Summer 2012

New synthesis and reactions of phosphonates

Rebekah Marie Richardson
University of Iowa

NEW SYNTHESIS AND REACTIONS OF PHOSPHONATES

by

Rebekah Marie Richardson

An Abstract

Of a thesis submitted in partial fulfillment
of the requirements for the
Doctor of Philosophy degree in Chemistry
in the Graduate College of
The University of Iowa

July 2012

Thesis Supervisor: Professor David F. Wiemer

ABSTRACT

The importance of phosphorus can be highlighted not only through its biological significance, but also in its many varied industrial, medicinal, and synthetic applications. Phosphonate moieties in particular have broad applications including their use as reagents in the Horner-Wadsworth-Emmons olefination reaction, a widely used synthetic strategy. As an alternative to the often harsh conditions required for phosphonate synthesis, a mild and versatile one-flask protocol has been developed in which a benzylic alcohol can be directly converted to the diethyl benzylphosphonate ester. Moreover, this zinc iodide mediated process provides good yields on both small and larger scale reactions. Explorations into this unique transformation with non-racemic substrates revealed that the reaction may proceed through an S_N1–like mechanism.

The new phosphonate methodology has been utilized successfully on allylic, heterocyclic, and both electron poor and rich benzylic systems. This allows the synthesis of many types of dialkyl benzylphosphonate esters. Specific examples include compounds used towards the synthesis of natural product analogues and at least one phosphonate ester not previously attainable under standard conditions. Isotopic labelling experiments provided additional mechanistic insight suggesting a probable carbocation process. The mild and facile reaction conditions and the good yields of diverse, complex phosphonate products emphasize the broad applicability of this protocol.

To demonstrate the utility of this phosphorus-based methodology, synthetic sequences and Lewis acid–mediated cascade cyclizations towards the synthesis of natural products have been developed. The natural radulanins, isolated from liverworts, possess a plethora of biological properties and present the opportunity to utilize and expand upon many aspects of this research. Formation of the benzoxepin core of the radulanins through a Lewis acid–mediated cyclization ultimately led to the total synthesis of radulanin A. An additional product consisting of cyclization with electrophilic aromatic

substitution of a methoxymethyl substituent originating in the MOM-protecting group also was discovered, leading to a highly substituted benzoxepin that should be of value in the synthesis of radulanin E.

Abstract Approved: _____
Thesis Supervisor

_____
Title and Department

_____
Date

NEW SYNTHESIS AND REACTIONS OF PHOSPHONATES

by

Rebekah Marie Richardson

A thesis submitted in partial fulfillment
of the requirements for the
Doctor of Philosophy degree in Chemistry
in the Graduate College of
The University of Iowa

July 2012

Thesis Supervisor: Professor David F. Wiemer

Graduate College
The University of Iowa
Iowa City, Iowa

CERTIFICATE OF APPROVAL

PH.D. THESIS

This is to certify that the Ph.D. thesis of

Rebekah Marie Richardson

has been approved by the Examining Committee
for the thesis requirement for the Doctor of Philosophy
degree in Chemistry at the July 2012 graduation.

Thesis Committee:
David F. Wiemer, Thesis Supervisor

Daniel M. Quinn

Leonard R. MacGillivray

Edward G. Gillan

Horacio F. Olivo

To my grandparents

You can’t always get what you want,
But if you try sometimes, well you just might find
You get what you need.

The Rolling Stones, You Can’t Always Get What You Want

ACKNOWLEDGMENTS

I would like to express my gratitude to my advisor, Dr. Wiemer. He has been an amazing, understanding, and accommodating boss who dealt with my crazy work schedule. I would also like to thank the Wiemer group for their guidance and friendship, especially Natalie Ulrich (editor extraordinaire), Rocky Barney, Mike Callahan, and Larry Schull. I am also so lucky to have befriended my colleague, Jaci Smits. In addition to understanding my chemistry frustrations and joys, she has become a wonderful friend (Ka Kaw!). Many thanks also to Sherif Ibrahim for his help obtaining the HPLC data, Brandon Van Cleave for his assistance on the phosphonate methodology, and to the invaluable faculty and staff in the chemistry building.

My friendships have gotten me through all the rough patches in my research. When nothing was working, my friends listened to my complaints, even though they had no idea what I was talking about. Jessie Sue, "the girls," and Emily: thank you so much. I would also like to thank the Caulkins, Quades, and my stepfamily for welcoming me into your lives. Mr. Quade, you are awesome.

I would never have been able to do this without my family (this includes you Vic). You have given me so much. You have always been unwavering in your support and love. Above all else, I need to thank my grandparents. There are no words to describe how much you have positively impacted my life. I owe you everything and love you more than you can possibly know.

ABSTRACT

The importance of phosphorus can be highlighted not only through its biological significance, but also in its many varied industrial, medicinal, and synthetic applications. Phosphonate moieties in particular have broad applications including their use as reagents in the Horner-Wadsworth-Emmons olefination reaction, a widely used synthetic strategy. As an alternative to the often harsh conditions required for phosphonate synthesis, a mild and versatile one-flask protocol has been developed in which a benzylic alcohol can be directly converted to the diethyl benzylphosphonate ester. Moreover, this zinc iodide mediated process provides good yields on both small and larger scale reactions. Explorations into this unique transformation with non-racemic substrates revealed that the reaction may proceed through an S_N1–like mechanism.

The new phosphonate methodology has been utilized successfully on allylic, heterocyclic, and both electron poor and rich benzylic systems. This allows the synthesis of many types of dialkyl benzylphosphonate esters. Specific examples include compounds used towards the synthesis of natural product analogues and at least one phosphonate ester not previously attainable under standard conditions. Isotopic labelling experiments provided additional mechanistic insight suggesting a probable carbocation process. The mild and facile reaction conditions and the good yields of diverse, complex phosphonate products emphasize the broad applicability of this protocol.

To demonstrate the utility of this phosphorus-based methodology, synthetic sequences and Lewis acid–mediated cascade cyclizations towards the synthesis of natural products have been developed. The natural radulanins, isolated from liverworts, possess a plethora of biological properties and present the opportunity to utilize and expand upon many aspects of this research. Formation of the benzoxepin core of the radulanins through a Lewis acid–mediated cyclization ultimately led to the total synthesis of radulanin A. An additional product consisting of cyclization with electrophilic aromatic

substitution of a methoxymethyl substituent originating in the MOM-protecting group also was discovered, leading to a highly substituted benzoxepin that should be of value in the synthesis of radulanin E.

TABLE OF CONTENTS

LIST OF TABLES

Table

LIST OF FIGURES

Figure

LIST OF ABBREVIATIONS

Ac	Acetate
Anal.	Analysis
Aq	Aqueous
ATP	Adenosine Triphosphate
BINAP	2,2’-Bis(diphenylphosphino)-1,1’-binaphthyl
br	Broad
BRSM	Based on Recovered Starting Material
Bu	Butyl
C	Celsius
cal	Calories
calcd	Calculated
COX	Cyclooxygenase
DBU	1,8-Diazabicylco[5.4.0]undec-7-ene
d	Doublet
dba	Dibenzylideneacetone
dd	Doublet of doublets
DDQ	2,3–Dichloro–5,6–dicyano–1,4–benzoquinone
DEAD	Diethyl Azodicarboxylate
DFP	Diisopropyl Phosphofluoridate
DIBAL	Diisobutylaluminum Hydride
DIPEA	Diisopropylethylamine
DMAP	Dimethylallyl Pyrophosphate
DMF	Dimethylformamide
DMS	Dimethyl Sulfide
DNA	Deoxyribonucleic Acid

DoM	Directed *Ortho*–Metalation
dt	Doublet of Triplets
EAS	Electrophilic Aromatic Substitution
ee	Enantiomeric Excess
EI	Electron Impact
ES	Electrospray
Et	Ethyl
g	Gram
GC-MS	Gas Chromatography-Mass Spectrometry
hr	Hour
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectroscopy
HWE	Horner–Wadsworth–Emmons
Hz	Hertz
IPP	Isopentenyl Pyrophosphate
iPr	Isopropyl
J	Coupling Constant
KB	Oral Carcinoma cell line
KHMDS	Potassium Hexamethyldisilyl Azide
LA	Lewis Acid
5-LOX	5-Lipooxygenase
m	Multiplet
M	Molar
MCP	2-Methylcinnolinium-4-(*o*-methylphosphonate)
Me	Methyl
mg	Milligram

min.	minutes
mL	Milliliter
mmol	Millimole
MOM	Methoxymethyl
Ms	Methanesulfonyl
m/*z*	Mass/Charge
NADH	Nicotinamide Adenine Dinucleotide
n–BuLi	*n*–Butyl Lithium
NMMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear Magnetic Resonance
NO	Nitric Oxide
NOE	Nuclear Overhauser Enhancement
NOESY	Nuclear Overhauser Enhancement Spectroscopy
P-338	Murine Lyphocytic Leukemia cell line
Ph	Phenyl
PIV	Pivaloyl
POM	Pivaloyloxymethyl
ppm	Parts Per Million
*p*TsOH	*p*–Toluene Sulfonic Acid
q	Quartet
quant.	Quantitative
RNA	Ribonucleic acid
rt	Room Temperature
s	Singlet
s–BuLi	*sec*–Butyl Lithium
SM	Starting Material
sat.	Saturated

t	Triplet
TBABr	Tetrabutylammonium Bromide
TBDPS	*tert*–Butyldiphenylsilyl
TBS	*tert*–Butyldimethylsilyl
^{t}BuOK	Potassium *tert*–Butoxide
TEA	Triethylamine
TMG	1,1,3,3-Tetramethylguanidine
Tf	Triflate
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	*p*–Toluene Sulfonyl

CHAPTER I
A BRIEF HISTORY OF PHOSPHORUS

Phosphorus compounds …..are essential, not only for hereditary processes, but for growth development and maintenance of all plants and animals……They are present in soil, bone, teeth, blood and all cellular organisms….. Energy-transfer processes such as photosynthesis, metabolism, nerve function, and muscle action….

D. E.C. Corbridge, *Phosphorus: an outline of its chemistry, biochemistry, and technology*[1]

While the discovery of phosphorus could arguably date back to the 12th century and the court of King Henri II, a German glassmaker named Hennig Brand is often credited with the discovery in 1669 while on his search for the famed philosopher's stone.[1-5] After abandoning his profession for alchemy, he became convinced that the fabled stone could be uncovered through the distillation of putrefied urine at a very high temperature, but only obtained a white, waxy, glowing substance now known to be phosphorus.[2, 3] With the discovery of the element in urine, the next logical question was why and where did it originate. Approximately 70 years later, Andreas Sigismund Marggraf found the luminescent and combustible material in plant seeds and concluded that humans obtain phosphorus from edible plant material and subsequently it was excreted by the body in urine.[3] Advances in science would later validate this conclusion, as well as prove that phosphorus is an essential element for life and that it is found in a multitude of organs, bones, and biological process.[2-4]

The 18th century saw a major increase in the use of phosphorus. The variety of applications included matches, poisons, and medicinal treatments for epilepsy, melancholia, and cramps.[1, 4] It was not until the 1770's that Scheele[1] found that it was essential for animal bones and teeth. The high expense of the element at this time was in part due to the lack of large scale production. Even then it was still largely produced

through the distillation of urine or through the solubilization of bones with sulfuric acid.[2, 4] Battlefields were even raided for their bones to secure raw material.[2]

Major advances in both production of elemental phosphorus and structural elucidation of phosphorus compounds began in the 19th century when compounds such as orthophosphates, pyrophosphate, metaphosphate, alkyl phosphonates, and phosphine became known,[1] to name a few. In the 1850's, serious fertilizer production and mining of crude phosphate ores also began with the development of wet process chemistry.[1, 5, 6] Patented in 1842, this method allowed the extraction of the crude material from calcium phosphate rock.[1, 2] Although major mining is still occurring in Florida, the western U.S., China, Morocco, and Russia, this technique is largely only clean enough to provide material for fertilizer.[1, 2, 5] However, the electric arc or electric furnace method developed in 1888 allowed the introduction of phosphorus into more complex synthetic schemes.[1, 2, 6] White phosphorus vapours are formed, cleaned, and collected by passing them through an electrostatic precipitator to create very high temperatures (1200-1450 °C) followed by condensation of the P_4 into a white powder.[1, 2, 5, 6]

The greater production needs of modern industry also led to the exposure of factory workers to harmful amounts of vaporous phosphorus.[1] The worst effects may be necrosis of the jawbone or "phossy jaw."[1, 2] Although the exact cause of the necrosis still is debatable, it has been argued that this was the single most disfiguring occupational disease of the 19th and early 20th century.[6] Other common ailments resulting from overexposure to phosphorus include weakness, malaise, headache, vertigo, tracheobronchitis, laryngitis, and tenderness or enlargement of the liver.[6] Oral and dermal exposure is also particularly harmful, resulting in severe burns and renal failure upon the absorption of as little as 15 mg by a 150 pound person.[6] Another by-product of the increased production through mining and industry is the leaching of phosphorus into the environment. Eutrophication or the contamination of major lakes, rivers, and streams is problematic and is a result of increased fertilizer and sewage waste.[2, 4, 5]

Modern day methods have allowed mass production of elemental phosphorus in multiple forms. Likely born out of necessity, phosphorus now is used in any number of industrial applications including detergents, fireworks, insecticides, as a drying agent, and in rat poisons.[2, 7] It is even more commonly utilized in intermediates for gasoline additives, matches, surfactants, pesticides, and the pharmaceutical industry.[2] In 1988 alone, 11,717 tons of phosphoric acid was produced largely for fertilizers, but also as an intermediate for phosphate salts, activated carbon production, ceramics, animal feed, dental cement, soft drinks, and many others. [2, 6] Its highly reactive nature with oxygen, sulfur, chlorine, and water make PCl_3 very useful, and it was the second most produced phosphorus compound reported in 1988.[6]

Although phosphorus is the 12th most abundant element in nature, it most commonly occurs as phosphates in minerals, fertilized soil, or small quantities in graphite.[1, 2, 6] The lack of appearance in its free state could explain the fact that it was not until the 1930's that the three major allotropes of the non-metallic, essential element phosphorus were recognized: white, red, and black (Figure 1).[1, 4, 6] White phosphorus, which often ignites spontaneously in air, is the most reactive form, the most used industrially and pharmaceutically, and also the most toxic.[2, 6] Although it possesses a tetrahedral geometry, it is almost always found as the inorganic salt of phosphoric acid (Figure 1).[6] Almost all other phosphorus compounds can be made from white phosphorus directly or indirectly.[1]

First discovered by Von Schrotter in 1847, the red variety is less reactive due to the polymeric chain structure of P_4 compounds, and it can be produced through heating white phosphorus in an inert atmosphere (Figure 1).[1, 2] Black phosphorus, not recognized until 1914 by Bridgeman, is thermodynamically the most stable, resembles graphite, and is produced by subjecting white phosphorus to pressure.[1, 6] It is found naturally in 3 geometrical configurations, rhombohedral, cubic, and orthorhombohedral.[1, 6] An additional allotrope or sub-allotrope, gaseous diphosphorus,[1] was later discovered upon

subjection of white phosphorus to an extreme heat of at least 1100 Kelvin, although transition metal stabilization has allowed for more mild isolation conditions.[8, 9]

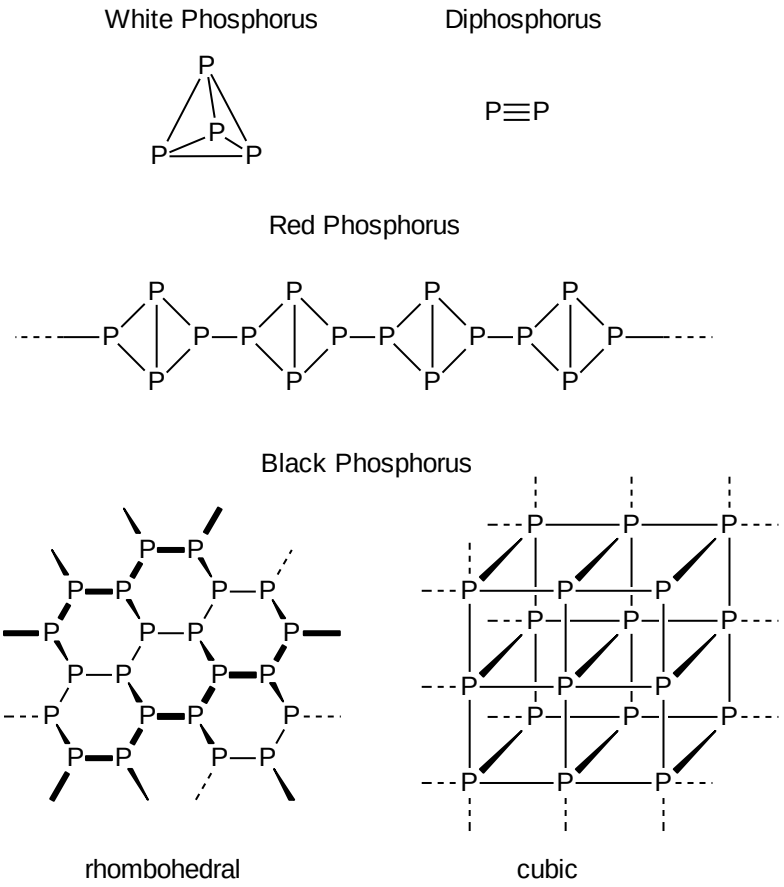


Figure 1. Allotropes of phosphorus. The orthorhombic structure for black phosphorus is not shown.[1, 2]

Phosphorus itself is a versatile element. It can form a variety of covalent bonds and subsequent compounds, including inorganic salts (often sodium, ammonium, or calcium salts of phosphates), transition metal complexes, and perhaps most importantly organophosphorus compounds, which are integral to the continuation of important biological processes (Figure 2).[1, 2, 5] By breaking the octet rule and expanding its electron shell to include d orbitals, it can range in oxidation state from -3 to +5, although it is

almost always found as a tri- or pentavalent species in nature (Figure 3).[1, 5] The high affinity phosphorus has for oxygen is particularly relevant and is observed in most natural phosphorus compounds. In oxygenated compounds such as phosphine oxides, the back donation of the vacant d orbitals overlaps with the oxygen lone pairs for a 2pπ-3dπ bond, which can be highly exploited in synthetic chemistry (Figure 3).[1, 5, 10] In addition, phosphorus compounds can have a diphilic nature, acting as both nucleophile and electrophile at different stages in the same reaction mechanism. [1, 5, 11, 12] Although commonly compared to nitrogen, its d orbital chemistry allows it to have a greater polarizability[10] and decreased electronegativity which make it more closely resemble the chemistry of arsenic.[1]

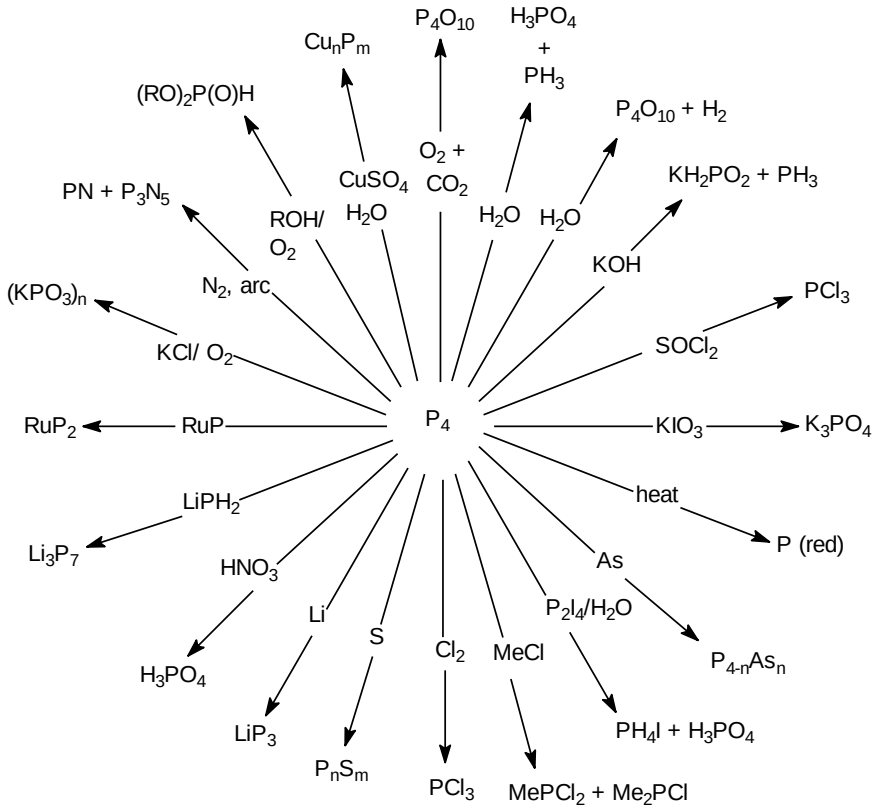


Figure 2. Various reactions of white phosphorus.[1]

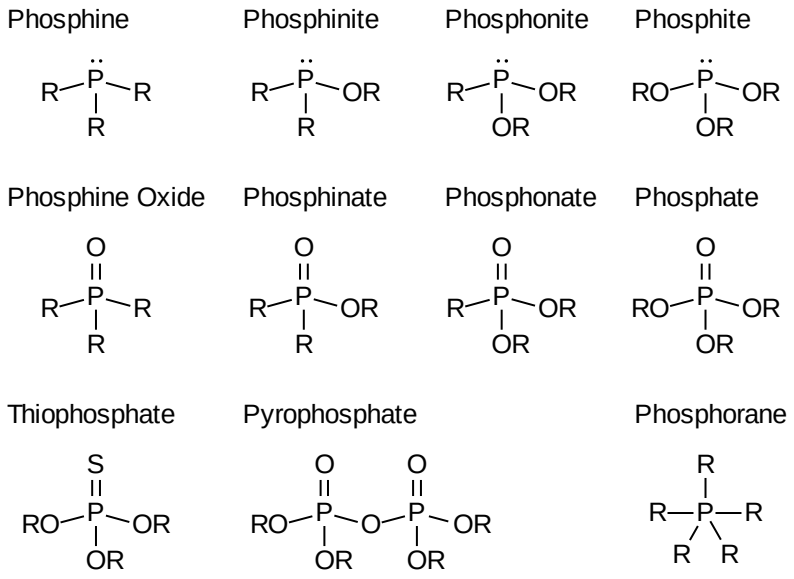


Figure 3. Some representative organophosphorus moieties where R can represent an H, alkyl moiety, halide, or counter cation. [1, 2, 5]

With advances in science came a greater understanding of biological systems and the necessity of phosphorus within those systems. It is integral to plant life, particularly photosynthesis and the generation of energy storing compounds such as adenosine triphosphate (ATP, **1**)[3] and nicotinamide adenine dinucleotide (NADH, **2**) (Figure 4).[1, 7] These phosphates are then employed in the second light-independent stage of photosynthesis, the Calvin cycle, for the energy production which fuels biological functions.[1, 3] This is in turn used in a number of processes including anaerobic oxidation of glucose (Embden-Meyerhof cycle) and the aerobic oxidation of glucose (Krebs cycle).[1, 2] As with plants, these biological processes involve the generation and storage of energy through the cleavage and formation of phosphate bonds in ATP or redox reactions involving NAD.[1, 2, 13] Dimethylallyl pyrophosphate (DMAPP, **4**) and isopentenyl pyrophosphate (IPP, **3**) are generated in the mevalonate and non-mevalonate pathways, which are responsible for supplying the building blocks for the biosynthesis of complex terpenoids (Figure 4).[1, 14] Arguably the most important phosphates in the body are those

that form the linkages between nucleosides in the backbone of both deoxyribonucleic acid (DNA, **5**) and ribonucleic acid (RNA) (Figure 4).[2, 7] In 1962 Watson and Crick even earned a Nobel Prize for their research regarding the structure of DNA and RNA, which contain the genetic code of all living organisms.[2]

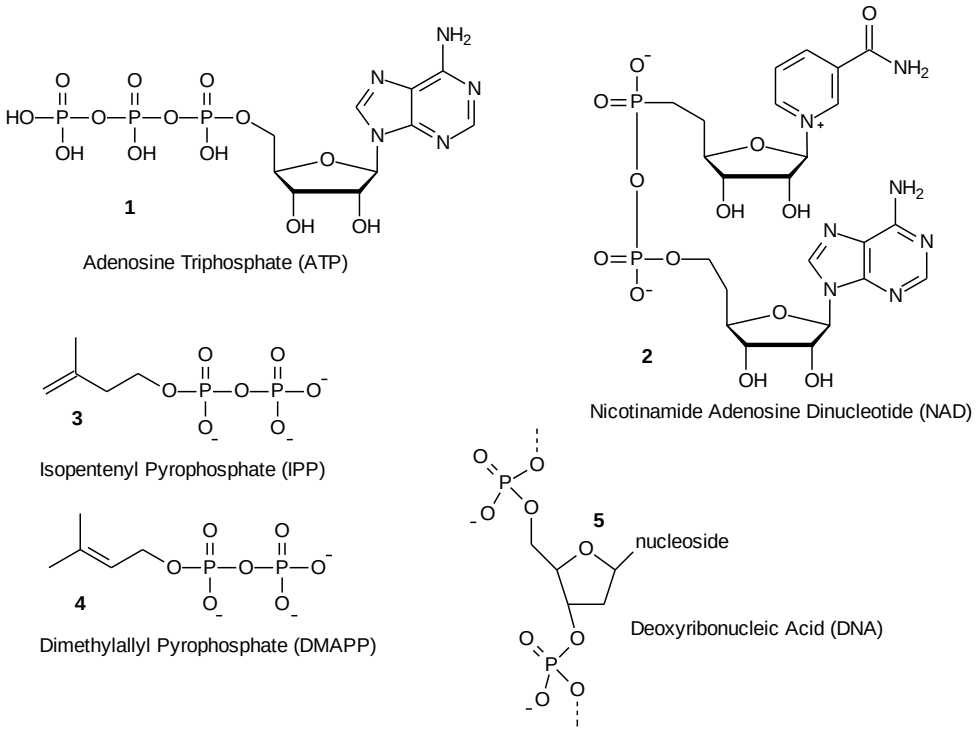


Figure 4. Biological phosphate compounds.

In addition to their involvement with natural physiological processes, phosphorus-containing compounds have been employed in medicinal applications for many varied purposes and a broad range of ailments.[1, 4] For example, organic phosphate salts can be used to enhance drug efficacy, often by increasing the drug solubility within the body and /or maintaining the body's natural pH (Figure 5).[7] Codeine (a well-known analgesic), amphetamine (**6**, as an antidepressant), and histamine (**7**, when used to treat parasitic worms) are all utilized as their phosphate salts.[1] Although marketed as the alcohol, *in*

vivo enzymes convert Acyclovir to the active triphosphate form (**8**) which can then inhibit the viral DNA polymerase activity of herpes simplex viruses.[1, 15, 16] The phosphate derivative of an amine, echothiopate iodide (**9**), is clinically used in the treatment of glaucoma and acts as a cholinesterase inhibitor.[1] Inorganic phosphorus salts also have found wide applicability (**10-13**). Radioactive $CrPO_4$ (**14**) is used in cancer therapies, and gold-phosphorus salts such as Auranofin (**15**) can reduce inflammation associated with rheumatoid arthritis (Figure 5).[1]

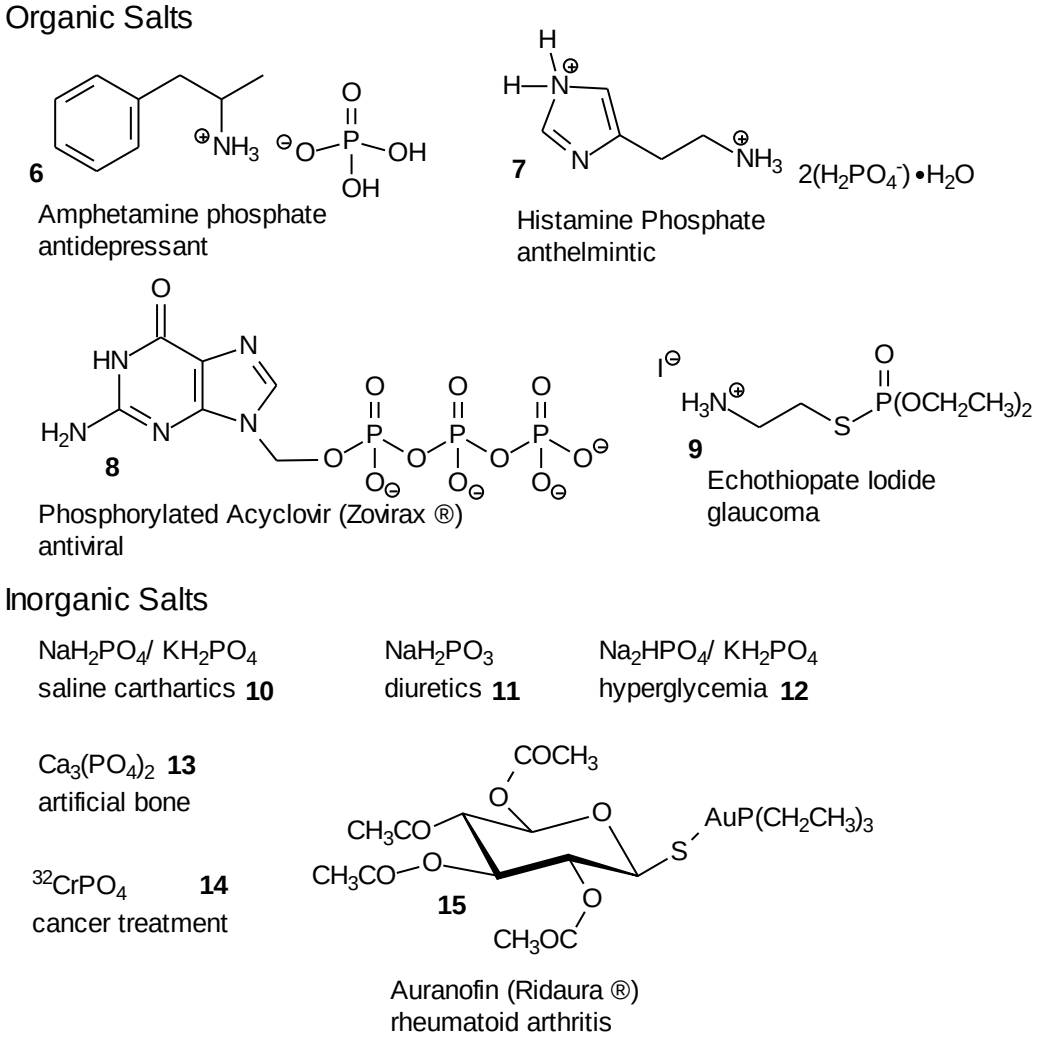


Figure 5. Some medicinal phosphorus compounds.[1]

Although initially used as an insecticide, diisopropyl phosphofluoridate (DFP, **16**)[2] and parathion (**17**) were later taken off the market after they were found to be particularly toxic to mammals (Figure 6).[1, 3, 5] The inherent toxicity usually originates from the ability of the compounds to inhibit acetylcholinesterase activity, thereby disrupting the nerve communication leading to paralysis and ultimately death.[2, 3, 5] Slight modification to the structure can have a profound impact though. For example, the addition of a methyl group in Sumithion (**19**) leads to a fairly non-toxic insecticide, especially when compared to toxic methyl parathion (**17**).[1, 2] Originally used as an insecticide, Dipterex (**20**),[3] has even been applied towards treatment of schistosomiasis under the name Metrifonate (**20**).[1, 17] Other medical advances including treatments of glaucoma and muscle fatigue have evolved from research into insecticides, pesticides, and even chemical warfare.[5]

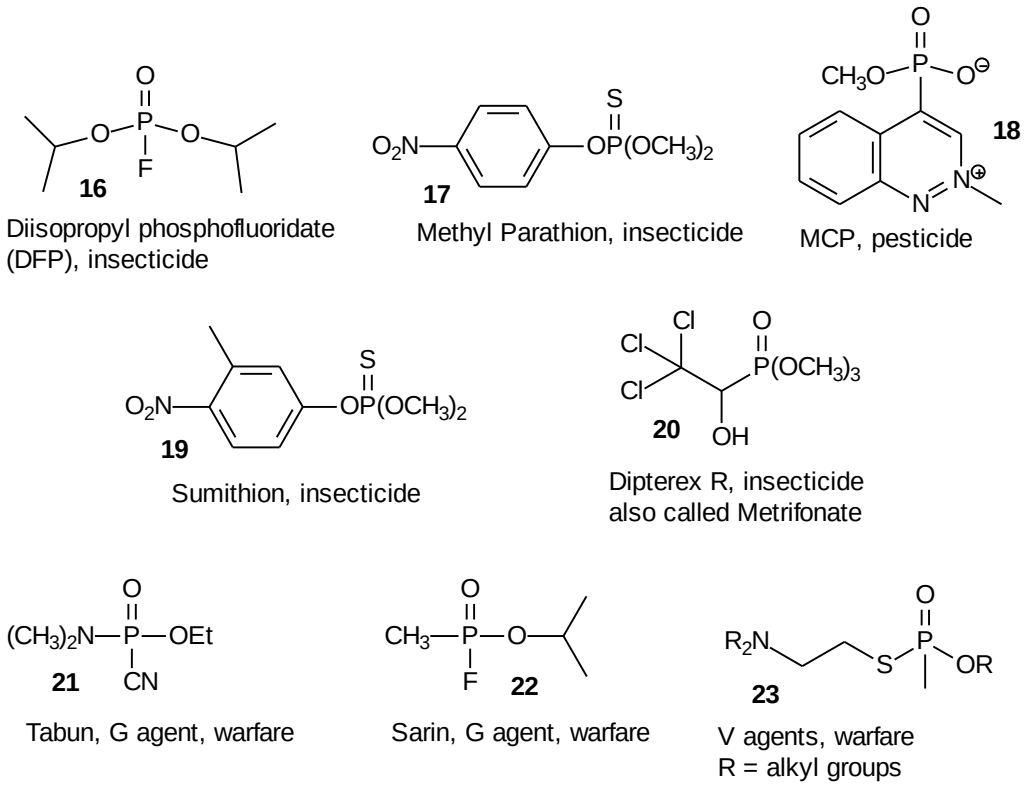
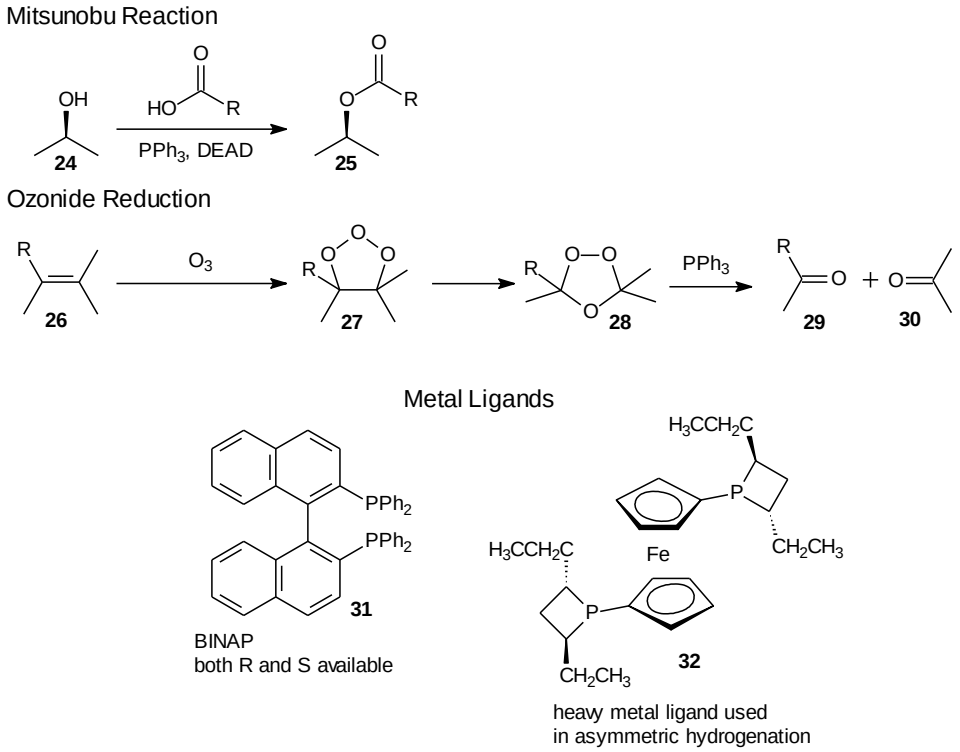
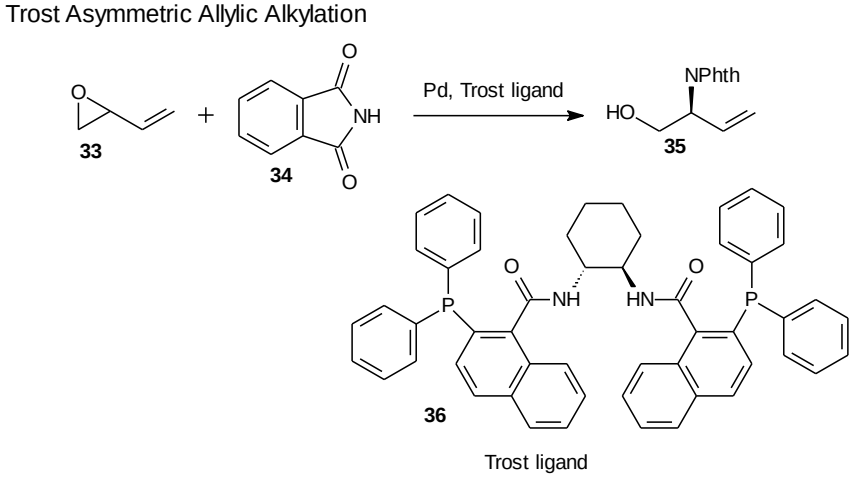


Figure 6. Some examples of toxic chemical phosphorus agents.[1, 2, 5]

Early generation chemical warfare in World War II, consisted of munition shells of phosphorous oxide which were used to form clouds of smoke and obscure movement.[2, 4] Shells of elemental phosphorus also were used, causing burns which were practically impossible to quench. A slight adaption led to the infamous Molotov cocktail in which phosphorus and benzene were stored in bottles for use as a closer range weapon.[2] Although many studies of synthetic phosphorus agents may have begun with attempts to make insecticides, pesticides (**18**), and herbicides, they also advanced into a devastating form of chemical warfare, nerve agents (Figure 6, **21**-**23**).[2, 4, 5] The structural similarities can be seen between DFP (**16**) and the very toxic nerve agent Sarin (**22**) for example. A common thread was discovered in which certain phosphorus bonds and chemical types (usually phosphonic acid derivatives with P-F bonds)[2, 3] were particularly toxic to humans because of their resistance to hydrolysis within the body.[2] The oxyphosphorus compounds were also found to be significantly more toxic to mammals in comparison to those with P=S bonds.[5] This is observed in the extremely minimal exposure dosage needed to cause death from the V agents (**23**), one of the most deadly poisons known.[1, 4, 5]

The many varied types of phosphorus compounds have led to their exploitation as important synthetic tools. The STREM catalogue alone currently has over 140 pages devoted to phosphorus catalysts and ligands, all of which have chemical applications. The simple compound triphenyl phosphine, is utilized in any number of reactions. Some important examples include the initiation of the Mitsunobu reaction[18-21] for conversion of an alcohol to a variety of functional groups, although commonly an ester (Figure 7). The explosive ozonide intermediate (**28**) produced in the oxidation of alkenes to the respective aldehyde or ketone are reduced upon the addition of triphenyl phosphine in ozonolyis reactions.[22-27] Phosphorus is also very commonly used to form ligands in transition and heavy metal complexes (**31** and **32**).[28-32] The aryl compound BINAP (**31**) for example, can be used in asymmetric hydrogenations and also can serve as a common chiral ligand for controlling the stereochemical outcome of reactions.[31, 32] The phosphine





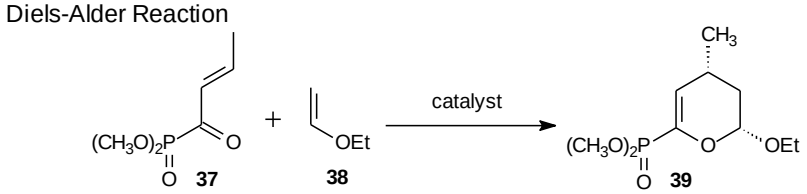


Figure 7. Some synthetic applications of organophosphorus reagents.

ligand **36** created by Trost can direct the allylic alkylation in a stereoselective fashion.[33, 34] The unique diphilic character also allows the dimethyl phosphonate **37** to participate in Diels-Alder type reactions.[11, 12] This is only a small sample of the phosphorus reagents and their applications in current literature.

In 1958, Wittig adapted a previous work by Luscher, in which a phosphonium ylide was allowed to react with diphenyl ketone (**41**) to form a new C-C bond (Figure 8).[35] The process revolutionized olefin synthesis and has evolved into one of the arguably most popular and utilized reactions in synthetic chemistry. The research led to Wittig achieving the Nobel Prize in 1979.[36] In a broader sense, the Wittig reaction involves the reaction of a nonstabilized (or unconjugated) phosphorus ylide (**40** and **40'**) reacting with an aldehyde or ketone to form a cis alkene, generally with good selectively.[7, 13, 37-39] While these resulting ylide species have the ability to react with a plethora of electrophiles, the most widely studied and utilized are those that form carbon-carbon bonds.[35, 38, 40]

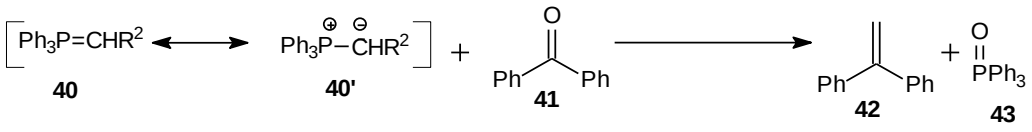


Figure 8. Original phosphonium salt experiment conducted by Wittig.[35]

Despite over 50 years of research, the exact mechanism of the Wittig reaction has not been elucidated and is still a controversial topic. Early works suggested a step-wise mechanism in which the initial C-C bond formed through an erythro betaine intermediate (**46**) followed by rapid decomposition of the 4-membered oxaphosphetane **48** (Figure 9).[5, 7, 35, 38, 39, 41] To date, there has been no chemical evidence for the betaine intermediate.[38] However, the oxaphosphetane has been isolated and studied in some species, which led to the argument of a direct formation of the oxaphosphetane intermediate. [38, 42] Molecular

orbital calculations support the oxaphosphetane theory.[7, 39, 43] The betaine was found to be much higher in energy (32kcal/mol) than the oxaphosphetane (7 kcal/mol) and its activation energy was also significantly higher.[38] Currently, the generally accepted theory is a kinetically controlled reaction which is believed to proceed through a nonsynchronous 4-membered cycloaddition, where the C-C bond is formed first then the P-O bond.[7, 13, 39, 44] The strong P-O affinity then leads to the decomposition of the oxaphosphetane with retention of configuration.[38] Arguments for stereochemical drift,[38, 43] the reversal of the cis and trans intermediate through equilibrium, have for the most part been discredited.[38, 45]

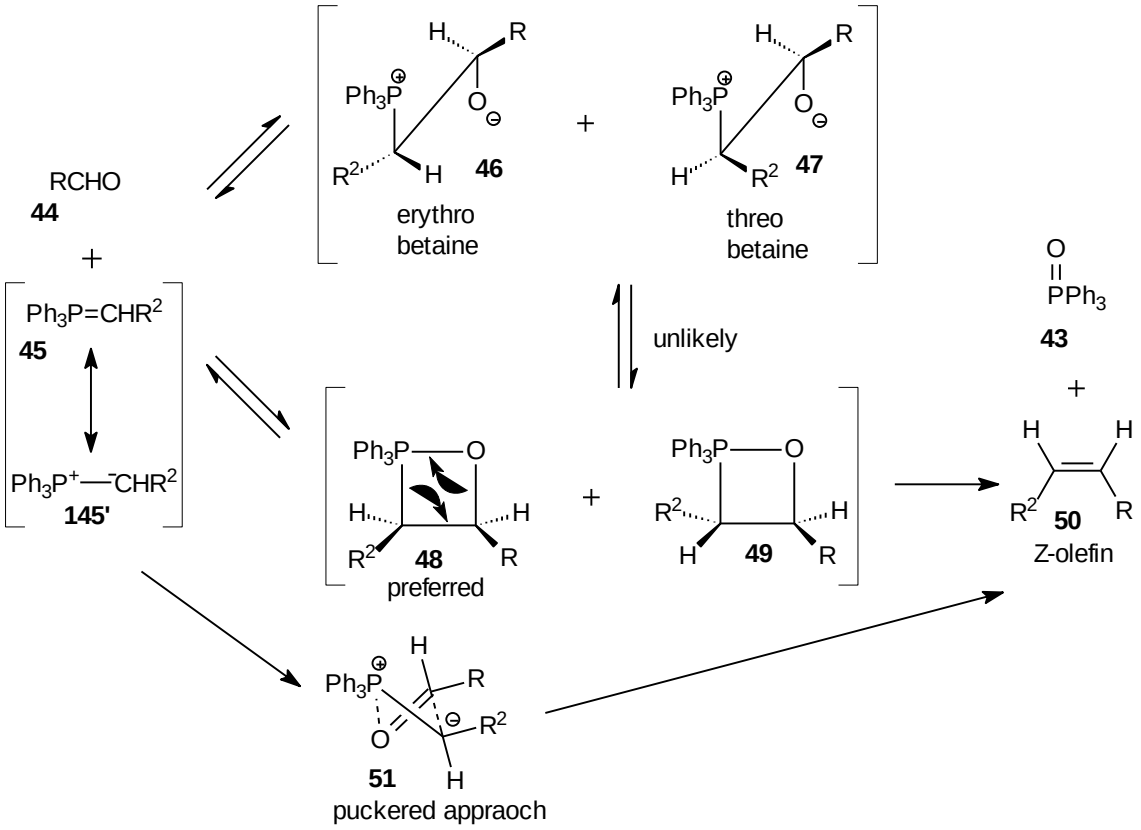


Figure 9. Proposed Wittig reaction mechanism.[38]

Even among those who concur with a nonsynchronous mechanism, there is disagreement.[42, 45] The initial C-C bond formation step generally has been explained as planar transition state.[39] Vedejs[45] suggested the initial antiperiplanar approach occurred through a puckered transition state thereby providing the cis–selectivity of the Wittig reaction, which was later supported through calculations by Yamataka.[46] Making these studies more difficult are the large effects that solvent, temperature, metal cation, and concentration can play on the reaction.[7, 38, 39] Using a trialkyl phosphonium salt also has been found to produce a larger ratio of the thermodynamic trans product, suggesting that the phenyl moiety also plays a part.[13, 47]

The Horner-Wadsworth-Emmons (HWE) reaction, an adaption to the described Wittig reaction, also utilizes a phosphorus ylide and is widely popular. Unlike the Wittig reaction however, a stabilized ylide is used to form a predominantly trans olefin product (Figure 10).[38, 40, 43, 48] The first example of a phosphonate stabilized carbanion that was allowed to react with a ketone was published by Horner, but Wadsworth and Emmons further developed the method and were largely responsible for the popularity of the phosphonate reagent of this reaction.[37, 40]

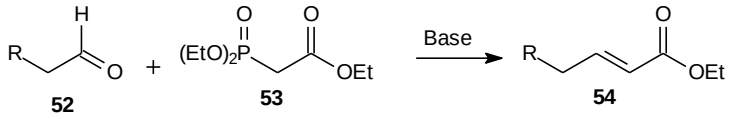


Figure 10. Representative Horner-Wadsworth-Emmons olefination reaction.

After deprotonation of the phosphonate with base, the nucleophilic carbanion attacks a carbonyl group in a stepwise manner to form the initial C-C bond (Figure 11).[38, 40, 48] Unlike the Wittig reaction, the thermodynamic threo adduct **60** is favored and believed to be in equilibrium with the oxaphosphetane **61**.[43] In fact, interconversion

between these intermediates is thought to assist in formation of the mainly trans products (**62**) as well as the stereoselectivity in the initial C-C bond formation.[38, 48] The use of the phosphonate moiety leads to certain advantages of the HWE methodology over the Wittig reaction,[10] including the generally easier synthesis[40] of the phosphonate reagent.[37, 48] The phosphonate–stabilized carbanion **53** (pKa ~ 18)[49, 50] is more nucleophilic and basic than the corresponding phosphonium ylide **45** where R^2 = $COEt_2$ (pKa ~ 8).[5, 35, 41, 48, 49, 51] The water soluble phosphate salt by-product[40, 48] (**59**) also allows for more facile purifications over a triphenylphosphine by-product (Figures 10 and 11).

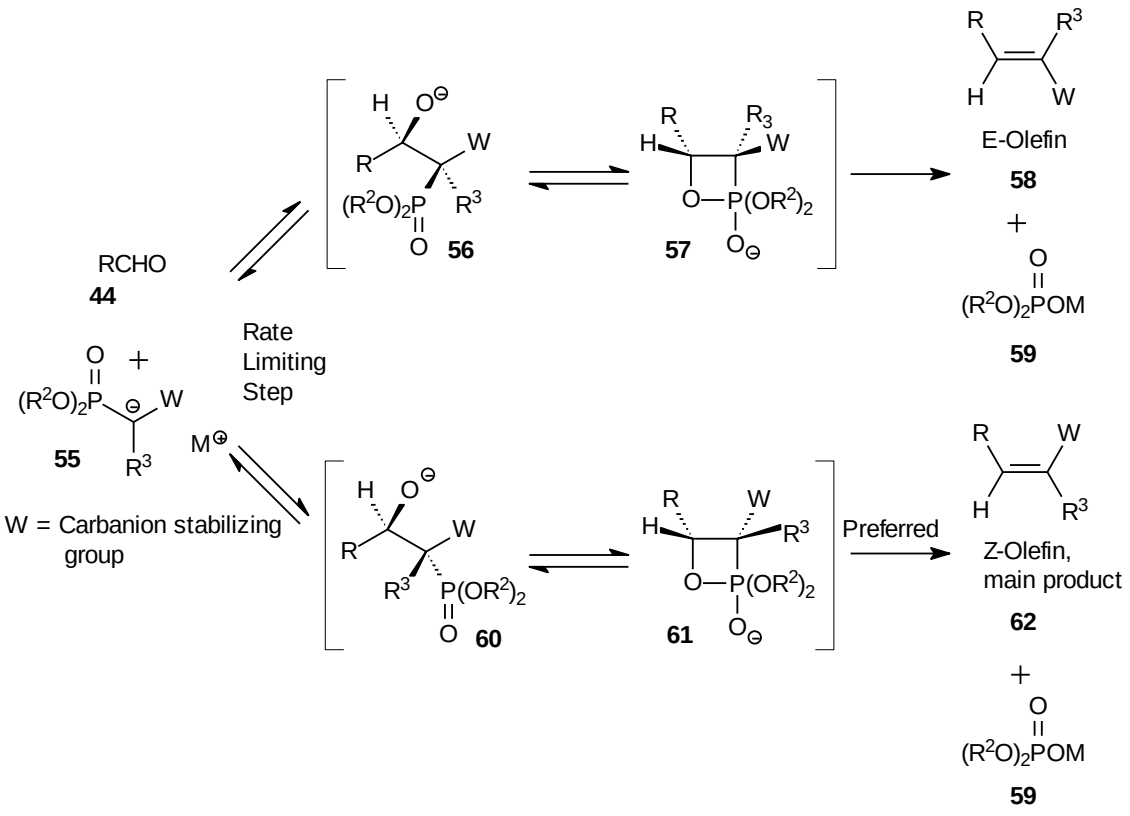
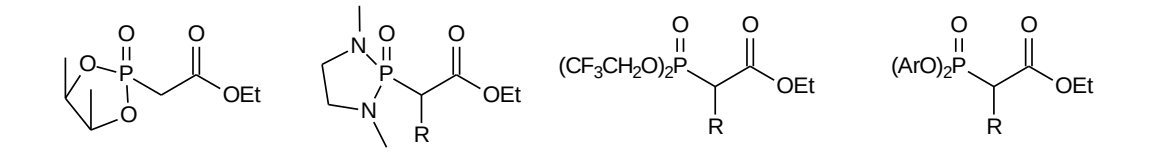


Figure 11. Proposed HWE mechanism.[52]

Another advantage of the HWE protocol is its versatility and amenability to diverse reaction conditions leading to the kinetically favored cis olefin.[43] There are modifications to achieve this goal by Breuer (**63**)[53] and Patois and Savignac (**64**)[54, 55] who utilized phosphonates with bulky 5-membered heterocyclic ring systems, Still and Gennari who used trifluoroethyl phosphonate **65**,[37, 56, 57] and most recently Ando who used phosphonate **66** (Figure 12).[58-61] These modifications use steric and/or electronic effects to favor the kinetic erythro intermediate and subsequent cis alkene. The strongly electron withdrawing trifluoroethyl groups in the Still phosphonate are believed to favor a quick elimination of the cis intermediate over the trans olefin and equilibrium product.[57] While the Still conditions can provide good yields from a variety of aromatic and aliphatic aldehydes, this approach often requires cold temperatures and a crown ether additive.



63 Breuer Phosphonate

*R = H or alkyl

64 Patois and Savignac Phosphonate

65 Still and Gennari Phosphonate

66 Ando Phosphonate (includes a variety of substituted aromatics)

Figure 12. Examples of phosphonates used for cis olefin formation through modified HWE reactions.

The phosphonates employed by Ando often can be used at warmer temperatures and without the hygroscopic crown ether. Many bases, solvents, and temperatures have been explored in an effort to increase the Z selectivity of these modified protocols. For example, it has been found that potassium counter ions will often lead to a higher ratio of cis products, [59] but this can also be highly dependent upon the substrate. Overall, the phosphorus ylide, whether the phosphonium or phosphonate variety, is a very versatile

moiety that allows C-C bond formation strategies that are applied widely in synthetic chemistry.

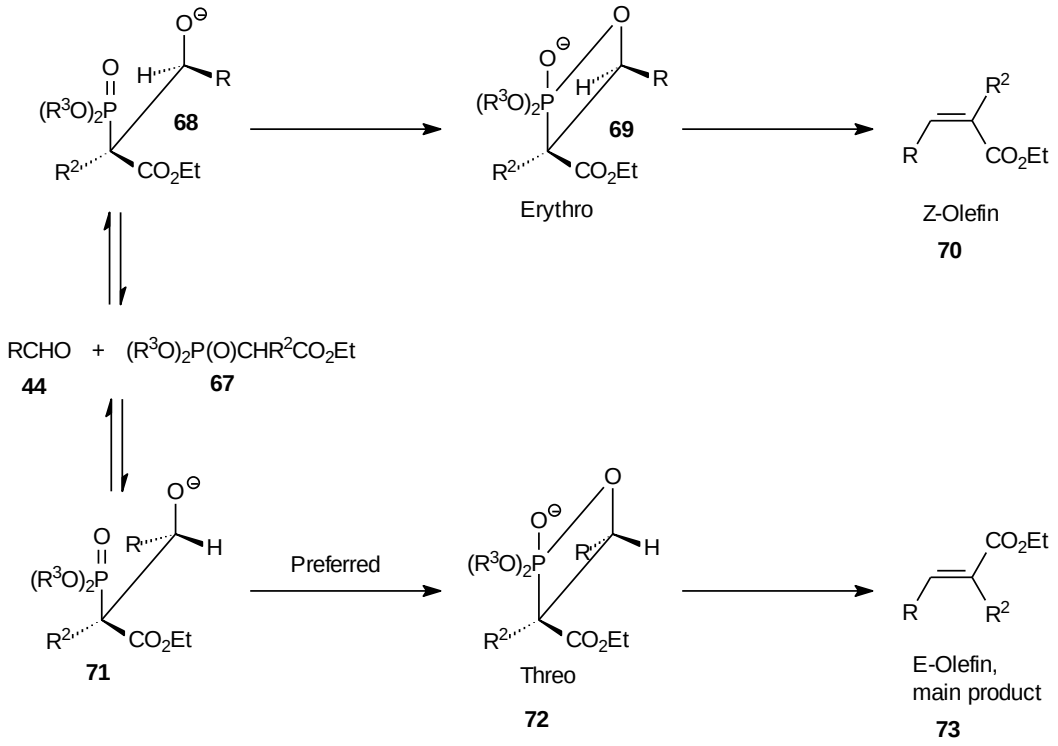


Figure 13. Ando adaption of the HWE reaction.[59]

As incredible as it may seem, the search to transform everyday metals into gold and silver led to the fortuitous distillation of phosphorus in urine. Approximately 350 years later, phosphorus compounds are now known to be an essential building block of life, an important industrial tool, a medicinal drug or deadly poison, and an invaluable synthetic moiety for chemical transformations.[1] Although this is not a complete summary of phosphorus compounds, their applications in industry and medicine, their synthetic applications, or biological roles, the importance of phosphorus is highlighted. In due

course a new synthesis of phosphonates and applications of organophosphorus in organic synthesis will be described.

CHAPTER II
ZINC MEDIATED PHOSPHONATE FORMATION

Phosphonates represent a large group of chemical compounds with many varied applications. Phosphonate moieties are found not only in therapeutic drugs[62, 63] and industrial chemicals,[7, 62, 64] but also as significant intermediates in synthetic chemistry (Chapter 1, Figure 7). Several methods have been utilized for the synthesis of phosphonate esters, most notably, the Michaelis-Arbuzov reaction (Figure 14).[38, 65, 66] The resulting functionality can be applied in Horner-Wadsworth-Emmons condensations[40, 48, 67] and other coupling reactions, and this strategy has been employed for preparation of a variety of biologically active products.

With the multitude of industrial and synthetic applications of phosphonates, one of the surprising difficulties encountered in this chemistry is the relatively small set of methods available for phosphonate synthesis. Perhaps the most widely applied, and generally high yielding strategy, is the Michaelis-Arbuzov (or commonly truncated Arbuzov) methodology discovered by Michaelis and Kaehne and further developed by Arbuzov.[38, 65, 66] The current three step protocol involves the conversion of an alcohol to a better leaving group and then halide formation before treatment with trialkyl phosphite (Figure 14). The driving force of the Arbuzov reaction lies in the P=O bond formation after an S_N2 nucleophilic attack by the displaced halide, which affords 32-65 kcal of bond stability in the final conversion of the halide to the phosphonate ester.[65] Although Lewis acid mediated alternatives to this protocol allow some modifications (Figure 15), few alternative methods are available when the classic strategy proves difficult or the necessary reagents prove unreactive.[68, 69]

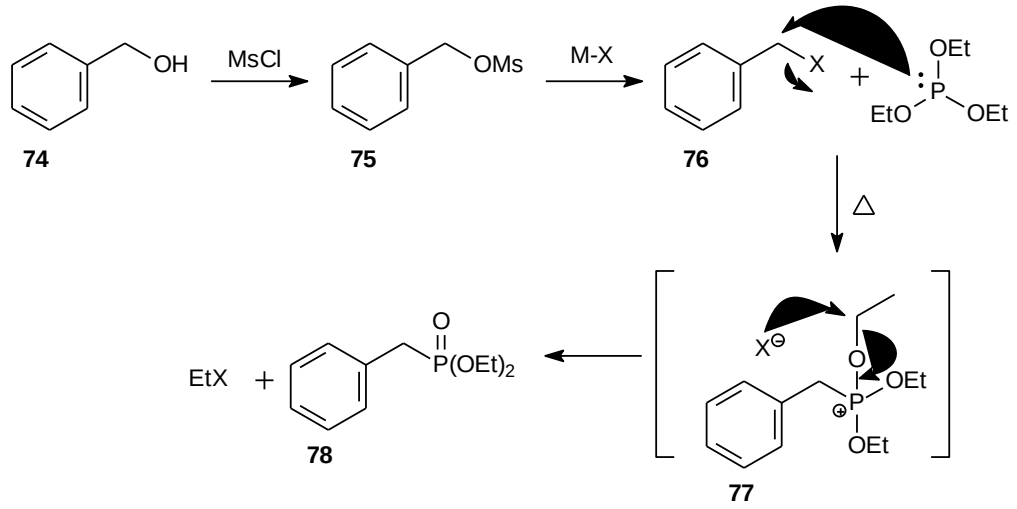


Figure 14. An Arbuzov sequence illustrated with benzyl alcohol.

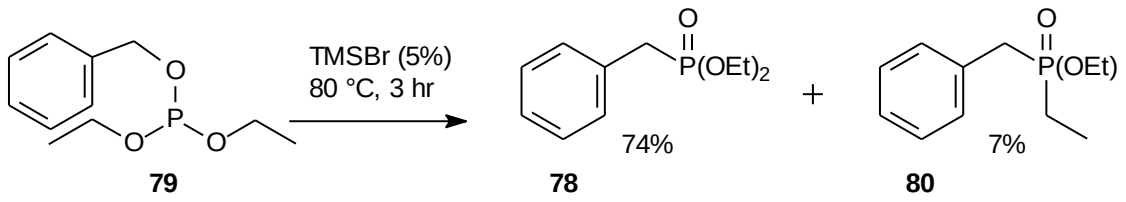
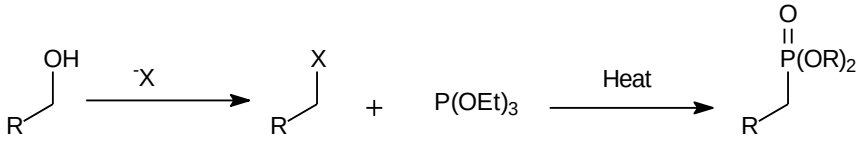


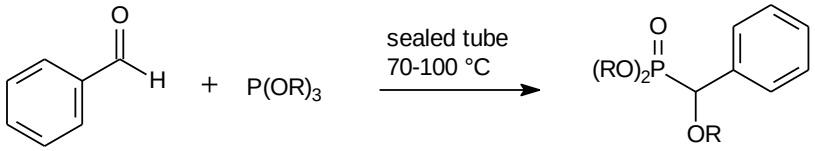
Figure 15. An example of the halide-promoted Michaelis-Arbuzov rearrangement.[68, 69]

As already mentioned, the Michaelis-Arbuzov reaction is the most commonly employed reaction for synthesis of phosphonates, but some of the other methods of note are the Abramov, Pudovik, and Michaelis-Becker reactions (Figure 14 and 16).[70] The Abramov and Pudovik procedures afford α–hydroxy phosphonates from the requisite tri- or dialkyl phosphites and an aldehyde or ketone. Whereas the Abramov reaction utilizes the phosphite triester, the Pudovik reaction involves the attack of an anionic phosphorus species followed by neutralization. In contrast to the previously mentioned methods, the Michaelis-Becker reaction is a base promoted nucleophilic substitution on an alkyl halide by an anionic phosphorus reagent, ultimately affording an alkyl phosphonate.

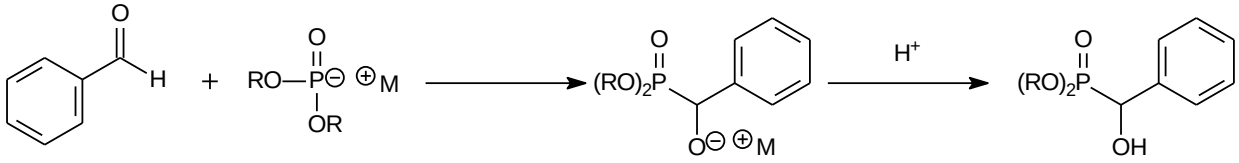
Michaelis-Arbuzov Reaction



Abramov reaction



Pudovik reaction



Michaelis-Becker reaction

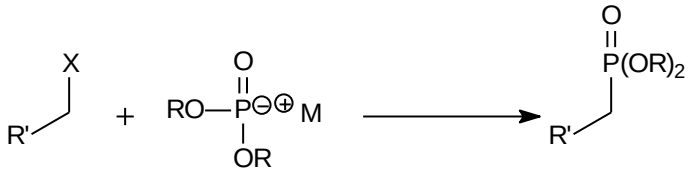


Figure 16. Methods of phosphonate synthesis.

With the Wiemer groups' longstanding interest in C-P bond formation[71-76] and their many applications of HWE condensations towards natural product synthesis (Figure 17), supplementary options to the Arbuzov reaction were of interest. Synthetic methodologies leading to mono-, bis-,[77-79] and trisphosphonates[80, 81] along with biological testing of phosphonates compose a substantial fraction of our research. Furthermore, the schweinfurthins,[82-91] pawhuskins,[92-94] and radulanins[20, 95-104] all utilize benzyl phosphonates for a traditional Horner-Wadsworth-Evans olefination to afford stilbenoid moieties.

Given this extensive background in phosphorus chemistry, particularly the formation and application of phosphonate esters, methods alternative to the three-step Arbuzov protocol were explored.[105, 106]

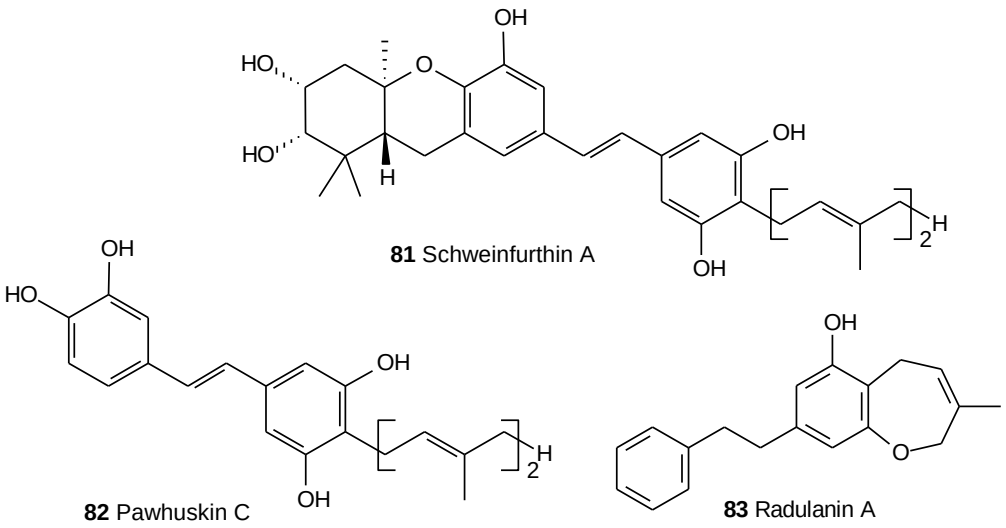


Figure 17. Natural products prepared through HWE olefination reactions.

It is well-known that metals and Lewis acids have been utilized to activate allylic, benzylic, and tertiary carbocation formation and allow subsequent nucleophilic substitutions. Previously, zinc halides have been employed in such reactions, providing alcohols,[107] thiol acids,[108] thioethers,[109] selenides,[110] and hydrides (Figure 18).[111,112] Zinc iodide has been reported to facilitate a reductive deoxygenation reaction which allows removal of the benzylic alcohol moiety through a radical mechanism and hydrogen radical insertion (Figure 18).[112] In addition, allylic alcohols act as nucleophilic agents in zinc chloride mediated etherification reactions (Figure 18).[107]

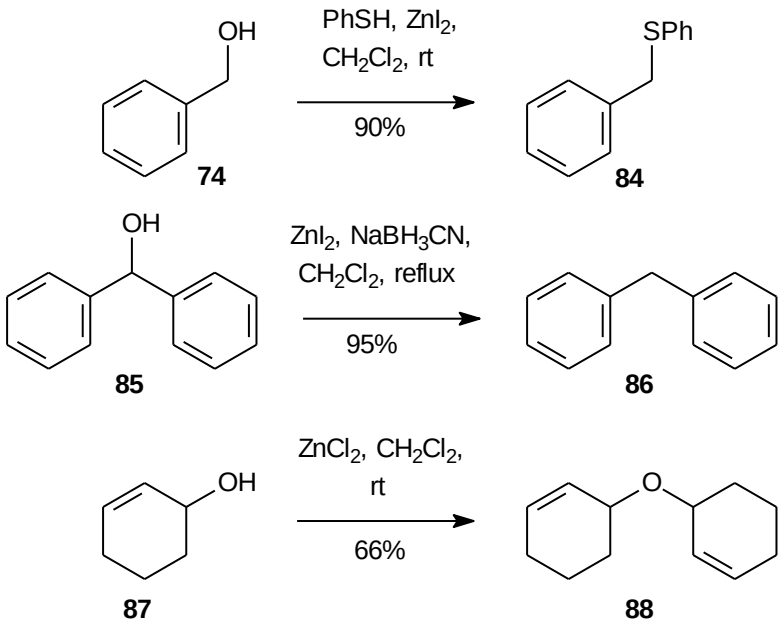


Figure 18. Lewis acid activated alcohol reactions.

A thorough literature search uncovered few examples exploiting phosphorus as a nucleophile in similar systems (Figure 19). Work by Ivanov[113-116] and later Chasar[117] utilized an ortho phenol to access the phosphonate through a 5-membered heterocyclic intermediate.[113-117] The required ortho phenol functionality significantly limits the applicability of this method. Work by Shahsavari-Ford[118] and co-workers demonstrated activation of epoxide moieties through a tetra-coordinate zinc species leading to a phosphonate product (Figure 19), and other literature examples show demethylation of ethers through reaction with phosphorus nucleophiles.[119] A single case involving the trapping of a stabilized carbocation with phosphorus was thought to involve formation of a quinonoid intermediate and subsequent phosphonate formation (Figure 19).[120] Although there are examples of the direct conversion of alcohols to phosphonate species, they tend to involve very specialized sets of conditions and circumstances. The combination of our longstanding interest in C-P bond formation and the precedence for the attack of carbocations by various nucleophilic moieties led to the development of an expedited,

mild, and broadly applicable alternative to the Arbuzov sequence with zinc halide activated alcohols.

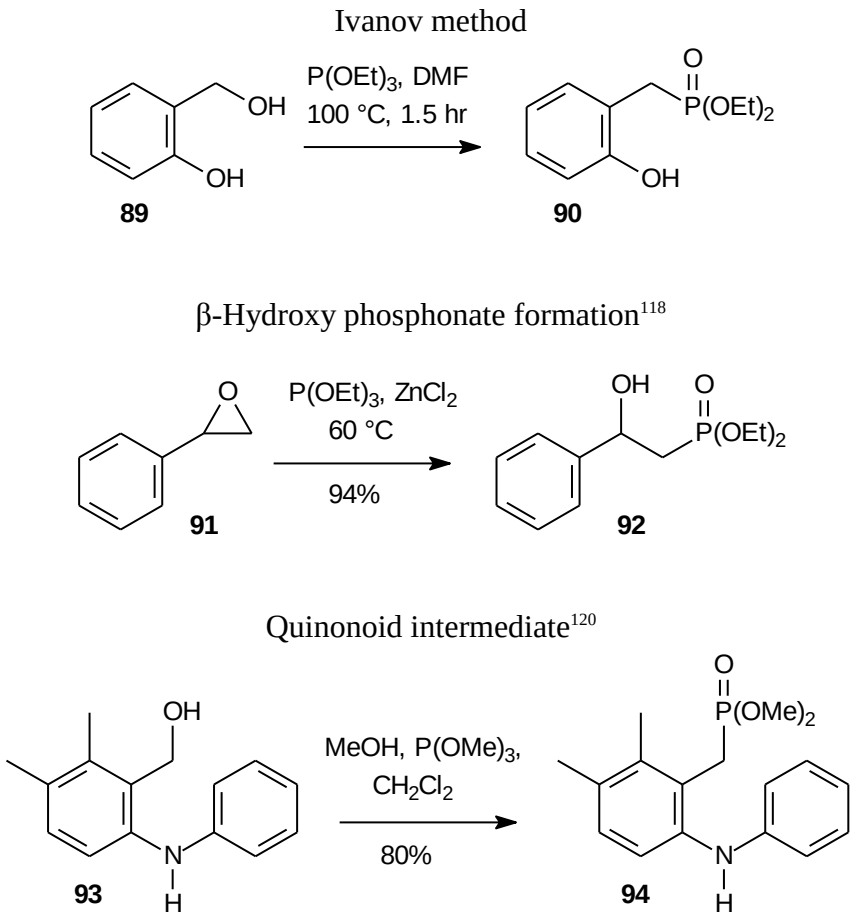


Figure 19. Application of phosphorus nucleophiles in Lewis acid activated reactions.

As an initial test case, benzyl alcohol was utilized for the attempted Lewis acid mediated phosphonylation (Figure 20). Interestingly, dissipation of solid ZnI_2 into solution upon addition of triethyl phosphite was observed, indicating interaction between the zinc and phosphite moieties. Following addition of benzyl alcohol to the reaction mixture, the reaction progress was monitored through ^{31}P NMR spectroscopy. Formation of the desired phosphonate [121] was evident upon observation of a resonance at 27.8 ppm,

and the NMR analyses indicated that an overnight reaction time was convenient. The resulting solution was immediately placed on the vacuum line to remove volatiles. Treatment of the residue with 2N NaOH allowed removal of the white ZnO byproduct through its subsequent conversion to the zincate.[122] Following extraction with diethyl ether, the desired organic product was purified through flash column chromatography. After initial attempts utilizing zinc iodide gave moderate to good yields of diethyl benzylphosphonate (**78**), optimized reaction conditions ultimately were investigated with benzyl alcohol as the standard substrate.

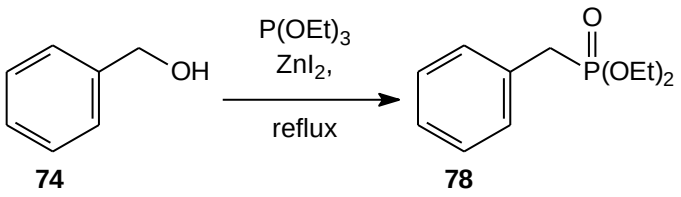
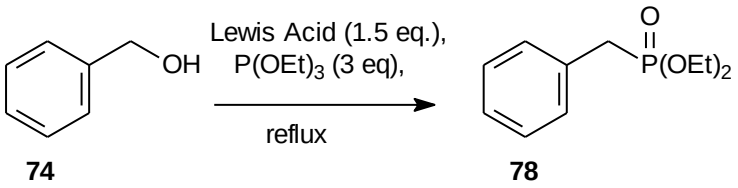


Figure 20. Direct conversion to the phosphonate ester.

The success of the ZnI_2 mediated phosphonylation also prompted the examination of other Lewis acids in the protocol (Table 1). The less hygroscopic nature and inexpensive commercially availability of $ZnBr_2$ made it an attractive substitute. Although the reactions proceeded in good yield, a longer reaction time of three days was required, unlike the general overnight reaction time employed with ZnI_2. Shortly after our paper was submitted, another report utilizing $ZnBr_2$ for the direct conversion of alcohols to phosphonates also was submitted and that paper described much shorter reaction times.[123] In addition, aluminum triiodide has been established as a method for generating allylic, benzylic, and tertiary iodides from alcohols.[124] Regrettably, under the reported reaction conditions for formation of iodides,[106, 125] there was no evident conversion to the anticipated benzyl phosphonate when AlI_3 was used. It is possible that

undesired associations with the phosphite or decomposition of the alkyl halide proved detrimental to the desired reaction. It is also possible that the lack of a halide intermediate results in deviation from the traditional Michaelis-Arbuzov reaction manifold.



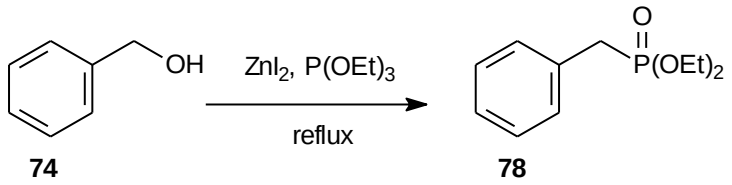
74 **78**

Lewis Acid	Solvent	Yield
ZnI_2	Toluene	84%
$ZnBr_2$	Toluene	75%
AlI_3	Toluene or CH_3CN	NA

Table 1. Variation in Lewis acids.

Optimal reaction conditions for the ZnI_2 mediated protocol for phosphonate synthesis were determined on the benzyl alcohol substrate through an extensive investigation of reagent equivalents, solvent, and temperature effects. In both THF and toluene at reflux, trends indicate a slight excess of ZnI_2 was required (Table 2, Entries 2, 3, 4, 6, and 9). Utilization of catalytic amounts of the Lewis acid provided a low yield (27%), although if ZnI_2 was viewed as the limiting reagent, a yield of 88% was achieved. Parallel trends were observed upon treatment of 4-methoxybenzyl alcohol[126] under similar reaction conditions. A large excess of the zinc reagent was even more detrimental to yield in this case (Entry 5), possibly due to overexpression of side products or competitive coordination of the metal site. In addition to ZnI_2, a slight excess of triethyl phosphite also was beneficial (Table 2), hinting at the importance of the reactive

phosphite and zinc species. Although most reactions were conducted with a 2 to 1 ratio of the phosphite to zinc iodide, only a 1 to 1 ratio appears to be necessary for attractive results (Entry 4).



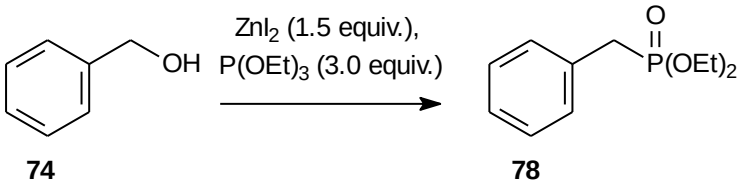
Entry	ZnI_2 (Equiv.)	$P(OEt)_3$ (Equiv.)	Solvent	Yield
1	0.3	3.0	THF	27%
2	1.5	3.0	THF	74%
3	1.1	1.5	THF	90%[a]
4	1.5	1.5	THF	83%
5	3.0	1.5	THF	5%
6	1.1	1.5	Toluene	67%[a]
7	0.6	2.0	Toluene	60%
8	1.0	2.0	Toluene	82%
9	1.5	3.0	Toluene	84%

[a]Yield based on ^{31}P NMR integration of phosphonate and phosphate mix.

Table 2. Variation of equivalents.

Temperature and solvent effects on the reaction progress also were studied in some detail on benzyl alcohol (Table 3). The best yields with the shown equivalents of reagents were obtained when the zinc mediated reaction was conducted at 80 °C (Table 3, Entry 2 and 3), an improvement upon the generally high temperatures required for the Michaelis-Arbuzov reaction.[65] Whereas the lower yields at higher temperatures could be explained through an increase in side reactions or decomposition, those experiments done at room temperature appeared to require long reaction times. Although these general

conditions usually provide the best results, for some substrates varying temperature and solvent were found to have a significant impact.



74 **78**

Entry	Temperature	Solvent	Yield
1	rt	THF	14%
2	66 °C	THF	74%
3	80 °C	DMF	75%
4	80 °C	Toluene	92%
5	110 °C	Toluene	84%
6	120 °C	DMF	36%

Table 3. Effects of temperature and solvent.

Despite the more attractive yields obtained in toluene, the results were also more variable than those from parallel reactions conducted in THF or DMF. Work-up and purification of the reaction also proved more facile in THF. This is in direct contrast to most literature procedures[107-109, 112, 119] which describe the coordinating ability of THF or DMF to the zinc halide as detrimental to the reaction progress and use methylene chloride instead.[123] However, in our case use of methylene chloride was not successful. Solvent effects also were evident through byproduct formation as seen in the ^{31}P NMR spectra (Spectrum 1). Reactions conducted in both THF and toluene show evidence of the diethyl benzylphosphonate product at 27.7 ppm, but the reaction in THF shows an additional peak, likely a mixed ester phosphonate at 35.4 ppm, and in reactions conducted in toluene a resonance at 5.2 ppm often was observed.

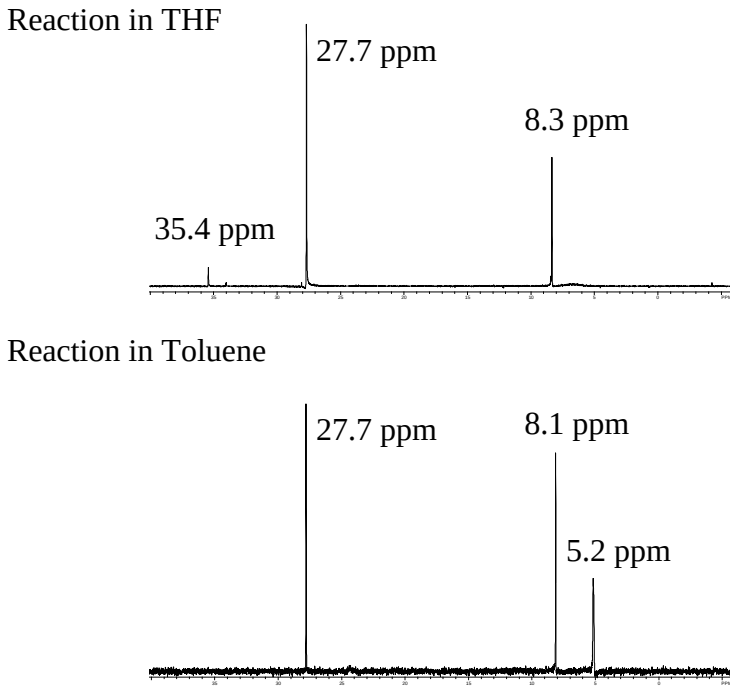
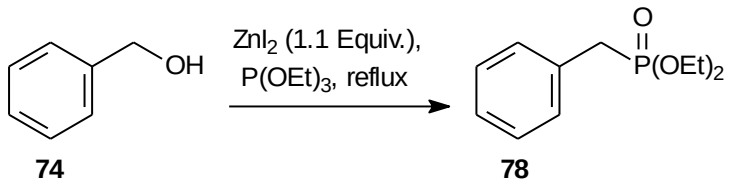


Figure 21. Spectrum of solvent effects on the reaction mixture.

Although the protocol had been optimized on small scale (0.3 mL, 2.90 mmol), more practical uses might benefit from a larger scale reaction. In addition, an invitation to submit our protocol to *Organic Synthesis* required a final product of at least 5 grams (Table 4).[125] With financial considerations in mind, and previous work showing that a large excess of reagents is not required, the initial equivalents were decreased even further to 1.1 equivalents of ZnI_2 and 1.2 equivalents of $P(OEt)_3$. Initial efforts in toluene and under neat conditions indicated that 1.5 equivalents of $P(OEt)_3$ produced the best results (Table 2). Unlike the results for the smaller scale reactions, the utilization of THF as a solvent also provided the best yields, even over toluene where the observed yield was significantly lower. Treatment of benzyl alcohol (3.3 mL, 31.9 mmol) with an increase of the ZnI_2 equivalents (1.2) led to the successful synthesis of 5.5 grams of the diethyl

benzyl product with only a slight decrease in isolated yield when compared to the small scale optimization results.



74 **78**

Entry	$P(OEt)_3$	Temp.	Solvent	Isolated Yield	Product (g)
1	1.2	80 °C	Toluene	41%	2.45
2	1.5[b]	80 °C	Toluene	39% (50%)[a]	3.65
3	1.2	80 °C	Neat	41%	2.43
4	1.4	80 °C	Neat	63%[a]	3.77
5	1.5	80 °C	Neat	69%[a]	4.13
6	1.5	66 °C	THF	72% (74%)[a]	4.28
7	1.5	66 °C	THF	70% (74%)[a]	4.19
8	1.5[b]	66 °C	THF	68% (76%)[a]	4.96
9	1.5[b]	66 °C	THF	73% (79%)[a]	5.33
10	1.5[b]	66 °C	THF	76% (79%)[a]	5.50

[a]Yield determined by ^1H NMR and ^{31}P NMR integrations. [b]1.2 equivalents of ZnI_2 were used.

Table 4. One-flask phosphonate synthesis on a larger scale.

On a larger scale, column chromatography was less practical and distillation was explored as a purification method. Excess ZnI_2 provided better yields based on ^1H and ^{31}P NMR spectra analysis, but contaminants from excess ZnI_2 were somewhat difficult to remove. This factor required a balance to be reached between the amount of the Lewis acid, the ease of distillation, and the subsequent isolated yield. Although initial attempts proved problematic, it was possible to determine conditions which provided the desired product in good yield with minimal effort. After bulb-to-bulb distillation at 0.1-0.3 mm Hg, the product was sufficiently pure (>98% by ^{31}P NMR) for most applications with

only a small peak evident in the ^{31}P NMR at 32 ppm. Unfortunately, a common contaminant was evident through TLC analysis and in three separate trials materials prepared this way failed elemental analysis. The elemental analysis was consistently low on the carbon value and a wash of the distillation apparatus with the solvent turned bright purple, showing that the contaminant was likely iodine. Therefore, in the final trial submitted for analysis, a small sample of the distillate was successfully purified through a subsequent silica gel column chromatography and the material obtained was of sufficient purity to pass elemental analysis.

These results do not afford a complete mechanistic picture, but some aspects of the reaction sequence are apparent. While a process involving formation of an intermediate benzylic iodide and a subsequent Arbuzov reaction would explain formation of the phosphonate products, past work indicates that treatment of an alcohol with ZnI_2 is more likely to afford the corresponding ether than the iodide.[107, 112, 120] Furthermore, no evidence for an intermediate iodide was found in this case and the absence of a phosphonate product from the AlI_3 trial (Table 1) also argues against iodide formation. Addition of a substantial excess of ZnI_2 was detrimental to isolated yields, contrary to what one might expect if formation of an intermediate iodide were required, and when sub-stoichiometric amounts of ZnI_2 were employed, it became the limiting reagent.

Formation of a zinc-phosphite complex[118] may be a more likely conclusion, and is supported both by the dissolution of zinc iodide upon addition of triethyl phosphite and a shift in the ^{31}P NMR resonance when ZnI_2 is added to a solution of $P(OEt)_3$. The ^{31}P NMR spectrum of the mixture of triethyl phosphite and zinc iodide (Figure 22) shows the disappearance of the phosphite resonance at 138.6 ppm and the appearance of a peak at 8.3 ppm that likely represents a complex. Not only does the 8.3 ppm resonance disappear after standard work-up in 2N NaOH (Figure 23), but similar resonances also were observed in both THF and toluene when the reaction mixture was analyzed by ^{31}P NMR spectroscopy (Figure 22). Removal of the metal species after work-up shifted the

observed peaks downfield, thereby showing evidence of the product in a resonance at 26.4 ppm as reported in the literature for diethyl benzylphosphonate.[68]

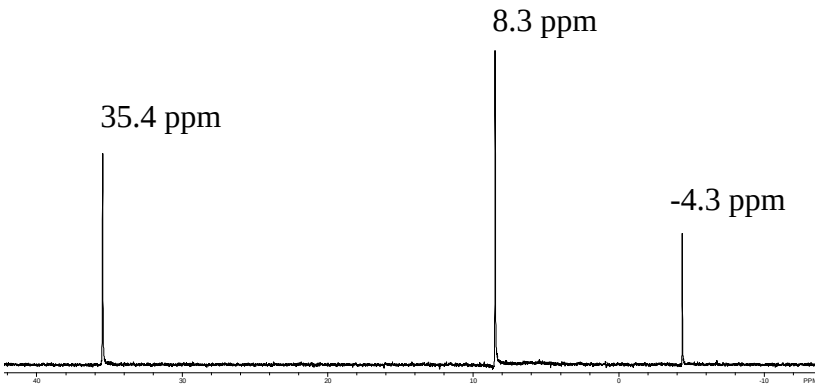


Figure 22. A representative ^{31}P NMR spectrum of the phosphite-ZnI_2 mixture in THF after being subjected to standard reaction conditions in the absence of alcohol.

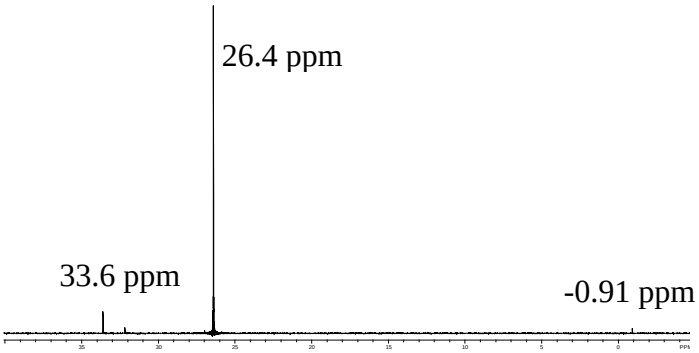


Figure 23. A representative ^{31}P NMR spectrum of the reaction mixture after NaOH work-up.

Application of this protocol to (*S*)-1-phenylethanol gave phosphonate[127, 128] that was essentially racemic by chiral HPLC analysis (~3% ee), which suggests an S_N1-like process (Figure 24). The S_N1 character also could explain the effects solvent has on the reaction mixture as observed through ^{31}P NMR. The tertiary alcohol 2-phenyl-2-propanol failed to react under these conditions, which may reflect the importance of steric

effects as noted above. Taken together, these factors lead to the mechanistic picture offered in Figure 25.

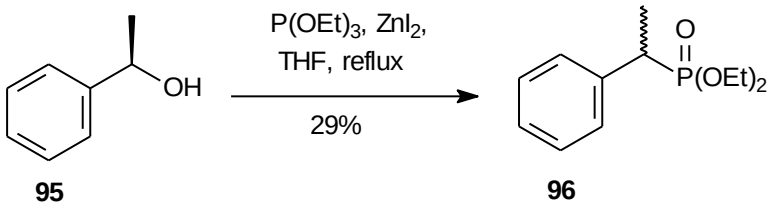


Figure 24. Reaction of a non-racemic alcohol.

If formation of a tetra-coordinate zinc species[118] such as the complex **97** (Figure 25) were followed by formation of a C-P bond through a process with S_N1 character, the loss of stereochemistry from a non-racemic substrate could be explained. Formation of such a complex might be sensitive to steric factors in the original alcohol, which would be consistent with the lack of product from the tertiary alcohol. Finally, the last Arbuzov-like step on an intermediate such as **98** might be assisted by the presence of zinc halide serving as a Lewis acid,[68, 69] which would explain why a slight excess (1.1 to 1.5 eq.) of the ZnI_2 is beneficial.

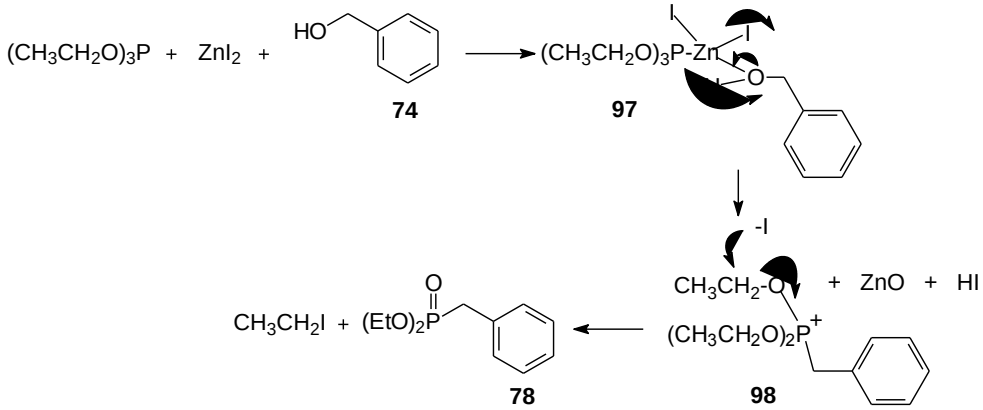


Figure 25. A partial mechanistic rationale.

In summary, a new and mild alternative to the Arbuzov sequence for phosphonate synthesis has been developed and optimized. Despite initial difficulties with purification and determination of the ideal conditions for the reagents, the method has been shown to work on a 5–gram scale, providing further evidence of the versatility of the new protocol. The Lewis acid mediated protocol utilizes ZnI_2 to facilitate the direct conversion of an alcohol to a diethyl phosphonate likely through nucleophilic attack of a phosphorus species upon a stabilized carbocation center. Furthermore, it is believed that this process proceeds through an S_N1-like mechanism to provide a racemic product from a non-racemic alcohol. Due to the complex synthetic intermediates needed for natural product syntheses and the need for further substrate development, an expansion of this protocol would be desirable.

CHAPTER III
ZINC MEDIATED PHOSPHONATE SCOPE EXPANSION

The utilization of phosphonates in Horner-Wadsworth-Emmons olefination reactions, and especially their applications in natural product synthesis, comprise a large area of research.[43, 86, 88, 93, 94, 129-131] The wide variety of complex and highly substituted phosphonates exploited can provide a synthetic challenge in themselves. In addition to a plethora of other natural products,[37, 40, 56, 131-135] classes of compounds in the schweinfurthin and pawhuskin family, both extensively studied by the Wiemer group,[86-91, 93, 94, 129, 130, 136, 137] hold readily available applications through a traditional Horner-Wadsworth-Emmons (HWE) olefination to form stilbene moiety (Figure 26). With over 100 analogues prepared of these types of compounds alone, the necessity to form complex phosphonates is easily demonstrated.

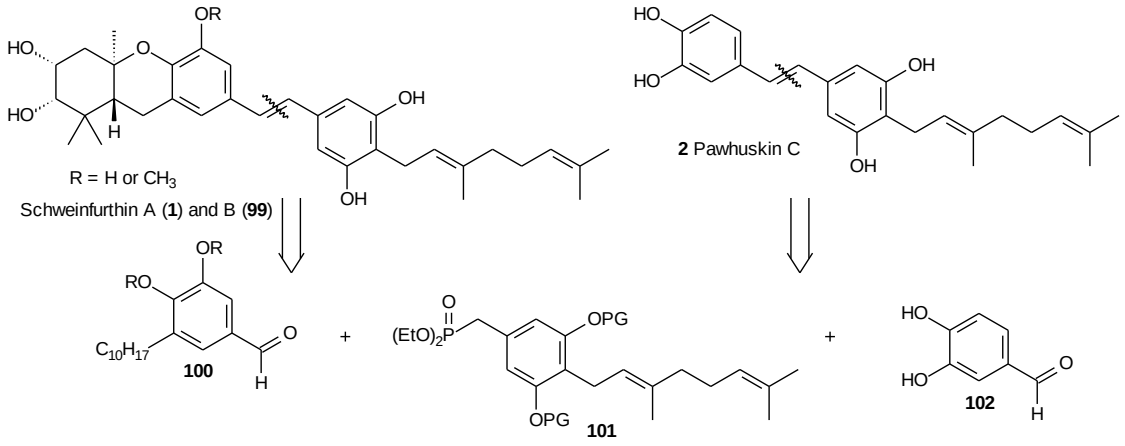


Figure 26. Representative retrosyntheses of schweinfurthin and pawhuskin analogues showing phosphonate applications through an HWE reaction.

With so many applications in view, and the optimized results of the new zinc mediated conversion of benzyl alcohol to the requisite phosphonate in mind, further

studies into the scope of the one-flask protocol for phosphonate synthesis were pursued. A variety of readily available starting materials was studied under the established reaction conditions to gauge the generality of the zinc mediated process. The reaction shows 3,4-dimethylbenzyl alcohol (**103**) and 3-bromobenzyl alcohol (**105**) afforded the desired phosphonates **104** and **106** in good yields (Figure 27).[106] Despite the introduction of an oxygen heteroatom which might complex with zinc, the reaction of 3-methoxybenyl alcohol (**107**) also proceeded in good yield (76%). Solvent effects observed in the benzyl alcohol trials in Chapter II, also were seen upon treatment of substrate **107** with zinc iodide and triethyl phosphite. When conducted in toluene, the yields for phosphonate **108**[106] were inconsistent and ranged from a meager 27% to a much more attractive 76%. The low yields could be due to a competitive demethylation enhanced by the increased temperature of the toluene reactions compared to the THF.[119, 138] When performed in THF, high yields were successfully reproduced with more facile purifications. Despite the second oxygen heteroatom in 2,5-dimethoxybenzyl alcohol (**109**), use of THF allowed formation of the desired phosphonate in good yield as well. When this reaction was conducted in xylene however, lower yields resulted. The addition of the second methoxy functionality and decreased yield (35%) corroborates possible demethylations at higher temperatures.[139]

Considering the effectiveness of the zinc protocol on the previously described substituted benzylic alcohols, more complex functional groups also were probed (Figure 28). Treatment of the nitro compound **111** under standard conditions in toluene afforded no evidence of the desired phosphonate **112** in the ^{31}P NMR spectrum of the reaction mixture.[140] However, when conducted at reflux in THF, the desired product was attained in a modest 15% yield.[106] Although the electron withdrawing character of the nitro moiety could account for this, it is more likely that the desired reaction is affected by the coordination of the nitro functionality to the zinc or nitrene formation facilitated by the higher reaction temperatures.[141, 142]

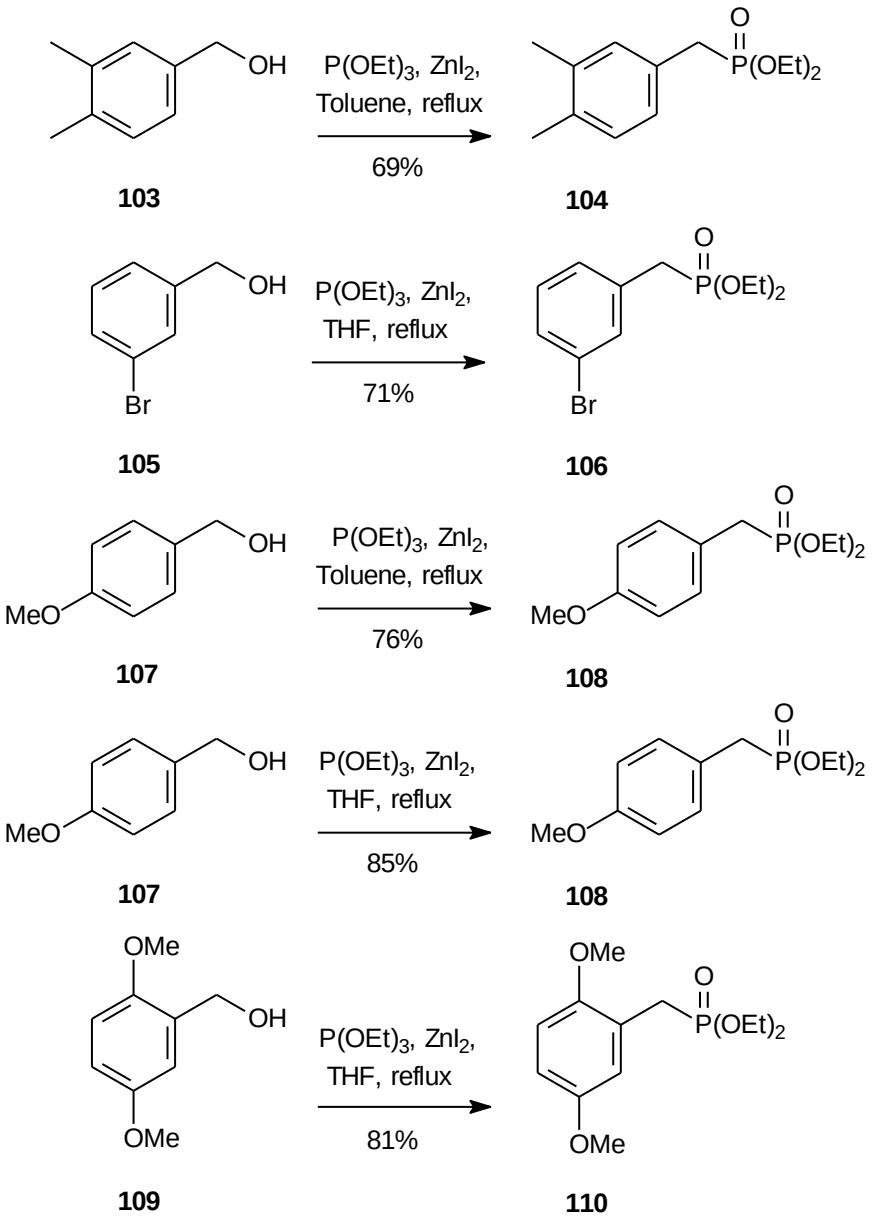
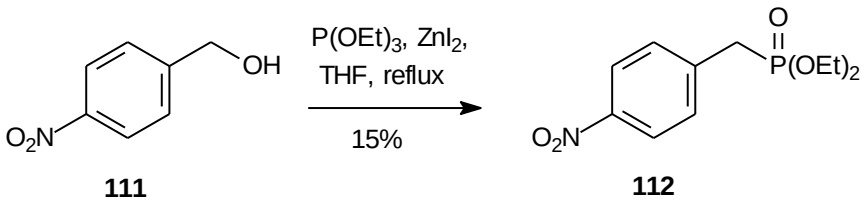


Figure 27. Phosphonylation of benzylic alcohols.

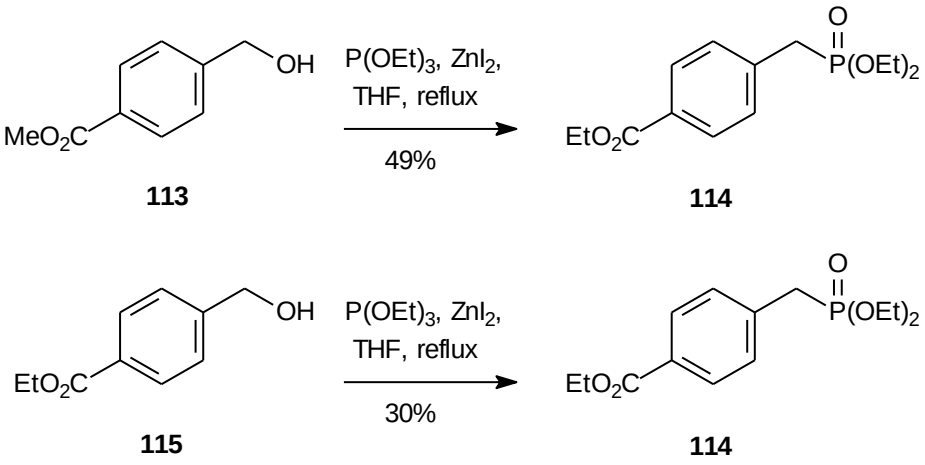
The effects of ester substituents on the benzylic alcohols also were examined under standard conditions (Figure 29). The methyl ether **113** proceeded with an average yield, despite the carbonyl's electron withdrawing nature. In addition to the expected C-

P bond formation, ester exchange at the carbonyl group also was observed.[143] It is unlikely that ester exchange is responsible for the lower yields given the 30% yield obtained upon treatment of ethyl ester **115**. A more plausible explanation may be preferential coordination of the carbonyl oxygen to the zinc over the phosphorus atom of the triethyl phosphite.[122]



111 **112**

Figure 28. Phosphonylation of a nitro-substituted benzyl alcohol.



113 **114**

115 **114**

Figure 29. Phosphonylation of ester-substituted benzyl alcohols.

The successful transformations of substituted benzylic alcohols and the necessity for protected aromatic substrates in synthetic applications led to further examinations of the reaction protocol with phenol-protected moieties (Figure 30). Additionally, the

presence of protected phenolic moieties in stilbenoid natural products is of interest to our group, including such compounds as the schweinfurthins, pawhuskins, and radulanins (Figure 17, Chapter II). The extent of the protecting group tolerance was first examined on the readily obtained 3,5-dimethoxymethoxy (MOM) protected compound **116**.[106] The

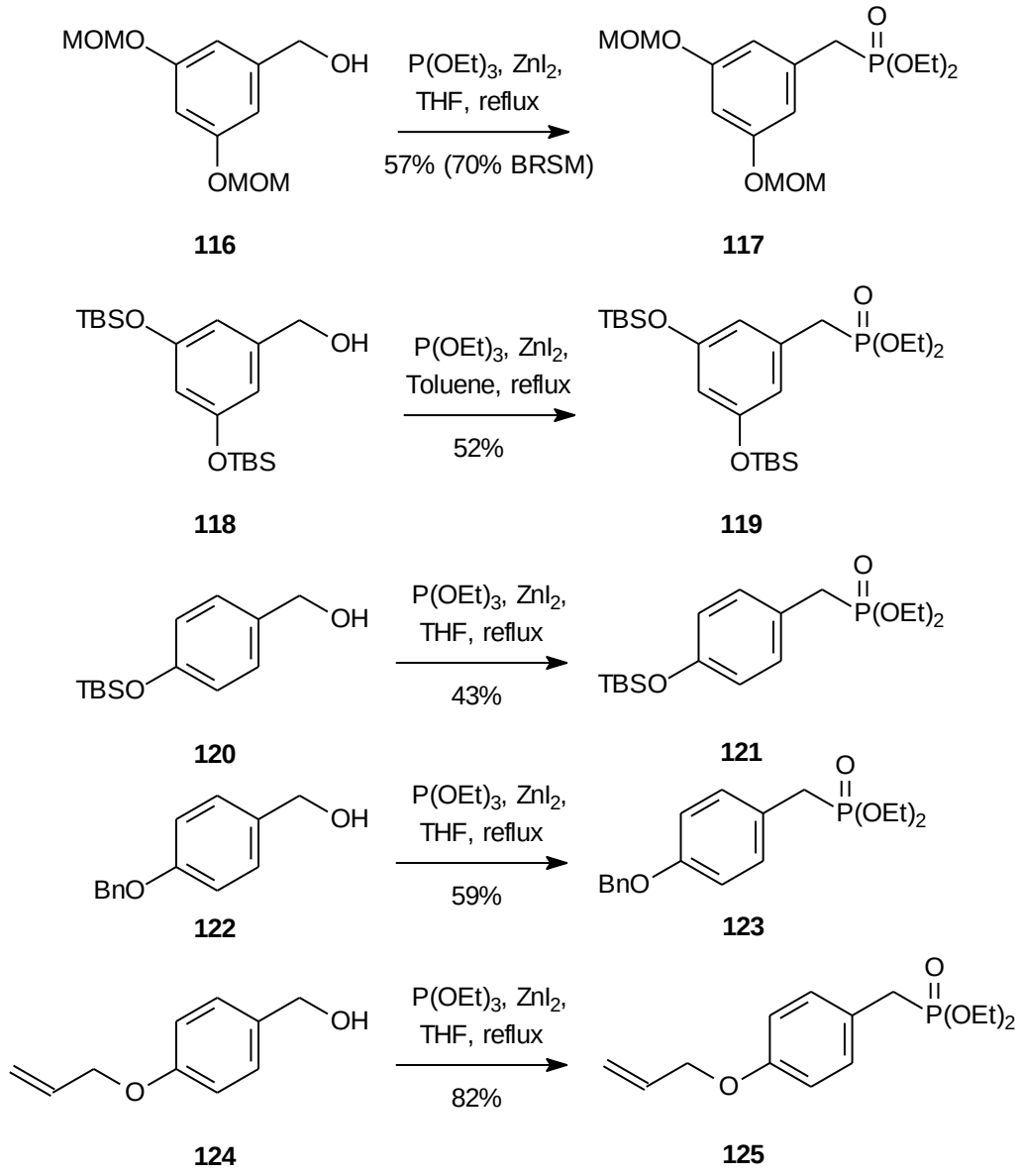


Figure 30. Protecting group tolerance examination.

desired phosphonate **117** was obtained, but the yields were modest which may be due to the coordination of the methoxymethoxy oxygen moieties to zinc. As previously mentioned, when conducted in toluene, the yields were inconsistent and purification was more difficult.

The bis-*t*-butyldimethylsilyl protected compound **118**[106] was transformed to the requisite phosphonate, although also in diminished yield (Figure 30) relative to benzyl alcohol. Interestingly, this substrate showed no evidence of the phosphonate product in the ^{31}P NMR spectrum when THF was utilized as a solvent. Even more surprising, when the reaction was conducted in THF the mono-substituted para *t*-butyldimethylsilyl compound **120** proceeded in comparable yield to the disubstituted substrate **118**. Alkyl protecting groups proved more amenable to the standard reaction conditions as demonstrated by an undergraduate, Brandon Van Cleave. The benzyl protected compound **122**[144-146] and allyl protected **124** compounds were converted in good yield to the desired phosphonates **123** and **125**.[19, 146, 147]

Interest in HWE olefination applications towards the total synthesis of schweinfurthin analogues led to studies of the zinc methodology for phosphonate synthesis on some heteroaromatic substrates provided by Dr. John Kodet (Figure 31). Attempted preparations of indole phosphonates **127** and **129**[148] were either unsuccessful or low yielding with difficult purification. Compounds with either hydrogen bonding atoms or MOM protecting groups appear to decrease or inhibit reaction progress. A more attractive yield (64%) was obtained with the benzofuran **130**.[106] Moreover, when this last transformation was attempted via a traditional Arbuzov protocol, the desired phosphonate was not formed and the reaction only led to decomposition.[129, 148] Conversion of furan **132** to phosphonate **133**[149] proceeded smoothly at reflux in THF, but had a decreased yield and purification difficulties when the reaction was attempted in toluene.

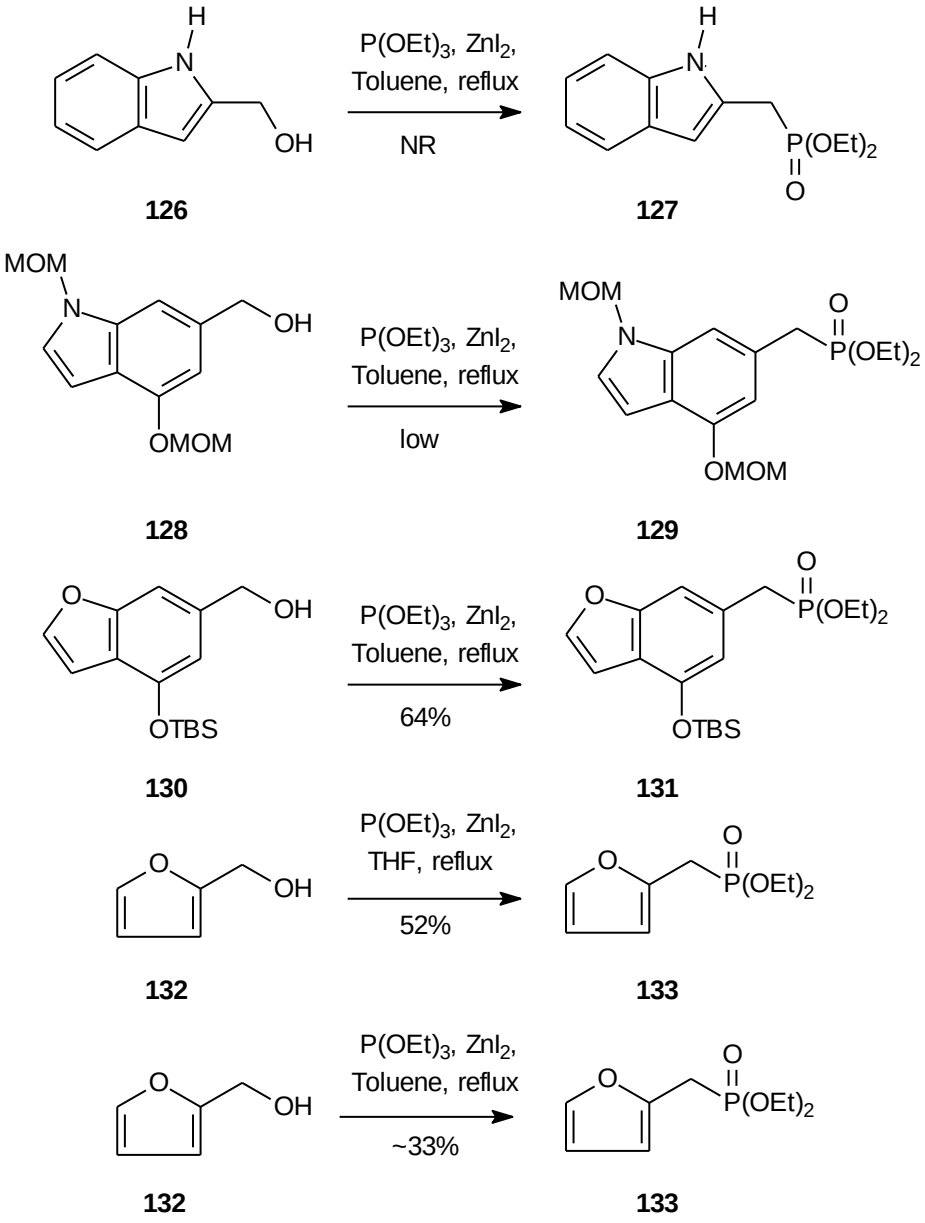


Figure 31. Application of zinc protocol on heteroaromatic substrates.[106, 148]

The general applicability of this protocol on substituted benzylic substrates prompted further investigation into aspects of the mechanism. In an effort to build upon the details presented in Chapter II, an isotopic labeling experiment was undertaken with a deuterated alcohol to be used in the final conversion to the phosphonate. Initial attempts

to prepare the deuterated substrate utilizing propargyl alcohol **134** unfortunately led to a mixture of inseparable deuterated products (Figure 32).[150] In addition to the 1.00:0.07:0.65:0.20 ratio of isomers observed, the modified Grignard addition and subsequent deuterium oxide quench proceeded in an overall low yield. An alternative route was first undertaken with a model sequence in which a Knovegnagel type condensation afforded the α,β-unsaturated methyl ester **137** (Figure 32). Although there were difficulties in the initial $LiAlH_4$ reduction attempts, reduction with DIBAL-H led to the desired allylic alcohol **138**. The successful conversion to the phosphonate with the one-flask zinc protocol afforded a plausible route for conversion of a deuterated alcohol to the phosphonate, even though it proceeded in low yield.

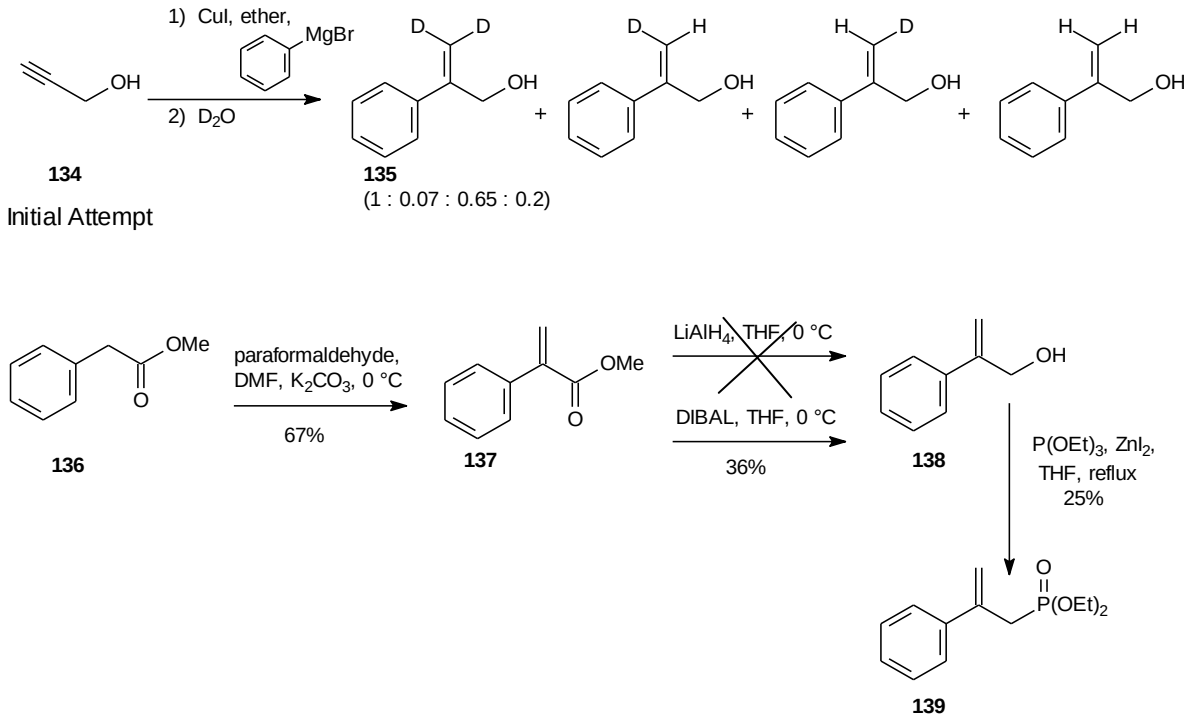


Figure 32. Isotopic labeling attempts.

Although the above sequence yielded the desired phosphonate and could be repeated to provide the analogous phosphonate with deuterated methylene units, isotopic labeling introduces additional difficulties to the sequence. While $LiAlD_4$ is relatively inexpensive as far as isotopic reagents are concerned, DIBAL-D is not. It was thought that the acid chloride might be more amenable to reduction with a lithium aluminum deuteride reagent, but treatment of the acid chloride with allane provided an over-deuterated product. Fortunately, reduction of the ester **137** with deuterated allane afforded the desired isotopically labeled alcohol **141** (Figure 33). Subsequent treatment of compound **141** with zinc iodide and triethyl phosphite in THF provided an inseparable mixture of both methylene and vinyl deuterated phosphonates (56:44 ratio of methylene ^2H to vinyl ^2H, Figure 34).

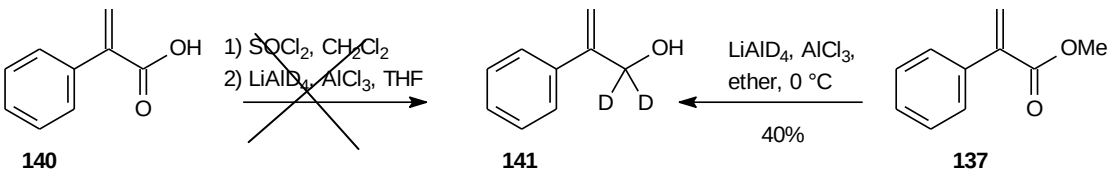


Figure 33. Isotopically labeled alcohol.

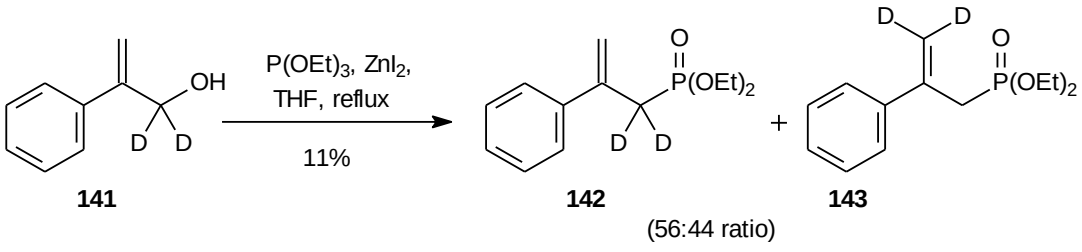


Figure 34. Deuteration experiment.

Spectral comparisons between the deuterated alcohol and the deuterated phosphonate product clearly show a scrambling of the isotopic center (Figure 35). After being subjected to the developed methodology, there is evidence of deuterium hydrogen atoms at both the methylene and vinyl carbons (Figure 35). Distinct doublets (5.48 and 5.36 ppm, Figure 35, Spectrum a) representing the vinyl hydrogens of the alcohol are visible. There is no indication of the deuterated methylene units (B, Figure 35, Spectrum a), as would be expected in the ^{1}H NMR spectrum of this isomer. In the ^{1}H NMR

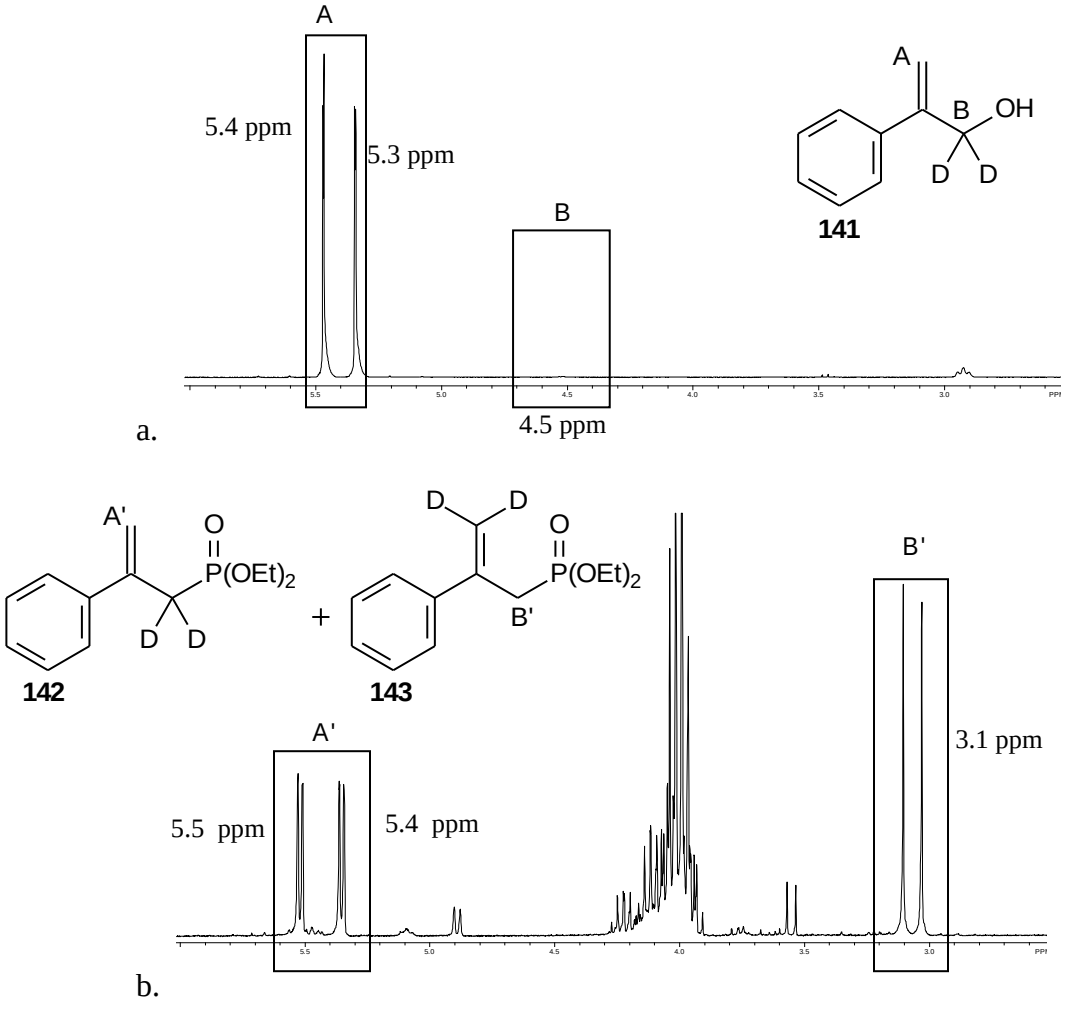


Figure 35. Spectrum a is the deuterated starting material and spectrum b is the phosphonate product.

spectrum for phosphonates **142** and **143**, peaks for both the vinyl hydrogens (5.38 and 5.25 ppm, Figure 35, Spectrum b) and the doublet representing the methylene hydrogens (3.07 ppm, Figure 35, Spectrum b) are evident in an almost 1:1 ratio based on ^{1}H NMR integrations. These results suggest that the zinc mediated protocol likely proceeds through a carbocation mechanism and supports the conclusions drawn in Chapter II in which an S_N1 like mechanism is suggested.

The promising results observed with the aromatic and heteroaromatic substrates and the successful conversion of the isotopically labeled allylic alcohol **141** to the expected phosphonates prompted further study into allylic systems. Literature precedence for metal mediated reactions of nucleophiles[107-112] with substrates that provide stable cationic species also supports expanded investigations into allylic substrates. Terpenoid diphosphates are integral to isoprenoid metabolic pathways, thereby accounting for the pharmaceutical applications of isoprenoid phosphonates as inhibitors.[151] Geranyl alcohol **144** was explored first for these reasons, and was transformed to the desired product **145**[152] in good yield under standard conditions (Figure 36). Unlike the ease of conversion for geranyl alcohol, the tertiary alcohol linalool (**146**) underwent a rearrangement to afford geranyl phosphonate in low yield (21%) as part of a complex mixture; formation of the observed product possibly is facilitated via an S_N1 mechanism with a delocalized allylic cation.

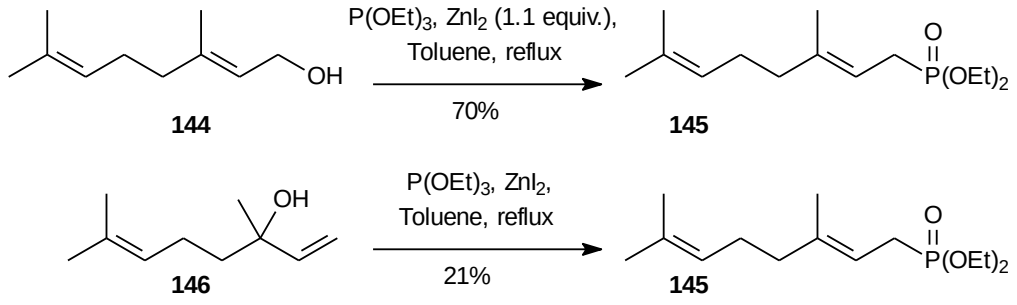


Figure 36. Terpenoid substrates.

In addition to the linear isoprenoid compounds, other allylic substrates were explored under the standard reaction conditions. Perillyl and cinnamyl phosphonates **147**[106, 151] and **149**[153] were obtained in good yields from the corresponding alcohols (Figure 37). In contrast, conversion of alcohol **138**[154] proved low yielding, perhaps due to the vinyligous relationship of the olefin substituents creating problematic steric interactions. Modest yields also were observed in the conversion of the deuterated alcohol **141** (Figure 34) to the phosphonate products **142** and **143**. The propargyl alcohol (**134**) gave only a complex mixture of products.

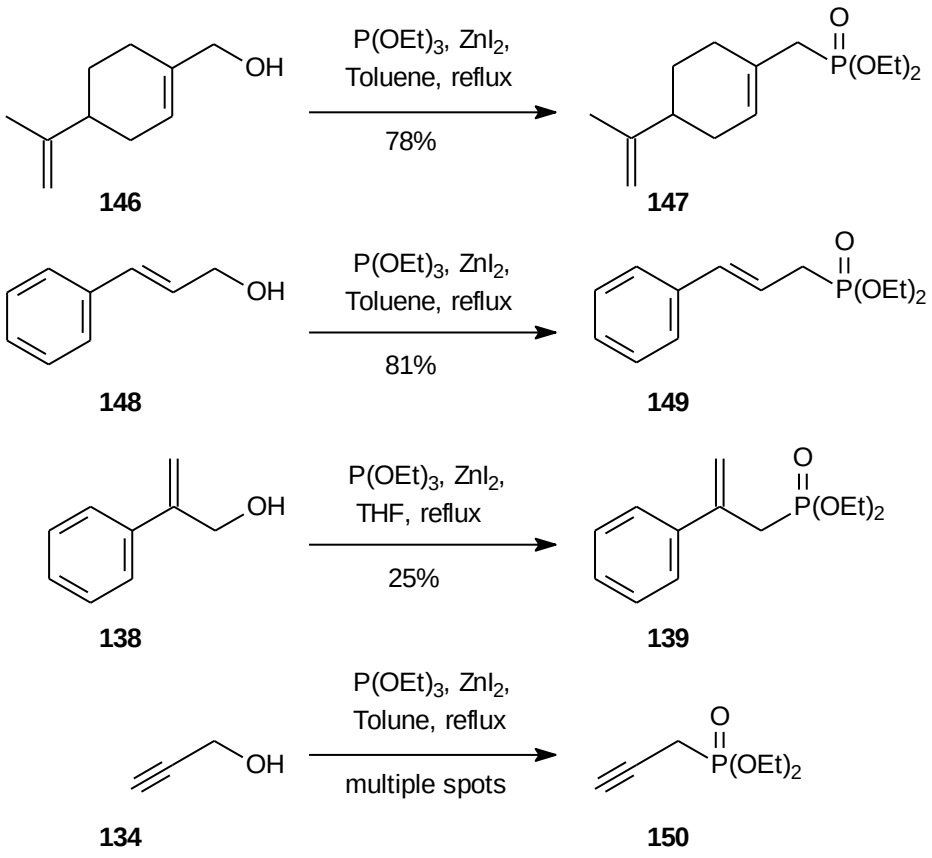


Figure 37. Application of zinc protocol on allylic substrates.

The broad applicability and high yields observed for the zinc mediated phosphonylation, and previous literature precedence for the zinc halide facilitated conversion of benzylic and allylic alcohols to various moieties through nucleophilic additions,[107-110, 112] encouraged further exploration of this process with aliphatic alcohols. Despite the lack of a stabilized cation, believed to be necessary for the reaction sequence, a simple primary alcohol **151** was subjected to standard conditions in toluene (Figure 38). After close examination of the ^{1}H NMR and ^{13}C NMR spectra, it was obvious that the expected phosphonate **152** was not the product obtained (Figure 38).

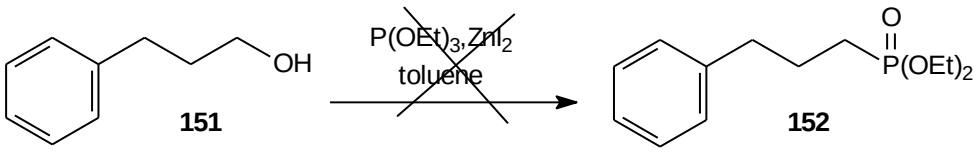


Figure 38. Expected phosphonate product is not formed under standard conditions.

In an effort to verify the unexpected results of the ZnI_2 mediated process with compound **151** an authentic sample of phosphonate **152**[155] was synthesized in quantitative yield through catalytic hydrogenation of phosphonate **149** (Figure 39). Based upon NMR data comparisons with the authentic sample **152**, the zinc mediated structure was elucidated as the isomeric phosphonate **153**.[106] Overlap in the ^{1}H NMR spectrum of the methylene ester protons provided inconclusive data for structural interpretation. Fortunately, the corresponding methylene units were distinct in the ^{13}C NMR spectrum, indicating asymmetry around the phosphonate moiety. In addition, a direct C-P bond was evident in the carbon spectrum for the resonance observed at 18.3 ppm (J_{CP} = 142 Hz).

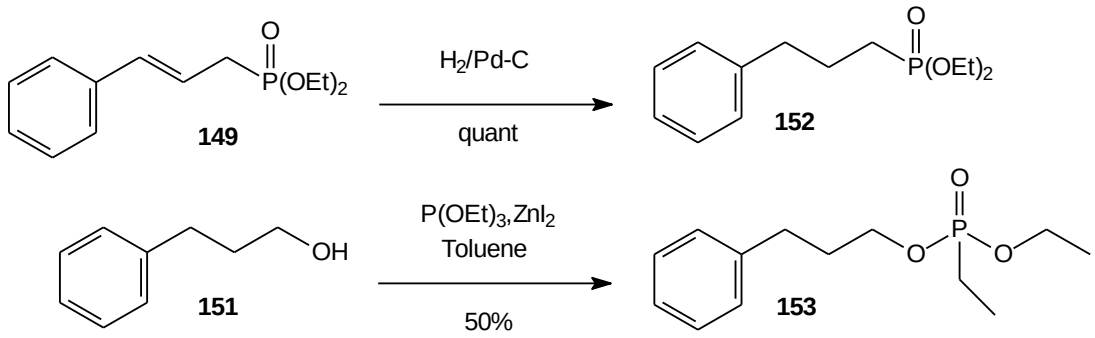


Figure 39. Authentic sample comparison.

A reaction sequence leading to phosphonate **153** might be based on a Lewis acid mediated ester exchange between the aliphatic alcohol and triethyl phosphite, followed by a more traditional Arbuzov reaction (Figure 40). Interestingly, when 3-phenylpropanol **151** was treated with ZnI_2 in THF, phosphonate **153** was accompanied by ethyl 3-phenylpropyl phosphite **154**[106] in nearly a 1:1 ratio; confirming that ester exchange can occur under these reaction conditions. When subjected to parallel reaction

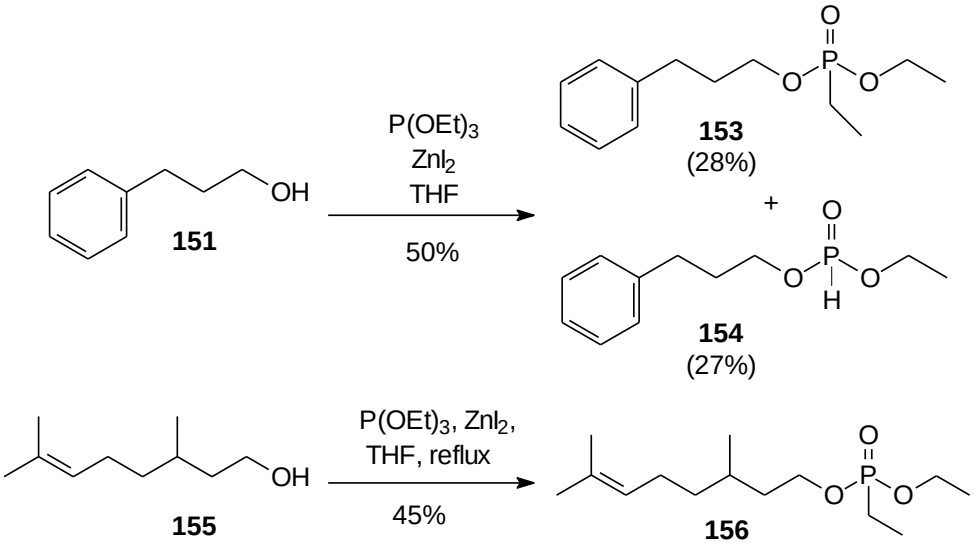


Figure 40. Additional aliphatic applications.

conditions, citronellol **155** yielded the expected mixed ester phosphonate **156**[105] as the product (45%) with no phosphite evident during isolation. Although the scope of this reaction with primary aliphatic alcohols has not yet been established, formation of phosphonate **153** and phosphite **154** does indicate the importance of a benzylic or allylic system for direct conversion of an alcohol to the corresponding phosphonate in the ZnI_2 mediated reactions.

In summary, it has been demonstrated that benzylic, heteroaromatic, and allylic alcohols can be converted to the corresponding phosphonates through reactions with triethyl phosphite mediated by zinc iodide. While the exact solvent and temperature conditions for optimal yields can vary slightly for individual substrates, the diversity of the conditions, including the polar and nonpolar solvent systems utilized, also emphasizes the versatility this protocol can afford when complex systems lead to unexpected constraints on the reaction conditions. The mild conditions and broad applicability provide a convenient substitute for the standard Arbuzov protocol. In addition, isotopic labeling experiments demonstrate a probable carbocation mechanism in allylic substrates. Although this procedure did not afford the desired diethyl phosphonate products in aliphatic systems, the mixed phosphonate ester products obtained may be useful in their own right. The overall utility of this reaction protocol is highlighted by the facile one-flask procedure and at least modest yields obtained from diverse benzylic and allylic systems.

CHAPTER IV
SYNTHESIS OF RADULANINS THROUGH ORGANOPHOPSHORUS REACTIONS

Bryophytes are a rich source of unique plant material. The non-vascular land plants contain over 24,000 species worldwide and have been speculated to have originated over 500 million years ago.[102, 156-158] The bryophytes have taxonomically been split into three classes including the musci, anthocerotae, and the hepaticae which are perhaps more commonly referred to as liverworts.[102, 156-158] Of the approximately 6000 species of liverworts, only around 6% have had their chemical constituents isolated and studied (approximately 300 as of 1999),[159] in part due to the difficulties encountered in isolating large samples of sufficient purity.[158] The hepaticae have been the most studied due to the oil bodies specific to the class which allows more facile isolation of compounds into the organic extract.[97-102, 156-166] Historically, these plants have been used for curing various ailments including bruises, burns, and even poisonous snake bites.[156] More than 400 years ago, the Chinese were even reported to have used these plants as diuretics and for hair growth.[157, 158, 161]

Liverwort extracts mainly consist of mono-, sesqui-, and diterpenoids, aromatics (including but not limited to bibenzyls, heterocycles, and long-chain alkyl phenols), and acetogenins (Figure 41). [97-102, 156-166] Interestingly, the sesqui- and diterpenoids isolated are often the enantiomers of compounds obtained from higher order plants.[156, 157, 159] Although very uncommon in liverworts, nitrogen- and sulfur-containing compounds have also been recently isolated from the species *Corsinia coriandrina* (**163**, Figure 41).[156, 158] Studies within the last 30 years have revealed a vast plethora of biological activities from these extracts; including insecticides, antifeedants, muscle relaxants, and compounds that demonstrate allergenic dermatitis, anti-HIV, DNA polymerase β, 5-lipooxygenase (5-LOX), calmodium inhibitory, cyclooxygenase (COX), antimicrobial, and antifungal activity to name a few.[102, 156-159] Specific examples include the bibenzyl marchantin A

(**160**) which has been found to exhibit cytotoxicity in the P-388 cancer cell line, 5-lipooxygenase and NO inhibitory activity, muscle relaxing effects, and significant cyclooxygenase activity (Figure 41).[102, 156-160, 164, 167] Additionally, perrottetin D (**158**) shows calmodulin and COX inhibitory activity while perrottetin E (**161**) is active against KB cells.[102, 156-160, 164, 167] The sesquiterpene plagiochilane A (**159**) also shows cytotoxicity against P-388 cells as well as potent antifeedant and nematocidal activity.[102, 156-159]

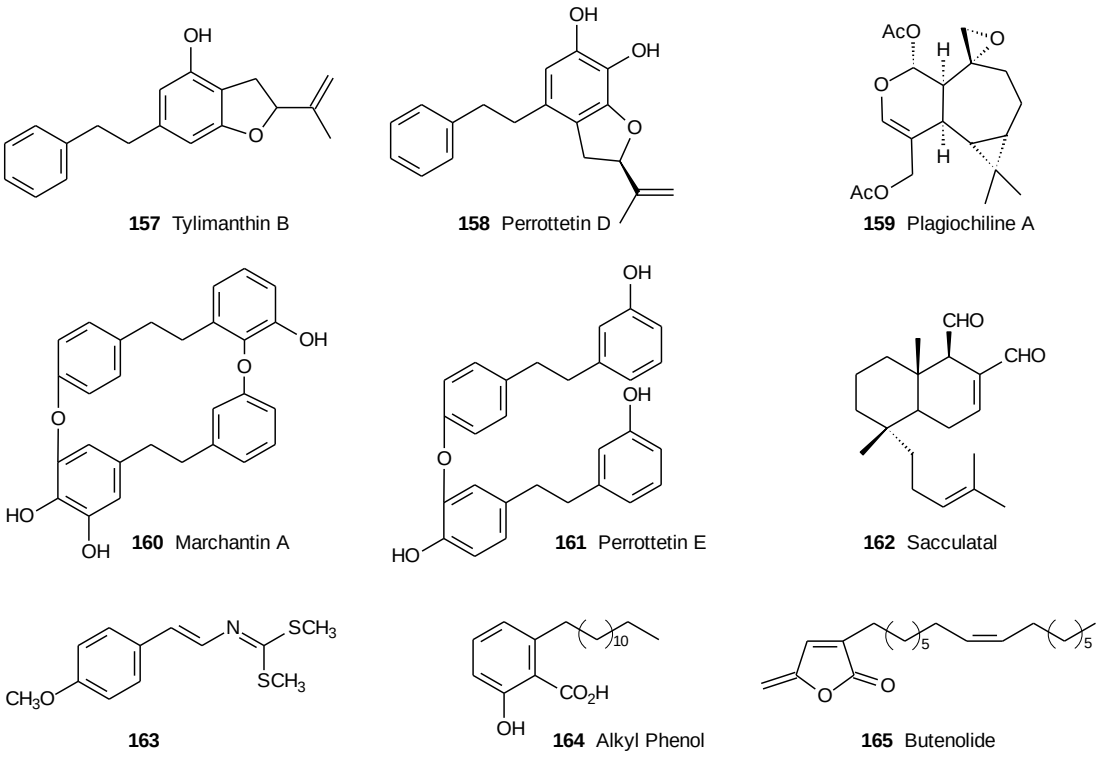


Figure 41. Sample compounds isolated from liverworts.[157, 158, 166]

Within the hepaticae class, the radula group is unique in that its chemical extracts most commonly consist of bibenzyl and prenylated bibenzyl compounds (Figure 42).[158, 159] As with other species within the bryophytes, those in the radula genus (150-200 species)[165] also possess a host of biological activities.[102, 156-159] In addition to calmodulin

inhibitory effects, radulanin H (**168**) has also been found to possess potent COX inhibitory activity, which is important for inflammation and pain relief in ailments such as rheumatoid arthritis (Figure 42).[157, 158, 160, 164] It is believed to accomplish this by acting as a scavenger of oxygen free radicals, which is also an important aspect in cardiac infarctions, cancer, and even the aging process.[164] Radulanin L (**179**) has weak NO inhibitory activity and Radulanin K (**177**) has been shown to have anion radical release inhibitory activity, thereby reducing the risk of cardiac infarctions and arterial sclerosis (Figure 42).[157, 158, 168] With new therapeutic and practical applications of these compounds constantly being studied, it is important to have samples of these natural products and their analogues available for testing, especially considering the difficulties and environmental variability introduced with the extraction of plant material.

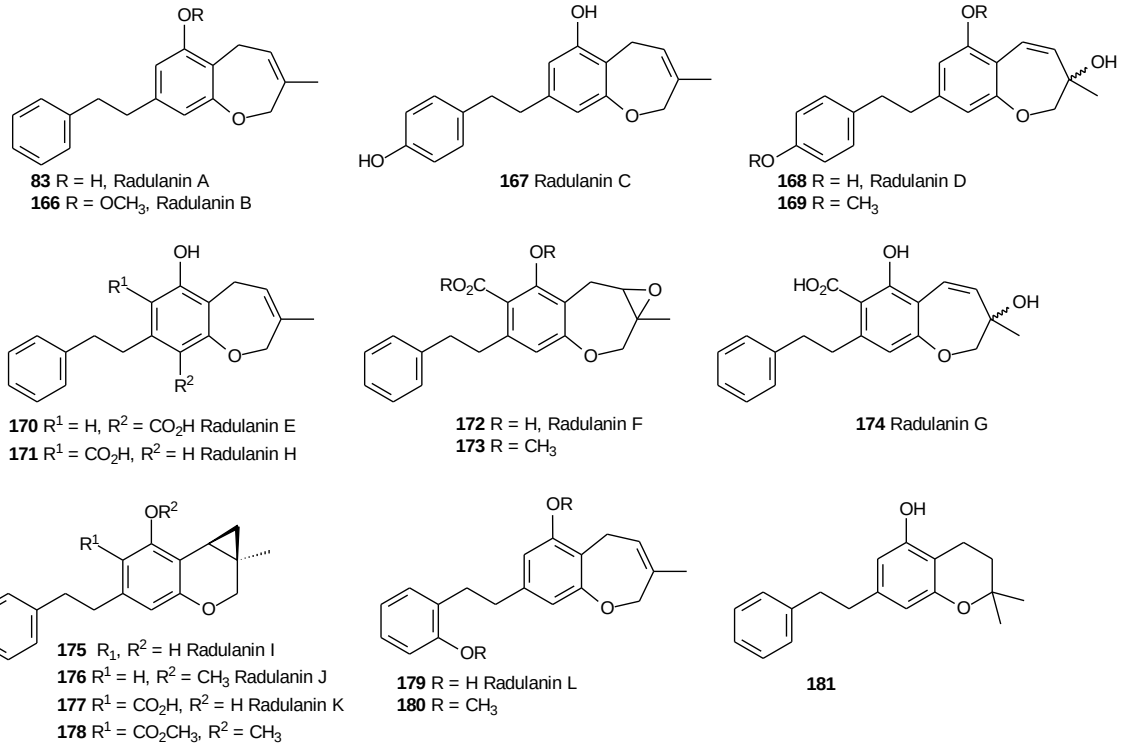


Figure 42. Representative radulanins and analogues.[99, 101, 156, 159, 160]

The natural radulanins and their analogues tend to contain bibenzyl moieties with a variety of substituents and substitution patterns surrounding the benzoxepin (or heterocyclic) cores (Figure 42).[97-102, 159-162] These structures present unique opportunities in organic synthesis.[20, 95, 96, 103, 104, 169-171] Previous works have utilized costly Grubbs metathesis,[95, 96, 104, 170, 171] Claisen condensations,[96, 171] Mitsunobu ring closures,[20, 103, 169, 172] a titanium catalyzed [3+3] cycloaddition,[170] and an unattractive tin reagent[20, 103, 169] towards the total synthesis of these natural products. Radulanin A (**83**) specifically not only represents a simplified target for an initial synthesis but also a viable target on which to utilize an array of organophosphorus methodologies developed in the Wiemer lab.

The reduced stilbene of radulanin A could be obtained through a traditional HWE and the benzoxepin core through a modified version, thereby allowing utilization of the newly developed phosphonate formation methodology on the condensation partners (Figure 43). A modified Wittig approach developed by Dr. Jose Yu could also be applied towards formation of a *cis*-allylic alcohol moiety (**183**) which would later be cyclized to form the seven-membered heterocyclic ring (Figure 43). The new approach to the synthesis of the radulanin family of natural products could provide a vehicle in which to highlight the versatility of the developed phosphorus chemistry and also lead to more facile formation of analogues for biological testing.

For the total synthesis of radulanin A, the first disconnection seen is at the ether linkage of the benzoxepin core (Figure 44), which could be obtained from a *cis*-allylic alcohol moiety. A modified Wittig or an Ando variation on the HWE condensation could afford the desired cis stereochemistry from the aldehyde. Intermediate **186** could then arise from an oxidative cleavage of the allyl substituent and a selective reduction of the stilbene. Disconnection of the stilbene could be obtained through a traditional HWE from diethyl benzylphosphonate and aldehyde **187**.

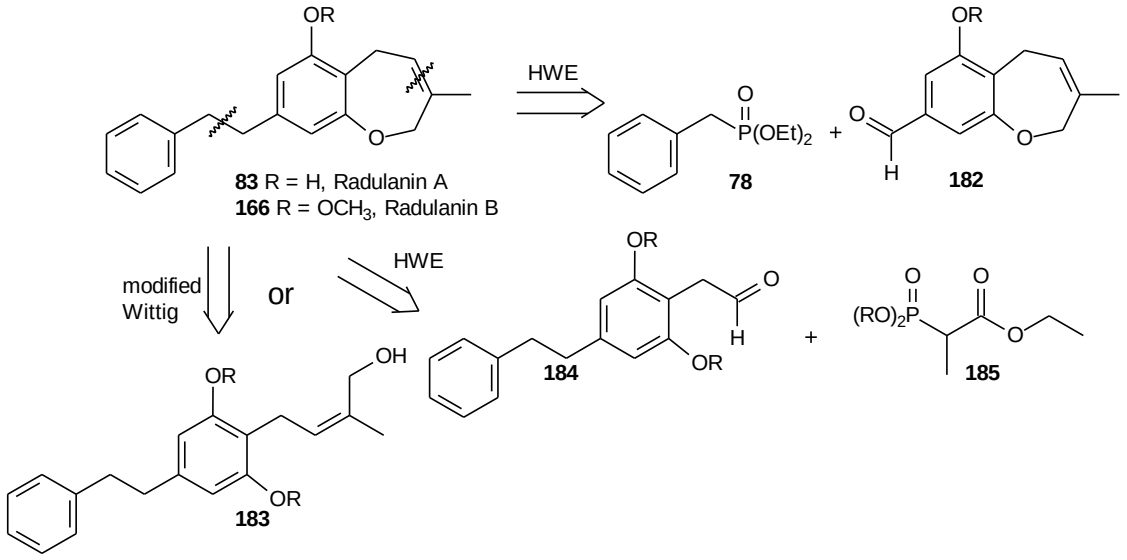


Figure 43. Possible organophosphorus reactions in radulanins synthesis.

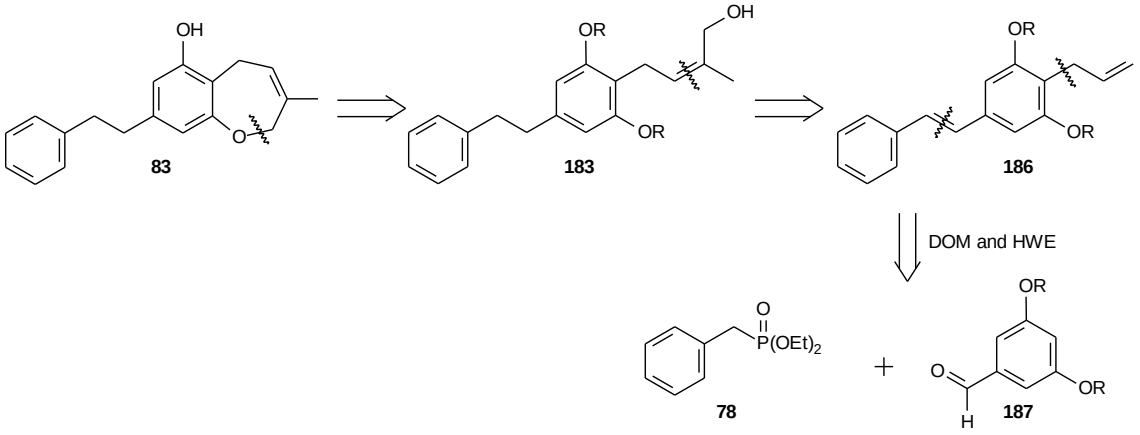


Figure 44. Retrosynthetic analysis of radulanin A.

Our total synthesis of radulanin A and its analogues began with the commercially available benzoic acid **188** (Figure 45). After allowing acid **188** to reflux in the presence of sulfuric acid in methanol, the Fischer esterification product was obtained and then protected at the phenolic positions as the methoxymethoxy (MOM) ethers **189**.[86, 173]

Subsequent reduction of the ester with lithium aluminum hydride and methylation[174] of the resulting alcohol provided methyl ether **191**. The directed *ortho*–metalation (DoM) was first attempted on small scale and afforded only the starting material (**191**).[175] After an increase in scale and additional drying of the CuBr•DMS reagent on the vacuum line, a mixture of the desired *ortho*-alkylated product **192** (28%) and an undesired isomer **193** (18%) was isolated in low yield. Although, it is possible the reaction time as well as other reaction conditions could be adjusted to enhance the yield of the *ortho*-metalated product over the benzylic addition byproduct, an alternative route was determined to be more efficient.

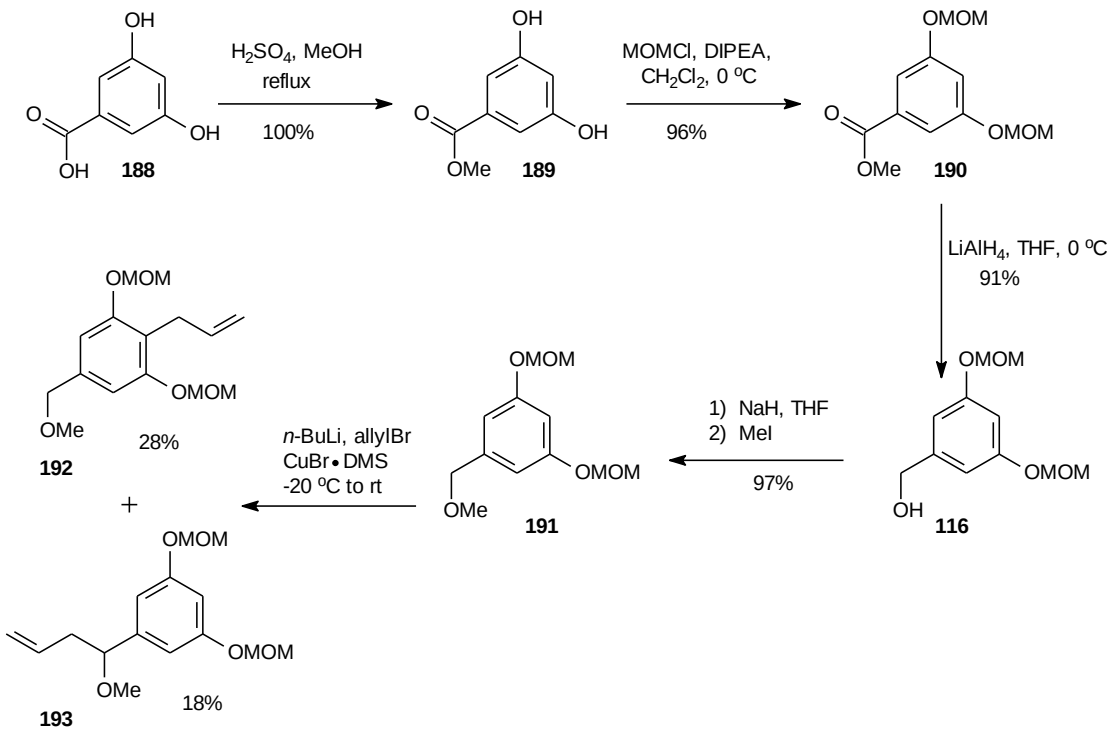


Figure 45. Beginning sequence leading to a mixture of isomers.

It was envisioned that rearranging the synthetic sequence and postponing the DoM step until a later stage would provide a more effective route to the alkylated stilbene

intermediate **196** (Figure 46). The already synthesized methyl ether **191** was oxidized to the aldehyde with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[176, 177] Initial attempts led to an inseparable mixture of the product and the starting material, but a slight increase in the equivalents of DDQ and longer reaction times provided the desired aldehyde **194** in good yield (90%) without the need for extensive purification. After further consideration, the methylation step was avoided through the oxidation of the alcohol (**116**) directly to the aldehyde. Although the DDQ oxidation once again proceeded in good yield to afford the aldehyde (84%), an oxidation with MnO_2 proved more cost effective and mild with comparable yields. A traditional HWE olefination with

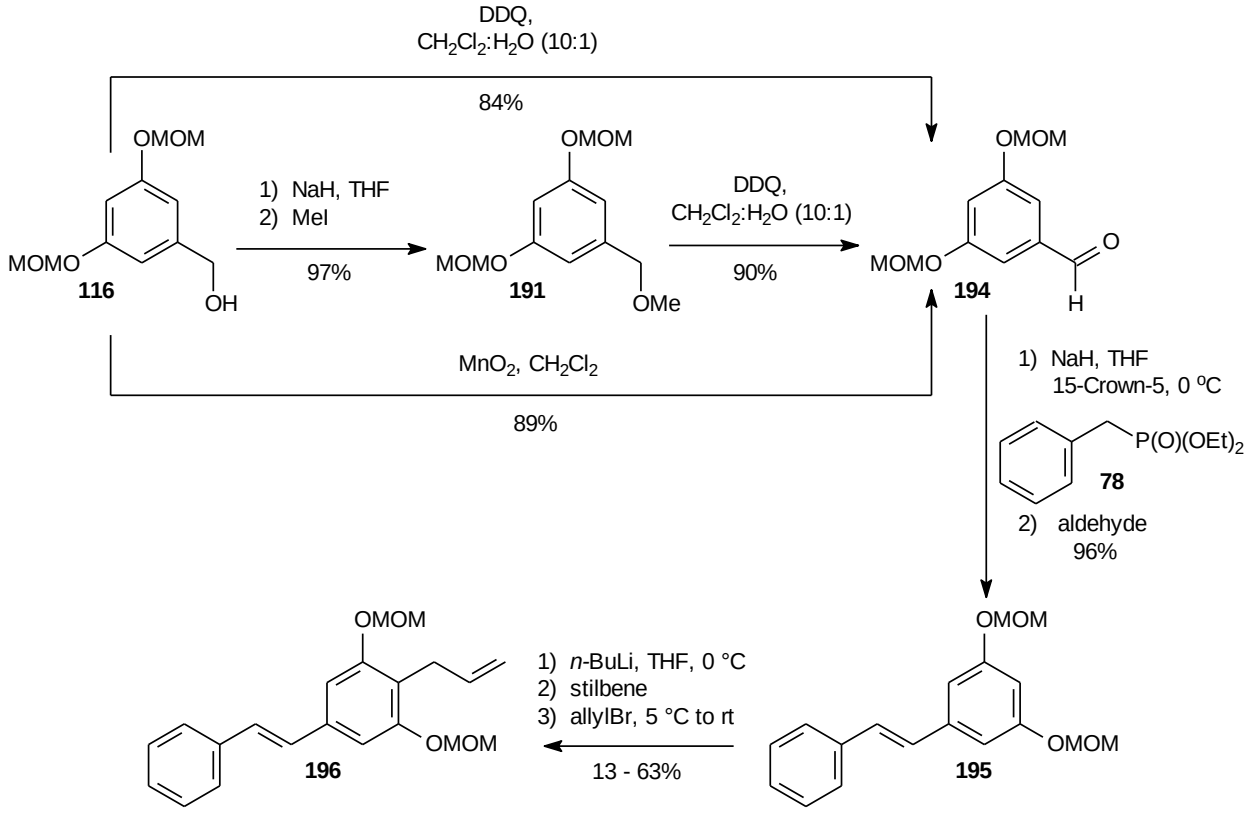
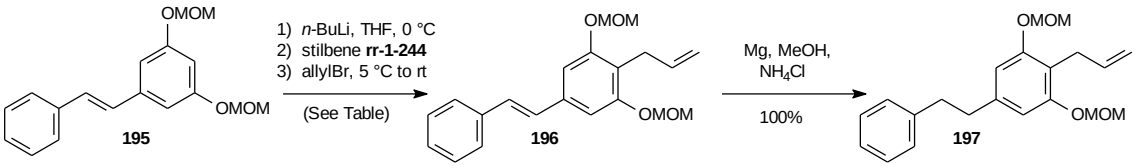


Figure 46. Reorganization of the synthetic sequence.

diethyl benzylphosphonate (obtainable through the one-flask protocol developed for phosphonate synthesis, page 27)[106, 125] then proceeded in excellent yield to afford *trans*-stilbene **195**. With no benzylic position available for alkylation, the previously obtained side product was avoided and a DoM reaction was utilized for clean formation of the allyl stilbene intermediate **196**.

With the stilbene moiety in place, the possibility of alkylation at the benzyl ether was no longer possible, but initial attempts led to mediocre yields of the *ortho*-alkylated product (Table 5, Entry 1).[175] The difficulties often encountered in the work-up with CuI reactions prompted a trial without this reagent (Table 5, Entry 2), and the resulting lower yield (13%) obtained with only a TMEDA additive encouraged the avoidance of additional reagents altogether. While keeping the equivalents of *n*–BuLi the same, comparable yields (Table 5, Entries 3 and 4) were obtained. Increasing the equivalents of allyl bromide (Table 5, Entry 4) and then also the lithiating agent (Table 5, Entries 5, 6, and 8) led to increasingly improved yields. The one trial exception (Table 5, Entry 7), could be explained by the water sensitive nature of the reaction and its possible exposure to the atmosphere.

At 2.7 equivalents of allyl bromide, the yield was satisfactory but purification became more difficult (Table 5, Entry 9). Although the initial attempt with a zinc halide additive seemed promising, the results were not reproducible (Table 5, Entry 10-14), even after changing the order of addition. Because they provided consistent yields (around 60%), the optimized conditions with a 1.5 to 2.1 fold excess of *n*–BuLi (Table 5, Entry 6 and 8) for the directed *ortho*–metalation were then utilized for the allylation. Finally a selective reduction of the stilbene moiety through a dissolving metal reaction with magnesium turnings gave the desired product **197** in quantitative yield.[178, 179]



Entry	*n*–BuLi	AllylBr (Equiv.)	Additive	Isolated Yield
1	1.2	1.3	CuI, TMEDA	44%
2	1.2	1.8	TMEDA	13% (24% BRSM)
3	1.2	2.1	NA	42% (59% BRSM)
4	1.3	2.0	NA	44% (67 % BRSM)
5	2.0	1.2	NA	48%
6	1.5	1.5	NA	56%
7	2.1	2.1	NA	Mainly SM
8	2.1	2.1	NA	60%
9	2.7	2.1	NA	57%[a]
10	2.1	2.1	ZnI_2	63%
11	2.1	2.1	ZnI_2	39%
12	2.2	2.0	ZnI_2[b]	NA
13	2.2	2.0	ZnI_2	NA
14	2.2	2.0	$ZnBr_2$	NA

[a]Product was crude mixture. [b]Order of addition was changed.

Table 5. Directed *ortho*–metalation optimization.

Reduction of the stilbene leaves only one alkene for oxidative cleavage and could afford the desired aldehyde **198** without the complications an additional olefin would present. Standard osmium tetroxide dihydroxylation and subsequent sodium periodate cleavage conditions[180] were unsuccessfully attempted until application of a slightly modified version by Yu and co-workers (Figure 47).[181] Yu reports that the addition of lutidine to the reaction mixture leads to an increased rate of formation of the product as well as higher yields through the suppression of side products. Formation of acidic side products also could lead to deprotection of acid sensitive protecting groups such as MOM ethers.

Although the OsO_4 reaction proceeded in good yield, a substitute oxidant was considered. Ozonolysis provided an opportunity not only for a quicker reaction time and more facile protocol, but also a more cost effective route towards procurement of the aldehyde. Limited attempts at a traditional ozonolysis procedure[22] led to poor results (15% yield), but two procedures reported by Dussault were successful.[23-25] Both Dussault ozonolysis procedures are attractive due to the convenience of the reaction and because the explosive ozonide usually associated with the reaction is not formed (Figure 47).

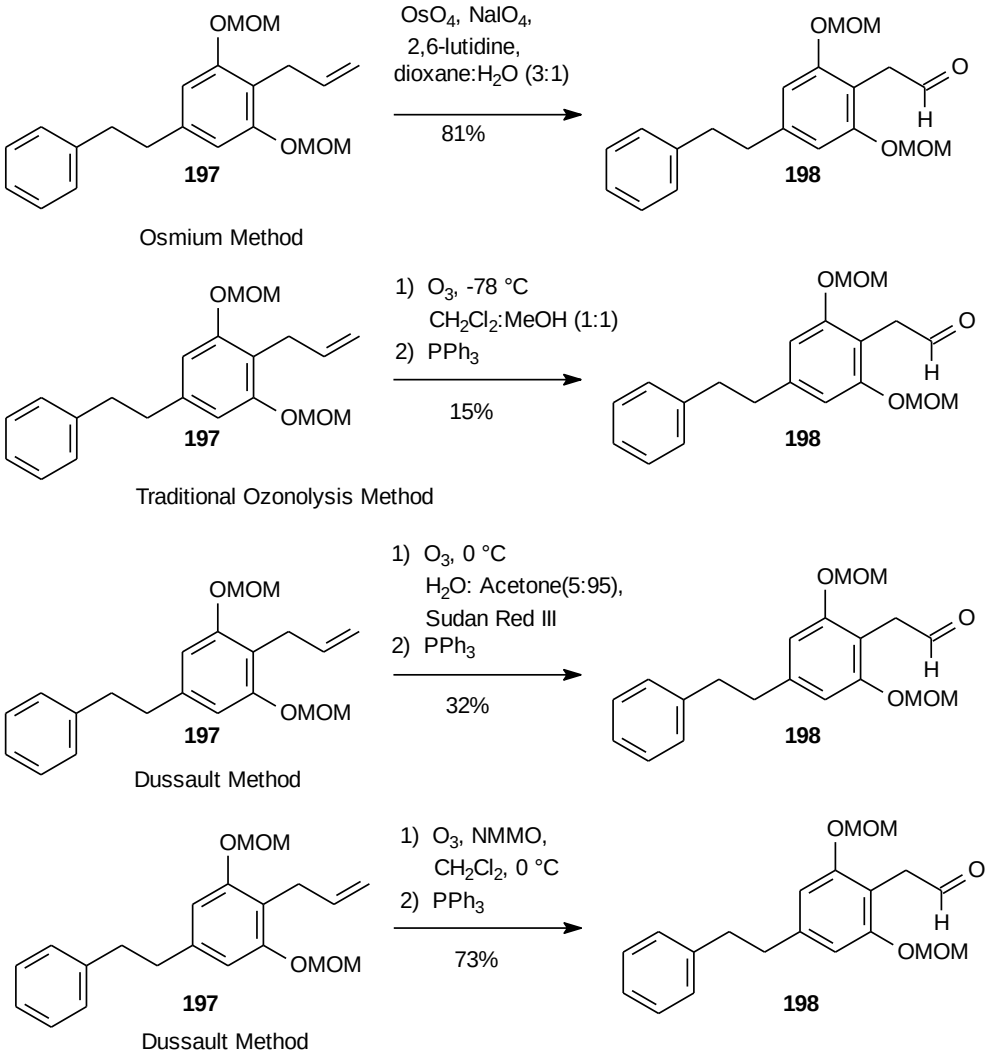


Figure 47. Ozonolysis trials.

Dussault refers to his route as a "reductive ozonolysis" in which the carbonyl oxide intermediate is trapped by water or *N*-methylmorpholine *N*-oxide (NMMO), and then fragments before it can form the explosive ozonides encountered during ozonolysis.[23-25] With a nonacidic work–up or in the presence of excess NMMO, there was no evidence of ozonide formation reported in the reaction sequences[23-25] and triphenyl phosphine was only added in my procedures as a precautionary measure. Although more consistency with the ozone formation rate might still improve the yields,[23-25] it appears that the ozonolysis using NMMO produces yields of the aldehyde (73%), comparable to those obtained with osmium reagents.

Aldehyde **198** presented a unique opportunity to utilize a modified Wittig protocol for installation of the *cis*–allylic alcohol functionality (**183**, Figure 44) required for cyclization of the radulanin 7–membered benzoxepin core. Previous work by Corey[182, 183] and Schlosser[47, 184] demonstrated that the cis selectivity of the traditional

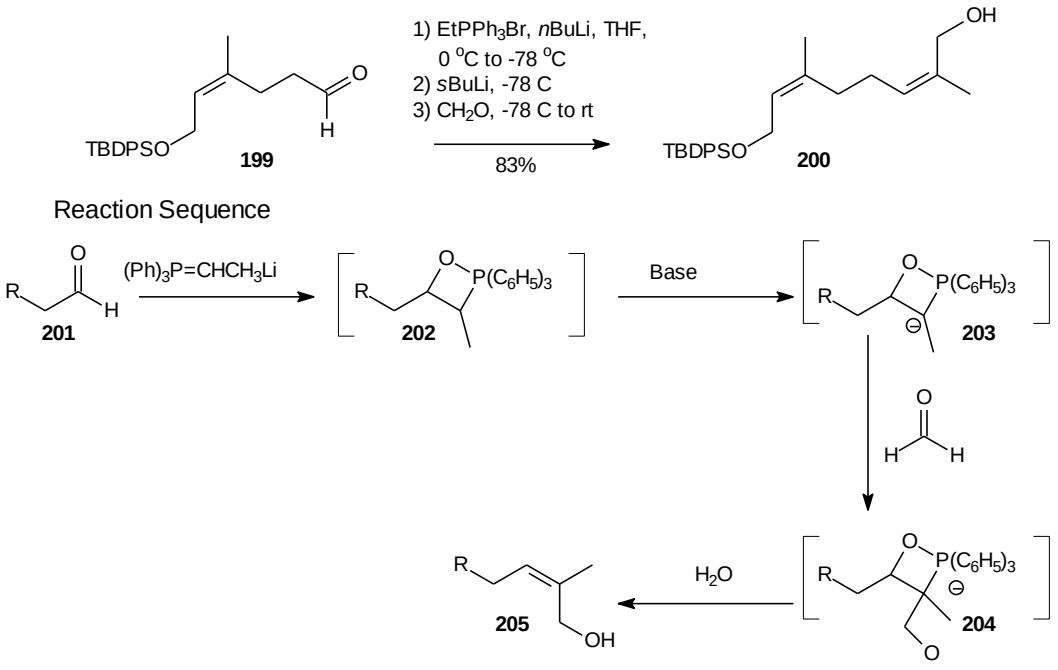


Figure 48. Modified Wittig procedure and suspected reaction sequence.[185, 186]

Wittig transformation can be exploited to form such moieties through trapping of a β–oxido ylide (**203**, Figure 48) with paraformaldehyde in modest yields. Examination of this transformation in our group by Dr. Yu[185, 186] led to optimization of this sensitive procedure through manipulations of temperature, base, and the use of monomeric formaldehyde as an electrophile (Figure 48). He was able to isolate the desired alcohol in a much improved 83% yield as well as to extend this procedure to include ketones.

The reaction is believed to proceed initially through a standard Wittig mechanism (Chapter I, Figure 9). However, low reaction temperatures allow the oxaphosphetane to be trapped before it can collapse to the olefin product and triphenylphosphine. A second addition of base then allows formation of the β–oxido ylide and subsequent nucleophilic attack of an electrophile. Initial attempts to apply Dr. Yu's reaction conditions to the radulanin aldehyde intermediate **198** showed no evidence of the desired allylic alcohol product **205**. Further attempts were conducted on substrate **206** as a model compound in order to preserve the natural product intermediate for later reactions. Unfortunately, aldehyde **206** was not successfully converted to the alcohol **207**.

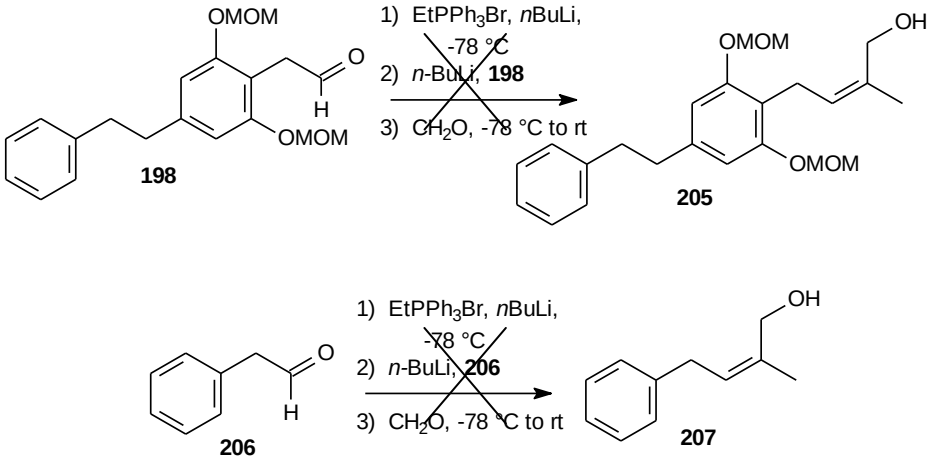


Figure 49. Initial modified Wittig attempts.

Duplicate reactions under parallel conditions were then conducted on geranylacetone[185, 186] and heptanal[182] in an effort to gain a better understanding of the complex and sensitive reaction sequence (Figure 50). Still, no evidence of an allylic alcohol was observed in either reaction, despite the reported 42% yield for farnesol **209**[185, 186] and 73% yield of alcohol **211**.[182] After closer inspection of the reagents, it was discovered that the starting materials were impure, which could account for part of the difficulties encountered in the already complicated sequences. Further modifications to the temperature, time between the additions of reagents, equivalents, solvent concentrations, and utilization of both para– and monomeric formaldehyde provided no observable evidence of the desired alcohol.

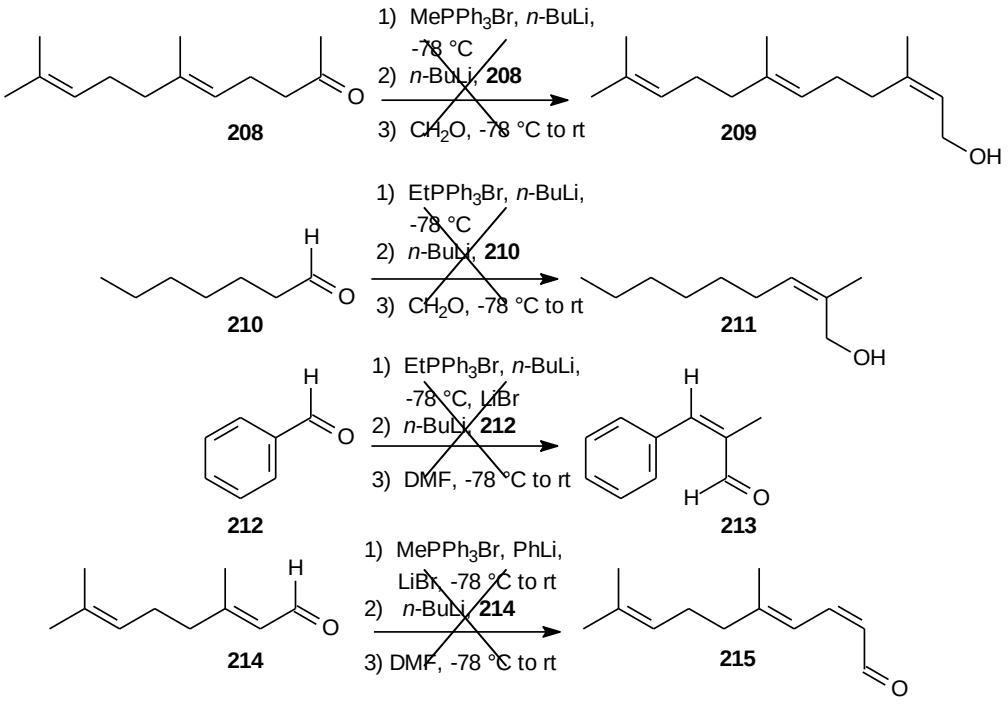


Figure 50. Additional modified Wittig attempts.

Formation of a *cis*–allylic alcohol was attempted on both benzaldehyde **212** and geranial **214** with ^{1}H NMR spectra confirming the purity of these starting materials. A modification to the protocol by Hodgson was used in which PhLi was utilized as the base and a LiBr additive was employed (Figure 50). It is generally agreed that lithium salts influence the reaction.[38, 47, 184, 187-189] However, the end product, be it cis[187-189] or trans,[47, 184] has been disputed. Additional reaction conditions were sought after multiple unsuccessful experiments. DMF also was employed as an electrophile. This route could not only lead to the desired alcohol after reduction, but also introduce a new method for aldehyde homologation. The standard olefin Wittig product and starting material were often the only observable products. After a closer examination of the ^{1}H NMR spectra, it also appears that the anion was directly attacking the aldehyde or ketone starting material, thereby providing the nucleophilic addition products **216** and similarly **217** in modest yield (Figure 51).

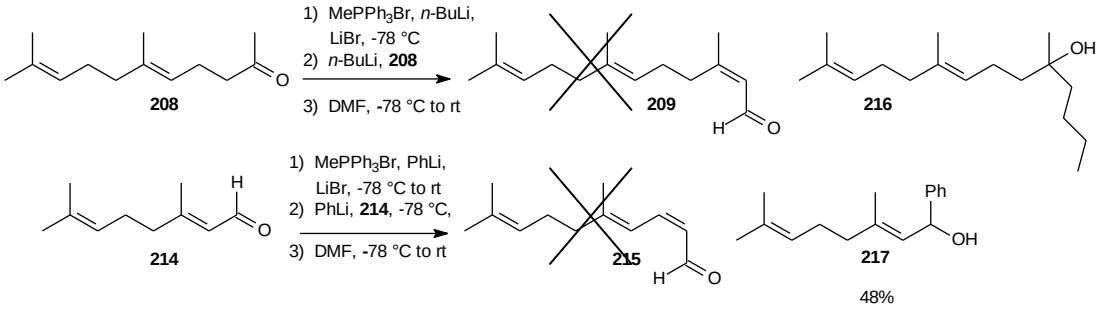


Figure 51. Observed byproducts.

Hodgson reports that better yields and stereoselectivity are achieved when applying chloromethyl pivalate (PIVCl) and methyl bromoacetate as electrophiles.[187] Although the yields were low, the two model pivaloyl (PIV) protected alcohols were successfully isolated (Figure 52). Distinct peaks at approximately 5.8 ppm and 5.7 ppm in the ^{1}H NMR spectrum were identified for the olefinic hydrogens (Figure 53).

Doublets for the methylene hydrogens H^D (4.72 ppm, Figure 53) and H^A (3.48 ppm, Figure 53) also were observed. The low yields did not warrant additional experiments towards verification of the alkene stereochemistry. Significant amounts of the nucleophilic addition products once again were observed, thereby decreasing the likelihood of the formation of the β–oxido ylide and subsequent reaction with the electrophile. Despite increasing the temperature and prolonging the time given for the initial ylide formation, the starting aldehyde was still prevalent.

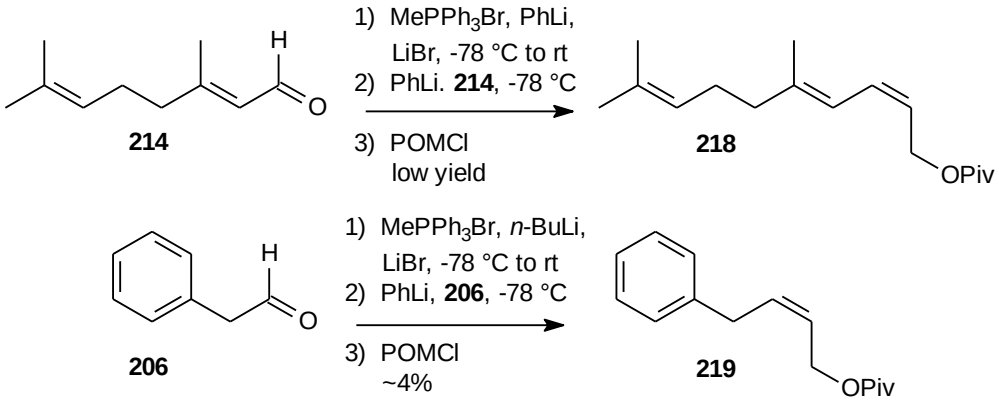


Figure 52. Successful modified Wittig conversions.

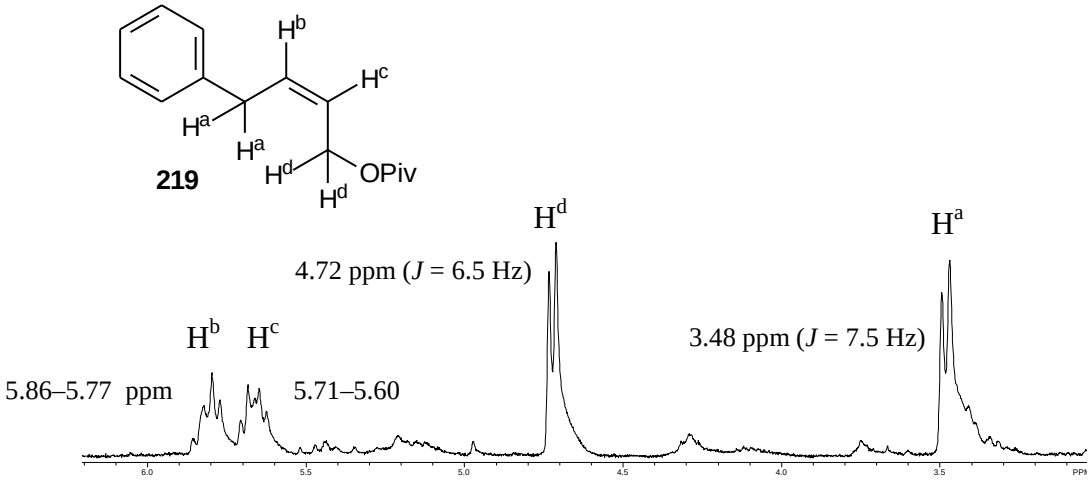


Figure 53. ^{1}H NMR spectrum of aromatic modified Wittig product.

After the limited success of the modified Wittig approach, an alternative strategy was examined in which a prenyl group was utilized towards a possible radical cyclization (Figure 54). [190] The prenyl derivative **220** was synthesized through methods parallel to those used for the allyl compound **197** (Table 5). Intermediate stilbenoid **195** was first subjected to the optimized DoM procedures for alkylation with prenyl bromide before subsequent reduction[178, 179] of the stilbene to afford the desired prenyl compound **221**.

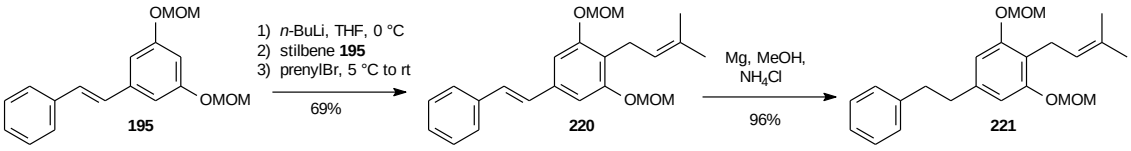


Figure 54. Synthesis of the prenyl substituted intermediate.

Initial attempts at removal of the MOM protecting groups from compound **221** led to a complex mixture of products (Figure 55). Treatment with *p*TsOH, Lewis acid assisted conditions with $ZnBr_2$,[191] or 3% HCl[104] all led to major products with similar rf's and all were less polar than the protected starting material. After examination of the literature, it was discovered that Asakawa reported the unprotected compound **221** was found to cyclize to the 6-member heterocyclic compound **181** (Figure 42) when subjected to acidic conditions[98] or BBr_3.[101] Analyses of the ^1H and ^{13}C NMR spectra however were not consistent with the reported data for such a product.

A closer inspection of the spectra revealed that in addition to removal of the MOM protecting groups, there was methyl ether addition to the olefin and formation of compound **222**. Due to these difficulties, the cyclization was attempted with the protecting groups in place but TLC analysis only showed starting material. After the MOM-protected compound **221** failed to undergo the desired cyclization, it was thought that the free phenol was integral to the reaction progression and more work towards the

deprotection was undertaken.[190] Catalytic conditions without heating were found to provide the desired deprotected compound **223** in moderate yield (35%), but subsequent attempts at cyclization of the prenyl derivative were unsuccessful. A more favorable route using an Ando variation of the HWE was pursued, so further modifications of the experimental reaction conditions of this cyclization were not explored.

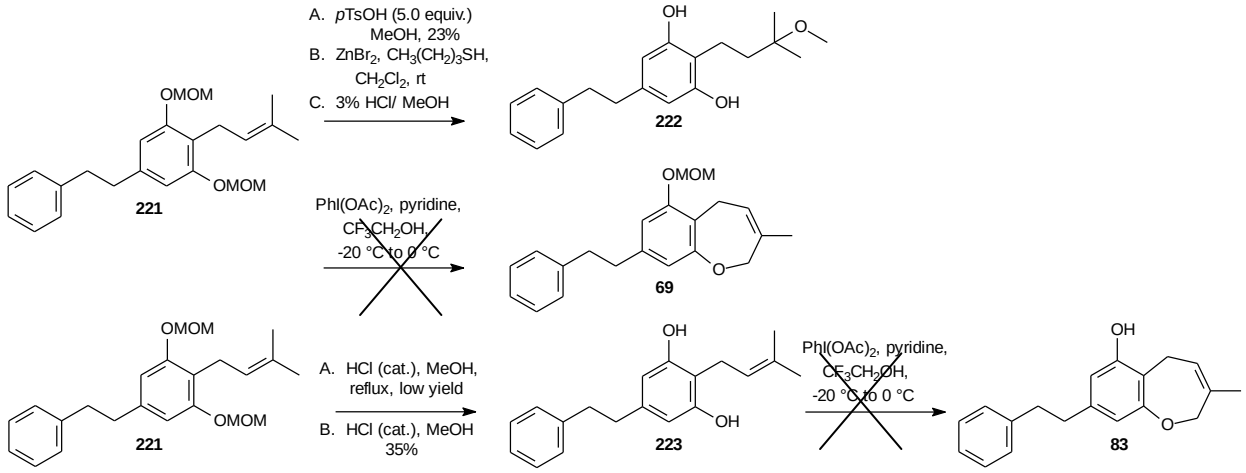


Figure 55. Attempted radical cyclization procedure.

For the next approach, installation of the *cis*-allylic alcohol moiety was envisioned through an Ando HWE[58-61, 192, 193] (Figure 56) and subsequent reduction of the resulting conjugated ester product **225**. Not only would this route afford the desired cis stereochemistry but also it would allow a possible expansion of the new one-flask phosphonate formation methodology to form the tolyl phosphonate. In contrast to a traditional HWE condensation reaction, the Ando modification utilizes the steric restrictions of the bulky tolyl phosphonate and also the electron withdrawing ability of the aryloxy substituent of the phosphonate to form the cis isomer over the trans (Chapter I, Figure 12 and 13).[60]

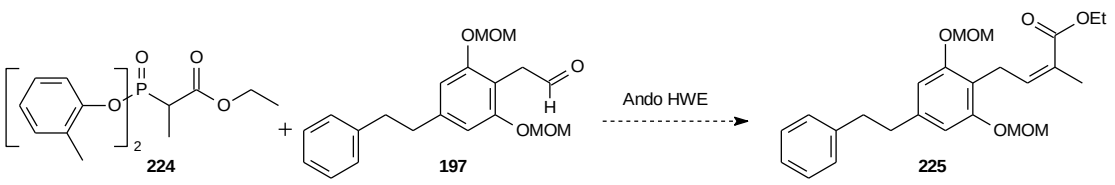


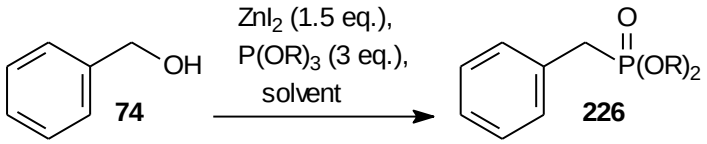
Figure 56. Ando HWE application.

Conditions for variation of the phosphite used in the zinc mediated phosphonate reaction were first attempted on benzyl alcohol because it was the model compound used in Chapter II.[106, 125] Considering the mild reaction conditions and good yields achieved with triethyl phosphite, other alkyl, aryl, and TMS phosphites were explored under standard reaction conditions (Table 6). Less bulky phosphites were explored first and, given the structure similarity, trimethyl phosphite (Table 6, Entry 1)[194] was studied under otherwise standard reaction conditions. While the desired dimethyl phosphonate was obtained, it was isolated in just 19% yield versus 83% for the reaction with $P(OEt)_3$ (Chapter I, Table 2, Entry 4). The low yield could be explained by the prevalence of the disproportionation product dimethyl methylphosphonate, evident from the ^{31}P NMR spectrum of the starting phosphite. If the trifluoromethyl phosphonate (Table 6, Entry 2)[195] could be prepared through a Zn-mediated reaction, it would be a mild and convenient route for preparation of a Still phosphonate, but unfortunately this reaction was unsuccessful. This may be due to the strong electron withdrawing nature of the phosphite. The attempted reaction with TMS phosphite[196] also failed to produce the desired phosphonate ester (Table 6, Entry 3).

Perhaps most surprising was the effectiveness of the bulkiest phosphite esters under standard reaction conditions. Both triisopropyl phosphite in THF and triphenyl phosphite in DMF at an increased reaction temperature gave moderate yields of the desired phosphonates (Table 6, Entry 4 and 7). Substituting DMF as the solvent drastically improved both yields, to an impressive 97% and 81%, with lower reaction

temperatures proving the most effective (Table 6, Entry 5 and 6). Alternatively, *o*-tolyl phosphite proceeded in poor yield and proved very difficult to isolate when the reaction was done in DMF. However when toluene was utilized, a 35% yield of the very sterically hindered *o*–tolyl phosphonate was achieved (Table 6, Entry 8).

The bulky nature of these nucleophiles would indicate that a simple Arbuzov mechanism is unlikely as the phosphite is a poor S_N2 participant. For example, benzyl bromide was treated under Arbuzov conditions with variations in solvent, temperature, and reaction duration with triphenyl phosphite and only minor evidence of the desired phosphonate was observed in the ^{31}P NMR spectrum. While the isopropyl adduct has been achieved in 70% yield under standard Arbuzov conditions,[197] the phenyl analogue required a nickel catalyst to be obtained in good yield (92%),[198] and the *o*–tolyl



Entry	R	Solvent	Temperature	Isolated Yield
1	Me	THF	66 °C	19%
2	CH_2CF_3	DMF	120 °C	NA
3	TMS	THF	66 °C	NA
4	$(CH)(CH_3)_2$	THF	66 °C	59%
5	$(CH)(CH_3)_2$	DMF	80 °C	97%
6	Ph	DMF	120 °C	81%
7	Ph	DMF	140 °C	61%
8	*o*-tolyl	Toluene	111 °C	34%

Table 6. Phosphite scope expansion on a model substrate.

benzylphosphonate has not been synthesized before this study. The poor yields under traditional Arbuzov conditions reinforce the unlikeliness of a displacement through a

simple S_N2 mechanism and emphasize the necessity of excess zinc iodide as a likely facilitator of a final Arbuzov-like rearrangement in the general reaction mechanism.

Although the transformation of alcohols alpha to an ester has not been attempted with the new phosphonate protocol, the results of the mixed ester products obtained on aliphatic substrates did give cause for hesitation (Chapter III, Figure 39 and 36). The successful conversion of benzyl alcohol to the bulky *o*–tolyl phosphonate ester through the zinc-mediated procedure justified an attempt to apply the methodology on the Ando precursor. The conversion of alcohol **227** to the diethyl ester **228** was first attempted in an effort to judge the efficacy of the protocol on the substrate without the added steric considerations of the *o*–tolyl phosphite. Unfortunately there was no evidence of phosphonate formation in the ^{31}P NMR spectrum of the reaction mixture (Figure 57).

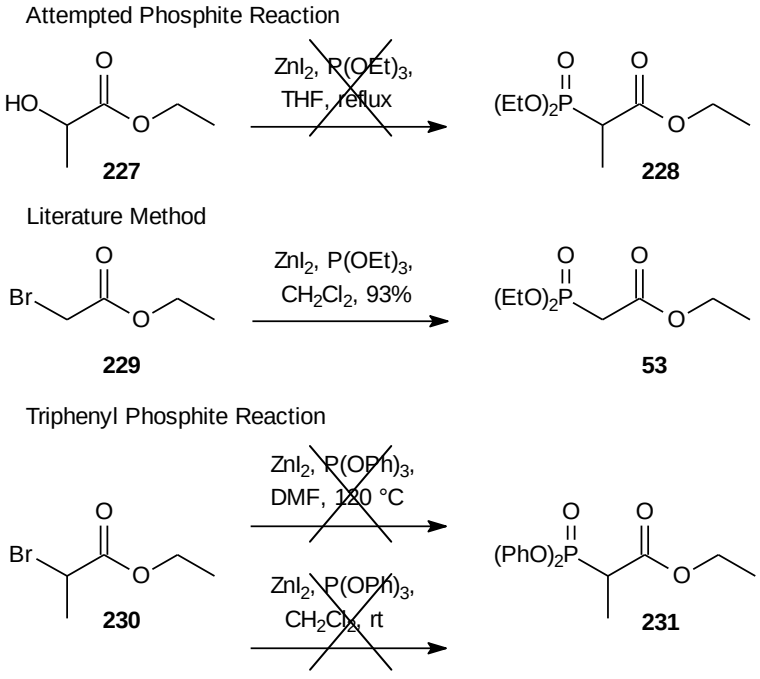


Figure 57. Attempted Zinc-mediated reactions towards an Ando phosphonate.

Encouraged by the work of Mohanakrishnan[123] and co–workers, who used similar methods to successfully convert ethyl 2-bromoacetate to the diethyl phosphonate ester (Figure 57), the more activated bromide substrate was examined in an effort to provide better access to the diphenyl phosphonate. Substitution of triphenyl phosphite into the standard conditions employed by both the Wiemer group[106, 125] and Mohanakrishan[123] did not provide any evidence of the desired diphenyl phosphonate product. It is likely that the steric hindrance generated by the triphenyl phosphite reagent in addition to the methyl substituent of substrate **230** prevented formation of the desired phosphonate.

After the new phosphonate protocol failed to produce the desired Ando phosphonate on an aliphatic ester (Figure 57), an alternative route exploiting literature precedence was applied (Figure 58). Bromide **230** was first converted to the phosphonate following slightly modified literature procedures.[199, 200] Upon addition of catalytic iodine

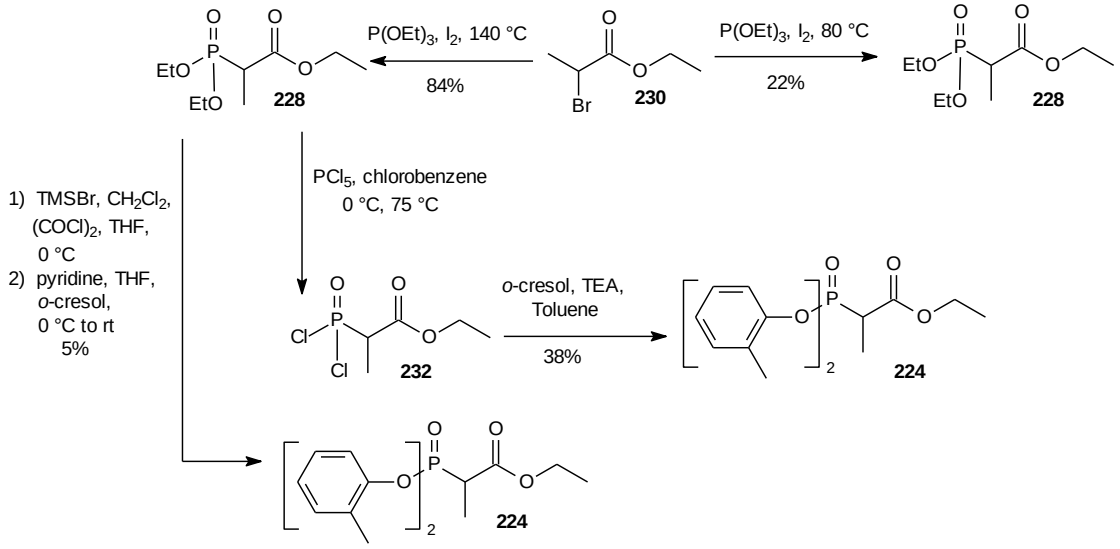


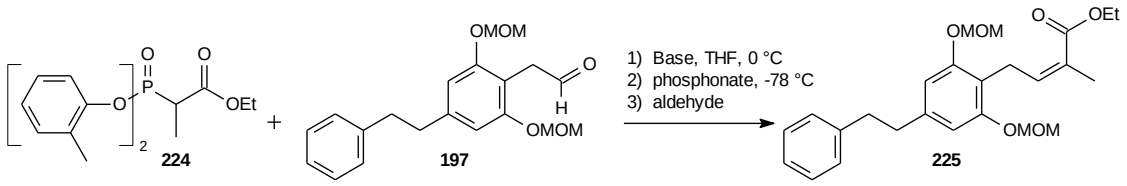
Figure 58. Synthesis of the Ando tolyl phosphonate.

and increasing the reaction temperature to 140 °C, a dramatic increase in yield was observed. Diethyl phosphonate **228** was then converted to the dichloride by treatment

with phosphorus pentachloride,[60, 61, 192, 193, 199] followed by subsequent treatment with *o*-tolyl to afford the desired phosphonate **224.**[59-61, 199] Another more facile route was sought through the utilization of oxalyl chloride but was very low yielding (Figure 58).[201]

The olefin stereochemistry resulting from condensations of phosphonates developed by Ando can be sensitive to many factors including base and temperature (Chapter I, Figure 12 and 13).[58-61, 202, 203] In general, it has been found that the modified HWE reaction produces better cis to trans olefin ratios when Triton B or *t*–BuOK are used as bases with aromatic and α,β–unsaturated aldehydes and NaH is used for aliphatic substrates.[59] The allylic positioning of the radulanin aldehyde intermediate **197** as well as the MOM protecting groups could complicate this simplified formula. For this reason, many trials were undertaken to determine the best conditions for application to the radulanin aldehyde intermediate **197** (Table 7).

Because potassium cations are believed to increase Z isomer formation with conjugated substrates, initial attempts at the modified Horner-Wadsworth-Emmons olefination with the *o*–tolyl phosphonate ester were undertaken with KHMDS and *t*–BuOK as the deprotonating agents.[59, 204] Despite varying the reaction temperature, KHMDS gave mediocre Z:E ratios and yields (Table 7, Entry 1 and 2). Substituting *t*–BuOK as the base was promising with a high yield (81%, Table 7, Entry 3) and a 96:4 ratio of the Z:E isomers. Maintaining the reaction mixture at –78 °C for the duration of the reaction initially appeared advantageous, but although later attempts showed impressive yields (Table 7, Entry 4 and 5), the high isomer ratios were not reproducible even with added 18-crown-6 (Table 7, Entry 7). Increasing the reaction temperature led to a significantly lower 24% yield (Table 7, Entry 6). The inconsistent results with *t*–BuOK could be due to the hygroscopic nature of the reagent resulting in quenching by moisture from the air, especially considering the small scale on which the reactions were performed. Both tetramethylguanidine (TMG)[204] and Triton B gave equally unimpressive results (Table 7, Entry 8 and 9).



Entry	Base	Reaction Conditions (Step 3)	Z:E Ratio	Isolated Yield
1	KHMDS, 18-Crown-6	–78 °C, 1 hr to rt overnight	73:27	57%
2	KHMDS, 18-Crown-6	–78 °C 5 min, 0 °C 30 min to rt	65:35	17%[a]
3	*t*–BuOK	–78 °C, 1 hr 15 min	96:4	84%
4	*t*–BuOK	–78 °C, 1 hr 15 min	80:20	81%
5	*t*–BuOK	–78 °C, 1 hr 15 min	78:22	72% (80%) BRSM)
6	*t*–BuOK	–78 °C 10 min, 0 °C 30 min to	75:25	24%
7	*t*–BuOK, 18-Crown-6	–78 °C, 1 hr 15 min	81:19	53%[a]
8	TMG, NaI	–78 °C for 7.5 hrs	94:6	28%
9	Triton B (40%)	–78 °C, 1 hr to rt overnight	59:41	12%[a]
10	NaH	–78 °C, 1 hr to rt overnight	88:12	48% (76%) BRSM)
11	NaH	–78 °C, 2 hr to rt overnight	59:41	41% (78%) BRSM)
12	NaH	–78 °C 5 min to rt over 30 min.	95:5	18% (46%) BRSM)
13	NaH	–78 °C 5 min, 0 °C 30 min to rt	95:5	65%
14	NaH	–78 °C 5 min, 0 °C 30 min to rt	94:6	56%
15	NaH	–78 °C 5 min, 0 °C 40 min to rt	67:33	56% (85%) BRSM)
16	NaH (5.2 equiv.)	–78 °C 5 min, 0 °C 30 min to rt	90:10	94%[a]
17	NaH, NaI	–78 °C 5 min, 0 °C 30 min to rt	NA	NA
18	NaH, LiBr	–78 °C 5 min, 0 °C 30 min	90:10	80%[a]
19	NaH, 15-Crown-5	–78 °C 5 min, 0 °C 30 min to rt	54:46	59% (67%) BRSM)
20	NaH, 18-Crown-6	–78 °C 5 min, 0 °C 30 min to rt	90:10	89%
21	NaH, 18-Crown-6	–78 °C 5 min to rt 1 hr	89:11	68% (75%)
22	NaH, 18-Crown-6	–78 °C 5 min to rt 1 hr	88:12	73%
23	NaH, 18-Crown-6	0 °C 5 hrs to rt over 15 min	65:35	30% (60%) BRSM)
24	NaH, 18-Crown-6	0 °C 2.5 hrs to rt 15 min	94:6	59%
25	NaH, 18-Crown-6	–40 °C 5 min, 40 °C 30 min	86:14	78%
26	DBU, NaI	–78 °C 1 hr to rt overnight	92:8	87%[a]

[a]Yield determined through relative integration by GC-MS.

Table 7. Ando HWE optimization.

The poor results using conditions typical for conjugated aldehydes warranted experimentation with NaH, which is associated with better results with aliphatic substrates. Under similar conditions to the initial KHMDS trial, sodium hydride was used as the base and this reaction also exhibited average yields and poor to mediocre isomer ratios (Table 7, Entry 10 and 11). Instead of maintaining the reaction mixture at -78 °C over a period of one to two hours, after addition of the aldehyde **197**, it was warmed to 0 °C after only 5 minutes and then to room temperature after 30 minutes (Table 7, Entry 13 and 14). The adjusted conditions led to a slight decrease in yield but, unlike the *t*–BuOK trial (Table 7, Entry 6), NaH showed consistency in the high ratio of cis isomer formation (Table 7, Entry 12-14). The decreased ratio in Entry 15 could be due to exposure of NaH to moisture in the air and a subsequent partial quenching of the base.

Although good isomeric ratios have been obtained, an increased yield was still desired. Just as the complexing ability of 18-crown-6 often assists reactions with potassium cations, 15-crown-5 was used in company with sodium hydride due to its affinity for sodium cations. Unfortunately, neither a good yield nor ratio was acquired (Table 7, Entry 19). Unexpectedly, with an 18-crown-6 additive under various temperature conditions, yields of ~70% or above were consistently attained and high ratios were found (Table 7, Entry 20-25).

It has also been speculated that an excess of sodium cations can lead to improved Z selectivity in Ando type olefination conditions.[204, 205] With an excess of NaI, none of the desired ester product **225** was observed (Table 7, Entry 17). When DBU was substituted as the base and the reaction was allowed to warm to room temperature, however, a good 87% yield was achieved in combination with a high isomeric ratio (Table 7, Entry 26). DBU also has been utilized in the presence of lithium salts.[202, 203] For this reason, NaH was exposed to LiBr under the warmer reaction temperatures that lead to better yields and ratios (Table 7, Entry 18).

After a close examination of all the reaction conditions, a few trends became clear. One of the most important factors in the NaH trials and DBU trial was the correlation identified between base equivalents and improved yields and ratios (Table 8, Page 117). The HWE protocol provides excellent yields (above 80%) and at least 90:10 ratios when 2.3 equivalents of base or greater were employed (Table 7, Entry 16, 18, 20, and 26). The NaI, LiBr, and 18-crown-6 additive trials (Table 7, Entry 18, 20, and 26) had comparable results to the entry with a large excess of base and no additive (Table 7, Entry 16). These results suggest that the equivalents and not the additives are leading to the best results when NaH and DBU are utilized. It is also possible that the additives allow for good results with slightly lower equivalents of base, although an excess is still necessary. Another commonality of all these favorable trials was the warmer temperatures (0 °C or above).

Further literature explorations led to the discovery of work done by Yamaguchi which parallels the described reduction of the Ando ester to afford a *cis*-allylic alcohol.[169] Although the work was done on a radulanin H intermediate, the specific details are not reported. Nevertheless, this report….

With the cis ester intermediate **225** in hand, the final steps towards completion of the synthesis of radulanin A were undertaken (Figure 59). Reduction of the saturated ester with both DIBAL and allane was accomplished in excellent yield despite initial difficulties with decomposition (Figure 59). The desired alcohol appeared slightly acid sensitive upon prolonged exposure to $MgSO_4$ or silica gel. Direct cyclization of the MOM protected alcohol was attempted with BF_3•OEt_2. Due to the complex mixture of observed products, an alternative known route was utilized in order to obtain an authentic sample of radulanins A. Removal of the MOM ether moieties by treatment with HCl, followed by cyclization using Mitsunobu conditions afforded the natural product radulanin A in 12 steps and an overall 8% yield.[20, 103] An alternative cyclization also was attempted through a $ZnCl_2$ mediated process,[107] but only starting material was isolated

(Figure 59). It is possible that the metal reagent was no longer anhydrous and therefore recrystallized $ZnCl_2$ would need to be used in future efforts. This was not pursued because of the positive results obtained with the Mitsunobu reaction.

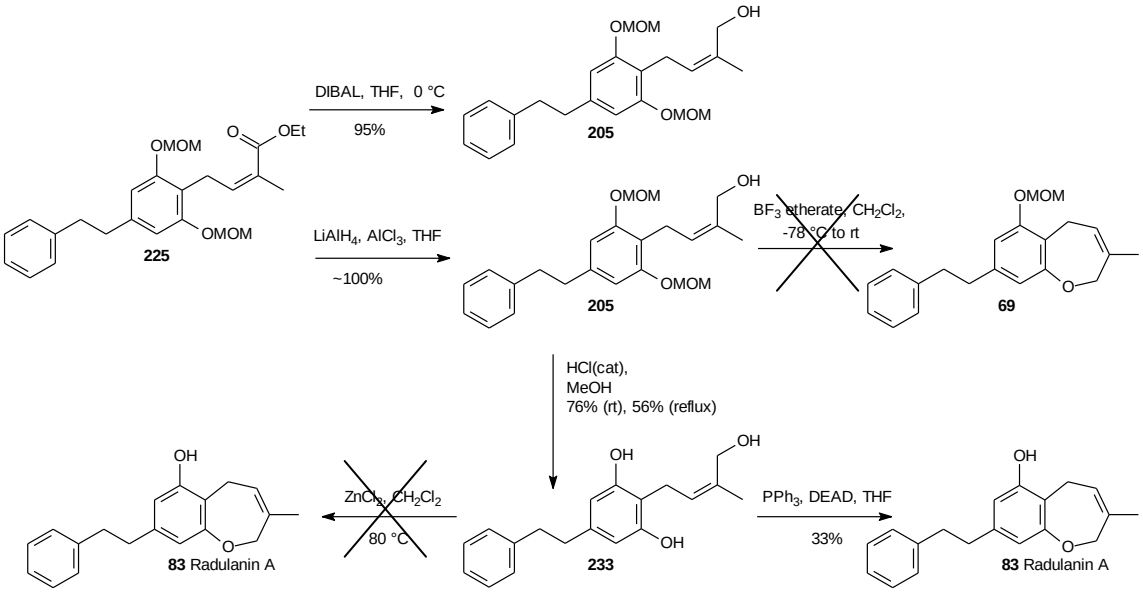
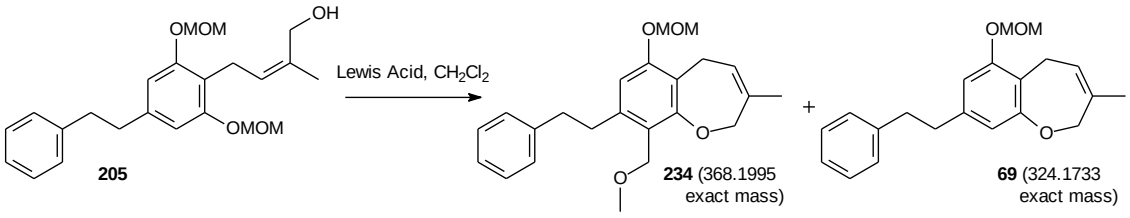


Figure 59. Completion of radulanin A synthesis.

As mentioned previously, the attempted $BF_3{\cdot}O(CH_2CH_3)_2$ initiated cyclization of the protected intermediate **205** under standard conditions for our group[206] led to a complex mixture of products (Figure 59). However, when the reaction was warmed to room temperature the observed product mixture was more promising. A variety of other Lewis acids and conditions were then utilized to determine if the molecular ions associated with the cyclized products **234** and **69** could be detected through GC-MS analysis (Table 8). Additional temperature conditions were first examined with $BF_3{\cdot}O(CH_2CH_3)_2$. Previous cyclization work on the schweinfurthins (where the reaction is usually done at –78 °C)[206] suggested that $BF_3{\cdot}OEt_2$ is simply too reactive at room

temperature, a conclusion supported by the complex mixture once again observed when this reaction was conducted at room temperature (Table 8, Entry 1). At –78 °C, the reaction proved very sluggish (Table 8, Entry 2). Closer monitoring of the reaction progress revealed that at about –20 °C, a complex mixture of products was visible through TLC analysis. This suggested decomposition and another trial was then conducted in which the temperature was kept between –30 °C and –20 °C. Although the resulting reaction mixture contained the desired molecular ions representing compounds **234** and **69**, they were present only in trace amounts and only as components of a very complex mixture (Table 8, Entry 3). Previous work in our group on the schweinfurthins[206] suggests that the substitution would be at the closest aromatic position as shown in compound **234**. It is possible however that either compounds **235** or **236** could be formed as well (Figure 60).



Entry	Lewis Acid (equiv.)	Temperature	Molecular Ions (m/z)[a]
1	[b]$BF_3.O(CH_2CH_3)_2$ (4.0)	rt	Not Performed
2	[b]$BF_3.O(CH_2CH_3)_2$	-78 °C for 40 min.	Trace 368 and 324
3	[b]$BF_3.O(CH_2CH_3)_2$ (4.7)	-30 °C to -20 °C for 40 min.	Trace 368 and 324
4	[c]BCl_3 (2.5)	-78 °C to 0 °C for 1hr	368 and trace 324
5	DEAD (2.4), PPh_3 (2.0)	rt[d]	Not detected
6	$InCl_3$ (2.1)	rt	Not detected
7	$In(OTf)_3$ (2.4)	rt	**234** (28%)[e] **69** (32%)[e]

[a]The molecular ion was detected through GC-MS analysis. [b]The Lewis acid was used as a 46.5% solution in ether. [c]The Lewis acid was used as a 1 M solution in CH_2Cl_2. [d]The reaction was done in THF. [e]Yield determined by GC-MS through relative integration of reaction mixture.

Table 8. Lewis acid–mediated cyclization trials.

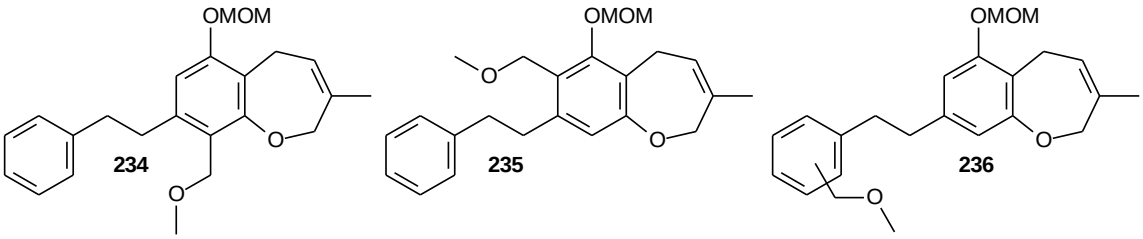
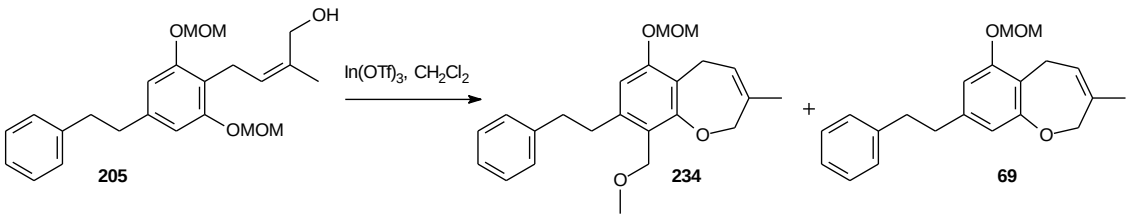


Figure 60. Possible EAS sites.

Minor success was achieved when the *cis*–allylic alcohol **205** was treated with BCl_3 or an indium-based Lewis acid (Table 8, Entry 4 and 7). BCl_3 has been shown to initiate the conversion of MOM protected ethers to chloromethyl ethers.[207] In this trial GC-MS analysis showed evidence of products that could be the MOM protected cyclized product **69** and, even more exciting, the methyl ether **234** which suggests electrophilic aromatic substitution of the liberated MOM group. The reaction with $In(OTf)_3$ appeared to proceed more cleanly and approximate yields were attainable through crude integrations of the GC-MS spectrum (Table 8, Entry 7). After isolation of all reaction products through preparative TLC purification and subsequent GC-MS analysis, the desired products **234** and **69** were confirmed through analysis of their ^{1}H and ^{13}C NMR spectra. Although considerably less intense, an additional molecular ion at 368 m/z was observed that is likely to be compound **235**. A larger scale reaction and more thorough isolation will be needed to confirm the structure of this minor product.

The promising results with the $In(OTf)_3$ trial (Table 8, Entry 7) prompted further examination and modifications of the reaction conditions. It is envisioned that such a transformation could proceed through deprotection of the MOM protecting group followed by the 7–membered ring formation initiated by the Lewis acid. Alternatively, the reaction sequence could proceed through formation of an allylic cation, subsequent attack on the carbocation by an electron pair from a MOM oxygen, and loss of a methoxy

methyl electrophile. The later reaction sequence seems to be more likely due to the observed electrophilic aromatic substitution product **234** and the lack of deprotection seen at the second MOM protected phenolic position. The use of the molecular sieves as well as warmer reaction temperatures generally resulted in formation of a majority of compound **69** compared to compound **234** as well as an increase in side product formation visible through TLC analysis (Table 9, Entry 1, 2, and 6). Maintaining the reaction at 0 °C without molecular sieves appears to produce the cleaner product but at a lower yield (Table 9, Entry 3).



Entry	Lewis Acid (equiv.)	Temperature	**234** Yield	**69** Yield
[a]1	[c]2.0	0 °C to rt overnight	3%	40%
[b]2	[c]2.5	0 °C to rt overnight	8%	12%
[a]3	2.4	0 °C for 3 hr	6%	4%
[b]4	[c]2.8	0 °C for 4 hr	14%	NA
[b]5	4.0	0 °C to rt	NA	NA
[a]6	[c]1.5	0 °C for 8 hr	11% (14% BRSM)	25% (34% BRSM)

[a]The starting alcohol was a ratio of 65:35 Z:E isomers. [b]The starting alcohol was a ratio of 90:10 Z:E isomers. [c]Molecular sieves were used.

Table 9. $In(OTf)_3$ mediated cyclization trials.

Another consideration was the importance of the cis stereochemistry of the alcohol to the cyclization. To gauge the utility of these conditions, a 65:35 mixture of Z and E allylic alcohols was used in the early reactions. However, it is possible that only

the cis alcohol **205** leads to the desired products. The trans alcohol was synthesized in order to determine the importance of the olefin stereochemistry. A traditional HWE reaction of aldehyde **198** with the diethyl phosphonate ester **228** followed by DIBAL reduction afforded the *trans*-allylic alcohol **238** for further testing of the Lewis acid–mediated cyclization.

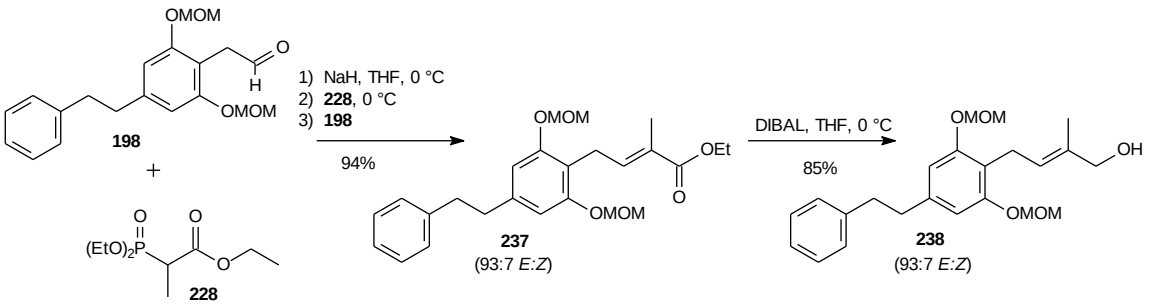
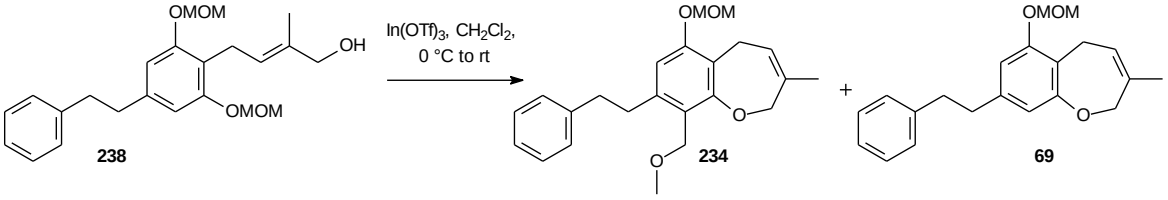


Figure 61. Synthesis of trans alcohol intermediate **238**.

Although initial trials employing the trans alcohol **238** do not provide definitive evidence of the importance of the olefin stereochemistry, they do provide some insight into the reaction. Both trials gave very low yields of any cyclization product. In trial 1, the lower yields could be due to the limited amount of Lewis acid used in the reaction. Allowing the reaction to warm to room temperature could also explain the multiple side products obtained in Entry 2. Close observation of the reaction progress did show considerably slower product formation through TLC analysis of both trials (Table 10, Entry 1 and 2). It is suspected based on the current results that the cis olefin is much more amenable to the cationic Lewis acid–mediated cyclizations and could be responsible for the observed yields. More experiments are necessary before this can be concluded however.



Entry	Lewis Acid (equiv.)	Temperature	Yield **234**	Yield **69**
1	0.2 [a]	0 °C to rt overnight	10% (17% BRSM)	2% (4% BRSM)
2	2.0[a]	0 °C to rt overnight	2%	3%

[a]The starting alcohol was a ratio of 93:7 E:Z isomers. Molecular sieves were used.

Table10. Lewis acid–mediated cyclization trials on trans isomer **238**.

These studies establish that the Lewis acid–mediated cationic cyclizations[206] will allow the closing of 7–membered benzoxepin ring system of the radulanins. This presents the unique opportunity for a new synthesis of radulanin A from benzoxepin **69** as well as the formal synthesis of radulanin E from methyl ether **234**. A simple deprotection of compound **69** would lead to an alternative total synthesis of radulanin A (Figure 62). Initial attempts at room temperature showed minimal conversion to the phenol. This is not surprising since the literature demonstrates good yields when the reaction is performed at reflux.[20, 96, 103] Oxidation of the EAS product followed by a deprotection could lead to the synthesis of radulanin E. Initial oxidation efforts conducted on a very small scale provided only starting material. The model substrate **241** was tested under more forceful reaction conditions to determine if the allylic ether would also react (Figure 63). The lack of any observed reactions suggests that increasing the equivalents of DDQ and/or the reaction temperature would be tolerated by the methyl ether **234**. Aldehyde **239** already has been synthesized through alternative methods and

oxidized to the carboxylic acid.[96] Therefore, upon deprotection of aldehyde **240**, the formal synthesis of radulanins E would be achieved.

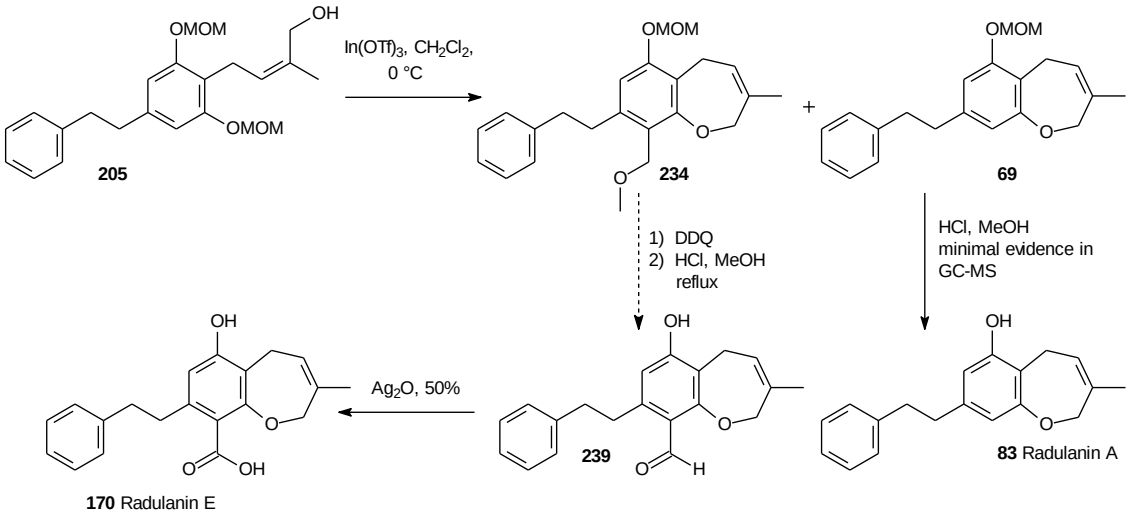


Figure 62. A total synthesis of radulanin A and a formal synthesis of radulanin E.[103]

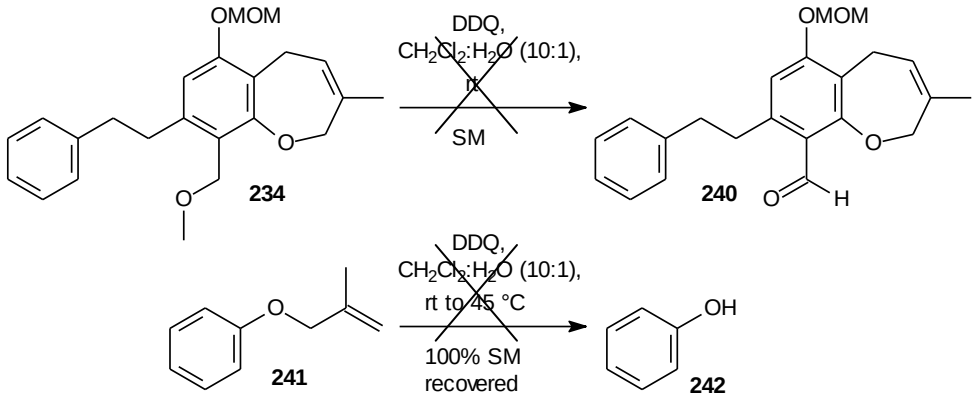


Figure 63. DDQ oxidation on model substrate.

In conclusion, the total synthesis of the natural product radulanin A was accomplished through a Mitsunobu cyclization in 12 steps and an overall 8% yield. Synthesis of radulanin A from the known aldehyde **194** required only 7 steps and was

achieved in a 32% overall yield. Initial difficulties were overcome through the reorganization of the reaction sequence to include a later stage DoM reaction which was further optimized. Attempts to employ a modified Wittig protocol were met with limited success and the radical cyclization of prenyl **223** failed. However, formation of the *cis*–allylic alcohol was achieved through the Ando modification to the traditional HWE reaction.

Formation of the 7–membered benzoxepin core of the radulanins, along with EAS, also was achieved through a novel $In(OTf)_3$ mediated cyclization. This protocol could allow for not only a new synthesis of radulanin A, but also the formal synthesis of radulanin E. Further manipulations of the reaction conditions could offer greater selectivity in product formation and applications to a greater diversity of natural products. Finally, analogues could be synthesized by application of the current chemistry to compounds with alternate substitution patterns on the benzoxepin core. The many biological properties of the radulanins could then be explored with access to this array of natural products.

CHAPTER V
SUMMARY AND FUTURE DIRECTIONS

We have shown that a diverse set of aromatic, allylic, and heteroaromatic alcohols is amenable to the new methodology for ZnI_2–mediated phosphonate synthesis. Good to excellent yields were achieved in the one–flask, direct conversions of the alcohol substrates to the desired phosphonates. The ZnI_2 mediated protocol also is amenable to variations in solvent and temperature which may lead to a wider applicability in the complex systems of many natural products. After some optimization of the purification techniques, excellent results were obtained upon scale-up of the reaction conditions as well. Although it does not provide a complete mechanistic picture, isotopic labeling experiments as well as application of this protocol to an enantiomerically pure substrate provided more mechanistic insight. Formation of a tetra-coordinate zinc species is probably followed by formation of a C-P bond through a process with S_N1 character.

Under standard reaction conditions mixed ester and hydrogen phosphonate ester products were obtained from aliphatic alcohols and not the desired diethyl phosphonate ester. A reaction sequence based on a Lewis acid mediated ester exchange between the aliphatic alcohol and triethyl phosphite, followed by a more traditional Arbuzov reaction could explain this result (Chapter III, Figure 40). The usefulness of the isolated phosphonate ester products has not yet been determined fully. It is possible that alternate conditions, solvents, or Lewis acids could be used to form either aliphatic product selectively, thereby delivering even more value to the protocol.

Continued development of the one-flask phosphonate formation methodology was pursued through replacement of triethyl phosphite with other phosphite reagents. Formation of phosphonates from these experiments not only confirms that a standard Arbuzov sequence is unlikely, but the success with the bulky *o*-tolyl phosphonate suggests that even more complex phosphonates could be synthesized this way. Although there is already literature demonstrating the usefulness and synthesis of chiral

phosphonates,[208-211] there is still considerable room for growth in this area. The new phosphonate formation protocol could prove effective as a more facile means for the synthesis of chiral phosphonate esters. Another conceivable route for expansion of this method involves the utilization of the phosphonate esters obtained from these phosphite substitution reactions. Diphenyl benzylphosphonate **243** for example, could prove valuable towards cis selective stilbene synthesis (Figure 64). Initial attempts proved low yielding with poor Z:E selectivity, but further modifications to the base and/or reaction temperature could provide better results (Figure 64).

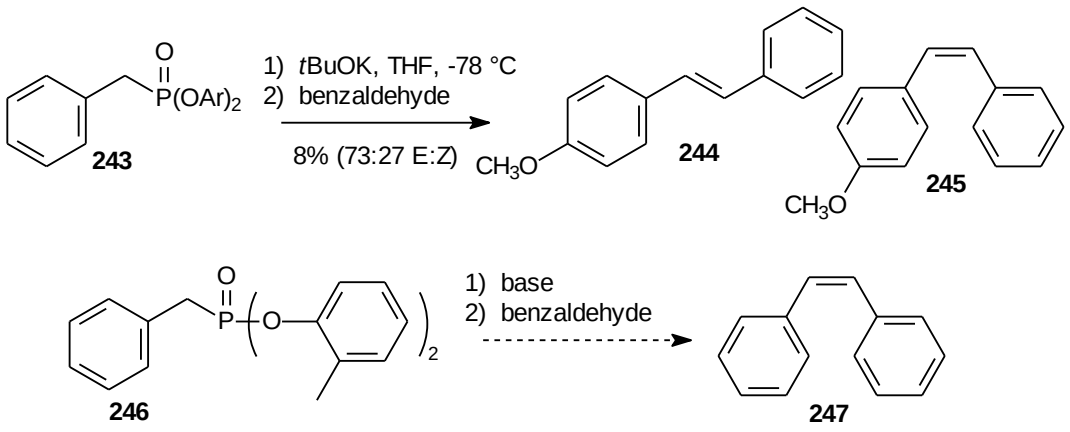


Figure 64. Possible application of a di–*o*–tolyl phosphonate ester for selective cis-stilbene synthesis.

Radulanin A was successfully synthesized despite initial problems with the original DoM sequence and limited success of the modified Wittig approach to install the *cis*–allylic alcohol moiety. An alternative synthetic sequence led to the formation of the desired allylic alcohol through a DoM reaction, ozonolysis, and an variation on the traditional HWE reaction. After extensive studies to optimize these conditions, using a large excess of the NaH base was found to provide the best yields and isomer ratios. The

Z:E ratios might be further improved through the use of the bulky phosphonate reagent **248** (Figure 65).[60]

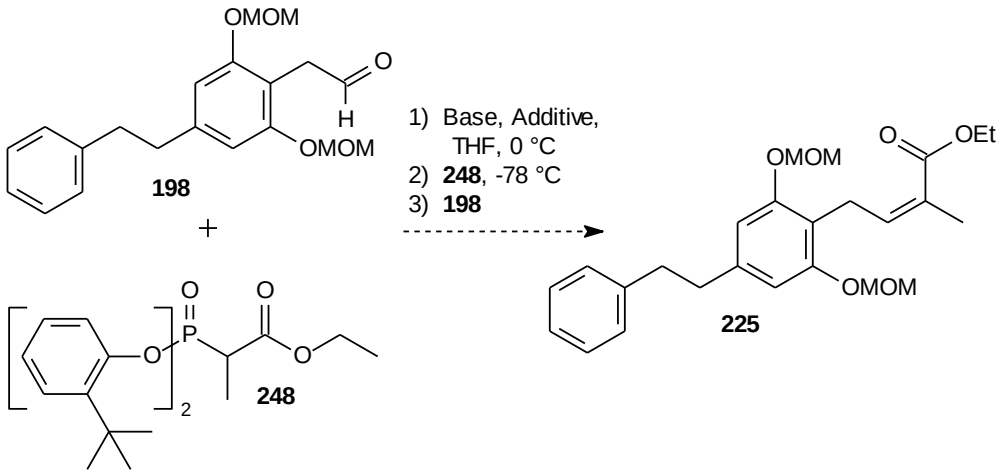


Figure 65. Utilization of a *t*–butyl arylphosphonate in the Ando modification of the HWE reaction.

A final cyclization of compound **205** under Mitsunobu conditions allowed the total synthesis of radulanin A. The MOM-protected precursor **69** also was achieved through application of a new Lewis acid–mediated methodology. When exposed to $In(OTf)_3$, alcohol **205** provided two products of interest, the simple cyclization product **69** and the more exciting cyclization-EAS product **234**. More work towards optimizing these conditions would be desirable and could lead to an increase in yield and perhaps greater selectivity in the formation of the cyclized versus cyclization–EAS product. The substitution pattern and protecting group strategy of the radulanin synthesis also could be altered to afford a variety of analogues. In particular, alteration of the strategy might afford a variety of EAS products. Previous work in the Wiemer group has highlighted that differing protecting groups can affect the yield and product ratios.[212]

The current strategy could allow the facile and divergent synthesis of 5-membered heterocyclic natural products such as tylimanthin, perrottetin, and analogues from radulanin intermediates already in hand (of Chapter III, Figure 41). Previous work that used stannous reagents or manipulations of a prenyl moiety afforded these natural products in poor to modest yields.[101] The literature describes ruthenium[213] and Pd[214-219] catalyzed reaction conditions for transformations to similar 5-membered heterocyclic substructures through phenols or acetate protected substrates. A variation to this strategy should provide the desired products in good yield with minimal steps. Deprotection of the already synthesized stilbene **195** followed by selective iodination at the *ortho*–position proceeded in good yield to afford the iodide **252**. Acetate protection of compound **252** also proceeded smoothly. Although initial trials under an argon

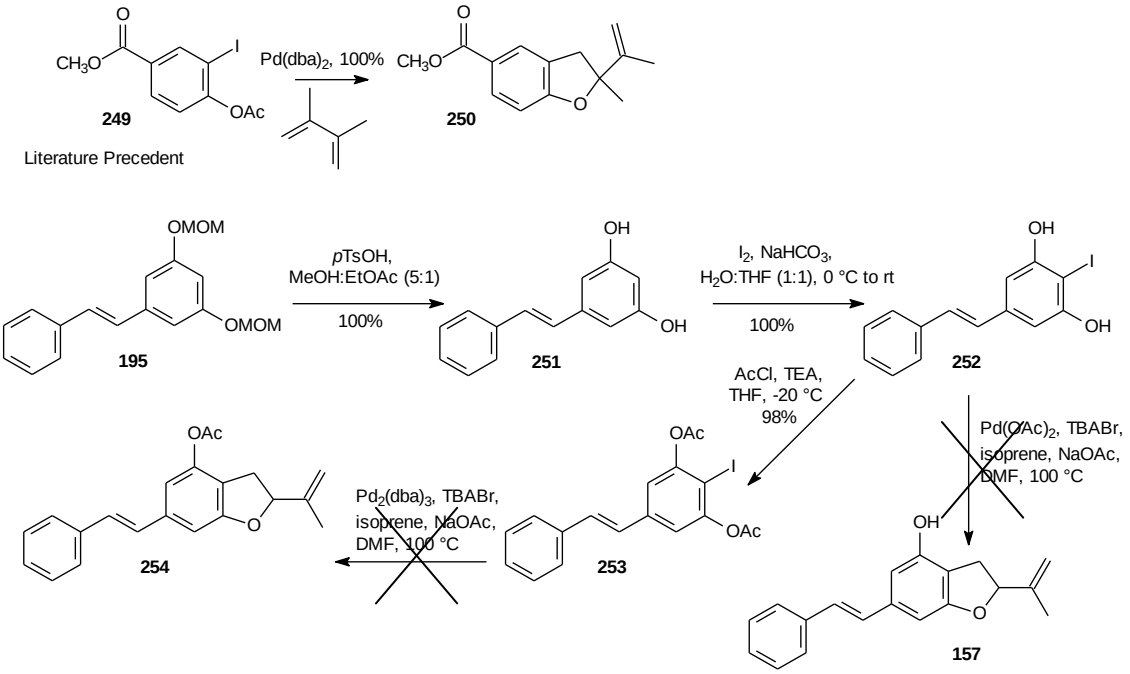


Figure 66. Possible synthesis of tylimanthin B and analogues.[215]

atmosphere did not show any evidence of the desired products upon GC-MS analysis of the reaction mixtures, closed vial conditions did show a molecular ion that may be the 5–membered heterocyclic **157** (Figure 66). Many more conditions could be examined and subsequent selective reduction of the stilbene should afford natural products like tylimanthin analogue **254**.

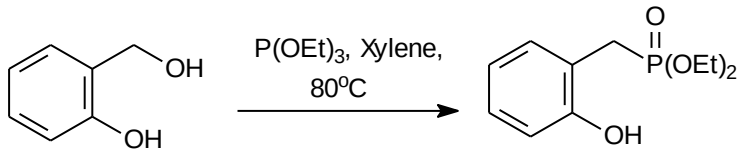
Overall, these studies have demonstrated the value of a new, mild methodology for the direct conversion of allylic, substituted benzylic, and heteroaromatic alcohols to diethyl phosphonate esters. This protocol is amenable to scale up to at least a 5 gram scale, and bulky phosphite moieties are reactive under the general procedure. Mechanistic studies including isotopic labeling have given insight into a likely S_N1–type process. Phosphonates prepared in this way can be used in the total synthesis of radulanin A. Through the course of this research, the Lewis acid–mediated cyclizations have been expanded to include the closing of the 7–membered benzoxepin ring system of the radulanins. Even more promising is the ability of these reaction conditions to afford the aforementioned ring closure in conjunction with electrophilic aromatic substitution of the displaced MOM group, which may allow a formal synthesis of radulanin E.

CHAPTER VI
EXPERIMENTAL PROCEDURES

General experimental conditions.[106] Tetrahydrofuran (THF) and diethyl ether were distilled from sodium and benzophenone and methylene chloride from CaH immediately prior to use while toluene was dried over activated molecular sieves or bought anhydrous from a commercial source. DMF was dried over activated molecular sieves or distilled over CaH *in vacuo*. Solvent ratios were determined by volume. All non-aqueous reactions were done under an argon atmosphere, in oven-dried or flame-dried glassware and with magnetic stirring. Butyl lithium, *sec*–butyl lithium, and phenyl lithium solutions were purchased from a commercial source and their titer determined with diphenyl acetic acid before use. All other reagents and solvents were purchased from commercial sources and used without further purification.[185] Flash chromatography was done on silica gel with an average particle size of 40-63 μm. The ^{1}H spectra were recorded at 300 MHz (75 MHz for ^{13}C), 400 MHz (100 MHz for ^{13}C), or 500 MHz (125 MHz for ^{13}C) with $CDCl_3$ or $(CD_3)_2CO$ as solvent and $(CH_3)_4Si$ (^{1}H, 0.0 ppm) or $CDCl_3$ (^{13}C, 77.0 ppm) as internal standards. Ozonolysis was performed on a Welsbach Model T-408 ozonator. High resolution (ES) mass spectra and gas chromatography–mass spectrometry (GC–MS) data were obtained at the University of Iowa Mass Spectrometry Facility. The elemental analyses were conducted by a commercial facility. Analyses of enantiomeric purity were performed using a chrial HPLC column with photodiode array UV-Vis analysis and samples were eluted with a gradient of hexanes and isopropyl alcohol.

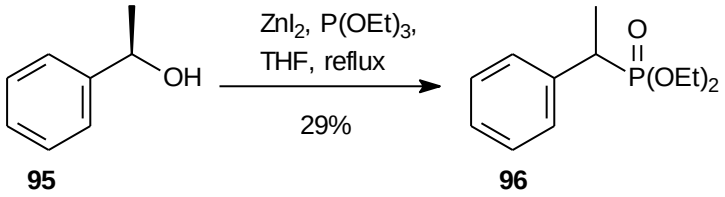
General Experimental Procedure for Phosphonate Synthesis.[106] To a stirred solution of ZnI_2 (1.5 eq) in anhydrous toluene or freshly distilled THF was added $P(OEt)_3$ (1.5–3 eq) followed by the alcohol. The reaction mixture was allowed to stir at reflux overnight (approximately 12 hours). After it had cooled to room temperature, the

reaction mixture was immediately placed on a vacuum line to remove volatiles. The residue then was washed with NaOH until the solids dissolved, extracted with ether, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified via flash column chromatography on silica gel to afford the desired diethyl phosphonate.



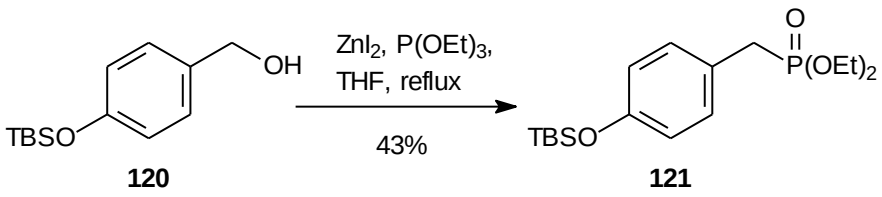
89 **90**

Diethyl 2-hydroxybenzylphosphonate (90). Commercially available 2-(hydroxymethyl)phenol **89** (502 mg, 4.04 mmol), xylene, and $P(OEt)_3$ (2.8 mL, 16 mmol) were combined and the resulting solution was heated at 80 ºC for three days. After the solution had cooled to room temperature, the reaction mixture was immediately placed on a vacuum line and concentrated. The resulting colorless oil was purified via flash column chromatography (30% to 60% EtOAc in hexane) to give the desired product **90** (919 mg, 93%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (br s, 1H), 7.19-7.13 (m, 1H), 7.07 (dt, J = 7.5, 1.8 Hz, 1H), 6.96 (d, J = 7.8 Hz, 1H), 6.86 (tt, J = 7.5, 1.2 Hz, 1H), 4.12-3.97 (m, 4H), 3.20 (d, J_{HP} = 21 Hz, 2H), 1.25 (t, J = 7.0, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6 (d, J_{CP} = 5.4 Hz), 131.2 (d, J_{CP} = 7.6 Hz), 128.8 (br s), 120.6 (d, J_{CP} = 4.4), 118.6 (br s), 118.4 (br s), 62.9 (d, J_{CP} = 6.4 Hz, 2C) 29.6 (d, J_{CP} = 137.6 Hz), 16.2 (d, J_{CP} = 6.0 Hz, 2C); ^{31}P NMR (121 MHz, $CDCl_3$) δ 29.5. The ^{1}H NMR spectrum was consistent with literature data.[220]



95 **96**

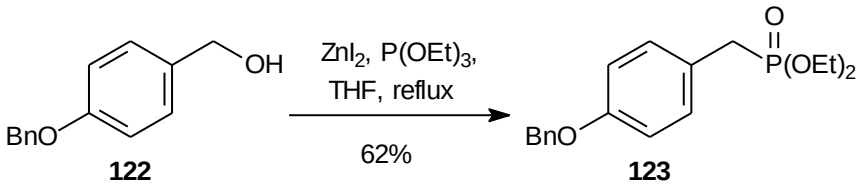
Diethyl 1-phenylethylphosphonate (96). Treatment of the alcohol **95** (0.30 mL, 2.5 mmol, 100% ee) under standard conditions in THF at reflux gave phosphonate **96** (174 mg, 29%) as a colorless oil after purification by column chromatography (55% EtOAc in hexane): 3.4% ee by HPLC; HPLC (Chiralpak AD-H, eluent = 5% *i*PrOH/ 95% *n*-hexane, flow rate = 1.0 mL/min, detector = 215 nm), (*S*) t_1 = 7.45 min; (*R*) t_2 = 8.15 min. $[\alpha]^{25}_D$ = -0.19 (*c* 0.10, CH_3Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.32 (m, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.26–7.22 (m, 1H), 4.07–3.98 (m, 2H), 3.95–3.88 (m, 1H), 3.82–3.74 (m, 1H), 3.17 (dq, J_{HP} = 22.6, *J* = 7.4 Hz, 1H), 1.58 (dd, J_{HP} = 18.5, *J* = 7.4 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 29.7. The ^{1}H NMR spectrum was consistent with literature data.[127, 128]



120 **121**

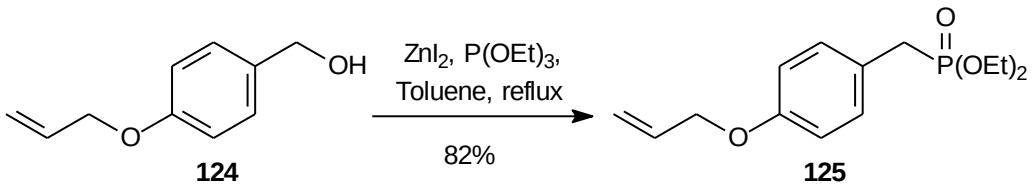
4-(*tert*-Butyldimethylsilyloxy)methyl phosphonic acid, diethyl ester (121). Treatment of alcohol **120** (50 mg, 2.3 mmol) under standard conditions in THF at reflux gave phosphonate **121** (345 mg, 43%) as a colorless oil after purification by column chromatography (45% EtOAc in hexane): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (dd, *J* = 8.9 Hz, J_{HP} = 2.7 Hz, 2H), 6.78 (d, *J* = 8.3 Hz, 2H), 4.01–3.95 (m, 4H), 3.08 (d, J_{HP} = 20.9 Hz, 2H), 1.22 (t, *J* = 6.9 Hz, 6H), 0.97 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5 (d, J_{CP} = 3.8 Hz), 130.6 (d, J_{CP} = 6.6 Hz, 2C), 124.0 (d, J_{CP} = 9.2 Hz),

120.1 (d, J_{CP} = 3.1 Hz, 2C), 61.9 (d, J_{CP} = 6.6 Hz, 2C), 32.8 (d, J_{CP} = 138.8 Hz), 25.6 (3C), 18.1, 16.3 (d, J_{CP} = 6.1 Hz, 2C), –4.6 (2C); ^{31}P NMR (121 MHz, $CDCl_3$) δ 26.8; HRMS (EI^+) calcd for $C_{17}H_{31}O_4PSi$ [M^+] 358.1729; found 358.1732.



122 **123**

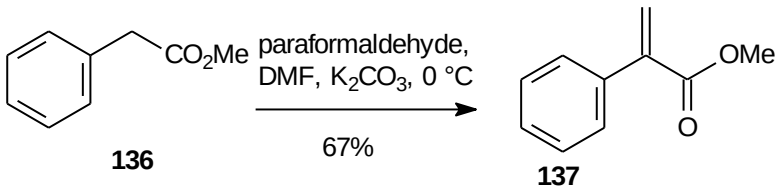
Diethyl 4-(benzyloxy)benzylphosphonate (123). Treatment of the alcohol **122** (0.11 g, 0.50 mmol) under standard conditions in THF at reflux gave phosphonate **123** (0.17 mg, 62%) as a cloudy oil after purification by column chromatography (35% EtOAc in hexane): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.31 (m, 5H), 7.23–7.19 (m, 2H), 6.92 (d, J = 8.4 Hz, 2H), 5.04 (s, 2H), 4.06–3.95 (m, 4H), 3.08 (d, J_{HP} = 20.8 Hz, 2H), 1.24 (t, J = 6.9 Hz, 6H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 26.8. The ^{1}H NMR spectrum was consistent with literature data.[146]



124 **125**

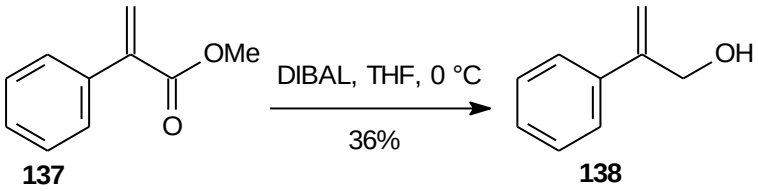
Diethyl 4-(allyloxy)benzylphosphonate (125). Treatment of alcohol **124** (0.10 g, 0.56 mmol) under standard conditions in toluene at reflux gave phosphonate **125** (0.13 mg, 82%) as a yellow oil after purification by column chromatography (35% EtOAc in hexane to EtOAc): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (dd, J_{HP} = 2.5 Hz, J = 8.8 Hz, 2H), 6.86 (d, J = 7.8 Hz, 2H), 6.05 (tdd, J = 5.2, 10.6, 17.2 Hz, 1H), 5.40 (dq, J = 1.6,

17.2 Hz, 1H), 5.27 (dq, J = 1.4, 10.5 Hz, 1H), 4.51 (dt, J = 4.8, 1.5 Hz, 2H), 3.93 (m, 4H), 3.08 (d, J_{HP} = 21.1 Hz, 2H), 1.24 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5 (d, J_{CP} = 3.5 Hz), 133.1, 130.6 (d, J_{CP} = 6.6 Hz, 2C), 123.5 (d, J_{CP} = 9.1 Hz), 117.5, 114.7 (d, J_{CP} = 2.9 Hz, 2C), 68.7, 62.0 (d, J_{CP} = 6.8 Hz, 2C), 32.6 (d, J_{CP} = 139.1 Hz), 16.3 (d, J_{CP} = 6.1 Hz, 2C); ^{31}P NMR (121 MHz, $CDCl_3$) δ 26.8; HRMS (ES^+) calcd for $C_{14}H_{22}O_4P$ [M^+] 285.1256; found: 285.1260.



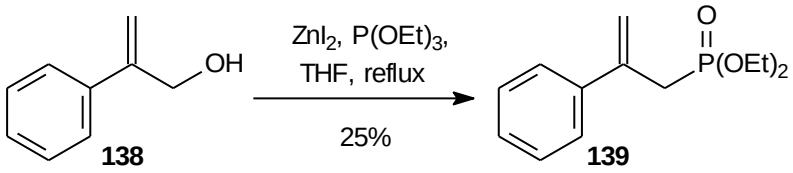
136 **137**

2-Phenylacrylic acid methyl ester (137). To a stirred solution of methyl phenylacetate **136** (1.0 mL, 7.0 mmol) in DMF was added K_2CO_3 (0.70 g, 7.0 mmol) and paraformaldehyde prills (313 mg, 10.4 mmol). After the solution was heated at 100 °C for 3 hours, the reaction was quenched by addition of H_2O and extracted with ether. The combined organic extracts were washed with H_2O and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified via flash column chromatography (24% EtOAc in hexane) to give the desired product **137** as a colorless oil (757 mg, 67%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.39 (m, 2H), 7.37–7.33 (m, 3H), 6.35 (s, 1H), 5.88 (s, 1H), 3.18 (s, 3H). The ^{1}H NMR spectrum was consistent with literature data.[221]



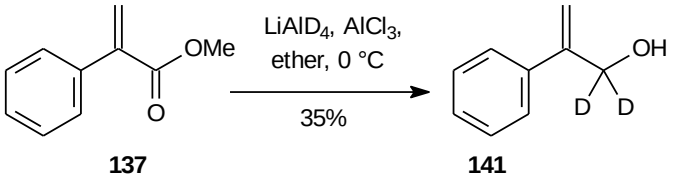
137 **138**

2-Phenyl-2-propen-1-ol (138). To a stirred solution of ester **137** (90 mg, 0.56 mmol) in THF at 0 ºC was added neat DIBAL (0.4 mL, 2.2 mmol) dropwise. The reaction was quenched by addition of H_2O, extracted into EtOAc, washed with 1N HCl until the precipitate dissolved, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified via flash column chromatography (15% EtOAc in hexane) to give the desired product as a colorless oil **138** (27 mg, 36%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.43 (m, 2H), 7.37–7.29 (m, 3H), 5.46 (q, *J* = 1.0 Hz, 1H), 5.34 (q, *J* = 1.4 Hz, 1H), 4.53 (dd, *J* = 1.4, 0.9 Hz, 2H), 1.84 (s, 1H). The ^{1}H NMR spectrum of the product was consistent with the literature data.[222]



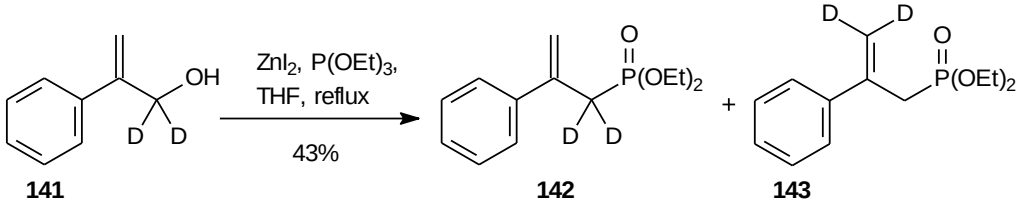
138 **139**

Diethyl 2-phenylallylphosphonate (139). Treatment of the alcohol (19 mg, 0.1 mmol) under standard conditions in THF at reflux gave phosphonate **139** (9 mg, 25%) as a colorless oil after purification by column chromatography (28% EtOAc in hexane): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–7.45 (m, 2H), 7.37–7.27 (m, 3H), 5.52 (d, *J* = 5.5 Hz, 1H), 5.36 (d, *J* = 5.6 Hz, 1H), 4.05–3.94 (m, 4H), 3.07 (d, J_{HP} = 22.1 Hz, 2H), 1.37–1.32 (m, 6H). The ^{1}H NMR spectrum was consistent with literature data.[154]



137 **141**

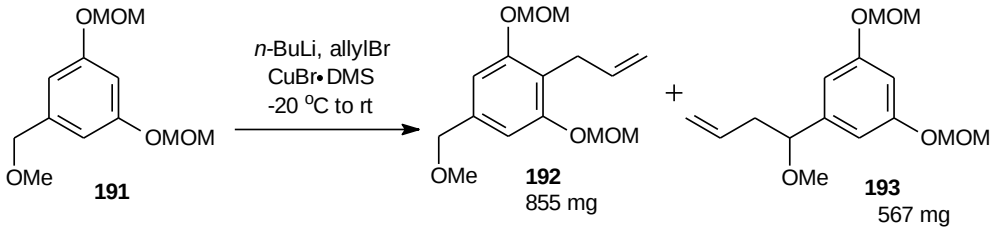
[1,1-D]-2-Phenyl-2-propen-1-ol (141). A solution of $LiAlD_4$ (95 mg, 2.3 mmol) and $AlCl_3$ (100 mg, 0.75 mmol) in THF was allowed to stir for 10 minutes before the addition of ester **137** (120 mg, 0.74 mmol) in THF. After 1.5 hours, the solution was quenched by addition of H_2O, extracted with ether, and the ether extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil was purified via flash column chromatography (15% EtOAc in hexane) to give the desired product **141** as a white solid (35 mg, 35%): ^{1}H NMR (300 MHz, $CDCl_3$) 7.46–7.43 (m, 2H), 7.37–7.29 (m, 3H), 5.48 (d, J = 1.0 Hz, 1H), 5.36 (d, J = 1.1 Hz, 1H), 1.69 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2, 138.5, 128.5 (2C), 127.9, 126.0 (2C), 112.7, 64.3 (t, J_{CD} = 21.8 Hz,); HRMS (EI^+) calcd for $C_9H_8D_2O$ [M^+] 136.0868; found 136.0857.



141 **142** **143**

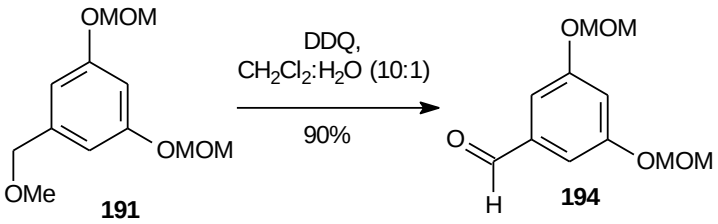
[1,1-D]-Diethyl 2-phenylallylphosphonate (142) and β-(methylene-D2)-Diethyl 2-phenylallylphosphonate (143). Treatment of the alcohol **141** (58 mg, 0.43 mmol) under standard conditions in THF at reflux gave a mixture (56:44) of phosphonate **142** and **143** (12 mg, 11%) as a colorless oil after purification by column chromatography (35% EtOAc in hexane). **For compound 142**: ^{1}H NMR (300 MHz, $CDCl_3$) 7.46–7.43 (m, 2H), 7.37–7.29 (m, 3H), 5.38 (d, J = 1.2, 1H), 5.25 (d, J = 1.5 Hz, 1H), 4.05–3.96 (m, 4H), 1.20 (t, J = 6.9 Hz, 6H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 26.6. **For compound 143**:

^{1}H NMR (300 MHz, $CDCl_3$) 7.49–7.46 (m, 2H), 7.36–7.27 (m, 3H), 4.05–3.96 (m, 4H), 3.07 (d, J_{HP} = 22.3 Hz, 2H), 1.20 (t, J = 6.9 Hz, 6H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 26.4; HRMS (EI^+) calcd for $C_{13}H_{17}D_2O_3P$ [M^+] 256.1197; found: 256.1210.

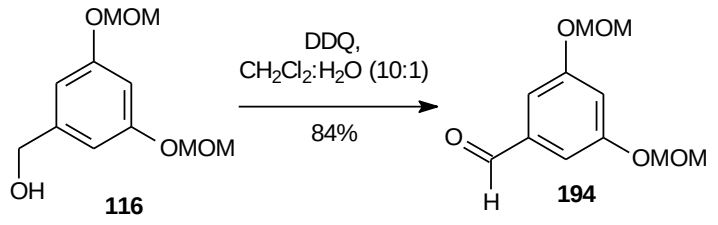


2-Allyl-1,3-bis(methoxymethoxy)-5-(methoxymethyl)benzene (192) and **1-(1-methoxybut-3-enyl)-3,5-bis(methoxymethoxy)benzene (193)**. To a stirred solution of ether **237** (2.66 g, 11.0 mmol) in THF at –20 ºC was added *n*-BuLi (5.8 mL, 13 mmol). After 1 hour CuBr•DMS was added followed by allyl bromide one hour later. The solution was allowed to warm to room temperature and stirred overnight. After the reaction was quenched by the addition of H_2O, it was washed with NH_4Cl and extracted into EtOAc. The organic portions were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting yellow oil was purified via column chromatography (5% EtOAc in hexane) to give the desired product **192** (855 mg, 28%) as an oil and the isomeric product **193** as a pale yellow oil (567 mg, 18%): For compound **192**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (s, 2H), 5.94 (ddt, J = 17.0, 10.0, 6.1 Hz, 1H), 5.17 (s, 4H), 4.97 (dd, J = 17.0, 2.0 Hz, 1H), 4.92 (dd, J = 10.1, 2.0 Hz, 1H), 4.37 (s, 2H), 3.44 (s, 8H) 3.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 137.7, 136.7, 117.39, 114.1, 107.1 (2C), 94.3 (2C), 74.7, 58.1, 55.9 (2C), 27.6. Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.88; H, 7.99. For compound **193**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (t, J = 2.3 Hz, 1H), 6.64 (d, J = 2.2 Hz, 2H), 5.84-5.74 (m, 1H), 5.15 (s, 4H), 5.09-5.01 (m, 2H), 4.10 (dd, J = 7.6, 5.6 Hz, 1H) 3.46 (s, 6H), 3.24 (s, 3H), 2.51-2.40 (m, 2H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 158.44, 144.58, 134.84, 116.85, 108.01 (2C), 103.85, 94.56 (2C), 83.51, 56.78, 56.06 (2C), 42.44. Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 64.04; H, 7.95.

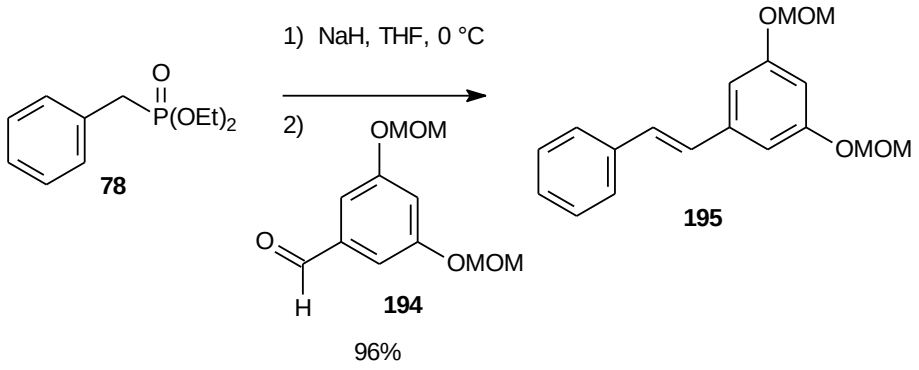


3,5-bis(Methoxymethoxy)benzaldehyde (194). To a stirred solution of ether **191** (1.51 g, 6.22 mmol) in a 10:1 CH_2Cl_2:H_2O solution was added DDQ (2.11 g, 9.31 mmol). The resulting black solution was stirred overnight before it was quenched by addition of water, filtered (celite), extracted into CH_2Cl_2, and washed with saturated $NaHCO_3$ and brine. The organic portion was dried ($MgSO_4$) and concentrated *in vacuo* to give the desired product **194** as an orange oil (1.23 g, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.21 (d, *J* = 2.4 Hz, 2H), 6.98 (t, *J* = 2.4 Hz, 1H), 5.21 (s, 4H), 3.49 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.5, 158.6 (2C), 138.4, 111.0, 110.3 (2C), 94.3 (2C), 56.1 (2C). The ^{1}H NMR spectrum was consistent with literature data.[223]



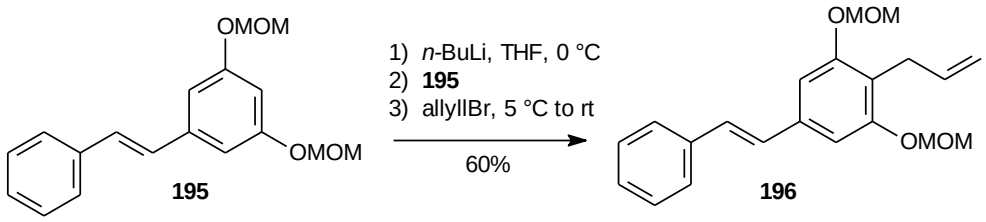
3,5-bis(Methoxymethoxy)benzaldehyde (194). To a stirred solution of alcohol **116** (506 mg, 2.24 mmol) in a 10:1 CH_2Cl_2:H_2O solution was added DDQ (763 mg, 3.36

mmol). The resulting black solution was stirred overnight before it was quenched by addition of water, filtered (celite), extracted with CH_2Cl_2, and washed with saturated $NaHCO_3$ and brine. The organic portion was dried ($MgSO_4$) and concentrated *in vacuo* to give the desired product as a yellow oil **194** (425 mg, 84%). The ^{1}H NMR spectrum was consistent with literature data.[223]

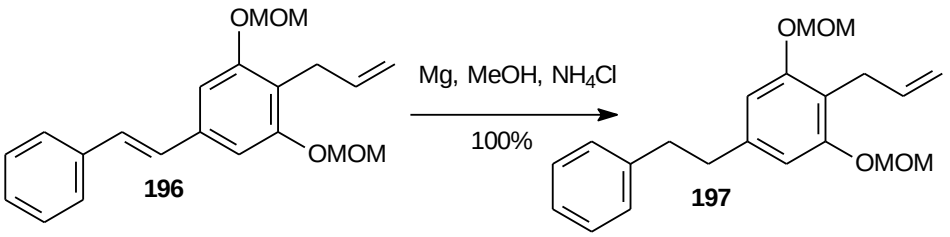


(*E*)-3,5-bis(Methoxymethoxy)stilbene (195). To a stirred solution of 15-crown-5 and NaH (247 mg, 10.3 mmol, 60% dispersion in oil) in THF (20 mL) at 0 °C was added commercially available benzyl phosphonate **78** (0.42 mL, 2.0 mmol) and benzaldehyde **194** (504 mg, 2.23 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. After the solution was quenched by addition of water, it was extracted with EtOAc. After concentration *en vacuo*, the resulting thick, cloudy oil was purified via flash column chromatography (10% EtOAc in hexane) to give the desired product **195** (583 mg, 96%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–7.48 (m, 2H), 7.37–7.32 (m, 2H), 7.27–7.22 (m, 1H), 7.09 (d, *J* = 16.2 Hz, 1H), 7.01 (d, *J* = 16.2 Hz, 1H), 6.88 (d, *J* = 2.1 Hz, 2H), 6.66 (t, *J* = 2.2 Hz, 1H), 5.18 (s, 4H), 3.49 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5 (2C), 139.5, 137.0, 129.3, 128.6 (2C), 128.3, 127.7, 126.5 (2C), 107.8 (C), 104.3, 94.4 (2C), 56.0 (2C); HRMS (EI^+) calcd for $C_{18}H_{20}O_4$ [M^+] 300.1362; found 300.1352. The ^{1}H NMR spectrum was consistent with literature data.[224]

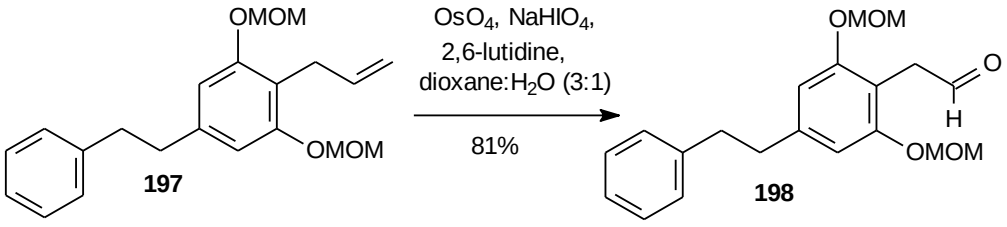
General Experimental Procedure for Directed *ortho*–Metalation (DoM) Reaction. To a stirred solution of *n*–BuLi (1.2–2.7 eq) and additives (1–1.1 eq), when applicable, in THF at 0 ºC was added stilbene **195**. After 35 minutes, allyl bromide (1.2–2.1 eq) was added to the yellow solution, it was allowed to warm to room temperature, and then stirred overnight. The reaction mixture was diluted with EtOAc, washed with water and 2N NaOH, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified via flash column chromatography (4.5% EtOAc in hexane) to give the desired product as a pale yellow oil. Entry 1 in Table 7 was performed at -7 °C in ether. CuI was also added after the stilbene and stirred an additional hour before addition of allyl bromide.



(*E*)-4-Allyl-3,5-bis(methoxymethoxy)stilbene (196). Treatment of stilbene **195** (1.0 g, 3.3 mmol) under standard conditions with *n*–BuLi (2.8 mL, 7.1 mmol) and allyl bromide (0.61 mL, 7.0 mmol) gave compound **88** as a pale yellow oil (684 mg, 60%): ^{1}H NMR (400 MHz, $CDCl_3$) 7.51–7.49 (m, 2H), 7.36–7.32 (m, 2H), 7.26–7.22 (m, 1H), 7.05 (d, J = 0.9 Hz, 2H), 6.96 (d, J = 1.2 Hz, 2H), 6.02–5.92 (m, 1H), 5.23 (s, 4H), 5.00 (dt, J = 17.2, 1.6 Hz, 1H), 4.95 (dt, J = 10.0, 1.6 Hz, 1H), 3.49 (s, 3H), 3.49 (s, 3H), 3.47–3.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9 (2C), 137.2, 136.7, 136.6, 128.7, 128.6 (2C), 128.4, 127.5, 126.4 (2C), 118.0, 114.2, 106.2 (2C), 94.4 (2C), 56.0 (2C), 27.7; HRMS (EI^+) calcd for $C_{21}H_{24}O_4$ [M^+] 340.1675; found 340.1663.



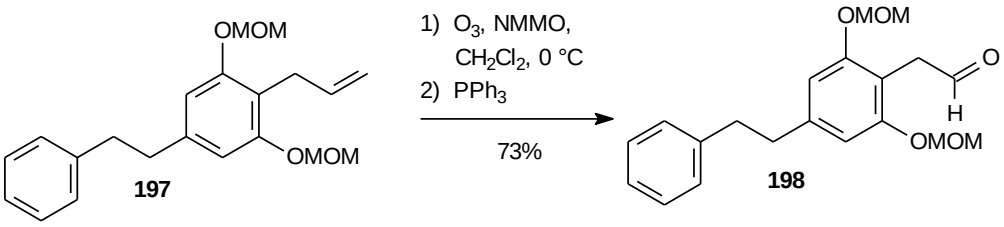
2-Allyl-1,3-bis(methoxymethoxy)phenylethylbenzene (197). To a stirred solution of stilbene **196** (657 mg, 1.93 mmol) in methanol was added ground Mg turnings (1.36 g, 55.8 mmol) and solid NH_4Cl (1.76 g, 32.8 mmol). After the reaction was stirred 72 hours, it was poured into saturated NH_4Cl, extracted with EtOAc, acidified with 1N HCl until the precipitate dissolved, extracted with EtOAc, and the organic extracts were washed with $NaHCO_3$ and brine. The organic portions were combined, dried ($MgSO_4$), and concentrated *in vacuo* to give the desired product **197** as a colorless oil (658 mg, 100%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.24 (m, 2H), 7.21–7.16 (m, 3H), 6.61 (s, 1H), 5.96 (ddt, *J* = 16.9, 9.9, 6.1 Hz, 1H), 5.15 (s, 4H), 5.01–4.91 (m, 2H), 3.46 (s, 6H), 3.43 (dt, *J* = 6.0, 1.5 Hz, 2H), 2.94–2.81 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6 (2C), 141.7, 141.3, 136.9, 128.5 (2C), 128.3 (2C), 125.8, 115.8, 114.0, 108.1 (2C), 94.4 (2C), 56.0 (2C), 38.3, 37.8, 27.5; HRMS (EI^+) calcd for $C_{21}H_{26}O_4$ [M^+] 342.1831; found 342.1835.



2-(2,6-bis(Methoxymethoxy)-4-phenethylphenyl)acetaldehyde (198). Olefin **197** (1.14 g, 3.32 mmol), 2,6-lutidine (0.77 mL, 6.6 mmol), OsO_4 (3.32 mL, 0.02M), and $NaIO_4$ (3.46 g, 16.2 mmol) were dissolved in a dioxane:H_2O solution (3:1). After 4

hours, the reaction was quenched by addition of a CH_2Cl_2: H_2O (2:1) solution, and the combined organic layers were washed with brine and dried ($MgSO_4$). The organic portion was filtered through a fritted funnel with celite and silica layers and then concentrated *in vacuo*. The resulting oil was purified via flash column chromatography (18% EtOAc in hexane) to give the desired product **198** as a cloudy oil (928 mg, 81%). The ^{1}H NMR data were consistent with the corresponding ozonolysis as described below.

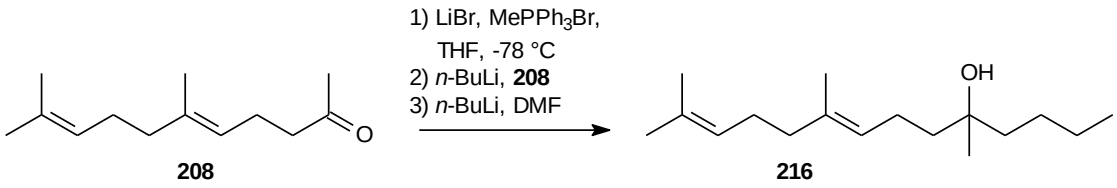
General Experimental Procedure for Ozonolysis. Alkene **197** and additives were dissolved in solvent and the solution was cooled to -78 °C or 0 °C. After oxygen was bubbled through the reaction mixture for 2 minutes, it was treated with ozone until there was no evidence of the starting material by TLC analysis, followed by addition of PPh_3 (1-2 eq). The resulting oil was concentrated *en vacuo* and purified via flash column chromatography (15% EtOAc in hexane) to give the desired aldehyde product as a colorless oil.



2-(2,6-bis(Methoxymethoxy)-4-phenethylphenyl)acetaldehyde (198). Olefin **197** (207 mg, 0.60 mmol) and NMMO (206 mg, 1.76 mmol) were dissolved in distilled CH_2Cl_2 and the solution was cooled to 0 °C and treated under standard reaction conditions. After addition of PPh_3 (148 mg, 0.56 mmol), the resulting oil was concentrated to give the desired product **198** as a colorless oil (151 mg, 73%): ^{1}H NMR (400 MHz, $CDCl_3$) 9.64 (t, J = 2.0 Hz, 1H), 7.30–7.26 (m, 2H), 7.20–7.17 (m, 3H), 6.65

(s, 2H), 5.13 (s, 4H), 3.71 (d, *J* = 1.9 Hz, 2H), 3.43 (s, 6H), 2.90–2.89 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 156.0 (2C), 143.1, 141.4, 128.4 (2C), 128.3 (2C), 125.9, 108.7, 107.9 (2C), 94.4 (2C), 56.1 (2C), 38.5, 38.3, 37.7. Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.51; H, 6.95.

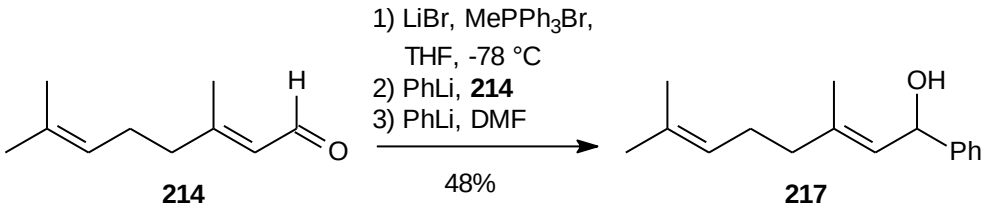
General Experimental Procedure for Modified Wittig. $MePPh_3$ (1.0 eq) and LiBr (2.0 eq) were dissolved in THF and stirred for 10 minutes before being cooled to -78 °C. PhLi (1 eq) or *n*–BuLi (1–1.08 eq) were then added and the solution was stirred an additional 30 minutes at room temperature. After cooling the reaction mixture to -78 °C, the aldehyde or ketone starting material was added and stirred 10–20 minutes before the addition of PhLi (1.05–1.2 eq) or *n*–BuLi (1.05 eq). After it was stirred for 30 minutes, the -78 °C cooling bath was removed with additional stirring at room temperature for 30 minutes. The solution was again cooled to -78 °C before the addition of the electrophile (1.5–8.8 eq) and kept at -78 °C for 30 minutes. After stirring 2.5 hours to overnight at room temperature, the solution was quenched by addition of H_2O, extracted into hexanes, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified via flash column chromatography (5% EtOAc in hexane).



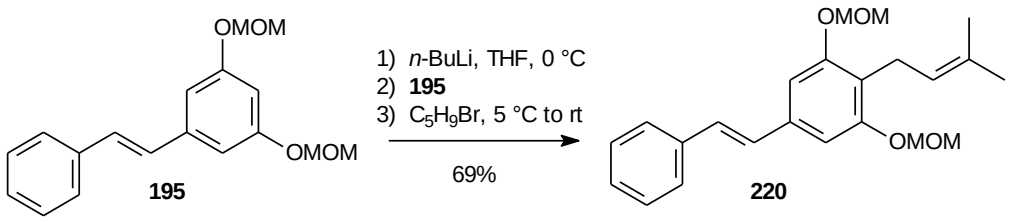
208 **216**

(*E*)-5,9,13-Trimethyltetradeca-8,12-dien-5-ol (216). Ketone **208** (1.0 mL, 4.7 mmol), LiBr (0.81 g, 9.3 mmol), $MePPh_3Br$ (1.67 g, 4.7 mmol), and *n*-BuLi (1.9 mL, 4.56 mmol) were combined according to the standard conditions for the modified Wittig protocol. The second equivalent of *n*–BuLi (1.95 mL, 4.88 mmol) was added after the

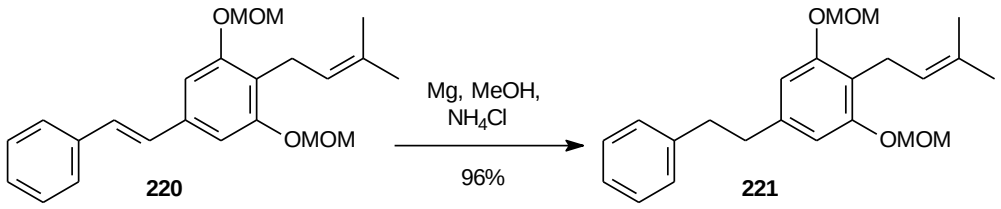
reaction mixture stirred for 10 minutes. After addition of DMF (1.1 mL, 14 mmol), standard work-up afforded alcohol **216** (yield not determined) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) 5.18–5.06 (m, 2H), 2.11–1.96 (m, 6H), 1.69–1.68 (m, 3H), 1.62 (s, 3H), 1.60 (s, 3H), 1.51–1.43 (m, 4H), 1.34–1.29 (m, 4H), 1.16 (s, 3H), 0.92 (t, J = 6.9 Hz, 3H). The known compound **216** has previously been prepared through alternative methods.[225, 226]



(*E*)-3,7-Dimethyl-1-phenylocta-2,6-dien-1-ol (217). Aldehyde **214** (0.25 mL, 1.5 mmol), LiBr (2 eq, 0.25 g, 2.9 mmol), $MePPh_3Br$ (0.52 g, 1.5 mmol), and PhLi (0.83 mL, 1.8 M) were combined according to the standard conditions outlined above for the modified Wittig protocol. The second equivalent of PhLi (0.88 mL, 1.8 M) was added after the reaction mixture was stirred 10 minutes. Addition of DMF (1 mL, 13 mmol) and standard work-up afforded alcohol **217** (162 mg, 48%) as a colorless oil after purification by column chromatography (5% EtOAc in hexane): ^{1}H NMR (300 MHz, $CDCl_3$) 7.40–7.22 (m, 5H), 5.48–5.39 (m, 2H), 5.08–5.03 (m, 1H), 2.12–2.04 (m, 4H), 1.84 (br s, 1H), 1.78 (s, 3H), 1.66 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 138.7, 131.7, 128.4 (2C), 127.5, 127.2, 125.9 (2C), 123.8, 70.6, 39.5, 26.2, 25.6, 17.6, 16.7; HRMS (EI^+) calcd for $C_{16}H_{21}$ [M^+–H_2O] 212.1565; found 212.1582. The ^{1}H NMR spectrum was consistent with literature data for the prenyl analogue.[227]

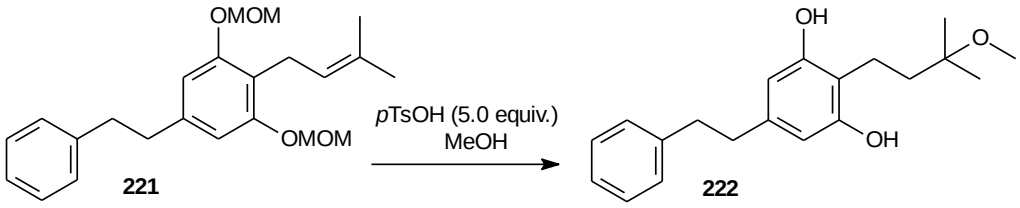


4-Prenyl-3,5-bis(methoxymethoxy)stilbene (220). To a stirred solution of *n*–BuLi (1.1 mL, 2.8 mmol) in THF at 0 ºC was added stilbene **195** (401 mg, 2.34 mmol). After 35 minutes, prenyl bromide (0.19 mL, 1.7 mmol) was added to the yellow solution, it was allowed to warm to room temperature, and then to stir overnight. The reaction mixture was diluted with EtOAc, washed with water and 2N NaOH, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified via flash column chromatography (4.5% EtOAc in hexane) to give the desired product as a pale yellow oil **220** (338 mg, 69%): ^{1}H NMR (400 MHz, $CDCl_3$) 7.50 (d, *J* = 8.4 Hz, 2H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.24 (tt, *J* = 7.3, 1.7 Hz, 1H), 7.04 (s, 2H), 6.94 (s, 2H), 5.24 (s, 4H), 5.23–5.19 (m, 1H), 3.50 (s, 6H), 3.40 (d, *J* = 7.5 Hz, 2H), 1.79 (d, *J* = 0.7 Hz, 3H), 1.66 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8 (2C), 137.3, 136.3, 131.1, 128.8, 128.6 (2C), 128.3, 127.5, 126.5 (2C), 122.7, 119.9, 106.2 (2C), 94.5 (2C), 56.0 (2C), 25.8, 22.8, 17.8; HRMS (EI^+) calcd for $C_{23}H_{28}O_4$ [M^+] 368.1988; found 368.1986.

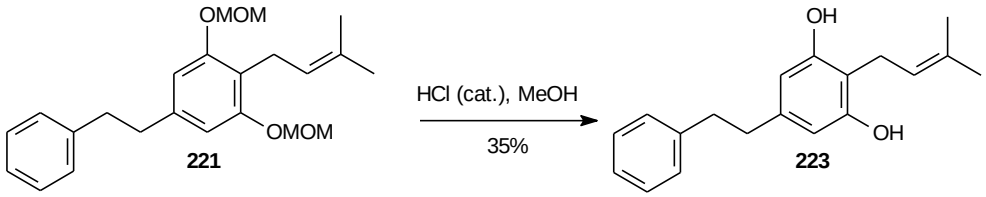


2-Prenyl-1,3-bis(methoxymethoxy)phenylethylbenzene (221). To a stirred solution of stilbene **220** (281 mg, 0.76 mmol) in methanol was added ground Mg turnings (477 mg, 19.6 mmol) and excess NH_4Cl. After the reaction was stirred overnight, it was

poured into saturated NH_4Cl, extracted with EtOAc, acidified with 1N HCl until the precipitate dissolved, extracted with EtOAc, and the extracts were washed with $NaHCO_3$ and brine. The organic portions were combined, dried ($MgSO_4$), and concentrated *in vacuo* to give the desired product **221** as a colorless oil (271 mg, 96%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.25 (m, 2H), 7.20–7.15 (m, 3H), 6.60 (s, 2H), 5.21 (t, *J* = 6.9 Hz, 1H), 5.14 (s, 4H), 3.46 (s, 6H), 3.36 (d, *J* = 6.6 Hz, 2H), 2.93–2.80 (m, 4H), 1.78 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5 (2C), 141.8, 140.8, 130.7, 128.4 (2C), 128.3 (2C), 125.8, 123.1, 117.7, 108.2 (2C), 94.5 (2C), 55.9 (2C), 38.2, 37.8, 25.7, 22.5, 17.7; HRMS (EI$^+$) calcd for $C_{23}H_{30}O_4$ [M^+] 370.2144; found 370.2135.

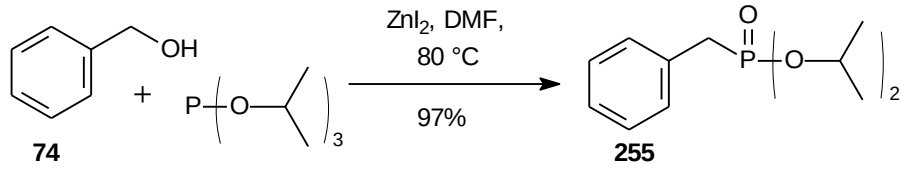


2-(3-Methoxy-3-methylbutyl)-5-phenethylbenzene-1,3-diol (222). To a stirred solution of compound **221** (0.11 g, 0.28 mmol) in MeOH was added *p*TsOH (0.27 g, 1.4 mmol) and the solution was stirred overnight. After addition of H_2O, the solution was extracted with EtOAc, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified via flash column chromatography (10% to 50% EtOAc in hexane) to give the product **222** as an oil (29 mg, 36%): ^{1}H NMR (300 MHz, $CDCl_3$) 7.29–7.25 (m, 2H), 7.20–7.16 (m, 3H), 6.27 (s, 4H), 3.29 (s, 3H), 2.87–2.84 (m, 2H), 2.79–2.75 (m, 2H), 2.68 (t, *J* = 6.9 Hz, 2H), 1.79 (t, *J* = 6.7 Hz, 2H), 1.19 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7 (2C), 141.9, 141.2, 128.4 (2C), 128.3 (2C), 125.8, 113.8, 108.3 (2C), 75.9, 49.5, 41.0, 37.5, 37.5, 24.2 (2C), 16.6; HRMS (EI$^+$) calcd for $C_{20}H_{26}O_3Na$ [M^+Na] 337.1803; found 337.1804.



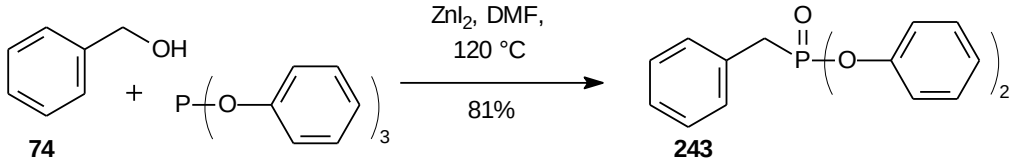
2-(3-Methyl-2-butenyl)-5-phenethylresorcin (223). Protected compound **221** (107 mg, 0.29 mmol) was dissolved in MeOH before the addition of HCl (12 N, 2 drops). After stirring for 2 days at room temperature, the solution was quenched by addition of water and the solvent removed *in vacuo*. The reaction mixture was diluted with EtOAc, washed with $NaHCO_3$, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified via flash column chromatography (6% EtOAc in hexane) to give the desired product as a pale yellow solid **223** (29 mg, 35%): ^{1}H NMR (300 MHz, $CDCl_3$) 7.29–7.23 (m, 2H), 7.19–7.15 (m, 3H), 6.24 (s, 2H), 5.26 (t, J = 7.1 Hz, 1H), 5.02 (s, 2H), 3.38 (d, J = 6.9 Hz, 2H), 2.89–2.83 (m, 2H), 2.78–2.72 (m, 2H), 1.80 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8 (2C), 141.7, 141.5, 135.3, 128.4 (2C), 128.3 (2C), 125.9, 121.7, 110.9, 108.3 (2C), 37.5, 37.4, 25.8, 22.3, 17.9. The ^{1}H NMR spectrum was consistent with literature data.[98, 104]

General Experimental Procedure for Phosphonate Synthesis with Various Phosphites. To a stirred solution of ZnI_2 (1.5 eq) in anhydrous toluene or DMF was added a trialkyl phosphite (3 eq) followed by benzyl alcohol. The reaction mixture was allowed to stir and heated overnight (approximately 12 hours). After it had cooled to room temperature, the reaction mixture was immediately placed on a vacuum line to remove volatiles. The residue then was washed with NaOH until the solids dissolved, extracted with ether, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified via flash column chromatography on silica gel to afford the desired phosphonate.



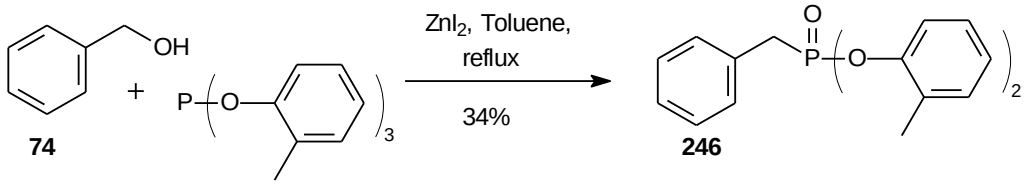
74 **255**

Diisopropyl benzylphosphonate (255). Treatment of the alcohol (0.3 mL, 2.9 mmol) with $P(OC_3H_7)_3$ (2.2 mL, 8.7 mmol) under standard conditions in anhydrous DMF at 80 °C gave phosphonate **255** (0.72 g, 97%) as a pale yellow oil after purification by column chromatography (40% EtOAc in hexane): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.23 (m, 9H), 4.63–4.56 (m, 2H), 3.10 (d, J_{HP} = 21.3 Hz, 2H), 1.21 (dd, J_{HP} = 35.2 Hz, J = 6.2 Hz, 12H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 24.5. The ^{1}H NMR spectrum was consistent with literature data.[197]

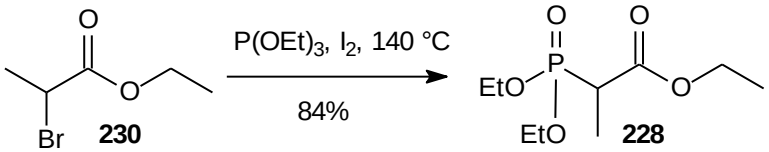


74 **243**

Diphenyl benzylphosphonate (243). Treatment of the alcohol (0.3 mL, 2.9 mmol) with $P(OC_6H_5)_3$ (2.3 mL, 8.8 mmol) under standard conditions in anhydrous DMF at 120 °C gave phosphonate **243** (0.76 g, 81%) as a cloudy oil after work-up and purification by column chromatography (15% EtOAc in hexane): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.20 (m, 9H), 7.10 (d, J = 7.2 Hz, 2H), 7.01 (d, J = 7.8 Hz, 4H), 3.47 (d, J_{HP} = 21.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.4 (d, J_{CP} = 9.2 Hz, 2C), 130.3 (d, J_{CP} = 9.6 Hz), 130.1 (d, J_{CP} = 6.9 Hz, 2C), 129.7 (d, J_{CP} = 0.9 Hz, 4C), 128.7 (d, J_{CP} = 3.2 Hz, 2C), 127.3 (d, J_{CP} = 3.8 Hz), 125.1 (d, J_{CP} = 1.2 Hz, 2C), 120.5 (d, J_{CP} = 4.4 Hz, 4C), 33.8 (d, J_{CP} = 139.2 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 19.5. The ^{1}H NMR spectrum was consistent with literature data.[198]

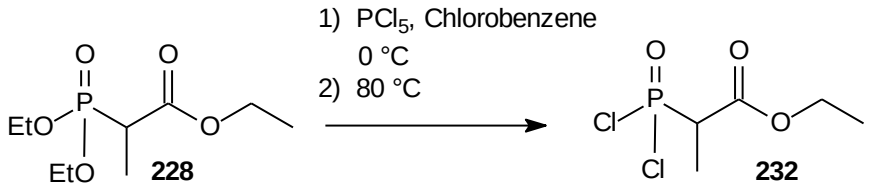


Di-*o*-tolyl Benzylphosphonate (246). Treatment of alcohol **74** (0.1 mL, 1.0 mmol) with tri(*o*-tolyl) phosphite (0.9 mL, 2.9 mmol) under standard conditions in toluene at reflux gave phosphonate **246** (0.11 g, 34%) as a cloudy oil after standard work-up and purification by column chromatography (15% EtOAc in hexane): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.25 (m, 5H), 7.15–7.02 (m, 8H), 3.54 (d, J_{HP} = 21.7 Hz, 2H), 2.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0 (d, J_{CP} = 9.4 Hz, 2C), 131.3 (2C), 130.6 (d, J_{CP} = 9.9 Hz), 130.1 (d, J_{CP} = 6.9 Hz, 2C), 129.3 (d, J_{CP} = 5.6 Hz, 2C), 128.6 (d, J_{CP} = 3.2 Hz, 2C), 127.2 (d, J_{CP} = 3.7 Hz), 127.0 (d, J_{CP} = 1.4 Hz, 2C), 124.9 (d, J_{CP} = 1.1 Hz, 2C), 120.2 (d, J_{CP} = 2.6 Hz, 2C), 34.1 (d, J_{CP} = 139.2 Hz), 16.2 (d, 2C); ^{31}P NMR (121 MHz, $CDCl_3$) δ 19.1; HRMS (ES^+) calcd for $C_{14}H_{22}O_4P$ [M^+] 375.1120; found: 375.1126.

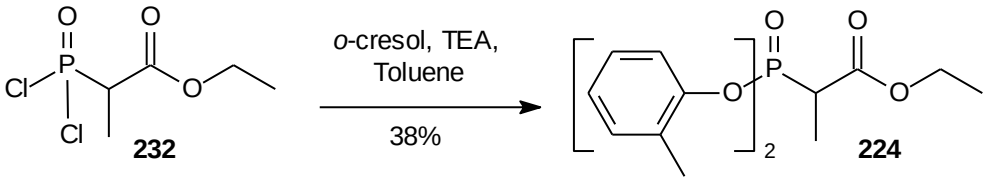


Triethyl 2-phosphonopropionate (228). To a stirred solution of bromide **230** (0.10 mL, 0.77 mmol) and I_2 (10 mg, 0.04 mmol) at 60 °C was added $P(OEt)_3$ (0.15 mL, 0.88 mmol), and the reaction mixture was then heated to 140 °C and stirred overnight. After concentration at low vacuum, the resulting pale yellow oil was purified via flash column chromatography (65% EtOAc in hexane) to give the desired product **228** (154

mg, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27–4.10 (m, 6H), 3.05 (dq, J_{HP} = 23.5, J_{HH} = 7.3 Hz, 1H), 1.49–1.27 (m, 12H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 23.6. The ^{1}H NMR spectrum was consistent with literature data.[60, 199]

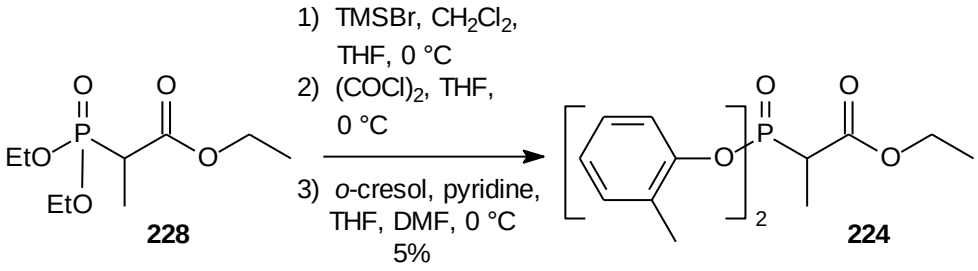


1-Ethoxycarbonylethylphosphonic dichloride (232). To a stirred solution of phosphonate **228** (1 mL, 4.7 mmol) in chlorobenzene at 0 °C was added PCl_5 (2.42 g, 11.6 mmol). After the solution was allowed to stir for 30 minutes, the reaction mixture heated at 80 °C for 8 hours and then was placed on the vacuum line overnight. The deep red solution was then heated to 100 °C (3 mm Hg) on the vacuum line for 1 hour before it was used in the next step without further purification.[60, 61, 192]

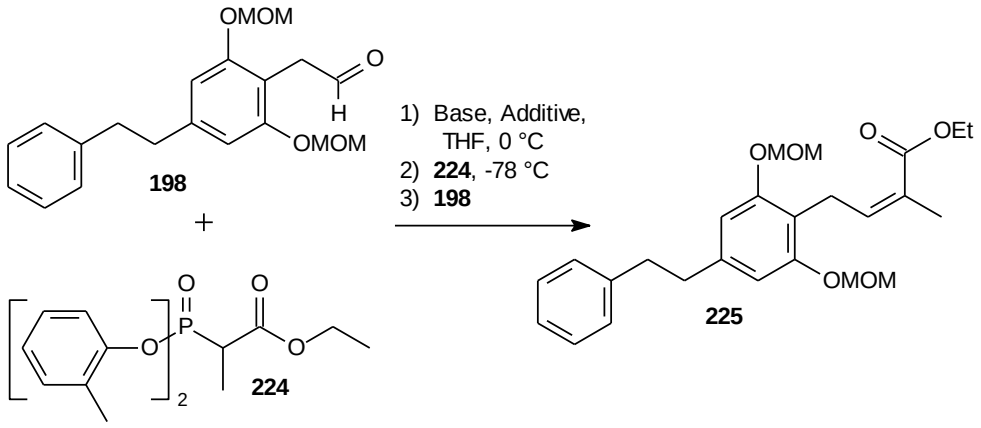


Ethyl 2-(di-*o*-tolylphosphono)propanoate (224). To a stirred solution of dichloride **232** (1.02 g, 4.67 mmol) in toluene was added *o*–tolyl (994 mg, 9.19 mmol) and anhydrous TEA (1.6 mL, 11 mmol). After it was stirred overnight, the solution was filtered (celite), washed with 1N NaOH, NH_4Cl, and brine, and the aqueous solutions were extracted with EtOAc. The organic portions were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting yellow oil was purified via flash column

chromatography (15% EtOAc in hexane) to give the desired product **224** (638 mg, 38%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.25 (m, 2H), 7.19–7.02 (m, 6H), 4.21 (q, J = 7.2 Hz, 2H), 3.43 (dq, J_{PH} = 24.2 Hz, J_{HH} = 7.3 Hz, 1H), 2.25 (s, 3H), 2.22 (s, 3H), 1.69 (dd, J_{HP} = 19.3, J_{HH} = 7.4 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 16.5. The ^{1}H NMR spectrum was consistent with literature data.[199]



Ethyl 2-(di-*o*-tolylphosphono)propanoate (224). To a stirred solution of phosphonate **228** (0.5 mL, 2.3 mmol) in CH_2Cl_2 at 0 °C was added TMSBr (1.0 mL, 7.7 mmol). After the solution was allowed to stir for 15 minutes, the reaction mixture was placed on the vacuum line for 1 hour before it was used in the next step without further purification. The reaction mixture was then dissolved in CH_2Cl_2 and DMF and oxalyl chloride (0.81 mL, 9.29 mmol) was added. After the solution was allowed to stir for 1 hour, it was placed on the vacuum line for 1 hour before being used in the next step without further purification. The crude dichloride was then dissolved in THF at 0 °C and *o*–tolyl (559 mg, 5.17 mmol) and pyridine (0.49 mL, 6.1 mmol) were added. After it was stirred overnight, the solution was filtered (celite), washed with 1N NaOH, NH_4Cl, and brine, and the aqueous solutions were extracted with EtOAc. The organic portions were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting reddish–brown oil was purified via flash column chromatography (15% EtOAc in hexane) to give the desired product **224** (43 mg, 5%). The ^{1}H NMR data were consistent with the corresponding phosphonate as described above.

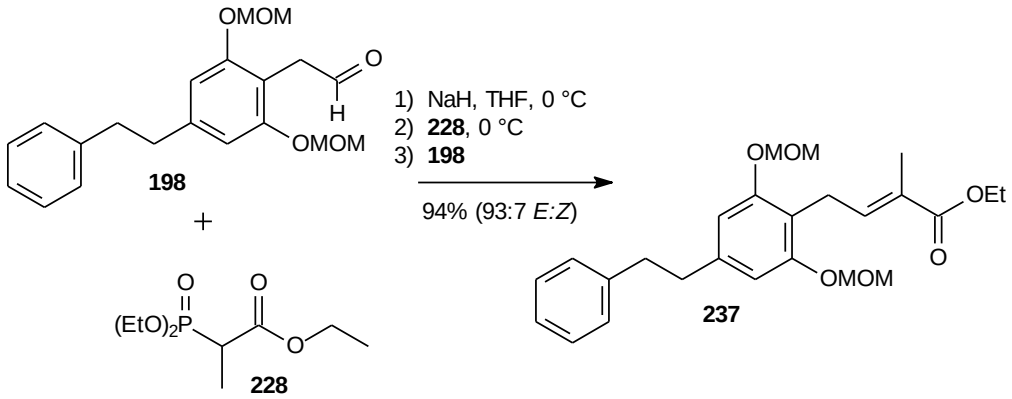


General Experimental Procedure for the Ando Modification to the HWE Reaction. To a stirred solution of base and additives (when applicable, see Table 7) in THF (0.01 M) at –78 °C was added phosphonate **224** (1.2 eq). The reaction mixture was stirred 15–20 minutes before aldehyde **198** was added. Temperature conditions as described in Table 7 (Page 77) were then followed until the reaction was quenched by the addition of NH_4Cl, extracted with EtOAc, and the extracts washed with H_2O and brine. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting pale yellow oil was purified via flash column chromatography (7% EtOAc in hexane) to give the desired product **225**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.24 (m, 2H), 7.20–7.15 (m, 3H), 6.60 (s, 2H), 5.88 (t, *J* = 6.8 Hz, 1H), 5.12 (s, 4H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.87 (d, *J* = 6.4 Hz, 2H), 3.44 (s, 6H), 2.90–2.85 (m, 4H), 1.87 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 155.8 (2C), 141.6, 141.5, 141.2, 128.4 (2C), 128.3 (2C), 126.4, 125.8, 116.3, 108.2 (2C), 94.5 (2C), 60.0, 56.0, 55.9, 38.2, 37.7, 24.1, 20.5, 14.4; HRMS (EI^+) calcd for $C_{25}H_{32}O_6Na[M^+]$ 451.2097; found: 451.2097.

Entry	Base (equiv.)	Additive (equiv.)	Entry	Base (equiv.)	Additive (equiv)
1	[a]KHMDS	18-Crown-6 (5.2)	14	[a]NaH (2.2)	NA
2	[a]KHMDS	18-Crown-6 (4.5)	15	[a]NaH (1.6)	NA
3	*t*BuOK (1.5)	NA	16	[a]NaH (5.2)	NA
4	*t*BuOK (1.5)	NA	17	[a]NaH (1.6)	NaI (5.0)
5	*t*BuOK (1.5)	NA	18	[a]NaH (2.3)	LiBr (1.0)
6	*t*BuOK (1.5)	NA	19	[a]NaH (1.9)	15-Crown-5 (5.1)
7	*t*BuOK (2.4)	18-Crown-6 (5.0)	20	[a]NaH (2.5)	18-Crown-6 (3.0)
8	TMG (1.3)	NaI (4.7)	21	[a]NaH (1.8)	18-Crown-6 (5.1)
9	[a]Triton B (1.3)	NA	22	[a]NaH (1.8 and	18-Crown-6 (5.1)
10	[a]NaH (1.5)	NA	23	[a]NaH (2.1)	18-Crown-6 (5.0)
11	[a]NaH (1.6)	NA	24	[a]NaH (1.9)	18-Crown-6 (4.8)
12	[a]NaH (1.6)	NA	25	[a]NaH (2.5)	18-Crown-6 (2.9)
13	[a]NaH (1.6)	NA	26	DBU (2.3)	NaI (1.6)

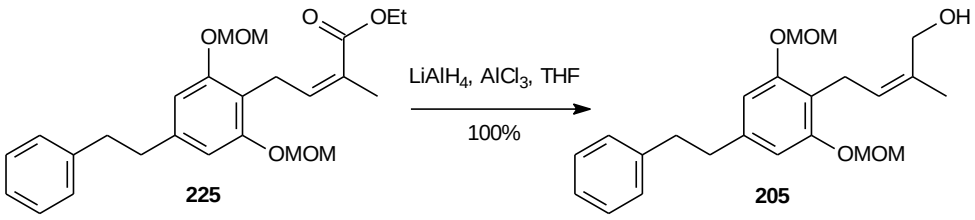
[a]KHMDS was used as a 0.5M solution, NaH was used as a 60% dispersion in oil, and Triton B was used as a 40% solution in MeOH.

Table 11. Stoichiometry used in studies of the Ando modification to the HWE reaction.



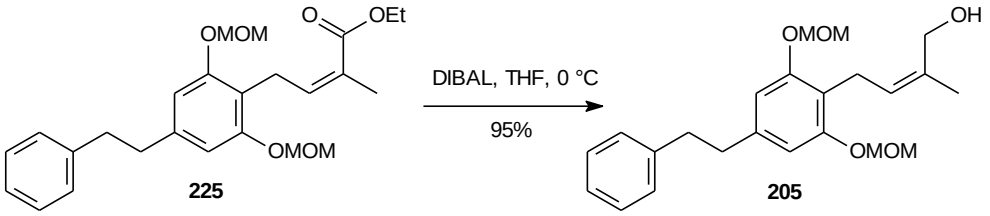
Ethyl (*E*)-4-(2,6-bis(methoxymethoxy)phenethylphenyl)-2-methylbut-2-enoate (52). To a stirred solution of NaH (15 mg, 0.63 mmol, 60% dispersion in oil) in THF (5 mL) at 0 °C was added phosphonate **228** (96 mg, 0.40 mmol). The reaction mixture was stirred 20 minutes before aldehyde (**198**, 101 mg, 0.29 mmol) was added. After 80 minutes at 0 °C, the solution was quenched by the addition of H_2O. Standard

work-up and purification by column chromatography gave the desired product **148** as a white solid (119 mg, 94%, 93:7 *E*:*Z*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.26 (m, 2H), 7.22–7.19 (m, 3H), 6.80 (t, *J* = 7.4 Hz, 1H), 6.61 (s, 2H), 5.17 (s, 4H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.54 (d, *J* = 7.6 Hz, 2H), 3.46 (s, 6H), 2.95–2.83 (m, 4H), 2.00 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 155.7 (2C), 141.8, 141.6, 140.8, 128.5 (2C), 128.3 (2C), 127.1, 125.9, 114.7, 107.8 (2C), 94.4 (2C), 60.3, 56.0 (2C), 38.3, 37.8, 23.2, 14.2, 12.3; HRMS (EI^+) calcd for $C_{25}H_{32}O_6Na[M^+]$ 451.2097; found: 451.2101.

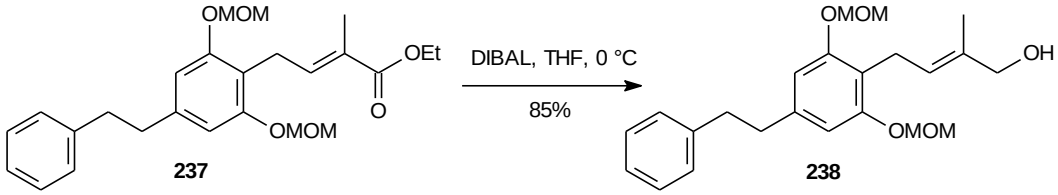


(*Z*)-4-(2,6-bis(Methoxymethoxy)-4-phenethylphenyl)-2-methylbut-2-en-1-ol (205). A solution of $LiAlH_4$ (87 mg, 2.3 mmol) and $AlCl_3$ (101 mg, 0.76 mmol) in THF was allowed to stir for 10 minutes before the addition of ester **225** (324 mg, 0.76 mmol) in THF. The resulting solution was quenched by addition of ice/H_2O, extracted with ether, washed with brine, dried ($CaCO_3$), and concentrated *in vacuo*. The resulting cloudy oil **205**, which sometimes contained trace amounts of the isomeric *E*-olefin, was carried onto the next step without further purification (291 mg, 100%): ^{1}H NMR (300 MHz, $CDCl_3$) 7.30–7.24 (m, 2H), 7.20–7.16 (m, 3H), 6.60 (s, 2H), 5.36 (t, *J* = 7.3 Hz, 1H), 5.16 (s, 4H), 4.26 (s, 2H), 3.48 (s, 3H), 3.48 (s, 3H), 2.45–3.41 (m, 2H), 2.89–2.82 (m, 4H), 1.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4 (2C), 141.6, 141.4, 134.2, 128.4 (2C), 128.4 (2C), 126.3, 125.9, 116.5, 108.4 (2C), 94.8 (2C), 61.6, 56.2 (2C), 38.2, 37.7, 22.2, 21.8; HRMS (ES^+) calcd for $C_{23}H_{30}O_5Na$ $[M^+]$ 409.2006; found: 409.1991.

General Experimental Procedure for DIBAL Reduction. To a stirred solution of ester **225** or **237** in THF at 0 ºC was added DIBAL (2.5 eq) dropwise. After 10 minutes, the reaction was quenched by addition of H_2O, extracted into EtOAc, washed with 1N HCl until the precipitate dissolved, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified via flash column chromatography to give the desired alcohol product.

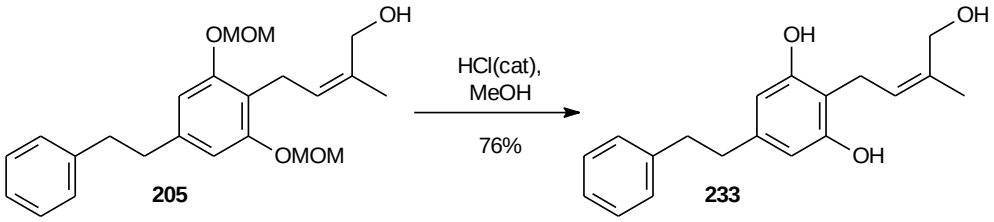


(*Z*)-4-(2,6-bis(Methoxymethoxy)-4-phenethylphenyl)-2-methylbut-2-en-1-ol (205). Ester **225** (148 mg, 0.35 mmol) was treated with DIBAL (0.15 mL, 0.84 mmol) under standard DIBAL reduction conditions to give the desired product as a colorless oil **205** (126 mg, 95%) that was used without further purification. The ^{1}H NMR data were consistent with that of material determined from the corresponding allane reduction as described above.

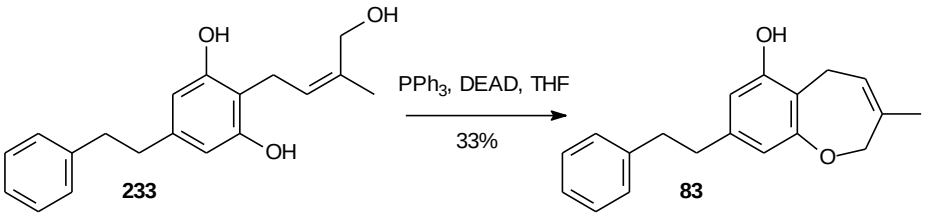


(*E*)-4-(2,6-bis(Methoxymethoxy)-4-phenethylphenyl)-2-methylbut-2-en-1-ol (238). Ester **237** (110 mg, 0.26 mmol) was treated with DIBAL (0.12 mL, 0.67 mmol) under standard DIBAL reduction conditions to give the desired product as a colorless oil

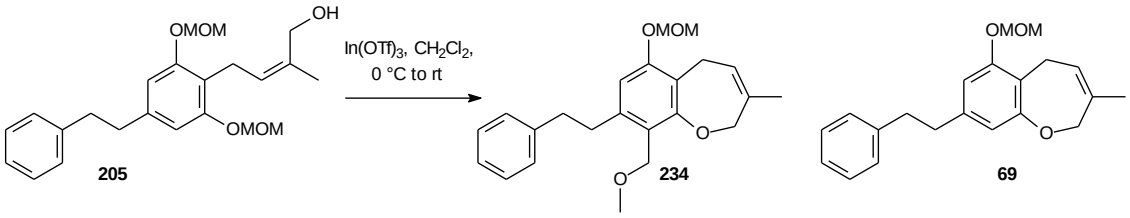
238 (84 mg, 85%) after purification via flash column chromatography (22% EtOAc in hexane): ^{1}H NMR (300 MHz, $CDCl_3$) 7.30–7.25 (m, 2H), 7.21–7.18 (m, 3H), 6.60 (s, 2H), 5.50 (t, *J* = 7.1 Hz, 1H), 5.15 (s, 4H), 3.96 (s, 2H), 3.47 (s, 6H), 3.42 (d, *J* = 7.0 Hz, 2H), 2.92–2.83 (m, 4H), 1.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6 (2C), 141.7, 141.2, 134.2, 128.5 (2C), 128.3 (2C), 125.9, 124.9, 116.8, 108.1 (2C), 94.5 (2C), 69.1, 56.0 (2C), 38.2, 37.8, 22.2, 13.7; HRMS (ES^+) calcd for $C_{23}H_{31}O_5$ [M^+] 387.2162; found: 387.2171.



(Z)-2-(4-Hydroxy-3-methylbut-2-enyl)-5-phenethylbenzene-1,3-diol (233). Protected compound **205** (76 mg, 0.20 mmol) was dissolved in MeOH before the addition of HCl (12N, 3 drops). After stirring for 4 days at room temperature, the solution was quenched by addition of water and the solvent was removed *in vacuo*. The reaction mixture was diluted with EtOAc, washed with H_2O, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified via flash column chromatography (15% to 25% EtOAc in hexane) to give the desired product as a pale yellow oil (45 mg, 76%): ^{1}H NMR (300 MHz, $CDCl_3$) 7.27–7.24 (m, 2H), 7.20–7.15 (m, 3H), 6.25 (s, 2H), 5.45 (t, *J* = 8.1 Hz, 1H), 4.28 (s, 2H), 3.45 (d, *J* = 8.0 Hz, 2H), 2.87–2.80 (m, 2H), 2.76–2.70 (m, 2H), 1.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6 (2C), 141.8, 141.5, 133.4, 128.3 (2C), 128.3 (2C), 127.1, 125.9, 110.9, 108.3 (2C), 62.3, 37.4, 22.8, 22.3, 21.0, 14.1. The compound has been reported but spectral data were unavailable.[20, 103169]

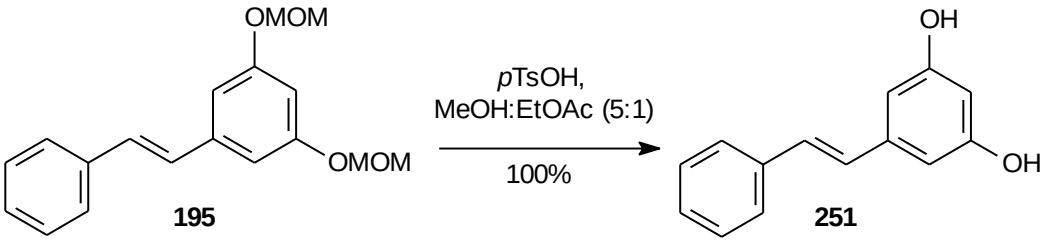


Radulanin A (83). To a stirred solution of alcohol **233** (45 mg, 0.15 mmol) and PPh_3 (79 mg, 0.30 mmol) in THF (0.8 mL) was added DEAD (0.5 mL, 0.3 mmol) in THF (0.7 mL). After stirring overnight, the solution was quenched by addition of H_2O, extracted with ether, dried ($CaCO_3$), and concentrated *in vacuo*. The resulting oil was purified via flash column chromatography (4% EtOAc in hexane) to give the desired product as a yellow-orange oil (14 mg, 33%): ^{1}H NMR (300 MHz, $CDCl_3$) 7.30–7.24 (m, 2H), 7.20–7.15 (m, 3H), 6.52 (d, *J* = 1.2 Hz, 1H), 6.36 (d, *J* = 1.6 Hz, 1H), 5.63–5.58 (m, 1H), 4.73 (br s, 1H), 4.40 (s, 2H), 3.41–3.39 (m, 2H), 2.91–2.85 (m, 2H), 2.82–2.76 (m, 2H), 1.54 (s, 3H). The ^{1}H NMR spectrum was consistent with literature data.[103]



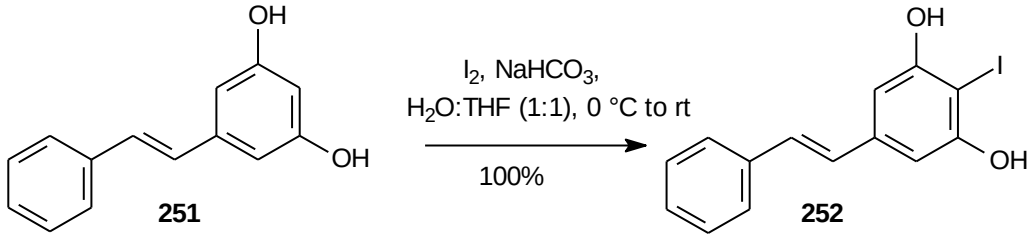
(*Z*)-6-(Methoxymethoxy)-9-(methoxymethyl)-3-methyl-8-phenethyl-2,5-dihydrobenzo(*b*)oxepine (234) and (*Z*)-6-(Methoxymethoxy)-3-methyl-8-phenethyl-2,5-dihydrobenzo(*b*)oxepine (69). To a stirred solution of alcohol **205** (9 mg, 0.02 mmol, Z:E 65:35) in CH_2Cl_2 (2.5 mL) at 0 °C was added $In(OTf)_3$ (21 mg, 0.04 mmol). After 8 hours, the solution was quenched by addition of H_2O, extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified via flash preparative thin layer chromatography (30% EtOAc in hexane) to give the EAS product

234 as a yellow oil (1 mg, 11%, 14% BRSM) and the cyclized product **69** as a yellow oil (2 mg, 25%, 34% BRSM): For compound **234** ^{1}H NMR (500 MHz, $CDCl_3$) 7.29–7.26 (m, 2H), 7.20–7.19 (m, 3H), 6.60 (s, 1H), 5.45 (t, *J* = 6.7 Hz, 1H), 5.15 (s, 2H), 4.68 (s, 2H), 4.28 (s, 2H), 3.46 (s, 3H), 3.45–3.42 (m, 2H), 3.43 (s, 3H), 2.91–2.82 (m, 4H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5 (2C), 141.7, 141.2, 130.9, 128.5 (2C), 128.3 (2C), 128.0, 125.9, 116.6, 108.0, 95.5, 94.5, 65.8, 56.0 (2C), 55.2, 38.3, 37.8, 22.3, 21.7. HRMS (ES^+) calcd for $C_{23}H_{29}O_4$ [M^+] 369.2065; found: 369.2066; For compound **69** ^{1}H NMR (500 MHz, $CDCl_3$) 7.29–7.26 (m, 2H), 7.21–7.15 (m, 3H), 6.48 (s, 1H), 6.45 (s, 1H), 5.44 (t, *J* = 7.5 Hz, 1H), 5.16 (s, 2H), 4.21 (s, 2H), 3.48 (s, 3H), 3.47–3.46 (m, 2H), 2.91–2.80 (m, 4H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 155.5, 141.9, 141.7, 130.8, 128.7, 128.4 (2C), 128.3 (2C), 125.8, 112.6, 110.3, 106.4, 95.6, 66.5, 56.1, 37.9, 37.7, 22.9, 22.6. The ^{1}H NMR spectrum was consistent with literature data.[103]



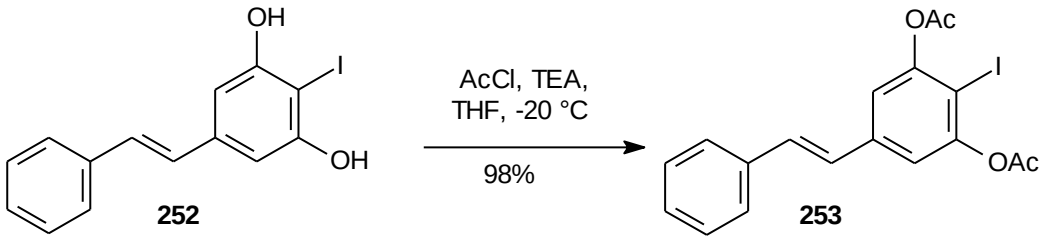
(*E*)-3,5-Dihydroxystilbene (251). The protected compound **195** (0.50 g, 1.7 mmol) was dissolved in a 5:1 MeOH:EtOAc solution before addition of *p*TsOH monohydrate (1.69 g, 8.90 mmol). After stirring overnight, the reaction mixture was quenched by addition of H_2O. The solution was then extracted with EtOAc, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified via flash column chromatography (35% EtOAc in hexane) to give the product **251** as an off-white solid (355 mg, 100%): ^{1}H NMR (300 MHz, $CDCl_3$) 7.49 (d, *J* = 6.7 Hz, 2H), 7.36 (t, *J* = 7.3 Hz, 2H), 7.29 (t, *J* = 1.3 Hz, 1H), 7.06 (d, *J* = 15.8 Hz, 1H), 7.0 (d, *J* = 16.0 Hz, 1H), 6.58

(d, *J* = 2.1 Hz, 2H), 6.27 (t, *J* = 2.4 Hz, 1H). The ^{1}H NMR spectrum was consistent with literature data.[228]



251 **252**

(*E*)-4-Iodo-3,5-dihydroxystilbene (252). Stilbene **251** (68 mg, 0.32 mmol) was dissolved in a 1:1 H_2O:THF solution before addition of I_2 (92 mg, 0.36 mmol) at 0 °C. $NaHCO_3$ was then added in portions and the solution was allowed to warm to room temperature over 10 minutes. After it was stirred for an additional 10 minutes, the reaction mixture was diluted with EtOAc, washed with brine, and dried ($MgSO_4$). The residue was concentrated *in vacuo* to give the desired product **252** as pale yellow needles (108 mg, 100%): ^{1}H NMR (300 MHz, $(CD_3)_2CO$) 8.84 (s, 2H), 7.57 (d, *J* = 5.6 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.26 (t, *J* = 7.4, 1H), 7.14 (d, *J* = 16.6 Hz, 1H), 7.07 (d, *J* = 16.2 Hz, 1H), 6.73 (s, 2H). The ^{1}H NMR spectrum was consistent with literature data.[229]



252 **253**

(*E*)-4-Iodo-3,5-diacetoxystilbene (253). To a stirred solution of stilbene **252** (47 mg, 0.14 mmol) in THF at 0 °C was added TEA (0.08 mL, 0.6 mmol) and acetyl chloride (0.02 mL, 0.3 mmol). After it was stirred for 30 minutes, the solution was quenched by

the addition of NH_4Cl, extracted with EtOAc, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified via flash column chromatography (10% EtOAc in hexane) to give the desired product as a white solid (58 mg, 98%): ^{1}H NMR (300 MHz, $CDCl_3$) 7.48 (d, *J* = 6.8 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.30 (d, *J* = 7.3 Hz, 1H), 7.14 (s, 2H), 7.08 (d, *J* = 16.2 Hz, 1H), 7.03 (d, *J* = 16.2 Hz, 1H), 2.39 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3 (2C), 152.7 (2C), 139.7, 136.4, 131.4, 128.8 (2C), 128.3, 126.8 (2C), 126.1, 118.2 (2C), 86.4, 21.2 (2C); HRMS (ES^+) calcd for $C_{18}H_{15}IO_4$ [M^+] 444.9921; found: 444.9913.

APPENDIX
SELECTED NMR SPECTRA

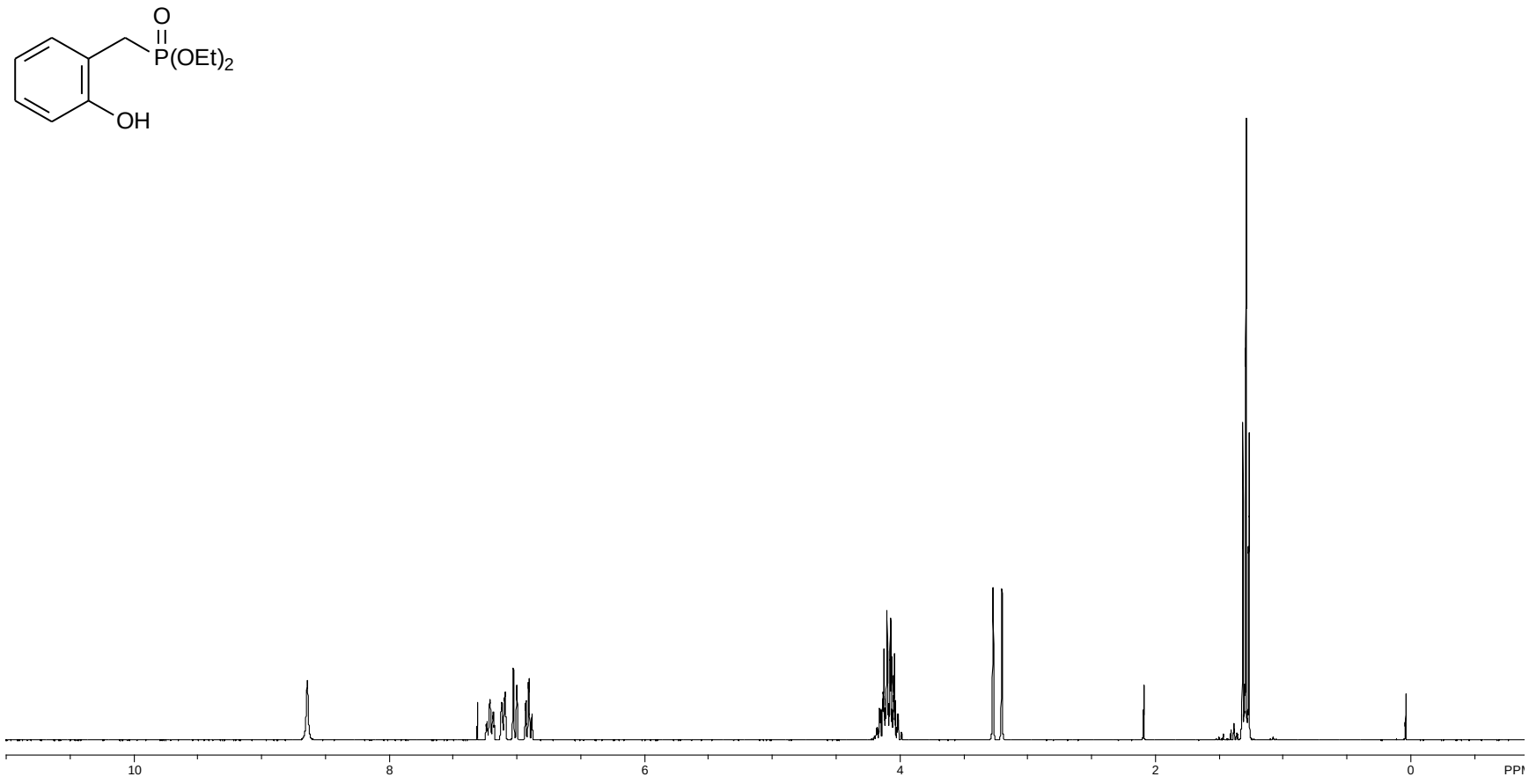


Figure A1. 300 MHz ^{1}H NMR Spectrum of Compound **90**.

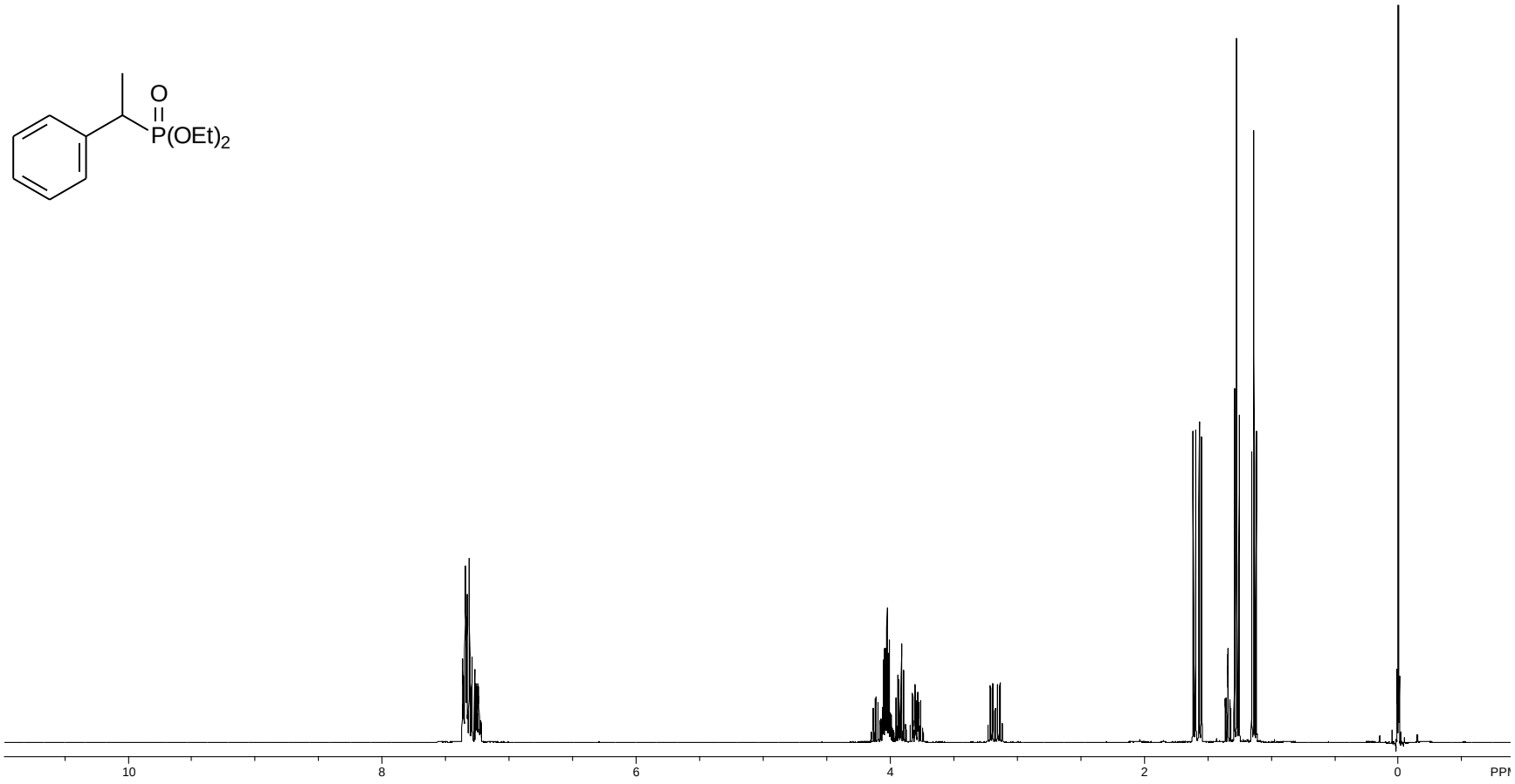


Figure A2. 400 MHz ^{1}H NMR Spectrum of Compound **96**.

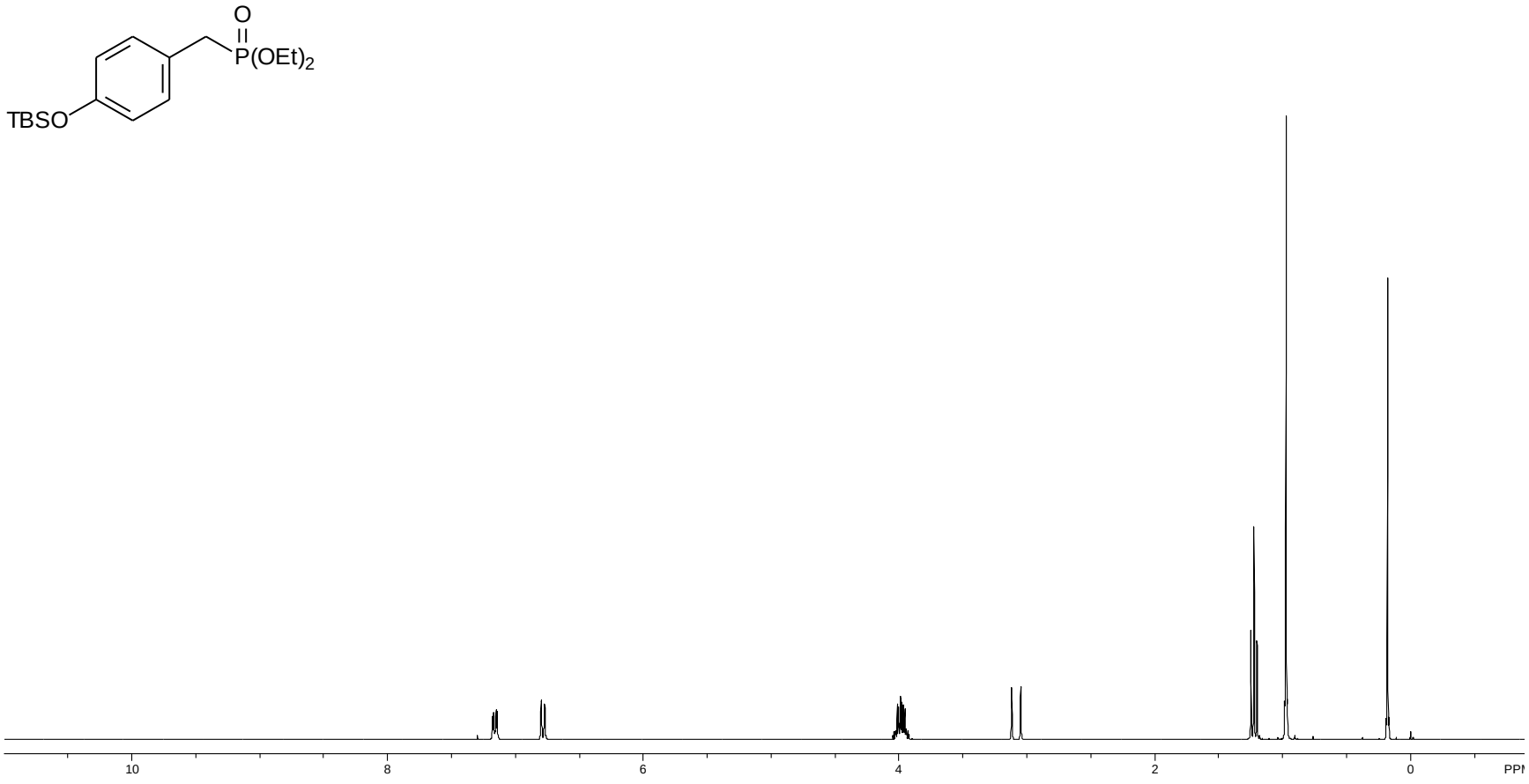


Figure A3. 300 MHz ^{1}H NMR Spectrum of Compound **121**.

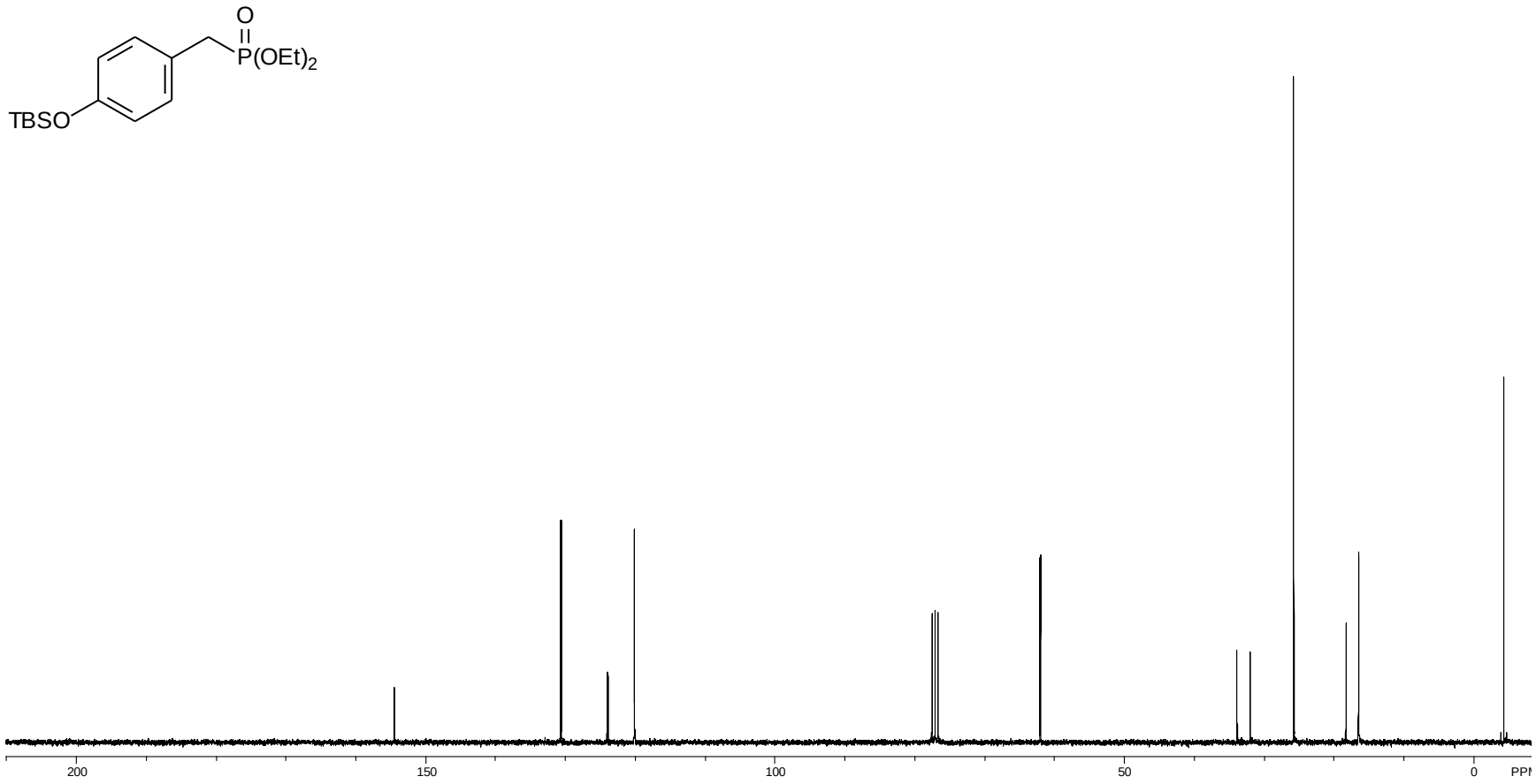


Figure A4. 75 MHz ^{13}C NMR Spectrum of Compound **121**.

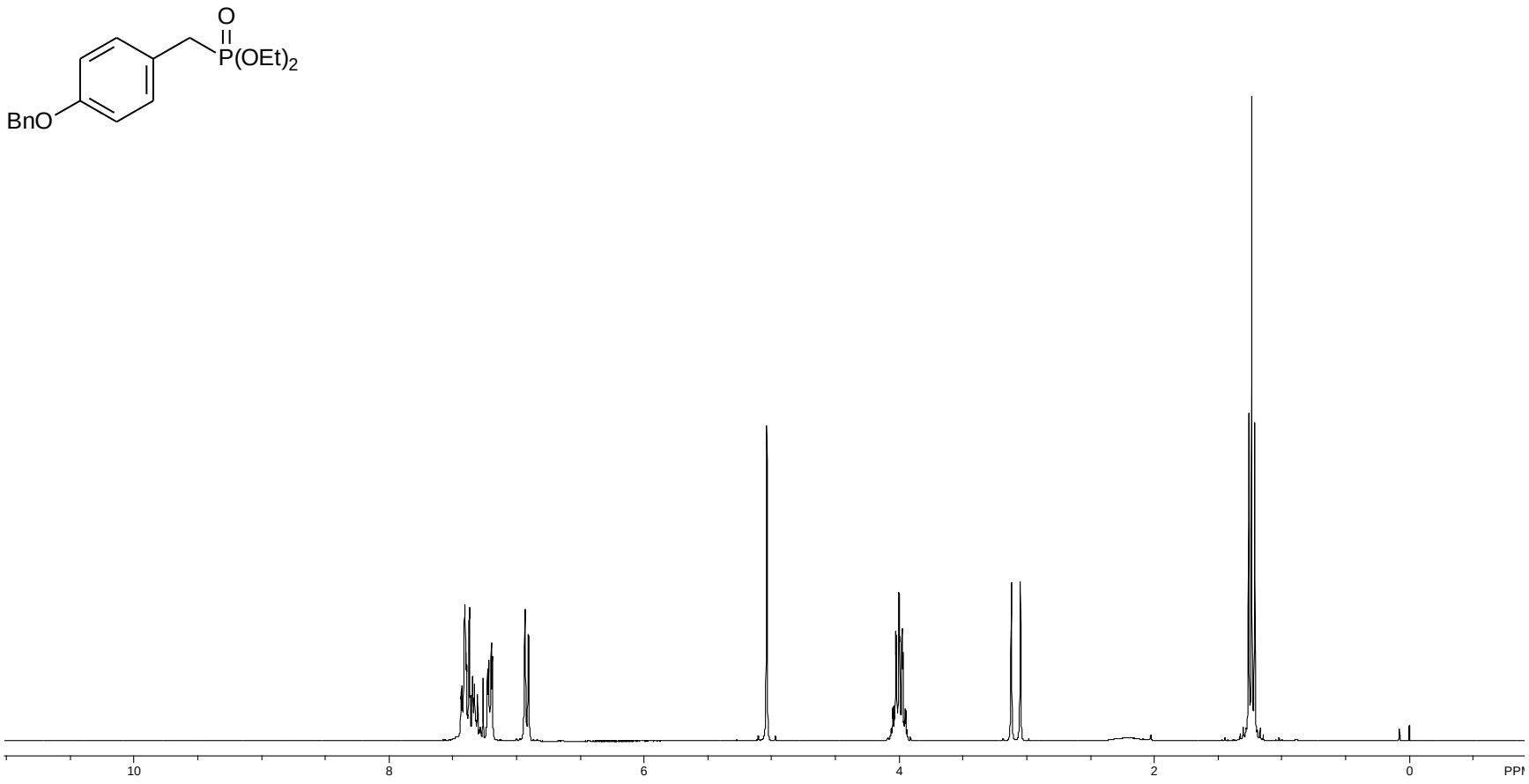


Figure A5. 300 MHz ^{1}H NMR Spectrum of Compound **123**.

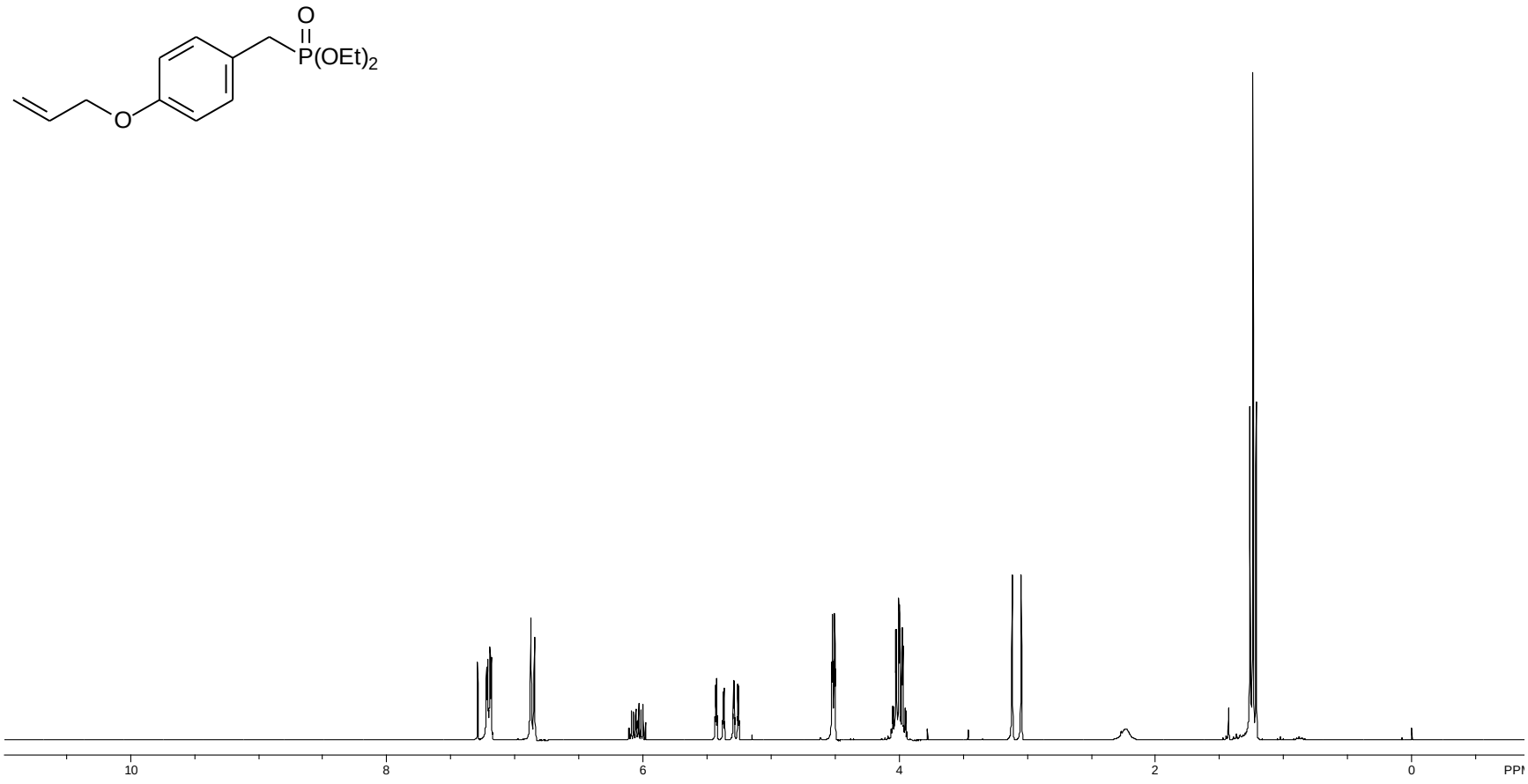


Figure A6. 300 MHz ^{1}H NMR Spectrum of Compound **125**.

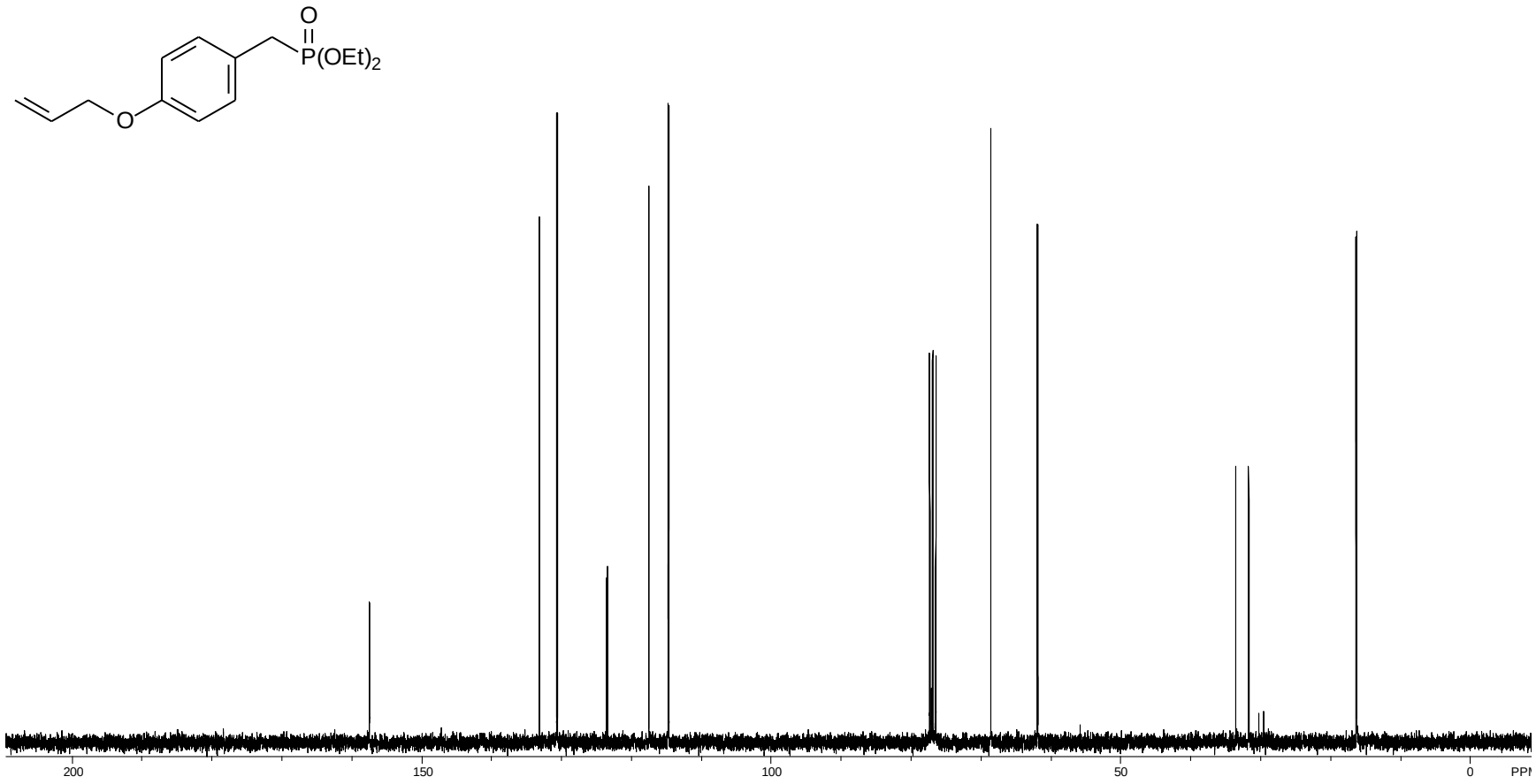


Figure A7. 75 MHz ^{13}C NMR Spectrum of Compound **125**.

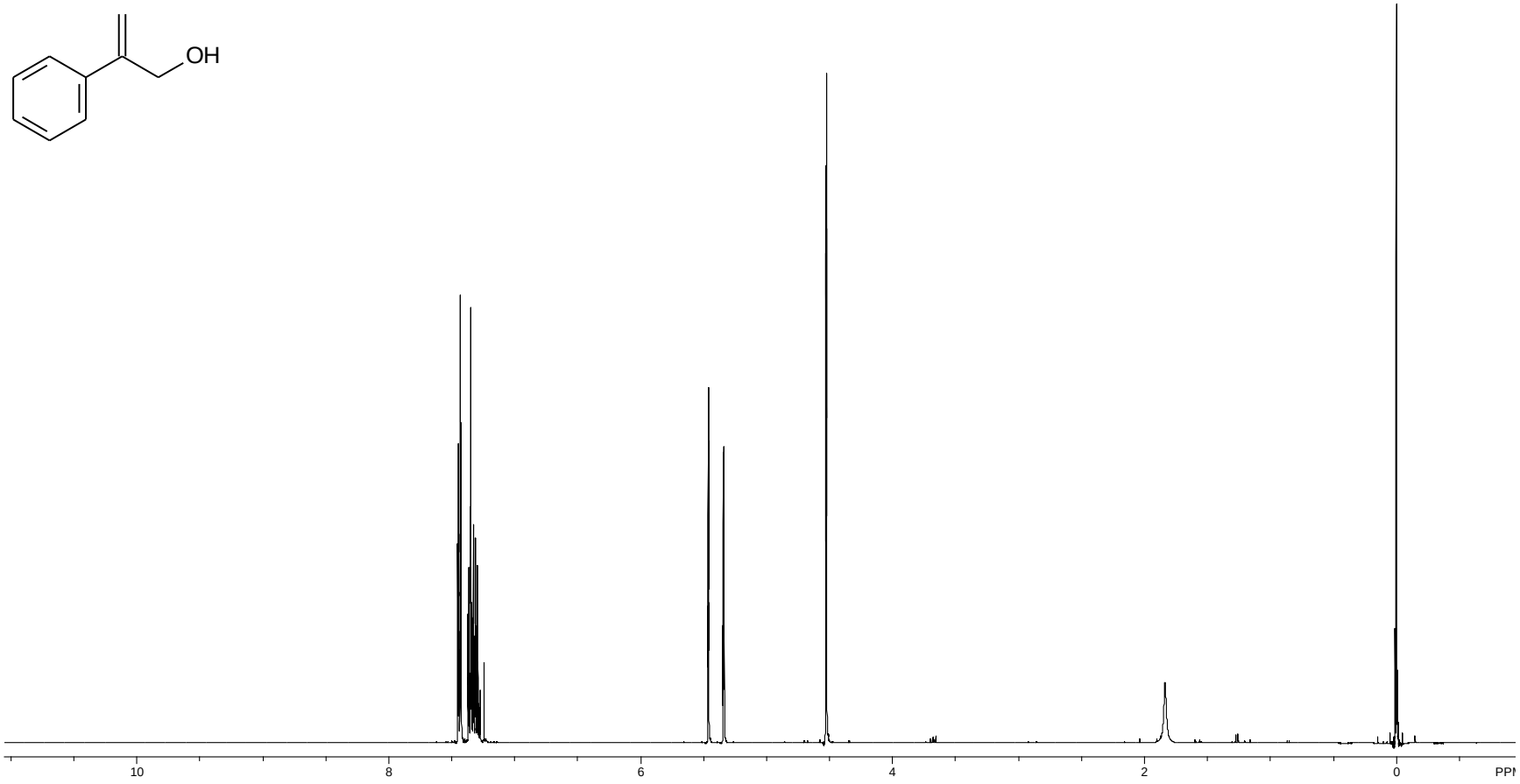


Figure A8. 400 MHz ^{1}H NMR Spectrum of Compound **138**.

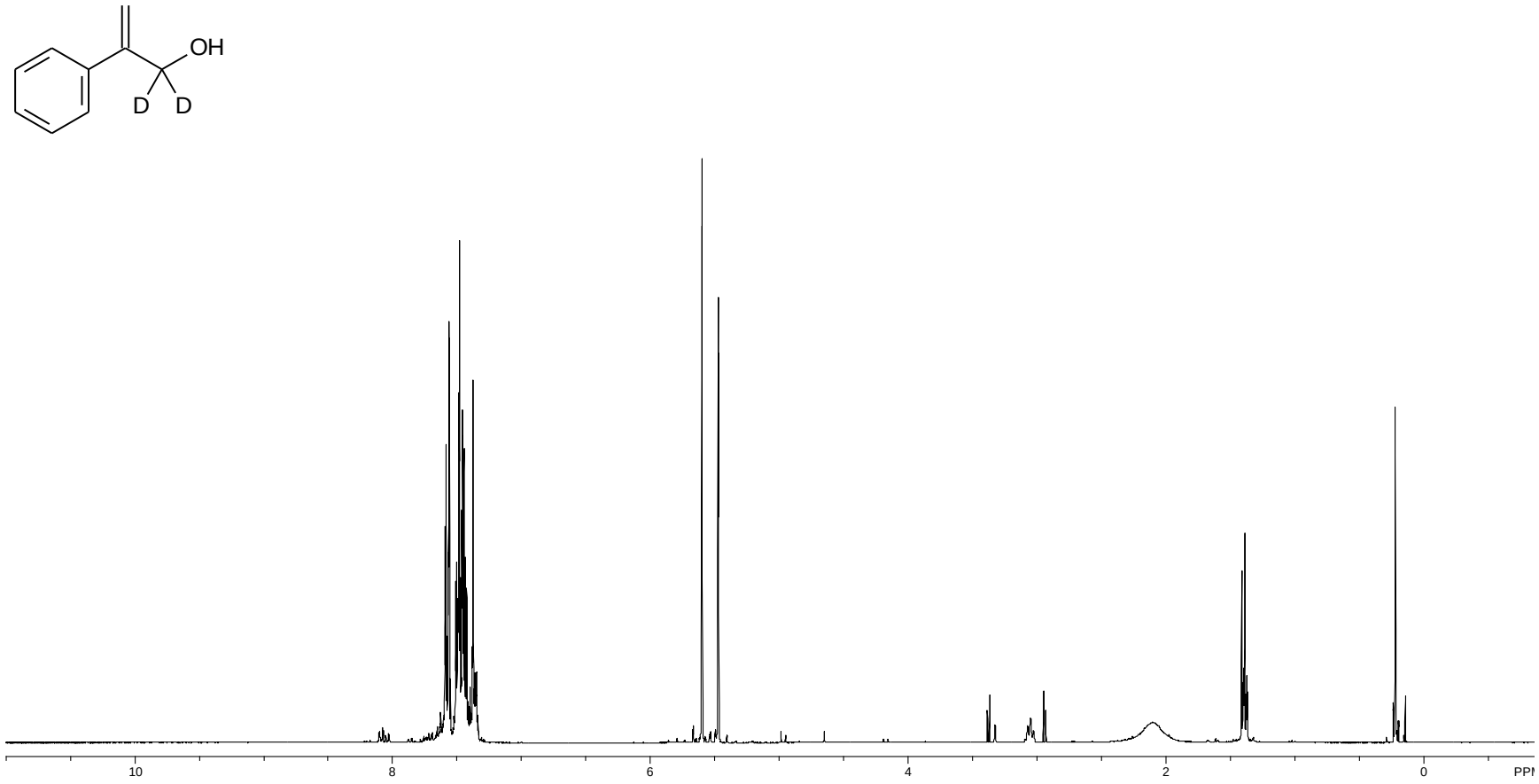


Figure A9. 300 MHz ^{1}H NMR Spectrum of Compound **141**.

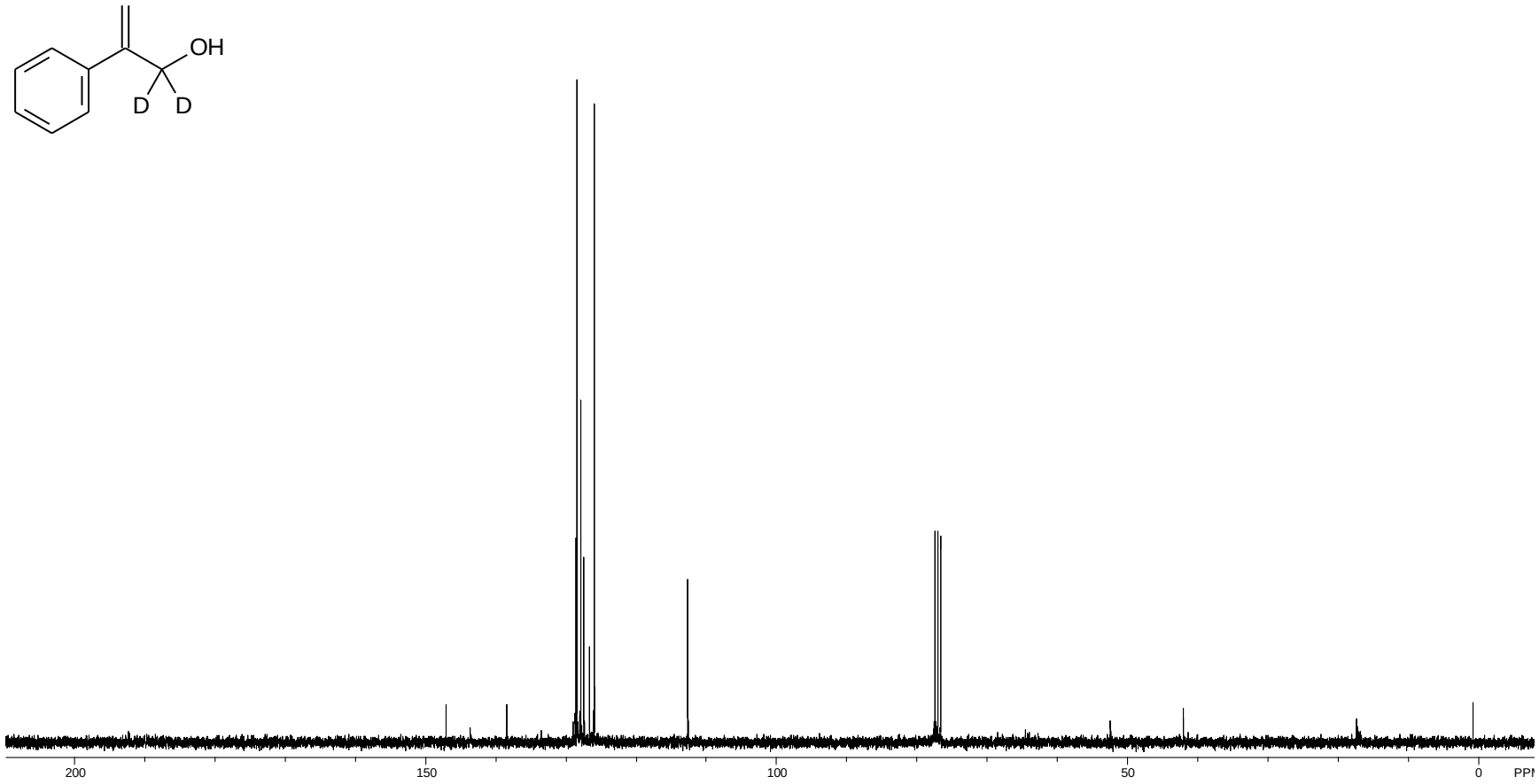


Figure A10. 75 MHz ^{13}C NMR Spectrum of Compound **141**.

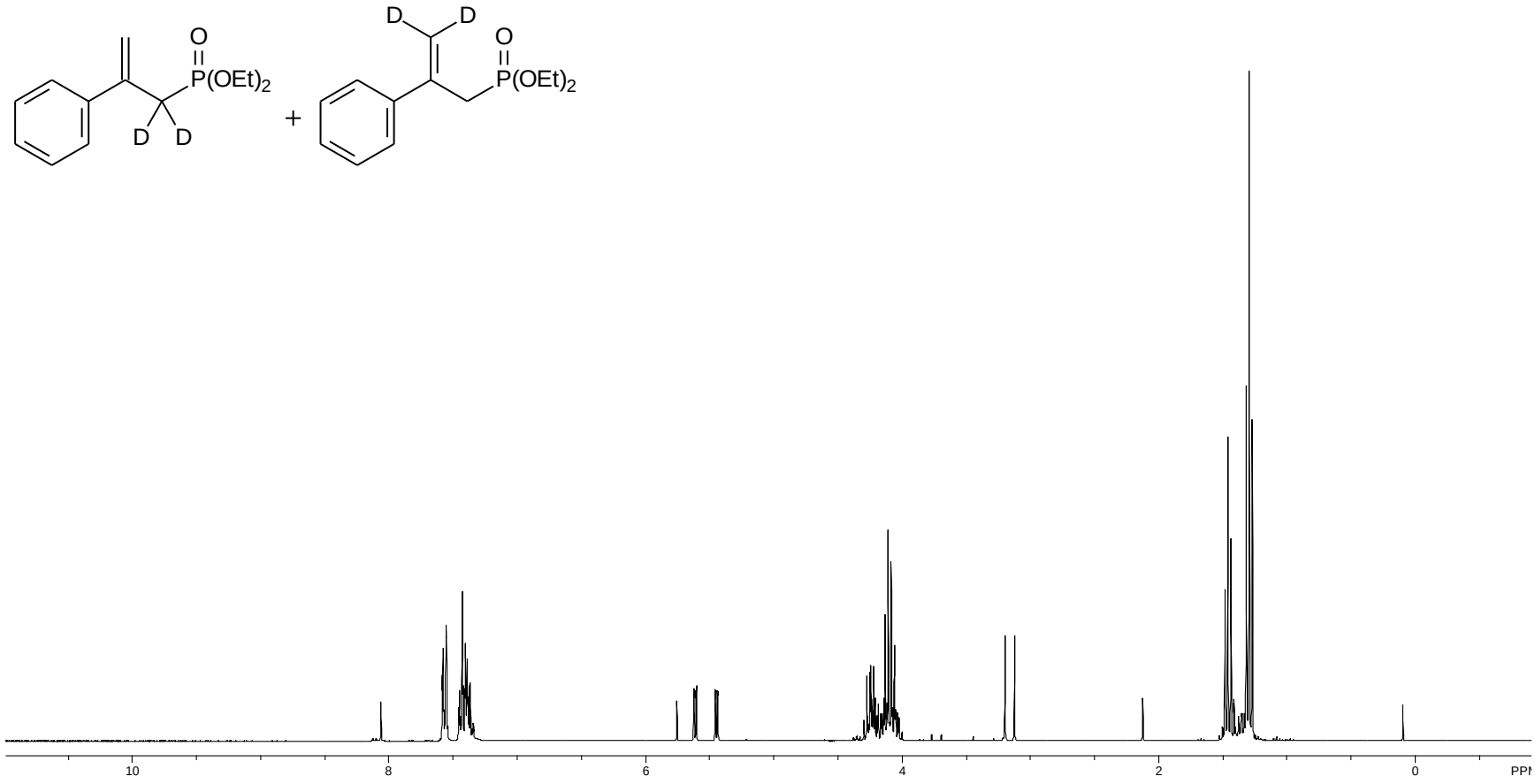


Figure A11. 300 MHz ^{1}H NMR Spectrum of Compounds **142** and **143**.

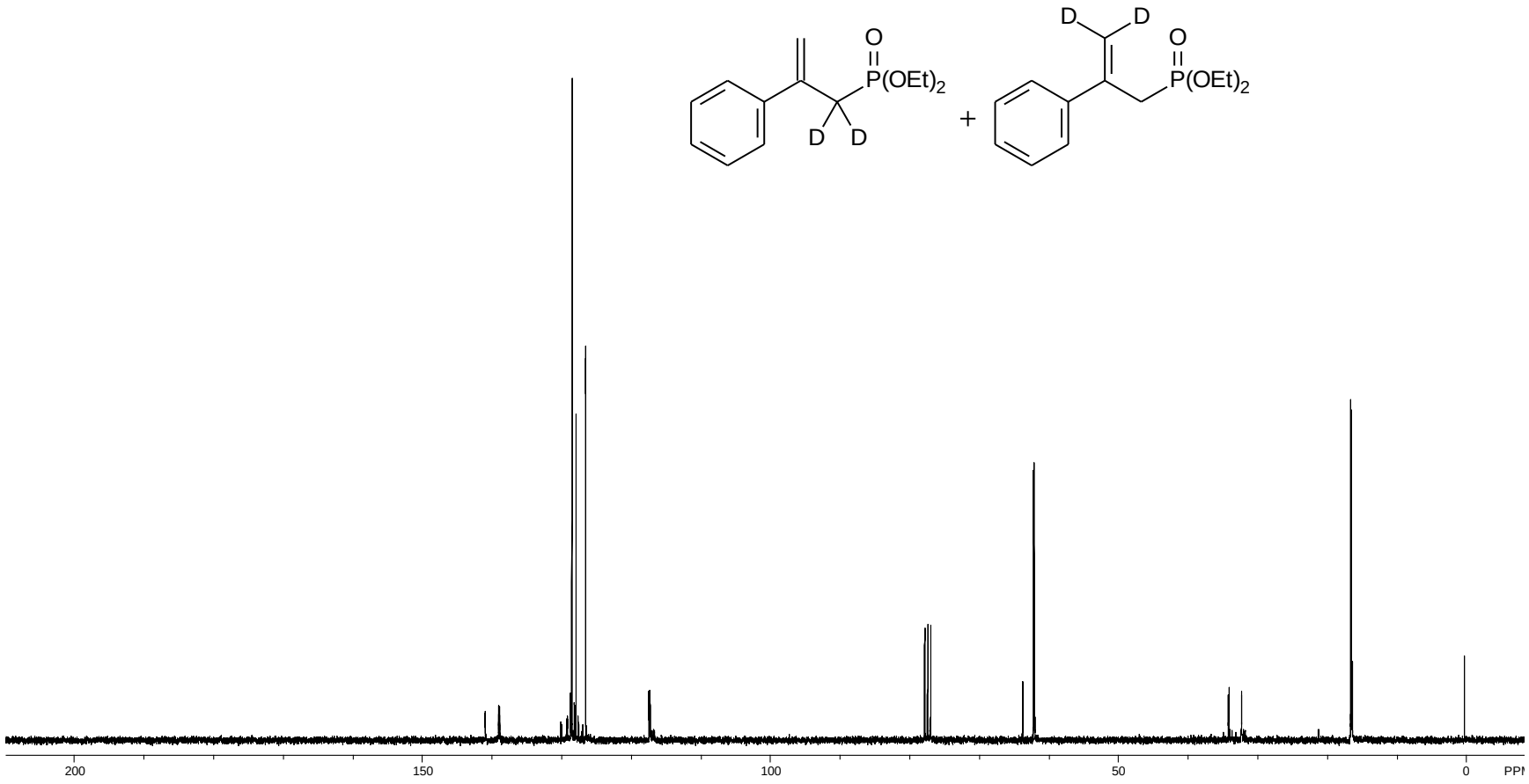


Figure A12. 75 MHz ^{13}C NMR Spectrum of Compounds **142** and **143**.

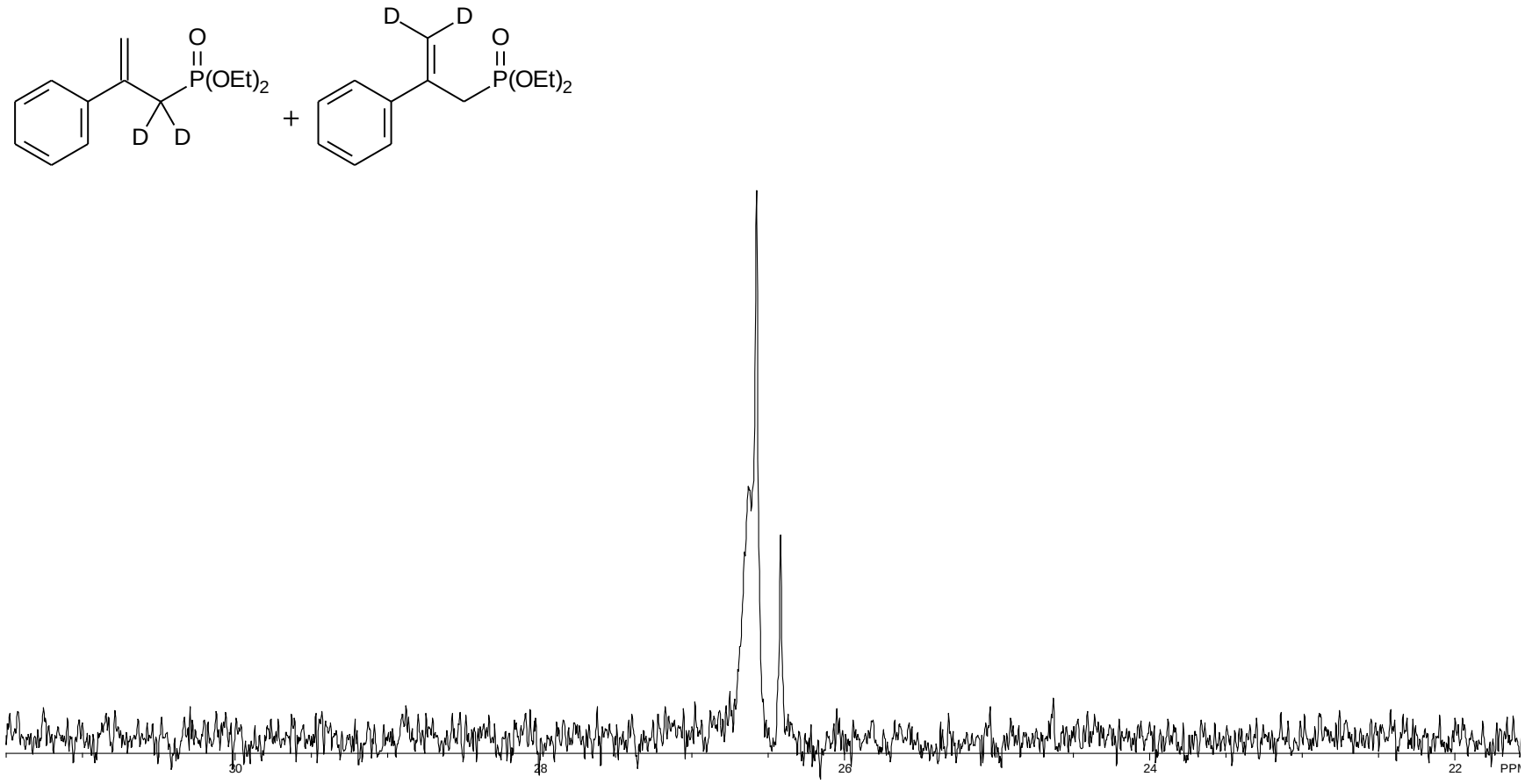


Figure A13. 121 MHz ^{31}P NMR Spectrum of Compounds **142** and **143**.

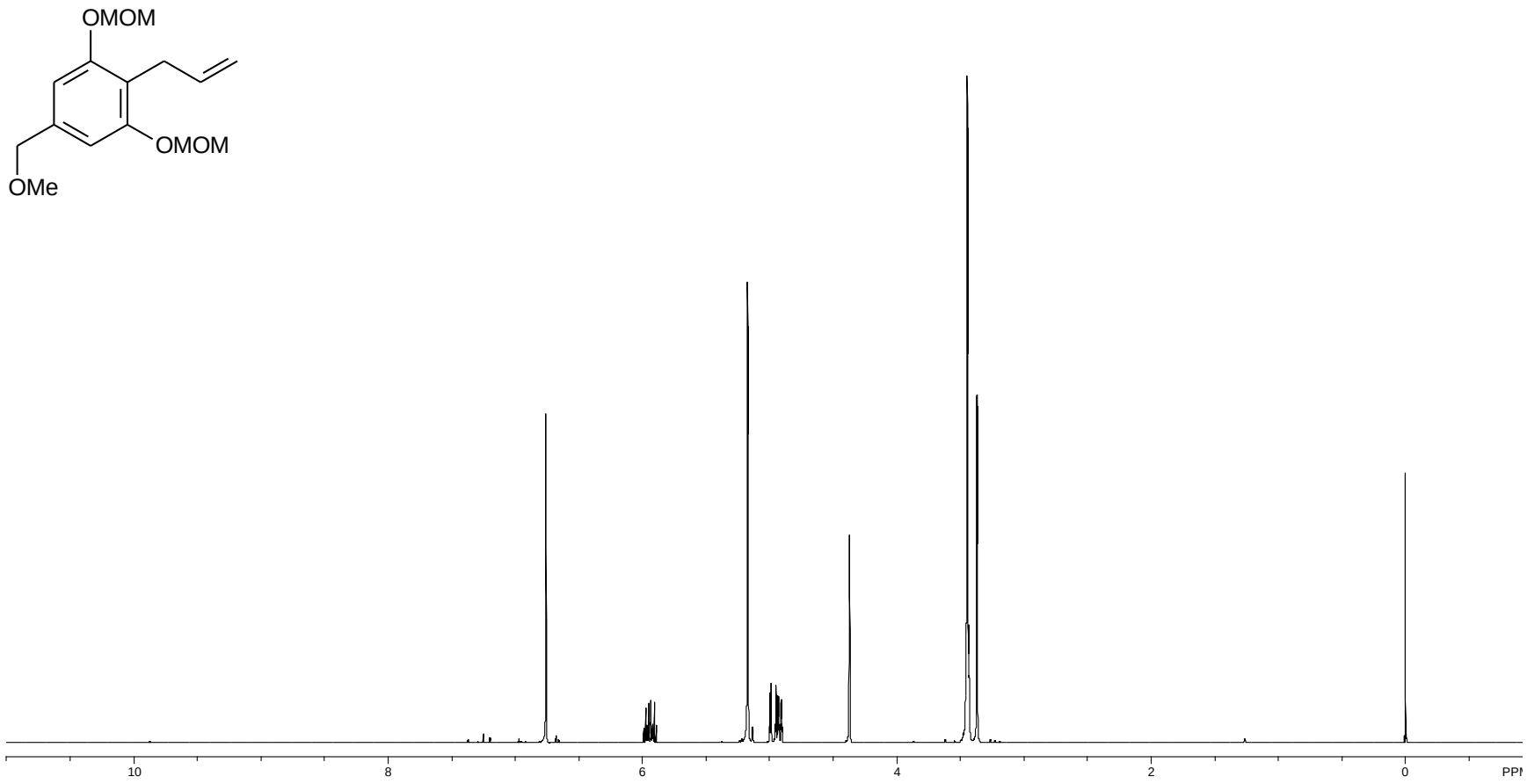


Figure A14. 400 MHz ^{1}H NMR Spectrum of Compound **192**.

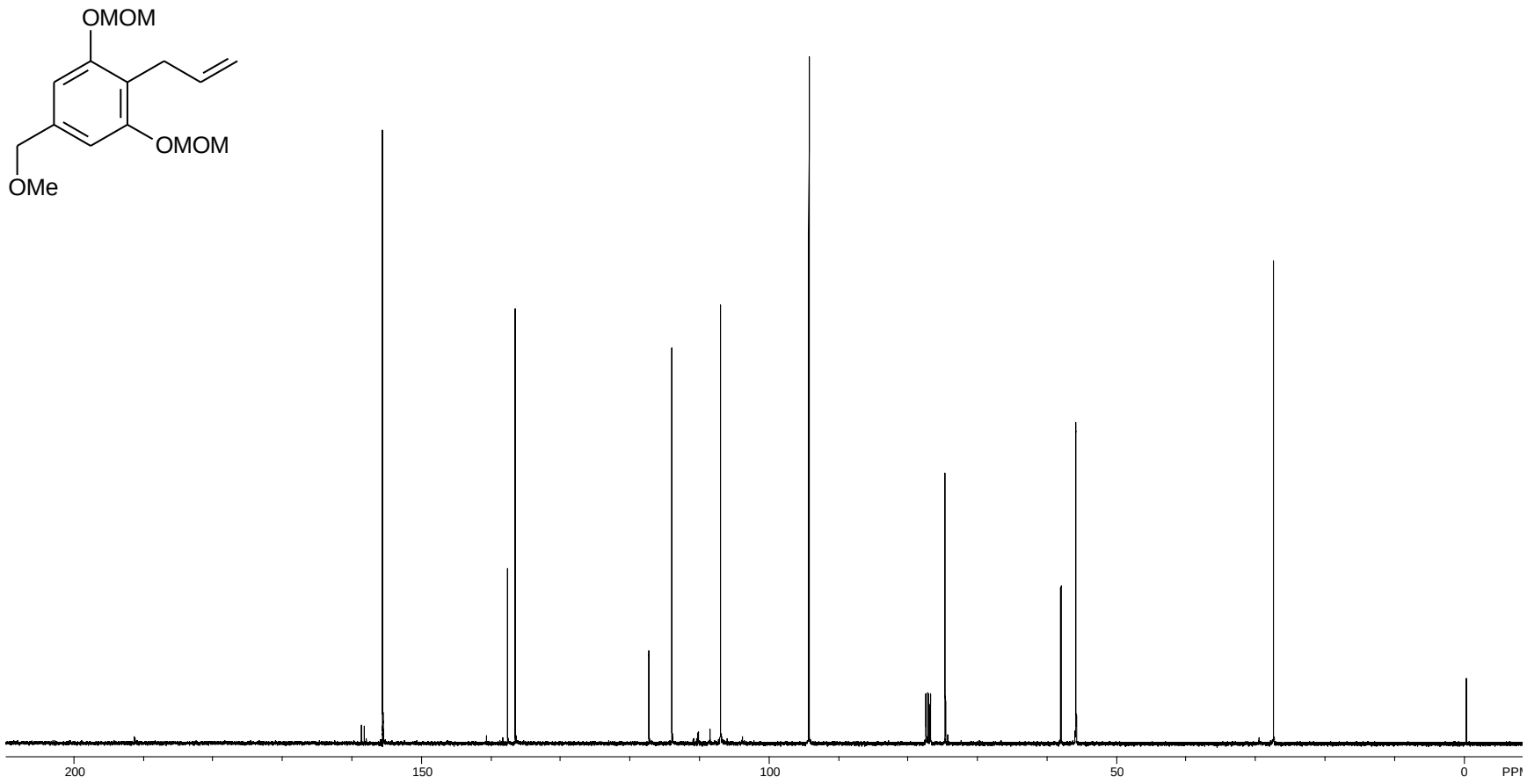


Figure A15. 100 MHz ^{13}C NMR Spectrum of Compound **192**.

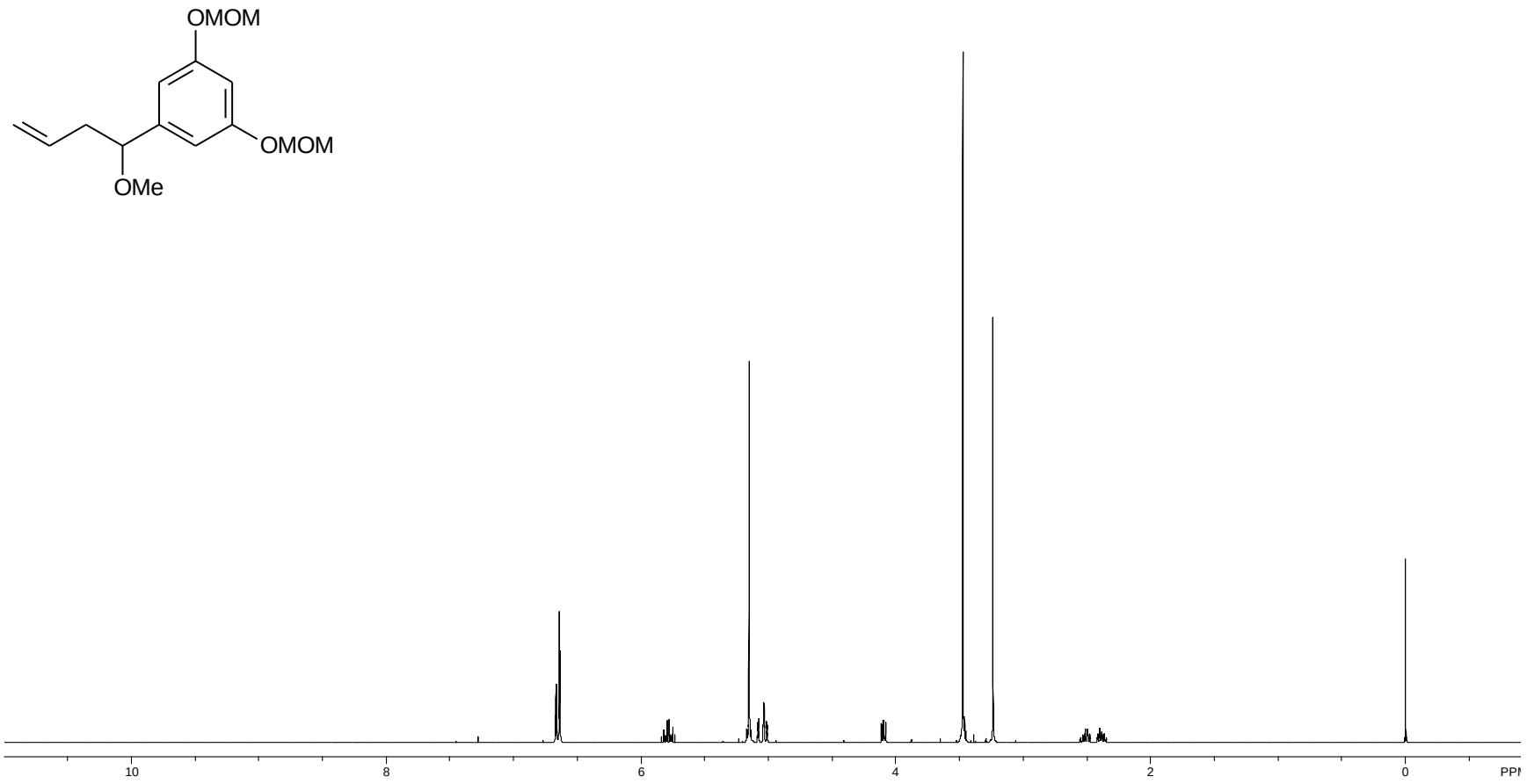


Figure A16. 400 MHz ^{1}H NMR Spectrum of Compound **193**.

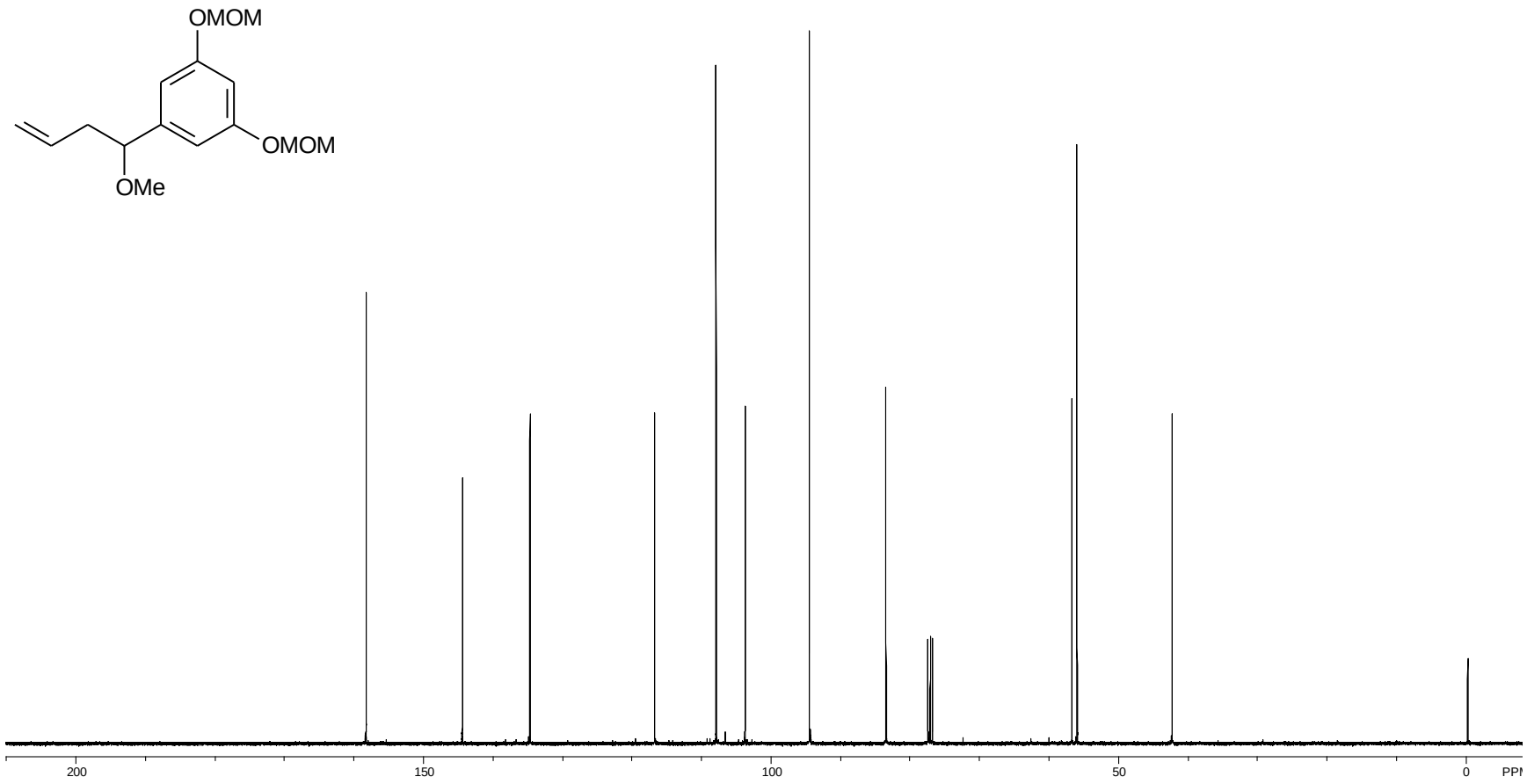


Figure A17. 100 MHz ^{13}C NMR Spectrum of Compound **193**.

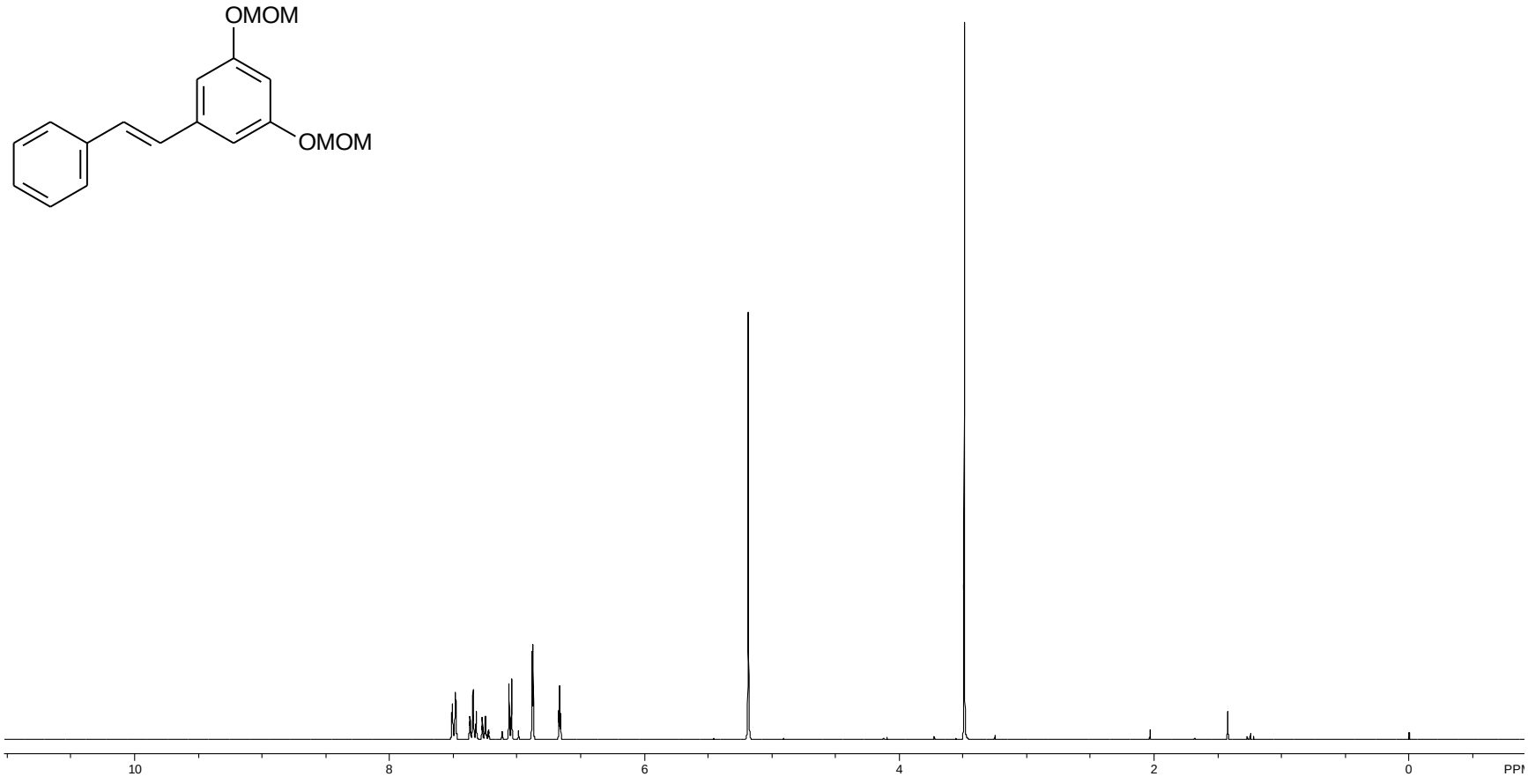


Figure A18. 300 MHz ^{1}H NMR Spectrum of Compound **195**.

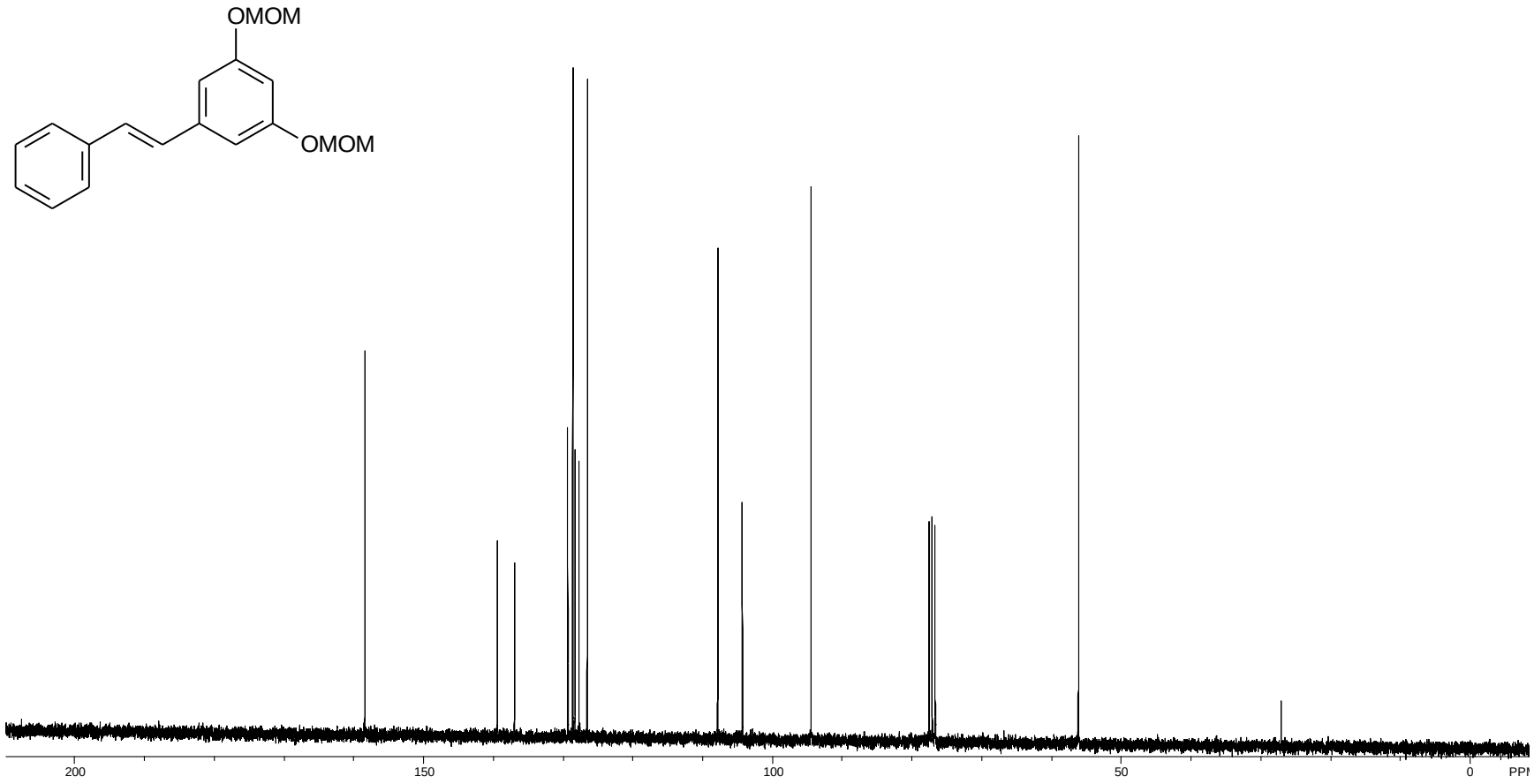


Figure A19. 75 MHz ^{13}C NMR Spectrum of Compound **195**.

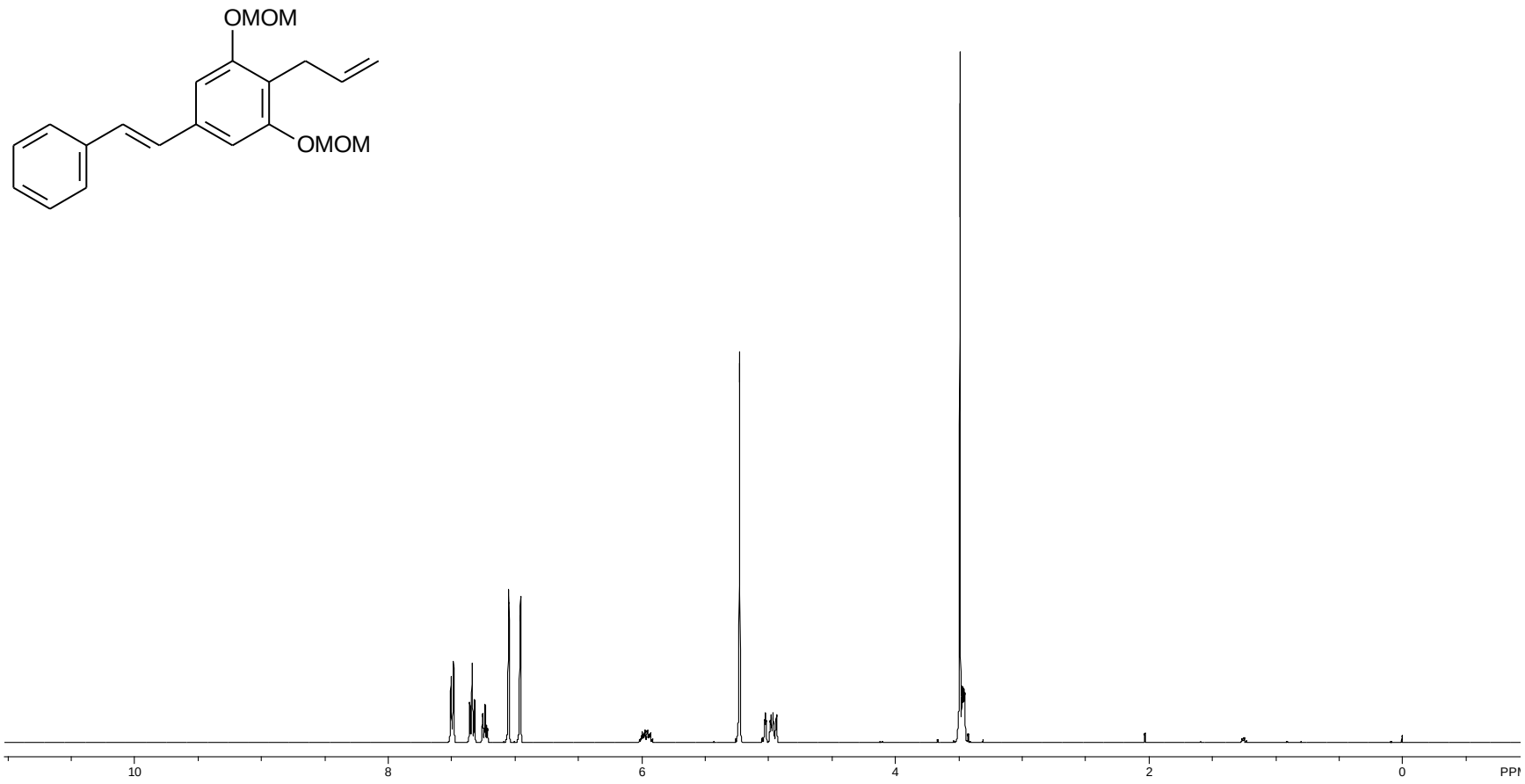


Figure A20. 400 MHz ^{1}H NMR Spectrum of Compound **196**.

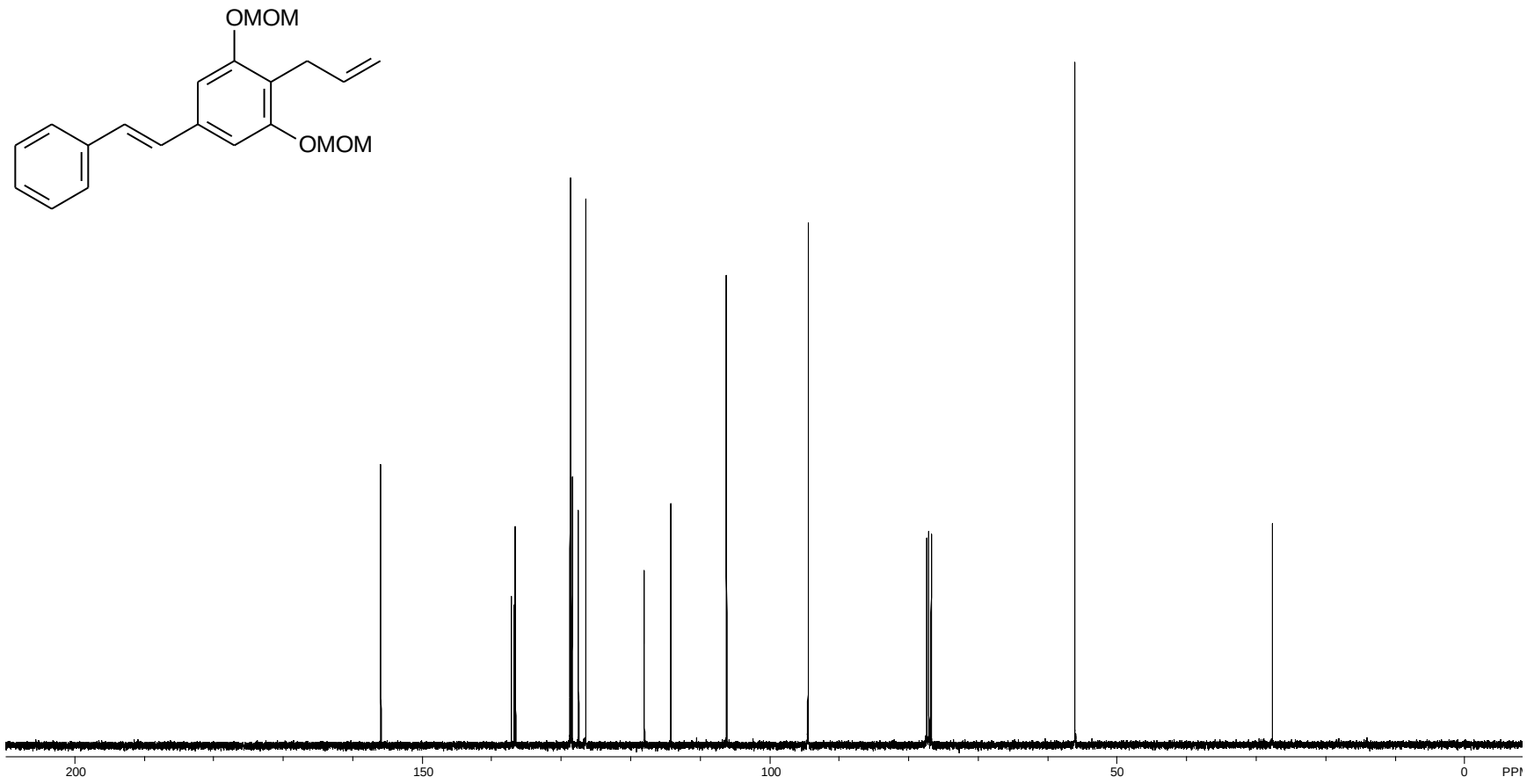


Figure A21. 100 MHz ^{13}C NMR Spectrum of Compound **196**.

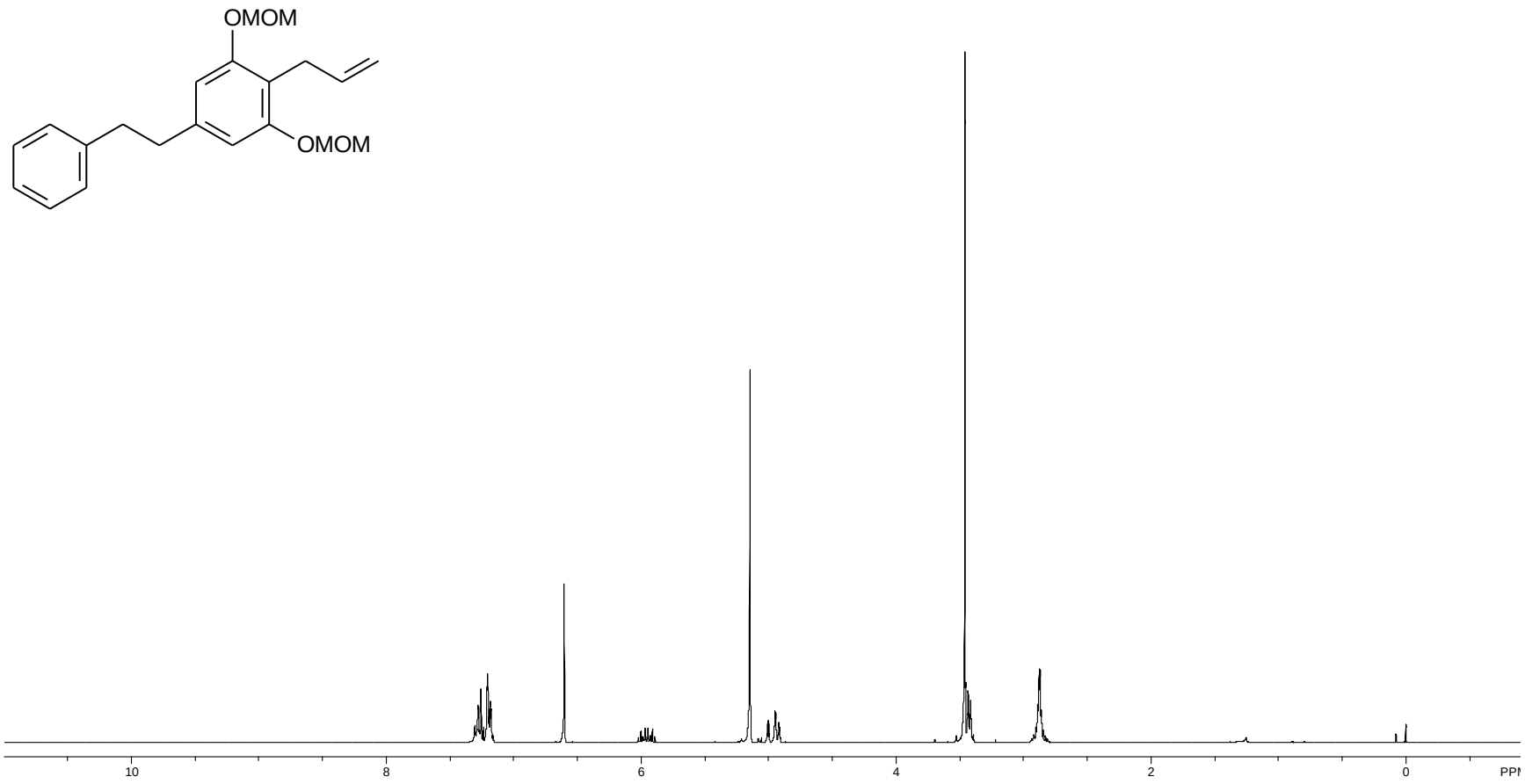


Figure A22. 300 MHz ^{1}H NMR Spectrum of Compound **197**.

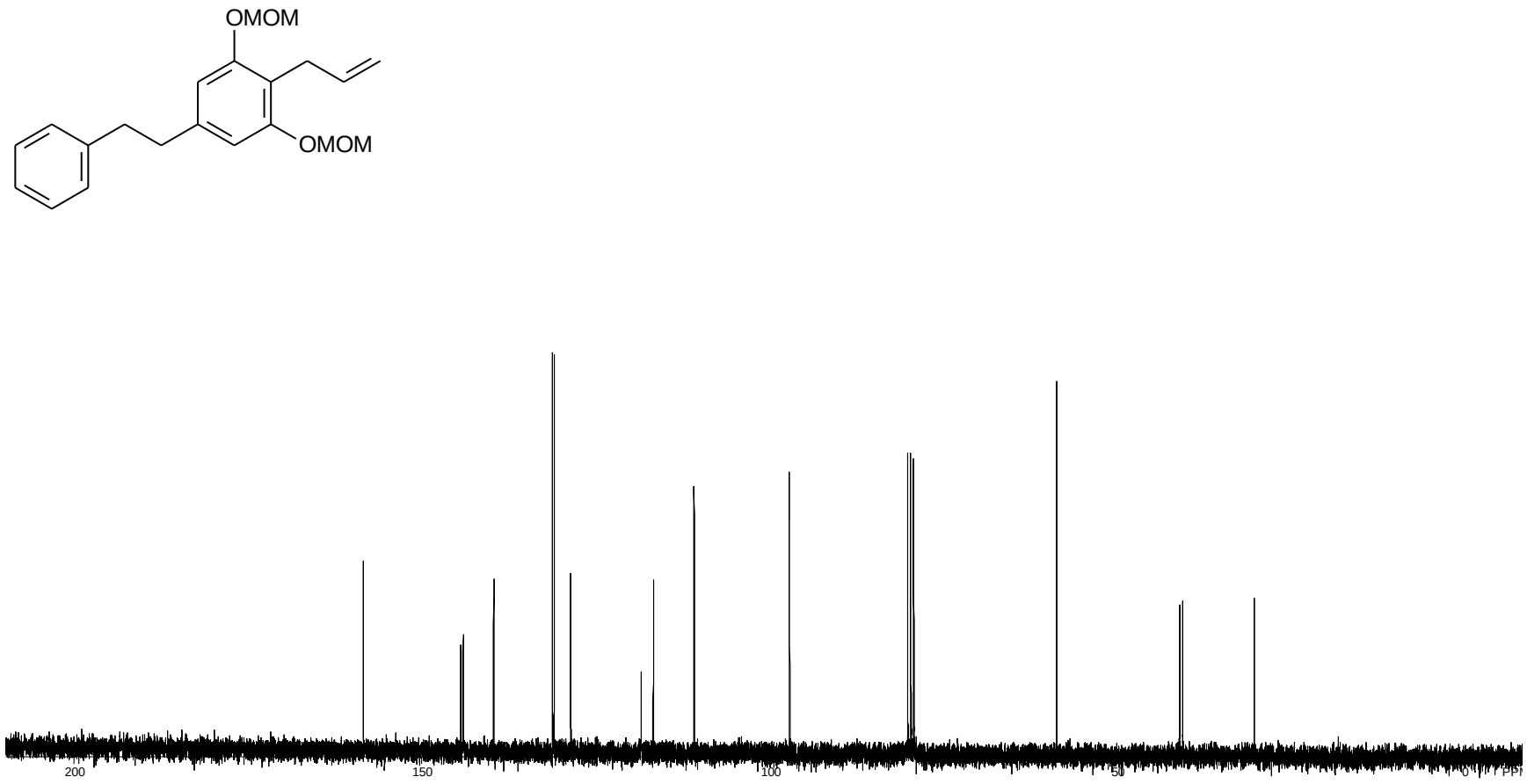


Figure A23. 75 MHz ^{13}C NMR Spectrum of Compound **197**.

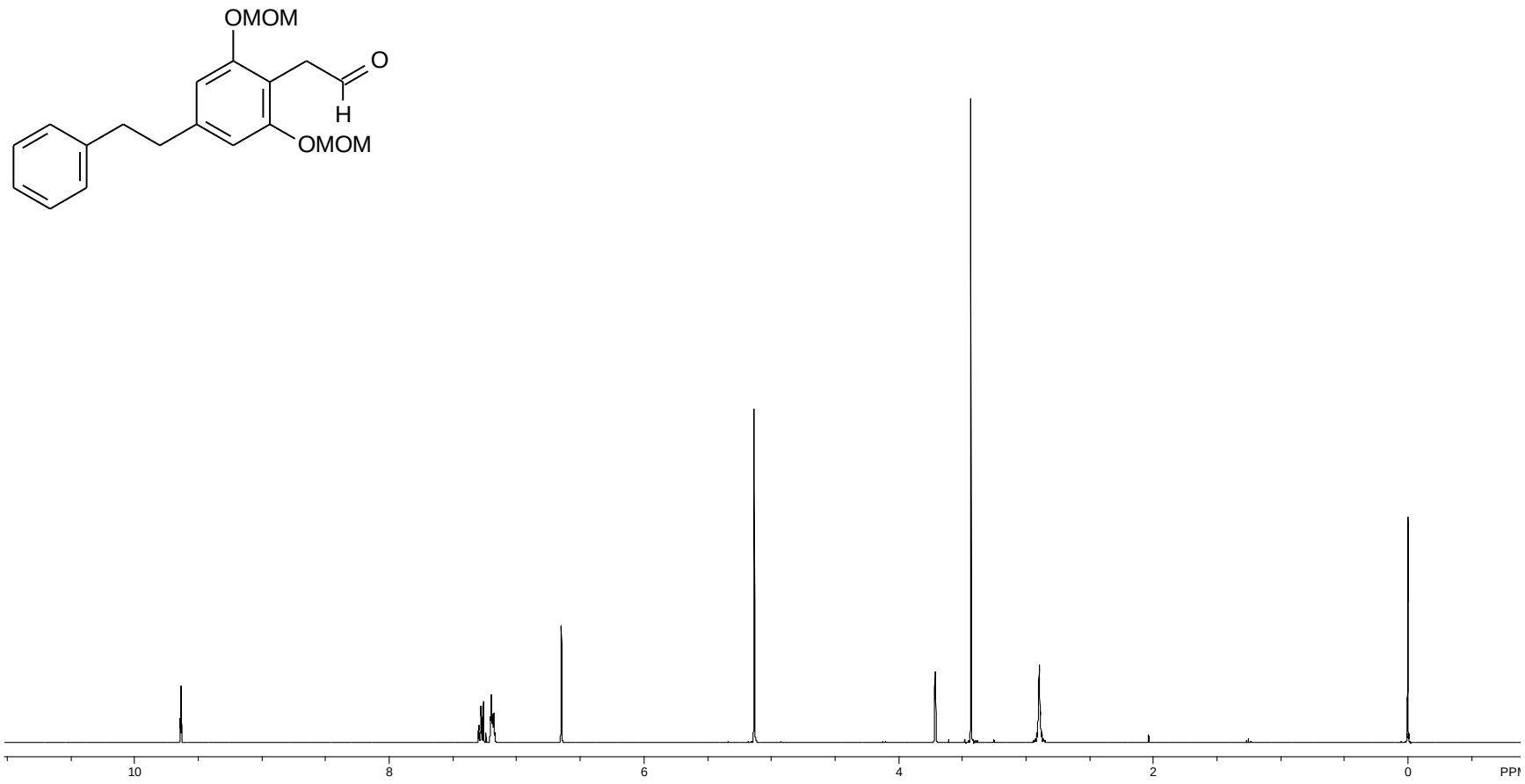


Figure A24. 400 MHz ^{1}H NMR Spectrum of Compound **198**.

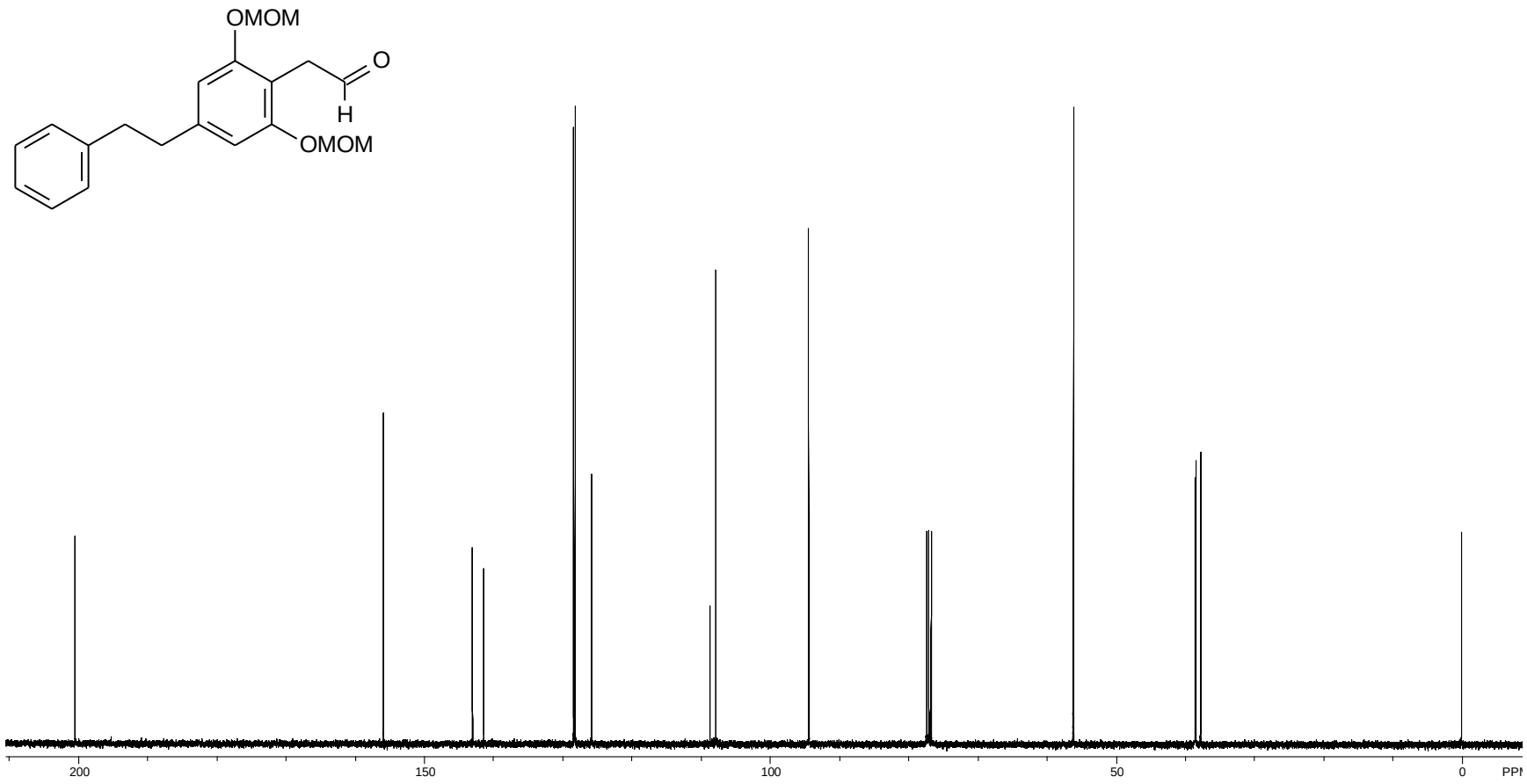


Figure A25. 100 MHz ^{13}C NMR Spectrum of Compound **198**.

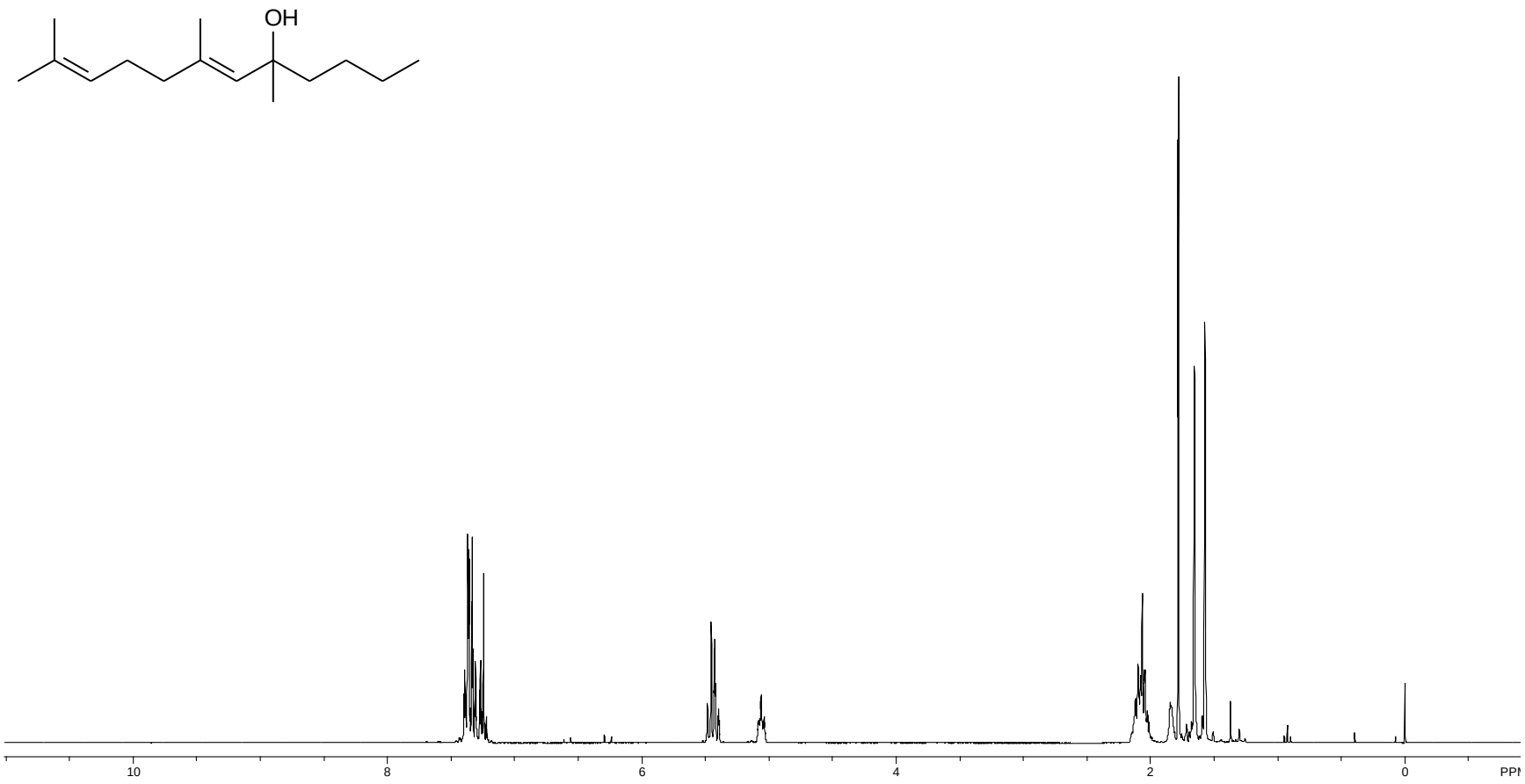


Figure A26. 300 MHz ^{1}H NMR Spectrum of Compound **216**.

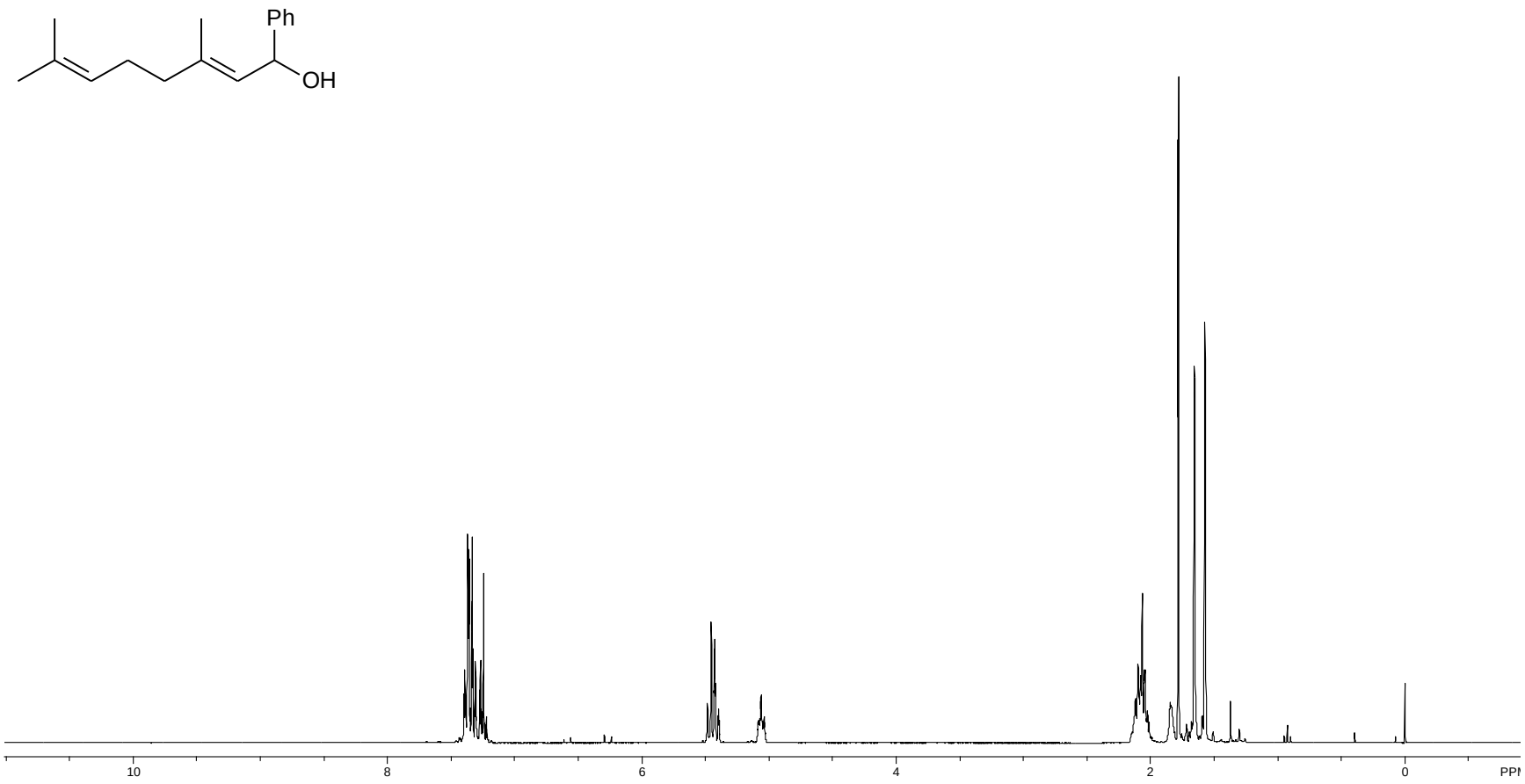


Figure A27. 300 MHz ^{1}H NMR Spectrum of Compound **217**.

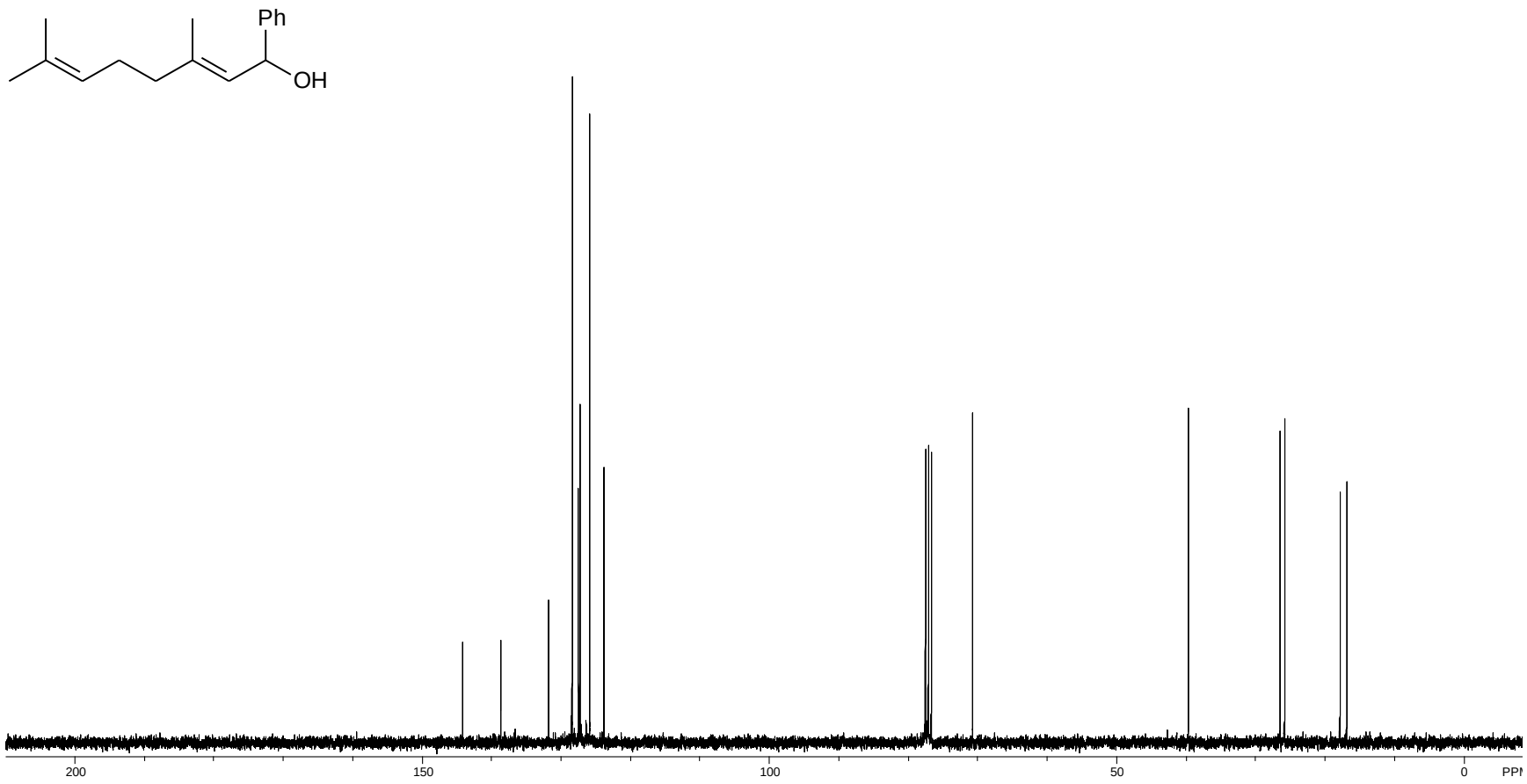


Figure A28. 75 MHz ^{13}C NMR Spectrum of Compound **217**.

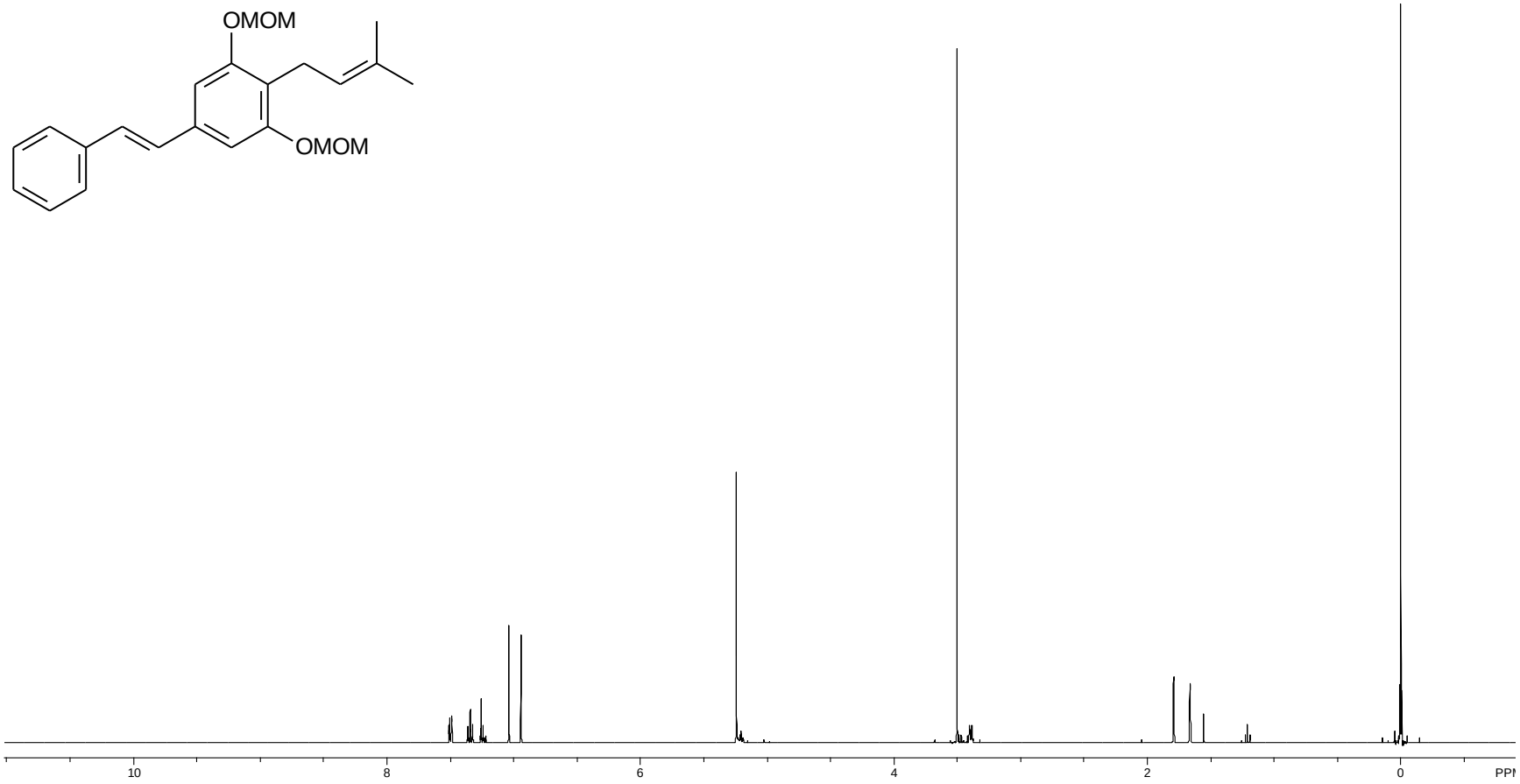


Figure A29. 400 MHz ^{1}H NMR Spectrum of Compound **220**.

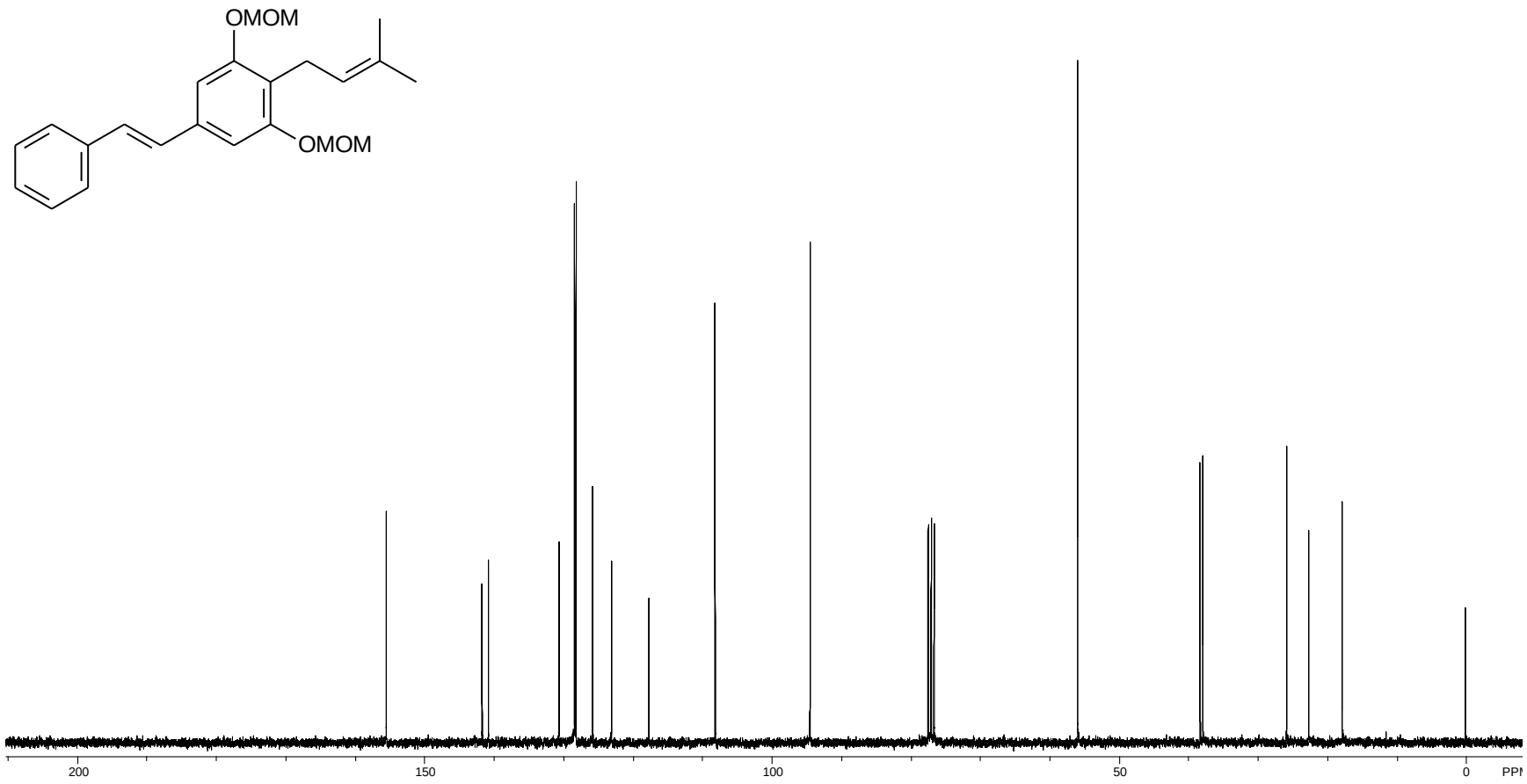


Figure A30. 100 MHz ^{13}C NMR Spectrum of Compound **220**.

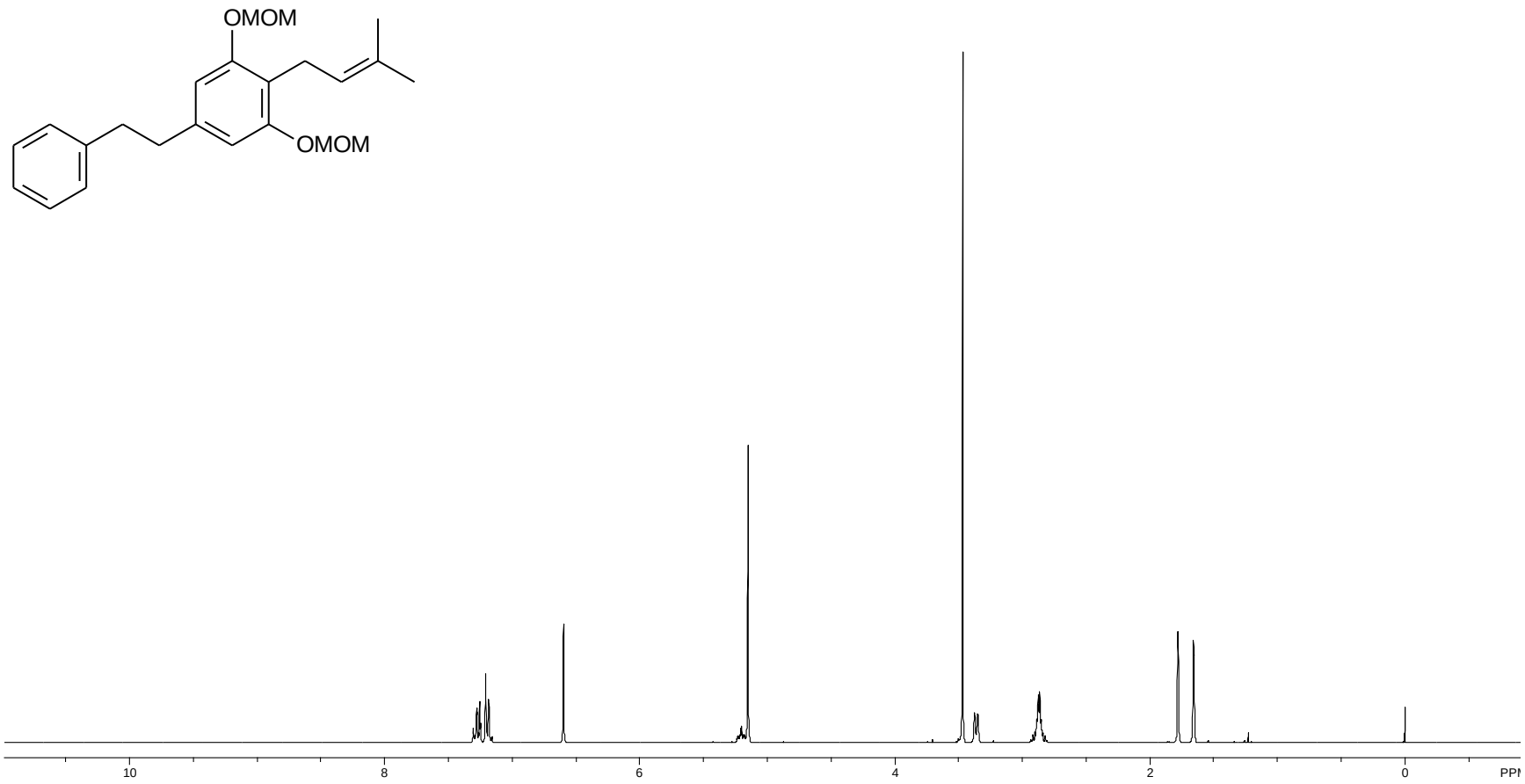


Figure A31. 300 MHz ^{1}H NMR Spectrum of Compound **221**.

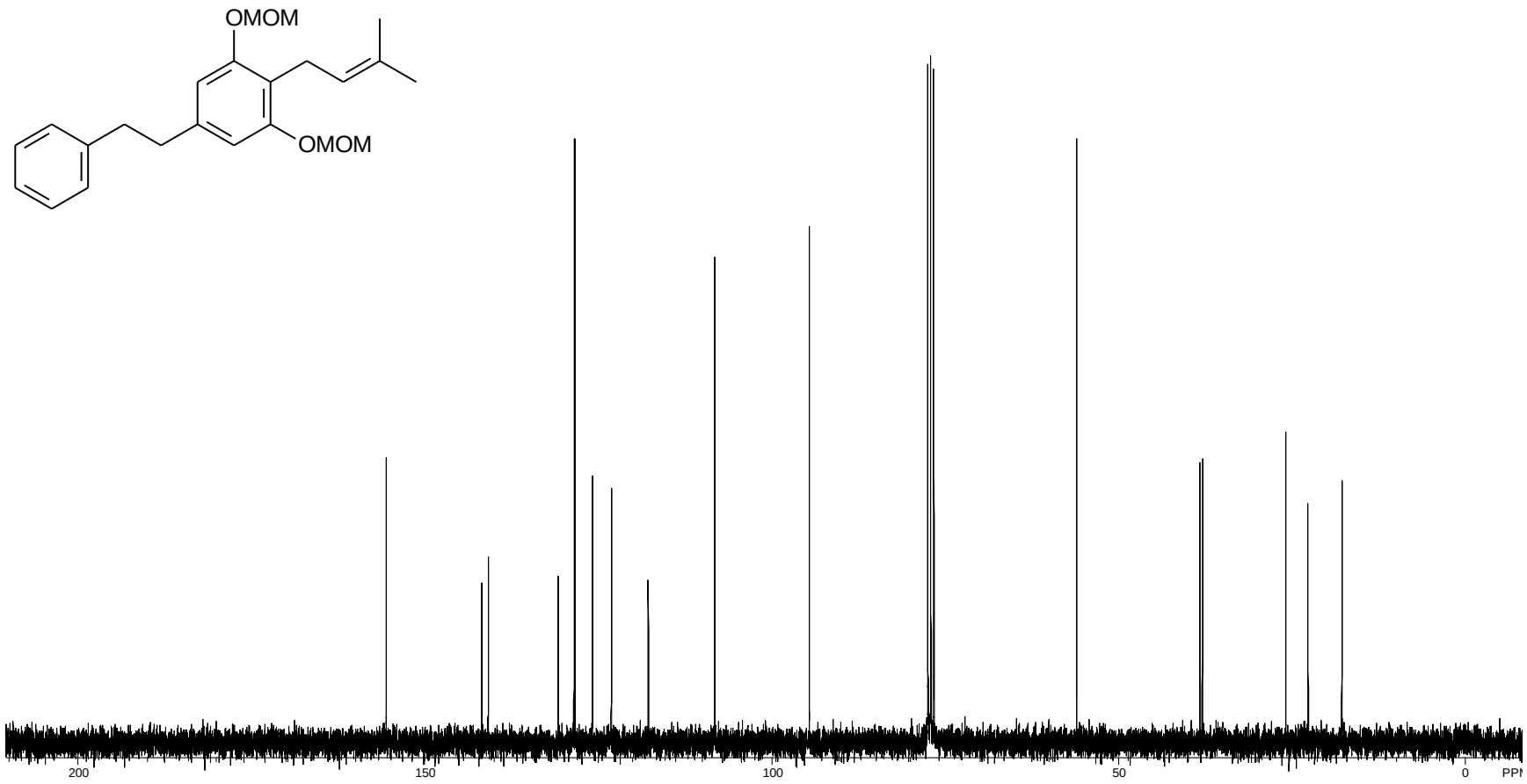


Figure A32. 75 MHz ^{13}C NMR Spectrum of Compound **221**.

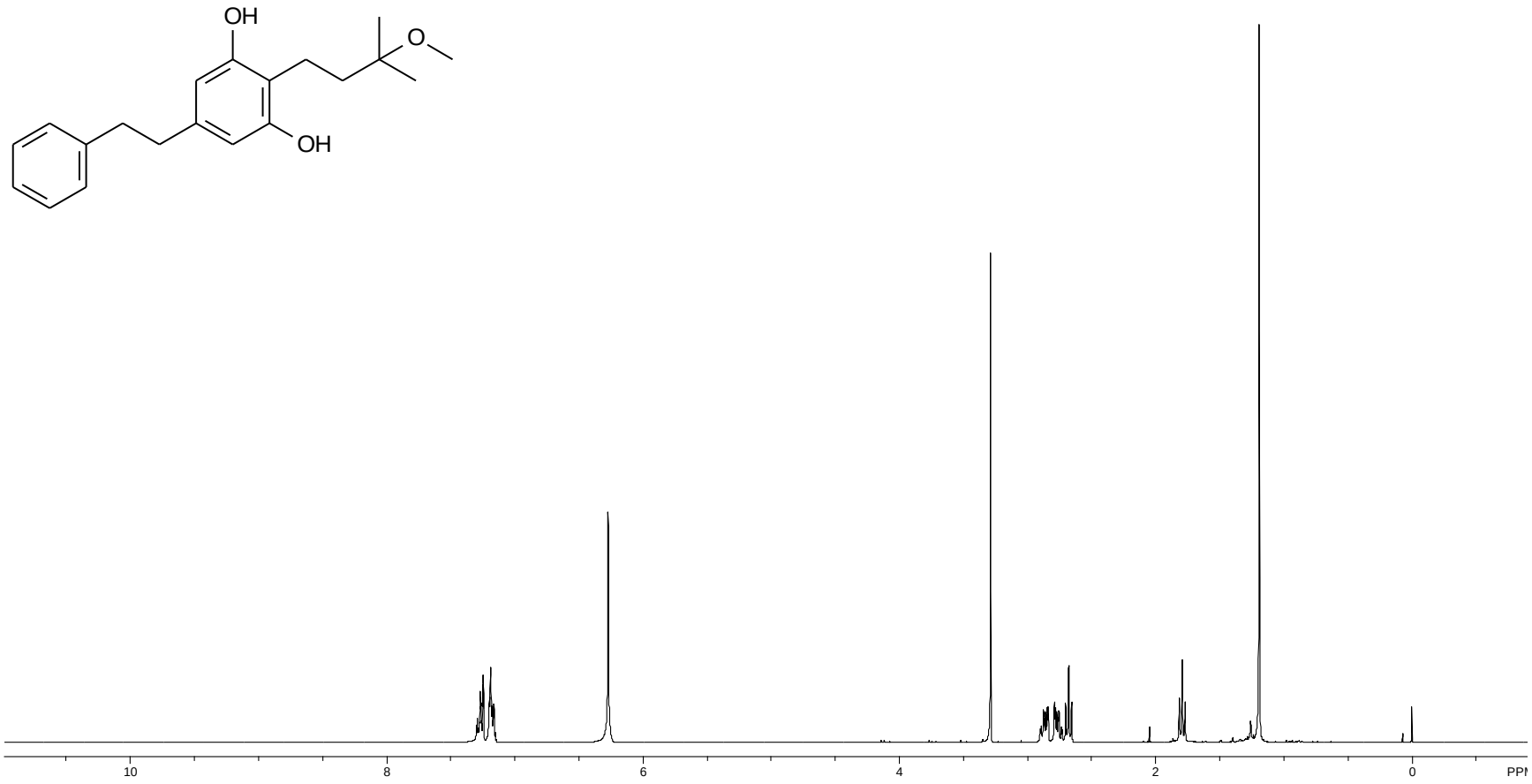


Figure A33. 300 MHz ^{1}H NMR Spectrum of Compound **222**.

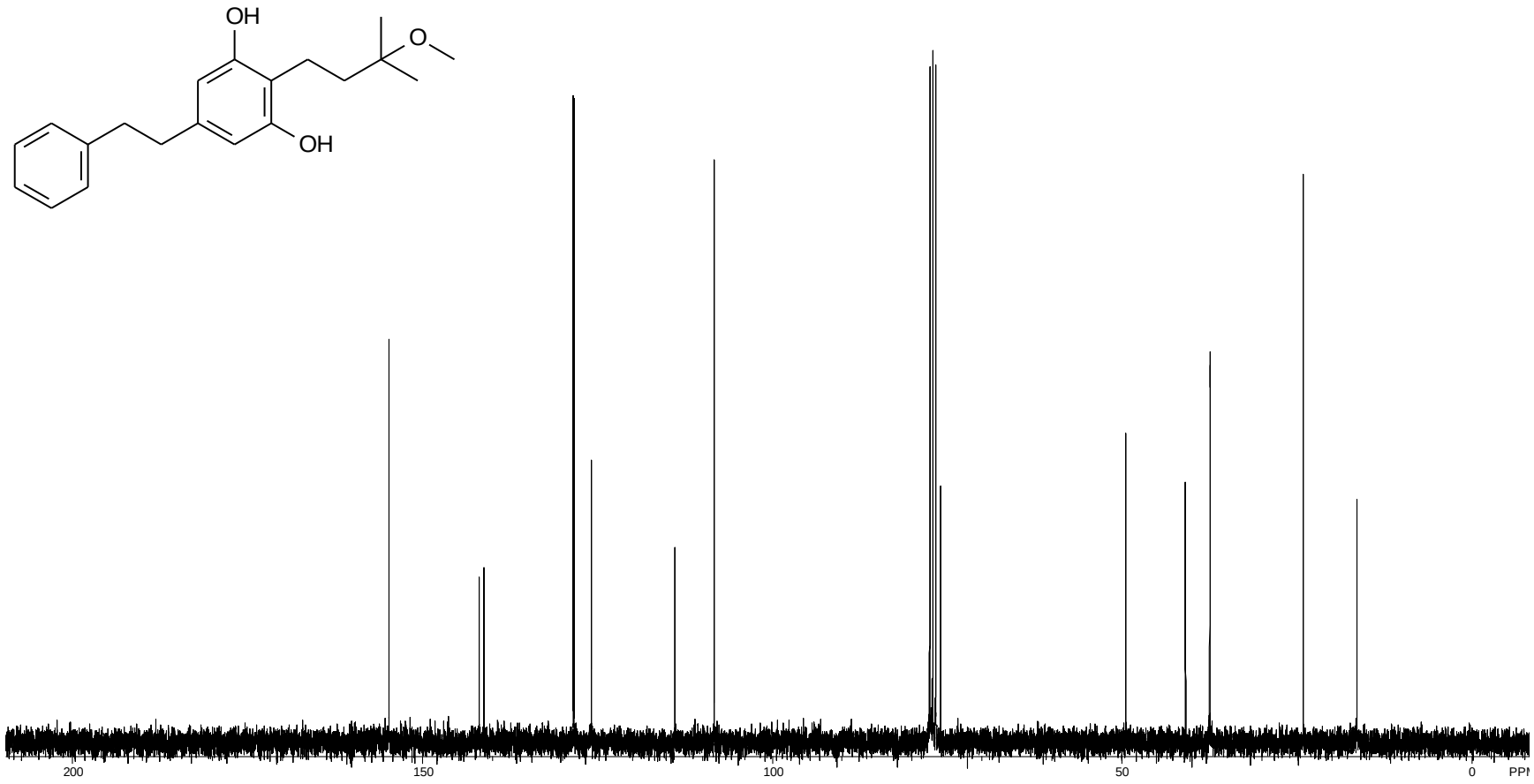


Figure A34. 75 MHz ^{13}C NMR Spectrum of Compound **222**.

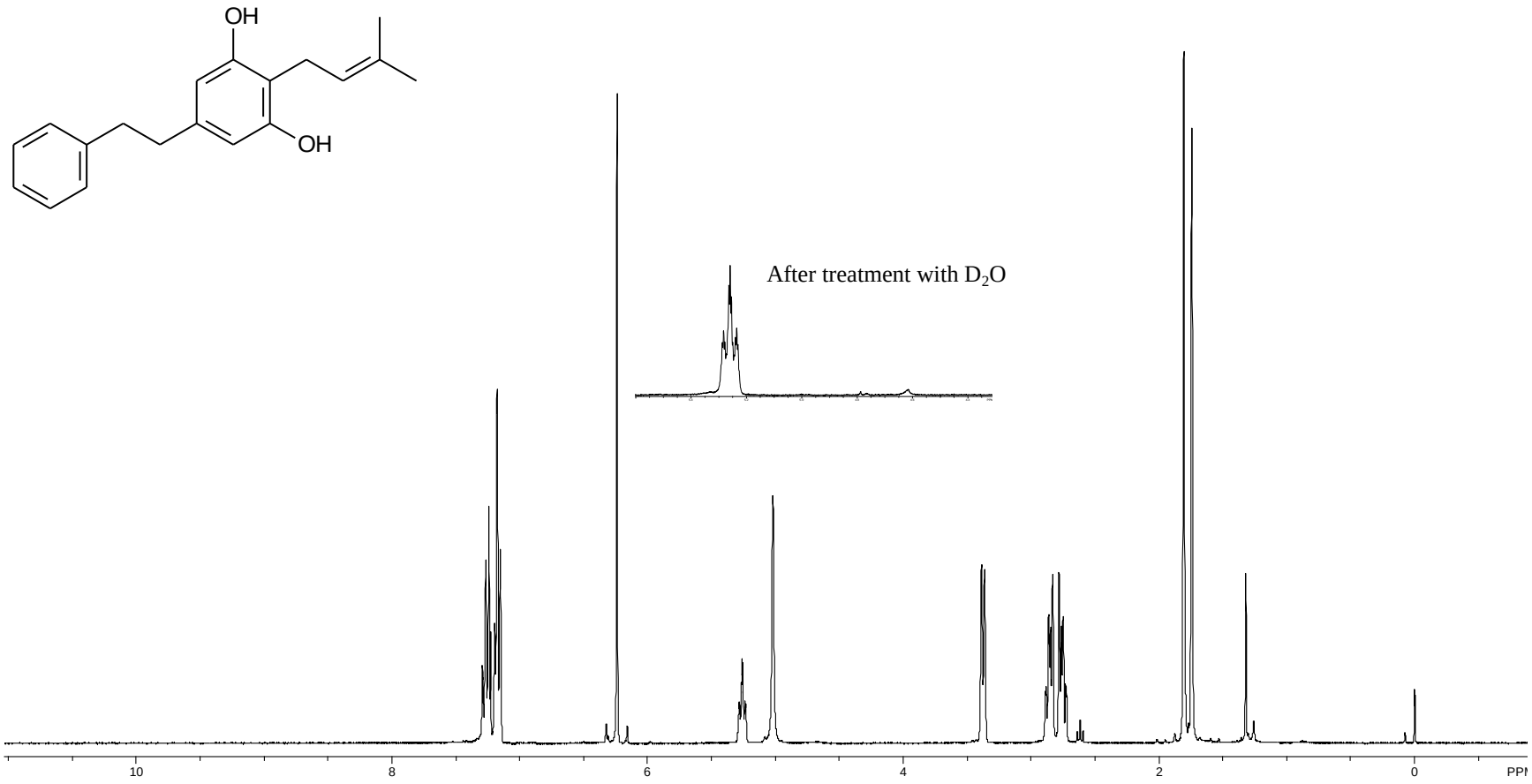


Figure A35. 300 MHz ^{1}H NMR Spectrum of Compound **223**.

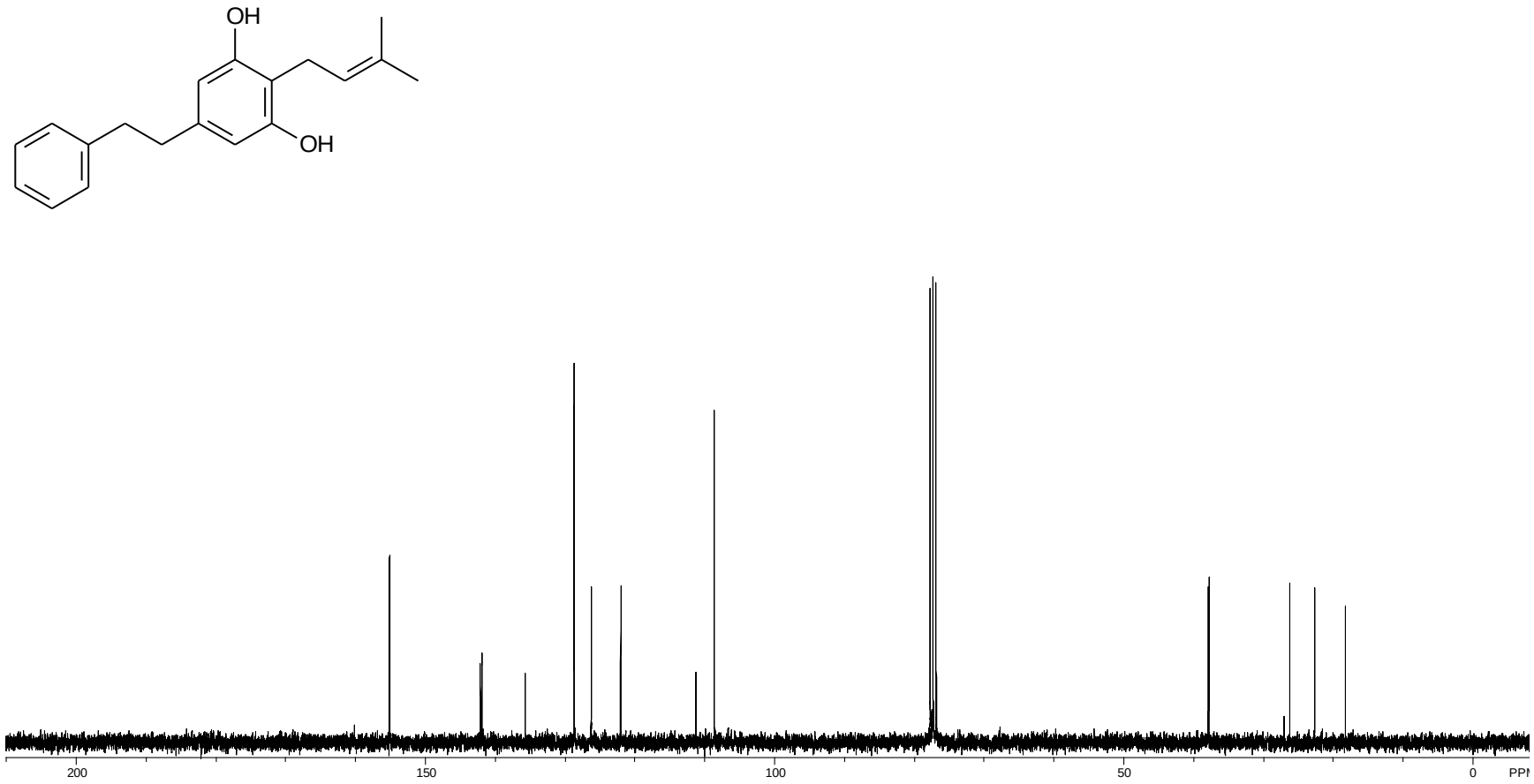


Figure A36. 75 MHz ^{13}C NMR Spectrum of Compound **223**.

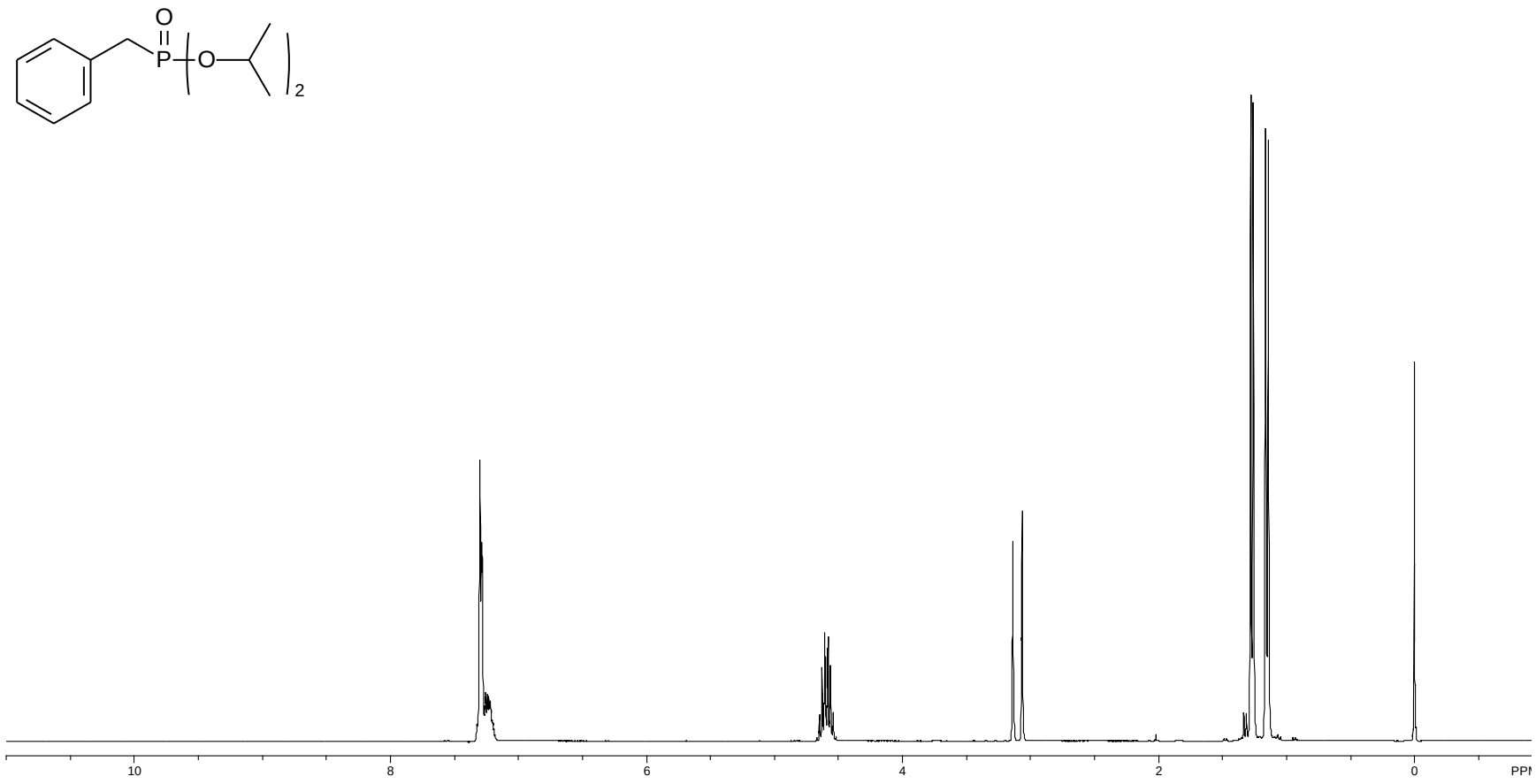


Figure A37. 300 MHz ^{1}H NMR Spectrum of Compound **255**.

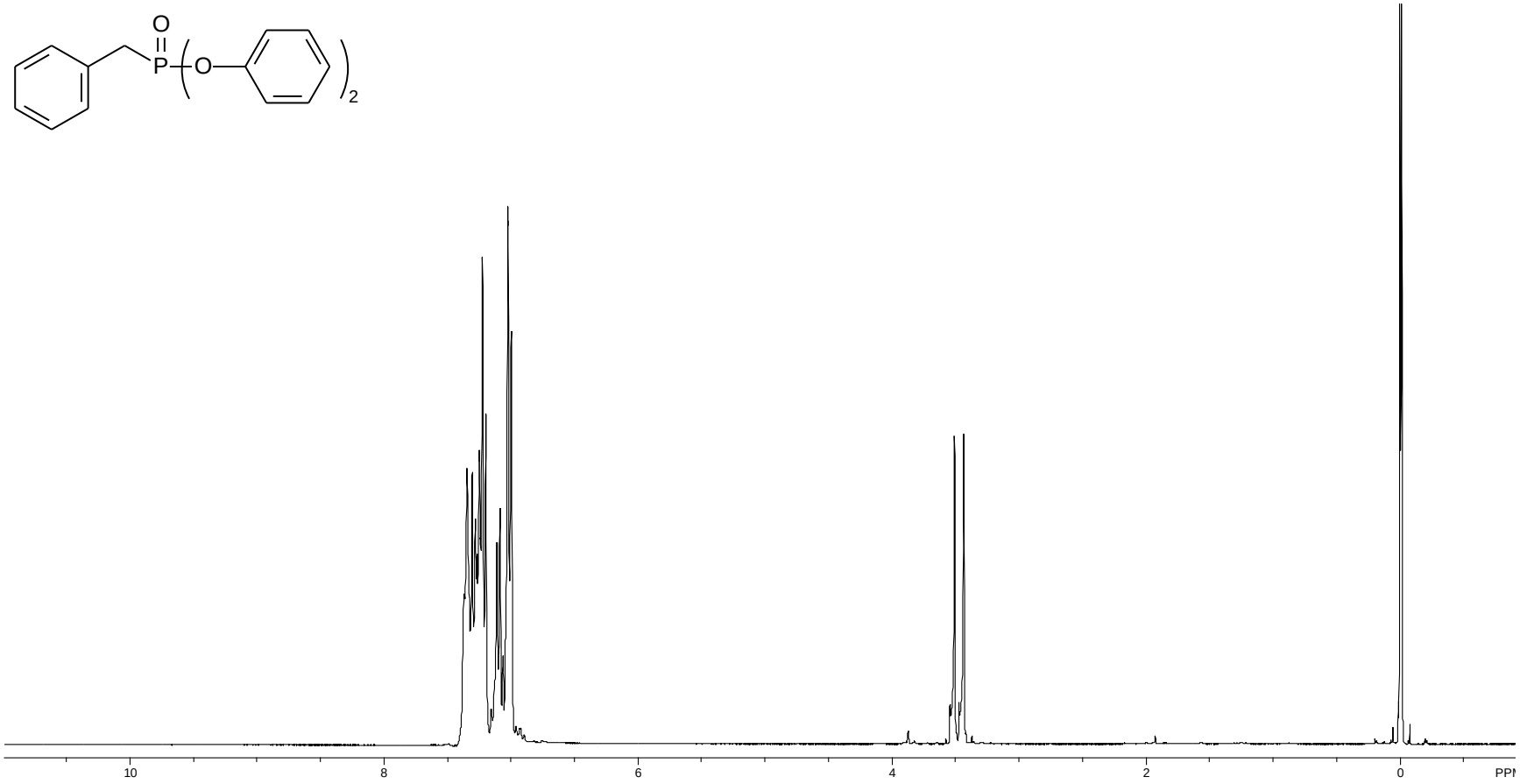


Figure A38. 300 MHz ^{1}H NMR Spectrum of Compound **243**.

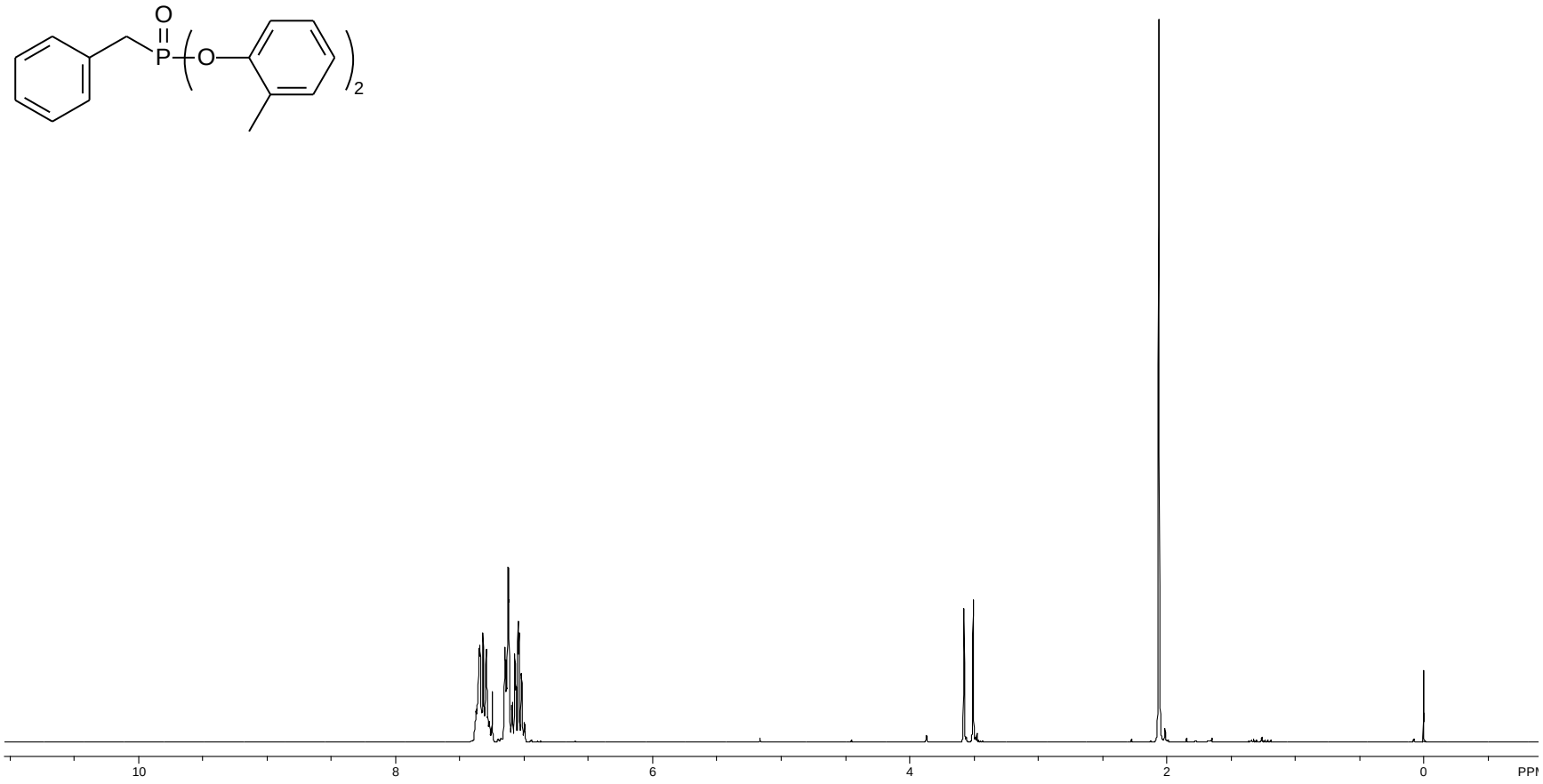


Figure A39. 300 MHz ^{1}H NMR Spectrum of Compound **246**.

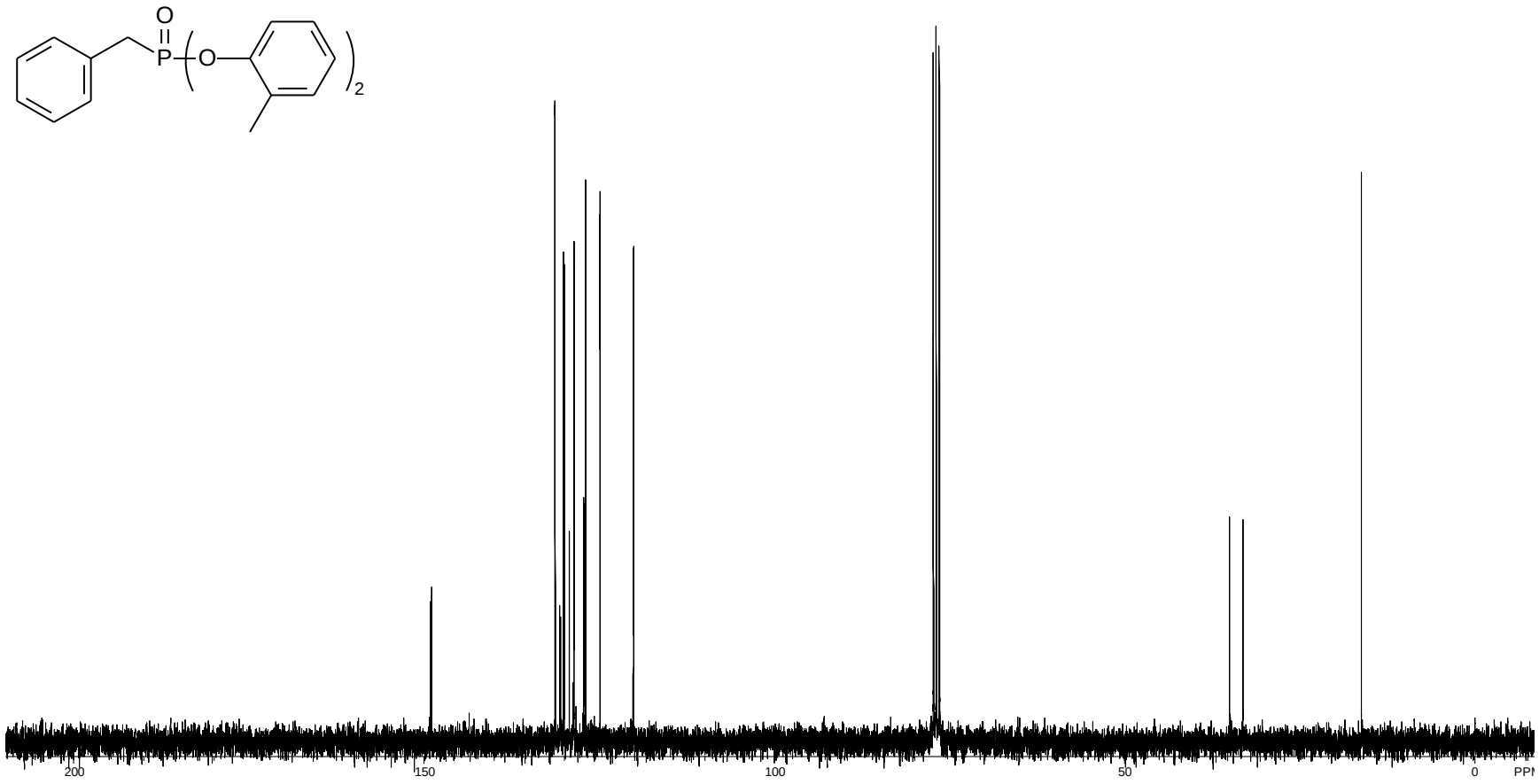


Figure A40. 75 MHz ^{13}C NMR Spectrum of Compound **246**.

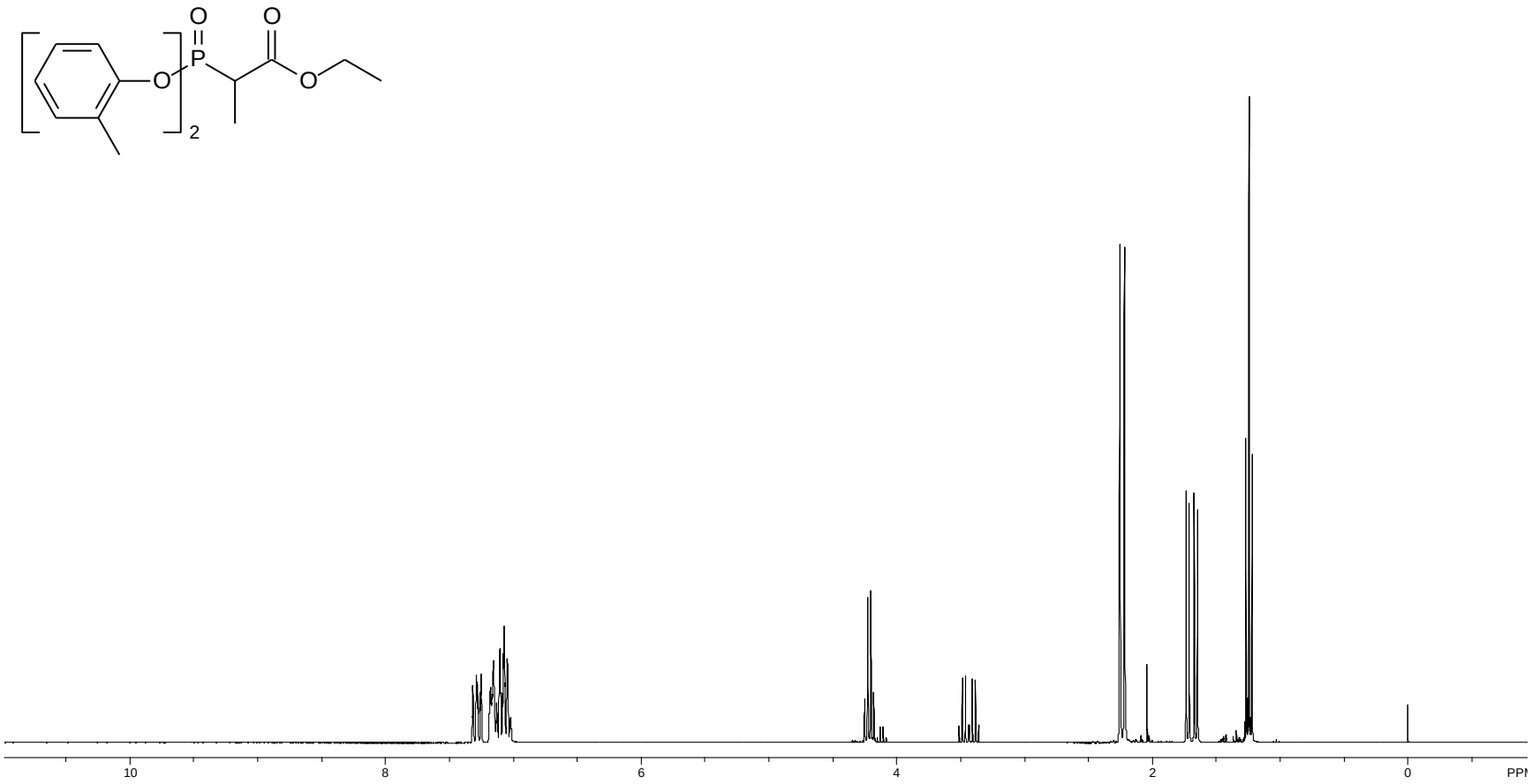


Figure A41. 300 MHz ^{1}H NMR Spectrum of Compound **224**.

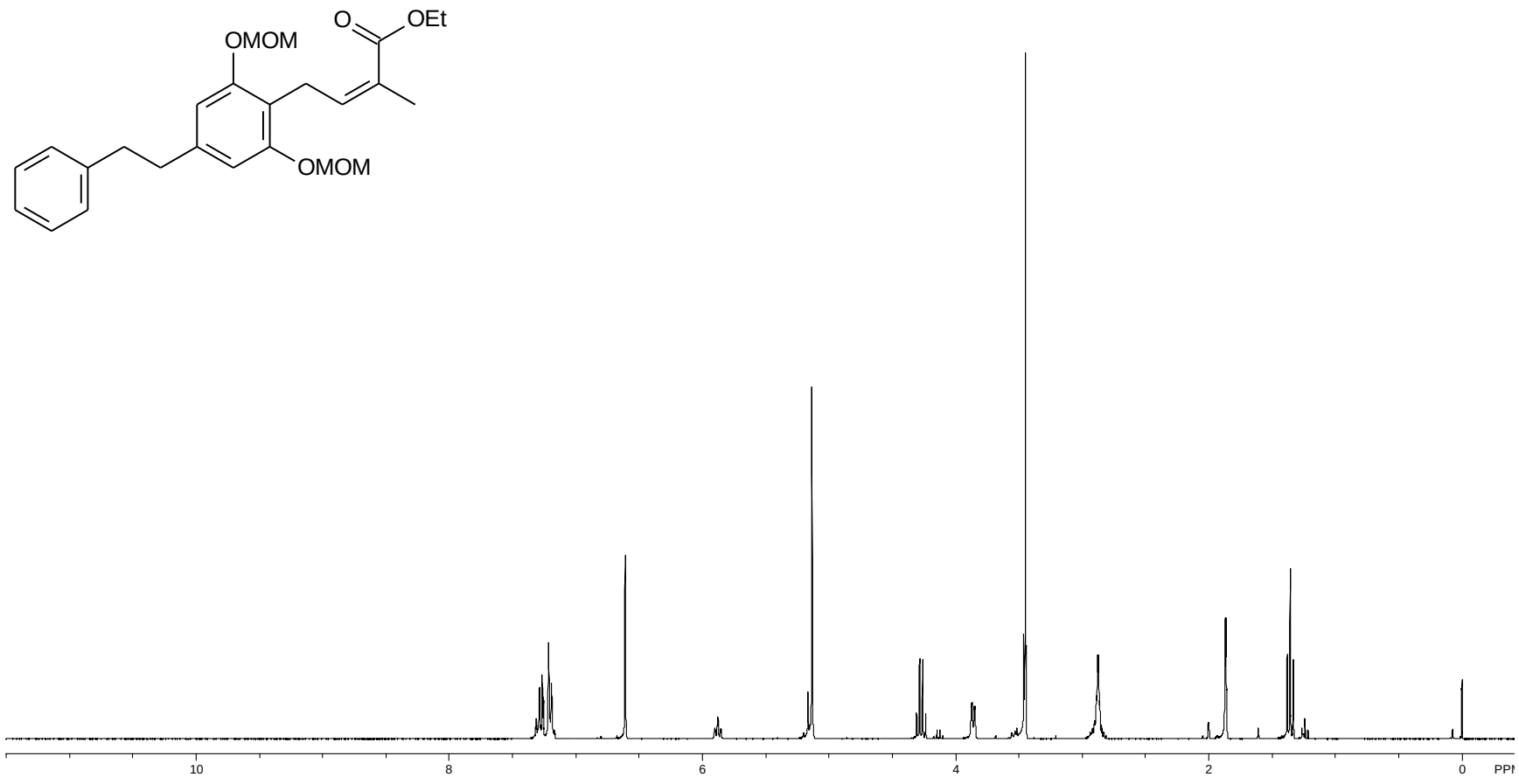


Figure A42. 300 MHz ^{1}H NMR Spectrum of Compound **225**.

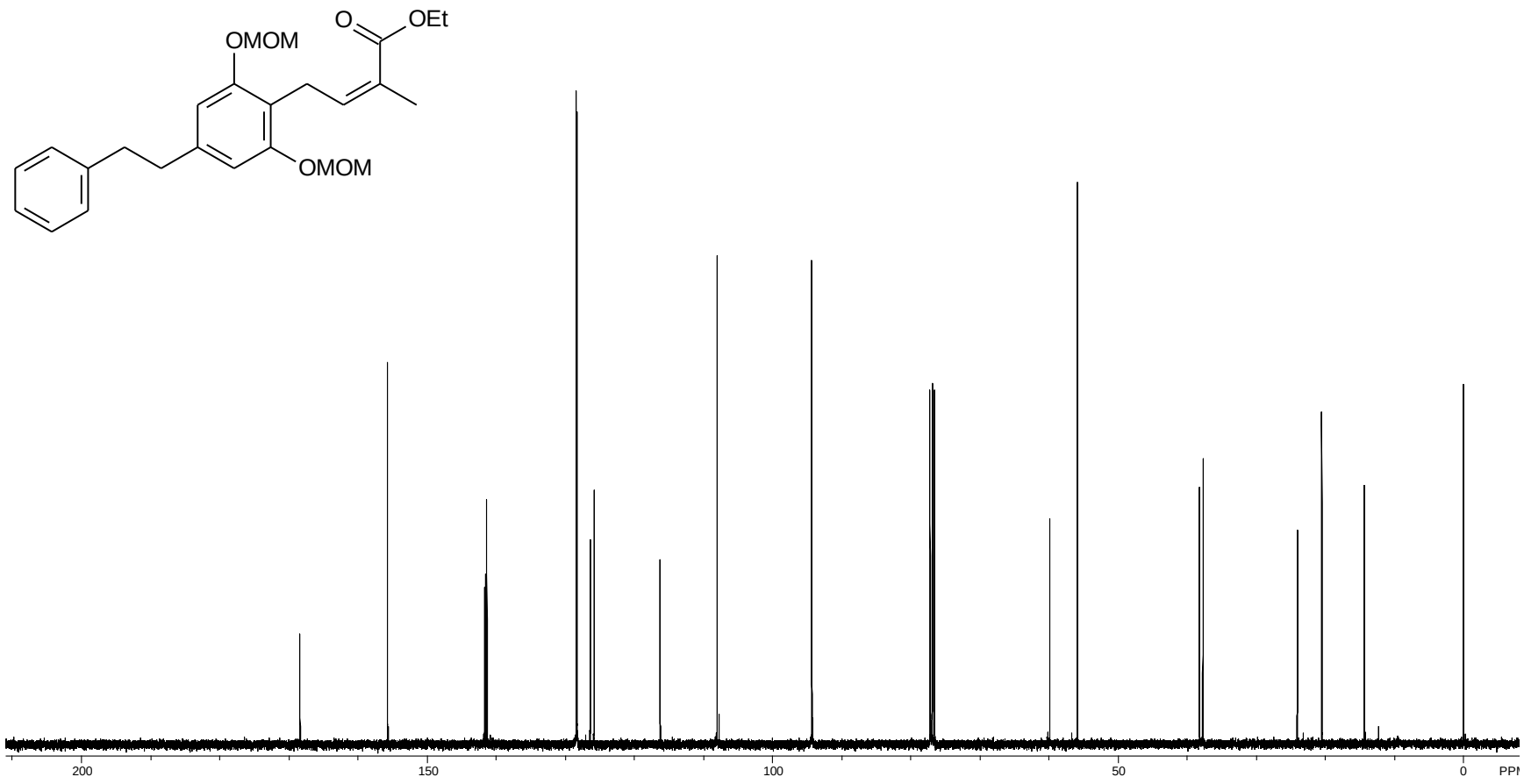


Figure A43. 100 MHz ^{13}C NMR Spectrum of Compound **225**.

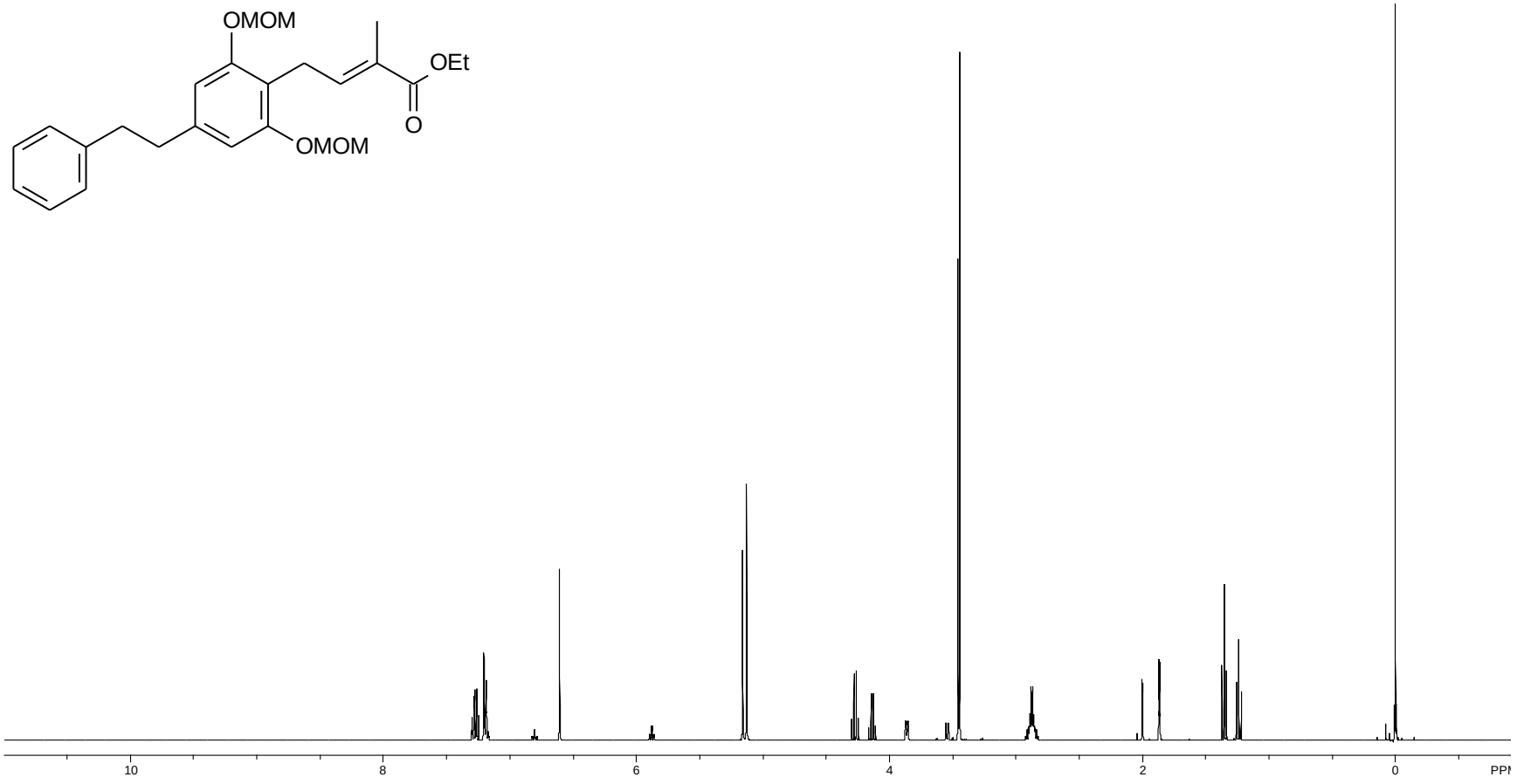


Figure A44. 400 MHz ^{1}H NMR Spectrum of Compound **237**.

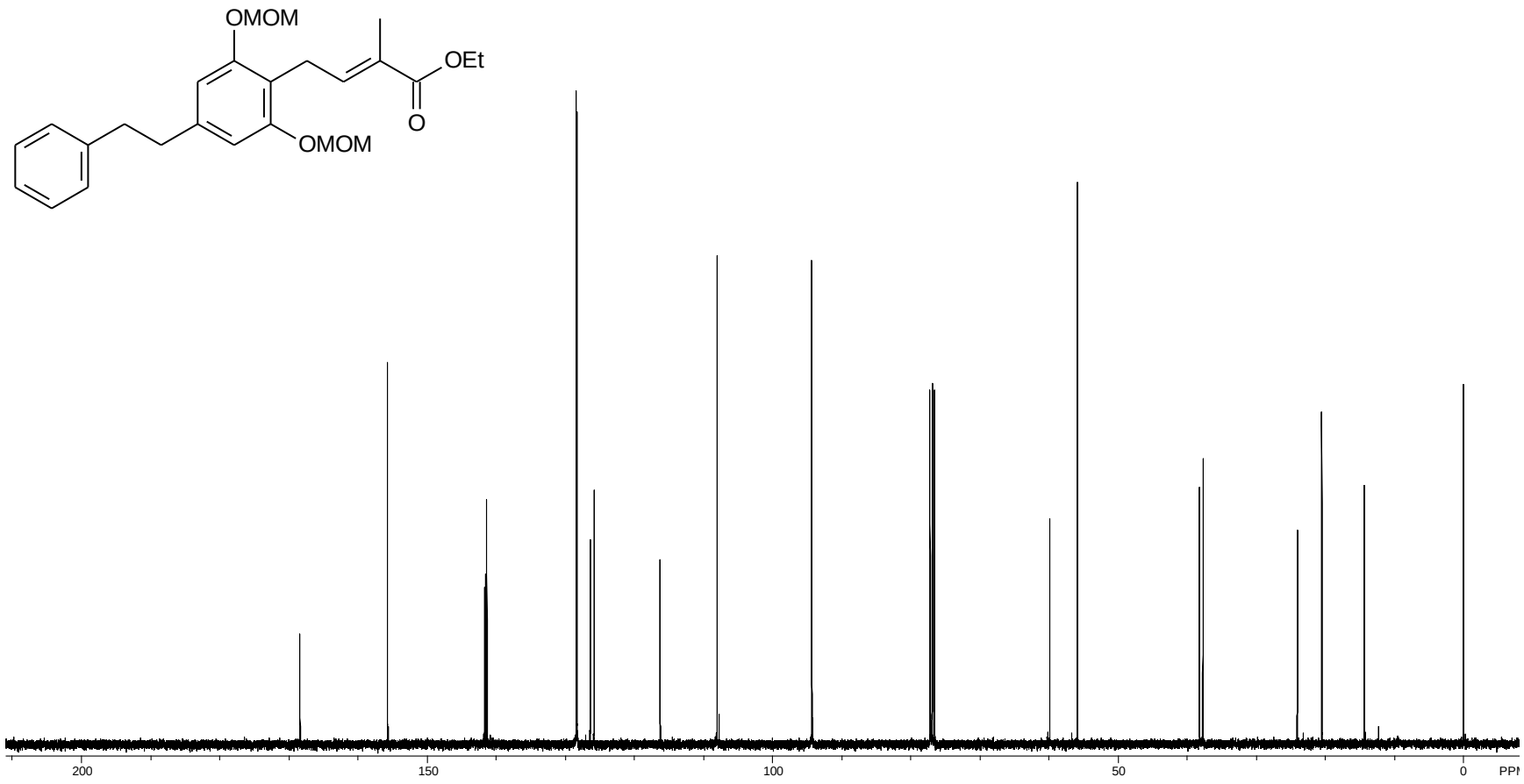


Figure A45. 100 MHz ^{13}C NMR Spectrum of Compound **237**.

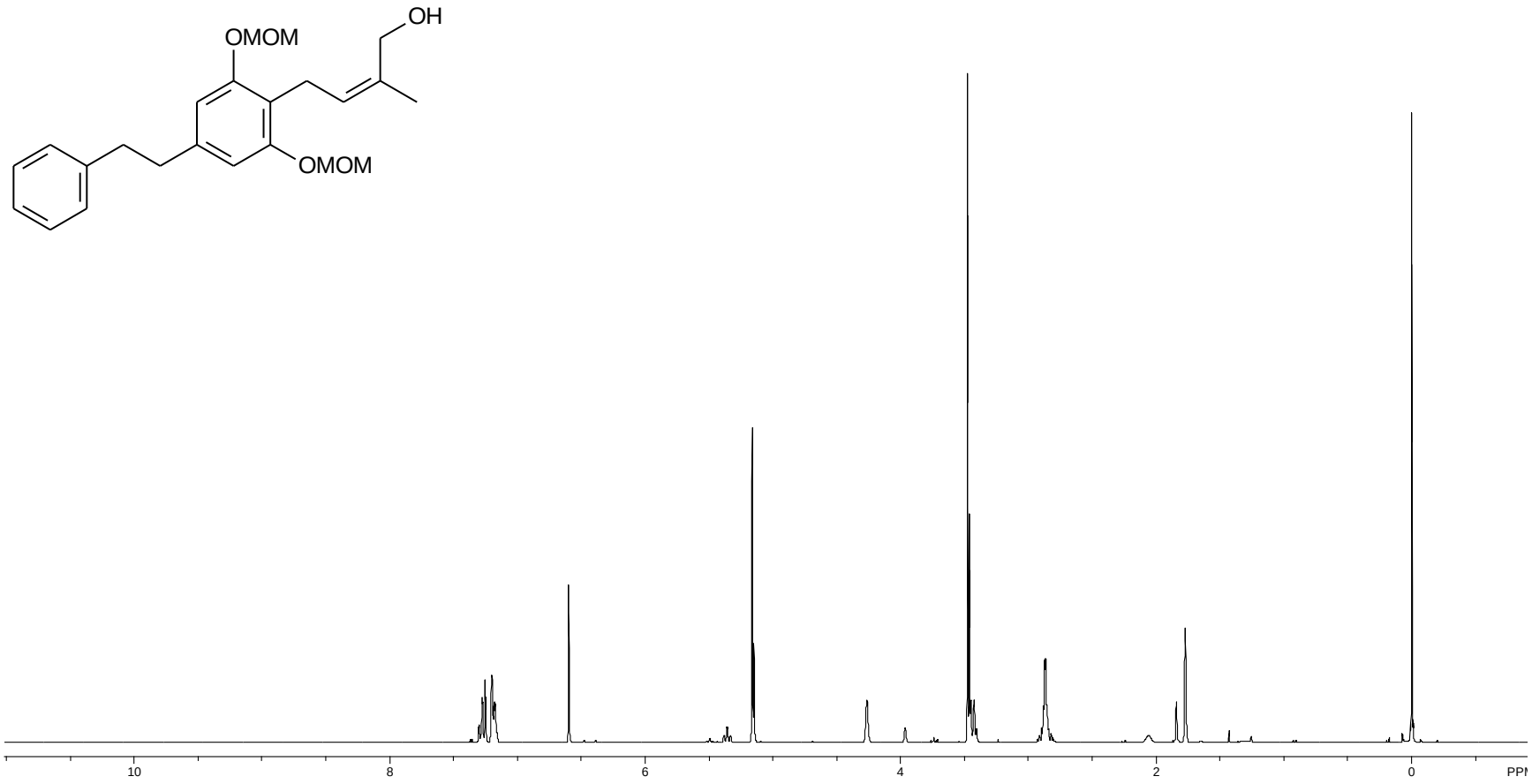


Figure A46. 300 MHz ^{1}H NMR Spectrum of Compound **205**.

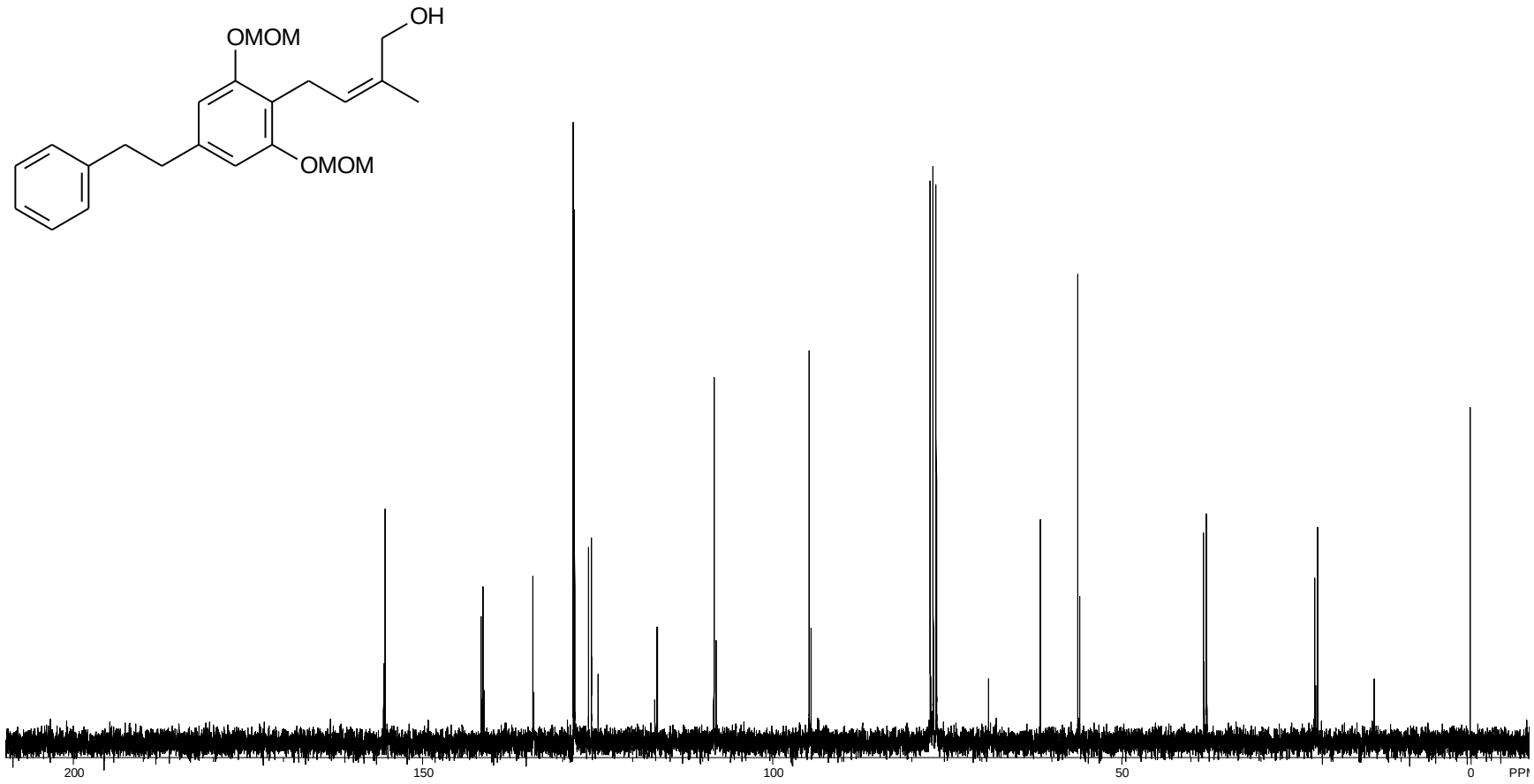


Figure A47. 75 MHz ^{13}C NMR Spectrum of Compound **205**.

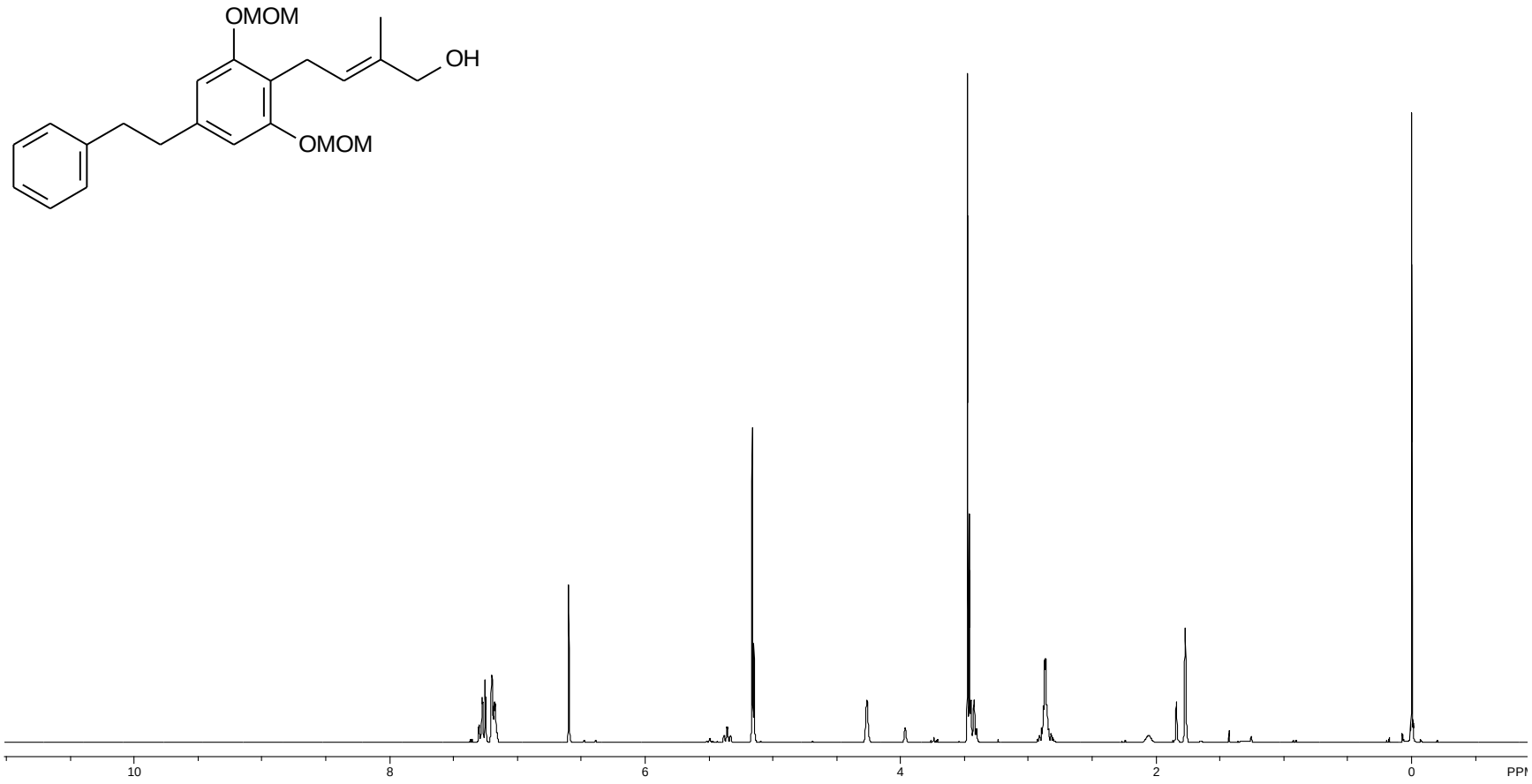


Figure A48. 300 MHz ^{1}H NMR Spectrum of Compound **238**.

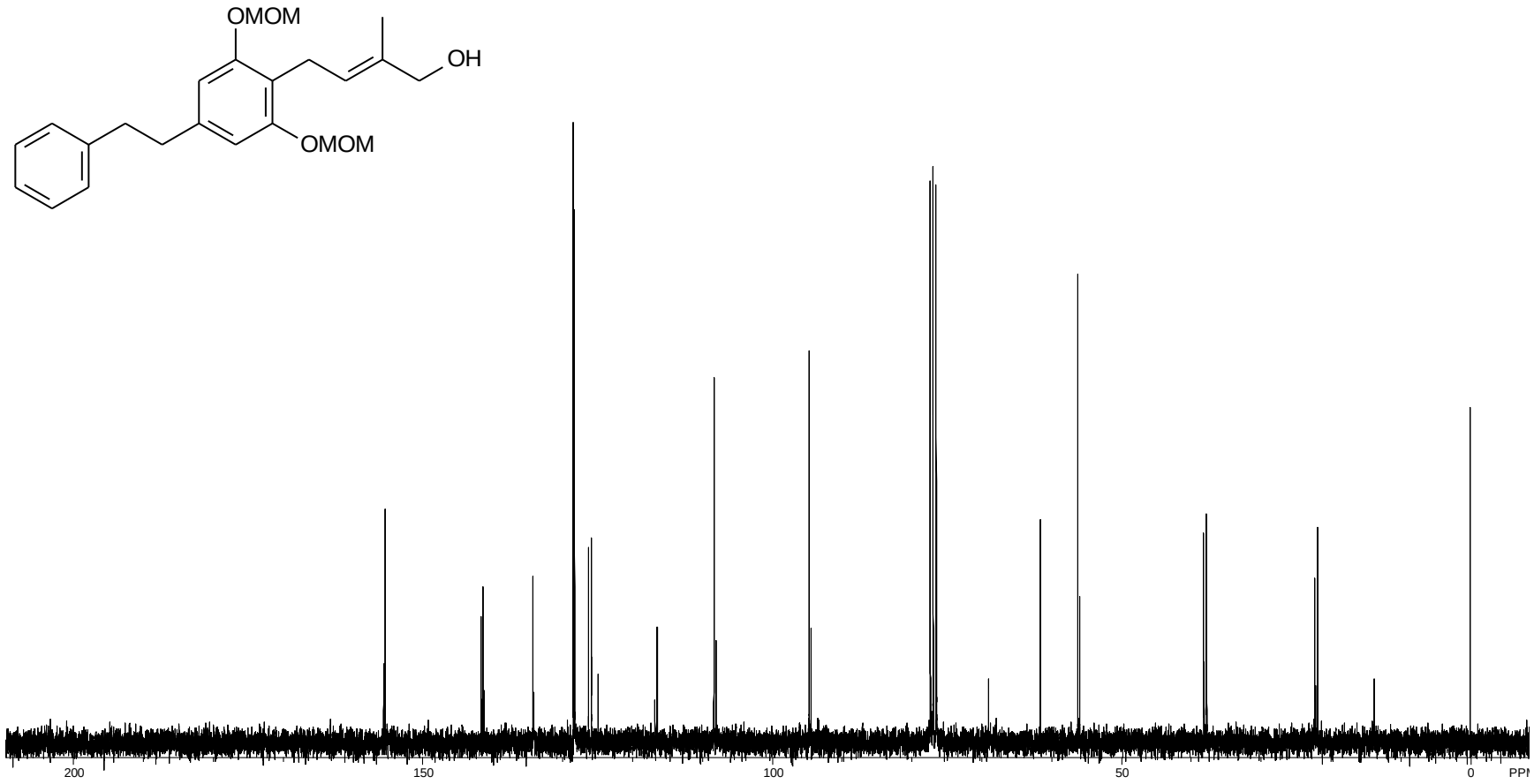


Figure A49. 75 MHz ^{13}C NMR Spectrum of Compound **238**.

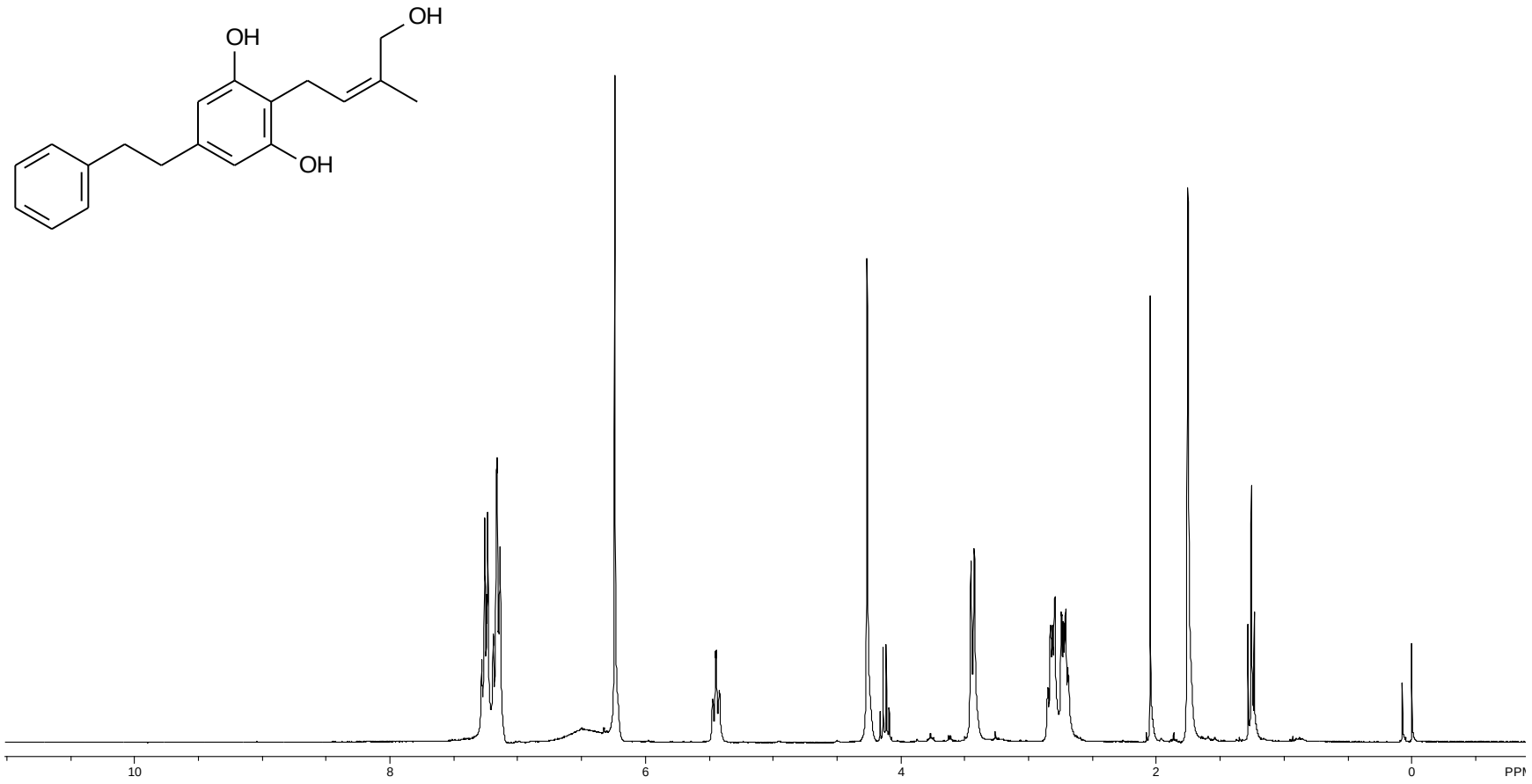


Figure A50. 300 MHz ^{1}H NMR Spectrum of Compound **233**.

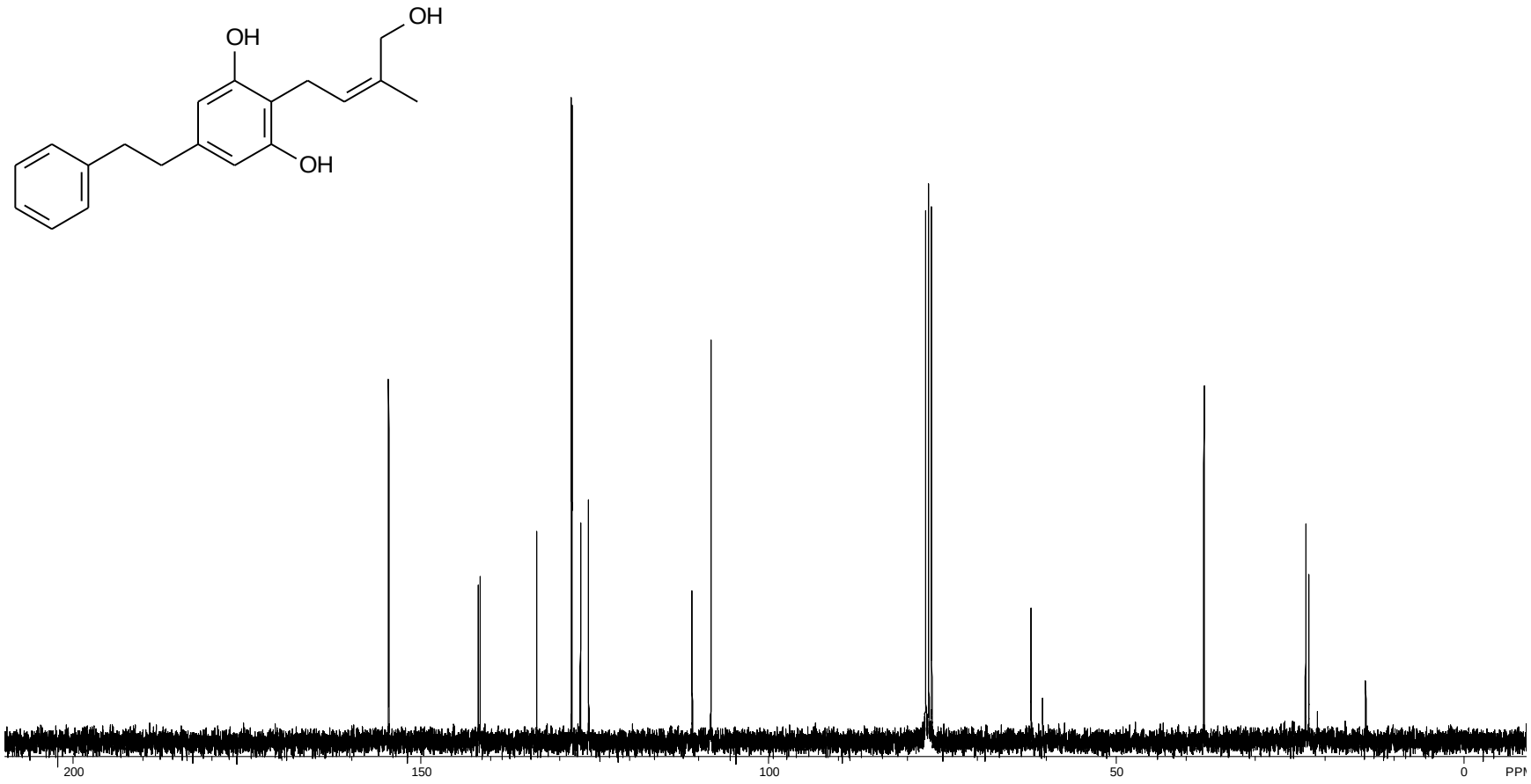


Figure A51. 75 MHz ^{13}C NMR Spectrum of Compound **233**.

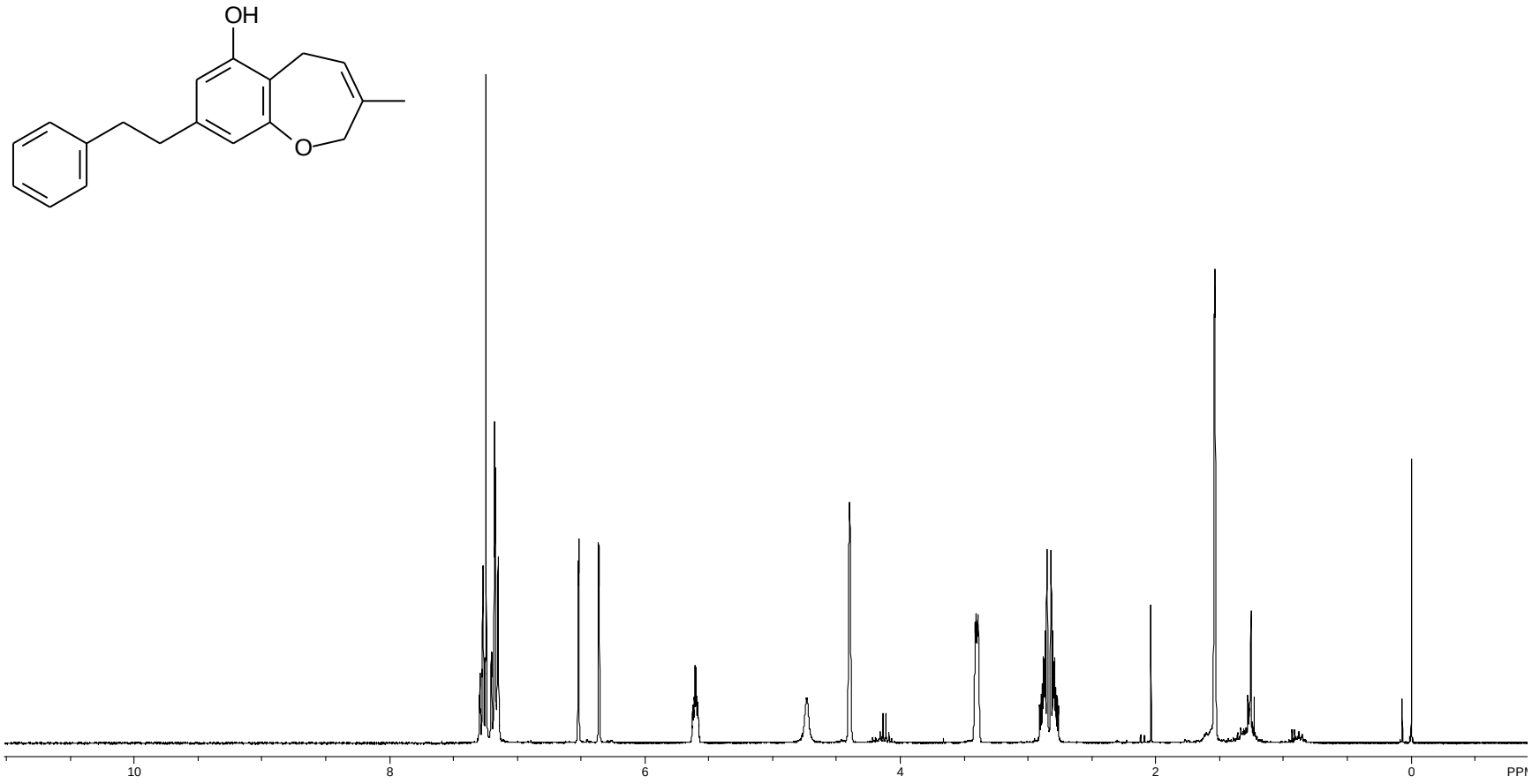


Figure A52. 300 MHz ^{1}H NMR Spectrum of Compound **83**.

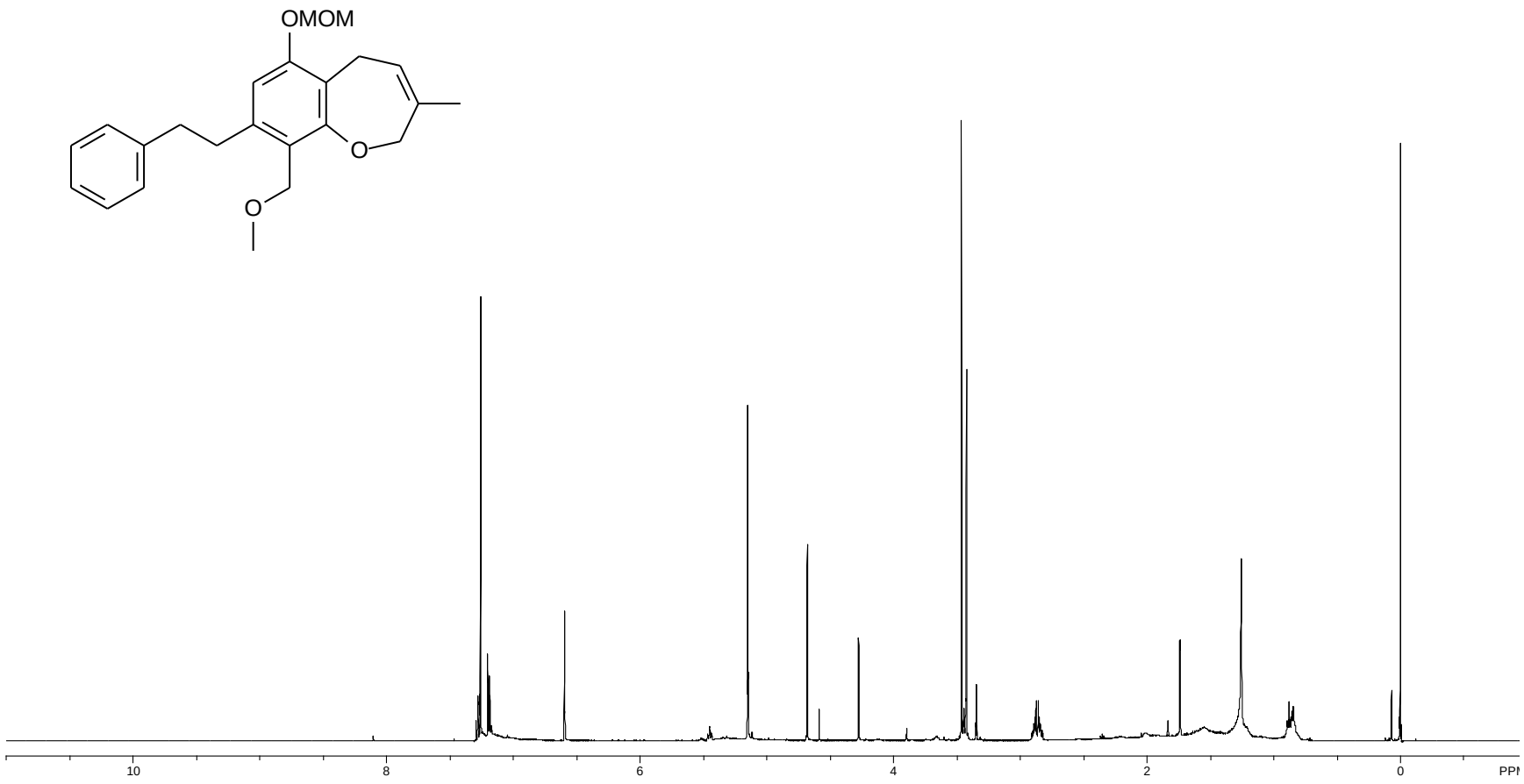


Figure A53. 500 MHz ^{1}H NMR Spectrum of Compound **234**.

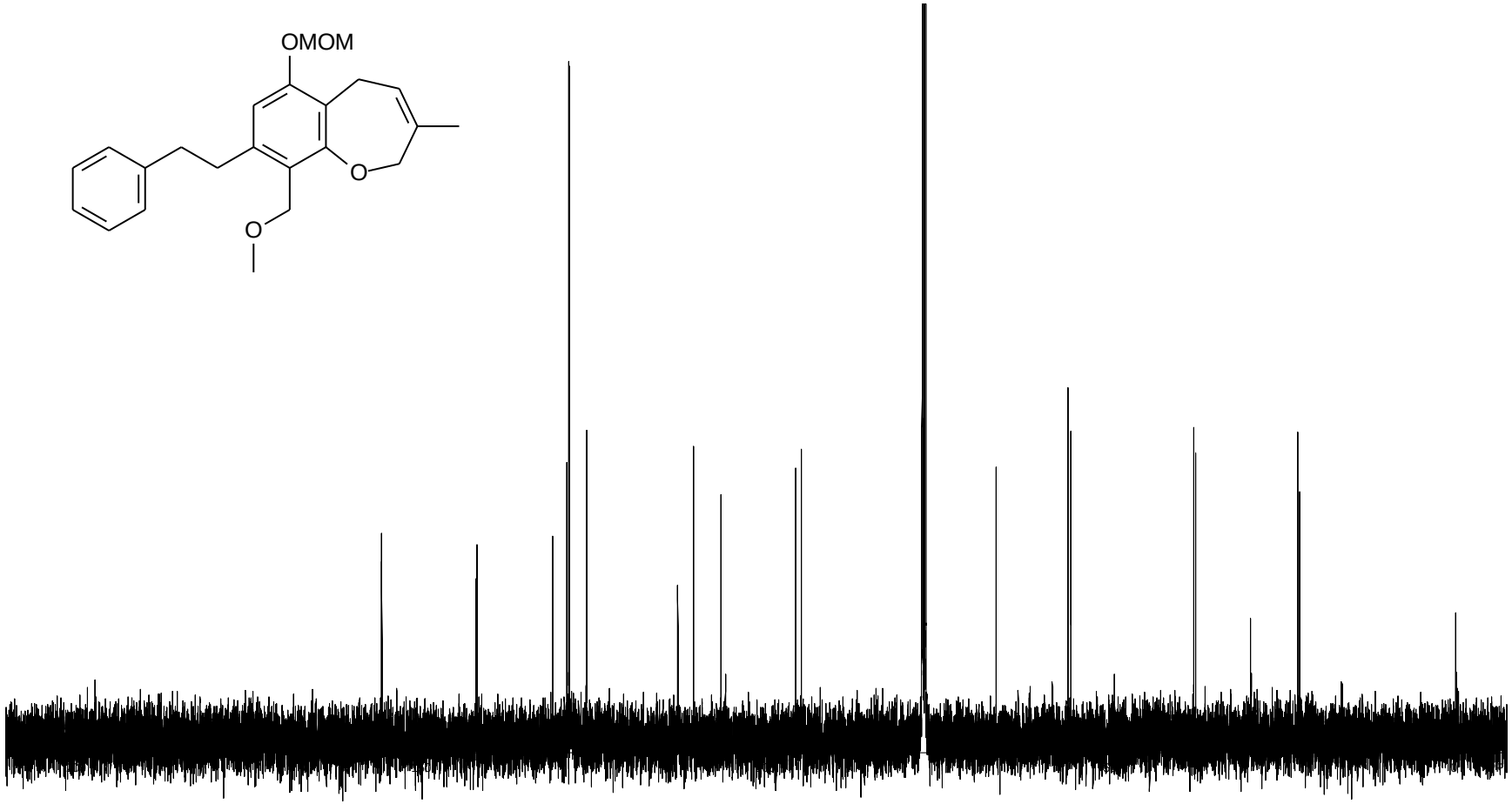


Figure A54. 125 MHz ^{13}C NMR Spectrum of Compound **234**.

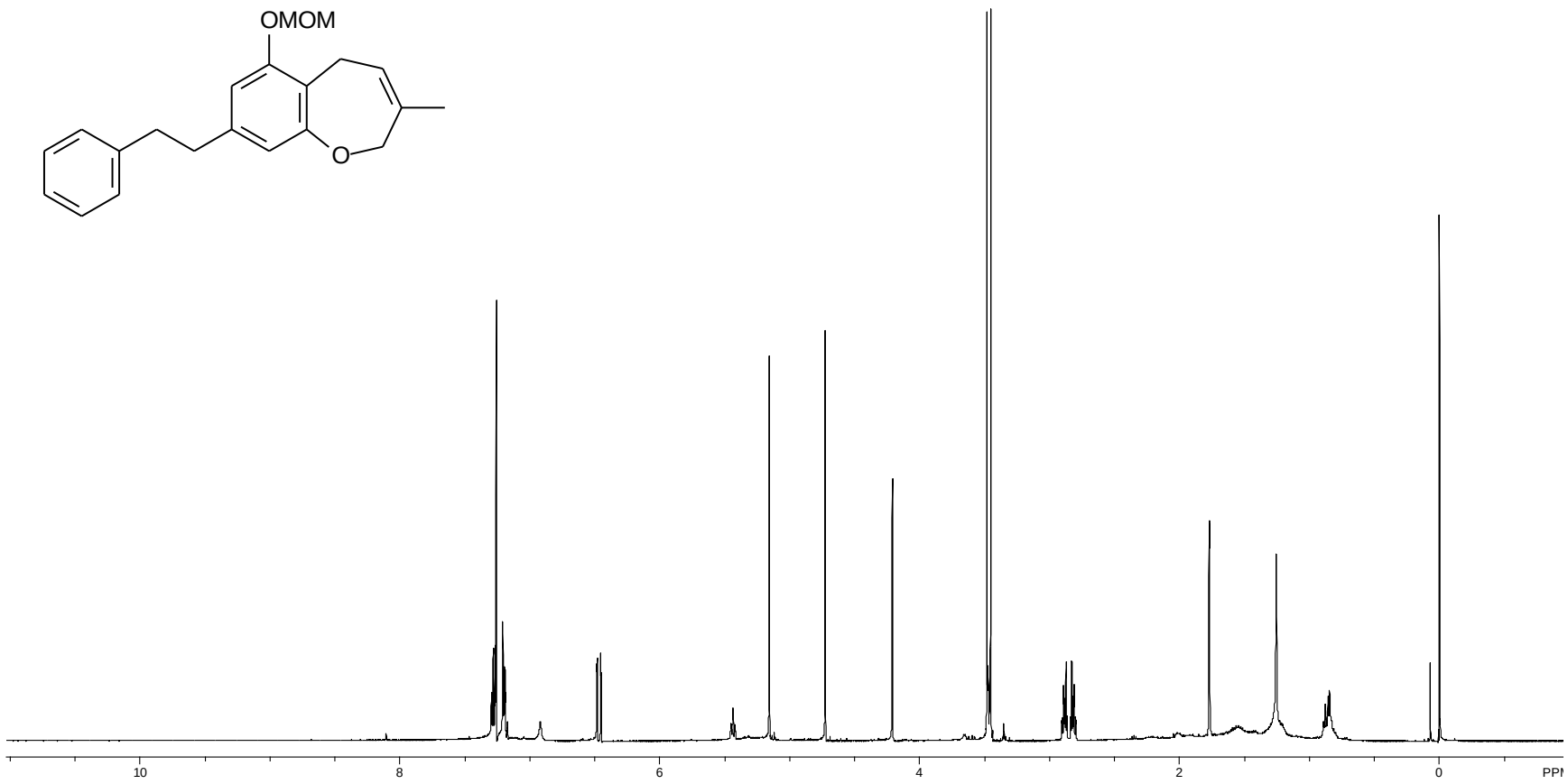


Figure A55. 500 MHz ^{1}H NMR Spectrum of Compound **69**.

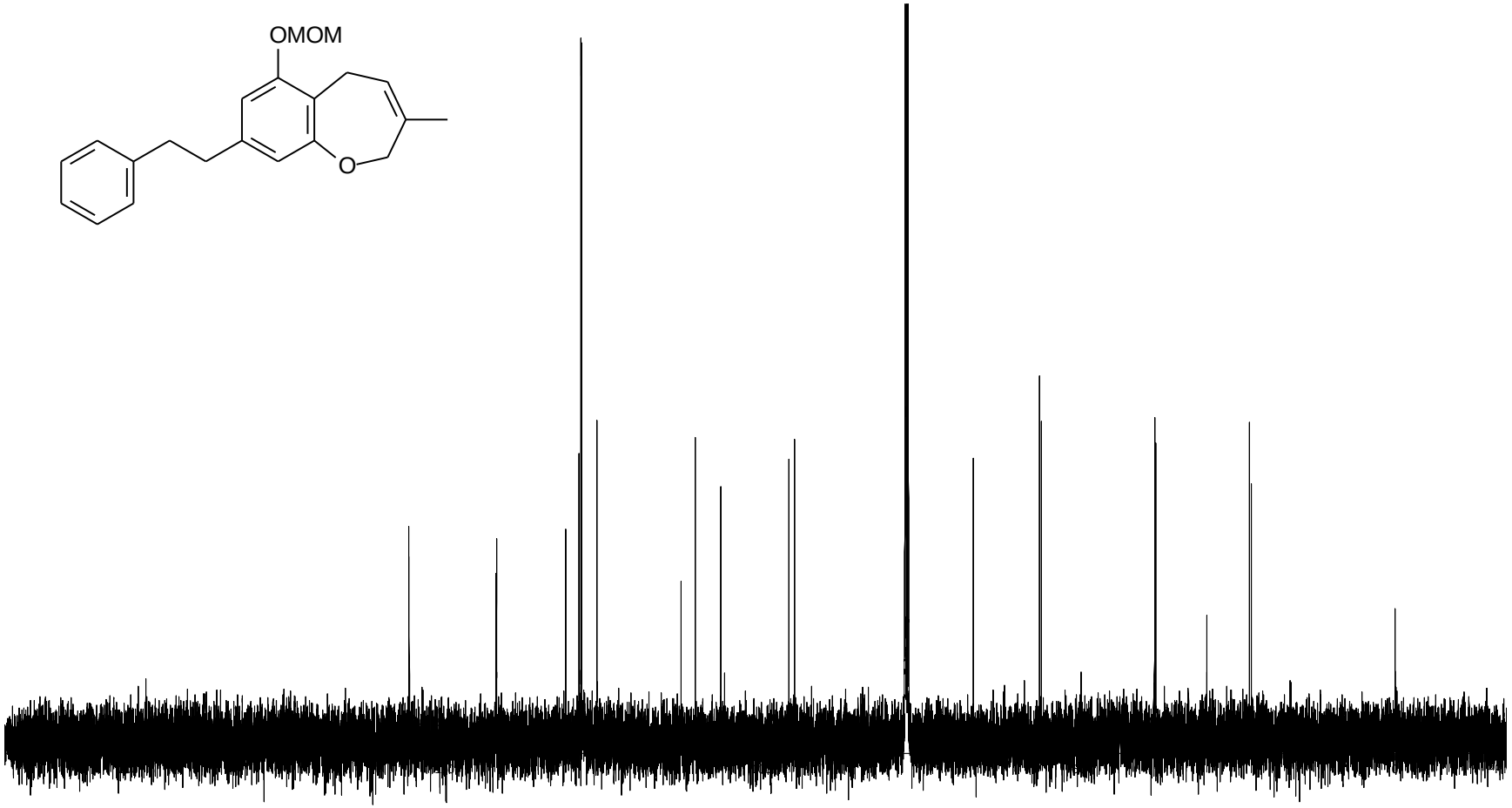


Figure A56. 125 MHz ^{13}C NMR Spectrum of Compound **69**.

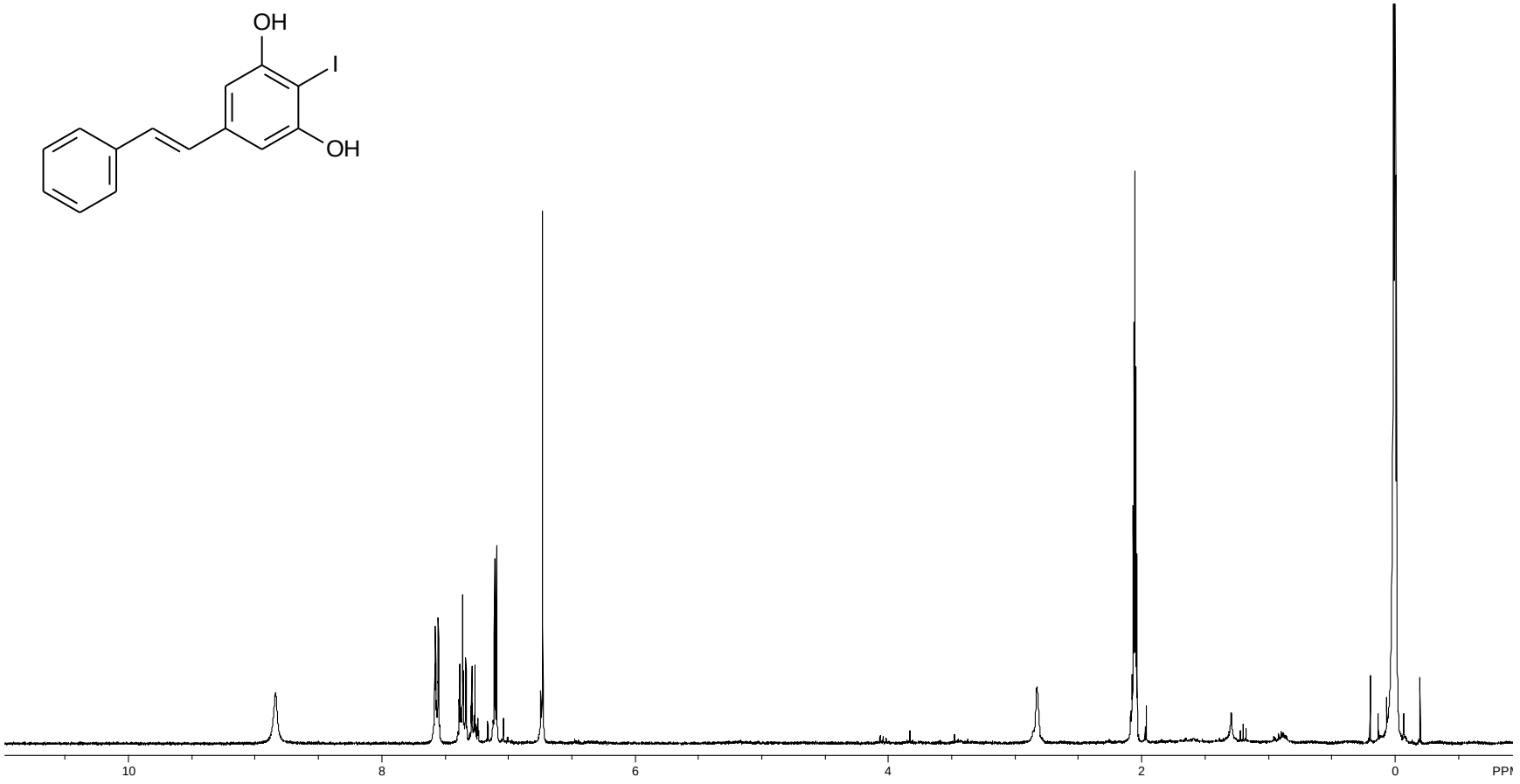


Figure A57. 300 MHz ^{1}H NMR Spectrum of Compound **252**.

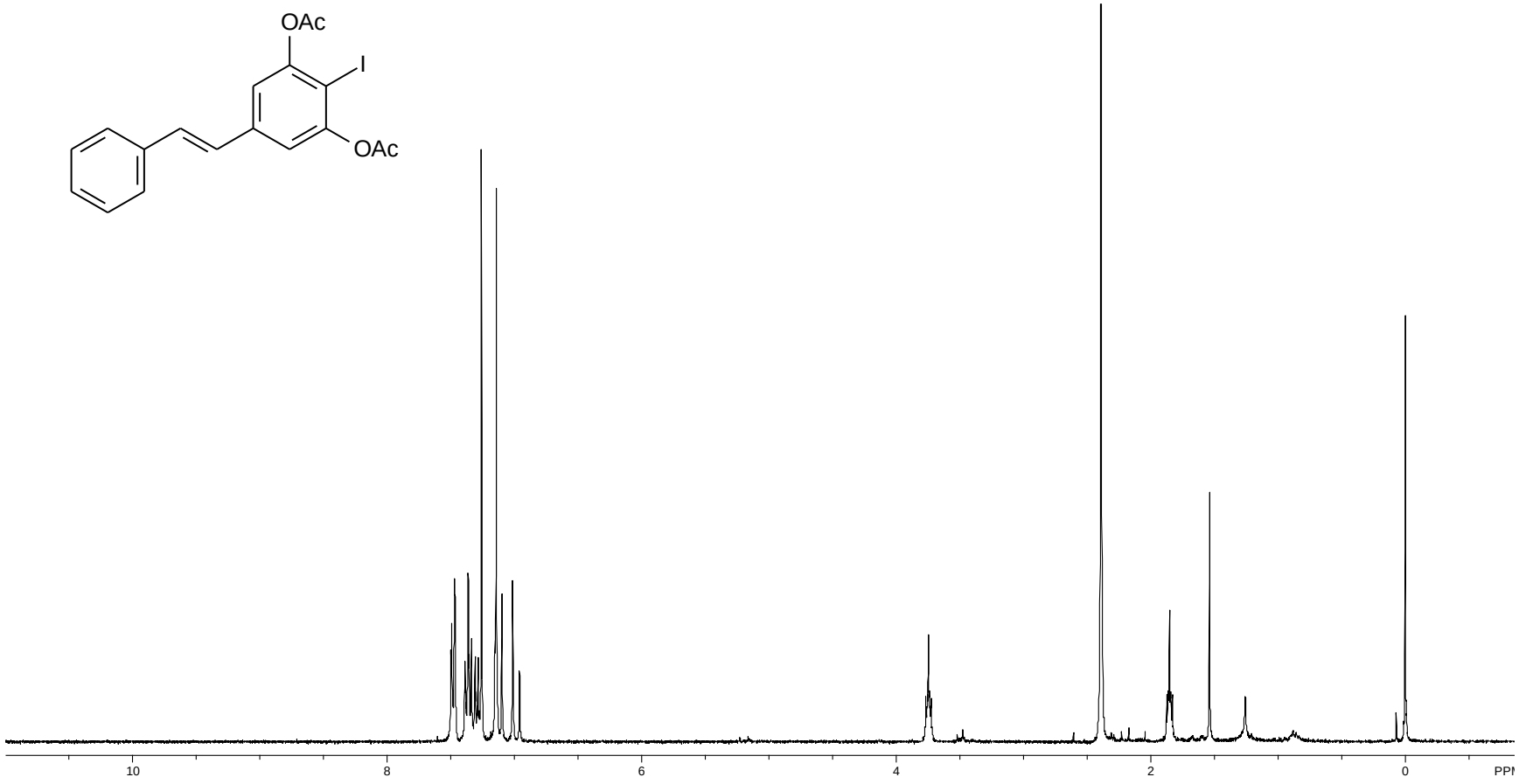


Figure A58. 300 MHz ^{1}H NMR Spectrum of Compound **253** with residual EtOAc peaks.

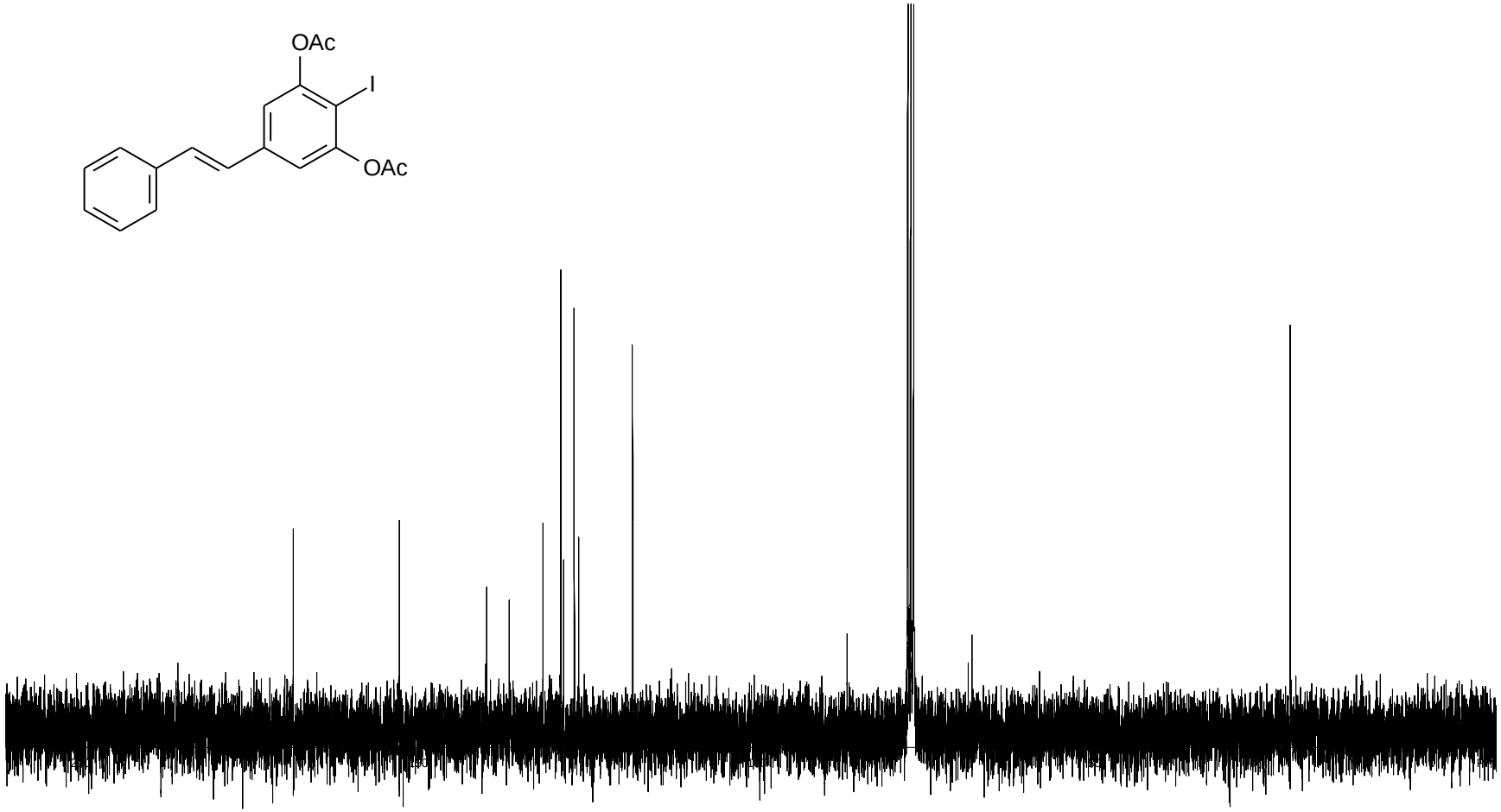


Figure A59. 75 MHz ^{13}C NMR Spectrum of Compound **253**.

REFERENCES

(1) Corbridge, D. E. C. *Phosphorus: an outline of its chemistry, biochemistry, and technology*,4th Ed.; Elsevier: New York, 1990.

(2) Toy, A. D. F. *Phosphorus chemistry in everyday living*; American Chemical Society: Washington, D.C., 1976.

(3) Project Gutenberg. History of Phosphorus by Eduard Farber. http://www.gutenberg.org/ebooks/33766 (accessed april/ 30, 2012).

(4) Ashley, K.; Cordell, D.; Mavinic, D. *Chemosphere* **2011**, *84*, 737-746.

(5) Emsley, J.; Hall, D., *The chemistry of phosphorus : environmental, organic, inorganic, biochemical, and spectroscopic aspects;* Wiley: New York, 1976.

(6) Oak Ridge National Laboraotry. *Summary review of Health Effects Associated with Elemental and Inorganic Phosphorus Compounds: Health Issue Assessment;* United States Environmental Protection Agency: Research Triangle Park, NC, 1990.

(7) Westheimer, F.H. The Role of Phosphorus in Chemisry and Biochemistry. In *Phosphorus Chemistry Developments in American Science*; Walsh, E. N. Griffith, E. J.; Parry, R. W.; Quin, L. D., Eds., American Chemical Society: Washington, D.C., 1992; pp 1-17.

(8) Piro, N. A.; Figueroa, J. S.; McKellar, J. T.; Cummins, C. C. *Science* **2006**, *313*, 1276-1279.

(9) Russell, C. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 9572-9573.

(10) Izod, K. *Coord. Chem. Rev.* **2002**, *227*, 153-173.

(11) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635-1649.

(12) Evans, D. A.; Johnson, J. S.; Burgey, C. S.; Campos, K. R. *Tetrahedron Lett.* **1999**, *40*, 2879-2882.

(13) Isaacs, N. S. *Physical organic chemistry*, 2nd ed.; Longman: New York, 1995.

(14) Skorupinska-Tudek, K.; Wojcik, J.; Swiezewska, E. *The Chemical Record* **2008**, *8*, 33-45.

(15) De Clercq, E. *Med. Res. Rev.* **2009**, *29*, 611-645.

(16) Piret, J.; Boivin, G. *Antimicrob. Agents Chemother.* **2011**, *55*, 459-472.

(17) Danso-Appiah, A.; Garner, P.; Olliaro, P. L.; Utzinger, J. *Parasitology* **2009**, *136*, 1837-1849.

(18) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380-2382.

(19) Gellerman, G.; Shitrit, S.; Shalit, T.; Ganot, O.; Albeck, A. *Tetrahedron* **2010**, *66*, 878-886.

(20) Yamaguchi, S.; Furihata, K.; Miyazawa, M.; Yokoyama, H.; Hirai, Y. *Tetrahedron Lett.* **2000**, *41*, 4787-4790.

(21) Mitsunobu, O. *Synthesis* **1981**, *1981*, 1-28.

(22) Schnabel, C.; Hiersemann, M. *Org. Lett.* **2009**, *11*, 2555-2558.

(23) Schiaffo, C. E.; Dussault, P. H. *J. Org. Chem.* **2008**, *73*, 4688-4690.

(24) Schwartz, C.; Raible, J.; Mott, K.; Dussault, P. H. *Tetrahedron* **2006**, *62*, 10747-10752.

(25) Schwartz, C.; Raible, J.; Mott, K.; Dussault, P. H. *Org. Lett.* **2006**, *8*, 3199-3201.

(26) Criegee, R. *Angew. Chem., Int. Ed.* **1975**, *14*, 745-752.

(27) Geletneky, C.; Berger, S. *Eur. J. Org. Chem.* **1998**, *1998*, 1625-1627.

(28) Schnepf, A.; Köppe, R. *Angew. Chem., Int. Ed.* **2003**, *42*, 911-913.

(29) Berens, U.; Burk, M. J.; Gerlach, A.; Hems, W. *Angew. Chem, Int. Ed.* **2000**, *39*, 1981-1984.

(30) Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2003**, *125*, 7198-7199.

(31) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629-631.

(32) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546-9547.

(33) Trost, B. M.; Fandrick, D. R.; Dinh, D. C. *J. Am. Chem. Soc.* **2005**, *127*, 14186-14187.

(34) Trost, B. M.; Bunt, R. C. *Angew. Chem., Int. Ed.* **1996**, *35*, 99-102.

(35) Johnson, A. W. *Ylide chemistry*; Blomquist, A. T., Eds.; Academic Press: New York, 1966.

(36) Nobelprize.org *http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1979/* (accessed may/ 31, 2012).

(37) Nicolaou, K. C.; Härter, M. W.; Gunzner, J. L.; Nadin, A. *Liebigs Annalen* **1997**, *1997*, 1283-1301.

(38) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863-927.

(39) McEwan, W. E.; Mari, F.; Lahti, P. M.; Baughman, L. L.; Ward, W. J., Jr. Mechanisms of the Wittig Reaction. In *Phosphorus Chemistry Developments in American Science*; Walsh, E. N. Griffith, E. J.; Parry, R. W.; Quin, L. D., Eds., American Chemical Society: Washington, D.C., 1992; pp 149-161.

(40) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73-253.

(41) Hudson, R. F. *Structure and mechanism is organo-phosphorus chemistry*; Blomquist, A. T., Eds.; Academic Press: New York, 1965.

(42) Vedejs, E.; Marth, C. F. *J. Am. Chem. Soc.* **1990**, *112*, 3905-3909.

(43) Rong, F. *Carbon-Chain Homologations;* In Name Reactions for Homologations, Part I; Li, J. J., Eds.; John Wiley & Sons, Inc.: Hoboken, NJ, 2009; pp 335-612.

(44) Vedejs, E.; Marth, C. F. *J. Am. Chem. Soc.* **1988**, *110*, 3948-3958.

(45) Vedejs, E.; Fleck, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 5861-5871.

(46) Yamataka, H.; Nagase, S. *J. Am. Chem. Soc.* **1998**, *120*, 7530-7536.

(47) Schlosser, M.; Schaub, B. *J. Am. Chem. Soc.* **1982**, *104*, 5821-5823.

(48) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87-99.

(49) Qi, C.; Du, Y.; Lu, Y.; Sun, X.; Zhang, X. *J. Org. Chem.* **2009**, *74*, 8078-8085.

(50) Wang, Q.; Deredas, D.; Huynh, C.; Schlosser, M. *Chem. Eur. J.* **2003**, *9*, 570-574.

(51) Zhang, X. M.; Bordwell, F. G. *J. Am. Chem. Soc.* **1994**, *116*, 968-972.

(52) Myers, A. G. *http://www.chem.harvard.edu/groups/myers/handouts/15_Horner-Wadsworth.pdf* (accessed may/ 31, 2012).

(53) Breuer, E.; Bannet, D. M. *Tetrahedron Lett.* **1977**, *18*, 1141-1144.

(54) Patois, C.; Savignac, P. *Synlett* **1991**, *1991*, 517-19.

(55) Patois, C.; Savignac, P. *Tetrahedron Lett.* **1991**, *32*, 1317-1320.

(56) Sakai, H.; Hirano, T.; Mori, S.; Fujii, S.; Masuno, H.; Kinoshita, M.; Kagechika, H.; Tanatani, A. *J. Med. Chem.* **2011**, *54*, 7055-7065.

(57) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405-4408.

(58) Ando, K. *J. Org. Chem.* **1999**, *64*, 8406-8408.

(59) Ando, K. *J. Org. Chem.* **1998**, *63*, 8411-8416.

(60) Ando, K. *J. Org. Chem.* **1997**, *62*, 1934-1939.

(61) Ando, K. *Tetrahedron Lett.* **1995**, *36*, 4105-4108.

(62) Abdou, W. M.; Shaddy, A. A. *ARKIVOC* **2009**, *9*, 143-182.

(63) Clézardin, P.; Ebetino, F. H.; Fournier, P. G. J. *Cancer Res.* **2005**, *65*, 4971-4974.

(64) Nancollas, G. H.; Tang, R.; Phipps, R. J.; Henneman, Z.; Gulde, S.; Wu, W.; Mangood, A.; Russell, R. G. G.; Ebetino, F. H. *Bone* **2006**, *38*, 617-627.

(65) Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415-430.

(66) Brill, T. B.; Landon, S. J. *Chem. Rev.* **1984**, *84*, 577-585.

(67) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733-1738.

(68) Renard, P.; Vayron, P.; Leclerc, E.; Valleix, A.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 2389-2392.

(69) Renard, P.; Vayron, P.; Mioskowski, C. *Org. Lett.* **2003**, *5*, 1661-1664.

(70) Engel, R.; Cohen, J. L. *Synthesis of Carbon–Phosphorus Bonds*, 2nd ed.; CRC Press: Boca Raton, 2003.

(71) Hammond, G. B.; Calogeropoulou, T.; Wiemer, D. F. *Tetrahedron Lett.* **1986**, *27*, 4265-4268.

(72) Calogeropoulou, T.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1987**, *52*, 4185-4190.

(73) Baker, T. J.; Wiemer, D. F. *J. Org. Chem.* **1998**, *63*, 2613-2618.

(74) Lee, K.; Wiemer, D. F. *J. Org. Chem.* **1991**, *56*, 5556-5560.

(75) Du, Y.; Wiemer, D. F. *J. Org. Chem.* **2002**, *67*, 5701-5708.

(76) Chen, X.; Wiemer, A. J.; Hohl, R. J.; Wiemer, D. F. *J. Org. Chem.* **2002**, *67*, 9331-9339.

(77) Barney, R. J.; Wasko, B. M.; Dudakovic, A.; Hohl, R. J.; Wiemer, D. F. *Bioorg. Med. Chem.* **2010**, *18*, 7212-7220.

(78) Wiemer, A. J.; Yu, J. S.; Lamb, K. M.; Hohl, R. J.; Wiemer, D. F. *Bioorg. Med. Chem.* **2008**, *16*, 390-399.

(79) Shull, L. W.; Wiemer, A. J.; Hohl, R. J.; Wiemer, D. F. *Bioorg. Med. Chem.* **2006**, *14*, 4130-4136.

(80) Smits, J. P. Synthesis and evaluation of novel bis-and trisphosphonates. Ph.D. dissertation, University of Iowa, Iowa City, IA, 2011.

(81) Smits, J. P.; Wiemer, D. F. *J. Org. Chem.* **2011**, *76*, 8807-8813.

(82) Beutler, J. A.; Shoemaker, R. H.; Johnson, T.; Boyd, M. R. *J. Nat. Prod.* **1998**, *61*, 1509-1512.

(83) Beutler, J. A.; Jato, J.; Cragg, G. M.; Boyd, M. R. *Nat. Prod. Lett.* **2000**, *14*, 399-404.

(84) Yoder, B. J.; Cao, S.; Norris, A.; Miller, J. S.; Ratovoson, F.; Razafitsalama, J.; Andriantsiferana, R.; Rasamison, V. E.; Kingston, D. G. I. *J. Nat. Prod.* **2007**, *70*, 342-346.

(85) Thoison, O.; Hnawia, E.; Guiéritte-Voegelein, F.; Sévenet, T. *Phytochemistry* **1992**, *31*, 1439-1442.

(86) Treadwell, E. M.; Cermak, S. C.; Wiemer, D. F. *J. Org. Chem.* **1999**, *64*, 8718-8723.

(87) Neighbors, J. D.; Beutler, J. A.; Wiemer, D. F. *J. Org. Chem.* **2005**, *70*, 925-931.

(88) Mente, N. R.; Wiemer, A. J.; Neighbors, J. D.; Beutler, J. A.; Hohl, R. J.; Wiemer, D. F. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 911-915.

(89) Mente, N. R.; Neighbors, J. D.; Wiemer, D. F. *J. Org. Chem.* **2008**, *73*, 7963-7970.

(90) Topczewski, J. J.; Neighbors, J. D.; Wiemer, D. F. *J. Org. Chem.* **2009**, *74*, 6965-6972.

(91) Topczewski, J. J.; Kodet, J. G.; Wiemer, D. F. *J. Org. Chem.* **2011**, *76*, 909-919.

(92) Belofsky, G.; French, A. N.; Wallace, D. R.; Dodson, S. L. *J. Nat. Prod.* **2004**, *67*, 26-30.

(93) Neighbors, J. D.; Salnikova, M. S.; Wiemer, D. F. *Tetrahedron Lett.* **2005**, *46*, 1321-1324.

(94) Neighbors, J. D.; Buller, M. J.; Boss, K. D.; Wiemer, D. F. *J. Nat. Prod.* **2008**, *71*, 1949-1952.

(95) Stefinovic, M.; Snieckus, V. *J. Org. Chem.* **1998**, *63*, 2808-2809.

(96) Yoshida, M.; Nakatani, K.; Shishido, K. *Tetrahedron* **2009**, *65*, 5702-5708.

(97) Asakawa, Y.; Toyota, M.; Takemoto, T. *Phytochemistry* **1978**, *17*, 2005-2010.

(98) Asakawa, Y.; Kusube, E.; Takemoto, T.; Suire, C. *Phytochemistry* **1978**, *17*, 2115-2117.

(99) Asakawa, Y.; Kondo, K.; Tori, M. *Phytochemistry* **1991**, *30*, 325-328.

(100) Asakawa, Y.; Takeda, R.; Toyota, M.; Takemoto, T. *Phytochemistry* **1981**, *20*, 858-859.

(101) Asakawa, Y.; Hashimoto, T.; Takikawa, K.; Tori, M.; Ogawa, S. *Phytochemistry* **1991**, *30*, 235-251.

(102) Asakawa, Y. *Pure Appl. Chem.* **2007**, *79*, 557-580.

(103) Yamaguchi, S.; Tsuchida, N.; Miyazawa, M.; Hirai, Y. *J. Org. Chem.* **2005**, *70*, 7505-7511.

(104) Eicher, T.; Tiefensee, K.; Dönig, R.; Pick, R. *Synthesis* **1991**, *1991*, 98-102.

(105) Barney, R. J. Synthesis and Biological Evaluation of Novel Phosphonates. Ph.D. dissertation, University of Iowa, Iowa City, IA, 2010.

(106) Barney, R. J.; Richardson, R. M.; Wiemer, D. F. *J. Org. Chem.* **2011**, *76*, 2875-2879.

(107) Kim, S.; Chung, K. N.; Yang, S. *J. Org. Chem.* **1987**, *52*, 3917-3919.

(108) Gauthier, J. Y.; Bourdon, F.; Young, R. N. *Tetrahedron Lett.* **1986**, *27*, 15-18.

(109) Guindon, Y.; Frenette, R.; Fortin, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 1357-1359.

(110) Clarembeau, M.; Krief, A. *Tetrahedron Lett.* **1984**, *25*, 3625-3628.

(111) Kim, S.; Kim, Y. J.; Ahn, K. H. *Tetrahedron Lett.* **1983**, *24*, 3369-3372.

(112) Lau, C. K.; Dufresne, C.; Belanger, P. C.; Pietre, S.; Scheigetz, J. *J. Org. Chem.* **1986**, *51*, 3038-3043.

(113) Ivanov, B. E.; Ageeva, A. B.; Abul 'Khanov, A. G.; Zyablikova, T. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* 1912 (1969); Chem. Abst. **72**, 21110n (1970).

(114) Ageeva, A. B.; Ivanov, B. E. *Izv. Akad. Nauk SSSR, Ser. Khim.* 1494 (1967); Chem. Abst. **68**, 39738a (1968).

(115) Ivanov, B. E.; Valitova, L. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* 1087 (1967); Chem. Abst. **68**, 3972 (1968).

(116) Ivanov, B. E.; Valitova, L. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1967**, , 1087.

(117) Chasar, D. W. *J. Org. Chem.* **1983**, *48*, 4768-4769.

(118) Sardariana, A. R.; Shahsavari-Farda, Z. *Synth. Commun.* **2007**, *37*, 289-295.

(119) Hanessian, S.; Guindon, Y. *Tetrahedron Lett.* **1980**, *21*, 2305-2308.

(120) Mugrage, B.; Diefenbacher, C.; Somers, J.; Parker, D. T.; Parker, T. *Tetrahedron Lett.* **2000**, *41*, 2047-2050.

(121) Plabst, M.; Stock, N.; Bein, T. *Cryst. Growth Des.* **2009**, *9*, 5049-5060.

(122) Greenwood, N. N. Earnshaw, A. In *Chemistry of the Elements;* Oxford: Butterworth-Heinemann: Boston, Mass., 1997; pp 1206-1209.

(123) Rajeshwaran, G. G.; Nandakumar, M.; Sureshbabu, R.; Mohanakrishnan, A. K. *Org. Lett.* **2011**, *13*, 1270-1273.

(124) Sarmah, P.; Barua, N. C. *Tetrahedron* **1989**, *45*, 3569-3574.

(125) Richardson, R. M.; Wiemer, D. F. *Org. Synth.* **2012**, Submitted.

(126) Khartulyari, A. S.; Kapur, M.; Maier, M. E. *Org. Lett.* **2006**, *8*, 5833-5836.

(127) Wang, D.; Hu, X.; Deng, J.; Yu, S.; Duan, Z.; Zheng, Z. *J. Org. Chem.* **2009**, *74*, 4408-4410.

(128) Cheruku, P.; Paptchikhine, A.; Church, T. L.; Andersson, P. G. *J. Am. Chem. Soc.* **2009**, *131*, 8285-8289.

(129) Ulrich, N. C.; Kodet, J. G.; Mente, N. R.; Kuder, C. H.; Beutler, J. A.; Hohl, R. J.; Wiemer, D. F. *Bioorg. Med. Chem.* **2010**, *18*, 1676-1683.

(130) Neighbors, J. D.; Mente, N. R.; Boss, K. D.; Zehnder II, D. W.; Wiemer, D. F. *Tetrahedron Lett.* **2008**, *49*, 516-519.

(131) Kim, H.; Bae, H.; Kim, S.; Kim, D.; Lee, D.; Paton, R. S. *Tetrahedron* **2011**, *67*, 10017-10025.

(132) Liu, K. K. -.; Sakya, S. M.; O'Donnell, C. J.; Flick, A. C.; Ding, H. X. *Bioorg. Med. Chem.* **2012**, *20*, 1155-1174.

(133) Paterson, I.; Britton, R.; Delgado, O.; Meyer, A.; Poullennec, K. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 4629-4633.

(134) Gaul, C.; Njardarson, J.; Shan, D.; Dorn, D. C.; Wu, K.; Tong, W. P.; Huang, X.; Moore, M. A. S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 11326-11337.

(135) Evans, D. A.; Carter, P. H.; Carreira, E. M.; Charette, A. B.; Prunet, J. A.; Lautens, M. *J. Am. Chem. Soc.* **1999**, *121*, 7540-7552.

(136) Neighbors, J. D.; Topczewski, J. J.; Swenson, D. C.; Wiemer, D. F. *Tetrahedron Lett.* **2009**, *50*, 3881-3884.

(137) Neighbors, J. D.; Salnikova, M. S.; Beutler, J. A.; Wiemer, D. F. *Bioorg. Med. Chem.* **2006**, *14*, 1771-1784.

(138) Violeta Benedetti, M. O.; Monteagudo, E. S.; Burton, G. *J. Chem. Research (S)* **1990**, *1990*, 248-249.

(139) Rakov, A. P.; Rudnitskaya, G. F.; Andreev, G. F. *J. Gen. Chem. USSR* **1976**, *46*, 1450-1452.

(140) Marcos Ramos, A.; Beckers, E. H. A.; Offermans, T.; Meskers, S. C. J.; Janssen, R. A. J. *J. Phys. Chem. A* **2004**, *108*, 8201-8211.

(141) Smolinsky, G.; Feuer, B. I. *J. Org. Chem.* **1966**, *31*, 3882-3884.

(142) Cadogan, J. I. G.; Cameron-Wood, M.; Mackie, R. K.; Searle, R. J. G. *J. Chem. Soc.* **1965**, *1965*, 4831-4837.

(143) Chaplais, G.; Le Bideau, J.; Leclercq, D.; Vioux, A. *Chem. Mater.* **2003**, *15*, 1950-1956.

(144) Lühr, S.; Vilches-Herrera, M.; Fierro, A.; Ramsay, R. R.; Edmondson, D. E.; Reyes-Parada, M.; Cassels, B. K.; Iturriaga-Vásquez, P. *Bioorg. Med. Chem.* **2010**, *18*, 1388-1395.

(145) Chakraborti, A. K.; Chankeshwara, S. V. *J. Org. Chem.* **2009**, *74*, 1367-1370.

(146) Flaherty, D. P.; Kiyota, T.; Dong, Y.; Ikezu, T.; Vennerstrom, J. L. *J. Med. Chem.* **2010**, *53*, 7992-7999.

(147) Kopitzki, S.; Jensen, K.; Thiem, J. *Chem. Eur. J.* **2010**, *16*, 7017-7029.

(148) Kodet, J. G. Studies on Heteroaromatic Schweinfurthin Analogues. Ph.D. dissertation, University of Iowa, Iowa City, IA, 2010.

(149) Tsuge, O.; Kanemasa, S.; Suga, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2133-2146.

(150) Duboudin, J.; Jousseaume, B. *Synth. Commun.* **1979**, *9*, 53-56.

(151) Eummer, J. T.; Gibbs, B. S.; Zahn, T. J.; Sebolt-Leopold, J. S.; Gibbs, R. A. *Bioorg. Med. Chem.* **1999**, *7*, 241-250.

(152) Blau, N. F.; Wang, T. T. S.; Buess, C. M. *J. Chem. Eng. Data* **1970**, *15*, 206-208.

(153) Drew, J.; Letellier, M.; Morand, P.; Szabo, A. G. *J. Org. Chem.* **1987**, *52*, 4047-4052.

(154) Duan, Z.; Hu, X.; Zhang, C.; Wang, D.; Yu, S.; Zheng, Z. *J. Org. Chem.* **2009**, *74*, 9191-9194.

(155) Takahashi, H.; Inagaki, S.; Yoshii, N.; Gao, F.; Nishihara, Y.; Takagi, K. *J. Org. Chem.* **2009**, *74*, 2794-2797.

(156) Asakawa, Y. In Romeo, J., Ed.; Kluwer Academic/ Plenum Publishers: New York, 1999; pp 319-342.

(157) Asakawa, Y. *Curr. Pharm. Des.* **2008**, *14*, 3067-3088.

(158) Asakawa, Y.; Ludwiczuk, A.; Nagashima, F.; Toyota, M.; Hashimoto, T.; Tori, M.; Fukuyama, Y.; Harinantenaina, L. *Heterocycles* **2009**, *77*, 99-150.

(159) Asakawa, Y. *Heterocycles* **1997**, *46*, 795-848.

(160) Asakawa, Y.; Takikawa, K.; Toyota, M.; Takemoto, T. *Phytochemistry* **1982**, *21*, 2481-2490.

(161) Asakawa, Y. Terpenoids and aromatic compounds with pharmacological activity from bryophytes. In Bryophytes Their Chemistry and Chemical Taxonomy; Zinmeister, H. D., Mues, R., Eds.; Oxford University Press: Oxford, 1990; pp 369-410.

(162) Toyota, M.; Kinugawa, T.; Asakawa, Y. *Phytochemistry* **1994**, *37*, 859-862.

(163) Asakawa, Y.; Bardón, A. *Rev. Latinoamer. Quím.* **2001**, *29*, 5-22.

(164) Schwartner, C.; Bors, W.; Michel, C.; Franck, U.; Müller-Jakic, B.; Nenninger, A.; Asakawa, Y.; Wagner, H. *Phytomedicine* **1995**, *2*, 113-117.

(165) Figueiredo, A. C.; Sim-Sim, M.; Barroso, J. G.; Pedro, L. G.; M. Esquível, G.; Fontinha, S.; Luís, L.; Martins, S.; Lobo, C.; Stech, M. *Flavour Fragr. J.* **2009**, *24*, 316-325.

(166) Gorham, J. Phenolic compounds, other than flavanoids, from bryophytes. In Bryophytes Their Chemistry and Chemical Taxonomy; Zinmeister, H. D., Mues, R., Eds.; Oxford University Press: Oxford, 1990; pp 171-207.

(167) Orsini, F.; Verotta, L. Stilbenes and bibenzyls with potent anticancer or chemopreventive activity. In Advances in nutrition and cancer 2, Zappia, V., Ragione, F. D., Barbarisi, A., Russo, G. L. and Iacovo, R. D., Eds.; Kluwer Academic/ Plenum Publishers: New York, 1999; pp 169-186.

(168) Harinantenaina, L.; Takahara, Y.; Takashi, N.; Chie, K.; Gen-Ichiro, S.; Asakawa, Y. *Chem. Pharm. Bull.* **2006**, *54*, 1046-1049.

(169) Yamaguchi, S. *Heterocycles* **2009**, *79*, 243-263.

(170) Nguyen, V. T. H.; Bellur, E.; Langer, P. *Tetrahedron Lett.* **2006**, *47*, 113-116.

(171) Bruder, M.; Haseler, P. L.; Muscarella, M.; Lewis, W.; Moody, C. J. *J. Org. Chem.* **2010**, *75*, 353-358.

(172) Eicher, T. Recent Results from the synthesis of chemical constituents of bryophytes. In Bryophytes Their Chemistry and Chemical Taxonomy; Zinmeister, H. D., Mues, R., Eds.; Oxford University Press: Oxford, 1990; pp 209-223.

(173) Katoh, T.; Ohmori, O.; Iwasaki, K.; Inoue, M. *Tetrahedron* **2002**, *58*, 1289-1299.

(174) Graybill, T. L.; Casillas, E. G.; Pal, K.; Townsend, C. A. *J. Am. Chem. Soc.* **1999**, *121*, 7729-7746.

(175) Pelly, S. C.; Govender, S.; Fernandes, M. A.; Schmalz, H.; de Koning, C. B. *J. Org. Chem.* **2007**, *72*, 2857-2864.

(176) Lee-Ruff, E.; Ablenas, F. J. *Can. J. Chem.* **1989**, *67*, 699-702.

(177) Wang, W.; Li, T.; Attardo, G. *J. Org. Chem.* **1997**, *62*, 6598-6602.

(178) Hutchins, R. O.; Suchismita; Zipkin, R. E.; Taffer, I. M.; Sivakumar, R.; Monaghan, A.; Elisseou, E. M. *Tetrahedron Lett.* **1989**, *30*, 55-56.

(179) Profitt, J. A.; Ong, H. H. *J. Org. Chem.* **1979**, *44*, 3972-3974.

(180) Malona, J. A.; Cariou, K.; Frontier, A. J. *J. Am. Chem. Soc.* **2009**, *131*, 7560-7561.

(181) Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217-3219.

(182) Corey, E. J.; Yamamoto, H. *J. Am. Chem. Soc.* **1970**, *92*, 226-228.

(183) Corey, E. J.; Yamamoto, H.; Herron, D. K.; Achiwa, K. *J. Am. Chem. Soc.* **1970**, *92*, 6635-6636.

(184) Schlosser, M.; Müller, G.; Christmann, K. F. *Angew. Chem., Int. Ed.* **1966**, *5*, 667-668.

(185) Yu, J. S. Stereocontrolled Olefin Synthesis in Preparation of Biologically Active Isoprenoid Organophosphorus Compounds, Ph.D. dissertation, University of Iowa, Iowa City, IA, 2007.

(186) Yu, J. S.; Kleckley, T. S.; Wiemer, D. F. *Org. Lett.* **2005**, *7*, 4803-4806.

(187) Hodgson, D. M.; Arif, T. *Chem. Commun.* **2011**, *47*, 2685-2687.

(188) Hodgson, D. M.; Arif, T. *ChemInform* **2011**, *42*.

(189) Hodgson, D. M.; Arif, T. *Org. Lett.* **2010**, *12*, 4204-4207.

(190) Nicolaou, K. C.; Sasmal, P. K.; Xu, H. *J. Am. Chem. Soc.* **2004**, *126*, 5493-5501.

(191) Han, J. H.; Kwon, Y. E.; Sohn, J.; Ryu, D. H. *Tetrahedron* **2010**, *66*, 1673-1677.

(192) Martina, S. L. X.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 3279-3282.

(193) Motoyoshiya, J.; Kusaura, T.; Kokin, K.; Yokoya, S.; Takaguchi, Y.; Narita, S.; Aoyama, H. *Tetrahedron* **2001**, *57*, 1715-1721.

(194) Collins, D. J.; Drygala, P. F.; Swan, J. M. *Aust. J. Chem.* **1983**, *36*, 2095-2110.

(195) Cohen, R. J.; Fox, D. L.; Eubank, J. F.; Salvatore, R. N. *Tetrahedron Lett.* **2003**, *44*, 8617-8621.

(196) Morita, T.; Okamoto, Y.; Sakurai, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 267-273.

(197) Chakraborty, S. K.; Engel, R. *Synth. Commun.* **1991**, *21*, 1039-1046.

(198) Yao, Q.; Levchik, S. *Tetrahedron Lett.* **2006**, *47*, 277-281.

(199) Mori, K. *Tetrahedron: Asymmetry* **2007**, *18*, 838-846.

(200) Borszeky, K.; Mallat, T.; Baiker, A. *Tetrahedron: Asymmetry* **1997**, *8*, 3745-3753.

(201) Monbaliu, J.; Tinant, B.; Peeters, D.; Marchand-Brynaert, J. *Tetrahedron Lett.* **2010**, *51*, 1052-1055.

(202) Ando, K.; Narumiya, K.; Takada, H.; Teruya, T. *Org. Lett.* **2010**, *12*, 1460-1463.

(203) Ando, K.; Sato, K. *Tetrahedron Lett.* **2011**, *52*, 1284-1287.

(204) Touchard, F. P. *Eur. J. Org. Chem.* **2005**, *2005*, 1790-1794.

(205) Pihko, P. M.; Salo, T. M. *Tetrahedron Lett.* **2003**, *44*, 4361-4364.

(206) Topczewski, J. J.; Callahan, M. P.; Neighbors, J. D.; Wiemer, D. F. *J. Am. Chem. Soc.* **2009**, *131*, 14630-14631.

(207) Goff, D. A.; Harris, R. N.; Bottaro, J. C.; Bedford, C. D. *J. Org. Chem.* **1986**, *51*, 4711-4714.

(208) Pedersen, T. M.; Hansen, E. L.; Kane, J.; Rein, T.; Helquist, P.; Norrby, P.; Tanner, D. *J. Am. Chem. Soc.* **2001**, *123*, 9738-9742.

(209) Li, A.; Dai, L.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341-2372.

(210) Kolodiazhnyi, O. I. *Tetrahedron: Asymmetry* **1998**, *9*, 1279-1332.

(211) Rein, T.; Reiser, O. *Acta Chemica Scandinavica* **1996**, *50*, 369-379.

(212) Topczewski, J. J.; Kodet, J. G.; Wiemer, D. F. *J. Org. Chem.* **2011**, *76*, 909-919.

(213) Tanaka, S.; Seki, T.; Kitamura, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8948-8951.

(214) Larock, R. C.; Berrios-Pena, N.; Narayanan, K. *J. Org. Chem.* **1990**, *55*, 3447-3450.

(215) Rozhkov, R. V.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 4131-4134.

(216) Heald, R. A.; Dexheimer, T. S.; Vankayalapati, H.; Siddiqui-Jain, A.; Szabo, L. Z.; Gleason-Guzman, M.; Hurley, L. H. *J. Med. Chem.* **2005**, *48*, 2993-3004.

(217) Larock, R. C.; Yang, H.; Pace, P.; Cacchi, S.; Fabrizi, G. *Tetrahedron Lett.* **1998**, *39*, 237-240.

(218) Widenhoefer, R. A.; Zhong, H. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6787-6795.

(219) Muñiz, K. *Adv. Synth. Catal.* **2004**, *346*, 1425-1428.

(220) Pérez-Prieto, J.; Galian, R. E.; Burgos, P. O.; del Carmen, M. M.; Miranda, M. A.; López-Ortiz, F. *Org. Lett.* **2005**, *7*, 3869-3872.

(221) Hin, B.; Majer, P.; Tsukamoto, T. *J. Org. Chem.* **2002**, *67*, 7365-7368.

(222) Newman-Evans, R.; Simon, R. J.; Carpenter, B. K. *J. Org. Chem.* **1990**, *55*, 695-711.

(223) Townsend, C. A.; Christensen, S. B.; Davis, S. G. *J. Chem. Soc., Perkin Trans. 1* **1988**, 839-861.

(224) Ho Park, Y.; Lee, R.; Hong Kim, S. *Bull. Korean Chem. Soc.* **2011**, *32*, 566-570.

(225) Ushakova, I. B.; Rozenberg, L. M.; Genekh, I. S.; Sanin, P. I. *Neftekhimiya* **1968**, *8*, 651-4.

(226) Ofner, A.; Kimel, W.; Holmgren, A.; Forrester, F. *Helv. Chim. Acta* **1959**, *42*, 2577-84.

(227) Fuchter, M. J.; Levy, J. *Org. Lett.* **2008**, *10*, 4919-4922.

(228) Mizuno, C. S.; Schrader, K. K.; Rimando, A. M. *J. Agric. Food Chem.* **2008**, *56*, 9140-9145.

(229) Ali, M. A.; Kondo, K.; Tsuda, Y. *Chem. Pharm. Bull.* **1992**, *40*, 1130-1136.