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SYNTHETIC & MECHANISTIC INVESTIGATIONS OF
THE WITTIG REARRANGEMENTS AND
SYNTHETIC STUDIES TOWARD AMPHIDINOLIDE A

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FENG GENG

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Major professor

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SYNTHETIC & MECHANISTIC INVESTIGATIONS OF THE WITTIG REARRANGEMENTS AND SYNTHETIC STUDIES TOWARD AMPHIDINOLIDE A

By

Feng Geng

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ABSTRACT

SYNTHETIC & MECHANISTIC INVESTIGATIONS OF
THE WITTIG REARRANGEMENTS AND
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By

Feng Geng

Synthetic & Mechanistic Investigations of The Wittig Rearrangements

Stereospecificity of [1,2]-Wittig rearrangement reactions

The [1,2]-Wittig rearrangement is an unique radical pair dissociation-recombination process which can be highly stereoselective. Recent studies suggest that there could be two distinct mechanisms by which the stereochemical outcome is decided. Schreiber reported a case in which chelation control sets up the stereochemistry, while Nakai showed that the [1,2]-Wittig rearrangements of enantiodefined α metallated ether proceeds with inversion of the metal bearing terminus.

We thought it intriguing to consider substrates with an ether oxygen capable of coordinating with the lithium of the stereodefined lithium terminus, such that Schreiber's and Nakai's mechanism would be in stereochemical conflict. Thus we prepared a set of stereodefined stannanes and studied their Wittig rearrangements. Our results show that the "normal" tendency for the α-oxy lithium species to undergo an inversion of configuration can be suppressed, and even overturned, by controling chelation.

Wittig rearrangements of α-alkoxysilanes

Lewis acid catalized reaction of allyl and benzyl trichloroacetimidates with α-silyl alcohols was found to be a general method for the synthesis of α-alkoxysilanes. Upon exposure to CsF, these α-alkoxysilanes could undergo [2,3]-Wittig rearrangement with an

efficiency similar to that realized by the analogous but more toxic α-alkoxylstannanes. The Wittig rearrangements of these α-alkoxysilanes promoted by alkyllithiums were also studied. Depending on both the substrates and reaction conditions employed, the [2,3]-, [1,2]- or [1,4]-Wittig products can be realized. These rearrangements were shown to be initiated by either Si/Li exchange or deprotonation α to the silane, giving synthetically valuable silicon containing compounds.

Synthetic Studies Toward Amphidinolide A

Amphidinolide A, isolated by Kobayashi in 1986 from the marine dinoflagellate *Amphidinum sp*, is the first member of the amphidinolide family of ca. 20 natural products. It has marked biological properties, especially activity against L1210 marine leukemia cells and human epidermoid carcinoma KB cells in vitro. In addition, this 20-membered lactone has several striking structural features, including the exocyclic olefins and both conjugated and non-conjugated dienes. Giving these intriguing structural and biological features, we chose amphidinolide A as a target for total synthesis.

The purpose of this synthetic project is two fold. As this biologically active compound exists in only extremely limited quantities, part of our goal is to prepare more material and analogs so as to fully evaluate the biology of these compounds. On the other hand, the structural features of this molecule provide the challenge and opportunity for us to invent and develop synthetic methods. Of particular interest are organometallic methods such as Stille reactions, indium-induced allylations of alkynes, and ring closing metathesis (RCM) reactions. As a result of out synthetic studies, a molecule with the proposed amphidinolide A structure was synthesized. During this synthesis, the aforementioned organometallic reactions were studied and utilized in the key steps, and valuable insight into these reactions was obtained.

To Eun-Young

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Scheme 1

Scheme 1

Scheme 1

Scheme 1

Scheme 1

Scheme 1

Scheme 1

Scheme 1

Scheme 1

Ac

acac

AIBN

aq

CI

Cy

DCC

DBU

de

DIAD

DIBAL

DMAP

DME

DMF

DMSO

EI

eq

FAB

h

HMPA

HRMS

HWE

KHMDS

LHMDS

mCPBA

LIST OF SYMBOLS AND ABBREVIATIONS

Ac	acetyl
acac	acetylacetonate
AIBN	2,2'-azobisisobutyronitrile
aq	aqueous
CI	chemical ionization
Cy	cyclohexyl
DCC	dicycloheylcarbodiimide
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
de	diastereomeric excess
DIAD	diisopropyl azodicarboxylate
DIBAL	disiobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DME	dimethoxylethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
EI	electric ionization
eq	equivalent
FAB	fast atom bombardment
h	hour
HMPA	hexamethyl phosphoramide
HRMS	high resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons reaction
KHMDS	potassium bis(trimethylsilyl)amide
LHMDS	lithium bis(trimethylsilyl)amide
mCPBA	m-chloroperbenzoic acid

Mes

Mesyl

min

mL

mmol

MOM

MS

NaHMDS

NBS

NMP

NOE

PMB

Py

RCM

rt

TBAF

TBS

Tf

THF

TMS

Tosyl

Tr

TSA

Mes	2,4,6-trimethyl phenyl
Mesyl	methanesulfonyl
min	minute
mL	milliliter
mmol	millimole
MOM	methoxymethyl
MS	molecular sieves
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NMP	N-methyl prolidinone
NOE	nuclear Overhauser effect
PMB	*p*-methoxybenzyl
Py	pyridine
RCM	ring closing metathesis
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBS	*t*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TMS	trimethylsilyl
Tosyl	toluenesulfonyl
Tr	triphenylmethyl
TSA	*p*-toluenesulfonic acid

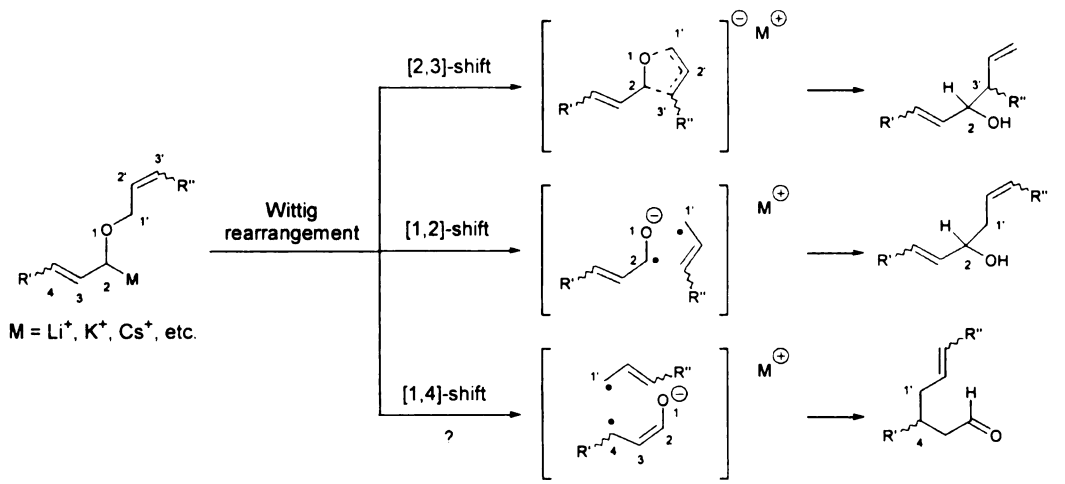
CHAPTER 1

INTRODUCTION

1.1. Mechanism studies on the Wittig rearrangement reactions

In 1942 Wittig and Löhmann first described the rearrangement reaction of α-lithiated ethers to lithio alkoxides.[1] Since then such reactions of α-metallated ethers have been termed "Wittig rearrangements", and involve the breaking of a C–O bond and formation of a C–C bond (Scheme 1.1).[2] Among them, the [2,3]-rearrangement is a concerted process, allowed by Woodward-Hoffman rules.[2] The [1,2]-rearrangement is now generally accepted as a diradical dissociation-recombination process.[3] Less is known about [1,4]-rearrangement. However, it is likely to proceed via a mechanism similar to that of the [1,2]-rearrangement.[2]

Scheme 1.1. Wittig rearrangements



In the years following its discovery, the [2,3]-rearrangement has been well studied and has found wide applications in organic synthesis.[2] Early studies on the [1,2]-rearrangement have been mainly mechanistic in origin due to limitations in substrate scope and the frequently observed low yields of this process. Over the past two decades, however, the [1,2]-rearrangement has attracted more attention.[3,4] It was found that this

unique reaction, although of radical nature, can be highly stereoselective.[4] This intriguing feature opened the door for useful applications in asymmetric organic synthesis.

In our studies, we aimed to gain a deeper understanding of the [1,2]-rearrangement, namely how chelation affects the stereochemical outcome of the rearrangement of stereodefined α-lithiated ethers.

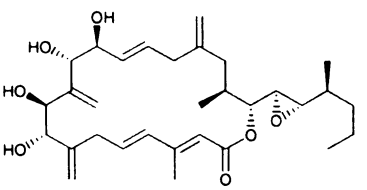
We also looked at modifying these old reactions by using α-silyl ethers as the starting substrates. By comparing the chemistry of α-silyl ethers with their stannane analogs, we obtained new and valuable insight into these rearrangements. Our studies of the Wittig rearrangement of α-silyl ethers also expanded the scope of this reaction.

1.2. Synthetic studies toward amphidinolide A

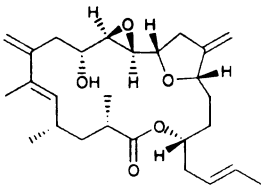
The construction of natural and unnatural compounds is the ultimate goal of synthetic organic chemistry. Total synthesis of natural products serves medical science by providing bioactive substances and new chemotherapeutic regiments. Organic synthesis is also a means to measure the aptitude of contemporary organic chemistry, a theater for the debut of new reactions and reagents, and a driving force for the exploration and discovery of new chemistry.

Amphidinolide A was isolated by Kobayashi in 1986 from the marine dinoflagellate *Amphidinum sp.*[5a] It was the first of the amphidinolides (Scheme 1.2), a novel class of approximately 20 natural products, to be isolated.[5c] The amphidinolides have marked biological properties, especially activity against L1210 marine leukemia cells and human epidermoid carcinoma KB cells *in vitro*. Following their discovery, these compounds have been the subject of much synthetic effort.[6] Williams' group first achieved the total synthesis of amphidinolide J in 1998.[6a] One year later, the total synthesis of amphidinolide K was also reported by the same group.[6b,c] In 2000, they also accomplished the total synthesis of amphidinolide P.[6d] However, despite two reported efforts from Williard and Pattenden,[7] amphidinolide A has not been synthesized.

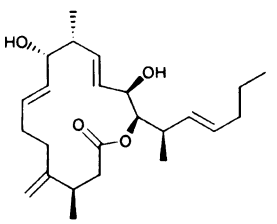
Scheme 1.2. Representative amphidinolides



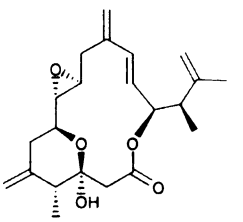
Amphidinolide A



Amphidinolide K



Amphidinolide J

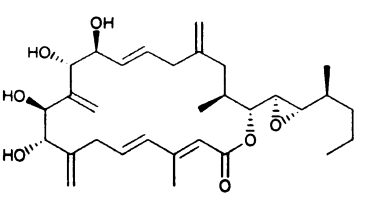


Amphidinolide P

In addition to its impressive anti-cancer activity, the 20-membered lactone has several striking structural features, including the presence of lipophilic and hydrophilic moieties as well as the presence of exocyclic olefins and both 1,3 and 1,4 dienes. It is for these structural and biological features that amphidinolide A was chosen as a target for our total synthesis.

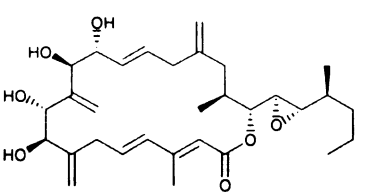
The relative stereochemistry of amphidinolide A was proposed in 1991 by Kobayashi based on "suggested information" provided by nOe NMR data.[5b] However, as the author pointed out, the "interpretation of the relative stereochemistry of chiral centers of macrocyclic compounds by spectral means is still not easy".[5b] In this particular case, the correlation between the relative stereochemistry of the hydrophilic moiety and the lipophilic moiety is especially weak, thus the assigned relative stereochemical relationship between the right and left "halves" of amphidinolide A may be in error.

Scheme 1.3. Questions about the relative stereochemistry of amphidinolide A



proposed stereostructure

or



possible structure (or its enantiomer)

The purpose of this project is many-fold. Considering the fact that this biologically active compound exists in only extremely limited quantities, part of our goal is to prepare more material and analogs so as to more fully evaluate the biologic influence of these compounds. It is possible that via total synthesis, bioactive unnatural isomers or derivatives may prove chemotherapeutically superior to the natural product or prove valuable as tools in evaluating the mechanism by which the amphidinolides act. Furthermore, we expect our total synthesis to provide unambiguous confirmation of the proposed structure of this compound. The structural features of this molecule also provide us with the challenge and opportunity to explore new synthetic methodologies. Of particular interest are organometallic methods such as Stille reactions,[8] indium-induced allylations of alkynes,[9] and ring closing metathesis (RCM) reactions.[10]

CHAPTER 2

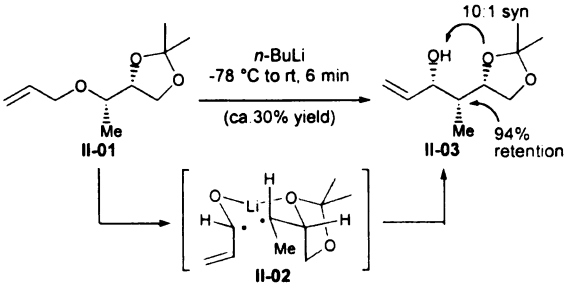
STEREOSPECIFICITY OF 1,2-WITTIG REARRANGEMENT REACTION

2.1. Introduction

Since its discovery the rearrangement of α-metallated ethers, particularly the [2,3]-Wittig rearrangement, has been the subject of intensive mechanistic and synthetic investigations.[1] Relative to the [2,3]-shift, the [1,2]-Wittig rearrangement has received relatively little publicity. Most studies of the [1,2]-Wittig have been mechanistic in origin, resulting in the widely accepted theory that the reaction proceeds via a radical pair dissociation-recombination mechanism.[2]

In 1987, Schreiber[3] reported an important observation on the stereospecific nature of this rearrangement (Scheme 2.1). Deprotonation of **II-01** resulted in "synthetically useful levels" of the [1,2]-rearrangement product that was heavily biased towards the *syn* isomer (**II-03**). Schreiber postulated that the product arose from bond reorganization via a diradical transition state in which a lithium tether (**II-02**) sets up the *syn* stereochemistry. Another surprising stereochemical feature of this rearrangement was the high level of retention (94%) at the migrating center.

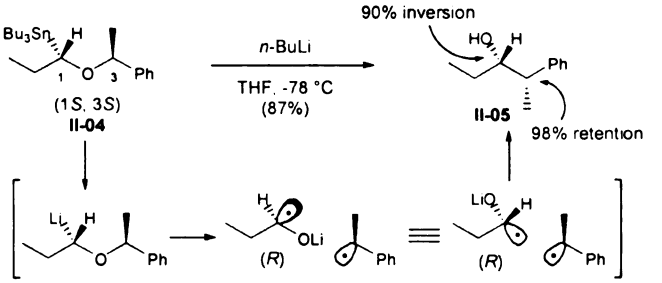
Scheme 2.1. [1,2]-Wittig rearrangement where chelation sets the stereochemistry of the newly formed alcohol



This observation became more interesting upon Cohen's[4] and Brückner's[5] recent evidence that [1,2]-Wittig rearrangements proceeded with inversion of the lithium

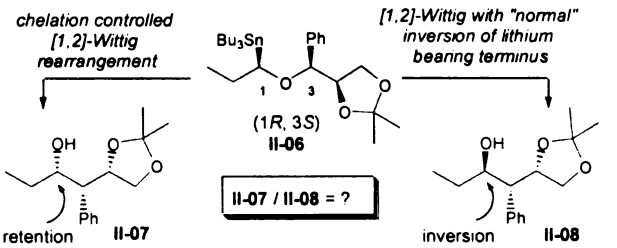
bearing terminus. Nakai[6] addressed this question and showed clearly that the [1,2]-Wittig rearrangements of enantiodefined α-alkoxy lithium's proceed with retention of the migrating center *and* with inversion of the lithium bearing terminus (Scheme 2.2). In these examples the stereochemistry of the product alcohols is not the result of chelation control, but rather decided by the configuration of the stannane precursor.

Scheme 2.2. [1,2]-Wittig rearrangement with "normal" inversion of configuration at the metal terminus



While there is little argument with either mechanistic explanation for the observed stereochemistries, it is important to note that the examples reported by Nakai (as well as those reported by Cohen and Brückner) did not have the possibility of chelation control.[7] We found it intriguing to consider substrates with an ether oxygen capable of coordinating with the lithium of the stereo defined lithium terminus. In such substrates the appropriate stereochemical combination could put Schreiber's mechanism in stereochemical conflict with the results of Nakai, Cohen, and Brückner (Scheme 2.3).

Scheme 2.3. Experimental setup



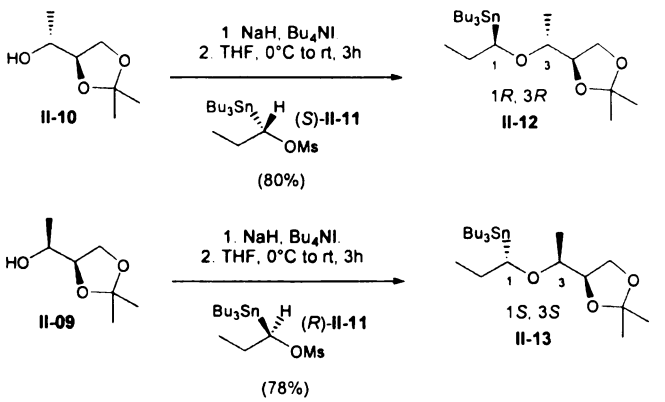
We therefore sought to prepare and study such substrates so as to provide a deeper understanding of the [1,2]-Wittig rearrangement. We believed that knowledge of the stereochemical influences imparted by these two mechanistic pathways, would allow the

discovery of new reaction conditions which should enable the practitioner to predict and control the stereochemical course of the [1,2]-Wittig rearrangement. Such reaction control would be of considerable value as it would represent a means for the selective construction of either syn and anti-1,3 polyols, via a common reaction mannifold.

2.2. Preparation of the model compounds

Our experiments began with the preparation of the stereodefined stannanes **II-12** and **II-13**. We initially chose these compounds as our model compounds because it would be convenient to analyze and determine the stereochemistry of the Wittig rearrangement products (*vide infra*). The syntheses of these compounds paralleled established procedures[8] and involved the displacement of the known enantiodefined stannyl mesylates[9] (*R*)- and (*S*)-**II-11** by alkoxides of the erythro and threo forms of 1-*C*-phenyl-2,3-*O*-isopropylidene-*D*-glycerols **II-09** and **II-10**[10] (Scheme 2.4). This method provided the desired stannanes in 80-90% yield and in greater than 95% de as judged by the ^{1}H-NMR.

Scheme 2.4. Preparation of the model compounds

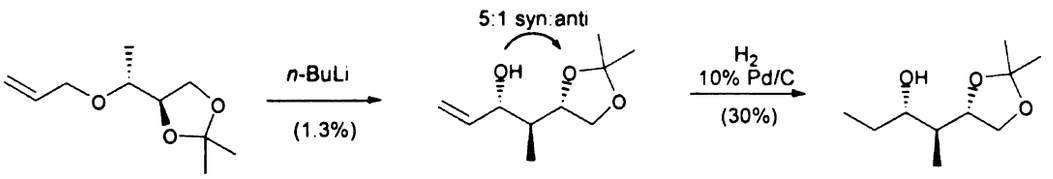


2.3. [1,2]-Wittig rearrangements of the model compounds

2.3.1. Investigation of the [1,2]-Wittig rearrangement of compounds **II-12** and **II-13**

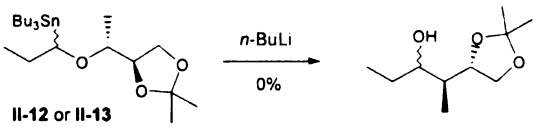
The predicted products of model compounds **II-12** and **II-13** can be easily obtained by hydrogenation of the products formed during Schreiber's study (Scheme 2.5). Thus it would be useful to repeat Schreiber's experiments, establish the stereochemistry of the predicted products, and then study the Wittig rearrangement of our model compounds. Unfortunately, many attempts to repeat the Schreiber chemistry under the conditions reported in their Tetrahedron Letters publication[3a] failed. Attempts to carry out the Wittig rearrangement of these compounds at –20 °C in THF gave only very complex mixtures, from which no desired compounds were isolated. After checking the doctoral dissertation of Goulet,[3b] we found there was a slight but crucial difference between the reported conditions and those in the dissertation. Instead of a reaction temperature of –20 °C as indicated in the paper, the detailed experimental procedure in the dissertation involved adding *n*-BuLi at –76 °C and warming the reaction to rt in 6 min prior to workup. After we adopted the conditions in the thesis, the Wittig rearrangements were successful albeit low yielding. Thus following this protocol with saturation of the alkene the enantiodefined products expected from our own rearrangements were prepared.

Scheme 2.5. Preparation of the predicted Wittig products of **II-12** and **II-13**



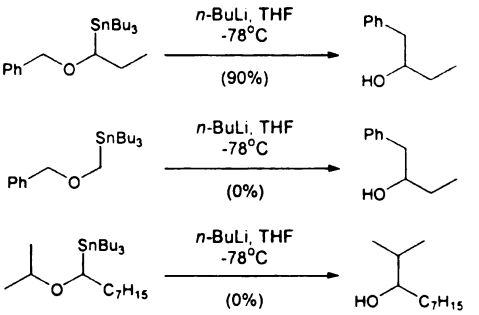
With our enantiodefined Wittig products in hand, we attempted the Wittig rearrangements of model compounds **II-12** and **II-13**. However, under Wittig conditions, the reactions gave complex mixtures, from which no Wittig rearrangement product was isolated (Scheme 2.6).

Scheme 2.6. [1,2]-Wittig rearrangement of model compounds **II-12** and **II-13**



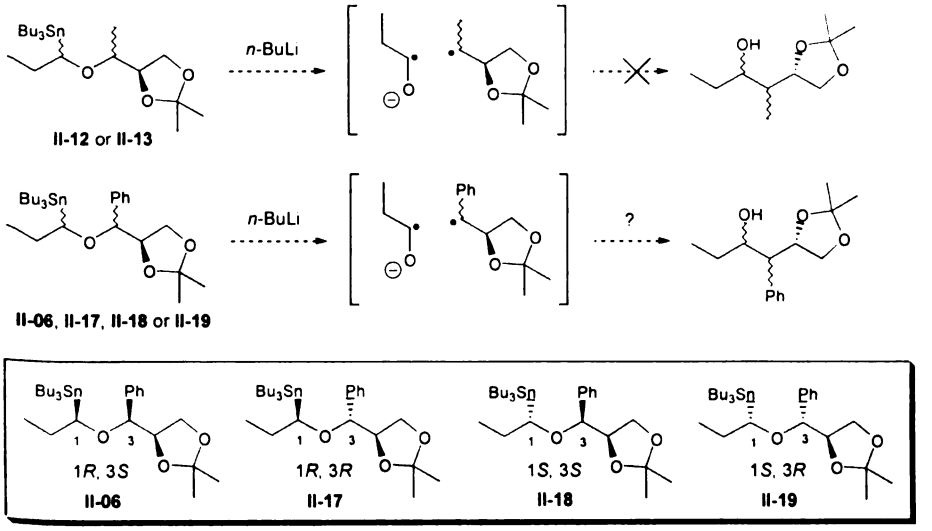
This observation echoed Nakai's conclusions from a study[6b,11] reported at about the same time, that for the Wittig rearrangement reaction to proceed, at least one of the fragments must have some radical stabilizing features (Scheme 2.7).

Scheme 2.7. Nakai's observations on the [1,2]-Wittig rearrangement



2.3.2. [1,2]-Wittig rearrangements of compound **II-06**, **II-17**, **II-18** and **II-19**

Scheme 2.8. The design of new model compounds

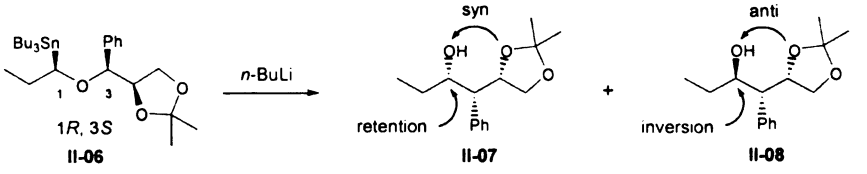


Given the experimental results with compounds **II-12** and **II-13**, we reasoned that a phenyl group instead of the methyl group at C3 should provide the needed radical stabilization (Scheme 2.8). Thus we prepared compound **II-06** and three of its diastereomers **II-17**, **II-18**, and **II-19** via a parallal route to that used before (Scheme 2.4), and then studied their Wittig rearrangements.

When a racemic mixture of compounds **II-06**, **II-17**, **II-18**, and **II-19** was subjected to the Wittig conditions in THF, we were pleased to see the Wittig rearrangement products were formed in a combined 95% yield. The dramatic difference between the behavior of **II-06**, **II-17**, **II-18**, **II-19** and their methyl substituted counterparts **II-12** and **II-13** convincingly demonstrated the importance of the radical stabilizing effect.

The [1,2]-Wittig rearrangement of compound **II-06** was first investigated by exposing it to *n*-BuLi in 30% THF/hexanes, the same solvent system employed by Schreiber. The reaction product was a mixture of both the *syn* and *anti* alcohols (*vide infra*),[12] with the *syn* alcohol (**II-07**) in slight excess. While the selectivity was not great, it did represent evidence that the chelation controlled reaction pathway was operative (Scheme 2.9).

Scheme 2.9. [1,2]-Wittig rearrangement of model compound **II-06**



Solvent	II-07/II-08
10% THF/ Hexanes	68 / 32
30% THF/ Hexanes	63 / 37
THF	43 / 57
LiCl saturated THF	37 / 63

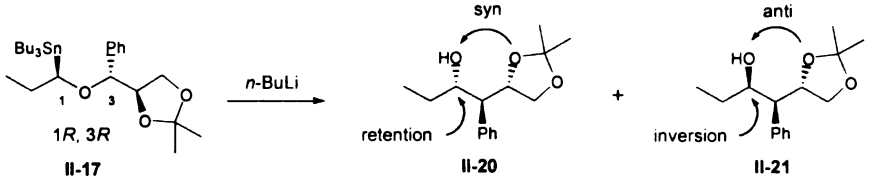
We reasoned that a less polar solvent would further favor the chelation controlled product. This proved to be the case as an experiment using 10%THF/hexanes as the solvent increased the ratio of **II-07**:**II-08** to 68:32 (Scheme 2.9). The same line of

thinking would suggest that a more polar solvent would disfavor the production of the chelation controlled product. Indeed, running the reaction in pure THF reversed the stereochemical outcome. Compound **II-08**, which results from an inversion of the configuration at the C1 center, became the major product albeit in only slight excess (**II-07**:**II-08**; 43:57). Finally, THF saturated with LiCl was examined in the expectation that the excess lithium counter ion would break up the intramolecular chelation even further. In fact, this experiment resulted in a stereochemical turnaround from the 10%THF/hexanes solvent system. The inversion product **II-08** was now favored by a ratio of 2:1.

Consistent with previous studies, it was found that there was a high level of retention of configuration at the migrating carbon center. In this case the observed level of retention was always higher than 90%.

We observed the same pattern upon [1,2]-Wittig rearrangement of compound **II-17** (Scheme 2.10). With this substrate however, changing the solvent polarity had an even more dramatic effect. Here, we were able to reverse the ratio of **II-20**:**II-21** from 2:1 under conditions for retention of configuration or chelation control (10%THF/hexanes) to 1:4 in favor of the inversion of configuration or non-chelation controlled *anti* product.[12]

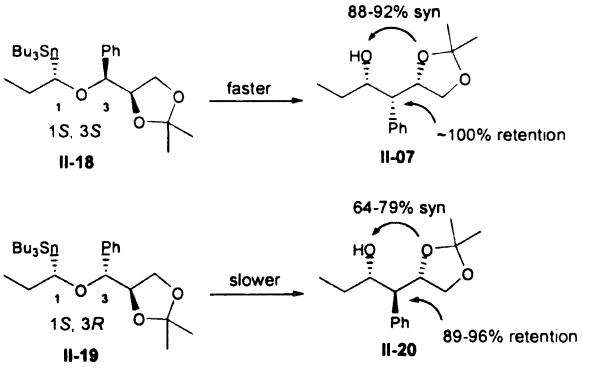
Scheme 2.10. [1,2]-Wittig rearrangement of model compound **II-17**



Solvent	II-20/II-21
10% THF/ Hexanes	70 / 30
30% THF/ Hexanes	47 / 53
THF	28 / 72
LiCl saturated THF	19 / 81

For **II-18** and **II-19**, the chelation controlled reaction pathway leads to the inversion of C1 configuration. So even if a change in the solvent system were to influence the extent of chelation during the reaction, it should not greatly affect the stereochemistry of the products. Indeed, the [1,2]-Wittig rearrangement of **II-18** and **II-19** always gave the *syn* alcohol as the main product, regardless of variations in the solvent system (Scheme 2.11).[12]

Scheme 2.11. [1,2]-Wittig rearrangement of model compounds **II-18** and **II-19**



It should be noted that regardless of solvent the rearrangment of **II-18** was always more stereoselective than for that of **II-19**. This suggests that there is a mutual recognition on the enantiomers during the recombination of the two radical species.[6] Apparently, the *R,S* radical pair is the matched pair and recombines faster than the *R,R* or mis-matched pair (Scheme 2.11).

These results clearly show that the "normal" tendency for the α-oxy lithium species to undergo an inversion of configuration can be suppressed, and even overturned, by the solvent effect on chelation. In systems like **II-06** and **II-17**, the stereochemical course can be controlled to give *either* syn or anti 1,3-diol compounds as the main products.

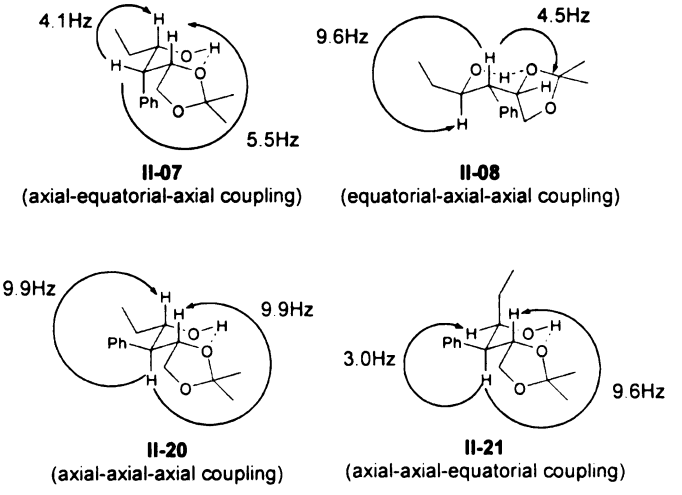
2.3.3. Assignment of the stereochemistry

To determine the influence of chelation effect on the stereochemical outcome of the reaction, we measured the ratio of the products formed under different conditions by

HPLC. Due to the low UV absorbance of the Wittig products, we decided to first esterify the reaction mixture with 3,5-dinitrobenzoyl chloride, and then measure the product mixture.

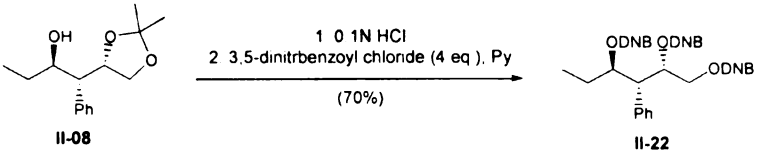
The stereostructure of the alcohols **II-07**, **II-08**, **II-20** and **II-21** were assigned using both ^{1}H-NMR and single crystal X-ray analysis. The benzyl protons of these alcohols showed very different coupling patterns (Scheme 2.12). The relative stereochemistries of diastereomers **II-07** and **II-20** were easily determined by the ^{1}H-NMR method employed by Brückner *et al.* on similar molecules, due to their distinctive axial-equatorial-axial and axial-axial-axial couplings respectively.[12]

Scheme 2.12. ^{1}H-NMR coupling patterns of Wittig rearrangement products



The sterochemistry of **II-08** was secured by a combination of ^{1}H-NMR and single crystal X-Ray analysis of the tris-3,5-dinitrobenzoate derivative of **II-08,** compound **II-22** (Scheme 2.13). The stereochemistry of the last diastereomer, compound **II-21**, was thus assigned by default.

Scheme 2.13. The determination of the stereochemical structure of **II-08**



2.4. Conclusions

Our results showed that the "normal" tendency for the α-oxy lithium species to undergo an inversion of configuration could be suppressed, and even overturned, by the solvent effect on chelation. It was also demonstrated, by the sharp contrast between the efficiency by which the methyl and phenyl substituted compounds undergo Wittig rearrangement, that the presence of a radical-stabilizing functionality is crucial for [1,2]-Wittig rearrangement.

CHAPTER 3

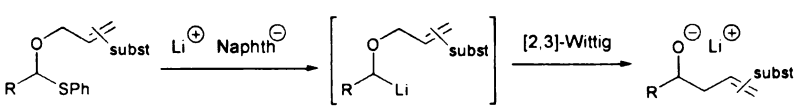
THE PREPARATION AND WITTIG REARRANGEMENTS OF α-ALKOXYSILANES

3.1. Introduction

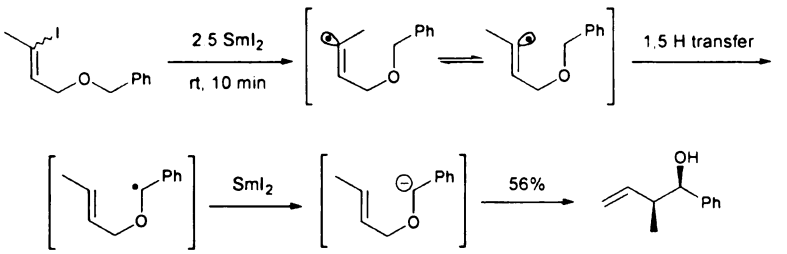
As seen in the previous chapter, Wittig rearrangements are typically initiated by the formation of an α-metallated ether which undergoes a subsequent rearrangement, usually in the form of a [2,3], [1,2], or [1,4] shift. While direct deprotonation of an ether at the α-carbon, usually facilitated by the presence of anion stabilizing groups such as carbonyls, nitriles, as well as vinyl, phenyl, or alkynyl moieties,[1] can be used to initiate the sigmatropic event, this approach is limited to those compounds possessing sufficiently acidic α hydrogens. In 1978, Still and Mitra showed that this restriction could be overcome by generating the α-alkoxy carbanion via tin-lithium exchange.[2] In the years following their pioneering work, the Wittig-Still rearrangement has earned its place as a powerful synthetic tool. Despite its demonstrated potential, broad application of this protocol has been governed by its reliance on the relatively toxic[3] organnostannes as well as the need for strong air and moisture-sensitive bases such as *n*-BuLi.

In order to circumvent these two limitations, several groups have sought "tin free" alternatives to the regioselective generation of α-ethereal carbanions. Some successful approaches to this problem have been based on the reductive cleavage of *O,S*-acetals with lithium naphthalenide[4] (Scheme 3.1), while others involve SmI_2 mediated reduction of diallyl acetals[5] or vinyl halides capable of 1,5-hydrogen transfer[6] (Scheme 3.2).

Scheme 3.1. Wittig rearrangements of *O,S*-acetals initiated by lithium naphthalenide

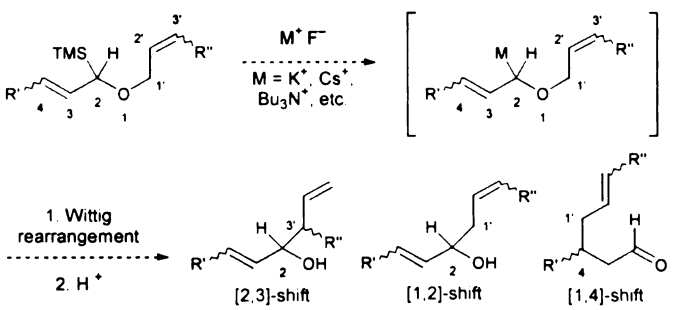


Scheme 3.2. Wittig rearrangements initiated by 1,5-hydrogen transfer



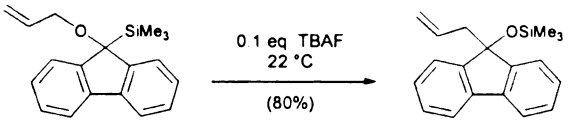
In our research group, there were several ongoing projects focusing on the development of "tin free" alternatives for reactions such as the Stille coupling.[7] Thus we were drawn to the idea of combining our interest in the synthetic utility of the Wittig rearrangement with our goal of minimizing the tin requirements in reactions involving organostannane reactants. In considering tin free alternations for the Wittig-Still reaction, we envisaged the possibility of α-alkoxysilanes being made to undergo Wittig rearrangements by the action of fluoride (Scheme 3.3).

Scheme 3.3. Fluoride induced Wittig rearrangements ?



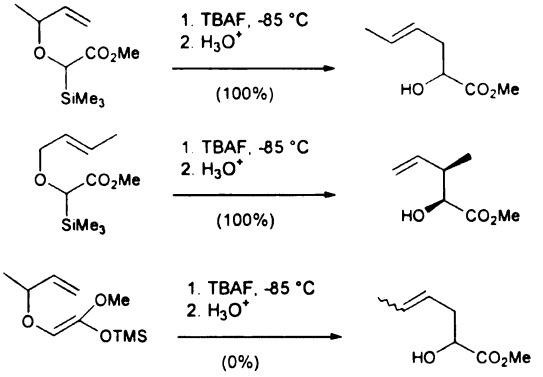
Not surprisingly such an approach has been the subject of prior, though very limited, investigations.[8-10] In fact, prior to the original disclosure of Still,[2] Reetz and Greif had shown[8] (Scheme 3.4) that the thermal rearrangement of fluorene derivatives could be facilitated by catalytic quantities of tetrabutylammonium fluoride (TBAF).

Scheme 3.4. Relevant previous studies by Reetz



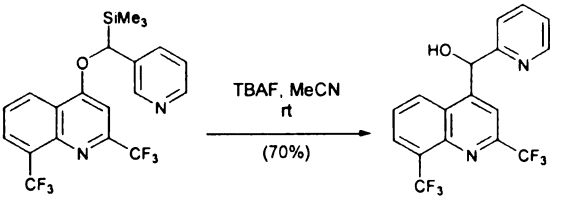
Several years later, Nakai reported the fluoride ion-promoted [2,3]-Wittig rearrangement of two *C*-silylated α-allyloxy esters[9] (Scheme 3.5). Interestingly, he noted that the attempted Wittig rerrangement of the TMS vinyl ether failed.

Scheme 3.5. Relevant previous studies by Nakai



To our knowledge the only other report of a fluoride triggered Wittig rearrangement was by Adam, who converted α-phenoxybenzylsilane into an alcohol which would appear to be the product of a [1,2]-Wittig (Scheme 3.6).[10] However, the author makes the point that this reaction proceeds via an intramolecular *ipso*-substitution

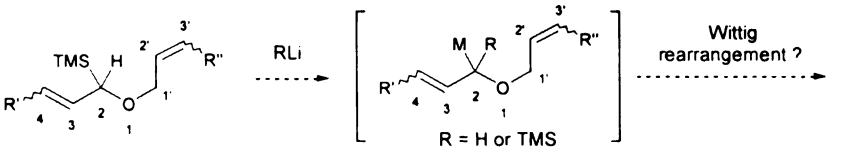
Scheme 3.6. Relevant previous studies by Adam



as opposed to the radical pair dissociation-recombination mechanism[11] of an actual [1,2]-Wittig rearrangement.

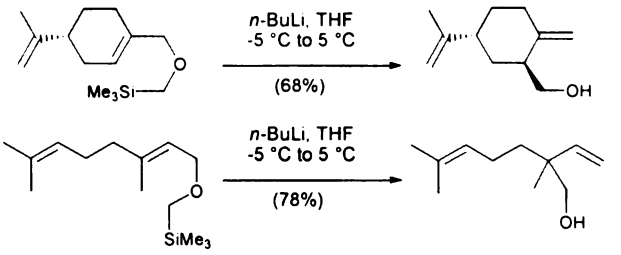
At the same time, we noted that there are two Wittig rearrangement manifolds available to α-alkoxysilanes under traditional conditions, such as deprotonation by MeLi or *n*-BuLi. In addition to serving as a carbanion mask, the silyl moiety in α-alkoxysilanes can also be viewed as an anion stabilizing group,[12, 13b,c] thus both Si/Li exchange and deprotonation are plausible ways to initiate the Wittig rearrangements of α-alkoxysilanes (Scheme 3.7).

Scheme 3.7. Wittig rearrangements of α-alkoxytrimethylsilanes ?



Interestingly, the Si/Li exchange of α-alkoxytrimethylsilanes, a seemingly straightforward alternatives to the Wittig-Still rearrangement, has received little attention, even though such exchange reactions are well precedented.[13] To the best of our knowledge, only two examples (Scheme 3.8), both reported by Muzler and List,[13a] stand alone as the only [2,3]-Wittig rearrangements triggered by Si/Li substitution.

Scheme 3.8. Wittig rearrangemnets of α-alkoxysilanes triggered by Si/Li substitution



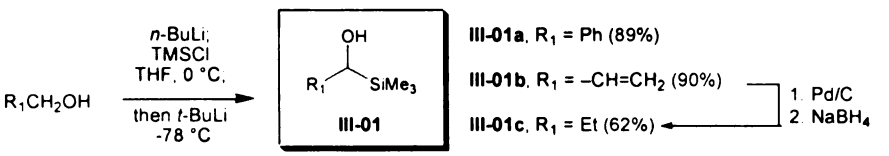
Surprisingly, in spite of the fact that the deprotonation path would afford an unique access to the synthetically malleable silanes,[14] we are unaware of any examples where the direct deprotonation of α-alkoxysilanes has been used to initiate a Wittig rearrangement.[15,16]

Given the mechanistic uncertainties and narrow substrate scope of these previous studies, coupled with little advancement of this chemistry for over a decade, we decided to explore the possibilities of Wittig rearrangements of α-alkoxysilanes. Key to our study would be an examination of substrates which would allow the direct comparison of α-alkoxysilanes with the more established α-alkoxystannanes.

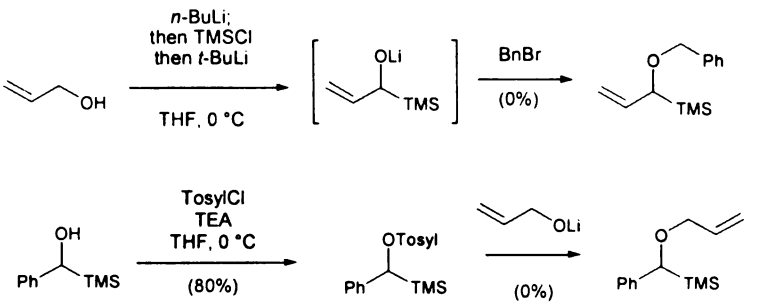
3.2. Preparation of α-alkoxysilanes

Upon beginning our study, we were quick to realize that few general methods exist for the synthesis of α-alkoxysilanes with more complexity than that of the (TMS) methyl ethers.[17,18] (Perhaps the main reason for lack of progress in this area.) Although substituted α-hydroxysilanes are easily obtained via retro-Brook rearrangement[19] (Scheme 3.9), the alkylation of these alcohols *in situ*[20] or under basic conditions proved difficult[21] (Scheme 3.10). Furthermore, while we could efficiently tosylate α-hydroxybenzylsilane, nucleophilc displacement of the product also failed to provide any of the desired ethers (Scheme 3.10).

Scheme 3.9. Preparation of various α-hydroxysilanes



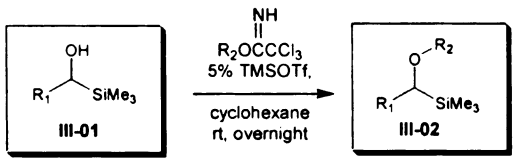
Scheme 3.10. Failed attempts to prepare various α-alkoxysilanes



Several literature reports had demonstrated the compatibility of α-hydroxysilanes to acid catalyzed methylation and acetalizations.[20,22] Following this lead, we found that

TMSOTf catalyzed etherification of α-hydroxybenzyl and α-hydroxyallylsilane via the trichloroacetimidates of benzyl, propargyl, and various allylic alcohols[23] afforded the desired α-alkoxysilanes in 50-95% yields[24] after silica gel chromatography (Scheme 3.11).

Scheme 3.11. Preparation of various α-alkoxysilanes



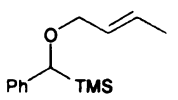
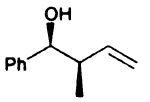
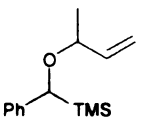
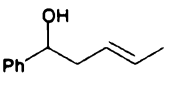
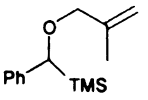
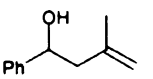
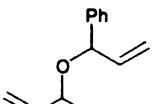
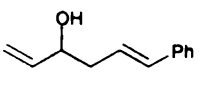
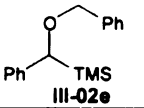
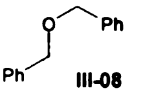
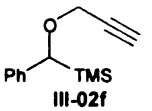
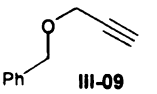
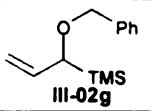
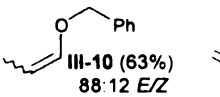
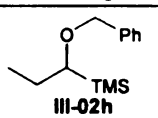
	R_1	R_2	Yield(%)
III-02a	Ph	(*E*)-$CH_2CH{=}CHCH_3$	67
III-02b	Ph	-$CH(CH_3)CH{=}CH_2$	25
III-02c	Ph	-$CH_2(CH_3)C{=}CH_2$	55
III-02d	-$CH{=}CH_2$	-$CH(Ph)CH{=}CH_2$	67
III-02e	Ph	-CH_2Ph	52
III-02f	Ph	-$CH_2C{\equiv}CH$	54
III-02g	-$CH{=}CH_2$	-CH_2Ph	53
III-02h	Et	-CH_2Ph	63
III-02i	-$CH{=}CH_2$	(*Z*)-$CH_2CH{=}CHEt$	31

3.3. Wittig rearrangements of α-alkoxysilanes induced by CsF

With our general route to α-alkoxysilanes in place, we set out to explore the action of fluoride on these substrates. Surveying several fluoride sources, we found that contrary to previous reports, TBAF was not especially effective at promoting Wittig rearrangement. For example, reaction of **III-02b** with TBAF in the presence of 4Å molecular sieves gave the [2,3]-rearrangement product **III-04** in only 20% yield. Similarly, neither KF or tetrabutylammonium difluorotriphenylstannate[25] provided any Wittig products. On the other hand, CsF in DMF proved to be relatively efficient at the promotion of [2,3]-Wittig rearrangements (Table 3.1). With CsF all of our substrates

capable of undergoing a [2,3]-shift (**III-02a-d**) gave [2,3]-products in yields that were comparable to the analogous lithium anion initiated rearrangements.[1]

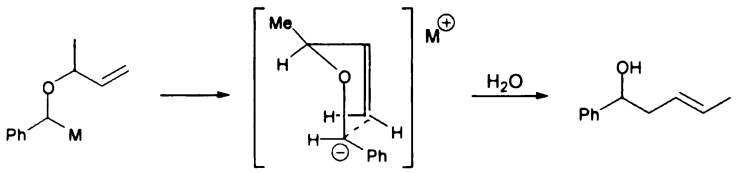
Table 3.1. CsF promoted Wittig rearrangements of α-alkoxysilanes

entry	starting material	products (yield)
1	 **III-02a**	 **III-03** [2,3]-Wittig (80%) 55:45 *erythro/threo*
2	 **III-02b**	 **III-04** [2,3]-Wittig (60%)
3	 **III-02c**	 **III-05** [2,3]-Wittig (79%)
4	 **III-02d**	 **III-06** [2,3]-Wittig (54%) **III-07** [1,2]-Wittig (13%)
5	 **III-02e**	 **III-08** (61%)
6	 **III-02f**	 **III-09** (54%)
7	 **III-02g**	 **III-10** (63%) 88:12 *E/Z* **III-11** (14%)
8	 **III-02h**	No Reaction (80% recovery of **III-02h**)

While the scope of this preliminary investigation limits us in making any extensive stereochemical comparisons to the rearrangement of analogous α-lithio compounds, the rearrangement of **III-02a** did exhibit the same (albeit poor) inherent stereochemical bias towards the erythro product, as its lithio counterpart.[1,26] Likewise, the exclusive *E*-olefin formation observed in entries 2 and 4 (Table 3.1) would suggest

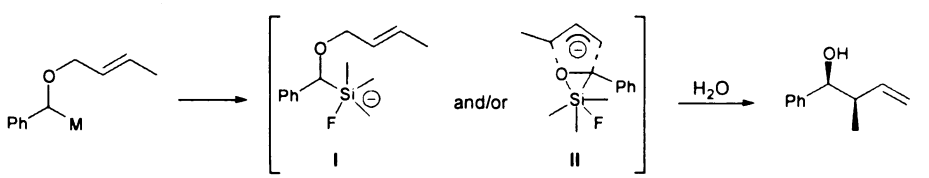
that the fluoride induced Wittigs proceed via an *exo* transition state as proposed by Nakai for traditional Wittig rearrangements of this type (Scheme 12).[1,27]

Scheme 3.12. *exo*-Transition state of Wittig rearrangements



Our initial results indicate that efficient fluoride promotion may be primarily limited to [2,3]-sigmatropic events. Only entry 4 (Table 3.1) showed any propensity for another Wittig manifold, providing the [1,2]-species as a minor product. Only loss of the silyl group was observed for other substrates set up to undergo [1,2]-Wittig rearrangement (Table 3.1; entries 5-7). This observation that the fluoride promoted rearrangements mimic their lithio counterparts during the concerted [2,3]-shift, but not during the radical pair dissociation-recombination driven [1,2]-Wittig rearrangement, suggests the involvement of a metal associated carbanionic intermediate. This would contrast with the traditional Wittig-Still, for which Brückner[28] has put forth experimental evidence of a metal free carbanion. What is less clear is whether these fluoride promoted Wittigs involve a pentavalent silicon intermediate (Scheme 3.13, **I**)[17b,29] and/or the type of cation coordinated species suggested by *ab initio* calculations (Scheme 3.13, **II**).[30]

Scheme 3.13. Possible intermediate species of fluoride promoted Wittigs of α-alkoxysilane

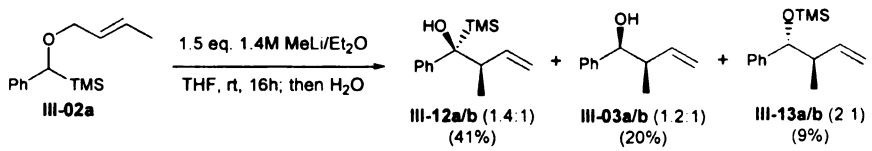


Finally, it would appear that some activation of the starting material (benzylic or allylic) is required. Aliphatic α-alkoxysilanes (Table 3.1; entry 8), for example, failed to react under our conditions.

3.4. Wittig rearrangements of α-alkoxysilanes induced by MeLi

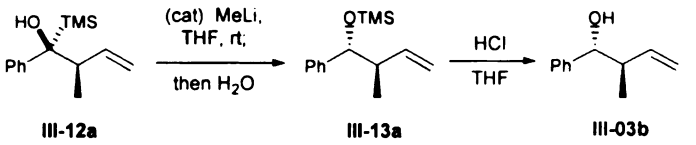
Next, we evaluated these α-alkoxysilanes under "standard" Wittig rearrangement conditions. Thus a solution of α-alkoxysilane **III-02a** in THF was subjected to 1.5 eq. of a 1.4M ethereal solution of MeLi at room temperature (Scheme 3.14). We were immediately struck by the formation of *C*-silyl containing reaction products (**III-12a/b**), providing clear evidence of **III-02a** undergoing deprotonation followed by subsequent Wittig rearrangement. This is in contrast to exclusive silicon-lithium exchange reported for the two Wittig precursors studied by Muzler.[13a] The *C*-silyl alcohols were accompanied by a diasteromeric mixture of desilylated alcohols (**III-03a/b**), along with a small amount of the corresponding silyl ethers (**III-13a/b**).

Scheme 3.14. Wittig rearrangements of α-alkoxysilane **III-02a** induced by MeLi



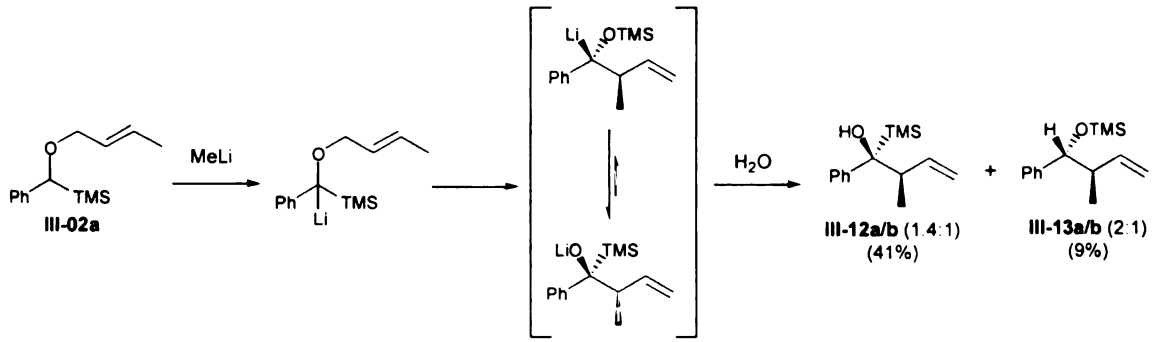
The formation of such a reaction mixture posed several challenges. First, although the level of stereocontrol displayed by the reaction was poor,[31] we wished to specifically identify the stereochemistry of **III-12a** and **III-12b**. Fortunately, both diastereomers proved readily separable by flash silica gel chromatography. Therefore, we could subject pure **III-12a** (the *major* isomer) to base catalyzed Brook rearrangement (Scheme 3.15).[32] Since such rearrangements proceed with an inversion of configuration at carbon,[33] the reaction afforded a single silyl ether. Desilylation then afforded the known alcohol **III-03b**[31,34], which was the *minor* alcohol produced by the reaction. Thus the Brook product could be assigned as **III-13a**, furthermore given the stereospecificity of the Brook rearrangement, we could also confidently assign the relative stereochemistries of **III-12a** and **III-12b**.

Scheme 3.15. Brook rearrangement of **III-12a** initiated by a catalytic amount of base



Additionally, the contrasting (albeit small) stereoselective preferences observed in the formation of the *C*-silyl alcohols (*syn* with respect to the oxygen and Me group preferred) vs. the silyl ethers (*anti* with respect to the oxygen and Me group preferred) is evidence that **III-13a/b** are the result of **III-12a** and **III-12b** undergoing *in situ* Brook rearrangement prior to quenching (Scheme 3.16).

Scheme 3.16. Origin of **III-13a/b**

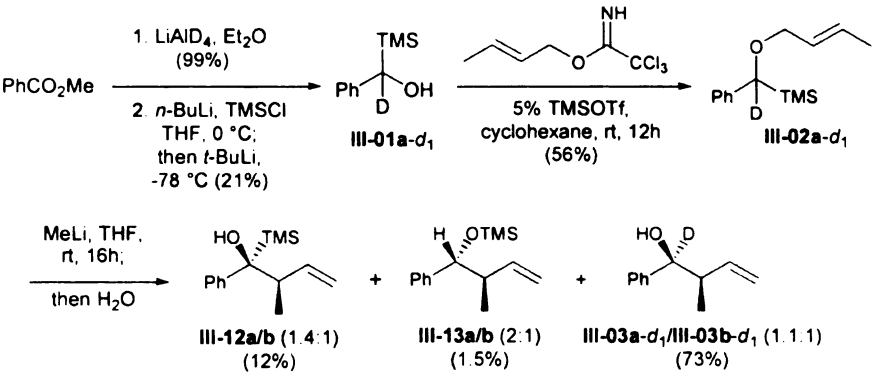


What was less clear was the origin of the desilylated alcohols (**III-03a/b**). Obviously, Si/Li exchange initiated [2,3]-rearrangement would account for their formation, but an alternative path involving *in situ* loss of the silyl group from either **III-12a/b** or **III-13a/b** was also envisaged.

While the stereochemical course of the reaction could again be used to argue against the *in situ* conversion of **III-13** to **III-03**, the very low levels of selectivity made it difficult to rule out this option with any significant degree of certainty. So to bring more clarity to this issue, we decided to prepare and react (Scheme 3.17) the deuterated analog of **III-02a** (**III-02a**-d_1). The starting material was prepared by LAD reduction of methyl benzoate,[35] followed by a retro-Brook sequence[36] and then etherifcation. Wittig rearrangement of **III-02a**-d_1 gave the *C*-silyl, dessilyl, and *O*-silyl materials, although in

this case the dessilyl alcohols (**III-03a/b-d_1**) were the major products, reflecting a relatively large deuterium isotope effect.[37] Significantly this material appeared to be fully deuterated as judged by ^{1}H-NMR, providing strong evidence that it is produced solely via the Si/Li exchange pathway.

Scheme 3.17. Isotopic studies of the Wittig rearrangements of α-alkoxylsilanes

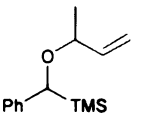
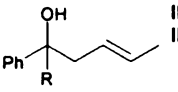
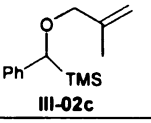
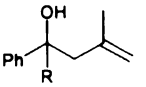
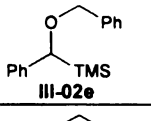
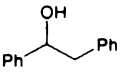
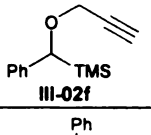
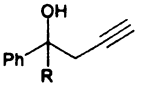
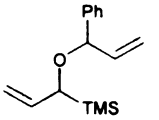
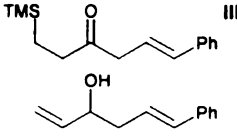
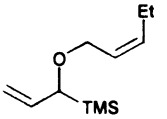
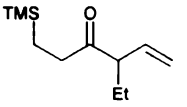
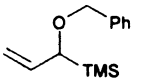
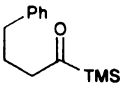
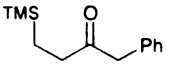


Having gained a reasonable understanding of the behavior of **III-02a** towards Wittig-Still conditions, we next subjected several other α-alkoxylsilanes to methyllithium (Table 3.2). With substrates set up for [2,3]-Wittig reaction (entries 1 and 2), the overall efficiency of the rearrangements were good. However, once again, the rearrangements proceeded via both the Si/Li exchange and α-silyl anion manifolds. With substrates set up to only undergo [1,2]-Wittig rearrangement (entries 3 and 4), the anticipated reaction did occur. However, as is often the observation with [1,2]-Wittigs, the yields were low and again both Si/Li exchange and α-silyl anion formation appeared operative. Unfortunately, our attempts to drive these rearrangements down a single reaction path via standard methods were less than fruitful.

Intriguingly, when we moved from the α-alkoxylbenzylsilanes to α-alkoxylallylsilanes (entries 5-7), the extent of Si/Li exchange was significantly curtailed. However, these substrates did displayed a propensity for silyl migration to afford β-silyl ketones. For example, α-alkoxylallylsilane **III-02i** gave the β-silyl ketone **III-21** in a remarkable 92% yield. We propose that this product comes about via [2,3]-

Wittig rearrangement of the α-silyl anion followed by a net 1,3-silyl migration (Scheme 3.18)[38].

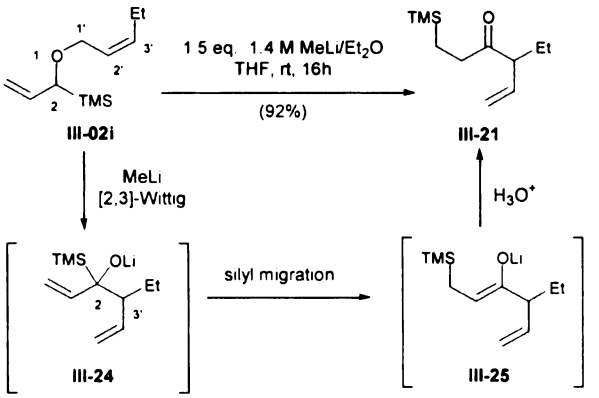
Table 3.2. Methyllithium induced Wittig rearrangements of α-alkoxylsilanes

entry	starting material	products (yield)
1	 **III-02b**	 **III-04** R = H (75%) **III-14** R = TMS (21%) [3,2]-Wittig
2	 **III-02c**	 **III-15** R =TMS (50%) **III-05** R = H (32%) [3,2]-Wittig
3	 **III-02e**	 **III-16** (9%) [1,2]-Wittig
4	 **III-02f**	 **III-17** R = H (33%) **III-18** R = TMS (15%) [1,2]-Wittig
5	 **III-02d**	 **III-19** (60%) via [2,3]-Wittig **III-20** (20%) [2,3]-Wittig
6	 **III-02i**	 **III-21** (92%) via [2,3]-Wittig
7	 **III-02g**	 **III-22** (60%) [1,4]-Wittig  **III-23** (21%) via [1,2]-Wittig

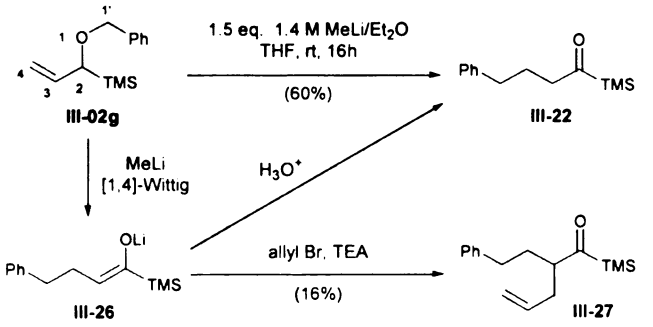
In a further departure from the α-alkoxylbenzylsilanes, allysilane **III-02g** rearranged in high yields albeit via a mixture of both [1,4]- and [1,2]-Wittigs (**III-22** and **III-23**). Given the synthetic utility reported for acylsilanes[13c,39] and β-silyl ketones,[13c,40] this route enhanced the synthetic value of both the α-alkoxysilanes and the Wittig rearrangement reactions. Additionally, since this compound is formed via an enolate intermediate, it is also perceiveable that combining these rearrangements with the capture of various electrophiles will lead to an even more diversified group of acylsilanes.

Indeed, our preliminary results showed that, when the Wittig rearrangement reaction was quenched with allyl bromide, the α-allylated product **III-27** could be formed in 16% yield (Scheme 3.19).

Scheme 3.18. Formation of β-silyl ketones



Scheme 3.19. Formation of acylsilanes



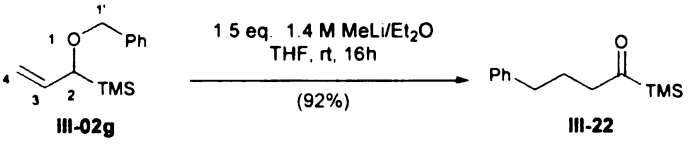
CHAPTER 4

PALLADIUM CATALYZED SYNTHESIS OF ACYLSILANES

4.1. Introduction

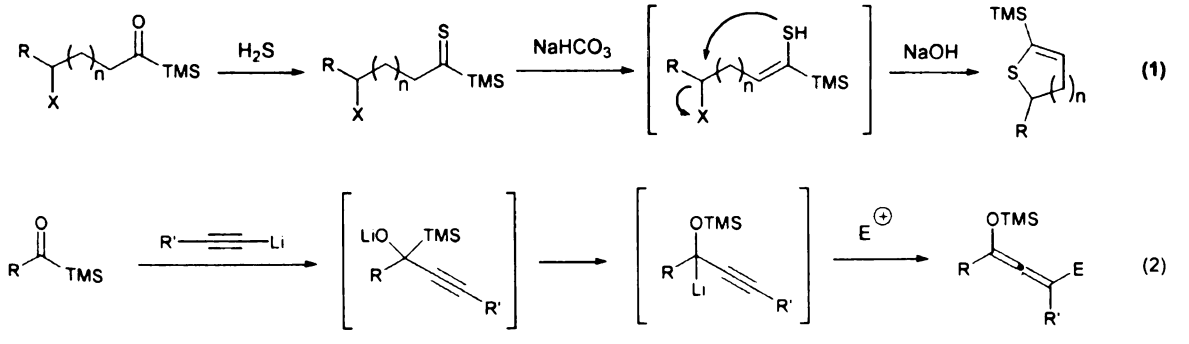
During our study on the Wittig rearrangement reactions of α-alkoxylsilanes, acylsilane (**III-22**) was isolated in very high yields from one of the reactions. This is the first time an acylsilane has been prepared via a Wittig rearrangement reaction. Because this reaction proceeds through an enolate intermediate, a variety of acylsilanes are accessable through the same path. This discovery opened the door for a new route to these useful compounds.

Scheme 4.1. Formation of acylsilanes



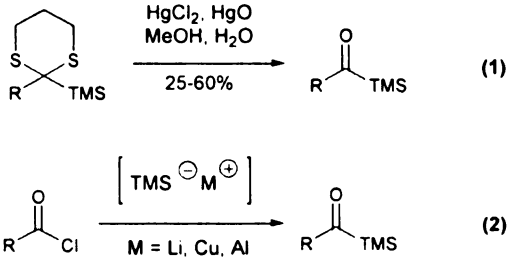
Indeed, acylsilanes have attracted much attention as a versatile tool in organic synthesis since many unique and valuable reactions can take place with these compounds.[1] Scheme 4.2 illustrated two such possible transformations. Via simple reactions, both 2-silylthiacycloalk-2-enes of various ring sizes[1a] and variety of enol ethers[1b] can be obtained.

Scheme 4.2. Reactions of acylsilanes



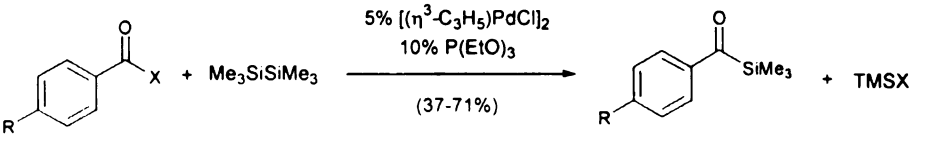
Along with these studies, many methods have been developed to synthesize this family of compounds. One of the most common methods mirrors the synthesis of normal ketones, namely hydrolysis of silylated 1,3-dithianes.[2] However, this method suffers from mediocre yields and requires the often difficult hydrolysis of the dithianes (Scheme 4.3, entry 1).[2] Another general method is the acylation of silyl-metal compounds, but this method often suffers from rather poor yields (Scheme 4.3, entry 2).[3]

Scheme 4.3. Preparation of acylsilanes



Recently, a very convenient and safe method was reported by Yamamoto.[4] When substituted benzoyl chlorides reacted with hexamethyldisilane under palladium catalyst, acylsilanes were produced in 37-81% yields. However, the authors reported that this method failed to provide aliphatic acylsilanes.[4, 5]

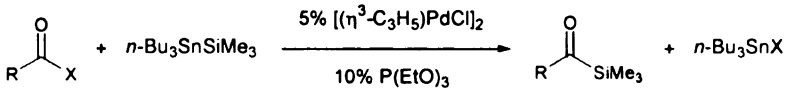
Scheme 4.4. Preparation of acylsilanes



Due to the absence of a general and convenient method to prepare these synthetically useful acysilanes, we decided to investigate the possibility of modifying Yamamoto's method to allow the preparation of both aromatic and aliphatic acylsilanes. Based on the fact that the transmetallation of tin is much more facile than that of silicon,[6] we speculated that trimethylsilyltributylstannane (TMSTBS), a commercially available and easily prepared compound,[7] should be a good silicon source for this reaction.

4.2. Results and discussion

Scheme 4.5. Pd catalyzed coupling of TMSTBS with carbonyl compounds



Entry	R	X	Temp. (°C)	Time	Yield (%)
1	n-C_4H_9	Cl	100-110	20 min	63
2	n-C_7H_{15}	Cl	rt	15 days	43
3	n-C_7H_{15}	Cl	100-110	16 h	74
4	C_4H_9(Et)CH	Cl	75	10 h	45[a]
5	cyclo-C_6H_{11}	Cl	75	12 h	56
6	Ph	Cl	100-110	20 min	66
7	Ph	PhCOO	100-110	20 min	18
8	Ph	Cl	75	100 min	57[a]
9	o-ClPh	Cl	100-110	20 min	30
10	p-MeOPh	Cl	100-110	20 min	35

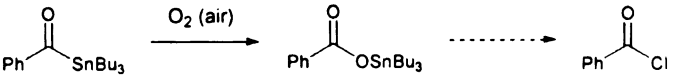
a. reactions were carried out under CO atmosphere

Thus TMSTBS and benzoyl chloride were mixed together with di-m-chloro-bis(η^3-allyl)dipalladium and triethylphosphide[4] at 110 °C, the same catalyst and temperature used by Yamamoto. We were pleased to see the pale yellow solution turned black after 10 min due to the formation of metallic Pd, suggesting sucessful coupling. Indeed, GC analysis showed that at this point the acyl chloride was completely consumed. With hexamethyldisilane, the reaction needed more than 1.8 h according to Yamamoto's report. Later it was found that even at room temperature the reaction also took place. A reaction of *n*-octonyl chloride at rt over 15 days gave the acylsilane in 43% yield. In light of this observation, the reaction temperature was later set at 75 °C. Although the reaction of aliphatic compounds took ca. 10 h to complete, those of aromatic compounds were

complete in 2-3 h. The possibility of carrying out the reaction at lower temperature is important since some of the acylsilane compounds are not very stable. In the original method, the reaction did not occur at 70 °C.

This method appears to be general. Both aliphatic and aromatic acysilanes can be obtained with fair yields (Table 4.1). The major drawback of this method is the competing formation of the corresponding acylstannane species. For example, although the reaction of benzoyl chloride proceeded clean and fast, significant amount of benzoylstannane was formed (29%), diminishing the yield of the acylsilane. However, the unstable acylstannane compounds[8] can be easily separated from the acylsilane and ultimately converted back to the starting acid chloride.

Scheme 4.6. The formation of tributyltinbenzoate

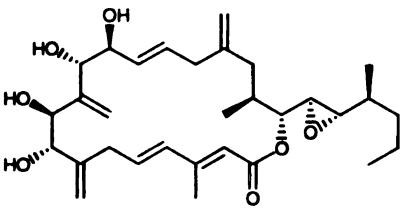


CHAPTER 5

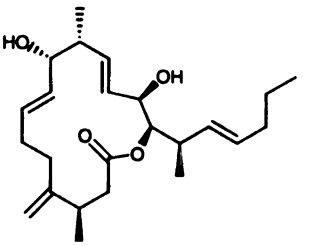
SYNTHETIC STUDIES TOWARD AMPHIDINOLIDE A

5.1. Introduction

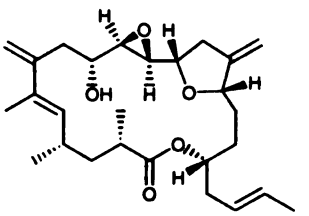
Scheme 5.1 Amphidinolides



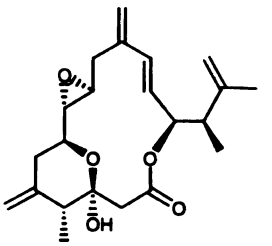
Amphidinolide A (V-01)



Amphidinolide J (V-02)



Amphidinolide K (V-03)



Amphidinolide P (V-04)

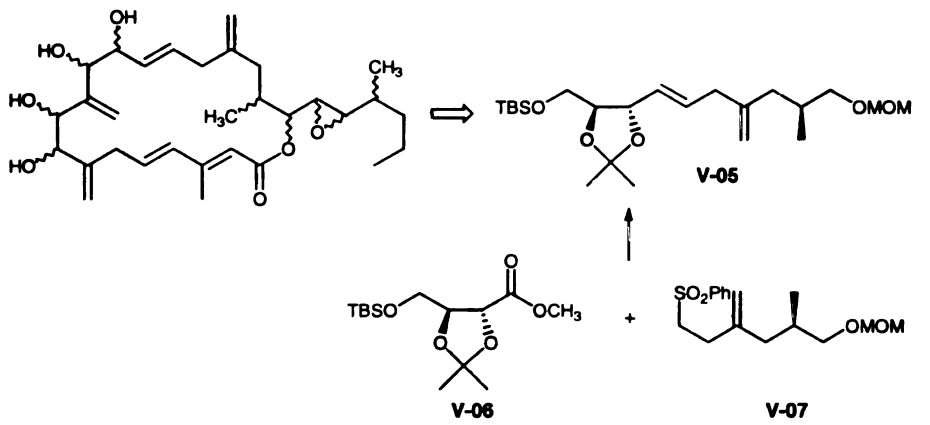
Marine microalgae are of considerable interest as new promising sources of bioactive substances. The amphidinolides (A-V) (Scheme 5.1), a novel and significant class of natural products, were isolated by Kobayashi from such algae.[1] Amphidinolide A (**V-01**) was isolated and identified in 1986 from the marine dinoflagellate *Amphidinum sp.*[1a] Since 1986, approximately twenty members of this unique series of polyolefinic macrolide compounds have been isolated. However only a few amphidinolides have had their stereochemistries fully elucidated. The relative stereochemistry of amphidinolide A was proposed in 1991 by Kobayashi based on information provided by nOe NMR data.[1b] However, as the author pointed out, the "interpretation of the relative stereochemistry of chiral centers of macrocyclic compounds by spectral means is still not easy".[5b] In this particular case, the correlation between the relative stereochemistry of the C8-C12 moiety

and the C18-C22 moiety is especially weak; thus the assigned relative stereochemical relationship between the right and left "halves" of amphidinolide A may be in error (Scheme 1.3).

In addition, this 20-membered lactone has several striking structural features, including the presence of lipophilic and hydrophilic moieties, as well as the presence of exocyclic olefins and both conjugated and non-conjugated dienes. Amphidinolide A also has marked biological properties, especially activities against L1210 marine leukemia cells and human epidermoid carcinoma KB cells in vitro. It is for these biological and structural features that amphidinolide A is a current target for total synthesis.[2]

To date, only two other groups in addition to ours[3a] have reported synthetic efforts toward this target. The first reported synthetic work was from Williard in 1989.[3b]

Scheme 5.2. The first synthetic work by Williard

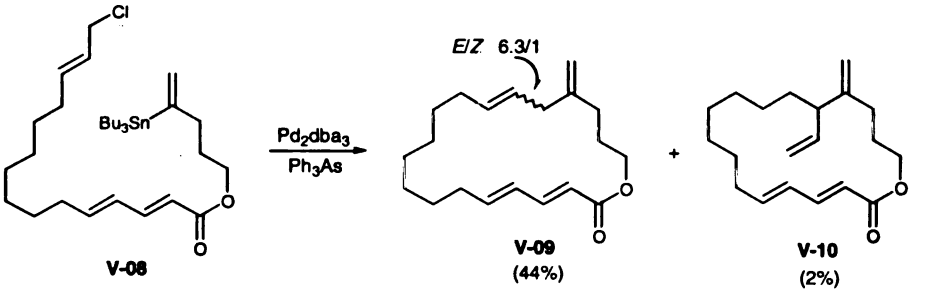


Williard's work was done prior to Kobayashi's stereochemistry elucidation. Therefore in his approach, methodology was developed to prepare all possible stereoisomers of the C_{10}-C_{19} fragment **V-05**, in order to make an unambiguous assignment of the stereochemistry. From his reaction sequences, the other stereoisomers were readily available through the simple change of chirality in the starting material. Either enantiomer of ester **V-06** was readily available from (+) or (-)-tartaric acid; and sulfone **V-07** was prepared from commercially available (*S*)-(+)-methyl-3-hydroxy-2-

methylpropinate, whose enantiomer is also commercially available. Since this early and limited publication in 1989, no other effort has been reported by the Williard group.

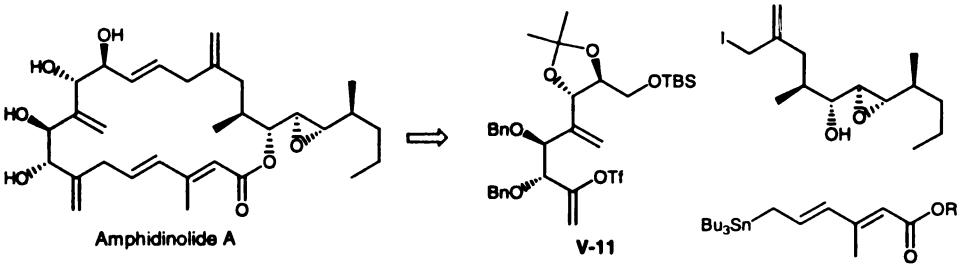
The second group to embark on the challenging task of synthesizing amphidinolide A was Pattenden's.[3c,d] In 1994, Pattenden published his first of two studies on amphidinolide A, in which a model study was undertaken to investigate the feasibility of a cross-coupling macrocyclization (Scheme 5.3).[3c] The chemical transformation investigated was a palladium mediated intramoleculer coupling of an alkenyl stannane and an allylic halide. The methodology proved moderately successful when applied to the model system **V-08**. The desired macrocycle **V-09** was obtained in a 38% yield along with the *Z*-isomer (6%) and the allylic isomer **V-10** (2%).

Scheme 5.3. Pattenden's model study on amphidinolide A



In his second publication, Pattenden outlined his synthetic approach towards the natural product (Scheme 5.4).[3d] The underlying theme of this retro-analysis was the application of the above mentioned sp^2-sp^3 coupling methodology. In studies aimed at providing the properly functionalized coupling partners, he prepared the C7-C13

Scheme 5.4. Pattenden's study towards amphidinolide A



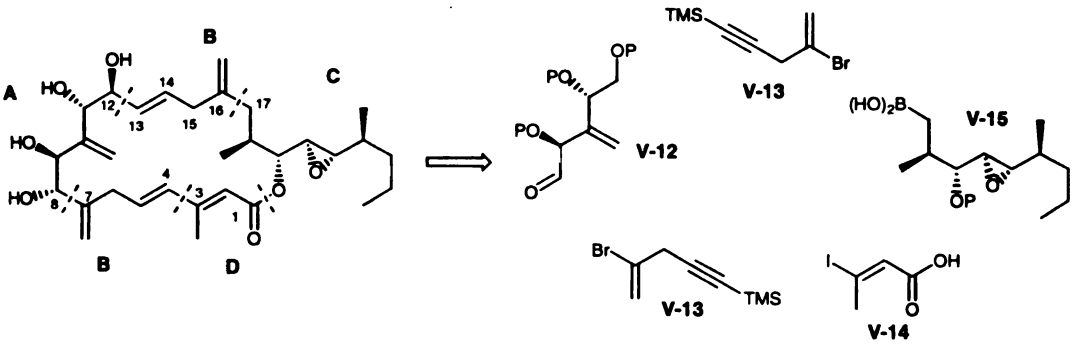
ene-tetrol unit **V-11**, from a readily available derivative of D-glucose in 13 linear steps with an overall yield of 2%.

Although to date no total synthesis of amphidinolide A has been reported, the total synthesis of three members of this unique series of natural products, amphidinolide J, K, and P, have been accomplished by Williams.[2]

Besides the desire to obtain amphidinolide A, its isomers, and derivatives for biological testing, a goal of this research venture was to apply and evaluate new synthetic methodologies, especially those involving organometallic chemistry.

5.2. Retrosynthetic analysis

Scheme 5.5. Retrosynthetic analysis



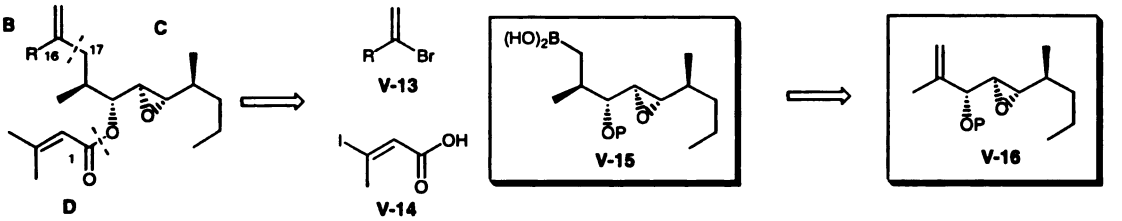
An early retrosynthetic analysis, shown in Scheme 5.5, gave four unique building blocks, with **V-13** being utilized twice. This convergent plan allowed us the freedom of choosing the sequence and order in which the fragments would be joined. Formation of the C7-C8 and C12-C13 bonds can be envisaged via a chelation controlled nucleophilic addition of a vinyl metallic species to the precursor aldehydes. The conjugated diene can be constructed via Stille type[6] cross-coupling to form the C3-C4 σ bond, while the lactone linkage can be formed with traditional methods such as DCC or Mitsunobu coupling. To form the C16-C17 bond, we decided to first explore a Suzuki type[8] coupling of **V-15** and **V-13** or their derivatives.

5.3. Synthesis of the **BCD** piece

5.3.1. Suzuki coupling route

5.3.1.a Synthetic plan

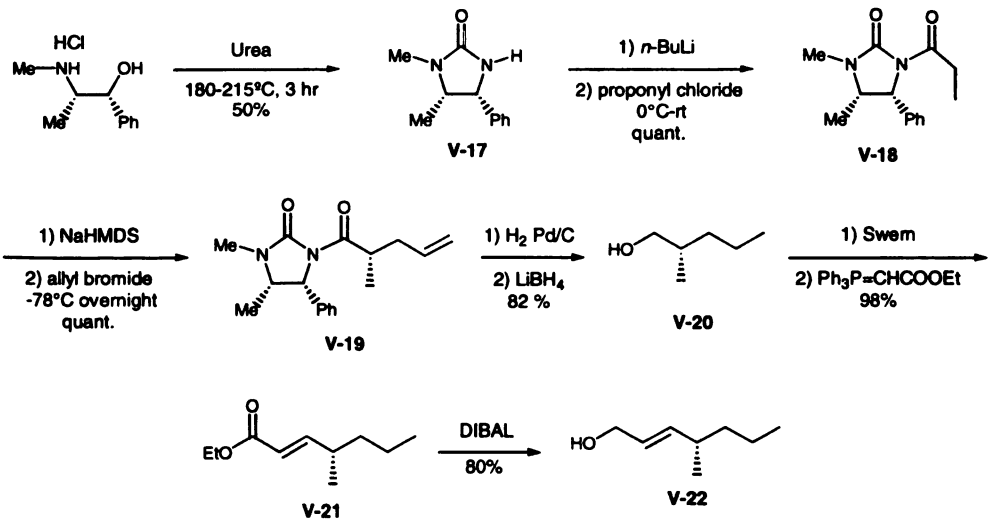
Scheme 5.6. Retrosynthetic analysis of Suzuki coupling route



To explore the planned construction of the C16-C17 bond through a Suzuki coupling,[8] we would need to prepare boronic acid **V-15**. Thus alkene **V-16**, which could be readily hydroborated, became our initial target.

5.3.1.b Preparation of compound **V-16**

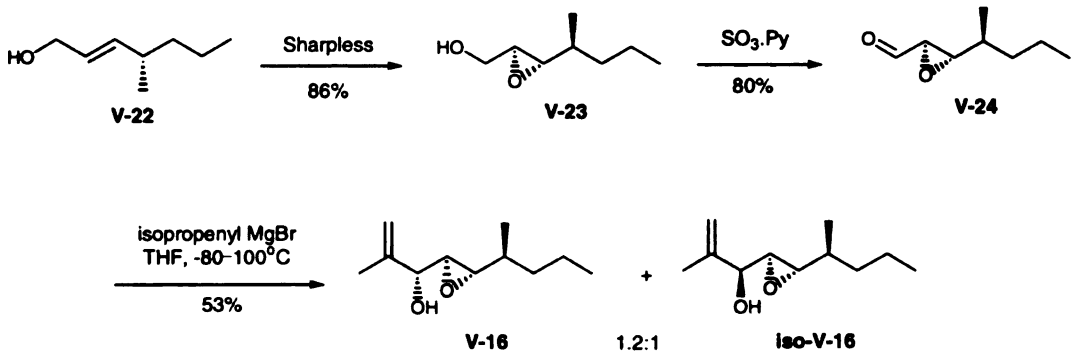
Scheme 5.7. Preparation of **V-22**



The preparation of **V-16** followed the procedure shown in Schemes 5.7 and 5.8. Following well established procedures, the acylation of **V-17** and subsequent allylation proceeded with nearly quantitative yields. No column chromatography was needed until

the isolation of **V-20**. One-pot Swern oxidation and Wittig olefination provided **V-21** in very high yield. The Sharpless epoxidation of **V-22** also proceeded smoothly (Scheme 5.8) as did oxidation to the aldehyde. However, the addition of isopropenyl magnesium bromide to **V-24** gave a mixture of two diastereomers. A simple model study suggested that a chelated addition should lead to the desired *R* configuration at the alcohol center. However, the reactions carried out in THF with magnesium bromide etherate added as a chelating reagent gave a separable 1.2:1mixture of **V-16** and its diastereomer iso-**V-16**.

Scheme 5.8. Preparation of **V-16**



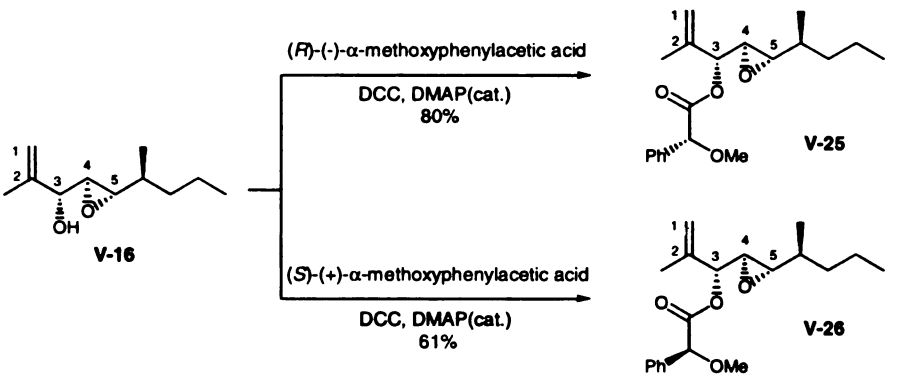
In pure benzene, the addition of isopropenyl magnesium bromide to aldehyde **V-24** gave a complex mixture. Crude ^{1}H NMR of the major products suggested that the epoxide ring was not tolerated under these reaction conditions.

Given the difficulty of controlling the stereoselectivity of this addition, we decided to solve this problem by correcting the "wrong" chiral center later during the esterification step. This of course would be possible by joining **V-16** and **V-14** by way of a Mitsunobu type reaction (*vide infra*).[9]

To determine the stereostructure of the two diastereomers **V-16** and iso-**V-16**, the (*S*)-(+)- and (*R*)-(-)-methoxyphenylacetates of **V-16** were prepared. By comparing the chemical shifts in the ^{1}H-NMR of these compounds, the stereostructure of the secondary alcohol center in compounds **V-25** and **V-26** was determined using methods developed by Mislow, Mosher, and Trost.[10] The ^{1}H NMR signals of the C1 protons of **V-26** (4.72

and 4.60 ppm) appear at higher fields than those of **V-25** (4.99 and 4.93 ppm) as a result of the shielding effect of the phenyl group. Similarly, the C4 proton of **V-25** (2.30 ppm) appears at higher field than that of **V-26** (2.64 ppm). Applying the empirical rules described by Trost,[10] it was clear that **V-16** has an *R* configuration at C3, the same configuration as the C19 center of amphidinolide A.

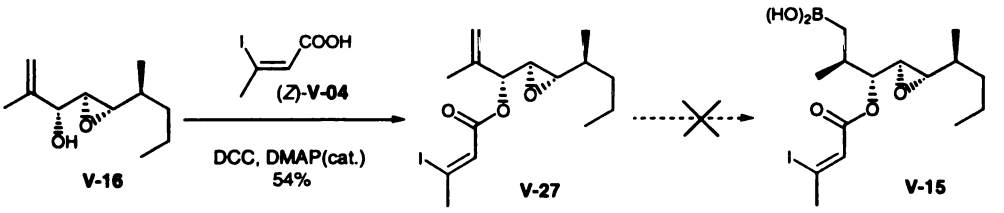
Scheme 5.9. The stereochemistry of **V-16**



5.3.1.c Connection of fragment **C** to **B** and **D**

Knowing the stereochemistry of this carbon center, we then subjected **V-16** to a DCC coupling with (*E*)-**V-14**. This reaction successfully provided compound **V-27** in 54% yield. Unfortunately, the stereoselective hydroboration of compound **V-27** to form **V-15** was problematic.[15] Thus despite all efforts this route was abandoned.

Scheme 5.10. DCC coupling of **V-16** and (*Z*)-**V-14**

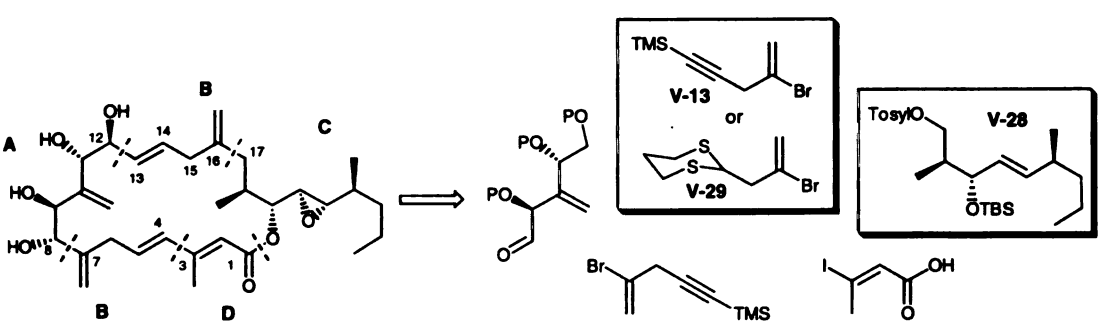


5.3.2. Nucleophilic replacement route

5.3.2.a Synthetic plan

After abandoning the Suzuki approach, we investigated the possibility of forming the C16-C17 bond by S_N2 displacement of an activated oxy group or halide at C17 by a vinyl metal species. The original plan was to metallate **V-13**, and react it with a primary halide or tosylate (**V-28**). However, the vinyl cuprate of **V-13** could not effect the S_N2 displacement of tosylate **V-28**. Attempts at generating and reacting the corresponding vinyl lithium also failed to provide any desired coupling. However, the failure of this reaction may have been due to difficulties in generating the active lithium species (i.e. allene formation). Thus it was decided that this approach should be further investigated, but with a different building block, compound **V-29**.

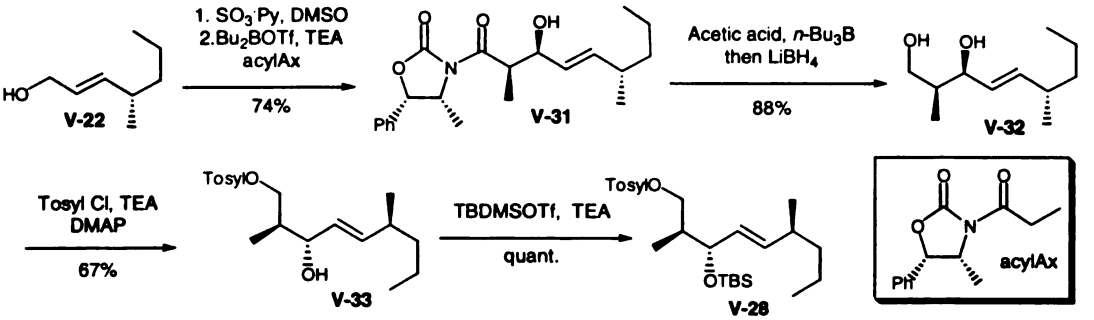
Scheme 5.11. Retrosynthetic analysis of nucleophilic replacement route



5.3.2.b Synthesis of compound **V-28**

The synthesis of compound **V-28** paralleled that of compound **V-16** (Scheme 5.12). Compound **V-22** was oxidized to aldehyde **V-30**, which was then subjected to an Evans aldol reaction,[11] providing compound **V-31** as the sole product in fair yield. After prechelating the hydroxyl group with tri-*n*-butylborane,[11] it was then reduced with $LiBH_4$ to give the diol **V-32** in good yield. Monotosylation was also successful, and after protection of the secondary alcohol, this modified **C** fragment (compound **V-28**) was ready to be coupled.

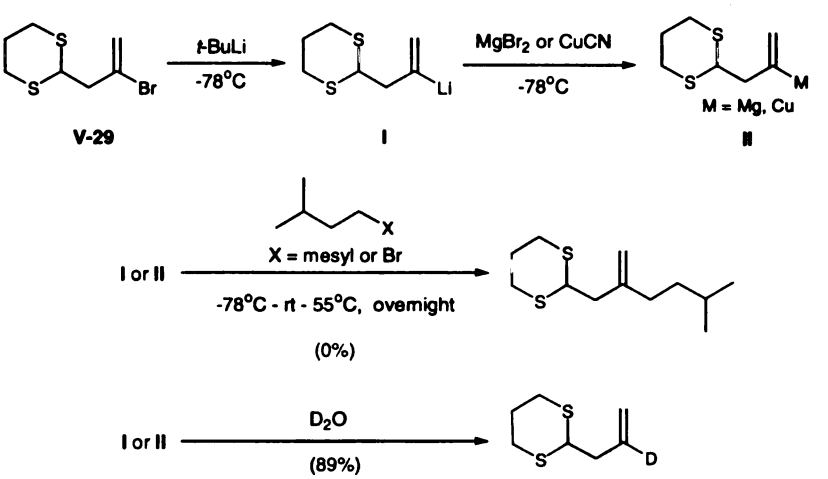
Scheme 5.12. The synthesis of **V-28**



5.3.2.c S_N2 coupling: model study

Dithiane **V-29** was subjected to the lithium-halogen exchange by *t*-BuLi (Scheme 5.13). The resultant vinyl lithium species was treated with mesylate and alkyl halides. Alternatively, it was pre-treated with $MgBr_2$ to form the corresponding vinyl Grignard prior to addition of the halide. Judging from the experimental observation of color change and deuterium quenching results, it is clear that the vinyl metallic species **I** and **II** were formed successfully (Scheme 5.13). However, no displacement of the bromide or mesylate occurred. After overnight stirring at rt or 50-60°C, the vinyl metallic species were protonated before workup.

Scheme 5.13. Model study of possible S_N2 coupling route

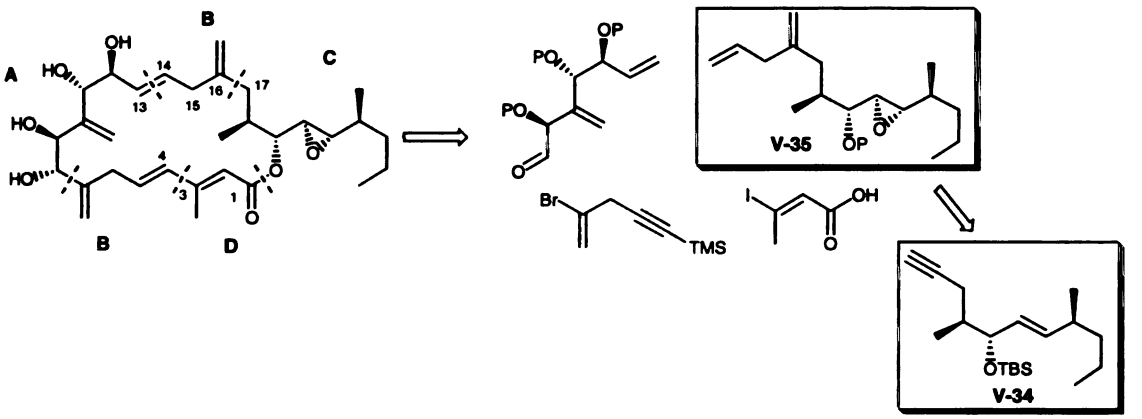


5.3.3. Ring-closing metathesis (RCM) route

5.3.3.a Synthetic plan

Given the unsuccessful attempts to form the C16-C17 bond by coupling fragment **B** and **C**, we sought alternative means to construct the C14-C17 skipped diene. Literature reports indicated that In(0) mediated allylation of alkynes proceeded in a Markovinikov fashion to give 1,4-dienes.[4] Thus if tosylate **V-28** could be displaced by lithium acetylide, reaction of the product (**V-34**) with allyl bromide and indium should provide a 1,4-diene. That diene, **V-35** (Scheme 5.14), could then partake in a ring closing metathesis (RCM) to form the macrocycle.[7]

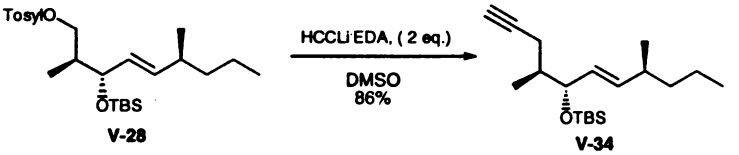
Scheme 5.14. Retrosynthetic analysis of RCM route



5.3.3.b Preparation of compound **V-35**

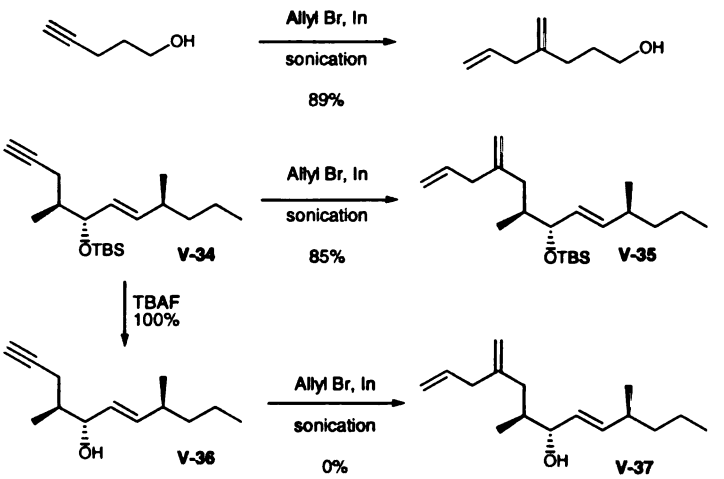
Thus we investigated the displacement of the tosylate on **V-28** by lithium acetylide. Although it is necessary to carry out the reaction in a glove bag, and crucial to keep the concentration of the lithium acetylide at 2 M,[12] displacement of tosylate **V-28** under these conditions consistently gave **V-34** in high yields (Scheme 5.15).

Scheme 5.15. Preparation of **V-34**



Next, we tested the indium-mediated allylation of alkynes (Scheme 5.16). The original paper showed regiochemical differences (anti-Markovinikov) for reaction of propargylic alcohols.[4] We needed to know if this was due to the hydroxyl group being proximal to the alkyne or if it was a problem for all free alcohols. A model study using 4-pentyn-1-ol consistently and cleanly provided the 1,4-diene in high yields. However, several trials failed when allyl alcohol **V-36** was subjected to these reaction conditions (Scheme 5.16). Each time a complex mixture formed, and the NMR and IR spectrum of the major product suggested loss of the hydroxyl group. Literature stated that a free hydroxyl group in the alkyne could speed up the reaction and slightly improve yields.[4] However, no previous studies involved allyl alcohols. These results suggest that allylic alcohols are not tolerated in this reaction. Indeed, when TBS ether **V-34** was employed, the reaction proceeded smoothly and provided the desired 1,4-diene **V-35** as the sole product in consistently high yields (Scheme 5.16).

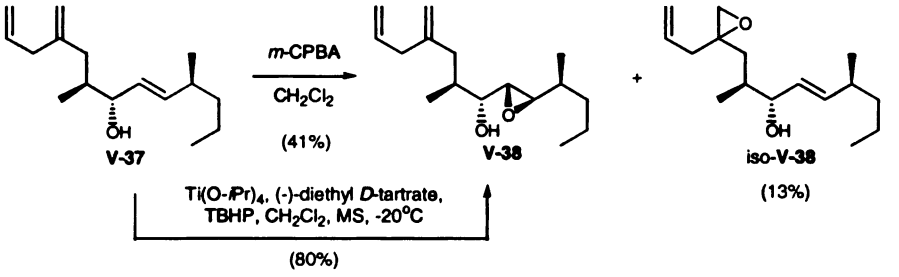
Scheme 5.16. Indium mediated allylation: Formation of the 1,4-diene



With compound **V-35** in hand, we turned to the problem of forming the epoxide. Since **V-37** is stereochemically mismatched for Sharpless epoxidation conditions,[13] we decided to first try the epoxidation with *m*-CPBA. The epoxidation of compound **V-37** in CH_2Cl_2 gave a mixture of two products (Scheme 5.17). Unfortunately, compound **V-38**

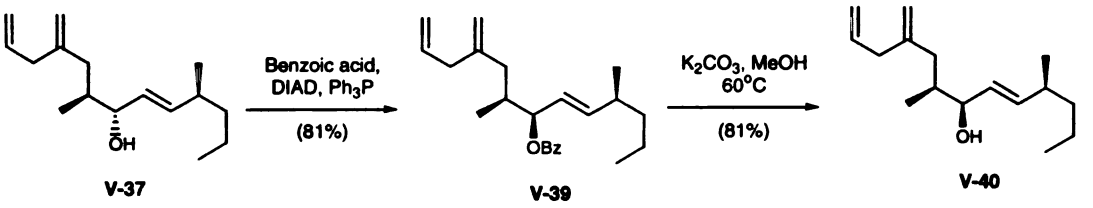
was found to possess the undesired epoxide stereochemistry. This assignment was made by comparing the *m*-CPBA product with the matched Sharpless epoxidation product. They were found to be identical.

Scheme 5.17. Epoxidation of **V-37**



At this point we decided to invert the stereostructure of the allyl alcohol so the correct epoxide can be installed by a matched Sharpless epoxidation. The inverted carbon center would later be "corrected" via the Mitsunobu coupling of the resulted compound with **V-14**.[9] The inversion of the secondary alcohol was realized by Mitsunobu esterification[9] followed by hydrolysis. However, Mitsunobu esterification of allyl alcohols has potential complications of regeoselectivity. It has been observed that acid attack of the activated allyl alchol in S_N2' fashion, can lead to the other regioisomer.[9]

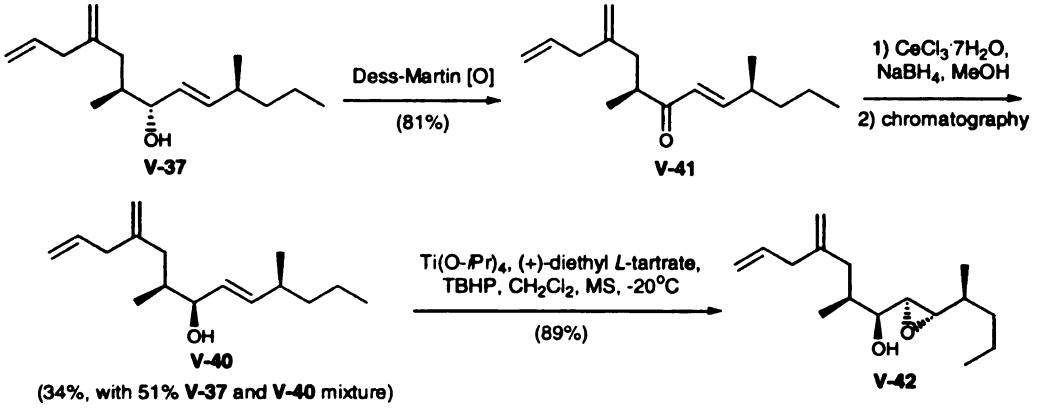
Scheme 5.18. Inversion of the secondary alcohol via Mitsunobu esterification



To prove that **V-40** was indeed the desired regioisomer, **V-37** was oxidized and the resultant ketone **V-41** was reduced to give a mixture of two diastereomers (Scheme 5.19). The new diastereomer was separated from **V-37** by careful silica gel chromatography and proved to be identical with **V-40**.

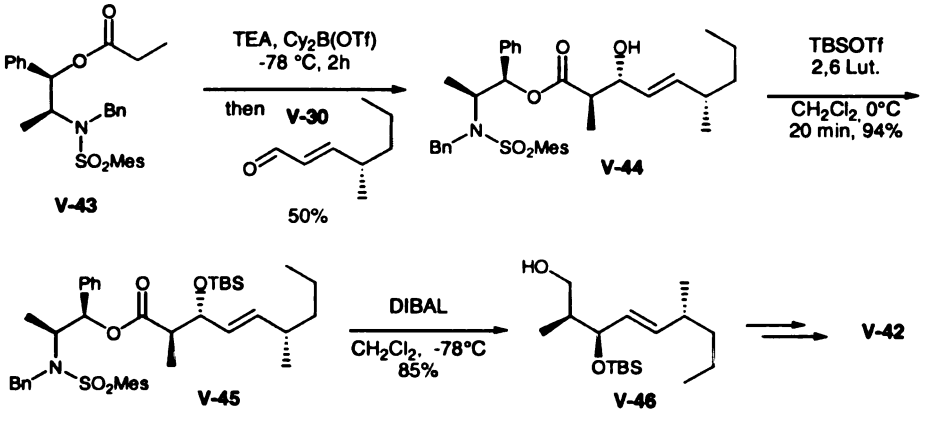
Sharpless epoxidation of compound **V-40** proceeded smoothly (Scheme 5.19). Only one isomer was observed by NMR spectra and TLC.

Scheme 5.19. Inversion of the secondary alcohol via oxidation-reduction



The preparation of **V-42**, although successful, was further improved by carrying out an anti-aldol reaction of aldehyde **V-30** with the Abiko-Masamune auxiliary (**V-43**) (Scheme 5.20).[14] Thus by directly making the anti-aldol product,[15] the initial Mitsunobu reaction could be bypassed.

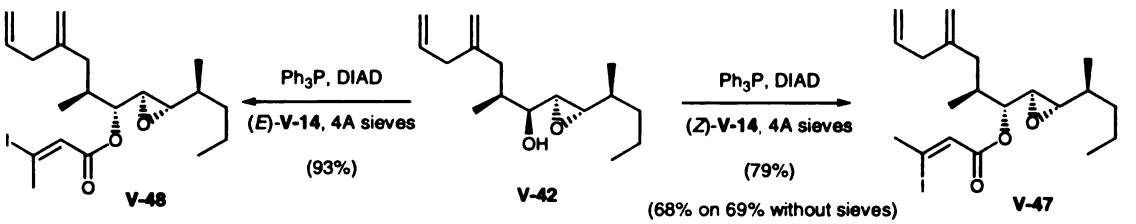
Scheme 5.20. The preparation of compound **V-42** via anti-aldol reaction



Compound **V-42** was subjected to Mitsunobu esterification with (*Z*)-**V-14**. This reaction proved somewhat inefficient. Many modified procedures were examined, but the reaction was never able to proceed to completion. This problem was believed to be due to the low nucleophilicity of the acid, which not only is conjugated, but also contains the electron withdrawing iodine. Under traditional conditions, the desired compound

V-47 was prepared in modest yields and less than 70% conversion. It was later found that adding molecular sieves to the reaction improved the yield and conversion significantly. Though the reasons remain unclear, carrying out the reaction with freshly activated 4Å molecular sieves provided **V-47** in 79% yield.

Scheme 5.21. The preparation of **BCD** fragment



Under the same reaction conditions, the other isomer (*E*)-**V-14** coupled with **V-42** smoothly, routinely gave **V-48**, the **BCD** fragment of amphidinolide A, in high yields.

To further solidify the regiochemical structure assignment of **V-48**, a sample was subjected to hydrolysis, and the resultant alcohol was then oxidized to the ketone. This ketone was found to be identical to that formed via oxidation of **V-42**.

5.4. Synthesis of fragment **A**

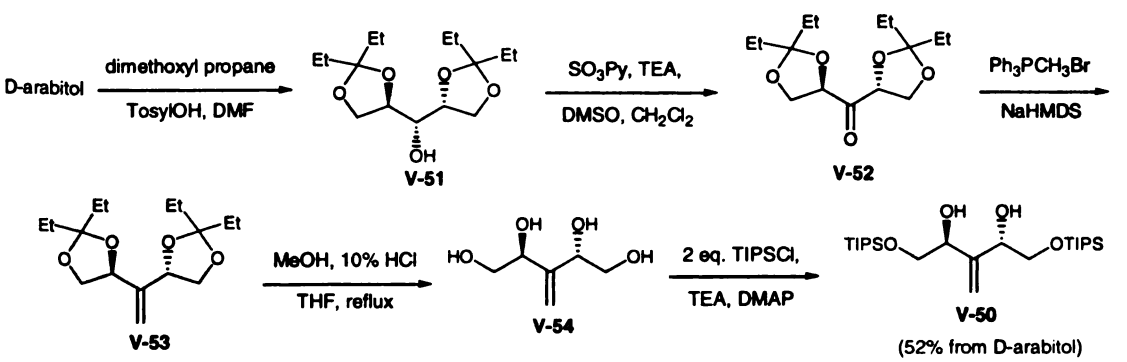
5.4.1. Introduction

With the **BCD** fragment in hand, we started to investigate an alternative route toward **A**, which had been previously synthesized from D-mannitol.[2a] Specifically, we sought to take advantage of D-arabitol, which possess the desired stereochemistry for the C9 and C11 alcohols along with the two primary hydroxyl groups which could be used for further manipulation.

5.4.2. Arabitol route

Transformation of D-arabitol to the diol **V-50** proceeded smoothly (Scheme 5.22). For the dipentylidenation of arabitol, DMF was found to be a better solvent than 1,2-dimethoxyl ethane. Although at rt the reaction was very slow, elevated temperature led to poor regeoselectivity, thus the optimum reaction temperature was determined to be 35-40 °C. For the subsequent Wittig olefination, the sequence in which reagents were added proved crucial. For example, when the freshly generated Wittig reagent was added to the crude ketone, heavy epimerization at the allylic carbon center occurred. Whereas when the reaction was carried out by adding the ketone into the Wittig reagent, no such epimerization was observed, and the alkene was formed as a single diastereomer. After deprotection of the dipentylidene the two primary hydroxyl groups were protected as TIPS ethers.

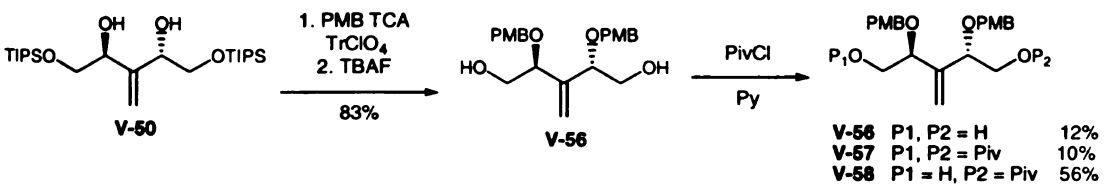
Scheme 5.22. The synthesis of **V-50** from D-arabitol



Next, the two secondary hydroxyl groups were to be protected as PMB ethers. This protective group was chosen because PMB groups are amenable to chelation controlled addition reactions (necessary to selectively form the C12-C13 and C7-C8 bonds of amphidinolide A). Furthermore, they can be removed with DDQ oxidation, a method mild enough to be tolerated by the variety of functional groups present in the final stages of our synthetic plan.

Surprisingly, I encountered great difficulties with traditional etherification methods. With both KH and NaHMDS as the base, the reactions were very sluggish and slow decomposition of the alcohol was observed. The desired compound was isolated in only low yields. Giving these difficulties, I examined the protection reaction under acidic conditions. The protection of hydroxyl groups with the PMB trichloroacetimidate (PMB TCA) reagent under acid catalyst has been widely used,[16a] with the acid usually being HOTf, HCl, TsOH, or TMSOTf. However, only moderate success was achieved with TMSOTf or toluene sulfonic acid as the catalyst. Eventually, I found that yields could be much-improved with trityl perchloride as the catalyst (Scheme 5.23).[16b]

Scheme 5.23. The synthesis of **V-58**



Compound **V-55** was deprotected to give compound **V-56**. The subsequent monoprotection with PivCl was also troublesome. With 1.1 eq. of PivCl, a mixture of the desired monoprotected **V-58**, the diprotected **V-57**, as well as the starting material **V-56** was formed each time. However, compounds **V-57** and **V-56** could be easily separated from **V-58** and recycled, giving a good overall yield of **V-58**. Thus despite this selectivity problem, the synthesis of compound **V-58** was more efficient compared to our

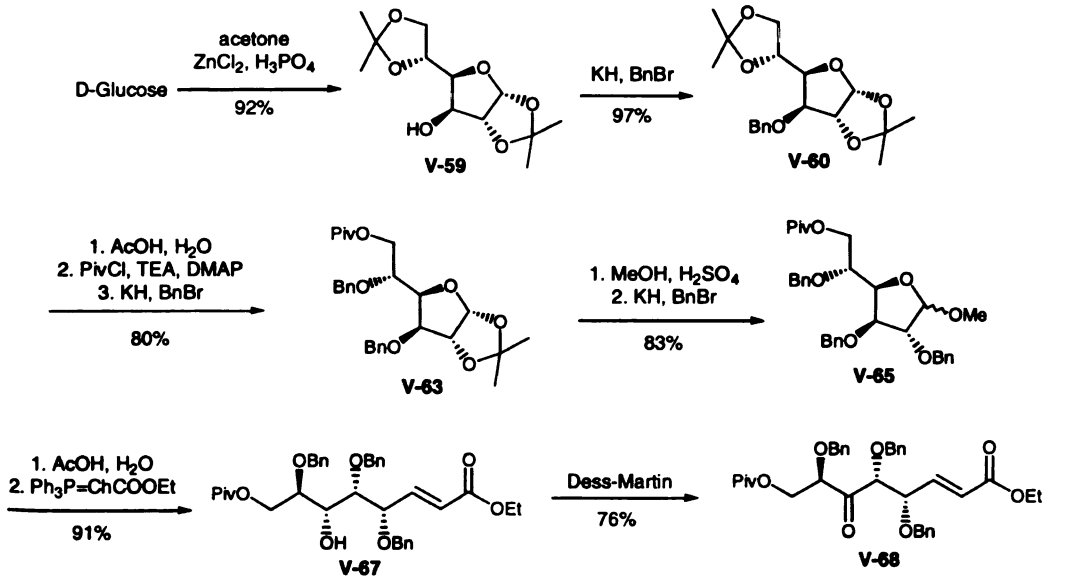
previous synthesis of a similar intermidiate.[3a] Thus this synthesis was adopted for our final route to amphidinolide A.[17]

5.4.3. Synthetic investigations towards fragment **AB** from D-Glucose

Having established a better route toward subtarget **A**, we set out to look into a third route starting from D-glucose. The stereostructure of the C2, C3, and C5 carbon centers in D-glucose coincide with those of C9, C11, and C12 in amphidinolide A. The C4 hydroxyl group should well serve the purpose of installing the alkene, while the C6 hydroxyl group would be a handle for joining other fragments. Indeed, in Pattenden's synthetic approach, he started with D-glucose and prepared the properly functionalized C7-C13 ene-tetraol unit **V-11** (Scheme 5.4) in 13 linear steps with an overall yield of 2%.

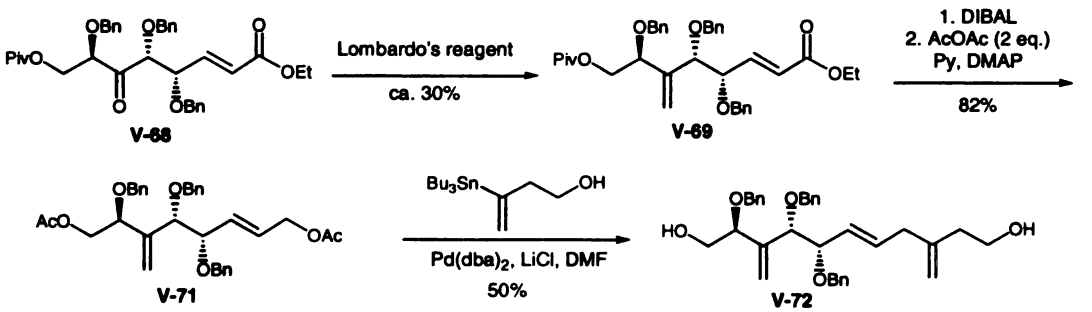
A major difference in our synthetic plan from Pattenden's was that we would utilize the aldehyde functionality in glucose to install the C13-C14 alkene, via a Wittig olefination. This step would simultaneously install the ester group at C15, which could be transformed into an activated allylic alcohol and coupled with a vinyl species to form the crucial 1,4-diene moiety.

Scheme 5.24. Synthetic investigations towards fragment **AB** from D-Glucose



Thus starting from D-glucose, **V-68** was easily obtained via a series of highly reliable and routine transformations, with no chromatographic separation needed except for compounds **V-63**, **V-67**, and **V-68**. The only challenging step was the Wittig reaction at C10. With $Ph_3P{=}CH_2$, no product was isolated, presumably due to the basicity of this reagent. Even with the milder Lombardo's reagent,[18,3d] decomposition was still a serious problem. However, this reagent did provide the desired product in a modest 30-50% yield. Compound **V-71** was then prepared and coupled with the vinyl stannane under standard conditions.[19]

Scheme 5.25. Synthetic investigations towards fragment **AB** from D-Glucose

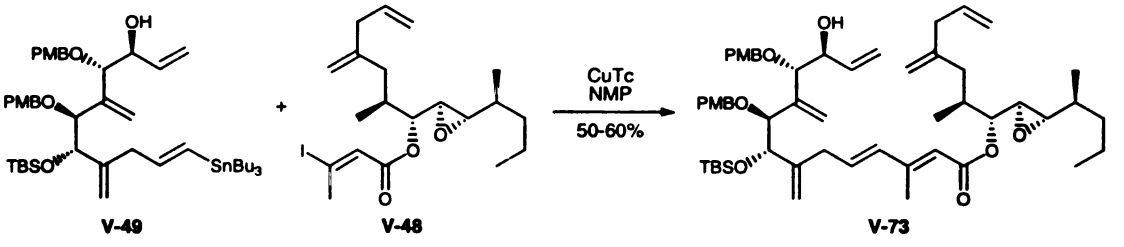


In the end, though, this route was not as successful when we tried to use PMB protective groups instead of benzyl groups. Thus it was not adopted to our synthesis of amphidinolide A.

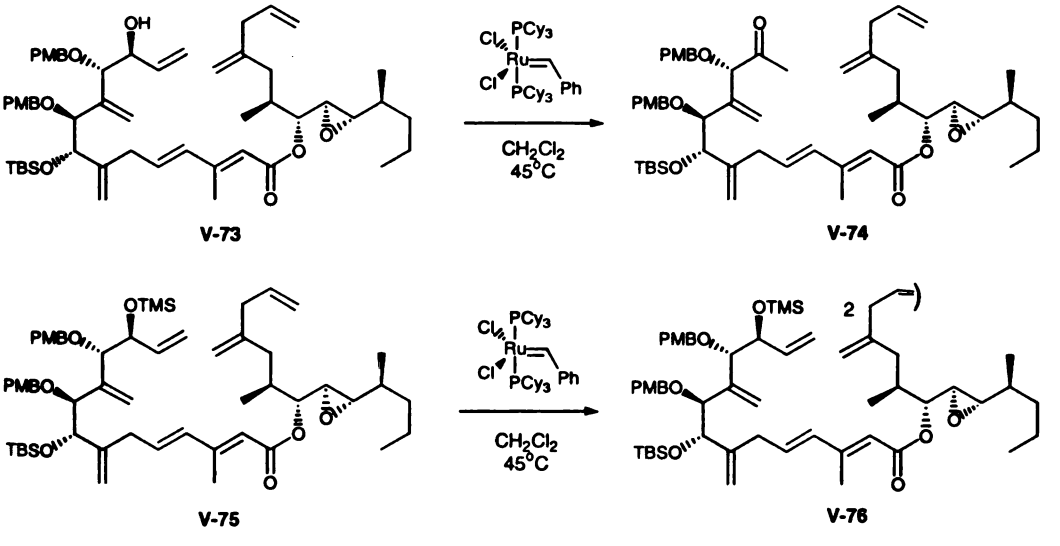
5.5. Coupling of fragment **AB** with fragment **BCD** and subsequent ring closing efforts

With the synthesis of all the subunits in place, we were ready to explore their union and final elaboration of amphidinolide A. Compounds **V-48** and **V-49** were joined via Cu catalyzed cross-coupling reaction (Scheme 5.26).[20] The resultant compound **V-73** was then subjected to Grubbs' RCM conditions (Scheme 5.27).[7] Unfortunately, the ring closing reaction was complicated by the truncation of the allylic olefin.[21] Although this process can be prevented by protecting the hydroxyl group, reaction of the TMS ether led to another side reaction, the homo-metathesis of compound **V-75** at the C16 double bond (Scheme 5.27).

Scheme 5.26. Preparation of **V-73**



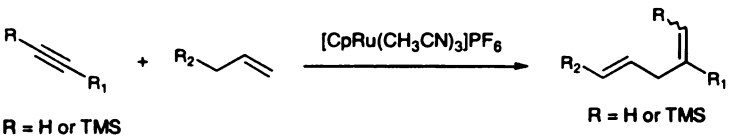
Scheme 5.27. Attempted RCM of **V-73** and **V-75**



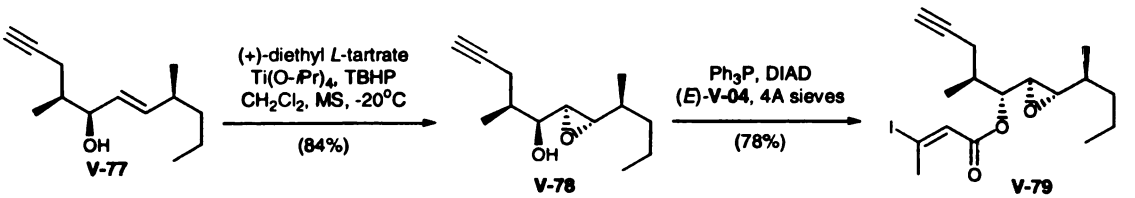
Due to the difficulties encountered with compound **V-73**, we briefly investigated the Ru mediated alder-ene reaction, developed by Trost,[5] to close the ring (Scheme 5.28).

Thus two new building blocks **V-79** and **V-82** were prepared (Scheme 5.29 and 5.30). From these compounds, the corresponding compounds **V-83** and **V-84** were prepared (Scheme 5.31) and subjected to Trost conditions (Scheme 5.32). However, this effort was not fruitful.

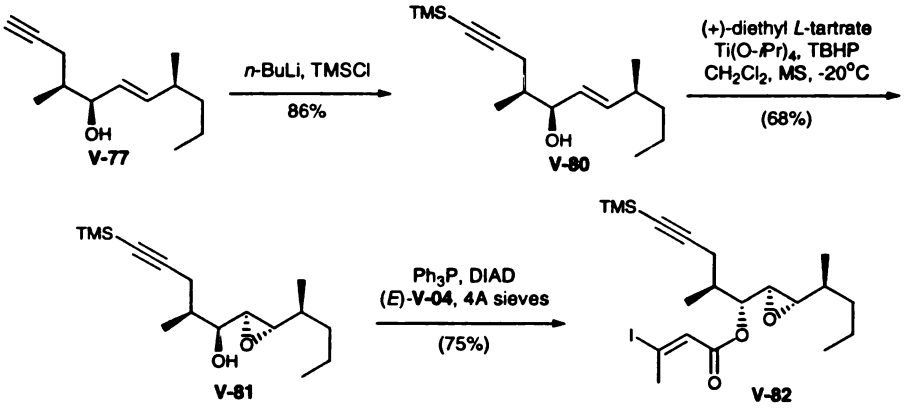
Scheme 5.28. Trost's alder-ene reaction



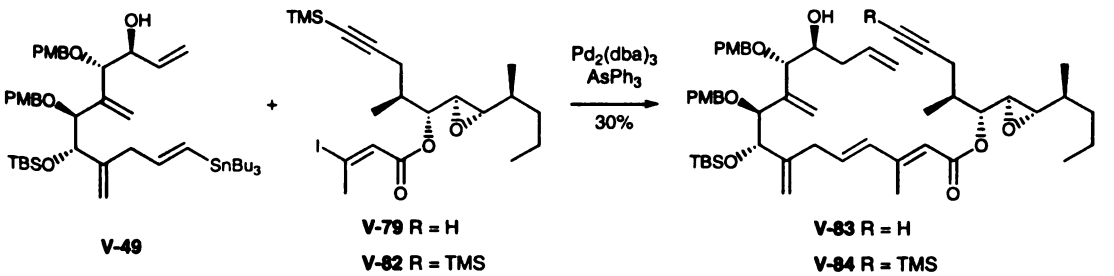
Scheme 5.29. Preparation of **V-79**



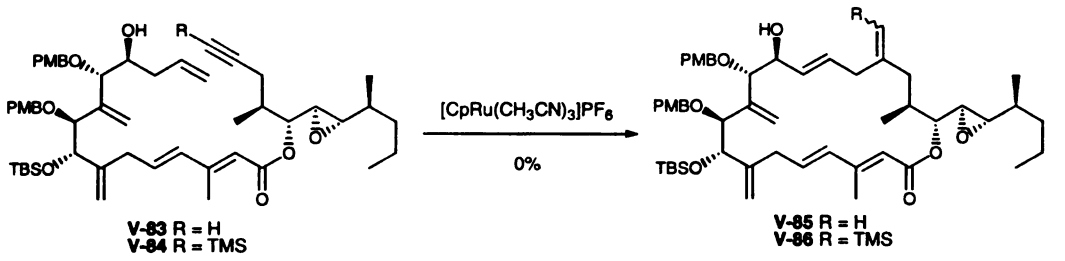
Scheme 5.30. Preparation of **V-82**



Scheme 5.31. Preparation of **V-83** and **V-84**



Scheme 5.32. Ring closing attempts using Trost's alder-ene reaction

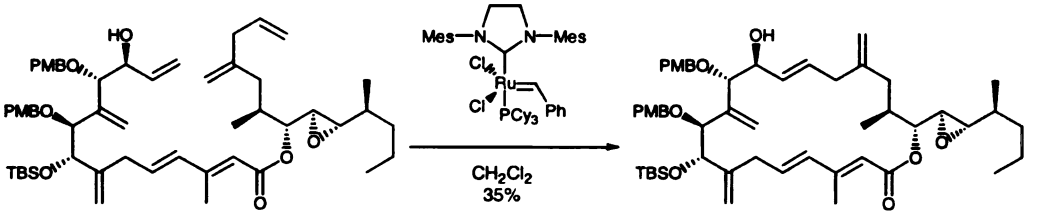


V-83 R = H
V-84 R = TMS

V-85 R = H
V-86 R = TMS

Given the failure of the alder-ene reaction, we decided to re-examine the RCM approach. Literature reports suggested that the second generation Grubbs' catalyst was not prone to the truncation reaction.[7c] Indeed, when we used the second generation catalyst developed by Grubbs (Scheme 5.33),[7] the desired ring-closing product was obtained in 88% yield. After a three-step deprotection, the material with the proposed structure of amphidinolide A (**V-01**) was obtained (Scheme 5.34).

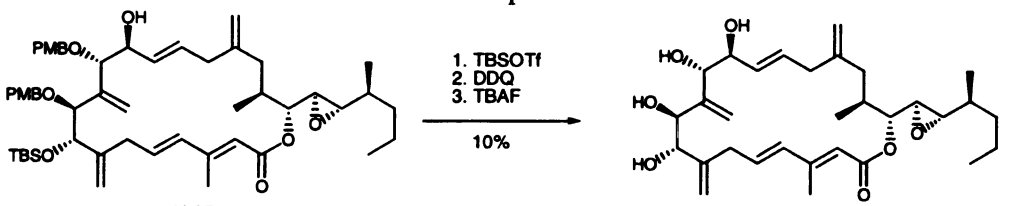
Scheme 5.33. Ring closing metathesis of **V-73**



V-73

V-87

Scheme 5.34. Preparation of **V-01**



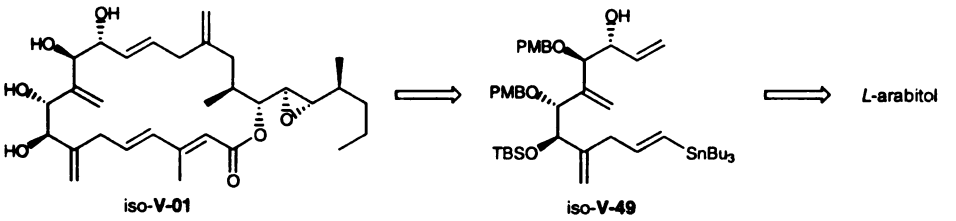
V-87

V-01

However, the ^{1}H and ^{13}C NMR spectra of **V-01** did not match those of the natural compound. Guided by our early concerns about the potential error in the stereochemical relationship between the hydrophilic and lipophilic halves, we are currently undertaking the synthesis of the hydrophilic half from *L*-arabitol following the same route.[17] This would provide us iso-**V-49**, the enantiomer of compound **V-49**, which will be coupled

with compound **V-48** to eventually form iso-**V-01**. Hopefully we will then have prepared the natural material or its enantiomer. Thus the total synthesis and structure of amphidinolide A will be secured.

Scheme 5.35. Synthesis of iso-**V-01**



EXPERIMENTAL PROCEDURES

Materials and Methods

All air or moisture sensitive reactions were carried out in oven- or flame-dried glassware under nitrogen atmosphere, unless otherwise noted. All solvents were reagent grade. Anhydrous diethyl ether and tetrahydrofuran (THF) were freshly distilled under nitrogen from sodium benzophenoneketyl. Dichloromethane was freshly distilled from calcium hydride under nitrogen. Triethylamine and diisopropylethylamine (Hunnig base) were distilled under nitrogen from calcium hydride and stored over freshly activated 4 Å molecular sieves. *N,N'*-Dimethylformamide (DMF), dimethylsulfoxide (DMSO), and acetonitrile were distilled under nitrogen from anhydrous calcium sulfate. Anhydrous pyridine was purchased from Aldrich and stored over freshly activated 4 Å molecular sieves. *n*-Butyllithium was purchased from Aldrich as a hexane solution. Except as otherwise indicated, all reactions were magnetically stirred and monitored by thin layer chromatography with Whatman 0.25-mm precoated silica gel plates. Flash chromatography was performed with silica gel 60 Å (particle size 230-400 Mesh ASTM) supplied by Whatman Inc. High performance liquid chromatography (HPLC) was performed with Ranin component analytical/semiprep system. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. Melting points were determined on a Thomas-Hoover apparatus, uncorrected. Infrared spectra were recorded on a Nicolet IR/42 spectrometer. Proton and carbon NMR spectra were recorded on Varian Gemini-300 or VXR 500 spectrometer. Chemical shifts for ^{1}H NMR and ^{13}C NMR are reported in parts per million (ppm) relative to $CDCl_3$ (δ = 7.24 ppm for ^{1}H NMR or δ = 77.0 ppm for ^{13}C NMR). Optical rotations were measured with a Perkin-Elmer Model 341 polarimeter. High resolution mass spectra (HRMS) data were

obtained: (a) at the Michigan State University Mass Spectrometry Facility; (b) at the Mass Spectrometry Laboratory in Department of Chemistry & Biochemistry at the University of South Carolina. Combustion analysis was performed by Robertson Microlit Laboratories, Inc., Madison, NJ 07940. Single-crystal X-ray structure determinations were performed at the Michigan State University with a Siemens CCD diffractometer.

Preparation of model compounds II-06, II-17, II-18 and II-19. General procedure: A solution of alcohol **II-14** (210 mg, 1.0 mmol) and Bu_4NI (ca. 50 mg) in THF (5 mL) was cooled to 0°C. NaH (60%, suspended in mineral oil, 48 mg, 1.2 mmol) was added in portions while the flask was purged with nitrogen from a side arm. The suspension was stirred under nitrogen at 0 °C for 15 min. To the resulting cloudy solution was added dropwise a solution of (*R*)-**II-11** (430 mg, 1.0 mmol) in 1 mL THF. After an additional 2 h during which the reaction temperature was allowed to warm to room temperature, the reaction was quenched with saturated aqueous NH_4Cl (2 mL), diluted with ether (5 mL), washed with water and brine. The organic phase was dried over $MgSO_4$ and concentrated. Flash chromatography (light petroleum ether/ether, 95:5) furnished **II-06** (440 mg, 84% yield) as a colorless oil: $[\alpha]_D^{20}$ +17.1° (c 1.08, THF); IR (neat) 2959 (m), 1595 (s), 1456 (s), 1379 (s), 1215 (s), 1070 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.22 (m, 5 H), 4.30 (dd, *J* = 14.0, 6.9 Hz, 1 H), 4.15 (d, *J* = 6.9 Hz, 1 H), 3.71 (dd, *J* = 8.5, 5.2 Hz, 1 H), 3.64-3.50 (m, 2 H), 1.92-1.74 (m, 1 H), 1.76-1.60 (m, 1 H), 1.60-1.40 (m, 6 H), 1.40-1.20 (m, 12 H), 1.35 (s, 3 H), 1.31 (s, 3 H), 1.00-0.80 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 128.2, 128.1, 127.8, 109.8, 83.6, 78.9, 77.2, 66.0, 29.3, 28.6, 27.6, 26.4, 25.5, 13.7, 12.7, 9.4; HRMS (EI) *m/z* 525.2383 [$(M-CH_3)^+$; calcd for $C_{26}H_{45}O_3Sn$, 525.2390]. Anal. Calcd for $C_{27}H_{48}O_3Sn$: C, 59.97, H, 8.95. Found: C, 60.28, H, 8.92.

Applying the procedure above to 60 mg (0.28 mol) of **II-15** and 60 mg (0.14 mol) (*R*)-**II-11** furnished 45 mg **II-17** as colorless oil in 60% yield: $[\alpha]_D^{20}$ -80.7° (c 3.30, THF); IR (neat) 2957 (m), 1454 (s), 1379 (s), 1215 (s), 1076 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21-7.41 (m, 5 H), 4.37 (d, *J* = 6.6 Hz, 1 H), 4.04-4.20 (m, 3 H), 3.72 (dd, *J* = 7.2, 3.6 Hz, 1 H), 1.94-2.10 (m, 1 H), 1.78-1.64 (m, 1 H), 1.44 (s, 3 H), 1.31 (s, 3 H), 1.54-1.38 (m, 6 H), 1.36-1.20 (m, 12 H), 1.00-0.80 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.7, 128.2, 127.9, 127.9, 109.2, 79.9, 79.3, 74.1, 67.1, 29.1, 27.5, 26.7, 25.4, 25.1, 13.7, 11.7, 9.2; HRMS (EI) *m/z* 525.1942 $[(M-CH_3)^+$; calcd for $C_{26}H_{45}O_3Sn$, 525.2390].

Applying the procedure above to 350 mg (1.7 mol) of **II-14** and 600 mg (1.4 mol) (*S*)-**II-11** furnished 600 mg **II-18** as colorless oil in 79% yield: $[\alpha]_D^{20}$ +75.2° (c 1.22, THF); IR (neat) 2957 (m), 1599 (s), 1458 (s), 1377 (s), 1257 (s), 1174 (s), 1037 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.20 (m, 5 H), 4.39 (d, *J* = 6.6 Hz, 1 H), 4.30 (dd, *J* = 13.2, 6.6 Hz, 1 H), 3.76-3.65 (m, 2 H), 3.60 (dd, *J* = 8.5, 6.8 Hz, 1 H), 2.06-1.88 (m, 1 H), 1.84-1.66 (m, 1 H), 1.34 (s, 3 H), 1.27 (s, 3 H), 1.52-1.16 (m, 15 H), 0.95 (t, *J* = 7.2 Hz, 3 H), 0.85-0.65 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 128.2, 128.0, 127.9, 109.5, 81.3, 78.7, 75.4, 65.7, 29.1, 27.5, 26.4, 26.1, 25.6, 13.7, 11.8, 9.2; HRMS (EI) *m/z* 541.2712 $[(M+H)^+$; calcd for $C_{27}H_{49}O_3Sn$, 541.2703].

Applying the procedure above to 160 mg (0.77 mol) of **II-15** and 300 mg (0.70 mol) (*S*)-**II-11** furnished 287 mg **II-19** as colorless oil in 76% yield: $[\alpha]_D^{20}$ -22.4° (c 3.70, THF); IR (neat) 2932 (m), 1454 (s), 1368 (s), 1253 (s), 1215 (s), 1064 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.22 (m, 5 H), 4.20 (m, 4 H), 3.78 (t, *J* = 6.0 Hz, 1 H), 1.76-1.62 (m, 2 H), 1.60-1.15 (m, 24 H), 0.96-0.76 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2, 128.1, 127.8, 127.7, 109.3, 82.8, 79.5, 77.3, 66.7, 29.1, 27.5, 26.4, 26.1, 25.6, 13.7, 11.8, 9.2; HRMS (EI) *m/z* 525.2394 $[(M-CH_3)^+$; calcd for $C_{26}H_{45}O_3Sn$, 525.2390].

Applying the procedure above to 120 mg (0.8 mmol) of **II-09** and 300 mg (0.70 mmol) (*R*)-**II-11** furnished 265 mg **II-13** as colorless oil in 80% yield: $[\alpha]_D^{20}$ +30.4° (c 2.30, toluene); IR (neat) 2959 (s), 1456 (s), 1377 (s), 1070 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.94-4.06 (m, 1 H), 3.74-3.95 (m, 3 H), 3.41 (p, *J* = 6.3 Hz, 1 H), 1.60-1.90 (m, 2 H), 1.15-1.56 (m, 18 H), 1.11 (d, *J* = 6.0 Hz, 3 H), 0.79-0.95 (m, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.9, 79.2, 74.5, 74.1, 67.3, 29.2, 27.5, 26.7, 26.4, 25.5, 16.5, 13.7, 11.8, 9.2; HRMS (EI) *m/z* 421.1767 [$(M-C_4H_9)^+$; calcd. for $C_{18}H_{37}O_3Sn$, 421.1765].

Applying the procedure above to 330 mg (2.26 mmol) of **II-10** and 750 mg (1.76 mmol) (*S*)-**II-11** furnished 650 mg **II-12** as colorless oil in 78% yield: $[\alpha]_D^{20}$ -13.0° (c 2.2, toluene); IR (neat) 2957 (s), 1458 (s), 1377 (s), 1072 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.05 (dd, *J* = 6.6, 12.9 Hz, 1 H), 3.84-3.95 (m, 2 H), 3.67 (dd, *J* = 7.8, 8.4 Hz, 1 H), 3.41 (p, *J* = 6.0 Hz, 1 H), 1.7-1.9 (m, 2 H), 1.2-1.6 (m, 18 H), 1.05 (d, *J* = 6.0 Hz, 3 H), 0.79-1.00 (m, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 109.1, 78.3, 77.7, 76.0, 65.4, 29.3, 28.3, 27.5, 26.5, 25.2, 15.4, 13.7, 12.3, 9.1; HRMS (EI) *m/z* 421.1770 [$(M-C_4H_9)^+$; calcd. for $C_{18}H_{37}O_3Sn$, 421.1765].

[1,2]-Wittig rearrangement reaction of the model compounds II-06, II-17, II-18 and II-19. General procedure: Compound **II-06** (60 mg, 0.11 mmol) was dissolved in 4 mL solvent (10 mL when using LiCl saturated THF) and the solution was cooled to -76 °C. *n*-BuLi (1.6 M in hexanes, 0.36 mL, 0.57 mmol) was added dropwise via a syringe. After an additional 45 min the reaction was quenched with saturated aqueous NH_4Cl (2 mL), diluted with ether (5 mL), washed with water and brine. The organic phase was dried over $MgSO_4$ and concentrated. The crude product was dissolved in 1 mL dry pyridine and the solution was cooled to 0 °C. 3,5-Dinitrobenzoyl chloride (75 mg, 0.3 mmol) was then added and the solution was stirred overnight at ambient temperature. The dark red solution was then diluted with 5 mL ether and washed with 0.1 N HCl, water and brine. The organic phase was then dried over $MgSO_4$ and concentrated. This

crude product mixture was then analyzed by HPLC to measure the ratio of the four diastereomers (hexanes/ether, 90:10, 1 mL/min).

Preparation of alcohols II-07, II-08, II-20, and II-21. A diastereomeric mixture of **II-06**, **II-17**, **II-18**, and **II-19** (0.9 g, 1.7 mmol) was dissolved in 50 mL THF and the solution was cooled to -76°C. *n*-BuLi (2.5 M in hexanes, 1.4 mL, 3.4 mmol) was added dropwise via a syringe. After an additional 45 min the reaction was quenched with saturated aqueous NH_4Cl (3 mL), diluted with ether (20 mL), washed with water and brine. The organic phase was dried over $MgSO_4$, concentrated. Column chromatography (hexanes/ether, 85:15) furnished **II-07**, **II-08**, **II-20**, and **II-21** (in equal amounts, 95% total yield) as colorless oils.

II-07: R_f 0.24 (petroleum ether/ether, 5:1); $[\alpha]_D^{20}$ -29.7° (c 2.6, $CHCl_3$); IR (neat) 3460 (br), 2984 (m), 2934(s), 1454(s), 1369(s), 1221(s), 1062(s) $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.19 (m, 5 H), 4.59 (ddd, *J* = 11.5, 8.0, 5.5 Hz, 1 H), 4.04 (dd, *J* = 8.0, 6.0 Hz, 1 H), 3.90 (ddd, *J* = 12.1, 8.0, 4.4 Hz, 1 H), 3.51 (m, 1 H), 2.75 (dd, *J* = 5.5, 4.1 Hz, 1 H), 2.09 (s br, 1 H), 1.60-1.20 (m, 2 H), 1.34 (s, 3 H), 1.30 (s, 3 H), 0.94 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9, 130.4, 128.1, 127.1, 109.1, 77.5, 75.0, 67.6, 52.3, 28.0, 26.5, 25.6, 10.2; LRMS (EI) *m/z* 235.2 $[(M-CH_3)^+$; calcd for $C_{14}H_{19}O_3$, 235.1334].

II-08: R_f 0.14 (petroleum ether/ether, 5:1); $[\alpha]_D^{20}$ +15.1° (c 0.63, $CHCl_3$); IR (neat) 3478 (br), 2988 (m), 2937 (s), 1455 (s), 1381 (s), 1203 (s), 1066 (s) $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.18 (m, 5 H), 4.66 (ddd, *J* = 8.5, 6.1, 4.4 Hz, 1 H), 4.03 (ddd, *J* = 9.1, 9.1, 2.8 Hz, 1 H), 3.98 (dd, *J* = 8.0, 6.0 Hz, 1 H), 3.54 (dd, *J* = 8.5, 8.0 Hz, 1 H), 2.78 (dd, *J* = 9.6, 4.5 Hz, 1 H), 2.30 (s br, 1 H), 1.35 (s, 3 H), 1.30 (s, 3 H), 1.32-1.12 (m, 2 H), 0.89 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 129.5, 128.2, 126.9, 108.6, 76.2, 73.8, 67.1, 53.0, 28.3, 26.3, 25.5, 9.6.

II-20: R_f 0.37 (petroleum ether/ether, 5:1); $[\alpha]_D^{20}$ -5.3° (c 0.49, $CHCl_3$); IR (neat) 3524 (br), 2986 (m), 2936 (s), 1454 (s), 1371 (s), 1217 (s), 1061 (s) $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.01 (m, 5 H), 4.50 (ddd, *J* = 9.9, 7.4, 5.8 Hz, 1 H), 4.21 (s br, 1 H), 4.03 (ddd, *J* = 9.1, 8.3, 3.3 Hz, 1 H), 3.67 (dd, *J* = 8.5, 5.8 Hz, 1 H), 3.49 (dd, *J* = 8.5, 7.4 Hz, 1 H), 2.64 (t, *J* = 9.9 Hz, 1 H), 1.48 (s, 3 H), 1.40 (s, 3 H), 1.32-1.02 (m, 2 H), 0.87 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 128.8, 128.2, 127.2, 110.4, 80.6, 76.6, 69.3, 55.4, 27.5, 26.7, 25.8, 9.3.

II-21: R_f 0.30 (petroleum ether/ether, 5:1); $[\alpha]_D^{20}$ +48.7° (c 0.29, $CHCl_3$); IR (neat) 3486 (br), 2986 (m), 2936 (s), 1496 (s), 1369 (s), 1217 (s), 1064 (s) $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.20 (m, 5 H), 4.69 (ddd, *J* = 9.6, 6.3, 6.3 Hz, 1 H), 4.02 (ddd, *J* = 8.2, 4.7, 3.0 Hz, 1 H), 3.81 (dd, *J* = 8.5, 6.0 Hz, 1 H), 3.47 (dd, *J* = 8.2, 6.9 Hz, 1 H), 2.73 (dd, *J* = 9.6, 3.0 Hz, 1 H), 1.95 (s br, 1 H), 1.46 (s, 3 H), 1.40 (s, 3 H), 1.46-1.14 (m, 2 H), 0.93 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 129.4, 128.4, 127.1, 129.5, 76.3, 73.2, 68.8, 54.4, 27.7, 27.0, 25.7, 10.5; LRMS (EI) *m/z* 235.2 $[(M\text{-}CH_3)^+$; calcd for $C_{14}H_{19}O_3$, 235.1334]; Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.95; H, 8.86. Found: C, 71.86; H, 8.85.

3,5-Dinitrobenzoyl esters of alcohol II-07, II-08, II-20 and II-21. General procedure: Alcohol **II-07** (78 mg, 0.3 mmol) was dissolved in 2 mL dry pyridine and the solution was cooled to 0°C. 3,5-Dinitrobenzoyl chloride (92 mg, 0.4 mmol) was then added and the solution was stirred overnight before being diluted with 5 mL ether and washed with 0.1 N HCl, water and brine. The organic phase was then dried over $MgSO_4$ and concentrated. Column chromatography (petroleum ether/ether, 90:10) furnished 115 mg (83%) the 3,5-dinitrobenzoic ester of alcohol **II-07** (**II-07-DNB**) as pale yellow crystals: mp 126-127 °C; $[\alpha]_D^{20}$ –14.2° (c 0.35, $CHCl_3$); IR ($CHCl_3$) 2980 (m), 1732 (s), 1547 (s), 1344 (s), 1275 (s) $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$) δ 9.17 (m, 1 H), 8.97 (m, 2 H), 7.46-7.16 (m, 5 H), 5.61 (ddd, *J* = 12.3, 7.8, 6.3 Hz, 1 H), 4.48 (ddd, *J* = 7.8, 6.0, 5.4

Hz, 1 H), 4.05 (dd, J = 7.8, 6.0 Hz, 1 H), 3.48 (t, J = 7.8 Hz, 1 H), 3.10 (t, J = 5.4 Hz, 1 H), 1.96-1.80 (m, 1 H), 1.80-1.66 (m, 1 H), 1.28 (s, 3 H), 1.22 (s, 3 H), 0.98 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2, 148.5, 136.4, 134.1, 130.0, 129.2, 128.3, 127.5, 122.2, 109.2, 79.1, 75.5, 67.5, 51.0, 26.3, 25.5 (2 C), 9.7; HRMS (EI) *m/z* 445.1603 [$(M+H)^+$; calcd. for $C_{22}H_{25}N_2O_8$, 445.1610].

Applying the procedure above to 48 mg (0.19 mmol) of **II-08** furnished 76 mg **II-08-DNB** in 88% yield as pale yellow crystals. mp 128-129 °C; IR ($CHCl_3$) 2980 (m), 1730 (s), 1547 (s), 1344 (s), 1275 (s) $cm^{-1;}$ ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.25 (t, J = 2.1 Hz, 1 H), 9.19 (t, J = 2.1 Hz, 2 H), 7.31 (s, 5 H), 5.68 (ddd, J = 9.6, 5.4, 3.6 Hz, 1 H), 4.44 (ddd, J = 8.4, 6.3, 4.2 Hz, 1 H), 3.90 (dd, J = 7.8, 6.0 Hz, 1 H), 3.36 (t, J = 7.8 Hz, 1 H), 3.13 (dd, J = 9.6, 4.5 Hz, 1 H), 1.78-1.60 (m, 1 H), 1.60-1.46 (m, 1 H), 1.19 (s, 3 H), 1.18 (s, 3 H), 0.84 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 148.8, 136.5, 134.1, 130.0, 129.3, 128.4, 127.6, 122.5, 109.0, 78.9, 74.7, 67.2, 50.6, 26.2, 25.5 (2 C), 9.1; HRMS (EI) *m/z* 444.1501 [$(M)^+$; calcd. for $C_{22}H_{24}N_2O_8$, 444.1532].

Applying the procedure above to 94 mg (0.37 mmol) of **II-20** furnished 137 mg **II-20-DNB** in 82% yield as pale yellow crystals; mp 126-129 °C; IR ($CHCl_3$) 3103 (m), 1732 (s), 1549 (s), 1346 (s), 1275 (s) $cm^{-1;}$ ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.24-9.18 (m, 3 H), 7.37-7.19 (m, 5 H), 5.64 (ddd, J = 12.4, 8.8, 3.6 Hz, 1 H), 4.49 (ddd, J = 9.3, 8.2, 5.8 Hz, 1 H), 3.57 (dd, J = 8.5, 5.8 Hz, 1 H), 3.34 (t, J = 8.2 Hz, 1 H), 3.11 (t, J = 8.8 Hz, 1 H), 1.72-1.49 (m, 2 H), 1.26 (s, 3 H), 1.09 (s, 3 H), 0.88 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.9, 148.5, 137.3, 135.1, 129.5, 129.1, 128.5, 127.9, 122.0, 109.8, 80.0, 77.7, 69.1, 53.8, 26.8, 25.6, 24.8, 9.7; HRMS (EI) *m/z* 445.1615 [$(M+H)^+$; calcd. for $C_{22}H_{25}N_2O_8$, 445.1610].

Applying the procedure above to 56 mg (0.23 mmol) of **II-21** furnished 75 mg **II-21-DNB** in 74% yield as pale yellow crystals; mp 127-129 °C; IR (in $CHCl_3$) 2982 (m),

1728 (s), 1547 (s), 1344 (s), 1275 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.21 (s, 1 H), 9.09 (d, *J* = 2.1 Hz, 2 H), 7.45-7.21 (m, 5 H), 5.68 (m, 1 H), 4.48 (ddd, *J* = 12.4, 10.2, 6.3 Hz, 1 H), 3.77 (dd, *J* = 8.2, 5.7 Hz, 1 H), 3.46 (dd, *J* = 8.2, 6.6 Hz, 1 H), 3.02 (dd, *J* = 10.2, 3.8 Hz, 1 H), 1.72 (q, *J* = 7.14 Hz, 2 H), 1.45 (s, 3 H), 1.34 (s, 3 H), 0.96 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 148.6, 136.7, 134.2, 129.4, 129.2, 128.8, 127.8, 122.2, 109.9, 78.3, 75.7, 68.6, 52.6, 27.1, 25.6 (2 C), 10.0; HRMS (EI) *m/z* 445.1615 [$(M+H)^+$; calcd. for $C_{22}H_{25}N_2O_8$, 445.1610].

Preparation of II-22. To a solution of **II-08** (73 mg, 0.29 mmol) in THF (3 mL) was added 1 N HCl (2 mL) and the solution was refluxed for 10 min at which time TLC indicated the reaction complete. The solution was cooled and sodium bicarbonate powder was added in small portions with vigorous stirring until the pH of the mixture was 7. The mixture was then extracted with *n*-BuOH (3 mL X 4). The combined organic phase was dried over $MgSO_4$ and concentrated to dryness. The crude triol (white powder) was dissolved in 5 mL pyridine and the solution was cooled to 0 °C. 3,5-dinitrobenzoyl chloride (200 mg, 0.86 mmol) was then added and the solution was stirred overnight before it was diluted with 10 mL CH_2Cl_2 and washed with 0.1 N HCl, water and brine. The organic phase was then dried over $MgSO_4$. Column chromatography (hexanes/ether, 80:20) furnished 159 mg (70%) tris-3,5-dinitrobenzoyl ester **II-22** as yellow crystals: mp 195-196°C; $[\alpha]_D^{20}$ +2.3° (c 0.42, $CHCl_3$); IR ($CHCl_3$) 2924 (m), 1734 (s), 1545 (s), 1344 (s), 1271 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.29 (t, *J* = 2.1 Hz, 1 H), 9.26 (t, *J* = 2.1 Hz, 1 H), 9.16-9.08 (m, 5 H), 8.82 (d, *J* = 2.1 Hz, 2 H), 7.60-7.40 (m, 5 H), 6.06 (m, 1 H), 5.78 (m, 1 H), 4.80 (dd, *J* = 12.3, 2.7 Hz, 1 H), 4.05 (dd, *J* = 12.3, 8.7 Hz, 1 H), 3.55 (dd, *J* = 10.8, 3.0 Hz, 1 H), 1.64-1.52 (m, 2 H), 0.86 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 162.6, 162.0, 148.9, 148.8, 148.6, 134.5, 133.3, 132.8, 132.6, 129.7, 129.5, 129.4, 129.3, 129.1, 129.0, 123.0, 122.9, 122.7, 76.0, 71.3,

67.0, 50.6, 25.6, 9.1; HRMS (EI) *m/z* 581.1140 [$(M-C_7H_3N_2O_6)^+$; calcd. for $C_{26}H_{21}N_4O_{12}$, 581.1155].

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Preparation of α-(trimethylsilyl)benzyl alcohol (III-01a). A solution of benzyl alcohol (12 g, 0.11 mol) in 200 mL THF was cooled to 0 °C under nitrogen atmosphere. *n*-BuLi (1.6 M in hexanes, 75 mL, 0.12 mol) was added dropwise. After an additional 15 min 15 mL (0.12 mol) TMSCl was added dropwise while the solution was well stirred. The solution was stirred under nitrogen at 0 °C for 15 min before it was cooled to -76 °C. *t*-BuLi (1.7 M in hexanes, 82 mL, 0.14 mol) was than added dropwise. After an additional 1 hr during which time the reaction temperature was allowed to warm to room temperature, the reaction was diluted with diethyl ether, quenched with saturated aqueous NH_4Cl and washed with water and brine. The organic phase was dried over $MgSO_4$ and concentrated. Distillation (0.3 mm Hg, 65-68 °C) gave 17.6 g (89%) of **1a** as a light yellow liquid. The spectroscopic data for **III-01a** were consistent with those previously reported in the literature (Chuang, T.-H.; Fang, J.-M.; Jiaang, W.-T.; Tsai, Y.-M. *J. Org. Chem.* **1996**, *61*, 1794-1805).

Preparation of α-(trimethylsilyl) α-*d*-benzyl alcohol (III-01-d_1). A solution of α,α-d_2-benzyl alcohol (1.1 g, 10 mmol) in THF was cooled to 0 °C under a nitrogen atmosphere. MeLi (7.9 mL, 1.4 M in diethyl ether, 11 mmol) was added dropwise via syringe. Upon complete addition the reaction was stirred for another 15 min before 1.52 mL (12 mmol) TMSCl was added dropwise. The solution was then stirred under nitrogen at 0 °C for an additional 15 min before being cooled to -76 °C. *t*-BuLi (10 mL, 1.7 M in hexanes, 14 mmol) was then added dropwise. After 5 min the dry ice-acetone bath was removed. The solution was stirred for an additional 1 hr before it was diluted with diethyl ether and quenched with saturated aqueous NH_4Cl. The organic phase was washed with water and brine. It was then dried over $MgSO_4$ and concentrated. Silica gel chromatography (3 to 10% diethyl ether in pentane gradient) afforded 0.38 g (21%) of **III-01**-d_1 (along with 1.22 g (67%) of α,α-d_2-benzyltrimethylsilyl ether) as a colorless liquid. The spectroscopic data for **III-01**-d_1 were consistent with those previously

reported in the literature (Chuang, T.-H.; Fang, J.-M.; Jiaang, W.-T.; Tsai, Y.-M. *J. Org. Chem.* **1996**, *61*, 1794-1805).

Preparation of α-(trimethylsilyl)allyl alcohol (III-01b). Applying the procedure above to 10 g (0.17 mol) of allyl alcohol furnished 20 g crude product (**III-01b**) as a greenish yellow liquid in 89% yield which was used without further purification. The spectroscopic data for **III-01b** were consistent with those previously reported in the literature (Danheiser, R. L.; Fink, D. M.; Okano, K.; Tsai, Y.-M.; Szczepanski, S. W. *Org. Syn.* **1987**, *66*, 14-21).

Preparation of α-(trimethylsilyl) *n*-propyl alcohol (III-01c). To a solution of 0.8 g (6.2 mmol) α-(trimethylsilyl)allyl alcohol **III-01b** in 10 mL EtOAc was added 0.1 g 10% Pd/C(10%). The mixture was stirred overnight at room temperature. The catalyst was then removed via filtration and the solvent was carefully distilled off. The crude material was disolved in 20 mL 95% MeOH and the solution was cooled to 0°C before 0.15 g (3.0 mmol) $NaBH_4$ was added carefully. After refluxing for 30 min, the reaction was carefully concentrated. The mixture was diluted with water and extracted with ether. The organic phase was washed with water and brine. It was then dried over $MgSO_4$ and concentrated to give the crude **III-01c**, which was used without further purification. However, an analytical sample was obtained by distillation using a distillation head with a vacuum jacket. The spectroscopic data for **III-01c** were consistent with those previously reported in the literature (Soderquist, J. A.; Lee, S.-J. H. *Tetrahedron* **1988**, *44*, 4033-4042).

Preparation of trichloroacetimidates.

Benzyl trichloroacetimidate: To a suspension of 60 mg (1.5 mmol) NaH in 25 mL Et_2O was added 1.6 g benzyl alcohol (15 mmol) at rt. The mixture was stirred at rt for 15 min before it was cooled to 0°C, and 1.5 mL (15 mmol) trichloroacetonitrile was added.

The pale yellow solution was stirred for 10 min at 0 °C and 60 min at rt, before concentrated under reduced pressure. The residue was then diluted with 50 mL cyclohexane containing 0.07 mL (1.5 mmol) MeOH. After vigorous shaking, the mixture was filtered through a celite pad. The crude benzyl trichloroacetimidate was stored as a cyclohexane solution under N_2 in a freezer and used without further purification.

Applying the procedure above to 7.5 g (104 mmol) crotyl alcohol and 10 mL (100 mmol) trichloroacetonitrile furnished a cyclohexane solution of crotyl trichloroacetimidate which was used without further purification.

Applying the procedure above to 7.2 g (100 mmol) 2-methy-2-propen-1-ol and 10 mL (100 mmol) trichloroacetonitrile furnished a cyclohexane solution of the trichloroacetimidate of 2-methy-2-propen-1-ol which was used without further purification.

Applying the procedure above to 8 g (60 mmol) cinnamyl alcohol and 6 mL (60 mmol) trichloroacetonitrile furnished a cyclohexane solution of cinnamyl trichloroacetimidate which was used without further purification.

Applying the procedure above to 1.7 g (30 mmol) propargyl alcohol and 3 mL (30 mmol) trichloroacetonitrile furnished a cyclohexane solution of propargyl trichloroacetimidate which was used without further purification.

Applying the procedure above to 5.2 g *cis*-2-penten-1-ol (60 mmol) and 6 mL (60 mmol) trichloroacetonitrile furnished a cyclohexane solution of the trichloroacetimidate of *cis*-2-penten-1-ol which was used without further purification.

Preparation of III-02a and III-02b. To a solution of α-(trimethylsilyl)benzyl alcohol **III-01a** (0.85 g, 4.7 mmol) in 50 mL cyclohexane was added the trichloroacetimidate of crotyl alcohol (2.0 g, 9.2 mmol). To the well stirred solution was

added 0.1 mL TMSOTf in 1 mL cyclohexane via syringe. A white precipitation formed in several minutes. The reaction mixture was stirred at room temperature overnight before being filtered. The filtrate was diluted with petroleum ether, washed with saturated aqueous $NaHCO_3$, 1 N HCl, and brine. The organic phase was dried over $MgSO_4$ and concentrated. Silica gel chromatography (1% diethyl ether in pentane) furnished 740 mg (67%) of **III-02a** and 277 mg (25%) of **III-02b** as colorless oils.

For **III-02a**: IR (neat) 3024, 2959, 1600, 1450, 1248, 1051 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.12 (m, 5 H), 5.60 (m, 2 H), 4.14 (s, 1 H), 4.09-4.01 (m, 1 H), 3.72-3.63 (m, 1 H), 1.73 (dd, J = 4.8, 1.0 Hz, 3 H), 0.0 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.7, 128.6, 128.3, 128.0, 125.9, 125.5, 76.9, 71.1, 17.8, -3.9; HRMS (EI) *m/z* 233.1361 [$(M-H)^+$; calcd for $C_{14}H_{21}OSi$, 233.1362].

For **III-02b**: A 1:1 mixture of two diastereomers; IR (neat) 3024, 2928, 1450, 1248, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18-7.13 and 7.33-7.26 (m, 5 H), 5.83 and 5.65 (ddd, J = 5.5, 10.4, 17.3 Hz and 7.7, 10.2, 17.3 Hz, 1 H), 5.23-4.98 (m, 2 H), 4.26 and 4.23 (s, 1 H), 3.88 and 3.74 (q, J = 6.32 and 6.32 Hz, 1 H), 1.20 and 1.23 (d, J = 6.30 and 6.30 Hz, 3 H), 0.00 and -0.02 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.3 and 142.2, 141.4 and 140.5, 127.9 and 127.8, 125.9 and 125.7, 125.4 and 125.4, 116.2 and 113.6, 75.5 and 75.0, 74.7 and 74.0, 22.4 and 22.2, -3.96 and -3.96; HRMS (EI) *m/z* 233.1356 [$(M-H)^+$; calcd for $C_{14}H_{21}OSi$ 233.1362].

Preparation of III-02a-d_1. Applying the representative procedure above to 0.53 g (2.9 mmol) of **III-01**-d_1 and 1.6 g (7.3 mmol) of the trichloroacetimidate of crotyl alcohol afforded after silica gel chromatography (3% diethyl ether/pentane) 0.71 g (56%) of **III-02a**-d_1 as a colorless oil. IR (neat) 2963, 2070, 1601, 1493, 1440, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.12 (m, 5 H), 5.60 (m, 2 H), 4.09-4.01 (m, 1 H), 3.72-

3.63 (m, 1 H), 1.73 (dd, J = 4.8, 1.0 Hz, 3 H), 0.0 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6, 128.5, 128.3, 128.0, 125.8, 125.5, 76.3 (t, $J_{C\text{-}D}$ = 19.8 Hz), 71.0, 17.8, -3.9.

Preparation of III-02c: Applying the representative procedure above to 1.0 g (5.5 mmol) of **III-01a** and 2.4 g (11 mmol) of the trichloroacetimidate of 2-methyl-2-propen-1-ol afforded after silica gel chromatography (1% diethyl ether in pentane) 0.71 g (55%) of **III-02c** as a colorless liquid. IR (neat) 2959, 1769, 1451, 1248, 841 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.10 (m, 5 H), 4.89 (m, 2 H), 4.13 (s, 1 H), 3.81, (AB, Δ = 105.5 Hz, J = 12.4 Hz, 2 H), 1.74, (s, 3 H), 0.00 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 141.4, 128.0, 125.9, 125.6, 111.8, 76.9, 74.1, 19.6, -3.9; GC/MS (EI) *m/z* 179.2, 77.0, 73.1; Anal. Calcd. for $C_{14}H_{22}OSi$: C, 71.75; H, 9.47; Found: C, 71.62; H, 9.39.

Preparation of III-02d: Applying the representative procedure above to 1.0 g (7.7 mmol) of **III-01b** and 3.9 g (14 mmol) of the trichloroacetimidate of cinnamyl alcohol afforded after silica gel chromatography (1% diethyl ether in pentane) 1.25 g (67%) of **III-02d** as a colorless liquid. IR (neat) 2959, 1628, 1451, 1248, 1030, 841 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.20 (m, 5 H), 5.89-5.65 (m, 2 H), 5.35-5.15 (m, 2 H), 5.15-4.95 (m, 2 H), 4.85 (d, J = 8.2 Hz, 1 H), 3.94 (dt, J = 6.9, 1.4 Hz, 1 H), 0.09 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4, 139.0, 137.2, 128.1, 127.0, 126.3, 117.4, 112.4, 80.8, 72.8, -3.9; HRMS (EI) *m/z* 246.1440 [$(M)^+$; calcd. for $C_{15}H_{22}OSi$, 246.1433].

Preparation of III-02e: Applying the representative procedure above to 0.9 g (5 mmol) of **III-01a** and 2.5 g (10 mmol) benzyl trichloroacetimidate afforded after silica gel chromatography (1% diethyl ether in pentane) 0.7 g (52%) of **III-02e** as a colorless liquid. IR (neat) 3027, 2959, 1496, 1451, 1248, 1059, 841 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.12 (m, 10 H), 4.46 (ABq, Δ = 124.5 Hz, J = 12.0 Hz, 2 H), 4.15 (s, 1 H), 0.00 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 139.1, 128.2, 128.1, 127.7, 127.3,

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126.0, 125.7, 77.2, 72.0, -3.93; GC/MS (EI) *m/z* 179.1, 163.2, 73.1; Anal. Calcd. for $C_{17}H_{22}OSi$: C, 75.52; H, 8.21; Found: C, 75.17; H, 7.98.

Preparation of III-02f: Applying the representative procedure above to 1.0 g (5.5 mmol) of **III-01a** and 2.6 g (13 mmol) of the trichloroacetimidate of propargyl alcohol afforded after silica gel chromatography 0.78 g (64%) of **III-02f** as a colorless liquid. IR (neat) 3308, 2959, 1767, 1450, 1248, 1059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.10 (m, 5 H), 4.39 (s, 1 H), 4.08 (ABq, Δ = 87.0 Hz, *J* = 15.6, 2.1 Hz, 2 H), 2.38 (t, *J* = 2.4 Hz, 1 H), 0.00 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3, 128.2, 126.1, 126.1, 80.5, 76.6, 73.7, 57.3, -4.0; HRMS [CI (NH_3)] *m/z* 236.1468 [$(M+NH_4)^+$; calcd for $C_{13}H_{22}NOSi$, 236.1471].

Preparation of III-02g: Applying the representative procedure above to 0.9 g (6.8 mmol) of **III-01b** and 3.5 g (14 mmol) benzyl trichloroacetimidate afforded after silica gel chromatography 0.8 g (53%) of **III-02g** as a colorless liquid. IR (neat) 3032, 2959, 1248, 1055 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43-7.25 (m, 5 H), 5.91-5.79 (m, 1 H), 5.15-5.07 (m, 2 H), 4.72 (d, *J* = 12.1 Hz, 1 H), 4.34 (d, *J* = 12.1 Hz, 1 H), 3.64 (dt, *J* = 7.14, 1.37 Hz, 1 H), 0.04 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 137.3, 128.2, 127.6, 127.2, 112.6, 75.9, 71.8, -3.98; HRMS (EI) *m/z* 220.1287 [$(M)^+$; calcd for $C_{13}H_{20}OSi$, 220.1283].

Preparation of III-02h: Applying the representative procedure to 0.5 g (3.8 mmol) of **III-01c** and 2.5 g (10 mmol) benzyl trichloroacetimidate afforded after silica gel chromatography 0.52 g (63%) of **III-02h** as a colorless liquid. IR (neat) 2959, 1454, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.20 (m, 5 H), 4.52 (ABq, Δ = 48 Hz, *J* = 11.4 Hz, 2 H), 3.04 (dd, *J* = 7.5, 5.7 Hz, 1 H), 1.80-1.58 (m, 2 H), 1.01 (t, *J* = 7.2 Hz, 3 H), 0.07 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3, 128.2, 127.7, 127.3, 75.4, 73.4,

23.8, 11.7, -2.80; HRMS [CI (NH_3)] *m/z* 223.1514 [$(M+H)^+$; calcd for $C_{13}H_{23}OSi$, 223.1518].

Preparation of III-02i. Applying the representative procedure above to 1.32 g (10 mmol) α-(trimethylsilyl)allyl alcohol and 4.3 g (18.6 mmol) of the trichloroacetimidate of *cis*-2-penten-1-ol afforded after silica gel chromatography (3% diethyl ether in pentane) 0.61 g (31%) of **III-02i** as a colorless liquid. IR (neat) 2967, 1767, 1746, 1458, 1248, 841 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.77 (ddd, *J* = 18.0, 10.8, 7.2 Hz, 1 H), 5.59-5.39 (m, 2 H), 5.10-4.90 (m, 2 H), 4.13-4.06 (m, 1 H), 3.93-3.89 (m, 1 H), 3.57 (dt, *J* = 7.2, 3.0, 1.5 Hz, 1 H), 2.03 (quent, *J* = 7.2 Hz, 2 H), 0.94 (t, *J* = 7.2, 14.4 Hz, 3 H), 0.00 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 135.0, 126.2, 112.1, 75.7, 65.7, 20.9, 14.3, -3.98; HRMS (EI) *m/z* 198.1438 [$(M)^+$; calcd for $C_{11}H_{22}OSi$, 198.1440].

Wittig rearrangement reaction of III-02a with CsF. In a glove bag purged with nitrogen, CsF powder (ca. 100 mg, 6.4 mmol) was suspended in DMF (4 mL). The resulting mixture was stirred for 5 min before **III-02a** (50 mg, 0.21 mmol) was added dropwise via syringe. The solution was stirred overnight at room temperature, before being diluted with diethyl ether, quenched with saturated aqueous NH_4Cl, washed with 0.1 N HCl, water, and then brine. The organic phase was dried over $MgSO_4$ and concentrated. Silica gel chromatography (5 to 10% diethyl ether in pentane gradient) afforded 28 mg (80%) of **III-03** as an inseparable mixture (1.2:1) of *syn* and *anti* diastereomers. The spectroscopic data were consistent with those previously reported (Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620-6628; also see: Kang, S-K.; Kim, D-Y.; Hong, R-K.; Ho, P-S. *Synth. Commun.* **1996**, *26*, 1493-1498).

Wittig rearrangement reaction of III-02b with CsF. Applying the Wittig rearrangement conditions above to 48 mg (0.20 mmol) of **III-02b** afforded after silica gel

chromatography (10% diethyl ether in pentane) 20 mg (60%) of **III-04** as a colorless oil. The spectroscopic data were consistent with those reported in the literature (Kang, S-K.; Kim, D-Y.; Hong, R-K.; Ho, P-S. *Synth. Commun.* **1996**, *26*, 1493-1498).

Wittig rearrangement reaction of III-02c with CsF. Applying the Wittig rearrangement conditions above to 35 mg (0.15 mmol) of **III-02c** afforded after silica gel chromatography (10% diethyl ether in pentane) 19 mg (79%) of **III-05** as a colorless oil. The spectroscopic data were consistent with those previously reported in the literature (Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620-6628).

Wittig rearrangement reaction of III-02d with CsF. Applying the Wittig rearrangement conditions above to 45 mg (0.18 mmol) of **III-02d** afforded after silica gel chromatography (10% diethyl ether in pentane) 17 mg (54%) of **III-06** and 4 mg (13%) of **III-07** as an inseparable mixture (1:1) of syn and anti diastereomers. The spectroscopic data for these products were consistent with those reported in the literature (For **III-06** see: Enholm, E. J.; Satici, H.; Prasad, G. *J. Org. Chem.* **1990**, *55*, 324-329. For **III-07** see: Newman-Evans, R. H.; Simon, R.; Carpenter, B. K. *J. Org. Chem.* **1990**, *55*, 695-711).

Attempted Wittig rearrangement reaction of III-02e with CsF. Applying the Wittig rearrangement conditions above to 71 mg (0.26 mmol) of **III-02e** afforded no Wittig rearrangement reaction product. After silica gel chromatography (1:5 diethyl ether in pentane) 43 mg of dibenzyl ether **III-08** was isolated in 82% yield. The spectroscopic data were consistent with those previously reported in the literature (Herzog, H.; Scharf, H.-D. *Synthesis* **1986**, 788-790).

Attempted Wittig rearrangement reaction of III-02f with CsF. The Wittig rearrangement conditions above were applied to 110 mg (0.50 mmol) of **2f** but no rearrangement product was observed. Silica gel chromatography (1:20 diethyl ether in

pentane) afforded 40 mg (54%) of desilylated compound **III-09**. The spectroscopic data of this product were consistent with those previously reported in the literature (Boger, D. L.; Palanki, M. S. S. *J. Am. Chem. Soc.* **1992**, *114*, 9318-9327).

Attempted Wittig rearrangement reaction of III-02g with CsF. The Wittig rearrangement conditions above were applied to 88 mg (0.40 mmol) of **III-02g** but no Wittig was observed. Silica gel chromatography (1:50 diethyl ether in pentane) afforded 37 mg (63%) of **III-10** as an inseparable mixture of geometric isomers (*E:Z* 88:12) and 8 mg (14%) of **III-11**. The spectroscopic data were consistent with those previously reported in the literature (For **III-10** see: Dickinson, J. M.; Murphy, J. A.; Patterson, C. W.; Wooster, N. F. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1179-1184. For **III-11** see: Zimmerman, S. C.; Cramer, K. D.; Galan, A. A. *J. Org. Chem.* **1989**, *54*, 1256-1264).

Attempted Wittig rearrangement reaction of III-02h with CsF. The Wittig rearrangement conditions above were applied to 50 mg of **III-02h** but no reaction was observed. The starting material was recovered in 81% yield.

Wittig rearrangement reaction of III-02a with MeLi. A solution of 176 mg (0.73 mmol) of silane **III-02a** in 10 mL THF was cooled to 0 °C under nitrogen. MeLi (1.4 M in diethyl ether, 0.9 mL, 1.26 mmol) was added dropwise via syringe. The solution was stirred overnight at room temperature. It was then quenched with saturated aqueous NH_4Cl, diluted with diethyl ether, washed with 1 N HCl, water, and brine. The organic phase was dried over $MgSO_4$ and concentrated. Silica gel chromatography (1 to 5% diethyl ether in hexane gradient) afforded 35 mg (20%) of **III-12a**, 38 mg (22%) of **III-12b**, 24 mg (20%) of **III-03a/b** as an inseparable mixture (1.2:1) of diastereomers, and 16 mg (9%) of **III-13a/b** as an inseparable mixture (2:1) of diastereomers, all as colorless oils.

For **III-12a**: IR (neat) 3567, 3065, 2961, 1444, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.03 (m, 5 H), 5.51 (ddd, J = 17.1, 10.8, 5.4 Hz, 1 H), 5.12-4.98 (m, 2 H), 3.15 (m, 1 H), 1.59 (bs, 1 H), 1.25 (d, J = 6.9 Hz, 3 H), -0.02 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2, 138.8, 128.0, 125.1, 124.1, 116.7, 72.8, 43.4, 14.5, -2.3; HRMS (EI) *m/z* 233.1359 [$(M-H)^+$; calcd for $C_{14}H_{21}OSi$, 233.1362].

For **III-12b**: IR (neat) 3567, 3065, 2961, 1444, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.10 (m, 5 H), 6.06 (m, 1 H), 5.30-5.10 (m, 2 H), 2.98 (m, 1 H), 1.60 (bs, 1 H), 0.77 (d, J = 6.9 Hz, 3 H), -0.05 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.9, 141.4, 128.0, 125.0, 124.3, 115.6, 74.1, 45.3, 13.4, -2.44; HRMS (EI) *m/z* 233.1359 [$(M-H)^+$; calcd for $C_{14}H_{21}OSi$, 233.1362].

For **III-03a/b**: The spectroscopic data were consistent with those previously reported in the literature (For **III-03a** see: Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620-6628. For **III-03b** see: Kang, S-K.; Kim, D-Y.; Hong, R-K.; Ho, P-S. *Synth. Commun.* **1996**, *26*, 1493-1498).

For **III-13a/b**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.10 (m, 5 H), 5.85 and 5.70 (m, 1 H), 5.05-4.86 (m, 2 H), 4.46 and 4.44 (d, J = 6.6 Hz, 1 H), 2.52-2.38 (m, 1 H), 1.00 and 0.88 (d, J = 6.9 Hz, 3 H), 0.00 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8 and 143.7, 141.3 and 140.9, 127.7 and 127.6, 126.9 and 126.8, 127.7 and 126.6, 114.3 and 114.2, 79.0 and 78.7, 46.0 and 45.8, 16.2 and 14.6, 0.1 and 0.1. For a prior preparation see: Hollis, T. K.; Robinson, N. P.; Whelan, J.; Bosnich, B. *Tetrahedron Lett.* **1993**, *34*, 4309-4312.

Wittig rearrangement reaction of III-02a-d_1 with MeLi. Applying the representative procedure above to 90 mg (0.38 mmol) of **III-02a**-d_1 afforded after silica gel chromatography (3 to 10% diethyl ether in pentane gradient) 11 mg (12%) of **III-12a/b** as a mixture (1.4:1) of diastereomers, 66 mg (73 %) of **III-03a/b**-d_1 as a mixture

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(1.1:1) of diastereomers, all as colorless oils. (Though not isolated, ^{1}H NMR spectrum of the crude reaction mixture revealed that a 1.2:1 mixture of **III-13a/b** was also formed in approximately 1.5% yield.)

For **III-03a/b-d_1**: IR (neat) 3412, 2961, 1640, 1449 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.20 (m, 5 H), 5.87-5.70 (m, 1 H), 5.25-5.00 (m, 2 H), 2.59 and 2.48 (m, 1 H), 1.82 (bs, 1 H), 1.10 and 0.87 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5 and 142.4, 140.6 and 140.2, 128.2 and 128.1, 127.6 and 127.3, 126.8 and 126.5, 116.9 and 115.6, 77.8 and 77.2, 46.2 and 44.5, 16.5 and 13.9; GC/MS (EI) *m/z* 162.0, 107.1, 77.0.

Wittig rearrangement reaction of III-02b with MeLi. Applying the representative procedure above to 117 mg (0.50 mmol) of silane **III-02b** afforded after silica gel chromatography (3 to 10% diethyl ether in pentane gradient) 61 mg (75%) of **III-04** and 24 mg (21%) of **III-14** as colorless oils.

For **III-04**: The spectroscopic data were consistent with those previously reported in the literature (Kang, S-K.; Kim, D-Y.; Hong, R-K.; Ho, P-S. *Synth. Commun.* **1996**, *26*, 1493-1498).

For **III-14**: IR (neat) 3341, 2961, 1696, 1450, 1248 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.03 (m, 5 H), 5.54-5.50 (m, 1 H), 5.20-5.00 (m, 1 H), 2.80-3.00 (m, 1 H), 2.54 (dd, J = 14.1, 9.9 Hz, 1 H), 1.89 (br s, 1 H), 1.60 (dt, J = 6.3, 1.5, 1.5 Hz, 3 H), 0.03 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.9, 131.3, 127.9, 125.0, 124.9, 124.6, 70.5, 39.9, 18.0, -4.18; HRMS (EI) *m/z* 233.1359 [(M-H)$^+$; calcd for $C_{14}H_{21}OSi$ 233.1362].

Wittig rearrangement reaction of III-02c with MeLi. Applying the representative procedure above to 118 mg (0.51 mmol) of silane **III-02c** afforded after

silica gel chromatography (3 to 10% diethyl ether in pentane gradient) 59 mg (50%) of **III-15** and 26 mg (32%) of **III-05** as colorless oils.

For **III-15**: IR (neat) 3503, 2967, 1634, 1487, 1223, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.20 (m, 5 H), 4.88 (m, 1 H), 4.68 (m, 1 H), 2.76 (AB, Δ = 74.7 Hz, *J* = 13.8 Hz, 2 H), 1.58 (bs, 1 H), 1.26 (s, 3 H), -0.01 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.1, 141.3, 127.7, 125.0, 124.7, 115.8, 69.0, 44.3, 24.7, -4.1; GC/MS (EI) *m/z* 234.2, 233.2, 219.2, 179.2, 73.0, 55.0; HRMS (EI) *m/z* 233.1355 [$(M-H)^+$; calcd for $C_{14}H_{21}OSi$, 233.1362].

Wittig rearrangement reaction of III-02e with MeLi. Applying the representative procedure above to 74 mg (0.27 mmol) of silane **III-02e** afforded after silica gel chromatography (10% diethyl ether in pentane) 5 mg (9%) of **III-16** as the sole rearrangement product. The spectroscopic data for **III-16** were consistent with those previously reported in the literature (Sidduri, A.; Rozema, M. J.; Knochel, P. *J. Org. Chem.* **1993**, *58*, 2694-2713).

Wittig rearrangement reaction of III-02f with MeLi. Applying the representative procedure above to 400 mg (1.83 mmol) of silane **III-02f** and 3.3 mL (4.6 mmol) MeLi afforded after silica gel chromatography (5 to 10% diethyl ether in pentane gradient) 89 mg (33%) of **III-17** and 60 mg (15%) of **III-18** as colorless oils.

For **III-17**: The spectroscopic data were consistent with those previously reported in the literature (Shinokubo, H.; Miki, H.; Yokoo, T.; Oshima, K.; Utimoto, K. *Tetrahedron* **1995**, *51*, 11681-11692).

For **III-18**: IR (neat) 3509, 3305, 2959, 1248, 841 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.16 (m, 5 H), 2.92 (ABd, Δ = 39.3 Hz, *J* = 16.8, 2.7 Hz, 2 H), 2.22 (br s, 1 H), 1.89 (t, *J* = 2.4 Hz, 1 H), 0.00 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 128.0,

125.7, 124.8, 79.8, 72.0, 70.3, 28.2, -4.1; HRMS (EI) *m/z* 217.1041 [$(M-H)^+$; calcd for $C_{13}H_{17}OSi$, 217.1049].

Wittig rearrangement reaction of III-02d with MeLi. Applying the representative procedure above to 73 mg (0.30 mmol) of silane **III-02d** afforded after silica gel chromatography (5 to 10% diethyl ether in pentane gradient) 43 mg (59%) of **III-17** and 10 mg (19%) of **III-18** as colorless oils.

For **III-17**: IR (neat) 2953, 1716, 1240, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.10 (m, 5 H), 6.47 (d, J = 16.2 Hz, 1 H), 6.31 (dt, J = 6.6, 16.2 Hz, 1 H), 3.34 (d, J = 6.6 Hz, 2 H), 2.41-2.48 (m, 2 H), 0.74-0.81 (m, 2 H), 0.00 (s, 9 H); 13C NMR (75 MHz, $CDCl_3$) δ 209.7, 136.9, 133.4, 128.5, 127.5, 126.2, 122.3, 46.2, 37.1, 10.2, -1.8; HRMS (EI) *m/z* 246.1432 [calcd for $C_{15}H_{22}OSi$, 246.1440].

For **III-18**: The spectroscopic data were consistent with those previously reported in the literature (Enholm, E. J.; Satici, H.; Prasad, G. *J. Org. Chem.* **1990**, *55*, 324-329).

Wittig rearrangement reaction of III-02i with MeLi. Applying the representative procedure above to 130 mg (0.66 mmol) of silane **III-02i** afforded after silica gel chromatography (10% diethyl ether in pentane) 119 mg (92%) of **III-19** as a clear oil. IR (neat) 2959, 1717, 1636, 1250, 839 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.76-5.64 (m, 1 H), 5.17-5.11 (m, 2 H), 3.03 (q, J = 7.8 Hz, 1 H), 2.50-2.24 (m, 2 H), 1.75 (sep, J = 7.5 Hz, 1 H), 1.48 (sep, J = 7.5 Hz, 1 H), 0.85 (t, J = 7.5 Hz, 3 H), 0.75-0.69 (m, 2 H), -0.02 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.7, 136.5, 117.5, 58.9, 36.1, 24.3, 11.7, 9.9, -1.8; HRMS (EI) *m/z* 198.1424 [calcd for $C_{11}H_{22}OSi$ 198.1440].

Wittig rearrangement reaction of III-02g with MeLi. Applying the representative procedure above to 82 mg (0.37 mmol) of silane **III-02g** afforded after

silica gel chromatography (3% diethyl ether in pentane) 49 mg (60%) of **III-22** and 16 mg (20%) of **III-23** as colorless oils.

For **III-22**: IR (neat) 2942, 1716, 1640, 1497, 1252, 847 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.10 (m, 5 H), 2.62 (t, J = 7.4 Hz, 2 H), 2.58 (t, J = 7.5 Hz, 2 H), 1.85 (q, J = 7.5 Hz, 2 H), 0.18 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 247.9, 141.8, 128.4, 128.3, 125.9, 47.6, 35.2, 23.7, -3.2; HRMS (EI) *m/z* 219.1210 [$(M-H)^+$; calcd for $C_{13}H_{19}OSi$ 219.1210].

For **III-23**: IR (neat) 2953, 1718, 1250, 841 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.10 (m, 5 H), 2.70 (s, 2 H), 2.39-2.45 (m, 2 H), 0.71-0.77 (m, 2 H), -0.05 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.2, 134.4, 129.3, 128.6, 126.9, 49.3, 36.6, 10.2, -1.9; HRMS (EI) *m/z* 233.1279 [calcd for $C_{13}H_{20}OSi$ 220.1283].

Preparation of III-27. A solution of 74 mg (0.73 mmol) of silane **III-02g** in 3 mL THF was cooled to 0°C under nitrogen. MeLi (1.4 M in diethyl ether, 0.48 mL, 0.67 mmol) was added dropwise via syringe. The solution was stirred for 2 hr at rt. To the reaction mixture was added a mixture of 0.07 mL (0.5 mmol) TEA and 0.05 mL (0.5 mmol) freshly distilled allyl bromide. The reaction mixture was stirred for 4.5 hr at rt before quenched with saturated aqueous NH_4Cl, diluted with diethyl ether, washed with 1 N HCl, water, and brine. The organic phase was dried over $MgSO_4$ and concentrated. Silica gel chromatography (1 to 5% diethyl ether in hexane gradient) afforded 14 mg (16%) of **III-27** as colorless oil: IR (neat) 2955, 1713, 1639, 1454, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.3-7.1 (m, 5 H), 5.59-5.75 (m, 1 H), 4.95-5.10 (m, 2 H), 3.02 (pent, J = 6.6 Hz, 1 H), 2.25-2.42 (m, 1 H), 2.42-2.55 (m, 2 H), 2.01-2.15 (m, 1 H), 1.89-2.01 (m, 1 H), 1.50-1.65 (m, 1 H), 0.18 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 250.2, 141.8, 135.7, 128.3, 128.2, 125.8, 116.6, 54.7, 33.6, 33.5, 30.7, -2.63; HRMS (EI) *m/z* 260.1589 [$(M)^+$; calcd. for $C_{16}H_{24}OSi$, 260.1596].

Preparation of the acylsilanes. Representative procedure: Under an argon atmosphere, di-m-chloro-bis(η^3-allyl)dipalladium (38 mg, 0.2 mmol) was placed into a 5 mL round bottle flask and the flask was sealed with a septum. Triethylphosphite (96 mg, 0.4 mmol) and $Me_3SiSnBu_3$ (1.6 g, 4.4 mmol) were added via a syringe and the mixture was stirred at ambient temperature for 3 min. Octonyl chloride (0.69 mL, 4.0 mmol) was then added via a syringe and the solution was heated to 110 °C for 16 h. It was then allowed to cool to room temperature. The mixture was transferred onto a short silica gel column (3% ether in pentane) and a crude product was separated, the main impurity being tributyltin chloride. This semicrude material was purified by flush chromatography with pure pentane to furnish octonyl silane (Scheme 4.5; entry 3) in 74% yield as a pale yellow liquid. The spectroscopic data were consistent with those previously reported in the literature (Yamamoto, K.; Suzuki, S.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 1653-1656).

The synthesis of other acyl silanes were carried out using the same procedure, with variations of temperature and reaction time (see Scheme 4.5). The spectroscopic data of these acyl silanes were consistent with those previously reported in the literature:

For pentanoyl silane (Scheme 4.5; entry 1) and cyclohexanecarbonyl silane (Scheme 4.5; entry 5), see: Kuwajima, I.; Mori, A.; Kato, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2634-2638.

For benzoyl silane (Scheme 4.5; entries 6-8), see: Tongco, E. C.; Wang, Q.; Prakash, G. K. S. *Synth. Commun.* **1997**, *27*, 2117-2124.

For *o*-chlorobenzoyl silane (Scheme 4.5; entry 9), see: Picard, J-P.; Calas, R.; Dunogues, J.; Duffaut, N.; Gerval, J.; Lapouyade, P. *J. Org. Chem.* **1979**, *44*, 420-423.

For *p*-methoylbenzoyl silane (Scheme 4.5; entry 10), see: Cambie, R. C.; Mui, L. C. M.; Putledge, P. S.; Woodgate, P. D. *J. Organomet. Chem.* **1994**, *464*, 171-182.

Preparation of (V-17). A mixture of 50 g (-)-ephedrine hydrochloride (247.8 mmol) and 45 g urea (750 mmol) was heated for 100 min at 170-175 °C. The clear liquid was then heated to 200-210 °C for 1 hour before it was cooled to 80 °C and quenched with water. The solid was filtered and washed thoroughly with 5% HCl and water. Recrystalization from 95% ethanol afforded 28 g **V-17** (50%) as a white solid. mp 174-177 °C (lit. 177°C); $[\alpha]_D^{20}$ -45.0° (c 0.97, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3 (m, 5 H), 4.7 (d, J = 8.4 Hz, 1 H), 4.6 (br s, 1 H), 3.8 (dq, J = 9.0, 6.3 Hz, 1 H), 2.7 (s, 3 H), 0.73 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 138.1, 128.5, 128.0, 127.2, 58.2, 57.5, 28.2, 14.3. For a previous synthesis, see: Clark, W. M.; Bender, C. *J. Org. Chem.* **1998**, *63*, 6732-6734.

Preparation of V-18. Compound **V-17** (27.5 g, 147 mmol) was disolved in 560 mL THF with the help of gentle heating. The solution was cooled to 0 °C and 100 mL *n*-BuLi (1.6 M in hexanes, 160 mmol) was added dropwise. The dark purple solution was stirred at 0 °C for 30 minutes. Then propionyl chloride (15.6 mL, 180 mmol) was added and the clear solution was allowed to stir for 1 h and warm to room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) and the organic layer was washed with brine and dried over $MgSO_4$. Concentration of the organic layer afforded 36 g (quantitative yield) of **V-18** as a white solid. mp 105-106 °C (lit. 106°C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3 (m, 5 H), 5.2 (d, J = 6.3 Hz, 1 H), 3.8 (dq, J = 9.0, 7.0 Hz, 1 H), 2.9 (q, J = 7.0 Hz, 2 H) 2.7 (s, 3H), 1.0 (t, J = 7.0, 3 H), 0.75 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 155.9, 136.7, 128.4, 127.9, 126.8, 59.2, 53.9, 29.3, 28.1, 14.8, 8.5. For a previous synthesis, see: Drewes, S. E.; Malissar, D. G. S.; Roos, G. H. P. *Chem. Ber.* **1993**, 2663-2673.

Preparation of V-19. NaHMDS (100 mL, 1 M in THF, 100 mmol) was cooled to −78 °C. A solution of **V-18** (22.0 g, 90 mmol) in 200 mL THF was added dropwise via a cannula. The cannula was passed though a dry ice/acetone bath to precool the solution,

and the addition process took about 3 h. After an additional 2 h at –75°C, allyl bromide (9.0 mL, 100 mmol) was added dropwise over 90 min. The resulting solution was stirred at –78 °C for 12 h before it was quenched with 50 mL 1 N HCl and diluted with 200 mL Et_2O. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated to gave 25.5 g colorless oil (quantitative yield) which solidified upon sitting. This waxy material was shown by NMR to be pure **V-19**. $[\alpha]_D^{20}$ -50.3° (c 0.55, $CHCl_3$); IR (neat) 2976, 1730, 1684, 1387, 1234 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.3 (m, 5 H), 5.6 (m, 1 H), 5.2 (d, J = 8.7 Hz, 1 H), 4.9 (m, 2 H), 3.9 (m, 1 H), 3.8 (m, 1 H), 2.7 (s, 3 H), 2.3 (m, 1 H), 2.0 (m, 1 H), 1.0 (d, J = 6.9 Hz, 3 H) 0.75 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 155.5, 136.6, 128.4, 128.3, 127.8, 126.9, 116.5, 59.2, 53.6, 37.9, 37.1, 28.1, 16.1, 14.9; HRMS (EI) *m/z* 287.1758 $[(M+H)^+$, calcd. for $C_{17}H_{23}N_2O_2$, 287.1760].

Preparation of V-20. To a solution of 25.5 g **V-19** in 250 mL ethyl acetate was added 1.4 g Pd/C (10%). The flask was evacuated via aspirator and then charged with H_2 via balloon. The process was repeated 3 times to sufficiently degas the sample. Then reaction was allowed to stir under a hydrogen atmosphere for 6 h, at which time NMR showed the reaction complete. The suspension was then filtered and concentrated to furnish 26 g of a colorless oil (quant. yield). No impurity was observed by NMR. $[\alpha]_D^{20}$ -37.0° (c 0.30, $CHCl_3$); IR (neat) 2961, 1734, 1686, 1337, 1224 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.00 (m, 5 H), 5.28 (d, J = 9.0 Hz, 1 H), 4.00-3.80 (m, 2 H), 2.81 (s, 3 H), 1.75-1.55 (m, 1 H), 1.40-1.10 (m, 3 H), 1.08 (d, J = 6.9 Hz, 3 H), 0.81 (t, J = 7.2 Hz, 3 H), 0.79 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 155.6, 136.8, 128.3, 127.8, 126.8, 59.2, 53.5, 37.2, 35.9, 28.1, 19.9, 16.6, 14.9, 13.9; HRMS (EI) *m/z* 289.1923 $[(M+H)^+$, calcd. for $C_{17}H_{25}N_2O_2$, 289.1916].

To the solution of 25.5 g this crude product (ca. 88.5 mmol) in diethyl ether (250 mL) was added 1.8 mL water (100 mmol) and the solution cooled to –10 °C (internal

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temperature). Then 52 mL $LiBH_4$ (100 mmol, 2M in THF) was added dropwise. Clouding and gas evolsion was observed. The reaction was warmed to room temperature after 3 h. After an additional 2 h the reaction was cooled to –10 °C and quenched by the addition of 1 M aq. NaOH. Large amounts of white solid formed at this point. It was filtered and air dried. ^{1}H NMR indicated it was a mixture of **V-20** and an unidentified inorganic salt. The filtrate was concentrated and the resulting residue was chromatographed (30% EtOAc/hexanes) on silica gel to afford 7.4 g **V-20** as a colorless liquid (82%). The spectroscopic data were consistent with those previously reported in the literature. $[\alpha]_D^{20}$ -12.0° (c 1.80, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.42 (qd, J = 8.0, 5.7 Hz, 2 H), 1.60 (m, 1 H), 1.28 (m, 4 H), 1.08 (m, 1 H), 0.89 (d, J = 6.8 Hz, 3 H), 0.88 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 68.4, 34.5, 35.4, 20.0, 16.5, 14.3.

Preparation of V-21. Oxalyl chloride 5.3 mL (60 mmol) was added to CH_2Cl_2 at –50°C and the temperature was further lowered to –70 °C. DMSO 8.5 mL (120 mmol) was added dropwise (gas evolsion). After 10 min, a solution of 5.7 g **V-20** (56 mmol) in CH_2Cl_2 (70 mL) was added dropwise via a cannula. After 5 min, *i*-Pr_2NEt 43.5 mL (250 mmol) was added. The dry ice bath was replaced by an ice bath after 15 min before the Wittig reagent $Ph_3P{=}CHCO_2Et$ was added in portions under nitrogen. The mixture was further stirred for 2.5 h before it was quenched by the addition of 1 M aq. HCl, and was extracted with Et_2O. The organic phase was washed with brine, dried over magnesium sulfate, and concentrated. The resulting residue was chromatographed (10% Et_2O in pentane) on silica gel to afford 9.5 g (quant. yield) of **V-21** as colorless liquid. IR (neat) 2963, 1722, 1653, 1224 cm^{-1}; $[\alpha]_D^{20}$ +14.6° (c 4.38, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (dd, J = 8.0, 15.5 Hz, 1 H), 5.75 (d, J = 14.1 Hz, 1 H), 4.16 (dd, J = 14.3, 7.2 Hz, 2 H), 2.29 (m, 1 H), 1.27 (t, J = 7.2 Hz, 3 H), 1.2-1.4 (m, 4 H), 1.02 (d, J = 6.8 Hz, 3 H), 0.81-0.91 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 154.7, 119.5, 60.1, 38.2, 36.2, 20.3, 19.4, 14.2, 14.0; HRMS (EI) *m/z* 170.1307 [$(M)^+$, calcd. for $C_{10}H_{18}O_2$, 170.1306].

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Preparation of V-22. To a -70°C solution of 162 g DIBAL (1 M in hexanes, d 0.7, 206 mmol) in 250 mL CH_2Cl_2 was added a solution of 14 g (82.3 mmol) **V-21** in 100 mL CH_2Cl_2 via a cannula. After 50 min the temperature was warmed to 0 °C. After an additional 30 min the reaction mixture was poured into 420 mL 0.5 M solution of sodium potassium tartrate and stirred overnight at rt. The mixture was extracted with CH_2Cl_2 and Et_2O. The organic phase was combined, washed with brine, dried over magnesium sulfate, and concentrated. The resulting residue was chromatographed (10% Et_2O in hexanes) on silica gel to afford 9.1 g **V-22** as a colorless liquid (82%). IR (neat) 3327, 2961, 1456, 1379, 972 cm^{-1}; $[\alpha]_D^{20}$ +23.6° (c 2.06, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.55-5.65 (m, 2 H), 4.06-4.12 (m, 2 H), 2.04-2.22 (m, 1 H), 1.43, (s, 1 H), 1.20-1.34 (m, 4 H), 0.97 (d, J = 6.8 Hz, 3 H), 0.87 (t, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3, 126.9, 63.8, 39.0, 36.0, 20.3, 20.3, 14.0; HRMS (EI) *m/z* 127.1123 [$(M-H)^+$, calcd. for $C_8H_{15}O$, 127.1123].

Preparation of V-23. Freshly activated 4 Å molecular sieves were added to a 250 mL round bottom flask and was flame dried under vaccum for 5 min. After cooling under N_2, 50 mL CH_2Cl_2 was added followed by 2.98 mL (10 mmol) $Ti(O\text{-}iPr)_4$. The temperature was further lowered to –20 °C before 2.06 g (10 mmol) (+)-diethyl *L*-tartrate in 8 mL CH_2Cl_2 was added dropwise (1 mL / min). The solution was stirred for 50 min during which time the temperature slowly warmed to –5 °C. The temperature was then lowered to –40 °C and a solution of 1.28 g **V-22** (10 mmol) in 10 mL CH_2Cl_2 was added dropwise. Upon complete addition the solution was stirred for 10 min at –25 °C. *tert*-Butyl hydroperoxide 4.9 mL (4.1 M in toluene, 20 mmol) was added, and the mixture was stirred overnight at -20°C before it was quenched with 10 mL saturated Na_2SO_3 aqueous solution and 10 mL saturated Na_2SO_4 aqueous solution. The reaction mixture was diluted with 40 mL diethyl ether and stirred overnight. The mixture was extracted with CH_2Cl_2 and Et_2O. The organic phase was combined, washed with brine, dried over magnesium

sulfate, and concentrated. Silica gel chromatography (10% EtOAc in hexanes) furnished 1.24 g **V-23** (86%) as a colorless oil. $[\alpha]_D^{20}$ -24.0° (c 3.24, $CHCl_3$); IR (neat) 3422, 2961, 1458, 1379, 1070, 893 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.91 (d, *J* = 12.2 Hz, 1 H), 3.61 (dd, *J* = 12.6, 3.7 Hz, 1 H), 2.93 (p, *J* = 2.2 Hz, 1 H), 2.76 (dd, *J* = 7.1, 2.2 Hz, 1 H), 1.70 (br s, 1 H), 1.15-1.55 (m, 5 H), 0.84-0.96 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.9, 60.6, 57.3, 36.5, 34.9, 19.8, 15.5, 14.0; HRMS (EI) *m/z* 145.1229 [$(M+H)^+$, calcd. for $C_8H_{17}O_2$, 145.1228].

Preparation of V-24. To a solution of 251 mg (1.7 mmol) **V-23** in 4 mL DMSO and 10 mL was added SO_3·Py 560 mg (3.5 mmol) at 0 °C. The reaction was stirred at this temperature for 120 min before it was quenched by the addition of water. It was diluted with pentane and was extracted with Et_2O. The organic phase was washed with brine, dried over magnesium sulfate, and concentrated to give 198 mg (80%) crude product. This material was immediately used in the next reaction without further purification.

Preparation of V-16 and iso-V-16. A solution of **V-24** (195 mg, 1.37 mmol) in THF (30 mL) was cooled to 0 °C. Magnesium bromide etherate (336 mg, 1.3 mmol) was desolved in 3 mL Et_2O/3 mL benzene, and this solution was added dropwise to the aldehyde solution at 0 °C. After stirring at rt for 3-5 min the clear solution was cooled to –95 °C and the Grignard reagent isopropenyl MgBr (0.5 M in THF, 2.5 mmol) was added dropwise. The mixture was kept in a sealed dry ice bath overnight. The reaction was quenched by the addition of 1 M aq. HCl and was diluted with Et_2O. The organic phase was washed with brine, dried over magnesium sulfate, and concentrated in vaccum. ^1H NMR spectrum of the resulting residue showed that **V-16** and iso-**V-16** was formed in a 1.2 to 1 ratio. Flash chromatography (15% Et_2O in pentane) on silica gel furnished 30 mg (9%) iso-**V-06**, 62 mg (19%) **V-16,** and 78 mg (24%) mixture of the two diastereomers all as oils.

For **V-16**: IR (neat) 3449, 2961, 1716, 1653, 1456, 1379, 1242 cm^{-1}; $[\alpha]_D^{20}$ -22° (c 0.15, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.08 (m, 1 H), 4.94 (m, 1 H), 3.86 (d, *J* = 5.1 Hz, 1 H), 2.83 (dd, *J* = 5.1, 2.4 Hz, 1 H), 2.75 (dd, *J* = 7.2, 2.4 Hz, 1 H), 2.1 (br s, I H), 1.80 (s, 3 H), 1.6-1.2 (m, 5 H), 1.0-0.8 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 112.1, 74.9, 61.5, 59.5, 36.7, 35.1, 20.0, 18.9, 15.7, 14.2, HRMS (EI) *m/z* 185.1542 [$(M+H)^+$, calcd. for $C_{11}H_{21}O_2$, 185.1541].

For iso-**V-16**: $[\alpha]_D^{20}$ +5.1° (c 0.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.07 (m, 1 H), 4.96 (m, 1 H), 4.27 (d, *J* = 2.7 Hz, 1 H), 2.9-2.8 (m, 2 H), 1.79 (s, 3 H), 1.6-1.2 (m, 5 H), 1.0-0.8 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 112.9, 72.3, 59.6, 58.6, 36.7, 35.1, 20.0, 18.2, 15.8, 14.2.

Preparation of V-26. To a solution of **V-16** (22 mg, 0.12 mmol) in CH_2Cl_2 (5 mL) was added DCC (31 mg, 0.15 mmol), DMAP (2.5 mg, 0.02 mmol) and (*S*)-(+)-α-methoxyphenylacetic acid (25 mg, 0.15 mmol). After stirring at rt overnight the mixture was diluted with Et_2O and was washed with 1 N aq. HCl, brine, dried over magnesium sulfate, and concentrated in vacuum. The resulting residue was chromatographed (10% Et_2O in pentane) on silica gel to afford **V-26** (24 mg, 61%) as a colorless oil. $[\alpha]_D^{20}$ +76° (c 0.24, $CHCl_3$); IR (neat) 2930, 1755, 1456, 1172, 1116 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.5-7.2 (m, 5 H), 4.87 (d, *J* = 6.9 Hz, 1 H), 4.81 (s, 1 H), 4.72 (m, 1 H), 4.60 (m, 1 H), 3.41 (s, 3 H), 2.84 (dd, *J* = 6.9, 2.4 Hz, 1 H), 2.64 (dd, *J* = 7.2, 2.4 Hz, 1 H), 1.56 (s, 3 H), 1.6-1.1 (m, 5 H), 1.0-0.8 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 139.7, 136.1, 128.8, 128.6, 127.4, 113.4, 82.3, 78.2, 61.6, 57.4, 56.9, 36.6, 35.1, 20.0, 19.1, 15.7, 14.2, HRMS (EI) *m/z* 333.2066 [$(M+H)^+$, calcd. for $C_{20}H_{29}O_4$, 333.2067].

Preparation of V-25. This compound was prepared by the same method as **V-26**, using 34 mg (0.19 mmol) **V-06** and 40 mg (0.24 mmol) (*R*)-(-)-α-methoxyphenylacetic acid. Silica gel chromatography (10% Et_2O in pentane) afforded **V-25** (49 mg, 80%) as a

colorless oil. $[\alpha]_D^{20}$ -56° (c 0.29, $CHCl_3$); IR (neat) 2959, 1757, 1456, 1172, 1116 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.5-7.2 (m, 5 H), 5.06 (d, *J* = 5.4 Hz, 1 H), 4.99 (m, 1 H), 4.93 (m, 1 H), 4.82 (s, 1 H), 3.44 (s, 3 H), 2.85 (dd, *J* = 5.4, 2.1 Hz, 1 H), 2.30 (dd, *J* = 7.2, 2.1 Hz, 1 H), 1.76 (s, 3 H), 1.5-1.1 (series of m, 5 H), 0.86 (t, *J* = 6.9 Hz, 3 H), 0.77 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 140.2, 136.1, 128.8, 128.6, 127.1, 113.8, 82.6, 76.8, 60.7, 57.4, 57.0, 36.5, 35.0, 19.8, 19.4, 15.6, 14.2, HRMS (EI) *m/z* 333.2064 [$(M+H)^+$, calcd. for $C_{20}H_{29}O_4$, 333.2067].

Preparation of V-27. To a solution of **V-26** (11 mg, 0.06 mmol) in CH_2Cl_2 (5 mL) was added DCC (21 mg, 0.10 mmol), DMAP (2.5 mg, 0.02 mmol) and (*Z*)-**V-04** (22 mg, 0.10 mmol). After stirring at rt overnight the mixture was diluted with Et_2O and was washed with 1 N aq. HCl, brine, dried over magnesium sulfate, and concentrated in vacuum. The resulting residue was chromatographed (10% Et_2O in pentane) on silica gel to afford **V-27** (12 mg, 54%) as a colorless oil. $[\alpha]_D^{20}$ -6° (c 0.2, $CHCl_3$); IR (neat) 2959, 1704, 1628, 1169 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.39 (d, *J* = 1.8 Hz, 1 H), 5.07(s, 1 H), 5.00 (s, 1 H), 4.95 (s, 1 H), 2.93 (dd, *J* = 6.6, 1.8 Hz, 1 H), 2.75 (d, *J* = 1.5 Hz, 3 H), 2.71 (dd, *J* = 7.2, 1.8 Hz, 1 H), 1.82 (s, 3 H), 1.6-1.2 (series of m, 6 H), 1.0-0.8 (m, 6 H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 163.1, 140.3, 125.1, 114.7, 113.8, 77.6, 61.5, 57.2, 36.7, 36.6, 35.2, 20.0, 19.5, 15.8, 14.2, HRMS (EI) *m/z* 379.0770 [$(M+H)^+$, calcd. for $C_{15}H_{25}O_3I$, 379.0769].

Preparation of V-30. A solution of **V-22** (2.29 g, 17.9 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C and 40 mL DMSO was added followed by 5.6 mL TEA (40 mmol). SO_3 pyridine complex (6 g, 37 mmol) was then added in small portions. After 3 h stirring at 0 °C the reaction was quenched by the addition of 10% HCl. The layers were separated and the aq. phase extracted with ether (20 mL X 2). The organic phases were combined, and washed with 10% HCl, brine, dried over $MgSO_4$, and concentrated. Chromatography (silica gel, 20% ether in hexanes, 1% TEA buffered) afforded the desired product **V-30**

(1.98 g, 88%) as a oil. $[\alpha]_D^{20}$ +27.7° (c 0.82, $CHCl_3$); IR (neat) 2932 (s), 1738 (s), 1687 (s), 1458 (s), 1373 (s), 1240 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.4 (d, *J* = 7.7 Hz, 1H), 6.7 (ABq, *J* = 15.6, 7.4 Hz, 1 H), 6.0 (ABq, *J* = 15.6, 7.9 Hz, 1 H), 2.4 (9, *J* = 6.6 Hz, 1 H), 1.0 (m, 6 H), 0.8 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.3, 164.3, 131.2, 38.0, 36.7, 20.2, 19.1, 14.0, HRMS (EI) *m/z* 126.1041 [$(M+H)^+$, calcd. for $C_8H_{15}O$, 126.1045].

Preparation of V-31. To a –15 °C solution of N-acyl oxazolidinone (7.8 g, 33.5 mmol) in CH_2Cl_2 (50 mL) was added di-*n*-butylboryl triflate (36.8 mL of a 1 M in THF soln., 36.8 mmol) dropwise via syringe pump. After 5 min freshly distilled TEA (5.6 mL, 40 mmol) was added dropwise via syringe pump. The reaction temperature was maintained at 0 °C for 45 min. The solution was cooled to –78 °C and **V-30** (3.9 g, 31 mmol) in CH_2Cl_2 (50 mL) was added dropwise. The reaction was then stirred at –75 °C overnight. The reaction was quenched by the addition of pH 7 phosphate buffer (30 mL) followed by 150 mL MeOH. After 15 min 30 mL of 30% H_2O_2 in 30 mL MeOH was added and the resulting mixture was stirred at 0 °C for 1 h. The mixture was extracted with CH_2Cl_2 (50 mL X 3) and the combined extracts were washed with 5% $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated to yield a yellow oil. Silica gel chromatography (1:3 EtOAc:hexanes) furnished the desired product **V-31** (8.2 g, 74% yield) as a colorless oil. $[\alpha]_D^{20}$ +18.5° (c 0.465, $CHCl_3$); IR ($CDCl_3$) 3537 (m), 3155 (s), 3020 (m), 2961 (s), 1782 (s), 1697 (s), 1458 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45-7.20 (m, 5 H), 5.66 (d, *J* = 7.8 Hz, 1 H), 5.65 (ddd, *J* = 15.9, 7.8, 1.2 Hz, 1 H), 5.40 (ddd, *J* = 15.3, 6.9, 0.9 Hz, 1 H), 4.78 (p, *J* = 6.7 Hz, 1 H), 4.41 (m, 1 H), 3.82 (m, 1 H), 2.80 (br s, 1 H), 2.76 (d, *J* = 3.0 Hz, 1 H), 2.15 (m, 1 H), 1.25 (m, 4 H), 1.19 (d, *J* = 6.9 Hz, 3 H), 0.9 (d, *J* = 6.3 Hz, 3 H), 0.8 (d, *J* = 6.6 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 152.7, 139.1, 133.0, 128.8, 128.7, 127.0, 125.6, 78.9, 72.7, 54.8, 42.8, 39.0, 36.1, 20.5, 20.4, 14.3, 14.1, 10.9; HRMS (EI) m/z 359.2088 [$(M)^+$; calcd. for $C_{21}H_{29}NO_4$: 359.2097].

Preparation of V-32. To a solution of **V-31** (114 mg, 0.32 mmol) in THF (10 mL) was added dropwise 0.03 mL acetic acid (0.48 mmol) followed by 0.35 mL of Bu_3B (1 M in THF, 0.35 mmol). This mixture was stirred at rt for 1.5 h. The reaction was cooled to 0 °C and $LiBH_4$ (0.4 mL, 2 M in THF, 0.8 mmol) was added dropwise. The reaction was stirred at 0 °C for 6 h. Then 1.2 mL MeOH, 0.6 mL pH 7 buffer was added, followed by 0.6 mL of 30% H_2O_2. The reaction was stirred for 12 h at rt and extracted with CH_2Cl_2 (5 x 15 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, and concentrated. Chromatography (50% EtOAc in hexanes) afforded **V-32** (52 mg, 88%) as a oil. $[\alpha]_D^{20}$ +15.6° (c 1.9, $CHCl_3$); IR (neat) 3360 (br s), 2959 (s), 2874 (s), 1728 (m, 1458 (m), 1379 (m), 1288 (m), 1032 (m) 972 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.5 (m, 2 H), 4.2 (m, 1 H), 3.6 (m, 2 H), 2.4 (br s, 2 H), 2.1 (m, 1 H), 1.9 (m, 1 H), 1.2 (m, 4 H), 0.96 (d, J = 6.9 Hz, 3 H), 0.86 (t, J = 6.9 Hz, 3 H), 0.84 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 127.8, 76.1, 66.2, 39.8, 39.0, 36.2, 20.5, 20.3, 14.1, 11.5; HRMS (EI) *m/z* 185.1540 [$(M-H)^+$, calcd. for $C_{11}H_{21}O_2$, 185.1541].

Preparation of V-33. To a solution of **V-32** (52 mg, 0.28 mmol) in 15 mL CH_2Cl_2 was added 65 mg tosyl chloride (0.34 mmol) followed by 0.05 mL TEA (0.35 mmol), and a catalytic amount of DMAP. The solution was stirred at rt overnight. It was then diluted with 50 mL CH_2Cl_2 and washed with 10% HCl, water and brine. The organic phase was dried over $MgSO_4$ and concentrated. Chromatography (25% EtOAc/hexane) afforded 49 mg **V-33** (67%) as an oil. 12 mg of compound **V-32** (23%) was recovered. $[\alpha]_D^{20}$ +3.4° (c 1.5, $CHCl_3$); IR (neat) 3547 (br s), 2959 (s), 1599 (s), 1458 (s), 1359 (s), 1176 (s), 968 (s), 814 (s), 667 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.7 (d, J = 8.1 Hz, 2 H), 7.3 (d, J = 8.1 Hz, 2 H), 5.47 (dd, J = 15.6, 7.8 Hz, 1 H), 5.34 (dd, J = 15.6, 6.6 Hz, 1 H), 4.0 (m, 2 H), 3.89 (m, 1 H), 2.44 (s, 3 H), 2.0 (m, 1 H), 1.91 (m, 1 H), 1.46 (d, J = 4.2 Hz, 1 H), 1.23 (m, 4 H), 0.92 (d, J = 6.6 Hz, 3 H), 0.87 (d, J = 6.6 Hz, 3 H), 0.86 (t, J = 5.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 139.1, 132.9, 129.8,

128.0, 127.8, 72.3, 72.28, 38.9, 38.5, 36.1, 21.6, 20.4, 20.36, 14.1, 10.8, HRMS (EI) *m/z* 341.1782 [$(M+H)^+$, calcd. for $C_{18}H_{29}O_4S$, 341.1787].

Preparation of V-28. To a solution of **V-33** (4.02 g, 11.8 mmol) in CH_2Cl_2 (50 mL) was added TEA (2.8 mL, 20 mmol) at 0 °C followed by 4.8 g TBSOTf (18 mmol) and the solution was stirred at rt for 4 h. The reaction was quenched with 10% HCl and diluted with 100 mL CH_2Cl_2. The organic phase was washed with 10% HCl, water and brine, dried over $MgSO_4$ and concentrated. Silica gel chromatography (10% EtOAc/hexanes) furnished 5.45 g **V-28** (quant. yield) as colorless oil. $[\alpha]_D^{20}$ +10.4 (c 1.42, $CHCl_3$); IR (neat) 2959 (s), 2930 (s), 2858 (s), 1599 (m), 1464 (s), 1367 (s), 1251 (2), 1178 (s), 1097 (s), 972 (s), 837 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 9.0 Hz, 2 H), 7.30 (d, *J* = 9.0 Hz, 2 H), 5.35 (dd, *J* = 16.2, 8.7 Hz, 1 H), 5.22 (dd, *J* = 16.2, 6.9 Hz, 1 H), 4.01 (m, 2 H), 3.80 (dd, *J* = 9.3, 6.9 Hz, 1 H), 2.42 (s, 3 H), 2.01 (m, 1 H), 1.82 (m, 1 H), 1.22 (m, 4 H), 0.90 (d, *J* = 6.9 Hz, 3 H), 0.84 (d, *J* = 6.9 Hz, 3 H), 0.83 (t, *J* = 6.9 Hz, 3 H), 0.79 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 138.2, 133.0, 129.7, 128.5, 127.9, 73.3, 72.6, 39.8, 38.9, 36.0, 25.7, 21.6, 20.5, 20.4, 18.0, 14.1, 11.4, -4.0, -5.1, HRMS (EI) *m/z* 453.2488 [$(M-H)^+$, calcd. for $C_{24}H_{41}O_4SSi$, 453.2495].

Preparation of V-34. In a glove bag purged with nitrogen, 1.54 g lithium acetylide ethylene diamine complex (16.7 mmol) was placed in a round bottom flask and 8 mL DMSO was added. The suspension was well stirred while 2.95 g neat **V-28** (6.5 mmol) was added dropwise. TLC indicated product forming after 30 min, and the reaction was complete after 6 h. The reaction mixture was diluted with 50 mL diethyl ether and washed with 10% HCl, water, and brine. The organic layer was dried over $MgSO_4$ and concentrated. Chromatography (100% hexanes) furnished 1.74 g **V-34** (86%) as a colorless oil. $[\alpha]_D^{20}$ +13.7 (c 0.903, $CHCl_3$); IR (neat) 3316 (s), 2959 (s), 2858 (s), 1471 (s), 1251 (s), 1030 (s), 837 (s), 775 (s), 630 (s); ^1H NMR (300 MHz, $CDCl_3$) δ 5.36 (ABd, Δ = 39.6 Hz, *J* = 15.6, 6.8 Hz, 2 H), 4.03 (dd, *J* = 4.7, 6.6 Hz, 1 H), 2.32 (dd,

J = 6.3, 3.3 Hz, 1 H), 2.27 (dd, J = 5.7, 3.3 Hz, 1 H), 2.11 (p, J = 6.6 Hz, 1 H), 1.92-2.04 (m, 1 H), 1.7 (p, J = 6.9 Hz, 1 H), 1.20-1.21 (m, 4 H), 0.96 (d, J = 6.6 Hz, 3 H), 0.94 (d, J = 6.6 Hz, 3 H), 0.84-0.90 (m, 3 H), 0.88 (s, 9 H), 0.03 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 129.3, 75.7, 68.8, 39.6, 39.1, 36.0, 25.8, 22.0, 20.6, 20.3, 18.2, 14.4, 14.1, -4.1, -4.9, HRMS (EI) *m/z* 309.2619 [$(M+H)^+$, calcd. for $C_{19}H_{37}OSi$, 309.2614].

Preparation of V-35. To a mixture of 191 mg **V-34** (0.62 mmol) and 0.43 mL freshly distilled allyl bromide (5 mmol) was added 143 mg indium metal (1.24 mmol). 0.7 mL THF was added and the flask was purged with nitrogen and sonicated for 5.5 h. The metal dissolved within 5 min. The reaction mixture was diluted with 50 mL diethyl ether and washed with 1 M HCl, water, and brine. The organic phase was dried over $MgSO_4$, and concentrated. Silica gel chromatography (hexanes) furnished 184 mg **V-35** (85%) as a colorless oil. $[\alpha]_D^{20}$ +19.4 (c 0.45, $CHCl_3$); IR (neat) 2959 (s), 1643 (s), 1402 (s), 1251 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72-5.90 (m, 1 H), 5.24-5.44 (m, 2 H), 4.97-5.10 (m, 2 H), 4.77 (s, 1 H), 4.73, (s, 1 H), 3.86 (dd, J = 4.4, 5.8 Hz, 1 H), 2.62-2.80 (m, 2 H), 2.27 (dd, J = 9.3, 19.1 Hz, 1 H), 2.05-2.17 (m, 1 H), 1.58-1.74 (m, 2 H), 1.17-1.37 (m, 4 H), 0.95 (d, J = 6.8 Hz, 3 H), 0.83-0.91 (m, 12 H), 0.77-0.83 (m, 3 H), 0.02 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 137.5, 136.5, 129.8, 116.0, 111.3, 77.5, 40.4, 39.3, 39.2, 37.8, 36.1, 25.9, 20.7, 20.4, 18.2, 14.6, 14.2, -4.0, -4.8, HRMS (EI) *m/z* 351.3059 [$(M+H)^+$, calcd. for $C_{22}H_{43}OSi$, 351.3083].

Through a parallel route, starting from **V-46** (Scheme 5.20), compounds iso-**V-28**, iso-**V-34**, and iso-**V-35** were prepared. These compounds differ from **V-28**, **V-34**, and **V-35** in the configuration of the allylic alcohol center.

Preparation of iso-V-28. To a solution of **V-46** (920 mg, 2.7 mmol) in 20 mL CH_2Cl_2 was added *i*-Pr_2NEt (0.7 mL, 4.0 mmol) at 0 °C followed by 0.8 g TBSOTf (3

mmol) and the solution was stirred at rt for 20 min. The reaction was quenched with 10% HCl and diluted with 100 mL CH_2Cl_2. The organic phase was washed with 10% HCl, water and brine, dried over $MgSO_4$ and concentrated. Silica gel chromatography (10% EtOAc/hexanes) furnished 0.72 g iso-**V-28** (59%) as colorless oil. $[\alpha]_D^{20}$ +0.9° (c 0.94, $CHCl_3$); IR (neat) 2959 (s), 2858(s), 1599 (s), 1464 (s), 1367 (s), 1251 (s), 1176 (s), 939 (s), 837 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 8.4 Hz, 2 H), 7.34 (d, J = 8.4 Hz, 2 H), 5.26 (ABd, Δ = 42.9 Hz, J = 15.6, 7.4 Hz, 2 H), 4.06 (ab, J = 9.6, 6.0 Hz, 1 H), 3.82-3.98 (m, 2 H), 2.45 (s, 3 H), 2.01-2.15 (m, 1 H), 1.76-1.91 (m, 1 H), 1.16-1.30 (m, 4 H), 0.95 (d, J = 6.6 Hz, 3 H), 0.78-0.91 (m, 6 H), 0.81 (s, 9 H), -0.01 (s, 3 H), -0.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 139.0, 133.0, 129.7, 129.0, 127.9, 75.0, 72.6, 39.6, 39.0, 36.2, 25.7, 20.4, 20.3, 20.0, 14.0, 13.1,-3.8, -5.0; HRMS (CI, NH_4) *m/z* 472.2910 [$(M+NH_4)^+$, calcd. for $C_{24}H_{46}NO_4SSi$, 472.2917].

Preparation of iso-V-34. In a glove bag purged with nitrogen, 266 mg lithium acetylide ethylene diamine complex (2.8 mmol) was placed in a round bottom flask and 1.2 mL DMSO was added. The suspension was well stirred while 430 mg iso-**V-28** (0.94 mmol) was added neat. The reaction was stirred overnight at rt before it was diluted with 10 mL diethyl ether and washed with 10% HCl, water, and brine. The organic layer was dried over $MgSO_4$ and concentrated. Chromatography (100% hexanes) furnished 230 mg iso-**V-34** (80%) as a colorless oil. $[\alpha]_D^{20}$ +10.3 (c 1.56, $CHCl_3$); IR (neat) 2959 (s), 2858 (s), 2174 (s), 1471 (s), 1250 (s); ^1H NMR (300 MHz, $CDCl_3$) δ 5.34 (ABd, Δ = 36.9 Hz, J = 15.6, 7.5 Hz, 2 H), 3.91 (t, J = 6.9 Hz, 1 H), 2.33 (ddd, J = 16.8, 4.8, 2.7 Hz, 1 H), 2.07-2.22 (m, 2 H), 1.96 (t, J = 2.7 Hz, 1 H), 1.66-1.78 (m, 1 H), 1.22-1.34 (m, 4 H), 0.99 (d, J = 6.9 Hz, 3 H), 0.95 (d, J = 6.9 Hz, 3 H), 0.93-0.99 (m, 3 H), 0.89 (s, 9 H), 0.06 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 129.6, 83.6, 76.9, 69.0, 39.2, 39.0, 36.3, 25.9, 22.6, 20.5, 18.1, 15.4, 14.1, -3.9, -4.9; HRMS (EI) *m/z* 309.2619 [$(M+H)^+$, calcd. for $C_{19}H_{37}OSi$, 309.2614].

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Preparation of iso-V-35. To a mixture of 458 mg iso-**V-34** (1.48 mmol) and 1.0 mL freshly distilled allyl bromide (12 mmol) was added 345 mg indium metal (3 mmol). 1.5 mL THF was added and the flask was purged with nitrogen and sonicated for 5 h at 18 °C. The metal dissolved within 7 min. The reaction mixture was diluted with 20 mL diethyl ether and washed with 1 M HCl, water, and brine. The organic phase was dried over $MgSO_4$, and concentrated. Silica gel chromatography (hexanes) furnished 420 mg iso-**V-35** (81%) as a colorless oil. $[\alpha]_D^{20}$ +17.86 (c 3.74, $CHCl_3$); IR (neat) 3078 (m), 2959 (s), 2858 (s), 1645 (s), 1462 (s), 1253 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75-5.85 (m, 1 H), 5.25-5.42 (m, 2 H), 4.99-5.12 (m, 2 H), 4.80 (s, 1 H), 4.76, (s, 1 H), 3.84 (d, *J* = 6.0 Hz, 1 H), 2.65-2.82 (m, 2 H), 2.25-2.40 (m, 1 H), 2.05-2.20 (m, 1 H), 1.62-1.78 (m, 2 H), 1.22-1.32 (m, 4 H), 0.98 (d, *J* = 6.6 Hz, 3 H), 0.90 (m, 9 H), 0.84-0.94 (m, 3 H), 0.79 (d, *J* = 6.6 Hz, 3 H), 0.04 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 137.8, 136.5, 129.6, 116.0, 111.5, 77.8, 40.3, 39.4, 39.2, 37.6, 36.4, 25.9, 20.8, 20.7, 18.2, 15.0, 14.1, -3.9, -4.8; HRMS (EI) *m/z* 351.3083 [$(M+H)^+$, calcd. for $C_{22}H_{43}OSi$, 351.3083].

Preparation of V-37. To a solution of 184 mg **V-35** (0.52 mmol) in 5 mL THF was added 1.0 mL TBAF (1.0 M in THF, 1.0 mmol) and 60 mg HOAc (1.0 mmol). The solution was stirred at rt overnight. TLC indicates the reaction was not complete. Another 1.0 mL TBAF was added and the temperature was warmed to 40 °C. The reaction was stirred for 4 h before it was diluted with Et_2O, washed with 1 N HCl and brine, dried over magnesium sulfate, and concentrated under reduced pressure. Silica gel chromatography (1-10% Et_2O in pentane) afforded 77 mg **V-37** (62%) as a yellow oil, with 55 mg **V-35** (30%) recovered. $[\alpha]_D^{20}$ +13.0° (c 0.20, $CHCl_3$); IR (neat) 3400, 2961, 1645, 1456 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75-5.91 (m, 1 H), 5.48 (ABd, Δ = 30.7 Hz, *J* = 15.8, 6.9 Hz, 2 H), 5.02-5.12 (m, 2 H), 4.83 (s, 1 H), 4.80, (s, 1 H), 3.95 (dd, *J* = 4.3, 6.1 Hz, 1 H), 2.76 (d, *J* = 7.3 Hz, 2 H), 2.07-2.37 (m, 2 H), 1.72-1.87 (m, 2 H), 1.17-1.39 (m, 4 H), 0.99 (d, *J* = 6.8 Hz, 3 H), 0.83-0.94 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$)

δ 146.6, 138.5, 136.4, 129.3, 116.1, 111.8, 76.3, 40.3, 39.4, 39.1, 36.5, 36.2, 20.6, 20.4, 14.4, 14.1; HRMS (EI) *m/z* 235.2064 [$(M-H)^+$, calcd. for $C_{16}H_{27}O$, 235.2062].

***m*-CPBA Epoxidation of V-37 (Preparation of V-38).** A solution of 104 mg **V-37** (0.44 mmol) in 10 mL CH_2Cl_2 was cooled to 0 °C. *m*-CPBA (103 mg, 0.6 mmol) was added as a fine powder. The mixture was stirred for 12 h at 0 °C before it was quenched with water. The reaction was not completed (another trail showed the reaction did not go to completion after 24 h). The reaction mixture was diluted with 50 mL diethyl ether and washed with 1M HCl, water, and brine. The organic phase was dried over $MgSO_4$, and concentrated. Silica gel chromatography (5%-15% EtOAc in hexanes) furnished 45 mg **V-38** (41%) and 14 mg iso-**V-38** (13%) as colorless oils. 12 mg **V-37** (12%) was recovered.

For **V-38**: $[\alpha]_D^{20}$ -0.4° (c 0.60, $CHCl_3$); IR (neat) 3470, 2961, 2926, 1734, 1645, 1458, 1261 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.92-5.70 (m, 1 H), 5.15-5.00 (m, 2 H), 4.82 (d, *J* = 9.89 Hz, 2 H), 3.64-3.72 (m, 2 H), 2.74 (d, *J* = 6.59 Hz, 2 H), 2.35-2.20 (m, 1 H), 2.03-1.83 (m, 2 H), 1.77 (d, *J* = 2.93 Hz, 1 H), 1.62 (br s, 1 H), 1.48-1.10 (m, 5 H), 1.00 (d, *J* = 6.59 Hz, 3 H), 0.97-0.81 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.9, 136.2, 116.3, 112.3, 71.4, 60.2, 59.2, 40.3, 39.8, 35.5, 35.1, 33.8, 20.1, 16.7, 14.2, 14.0; HRMS (EI) *m/z* 253.2162 [$(M+H)^+$, calcd. for $C_{16}H_{29}O_2$, 253.2168].

For iso-**V-38**: $[\alpha]_D^{20}$ -47.0° (c 0.24, $CHCl_3$); IR (neat) 3441, 2961, 1718, 1643, 1458, 1182 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.71-5.90 (m, 1 H), 5.53 (dd, *J* = 15.38, 7.14 Hz, 1 H), 5.36 (dd, *J* = 15.38, 7.69 Hz, 1 H), 5.07-5.13 (m, 2 H), 4.37 (t, *J* = 7.41 Hz, 1 H), 3.31-3.51 (m, 2 H), 2.29-2.57 (m, 2 H), 2.08-2.23 (m, 1 H), 1.84 (dd, *J* = 12.63, 7.69 Hz, 1 H), 1.62 (br s, 1 H), 1.53 (dd, *J* = 12.63, 8.24 Hz, 1 H), 1.16-1.37 (m, 5 H), 0.97 (d, *J* = 6.59 Hz, 3 H), 0.79-0.94 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6, 134.4, 126.1, 118.0, 84.1, 83.4, 67.0, 42.3, 39.9, 39.1, 37.1, 36.1, 20.4, 20.3, 15.5, 14.1;

HRMS (CI, NH_4) *m/z* 253.2165 [$(M+H)^+$, calcd. for $C_{16}H_{29}O_2$, 253.2168].

Sharpless epoxidation of V-37 (Preparation of V-38). 4 Å Molecular sieves were added to a 25 mL round bottom flask that was then flame dried under vacuum for 5 min. After cooling under N_2, 7 mL CH_2Cl_2 was added followed by 60 µl (0.2 mmol) Ti(O-*i*Pr)$_4$. The temperature was further lowered to –20 °C before 34 µl (0.2 mmol) (-)-diethyl *D*-tartrate in 1 mL CH_2Cl_2 was added dropwise. The solution was stirred for 50 min during which the temperature slowly warmed to –5 °C. The temperature was then lowered to –40 °C and a solution of 47 mg **V-37** (0.2 mmol) in 1 mL CH_2Cl_2 was added dropwise. Upon complete addition the solution was stirred for 10 min at –25 °C. *tert*-Butyl hydroperoxide 0.1 mL (4.2 M in toluene) was added, and the mixture was stirred overnight at –20 °C before it was quenched with 1 mL saturated Na_2SO_3 aqueous solution and 1 mL saturated Na_2SO_4 aqueous solution. The reaction mixture was diluted with 10 mL diethyl ether and meso-tartraric acid was added. The mixture was then stirred for 2 h and washed with 1 M HCl, water and brine. The organic phase was dried over $MgSO_4$, and concentrated. Silica gel chromatography (10% EtOAc in hexanes) furnished 31 mg **V-38** (66%) as a colorless oil, which was spectroscopically identical to the previously prepared material.

Preparation of V-39. To a solution of 72 mg **V-37** (0.31 mmol) in 5 mL THF was added 83 mg (0.68 mmol) benzoic acid. The solution was cooled to 0 °C before 178 mg (0.68 mmol) Ph_3P was added, followed by 137 mg (0.68 mL) DIAD in 1 mL THF. The reaction was stirred at rt for 6 h, at which time TLC showed no starting material. The reaction mixture was diluted with diethyl ether and washed with 1 M HCl, water, and brine. The organic phase was dried over $MgSO_4$, and concentrated. The resulting material was passed through a short column and the crude material (**V-39**) (84 mg, 81%) was subjected to hydrolysis without further purification.

Preparation of V-40 (Hydrolysis of V-39). The crude **V-39** from above (84 mg, 0.25 mmol) was disolved in 10 mL MeOH and 1 mL sat. K_2CO_3 was added. The mixture was stirred at 60°C for 4 h. TLC showed no starting material and the formation of one major product with slightly more polarity that **V-37**. The mixture was concentrated, diluted with 10 mL diethyl ether and washed with 1M HCl, water, and brine. The organic phase was dried over $MgSO_4$ and concentrated. Silica gel chromatography (5%-15% EtOAc in hexanes) furnished 33 mg **V-40** (57%) as a colorless oil. $[\alpha]_D^{20}$ +12.8° (c 0.5, $CHCl_3$); IR (neat) 3441, 2961, 1724, 1643, 1456, 1377 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.93-5.72 (m, 1 H), 5.35-5.60 (m, 2 H), 5.01-5.17 (m, 2 H), 4.81 (d, J = 11.54 Hz, 2 H), 3.82-3.99 (m, 1 H), 2.67-2.83 (m, 2 H), 2.08-2.35 (m, 2 H), 1.71-1.94 (m, 2 H), 1.62 (br s, 1H), 1.14-1.40 (m, 4 H), 0.99 (d, J = 7.14 Hz, 3 H), 0.70-0.95 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.6, 139.5, 136.3, 128.5, 116.1, 111.7, 77.2, 40.4, 39.6, 39.1, 36.5, 36.4, 20.7, 20.5, 14.9, 14.1; HRMS (EI) *m/z* 236.2140 [$(M)^+$, calcd. for $C_{16}H_{28}O$, 236.2139].

Preparation of V-41. To a 0 °C solution of 29 mg **V-27** (0.12 mmol) in CH_2Cl_2 was added 64 mg (0.15 mmol) of Dess-Martin periodinane (Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155-4156.). TLC indicated the reaction was complete after 15 min. The mixture was diluted with 10 mL CH_2Cl_2 and washed with 1M HCl, sat. $NaHCO_3$, water, and brine. The organic phase was dried over $MgSO_4$, and concentrated to furnish 23 mg **V-41** (80%) as colorless oil. IR (neat) 2963, 1695, 1672, 1628, 1458, 983 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.78 (dd, J = 15.93, 7.69 Hz, 1 H), 6.12 (d, J = 15.93 Hz, 1 H), 5.70-5.91 (m, 1 H), 5.01-5.15 (m, 2 H), 4.79 (d, J = 18.68 Hz, 2 H), 2.90-3.07 (m, 1 H), 2.77 (d, J = 7.14 Hz, 2 H), 2.46 (dd, J = 14.83, 6.59 Hz, 1 H), 2.24-2.40 (m, 1 H), 2.02 (dd, J = 14.28, 7.69 Hz, 1 H), 1.17-1.43 (m, 4 H), 0.97-1.13 (m, 6 H), 0.90 (t, J = 7.14 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.6 152.9, 145.3, 136.1, 127.0, 116.4, 112.3, 41.6, 40.7, 39.3, 38.3, 36.6, 20.4, 19.5, 16.5, 14.0.

Preparation of V-40 (Reduction of V-41). To a solution of 33 mg **V-31** (0.14 mmol) in 10 mL MeOH was added 52 mg (0.14 mmol) $CeCl_3 \cdot 7H_2O$ and the solution was cooled to –78 °C. $NaBH_4$ 17 mg (0.4 mmol) was carefully added to the solution and the mixture was stirred for 2 h during which the temperature warmed to rt. TLC indicated the reaction was complete and two products were formed. The reaction was carefully quenched with water and the mixture was concentrated and diluted with 20 mL diethyl ether, washed with 1 M HCl, water, and brine. The organic phase was dried over $MgSO_4$, and concentrated. Silica gel chromatography (12% EtOAc in hexanes) furnished 11 mg **V-40** (34%) and 17 mg mixture (51%) of **V-40** and **V-37** (1:4.5) as colorless oils.

For **V-40**: $[\alpha]_D^{20}$ +12.8° (c 0.50, $CHCl_3$); IR (neat) 3441, 2961, 1724, 1456, 1377, 972 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.93-5.72 (m, 1 H), 5.35-5.60 (m, 2 H), 5.01-5.17 (m, 2 H), 4.81 (d, J = 11.54 Hz, 2 H), 3.82-3.99 (m, 1 H), 2.67-2.83 (m, 2 H), 2.08-2.35 (m, 2 H), 1.71-1.94 (m, 2 H), 1.62 (br s, 1 H), 1.14-1.40 (m, 4 H), 0.99 (d, J = 7.14 Hz, 3 H), 0.70-0.95 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.6, 139.5, 136.3, 128.5, 116.1, 111.7, 77.2, 40.4, 39.6, 39.1, 36.5, 36.4, 20.7, 20.5, 14.9, 14.1; HRMS (EI) *m/z* 236.2140 [$(M)^+$, calcd. for $C_{16}H_{28}O$, 236.2139].

Preparation of V-42. Molecular sieves (4 Å) were added to a 25 mL round bottom flask that was then flame dried under vaccum for 5 min. After cooling under N_2, 8 mL CH_2Cl_2 was added followed by 42 mg (0.148 mmol) Ti(O-*i*Pr)$_4$. The temperature was further lowered to –20 °C before 46 mg (0.197 mmol) (+)-diethyl *L*-tartrate in 1 mL CH_2Cl_2 was added dropwise. The solution was stirred for 50 min during which time the temperature slowly warmed to –5 °C. The temperature was lowered to –40 °C and a solution of 52 mg **V-40** (0.220 mmol) in 1 mL CH_2Cl_2 was added dropwise. Upon complete addition the solution was stirred for 10 min at –25 °C. *tert*-Butyl hydroperoxide 55 μl (4.2 M in toluene, 0.231 mmol) was added, and the mixture was stirred overnight at –20 °C before it was quenched with 0.5 mL saturated Na_2SO_3 aqueous solution and 0.5

mL saturated Na_2SO_4 aqueous solution. The reaction mixture was diluted with 10 mL diethyl ether and one drop of glycerol was added via pipette. The mixture was then stirred for 3 h, then washed with 1M HCl, water, and brine. The organic phase was dried over $MgSO_4$, and concentrated. Silica gel chromatography (10% EtOAc in hexanes) furnished 48 mg **V-42** (89%) as a colorless oil. $[\alpha]_D^{20}$ +16.7° (c 0.90, $CHCl_3$); IR (neat) 3445, 2928, 1728, 1641, 1458, 1379, 1288, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.73-5.93 (m, 1 H), 5.01-5.16 (m, 2 H), 4.84 (d, J = 9.89 Hz, 2 H), 3.69 (br s, 1 H), 2.82-2.92 (m, 2 H), 2.77 (d, J = 6.59 Hz, 2 H), 2.33-2.47 (m, 1 H), 1.83-1.99 (m, 3 H), 1.61 (br s, 1 H), 1.20-1.59 (m, 4 H), 0.83-1.00 (m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.0, 136.3, 116.3, 112.2, 72.0, 59.5, 57.9, 40.3, 39.1, 36.7, 35.2, 34.6, 20.0, 15.9, 15.0, 14.2; HRMS (EI) *m/z* 253.2165 [$(M+H)^+$, calcd. for $C_{16}H_{29}O_2$, 253.2168].

Preparation of V-47. To a solution of 262 mg (0.97 mmol) Ph_3P in 5 mL THF was added 4 Å MS followed by 202 mg (0.97 mL) DIAD at 0 °C. After about 2 min, large amounts of white precipitation formed. To this milky suspension was quickly added a premixed solution of 122 mg (0.48 mmol) **V-42** and 212 mg (*Z*)-**V-14** (0.97 mmol) in 3 mL THF. Shortly after the addition the solution turned clear. The reaction was stirred at 0 °C for 30 min before a white precipitate formed again. The reaction was stirred overnight at rt and was diluted with diethyl ether and washed with 1M HCl, water, and brine. The organic phase was dried over $MgSO_4$, and concentrated. Silica gel chromatography (1% EtOAc in hexanes) furnished 155 mg **V-47** (71%) along with 20 mg (16%) **V-42** recovered, both as colorless oils. $[\alpha]_D^{20}$ -4.5° (c 1.6, $CHCl_3$); IR (neat) 2963, 1734, 1628, 1458, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.36 (s, 1 H), 5.68-5.88 (m, 1 H), 4.98-5.12 (m, 2 H), 4.86 (s, 1 H), 4.79 (s, 1 H), 4.72 (dd, J = 6.04, 4.94 Hz, 1 H), 2.91 (dd, J = 6.59, 2.20 Hz, 1 H), 2.69-2.77 (m, 5 H), 2.64 (dd, J = 7.14, 2.20 Hz, 1 H), 2.34 (dd, J = 13.73, 4.40 Hz, 1 H), 2.01-2.16 (m, 1 H), 1.85 (dd, J = 13.73, 9.89 Hz, 1 H), 1.17-1.55 (m, 5 H), 0.82-1.01 (m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 145.0,

136.1, 125.3, 116.4, 114.2, 112.8, 77.0, 61.6, 56.5, 40.3, 39.0, 36.6, 36.6, 35.3, 33.5, 19.9, 15.8, 15.0, 14.2; HRMS (CI, CH_4) *m/z* 447.1406 [$(M+H)^+$, calcd for $C_{20}H_{32}IO_3$, 447.1396].

Preparation of V-48. To a solution of 613 mg (2.34 mmol) Ph_3P in 10 mL THF was added 473 mg (2.34 mL) DIAD at 0°C. After about 2 min, large amounts of white precipitate formed. To this milky suspension was quickly added a premixed solution of 295 mg (1.17 mmol) **V-42** and 496 mg (*E*)-**V-14** (2.34 mmol) in 5 mL THF. Shortly after the addition the solution turned clear. The reaction was stirred overnight at rt and was diluted with diethyl ether and washed with 1 M HCl, water, and brine. The organic phase was dried over $MgSO_4$, and concentrated. Silica gel chromatography (1% EtOAc in hexanes) furnished 484 mg **V-48** (93%) as a colorless oil. $[\alpha]_D^{20}$ -19.5° (c 1.46, $CHCl_3$); IR (neat) 2963, 1718, 1616, 1332, 1178, 1074 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.66-6.74 (m, 1 H), 5.71-5.91 (m, 1 H), 4.98-5.14 (m, 2 H), 4.87 (s, 1 H), 4.78 (s, 1 H), 4.62 (dd, *J* = 5.1, 6.9 Hz, 1 H), 3.01 (s, 3 H), 2.89 (dd, *J* = 6.9, 2.1 Hz, 1 H), 2.68-2.78 (m, 2 H), 2.65 (dd, *J* = 5.1, 7.2 Hz, 1 H), 2.30 (dd, *J* = 8.7, 13.8 Hz, 1 H), 1.98-2.14 (m, 1 H), 1.85 (dd, *J* = 6.9, 13.8 Hz, 1 H), 1.22-1.57 (m, 5 H), 0.86-1.03 (m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 144.9, 136.0, 131.0, 121.3, 116.4, 112.9, 61.6, 56.7, 54.1, 40.2, 39.1, 36.6, 35.2, 33.5, 31.1, 19.9, 15.8, 14.9, 14.2; HRMS (CI, CH_4) *m/z* 447.1395 [$(M+H)^+$, calcd. for $C_{20}H_{32}IO_3$, 447.1396].

Preparation of V-51. A mixture of 9.6 g D-arabitol (63 mmol), 18 g 3,3-dimethoxyl propane (136 mmol), and 0.45 g TosylOH in 65 mL DMF was slowly heated to 35 °C and stirred at that temperature for 3.5 h. TLC indicated the reaction was complete. Approximately 3 mL TEA were added and the mixture was concentrated under reduced pressure. The resulting thick oil was disolved in 200 mL diethyl ether and washed with 1 M HCl, sat. $NaHCO_3$, water, and brine. The organic phase was dried over $MgSO_4$, and concentrated to give ca. 18 g of a clear liquid (quant. yield). This material

was used in the next reaction without further purification.

Preparation of V-52. To a solution of crude **V-51** (18 g; 63 mmol) in 100 mL CH_2Cl_2 and 100 mL DMSO (both solvent were anhydrous) was added 20 mL TEA (138 mmol) at 0 °C. 20 g (123 mmol) SO_3·Py was then added in portions. TLC indicated the reaction was complete in 1 h. The mixture was diluted with 200 mL CH_2Cl_2 and washed with 1M HCl, sat. $NaHCO_3$, water and brine. The organic phase was dried over $MgSO_4$, and concentrated to give ca. 17 g of a clear liquid (quant. yield). ^{1}H NMR of this material showed that it was mainly **V-52**, with almost no aldehyde by-product. This material was used in the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.79 (t, J = 7.5 Hz, 2 H), 4.28 (t, J = 8.1 Hz, 2 H), 3.94 (dd, J = 8.1, 6.9 Hz, 2 H), 1.50-1.79 (m, 8 H), 0.81-1.01 (m, 12 H).

Preparation of V-53. To a well stirred suspension of 32.5 g Ph_3PCH_3Br (91 mmol) in 200 mL THF was added 70 mL NaHMDS (1 M in THF, 70 mmol) at 0°C. The mixture turned bright yellow. The ice bath was removed and the mixture was stirred at rt for 30 min before it was cooled down to 0 °C. A solution of 17 g **V-52** (60 mmol) in 150 mL THF was added dropwise. The reaction was stirred at 0 °C for 3 h, TLC showed no starting material remaining. The reaction mixture was filtered though a celite pad, concentrated and diluted with 100 mL diethyl ether/hexanes (1:1). More solid precipitated. The mixture was then passed though a short silica gel column and concentrated. NMR of the resulting light yellow oil showed that it was mainly **V-53**, and no terminal alkene or racemized diastereomer was observed. It was subjected to hydrolysis without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.33 (s, 1 H), 5.32 (s, 1 H), 4.54 (dd, J = 7.8, 6.6 Hz, 2 H), 4.21 (t, J = 7.5 Hz, 2 H), 3.58 (t, J = 6.0 Hz, 2 H), 1.50-1.79 (m, 8 H), 0.75-1.01 (m, 12 H).

Preparation of V-54. Crude **V-53** from above (18 g, 63 mmol) was disolved in

30 mL THF and 30 mL MeOH was added followed by 30 mL 10% HCl. The mixture was refluxed for 2 h, during which time the mixture turned homogeneous. The solution was concentrated under reduced pressure and then put under high vacuum to remove the volatiles. A thick brown oil was obtained (10 g). TLC indicated this material to be mainly one compound (**V-54**). This material was used in the next reaction without further purification.

Preparation of V-50. Crude **V-54** from above (10 g, ca. 63 mmol) was disolved in 100 mL CH_2Cl_2 and DMF (1:1) mixture. TEA (21 mL, 150 mmol) and DMAP (1.8 g, 15 mmol) were added and the solution was cooled to 0 °C. 24.3 g TIPSCl (126 mmol) was added dropwise. The reaction was stirred for 3 h, during which the temperature warmed to rt. The reaction mixture was diluted with CH_2Cl_2 and washed with 1 M HCl, water and brine. The organic phase was dried over $MgSO_4$, and concentrated. Silica gel chromatography (5-10% EtOAc in hexanes) furnished 15.1 g **V-50** (52% based on D-arabitol) and 2.7 g mono protected **V-54** (14%) both as colorless oils.

For **V-50**: $[\alpha]_D^{20}$ +18.6° (c 1.0, $CHCl_3$); IR (neat) 3443, 2866, 1464, 1385, 1248, 1107 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 5.31 (s, 2 H), 4.27 (dd, J = 8.1, 3.9 Hz, 2 H), 3.87 (dd, J = 9.6, 3.9 Hz, 2 H), 3.64 (dd, J = 9.6, 8.1 Hz, 2 H), 3.15 (br, 2 OH), 1.00-1.19 (m, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.1, 113.4, 73.4, 67.3, 17.9, 11.8; HRMS (CI) *m/z* 461.3470 [$(M-H)^+$, calcd. for $C_{24}H_{53}O_4Si_2$, 461.3482].

Preparation of V-55. *Procedure A:* To a well stirred solution of 5.4 g **V-50** (11.7 mmol) in 80 mL 3:1 mixture of THF and DMSO was added 26 mL NaHMDS (1 M in THF, 26 mmol) at 0°C, followed by 4.0 g PMBCl (26 mmol). The solution was stirred overnight during which time the temperature warmed to rt. TLC showed no starting material. The reaction mixture was quenched with water, concentrated and diluted with 100 mL diethyl ether and washed with 1 M HCl, water and brine. The organic phase was

dried over $MgSO_4$, and concentrated. Silica gel chromatography (5-10% EtOAc in hexanes) furnished 2.4 g **V-55** (29%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.24-7.30 (m, 4 H), 6.82-6.88 (m, 4 H), 5.43 (s, 2 H), 4.60 (d, J = 11.7 Hz, 2 H), 4.42 (d, J = 12.0 Hz, 2 H), 3.90-4.00 (m, 2 H), 3.81 (s, 6 H), 3.61-3.81 (m, 4 H), 1.00 (s, 42 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 144.7, 130.8, 129.2, 129.0, 113.6, 80.5, 70.4, 67.0, 55.2, 18.0, 11.9; HRMS (CI, NH_4) *m/z* 701.4627 [$(M+H)^+$, calcd. for $C_{40}H_{68}O_6Si_2$, 701.4633]..

Preparation of V-55. *Procedure B:* In a glove bag, 5 mg (15 μmol) $TrClO_4$ was added to a tared bottle. 25 mL Et_2O was added and to this well stirred suspension was added 565 mg (2 mmol) PMB trichloroacetimidate and 180 mg (0.39 mmol) **V-50**. The solution was stirred overnight before it was quenched with water, diluted with CH_2Cl_2 and washed with 1 M HCl, water and brine. The organic phase was dried over $MgSO_4$, and concentrated. Silica gel chromatography furnished 365 mg of a colorless oil. This material was mainly **V-55**, but contained inseparable inpurities. **V-55** was used in the next reaction without further purification.

Preparation of V-56. TBAF 1 mL (1 M in THF, 1 mmol) was added to a solution of crude **V-55** (see above) (365 mg, 3.4 mmol) in 8 mL THF and the solution was stirred at rt overnight. It was quenched with water and concentrated. Silica gel chromatography of the resultant material furnished 125 mg (83%) **V-56** as a viscous oil. IR (neat) 3381, 2936, 1710, 1612, 1514, 1250 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 7.26(d, J = 8.7 Hz, 4 H), 6.90 (d, J = 9.0 Hz, 4 H), 5.52 (s, 2 H), 4.59 (d, J = 11.4 Hz, 2 H), 4.31 (d, J = 11.1 Hz, 2 H), 3.91-4.01 (m, 2 H), 3.82 (s, 6 H), 3.61-3.63 (m, 4 H), 1.60 (br, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 142.7, 129.7, 129.4, 117.2, 113.9, 80.1, 77.4, 77.0, 76.6, 70.5, 65.1, 55.2; HRMS (CI, NH_4) *m/z* 406.2224 [$(M+NH_4)^+$, calcd. for $C_{22}H_{32}NO_6$, 406.2230]..

Preparation of V-58. To a solution of 1.3 g **V-56** (3.4 mmol) in 20 mL CH_2Cl_2 was added 10 mL pyridine and the solution was cooled to –78 °C. 0.42 mL PivCl (3.4 mmol) was added dropwise. The reaction was stirred for 4 h, during which time the temperature warmed to rt. The reaction mixture was diluted with CH_2Cl_2 and washed with 1 M HCl, water and brine. The organic phase was dried over $MgSO_4$, and concentrated. Silica gel chromatography (5-30% EtOAc in hexanes) furnished 900 mg **V-58** (56%), 190 mg diacylated **V-57** (10%) and 120 mg starting material **V-56** (12%) as colorless oils.

For **V-57**: IR (neat) 2968, 1728, 1612, 1514, 1464, 1251 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 8.4 Hz, 4 H); 6.84-6.89 (m, 4 H), 5.54 (s, 2 H), 4.56 (d, J = 11.7 Hz, 2 H), 4.35 (d, J = 11.1 Hz, 2 H), 4.05-4.28 (m, 6 H), 3.80 (s, 6 H), 1.21 (s, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 159.2, 142.5, 129.9, 129.3, 117.7, 113.8, 76.9, 70.6, 65.8, 55.2, 38.7, 27.2; HRMS (CI, NH_4) *m/z* 574.3378 [$(M+NH_4)^+$, calcd. for $C_{32}H_{48}O_8N$, 574.3380].

For **V-58**: $[\alpha]_D^{20}$ +73.8° (c 0.89, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 8.4 Hz, 4 H); 6.84-6.94 (m, 4 H), 5.53 (s, 2 H), 4.58 (dd, J = 11.1, 2.1 Hz, 2 H), 3.97-4.40 (series of m, 8 H), 3.81 (s, 3 H), 3.82 (s, 3 H), 2.22 (br s, 1 H), 1.21 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 159.2, 159.1, 142.5, 129.8, 129.7, 129.4, 129.2, 117.1, 113.8, 113.7, 80.0, 76.9, 70.4, 65.7, 65.1, 55.1, 38.6, 27.1.

Preparation of V-61. To a solution of 14 g (40 mmol) **V-60** in 100 mL MeOH was added a 0 °C solution of 70 mL acetic acid and 28 mL formic acid in 21 mL water. The reaction was stirred for 6 h at rt. TLC indicated that the reaction was complete. The reaction mixture was concentrated under reduced pressure. The resulting syrup was diluted with water, and Na_2CO_3 powder was added until gas evolsion ceased. The mixture was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, and

concentrated. Silica gel chromatography (30% EtOAc in hexanes) furnished 13.5 g **V-61** (quant.) as a thick syrup. This material was used in the next reaction without further purification.

Preparation of V-62. To a solution of crude **V-61** (13.5 g, 43.4 mmol) in 100 mL CH_2Cl_2 was added 6 mL pyridine and the solution was cooled to 0 °C. 5.25 g PivCl (43.5 mmol) was added dropwise. The reaction was stirred for 14 h, during which time the temperature warmed to rt. TLC indicated that the reaction complete. The reaction mixture was diluted with CH_2Cl_2 and washed with 1 M HCl, water and brine. The organic phase was dried over $MgSO_4$, and concentrated under reduced pressure to give a syrup. This material was used in the next reaction without further purification. IR (neat) 3485, 2936, 1728, 1456, 1373, 1089 cm^{-1}; HRMS (EI) *m/z* 395.2074 $[(M+H)^+$, calcd. for $C_{21}H_{31}O_7$, 395.2070].

Preparation of V-63. To a suspension of 1.76 g KH (44 mmol) in 100 mL THF was added a solution of 15 g crude **V-62** (38 mmol) in 100 mL THF at rt in 30 min. Upon complete addition, 5.44 mL BnBr (46 mmol) was added followed by catalytic amount of Bu_4NI. The reaction was stirred for 3 h at rt. The reaction mixture was quenched with 1 N HCl and extacted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, and concentrated under reduced pressure. Silica gel chromatography (20% Et_2O in hexanes) furnished 17 g **V-63** (80% from **V-60**) as a thick syrup. IR (neat) 2934, 1734, 1701, 1456, 1078 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.2-7.4 (m, 10 H), 5.93 (d, J = 3.6 Hz, 1 H), 4.3-4.8 (m, 7 H), 4.0-4.3 (m, 3 H), 1.49 (s, 3 H), 1.33 (s, 3 H), 1.24 (m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 138.2, 137.4, 127.4-128.5 (6 C), 111.8, 105.0, 81.8, 81.5, 78.6, 74.2, 71.9, 72.0, 63.3, 38.8, 27.2, 26.7, 26.3; HRMS (EI) *m/z* 485.2521 $[(M+H)^+$, calcd. for $C_{28}H_{37}O_7$, 485.2539].

Preparation of V-64. To a solution of 10 g **V-63** (20 mmol) in 200 mL MeOH

was added 3 mL concentrated H_2SO_4. The mixture was stirred for 30 h at rt. TLC indicated the reaction was complete, and two new spots appeared coresponding to the two anomers. Na_2CO_3 powder was added to the reaction mixture until no gas evolsion and the mixture was concentrated under reduced pressure. The resulted syrup was diluted with water, and was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, and concentrated to give a thick syrup. This material was used for the next reaction without further purification.

Preparation of V-65. A solution of 1.14 g (2.5 mmol) of crude **V-64** in 20 mL THF was added dropwise to a suspension of 0.1 g KH (2.5 mmol) in 30 mL THF at rt in 30 min. Upon complete addition, catalytic amount of Bu_4NI was added followed by a solution of 0.3 mL BnBr (2.5 mmol) in 10 mL THF, which was added dropwise via cannula. The reaction was stirred overnight at rt before it was quenched with 1 N HCl and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, and concentrated under reduced pressure to give 1.7 g **V-65** as a thick syrup. This material was used for the next reaction without further purification.

Preparation of V-66. A 60% aqueous TFA solution was cooled to 0 °C and poured in a solution of 1.7 g crude **V-65** in 10 mL dioxane. The mixture was stirred for 20 h at rt. TLC indicated the reaction was complete. The reaction mixture was concentrated under reduced pressure. The resulted syrup was diluted with water, and Na_2CO_3 powder was added until gas evolsion ceased. The mixture was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, and concentrated to give 0.85 g **V-66** (87%) as a thick syrup. This material was used for the next reaction without further purification.

Preparation of V-67. To a solution of 545 mg **V-66** (1 mmol) in 10 mL CH_2Cl_2 was added 1 g Ph_3P=CHCOOEt (3 mmol) and the reaction was refluxed overnight. The

reaction mixture was quenched with 1 N HCl and extacted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, and concentrated under reduced pressure. This mixture was passed though a short silica gel pad before it was purified by silica gel chromatography to give 561 mg **V-67** (91%) as an oil. $[\alpha]_D^{20}$ -0.5° (c 0.72, $CHCl_3$); IR (neat) 3503, 2974, 1728, 1454, 1284, 1165 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2-7.4 (m, 15 H), 7.00 (dd, *J* = 6.8, 15.8 Hz, 1 H), 6.15 (dd, *J* = 15.8, 1.2 Hz, 1 H), 3.5-4.9 (m, 14 H), 3.3 (br s, 1 H), 1.34 (t, *J* = 7.1 Hz, 3 H), 1.23 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.5, 165.8, 144.2, 138.0, 137.8, 137.5, 127.6-128.3 (15 C), 123.9, 80.1, 78.2, 77.0, 74.5, 71.6, 71.3, 69.4, 61.8, 60.4, 38.8, 27.1, 14.1; HRMS (EI) *m/z* 605.3114 [$(M+H)^+$, calcd for $C_{36}H_{45}O_8$, 605.3114].

Preparation of V-68. To a solution of 0.89 g **V-67** (1.47 mmol) in 25 mL CH_2Cl_2 was added 0.75 g of the Dess-Martin periodinane (Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155-4156.) (1.77 mmol) at 0°C. The reaction was stirred for 14 h, during which the temperature rised to rt. TLC indicated the reaction was complete. The reaction mixture was quenched with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, and concentrated under reduced pressure to give a syrup. Silica gel chromatography (20% EtOAc in hexanes) furnished 0.67 g **V-68** (76%) as a thick syrup. $[\alpha]_D^{20}$ +45.1° (c 1.50, $CHCl_3$); IR (neat) 2976, 1728, 1456, 1175 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2-7.5 (m, 15 H), 6.94 (dd, *J* = 6.2, 15.8 Hz, 1 H), 6.06 (dd, *J* = 15.8, 1.3 Hz, 1 H), 4.0-4.8 (m, 13 H), 1.34 (t, *J* = 7.1 Hz, 3 H), 1.20 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.2, 177.9, 165.5, 143.3, 137.2, 136.8, 136.7, 127.7-128.4 (15 C), 124.2, 82.8, 80.8, 78.3, 73.9, 72.6, 71.8, 63.2, 60.5, 38.6, 27.0, 14.1; HRMS (EI) *m/z* 603.2965 [$(M+H)^+$, calcd for $C_{36}H_{43}O_8$, 603.2958].

Preparation of V-69. To a solution of 55 mg **V-68** (0.09 mmol) in 5 mL CH_2Cl_2 was added at rt 0.7 mL (ca. 0.3 mmol) Lombardo's reagent (Lombardo, L. *Tetrahedron Lett.* **1982**, *41*, 4293-4296.). The reaction was stirred for 3 h at rt. The reaction mixture

was quenched with 1 N HCl and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, and concentrated under reduced pressure to give a syrup. Silica gel chromatography (20% EtOAc in hexanes) furnished 16 mg **V-69** (30%) as a thick syrup. $[\alpha]_D^{20}$ +49.5° (c 0.60, $CHCl_3$); IR (neat) 2976, 1724, 1454, 1280, 1159 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2-7.5 (m, 15 H), 7.00 (dd, *J* = 5.3, 15.8 Hz, 1 H), 6.11 (dd, *J* = 15.8, 1.5 Hz, 1 H), 5.63 (s, 1 H), 5.47 (s, 1 H), 3.8-4.8 (series of m, 13 H), 1.32 (t, *J* = 7.2 Hz, 3 H), 1.21 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 144.6, 142.0, 138.3, 137.8, 137.5, 127.4-128.4 (16 C), 123.4, 116.5, 80.3, 79.4, 78.2, 72.0, 71.2, 71.1, 66.1, 60.5, 38.7, 27.1, 14.2; HRMS (EI) *m/z* 601.3144 [$(M+H)^+$, calcd for $C_{37}H_{45}O_7$, 601.3165].

Preparation of V-70. To a –70 °C solution 30 mg (0.05 mmol) **V-69** in 3 mL CH_2Cl_2 was added 3 mL DIBAL (1 M in hexanes, 3 mmol). After 3 h the reaction mixture was quenched with pH 7 buffer and tartrate acid. The mix was stirred for 30 min. The mixture was extracted with CH_2Cl_2 and Et_2O. The organic phase was combined, washed with brine, dried over magnesium sulfate, and concentrated. The resulting residue was chromatographed on silica gel to afford 25 mg **V-70** as a colorless oil (quant.). $[\alpha]_D^{20}$ +57.9° (c 2.0, $CHCl_3$); IR (neat) 3420, 2924, 2864, 1454, 1068 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2-7.5 (m, 15 H), 5.90 (dt, *J* = 5.1, 15.7 Hz, 1 H), 5.75 (dd, *J* = 15.7, 6.9 Hz, 1 H), 5.57 (s, 1 H), 5.49 (s, 1 H), 3.9-4.8 (m, 11 H), 3.64 (dd, *J* = 3.7, 11.7 Hz, 1 H), 3.49 (dd, *J* = 7.2, 11.7 Hz, 1 H), 1.28 (br s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 138.2, 138.0, 133.6, 127.6-128.4 (16 C), 116.8, 80.9, 80.7, 80.4, 71.0, 70.9, 70.8, 64.8, 62.8; HRMS (EI) *m/z* 475.2485 [$(M+H)^+$, calcd. for $C_{30}H_{35}O_5$, 475.2484].

Preparation of V-71. To a solution of 0.35 g **V-70** (0.75 mmol) in 30 mL CH_2Cl_2 was added 0.16 mL pyridine (2 mmol) and the solution was cooled to 0 °C. Acetic anhydride (153 mg, 1.5 mmol) was added dropwise, followed by a catalytic amount of DMAP. The reaction was stirred for 14 h, during which time the temperature warmed to rt. The reaction mixture was diluted with CH_2Cl_2 and washed with 1 M HCl,

water, and brine. The organic phase was dried over $MgSO_4$, and concentrated under reduced pressure to give 0.51 g syrup. This material was used in the next reaction without further purification.

Preparation of V-72. To a solution of 40 mg **V-71** (0.07 mmol) in 0.1 mL DMF was added 36 mg 3-tributyltin-1-butenol (0.1 mmol) and 8.8 mg LiCl (0.21 mmol). The mixture was well stirred and $Pd(dba)_2$ 45 mg (8 μmol) was added. The reaction was stirred for 24 h at rt before it was diluted with CH_2Cl_2 and washed with 1 M HCl, water and brine. The organic phase was dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel to afford 19 mg (50%) **V-72** as a thick syrup. IR (neat) 3439, 2959, 2926, 1726, 1454, 1377, 1271, 1072 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.4-7.2 (m, 15 H), 5.45-5.85 (m, 2 H), 5.57 (s, 1 H), 5.47 (s, 1 H), 4.93 (s, 1 H), 4.89 (s, 1 H), 4.7-4.5 (m, 3 H), 4.5-3.8 (m, 6 H), 3.8-3.6 (m, 2 H), 3.62 (dd, J = 11.7, 3.9 Hz, 1 H), 3.47 (dd, J = 11.7, 7.5 Hz, 1 H), 2.7-2.9 (m, 2 H), 2.31 (t, J = 6.3 Hz, 2 H), 2.0 (s, OH, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 142.8, 138.1, 133.0, 128.5-127.5 (18 C), 116.4, 113.0, 81.4, 80.9, 80.1, 71.0, 70.9, 70.5, 65.0, 60.2, 39.1, 38.9.

Preparation of V-78. Molecular sieves (4 Å) was added to a 10 mL round bottom flask that was then flame dried under vaccum for 5 min. After cooling under N_2, 167 mg (0.59 mmol) $Ti(O\text{-}iPr)_4$ was added followed by 3 mL CH_2Cl_2. The temperature was lowered to –40 °C before 171 mg (0.73 mmol) (+)-diethyl *L*-tartrate in 1 mL CH_2Cl_2 was added dropwise. The solution was stirred for 40 min during which time the temperature slowly warmed to –5 °C. The temperature was lowered to –25 °C and a solution of 0.18 mL *tert*-butyl hydroperoxide (4.2 M in toluene, 0.75 mmol) was added dropwise. Upon complete addition the solution was stirred for 15 min at –25 °C. Then 110 mg **V-77** (0.56 mmol) in 2 mL CH_2Cl_2 was added, and the mixture was stirred overnight at –20 °C before it was quenched with 0.5 mL saturated Na_2SO_3 aqueous

solution and 0.5 mL saturated Na_2SO_4 aqueous solution. The reaction mixture was diluted with 10 mL diethyl ether and one drop of glycerol was added via a pipette. The mixture was then stirred for 3 h and washed with 1 M HCl, water, and brine. The organic phase was dried over $MgSO_4$, and concentrated. Silica gel chromatography (10% EtOAc in hexanes) furnished 100 mg **V-78** (84%) as a colorless oil. $[\alpha]_D^{20}$ -6° (c 0.28, $CHCl_3$); IR (neat) 3456, 3312, 2963, 1458, 1381, 1250, 904 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 3.71 (dd, J = 3.3, 7.3 Hz, 1 H), 2.91 (dd, J = 3.3, 2.5 Hz, 1 H), 2.82 (dd, J = 2.3, 7.3 Hz, 1 H), 2.39 (ABdd, Δ = 30.9 Hz, J = 16.8 Hz, J = 2.7, 7.3 Hz, 2 H), 2.01 (t, J = 2.7 Hz, 1 H), 1.78-1.92 (m, 1 H), 1.64 (br s, 1 H), 1.23-1.59 (m, 5 H), 1.15 (d, J = 6.9 Hz, 3 H), 0.89-1.00 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 128.7, 83.0, 76.1, 69.4, 39.0, 37.9, 36.3, 25.6, 21.8, 20.4, 15.4, 14.1; HRMS (Fab) *m/z* 193.1597 [$(M-HO)^+$, calcd for $C_{13}H_{21}O$, 193.1592].

Preparation of V-79. To a solution of 249 mg (0.95 mmol) Ph_3P in 6 mL THF was added 4 Å MS followed by 192 mg (0.95 mL) DIAD at 0 °C. After about 3 min, large amounts of white precipitation formed. To this milky suspension was quickly added a premixed solution of 94 mg (0.48 mmol) **V-78** and 201 mg (*E*)-**V-14** (0.95 mmol) in 3 mL THF. Shortly after the addition the solution turned clear. The reaction was stirred at 0 °C for 15 min before the ice bath was removed. The reaction was stirred overnight and was diluted with diethyl ether and washed with 1M HCl, water, and brine. The organic phase was dried over $MgSO_4$ and concentrated. Silica gel chromatography (2% EtOAc in hexanes) furnished 141 mg **V-79** (78%) as a colorless oil. $[\alpha]_D^{20}$ -11.4° (c 0.55, $CHCl_3$); IR (neat) 3306, 2961, 1724, 1616, 1334, 1176, 1074 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 6.88-6.71 (m, 1H), 4.79 (t, J = 6.2 Hz, 1 H), 2.98-3.05 (m, 3 H), 2.92 (dd, J = 2.3, 6.4 Hz, 1 H), 2.70 (dd, J = 2.2, 7.2 Hz, 1 H), 2.31 (ABd, Δ = 30.4 Hz, J = 17.0 Hz, J = 2.6, 5.5 Hz, 2 H), 2.10 (p, J = 5.8 Hz, 1 H), 2.01-2.06 (m, 1 H), 1.20-1.55 (series of m, 5 H), 1.14 (d, J = 6.8 Hz, 3 H), 0.95 (d, J = 6.7 Hz, 3 H), 0.91 (t, J = 7.0 Hz, 3 H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 130.8, 121.8, 81.5, 75.9, 70.4, 61.6, 56.6, 36.6, 35.2, 34.9, 31.1, 22.2, 19.9, 15.7, 15.1, 14.2; HRMS (FAB) *m/z* 405.0918 [$(M+H)^+$, calcd for $C_{17}H_{26}IO_3$, 405.0928].

Preparation of V-80. To a solution of 266 mg **V-77** (1.37 mmol) in 10 mL THF was added 1.94 mL (1.6 M in Et_2O, 3.1 mmol) *n*-BuLi at -55 °C and the solution was stirred for 15 min during which time the temperature warmed to -38°C. The temperature was cooled to -55 °C before 0.19 mL TMSCl (1.5 mmol) was added. The solution was stirred for 20 min during which time the temperature warmed to rt. The reaction was quenched with 6 mL 1 N HCl and the mixture was stirred for 4 h at rt. TLC indicated only one product had formed. The mixture was diluted with 20 mL diethyl ether, washed with 1 M HCl, water and brine. The organic phase was dried over $MgSO_4$ and concentrated. Silica gel chromatography (hexanes) furnished 330 mg **V-80** (86%), with 39 mg of a mixture of **V-77** and **V-80**, all as oils. $[\alpha]_D^{20}$ +32.4° (c 0.94, $CHCl_3$); IR (neat) 3366, 2961, 2175, 1458, 1377, 1250, 1026 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.47 (ABd, Δ = 43.6 Hz, *J* = 15.3, 7.6 Hz, 2 H), 3.97 (t, *J* = 7.1 Hz, 1 H), 2.31 (ABd, Δ = 28.0 Hz, *J* = 16.8, 7.0 Hz, 2 H), 2.09-2.21 (m, 1H), 1.81 (p, *J* = 6.8 Hz, 1 H), 1.60 (br s, 1 H), 1.21-1.38 (m, 4 H), 1.00 (d, *J* = 6.7 Hz, 3 H), 0.98 (d, *J* = 6.7 Hz, 3 H), 0.90 (t, *J* = 6.8 Hz, 3 H), 0.17 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.7, 128.7, 106.0, 85.9, 76.4, 39.1, 38.2, 36.3, 23.3, 20.6, 20.4, 15.5, 14.0, 0.1; HRMS (FAB) *m/z* 267.2140 [$(M+H)^+$, calcd for $C_{16}H_{31}OSi$, 267.2144].

Preparation of V-81. Molecular sieves (4 Å) were added to a 25 mL round bottom flask that was then flame dried under vaccum for 5 min. After cooling under N_2, 340 mg (1.2 mmol) Ti(O-*i*Pr)$_4$ was added followed by 6 mL CH_2Cl_2. The temperature was lowered to -40 °C before 351 mg (1.5 mmol) (+)-diethyl *L*-tartrate in 3 mL CH_2Cl_2 was added dropwise. The solution was stirred for 40 min during which time the temperature slowly warmed to –5 °C. The temperature was lowered to –25 °C and a

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solution of 0.38 mL *tert*-butyl hydroperoxide (4.2 M in toluene, 1.6 mmol) was added dropwise. Upon complete addition the solution was stirred for 15 min at –25 °C. Then 330 mg **V-80** (1.24 mmol) in 3 mL CH_2Cl_2 was added, and the mixture was stirred overnight at -20 °C before it was quenched with 0.5 mL saturated Na_2SO_3 aqueous solution and 0.5 mL saturated Na_2SO_4 aqueous solution. The reaction mixture was diluted with 10 mL diethyl ether and one drop of glycerol was added via a pipette. The mixture was then stirred for 3 h and washed with 1 M HCl, water, and brine. The organic phase was dried over $MgSO_4$ and concentrated. Silica gel chromatography (10% EtOAc in hexanes) furnished 237 mg **V-81** (68%) as a colorless oil. $[\alpha]_D^{20}$ -2° (c 0.2, $CHCl_3$); IR (neat) 3458, 2963, 2175, 1459, 1250, 1032 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 3.69 (dd, J = 3.1, 6.9 Hz, 1 H), 2.91 (t, J = 3.0 Hz, 1 H), 2.82 (dd, J = 2.4, 7.4 Hz, 1 H), 2.41 (ABd, Δ = 30.2 Hz, J = 16.8, 7.2 Hz, 2 H), 2.05 (br s, 1 H), 1.80-1.95 (m, 1 H), 1.22-1.57 (m, 5 H), 1.13 (d, J = 6.9 Hz, 3 H), 0.89-1.00 (m, 6 H), 0.17 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 105.3, 86.4, 71.3, 59.5, 58.0, 36.7, 36.5, 35.1, 23.4, 20.0, 15.9, 15.2, 14.2, 0.1; HRMS (FAB) *m/z* 283.2096 [$(M+H)^+$, calcd for $C_{16}H_{31}O_2Si$, 283.2093].

Preparation of V-82. To a solution of 325 mg (1.24 mmol) Ph_3P in 10 mL THF was added 4 Å MS followed by 250 mg (1.24 mL) DIAD at 0°C. Upon complete addition, large amounts of white precipitate formed. To this milky suspension was quickly added a premixed solution of 219 mg (0.77 mmol) **V-81** and 210 mg (*E*)-**V-14** (1.0 mmol) in 6 mL THF. Shortly after the addition the solution turned clear. The reaction was stirred at 0 °C for 15 min before the ice bath was removed. The reaction was stirred overnight and was diluted with diethyl ether and washed with 1 M HCl, water, and brine. The organic phase was dried over $MgSO_4$ and concentrated. Silica gel chromatography (2% EtOAc in hexanes) furnished 278 mg **V-82** (75%) as colorless oil. $[\alpha]_D^{20}$ -7.3° (c 1.55, $CHCl_3$); IR (neat) 2961, 2175, 1726, 1616, 1458, 1332, 1250, 1176, 1074 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.62-6.70 (m, 1 H), 4.70 (t, J = 6.3 Hz, 1 H),

2.7 (s, 3 H), 2.88 (dd, J = 1.5, 6.6 Hz, 1 H), 2.66 (dd, J = 1.5, 6.9 Hz, 1 H), 2.31 (ABd, Δ = 33.9 Hz, J = 17.1, 6.6 Hz, 2 H), 2.04 (p, J = 6.3 Hz, 1 H), 1.15-1.55 (m, 5 H), 1.08 (d, J = 6.9 Hz, 3 H), 0.93 (d, J = 6.6 Hz, 3 H), 0.89 (t, J = 6.9 Hz, 3 H), 0.13 (m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 130.9, 121.4, 104.1, 86.9, 76.4, 61.7, 56.5, 36.6, 35.2, 35.0, 31.1, 23.5, 19.9, 15.7, 15.2, 14.1, 0.0; HRMS (FAB) *m/z* 477.1320 [$(M+H)^+$, calcd for $C_{20}H_{34}IO_3Si$, 477.1324].

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36. While the retro-Brook sequence only gave 21% of the desired α-hydroxysilane, 67% of the silylether was also recovered. Presumably this material could be recycled, however no attempt to optimize the process was made.

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38. Although we have no direct evidence of any *O*-silyl products, the 1,3-silyl migration probably takes place via Brook rearrangement (ref. 19) of **III-24** followed by rearrangement of the resulting homoenolate. For similar examples see (a) Kuwajima, I. *J. Organomet. Chem.* **1985**, *285*, 137-148. (b) Still, W. C. *J. Org. Chem.* **1976**, *41*, 3063-3064.

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CHAPTER 4

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CHAPTER 5

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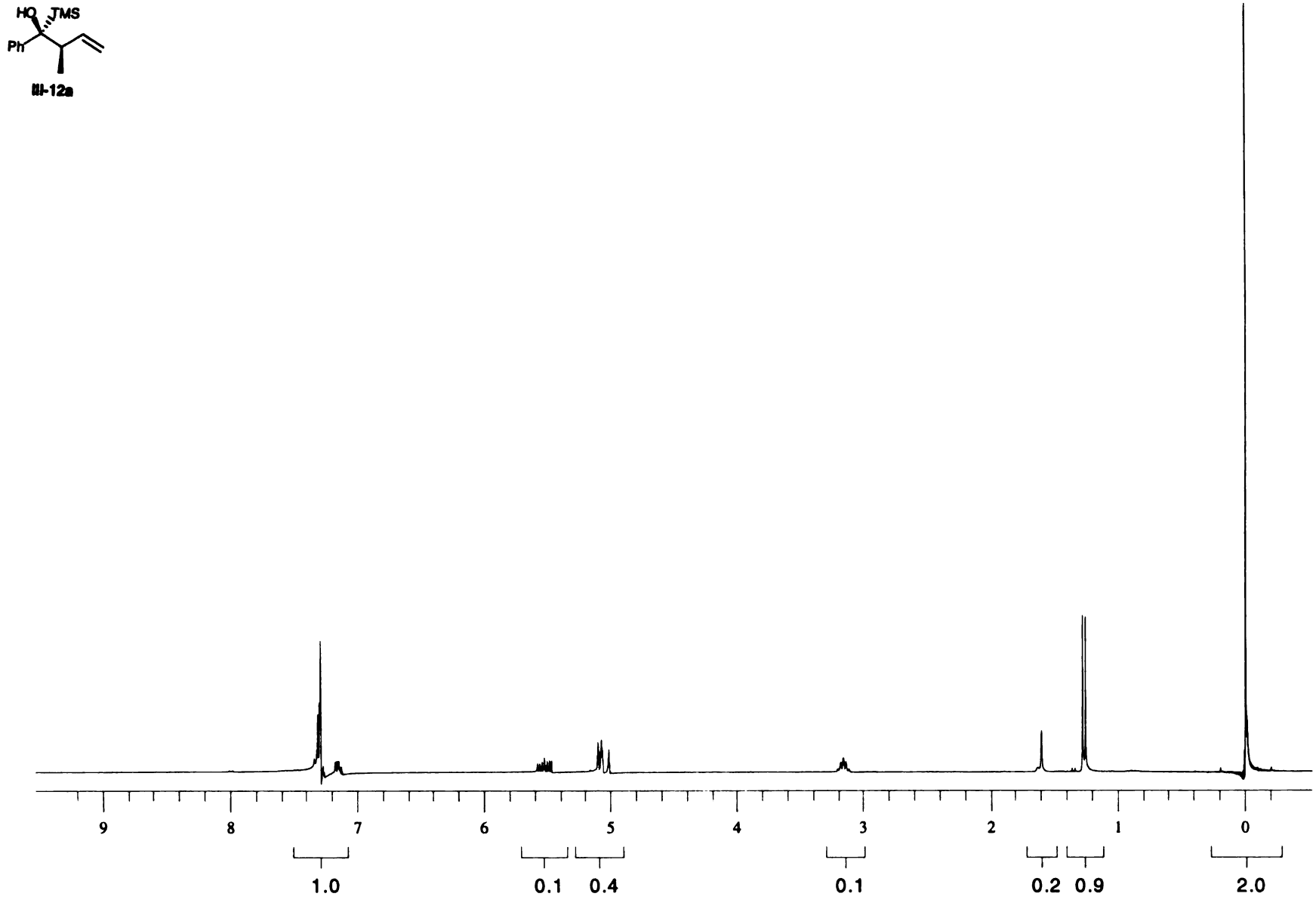
APPENDICES

APPENDIX 1

NMR SPECTRA OF NEW COMPOUNDS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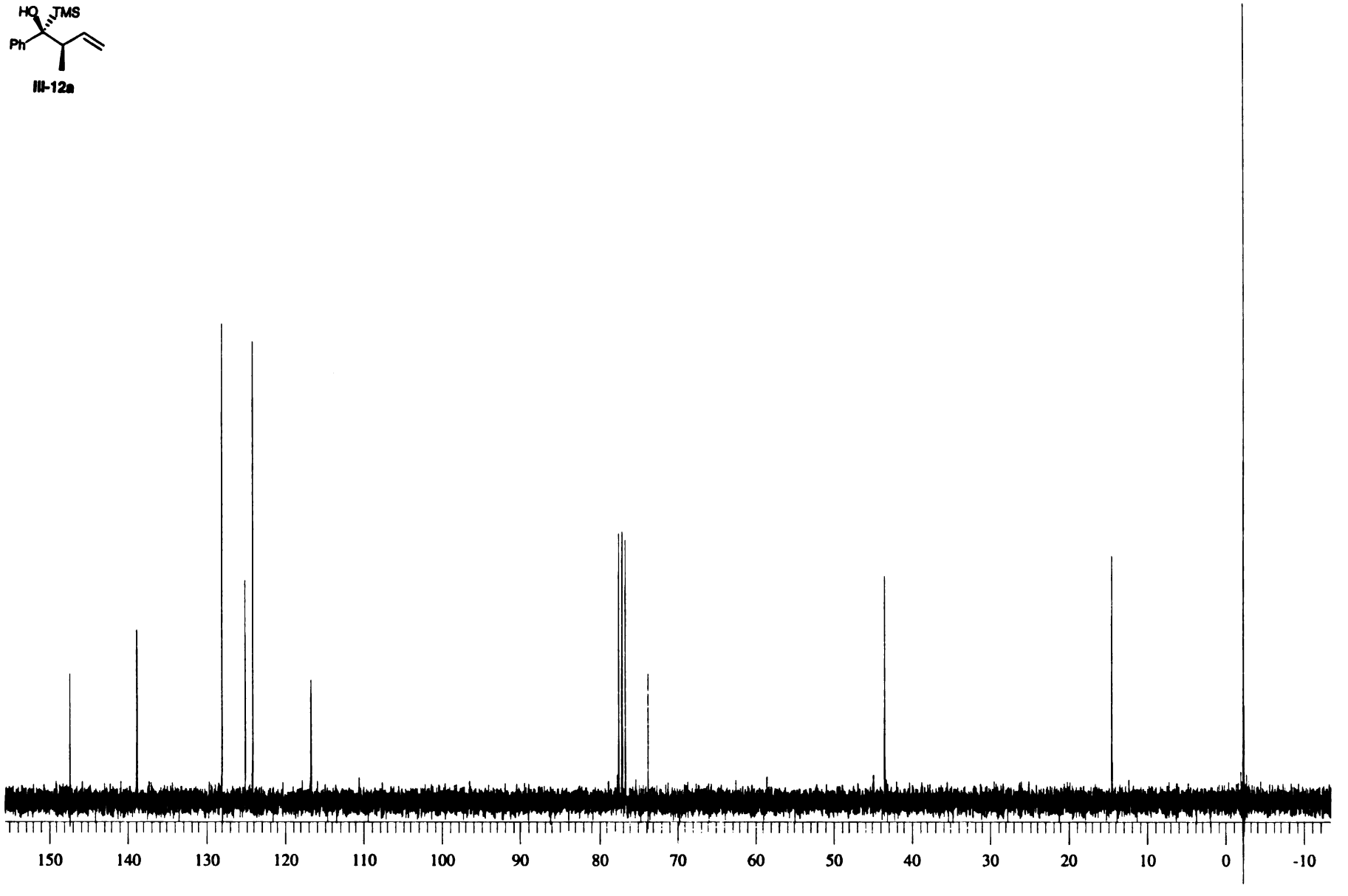
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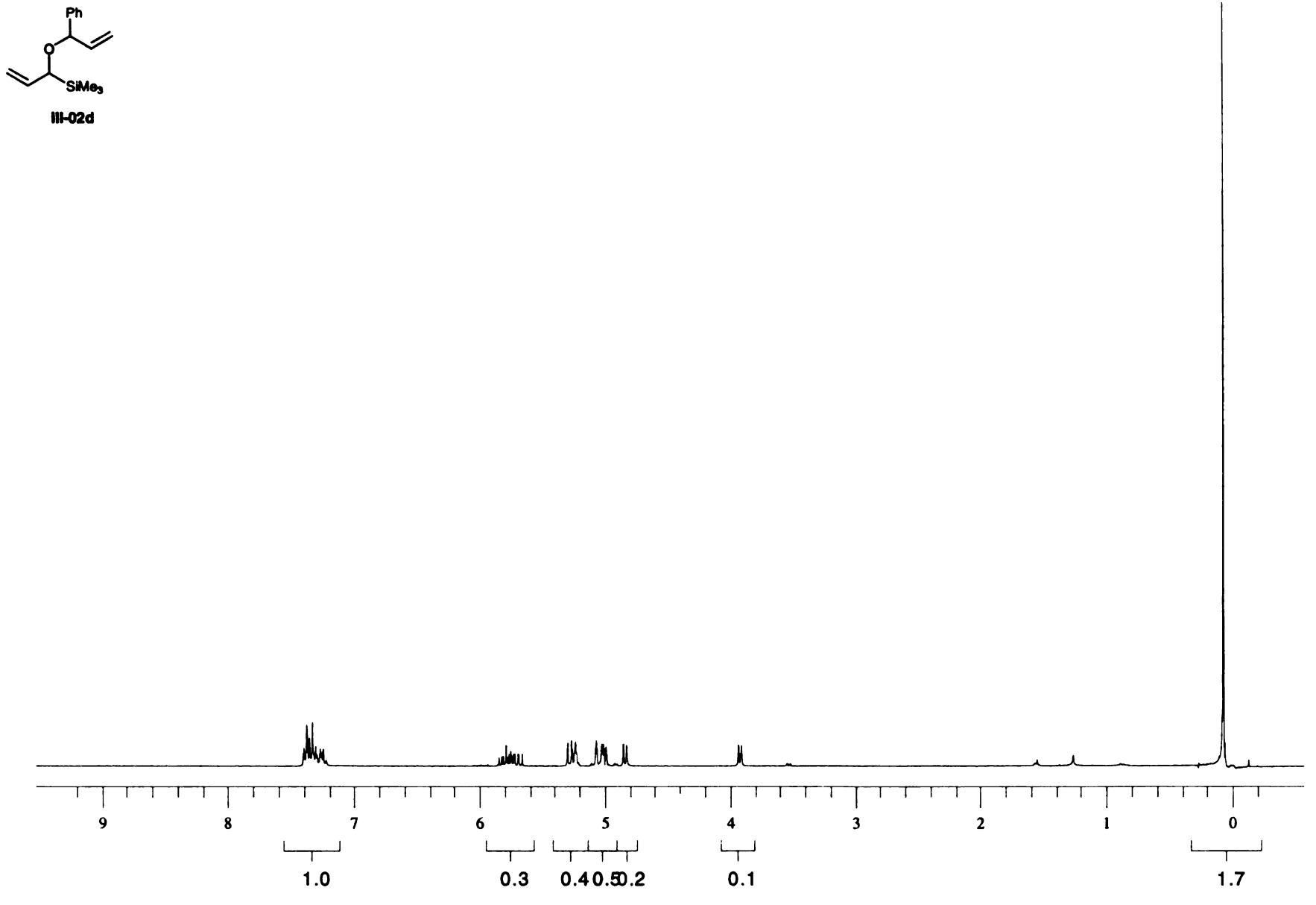
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0.1
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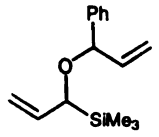

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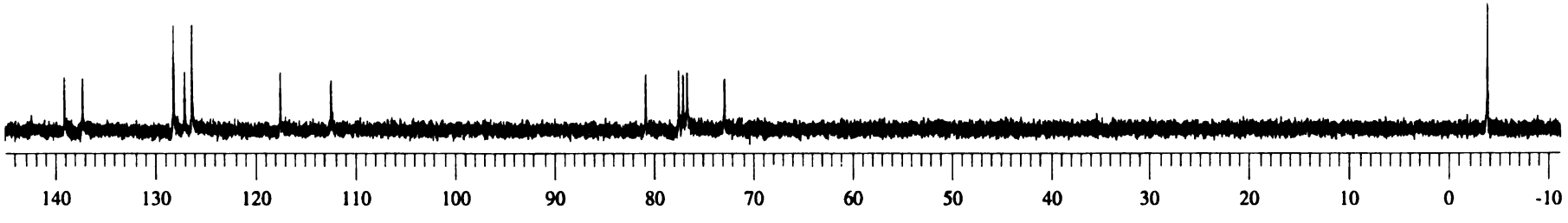

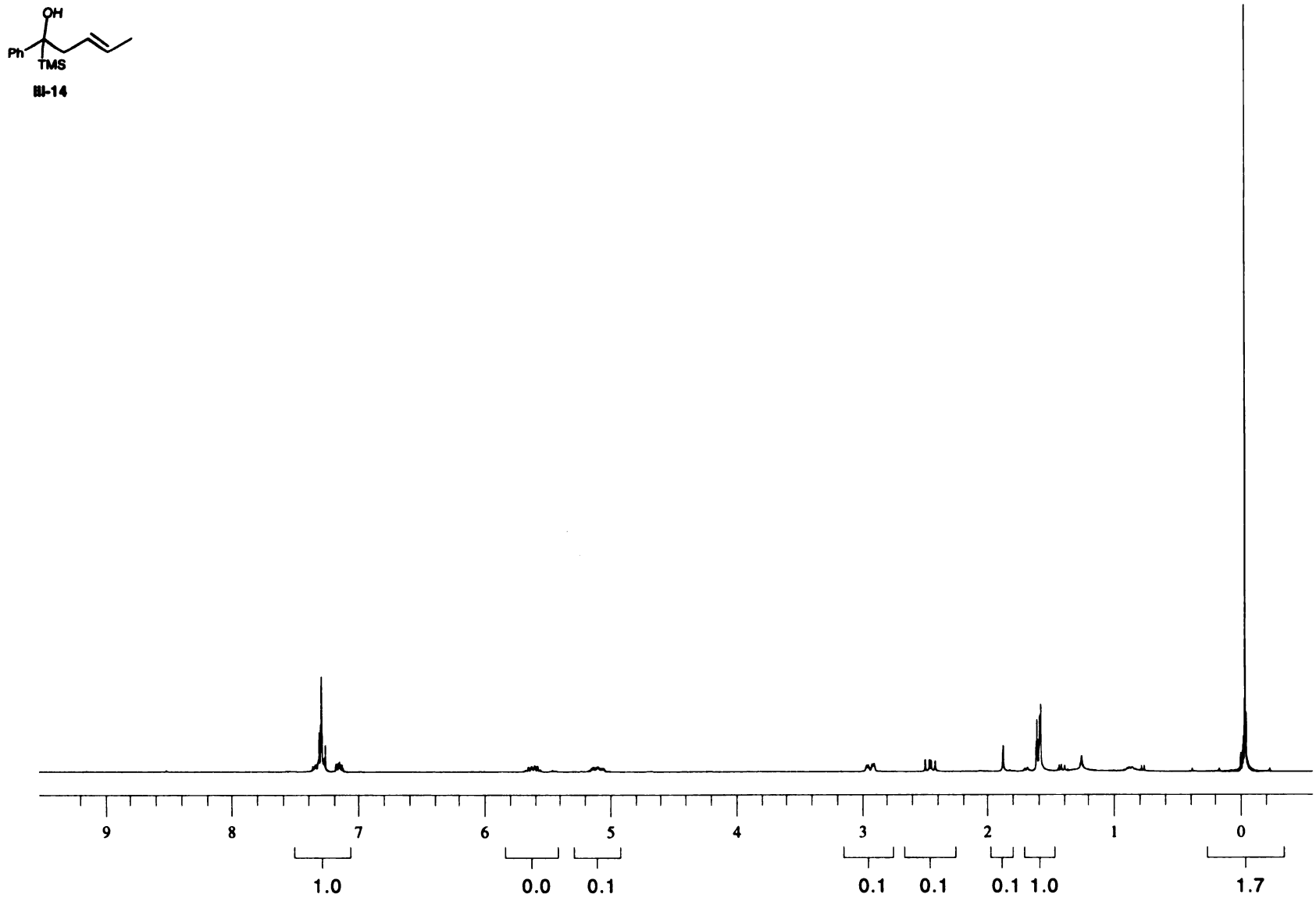
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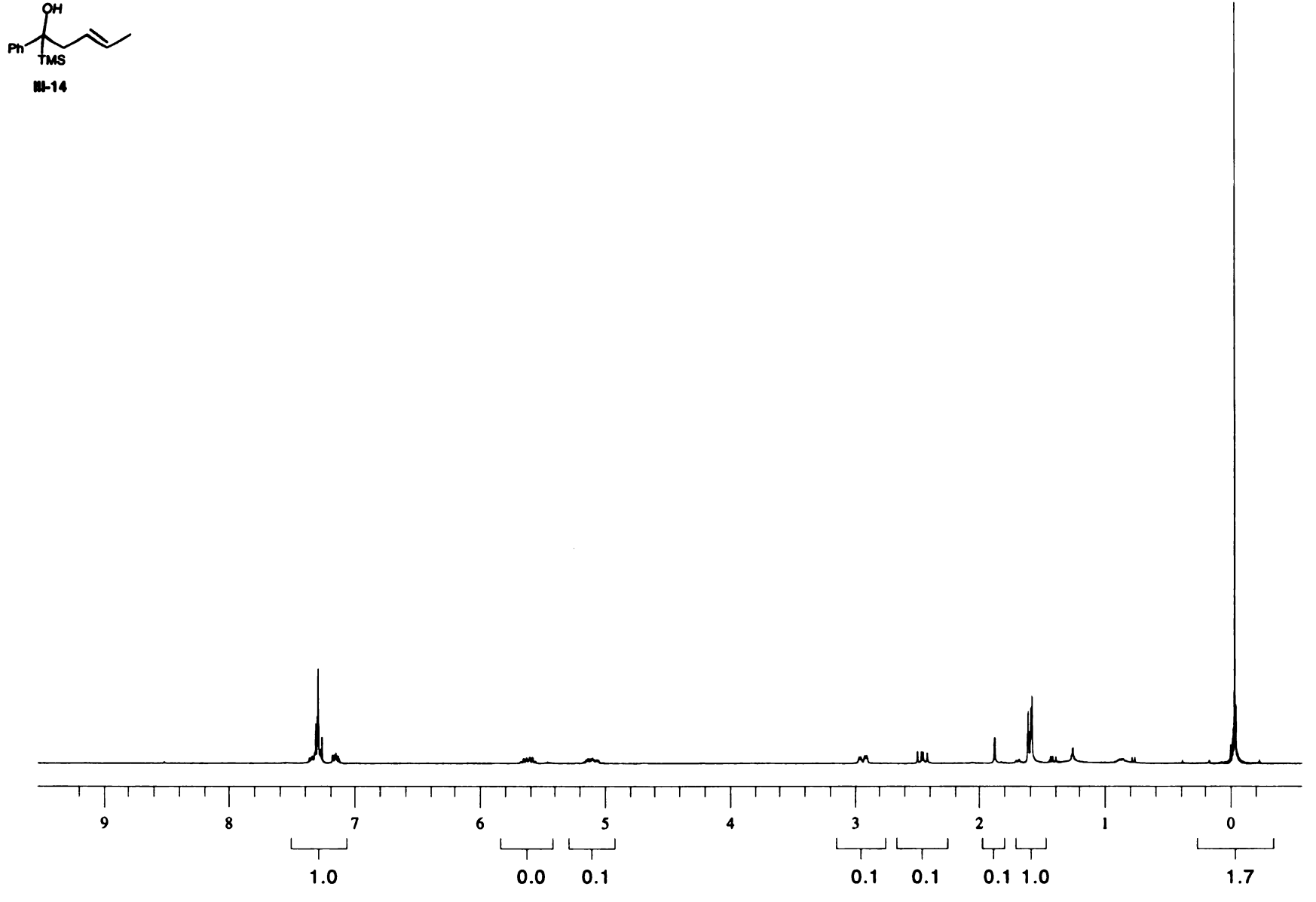
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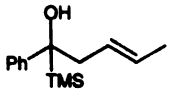

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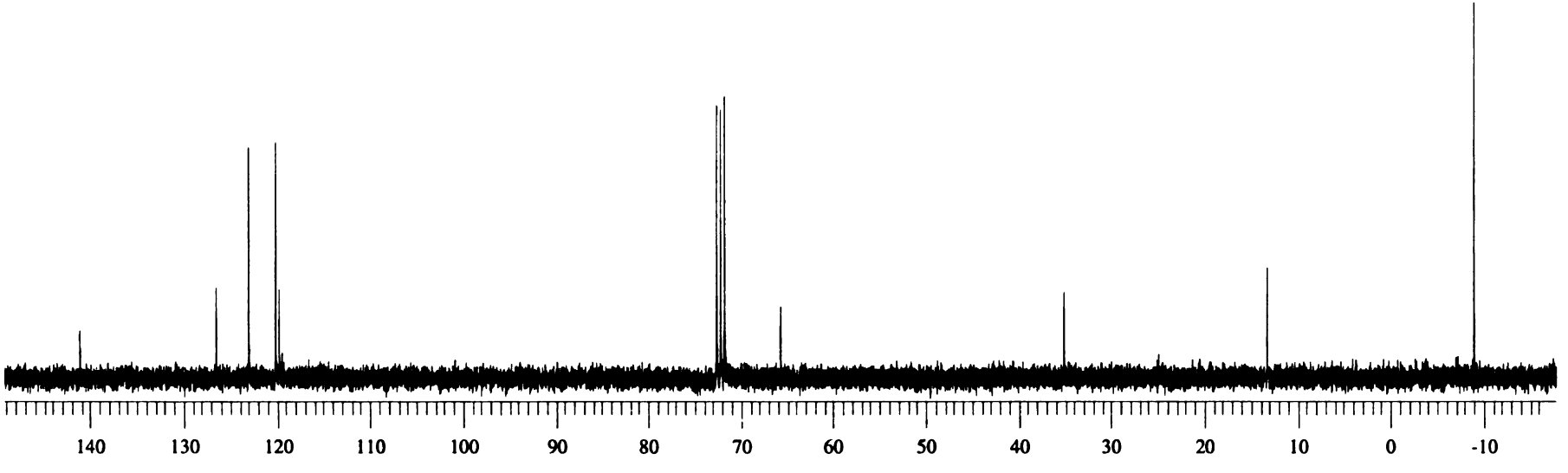

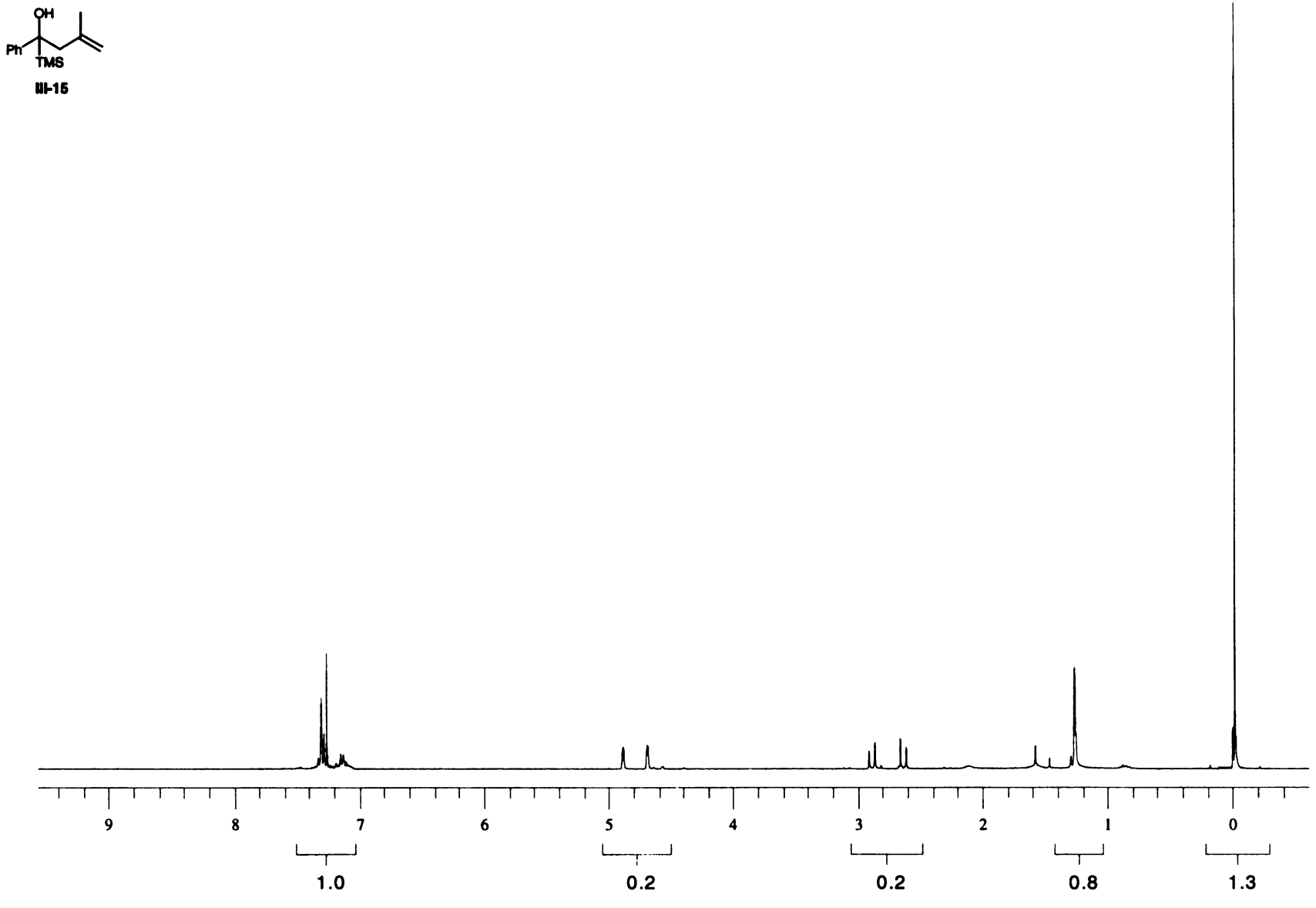
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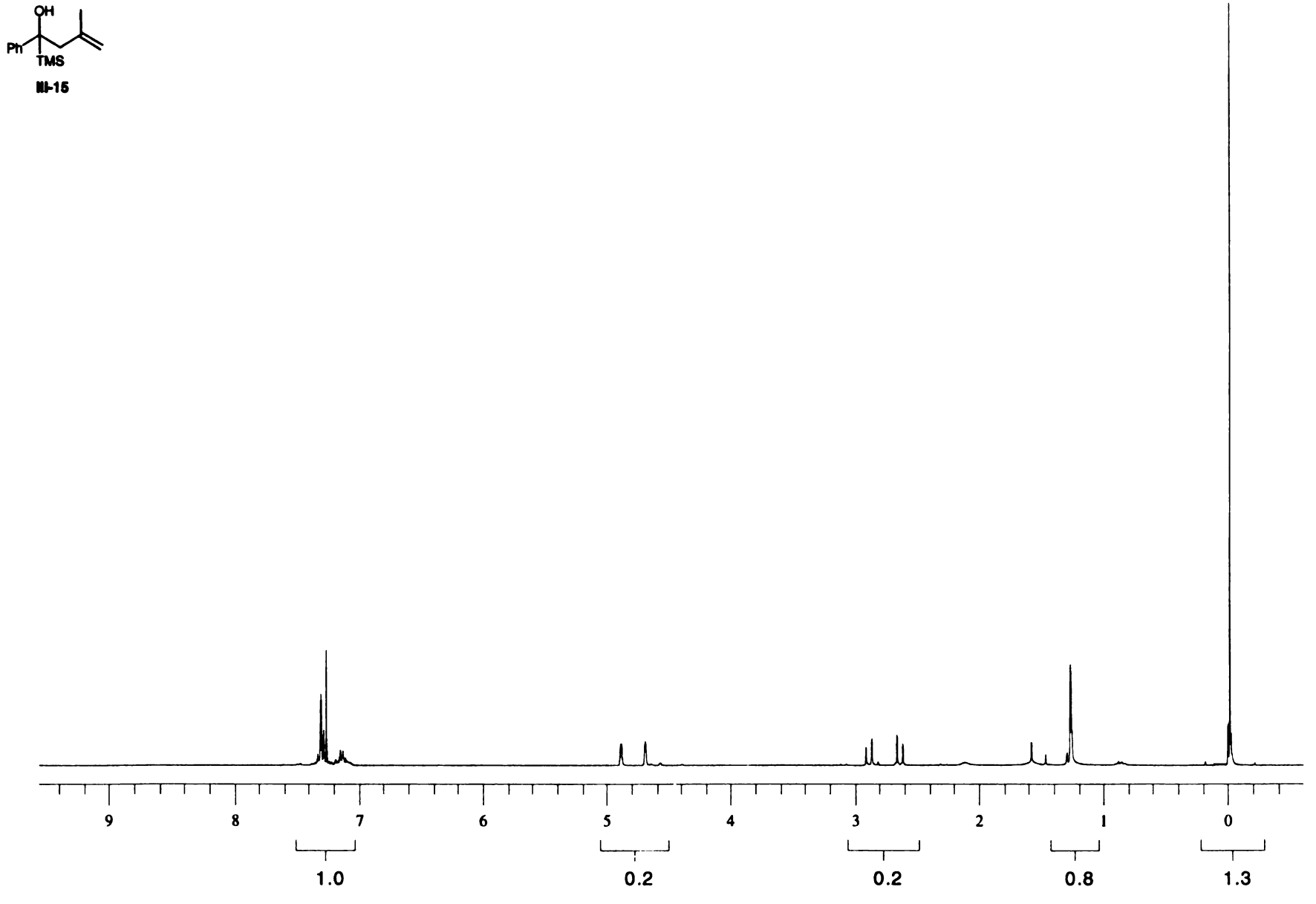
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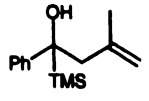

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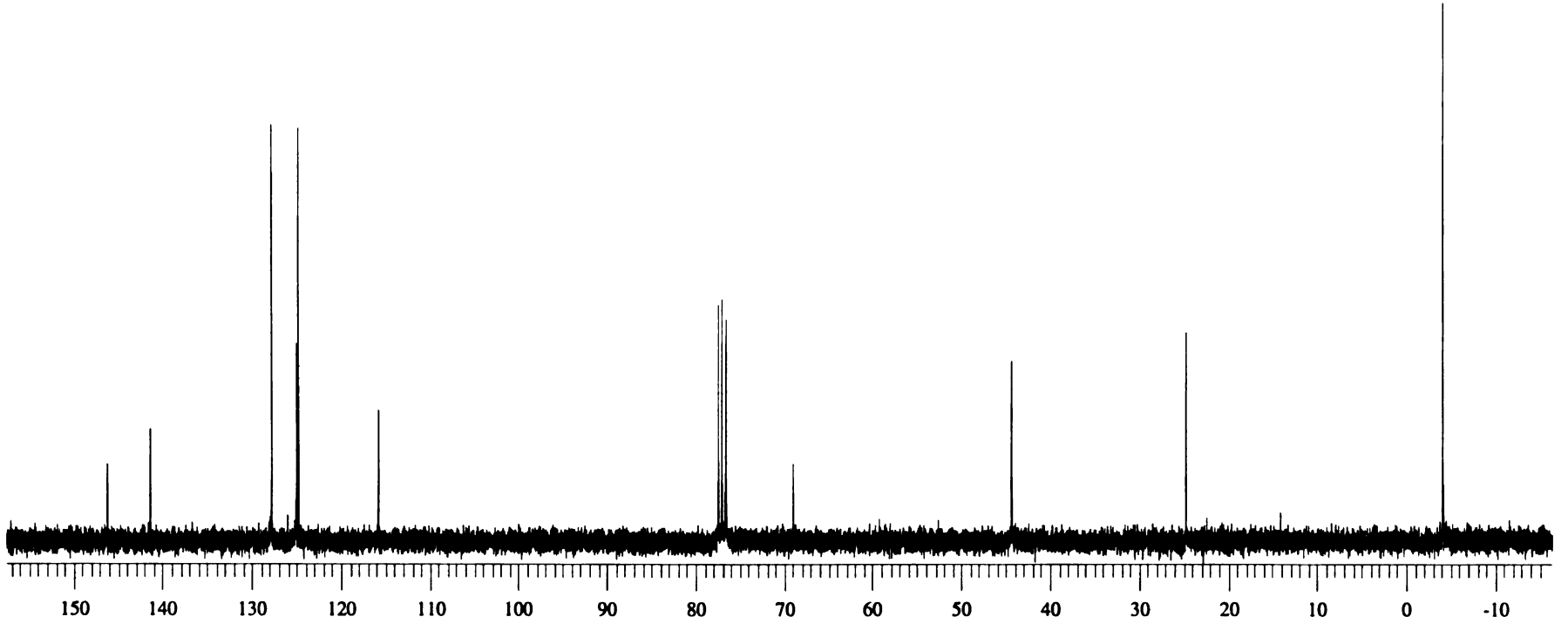

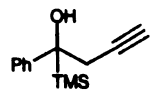

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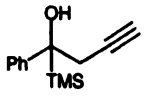

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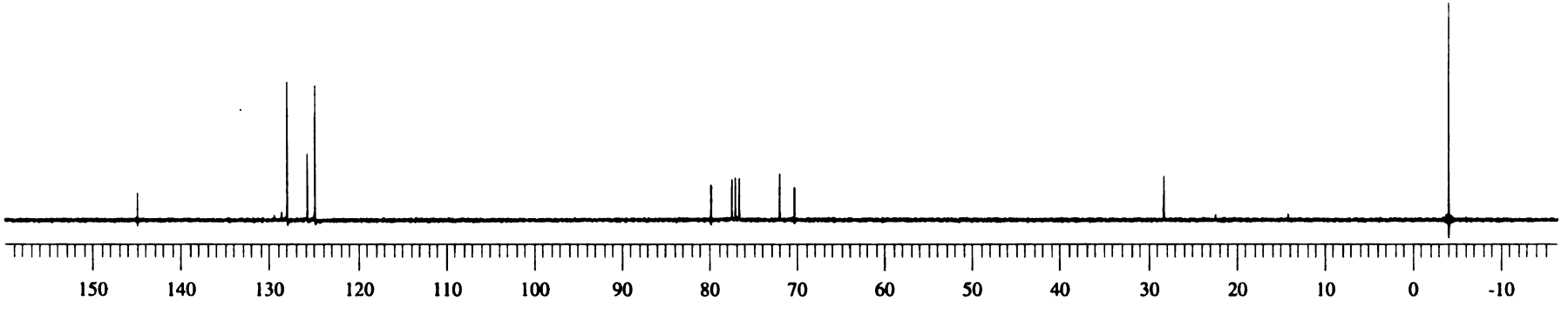

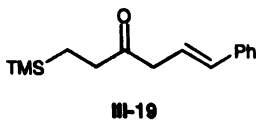

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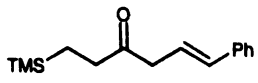

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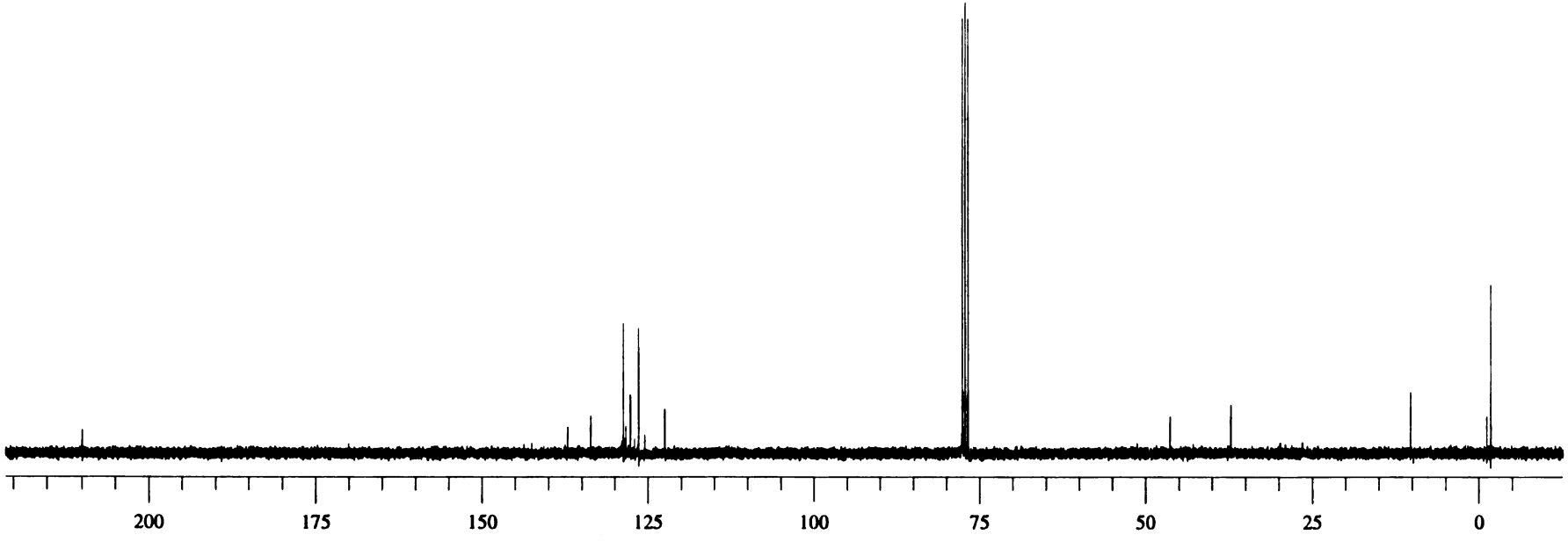

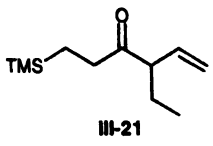

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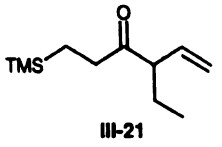

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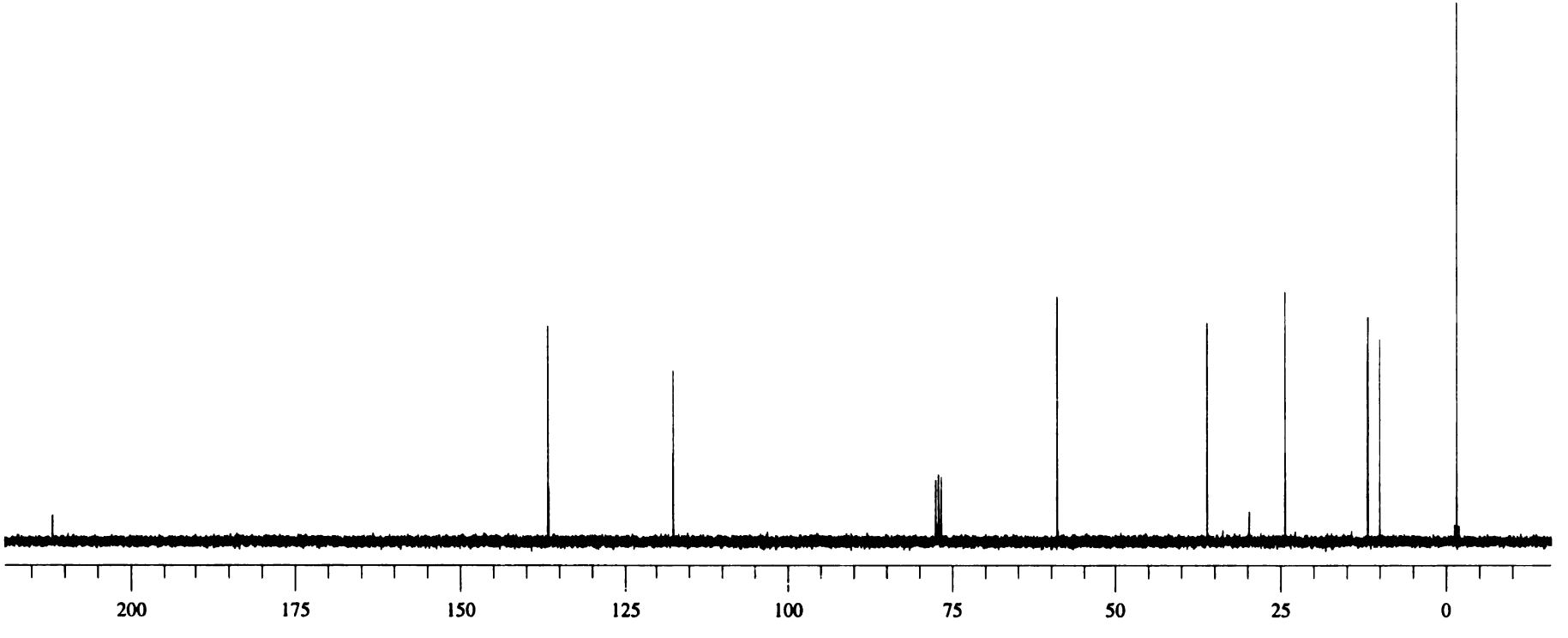

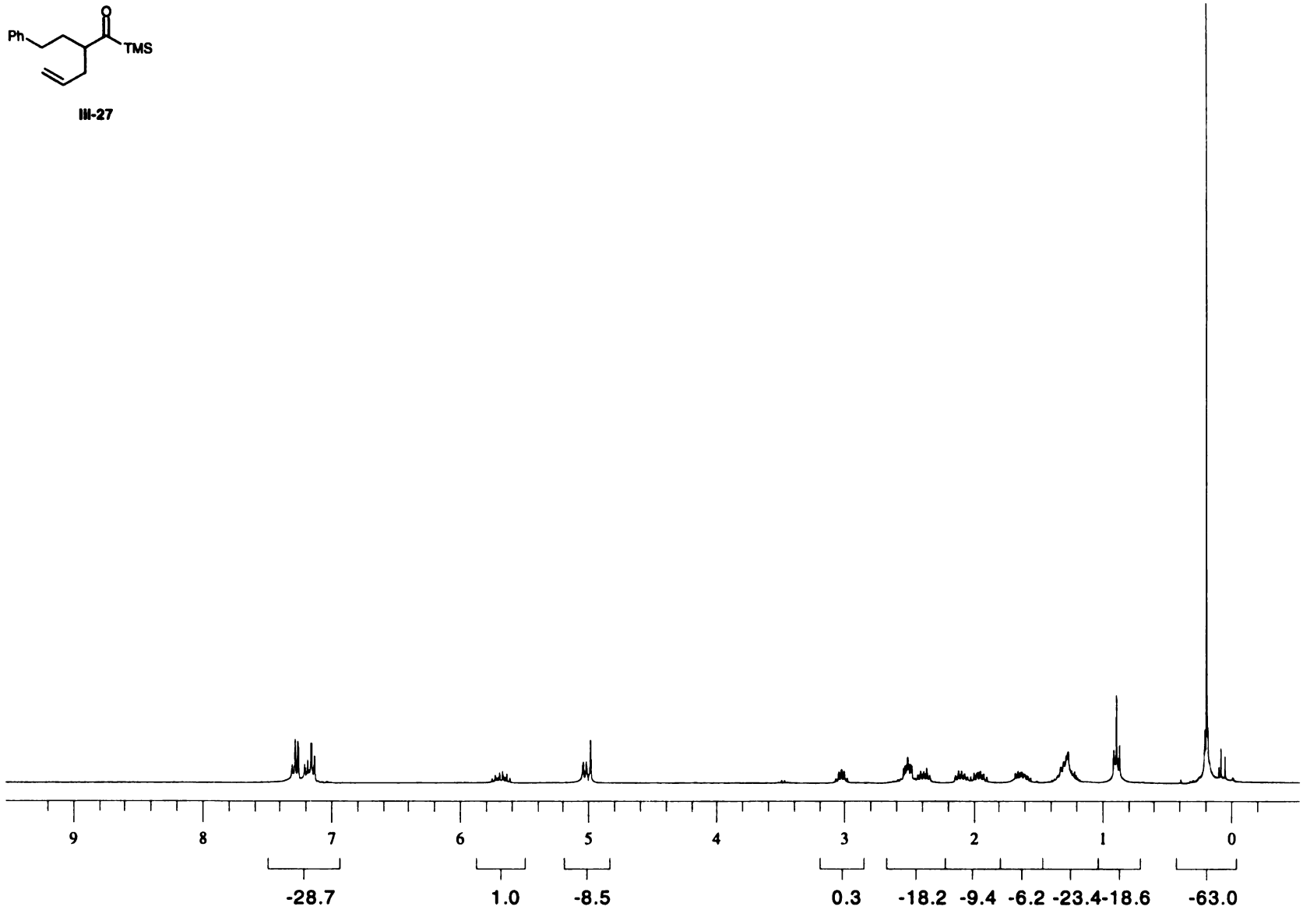
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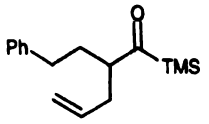

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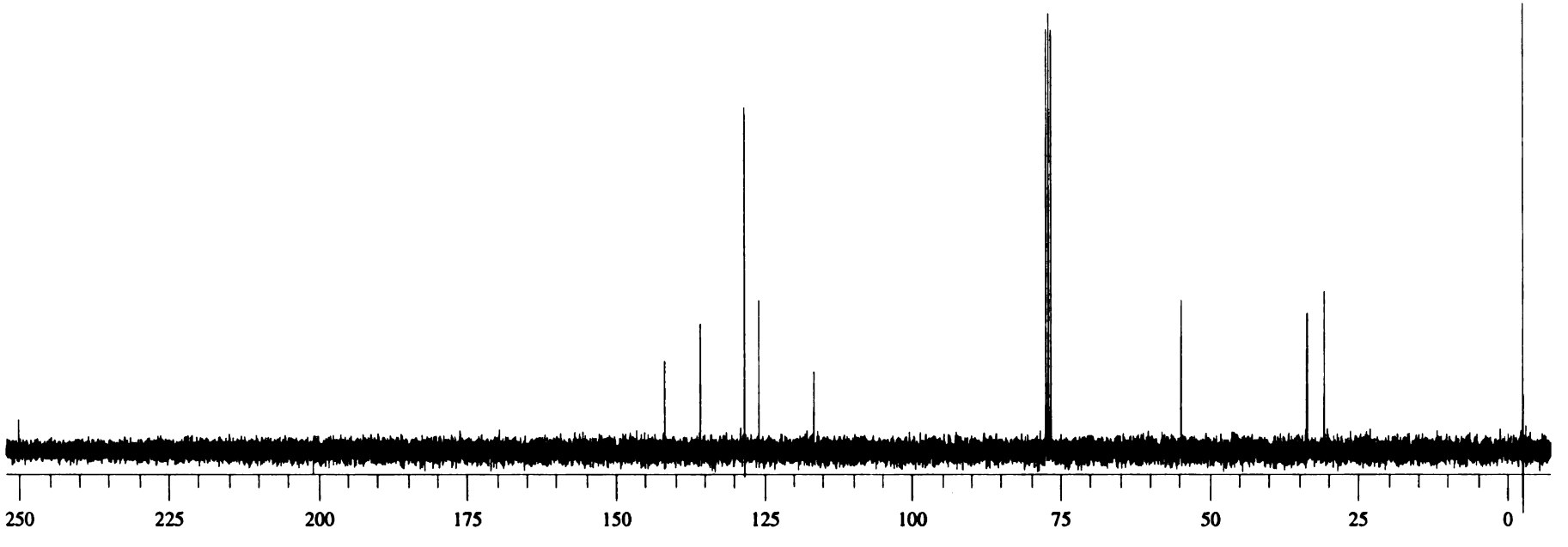

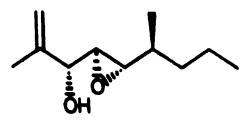

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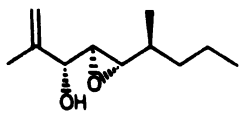

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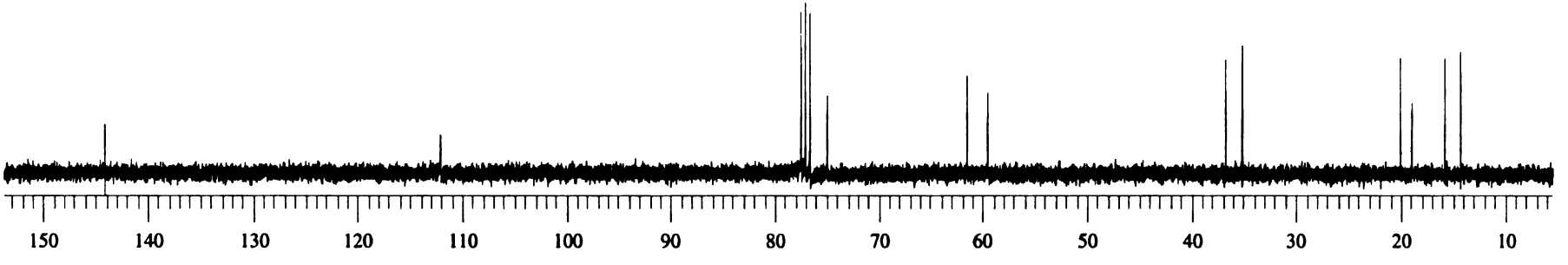

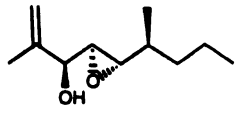

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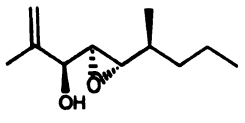

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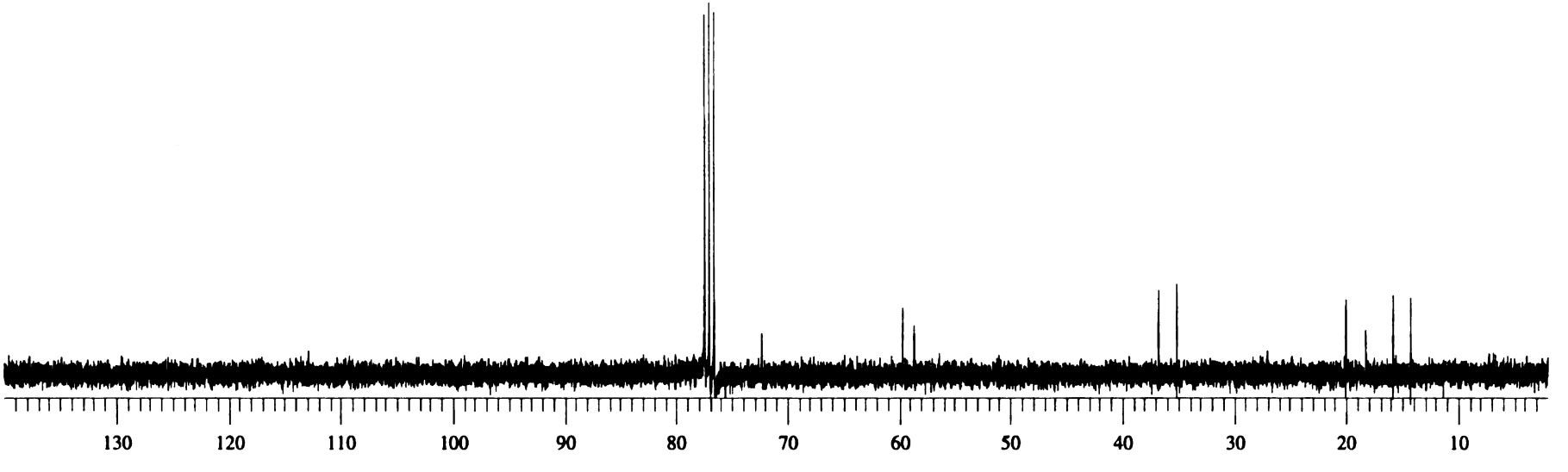

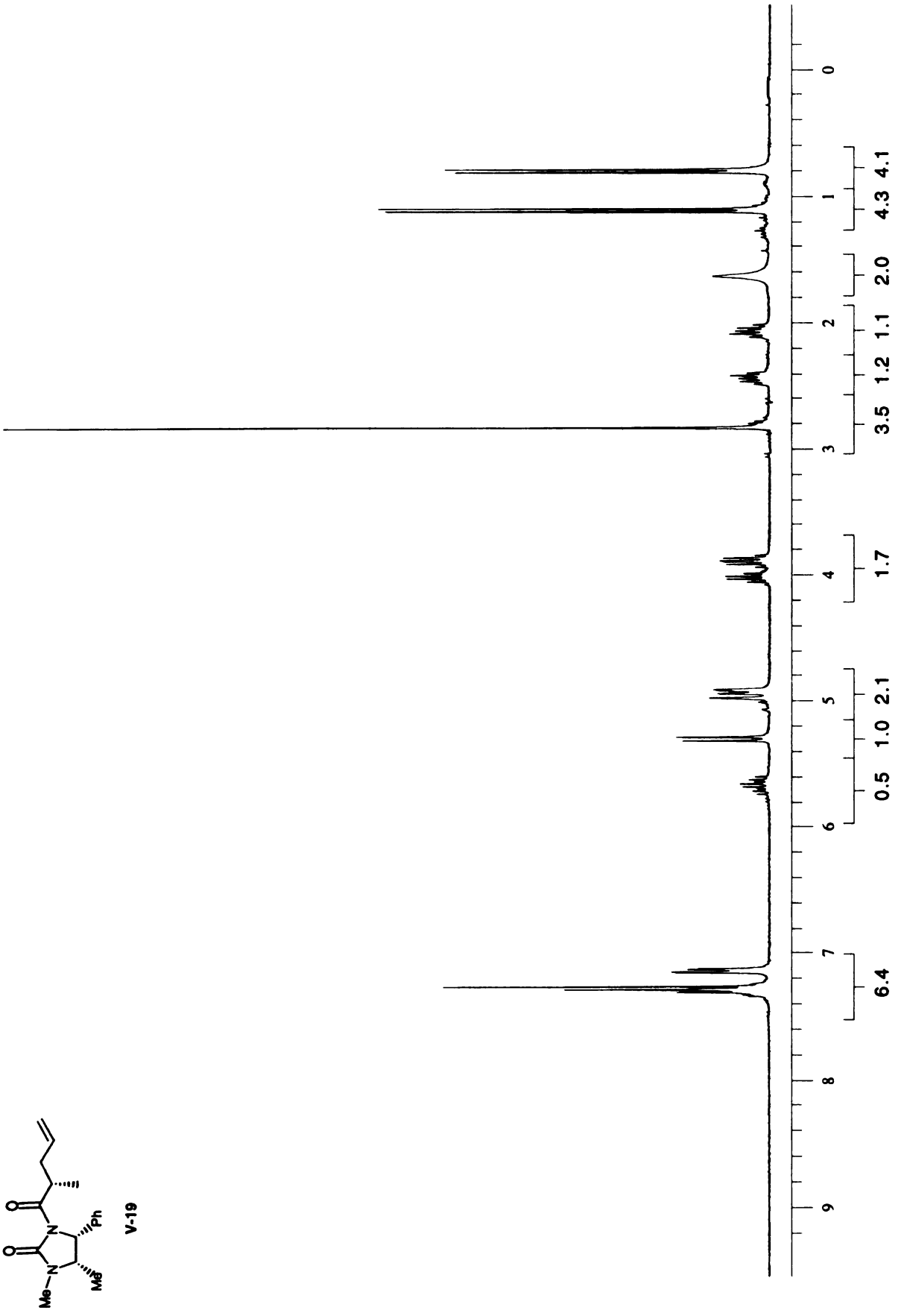

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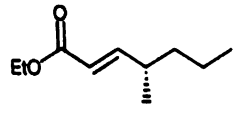

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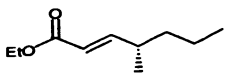

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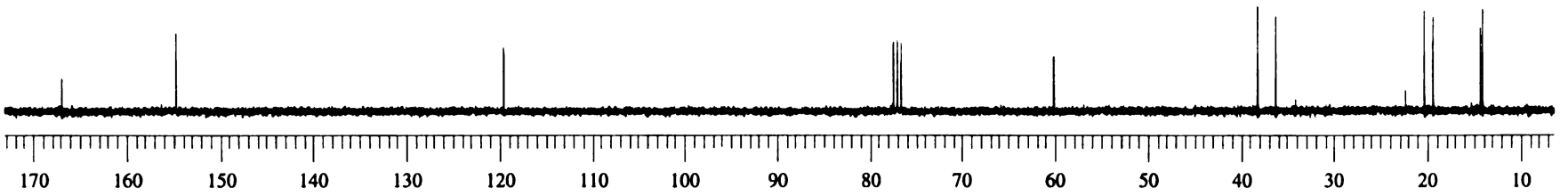

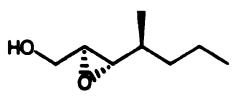

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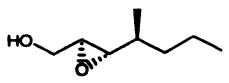

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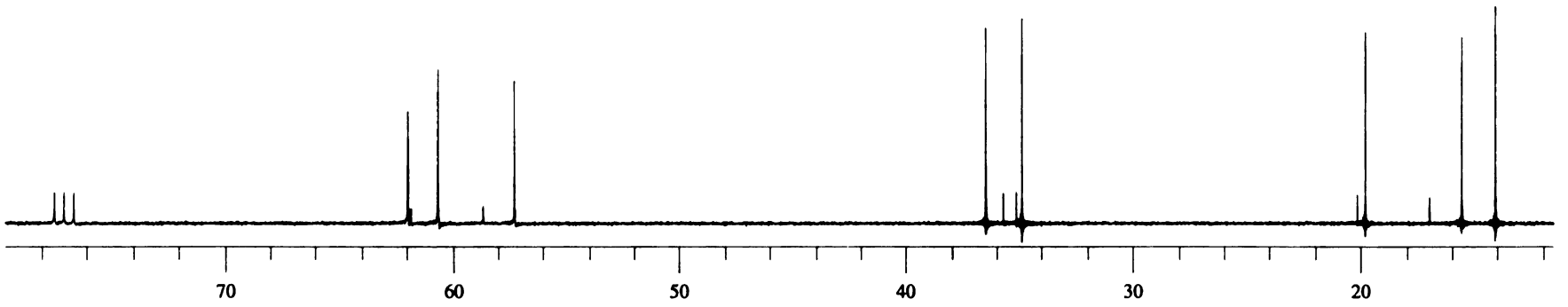

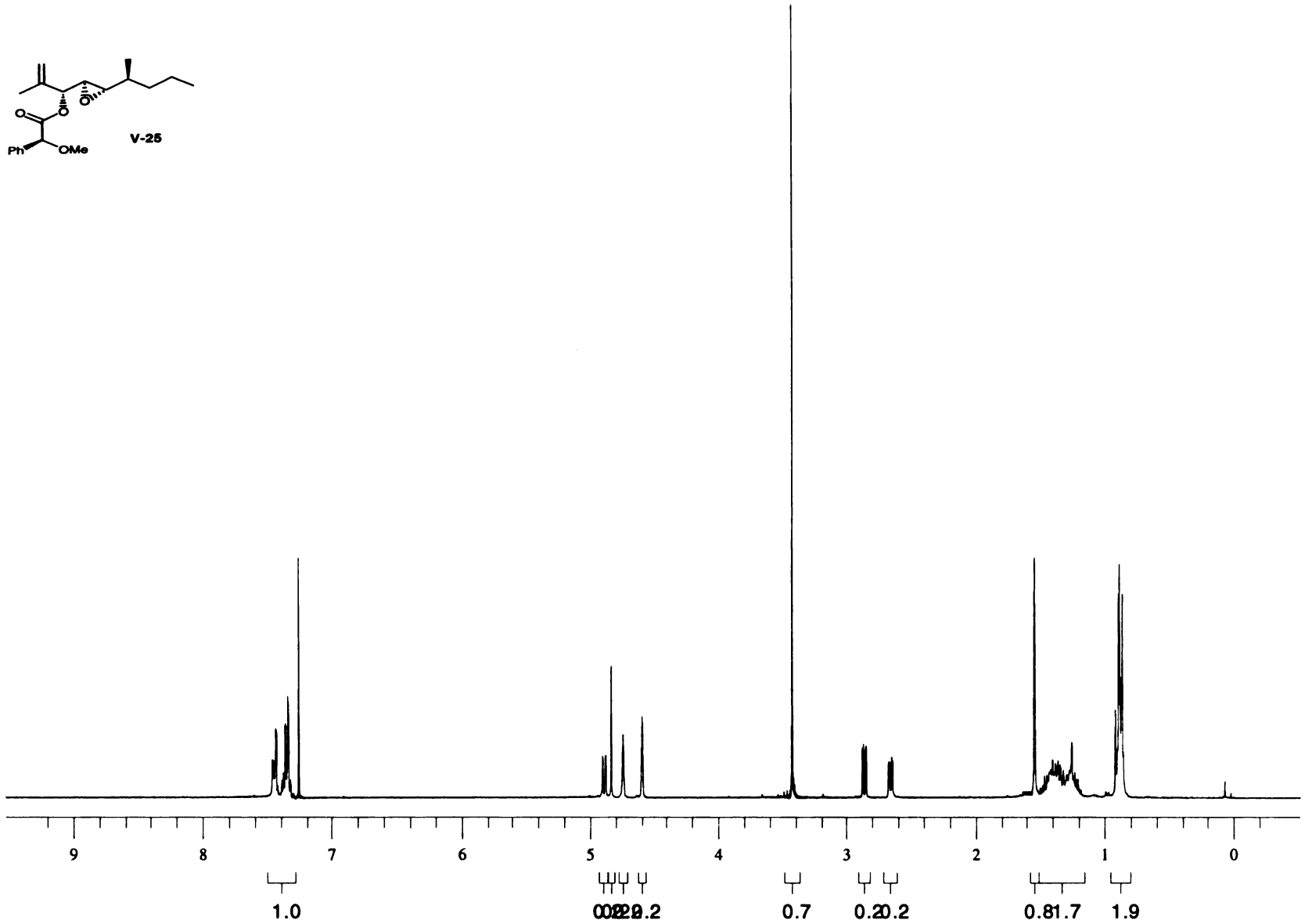
V-25
Ph
OMe
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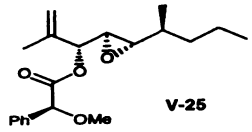
1.9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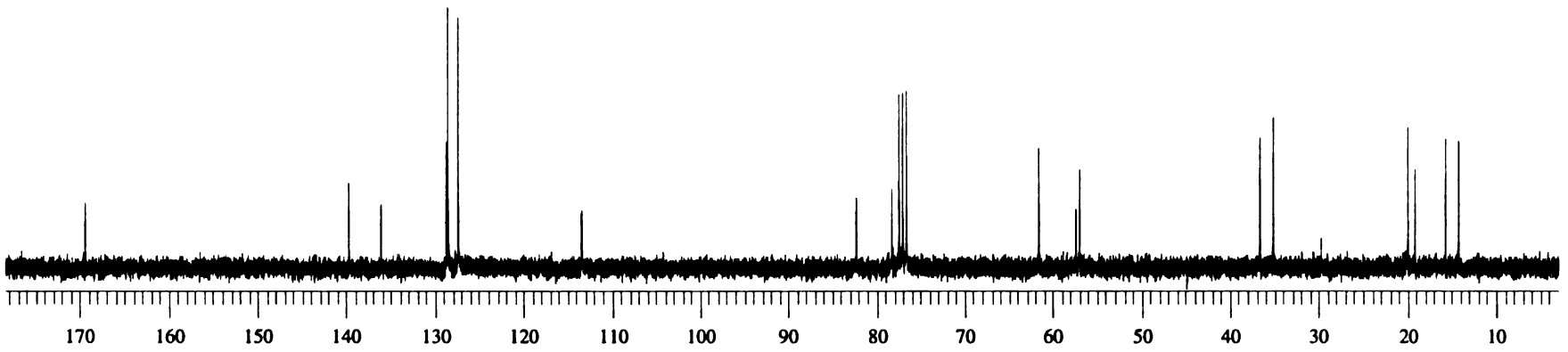
V-25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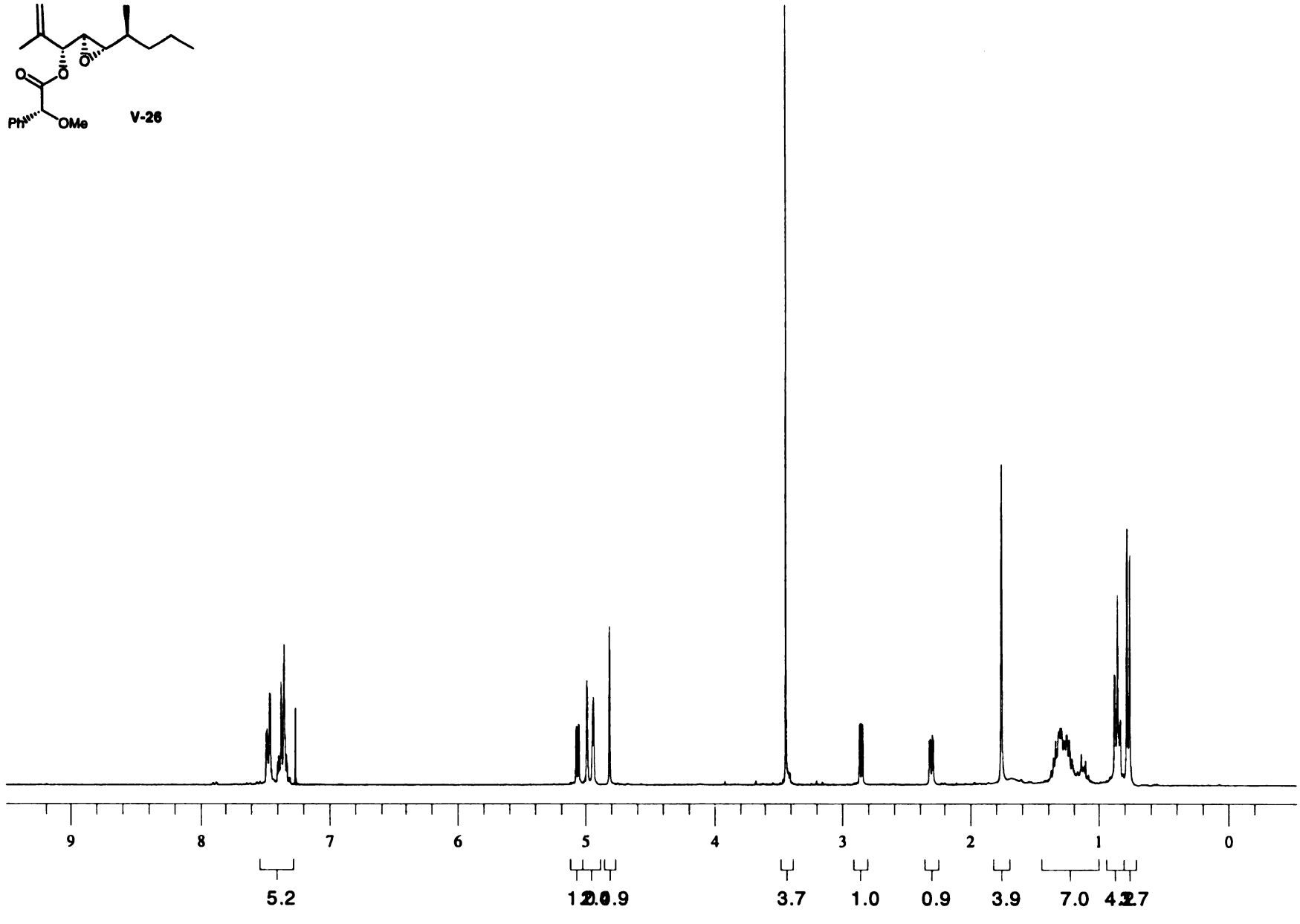
V-26
Ph
OMe
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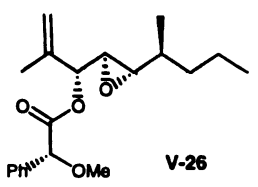
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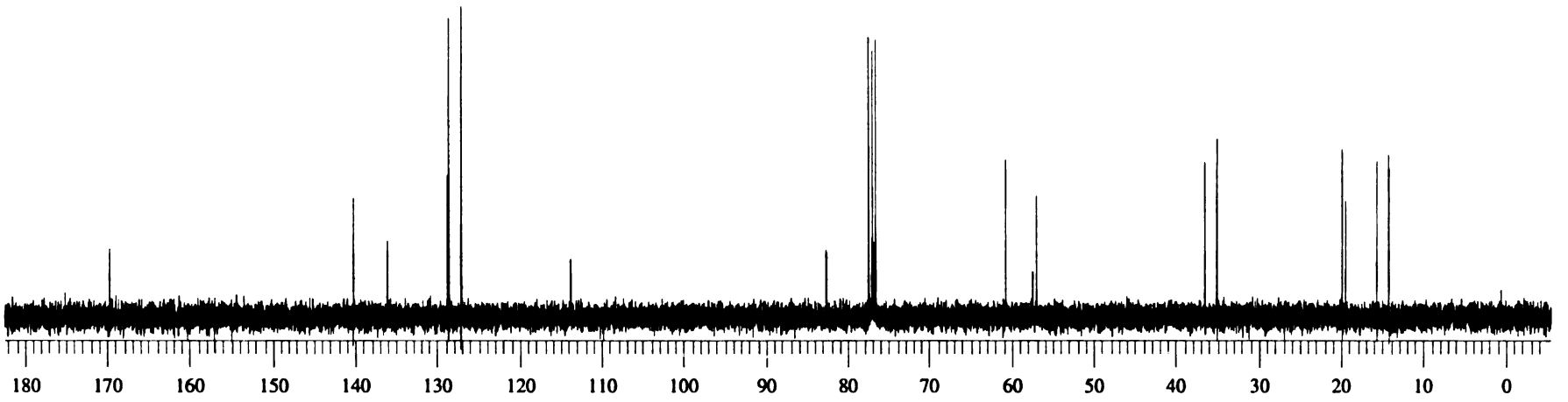
V-26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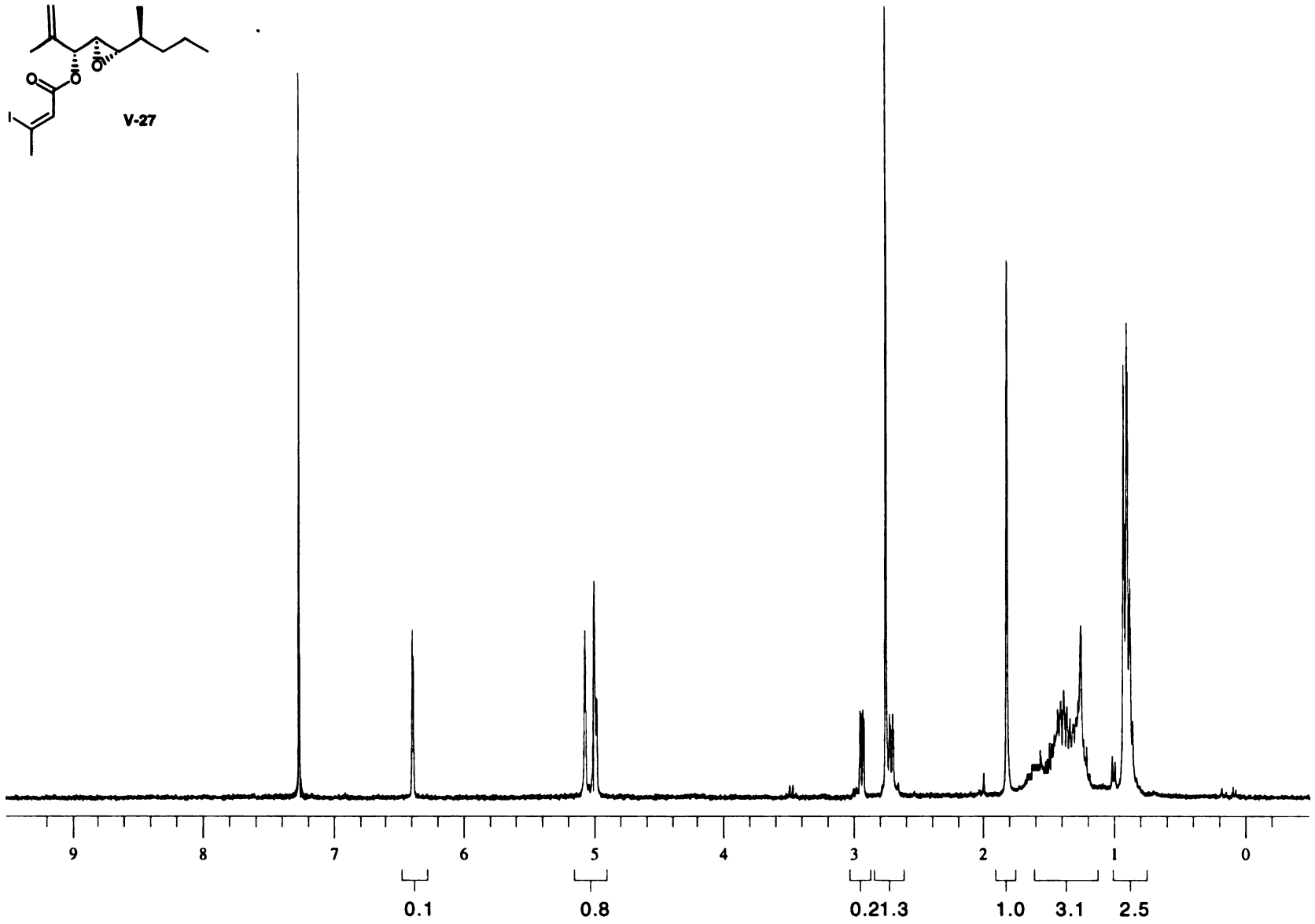
V-27
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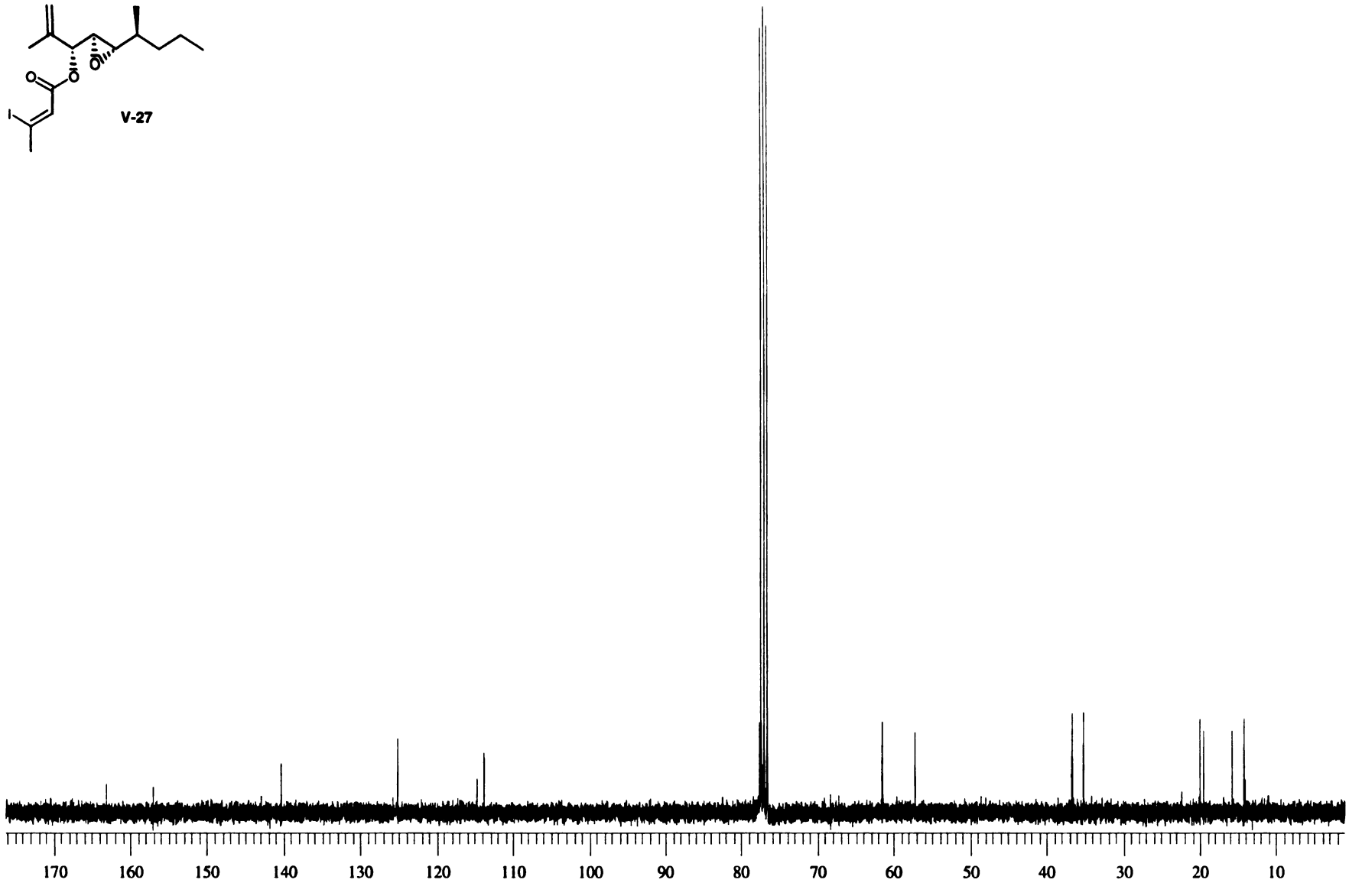
2.5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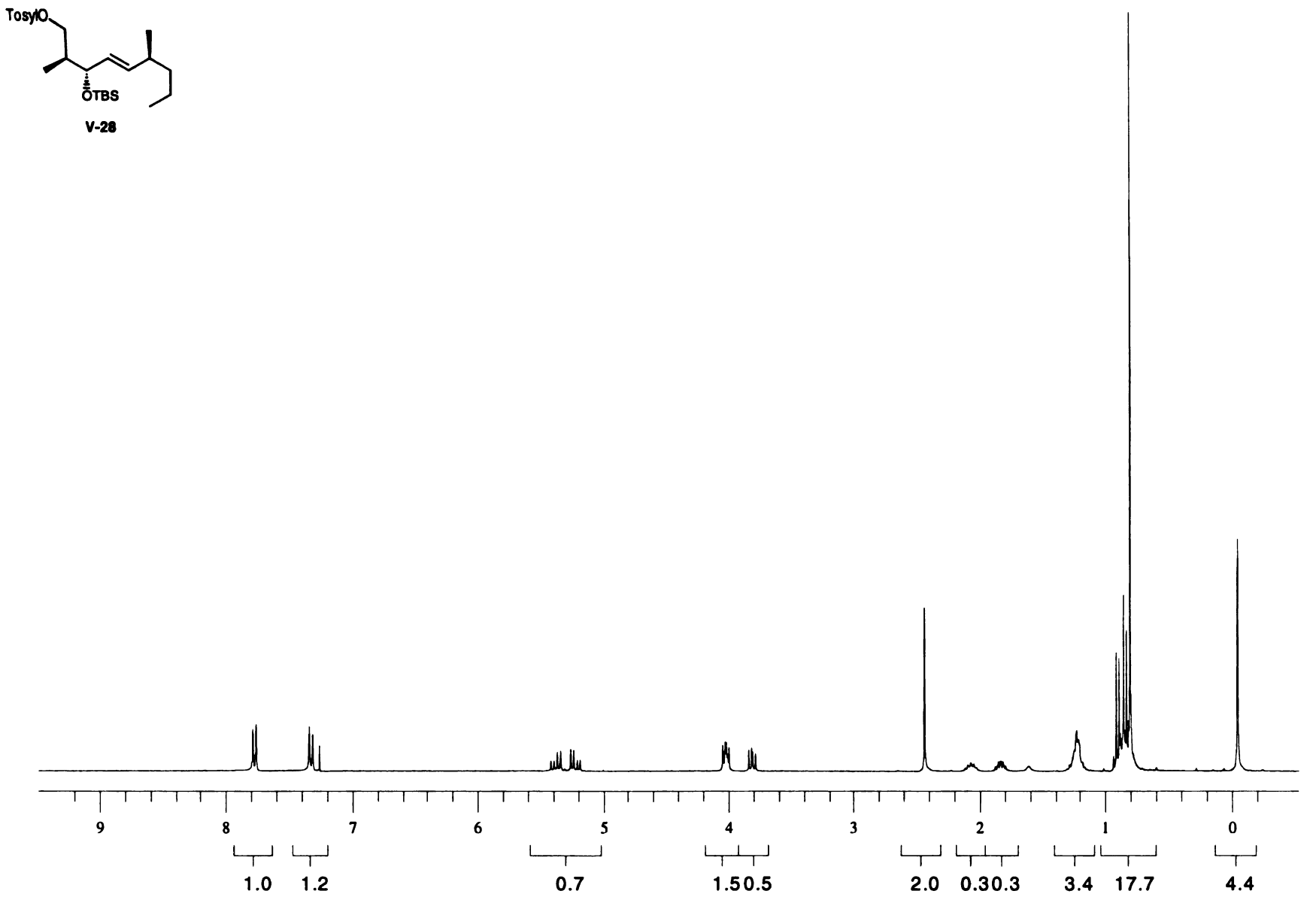
TosylO
OTBS
V-28
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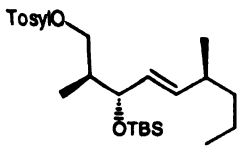
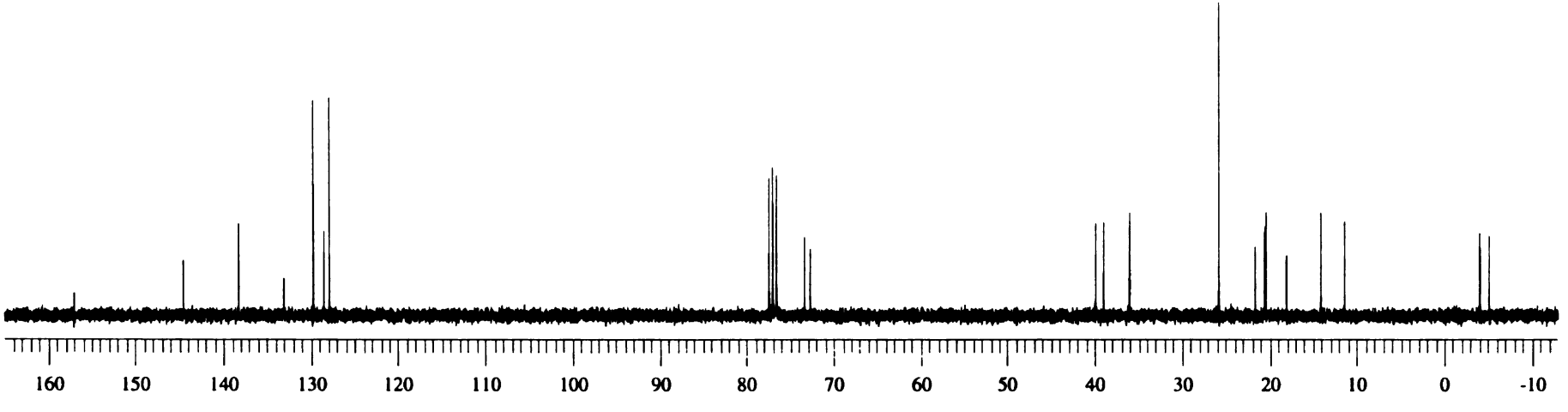
4.4


TosylO
OTBS

V-28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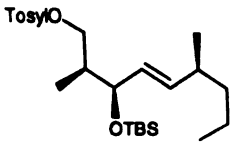
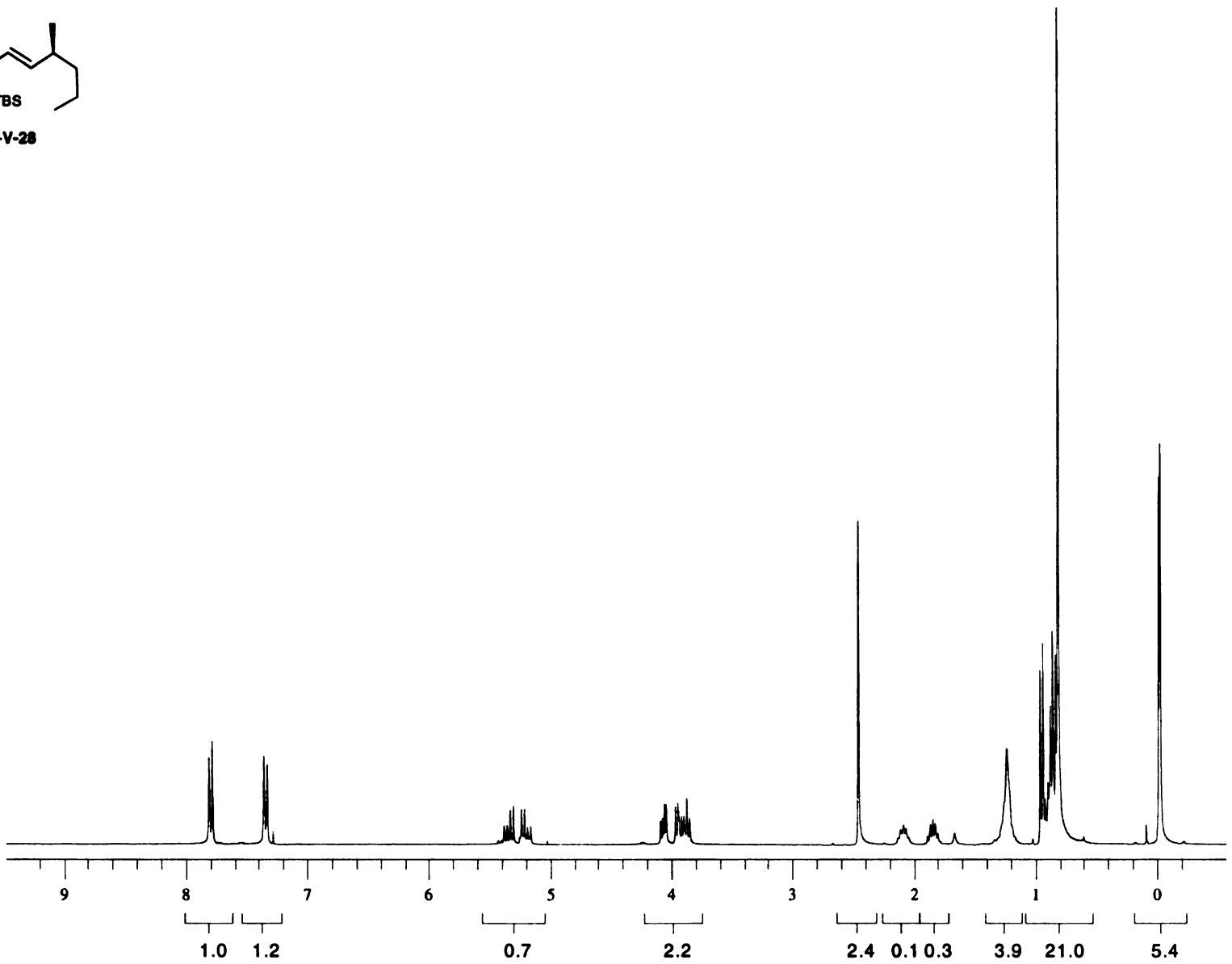
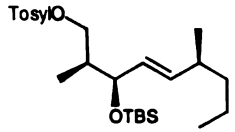
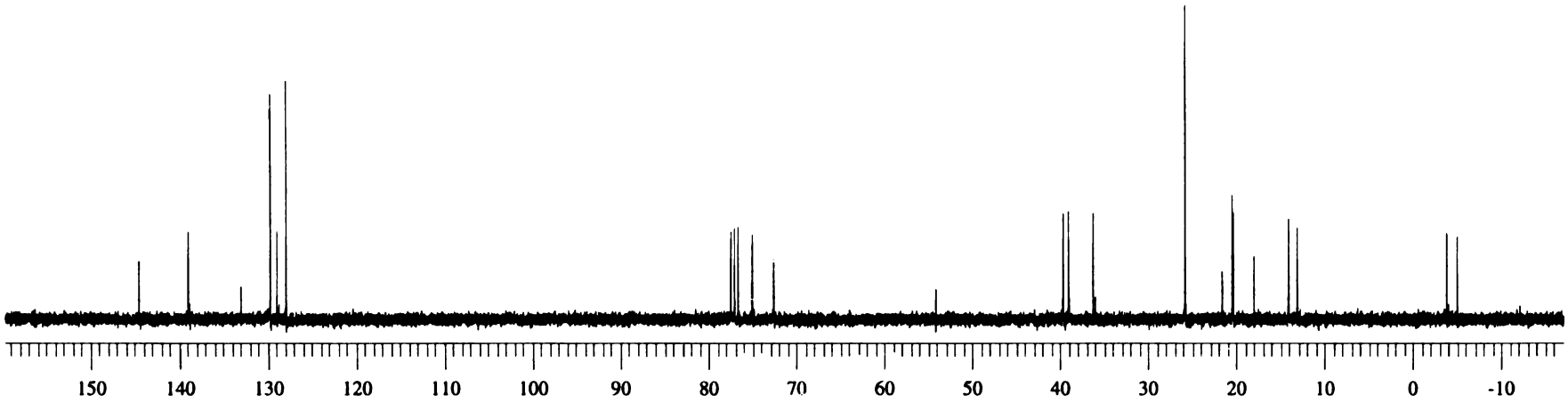


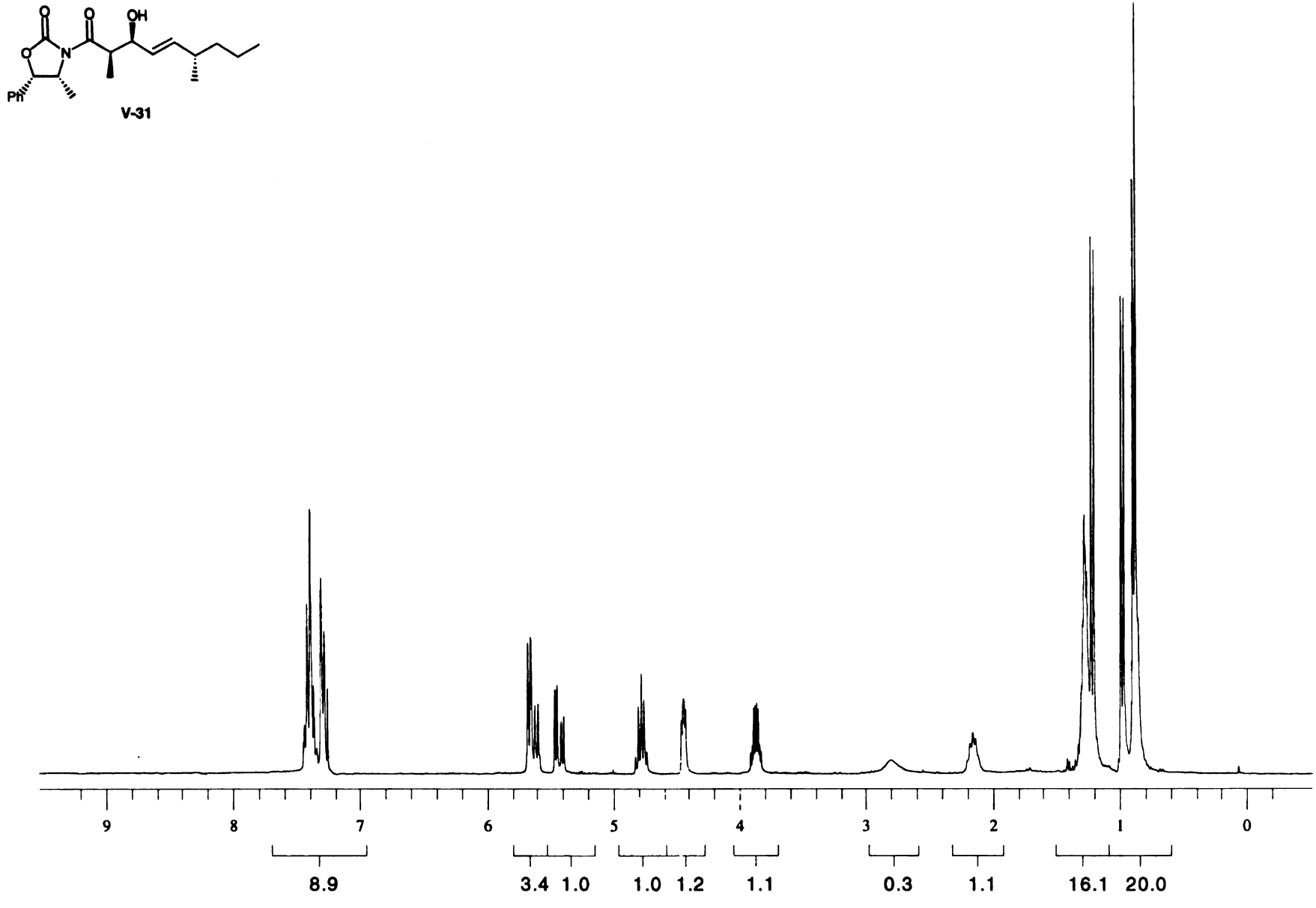
iso-V-28





iso-V-28




V-31
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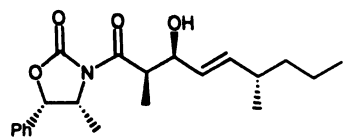
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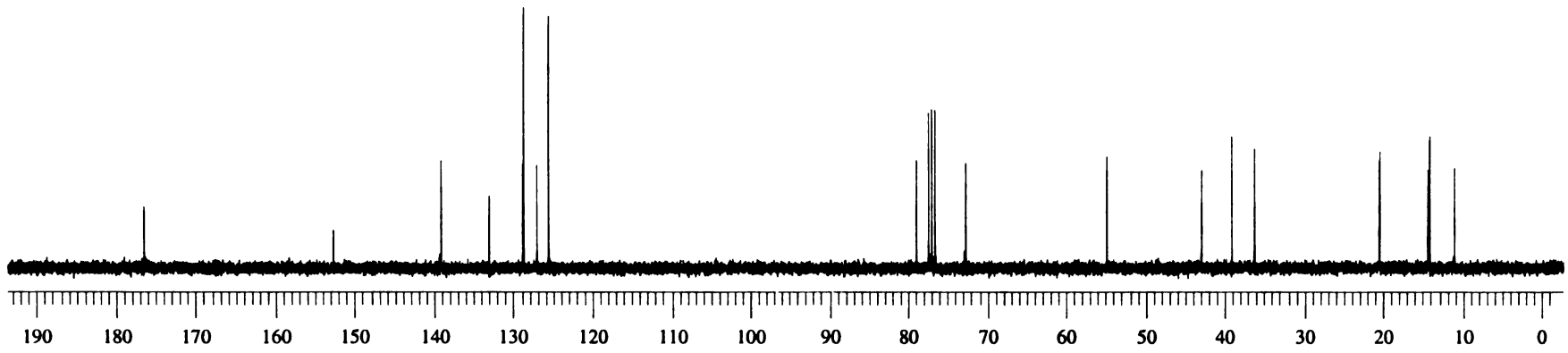
V-31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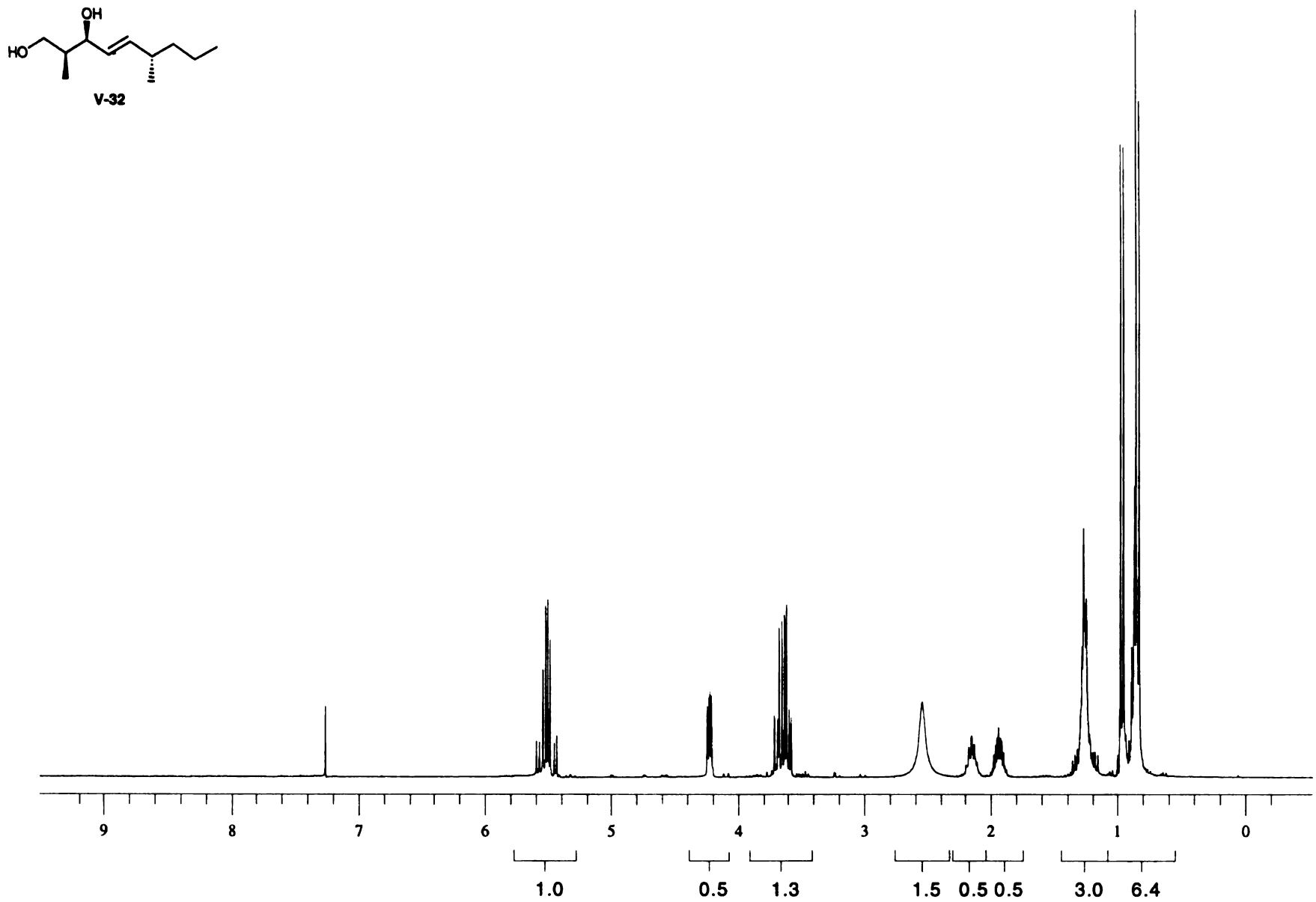
OH
HO
V-32
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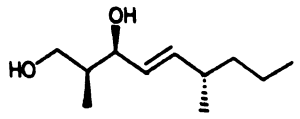
6.4



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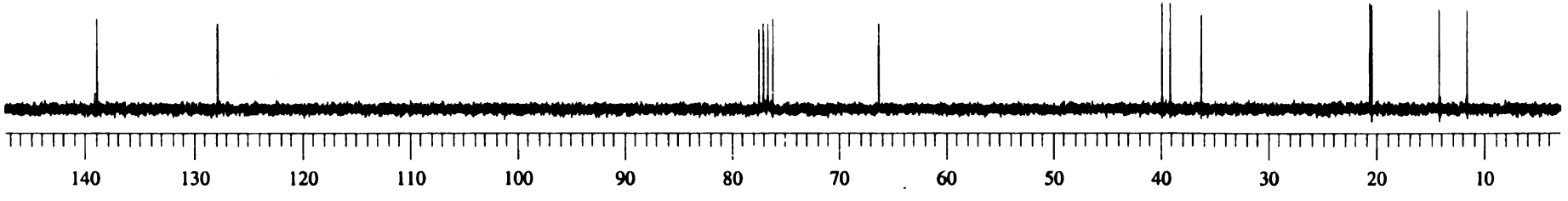

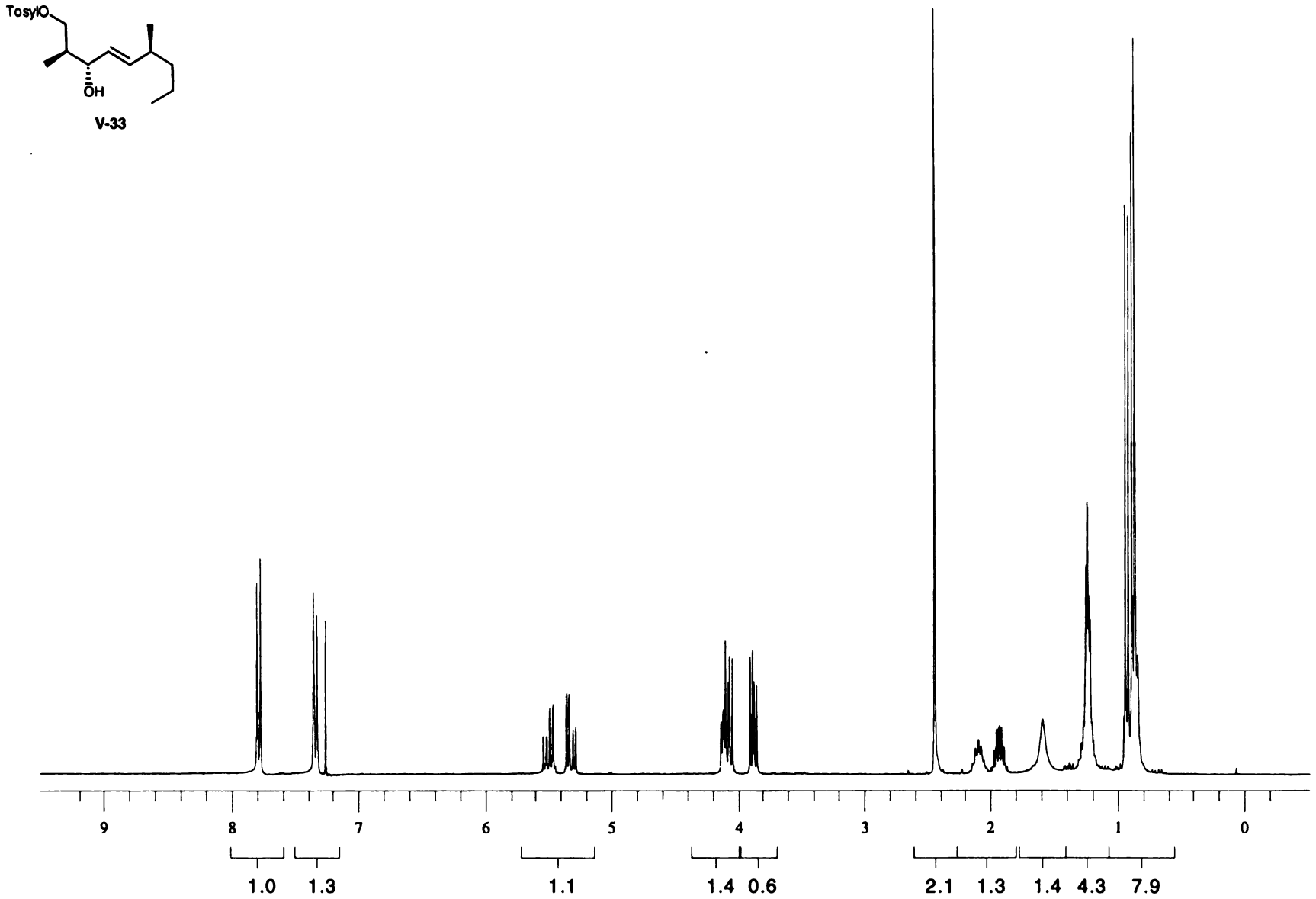
TosylO
OH
V-33
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2.1
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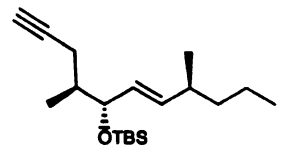
7.9



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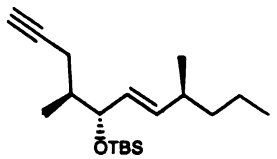

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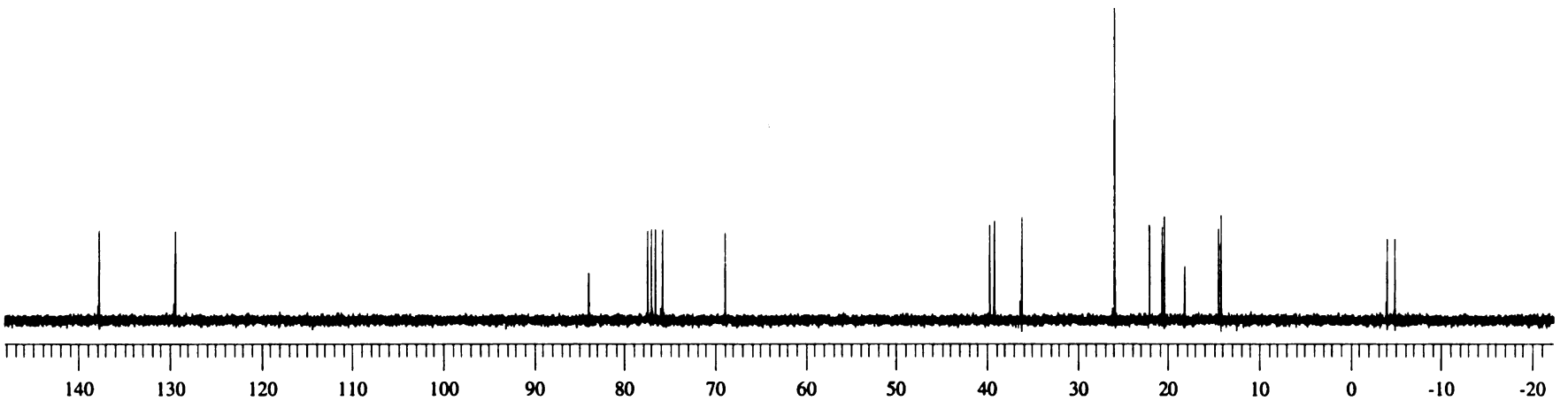
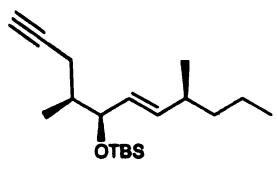
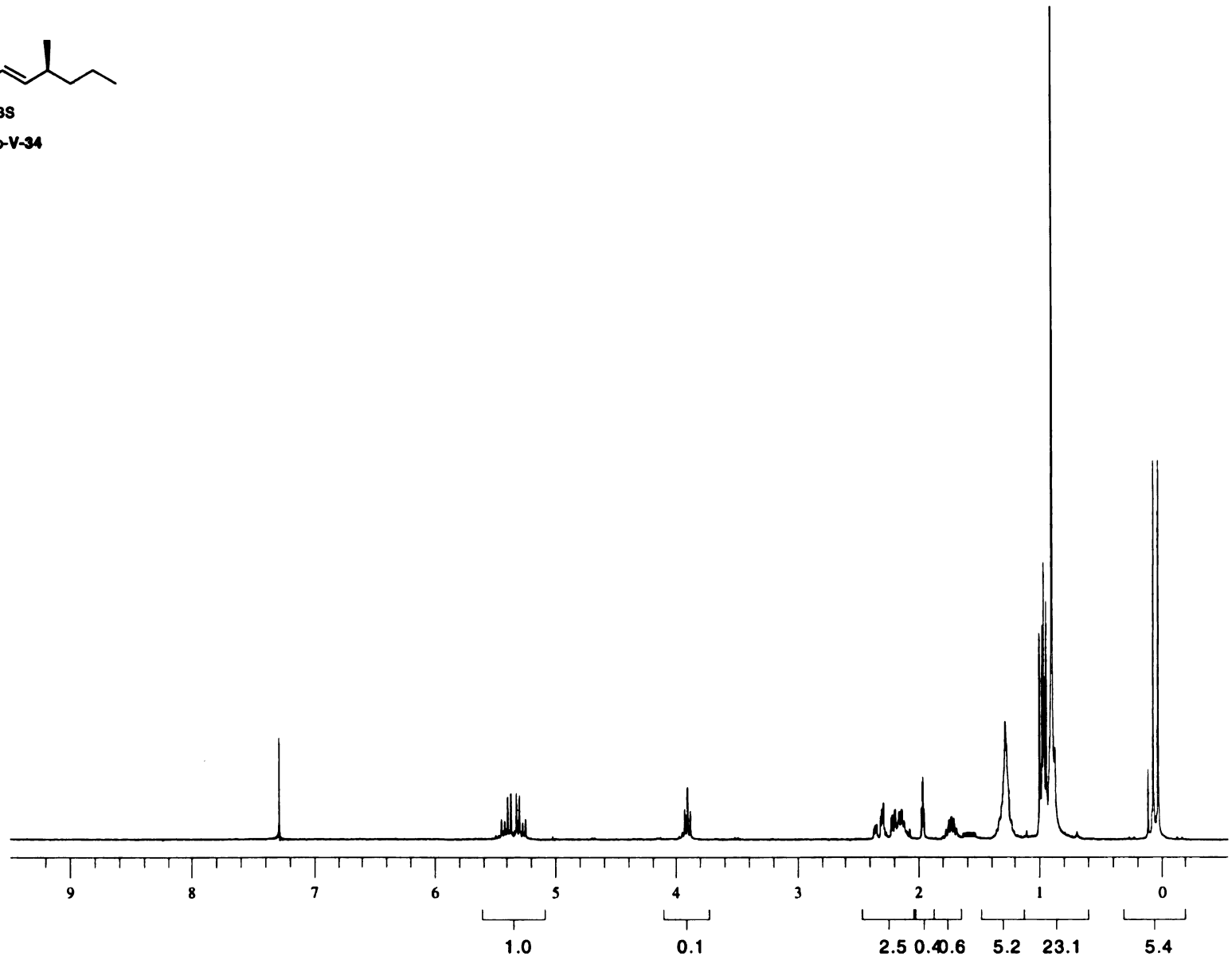
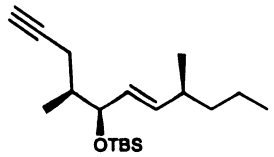


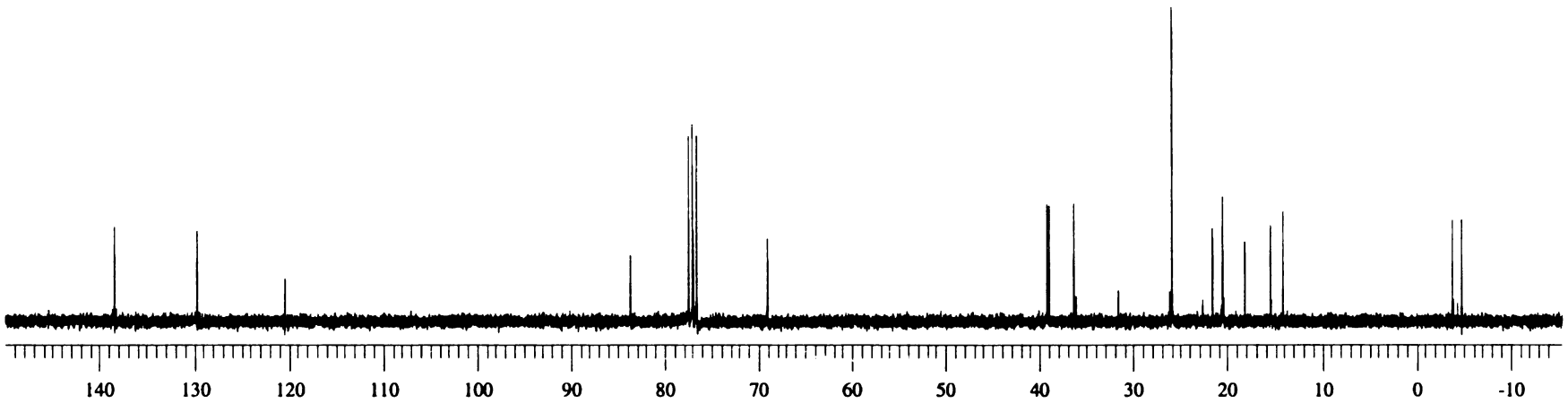


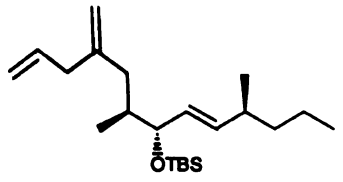
iso-V-34





iso-V-34





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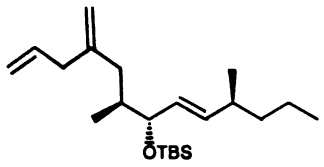

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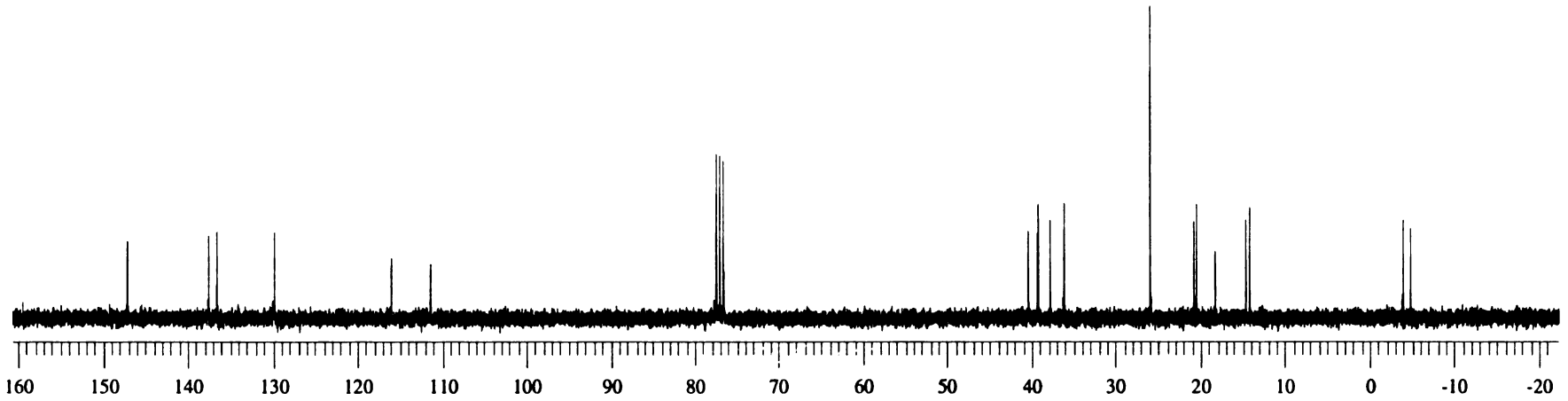
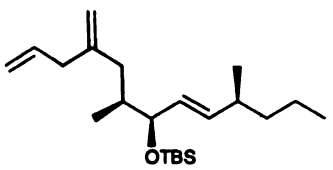
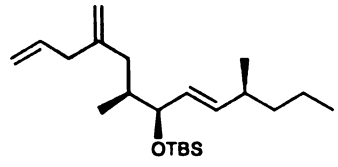




iso-V-35



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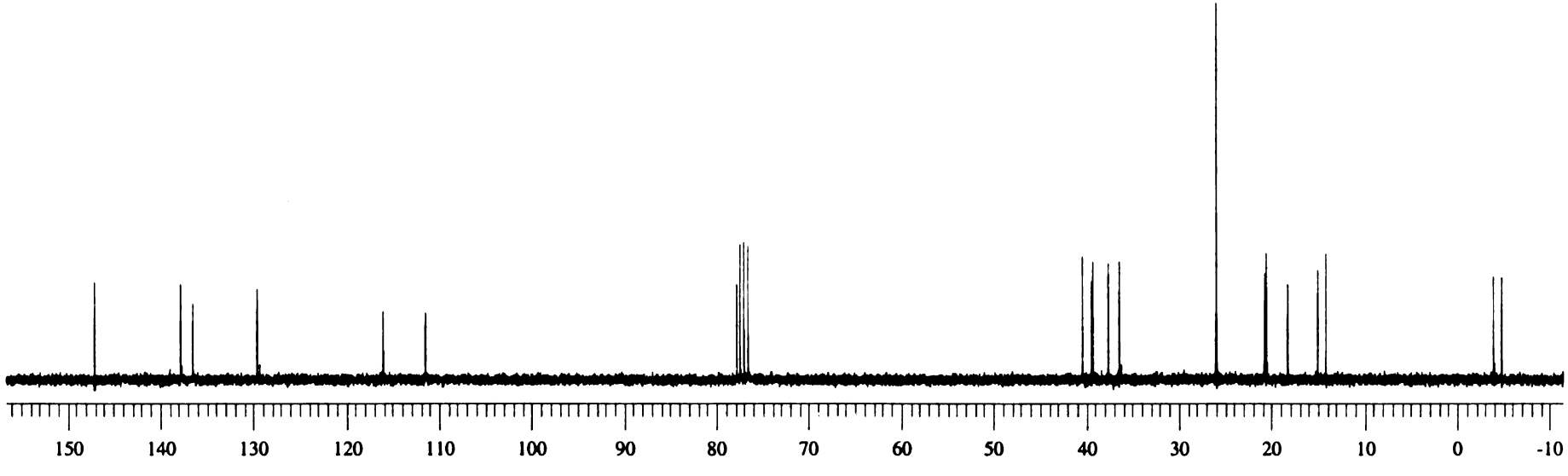

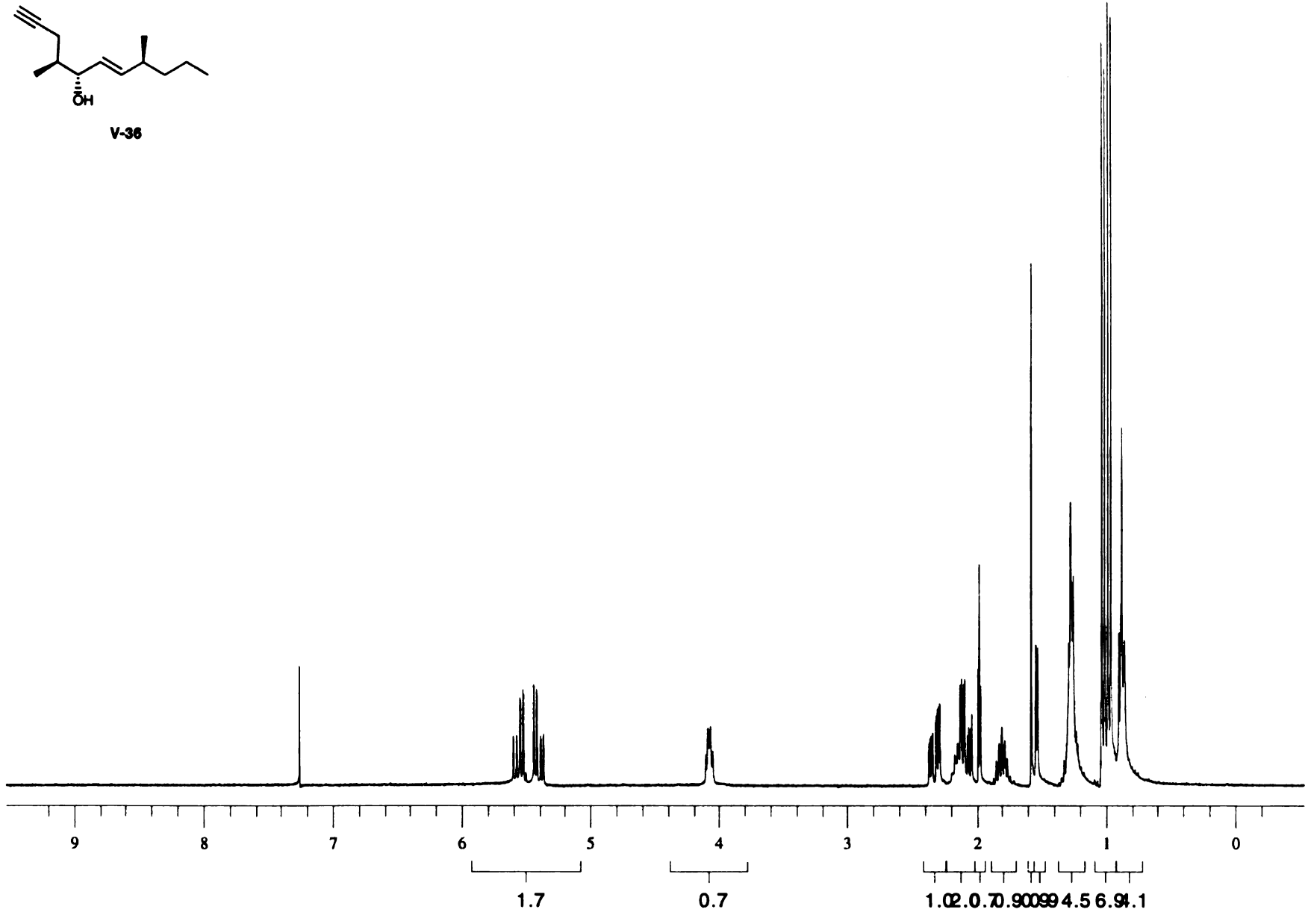
OH
V-36
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7
6
5
4
3
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2.0
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0.9
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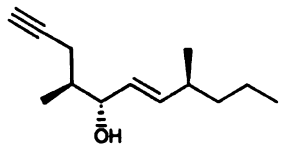
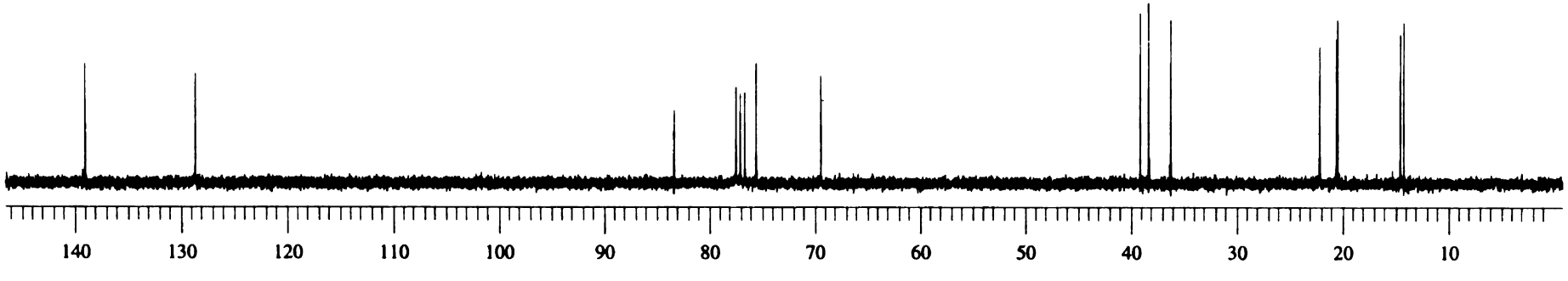
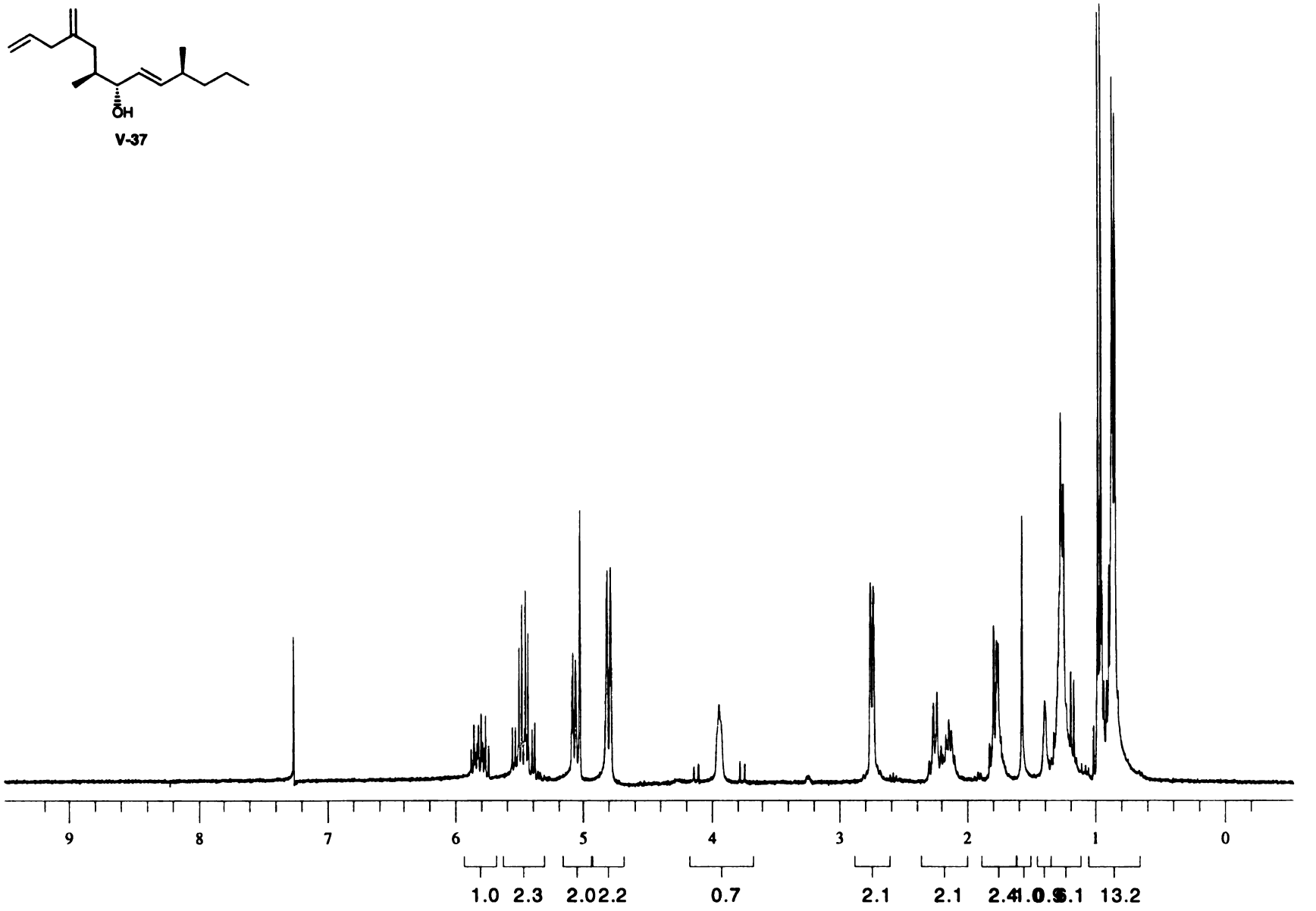
6.9
4.1



V-36




OH
V-37
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1.0
2.3
2.02.2
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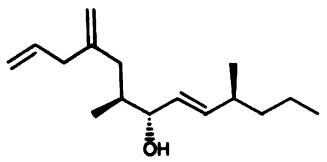
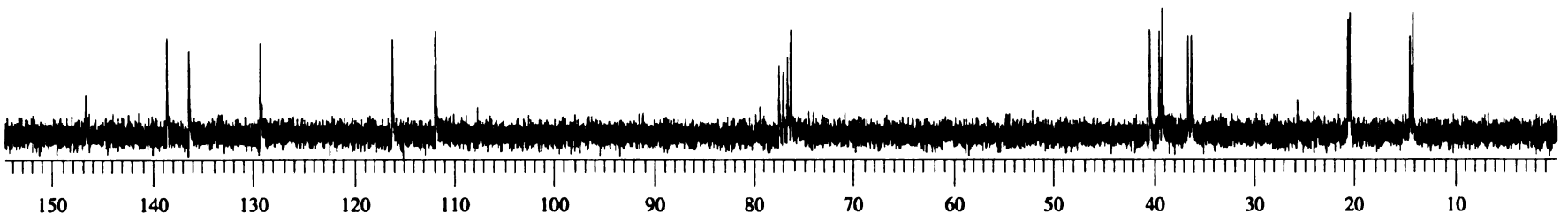
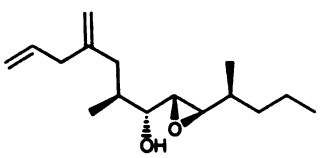
2.1
2.1
13.2

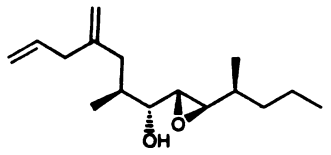


V-37

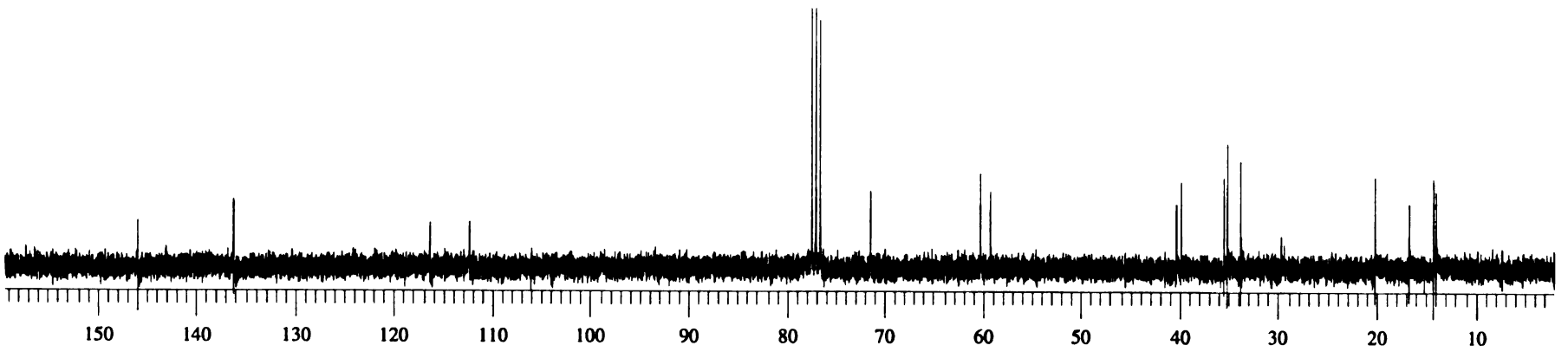


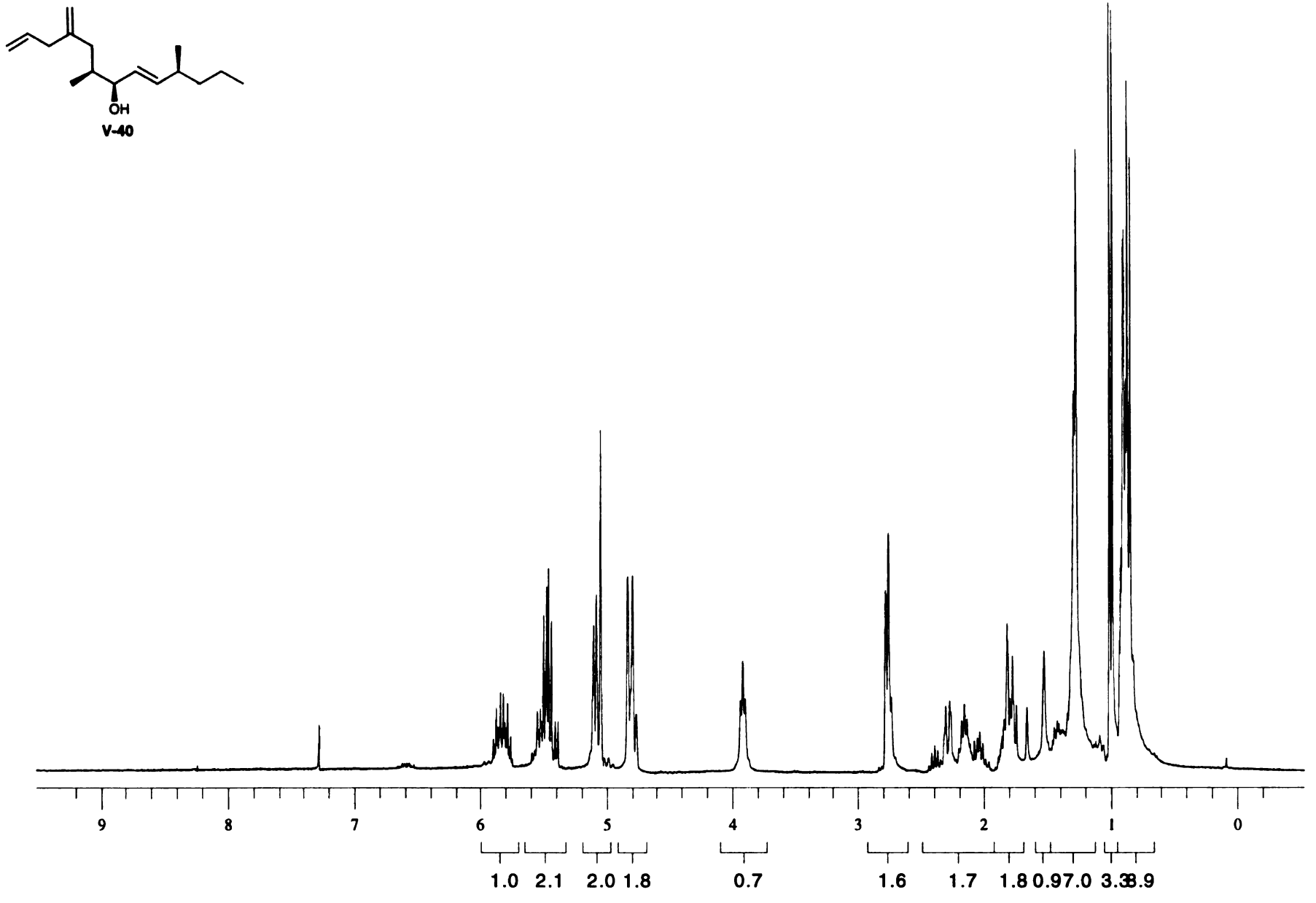


V-38



V-38




OH
V-40
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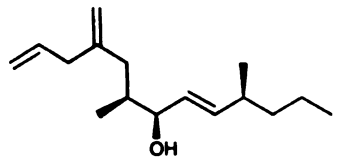
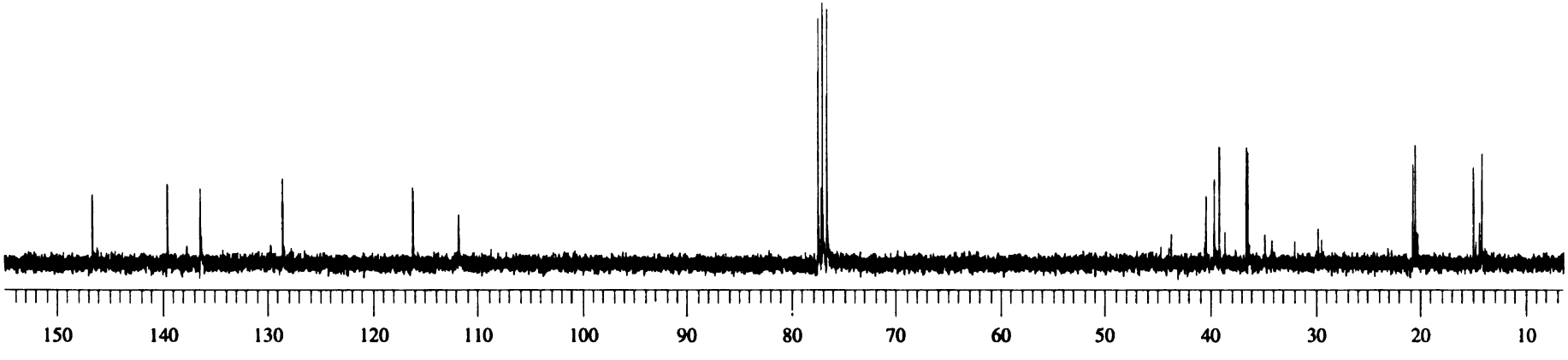
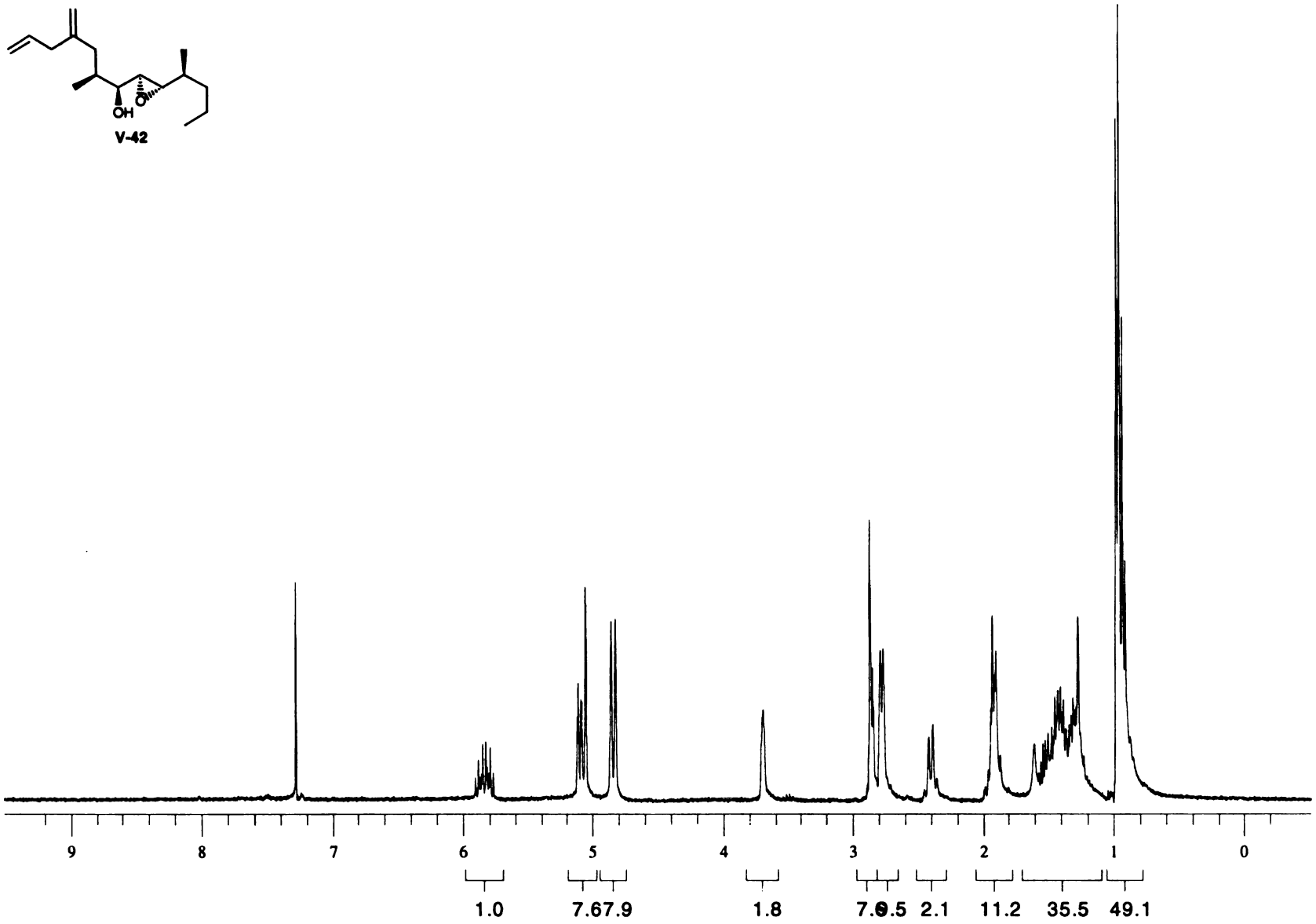
2.1
2.0
1.8
0.7
1.6
1.7
1.8
0.9
7.0
3.3
8.9



V-40




OH
V-42
9
8
7
6
5
4
3
2
1
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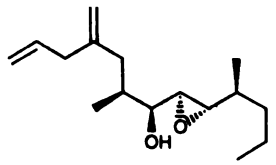
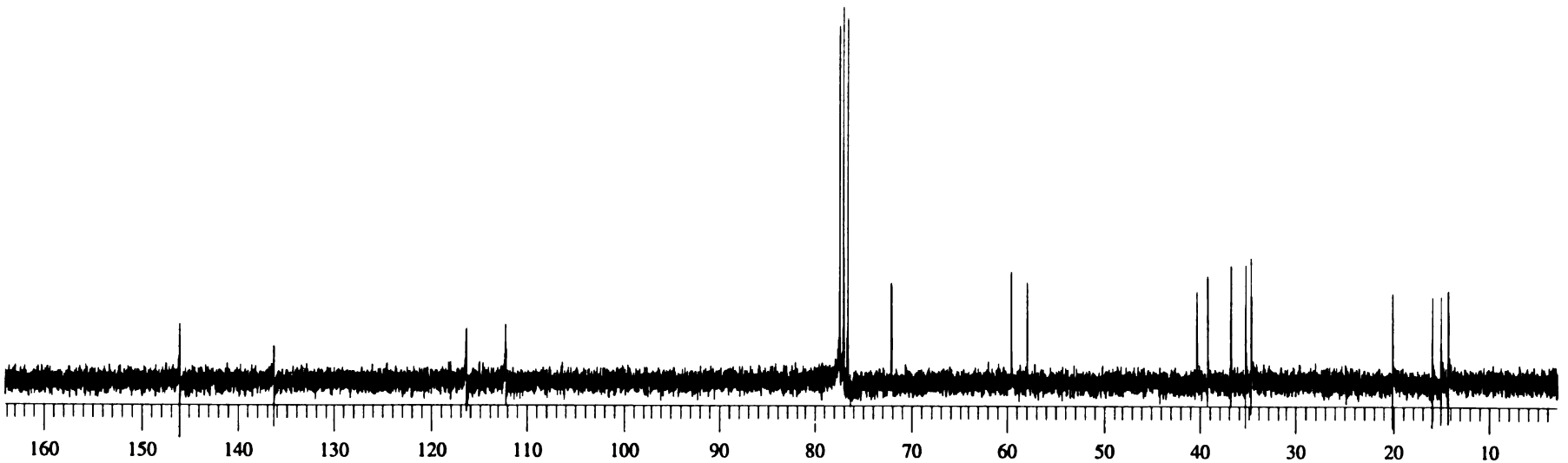
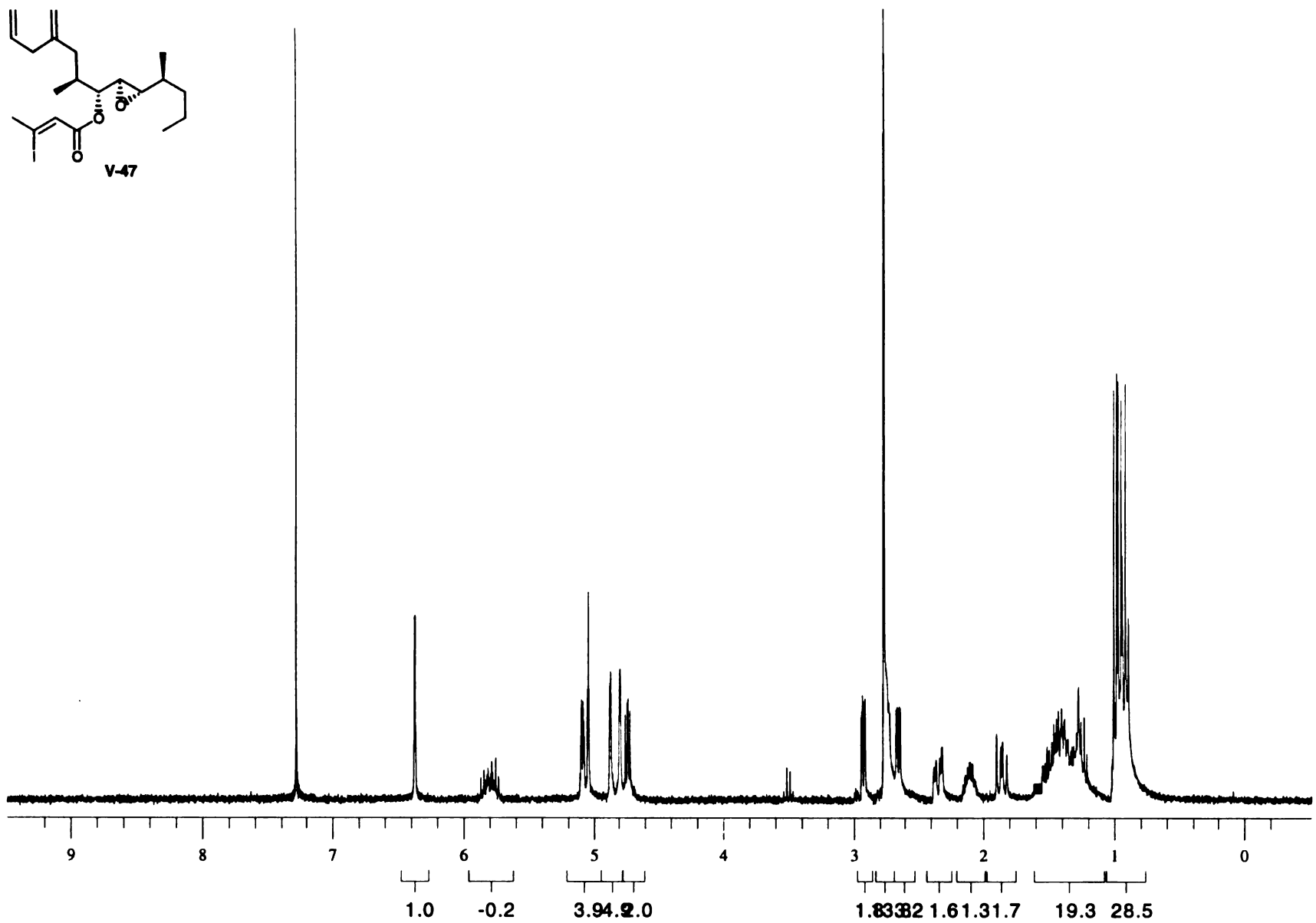
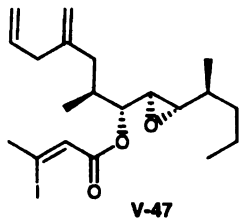
1.0
7.6
7.9
1.8
7.0
9.5
2.1
11.2
35.5
49.1



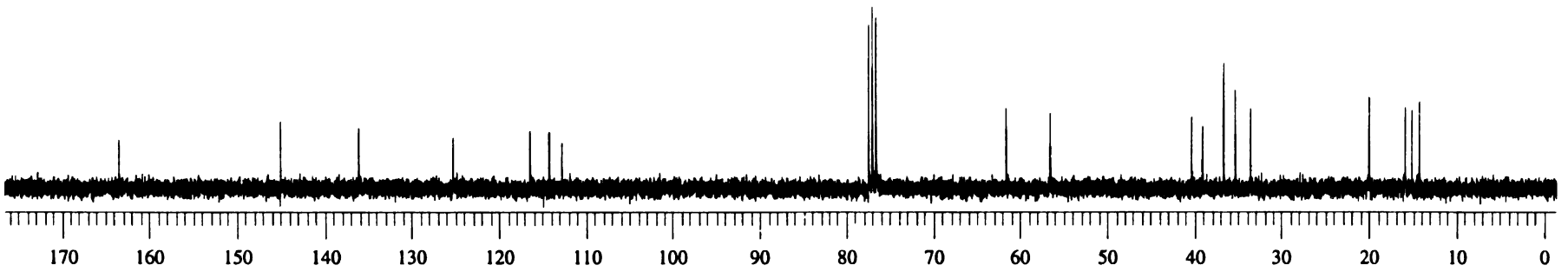
V-42

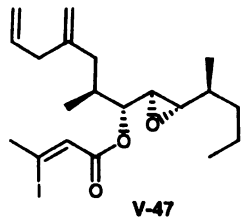



V-47
9
8
7
6
5
4
3
2
1
0
1.0
-0.2
3.9
4.2
2.0
1.8
3.3
3.2
1.6
1.3
1.7
19.3
28.5

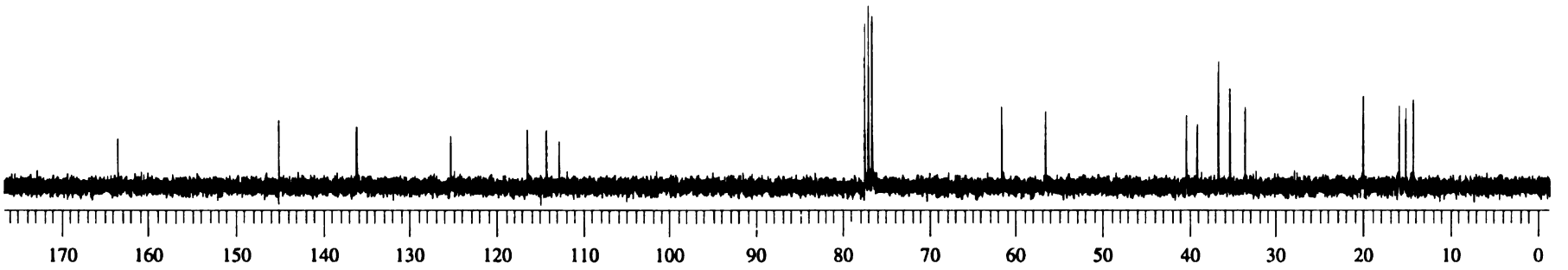


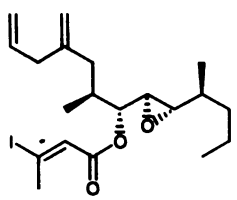
V-47



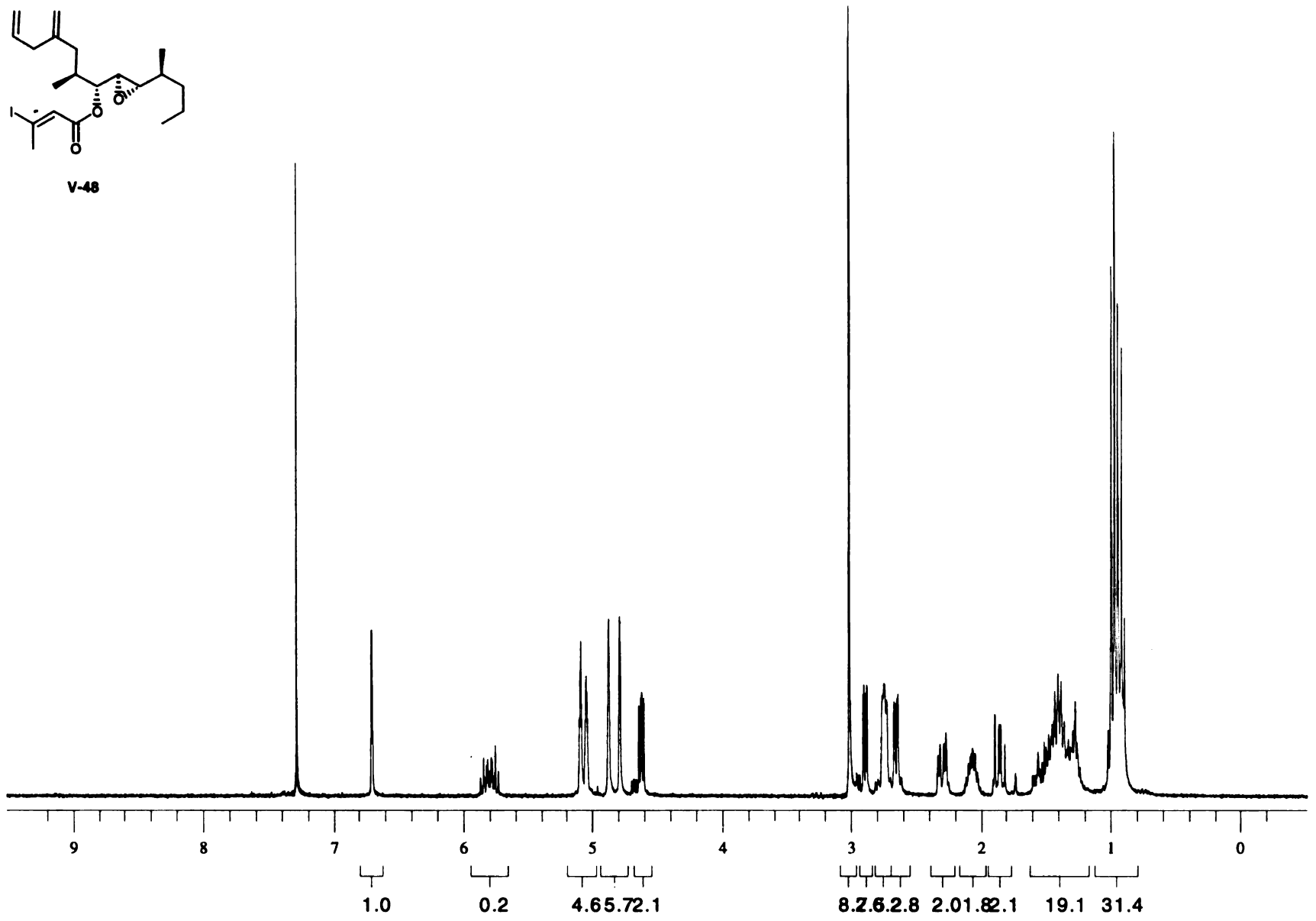


V-47





V-48


V-48
9
8
7
6
5
4
3
2
1
0
1.0
0.2
4.6
5.7
2.1
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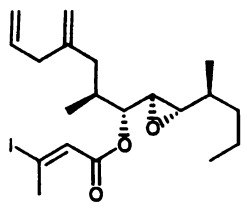
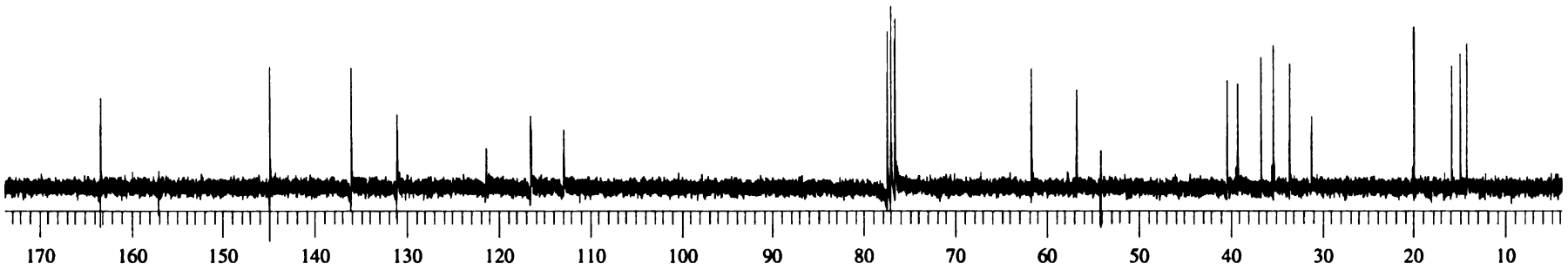
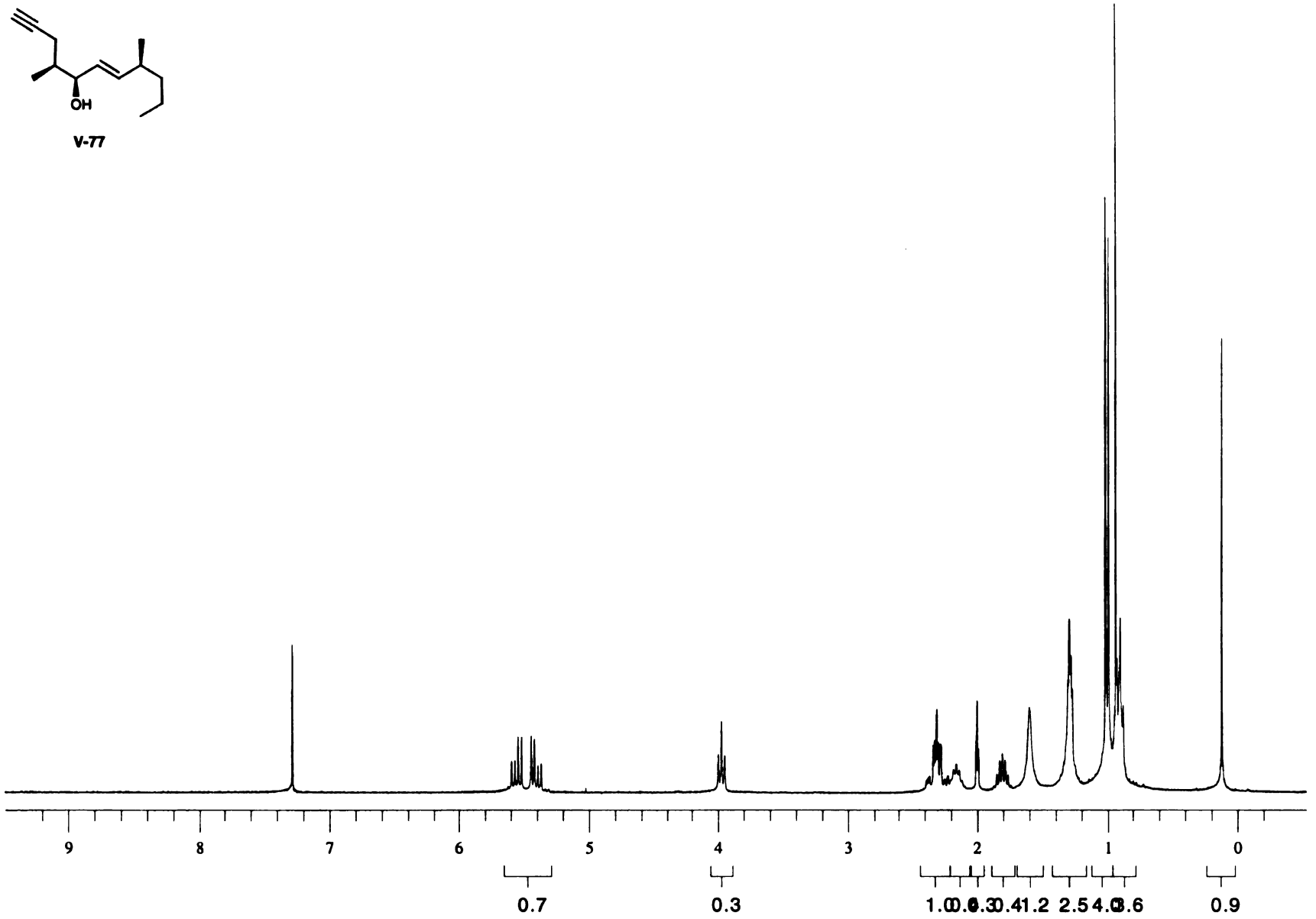
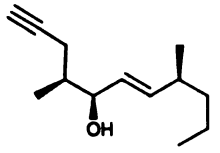
8.8
2.0
1.8
2.1
19.1
31.4



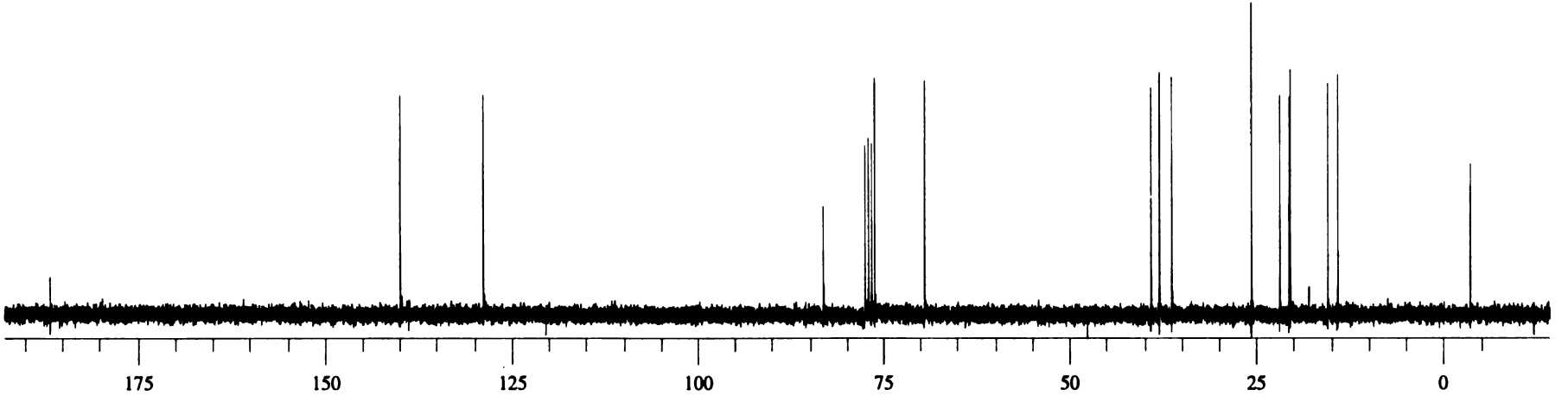
V-48

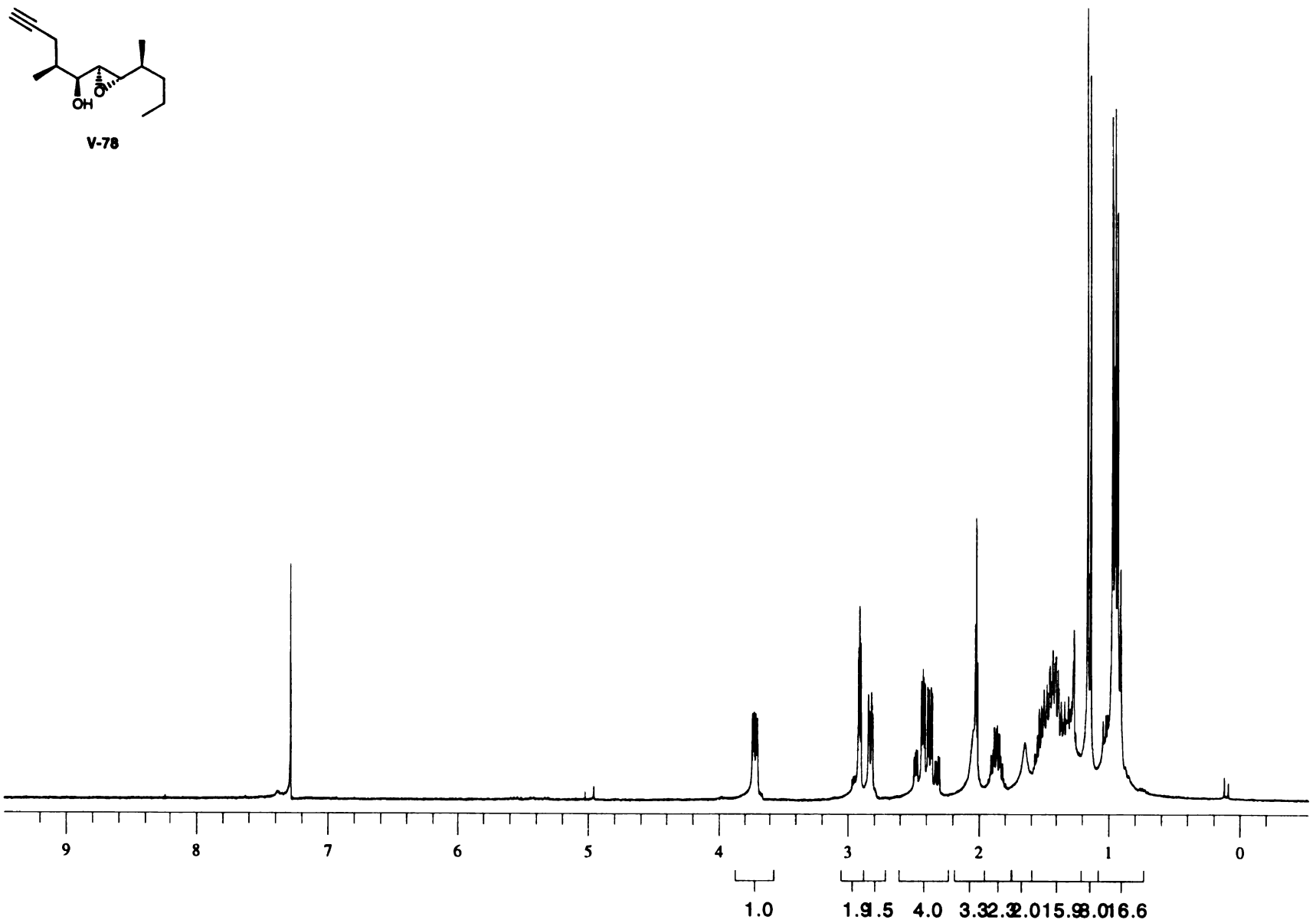



OH
V-77
9
8
7
6
5
4
3
2
1
0
0.7
0.3
0.9



V-77




OH
O
V-78
9
8
7
6
5
4
3
2
1
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1.9
1.5
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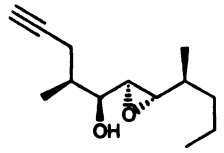
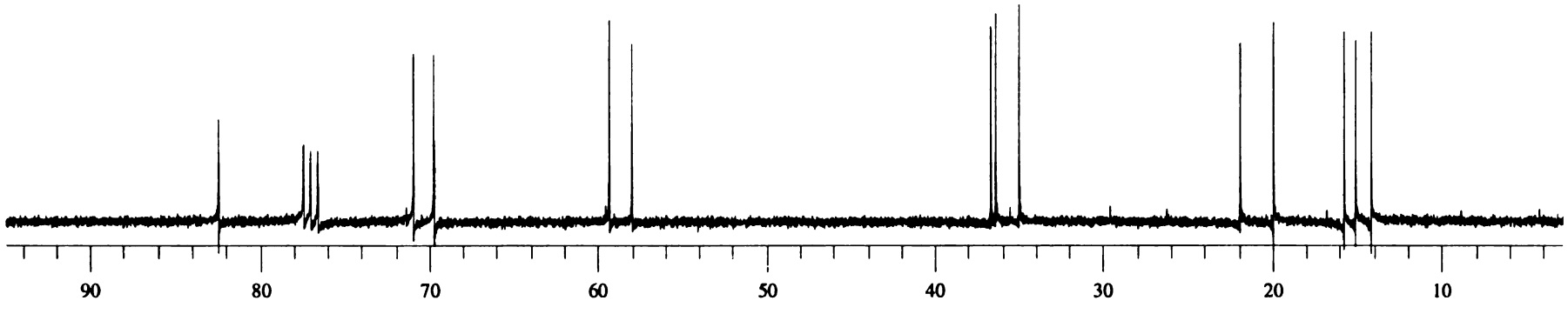
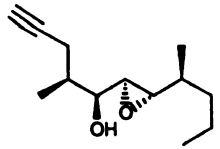
2.0
1
5.9
8.0
16.6



V-78





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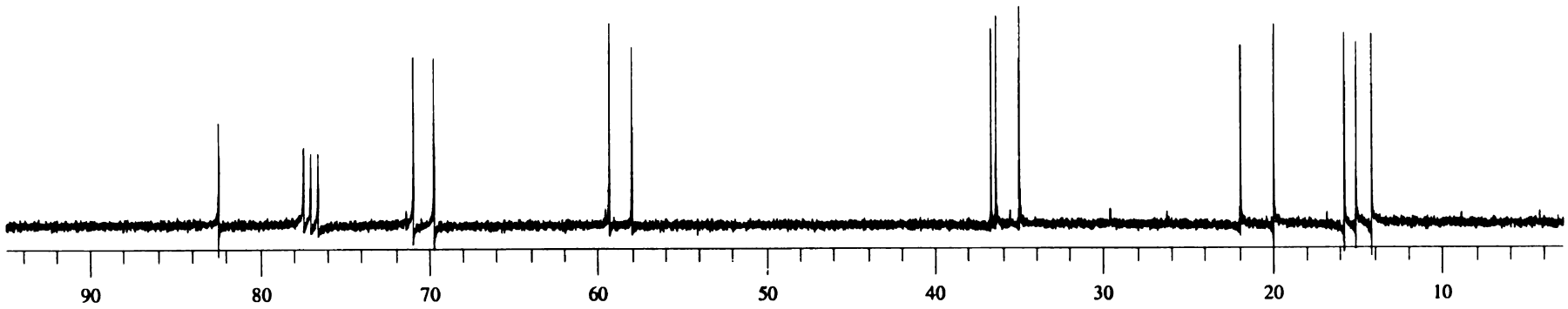

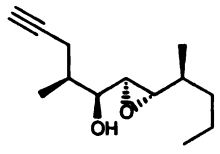

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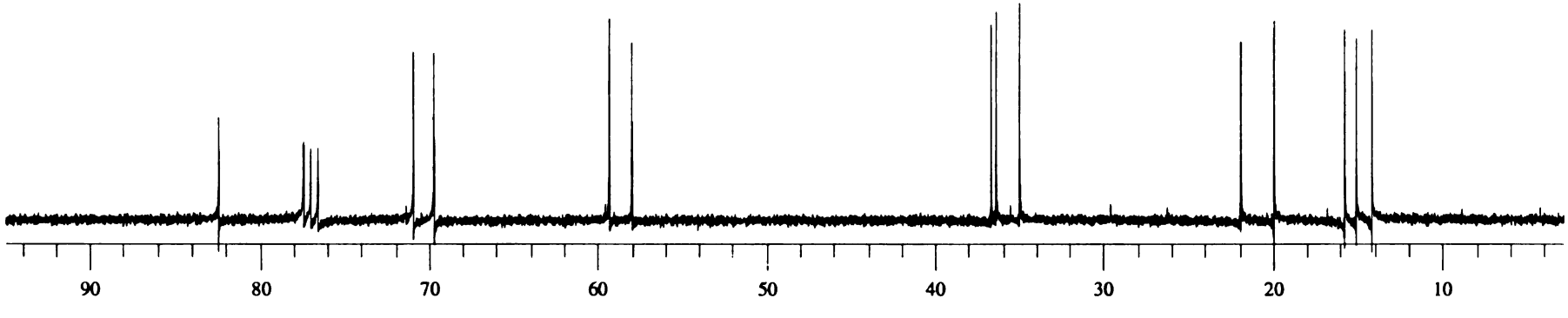
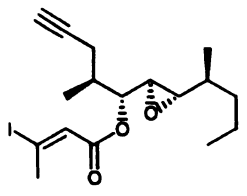
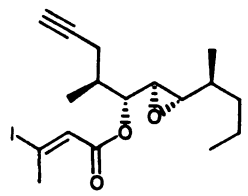
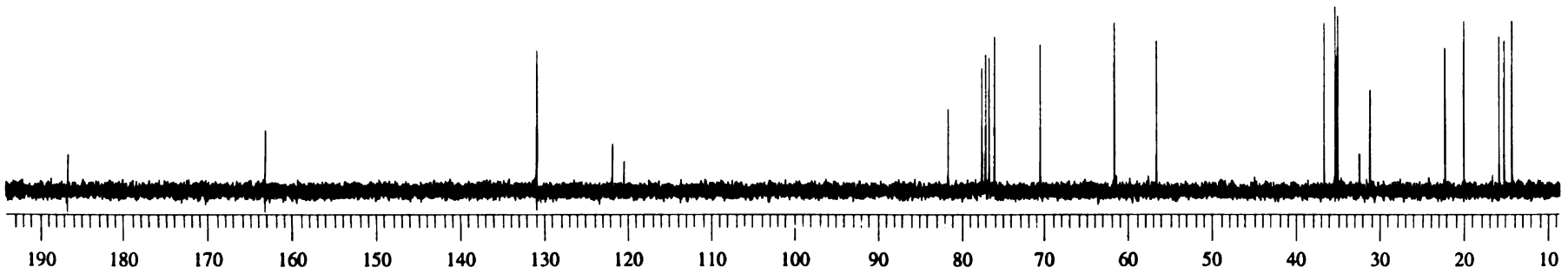


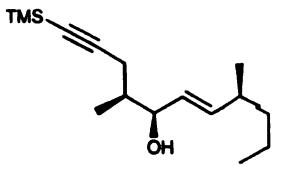


V-79



V-79





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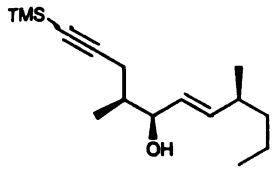
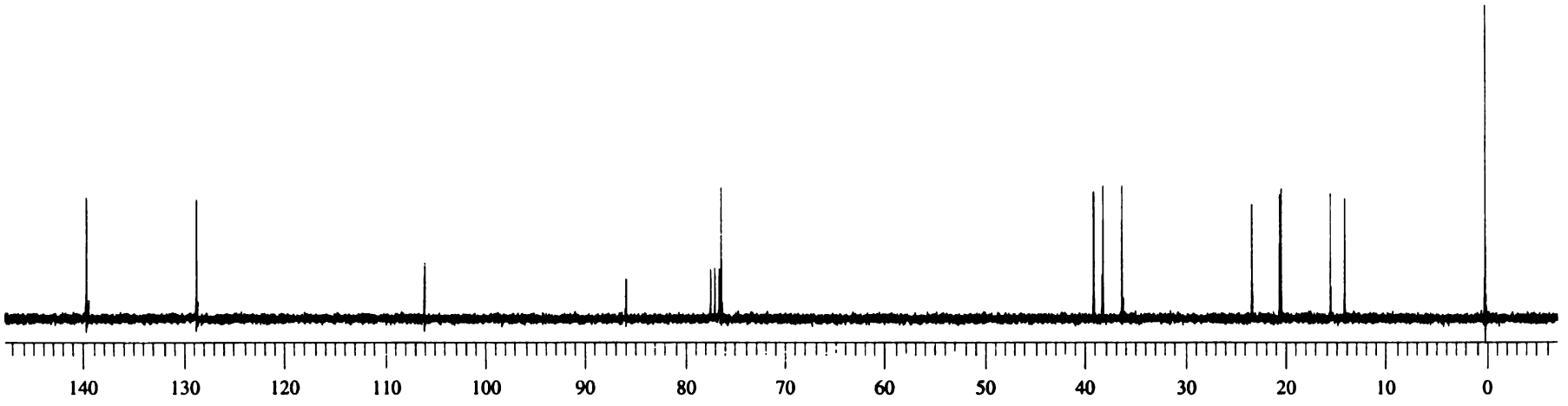
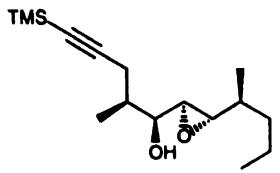
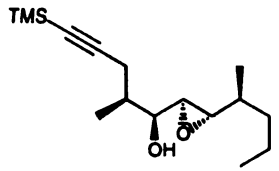


V-80

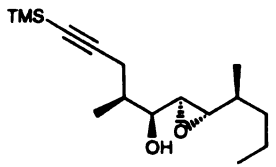




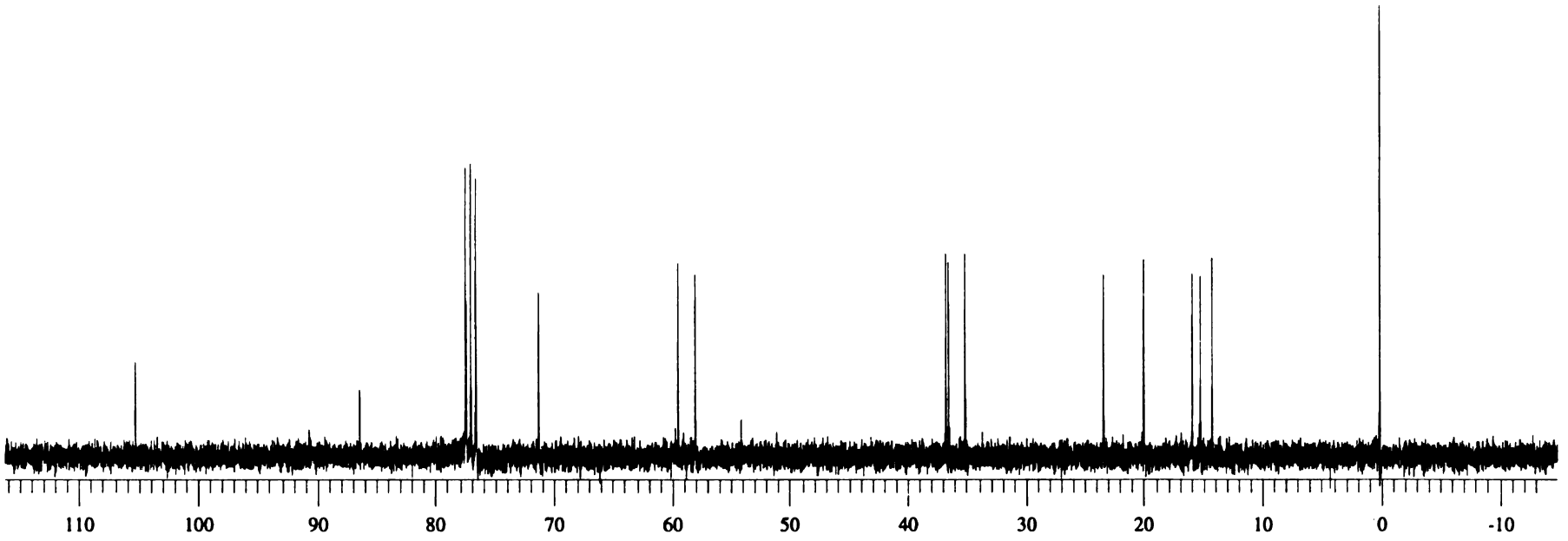
V-81

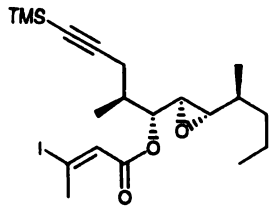


V-81

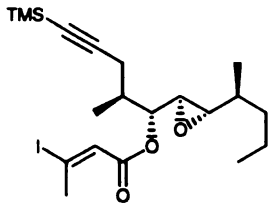


V-81

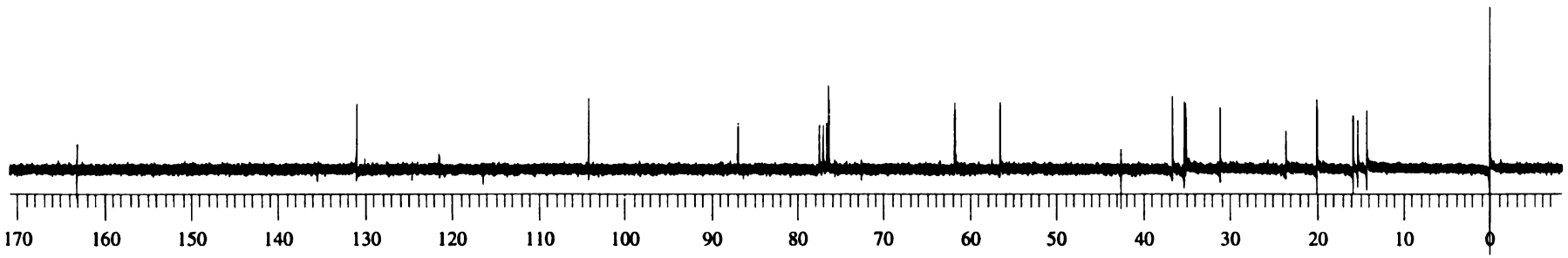




V-82


TMS
I
O
O
O

V-82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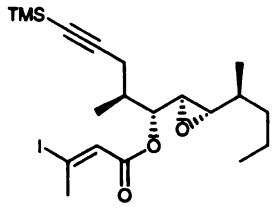
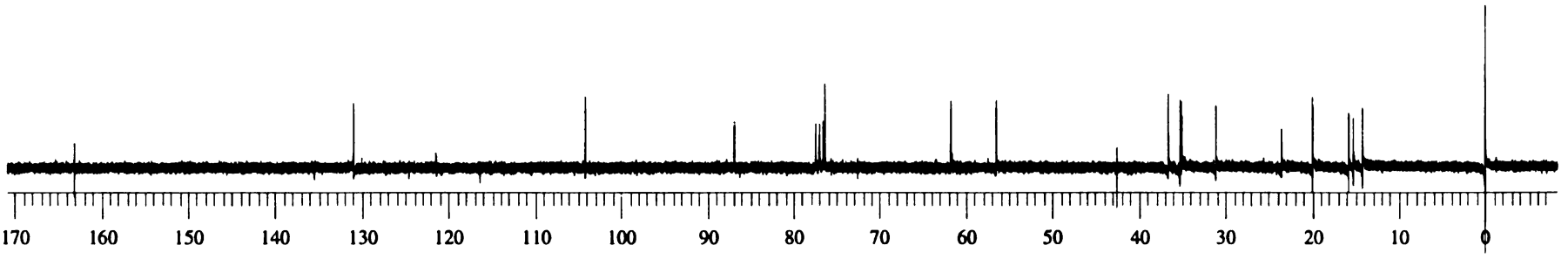
20
10
0


TMS
I
O
O
O

V-82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130
120
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90
80
70
60
50
40
30
20
10
0

APPENDIX 2

ORTEP REPRESENTATION OF COMPOUND **II-22**

ORTEP representation of **II-22**