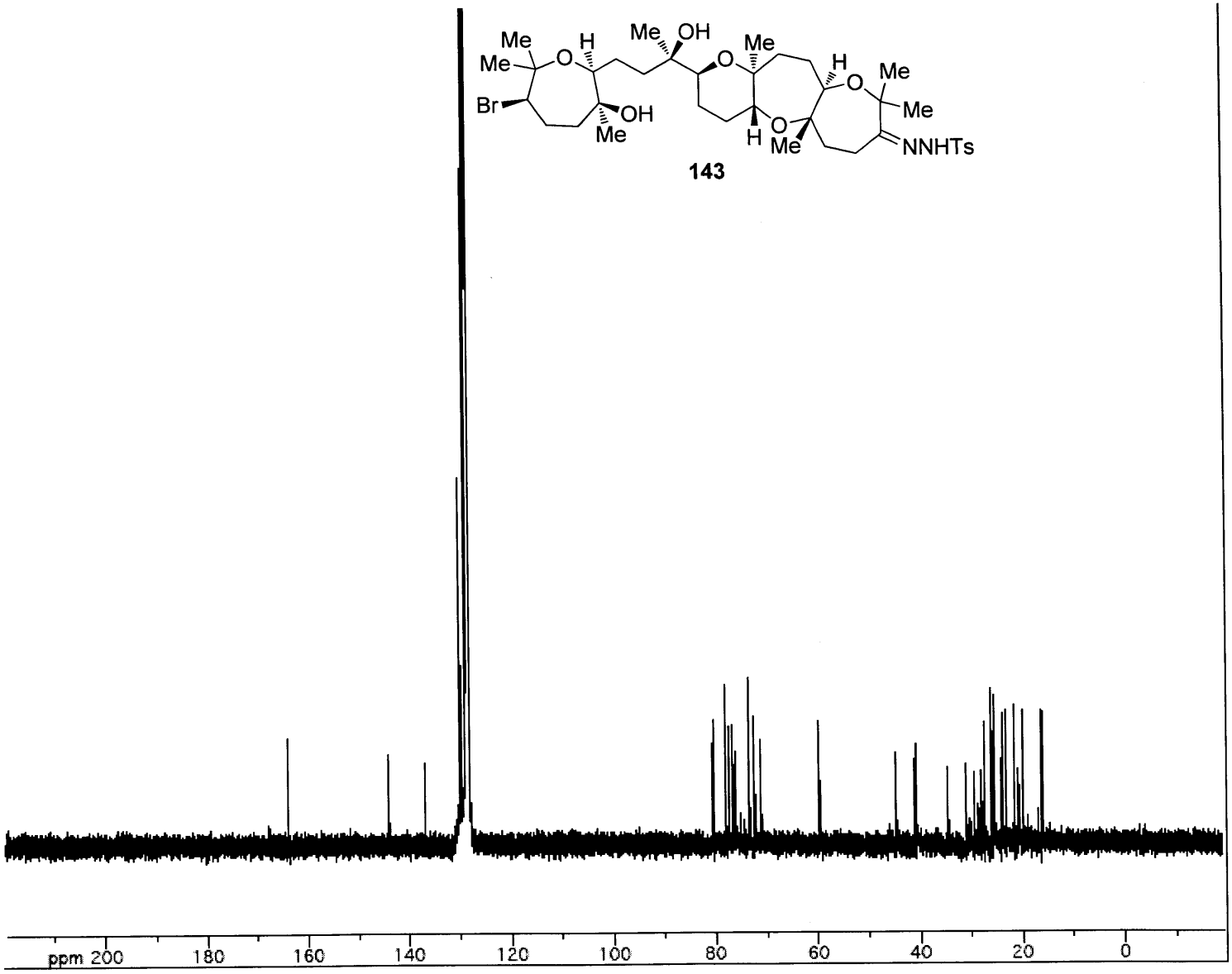

Me
Me
H
O
Me
OH
Br
OH
Me
O
Me
H
O
Me
Me
H
O
Me
O
142
ppm 200
180
160
140
120
100
80
60
40
20
0

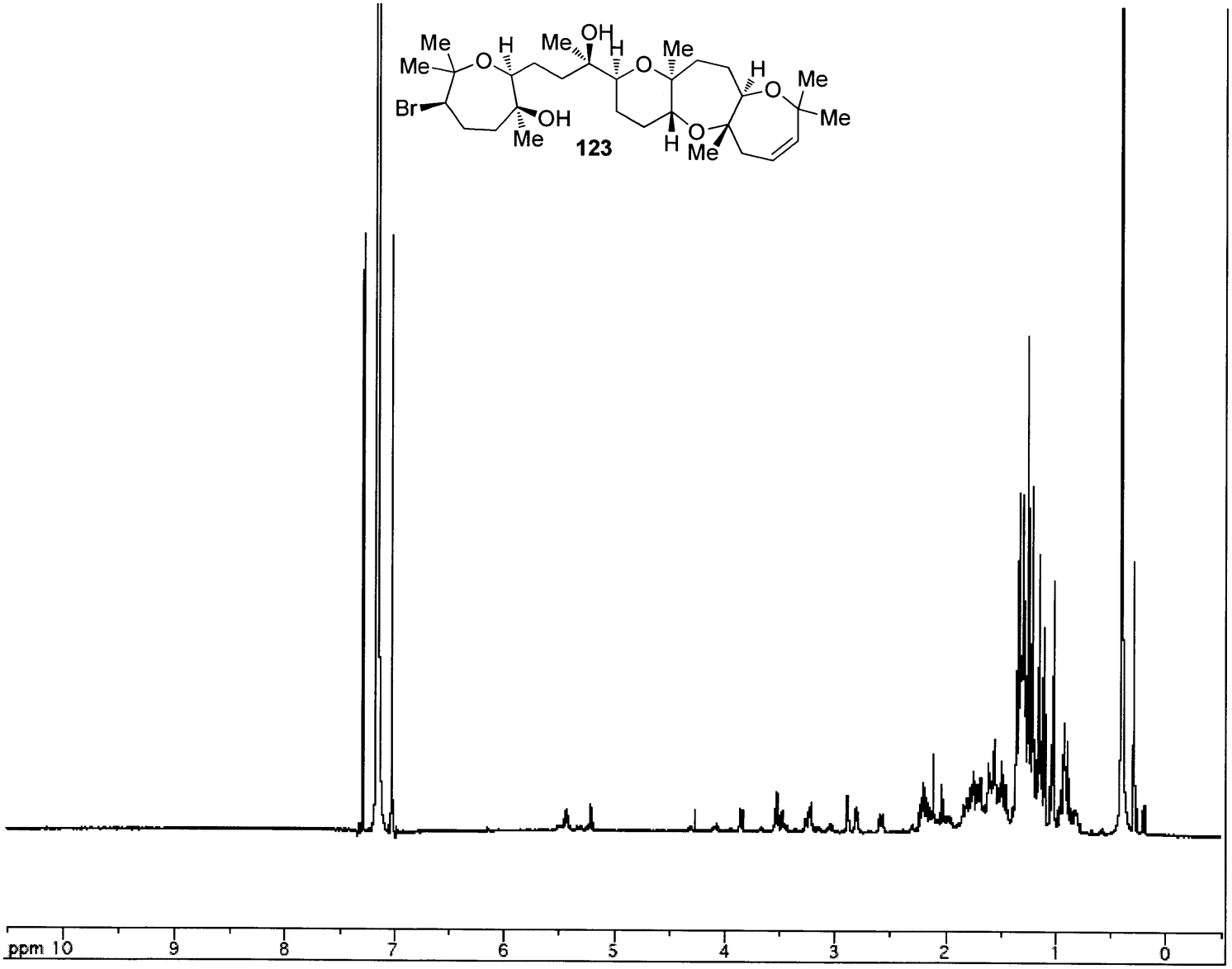


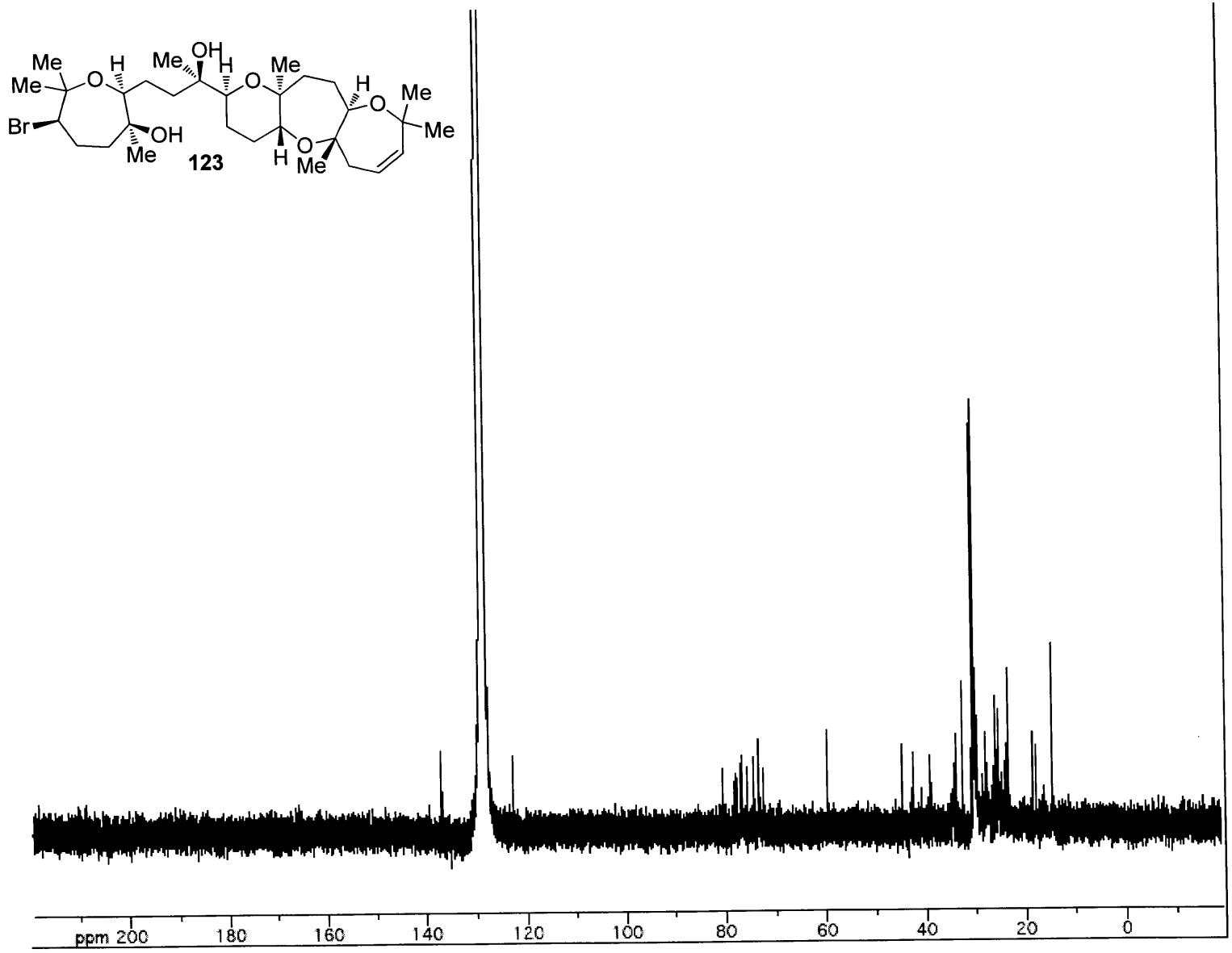
141

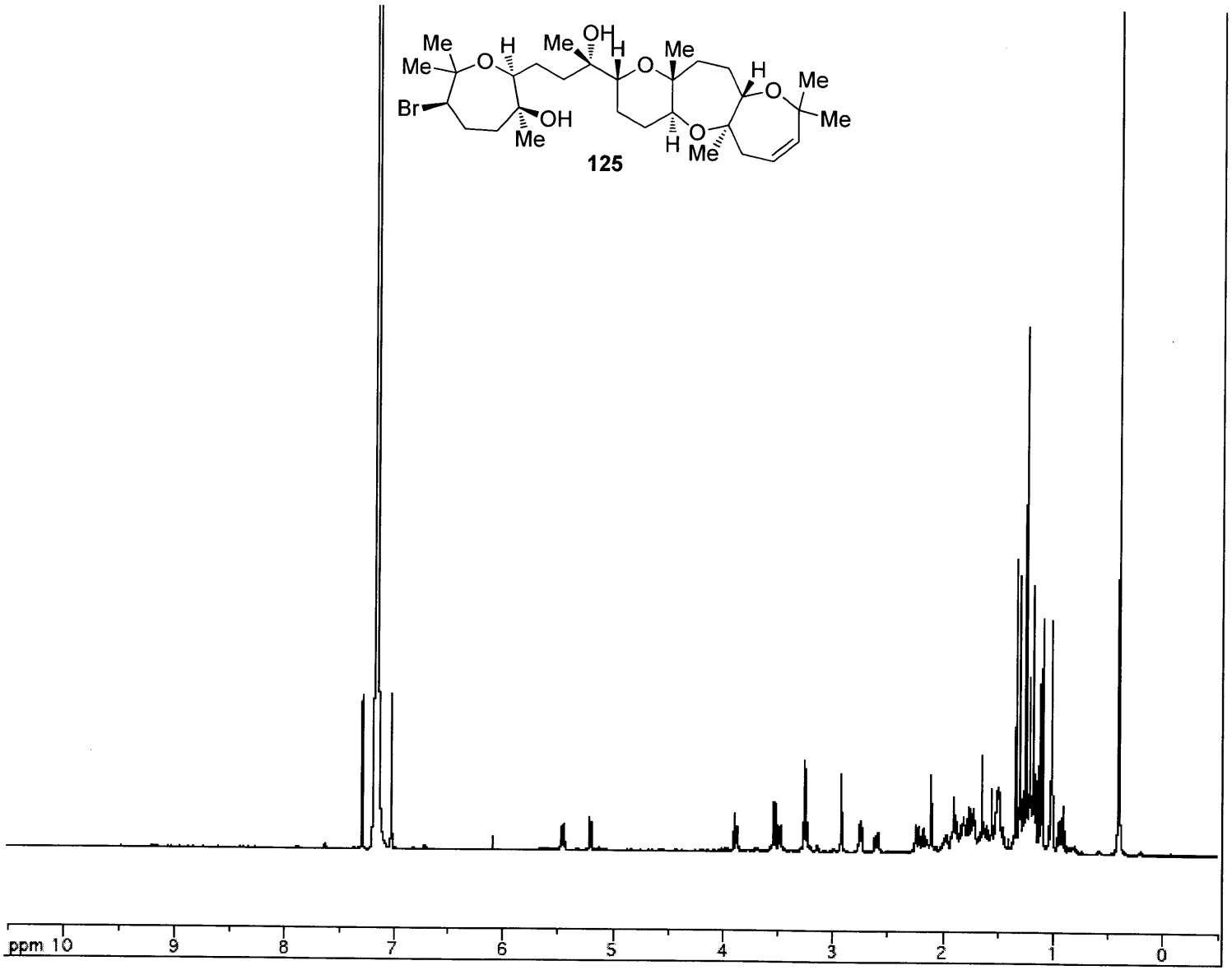

Me
Me
O
H
Me
OH
Me
O
H
O
Me
Me
Br
OH
Me
O
H
Me
NNHTs
141
ppm 200
180
160
140
120
100
80
60
40
20
0

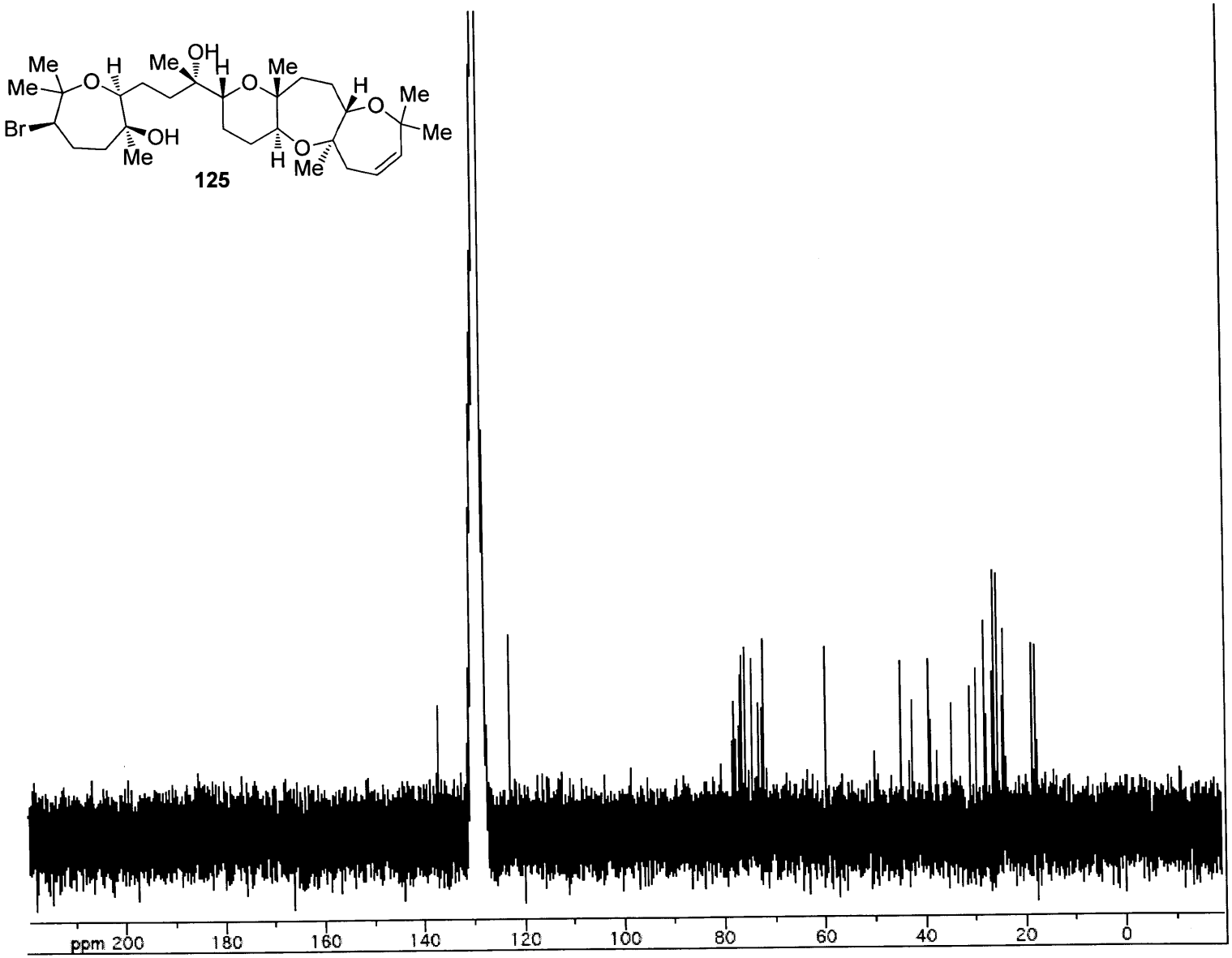

Me
Me
O
H
Me
OH
Br
OH
Me
O
Me
H
O
Me
Me
H
O
Me
NNHTs
143
ppm 10
9
8
7
6
5
4
3
2
1
0

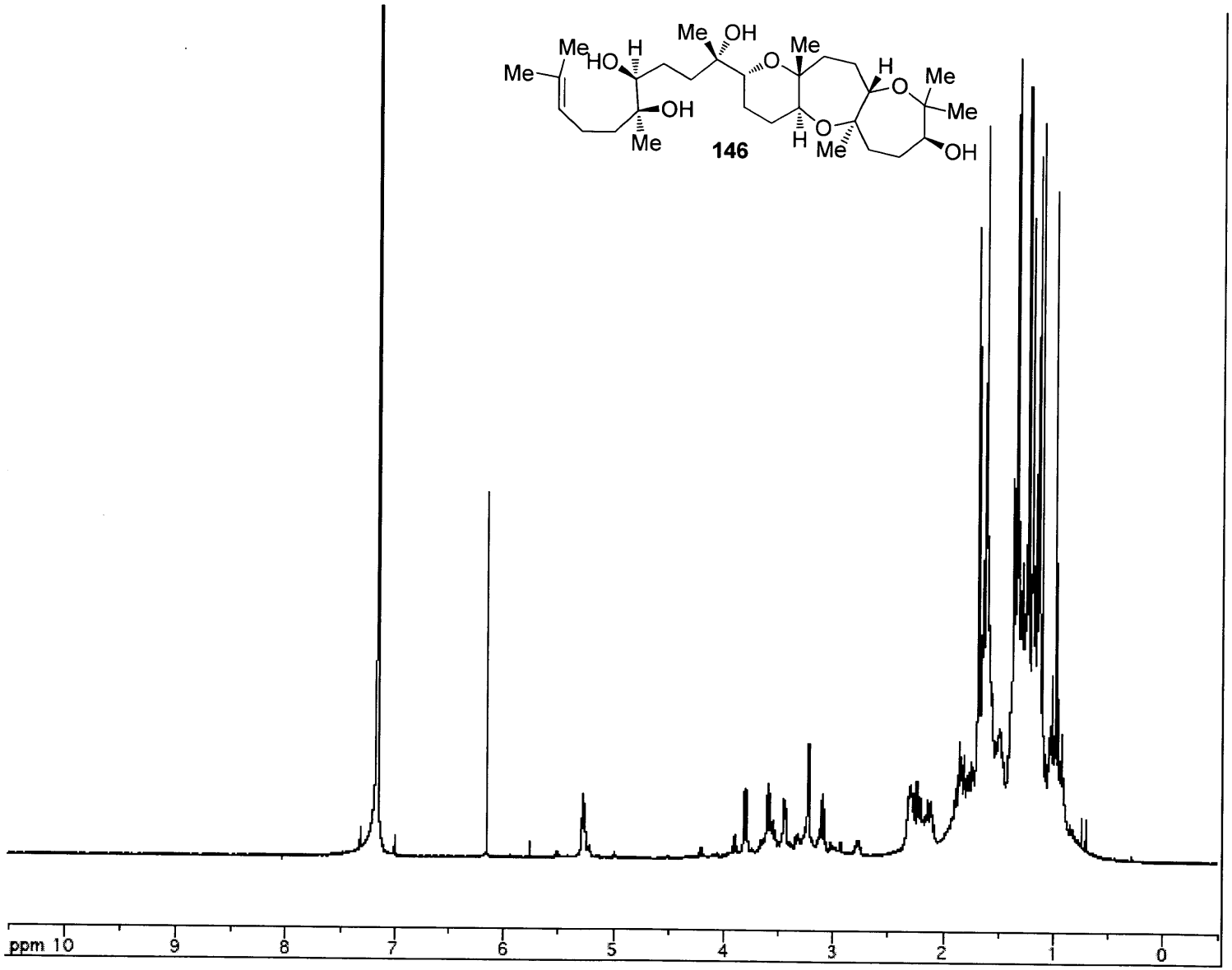

Me
Me
H
O
Me
OH
Br
OH
Me
O
Me
H
O
Me
Me
H
O
Me
NNHTs
143
ppm 200
180
160
140
120
100
80
60
40
20
0

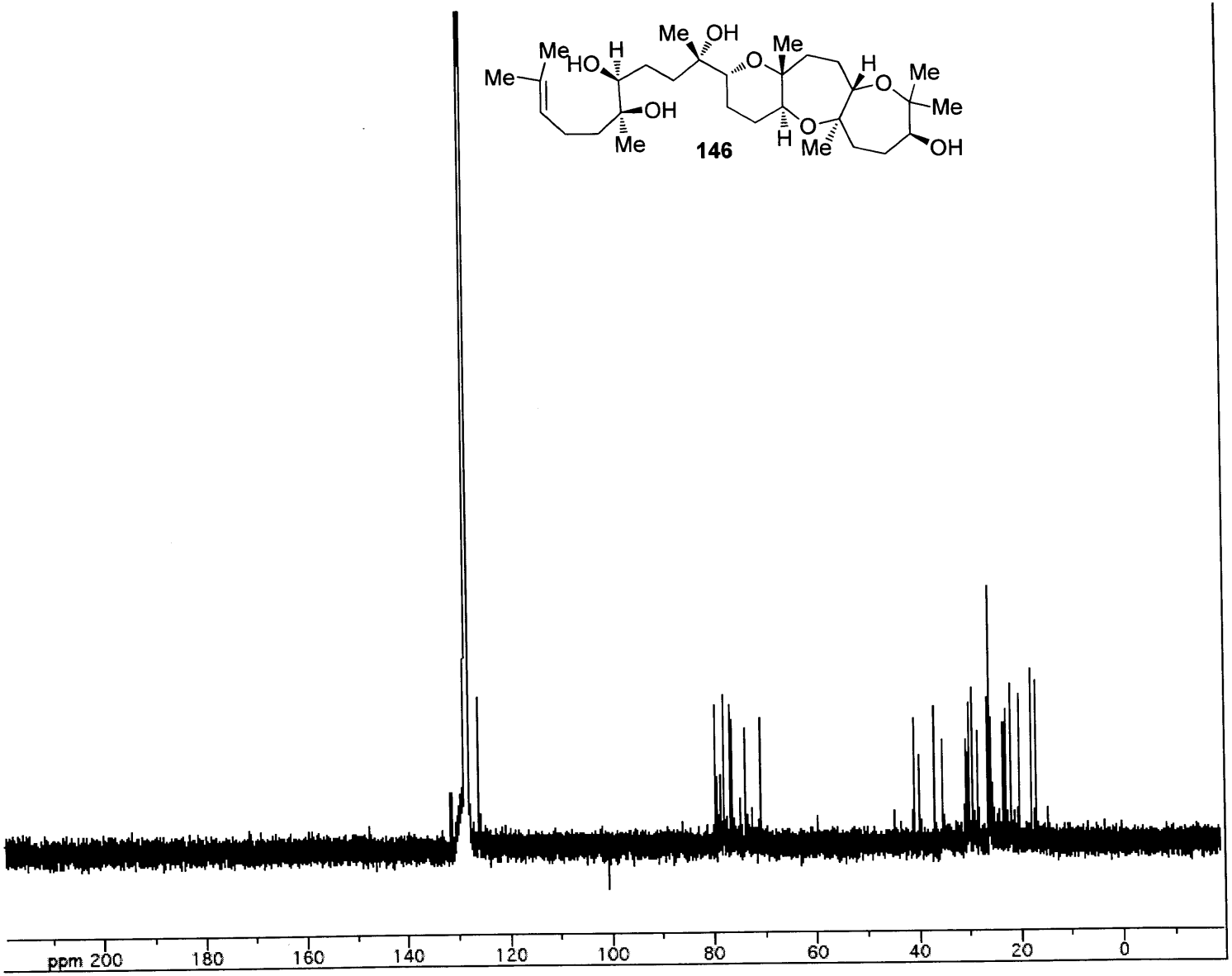

Me
Me
Br
O
H
OH
Me
Me
OH
H
O
Me
H
O
Me
Me
H
O
Me
123
ppm 10
9
8
7
6
5
4
3
2
1
0


Me
Me
O
H
Me
OH
H
O
Me
H
O
Me
Me
Br
OH
Me
123
H
O
Me
ppm 200
180
160
140
120
100
80
60
40
20
0


Me
Me
O
H
Me
OH
H
O
Me
H
O
Me
Me
Br
OH
Me
H
O
Me
Me
125
ppm 10
9
8
7
6
5
4
3
2
1
0


Me
Me
O
H
Me
OH
H
O
Me
H
O
Me
Me
Br
OH
Me
H
O
Me
Me
125
ppm 200
180
160
140
120
100
80
60
40
20
0


Me
HO
H
Me
OH
Me
OH
Me
O
Me
H
O
Me
Me
O
H
Me
OH
Me
146
ppm 10
9
8
7
6
5
4
3
2
1
0


Me
HO
H
Me
OH
Me
OH
Me
O
Me
H
O
Me
Me
OH
Me
O
H
Me
146
ppm 200
180
160
140
120
100
80
60
40
20
0

Brian S. Underwood *Curriculum Vitae*

Department of Chemistry
Massachusetts Institute of Technology
77 Massachusetts Avenue, Bldg.18-205
Cambridge, MA 02139

Phone: (610) 761-3272 (cell)
E-mail: brianu@mit.edu

Education

Massachusetts Institute of Technology, Cambridge, MA 2005-2010
Ph.D. in Organic Chemistry

Thesis: "Synthesis and Determination of the Absolute Configuration of Armatol A Through a Polyepoxide Cyclization Cascade. Revision of the Proposed Structures of Armatol A-F."

Thesis Advisor: Professor Timothy F. Jamison

California Institute of Technology, Pasadena, CA 2001-2005
B.S. in Chemistry and Electrical Engineering

- Graduated with honors in June 2005

Professional Experience

Massachusetts Institute of Technology, Cambridge, MA
Graduate Research Assistant 2005-2010

- Evaluated a variety of approaches to construct squalenoid polyether natural products using epoxide-opening cascade reactions.
- Successfully completed the total synthesis of armatol A and determined the absolute structure of the natural product.

Graduate Teaching Assistant 2005-2006

- Chemistry 5.112, Principles of Chemical Science-Fall 2005
- Chemistry 5.12, Organic Chemistry I-Spring 2006

GlaxoSmithKline, Upper Merion, PA Summer 2004
Intern for Medicinal Chemistry group

- Prepared pharmacologically active compounds for the treatment of Chronic Obstructive Pulmonary Disease.

California Institute of Technology, Pasadena, CA 2002-2004
Undergraduate researcher in the Brian M. Stoltz group

- Synthesized terpenoid systems by expanding the scope of the rhodium-catalyzed Bamford-Stevens Claisen reaction by successive stereoselective addition of substituted isoprene subunits.
- Worked on the development of a tandem [2, 3]-dipolar/oxyanion acetal Claisen rearrangement involving rhodium-catalyzed carbene chemistry.
- Discovered a new reaction mechanism to produce 1,3-diols from β-hydroxy ketones.

Siemens Health Services, Malvern, PA Summer 2001
Intern in the Financial Accounting Support Group

- Helped to implement PeopleSoft Financials and Accounts Payable software.

Publication

- Lainé, D. I.; McCleland, B.; Thomas, S.; Neipp, C.; Underwood, B.; Dufour, J.; Widdowson, K. L.; Palovich, M. R.; Blaney, F. E.; Foley, J. J.; Webb, E. F.; Luttmann, M. A.; Burman, M.; Belmonte, K.; Salmon, M. "Discovery of Novel 1-Azoniabicyclo[2.2.2]octane Muscarinic Acetylcholine Receptor Antagonists," *J. Med. Chem.* **2009**, *52*, 2493-2505.

Presentation

- Underwood, B. S.; Jamison, T. F. *Books of Abstracts*, 234th ACS National Meeting, Boston, MA, August 19-23, **2007**; American Chemical Society: Washington, DC, **2007**; ORGN-245.