PREPARATION OF SUBSTITUTED ENOL DERIVATIVES FROM TERMINAL ALKYNES AND PROGRESS TOWARD THE TOTAL SYNTHESIS OF NIGRICANOSIDE A

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DEDICATION

For My Family and Friends

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Undoubtedly, my lovely wife Serena is the most important person to acknowledge. She took quite a leap of faith when she moved to Dallas, a city where she had few friends, no family, and no job. She coped with my demanding work schedule without complaint, and the special occasions we were able to spend together were the highlights of my week. Thus for her faith, love, and support, I am forever grateful.

PREPARATION OF SUBSTITUTED ENOL DERIVATIVES FROM TERMINAL ALKYNES AND PROGRESS TOWARD THE TOTAL SYNTHESIS OF NIGRICANOSIDE A

by

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DISSERTATION

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ABSTRACT

PREPARATION OF SUBSTITUTED ENOL DERIVATIVES FROM TERMINAL ALKYNES AND PROGRESS TOWARD THE TOTAL SYNTHESIS OF NIGRICANOSIDE A

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This manuscript consists of two chapters. The first chapter describes the preparation of stereodefined enol derivates of α-branched aldehydes from terminal alkynes. Specifically, alkenyl alanes, derived from the methylalumination of alkynes, are shown to be efficiently oxygenated with peroxyzinc species. The resulting metallo-enolate may be trapped with benzoic anhydride, acetic anhydride, and TESOTf to generate *E*-trisubstituted enol esters and silanes. Traditional approaches to these types of olefins involve enolization of aldehydes; these methods are often inefficient and generally afford mixtures of olefin stereoisomers. Therefore, the methodology presented Chapter One represents a conceptually novel and useful strategy. The development and scope of the methylalumination-oxygenation reaction is discussed along with applications of the enol derivatives in the context of asymmetric and natural product synthesis. Finally, the alkenyl alane intermediates are shown to be efficiently aminated to afford ene-hydrazine products.

The second chapter involves the progress towards the asymmetric synthesis and structural assignment of nigricanoside A, a potent antimitotic glycolipid isolated from marine green algae. A convergent synthetic route is presented along with an analysis the natural product's relative and absolute

stereochemistry. Various diastereomers of orthogonally protected subunits of nigricanoside A were prepared through vinyl-metal additions to α-hydroxy aldehydes. The chapter includes attempts to join the subunits through etherification reactions as well as descriptions of future strategies to effect etherification.

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PRIOR PUBLICATIONS

Espindola, Ana Paula D. M.; Crouch, Ronald; DeBergh, John R.; Ready, Joseph M.; MacMillan, John B. **"**Deconvolution of Complex NMR Spectra in Small Molecules by Multi Frequency Homonuclear Decoupling (MDEC)" *J. Am. Chem. Soc.* **2009**, 131, 15994-15995.

DeBergh, J.R.; Spivey, K.M.; Ready, J.M. "Preparation of Substituted Enol Derivatives From Terminal Alkynes and Their Synthetic Utility" *J. Am. Chem. Soc.* **2008**, 130, 7828-7829.

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Ac	acetyl
acac	acetylacetonyl
AD	asymmetric dihydroxylation
anhyd.	anhydrous
APCI	atmospheric pressure chemical ionization
aq.	Aqueous
Ar	aryl (substituted aromatic ring)
BBN (9-BBN)	9-borabicyclo[3.3.1]nonane (9-BBN)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
t-Bu	*tert*-butyl
BuLi	butyl lithium
Bz	benzoyl
calc'd	calculated
cat.	Catalytic
ca	cerca (approximately)
°C	degrees Celsius
conc.	concentrated
Cp	cyclopentadienide
Cp^*	pentamethyl cyclopentadienide
Cy	cyclohexyl
δ	chemical shift downfield from $(CH_3)_4Si$
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-benzoquinone
DIAD	diisopropyl azodicarboxylate

DIBAL	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMDO	dimethyldioxirane
DMAP	*N*,*N*-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMPM	3,4-dimethoxybenzyl
DMPMCl	3,4-dimethoxybenzyl chloride
DMSO	dimethylsulfoxide
DMS	dimethylsulfide
DMP	Dess-Martin periodinane
dr	diastereomeric ratio
dt	doublet of triplets
E^+	electrophile (denotes any electrophile in general)
ee	enantiomeric excess
eq.	equation
equiv	equivalent
ES+	electrospray, positive ionization mode
Et	ethyl
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
E-X	electrophile (denotes any electrophile in general)
FT-IR	Fourier transform infrared
g	gram
GC	gas chromatography
h	hour
[H]	reductant
Hg mm	millimeter of mercury (760 Hg mm = 1 atm = 760 Torr)
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear Single quantum coherence

hν	light
Hz	hertz
IPA	isopropyl alcohol
i-Pr	isopropyl
IR	infrared
J	coupling constant
L	ligand
LA	Lewis acid
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
liq.	liquid
LTBP	lithium *tert*-butyl peroxide
LUMO	lowest unoccupied molecular orbital
M	molar
m	multiplet or medium
[M]	metal
MAO	methylaluminoxane
m-CPBA	*m*-chloroperoxybenzoic acid
MDR	multiple drug resistance
Me	methyl
MeCN	acetonitrile
Mes	mesityl
mg	milligram
MHz	megahertz
min	minutes
mL	milliliter
mmol	millimole
MOM	methoxymethyl
m/z	mass / charge
Ms	methane sulfonyl
MS	molecular sieves
N	normal
NBS	*N*-bromosuccinimide

NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine oxide
NMR	nuclear magnetic resonance
n-Pr	propyl
Nu	nucleophile
o-	ortho
[O]	oxidant
OAc	acetate
OMs	mesylate
OTf	triflate
p-	para
Ph	phenyl
PCC	pyridinium chlorochromate
PhH	benzene
PhMe	toluene
PMB (MPM)	*p*-methoxybenzyl
PMBTCA	PMB-acetimidate
PPh_3	triphenylphosphine
ppm	part per million
PPTS	pyridinium *p*-toluenesulfonate
pyr	pyridine
q	quartet
rac	racemic
R_f	retention factor in chromatography
ROESY	rotating-frame overhauser effect spectroscopy
rt	room temperature
Salen	*N,N'*-ethylenebis(salicylideneiminato)bis (salicylidene)
s	singlet or strong
t	triplet
TBAF	tetrabutylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl

Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylenediamine
TMS	trimethylsilyl
tol	toluene
T_r	retention time
p-TsOH	*p*-toluenesulfonic acid
Ts	toluenesulfonyl
UV	ultraviolet
w	weak
y	yield
Δ	heat at reflux

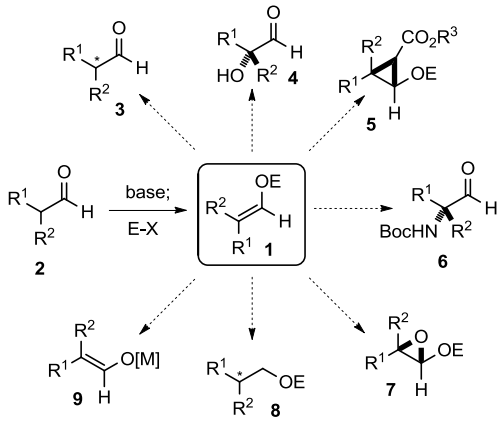
1. CHAPTER ONE

Preparation of Enol Derivatives from Terminal Alkynes

1.1. Introduction

Enol derivatives of α-branched aldehydes (**1**, Figure 1.1.1) represent valuable building blocks for organic synthesis, but efficient methods for preparing **1** stereoselectively remain scarce. These densely functionalized olefins are potential precursors to stereodefined enolate anions (**9**)[1, 2] and various optically active compounds (**3**-**8**) such as those represented in Figure 1.1.1.[3-5] Traditional approaches to **1** involve enolization of the corresponding α-branched aldehyde (**2**), but these protocols offer little stereocontrol. Furthermore, the aldehyde starting materials *themselves* are difficult to prepare and often require multiple synthetic transformations. As such, the limited access to enol derivatives of α-branched aldehydes has prevented extensive investigations into this area of organic chemistry and rendered these resources underutilized.

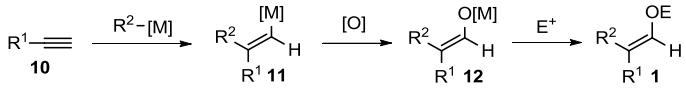
Figure 1.1.1 Synthetic Utility of Enol Derivatives of α-Branched Aldehydes



In principle, an alternative strategy might involve tandem carbometalation-oxygenation of terminal alkynes (**10**, Scheme 1.1.1). In this way, carbometalation of the terminal acetylene generates a stereodefined vinyl metal intermediate (**11**) that may react with various electrophiles. Reacting **11** with an electrophilic oxygen donor would generate a specific enolate geometric isomer (**12**), and subsequent electrophilic trapping of the resulting metallo-enolate would provide the stereodefined enol derivative **1**. A previous report from the Ready Laboratory documented the tandem carbocupration-oxygenation of terminal alkynes **10**, in which a vinyl copper intermediate (**11**, [M] = Cu) was oxidized with lithium *tert*-

butyl peroxide (^{t}BuOOLi).[6] This method granted access to various alkyl-substituted enol esters and silanes (**1**, R^2 = alkyl, E = COR or SiR_3) with the exception, however, of their methyl-substituted analogs (**1**, R^2 = CH_3). Accordingly, the preparation of methyl-substituted enol derivatives from terminal acetylenes remained an unanswered problem.

Scheme 1.1.1 Preparation of Enol Derivatives from Terminal Acetylenes



Presented herein is an account of the successful development and scope of a methylalumination-oxygenation reaction of terminal alkynes. This Chapter includes novel applications of the previously inaccessible enol products in asymmetric and natural product synthesis, as well as advances toward an analogous electrophilic amination reaction offering stereodefined enamine products. The results of these explorations are prefaced by a brief literature review of traditional approaches to **1**, alkyne carbometalation, electrophilic oxygenation of carbanions, and a more detailed discussion of previous work from this laboratory.

1.2. Background

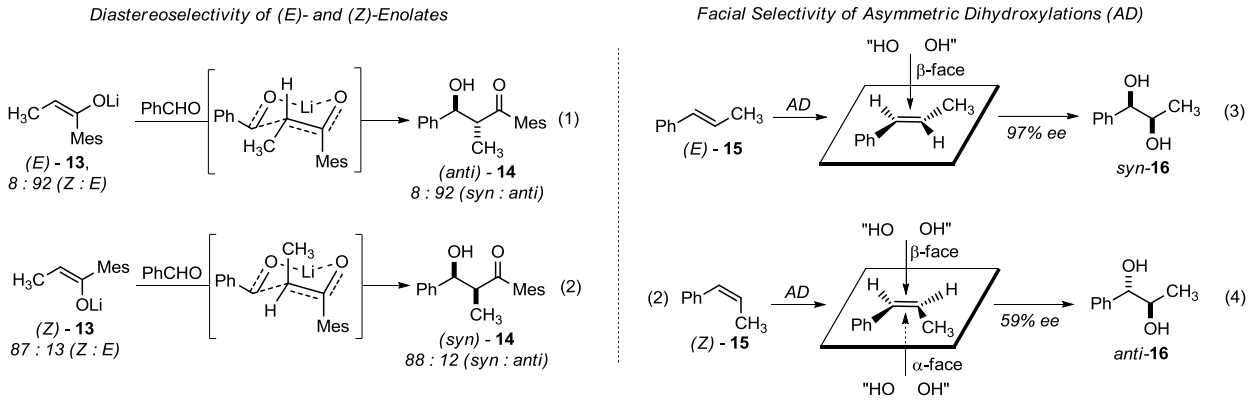
1.2.1. Enol Derivatives of α-Branched Aldehydes

1.2.1.1. Importance of Olefin Geometry

An efficient route to enol derivatives of substituted aldehydes would require the complete stereocontrol over the geometric isomers, as the purity of **1** would be crucial to achieve high selectivity in subsequent transformations. The effects of enol configuration on diastereoselectivity may be best represented in terms of enolate functionalizations, since lithium enolates may be generated by treating enol silanes and enol acetates with methyl lithium.[2] Specifically, in aldol condensation reactions the enolate stereostructure is of particular importance because it defines the relative configurations of the two newly created chiral centers (Scheme 1.2.1, eqs. 1 and 2).[7, 8] As exemplified below, the *E*-lithium enolate (*E* - **13**) reacts with benzaldehyde to form the *anti*-aldol adduct (*anti*-**14**, eq. 1), while the *Z*-isomer (*Z*-**13**) produces the opposite diastereomer (*syn*-**14**, eq. 2).[9] Importantly, in both cases the distribution of products directly reflects the ratio of olefin diastereomers in the starting material. Similarly, in dihydroxylations of alkenes (eqs. 3 and 4), the geometry of the prochiral substrate governs the relationship of the stereocenters in the product, and this observation is consistent with most concerted, stereospecific processes involving

1, 2-substituted alkenes. Furthermore, in the context of *enantioselective* transformations, the configuration of a double bond is generally critical for high facial selectivity (Scheme 1.2.1, eqs. 3 and 4). For example, the chiral cinchona alkaloid ligand employed in Equations 3 and 4 is well-suited to accommodate the structure of (*E*)-**15**, which undergoes oxidation from the β-face with high selectivity (eq. 3).[10] The converse is true for (*Z)*-**15** and most other *cis*-1,2-disubstituted olefins which are notoriously poor substrates for AD reactions. Subjecting a mixture of geometric isomers to AD would afford both diol diastereomers; if *anti*-**16** and *syn*-**16** were separable, then ultimately the desired diol (*anti*-**16**) would be obtained in lower yield than if a pure sample were employed.

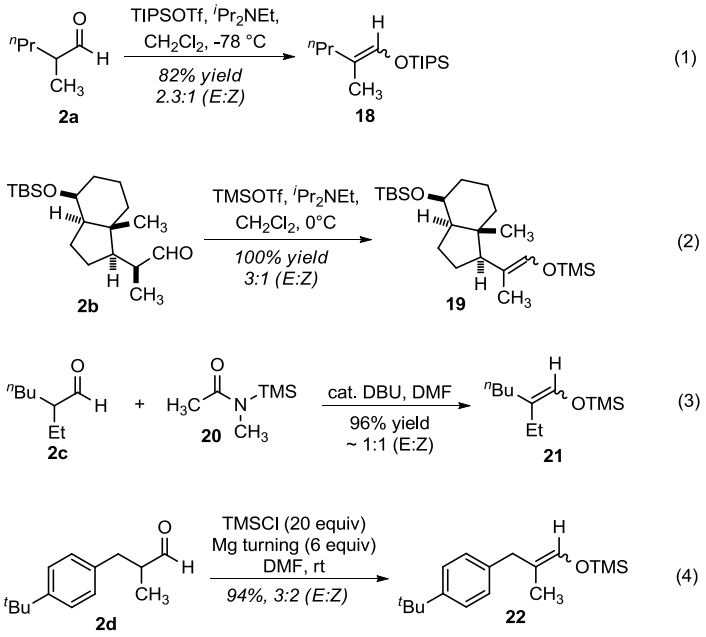
Scheme 1.2.1 Importance of Olefin Geometry



1.2.1.2. Preparations of Enol Derivatives of Branched Aldehydes

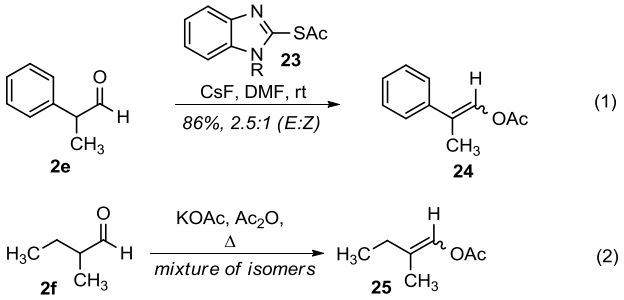
Enol derivatives of this nature (**1**) are most often prepared from the corresponding α-substituted aldehyde **2**, although these approaches generally afford mixtures of olefin stereoisomers. Conventional strategies for obtaining silyl enol ethers involve the use of chlorosilanes or silyl triflates with amine bases (e.g. $^{i}Pr_2NEt$). In the two representative examples in Scheme 1.2.2 (eqs. 1 and 2),[11,12] the standard conditions produce mixtures of geometric olefin isomers (of **18** and **19**); the diastereomers of **18** were separable while those of **19** were not. More elaborate entries to enol silanes have surfaced (eqs. 3 and 4), but these appear to have little advantage over those previously mentioned. In particular, TMS-acetamide **20** allows the use of a catalytic base, but yields **21** as a 1:1 ratio of *E*- and *Z*-enol silanes (eq. 3).[13] Finally, a method employing Mg turnings affords high yields of the olefin products as well, but again, the reaction leads to an unsatisfactory distribution of olefin stereoisomers (eq. 4).[14]

Scheme 1.2.2 Synthesis of Enol Silanes from Aldehydes



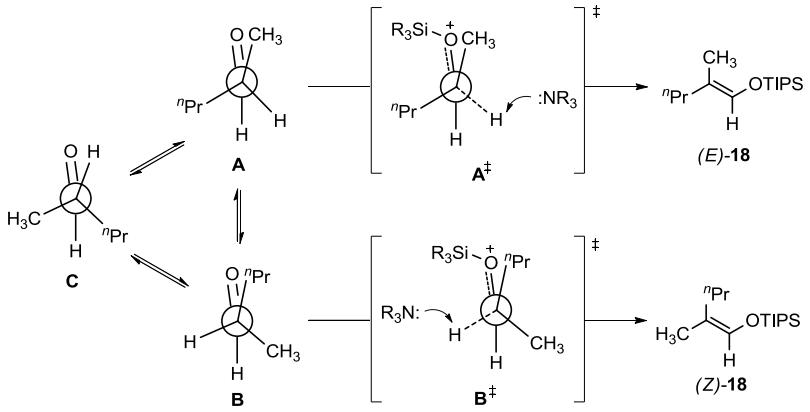
Trisubstituted enol *esters* of α-branched aldehydes are even more challenging to access. Under basic conditions, a chemoselectivity issue may complicate matters as C-alkylation often competes with acylation of the enolate oxygen atom.[15] Furthermore, acylation with acetic anhydride or acetyl chloride introduces acidic α-protons which may lead to over-alkylation. These problems may be circumvented by using vinyl acetate and a strong, usually sulfonic-, acid; however this method is incompatible with acid-labile substrates.[16] In one particular procedure specific to aldehydes, *S*-(2-benzimidazolyl) alkyl thiolates (**23**) delivers various enol esters in good yields, albeit with low selectivity (Scheme 1.2.3, eq. 1).[17] A more traditional approach for preparing enol acetates (**25**) from aldehydes (**2f**) involves refluxing the substrate in acetic anhydride in the presence of potassium acetate (eq. 2),[18] but these forcing conditions would be incompatible with thermally-labile compounds. More problematic, the procedure offers little stereocontrol.

Scheme 1.2.3 Synthesis of Enol Esters from Aldehydes



The origin of poor stereocontrol may be rationalized by examining the low-energy conformations of 2-methyl pentanal (**2a,** Scheme 1.2.2), for example. In general, the 1,3-eclipsing interaction of a substituent (alkyl or proton) and the C-O bond of the aldehyde (as in **A**-**C** in Figure 1.2.1) is favored slightly over that between the same substituent and the carbonyl hydrogen.[19] Therefore, let us represent the three relevant conformers as **A**-**C** in the figure below, where enolization of **A** provides the *E*-enol silane while its counterpart (**B**) leads to the corresponding *Z*-isomer.[9] The conformer in which the α-methyl substituent eclipses the carbonyl oxygen (**A**) is more stable than rotamer (**B)** by roughly 0.2 kcal•mol^{-1}.[19] The similar steric demands of the α-CH_3 and α-CH_2 substituents may explain the low activation energy for **A** ↔ **B** interconversion, which in turn reflects the distribution of isomeric products obtained from soft enolization of **2a** (2.3:1, *E* / *Z)*. This reasoning would suggest that an acetaldehyde derivative substituted with a bulkier alkyl group (> *n*-propyl) would lead to products with higher *E*-isomer content. Although only slightly more selective, the enolization of aldehyde **2b** produces **19** with a 3:1 ratio of *E*- and *Z*-olefins. Finally, the small difference in size of the carbonyl oxygen and hydrogen atoms of **2** likely contributes to the poor stereocontrol of these reactions as well; enolizations of ketones generally display higher selectivity under both kinetic and thermodynamic conditions.[20]

Figure 1.2.1 Conformers of 2-methyl pentanal (2a)



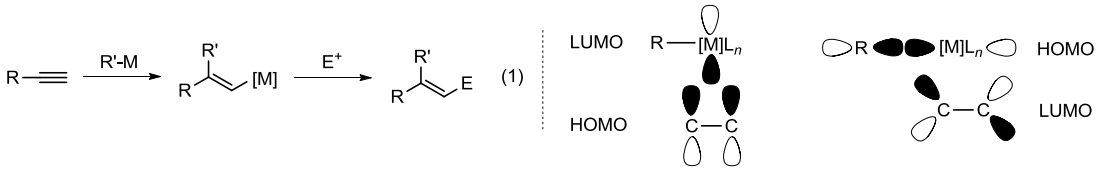
In this regard, the examples in Scheme 1.2.2 and Scheme 1.2.3 do not represent worst-case scenarios; conversely, they are typical examples that inadvertently provide insight into the problems associated with accessing geometrically pure samples of **1**. The necessity for an alternative approach to stereodefined enol derivatives may be further emphasized when considering their traditional precursors **2**. Strategies for obtaining the α-branched aldehydes *themselves* are limited in reaction scope and may require multiple synthetic operations.[21-25] Hydroformylation provides an alternative to enolate alkylation, but general methods to control regioselectivity remain elusive.[26] Considering these difficulties

collectively, an unconventional yet viable entry to **1** would certainly contribute a great deal to the synthetic community.

1.2.2. Carbometalation

In principle, controlled carbometalation of alkynes provides an attractive approach to trisubstituted alkenes (Scheme 1.2.4, eq. 1). In this regard, carbometalation proceeding via a concerted mechanism would be especially attractive because the alkyne addition may be more facile and highly stereoselective. Analysis of the frontier molecular orbitals suggests a four-centered, *syn*-addition of the R—M bond to the C—C triple bond occurs depending on the availability of a low-lying, empty metal orbital (Scheme 1.2.4).[16] Many organotransition metals are capable of mediating carbometalation; however, examples of controlled, single-stage carbometalations of unactivated alkynes are scarce.[27, 28] Two of the most general methods that effect this transformation are carbocupration and its complimentary zirconium-catalyzed methylalumination reaction. These are the most relevant carbometalation strategies in the context of this chapter; therefore, this section will be limited to discussing these two processes.[29]

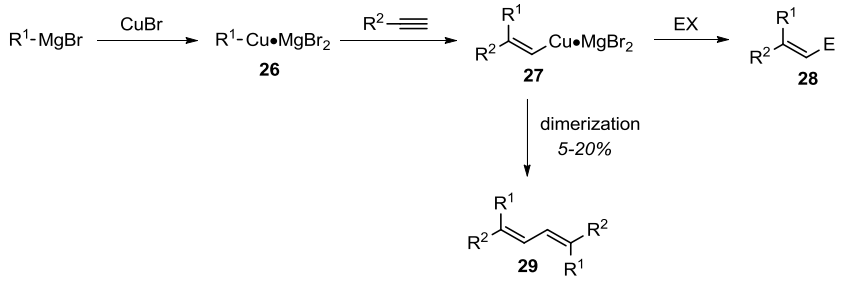
Scheme 1.2.4 Carbometalation of Alkynes



1.2.2.1. Carbocupration of Terminal Alkynes

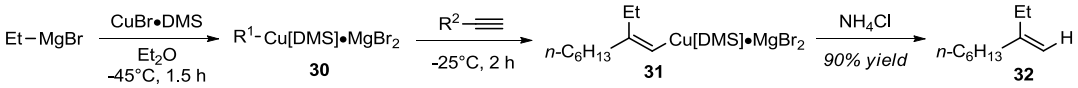
Among the various carbometalation protocols, those based on organocopper reagents display the broadest generality with respect to the range of compatible organometallic nucleophiles.[30] The development of alkyne carbocupration commenced in 1971 with Normant's report that organocopper reagents (**26**), prepared from Grignard and CuBr, effect the carbocupration of unactivated terminal acetylenes (Scheme 1.2.5).[31] As discussed above, the addition across the acetylene triple bond occurs in a *syn* Markovnikov sense and generates a reactive vinyl copper species (**27**). This may be trapped with carbon-centered electrophiles to produce trisubstituted olefins (**28**). However, Normant's original conditions often yield significant amounts of 1,3-diene byproducts (**29**) derived from oxidative coupling of the alkenylcopper intermediates. This dimerization is well-known to be induced thermally[32] or by oxidants, including Cu(II) salt impurities present in commercial sources of cuprous halides.[33]

Scheme 1.2.5 Carbocupration of Terminal Alkynes



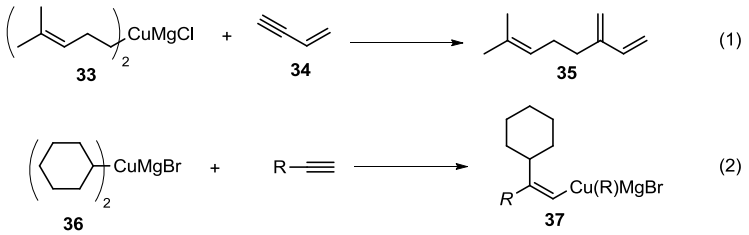
In 1973, House and coworkers reported a procedure for preparing a highly pure copper(I) bromide dimethyl sulfide complex free of Cu(II) salts and other contaminants.[34] By generating the organocopper reagents from the CuBr•DMS complex (**30**, Scheme 1.2.6), Helquist *et al.* found that the undesired oxidative dimerization side reaction could be suppressed.[35, 36] The organocopper species are typically prepared from the corresponding Grignard reagents as represented in the example below. In this case, treating 1-octyne with **30** followed by an aqueous workup afforded terminal olefin **32** in 90 % yield along with less than 2% of the corresponding diene. Vinyl copper species **31** may react with a variety of electrophiles such as allyl bromide, methyliodide, epoxides and unsaturated carbonyls, but their diorganocuprate counterparts (R_2CuMgX, R = alkenyl) are considerably more reactive toward certain electrophiles to which both R-groups may be transferred.[30]

Scheme 1.2.6 Carbocupration with CuBr•DMS Complex



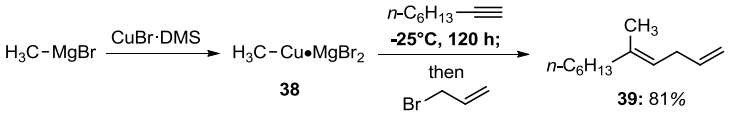
Diorganocuprates (**33**, Scheme 1.2.7) of the type R_2CuMgX are especially useful for carbocuprations with higher alkyl nucleophiles (R > ethyl). For example, in a short synthesis of myrcene (**35**, Scheme 1.2.7, eq. 1), the enyne triple bond in **34** underwent carbometalation efficiently, while lower yields were observed when the organocopper reagent was used.[37] In a second example, Ready and Zhang recently showed that successful carbocuprations with secondary and tertiary Grignard reagents was achieved only with the diorganocuprate complexes (R_2CuMgX, where R = *c*-C_6H_{11}, ^{t}Bu, and ^{i}Pr). The corresponding organocopper reagents prepared from these nucleophiles were unreactive toward alkynes (eq. 2).[6] Of note, diamine additives were used presumably to stabilize the cuprate intermediate at the temperatures necessary for alkyne addition.

Scheme 1.2.7 Carbocupration with Diorganocuprates (R_2CuMgX)



In general, Grignard nucleophiles are the most compatible organometallic reagents with acetylene carbocupration. Organocopper reagents derived from *n*-butyllithium tend to deprotonate terminal acetylenes,[38] although isolated reports document successful carbocuprations with organolithium reagents.[6] A more serious limitation of alkyne carbocupration, however, involves the inefficiency of *methyl*cupration; methylcopper addition to terminal, unactivated acetylenes requires extended reaction times at subzero temperatures. For example, under optimized conditions, complete methylcupration of 1-octyne is achieved after 120 hours at -25°C (Scheme 1.2.8).[35] The inefficiency has been attributed to the decreased solubility and lower reactivity of methylcopper (**38**) when compared to higher alkylcopper complexes.[39] Moreover, conducting the reactions at higher temperatures promotes thermal decomposition of alkenylcopper complexes to yield unwanted 1,3-dienes.[40]

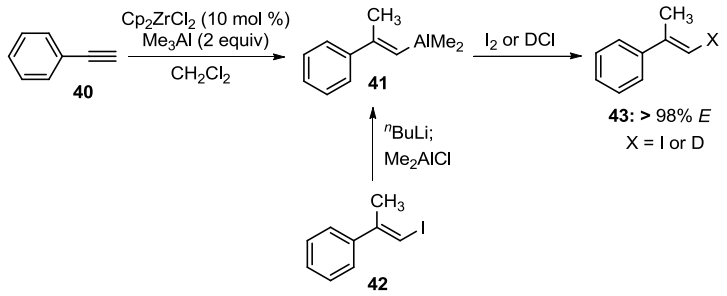
Scheme 1.2.8 Methylcupration of Unactivated Acetylenes



1.2.2.2. Methylalumination of Terminal Alkynes

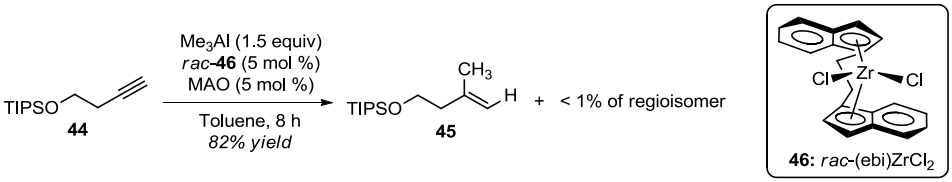
As mentioned previously, examples of controlled, single-stage carbometalations of unactivated alkynes are scarce. Along with carbocupration, Negishi's zirconocene-catalyzed methylalumination of terminal alkynes is essentially the only other such reaction that offers broad scope and high yields.[27] Considering the numerous naturally occurring methyl-substituted olefins, along with the difficulties associated with the use of methylcopper reagents, the Zr-catalyzed methylalumination has proven itself a useful synthetic tool.

Scheme 1.2.9 Negishi's Zr-Catalyzed Methylalumination



In 1978, Negishi reported that Cp_2ZrCl_2 catalyzes the methylalumination of phenylacetylene in the presence of excess Me_3Al (Scheme 1.2.9).[41] The ^1H NMR spectrum of an authentic sample of vinyl alane **41**, prepared from a lithium halogen exchange-transmetalation sequence, confirmed that this was indeed the alkenyl metal intermediate. The stereospecificity of the addition was established by trapping **41** with I_2 or DCl, affording over 98% of the *E*-olefin, or the *syn*-adduct (**43**). This high selectivity is typical in Zr-catalyzed alkyne methylaluminations unless a proximal directing group is present in the alkyne starting material.[42] The regioselectivity of the Cp_2ZrCl_2-catalyzed reaction is generally high as well; when **41** was trapped with a proton, only 4% of the regioisomer, or 1,2-disubstituted olefin was detected. The regioselectivity may be increased with the appropriate choice of Zr-catalyst, as reported by Lipshutz *et al*. For example, replacing Cp_2ZrCl_2 with *rac*-(ebi)$ZrCl_2$ (**46**, Scheme 1.2.10), the Brintzinger zirconocene catalyst, increases the regioselectivity of **45** from 96% to over 99%.[43] However, these conditions are seldom used due to the already high selectivity of the Cp_2ZrCl_2-catalyzed reaction, the cost of the Brintzinger catalyst, and the significant decrease in reaction rate observed with **46**.

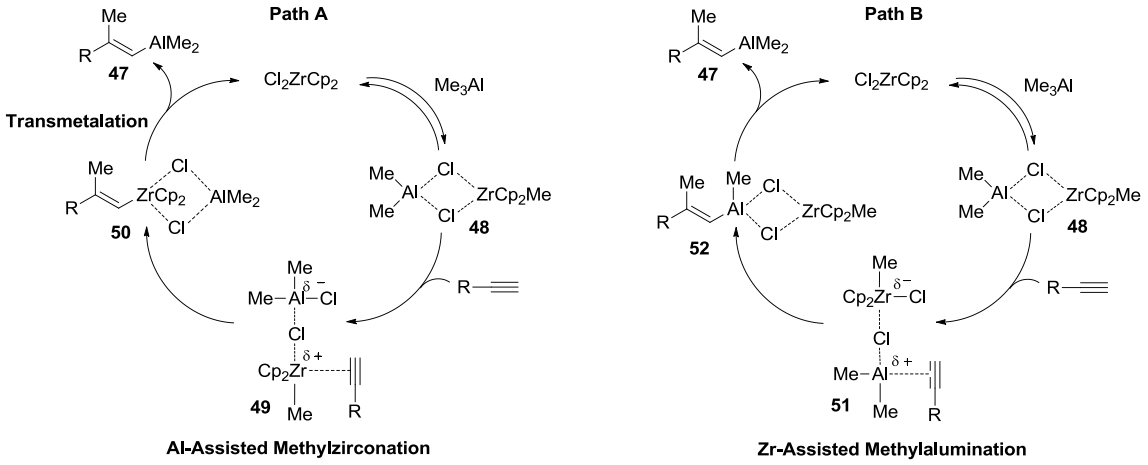
Scheme 1.2.10 Increased Regioselectivity in Methylalumination Reactions



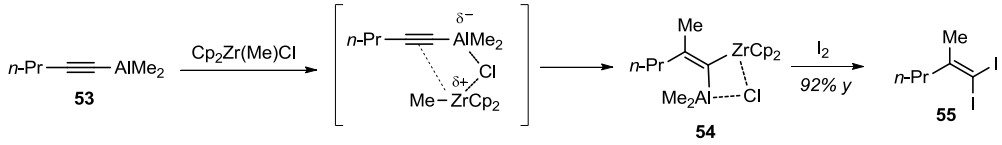
Two mechanisms for the Zr-catalyzed methylalumination have been proposed, as outlined in Paths A and B in Scheme 1.2.11.[44] Path A involves an Al-assisted methylzirconation followed by transmetalation from alkenyl zirconium to alkenyl alane, while Path B involves a Zr-assisted, direct methylalumination of the alkyne. Negishi and coworkers initially suggested the mechanism in Path A based on NMR experiments from which they observed a reversible methyl-chloro exchange between Me_3Al and Cp_2ZrCl_2. This transfer presumably forms a complex containing a $Cp_2Zr(Me)Cl$ species, such as **48**.[41] The Me-Cl exchange is rapid on the NMR time scale at room temperature; the ^1H NMR spectrum

of a 1:2 mixture of Cp_2ZrCl_2 and Me_3Al exhibits only two broad signals, one for the Cp and one for the methyl groups, neither of which correlate to the reactants alone. In addition, regarding transmetalation (**50** → **47**), alkenyl zirconium species are well known to readily convert to the corresponding alkenyl aluminum species on treatment with the appropriate aluminum reagents.[45]

Scheme 1.2.11 Proposed Mechanisms of Methylalumination

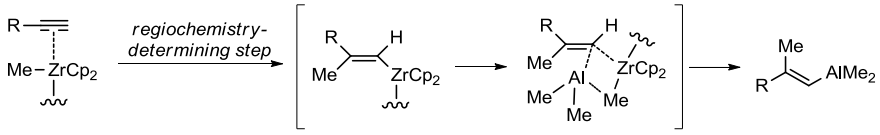


Scheme 1.2.12 Direct Methylzirconation of Alkynyl Alanes



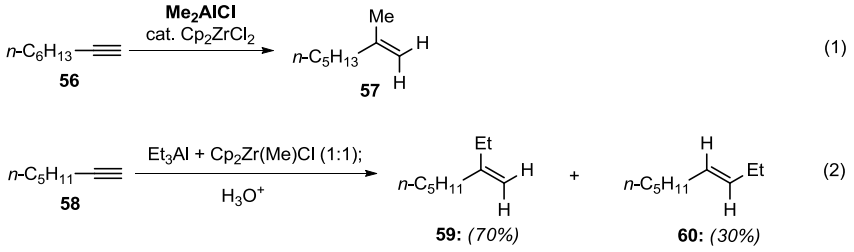
In further support of Path A, Negishi and Yoshida conducted an interesting experiment (Scheme 1.2.12) in which alkynyl alane **53** was treated with one equivalent of $Cp_2Zr(Me)Cl$,[46] a stable zirconocene complex that is essentially inert to alkynes. Through an apparent Al-assisted carbozirconation, these conditions generate the 1,1-dimetalloalkene **54**, which upon iodinolysis affords 1,1-diiodoalkene **55**.[47] Finally, it is worth noting that Lipshutz has suggested a mechanism similar to Path A based on increased regioselectivity of carbometalations when catalyzed by the more sterically demanding Brintzinger zirconocene (Scheme 1.2.13).[43]

Scheme 1.2.13 Lipshutz's Proposed Methylzirconation/Transmetalation Mechanism



Later studies from Negishi's group indicate that the reaction may involve the Zr-assisted direct, formal addition of trimethylaluminum to alkynes (Path B).[48] In particular, Me_2AlCl-Cp_2ZrCl_2 effects methylalumination of 1-octyne (**56,** Scheme 1.2.14) while no Me-Cl exchange is detected by NMR spectroscopy under these conditions. In further support of Path B, 1-heptyne reacts with a 1:1 mixture of Et_3Al and $Cp_2Zr(Me)Cl$[46] to afford a 70:30 mixture of **59** and **60** after protonolysis. In this experiment, no methylated alkenes or reduced, monosubstituted alkenes, from zirconium hydride species via β-hydride elimination of Zr-CH_2CH_3, were detected. Of note, the addition of H-Zr across terminal alkynes is possible without aluminum present, as hydrozirconation with $Cp_2Zr(H)Cl$ (Schwartz reagent) is common practice.[49] Based on the data presented in Scheme 1.2.14, Negishi stressed that the reaction shown in Scheme 1.2.12 is likely an "isolated, albeit special case of Al-assisted carbozirconation; however, rigorous exclusion of the mechanism in Path A cannot be made."[50]

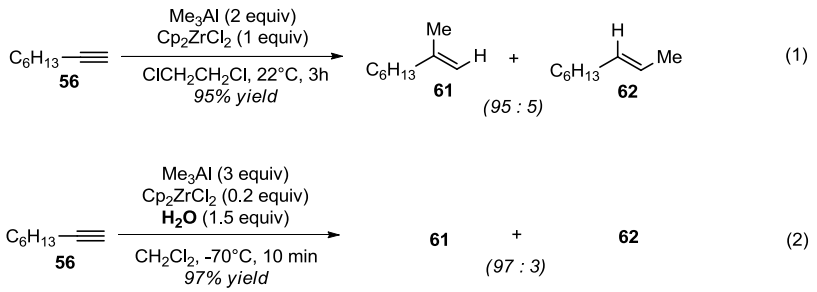
Scheme 1.2.14 Carboalumination with Other Organoaluminum Reagents



Negishi's original methylalumination reaction conditions remain the reliable standard for simple alkyl and aryl substituted alkynes (Scheme 1.2.9). Methylene chloride and dichloroethylene are the most common solvents for the transformation; Zr-catalyzed methylaluminations are sluggish in toluene and simply do not proceed in donor solvents. Furthermore, reaction rates may be reduced significantly with substrates containing accessible Lewis basic functionalities, such as ethers, esters, and amines. However, that a stoichiometric Lewis base would inhibit the active Lewis acidic carbometalation complex seems sensible. In this regard, the previously mentioned mechanistic NMR studies from Negishi's group revealed that addition of a stoichiometric amount of THF disrupted the Zr-Al complex (**48**, Scheme 1.2.11).[41] Whereas the NMR spectrum of a 1:2 mixture of Cp_2ZrCl_2 and Me_3Al shows only two broad signals, a mixture containing THF (1:2:2, Zr:Al:THF) exhibits three sharp methyl signals and two sharp Cp signals. These correlate to Cp_2ZrCl_2, $Cp_2Zr(Me)Cl$, Me_3Al•THF and Me_2AlCl•THF and suggest that in essence, one equivalent of THF (to Me_3Al) is sufficient to quench the active carbometalation reagent. Therefore, higher catalyst loadings and the use of additives are often necessary to achieve complete methylalumination of more functionalized substrates.

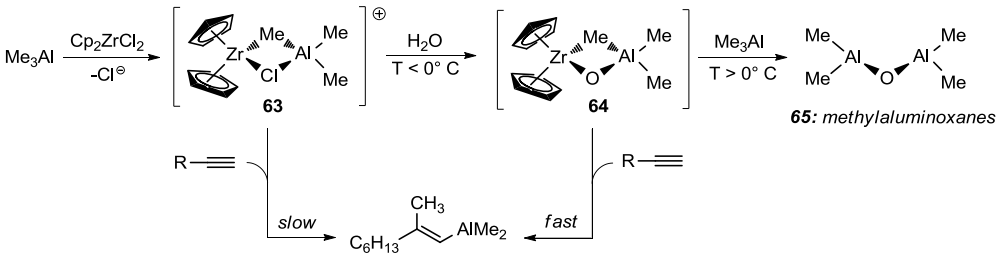
Introduction of water to a system containing excess Me_3Al and catalytic Cp_2ZrCl_2 at low temperatures dramatically increases the rate of methylalumination of alkynes, as described by Wipf and coworkers (Scheme 1.2.15).[51-53] Whereas the stoichiometric Zr-catalyzed methylalumination of 1-octyne required 3 hours for completion (Scheme 1.2.15, eq. 1), the catalytic reaction in the presence of 1.5 equivalents of water was complete in 10 minutes at -70°C (eq. 2).[51] The rate-enhancing effect is dramatic only at temperatures below 0°C, and other additives such as H_2S, alcohols, silanols, and diphenylborinic acid (Ph_2BOH) failed to reproduce the results with water. At higher temperatures, the reactive catalytic species apparently decomposes to methylaluminoxane (MAO, **65**) which failed to show appreciable accelerating effects in carboalumination reactions. Based on these results, Wipf proposed the formation of a thermodynamically labile oxo-bridged dimer (**64,** Scheme 1.2.16) as the highly active carbometalation reagent. Complex **64** is a likely product from the reaction of water with Me_3Al and Cp_2ZrCl_2, but the authors offer no further explanation regarding the origin of complex's (**64**) high reactivity.

Scheme 1.2.15 Rate-Enhancing Effects of Water on Methylalumination Reactions



Lipshutz, however, observed marked improvements in reaction rates when Brintzinger zirconocene-catalyzed methylaluminations were conducted in the presence of MAO as a cocatalyst (Scheme 1.2.10). Methylaluminoxane **65** is thought to exist as an oligomer of the formula Me_2Al—[O-AlMe]$_n$—O$AlMe_2$, where n = ~5-20, and the degree to which it activates Zr-based catalysts in Ziegler-Nata type polymerizations is relatively well known.[54] Analogous to the Ziegler-Nata process, the effects of MAO on Zr-catalyzed methylaluminations may involve the formation of a reactive cationic zirconocene complex.[52]

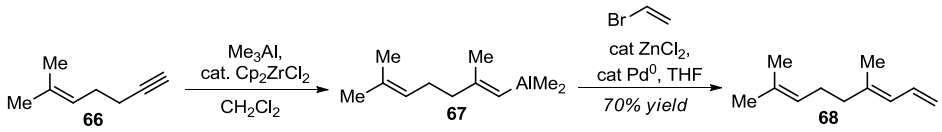
Scheme 1.2.16 Proposed Active Methylalumination Reagent



Applications of Alkyne Methylalumination:

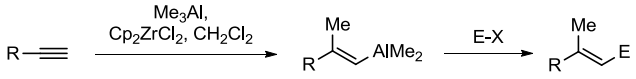
Carbon-centered electrophiles are among the most important coupling partners in organic synthesis, and trapping the nucleophilic vinyl alane intermediate to form trisubstituted olefins is highly desirable. In 1978, Negishi and coworkers reported that zinc salts facilitate Pd- and Ni-catalyzed cross-coupling reactions of alkenyl zirconium and alkenyl aluminum nucleophiles with organohalides (Scheme 1.2.17).[55] In these types of Negishi cross-coupling reactions, zinc salt additives are necessary to form the active nucleophile via transmetalation of **67** to the requisite vinyl zinc. Following this seminal publication, the reaction of vinyl alane intermediates with carbon-based electrophiles has been investigated extensively. A few noteworthy examples representing various classes of electrophiles are summarized below.

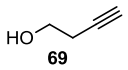
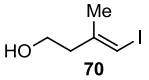
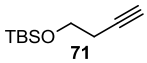
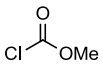
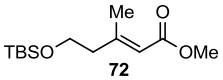
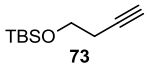
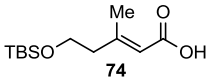
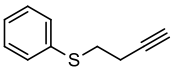
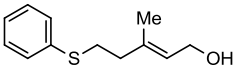
Scheme 1.2.17 Negishi Coupling Of Vinyl Alanes



In practice, the organozinc Negishi-coupling partners are frequently prepared through a lithium-halogen exchange and transmetalation sequence from the corresponding vinyl halides; both vinyl iodides (**70**, Table 1.2.1, entry 1)[56] and vinyl bromides (**78**, Scheme 1.2.18, eq. 1)[43] are accessible from alkyne methylaluminations. As shown in Table 1.2.1,[56] the intermediacy of a nucleophilic alkenyl alane species grants access to other types of functionalized, trisubstituted olefins through electrophilic trapping with methyl chloroformate, CO_2, and paraformaldehyde. For entries 3 and 4, preforming the aluminate complex with ^{n}BuLi treatment was necessary for nucleophilic addition to occur.

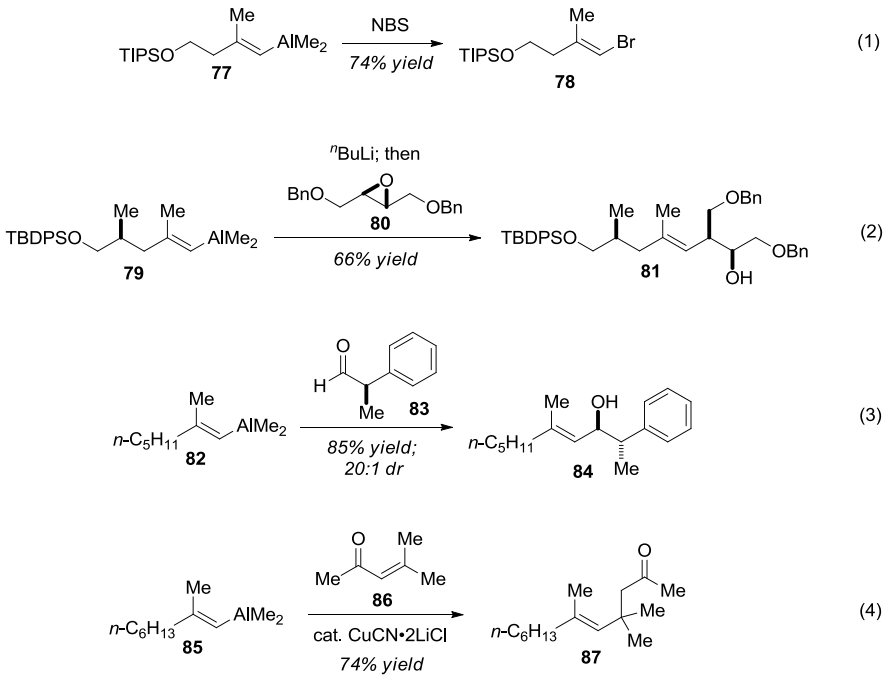
Table 1.2.1 Electrophilic Trapping of Vinyl Alanes to Produce Trisubstituted Alkenes



Entry	Alkyne	E-X (Conditions)	Product	Yield (%)
1	 **69**	I_2	 **70**	62
2	 **71**		 **72**	74
3	 **73**	^{n}BuLi; then CO_2	 **74**	62
4	 **75**	^{n}BuLi; then $(CH_2O)_n$	 **76**	78

Other carbon-centered electrophiles are compatible with the Zr-catalyzed methylalumination as well (Scheme 1.2.18). For example, the corresponding aluminate complex of **79** opens epoxide **80** to form a homoallylic alcohol (**81**).[57] Although less common, additions to aldehydes are also possible as exemplified by the stereoselective addition of **82** to **83** (eq. 3).[58] Finally, as depicted in Equation 4, Michael additions of vinyl alanes proceed in the presence of Cu(I) salts. Specifically, **85** undergoes 1,4-addition to the hindered α,β-unsaturated carbonyl compound (**86**) in the presence of CuCN•2LiCl.[59]

Scheme 1.2.18 Trapping Vinyl alanes with Various Carbon-Centered Electrophiles



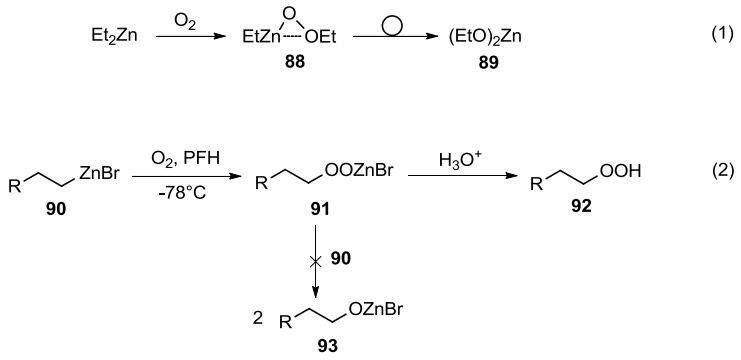
Methylaluminations of alkynes and alkylations of the resulting alkenyl alanes have developed into fundamental, routine processes. The ready availability of vinyl alane nucleophiles and the wide range of compatible coupling partners contribute to the success and wide use of these types of reactions. In this regard, it is noteworthy that examples of electrophilic aminations or oxygenations of alkenyl aluminum species are essentially nonexistent.

1.2.3. Oxygenation of Carbanions

1.2.3.1. Oxidation of Organometallics with O_2

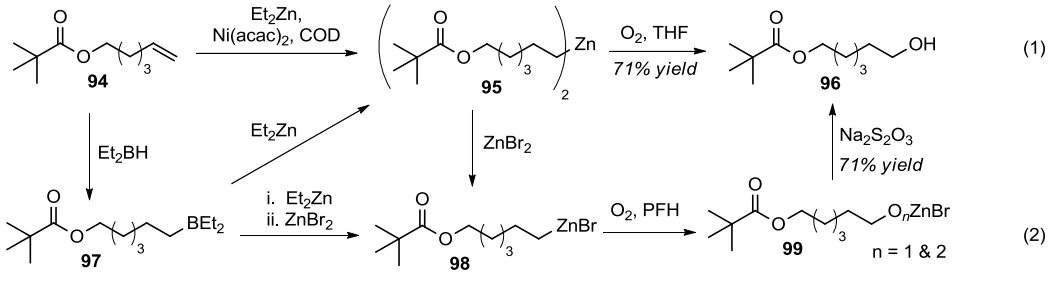
The oxidation of organometallic reagents commenced over 150 years ago in Marburg, Germany when Frankland reported the autoxidation of diorganozinc reagents (Scheme 1.2.19, eq. 1).[60] In the earliest experiments, diethylzinc was reacted with dioxygen to afford zinc diethoxide **89**. In 1890, Demuth and Meyer proposed the formation of peroxymetal species **88**[61] as a likely intermediate, resulting from the "insertion" of an O_2 molecule into the Zn-C bond;[62] a fast intramolecular rearrangement of **88** would produce the oxygenated zinc species **89**.

Scheme 1.2.19 Autoxidation of Organozinc Reagents



Almost 150 years later, Knochel and Klement were the first to isolate the hydroperoxide derivatives in good yields by treating O_2-saturated solvent with alkylzinc bromides (**90**).[63] The formation of the most commonly observed alkoxides (**93**) could be suppressed by conducting the autoxidations in perfluorinated hexanes (PFH), a solvent known to dissolve large quantities of O_2. Thus by slow addition of **90** to a high concentration of oxygen, the authors were able to avoid the intermolecular reduction of ROOZnBr (**91**) by starting material (**90**). The same authors later reported the controlled autoxidation of diorganozinc organometallics prepared by various methods (Scheme 1.2.20).[64] These experiments showed that functionalized dialkylzinc compounds, such as **95,** could be generated through a Ni-catalyzed hydrozincation (eq. 1) or a hydroboration-transmetalation sequence with diethylzinc (eq. 2). Upon exposure to dry O_2, **95** was cleanly oxidized to the corresponding primary alcohol **96**. Furthermore, **95** could be converted to the alkylzinc bromide (**98**) which was efficiently oxidized with O_2 as well.[65, 66] The authors obtained a mixture of the hydroperoxide and alkoxide (**99**) in Equation 2, thus a reductive workup was necessary to obtain **96** in good yields.

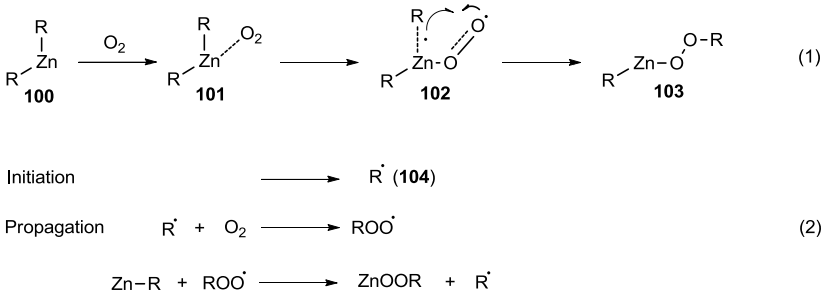
Scheme 1.2.20 Hydrozincation-Oxygenation of Olefins



The mechanism of O_2 activation by organozinc reagents, the nature of the reactive oxygenated organometallic species, and the origins of the reaction outcomes have been the subject of considerable interest.[61] As mentioned previously, Demith and Meyer were the first to suggest a peroxymetal

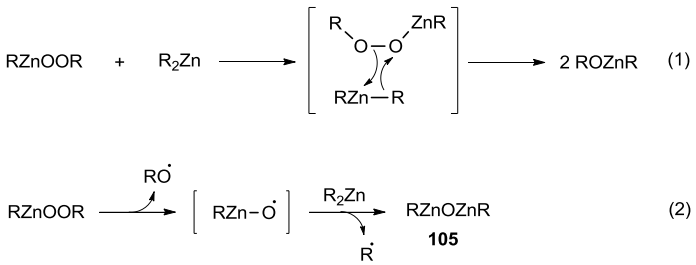
intermediate to account for the oxidized zinc species (**89**). The first *detailed* mechanism regarding the zinc activation of oxygen was proposed by Abraham in 1960. This involved coordination of oxygen to the zinc atom (**101**) and subsequent alkyl migration from zinc to oxygen to form the alkyl peroxide **103** (Scheme 1.2.21, eq. 1).[67] Another possibility, which until recently was widely accepted, involves an uncontrolled free-radical chain process initiated by adventitious alkyl radicals R$^{\bullet}$ (**104**, eq. 2).[68] More recently, Lewinski and coworkers reported the isolation and structural characterization of various ligated zinc alkyl peroxide complexes.[69-71] In this series of publications, the authors support Abraham's original hypothesis and suggest a more controlled oxidation in which dioxygen attack occurs at the metal center (**101**, eq. 1). Oxygen coordination is followed by an inner sphere Zn-R bond homolysis (**102**) which generates the rearranged peroxyzinc species **103**.[69]

Scheme 1.2.21 Possible Mechanisms for the Zinc Activation of Dioxygen



The decomposition of the RZnOOR species and the formation of the most commonly observed alkoxide products (RZnOR and $Zn(OR)_2$) has traditionally been explained by σ-bond metathesis between an alkyl peroxide intermediate and starting dialkylzinc (Scheme 1.2.22, eq. 1). Another mode of peroxyzinc decomposition may involve an intramolecular rearrangement to form zinc alcoholates as originally postulated by Demuth and Meyer (Scheme 1.2.19, eq. 1).[62] More recently however, Lewinski and coworkers suggested a mechanism in which homolysis of the RZnO-OR bond yields MeZnO$^{\bullet}$ and MeO$^{\bullet}$ radicals which react with a second equivalent of R_2Zn (eq. 2).[72-74] Evidence for the latter is based on crystal structures of a zinc-oxo species (**105**) derived from oxygenated dialkylzinc complexes.[72]

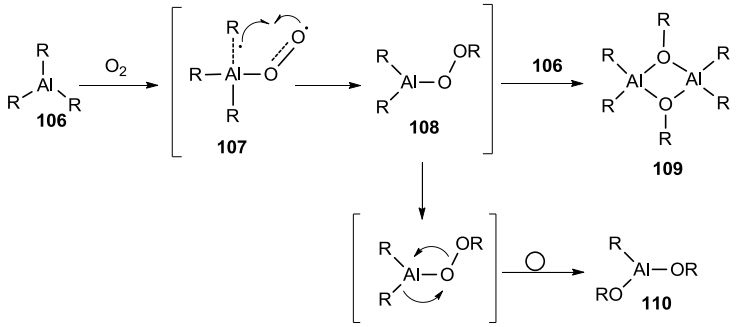
Scheme 1.2.22 Decomposition of Peroxyzinc Species



Oxidations of Trialkyl Aluminum Compounds with O_2:

Autoxidations of Group 13 organometallic compounds (R_3B, R_3Al, R_3Ga, and R_3In) are usually uncontrollably fast, hence the pyrophoric nature of neat trialkylborane and trialkylaluminum compounds (**106**, Scheme 1.2.23). If the introduction of O_2 to these species is controlled, however, oxygenation yields alkoxide compounds **109** and **110** via alkylperoxo intermediates **108**.[61, 75] The reaction of dioxygen with trialkylaluminum species has been investigated in detail, and this process is represented in Scheme 1.2.23.[76] Analogous to the Zn-O_2 activation pathway, the origin of **108** is thought to involve O_2 coordination at the Al-metal center through which a transient radical intermediate is formed (**107**).[70] Depending on the nature of the R-groups and reaction conditions, the decomposition of the peroxide **108** occurs through either an intermolecular reaction with a second molecule of the parent compound **106** or a dyotropic rearrangement to form the higher oxidized compound **110**.[77, 78] In both cases, the existence of the peroxide intermediate is fleeting and the resulting aluminum alkoxides are formed rapidly.

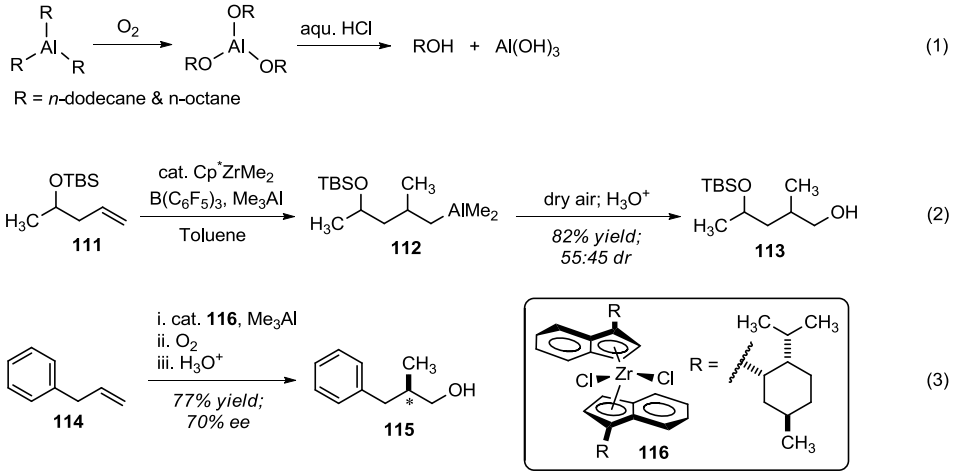
Scheme 1.2.23 Reaction of Organoaluminum Compounds with Dioxygen



The autoxidation of trialkylaluminum reagents to primary alcohols has found practical use in both industrial and academic settings. This reaction was initially developed into an industrial process to generate 1-octanol and 1-decanol by exposing the corresponding trialkylaluminum reagents to O_2 (Scheme 1.2.24, eq. 1).[79] The scope of this strategy increased dramatically with the advent of alkene hydroalumination[80] and carboalumination reactions,[27] which granted access to more functionalized organoaluminum species (such as **112**, eq. 2). In 1995, Waymouth and Shaughnessy described the first efficient Zr-catalyzed methylalumination of terminal alkenes to generate 2-methyl-organo aluminum species **112**.[81] Upon exposure to dry air, these intermediates were oxidized to the corresponding primary alcohols (**113**). The overall transformation proved to be nonstereoselective under substrate control; the formal methyl-oxygenation of TBS-protected homoallylic alcohol **111** produced **113** in a near 1:1 ratio of diastereomers. The same year, Negishi and Kondakov discovered that a chiral zirconocene derivative **116** catalyzes the enantioselective methylalumination of monosubstituted alkenes **114** (Scheme 1.2.24, eq.

3).[82, 83] Similarly, the authors oxidized the resulting chiral organoaluminum intermediates with O_2 to afford optically active 2-methyl-1-alkanols (**115**).

Scheme 1.2.24 Preparations of Primary Alcohols from Trialkylaluminum Species

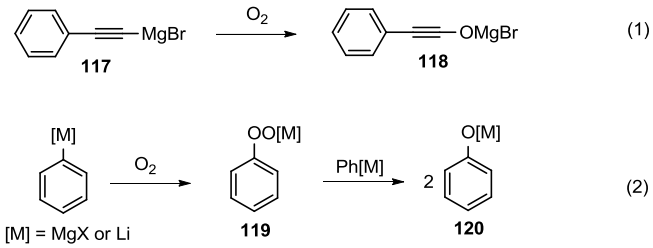


In this regard it should be noted that the literature contains no reports of the analogous reaction with terminal alkynes, that is, the preparation of the methyl-substituted aldehyde derivatives through a carbometalation-oxygenation sequence. This is surprising considering the progress made toward asymmetric methylaluminations of alkenes and controlled oxidations of *alkyl* aluminum species. Furthermore, Negishi disclosed the methylalumination of terminal alkynes almost 20 years before Waymouth showed that alkenes undergo the same transformation efficiently.

Oxidations of Grignard and Organolithium Compounds with O_2:

The autoxidations of Grignard and organolithium reagents was noticed early on as well, as Victor Grignard himself reported the oxidation of alkynyl magnesium halides (**117**) with molecular oxygen to yield carboxylate products from ynolates (**118**, Scheme 1.2.25, eq. 1).[84] Furthermore, Bodroux[85] and Wuyts[86] independently detected the formation of phenols from arylmagnesium halides and phenyllithium (eq. 2). In this regard, a transient metalated aryl peroxide **119** was proposed to compete successfully with oxygen for additional arylmetal; a second equivalent of PhLi or PhMgX would readily add to **119** forming two metalated phenolates (**120**).[87, 88] Together with the early observations from organozinc autoxidations, the experiments in Scheme 1.2.25 revealed the electrophilic nature of the intermediate peroxy metal species. The reactivity of these oxidants may be rationalized by considering their structure, which consists of an active oxygen bonded to a metal [M] and a leaving group (X), or [M]OX where X = OR (as in **119**). The structure and reactivity of the metalated peroxides are analogous to those of carbenoids, or $[M]C(X)R_2$. Accordingly, species such as **119** were termed oxenoids.[89]

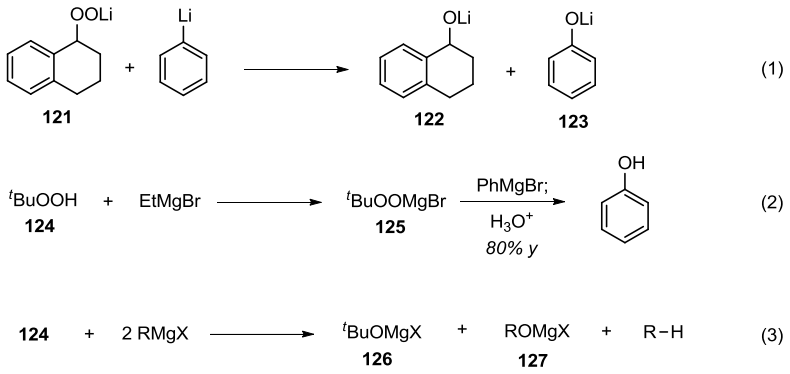
Scheme 1.2.25 Autoxidation of Grignard & Organolithium Reagents



1.2.3.2. Oxidations of Organometallic Compounds With Oxenoids

Oxenoids such as **119** proved to be capable oxidants when prepared *in situ* with dioxygen through the usually undesired autoxidation; however, the reaction of organometallics with oxenoids would not find general use until after important discoveries by Muller and Topel. In 1939, these authors demonstrated that independently prepared lithiated peroxide **121** effects the oxidation of phenyllithium (Scheme 1.2.26, eq. 1).[90] Furthermore, MgBr-peroxide **125**, prepared by the deprotonation of *tert*-butyl hydroperoxide (**124**, or TBHP) with ethyl Grignard, was shown to react with various Grignard reagents to produce alcohols (Scheme 1.2.26, eq. 2).[91] In both cases, the stoichiometry of the organometallic base was found to be critical for deprotonation; addition of two equivalents of Grignard to TBHP (**124**) consumed the oxidant and produced magnesium alkoxides **126** and **127** exclusively (Scheme 1.2.26, eq. 3).

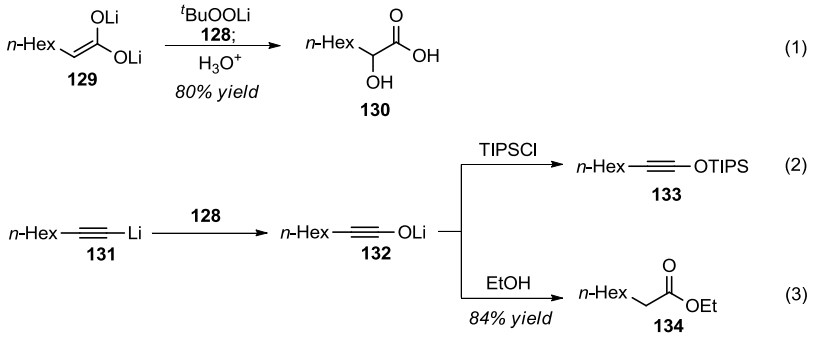
Scheme 1.2.26 Oxidation of Grignard and Organolithium Compounds with ROO[M]



The experiments in Equations 1-3 (Scheme 1.2.26) revealed that controlling the amount of oxidant is in fact possible, and in this way, lithiated peroxide oxenoids were developed for synthetically useful oxygenations of more complex organometallic reagents.[92] Julia *et al.* reported the use of lithium *tert*-butylperoxide (**128**, LTBP) in oxygenations of various organolithium compounds (Scheme 1.2.27).[93, 94] The authors showed that enolates could be oxidized to the corresponding α-hydroxycarbonyl compounds, including the dianion of 1-octanoic acid (**130**, eq. 1). In addition, LTBP oxygenates lithium

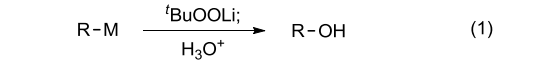
acetylides to generate lithium ynolates (**132**) which may be silylated (**133**, eq. 2) or treated with ethanol to form the corresponding esters (**134**, eq. 3).[89]

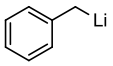
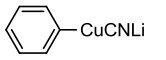
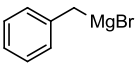
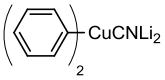
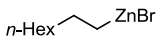
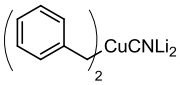
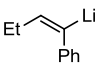
Scheme 1.2.27 Oxygenation of Lithium Carbanions with LTBP



LTBP effects oxygenation of other organometallic reagents to their corresponding alcoholates as well. Boche and coworkers have investigated these types of oxidations extensively,[95] and excerpts from their work are summarized in Table 1.2.2. Significant examples include oxidations of benzyl- lithium (entry 1) and Grignard (entry 2) compounds, alkylzinc halides (entry 3), alkenyl lithium species (entry 4), lower-order cyanocuprates (entry 5), and cyano-Gilman cuprates (entries 6 & 7).The authors note that the oxidation reactions with the cuprates are of special interest, since cuprates are known for their facile dimerization upon oxidation with O_2.[96]

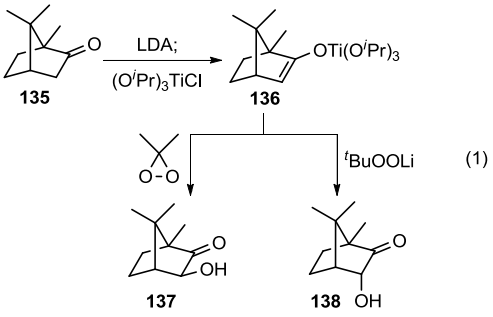
Table 1.2.2 Oxygenations of Various Carbanions with LTBP

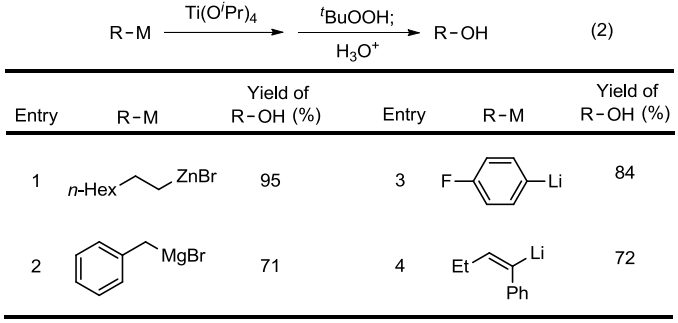


Entry	R-M	Yield of R-OH (%)	Entry	R-M	Yield of R-OH (%)
1		85	5		83
2		67	6		78
3		91	7		67
4		45			

overturned the selectivity by affording the *endo*-diastereomer (**138**). More interesting, however, is that the *protic* system Ti(^{i}PrO)$_4$ / ^{t}BuOOH used in Sharpless asymmetric epoxidations, effectively oxidizes certain carbanions (eq. 2). Boche *et al*. compared oxidations of various organometallics employing LTBP (Table 1.2.2) with those using the Ti(^{i}PrO)$_4$ / TBHP system, and examples of the latter are listed under Equation 2 below.[96] In general, the yields of the corresponding alcohols from both types of oxygenations are similar, but with two major exceptions. Oxidations of alkenyl lithium substrates are more efficient with the Ti(^{i}PrO)$_4$ / TBHP system (Scheme 1.2.28 entry 4 vs. Table 1.2.2 entry 4); but in contrast with LTBP (Table 1.2.2, entries 6 & 7), the Ti-based reagent proved insufficient for cyano-cuprate oxygenations. Of note, the yields of vinyl lithium oxidations refer to those of their enol acetate analogs, derived from quenching the resulting enolates with acetic anhydride.

Scheme 1.2.28 Oxygenations of Carbanions with LTBP / Titanium-System

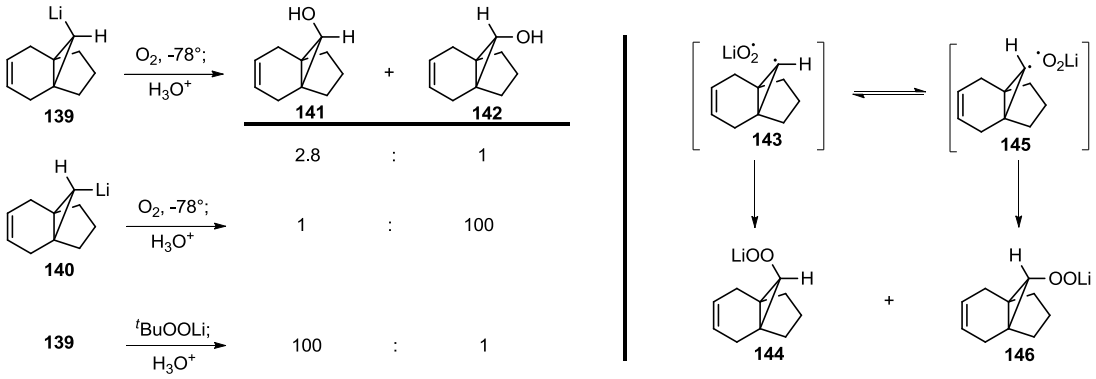




Entry	R-M	Yield of R-OH (%)	Entry	R-M	Yield of R-OH (%)
1	*n*-Hex–ZnBr	95	3	F–Li	84
2	MgBr	71	4	Et, Li, Ph	72

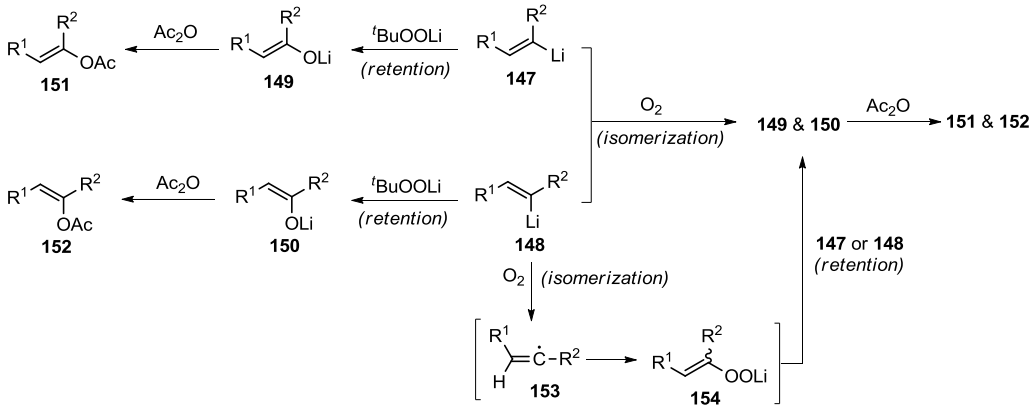
Early interests in electrophilic oxygenation reactions led to mechanistic studies in which oxidations of organolithium reagents with LTBP were compared to those with dioxygen. In the first of two noteworthy experiments, configurationally-stable cyclopropyllithium compound **139** reacted with O_2 to afford two isomeric alcohols, **141** and **142** in a 2.8:1 ratio (Scheme 1.2.29).[98] Reacting the other cyclopropyllithium isomer (**140**) with O_2 delivered cyclopropanol **142** exclusively. The authors invoked an electron transfer process in which transient radical pairs (**143**) and (**145**) allow for fast epimerization at the cyclopropyl radical center. Recombination results in the formation of peroxide isomers **144** and **146**, which would react with an additional equivalent of starting material, either **139** or **140**, with configurational retention. To determine whether the first step, *i.e.* the formation of **144** and **146** via O_2 oxidation, indeed determines the stereochemical outcome, **139** was treated with LTBP. This oxidation proceeded with stereochemical retention and led to the exclusive formation of **141**. The authors attribute this observed retention of stereochemistry in the latter example to an apparent S_N2-type reduction of LTBP.

Scheme 1.2.29 Mechanism of LTBP and O_2 Oxidation of Lithium Carbanions



In a similar study, Whitesides *et al*. oxidized *E*- and *Z*-alkenyllithium species **147** and **148** with dioxygen and LTBP to form the corresponding enolates **149** and **150** (Scheme 1.2.30).[99] Reaction of the individual vinyllithium diastereomers with dioxygen, followed by electrophilic trapping with acetic anhydride afforded mixtures of *E*- and *Z*-enol acetates **151** and **152**. The stereochemical outcome of these oxidations implicates a linear vinylic radical intermediate such as **153**, which recombines to form a mixture of vinyl peroxide diastereomers (**154**). The diastereomeric ratio of **151** and **152** obtained from the O_2 oxidations is consistent with further reduction of **154** by starting organolithium (either **147** or **148**), which proceeds with retention of configuration. In contrast, the parallel reactions in which LTBP is employed proceeded with configurational preservation; **151** is produced from **147**, and **152** is obtained from **148**. This again implies an S_N2-type mechanism for LTBP oxidations.

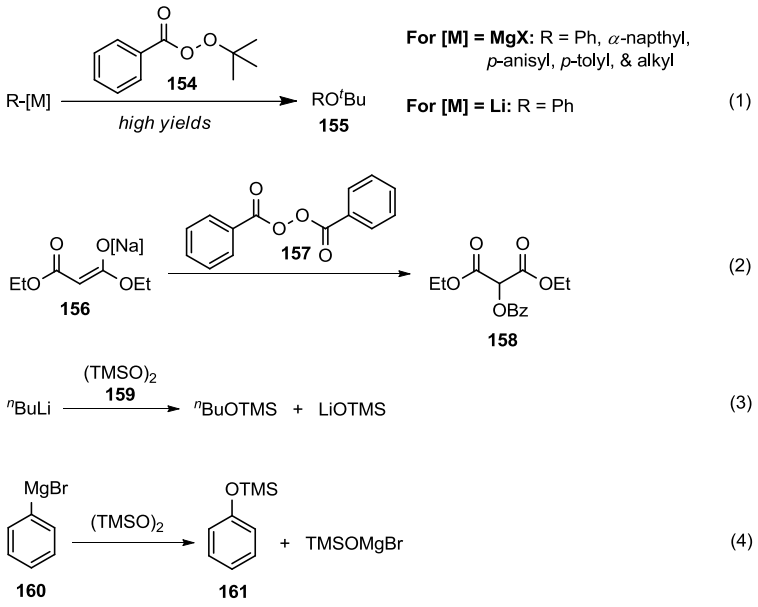
Scheme 1.2.30 Mechanism of LTBP and O_2 Oxidation of Lithium Carbanions



1.2.3.3. Oxidations of Organometallic Compounds With Neutral Oxidants

Grignard and organolithium reagents are known to react with neutral peroxides such as diacyl peroxides (**157**), alkyl perbenzoates (**154**), and *bis*(trialkylsilyl) peroxides (**159**) to afford the corresponding ethers and esters. Selections from early examples of these oxygenations are represented in Scheme 1.2.31. In 1959, Lawesson and Yang reported that phenyllithium and a variety of Grignards react with *tert*-butyl perbenzoate **154** to form *tert*-butyl ethers (eq. 1).[91] This protocol is often overlooked although *tert*-butyl ethers essentially cannot be formed by the conventional Williamson etherification. With respect to benzoyl peroxide oxidations, non-stabilized carbanions tend to react with the carbonyl carbon and peroxide oxygen atoms of **157** indiscriminately (eq. 2);[100] however, metallo-enolates (**156**) react selectively with the O-atoms of the peroxide moiety in **157**.[101] In addition, investigations in the early 1970s revealed that $(TMSO)_2$ (**159**) oxidizes simple commercially available Grignard and alkyllithium reagents to form the corresponding silyl ethers (eqs. 3 & 4).[102] Although certain peroxides such as **159** are explosive, the reagents exemplified in Scheme 1.2.31 represent alternatives to oxenoids if a protected alcohol is the desired outcome.

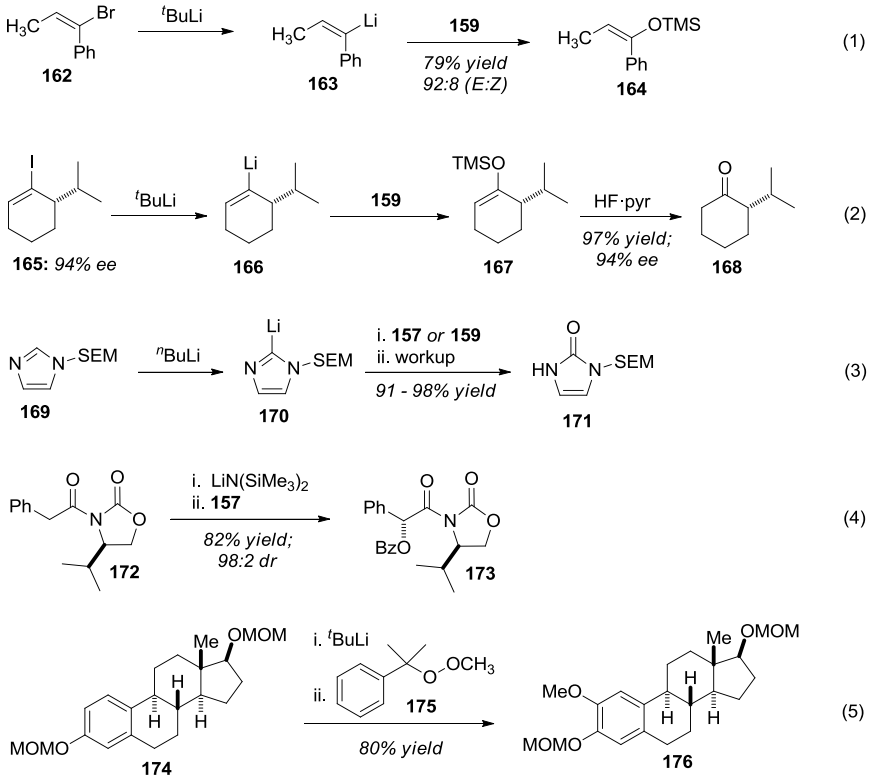
Scheme 1.2.31 Early Oxidations of Carbanions with Neutral Peroxides



Scheme 1.2.32 displays additional, but more recent applications of organometallic oxidations with neutral peroxides in which more complex, functionalized substrates were utilized. Davis reported that silyl enol ethers (**164**) may be prepared through lithium-halogen exchange followed by $(TMSO)_2$-oxygenation,[103] the products of which were obtained with high retention of the starting olefin geometry. $(TMSO)_2$ has also been used to oxidize cyclic alkenyllithium species (**166**) to cyclohexanone compounds

(**168**) with subsequent deprotection of the silyl ether (**167**).[104] In addition, lithiated SEM-protected imidazoles **170** may be oxidized to their corresponding imidazolinones (**171**) with Bz_2O_2 or $(TMSO)_2$, both of which deliver similar, high yields (eq. 3).[105] In a stereoselective example, Bz_2O_2 effects the α-hydroxylation of a chiral Li-enolate derived from Evans oxazolidinone carboxamides (**172**, eq. 4). The oxidation is apparently rapid and, in this case, the major benzoyloxy carboxamide diastereomer (**173**) was isolated in high yield and optical purity.[106] Finally, in a short synthesis of 2-methoxyestradiol, an anticancer agent currently in clinical trials, oxygenated intermediate **176** was synthesized by an interesting directed lithiation-oxidation reaction. In this case, the aryl anion derived from **174** reacts preferentially with the O-CH_3 portion of the neutral peroxide to install the methoxy functional group in the product (**176**, eq. 5).[107]

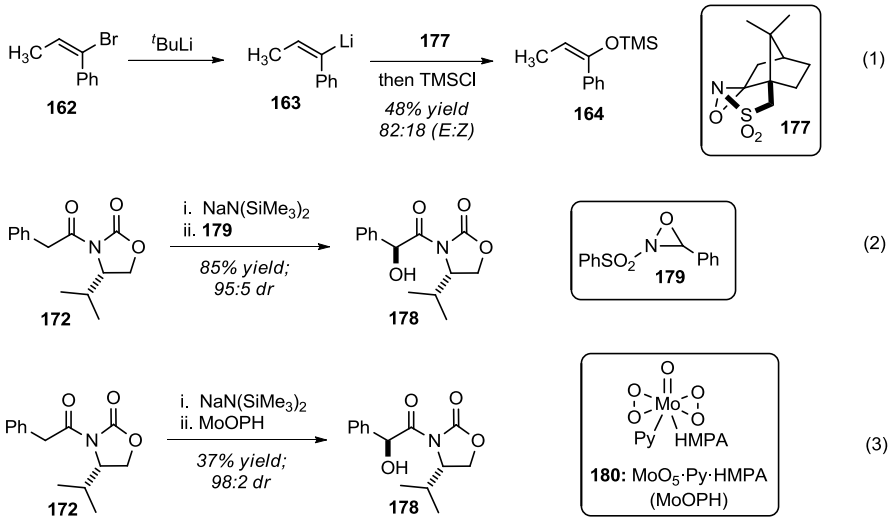
Scheme 1.2.32 Recent Oxidations of Carbanions with Neutral Peroxides



Several electrophilic oxygenation agents, such as oxaziridines (**177** and **179**) and peroxy molybdenum reagents (**180**), are primarily used for hydroxylation of metallo-enolates and other stabilized carbanions (Scheme 1.2.33). In general, non-stabilized lithium and Grignard reagents are hydroxylated with N-sulfonyloxaziridines **177** and **179** in modest yields as these reaction are often plagued by the side reaction of R-M with the sulfonimine byproducts.[108] This undesired process was observed in the oxidation

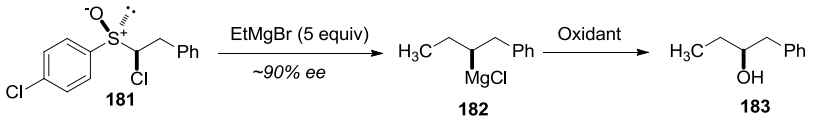
of alkenyl lithium **163** with chiral, camphor-derived oxaziridine **177** (eq. 1); enol silane **164** was isolated in low yield compared to the same transformation facilitated by $(TMSO)_2$ (Scheme 1.2.32, eq. 1).[103] When employed in the setting of enolate chemistry, however, N-sulfonyloxaziridines often afford α-hydroxy carbonyls (**178**) in good yields and with high selectivity (eq. 2). [20, 109] The molybdenum-based oxidant, MoO_5·Py·HMPA (**180**, or MoOPH), is also a useful reagent for enolate oxidations.[110] This bulky peroxy metal species is less reactive than oxaziridines toward most substrates, but often displays higher stereoselectivity (eq. 3).[111] Oxidations of carboxamide **172** with oxidants Bz_2O_2 (Scheme 1.2.32, eq. 4), oxaziridine **179** (Scheme 1.2.33, eq. 2), and MoOPH (Scheme 1.2.33, eq. 3), have been illustrated in the previous schemes so their results may be compared conveniently.

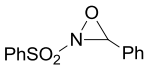
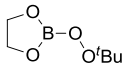
Scheme 1.2.33 Oxidations of Carbanions with Oxaziridines and MoOPH



In 2000, Hoffmann and coworkers reported the asymmetric synthesis of chiral Grignard reagent **182** in 90% enantiomeric excess (Table 1.2.3).[112, 113] The authors used this model as a mechanistic tool to study Grignard oxidations, which may occur through a direct oxygen transfer or an initial single electron transfer to the oxidizing agent. Therefore, no loss in ee would imply an S_N2-type process while racemization would suggest a radical mechanism.

Table 1.2.3 Oxidations of a Chiral Grignard Reagent with Various Oxidants



Entry	Oxidant	Yield **8** (%)	*ee* **8** %
1	MoO_5·Py·HMPA	84	92
2		80	91
3	**184:** 	80	88
4	$(TMSO)_2$	20	82
5	$Ti(O^iPr)_4$ / ^{t}BuOOH	82	71
6	^{t}BuOOLi	75	32
7	O_2	89	15

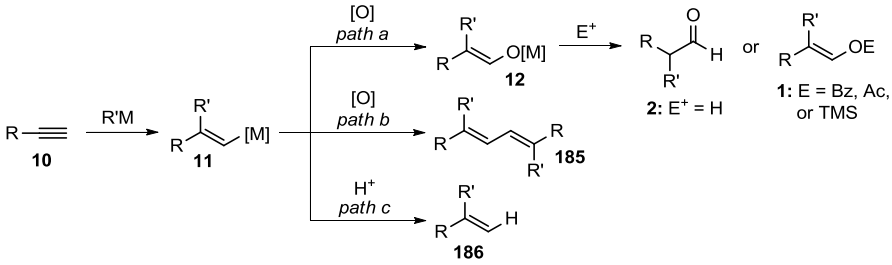
A variety of oxidants were examined as displayed in Table 1.2.3. MoOPH, the Davis oxaziridine, and peroxyborate **184** oxidize **182** to **183** with essentially complete retention of configuration and optical purity (entries 1-3). It should be noted that Hoffman previously used the peroxyborate species **184** to oxidize aryl Grignards and aryllithiums to phenols.[114] Oxidations with $(TMSO)_2$ (entry 4) proceeded with noticeable racemization, while $Ti(O^iPr)_4$ / TBHP, ^{t}BuOOLi, and O_2 progressed with significant to extensive racemization (entries 5-7). Comparison of these results provides insight into the predominate mechanisms through which various Grignard oxidations occur. Additionally, this serves as a unique example in which oxidants of a very different nature were employed in a specific synthetic transformation.

1.3. Prior Work in the Ready Laboratory

The Ready Group's rich history involving selective functionalizations of alkynes began with a solution to a longstanding problem: efficient preparations of α-branched aldehydes (**2**) and their stereodefined enol derivatives (**1**). Professor Ready and postdoctoral associate Donghui Zhang designed an approach to these elusive compounds based on the intermediacy of a stereodefined vinyl metal species (**11**), accessible through the stereo- and regioselective carbocupration of terminal acetylenes (Scheme 1.3.1).[6] They reasoned that **11,** in principle, could be trapped with an electrophilic oxygen donor to generate a stereodefined metallo-enolate (**12**) from which **1** or **2** could be accessed. This section will serve

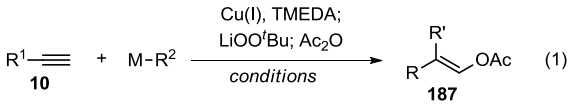
to summarize their results and highlight certain applications and restrictions that were addressed in subsequent studies.

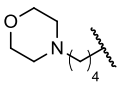
Scheme 1.3.1 Carbocupration / Oxygenation of Terminal Alkynes



Initial efforts to effect oxygenation of vinyl copper species with DMDO and nitrosobenzene resulted in dimerization, a reaction known to be induced by oxidizing agents (Scheme 1.3.1, path b). Other oxidants, including, *N*-methyl morpholine *N*-oxide and metal salts of *m*-CPBA were unreactive, and terminal olefin (**186**) was recovered from these experiments. They discovered, however, that ^{t}BuOOLi effects the oxygenation of the vinyl copper intermediates from carbocupration (Table 1.3.1, eq. 1). Addition of *N*, *N*, *N*, *N*-tetramethylethylenediamine (TMEDA) to the reactions inhibited dimerization, which in turn increased both yields and reproducibility.

Table 1.3.1 Carbocupration / Oxygenation Substrate Scope



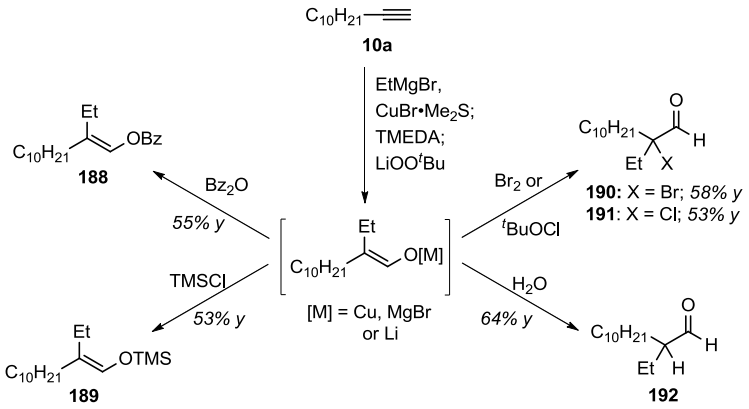
entry	**10**, R^1=	M-R^2	Yield (%)
1	*n*-$C_{10}H_{21}$	EtMgBr	71
2	*n*-$C_{10}H_{21}$	*n*-BuLi	69
3	*n*-$C_{10}H_{21}$	*t*-BuMgCl	50
4	$BnO(CH_2)_4$	EtMgBr	61
5	$TBSO(CH_2)_4$	*cy*-HexMgCl	66
6	$BzO(CH_2)_4$	*n*-BuLi	55
7	$Bn_2N(CH_2)_4$	EtMgBr	52
8		*cy*-HexMgCl	63

Electrophilic trapping of the resulting enolate with acetic anhydride afforded various trisubstituted *E*-enol acetates **187** in good yields (Table 1.3.1). Importantly, previously inaccessible stereodefined enol acetates were isolated as one geometric isomer in each case. Under the optimized

conditions, primary, secondary, and tertiary Grignard and primary alkyllithium reagents were compatible with a variety of alkynes; however, methyl nucleophiles proved unreactive. This result is consistent with the well-known difficulties associated with methylcuprations as previously discussed in Section 1.2.1.

Depending on the nature of the electrophile, the enolate intermediate can be trapped effectively on oxygen or carbon (Scheme 1.3.2). Quenching with benzoic anhydride and chlorotrimethylsilane yields the corresponding enol benzoate **188** and enol silane **189**. Alternatively, α-haloaldehydes (**190**-**191**) can be isolated following addition of electrophilic halogen donors, such as Br_2 and ^{t}BuOCl, to the reaction. Altogether, results from this body of work proved the concept that substituted aldehydes and stereodefined enol derivatives may be accessed from simple, terminal acetylene starting materials. The intriguing notion of readily available substituted enols coupled with the restricted access to methyl-substituted enols (**1**) prompted further investigations from the Ready Laboratory.

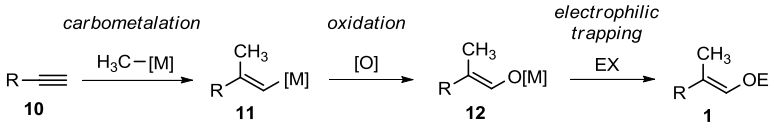
Scheme 1.3.2 Trapping Metallo-Enolate Intermediate



1.4. Preparation of Me-Substituted Enol Derivatives from Terminal Alkynes

Methyl-substituted enol derivatives **1** (Scheme 1.4.1) were inaccessible from terminal alkynes due to an inherent limitation of the previously discussed carbocupration-oxygenation chemistry, that is, the inefficiency of methylcupration under the reaction conditions. The large number of biologically active natural products bearing methyl-substituted olefins and isolated methyl groups, especially of terpene origin, further emphasizes the potential value of a direct approach to **1**.[115] Accordingly, we sought a method complimentary to the carbocupration strategy in which the *E*-trisubstituted enol products would be adorned with a methyl group.[116] Achieving this essentially required us to address issues associated with three sequential reactions, since the desired overall transformation requires efficient carbometalation, oxidation, and electrophilic trapping steps as outlined in Scheme 1.4.1.

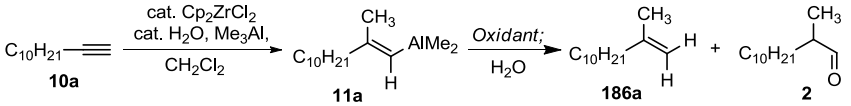
Scheme 1.4.1 Methylmetalation-Oxygenation of Terminal Acetylenes



Regarding carbometalation, we chose to employ Negishi's zirconocene-catalyzed methylalumination of terminal alkynes as a conduit to generate the requisite vinyl metal intermediates **11** ([M] = $AlMe_2$). Methylaluminations of simple, unfunctionalized monosubstituted acetylenes are generally reliable. And although no previous examples of oxidizing alkenyl alanes **11** ([M] = $AlMe_2$) appeared in the literature, the trialkylalane products of 1-alkene methylalumination are oxidized cleanly with dioxygen to afford alcohols. At the outset of our investigations, using 1-dodecyne (**10a**) as a test substrate, we observed inconsistent methylalumination rates and incomplete conversions to the corresponding organoalane **11a**. We soon found that pretreating Cp_2ZrCl_2 (10 mol %) and Me_3Al (1.5 equiv) with a catalytic amount of water (2.5 mol %) led to full conversion to **11a** within a few hours. For small scale reactions, using undistilled, degassed CH_2Cl_2 from commercially available 4 L bottles gave similar results. Methylalumination conditions for more functionalized substrates required further optimization and will be discussed along with the substrate scope.

After achieving consistent methylalumination, our preliminary oxidation experiments aimed to oxygenate alkenyl aluminum intermediate **11a** to its corresponding aldehyde **2** with O_2. These reactions proved unsuccessful as incomplete conversion and over-oxidation limited yields (Table 1.4.1, entry 1). Results with the oxenoids ^{t}BuOOLi and peroxyborate **184** were more promising (entries 2 and 4, respectively). With these reagents, we observed 50% and 41% conversions of **11a** to the corresponding aldehyde **2**, respectively, with 2-methyl-1-dodecene **186** (protio quenched **11a**) accounting for the remainder of the starting material. Using ^{t}BuOOLi prepared from fresh, anhydrous ^{t}BuOOH in toluene[117] (entry 3) increased the conversion to a maximum of 66-67%; however, we observed deuterium incorporation in **186a** when these reactions were quenched with DCl following the oxidation. This suggested that oxidation under these conditions simply ceased after roughly two-thirds conversion of the alane intermediate, **11a**.

Table 1.4.1 Oxidation of Vinyl Alane 11a with Various Oxidants



Entry	*Oxidant*	**186a** (%)	**2** (%)
1	O_2	50	15
2	^{t}BuOOLi (Fluka 5.5 M in decane)	50	50
3	^{t}BuOOLi (Anhydrous in Tol)	33	67
4	^{t}BuOOB(O)O (**184**)	59	41
5	^{t}BuOOZnEt	15	85
6	^{t}BuOOZnCl	28	73
7	^{t}BuOOZnMe (**193**)	2	98

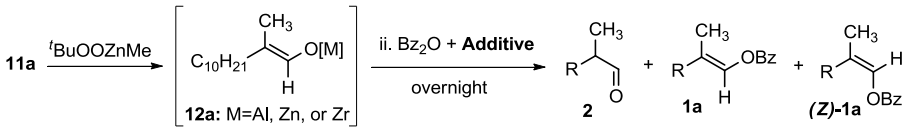
Further evaluation of peroxymetal oxidants revealed that peroxyzinc reagents ClZnOO^{t}Bu, EtZnOO^{t}Bu, and MeZnOO^{t}Bu effected the oxidation of **11a** to the corresponding aldehyde with 73%, 85%, and 98% conversions, respectively (entries 5-7). As previously mention in Section 1.2.3, zinc peroxides prepared in situ from dioxygen have been shown to oxidize the parent organozinc reagents; however, these types of peroxides prepared independently from dialkylzincs and organic hydroperoxides (ROOH) have not been employed in the setting of carbanion oxidations.[70, 118-120] The reagent **193** consistently delivered the best results and was thus used as the standard oxidant for the remainder of this study.

The oxidation is conducted by adding a solution of alkenyl alane via cannula into a solution of freshly prepared MeZnOO^{t}Bu (1.3 equiv to $AlMe_3$) in toluene at 0°C. Inverse addition provided significantly higher yields than the addition of oxidant to the methylalumination reaction vessel. In turn, **193** should be prepared at -78°C by slow addition of anhydrous TBHP to Me_2Zn; presumably, low temperatures suppress the undesired side reaction of metalated peroxide **193** with unreacted dialkylzinc (discussed in Section 1.2.2.1). Subsequent to TBHP addition, the solution should be warmed to 0°C to ensure complete deprotonation of the hydroperoxide and thus complete oxygenation of vinyl alane in the ensuing oxidation. In general, full conversion of vinyl alane is achieved within two hours at 0°C, after which the resulting enolate may be quenched with the desired electrophile.

Trapping the metallo-enolate **12a** with electrophiles other than a proton proved more difficult than expected.[121] In the absence of additives to facilitate benzoylation, we observed incomplete conversions to the desired enol benzoate **1a** (Table 1.4.2). However, benzoylations with Bz_2O and DMAP yielded significant amounts of the undesired (*Z*)-**1a**, presumably derived from isomerization of the recalcitrant enolate (entry 2). Ultimately, we found that catalytic amounts of $ZnCl_2$ or ^{n}Bu$_3$P suppress this side reaction and concomitantly increase conversions to **1a** (entries 3 and 4, respectively).[122, 123] Our most

promising result was obtained by treating enolate **12a** with a premixed solution of Bz_2O and $^nBu_3P$, which provided enol benzoate **1a** in 79% isolated yield (Table 1.4.3, entry a).

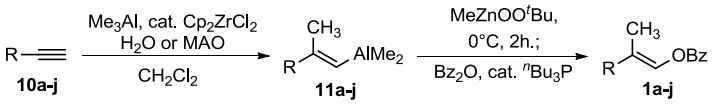
Table 1.4.2 Trapping the Metallo-Enolate 12 with Benzoic Anhydride

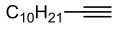
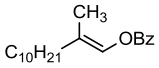
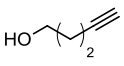
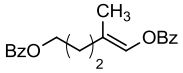
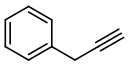
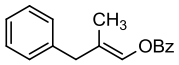
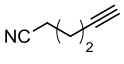
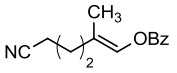
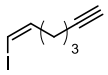
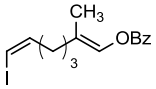
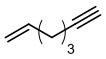
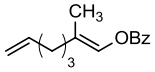
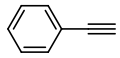
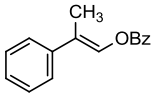
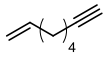
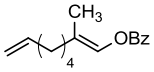
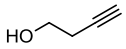
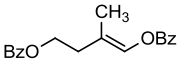
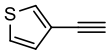
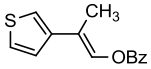


Entry	**Additive**	Equiv	T (°C)	Ratio determined by GC: **2** : **1a** : ***(Z)*-1a**
1	None	N/A	40	18 : 80 : 2
2	DMAP	2.0	40	4 : 89 : 7
3	$ZnCl_2$	0.25	30	5 : 92 : 3
4	$^nBu_3P$	0.2	r.t.	2 : 97 : 1

The scope of the tandem methylalumination-oxygenation displays several noteworthy features (Table 1.4.3). The reaction tolerates considerable functionality including protected and free alcohols, heterocycles, and nitriles. The C-C double bonds in enynes **10h** and **10i** are unreactive under the reaction conditions, while the free hydroxyl groups in **10e** and **10f** are benzoylated over the course of electrophilic trapping. Worth noting is that substrates containing free alcohols must be pretreated with an additional equivalent of Me_3Al and catalytic MAO before the zirconocene catalyst is introduced to the system (entries e and f). In addition, heterocyclic substrates, nitriles, and benzyl ethers require 30 mol % Zr-catalyst loadings compared to the standard 10 mol % sufficient for simple hydrocarbon substrates. Although the Zr-catalyzed methylalumination occurs with ca. 95:5 regioselectivity, no products derived from oxidation of the minor regioisomer were detected in the crude reaction mixtures.[43] Furthermore, in every case studied to date, the enol derivative has been isolated as a single diastereomer with a high *E*-isomer content (all *E*/*Z* ratios > 20/1).

Table 1.4.3 Preparation of Enol Benzoates from Terminal Alkynes

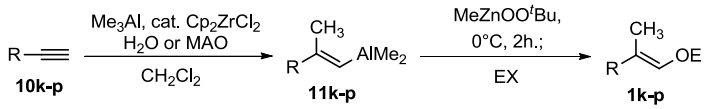


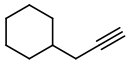
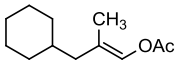
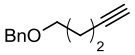
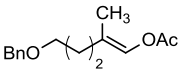
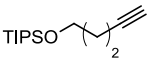
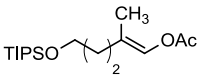
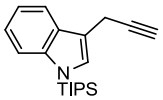
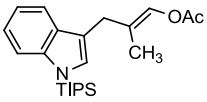
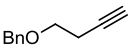
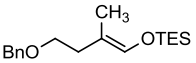
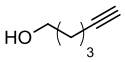
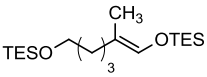
Entry	Alkyne (**10a-e**)	Product (**1a-e**)	Yield (%)	Entry	Alkyne (**10f-j**)	Product (**1f-j**)	Yield (%)
a			7	**f**[a]			79
b			89	**g**[a]			71
c			82	**h**			75
d			80	**i**			76
e[a]			59	**j**[a]			83

[a] 5-30 mol % added MAO was required to achieve complete methylalumination

Electrophilic trapping is not limited to benzoylation: enol acetates and TES enol ethers were prepared in high yields as well (Table 1.4.4). In contrast with the enolate benzoylations, acylations with acetic anhydride do not require a phosphine catalyst to achieve complete conversion to the enol ester. Pretreating a solution of TESOTf with pyridine facilitates silylation, and under these conditions free alcohols are protected as well (entry p). Finally, in every experiment thus far, the vinyl alanes derived from Zr-catalyzed methylalumination (**11a-p**) undergo clean oxygenation with ^{t}BuOOZnMe. This suggests that the reaction scope is primarily limited by the generality of the carbometalation, not oxygenation with **193**.

Table 1.4.4 Preparation of Enol Acetates and Enol Silanes from Terminal Alkynes



Entry	Alkyne (**10k-p**)	EX	Product (**k-p**)	Yield (%)
k		Ac_2O		91
l[a]		Ac_2O		97
m		Ac_2O		92
n[a]		Ac_2O		90
o[a]		TESOTf, pyr		79
p[a]		TESOTf, pyr		83

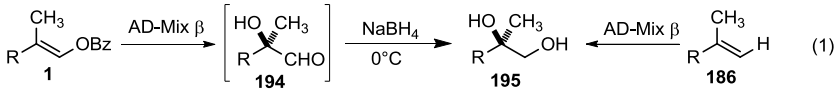
[a] 5-20 mol % added MAO was required to achieve complete methylalumination

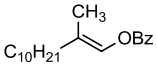
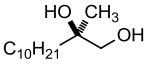
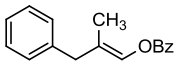
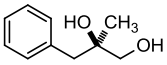
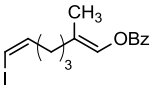
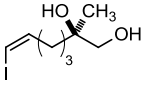
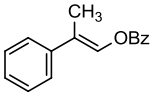
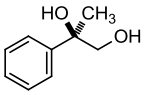
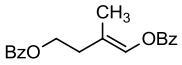
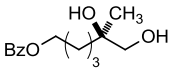
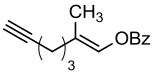
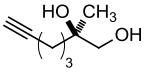
1.5. Asymmetric Dihydroxylation of Enol Benzoates

Trisubstituted, stereodefined enol derivatives of this type were previously inaccessible, and their ready availability allowed us to explore new chemistry and evaluate their synthetic utility. A first-year graduate student, Kathleen Lee, joined the group at this juncture and assisted with this portion of the project. She performed crucial experiments and her efforts proved invaluable toward the success of this methodology.

Corey and coworkers have previously shown that proximal benzoyloxy-substituents interact favorably with AD cinchona alkaloid ligands.[124, 125] Thus, we envisioned an entry to chiral α-hydroxy aldehydes (**194**) and 1,2-diols (**195**) by employing the enol benzoates in catalytic asymmetric dihydroxylation (AD) reactions.[3, 126, 127] As expected, the enol benzoate substrates afforded dihydroxylated products in high enantiomeric purity (Table 1.5.1, all entries ≥ 94% *ee* from **1**). Many 1,1-disubstituted olefins (**186**) are poor substrates for asymmetric dihydroxylation. Results from asymmetric dihydroxylations of a few of these compounds compared to their enol benzoate analogs clearly show the superiority of the latter (entries 1, 4 and 6). Therefore, AD of the enol benzoates, followed by a reductive workup with $NaBH_4$, presents a highly enantioselective route to these substances.

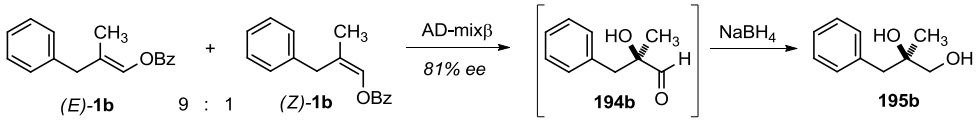
Table 1.5.1 Asymmetric Dihydroxylation of Enol Benzoates



Entry	Enol Benzoate (**1**)	*ee* (%) from: **1**	*ee* (%) from: **186**	1,2-Diol (**195**)	Yield from **1** (%)
a		96	78		78
b		94			84
c		96			59
e		95	94		75
f		96			87
q		95	32		75

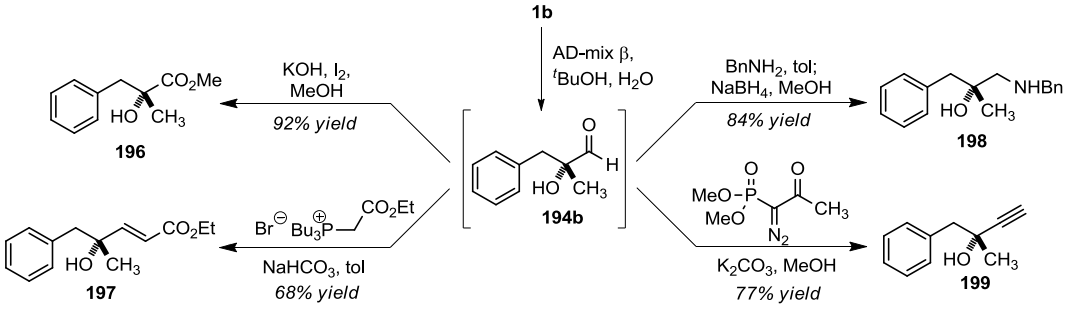
At the outset of this investigation, we hypothesized that controlling the geometry of **1** would be important to achieve high selectivity in AD reactions. Let us suppose a scenario for enol derivatives (**1**) similar to that for the AD of 1,2-disubstituted olefins in Scheme 1.2.1 (eqs. 3 and 4); that is, the *E*-isomer undergoes AD with high enantioselectivity while the *Z*-isomer does not. In principle, if **1** were achiral, the asymmetric dihydroxylation of (*E)*- and (*Z)*-**1** would afford *enantiomers* (**194**, Table 1.5.1, eq. 1), as opposed to diastereomers (**16**) from (*E*)-**15** and (*Z*)-**15** (Scheme 1.2.1, eqs. 3 and 4). In general, alkene diastereomers are difficult to separate by chromatography. Thus if **1** were obtained as an inseparable mixture of *E*- and *Z*-isomers, the asymmetric dihydroxylation of these olefins would produce **194** with low enantioselectivity. In fact, controlling stereochemistry of the olefin proved critical: an inseparable 9:1 E/Z mixture of **1b** was converted to **195b** in 81% ee under the standard AD conditions (Scheme 1.5.1).

Scheme 1.5.1 Asymmetric Dihydroxylation of Enol Derivatives



The enantioenriched α-hydroxy aldehydes (**194**, Table 1.5.1) obtained from the dihydroxylations are useful materials for further synthetic manipulation. These types of aldehydes are relatively unstable to chromatography and tend to dimerize when concentrated; however, the crude AD products could be subjected to various synthetic transformations. For example, an Ohira-Bestmann homologation[128] of aldehyde **194b** provided propargylic alcohol **199** in 77% yield. Reductive amination of **194b** proceeded smoothly to yield the corresponding amino alcohol (**198**, 85% yield).[129] Alternatively, the same starting material (**194b**) could be oxidized to its methyl ester (**196**, 92%),[130] or undergo olefination to afford an α,β-unsaturated ester (**197**, 68%, E:Z = 14.3:1).[131]

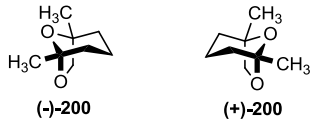
Scheme 1.5.2 Functionalizations of α-Hydroxy Aldehyde Intermediates



1.6. Total Synthesis of (-)-Frontalin

1.6.1. Background

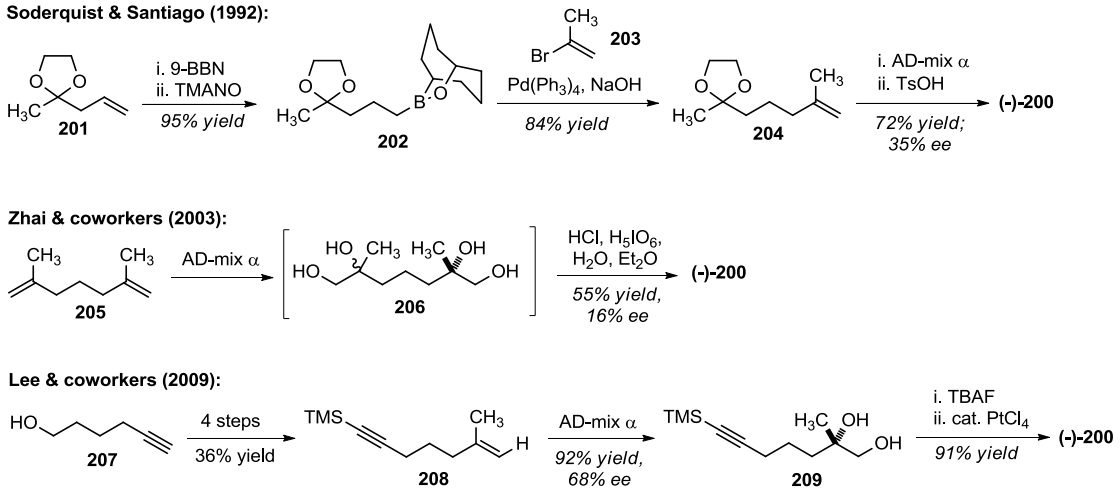
The fused bicyclic acetal core of frontalin (**200**), or 6,8-dioxabicyclo[3.2.1]octane, represents a common scaffold present in more complex, biologically active natural products.[132] (-)-Frontalin was first isolated by Kinzer in 1969 as a component of the *Dendroctonus* pine beetle aggregation pheromone.[133] Both enantiomers of the natural product were later isolated from temporal gland secretion in the male Asian elephant during the musth cycle.[134] Only the (-)-**200** enantiomer is believed to be biologically active in beetles,[135] but in elephants, both antipodes are secreted in various ratios depending on the elephants' age and stage in the musth cycle.[136] Due to its relatively simple structure and interesting biological activity, more than 40 syntheses have been reported; however, for these same reasons, frontalin also represents a valuable system to test newly developed asymmetric methods. To avoid a lengthy description of the numerous frontalin syntheses, the following text will focus on those relevant in the context of this chapter and those representative of more common synthetic strategies.



Of the nonracemic frontalin syntheses, three have been reported in which the tertiary alcohol stereocenter is formed by the Sharpless asymmetric dihydroxylation (AD) (Scheme 1.6.1).[137-139] The first of these, by Soderquist and Santiago, highlights a Suzuki coupling of primary borinate ester **202** with 2-bromopropene to prepare the AD precursor (**204**). Asymmetric dihydroxylation of the terminal olefin, followed by acetylation presented the natural product in 72% yield and 35% ee. The authors note that the chiral catalyst is likely forced to differentiate between the two similar reacting faces in **204** (*i.e.*, CH_2 versus CH_3), thus contributing to the low enantioselectivity.[137]

Zhai and coworkers employed a double dihydroxylation reaction to prepare tetraol **206**, which upon oxidative cleavage cyclizes to **(-)-200** in 16% ee. Presumably, the second dihydroxylation proceeds with even lower selectivity than the first due to interference from the newly generated tertiary hydroxyl group.[138] After publication of our work, Lee *et al*. subject enyne **208** to AD yielding the corresponding diol **209** in 68% ee. Desilylation followed by a Pt(II)-catalyzed cycloisomerization afforded (-)-frontalin in 72% yield.[139] It is worth noting the conflicting ee values in the latter example compared to those obtained in the Ready lab using a similar substrate (**186q**, Table 1.5.1, last entry); AD of the desilylated analog of **208** afforded the corresponding diol **195q** in 32% ee. This value is much lower than their observed ee value of 68%. Our results are in agreement, however, with the dihydroxylation of acetal **204** reported by Soderquist *et al*.

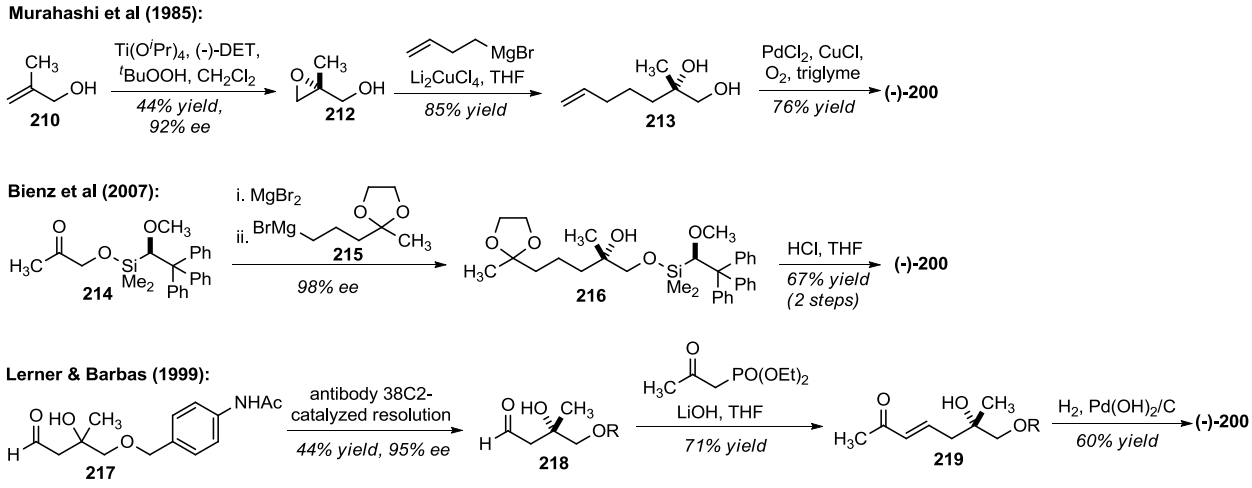
Scheme 1.6.1 Frontalin Syntheses Using Asymmetric Dihydroxylation



In a noteworthy synthesis of frontalin, the requisite tertiary stereocenter is prepared through an asymmetric Sharpless epoxidation, from which **212** is obtained in 92% ee (Scheme 1.6.2). [140] An organocuprate mediated epoxide-opening furnishes the diol (**213**), which cyclizes to **(-)-200** when subjected to a Wacker-type oxidation. This synthesis exemplifies one of the earliest, shortest and most efficient asymmetric routes to the natural product.

The use of α-hydroxy ketones (**214**, Scheme 1.6.2) and α-keto esters protected with chiral auxiliaries represents a common tactic for preparing the optically active tertiary alcohol intermediate.[141] For instance, the optically pure silane protecting group induces asymmetry in **214** for the ensuing Grignard addition, which delivers the monoprotected diol **216** in 98% ee.[142] This compound undergoes both desilylation and cyclization in the presence of HCl. The authors are able to recover and reuse the chiral silane moiety by reductive cleavage with LAH.[142] Other frequent strategies exploit enzymatic resolution reactions to obtain the optically active diol precursors to frontalin. Lerner and Barbas used a catalytic antibody to discriminate between **218** and its enantiomer, the latter of which decomposes through a retro-aldol reaction to form acetaldehyde and the corresponding methyl ketone. Following a Horner-Wadsworth-Emmons olefination, the enone (**219**) undergoes a facile cyclization when hydrogenated with $Pd(OH)_2$ and H_2.[143]

Scheme 1.6.2 Other Asymmetric Syntheses of Frontalin

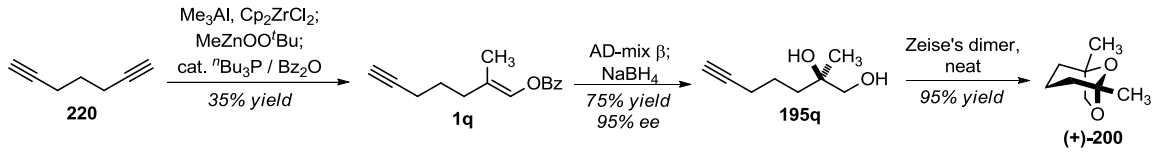


1.6.2. Syntheses of (+)-Frontalin from the Ready Group

Our initial approach to frontalin began with commercially available diyne **220**, from which we obtained the mono-benzoylated enyne **1q**, albeit in 35% yield. To account for these yields, we observed a near statistical mixture of diyne, enyne, and diene in crude ^{1}H NMR spectra and GC traces. Bringing **1q** into the asymmetric dihydroxylation reaction, followed by a reductive workup, furnishes diol **195q** in

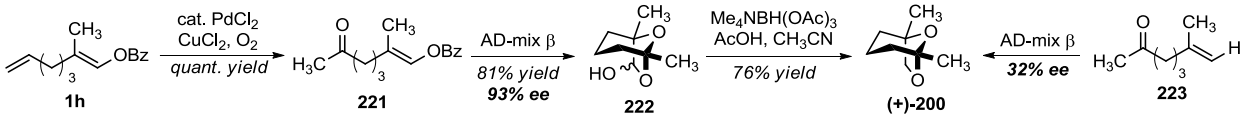
95% *ee* and 75% yield. The final transformation exploited an efficient Pt-catalyzed cycloisomerization reaction developed in the DeBrabander laboratory. Thus treating the neat diol **195q** with a catalytic amount of Zeise's dimer afforded (+)-frontalin in 95% yield.[144, 145]

Scheme 1.6.3 First Generation Synthesis of Frontalin



Due to the inefficiency of the methylalumination reaction in the previous synthesis of frontalin, we sought an alternative strategy. We had previously shown that the triple C-C bond in enynes such as **1h** and **1i** (Table 1.4.3) undergo selective methylalumination/oxygenation to deliver enol benzoates in 75-76% yields, respectively. Therefore, with enol benzoate **1h** in hand, we were able to access the corresponding methyl ketone **221** through a high-yielding Wacker oxidation (Scheme 1.6.4). Subjecting enol benzoate **221** to asymmetric dihydroxylation produced 7-hydroxy-frontalin (**222**) as a mixture of *endo*- and *exo*-diastereomers. Interestingly, of the 40 or 50 syntheses of frontalin, none have proceeded through an intermediate in which C-7 exists at the oxidation state of an aldehyde. This may be explained by the difficulties we encountered while attempting to selectively reduce the hemiacetal in the presence of a neighboring ketal in **222**. Ultimately, we found that under mildly acidic conditions, $Me_4NBH(OAc)_3$ selectively deoxygenates the hemiacetal moiety in **222** to form the natural product in 76% yield. Finally, it should be noted that 1,1,-disubstituted olefin **223** performed poorly in the asymmetric dihydroxylation reaction delivering **(+)-200** in only 32% ee.

Scheme 1.6.4 Second Generation Synthesis of Frontalin



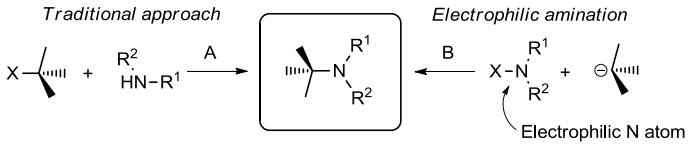
1.7. Amination of Alkenyl-Metal Intermediates

1.7.1. Background: Aminations of Vinyl Metal Compounds

Carbon-nitrogen bonds are traditionally formed through S_N2-type displacement reactions of carbon-based electrophiles with nitrogen nucleophiles. However, electrophilic carbon precursors are often difficult to access, and enamine-type products are not accessible through S_N2 substitution at sp^2-carbon

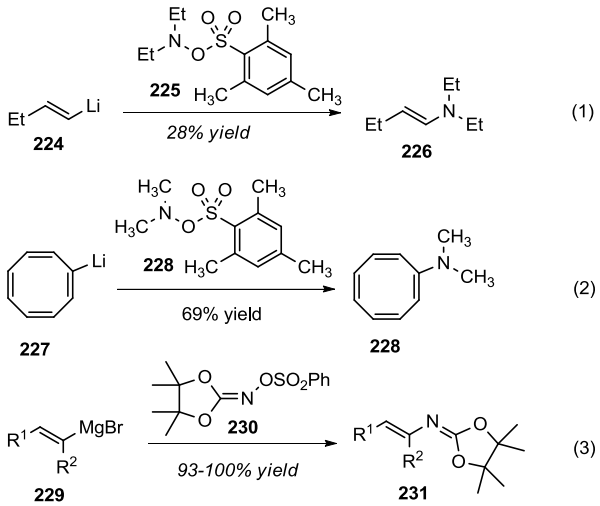
centers. In these cases, electrophilic amination may provide a complimentary strategy.[146] With this umpolung approach, an electrophilic aminating agent bears a good leaving group attached to the nitrogen atom, and this may be substituted by a sufficiently nucleophilic carbanion or organometallic reagent (Scheme 1.7.1).[92] Considering the increasing number of direct metalation methods, this unconventional approach now represents a valuable C-N bond-forming process.[147]

Scheme 1.7.1 Electrophilic Amination of Carbanions



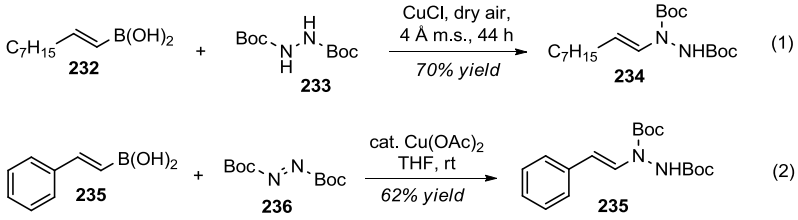
Although numerous electrophilic amination examples with alkyl, aryl, and alkynyl-organometallic reagents appear in the literature, there are very few protocols that employ *alkenyl*-metal nucleophiles. In fact, a thorough literature search revealed only four isolated examples, two of which involve amination of alkenyllithium reagents with *O*-sulfonylhydroxylamines **225** and **228** (Scheme 1.7.2, eqs. 1 & 2).[148, 149] The dearth of alkenyl metal aminations might be attributed to the tendency of the enamine products, such as **226** and **228**, to hydrolyze in the presence of water; therefore, electrophilic sources of nitrogen that lead to stable enamine products would prove more practical. For instance, in a more recent report, alkenyl Grignard reagents (**229**) were reacted with *O*-sulfonyloximes (**230**) to afford azadienes such as **231** (eq. 3).[150] The resulting azadiene products were stable to neutral aqueous workup conditions but readily hydrolyzed when treated with HCl.

Scheme 1.7.2 Electrophilic Amination of Vinyl Carbanions



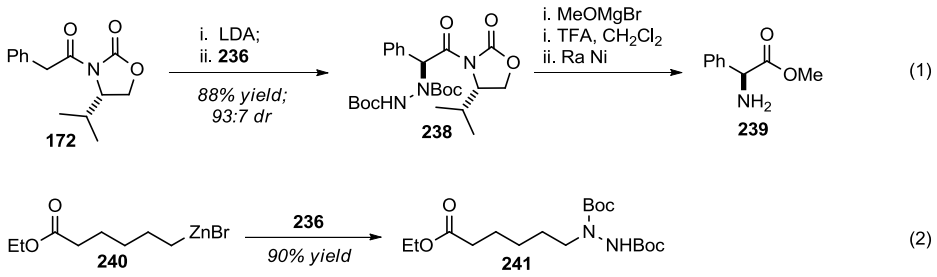
Within the last few years, however, a number of examples have surfaced involving the preparation of stable ene-hydrazine derivatives through Cu-catalyzed amination reactions.[151, 152] The majority of these are Goldberg-type coupling reactions, but there are two reports that describe the Cu-catalyzed aminations of alkenyl boronic acid nucleophiles (Scheme 1.7.3). The reaction in Equation 1 represents an oxidative coupling-based process in which the boronic acid (**232**) alkylates a carbazate (**233**) in the presence of O_2.[153] In the second example, depicted in Equation 2, the boronic acid (**235**) reacts with an azodicarboxylate (**236**) to deliver the ene-hydrazine product **237**. In contrast to the former method, this particular process may be considered an electrophilic amination; the boronic acid presumably undergoes transmetalation to form a reactive vinylcopper species, which subsequently adds to the azodicarboxylate electrophile.[154]

Scheme 1.7.3 Amination of Vinyl Boronic Acids



Dialkyl azodicarboxylates are stable and commercially available sources of electrophilic nitrogen most often used in the context of enolate chemistry.[146] The di-*t*-butyl azodicarboxylate **236** is the most widely employed in aminations because the corresponding hydrazino dicarboxylate derivatives (**238**) undergo clean decarboxylation under acidic conditions.[155] A number of reports have appeared regarding asymmetric syntheses of α–hydrazino and α–amino acid derivatives through amination of chiral enolates.[156, 157] For example, the lithium enolate of carboxamide **172** (Scheme 1.7.4) attacks **236** with high selectivity and in good yield.[156] The reaction products are direct precursors to the hydrazino and amine (**239**) derivatives through a TFA-mediated Boc-deprotection and subsequent reductive cleavage of the N-N bond.

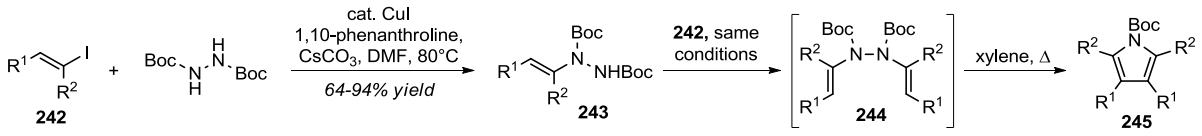
Scheme 1.7.4 Electrophilic Amination with Dialkyl Azodicarboxylates



The reaction of azodicarboxylates with *non-stabilized* carbanions may yield useful products as well, although this transformation has been relatively unexplored. One particular account by Rieke *et al*. shows that primary, secondary, and tertiary organozinc bromides and arylzinc halides react with **236** to form the corresponding hydrazino dicarboxylates **241** (Scheme 1.7.4, eq. 2).[158] However, aside from the examples in Scheme 1.7.3 and Scheme 1.7.4, azodicarboxylates have only been used to aminate stabilized carbanions.

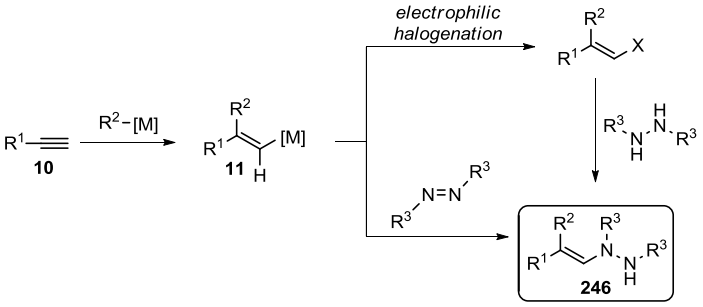
As alluded to previously, the Cu-catalyzed Goldberg reaction remains the standard for synthesizing ene-hydrazines such as **243** (Scheme 1.7.5). Buchwald's laboratory has investigated these reactions extensively, especially in the context of the synthesis of nitrogen heterocycles such as pyrroles,[159] indoles[160] and pyrazoles.[161] For instance, Buchwald and coworkers reported a copper-catalyzed vinylation of protected hydrazines to afford stable alkenyl hydrazines (**243**, Scheme 1.7.5). To demonstrate the synthetic utility of these types of products, the authors synthesized substituted pyrroles (**245**) through sequential vinylations followed by a thermal rearrangement-cyclization.[159]

Scheme 1.7.5 Preparation of Ene-Hydrazines through Buchwald-Hartwig Coupling



Analogous to the carbometalation-oxygenations chemistry, a more direct entry into ene-hydrazines might involve alkyne precursors (**10**, Scheme 1.7.6). Carbometalation or hydrometalation of an alkyne would generate a nucleophilic vinyl-metal species that may react with an electrophilic nitrogen donor. This strategy would circumvent the timely preparations of vinyl halide and boronic acid substrates (**232** and **235**) used in previous syntheses of alkenyl hydrazines (Scheme 1.7.5 and 1.7.3).

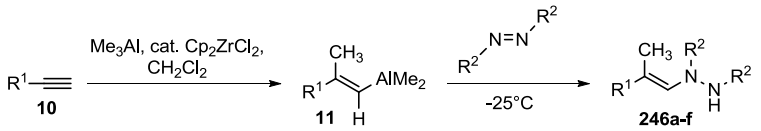
Scheme 1.7.6 Carbometalation-Amination of Terminal Alkynes



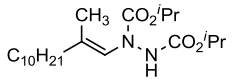
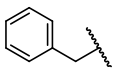
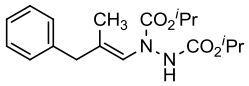
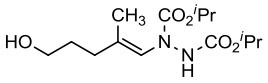
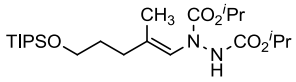
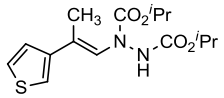
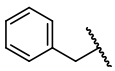
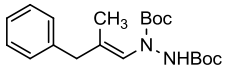
1.7.2. Electrophilic Amination of Vinyl Alanes

As an extension of the methylalumination/oxygenation chemistry we were interested in preparing enamine derivatives through electrophilic amination of vinyl alanes **11** (Table 1.7.1, eq. 1). We reasoned that this strategy would shorten synthetic routes by removing the vinyl halide intermediates. Indeed, we discovered that dialkyl azodicarboxylates effect the amination of **11**, derived from the Zr-catalyzed methylalumination of terminal alkynes.

Table 1.7.1 Preparation of Ene-Hydrazines from Vinyl Aluminum Species



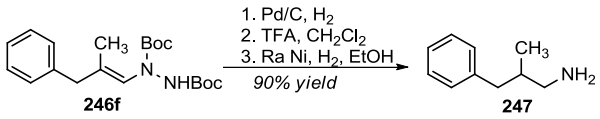
(1)

Entry	R^1	R^2	Product	Yield (%)
1	$C_{10}H_{21}$	$CO_2{}^iPr$	**246a:** 	79
2		$CO_2{}^iPr$	**246b:** 	90
3	HO	$CO_2{}^iPr$	**246c:** 	86
4	TIPSO	$CO_2{}^iPr$	**246d:** 	83
5		$CO_2{}^iPr$	**246e:** 	77
6		Boc	**246f:** 	84

The reactions are very simple in the practical sense; the neat, commercially available azodicarboxylate is simply added dropwise to a cooled solution of vinyl alane at -25°C followed by a standard aqueous workup. The reaction scope is tabulated above and exhibits several significant features (Table 1.7.1). Substantial functionality is tolerated in the transformation, including heterocycles (entry 5), TIPS-protected alcohols (entry 4), and free hydroxyl groups (entry 3). Although these results are fairly preliminary, to date all vinyl alanes treated with azodicarboxylates undergo clean amination. In addition, only the *E*-olefin stereoisomers have been detected. Finally, in accordance with the results from the oxygenation reactions, no products derived from amination of the minor vinyl alane regioisomer were isolated.

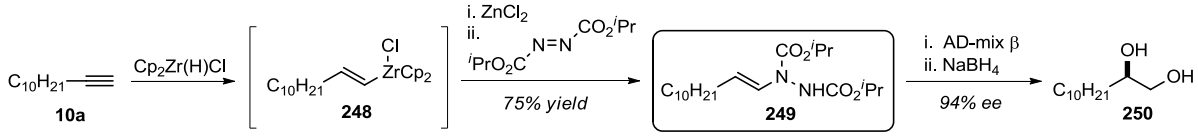
The Boc-protected ene-hydrazines (**246f,** R^2 = Boc) can be transformed into their corresponding primary amines in high yields (Scheme 1.7.7). In this way, the olefin is first reduced with Pd/C and the Boc-protecting group is removed with TFA under standard conditions. Reductive cleavage with Raney Ni delivers the primary amine **247** after three steps involving no chromatography.

Scheme 1.7.7 Preparation of Primary Amines from Ene-hydrazines



This reaction is not limited to preparing trisubstituted ene-hydrazine products. In preliminary investigations we found that vinyl zirconium **248** (Scheme 1.7.8) could be aminated with diisopropoxy azodicaroxylate in the presence of $ZnCl_2$. The role of $ZnCl_2$ is unclear at this point; however, both the transmetalation with zinc salts and the electrophilic amination of alkylzinc halides with azodicarboxylates are known (Scheme 1.7.4). This reaction may also be catalytic in zinc salts, but this, along with the scope of this reaction deserves further investigation.

Scheme 1.7.8 Preparation of Ene-Hydrazines from Vinyl Zirconium Species



The synthetic utility of the ene-hydrazine product **249** has been examined briefly as well. Since monosubstituted olefins are, at best, mediocre substrates for asymmetric dihydroxylation reactions, we reasoned that ene-hydrazines may represent useful alternatives.[126] For example, AD of 1-hexene affords the corresponding diol in 80% ee.[126] Subjecting ene-hydrazine **249** to the same asymmetric dihydroxylation conditions, followed by a reductive workup, delivered the corresponding diol **250** in 79%

yield and 95% ee. Of note, controlling the olefin stereostructure proved crucial for the asymmetric dihydroxylation; subjecting the *Z*-stereoisomer of **250** to identical AD conditions provided the racemic mixture of **250**. Considering these types of 1,2-disubstituted ene-hydrazines as precursors to optically active diols and nitrogen heterocycles (Scheme 1.7.5), the development of the hydrozirconation-amination reaction would certainly present a practical entry to synthetically useful amine products.

1.8. Chapter One Conclusions

In this body of work, peroxyzinc reagents, namely MeZnOO^{t}Bu, were shown to oxygenate vinyl alanes derived from the methylalumination of terminal alkynes. The resulting metallo-enolate may be trapped with benzoic anhydride, acetic anhydride, and TESOTf to generate *E*-trisubstituted enol esters and silanes in high yields. The preparation of these types of enol derivatives displays remarkable generality with respect to the terminal alkyne substrate and functional group tolerance. The enol benzoate compounds are ideal substrates for asymmetric dihydroxylation reactions, and high ee's are obtained in the corresponding diols following a reductive workup procedure. The intermediate α-hydroxy aldehydes derived from the AD of enol benzoates can be further functionalized to propargylic alcohols, α,β-unsaturated esters, secondary amines, and α–hydroxy esters. Furthermore, this methodology was exploited in a short, highly enantioselective synthesis of (+)-frontalin.

Alkenyl alanes derived from the methylalumination of terminal acetylenes were shown to be efficiently aminated with dialkyl azodicarboxylates. This reaction tolerates a variety of functional groups and leads to *E*-ene hydrazines in good yields. Preliminary results indicated that vinyl zirconium species could be aminated with azodicarboxylates as well. Together, the oxygenations and aminations of vinyl alane and zirconium intermediates, which were previously unknown, represent practical approaches to the corresponding, highly functionalized enol and enamine derivatives.

1.9. Chapter One Experimental

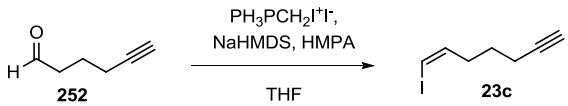
1.9.1. Materials and Methods

General. Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly purified solvents. Solvents were purified using solvent purification columns purchased from Glass Contour, Laguna Beach, CA. All reactions were monitored by thin-layer chromatography with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). Gas chromatography (GC) was performed on an HP 6890N autosampling GC with an HP-5 capillary column and equipped with a FID detector. Flash chromatography was performed with indicated solvents using silica gel (particle size 0.032-0.063 μm) purchased from Sorbent Technologies. ^{1}H and ^{13}C NMR spectra were recorded on Varian Inova-400 or Mercury-300 spectrometer. Chemical shifts are reported relative to internal chloroform ($CDCl_3$: ^{1}H, δ = 7.27, ^{13}C, δ = 77.26). Coupling constants are in Hz and are reported as d (doublet), t (triplet), q (quartet), p (pentet) sep (septet), and app for apparent. For signals having multiple coupling patterns, the coupling constant are listed in the same order as the pattern (e.g. dt, J = 2.0, 4.0; 2.0 is the coupling constant for the doublet and 4.0 is for the coupling constant for the triplet). Infrared spectra were recorded on a Perkin-Elmer 1000 series FTIR. Low-resolution mass spectra were acquired on a Shimadzu QP5000 GC/MS using the indicated ionization method. HPLC analyses were carried out on a Shimadzu LC-2010A system. Optical rotations were measured on a Rudolph Research Analytical Autopol® IV Polarimeter.

Materials. Cp_2ZrCl_2 was purchased from Strem Chemicals Inc. Me_3Al (2.0M in toluene), Me_2Zn (2.0M in toluene), and AD-mix α and β were purchased from Aldrich. Anhydrous ^{t}BuOOH in toluene was prepared from the known Sharpless procedure.[117] Unless otherwise noted, all terminal alkyne starting materials were purchased from Aldrich. 1-Hepten-6-yne (**23i**, Table 1.4.3)[162] and 1-octen-7-yne (**23j**, Table 1.4.3)[163] were prepared following the known literature procedures.

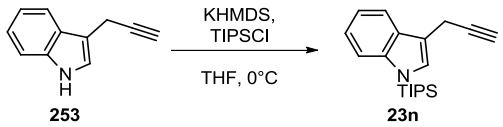
1.9.2. Preparative Methods.

Preparation of alkyne starting materials:



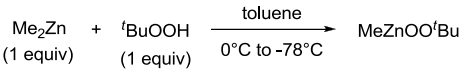
23c (Table 1.4.3, entry c)**:** Vinyl iodide **23c** was prepared from the reaction of aldehyde **252**[164] with $PH_3PCH_2I[I]$[165] following a similar olefination procedure.[166] The crude vinyl iodide was purified by flash chromatography (100% pentane) and the fractions were analyzed by GC. The desired compound was obtained as pink solution in pentane (0.734 g, 45%, Z/E ratio 25/1). ^{1}H NMR ($CDCl_3$) δ = 1.68 (app p, J

= 7.4, 2H), 1.98 (t, *J* = 2.4, 1H), 2.22-2.29 (m, 4H), 6.18 (q, *J* = 6.8, 1H), 6.25 (d, *J* = 7.4, 1H). ^{13}C NMR ($CDCl_3$) δ = 18.21, 27.09, 33.99, 69.02, 83.53, 84.08, 140.35. EI-MS (m/z): 220 $[M]^+$.



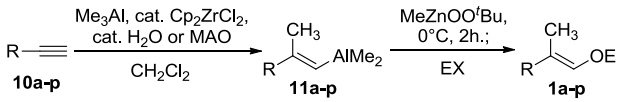
253 **23n**

23n (Table 1.4.4, entry n)**:** To a stirred solution of indole **253**[167] (7.1 mmol) in 15 mL of THF at 0˚C was added KHMDS (in 15 mL THF, 1.56 g, 7.46 mmol, 1.05 equiv). The reaction was stirred for 30 minutes at this temperature, at which time TIPSCl (1.84 mL, 7.81 mmol, 1.1 equiv) was added. The reaction was stirred overnight, quenched with water, and extracted 3 times with EtOAc. The combined organic extracts were concentrated and the crude indole was purified by flash chromatography (5% EtOAc in hexanes) to give the desired product as a white solid (1.5 g, 68% yield). ^{1}H NMR ($CDCl_3$) δ = 1.34 (d, *J* = 7.2, 18H), 1.63-1.75 (m, 3H), 2.14 (t, *J* = 2.4, 1H), 3.69 (dd, *J* = 2.4, *J* = 1.2, 2H), 7.11-7.18 (m, 2H), 7.18 (s, 1H), 7.48 (dd, *J* = 7.2, *J* = 2, 1H), 7.61 (dd, *J* = 6.4, *J* = 2, 1H). ^{13}C NMR ($CDCl_3$) δ = 13.06, 15.64, 18.39, 69.21, 82.66, 112.83, 114.26, 118.65, 119.72, 121.85, 129.04, 130.33, 141.71. EI-MS (m/z): 311 $[M]^+$.



Procedure for preparing MeZnOO^{t}Bu: To a stirred solution of Me_2Zn (1.0 equiv) in dry toluene at -78˚C was added dropwise anhydrous ^{t}BuOOH (3.9M in toluene, 1.0 equiv).[117] After adding the solution of ^{t}BuOOH, the concentration of peroxide should be 0.3M in toluene. The resulting mixture was stirred for 15 minutes at -78˚C, at which time the flask was quickly transferred to an ice-water bath to warm the solution to 0˚C. The reaction was complete after stirring for an additional 15 minutes at 0˚C. At this time a solution of vinyl alane was immediately transferred to the zinc peroxide at 0˚C.

Preparation of Enol Benzoates from Terminal Alkynes:



Methylalumination-Oxygenation:

Method A (Table 1.4.3, entries a-d; Table 1.4.4, entries k-m): To a stirred solution of Cp_2ZrCl_2 (0.59 g, 0.2 mmol, 0.1 equiv.) and Me_3Al (2.0M in Toluene, 1.5 mL, 3.0 mmol, 1.5 equiv.) in 6.5 mL CH_2Cl_2 at 0˚C was slowly added H_2O (0.9 µL, 0.05 mmol, 2.5 mol%) (reaction is exothermic and produces smoke). The reaction was allowed to warm to room temperature, and after 10 minutes the terminal alkyne (2.0

mmol, 1.0 equiv.) was added. When the methylalumination appeared complete by TLC, the reaction solution was quickly transferred via canula into a stirred solution of $MeZnOO^tBu$ (0.3M in toluene, 14 mL, 4.0 mmol, 2.0 equiv) at 0˚C. The oxygenation was complete after stirring for 2 hours at 0˚C. Electrophilic was trapping performed as described below.

Method B [(Table 1.4.3, entries e & f; Table 1.4.4, entry p) (for free alcohols)**]:** To a stirred solution of Me_3Al and MAO in 3.0mL CH_2Cl_2 at 0˚C was added terminal alkyne in 3.0mL CH_2Cl_2. The resulting solution was allowed to stir for 1 hour at room temperature before Cp_2ZrCl_2 in 1.0 mL CH_2Cl_2 was added. When the methylalumination appeared complete by TLC, the reaction solution was quickly transferred via canula into a stirred solution of $MeZnOO^tBu$ (0.3M in toluene) at 0˚C. The oxygenation was complete after stirring for 2 hours at 0˚C. Electrophilic trapping was performed as described below. In entry 5, after benzoylation of the enolate, BzCl (2 equiv) was added at 0^oC to benzoylate the primary alcohol.

Method C (Table 1.4.3, entries g & j; Table 1.4.4, entries n-p): To a stirred solution of Cp_2ZrCl_2 and Me_3Al in 6.5 mL CH_2Cl_2 at room temperature was added MAO and terminal alkyne. When the methylalumination appeared complete by TLC, the reaction solution was quickly transferred via canula into a stirred solution of $MeZnOO^tBu$ (0.3M in toluene) at 0˚C. The oxygenation was complete after stirring for 2 hours at 0˚C. Electrophilic trapping was performed as described below.

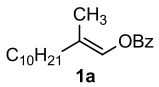
Electrophilic trapping:

Benzoylation (Table 1.4.3, all entries): After methylalumination-oxygenation was complete, $^nBu_3P$ (0.4 mmol, 0.2 equiv) and Bz_2O (16 mmol, 8 equiv) in 10-15 mL CH_2Cl_2 (pre-mixed at 0˚C for 10 minutes) were transferred to the methylalumination-oxygenation reaction mixture via canula at 0˚C. The reaction was allowed to warm to room temperature and the benzoylation was complete after 15 hours. The reaction was quenched by transferring the contents of the flask into 100 mL of a stirred 10% aqueous solution of citric acid (CA) at 0˚C. The reaction flask was washed with 10 mL CH_2Cl_2 (2 X 5) and this was transferred to the 10% CA solution as well. The resulting slurry was stirred for 3 hours or until the two phases were homogenous, at which time it was extracted 3 times with CH_2Cl_2. The combined organic extracts were washed once with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated. Before purification by flash chromatography (silica gel, EtOAc/hexanes), 2-3 mm of Et_3N was added to the top of the SiO_2 surface of the column. The crude enol benzoate was loaded onto the column when the Et_3N had receded to ½ mm above the SiO_2 surface. Pretreating the column with Et_sN in this fashion helps separate the desired product from a streaky yellow impurity. Reaction times, purification conditions and characterization data are provided below for all entries in Table 1.

Acylation (Table 1.4.4, entries k-n): After methylalumination-oxygenation was complete (2 hours at 0˚C), Ac_2O (1.1 mL, 12 mmol, 6.0 equiv.) was added to the reaction at 0˚C. The reaction was allowed to warmed r.t. and then heated to 35˚C. Acylation was complete in 4 hours at this temperature. The reaction was then cooled to 0˚C and 1.0 mL H_2O was added slowly with vigorous stirring. When H_2O addition was complete, the mixture was stirred for 15 minutes at room temperature, after which time 1.0 g $MgSO_4$ was added. The mixture was filtered through a plug of silica gel and the solvent was removed to give the crude enol acetate.

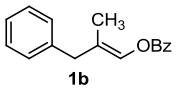
Silylation (Table 1.4.4, entries o & p): After methylalumination-oxygenation was complete (2 hours at 0˚C), a solution of TESOTf (3.2 mL, 14 mmol, 7.0 equiv) in 6.0 mL CH_2Cl_2 and 6.0 mL pyridine was transferred to the reaction at 0˚C. The solution was allowed to stir overnight at 4˚C. At this time, 1.5 mL H_2O was added slowly to the vigorous stirring reaction solution at 0˚C. After 15 min at r.t., 3.0g $MgSO_4$ was added and the resulting mixture was filtered through a plug of silica gel. The solvent was removed to give the crude TES enol ether.

Characterization data for enol benzoate compounds and reaction details (Table 1.4.3**):**



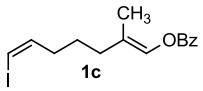
1a

1a (Table 1.4.3, entry a, Method A): Methylalumination was complete in 5 hours. Chromatography (0.5-1.0% EtOAc in hexane) provided 0.47g (78% yield) of a white solid. ^{1}H NMR ($CDCl_3$) δ = 0.88 (t, *J* = 6.5, 3H), 1.28 (m, 14H), 1.45 (t, *J* = 7.0, 2H), 1.81 (d, *J* = 1.3, 3H), 2.04 (t, *J* = 7.3, 2H), 7.15 (d, *J* = 1.3, 1H), 7.47 (t, *J* = 7.9, 2H), 7.59 (tt, *J* = 7.4, *J* = 1.2, 1H), 8.11 (dd, *J* = 8.4, *J* = 1.4, 2H). ^{13}C NMR ($CDCl_3$) δ = 14.1, 14.4, 22.9, 27.8, 29.5, 29.6, 29.7, 29.9, 29.9, 32.2, 34.3, 122.8, 128.6, 130.0, 130.4, 133.4, 163.8. FTIR (thin film) 2923, 1689, 1288 cm^{-1}. EI-MS (m/z): 302 $[M]^+$.



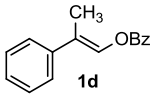
1b

1b (Table 1.4.3, entry b, Method A): Methylalumination was complete in 4.5 hours. Chromatography (1.0% EtOAc in hexane) provided 0.45g (89% yield) of a white solid. ^{1}H NMR ($CDCl_3$) δ = 1.74 (d, *J* = 1.2, 3H), 3.36 (s, 2H), 7.21-7.27 (m, 2H), 7.29-7.33 (m, 3H), 7.47 (t, *J* = 8.0, 2H), 7.60 (t, *J* = 7.6, 1H), 8.11 (d, *J* = 7.6, 2H). ^{13}C NMR ($CDCl_3$) δ = 14.1, 40.7, 122.1, 126.7, 128.7, 128.8, 129.1, 129.8, 130.1, 131.7, 133.6, 139.2, 163.9. FTIR (thin film) 2918, 1726, 1261 cm^{-1}. EI-MS (m/z): 252 $[M]^+$



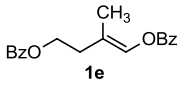
1c

1c (Table 1.4.3, entry c, Method A): Methylalumination was complete in 3.5 hours. Chromatography (1.0% EtOAc in hexane) provided 0.58g (82% yield) of a brown oil. ^{1}H NMR ($CDCl_3$) δ = 1.62 (app p, *J* = 7.8, 2H), 1.83 (d, *J* = 1.3, 3H), 2.10 (t, *J* = 7.6, 2H), 2.17 (dt, *J* = 6.2, *J* = 7.4, 2H), 6.17-6.24 (m, 2H), 7.18 (d, *J* = 1.2, 1H), 7.47 (t, *J* = 8, 2H), 7.59 (t, 7.6, 1H), 8.11 (d, *J* = 8, 2H). ^{13}C NMR ($CDCl_3$) δ = 14.1, 26.2, 33.7, 34.5, 83.2, 122.0, 128.7, 129.8, 130.0, 130.8, 133.5, 141.0, 163.8. FTIR (thin film) 2933, 1778, 1271 cm^{-1}. EI-MS (m/z): 229 $[M-I]^+$.



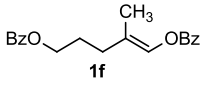
1d

1d (Table 1.4.3, entry d, Method A): Methylalumination was complete in 4 hours. Chromatography (1.0% EtOAc in hexane) provided 0.38g (80% yield) of a white solid. ^{1}H NMR ($CDCl_3$) δ = 2.25 (d, *J* = 1.2, 3H), 7.25-7.31 (m, 1H), 7.37 (t, *J* = 7.2, 2H), 7.45 (d, *J* = 7.2, 2H), 7.51 (t, *J* = 8, 2H), 7.63 (t, *J* = 7.6, 1H), 7.78 (s, 1H), 8.17 (d, *J* = 8, 2H). ^{13}C NMR ($CDCl_3$) δ = 14.1, 122.5, 126.1, 127.6, 128.7, 128.8, 129.6, 130.1, 132.9, 133.8, 139.3, 163.8. FTIR (thin film) 2362, 1721, 127 cm^{-1}. EI-MS (m/z): 238 $[M]^+$.



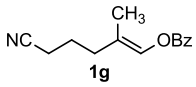
1e

1e (Table 1.4.3, entry e, Method B): Reagent amounts: Alkyne (2.0 mmol, 1.0 equiv), Me_3Al (8.0 mmol, 4.0 equiv), Cp_2ZrCl_2 (0.4 mmol, 0.2 equiv), MAO (0.1 mmol, 5 mol%), MeZnOO^{t}Bu (0.3M in tol, 32 mL, 9.6 mmol, 4.8 equiv), Bz_2O (24 mmol, 12 equiv), ^{n}Bu$_3$P (0.82mmol, 0.3 equiv). Methylalumination was complete in 8 hours. Chromatography (5.0% EtOAc in hexanes) provided 0.37g (59% yield) of a white solid. ^{1}H NMR ($CDCl_3$) δ = 1.91 (d, *J* = 1.4, 3H), 2.52 (t, *J* = 6.6, 2H), 4.45 (t, *J* = 6.6, 2H), 7.28 (d, *J* = 1.3, 1H), 7.28-7.48 (m, 4H), 7.52-7.61 (m, 2H), 8.04 (dd, *J* = 8.5, *J* = 1.1, 2H), 8.10 (dd, *J* = 8.5, *J* = 1.1, 2H). ^{13}C NMR ($CDCl_3$) δ = 14.3, 33. 7, 63.1, 118.7, 128.6, 128.7, 129.7, 129.8, 130.4, 133.3, 133.2, 133.2, 133.62 163.7, 166.8. FTIR (thin film) 2913, 1723, 1283 cm^{-1}. EI-MS (m/z): 205 $[M-PhCHO]^+$.



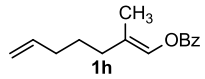
1f

1e (Table 1.4.3, entry f, Method B): Reagent amounts: Alkyne (2.0 mmol, 1.0 equiv), Me_3Al (6.0 mmol, 3.0 equiv), Cp_2ZrCl_2 (0.4 mmol, 0.2 equiv), MAO (0.1 mmol, 5 mol%), MeZnOO^{t}Bu (0.3M in tol, 23 mL, 7.0 mmol, 3.5 equiv), Bz_2O (18 mmol, 9 equiv), ^{n}Bu$_3$P (0.4 mmol, 0.2 equiv). Methylalumination was complete in 22 hours. Chromatography (2.0-5.0% EtOAc in hexanes) provided 0.5g (79% yield) of a colorless oil. ^{1}H NMR ($CDCl_3$) δ = 1.86 (d, *J* = 1.2, 3H), 1.93-2.00 (m, 2H), 2.24 (t, *J* = 7.2, 2H), 4.36 (t, *J* = 6.8, 2H), 7.22 (d, *J* = 1.2, 1H), 7.42-7.49 (m, 4H), 7.54-7.61 (m, 2H), 8.06 (dd, *J* = 8.4, *J* = 1.4, 2H), 8.11 (dd, *J* = 8.2, *J* = 1.5, 2H). ^{13}C NMR ($CDCl_3$) δ = 14.1, 27.0, 30.9, 64.6, 94.6, 121.5, 128.6, 128.7, 129.8, 130.0, 130.5, 131.0, 133.1, 133.6, 163.8, 166.8. FTIR (thin film) 2952, 1723, 1273 cm^{-1}. EI-MS (m/z): 324 $[M]^+$.



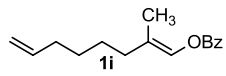
1g

1g (Table 1.4.3, entry g, Method C): Reagent amounts: Alkyne (2.0 mmol, 1.0 equiv), Me_3Al (6.0 mmol, 3.0 equiv), Cp_2ZrCl_2 (0.6 mmol, 0.3 equiv), MAO (0.4 mmol, 0.2 equiv), $MeZnO^tBu$ (0.3M in tol, 27 mL, 8.0 mmol, 4.0 equiv), Bz_2O (18 mmol, 9 equiv), $^nBu_3P$ (0.4 mmol, 0.2 equiv). Methylalumination was complete in 3 days. Chromatography (10% EtOAc in hexanes) provided 0.32g (71% yield) of a yellow oil. ^1H NMR ($CDCl_3$) δ = 1.82-1.91 (m, 2H), 1.84 (d, *J* = 1.5, 3H), 2.23 (t, *J* = 7.5, 2H), 2.37 (t, *J* = 7.2, 2H), 7.19-7.22 (m, 1H), 7.48 (tt, *J* = 7.7, *J* = 1.5, 2H), 7.60 (tt, *J* = 7.4, *J* = 1.4, 1H), 8.09-8.13 (m, 2H). ^{13}C NMR ($CDCl_3$) δ = 13.7, 16.5, 23.4, 32.9, 119.7, 120.2, 128.7, 129.5, 129.9, 131.5, 133.6, 163.6. FTIR (thin film) 2928, 1728, 1268 cm^{-1}. EI-MS (m/z): 229 $[M]^+$.



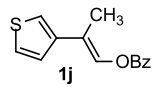
1h

1h (Table 1.4.3, entry h, Method D): Methylalumination was complete in 6.5 hours at 0˚C. Chromatography (1.0% EtOAc in hexanes) provided 0.37g (76% yield) of a pale yellow oil. ^1H NMR ($CDCl_3$) δ = 1.53-1.61 (m, 2H), 1.81 (d, *J* = 1.4, 3H), 2.05-2.11 (m, 4H), 4.96-5.07 (m, 2H), 5.77-5.88 (m, 1H), 7.16 (d, *J* = 1.4, 1H), 7.47 (t, *J* = 7.4, 2H), 7.59 (tt, *J* = 7.4, *J* = 1.3, 1H), 8.11 (dt, *J* = 8.1, *J* = 1.4, 2H). ^{13}C NMR ($CDCl_3$) δ = 14.0, 27.0, 33.4, 33.6, 115.0, 133.3, 128.7, 129.91, 123.0, 130.7, 133.4, 138.6, 163.8. FTIR (thin film) 2933, 1728, 1266 cm^{-1}. EI-MS (m/z): 230 $[M]^+$.



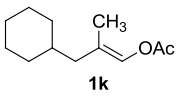
1i

1i (Table 1.4.3, entry i, Method D): Methylalumination was complete in 6.5 hours at 0˚C. Chromatography (1.0% EtOAc in hexanes) provided 0.35g (75% yield) of a pale yellow oil. ^1H NMR ($CDCl_3$) δ = 1.37-1.52 (m, 4H), 1.81 (d, *J* = 1.2, 3H), 2.04-2.11 (m, 4H), 4.94-5.04 (m, 2H), 5.76-5.87 (m, 1H), 7.15 (d, *J* = 1.3, 1H), 7.47 (t, *J* = 7.6, 2H), 7.59 (tt, *J* = 7.4, *J* = 1.2, 1H), 8.10 (dd, *J* = 8.0, *J* = 1.2, 2H). ^{13}C NMR ($CDCl_3$) δ = 14.0, 27.2, 28.6, 33.8, 34.0, 114.7, 122.6, 128.76, 129.9, 130.0, 130.5, 133.4, 139.0, 163.8. FTIR (thin film) 2933, 1728, 1266 cm^{-1}. EI-MS (m/z): 244 $[M]^+$.



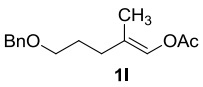
1j

1j (Table 1.4.3, entry j, Method C): Reagent amounts: Alkyne (2.0 mmol, 1.0 equiv), Me_3Al (6.0 mmol, 3.0 equiv), Cp_2ZrCl_2 (0.6 mmol, 0.2 equiv), MAO (0.4 mmol, 0.2 equiv), $MeZnO^tBu$ (0.3M in tol, 27 mL, 8.0 mmol, 4.0 equiv), Bz_2O (18 mmol, 9 equiv), $^nBu_3P$ (0.4 mmol, 0.2 equiv). Methylalumination was complete in 48 hours. Chromatography (1.5% EtOAc in hexanes) provided 0.4g (83% yield) of a yellow solid. ^1H NMR ($CDCl_3$) δ = 2.21 (d, *J* = 1.2, 3H), 7.20-7.22 (m, 1H), 7.28 (dd, *J* = 5.1, *J* = 1.5, 1H), 7.32 (app q, *J* = 3.0, 1H), 7.50 (t, *J* = 7.6, 2H), 7.62 (tt, *J* = 7.5, *J* = 1.3, 1H), 7.90 (d, *J* = 1.3, 1H), 8.15 (dd, *J* = 8.3, *J* = 1.3, 2H). ^{13}C NMR ($CDCl_3$) δ = 13.9, 118.0, 120.4, 124.8, 126.3, 128.9, 129.5, 130.2, 132.9, 133.8, 140.3, 163.6. FTIR (thin film) 3101, 1720, 1268 cm^{-1}. EI-MS (m/z): 244 $[M]^+$.



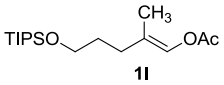
1k

1k (Table 1.4.4, entry k, Method A): Reagent amounts: Cp_2ZrCl_2 (0.59 g, 0.2 mmol, 0.1 equiv.), Me_3Al (2M in Toluene, 1.5 mL, 3.0 mmol, 1.5 equiv.), $MeZnOO^tBu$ (0.3M in toluene, 13.3 mL, 4 mmol, 2.0 equiv). Enol acetate **1k** (0.36 g, 91%) was obtained as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ = 0.78-0.87 (m, 2H), 1.14-1.25 (m, 4H), 1.34-1.45 (m, 1H), 1.59-1.72 (m, 4H), 1.64 (d, *J* = 1.4, 3H), 1.82 (d, *J* = 7.2, 2H), 2.13 (s, 3H), 6.84 (d, *J* = 1.3, 1H). ^{13}C NMR ($CDCl_3$) δ = 13.9, 21.0, 26.5, 26.8, 33.4, 35.3, 42.0, 120.5, 130.9, 168.6. FTIR (thin film) 2928, 1750, 1213 cm^{-1}. EI-MS (m/z): 196 $[M]^+$.



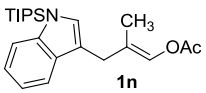
1l

1l (Table 1.4.4, entry l, Method A): Reagent amounts: Cp_2ZrCl_2 (0.117 g, 0.4 mmol, 0.2 equiv), Me_3Al (3.0 mL, 6.0 mmol, 3.0 equiv), 0.3M $MeZnOO^tBu$ in toluene (25 mL, 7.6 mmol, 3.8 equiv). Methylalumination was complete in 24 hours. Enol acetate **1l** was obtained as a yellow oil (0.48 g, 96%). ^{1}H NMR ($CDCl_3$) δ = 1.65 (d, *J* = 1.2, 3H), 1.73 (m, 2H), 2.06 (t, *J* = 7.0, 2H), 2.12 (s, 3H), 3.45 (t, *J* = 6.4, 2H), 4.49 (s, 2H), 6.89 (d, *J* = 1.1, 1H), 7.25-7.36 (m, 5H). ^{13}C NMR ($CDCl_3$) δ = 18.6, 25.7, 32.7, 35.5, 74.5, 77.7, 125.7, 132.5, 132.6, 133.3, 135.4, 143.8, 172.8. FTIR (thin film) 2864, 1745, 1222 cm^{-1}. EI-MS (m/z): 205 $[M\text{-}CH_3CHO]^+$.



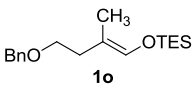
1l

1m (Table 1.4.4, entry m, Method A): Reagent amounts: Cp_2ZrCl_2 (0.117 g, 0.4 mmol, 0.2 equiv), Me_3Al (3.0 mL, 6.0 mmol, 3.0 equiv), 0.3M $MeZnOO^tBu$ in toluene (25 mL, 7.6 mmol, 3.8 equiv). Enol acetate **1m** was obtained as a pale yellow oil (0.43g, 92%). ^{1}H NMR ($CDCl_3$) δ = 1.04-1.07 (m, 18H), 1.62-1.68 (m, 3H), 1.68 (d, *J* = 1.2, 3H), 2.05 (t, *J* = 7.2, 2H), 2.13 (s, 3H), 3.67 (t, *J* = 6.4, 2H), 6.90 (d, *J* = 1.2, 1H). ^{13}C NMR ($CDCl_3$) δ = 12.2, 13.9, 18.2, 21.0, 30.5, 31.2, 63.0, 94.6, 121.8, 130.4. FTIR (thin film) 2928, 1750, 1219 cm^{-1}. EI-MS (m/z): 271 $[M\text{-}CH_2CH_3]^+$.



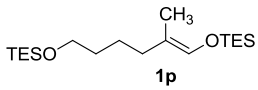
1n

1n (Table 1.4.4, entry n, Method C): Reagent amounts: Cp_2ZrCl_2 (0.175 g, 0.6 mmol, 0.3 equiv), Me_3Al (2.0M in toluene, 3.0 mL, 6.0 mmol, 3.0 equiv), MAO (10% solution, 0.133 mL, 0.2 mmol, 0.1 equiv) 0.3M $MeZnOO^tBu$ (25 mL, 7.6 mmol, 3.8 equiv). Enol acetate **1n** (0.71 g, 92%) was isolated as a yellow syrup. ^{1}H NMR ($CDCl_3$) δ = 1.14 (d, *J* = 7.6, 18H), 1.64 (d, *J* = 1.2, 3H), 1.65-1.73 (m, 3H), 2.13 (s, 3H), 3.43 (s, 2H), 7.02 (s, 1H), 7.08-7.15 (m,3H), 7.46 (d, *J* = 8, 1H), 7.58 (d, *J* = 8, 1H). ^{13}C NMR ($CDCl_3$) δ = 13.1, 14.0, 18.5, 21.1, 30.4, 114.2, 115.1, 119.2, 119.7, 121.4, 121.7, 129.6, 131.2, 131.3, 141.8, 168.5. FTIR (thin film) 2948, 2866, 1753, 1451, 1229 cm^{-1}. EI-MS (m/z): 385 $[M]^+$.



1o

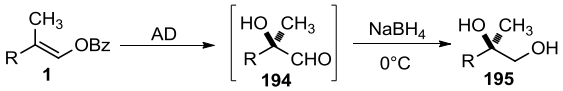
1o (Table 1.4.4, entry o, Method C): Reagent amounts: Cp_2ZrCl_2 (0.175 g, 0.6 mmol, 0.3 equiv), Me_3Al (2.0M in toluene, 3.0 mL, 6.0 mmol, 3.0 equiv), MAO (10% wt. solution, 0.265 mL, 0.4 mL, 0.2 equiv.) 0.3M MeZnOO^{t}Bu (25 mL, 7.6 mmol, 3.8 equiv). TES enol ether **1o** was isolated as a bright yellow oil (0.48 g, 79%). ^{1}H NMR ($CDCl_3$) δ = 0.65 (q, *J* = 8, 6H), 0.97 (t, *J* = 8, 9H), 1.62 (d, *J* = 1.4, 3H), 2.20 (t, *J* = 7.2, 2H), 3.50 (t, *J* = 7.2, 2H), 4.50 (s, 2H), 6.15 (d, *J* = 1.4, 1H), 7.25-7.31 (m, 2H), 7.33 (d, *J* = 4.5, 3H). ^{13}C NMR ($CDCl_3$) δ = 4.8, 6.9, 13.2, 34.5, 69.8, 73.1, 114.3, 127.7, 127.8, 128.6, 135.5, 138.9. FTIR (thin film) 2908, 1673, 1456, 1164 cm^{-1}. EI-MS (m/z): 277 [M-CH_2CH_3]$^+$.



1p

1p (Table 1.4.4, entry p, Method B): Reagent amounts: Alkyne (2.0 mmol, 1.0 equiv), Me_3Al (6.0 mmol, 3.0 equiv), Cp_2ZrCl_2 (0.4 mmol, 0.2 equiv), MAO (0.1 mmol, 5 mol%), MeZnOO^{t}Bu (0.3M in tol, 23 mL, 7.0 mmol, 3.5 equiv). TES enol ether **1p** was isolated as a colorless oil (0.54 g, 83%). ^{1}H NMR ($CDCl_3$) δ = 0.61-0.63 (m, 12H), 0.96 (t, *J* = 7.9, 9H), 0.97 (t, *J* = 7.9, 9H), 1.36-1.1.40 (m, 2H), 1.42-1.50 (m, 2H), 1.57 (d, *J* = 1.3, 3H), 1.86 (t, *J* = 7.1, 2H), 3.59 (t, *J* = 6.4, 2H), 6.06 (d, *J* = 1.3, 1H). ^{13}C NMR ($CDCl_3$) δ = 4.6, 4.7, 6.7, 6.9, 12.5, 24.5, 32.6, 33.7, 62.9, 117.3, 133.9. FTIR (thin film) 2918, 1671, 1457, 1160 cm^{-1}. EI-MS (m/z): 358 [M]$^+$.

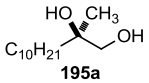
Preparation of 1,2-diols from enol benzoates (Table 1.5.1)**:**



General procedure for the preparation of 1,2-diols (195) from enol benzoates (1) (Table 1.5.1, all entries): All AD reactions performed followed Sharpless' general procedure.[168] Thus, a 1:1 mixture of ^{t}BuOH/H_2O (0.1M based on olefin) was added to flask containing AD-mix β (1.4 g per 1 mmol of olefin) and the mixture was stirred to produce two clear phases. The resulting solution was then stirred at 0˚C until the dissolved salts precipitated. The olefin (1.0 equiv) in ^{t}BuOH was added and the slurry was stirred vigorously at 0˚C until the reaction was complete (12-24 hours). Once complete, $NaBH_4$ (6 equiv to olefin) was added to the mixture at 0˚C and the reaction was kept at this temperature until reduction was complete (about 2 hours). Saturated NH_4Cl was added and the reaction was extracted 3 times with EtOAc. The combined organic extracts were dried with $MgSO_4$ and concentrated to give crude diol product. The diols were further purified by flash chromatography. The ee's of the diols were determined from their monobenzoylated analogues (BzCl, Et_3N, cat. DMAP, CH_2Cl_2). Specific HPLC conditions and chromatograms are located in the section of the supporting information containing NMR spectra. Absolute stereochemistry was assigned by comparison of the optical rotation to reported values the

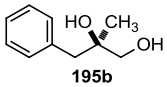
reported value for **195d**. For **195a**, **195d** and **195q**, we further confirmed that the major enantiomer was the same as obtained from dihydroxylation of the 1,1-disubstituted olefin. Other diols are assigned by analogy.

Characterization data for 1,2-diol compounds (Table 1.5.1**):**



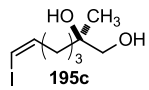
195a

195a (Table 1.5.1, entry a): Chromatography (35% EtOAc in hexanes) provided 66 mg (78% yield) of a colorless oil. ^{1}H NMR ($CDCl_3$) δ = 0.88 (t, *J* = 6.7, 3H), 1.16 (s, 3H), 1.19-1.41 (m, 16H), 1.45-1.51 (m, 2H), 1.9 (br s, 2H), 3.41 (d, *J* = 10.9, 1H), 3.47 (d, *J* = 10.9, 1H). ^{13}C NMR ($CDCl_3$) δ = 14.3, 14.4, 21.3, 23.5, 24.0, 29.6, 29.8, 30.5, 32.1, 39.0, 70.0, 73.2. EI-MS (m/z): 216 $[M\text{-}CH_3]^+$. HPLC analysis of the monobenzoate (Chiralcel AS-H, 1 mL/min, 3% iPrOH/Hexanes; $t_{r(minor)}$ = 7.1 min, $t_{r(major)}$ = 8.2 min) indicated 96% ee. $[\alpha]^{20}_D$ = -2.4 (c = 0.51, $CHCl_3$).



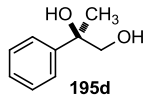
195b

195b (Table 1.5.1, entry b): Chromatography (50% EtOAc in hexanes) provided 56 mg (84% yield) of a colorless oil. ^{1}H NMR ($CDCl_3$) δ = 1.15 (s, 3H), 1.81 (br s, 1H), 1.84 (br t, *J* = 5, 1H), 2.79 (d, 13.3, 1H), 2.86 (d, *J* = 13.3, 1H), 3.45 (dd, *J* = 10.9, 5.6, 2H), 3.51 (dd, J = 10.9, 5.6), 7.25 (m, 3H), 7.32 (t, *J* = 6.9, 2H). ^{13}C NMR ($CDCl_3$) δ = 23.9, 44.9, 69.5, 73.2, 126.9, 128.6, 130.7, 137.2. EI-MS (m/z): 166 $[M]^+$. HPLC analysis of the monobenzoate (Chiralcel AS-H, 1 mL/min, 3% iPrOH/Hexanes; $t_{r(minor)}$ = 18.5 min, $t_{r(major)}$ = 19.5 min) indicated 95% ee. $[\alpha]^{20}_D$ = -2.2 (c = 0.63, $CHCl_3$).



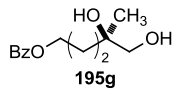
195c

195c (Table 1.5.1, entry c): Chromatography (50% EtOAc in hexanes) provided 48 mg (59% yield) of a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ = 1.18 (s, 3H), 1.52-1.53 (m, 4H), 2.15-2.19 (m, 2H), 2.27 (br s, 2H), 3.42 (d, *J* = 10.9, 1H), 3.48 (d, *J* = 10.9, 1H), 6.16-6.23 (m, 2H). ^{13}C NMR ($CDCl_3$) δ = 22.4, 23.5, 35.3, 38.2, 70.0, 73.1, 83.1, 141.1. EI-MS (m/z): 255 $[M\text{-}CH_3]^+$. HPLC analysis of the monobenzoate (Chiralcel AS-H, 1 mL/min, 4% iPrOH/Hexanes; $t_{r(minor)}$ = 15.0 min, $t_{r(major)}$ = 18.1 min) indicated 96% ee. $[\alpha]^{20}_D$ = -3.1 (c = 0.61, $CHCl_3$).



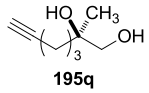
195d

195d (Table 1.5.1, entry d): Chromatography (50% EtOAc in hexanes) provided 11 mg (75% yield) of a colorless oil. ^{1}H NMR ($CDCl_3$) δ = 1.54 (s, 3H), 2.55 (br s, 2H), 3.64 (d, *J* = 11.2, 1H), 3.81 (d, *J* = 11.2, 1H), 7.29 (t, *J* = 8.5, 1H), 7.38 (t, *J* = 7.9, 2H), 7.46 (d, *J* = 7.9, 2H). ^{13}C NMR ($CDCl_3$) δ = 26.3, 71.3, 75.1, 125.3, 127.4, 128.7, 145.2. EI-MS (m/z): 152 $[M]^+$. HPLC analysis of the monobenzoate (Chiralcel AD-H, 1 mL/min, 3% EtOH/Hexanes; $t_{r(minor)}$ = 36.3 min, $t_{r(major)}$ = 39.9 min) indicated 95% ee. $[\alpha]^{20}_D$ = -5.8 (c = 0.55, EtOH); lit.[169] $[\alpha]^{23}_D$ = -5.8 (c = 0.17, EtOH).



195g

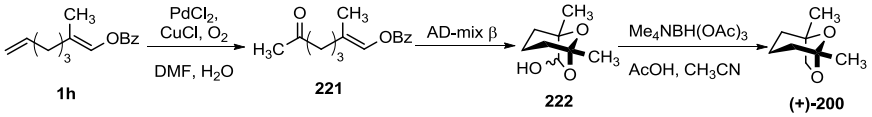
195g (Table 1.5.1, entry g): Chromatography (75% EtOAc in hexanes) provided 18 mg (87% yield) of a colorless oil. ^{1}H NMR ($CDCl_3$) δ = 1.23 (s, 1H), 1.57-1.72 (m, 2H), 1.82-1.93 (m, 3H), 3.50 (dd, *J* = 22.6, *J* = 10.8, 2H), 4.37 (t, *J* = 6.6, 2H), 7.45 (t, *J* = 7.8, 2H), 7.57 (t, *J* = 7.4, 1H), 8.04 (t, *J* = 8.4, 2H). ^{13}C NMR ($CDCl_3$) δ = 23.5, 23.5, 35.1, 65.5, 70.1, 72.8, 128.6, 129.8, 130.5, 133.7, 166.9. EI-MS (m/z): 131 $[M\text{-}PhCHO]^+$. HPLC analysis of the monobenzoate (Chiralcel AS-H, 1 mL/min, 6% iPrOH/Hexanes; $t_{r(minor)}$ = 25.5 min, $t_{r(major)}$ = 21.9 min) indicated 96% ee. $[\alpha]^{20}_D$ = -12.0 (c = 0.15, $CHCl_3$).



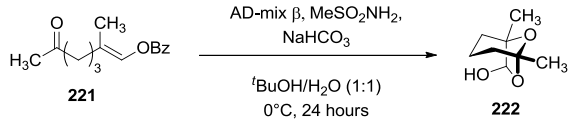
195q

195q (Table 1.5.1, entry q): Chromatography (40% EtOAc in hexanes) provided 14.5mg (75% yield) of a colorless oil. ^{1}H NMR ($CDCl_3$) δ = 1.17 (s, 3H), 1.57-1.62 (m, 4H), 1.73-2.26 (br s, 2H), 1.96 (t, *J* = 2.6, 1H), 2.19-2.23 (m, 2H), 3.42 (d, *J* = 10.9, 1H), 3.48 (d, *J* = 10.9, 1H). ^{13}C NMR ($CDCl_3$) δ = 19.1, 23.0, 23.4, 37.8, 68.9, 70.0, 73.0, 84.5. EI-MS (m/z): 142 $[M]^+$. HPLC analysis of the monobenzoate (Chiralcel OJ-H, 1 mL/min, 6% iPrOH/Hexanes; $t_{r(minor)}$ = 17.7 min, $t_{r(major)}$ = 15.7 min) indicated 95% ee. $[\alpha]^{20}_D$ = -3.0 (c = 0.67, $CHCl_3$).

Total synthesis of (+)-Frontalin (Scheme 1.6.4, **(+)-200**)**:**



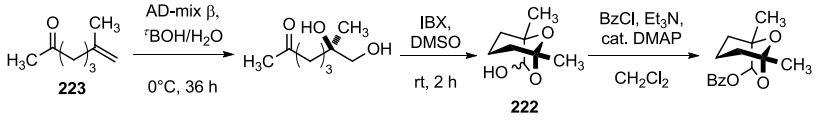
Preparation of methyl ketone 221 from 1h (Scheme 1.6.4)**:** A flask was charged with $PdCl_2$ (36 mg, 0.2 mmol, 0.1 equiv) and CuCl (0.2 g, 2.0 mmol, 1.0 equiv) and flushed with N_2. A 3.0 mL mixture of DMF/H_2O (7:1) was added and O_2 was bubbled through the suspension as it stirred vigorously for 1 hour. Olefin **1h** (0.46 g, 2.0 mmol, 1.0 equiv) was added to the reaction at room temperature and O_2 was bubbled through the mixture for an additional 30 minutes. At this time, the flask was sealed and the reaction was stirred overnight. When complete, the mixture was diluted with EtOAc and washed twice with a premixed solution of saturated aqueous NH_4Cl and 10% aqueous NH_4OH (1:1) (this dissolves copper and turns brilliant blue). The organic portion was dried with $MgSO_4$ and solvent was removed to give the pure product (**221**) as a yellow oil (0.49 g, 100%). ^{1}H NMR ($CDCl_3$) δ = 1.76 (m, 2H), 1.80 (d, *J* = 1.1, 3H), 2.06 (t, *J* = 7.2, 2H), 2.15 (s, 3H), 2.45 (t, *J* = 7.2, 2H), 7.14 (s, 1H), 7.47 (t, *J* = 7.7, 2H), 7.60 (t, *J* = 7.5, 1H), 8.11 (d, *J* = 7.2, 2H). ^{13}C NMR ($CDCl_3$) δ = 13.8, 21.5, 30.2, 33.4, 42.7, 121.8, 128.7, 129.7, 129.9, 130.8, 133.5, 163.7, 208.7. EI-MS (m/z): 228 $[M\text{-}H_2O]^+$.



Preparation of 7-hydroxy-frontalin (**222**, Scheme 1.6.4)**:** A 1:1 mixture of ^{t}BuOH/H_2O (7 mL) was added to flask containing AD-mix β (1.04 g, 1.5 g per mmol of olefin) and $NaHCO_3$ (0.174 g, 2.1 mmol, 3.0 equiv) at rt. The two clear phases were stirred at 0˚C until salts precipitated. The olefin (in 0.5 mL ^{t}BuOH, 0.17 g, 0.69 mmol, 1.0 equiv) was then added and the slurry was stirred for 24 hours at 0˚C. The reaction was quenched with Na_2SO_3 (1.1 g) at 0˚C and stirred at room temperature for 1 hour. The mixture was diluted with CH_2Cl_2, washed with brine, and extracted 3 times with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$ and the solvent was removed. The crude product was purified by flash chromatography (15-20% EtOAc in hexanes) to give a 7-hydroxy-frontalin as a 4:1 (endo:exo) mixture of diastereomers (93 mg, 86% yield, 93% ee). The ee of this compound (93%) was determined from its benzoate (BzCl, Et_3N, cat. DMAP, CH_2Cl_2) by HPLC (Chiralcel OD-H, 1 ml/min, 1% iPrOH/Hexanes, $t_{r(minor)}$ = 7.4 min, $t_{r(major)}$ = 6.0 min). Endo-7-hydroxy-frontalin: ^{1}H NMR ($CDCl_3$) δ = 1.27 (s, 3H), 1.49 (s, 3H), 1.44-1.85 (m, 6H), 2.34 (d, *J* = 9.6, 1H), 5.07 (d, *J* = 9.6, 1H). ^{13}C NMR ($CDCl_3$) δ = 17.6, 20.7, 25.6, 31.9, 33.1, 83.2, 98.3, 108.6. EI-MS (m/z): 141 $[M\text{-}OH]^{+}$. $[\alpha]^{20}_{D}$ = +28.3 (c = 0.72, $CHCl_3$). Exo-7-hydroxy-frontalin: ^{1}H NMR ($CDCl_3$) δ = 1.25 (s, 3H), 1.42 (s, 3H), 1.44-1.85 (m, 6H), 3.08 (d, *J* = 5.2, 1H), 5.10 (d, *J* = 5.2, 1H). ^{13}C NMR ($CDCl_3$) δ = 17.8, 22.4, 25.6, 29.5, 33.5, 80.9, 101.8, 107.6. EI-MS (m/z): 141 $[M\text{-}OH]^{+}$. $[\alpha]^{20}_{D}$ = +28.3 (c = 0.72, $CHCl_3$).

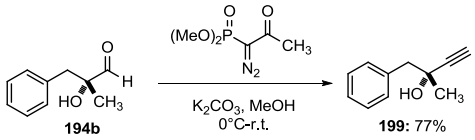
Preparation of frontalin (200) from 7-hydroxy-frontalin (**222**, Scheme 1.6.4)**:** 7-hydroxy-frontalin (**222**) (93 mg, 0.59 mmol, 1.0 equiv) was dissolved in 3.0 mL AcOH and 3.0 mL CH_3CN and cooled to 0˚C. $[Me_4N]BH(OAc)_3$ (0.33 g, 1.18 mmol, 2.0 equiv) was added at 0˚C and the reaction was allowed to stir overnight at room temperature. A solution of 10% citric acid was added and the reaction was stirred for an additional 30 minutes. The acid was slowly neutralized with aqueous $NaHCO_3$ and extracted 3 times with pentane. The combined organic extracts were dried with $MgSO_4$ and the solvent was evaporated to give (+)-frontalin (84% wt in pentane, 75 mg, 76% yield). ^{1}H NMR ($CDCl_3$) δ = 1.31 (s, 3H), 1.42 (s, 3H), 1.47-1.67 (m, 6H), 3.44 (dd, *J* = 6.8, *J* = 1.7, 1H), 3.90 (dd, *J* = 6.7, 1H). ^{13}C NMR ($CDCl_3$) δ = 18.26, 23.32, 24.96, 34.16, 34.77, 74.44, 80.29, 108.32. EI-MS (m/z): 142 $[M]^{+}$. $[\alpha]^{20}_{D}$ = +53.6 (c = 1.43, Et_2O); lit.[143] $[\alpha]^{23}_{D}$ = +54.4 (c = 1.33, Et_2O).

Asymmetric dihydroxylation of terminal olefin 223 (Scheme 1.6.4):

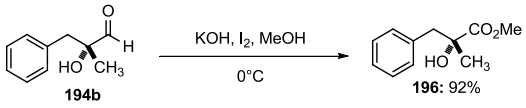


To compare the AD of **223** and **221**, we subjected terminal olefin **223** to the transformations outlined in the scheme above. **223** was dihydroxylated under the standard conditions (see general procedure for AD of enol benzoates), using AD-mix β in ^{t}BOH/H_2O (1:1) at 0˚C. The crude dihydroxylated product was oxidized with IBX (1.2 equiv to diol) in DMSO at rt for 2 hours. The ee was determined from benzoylated 7-hydroxy-frontalin.

Transformations of α-hydroxy aldehydes (Scheme 1.5.2)**:**

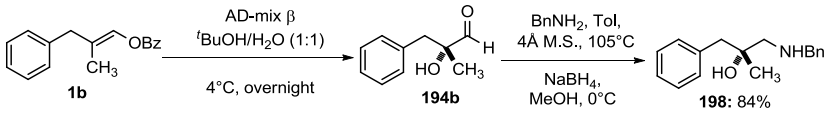


Preparation of propargylic alcohol 199 from 194b (Scheme 1.5.2)**:** α-Hydroxy aldehyde **194b** (0.52 mmol) was prepared as described in the general procedure from enol benzoate **1b** (0.52 mmol) except $NaHCO_3$ (3 equiv) was included during the dihydroxylation. After the asymmetric dihydroxylation reaction was quenched with Na_2SO_3, the reaction mixture was diluted with CH_2Cl_2, washed with brine, and extracted 3 times with CH_2Cl_2. The combined organic extracts were dried with Na_2SO_4 and concentrated to no less than 4 mL. The solvent was exchanged by adding 10 mL of dry MeOH and concentrating the volume to 4 mL. This was repeated 2 times and dry MeOH was again added to bring the final reaction concentration to ca 0.05 M (about 10 mL MeOH). This solution was cooled to 0˚C and K_2CO_3 (0.18 g, 1.3 mmol, 2.5 equiv) and $(MeO)_2POCN_2COMe$[170] (0.15 g, 0.78 mmol, 1.5 equiv, in 1.0 mL MeOH) were added sequentially. The reaction was stirred for 1 hour at 0˚C and 4 hours at room temperature, after which time it was diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$, and extracted 3 times with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$, concentrated, and purified by flash chromatography (10% EtOAc/Hexanes) to give pure alkyne (64 mg, 77% yield). ^{1}H NMR ($CDCl_3$) δ = 1.56 (s, 3H), 2.02 (s, 1H), 2.47 (s, 1H), 2.93 (d, *J* = 13.3, 1H), 3.01 (d, *J* = 13.2, 1H), 7.31-7.34 (m, 5H). ^{13}C NMR ($CDCl_3$) δ = 29.7, 49.5, 68.1, 72.9, 87.4, 127.3, 128.4, 131.0, 136.2. EI-MS (m/z): 160 $[M-1]^{+}$. $[\alpha]^{20}_{D}$ = +5.4 (c = 0.71, $CHCl_3$).



194b

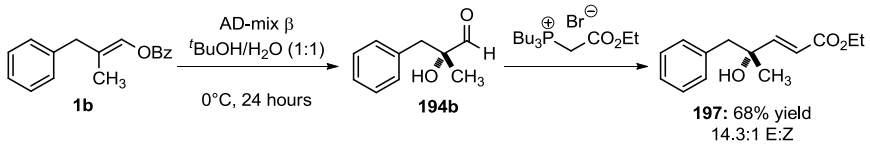
Preparation of methyl ester 196 from 194b (Scheme 1.5.2)**:** α-Hydroxy aldehyde **194b** (0.52 mmol) was prepared as described in the general procedure from enol benzoate **1b** (0.52 mmol) except $NaHCO_3$ (3 equiv) was included during the dihydroxylation. After the asymmetric dihydroxylation reaction was quenched with Na_2SO_3, the reaction mixture was diluted with CH_2Cl_2, washed with brine, and extracted 3 times with CH_2Cl_2. The combined organic extracts were dried with Na_2SO_4 and concentrated to no less than 4 mL. The solvent was exchanged by adding 10 mL of dry MeOH and concentrating the volume to 4 mL. Dry MeOH was again added to bring the final reaction concentration to 0.05M in MeOH (about 10 mL). This solution was brought to 0˚C and KOH (dissolved in 1.0 mL MeOH, 0.76 g, 1.3 5mmol, 2.6 equiv) and I_2 (dissolved in 1.0 mL MeOH, 0.86 g, 0.68 mmol, 1.3 equiv) were added sequentially. After 1.5 hours at 0˚C, starting material was still present, so KOH (0.76 g in MeOH) and I_2 (0.86 g in MeOH) were added again. After stirring an additional 1.5 hours at 0˚C, the reaction was quenched with saturated aqueous $Na_2S_2O_3$. The reaction was filtered, washed with aqueous $NaHCO_3$, and extracted 3 times with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$ and concentrated to give (*R*)-**196** (92% yield). ^{1}H NMR ($CDCl_3$) δ = 1.50 (s, 3H), 2.90 (d, *J* = 13.5, 1H), 3.01 (s, 1H), 3.07 (d, 13.5, 1H), 3.73 (s, 3H), 7.16 (m, 2H), 7.25 (m, 3H). ^{13}C NMR ($CDCl_3$) δ = 26.0, 46.7, 52.8, 75.5, 127.2, 128.4, 130.2, 136.2, 176.8. EI-MS (m/z): 194 $[M-1]^+$. $[\alpha]^{20}$ = +5.3 (c = 2.05, $CHCl_3$); lit. for (*S*)-**196** $[\alpha]^{20}$ = -113 (c = 1.0, $CHCl_3$).[171, 172]



1b 194b

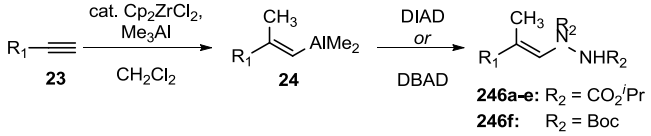
Preparation of amino alcohol 198 from 1b (Scheme 1.5.2)**:** α-Hydroxy aldehyde **194b** (0.52 mmol) was prepared as described in the general procedure from enol benzoate **1b** (0.52 mmol). After the asymmetric dihydroxylation reaction was complete the reaction was extracted three times with Et_2O and dried over Na_2SO_4. Without evaporating to dryness, the solvent was exchanged to approximately 10 mL toluene under reduced pressure. Benzylamine (0.3 mmol, 1.5 equiv) and 4Å molecular sieves were added before bringing the temperature to 105°C. Imine formation was monitored by GC/MS. Upon completion, the molecular sieves were removed and the toluene evaporated under reduced pressure. The residue was diluted in 10 mL methanol and cooled to 0°C. After 1 hour, the reaction was quenched with saturated $NaHCO_3$ and extracted with Et_2O three times. After concentrating the combined organic layers, the residue was dissolved in hexanes was extracted with 1M HCl. The aqueous layer was washed with

hexanes and then brought to pH 13 with 1M NaOH. After extracting the basic aqueous layer three times with EtOAc, the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to provide 42.5 mg (84% yield) of the desired compound. No additional purification was necessary. ^{1}H NMR ($CDCl_3$) δ = 1.14 (s, 3H), 2.10 (br s, 1H), 2.55 (d, *J* = 11.98, 1H), 2.66 (d, *J* = 11.98, 1H), 2.75 (d, *J* = 13.3, 1H), 2.82 (d, *J* = 13.3, 1H), 3.81 (d, *J* = 7.4, 2H), 3.83 (s, 1H), 7.21-7.37 (m, 10H). ^{13}C NMR ($CDCl_3$) δ = 25.9, 46.8, 54.7, 58.2, 71.8, 126.6, 127.3, 128.3, 128.4, 128.7, 130.6, 138.0, 140.5. $[\alpha]^{20}_D$ = -3.1 (c = 0.975, $CHCl_3$).



Preparation of α, β-unsaturated ester 197 from 1b (Scheme 1.5.2)**:** α-Hydroxy aldehyde **194b** (0.52 mmol) was prepared as described in the general procedure from enol benzoate **1b** (0.52 mmol). After the asymmetric dihydroxylation reaction was complete the reaction mixture was extracted three times with Et_2O and diluted with 4mL toluene. Ether was removed under reduced pressure. Separately, 0.3 mmol (1.5 equiv) phosphonium bromide was dissolved in 2 mL CH_2Cl_2 and washed twice with 1M NaOH. Methylene chloride was removed under reduced pressure after diluting with 4 mL toluene. To the aldehyde in toluene was added the prepared ylide, and the solution was heated to 90°C for 3 hours at which point a second 0.3 mmol of prepared ylide in 4 mL toluene was added. After 90 minutes, the reaction was cooled to room temperature, dried over anhydrous Na_2SO_4, filtered, and concentrated. The product was purified by flash silica gel chromatography (2:3 Et_2O:hexanes) to give 32.0 mg (68.3% isolated yield) of the desired compound. ^{1}H NMR ($CDCl_3$) δ = 1.28 (t, *J* = 7.1, 3H), 1.33 (s, 3H), 2.03 (s, 1H), 2.82 (d, *J* = 13.4, 1H), 2.92 (d, *J* = 13.4, 1H), 4.19 (dq, *J* = 7.1, *J* = 0.9, 2H), 5.92 (d, *J* = 15.6, 1H), 7.04 (d, *J* = 15.6, 1H), 7.16 (dd, *J* = 8.2, *J* = 1.7, 2H), 7.23-7.32 (m, 3H). ^{13}C NMR ($CDCl_3$) δ = 14.0, 27.0, 48.0, 60.2, 72.7, 118.9, 126.8, 128.2, 130.3, 135.6, 153.5, 166.4. FTIR (thin film) 3474, 2978, 1716, 1306 cm^{-1}. EI-MS (m/z): 189 $[M\text{-}OCH_2CH_3]^+$. $[\alpha]^{20}_D$ = +53.3 (c = 1.11, $CHCl_3$).

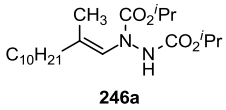
Preparation of Ene-hydrazines from Terminal Alkynes (Table 1.7.1**):**



General Procedure for preparation of ene-hydrazines:

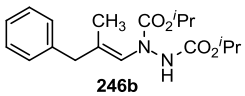
To a stirred solution of Cp_2ZrCl_2 and Me_3Al in CH_2Cl_2 (0.3M to alkyne) at room temperature was added terminal alkyne. Methylaluminoxane (MAO) was then added at room temperature and the yellow solution was stirred until the methylalumination was complete. Once complete, the reaction was brought to -25˚C and diisopropyl azodicarboxylate (DIAD, for 246a-e) or Di-tert-butyl azodicarboxylate (DBAD, for 246f) was added dropwise to the freshly prepared vinyl alane. This solution was stirred for an additional 3 hours at -25˚C, after which time the reaction was quenched by slow addition of AcOH (1 mL) at this temperature. The mixture was allowed to warm to room temperature and an aqueous solution of 10% citric acid was added slowly until gas evolution ceased. The resulting slurry was stirred for 15-30 minutes or until the two phases were homogenous, at which time it was extracted 3 times with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, concentrated, and purified by flash chromatography (silica gel, EtOAc/hexanes). Reaction times, reagent amounts, purification conditions and characterization data are provided below for all entries in Table 1.7.1

Characterization data for ene-hydrazine compounds and reaction details (Table 1.7.1**):**



246a

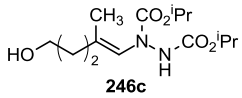
246a (Table 1.7.1, entry 1): Reagent amounts: 1-dodecyne (40 µL, 0.187 mmol, 1.0 equiv), Cp_2ZrCl_2 (11 mg, 0.0374 mmol, 0.2 equiv), Me_3Al (2.0M in Toluene, 1.61 mL, 3.22 mmol, 2.0 equiv), DIAD (43 µL, 0.206 mmol, 1.1 equiv). Methylalumination was complete in 4 hours (addition of MAO was not necessary). Chromatography (10% EtOAc in hexanes) provided 59 mg (79% yield) of a colorless syrup. ^{1}H NMR ($CDCl_3$) δ = 0.875 (t, *J* = 6.6, 3H), 1.18-1.33 (m, 28 H), 1.41 (m, 2H), 1.64 (d, *J* = 0.9, 3H), 2.00 (t, *J* = 7.3, 2H), 4.91-4.99 (m, 2H), 5.96 (br s, 1H), 6.51 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ = 14.3, 16.2, 22.2, 22.3, 22.9, 27.7, 29.6, 29.7, 29.8, 29.9, 32.1, 36.5, 36.6, 70.0, 70.6, 70.7, 122.7, 156.0. FTIR (thin film) 3294, 2919, 2359, 1718, 1373, 1108 cm^{-1}. EI-MS (m/z): 385 $[M]^+$.



246b

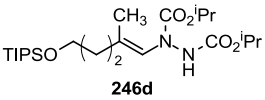
246b (Table 1.7.1, entry 2): Reagent amounts: phenyl-3-propyne (0.2 mL, 1.61 mmol, 1.0 equiv), Cp_2ZrCl_2 (94 mg, 0.322 mmol, 0.2 equiv), Me_3Al (2.0M in Toluene, 3.22 mL, 0.374 mmol, 2.0 equiv), DIAD (0.51 mL, 2.42 mmol, 1.5

equiv). Methylalumination was complete in 5.5 hours (addition of MAO was not necessary). Chromatography (11% EtOAc in hexanes) provided 0.48 g (89% yield) of a colorless syrup. ^{1}H NMR ($CDCl_3$) δ = 1.26 (d, *J* = 6.24, 14H), 1.59 (s, 3H), 3.33 (s, 2H), 4.98 (m, 2H), 5.90-6.40 (br s, 1H), 6.40-6.80 (br s, 1H), 7.18-7.21 (m, 3H), 7.29 (t, *J* = 1.6, 2H). ^{13}C NMR ($CDCl_3$) δ = 16.4, 22.1, 22.3, 42.95, 70.2, 70.9, 124.4, 124.5, 126.6, 128.5, 130.0, 139.3. FTIR (thin film) 3294, 2986, 1718, 1373, 1105 cm^{-1}. EI-MS (m/z): 334 [M]$^+$.



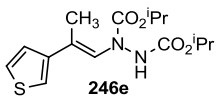
246c

246c (Table 1.7.1, entry 3): Reagent amounts: 4-Pentyne-1-ol (0.185 mL, 2.0 mmol, 1.0 equiv), Cp_2ZrCl_2 (0.117 g, 0.4 mmol, 0.2 equiv), Me_3Al (2.0M in Toluene, 3.0 mL, 6.0 mmol, 3.0 equiv), MAO (66 µL, 0.1 mmol, 5 mol %), DIAD (1.27 mL, 6.0 mmol, 3.0 equiv). Methylalumination was complete after allowing reaction to stir overnight. Chromatography (50% EtOAc in hexanes) provided 0.521 g (86% yield) of a colorless syrup. ^{1}H NMR ($CDCl_3$) δ = 1.26 (d, J = 6.3, 12H), 1.69 (s, 3H), 1.72 (m, 2H), 2.13 (t, J = 7.0, 2H), 2.25 (br s, 1H), 3.65 (t, J = 6.1, 2H), 4.96 (m, 2H), 5.99 (br s, 1H), 6.64 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ = 16.0, 22.1, 22.2, 30.4, 30.5, 33.2, 62.1, 69.9, 70.6, 122.9. FTIR (thin film) 3457, 3289, 2975, 1712, 1376, 1111 cm^{-1}. EI-MS (m/z): 243 [M-O^{i}Pr]$^+$.



246d

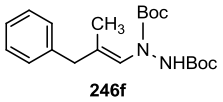
246d (Table 1.7.1, entry 4): Reagent amounts: 4-(triisopropylsilyloxy)-1-pentyne (0.509 g, 2.0 mmol, 1.0 equiv), Cp_2ZrCl_2 (0.117 g, 0.4 mmol, 0.2 equiv), Me_3Al (2.0M in Toluene, 3.0 mL, 6.0 mmol, 3.0 equiv), MAO (66 µL, 0.1 mmol, 5 mol %), DIAD (1.27 mL, 6.0 mmol, 3.0 equiv). Methylalumination was complete after allowing reaction to stir overnight. Chromatography (10% EtOAc in hexanes) provided 0.781 g (83% yield) of a colorless syrup. ^{1}H NMR ($CDCl_3$) δ = 1.07 (m, 18H), 1.25 (d, J = 6.2, 12H), 1.51(m, 2H), 1.65 (s, 3H), 2.04 (t, J = 5.9, 2H), 3.67 (t, J = 5.7, 2H), 4.97 (m, 2H), 5.98 (br s, 1H), 6.59 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ = 16.0, 18.2, 18.3, 22.2, 22.3, 24.1, 32.4, 36.4, 63.3, 70.0, 70.7, 122.8. FTIR (thin film) 3294, 2936, 2863, 1718, 1373, 1113 cm^{-1}. EI-MS (m/z): 458 [M]$^+$.



246e

246e (Table 1.7.1, entry 5): Reagent amounts: 2-ethynyl thiophene (0.197 mL, 2.0 mmol, 1.0 equiv), Cp_2ZrCl_2 (0.117 g, 0.4 mmol, 0.2 equiv), Me_3Al (2.0M in Toluene, 3.0 mL, 6.0 mmol, 3.0 equiv), MAO (66 µL, 0.1 mmol, 5 mol %), DIAD (1.27 mL, 6.0 mmol, 3.0 equiv). Methylalumination was complete in 3 days. Chromatography (12% EtOAc in hexanes) provided 0.502 g (77% yield) of a colorless syrup. ^{1}H NMR ($CDCl_3$) δ = 1.28 (m, 12H), 2.06 (s, 3H), 5.0 (m, 2H), 6.67 (br s, 1H), 6.71 (br s, 1H), 7.20 (s, 1H), 7.22 (d, J=4.9, 1H), 7.27 (d, J = 2.8, 1H).

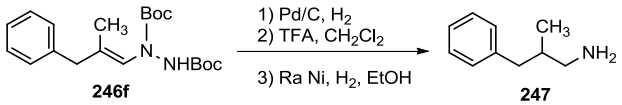
^{13}C NMR ($CDCl_3$) δ = 16.1, 22.3, 22.3, 70.3, 71.4, 120.7, 120.8, 124.6, 124.7, 125.3, 126.0, 142.0, 155.7. FTIR (thin film) 3294, 2986, 1715, 1373, 1236, 775 cm^{-1}. EI-MS (m/z): 326 $[M]^+$.



246f

246f (Table 1.7.1, entry 6): Reagent amounts: phenyl-3-propyne (0.249 mL, 2.0 mmol, 1.0 equiv), Cp_2ZrCl_2 (0.117 g, 0.4 mmol, 0.2 equiv), Me_3Al (2.0M in Toluene, 2.0 mL, 4.0 mmol, 2.0 equiv), MAO (66 µL, 0.1 mmol, 5 mol %), DBAD (in 5 mL CH_2Cl_2, 0.94 g, 4.0 mmol, 2.0 equiv). Methylalumination was complete after stirring overnight. Chromatography (10% EtOAc in hexanes) provided 0.609 g (84% yield) of a colorless syrup. Chromatography (11% EtOAc in hexanes) provided 0.48 g (89% yield) of a colorless syrup. ^{1}H NMR ($CDCl_3$) δ = 1.47 (s, 18H), 1.57 (s, 3H), 3.30 (s, 2H), 6.19 (br s, 1H), 6.49 (br s, 1H), 7.20 (d, J = 6.3, 2H), 7.27 (m, 3H). ^{13}C NMR ($CDCl_3$) δ = 16.2, 28.4, 28.44, 38.9, 43.0, 68.3, 81.9, 124.9, 126.4, 128.5, 129.0, 131.2, 139.5, 155.9. FTIR (thin film) cm^{-1}. EI-MS (m/z): 362 $[M]^+$.

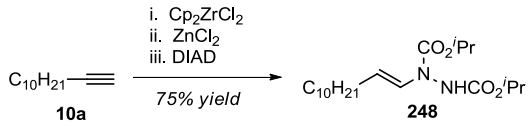
Procedure for preparing of primary amine 247 (Scheme 1.7.7**):**



246f **247**

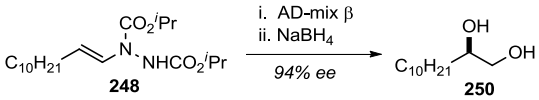
Nitrogen was bubbled through a solution of ene-hydrazine **246f** (0.185 g, 0.5 mmol, 1.0 equiv) in 4 mL EtOAc for 15 minutes. Once complete, Pd/C (53 mg, 0.05 mmol, 0.1 equiv) was added to the flask and H_2 was bubbled through the mixture for 30 minutes. The reaction was allowed to stir overnight at room temperature under an H_2 atmosphere, after which N_2 was once again bubbled through the mixture for 15 minutes. The mixture was filtered through celite, washed with EtOAc, and concentrated. The crude Boc-protected hydrazine was dissolved in 4 mL CH_2Cl_2 and brought to 0˚C, at which time 4 mL trifluoroacetic acid was added. After stirring for 45 minutes at 0˚C, the reaction was brought to room temperature and the solvent was removed *in vacuo*. The crude 2-methyl-3-phenylpropylhydrazine was dissolved in 5 mL EtOH and approximately 1.3 g of Raney-Nickel (activated catalyst, 50% slurry in H_2O; Acros Chemical) was added to the solution at room temperature. H_2 was bubbled through the slurry for 30 minutes and the reaction was stirred under an H_2 atmosphere for 39 hours. The Raney-Nickel residue was separated by filtration and the EtOH was removed *in vacuo*. The crude amine was diluted with CH_2Cl_2, washed with 1 M NaOH, and extracted 3 times with CH_2Cl_2. The combined organic extracts were dried with Na_2SO_4 and concentrated to give **247** (68 mg, 91%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ = 0.90 (d, J = 6.7, 3H), 1.39 (br s, 2H), 1.79 (m, 1H), 2.39 (dd, J = 13.4, J = 8.2, 1H), 2.54 (dd, J = 12.6, J = 6.9, 1H), 2.68 (dd, J = 12.2, J = 5.5, 1H), 2.71 (m, 3H), 7.18 (m, 3H), 7.29 (t, J = 7.9, 2H). ^{13}C NMR ($CDCl_3$) δ = 17.6, 36.2, 41.21, 48.0, 126.1, 128.5, 129.4, 141.0. EI-MS (m/z): 150 $[M+H]^+$.

Procedure for preparing ene-hydrazine 248 (Scheme 1.7.8)**:**



10a (0.819 g, 4.5 mmol, 1.0 equiv) was added to a stirred solution of $Cp_2Zr(H)Cl$ (1.35 g, 4.95 mmol, 1.1 equiv) in THF (15 mL) at 0°C. Hydrozirconation was complete after stirring for one hour. At this time, a solution of dry $ZnCl_2$ (0.97 g, 6.75 mmol, 1.5 equiv) in THF (10 mL) was added to the reaction at 0°C via cannula. After stirring for an additional 10 minutes at this temperature, the dialkyl azodicarboxylate (1.16 g, 4.95 mmol, 1.1 equiv), dissolved in a small amount of THF (1-2 mL), was added dropwise to the reaction. The solution turned from light orange to dark orange (almost red) after addition was complete. After stirring for 45 minutes at 0C, the reaction was quenched with water, washed with 10 % aq solution of citric acid, and extracted with CH_2Cl_2. The organic portions were pooled, dried with MgSO4, and concentrated. Purification by flash chromatography (5-10% EtOAc in hexanes) afforded **248** as a colorless oil (1.41 g, 3.41 mmol, 76% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96-6.58 (m, 1H), 6.58 – 6.06 (m, 1H), 5.17 – 5.04 (m, 1H), 5.04-4.86 (d, 2H), 2.11 – 1.90 (dt, *J* = 6.9, 6.4 Hz, 2H), 1.25 (m, 28H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.17, 125.86, 110.28, 71.51, 70.82, 70.25, 32.14, 30.34, 29.86, 29.77, 29.73, 29.66, 29.57, 29.36, 22.92, 22.21, 22.18, 14.35. EI-MS (m/z): 370 $[M]^+$.

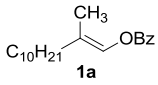
Asymmetric Dihydoxylation of 248 (Scheme 1.7.8)**:**



A 1:1 mixture of ^{t}BuOH/H_2O (0.15 mL) was added to flask containing AD-mix β (0.22 g, 1.6 g per mmol of **248**) and the mixture was stirred to produce two clear phases. The resulting solution was then stirred at 0˚C until the dissolved salts precipitated. The olefin (52 mg, 0.14 mmol, 1.0 equiv) in ^{t}BuOH was added and the slurry was stirred vigorously at 0˚C until the reaction was complete (20 hours). Once complete, $NaBH_4$ (32 mg, 0.84 mmol, 6.0 equiv) was added to the mixture at 0˚C and the reaction was kept at this temperature until reduction was complete (about 2 hours). The reaction was quenched with Na_2SO_3 (0.21 g) at 0˚C and stirred at room temperature for 1 hour. The mixture was diluted with CH_2Cl_2, washed with brine, and extracted 3 times with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$ and the solvent was removed. The crude product was purified by flash chromatography to afford **250** (21 mg, 0.105 mmol, 75% yield, 94% ee) as a white, waxy solid. The ee of the diol were determined from the dibenzoylated analog (BzCl in pyridine). The HPLC conditions and chromatogram is

located in the section of the supporting information containing NMR spectra. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.76 – 3.68 (m, 1H), 3.66 (dd, *J* = 11.0, 2.8 Hz, 1H), 3.43 (dd, *J* = 10.9, 7.7 Hz, 1H), 2.16 – 1.84 (m, 2H), 1.47 – 1.40 (m, 2H), 1.37 – 1.17 (m, 16H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 72.56, 67.10, 33.44, 32.15, 29.88, 29.85, 29.83, 29.79, 29.57, 25.78, 22.93, 14.38. EI-MS (m/z): 202 $[M]^+$.

APPENDIX A1: NMR SPECTRA RELEVANT TO CHAPTER ONE



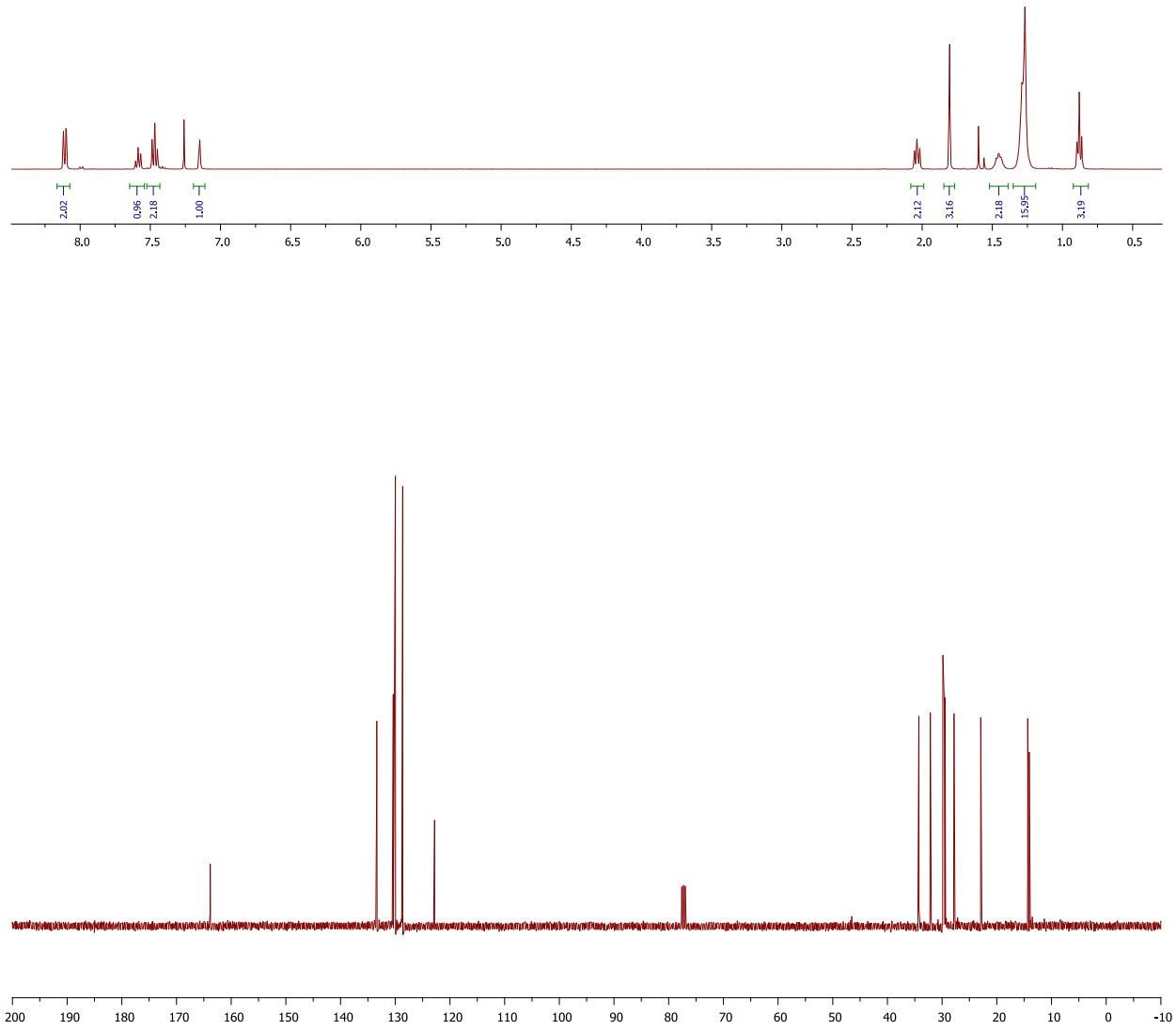
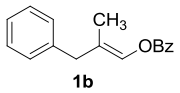


Figure A1. 11 ^{1}H NMR and ^{13}C NMR Spectra of Compound 1a



1b

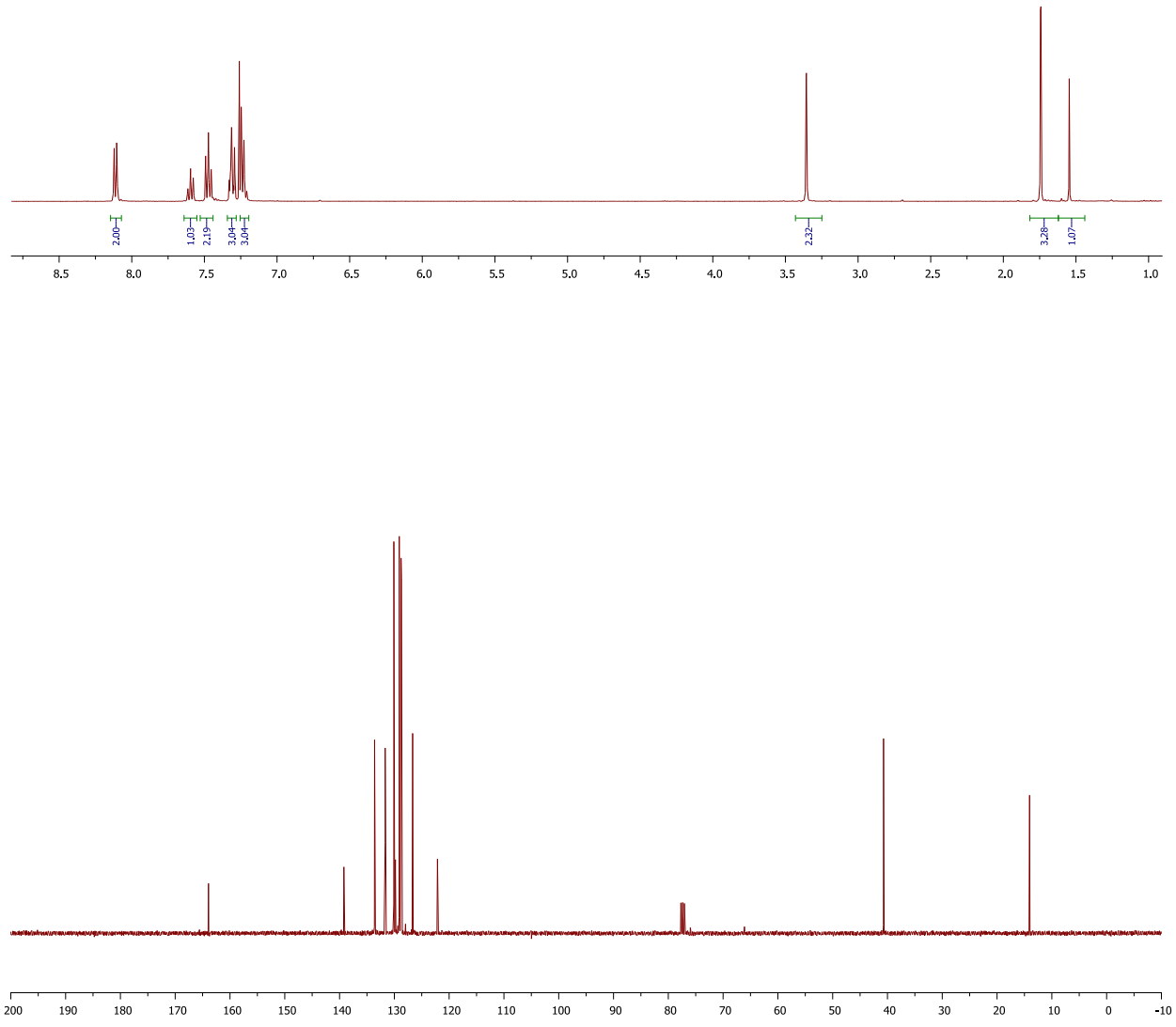
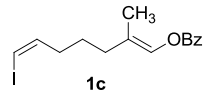


Figure A1. 2 ^{1}H NMR and ^{13}C NMR Spectra of Compound 1b



1c

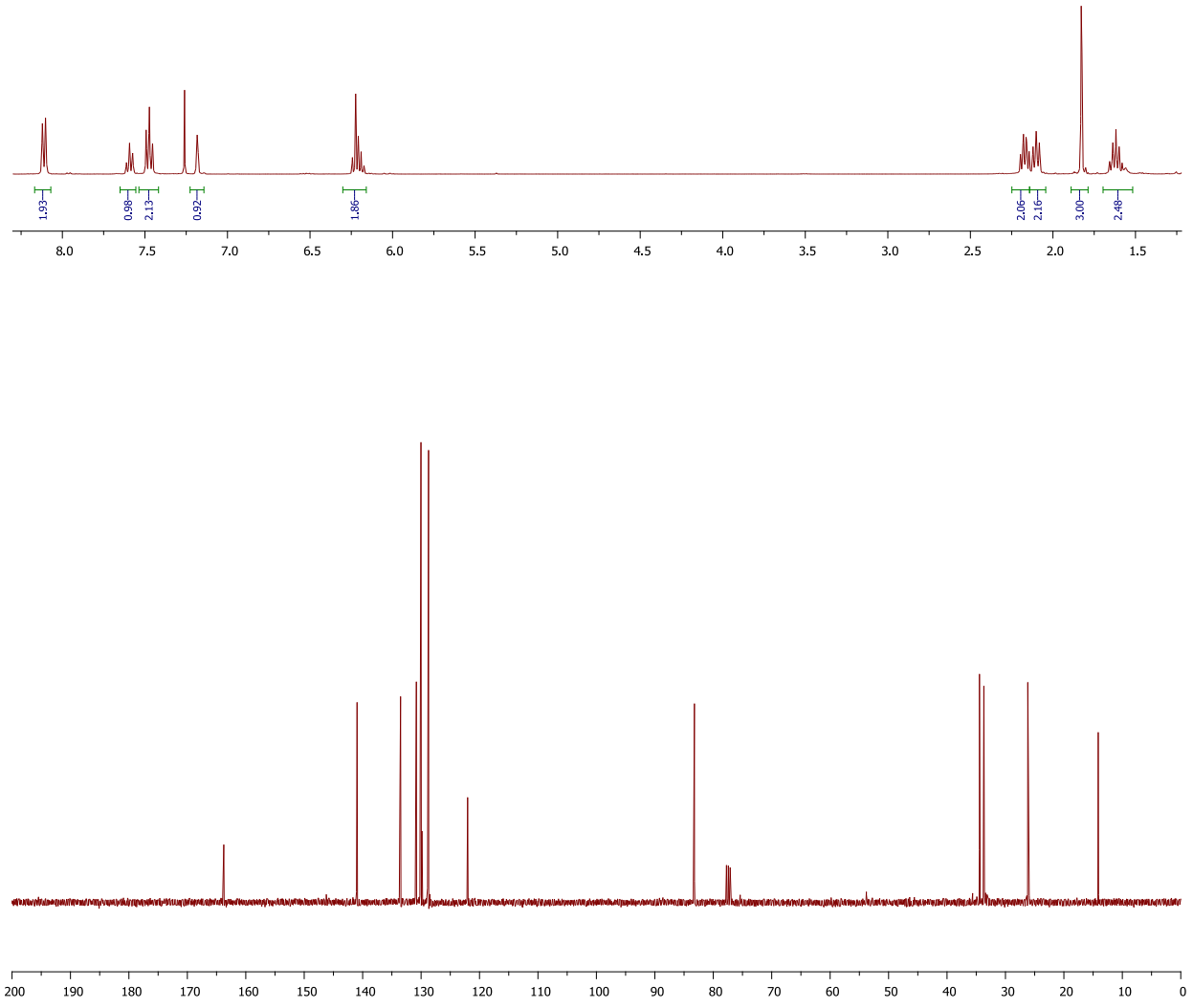


Figure A1. 3 ^{1}H NMR and ^{13}C NMR Spectra of Compound 1c

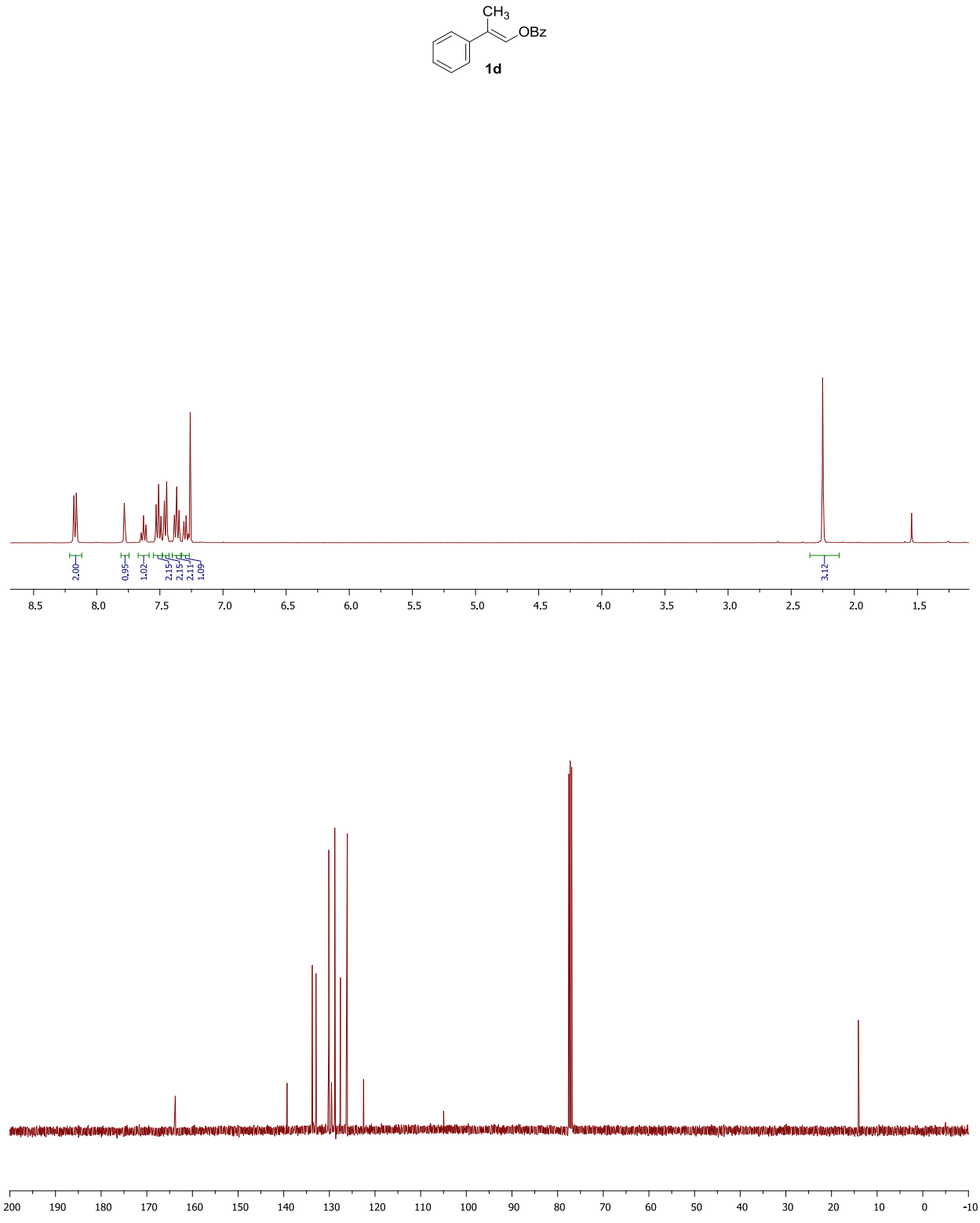
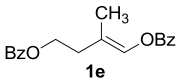


Figure A1. 4 ^{1}H NMR and ^{13}C NMR Spectra of Compound 1d



1e

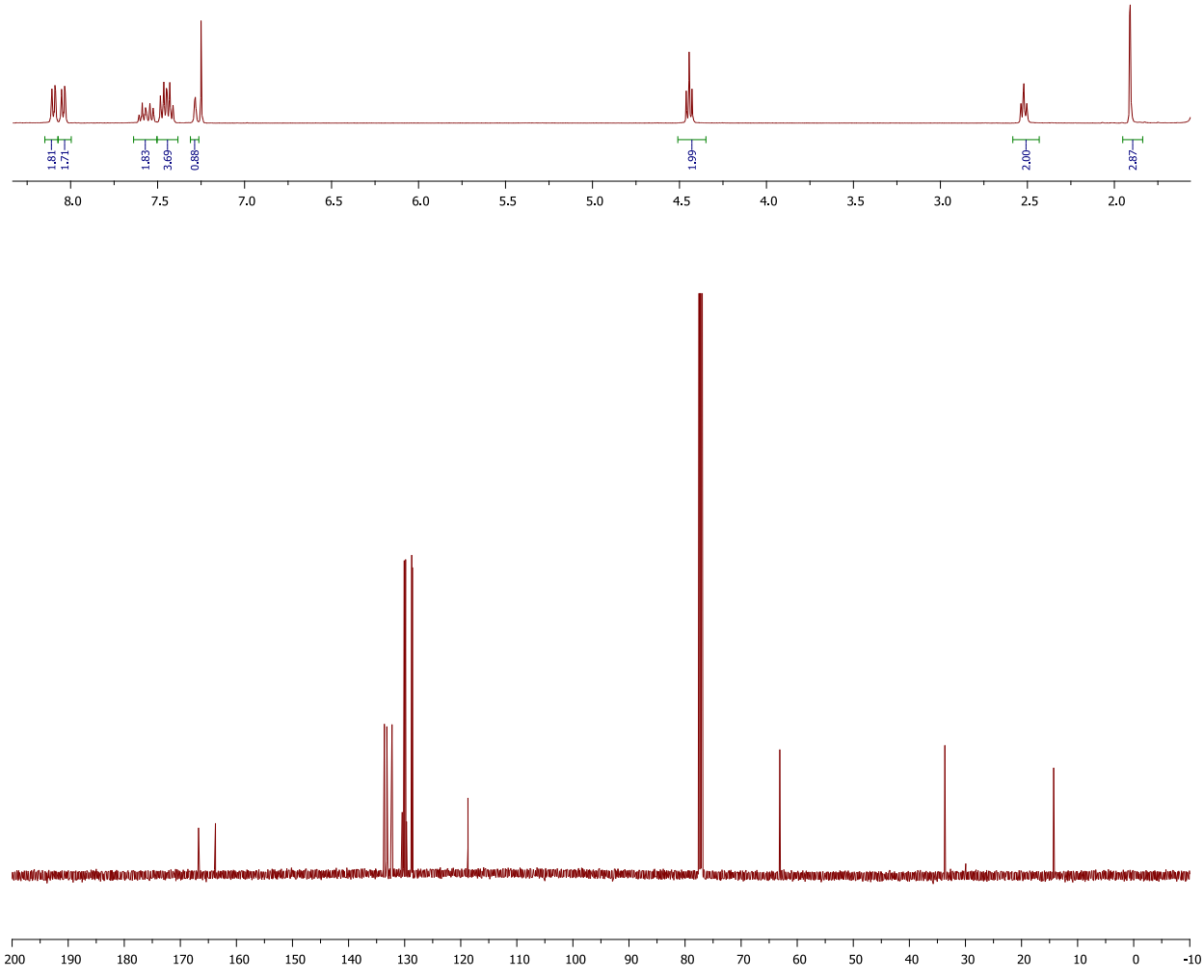
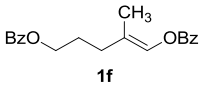


Figure A1. 5 ^{1}H NMR and ^{13}C NMR Spectra of Compound 1e



1f

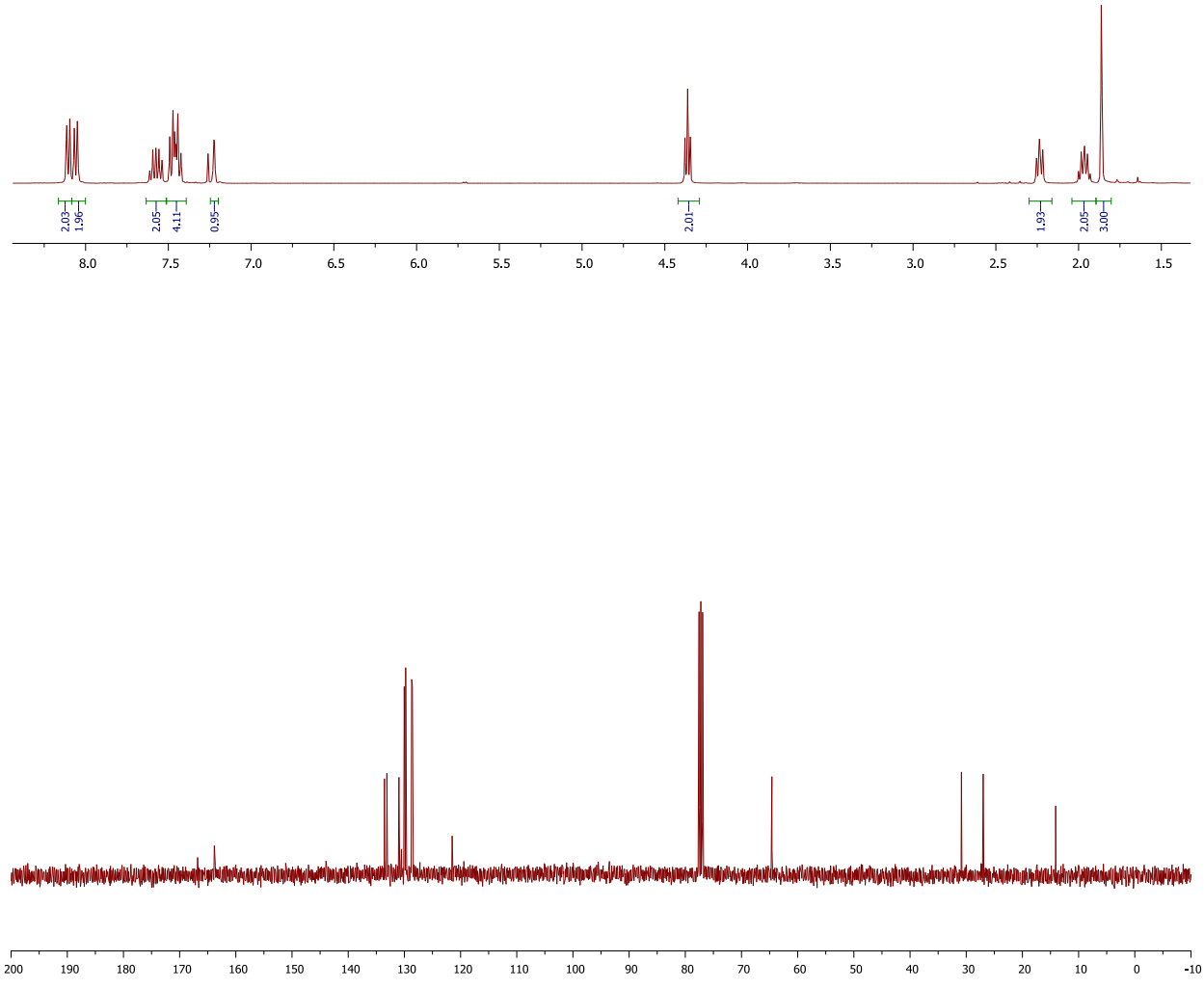


Figure A1. 6 ^{1}H NMR and ^{13}C NMR Spectra of Compound 1f

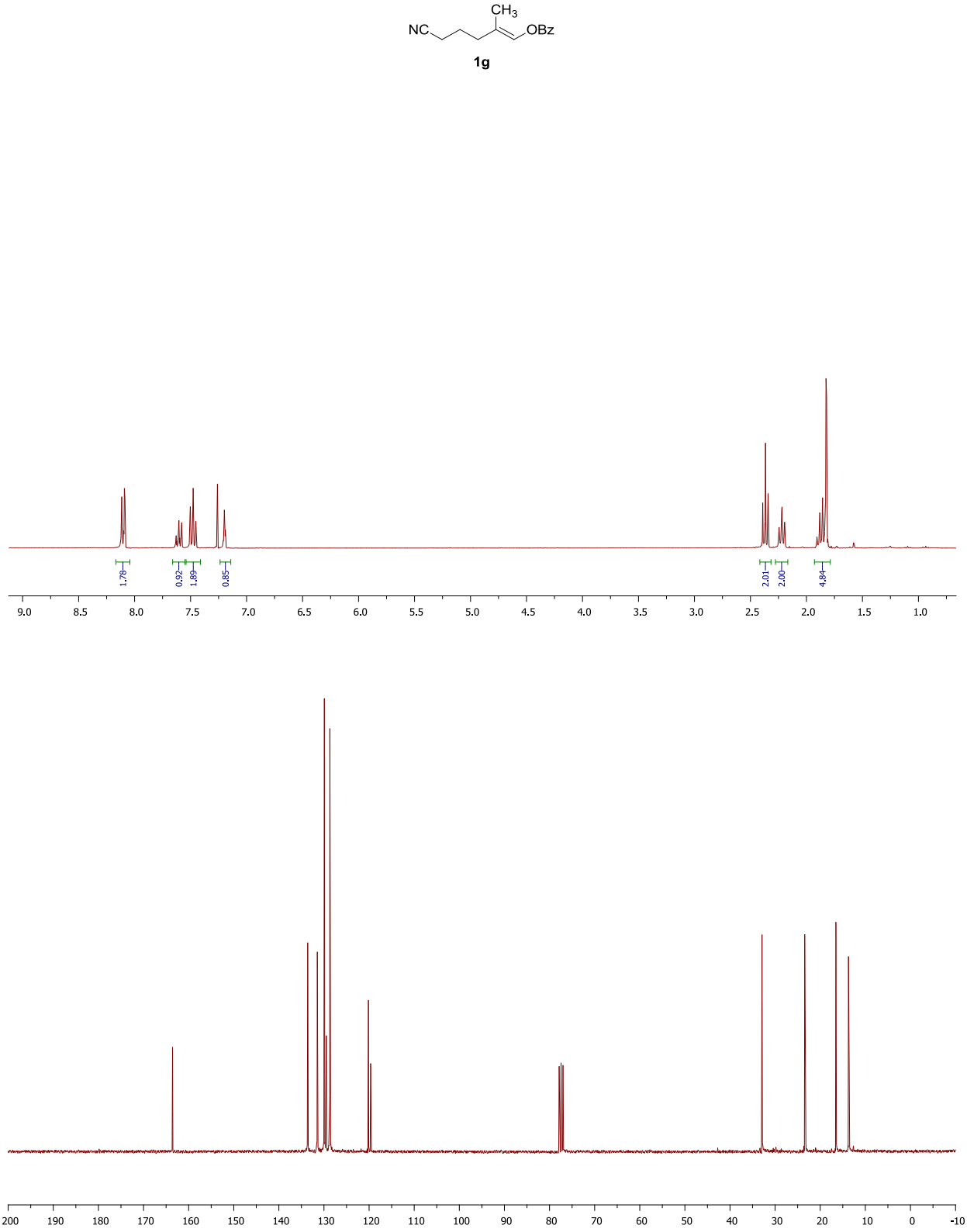
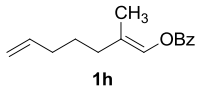


Figure A1. 7 ^{1}H NMR and ^{13}C NMR Spectra of Compound 1g



1h

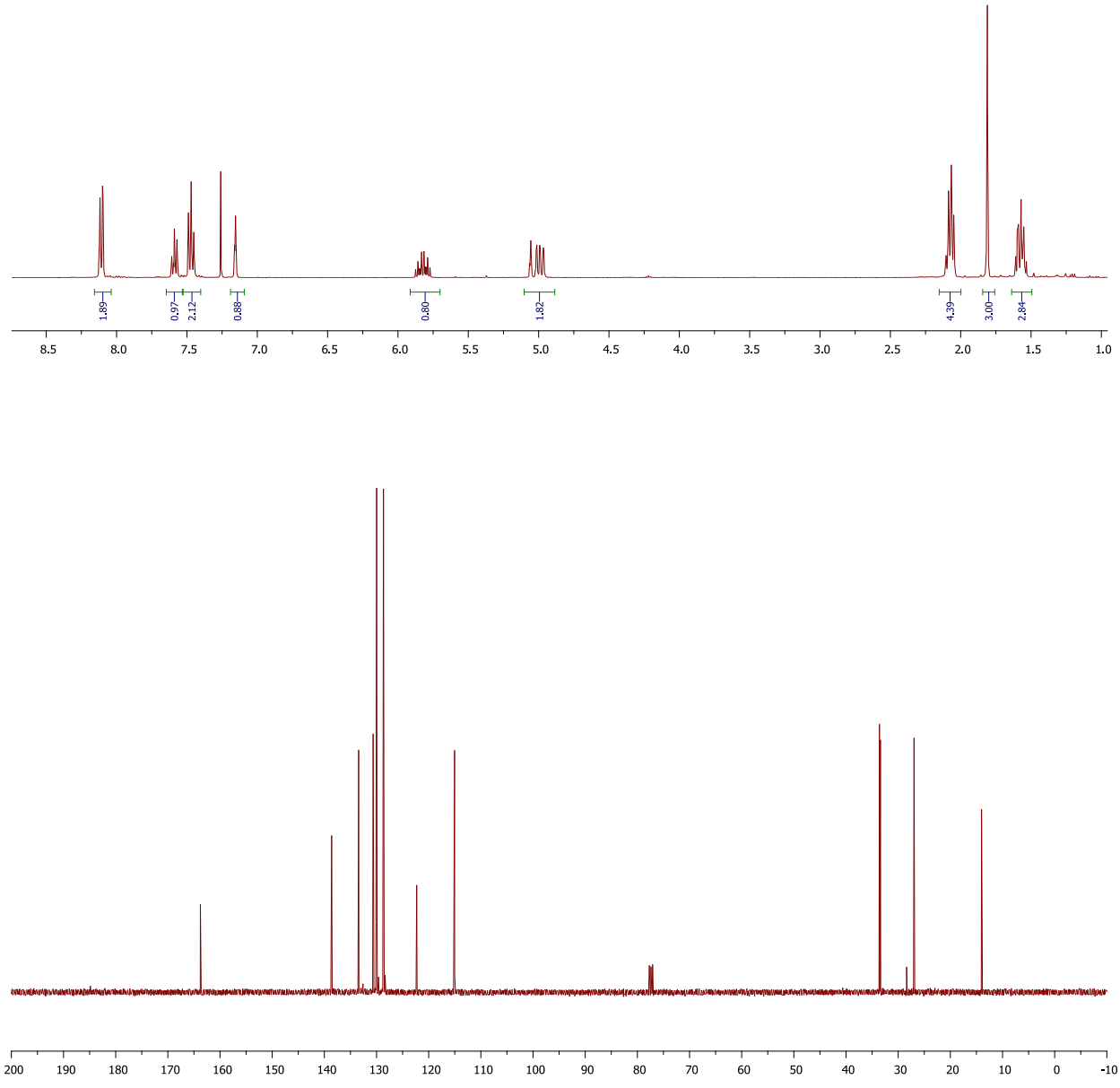
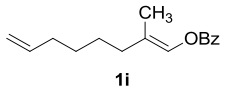


Figure A1. 8 ^{1}H NMR and ^{13}C NMR Spectra of Compound 1h



1i

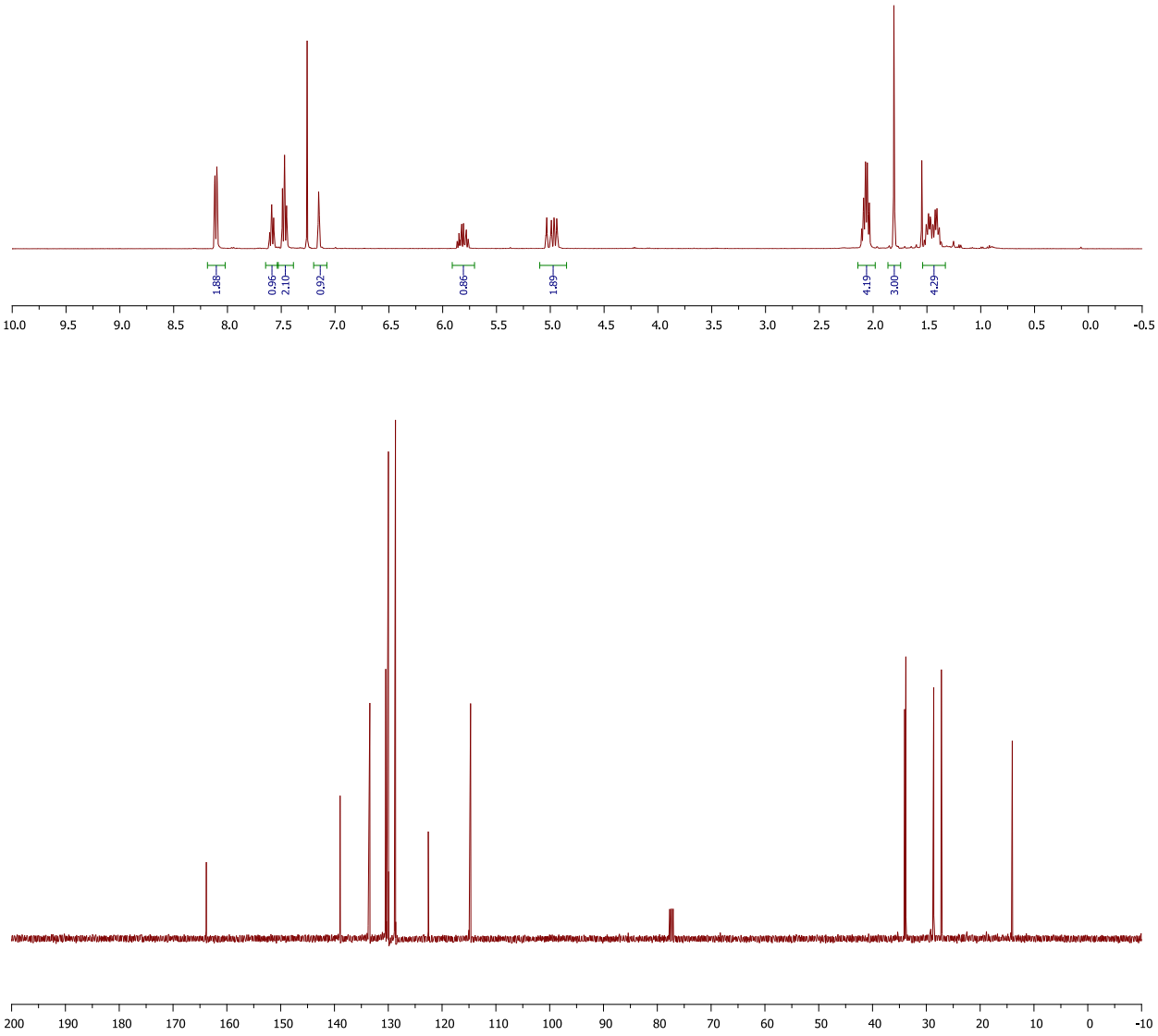
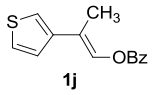


Figure A1. 9 ^{1}H NMR and ^{13}C NMR Spectra of Compound 1i



1j

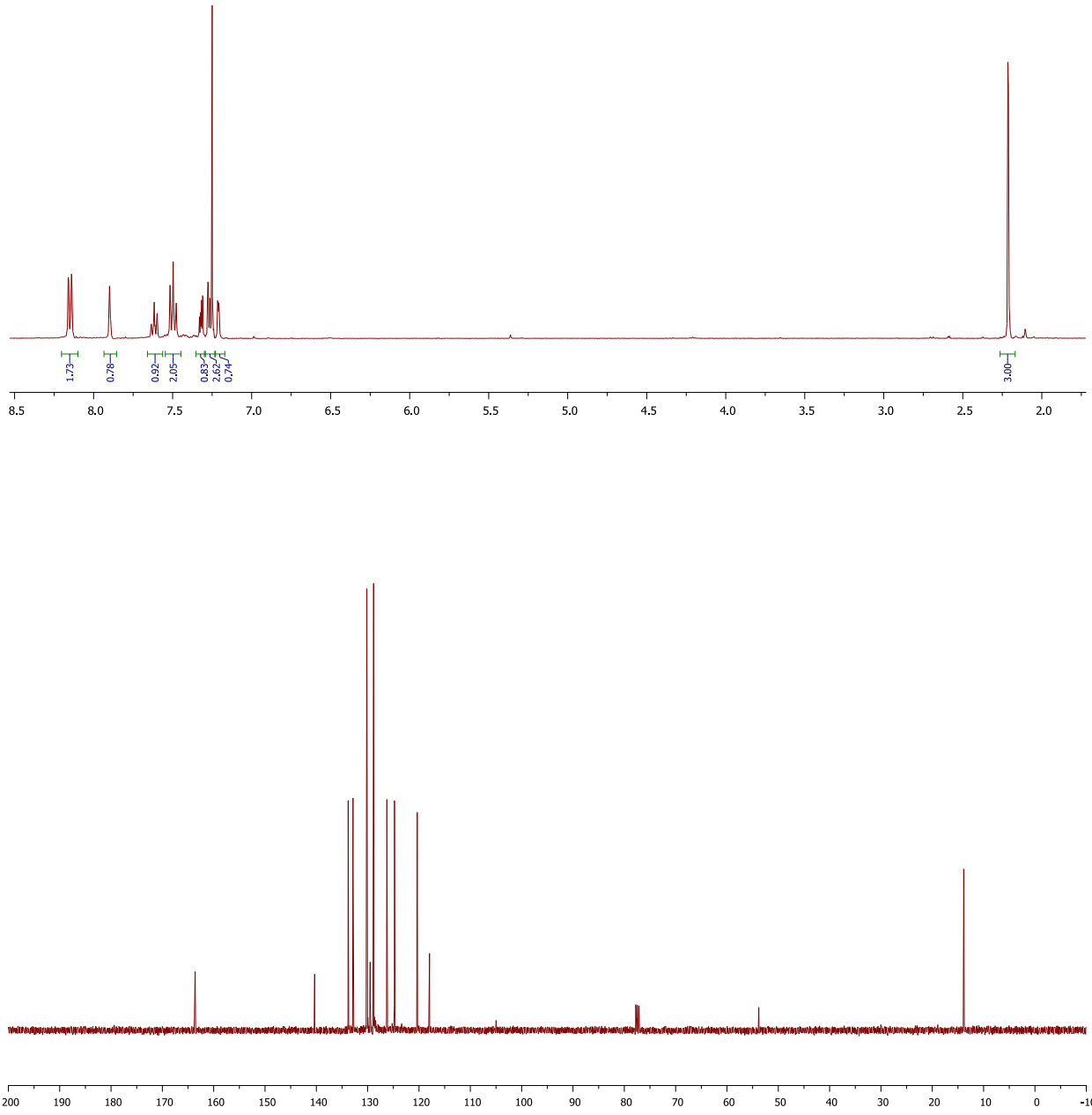


Figure A1. 10 ^{1}H NMR and ^{13}C NMR Spectra of Compound 1j

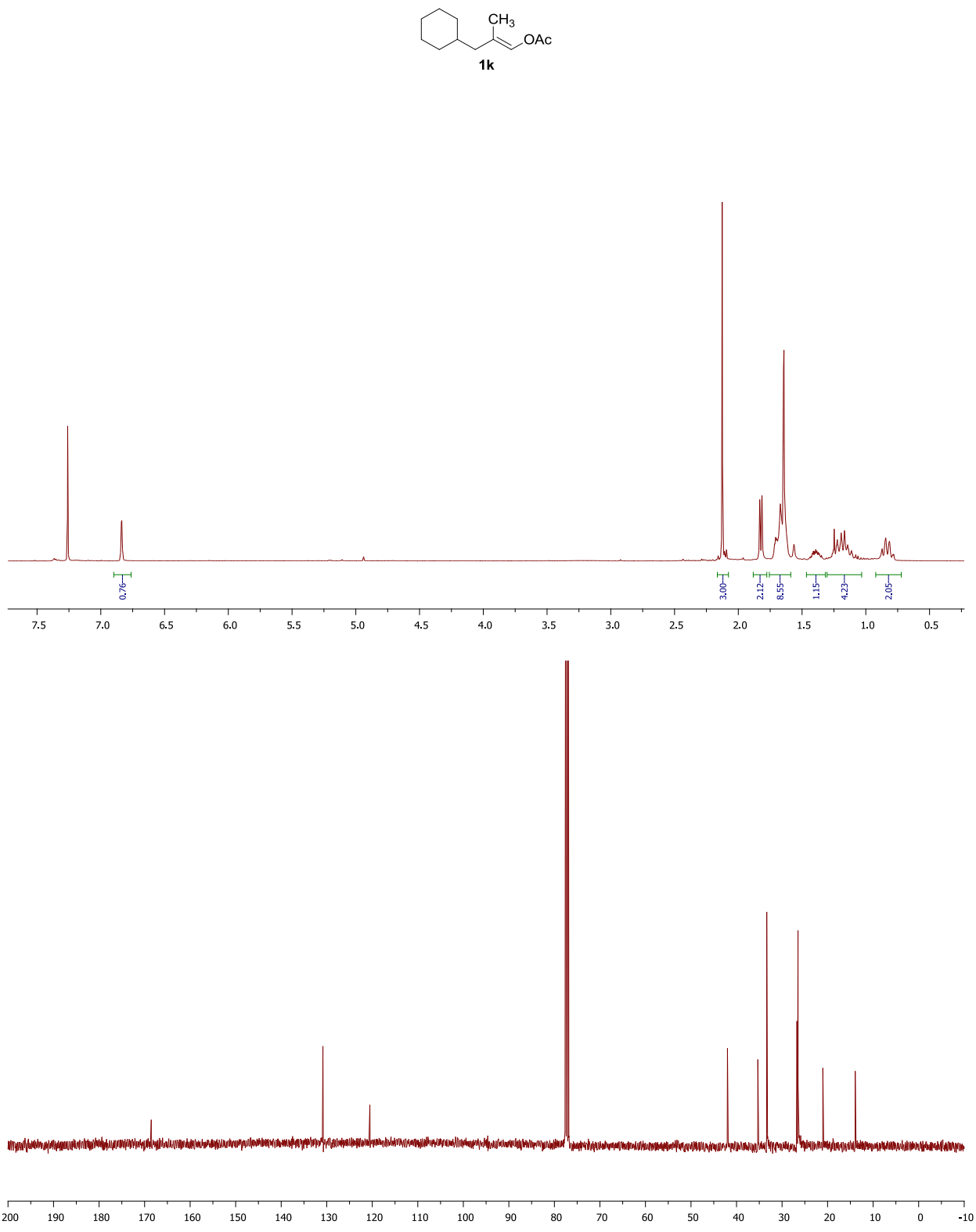
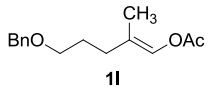


Figure A1. 11 ^{1}H NMR and ^{13}C NMR Spectra of Compound 1k



1l

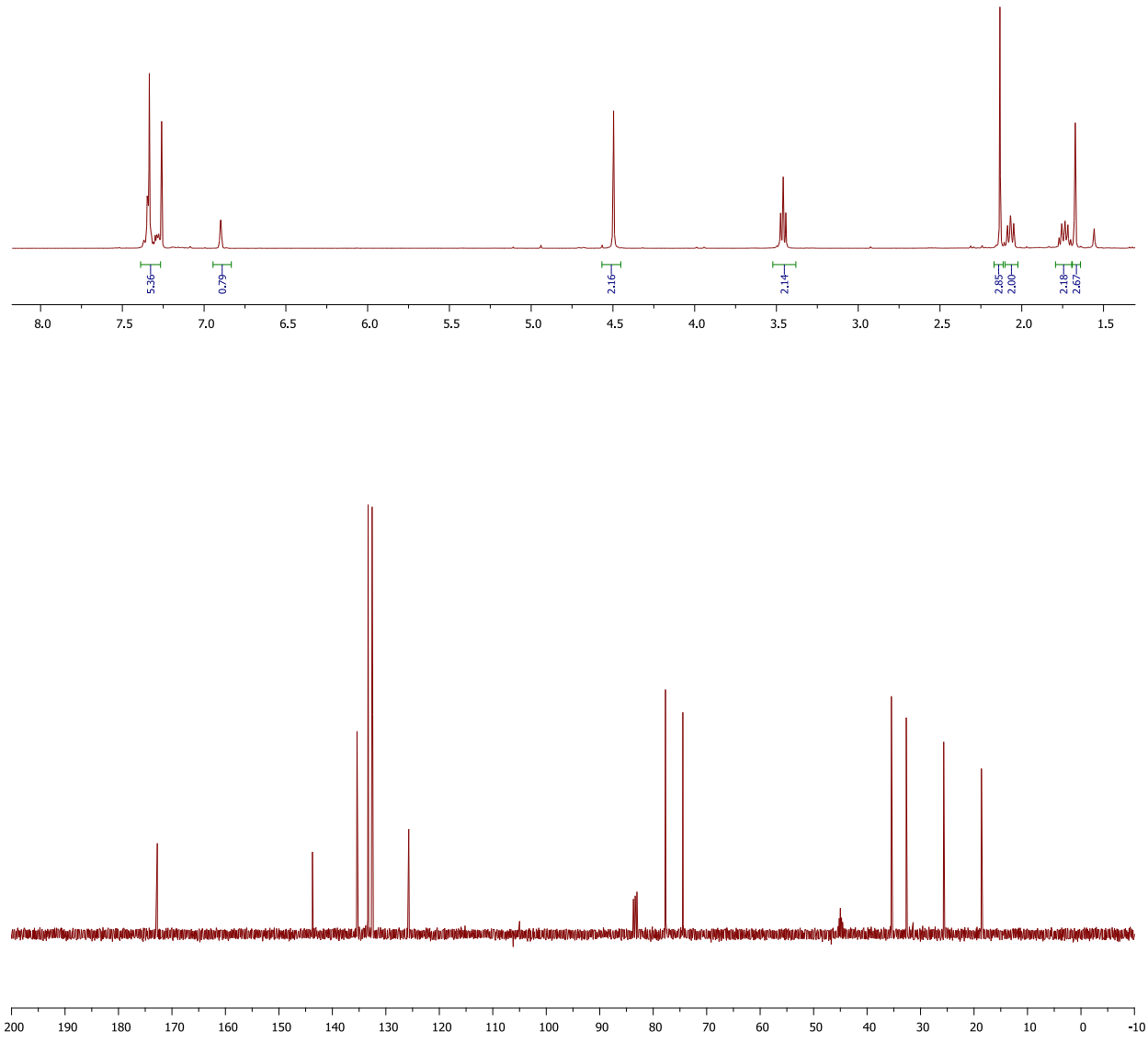


Figure A1. 12 ^{1}H NMR and ^{13}C NMR Spectra of Compound 1l

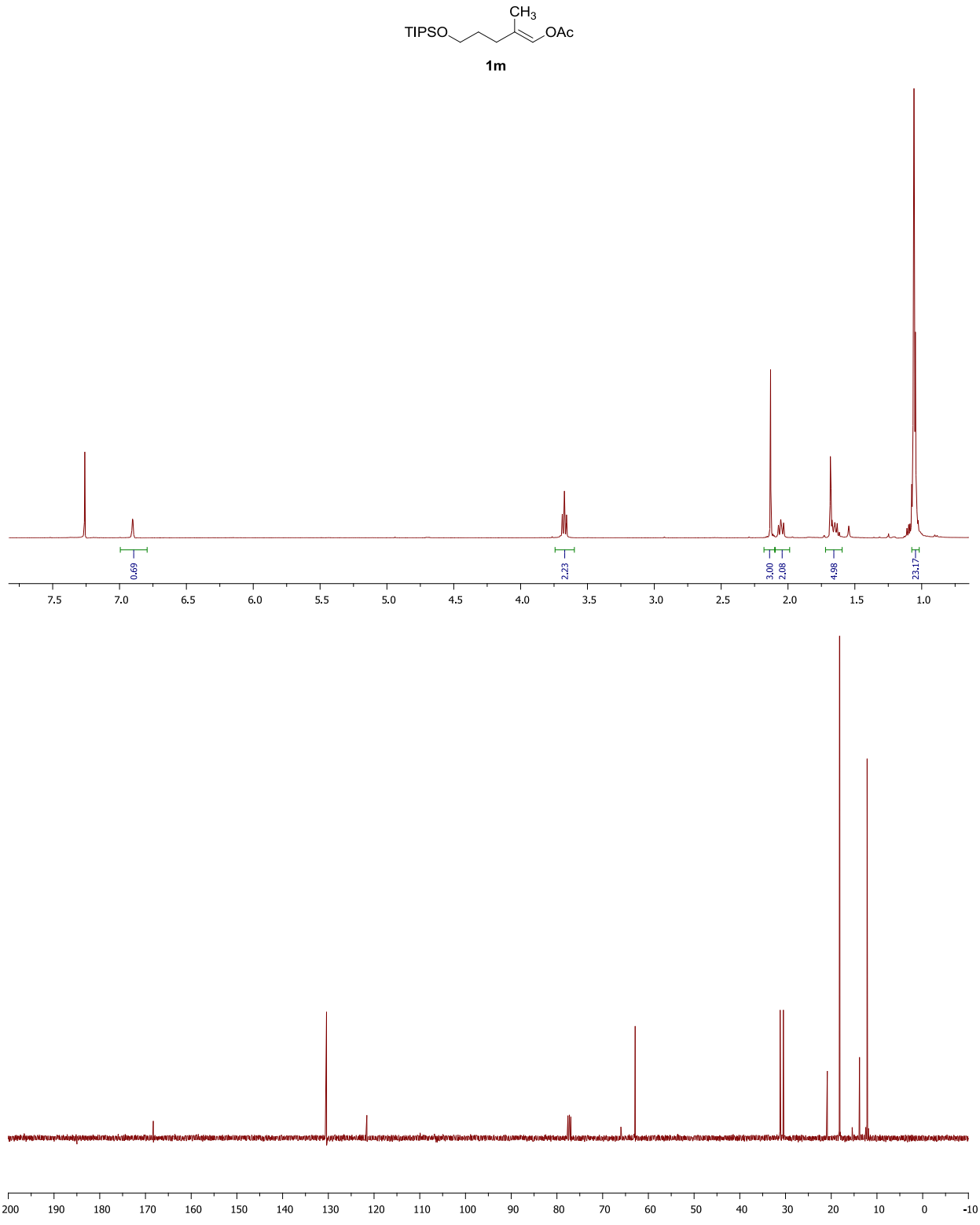


Figure A1. 13 ^{1}H NMR and ^{13}C NMR Spectra of Compound 1m

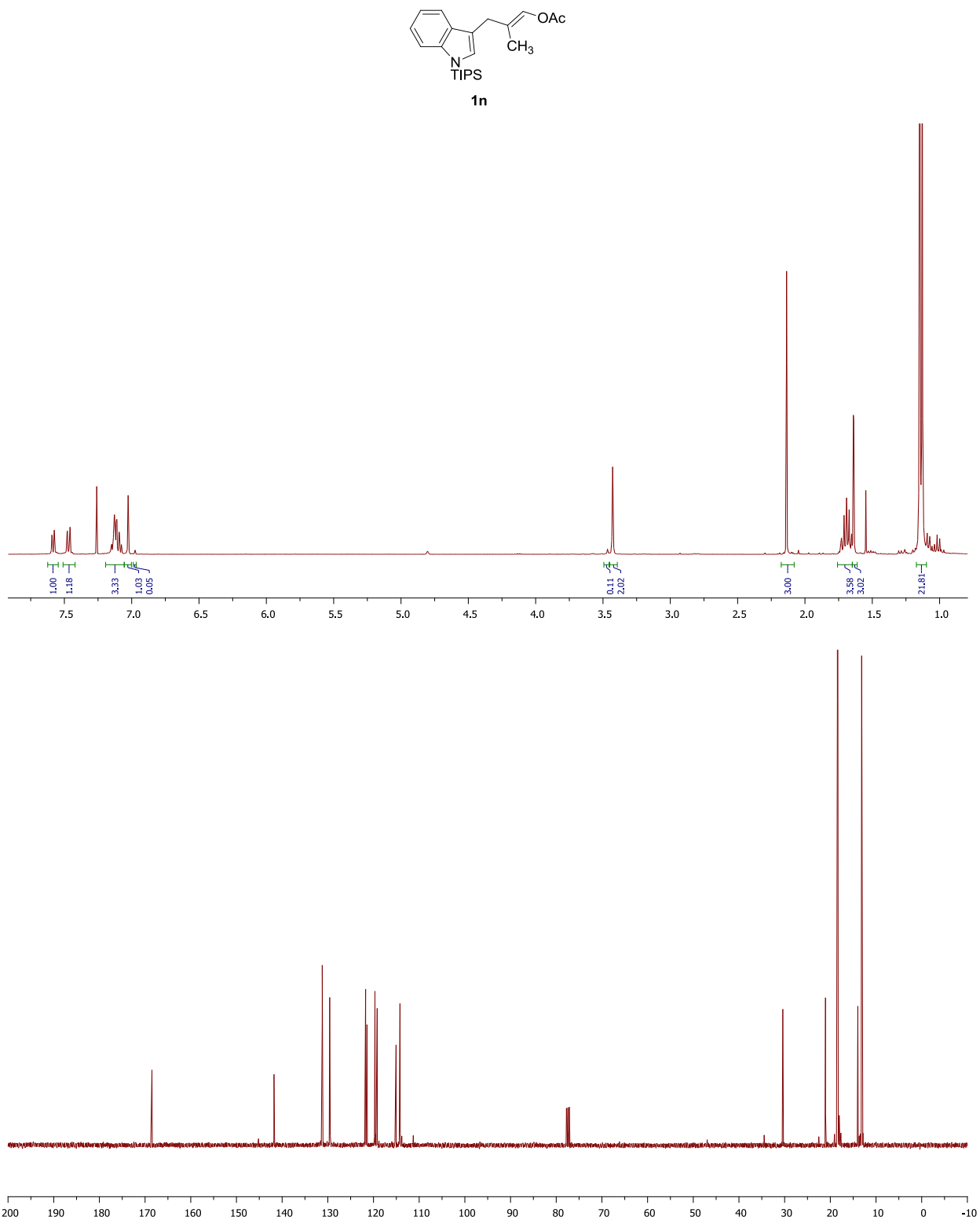
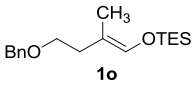


Figure A1. 14 ^{1}H NMR and ^{13}C NMR Spectra of Compound 1n



1o

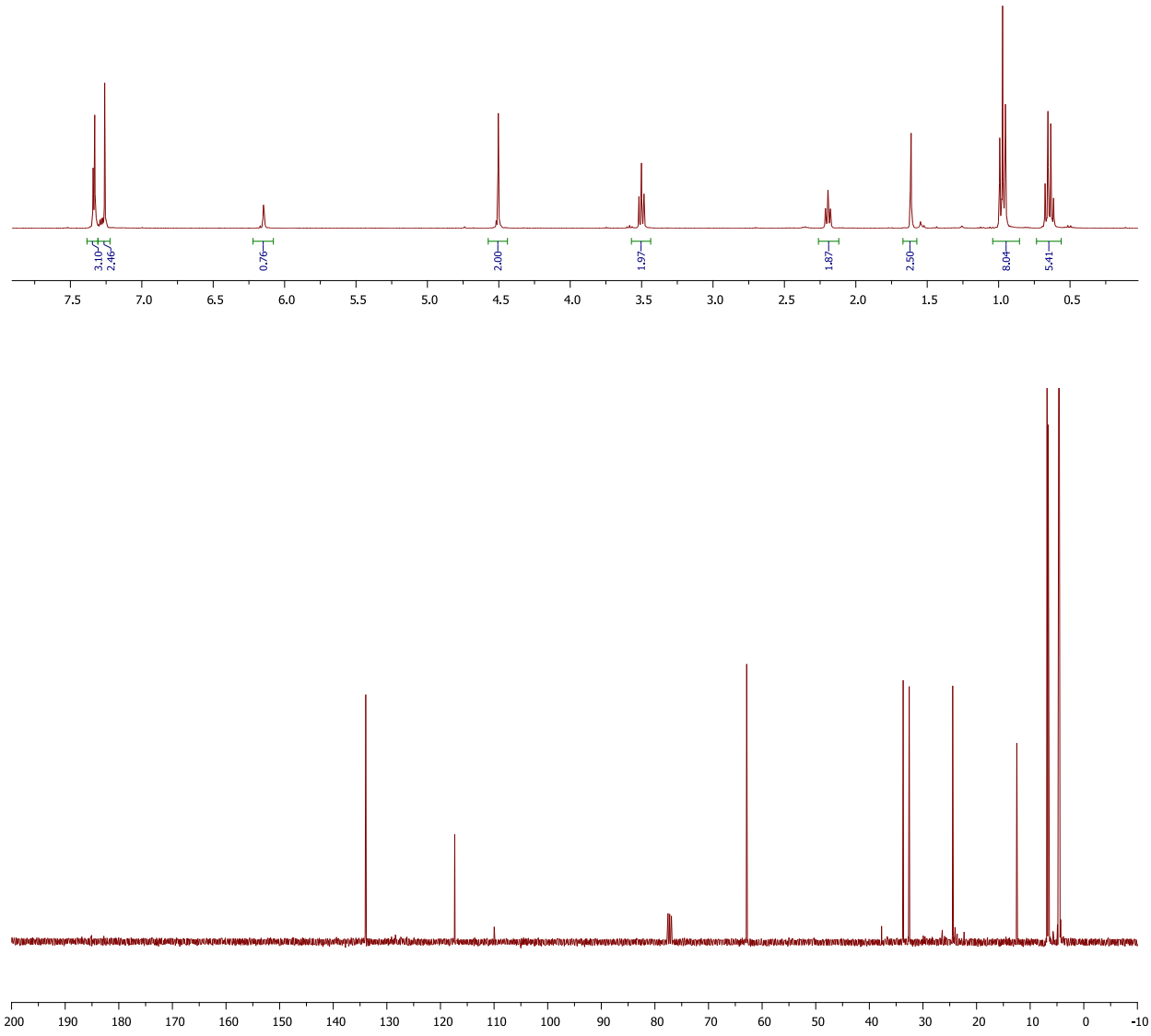


Figure A1. 15 ^{1}H NMR and ^{13}C NMR Spectra of Compound 1o

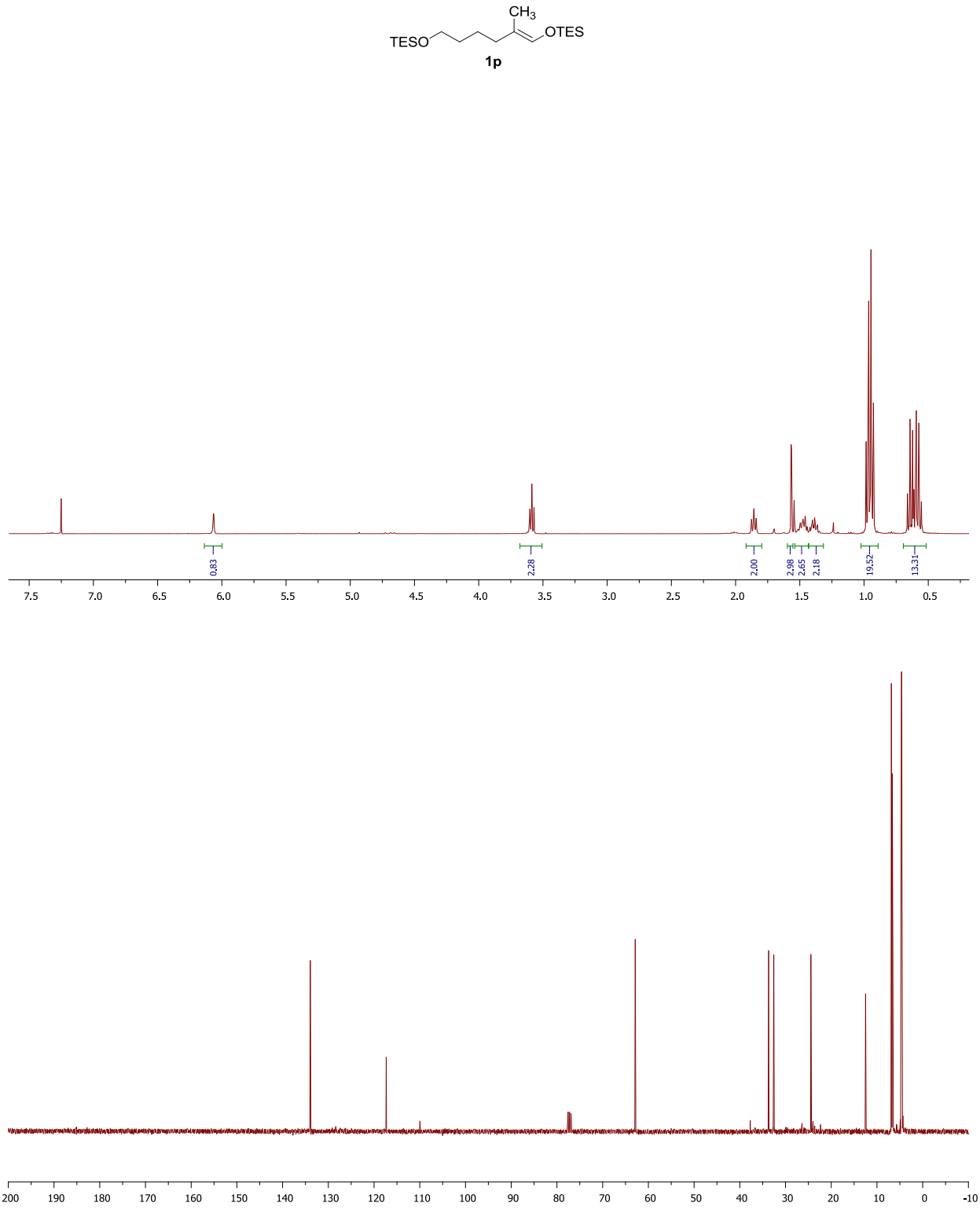
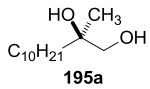


Figure A1. 16 ^{1}H NMR and ^{13}C NMR Spectra of Compound 1p



195a

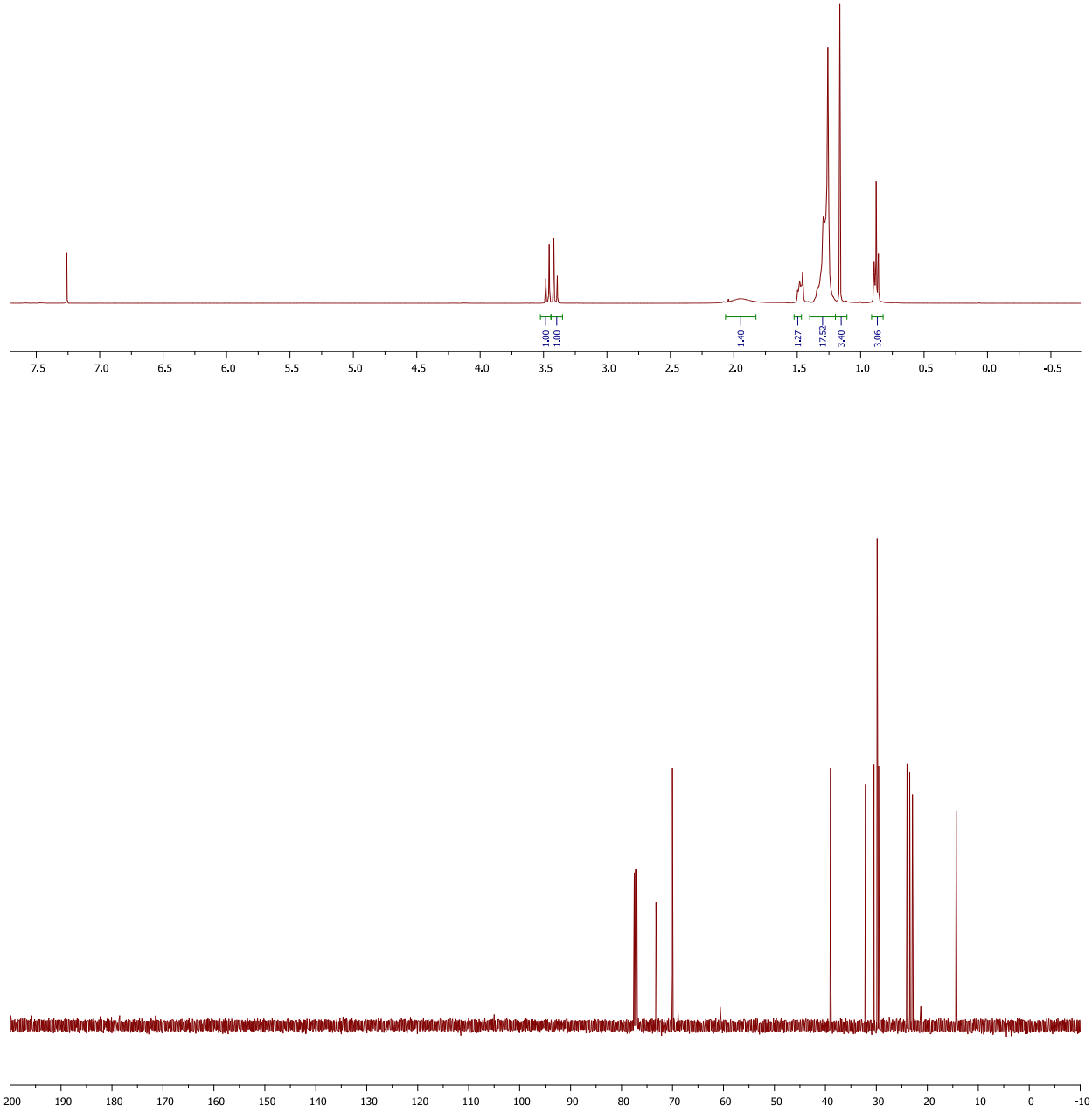


Figure A1. 17 ^{1}H NMR and ^{13}C NMR Spectra of Compound 195a

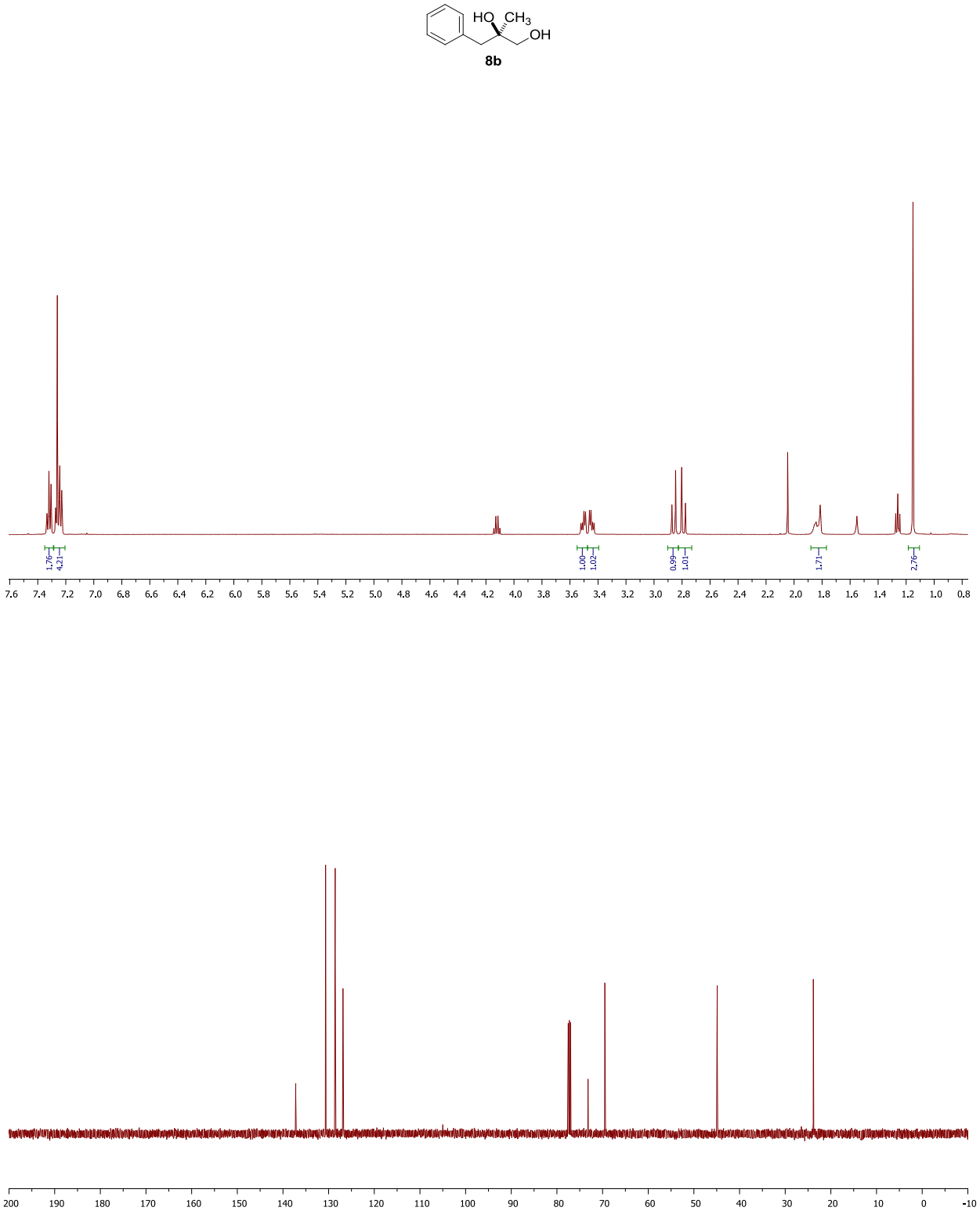


Figure A1. 18 ^{1}H NMR and ^{13}C NMR Spectra of Compound 195b

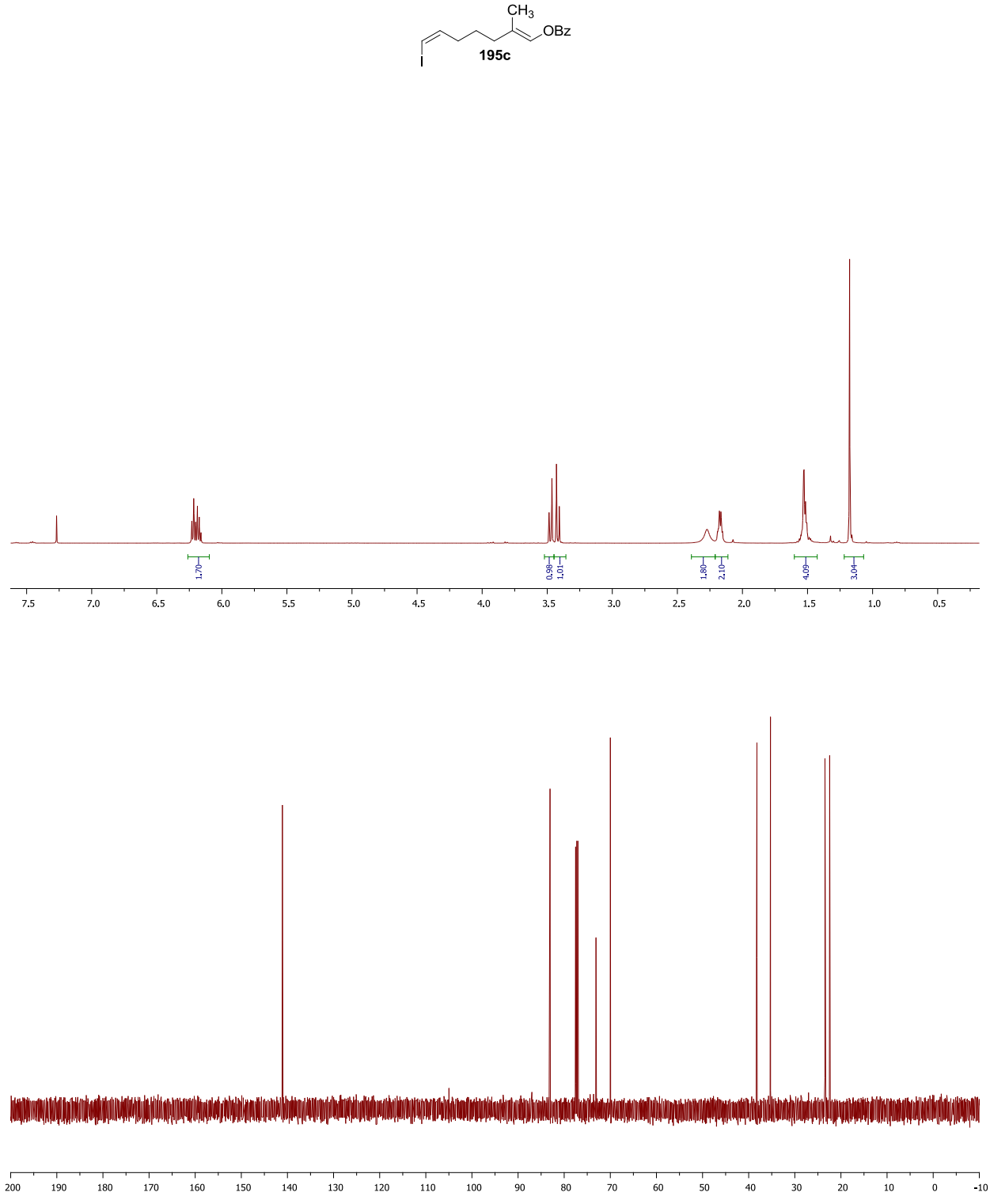


Figure A1. 19 ^{1}H NMR and ^{13}C NMR Spectra of Compound 195c

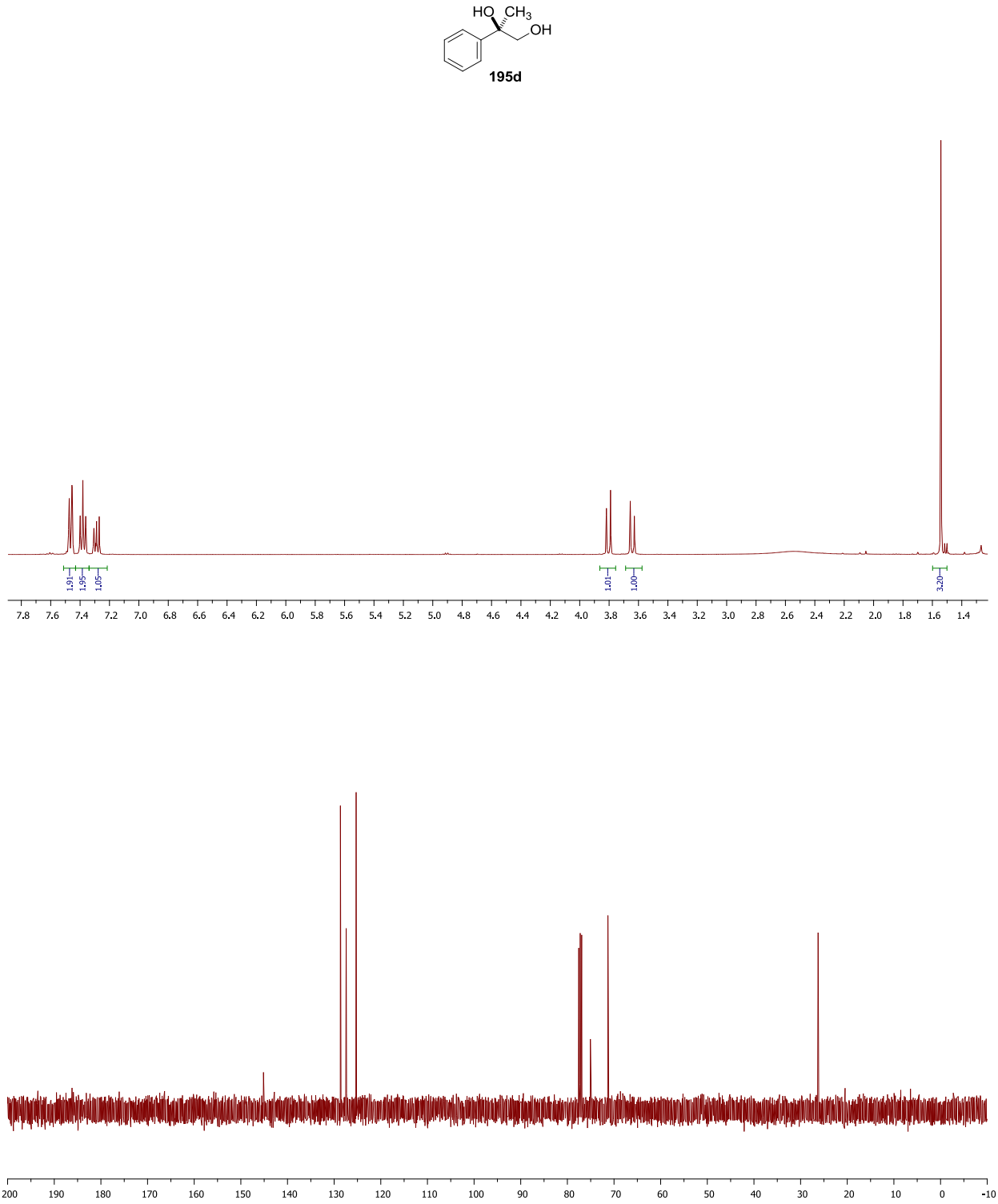
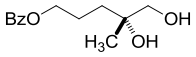


Figure A1. 20 ^{1}H NMR and ^{13}C NMR Spectra of Compound 195d



195g

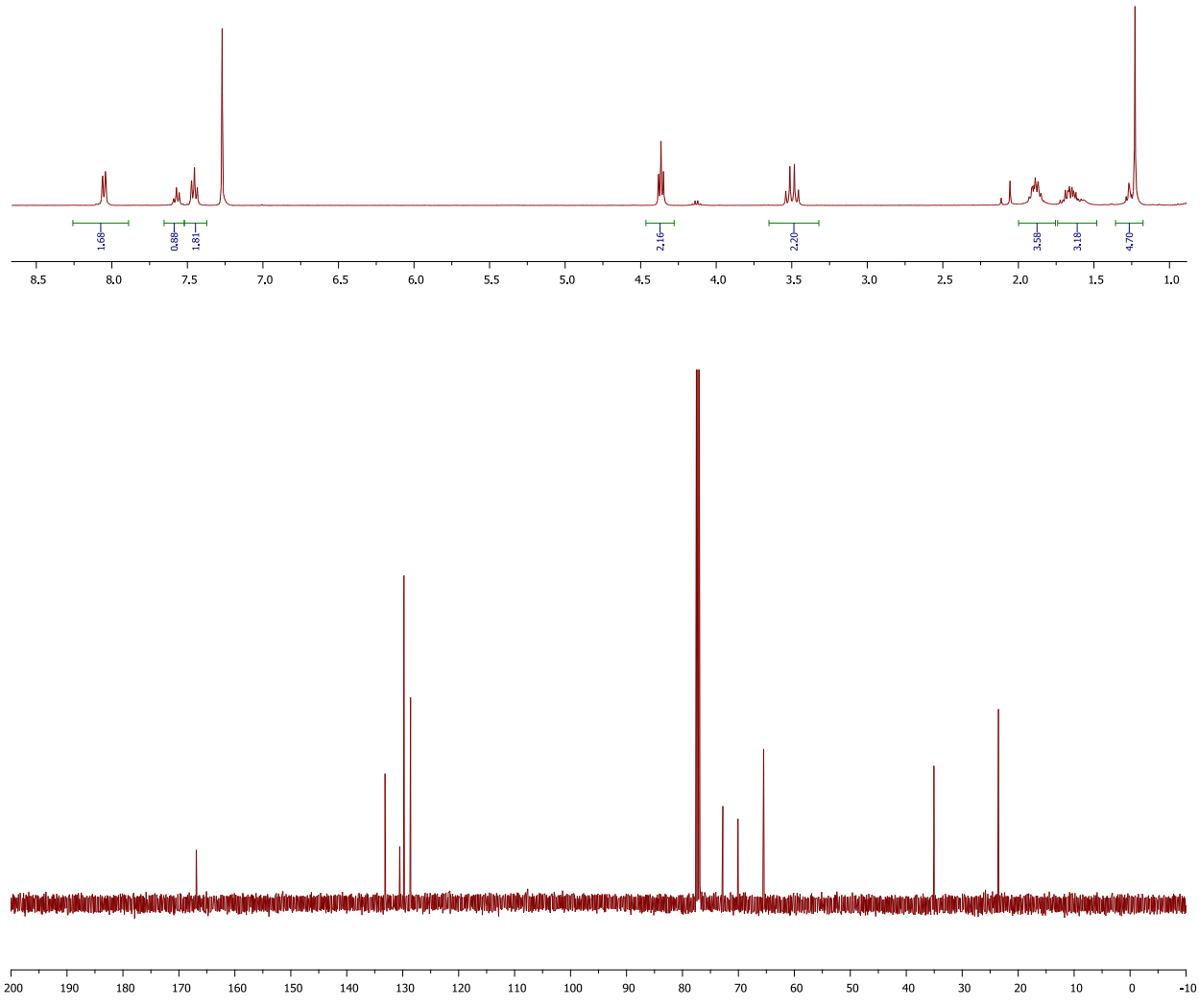
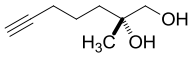


Figure A1. 21 ^{1}H NMR and ^{13}C NMR Spectra of Compound 195g



195q

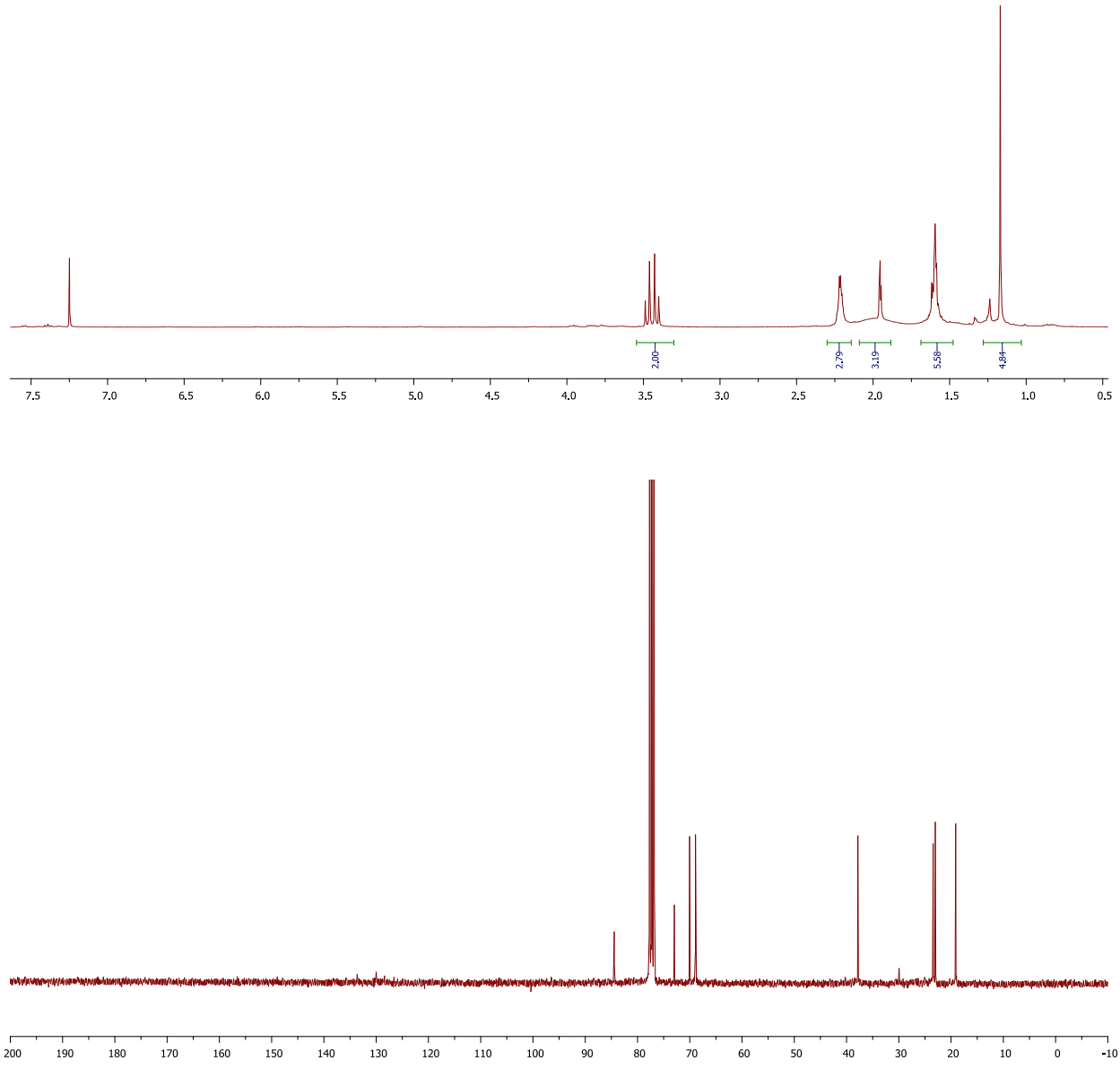
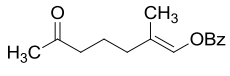


Figure A1. 22 ^{1}H NMR and ^{13}C NMR Spectra of Compound 195q



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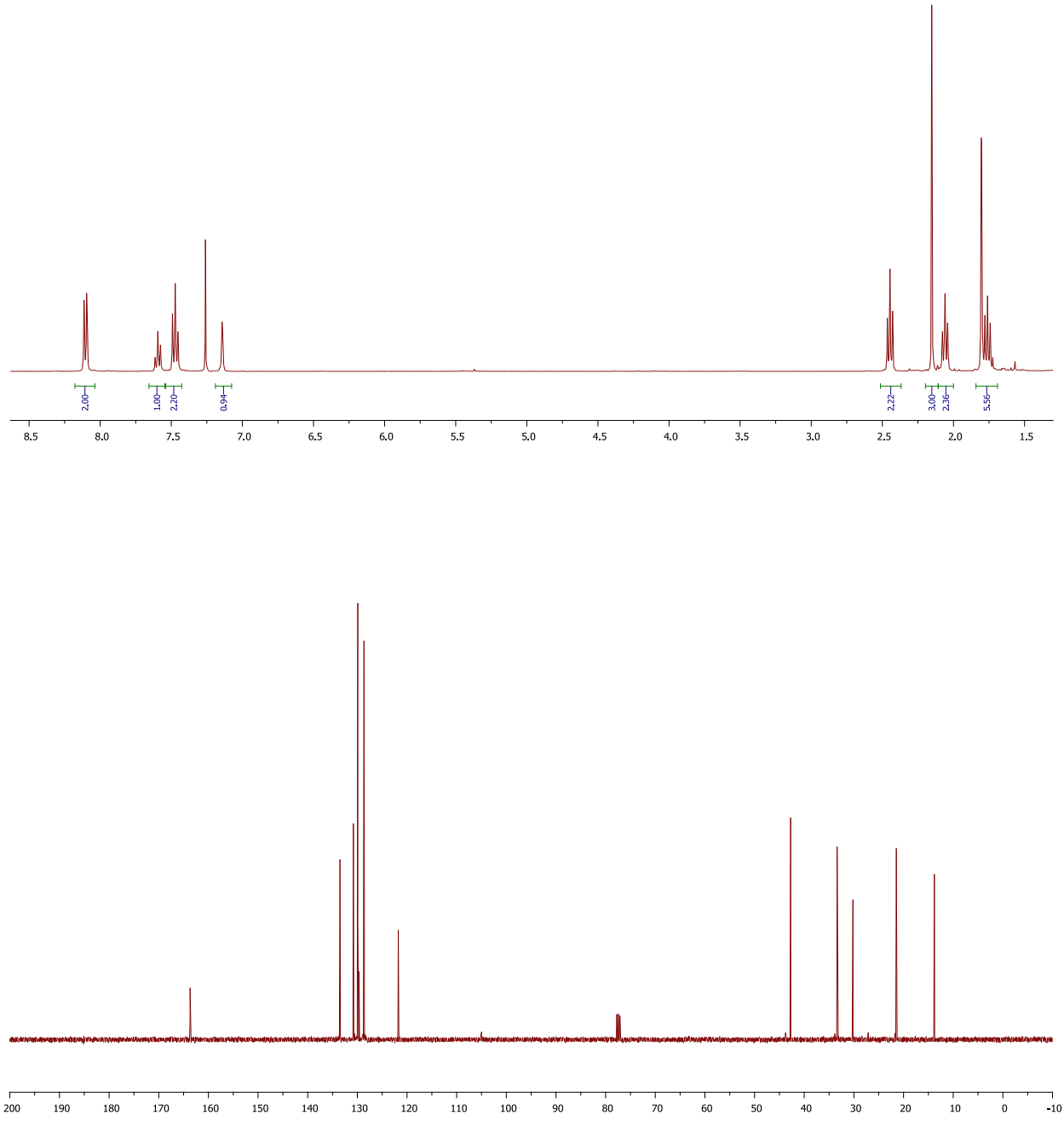
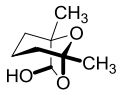


Figure A1. 23 ^{1}H NMR and ^{13}C NMR Spectra of Compound 221



222

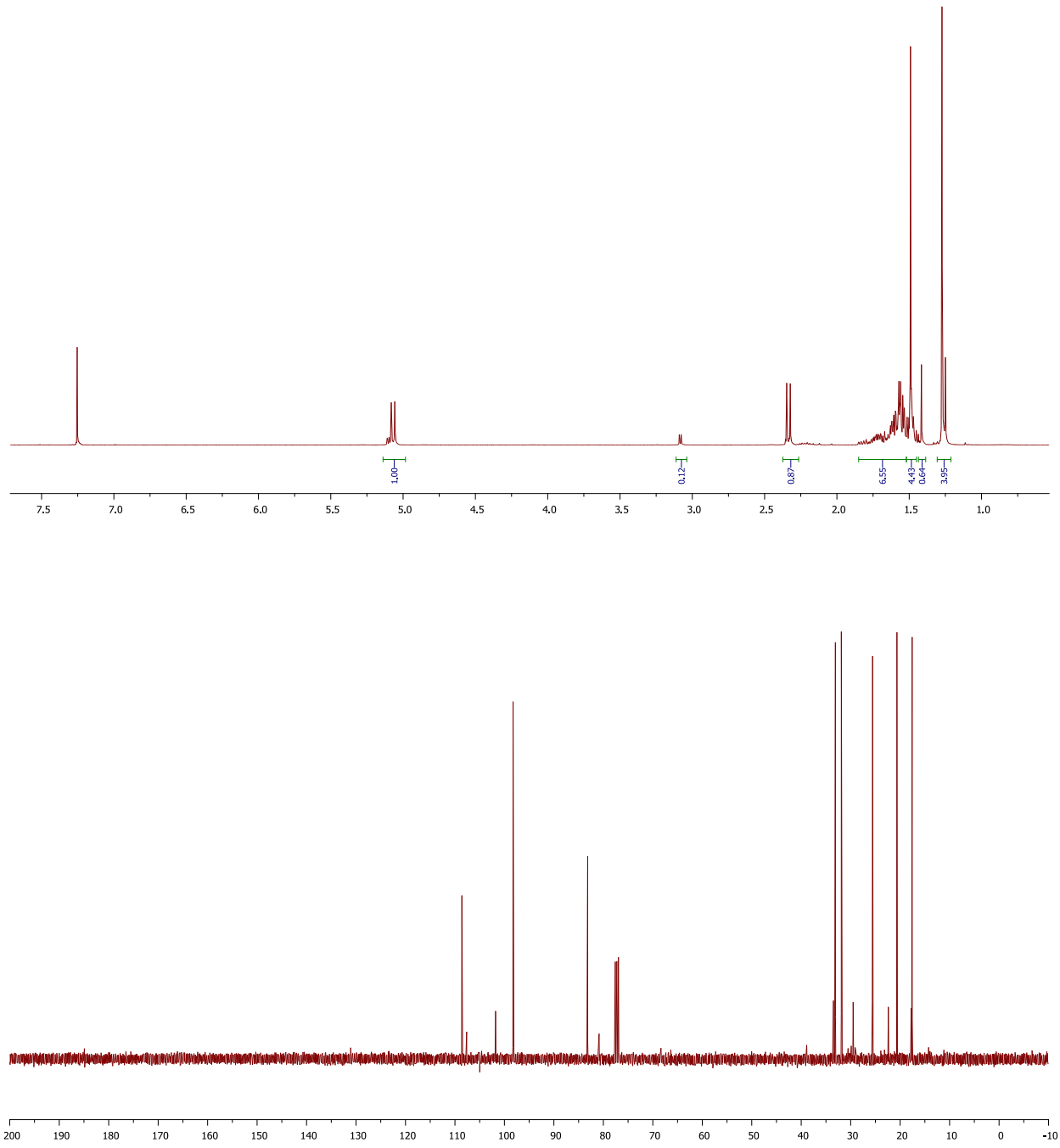


Figure A1. 24 ^{1}H NMR and ^{13}C NMR Spectra of Compound 222

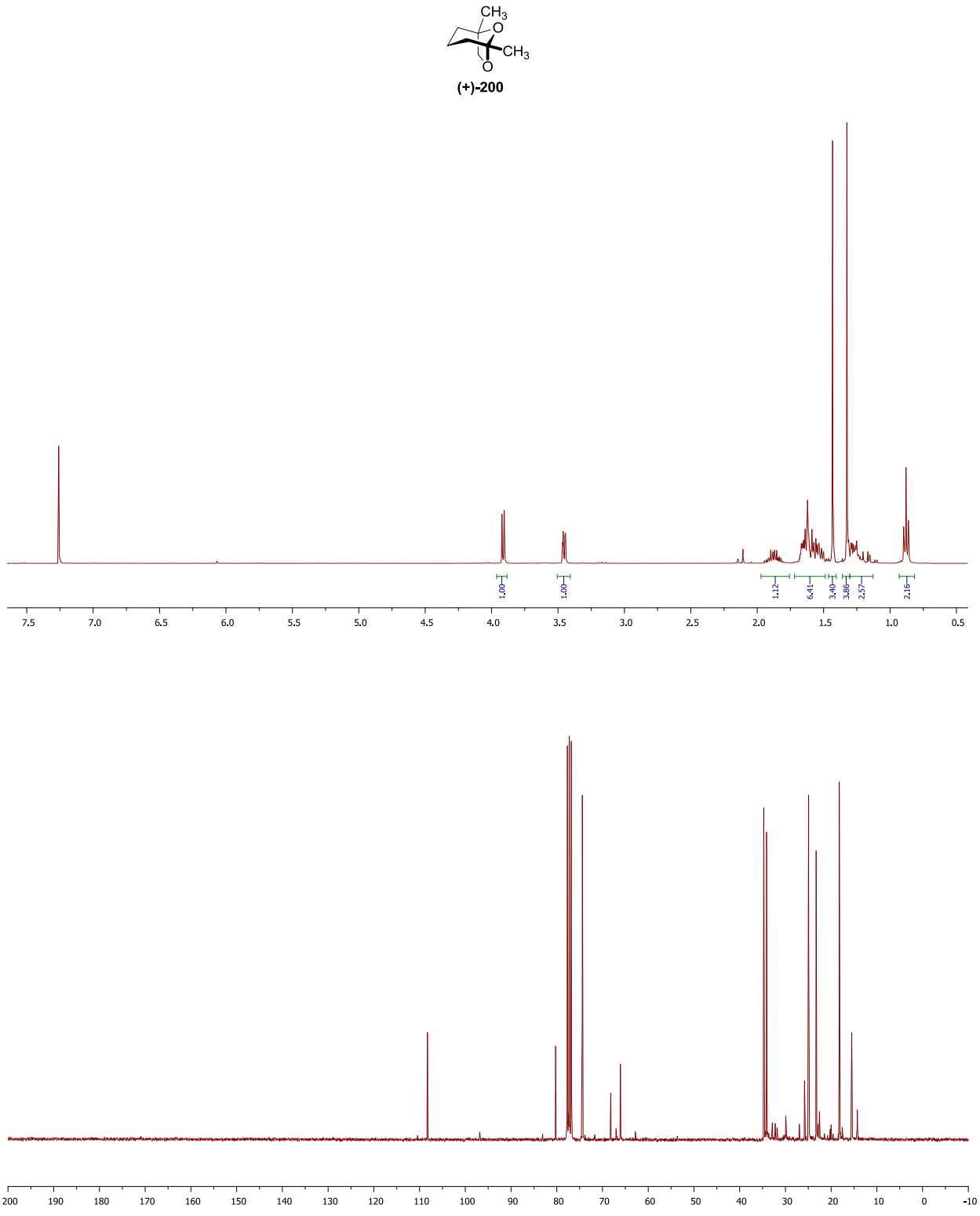
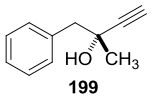


Figure A1. 25 ^{1}H NMR and ^{13}C NMR Spectra of (+)-Frontalin (200)



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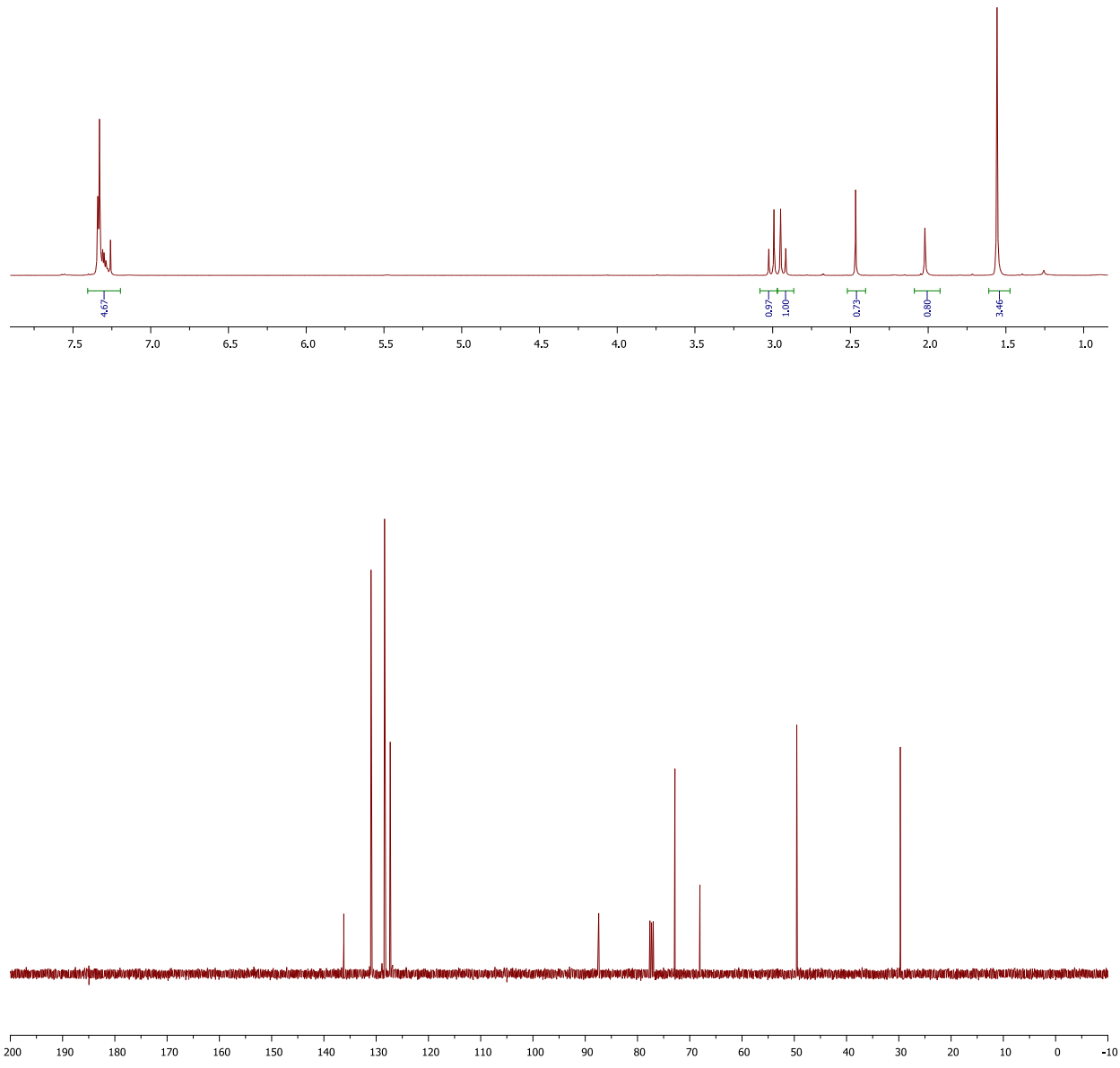
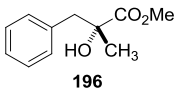


Figure A1. 26 ^{1}H NMR and ^{13}C NMR Spectra of Compound 199



196

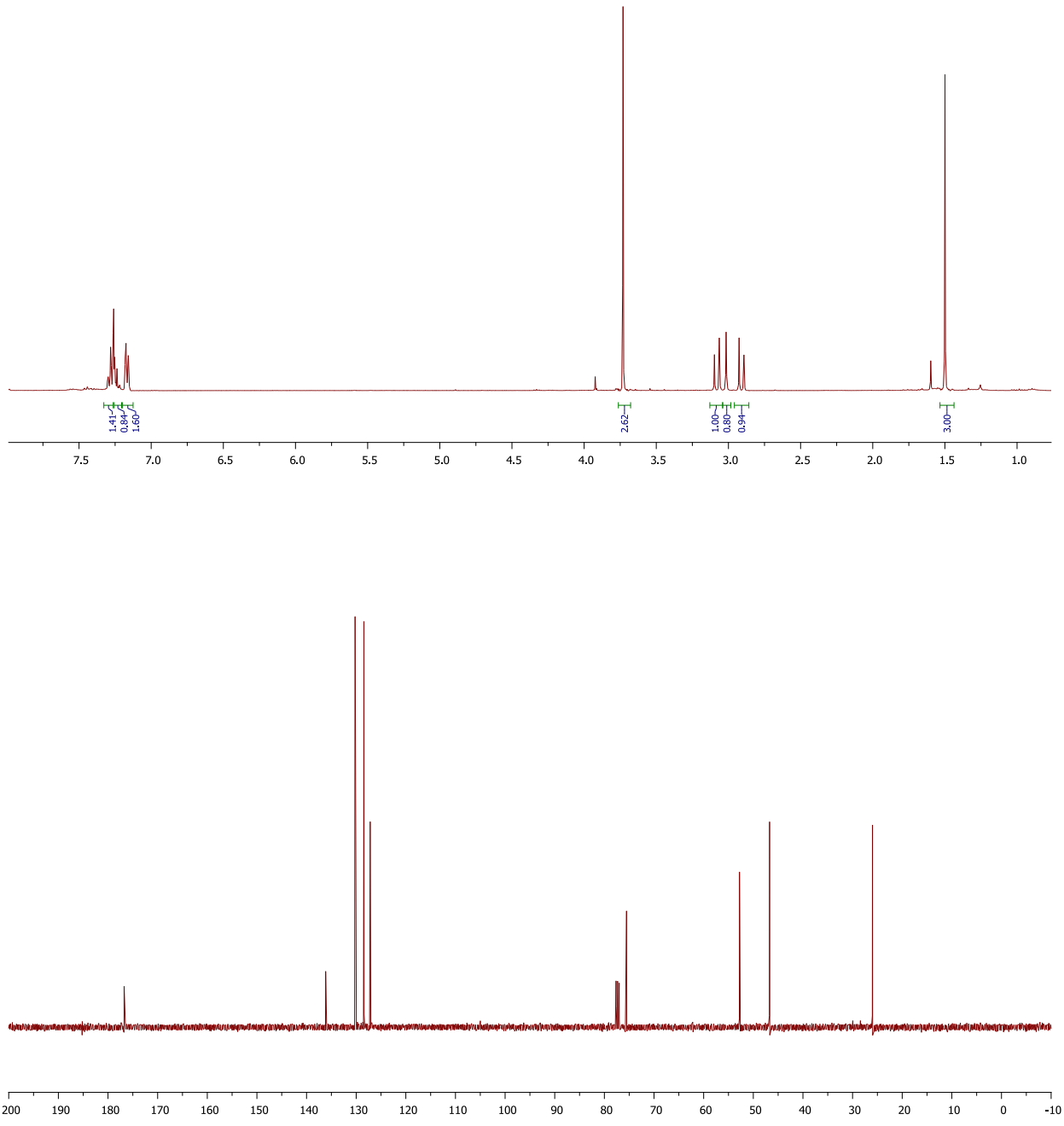
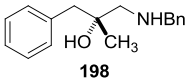


Figure A1. 27 ^{1}H NMR and ^{13}C NMR Spectra of Compound 196



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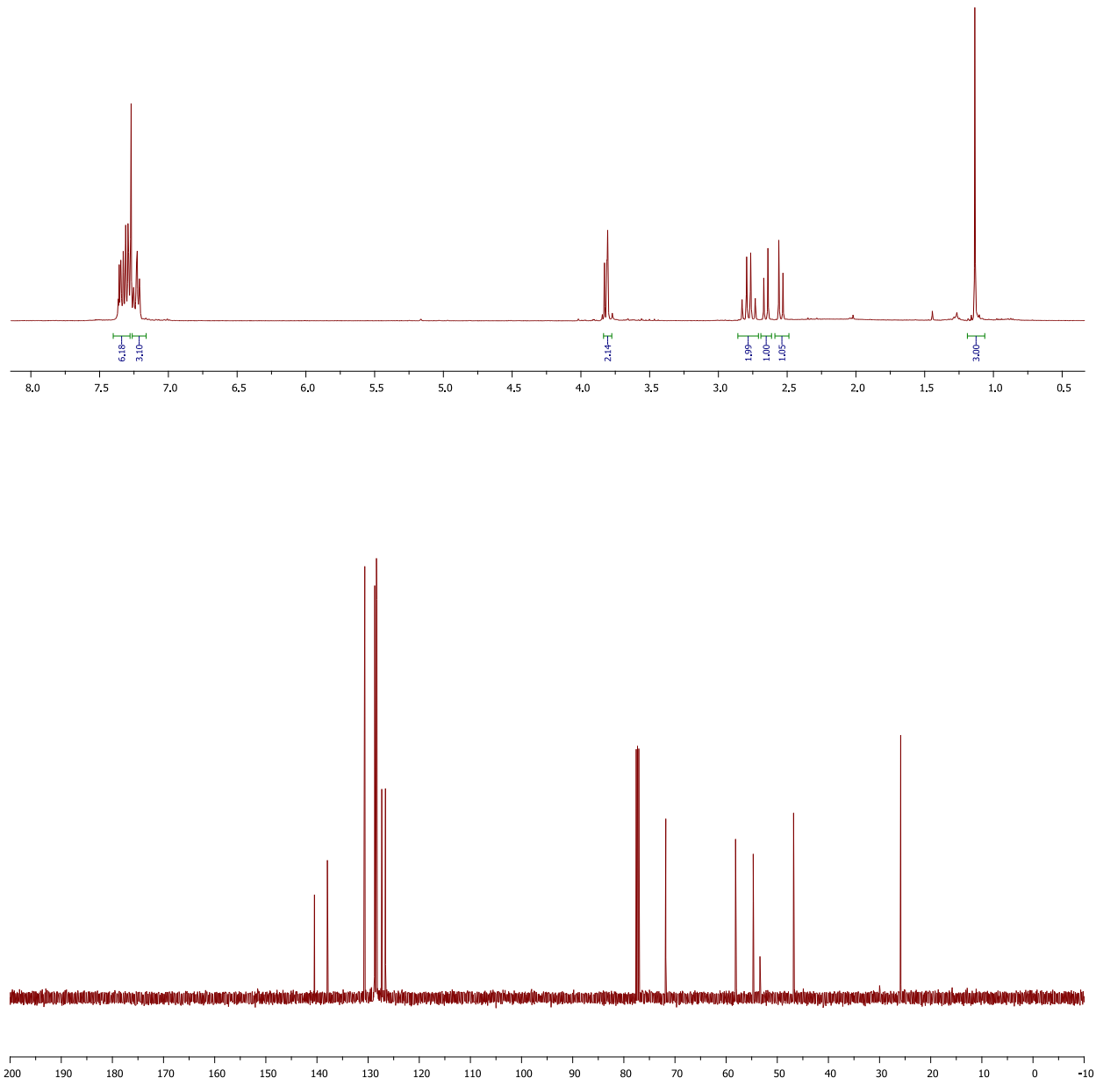
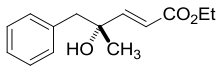


Figure A1. 28 ^{1}H NMR and ^{13}C NMR Spectra of Compound 198



197

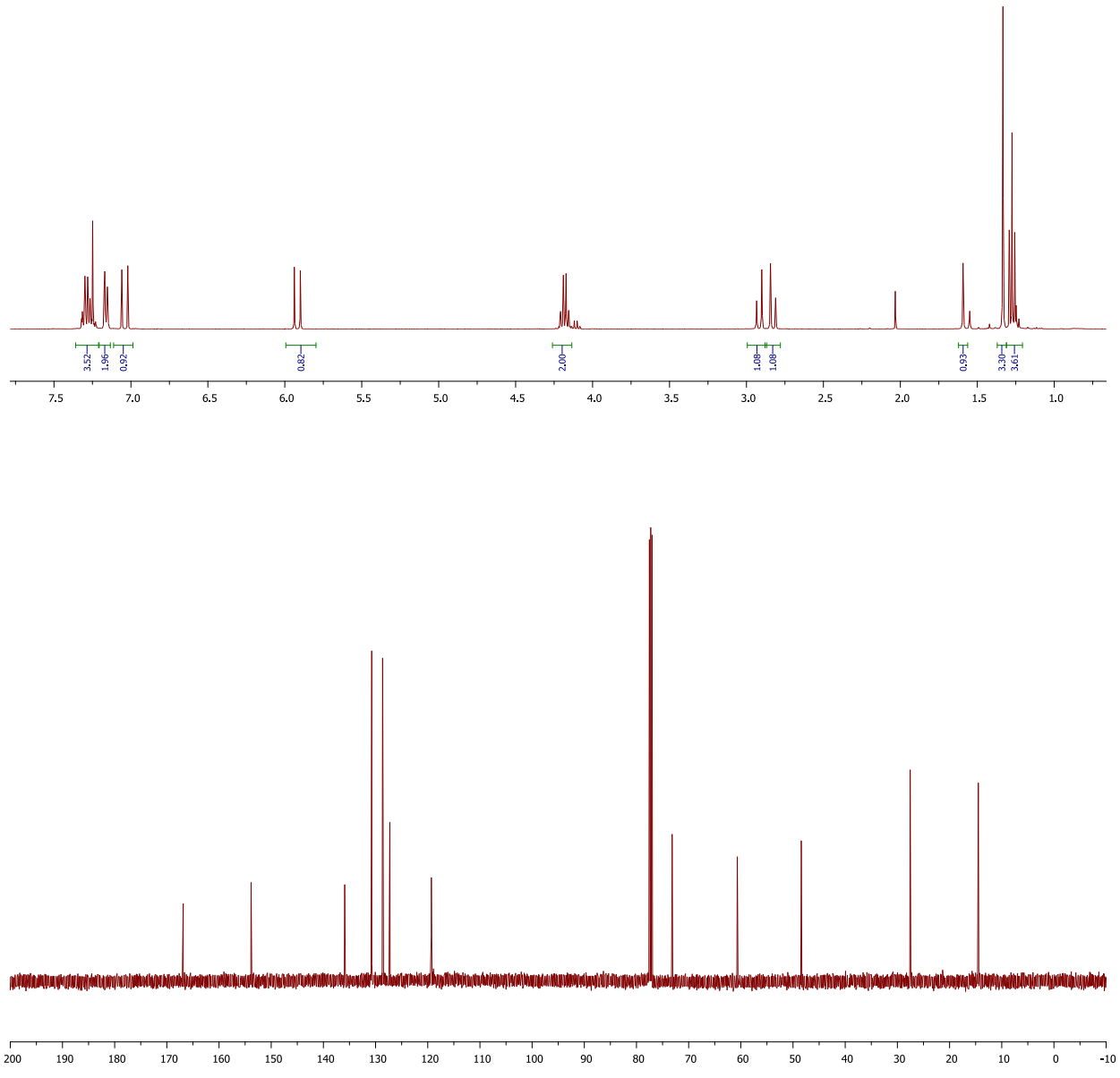


Figure A1. 29 ^{1}H NMR and ^{13}C NMR Spectra of Compound 197

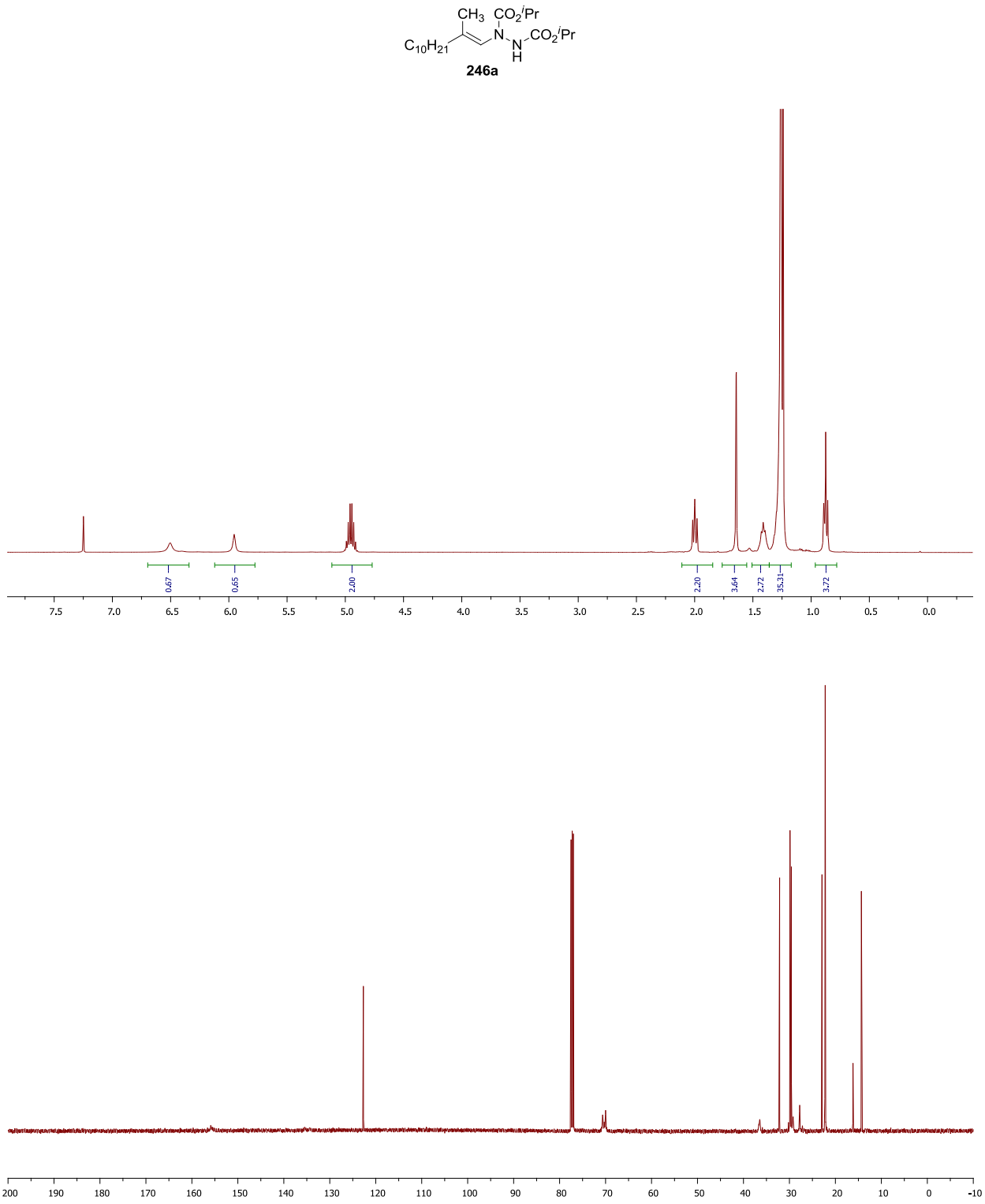


Figure A1. 30 ^{1}H NMR and ^{13}C NMR Spectra of Compound 246a

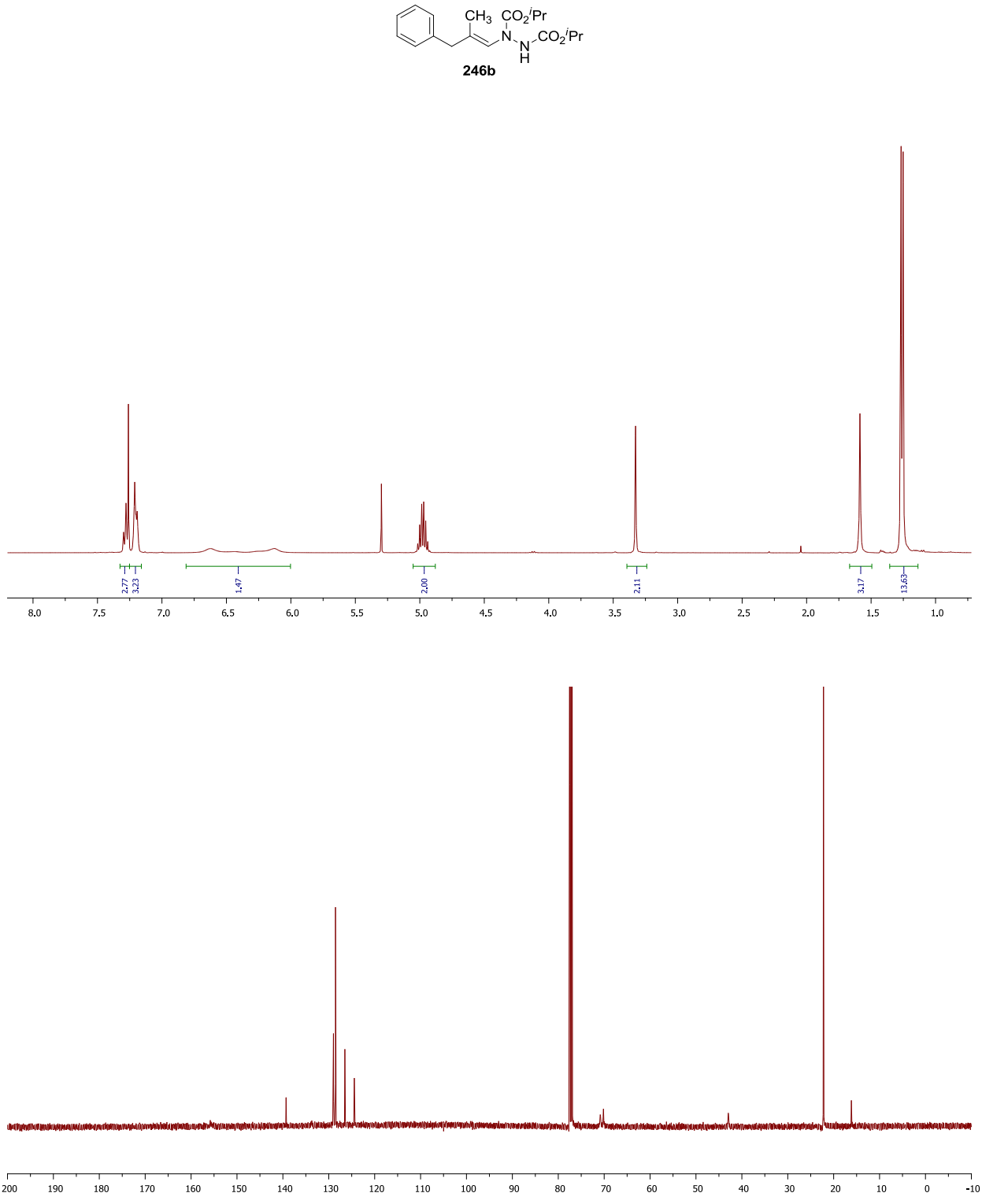
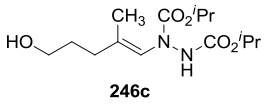


Figure A1. 31 ^{1}H NMR and ^{13}C NMR Spectra of Compound 246b



246c

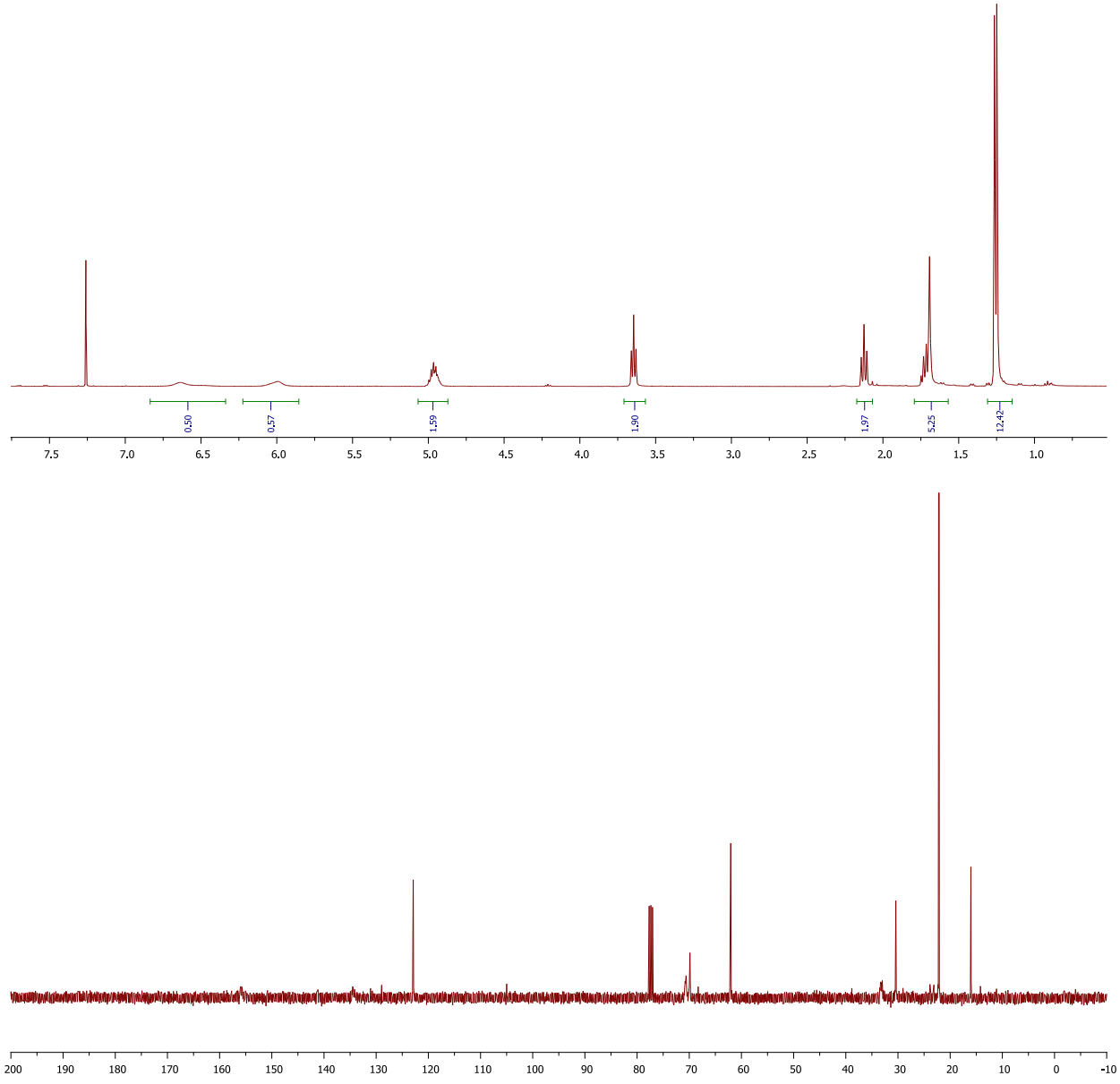


Figure A1. 32 ^{1}H NMR and ^{13}C NMR Spectra of Compound 246c

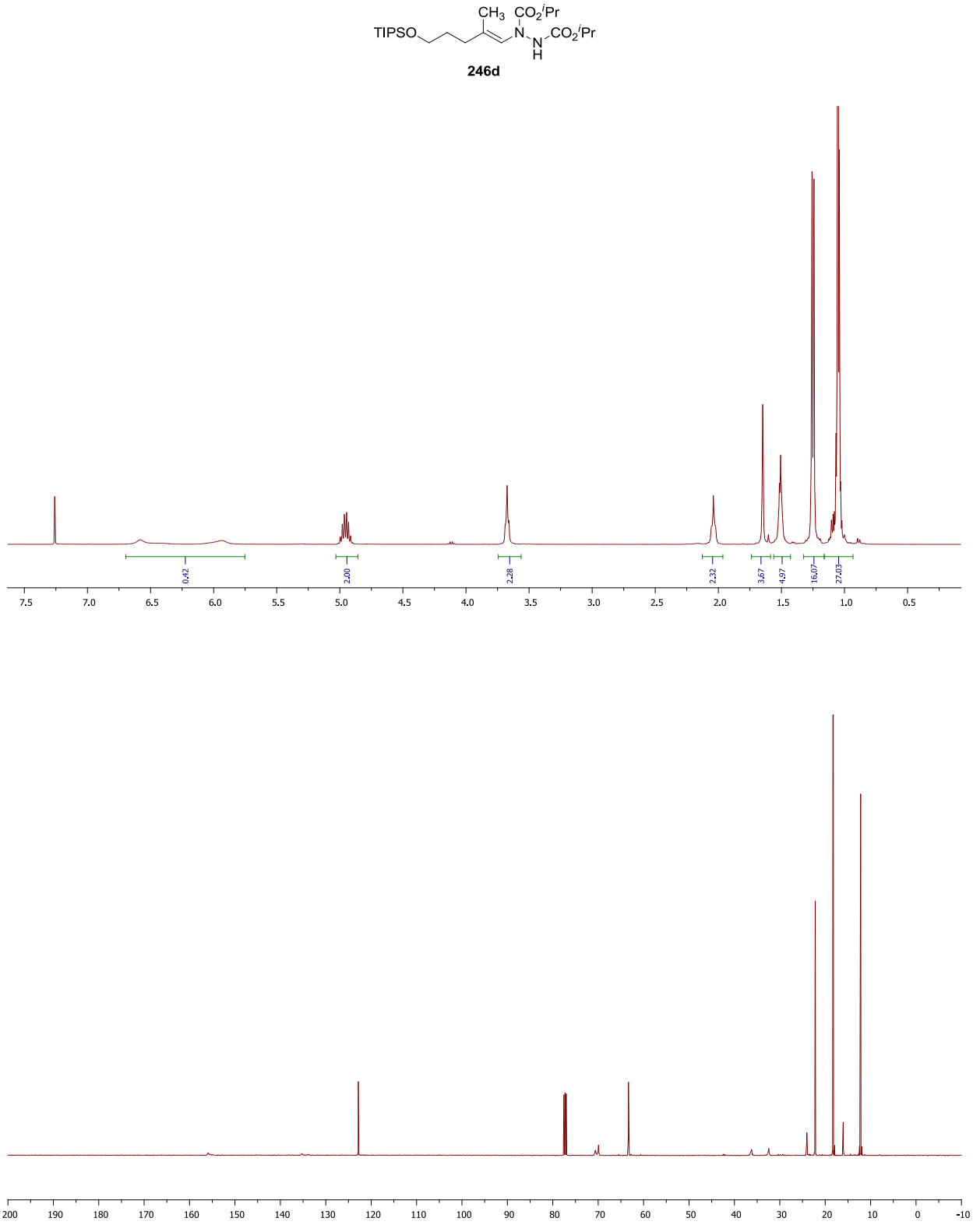
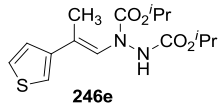


Figure A1. 33 ^{1}H NMR and ^{13}C NMR Spectra of Compound 246d



246e

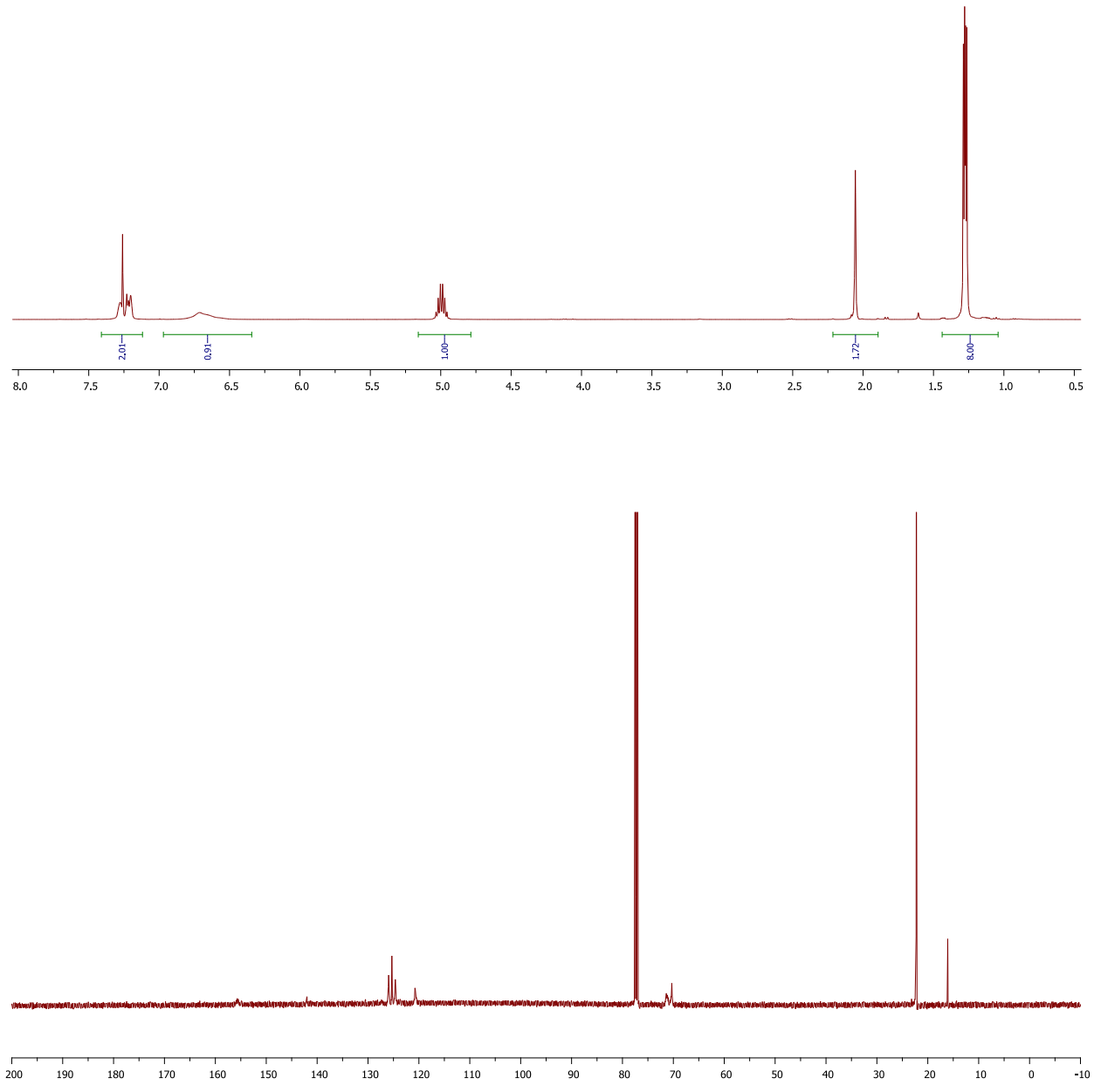


Figure A1. 34 ^{1}H NMR and ^{13}C NMR Spectra of Compound 246e

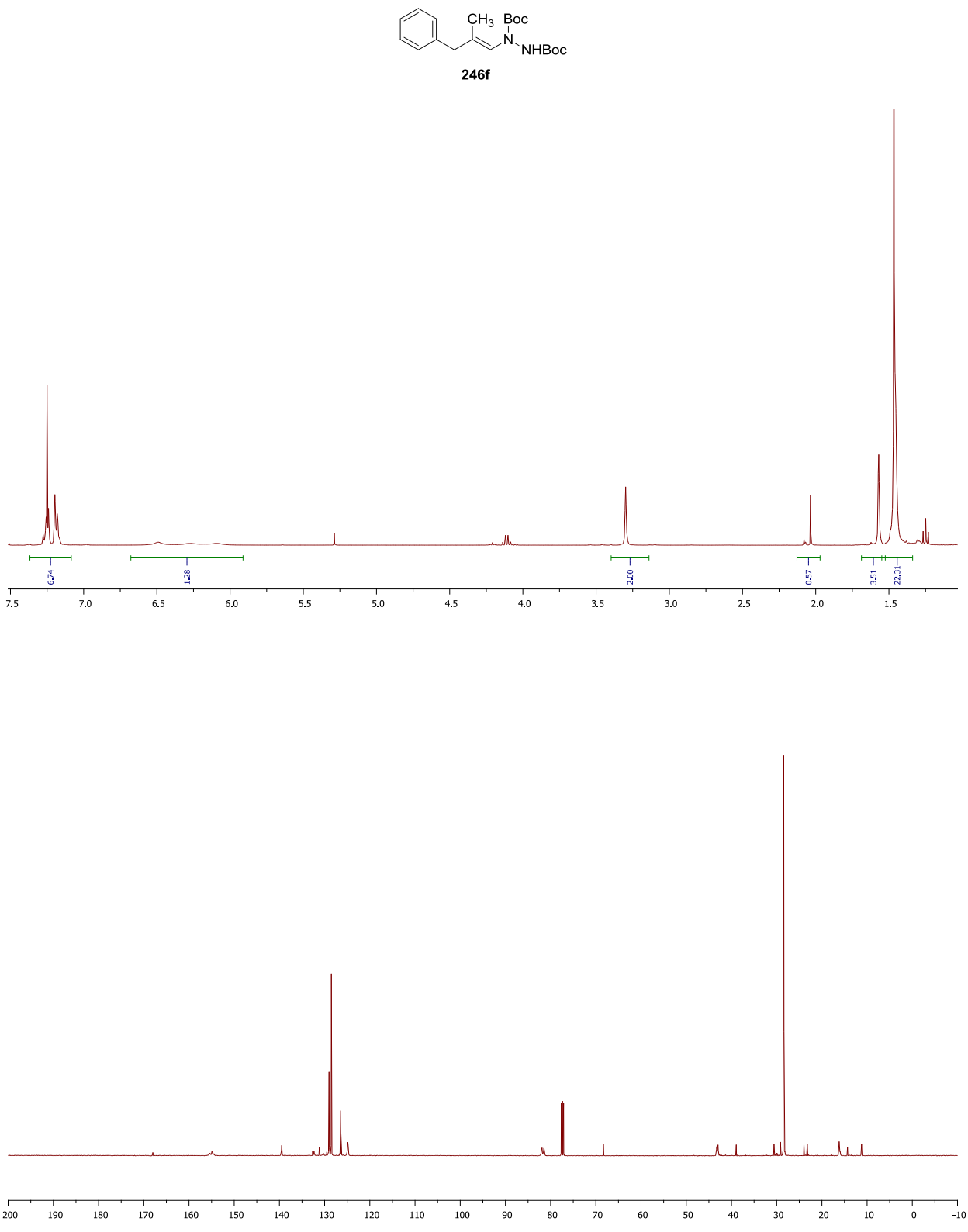


Figure A1. 35 ^{1}H NMR and ^{13}C NMR Spectra of Compound 246f

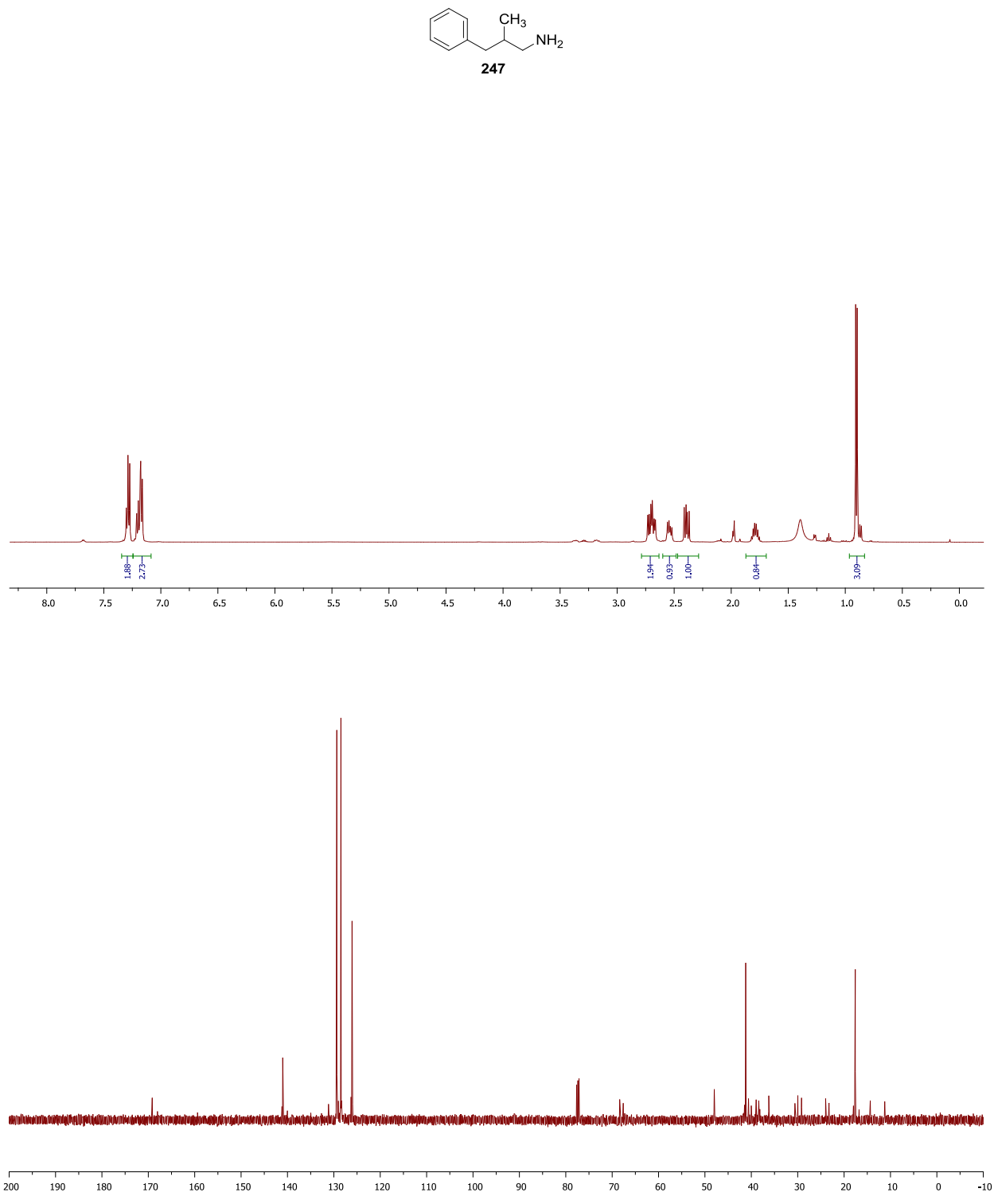


Figure A1. 36 ^{1}H NMR and ^{13}C NMR Spectra of Compound 247

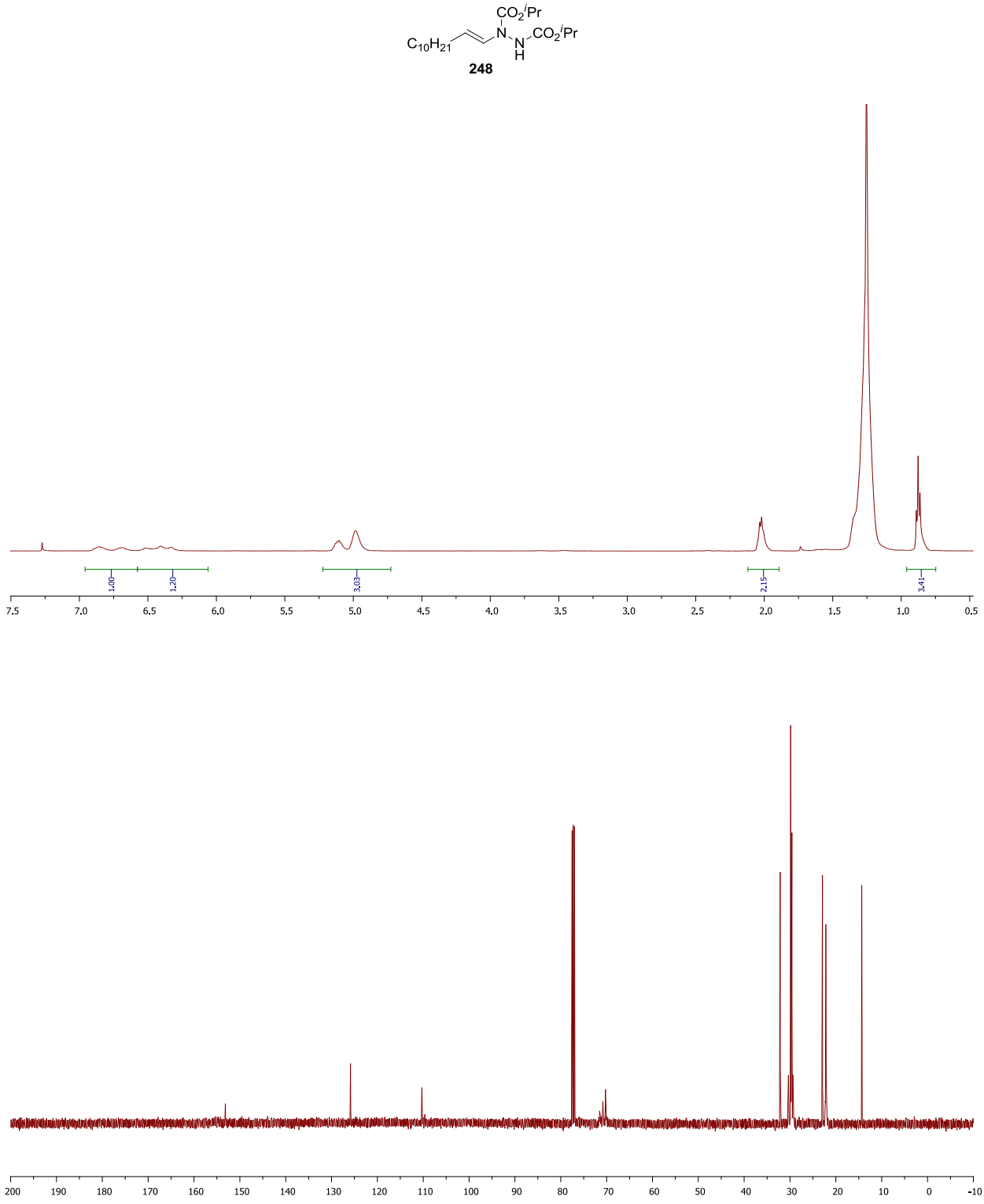
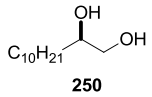


Figure A1. 37 ^{1}H NMR and ^{13}C NMR Spectra of Compound 248



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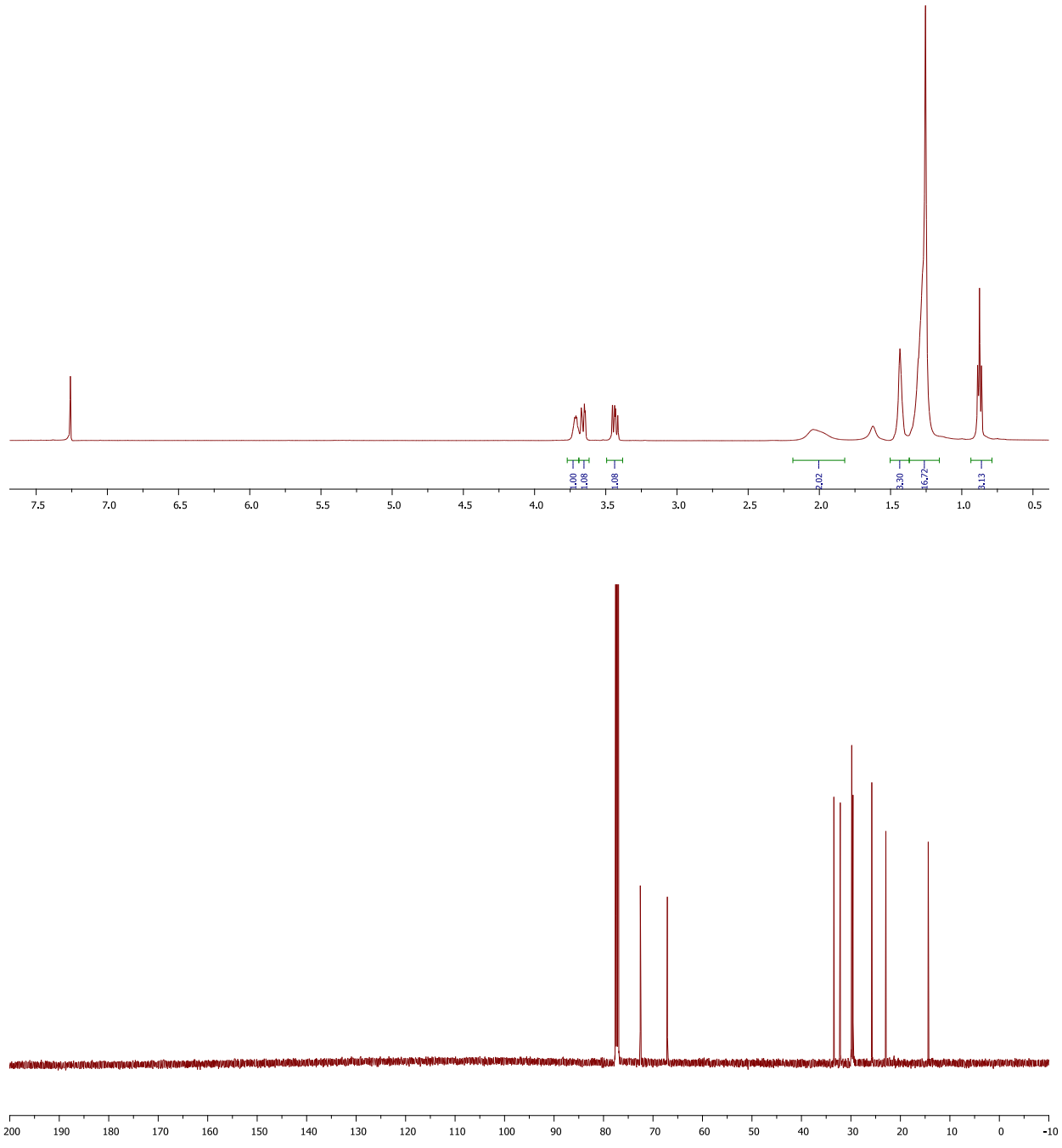
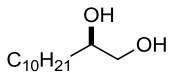
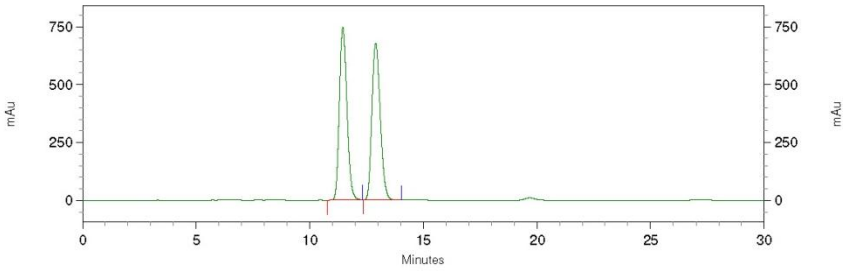


Figure A1. 38 ^{1}H NMR and ^{13}C NMR Spectra of Compound 250



250

Racemic Compound

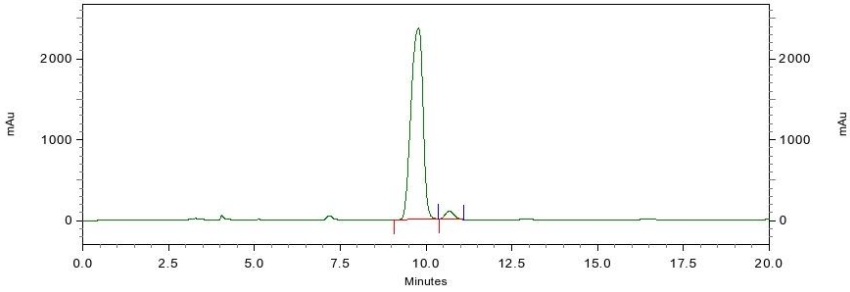


1: 229 nm, 8 nm
Results

Retention Time	Area	Area %	Height	Height %
11.451	17324851	50.01	746479	52.46
12.896	17315506	49.99	676593	47.54
Totals	34640357	100.00	1423072	100.00

HPLC Conditions: Chiralcel OD-H column, 1 mL/ min flow rate, 0.125% i-PrOH in hexanes

Scalemic Compound



3: 210 nm, 8 nm
Results

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10.683	1772421	3.00	98208	3.99
Totals	58985788	100.00	2462098	100.00

Figure A1. 39 HPLC Chromatogram for Compound 250

CHAPTER ONE BIBLIOGRAPHY

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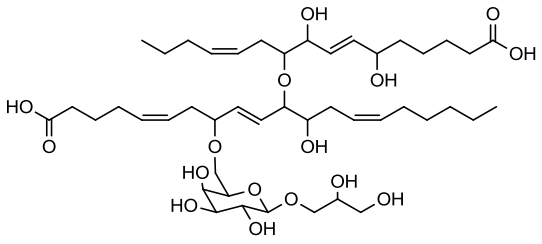
2. CHAPTER TWO

Progress Towards the Total Synthesis of Nigricanoside A

2.1. Introduction and Background

Nature has proven a reliable source for new and successful anticancer drugs.[1] In fact, a recent study revealed that 64% of anticancer drugs introduced in the last 25 years are either natural products or can be traced back to a natural product source.[2] But supplies of these desired small molecules may be limited, and in these cases, total synthesis of natural products represents an invaluable tool to facilitate biological testing and structural characterization. In this context, we were intrigued by the discovery of nigricanoside A (**1**), a very potent antimitotic natural product that was isolated in extremely low abundance.[3] The compound's limited availability has prevented full evaluation of its toxicity. Thus in view of its scarcity, interesting biological activity, and unique structure, nigricanoside A represents a perfect candidate for chemical synthesis. The ether-linked subunits and twelve unknown stereocenters of **1** present a great synthetic challenge, but currently, total chemical synthesis provides the only means of generating nigricanoside A in sufficient quantities. Accordingly, we designed a convergent synthetic route that would accommodate these stringencies, and presented in this Chapter is an account of our advances towards the total synthesis of nigricanoside A.

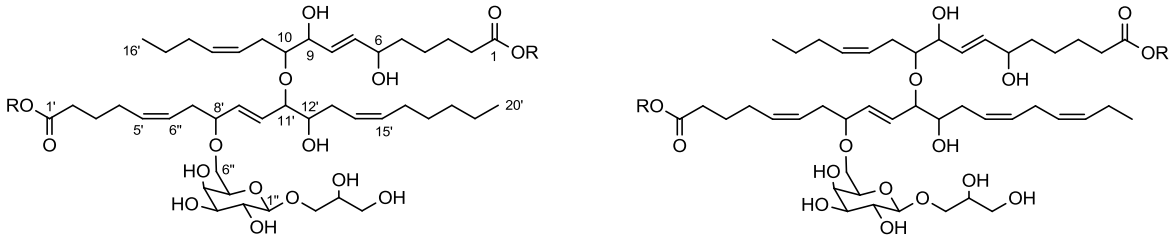


1: Nigricanoside A

2.1.1. Nigricanosides: Isolation and Structural Characterization

In 2000, Anderson and coworkers reported the use of a newly developed sensitive, cell-based assay that detects antimitotic activity in crude natural product extracts.[4] The assay proved especially useful for the discovery of agents present in very low abundance; a screen of over 24,000 extracts from various organisms identified 119 positive samples, many of which were not detected using other methods. In particular, an extract originating from tropical green alga *Avrainvillea nigricans* showed especially high activity, and in 2007, the group disclosed the isolation and structural elucidation of the active compounds, nigricanosides A (**1**) and B (**3**).[3] The isolation and structural characterization of the nigricanosides proved to be an arduous task. The initial algal collection from shallow reefs near Dominica delivered the active components in insufficient quantities for structural analysis. Even following an eight year endeavor of sample collection and pooling, the Anderson group was unable to isolate the naturally occurring diacids (**1** and **3**) themselves. Ultimately, methylation of the antimitotic fractions with CH_2N_2 enabled the group to isolate the nigricanoside A and B methyl esters (**2** and **4**, Figure 2.1.1), albeit in sub-milligram quantities (800 μg and 400 μg, respectively). Using purified samples, further assessment of nigricanoside A's antimitotic activity confirmed its potency, but subsequent attempts to isolate the natural product over the following five-year period proved unsuccessful.

Figure 2.1.1 Nigricanosides A and B and their Corresponding Dimethyl Esters



1: Nigricanoside A: R = H
2: Nigricanoside A dimethyl ester: R = Me

3: Nigricanoside B: R = H
4: Nigricanoside B dimethyl ester: R = Me

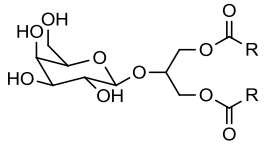
With less than 800 μg of **2**, the use of sensitive cryoprobe-assisted NMR techniques allowed the structural elucidation of its carbon skeleton. Nigricanoside A contains an unusual ether linkage joining the 16-carbon and 20-carbon oxidized fatty acid subunits (abbreviated C_{16}FA and C_{20}FA, respectively). The connectivity between these two subunits was assigned by HMBC correlations. Another set of HMBC correlations identified a second ether bond linking C-8' of the C_{20}FA to C-6'' of a hexapyranose ring, which in turn was assigned as galactose through the use of ROESY correlations and proton coupling constants. In addition, analysis of relevant proton coupling constants indicated that glycerol and galactose were connected by a β-glycosidic linkage. Unfortunately, the scant μg quantities of isolate proved

inadequate for complete stereochemical analysis; thus the absolute and relative configurations of nigricanoside A's twelve stereocenters remain unresolved.

2.1.2. Structurally Related Natural Products

The structure of nigricanoside A resembles that of monogalactodiacylglycerols (MGDG's, **5**, Figure 2.1.2), which constitute the majority of galactolipids found in chloroplast membranes of higher plants and alga.[5] MGDG's are comprised of a galactose and anomeric glycerol moiety, but in general, the remaining hydroxyl groups of glycerol are connected to unsaturated fatty acids through ester linkages. Nigricanoside A possesses the fundamental components of algal galactolipids, but in contrast, incorporates the fatty acid subunits through *ether* bonds. Moreover, this unusual connectivity leaves two free hydroxyl groups on the glycerol portion of the molecule; one of the ether-bonds links the two fatty acids while the other adjoins galactose to the C_{20}FA.[3] Thus the unprecedented architecture of **1** represents a new class of glycoglycerolipids.

Figure 2.1.2 General Structure of Monogalactodiacylglycerols



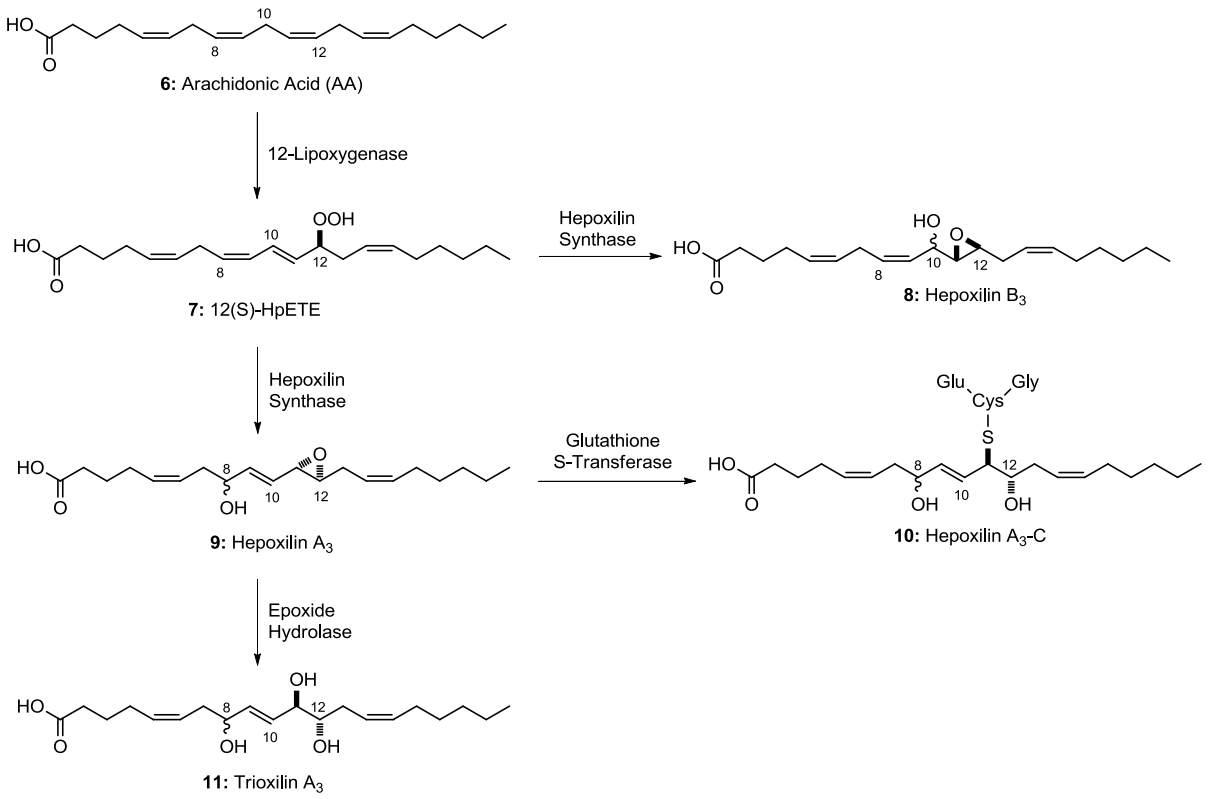
5: monogalactodiacylglycerol (MGDG)

While the C_{16}FA subunit is not known to exist apart from the nigricanosides, the C_{20}FA triol, or trioxilin A_3 (**11**), is a known natural product previously isolated from rat liver and other mammalian tissues (Figure 2.1.3).[6] This compound, along with its biologically active precursor hepoxilin A_3 (**9**),[7] are metabolites of arachidonic acid (**6**) in the 12-Lipoxygenase pathway.[8] In mammals, 12-lipoxygenase mediates the oxidation of arachidonic acid to the corresponding peroxide, 12(S)-HpETE (**7**). This allylic hydroperoxide, in turn, rearranges to form epoxy alcohol **9** and hepoxilin B_3 (**8**). The intramolecular isomerization is facilitated by the iron porphyrin-containing hepoxilin synthase and produces **8** and **9** as mixtures of epimers at C-10 and C-8, respectively. Finally, enzymatic hydrolysis of the reactive allylic epoxide in **9** generates the triol moiety in trioxilin A_3 (**11**).[7]

Although no ether-containing analogues of trioxilin A_3 have been reported, the biologically active *thioether* conjugate of hepoxilin A_3, hepoxilin A_3-C (**10**), was previously discovered in rat hippocampal tissue.[9] Inhibition of hepoxilin A_3 hydratase causes hepoxilin A_3 metabolism to occur through the glutathione *S*-transferase pathway, and as shown in Figure 2.1.3, the consumption of **9** by this enzyme results in the production of hepoxilin A_3-C. In this way, glutathione *S*-transferase catalyzes the

addition of the cysteine derivative, glutathione, to the epoxide moiety of hepoxilin A_3 forming the glutathione conjugate (**11**).

Figure 2.1.3 Metabolism of Arachidonic through 12-Lipoxygenase Pathway



The structural resemblances between nigricanoside A and eicosanoids **9**-**10** present the possibility that the two fatty acid subunits of **1** derive from analogous epoxides in nature. Granted that the vast majority of known 12-lipoxygenase intermediates are of mammalian, not alga, origin, it is important to note that hepoxilin B_3 (**8**) has been isolated from marine red alga collected near Puerto Rico.[10] However, to the best of my knowledge, no other member of the trioxilins or hepoxilins has been discovered in algae or higher plants. Nonetheless, the biosynthetic considerations outlined above may provide insight into the potential stereochemistry of our target. Accordingly, a more detailed analysis of the twelve unknown stereocenters of nigricanoside A will be addressed in Section 2.4.1.

2.2. Biological Activities

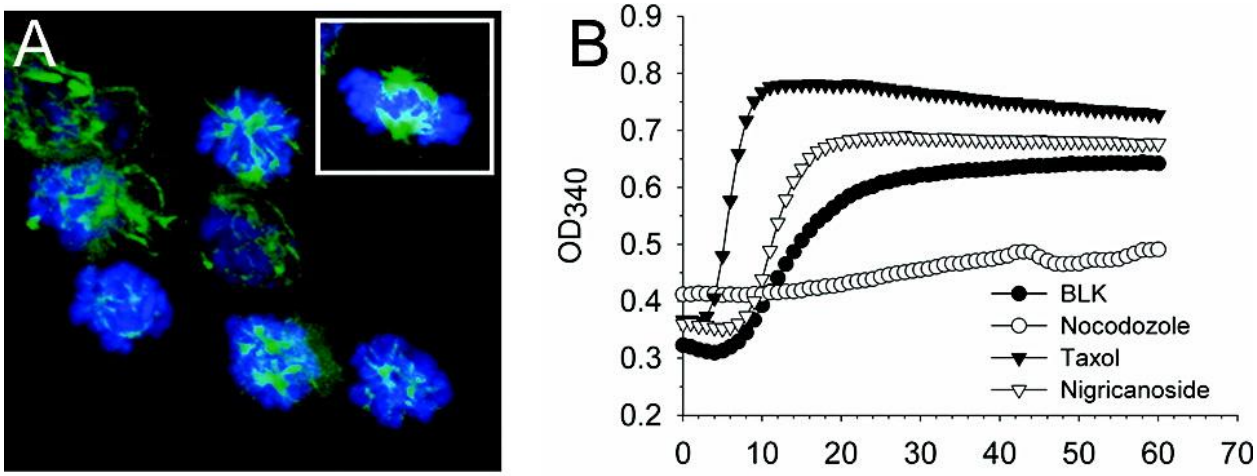
2.2.1. Biological Activities of the Hepoxilins

With respect to biological activity, hepoxilins A_3 and B_3 are among the most interesting natural products of the oxygenated arachidonic acid metabolites.[7] Both hepoxilins have been shown to enhance the release of insulin from rat pancreatic islets.[11] However, the C-8 epimers of hepoxilin A_3 have been demonstrated to effect a myriad of other biological actions and regulate a number of other processes as well. For instance, **9** is capable of modulating synaptic neurotransmission, raising cytosolic calcium levels in human neutrophils, and facilitating calcium transport across membranes. In addition, **9** was isolated from *Aplysia* (sea slug) neurons, on which it induced slow hyperpolarization.[12] The glutathione conjugate of hepoxilin A_3, HxA_3-C (**10**), exhibits similar biological activity as its biological precursor; for instance, **10** is known to function as a potent neuromodulator in rat brain hippocampus tissue.[9] The trioxilin series of 12-lipoxygenase intermediates are relatively inactive when compared to their multifunctional, biosynthetic precursors, the hepoxilins.[8]

2.2.2. Biological Activity of Nigricanoside A

While methylation of crude extracts facilitated isolation of the nigricanoside A methyl ester (**2**), the chemical modification apparently decreased the compound's antimitotic activity. This observation suggests that the parent dicarboxylic acid **1** is significantly more potent than the corresponding methyl ester **2**.[3] Initial biological assays demonstrated that **2** arrests human breast cancer MCF-7 cells and human colon cancer HCT-116 cells in mitosis with IC_{50} values of 3 nM. The saturated hydrocarbon structure of **2**, produced by hydrogenation of the five alkenes, displayed significant loss in antimitotic activity in both cell lines ($IC_{50} \approx 300$ nM). The nigricanoside A dimethyl ester elicited a distinct mitotic arrest phenotype, characterized by highly disorganized microtubule spindles as shown in Figure 2.2.1A. Moreover, an *in vitro* assay indicated that **2** induced the polymerization of tubulin at 10 μM, suggesting that the nigricanoside A methyl ester is a tubulin stabilization agent (Figure 2.2.1B). The difference in antimitotic activity from the *in vivo* (3 nM) versus *in vitro* (10 μM) experimental results may indicate that tubulin is not the sole or principle molecular target; however, the lack of sufficient quantities of **2** prevented additional biological studies.[3]

Figure 2.2.1 Effects of Nigricanoside A on Mitosis and Tubulin Polymerization[3]

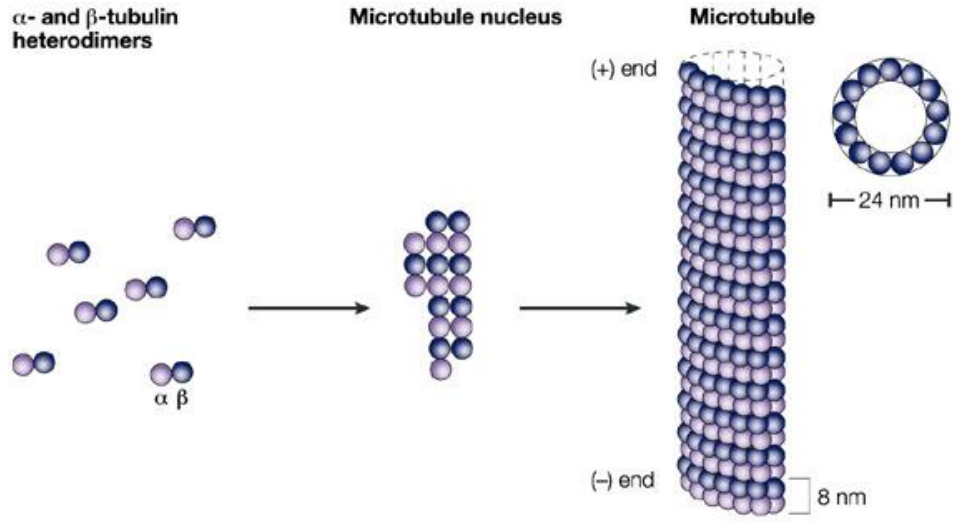


(A) Mitotic arrest phenotype elicited by nigricanoside dimethyl ester 3. Cells were exposed to 10 nM 3 for 20 h; microtubules were visualized by immunostaining (green) and DNA with Hoechst 33342 (blue). The inset shows a control metaphase cell. (B) Effect of 3 on tubulin polymerization at 37 °C. All compounds are 10 μM. X-Axis = Time (min). BLK = blank control. Figure reproduced from reference 3.

2.2.3. Antimitotic Natural Products

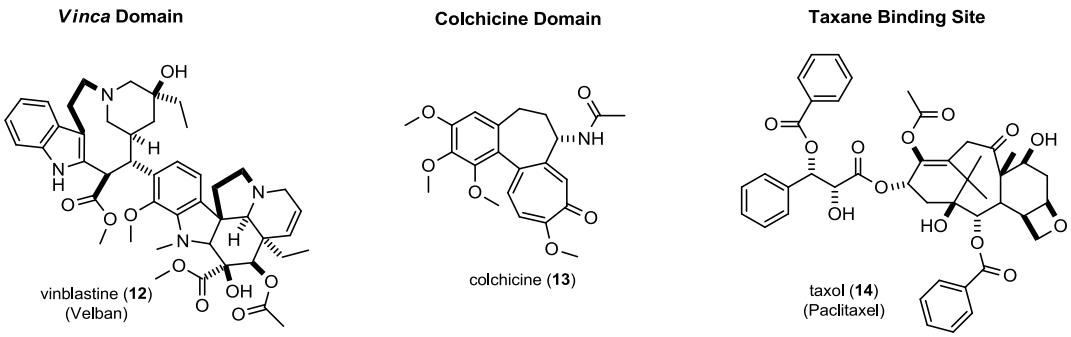
The majority of antimitotic agents arrest cells in mitosis by interfering with the dynamic stability of microtubules during various stages of cell division. The eukaryote cell cycle involves DNA replication, distribution of duplicated chromosomes to daughter cells, and cell division. Microtubules organize to form the highly dynamic mitotic spindle which separates the daughter chromosomes in mitosis. The rapid assembly and disassembly of microtubules through the polymerization or depolymerization of α- and β-tubulin heterodimers (Figure 2.2.2) is critical to cell division; interference with these cellular dynamics will block mitosis and cause cell death by apoptosis.[13] In this regard, the degree to which cancer cells quickly progress through mitosis may render them especially sensitive to antimitotic drugs that target tubulin polymers.[14]

Figure 2.2.2 Polymerization of Tublin Heterodimers into a Microtubule Filament[14]



Microtubules and their dynamics are popular targets for natural cytotoxins,[1, 15] but interestingly, the unique structure of nigricanoside A shares no resemblance to known antimitotic agents that target tubulin. The three characterized binding sites of tubulin agents are the *Vinca* alkaloid, colchicine (**13**), and taxane domains. In general, antimitotic agents cause mitotic arrest by obstructing the assembly or disassembly of α- and β-tubulin into microtubules (Figure 2.2.2). Compounds that target the *Vinca* or colchicine domain are known as microtubule-destabilizing agents because they inhibit microtubule polymerization at high concentrations. This class of drugs includes the clinically important *Vinca* alkaloids vinblastine (**12**), vincristine, and vinorelbine.[16] Conversely, natural products that compete for the taxane binding site are characterized as microtubule-stabilizing agents; they cause bundling of microtubules at high concentrations by stimulating tubulin polymerization. Taxanes paclitaxel (**14**) and docetaxel operate through this pathway and have found widespread use for the clinical treatment of cancer.

Figure 2.2.3 Representative Microtubule-Targeted Agents



Low concentrations of *Vinca* alkaloids,[16] colchicine,[17] or taxanes[18] are sufficient to block mitosis without the dramatic effects of microtubule depolymerization or bundling. Slight alterations in growth or shortening interfere with the sensitive polymerization dynamics of microtubules and the cells arrest in mitosis; prolonged arrest leads to apoptosis.[14] Therefore, proliferation of cancer cells may be inhibited at antimitotic concentrations significantly lower than those necessary to display the macroscopic effects observed in tubulin-targeted assays. A similar process may account for the difference in concentration of **2** necessary to promote polymerization of tubulin *in vitro* and mitotic arrest in cells; however, a discrepancy of this magnitutde (>1000 fold) would be unprecedented. The possibility exists that the interaction with tubulin is an artifact. Furthermore, cells treated with **2** may concentrate the compound and display characteristics that mimic higher potency. More intriguing, nigricanoside A may target a complex of microtubules and associated proteins or disrupt cellular dynamics through a novel mode of action. Future experiments will rely on the availability of the natural product, which will likely be obtained from chemical synthesis.

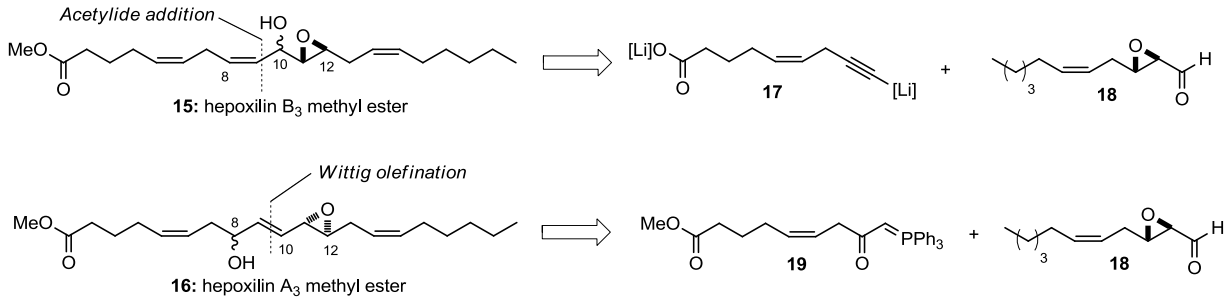
2.3. Prior Synthetic Work towards the Hepoxilins and Trioxilins

Despite the unique architecture and interesting biological activity of nigricanoside A, no synthetic studies of the natural product have been published to date. However, due to the interesting biological activities of the various arachidonic acid metabolites, *i.e.* the hepoxilins and trioxilins, several groups have published syntheses of these eicosanoids. This section will summarize the substantive synthetic studies towards the hepoxilins and trioxilins from the laboratories of E.J. Corey, J.R. Falck, and J.S. Yadav. It is worth reasserting that these natural products bear three stereocenters, one of which exists as the epimeric mixture in nature (Figure 2.1.3). Thus the *epi*-C(8)-hydroxyl of the the A_3 series and the *epi*-C(10)-hydroxyl of the B_3 series of hypoxilins and trioxilins are the most common synthetic targets.

2.3.1. Synthetic Studies by Corey and Coworkers

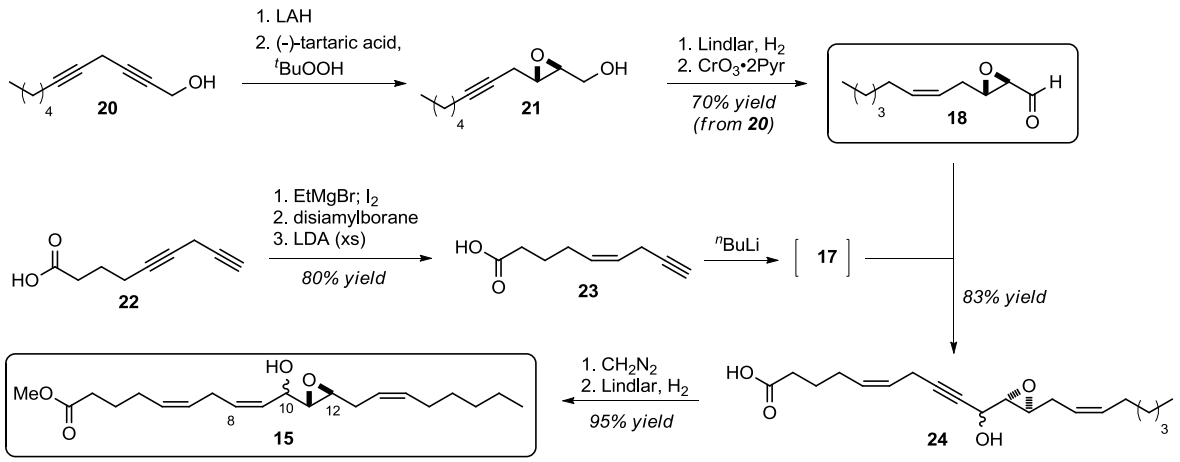
E.J. Corey's laboratories showed the earliest synthetic interest in metabolites of arachidonic acid and were thus the first to synthesize the methyl esters of hepoxilins A_3 and B_3, **16** and **15**, respectively. The group's convergent strategy is outlined in a brief retrosynthetic analysis below (Scheme 2.3.1). The asymmetric total syntheses of **15** and **16** both exploit the optically active epoxy aldehyde retron **18**. This approach allows for the C9—C10 bond of **15** to be formed through an acetylide addition to **18**, and the *E*-olefin in **16** to be prepared through a Wittig olefination. Furthermore, to emphasize the flexibility of this strategy, epoxide **18** represents an important intermediate in Corey's synthesis of various leukotrienes as well.[19]

Scheme 2.3.1 Retrosynthetic Analysis of Hepoxilin A_3 and B_3 from the Corey Lab



Corey and coworkers reported the asymmetric synthesis of hepoxilin B_3 in 1983. The preparation of the common aldehyde intermediate commenced with diyne **20**,[20] which afforded the corresponding allylic alcohol upon reduction with LAH (Scheme 2.3.2).[21, 22] The two relevant stereocenters of hepoxilin B_3 (and hepoxilin A_3) were configured through an early stage Sharpless asymmetric epoxidation. Of note, the authors report the optical rotation value of **21** and but the percent enantiomeric excess is not included. A partial reduction of the alkyne in **21** followed by a Cr-mediated oxidation furnishes the desired aldehyde **18**.

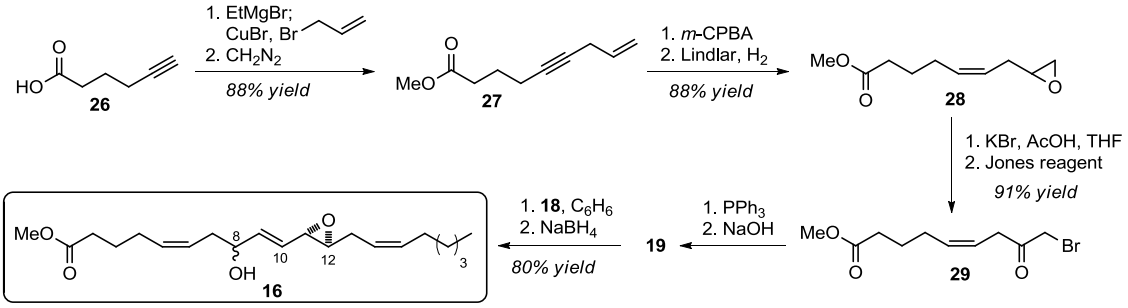
Scheme 2.3.2 Synthesis of Hepoxilin B_3 Methyl Ester



The synthesis of the alkyne coupling partner (**23**) was carried out from 5,8-nonadiynoic acid **22** (Scheme 2.3.2).[23] Deprotonation of **22** with EtMgBr generated the corresponding magnesium dianion, which was quenched with iodine to give 9-iodo-5,8-nonadiynoic acid. Selective hydroboration of the internal alkyne with disiamylborane followed by elimination of iodide with LDA produced enyne **23** in 80% yield. The corresponding lithium dianion of **23** was added to **18**, yielding propargylic alcohol **24** as a mixture of 10-(R/S)-diastereomers. Finally, treatment of **24** with diazomethane, followed by exposure to H_2 in the presence of Lindlar catalyst presented the methyl ester of hepoxilin B_3 (**15**) in 95% yield.

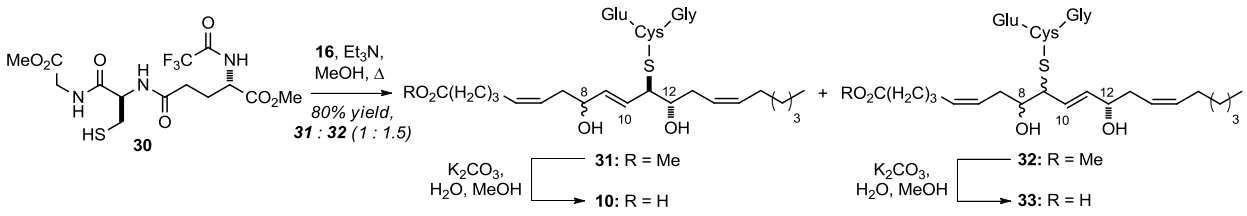
Corey's laboratory completed the enantioselective synthesis of hepoxilin A_3 in 1984. With ready access to **18**, comprising over one half of the natural product's carbon structure, Corey's synthesis of **16** focused on the preparation of the phosphonium ylide coupling partner (**19**, Scheme 2.3.1). In the forward sense, the synthetic route begins with commercially available hexynoic acid **26**, from which the enyne methyl ester **27** is prepared in two steps and 88% yield (Scheme 2.3.3).[24] The terminal olefin in **27** was epoxidized by reaction with *m*-CPBA while the internal alkyne was partially reduced with Lindlar catalyst and H_2. The resulting monosubstituted epoxide (**28**) was opened regioselectively with potassium bromide, and subsequent oxidation of the resulting bromohydrin afforded bromo ketone **29** in 91% yield. The stabilized ylide **19** was pre-formed by treatment of **29** with sodium hydroxide, and this reagent was isolated and reacted with aldehyde **18** to generate the corresponding enone. The ketone was reduced smoothly with sodium borohydride to present the C-8 epimers of methyl ester **16**.

Scheme 2.3.3 Synthesis of Hepoxilin A_3 Methyl Ester from the Corey Group



As mentioned previously, the 11-(R)-glutathione thiol conjugate (**10**) of hepoxilin A_3 shares biological activity with its precursor in some systems. As such, in 1990 the Corey group successfully synthesized **10** from the methyl ester (**16**) of its biological precursor. In this way, the dimethyl ester of *N*-trifluoroacetylglutathione (**30**) was reacted with **16** in methanol-triethylamine (4 : 1) to produce a mixture of 11-(R)-thioether conjugate **31** and two 9-(R)- and 9-(S)-thioether conjugates (**32**) in a ratio of 1 : 1.5, respectively.[25] Compound **31** was obtained as the 11-(R)-stereoisomer.

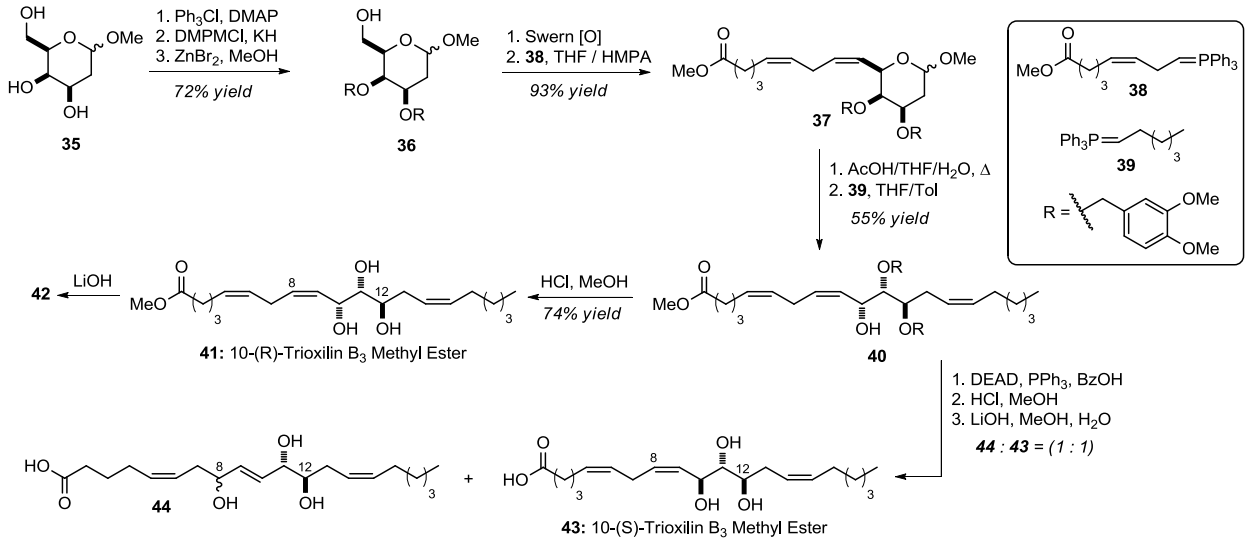
Scheme 2.3.4 Preparation of Hepoxilin A_3 Conjugates with Glutathione



2.3.2. Synthetic Studies by Falck and Coworkers

The group of J.R. Falck reported the first asymmetric total synthesis of trioxilin B_3 (**42**) in 1988. In contrast with Corey's approach, Falck and coworkers utilized naturally occurring D-galactose as a source of chirality. In this way, methyl pyranoside **35** was prepared from commercially available 2-deoxy-D-galactose in 88% yield (Scheme 2.3.5).[26] Compound **35** was converted to **36** by selective primary tritylation, protection of the secondary alcohols with 3,4-dimethoxybenzyl chloride (DMPMCl), and subsequent detritylation with $ZnBr_2$. Swern oxidation of **36** and reaction of the resulting aldehyde with phosphorane **38** furnished the *Z*-olefin **37** in 93% yield. Acidic hydrolysis of **37** generated the corresponding lactol, and this compound was treated with **39** to afford a mixture of 14-(*Z*)- and 14-(*E*)-olefins, with **40** representing the major product in 55% yield. Deprotection of the secondary alcohols with HCl in MeOH presented the methyl ester of 10-(R)-trioxilin B_3 (**41**).

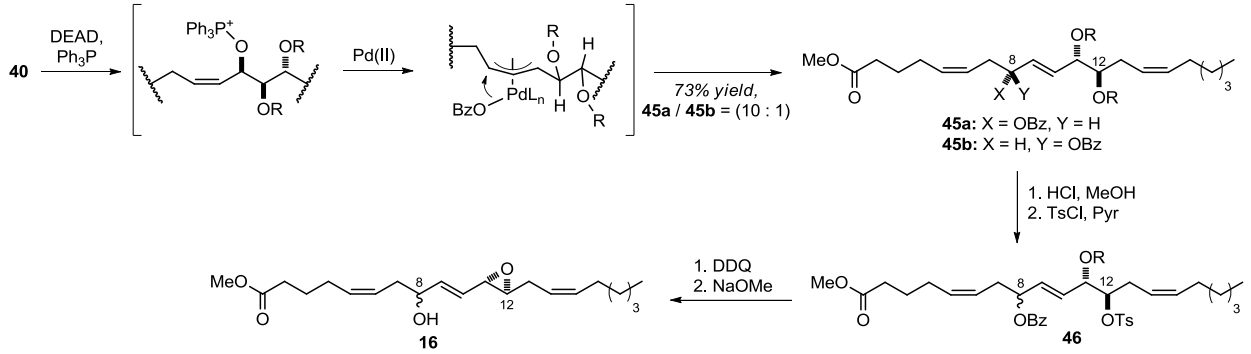
Scheme 2.3.5 Falck Group Synthesis of Trioxilin B_3



While attempting to prepare 10-(S)-trioxilin B_3 (**43**), Falck and coworkers serendipitously discovered methods for the interconversion of trioxilin B_3 to the enantiomer of trioxilin A_3 (**44**) through allylic transposition. To this end, a Mitsunobu inversion of **40** with benzoic acid followed by global deprotection generated the desired **43** in 30% yield. Unexpectedly, triol **44** was obtained as a near 1:1 mixture of 8(R)- and 8(S)-epimers. The group improved the selectivity of the allylic transposition by developing a Pd-mediated allylic Mitsunobu displacement reaction.[27] In this regard, subjecting **40** to Mitsunobu conditions in the presence of catalytic $PdCl_2(CH_3CN)_2$ resulted in the near exclusive formation of **45a** and **45b** in 73% yield (Scheme 2.3.6). The authors invoked a mechanism involving the interception of the initially-formed oxyphosphonium intermediate by palladium to generate a π-allyl

complex. A subsequent inner-sphere, *cis*-addition of benzoate to C-8 generates the observed major diastereomer. The methyl ester of hepoxilin A_3 is accessible from **45a** as depicted in the scheme below. This transformation involves selective deprotection of the C-12 benzyl ether followed by tosylation (no yields given), oxidative cleavage of the C-11 DMPM ether, and sodium methoxide-induced epoxide formation and benzoate removal.

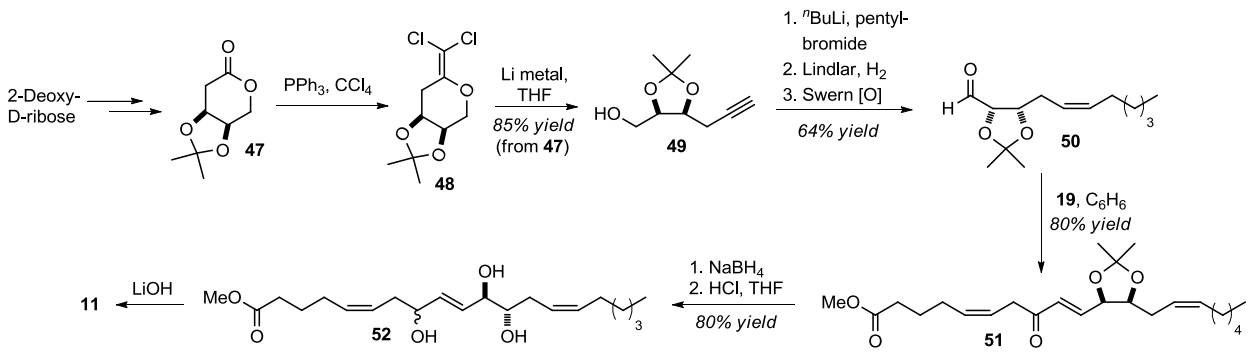
Scheme 2.3.6 Synthesis of Hepoxilin A_3 Methyl Ester from the Falck Group



2.3.3. Synthetic Studies Yadav and Coworkers

Yadav and Vadapalli reported the asymmetric synthesis of trioxilin A_3 in 1994. The authors' strategy involved the use of D-ribose from the chiral pool. Thus lactone **47** was obtained from 2-deoxy-D-ribose in two steps, and subsequent dichloromethylenation produced **48** in 85% yield (Scheme 2.3.7).[28] Exploiting methodology developed in Yadav's laboratory, **48** was reacted with lithium metal and through a reductive elimination process afforded terminal alkyne **49**. The lithium acetylide of **49** was alkylated with pentyl bromide, and the resulting product was subjected to a Lindlar reduction and Swern oxidation to furnish aldehyde **50** in 64% yield. The subsequent Wittig olefination of **50** and sodium borohydride reduction of **51** are similar to those employed in Corey's hepoxilin A_3 synthesis.[24] Finally, acetonide deprotection and saponification with lithium hydroxide afforded trioxilin A_3 (**11**).

Scheme 2.3.7 Synthesis of Trioxilin A_3 from Yadav Group

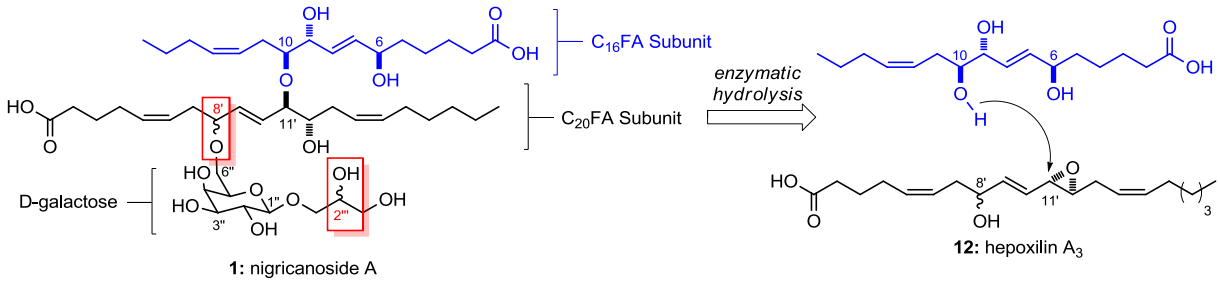


2.4. Synthesis of the Nigricanoside A Subunits and Etherification Attempts

2.4.1. Stereochemical Analysis

The total synthesis of nigricanoside A (**1**) provides the sole means of accessing the natural product in sufficient quantities for biological testing. However, the chemical synthesis of **1** represents a formidable task; indeed, with 12 unassigned stereocenters, choosing the correct target from the 4,096 possible configurations is challenging and unlikely. Thus a discussion of our strategy to simplify the number of possible diastereomeric targets through stereochemical analysis deserves attention. The Andersen group identified the hexapyranose residue as β-galactose, the D-configuration of which is present in all galactose-containing glycoglycerolipids isolated to date. Based on this and the fact that only one natural product with an L-galactose moiety has been isolated from algae, we may safely assume the sugar of the D-configuration (Figure 2.4.1).[29] This assignment reduces the number of unknown stereocenters to seven, as both the (R) and (S)-configurations of the C-2''' stereocenter in the glycerol portion of **1** are possible.[30] As mentioned previously, a similar C_{20}FA (trioxilin A_3, **11**) and its biogenetic precursor epoxide, hepoxilin A_3 (**9**), have been isolated from various mammalian tissues. Furthermore, in rat brain homogenates, glutathione *S*-transferase catalyses the epoxide opening of **9** to produce thioether HxA_3-C (**10**, Figure 2.1.3). The eicosanoids of discussion are natural C-8' epimers, but the possibilty exists that the absolute and relative configurations of the C-11' and C-12' stereocenters of nigricanoside A are established from an analogous enzymatic process show below (Figure 2.4.1).

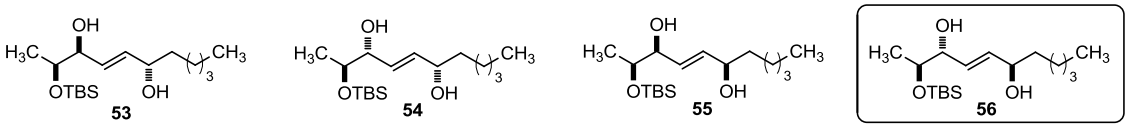
Figure 2.4.1 Proposed Stereochemistry of nigricanoside A



Importantly, the same 1,2,5-trihydroxy-3-alkene subunit appears in the C_{16}FA subunit, which, like the *anti*-1,2-diol in trioxilin A_3, may be derived from enzymatic hydrolysis of a *trans*-epoxide. Investigations from Professor John MacMillan's group at UT Southwestern support this hypothesis.[31] MacMillan and postdoctoral fellow Ana Paula Espindola synthesized model compounds **53**-**56**, representing the four possible diastereomers of the C_{16}FA of nigricanoside A (Figure 2.4.2). The four diastereomers displayed substantial differences in the ^{1}H and ^{13}C NMR spectra, and comparison of ^{1}H

coupling constants and ^{13}C chemical shifts of **53**-**56** to the natural product indicated that **56** was a clear match to the C_{16}FA. Therefore, they assigned an *anti-anti* relationship to the C6/C9/C10 stereotriad of the C_{16}FA. With these data, along with the biosynthetic considerations, the number of nigricanoside A diastereomers may be reduced to 8 possibilities. This number is based on the unknown configurations of C-8'and C-2''', outlined in red (Figure 2.4.1), in addition to the two possible enantiomers of the C_{16}FA. The stereocenters of the C_{16}FA and of C-11' and C-12' are assigned tentatively in the representation of **1** in Figure 2.4.1.

Figure 2.4.2 1, 2, 5-Triol Model Compounds Prepared by MacMillan Laborator[31]

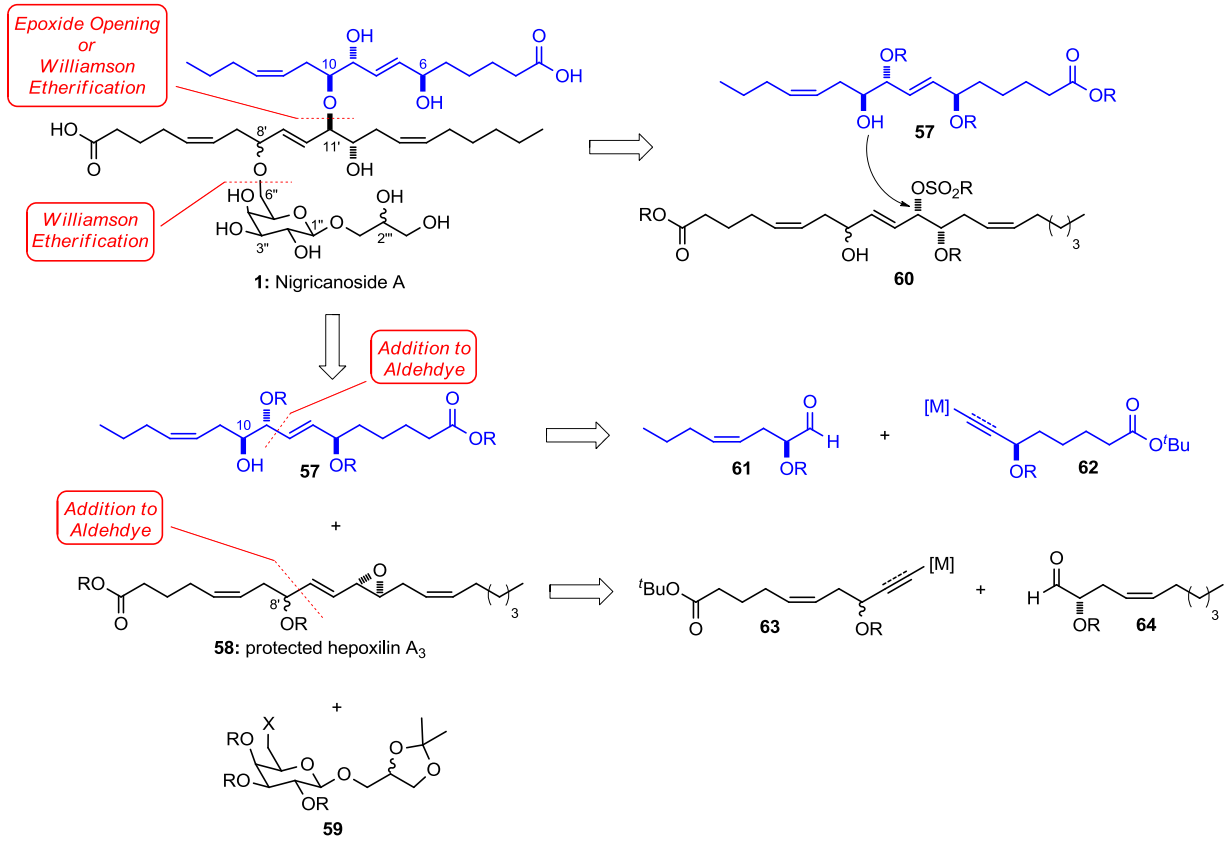


2.4.2. Synthetic Strategy

To provide access to all diastereomers, we designed a convergent synthetic route to the natural product (Scheme 2.4.1).The C_{16} and C_{20} fatty acid (FA) subunits will be joined through etherification; we envisioned the addition of alcohol **57** to an activated allylic position such as that of epoxide (**58**) or that of an allylic sulfonate (**60**). Similarly, the galactose ring will be appended through substitution of primary electrophile **59** with the free C_{20}FA hydroxyl. To maximize flexibility, each fatty acid subunit will be prepared from the convergence of two simple, chiral building blocks; that is, the addition of vinyl metal reagents (**62** and **63**) to α-hydroxy aldehydes (**61** and **64**).

The stereochemistry of the fatty acids will be dictated by a) the stereochemistry of the α-hydroxy aldehyde, b) the stereochemistry of the vinyl metal reagent, and c) the diastereoselectivity of the aldehyde addition reaction. Therefore, by choice of starting materials and reaction conditions (chelate vs. non-chelate control) we will have access to all possible diastereoisomers of the natural product. The stereocenters in the aldehyde and alkyne coupling partners will be configured through asymmetric, catalytic methods that allow access to all possible enantiomers. Importantly, the approach in Scheme 2.4.1 will require orthogonal protection of the numerous hydroxyl groups in **57**-**64** and esters in **57** and **58**; the requisite C-10 (**57**) and C-8' (**58**) free hydroxyls will be unmasked at different stages of the synthesis for the key ether-bond formations. The flexibility of our strategy is exemplified in the schemes below, which outline the preparations of the optically active starting materials as well as the complete syntheses of the C_{16}FA and C_{20}FA subunits themselves. This will be followed by a more in-depth discussion of our choice of protecting groups.

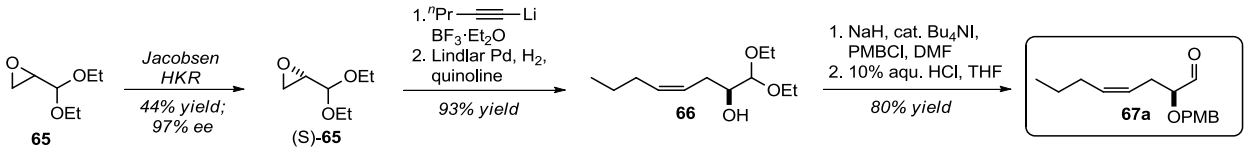
Scheme 2.4.1 Retrosynthetic Analysis of Nigricanoside A



2.4.3. Synthesis of Orthogonally-Protected C_{16}FA Subunit

The optically pure aldehyde (**67a**, Scheme 2.4.2) portion of the C_{16}FA subunit (**57**) is derived from the kinetically resolved diethyl acetal of glycidal (**65**).[32, 33] The epoxide was opened with the lithium acetylide of 1-pentyne in the presence of BF_3•OEt_2,[34] and the resulting alkyne was partially hydrogenated with Lindlar's catalyst poisoned with quinoline. PMB-protection of the secondary alcohol (**66**) and hydrolysis of the diethyl acetal furnished α–hydroxy aldehyde **67a** in 74% overall yield.

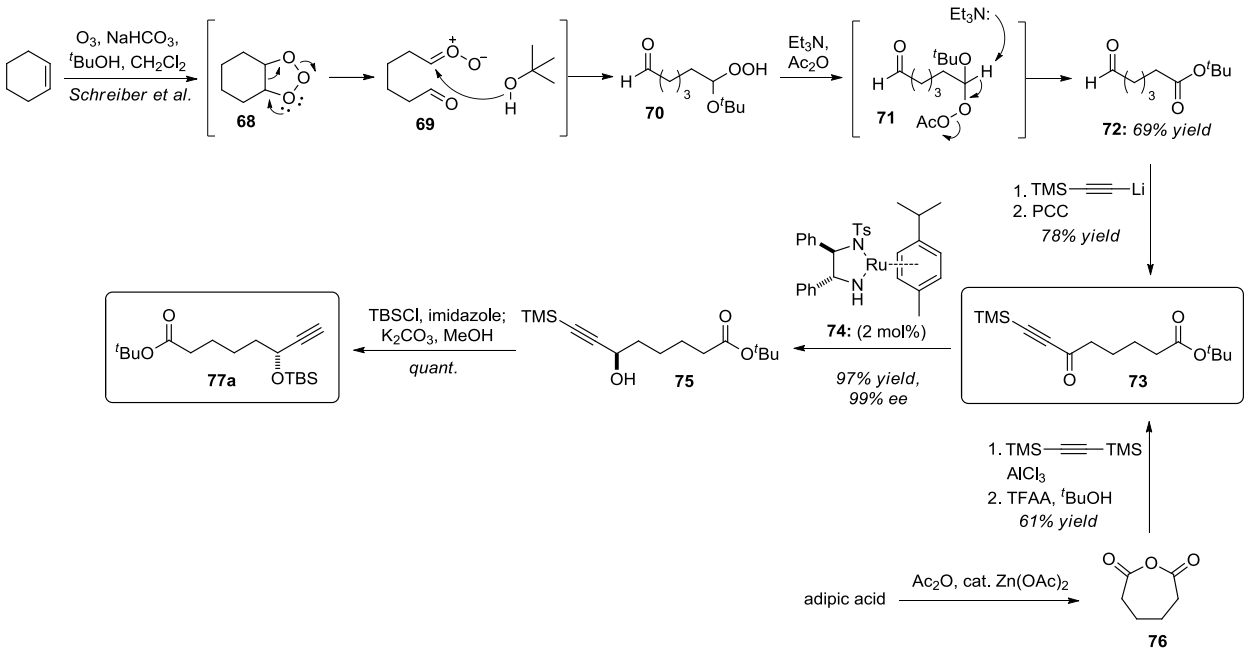
Scheme 2.4.2 Synthesis of Nigricanoside A C_{16}FA Aldehyde



The stereocenter of compound **77a**, the alkyne portion of the C_{16}FA adduct, is established by a Noyori reduction of ynone **73**, which produces propargylic alcohol **75** in high yield with > 99% ee (Scheme 2.4.3).[35, 36] Subsequent TBS-protection and TMS-acetylene solvolysis affords the alkyne

coupling partner (**77a**) in high yield. The requisite ynone **73** may be prepared by two methods of equal efficiency. The first approach involves ozonolytic cleavage of cyclohexene to terminally differentiated aldehyde ester **72**, as reported by Shreiber *et al*.[37] In this way, the carbonyl oxide **69** is intercepted by solvent (^{t}BuOH) to form an aldehyde-alkoxy hydroperoxide species (**70**); subsequent acylation and dehydration forms the desired aldehyde-ester **72**. A simple alkyne addition and oxidation with PCC affords **73**. The second approach involves a Lewis acid-promoted addition of *bis*-TMS acetylene[38] to the adipic anhydride monomer (**76**).[39] Finally, the resulting free acid was admixed with TFAA to generate the corresponding mixed anhydride, which was subsequently protected as the *tert*-butyl-ester on cleavage with ^{t}BuOH.[40]

Scheme 2.4.3 Synthesis of Nigricanoside A C_{16}FA Alkyne

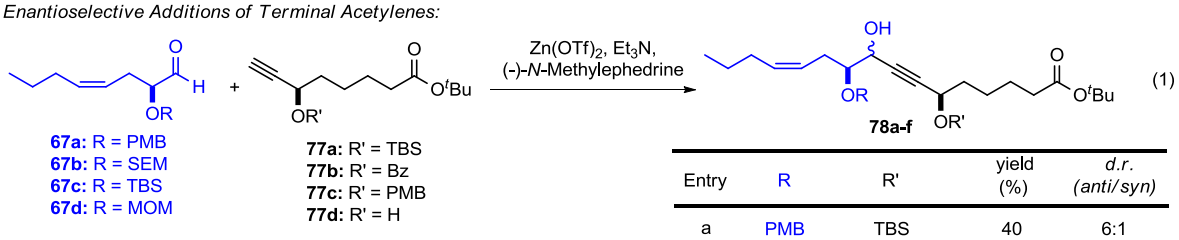


With ready access to protected α-hydroxy aldehydes (**67**) and their alkyne coupling partners (**77**), our next efforts focused on *anti*-selective additions of alkynyl metal reagents. To this end, we examined a number of protecting group schemes with respect to both the aldehyde and alkyne coupling partners. In general, additions of the lithium acetylides derived from **77** proceeded with poor selectivity,[41] while results from asymmetric alkynyl zinc additions to **67** were more promising (Scheme 2.4.4, eq. 1).[42, 43] For example, the addition of **77a** to **67a** in the presence $Zn(OTF)_2$ produced **78a** with a 6:1 ratio of *anti* to *syn* diastereomers, albeit in low yield (see table in Scheme 2.4.4, entry a). Both excellent yield and high selectivity were achieved with substrates **67c** (R = TBS) and **77c** (R' = PMB), which coupled to form compound **78d** in 96% yield as essential one diastereomer (entry d). The *anti*-selective reduction of

alkyne **78d** proved to be difficult; although treating **78d** with Red-Al at low temperatures provided **79d** in higher yields than other reducing agents (Scheme 2.4.4, eq. 2),[44] significant desilylation of starting material and product was observed under these conditions. Higher temperatures and longer reaction times resulted in higher conversion to the *E*-alkene with concommitant reduction of the ester moiety. Of note, the PMB- and MOM-protected homopropargylic alcohols, in **78a** and **78e**, respectively, survived the Red-Al reduction (eq. 3); however, either poor yields or lower selectivity in the alkynyl zinc additions (eq. 1) limited the efficiency of this synthetic route to **79**.

Scheme 2.4.4 Asymmetric Alkynyl Zinc Additions to α-Hydroxy Aldehydes

Enantioselective Additions of Terminal Acetylenes:

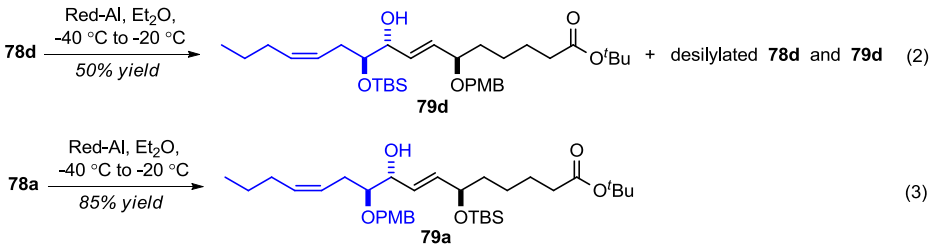


67a: R = PMB
67b: R = SEM
67c: R = TBS
67d: R = MOM

77a: R' = TBS
77b: R' = Bz
77c: R' = PMB
77d: R' = H

Entry	R	R'	yield (%)	*d.r. (anti/syn)*
a	PMB	TBS	40	6:1
b	SEM	Bz	0	NA
c	SEM	PMB	0	NA
d	TBS	PMB	96	> 25:1
e	MOM	PMB	72	5:1
f	MOM	H	85	7:1

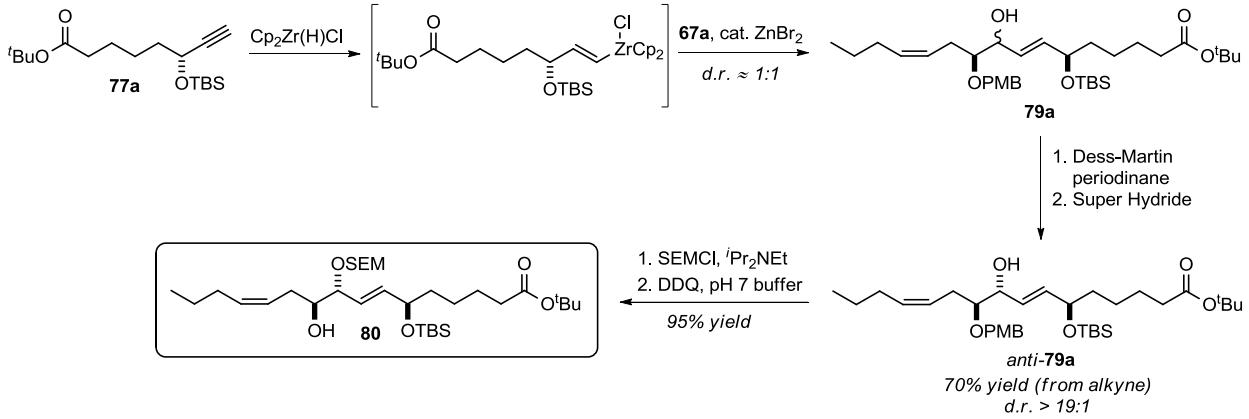
Stereoselective Reduction of Propargylic Alcohols:



Similarly, we investigated the diastereoselectivity of additions of alkenyl zinc reagents derived from the hydrozirconation of **77** (Scheme 2.4.5). Unfortunately, poor selectivity was observed in reactions with and without added chiral aminoalcohol or amino thiol ligands.[45] Eventually, this problem was solved with recourse to the oxidation/directed-reduction sequence outlined in Scheme 2.4.5. The reaction of **67a** with the corresponding vinyl zirconium derivative of **77a** produced **79a** as a near 1:1 mixture of diastereomers.[46] Fortunately, the chelating PMB-ether moiety in **79a** was sufficient to assist the Super Hydride-reduction of the corresponding enone, and the desired *anti*-**79a** was obtained with high selectivity (d.r. > 19:1).[47] The synthesis of an orthogonally protected analog of the nigricanoside A C_{16}FA

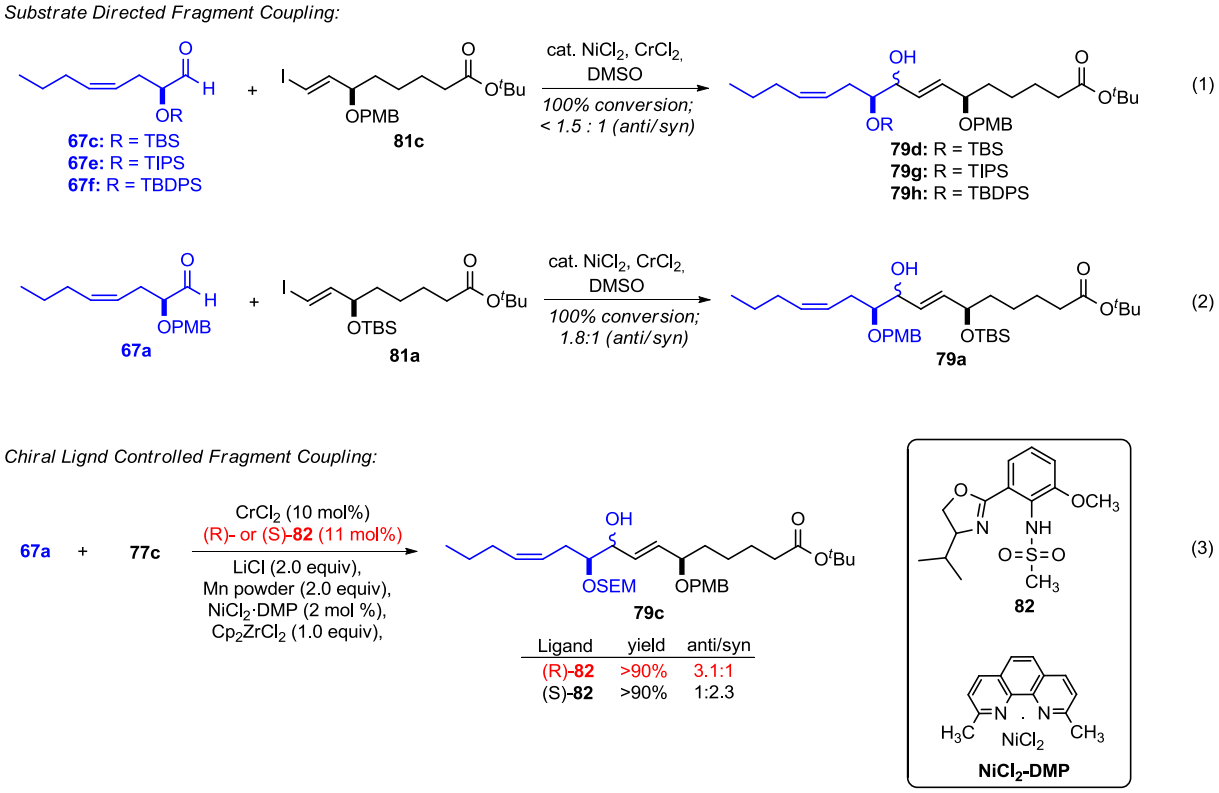
subunit (**80**) was completed following SEM-protection of the allylic alcohol in *anti*-**79a** and oxidative cleavage of the homoallylic PMB-ether. The free hydroxyl of compound **80** would serve as the nucleophile in the ensuing epoxide opening or nucleophilic displacement reactions.

Scheme 2.4.5 Synthesis of Nigricanoside A C_{16}FA



Moving forward, we needed to improve the diastereoselectivity of the coupling reactions. In particular, fragment coupling under Cr-mediated conditions presents a mild and selective alternative to the Zr-based chemistry. To this end, we examined the utility of Ni(II)/Cr(II)-mediated coupling reactions between **67** and vinyl iodides **81a** and **81c** (Scheme 2.4.6).[48] Under standard Nozaki-Hiyama-Kishi reaction conditions, in which an excess of $CrCl_2$ was employed, neither silyl-protected aldehydes (**67c, e**, and **f**, eq. 1) nor PMB-protected aldehyde **67a** (eq. 2) were sufficient to induce high diastereoselectivity in the organochromium(III) additions. Therefore we were curious whether we could layer reagent control on top of substrate control. Encouragingly, in preliminary experiments we found that sulfamate-based ligands (**82**, eq. 3) can yield either the *syn* or *anti* product (**79c**) selectively under conditions developed by Kishi and coworkers.[49] Three aspects of this experiment are important. First, the reaction is susceptible to catalyst control. Second, we appear to operating in a stereochemically matched regime (i.e. substrate control and catalyst control are reinforcing). Third, these additions are clean and high-yielding. In the future, we plan to complete structure-activity relationship studies regarding the effect of the ligand on the diastereoselectivity and use this methodology in the asymmetric synthesis of orthogonally protected **79**.

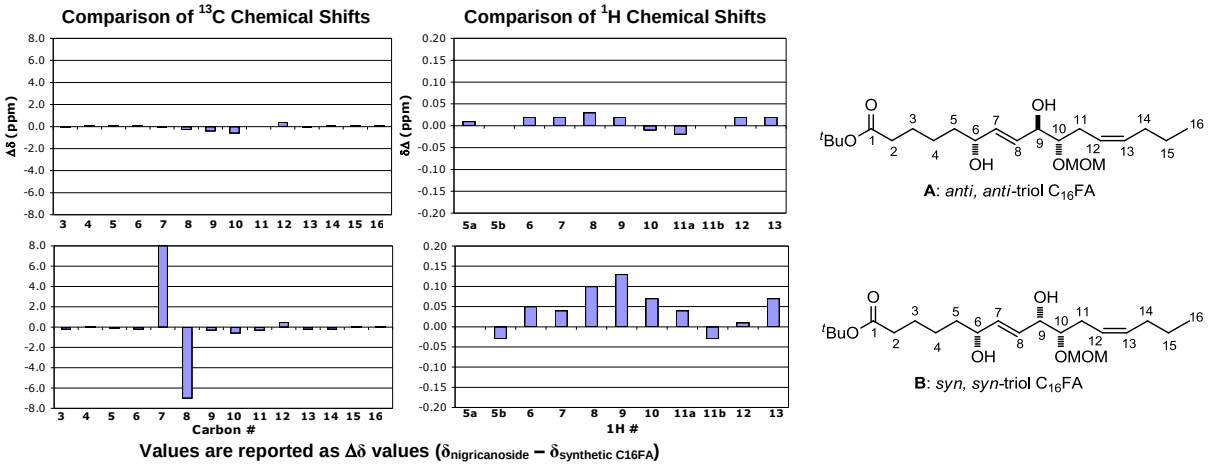
Scheme 2.4.6 Nozaki-Hiyama-Kishi Reactions



2.4.4. Comparisons of the Synthetic C_{16} FA to the Natural Product

Using a strategy similar to that described in Scheme 2.4.5, we prepared two diastereomers of the C_{16} oxidized fatty acid subunit of **2** (**A** and **B**, Figure 2.4.3) from MOM-protected α-hydroxy aldehyde **67d**. Although this protecting-group scheme proved impractical in our synthetic route, we speculated that a C-10 MOM-ether would model the ether linkage between the lipid portions of the natural product. We separated the C9-C10 *anti*- and *syn*-diols, **A** and **B**, respectively, and in collaboration with the MacMillan group, compared NMR data of these model compounds to the natural product.[31] The NMR spectra of the synthetic C_{16}FA revealed an excellent correlation with the C9-C10 *anti*-diol **A** and a poor correlation with its *syn* diastereomer (**B**) (Figure 2.4.3). The most dramatic differences between the two synthetic models were observed from the ^{13}C spectra; the C-7 and C-8 chemical shifts of **B** differed from those of **2** as much as 8.0 ppm. Of note, assignment of key ^{1}H NMR coupling constants was facilitated by the use of advanced homonuclear decoupling NMR experiments developed in the MacMillan laboratory.[50] These data are in complete accordance with previous results from the model studies of truncated C_{16}FA's **53-56** (Figure 2.4.2), and thus, our assignment of the *anti,anti*-C_{16}FA triol.

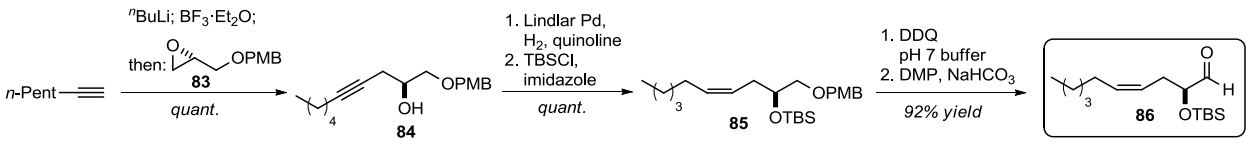
Figure 2.4.3 Comparison of NMR Data of Nigricanoside A to the Synthetic C_{16}FA Triols[31]



2.4.5. Synthesis of Orthogonally-Protected Hepoxilin A_3

With the *anti,anti*-triol **80** in hand, we commenced the synthesis of its epoxide coupling partner, an orthogonally protected analog of hepoxilin A_3 (Scheme 2.4.7). The optically active aldehyde (**86**) portion of the C_{20} fatty acid subunit was prepared similarly to that of the C_{16}FA. This compound is derived from enantioenriched PMB-protected glycidol (**83**), which is opened with the lithium acetylide of 1-heptyne under conditions identical to those described in Scheme 2.4.2. As outlined below, the TBS-protected α-hydroxy aldehyde **86** was prepared in 92% yield over five efficient, synthetic steps.

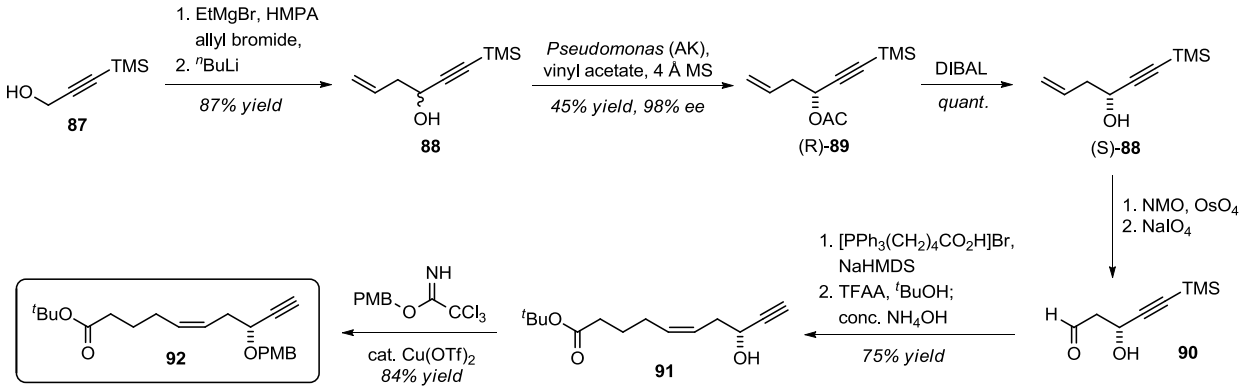
Scheme 2.4.7 Synthesis of Nigricanoside A C_{20}FA Aldehyde



Our route to the propargylic alcohol coupling partner **92** begins with 3-TMS-propargyl alcohol **87** which was allylated in the presence of HMPA as a cosolvent; unfortunately, little to no conversion is observed when HMPA is omitted. Upon treatment with ^{n}BuLi, the resulting allyl ether undergoes a 2,3-Wittig rearrangement to generate **88** in 87% yield over two steps.[51] Importantly, both enantiomers of **88** are easily accessed from a highly enantioselective, enzyme-catalyzed resolution of the corresponding racemate.[52] This strategy represents an ideal scenario for the synthesis of hepoxilin and trioxilin A_3 derivatives because these natural products exist as the C-8 epimers. To be consistent with the *anti, anti*-triol relative configuration of **80**, we otherwise arbitrarily employed the (R)-enantiomer of **89** in the following synthetic transformations. A two-step dihydroxylation and oxidative cleavage process formed the very unstable β–hydroxy aldehyde **90**. Thus, the aldehyde was exposed immediately to the

phosphonium ylide derived from commercially available $[PPh_3(CH_2)_4CO_2H]Br$ to generate the *Z*-olefin exclusively. In this regard, it is worth noting that the *cis*-selective Wittig olefination of **90** represents optimized conditions. Subjecting a PMB-protected analog of **90** to the olefination reaction led to a mixture of olefin isomers, while benzoyl- and silyl-protected aldehyde derivatives underwent facile β-elimination under the basic conditions. Therefore, the free β-hydroxyl of **90** was necessary to achieve high selectivity and yield.

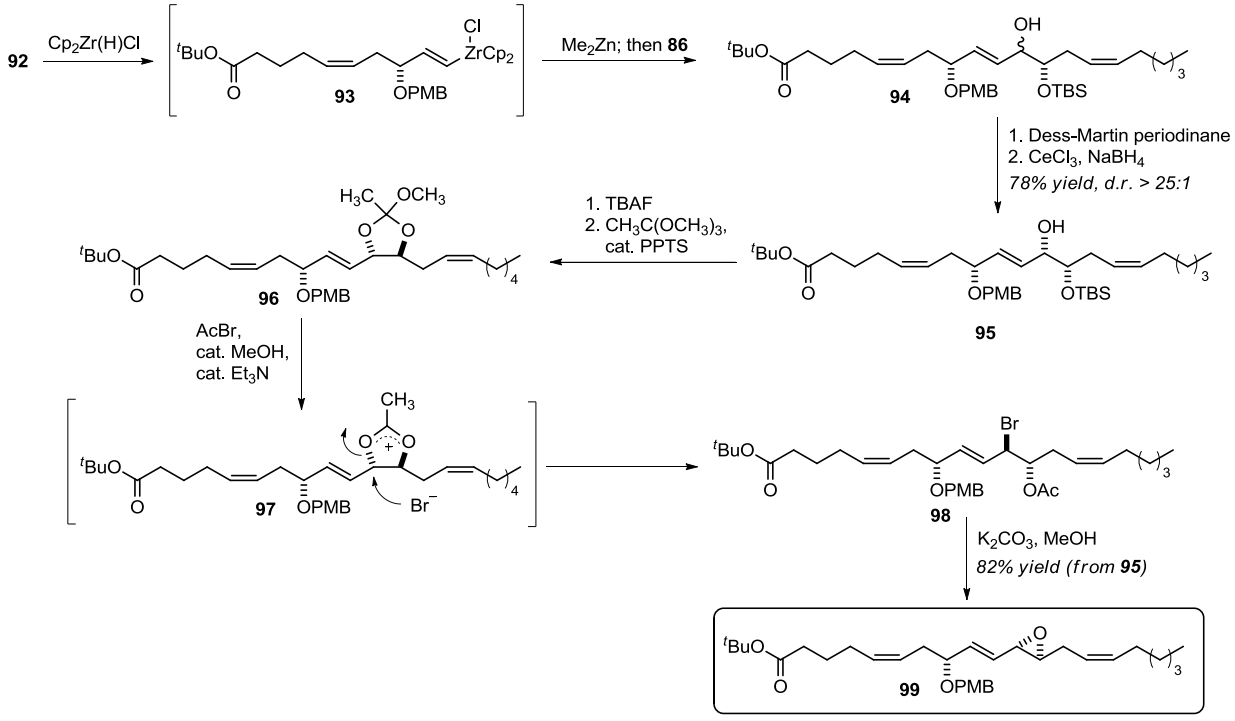
Scheme 2.4.8 Synthesis of Nigricanoside A C_{20}FA Alkyne



The free acid of the resulting Wittig adduct was protected selectively as the *tert*-butyl ester (**91**) in the presence of the free propargylic hydroxyl group.[53] This transformation was achieved by treating the crude reaction mixture with excess TFAA, presumably forming both the mixed anhydride and trifluoromethyl propargylic ester, the latter of which was hydrolyzed *in situ* on treatment with concentrated NH_4OH. Finally, the free propargylic alcohol (**91**) was treated with PMB-acetimidate in the presence of $Cu(OTf)_2$ to afford the protected alkyne coupling partner **92**.[54]

As expected, reacting the alkenyl zirconium derivative (**93**, Scheme 2.4.9) with aldehyde **86** in the presence of Me_2Zn proceeded with poor selectivity, yielding **94** as a mixture of diastereomers (3.3 : 1, *syn* / *anti*).[45] Therefore, compound **94** was oxidized to the corresponding enone and subjected to a *syn*-selective Luche reduction. In contrast to a Lewis basic PMB-ether, the bulky TBS-ether in **94** promotes the exclusive formation of the *syn*-1,2-diol diastereomer in **95**. The TBS-ether was removed with TBAF, and using a procedure developed by Kolb and Sharpless, the protected version of hepoxilin A_3 (**99**) was formed directly from the crude 1,2-diol in 82% yield (from **95**).[55] In this one-pot sequence, a cyclic orthoester (**96**) is formed initially by treatment with trimethyl orthoacetate; the volatiles are partially removed leaving the catalytic amount of methanol necessary to react with acetyl bromide. The generated HBr opens **96** to form acetoxy bromide **98**; this species may be isolated or treated directly with K_2CO_3 in MeOH to produce epoxide **99**.

Scheme 2.4.9 Synthesis of Hepoxilin A_3 Analog

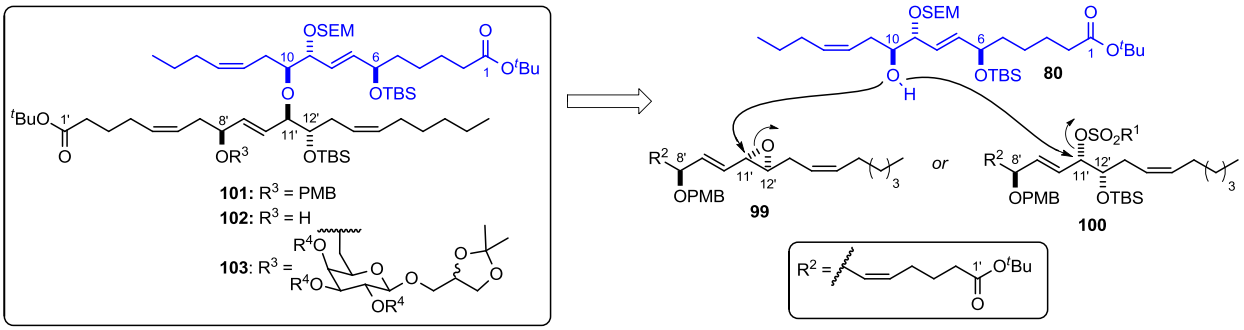


2.4.6. Orthogonal Protection of the Oxidized Fatty Acid Subunits

The previous sections introduce our synthetic approaches to the orthogonally-protected fatty acid subunits (**81** and **99**) of nigricanoside A. Therefore, at this juncture let us briefly review the reasons for our choice of protecting groups. The SEM-group at C-9 (**80**, Scheme 2.4.10) was chosen for these reasons: 1) SEM should be relatively stable under the Lewis acidic conditions required for epoxide opening. 2) In contrast with silyl ether and ester-protecting groups, the SEM group should not migrate to the neighboring alcohol under the basic conditions required for Williamson etherification. 3) SEM is small in size relative to other ethers, and 4), unlike the MOM variant SEM may be removed with fluoride.[56] In principle, the latter fact would allow for simultaneous deprotection of the C-9 SEM-, C-6 TBS-, and C-12'-TBS ethers of **103** in the final stages of our synthesis.

The major requirement for our choice of alkyl group for the C-1 and C-1' carboxylates involved the stability of the esters in the presence of Schwartz reagent. Although benzyl esters are known to survive hydrozirconation,[57] we observed significant reduction of the benzyl ester analog of **77a** under the conditions outlined in Scheme 2.4.5. Both TIPS- and *tert*-butyl esters were stable to $Cp_2Zr(H)Cl$, but not surprisingly, TIPS proved sensitive to acidic and basic hydrolysis. Additionally, the employment of *tert*-butyl esters provides some flexibility in that these alkyl groups may be removed under acidic conditions or basic hydrolysis (*i.e.* 2 N KOH).[58]

Scheme 2.4.10 Epoxide Opening of Hepoxilin A_3 Analog



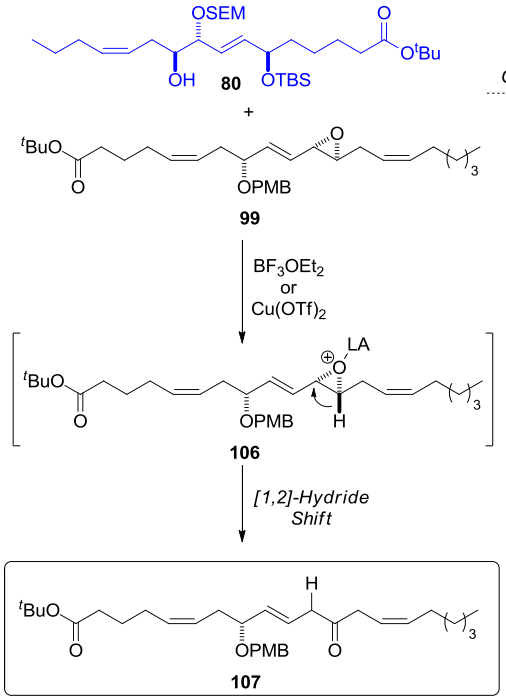
The C-12'-TBS group of **100** and **101**-**103** was chosen to achieve high *syn*-selectivity in the Luche reduction as described previously (Scheme 2.4.9). Epoxide opening of **99** (Scheme 2.4.10) will generate a free alcohol at the C-12' position (**105**, Scheme 2.4.11), which will be protected with TBS before revealing the requisite C-8' free hydroxyl group (**102**) for the second etherification. Therefore, orthogonal protection would require the selective removal of the C-8' protecting group (R^3) in the presence of a SEM-ether, two TBS-ethers, and two *tert*-butyl esters. In general, conditions for the preparation and cleavage of PMB-ethers are more facile than those for their benzyl analogs; in addition, Pd-catalyzed hydrogenolysis of a C-8' benzyl ether would be challenging in the presence of five olefins. On this basis, we reasoned that a C-8' PMB-ether (**101**) would accommodate these stringencies. In principle, a facile DDQ oxidative cleavage of PMB in **101** would reveal the corresponding C-8' free alcohol (**102**). This hydroxyl group will react with a galactose-glycerol electrophile in the ensuing Williamson ether synthesis to form the carbon skeleton of nigricanoside A (**103**).

2.4.7. Epoxide Opening-Attempts

Our initial attempts to effect etherification between the oxidized fatty acid subunits of nigricanoside A focused on epoxide opening reactions. At the outset of this investigation we were concerned about the potential side reaction of product **105** with **99**, since both **80** and **105** contain one free secondary alcohol (Scheme 2.4.11). However, certain Lewis acids are known to catalyze the regiospecific opening of vinyl epoxides by alcohols, although the alcohol reactants are most often employed in excess.[59] Nonetheless, we sought conditions to open epoxide **99** with free alcohol **80**. A screen of various Lewis acids proved unrewarding as we observed no desired ether or products derived from the polymerization of product with starting epoxide (see Table of Conditions in Scheme 2.4.11). Instead these reactions were plagued by a Lewis acid-catalyzed isomerization of the vinyl epoxide to the corresponding ketone **107**. In particular, experiments conducted at low temperatures in the presence of BF_3•OEt_2[60] or $Cu(OTf)_2$[61] produced the undesired ketone cleanly with near full consumption of the epoxide (entries 3-6).

Unfortunately, higher concentrations of reactants and use of large excesses of alcohol **80** had little or no effect on the outcome of the reactions. In principle, the undesired 1,2-hydride shift should be unfavorable under basic conditions.[62] As such, **99** was treated with the preformed lithium alkoxide derivative of **80**; however, these experiments proved unsuccessful as no reaction was observed even at elevated temperatures (entries 6-8).

Scheme 2.4.11 Epoxide Opening Attempts



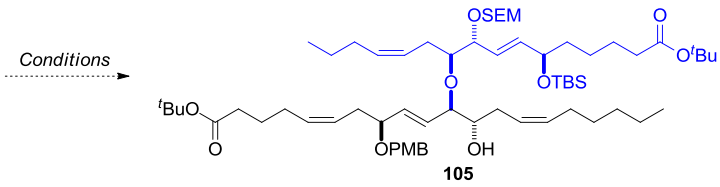
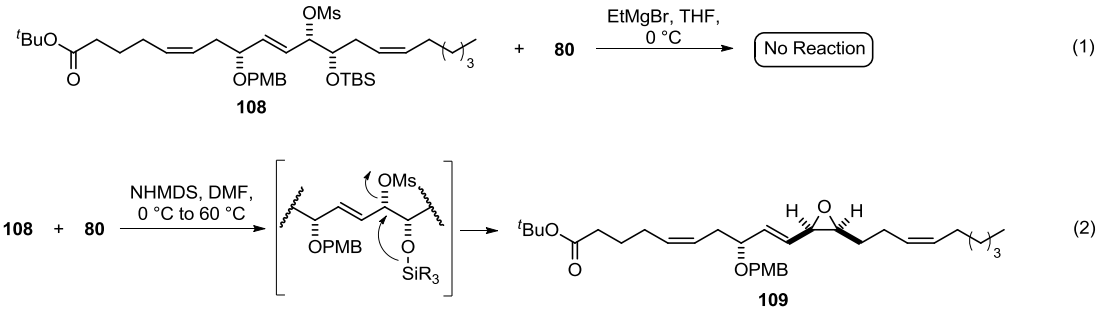


Table of Conditions

Entry	Lewis Acid	Base	Solvent	Temp (°C)	Result
1	TMSOTf	none	CH_2Cl_2	-78	**99** decomp.
2	Cu(OTf)$_2$	none	CH_2Cl_2	0	**99** decomp.
3	Cu(OTf)$_2$	none	CH_2Cl_2	-40	**99** decomp. + **107**
4	Cu(OTf)$_2$	none	CH_2Cl_2	-78	**99** decomp. + **107**
5	BF_3•OEt_2	none	CH_2Cl_2	-78	recovered **99** + **107**
6	BF_3•OEt_2	MeLi	THF	-78	recovered **99** + **107**
7	none	MeLi	THF	-78 to rt	recovered **99**
8	none	MeLi	THF/HMPA	-78 to rt	recovered **99**
9	none	none	H_2O	100	recovered **99**

Moving forward, we reasoned that an activated sulfonate, such as **108**, may act as a sufficient electrophile in etherifications of **80** under similar, basic conditions.[63] Multiple attempts to access the C-11' triflate of **95** (Scheme 2.4.9) proved unrewarding; the allylic triflate was unstable and readily decomposed upon workup. However, we were able to prepare mesylate **108** from the free alcohol and thus probe the viability of this approach (Scheme 2.4.12). No reaction occurred at lower temperatures (eqs. 1 and 2), but when the reactions were heated, we observed complete consumption of the mesylate (eq. 2). Unfortunately, further analysis of the reaction products revealed unreacted alcohol **80** along with cis-epoxide **109**, derived from an intramolecular displacement of methyl sulfonate (eq. 2).

Scheme 2.4.12 Mesylate Displacement Attempts



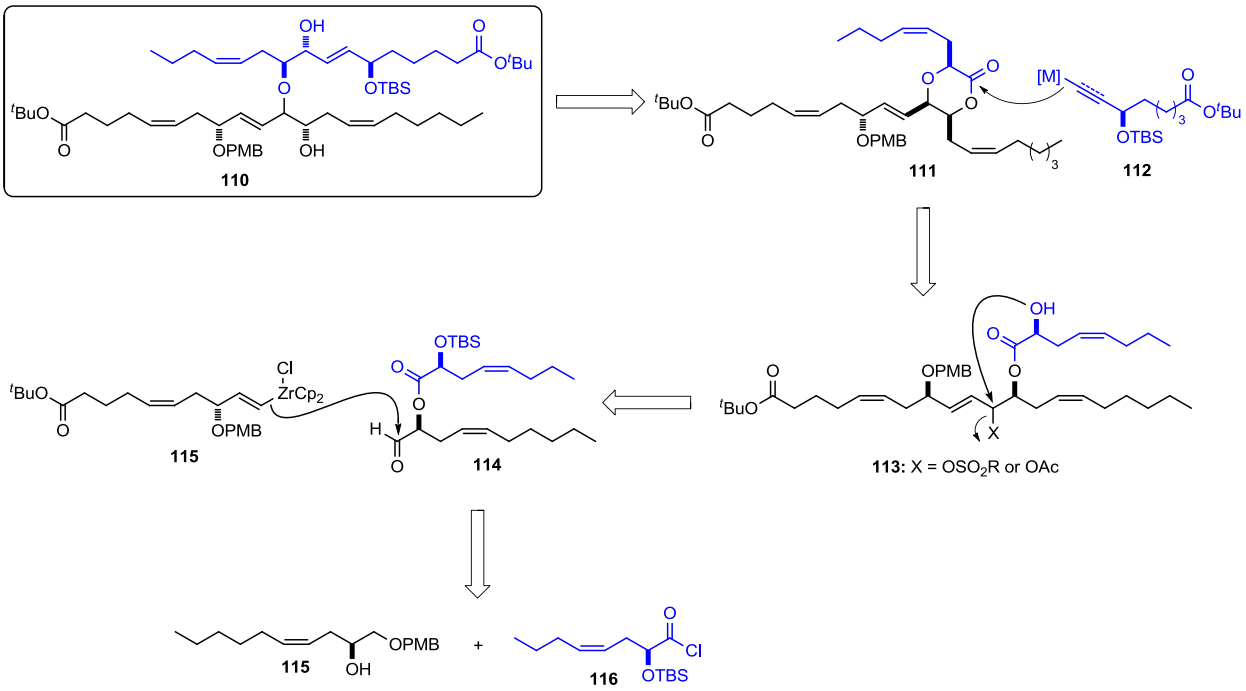
The results displayed in Scheme 2.4.11 and Scheme 2.4.12 suggest that steric hindrance between the secondary alcohol **80** and epoxide **99** or secondary mesylate **108** is sufficient to block the desired etherification. The more stable **80** was recovered completely from nearly every etherification attempt, while the reactive electrophiles **99** and **108** decomposed through intramolecular pathways under more forcing conditions. Again, similar results were obtained from experiments conducted with large excesses of the alcohol nucleophile and higher concentrations of both reactants. If our strategy for the epoxide opening of hepoxilin A_3 is in fact biomimetic, then conditions aimed to reproduce the results from the enzyme-catalyzed process in alga remain elusive.

2.5. Future Directions

Currently, we are pursuing several alternative strategies to effect etherification of the fatty acid subunits of nigricanoside A. Considering the difficulties we encountered with the intermolecular epoxide opening reactions, an intramolecular approach may prove advantageous. In principle, the lipid portion of nigricanoside A could be synthesized through the retrosynthetic route outlined in Scheme 2.5.1. Addition of a vinyl or alkynyl metal (**112**) to the carbonyl of 1, 4-dioxanone **111** could form the ether-linked C_{16}FA and C_{20}FA subunits in **110**. The six-membered ring, in turn, might be derived from an allylic displacement of a leaving group (X) by the α-hydroxy ester in **113**, a transformation that may be effected through direct S_N2-type substitution or palladium-mediated ring-closure.[64, 65] This ester precursor (**113**) may be prepared from an alkenyl zirconium (**115**) addition to aldehyde **114**. Interestingly, the α-carboxy aldehyde (**114**) is protected with essentially one-half of the carbon atoms of the C_{16}FA; therefore, the vinyl metal-addition adduct (**113**) represents 75% of nigricanoside's lipid substructure. In principle, aldehyde **114** could be generated from a simple esterification of **115** with an α–siloxy acid chloride (**116**). Preliminary results demonstrate that we can access various allylic acetate and mesylate analogs of **113** through a similar route. We have yet to prepare **111** through intramolecular etherification, but this

transformation is still under investigation as we have not exhausted all possible methods to effect cyclization.

Scheme 2.5.1 An Intramolecular Approach to Etherification

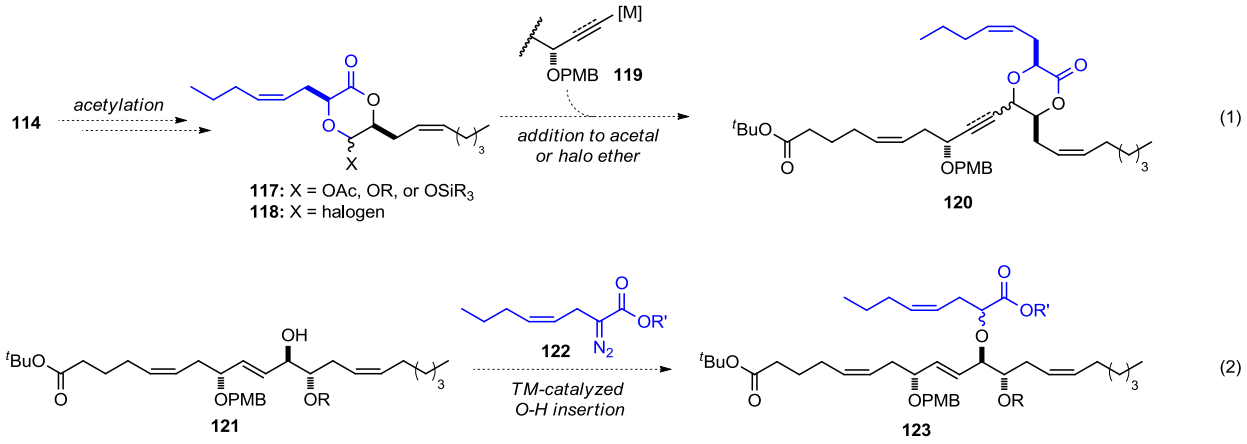


We are also interested in exploring two other tactics to form the ether linkage of discussion, and these approaches are represented in the forward sense below (Scheme 2.5.2). Similar to the intramolecular strategy, the synthetic route depicted in Equation 1 targets the 1,4-dioxanone ring in **117** and **118**. As described in the previous scheme, this lactone could potentially be opened by organometallic reagents. In principle, both hemiacetal **117** and halo ether **118**[66] may be derived from a Bronsted or Lewis acid-mediated cyclization of α-carboxy aldehyde **114**. A vinyl or alkynyl metal nucleophile (**119**) may be sufficient to displace the halogen from **118** or add to an oxocarbenium derived from either **117** or **118**.

In particular, organometallic reagents such as, alkynyl stannanes,[67] alkynyl alanes,[68] alkenyl copper reagents,[69] organo trifluoroborates,[70] and organozinc reagents[71] are known to undergo Lewis acid-mediated additions to acetals. In addition, carbon-carbon bonds can be formed between α–halo ethers and various organometallics, including alkenyl zirconocenes[72] and organozinc compounds.[73] However, problems with Equation 1 may arise from issues of stereocontrol in the critical C-C bond-forming process. The facial selectivity of the addition will likely depend on the choice nucleophile (**119**) or be dictated by the configurational stability of the oxonium intermediate. Depending on the reaction conditions, substitution of the C-X bond in **118** may proceed through an S_N2-type displacement with overall configurational inversion of the electrophilic stereocenter; however, the halo ether *itself* may be

difficult to prepare as one anomer.[74] Considering the number of organometallic reagents that efficiently cleave acetals and add to halo ethers, the correct choice of metal ([M] in **119**) may facilitate our advancement through this synthetic route (eq. 1).

Scheme 2.5.2 Other Strategies to Form the Ether Linkage



The second approach represented in Scheme 2.5.2 involves a transition-metal-catalyzed O-H insertion process (eq. 2)[75] In principle, the secondary alcohol nucleophile in (**121**) could react with a carbenoid derived from α-diazo ester (**122**) to produce α-alkoxy ester (**123**). In this way, achieving high diastereoselectivity through substrate control would likely prove challenging. There are asymmetric variants of these types of etherifications, and the proper choice of chiral transition-metal complex may induce asymmetry in the prochiral substrate.[76] In addition, use of a chiral diazoester (**122**, R' = *L) may be sufficient to control the diastereoselectivity of the O–H insertion.[77, 78]

2.6. Chapter Two Conclusions

The nigricanosides are intriguing natural products for a number of reasons. Their unique architecture is unprecedented while their antimitotic potency is unparalleled by any previously discovered glycolipid. Furthermore, the structure of the nigricanosides is dissimilar to other molecules known to inhibit or induce tubulin polymerization. But the scarcity of **1** has limited its complete structural and biological analysis, thus rendering Nigricanoside A an ideal target for total synthesis.

Described in this chapter is the synthesis of the two oxidized fatty acid subunits of nigricanoside A, both of which were accessible through vinyl-metal additions to α-hydroxy aldehydes. Collaborating with Professor John MacMillan's group, we used advanced homonuclear decoupling NMR experiments to propose the relative *anti,anti*-configuration of the unknown C_{16}-triol (C_{16}FA). Initial attempts to join the orthogonally-protected C_{16}FA and C_{20}FA subunits through epoxide opening and mesylate

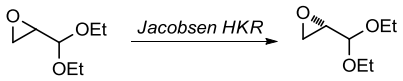
displacement reactions were unsuccessful. Therefore, we devised three different strategies which we are currently pursuing. We expect to encounter difficulties associated with the critical bond-forming processes; however, the alternative approaches summarized in the previous section represent viable, synthetic routes to the ether-linked fatty acids. In conclusion, we learned a great deal from the two-year endeavor represented in this chapter, and with this knowledge, we are confident our future studies will culminate in the successful total synthesis of nigricanoside A.

2.7. Chapter Two Experimental

2.7.1. Materials and Methods

General. Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly purified solvents. Solvents were purified using solvent purification columns purchased from Glass Contour, Laguna Beach, CA. All reactions were monitored by thin-layer chromatography with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). Gas chromatography (GC) was performed on an HP 6890N autosampling GC with an HP-5 capillary column and equipped with a FID detector. Flash chromatography was performed with indicated solvents using silica gel (particle size 0.032-0.063 μm) purchased from Sorbent Technologies.^{1}H and ^{13}C NMR spectra were recorded on Varian Inova-400 or Mercury-300 spectrometer. Chemical shifts are reported relative to internal chloroform ($CDCl_3$: ^{1}H, δ = 7.27, ^{13}C, δ = 77.26). Coupling constants are in Hz and are reported as d (doublet), t (triplet), q (quartet), p (pentet) sep (septet), and app for apparent. For signals having multiple coupling patterns, the coupling constant are listed in the same order as the pattern (e.g. dt, J = 2.0, 4.0; 2.0 is the coupling constant for the doublet and 4.0 is for the coupling constant for the triplet). Infrared spectra were recorded on a Perkin-Elmer 1000 series FTIR. Low-resolution mass spectra were acquired on a Shimadzu QP5000 GC/MS using the indicated ionization method. HPLC analyses were carried out on a Shimadzu LC-2010A system. Optical rotations were measured on a Rudolph Research Analytical Autopol® IV Polarimeter.

2.7.2. Preparative Methods:



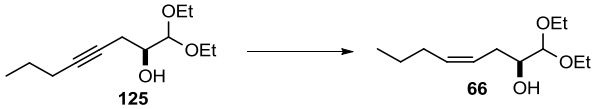
65 (S)-**65**

(S)-65: (S)-Glycidaldehyde diethyl acetal (S)-**65**[79, 80] was resolved from racemic **65** using the HKR method developed by Jacobsen.[33] *p*-Toluenesulfonic acid (0.8 g, 1.33 mmol, 1.4 mol%) was added to a 100 mL round-bottomed flask containing a stirred solution of (R, R)-(-)-*N,N'*-bis(3,5-di-*tert*-butylsalicicylidene)-1,2-cyclohexanediaminocobalt^{II} (0.27 g, 1.4 mmol, 1.5 mol%) in CH_2Cl_2 (20 mL) at room temperature. The reaction was allowed to stir open to air for one hour, after which the stir bar was removed and the solution was concentrated by rotary evaporation. The contents of the flask were placed under high vacuum for one hour to remove the remaining solvent. The stir bar was returned to the flask and racemic glycidaldehyde diethyl acetal (13.7 g, 93.7 mmol, 1.0 equiv) was added to the (salen)Co^{III}-OTs catalyst at room temperature. The flask was capped and stirred vigorously for 24 hours. The epoxide was transferred to a -78˚C receiving flask by distillation (60˚C, 10 mmHg) to afford **(S)-65** (5.81 g, 40.1 mmol, 43% yield, 97% ee) as a clear liquid, which was stored over 4Å molecular sieves in the freezer.

The ee of **65** (97%) was determined by chiral GC. Specific GC conditions and chromatograms are located in at the end of Appendix 2. $[\alpha]^{20}_D$ = -5.4 (*c* = 1.0, EtOH); lit.[81] $[\alpha]^{25}_D$ = -5.4 (*c* = 1.04, EtOH). ^{1}H NMR ($CDCl_3$) δ = 4.34 (dd, *J* = 4.3, *J* = 1.5, 1H), 3.74 (m, 2H), 3.60 (m, 2H), 3.10 (m, 1H), 2.78 (m, 2H), 1.24 (m, 6H). ^{13}C NMR ($CDCl_3$) δ = 101.5, 62.9, 62.3, 51.8, 43.8, 15.2, 15.1. EI-MS (m/z): 146 $[M]^+$.

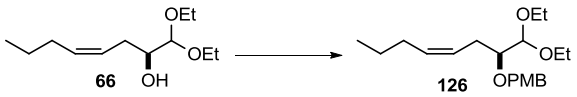
(S)-**65** **125**

125: To a stirred solution of 1-pentyne (3.0 mL, 30 mmol, 2.0 equiv) in THF (100 mL) at -78˚C was added ^{n}BuLi (12 mL, 30 mmol, 2.0 equiv). After stirring for one hour at -78˚C, $BF_3{\cdot}OEt_2$ (2.5 mL, 19.5 mmol, 1.3 equiv) was added at this temperature. The solution stirred for 25 minutes, at which time (S)-glycidaldehyde diethyl acetal (2.2 g in 15 mL THF, 15 mmol, 1.0 equiv) was added dropwise at -78˚C. The reaction was stirred at -78˚C for 4 hours, quenched with sat. aqu. NH_4Cl, and extracted 3 times with Et_2O. The combined organic layers was dried with $MgSO_4$, concentrated, and purified by flash chromatography (6-30% EtOAc/Hexanes) to give pure **125** (2.98 g, 13.9 mmol, 93% yield) as a yellow oil. $[\alpha]^{20}_D$ = -14 (*c* = 0.1.19, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ = 4.48 (d, *J* = 5.6, 1H), 3.77 (m, 1H), 3.68 (m, 1H), 3.61 (m, 2H), 2.52 (m, 1H), 2.42 (m, 1H), 2.32 (d, *J* = 4.1, 1H), 2.15 (tt, *J* = 7.0, *J* = 2.4, 2H), 1.51 (m, 2H), 1.24 (t, *J* = 7.1, 3H), 1.23 (t, *J* = 7.1, 3H), 0.97 (t, *J* = 7.4, 3H). ^{13}C NMR ($CDCl_3$) δ = 103.7, 82.2, 76.1, 70.6, 63.8, 63.5, 22.6, 22.5, 20.9, 15.4, 13.6, 13.5. EI-MS (m/z): 169 $[M\text{-}OCH_2CH_3]^+$.



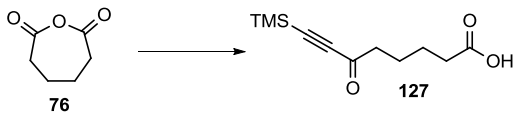
125 **66**

66: A stirred mixture of **125** (1.5 g, 7.0 mmol, 1.0 equiv), quinoline (42 μL, 0.35 mmol, 5 mol%), and Lindlar catalyst (0.149 g, 0.07 mmol, 1.0 mol %) in MeOH (25 mL) was sparged with N_2 for 15 minutes. H_2 gas was then bubbled through the stirred mixture for 1 hour. The reaction was filtered through a plug of Celite and concentrated to afford **66** (1.51 g, quantitative yield) as a yellow oil which was used without further purification. $[\alpha]^{20}_D$ = -6.4 (*c* = 1.06, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ = 5.64 – 5.38 (m, 2H), 4.31 (d, *J* = 5.8, 1H), 3.87 – 3.68 (m, 2H), 3.68 – 3.49 (m, 3H), 2.46 – 2.32 (m, 1H), 2.32 – 2.19 (m, 1H), 2.15 (d, *J* = 3.5, 1H), 2.04 (dt, *J* = 7.6, 6.5, 2H), 1.47 – 1.31 (m, 2H), 1.24 (q, *J* = 7.0, 6H), 0.91 (t, *J* = 7.3, 3H).^{13}C NMR ($CDCl_3$) δ = 132.2, 125.4, 104.6, 71.2, 63.5, 63.4, 29.9, 29.6, 22.9, 15.6, 15.5, 13.9. EI-MS (m/z): 216 $[M]^+$.



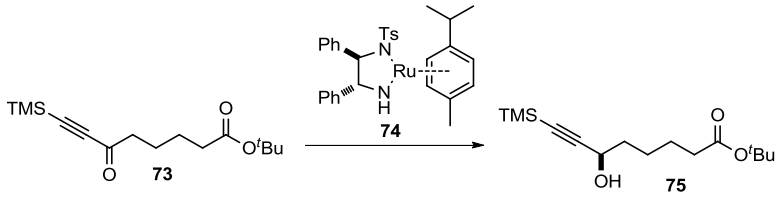
126: To a stirred suspension of NaH (0.21 g, 5.25 mmol, 1.5 equiv) and tetrabutylammonium iodide (0.132 g, 0.35 mmol, 0.1 equiv) in DMF (25 mL) at 0˚C was slowly added **66** (0.76 g in 5 mL DMF, 3.5 mmol, 1.0 equiv). After stirring for 1 hour at 0˚C, PMBCl (0.97 mL, 7.0 mmol, 2.0 equiv) was added at this temperature and the reaction was allowed to warm to rt. The reaction was allowed to stir for 24 hours, after which it was quenched by slow addition of H_2O at 0˚C. The reaction was extracted 3 times with Et_2O, and the combined organic portions was washed with brine, dried with $MgSO_4$ and concentrated. The crude mixture was purified by flash chromatography (2-10% EtOAc in hexanes) to afford **126** (1.11 g, 94% yield) as a light yellow oil. $[\alpha]^{20}_D$ = +13 (*c* =, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ = 7.36 – 7.19 (m, 2H), 6.90 – 6.76 (m, 2H), 5.56 – 5.36 (m, 2H), 4.64 (d, *J* = 11.2, 1H), 4.54 (d, *J* = 11.2, 1H), 4.37 (d, *J* = 6.0, 1H), 3.76 (s, 3H), 3.76 – 3.66 (m, 2H), 3.66 – 3.57 (m, 1H), 3.57 – 3.48 (m, 1H), 3.46 – 3.37 (m, 1H), 2.46 – 2.33 (m, 1H), 2.33 – 2.22 (m, 1H), 2.10 – 1.91 (m, 2H), 1.44 – 1.29 (m, 2H), 1.29 – 1.14 (m, 6H), 0.89 (t, *J* = 7.4, 3H). ^{13}CNMR ($CDCl_3$) δ = 159.3, 131.6, 131.2, 129.6, 126.0, 113.8, 104.8, 79.8, 72.9, 64.0, 63.4, 55.3, 29.7, 28.7, 23.0, 15.7, 15.5, 14.0. EI-MS (m/z): 336 $[M]^+$.

67a: To a stirred solution of **126** (0.22 g, 0.654 mmol, 1.0 equiv) in THF (45 mL) at 0°C was added a freshly prepared solution of 10% HCl (15 ml). Hydrolysis of the diethyl acetal was complete after 44 hours of stirring at 0°C, after which the solution was poured into a stirred solution of saturated aqueous $NaHCO_3$ (200 mL) at 0°C. The crude aldehyde was extracted from the aqueous layer by washing once with EtOAc and twice with CH_2CL_2. The organic fractions were pooled, dried with $MgSO_4$ and concentrated. The crude aldehyde was unstable so it was purified quickly by flash chromatography (2.5-10% EtOAc in hexanes + 0.1% Et_3N) afforded the aldehyde **67a** (0.145 g, 85% yield) as a colorless oil. This α–hydroxy aldehyde is very unstable and was used directly in the following step without being completely characterized. Significant decomposition occurs when stored overnight in the freezer; however, a small aliquot was removed to obtain the ^{1}H NMR spectrum. ^{1}H NMR ($CDCl_3$) δ 9.62 (d, *J* = 2.1 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.57 – 5.47 (m, 1H), 5.46 – 5.35 (m, 1H), 4.59 (d, *J* = 11.5 Hz, 2H), 4.53 (d, *J* = 11.5 Hz, 2H), 3.81 (s, 3H), 3.77 (dt, *J* = 6.5, 2.2 Hz, 1H), 2.49-2.42 (dd, *J* = 10.1, 3.9 Hz, 2H), 2.04 – 1.95 (m, 2H), 1.42 – 1.30 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H).



127: Following a similar procedure,[82] freshly cracked adipic anhydride monomer[39] (12.8 g, 100 mmol, 2.0 equiv) and bis(trimethylsilyl)-acetylene (8.7 g, 50 mmol, 1.0 equiv) were dissolved in 600 mL CH_2Cl_2 and brought to 0˚C. $AlCl_3$ (20 g, 150 mmol, 3.0 equiv) was added in four portions to the stirred solution at 0˚C. The dark mixture was stirred for an additional 2.5 hours at this temperature and then 19 hours at room temperature. The reaction was quenched by slowly adding 1N HCl at 0˚C and the organic layer was separated, washed with 1N HCl, H_2O, and brine. The solution was dried with $MgSO_4$, concentrated, and purified by flash chromatography (5-50% EtOAc in hexanes) to afford **127** (6.91 g, 61% yield) as a viscous oil. ^{1}H NMR ($CDCl_3$) δ = 2.60 (t, *J* = 6.8, 2H), 2.39 (t, *J* = 7.0, 2H), 1.71-1.67 (m, 4H), 0.24 (s, 9H). ^{13}C NMR ($CDCl_3$) δ = 187.4, 179.9, 102.0, 98.2, 44.9, 33.9, 24.0, 23.3, 0.63. EI-MS (m/z): 226 $[M]^+$.

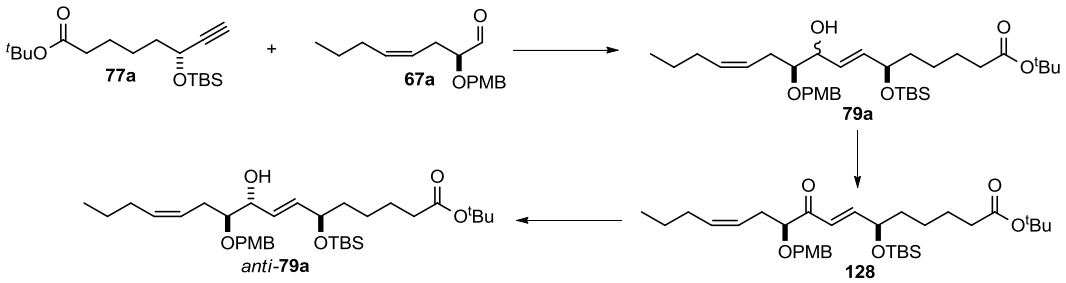
73: Trifluoroacetic anhydride (4.6 mL, 33 mmol, 2.2 equiv) was added slowly (over 10 minutes) to **127** (3.4 g, 15 mmol, 1.0 equiv) in 65 mL CH_2Cl_2 at 0˚C and the reaction solution was allowed to stir for 2.5 hours at this temperature. ^{t}BuOH (5 mL) was then added slowly to the stirred solution at 0˚C and the reaction was allowed to slowly warm to room temperature. After stirring for 23 hours at room temperature, the reaction was quenched with 50 mL H_2O, diluted with Et_2O, and extracted 3 times with Et_2O. The organic portions were dried with $MgSO_4$, concentrated, and purified by flash chromatography (2-3% EtOAc in hexanes) to afford 3.57 g (84% yield) of a yellow oil, **73**. ^{1}H NMR ($CDCl_3$) δ = 2.58 (t, *J* = 7.2, 2H), 2.23 (t, *J* = 7.2, 2H), 1.72-1.57 (m, 4H), 1.44 (s, 9H), 0.24 (s, 9H). ^{13}C NMR ($CDCl_3$) δ = 187.4, 172.7, 102.1, 97.8, 80.3, 45.0, 35.3, 28.2, 24.5, 23.4, 0.62. EI-MS (m/z): 283 $[M]^+$.



75: Catalyst **74**[36] (70 mg, 0.117 mmol, 1 mol %) was added to a stirred solution of **73** (3.3 g, 11.7 mmol, 1.0 equiv) in 120 mL ^{i}PrOH at room temperature and the reaction was allowed to stir for 18 hours. The solution was concentrated and purified by flash chromatography (5-20% EtOAc) to afford pure **75** (3.24 g, 97% yield, 99% ee) as a yellow oil. The ee of **75** (99%) was determined from the benzoylated analog

(BzCl, Et_3N, cat. DMAP, CH_2Cl_2) by HPLC (Chiralcel OD-H column, 1 mL/ min flow rate, 1% ^{i}PrOH/Hexanes; $t_{r(minor)}$ = 7.95 min, $t_{r(major)}$ = 9.18 min). HPLC chromatograms are located in Appendix 2. $[\alpha]^{20}_{D}$ = +0.6 (*c* = 1.04, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ = 4.36 (dt, *J* = 6.5, 5.6, 1H), 2.23 (t, *J* = 7.4, 2H), 1.87 (dd, *J* = 5.4, 3.2, 1H), 1.76 – 1.66 (m, 2H), 1.66 – 1.56 (m, 2H), 1.53 – 1.45 (m, 2H), 1.44 (s, 9H), 0.16 (s, 9H). ^{13}C NMR ($CDCl_3$) δ = 173.4, 107.2, 89.3, 80.4, 62.7, 62.6, 37.7, 35.7, 28.4, 25.0, 24.9, 0.16. EI-MS (m/z): 228 $[M - C(CH_3)_3]^+$.

77a: TBSCl (0.82 g, 5.28 mmol, 1.5 eqiv) was added to a solution of **75** (1.0 g, 3.52 mmol, 1.0 equiv), imidazole (0.72 g, 10.56 mmol, 3.0 equiv), and DMAP (43 mg, 0.352 mmol, 0.1 equiv) in CH_2Cl_2 (20 mL) at 0˚C. The reaction was stirred for 30 minutes at 0˚C and 2.5 hours at room temperature. MeOH (30 mL) and K_2CO_3 (1.7 g, 12.32 mmol, 3.5 equiv) were then added to the reaction sequentially at room temperature. After stirring overnight, the reaction was quenched with sat. aqueous $NaHCO_3$ and extracted 3 times with EtOAc. The organic portions were combined, dried with $MgSO_4$ and concentrated. The crude mixture was filtered through a plug of SiO_2 with 10% EtOAc in hexanes to afford **77a** (1.18 g, quantitative yield) which was used without further purification. $[\alpha]^{20}_{D}$ = +30.9 (*c* = 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ = 4.34 (dt, *J* = 6.4, 2.1, 1H), 2.37 (d, *J* = 2.1, 1H), 2.22 (t, *J* = 7.5, 2H), 1.73 – 1.64 (m, 2H), 1.64 – 1.56 (m, 2H), 1.51 – 1.45 (m, 2H), 1.45 (s, 9H), 0.90 (s, 9H), 0.11 (d, *J* = 10.1, 6H). ^{13}C NMR ($CDCl_3$) δ = 173.0, 85.5, 80.0, 72.3, 62.7, 38.3, 35.6, 28.2, 25.9, 24.9, 24.7, 18.3, 4.43, 4.96. EI-MS (m/z): 326 $[M]^+$.



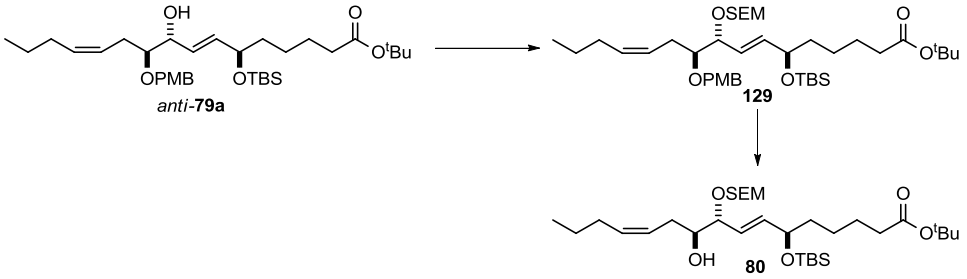
79a: Solid $Cp_2Zr(H)Cl$ (0.614 g, 2.26 mmol, 1.7 equiv) was added to a stirred solution of **77a** (0.652 g, 2.00 mmol, 1.5 equiv) in 7 mL CH_2Cl_2 at 0°C. The hydrozirconation was complete after 2 hours, at which time a solution of $ZnBr_2$ (1 M in THF, 0.133 mL, 0.133 mmol, 0.1 equiv) was added to the reaction mixture. After stirring for an addition 15 minutes at 0°C, a solution of the aldehyde (**67a**, 0.35 g, 1.33 mmol, 1.0 equiv) in CH_2Cl_2 (1-2 mL) was added at the same temperature. The aldehyde was allowed to

react overnight at 0°C and the reaction was quenched with a 10% aqueous solution of citric acid (15 mL). The organic layer was separated, and the aqueous layer was washed 3 times with CH_2CL_2. The organic portions were dried with $MgSO_4$ and concentrated to afford alcohol **79a** as a 1:1 mixture of diastereomers. The crude oil was taken directly into the Dess-Martin oxidation without further purification.

128: The crude mixture of diastereomers **79a** (~ 1.3 mmol) was dissolved in CH_2Cl_2 (15 mL), treated with NaH_2CO_3 (0.328 g, 3.9 mmol, 3.0 equiv), and cooled to 0°C. At this time, solid Dess-Martin periodinane (1.14 g, 2.6 mmol, 2.0 equiv) was added to the stirred suspension in 3 portions. After 15 minutes, the reaction was removed from the ice bath and allowed to slowly warm to rt. The oxidation was complete after stirring for 1.5 hours at rt. The reaction was quenched with a 1:1 solution of 20% aqueous $Na_2S_2O_3$ / sat.aqueous NaH_2CO_3 (1:1), extracted with CH_2Cl_2, and dried with $MgSO_4$. Purification by flash chromatography (5-8% EtOAc in hexanes) afforded of ketone **128** (0.646 g, 84 % yield) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.25 – 7.21 (m, 2H), 6.98 (dd, *J* = 15.6, 4.5 Hz, 1H), 6.88 – 6.84 (m, 2H), 6.66 (dd, *J* = 15.6, 1.6 Hz, 1H), 5.48 (dt, *J* = 10.9, 7.2 Hz, 1H), 5.42 – 5.32 (m, 1H), 4.53 (d, *J* = 11.5 Hz, 1H), 4.34 – 4.29 (m, 2H), 3.92 (t, *J* = 6.6 Hz, 1H), 3.80 (s, *J* = 2.4 Hz, 3H), 2.44 (t, *J* = 7.1 Hz, 2H), 2.19 (t, *J* = 7.5 Hz, 2H), 2.02 – 1.92 (m, 2H), 1.63 – 1.51 (m, 4H), 1.43 (s, 9H), 1.40 – 1.30 (m, 4H), 0.89 (s, 9H), 0.87 (t, *J* = 7.4 Hz, 3H), 0.07 – -0.02 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 173.4, 159.4, 136.28, 132.1, 130.8, 129.5, 127.9, 125.9, 114.0, 82.3, 80.2, 73.2, 72.9, 72.1, 55.5, 38.2, 35.8, 29.7, 28.4, 27.9, 26.1, 25.3, 24.9, 22.9, 18.5, 14.1, -4.03, -4.52. MS (ESI) calculated for $C_{34}H_{56}O_6SiNa^+$ $[MNa]^+$ 611.9, found 611.4.

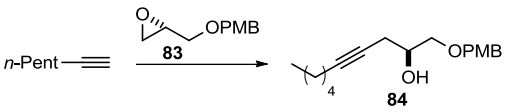
anti-**79a:** α, β-Unsaturated ketone **128** (0.3 g, 0.5 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (10 mL) and cooled to -78°C. A solution of Super Hydride (1.0 M in THF, 0.6 mL, 1.2 equiv) was added slowly along the side of the reaction vessel and the resulting solution was allowed to stir for 20 minutes at -78°C. At this time, the reaction was quenched with a 10% aqueous solution of citric acid (15 mL), allowed to warm to rt, and stirred until two clear layers were evident (~ 1 hour) The aqueous layer was washed 3 times with CH_2CL_2 and the organic portions were pooled, dried with $MgSO_4$ and concentrated. The crude mixture was purified by flash chromatography (8-18% EtOAc in hexanes) to afford of the desired alcohol *anti*-**79a** (83% yield, 0.244 g, 0.413 mmol) as a 19:1 (anti / syn) mixture of diastereomers. ^{1}H NMR ($CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.76 – 5.59 (m, 2H), 5.53 – 5.35 (m, 2H), 4.58 (d, *J* = 11.3 Hz, 1H), 4.52 (d, *J* = 11.3 Hz, 1H), 4.25 (dd, *J* = 8.4, 5.0 Hz, 1H), 4.18 – 4.09 (m, 1H), 3.81 (s, 3H), 3.51 – 3.39 (m, 1H), 2.42 – 2.30 (m, 1H), 2.24 – 2.12 (m, 4H), 2.04 – 1.96 (m, 2H), 1.62 – 1.46 (m, 4H), 1.43 (s, 9H), 1.39 – 1.28 (m, 4H), 0.91 – 0.85 (m, 12H), 0.03 (d, *J* = 8.8 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 173.4, 159.4, 136.3, 132.1, 130.8, 129.5, 127.9, 125.9, 114.0, 82.3, 80.2, 73.2, 72.9, 72.1, 55.5,

38.2, 35.8, 29.7, 28.4, 27.9, 26.1, 25.3, 24.9, 23.0, 18.5, 14.1, -4.03, -4.52. MS (ESI) calculated $C_{34}H_{58}O_6SiNa^+$ $[MNa]^+$ 613.9, found 613.4.



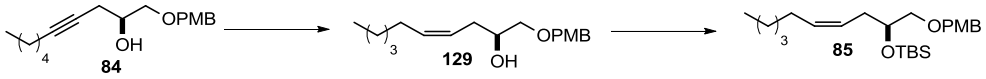
129: SEMCl (0.105 mL, 0.563 mmol, 1.3 equiv) was added dropwise to a stirred solution of **80** (0.256 g, 0.433 mmol, 1.0 equiv) and iPr^{2}EtN (0.13 mL, 0.736 mmol, 1.7 equiv) in CH_2Cl_2 (2.0 mL) at 0°C. The solution was allowed to slowly warm to rt overnight and quenched with MeOH (2 equiv). After 10 minutes, the reaction was washed with sat. aq. NH_4Cl, sat. aq. $NaHCO_3$, and brine. The organic portions were pooled, dried with $MgSO_4$ and concentrated to afford the crude SEM-protected alcohol. A small aliquot was removed to characterize by ^{1}H NMR and the crude compound (**129**) was taken directly into the following reaction without further purification. ^{1}H NMR ($CDCl_3$) δ 7.22 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 5.65 (dd, *J* = 15.6, 5.5 Hz, 1H), 5.56 (dd, *J* = 15.6, 7.5 Hz, 1H), 5.45 – 5.31 (m, 2H), 4.68 – 4.55 (m, 3H), 4.47 (d, *J* = 11.3 Hz, 1H), 4.15 – 4.05 (m, 2H), 3.83-3.75 (m, 1H), 3.75 (s, 3H), 3.73 – 3.45 (m, 2H), 2.31-2.16 (m, 2H), 2.14 (t, *J* = 7.5 Hz, 2H), 2.01 – 1.86 (m, 2H), 1.58 – 1.42 (m, 5H), 1.40 (s, 9H), 1.36 – 1.17 (m, 3H), 1.03 – 0.87 (m, 2H), 0.94 – 0.79 (m, 12H), 0.06 – -0.10 (m, 15H).

80: pH 7 phosphate buffer (1.0 M in H_2O, 0.31 mL) was added to crude **129** (0.433 mmol, 1.0 equiv) in CH_2Cl_2 (5.5 mL) and the heterogeneous mixture was cooled to 0°C. DDQ (0.151 g, 0.65 mmol, 1.5 equiv) was then added in two portions and the resulting mixture was allowed to stir overnight at 0°C, after which the reaction was filtered Celite, washed with $NaHCO_3$ and extracted with CH_2Cl_2. The organic portions were dried with Mg_2SO_4, concentrated, and purified by flash chromatography (5-8% EtOAc in hexanes). This afforded **80** (0.241 g, 0.412 mmol, 95% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 5.73 (dd, *J* = 15.6, 5.9 Hz, 1H), 5.62 – 5.49 (m, 2H), 5.49 – 5.39 (m, 1H), 4.70 – 4.62 (m, 2H), 4.15 (app q, *J* = 5.8 Hz, 1H), 4.04 (dd, *J* = 7.7, 3.6 Hz, 1H), 3.80 – 3.65 (m, 2H), 3.52 (dt, *J* = 9.8, 6.6 Hz, 1H), 2.25 (d, *J* = 4.5 Hz, 1H), 2.24 – 2.13 (m, 6H), 2.02 (dt, *J* = 7.3, 6.9 Hz, 2H), 1.62 – 1.46 (m, 5H), 1.44 (s, 9H), 1.41 – 1.33 (m, 3H), 0.94 – 0.89 (m, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.02 (s, 12H). ^{13}C NMR ($CDCl_3$) δ 173.3, 139.8, 132.7, 125.6, 124.8, 92.4, 80.2, 79.7, 73.9, 72.8, 65.7, 38.3, 35.8, 30.7, 29.9, 29.8, 28.3, 26.1, 25.3, 25.3, 25.0, 23.0, 18.4, 18.3, 14.0, -1.18, -4.10, -4.56. MS (ESI) calculated $C_{32}H_{64}O_6Si_2Na^+$ $[MNa]^+$ 624.0, found 623.4.



83: Glycidyl ether **83** was obtained from the reaction of commercially available (R)-glycidol (from Aldrich, 9.58 mL, 140 mmol, 1.0 equiv) with NaH (60% in mineroil oil, 6.16 g, 154 mmol, 1.1 equiv) and PMBCl (21.3 mL, 154 mmol, 1.1 g) in DMF (280 mL) following a known procedure.[83] Distilation (120°C) under high vacuum yielded the epoxide contaminated with mineral oil (from NaH). The mineral oil could be removed by filtering the sample through a plug of SiO_2 (100% hexanes). When the mineral oil was removed from the plug, the desired product was eluted from the SiO_2 with a second wash (100% EtOAc). The resulting solution was concentrated to afford pure glycidyl ether **83** (24.8 g, 128 mmol, 91% yield).

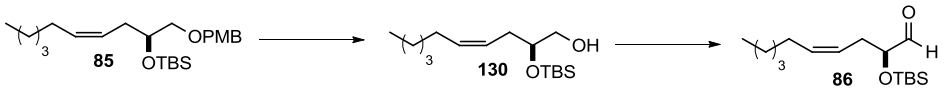
84: To a stirred solution of 1-heptyne (2.9 mL, 22 mmol, 2.0 equiv) in THF (60 mL) at -78˚C was added ^{n}BuLi (8.8 mL, 22 mmol, 2.0 equiv). After stirring for one hour at -78˚C, $BF_3{\cdot}OEt_2$ (1.8 mL, 14.3 mmol, 1.3 equiv) was added at this temperature. The solution stirred for 15 minutes, at which time glycidyl ether **83** (2.14 g in 20 mL THF, 11 mmol, 1.0 equiv) was added dropwise at -78˚C. The reaction was stirred at -78˚C for 4 hours, quenched with saturated aqueous NH_4Cl, and extracted 3 times with Et_2O. The combined organic layers was dried with $MgSO_4$ and concentrated afford **84** (2.98 g, 13.9 mmol, quantitative yield) as a yellow oil. The ^{1}HNMR spectrum of the crude sample was very clean and so the alcohol (**84**) was brought into the following step without further purification. ^{1}H NMR ($CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.50 (s, *J* = 7.9 Hz, 2H), 3.96 – 3.85 (m, 1H), 3.81 (s, *J* = 6.2 Hz, 3H), 3.58 (dd, *J* = 9.5, 3.9 Hz, 1H), 3.46 (dd, *J* = 9.5, 6.7 Hz, 1H), 2.45 – 2.35 (m, 3H), 2.18 – 2.09 (m, 2H), 1.52 – 1.41 (m, 2H), 1.38 – 1.27 (m, 4H), 0.89 (t, *J* = 7.1 Hz, 3H).^{13}C NMR ($CDCl_3$) δ 159.5, 130.3, 129.6, 114.1, 83.2, 75.7, 73.3, 73.0, 69.4, 55.5, 31.3, 28.9, 24.1, 22.4, 19.0, 14.3. EI-MS (m/z): 290 $[M]^+$.



129: A stirred mixture of alcohol **84** (2.9 g, 10.0 mmol, 1.0 equiv), quinoline (60 μL, 0.5 mmol, 5 mol%), and Lindlar catalyst (0.213 g, 0.1 mmol, 1.0 mol %) in MeOH (40 mL) was sparged with N_2 for 15 minutes. H_2 gas was then bubbled through the stirred mixture for 1 hour. The reaction was filtered through a plug of Celite and concentrated to afford alkene **129** (2.92 g, quantitative yield) as a yellow oil. The ^{1}HNMR spectrum of crude alcohol was clean and therefore was used in the following transformation without further purification. ^{1}H NMR ($CDCl_3$) δ 7.26 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.58 – 5.45 (m, 1H), 5.45 – 5.29 (m, 1H), 4.48 (s, 2H), 3.90 – 3.83 (m, 1H), 3.81 (s, 3H), 3.50 (dd, *J* = 9.5, 3.2

Hz, 1H), 3.34 (dd, *J* = 9.5, 7.5 Hz, 1H), 2.31 (d, *J* = 3.0 Hz, 1H), 2.25 (dd, *J* = 7.0, 6.6 Hz, 2H), 2.02 (dt, *J* = 7.0, 6.9 Hz, 2H), 1.40 – 1.19 (m, 6H), 0.88 (t, *J* = 6.9 Hz, 3H). EI-MS (m/z): 292 $[M]^+$.

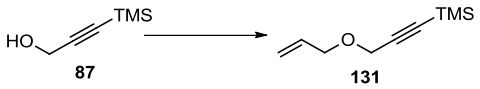
85: To a stirred solution of alcohol **129** (1.0 g, 3.4 mmol, 1.0 equiv), imidazole (0.69 g, 10.2 mmol, 3.0 equiv), and DMAP (42 mg, 0.34 mmol, 10 mol %) in CH2Cl2 (20 mL) was added solid TBSCl (0.78 g, 5.13 mmol, 1,5 equiv) at 0°C. The reaction was stirred overnight at rt and quenched with MeOH (0.14 ml, 3.4 mmol, 1.0 equiv). The solution was diluted with Et_2O, washed with sat. aq. NaHCO3, sat. aq. NH4Cl, and brine. The organic portion was dried with MgSO4 and concentrated to afford crude **85** (1.47 g, quantitative yield) which was used in the following transformation without further purification. ^{1}H NMR ($CDCl_3$) δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.51 – 5.29 (m, 2H), 4.45 (s, 2H), 3.89 – 3.82 (m, 1H), 3.81 (s, 3H), 3.36 (d, *J* = 5.4 Hz, 2H), 2.36 – 2.15 (m, 2H), 2.01 (dt, *J* = 6.9, 6.7 Hz, 2H), 1.40 – 1.17 (m, 6H), 0.97 – 0.80 (m, 12H), 0.05 (d, *J* = 1.6 Hz, 6H).^{13}C NMR ($CDCl_3$) δ 159.3, 132.2, 130.9, 129.4, 125.6, 113.9, 74.4, 73.2, 71.9, 55.5, 32.9, 31.8, 29.6, 27.6, 26.1, 22.8, 18.4, 14.3, -4.24, -0.45. EI-MS (m/z): 350 $[M - C(CH_3)_3]^+$.



130: To a stirred solution of **85** (1.28 g, 3.15 mmol, 1.0 equiv) in NaH_2PO_4 buffer (pH 7, 2.0 mL) and CH_2Cl_2 (32 mL) at 0°C was added solid DDQ (1.1 g, 4.73 mmol, 1.5 equiv) in two portions. The reaction was allowed to stir overnight at 0°C after which the solids were removed by filtering the mixture through a plug of Celite. The solution was diluted with $CHCl_3$ and washed 3 times with saturated aqueous $NaHCO_3$. The organic portion was dried with MgSO4 and concentrated to afford the crude mixture of **130** that was used directly in the following oxidation.

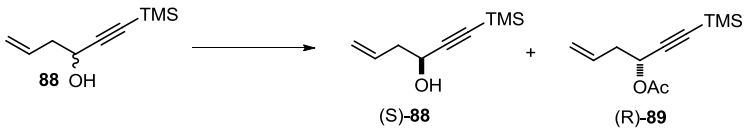
86: Primary alcohol **130** (0.374 g, 1.3 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (8.0 mL), treated with NaH_2CO_3 (0.33 g, 3.9 mmol, 3.0 equiv), and cooled to 0°C. At this time, solid Dess-Martin periodinane (0.853 g, 1.95 mmol, 1.5 equiv) was added to the stirred suspension in 2 portions. The oxidation was complete after stirring for 3 hours at 0°C. The reaction was quenched with a 1:1 solution of 20% aqueous $Na_2S_2O_3$ / sat.aqueous NaH_2CO_3 (1:1), extracted with CH_2Cl_2, and dried with $MgSO_4$. Purification by flash chromatography (1-4 % EtOAc in hexanes) afforded aldehyde **86** (0.34 g, 1.2 mmol, 92 % yield) as a yellow oil. This α–hydroxy aldehyde is very unstable and was used directly in the following step without being completely characterized. A small aliquot was removed to obtain the ^{1}H NMR spectrum. ^{1}H NMR ($CDCl_3$) δ 9.6 (s, *J* = 1.3 Hz, 1H), 5.58 – 5.48 (m, 1H), 5.44 – 5.32 (m, 1H), 3.99 (dt, *J* = 6.3, 1.7

Hz, 1H), 2.39 (t, *J* = 6.7 Hz, 2H), 2.02 (dt, *J* = 7.0, J = 6.9 Hz, 2H), 1.40 – 1.19 (m, 6H), 0.93 – 0.91 (m, 9H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.08 (d, *J* = 4.2 Hz, 6H).



131: This reaction was conducted following a similar, known procedure.[51] EtMgBr (3.0 M in Et_2O, 16.7 mL, 50 mmol, 1.0 equiv) was added slowly to a solution of 3-(Trimethylsilyl)propargyl alcohol (7.39 mL, 50 mmol, 1.0 equiv), 1,10-phenanthroline (25 mg), and HMPA (35 mL, 100 mmol, 4 equiv) in THF (250 mL) at 0°C. After stirring for 10 minutes, allyl bromide (6.59 mL, 75 mmol, 1.5 equiv) was added at 0°C and the reaction was heated to reflux for 4 hours. The reaction was allowed to cool to rt, quenched with 0.1 N HCl, and extracted with 3 times with Et_2O. The organic portions were combined, washed with H_2O and brine, dried with $MgSO_4$, and concentrated. The crude mixture was filtered through a plug of SiO_2 with 5% Et_2O in hexanes to afford pure **131** (7.6 g, 45.2 mmol, 90% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ = 5.98 – 5.84 (m, 1H), 5.42 – 5.09 (m, 2H), 4.15 (s, 2H), 4.06 (dt, *J* = 5.8, 1.4 Hz, 2H), 0.19 (s, 9H). ^{13}C NMR ($CDCl_3$) δ = 134.2, 118.2, 101.6, 91.6, 70.9, 58.2, 0.07. EI-MS (m/z): 168 $[M]^+$.

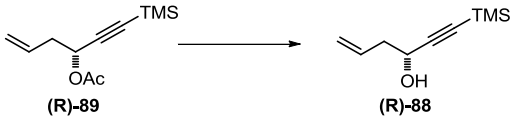
88: ^{n}BuLi (2.5 M in hexanes, 18.1 mL, 45.2 mmol, 1.0 equiv) was added to a stirred solution of **31** (7.6 g, 45.2 mmol, 1.0 equiv) in THF (220mL) at -78°C. The reaction stirred for 20 minutes at this temperature, warmed to -30°C, quenched with 0.5 N HCL (100 mL) and allowed to warm to rt. The mixture was extracted with Et_2O and the organic portion was washed twice with H_2O, once with brine, and dried with $MdSO_4$. Concentrating the material afforded **88** (7.28 g, 43.3 mmol, 96% yield) as a yellow oil, which was used in the following step without further purification. ^{1}H NMR ($CDCl_3$) δ = 5.97 – 5.74 (m, 1H), 5.25 – 5.06 (m, 2H), 4.40 (dt, *J* = 6.1, 6.0 Hz, 1H), 2.46 (ddd, *J* = 7.2, 6.2, 1.1 Hz, 2H), 1.99 (d, *J* = 6.0 Hz, 1H), 0.16 (s, 9H). ^{13}C NMR ($CDCl_3$) δ = 133.2, 118.7, 106.4, 89.7, 62.0, 42.2, -0.03. EI-MS (m/z): 168 $[M]^+$.



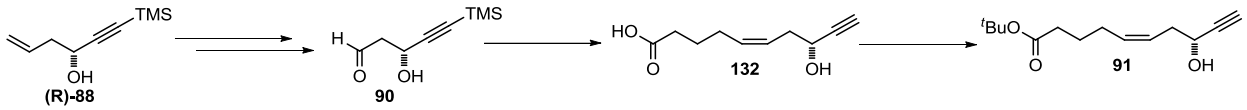
(S)-**88** & (R)-**89**: (S)-**88** and (R)-**89** were resolved from racemic propargylic alcohol **88** following a known procedure.[84] The crude products were isolated using flash chromatography (2.5% - 20% EtOAC in hexanes) to afford pure (S)-**88** (3.31 g, 19.7 mmol, 46% yield) and (R)-**89** (4.09 g, 19.5 mmol, 45% yield, 97% ee). The ee of (R)-**89** (97%) was determined from its benzoylated analog (BzCl, Et_3N, cat. DMAP, CH_2Cl_2) by HPLC. Specific HPLC conditions and chromatograms are located in Appendix 2.

(S) - **88**: ^{1}H NMR ($CDCl_3$) δ = 5.97 – 5.74 (m, 1H), 5.25 – 5.06 (m, 2H), 4.40 (dt, *J* = 6.1, 6.0 Hz, 1H), 2.46 (ddd, *J* = 7.2, 6.2, 1.1 Hz, 2H), 1.99 (d, *J* = 6.0 Hz, 1H), 0.16 (s, 9H). ^{13}C NMR ($CDCl_3$) δ = 133.2, 118.7, 106.4, 89.7, 62.0, 42.2, -0.03. EI-MS (m/z): 168 $[M]^+$.

(R)-**89**: 1H NMR ($CDCl_3$) δ = 5.81 (m, 1H), 5.42 (t, *J* = 6.4 Hz, 1H), 5.20 – 5.07 (m, 2H), 2.51 (dt, *J* = 6.8, 6.7, 2H), 2.08 (s, 3H), 0.17 (s, Hz, 9H). ^{13}C NMR ($CDCl_3$) δ = 169.9, 132.4, 118.9, 102.2, 91.0, 63.7, 39.5, 21.2, -0.04. EI-MS (m/z): 210 $[M]^+$.



(R)-**88:** (R)-**89** was reduced to the corresponding free propargylic alcohol **(R)-88** following a similar literature procedure. DIBAL (1.0 M in heptane, 48.4 mL, 48.4 mmol, 1.7 equiv) was slowly added to a stirred solution of (R)-**89** (5.99 g, 28.5 mmol, 1.0 equiv) in CH_2Cl_2 (23 mL) at -78°C. The reaction was complete after one hour, at which time the excess DIBAL was quenched by adding 3 mL EtOAc at -78°C. After stirring for an additional 20 minutes, a 10% aqueous solution of citric acid (~100 mL) was added and the reaction was allowed to stir for one hour at rt. The layers were separated and the aqueous portion was extracted with CH_2Cl_2. The combined organic fractions were pooled, dried with $MgSO_4$, and concentrated to afford (R)-**88** (4.9 g, 29 mmol, quantitative yield) as a colorless oil which was used without further purification. ^{1}H NMR and ^{13}C NMR spectra were identical to those of the corresponding enantiomer, (S)-**88** (see above). The ee of (R)-**88** (97%) was determined from its benzoylated analog (BzCl, Et_3N, cat. DMAP, CH_2Cl_2) by HPLC. Specific HPLC conditions and chromatograms are located in Appendix 2.

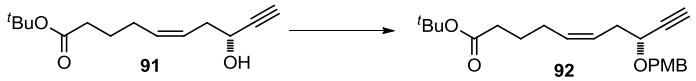


90: *tert*-Butyl etser **91** was prepared from (R)-**88** using a 4-step procedure:[85] NMO (1.81 g, mmol, 1.5 equiv) was added to stirred solution of terminal olefin **88** (1.68 g, mmol, 1.0 equiv) in acetone/CH_3CN (1:1, 55 mL) and H_2O (5 mL) at rt. The mixture was brought to 0°C and a solution of OsO_4 (10 mg/1.0 mL solution in H_2O, 6.4 mL, 0.25 mmol, 2.5 mol %) was added. The reaction stirred overnight at 0°C and was quenched with a 20% $Na_2S_2O_3$. The solution was warmed to rt, the organic solvents were removed in vacuo leaving the aqueous portion from which the desired triol was rigorously extracted with EtOAc. The organic portion was dried with Na_2SO_4 and concentrated to afford the crude triol which was dissolved in THF (75 mL) and H_2O (75 mL). $NaHCO_3$ (1.26 g, 15 mmol, 1.5 equiv) was added to stirred solution of triol and the mixture was cooled to 0°C, after which $NaIO_4$ (6.4 g, 30 mmol, 3 equiv) was added. After stirring for 20 minutes, the reaction was allowed to warm to rt and stirred for one hour before the solids were filtered. The filtrate was diluted with H_2O and Et_2O, extracted with Et_2O, dried with $MgSO_4$, and concentrated to volume of ~ 5 mL. This was diluted with THF (30 mL) and allowed to sit in the presence of activated 3Å molecular sieves for one hour. The dry solution of aldehyde (**90**) was unstable and immediately used in the following Wittig olefination without further purification.

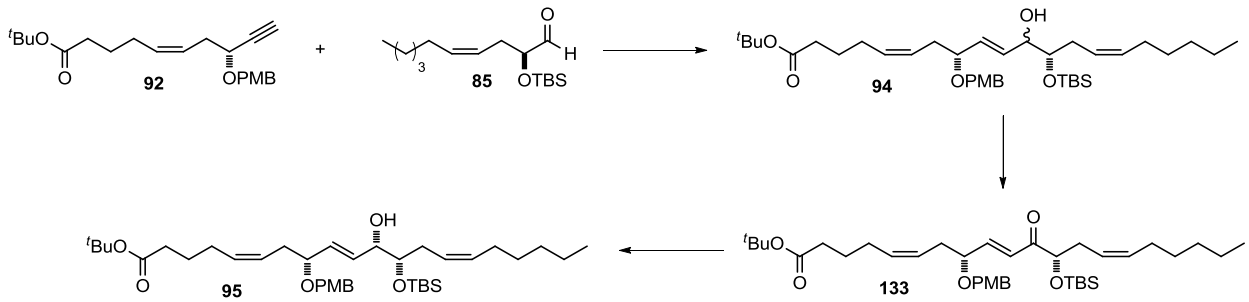
132: NaHMDS (1.0 M in THF, 40 mL, 40 mmol, 4 equiv) was slowly added to a stirred suspension of $[Ph_3P(CH_2)_4CO_2H]Br$ (6.79 g, 15 mmol, 1.5 equiv) in THF (200 mL) at 0°C and the resulting dark red solution was stirred at this temperature for one hour until complete dissolution of the phosphonium salt was observed. The solution was then cooled to -78°C and the dry solution of crude aldehyde (**90**) in THF (30 mL) was added to the reaction via canula. The reaction was stirred for one hour at -78°C and allowed to slowly warm to 0°C over 3 hours. To cleave the trimethylsilyl protecting group, 10 mL H_2O was added at 0°C and the resulting solution stirred for an additional 10 minutes at rt. The THF was then removed in vacuo and the remaining mixture was acidified with 1 N HCl, extracted with EtOAc, dried with $MgSO_4$ and concentrated. The crude hydroxy acid was filtered through a plug of SiO_2 with 75% EtOAc in hexanes to afford an inseparable mixture of the desired **132** and triphenylphosphine oxide. A small sample was kept for characterization purposes (^{1}H NMR) while the remainder of the hydroxy acid (contaminated with Ph_3PO) was protected as the *tert*-butyl ester in the following step. ^{1}H NMR ($CDCl_3$) δ = 5.66 – 5.43 (m, 2H), 4.40 (dt, *J* = 6.2, 2.1 Hz, 1H), 2.48 (t, *J* = 6.4 Hz, 2H), 2.45 (d, *J* = 2.1 Hz, 1H), 2.35 (t, *J* = 7.3 Hz, 2H), 2.13 (dt, *J* = 7.0, 6.8 Hz, 2H), 2.04 (s, 1H), 1.77 – 1.67 (m, 2H).

91: Hydroxy acid **132** was protected as the *tert*-butyl ester **91** following a similar, known procedure.[53] Trifluoroacetic anhydride (14.2 mL, 100 mmol, 10 equiv) was added to a stirred solution of crude

hydroxy acid **132** (~10 mmol, see previous step above) in THF (100mL) at 0°C and the reaction was allowed to stir for 1.5 hours at rt. The reaction was then cooled to 0°C, treated with ^{t}BuOH (21.3 mL, 220 mmol, 22 equiv), and allowed to stir for 16 hours at rt. The reaction was again cooled to 0°C and conc. NH_4OH (25 mL) was slowly added. After stirring for an addition 3 hours at rt, the THF was removed in vacuo, and the mixture was diluted with Et_2O, washed with 5% HCl, extracted with Et_2O, and dried with $MgSO_4$. The crude material was purified by flash chromatography (5-15% EtOAc in hexanes) to afford **91** as a yellow oil (1.55 g, 6.32 mmol, 63% yield). ^{1}H NMR ($CDCl_3$) δ 5.54 – 5.43 (m, 2H), 4.37 – 4.30 (m, 1H), 2.93 (s, 1H), 2.44 – 2.41 (m, 2H), 2.40 (d, *J* = 1.1 Hz, 1H), 2.16 (t, *J* = 7.4 Hz, 2H), 2.04 (dt, *J* = 7.1, 7.0 Hz, 2H), 1.65 – 1.55 (m, 2H), 1.38 (s, 9H). ^{13}C NMR ($CDCl_3$) δ = 173.4, 132.7, 124.7, 84.8, 80.4, 73.0, 61.7, 35.6, 35.0, 28.2, 26.8, 25.0. EI-MS (m/z): 338 $[M]^+$.



92: To a stirred solution of **91** (0.715 g, 3.0 mmol, 1.0 equiv) and PMB acetimidate (0.934 g, 4.5 mmol, 1.5 equiv) in toluene (20 mL) at 0°C was added solid $Cu(OTf)_2$ (0.109 g, 0.3 mmol, 0.1 equiv).[54] After stirring for one hour at this temperature, the reaction was quenched with MeOH (1-2 equiv). The resulting solution was washed with a 1:1 mixture of saturated aqueous NH_4Cl and 10% NH_4OH and extracted 3 times with Et_2O. The organic portions were pooled, dried with MgSO4, and concentrated. The crude alkyne was purified by flash chromatography (3-10% EtOAC in hexanes) to afford **92** (0.897 g, 2.51 mmol, 84% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.29 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.53 – 5.48 (m, 2H), 4.74 (d, *J* = 11.4 Hz, 1H), 4.45 (d, *J* = 11.4 Hz, 1H), 4.05 (dt, *J* = 6.6, 2.0 Hz, 1H), 3.80 (s, 3H), 2.52 – 2.47 (m, 2H), 2.47 (d, *J* = 2.0 Hz, 1H), 2.20 (t, *J* = 7.5 Hz, 2H), 2.06 (dt, *J* = 7.2, 7.0 Hz, 2H), 1.70 – 1.58 (m, 2H), 1.44 (s, 9H).^{13}C NMR ($CDCl_3$) δ 173.2, 159.5, 132.0, 130.0, 129.9, 125.1, 114.0, 82.9, 80.3, 74.3, 70.4, 68.0, 55.5, 35.2, 33.8, 28.4, 27.1, 25.1. EI-MS (m/z): 358 $[M]^+$.

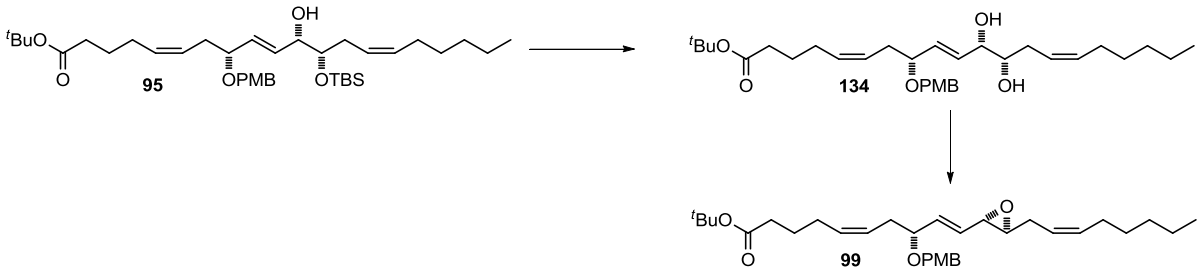


94: Solid $Cp_2Zr(H)Cl$ (0.392 g, 1.45 mmol, 1.15 equiv) was added to a stirred solution of alkyne **92** (0.45 g, 1.26 mmol, 1.0 equiv) in 7 mL CH_2Cl_2 at 0°C. The hydrozirconation was complete after 1.5 hours, after which the solution was cooled to -78°C. At this time, a solution of Me_2Zn (2.0 M in toluene, 0.73 mL, 1.45 mmol, 1.15 equiv) was added slowly over 10 minutes to the solution of vinyl zirconium at -78°C. After stirring for 15 minutes at -78°C the reaction was place in an ice bath and allowed to warm to 0°C. The solution was then allowed to stir for an additional 15 minutes at 0°C, after which a solution of the aldehyde **85** (0.31 g, 1.1 mmol, 0.87 equiv) in CH_2Cl_2 (1.0 mL) was added at the same temperature. The aldehyde was allowed to react overnight at 0°C. The reaction was quenched with a 10% aqueous solution of citric acid (15 mL) and the heterogeneous mixture was stirred for one hour until two clear phases were present. The organic layer was separated and the aqueous layer was washed 3 times with CH_2CL_2. The organic portions were dried with $MgSO_4$ and concentrated to afford alcohol **94** as a 3.3 : 1 mixture of diastereomers (*syn* / *anti*). The crude oil was taken directly into the Dess-Martin oxidation without further purification.

133: The crude mixture of diastereomers (~ 1.1 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (5.5 mL), treated with NaH_2CO_3 (0.37 g, 4.4 mmol, 4.0 equiv), and cooled to 0°C. At this time, solid Dess-Martin periodinane (0.96 g, 2.2 mmol, 2.0 equiv) was added to the stirred suspension in 3 portions. After 20 minutes, the reaction was removed from the ice bath and allowed to slowly warm to rt. The oxidation was complete after stirring for 1.5 hours at rt. The reaction was quenched with a 1:1 solution of 20% aqueous $Na_2S_2O_3$ / sat.aqueous NaH_2CO_3 (1:1), extracted with CH_2Cl_2, and dried with $MgSO_4$. The solution was concentrated to afford the crude α,β-unsaturated ketone which was used in the following reduction without further purification.

95: To a stirred suspension of crude **133** (~1.1 mmol, 1.0 equiv) and $CeCl_3$ (0.414 g, 1.1 mmol, 1.0 equiv) in MeOH (11 mL) at -78°C was added solid $NaBH_4$ (42 mg, 1.1 mmol, 1.0 equiv). After stirring for one hour, the reaction was warmed to 0C and quenched according to a known procedure.[86] The reaction was

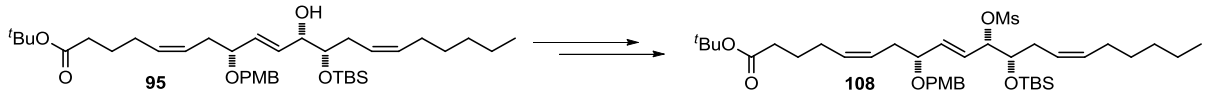
extracted with EtOAc and the organic portions were pooled, washed with brine and dried with $MgSO_4$. Purification by flash chromatography (5-15% EtOAc in hexanes) afforded the syn-diol (**95**, 0.554 g, 0.86 mmol) as a single diastereomer in 78% yield over 3 steps. ^{1}H NMR ($CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.69 – 5.64 (m, 2H), 5.54 – 5.44 (m, 1H), 5.45 – 5.33 (m, 3H), 4.53 (d, *J* = 11.5 Hz, 1H), 4.30 (d, *J* = 11.5 Hz, 1H), 4.03 – 3.98 (m, 1H), 3.80 (s, 3H), 3.79 – 3.73 (m, 1H), 3.60 (dt, *J* = 6.8, 4.9 Hz, 1H), 2.44 (d, *J* = 6.2 Hz, 1H), 2.43 – 2.34 (m, 2H), 2.30 – 2.21 (m, 1H), 2.19 (t, *J* = 7.6 Hz, 2H), 2.09 – 1.96 (m, 4H), 1.69 – 1.57 (m, 2H), 1.44 (s, 9H), 1.40 – 1.19 (m, 6H), 0.91 (s, 9H), 0.88 (t, *J* = 6.9 Hz, 3H), 0.09 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 173.3, 159.2, 133.6, 132.9, 132.7, 131.0, 130.9, 129.5, 126.3, 124.8, 113.9, 80.3, 79.3, 75.8, 73.6, 70.1, 55.5, 35.3, 33.8, 31.8, 29.5, 28.4, 27.7, 27.0, 26.1, 25.1, 22.8, 18.3, 14.3, -3.91, -4.33.[87] MS (ESI) calculated $C_{38}H_{64}O_6SiNa^+$ $[MNa]^+$ 668.0, found 667.5.



134: To a stirred solution of **95** (10 mg, 0.0159 mmol, 1.0 equiv) in THF (0.2 mL) at 0C was added a solution of TBAF (1.0 M in THF, 0.24 μL, 0.024 mmol, 1.5 equiv) dropwise. After stirring for two hours at this temperature, the reaction was quenched with 0.6 mL H_2O. The resulting biphasic mixture was stirred for an additional 30 minutes and extracted 3 times with Et_2O. The organic portions were washed with brine, dried with Na_2SO_4 and concentrated to afford the crude diol **134** (8.1 mg, 0.0152 mmol, 96% yield). A small aliquot was removed to characterize by ^{1}H NMR and the crude compound (**134**) was taken directly into the following reaction without further purification. ^{1}H NMR ($CDCl_3$) δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.72 – 5.67 (m, 2H), 5.58 (dt, *J* = 10.8, 7.3 Hz, 1H), 5.50 – 5.32 (m, 3H), 4.52 (d, *J* = 11.5 Hz, 1H), 4.33 (d, *J* = 11.5 Hz, 1H), 4.08 – 3.96 (m, 1H), 3.86 – 3.74 (m, 4H), 3.59 – 3.44 (m, 1H), 2.57 (d, *J* = 3.9 Hz, 1H), 2.45 – 2.22 (m, 5H), 2.19 (t, *J* = 7.5 Hz, 2H), 2.10 – 1.94 (m, 4H), 1.68 – 1.57 (m, 2H), 1.44 (s, 9H), 1.40 – 1.24 (m, 6H), 0.88 (t, *J* = 6.8 Hz, 3H).

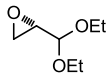
99: Epoxide **99** was prepared from diol **134** following a procedure reported by Sharpless *et al*.[55] To a stirred solution of **134** (8.1 mg, 0.0152 mmol, 1.0 equiv) and PPTS (0.2 mg, 0.0008 mmol, 5 mol %) in CH_2Cl_2 (0.3 mL) at rt was added trimethoxy orthoacetate (2.7 μL, 0.0213 mmol, 1.4 equiv). TLC showed no starting material after 45 minutes, at which time the solvent was removed by rotary evaporation. The

reaction vessel (1 dram vial) was placed under high vacuum (oil pump) for three minutes, after which the residue was suspended in CH_2Cl_2 (0.3 mL) and cooled to 0°C. At this time, Et_3N (0.2 μL, 0.0023 mmol, 0.1 equiv) and AcBr (1.7 μL, 0.0228 mmol, 1.5 equiv) were added sequentially to the suspension at 0°C. After stirring for one hour at this temperature, the reaction was removed from the ice bath, allowed to warm to rt, and stirred for one additional hour. The solvent was then removed and the vial was placed under high vacuum for 15 minutes. The crude acetoxy bromide was suspended in MeOH (0.4 mL), cooled to 0°C, and treated with K_2CO_3 (4.2 mg, 0.0304 mmol, 2.0 equiv). After 5 minutes of stirring, the vial was removed from the ice bath, allowed to warm to rt, and stirred for an additional 2 hours at this temperature. The reaction was diluted with Et_2O, washed with saturated aqueous NH_4Cl, and extracted three times with Et_2O. The organic portion was dried with Na_2SO_4, concentrated, and subjected to flash chromatography (3-4% EtOAc in hexanes) to afford 6.5 mg of epoxide **99** (0.0126 mmol, 82% yield). ^{1}H NMR ($CDCl_3$) δ 7.23 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.82 (dd, *J* = 15.6, 7.8 Hz, 1H), 5.60 – 5.49 (m, 1H), 5.48 – 5.32 (m, 4H), 4.51 (d, *J* = 11.5 Hz, 1H), 4.29 (d, *J* = 11.5 Hz, 1H), 3.80 (s, 3H), 3.79 – 3.70 (m, 1H), 3.17 (dd, *J* = 7.9, 1.9 Hz, 1H), 2.87 (dt, *J* = 5.3, 2.0 Hz, 1H), 2.49 – 2.22 (m, 4H), 2.19 (t, *J* = 7.5 Hz, 2H), 2.09 – 1.98 (m, 4H), 1.67 – 1.58 (m, 2H), 1.44 (s, 9H), 1.41 – 1.19 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 173.3, 159.3, 136.0, 133.6, 131.1, 130.8, 129.5, 125.9, 123.1, 114.0, 80.3, 78.8, 70.2, 60.0, 57.7, 55.5, 35.2, 33.6, 32.2, 31.7, 23.0, 29.5, 28.4, 27.6, 27.3, 25.1, 22.8, 14.3. MS (ESI) calculated $C_{32}H_{48}O_5Na^+$ $[MNa]^+$ 535.7, found 535.3.



108: To a stirred solution of alcohol **95** (7.7 mg, 0.0119 mmol, 1.0 equiv) and Et_3N (2.2 μL, 0.016 mmol, 1.3 equiv) in CH_2Cl_2 (0.2 mL) at 0°C was added MsCl (1.1 μL, 0.0143 mmol, 1.2 equiv). TLC showed complete mesylation after 1.5 hours at 0°C. At this time, the reaction mixture was filtered through a plug of SiO_2 with 40% EtOAc in hexanes. Solvent removal revealed the crude allylic mesylate **108** (8.5 mg) in quantitative yield. The mesylate is unstable and could not be stored for extended periods of time. The structure of **108** was confirmed by ^{1}HNMR and the crude product was used in the following transformation without further purification. ^{1}H NMR ($CDCl_3$) δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.87 – 5.73 (m, 2H), 5.54 – 5.34 (m, 4H), 4.94 (app t, *J* = 5.8 Hz, 1H), 4.53 (d, *J* = 11.5 Hz, 1H), 4.34 (d, *J* = 11.5 Hz, 1H), 3.88 – 3.81 (m, 2H), 3.80 (s, 3H), 2.98 (s, 3H), 2.48 – 2.21 (m, 4H), 2.19 (t, *J* = 7.5 Hz, 2H), 2.08 – 1.90 (m, 4H), 1.72 – 1.57 (m, 2H), 1.44 (s, 9H), 1.38 – 1.19 (m, 6H), 0.98 – 0.79 (m, 12H), 0.09 (d, *J* = 10.7 Hz, 6H).

APPENDIX A2: NMR SPECTRA RELEVANT TO CHAPTER TWO



(S)-**65**

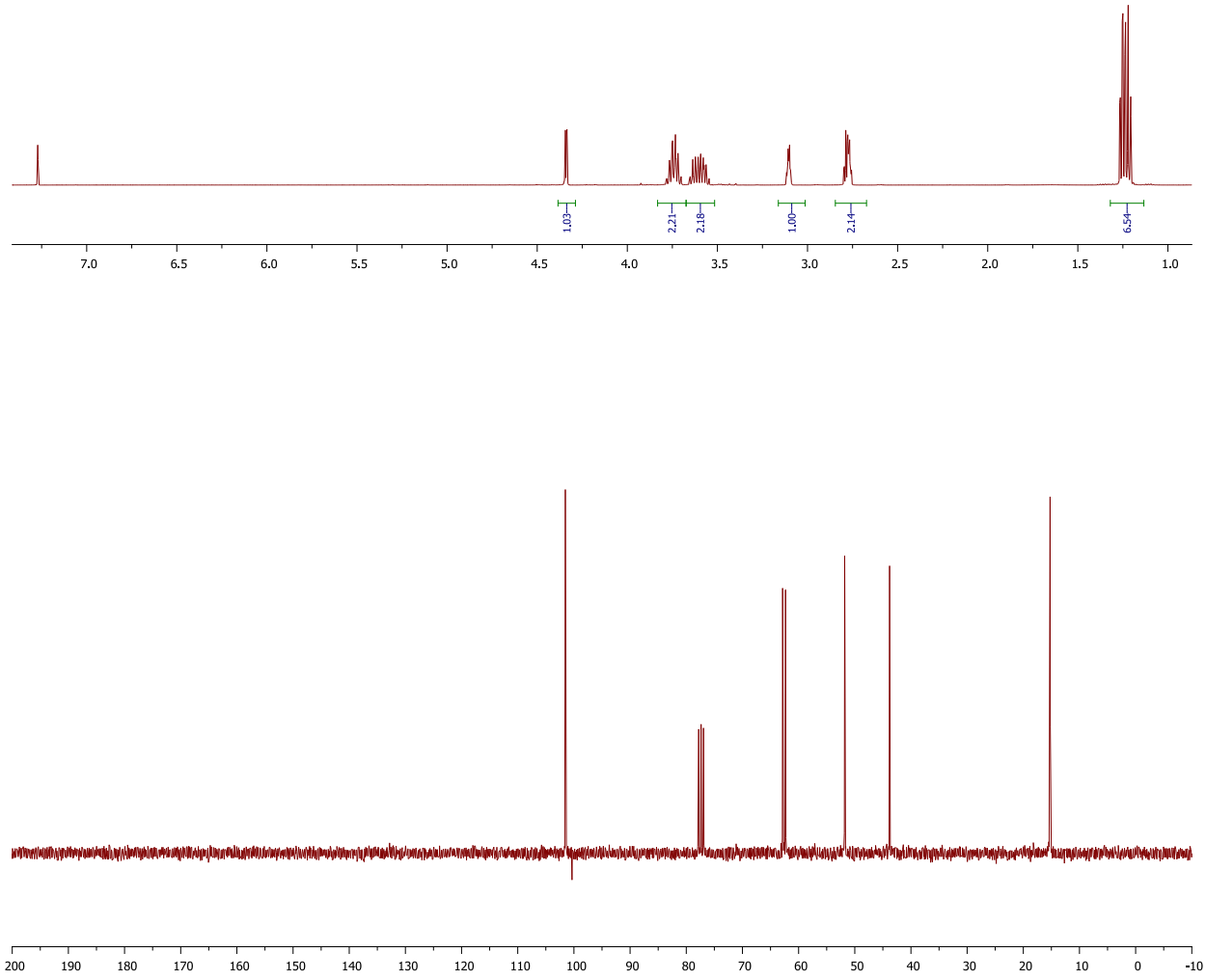
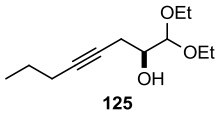


Figure A2. 1 ^{1}H and ^{13}C NMR Spectra for Compound (S)-65



125

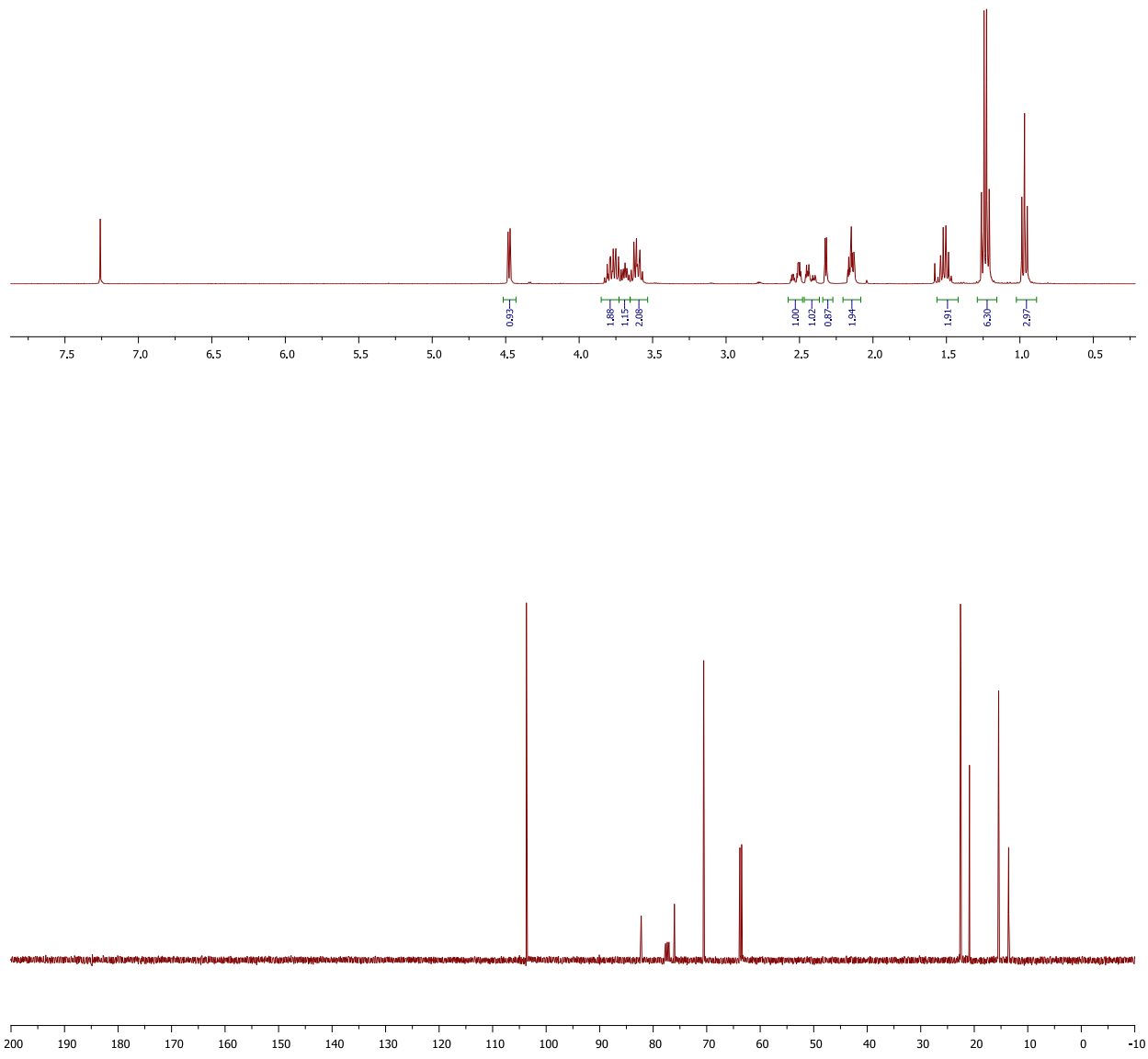
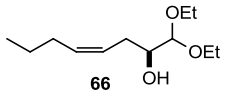


Figure A2. 2 ^{1}H and ^{13}C NMR Spectra for Compound 125



66

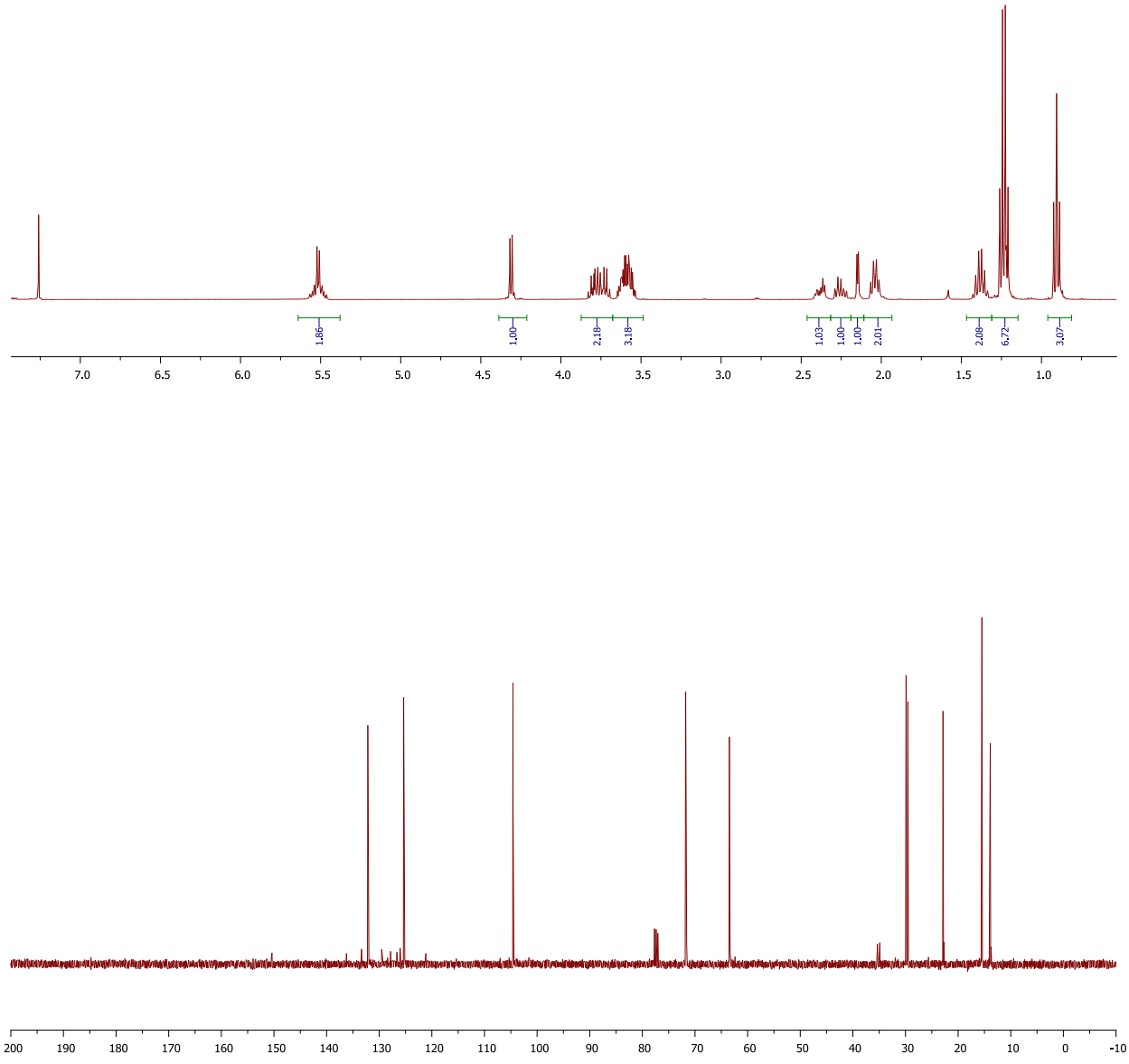
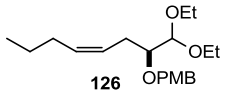


Figure A2. 3 ^{1}H and ^{13}C NMR Spectra for Compound 66



126

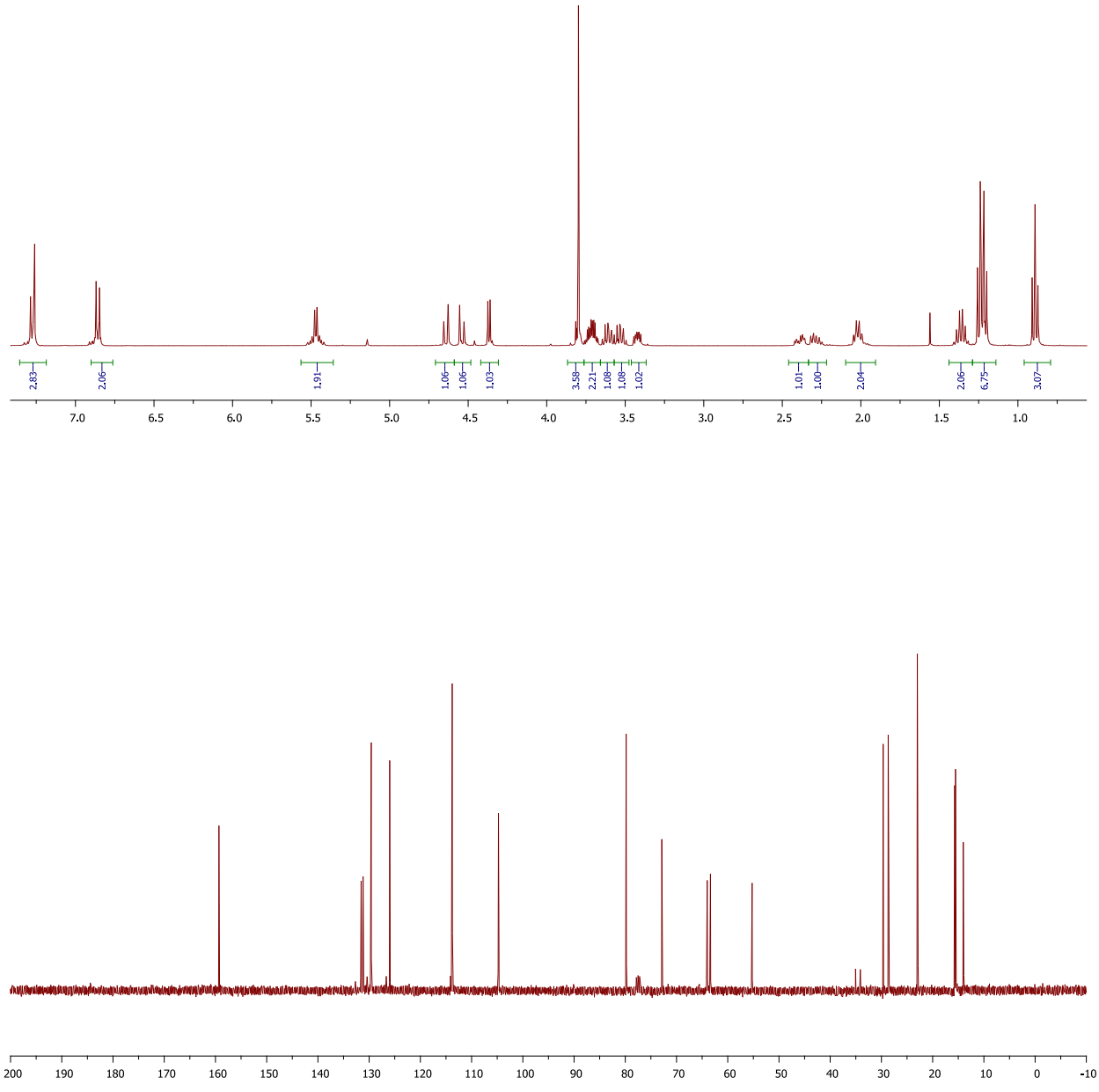


Figure A2. 4 ^{1}H and ^{13}C NMR Spectra for Compound 126

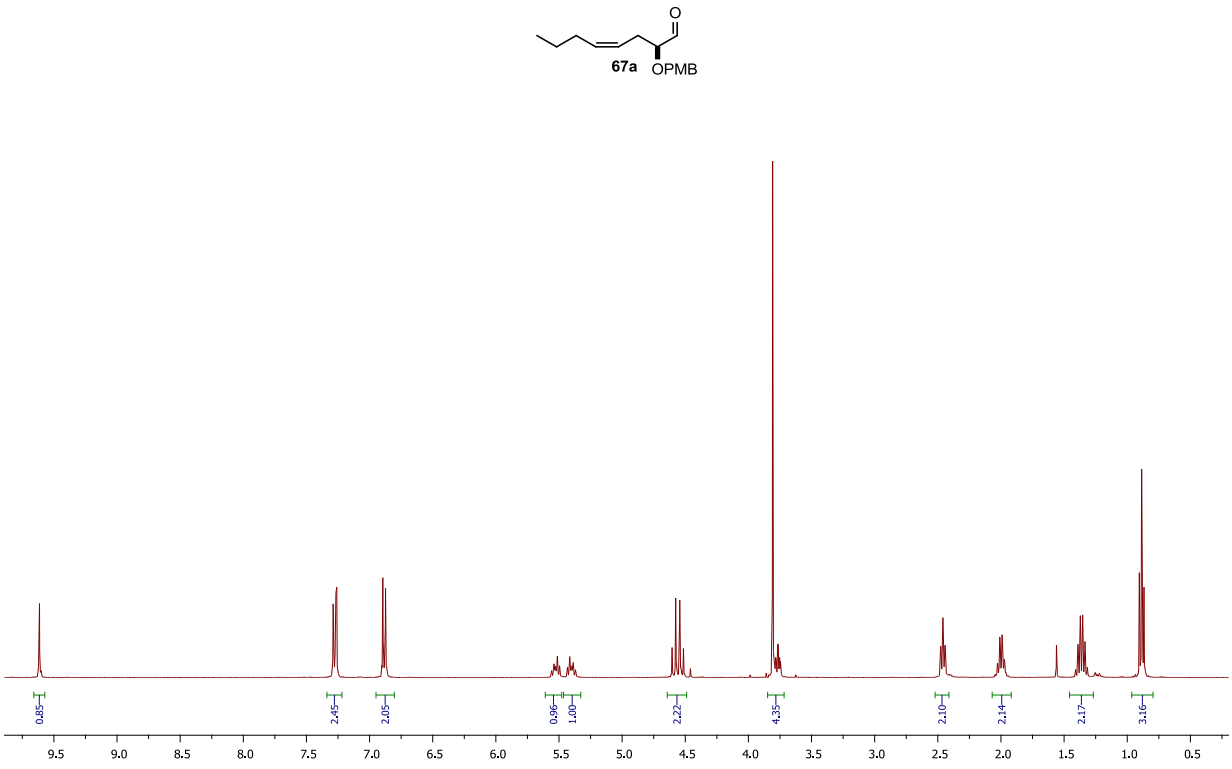


Figure A2. 5 ^{1}H NMR Spectrum of Compound 67a

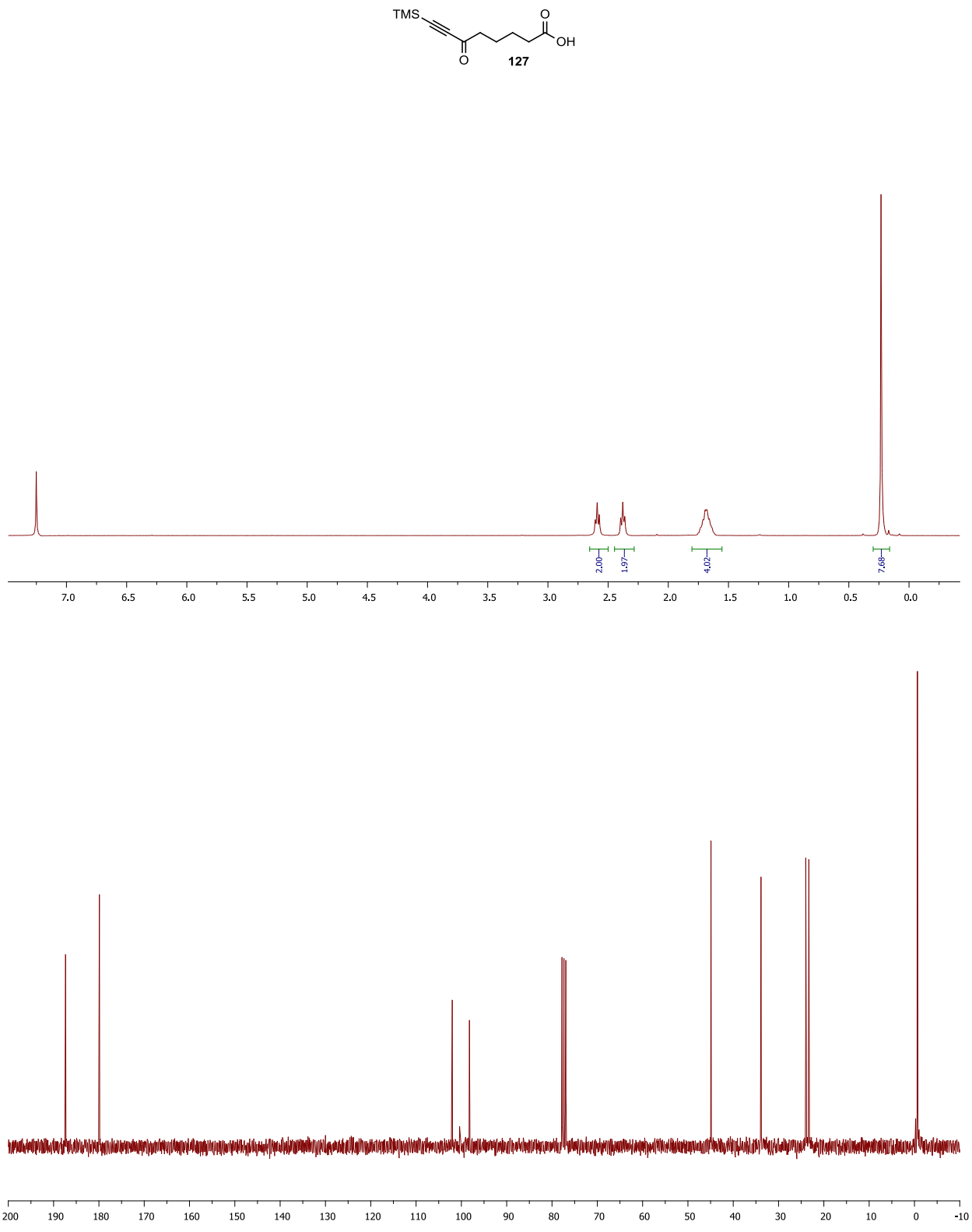


Figure A2. 6 ^{1}H and ^{13}C NMR Spectra for Compound 127

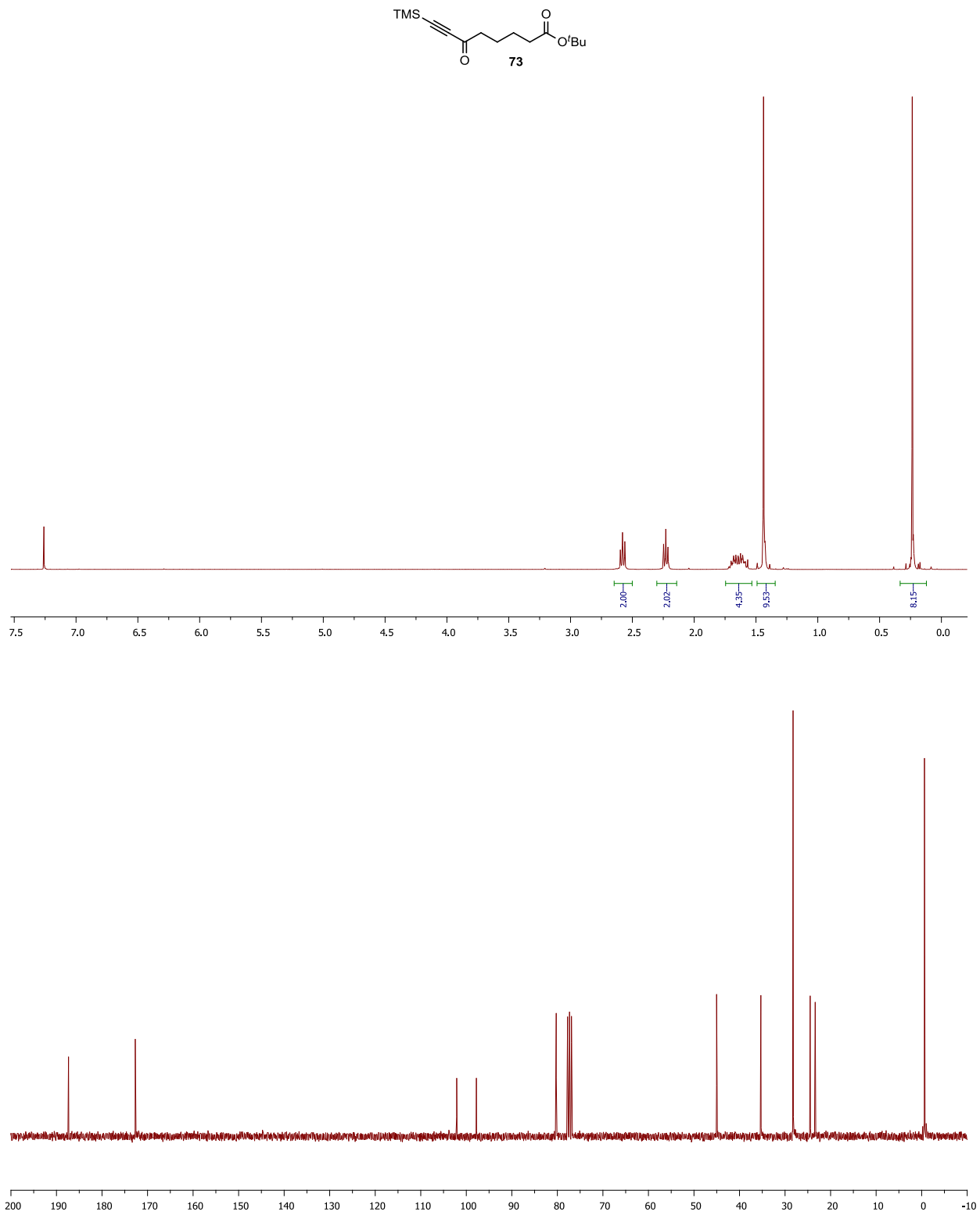


Figure A2. 7 ^{1}H and ^{13}C NMR Spectra for Compound 73

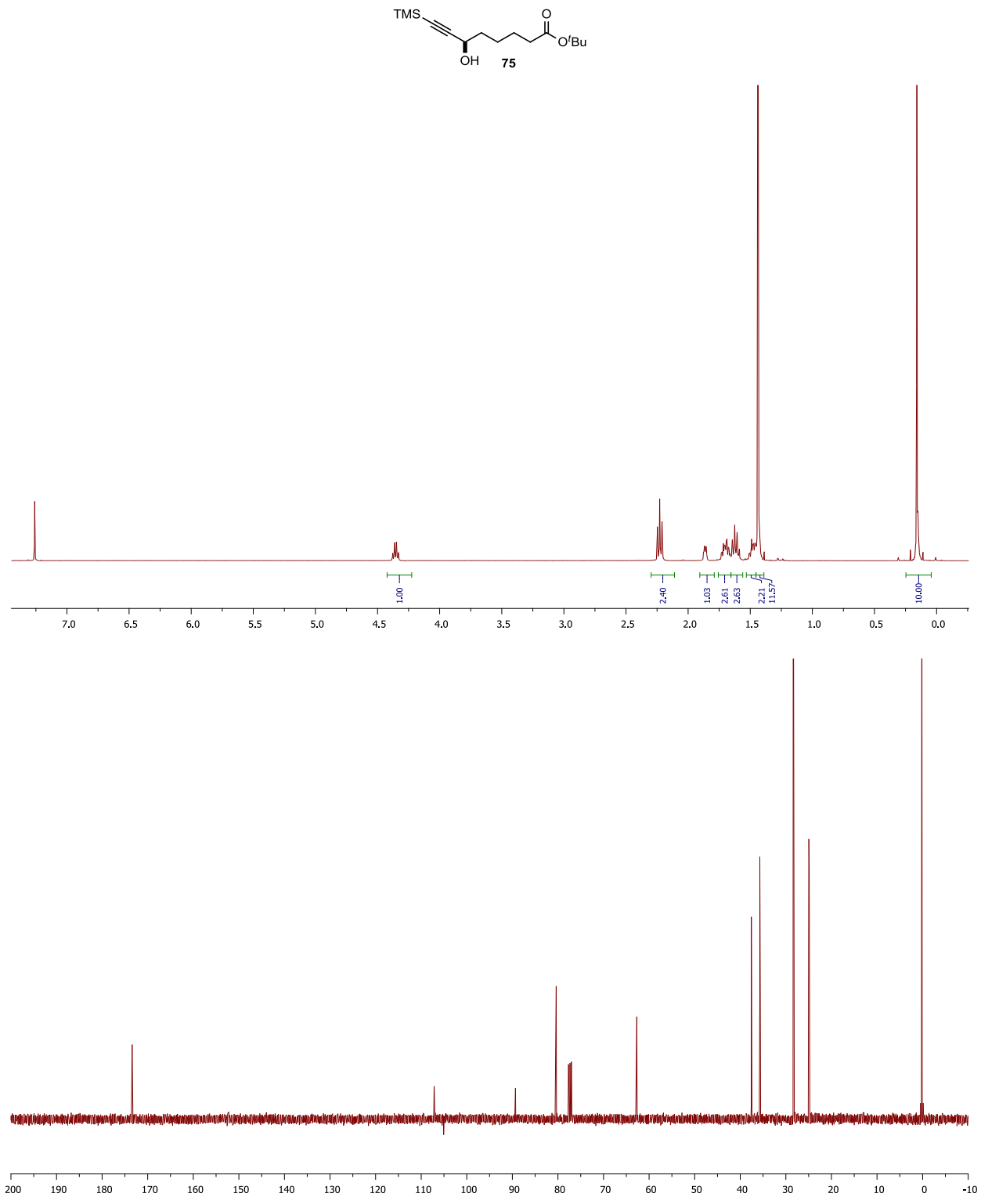


Figure A2. 8 ^{1}H NMR and ^{13}C NMR Spectra for Compound 75

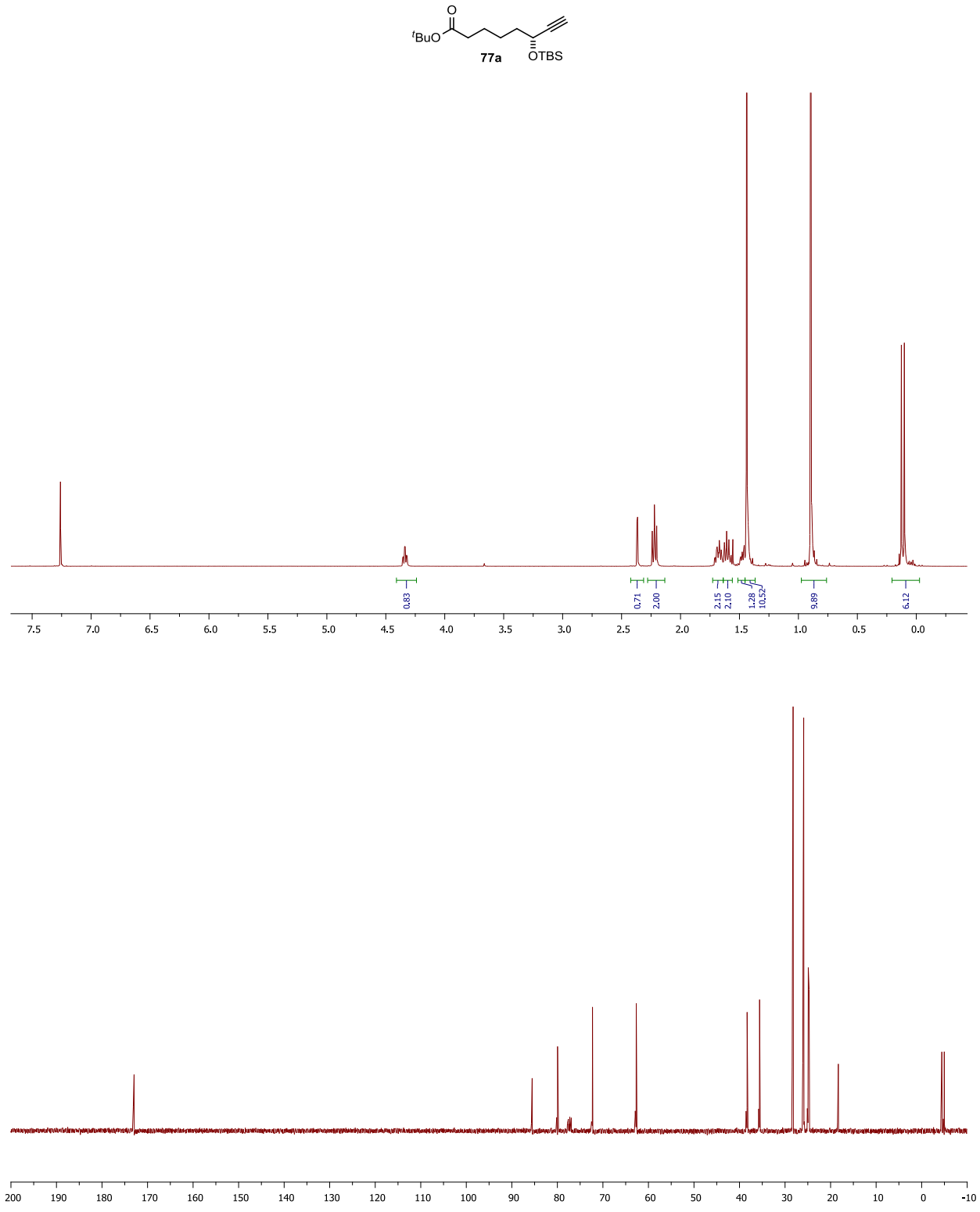


Figure A2. 9 ^{1}H NMR and ^{13}C NMR Spectra for Compound 77a

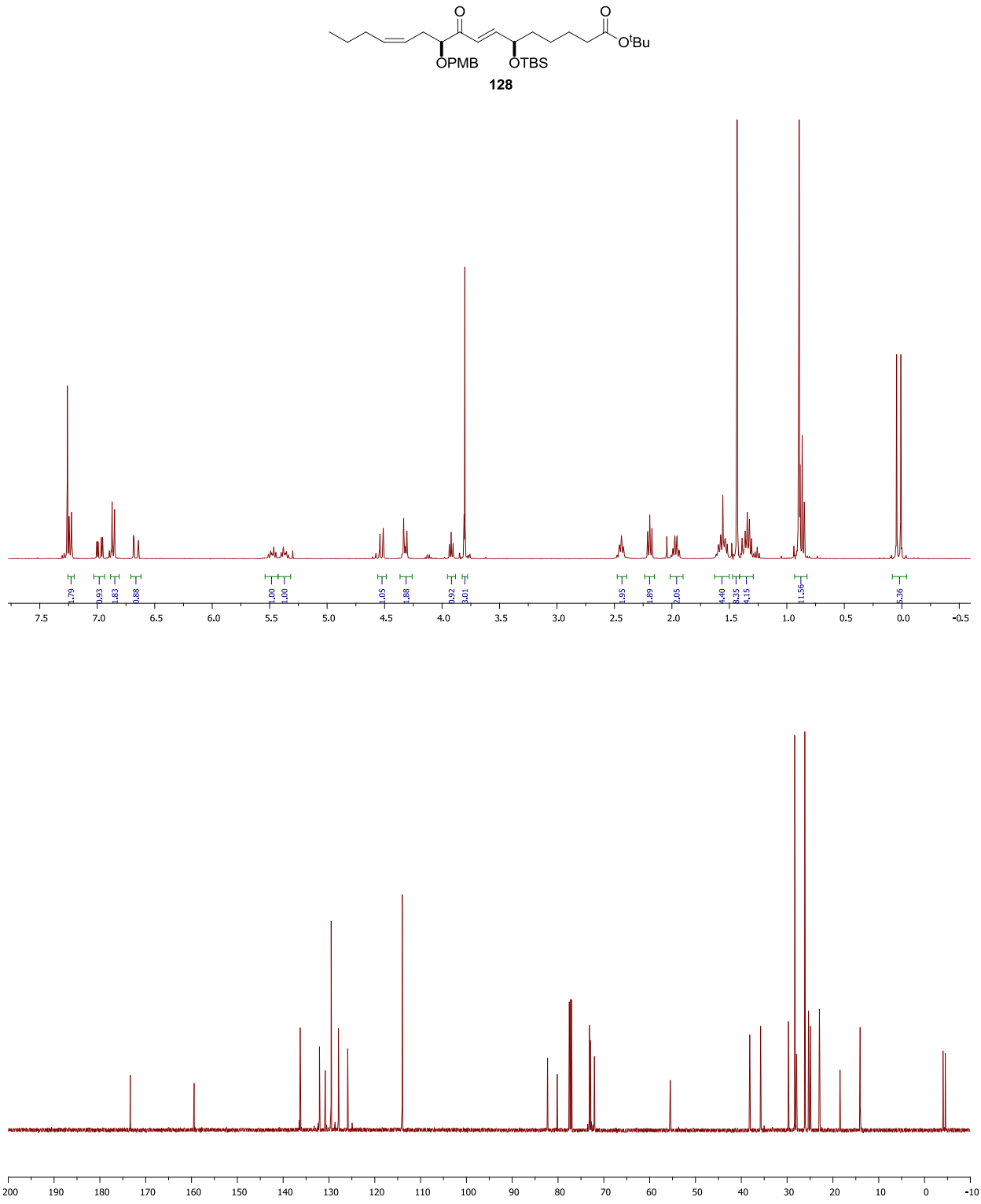


Figure A2. 10 ^{1}H NMR and ^{13}C NMR Spectra for Compound 128

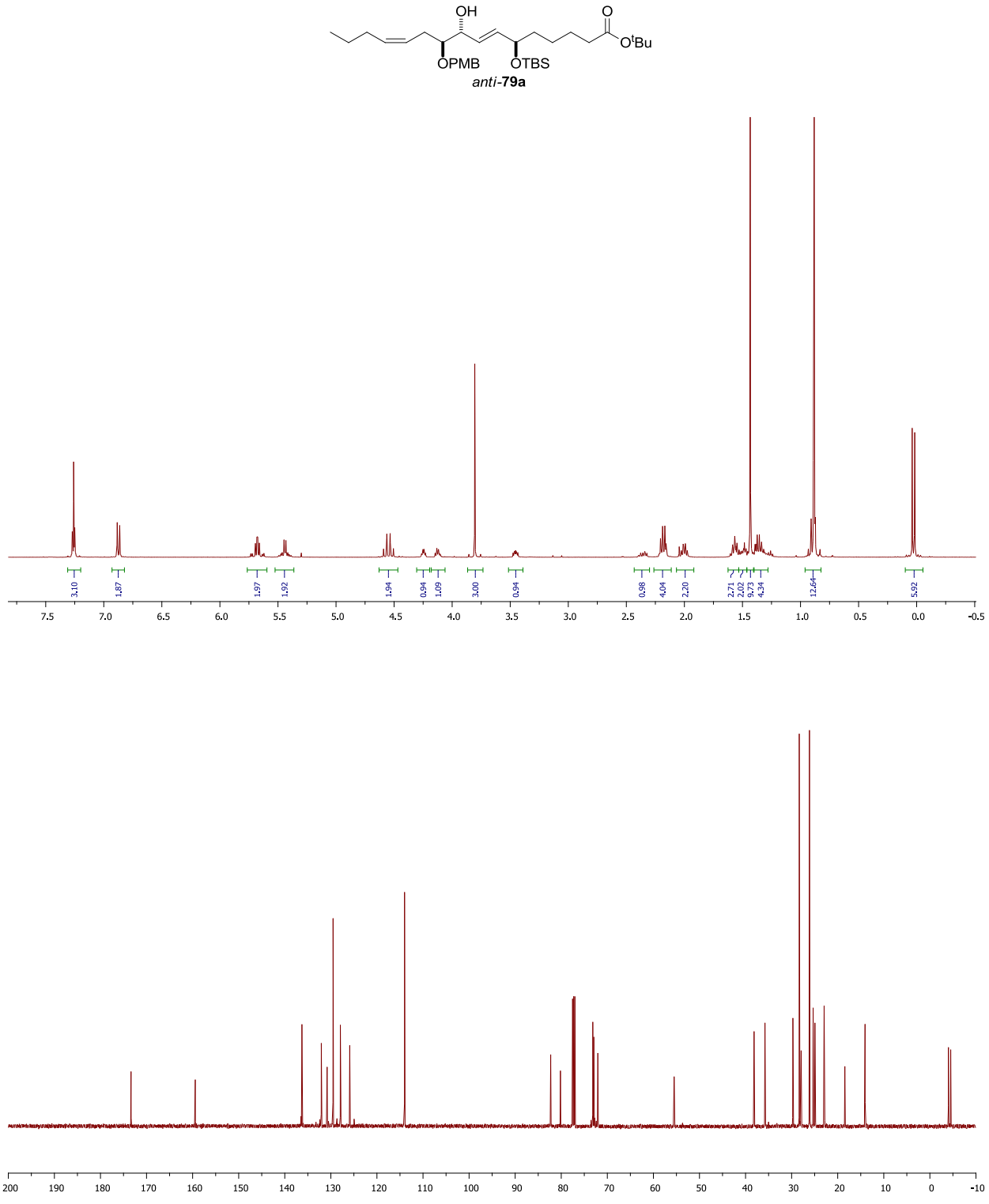


Figure A2. 11 ^{1}H NMR and ^{13}C NMR Spectra for Compound anti-79a

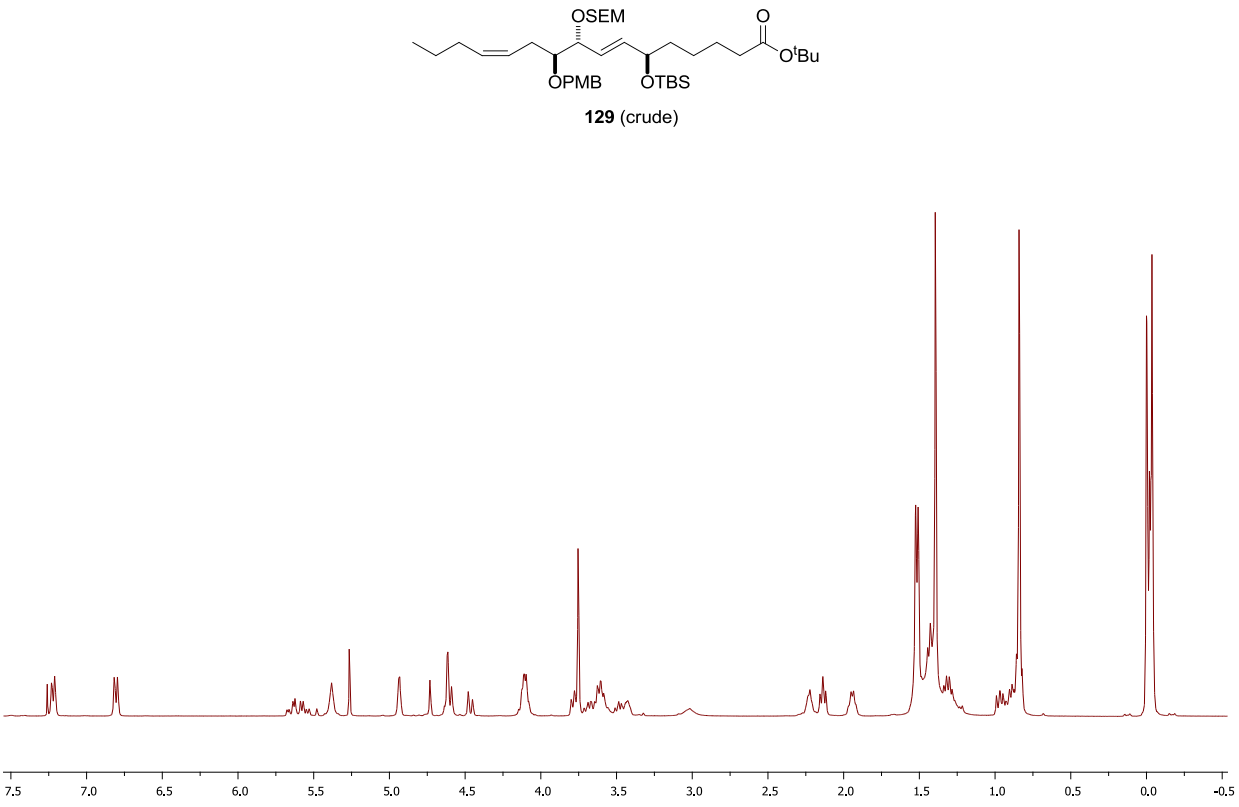


Figure A2. 12 ^{1}H NMR Spectrum of Compound 129

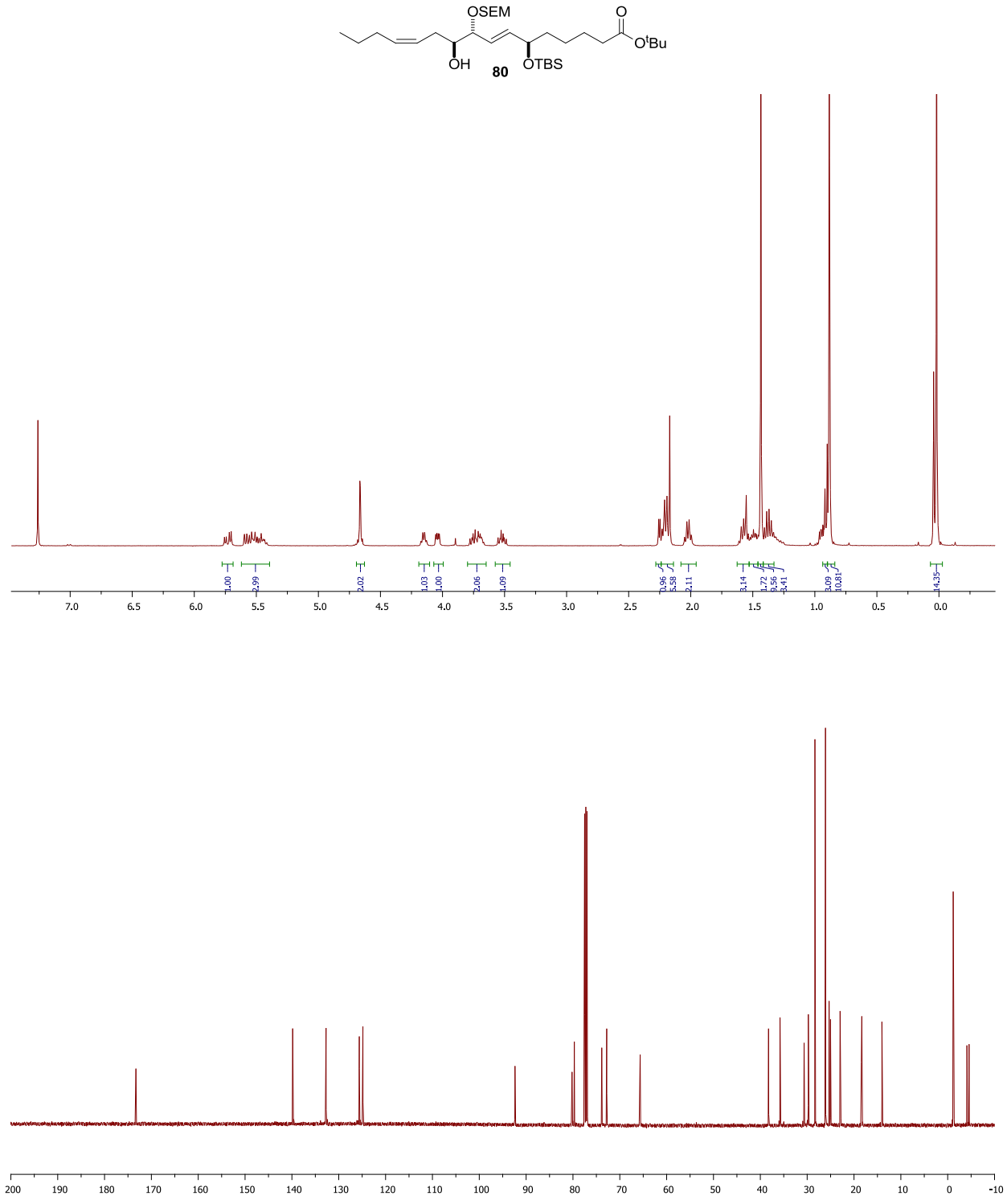


Figure A2. 13 ^{1}H NMR and ^{13}C NMR Spectra for Compound 80

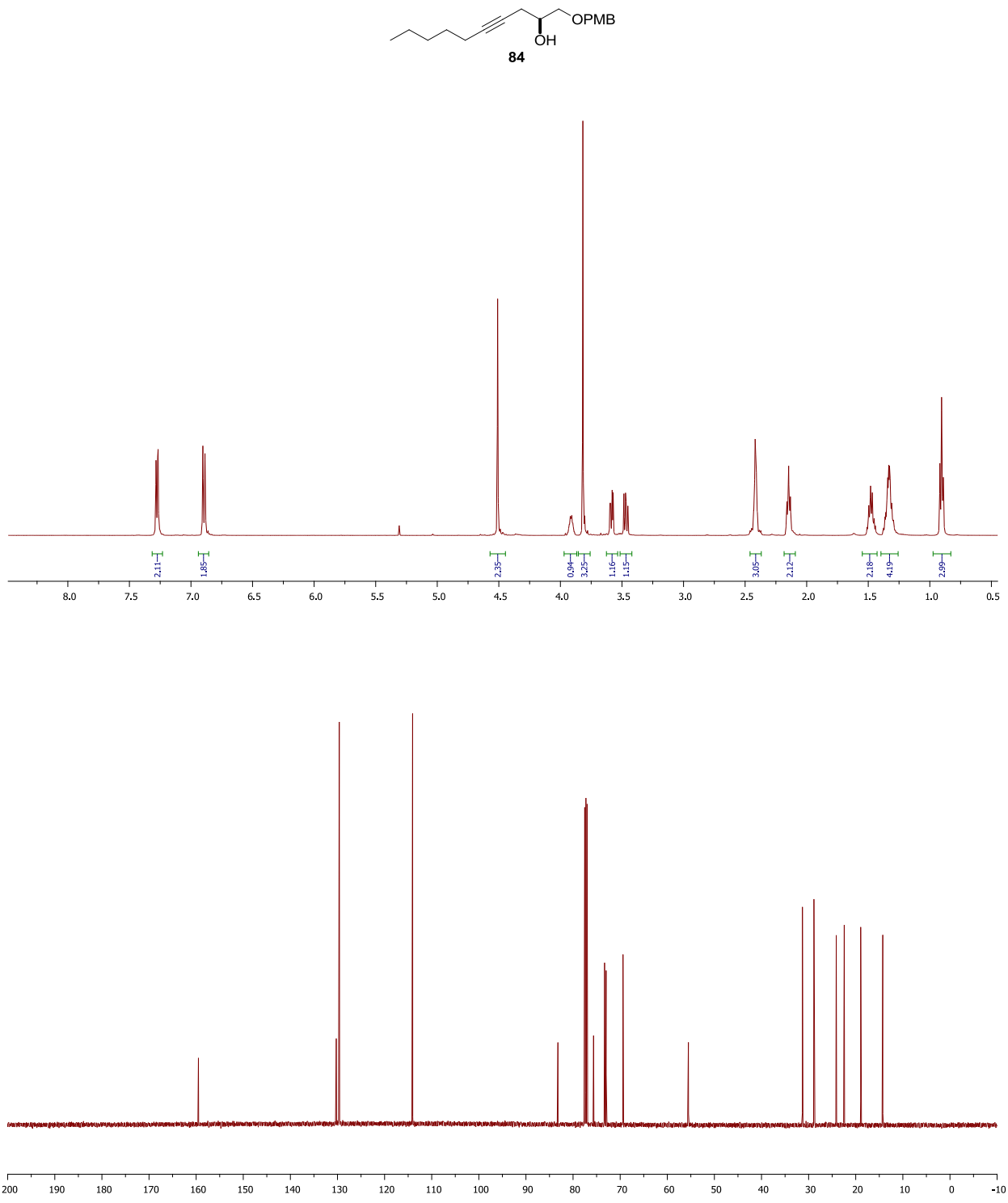


Figure A2. 14 ^{1}H NMR and ^{13}C NMR Spectra for Compound 84

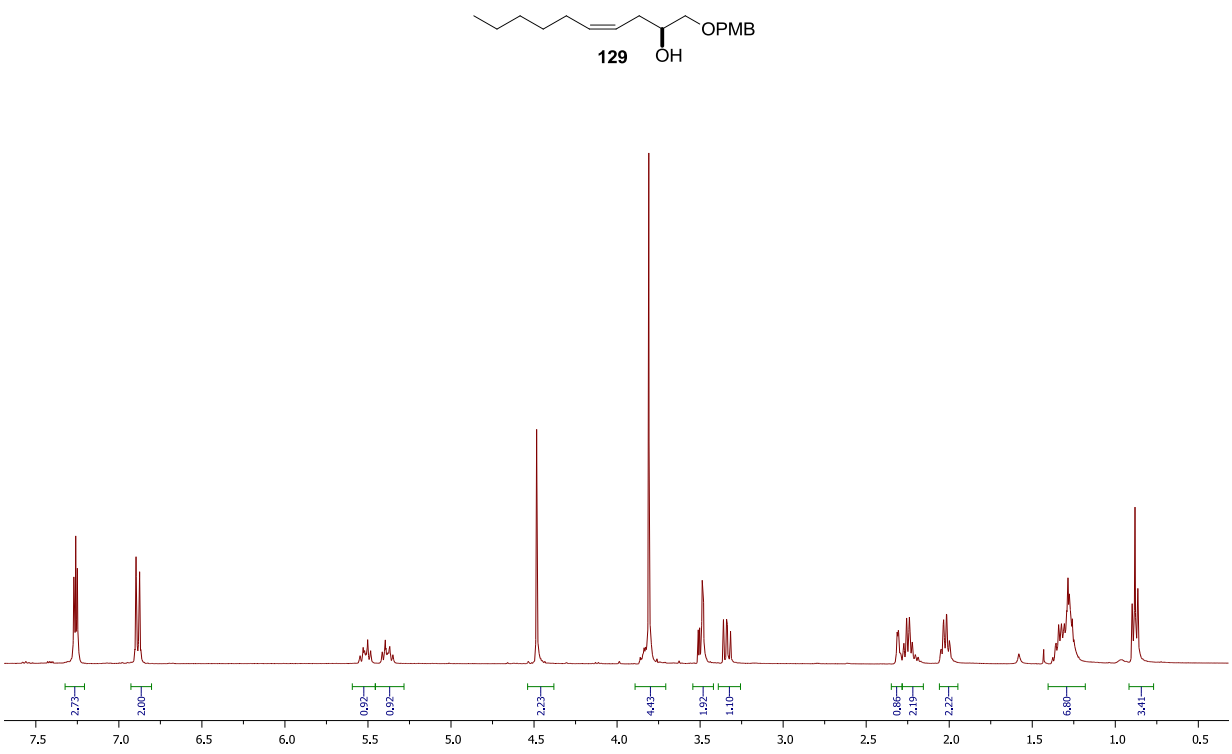


Figure A2. 15 ^{1}H NMR Spectrum of Compound 129

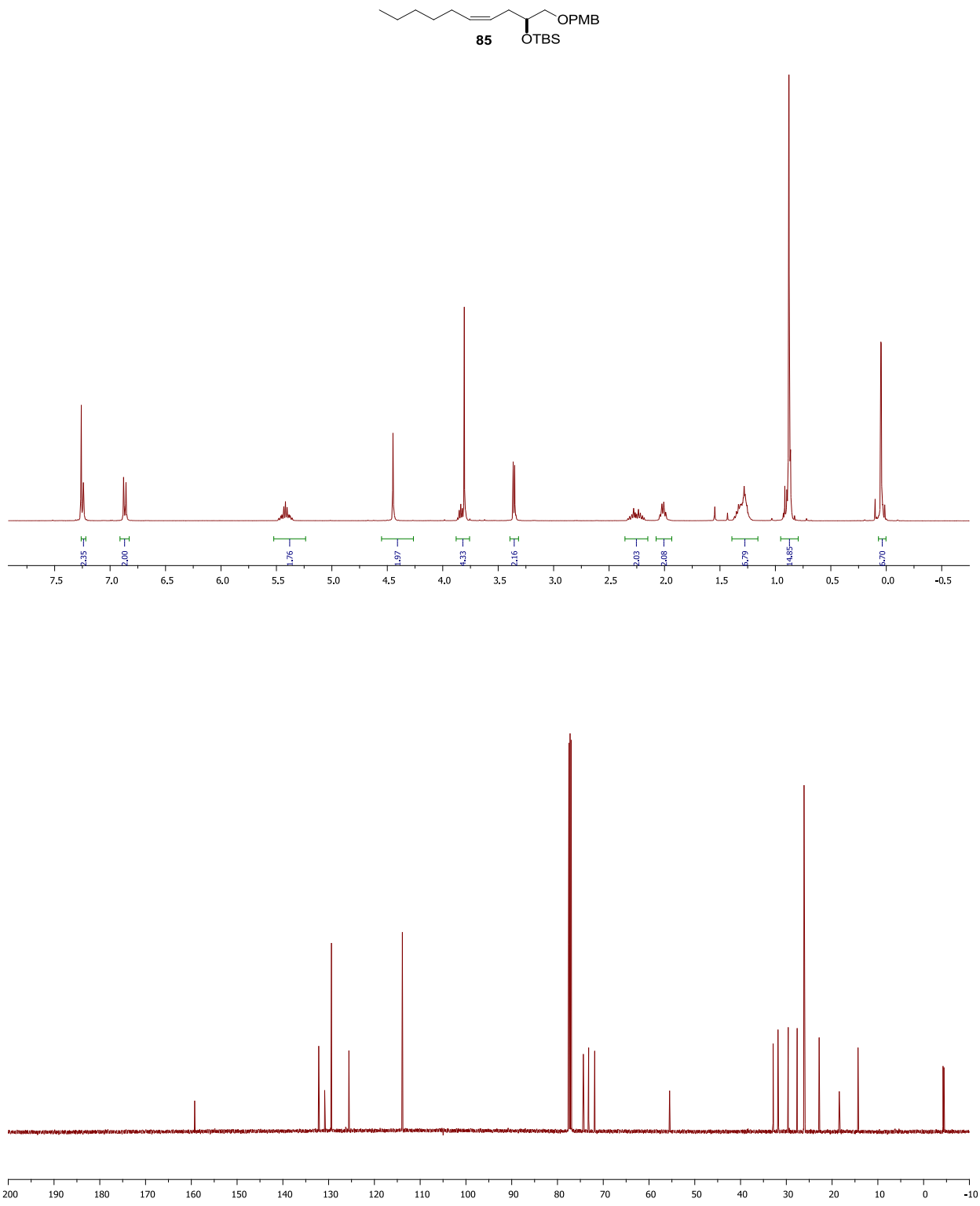


Figure A2. 16 ^{1}H NMR and ^{13}C NMR Spectra for Compound 85

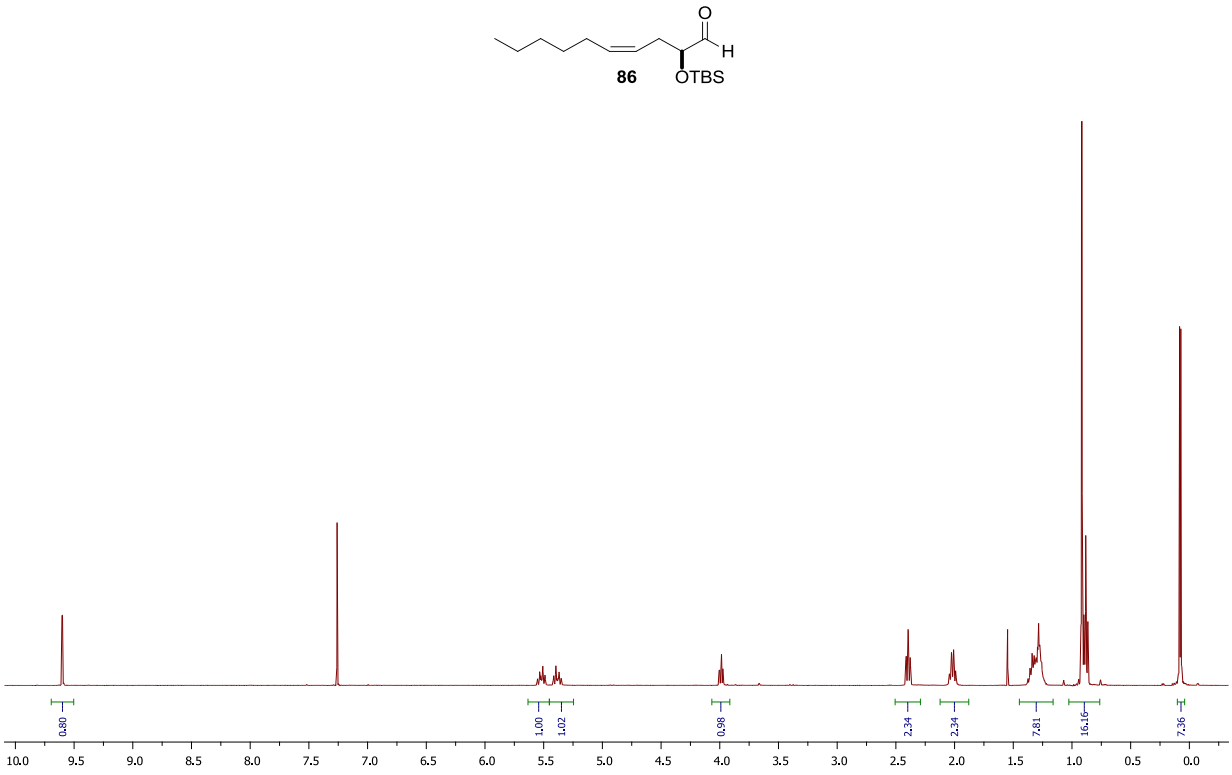


Figure A2. 17 ^{1}H NMR Spectrum of Compound 86

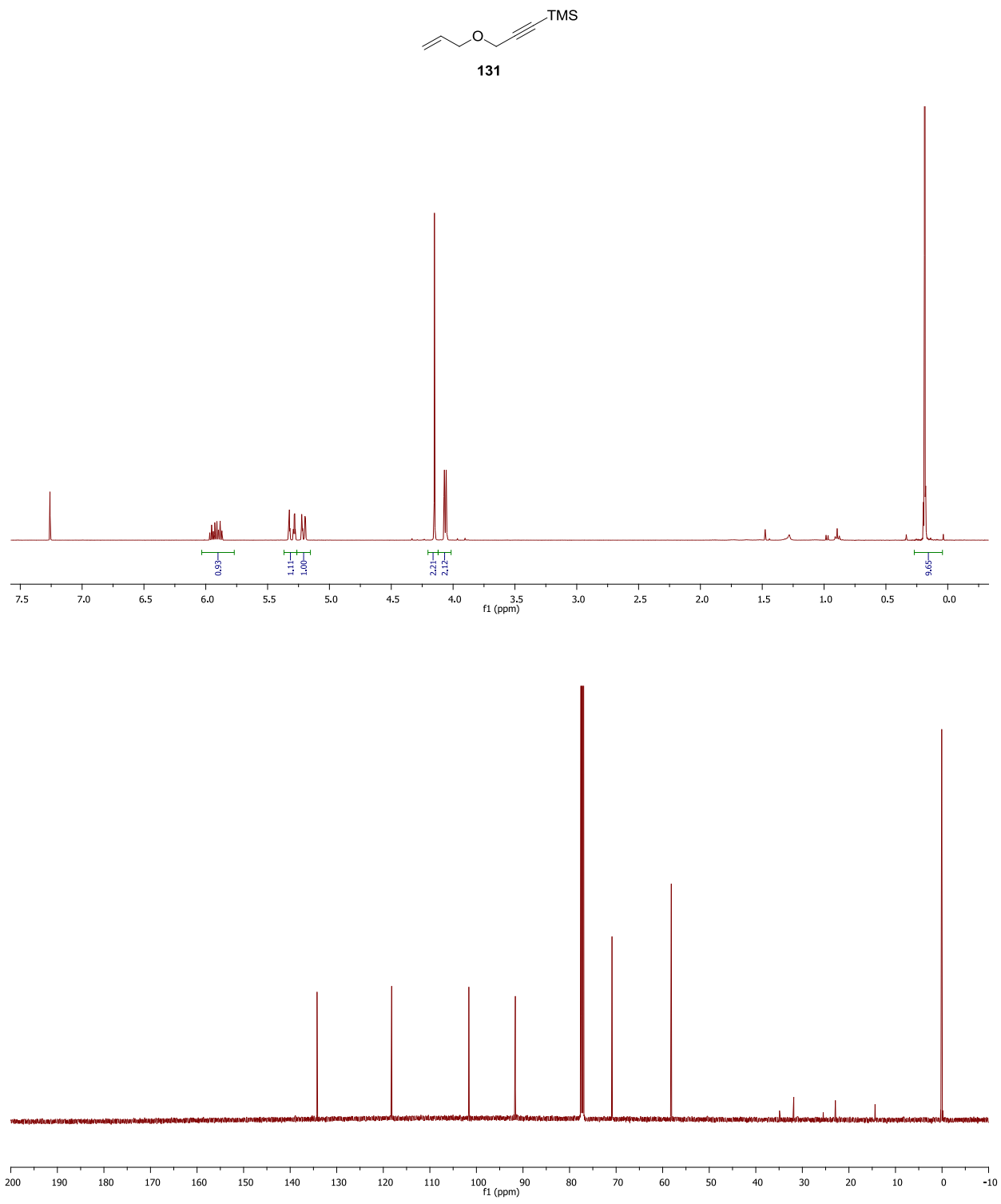


Figure A2. 18 ^{1}H NMR and ^{13}C NMR Spectra for Compound 131

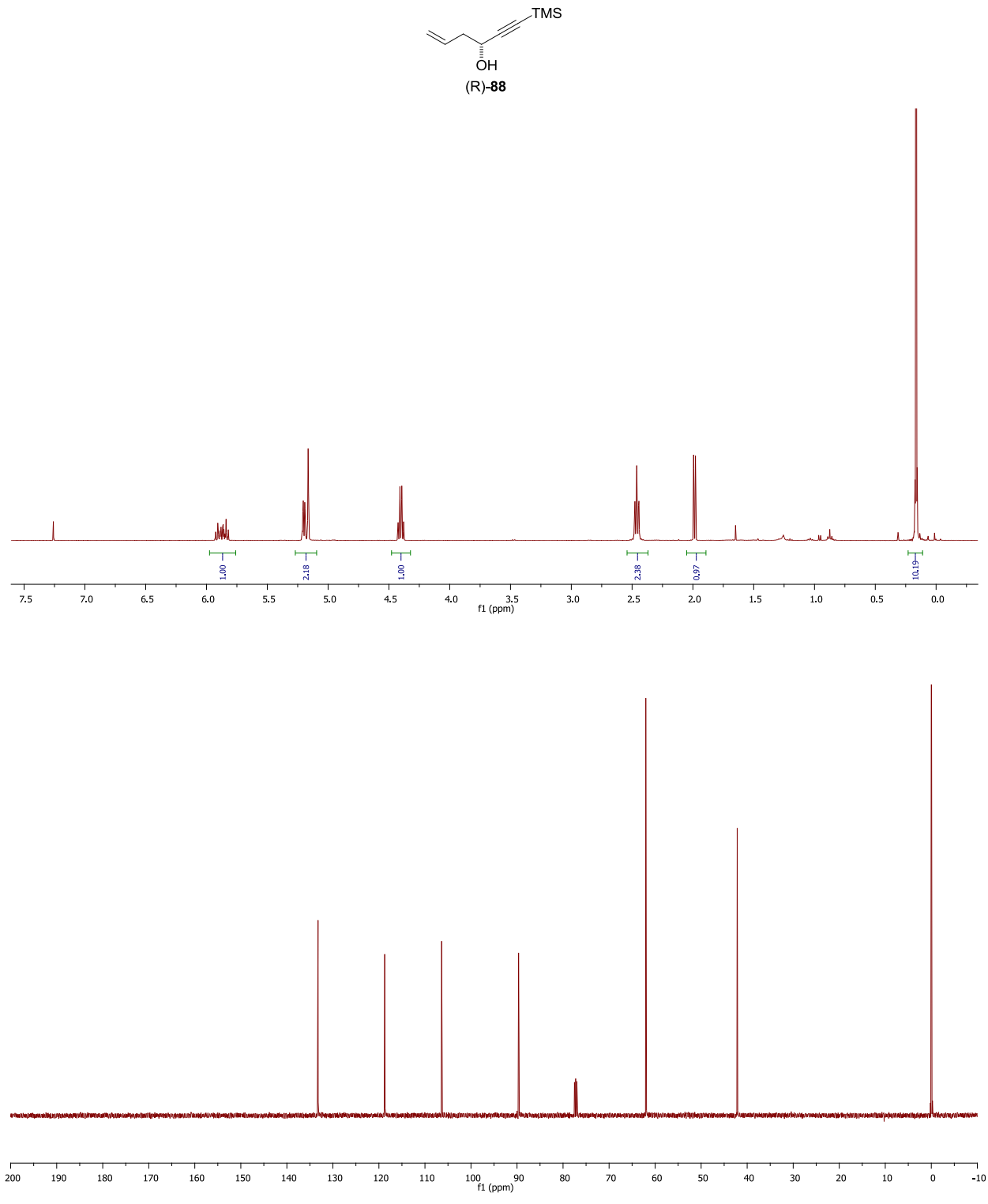


Figure A2. 19 ^{1}H NMR and ^{13}C NMR Spectra for Compound (R)-88

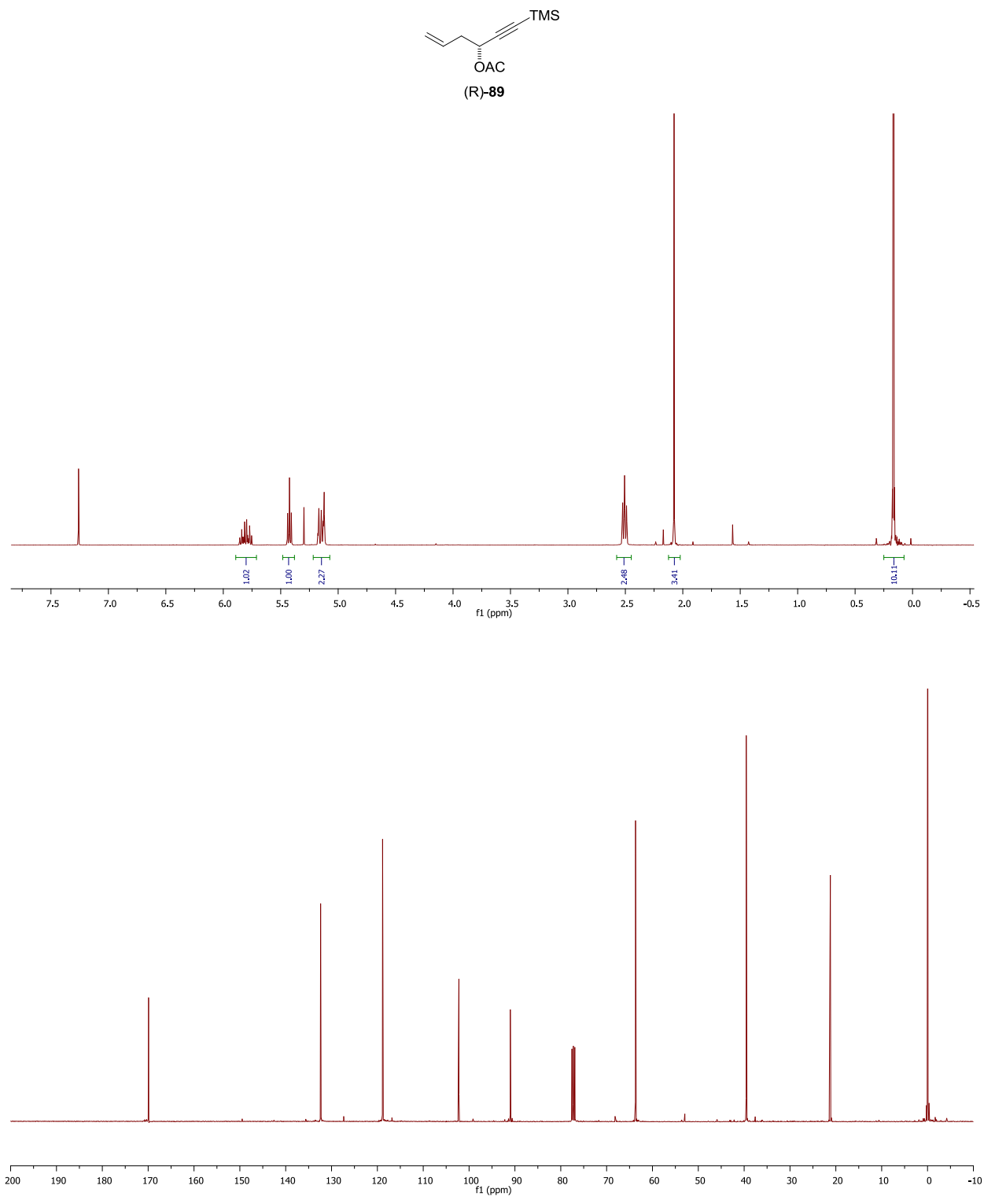


Figure A2. 20 ^{1}H NMR and ^{13}C NMR Spectra for Compound (R)-89

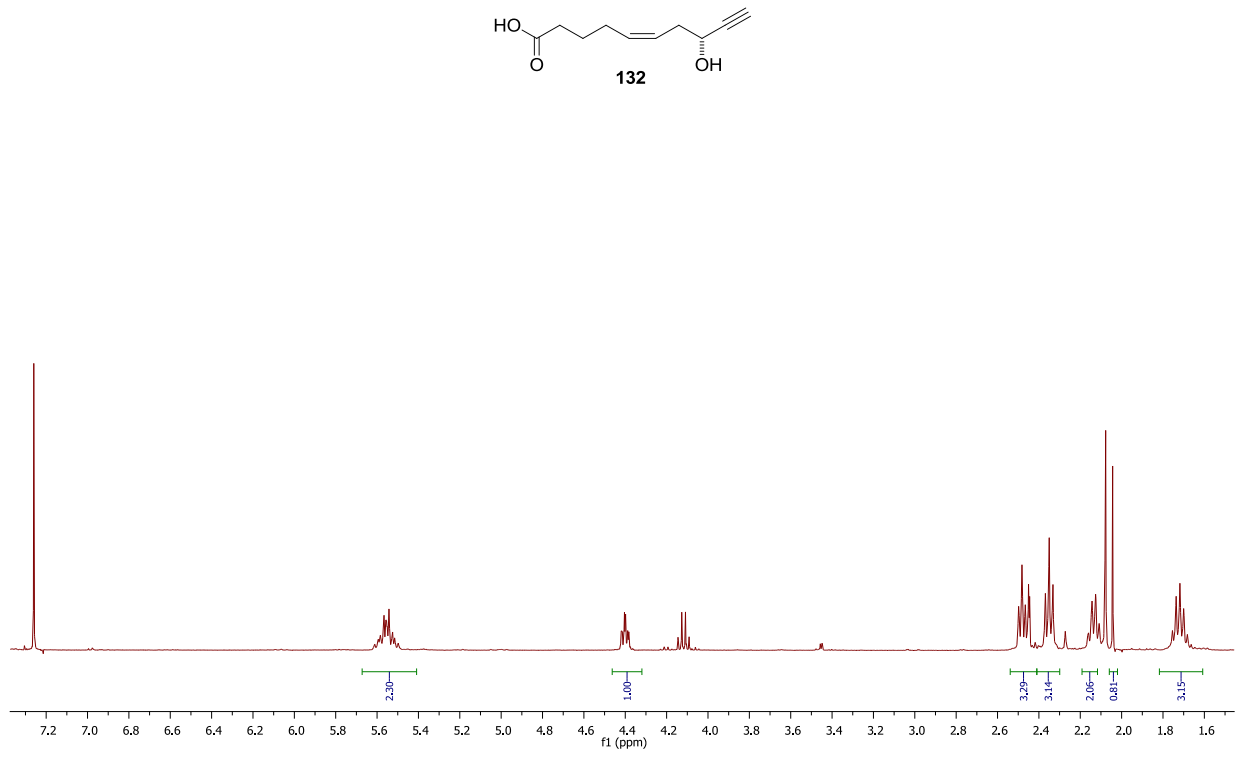


Figure A2. 21 ^{1}H NMR and ^{13}C NMR Spectra for Compound 132

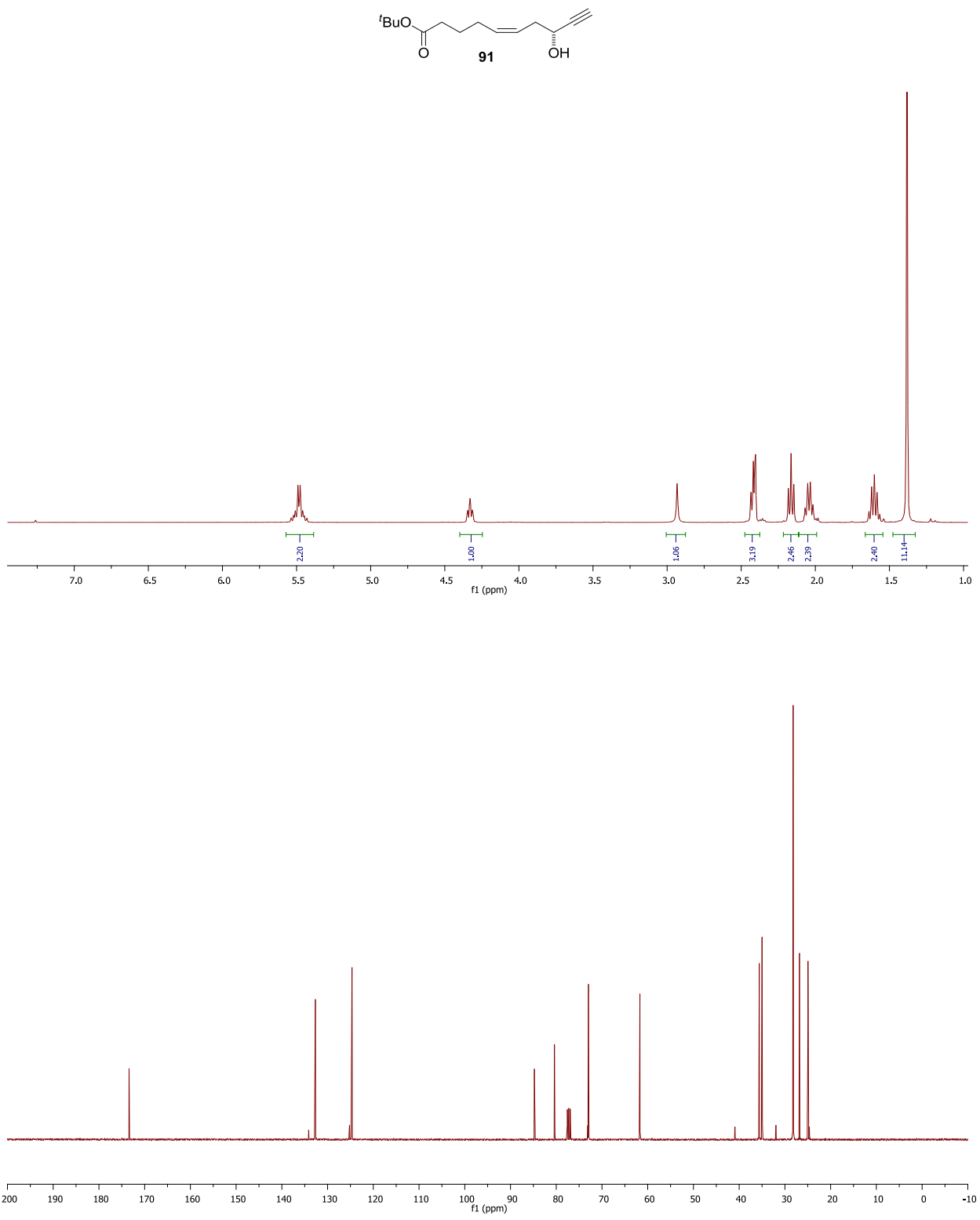


Figure A2. 22 ^{1}H NMR and ^{13}C NMR Spectra for Compound 91

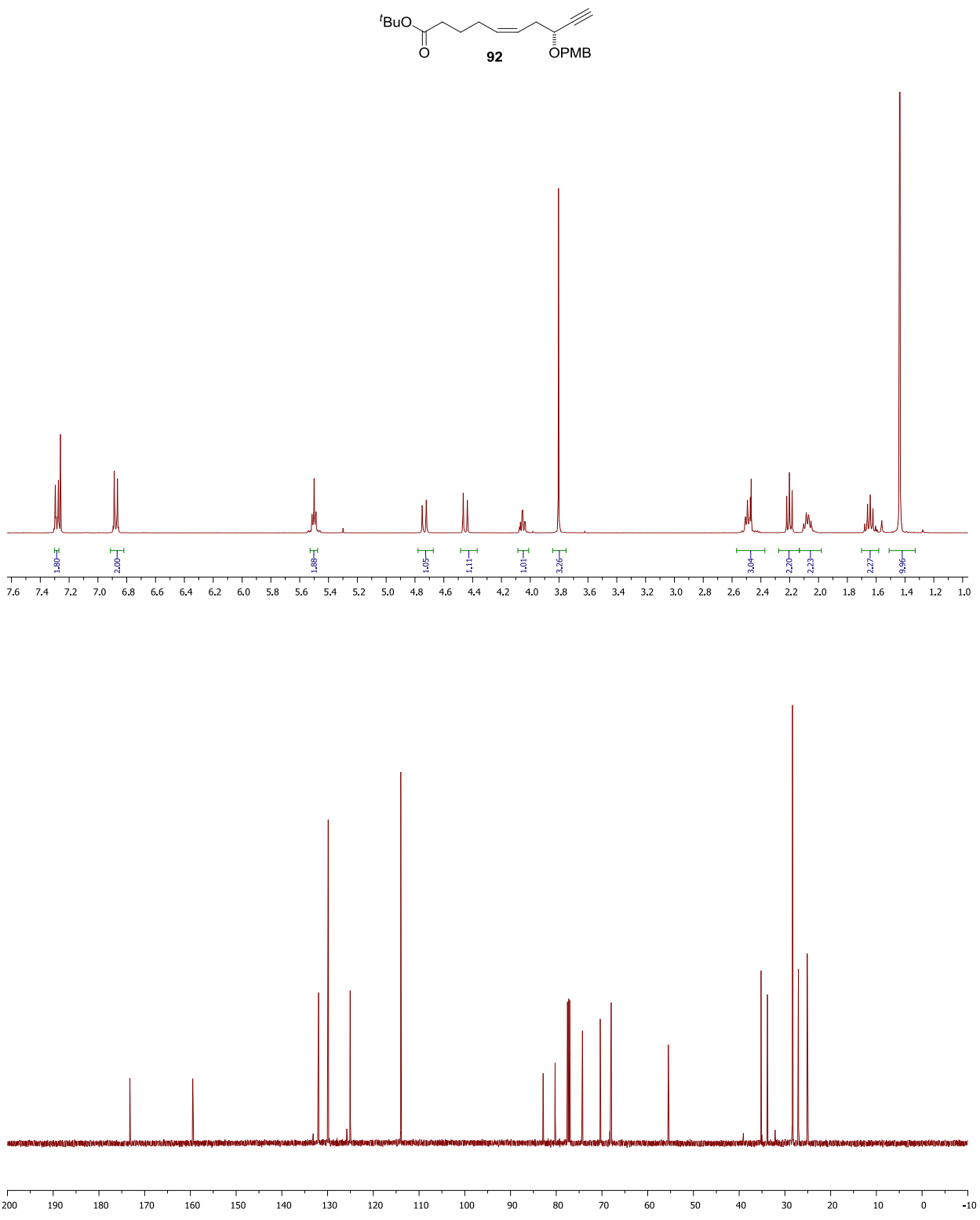


Figure A2. 23 ^{1}H NMR and ^{13}C NMR Spectra for Compound 92

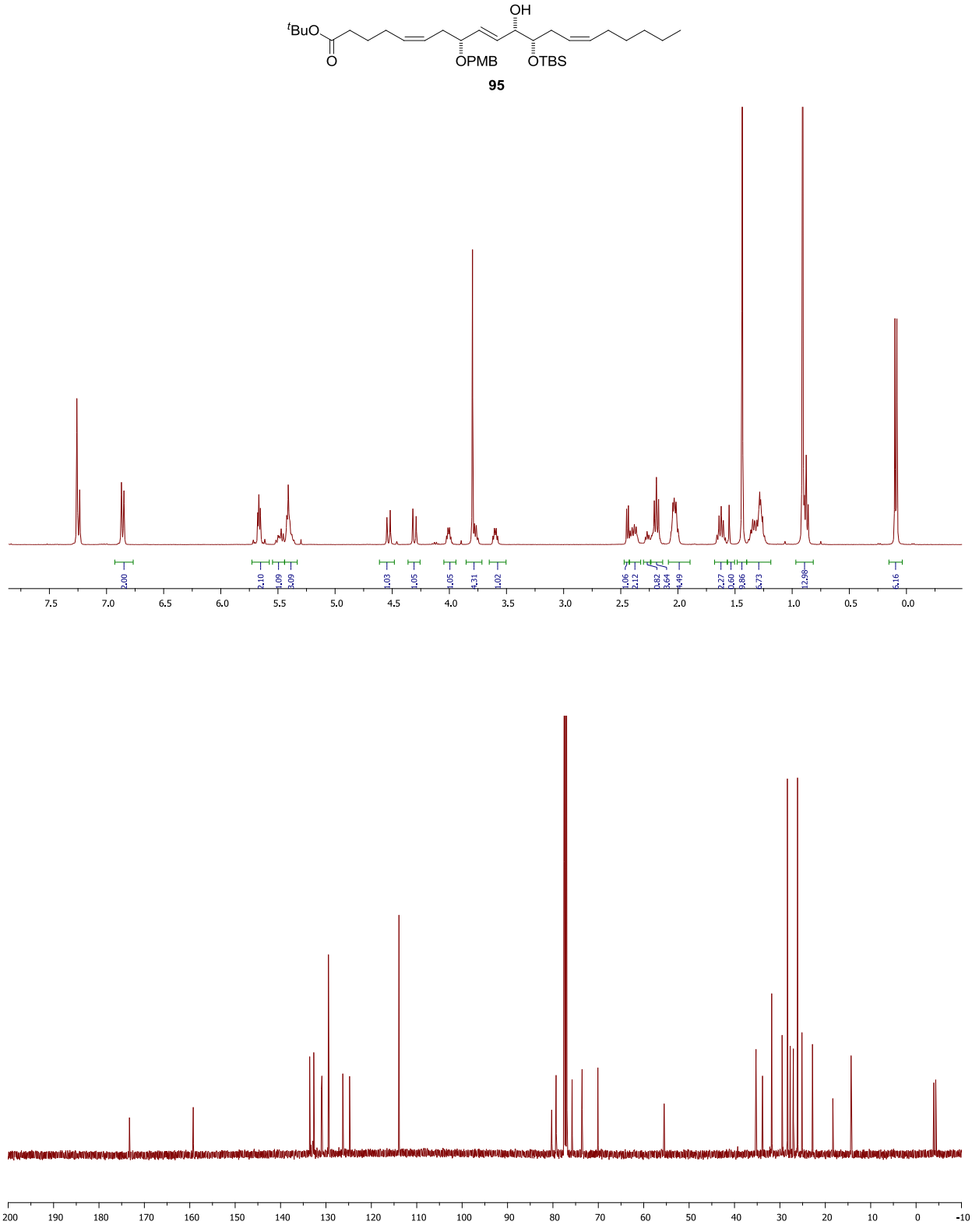


Figure A2. 24 ^{1}H NMR and ^{13}C NMR Spectra for Compound 95

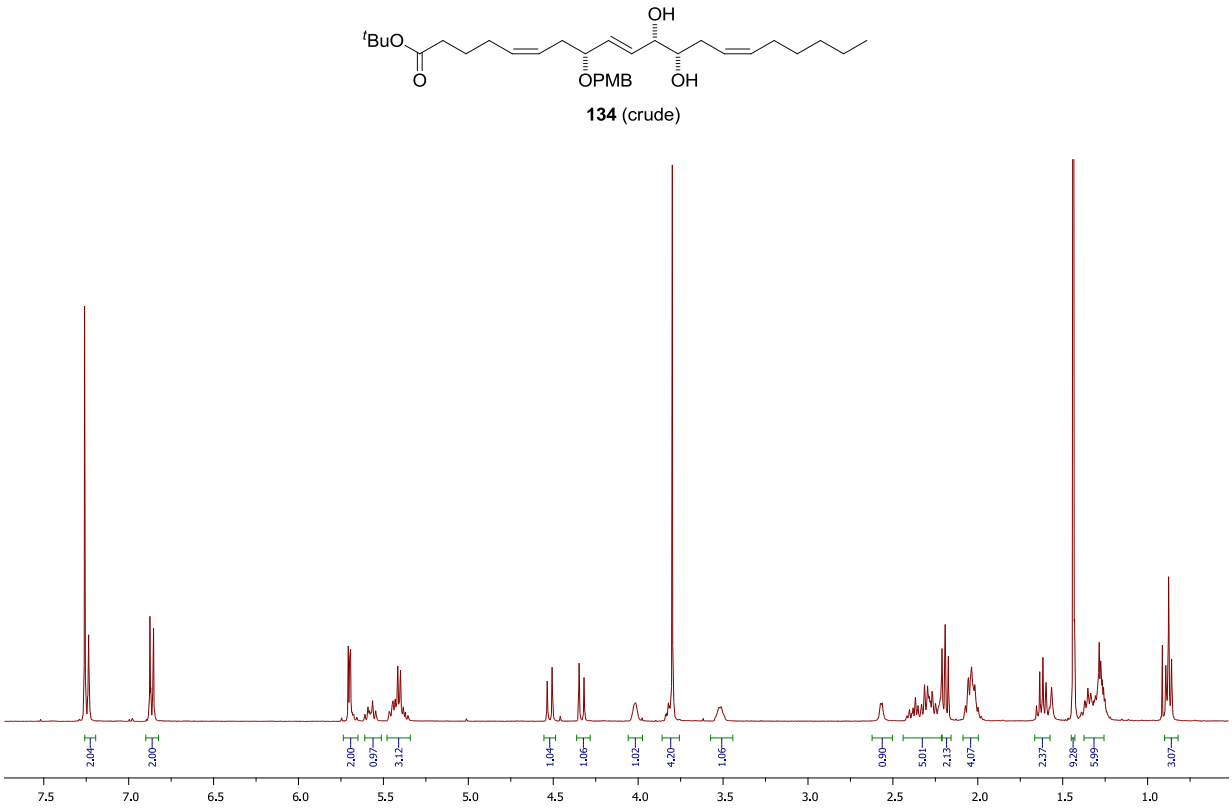


Figure A2. 25 ^{1}H NMR Spectrum for Compound 134

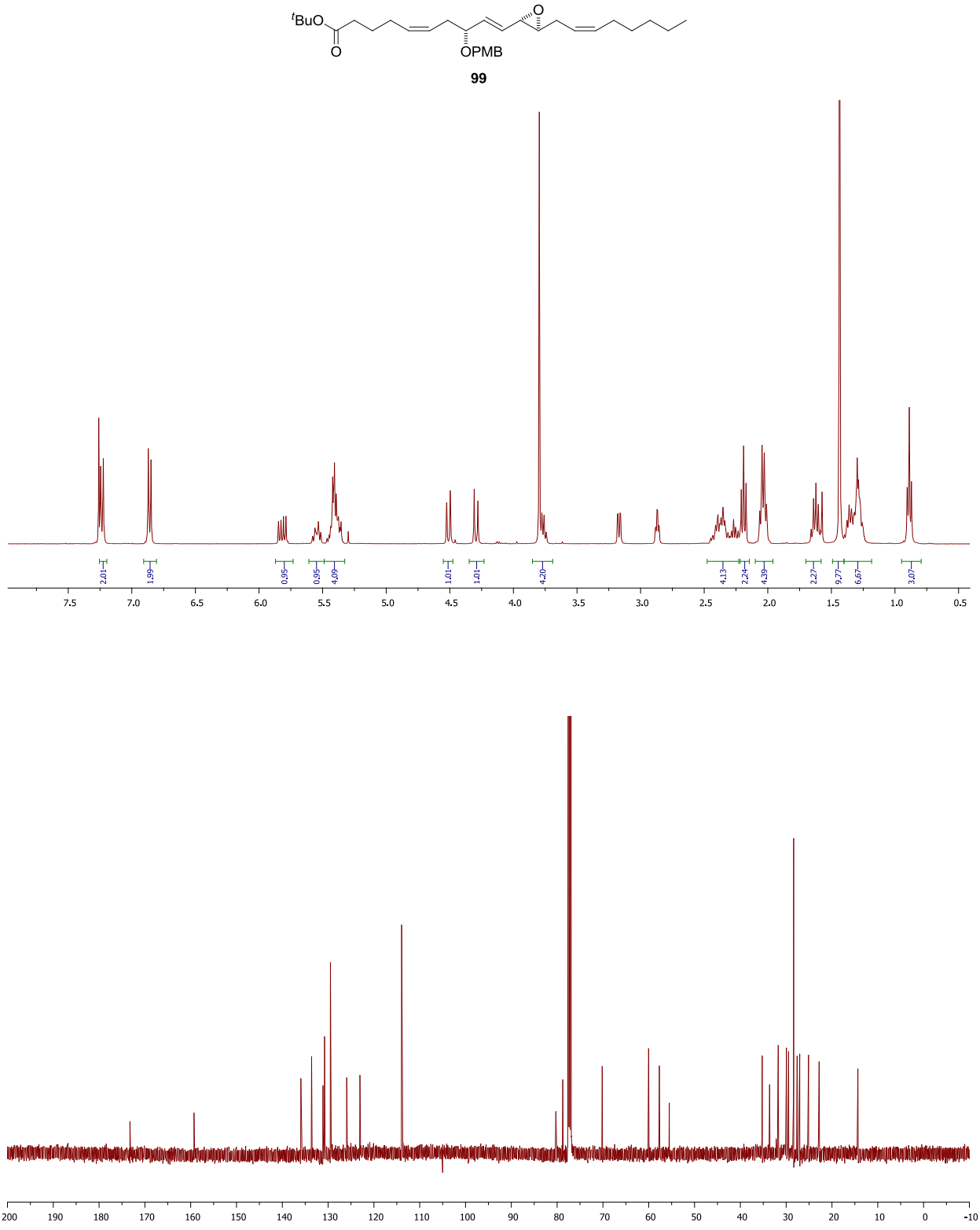


Figure A2. 26 ^{1}H NMR and ^{13}C NMR Spectra for Compound 99

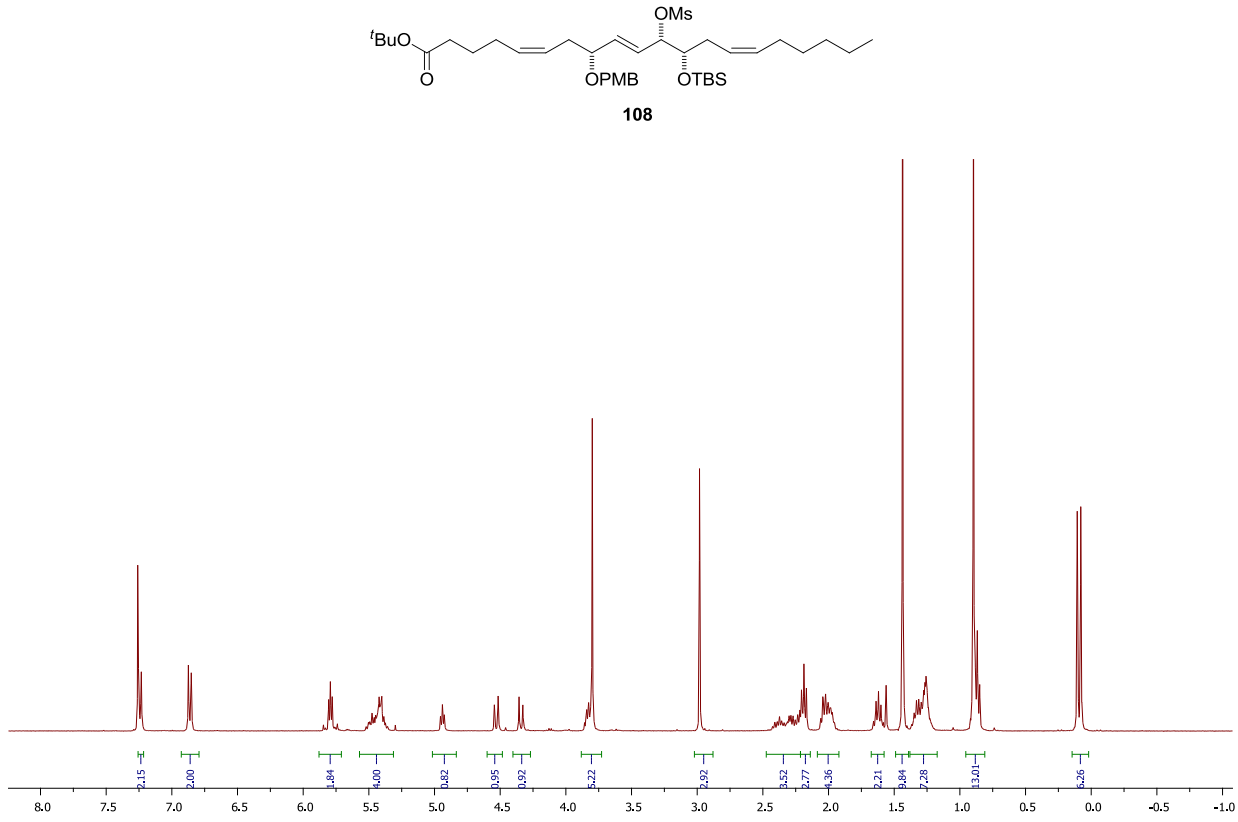
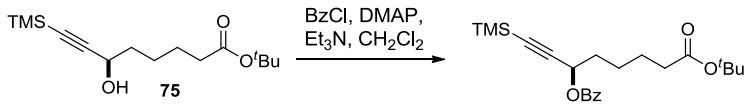
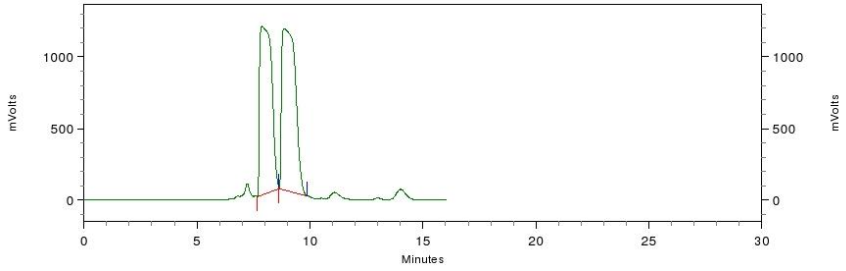


Figure A2. 27 ^{1}H NMR Spectrum of Compound 108



Racemate

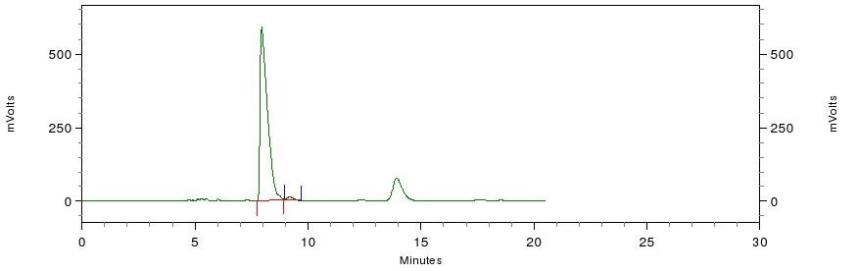


UV Detector
Ch2-229nm
Results

Retention Time	Area	Area %	Height	Height %
7.883	42989666	47.38	1174800	51.11
8.850	47741692	52.62	1123842	48.89
Totals	90731358	100.00	2298642	100.00

HPLC Conditions: Chiralcel OD-H column, 1 mL/ min flow rate, 1% i-PrOH in hexanes

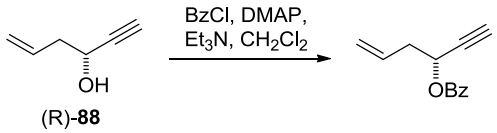
Scalemic Compound



UV Detector
Ch1-254nm
Results

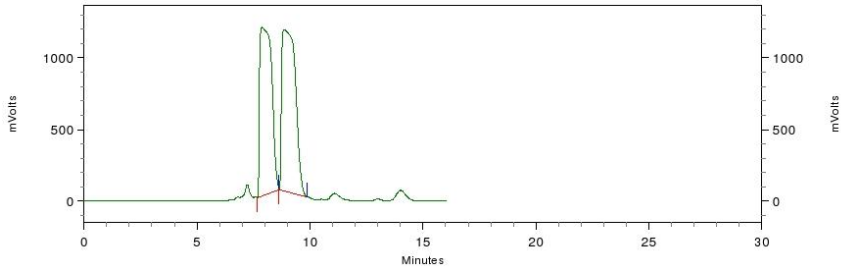
Retention Time	Area	Area %	Height	Height %
7.950	13252711	98.70	588536	98.51
9.183	174405	1.30	8931	1.49
Totals	13427116	100.00	597467	100.00

Figure A2. 28 HPLC Chromatogram for Compound 75



(R)-**88**

Racemate

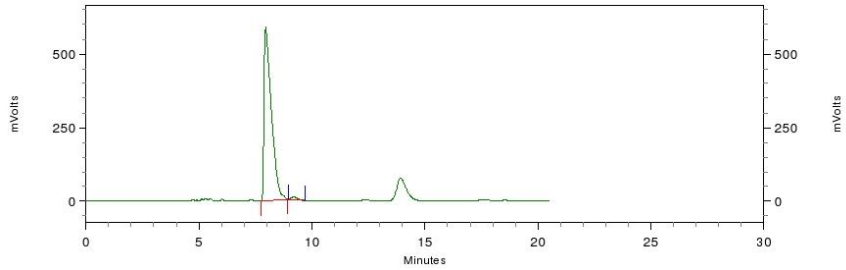


UV Detector
Ch2-229nm
Results

Retention Time	Area	Area %	Height	Height %
7.883	42989666	47.38	1174800	51.11
8.850	47741692	52.62	1123842	48.89
Totals	90731358	100.00	2298642	100.00

HPLC Conditions: Chiralcel OD-H column, 1 mL/ min flow rate, 0.125% i-PrOH in hexanes

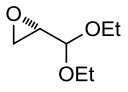
Scalemic Compound



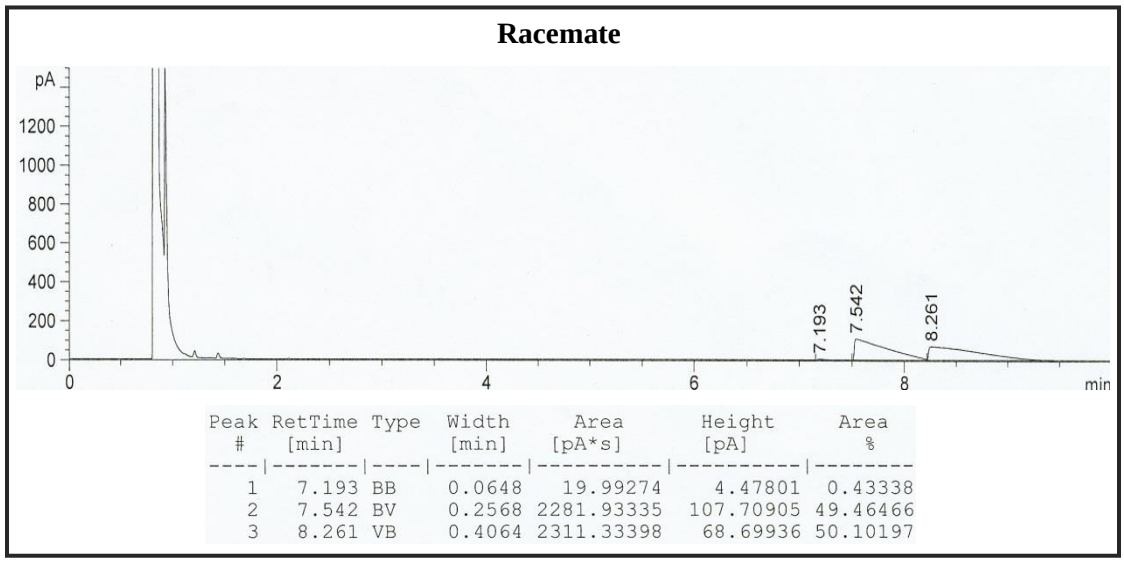
UV Detector
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
7.950	13252711	98.70	588536	98.51
9.183	174405	1.30	8931	1.49
Totals	13427116	100.00	597467	100.00

Figure A2. 29 HPLC Chromatogram for Compound (R)-88

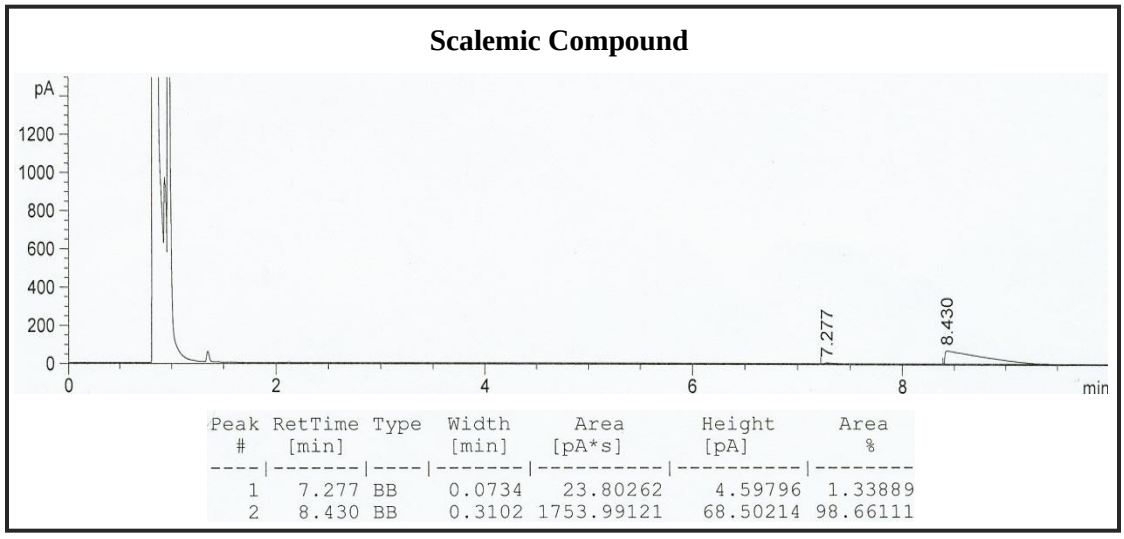


(S)-**65**



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	7.193	BB	0.0648	19.99274	4.47801	0.43338
2	7.542	BV	0.2568	2281.93335	107.70905	49.46466
3	8.261	VB	0.4064	2311.33398	68.69936	50.10197

GC Conditions: Lipodex E (Column V, Macherey-Nagel), 60°C, 19.4 min



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	7.277	BB	0.0734	23.80262	4.59796	1.33889
2	8.430	BB	0.3102	1753.99121	68.50214	98.66111

Figure A2. 30 GC Trace for Compound (S)-65

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87. Only 31 carbon peaks are observed in the 13C NMR spectrum. Based on spectra of similar structures, we would expect to see 32 carbons because of the diastereotopic methyl groups on -OTBS.