Directing Group-Free *endo*-Selective Epoxide-Opening Cascades

by

Ivan Vilotijević

B.Sc. Chemistry
University of Belgrade, 2005

Submitted to the Department of Chemistry
in Partial Fulfillment of the Requirements
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To Stanika, Vaso, Branko and Saša

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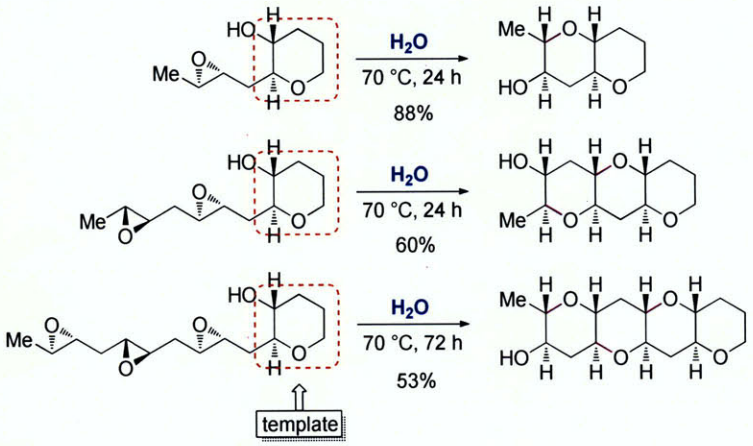
ABSTRACT



The proposed biogenesis of the ladder polyethers features a dramatic series of epoxide opening reactions, elegantly accounts for the structural and stereochemical features of all related natural products, and, in principle, could significantly simplify the synthesis of these extraordinarily complex molecules. In practice, however, such cascades are strongly disfavored, and non-natural directing groups must be covalently attached to each epoxide to overcome this inherent bias. We report herein a general method for directing group-free cascades that also supports the postulated biosynthesis. The two salient aspects of this strategy are a single design principle (a template) and a promoter that both donates and accepts hydrogen bonds. Water is the superior promoter, and it is most effective at approximately pH 7.

Thesis Supervisor: Timothy F. Jamison
Title: Professor of Chemistry

PREFACE

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

Epoxide-Opening Cascades Promoted by Water.
Vilotijevic, Ivan; Jamison, Timothy F. *Science* **2007**, *317*, 1189–1192.

Epoxide-Opening Cascades in Synthesis of Polycyclic Polyether Natural Products.
Vilotijevic, Ivan; Jamison, Timothy F. *Angew. Chem. Int. Ed.* **2009**, *48*, 5250–5281.

The Development of *endo*-Selective Epoxide-Opening Cascades in Water.
Morten, Christopher J.; Byers, Jeffery A.; Van Dyke, Aaron R.; Vilotijevic, Ivan; Jamison, Timothy F. *Chem. Soc. Rev.* **2009**, *38*, 3175–3192.

Synthesis of Marine Polycyclic Polyethers via *endo*-Selective Epoxide-Opening Cascades.
Vilotijevic, Ivan; Jamison, Timothy F. *Mar. Drugs* **2010**, *8*, 763–809.

Biomimetic Synthesis of Polyether Natural Products via Polyepoxide Opening.
Vilotijevic, Ivan; Jamison, Timothy F. In *Biomimetic Organic Synthesis*; Nay, B., Poupon, E. Eds.; Wiley-VCH: Weinheim, 2010; *manuscript submitted for publication.*

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My graduate experience was quite different from what I anticipated when I started my studies at MIT. At times it was a struggle, but most of the time it was inspiring, uplifting, and thrilling. I was fortunate to have the professional and personal support of the people surrounding me throughout my days at MIT. For keeping me on track to finishing my doctoral studies, I owe them my deepest gratitude.

Foremost deserving of credit is my research advisor, Tim Jamison. Tim allowed me to join his team and provided me with remarkable freedom in my research and studies. His perseverance in pursuing *endo*-selective epoxide-opening cascades was not only inspiring but also crucial in driving our success in this field. I am thankful to Tim for constantly stimulating my interests and my scientific development. Furthermore, going beyond what is expected from an academic advisor, he was understanding of me as a person. The knowledge and experience I've gained working with Tim and from his style in managing a group of scientists will, I am confident, be of great help in my future career.

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I could not have chosen a better environment for my graduate work than the Jamison group. Tim has assembled an outstanding group of scientists of various backgrounds with whom I could collaborate and from whom I have learned on a daily basis. During my early days in Jamison lab I was fortunate to have the opportunity to learn from Dr. Graham Simpson, Dr. Neil Langille, Dr. Ryan Moslin, Dr. Chudi Ndubaku and Dr. Sze-Sze Ng. They are all excellent scientists and I wish them all the best in their careers. Ms. Katrina Woodin has always kept the spirits up in our lab, created a friendly atmosphere, and made my freshman experience easier than it could have been.

Research on the epoxide-opening cascades for synthesis of ladder polyethers in the Jamison group during my time in this lab was a collaborative effort of Dr. Graham Simpson, Dr. Aaron Van Dyke, Christopher Morten, Dr. Jeffery Byers, Dr. Alessandro Agosti, Dr. Denise Colby and Satapanawat Sittihan. Graham introduced me to the epoxide-opening project. Chris and Jeff, in particular, contributed to my understanding of these processes. Although Chris joined the group a year after I started, his knowledge and skills excelled rapidly and, towards the end of my stay in the Jamison group, I found myself learning from him and his contributions to the project. I have utmost respect for the way Chris conducted his work and the diligence he showed. When Jeff joined the project, he brought a new perspective to our research. The problems he tackled

while working on this project are truly difficult and I have always admired his ability to come up with and implement creative solutions. My departure from MIT is easier knowing that the epoxide-opening cascades in synthesis of ladder polyethers project remains in the capable hands of Dr. Denise Colby and Pat Sittihan.

A surprisingly large number of students and postdocs have passed through the Jamison lab during my stay at MIT. Each one contributed to my learning and knowledge of chemistry with their expertise and willingness to share. Many deserve more than a single line in this text. Among those that departed while I was at MIT, I wish to thank Dr. Megan Foley, Dr. Andrew Lauer, Dr. Yutaka Ikeuchi, Nikolas Huwyler, Dr. Azusa Kondoh, Ngan Nguyen, Yuta Nishina, Dr. Lukas Brändli, Dr. Victor Gehling, Yu Hinata, Brian Sparling, Dr. Hirohisa Ohmiya, Kazuhiko Nakano, Dr. James Trenkle, Dr. Chun-Yu (Jason) Ho, and Dr. Stefan Kaiser. Among those that are still doing research in the Jamison group, I'd like to thank Brian Underwood, Kristin Schleicher, Jessica Tanuwidjaja, Kurt Armbrust, Hyung-Kyoo Kwon, Dr. Matt Bedore, Dr. Adam Sniady, Dr. Ryosuke Matsubara, Dr. Andreas Tschöp, Dr. Damien Webb, Dr. Andrew Leduc, Dr. Prakash Palde, and Dr. Thomas Steinlin.

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Going home after work was much easier knowing that my housemates, Vijay Kumar Sreenivasa Gopalan and Sharat Chikkerur, will be there for a late night conversation and an occasional night out on the town. Their friendship means more to me than they can imagine and I hope our paths will cross again in future. Many of my close friends from Serbia studied in Boston during my stay at MIT. I enjoyed the time spent in company of Jelena Lukić, Zoran Popović and Iva Perović. Dragan Mihajlović, Vesna Vuksan, Valentina Karas and Eleana Kazantzoglou have remained close friends despite the physical distance between us. I am particularly grateful to Vladimir Petrović and Marko Jovanov for their company and support during most of my time at MIT.

My parents and brother have always been there to support me and help me in every possible way. Anything I could write would be an inadequate attempt to thank them for all they have given me. The same is true for my beloved Saša who's been my companion and best friend for the past 7 years. Every day, I try to be the person worth the sacrifice, care and attention that my family, friends, colleagues and mentors have given me.

Ivan Vilotijevic
Cambridge, May 2010

TABLE OF CONTENTS

ABBREVIATIONS

Ac - acetyl

Bn – benzyl

BIPHEN - 3,3'-di-*tert*-butyl-5,5',6,6'-tetramethylbiphenyl-2,2'-diol

BOM - benzyloxymethyl

Bu - butyl

CSA - camphorsulfonic acid

DDQ - 2,3-dichloro-5,6-dicyanobenzoquinone

DMAP - 4-dimethylaminopyridine

DMF - *N*,*N*'-dimethylformamide

DMM - dimethoxymethane

DMSO - dimethylsulfoxide

dr - diastereomeric ratio

DTBMP - 2,6-di-*tert*-butyl-4-methylpyridine.

EDTA - ethylenediaminetetraacetic acid

ee - enantiomeric excess

EI - electron ionization

ESI - electron spray ionization

Et - ethyl

EtOAc - ethyl acetate

g - gram(s)

h - hour(s)

HFIP - hexafluoro-*iso*-propanol

HMDS - hexamethyldisilazane

HPLC - high-performance liquid chromatography

HRMS - high-resolution mass spectrometry

imid. – imidazole

LiHMDS - lithium bis(trimethylsilyl)amide

m-CPBA - 3-chloroperoxybenzoic acid

Me - methyl

mg - milligram(s)

min - minute(s)

mol - mole

MOM - methoxymethyl

MS - molecular sieves

n-Bu - *n*-butyl

nm - nanometer

NMR - nuclear magnetic resonance

NOESY - nucler Overhauser effect spectroscopy

Ph - phenyl

PMB - *para*-methoxybenzyl

PPTS - pyridinium *p*-toluenesulfonate

Pr - propyl

Pyr - pyridine

r.t. – room temperature

TBAF - tetrabutylammonium fluoride

TBAI - tetrabutylammonium iodide

TBDPS - *tert*-butyldiphenylsilyl

TBS - *tert*-butyldimethylsilyl

TES - triethylsilyl

Tf - trifluoromethanesulfonyl

TFA - trifluoroacetic acid

THF - tetrahydrofuran

THP - tetrahydropyran

TIPS - triisopropylsilyl

TLC - thin layer chromatography

TMEDA - *N*,*N*,*N*',*N*'-tetramethylethylenediamine

TMS - trimethylsilyl

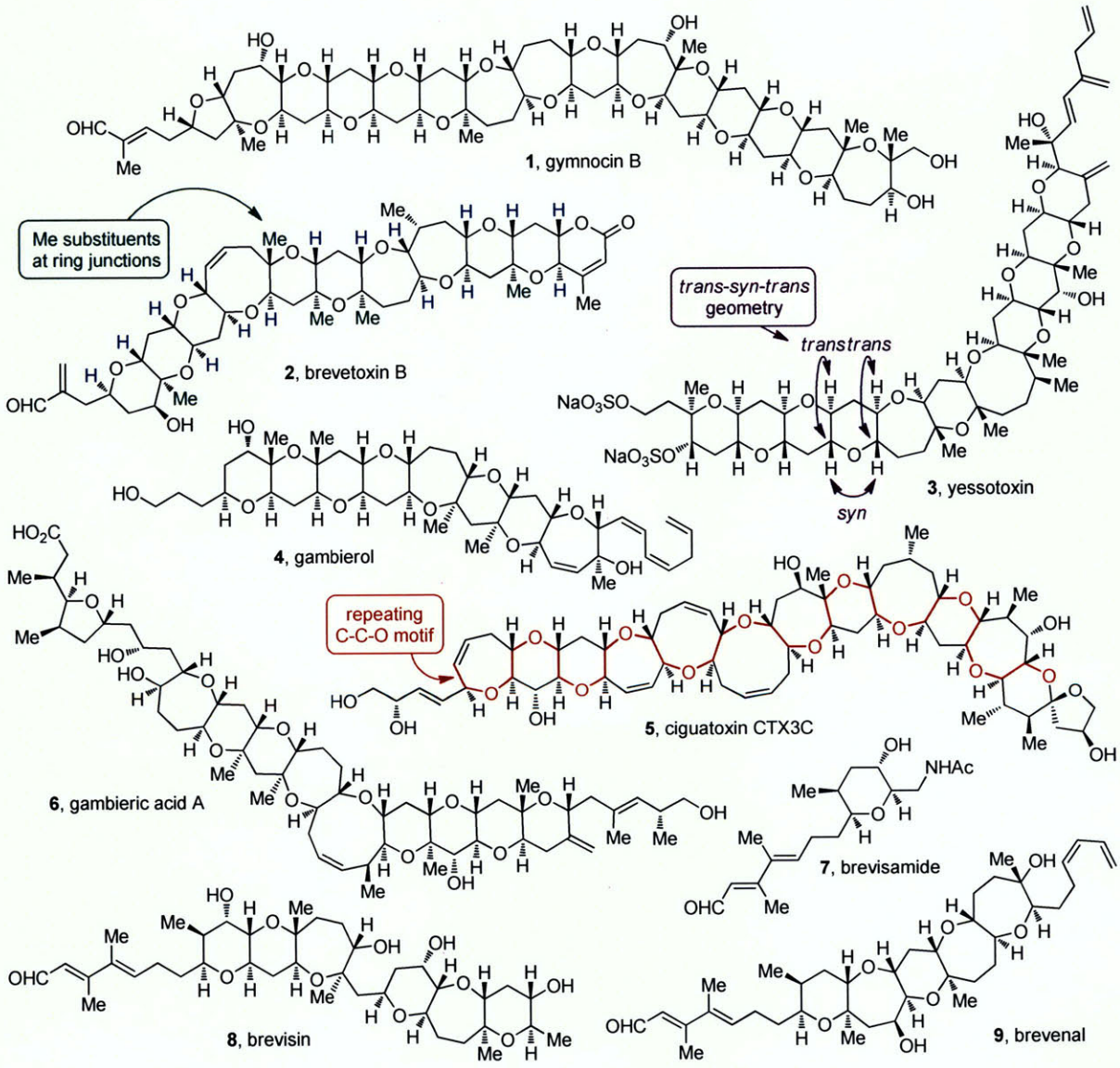
Introduction

Ladder polyether natural products are among the active constituents of many harmful algal blooms, marine phenomena also known collectively as red tides. They poison and devastate fish, mammal, bird, and other marine populations off the coasts of regions as disparate as Tahiti, Japan, Vietnam, New Caledonia, and the United States, crippling the fishing, tourism, and other industries that depend on their continued health. Some marine species not affected by red tides accumulate and, occasionally, further elaborate the toxins,[1,2] transferring them up the food chain, resulting in human poisoning by ingestion of shellfish exposed to a red tide.[3] These molecules exhibit diverse biological activities ranging from extreme toxicity[4-6] to anti-cancer[7-9] and antifungal[10,11] properties. Recently, a member of this family, brevenal (**9**, Figure 1), has been shown to protect fish from the neurotoxic effects of brevetoxins,[12,13] and has been identified as a potential therapeutic for cystic fibrosis.[14,15] While their mode of action is not well understood on the molecular level, it is known that brevetoxins (i.e., **2**) and ciguatoxins (i.e., **5**) bind and disrupt voltage-sensitive sodium channels,[16-20] gambierol (**4**) blocks voltage-gated potassium channels,[21] and maitotoxin causes influx of calcium ions into cells that in turn causes uncontrolled secretion of neurotransmitters and severe muscle contractions.[22-25] Binding of yessotoxin (**3**) to the transmembrane α-helix of glycophorin A causes the dissociation of oligomeric protein.[26]

The ladder polyether family of natural products consists of molecules featuring anywhere from 4 to 32 five- to nine-membered fused cyclic ethers (Figure 1). While most ring junctions are substituted with two hydrogens, many bear a methyl substituent in place of one of the hydrogens. The first isolated member of this family, brevetoxin B (**2**), was reported by Nakanishi and Clardy in 1981.[27] It was followed by numerous others, including maitotoxin, the largest

nonpolymeric molecule isolated from natural sources to date.[28-30] The minimal availability combined with the unprecedented size of ladder polyethers have inspired herculean endeavors in the isolation and structural characterization of these compounds, and have pushed the limits of analytical methods, including chromatography, mass spectrometry, NMR, and X-ray diffraction.[31]

Figure 1. Structures of representative ladder polyether natural products.

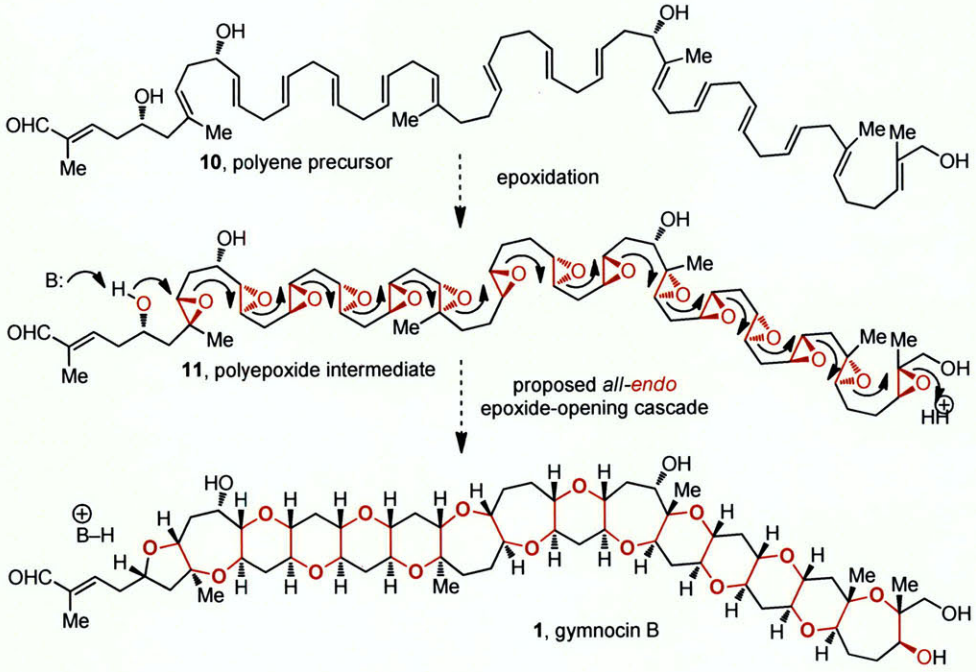


Although they are among the most complex secondary metabolites ever characterized, all ladder polyethers possess a structural pattern and stereochemical regularity that confer upon them a certain degree of simplicity. A backbone of repeating oxygen–carbon–carbon (O–C–C) units extends from one end of the polyether network to the other, regardless of the size of the intervening rings and of any functional groups present on the rings (**5**, Figure 1). The ladder topography is the consequence of consistent *trans* stereochemistry across the carbon-carbon bonds of the ring junctions, coupled with the relative *syn* configuration of adjacent junctions (**3**, Figure 1).

About 25 years ago, Nakanishi put forth a hypothesis that accounts for structural and stereochemical similarities among ladder polyethers (although similar proposals were advanced contemporaneously by Shimizu[32] and Nicolaou[33,34]). Nakanishi[35] hypothesized that these similarities are a direct consequence of their biosynthetic origin, and proposed that they arise through the transformation of a polyepoxide into a ladder polyether via a series or cascade of epoxide-opening events (Figure 2). The oxygen and two carbon atoms of each epoxide constitute the C–C–O backbone, and with the proviso that all of the ring openings proceed with inversion of configuration at each epoxide derived from an *E* alkene, the *trans-syn* topography can be explained by this mechanism. All alkenes in a hypothetical polyene precursor **10** would require identical stereoselectivity of epoxidation to produce either an all-(*S*,*S*) or all-(*R*,*R*) polyepoxide, suggesting that a single promiscuous oxidase could be sufficient.[36] Despite its intellectual appeal, the hypothesis relies upon a ring-opening process generally regarded to be disfavored. With few exceptions, epoxide-opening reactions of this type favor the smaller heterocycle, not the larger one. This means that the biosynthetic cascade that transforms polyepoxide precursor **11** to

gymnocin B would have to overcome fifteen consecutive disfavored epoxide opening steps (Figure 2).

Figure 2. Nakanishi's hypothesis in biosynthesis of gymnocin B.



In an effort to shed some light on the validity of Nakanishi's hypothesis, labeling studies have been reported for brevetoxin B,[37,38] brevetoxin A,[32] and yessotoxin.[39] These studies corroborated the polyketide origin of ladder polyethers, which is also supported by genetic studies,[40-43] but did not illuminate any subsequent epoxidation or cyclization steps. Some remote evidence in support of this hypothesis can be taken from biosynthetic studies on a related natural product, okadaic acid,[44,45] and isolation of 27,28-epoxybrevetoxin B from *Karenia brevis*.[46] The intriguing new natural products brevisamide (**7**, Figure 1),[47] a member of this family that features a single cyclic ether, and brevisin (**8**, Figure 1),[48] an aberrant polycyclic polyether with two distinct ring systems, have recently been isolated from *K. brevis*. Their structures differ from the majority of known polyethers, underlining the remarkable diversity of polyether structures found

in nature, and may help further the understanding of biosynthetic pathways involved in production of ladder polyethers.

According to a modification of Nakanishi's hypothesis by Spencer, biosynthesis of ladder polyethers might also proceed in an iterative fashion through the repeated action of a monooxygenase and an epoxide hydrolase enzymes with broad specificities.[36] In this scenario, rings of a ladder polyether molecule would be formed sequentially, each being formed immediately after the epoxidation of the appropriate *E*-alkene in the biosynthetic precursor, thus avoiding the polyepoxide intermediate proposed by Nakanishi. Giner's proposal[49,50] and Townsend-McDonald hypothesis[51,52] also suggest iterative pathways in biosynthesis of ladder polyethers from all-*Z* polyene precursors without evoking epoxide intermediates.

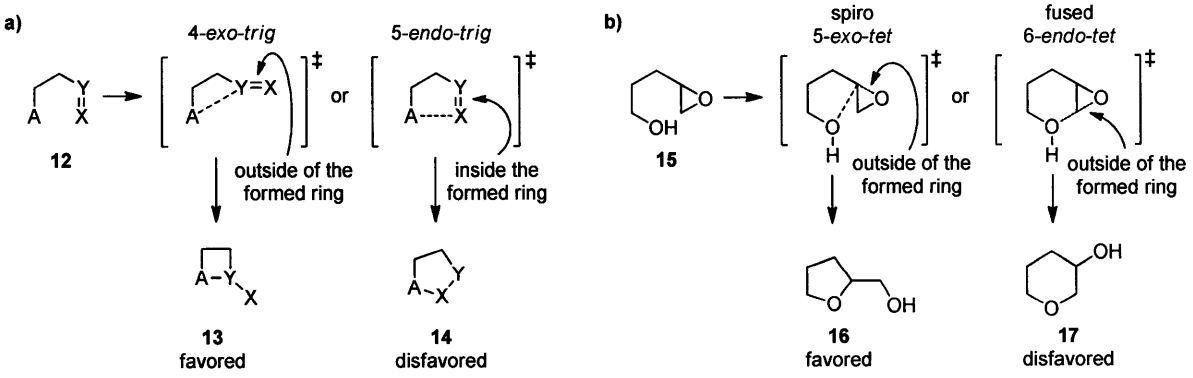
Nakanishi's hypothesis remains speculative due to the lack of strong experimental support in its favor. However, the stereochemical uniformity inferred from the polyene to polyepoxide to ladder polyether pathway has served as the basis for structural reassignment of brevenal,[53,54] and the speculative structural reassignment of the largest known natural product, maitotoxin.[36,55,56]

That there is little evidence to support this two-decade-old hypothesis has not deterred efforts to emulate such cascades. The structural challenges associated with synthesizing these molecules have stimulated development of many novel synthetic methodologies.[34,57-59] As in all complex molecule synthesis, convergence has been emphasized in the synthesis of ladder polyethers, and the prevalent strategy is the ring formation via cyclization or annulation steps, followed by the piecing together of ring systems, usually two to five rings at a time. However, cascade reactions are outstanding tools for improving the economy and efficiency of synthesis and, even among cascades, the proposed two-step conversion of polyene **10** to gymnocin B

(Figure 2) scores remarkably highly in terms of key synthetic principles such as step economy and atom economy.

The *in vitro* emulation of this proposal for the rapid assembly of multiple rings would greatly streamline the synthesis of ladder polyethers, however, the requisite disfavored regioselectivity of epoxide openings remains the major obstacle in attaining this goal. According to Baldwin's rules,[60,61] empirical guidelines for evaluation of ring forming processes, the favored ring-closing reactions are those in which the length and nature of the linking chain enable the terminal atoms to achieve the proper geometries for the reaction. The disfavored ring closing processes require distortions of bond angles and bond distances, rendering these reaction pathways higher in energy. For instance, 5-*endo*-trig ring closing reactions are predicted to be disfavored over 4-*exo*-trig reactions (Figure 3a).

Figure 3. Baldwin's rules: (a) general classification. (b) in intramolecular epoxide opening.



Baldwin's rules were not specifically formulated for epoxide-opening reactions.[61] However, intramolecular epoxide openings tend to follow rules that lie between those for tetrahedral and trigonal systems, generally favoring the *exo* processes, which proceed via spiro transition state (Figure 3b). Intramolecular epoxide-opening reactions, with few exceptions, favor the smaller over the larger heterocycle (e.g., tetrahydrofuran **16**, produced via a spiro transition state over the

tetrahydropyran **17**, from a fused transition state, Figure 3b). Baldwin's rules classify the fused and spiro transition states as *endo* and *exo*, respectively. However, because the epoxide C-O bond that breaks is outside the newly formed ring in both cases, each may also be considered to be an *exo* process under the same construct (Figure 3b). To avoid potential confusion, the terms "fused" and "spiro" that describe transition states leading to *endo* and *exo* products respectively can be used instead.

Epoxides have long been regarded to be useful and highly versatile intermediates in organic synthesis and many efficient methods for enantioselective epoxidation have been developed. The Sharpless asymmetric epoxidation of allylic and homoallylic alcohols,[62,63] Jacobsen epoxidation,[64-67] and the Shi epoxidation of unactivated alkenes,[68-71] in particular, represent irreplaceable tools for investigations of epoxide-opening cascades. To efficiently utilize epoxides as synthetic intermediates, effective ways to control the regioselectivity in epoxide-opening reactions are necessary. As described earlier, the *exo* mode of cyclization is typically preferred; therefore, methods to facilitate *endo* cyclization have constituted a particularly active area of research.

Previous Syntheses of THP Rings via *Endo*-Selective Epoxide Opening

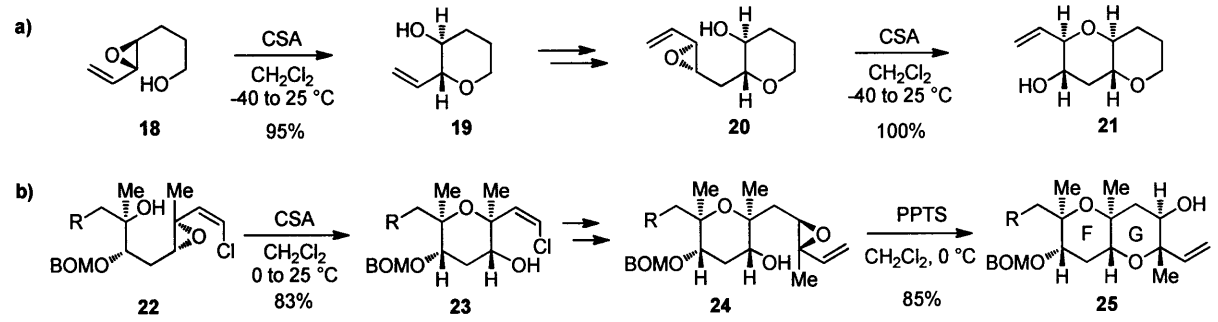
Most of the approaches to promote the desired, *endo* outcome of intramolecular epoxide openings rely on the effects of directing groups covalently attached to the epoxides. When chosen and positioned properly, the epoxide substituents provide an electronic bias, favoring *endo* cyclization and formation of the larger ring. These directing groups act either by stabilizing the desired transition state or, alternatively, by slowing the undesired cyclization pathway, thus promoting regioselective nucleophilic attack.

Reactions of electronically biased epoxides

Alkenylepoxides

Pioneering studies on the activation of the 6-*endo* over the 5-*exo* epoxide-opening pathway in intramolecular reactions of 4,5-epoxy alcohols were reported by Nicolaou.[72] The epoxy alcohol **18** bearing an alkenyl directing group undergoes Brønsted acid-catalyzed cyclization with excellent *endo* selectivity due to the ability of the alkenyl substituent to stabilize the partial positive charge in the transition state for *endo* cyclization (Scheme 1a).[73] These reactions established the first well-defined and predictable routes to tetrahydropyran systems via 6-*endo* epoxide opening.

Scheme 1. (a) Activation of the 6-*endo* over the 5-*exo* epoxide-opening pathway in alkenylepoxides. **(b)** Iterative synthesis of the FG fragment of brevetoxin B. R= prenyl.



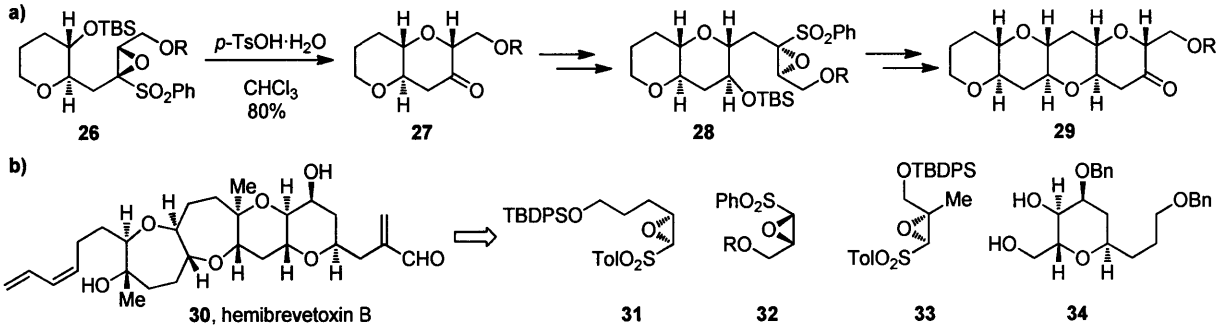
Additional flexibility in this methodology comes from the opportunity to fine tune the reactivity of the epoxide by changing the electronic characteristics of the alkenyl group (*i.e.*, unsaturated ester vs. vinyl halide).[73] The fact that disubstituted epoxides are generally considered to be good substrates in these reactions, together with various options for further elaboration of the alkenyl substituents of the reaction products made this approach a standard tool for the construction of tetrahydropyran rings of ladder polyethers. This approach has been utilized by the groups of Nicolaou, Yamamoto, Nakata, Mori, and Sasaki in their syntheses of hemibrevetoxin B,[74-77] brevetoxin B,[78-80] brevetoxin A,[81-85] gambierol,[86-88] and brevenal.[53,54]

Although not amenable to more than one epoxide-opening at a time, this approach was instrumental in various iterative syntheses of ladder polyethers and their fragments. The Nicolaou group utilized this methodology to prepare the FG fragment of brevetoxin B during the first total synthesis of a ladder polyether natural product.[89] Nicolaou's approach includes sequential acid-catalyzed openings of alkenyl epoxides to form both the F and G rings of brevetoxin B (Scheme 1b). Epoxy alcohol **22** was efficiently transformed to a corresponding tetrahydropyran **23** which could then be elaborated to **24**. Subsequent Brønsted acid-catalyzed epoxide opening of **24** affords **25**, containing the F and G rings of brevetoxin B.

α,β-Epoxysulfones

A conceptually orthogonal approach to the construction of tetrahydropyran rings via 6-*endo* intramolecular epoxide-openings was reported by Mori. Instead of activating the 6-*endo* pathway, the Mori group used sulfonyl substituents on the epoxide to destabilize the transition state that would lead to 5-*exo* epoxide opening.[90] Exposure of epoxysulfone **26** to Brønsted acids affords ketone **27** via 6-*endo* cyclization and subsequent loss of phenylsulfonate (Scheme 2a). A sequence involving alkylation of the sulfone-stabilized *cis*-oxyranyl anion completes the homologation process to **28**, the next epoxysulfone primed for *endo* selective cyclization. Repeating this procedure three times leads to formation of tetrad **29**. An obvious limitation of this approach is the inability to incorporate substituents other than sulfonyl group at the position of 5-*exo* attack. This may be circumvented via the addition of organomagnesium reagents to the ketone formed after cyclization, a reaction that typically proceeds with good stereoselectivity to ultimately produce fully substituted *trans*-fused fragments of ladder polyethers.[91]

Scheme 2. (a) Synthesis of oligotetrahydropyran fragments via iterative 6-*endo* cyclizations of epoxysulfones and **(b)** application in synthesis of hemibrevetoxin B. R= TBDPS.



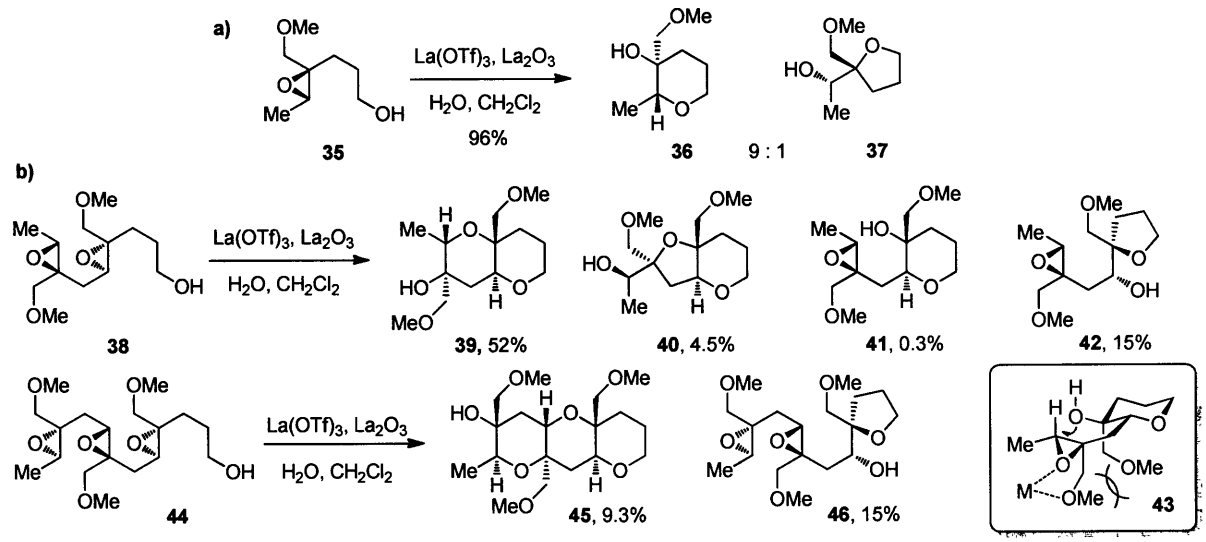
The tetrahydropyranones produced in reactions developed by the Mori group are amenable to a single-carbon homologation effected by trimethylsilyldiazomethane to produce ring expanded, seven-membered cyclic ethers.[92] Mori and coworkers took advantage of this feature in the iterative synthesis of the ABCDEF ring system of the yessotoxins and adriatoxins,[93] and in the total syntheses of gambierol[86] and hemibrevetoxin B (Scheme 2b).[74,94] To introduce methyl substituents at the ring junctions of polyethers like **30** efficiently, Mori has developed two strategies.[95] The first requires elaboration of a 3-ketooxepane to a corresponding 3-methylideneoxepane, followed by epoxidation and reduction of the epoxide with lithium triethylborohydride.[93] The other method is the inherently more convergent incorporation of a methyl substituent into the epoxysulfone **33** that installs the methyl groups prior to formation of the cyclic ether.

Methoxymethyl substituted epoxides

The Murai group has reported a cascade approach to the synthesis of ladder polyethers involving *endo*-selective, lanthanide-promoted opening of epoxides bearing methoxymethyl groups. When epoxy alcohol **35** is treated with $La(OTf)_3$ in the presence of 2.2 equivalents of water in dichloromethane, it undergoes a clean cyclization to produce predominantly the six-

membered ether **36** with 9:1 selectivity (Scheme 3a).[96,97] The methoxymethyl group may exert a similar electronic bias as the sulfonyl group, as it inductively destabilizes the positive charge at the 5-*exo* position. However, these reactions require a unique set of conditions to proceed in good selectivity, suggesting that the lanthanide Lewis acid may chelate the epoxide oxygen and the oxygen in the directing group, thus providing geometrical constraints that are responsible for the observed selectivities.

Scheme 3. Methoxymethyl directed *endo*-selective epoxide-opening cascades.



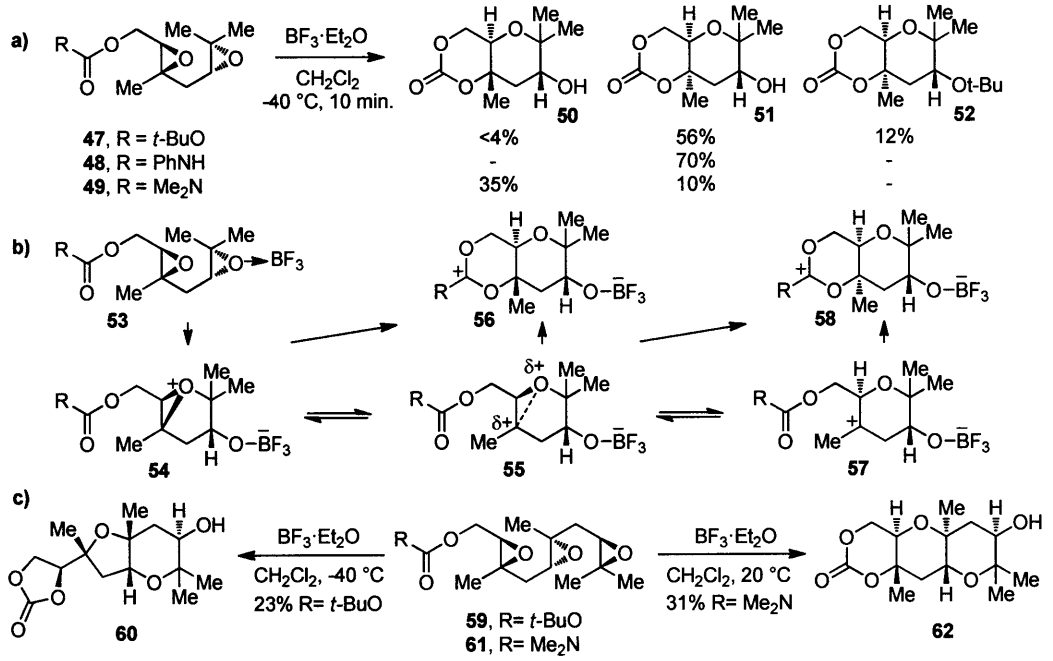
Early work on epoxide-opening cascades by the Murai group led to the development of methods for the *endo*-selective lanthanide-promoted opening of methoxymethyl substituted epoxides.[97] Murai and coworkers prepared polyepoxides **38** and **44**, which incorporate a methoxymethyl directing group at each epoxide.[98] Under conditions described for substrates containing one epoxide, diepoxide **38** was converted to a THP diad **39** with methoxymethyl groups present at the ring junctions (Scheme 3b). The side products isolated in this reaction are suggestive of a pathway that proceeds in a stepwise fashion from the primary alcohol, initially forming intermediate **41**. The intermediate epoxyalcohol **41** subsequently undergoes further

cyclization to afford **39** and **40**. The authors also reported that the other diastereomer of **38** fails to afford any of the corresponding THP diad, as the postulated intermediate **43** does not further react due to strain in the requisite boat-like transition state and steric repulsions between the two methoxymethyl substituents. Murai has also demonstrated that cascades directed by methoxymethyl groups in combination with an appropriate Lewis acid can be extended to larger ladder polyether type fragments such as triad **45**, albeit in low yield.

Trialkyl substituted epoxides

With the exception of the methoxymethyl-directed reactions, the *endo*-selective epoxide-opening reactions described so far are not amenable to cyclizations of more than one epoxide. Although these approaches can be quite useful in preparing tetrahydropyrans in various contexts in natural product synthesis, the products of these reactions require additional elaboration into naturally occurring ladder polyether structures via either removal of the directing group or elaboration of the functional groups present in the final product into the fragments of the naturally occurring compounds. These problems arise because the directing groups used to secure good *endo* selectivity are not present in the natural compounds. Unlike vinyl, sulfonyl or methoxymethyl groups, methyl groups often substitute hydrogens at ring junctions of both ladder polyethers and oxasqualenoids, and thus can be utilized to direct regioselectivity of epoxide opening without the need for their removal from the final product of such reactions in some cases. The ability of methyl groups to stabilize the positive charge in the intermediates of epoxide-opening reactions with trialkyl epoxides is well precedented,[99] and the first systematic reports on the directing effects of methyl groups attached to the epoxide were reported recently by the McDonald group.[100]

Scheme 4. (a) Stereochemical outcome of epoxide-opening cascades as function of the type of terminating nucleophile, **(b)** mechanistic rationale, and **(c)** related cascades of triepoxides.

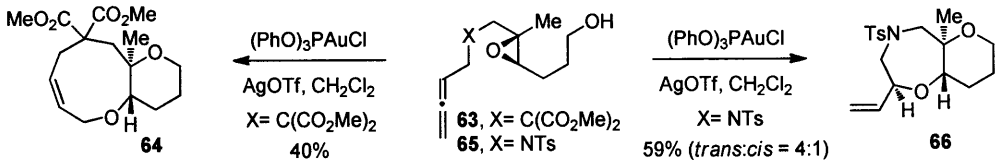


The McDonald group explored epoxide-opening cascades for the synthesis of polytetrahydropyrans from polyepoxy substrates featuring appropriately positioned methyl substituents at each of the epoxides (Scheme 4a).[100] The methyl groups are placed strategically at the carbon atoms expected to undergo nucleophilic attack in the *endo* transition states so that they can stabilize the positive charge developed in the transition state of these acid-catalyzed reactions. McDonald discovered that the nature of the terminating nucleophile plays an important role in these reactions as demonstrated in the epoxide-opening cascades of 1,4-diepoxides **47**–**49**. These reactions can proceed with either retention or inversion of configuration at the ring junction depending on the type of pendent nucleophile. Stronger nucleophiles at elevated temperatures tend to favor a clean inversion of stereochemistry in the opening of the internal epoxide, affording the *trans*-fused **50**. In contrast, less nucleophilic carbonates favor the production of diastereomeric *cis*-fused product **51**, corresponding to a retention of configuration.

The mechanism in which the terminating nucleophile intercepts a cationic intermediate at different points in the continuum between the extremes of epoxonium ion **54** and tertiary alkyl carbocation **57** explains these observations (Scheme 4b). The McDonald group proposed that *cis*-fused products arise from nucleophilic addition to the tertiary carbocation, whereas *trans*-fused products are favored with a stronger nucleophile, which intercepts a tight ion pair intermediate structurally related to the epoxonium ion **54.** [100]

Similar trends were observed in the more challenging epoxide-opening cascades of triepoxides **59** and **61**, which feature a methyl directing group on each of the epoxides.[100] When activated by a Lewis acid at an appropriate temperature, triepoxide **61**, featuring a stronger carbamate terminating nucleophile, is transformed into the ladder polyether-like tricycle **62** in 31% yield (Scheme 4c). In contrast, triepoxy carbonate **59** failed to afford any of the desired product, and instead produced a fused THF/THP product **60** at low temperatures. Product **60** is presumably produced through isomerization of the initially formed bicyclo[3.1.0]epoxonium intermediate, which leads to *cis* geometry at the ring junction, followed by 5-*exo* cyclization in the last epoxonium opening event of the cascade. The McDonald group also investigated a variety of conditions for the activation of the epoxide and demonstrated that, in some cases, the choice of Lewis acid may determine the final outcome of related epoxide-opening cascades.[101]

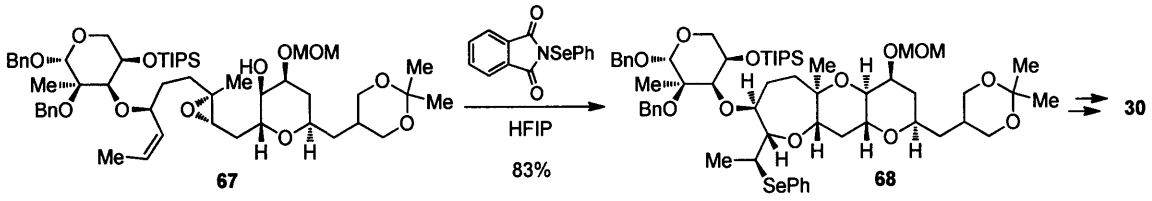
Scheme 5. Gold(I)-catalyzed cascade cyclization of allenyl epoxides.



Gagné and coworkers recently reported cascades that involve epoxide-opening in which the regioselectivity is controlled by the strategic incorporation of methyl substituents.[102] To initiate

the cyclization reaction, a cationic gold(I) phosphite catalyst is used to activate the allenes of **63** and **65** to form epoxonium intermediates that then undergo nucleophilic attack by the pendant alcohol (Scheme 5). By stabilizing the intermediary carbocation character, the methyl substituent serves as a directing group for nucleophilic attack. Substrates that feature more than one epoxide were not described in this study. Nonetheless, these experiments demonstrate the diversity of the initiating conditions in epoxide-opening cascades.

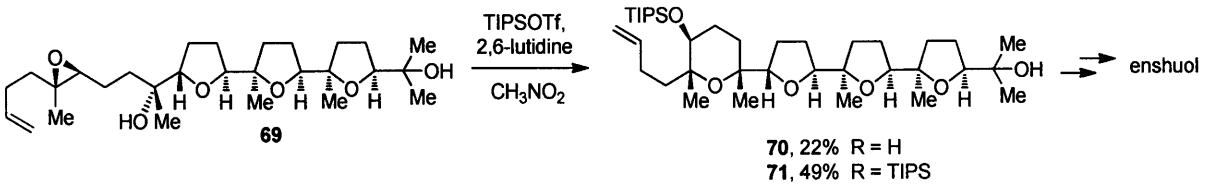
Scheme 6. Electrophile-initiated epoxide-opening cascade: synthesis of hemibrevetoxin B.



An epoxide-opening cascade that capitalizes upon the presence of a methyl group in an appropriate position was utilized by Holton and coworkers in the total synthesis of hemibrevetoxin B.[103] Although only one epoxide is involved in this reaction, two cyclic ethers of the natural product are produced in a single operation(Scheme 6). Activation of the Z-alkene in **67** with *N*-(phenylseleno)phthalimide via the formation of a selenonium ion sets the stage for *exo* opening by the epoxide nucleophile and formation of an epoxonium intermediate. The *endo* cyclization onto the epoxonium intermediate directed by the methyl substituent produces **68**, which contains the *trans*-fused BC ring system of hemibrevetoxin B (**30**, Scheme 2b). The use of a highly polar, non-nucleophilic solvent such as, HFIP increases the selectivity by enabling a higher degree of charge separation in the transition state. According to computational studies by Houk, the existence of this loose, S_N1-like transition state is required in alkyl group-directed 6-*endo* cyclizations.[104-106]

Morimoto and coworkers also took advantage of the directing effect of methyl groups.[107] They used methyl substituents to increase *exo* selectivity in epoxide-opening cascades that lead to polytetrahydrofuran segments of oxasqualenoids but also, when appropriately positioned, to promote *endo* selectivity in construction of the THP rings in the total synthesis of enshuol[108] and aurilol.[109] When treated with TIPSOTf, epoxy alcohol **69** undergoes cyclization to form a mixture of **70** and **71**, the penultimate precursor to enshuol. These reactions require a tertiary nucleophile and a bulky silyl triflate to avoid side reactions such as conversion of the alcohol nucleophile to the silyl ether (Scheme 7).

Scheme 7. Silyl triflate catalyzed *endo*-selective epoxide opening of a trisubstituted epoxides with a tertiary alcohol nucleophile: application to the synthesis of enshuol.



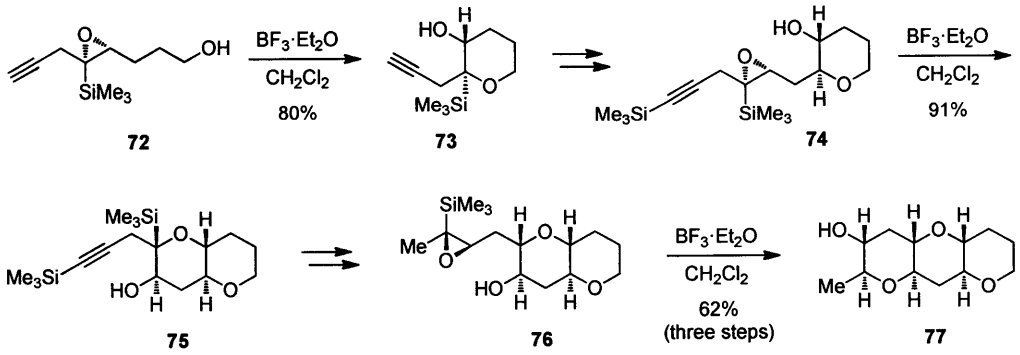
As demonstrated by the groups of McDonald,[100] Holton,[103] Gagné,[102] and Morimoto,[107-109] methyl substituents are reliable directing groups in epoxide-opening cascades leading to THPs. However, successful cascades usually require appropriately positioned methyl substituent at each of the epoxides. The products obtained this way contain methyl substituents uniformly distributed at ring junctions across the polyether ladder. Although methyl groups are present at the ring junctions of ladder polyethers, they are normally arranged in a random fashion, and generally appear at no more than half of the ring junctions. Hence, fragments produced via methyl group-directed epoxide-opening cascades rarely appear in natural products. Methods that can produce polytetrahydropyrans with no substituents (*i.e.*, only H atoms) at the ring junctions

further expand the utility of epoxide-opening cascades in the synthesis of naturally occurring oligotetrahydropyran fragments.

Epoxysilanes

Similar to alkyl substituents, trialkylsilyl groups also have the potential to stabilize the positive charge in the transition state leading to the 6-*endo* opening of epoxides. The structural effect of a silyl group attached directly to an epoxide has been studied in detail by Hudrlik[110-112] and Paquette.[113] These results have found application in the *endo*-selective intramolecular reactions of epoxysilanes developed in the Jamison group,[114] Lewis acid-catalyzed *endo*-selective intramolecular epoxide-opening reactions of epoxysilanes were utilized in iterative syntheses of *trans*-fused oligotetrahydropyran fragments (Scheme 8). Conveniently, after cyclization, removal of the directing group can be achieved cleanly with TBAF via a Brook rearrangement. This enables the synthesis of fragments that do not contain directing groups in the polyether ladders, as demonstrated by synthesis of the THP triad **77**.

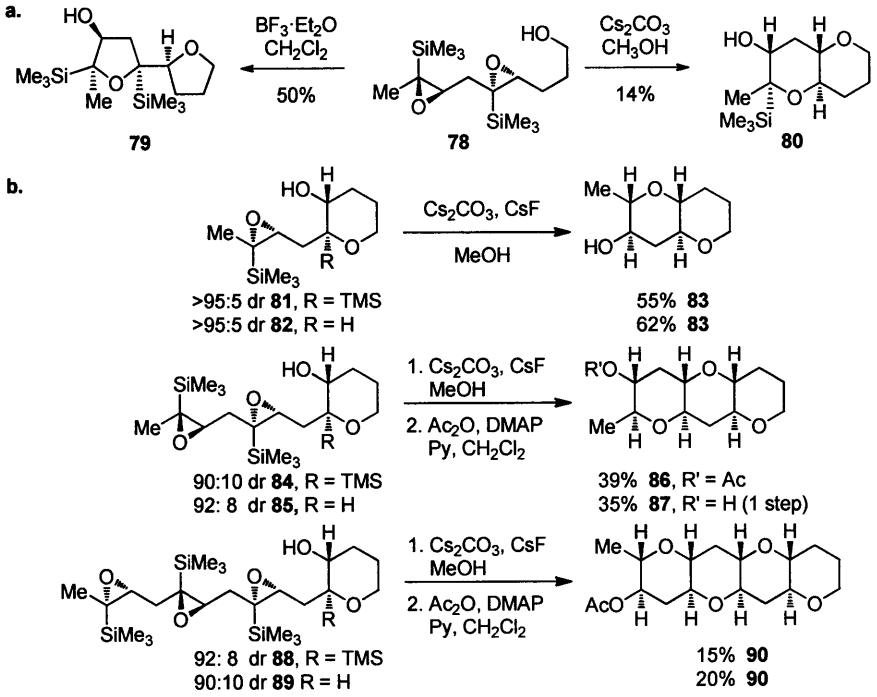
Scheme 8. 6-*endo* cyclization of epoxysilanes: iterative synthesis of oligotetrahydropyrans.



When extended to diepoxides, the Lewis acid-catalyzed epoxide opening reactions of epoxysilanes fail to provide the desired product. Despite the suitably positioned directing groups, when treated with Lewis acids, diepoxide **78** yields bistetrahydrofuran **79** as the only isolable

product (Scheme 9a). Thorough evaluation of reaction conditions revealed that the outcome of this reaction was very different when a Brønsted base in alcoholic solvents was used instead (Scheme 9a).[115] Under these conditions, diepoxide **78** undergoes a cascade reaction to produce THP diad **80**. It was noted in this transformation that the trimethylsilyl directing group was fortuitously absent from the ring junction in the product.

Scheme 9. Epoxide-opening cascades with a disappearing silyl group.



Further modifications to the design of polyepoxide substrates and reaction conditions resulted in the development of epoxide-opening cascades directed by "disappearing" silyl groups (Scheme 9b).[115] These modifications include the construction of one THP ring (as in **81**, **84** and **88**) prior to the cascade and the addition of cesium fluoride to facilitate the removal of the TMS groups. An increase in efficiency per epoxide was observed when one THP ring in the polyepoxide substrate is formed prior to the cascade. The authors suggest that the cascades proceed as a sequence of silyl-directed epoxide openings by the alcohol nucleophile followed by

protiodesilylation, which may occur via a homo-Brook rearrangement pathway. After each Brook rearrangement, removal of the silyl group by fluoride reveals the alcohol nucleophile for the next stage of the cascade reaction.

Although disappearing directing groups address problems related to the removal of substituents not present in the natural targets, these reactions suffer from the inability to incorporate the methyl substituents found occasionally at the ring junctions of ladder polyethers.

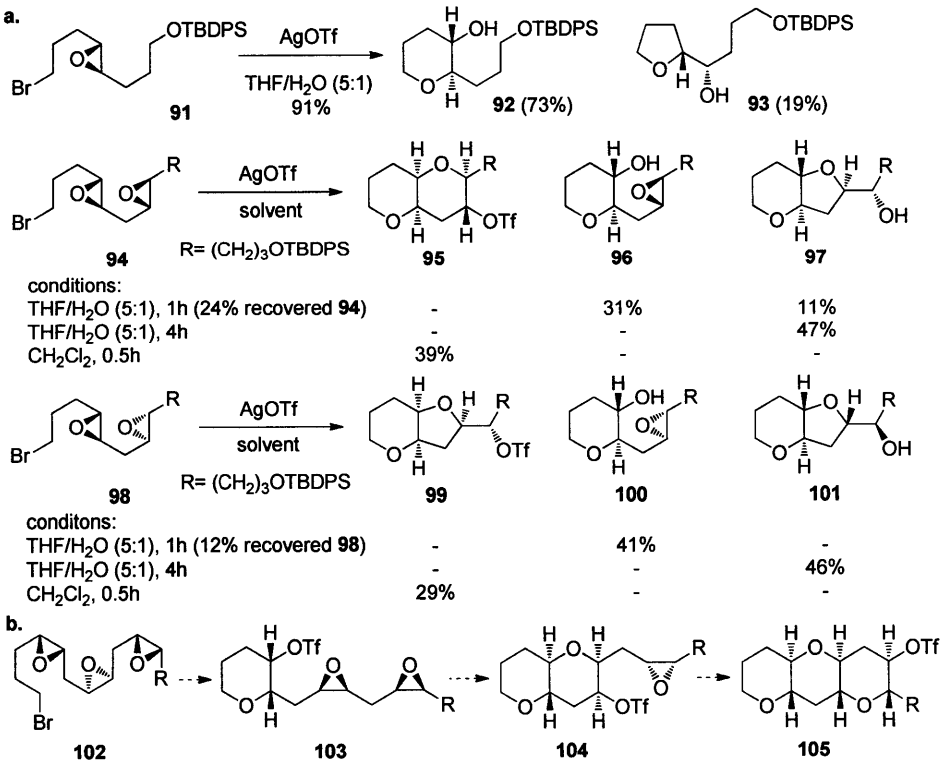
Reactions of disubstituted epoxides

The challenge of achieving high 6-*endo* selectivity in intramolecular epoxide-opening reactions has been approached by several research groups. The first attempt to perform a cascade reaction that does not rely on the effects of directing groups and incorporate only disubstituted epoxides was reported by Murai.[116,117] The Murai group attempted a conceptually different way of promoting an epoxide-opening cascade. They envisioned that the activation of an epoxy halide such as **91** with a silver salt would selectively generate an epoxonium ion at one end of the polyepoxide chain, thus ensuring selective activation of a single epoxide in the chain (Scheme 10a). This epoxonium ion would then serve as an electrophile for the nucleophilic attack by the neighboring epoxide, thereby forming a new ring and a new epoxonium intermediate, and thus propagating the cascade. The direction of the cascade in these reactions is therefore controlled by the position of the halide.

Murai and coworkers first showed that the opening of the epoxonium ion derived from bromo epoxide **91** with an external nucleophile can preferentially provide the desired tetrahydropyran **92** under appropriate conditions (Scheme 10a). However, when more than one epoxide is present in the starting material, the reactions proved to be more capricious, and diverse products from a number of different pathways were formed.[117] Similar investigations on

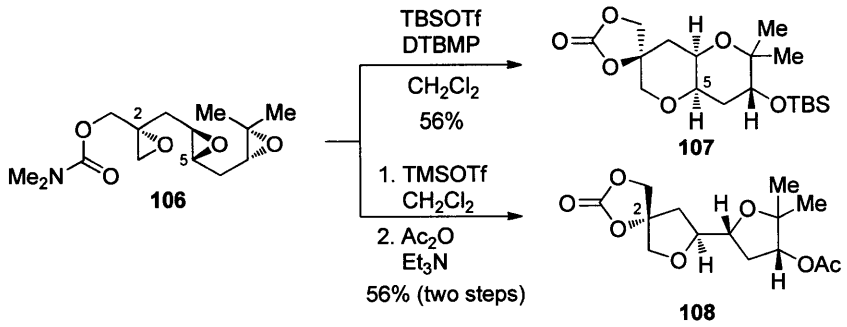
silver-salt promoted cyclizations of polyepoxy bromides by the Jamison group closely mirror the results obtained by Murai.[118] External nucleophiles present in the reaction mixture, such as water, competed with the epoxide oxygen in opening the epoxonium ion. If external nucleophiles were rigorously excluded and the reaction was activated with AgOTf, the triflate anion competed with the epoxide, thus producing yet another electrophilic species that underwent another displacement reaction to give the *cis* geometry at the ring junction via double inversion at the C4 position of **94** and **98** (Scheme 10a). If such a trend were to hold in the case of a polyepoxide, then an all-*cis* polyepoxide could lead to formation of the *trans-syn-trans* fragments of ladder polyethers (Scheme 10b). In this scenario, the initial epoxonium ion would be opened by a triflate anion that would, in turn, be displaced by the neighboring epoxide to generate the new epoxonium, thus propagating the cascade.

Scheme 10. (a) Cascades of epoxy halides and polyepoxy halides selectively activated with silver salts. **(b)** Proposed cascade of an all-*cis* polyepoxide propagated by the triflate anion.



The McDonald group has described efforts to incorporate a disubstituted epoxide in cascade substrates that also contain electronically biased epoxides such as **106**.[101] Aware of the effects that different Lewis acids can have on similar cascade reactions of electronically biased polyepoxides, McDonald and coworkers evaluated various Lewis acids as activators in epoxide-opening cascades of triepoxide **106**. When trimethylsilyl triflate was used with triepoxide **106**, the product of an all-*exo* epoxide-opening cascade **108** was isolated (Scheme 11). The stereochemistry at C2 was preserved in this cascade, suggesting that epoxide opening occurs with retention (or double inversion) at this site. In contrast, when *tert*-butyldimethylsilyl triflate was used, a *syn*-fused THP diad **107** was isolated, suggesting that opening of the epoxonium intermediate proceeds with retention of configuration. Although the reasons for these apparent differences are unclear, it was proposed that the weakly nucleophilic triflate anion may compete with the epoxide oxygen in the opening of the epoxonium intermediate, leading to double inversion and net retention of configuration at C5.

Scheme 11. Disubstituted epoxides in silyltriflate-promoted cascades.



All reported attempts to utilize unbiased disubstituted epoxides in the synthesis of tetrahydropyran rings in the ladder polyether fragments via *endo* cyclization, be it the formation of a single THP ring or a cascade that produces multiple fused rings, uniformly failed to generate the desired products. Thus, achieving *endo*-selective epoxide-opening cascades in the absence of

directing groups remains a significant challenge. If epoxide-opening reactions are used in ladder polyether biosynthesis, then how is this preference for the smaller ring overcome? Enzymatic control is a logical supposition, but there is as yet no evidence for such an intervention. With the joint aims of addressing this question and accelerating the synthesis of ladder polyethers, we have focused our efforts in this area on directing group-free, THP-selective cascades. Our approach stems from an analysis of the potential factors governing the regioselectivity of epoxide opening in these reactions, and uses a template to modulate them in the desired manner.

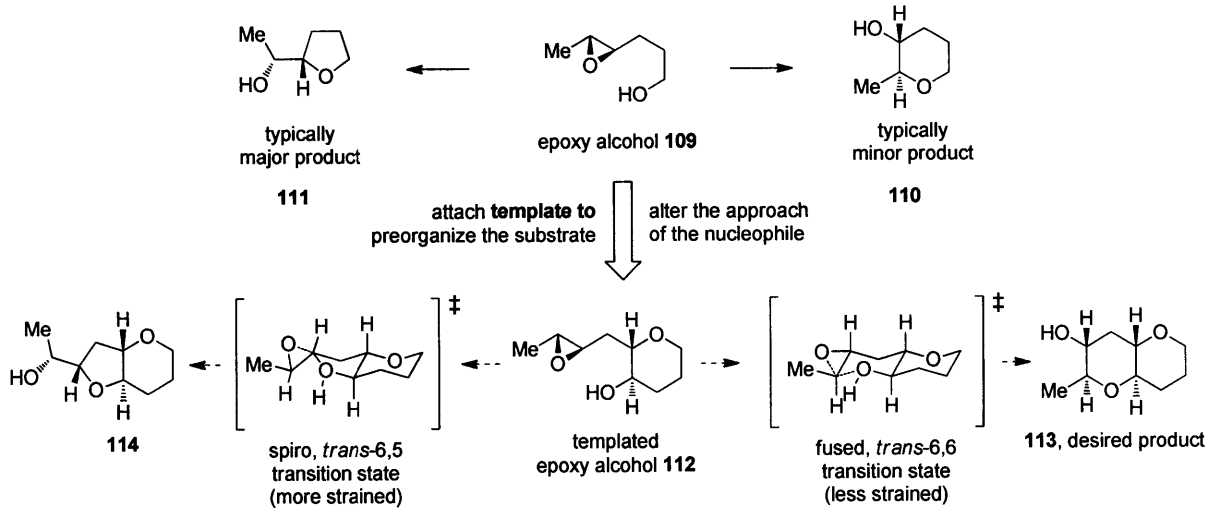
Results and Discussion

Abandoning directing groups reduces the number of possible approaches for control of regioselectivity in intramolecular epoxide-opening cyclization. While strong substrate control via powerful electronic directing groups on the epoxide electrophile would no longer be possible, we hoped that some element of substrate control could still play a role. The approach taken by our group stemmed from a rather simple analysis of the potential factors governing the regioselectivity of epoxide opening in these reactions (Figure 4).

We reasoned that pre-organization of the substrate in an appropriate fashion could encourage, or template, the cyclization towards the *endo* pathway. We will herein use the term template to describe a molecular architecture that induces otherwise atypical reactivity and/or selectivity. Our initial working hypothesis was that a molecular template could alter the approach of the alcohol nucleophile to the epoxide electrophile and bias the substrate towards *endo* cyclization. Our initial analysis was predicated on a single assumption—that the greater stability of the desired 6,6-fused *endo* product **113** as compared to the undesired 6,5-fused *exo* product **114** could, with judicious design of the template, be translated into a kinetic selectivity (Figure 4). We conjectured that the reaction of **112**, in which one THP is already in place and the epoxy

alcohol appeared primed for cyclization, might go through more product-like transition states. Furthermore, preliminary calculations suggested that the predicted *trans*-bicyclo[4.4.0]decane transition state en route to **113** should be substantially less strained than the *trans*-bicyclo[4.3.0]nonane transition state proposed en route to **114**. Were this difference in developing ring strain reflected in the transition states, then the desired THP product might be favored in this templated system under the appropriate reaction conditions.

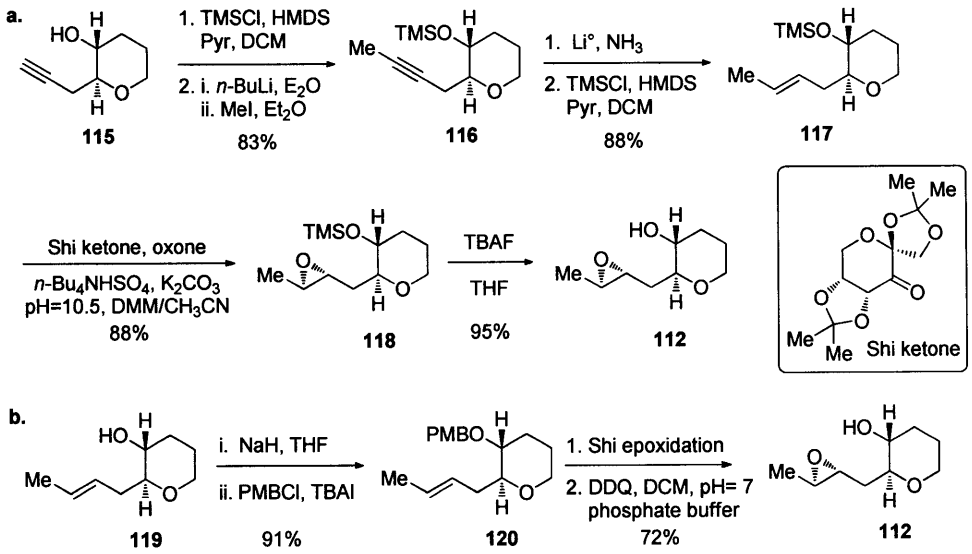
Figure 4. Design of the templated substrates for *endo*-selective epoxide opening.



To test our hypothesis, we prepared the templated epoxy alcohol **112** (Scheme 12a). Synthesis of the desired model system commenced from a common intermediate **115**, prepared via one of the routes previously reported by our group (nine steps from 4-pentyne-1-ol[114] or five steps from 2,3-dihydropyran[119]). Silyl protection followed by methylation of the terminal alkyne afforded **116** in good yield. Dissolving metal reduction proceeded with exclusive *E* selectivity, but also removed the silyl ether requiring subsequent protection of the secondary alcohol. Shi asymmetric epoxidation was utilized to produce the epoxide **118** in good yield and moderate diastereoselectivity. Cleavage of the silyl ether in **118** afforded the target model system **112** in good yield as a 6:1 mixture of epoxide diastereomers.

To produce material free of the other diastereomer, we intercepted intermediate **119** obtained upon dissolving metal reduction of **116**. The secondary alcohol of **119** was protected as PMB ether and this material was subjected to Shi epoxidation conditions to produce the epoxide in moderate, 7:1 diastereoselectivity. Having a chromophore in the molecule, this material was subjected to preparative chiral HPLC purification to afford a PMB derivative of **112** as a single diastereomer. Removal of PMB group under standard oxidative conditions provided pure **112** (Scheme 12b).

Scheme 12. Syntheses of the templated epoxy alcohol model system **112**.



With **112** in hand we attempted to initiate the cyclization reaction with wide range of combinations of acids, bases, solvents, and other additives (selected conditions are shown in Table 1). We discovered that regioselectivity in cyclization reactions of the templated epoxy alcohol **112** were significantly improved compared to the selectivities generally observed for simple epoxy alcohols (e.g., <1:6 favoring **111** over **110**, Figure 4).[120] Bases tended to favor the THF product **114**, whereas acids exhibited a slight preference for the desired THP product **113**. Combinations of acids and bases (Lewis or Brønsted) also favored **114**.

Table 1. *Endo:exo* selectivity as a function of cyclization conditions ([a] = low conversion)

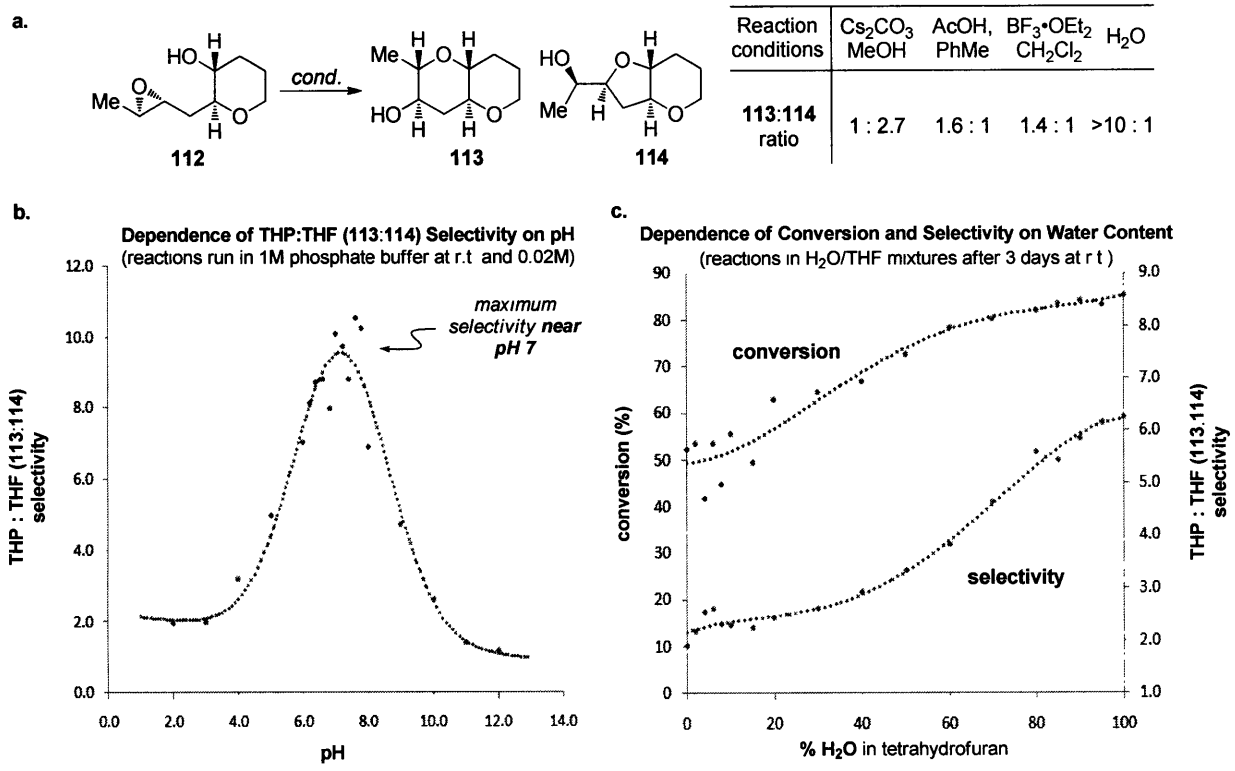
Entry	Solvent	Activator (equiv.)	T (°C)	Time	*endo:exo* **113:114**
1	MeOH	Cs_2CO_3 (10)	r.t.	3 days	1.0 : 2.7
2	MeCN	TMEDA (10)	r.t.	1 day	1.0 : 1.7[a]
3	THF	$NaCH_2SOCH_3$ (3)	r.t.	3 days	1.0 : 2.2
4	THF	LiHMDS (3)	r.t.	1 day	1.0 : 2.7
5	MeCN	LiOH (5)	r.t.	3 days	2.0 : 1.0
6	MeOH	CsOH (5)	r.t.	3 days	1.0 : 1.8
7	PhMe	AcOH (3)	r.t.	3 days	1.6 : 1.0
8	CH_2Cl_2	$BF_3 \cdot Et_2O$ (2), Cs_2CO_3 (5)	-78°C to r.t.	1 day	1.4 : 1.0
9	CH_2Cl_2	*R*–BIPHEN (3), Ti(O*i*-Pr)$_4$ (1)	-78°C to r.t.	3 days	2.0 : 1.0[a]
10	CH_2Cl_2	none	r.t.	3 days	<2% conv.
11	MeCN	none	r.t.	3 days	2.4 : 1.0[a]

While initial experiments proved our hypothesis to be correct, selectivities observed in these reactions were not sufficiently high to be extended into an epoxide-opening cascade. To better understand the requirements for activation of the nucleophile and the electrophile, we examined the pH dependence of THP to THF selectivity (**113:114**) by carrying out the cyclization reactions in a range of aqueous buffers (e.g., phosphate, tris, His) at various ionic strengths. These experiments revealed a clear and provocative trend (Figure 5b). In all cases, the selectivity for the desired THP product increases substantially as the pH of the reaction environment approaches neutrality, even exceeding 10:1 THP:THF selectivity near pH 7.

Several lines of evidence clearly implicate water in both the acceleration and increase of selectivity in these reactions. In less polar solvents (e.g., CH_2Cl_2 and toluene), low conversion of **112** is observed, and in polar aprotic solvents (e.g., CH_3CN, DMSO and DMF), although higher conversion to **113** and **114** occurs, the selectivity is greatly reduced (≤3:1 **113:114**). Furthermore, both increased THP:THF selectivity and increased conversion of **112** correlate with increased water content in the reaction milieu (Figure 5c). Finally, deionized H_2O, in which both the ionic strength and percentage of impurities are near zero, provides the highest selectivity (>11:1

THP:THF). The only other promoters that we have found, that approach the selectivity and rate exhibited by water, are ethylene glycol (9:1) and methanol (8:1), which along with water can both provide and accept hydrogen bonds.

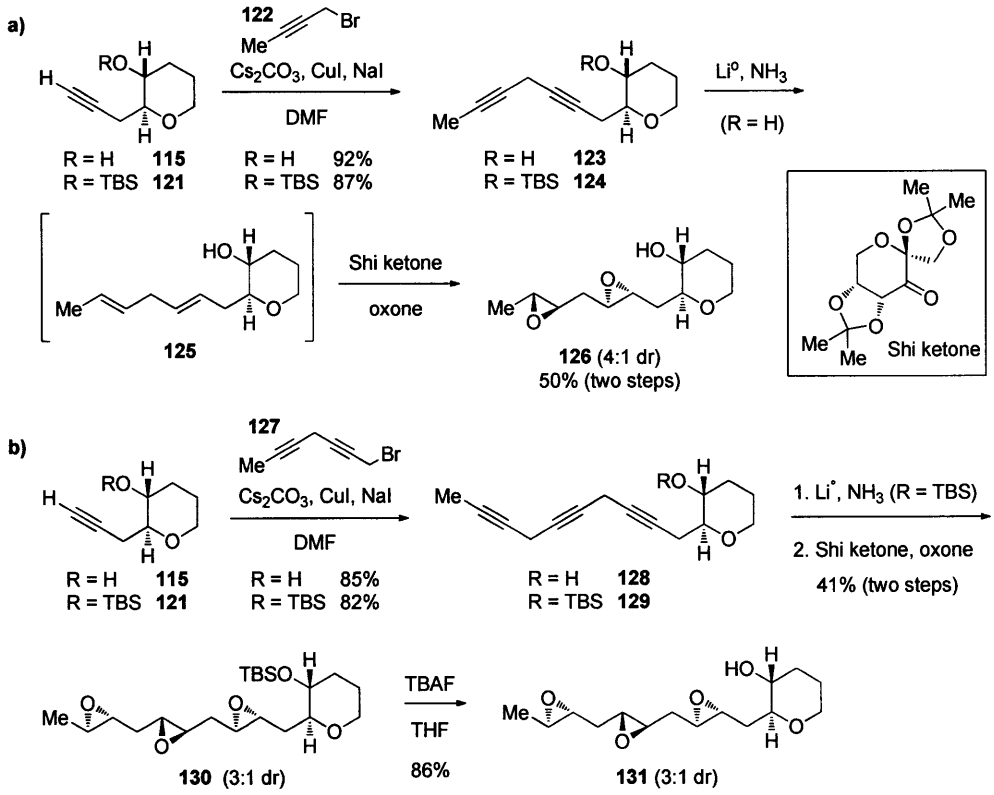
Figure 5. (**a**) Epoxide-opening reactions of templated epoxy alcohol **112**. (**b**) Regioselectivity as function of pH of the reaction medium. (**c**) Effect of water on conversion and selectivity.



Hydrogen bonding interactions between the THP template, epoxide, and water molecules were proposed as the origin of *endo* selectivity in the described reactions. Kinetic studies of the cyclization reactions of epoxy alcohol **112** and its carbocyclic analogue featuring a cyclohexane in place of the THP template suggest existence of at least two competing mechanisms that are first- and second-order in water, respectively (these and other mechanistic studies were preformed by Dr. Jeffery Byers in our group).[121] It was proposed that the selective pathway is second-order in water and operable only for the THP-templated epoxy alcohol **112**. Epoxy alcohol cyclizations in water may occur for hydrated conformations that possess the appropriate

geometry, which is possibly attained in the form of a twist-boat conformation that is stabilized by hydrogen bonding interactions with water molecules. The electron-withdrawing effects of the oxygen in the THP template may also provide electronic bias for *endo* cyclization via destabilization of the positive charge at the *exo* position.

Scheme 13. Synthesis of templated polyepoxides **126** and **131**.



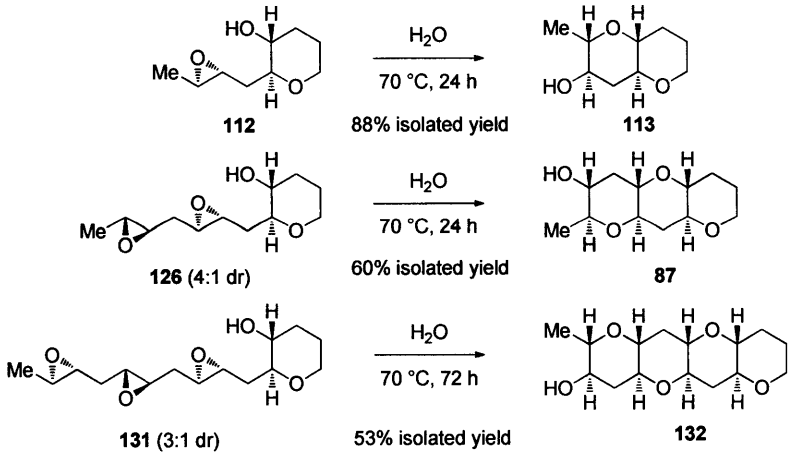
Having developed a THP-selective epoxide-opening method, we turned our attention to the possibility of using this approach in epoxide-opening cascades. However, we were well aware from our own work and from case studies reported by others that many highly-selective epoxide ring-opening methods summarily fail when extended to cascades.

The synthesis of the epoxides is shown in Scheme 13 and emulates another aspect of Nakanishi's hypothesis, polyepoxidation of a polyene. Alkyne **115** was extended to diyne **123** and triyne **128** in high yield by alkylation with the appropriate propargyl bromide (**122** and **127**,

respectively). Alkyne **121**, in which the hydroxyl group is protected as silyl ether, was converted to **124** and **129** in the same manner and similar yield. Dissolving metal reduction (Li/NH_3) of **123** provided a skipped diene **125** that was unstable enough to prohibit prolonged storage. The corresponding triene (not shown) from **129** was even less robust, requiring hydroxyl protection before reduction.

Shi epoxidation converted the diene and triene to the corresponding polyepoxides **126** and **130**. The moderate stereoselectivity, 4:1 for **126** and 3:1 for **130** determined by ^1H NMR as ratio of the desired to all other epoxide diastereomers, appears to be mostly due to the alkene proximal to the hydroxyl group; more remote alkenes do not suffer from this mismatched double diastereoselection. Diepoxide **126** and triepoxide **131** (after removal of the tert-butyldimethylsilyl protecting group) were obtained in 50% and 35% overall yield, respectively, from the diyne **123** and triyne **129**.

Scheme 14. Epoxide-opening cascades promoted by H_2O.

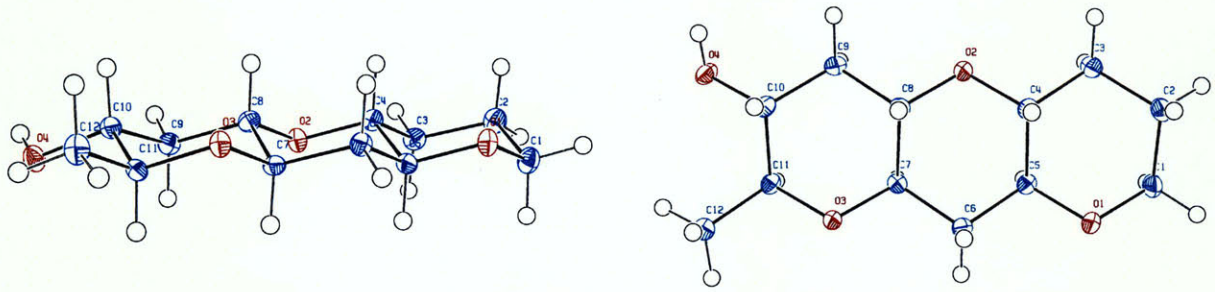


The suboptimal stereochemical purity of **126** and **131** turned out to be of little concern (Scheme 14). Heating **126** in deionized water for 24 hours at 70°C afforded a THP triad **87** in 60% isolated yield. Similarly, a THP tetrad **132,** representative of that found in more than half of the

known ladder polyethers (Figure 1), was obtained in 53% isolated yield starting from triepoxide **131**.

Structures of triad **87** and tetrad **132** were confirmed by comparison to the previously reported material (for **132** after acetylation of the secondary alcohol). In addition to comparison with the material prepared by other methods, structure of **87** was rigorously established by single crystal x-ray diffraction.[119]

Figure 6. X-ray crystal structure of triad **87** (thermal elipsoids displayed at 50% probability, courtesy of Christopher J. Morten).[119]



The effect of temperature on the reaction rate is substantial, but its impact on selectivity is minimal, consistent with the template concept of minimization of entropic contributions to the competing transition states. For example, about 1 month (28 days) was required for complete consumption of **126** at room temperature in pH 7.6 phosphate buffer (1.0 M), but polyether triad was nonetheless afforded in identical isolated yield (60%).

Attempted cyclizations of analogs of **112** and **126** that lack THP template but are otherwise identical to the templated epoxy alcohols (3-((2*R*,3*R*)-3-methyloxiran-2-yl)propan-1-ol and 3-((2*R*,3*R*)-3-(((2*R*,3*R*)-3-methyloxiran-2-yl)methyl)oxiran-2-yl)propan-1-ol), uniformly failed to produce any of the desired products, even under conditions that provided good *endo* selectivity for cyclizations of **112** and **126**. These experiments demonstrated that template, or some minimal

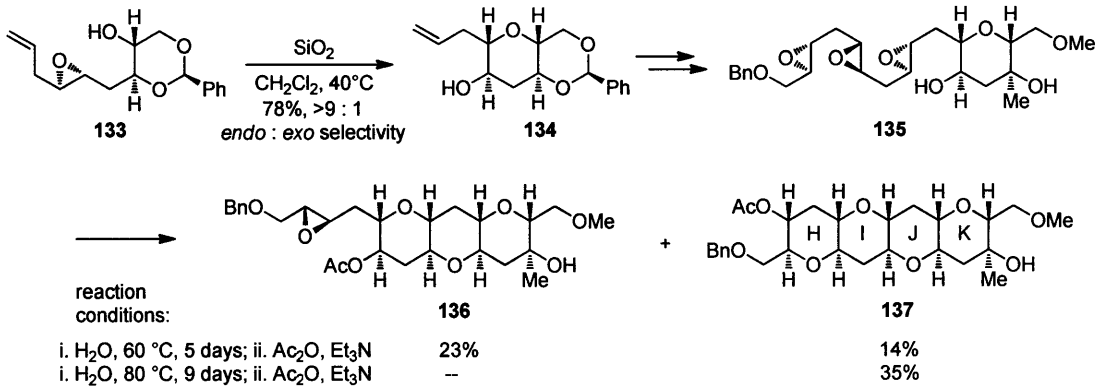
requirement that the THP template fulfills, is indeed necessary for these reactions to proceed with good *endo* selectivity.

Just as the development of all-THF epoxide-opening cascades[122,123] is taken as support of the Cane-Celmer-Westley hypothesis in the biosynthesis of polyether ionophores,[124] we believe that the all-THP *endo*-selective cascades in water represent long-sought evidence in favor of Nakanishi's hypothesis of ladder polyether biosynthesis (or at least the feasibility thereof). The template may be functioning as a surrogate for conformational constraints imposed by an enzyme active site, and because water is the superior promoter, it is reasonable to propose that such cascades would be promoted by hydrogen-bond activation of the epoxide in the natural systems perhaps similar to the epoxide hydrolase enzymes that appear to activate epoxides by hydrogen bonds donated by two conserved tyrosine residues.

In efforts to expand the utility of aqueous epoxide-opening cascades for synthesis of ladder polyether fragments, Aaron Van Dyke in our group investigated oxygen-containing templates that could produce fragments suitable for coupling and further elaboration to natural products.[125] Evaluation of a benzylidene acetal template revealed significant differences in the reactivity of epoxy alcohols templated by this motif (e.g., **133**, Scheme 15) compared to those templated by a THP. Slow cyclization rates in water and the instability of benzylidene acetals prevented these substrates from being used in aqueous reactions. However, silica gel was found to promote cyclization of benzylidene acetal templated epoxy alcohol **133** to **134** in good yield and with high *endo* selectivity. Elaboration of **134** to the triepoxy alcohol **135**, with a functionalized THP template, set the stage for an epoxide-opening cascade. Incubation of **135** in water at 60°C for 5 days afforded some of the desired THP tetrad **137** and a larger quantity of **136**, in which two THP rings had formed but the final epoxide remained intact (Scheme 15). More forceful

conditions (80 °C, 9 days) drove the cyclization reaction of **135** to completion and allowed the isolation of **137**, the HIJK fragment of gymnocin A, in 35% yield upon acetylation. THP tetrad **137** features four differently substituted hydroxyl groups ready for further synthetic elaboration.

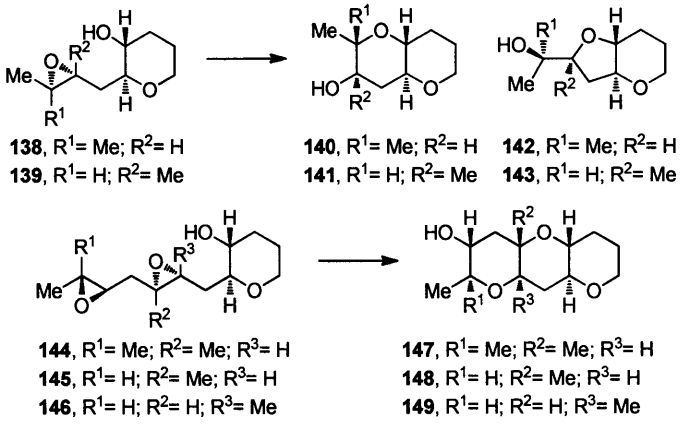
Scheme 15. Aqueous epoxide-opening cascade in synthesis of HIJK ring of gymnocin A.[125]



Methyl groups are commonly encountered at ladder polyether ring junctions, with approximately one in five ring junctions bearing a methyl substituent. Therefore, the putative polyepoxide precursors to ladder polyethers, in addition to disubstituted epoxides, regularly feature two types of trisubstituted epoxides. A methyl group on a trisubstituted epoxide can be situated in a position where its directing effect promotes *endo*-opening under acidic conditions (as in **138**, Scheme 16) or in a position that would normally promote *exo*-selective epoxide opening under the same conditions (as in **139**, Scheme 16). In order to incorporate methyl substituents at the ring junctions of the final products in epoxide-opening cascades, Christopher Morten in our group extended the work on aqueous directing group-free *endo*-selective epoxide openings by preparing and evaluating cyclization reactions of templated epoxy alcohols **138** and **139** which feature both types of methyl substitution on the epoxide (Scheme 16).[119,126] Acid-catalyzed cyclizations of epoxy alcohol **138** proceeded with high *endo* selectivity due to the electronic effect of the methyl substituent at the *endo* site of attack on the epoxide. Base-

promoted cyclizations of the same molecule, however, predominantly produced the *exo* product, bicycle **142**. In contrast, base-promoted cyclizations of the more challenging epoxy alcohol **139** proceeded with moderate *endo* selectivity, while acid-promoted reactions afforded *exo* product **143**. Both **138** and **139** produced *endo* products **140** and **141** with good selectivity when cyclized in deionized water. In addition to achieving high *endo* selectivity, aqueous cyclizations circumvent side reactions associated with other activation conditions, such as the rearrangement of epoxide **138** to an *iso*-propyl ketone via 1,2-hydride shifts under acidic conditions.

Scheme 16. Water overcomes methyl group directing effects in templated systems.[119]



Reaction conditions	Cs_2CO_3 MeOH	CSA CH_2Cl_2	$BF_3{\cdot}OEt_2$ CH_2Cl_2	H_2O
140:142 ratio	1 : 17	5.8 : 1	>20 : 1	>20 : 1
141:143 ratio	3.0 : 1	1 : 5.2	1 : 11	4.9 : 1
Isolated yield, **147**	0%	43%	61%	54%
Isolated yield, **148**	0%	46%	63%	67%
Isolated yield, **149**	0%	0%	0%	32%

Extending this work further, Christopher Morten demonstrated that methyl substituents on epoxides are also tolerated in aqueous cascades (Scheme 16).[119,126] Under aqueous conditions, diepoxides **144** and **145**, which incorporate methyl substituents at the positions of *endo* attack, afforded the triads **147** and **148**, respectively. Diepoxide **146**, with a methyl substituent at the *exo* site, afforded the THP triad **149**. While diepoxides **144** and **145** also produced some of the desired products upon acidic activation, only aqueous conditions afforded any of the THP triad **149** from diepoxide **146**. Aqueous epoxide-opening cascades overcome the need for methyl substituents to be uniformly distributed on each epoxide and can accommodate both types of trisubstituted epoxides in combination with disubstituted epoxides.[127]

Conclusion

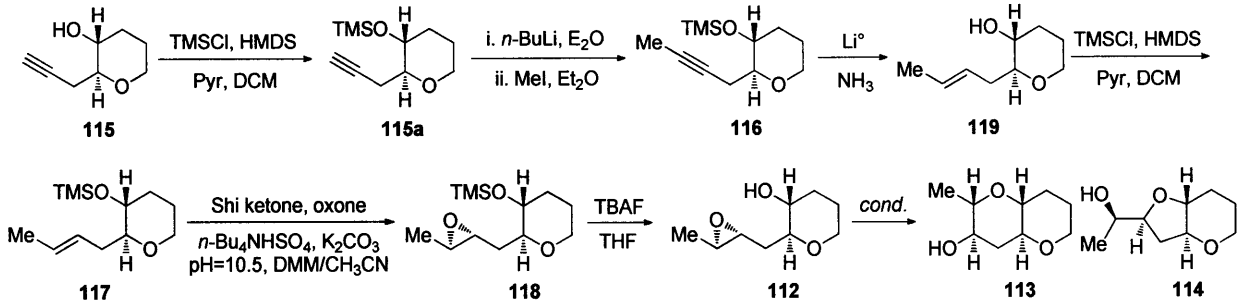
We have developed a general method for directing group-free epoxide-opening cascades that provide direct synthetic route to oligotetrahydropyran fragments, and demonstrate feasibility of such reactions in the biosynthesis of ladder polyethers. The two aspects of our strategy are a single design principle (a template) and a promoter that both donates and accepts hydrogen bonds (water). The utility of aqueous directing group-free cascades was further demonstrated in our group by synthesis of HIJK ring of gymnocin A and incorporation of methyl substituents at various positions in the THP triads diepoxide precursors.

Experimental section

Unless otherwise noted, all non-aqueous reactions were performed under an oxygen-free atmosphere of argon with rigid exclusion of moisture from reagents and glassware. Tetrahydrofuran (THF) and Et_2O were distilled from a blue solution of benzophenone ketyl. Toluene and dichloromethane were distilled from calcium hydride. Iodomethane was purified by washing with aqueous sodium thiosulfate, water, and then aqueous sodium carbonate, followed by distillation. *n*-Butyllithium was titrated prior to use (menthol, Et_2O, 0 °C, 1,10-phenanthroline indicator). All other reagents were used as supplied by the chemical manufacturers. Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F254 plates. The developed chromatogram was analyzed by UV lamp (254 nm) and ethanolic phosphomolybdic acid (PMA) or ceric ammonium molybdate (CAM). 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 in $CDCl_3$, unless otherwise noted, on a Varian Inova 500 MHz, a Bruker Avance 400 MHz or a Bruker Avance 600 MHz spectrometer. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.2 ppm), or C_6D_6 (128.4 ppm) on the δ scale. Infrared (IR) spectra were recorded on a Perkin-Elmer 2000 FT-IR. High Resolution mass spectra (HR-MS) were obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by Dr. Li Li of the MIT Department of Chemistry

Instrumentation Facility. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 589 nm.

Scheme E1. Synthesis of model epoxy alcohol **112** and cyclization to **113** and **114**.



Trimethyl((2*S*,3*R*)-2-(prop-2-ynyl)tetrahydro-2*H*-pyran-3-yloxy)silane (115a). To a stirred solution of (2*S*,3*R*)-2-(prop-2-ynyl)tetrahydro-2*H*-pyran-3-ol[114] (**115**) (2.04 g, 14.55 mmol) in dichloromethane (50 mL) and pyridine (8 mL) at 0°C was added hexamethyldisilazane (9.10 mL, 43.66 mmol) followed by chlorotrimethylsilane (5.54 mL, 43.66 mmol). The resulting white cloudy solution was stirred at ambient temperature for 30 minutes. After cooling to 0°C, the reaction was quenched by adding saturated aqueous solution of NH_4Cl. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with saturated NH_4Cl, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (5% EtOAc in hexane) to yield silyl ether **115a** (2.78 g, 90%): $[\alpha]^{25}_D$ = –48.4 (c = 2.8 in $CDCl_3$); IR (thin film, NaCl) 3314, 2955, 2853, 2122, 1252, 1098 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.94-3.90 (m, 1H), 3.48-3.43 (m, 1H), 3.33 (td, *J* = 11.5, 2.5 Hz, 1H), 3.16-3.12 (m, 1H), 2.61-2.56 (m, 1H), 2.44-2.39 (m, 1H), 1.99-1.96 (m, 1H), 1.98 (t, *J* = 2.6 Hz, 1H), 1.70-1.61 (m, 2H), 1,59-1.41 (m, 1H), 0.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.3, 80.3, 69.8, 69.7, 68.1, 33.4, 25.5, 22.1, 0.5 (3C); HR-MS (ESI) Calcd for $C_{11}H_{20}NaO_2Si$ $(M+Na)^+$ 235.1125, found 235.1133.

((2*S*,3*R*)-2-(But-2-ynyl)tetrahydro-2*H*-pyran-3-yloxy)trimethylsilane (116). To a stirred solution of **115a** (120 mg, 0.57 mmol) in Et_2O (5.7 mL) at –78°C, and *n*-BuLi (2.5 M in hexane, 238 μL, 0.59 mmol) was added dropwise. After stirring for 10 min at –78°C, the cold bath was removed and reaction mixture was stirred for 30 minutes. Upon cooling to –78°C iodomethane (53 μL, 0.85 mmol) was added dropwise, cooling bath was removed and reaction mixture was stirred at ambient temperature for 1 h. The reaction was quenched by addition of water at 0°C. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (5% EtOAc in hexane) to yield **116** (118 mg, 92%): $[\alpha]^{25}_D$ = –13.7 (c = 0.8 in $CDCl_3$); IR (thin film, NaCl) 2956, 2854, 2360, 1252, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.98-3.95 (m, 1H), 3.53-3.47 (m, 1H), 3.38 (td, *J* = 11.6, 2.8 Hz, 1H), 3.17-3.12 (m, 1H), 2.61-2.56 (m, 1H), 2.45-2.39 (m, 1H), 2.04-1.99 (m, 1H), 1.83 (t, *J* = 2.4 Hz, 3H), 1.74-1.62 (m, 2H), 1,57-1.43 (m, 1H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 80.9, 77.0, 75.8, 69.8, 68.1, 33.4, 25.6, 22.4, 3.9, 0.4 (3C); HR-MS (ESI) Calcd for $C_{12}H_{22}NaO_2Si$ $(M+Na)^+$ 249.1281, found 249.1273.

(2*S*,3*R*)-2-((*E*)-But-2-enyl)tetrahydro-2*H*-pyran-3-ol (119). To a stirring solution of **116** (118 mg, 0.52 mmol) in liquid ammonia (~10 mL) at –78°C was added lithium (18 mg, 2.61 mmol) and resulting deep blue solution was stirred for 1 h at –78°C. The reaction was quenched by slow addition of powdered NH_4Cl at –78°C. Resulting slurry was removed from the cooling bath and ammonia was allowed to evaporate. Upon removal of ammonia, solid residue was dissolved in water and Et_2O. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20%

EtOAc in hexane) to yield alkene **119** (76 mg, 93%, >95% *E*): $[\alpha]^{25}_D = -19.7$ (c = 2.0 in $CDCl_3$); IR (thin film, NaCl) 3407, 2937, 2855, 1439, 1270, 1098, 1029, 969 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.57-5.49 (m, 2H), 3.91-3.87 (m, 1H), 3.37-3.28 (m, 2H), 3.07-3.03 (m, 1H), 2.51-2.46 (m, 1H), 2.24-2.18 (m, 1H), 2.08-2.05 (m, 1H), 1.99 (br s, 1H), 1.70-1.63 (m, 5H), 1.42-1.34 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 127.61, 127.58, 82.2, 71.4, 67.8, 35.9, 32.8, 25.7, 18.3; HR-MS (ESI) Calcd for $C_9H_{16}NaO_2$ $(M+Na)^+$ 179.1043, found 179.1046.

((2*S*,3*R*)-2-((*E*)-But-2-enyl)tetrahydro-2*H*-pyran-3-yloxy)trimethylsilane (117). To a stirred solution of **119** (72 mg, 0.46 mmol) in dichloromethane (4.0 mL) and pyridine (0.6 mL) at 0°C was added hexamethyldisilazane (288 μL, 1.38 mmol) followed by chlorotrimethylsilane (175 μL, 1.38 mmol). The resulting white cloudy solution was stirred at ambient temperature for 30 minutes. After cooling to 0°C, the reaction was quenched by adding saturated aqueous solution of NH_4Cl. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with saturated NH_4Cl, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (5% EtOAc in hexane) to yield silyl ether **117** (100 mg, 95%): $[\alpha]^{25}_D = -32.9$ (c = 2.2 in $CDCl_3$); IR (thin film, NaCl) 2957, 2854, 1439, 1251, 1128, 1100 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.52-5.48 (m, 2H), 3.91-3.87 (m, 1H), 3.33-3.27 (m, 2H), 3.07-3.03 (m, 1H), 2.51-2.47 (m, 1H), 2.07-1.95 (m, 2H), 1.71-1.60 (m, 5H), 1.48-1.39 (m, 1H), 0.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 127.61, 127.58, 82.2, 71.4, 67.8, 35.9, 32.8, 25.7, 18.3; HR-MS (ESI) Calcd for $C_{12}H_{24}NaO_2Si$ $(M+Na)^+$ 251.1438, found 251.1438.

Trimethyl((2*S*,3*R*)-2-(((2*R*,3*R*)-3-methyloxiran-2-yl)methyl)tetrahydro-2*H*-pyran-3-yloxy)silane (118). To a solution of the alkene **117** (228 mg, 1.00 mmol) in CH_3CN/DMM (30 mL, 1:2 v:v) was added a 0.05 M solution of $Na_2B_4O_7 \cdot 10\ H_20$ in $4.0 \cdot 10^{-4}$ M Na_2EDTA (20 mL),

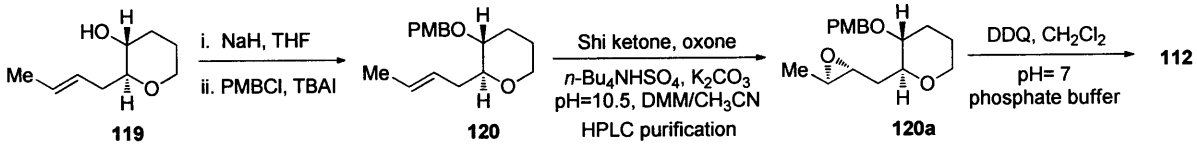
n-BuNHSO$_4$ (68 mg, 0.20 mmol), and Shi ketone (516 mg, 2.00 mmol). To this rapidly stirring solution was added, simultaneously over 20 min via syringe pump, a solution of Oxone® (2.46 g, 4.00 mmol) in $4.0 \cdot 10^{-4}$ M Na_2EDTA (17.0 mL) and a 0.89 M solution of K_2CO_3 (17.0 mL). After the Oxone® and K_2CO_3 solutions had been added, the resulting mixture was stirred for additional 40 minutes. The reaction mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The epoxide product was separated from the ketone catalyst by column chromatography (20% EtOAc in hexane) to afford epoxide **118** (215 mg, 88%, dr 6:1): $[\alpha]^{25}_D = -27.4$ (c = 2.6 in $CDCl_3$); IR (thin film, NaCl) 2957, 2853, 1439, 1379, 1252, 1098 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.89-3.85 (m, 1H), 3.33-3.28 (m, 2H), 3.13 (td, *J* = 8.5, 3.0 Hz, 1H), 2.82-2.79 (m, 1H), 2.74-2.71 (m, 1H), 1.98-1.94 (m, 1H), 1.89 (ddd, *J* = 14.0, 5.5, 2.5 Hz, 1H), 1.68-1.59 (m, 3H), 1.47-1.37 (m, 1H), 1.27 (d, *J* = 5.8 Hz, 3H), 0.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 80.9, 71.1, 67.9, 57.5, 54.1, 34.9, 33.7, 25.7, 17.8, 0.5 (3C); HR-MS (ESI) Calcd for $C_{12}H_{24}NaO_3Si$ $(M+Na)^+$ 267.1387, found 267.1390.

(2*S*,3*R*)-2-(((2*R*,3*R*)-3-methyloxiran-2-yl)methyl)tetrahydro-2*H*-pyran-3-ol (112). To a stirred solution of silyl ether **118** (174 mg, 0.71 mmol) in THF (7.1 mL) at ambient temperature was added TBAF (1 M in THF, 2.14 mL, 2.14 mmol) and resulting solution was stirred for 30 min. The reaction was quenched by addition of water. The reaction mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (70% EtOAc in hexane) to yield epoxy alcohol **112** (116 mg, 95%): $[\alpha]^{25}_D = -9.3$ (c = in $CDCl_3$); IR (thin film, NaCl) 3427, 2936, 2855, 1653, 1439, 1381, 1273, 1096 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89-3.85 (m, 1H), 3.54-3.48 (m, 1H), 3.34-3.28 (m, 1H), 3.17-3.11 (m, 1H), 2.90-2.87 (m, 1H), 2.81-2.76 (qd,

J = 5.2, 2.4 Hz, 1H), 2.43 (br s, 1H), 2.12-2.03 (m, 2H), 1.71-1.60 (m, 3H), 1.43-1.32 (m, 1H), 1.27 (d, J = 5.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.2, 70.3, 68.6, 57.3, 55.1, 35.4, 32.9, 26.5, 18.2; HR-MS (ESI) Calcd for $C_9H_{16}NaO_3$ $(M+Na)^+$ 195.0992, found 195.0996.

(2*S*,3*R*,4*aS*,8*aR*)-2-Methyloctahydropyrano[3,2-*b*]pyran-3-ol (113) and (*R*)-1-((2*S*,3*aS*,7*aR*)-Hexahydro-2*H*-furo[3,2-*b*]pyran-2-yl)ethanol (114). In a representative procedure, epoxy alcohol **112** (1 mg, 5.8 μmol) was dissolved in appropriate solvent (water, phosphate buffer, THF/H_2O mixture, dichloromethane etc.) (1 mL) and stirred at appropriate temperature for 3 days. Reaction mixture was diluted with brine and additional NaCl was added to saturate aqueous layer. The reaction mixture was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was analyzed by ^{1}H NMR spectroscopy to determine the ratio of **113**[114] and **114**. Data for **114**: $[\alpha]^{25}_D$ = –14.5 (c = 0.5 in $CDCl_3$); IR (thin film, NaCl) 3364, 2924, 2854, 1660, 1467, 1310, 1279 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.04-3.98 (m, 3H), 3.48 (td, J = 11.6, 3.2 Hz, 1H), 3.35-3.22 (m, 2H), 2.26-2.21 (m, 1H), 2.10-1.90 (m, 1H), 1.72-1.60 (m, 2H), 1.56-1.47 (m 1H), 1.16 (d, J = 5.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.9, 81.3, 79.4, 69.8, 69.5, 30.4, 30.3, 25.2, 18.6; HR-MS (ESI) Calcd for $C_9H_{16}NaO_3$ $(M+Na)^+$ 195.0992, found 195.0997.

Scheme E2. Preparation of pure **112** by HPLC purification of **120a**.



(2*S*,3*R*)-2-((*E*)-But-2-enyl)-3-(4-methoxybenzyloxy)tetrahydro-2*H*-pyran (120). To a stirred solution of **119** (237 mg, 1.52 mmol) in THF (15.2 mL) was added NaH (dry 95%, 58 mg, 2.28 mmol) and the resulting slurry was stirred at ambient temperature for 15 min. 4-

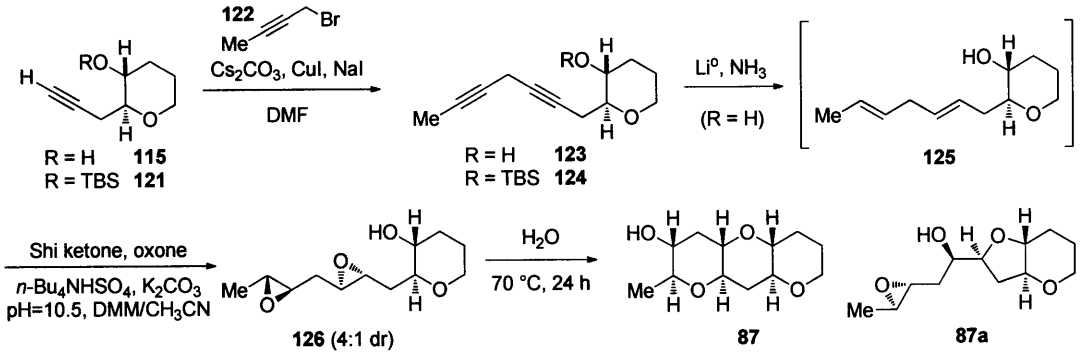
Methoxybenzyl chloride (309 μL, 2.28 mmol) was added to a reaction mixture followed by tetrabutylammonium iodide (560 mg, 1.52 mmol). Resulting slurry was stirred for 2 days. The reaction was quenched by addition of water at 0°C. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (5% EtOAc in hexane) to yield **120** (382 mg, 91%): $[\alpha]^{25}_D$ = –34.9 (c = 7.1 in $CDCl_3$); IR (thin film, NaCl) 2936, 2851, 1612, 1513, 1248, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 5.6 Hz, 2H), 6.91 (d, *J* = 5.6 Hz, 2H), 5.56-5.48 (m, 2H), 4.58 (d, *J* = 7.4 Hz, 1H), 4.41 (d, *J* = 7.4 Hz, 1H), 3.94-3.91 (m, 1H), 3.83 (s, 3H), 3.35 (td, *J* = 7.6, 2.0 Hz, 1H), 3.23-3.20 (m, 1H), 3.17-3.14 (m, 1H), 2.61-2.58 (m, 1H), 2.29-2.27 (m, 1H), 2.21-2.18 (m, 1H), 1.70-1.61 (m, 5H), 1.42-1.36 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 130.8, 129.6 (2C), 127.8, 127.2, 114.0 (2C), 81.0, 76.6, 70.6, 68.0, 55.5, 35.6, 29.4, 25.6, 18.3; HR-MS (ESI) Calcd for $C_{17}H_{24}NaO_3$ $(M+Na)^+$ 299.1618, found 299.1617.

(2*S*,3*R*)-3-(4-Methoxybenzyloxy)-2-(((2*R*,3*R*)-3-methyloxiran-2-yl)methyl)tetrahydro-2*H*-pyran (120a). To a solution of the alkene **120** (382 mg, 1.38 mmol) in CH_3CN/DMM (42 mL, 1:2 v:v) was added a 0.05 M solution of $Na_2B_4O_7 \cdot 10\ H_20$ in $4.0 \cdot 10^{-4}$ M Na_2EDTA (28 mL), *n*-$BuNHSO_4$ (95 mg, 0.28 mmol), and Shi ketone (713 mg, 2.76 mmol). To this rapidly stirring solution was added, simultaneously over 20 min via syringe pump, a solution of Oxone® (3.40 g, 5.53 mmol) in $4.0 \cdot 10^{-4}$ M Na_2EDTA (23.5 mL) and a 0.89 M solution of K_2CO_3 (23.5 mL). After the Oxone® and K_2CO_3 solutions had been added, the resulting mixture was stirred for an additional hour. The reaction mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The epoxide product could not be separated from the ketone catalyst and so was dissolved in CH_2Cl_2 (13.8 mL) and to

this was added $NaHCO_3$ (1.16 g, 13.8 mmol), and *m*-CPBA (77% dry, 1.00 g, 4.14 mmol) and the reaction stirred 30 min. The reaction was quenched with 1 M NaOH and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (20% EtOAc in hexane) to afford epoxide **120a** (335 mg, 83%, dr 7:1). Semipreparative HPLC separation afforded a single enantiomer of **120a**: $[\alpha]^{25}_D$ = 33.6 (c = 2.8 in $CDCl_3$); IR (thin film, NaCl) 2937, 2852, 1613, 1514, 1248, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.56 (d, *J* = 10.9 Hz, 1H), 4.41 (d, *J* = 10.9 Hz, 1H), 3.92-3.89 (m, 1H), 3.81 (s, 3H), 3.36-3.27 (m, 2H), 3.23-3.19 (m, 1H), 2.87-2,84 (m, 1H), 2.79-2.76 (m, 1H), 2.29-2.23 (m, 1H), 2.05 (ddd, *J* = 11.2, 5.2, 3.2 Hz, 1H), 1.78-1.62 (m, 3H), 1.41-1.33 (m, 1H), 1.29 (d, *J* = 5.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 130.7, 129.7 (2C), 114.0 (2C), 79.2, 76.9, 70.7, 67.9, 57.2, 55.5, 54.1, 34.9, 29.6, 25.5, 17.6; HR-MS (ESI) Calcd for $C_{17}H_{24}NaO_4$ $(M+Na)^+$ 315.1567, found 315.1558.

(2*S*,3*R*)-2-(((2*R*,3*R*)-3-Methyloxiran-2-yl)methyl)tetrahydro-2*H*-pyran-3-ol (112). To a stirred solution of **120a** (146 mg, 0.50 mmol) in dichloromethane (10 mL) at ambient temperature was added 1 M phosphate buffer pH 7.0 (2 mL) followed by 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (227 mg, 1.00 mmol). Resulting slurry was stirred at ambient temperature for 30 minutes. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (70% EtOAc in hexane) to yield recovered starting material (98 mg, 67%) and **112** (25 mg. 29%, 87% brsm).

Scheme E3. Preparation of diepoxide and epoxide-opening cascades of **126**.



***tert*-Butyldimethyl((2*S*,3*R*)-2-(prop-2-ynyl)tetrahydro-2*H*-pyran-3-yloxy)silane (121).** To a stirred solution of (2*S*,3*R*)-2-(prop-2-ynyl)tetrahydro-2*H*-pyran-3-ol[114] **115** (200 mg, 1.43 mmol) in Et_2O (14.3 mL) was added 2,6-lutidine (414 μL, 3.57 mmol) followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (393 μL, 1.71 mmol). Resulting solution was stirred for 1 h at ambient temperature. The reaction was quenched by addition of saturated NH_4Cl solution at 0°C. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with saturated NH_4Cl, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (5% EtOAc in hexane) to yield silyl ether **121** (338 mg. 93%): $[\alpha]^{25}_D = -48.1$ (c = 2.9 in $CDCl_3$); IR (thin film, NaCl) 3315, 2930, 2957, 2123, 14,72, 1252, 1128, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.97-3.93 (m, 1H), 3.49-3.45 (m, 1H), 3.36 (td, *J* = 11.6, 2.8 Hz, 1H), 3.17-3.12 (m, 1H), 2.64-2.59 (m, 1H), 2.45 (ddd, *J* = 14.0, 6.0, 2.8 Hz, 1H), 2.06-1.99 (m, 1H), 2.00 (t, *J* = 2.6 Hz, 1H), 1.73-1.59 (m, 2H) , 1.44-1.38 (m, 1H), 0.87 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.4, 80.6, 69.8, 69.7, 68.2, 33.5, 25.9 (3C), 25.6, 22.1, 18.1, -3.9, -4.7; HR-MS (ESI) Calcd for $C_{14}H_{26}NaO_2Si$ $(M+Na)^+$ 277.1594, found 277.1594.

(2*S*,3*R*)-2-(Hepta-2,5-diynyl)tetrahydro-2*H*-pyran-3-ol (123). Mixture of copper(I) iodide (380 mg, 2.00 mmol), sodium iodide (300 mg, 2.00 mmol) and cesium carbonate (652 mg,

2.00 mmol) was heated in the drying oven at 150°C for 2 h. After cooling to ambient temperature this mixture was suspended in solution of **115** (140 mg, 1.00 mmol) in dry DMF (8 mL). The solution of 1-bromo-2-butyne **122** (175 μL, 2.00 mmol) in dry DMF (2 mL) was added and the resulting slurry was stirred at ambient temperature for 2 days. The reaction was quenched by addition of saturated NH_4Cl solution at 0°C. The resulting mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (30% then 50% EtOAc in hexane) to yield skipped diyne **123** (178 mg, 92%): $[\alpha]^{25}_D = -13.7$ (c = 2.7 in C_6D_6); IR (thin film, NaCl) 3411, 2940, 2857, 2213, 1666, 1418, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.93-3.87 (m, 1H), 3.49-3.44 (m, 1H), 3.32 (td, *J* = 11.4, 2.8 Hz, 1H), 3.13-3.04 (m, 3H), 2.64-2.59 (m, 1H), 2.51-2.47 (m, 1H), 2.09-2.03 (m, 1H), 1.73 (s. 3H), 1.69-1.59 (m, 2H), 1.41-1.33 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 81.4, 81.3, 78.2, 76.4, 74.5, 70.1, 68.0, 33.3, 26.1, 23.4, 10.4, 3.6; HR-MS (ESI) Calcd for $C_{12}H_{17}O_2$ $(M+H)^+$ 215.1043, found 215.1035.

***tert*-Butyl((2*S*,3*R*)-2-(hepta-2,5-diynyl)tetrahydro-2*H*-pyran-3-yloxy)dimethylsilane (124).** Mixture of copper(I) iodide (190 mg, 1.00 mmol), sodium iodide (150 mg, 1.00 mmol) and cesium carbonate (326 mg, 1.00 mmol) was heated in the drying oven at 150°C for 2 h. After cooling to ambient temperature this mixture was suspended in solution of **121** (127 mg, 0.50 mmol) in dry DMF (4 mL). The solution of 1-bromo-2-butyne (87 μL, 1.00 mmol) in dry DMF (1 mL) was added and the resulting slurry was stirred at ambient temperature for 2 days. The reaction was quenched by addition of saturated NH_4Cl solution at 0°C. The resulting mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (2% then 5% EtOAc in hexane) to yield skipped diyne **124** (133 mg, 87%): $[\alpha]^{25}_D = -21.3$ (c = 2.1 in

C_6D_6); IR (thin film, NaCl) 2929, 2857, 2237, 1756, 1472, 1361, 1252, 1096 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 3.78-3.71 (m, 1H), 3.62-3.55 (m, 1H), 3.17-3.05 (m, 2H), 3.03-2.99 (m, 2H), 2.76-2.69 (m, 1H), 2.62-2.54 (m, 1H), 1.88-1.80 (m, 1H), 1.53-1.39 (m, 1H), 1.51 (t, J = 2.3 Hz, 3H), 1.33-1.17 (m, 2H), 0.99 (s, 9H), 0.15 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 81.0, 77.7, 76.1, 75.7, 74.11, 70.1, 67.6, 33.6, 25.9 (3C). 25.7, 22.8, 18.0, 10.0, 3.2, -41, -4.8; HR-MS (ESI) Calcd for $C_{18}H_{30}NaO_2Si$ $(M+Na)^+$ 329.1913, found 329.1907.

(2*S*,3*R*)-2-(((2*R*,3*R*)-3-(((2*R*,3*R*)-3-Methyloxiran-2-yl)methyl)oxiran-2-yl)methyl)tetrahydro-2*H*-pyran-3-ol (126). To a stirring solution of lithium (13 mg, 1.92 mmol) in liquid ammonia (~10 mL) at –78°C was added solution of diyne **123** (37 mg, 0.19 mmol) in THF (0.5 mL) and the resulting deep blue mixture was allowed to reflux for 1 h. The reaction was quenched by slow addition of powdered NH_4Cl at –78°C. Resulting slurry was removed from the cooling bath and ammonia was allowed to evaporate. Upon removal of ammonia, solid residue was dissolved in water and Et_2O. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Instability of skipped diene **125** did not allow for purification and the material was taken to the next step crude.

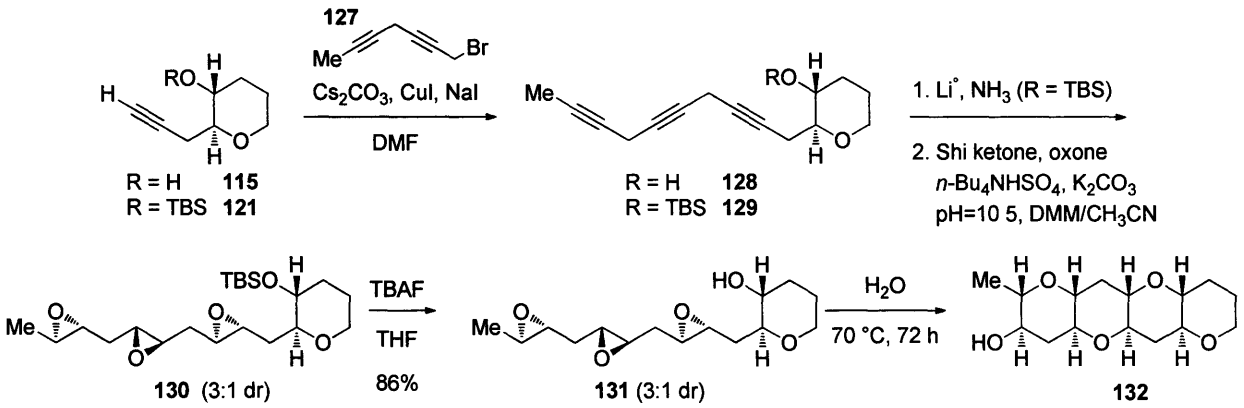
To a solution of the crude material from previous step in CH_3CN/DMM (11.5 mL, 1:2 v:v) was added a 0.05 M solution of $Na_2B_4O_7 \cdot 10\ H_2O$ in $4.0 \cdot 10^{-4}$ M Na_2EDTA (8.0 mL), *n*-$BuNHSO_4$ (26 mg, 0.08 mmol), and Shi ketone (99 mg, 0.38 mmol). To this rapidly stirring solution was added, simultaneously over 20 min via syringe pump, a solution of Oxone® (947 mg, 1.54 mmol) in $4.0 \cdot 10^{-4}$ M Na_2EDTA (6.5 mL) and a 0.89 M solution of K_2CO_3 (6.5 mL). After the Oxone® and K_2CO_3 solutions had been added, the resulting mixture was stirred for additional 2 hours. The reaction mixture was saturated with NaCl and extracted with Et_2O. The combined

organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography (30% then 50% EtOAc in hexane) to afford diepoxide **126** (22 mg, 50% over two steps, dr 4:1): $[\alpha]^{25}_D$ = +2.3 (c = 0.7 in $CDCl_3$); IR (thin film, NaCl) 3437, 2933, 1857, 1734, 1381, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.93-3.87 (m, 1H), 3.57-3.51 (m, 1H), 3.40-3.31 (m, 1H), 2.22-3.17 (m, 1H), 3.03-2.98 (m, 1H), 2.93-2.88 (m, 1H), 2.84-2.79 (m, 2H), 2.32 (br s, 1H), 2.17-2.09 (m, 2H), 1.80-1.65 (m, 5H), 1.48-1.39 (m, 1H), 1.32 (d, *J* = 5.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.1, 70.4, 68.6, 57.2, 56.3, 56.0, 55.2, 35.6, 35.4, 33.0, 26.5, 18.2; HR-MS (ESI) Calcd for $C_{12}H_{20}NaO_4$ $(M+Na)^+$ 251.1254, found 251.1252.

Triad (87) and (*R*)-1-((2*S*,3*aS*,7*aR*)-Hexahydro-2*H*-furo[3,2-*b*]pyran-2-yl)-2-((2*R*,3*R*)-3-methyloxiran-2-yl)ethanol (87a). Diepoxide **126** (15 mg, 66μmol, dr 4:1) was dissolved in 1 M phosphate buffer pH 7.6 (15 mL) and the resulting solution was stirred at ambient temperature for 28 days. The reaction mixture was saturated with NaCl and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography (30% then 50% and 70% EtOAc in hexane) to afford triad **87**[115] (9 mg, 60%) and epoxide **87a** (2.4 mg, 16%): $[\alpha]^{25}_D$ = –8.4 (c = 0.6 in CDCl3); IR (thin film, NaCl) 3364, 2924, 2854, 1660, 1467, 1310, 1279 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.08-3.98 (m, 3H), 3.46 (td, *J* = 11.6, 3.2 Hz, 1H), 3.31-3.19 (m, 2H), 2.93-2.88 (m, 2H), 2.43-2.39 (m, 1H), 2.24-2.11 (m, 2H), 1.91-1.80 (m, 1H), 1.75-1.45 (m, 4H), 1.56-1.47 (m 1H), 1.33 (d, *J* = 5.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.9, 80.1, 79.3, 71.7, 69.4, 57.9, 55.3, 34.9, 31.0, 30.4, 25.2, 18.2; HR-MS (ESI) Calcd for $C_{12}H_{20}NaO_4$ $(M+Na)^+$ 251.1254 found 251.1264.

Triad (87). Diepoxide **126** (11 mg, 48μmol, dr 4:1) was dissolved in water (11 mL) and the resulting solution was stirred for 24h at 70°C in a sealed tube. The reaction mixture was saturated with NaCl and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (30% then 50% EtOAc in hexane) to afford triad **87**[115] (6.6 mg, 60%).

Scheme E4. Preparation of triepoxide and epoxide-opening cascades of **131**.



1-Bromohepta-2,5-diyne (127). To a solution of hepta-2,5-diyn-1-ol[128] (300 mg, 2.77 mmol) in dichloromethane (28 mL) at 0°C was added triphenylphosphine (1.45 g, 5.55 mmol) and tetrabromomethane (1.84 g, 5.55 mmol). The resulting solution was stirred for 1 h at ambient temperature. Reaction mixture was filtered through a plug of silica, diluted with Et_2O and filtered through a plug of silica again. Resulting solution was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (1% then 2% EtOAc in hexane) to yield bromide **127** (446 mg, 94%): IR (thin film, NaCl) 2919, 2273, 2233, 1413, 1317, 1210, 1124 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 3.34 (t, J = 2.2 Hz, 2H), 2.81-2.77 (m, 2H), 1.41 (t, J = 2.6 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 82.7, 77.2, 76.1, 72.9, 15.1, 10.3, 3.5; HR-MS (EI) Calcd for C_7H_7Br $(M)^+$ 169.9731, found 169.9729.

(2*S*,3*R*)-2-(Deca-2,5,8-triynyl)tetrahydro-2*H*-pyran-3-ol (128). Mixture of copper(I) iodide (380 mg, 2.00 mmol), sodium iodide (300 mg, 2.00 mmol) and cesium carbonate (652 mg, 2.00 mmol) was heated in the drying oven at 150°C for 2 h. After cooling to ambient temperature this mixture was suspended in solution of **115** (140 mg, 1.00 mmol) in dry DMF (8 mL). The solution of 1-bromohepta-2,5-diyne **127** (342 mg, 2.00 mmol) in dry DMF (2 mL) was added and the resulting slurry was stirred at ambient temperature for 2 days. The reaction was quenched by addition of saturated NH_4Cl solution at 0°C. The resulting mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (30% then 50% EtOAc in hexane) to yield skipped diyne **128** (178 mg, 92%): $[\alpha]^{25}_D = -10.6$ (c = 1.2 in $CDCl_3$); IR (thin film, NaCl) 3414, 2940, 2856, 2218, 1673, 1418, 1319, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.93-3.89 (m, 1H), 3.53-3.49 (m, 1H), 3.34-3.29 (m, 2H), 3.09-2.99 (m, 4H), 2.66-2.60 (m, 1H), 2.58-2.53 (m, 1H), 2.07-2.02 (m, 1H), 1.76 (s, 3H), 1.68-1.59 (m, 2H), 1.41-1.34 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 81.3, 78.4, 76.6, 76.3, 75.8, 75.5, 73.9, 70.1, 68.0, 33.3, 26.1, 23.3, 10.3, 10.2, 3.5; HR-MS (ESI) Calcd for $C_{15}H_{18}NaO_2$ $(M+Na)^+$ 253.1199, found 253.1204.

***tert*-Butyl((2*S*,3*R*)-2-(deca-2,5,8-triynyl)tetrahydro-2*H*-pyran-3-yloxy)dimethylsilane (129).** Mixture of copper(I) iodide (190 mg, 1.00 mmol), sodium iodide (150 mg, 1.00 mmol) and cesium carbonate (326 mg, 1.00 mmol) was heated in the drying oven at 150°C for 2 h. After cooling to ambient temperature this mixture was suspended in solution of **121** (127 mg, 0.50 mmol) in dry DMF (4 mL). The solution of 1-bromohepta-2,5-diyne (171 mg, 1.00 mmol) in dry DMF (1 mL) was added and the resulting slurry was stirred at ambient temperature for 2 days. The reaction was quenched by addition of saturated NH_4Cl solution at 0°C. The resulting mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over

$MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (2% then 5% EtOAc in hexane) to yield skipped triyne **129** (195 mg, 85%): $[\alpha]^{25}_D$ = –9.7 (c = 16.8 in C_6D_6); IR (thin film, NaCl) 2929, 2857, 1718, 1472, 1252, 1097 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 3.71-3.67 (m, 1H), 3.53-3.48 (m, 1H), 3.09-2.99 (m, 2H), 2.91-2.89 (m, 2H), 2.87-2.84 (m, 2H), 2.66-2.61 (m, 1H), 2.53-2.47 (m, 1H), 1.81-1.77 (m, 1H), 1.44 (t, *J* = 11.6, 2.1 Hz, 3H), 1.48-1.37 (m, 1H), 1.23-1.12 (m, 2H), 0.92 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 81.4, 78.4, 76.4, 75.9, 75.6, 75.5, 74.0, 70.5, 68.1, 34.1, 26.4 (3C), 26.1, 23.2, 18.5, 10.3, 10.3, 3.6, -3.6, -4.3; HR-MS (ESI) Calcd for $C_{21}H_{32}NaO_2Si$ $(M+Na)^+$ 367.2064, found 367.2055.

***tert*-Butyldimethyl((2*S*,3*R*)-2-(((2*R*,3*R*)-3-(((2*R*,3*R*)-3-(((2*R*,3*R*)-3-methyloxiran-2-yl)methyl)oxiran-2-yl)methyl)oxiran-2-yl)methyl)tetrahydro-2*H*-pyran-3-yloxy)silane (130).**

To a stirring solution of lithium (21 mg, 3.02 mmol) in liquid ammonia (~25 mL) at –78°C was added solution of triyne **129** (68 mg, 0.20 mmol) in THF (2.0 mL) and the resulting deep blue mixture was allowed to reflux for 1 h. The reaction was quenched by slow addition of powdered NH_4Cl at –78°C. Resulting slurry was removed from the cooling bath and ammonia was allowed to evaporate. Upon removal of ammonia, solid residue was dissolved in water and Et_2O. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Instability of skipped triene did not allow for purification and the material was taken to the next step crude.

To a solution of the crude material from previous step in CH_3CN/DMM (18.0 mL, 1:2 v:v) was added a 0.05 M solution of $Na_2B_4O_7 \cdot 10\ H_20$ in $4.0 \cdot 10^{-4}$ M Na_2EDTA (12.0 mL), *n*-$BuNHSO_4$ (41 mg, 0.12 mmol), and Shi ketone (152 mg, 0.59 mmol). To this rapidly stirring

solution was added, simultaneously over 20 min via syringe pump, a solution of Oxone® (1.46 g, 2.37 mmol) in $4.0 \cdot 10^{-4}$ M Na_2EDTA (10.0 mL) and a 0.89 M solution of K_2CO_3 (10.0 mL). After the Oxone® and K_2CO_3 solutions had been added, the resulting mixture was stirred for additional 2.5 hours. The reaction mixture was saturated with NaCl and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The epoxide product could not be separated from the ketone catalyst and so was dissolved in CH_2Cl_2 (6.0 mL) and to this was added $NaHCO_3$ (248 mg, 2.95 mmol), and *m*-CPBA (77% dry, 216 mg, 0.89 mmol) and the reaction stirred for 30 min. The reaction was quenched with 1 M NaOH and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (20% EtOAc in hexane) to afford triepoxide **130** (32 mg, 41%, dr ~3:1): $[\alpha]^{25}_D = -0.8$ (c = 4.8 in $CDCl_3$); IR (thin film, NaCl) 2931, 2857, 175118, 1463, 1252, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.90-3.79 (m, 1H), 3.34-3.18 (m, 3H), 2.90-2.83 (m, 3H), 2.82-2.71 (m, 3H), 2.02-1.89 (m, 2H), 1.82-1.21 (series of m, 11H) 0.83 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.0, 71.1, 67.9, 56.6, 56.5, 55.7, 55.5, 54.8, 54.7, 35.24, 35.17, 34.7, 33.7, 26.0 (3C), 25.7, 18.2, 17.7, -3.8, -4.6; HR-MS (ESI) Calcd for $C_{21}H_{38}NaO_5Si$ $(M+Na)^+$ 421.2381, found 421.2387.

(2*S*,3*R*)-2-(((2*R*,3*R*)-3-(((2*R*,3*R*)-3-(((2*R*,3*R*)-3-Methyloxiran-2-yl)methyl)oxiran-2-yl)methyl)oxiran-2-yl)methyl)tetrahydro-2*H*-pyran-3-ol (131). To a stirred solution of triepoxide **130** (52 mg, 0.13 mmol) in THF (5.0 mL) was added TBAF (1 M in THF, 0.65 mL, 0.65 mmol). Reaction mixture was stirred at ambient temperature for 3 hours. The reaction was quenched by addition of brine. The resulting mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*.

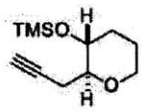
Purification of crude material by flash column chromatography (30% then 50% EtOAc in hexane) afforded alcohol **131** (32 mg, 86%, dr ~3:1): $[\alpha]^{25}_D$ = +7.5 (c = 1.2 in $CDCl_3$); IR (thin film, NaCl) 3442, 2932, 2856, 1438, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.96-3.88 (m, 1H), 3.57-3.50 (m, 1H), 3.40-3.33 (m, 1H), 3.23-3.17 (m, 1H), 3.04-3.00 (m, 1H), 2.93-2.87(m, 3H), 2.85-2.80 (m, 2H), 2.21-2.07 (m, 3H), 1.85-1.60 (series of m, 7H), 1.49-1.35 (m, 1H), 1.32 (d, *J* = 5.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.6, 70.0, 68.1, 56.6, 55.8, 55.7, 55.6, 55.4, 54.8, 35.2, 35.03, 34.96, 32.61, 26.0, 17.7; HR-MS (ESI) Calcd for $C_{15}H_{24}NaO_5$ $(M+Na)^+$ 307.1516 found, 307.1525.

Tetrad (132). Triepoxide **131** (32 mg, 0.11 mmol, dr ~3:1) was dissolved in water (32 mL) and the resulting solution was stirred for 3 days at 70°C in a sealed tube. Water was removed *in vacuo* and the residue was purified by column chromatography (50% EtOAc in hexane) to afford tetrad **132** (17 mg, 53%): $[\alpha]^{25}_D$ = +3.6 (c = 12.8 in $CDCl_3$); IR (thin film, NaCl) 3432, 2930, 2857, 1457, 1342, 1105, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.96-3.90 (m, 1H), 3.43-3.34 (m, 2H), 3.26-3.21 (m, 1H), 3.17-3.13 (m, 2H), 3.12-3.09 (m, 2H), 3.08-3.03 (m, 2H), 2.42-2.39 (m, 1H), 2.38-2.31 (m, 2H), 2.11-2.17 (m, 1H), 1.75-1.70 (m, 2H), 1.60, 1.43 (m, 5H), 1.31 (d, *J* = 5.2 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 79.1, 79.0, 78.2, 77.9, 77.8, 77.6, 77.3, 72.0, 68.1, 39.6, 36.7, 36.4, 30.1, 26.2, 18.5; HR-MS (ESI) Calcd for $C_{15}H_{24}NaO_5$ $(M+Na)^+$ 307.1516, found 307.1521.

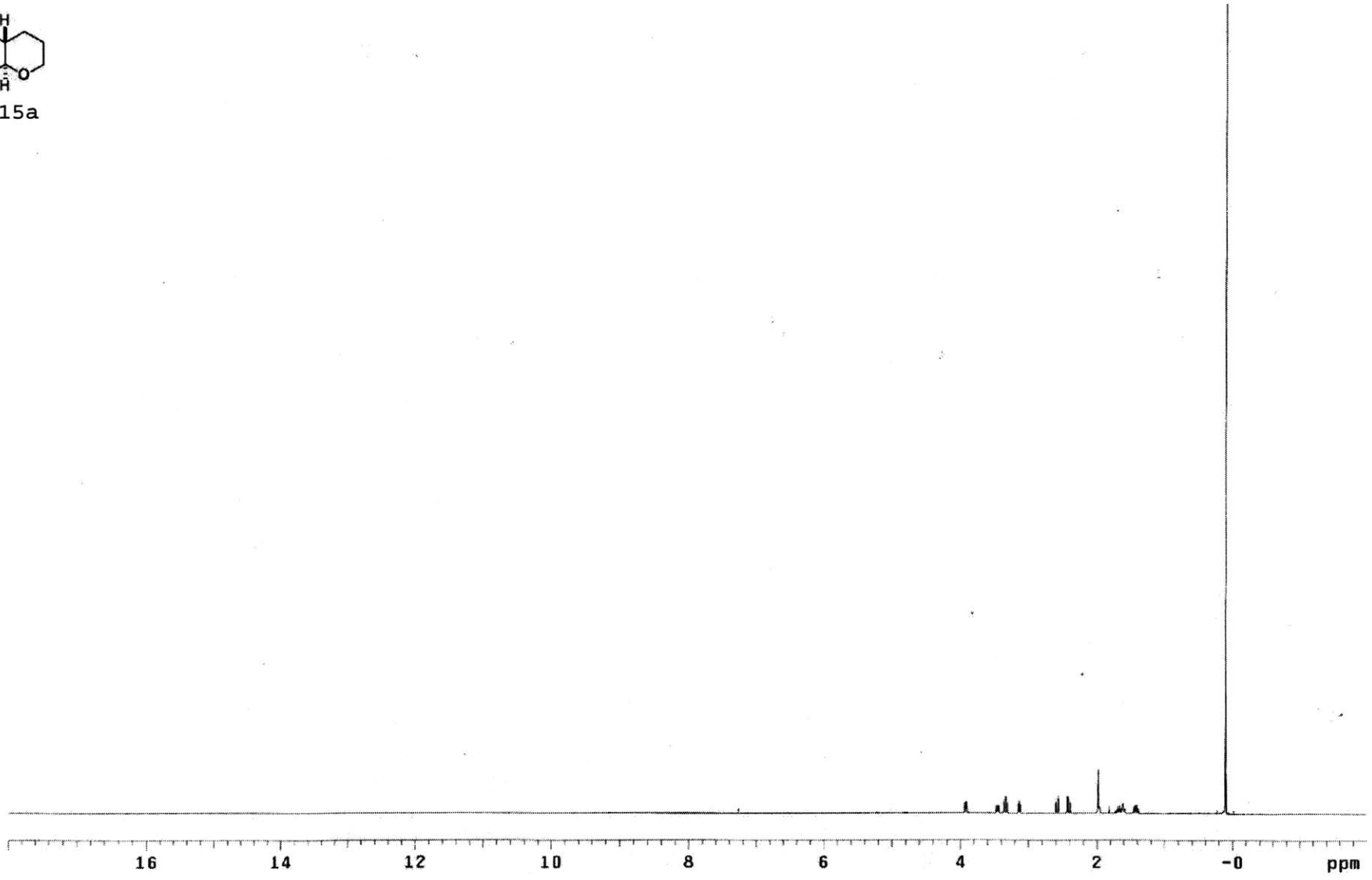
Tetrad Acetate (132a). Alcohol **132** (1.6 mg, 5.6 μmol) was dissolved in dichloromethane (1.0 mL) and treated successively with pyridine (4.5 μL, 56 μmol), 4-(dimethylamino)pyridine (0.7 mg, 5.6 μmol) and acetic anhydride (5.3 μL, 56 μmol). Reaction mixture was stirred for 12 h at ambient temperature and then quenched by addition of water. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were

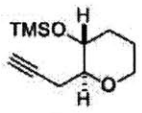
washed with saturated NH_4Cl, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (40% EtOAc in hexane) to yield tetrad acetate **132a**[115] (1.6 mg, 87%).

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

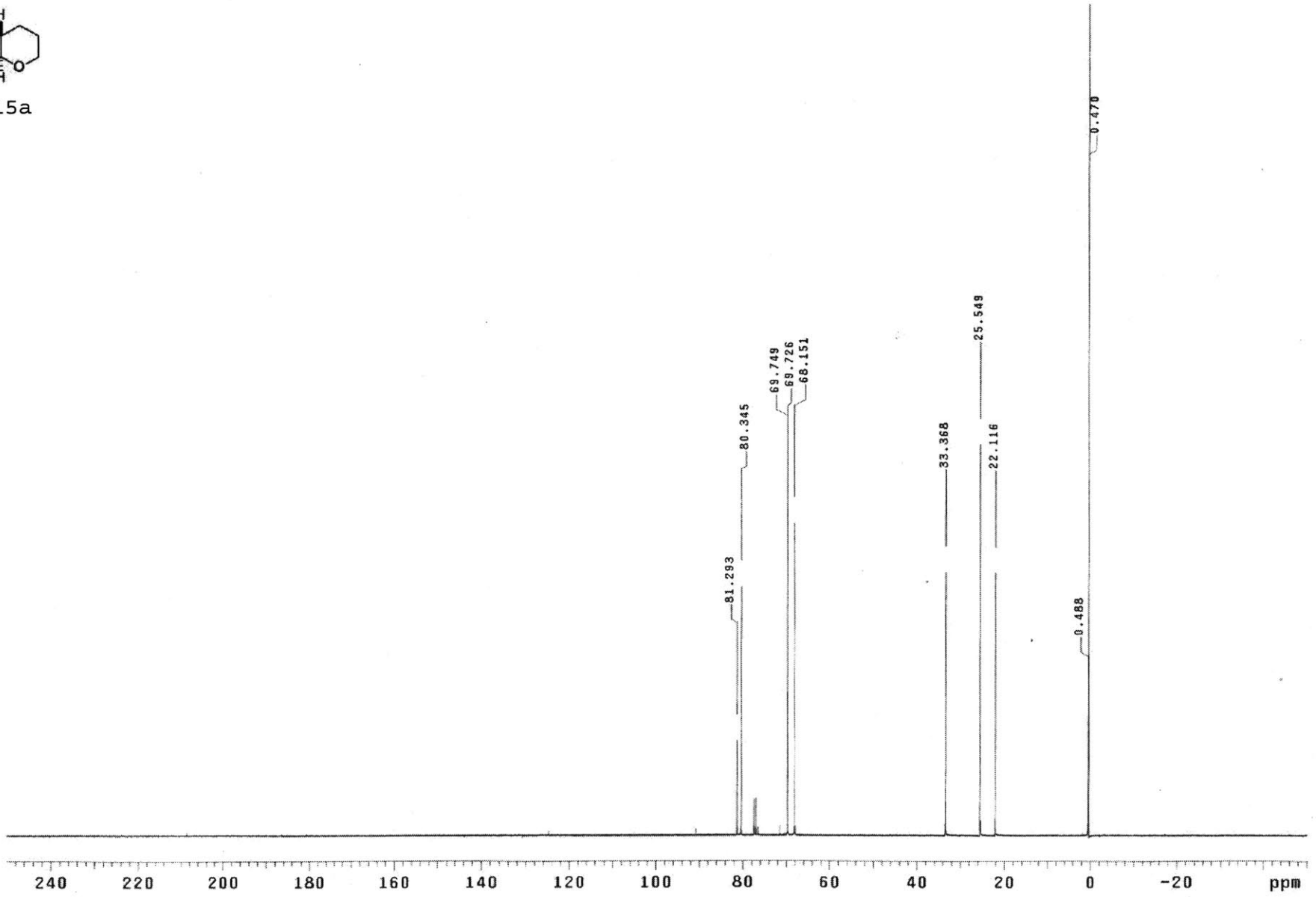


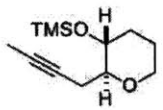
115a




TMSO
H
O
H

115a


81.293
80.345
69.749
69.726
68.151
33.368
25.549
22.116
0.488
0.470
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

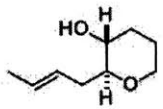


116

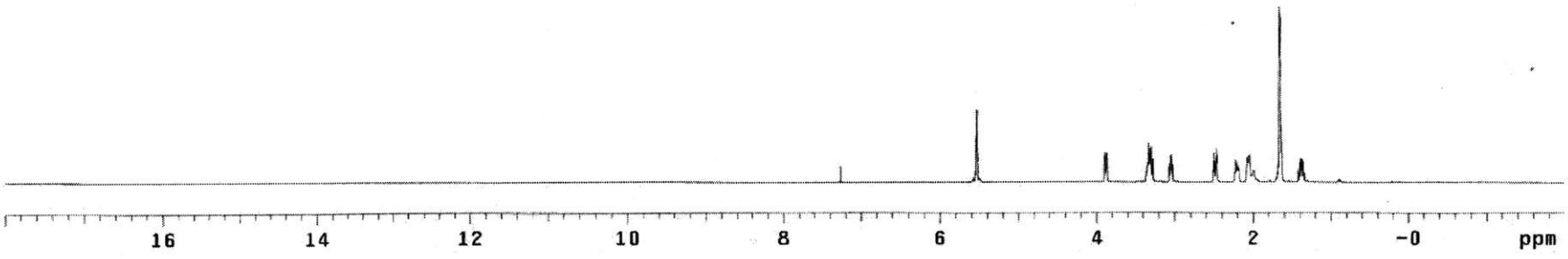
TMSO
H
H
O

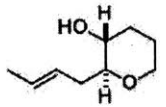
116

80.869
76.974
75.765
69.810
68.107
33.405
25.619
22.415
3.872
0.439
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

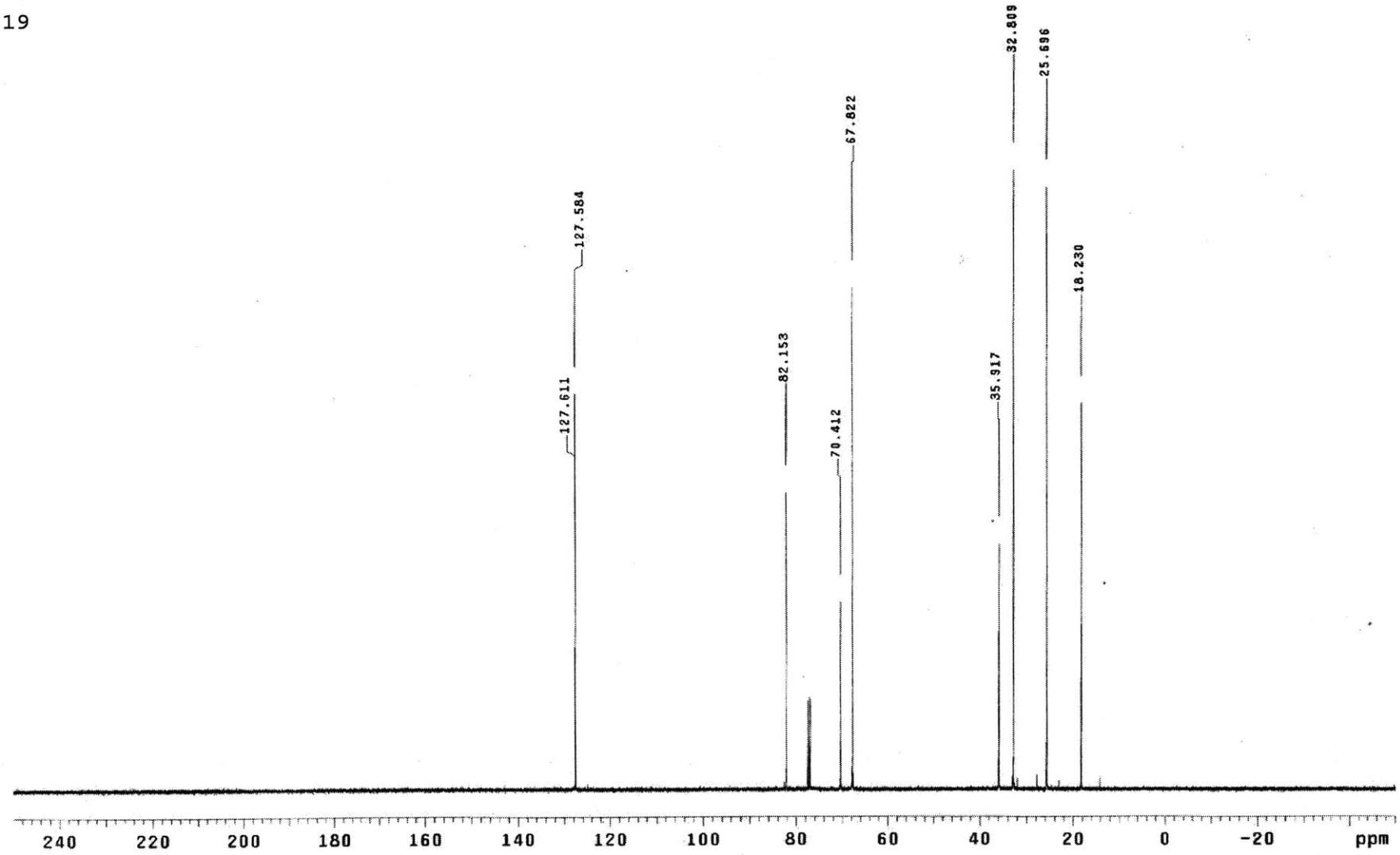


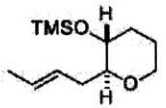
119



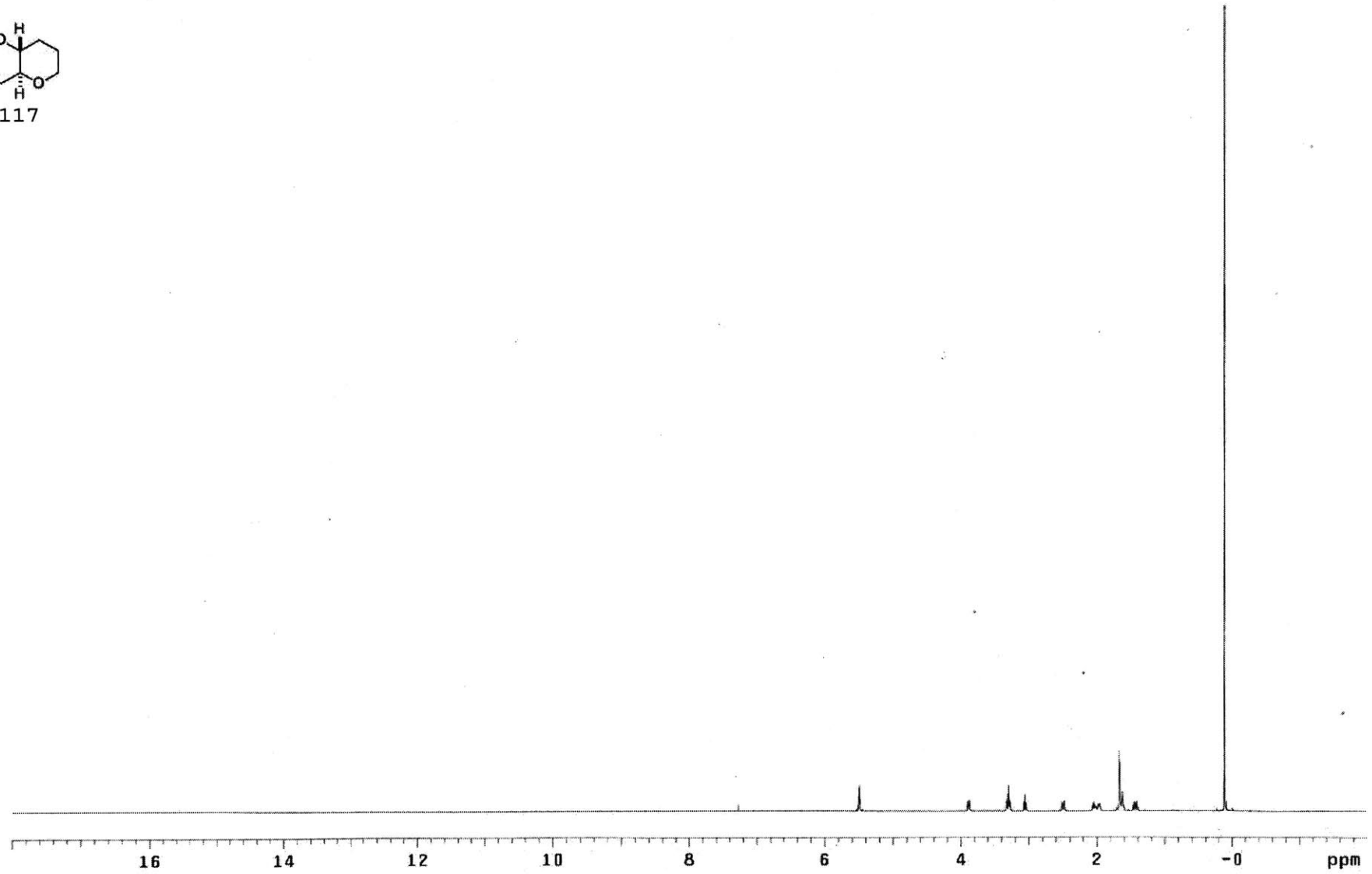

HO
H
O
H

119


127.611
127.584
82.153
70.412
67.822
35.917
32.809
25.696
18.230
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm



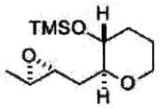
117



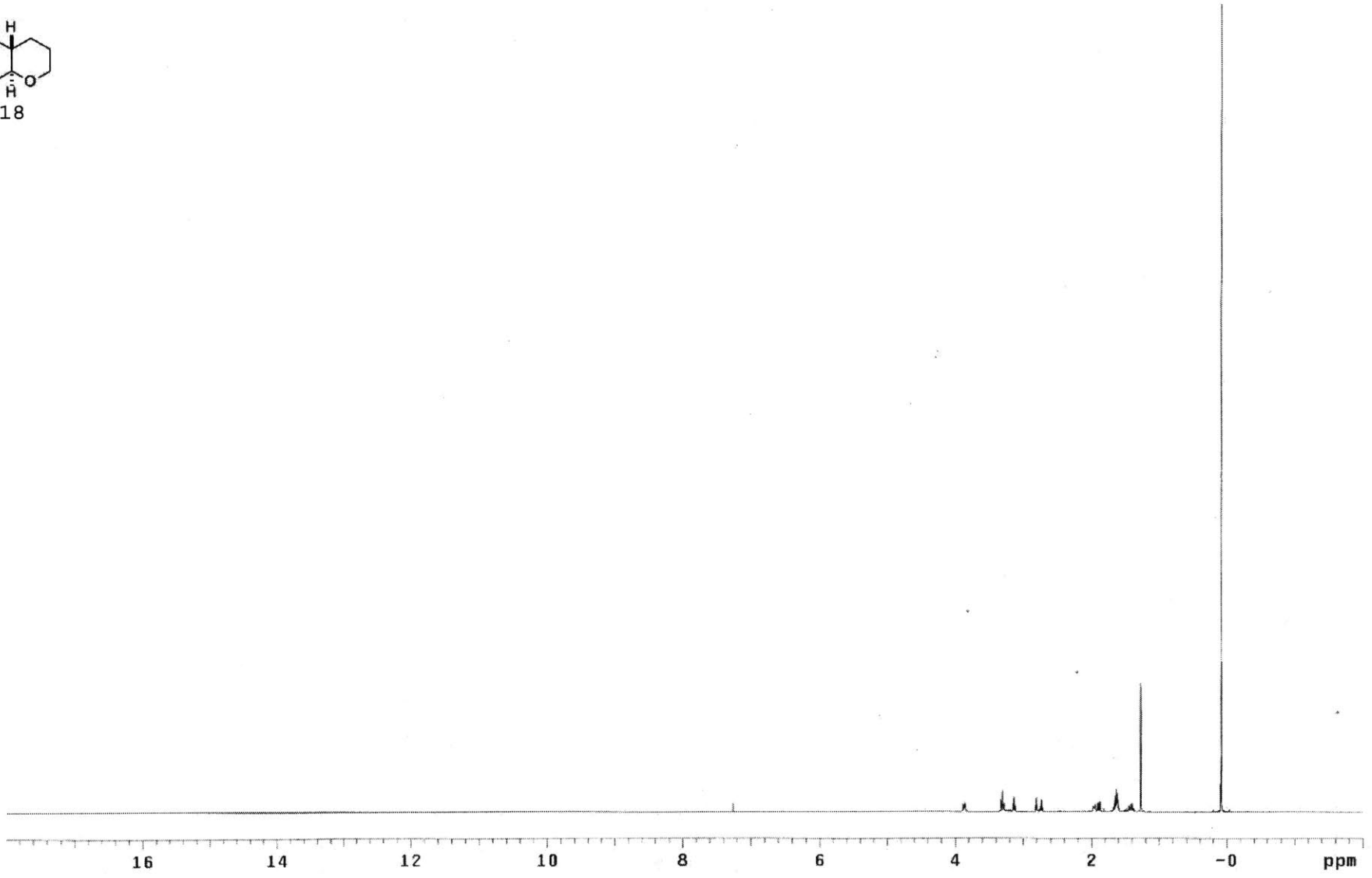
TMSO
H
H
O

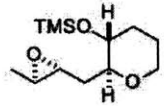
117

128.486
127.543
83.124
71.653
68.577
36.132
34.251
26.410
18.807
1.111
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

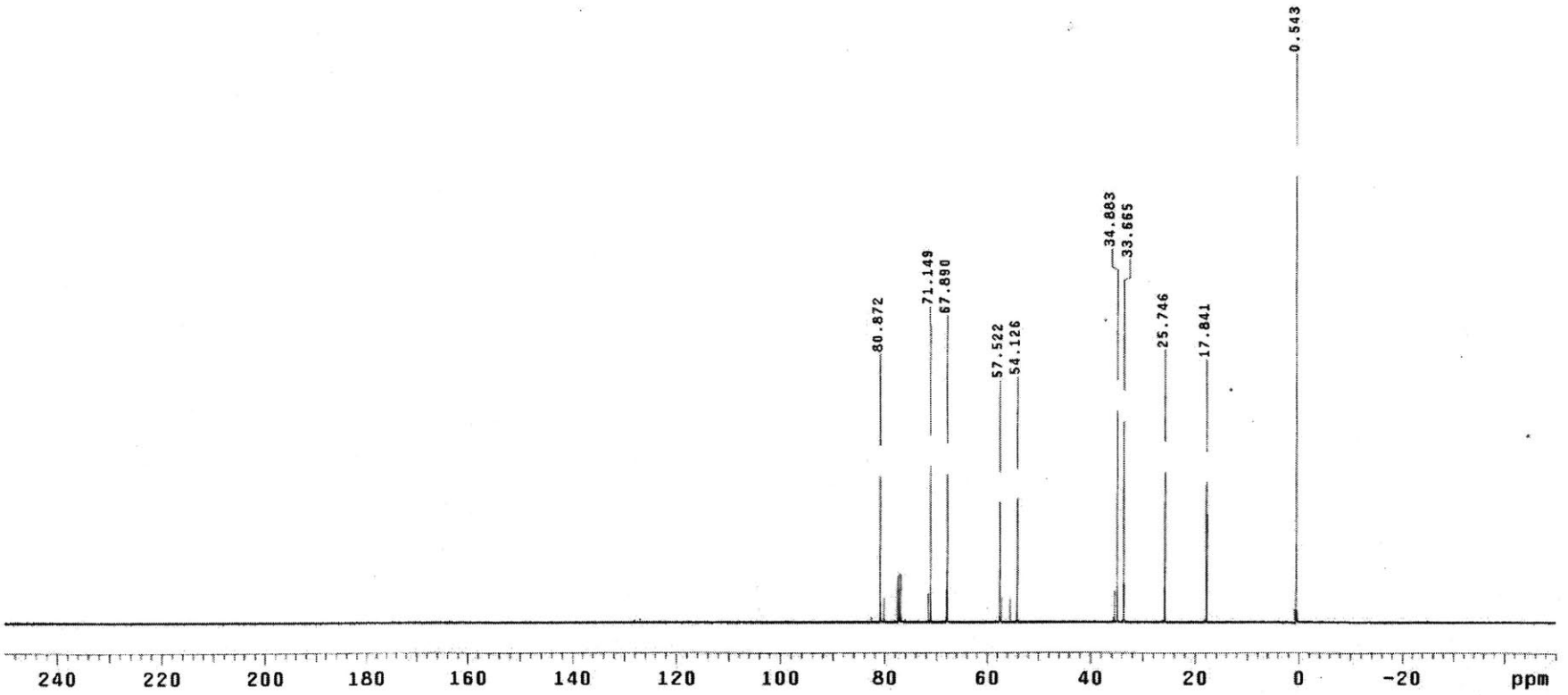


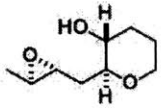
118



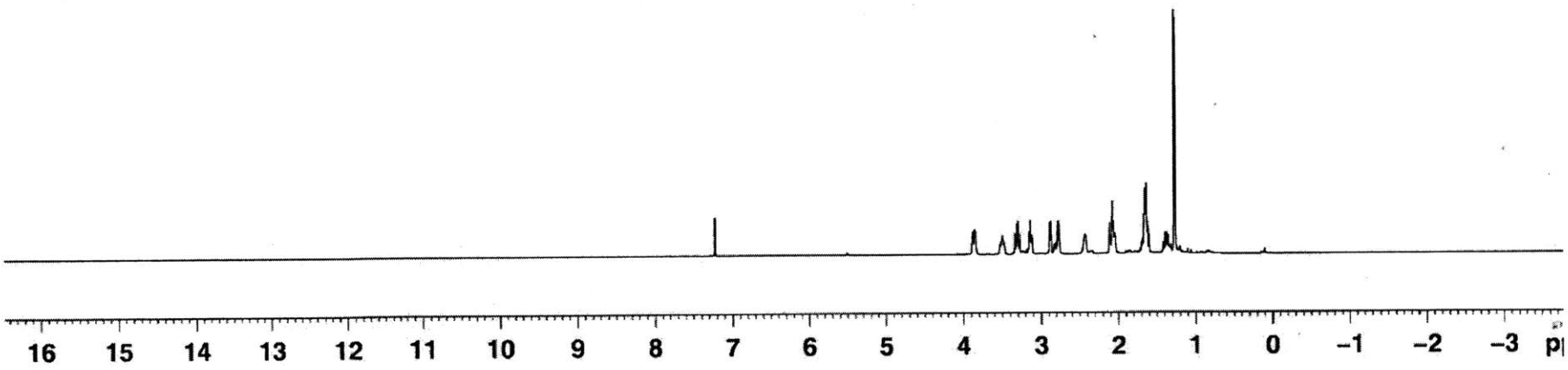

TMSO
H
O
O
H

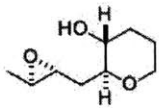
118


80.872
71.149
67.890
57.522
54.126
34.883
33.665
25.746
17.841
0.543
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

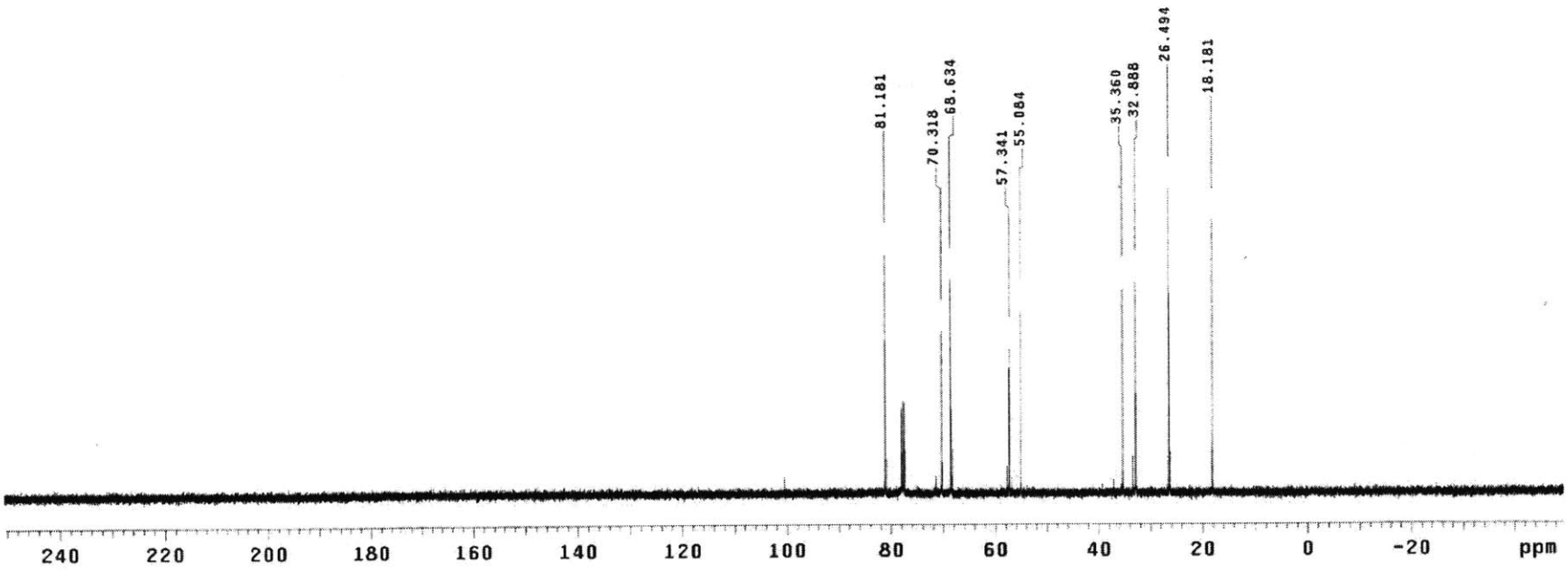


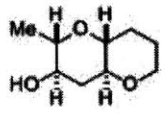
112



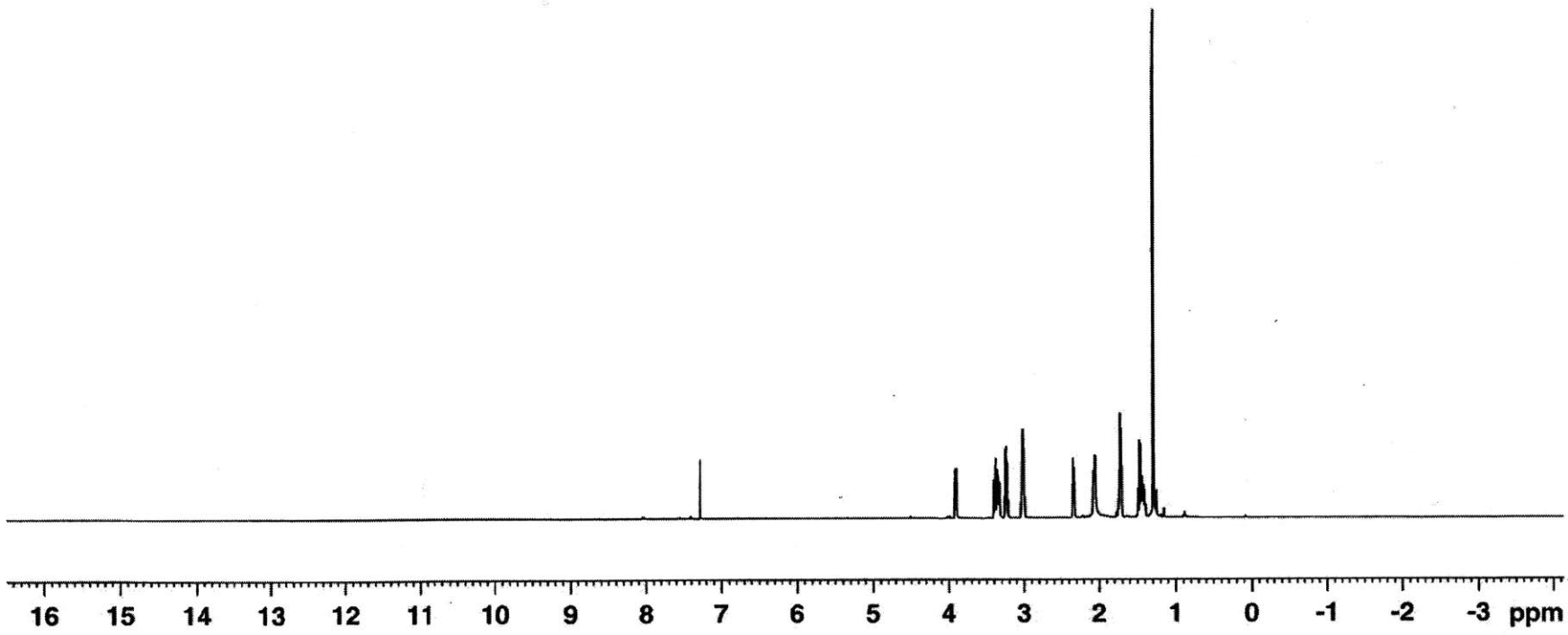

HO
H
O
O
H

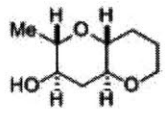
112


81.181
70.318
68.634
57.341
55.084
35.360
32.888
26.494
18.181
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

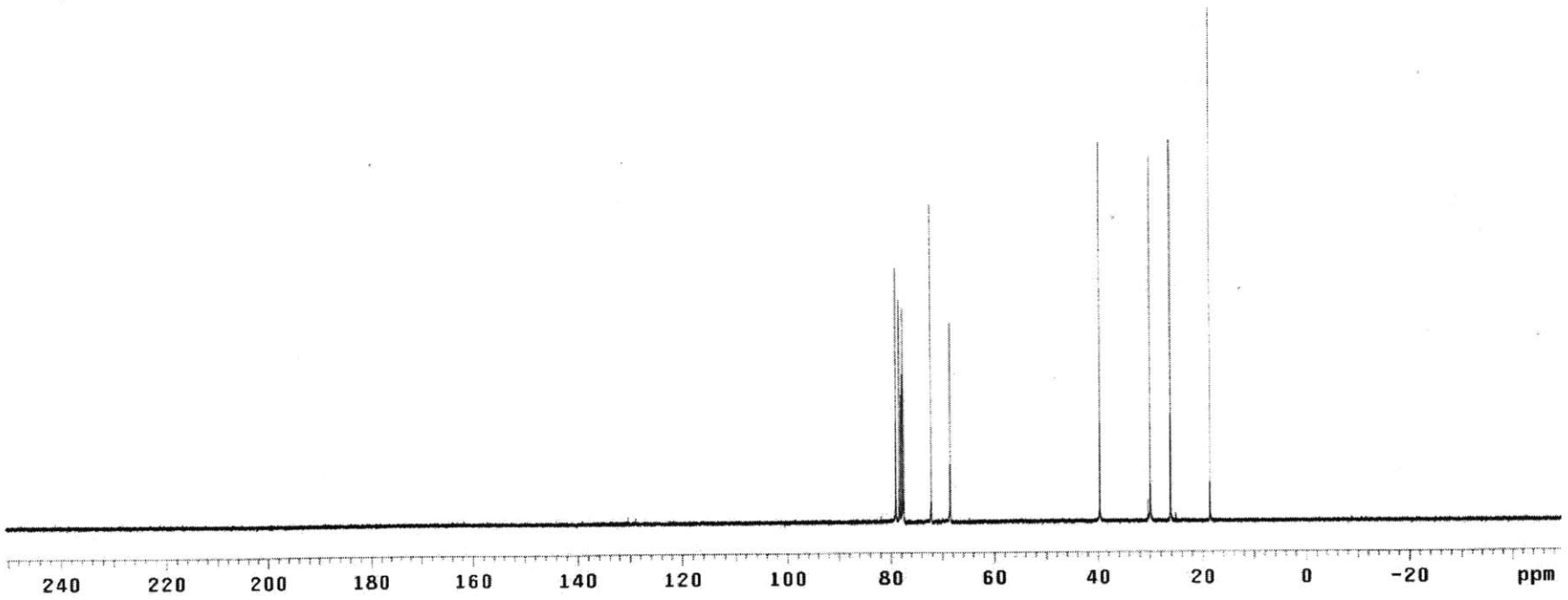


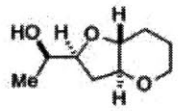
113



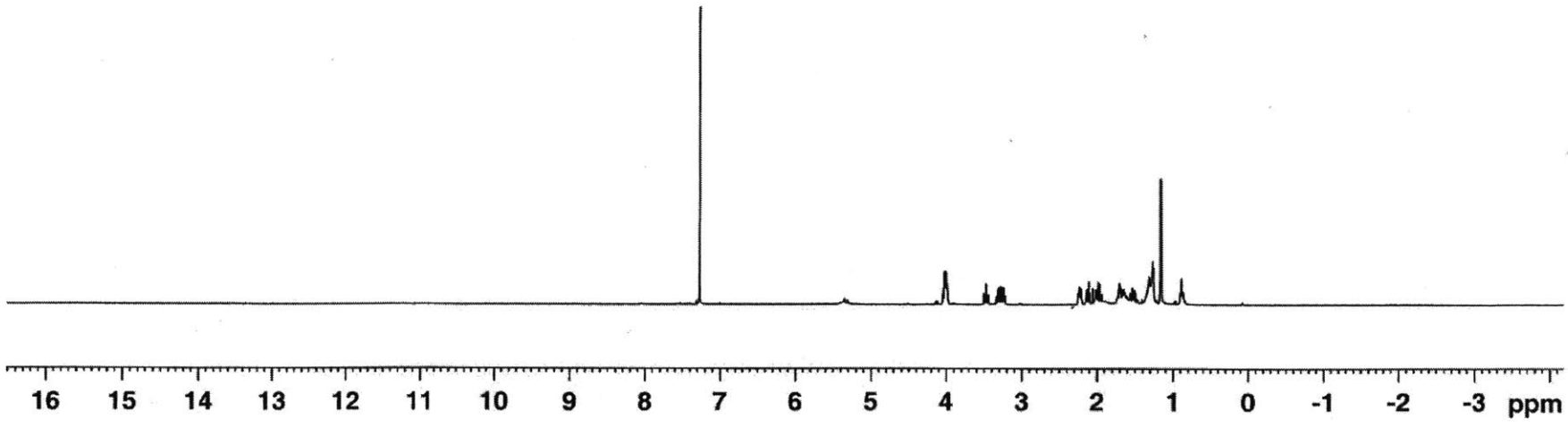


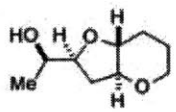
113



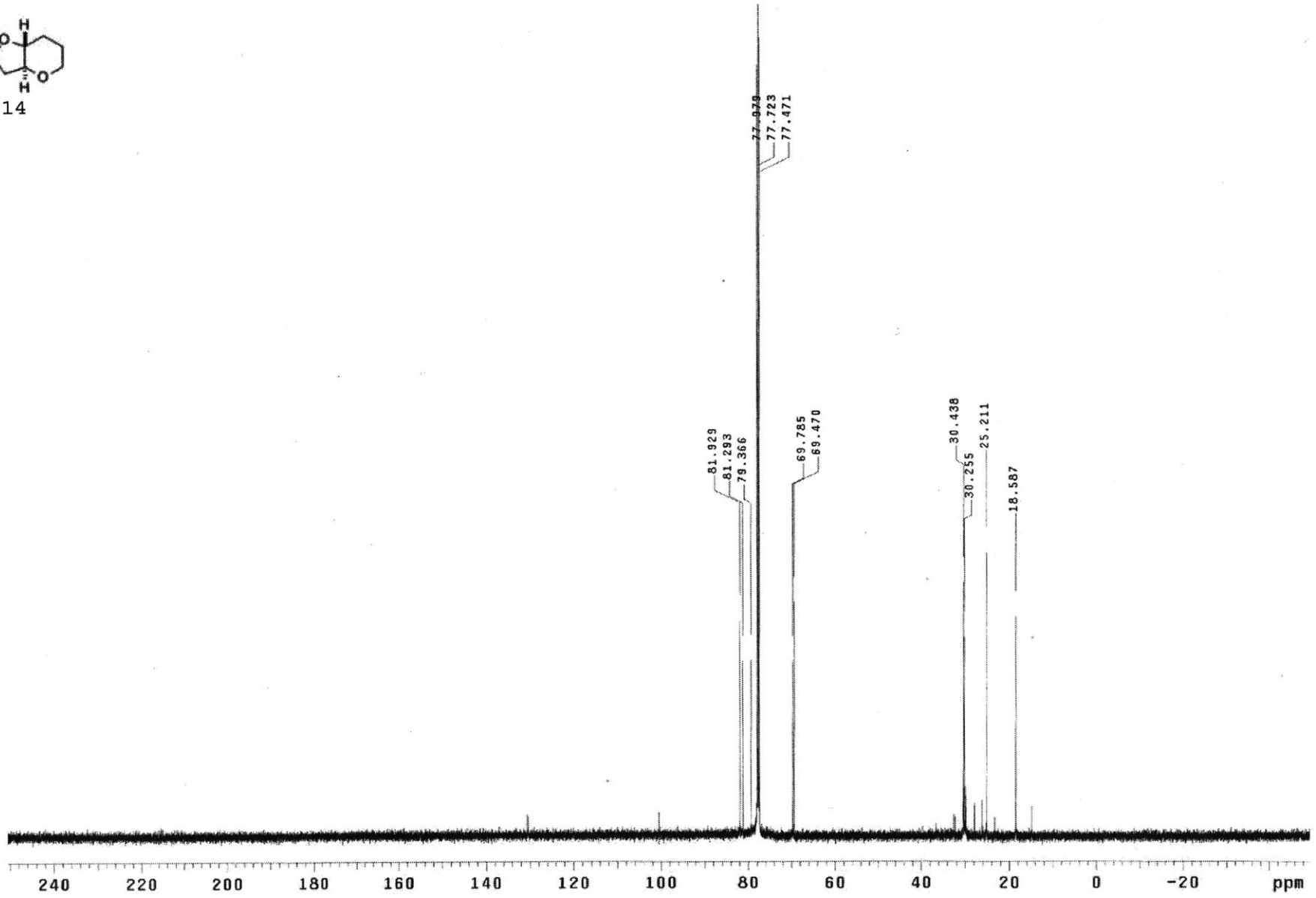


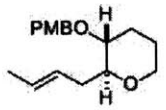
114



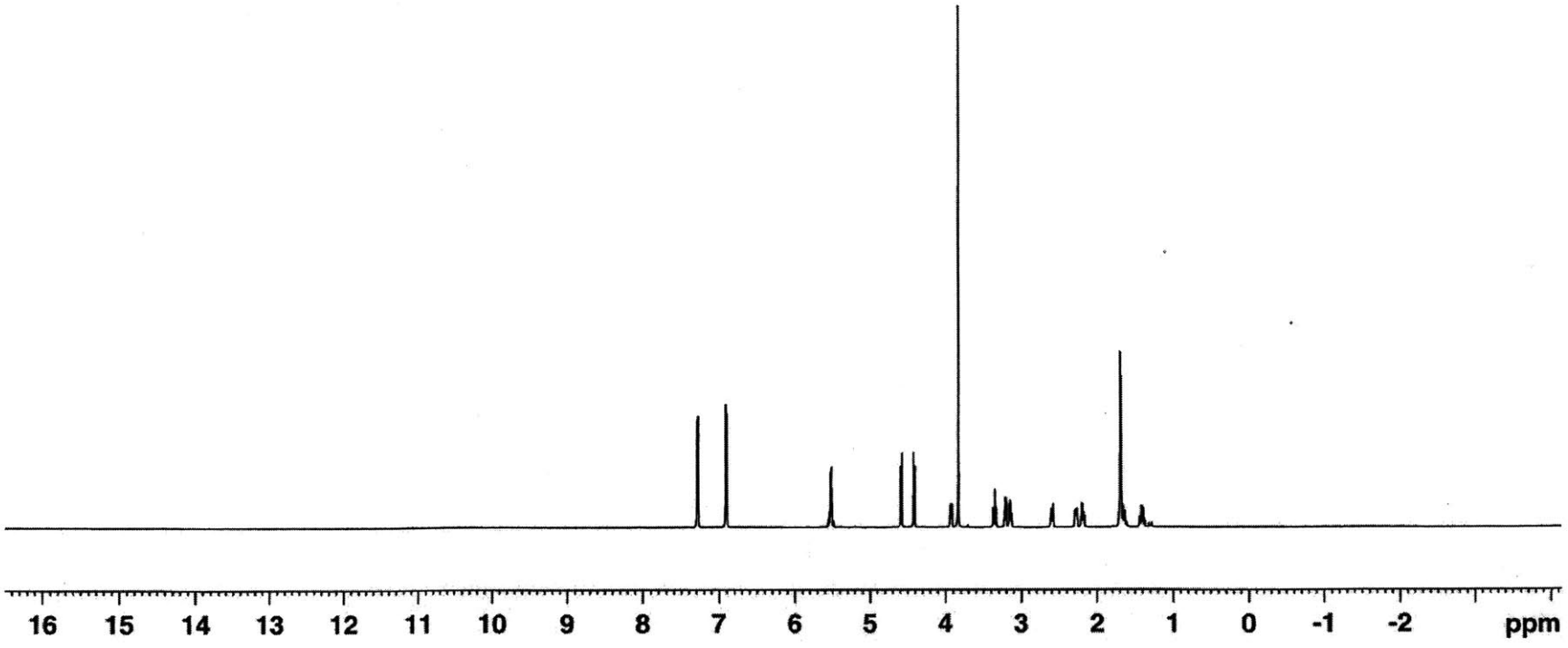

HO
H
O
H
Me
H
O

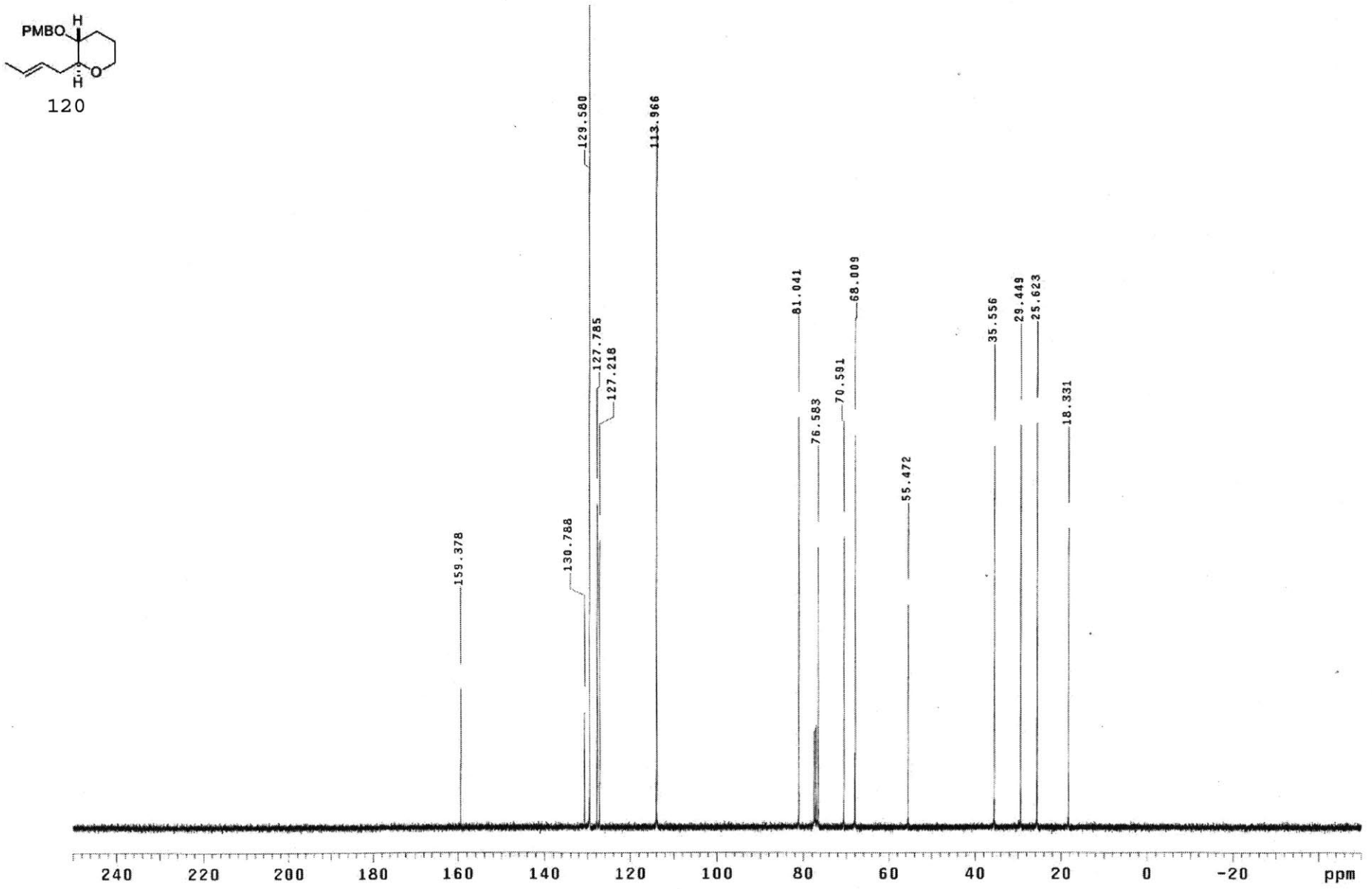
114

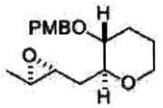

77.979
77.723
77.471
81.929
81.293
79.366
69.785
69.470
30.438
30.255
25.211
18.587
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm



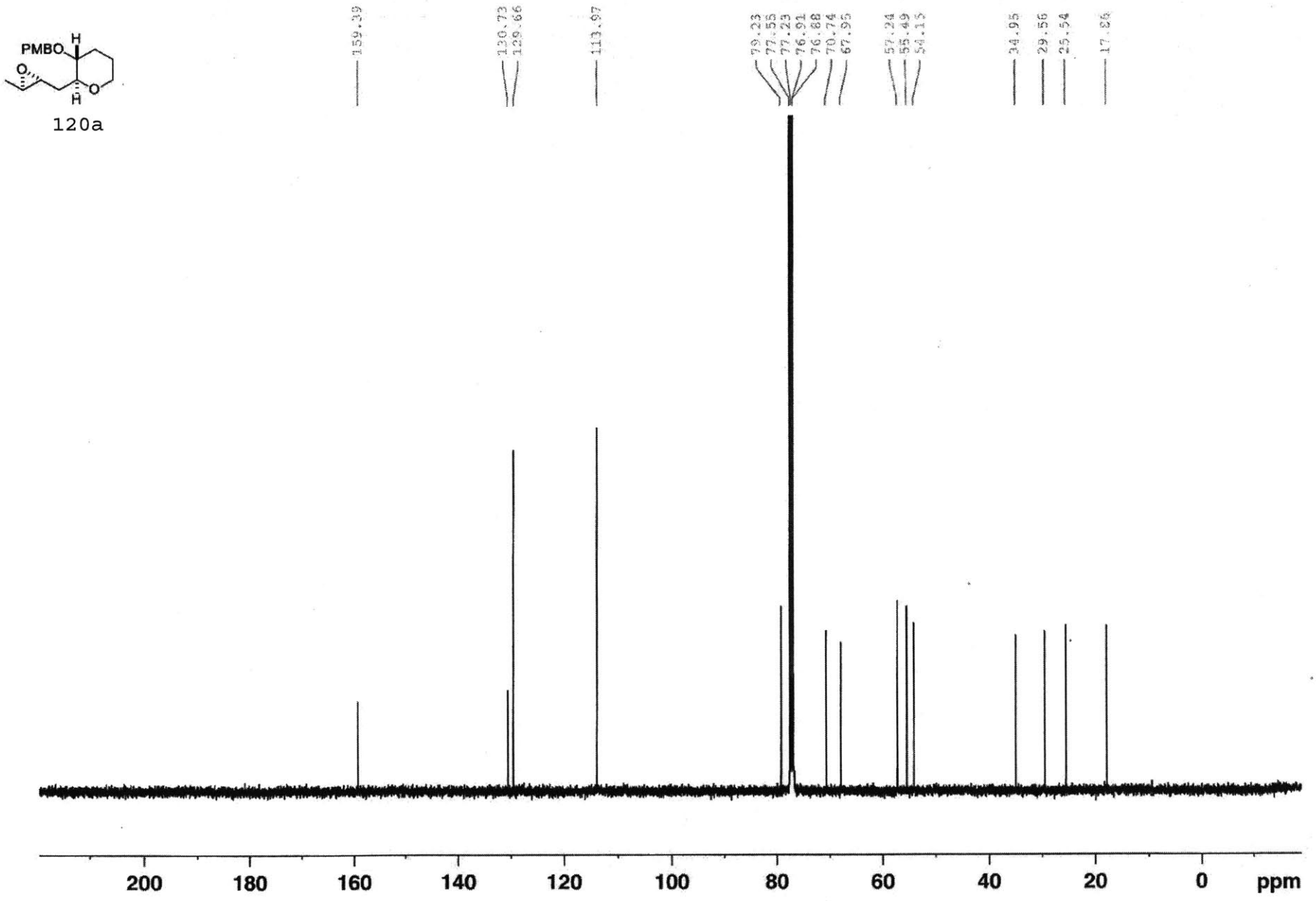
120

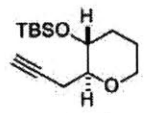



PMBO
H
H
O
120
159.378
130.788
129.580
127.785
127.218
113.966
81.041
76.583
70.591
68.009
55.472
35.556
29.449
25.623
18.331
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

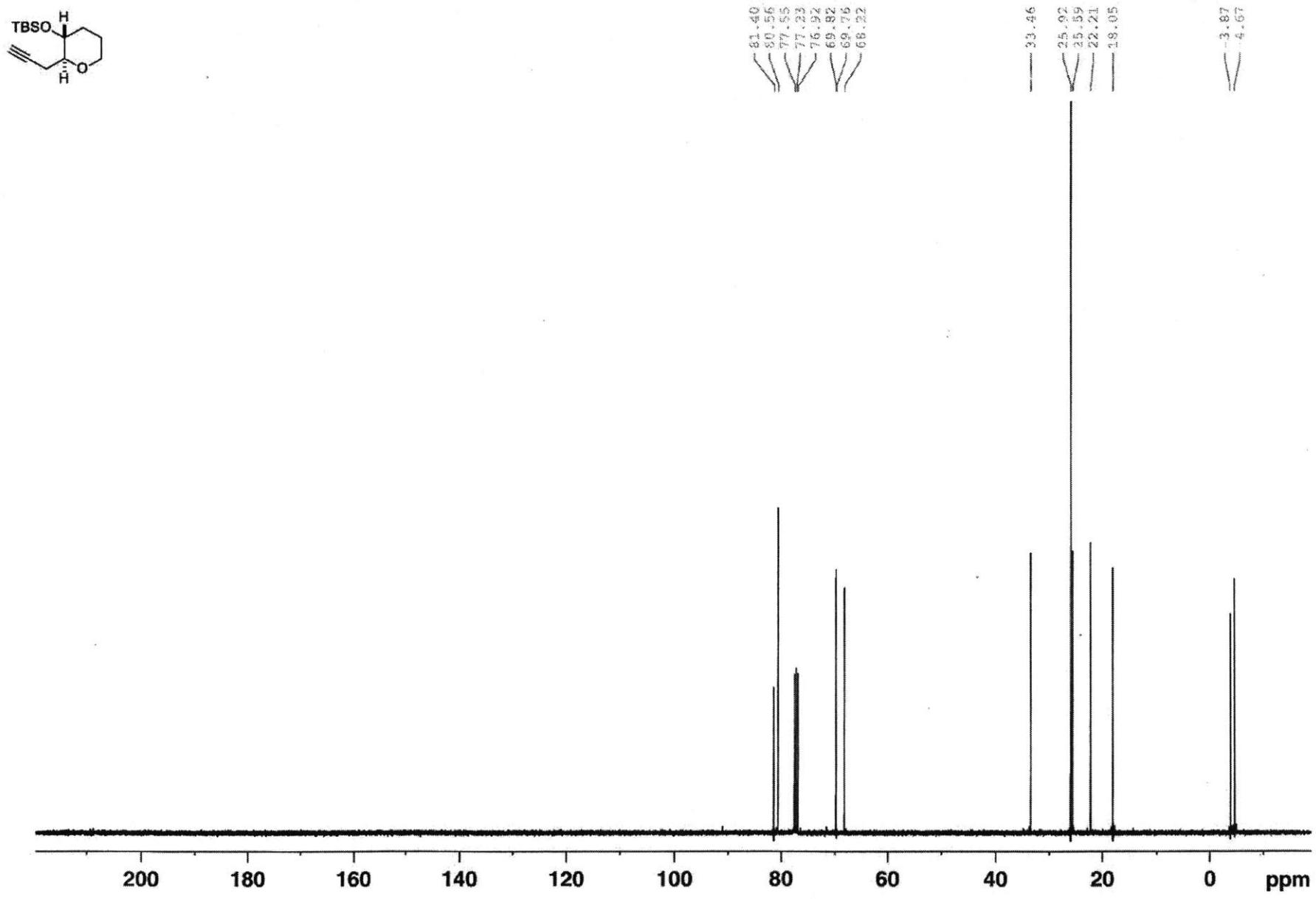


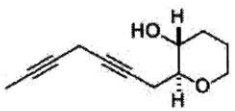
120a


PMBO
H
O
O
H
120a
159.39
130.73
129.66
113.97
79.23
77.55
77.23
76.91
76.88
70.74
67.95
57.24
55.49
54.15
34.95
29.56
25.54
17.86
200
180
160
140
120
100
80
60
40
20
0
ppm



121


TBSO
H
O
H
81.40
80.56
77.55
77.33
76.92
69.82
69.76
68.22
33.46
25.92
25.59
22.21
18.05
-3.87
-4.67
200
180
160
140
120
100
80
60
40
20
0
ppm

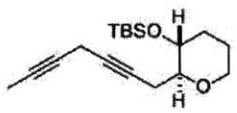


123

HO
H
O
H

123

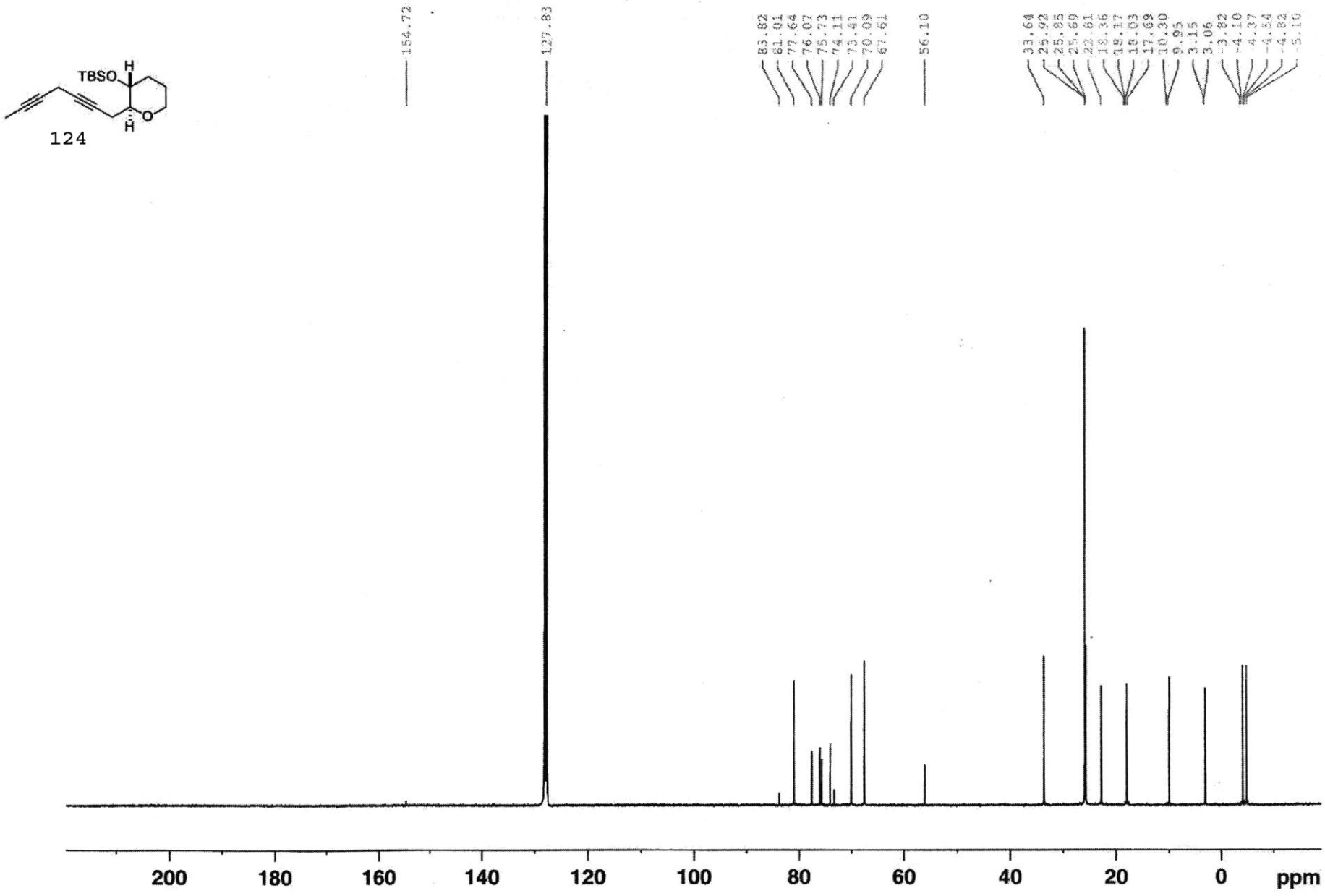
128.584
128.392
128.200
128.680
81.416
81.343
78.208
76.423
74.468
70.088
67.973
33.292
26.152
23.401
10.388
3.573
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

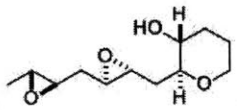


124

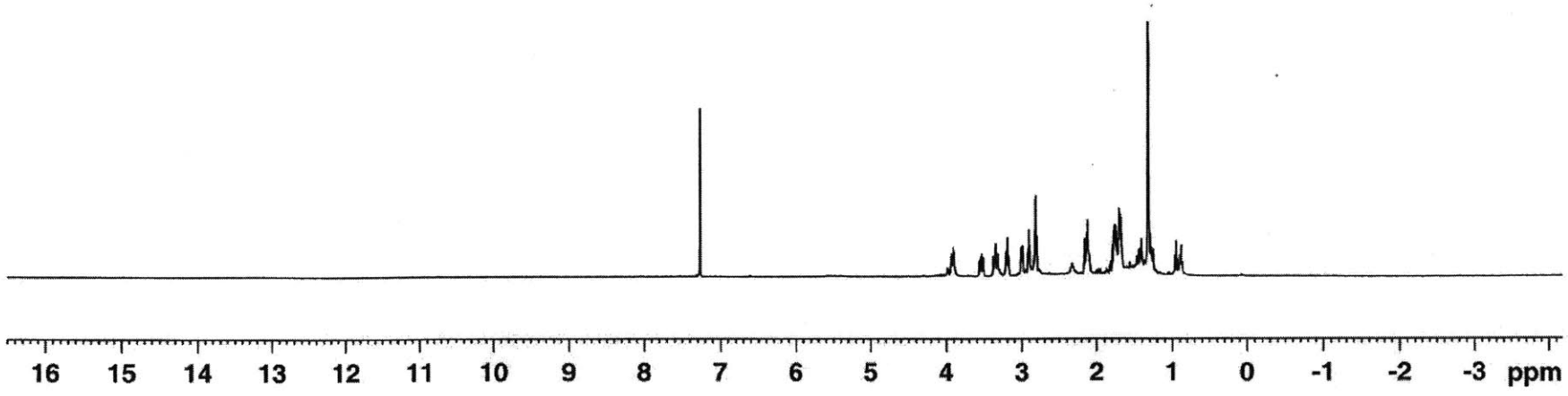
88

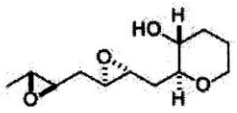
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 ppm


TBSO
H
H
O
124
154.72
127.83
83.82
81.01
77.64
76.07
75.73
74.11
73.41
70.09
67.61
56.10
33.64
25.92
25.85
25.60
22.61
18.36
18.17
18.03
17.69
10.30
9.95
3.15
3.06
-3.82
-4.10
-4.37
-4.54
-4.82
-5.10
200
180
160
140
120
100
80
60
40
20
0
ppm

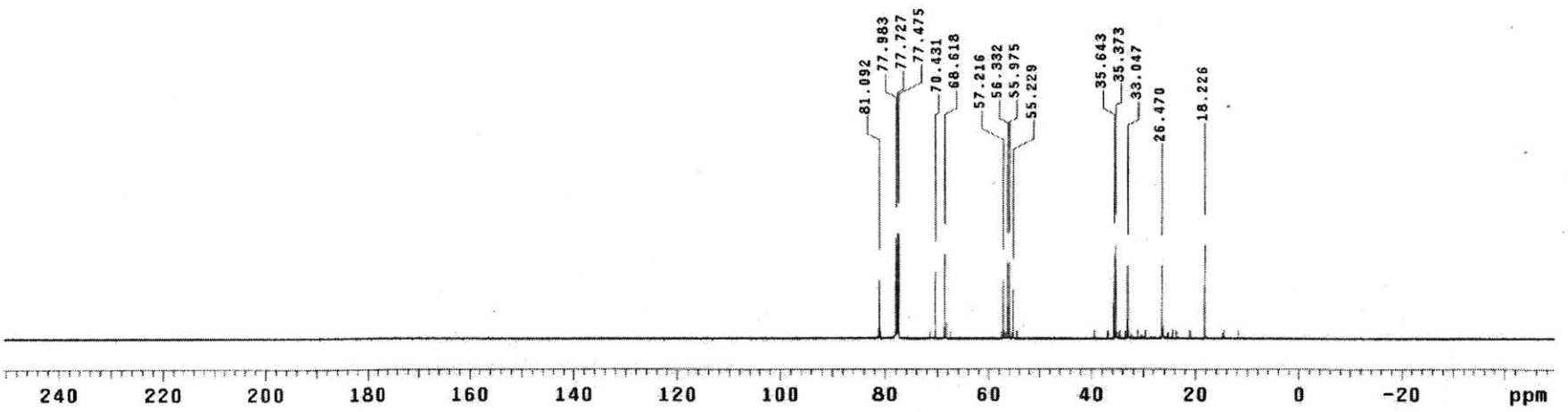


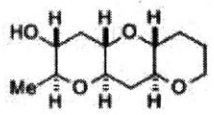
126



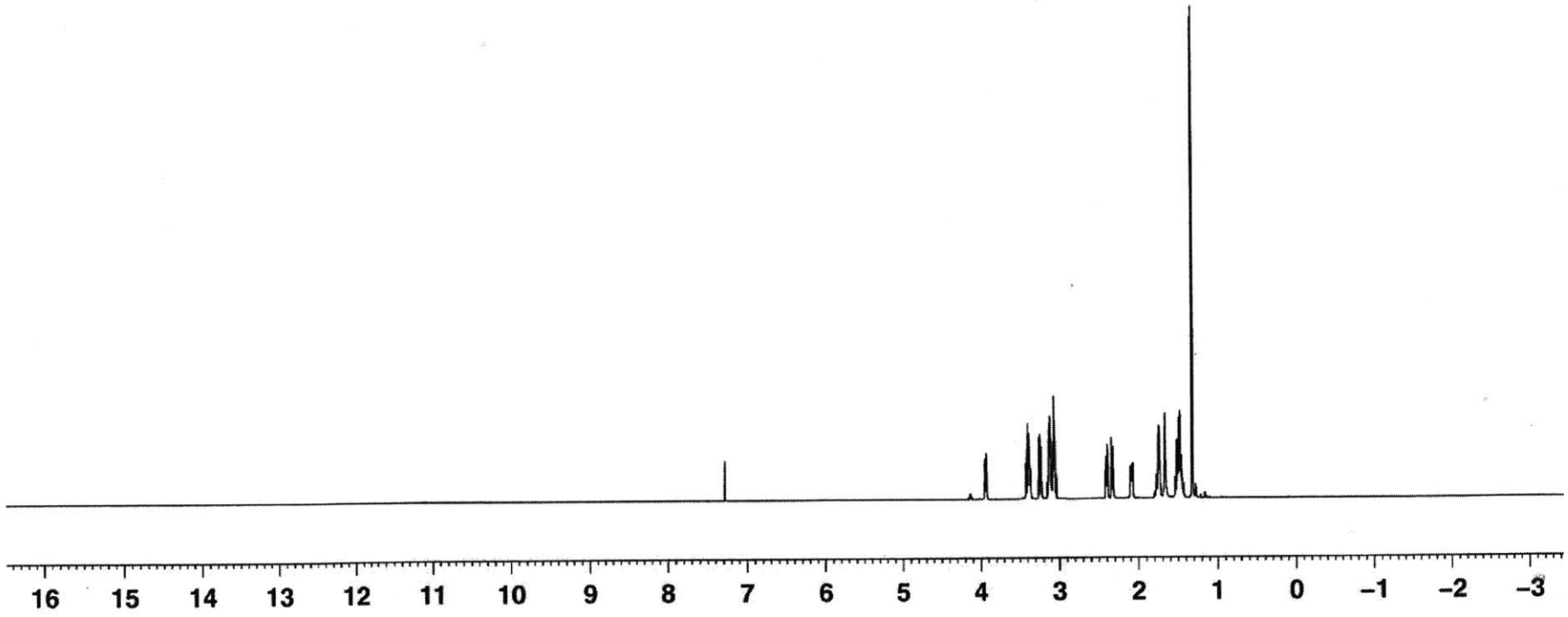

HO
H
O
O
H
O

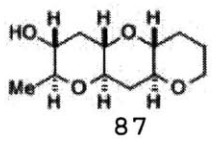
126


81.092
77.983
77.727
77.475
70.431
68.618
57.216
56.332
55.975
55.229
35.643
35.373
33.047
26.470
18.226
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

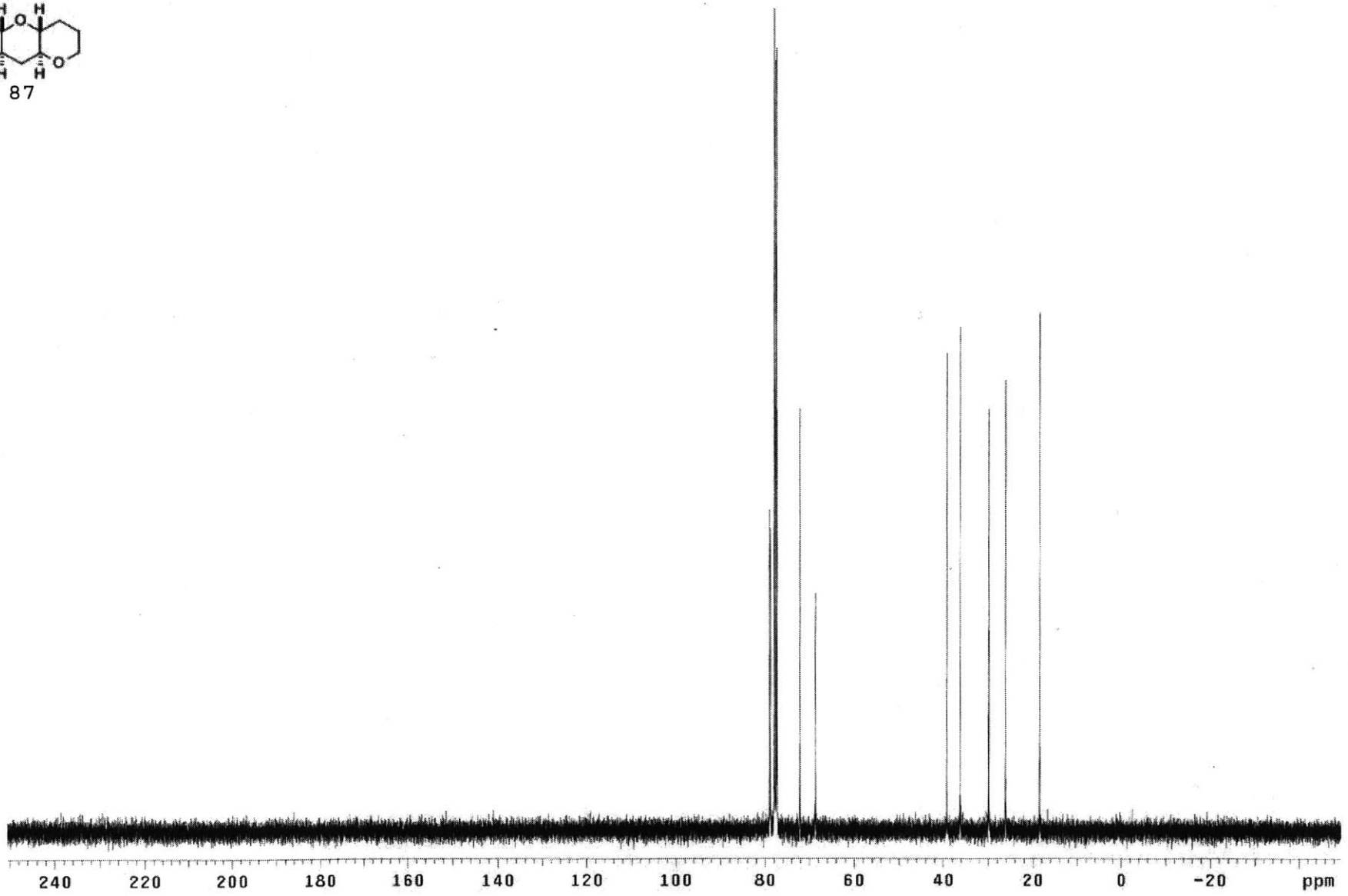


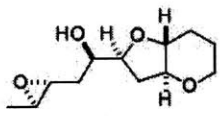
87



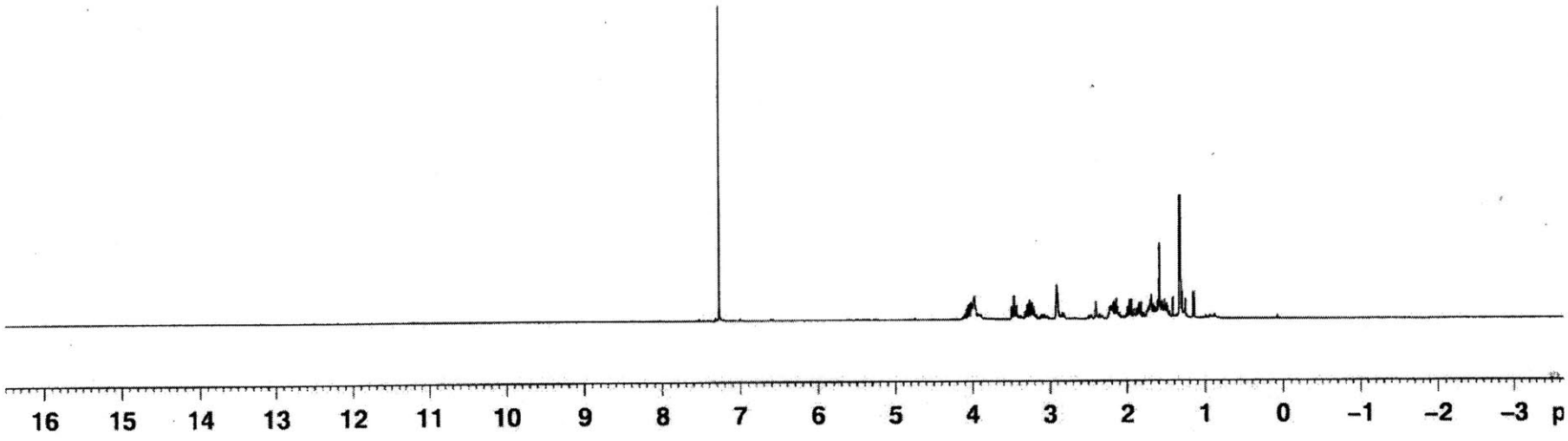

HO
H
H
H
O
Me
O
H
H
H
O

87


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



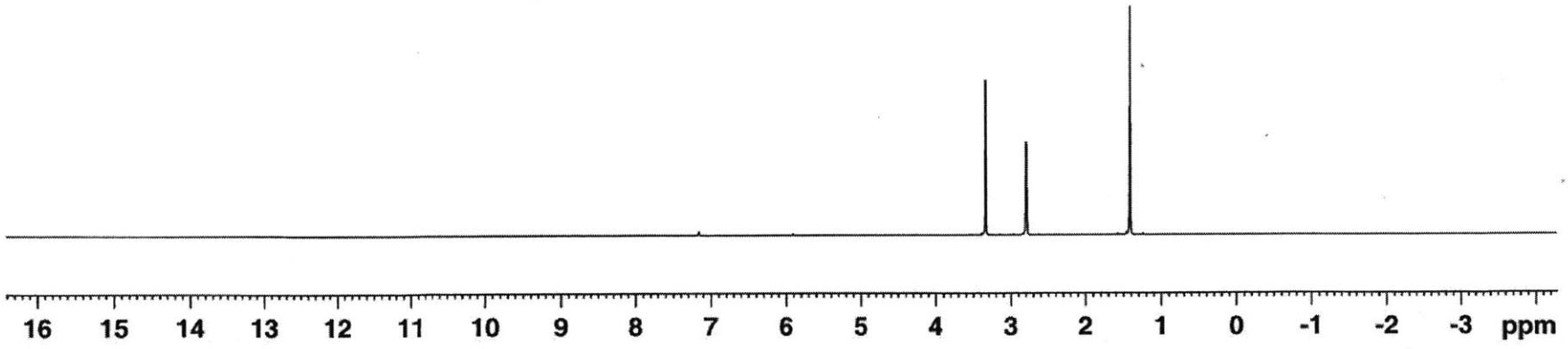
87a



HO
H
O
H
O
O
H
87a

81.895
80.105
79.281
77.715
77.464
71.737
69.453
57.941
55.267
34.930
31.025
30.366
25.184
18.236
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

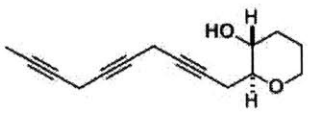
127



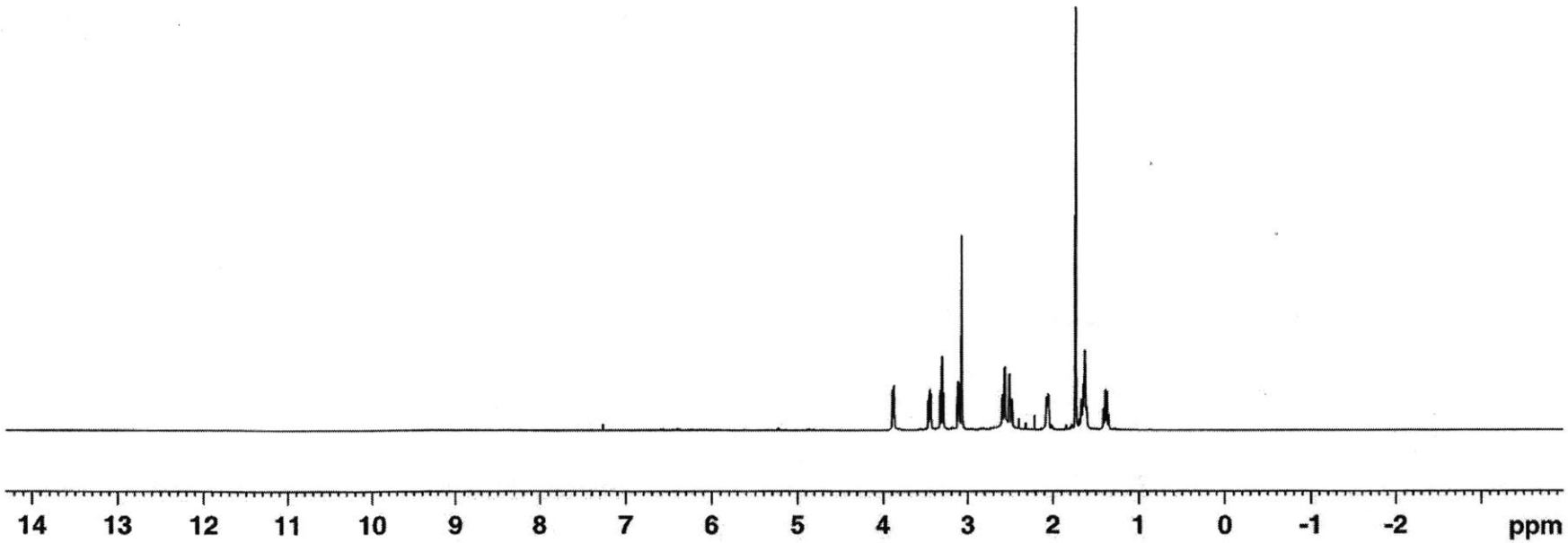
Br

127

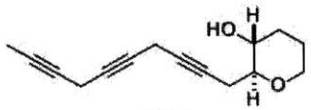
128.63
128.39
128.15
82.75
77.17
76.15
72.87
15.41
10.34
3.50
200
180
160
140
120
100
80
60
40
20
0
ppm



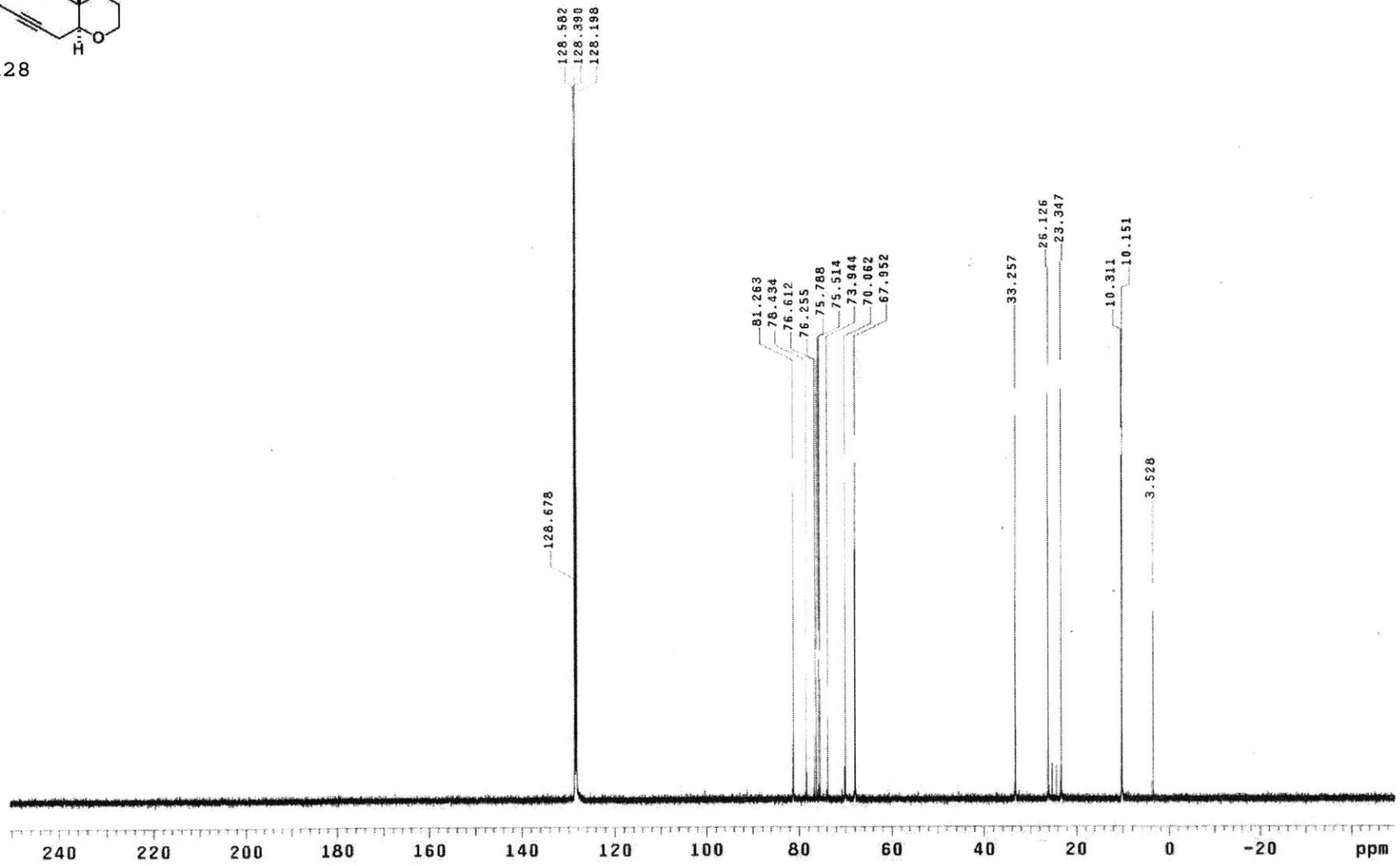
128

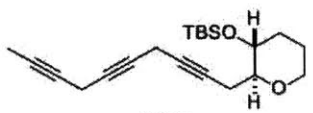


IVIII019



128

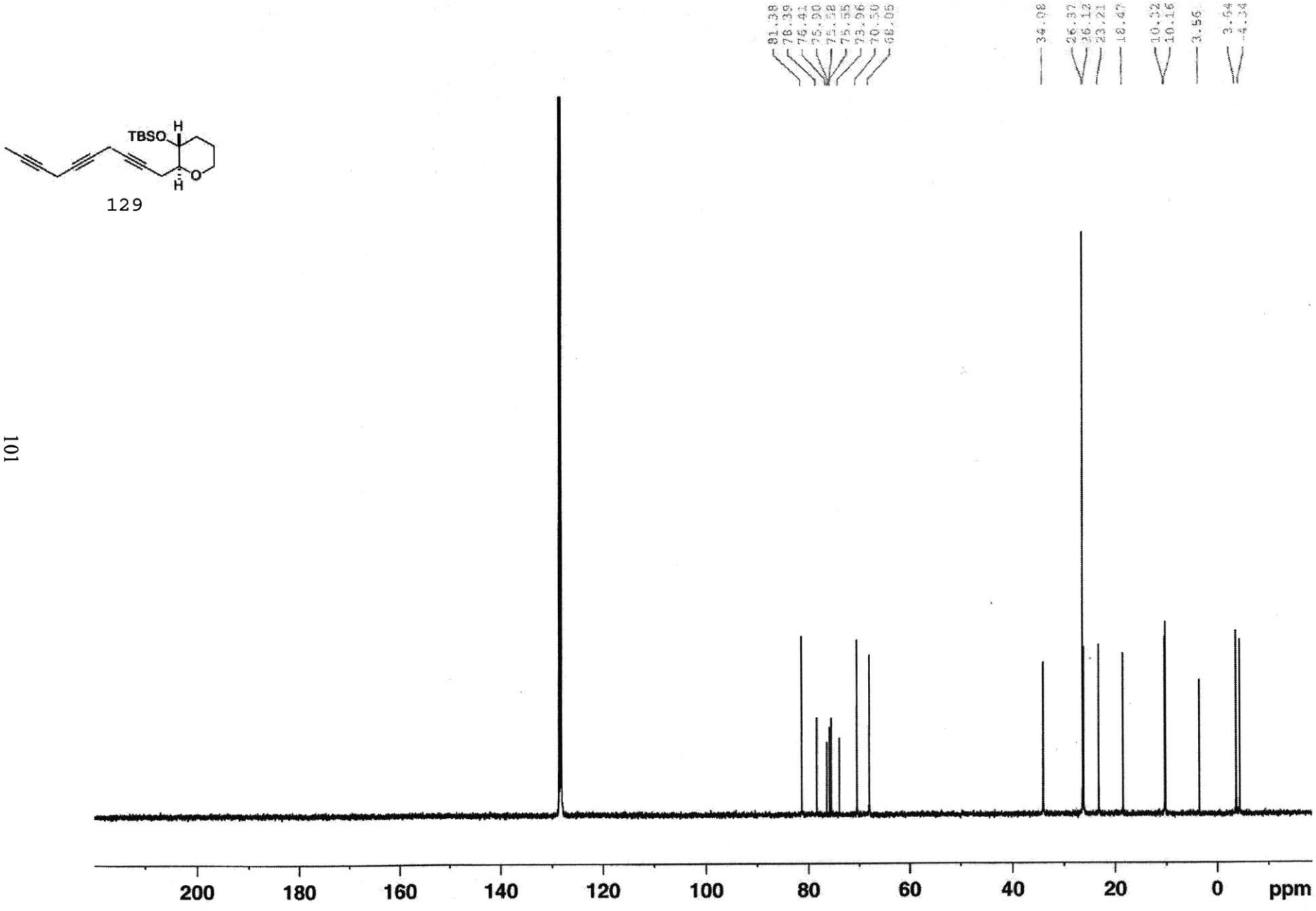


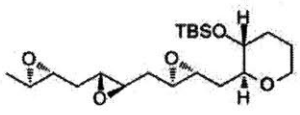


129

100

16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 ppm

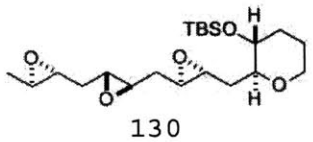

TBSO
H
O
H
129
81.38
78.39
76.41
75.90
75.58
75.55
73.96
70.50
68.05
34.08
26.37
26.12
23.21
18.47
10.32
10.16
3.55
3.54
-4.34
200
180
160
140
120
100
80
60
40
20
0
ppm



130

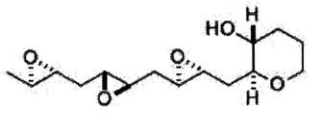
102

16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 ppm

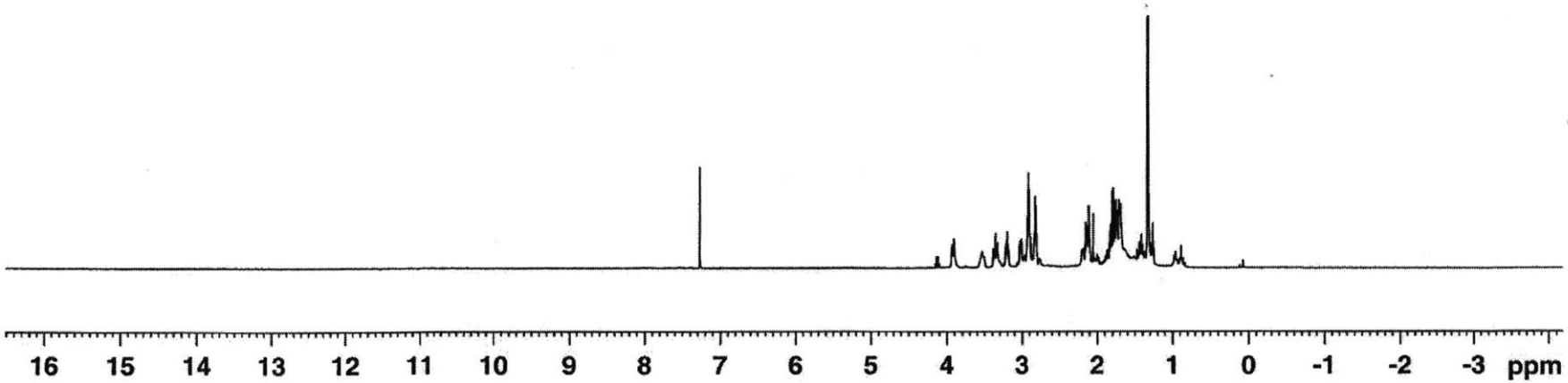

TBSO
H
O
O
O
H
O

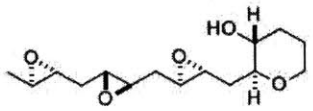
130

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0



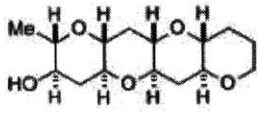
131



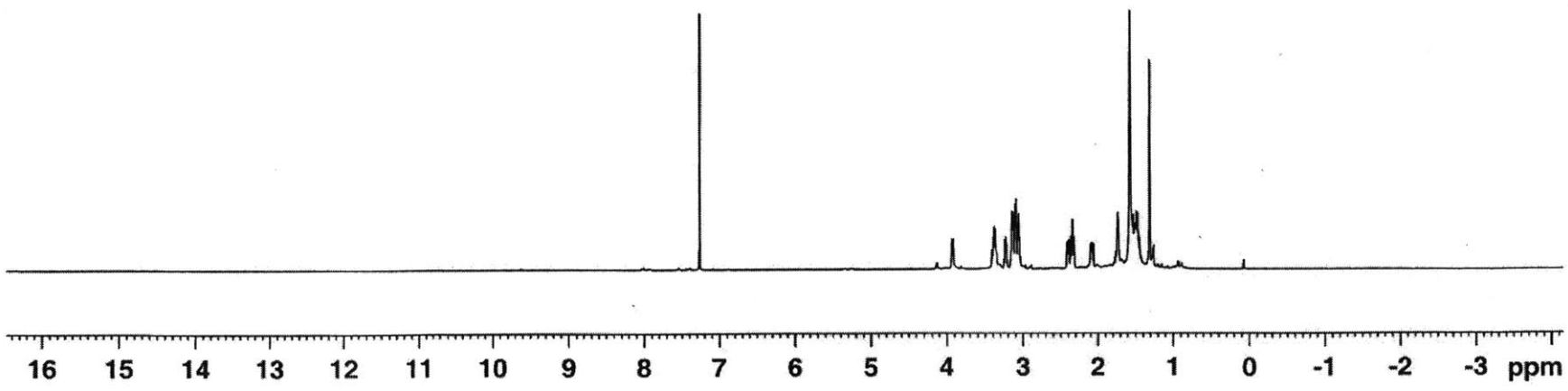

HO
H
O
O
O
H

131

80.58
69.99
68.13
56.64
55.85
55.67
55.58
55.40
54.77
35.22
35.03
34.96
32.61
25.98
17.71
200
180
160
140
120
100
80
60
40
20
0
ppm



132



Me
HO
H
O

132

128.663
128.562
128.370
128.178
79.082
79.023
78.153
77.938
77.842
77.604
77.311
71.964
68.119
39.553
36.724
36.408
30.091
26.224
18.474
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

Bibliography

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