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Cascade cyclizations in total synthesis: applications to the synthesis of cytotoxic natural products

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CASCADE CYCLIZATIONS IN TOTAL SYNTHESIS: APPLICATIONS TO THE SYNTHESIS OF CYTOTOXIC NATURAL PRODUCTS

by

Natalie Christine Ulrich

An Abstract

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

July 2010

Thesis Supervisor: Professor David F. Wiemer

ABSTRACT

Plant–derived natural products continue to be a valuable source of useful therapies for cancer as well as other diseases. As part of a continuing mission to obtain anticancer agents from natural sources, researchers at the National Cancer Institute (NCI) established the 60 human tumor cell line anticancer screen. The schweinfurthins are one family of unique natural products discovered through this screening process, and most of the schweinfurthins exhibit potent and differential activity in the 60–cell line screen. Importantly, the pattern of activity displayed by the schweinfurthins shows no correlation to any clinically used anticancer drug, indicating that this family of natural products probably acts via a novel mechanism or at a novel target. Our group has conducted extensive structure–activity relationship studies in an effort to illuminate the mechanism of action of the schweinfurthins. In this thesis, the preparation and biological activity of a number of new schweinfurthin F analogues possessing variations in the D–ring alkyl chain and stilbene moiety will be discussed. These studies have clarified the importance of the D–ring substituent to the schweinfurthins' pharmacophore.

Based on the results obtained from the exploration of the structural requirements of these natural products, it was determined that the right–half of the schweinfurthins would be an appropriate site for attachment of a molecular probe to be used in affinity experiments. The synthesis of these biotinylated probes will be presented in detail, and their use in pull–down assays will be summarized.

The preparation of key schweinfurthin intermediates has involved the extensive use of Lewis acid–mediated cationic cascade cyclizations terminated by methoxymethyl (MOM)–protected phenols. Those successes have inspired investigations of additional applications of these cyclizations. In particular, a variant of these cyclizations using "MOM–protected" enol ethers as reasonable substitutes for β–keto ester terminating moieties has been studied. These interrelated studies involving the synthesis of

schweinfurthin analogues and the exploration of new cascade cyclizations will be discussed in detail.

Abstract Approved: _____
Thesis Supervisor

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Title and Department

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Date

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CERTIFICATE OF APPROVAL

PH.D. THESIS

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

Natalie Christine Ulrich

has been approved by the Examining Committee
for the thesis requirement for the Doctor of Philosophy
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Nothing difficult is ever easy.

Dr. David F. Wiemer

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Plant–derived natural products continue to be a valuable source of useful therapies for cancer as well as other diseases. As part of a continuing mission to obtain anticancer agents from natural sources, researchers at the National Cancer Institute (NCI) established the 60 human tumor cell line anticancer screen. The schweinfurthins are one family of unique natural products discovered through this screening process, and most of the schweinfurthins exhibit potent and differential activity in the 60–cell screen. Importantly, the pattern of activity displayed by the schweinfurthins shows no correlation to any clinically used anticancer drug, indicating that this family of natural products probably acts via a novel mechanism or at a novel target. Our group has conducted extensive structure–activity relationship studies in an effort to illuminate the mechanism of action of the schweinfurthins. In this thesis, the preparation and biological activity of a number of new schweinfurthin F analogues possessing variations in the D–ring alkyl chain and stilbene moiety will be discussed. These studies have clarified the importance of the D–ring substituent to the schweinfurthins' pharmacophore.

Based on the results obtained from the exploration of the structural requirements of these natural products, it was determined that the right–half of the schweinfurthins would be an appropriate site for attachment of a molecular probe to be used in affinity experiments. The synthesis of these biotinylated probes will be presented in detail, and their use in pull–down assays will be summarized.

The preparation of key schweinfurthin intermediates has involved the extensive use of Lewis acid–mediated cationic cascade cyclizations terminated by MOM–protected phenols. Those successes have inspired investigations of additional applications of these cyclizations. In particular, a variant of these cyclizations using "MOM–protected" enol ethers as reasonable substitutes for β–keto ester terminating moieties has been studied.

These interrelated studies involving the synthesis of schweinfurthin analogues and the exploration of new cascade cyclizations will be discussed in detail.

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LIST OF ABBREVIATIONS

3dSB	3–deoxyschweinfurthin B
Å	Angstrom
A549	Human–Derived Lung Adenocarcinoma Cell Line
Ac	Acetate
Anal.	Analysis
Aq.	Aqueous
br	Broad
Bu	Butyl
C	Celsius
calcd	Calculated
CNS	Central Nervous System
COMPARE	NCI Based Computer Algorithm
CSA	Camphorsulfonic Acid
d	Doublet
DCM	Dichloromethane
dd	Doublet of doublets
DDQ	2,3–Dichloro–5,6–dicyano–1,4–benzoquinone
DEPT	Distortionless Enhancement for Polarization Transfer (NMR)
DIPEA	Diisopropylethylamine
DNA	Deoxyribonucleic Acid
DMF	Dimethylformamide
dt	Doublet of Triplets
ee	Enantiomeric Excess
EI	Electron Impact
Et	Ethyl

g	Gram
GI_{50}	Growth Inhibition at 50%
h	Hour
HMPA	Hexamethylphosphoramide
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectroscopy
HWE	Horner–Wadsworth–Emmons
Hz	Hertz
iPr	Isopropyl
J	Coupling Constant
KHMDS	Potassium Hexamethyldisilyl Azide
LDA	Lithium Diisopropyl Amide
cLogP	Octanol–water Partition Coefficient
m	Multiplet
M	Molar
*m*CPBA	*meta*–Chloroperbenzoic Acid
Me	Methyl
mg	Milligram
mL	Milliliter
mmol	Millimole
MOM	Methoxymethyl
MPNST	Malignant Peripheral Nerve Sheath Tumors
Ms	Methanesulfonyl
m/*z*	Mass/Charge
n–BuLi	*n*–Butyl Lithium
NP	Natural Product
NBS	N–bromosuccinimide

NCI	National Cancer Institute
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Enhancement
NOESY	Nuclear Overhauser Enhancement Spectroscopy
q	Quartet
rt	Room Temperature
s	Singlet
sat.	Saturated
SF–295	CNS Cancer Cell Line
SF–539	CNS Cancer Cell Line
t	Triplet
TBAF	Tetrabutylammonium Fluoride
TBDPS	*tert*–Butyldiphenylsilyl
TBS	*tert*–Butyldimethylsilyl
TEA	Triethylamine
Tf	Triflate
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	*p*–Toluene Sulfonyl
TsOH	*p*–Toluene Sulfonic Acid

CHAPTER 1
A BRIEF HISTORY OF THE USE OF NATURAL PRODUCTS AS ANTICANCER AGENTS

Cancer has plagued mankind since the beginning of recorded history.[1] Extensive evidence corroborates the identification of tumors, both benign and malignant, in early civilizations.[2-4] For example, as early as ca. 129 A.D., the Roman physician Galen provided physiologically correct descriptions of neoplastic tumors or *onkos*.[5] The Persian philosopher Avicenna (ca. 1000 A.D.) defined a "malignant" tumor as:

> "an atrabilious (black bile) swelling...(It is) accompanied by pain...and some degree of beating (throbbing) and rapid growth...as a manifestation of this substance boiling at its junction with the organ...On its onset it is concealed and when it is manifested it is problemic in most cases. Then its signs become apparent...And there is a kind of cancer that is unchanged, does not ulcerate."[6]

Plant–derived natural products (NPs) were an invaluable source of useful medicines for the ancients. One of the first known remedies for malignant tumors was described by the Greek physician Dioscorides in ca. 50 A.D.[7] Dioscorides instructed patients to soak the roots of the autumn crocus (*Colchicum autumnale* L.) in wine and apply the poultice to the affected area. Centuries later,[8] *C. autumnale* was found to contain the alkaloid colchicine (**1**, Figure 1), which, along with its usefulness as an anti–gout and anti–inflammatory agent, has been investigated for its potential use as an anti–cancer agent.[9]

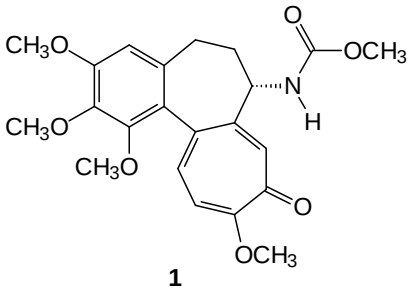

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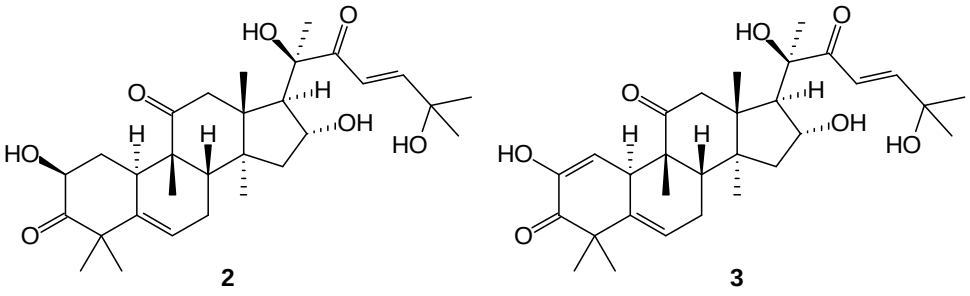
Figure 1. The alkaloid colchicine

Another example of a plant used by Dioscorides to treat a variety of skin conditions and "old, soft tumors" was the squirting cucumber (*Ecballium elaterium* L.).[1] Its use was revived centuries later when, in 1958, elatericins A and B (**2** and **3**, Figure 2) were isolated from the same plant and found to have strong activity against mouse sarcoma cells.[10] There are also relatively recent reports of oral ingestion of the plant for the treatment of cancer.[11]



2 **3**

Figure 2. Elatericins A (left) and B

Dioscorides also considered plants of *Vinca major* L. to be very useful in the treatment of cancers.[7] Plants of this species reportedly "dried tumors."[12] A very closely related genus, *Catharanthus*, is the source of *C. roseus* G. Don, from which the famous

alkaloids vinblastine and vincristine (**4** and **5**, Figure 3) are derived.[13] These antitumor alkaloids are active against a variety of cancer types including leukemia, lymphoma, breast, and lung,[14] and semi–synthetic analogues are currently used for the treatment of various leukemias as well as breast and lung cancers.[15]

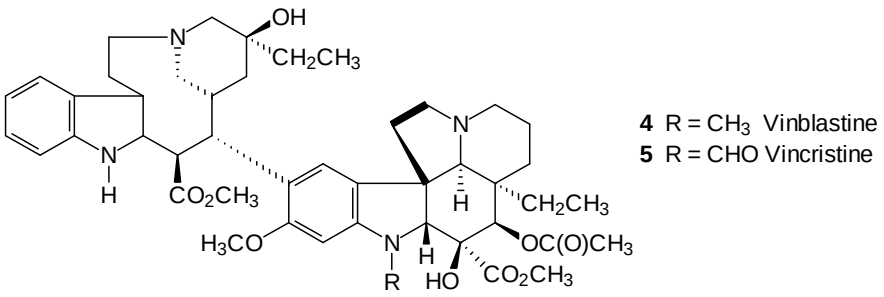


Figure 3. Well–known vinca alkaloids

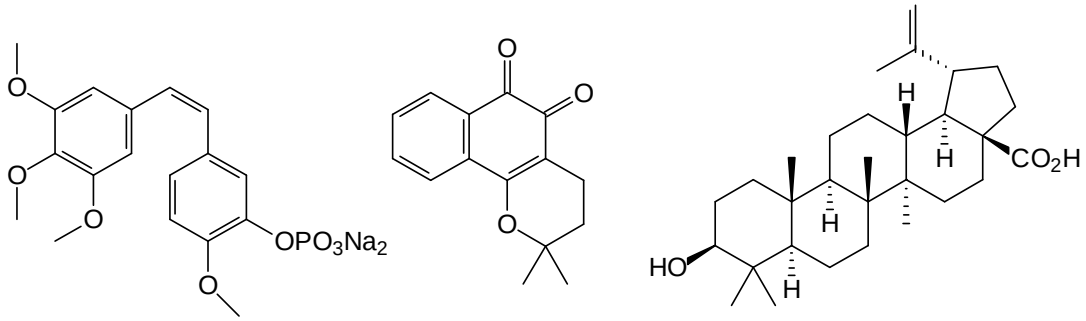
The extent of the efficacy of cancer treatments in ancient times is unknown. Standard practices dictated that information regarding dosage, application, etc. of the medicines was passed down by physicians via an apprentice system, and thus little information regarding these practices was physically recorded.[1] It is unlikely that the prescribed treatments resulted in complete cures; at best, some improvement in tumor appearance/size was observed.[1]

The use of chemotherapy experienced a re–birth in the early 20th century.[1] Prior to that time, surgery alone was the standard treatment for cancer, a practice which some believed to be an "unqualified condemnation" of the potential benefits of chemotherapy.[1] Isolated examples of work by numerous scientists eventually encouraged a more wide–spread interest in chemotherapeutic approaches. In 1908, Paul Ehrlich published his experiments on transplantable murine tumors.[16] In the 1930s, C. Gordon Zubrod reported

the effects of bacterial toxins on human cancers,[17] and A. P. Dustin reported his work on the various activities of colchicine (**1**).[18]

A major resurgence of interest in chemotherapy for the treatment of cancer occurred when Congress established the National Cancer Institute (NCI) in 1937.[1] This action reflects the public's increasing concern over the threat of cancer. Originally, the NCI's mission was to fund and maintain cancer research efforts through a range of independent entities. During the 1950s, the NCI developed the Cancer Chemotherapy National Service Centre (CCNSC),[19] whose mission was to expand the scope of the NCI's responsibilities. Their specific tasks involved the screening, pre–clinical testing, and clinical studies of potential anticancer drugs. Today, this work is performed by members of the Developmental Therapeutics Program (DTP), which is a subsidiary of the Division of Cancer Treatment and Diagnosis (DCTD).[19] The DTP's mission ranges from the funding and performance of cancer research to the education of the general public regarding cancer. Since its inception, the NCI has served as an invaluable resource for countless public and private institutions from the world over.

Over the past 50 years, the NCI itself has screened more than 500,000 compounds for potential cytotoxic activity.[19] The natural compounds of this group come from a variety of sources, including plants, marine organisms, and microorganisms.[20-23] Several plant–derived compounds including combretastatin A_4PO_4 (**6**),[24] β–lapachone (**7**),[25] and betulinic acid (**8**)[26] were obtained during this time and are currently in either preclinical or clinical trials (Figure 4).



6 Combretastatin A_4PO_4 **7** β-Lapachone **8** Betulinic Acid

Figure 4. Plant–derived NPs still in development

Researchers at the NCI also have discovered and advanced to clinical use a number of plant–derived natural products, some of which, as previously discussed, were "discovered" centuries ago.[19] One of the most well–known success stories is that of Taxol® (**9**, Figure 5).[26-28] In 1966, Dr. Wani and co–workers of the Research Triangle Institute, supported by funds from the NCI, isolated taxol from the bark of the Pacific Yew.[29] The structure of taxol was solved using single–crystal X–ray analysis of a derivative of the natural product, work which was reported in 1971.[29] Crystal formation was achieved following removal of taxol's amino acid side chain and subsequent derivatization.

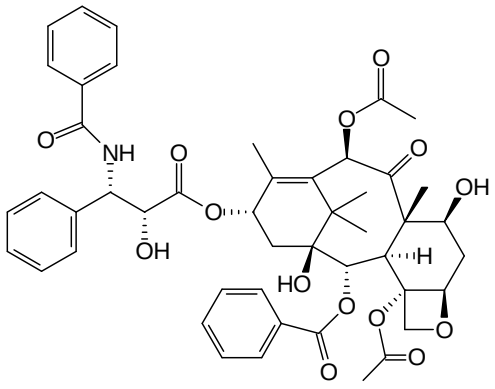


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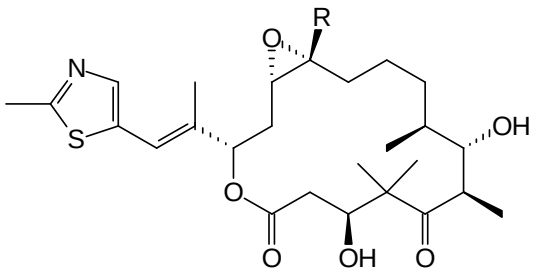
Figure 5. Taxol®

The story of taxol's journey to a clinically useful anti–cancer drug holds many valuable lessons for today's medicinal chemist.[30, 31] Following taxol's isolation, work to determine its mechanism of action commenced. Initial studies showed that taxol exhibited good activity against P1534 leukemia cells and solid human tumor xenografts in murine models,[31] findings which spurred further investigations. It was soon discovered that taxol acted in a very specific way on microtubules.[32] Conveniently, the technology used to visualize effects on microtubules was quite well–established at that time, making the necessary experiments very straightforward.[27] In a series of experiments, taxol was shown to stabilize microtubules and therefore prevent mitosis in proliferating cells.[33] Furthermore, it has been shown that taxol, through a complicated series of events, causes the delayed apoptosis of cells.[34, 35] Although several other new agents have been found to possess similar mechanisms of action[36] (e.g., epothilones A and B, **10**–**11**, Figure 6), these findings from the study of taxol significantly increased our understanding of cancer.



10 R = H Epothilone A
11 R = CH_3 Epothilone B

Figure 6. Epothilones A and B

Following the elucidation of the mechanism of action of taxol, the compound progressed into clinical trials in 1980 and subsequently moved through phase I–III studies. Taxol® was first approved for use against refractory ovarian cancer in 1992 by the Federal Drug Administration (FDA).[27] In subsequent years, taxol also was approved for use against several more types of cancer, including breast and colon cancers, and Kaposi's sarcoma. It is now known clinically as paclitaxel.

Taxol's success has led to the preparation of other clinically important analogues, the most notable of which is docetaxel (Taxotere®, **12**, Figure 7).[37] Docetaxel (**12**) was synthesized by Potier and coworkers in 1989 and now is used clinically for treating breast, ovarian, and various lung cancers.[38, 39] Its use has generated billions of dollars in revenue; in 2000 alone, the annual sales were almost $2 billion.[40, 41]

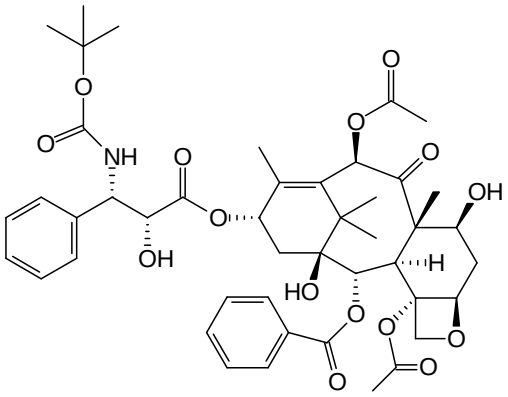


Figure 7. Docetaxel

The importance of taxol's discovery and the determination of its novel mechanism of action cannot be overemphasized. Its discovery led to the preparation of an entire drug class possessing a unique, previously unknown mechanism of action, which may never have been determined if not for taxol. Not only is the story of taxol's development fascinating from a scientific perspective, but its clinical use has had untold impact on the lives of many affected patients. While it is difficult to measure the number of lives taxol and its analogues have saved or prolonged, that number is certainly significant. In the particular case of ovarian cancer, the mean survival rate of affected patients has doubled since the introduction of taxol–based therapies.[37]

As part of a continuing mission to obtain anticancer agents from natural sources, in 1986 researchers at the NCI started to develop the 60 human tumor cell line anticancer screen, an extremely valuable resource still used extensively today.[42] Originally, researchers at the NCI used transplantable mouse tumors as a way to screen drugs. After it became apparent that activity against a mouse tumor did not necessarily correlate to activity against human tumors, the focus quickly shifted to solid human tumors. Eventually, a panel of 60 cell lines was established, and these cells could be categorized into nine different subpanels: leukemia, colon, lung, CNS, renal, melanoma, ovarian, breast, and prostate.[42] A program called COMPARE has been developed by K. Paull and

coworkers at the NCI to analyze similarities and differences among drug activity patterns, and these analyses can in turn provide insight into drugs that function through a similar mechanism of action in the 60–cell line cancer screen.[43]

Throughout the development of the NCI 60–cell line screen, the DTP became an increasingly popular repository for synthetic compounds and natural extracts and products.[44] In 1989, the process of screening new agents began in earnest.[42] Over the next two decades, nearly 100,000 crude extracts were processed using the NCI's system of isolation and cataloguing.

One family of unique natural products first discovered through this screening process was the schweinfurthins, most of which exhibit potent activity in the 60–cell line screen (Figure 8). The original collection of plant material was performed by D. W. Thomas of the Missouri Botanical Garden during a visit to Korup National Park, Cameroon, in 1987.[45] More than a decade later, Dr. John A. Beutler and coworkers of NCI–Frederick examined the dried leaves (425 g), and through bioassay–guided fractionation, isolated schweinfurthins A and B (SA, **13**, 50 mg, and SB, **14**, 38 mg), along with the less active schweinfurthin C (SC, **16**, 25 mg). Both SA (**13**) and SB (**14**) display potent and selective anti–proliferative activity in the NCI's 60–cell line screen (mean GI_{50} = 0.36 and 0.81 μM, respectively). Of particular interest is the range of activity displayed by the compounds: SA (**13**) had a GI_{50} of 11 nM against the CNS line SF–295, while the non–small cell lung cancer cell lines were relatively resistant with mean GI_{50}s ranging from 5–8 μM. Shortly thereafter, schweinfurthin D (**17**) was reported,[46] and the isolation of schweinfurthins E, F, G, and H (**18**–**21**) by the Kingston group at Virginia Tech followed some years later.[47] Finally, the isolation of schweinfurthins I and J (**22** and **23**) was reported very recently by Klausmeyer and coworkers at the NCI.[48]

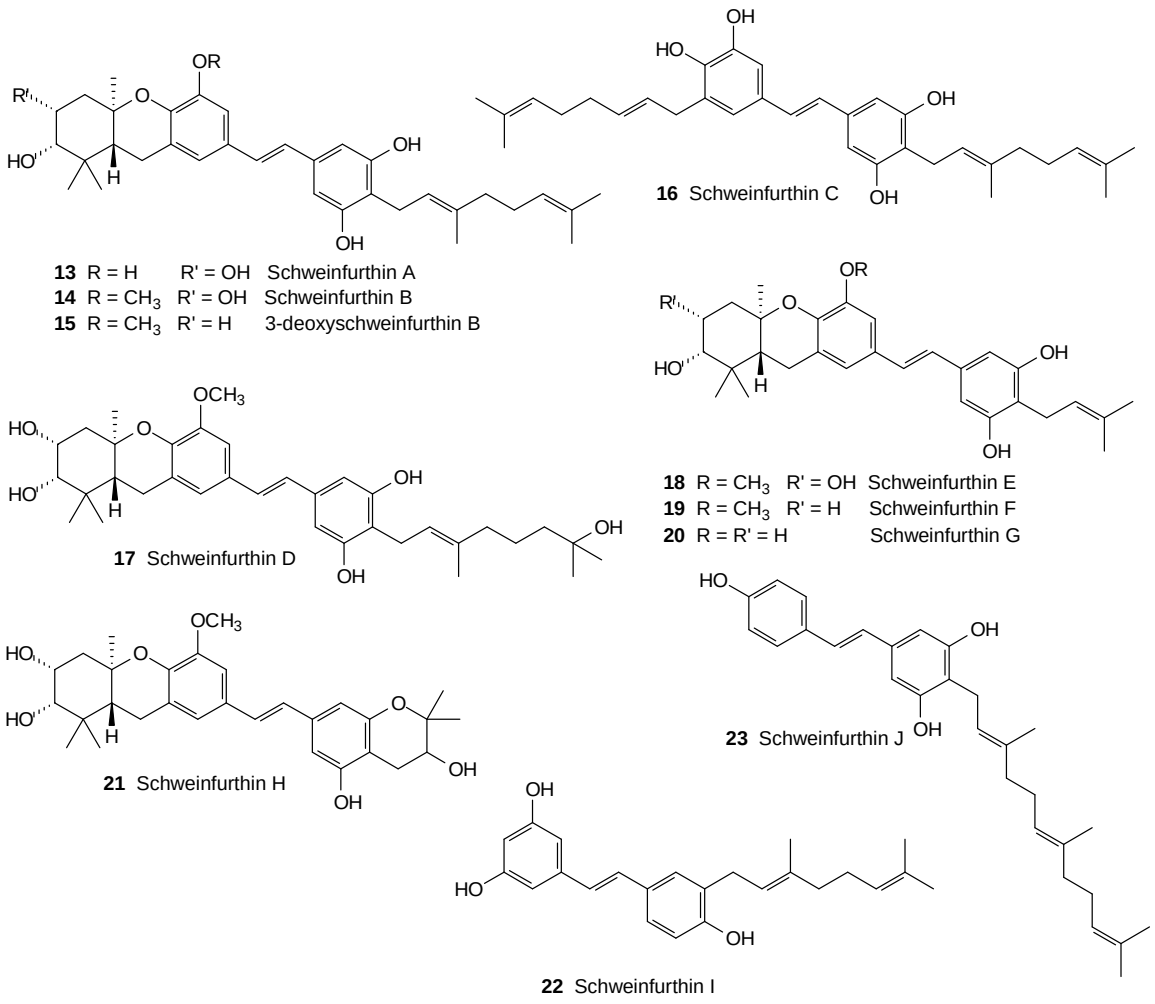


Figure 8. The schweinfurthin family of natural products

As mentioned previously, a compound's pattern of activity in the NCI's 60–cell line assay can be analyzed by the COMPARE program to determine whether it shows a significant correlation to any known agents in terms of mechanism of action.[43] Importantly, the pattern displayed in the 60–cell line screen by the schweinfurthins showed no correlation to any clinically used anti–neoplastic agent, indicating that this family of compounds probably acts via a novel mechanism or at a novel target. A COMPARE analysis of the schweinfurthins[45] at the GI_{50} and TGI levels of response does show a significant correlation to several structurally unrelated natural products (Figure

9): the cephalostatins,[49-51] the stellettins,[52-55] and OSW–1 (**26**).[56] It has been determined that the schweinfurthin–sensitive cell lines possess no shared biochemical features and differ substantially in DNA repair phenotype, *in vitro* doubling time, and MDR status,[45] suggesting that these compounds may act through a new cellular pathway. Discovery of the mechanism of action of the schweinfurthins may aid in determination of some or all of the others, in turn increasing understanding of prospective new therapeutic paradigms.

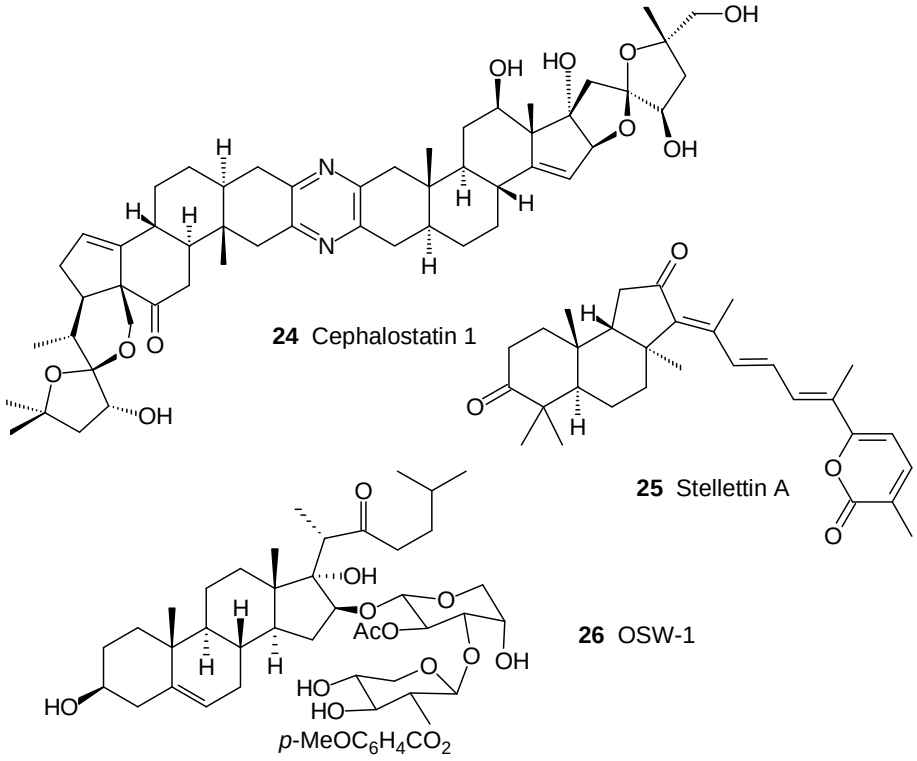


Figure 9. Correlated natural products

Because of our ongoing interest in the synthesis of prenylated stilbenes and the unique activity of the schweinfurthins, we undertook a synthetic effort aimed at these compounds. This endeavour led first to the total synthesis of SC (**16**), the simplest member of the family at the time of its discovery. This work, reported in 1999,[57]

established a precedent for a highly convergent, late–stage Horner–Wadsworth–Emmons coupling in formation of the central *trans*–stilbene moiety (Figure 10).

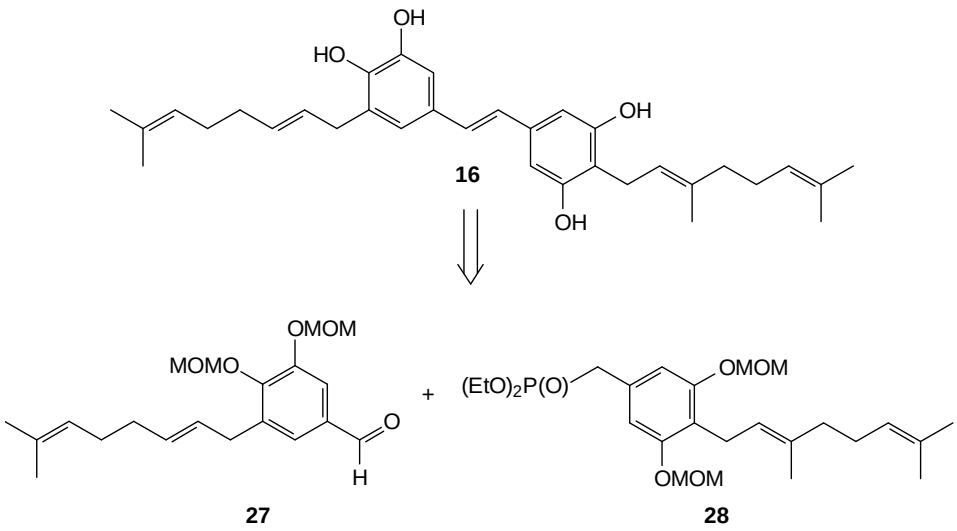


Figure 10. Convergent synthesis of schweinfurthin C (**16**)

Attempts to obtain the *cis*–diol moiety in the A–ring of the first schweinfurthins using standard methodologies met with little success for several years.[58] However, the synthesis of 3–deoxyschweinfurthin B (3dSB, **15**) was accomplished using a highly stereoselective cationic cascade cyclization of an enantiopure epoxide derived from geranylated vanillin (Figure 11).[59]

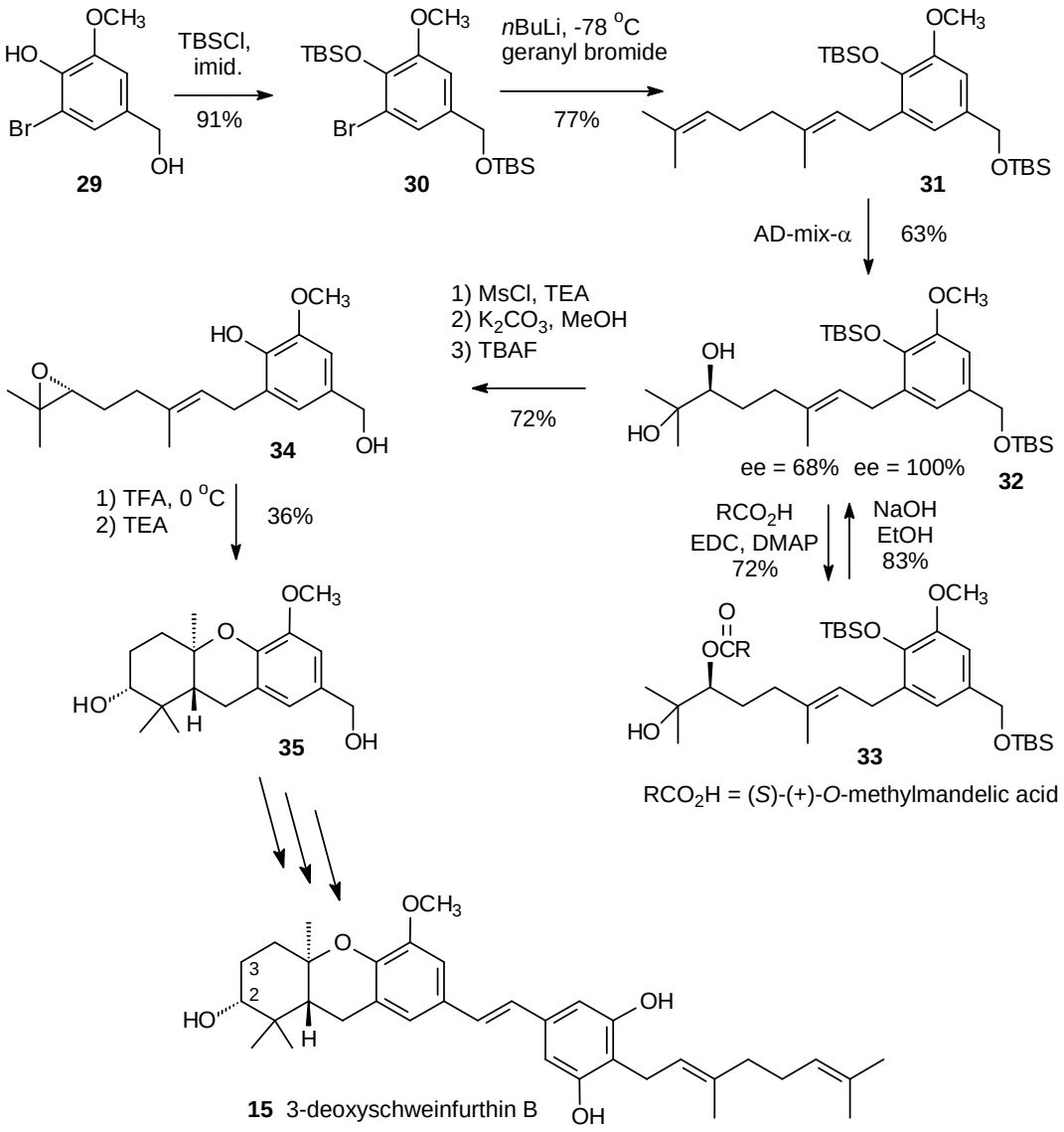


Figure 11. Key steps in the synthesis of 3–deoxyschweinfurthin B (**15**)

New strategies based upon a highly enantioselective Shi epoxidation and a methyl benzyl ether as a protected aldehyde provided an even more efficient way to construct the hexahydroxanthene left–half, making synthesis of gram–scale quantities of schweinfurthins routine (Figure 12).[58, 60]

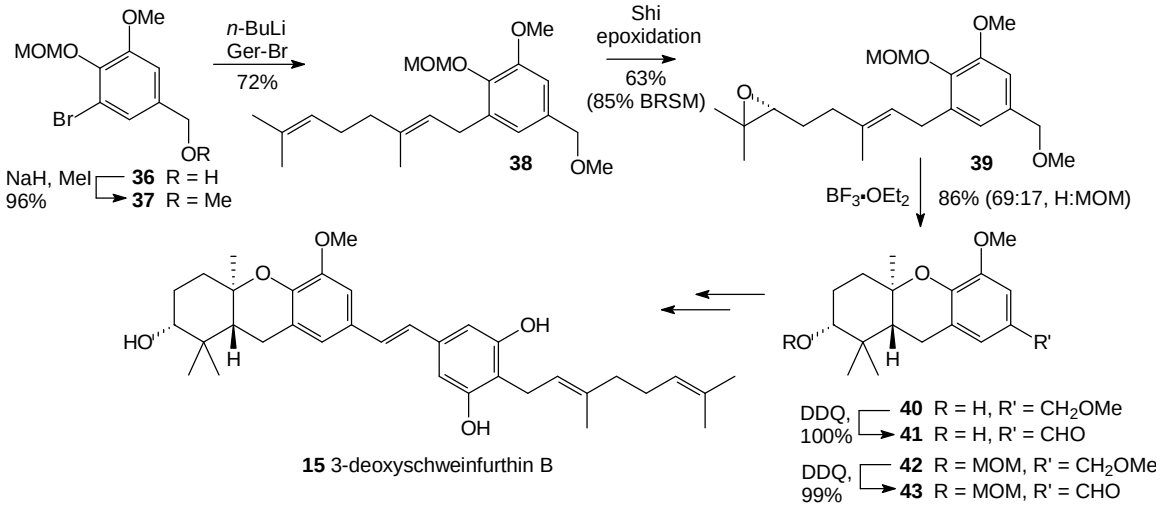


Figure 12. A more efficient synthesis of schweinfurthin analogues

We also have prepared a number of schweinfurthin analogues in an effort to illuminate the pharmacophore(s) responsible for the schweinfurthins' differential activity.[59, 61, 62] Those studies have led to a number of conclusions. First, based on the relative activity of SA (**13**) or SB (**14**) versus SC (**16**), it appears that the left–half hexahydroxanthene substructure is required for potent and selective activity.[45] Second, replacing the phenolic groups of the right–half resorcinol structure with hydrogen or fluorine demonstrated that at least one of the phenolic hydroxyl groups is important for differential activity.[59] Third, the effects of some D–ring substitutions have been examined.[59] Comparison of the activity of schweinfurthin F (**19**), 3dSB (**15**), and a previously synthesized 3dSB analogue (bearing prenyl, geranyl, and hydroxylated geranyl chains, respectively) with an analogue which lacks an alkyl chain, established that the absence of any isoprenoid chain led to somewhat reduced activity.[59] Finally, recent attempts at the NCI to obtain additional amounts of schweinfurthins from a natural source have resulted in the isolation of compounds tentatively identified as *cis*–stilbenes, raising questions about the importance of the central olefin stereochemistry. Therefore, we have prepared a number of new schweinfurthin F analogues possessing variations in

the D–ring alkyl chain and stilbene moiety. These analogues have been tested in relevant cancer cell lines and have illuminated further the structural requirements of the schweinfurthins.

As seen in the story of taxol's development from a biologically active natural product to a clinically approved drug, the identification of a drug's molecular target is very desirable for the elucidation of the underlying biological mechanisms of drug action and for the rational design of more effective therapeutics.[63] A wide variety of techniques, including yeast three–hybrid systems,[64] phage display,[65] and protein microarrays,[66] have been used successfully for the deconvolution of numerous small–molecule targets. Recently, affinity–based chromatography coupled with mass spectrometry (MS) methods has become increasingly popular due to the remarkable sensitivity and speed this technique offers.[63, 67-69]

Identifying a molecular target using affinity–based chromatography typically requires the synthesis of an appropriate molecular probe amenable to immobilization on a solid support.[63] Biotinylation has been commonly used for the purification/identification of a variety of targets[70-76] (e.g., the identification of trapoxin as a histone deacetylase inhibitor).[77] This methodology involves derivatization of the molecule in question with the small organic molecule biotin and relies on the extremely tight binding of biotin to streptavidin ($k_d = 10^{-15}$ M).[63]

A cartoon of the typical methodology employed in this technique is shown in Figure 13. First, a biotin tag is attached to the active library member. This hybrid analogue can then be attached to a streptavidin bead, placed in a column, and treated with a cell lysate that contains proteins obtained from, in this case, SF–295 cells. On the column, the biotin–streptavidin complex will interact with any schweinfurthin–binding proteins, and probably multiple other proteins through non–specific interactions. Extensive washing of the resin should remove or at least diminish any non–specific binding proteins, and then denaturing conditions or elution with a solution of the natural

product can be applied to elute the binding proteins from the column. These proteins then can be concentrated and resolved on an SDS–PAGE gel. Standard MS techniques then should allow identification of the binding proteins.[69]

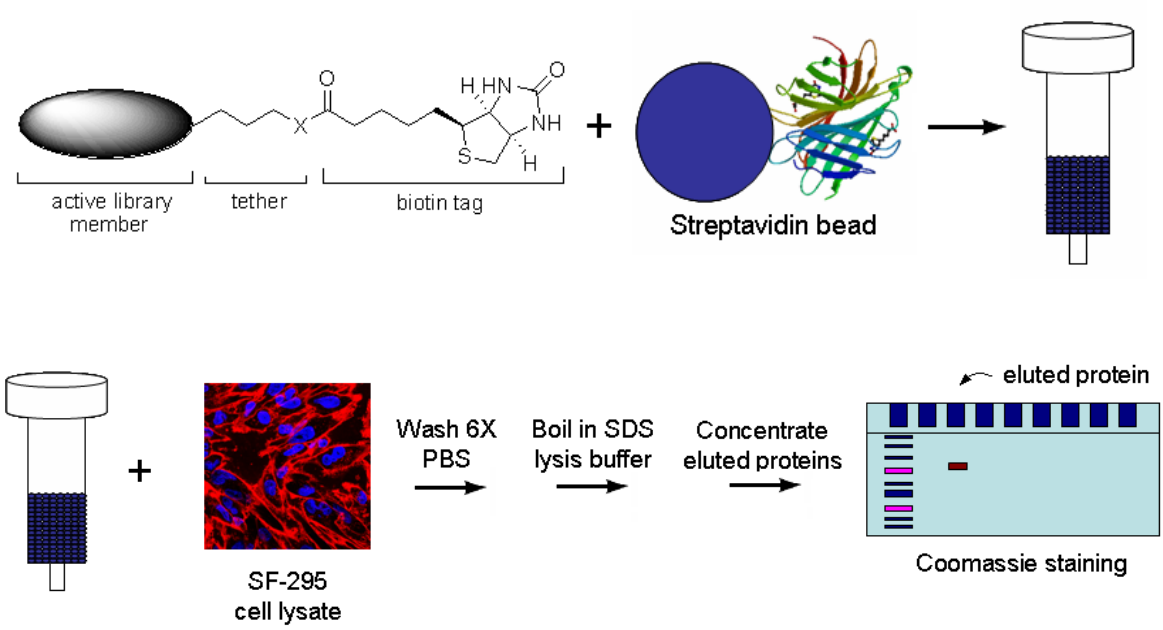


Figure 13. Typical affinity chromatographic purification procedure (Figure courtesy of C. Kuder, University of Iowa)

A classic example of the use of this methodology is found in the story of tacrolimus (or FK–506, **44**), a natural product isolated in 1987 from a fermentation broth of *Streptomyces tsukubaenis* by Imanaka and co–workers.[78] Tacrolimus (**44**) is a novel immunosuppressant indicated for use in organ transplant applications. In 2002, Kreider and co–workers synthesized an FK506–biotin derivative (**45**, Figure 14).[70] In conjunction with an mRNA display, this biotinylated derivative was used to identify the drug receptor FKBP12, a chaperone for proline–rich proteins.[63]

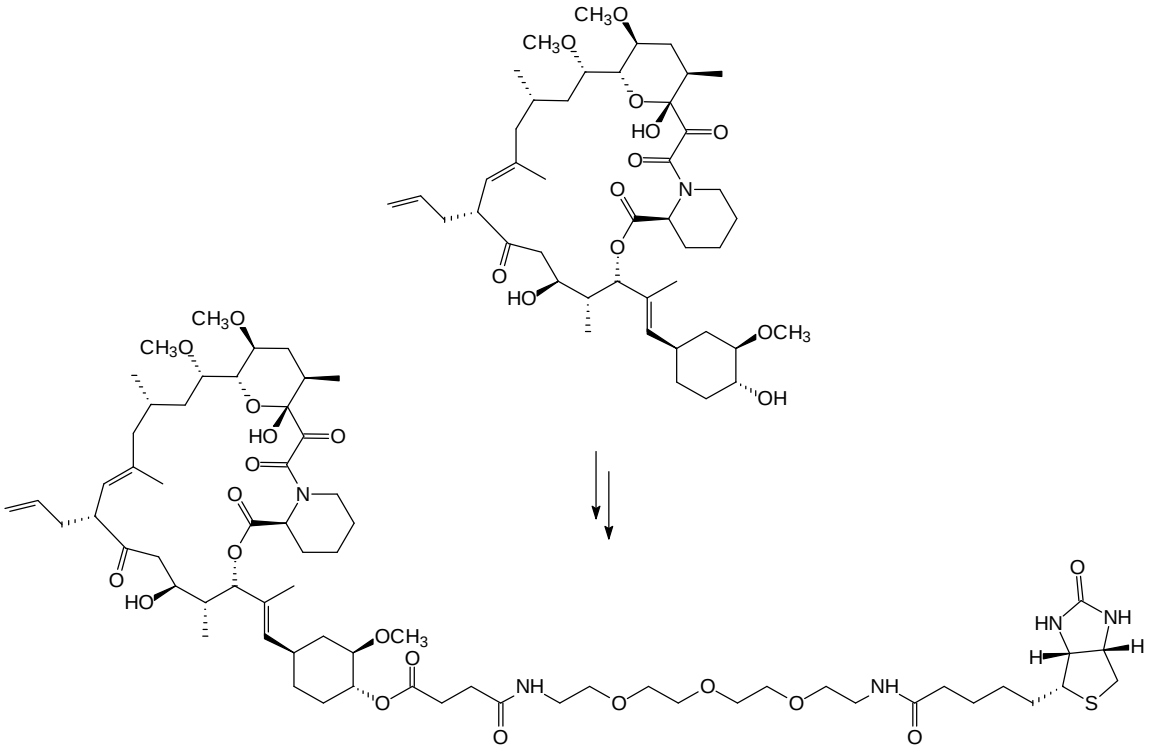


Figure 14. FK506–biotin derivative

One important aspect to consider when using this methodology is the length and solubility properties of the tether employed to attach a biotin tag to the active compound.[69] One major drawback of this methodology is that some proteins may not be found due to steric interactions between avidin, biotin, and a large receptor protein. The crystal structure of a biotin–avidin complex shows a 7 Å space between the biotin pocket and avidin's surface, so any tether should be at least that long.[72] While a variety of tether lengths has been utilized, often in a trial and error manner, it is generally accepted that the tether should be at least 20 Å long. Furthermore, the chemical nature of the tether must be taken into account. A wide range of both hydrophilic (i.e., PEG) and hydrophobic (i.e., alkyl) tethers has been utilized.[70, 79, 80] In the case of FK–506, a 23 Å PEG linker was successfully employed.[70]

Initial work on biotinylated schweinfurthin analogues utilized compounds possessing an approximately 9 Å length linker between the active schweinfurthin substructure and the biotin moiety (e.g. compound **46**, Figure 15). In the future, it may be advantageous to insert a longer spacer to make an analogue such as compound **47**.

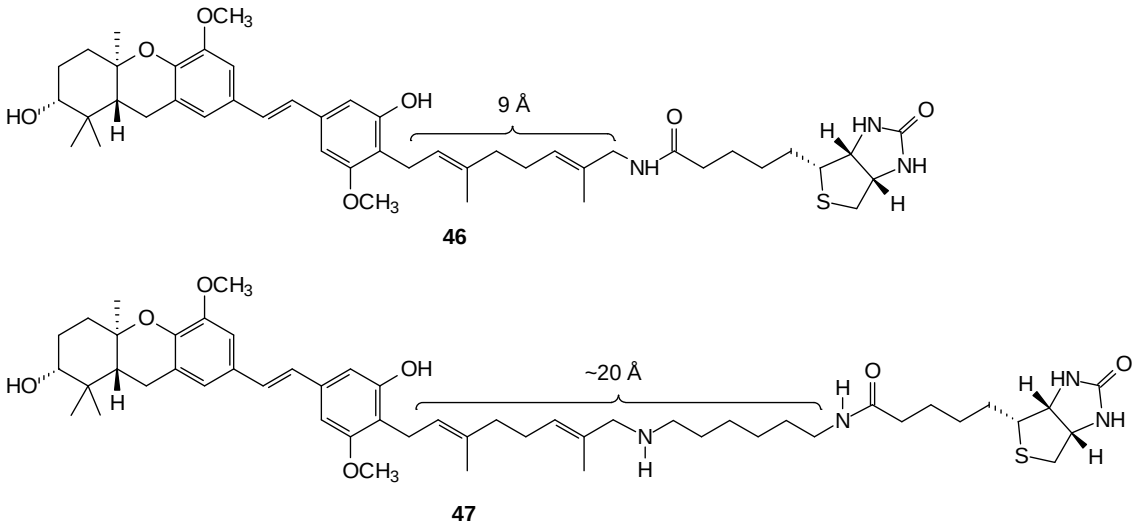


Figure 15. Comparison of linker lengths

This thesis will discuss various approaches to the synthesis of biotinylated schweinfurthins. Several biotinylated schweinfurthin analogues have been prepared, and their biological activity and use in pull–down assays will be described.

Cascade cyclizations have played a central role during the course of our studies on the schweinfurthins and related natural products.[58, 81-84] For example, in the synthesis of schweinfurthin G (**20**, Figure 16), a Lewis acid–mediated cationic cascade cyclization of an epoxy geranyl chain with a terminating MOM–phenolic moiety was used to construct the tricylic hexahydroxanthene core (**50**) in good overall yield.[84] This cyclization has found wide applicability in the synthesis of a variety of schweinfurthins,

and has allowed us to construct these complex structures through formation of several new C–C or C–O bonds and stereocenters in a single operation.

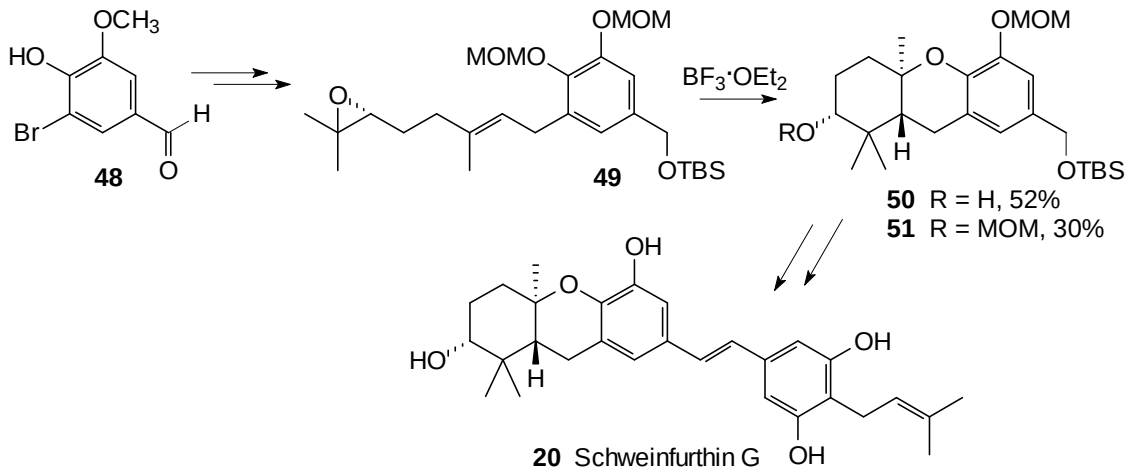


Figure 16. Cationic cascade cyclization in the synthesis of schweinfurthin G (**20**)

Due to the success of MOM–protected phenols as terminating groups in cascade cyclizations leading to the synthesis of schweinfurthins, we became interested in expanding this methodology to include other terminating moieties. Parker's total synthesis of (±)–GERI–BP001 in 1997 utilized a β–keto ester as the terminating moiety in an epoxy farnesyl cascade cyclization (Figure 17).[85] That cyclization was mediated by treatment with $SnCl_4$ and only proceeded in 8% yield to afford tricycle **55**. Those investigators eventually resorted to an organomercury–mediated cascade cyclization, which provided the desired product in better yield and as a single diastereomer, but also required the use of stoichiometric quantities of mercury.

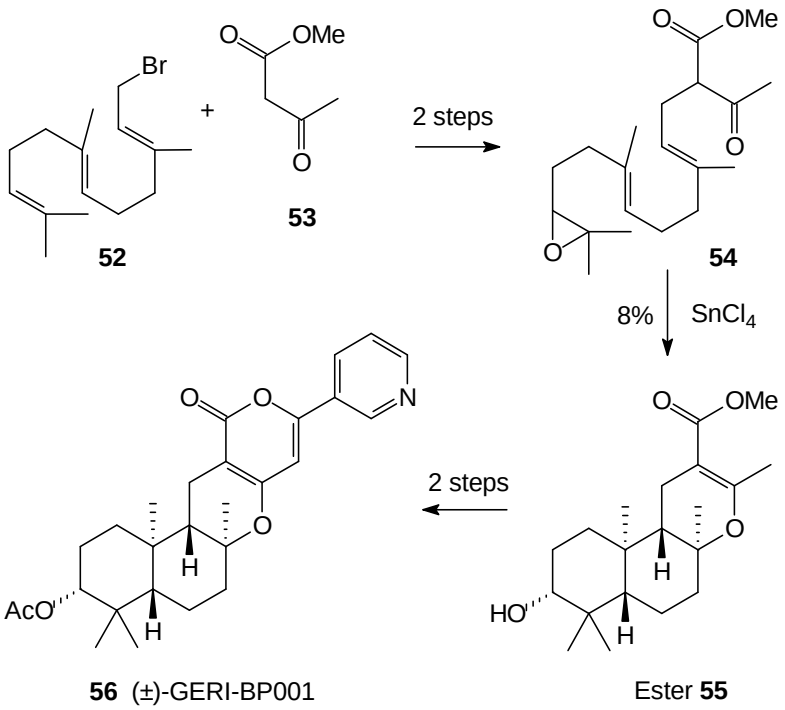


Figure 17. Parker's total synthesis of GERI–BP001

These previous synthetic efforts prompted questions into whether a derivative of an enol ether could be used in a similar manner to provide the desired product in increased yield. Instead of using a β–keto ester, we questioned whether an enol could be "protected" as the MOM–enol ether and still undergo a cascade cyclization (Figure 18). While the resonance–stabilized enol form of the β–keto ester in Parker's synthesis was presumably present in only minor amounts, a MOM–protected enol ether such as compound **58** would be exclusively present in the enol form. Our studies of cascade cyclizations have shown that MOM derivatives of phenols can be employed to terminate cationic processes, so it was reasonable to investigate MOM–protected enol ethers to determine if they display comparable reactivity.

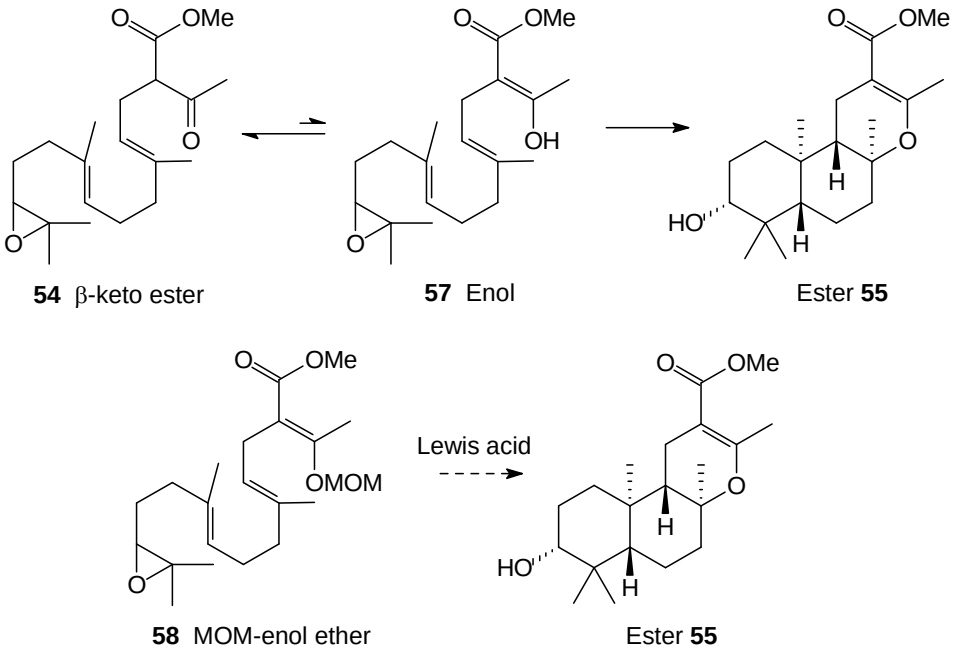


Figure 18. Cyclization of a β–keto ester versus a "MOM–protected" enol ether

Furthermore, formation of the enol ether also introduces an olefinic center with its attendant stereochemistry. Thus, if the cascade cyclization of a MOM–protected enol ether were successful, it would have to be determined whether the olefin stereochemistry of the starting enol ether determines the structure of the cyclization products (Figure 19). While cascade cyclization of the *E*–enol ether **58** might be expected to afford ester product **55** via termination by the MOM–protected enol, cyclization of the *Z*–enol ether **59** should afford the ketone product **60** via termination by the ester carbonyl. This matter will be discussed in detail in Chapter 5.

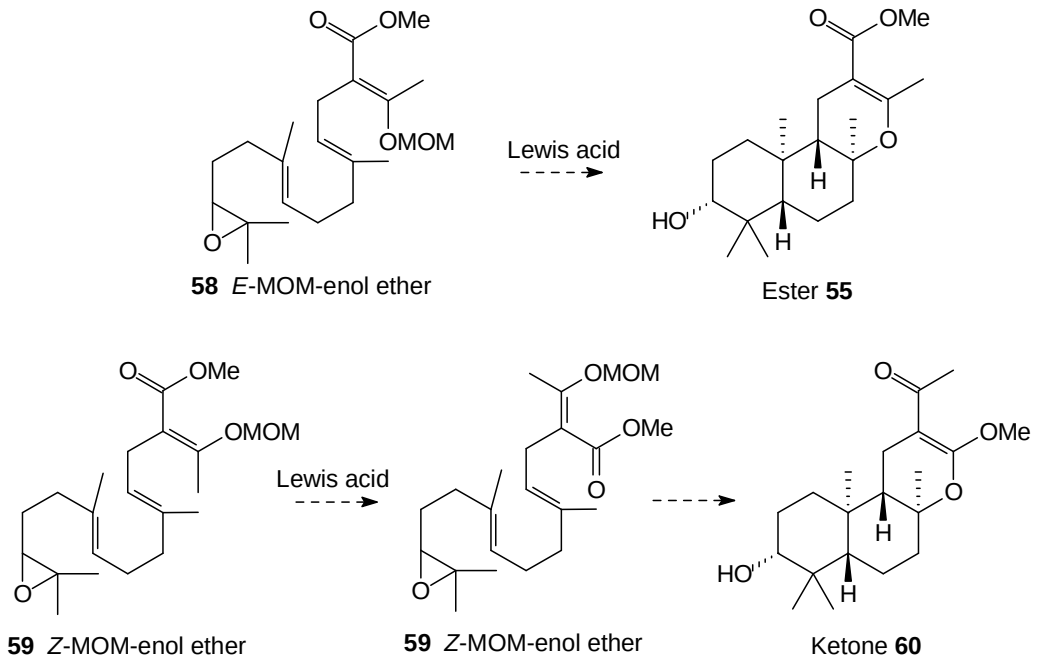


Figure 19. *E*– versus *Z*–enol ethers

In conclusion, natural products have a long history of use in treatment of cancer. Even today, though, new natural products are found periodically that offer new chemotherapeutic options for treatment of this disease. The schweinfurthins represent one recently discovered family of natural products with great potential as chemotherapeutic agents. Our SAR studies of the schweinfurthins have identified a suitable site for biotin incorporation. Use of cascade cyclizations terminated by MOM–protected phenols to prepare key schweinfurthin intermediates has inspired investigations of additional applications of this reaction. In this thesis, these interrelated studies will be discussed in detail.

CHAPTER 2
STRUCTURAL ANALOGUES OF SCHWEINFURTHIN F: PROBING THE STERIC, ELECTRONIC, AND HYDROPHOBIC PROPERTIES OF THE D–RING SUBSTRUCTURE

In our previous studies, we have prepared a number of analogues designed to illuminate the pharmacophore(s) responsible for the schweinfurthins' differential activity.[59] Variations in activity observed through these past studies prompted investigation into the significance of a hydrophobic substituent on the D–ring. Specifically, we wished to explore whether attaching a simplified tail to the D–ring or altering the electronics of the stilbene moiety would be tolerated. We therefore targeted the synthesis of several new schweinfurthin analogues based on schweinfurthin F as the lead structure. The preparation of these compounds and data on their biological activity are presented here.[62]

At the outset of this project, we envisioned numerous schweinfurthin F analogues featuring modifications to the stilbene moiety and the D–ring alkyl group (Figure 20). Compounds **61** and **62** possess D–ring chains comparable in length to a geranyl group, but lack all of the olefinic moieties and vary in degrees of hydrophobicity. An allyl analogue (**63**) would be useful not only for its ease of synthesis, but also for its ability to be converted easily to multiple other functionalities (e.g. the hydroxy propyl compound **64**, the *n*–propyl compound **65**, etc). Prenyl–length analogues **66** and **67** could help determine the effect of varying the isoprenoid chain, whether by moving or simply deleting the olefin. An alkynyl analogue (**68**) also would be interesting to compare to the allyl analogue in order to study the effect of increasing electron density at that position. The routes to the synthesis of analogues **61**–**68** will be described here in detail. John Kodet prepared analogues **69**–**73** and Nolan Mente prepared the *cis*–stilbene **74** as reported elsewhere.[62]

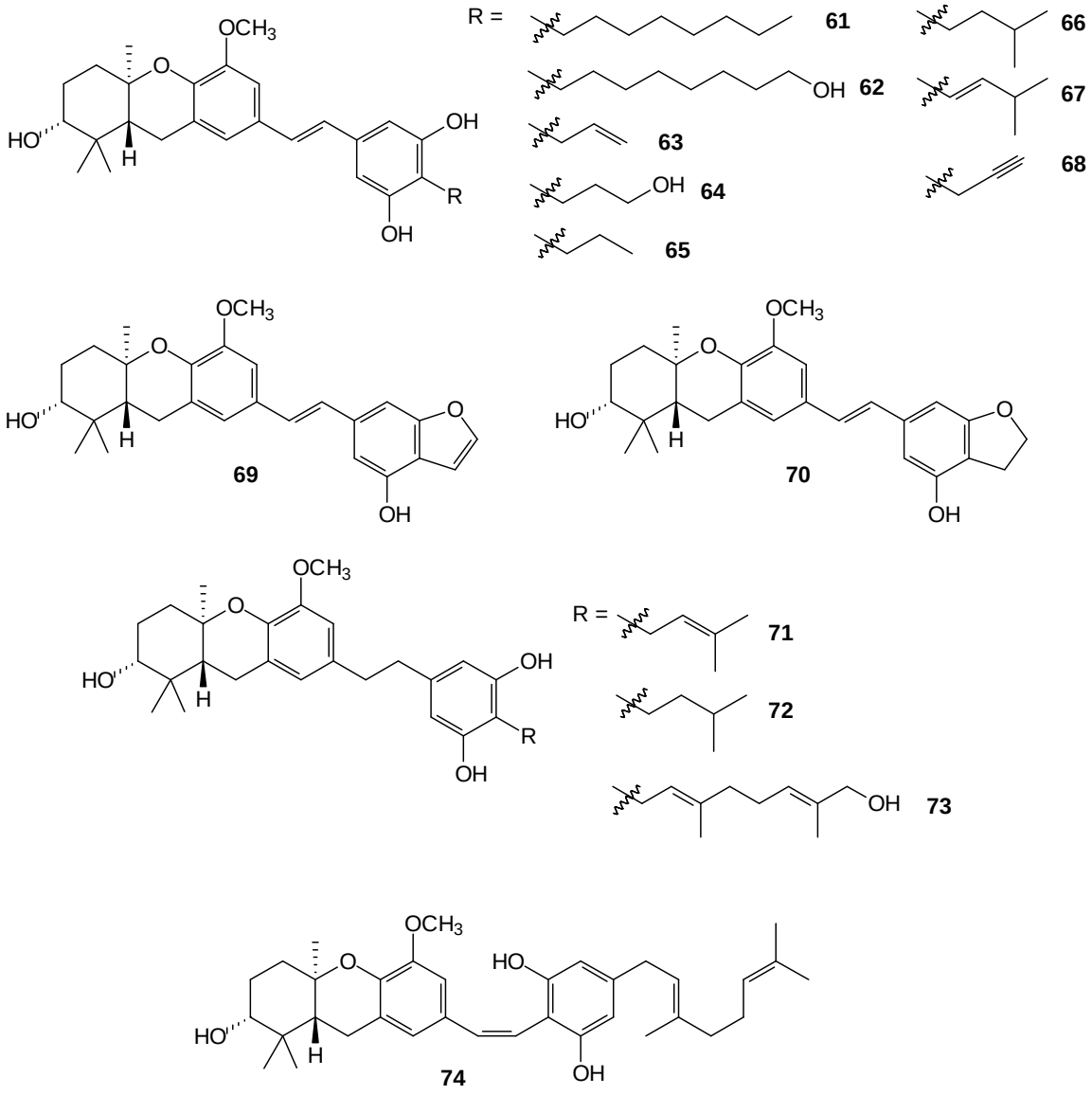


Figure 20. Targeted schweinfurthin F analogues **61**–**74**

A general retrosynthesis of analogue **63** is shown in Figure 21. Because aldehyde **75** is known and available via a relatively short synthetic sequence,[86] the first logical targets in the preparation of analogues **61**–**68** were the corresponding phosphonates (e.g., compound **76**).

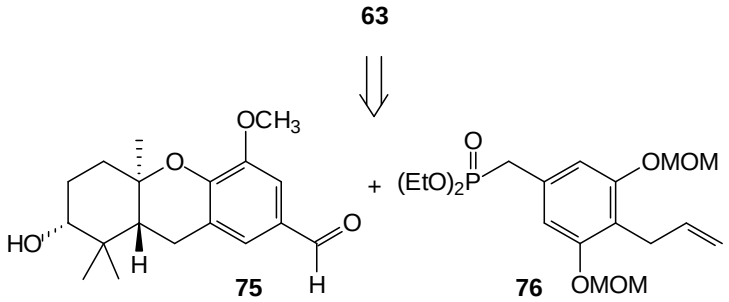


Figure 21. Retrosynthesis of allyl analogue **63**

Synthesis of the required phosphonates began with known protected benzyl alcohol **77**[87] (Figure 22). Initial efforts involved the attachment of octyl bromide (**78**) and the known silyl protected bromide **79**[88, 89] utilizing a directed *ortho* metallation/ transmetallation/alkylation protocol.[90] Unfortunately, these primary alkyl bromides proved reticent to displacement in both cases, yielding only trace amounts of the desired products.

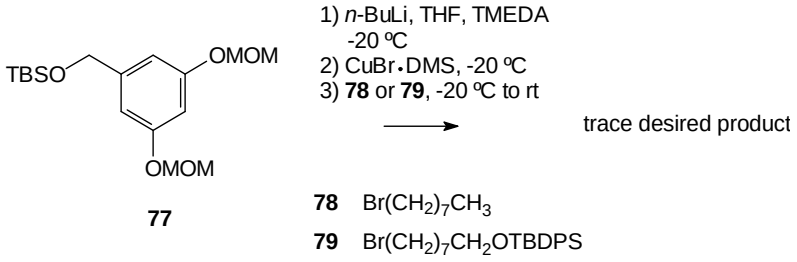


Figure 22. Attempted reactions with primary bromides **78** and **79**

In a related reaction, albeit with a simplified substrate (Figure 23),[91] formation of the aryl lithiate of compound **80** occurred at a higher temperature. Furthermore, the more reactive alkyl iodide was utilized. Evidently, unactivated primary bromides are insufficiently reactive in cases such as those described above in Figure 22.

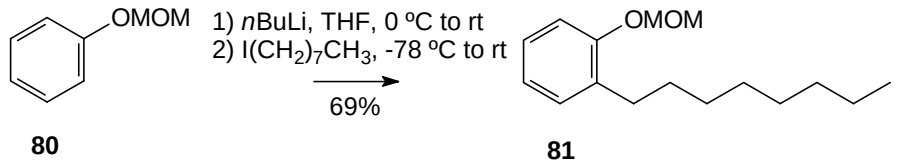


Figure 23. Alkylation of arene **80** with an alkyl iodide[91]

In light of these results, the next effort involved attempted alkylation using an activated allylic bromide such as known bromide **82**,[92] which is readily prepared from the corresponding commercially available allylic alcohol (Figure 24). If the desired alkylated product were obtained, it could be reduced to provide the fully saturated alkyl chain. However, a virtually inseparable mixture of the desired product **83** and compound **84** was obtained, arising from competitive S_N2' substitution on bromide **82**. This undesired reaction often is encountered in alkylations with the more hindered prenyl or geranyl bromides, but usually in a much more favourable ratio. The decreased steric hindrance at the S_N2' position of bromide **82** compared to prenyl or geranyl bromide apparently significantly increases the likelihood of nucleophilic attack at that position.

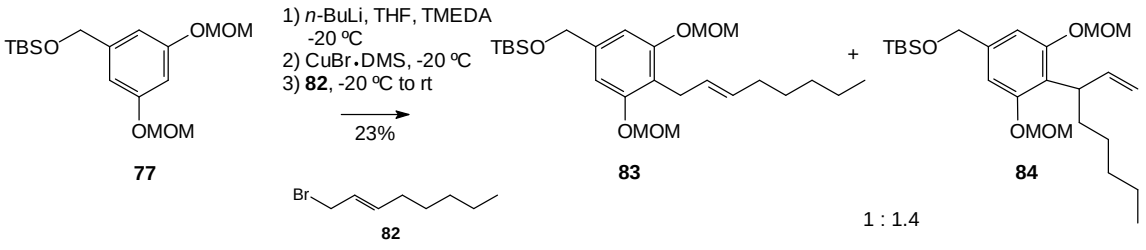


Figure 24. Formation of S_N2' product **84**

Once these results were obtained, focus then was directed to the synthesis of analogues possessing simpler alkyl chains. Alkylation of compound **77** with allyl

bromide would give identical products whether an S_N2 or S_N2' mechanism prevailed. Directed *ortho* metallation followed by transmetallation of the resulting aryl lithium to the cuprate and alkylation with allyl bromide afforded the C–alkylated product in reasonable yield (Figure 25). Removal of the silyl protecting group gave alcohol **85**, which was then treated with methanesulfonyl chloride to give the intermediate mesylate. Treatment of the mesylate with NaI in acetone afforded the iodide and standard Arbuzov reaction with triethyl phosphite provided the desired phosphonate **76**. Hydroboration/oxidation of compound **76** with 9–BBN and H_2O_2 gave the hydroxylated phosphonate **86**, while palladium–catalyzed hydrogenation of phosphonate **76** produced the *n*–propyl phosphonate **87**. This short reaction sequence provided three of the desired right–half phosphonates.

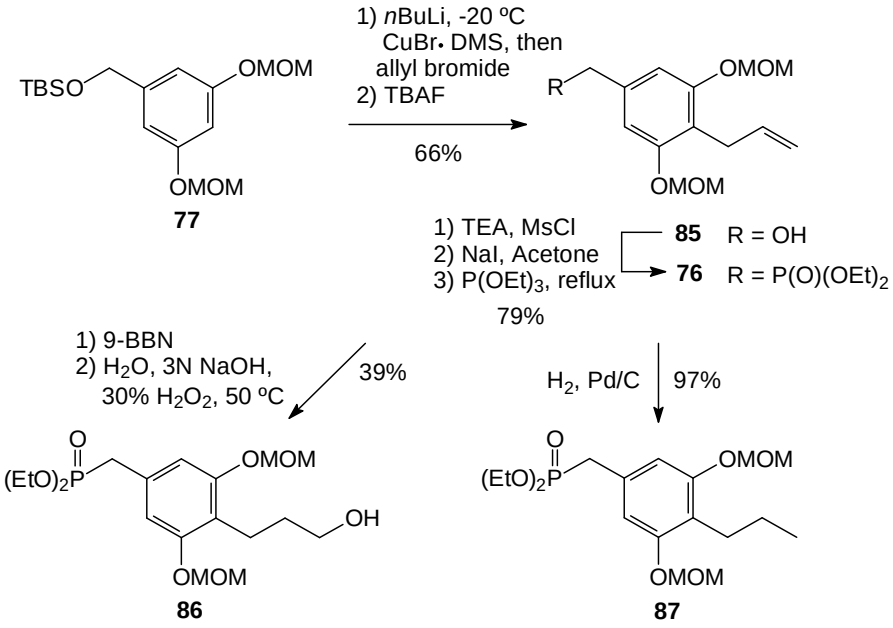


Figure 25. Preparation of phosphonates **76** and **86–87**

Hydrogenation of the known benzylic alcohol **88**[93] in the presence of Pd/C under standard conditions afforded arene **89** in low yield (Figure 26). The major product of this reaction was arene **90** in which the benzylic C–O bond had been cleaved.

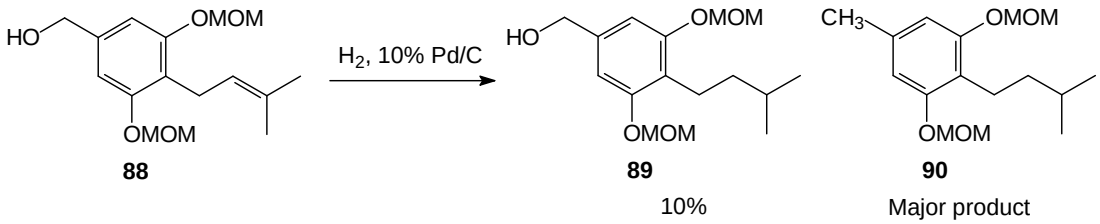


Figure 26. Hydrogenolysis of the benzylic C–O bond

After reviewing the pertinent literature, a protocol was found in which the addition of 0.5 equivalents of ammonium acetate would prevent the undesirable hydrogenolysis of the C–O bond.[94] Addition of ammonium acetate to the hydrogenation reaction mixture did indeed provide the desired reduced compound (Figure 27). After treatment with tetrabutylammonium fluoride to remove the silyl protecting group and provide compound **89**, conversion to phosphonate **92** was accomplished via the same 3–step procedure described previously.

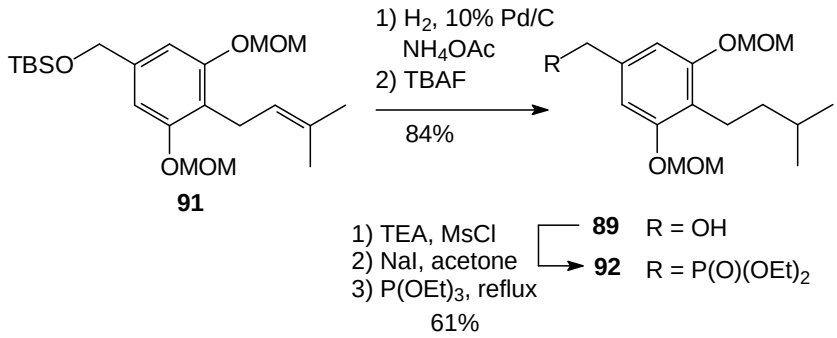
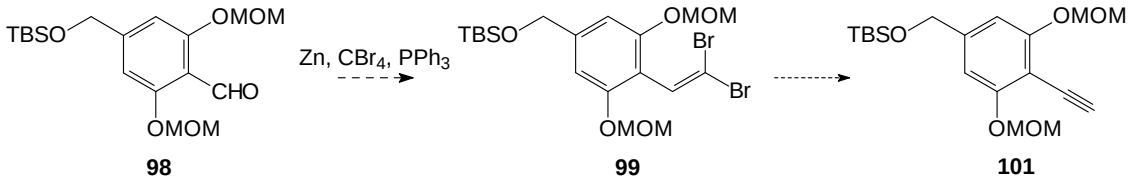


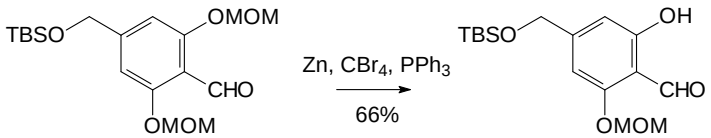
Figure 27. Synthesis of phosphonate **92**

After isopentenyl phosphonate **95** was obtained via previously reported methods (Mente, N. Unpublished results, University of Iowa), our next goal was to introduce an acetylene as a D–ring substituent. There are several literature precedents[95, 96] for the successful installation of a vinyl dibromide using Corey–Fuchs reaction conditions in the presence of an *ortho* MOM–acetal (e.g., the conversion of aldehyde **96** to dibromide **97**, Figure 30). Therefore, attempts to prepare an alkynyl phosphonate first relied on this strategy[97] to convert known aldehyde **98**[61] to vinyl dibromide **99** (Figure 28). Instead of the desired transformation, however, reaction of aldehyde **98** under the standard Corey–Fuchs reaction conditions resulted in unexpected removal of one of the MOM–protecting groups to provide phenol **100** (Figure 29). Based on the literature precedence of this reaction in similar substrates, it is unknown why the reaction does not work in the present case.



98 **99** **101**

Figure 28. Attempted preparation of alkyne **101**



98 **100**

Figure 29. Synthesis of phenol **100**

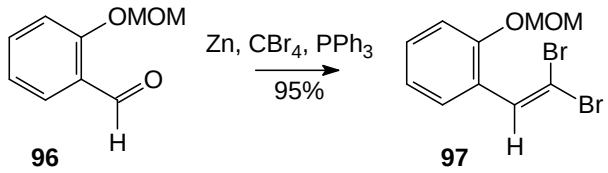


Figure 30. Literature precedence for vinyl dibromide formation[90]

In order to see if these conditions would remove a MOM–group in an even simpler system, TBS–protected benzyl alcohol **77** was allowed to react under the standard conditions (Figure 31). In that case, only a complex mixture of products was obtained, and purification was not attempted. This suggests that either the MOM or the TBS group, or both, do not survive under these reaction conditions. Furthermore, in order to verify that none of the reagents themselves were the problem, the reaction was performed upon commercially available aldehyde **102** (Figure 32). The desired vinyl dibromide **103**[98] was obtained in an unoptimized yield of 49%, proving that at least the reagents were still viable.

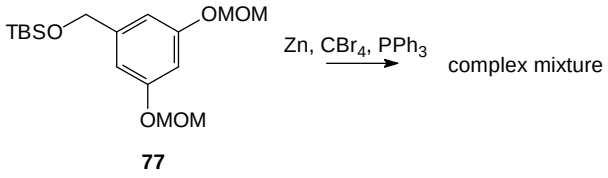


Figure 31. Attempted MOM–removal of compound **77**

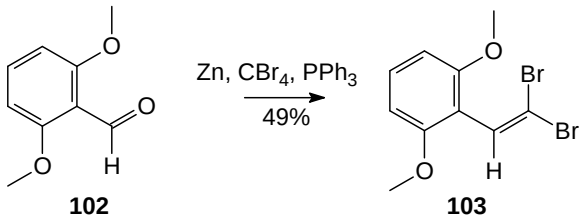


Figure 32. Successful preparation of vinyl dibromide **103**[98]

In order to circumvent these obstacles, in the end alkynyl phosphonate **108** was obtained via alkylation of known benzyl alcohol **104**[99] with 3–(trimethylsilyl)propargyl bromide (**105**, Figure 33), which was obtained via deprotonation of propargyl bromide and reaction with trimethylsilyl chloride. Conversion to the phosphonate **107** via the intermediate bromide, and fluoride–mediated removal of the TMS group, provided phosphonate **108** in good yield.

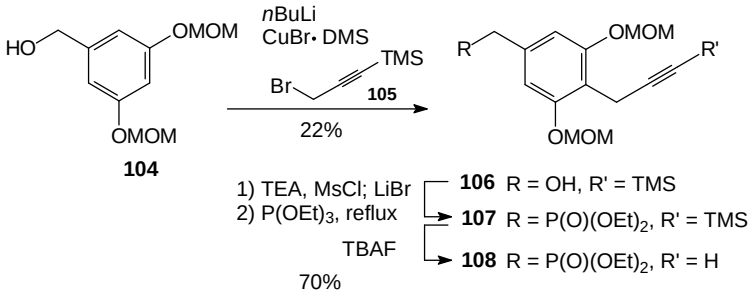


Figure 33. Synthesis of phosphonate **108**

With a majority of the targeted phosphonates in hand, the Horner–Wadsworth–Emmons condensations with aldehyde **75** were effected in the presence of NaH and 15–crown–5 (Figure 34). In all cases, only the desired *trans*–stilbene product was observed (Table 1). Subsequent hydrolysis of the MOM protecting groups was carried out in the presence of TsOH or CSA to provide analogues **63**–**66** and **68**. In the case of isopentenyl

analogue **67**, attempted hydrolysis of the protecting groups resulted in extensive decomposition and no recovery of the desired analogue. This could be due to a number of factors including isomerization or hydration of the prenyl olefin or cyclization of the resulting prenyl cation.

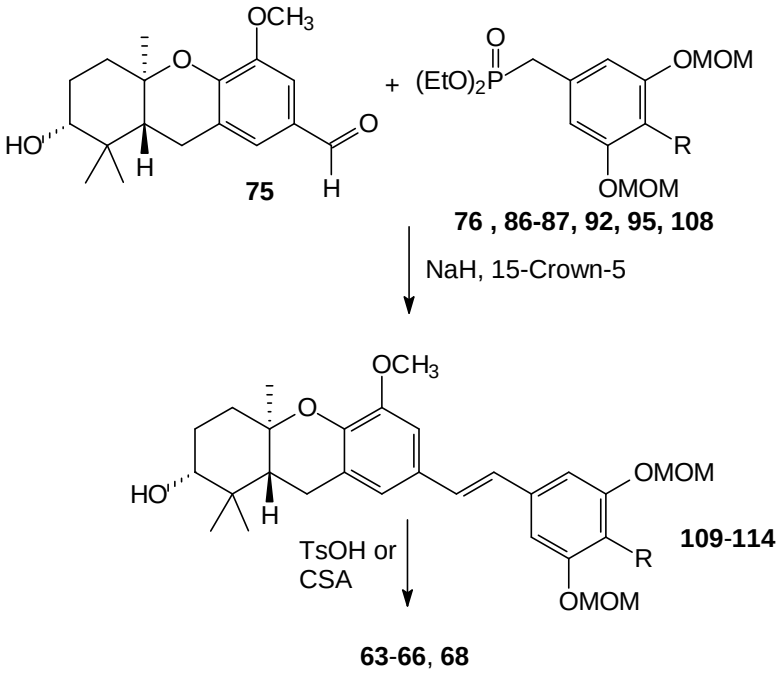


Figure 34. Completion of the analogues

Phosphonate	R	Stilbene	Yield (%)	Target	Yield (%) (TsOH)
76	Allyl	**109**	70	**63**	67
86	3–propanol	**110**	65	**64**	74
87	*n*–propyl	**111**	75	**65**	73
92	Isopentyl	**112**	—	**66**	73 (CSA) (2 steps)
95	Isopentenyl	**113**	62	**67**	—
108	Propynyl	**114**	—	**68**	26 (2 steps)

Table 1. HWE condensations and hydrolysis reactions[62]

As presented above, the natural schweinfurthins exhibit potent and differential cytotoxicity in the NCI's 60–cell line cancer screen. Of the cell lines tested in the NCI assay, the human–derived glioblastoma cell line SF–295 is one of the most sensitive to the growth inhibitory effects of the schweinfurthins, while the human–derived lung adenocarcinoma cell line A549 displays only moderate sensitivity to the schweinfurthins. Based on this difference in antiproliferative activities, a two–cell line screen was developed to determine whether synthetic analogues of the schweinfurthins exhibit the same basic pattern of cytotoxicity as the natural compounds. Within this testing scheme, all of the prepared compounds display schweinfurthin–like activity, but the observed potencies vary greatly.

One subset of these analogues can be viewed as the group with small alkyl substituents on the D–ring, compounds **63**–**66** and **68**. All five of these compounds showed anti–proliferative effects in the low or sub–micromolar range when tested against SF–295 cells (Table 2), and substantially less activity when tested in the A549 cells. The most potent compound in this set was the isopentyl compound **66**, indicating that the presence of an olefin at this position is unnecessary for activity in the SF–295 cell assay. This compound also showed approximately 10–fold lower potency against the A549 cells. Comparison of the ClogP values of compounds **64**–**66** reveals a tentative correlation between hydrophobicity and cytotoxic activity (Table 2). The hydroxyl moiety in analogue **64** leads to a decrease in activity in the sensitive cell line, while the presence of hydrophobic methyl groups in analogue **66** appears to contribute to slightly increased anti–proliferative activity relative to compound **65**.

Compared to the first set of compounds, the two heterocyclic compounds, benzofuran **69** and its dihydro analogue **70,** showed somewhat less potency against the SF–295 cell line, although dihydrofuran **70** was more active than its benzofuran counterpart. This result is in agreement with findings observed in a similar study.[100]

Compound	ClogP	SF–295 EC_{50} (μM)	A549 EC_{50} (μM)
63	5.75	1.7	>10
64	4.62	2.5	>10
65	6.05	0.9	>10
66	6.79	0.4	4.2
68	5.16	1.3	>10
69	5.11	4.8	>10
70	4.84	2.9	>10
71	6.98	2.8	>10
72	6.58	2.9	>10
73	6.95	>10	>10
74	8.04	>10	>10

Table 2. Activity of synthetic schweinfurthins in a two–cell screen

Assays on the final compounds suggest that reduction of the *trans*–stilbene olefin diminishes activity (e.g., **71–73** versus **66**). Isomerization of 3dSB (**15**, EC_{50}'s of 0.5 and 6.4 μM, respectively in this assay) to the *cis* olefin **74** has an even greater negative impact (EC_{50}s of >10 μM in both cell lines). This outcome is interesting given the varied potencies observed in *cis* and *trans* analogues of medicinally important stilbenes such as resveratrol[101] and combretastatin.[102]

Of the eleven compounds tested in the two–cell assay, compound **66** demonstrated the greatest potency against SF–295 cells, along with a 10–fold difference in activity between the two cell lines. When this compound was tested in the 60–cell line assay at the NCI, it also showed significant potency (Figure 35). In the NCI assay, the

average GI_{50} across the 60 cell lines was 0.29 μM, and the GI_{50} in the SF–295 cell line was ~33 nM, making this one of the most potent schweinfurthin analogues to date. Its potency in the 60–cell line screen exceeds that of several of the natural products (e.g. SA and SB), which will encourage additional efforts to improve the activity of schweinfurthin analogues. Furthermore, the GI_{50} values varied over the 60–cell lines examined by more than three orders of magnitude. This large range is indicative of selective toxicity. Conversely, compound **73** proved to be one of the least active compounds tested in the two–cell assay. When this compound was tested in the NCI's 60–cell line assay, its average GI_{50} was 4.9 μM, suggesting a weakly active compound, and it exhibited virtually no differential activity across the 60 cell lines (Figure 36). Taken together with the results obtained from testing compound **66**, this suggests that the two–cell line assay is an effective means for rapidly screening analogues to identify schweinfurthin–like activity.

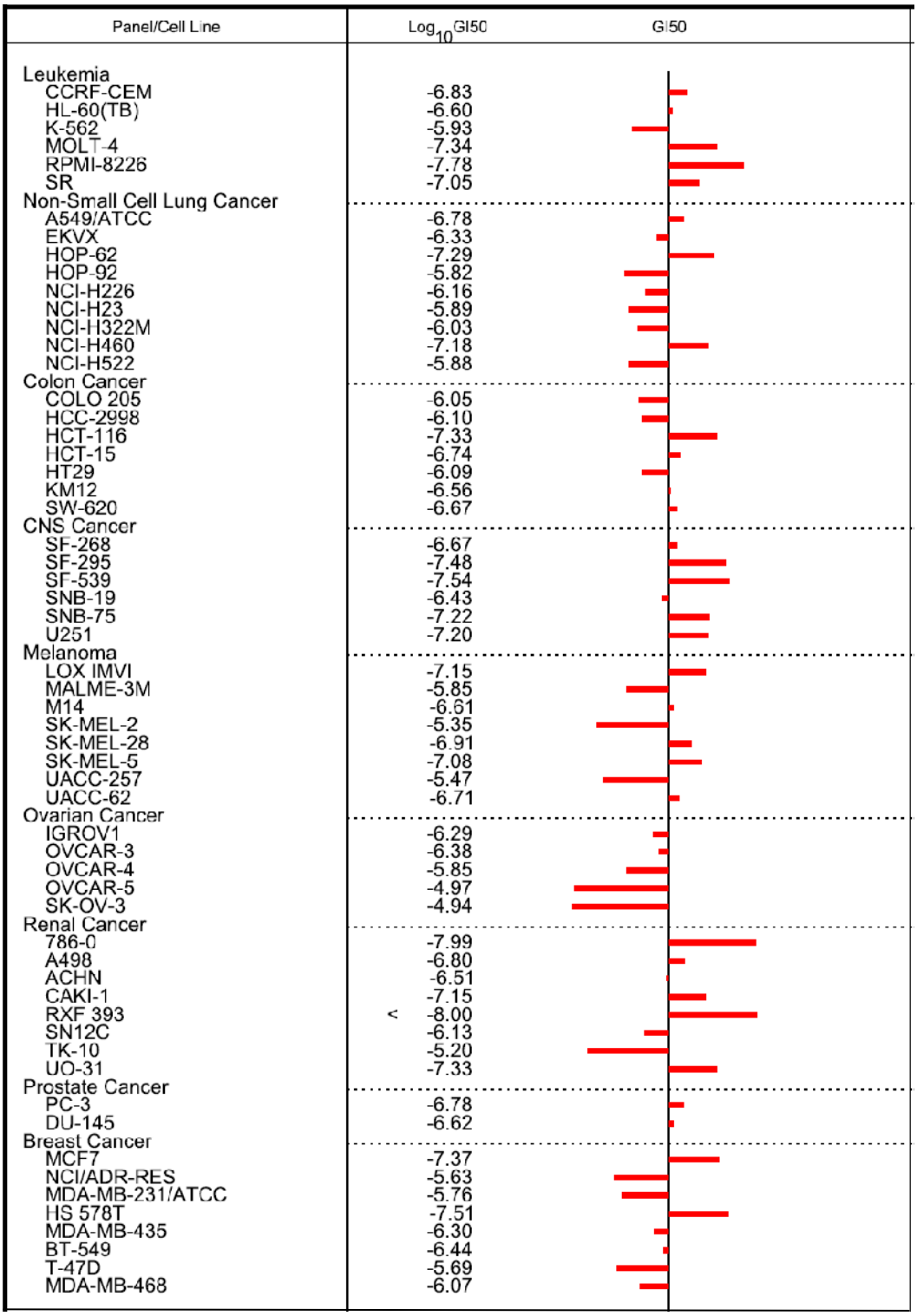


Figure 35. 60 cell line data, compound **66**

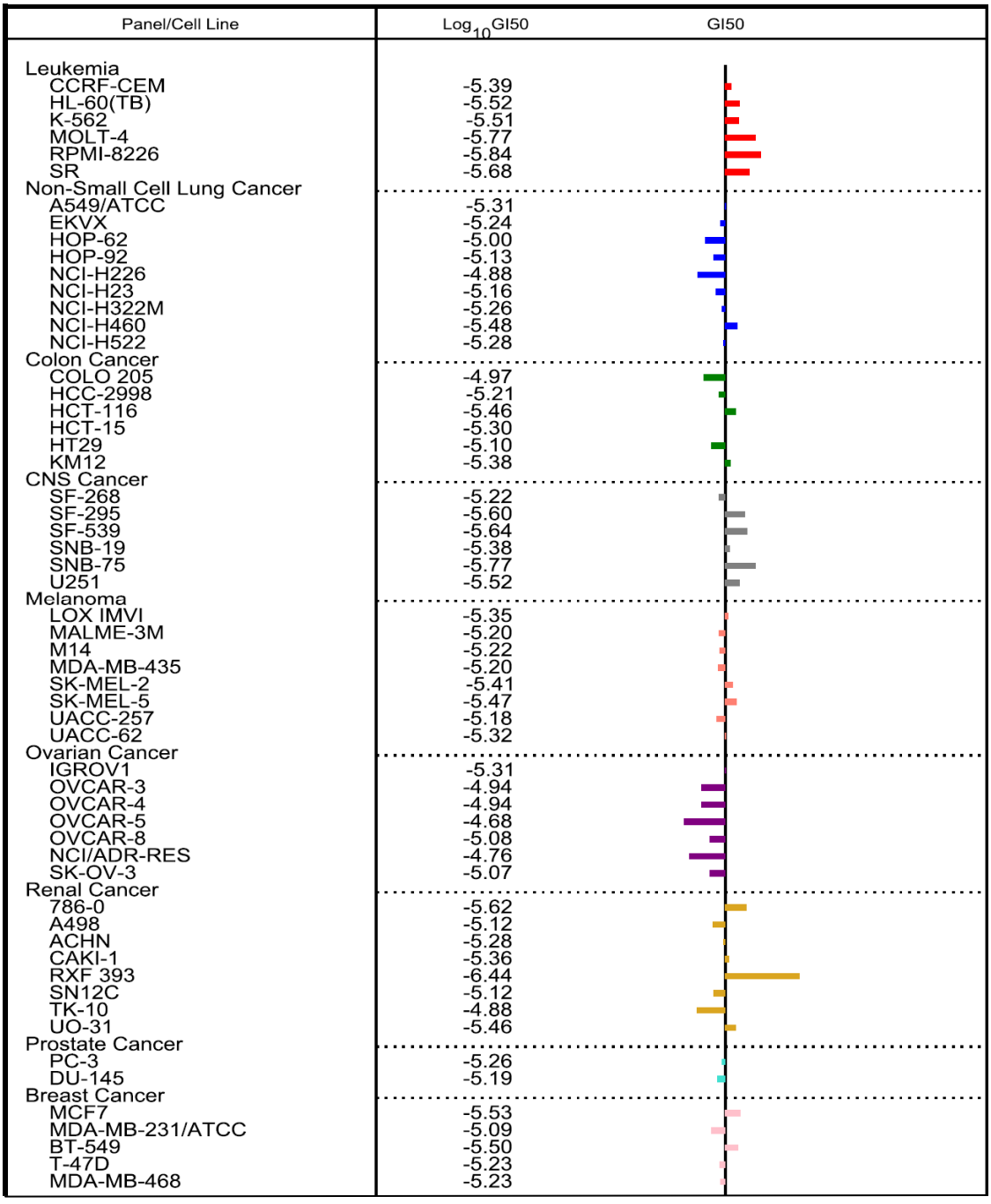


Figure 36. 60 cell line data, compound **73**

In conclusion, these studies have led to the preparation of a set of several new schweinfurthin analogues with variations in the nature of the stilbene olefin and the substituent at C–4' of the D–ring. The paucity of functionality in the side chain of the most potent compound, the isopentyl analogue **66**, may suggest that increasing hydrophobicity is more important than interaction with a specific functional group. Given this perspective, the activity observed in the heterocyclic compounds **69** and **70** encourages exploration of other heterocyclic systems, especially if they can be prepared with an additional alkyl substituent in the E–ring. Finally, either reduction of the stilbene olefin (e.g. **71**–**73**) or isomerization of the stilbene olefin from the *trans* stereochemistry to the *cis* (**74**) diminishes activity in the SF–295 cell line.

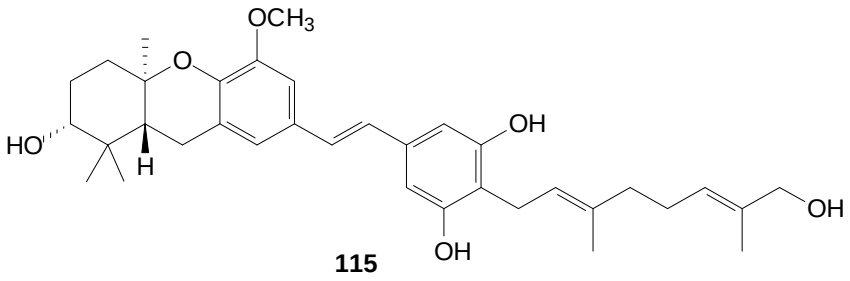
The two–cell assay for screening synthetic analogues has proven quite effective in quickly identifying potent and selective compounds. In this study, all eleven new schweinfurthin analogues were pre–screened in the two–cell assay. After the most potent compound of the set was identified, confirmation of this analogue's activity was obtained via the NCI's 60–cell line assay. As a proof of concept, one of the least active of the analogues in the two–cell assay also was tested in the 60–cell line assay and displayed both reduced cytotoxicity and lessened differential activity. Thus, it appears reasonable to use this facile screening process for more efficient testing of future synthetic analogues.

At this time, the mode of action and/or molecular target of the schweinfurthins remain unknown. Given the preservation of activity despite variations in the alkyl chains at C–4', this position appears to be a reasonable site for preparation of biotinylated derivatives.

CHAPTER 3
SYNTHESIS OF SCHWEINFURTHIN ANALOGUES FOR AFFINITY EXPERIMENTS

In order to elucidate the mechanism of schweinfurthin toxicity, it would be desirable to identify the intracellular binding partner(s). Although numerous kinds of interacting molecules are possible, including lipids, nucleotides, and proteins, we hypothesize that the schweinfurthins bind directly to a protein based on their reactivity, chemical structure, and overall pattern of cytotoxicity. This chapter will detail the exploration of chemical modifications to the schweinfurthins to yield useful analogues for affinity bioassays. For these analogues to serve as molecular probes, they must exhibit the characteristic schweinfurthin pattern of biological activity. Here we demonstrate that schweinfurthin analogues biotinylated off the D–ring: 1) display schweinfurthin–like activity in a relevant two–cell line screen; 2) induce the same characteristic morphological changes in cancer cells as the natural products; and 3) can be used in affinity bioassays to assist in the isolation/determination of possible schweinfurthin–binding proteins.

During the course of our studies, we have reported not only the total syntheses of several natural schweinfurthins, but also the preparation of numerous synthetic analogues for structure–activity–relationship (SAR) studies.[59, 61, 62] In particular, we have synthesized a schweinfurthin allylic alcohol (**115**, Figure 37)[59] which exhibits potent and differential cytotoxicity in the distinctive schweinfurthin pattern (mean GI_{50} = 1.0 μM in the 60–cell line assay), indicating that structural modifications at the distal end of the geranyl chain do not affect significantly the biological activity. Therefore, if schweinfurthins bind to a protein, then alterations to this region of the molecule presumably should not interfere with protein binding. Conversely, the limited activity of schweinfurthin C (**16**) suggests that the A– and B–rings of schweinfurthins A (**13**) and B (**14**) are essential for activity, and that extensive modifications in this region would not be tolerated.



115

Figure 37. Schweinfurthin allylic alcohol **115**

A retrosynthetic analysis of a biotinylated schweinfurthin analogue (**116**) is detailed in Figure 38. Late–stage esterification of D–biotin (**118**) and the schweinfurthin analogue **117** followed by removal of the phenolic protecting groups would provide the desired target. Disconnection of the stilbene olefin could afford the Horner–Wadsworth–Emmons coupling partners aldehyde **75** and phosphonate **119**. Phosphonate **119** could be obtained from benzyl alcohol **120**, which in turn could result from alkylation of the corresponding benzyl alcohol **121** under standard conditions.[103]

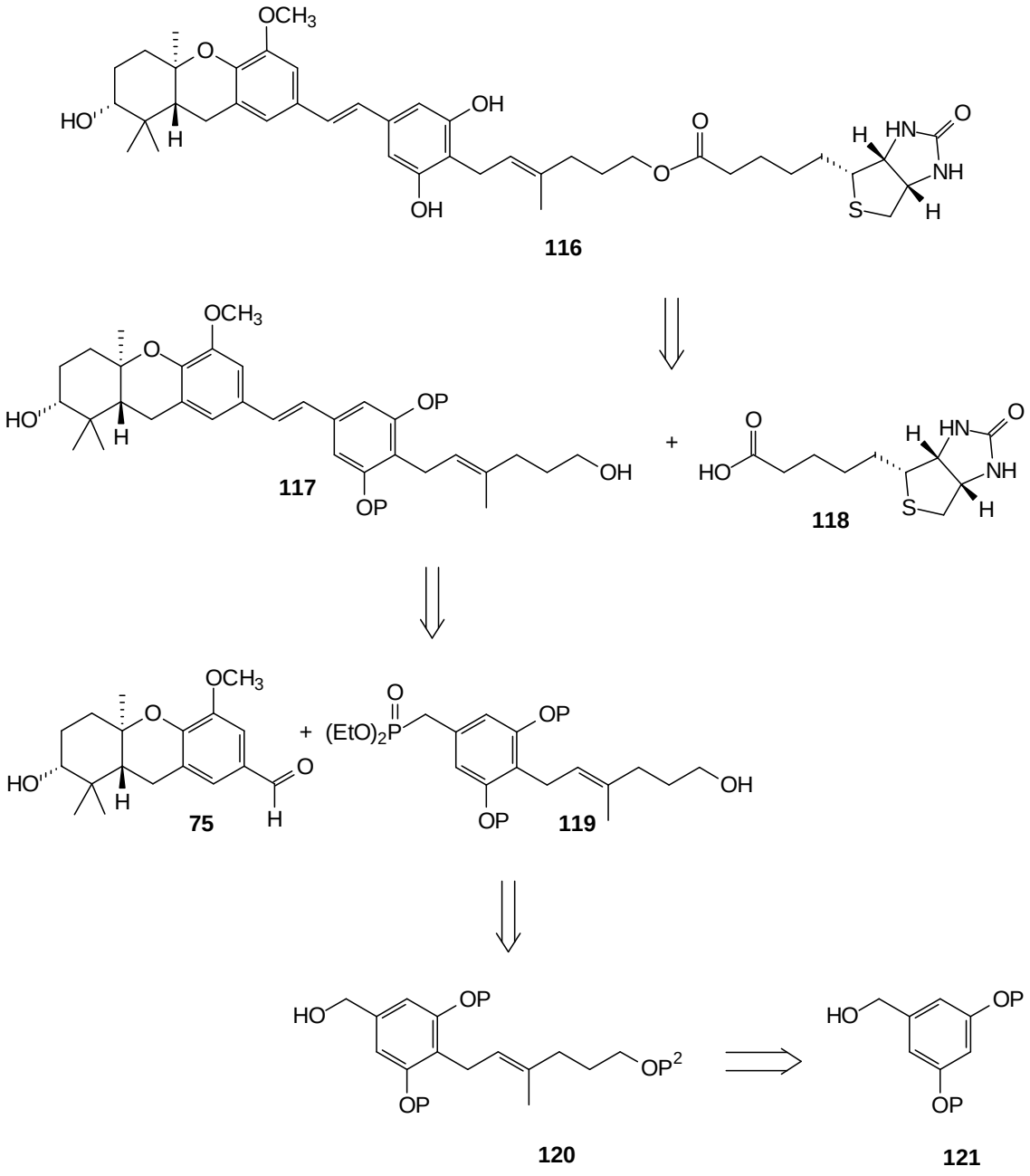


Figure 38. A retrosynthetic analysis of the biotinylated schweinfurthin analogue **116**

Several challenges were anticipated in the synthesis of the target compound **116**. First of all, an efficient alkylation of the right–half benzyl alcohol **121** to produce compound **120** was required. Second, differential protection and deprotection of the D–

ring phenol moieties might be problematic, especially at a late stage in the synthesis. Finally, attachment of the biotin moiety and isolation of the target compound could prove difficult in light of previous work in our labs (Salnikova, M. Unpublished results, University of Iowa).

Initial attempts to prepare a differentially protected D–ring substructure utilized the protected aldehyde **127** (Figure 39). The alkyl chain for the D–ring was prepared from commercially available geranyl acetate (**122**). Epoxidation of geranyl acetate (**122**) with *m*–CPBA provided the known epoxide **123**[104] in high yield, and periodate cleavage of the epoxide provided the known aldehyde **124** in modest yield.[105] Protection of aldehyde **124** as the dimethyl acetal and hydrolysis of the acetate under basic conditions provided known allylic alcohol **126**.[106] Conversion to bromide **127** was accomplished via the intermediate mesylate, yielding a product that was used without further purification.

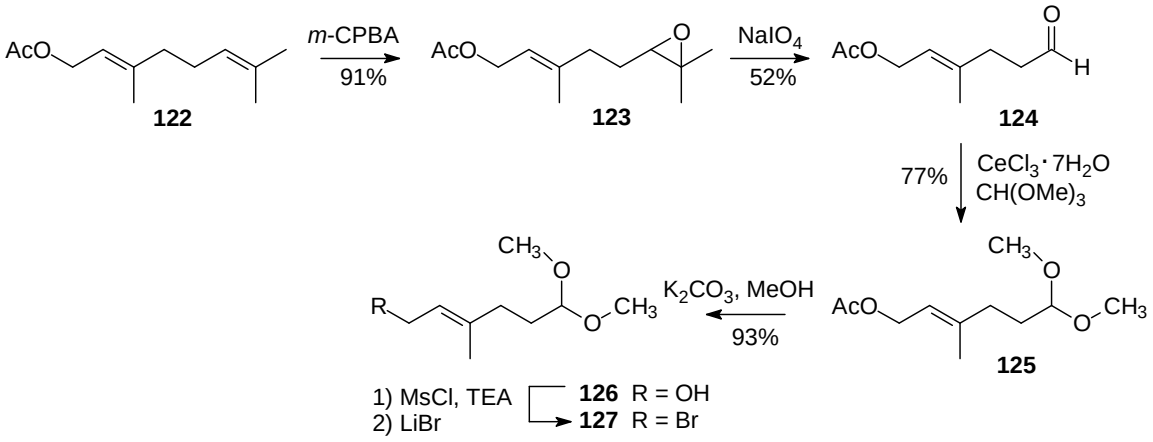


Figure 39. Synthesis of allylic bromide **127**

Treatment of benzyl alcohol **104** with 2 equivalents of strong base in the presence of TMEDA abstracts both the hydroxyl hydrogen and the hydrogen *ortho* to both of the MOM protecting groups to produce the corresponding dianion (Figure 40).

Transmetallation to the cuprate and subsequent treatment with bromide **127** should provide the C–alkylated product without the need for protection of the benzyl alcohol.[103] Unfortunately, only a trace amount of the desired product was obtained in this case. This may be due to the difficulty of forming the dianion; if any of the reagents is not strictly anhydrous or the equivalents of base are incorrectly measured, then formation of the dianion may not occur. After this failure to obtain the desired product, more care was taken to use strictly anhydrous reagents and to control reagent equivalents with special care.

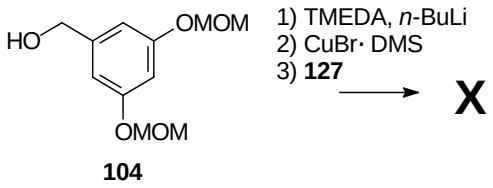


Figure 40. Attempted alkylation of benzyl alcohol **104**

As part of our studies on tandem cascade reactions, it has been demonstrated that similar alkylations can be accomplished using the more easily prepared epoxy bromide **129** (Figure 41).[82] Following epoxidation of geranyl acetate, removal of the allylic acetate provides alcohol **128**, which can be converted readily to bromide **129** via the intermediate mesylate.

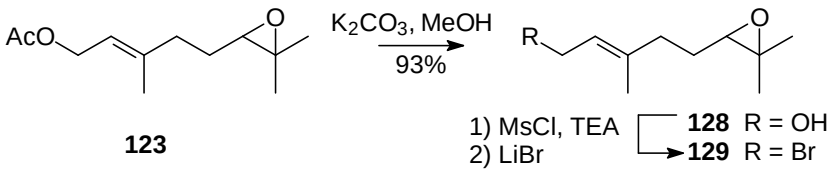


Figure 41. Preparation of bromide **129**

Using freshly distilled TMEDA and recrystallized CuBr•DMS, alkylation of compound **77** with bromide **129** afforded epoxide **130** in reasonable yield (Figure 42). Following deprotection of the benzylic alcohol upon treatment with TBAF, cleavage of the intermediate epoxide was accomplished in modest yield by treatment with 1 equivalent of periodic acid. It should be noted that cleavage conditions utilizing sodium periodate, an excess of periodic acid, or elevated temperatures resulted in significantly reduced yields. Instead of using a protected aldehyde, it was decided that an allyl–protected alcohol would be preferable due to the ease of deprotection.[107] Re–protection of the benzyl alcohol as the silyl ether and standard borohydride reduction of aldehyde **131** provided alcohol **132**. Treatment of alcohol **132** with NaH and allyl bromide afforded allyl ether **133** in good yield. Subsequent reaction of compound **133** with TsOH in MeOH resulted in the unexpected formation of ether **134** as the major product.

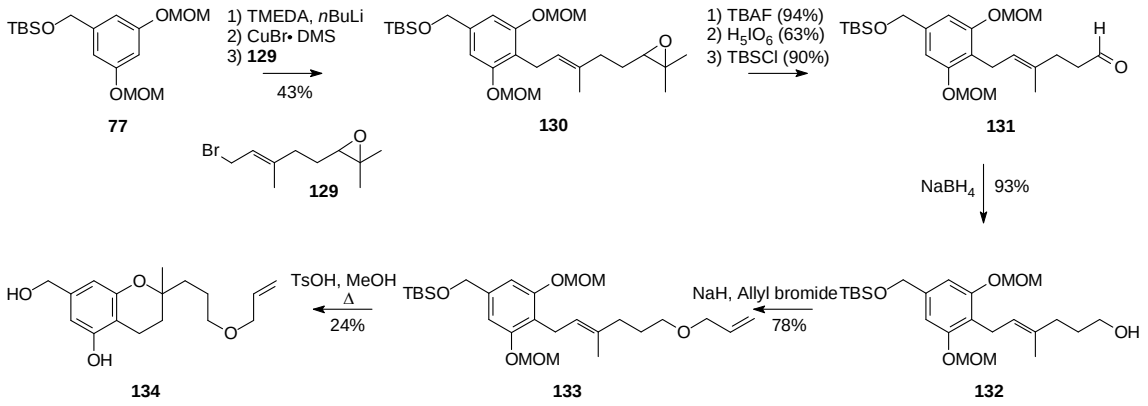


Figure 42. Unexpected cyclization to produce ether **134**

In light of these results, it was determined that our group has accomplished a MOM deprotection in a similar substrate using CSA (Figure 43).[59] However, when compound **133** was allowed to react with CSA, ether **134** again was obtained as the major product as indicated by TLC.

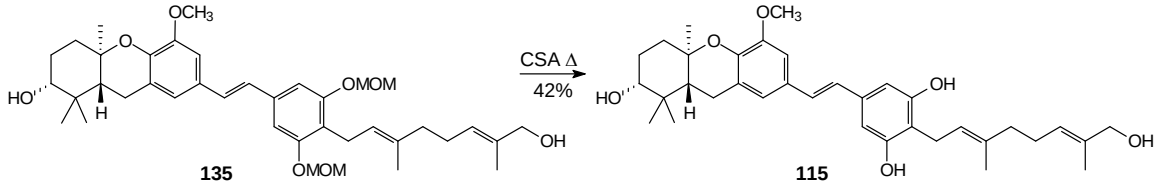


Figure 43. Acidic hydrolysis of schweinfurthin analogue **135**[59]

After these disappointing results, it was decided to study the previously reported schweinfurthin analogue **115**, a strategy which would improve the convergency of the route and minimize late–stage protecting group manipulations.[59] Regioselective oxidation of geranyl acetate (**122**) to the intermediate aldehyde followed by reduction provided allylic alcohol **136** (Figure 44).[108] Protection of the alcohol as either the TBS or TBDPSl ethers and removal of the acetate afforded known alcohols **137** and **138**.[109, 110] Conversion to the respective bromides **139** and **140** was straightforward.

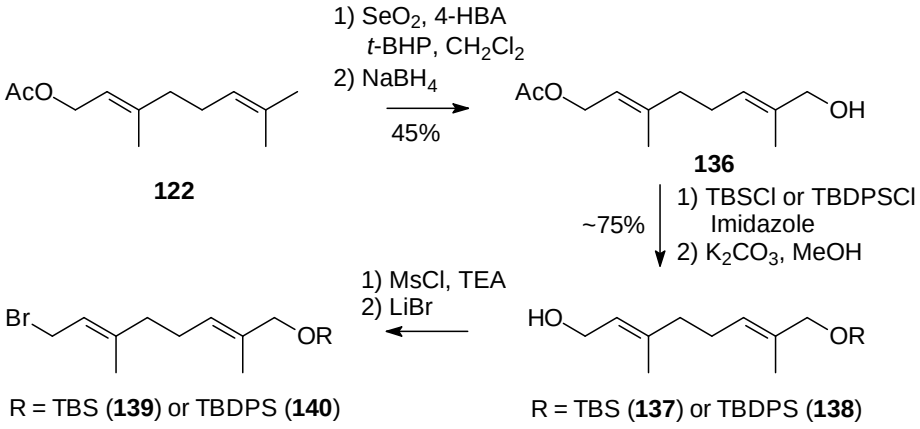


Figure 44. Synthesis of bromides **139** and **140**

Once the bromides **139** and **140** were in hand, a SEM–based protecting group strategy was explored (Figure 45). It was believed that a SEM–protected phenol would make the final global deprotection more facile while still exploiting the directing influence of the SEM group in the initial alkylation step. The requisite protected benzyl alcohol **144** was prepared as shown in Figure 45. Methylation of the SEM–protected phenol **141** proceeded in modest yield to produce ester **142**. Reduction of the ester functionality proceeded smoothly and was followed by TBS protection to provide the desired arene **144**. Unfortunately, attempted alkylation of the protected alcohol **144** with bromide **140** was unsuccessful. Only trace amounts of the desired product were detected by TLC, and due to the cost of commercial material and the problematic preparation of SEMCl, this reaction was not explored further.

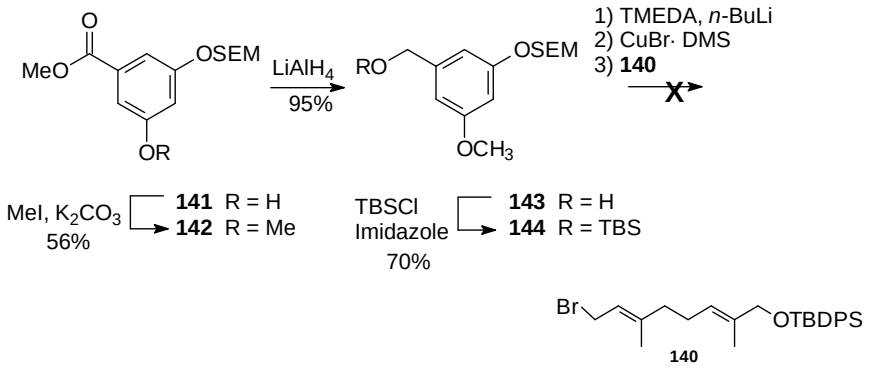
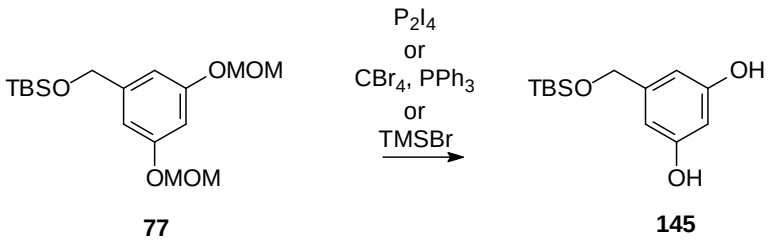


Figure 45. Attempted alkylation of a SEM–protected right half **144**

Several different methods for phenolic MOM–deprotections were explored using protected arene **77**. These conditions included P_2I_4,[111] CBr_4 and PPh_3,[112] and TMSBr in the presence of molecular sieves.[113] Each trial resulted in either recovered starting material or complex mixtures which were not purified.



77 **145**

Figure 46. Unsuccessful strategies for MOM–deprotection

Deprotection of the MOM acetals finally was accomplished on a more advanced phosphonate intermediate (Figure 47). Alkylation of benzyl alcohol **104** with bromide **139** and conversion to phosphonate **147** was accomplished in modest yield. Treatment of phosphonate **147** with TsOH in MeOH effected cleavage of the MOM–protecting groups without affecting the phosphonate moiety. Subsequent silylation with TBSCl and imidazole provided the tri–TBS protected phosphonate **148** in modest yield, presumably due to steric hindrance at the phenols. Unfortunately, the attempted HWE condensation of phosphonate **148** with aldehyde **75** was unsuccessful and provided only a small amount (< 2 mg) of a product possessing at least three different silyl ethers due to partial deprotection and/or migration. A review of the literature revealed that although phenolic silyl ethers commonly are believed to be stable to base, they often are prone to cleavage and/or rearrangement under basic conditions because phenoxide anion is a much more stable leaving group than a simple alkoxide.[114]

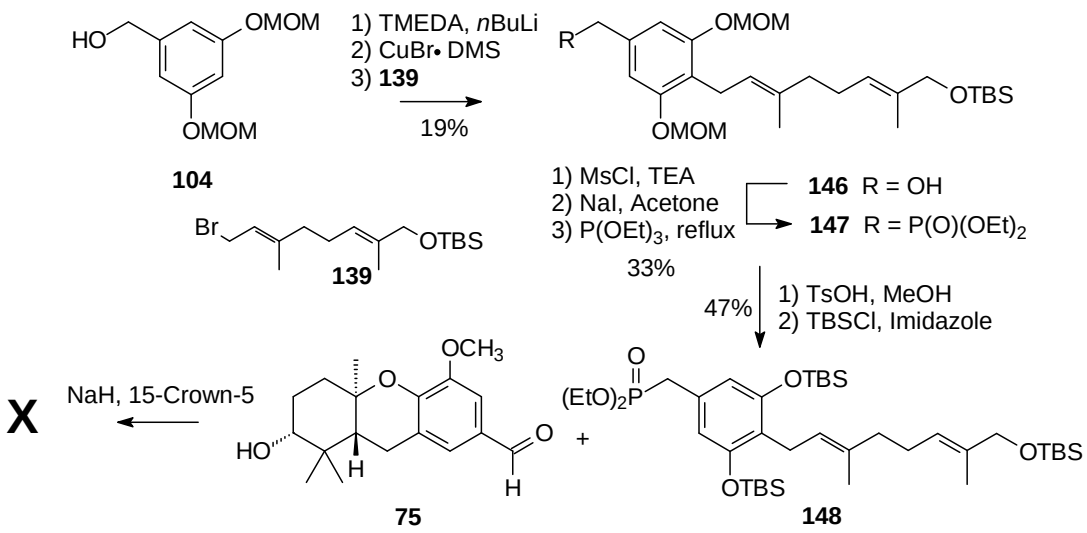


Figure 47. Attempted HWE olefination of aldehyde **75** and TBS–protected **148**

In light of these findings, a chemoselective esterification of unprotected schweinfurthin analogue **150** with D–biotin (**118**) was envisioned (Figure 48). In this scenario, the schweinfurthin analogue would be synthesized via standard procedures, deprotected, and then treated with D–biotin (**118**) to provide the desired compound **149**. During this work, it was discovered that protection of at least one of the D–ring phenols led to greatly increased stability of the resorcinol substructure. Therefore, all subsequent work utilized analogues comparable to compound **150**.

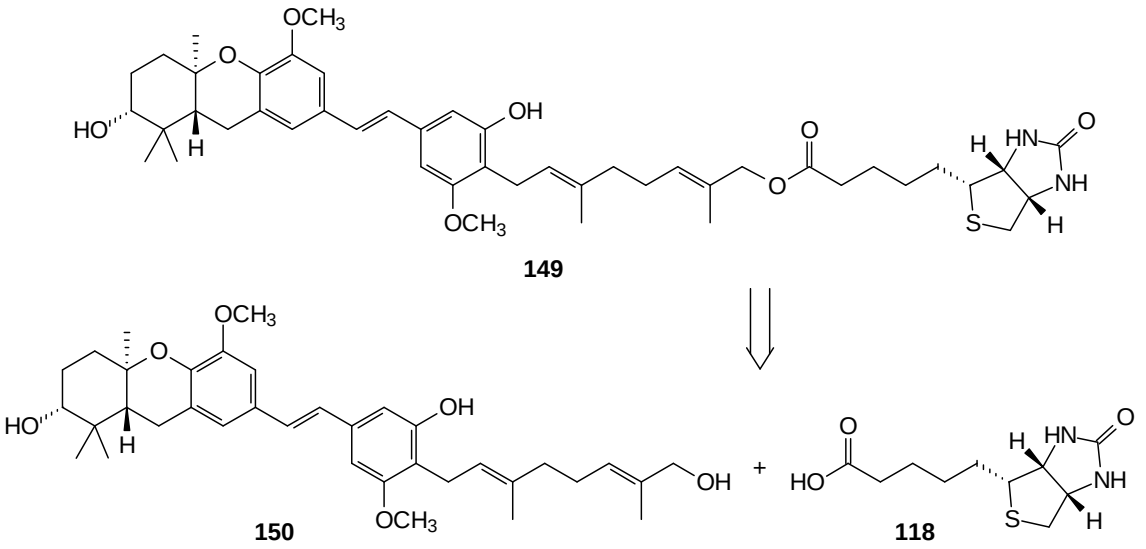


Figure 48. Esterification of schweinfurthin analogue **150** and D–biotin (**118**)

A survey of the literature revealed only a few examples of this type of transformation.[115, 116] In one relevant case, Smith and coworkers reported the use of Mitsunobu conditions to effect the chemoselective esterification of a primary alcohol (**151**) in the presence of a phenol (Figure 49).[117] Their reaction proceeded in excellent yield to provide the desired ester **153**.

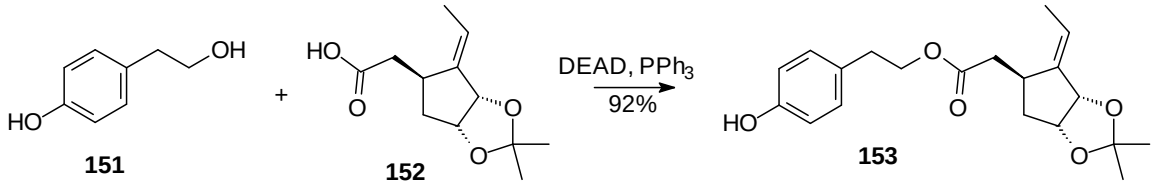


Figure 49. Chemoselective esterification in the presence of a phenol[117]

To test whether a parallel reaction would work in a simplified case, a chemoselective esterification of benzyl alcohol **154** and hexanoic acid (**155**) was

attempted (Figure 50). In this instance, however, despite carefully following the reported literature procedure, only diester **156** was obtained.

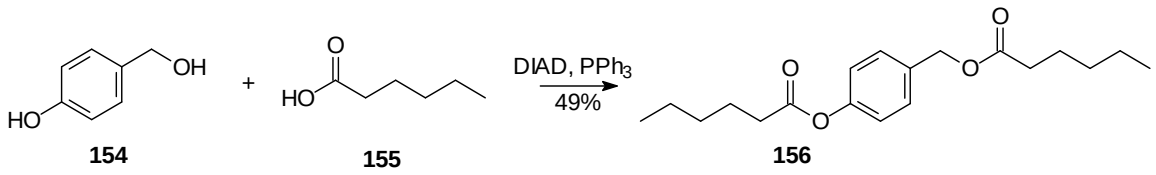


Figure 50. Synthesis of diester **156**

With the hope that steric hindrance at the D–ring phenol of schweinfurthin analogue **150** might limit esterification at this site, the EDC–mediated coupling of unprotected schweinfurthin analogue **150** with D–biotin (**118**) was examined (Figure 51). Synthesis of arene **158** began with known benzyl alcohol **157**.[61] Regioselective formation of the lithiate, transmetallation to the cuprate, and subsequent alkylation with bromide **139** gave the C–alkylated product **158** in modest yield. Subsequent conversion to the phosphonate was accomplished via standard reaction conditions, and fluoride–mediated silyl group removal afforded phosphonate **159**. Phosphonate **159** was allowed to react with tricyclic aldehyde **75** in the presence of NaH and 15–Crown–5 to provide the protected stilbene **160**. Deprotection of the MOM–acetal was effected using TsOH in MeOH to provide phenol **150** in good yield. Unfortunately, when schweinfurthin analogue **150** was treated with D–biotin (**118**) in the presence of EDC, no product was detected by TLC analysis.

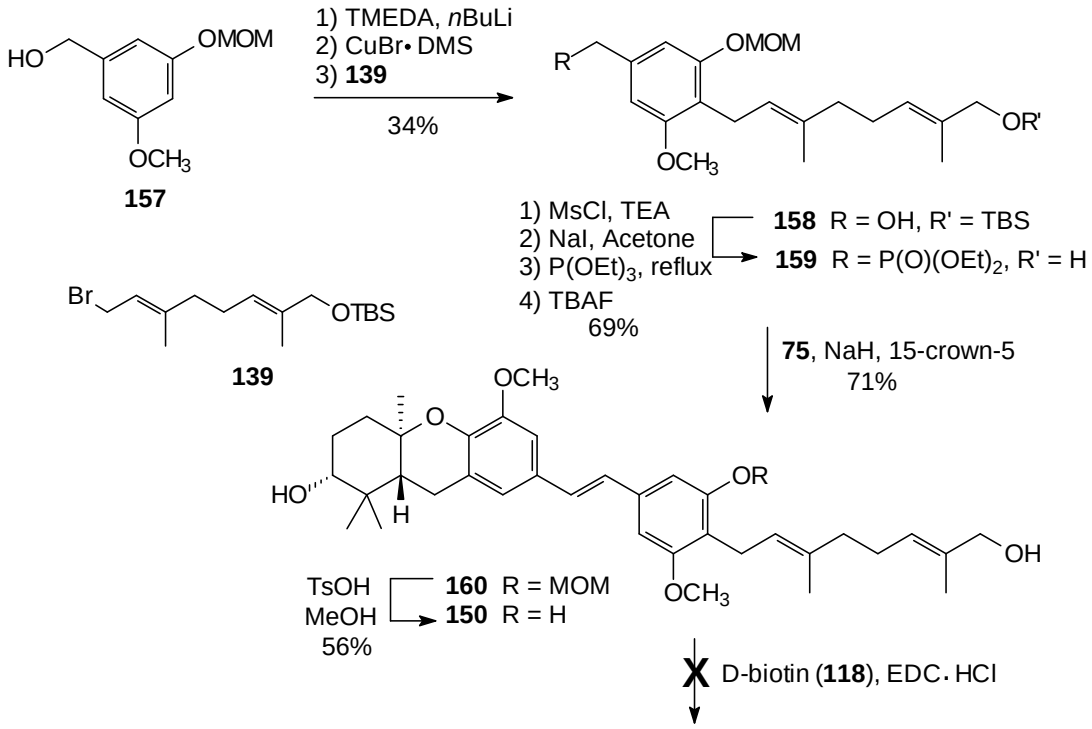


Figure 51. Attempted biotinylation of compound **150**

Based on the hypothesis that the esterification may have been successful but that the visualization and isolation of the product may have been difficult, the biotinylation of two relevant allylic alcohols (**161** and **136**) was attempted using the reaction conditions reported by Myers and coworkers (Figure 52).[118] Both of the desired products were obtained in low yield, but these experiments provided insight into the isolation and purification of biotinylated substrates. After this success, the chemoselective esterification of analogue **150** was attempted again, but once again no product was detected.

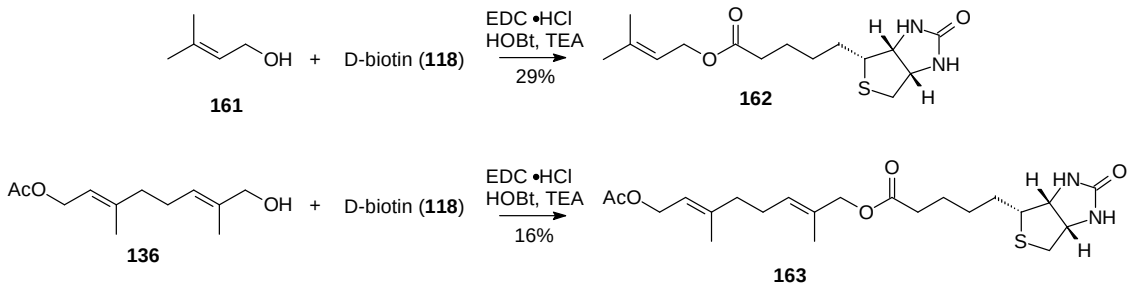


Figure 52. Biotinylation of prenol (**161**) and allylic alcohol **136**

Because the chemoselective esterification strategy failed to afford the desired target, it was decided to test whether MOM–deprotection would proceed in the presence of an allylic ester and biotin moiety. The EDC–mediated esterification of stilbene **160** and D–biotin (**118**) afforded biotinylated analogue **164** in modest yield (Figure 53). As expected, however, MOM–deprotection of compound **164** using various acidic conditions proved unsuccessful and resulted instead in cleavage of the allylic ester to afford alcohol **160**.

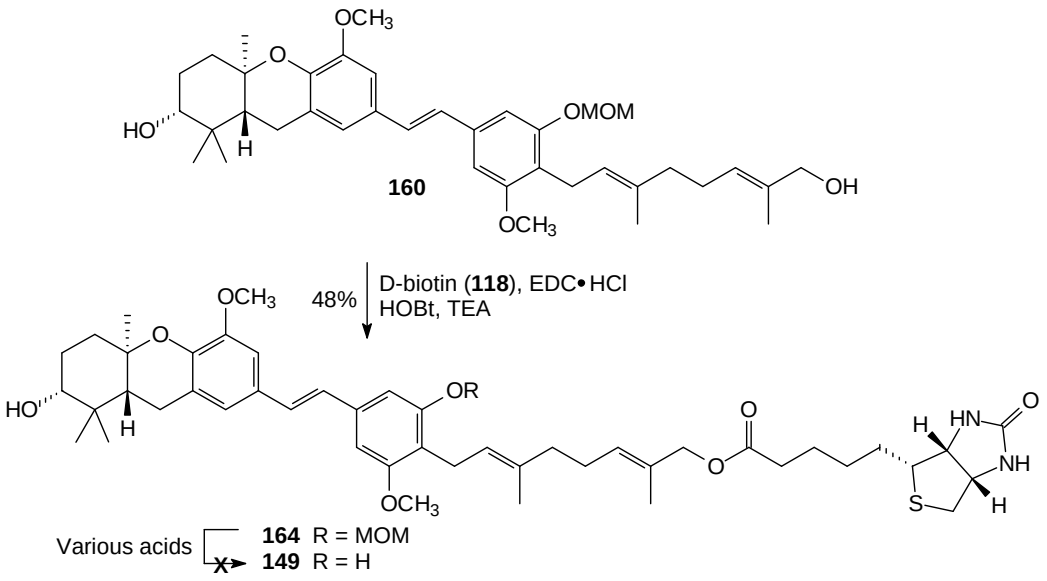


Figure 53. Acidic cleavage of allylic ester **164**

To avoid the possibility of ester hydrolysis, an amide linkage to the biotin moiety was examined because it should be more stable to acidic hydrolysis (Figure 54). Treatment of analogue **160** with phthalimide under standard Mitsunobu conditions gave the desired compound **165**.[119] Treatment of phthalimide **165** with hydrazine hydrate followed by EDC–mediated condensation with D–biotin (**118**) afforded the biotinylated schweinfurthin **166**. Finally, acidic hydrolysis of the MOM–acetal provided the target compound **46** in high yield.

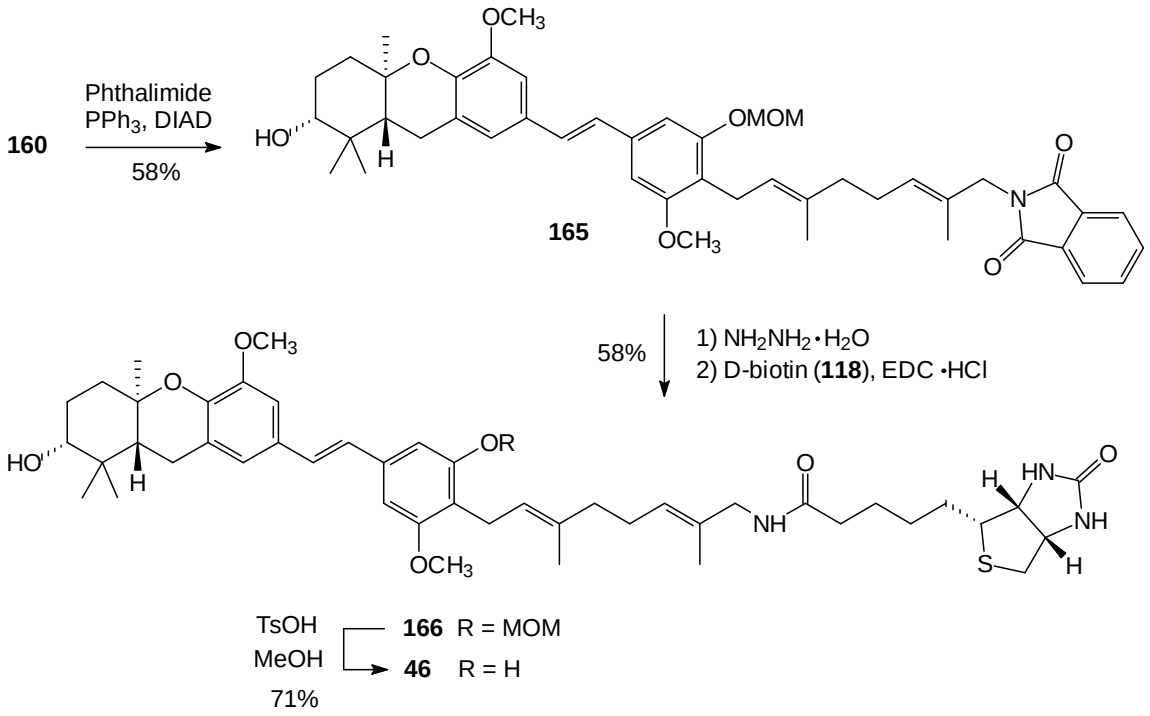


Figure 54. Successful preparation of biotinylated analogue **46**

We also decided to design and synthesize an appropriate control compound for use in the pull–down experiments (see Chapter 1). Stilbene **167**, which lacks the hexahydroxanthene left–half or "warhead" of the schweinfurthins, should function as a less active biotinylated analogue (Figure 55).

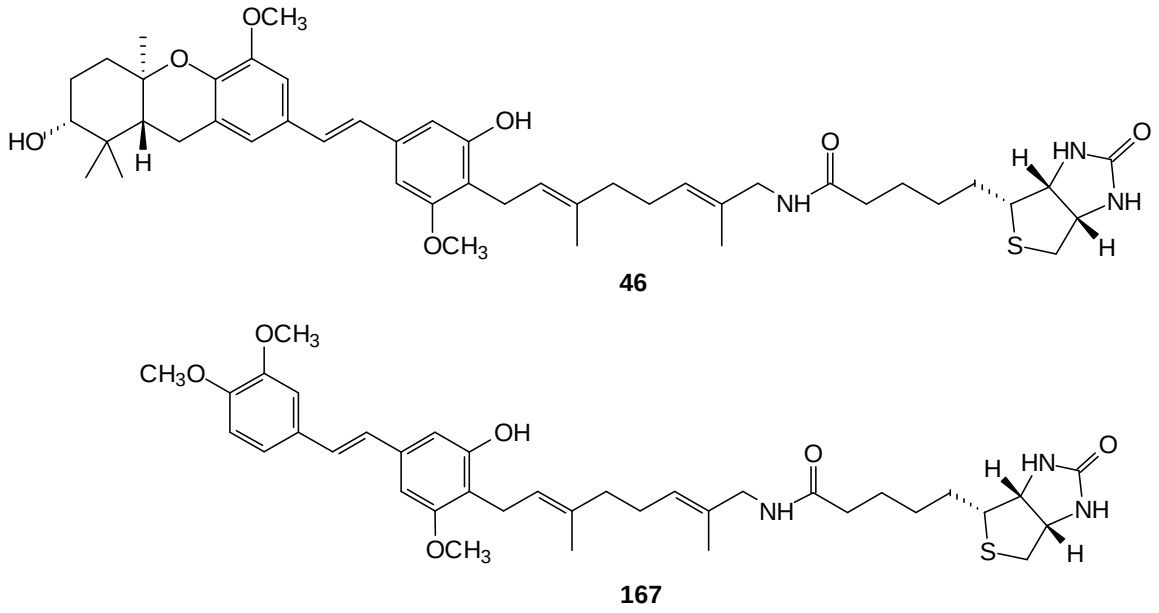


Figure 55. Biotinylated analogue **46** and target foil compound (**167**)

The condensation of 3,4–dimethoxybenzaldehyde (**168**) with phosphonate **159** proceeded in good yield to produce stilbene **169** (Figure 56). Conversion to the phthalimide **200** proceeded smoothly and subsequent reaction with hydrazine hydrate provided the intermediate amine, which was carried on without further purification. The amidation of the amine with D–biotin (**118**) appeared to be successful by TLC analysis, but following attempted purification of the reaction mixture, analysis of the NMR spectra revealed a ~1:1 mixture of the desired product **170** and the methyl ester of D–biotin (**171**).[120] When this mixture proved difficult to separate, the mixture was treated with TsOH in MeOH in hopes that the two compounds could be separated following deprotection of the MOM–acetal. However, this also produced an inseparable mixture of the two products. While liberation of a D–ring phenol has proven necessary to produce a biologically active schweinfurthin analogue, it may not be required in a control compound for the pulldown experiments. Even the presence of some methyl biotin (**171**)

may not be problematic in these experiments. Therefore, further efforts to purify compounds **167** and **170** were postponed pending determination of the needs of our biologist colleagues.

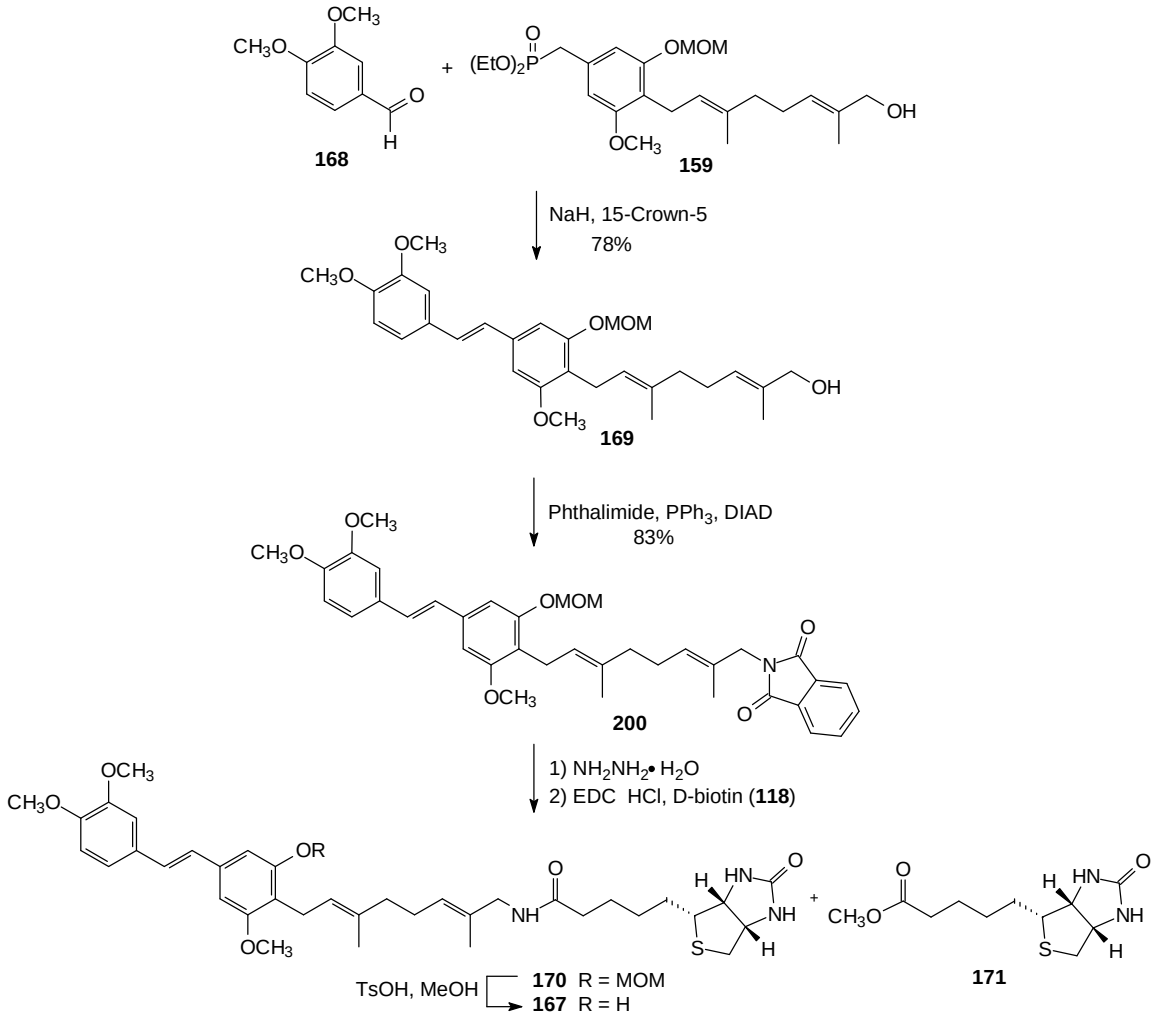


Figure 56. Inseparable mixture of target compound **167** and biotin ester **171**

With biotinylated schweinfurthin analogues **46**, **164**, and **166** in hand, it was decided that an even more potent biotinylated analogue might be relatively straightforward to prepare. Due to the availability of aldehyde **173**,[58] the synthesis of a

schweinfurthin B biotinylated analogue was undertaken (Figure 57). Oxidation of benzyl methyl ether **172** with DDQ proceeded in good yield,[58] and HWE olefination of aldehyde **173** with phosphonate **159** produced stilbene **174**. Treatment of alcohol **174** with phthalimide provided the desired compound **201** in low yield for unknown reasons. Reaction with hydrazine hydrate provided the intermediate amine, and EDC–mediated biotinylation proceeded efficiently as indicated by TLC analysis. Treatment of MOM–protected compound **175** with TsOH in MeOH hydrolyzed the MOM–acetals over several days as indicated by TLC analysis. Unfortunately, the isolation and purification of the target compound **176** by preparatory TLC proved problematic due to the very limited amount of material available after several low–yielding steps in succession.

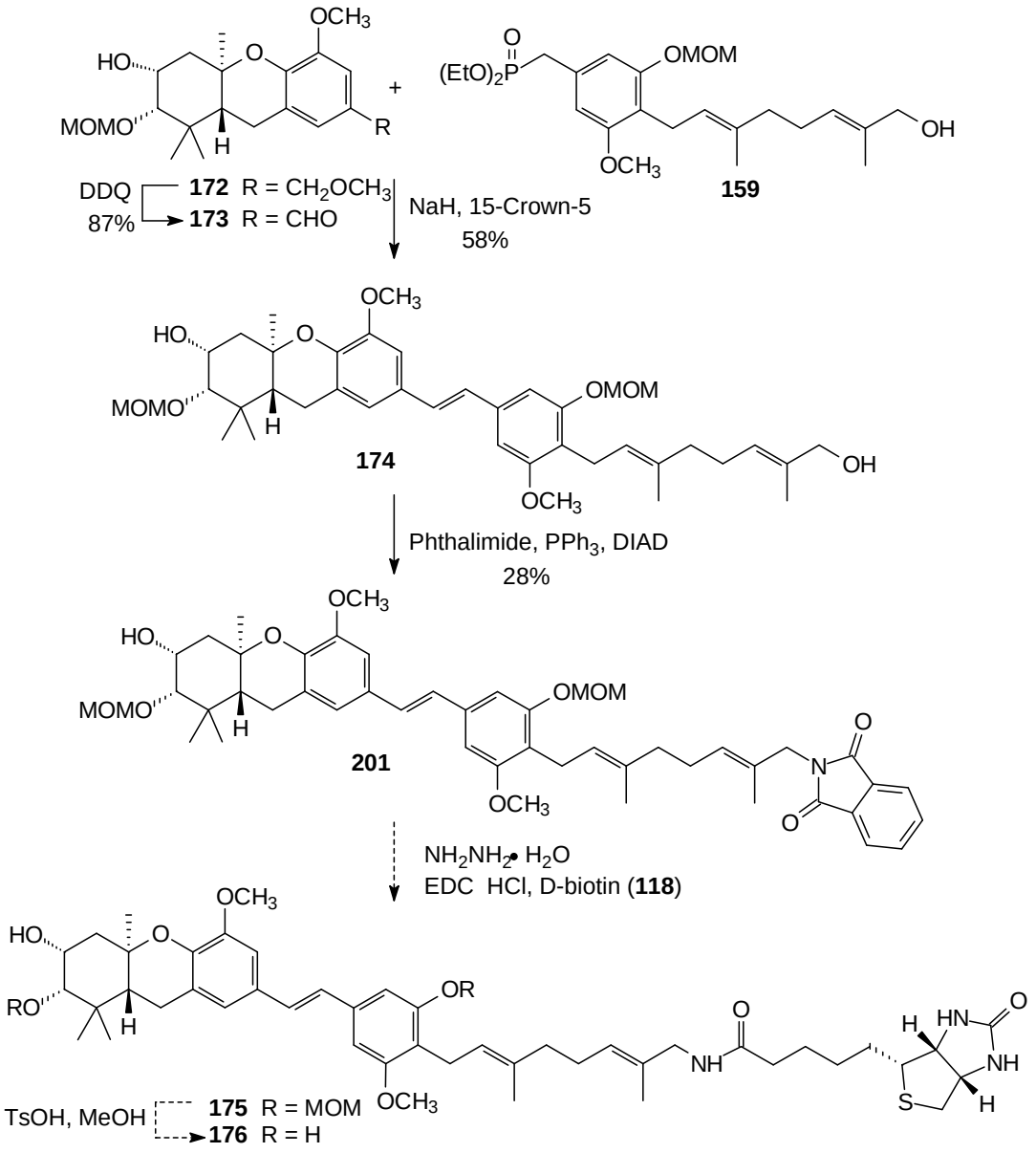


Figure 57. Attempted synthesis of biotinylated schweinfurthin B

When unprotected left–half aldehyde **177** became available, the previous sequence was attempted again (Figure 58). In this case, however, the HWE condensation of aldehyde **177** with phosphonate **159** was unsuccessful, producing < 1% of the desired product. Others in our group have experienced similar difficulties when using aldehyde

177 in attempted HWE condensations of related systems, work which will be reported elsewhere.

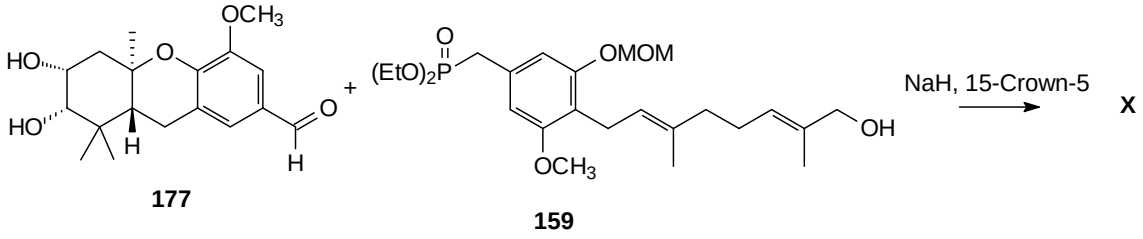


Figure 58. Attempted HWE condensation of aldehyde **177** and phosphonate **159**

Following a review of the pertinent literature it was decided that a longer linker between the schweinfurthin core and the biotin moiety might be advantageous (see Chapter 1). It was envisioned that a schweinfurthin allylic aldehyde such as **181** could be coupled to the known amido–biotin **180** (Figure 59), which was prepared via a known procedure from commercially available amine salt **178** and NHS–biotin (**179**).[121]

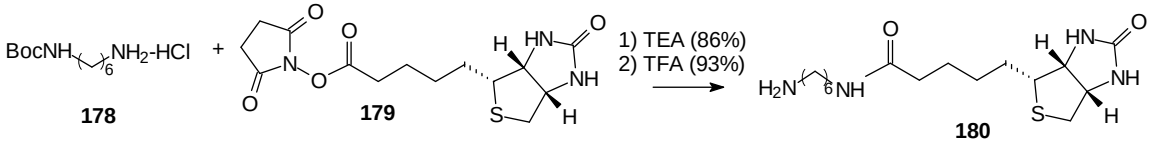


Figure 59. Known synthesis of biotin conjugate **180**[121]

To examine this approach, allylic alcohol **174** was oxidized to the intermediate aldehyde **181**, which was carried on without further purification (Figure 60). Attempted Pinnick oxidation[122] of aldehyde **181** led to extensive over–oxidation, giving a complex mixture. Due to the lack of additional material, this reaction was not attempted again.

Therefore we proceeded with biological evaluations of the biotin analogues **46**, **164**, and **166**, and resolved to return to the preparation of other biotinylated analogues only if needed for further pulldown experiments of the presumed protein target(s).

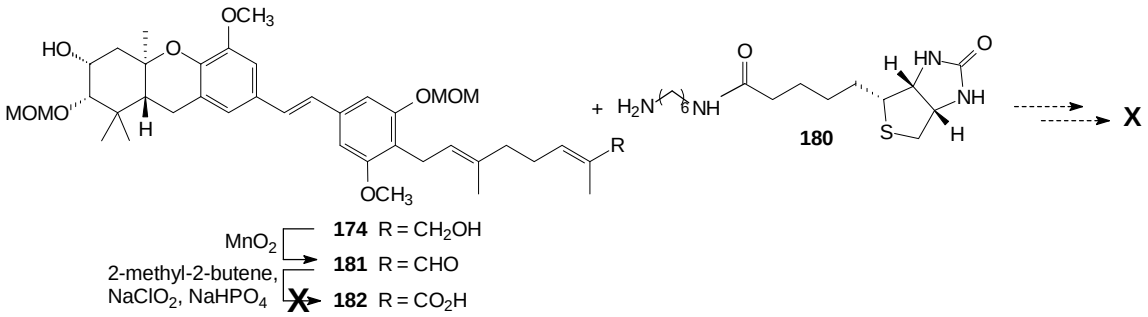


Figure 60. Over–oxidation of aldehyde **181**

As mentioned above, maintaining schweinfurthin–like activity probably is critical to the utility of these biotinylated compounds. To test whether biotinylated schweinfurthin analogues **46**, **164**, and **166** display schweinfurthin–like activity, they were tested against the human–derived glioblastoma multiforme cell line SF–295 and the lung adenocarcinoma cell line A549. In general, SF–295 cells are highly sensitive to schweinfurthin treatment, while A549 cells are relatively insensitive to schweinfurthin treatment. Results from these two assays are indicative of overall schweinfurthin–like activity in the 60–cell screen at the NCI, as demonstrated in a recent report.[62]

The results of these experiments are displayed in Figure 61. Analogues **164** and **166**, which possess MOM–protected D–ring phenols, exhibit decreased activity against SF–295 cells (EC_{50} = 3.08 and 1.07 μM, respectively) in comparison to 3–deoxyschweinfurthin B (3dSB, **15**, EC_{50} = 0.5 μM in this assay). This is not surprising due to the absence of D–ring hydrogen bond donors, a factor which has been shown to be important in previous studies.[59] As with the natural schweinfurthins, analogues **164** and

166 also are relatively inactive against the insensitive A549 cells (EC_{50} >10 and 5.04 μM, respectively). Amide schweinfurthin analogue **46**, which possesses a free phenol in the D–ring, demonstrates somewhat higher potency in the SF–295 cell line (EC_{50} = 0.98 μM) than analogues **164** and **166**, while displaying the characteristic lower sensitivity in the A549 cell line (EC_{50} = 6.4 μM). This not only makes analogue **46** a promising candidate as a biotinylated probe, but also indicates that attachment of biotin at this position does not significantly affect the interaction between the compound and its presumed target.

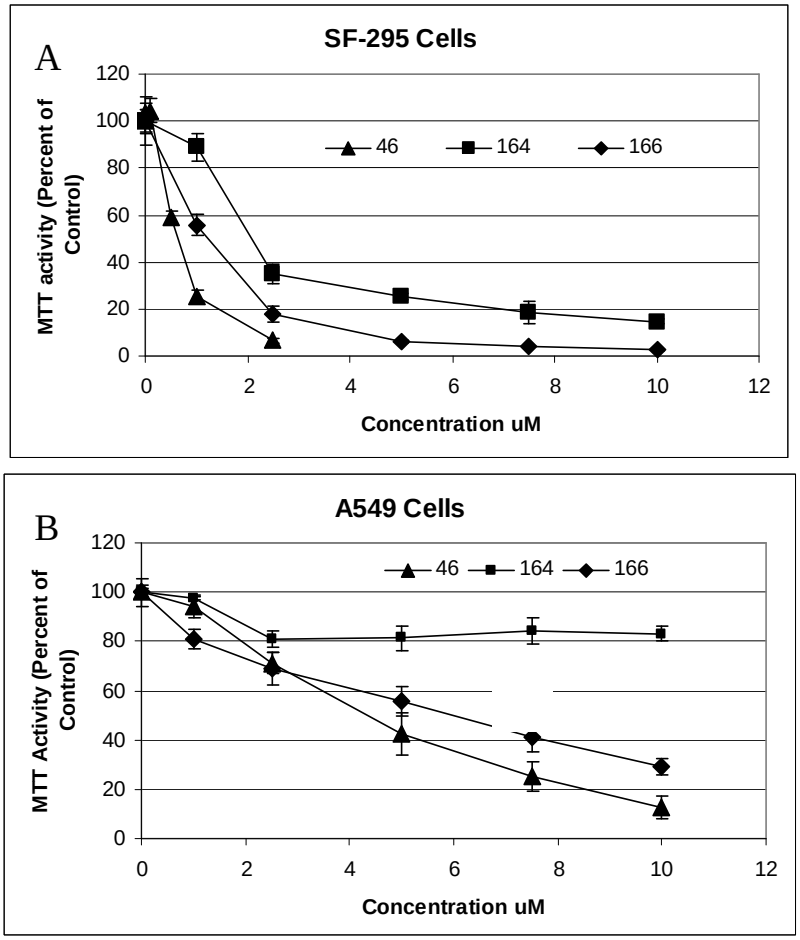


Figure 61. Concentration–response curves of compounds **46**, **164**, and **166** in SF–295 (A) and A549 cells (B).

In order to demonstrate further the "schweinfurthin–likeness" of biotinylated probe **46**, our collaborators at NCI–Frederick have performed experiments to confirm that this biotinylated compound induces the same morphological changes in KR158 astrocytoma and K16561 malignant peripheral nerve sheath tumour (MPNST) cells as schweinfurthin A (**13**).[123] Treatment of these cell lines with schweinfurthin A (**13**) causes a disassembly of the stress fiber network of the cells as a presumed result of SA acting as an on/off switch to Rho, a small GTPase that regulates the actin stress fiber network. Comparable morphological changes are observed upon treatment with biotinylated analogue **46**, indicating that it is probably acting at the same target as the natural schweinfurthins.

Once it was determined that the amide biotinylated analogue **46** demonstrates schweinfurthin–like activity in a relevant two–cell screen, and induces the same morphological changes on actin stress fiber as schweinfurthin A, it was then utilized in pull–down assays with SF–295 cell lysate. This data is discussed in detail elsewhere (C. Kuder, Unpublished data, University of Iowa), but several proteins were isolated as a result of these experiments. These proteins were identified by MS and include vimentin, a voltage dependent anion channel, keratin, and histone H2b. At this time, vimentin appears to be the most likely binding partner, but more work remains to be done in order to verify these findings.

In conclusion, the synthesis of biologically active biotinylated schweinfurthin analogues has been more challenging than anticipated. Multiple obstacles were encountered along the way, including the efficient alkylation of the D–ring substructure, the need for differential protection/deprotection sequences, and problems with the isolation and purification of the target compounds. Nevertheless, three biotinylated schweinfurthin analogues have been prepared and were tested by our collaborators against SF–295 and A549 cell lines to determine if they exhibit schweinfurthin–like activity. The MOM–protected analogues **164** and **166** exhibit decreased activity in the

SF–295 and A549 cell lines, while amido–biotinylated schweinfurthin **46** displays schweinfurthin–like activity in the SF–295 and A549 cell lines. Furthermore, the amide biotinylated analogue **46** has been shown to induce the same characteristic morphological changes in KR158 astrocytoma and K16561 MPNST cells as schweinfurthin A, indicating that it probably interacts with the same binding partner(s) as the natural schweinfurthins. Based on these results, biotinylated analogue **46** was used in pull–down experiments, and several proteins were isolated and identified. More work remains to be done to verify the identity of the protein(s) isolated in this way and to determine their importance. However, this work appears to confirm that the schweinfurthins target proteins as opposed to other potential biological targets. These efforts also have illuminated routes to synthesize more potent biotinylated analogues of the natural schweinfurthins if that should prove necessary.

CHAPTER 4
CHEMO– AND STEREOSELECTIVE SYNTHESIS OF *E*– AND *Z*–MOM–PROTECTED ENOL ETHERS

The usefulness of new methodology depends not only on the availability and cost of its starting materials, but also on its efficiency, generality, and the degree of complexity it achieves.[124] In our synthetic route to compounds such as tricycles **185** and **187** (Figure 62), we utilize economical and readily available starting materials: ethyl acetoacetate (**192**) is commercially available in kilogram quantities and readily undergoes alkylation to provide intermediates such as β–keto ester **183** in high yield. Furthermore, MOMCl is easily prepared in our labs on large scales from inexpensive starting materials.[125] At the outset, however, the efficient stereoselective synthesis of *Z*– and *E*–"MOM protected" enol ethers **184** and **186** proved problematic. Utilizing the conditions reported by Gibbs and coworkers in their stereoselective synthesis of enol triflates,[126] deprotonation of β–keto ester **183** by KHMDS in either THF or DMF at varying temperatures followed by treatment with MOMCl provided the desired MOM–enol ethers in poor to modest yields.

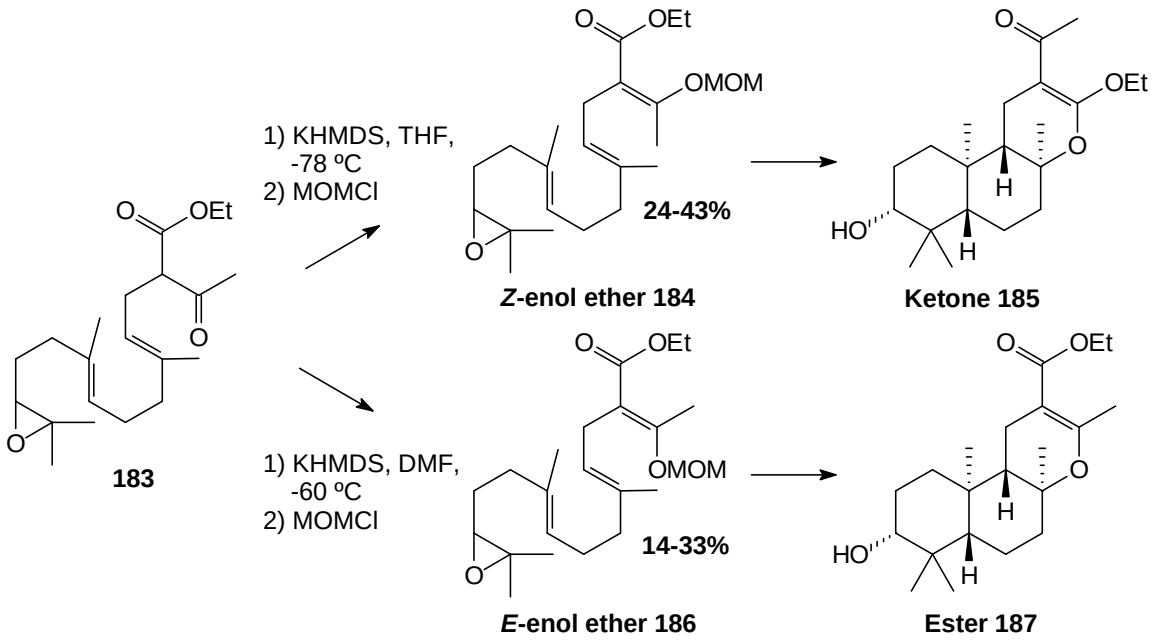


Figure 62. General route to tricycles **185** and **187**

In general, the two stereoisomers are readily separated by column chromatography, although their separation from the starting material is somewhat more difficult. The stereochemistry of the various products can be determined easily by examination of their ^{1}H NMR spectra. Benito and coworkers prepared methyl enol ethers **188** (*Z*) and **189** (*E*) from ethyl acetoacetate (Figure 63).[127] Following standard NOE experiments to determine the relative configurations of the enol ethers, they found they could then use the ^{1}H NMR chemical shifts of the vinylic methyl hydrogens as a simple indication of the stereochemistry. Due to the deshielding effect of the ethyl ester, the hydrogens of the *syn* methyl group appear somewhat further downfield than the hydrogens of the *anti* methyl group (2.3 versus 2.0 ppm, respectively). A similar trend is seen in the ^{1}H NMR shifts of the vinylic methylene hydrogens in *Z*– and *E*–vinyl triflates **190** and **191** (2.4 and 3.0 ppm, respectively).[128] This indicates that, at least in relatively simple substrates, the electronic nature of the new enol substituent has little effect on the trends observed for these key chemical shifts. In the case of *Z*– and *E*–MOM–protected

enol ethers, such as compounds **184** and **186** (Figure 62), the respective resonances appear at 1.9 and 2.3 ppm (cf. Appendix).

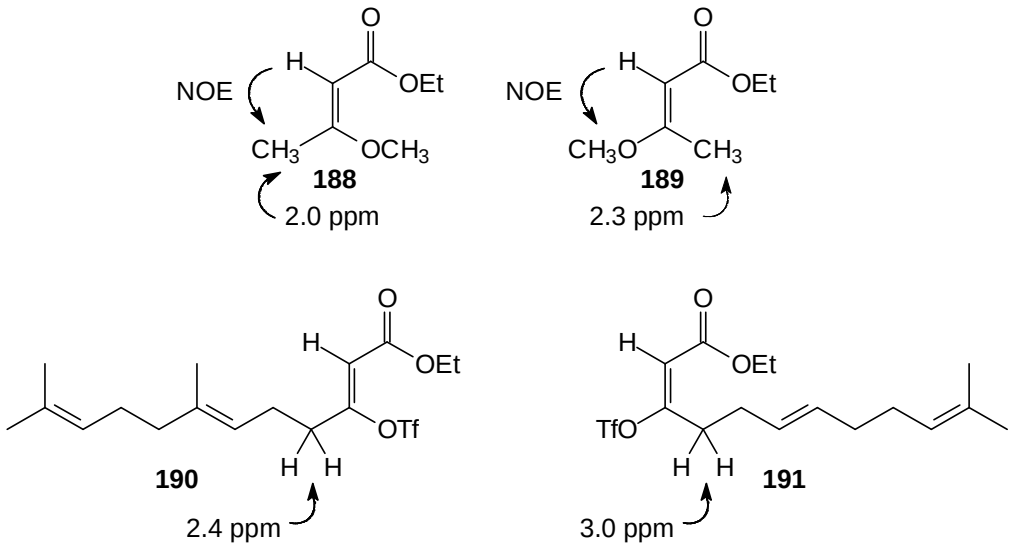
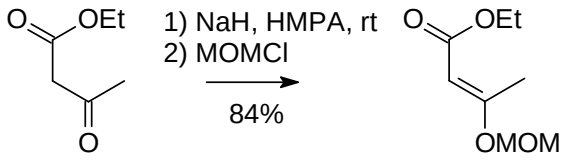


Figure 63. Assigning the stereochemistry of ethyl acetoacetate–derived enol ethers[127, 128]

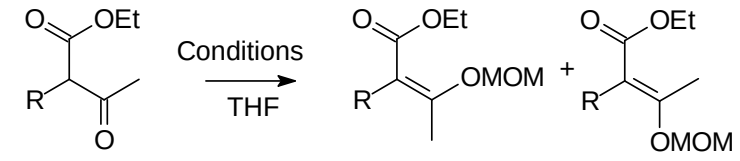
The only example of the alkylation of a β–keto ester with MOMCl was reported by Coates and coworkers in 1970.[129] Using the sodium enolate of ethyl acetoacetate in HMPA, they obtained MOM–enol ether **193** in good yield (Figure 64) and assigned its stereochemistry as *trans* based on comparison of its ^{1}H NMR spectrum to those of analogous cyclic substrates. While HMPA has been used widely as an additive in organolithiate applications, it is a known carcinogen and can complicate work–up procedures when used as the solvent.[130, 131] Clearly, a safe and efficient methodology for preparing these substrates is needed.



192 **193**

Figure 64. Synthesis of the *E*–MOM enol ether of ethyl acetoacetate[129]

Displayed in Table 3 are selected examples of various conditions explored in preliminary attempts to optimize the MOM–protection of variously substituted β–keto esters (Figure 65). In all cases, regardless of base, temperature, or additives, the desired products were isolated in low yields. At first, this was believed to be due to the presence of unreacted starting material as indicated by TLC analysis. However, increasing the equivalents of base (entries 2 and 3, 6 and 7) led to a reduction in yield of the desired product and apparently increased recovery of starting material. In the case of the β–keto ester **194**, this apparently conflicting result became clear when the actual product, which has an Rf identical to the starting material, was isolated and identified by NMR spectroscopy as the C–alkylated product **202** (Figure 66).



183, **194**-**195** **184, 196**-**197** **186, 198**-**199**

Figure 65. Preparation of various *Z*– and *E*–enol ethers

Entry	R	Base (eq)	Temp (°C)	Additive	*Z*[a]	*E*[a]
1	Epoxy geranyl (**194**)	LDA (1.3)	–78–rt	–	44 (**196**)	– (**198**)
2	"	LDA (1.3)	–78–rt	–	32	–
3	"	LDA (1.7)	–78–rt	–	29	–
4	"	Imidazole	rt	–	14	–
5	"	KO*t*Bu	–78–rt	–	–	19
6	Epoxy farnesyl (**183**)	LDA (1.3)	–78–rt	–	36 (**184**)	– (**186**)
7	"	LDA (1.7)	–78–rt	–	31	–
8[b]	"	K_2CO_3	rt	18–crown–6	–	–
9[c]	Farnesyl (**195**)[132]	KO*t*Bu	–78–rt	18–crown–6	31 (**197**)	– (**199**)
10[c]	"	LHMDS	–78–rt	–	43	–

a) Refers to isolated yields following purification by column chromatography, b) complex mixture of products by TLC analysis; c) performed by Jos S. Yu (Unpublished data, University of Iowa)

Table 3. Representative examples of synthesis of various enol ethers

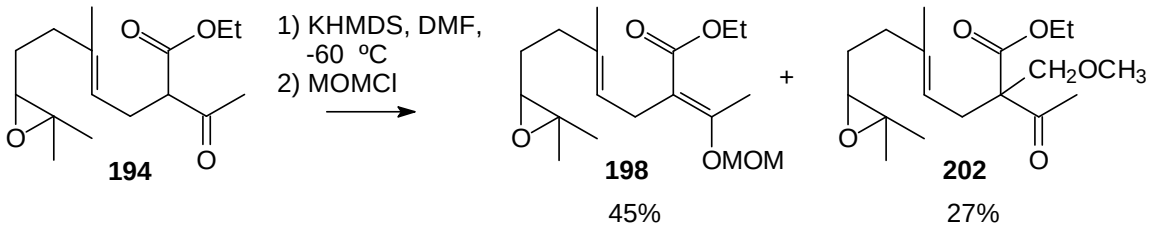


Figure 66. Formation of the C–alkylated product **202**

This finding, combined with the poor yields obtained in the preliminary alkylations, prompted a thorough examination of the literature pertaining to the chemo– and stereoselective alkylation of β–keto esters. Following is a brief discussion of the issues involved in this transformation.

The anion of a β–dicarbonyl compound such as ethyl acetoacetate (**192**) is ambident: it possesses two primary nucleophilic sites, the α–carbon and the ketonic oxygen (Figure 67).[133] Disregarding issues of stereochemistry,[133] there are at least four possible products resulting from the alkylation of ethyl acetoacetate: "O," "C," "CC," and "CO" products.[135] A variety of factors govern whether C– or O–alkylation predominates; these factors have been reviewed elsewhere[136] and only will be summarized here. The most important factors include solvent, counterion, additives or catalysts, structure of the alkylating agent, and concentration of the substrate.

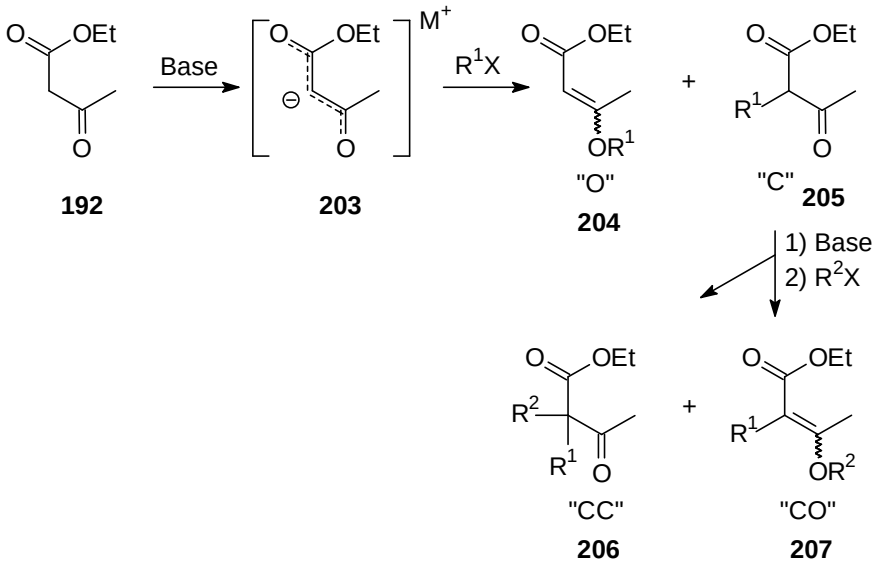


Figure 67. Oxygen versus carbon as the site of alkylation in ethyl acetoacetate (**192**)[135]

The most important factor governing the site of alkylation in β–keto esters is the choice of solvent.[133, 135-138] As a general rule, alkylation occurs predominantly at the more electronegative oxygen atom when it is as free as possible in solution.[133, 139] Dipolar aprotic solvents such as DMF, DMSO, acetonitrile, and HMPA possess highly polarized oxygen atoms which can strongly solvate metal cations, thereby causing increased enolate dissociation from ambient ion pairs and clusters and producing the highest O/C ratios.[140] Polar aprotic solvents such as THF do not possess polarized oxygen atoms capable of dissociating aggregates, and therefore this solvent promotes C–alkylation. Polar protic solvents such as alcohols and water, which can solvate the oxygen anion through hydrogen bonding, make the anion less reactive, favor C–alkylation, and generally are not as useful.[139] An example of this principle is the alkylation of the potassium enolate of ethyl acetoacetate in varying solvents (Figure 68, Table 4): reaction in HMPA affords mostly O–alkylated product, while alkylation in *t*–butanol or THF provides almost exclusively the C–alkylated product. A small amount of dialkylated

product was obtained in all cases, but no "CO" product (i.e. **207**) was detected in this study.[141]

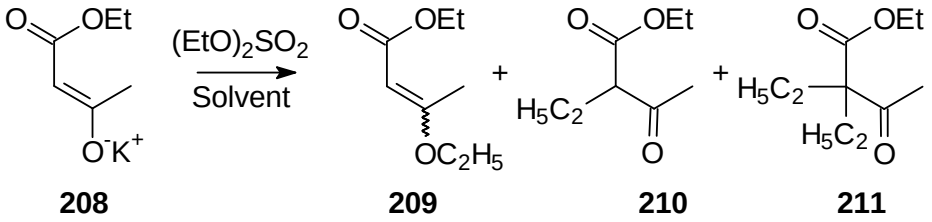


Figure 68. Preparation of various O– and C–alkylated products[141]

Entry	Solvent	% O	% C	% CC
1	HMPA	83	15	2
2	*t*–butanol	0	94	6
3	THF	0	94	6

Table 4. Solvent effect on O/C alkylation ratios

Choice of the metal counterion is the second most important factor in determining the ratio of O– versus C–alkylation.[136] The larger the cation, the softer it is, and the less strong the association between it and the ambident anion, making the more electronegative oxygen atom more likely to attack. Oxygen–alkylation is favored in the series $NR_4^+ > K^+ > Cs^+ > Na^+ > Li^+$.[137, 142] An early study on this principle is detailed in Figure 69, Table 5.[142]

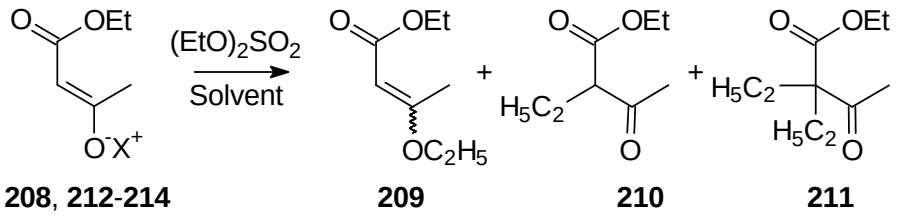


Figure 69. Reaction of various counterions with diethyl sulfate[141]

Trial	Counterion	Additive	% O	% C	% CC
1	Li	–	62	31	7
2	Na	–	69	24	7
3	Cs	–	81	19	<1
4	K	–	83	15	2
5	K	Bu_4NClO_4	91	9	<1

Table 5. Effect of counterion on O/C alkylation ratios

Entry 5 in the above table illustrates another important factor in these reactions: the effect of additives or catalysts. In the case of the potassium enolate of ethyl acetoacetate, the addition of one equivalent of Bu_4NClO_4 provides the best O/C ratio. In accordance with the principle that the more dissociated the anion, the more O–alkylation predominates, the use of chelating agents or catalysts can promote O–alkylation by lowering the concentration of aggregates.[136] Additives such as HMPA, TMEDA, and crown ethers have been used to promote O–alkylation in ketone enolates through competition with the anion for chelation of the metal counterion.[143]

Another important factor in determining O/C alkylation ratios is the structure of the alkylating agent.[136] A number of studies[135, 137, 138, 140] have shown that O– versus C–alkylation increases in the following series with respect to the leaving group: BF_4^-, ClO_4^-, $TosO^- > Cl^- > Br^- > I^-$. This trend can be explained using the theory of hard and soft ligands: the harder oxygen atom preferentially reacts with harder electrophiles, and conversely alkylation of the relatively soft carbon is favoured in reactions with softer electrophiles.[144] A representative study of this trend was reported by Kurts and coworkers (Figure 70, Table 6).[145]

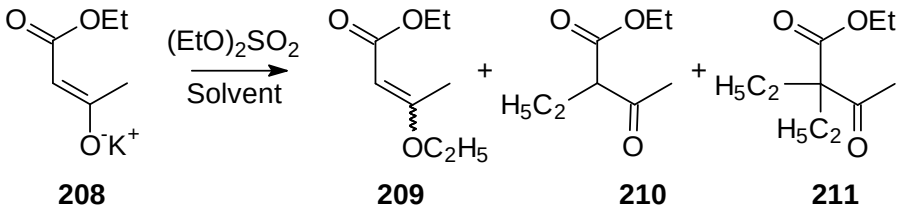


Figure 70. Alkylation of enolate **208**[145]

Entry	X	% O	% C	% CC
1	OTs	88	11	1
2	Cl	60	32	8
3	Br	39	38	23
4	I	13	71	16

Table 6. Effect of leaving group on O/C alkylation ratios

The steric factors of the alkylating agent also are important. Steric crowding at the 2–position of acetoacetate esters makes nucleophilic attack from this site more

difficult than at the less hindered ketonic oxygen. Therefore, in general, the more sterically hindered the alkylating agent, or the lower its S_N2 reactivity, the less the amount of C–alkylation observed. There have been multiple reports on this reactivity in the literature.[139, 140, 146] A representative study by Morris and coworkers is detailed below (Figure 71, Table 7).[139]

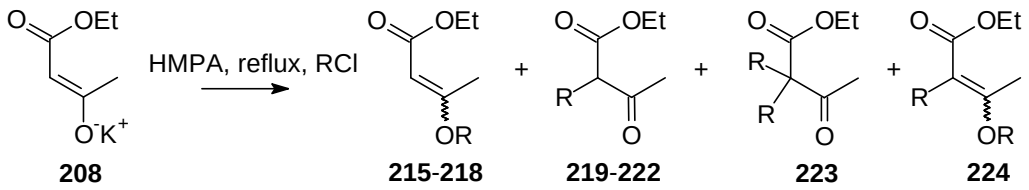


Figure 71. Alkylation of enolate **208** with various alkylating agents[139]

Entry	Chloride	% O	% C	% CC	% CO
1	*n*–propyl	61	23	4	4
2	*i*–propyl	81	19	–	–
3	s–butyl	86	14	–	–
4	*t*–butyl	99	1	–	–

Table 7. Effect of S_N2 reactivity of alkylating agent on O/C ratio

Finally, concentration of the substrate can affect O/C alkylation ratios. Because a more dilute solution equates to a larger number of free anions, higher dilution should lead to increased O–alkylation. Reutov and coworkers published their studies on the effect of concentration on the reaction of the potassium enolate of ethyl acetoacetate with ethyl *p*–

tosylate (Figure 72, Table 8).[145] At concentrations of 0.1 M or lower, oxygen–alkylation predominates; at higher concentrations, C–alkylation becomes more prevalent.

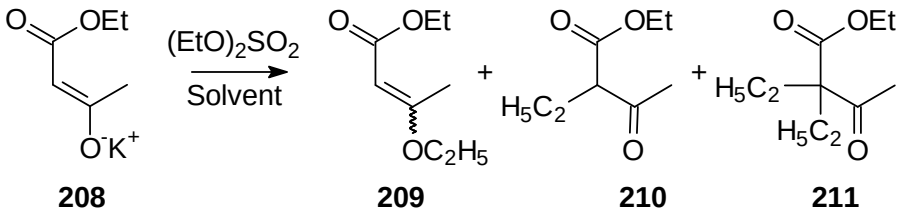


Figure 72. Alkylation of enolate **208** in various solvents[145]

Entry	Concentration (M)	% O	% C	% CC	% CO
1	0.01	89	11	1	<1
2	0.05	87	12	1	<1
3	0.1	84	15	1	<1
4	0.3	75	23	2	<1
5	3	50	47	3	<1
6	5	41	56	3	<1
7	7.5	30	60	10	<1

Table 8. Effect of substrate concentration on O/C alkylation ratios

In summary, the chemoselectivity of the alkylation of β–keto esters can be influenced by a variety of factors. Numerous studies have shown that the highest O/C alkylation ratios are achieved when the reactions are carried out using the following conditions: a dipolar aprotic solvent, a large metal counter ion, additives such as crown

ethers or ammonium salts, a hard, sterically hindered electrophile, and a relatively high dilution.

In addition to the issue of oxygen versus carbon alkylation in β–keto esters, the stereochemical outcome of these alkylations also must be considered. In the reaction, the structure of the intermediate resonance–stabilized enolate determines the stereochemistry of the final product.[145] A "U"–shaped *Z, Z*–configuration (**227**) is more common in protic solvents or ethers and results from either hydrogen–bond stabilization of the enolate or coordination of the anion to the cationic metal center. Subsequent reaction with an electrophile provides the corresponding *Z*–enol ether (**230**, Figure 73). In contrast, the more stable "W"–shaped *E¸E*–configuration **228** occurs in dipolar aprotic solvents and results from association of the metal center to solvent instead of the enolate. Treatment of this anion with an electrophile affords the *E*–enol ether (**231**).

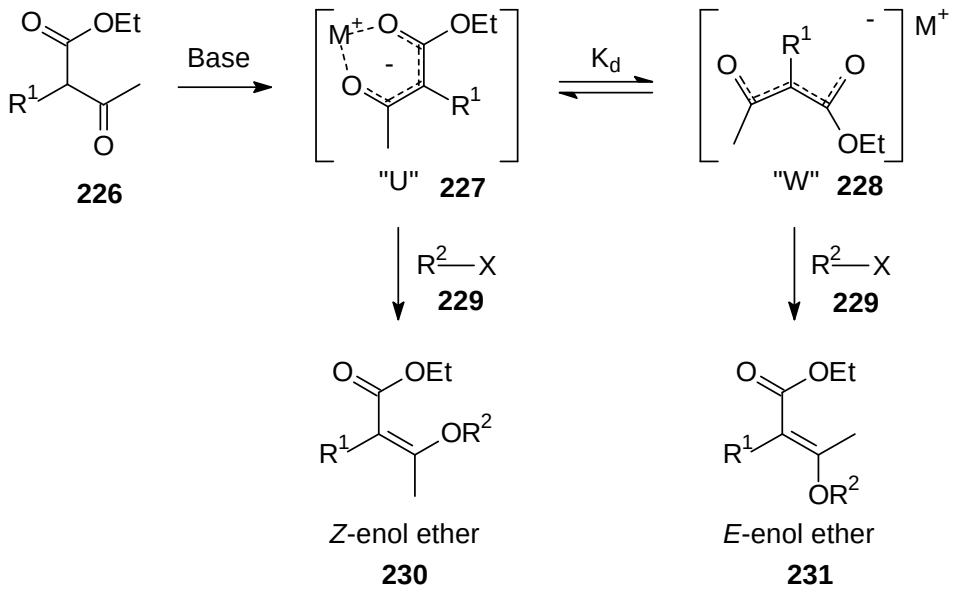


Figure 73. Ground state configurations leading to isomeric enol ethers[147]

Perhaps not surprisingly, there have been only sporadic reports on the stereoselective synthesis of acetoacetate–derived enol ethers (Figure 74). Table 9 provides a number of representative examples of the types of solvents and bases used in the alkylation of acyclic β–keto esters over the past several decades. In almost all cases, base–mediated conditions are used due to the acid–sensitive functionalities sometimes present in the starting materials.[148] Entry 1 is an example of an acid–catalyzed reaction of ethyl acetoacetate with isopropenyl acetate to provide the *Z*–enol acetate with high selectivity.[149] Conversely, use of the weak base TEA in HMPA gives almost exclusively the *E*–enol ether (entry 2).[149] Triethylamine in HMPA also has been used in the *E*–selective synthesis of enol phosphates (entry 3).[150]

In order to explore their methodology involving cross–coupling reactions of vinyl triflates, Meyer and coworkers required a *Z*–selective synthesis of enol triflates derived from both cyclic and acyclic β–keto esters.[151] The desired cyclic enol ethers were readily obtained by the use of DIPEA in CH_2Cl_2, but these conditions produced poor *Z*:*E* selectivity in acyclic β–keto esters (entry 4). Instead, employing KHMDS in THF at low temperature provided the desired *E*–enol triflate in good yield (entry 5).

The strong base NaH has been used to obtain both *E*– and *Z*–enol ethers, depending on the solvent employed. Keenan and coworkers reported the efficient conversion of β–keto esters to the corresponding *E*–enol triflates using NaH in DMF (entry 6),[152] Alternatively, Weiler and Sum found that deprotonation of methyl acetoacetate with NaH in Et_2O followed by reaction with diethyl chlorophosphate provided the *Z*–enol phosphate as a single isomer (as determined by NMR) in nearly quantitative yield (entry 7).[148]

Potassium enolates of unsubstituted β–keto esters in polar aprotic solvents (i.e. diethyl ether, THF, dimethoxy methane) have been shown to selectively provide the *Z*–enol ether in numerous instances (entries 8–10), while the use of potassium enolates in dipolar aprotic solvents (e.g. DMF) is highly *E*–selective (entry 11). In more highly

substituted cases, however, stereoselectivity is not so straightforward (entries 12–13).[153] There are only a few reports of the stereoselective preparation of enol ethers derived from 2–substituted β–keto esters,[152-157] indicating that stereoselective alkylation of more highly substituted substrates is inherently more difficult.

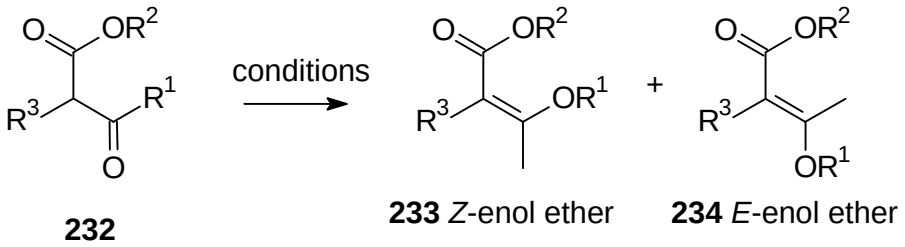


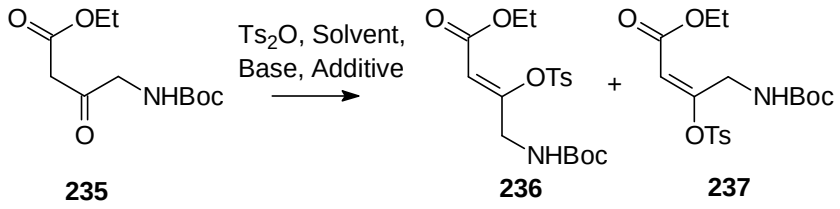
Figure 74. Literature examples of stereoselective enolate alkylations

Entry	R^1	R^2	R^3	Base	Solvent	Electrophile	*Z*:*E*	Yield (%)[a]
1[149, 158]	Me	Et	H	–	–	Isopropenyl acetate	18:1	79
2[149]	Me	Et	H	TEA	HMPA	AcCl	1:15	56
3[150]	Me	Me	H	TEA	HMPA	$ClPO(OEt)_2$	0:100	–[b]
4[154]	Me	Et	H	DIPEA	DCM	Tf_2O	1:2.2	–[c]
5[154]	Me	Et	H	KHMDS	THF	Tf_2NPh	100:0	76
6[152]	Bu	Et	H	NaH	DMF	Tf_2NPh	0:100	94
7[148]	Me	Me	H	NaH	Et_2O	$ClPO(OEt)_2$	100:0	97
8[159]	Ger	Et	H	KHMDS	THF	$ArN(SO_2CH_3)_2$	95:5	66
9[160]	Farn	Et	H	KH	THF	2–pyridyl–NTf_2	100:0	58
10[159]	Ger	Et	H	KHMDS	Et_2O	$ArN(SO_2CH_3)_2$	100:0	–[d]
11[159]	Ger	Et	H	KHMDS	DMF	$ArN(SO_2CH_3)_2$	0:100	70
12[161]	Me	Et	Me	KHMDS	THF	Tf_2NPh	~1:1	33/37
13[154]	Me	Et	Bn	KHMDS	THF	Tf_2NPh	1:3	12[d]

a) Refers to yield of major product, except where noted; b) yield after methylation with $LiMe_2Cu$ (40–50%/2 steps); c) not reported; d) reported as "modest"

Table 9. Selected examples of stereoselective synthesis of *E*– and *Z*–enol ethers

Very few systematic studies on the stereoselective synthesis of enol ethers derived from β–keto esters have been published. In 2005, Davies and coworkers reported their work on the stereoselective synthesis of enol tosylates derived from γ–amino β–keto esters (Figure 75, Table 10).[162] Not surprisingly, lithium enolates in the non–coordinating solvent THF favor the formation of the *Z*–isomer (entries 1 and 2). Use of a mixed solvent system (THF and 30 mol% DMF) decreases the *Z* selectivity, as expected (entry 3). Decreased *Z* selectivity also is observed with the use of LDA or NaHMDS (entries 4 and 5). Use of potassium enolates in THF actually promotes *E*–selectivity (entry 6) as opposed to the results from simpler substrates (Table 9). The addition of lithium bromide to solutions of the potassium enolate reverses the selectivity and promotes formation of the *Z*–isomer **236**, presumably due to coordination of the resonance–stabilized enolate to the lithium cation (entry 7). In addition, the group reports a remarkably simple and effective method for selectively preparing the *E*–tosylate **237** using TEA in CH_2Cl_2 (entry 8).



235 **236** **237**

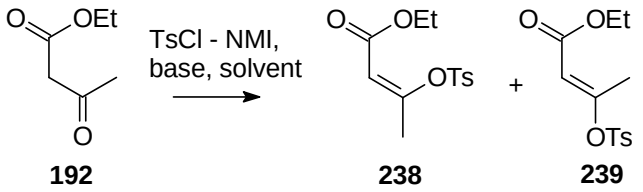
Figure 75. Alkylation of β–keto ester **235**[162]

Entry	Base	Solvent	Additive	*Z*:*E*	% yield[a]
1	LHMDS	THF	–	24:1	63
2	*n*BuLi	THF	–	30:1	65
3	LHMDS	THF/30 mol% DMF	–	7:1	23
4	LDA	THF	–	12:1	93
5	NaHMDS	THF	–	2:1	52
6	KHMDS	THF	–	1:7	72
7	KHMDS	THF	LiBr (1 eq)	16:1	46
8	TEA	DCM	–	1:25	83

a) Refers to assay yield (HPLC analysis of the crude reaction mixture in reference to pure standard)

Table 10. Synthesis of enol tosylates derived from γ–amino β–keto esters

Tanabe and coworkers published a highly efficient and practical stereoselective synthesis of ethyl acetoacetate–derived enol tosylates (Figure 76).[163] The group discovered that the combination of *N*–methylimidazole (NMI) and TsCl forms an extremely reactive sulfonylammonium intermediate capable of tosylating sterically congested alcohols. They then went on to apply this finding to the preparation of enol tosylates derived from ethyl acetoacetate, and representative examples of their work are displayed in Table 11.



192 **238** **239**

Figure 76. Stereoselective tosylation of ethyl acetoacetate (**192**)[163]

Entry	Base	Temp (°C)	Solvent	Z:E	Yield
1	TEA	Rt	C_6H_5Cl	2:98	92
2[a]	"	Rt	"	–	Trace
3	*n*BuLi	–45	THF	97:3	80
4	LDA	–45	"	92:8	70
5	LHMDS	"	"	90:10	39
6	KHMDS	"	"	65:35	23
7	NaHMDS	"	"	61:39	69
8	*t*BuOLi	0–rt	C_6H_5Cl	93:7	68
9	Li_2CO_3	"	"	–	NR
10	LiCl	"	"	–	NR
11	LiOH	"	"	96:4	86

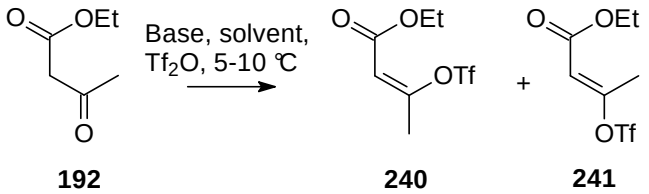
a) in the absence of NMI

Table 11. Stereoselective synthesis of enol tosylates using activated TsCl

The use of the weak base TEA in C_6H_5Cl resulted in excellent *E*–selectivity and yield (entry 1). In the absence of NMI, reaction of ethyl acetoacetate with TEA and Ts_2O gave only recovered starting material (entry 2). As expected, lithium enolates were highly *Z*–selective (entries 3–5 and 8), while use of potassium or sodium enolates decreased *Z* selectivity (entries 6 and 7). The use of Li_2CO_3 and LiCl gave no reaction

(entries 9 and 10), but LiOH effected efficient conversion to the *Z*–enol ether (entry 11). A variety of β–keto esters underwent tosylation with very high yields and stereoselectivity, including sterically hindered α–methylated ethyl acetoacetate.

Frantz and coworkers recently reported their work on the stereoselective synthesis of acetoacetate–derived enol triflates using Schotten–Baumann–type conditions (Figure 77).[124, 164] Different stereoselectivities were achieved by varying the counter ion of aqueous bases such as LiOH or NaOH (Table 12). The best *Z*–selectivities were obtained using sat. aqueous LiOH in either toluene or hexanes, and the best *E*– selectivities were obtained using tetra–alkylammonium hydroxides in aqueous solution with toluene or hexanes. This methodology also was effective in the triflation of sterically hindered 2–substituted β–keto esters. In general, they obtained the *Z*–enol ethers in much higher selectivities than the *E*–enol ethers.



192 **240** **241**

Figure 77. Stereoselective preparation of *Z*– and *E*–enol triflates[164]

Entry	Aqueous base	Solvent	Z:E	Yield (%)
1	2 N NaOH	THF	N/A	<5
2	“	MTBE	N/A	<5
3	“	Toluene	1:2.6	35
4	2 N KOH	Toluene	1:9.5	63
5	2 N CsOH	Toluene	1:6.1	76
6	2 N LiOH	Toluene	34:1	81
7	Sat. LiOH	Toluene	>150:1	91
8	“	Hexanes	>150:1	94
9	$(Bu)_4NOH$	Toluene	1:39	30
10	$(Me)_3BnNOH$	Toluene	1:20	61
11	$(Me)_4NOH$	Hexanes	1:23	79
12	$(Me)_4NOH$	Toluene	1:18	82
13	“	Hexanes	1:24	84

Table 12. Preparation of enol triflates using Schotten–Baumann–type conditions

Pale and coworkers recently reported their work on the stereoselective synthesis of *Z*–enol triflates derived from 1,3–dicarbonyl compounds (Figure 78).[165] Relying on the

hypothesis that pre–coordination of the intermediate anion using lithium triflate should polarize the carbonyl bond and thus lower the pKa of the α–hydrogen(s), they discovered that weak amine bases could be used to provide *Z*–enol triflates **245**–**247** in good to excellent yields and often >99:1 selectivity (Table 13). They also found the amount of time allowed for anion formation and equilibration was particularly important. In the absence of complete equilibration, greatly decreased selectivity was observed.

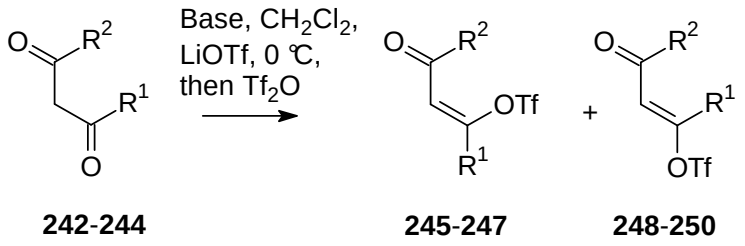


Figure 78. Stereoselective triflations to provide compounds **245**–**250**[166]

Entry	R^1	R^2	Base	Z:E	Yield[a]
1	Me	Me	TEA	>99:1	56
2	Me	Me	DIPEA	>99:1	47
3	Me	OEt	TEA	>99:1	74
4	Me	OEt	DIPEA	>99:1	88
5	Prenyl	OEt	TEA	>99:1	60
6	Prenyl	OEt	DIPEA	>99:1	89

a) isolated yields

Table 13. Stereoselective synthesis of enol triflates using pre–coordination conditions

As mentioned above, the attempted synthesis of the *E*– and *Z*–MOM protected enol ethers of our 2–substituted β–keto esters resulted in poor selectivity and significant C–alkylation. In an attempt to optimize this reaction, a simplified model substrate was prepared (Figure 79). Treatment of ethyl acetoacetate (**192**) with NaH and prenyl bromide (**251**) provided known compound **252**[167] in modest yield.

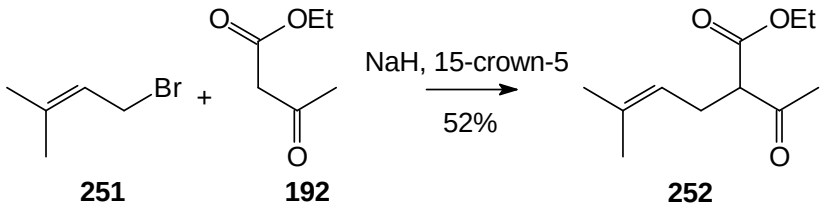
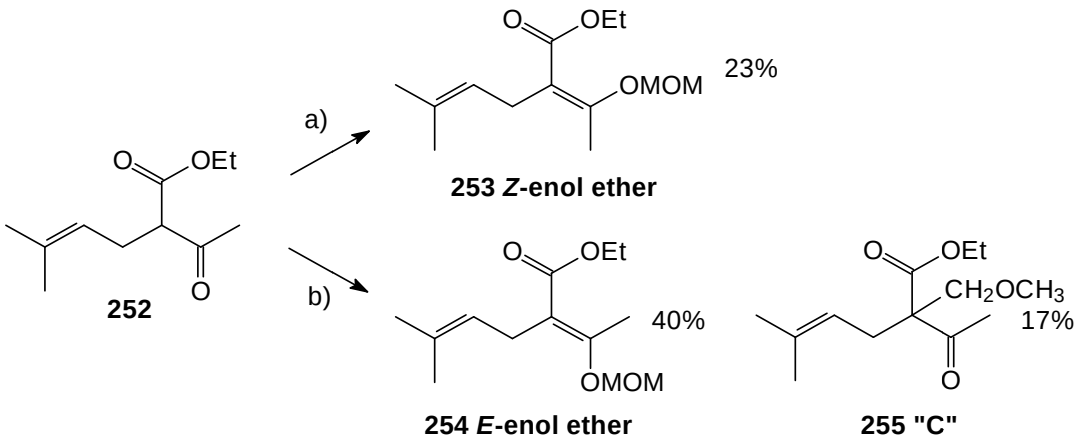


Figure 79. Preparation of prenylated ethyl acetoacetate (**252**)

The *Z*– and *E*–MOM enol ethers of prenylated acetoacetate **252** (**253** and **254**, respectively), as well as the C–alkylated product (**255**), were prepared, isolated, and characterized (Figure 80). This model system is useful because the simple ^{1}H NMR spectra of the products are readily interpreted. Determination of the stereochemistry of the enol ethers was accomplished by comparison of the chemical shifts of the vinylic methyl group with previously reported values in similar substrates as described above. For optimization of the MOM–alkylation, reactions could be carried out and the crude reaction mixtures analyzed directly by ^{1}H NMR to determine the relative abundance of products based on integration of the easily identifiable γ–methyl hydrogen resonances. A representative ^{1}H NMR spectrum featuring the relevant region is shown in Figure 81. In this example, integration of these ^{1}H resonances indicated a product ratio of approximately 59:1:38:2 (*E*:C:SM:*Z*).



Conditions: a) 1) LDA, THF, -78 ℃, 2) MOMCl, -78 ℃-rt; b) 1) KHMDS, DM F, -60 ℃, 2) MOMCl, -60 ℃-rt

Figure 80. Preparation of prenylated compounds **253**–**255**

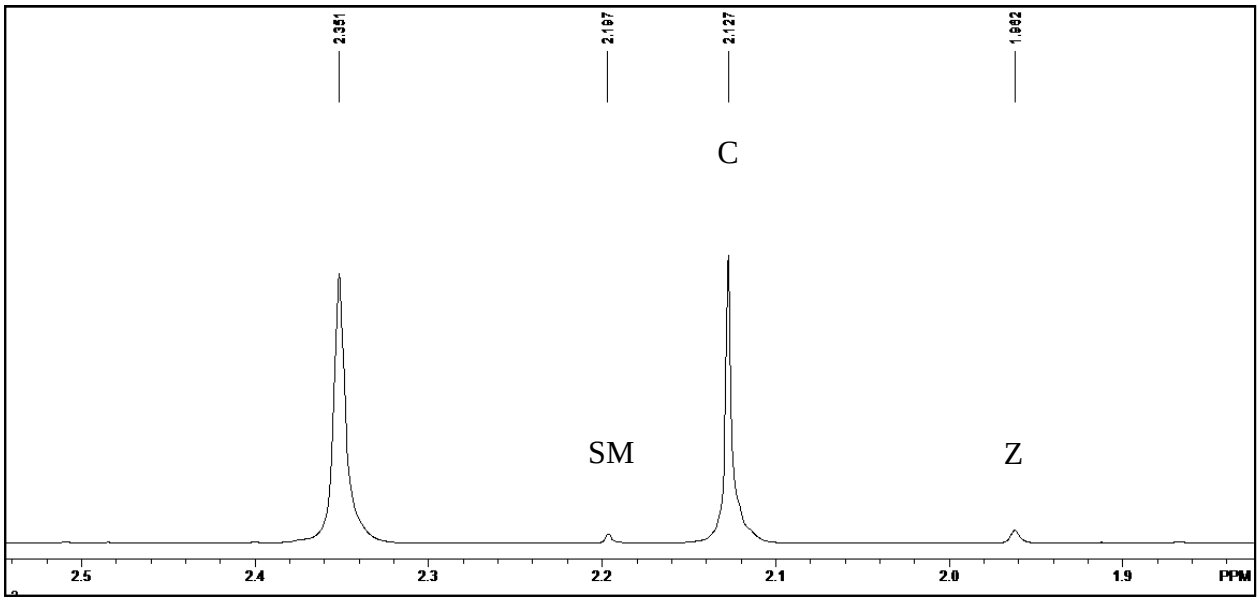


Figure 81. Representative example of ^{1}H NMR of crude reaction mixture

A number of trials using a variety of bases, solvents, temperatures, additives, and concentrations were conducted on compound **252** (Figure 82, Table 14). The use of LDA

in THF at low temperature proved to be somewhat *Z*–selective, especially with the addition of 1 equivalent of a 12–crown–4 (entries 1 and 2), but not to the extent of previous instances, where *E*/*Z* selectivities as high as 92:8 were reported.[162, 163] TLC analysis during trials 1 and 2 indicated that alkylation does not occur readily even at –40 °C. Given this information, an experiment was conducted in which the reaction temperature was maintained at 0 °C throughout (entry 3); however, this resulted in generation of a complex mixture whose ^{1}H NMR spectrum was difficult to interpret.

Given the success of potassium enolates in numerous instances,[152, 154, 159, 162] KHMDS was utilized in multiple trials. High *Z*/*E* selectivity was observed in Et_2O, but a significant amount of C–alkylated product **255** also was observed (entry 4). When a parallel reaction was conducted in THF, more C–alkylation product than *Z*–enol ether was observed, along with a small amount of *E*–enol ether **254** (entry 5). Similar results were observed when solid KHMDS was used, although the amount of C–alkylated product was decreased slightly (entry 6).

Reactions using KHMDS in DMF were highly *E*–selective, but also resulted in significant formation of the C–alkylated product (entries 7 and 8). Use of either solid KHMDS or KHMDS as a solution in toluene showed little to no impact on the *Z*/*E* and O/C ratios (entries 7 and 8). Use of additives (TMEDA, HMPA, 18–crown–6, and DMPU) had little effect (entries 9–12), although a significant amount of starting material was recovered in entry 9, indicating that the TMEDA used may not have been anhydrous. A decrease in concentration similarly had little effect (entries 13 and 14 versus entries 7 and 8). Differences in temperature were somewhat influential (entries 15 and 17 and 19 versus entry 8); the highest O/C ratios were observed at room temperature. Concentration and additives also had little effect at higher reaction temperatures (entries 20–21).

Based on the successes of previous authors as discussed above, multiple other bases were employed to carry out this reaction. The use of NaH in DMF (entry 23)

resulted in decreased selectivity. The use of DIPEA in CH_2Cl_2 (entry 24) afforded only starting material. Addition of LiCl to the reaction (entry 25) actually provided useful amounts of the desired products, although with little selectivity. Bases such as *t*BuOK and LiOH afforded either recovered starting material (entries 26–27) or indecipherable product mixtures (entry 28), presumably due to the insolubility of these bases in the respective solvents. Attempted *in situ* generation of MOMI via reaction of MOMCl with NaI and reaction with β–keto ester **252** provided, unfortunately, only starting material.

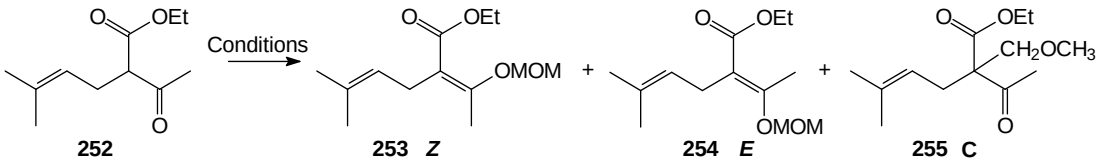


Figure 82. Synthesis of model compounds **253**–**255**

Trial	Base	Solvent	Temp (°C)	Additive	Conc (M)	Z	E	C	SM
1	LDA	THF	–78–rt	–	0.2	61	–	12	12
2	LDA	THF	–78–rt	12–crown–4	0.2	80	–	10	10
3	LDA	THF	0	–	0.2	–	–	–	–
4	KHMDS(t)	Et_2O	–78	–	0.2	49	–	39	4
5	KHMDS(t)	THF	–78	–	0.2	39	6	51	3
6	KHMDS(s)	THF	–78	–	0.2	47	9	37	–
7	KHMDS(s)	DMF	–60	–	0.2	3	48	30	1
8	KHMDS(t)	DMF	–60	–	0.2	3	51	32	5
9	KHMDS(t)	DMF	–60	TMEDA	0.2	3	44	27	14
10	KHMDS(t)	DMF	–60	HMPA	0.2	9	55	34	2
11	KHMDS(t)	DMF	–60	18–crown–6	0.2	2	51	38	4
12	KHMDS(t)	DMF	–60	DMPU	0.2	–	58	35	4
13	KHMDS(s)	DMF	–60	–	0.1	2	48	28	1
14	KHMDS(t)	DMF	–60	–	0.1	3	52	34	1
15	KHMDS(t)	DMF	–78–rt	–	0.2	2	52	34	1
16	KHMDS(s)	DMF	–78–rt	18–crown–6	0.2	2	52	39	1
17	KHMDS(t)	DMF	0	–	0.2	5	55	26	3
18	KHMDS(t)	DMF	rt	–	0.2	2	42	12	1
19	KHMDS(t)	DMF	rt–50	–	0.2	2	61	19	2
20	KHMDS(t)	DMF	rt	–	0.01	–	22	11	33
21	KHMDS(t)	DMF	rt	Bu_4NBr	0.2	1	51	25	19
22	KHMDS(t)	Toluene	rt	–	0.2	11	56	33	–
23	NaH	DMF	rt	–	0.2	7	49	28	7
24	DIPEA	DCM	rt	–	0.2	–	–	–	100
25	DIPEA	DCM	rt	LiCl	0.2	29	43	21	7
26	tBuOK	PhCl	0	–	0.2	–	–	–	100
27	LiOH	Toluene	0	–	0.2	–	–	–	100
28	LiOH	THF	0–rt	–	0.2	–	–	–	–
29	DIPEA	DMF	0–rt	NaI	0.2	–	–	–	100

Table 14. Stereoselective synthesis of *E*– and *Z*–enol ethers in model system **252**

In conclusion, we have encountered difficulties in the efficient chemo– and stereoselective synthesis of MOM–protected enol ethers *en route* to tricycles such as **185** and **187**. In an effort to overcome these obstacles, an extensive review of the pertinent literature was undertaken, and a number of factors were found to influence these alkylations. With this information in hand, a variety of conditions were employed in an attempt to increase the yield of the desired enol ethers in these alkylation reactions. These efforts have met with some success. In the case of the *Z*–enol ether, the best results were obtained with a combination of LDA at –78 °C in the presence of crown ether. In contrast, the best selectivity for the *E*–enol ether was obtained using KHMDS in DMF at room temperature. While not yet completely optimized, these reactions now provide the desired enol ethers in yields that enable studies of the cascade cyclization in some detail.

CHAPTER 5
CASCADE CYCLIZATIONS OF "MOM–PROTECTED" ENOL ETHERS AND RELATED DERIVATIVES

Previous efforts to prepare complex multicyclic structures such as compound **187** have proceeded in low yield and/or utilized stoichiometric quantities of mercury in the key cyclization step.[85, 168] For example, in the total synthesis of arisugacin F, the mercury–mediated cascade cyclization of β–keto ester **195** provided the organomercury intermediate **257** in only modest yield (Figure 83).[168] Oxidation of the organomercury compound and subsequent reduction provided the desired alcohol, but also in low yield. Although the undesired diastereomer could be subjected to another oxidation/reduction sequence to increase the yield of compound **187**, it is clear that this route could be greatly improved. The impact of several low–yielding steps in a succession is profound, and the use of organomercury intermediates raises concerns for any subsequent bioassays. The limitations of this published methodology have prompted our investigation into a more efficient way to construct carbon skeletons of this type.

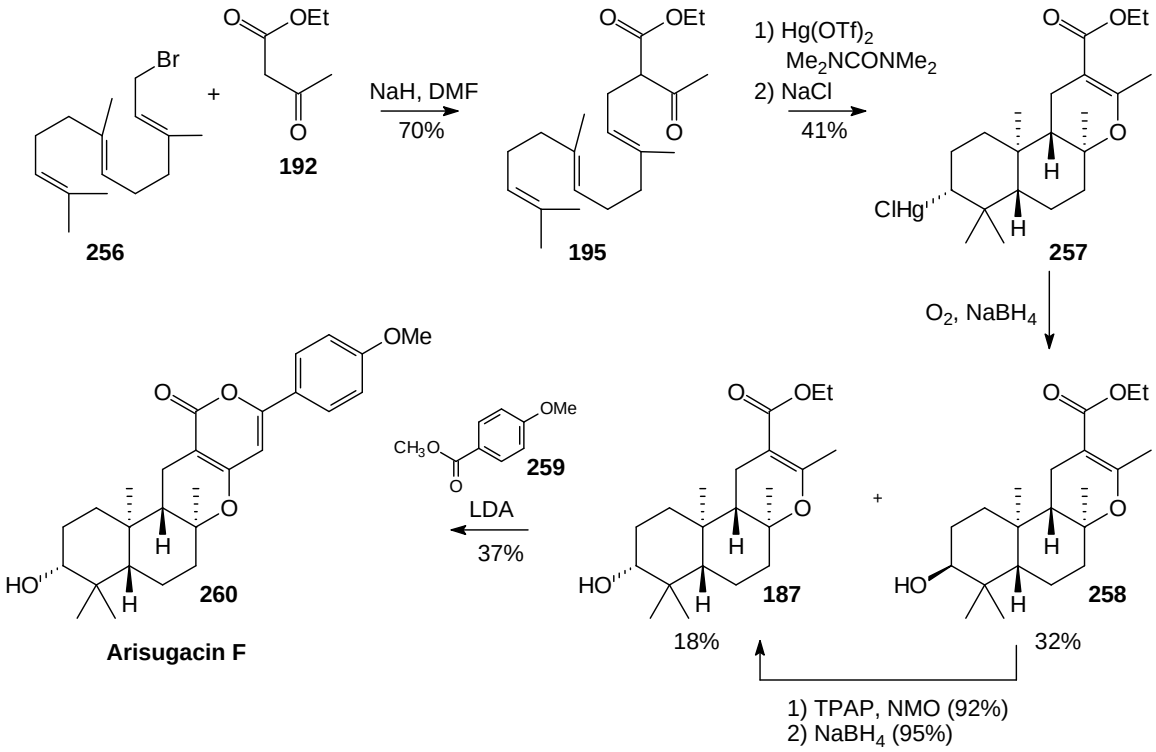


Figure 83. Total synthesis of arisugacin F[168]

Based on our previous experience using MOM–protected phenols as terminating moieties in Lewis acid–mediated cascade cyclizations,[81, 82, 84] we questioned whether an epoxide–initiated cascade cyclization utilizing a "MOM–protected" enol ether as the terminating moiety would exploit both the reactivity and rigidity of an enol ether and thus proceed more efficiently. While it is probable that there is a small amount of enol form present in the cyclization of a β–keto ester such as **195**, a MOM–protected enol ensures stoichiometric quantities of the more reactive enol ether form if the MOM derivatives of enols and phenols display parallel reactivity.

Due to the complexity of the C–15 farnesyl skeleton, it was decided to explore the cyclizations of MOM–protected enol ethers using a simplified C–10 geranyl model system first (**194**, Figure 84). Theoretically, cyclization of the simpler geranyl chain

should produce a relatively small number of readily identifiable products. The experience gained with a geranyl–length system should make the isolation and structure determination of the more complicated farnesyl–derived structures more facile.

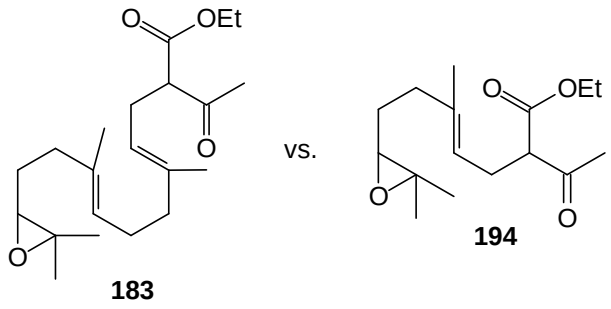


Figure 84. Farnesyl versus geranyl–length substrates

The synthesis of a MOM–protected enol ether introduces the concern of an olefin with its attendant stereochemistry. Presumably, the cascade cyclization of the *Z*– and *E*–stereoisomers could provide different products. Two possible conformers of the *Z*–enol ether **196** are shown in Figure 85. The first conformer **262** not only possesses unfavorable steric interactions between the two vinylic methyl groups, but also places the MOM–protected enol far from the neighboring tertiary carbocation, thus discouraging formation of the ester **263**. The second conformer **264** places the ester carbonyl in close proximity to the reactive carbocation; attack of the carbonyl followed by allylic transposition and loss of MOM^+ theoretically should lead to the ketone **265**.

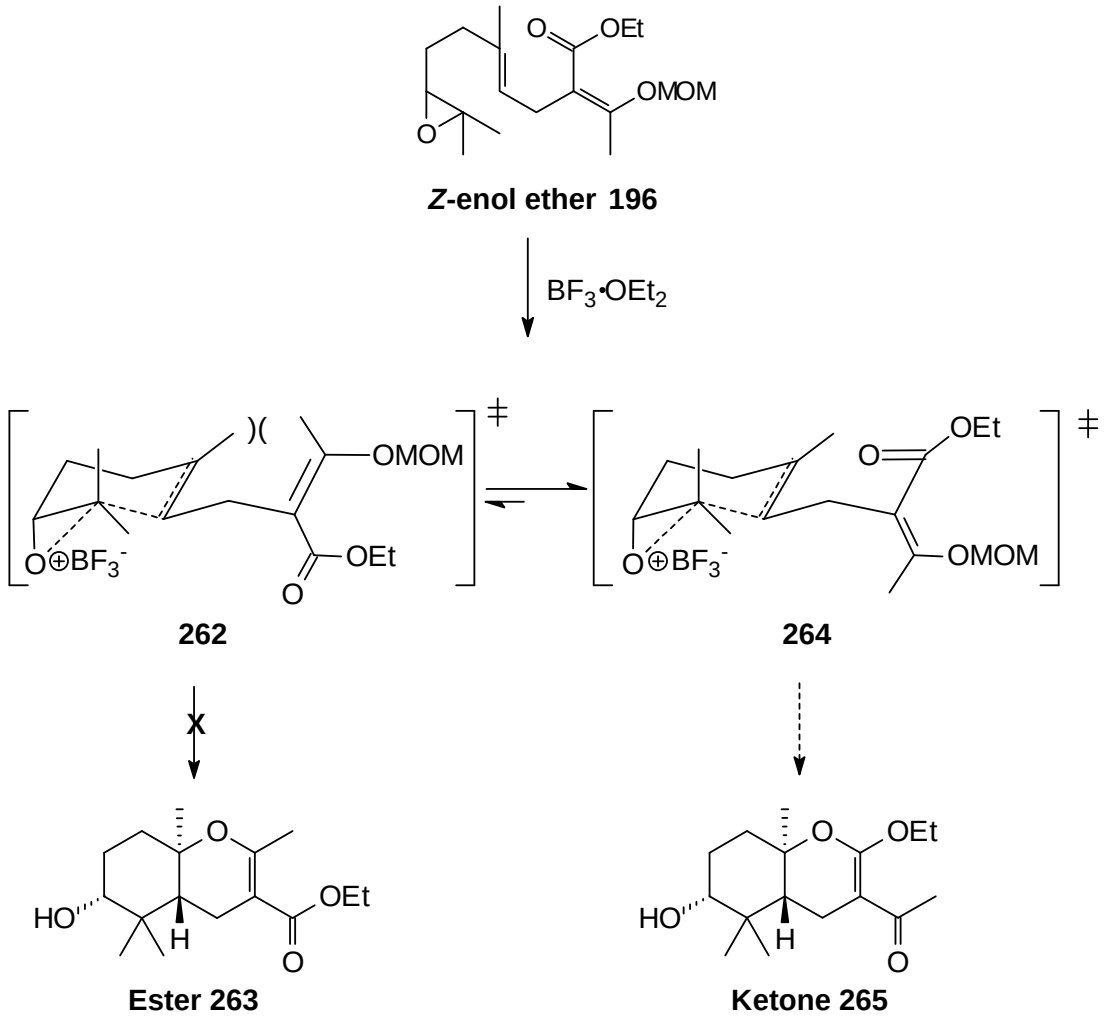


Figure 85. Conformations of *Z*–enol ether **196**

In the case of the isomeric *E*–enol ether **198**, either conformation **267** or **268** might be expected to cyclize, providing the ester **263** and/or ketone **265** (Figure 86). The MOM–protected enol of conformer **267** is poised for attack at the nearby reactive carbocation, while equilibration to the conformation **268** would place the ester carbonyl in close proximity to the neighboring carbocation, making it the reactive species and in turn providing the ketone **265**.

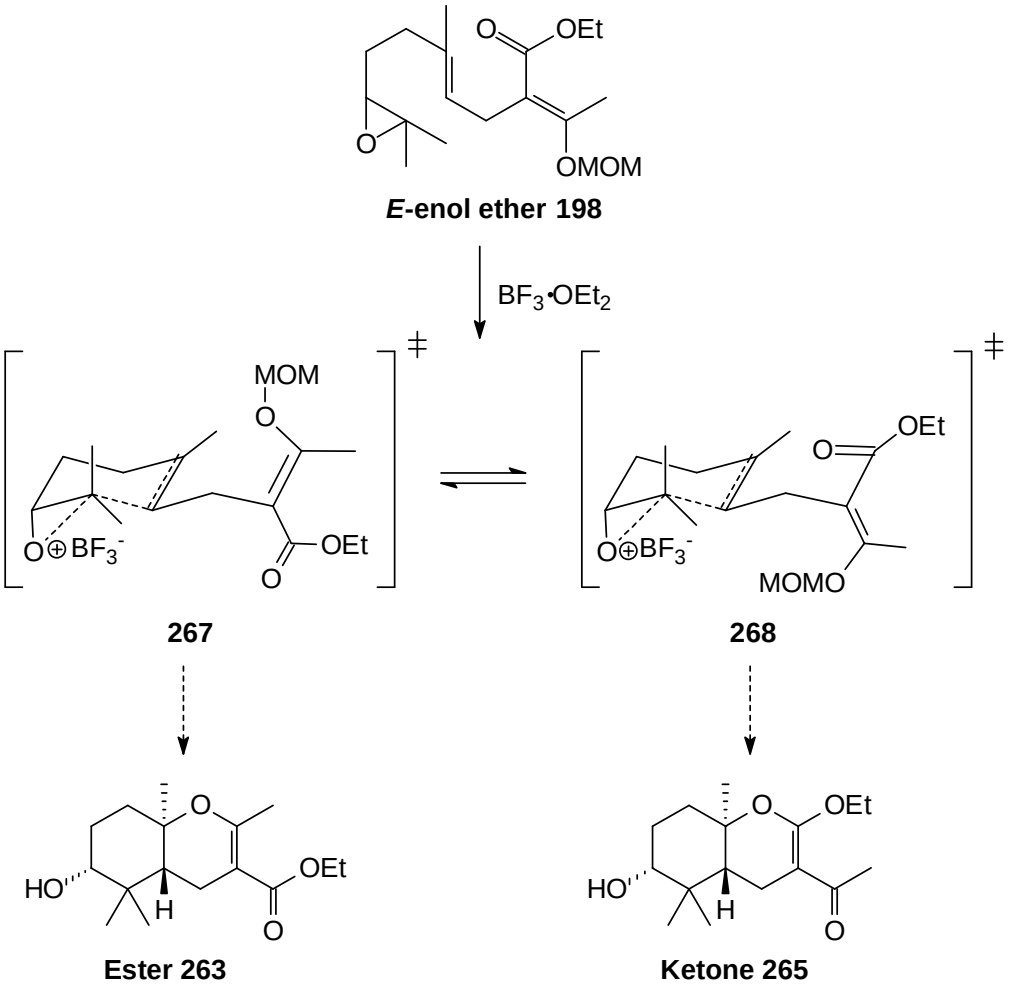


Figure 86. Conformations of *E*–enol ether **198**

With these hypotheses in mind, the synthesis of the requisite acyclic precursors was pursued (Figure 87). The alkylation of ethyl acetoacetate (**192**) with the known bromide **129**[82] proceeded in modest yield to provide C–alkylated product **194**. Using the optimum conditions discussed in Chapter 4 for the stereoselective synthesis of *E*– and *Z*–enol ethers, compounds **196** and **198** were prepared, albeit each in only modest yield. Reaction of β–keto ester **194** with KHMDS in DMF at room temperature followed by treatment with MOMCl provided the desired *E*–enol ether **198**, while reaction of β–keto ester **194** with LDA in THF at –78 °C followed by treatment with MOMCl provided the

Z–enol ether **196**. The stereoisomeric enol ethers are readily separable by column chromatography and easy to identify by either TLC analysis or ^{1}H NMR spectroscopy.

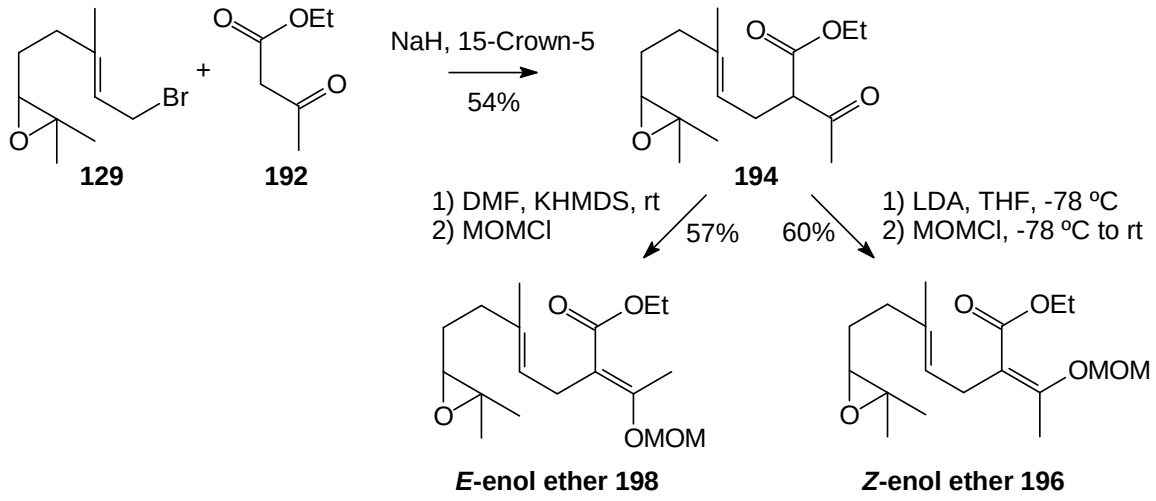


Figure 87. Preparation of *E*/*Z* enol ethers **198** and **196**

Both enol ethers **196** and **198** were subjected to the standard cyclization conditions employed in our labs[81, 82, 84] (Figures 88 and 89). Fortunately, the reaction products of these model systems were readily separable and identifiable. As expected, the major product resulting from the cyclization of *Z*–enol ether **196** is the ketone **265**. The ester **263** was not detected. Rather surprisingly, the two other major products are *E*–enol ether **198**, resulting perhaps from isomerization of the starting material, and compound **269**, resulting from incomplete cyclization.

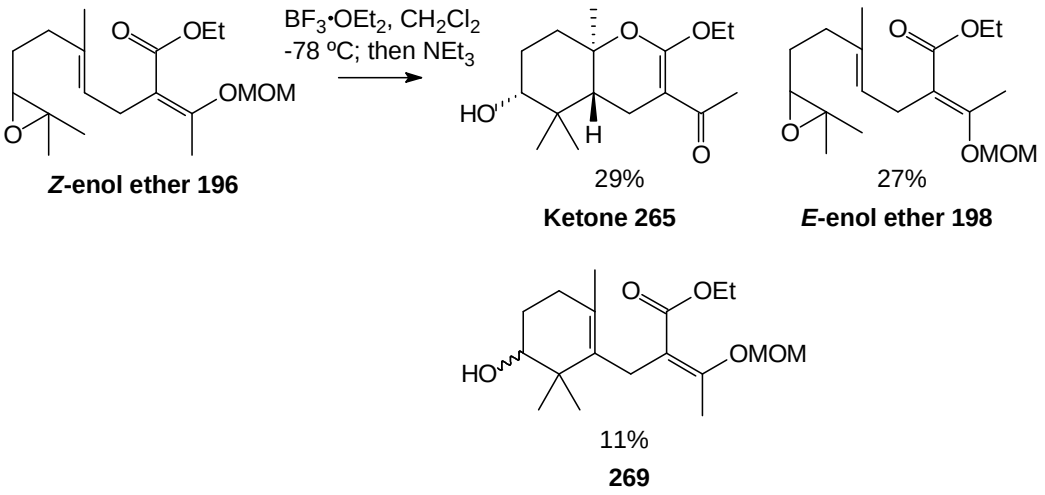


Figure 88. Cyclization of the *Z*–enol ether **196**

In contrast, the Lewis acid–mediated cascade cyclization of *E*–enol ether **198** afforded primarily the ester **263** and ketone **265**, with the ester **263** predominating (Figure 89). In addition, small amounts of MOM–protected ester **270**, cyclohexene **271**, and recovered starting material **198** were obtained. The proposed *E*–stereochemistry of the enol ether in cyclohexene **271** is based upon comparison of the chemical shift of its vinylic methyl hydrogens (2.17 ppm) to those of the *Z*–enol ether **261** (1.98 ppm).

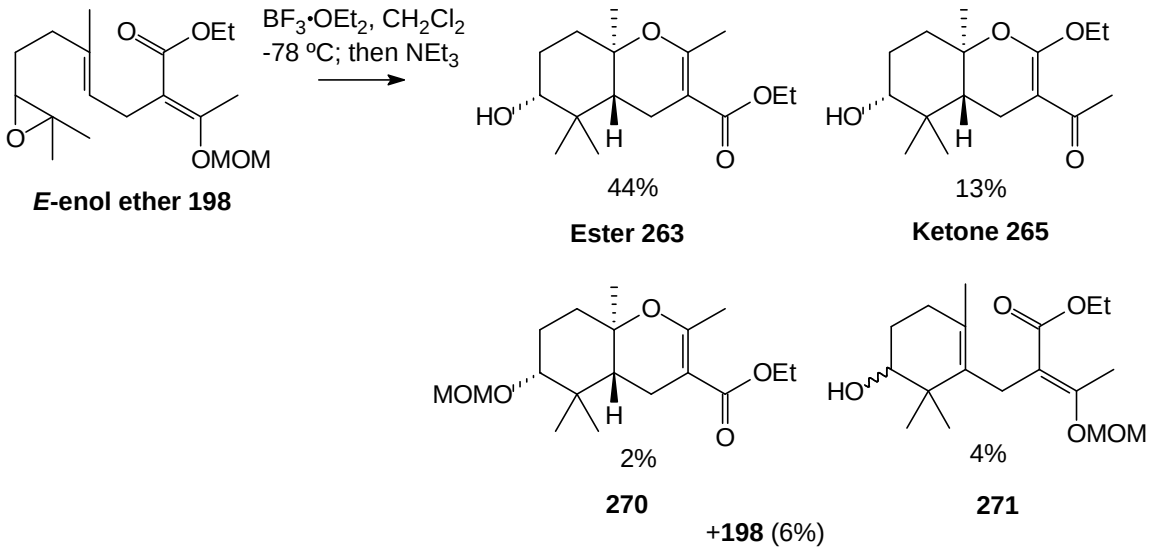


Figure 89. Cascade cyclization of *E*–enol ether **198**

The surprising isomerization of *Z*–enol ether **196** to the *E*–enol ether **198** during that cascade cyclization prompted further investigation into this process. It was of interest to determine whether MOM–protected enol ethers isomerize in the presence of a Lewis acid when there is a decreased likelihood of cyclization in the absence of an epoxide. A possible mechanism for this transformation is provided in Figure 90. Coordination of the ester carbonyl of *Z*–enol ether **261** to a Lewis acid followed by allylic transposition and loss of MOM^+ affords the corresponding "U" enolate **273** in which the ketone moiety is coordinated to the Lewis acid. Depending on the relative stability of the "U" versus the "W" enolate **274**, in which the ketone oxygen is no longer coordinated to the Lewis acid, the "U" enolate **273** may equilibrate to the "W" enolate **274**. In the case of the *E*–enol ether **266**, loss of MOM^+ and coordination of the ester carbonyl to the Lewis acid would afford the "W" enolate **274**, which can undergo rotation of the C–C single bond to produce the "U" enolate **273**, again, depending on which is more stable. After isomerization, recombination of the enolate with the MOM cation would form the MOM–enol ether.

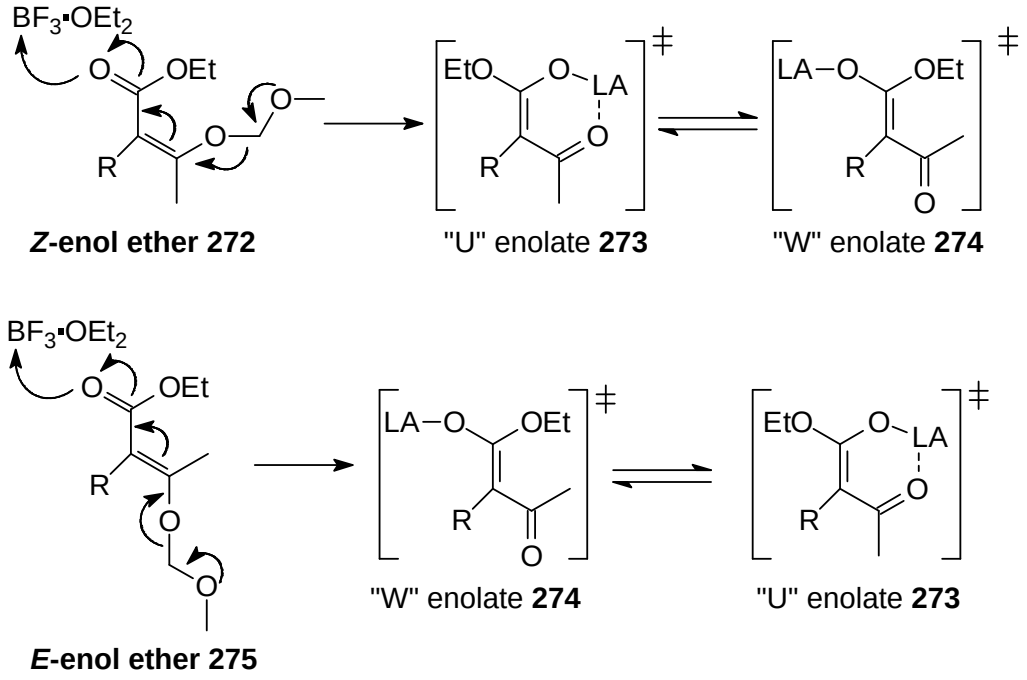


Figure 90. Proposed transition states for isomerization of enol ethers **272** and **278**

In a partial test of these hypotheses, the *Z*– and *E*–geranyl enol ethers **279** and **278** were prepared from the known β–keto ester **277**,[169] which is readily obtained via geranylation of ethyl acetoacetate (**192**, Figure 91). Although the yields were low, particularly in the case of the *E*–enol ether, enough material was obtained for further experiments.

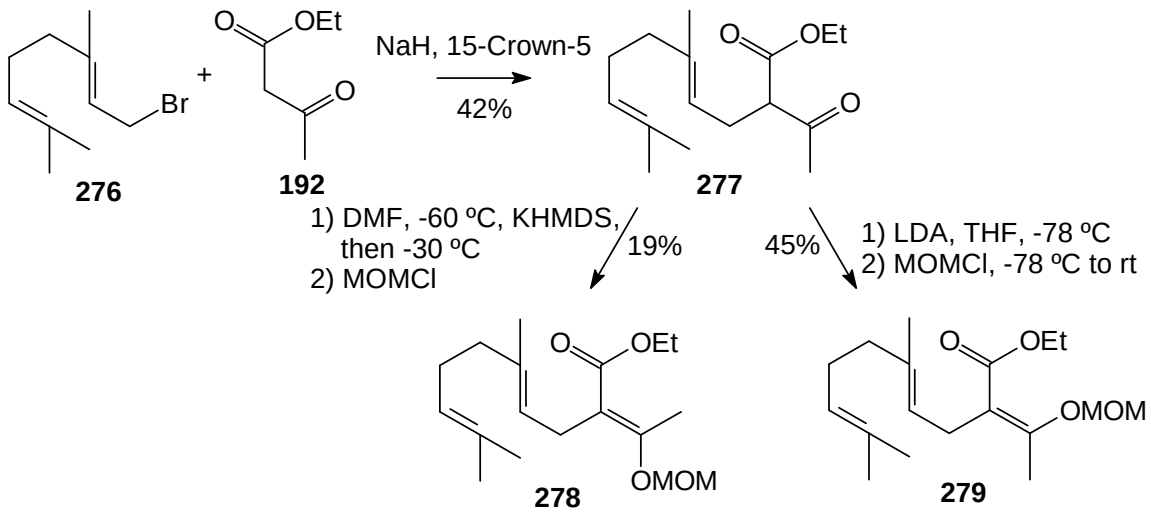


Figure 91. Preparation of geranyl enol ethers **278** and **279**

Both enol ethers **278** and **279** were subjected to standard cyclization conditions (Figure 92). In each case, however, no isomerization was observed as indicated by TLC and NMR analysis. Furthermore, treatment of either enol ether with BF_3•OEt_2 at higher temperature (0 °C) resulted in the production of complex product mixtures. These results indicate that the observed isomerization of *Z*–enol ether **261** may be due to a mechanism more complicated than the simple Lewis acid–catalyzed isomerization process shown in Figure 90.

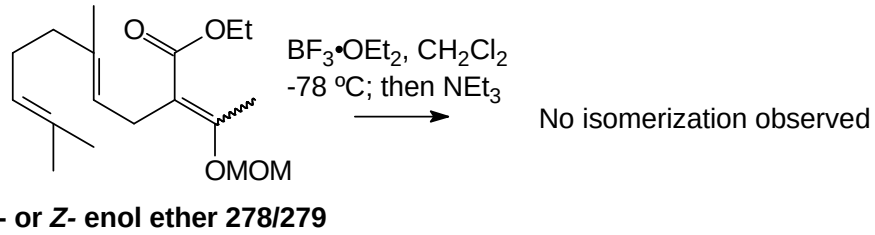


Figure 92. Attempted isomerization of enol ethers **278** and **279**

A surprising rearrangement was observed during an attempt to obtain an authentic sample of MOM–protected ketone **265** for characterization purposes (Figure 93). When ketone **265** was treated with DIPEA and MOMCl, the rearranged MOM–protected ester **270** was obtained.

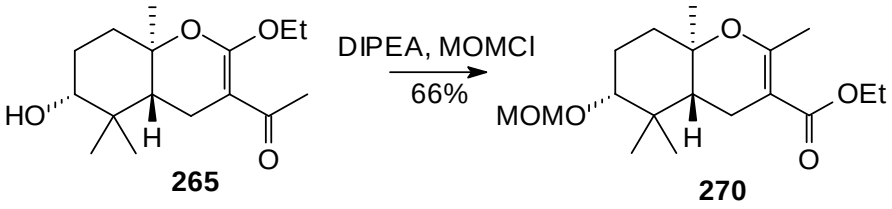


Figure 93. Attempted MOM–protection of decalin **265**

This result could be explained by a reaction catalyzed by the equivalent of diisopropylethylammonium chloride produced *in situ* under these reaction conditions. A proposed mechanism for this acid–catalyzed rearrangement is detailed in Figure 94. Protonation of ketone **265** could provide resonance stabilized cation **280**, which also can be represented as resonance structure **281**. Cleavage of the C–O bond would provide the tertiary carbocation **282**, which then could be attacked by the enol following rotation of the pertinent C–C single bond. Loss of H^+ could provide the rearranged ester **263**. Because all of these steps are theoretically reversible, the product distribution should depend only on the relative stability of the two products **265** and **263**.

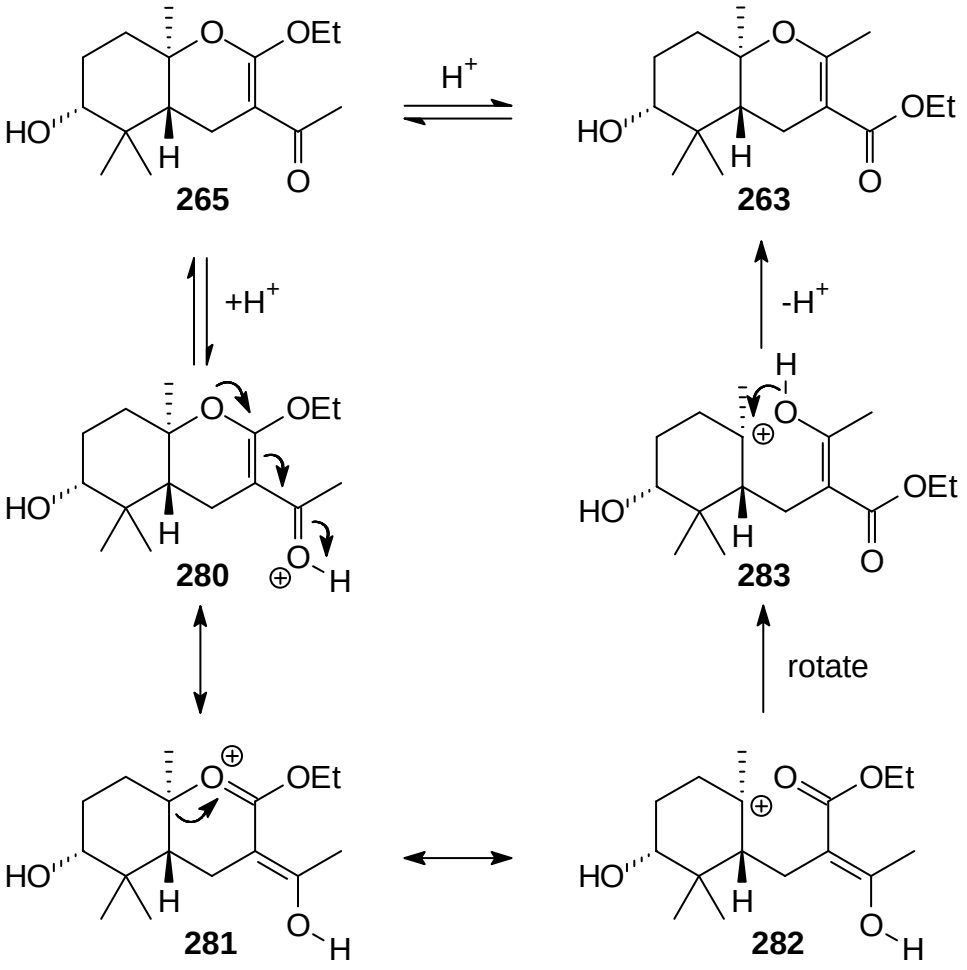


Figure 94. Proposed mechanism for acid–catalyzed rearrangement of ketone **265**

In order to determine whether ester and ketone **263** and **265** rearrange under acid–catalyzed conditions, both were treated with catalytic amounts of HCl in THF at room temperature (Figure 95). Ester **263** did not undergo rearrangement, and only starting material was obtained, as indicated by TLC and ^{1}H NMR analysis. Ketone **265**, however, immediately isomerized to ester **263** in excellent yield. These results indicate that ketone **265** is extremely acid labile, which may prove useful in synthesis. This matter will be re–visited in the farnesyl case (see below).

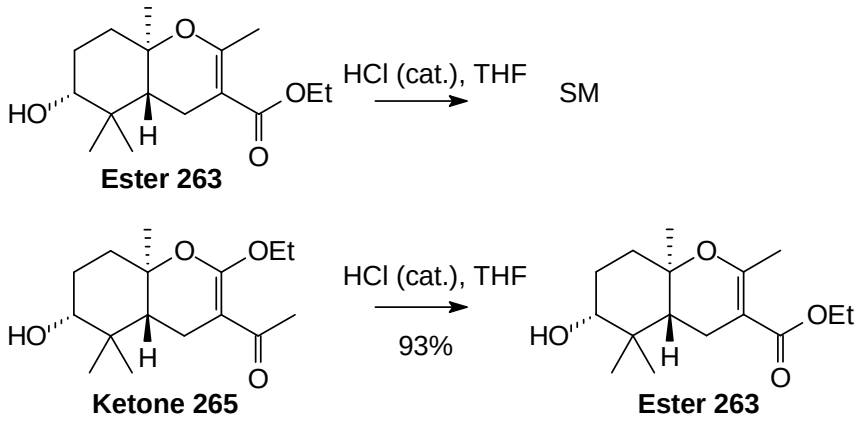


Figure 95. Treatment of the ester **263** and the ketone **265** with catalytic acid

The experience obtained in the study of the geranyl model system paved the way for exploration of cascade cyclizations of the more complex farnesyl chains. To begin this study, a synthesis of known farnesyl epoxy bromide **287**[170] was carried out (Figure 96). Acetylation of farnesol (**284**) followed by treatment with NBS in H_2O provided bromohydrin **285** in modest yield. Simultaneous removal of the acetate and formation of the epoxide occurred smoothly under basic conditions, and final conversion to the bromide **287** was accomplished via the intermediate mesylate.

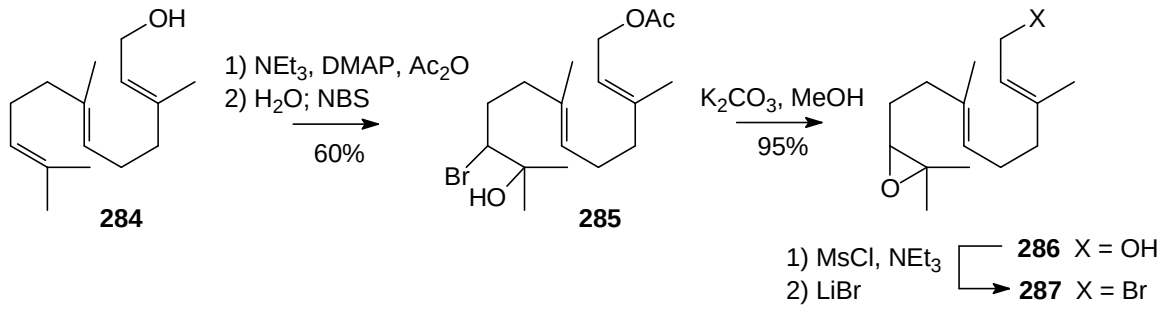


Figure 96. Synthesis of farnesyl epoxy bromide **287**

The alkylation of ethyl acetoacetate (**192**) with bromide **287** proceeded in high yield to provide the known β–keto ester **183** (Figure 97). Using conditions similar to those reported by Gibbs and coworkers,[126, 159] the desired enol ethers **184** and **186** were obtained in moderate yields.

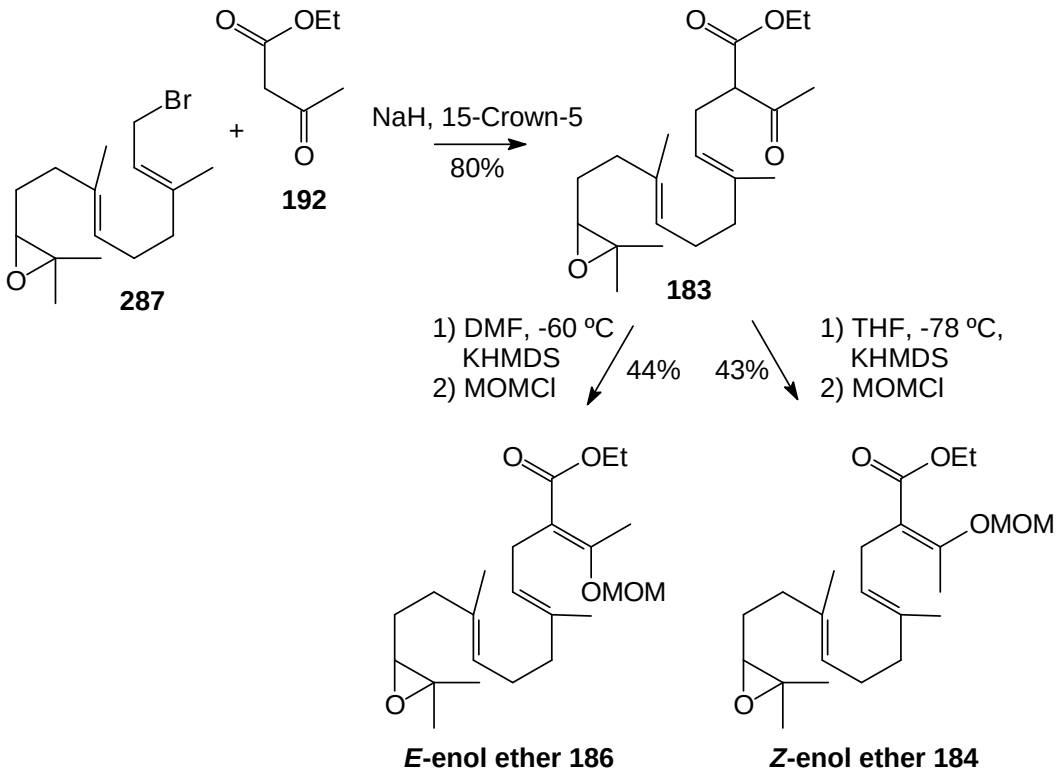
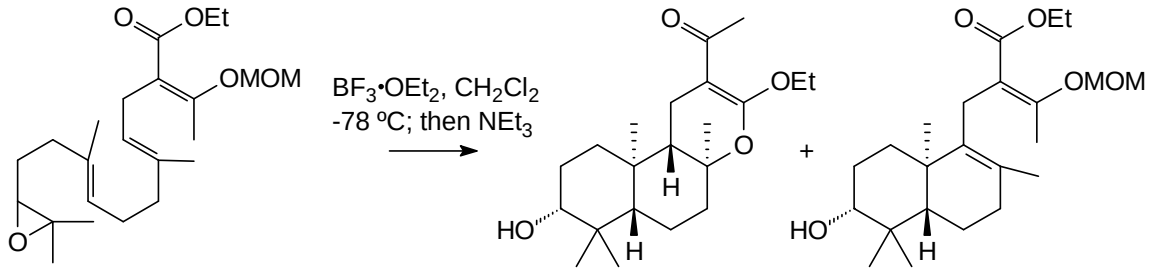


Figure 97. Preparation of *E*– and *Z*–enol ethers **186** and **184**

With the requisite *E*– and *Z*– farnesyl enol ethers in hand, the BF_3–mediated cyclizations were performed (Figures 98 and 100). As expected, these cyclizations produced substantially more products than the geranyl model system. In the case of *Z*–enol ether **184**, the two major products obtained are ketone **185** and decalin **288**. The proposed structure of decalin **288** is based on the presence of 5 resonances greater than 100 ppm in the ^{13}C spectrum, and a distinctive pair of doublets at approximately 2.8 ppm

in the ^{1}H NMR spectrum corresponding to the two doubly vinylic hydrogens. The proposed *Z*–stereochemistry of the enol ether of compound **288** is based on comparison of the chemical shift of its vinylic methyl hydrogens (1.87 ppm) to those of the *E*– and *Z*–enol ether starting materials (2.35 and 1.99 ppm, respectively). Multiple other trace products were observed by TLC analysis, but were not isolated in this case.



***Z*-enol ether 184** **Ketone 185** 15-21% **288** 17%

Figure 98. Cascade cyclization of *Z*–enol ether **184**

In an earlier study, Jos Yu was able to obtain a crystal structure of ketone **185**, thereby confirming the relative stereochemistry of this product (Figure 99). The A–ring alcohol is *syn* to the two bridgehead methyl groups, as observed in Parker's β–keto ester cascade cyclization.[85] Formation of ketone **185** represents the amplification of one stereocenter to provide four new stereogenic centers, three rings, two C–C bonds, and a C–O bond.

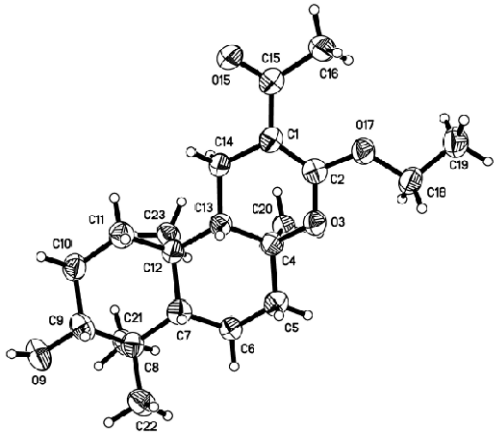
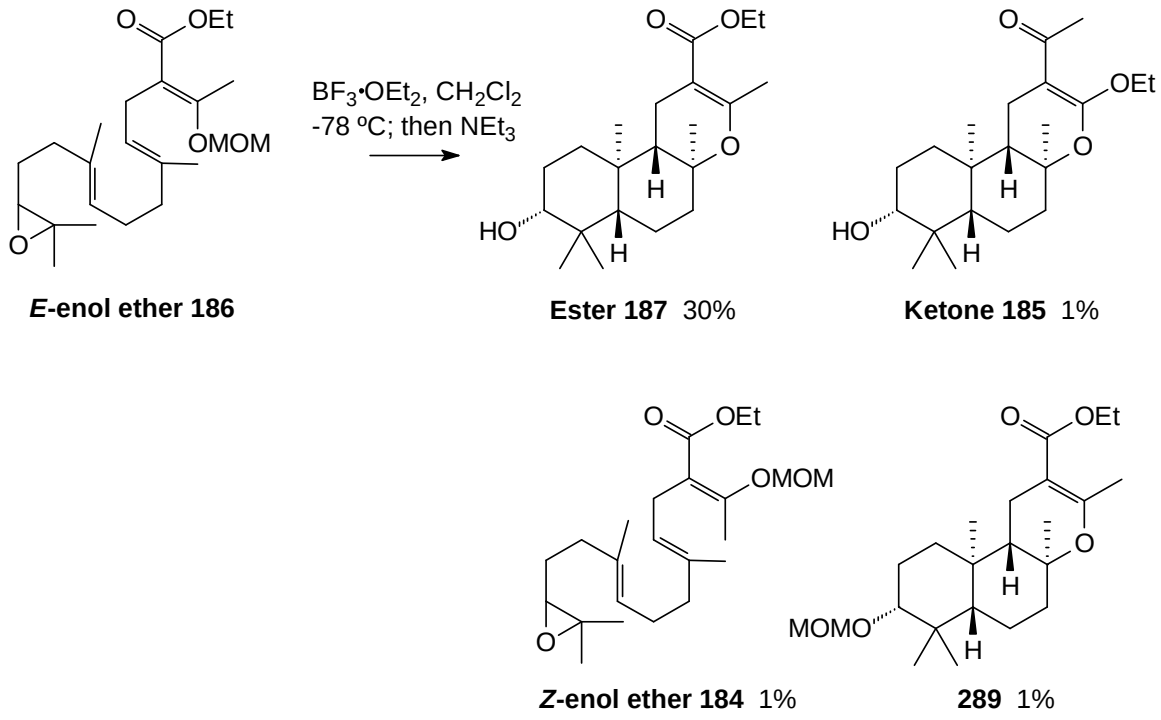


Figure 99. ORTEP of tricycle **185**

When *E*–enol ether **186** was treated with BF_3•OEt_2 under standard cyclization conditions, multiple products were isolated (Figure 100). Several of the products were difficult to analyze due to small sample size but four could be assigned. As with the cyclization of the corresponding geranyl *E*–enol ether **198**, the ester **187** was obtained as the major product. However, the ketone **185** was obtained only in trace amount, along with trace amounts of the ester **289** and the *Z*–enol ether **184**.



***E*-enol ether 186** **Ester 187** 30% **Ketone 185** 1%

***Z*-enol ether 184** 1% **289** 1%

Figure 100. Cascade cyclization of *E*–enol ether **186**

In order to obtain authentic samples of MOM–protected ester **185** and ketone **187**, these tricycles were treated with DIPEA and MOMCl (Figure 101). As in the geranyl ester **263** case, the MOM–protection of farnesyl ester **187** proceeded smoothly to provide the MOM–protected tricycle **289**. However, attempted MOM–protection of the ketone **185** resulted in rearrangement to the MOM–protected ester **289**.

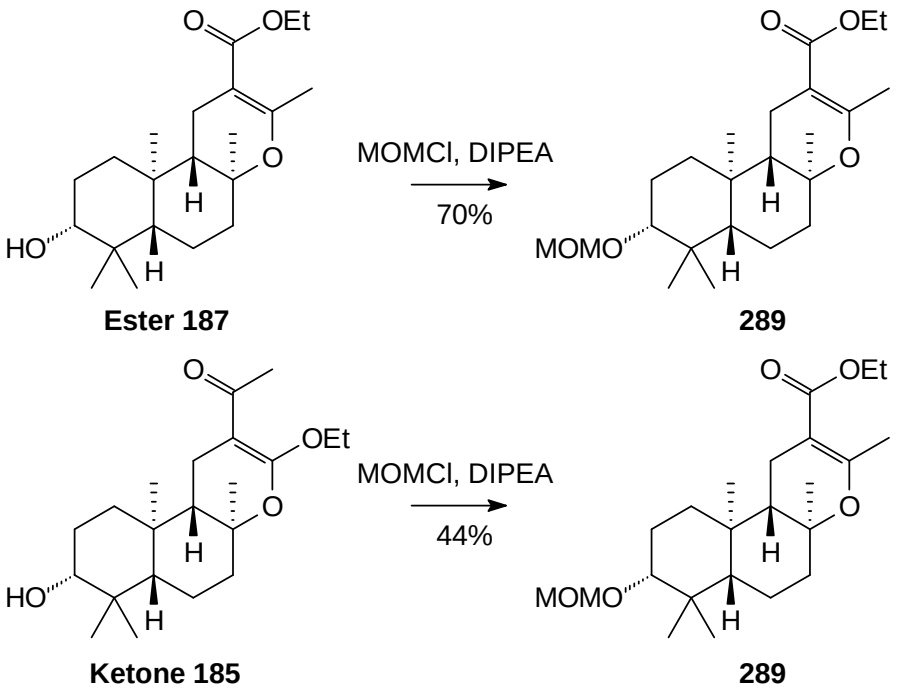


Figure 101. MOM–protection of tricycles **187** and **185**

Based on these results, ketone **185** was allowed to react with a catalytic amount of HCl in THF at room temperature (Figure 102). Analysis of the reaction mixture by TLC indicated immediate (<1 min) and complete conversion to the ester **187**.

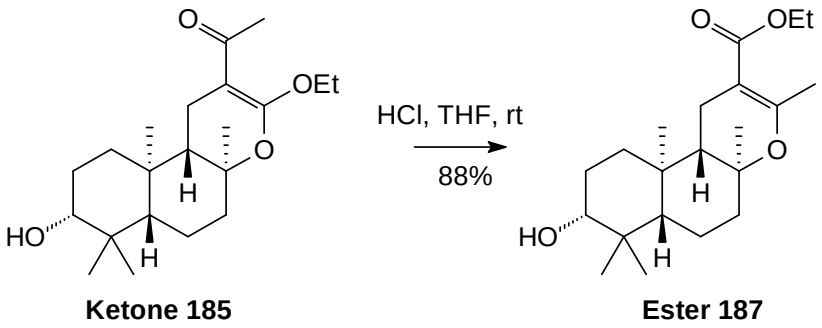


Figure 102. Acid–catalyzed isomerization of ketone **185** to ester **187**

In an effort to increase the selectivity of these cascade cyclizations, it was hypothesized that a bulky silyl–enol ether moiety could be utilized in place of a MOM–enol ether. The transition states used to explain the selectivity of *E*– and *Z*–geranyl enol ethers **198** and **196** also can be used to explain the selectivity expected in the case of silyl enol ethers. In the case of the *Z*–enol ether **290** (Figure 103), the only reactive conformer is intermediate **292**, which places the ester moiety near the resulting carbocation. Cascade cyclization of this enol ether should provide only the ketone **265**.

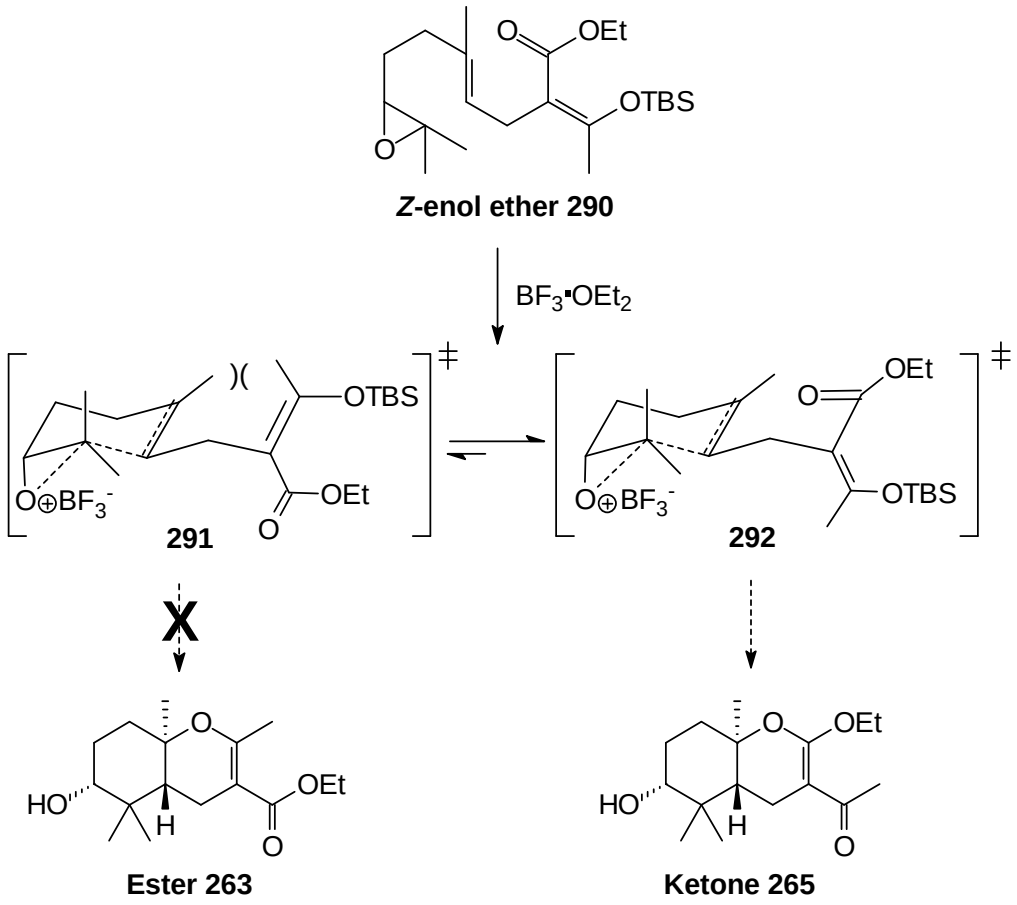


Figure 103. Transition states of the *Z*–silyl enol ether **290**

In the case of the *E*–silyl enol ether **293** (Figure 104), steric congestion between the TBS group and the nearby vinylic methyl group should lead to predominantly conformer **295**, which would in turn afford ketone **265** through loss of the silyl cation, allylic transposition, and attack of the ester carbonyl at the nearby tertiary carbocation. Another explanation for this reactivity could lie in the nature of a silyl group versus a MOM–acetal: loss of the resonance stabilized MOM^+ may be more favorable than loss of SiR_3^+, therefore increasing the nucleophilicity of the MOM–protected enol in comparison to a silyl–protected enol.

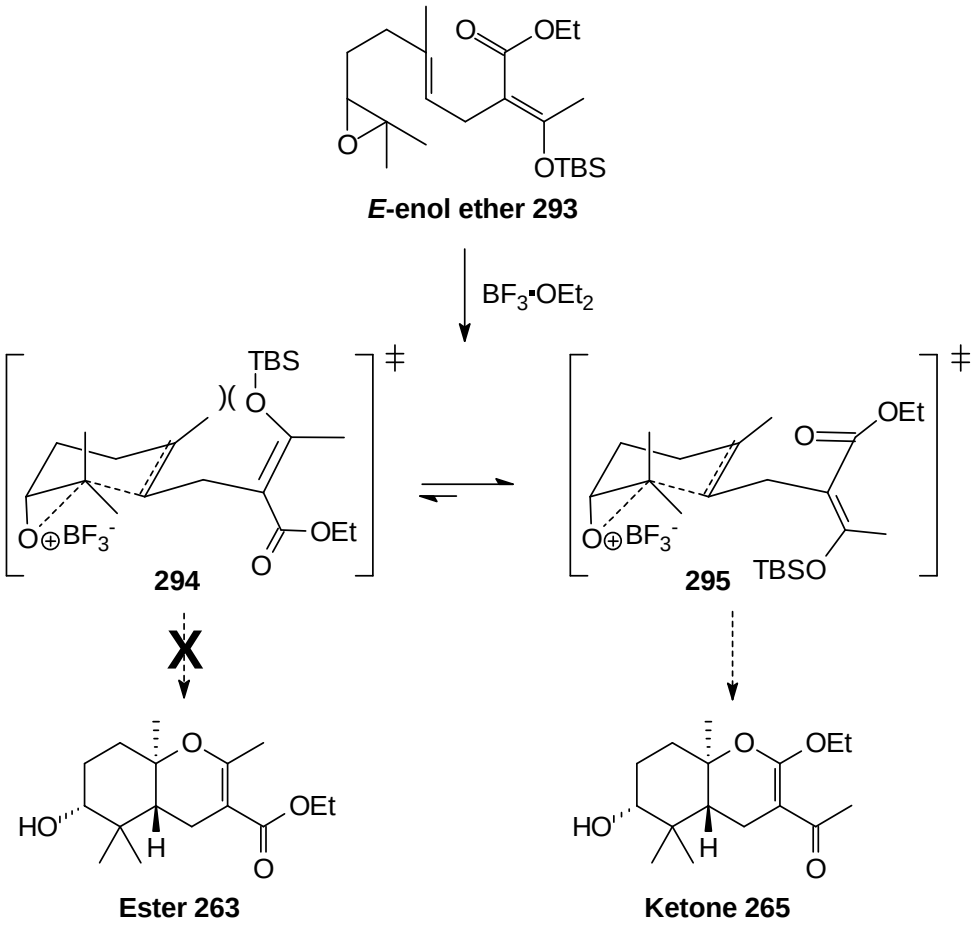
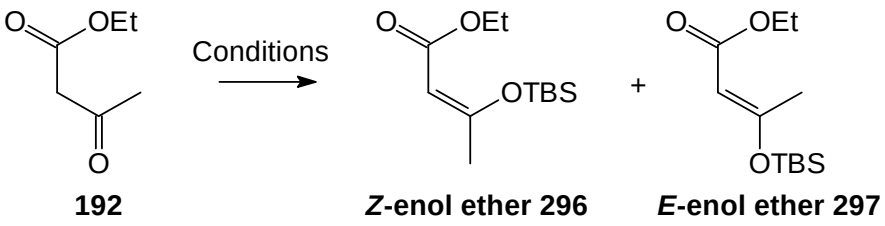


Figure 104. Transition states for *E*–silyl enol ether **293**

Given the problems experienced in the stereoselective synthesis of *E*– and Z–MOM enol ethers, it seemed wise to optimize the conditions for formation of the silyl enol ethers using the TBS–enol ethers of ethyl acetoacetate (**296** and **297**, Figure 105). The Z– and *E*–TMS enol ethers of ethyl acetoacetate are known and possess diagnostic ^{1}H NMR resonances for the vinylic methyl groups (1.8 and 2.2 ppm, respectively).[171] The ^{1}H NMR resonances of the vinylic methyl groups of the *Z*– and *E*–TBS enol ethers of ethyl acetoacetate appear at 1.9 and 2.3 ppm, respectively, making determination of the stereochemistry straightfoward. Therefore, the model silylations were carried out, the silyl ethers were purified by column chromatography and the *Z*/*E* ratios determined by analysis of the ^{1}H NMR spectra of the mixtures (Table 15). In the solvent system used, the enol ethers possess nearly equivalent Rf values. The *Z*–enol ether **296** was obtained selectively using multiple equivalents of NaH (entry 4), while the best yield and selectivity for the *E*–enol **297** was obtained with TEA in THF (entry 6).



192 ***Z*-enol ether 296** ***E*-enol ether 297**

Figure 105. Silylation of ethyl acetoacetate (**192**)

Trial	Conditions	Yield (%)	*Z* : *E*
1	LDA, THF, –78 °C	21	1:5
2	NaH (1.1 eq), THF, 0 °C – rt, 3h	57	1:8
3	NaH (4 eq), THF, 0 °C – rt, 1h	12	1:1
4	NaH (4 eq), THF, 0 °C, 1h	13	9:1
5	Imidazole, THF, rt, 12h	36	1:12
6	TEA, THF, rt, 12h	66	1:100

Table 15. Optimization of silyl enol ethers **296** and **297**

Using the optimized conditions for formation of the respective enol ethers, the Z– and *E*–enol ethers of geranyl β–keto ester **194** were obtained and subsequently subjected to standard cyclization conditions (Figure 106). Gratifyingly, cyclization of either enol ether provided primarily ketone **265** in moderate to good yields. In the case of the *Z*–enol ether **290**, substantial amounts of starting material were recovered.

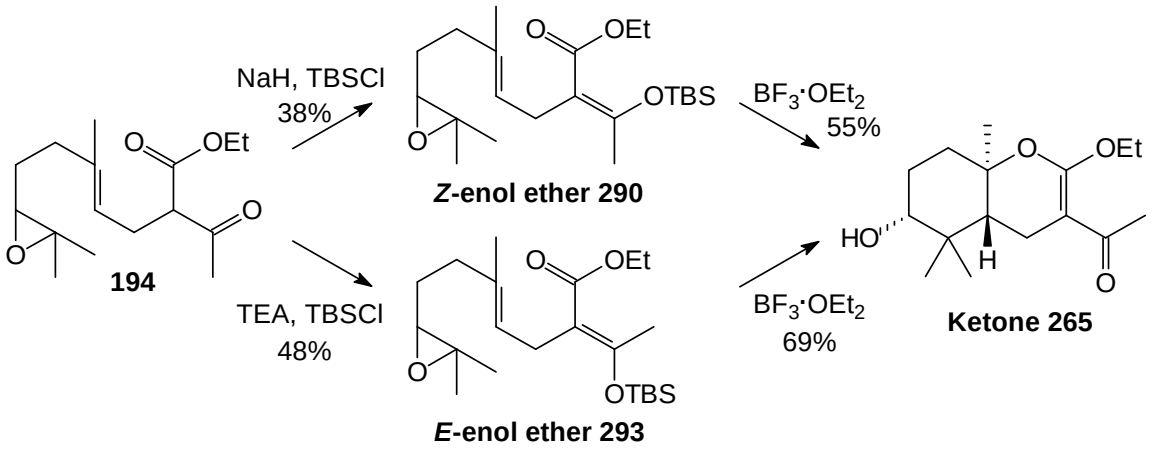


Figure 106. Preparation and cyclizations of *Z*– and *E*–enol ethers **290** and **293**

Following these results, the cyclization of a TBDPS–protected silyl enol ether was explored. Treatment of the β–keto ester **194** with strong base and TBDPSCl provided the *E*–silyl enol ether **298** in reasonable yield (Figure 107). The stereochemistry of this enol ether was determined by NOESY experiments. Treatment of this silyl enol ether with BF_3•OEt_2 afforded ketone **265** in only moderate yield.

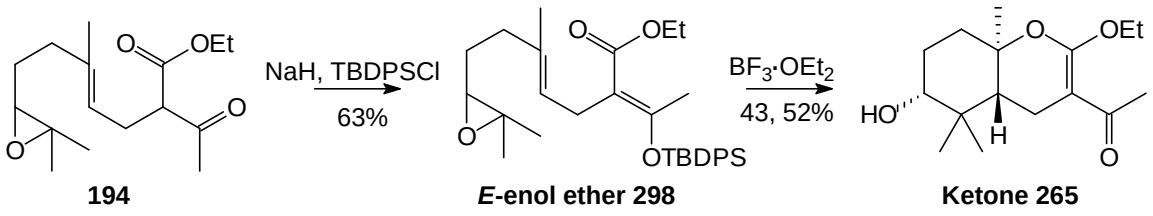
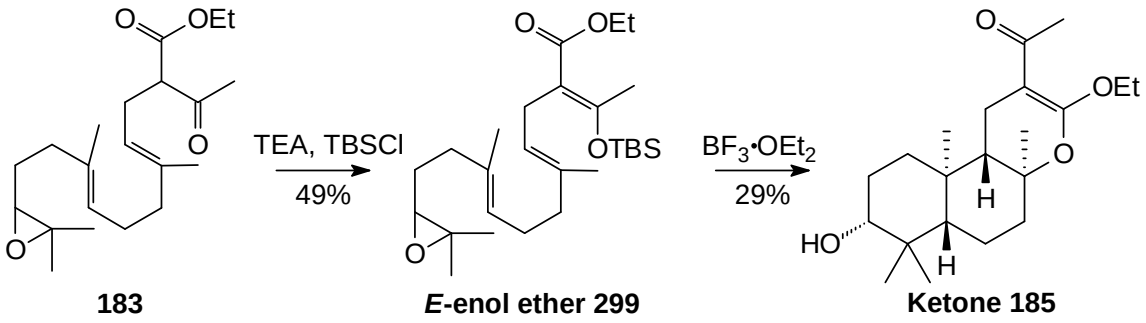


Figure 107. Preparation and cyclization of TBDPS–protected enol ether **298**

In light of these results, the *E*–TBS enol ether (**299**) of the farnesyl β–keto ester **183** was prepared (Figure 108). Unfortunately, the BF_3–mediated cascade cyclization of this silyl enol ether proceeded in only modest yield to provide ketone **185**. However,

exclusive formation of the ketone **185** is consistent with observed formation of ketone **265**, and supports the hypothesis offered in Figure 104.



183 **_E_-enol ether 299** **Ketone 185**

Figure 108. Synthesis and cyclization of the *E*–farnesyl silyl enol ether **299**

In conclusion, the preparation and cascade cyclizations of several MOM– and silyl–protected enol ethers have been carried out. A geranyl–length model system was utilized first in order to explore the types of products obtained from these reactions. These studies demonstrated that different types of products can be obtained based on the stereochemistry of the starting enol ether. In the course of this work, an acid–catalyzed isomerization and an acid–catalyzed rearrangement were explored in an effort to understand the relative stabilities of the various products. Based on these results, the more complicated farnesyl–length substrates were prepared and subjected to cascade cyclizations. Comparable results to the model system were obtained, but much work remains to be done in order to optimize these cascade cyclizations for the desired product. Finally, various silyl enol ethers were studied in an attempt to increase the yield of the ketone **185**. This proved successful in the geranyl case, but only slightly increased the yield of the ketone **185** in the case of the farnesyl–length substrate.

CHAPTER 6
SUMMARY AND FUTURE DIRECTIONS

In conclusion, the studies involving schweinfurthin F analogues have led to the preparation of a set of new analogues with variations in the nature of the stilbene olefin and the substituent at C–4' of the D–ring. The paucity of functionality in the D–ring substituent of the most potent compound may suggest that increasing hydrophobicity is more important than interaction with a specific functional group in the side chain. Given this perspective, the activity observed in heterocyclic analogues encourages exploration of other heterocyclic systems, especially if they can be prepared with an additional alkyl substituent in what would be the E–ring. Finally, either reduction of the stilbene olefin or isomerization of the stilbene from the *trans* stereochemistry to the *cis* diminishes activity in the SF–295 cell line.

The two–cell assay for screening synthetic analogues has proven quite effective in quickly identifying potent and selective compounds. In this study, new schweinfurthin analogues were screened in the two–cell assay. After the most potent compound of the set was identified, confirmation of this analogue's activity was obtained via the NCI's 60–cell line assay. As a proof of concept, one of the least active of the analogues in the two–cell assay also was tested in the 60–cell assay and it displayed both reduced cytotoxicity and lessened differential activity. Thus, it appears reasonable to use this facile screening process for more efficient testing of future synthetic analogues.

The synthesis of biotinylated schweinfurthin analogues was more challenging than anticipated. Multiple obstacles were encountered along the way, including the efficient alkylation of the desired D–ring substructure, the need for differential protection/deprotection sequences, and problems with the isolation and purification of the target compounds. Nevertheless, three biotinylated schweinfurthin analogues have been prepared and were tested by our collaborators against SF–295 and A549 cell lines to determine if they exhibit schweinfurthin–like activity. The MOM–protected analogues

164 and **166** exhibit decreased activity in both of these cell lines, while the D–ring phenol **46** displays promising schweinfurthin–like activity in the SF–295 and A549 cell lines. Furthermore, our collaborators at NCI–Frederick have shown that this analogue induces the same characteristic morphological changes in KR158 astrocytoma and K16561 MPNST cells as schweinfurthin A, indicating that it probably interacts with the same binding partner(s) as the natural schweinfurthins. Based on these results, biotinylated analogue **46** was used in pull–down experiments, and several proteins were isolated and identified. More work remains to be done to verify the identity of the protein(s) isolated in this way and to determine their importance. However, this work appears to confirm that the schweinfurthins target proteins as opposed to other potential biological targets. These efforts also have illuminated routes to synthesize more potent biotinylated analogues of the natural schweinfurthins if that should prove necessary.

In an effort to expand the scope of cascade cyclizations, the preparation and cascade cyclizations of several MOM– and silyl–protected enol ethers have been conducted. Problems in the efficient chemo– and stereoselective synthesis of these enol ethers were encountered. Extensive experimentation resulted in greatly increased yields of these enol ethers as well as improved control of the enol stereochemistry, but more work still is required to obtain optimum yields. To study the cascade cyclizations, a geranyl–length model system was utilized first in order to explore the types of products obtained from these reactions. These studies demonstrated that different types of products can be obtained based on the stereochemistry of the starting enol ether. During the course of this work, an acid–catalyzed isomerization and an acid–catalyzed rearrangement were explored in an effort to understand the relative stabilities of the various products. Based on these results, the more complicated farnesyl–length substrates were prepared and subjected to cascade cyclizations. Comparable results to the model system were obtained, but work remains to be done in order to optimize these cascade cyclizations for the desired products. Finally, various silyl enol ethers were

studied in an attempt to increase the isolated yields. This proved successful in the geranyl case, and resulted in greatly increased yields of the desired products. In the farnesyl–length substrates, however, only slightly increased yields were observed. These cyclizations must still be optimized in the farnesyl case if this route is to be competitive with previously published syntheses. The synthesis of these products in enantiopure form is an obvious next step, and once this goal is obtained, the total synthesis of several relevant natural products is readily imaginable.

CHAPTER 7
EXPERIMENTAL PROCEDURES

General experimental conditions. Tetrahydrofuran was distilled from sodium and benzophenone; methylene chloride and triethylamine were distilled from calcium hydride immediately before use. Butyl 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. All reactions in anhydrous solvents were conducted in flame–dried glassware under a positive pressure of argon and with magnetic stirring. NMR spectra were obtained at 300 MHz for ^{1}H and 75 MHz for ^{13}C with $CDCl_3$ as solvent and internal standard (^{1}H, 7.26 ppm; ^{13}C, 77.0 ppm) unless otherwise noted. Chemical shifts for ^{31}P NMR were reported in ppm relative to 85% H_3PO_4 (external standard). High resolution mass spectra were obtained at the University of Iowa Mass Spectrometry Facility. Silica gel (60 Å, 0.040–0.063 mm) was used for flash chromatography. Left–half aldehyde **75** had a 90% ee, as determined by HPLC.

Preparation of compounds 83 and 84. To a solution of the known silyl protected benzyl alcohol **77**[87] (467 mg, 1.4 mmol) in THF (10 mL) at –20 ºC was added *n*–BuLi (0.8 mL, 2.2 M in hexane, 1.8 mmol), and the reaction was allowed to warm to 0 ºC over 1 h. The solution was then cooled to –20 ºC, solid CuBr·DMS (280 mg, 1.4 mmol) was added in one portion, and the resulting solution was allowed to stir for 1 h. To the solution was added bromide **82** (131 mg, 0.7 mmol) and the resulting solution was allowed to stir for 2 h. After the reaction was quenched by addition of NH_4Cl (sat.), the aqueous layer was extracted with EtOAc, dried ($MgSO_4$), concentrated *in vacuo*, and purified by column chromatography (2% EtOAc/hexanes) to afford compounds **83** and **84** (72 mg, 23%, 1:1.4 **83**:**84**) as a virtually inseparable mixture: ^{1}H NMR δ 6.78–6.77 (m, 3.4 H), 6.32–6.21 (m, 1H), 5.53–5.42 (m, 1H), 5.17 (s, 2.9H), 5.16 (s, 4H), 5.03–5.01

(m, 0.5 H), 4.97–4.96 (m, 0.5H), 4.90–4.89 (m, 1H), 4.69 (s, 1.4H), 4.68 (s, 2H), 3.47 (s, 10.4H), 3.37 (d, *J* = 8.6 Hz, 1H), 1.95–1.79 (m, 3.2H), 1.35–1.16 (m, 16H), 0.95 (s, 16H), 0.92–0.84 (m, 7H), 0.10 (s, 11H); ^{13}C NMR δ 155.8, 155.6, 141.9, 140.9, 140.8, 130.3, 127.9, 120.7, 117.7, 113.2, 106.0, 105.7, 94.5, 94.5, 64.9, 64.8, 55.9, 55.8, 40.1, 33.0, 32.5, 31.9, 31.4, 29.2, 27.7, 25.9 (6C), 22.6, 22.5, 18.3, 14.1, 14.0, –5.3 (2C), –5.3 (2C).

Benzyl alcohol 85. To a solution of known silyl protected benzyl alcohol **77**[87] (634 mg, 1.9 mmol) in THF (12 mL) at –20 ºC was added *n*–BuLi (0.9 mL, 2.4 M in hexane, 2.2 mmol), and the reaction was allowed to warm to 0 ºC over 1 h. The solution was then cooled to –20 ºC, CuBr·DMS (380 mg, 1.9 mmol) was added in one portion, and the resulting solution was allowed to stir for 1 h. To the solution was added allyl bromide (0.2 mL, 2.1 mmol) and the resulting solution was allowed to stir for 2 h. After the reaction was quenched by addition of NH_4Cl (sat.), the aqueous layer was extracted with EtOAc, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was dissolved in THF (10 mL) at rt, TBAF (1.5 mL, 1.0 M in THF, 1.5 mmol) was added, and the reaction was allowed to stir for 2 h. Once TLC analysis indicated complete consumption of the starting material, the reaction was quenched by addition of H_2O and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified by column chromatography (60% EtOAc/hexanes) to afford compound **85** (329 mg, 66%) as a colorless oil: ^{1}H NMR δ 6.77 (s, 2H), 5.97–5.91 (m, 1H), 5.17 (s, 4H), 5.00–4.91 (m, 2H), 4.59 (s, 2H), 3.45 (s, 6H), 3.40–3.37 (m, 2H); ^{13}C NMR δ 155.7 (2C), 140.6, 136.6, 117.3, 114.2, 106.3 (2C), 94.3 (2C), 65.2, 56.0 (2C), 27.5; HRMS (EI^+) calcd for $C_{14}H_{20}O_5$ [M^+] 268.1311; found 268.1309.

Phosphonate 76. Methanesulfonyl chloride (0.1 mL, 1.6 mmol) was added dropwise to a solution of alcohol **85** (329 mg, 1.2 mmol) and Et_3N (0.3 mL, 1.8 mmol) in THF (7 mL) at 0 °C, and the solution was allowed to stir for 1 h. The resulting precipitate was dissolved by addition of H_2O, and the aqueous layer was extracted with

EtOAc, washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was dissolved in acetone (10 mL), and NaI (670 mg, 4.5 mmol) was added in one portion. After the mixture was allowed to stir for 24 h, it was quenched by addition of H_2O and extracted with EtOAc. The combined extracts were washed with $Na_2S_2O_3$ (sat.) until the color had disappeared, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting yellow oil was added to a solution of triethyl phosphite (0.2 mL, 1.4 mmol) in THF (3 mL), and the solution was heated at reflux overnight. After concentration *in vacuo*, the resulting oil was purified by column chromatography (2% MeOH/$CHCl_3$) to yield phosphonate **76** (375 mg, 79%) as a pale oil: ^{1}H NMR δ 6.70 (d, J_{PH} = 2.5 Hz, 2H), 6.01–5.86 (m, 1H), 5.18 (s, 4H), 5.00–4.90 (m, 2H), 4.09–3.99 (m, 4H), 3.45 (s, 6H), 3.44–3.40 (m, 2H), 3.08 (d, J_{PH} = 21.5 Hz, 2H), 1.38–1.32 (m, 6H); ^{13}C NMR δ 155.6 (d, J_{CP} = 2.6 Hz, 2C), 142.4, 136.7 (d, J_{CP} = 1.8 Hz), 116.8, 114.1, 109.5 (d, J_{CP} = 6.8 Hz, 2C), 94.4 (2C), 62.0 (d, J_{CP} = 6.6 Hz, 2C), 56.0 (2C), 33.0 (d, J_{CP} = 137.0 Hz), 27.5, 16.4 (d, J_{CP} = 7.2 Hz, 2C); ^{31}P NMR δ 26.9; HRMS (EI$^+$) calcd for $C_{18}H_{29}O_7P$ [M^+] 388.1651; found 388.1655.

Phosphonate 86. To a solution of phosphonate **76** (101 mg, 0.3 mmol) in THF (1 mL) at 0 ºC was added 9–BBN (2.0 mL, 0.5 M in THF, 1.0 mmol), and the solution was allowed to warm to rt and stirred overnight. To the solution was added H_2O (0.1 mL), 2 N NaOH (0.8 mL), and 30% H_2O_2 (0.4 mL), and the reaction was heated at 50 ºC for 2 h, then allowed to cool to rt and stirred for 2 days. After the resulting solution was extracted with EtOAc, washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*, the remaining oil was purified by flash column chromatography (2% MeOH/$CHCl_3$) to afford compound **86** (41 mg, 39%) as a colorless oil: ^{1}H NMR δ 6.66 (s, 2H), 5.11 (s, 4H), 3.99–3.94 (m, 4H), 3.47 (t, J = 6.0 Hz, 2H), 3.40 (s, 6H), 3.01 (d, J_{PH} = 21.4 Hz, 2H), 2.70 (t, J = 7.1 Hz, 2H), 2.10 (br s, 1H), 1.76–1.68 (m, 2H), 1.20 (t, J_{PH} = 5.9 Hz, 6H); ^{13}C NMR δ 155.8 (d, J_{CP} = 3.4 Hz, 2C), 130.7 (d, J_{CP} = 8.9 Hz), 118.1, 109.5 (d, J_{CP} = 6.7 Hz, 2C), 94.6 (2C), 62.0 (d, J_{CP} = 6.8 Hz, 2C), 61.6, 56.1 (2C), 33.8 (d, J_{CP} = 138.2

Hz), 31.7, 18.8, 16.3 (d, J_{CP} = 6.1 Hz, 2C); ^{31}P NMR δ 26.7; HRMS (EI$^+$) calcd for $C_{18}H_{31}O_8P$ [M$^+$] 406.1757; found 406.1761.

Phosphonate 87. To a solution of phosphonate **76** (69 mg, 0.2 mmol) in MeOH (3 mL) was added 10% Pd–C (67 mg, cat.) and an excess of H_2, and the mixture was agitated overnight. Following filtration through Celite, the resulting solution was concentrated *in vacuo* to afford compound **87** (67 mg, 97%) as a colorless oil: ^{1}H NMR δ 6.63 (s, 2H), 5.10 (s, 4H), 3.99–3.94 (m, 4H), 3.39 (s, 6H), 3.02 (d, J_{PH} = 21.6 Hz, 2H), 2.54 (t, J = 7.5 Hz, 2H), 1.48–1.40 (m, 2H), 1.19 (t, J_{PH} = 6.9 Hz, 6H), 0.86 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 155.7 (d, J_{CP} = 3.3 Hz, 2C), 129.9 (d, J_{CP} = 9.2 Hz), 119.5 (d, J_{CP} = 4.2 Hz), 109.2 (d, J_{CP} = 6.7 Hz, 2C), 94.3 (2C), 62.0 (d, J_{CP} = 6.7 Hz, 2C), 55.8 (2C), 33.7 (d, J_{CP} = 137.7 Hz), 25.1, 22.6 (d, J_{CP} = 2.4 Hz), 16.2 (d, J_{CP} = 6.1 Hz, 2C), 14.1; ^{31}P NMR δ 27.0; HRMS (EI$^+$) calcd for $C_{18}H_{31}O_7P$ [M$^+$] 390.1807; found 390.1811.

Arene 90. To a solution of benzyl alcohol **88** (309 mg, 1.0 mmol) in EtOAc (3 mL) was added 10% Pd–C (110 mg, cat.) and an excess of H_2, and the mixture was agitated overnight. Following filtration through Celite, the resulting solution was concentrated *in vacuo* and purified by column chromatography (30–100% EtOAc/hexanes) to afford compound **90** as the major product: ^{1}H NMR δ 6.61 (s, 2H), 5.19 (s, 4H), 3.50 (s, 6H), 2.69–2.64 (m, 2H), 2.31 (s, 3H), 1.68–1.55 (m, 1H), 1.43–1.33 (m, 2H), 0.96 (d, J = 6.6 Hz, 6H).

Phenol 100. To a solution of PPh_3 (136 mg, 0.5 mmol) and Zn dust (38 mg, 0.5 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added CBr_4 (173 mg, 0.5 mmol) in one portion, and the reaction was allowed to stir for 15 min at 0 °C and 15 min at rt. Aldehyde **98** (96 mg, 0.3 mmol) in CH_2Cl_2 (1 mL) was added via cannula, and the reaction was allowed to stir for 4 h at rt. When TLC analysis indicated complete consumption of the starting material, the solution was diluted with pentane (5 mL) and filtered through Celite. After CH_2Cl_2 (5 mL) was added to the filtrate, and the solution was triturated with pentane then filtered through Celite. The resulting solution was concentrated and the residue purified

by column chromatography (5% EtOAc/hexanes) to provide phenol **100** (56 mg, 66%) as a colorless oil: ^{1}H NMR δ 11.9 (s, 1H), 10.3 (s, 1H), 6.60 (s, 1H), 6.54 (s, 1H), 5.25 (s, 2H), 4.67 (s, 2H), 3.50 (s, 3H), 0.94 (s, 9H), 0.10 (s, 6H); ^{13}C NMR δ 193.7, 163.5, 160.0, 153.8, 110.1, 107.3, 101.3, 94.6, 64.5, 56.5, 25.8 (3C), 18.3, –5.4 (2C).

Stilbene 109. To a mixture of NaH (28 mg, 0.8 mmol) and 15–crown–5 (1 drop, cat.) in THF (5 mL) at 0 ºC was added a solution of phosphonate **76** (38 mg, 0.1 mmol) and aldehyde **75** (29 mg, 0.1 mmol) in THF (1 mL), and the reaction was allowed to stir for 1 h at 0 ºC. The reaction mixture was then quenched via dropwise addition of H_2O, extracted with ether, washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (45% EtOAc/hexanes) to afford stilbene **109** (37 mg, 70%) as a colorless oil: ^{1}H NMR δ 6.91–6.79 (m, 6H), 5.90–5.85 (m, 1H), 5.16 (s, 4H), 4.95–4.85 (m, 2H), 3.82 (s, 3H), 3.42 (s, 6H), 3.38–3.37 (m, 3H), 2.65–2.56 (m, 2H), 2.07–2.02 (m, 1H), 1.81–1.52 (m, 4H), 1.18 (s, 3H), 1.03 (s, 3H), 0.81 (s, 3H); ^{13}C NMR δ 155.9 (2C), 148.9, 142.6, 137.1, 136.6, 128.8, 128.4, 126.3, 122.6, 120.6, 117.5, 114.2, 106.8, 105.9 (2C), 94.4 (2C), 77.9, 77.1, 56.0 (2C), 55.9, 46.7, 38.4, 37.7, 29.2, 28.3, 27.7, 27.3, 23.1, 19.9; HRMS (EI^{+}) calcd for $C_{32}H_{42}O_7$ [M^{+}] 538.2931; found 538.2930.

Analogue 63. To a solution of stilbene **109** (37 mg, 0.07 mmol) in MeOH (2 mL) at rt was added TsOH (60 mg, 0.3 mmol) and the solution was allowed to stir for 18 h. The reaction was quenched by addition of $NaHCO_3$ (sat.) and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), concentrated *in vacuo*, and purified by flash column chromatography (50% EtOAc/hexanes) to afford analogue **63** (21 mg, 67%) as a yellow oil: ^{1}H NMR δ 6.83–6.65 (m, 4H), 6.49 (s, 2H), 5.99–5.88 (m, 1H), 5.14–5.03 (m, 2H), 3.79 (s, 3H), 3.41–3.33 (m, 3H), 2.65–2.62 (m, 2H), 2.07–2.02 (m, 1H), 1.82–1.51 (m, 4H), 1.14 (s, 3H), 1.02 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 155.3 (2C), 148.8, 142.7, 137.4, 136.1, 128.8, 128.6, 125.8, 122.7, 120.7, 115.8,

111.4, 107.0, 106.1 (2C), 78.1, 77.2, 56.0, 46.7, 38.4, 37.6, 29.2, 28.2, 27.6, 27.3, 23.1, 19.8; HRMS (EI^+) calcd for $C_{28}H_{34}O_5$ [M^+] 450.2406; found 450.2408.

Stilbene 113. To a mixture of NaH (50 mg, 1.4 mmol) and 15–crown–5 (1 drop, cat.) in THF (5 mL) at 0 ºC was added a solution of phosphonate **95** (52 mg, 0.1 mmol) and aldehyde **75** (36 mg, 0.1 mmol) in THF (1 mL), and the reaction was allowed to stir for 1 h at 0 ºC. After standard workup, the resulting oil was purified by flash column chromatography (50% EtOAc/hexanes) to afford stilbene **113** (43 mg, 62%) as a colorless oil: ^{1}H NMR δ 6.99–6.83 (m, 6H), 6.59–6.58 (m, 2H), 5.25 (s, 4H), 3.89 (s, 3H), 3.53 (s, 6H), 3.45–3.40 (m, 1H), 2.72–2.69 (m, 2H), 2.51–2.44 (m, 1H), 2.16–2.11 (m, 1H), 1.89–1.59 (m, 4H), 1.25 (s, 3H), 1.11 (d, *J* = 6.6 Hz, 6H), 1.10 (s, 3H); ^{13}C NMR δ 158.8 (2C), 148.9, 142.8, 142.6, 136.8, 128.8, 128.6, 126.1, 122.6, 120.6, 117.2, 116.6, 106.8, 106.7 (2C), 94.8 (2C), 78.0, 77.0, 56.2 (2C), 55.9, 46.7, 38.3, 37.6, 33.1, 28.2, 27.3, 23.1, 22.7 (2C), 19.8, 14.3; HRMS (EI^+) calcd for $C_{34}H_{46}O_7$ [M^+] 566.3244; found 566.3245.

Epoxide 130. To a solution of compound **77** (5.5 g, 16.0 mmol) in THF (100 mL) at –20 ºC was added TMEDA (2.4 mL, 16.0 mmol) and *n*BuLi (7.6 mL, 2.4 M soln in hexane, 18.2 mmol), and the reaction was allowed to warm to 0 ºC over 1 h. The solution was cooled to –20 ºC, CuBr•DMS (3 g, 14.6 mmol) was added in one portion, and the resulting solution was allowed to stir for 1 h at –20 ºC. To the solution was added bromide **129** (1.5 eq.) and the resulting solution was allowed to stir for 2 h. After standard workup, the resulting oil was purified by column chromatography (10% EtOAc/hexanes) to afford compound **130** (3.4 g, 43%) as a colorless oil: ^{1}H NMR δ 6.75 (s, 2H), 5.25 (t, *J* = 7.1 Hz, 1H), 5.17 (s, 4H), 4.67 (s, 2H), 3.46 (s, 6H), 3.38 (d, *J* = 7.1 Hz, 2H), 2.66 (t, *J* = 6.2 Hz, 1H), 2.13–2.04 (m, 2H), 1.79 (s, 3H), 1.66–1.54 (m, 2H), 1.23 (s, 3H), 1.21 (s, 3H), 0.94 (s, 9H), 0.09 (s, 6H); ^{13}C NMR δ 155.4 (2C), 140.5, 133.0, 123.5, 117.9, 105.3 (2C), 94.2 (2C), 64.6, 63.9, 57.9, 55.5 (2C), 36.1, 27.1, 25.7,

24.5 (3C), 22.3, 18.4, 18.1, 15.8, –5.5 (2C); HRMS (EI) calcd for $C_{27}H_{46}O_6Si$ [M^+] 494.3064; found 494.3075.

Aldehyde 131. To a solution of epoxide **130** (2.05 g, 4.1 mmol) in THF (50 mL) at rt was added TBAF (17 mL, 1 M soln in THF, 17.0 mmol), and the solution was allowed to stir for 1 h then quenched by addition of H_2O. Following extraction of the aqueous portion with EtOAc, the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to provide the intermediate benzyl alcohol (1.473 g, 94%) as a colorless oil which was carried on without further purification. To a solution of the benzyl alcohol (88 mg, 0.2 mmol) in Et_2O (10 mL) at 0 °C was added slowly a solution of H_5IO_6 (54 mg, 0.2 mmol) in H_2O and THF (1:1 mixture, 10 mL), and the resulting mixture was stirred for 30 min then quenched by addition of sat. $NaHCO_3$. Following extraction of the aqueous portion with EtOAc, the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (50% EtOAC/hexanes) provided the intermediate aldehyde (49 mg, 63%) as a colorless oil. To a solution of the aldehyde (752 mg, 2.2 mmol) in THF (15 mL) was added imidazole (600 mg, 8.8 mmol) and TBSCl (2.5 mmol), and the reaction was allowed to stir at rt for 1 h then quenched by addition of H_2O. Following extraction of the aqueous portion with EtOAc, the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (17% EtOAC/hexanes) provided compound **131** (909 mg, 90%) as a colorless oil: ^{1}H NMR δ 9.72 (t, *J* = 1.8 Hz, 1H), 6.76 (s, 2H), 5.25 (t, *J* = 7.1 Hz, 1H), 5.17 (s, 4H), 4.68 (s, 2H), 3.46 (s, 6H), 3.37 (d, *J* = 7.1 Hz, 2H), 2.48 (td, *J* = 6.4, 1.6 Hz, 2H), 2.28 (t, *J* = 6.4 Hz, 2H), 1.79 (s, 3H), 0.94 (s, 9H), 0.09 (s, 6H); ^{13}C NMR δ 202.8, 155.5 (2C), 140.8, 132.3, 124.1, 117.9, 105.6 (2C), 94.5 (2C), 64.8, 55.9 (2C), 42.1, 31.9, 25.9 (3C), 22.5, 18.3, 16.1, –5.3 (2C).

Alcohol 132. To a solution of aldehyde **131** (909 mg, 2.0 mmol) in EtOH (10 mL) at 0 °C was added $NaBH_4$ (80 mg, 2.0 mmol) in one portion. The resulting mixture

was stirred for 1 h at 0 °C then quenched by slow addition of NH_4Cl (sat.). The mixture was then evaporated to dryness, and water was added to dissolve the resulting solid. Following extraction of the aqueous solution with EtOAc, the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to yield alcohol **132** (849 mg, 93%) as a colorless oil: ^{1}H NMR δ 6.76 (s, 2H), 5.24 (t, *J* = 6.8 Hz, 1H), 5.17 (s, 4H), 4.68 (s, 2H), 3.59 (t, *J* = 6.5 Hz, 2H), 3.46 (s, 6H), 3.38 (d, *J* = 7.1 Hz, 2H), 2.03 (t, *J* = 7.3 Hz, 2H), 1.79 (s, 3H), 1.65 (m, 2H), 1.56 (br s, 1H), 0.94 (s, 9H), 0.09 (s, 6H); ^{13}C NMR δ 155.6 (2C), 140.7, 134.2 (2C), 123.5, 118.3, 105.7, 94.5 (2C), 64.8, 62.9, 55.9 (2C), 36.3, 30.6, 25.9 (3C), 22.5, 18.3, 15.8, –5.3 (2C); HRMS (EI) calcd for $C_{24}H_{42}O_6Si$ [M^+] 454.2751; found 454.2758.

Arene 133. To a solution of alcohol **132** (849 mg, 1.9 mmol) in THF (10 mL) at 0 °C was added NaH (530 mg, 13 mmol) and allyl bromide (0.2 mL, 2.3 mmol). The resulting mixture was allowed to warm to rt and stirred overnight. The reaction was then cooled to 0 °C, quenched by slow addition of H_2O, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), concentrated *in vacuo*, and purified by column chromatography (9% EtOAc in hexanes) to yield allyl ether **133** (722 mg, 78%) as a colorless oil: ^{1}H NMR δ 6.76 (s, 2H), 5.95–5.82 (m, 1H), 5.20 (m, 3H), 5.17 (s, 4H), 4.68 (s, 2H), 3.90 (td, *J* = 5.8, 1.5 Hz, 2H), 3.45 (s, 6H), 3.39 (d, *J* = 7.4 Hz, 2H), 3.35 (t, *J* = 6.4 Hz, 2H), 2.01 (t, *J* = 7.0 Hz, 2H), 1.78 (s, 3H), 1.67 (m, 2H), 0.95 (s, 9H), 0.09 (s, 6H); ^{13}C NMR δ 155.5 (2C), 140.6, 135.0, 133.7 (2C), 123.2, 118.4, 116.5, 105.6, 94.4 (2C), 71.7, 70.0, 64.8, 55.8 (2C), 36.0, 27.9, 25.8 (3C), 22.5, 18.3, 15.8, –5.3 (2C); HRMS (EI) calcd for $C_{27}H_{46}O_6Si$ [M^+] 494.3064; found 494.3074.

Bicycle 134. Compound **133** (244 mg, 0.5 mmol) and TsOH (510 mg, 3.0 mmol) were stirred in MeOH (10 mL) at rt for 2 days, then at 50 °C for 4 h. The reaction was then quenched by addition of $NaHCO_3$ (sat.), the solution was evaporated to dryness, and water was added to dissolve the resulting solid. After the aqueous layer was extracted

with EtOAc, the combined organic layers were washed with brine, dried ($MgSO_4$), concentrated *in vacuo*, and purified by column chromatography (50% EtOAc in hexanes) to yield bicycle **134** (35 mg, 24%) as a colorless oil: ^{1}H NMR δ 6.35 (s, 1H), 6.31 (s, 1H), 5.95–5.82 (m, 1H), 5.20 (m, 2H), 4.45 (s, 2H), 3.95 (td, *J* = 5.6, 1.3 Hz, 2H), 3.44 (m, 2H), 2.60 (m, 2H), 1.69 (m, 6H), 1.25 (s, 3H); ^{13}C NMR δ 154.4 (s), 154.2 (s), 139.5 (s), 134.4 (d), 116.7 (t), 107.9 (s), 107.5 (d), 104.6 (d), 75.4 (s), 71.4 (t), 70.2 (t), 64.6 (t), 35.5 (t), 30.0 (t), 23.9 (q), 23.8 (q), 16.2 (t); ^{13}C NMR multiplicities determined by DEPT experiments.

Ester 142. To a solution of phenol **141** (488 mg, 1.6 mmol) in anhydrous acetone (5 mL) was added K_2CO_3 (1.4 g, 10.0 mmol) and MeI (0.13 mL, 2.1 mmol), and the resulting solution was stirred at rt overnight. The reaction was quenched by addition of water, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), concentrated *in vacuo*, and purified by column chromatography (10% EtOAc in hexanes) to yield ester **142** (290 mg, 56%) as a colorless oil: ^{1}H NMR δ 7.52 (dd, *J* = 2.3, 1.3 Hz, 1H), 7.43 (dd, *J* = 2.2, 1.3 Hz, 1H), 7.00 (m, 1H), 5.44 (s, 2H), 4.10 (s, 3H), 4.03 (s, 3H), 3.95 (m, 2H), 1.16 (m, 2H), 0.20 (s, 9H); ^{13}C NMR δ 166.8, 160.5, 158.3, 132.0, 109.7, 107.8, 107.6, 92.9, 66.4, 55.6, 52.2, 18.0, –1.5 (3C).

Benzyl alcohol 143. A solution of ester **142** in THF (3 mL) was added slowly to a mixture of $LiAlH_4$ (26 mg, 0.7 mmol) in THF (5 mL) at 0 °C, and the reaction was stirred at 0 °C for 1 h and then quenched by slow addition of water. The aqueous portion was extracted with EtOAc and the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to yield compound **143** (241mg, 95%) as a colorless oil: ^{1}H NMR δ 6.83 (s, 1H), 6.77 (s, 1H), 6.72 (s, 1H), 5.40 (s, 2H), 4.81 (s, 2H), 3.96 (s, 3H), 3.93 (m, 2H), 2.4 (br s, 1H), 1.15 (m, 2H), 0.20 (s, 9H); ^{13}C NMR δ 160.8, 158.6, 143.4, 106.6, 105.5, 101.5, 92.8, 66.2, 66.1, 55.2, 17.9, –1.5 (3C).

Arene 144. To a solution of benzyl alcohol **143** (241 mg, 0.9 mmol) in CH_2Cl_2 (5 mL) was added imidazole (300 mg, 4.4 mmol) and TBSCl (150 mg, 1.0 mmol), the reaction was allowed to stir at rt for 1 h, and then quenched by addition of H_2O. Following extraction of the aqueous portion with EtOAc, the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Final purification by column chromatography (4% EtOAC/hexanes) provided compound **144** (238 mg, 70%) as a colorless oil: ^{1}H NMR δ 6.63–6.62 (m, 1H), 6.57–6.52 (m, 1H), 6.49 (t, *J* = 2.3 Hz, 1H), 5.20 (s, 2H), 4.69 (s, 2H), 3.79 (s, 3H), 3.77–3.73 (m, 2H), 0.97–0.94 (m, 2H), 0.94 (s, 9H), 0.09 (s, 6H), 0.01 (s, 9H); ^{13}C NMR 160.6, 158.8, 144.0, 106.0, 104.9, 100.9, 93.0, 66.1, 64.8, 55.2, 25.9 (3C), 18.4, 18.0, –1.4 (3C), –5.3 (2C).

Benzyl alcohol 146. To a solution of benzyl alcohol **104** (4.2 g, 18.4 mmol) in THF at –20 ºC was added TMEDA (1.8 mL, 18.4 mmol) and *n*–BuLi (12.3 mL, 2.4 M in hexane, 29.5 mmol), and the reaction was stirred for 1 h. Solid CuBr•DMS (4.3 g, 20.9 mmol) was added in one portion and the resulting solution was stirred for 1 h. The solution was then treated with freshly prepared bromide **139** (4.3 g, 12.5 mmol) and stirred for 2 h. Standard workup and purification of the crude residue by flash column chromatography (40% EtOAc/hexanes) afforded compound **146** (1.2 g, 19%) as a colorless oil: ^{1}H NMR δ 6.77 (s, 2H), 5.37–5.32 (m, 1H), 5.23–5.18 (m, 1H), 4.18 (s, 4H), 4.59 (s, 2H), 3.97 (s, 2H), 3.45 (s, 6H), 3.38 (d, *J* = 7 Hz, 2H), 2.44 (br s, 1H), 2.13–2.08 (m, 2H), 2.03–1.99 (m, 2H), 1.79 (s, 3H), 1.57 (s, 3H), 0.90 (s, 9H), 0.04 (s, 6H); ^{13}C NMR δ 155.6 (2C), 140.1, 134.4 (2C), 134.1, 124.4, 122.6, 119.1, 106.3, 94.2 (2C), 68.6 (2C), 65.2, 55.9, 39.4 , 26.2, 26.1 (3C), 22.4, 18.3, 15.9, 13.3, –5.4 (2C).

Phosphonate 147. Methanesulfonyl chloride (0.3 mL, 3.6 mmol) was added dropwise to a solution of alcohol **146** (1.2 g, 2.4 mmol) and Et_3N (1.0 mL, 7.2 mmol) in CH_2Cl_2, and the solution was stirred at 0 °C for 1 h. The reaction mixture was quenched by addition of H_2O, extracted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Without further purification, the resulting residue was dissolved

in acetone (15 mL) and NaI (1.1 g, 7.3 mmol) was added in one portion. After the mixture had stirred for 2 h, it was quenched by addition of H_2O, extracted with EtOAc, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting yellow oil was added to triethyl phosphite (5 mL) and the solution was heated at 50 °C for 4 h. Following a quench by addition of H_2O, the aqueous layer was extracted with EtOAc and the combined organic layers were dried ($MgSO_4$), concentrated *in vacuo*, and purified by column chromatography (50% EtOAc) to yield phosphonate **147** (494 mg, 33%) as a colorless oil: ^{1}H NMR δ 6.70 (d, J = 2.7 Hz, 2H), 5.37–5.32 (m, 1H), 5.22–5.17 (m, 1H), 5.17 (s, 4H), 4.11–3.98 (m, 4H), 3.97 (s, 2H), 3.45 (s, 6H), 3.36 (d, J = 7.1 Hz, 2H), 3.08 (d, J = 21.5 Hz, 2H), 2.13–2.05 (m, 2H), 1.99–1.94 (m, 2H), 1.77 (s, 3H), 1.57 (s, 3H), 1.27 (t, J = 7.0 Hz, 6H), 0.91 (s, 9H), 0.05 (s, 6H); ^{13}C NMR δ 155.6 (d, J_{CP} = 3.6 Hz, 2C), 134.4, 134.2 (2C), 130.3 (d, J_{CP} = 7.2 Hz), 124.5, 122.7, 118.7 (d, J_{CP} = 4.1 Hz), 109.5 (d, J_{CP} = 6.6 Hz), 94.4 (2C), 68.7 (2C), 62.1 (d, J_{CP} = 6.7 Hz, 2C), 55.9, 39.5, 33.8 (d, J = 138.3 Hz), 26.2, 25.9 (3C), 22.4, 18.4, 16.4, 16.3, 16.0, 13.4, –5.3 (2C); ^{31}P NMR δ +26.4.

Phosphonate 148. To a solution of phosphonate **147** (494 mg, 0.08 mmol) in MeOH (10 mL) was added TsOH (1.4 g, 8.1 mmol) and the reaction was allowed to stir for 12 h. After the reaction was quenched by addition of $NaHCO_3$ (sat.), the solvent was removed *in vacuo* and the resulting oil was carried on without further purification. To this material in CH_2Cl_2 (10 mL) was added imidazole (600 mg, 8.8 mmol) and TBSCl (720 mg, 4.8 mmol), and the reaction was allowed to stir for 2 h at rt. After the reaction was quenched by addition of H_2O, the aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried ($MgSO_4$), concentrated *in vacuo*, and purified by column chromatography (38% EtOAc in hexanes) to yield phosphonate **148** (284 mg, 47%) as a colorless oil: ^{1}H NMR δ 6.58 (d, J = 2.4 Hz, 2H), 5.27 (t, J = 7.1 Hz, 1H), 5.06 (t, J = 5.4 Hz, 1H), 4.00–4.13 (m, 4H), 4.13 (s, 2H), 3.19 (d, J = 5.5 Hz, 2H), 2.93 (d, J = 21.5 Hz, 2H), 1.90–1.97 (m, 2H), 1.90–1.85 (m, 2H), 1.61 (s, 3H), 1.49 (s, 3H), 1.16 (t, J = 7.1 Hz, 6H), 0.91 (s, 18H), 0.81 (s, 9H), 0.14 (s, 12H), –

0.04 (s, 6H); ^{13}C NMR δ 154.3 (d, J_{CP} = 3.0 Hz, 2C), 139.9, 133.7 (2C), 129.0 (d, J_{CP} = 8.8 Hz), 124.6, 123.7 (d, J_{CP} = 2.0 Hz), 122.1 (d, J_{CP} = 3.6 Hz), 113.2 (d, J_{CP} = 6.8 Hz), 68.6, 61.7 (d, J_{CP} = 6.7 Hz, 2C), 39.0, 33.3 (d, J_{CP} = 138.6 Hz), 30.5, 26.1, 25.7 (3C), 25.5 (6C), 18.1 (d, J_{CP} = 0.3 Hz), 18.0 (2C), 16.2 (d, J_{CP} = 1.3 Hz, 2C), 16.1, 13.0, –4.38 (d, J_{CP} = 1.4 Hz, 4C), –5.53 (2C); ^{31}P NMR δ +26.6.

Diester 156. To a solution of benzyl alcohol **154** (124 mg, 1.0 mmol) and hexanoic acid (**155**, 0.1 mL, 1.0 mmol) in THF (3 mL) at 0 °C was added PPh_3 (264 mg, 1.0 mmol) and DIAD (0.2 mL, 1.0 mmol) in THF (2 mL), and the reaction was allowed to warm to rt and stirred for 12 h. The reaction mixture was concentrated and the resulting oil was purified by column chromatography (20% EtOAc/hexanes) to afford diester **156** (78 mg, 49%) as a pale oil: ^{1}H NMR δ 7.23 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 5.05 (s, 2H), 2.39–2.31 (m, 4H), 1.68–1.58 (m, 4H), 1.34–1.22 (m, 8H), 0.92–0.84 (m, 6H).

Benzyl alcohol 158. To a solution of known benzyl alcohol **157**[61] (2.2 g, 11.3 mmol) in THF (150 mL) at –20 ºC was added TMEDA (3.4 mL, 22.7 mmol) and *n*BuLi (11.3 mL, 2.3 M in hexane, 26.0 mmol) and the reaction was allowed to stir for 1 h. Solid CuBr·DMS (4.5 g, 21.9 mmol) was added in one portion and the resulting mixture was stirred for 1 h then treated with freshly prepared bromide **139** (1.1 eq). After stirring for an additional 2 h, the reaction worked up via standard conditions, and purification of the resulting oil by flash column chromatography (40% EtOAc/hexanes) afforded compound **158** (1.8 g, 34%) as a colorless oil: ^{1}H NMR δ 6.71 (s, 1H), 6.61 (s, 1H), 5.37–5.32 (m, 1H), 5.23–5.17 (m, 1H), 5.18 (s, 2H), 4.61 (s, 2H), 3.97 (s, 2H), 3.82 (s, 3H), 3.46 (s, 3H), 3.35 (d, J = 7.1 Hz, 2H), 2.17–2.04 (m, 4H), 1.77 (s, 3H), 1.57 (s, 3H), 0.90 (s, 9H), 0.04 (s, 6H); ^{13}C NMR δ 158.2, 155.5, 139.9, 134.5, 134.1, 124.5, 122.7, 118.4, 105.5, 103.2, 94.2, 68.7, 65.6, 55.9, 55.7, 39.5, 26.2, 25.9 (3C), 22.3, 18.4, 16.0, 13.3, –5.3 (2C); HRMS (EI$^+$) calcd for $C_{26}H_{44}O_5Si$ [M$^+$] 464.2958; found 464.2952.

Phosphonate 159. Methanesulfonyl chloride (0.4 mL, 5.2 mmol) was added dropwise to a solution of alcohol **158** (1.8 g, 3.9 mmol) and Et_3N (0.8 mL, 5.9 mmol) in CH_2Cl_2 (25 mL) at 0 °C, and the reaction was allowed to stir for 1 h, then quenched by addition of H_2O. The aqueous layer was extracted with EtOAc, washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was dissolved in acetone (10 mL), and NaI (1.0 g, 11.5 mmol) was added in one portion. After the mixture was allowed to stir for 12 h, it was quenched by addition of H_2O and extracted with EtOAc. The combined extracts were washed with $Na_2S_2O_3$ (sat.) until the color had disappeared, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting yellow oil was added to triethyl phosphite (3 mL, excess) and the solution was heated at reflux overnight. After concentration *in vacuo*, the crude phosphonate was dissolved in THF (20 mL) and treated with TBAF (7.8 mL, 1 M in THF, 7.8 mmol). After the solution was stirred for 3 h, standard workup, concentration *in vacuo*, and purification by column chromatography (100% EtOAc) provided phosphonate **159** (1.3 g, 69%) as a colorless oil: ^{1}H NMR δ 6.64 (s, 1H), 6.53 (s, 1H), 5.37–5.31 (m, 1H), 5.14–5.00 (m, 1H), 5.12 (s, 2H), 4.09–3.99 (m, 4H), 3.86 (s, 2H), 3.81 (s, 3H), 3.45 (s, 3H), 3.33 (d, J = 6.2 Hz, 2H), 3.10 (d, J_{PH} = 21.5 Hz, 2H), 2.46 (br s, 1H), 2.10–1.95 (m, 4H), 1.76 (s, 3H), 1.57 (s, 3H), 1.27 (t, J_{PH} = 12.8 Hz, 6H); ^{13}C NMR δ 157.8 (d, J_{CP} = 3.3 Hz), 155.3 (d, J_{CP} = 3.3 Hz), 134.7, 133.8, 129.8 (d, J_{CP} = 9.1 Hz), 125.4, 122.9 (d, J_{CP} = 1.6 Hz), 117.7 (d, J_{CP} = 4.5 Hz), 108.6 (d, J_{CP} = 4.8 Hz), 106.2 (d, J_{CP} = 6.2 Hz), 94.3, 68.4, 62.0 (d, J_{CP} = 6.5 Hz, 2C), 55.8, 55.5, 39.2, 33.7 (d, J_{CP} = 138.6 Hz), 25.8, 22.1, 16.3 (d, J_{CP} = 6.1 Hz, 2C), 15.8, 13.4; ^{31}P NMR δ 27.3; HRMS (EI$^+$) calcd for $C_{24}H_{39}O_7P$ [M^+] 470.2412; found 470.2413.

Stilbene 160. To a solution of NaH (312 mg, 60% dispersion in oil, 8.5 mmol) and 15–crown–5 (1 drop, cat.) in THF (12 mL) at 0 ºC was added a solution of phosphonate **159** (333 mg, 0.7 mmol) and aldehyde **75** (243 mg, 0.8 mmol) in THF (1 mL). Following addition, the reaction was allowed to warm to rt and stirred for 12 h. The reaction mixture was quenched via dropwise addition of H_2O, and the aqueous layer

extracted with EtOAc, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (65% EtOAc/hexanes) afforded compound **160** (311 mg, 71%) as a yellow oil: ^{1}H NMR δ 7.00–6.87 (m, 5H), 6.73 (s, 1H), 5.36–5.31 (m, 1H), 5.23 (s, 2H), 5.22–5.18 (m, 1H), 3.94 (s, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.50 (s, 3H), 3.48–3.41 (m, 1H), 3.37 (d, *J* = 7.1 Hz, 2H), 2.74–2.71 (m, 2H), 2.16–2.11 (m, 3H), 2.02–1.97 (m, 2H), 1.90–1.84 (m, 2H), 1.78 (s, 3H), 1.74–1.68 (m, 2H), 1.63 (s, 3H) 1.26 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 158.0, 155.5, 148.7, 142.4, 136.4, 134.4, 134.0, 128.7, 128.0, 126.3, 125.7, 122.8, 122.4, 120.4, 118.4, 106.6, 105.2, 102.3, 94.3, 77.6, 76.9, 68.6, 55.8, 55.7, 55.5, 46.6, 39.2, 38.2, 37.5, 28.0, 27.2, 25.9, 22.9, 22.3, 19.7, 15.8, 14.1, 13.5; HRMS (EI^+) calcd for $C_{38}H_{52}O_7$ [M^+] 620.3713; found 620.3699.

Schweinfurthin analogue 150. To a solution of stilbene **160** (30 mg, 0.05 mmol) in MeOH (2 mL) at rt was added TsOH (48 mg, 0.3 mmol), and the reaction was allowed to stir for 16 h. After the reaction was quenched by addition of $NaHCO_3$ (sat.), the solvent was removed *in vacuo* and H_2O was added. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to provide phenol **150** (16 mg, 57%) as a yellow oil which used without further purification: ^{1}H NMR δ 6.97–6.81 (m, 4H), 6.64 (s, 1H), 6.60 (s, 1H), 5.27–5.24 (m, 2H), 3.98 (s, 2H), 3.89 (s, 3H), 3.85 (s, 3H), 3.46–3.41 (m, 3H), 2.73–2.70 (m, 2H), 2.26–2.15 (m, 4H), 2.12–2.08 (m, 1H), 1.90–1.85 (m, 2H), 1.78 (s, 3H), 1.76–1.86 (m, 2H), 1.66 (s, 3H), 1.25 (s, 3H), 1.10 (s, 3H), 0.86 (s, 3H); ^{13}C NMR δ 157.9, 155.5, 148.9, 142.6, 142.5, 137.1, 136.0, 128.8, 126.1, 126.1, 125.0, 122.8, 122.6, 120.5, 106.9, 106.8, 106.8, 101.4, 78.0, 77.1, 68.9, 56.0, 55.8, 46.7, 39.2, 38.4, 37.6, 28.2, 27.3, 25.0, 23.1, 22.3, 19.8, 15.6, 14.3, 13.7; HRMS (EI^+) calcd for $C_{36}H_{48}O_6$ [M^+] 576.3451.

Biotinylated prenol 162. To a solution of D–biotin (**118**, 183 mg, 0.8 mmol), EDC•HCl (175 mg, 0.9 mmol), and HOBt (120 mg, 0.9 mmol) in DMF (3 mL) at rt was added a solution of 3–methyl–2–buten–1–ol (**161**, 0.1 mL, 1.0 mmol) and TEA (0.6 mL,

4.5 mmol) in DMF (1 mL), the reaction was allowed to stir for 16 h, and then diluted with CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2 and the organic layers were combined, dried ($MgSO_4$), concentrated *in vacuo*, and purified by flash column chromatography (10% MeOH/$CHCl_3$) to afford compound **162** (72 mg, 29%) as a colorless solid: ^{1}H NMR δ (CD_3OD) 5.35–5.29 (m, 1H), 4.56 (d, *J* = 7.3 Hz, 2H), 4.48 (dd, *J* = 7.9, 4.9 Hz, 1H), 4.30–4.26 (m, 1H), 3.21–3.15 (m, 1H), 2.94–2.88 (m, 1H), 2.71–2.67 (m, 1H), 2.31 (t, *J* = 7.3 Hz, 2H), 1.74 (s, 3H), 1.70 (s, 3H), 1.69–1.51 (m, 4H), 1.47–1.36 (m, 2H).

Biotinylated alcohol 163. In a manner similar to the preparation of compound **162**, to a solution of D–biotin (**118**, 200 mg, 0.8 mmol), EDC•HCl (180 mg, 1.0 mmol), and HOBt (130 mg, 1.0 mmol) in DMF (3 mL) was added a solution of alcohol **136** (250 mg, 1.2 mmol) in DMF (1 mL), and the reaction was allowed to stir for 16 h. Following standard workup and purification via column chromatography (11% MeOH/$CHCl_3$), compound **163** (51 mg, 16%) was obtained as a white solid: ^{1}H NMR (CD_3OD) δ 5.48–5.43 (m, 1H), 5.38–5.32 (m, 1H), 4.59 (d, *J* = 7.1 Hz, 2H), 4.52–4.48 (m, 1H), 4.47 (s, 2H), 4.33–4.29 (m, 1H), 3.24–3.18 (m, 1H), 2.94 (dd, *J* = 12.7, 4.9 Hz, 1H), 2.74–2.69 (m, 1H), 2.37 (t, *J* = 7.2 Hz, 2H), 2.24–2.17 (m, 2H), 2.13–2.08 (m, 2H), 2.03 (s, 3H), 1.79–1.70 (m, 2H), 1.73 (s, 3H), 1.67 (s, 3H), 1.66–1.57 (m, 2H), 1.51–1.44 (m, 2H).

Ester 164. To a solution of D–biotin (**118**, 41 mg, 0.2 mmol), EDC•HCl (33 mg, 0.2 mmol), and HOBt (23 mg, 0.2 mmol) in DMF (1 mL) was added a solution of compound **160** (88 mg, 0.1 mmol) and TEA (0.1 mL, 0.9 mmol) in DMF (1 mL), and the reaction was allowed to stir for 16 h then diluted with CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 and the organic layers were combined, dried ($MgSO_4$), concentrated *in vacuo*, and purified by flash column chromatography (5% MeOH/$CHCl_3$) to afford compound **164** (58 mg, 48%) as a colorless solid: ^{1}H NMR δ 6.95–6.87 (m, 5H), 6.72 (s, 1H), 5.99 (br s, 1H), 5.42 (br s, 1H), 5.44–5.40 (m, 1H), 5.23 (s, 2H), 5.22–5.19 (m, 1H), 4.46–4.45 (m, 1H), 4.41 (s, 2H), 4.29–4.25 (m, 1H), 3.90 (s, 3H), 3.87 (s,

3H), 3.50 (s, 3H), 3.44–3.40 (m, 1H), 3.37 (d, *J* = 7.1 Hz, 2H), 3.16–3.09 (m, 1H), 2.90–2.84 (m, 1H), 2.73–2.70 (m, 3H), 2.34 (t, *J* = 7.5 Hz, 2H), 2.16–2.08 (m, 3H), 2.01–1.96 (m, 2H), 1.88–1.85 (m, 2H), 1.78 (s, 3H), 1.73–1.55 (m, 6H), 1.61 (s, 3H), 1.48–1.39 (m, 2H), 1.25 (s, 3H), 1.10 (s, 3H), 0.88 (s, 3H); ^{13}C NMR δ 173.5, 158.2, 155.7, 148.8, 142.5, 136.5, 134.0, 129.7, 129.6, 128.8, 128.1, 126.4, 122.9, 122.5, 120.4, 118.4, 106.7, 105.2, 102.3, 99.9, 94.3, 77.8, 77.2, 70.1, 61.8, 60.0, 55.9, 55.8, 55.6, 53.7, 46.6, 40.4, 39.1, 38.3, 37.6, 33.8, 30.9, 29.2, 28.3, 28.1, 27.3, 26.3, 24.7, 23.0, 22.3, 15.9, 14.2, 13.9; HRMS (EI$^+$) calcd for $C_{48}H_{66}N_2O_9S$ [M$^+$] 846.4489; found 846.4483.

Phthalimide 165. To a solution of PPh_3 (37 mg, 0.1 mmol), DIAD (0.03 mL, 0.2 mmol), and phthalimide (17 mg, 0.1 mmol) in THF (2 mL) at 0 ºC was added a solution of stilbene **160** (80 mg, 0.1 mmol) in THF (1 mL), and the reaction was allowed to warm to rt and stirred for 12 h. Following concentration *in vacuo*, the material was diluted with CH_2Cl_2, washed with 2N NaOH (2x5 mL) and brine, dried (Na_2SO_4), concentrated, and purified by column chromatography (60% EtOAc/hexanes) to afford compound **165** (56 mg, 58%) as a pale solid: ^{1}H NMR δ 7.84–7.82 (m, 2H), 7.70–7.68 (m, 2H), 6.98–6.86 (m, 5H), 6.71 (s, 1H), 5.36 (t, *J* = 6.9 Hz, 1H), 5.22 (s, 2H), 5.21–5.17 (m, 1H), 4.15 (s, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.49 (s, 3H), 3.45–3.40 (m, 1H), 3.34 (d, *J* = 7.1 Hz, 2H), 2.72 (d, *J* = 8.9 Hz, 2H), 2.14–2.04 (m, 2H), 1.98–1.93 (m, 2H), 1.89–1.83 (m, 3H), 1.76 (s, 3H), 1.73–1.67 (m, 2H), 1.61 (s, 3H), 1.25 (s, 3H), 1.10 (s, 3H), 0.88 (s, 3H); ^{13}C NMR δ 168.2 (2C), 158.2, 155.8, 148.9, 142.6, 136.5, 134.2, 133.8, 132.0 (2C), 129.0 (2C), 128.9, 128.1, 127.8, 126.6, 123.1 (2C), 122.8, 122.6, 120.4, 118.6, 106.9, 105.3, 102.5, 94.5, 77.9, 77.0, 55.9, 55.8, 55.7, 46.7, 45.0, 39.2, 38.3, 37.6, 28.2, 27.3, 26.5, 23.1, 22.4, 19.8, 16.0, 14.4, 14.2; HRMS (EI$^+$) calcd for $C_{46}H_{55}NO_8$ [M$^+$] 749.3928; found 749.3938.

Amide 166. To a solution of phthalimide **165** (42 mg, 0.06 mmol) in MeOH (2 mL) at rt was added hydrazine hydrate (0.01 mL, 0.3 mmol), and the solution was heated at reflux for 2 h. After concentration *in vacuo*, the resulting white solid was dissolved in

1 N NaOH. The aqueous portion was extracted 5 times with CH_2Cl_2, and the organic layers were combined, washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was dissolved in MeOH (0.5 mL), and a solution of D–biotin (**118**, 14 mg, 0.06 mmol) and EDC·HCl (14 mg, 0.07 mmol) in CH_3CN (0.5 mL) was added. After the resulting solution had stirred for 3 h, it was concentrated *in vacuo*, and the resulting material was suspended in MeOH, filtered through Celite, concentrated *in vacuo*, and purified by flash column chromatography (5–10% MeOH/$CHCl_3$) to give MOM–protected stilbene **166** (28 mg, 60%) as a white semi–solid: ^{1}H NMR (CD_3OD) δ 7.03–6.80 (m, 6H), 5.26–5.19 (m, 2H), 5.23 (s, 2H), 4.43–4.40 (m, 1H), 4.23–4.20 (m, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.64 (br s, 2H), 3.48 (s, 3H), 3.36–3.33 (m, 3H), 3.14–3.09 (m, 1H), 2.90–2.83 (m, 1H), 2.71–2.63 (m, 3H), 2.12–1.97 (m, 5H), 1.82–1.56 (m, 10H), 1.78 (s, 3H), 1.54 (s, 3H), 1.45–1.36 (m, 2H), 1.21 (s, 3H), 1.09 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 175.8, 166.0, 159.6, 157.0, 150.1, 143.8, 138.6, 134.9, 132.6, 130.6, 129.4, 127.6, 126.9, 124.6, 124.1, 122.0, 119.5, 108.8, 108.4, 106.4, 95.7, 79.0, 78.7, 78.2, 63.3, 63.3, 61.6, 57.0, 56.9, 56.5, 48.4, 41.0, 40.5, 39.5, 38.9, 36.8, 32.1, 30.7, 29.8, 29.0, 27.9, 27.3, 24.1, 23.3, 20.3, 16.3, 14.9, 14.6; HRMS (ES^+) calcd for $C_{48}H_{68}N_3O_8S$ $[M+H]^+$ 846.4727; found 846.4724.

Amide 46. To a solution of compound **166** in MeOH (0.8 mL) was added TsOH (51 mg, 0.3 mmol), and the reaction was allowed to stir for 12 h. After $NaHCO_3$ (sat.) was added to quench the reaction, standard workup and filtration through a silica pad provided biotinylated **46** (35 mg, 71%) as a colorless semi–solid: ^{1}H NMR (CD_3OD) δ 7.00–6.85 (m, 4H), 6.65 (s, 2H), 5.27–5.21 (m, 2H), 4.43–4.39 (m, 1H), 4.26–4.20 (m, 1H), 3.84 (s, 6H), 3.66–3.60 (m, 2H), 3.34–3.33 (m, 3H), 3.15–3.08 (m, 1H), 2.90–2.83 (dd, J = 12.8, 4.5 Hz, 1H), 2.76–2.65 (m, 3H), 2.21–2.00 (m, 7H), 1.80–1.55 (m, 8H), 1.78 (s, 3H), 1.58 (s, 3H), 1.44–1.39 (m, 2H), 1.22 (s, 3H), 1.10 (s, 3H), 0.88 (s, 3H); ^{13}C NMR δ 176.6, 166.7, 160.7, 157.7, 150.8, 144.5, 138.6, 135.4, 133.2, 131.4, 129.7, 128.5, 127.7, 125.6, 124.8, 122.7, 118.0, 109.1, 108.0, 102.5, 80.2, 79.4, 79.0, 64.1, 62.3, 57.7,

57.3, 57.0, 48.3, 41.8, 41.3, 40.3, 39.7, 37.6, 30.6, 30.3, 29.8, 28.7, 28.0, 27.8, 24.9, 24.0, 21.1, 17.0, 15.7, 15.4; HRMS (ES^+) calcd for $C_{46}H_{63}N_3O_7S$ $[M+Na]^+$ 824.4284; found 824.4297.

Stilbene 169. In a manner similar to the preparation of stilbene **160**, a solution of aldehyde **168** (40 mg, 0.2 mmol) and phosphonate **159** (69 mg, 0.2 mmol) in THF (1 mL) were added to a suspension of NaH (41 mg, 60% dispersion in oil, 1.1 mmol) and 15–crown–5 (1 drop, cat.) in THF (3 mL) at 0 ºC, and the mixture was allowed to stir for 2 h. Following standard workup and purification by column chromatography (45% EtOAc/hexanes), compound **169** (55 mg, 78%) was obtained as a yellow oil: ^{1}H NMR δ 7.07–6.84 (m, 6H), 6.74 (s, 1H), 5.34 (t, J = 6.9 Hz, 1H), 5.24 (s, 2H), 5.20 (t, J = 7.1 Hz, 1H), 3.93 (s, 3H), 3.93 (s, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 3.50 (s, 3H), 3.37 (d, J = 7.1 Hz, 2H), 2.15–2.08 (m, 2H), 2.02–1.97 (m, 2H), 1.78 (s, 3H), 1.62 (s, 3H); ^{13}C NMR δ 158.1, 155.7, 148.9, 148.7, 136.4, 134.6, 134.1, 130.3, 127.8, 126.9, 126.0, 122.9, 119.7, 118.7, 111.0, 108.4, 105.4, 102.4, 94.4, 68.9, 56.0, 55.8, 55.7, 55.7, 39.3, 26.0, 22.4, 15.9, 13.6; HRMS (EI^+) calcd for $C_{29}H_{38}O_6$ $[M^+]$ 482.2668; found 482.2675.

Phthalimide 200. In a manner similar to the preparation of phthalimide **165**, a solution of stilbene **169** (59 mg, 0.1 mmol) in THF (1 mL) was added to a mixture of PPh_3 (50 mg, 0.2 mmol), DIAD (0.04 mL, 0.2 mmol), and phthalimide (29 mg, 0.2 mmol) in THF (2 mL) at 0 ºC. After the reaction was allowed to stir at rt for 12 h, standard workup and purification by column chromatography (35% EtOAc/hexanes) gave compound **200** (66 mg, 83%) as a pale solid: ^{1}H NMR δ 7.87–7.80 (m, 2H), 7.73–7.68 (m, 2H), 7.07–6.83 (m, 6H), 6.72 (s, 1H), 5.36 (t, *J* = 6.8 Hz, 1H), 5.23 (s, 2H), 5.19 (t, *J* = 7.3 Hz, 1H), 4.15 (s, 2H), 3.94 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 3.49 (s, 3H), 3.35 (d, *J* = 7.1 Hz, 2H), 2.12–2.04 (m, 2H), 1.98–1.93 (m, 2H), 1.75 (s, 3H), 1.61 (s, 3H); ^{13}C NMR δ 168.2 (2C), 158.3, 155.8, 149.2, 148.9, 136.4, 134.2, 133.8, 132.1 (2C), 130.5, 129.0 (2C), 127.9, 127.2, 127.0, 123.2 (2C), 122.9, 119.8, 118.9, 111.3, 108.8,

105.5, 102.6, 94.5, 55.9, 55.9, 55.8, 55.7, 45.0, 39.3, 26.6, 22.4, 16.0, 14.5; HRMS (EI^+) calcd for $C_{37}H_{41}NO_7$ [M^+] 611.2883; found 611.2884.

Preparation of Amide 170 and Compound 171. To a solution of phthalimide **200** (62 mg, 0.1 mmol) in MeOH (2 mL) at rt was added hydrazine hydrate (0.02 mL, 0.4 mmol), the solution was heated at reflux for 2 h, and then allowed to cool to rt and stirred overnight. After concentration *in vacuo*, the resulting white solid was dissolved in 1 N NaOH. The aqueous portion was extracted 5 times with CH_2Cl_2, and the organic layers were combined, washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was dissolved in MeOH (0.6 mL), and a solution of D–biotin (**118**, 29 mg, 0.1 mmol) and EDC·HCl (30 mg, 0.1 mmol) in CH_3CN (0.6 mL) was added. After the resulting solution had stirred for 3 h, it was concentrated *in vacuo*. The resulting material was suspended in MeOH, filtered through Celite, concentrated *in vacuo*, and purified by flash column chromatography (5–10% MeOH/$CHCl_3$) to give MOM–protected stilbene **170** as a mixture along with compound **171**: ^{1}H NMR ($CDCl_3$) δ 7.05–6.82 (m, 6H), 6.71 (s, 1H), 6.66 (br s, 1H), 6.24 (br s, 0.7H), 5.96 (t, *J* = 5.4 Hz, 1H), 5.90 (br s, 0.7H), 5.74 (br s, 0.7H), 5.21 (s, 2H), 5.19–5.14 (m, 1H), 4.48–4.41 (m, 1.7H), 4.28–4.20 (m, 1.8H), 3.93 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H), 3.69–3.68 (m, 2H), 3.64 (s, 3H), 3.48 (s, 3H), 3.34 (d, *J* = 7.1 Hz, 2H), 3.15–3.05 (m, 2H), 2.89–2.80 (m, 2H), 2.72–2.65 (m, 2H), 1.98–1.92 (m, 2H), 1.75 (s, 3H), 1.71–1.60 (m, 9H), 1.54 (s, 3H), 1.46–1.31 (m, 5H), 1.30–1.12 (m, 8H), 0.87–0.82 (m, 2H).

Preparation of Amide 167 and Compound 171. To a solution of compound **170** in MeOH (0.8 mL) was added TsOH (51 mg, 0.3 mmol), and the reaction was allowed to stir for 12 h. After $NaHCO_3$ (sat.) was added to quench the reaction, standard workup and purification by column chromatography (5–10% MeOH/$CHCl_3$) provided biotinylated amide **167** as a mixture along with ester **171**: ^{1}H NMR ($CDCl_3$) δ 8.06 (s, 1H), 7.05–6.81 (m, 5H), 6.69–6.68 (m, 2H), 6.57 (s, 1H), 6.12–6.09 (m, 2H), 5.78 (br s, 1H), 5.67 (br s, 1H), 5.18–5.08 (m, 2H), 4.49–4.44 (m, 1H), 4.41–4.37 (m, 1H), 4.29–

4.25 (m, 1H), 4.22–4.18 (m, 1H), 3.93 (s, 3H), 3.98 (s, 3H), 3.83 (s, 3H), 3.76–3.60 (m, 2H), 3.64 (s, 3H), 3.35 (d, *J* = 6.4 Hz, 2H), 3.15–3.00 (m, 2H), 2.89–2.77 (m, 2H), 2.77–2.64 (m, 2H), 2.89–2.77 (m, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.20–2.03 (m, 6H), 1.73 (s, 3H), 1.68–1.56 (m, 9H), 1.53 (s, 3H), 1.47–1.32 (m, 5H).

Stilbene 174. In a manner similar to the preparation of stilbene **160**, aldehyde **173** (22 mg, 0.1 mmol) and phosphonate **159** (36 mg, 0.1 mmol) in THF (1 mL) were added to a solution of NaH (20 mg, 60% dispersion in oil, 0.5 mmol) and 15–crown–5 (1 drop, cat.) in THF (2 mL) at 0 ºC, and the mixture was allowed to stir for 2 h. Standard workup and purification by column chromatography (75% EtOAc/hexanes) afforded compound **174** (24 mg, 58%) as a yellow oil: ^{1}H NMR δ 6.99–6.87 (m, 5H), 6.71 (s, 1H), 5.33 (t, *J* = 6.9 Hz, 1H), 5.22 (s, 2H), 5.23–5.18 (m, 1H), 4.83 (d, *J* = 6.7 Hz, 1H), 4.72 (d, *J* = 6.8 Hz, 1H), 4.33–4.30 (m, 1H), 3.93 (s, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 3.50 (s, 3H), 3.46 (s, 3H), 3.39–3.36 (m, 2H), 3.27 (d, *J* = 3.3 Hz, 1H), 2.85–2.68 (m, 2H), 2.17–2.08 (m, 2H), 2.02–1.94 (m, 3H), 1.81–1.75 (m, 2H), 1.78 (s, 3H), 1.62 (s, 3H), 1.47 (s, 3H), 1.12 (s, 3H), 1.09 (s, 3H); ^{13}C NMR δ 158.2, 155.8, 149.0, 142.3, 136.6, 134.6, 134.0, 128.8, 128.2, 126.5, 126.0, 123.0, 122.8, 120.4, 118.7, 107.0, 105.5, 102.3, 96.9, 94.5, 84.8, 76.4, 68.9, 68.6, 56.0, 56.0, 55.9, 55.7, 47.1, 42.3, 39.3, 37.8, 28.7, 26.0, 22.9, 22.4, 21.5, 16.6, 15.9, 13.6; HRMS (EI^{+}) calcd for $C_{40}H_{56}O_9$ [M^{+}] 680.3924.

Phthalimide 201. In a manner similar to the preparation of phthalimide **165**, a solution of stilbene **174** (55 mg, 0.1 mmol) in THF (2 mL) was added to a mixture of PPh_3 (25 mg, 0.1 mmol), DIAD (0.02 mL, 0.1 mmol), and phthalimide (14 mg, 0.1 mmol) in THF (1 mL) at 0 ºC. After the reaction was allowed to stir at rt for 2 h, standard workup and purification by column chromatography (60% EtOAc/hexanes) gave compound **201** (18 mg, 28%) as a yellow solid: ^{1}H NMR δ 7.85–7.83 (m, 2H), 7.72–7.69 (m, 2H), 6.97–6.86 (m, 5H), 6.71 (s, 1H), 5.35 (t, *J* = 6.8 Hz, 1H), 5.22 (s, 2H), 5.22–5.19 (m, 1H), 4.83 (d, *J* = 6.8 Hz, 1H), 4.72 (d, *J* = 6.9 Hz, 1H), 4.32–4.31 (m, 1H), 4.13 (s, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 3.65 (s, 1H), 3.50 (s, 3H), 3.46 (s, 3H), 3.39–3.36

(m, 2H), 3.27–3.26 (m, 1H), 2.79–2.74 (m, 2H), 2.09–2.04 (m, 2H), 2.00–1.93 (m, 3H), 1.81–1.77 (m, 2H), 1.75 (s, 3H), 1.61 (s, 3H), 1.47 (s, 3H), 1.45–1.21 (m, 14H), 1.12 (s, 3H), 1.07 (s, 3H), 0.90 (s, 3H).

Aldehyde 181. To a solution of allylic alcohol **174** (14 mg, 0.02 mmol) in CH_2Cl_2 (1.5 mL) was added MnO_2 (30 mg, 0.3 mmol) and the reaction was allowed to stir at rt for 5 h. After TLC analysis indicated complete consumption of starting material, the reaction was filtered through Celite and the resulting solution was concentrated *in vacuo* to provide aldehyde **181**, which was carried on without further purification or characterization.

***Z*–enol ether 253**. To a solution of diisopropylamine (0.3 mL, 2.1 mmol) in THF (7 mL) at 0 ºC was added *n*–BuLi (0.9 mL, 2.1 M soln in hexanes, 1.9 mmol), and the solution was cooled to –78 ºC. After 10 minutes, the reaction was treated with a solution of β–keto ester **252** (303 mg, 1.5 mmol) in THF (1 mL), and the reaction was allowed to stir at –78 ºC for 1 h. After addition of MOMCl (0.1 mL, 1.8 mmol), the reaction was allowed to warm to rt and stirred overnight. The reaction was quenched by addition of sat. NH_4Cl, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), concentrated *in vacuo*, and purified by column chromatography (10% EtOAc/hexanes) to give *Z*–enol ether **253** (86 mg, 23%) as a colorless liquid: ^{1}H NMR δ 5.02–4.98 (m, 1H), 4.92 (s, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.41 (s, 3H), 2.89 (d, *J* = 6.9 Hz, 2H), 1.95 (s, 3H), 1.63 (s, 3H), 1.61 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 168.0, 155.9, 132.0, 121.7, 113.8, 94.1, 59.9, 56.3, 27.7, 25.5, 17.6, 15.0, 14.2.

***E*–enol ether 254 and C–alkyl product 255**. To a solution of KHMDS (3.9 mL, 0.5 M soln in toluene, 2.0 mmol) in DMF (7 mL) at –60 ºC was added slowly β–keto ester **252** (295 mg, 1.5 mmol). The reaction was allowed to warm to 0 ºC over 1 h, then cooled to –60 ºC and treated with MOMCl (0.1 mL, 1.8 mmol). The reaction was allowed to warm to rt and stirred for 12 h. Standard workup and purification by column

chromatography (7–10% EtOAc/hexanes) afforded the C–alkyl product **255** (62 mg, 17%) and *E*–enol ether **254** (146 mg, 40%) as colorless liquids. For compound **254**: ^{1}H NMR δ 5.08–5.04 (m, 1H), 5.02 (s, 2H), 4.12 (q, *J* = 7.0 Hz, 2H), 3.38 (s, 3H), 3.03 (d, *J* = 7.1 Hz, 2H), 2.33 (s, 3H), 1.64 (s, 3H), 1.62 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR δ 169.0, 161.4, 130.9, 122.8, 112.3, 92.2, 59.7, 56.1, 25.6, 25.2, 17.6, 14.7, 14.2; HRMS (EI^+) calcd for $C_{13}H_{22}O_4$ [M^+] 242.1518; found 242.1524. For compound **255**, ^{1}H NMR δ 4.89–4.83 (s, 1H), 4.21–4.12 (m, 2H), 3.71 (d, *J* = 9.3 Hz, 1H), 3.63 (d, *J* = 9.3 Hz, 1H), 3.27 (s, 3H), 2.72–2.57 (m, 2H), 2.13 (s, 3H), 1.66 (s, 3H), 1.59 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 203.8, 170.4, 136.1, 117.4, 71.9, 64.2, 61.2, 59.2, 28.7, 26.8, 25.9, 17.6, 14.0.

β–keto ester 194. To a solution of NaH (866 mg, 24 mmol) and 15–crown–5 (1.0 mL, 5 mmol) in THF (250 mL) at 0 ºC was added slowly ethyl acetoacetate (8.8 mL, 70 mmol), and the resulting mixture was allowed to stir for 30 min. Freshly prepared bromide **129**[60] (23 mmol) was added dropwise via cannula, and the resulting mixture was allowed to stir for 4 h. After the reaction was quenched by addition of H_2O and sat. NH_4Cl, the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Removal of the excess ethyl acetoacetate by distillation at reduced pressure followed by final purification via column chromatography (15% EtOAc/hexanes) afforded compound **194** (3.6 g, 54%) as a colorless liquid: ^{1}H NMR δ 4.93 (t, *J* = 5.5 Hz, 1H), 4.04–3.99 (m, 2H), 3.31–3.26 (m, 1H), 2.51–2.49 (m, 1H), 2.42–2.35 (m, 2H), 2.07–1.91 (m, 2H), 2.04 (s, 3H), 1.50–1.39 (m, 2H), 1.49 (s, 3H), 1.14–1.07 (m, 9H); ^{13}C NMR δ 202.2, 169.1, 137.0, 120.1, 63.4, 60.8, 59.2, 57.7, 36.0, 28.7, 27.0, 26.4, 24.4, 18.3, 15.7, 13.7; HRMS (EI^+) calcd for $C_{16}H_{26}O_4$ [M^+] 282.1831; found 282.1835.

***Z*–enol ether 196**. To a solution of diisopropylamine (0.2 mL, 1.4 mmol) in THF at 0 ºC was added *n*–BuLi (0.6 mL, 2.2 M soln in hexanes, 1.4 mmol), and the solution was cooled to –78 ºC. After 10 minutes, the reaction was treated with a solution of β–

keto ester **194** (321 mg, 1.1 mmol) in THF (1 mL), and the reaction was allowed to stir at –78 ºC for 1 h. After addition of MOMCl (0.2 mL, 2.2 mmol), the reaction was allowed to warm to rt and stirred overnight. The reaction was quenched by addition of sat. NH_4Cl, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), concentrated *in vacuo*, and purified by column chromatography (20% EtOAc/hexanes) to give *Z*–enol ether **196** (163 mg, 44%) as a colorless liquid: ^{1}H NMR δ 5.12 (t, *J* = 5.9 Hz, 1H), 4.97 (s, 2H), 4.18 (q, *J* = 7.0 Hz, 2H), 3.46 (s, 3H), 2.96 (d, *J* = 7.0 Hz, 2H), 2.69 (t, *J* = 6.2 Hz, 1H), 2.17–2.06 (m, 2H), 2.00 (s, 3H), 1.67 (s, 3 H), 1.66–1.56 (m, 2H), 1.30–1.26 (m, 9H); ^{13}C NMR δ 167.7, 156.1, 134.6, 122.1, 113.4, 94.0, 63.8, 59.8, 58.0, 56.2, 36.0, 27.5, 27.1, 24.6, 18.5, 15.8, 14.9, 14.1; HRMS (EI$^+$) calcd for $C_{18}H_{30}O_5$ [M$^+$] 326.2093; found 326.2084.

***E*–enol ether 198 and C–alkyl product 202**. To a solution of KHMDS (3.0 mL, 0.5 M soln in toluene, 1.5 mmol) in DMF (7 mL) at –60 ºC was added slowly β–keto ester **194** (331 mg, 1.2 mmol) in DMF (1 mL). The reaction was allowed to warm to 0 ºC over 1 h, then cooled to –60 ºC and treated with MOMCl (0.1 mL, 1.4 mmol). After the reaction was allowed to warm to rt and stirred for 12 h, standard workup and purification by column chromatography (15–18% EtOAc/hexanes) afforded C–alkyl product **202** (105 mg, 27%) as a 1:1 mixture of diastereomers and *E*–enol ether **198** (172 mg, 45%) as a colorless liquid. For *E*–enol ether **198**: ^{1}H NMR δ 5.14 (t, *J* = 7.2 Hz, 1H), 5.07 (s, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.42 (s, 3H), 3.10 (d, *J* = 7.1 Hz, 2H), 2.69 (t, *J* = 6.3 Hz, 1H), 2.39 (s, 3H), 2.15–2.06 (m, 2H), 1.71 (s, 3H), 1.69–1.56 (m, 2H), 1.31–1.25 (m, 9H); ^{13}C NMR δ 168.9, 161.5, 133.6, 123.4, 112.1, 92.2, 64.0, 59.7, 58.2, 56.2, 36.2, 27.2, 25.1, 24.7, 18.6, 15.9, 14.7, 14.2; HRMS (EI$^+$) calcd for $C_{18}H_{30}O_4$ [M$^+$] 326.2093; found 326.2105; for C–alkyl product **202**: ^{1}H NMR δ 4.91 (t, *J* = 6.7 Hz, 1H), 4.19–4.08 (m, 2H), 3.68 (dd, *J* = 9.4, 2.1 Hz, 1H), 3.59 (d, *J* = 9.4 Hz, 1H), 3.24 (s, 3H), 2.72–2.47 (m, 3H), 2.17–1.98 (m, 2H), 2.10 (s, 3H), 1.65–1.51 (m, 2H), 1.59 (s, 3H), 1.25 (s, 3H), 1.22–1.17 (m, 6H); ^{13}C NMR δ 203.5, 170.2, 170.2, 138.7, 138.7, 118.1, 118.1, 71.8,

64.1, 64.0, 63.8, 63.7, 61.2, 61.2, 59.1, 58.2, 58.2, 36.5, 36.5, 28.5, 27.3, 27.3, 26.7, 24.7, 18.6, 15.9, 15.8, 13.9; HRMS (EI^+) calcd for $C_{18}H_{30}O_5$ [M^+] 326.2093; found 326.2094.

Representative cyclization procedure (geranyl): Ketone 265, **Ester 263, Cyclohexene 271, and Protected Ester 270**. To a solution of *E*–enol ether **198** (86 mg, 0.3 mmol) in CH_2Cl_2 (25 mL) at –78 ºC was added BF_3•OEt_2 (0.2 mL, 1.4 mmol), and the solution was allowed to stir for 10 min. The reaction was quenched by addition of TEA (0.2 mL, 1.4 mmol) and the cold bath was removed. After the solution had warmed considerably, H_2O was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), concentrated *in vacuo*, and purified by column chromatography (6–65% EtOAc/hexanes) to afford protected ester **270** (2 mg, 2%) as a colorless oil, cyclohexene **271** (3 mg, 4%) as a pale oil, ketone **265** (11 mg, 13%) as a colorless solid, and ester **263** (33 mg, 44%) as a colorless oil. For bicycle **263**: ^{1}H NMR δ 4.17 (q, *J* = 6.8 Hz, 2H), 3.37 (dd, *J* = 11.2, 4.8 Hz, 1H), 2.40 (dd, *J* = 16.5, 5.2 Hz, 1H), 2.19 (s, 3H), 2.09–1.78 (m, 4H), 1.67–1.53 (m, 2H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.16 (s, 3H), 1.07 (s, 3H), 0.83 (s, 3H); ^{13}C NMR δ 168.7, 162.7, 100.3, 77.9, 77.4, 59.6, 46.3, 38.2, 37.3, 28.0, 27.3, 20.5, 20.1, 19.4, 14.4, 14.2; HRMS (EI^+) calcd for $C_{16}H_{26}O_4$ [M^+] 282.1831; found 282.1832. For ketone **265**: ^{1}H NMR δ 4.20–4.11 (m, 2H), 3.38 (dd, *J* = 11.2, 4.0 Hz, 1H), 2.53 (dd, *J* = 15.8, 4.9 Hz, 1H), 2.35 (s, 3H), 2.09–1.54 (m, 6H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.25 (s, 3H), 1.09 (s, 3H), 0.84 (s, 3H); ^{13}C NMR δ 196.3, 164.0, 92.1, 82.0, 77.8, 63.5, 46.9, 38.4, 37.0, 31.1, 27.9, 27.4, 19.7, 19.0, 14.9, 14.1; HRMS (EI^+) calcd for $C_{16}H_{26}O_4$ [M^+] 282.1831; found 282.1825. For cyclohexene **271**: ^{1}H NMR δ 5.04 (s, 2H), 4.14 (q, *J* = 6.8 Hz, 2H), 3.45 (s, 3H), 3.24 (broad s, 1H), 2.17 (s, 3H), 1.87–1.77 (m, 2H), 1.66 (s, 3H), 1.64–1.57 (m, 2H), 1.27 (t, *J* = 7.6 Hz, 3H), 1.04 (s, 6H). For MOM–protected ester **270**: ^{1}H NMR δ 4.75 (d, *J* = 6.8 Hz, 1H), 4.63 (d, *J* = 6.8 Hz, 1H), 4.18 (q, *J* = 7.3 Hz, 2H), 3.40 (s, 3H), 3.22 (dd, *J* = 10.5, 3.4 Hz, 1H), 2.39 (dd, *J* = 16.4, 4.6 Hz, 1H), 2.19 (s, 3H), 2.08–1.90 (m, 3H), 1.60–1.35 (m, 3H), 1.30 (t, *J* = 7.3 Hz, 3H), 1.16 (s, 3H), 1.03 (s, 3H), 0.85 (s,

3H); ^{13}C NMR δ 168.7, 162.7, 100.3, 96.1, 84.0, 77.4, 59.6, 55.6, 46.7, 38.1, 37.2, 27.4, 25.1, 20.6, 20.1, 19.4, 15.1, 14.5; HRMS (EI$^+$) calcd for $C_{18}H_{30}O_5$ [M$^+$] 326.2093; found 326.2089.

Cyclohexene 269. Using standard cyclization conditions, reaction of *Z*–enol ether **196** (114 mg, 0.4 mmol) with BF_3•OEt_2 (0.2 ml, 1.8 mmol) afforded compound **269** (13 mg, 11%) as a colorless oil: ^{1}H NMR δ 4.90 (d, *J* = 6.9 Hz, 1H), 4.86 (d, *J* = 7.1 Hz, 1H), 4.15 (q, *J* = 7.3 Hz, 2H), 3.47–3.45 (m, 1H), 3.42 (s, 3H), 3.09 (d, *J* = 15.6 Hz, 1H), 2.98 (d, *J* = 15.9 Hz, 1H), 2.11–1.93 (m, 2H), 1.98 (s, 3H), 1.75–1.64 (m, 2H), 1.62 (s, 3H), 1.33–1.24 (m, 3H), 1.07 (s, 3H), 1.06 (s, 3H); ^{13}C NMR δ 169.4, 148.3, 130.9, 129.8, 117.4, 93.6, 75.8, 60.3, 56.3, 39.9, 29.2, 27.5, 27.2, 25.9, 22.5, 20.1, 14.2, 13.6.

***Z*–enol ether 279**. In a manner similar to the preparation of *Z*–enol ether **196**, a solution of LDA (0.9 mmol) in THF (4 mL) was treated sequentially with β–keto ester **277** (214 mg, 0.8 mmol) in THF (1 mL) and MOMCl (0.1 mL, 0.9 mmol). Following standard workup and purification by column chromatography (10% EtOAc/hexanes), the *Z*–enol ether **279** (101 mg, 45%) was obtained as a colorless oil: ^{1}H NMR δ 5.07–5.03 (m, 2H), 4.95 (s, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.44 (s, 3H), 2.93 (d, *J* = 6.8 Hz, 2H), 2.05–1.96 (m, 4H), 1.97 (s, 3H), 1.66 (s, 3H), 1.63 (s, 3H), 1.58 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 168.0, 156.1, 135.8, 131.3, 124.2, 121.7, 114.0, 100.0, 60.0, 56.4, 39.6, 27.7, 26.6, 25.6, 17.6, 16.0, 15.2, 14.3; HRMS (EI$^+$) calcd for $C_{18}H_{30}O_4$ [M$^+$] 310.2144; found 310.2135.

***E*–enol ether 278**. In a manner similar to the preparation of *E*–enol ether **198**, a solution of KHMDS (1.6 mL, 0.5 M soln in toluene, 0.8 mmol) in DMF (8 ml) was treated with β–keto ester **277** (162 mg, 0.6 mmol) and MOMCl (0.1 mL, 1.3 mmol). Following standard workup and purification by column chromatography (10% EtOAc/hexanes), *E*–enol ether **278** (33 mg, 19%) was obtained as a colorless oil: ^{1}H NMR δ 5.12–5.07 (m, 2H), 5.06 (s, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.42 (s, 3H), 3.09 (d, *J* = 7.0 Hz, 2H), 2.38 (s, 3H), 2.08–2.01 (m, 2H), 1.98–1.93 (m, 2H), 1.68 (s, 3H), 1.66 (s,

3H), 1.59 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR δ 169.2, 161.3, 134.8, 131.2, 124.4, 122.8, 112.8, 92.4, 59.8, 56.3, 39.8, 26.7, 25.7, 25.2, 17.6, 16.0, 14.9, 14.3; HRMS (EI$^+$) calcd for $C_{18}H_{30}O_4$ [M$^+$] 310.2138; found 310.2144.

β–keto ester 183. To a solution of NaH (134 mg, 3.3 mmol) and 15–crown–5 (0.5 mL, 2.3 mmol) in THF (50 mL) at 0 ºC was added slowly ethyl acetoacetate (**192**, 1.7 mL, 13.4 mmol), and the resulting mixture was allowed to stir for 30 min. Freshly prepared bromide **287**[172] (4.5 mmol) was added slowly, and the mixture was allowed to warm to rt and stirred for 4 h. After the reaction was quenched by addition of H_2O and sat. NH_4Cl, the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified by column chromatography (17% EtOAc/hexanes) to afford compound **183** (1.27 g, 80%) as a colorless liquid: ^{1}H NMR δ 5.09 (t, *J* = 5.9 Hz, 1H), 5.00 (t, *J* = 7.2 Hz, 1H), 4.15 (q, *J* = 1.2 Hz, 2H), 3.40 (t, *J* = 7.6 Hz, 1H), 2.66 (t, *J* = 6.0 Hz, 1H), 2.51 (t, *J* = 7.3 Hz, 2H), 2.19 (s, 3H), 2.11–1.92 (m, 6H), 1.63–1.54 (m, 2H), 1.59 (s, 3H), 1.57 (s, 3H), 1.26–1.20 (m, 9H); ^{13}C NMR δ 203.0, 169.5, 138.2, 134.2, 124.4, 119.6, 64.1, 61.2, 59.7, 58.2, 39.5, 36.2, 29.0, 27.3, 26.8, 26.4, 24.8, 18.7, 16.0, 15.9, 14.0; HRMS (EI$^+$) calcd for $C_{21}H_{34}O_4$ [M$^+$] 350.2457; found 350.2455.

***Z*–enol ether 184**. To a solution of KHMDS (2.6 mL, 1.3 mmol, 0.5 M soln in toluene) in THF (5 mL) at –78 ºC was added β–keto ester **183** (351 mg, 1.1 mmol) in THF (1 mL), and the solution was allowed to warm to –40 ºC over 1 h, then cooled to –78 ºC. After MOMCl (0.1 mL, 1.2 mmol) was added dropwise, the reaction was allowed to warm to rt and stirred overnight. After the reaction was quenched by addition of sat. NH_4Cl, the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), concentrated *in vacuo*, and the residue was purified by column chromatography (15% EtOAc/hexanes) to afford *Z*–enol ether **184** (98 mg, 43%) as a colorless oil: ^{1}H NMR δ 5.16–5.03 (m, 2H), 4.96 (s, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.45 (s, 3H), 2.94 (d, *J* = 7.0 Hz, 2H), 2.70 (t, *J* = 6.3 Hz, 1H), 2.27–1.99

(m, 5H), 1.94 (s, 3H), 1.65 (s, 3H), 1.60 (s, 3H), 1.56 (s, 3H), 1.30–1.26 (m, 9H); ^{13}C NMR δ 167.9, 155.9, 135.5, 133.9, 124.6, 121.6, 113.7, 94.1, 64.0, 59.8, 58.1, 56.2, 39.4, 36.1, 27.5, 27.2, 26.4, 24.7, 18.6, 15.9, 15.7, 15.0, 14.1; HRMS (EI$^+$) calcd for $C_{23}H_{38}O_5$ [M$^+$] 394.2719; found 394.2706.

***E*–enol ether 186**. To a solution of KHMDS (4.8 mL, 0.5 M soln in toluene, 2.4 mmol) in DMF (8 mL) at –60 ºC was added β–keto ester **183** (637 mg, 2.0 mmol) dissolved in DMF (1 mL). The reaction was allowed to warm to –10 ºC over 1 h and then cooled to –30 ºC and treated with MOMCl (0.2 mL, 2.1 mmol). The reaction was allowed to warm to rt and stirred 4 h. Following standard workup, purification by column chromatography (12% EtOAc/hexanes) provided *E*–enol ether **186** (336 mg, 44%) as a colorless oil: ^{1}H NMR δ 5.14–5.07 (m, 2H), 5.04 (d, *J* = 1.2 Hz, 2H), 4.13 (q, *J* = 1.6 Hz, 2H), 3.40 (s, 3H), 3.06 (d, *J* = 6.9 Hz, 2H), 2.67 (t, *J* = 6.2 Hz, 1H), 2.35 (s, 3H), 2.12–1.91 (m, 6H), 1.66 (s, 3H), 1.61–1.53 (m, 2H), 1.57 (s, 3H), 1.31–1.21 (m, 9H); ^{13}C NMR δ 169.1, 161.4, 134.6, 133.9, 124.8, 122.8, 112.5, 92.3, 64.1, 59.8, 58.2, 56.2, 39.7, 36.2, 27.3, 26.6, 25.1, 24.8, 18.7, 16.0, 15.9, 14.8, 14.3; HRMS (EI$^+$) calcd for $C_{23}H_{38}O_5$ [M$^+$] 394.2719; found 394.2713.

Representative cyclization procedure (farnesyl): Ester 187[165]. To a solution of *E*–enol ether **186** (70 mg, 0.2 mmol) in CH_2Cl_2 (22 mL) at –78 ºC was added $BF_3{\cdot}OEt_2$ (0.1 mL, 0.9 mmol), and the solution was allowed to stir for 10 min. The reaction was quenched by addition of TEA (0.1 mL, 0.9 mmol) and the cold bath was removed. After the solution had warmed considerably, H_2O was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), concentrated *in vacuo*, and the residue was purified by column chromatography (30% EtOAc/hexanes) to afford known ester **187**[165] (13 mg, 21%) as a colorless solid.

Ketone 185 and decalin 288. Using standard cyclization conditions, *Z*–enol ether **184** (97 mg, 0.3 mmol) in CH_2Cl_2 (25 mL) at –78 ºC was treated with $BF_3{\cdot}OEt_2$ (0.1

mL, 1.1 mmol). After the solution was allowed to stir for 10 min, it was quenched by addition of TEA (0.2 mL). Following standard workup, purification by column chromatography (65% EtOAc/hexanes) afforded decalin **288** (17 mg, 17%) as a colorless oil and ketone **185** (18 mg, 21%) as a colorless solid. For ketone **185**: ^{1}H NMR δ 4.20–4.09 (m, 2H), 3.22 (dd, *J* = 11.1, 5.2 Hz, 1H), 2.41 (dd, *J* = 15.9, 5.1 Hz, 1H), 2.34 (s, 3H), 2.08–1.82 (m, 2H), 1.81–1.54 (m, 6H), 1.46–1.21 (m, 3H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.23 (s, 3H), 1.01 (s, 3H), 0.86 (s, 3H), 0.79 (s, 3H); ^{13}C NMR δ 196.3, 164.0, 92.0, 82.6, 78.6, 63.8, 55.0, 52.0, 40.2, 38.7, 37.4, 36.4, 31.0, 28.1, 27.2, 20.6, 19.3, 18.4, 15.4, 14.9, 14.9; HRMS (EI^{+}) calcd for $C_{21}H_{34}O_4$ [M^{+}] 350.2457; found 350.2448. For decalin **288**: ^{1}H NMR δ 4.81 (d, *J* = 6.9 Hz, 1H), 4.78 (d, *J* = 6.9 Hz, 1H), 4.14–3.99 (m, 2H), 4.05 (s, 3H), 3.19–3.14 (m, 1H), 3.02 (d, *J* = 15.8 Hz, 1H), 2.83 (d, *J* = 15.8 Hz, 1H), 1.96–1.93 (m, 2H), 1.87 (s, 3H), 1.61–1.37 (m, 7H), 1.51 (s, 3H), 1.10 (t, *J* = 7.3 Hz, 3H), 0.92 (s, 3H), 0.91 (s, 3H), 0.73 (s, 3H); ^{13}C NMR δ 169.4, 147.6, 135.6, 129.2, 118.2, 93.7, 78.8, 60.2, 56.3, 50.5, 38.8, 38.6, 34.4, 33.9, 28.1, 27.7, 26.8, 20.4, 20.2, 18.7, 15.4, 14.3, 13.6.

Tricycle 289. To a solution of ester **187** (19 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL) at rt was slowly added DIPEA (0.02 mL, 0.1 mmol). After 10 minutes, MOMCl (0.01 mL, 0.1 mmol) was added dropwise. The reaction was allowed to stir for 1 h, and then was quenched by addition of sat. NH_4Cl, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), concentrated *in vacuo*, and the residue was purified by column chromatography (7% EtOAc/hexanes) to afford protected tricycle **289** (15 mg, 70%) as a colorless oil: ^{1}H NMR δ 4.75 (d, *J* = 7.1 Hz, 1H), 4.61 (d, *J* = 6.8 Hz, 1H), 4.17 (q, *J* = 7.5 Hz, 2H), 3.39 (s, 3H), 3.10 (dd, *J* = 11.3, 4.9 Hz, 1H), 2.28 (dd, *J* = 15.7, 3.9 Hz, 1H), 2.19 (s, 3H), 1.98–1.91 (m, 1H), 1.82–1.34 (m, 6H), 1.31–1.22 (m, 2H), 1.29 (t, *J* = 6.8 Hz, 3H), 1.14 (s, 3H), 0.99 (s, 3H), 0.98–0.92 (m, 2H), 0.86 (s, 3H), 0.85 (s, 3H); ^{13}C NMR δ 168.8, 162.7, 100.1, 96.0, 84.8, 78.0, 59.5, 55.6, 55.4, 51.5, 40.6, 38.6, 37.4, 35.3, 28.1, 24.0,

20.6, 20.3, 19.5, 19.3, 16.4, 15.0, 14.5; HRMS (EI^+) calcd for $C_{23}H_{38}O_5$ [M^+] 394.2719; found 394.2715.

***Z*–silyl enol ether 290**. To a suspension of NaH (157 mg, 4.0 mmol) and 15–crown–5 (1 drop, cat.) in THF (8 mL) at 0 ºC was added a solution of β–keto ester **194** (280 mg, 1.0 mmol) in THF (2 mL), and the reaction was allowed to stir for 30 min. Solid TBSCl (165 mg, 1.1 mmol) was added in one portion, and the reaction was allowed to stir for 1 h. After the reaction was quenched by addition of NH_4Cl (sat.), standard workup and purification by column chromatography (7% EtOAc/hexanes) gave *Z*–silyl enol ether **290** (150 mg, 38%, 11.5:1 *Z*:*E*) as a colorless oil: ^{1}H NMR δ 5.13–5.11 (m, 1H), 4.15 (q, *J* = 6.7 Hz, 2H), 2.93 (d, *J* = 6.7 Hz, 2H), 2.69 (t, *J* = 6.2 Hz, 1H), 2.15–2.07 (m, 2H), 1.92 (s, 3H), 1.67 (s, 3H), 1.66–1.56 (m, 2H), 1.31 (s, 3H), 1.26–1.24 (m, 6H), 0.93 (s, 9H), 0.17 (s, 6H); ^{13}C NMR δ 168.1, 155.4, 134.2, 122.9, 111.7, 64.0, 59.7, 58.2, 36.2, 27.9, 27.4, 25.6 (3C), 24.8, 20.6, 18.6, 18.2, 16.0, 14.3, –3.9 (2C); HRMS (EI^+) calcd for $C_{22}H_{40}O_4Si$ [M^+] 396.2696.

***E*–silyl enol ether 293**. To a solution of β–keto ester **194** (238 mg, 0.8 mmol) in THF (5 mL) at rt was added TEA (1.4 mL, 10 mmol) and TBSCl (633 mg, 4.2 mmol), and the reaction was allowed to stir for 36 h. Following standard workup and purification by column chromatography (7% EtOAc/hexanes), *E*–silyl enol ether **293** (161 mg, 48%) was obtained as a colorless oil: ^{1}H NMR δ 5.11–5.06 (m, 1H), 4.14 (q, *J* = 6.7 Hz, 2H), 3.04 (d, *J* = 6.4 Hz, 2H), 2.68 (t, *J* = 6.4 Hz, 1H), 2.29 (s, 3H), 2.16–2.00 (m, 2H), 1.71 (s, 3H), 1.69–1.50 (m, 2H), 1.31 (s, 3H), 1.28–1.23 (m, 6H), 0.95 (s, 9 H), 0.22 (s, 6H); ^{13}C NMR δ 169.2, 160.9, 133.6, 123.8, 112.5, 64.1, 59.5, 58.2, 36.2, 27.3, 25.6 (3C), 25.4, 24.8, 21.4, 18.6, 18.2, 16.1, 14.3, –3.38 (2C); HRMS (EI^+) calcd for $C_{22}H_{40}O_4Si$ [M^+] 396.2696.

***E*–silyl enol ether 298**. To a mixture of NaH (27 mg, 0.7 mmol) and 15–crown–5 (cat.) in THF (8 mL) at 0 ºC was added β–keto ester **194** (170 mg, 0.6 mmol) in THF (1 mL), and the reaction was allowed to stir for 30 min. After solid TBDPSCl was added in

one portion, the reaction was allowed to stir for 1 h and then quenched by addition of sat. NH_4Cl. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with brine, dried ($MgSO_4$), concentrated *in vacuo*, and the residue was purified by column chromatography (10% EtOAc/hexanes) to give *E*–silyl enol ether **298** (198 mg, 63%) as a single isomer: ^{1}H NMR δ 7.74–7.71 (m, 4H), 7.49–7.36 (m, 6H), 5.26 (t, *J* = 5.9 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.28 (d, *J* = 6.7 Hz, 2H), 2.73 (t, *J* = 7.0 Hz, 1H), 2.19–2.07 (m, 2H), 1.98 (s, 3H), 1.74 (s, 3H), 1.70–1.58 (m, 2H), 1.29 (s, 3H), 1.29–1.23 (m, 6H), 1.04 (s, 9H); ^{13}C NMR δ 169.4, 161.7, 135.0 (4C), 133.9, 133.0 (2C), 130.1 (2C), 127.9 (4C), 123.7, 112.3, 64.1, 59.7, 58.3, 36.2, 27.4, 26.3 (3C), 25.6, 24.8, 21.8, 19.4, 18.7, 16.3, 14.3; stereochemistry of the enol ether determined by an NOE experiment (cf. Appendix); HRMS (EI^+) calcd for $C_{32}H_{44}O_4Si$ [M^+] 520.3009.

***E*–silyl enol ether 299**. To a solution of farnesyl β–keto ester **183** (144 mg, 0.4 mmol) and triethylamine (0.1 mL, 0.7 mmol) in THF (3 mL) at rt was added TBSCl (75 mg, 0.5 mmol), and the reaction was allowed to stir for 2 days. The reaction was quenched by addition of sat. NH_4Cl, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), concentrated *in vacuo*, and purified by column chromatography (10% EtOAc/hexanes) to give *E*–silyl enol ether **299** (79 mg, 49%) as a colorless oil: ^{1}H NMR δ 5.12 (t, *J* = 7.0 Hz, 1H), 5.01 (t, *J* = 6.8 Hz, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.00 (d, *J* = 6.8 Hz, 2H), 2.66 (t, *J* = 6.2 Hz, 1H), 2.25 (s, 3H), 2.13–1.99 (m, 4H), 1.95–1.90 (m, 2H), 1.66–1.53 (m, 2H), 1.63 (s, 3H), 1.57 (s, 3H), 1.26 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.22 (s, 3H), 0.92 (s, 9H), 0.19 (s, 6H); ^{13}C NMR δ 169.5, 160.8, 134.4, 133.8, 124.9, 123.1, 112.6, 64.1, 59.2, 58.2, 39.6, 36.2, 27.3, 26.6, 25.6 (3C), 25.3, 24.8, 21.4, 18.6, 18.2, 16.1, 15.9, 14.3, –3.4 (2C); HRMS (EI^+) calcd for $C_{27}H_{48}O_4Si$ [M^+] 464.3322.

Cell culture: SF–295 cells and A549 cells were maintained in RPMI 1640 or F–12 media, respectively. Media were supplemented with 10% fetal bovine serum,

amphotericin B, pen–strep, and L–glutamine for both cell lines. Cell lines were incubated at 37° C in the presence of 5% CO_2.

Cytotoxicity Assay: SF–295 or A549 cells were treated with indicated compounds after reaching 60% confluency. Forty–four hours after treatment, the complete media were aspirated and switched to RPMI 1640 without phenol red or F–12 media containing MTT salt (Calbiochem, San Diego, CA, USA) for SF–295 or A549 cells, respectively. The MTT reaction was halted by addition of the MTT stop solution (10% 1 N HCl, 10% triton X–100, and isopropyl alcohol). Spectrophotometric values were obtained at 540 nm with a reference wavelength of 650 nm. The mean and standard deviation of quadruplicate samples were calculated in Microsoft Excel.

APPENDIX
SELECTED NMR SPECTRA

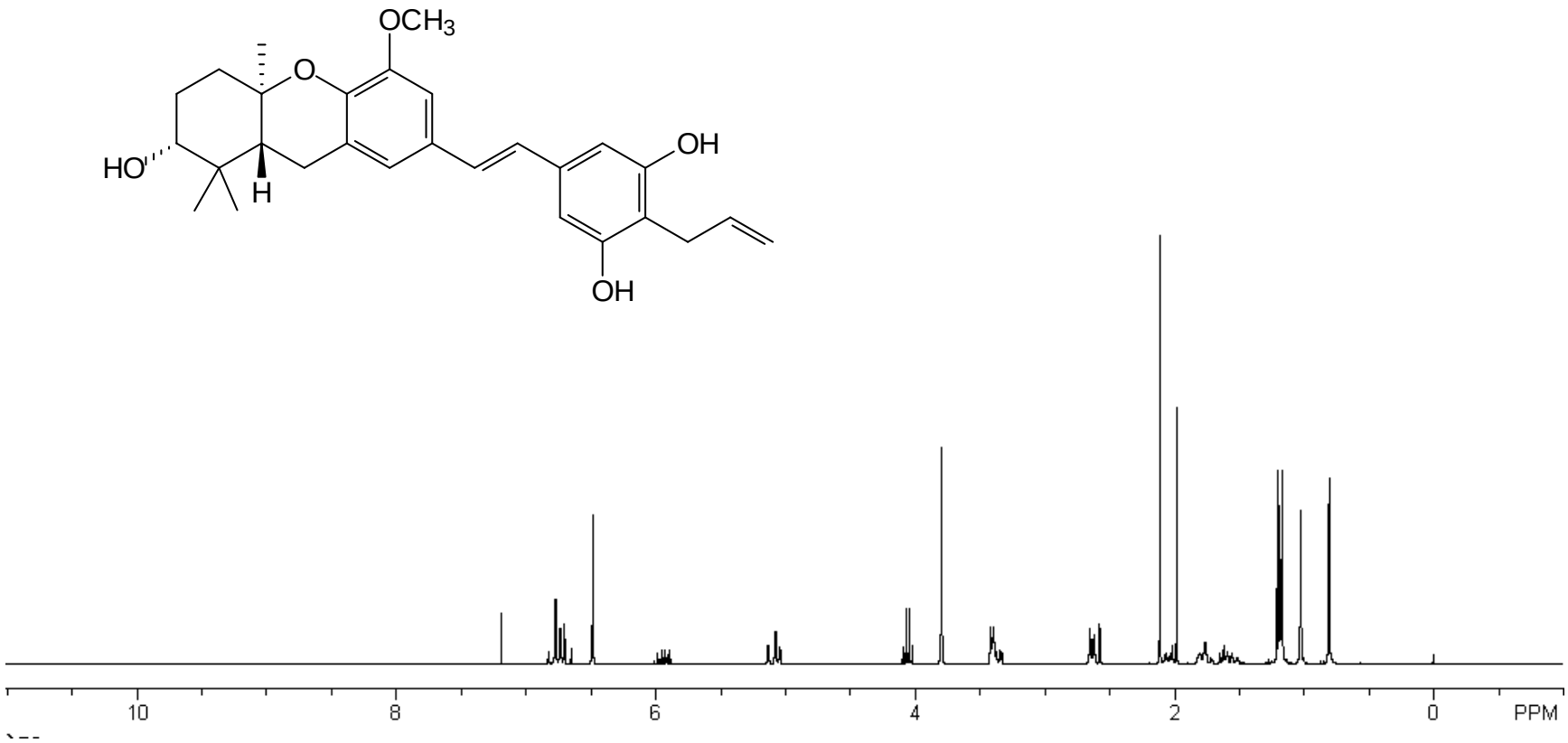


Figure A1. ^{1}H NMR spectrum of analogue **63**

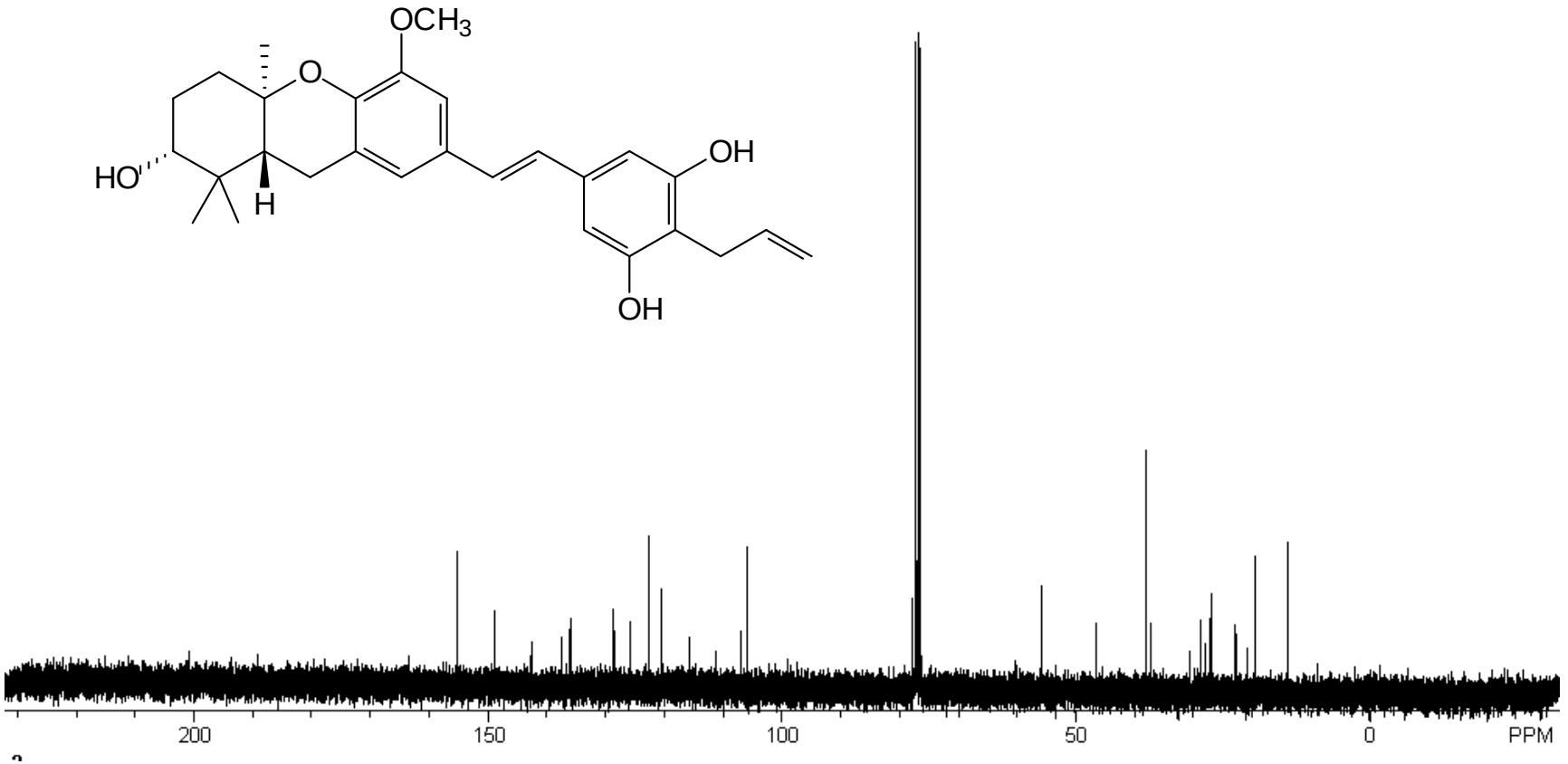


Figure A2. ^{13}C NMR spectrum of analogue **63**

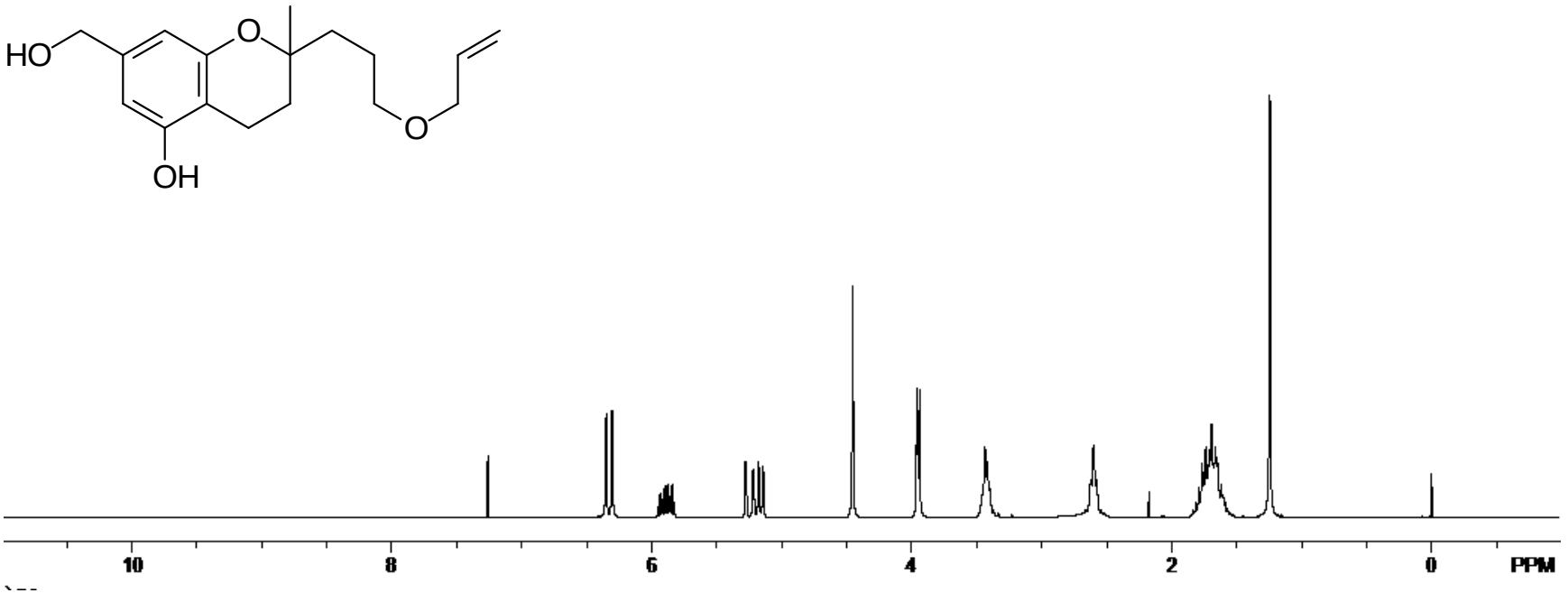


Figure A3. ^{1}H NMR spectrum of ether **134**

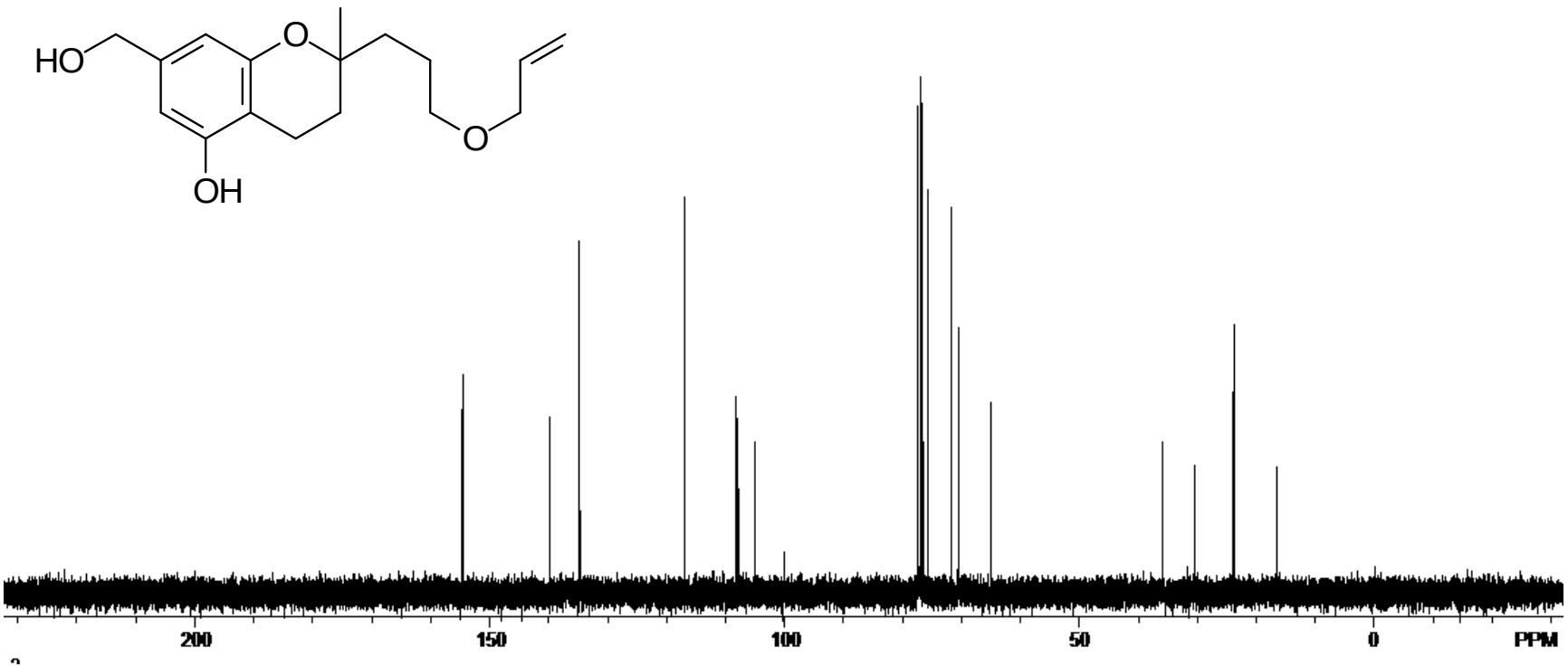


Figure A4. ^{13}C NMR spectrum of ether **134**

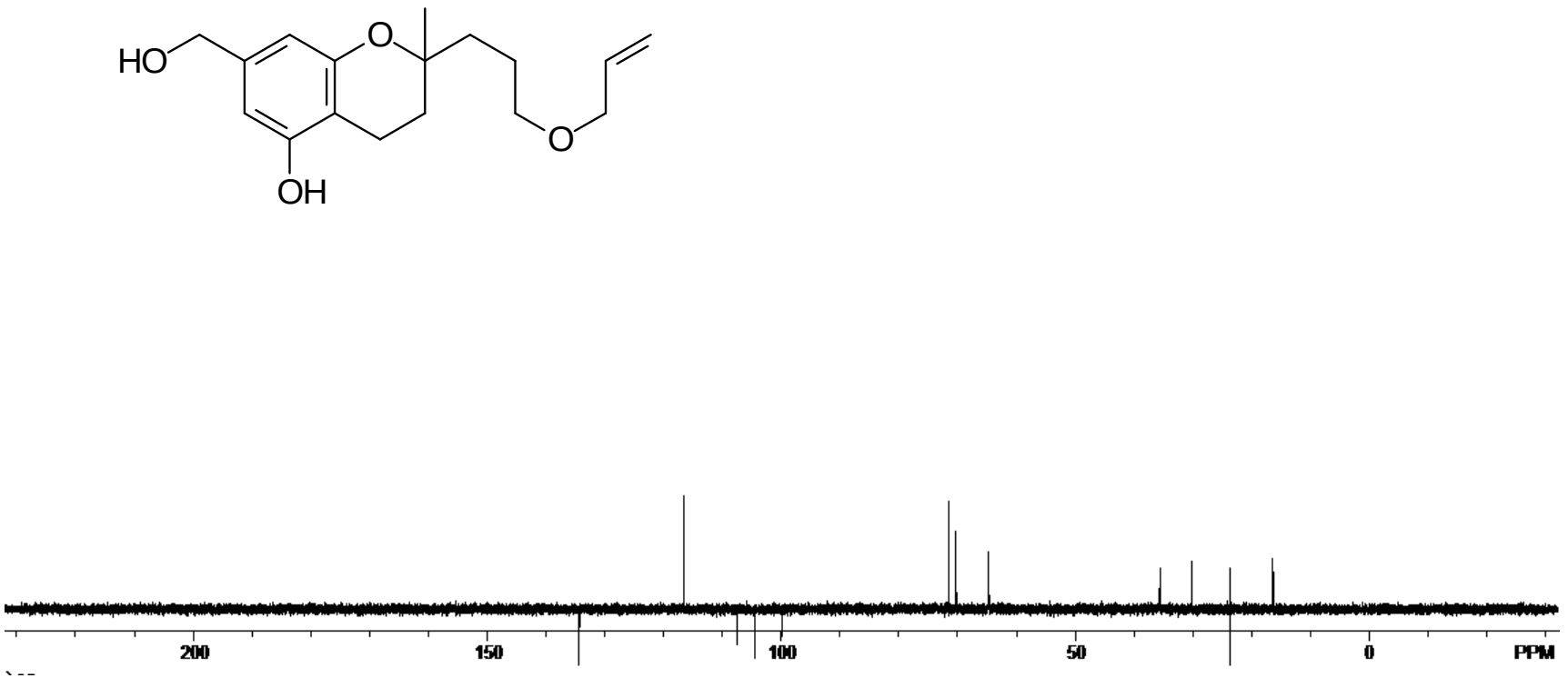


Figure A5. ^{13}C NMR DEPT spectrum of ether **134**

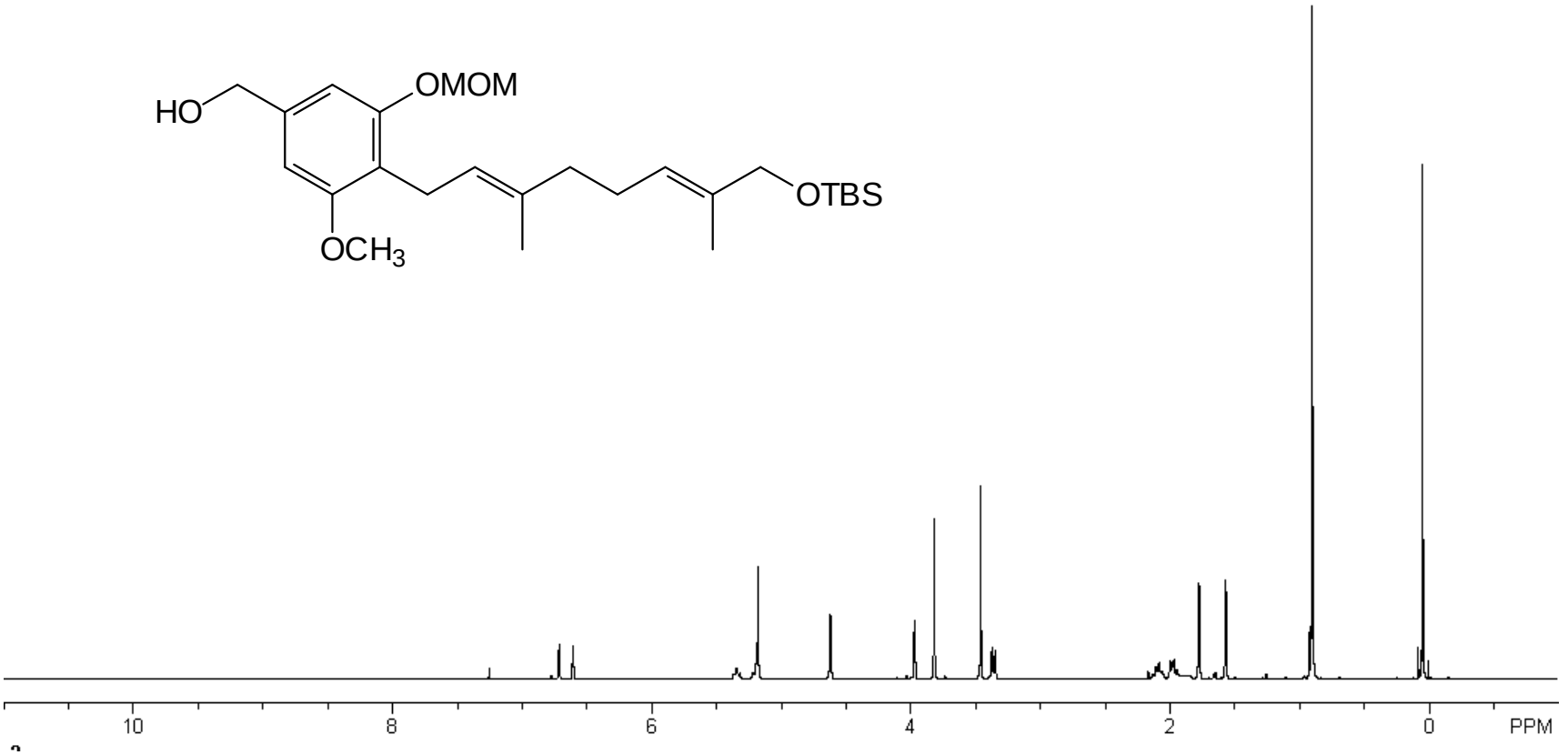


Figure A6. ^{1}H NMR spectrum of benzyl alcohol **158**

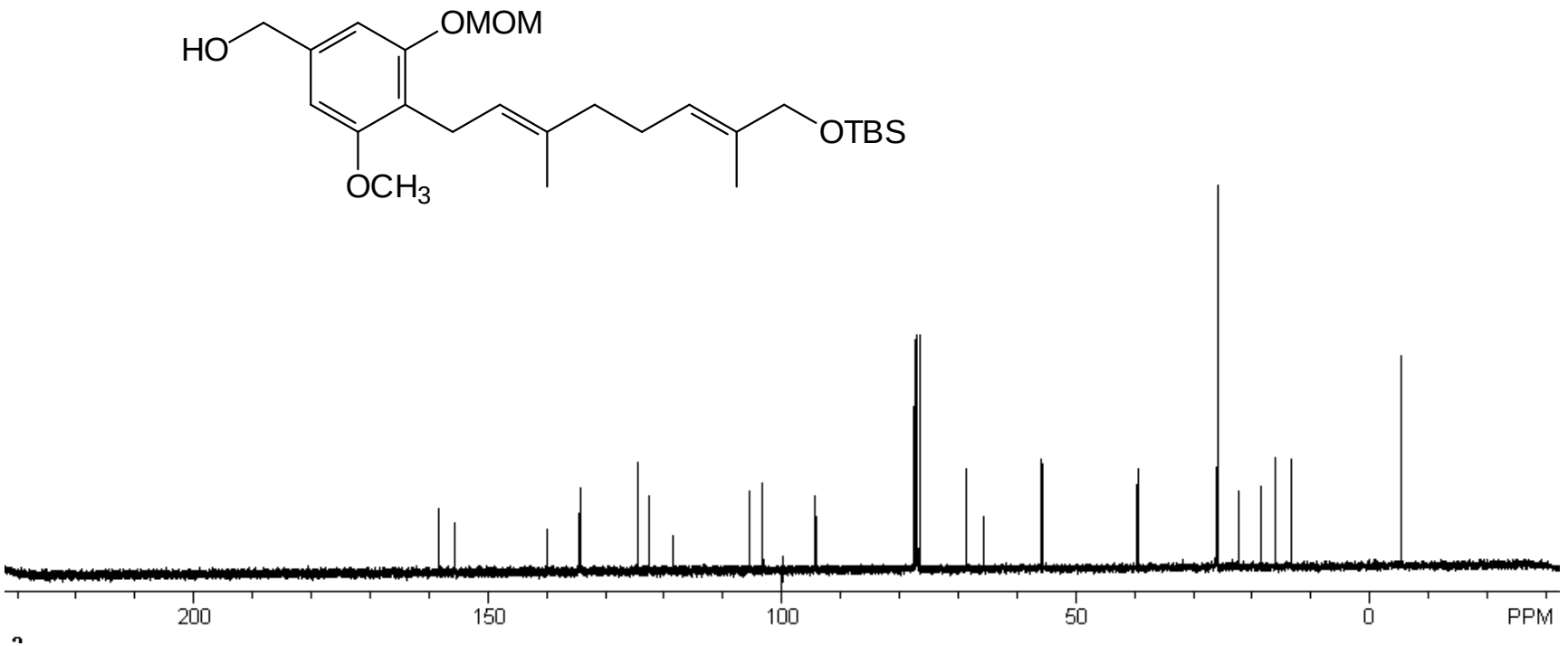


Figure A7. ^{13}C NMR spectrum of benzyl alcohol **158**

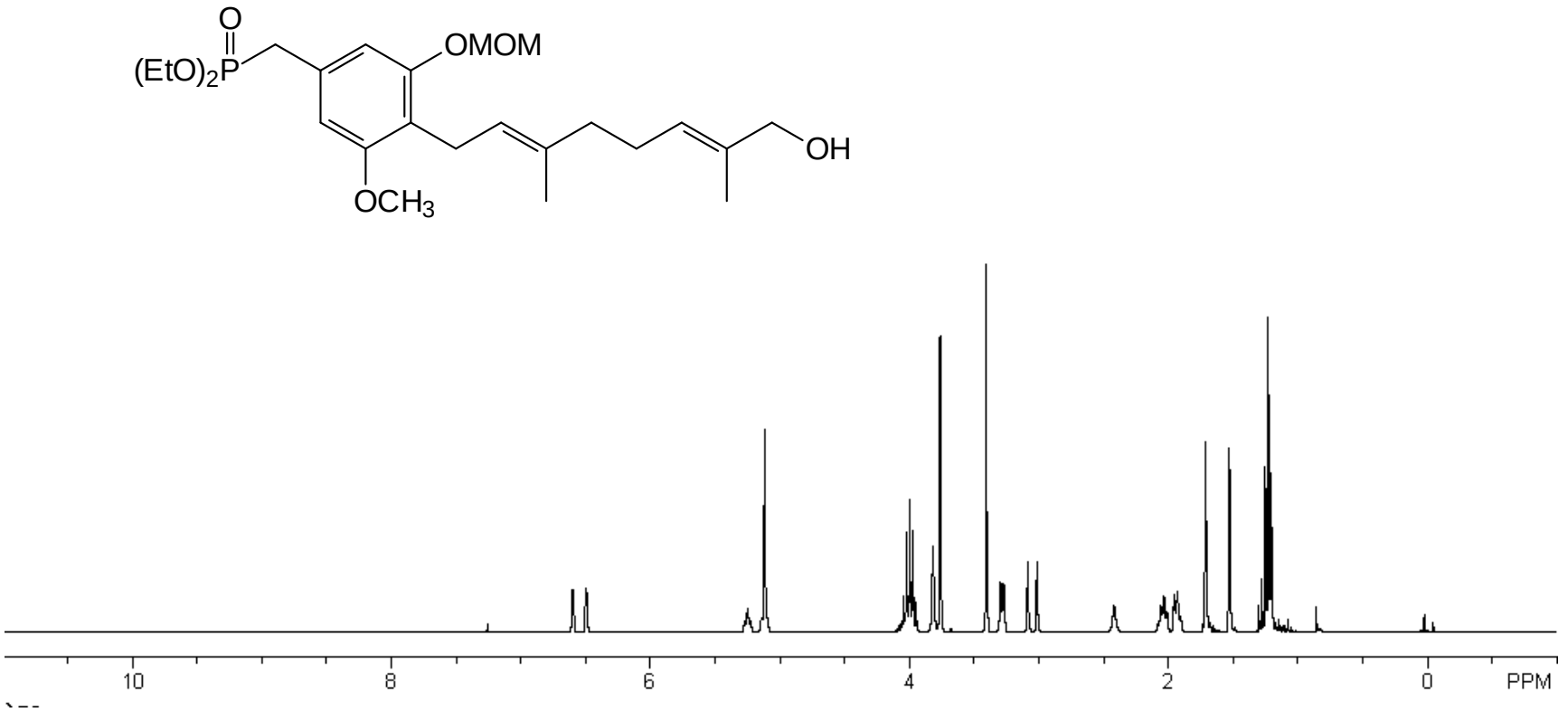


Figure A8. ^{1}H NMR spectrum of phosphonate **159**

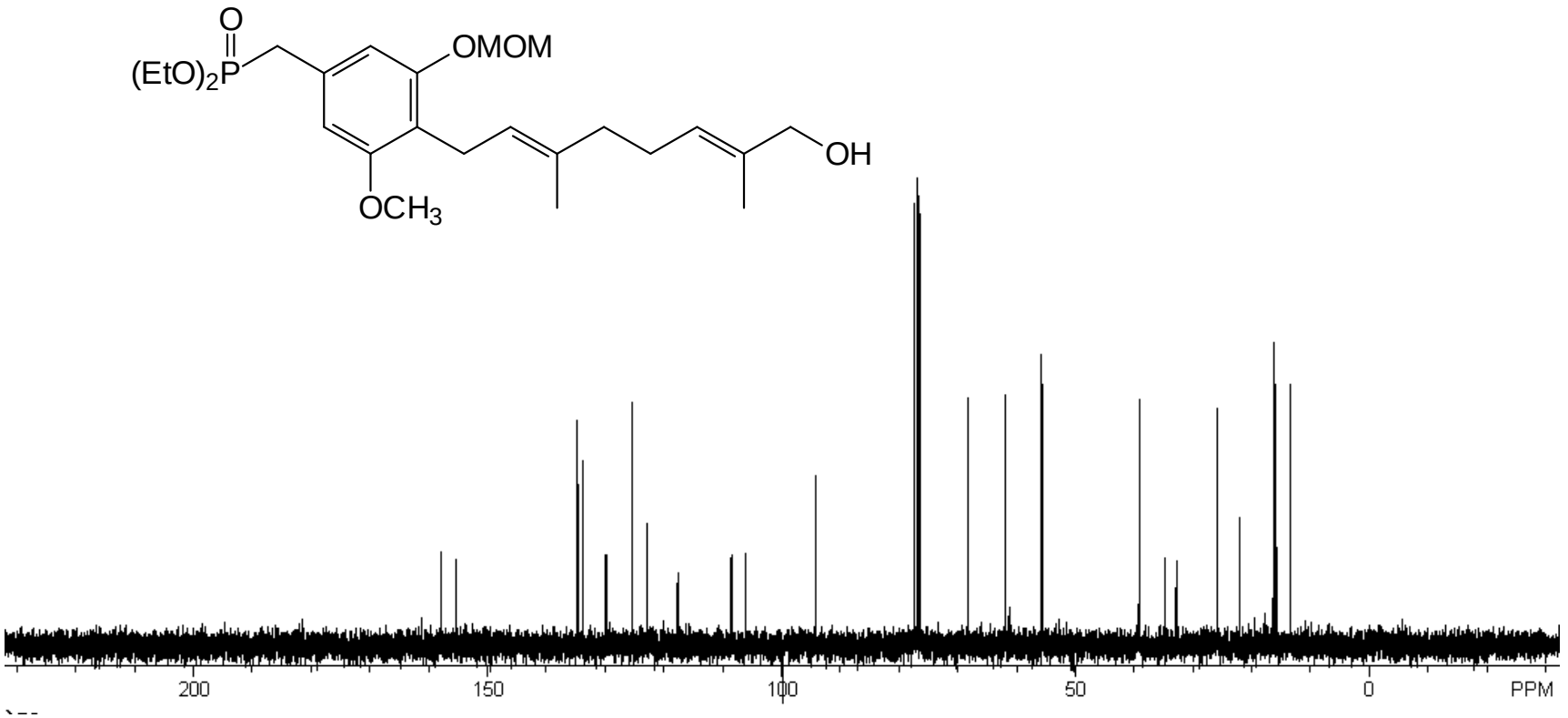


Figure A9. ^{13}C NMR spectrum of phosphonate **159**

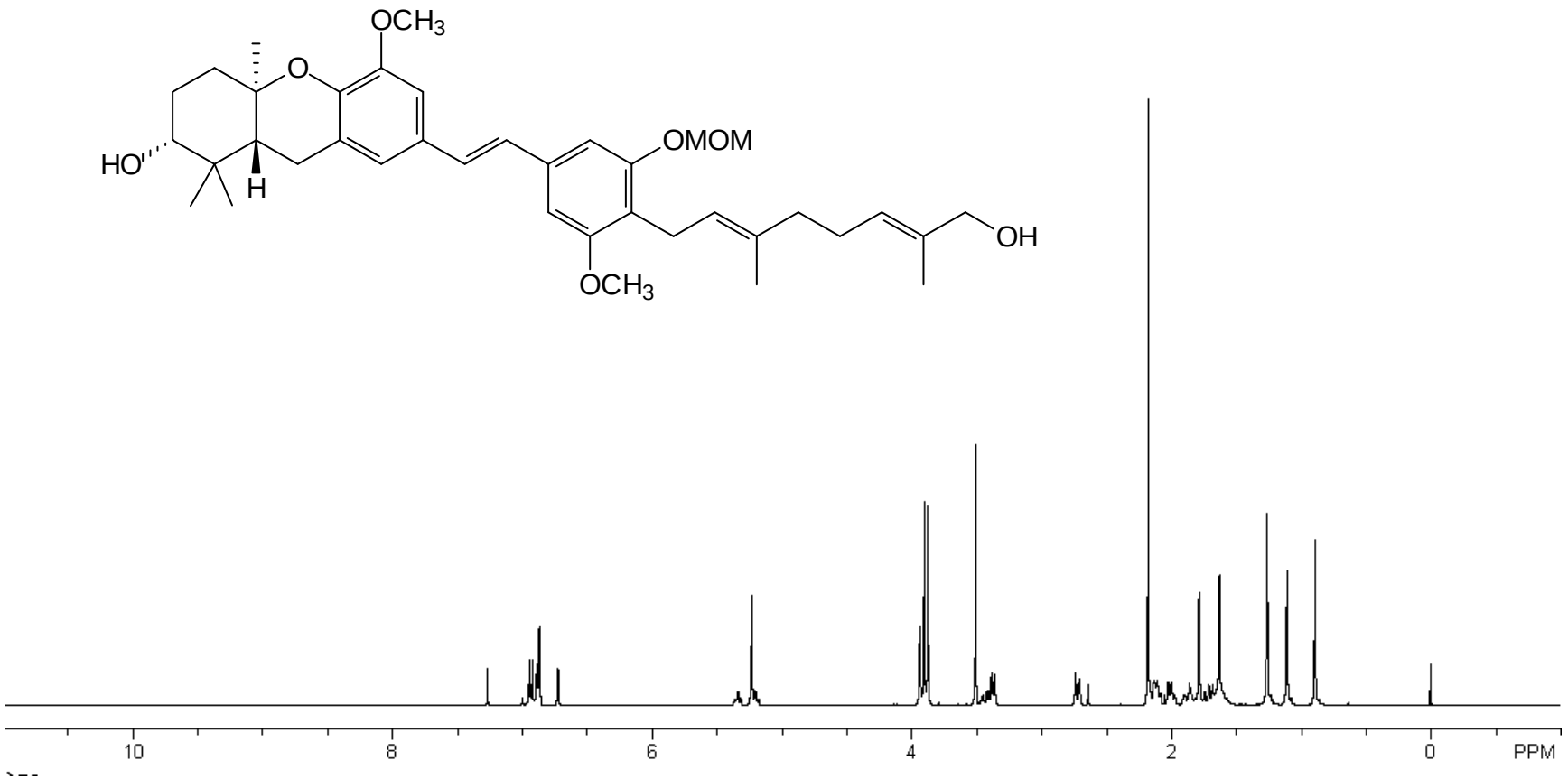


Figure A10. ^{1}H NMR spectrum of stilbene **160**

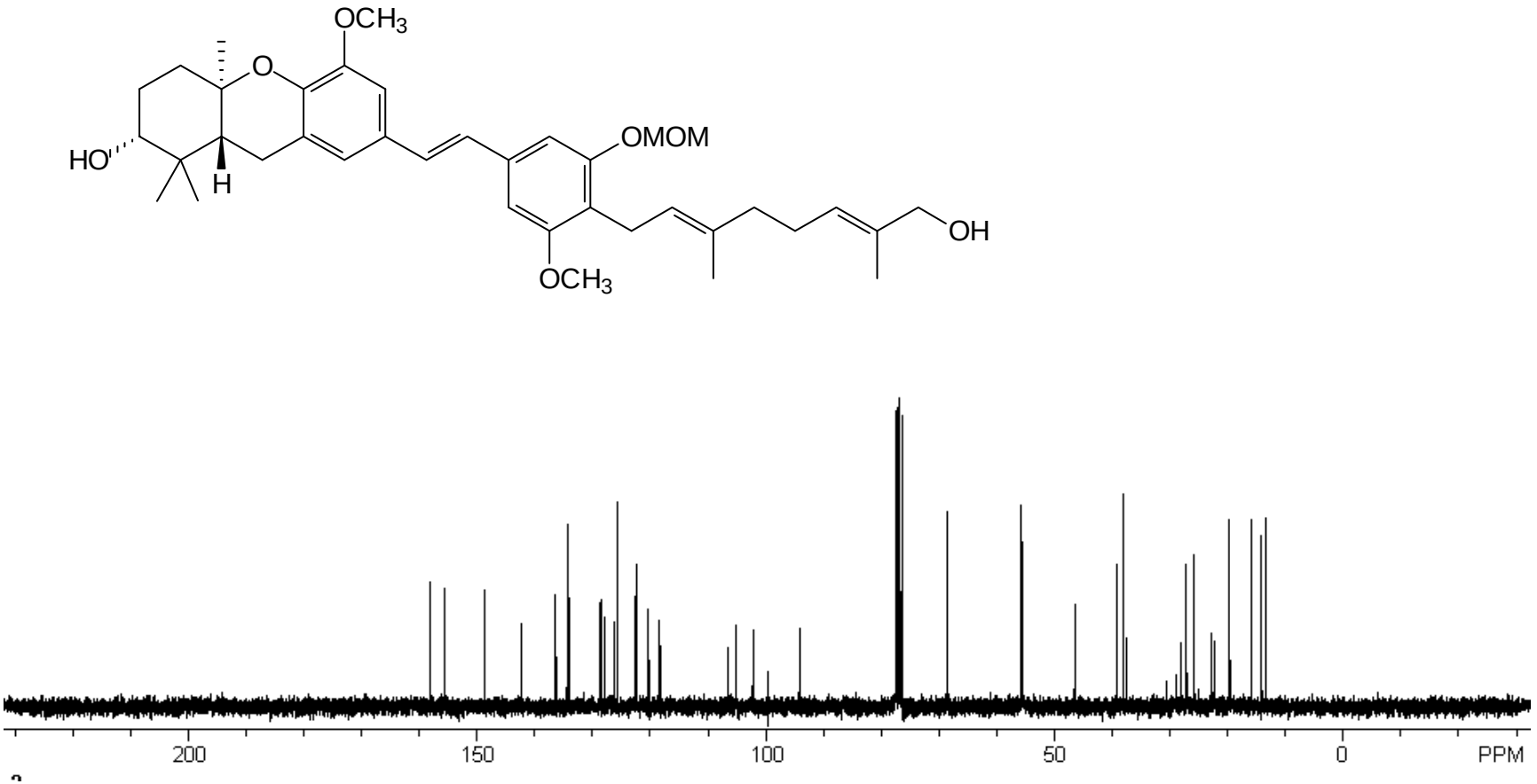


Figure A11. ^{13}C NMR spectrum of stilbene **160**

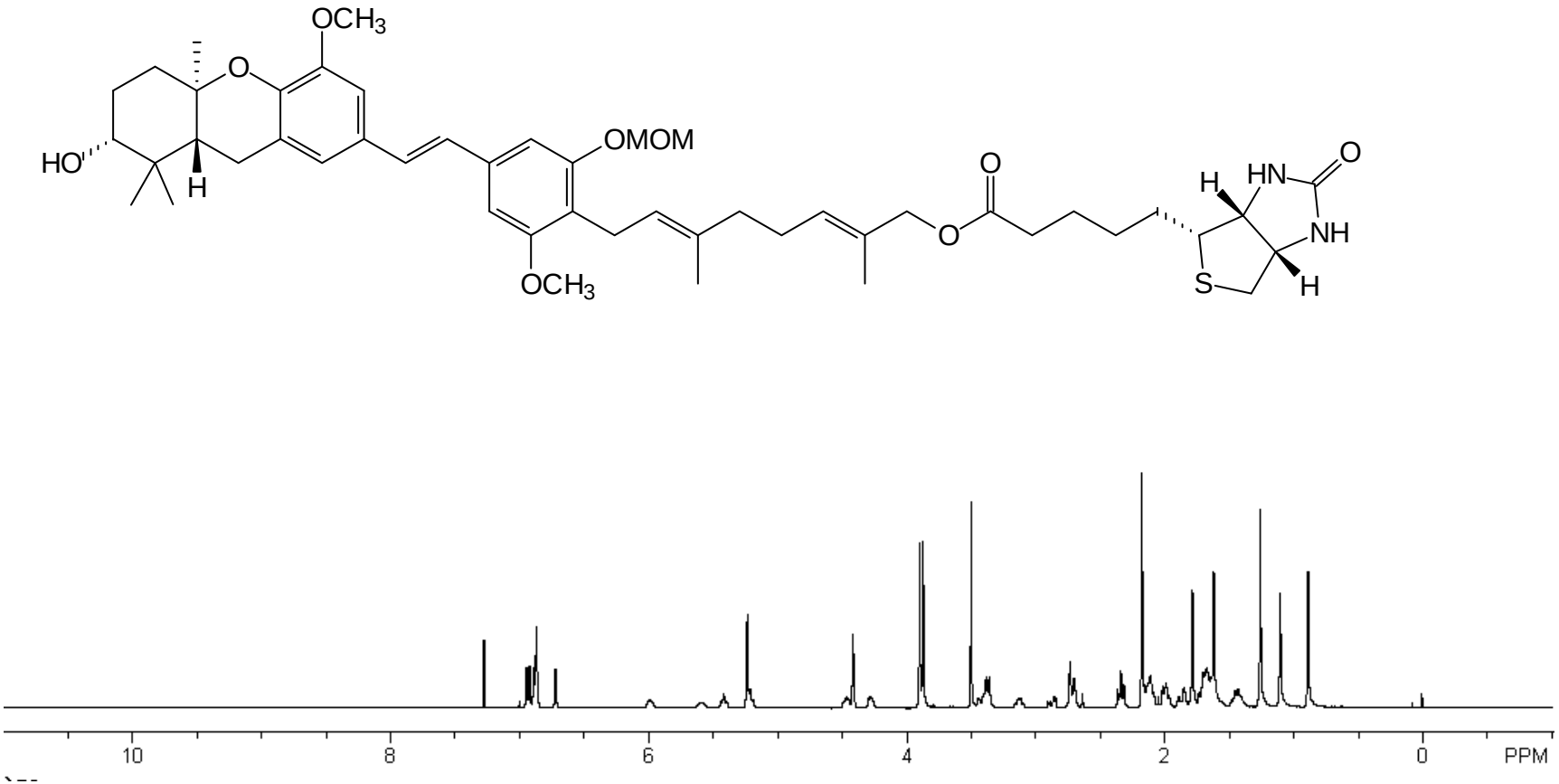


Figure A12. ^{1}H NMR spectrum of ester **164**

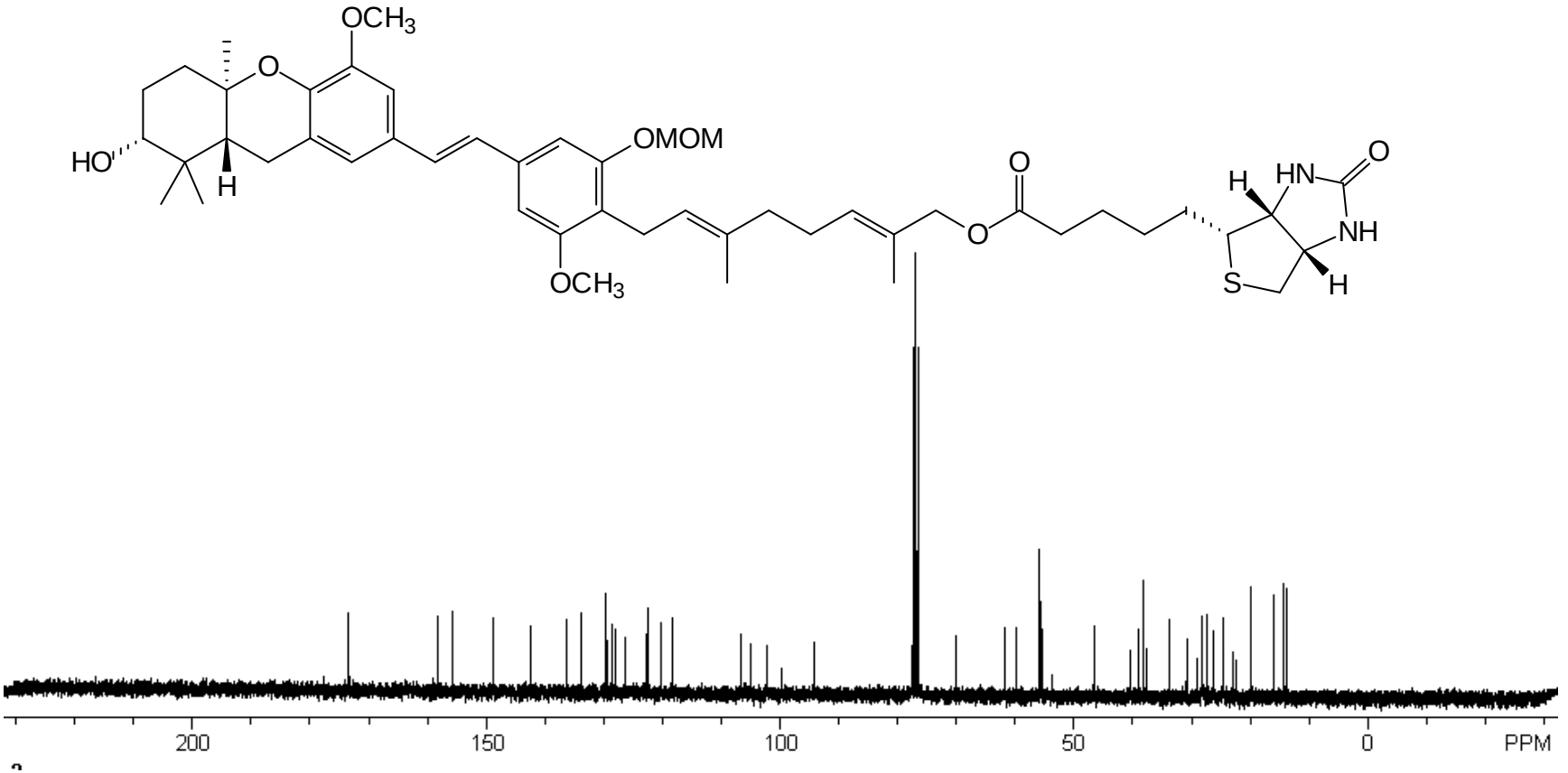


Figure A13. ^{13}C NMR spectrum of ester **164**

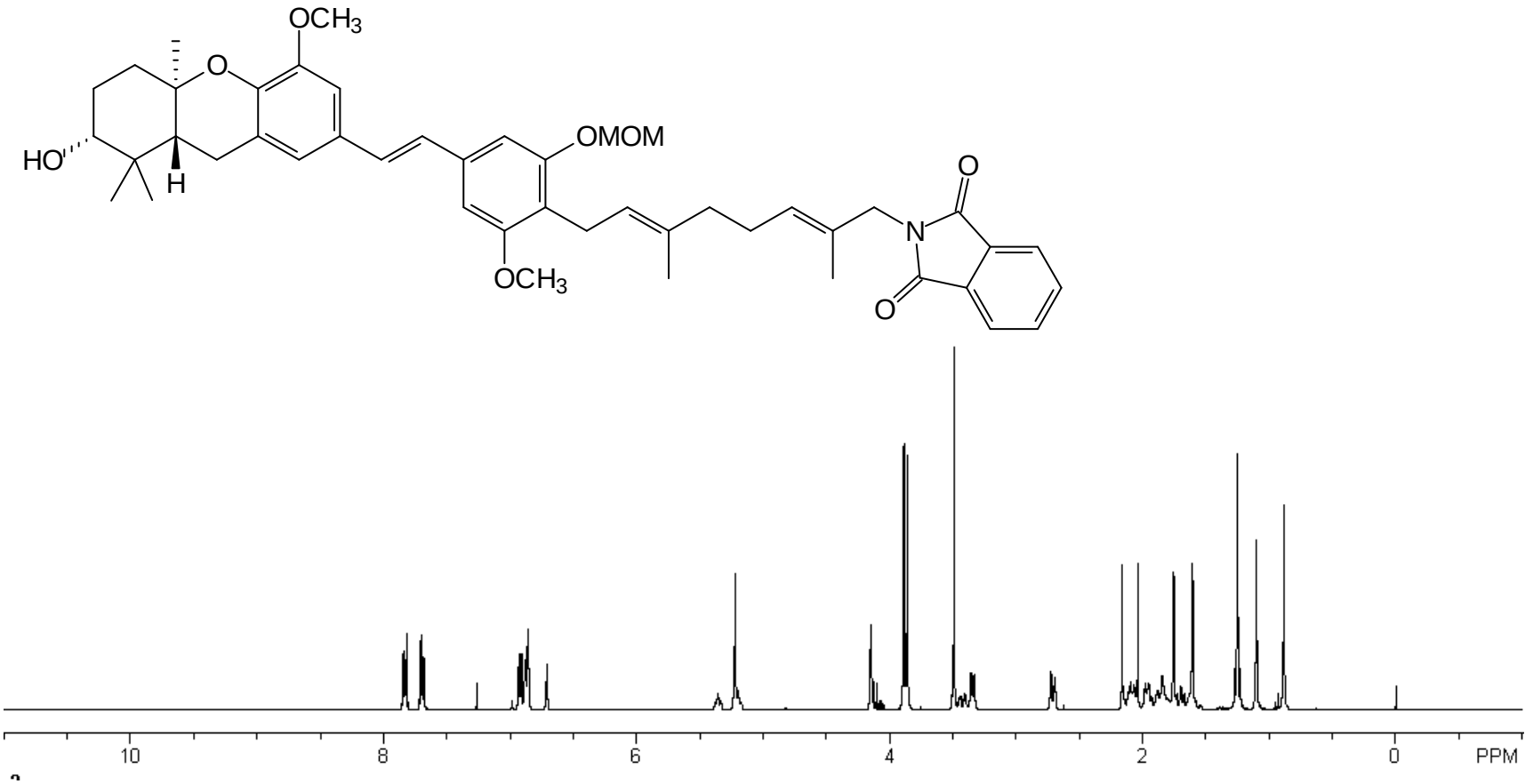


Figure A14. ^{1}H NMR spectrum of phthalimide **165**

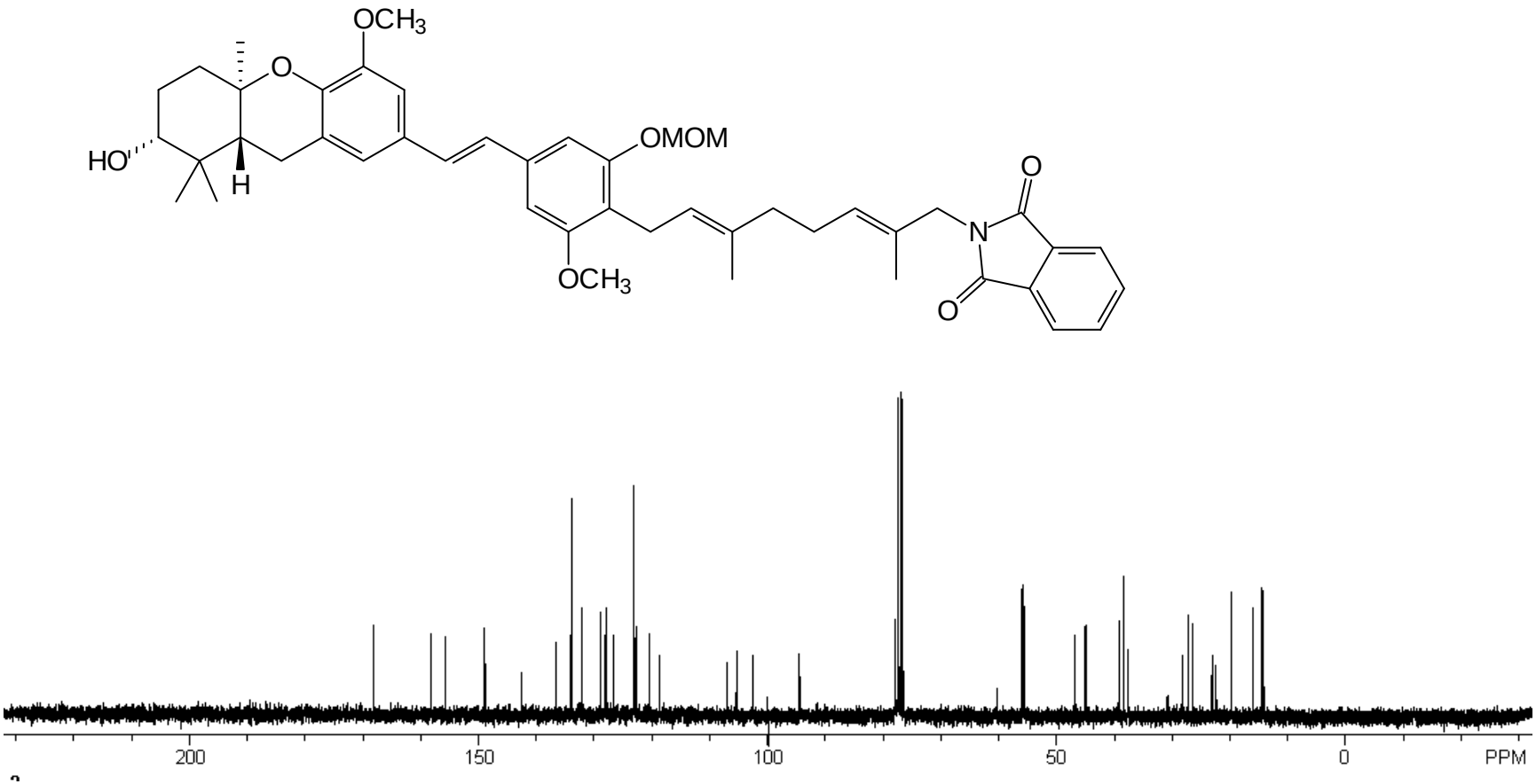


Figure A15. ^{13}C NMR spectrum of phthalimide **165**

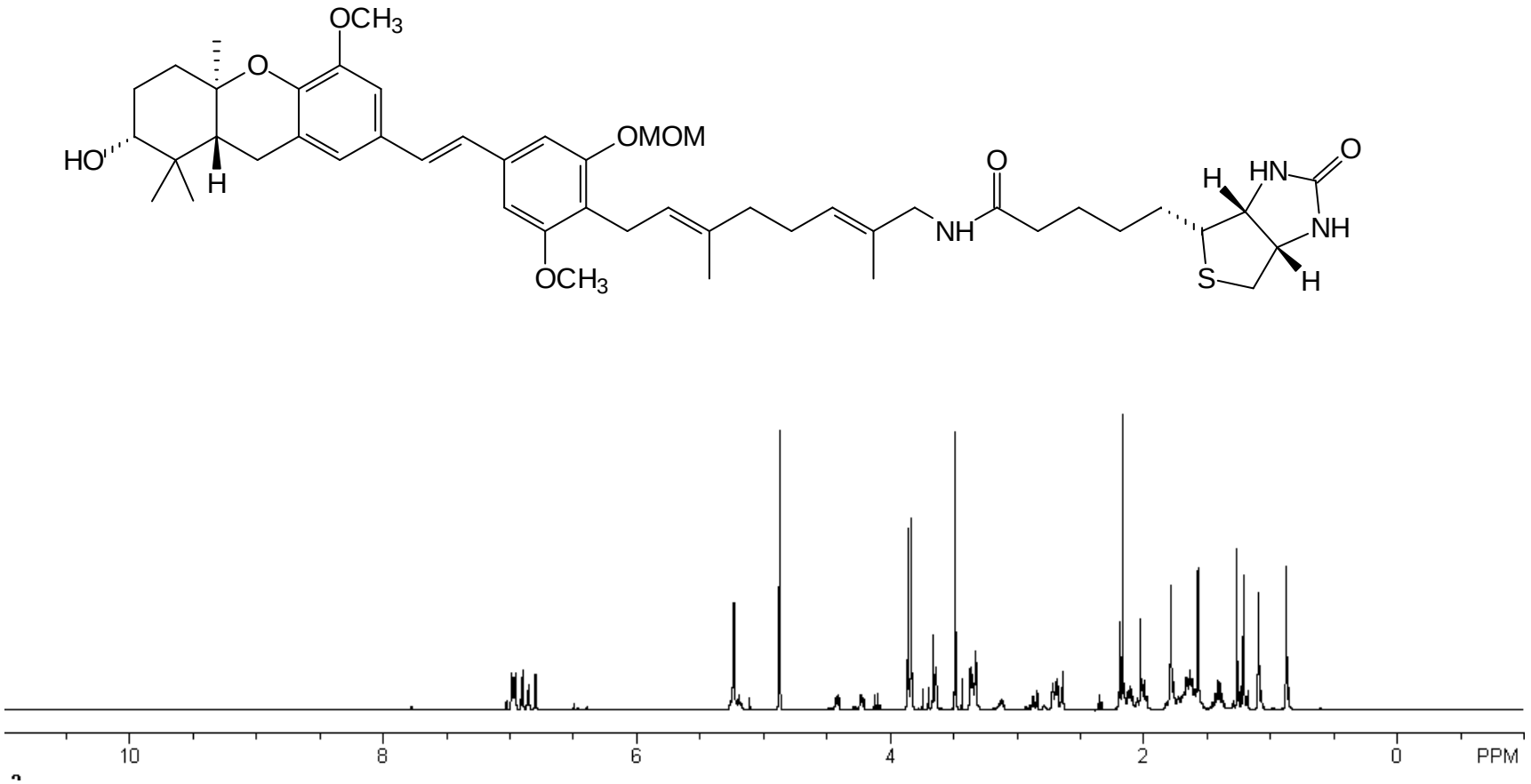


Figure A16. ^{1}H NMR spectrum of amide **166**

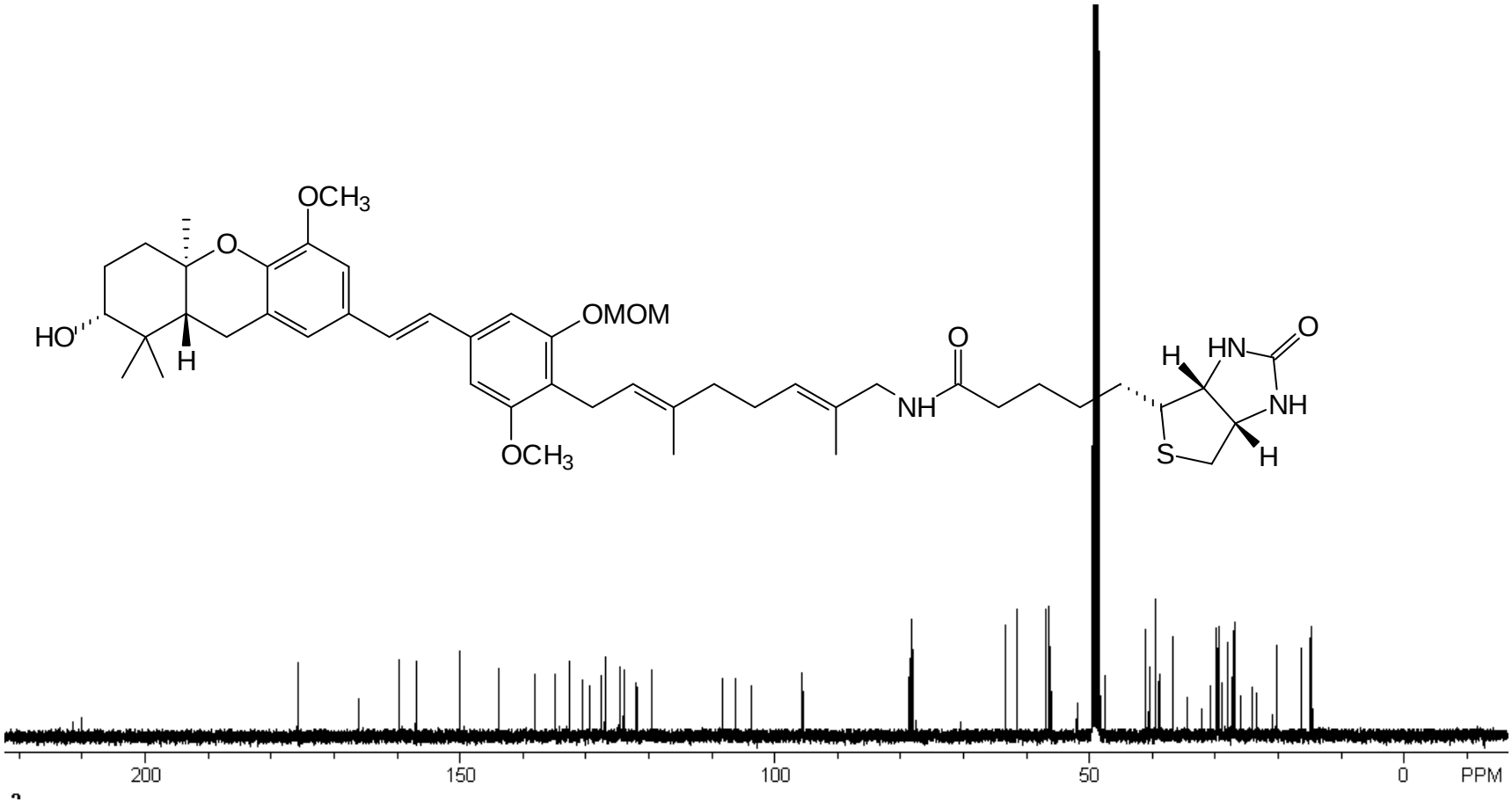


Figure A17. ^{13}C NMR spectrum of amide **166**

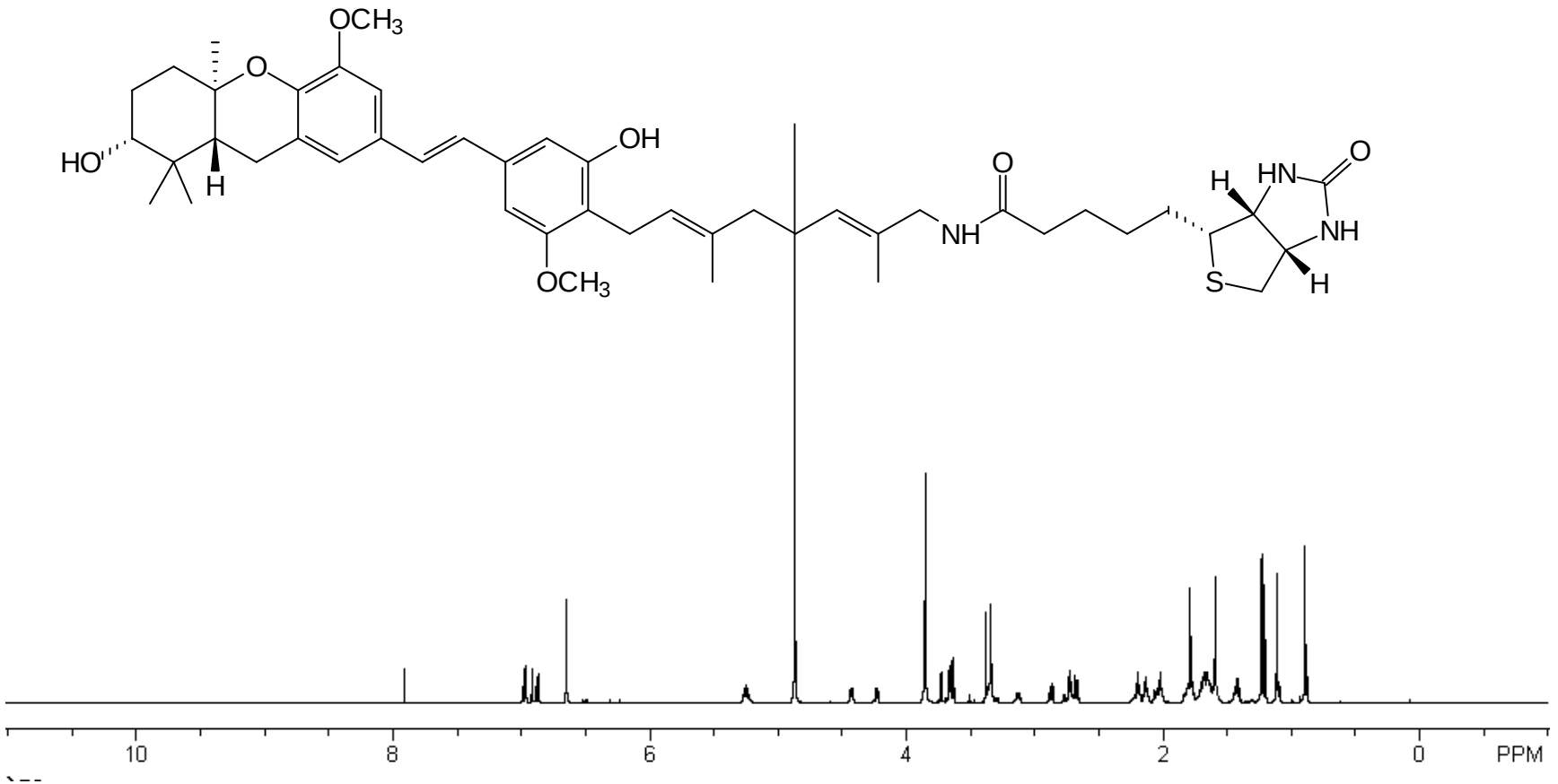


Figure A18. ^{1}H NMR spectrum of amide **46**

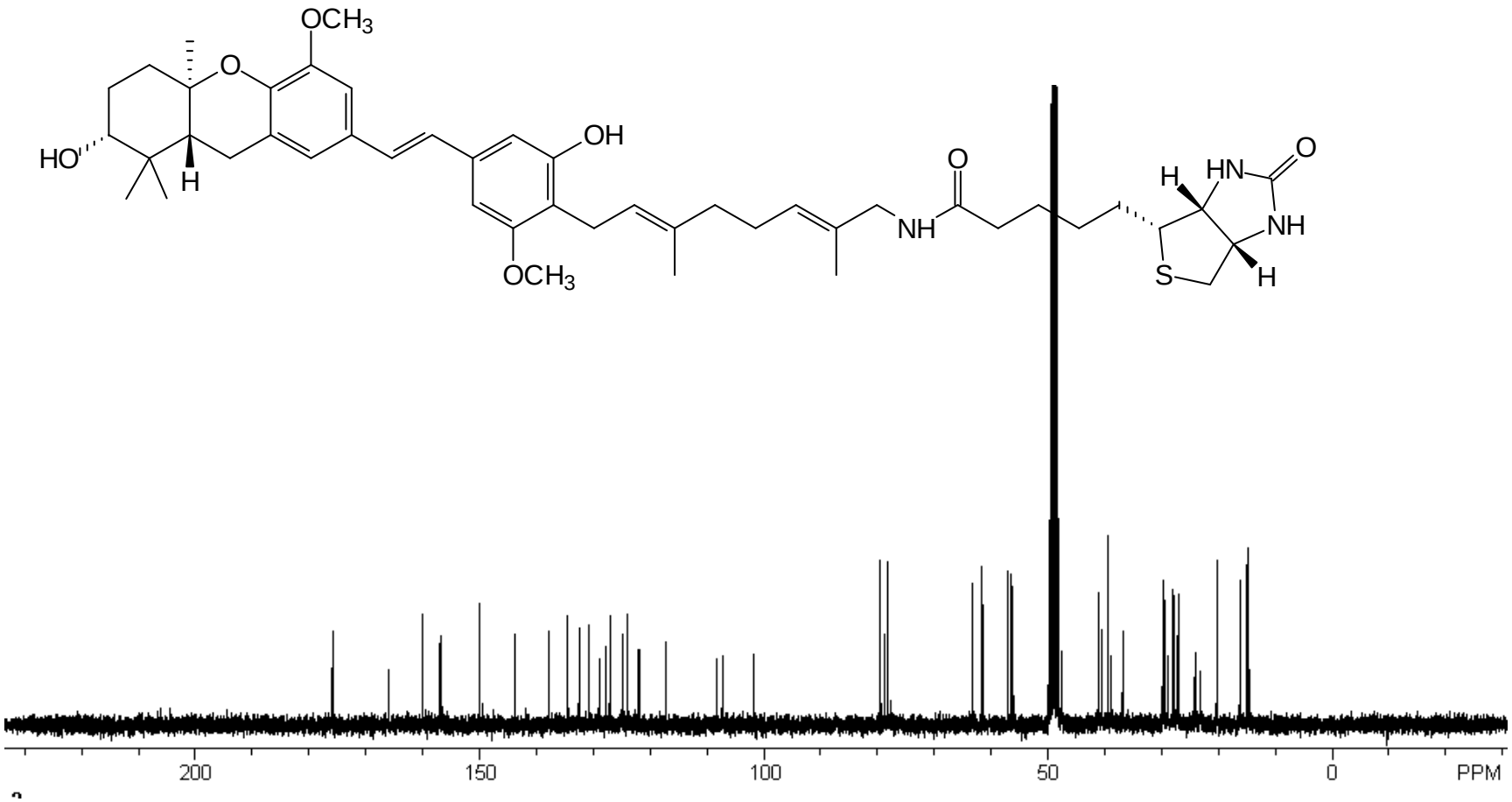


Figure A19. ^{13}C NMR spectrum of amide **46**

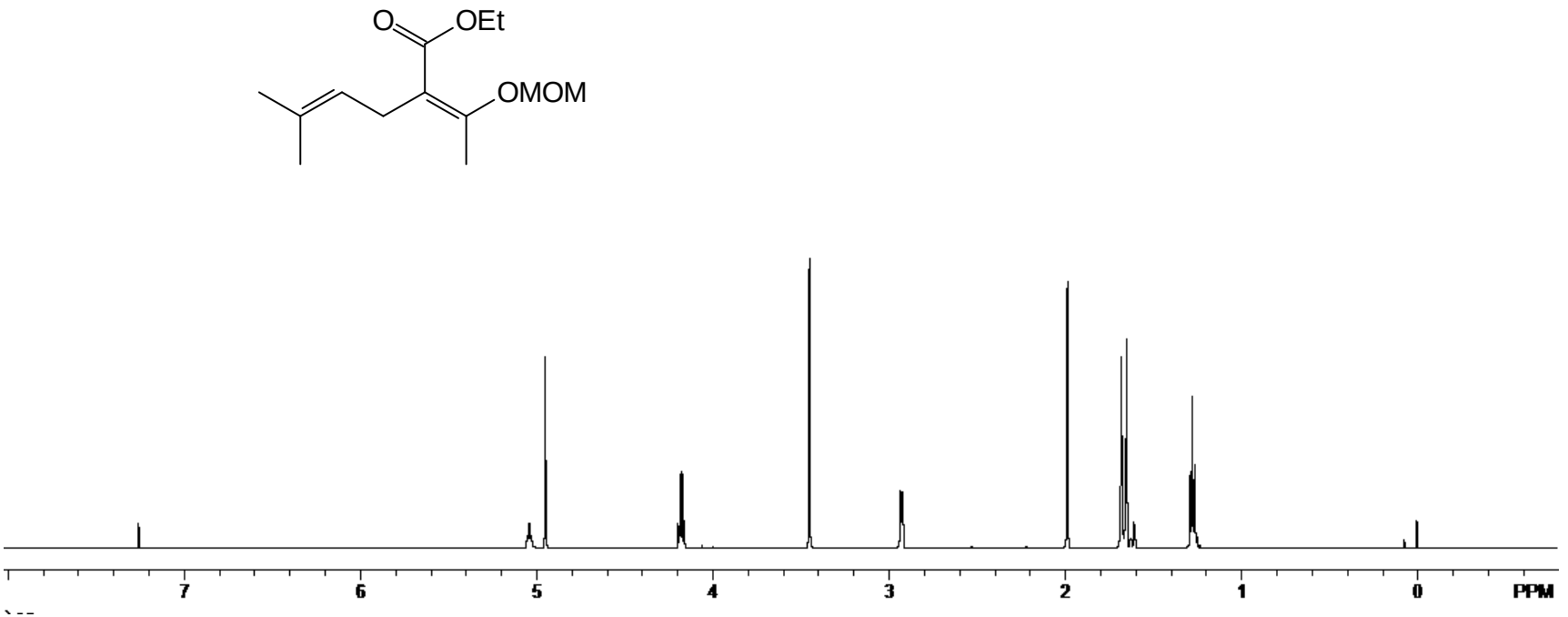


Figure A20. ^{1}H NMR spectrum of *Z*–enol ether **253**

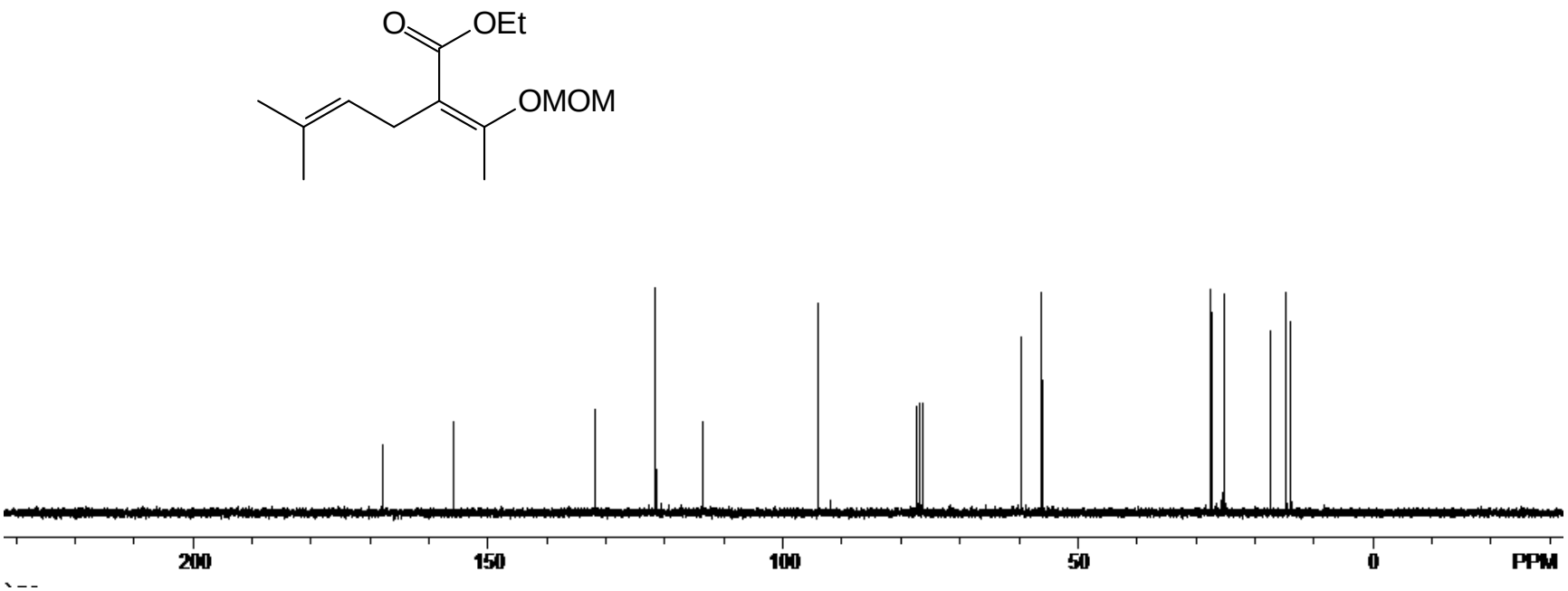


Figure A21. ^{13}C NMR spectrum of *Z*–enol ether **253**

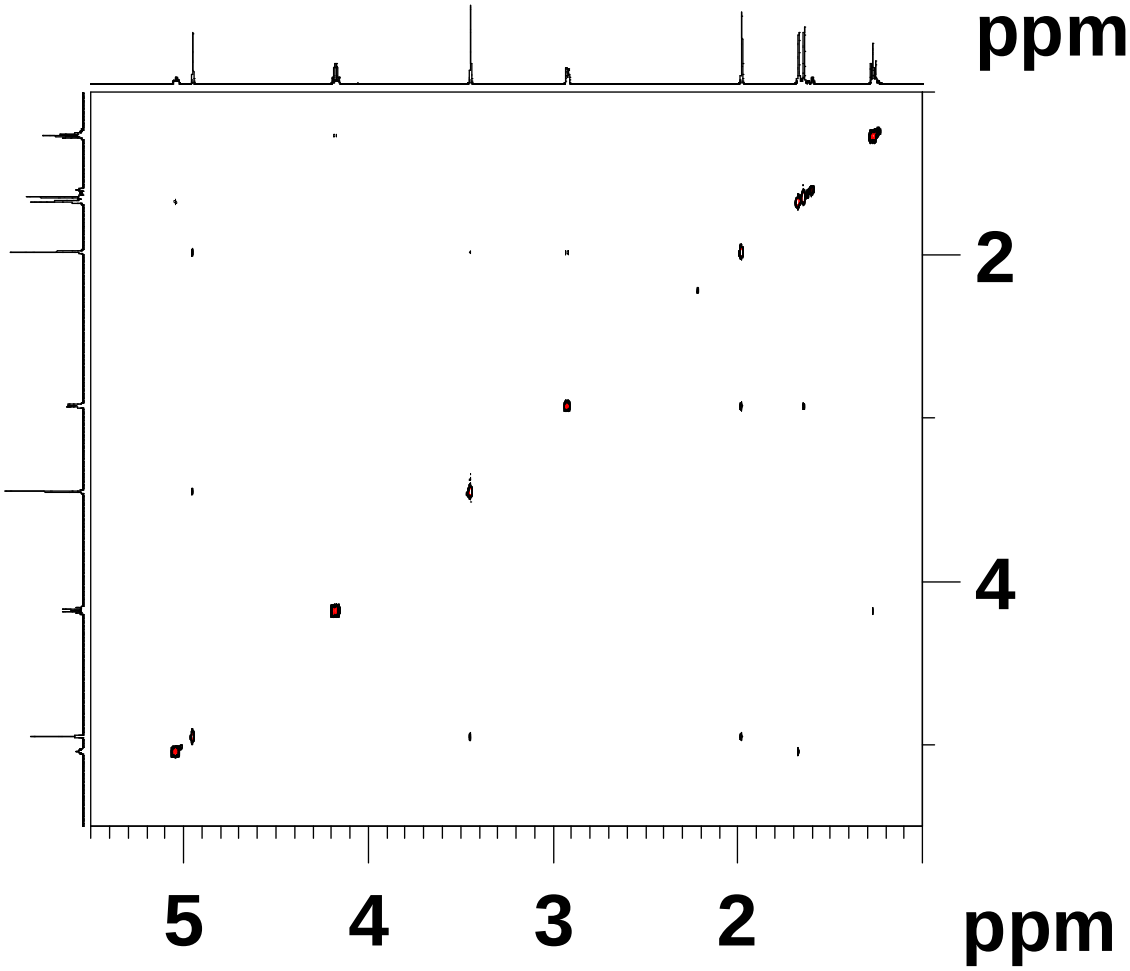


Figure A22. ^{1}H NOESY spectrum of *Z*–enol ether **253**

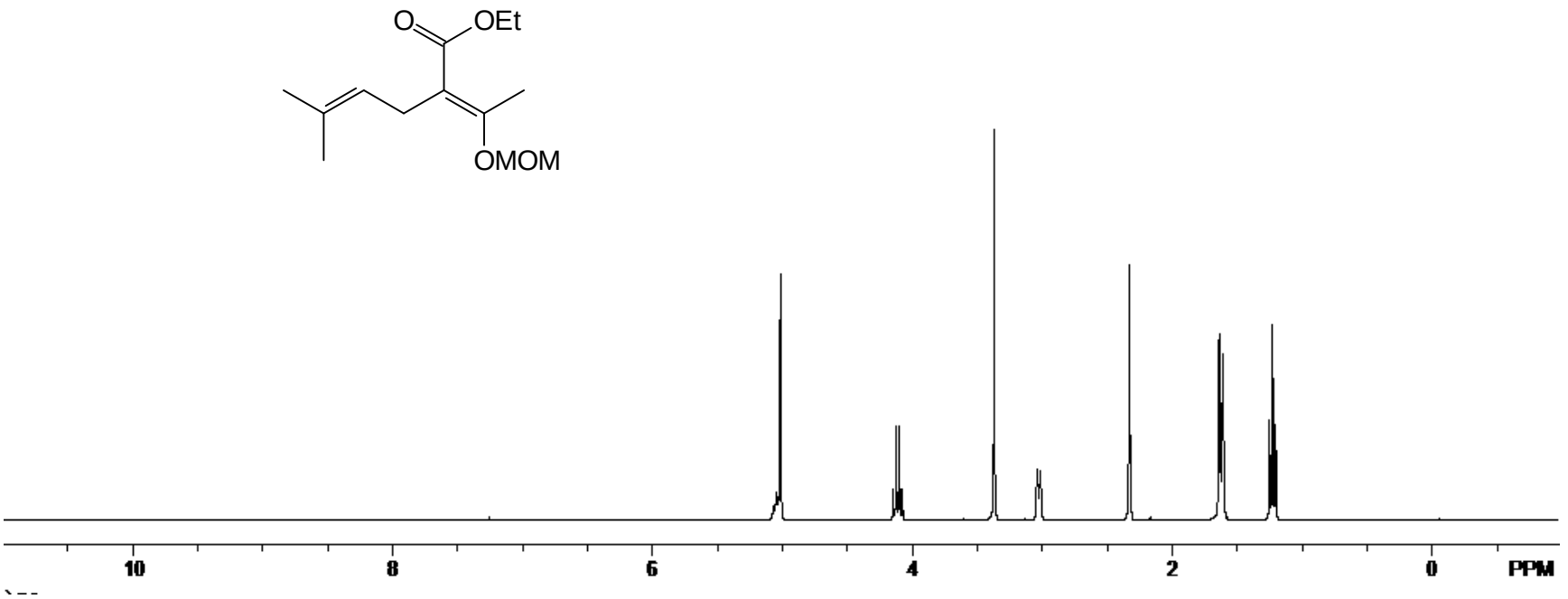


Figure A23. ^{1}H NMR spectrum of *E*–enol ether **254**

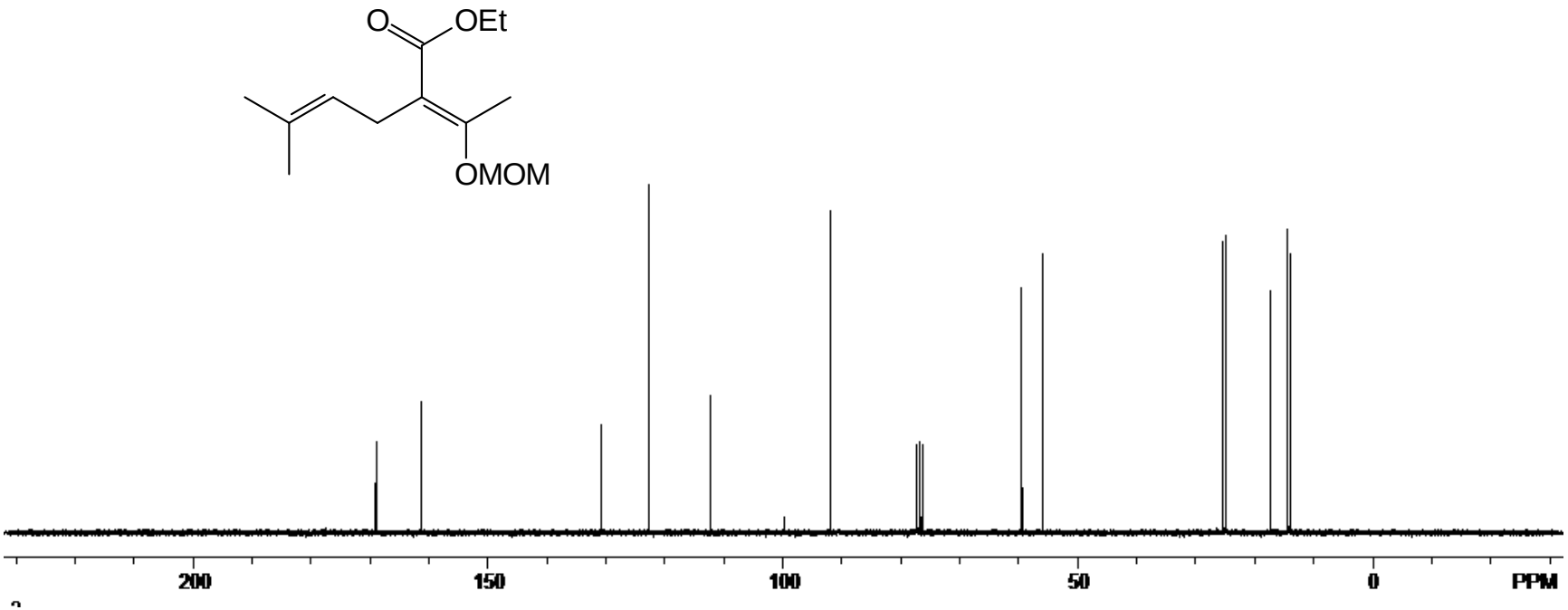


Figure A24. ^{13}C NMR spectrum of *E*–enol ether **254**

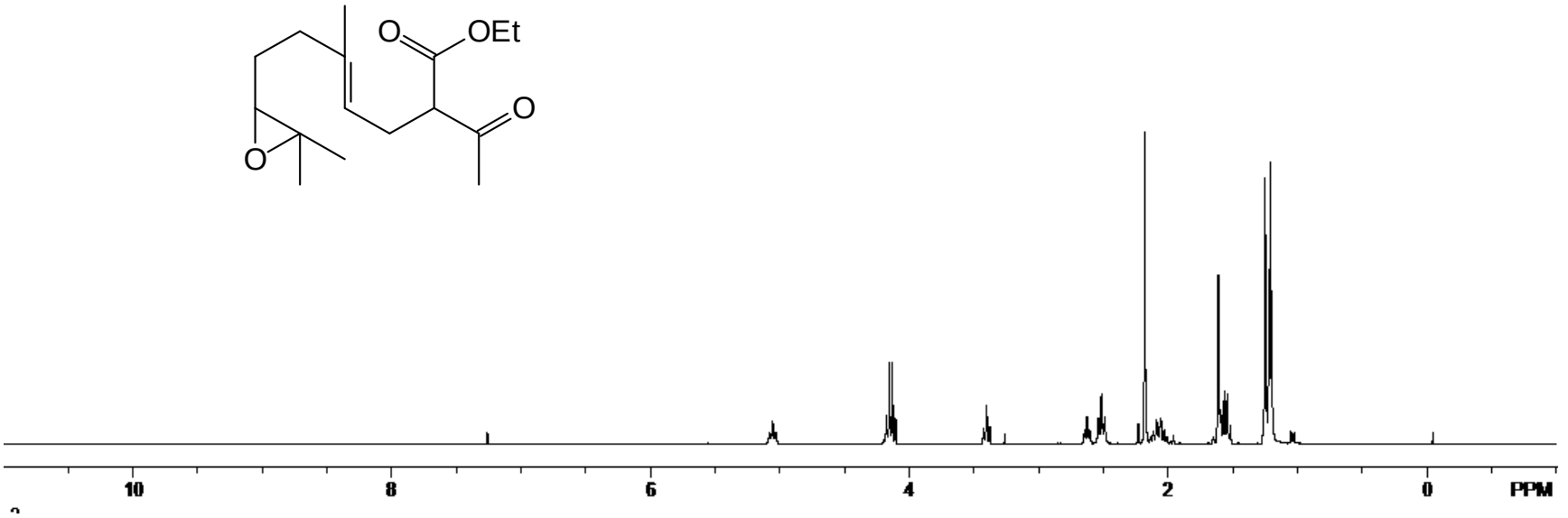


Figure A25. ^{1}H NMR spectrum of β–keto ester **194**

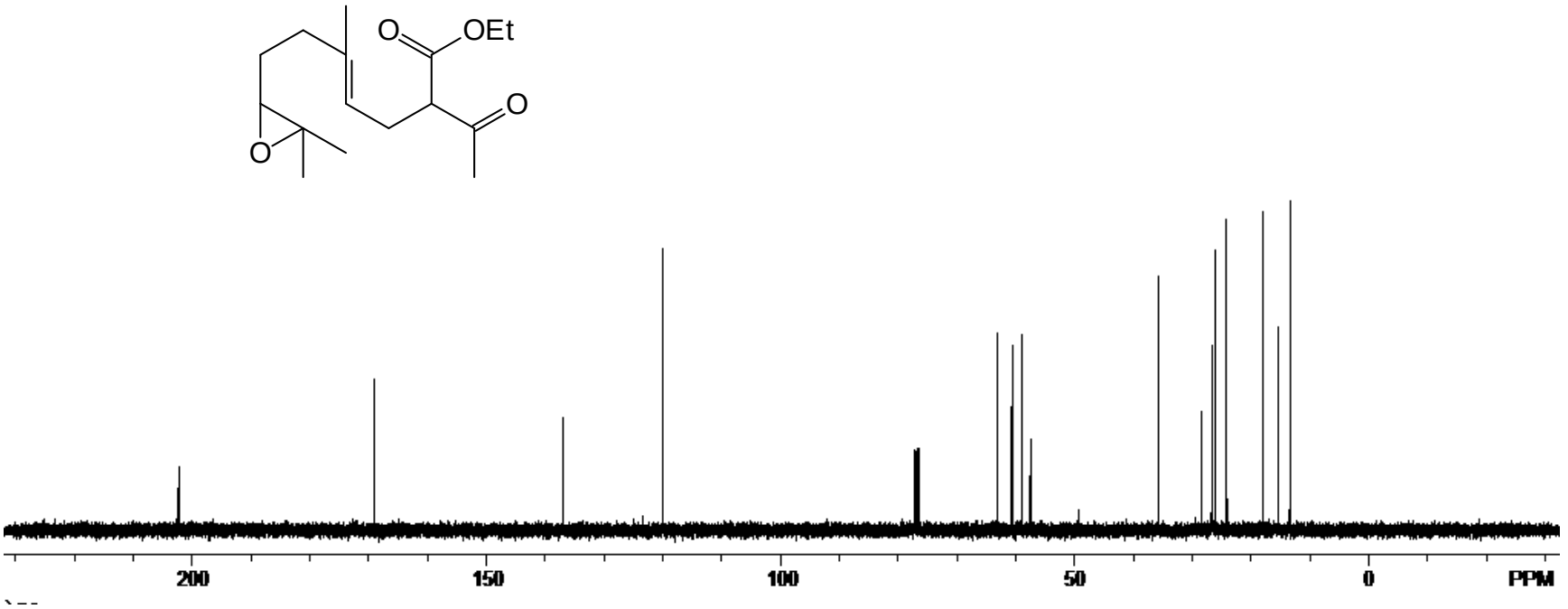


Figure A26. ^{13}C NMR spectrum of β–keto ester **194**

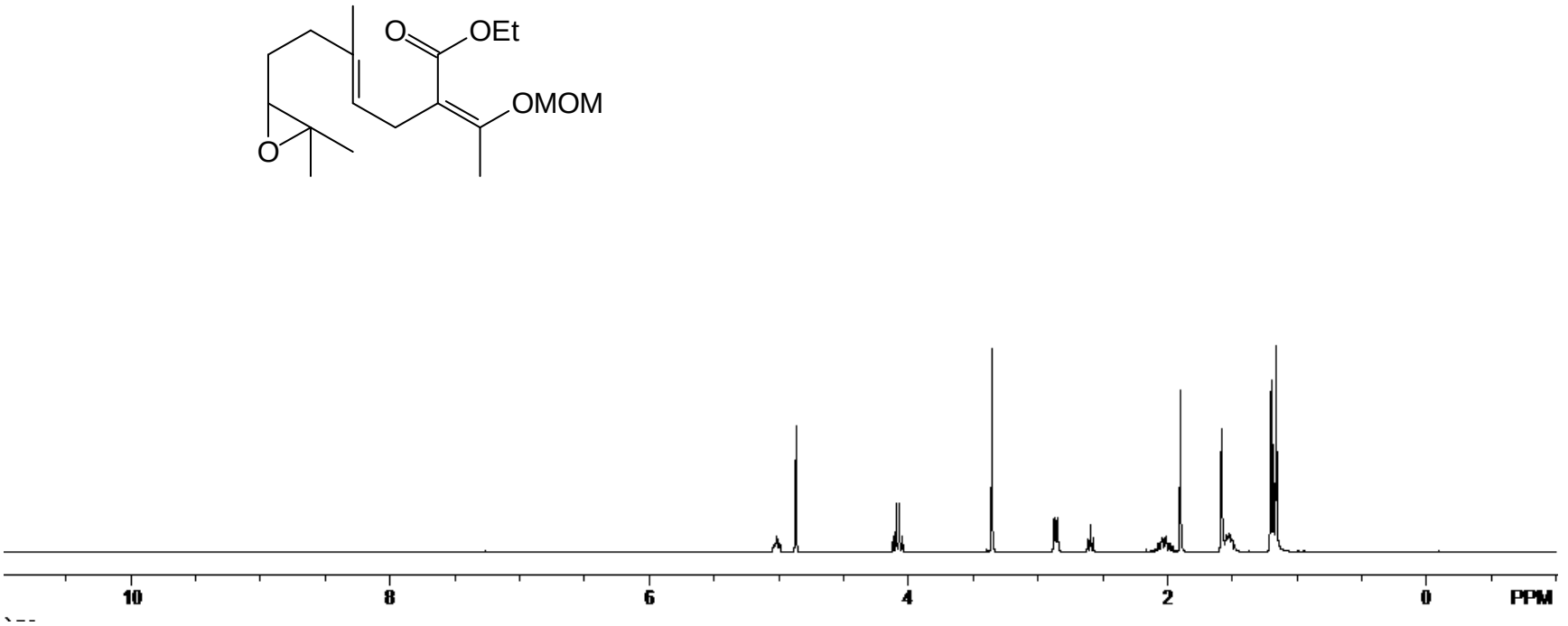


Figure A27. ^{1}H NMR spectrum of *Z*–enol ether **261**

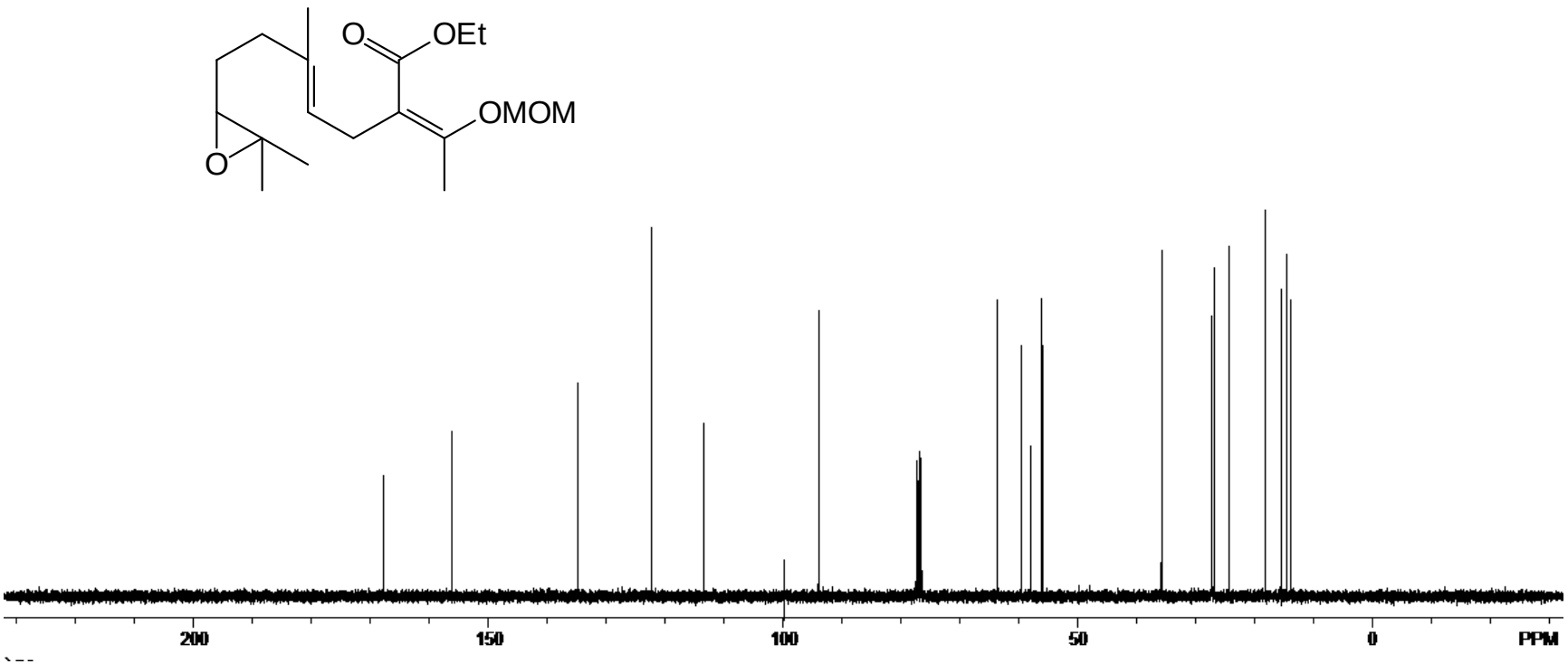


Figure A28. ^{13}C NMR spectrum of *Z*–enol ether **261**

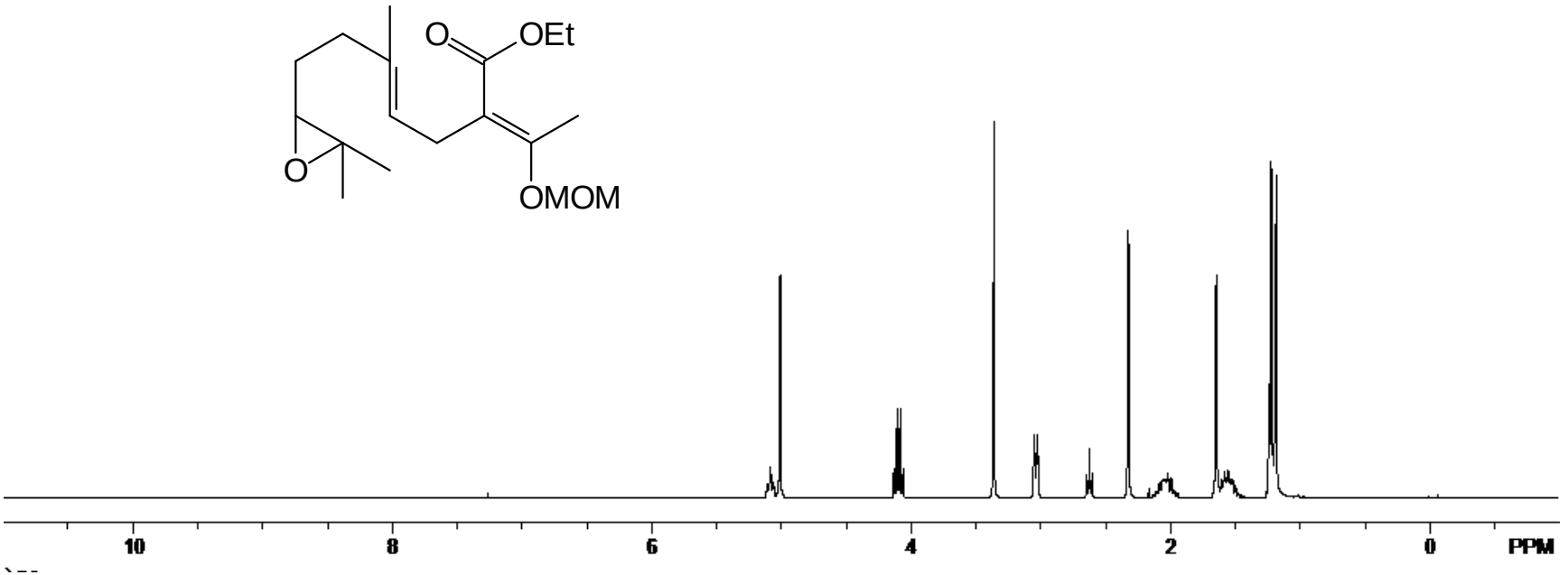


Figure A29. ^{1}H NMR spectrum of *E*–enol ether **266**

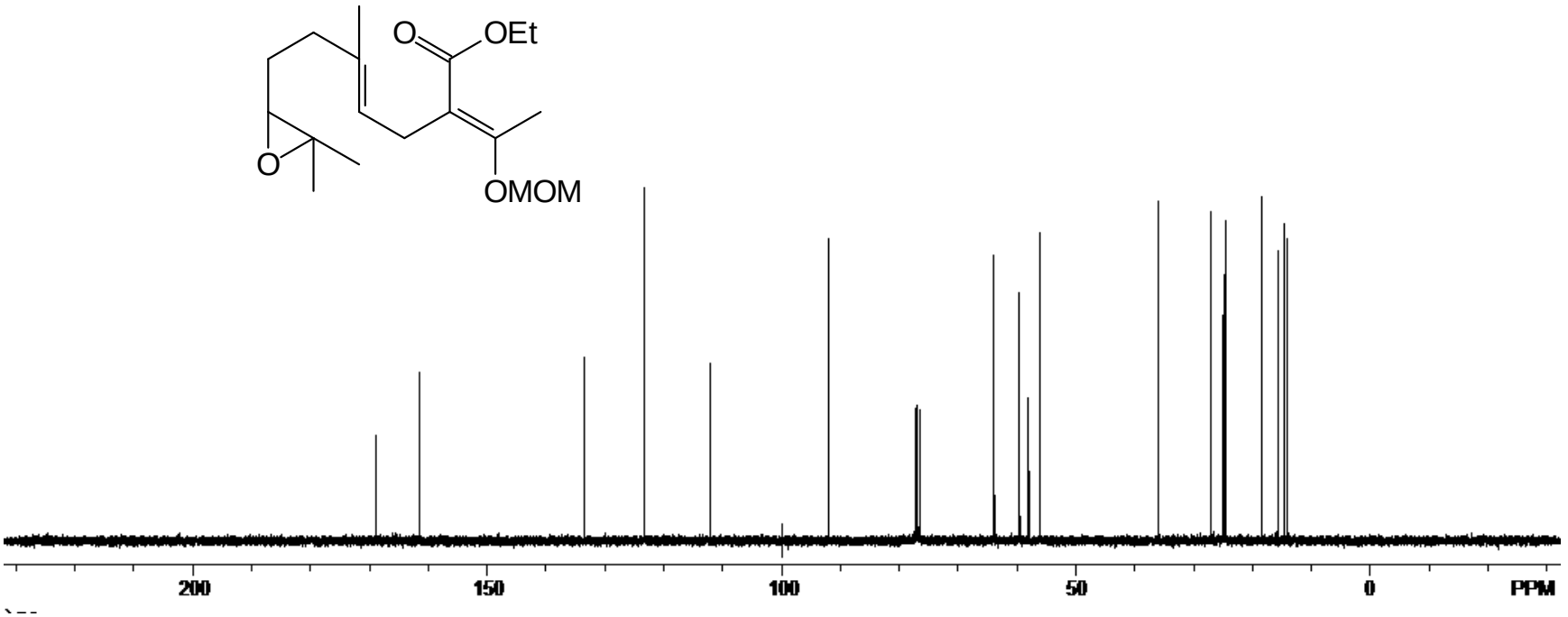


Figure A30. ^{13}C NMR spectrum of *E*–enol ether **266**

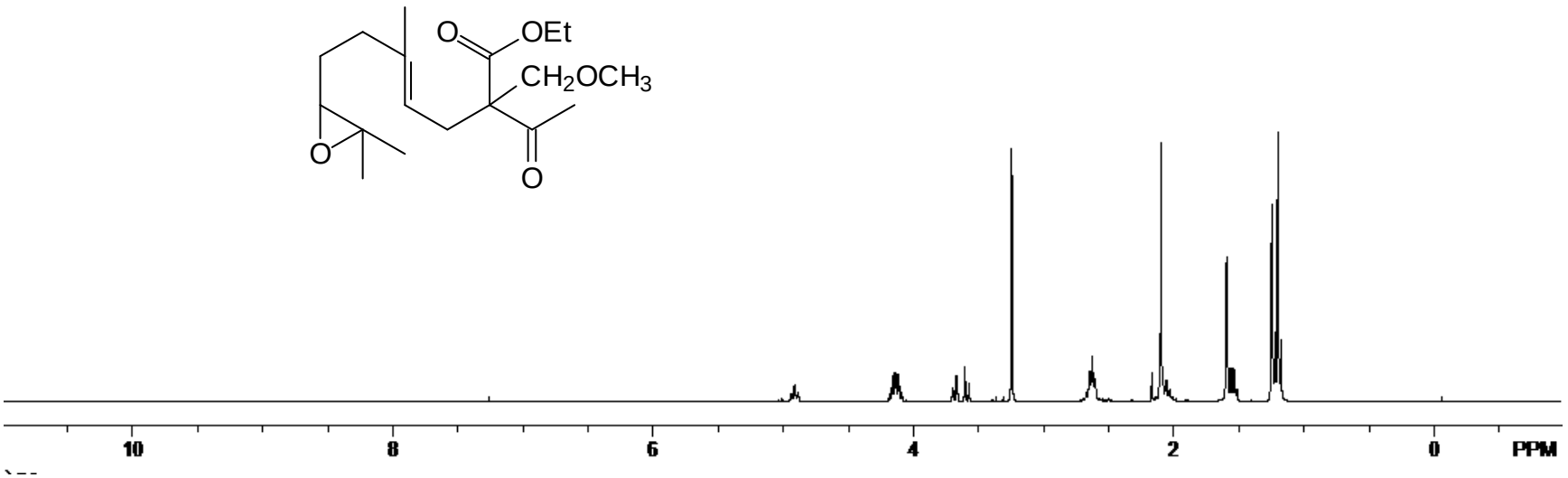


Figure A31. ^{1}H NMR spectrum of β–keto ester **202**

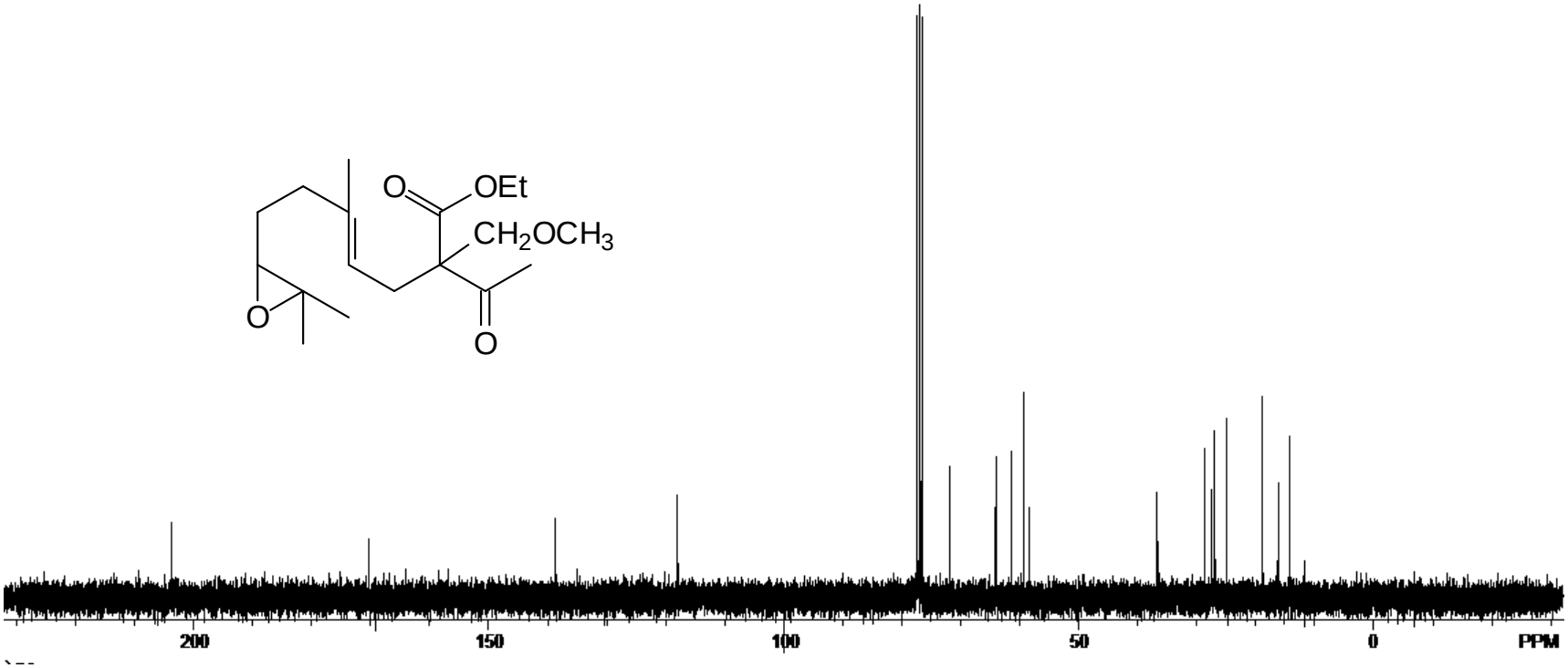


Figure A32. ^{13}C NMR spectrum of β–keto ester **202**

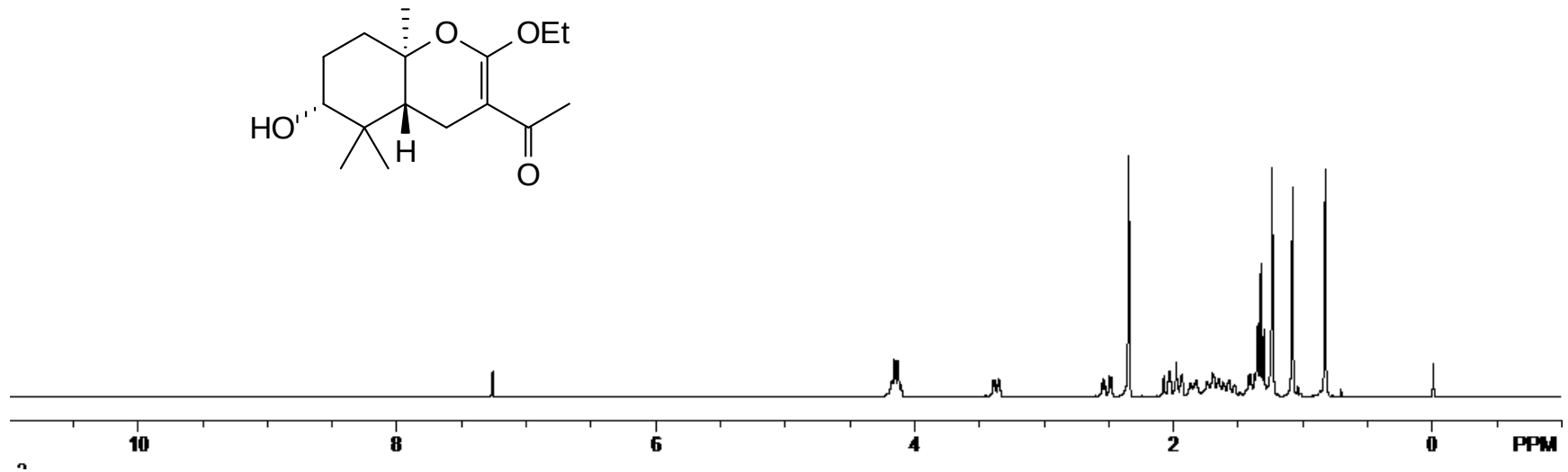


Figure A33. ^{1}H NMR spectrum of ketone **265**

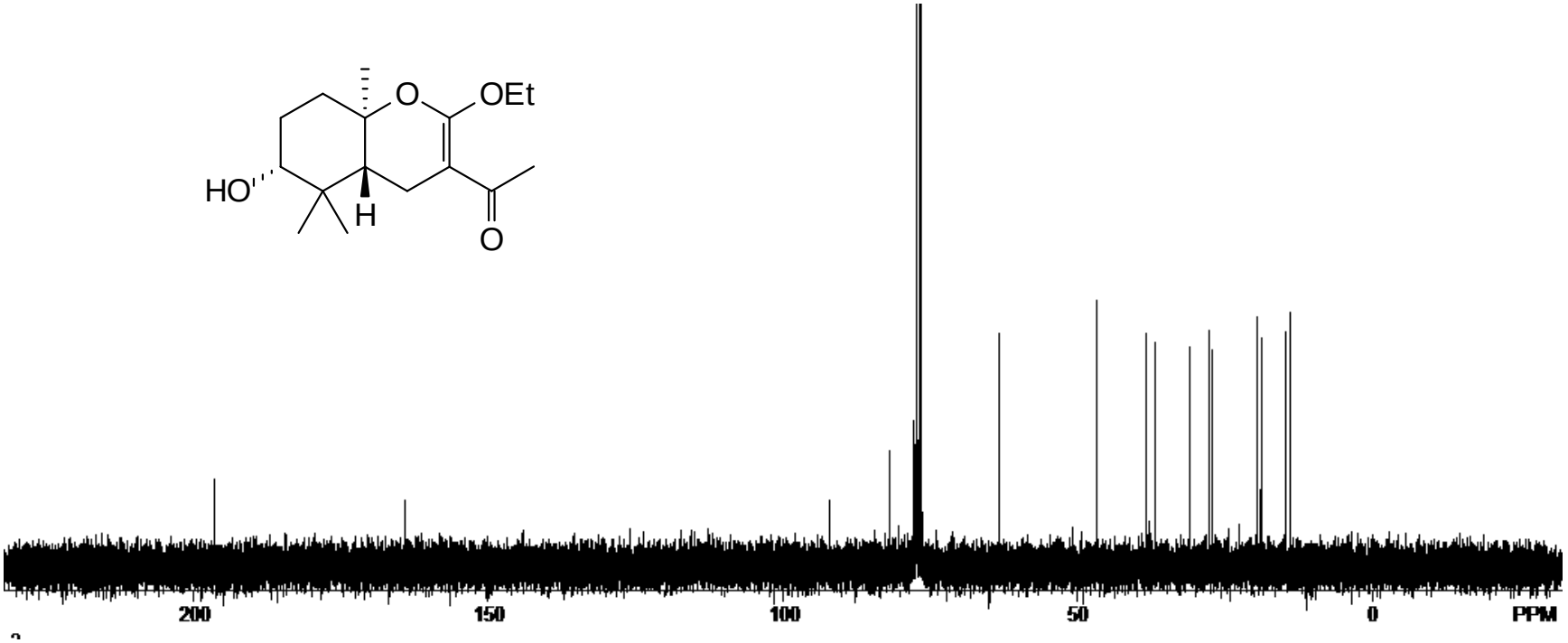


Figure A34. ^{13}C NMR spectrum of ketone **265**

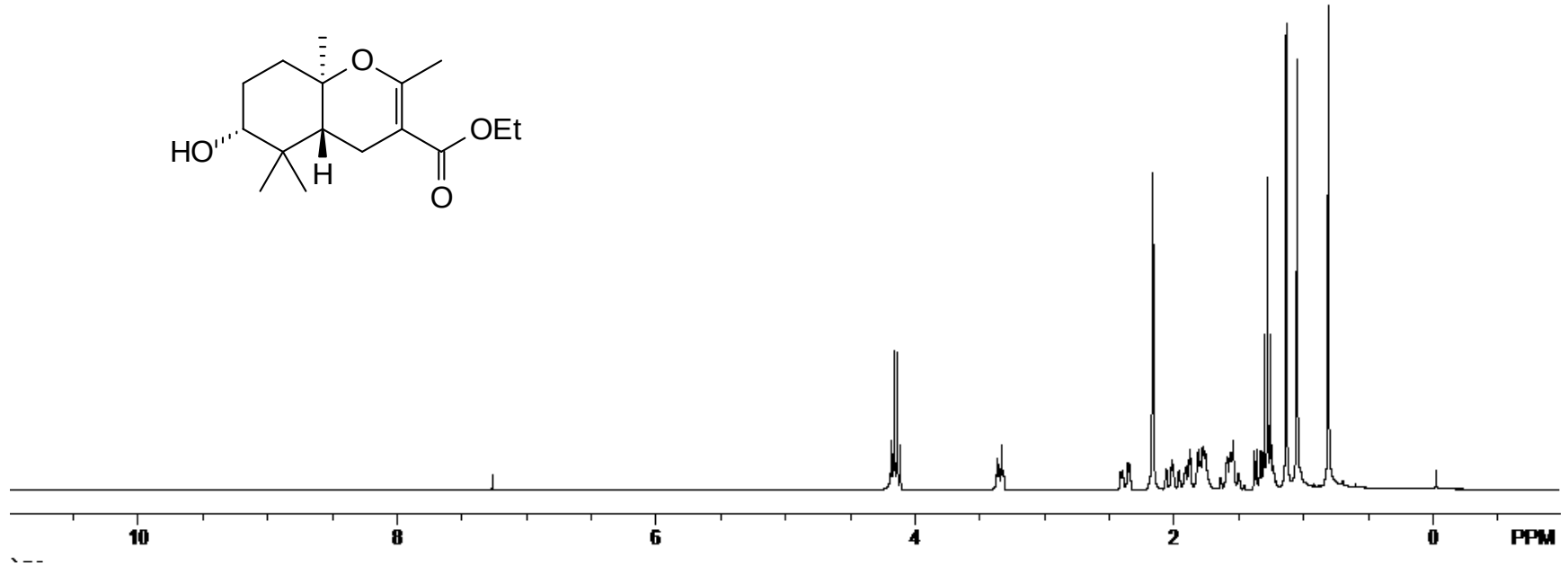


Figure A35. ^{1}H NMR spectrum of ester **263**

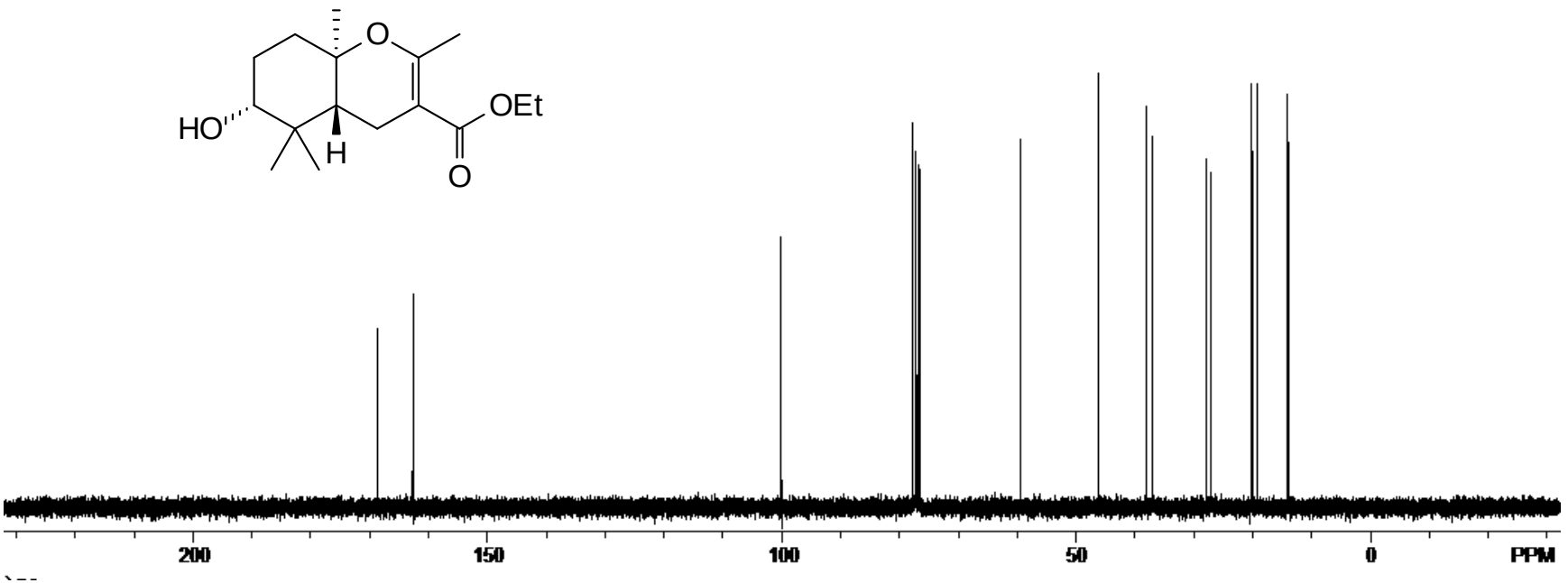


Figure A36. ^{13}C NMR spectrum of ester **263**

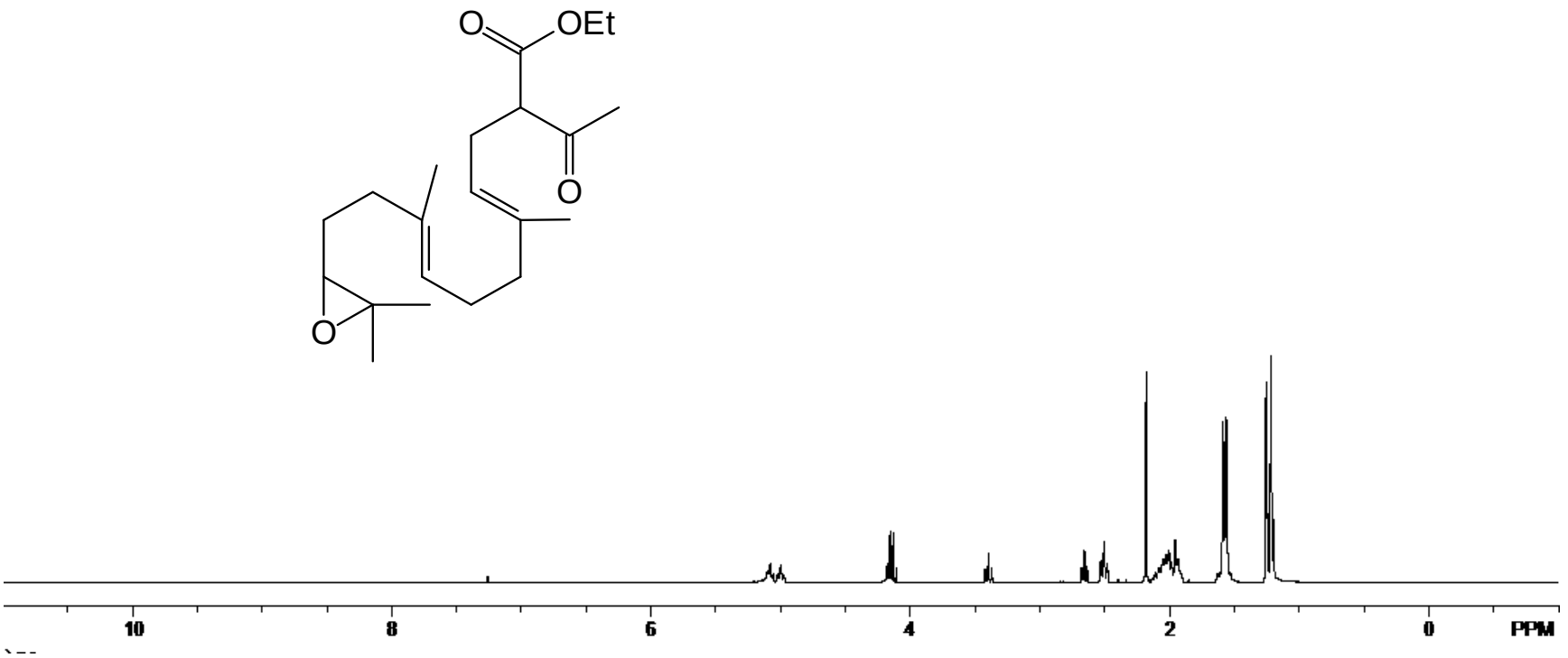


Figure A37. ^{1}H NMR spectrum of β–keto ester **183**

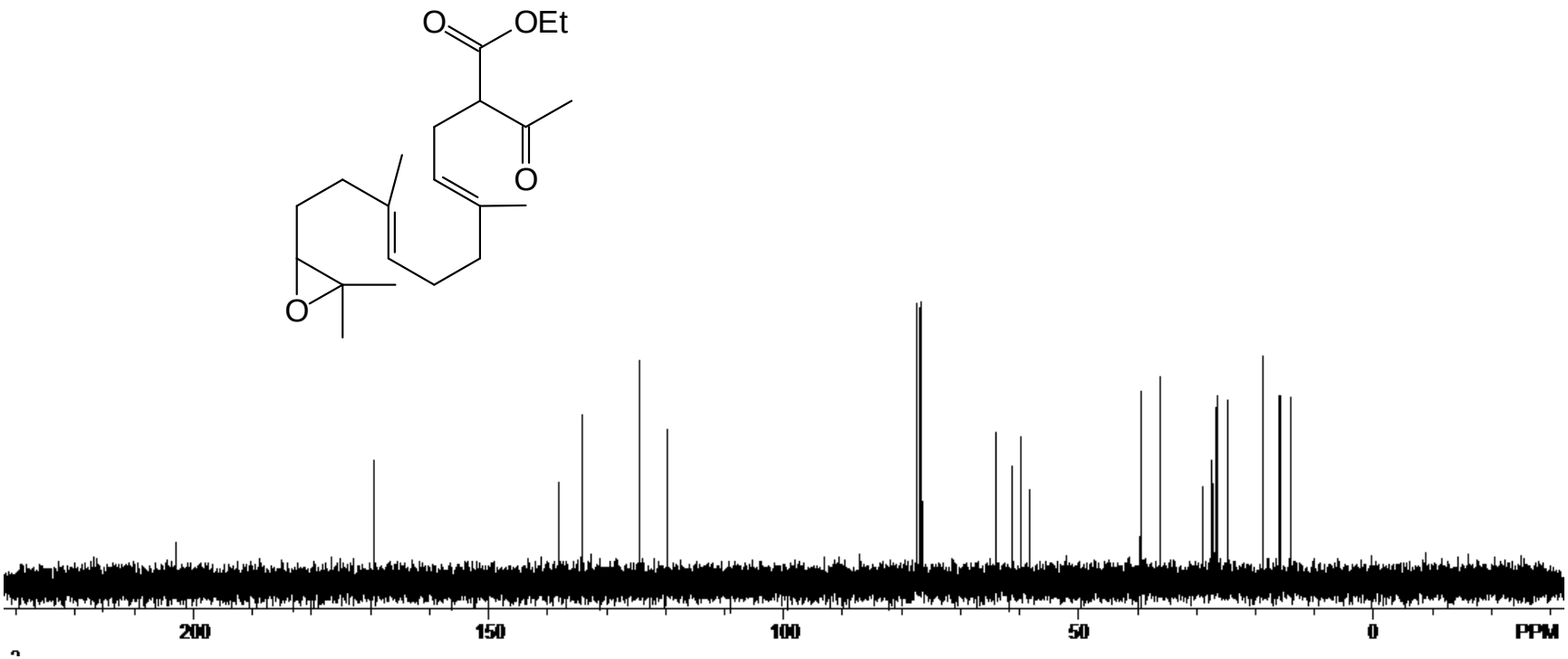


Figure A38. ^{13}C NMR spectrum of β–keto ester **183**

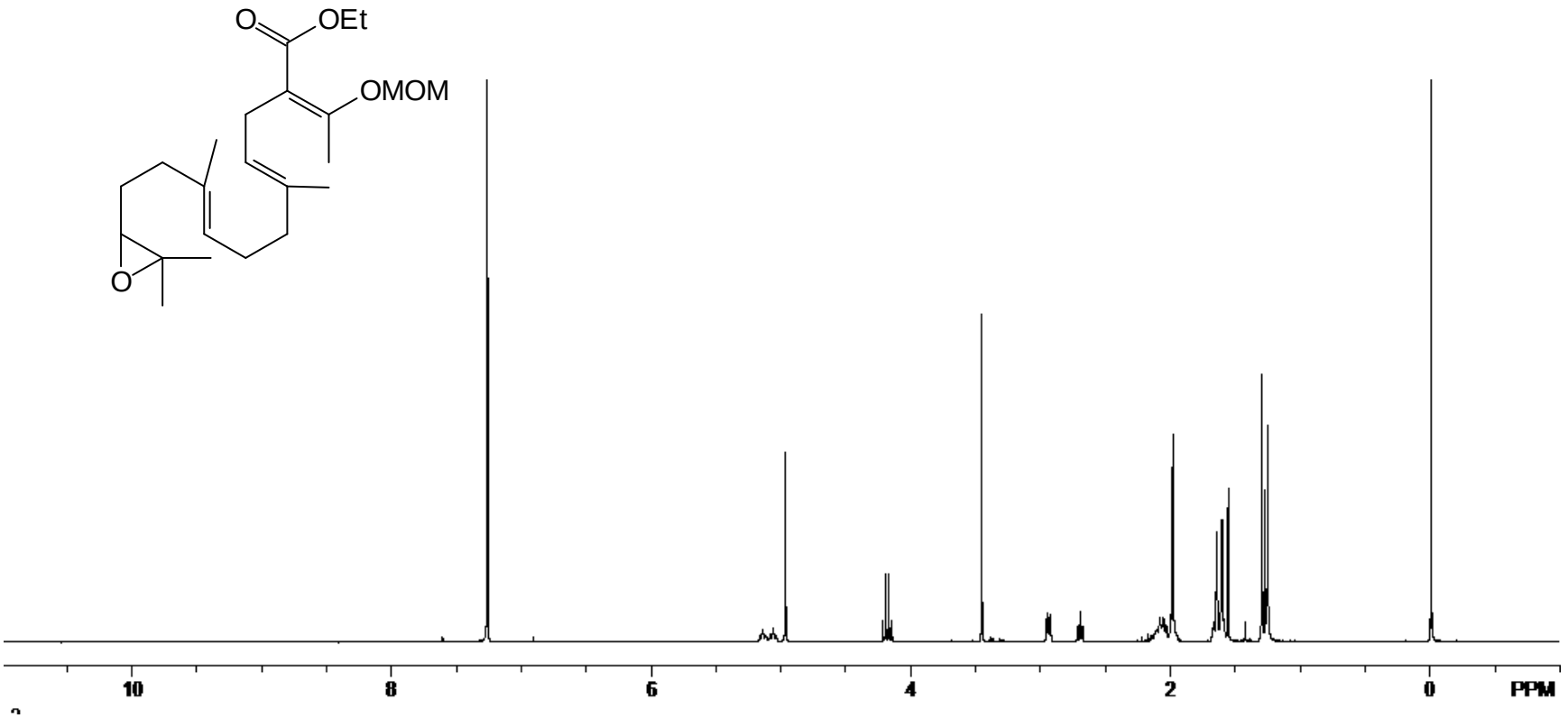


Figure A39. ^{1}H NMR spectrum of *Z*–enol ether **184**

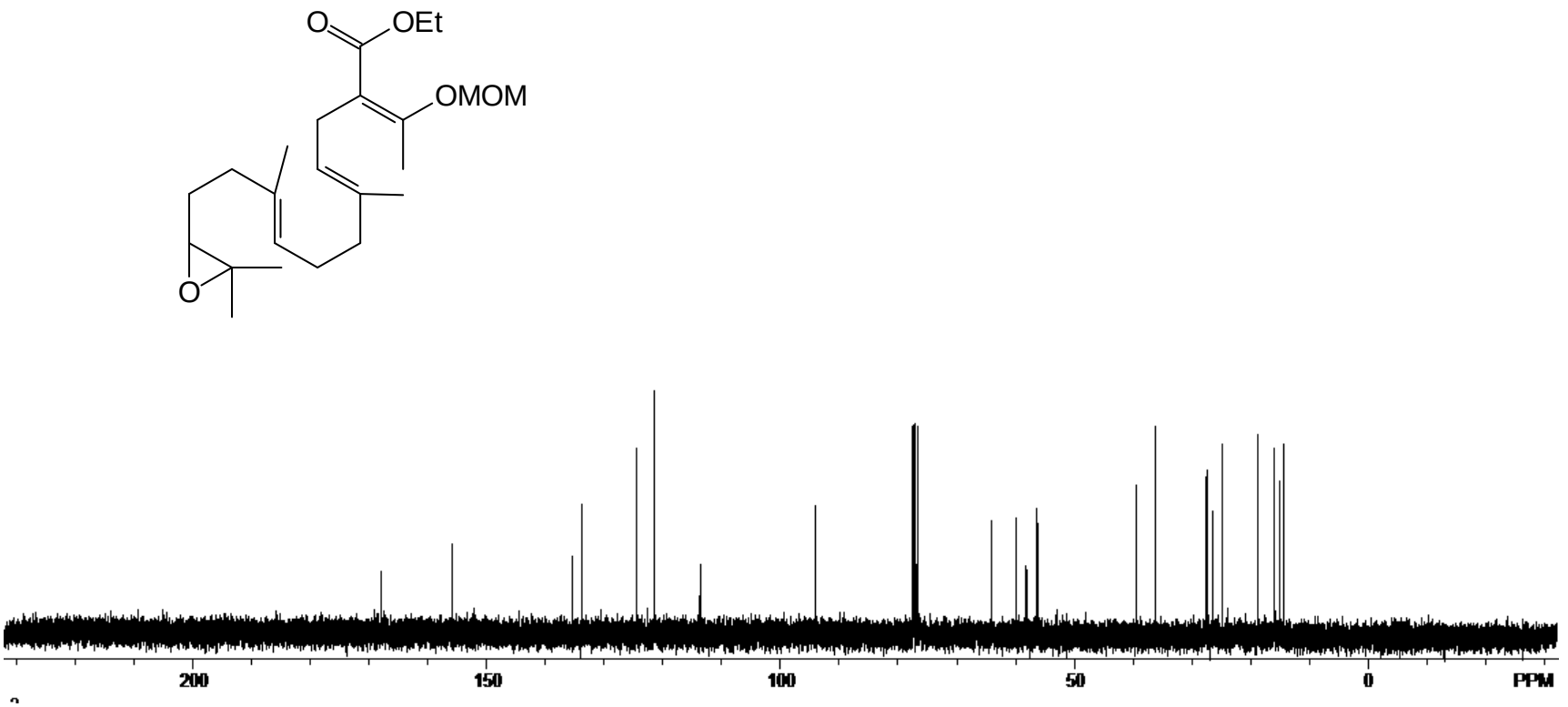


Figure A40. ^{13}C NMR spectrum of *Z*–enol ether **184**

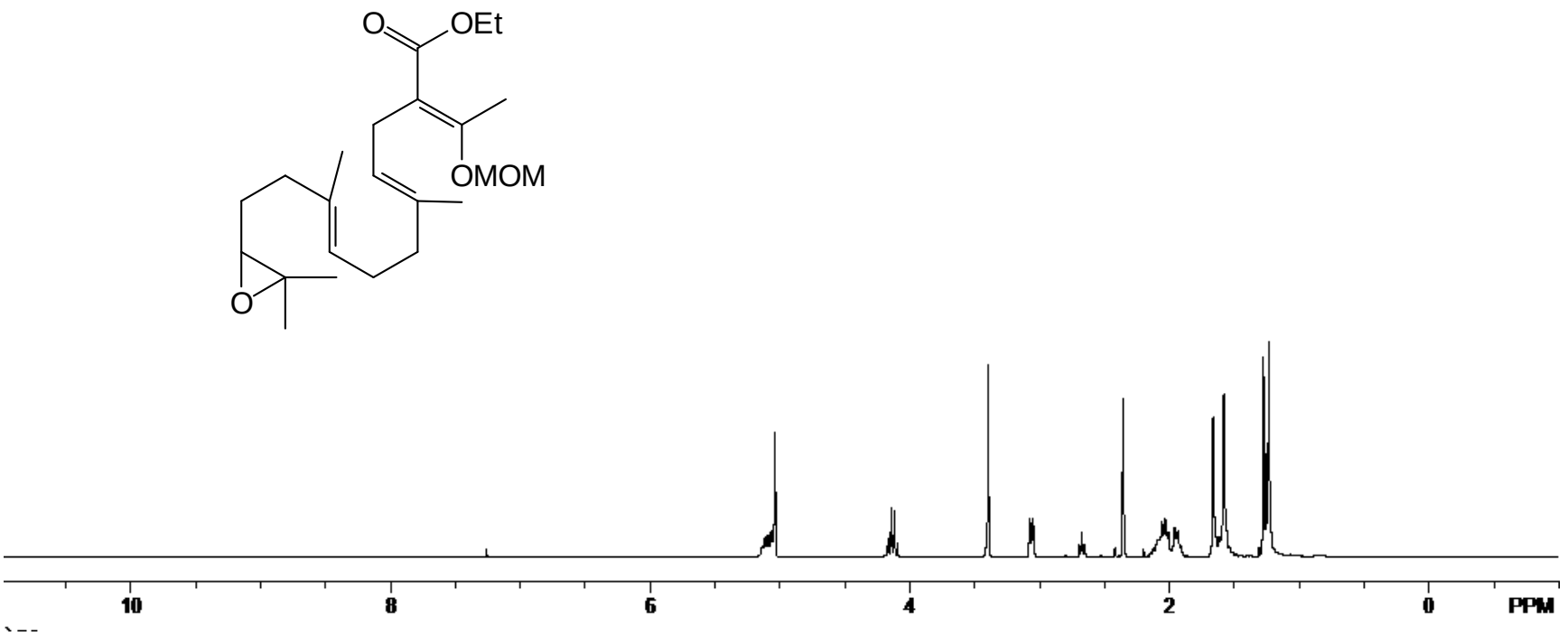


Figure A41. ^{1}H NMR spectrum of *E*–enol ether **186**

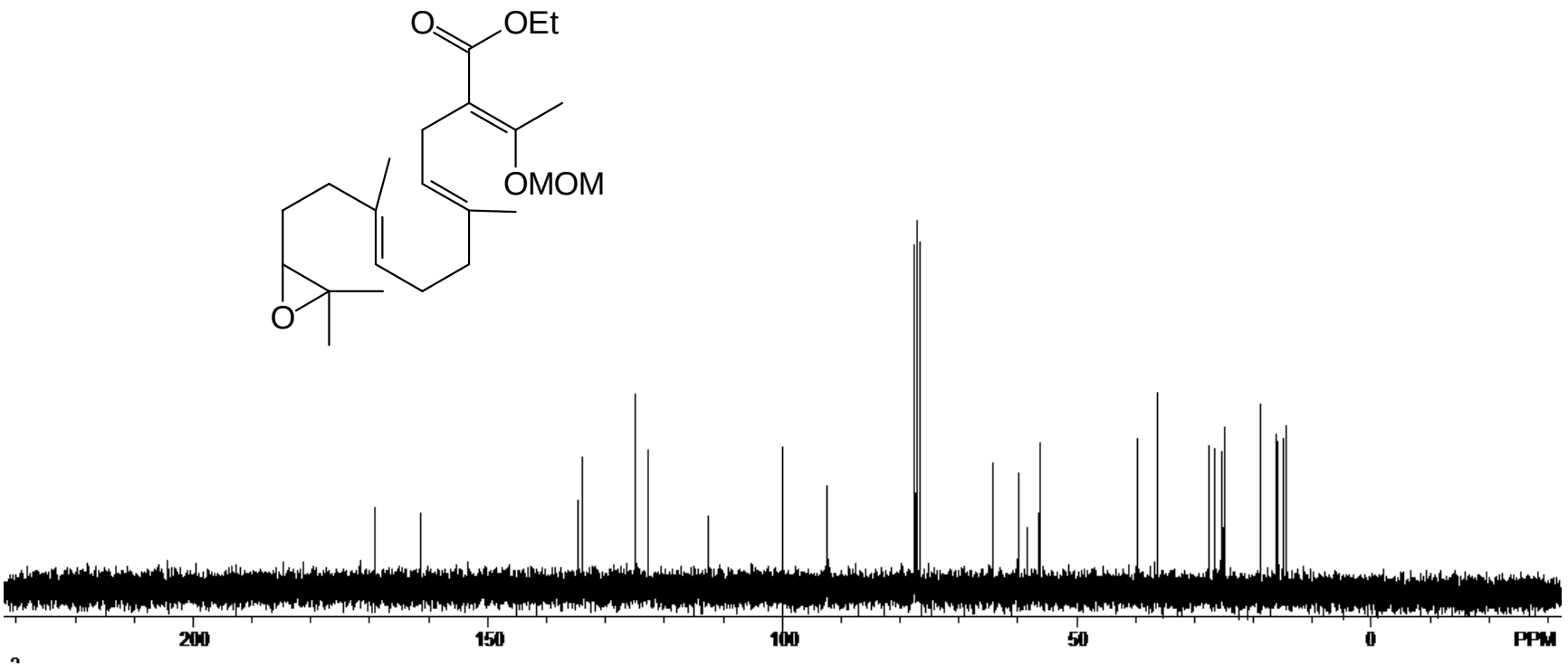


Figure A42. ^{13}C NMR spectrum of *E*–enol ether **186**

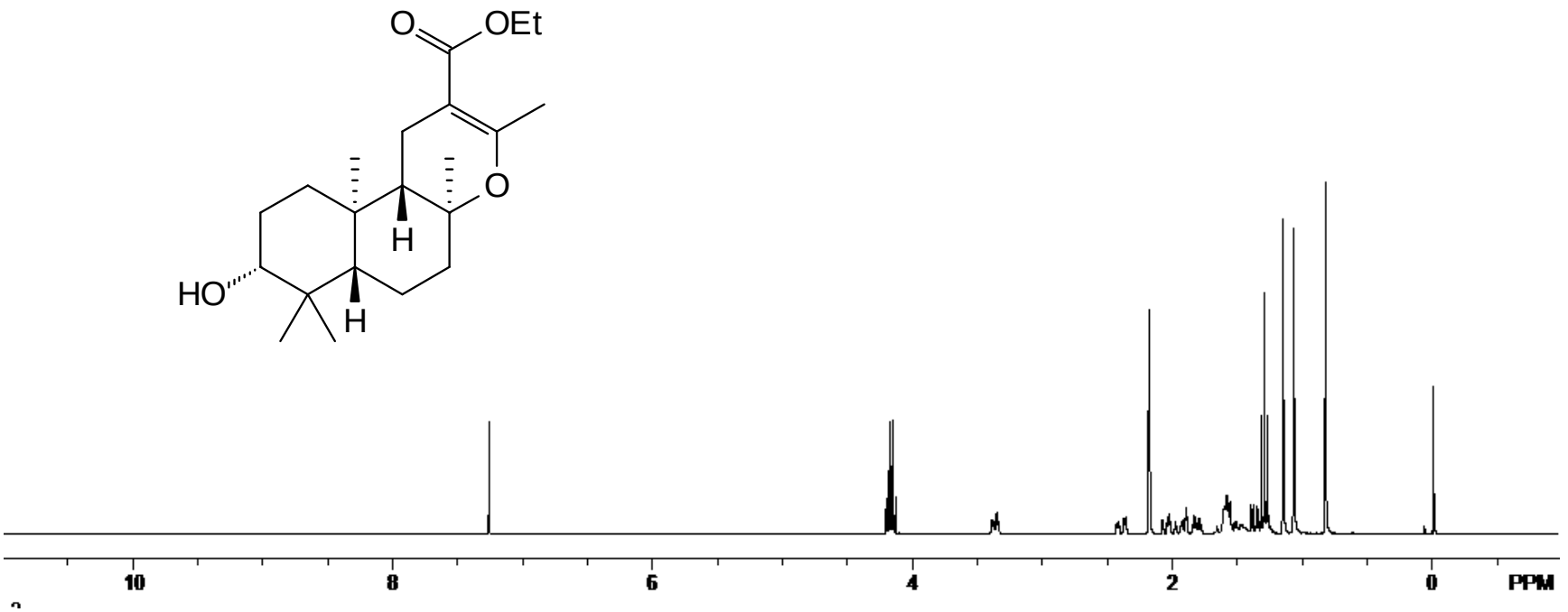


Figure A43. ^{1}H NMR spectrum of ester **187**

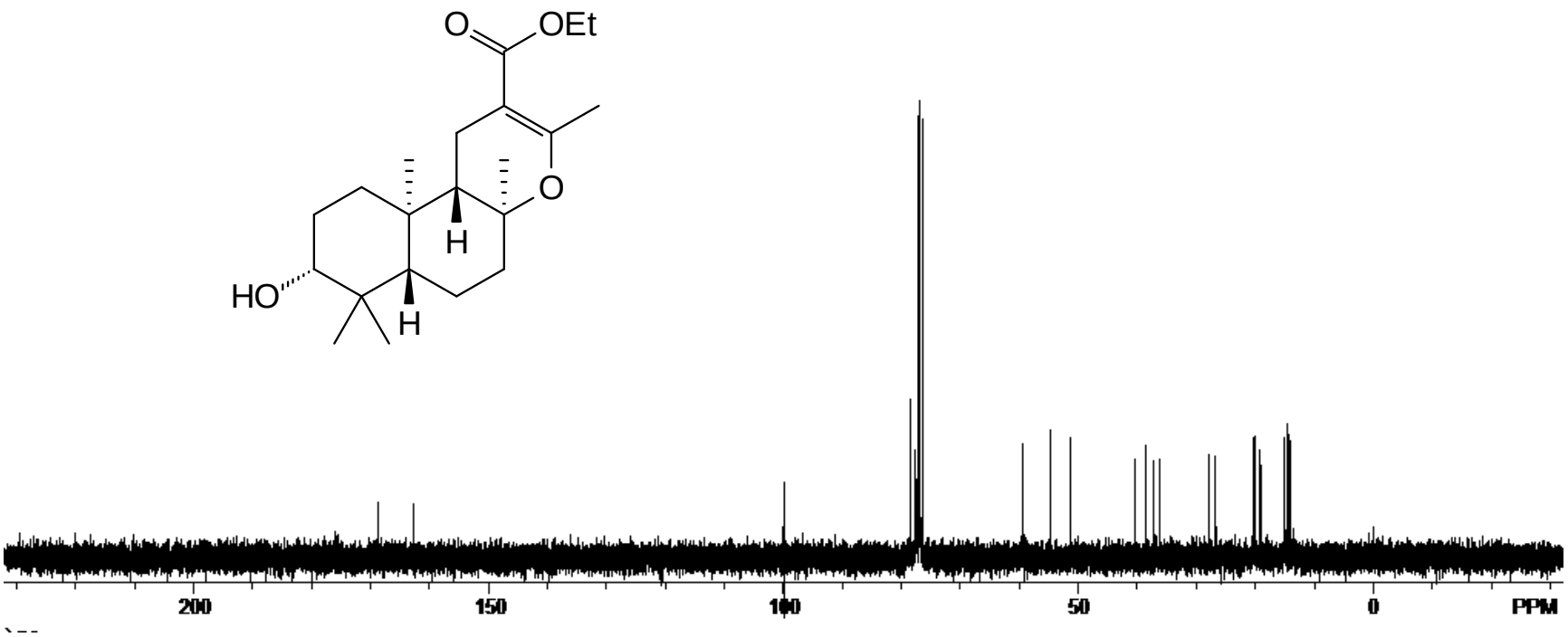


Figure A44. ^{13}C NMR spectrum of ester **187**

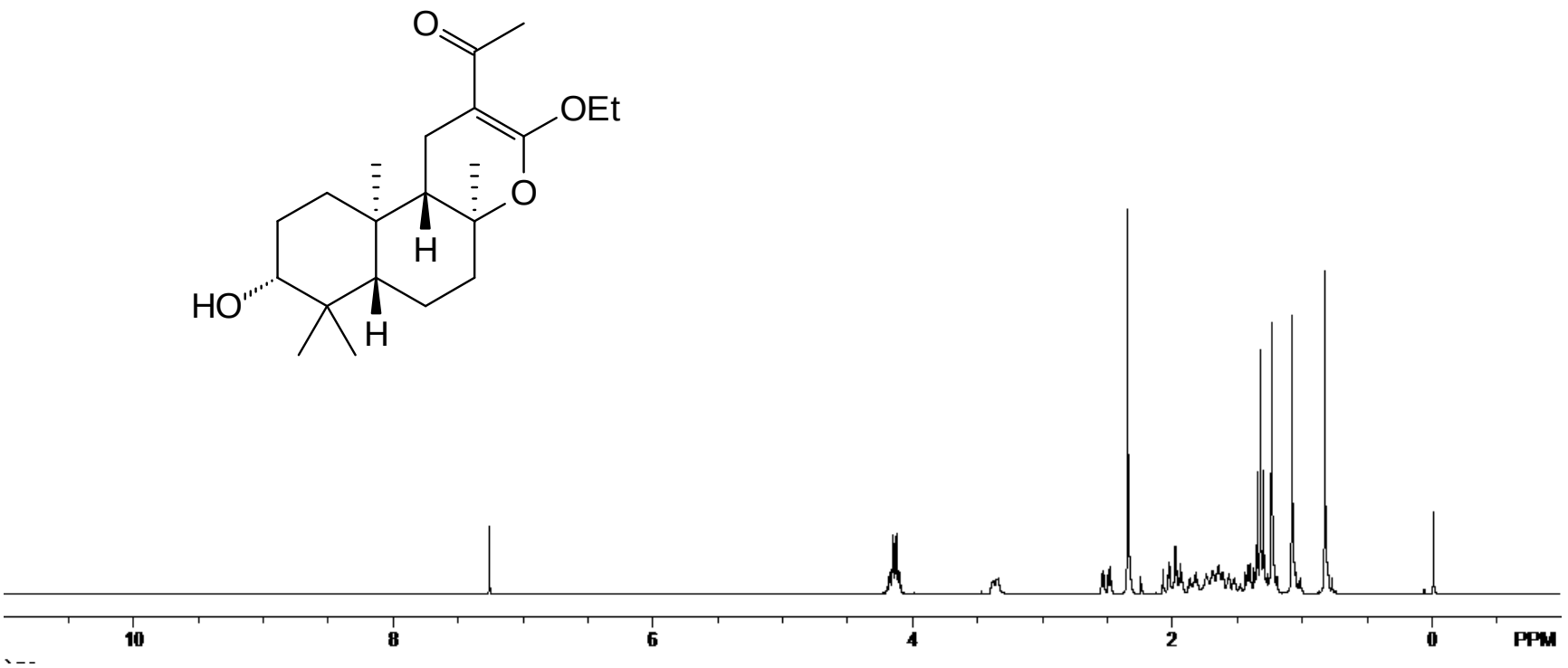


Figure A45. ^{1}H NMR spectrum of ketone **185**

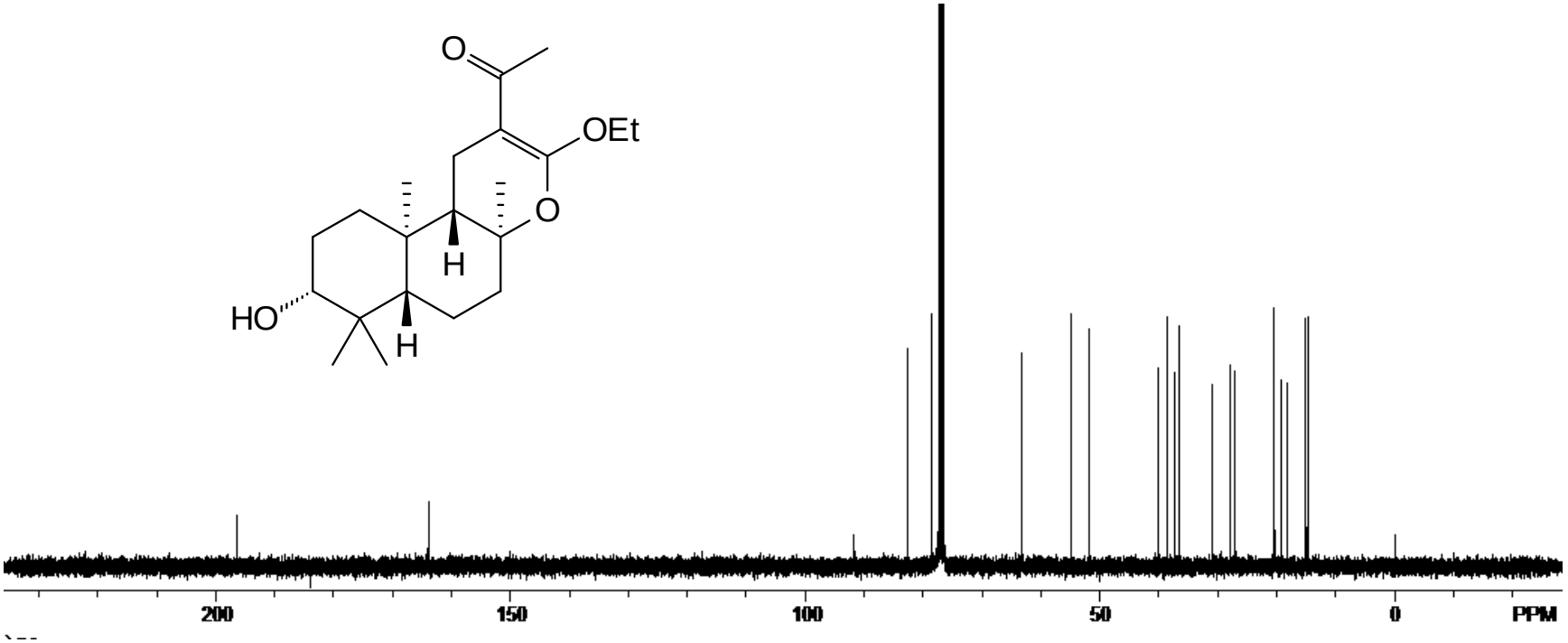


Figure A46. ^{13}C NMR spectrum of ketone **185**

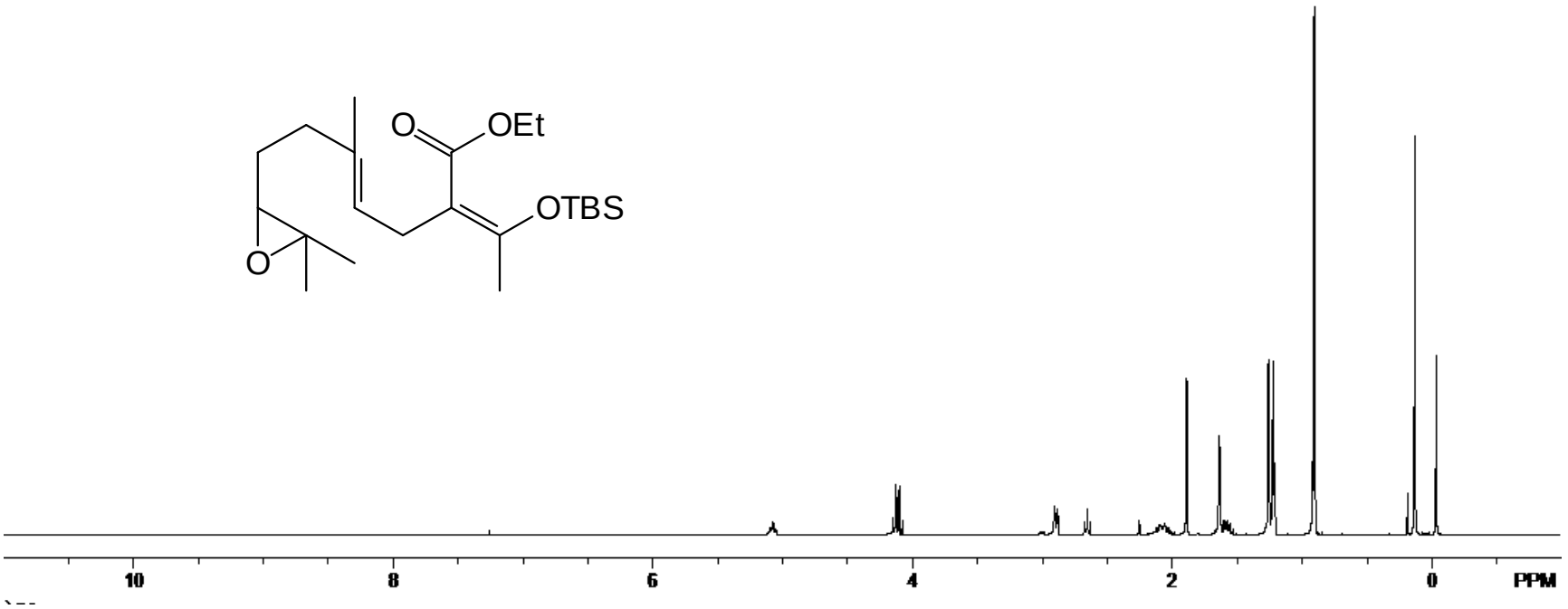


Figure A47. ^{1}H NMR spectrum of *Z*–silyl enol ether **290**

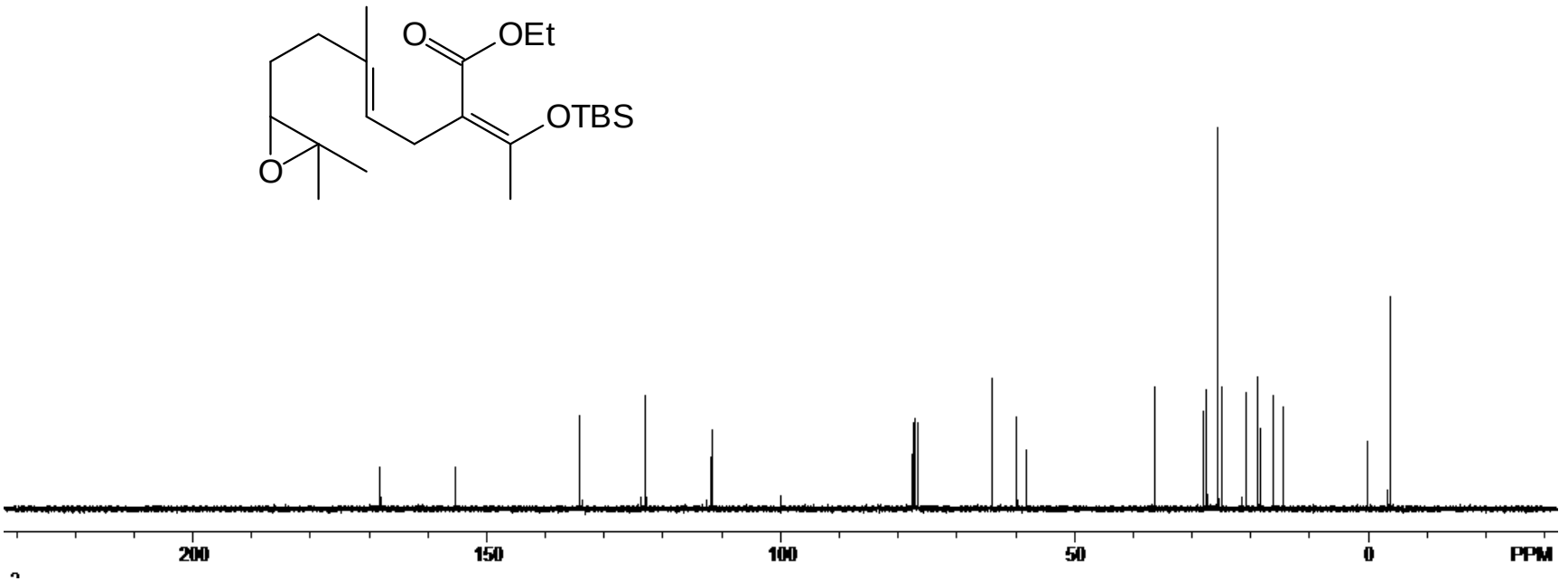


Figure A48. ^{13}C NMR spectrum of *Z*–silyl enol ether **290**

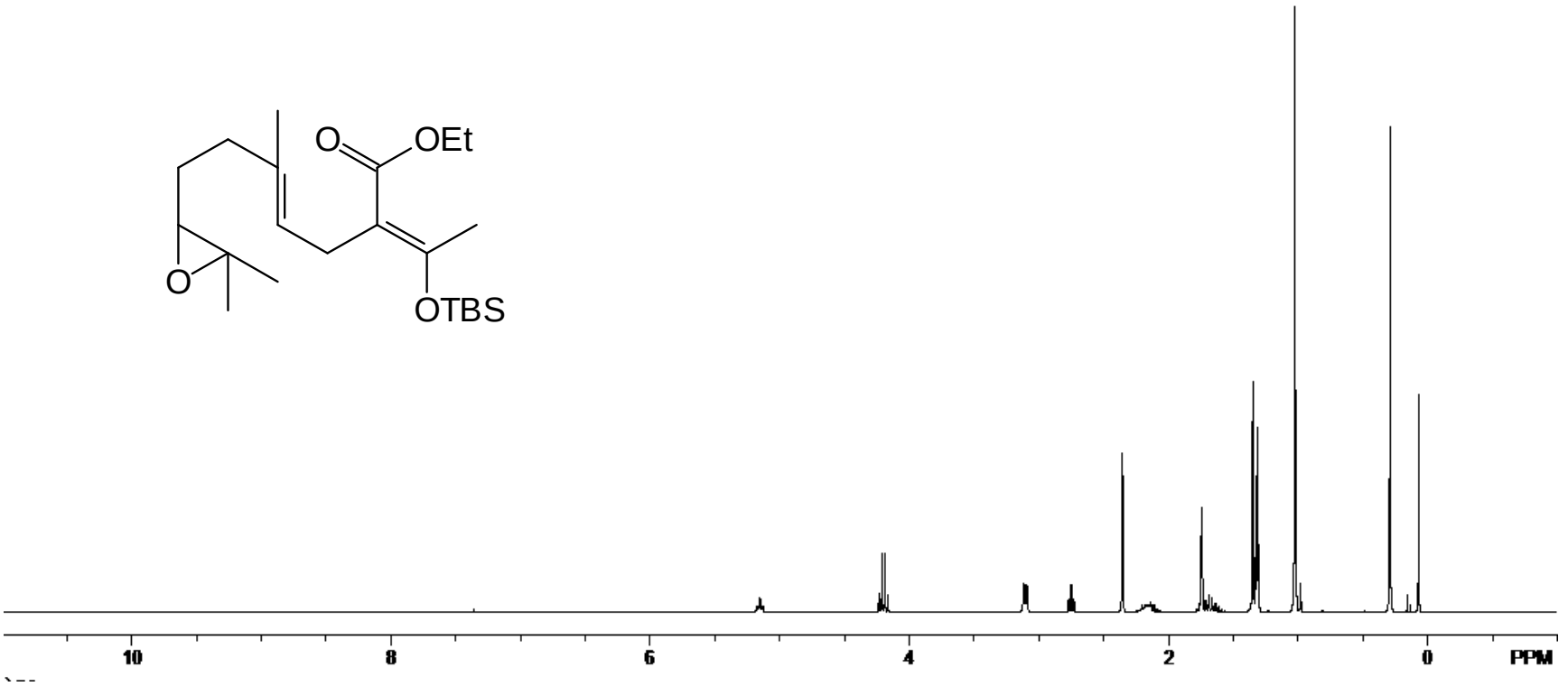


Figure A49. ^{1}H NMR spectrum of *E*–silyl enol ether **293**

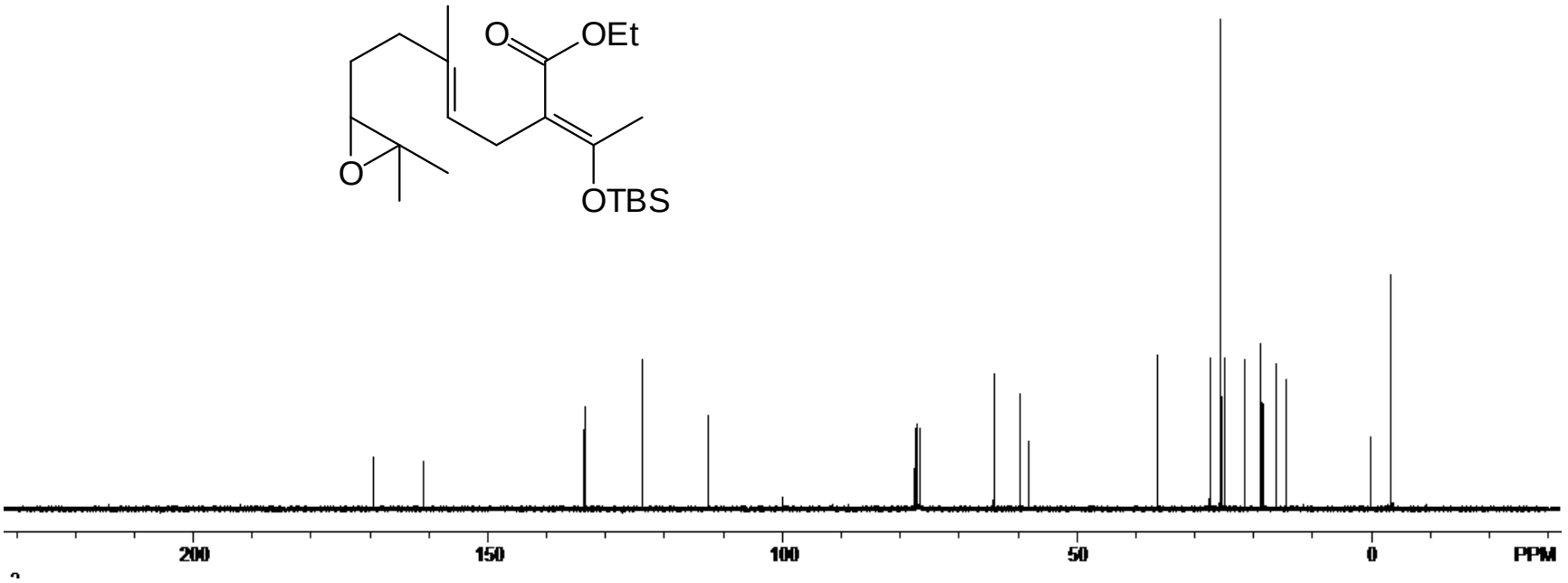


Figure A50. ^{13}C NMR spectrum of *E*–silyl enol ether **293**

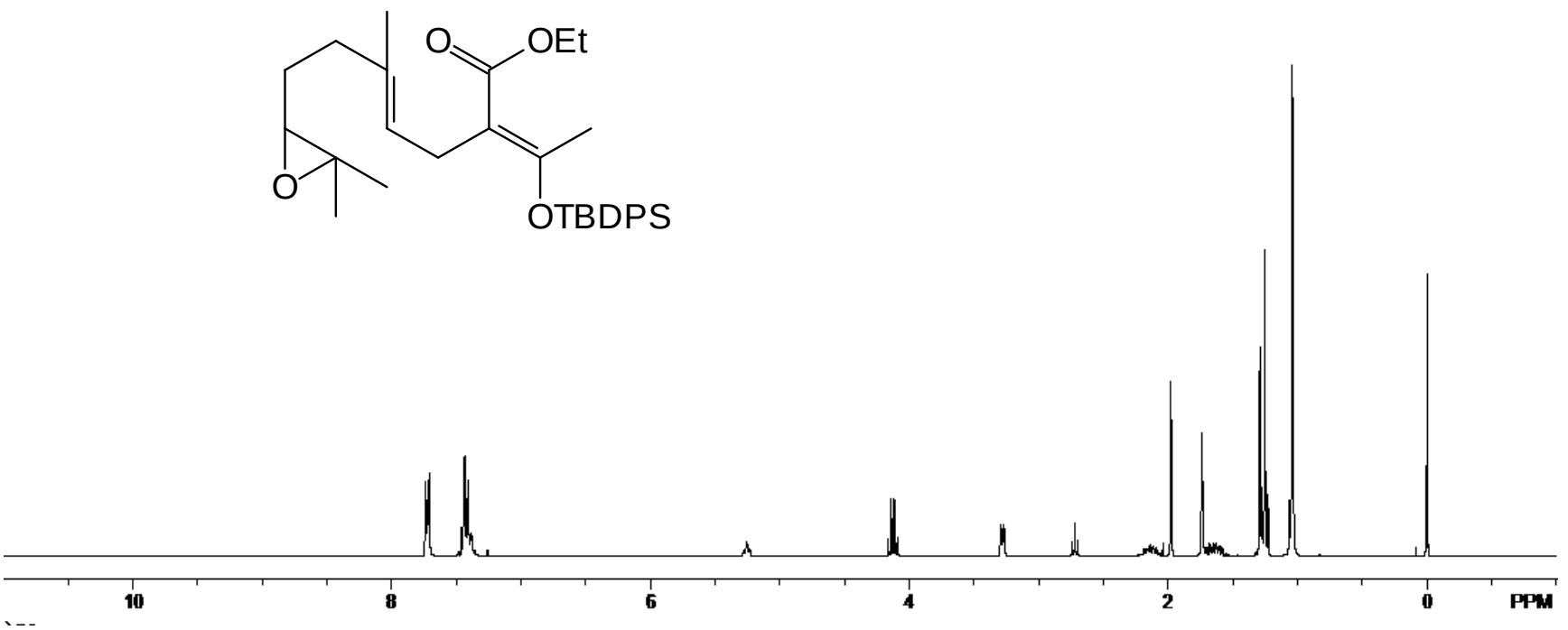


Figure A51. ^{1}H NMR spectrum of *E*–silyl enol ether **298**

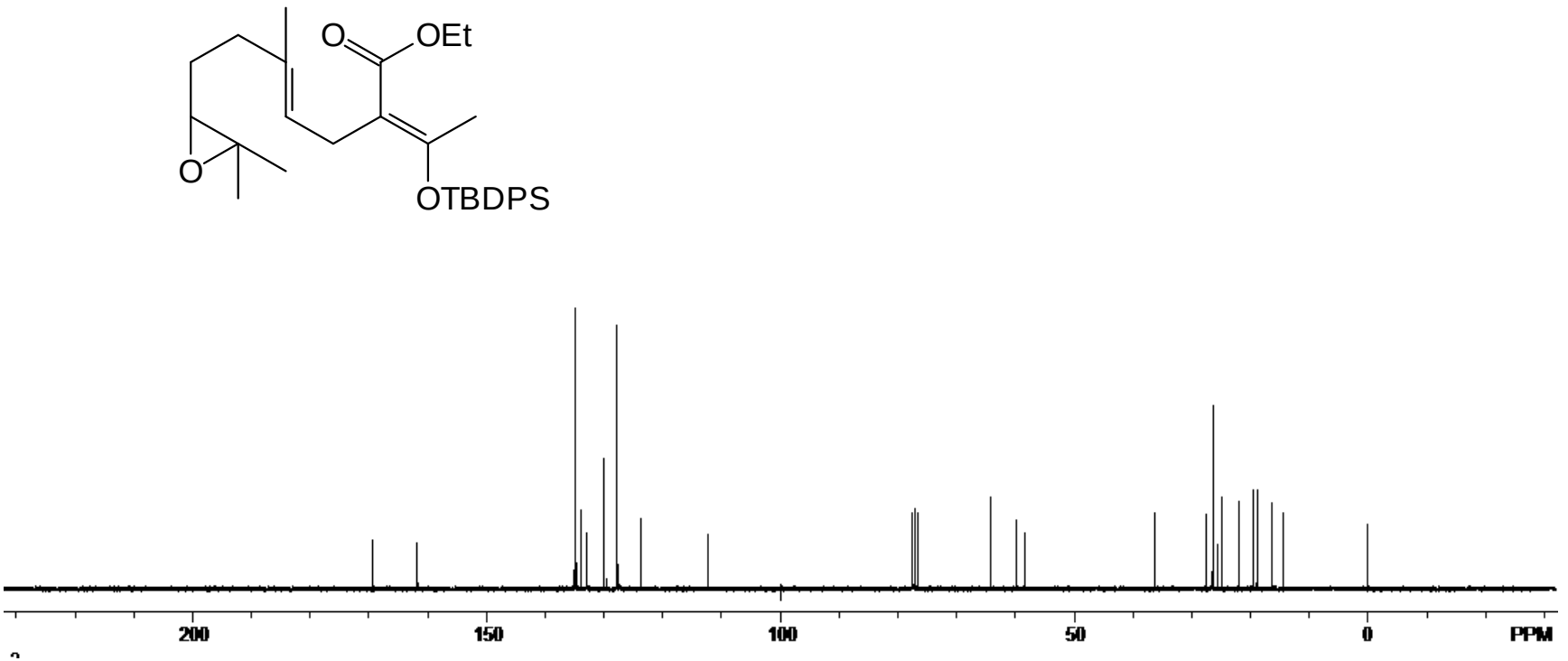


Figure A52. ^{13}C NMR spectrum of *E*–silyl enol ether **298**

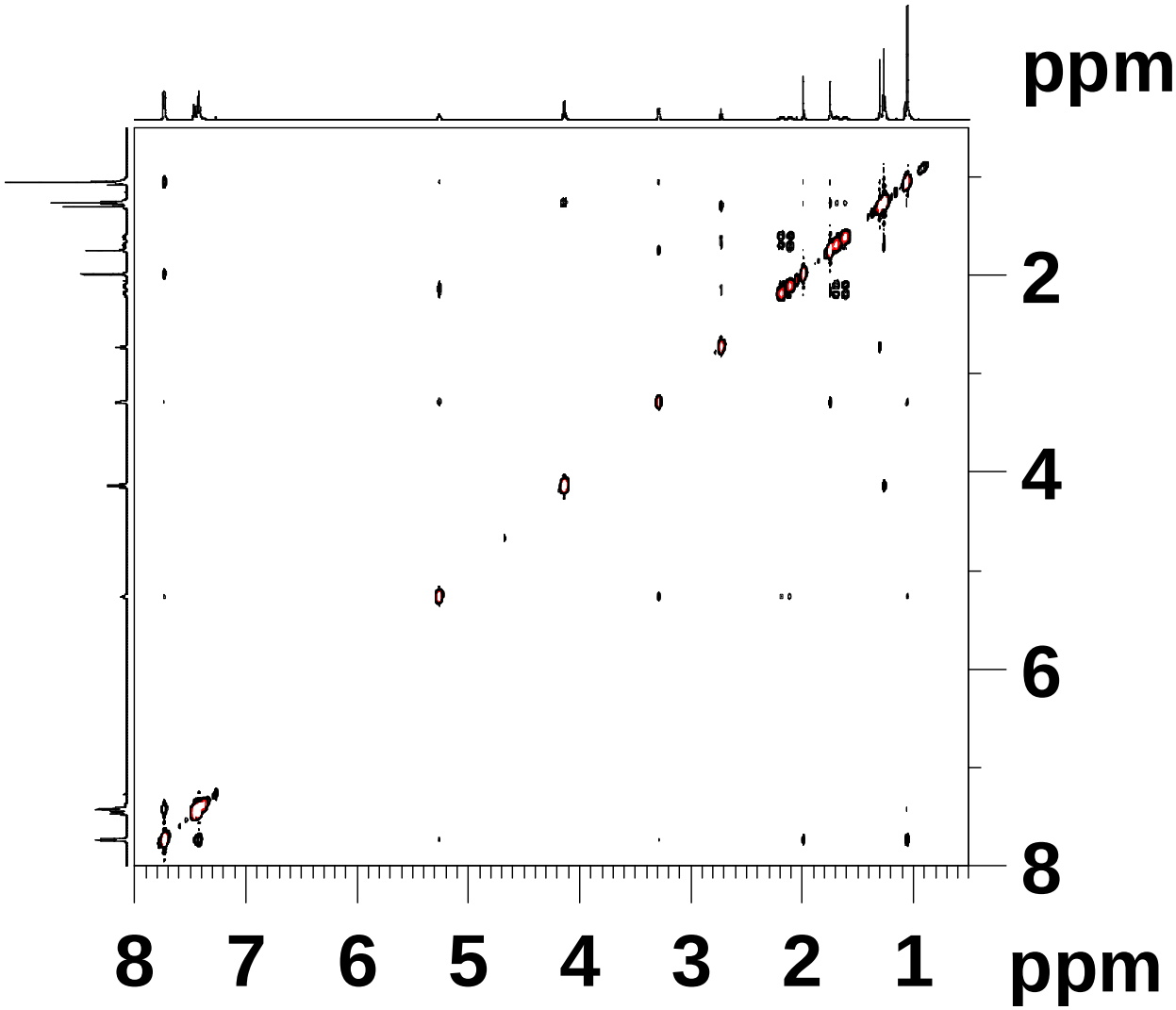


Figure A53. ^{1}H NMR NOESY spectrum of *E*–silyl enol ether **298**

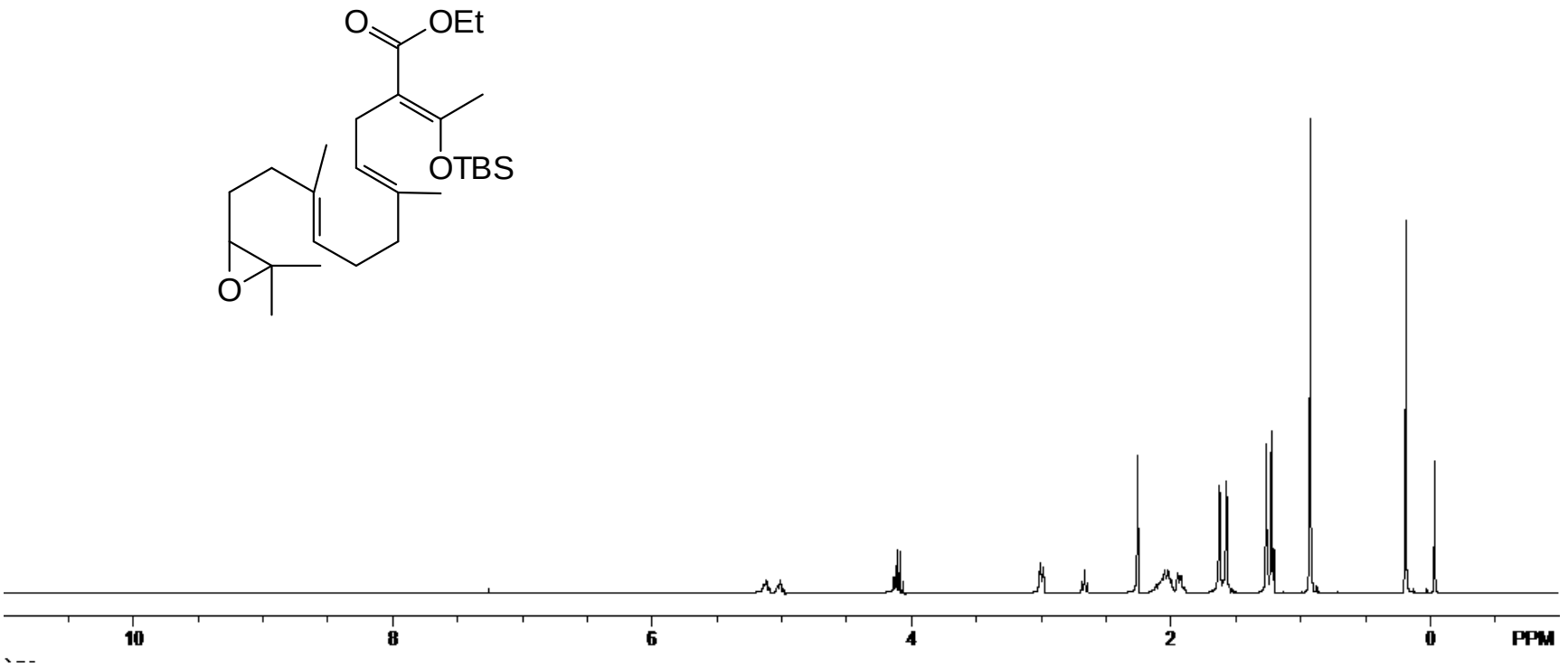


Figure A54. ^{1}H NMR spectrum of *E*–silyl enol ether **299**

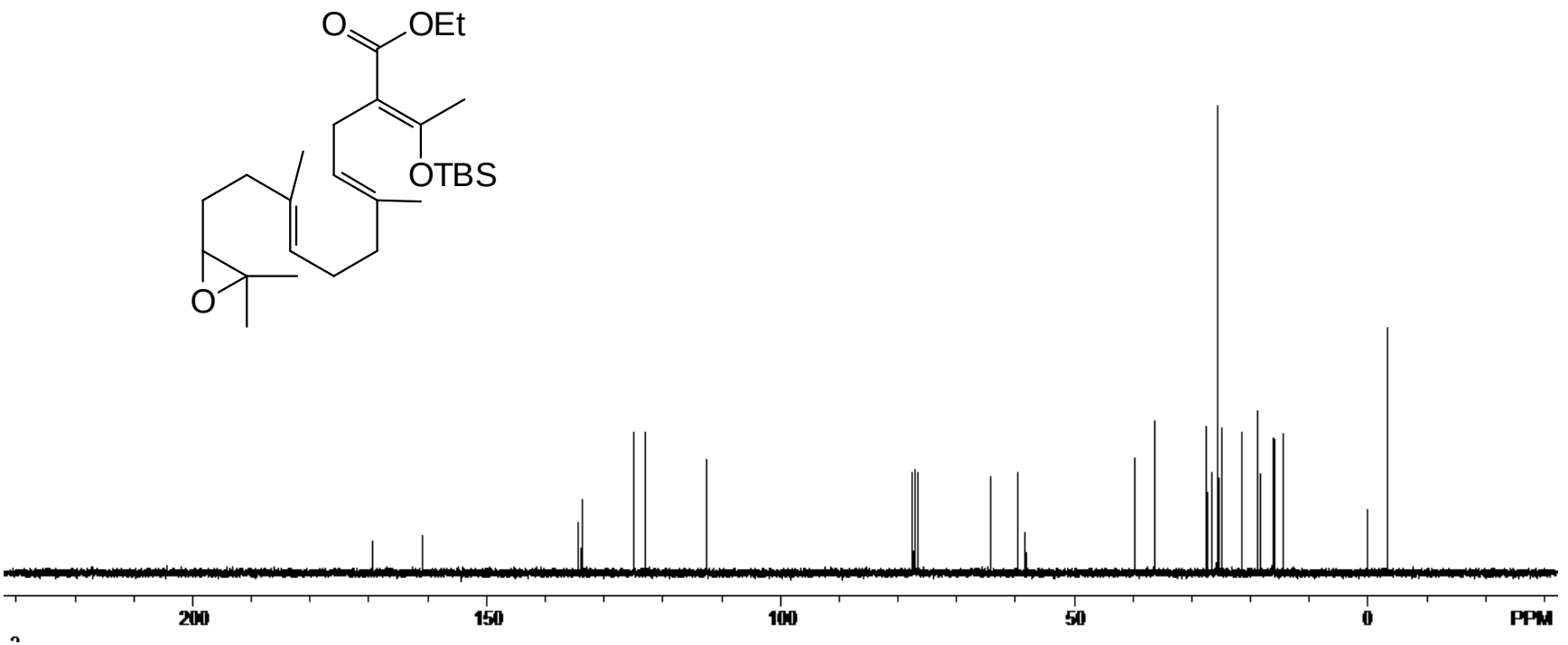


Figure A55. ^{13}C NMR spectrum of *E*–silyl enol ether **299**

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