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Cascade cyclizations & the schweinfurthins

Joseph John Topczewski
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CASCADE CYCLIZATIONS AND THE SCHWEINFURTHINS

by

Joseph John Topczewski

An Abstract

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

December 2011

Thesis Supervisor: Professor David F. Wiemer

ABSTRACT

For the last several decades, America has invested in a national program to alleviate cancer and cancer-related suffering, ultimately seeking a cure. As part of this goal, the National Cancer Institute (NCI) has spent significant effort scouring the globe to find naturally occurring compounds that can successfully combat cancer. This effort has uncovered many natural products with chemotherapeutic potential and many of the lead agents used in the fight against cancer are either natural products themselves or are compounds inspired by a natural product.

This work describes the synthesis of one family of natural products uncovered by the NCI that is being explored for chemotherapeutic applications, namely the schweinfurthins. The schweinfurthins were isolated from the plant *Macaranga schweinfurthii* but the natural source did not provide these compounds in a quantity sufficient to permit further study. The paucity of natural material indicated that a chemical synthesis of these compounds would be the most reliable method to provide meaningful amounts of schweinfurthins. The present work describes the chemical synthesis of four of the most potent schweinfurthins, reports the synthesis of numerous structural analogues, and details advances to the field of cascade cyclizations which makes their synthesis possible.

Abstract Approved:_____
Thesis Supervisor

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Title and Department

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Date

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Iowa City, Iowa

CERTIFICATE OF APPROVAL

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PH.D. THESIS

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

Joseph John Topczewski

has been approved by the Examining Committee
for the thesis requirement for the Doctor of Philosophy
degree in Chemistry at the December 2011 graduation.

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F. Christopher Pigge

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Horacio F. Olivo

To John, Janice, and Anna Topczewski

Winning is not a some time thing; it's an all the time thing. You don't win once in a while; you don't do things right once in a while; you do them right all the time. Winning is a habit. Unfortunately, so is losing. There is no room for second place. There is only one place in my game, and that's first place… It is a reality of life that men are competitive and the most competitive games draw the most competitive men. That's why they are there – to compete. The object is to win fairly, squarely, by the rules, but to win… I believe in human decency. But I firmly believe that any man's finest hour – his greatest fulfillment to all he holds dear – is that moment when he has worked his heart out in a good cause and lies exhausted on the field of battle – Victorious.

Vince Lombardi
World Champion Coach of Super Bowls I & II

ACKNOWLEDGEMENTS

This work would not have been possible without numerous contributions from others. Although I cannot thank all of them all here, I will do my best.

First, the completion of this work and my Ph.D. would not have been possible without the loving support of my beautiful wife Anna. For all of the Saturday afternoons spent in the lab, for all of the long waits in the car because I said I would be done in five but it took thirty minutes, for all of the nights she got stuck doing the dishes, for all of the days I was upset with a failed reaction or a poor review, for all of the long conversations about why, for all of the nights I ignored her to work - Thank You. Anna, you are a terrific person to share my life with and I love you dearly.

I would also like to thank my terrific parents, John and Janice, for all of the lessons they taught me throughout life and for supporting me in my endeavors. There were many instances when I was a young child and could not see the wisdom in their decisions. Having received the typical "You will thank me (us) when you are older!" I can now say, "I thank you now that I am older." (I bet they are happy to have this in writing.) Thank you to my siblings, Jeremy and Janell for their support. I love you all and many thanks are not enough.

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I would like to thank the Wiemer group for their support over the past several years. I sincerely appreciate the mentorship provided by Dr. Jeffery Neighbors during the first two years of my graduate career. It was in those initial months that I learned how to

be an organic chemist and how to think in the lab. His insights and support was invaluable to this work and likely to the future of my career. (He also thought me what corners I could cut to save time…like the old three columns at once trick!) I would also like the thank Dr. Rocky Barney for tolerating me in the lab and for always sharing a good story and a different perspective. Thank you for our many sanity saving conversations and a welcoming demeanor. I also thank the many members of the Wiemer group who have been co-authors on presentations and manuscripts, their contributions made much of this work possible or more complete.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

LIST OF ABBREVIATIONS

3dSB	3–deoxyschweinfurthin B
15-c-5	15-crown-5
9-BBN	9-borabicyclononane
calcd	calculated
CEAS	cascade cyclization terminated via electrophilic aromatic substitution
$CDCl_3$	deuterated chloroform
CH_2Cl_2	dichloromethane
CHO	aldehyde
CNS	central nervous system
COMPARE	NCI based computer algorithm
COSY	2-D ^1H-^1H NMR coupling experiment
CuI	copper iodide
DDQ	2,3–dichloro–5,6–dicyano–1,4–benzoquinone
DIPEA	diisopropylethylamine
DMF	dimethylformamide
ee	enantiomeric excess
eq	equivalents
ESI	electrospray ionization
Et_2O	ethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
GI_{50}	50% growth inhibitory concentration
Hex	Hexanes
HMDS	hexamethyldisilazide

HMPA	hexamethylphosphoric triamide
HOAc	acetic acid
HRMS	high resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons reaction
Hz	hertz
IPA	isopropyl alcohol
J	coupling constant (NMR)
LC_{50}	lethal to 50% of cells concentration
LDA	lithium diisopropylamide
m	multiplet (NMR)
m-CPBA	metachloroperoxy benzoic acid
MeOH	methyl alcohol
min	minute
mL	milliliter
mmol	millimoles
MOM	methoxymethyl
MsCl	methane sulfonyl chloride
$NaBH_4$	sodium borohydride
NaH	sodium hydride
NaOH	sodium hydroxide
n-BuLi	normal butyl lithium
NCI	National Cancer Institute
NCI-60	National Cancer Institute's 60-cell line assay
NH_4Cl	ammonium chloride
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser spectroscopy
OH	alcohol

pTsOH	*para*-toluenesulfonic acid
s	singlet (NMR)
t	triplet (NMR)
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TGI	total growth inhibitory concentration
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
δ	chemical shift in NMR
μM	micromolar

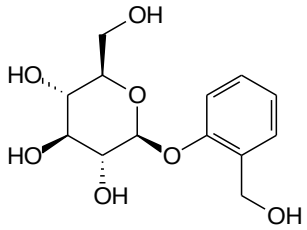
CHAPTER 1

INTRODUCTON

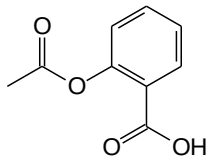
Mankind has been ingesting natural substances with curative properties for thousands of years and most likely much longer.[1, 2] The healing effects of various extracts, brews, tonics, and teas have been recognized since the dawn of civilization and post-industrial man varies little in this regard from his ancient predecessors. Indeed, some critiques insist the very essence of modern convenience places a greater requirement on our society for curative substances, with three of our society's most major aliments being ascribed as "Western Diseases" (diabetes, heart disease, and certain cancers).[3-6] One unique advantage granted to contemporary society over our ancient counterparts is the advent of modern chemistry, which allows for the isolation, identification, and modification of unique chemical entities which posseses therapeutic properties from natural sources.[1, 2] Two illustrative examples of this concept, aspirin and penicillin, can be given to emphasize the therapeutic importance of society's relationship with nature and natural products.

In the case of aspirin,[1, 2] ancient cultures from around the globe appreciated extracts from willow tree bark for their analgesic properties. Records of formulation and prescription of these extracts date back to pre-Roman Egypt, where materials now known to contain salicin were administered for fever and pain. Although the beneficial properties of willow bark were long recognized, it was not until the middle of the nineteenth century when the active chemical agent of these brews (salicin **1**, Figure 1) was identified. An independent synthesis of salicylic acid provided this active ingredient at a fraction of the cost of the natural source. Modification of salicylic acid resulted in the synthesis of aspirin by Felix Hoffmann of Bayer in 1897 (**2**, Figure **1**). Aspirin is now administered for almost any ailment, from pain or fever to stroke or heart attack, and it is recognized as "the most successful medication in history."[2]

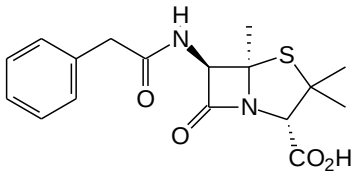
Figure 1. Natural Compounds and Their Pharmaceutical Counterparts.



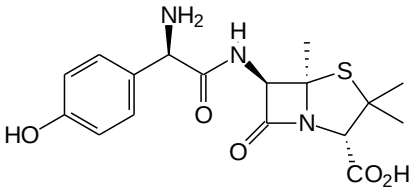
Salicin (**1**)



Aspirin (**2**)



Penicillin (**3**)



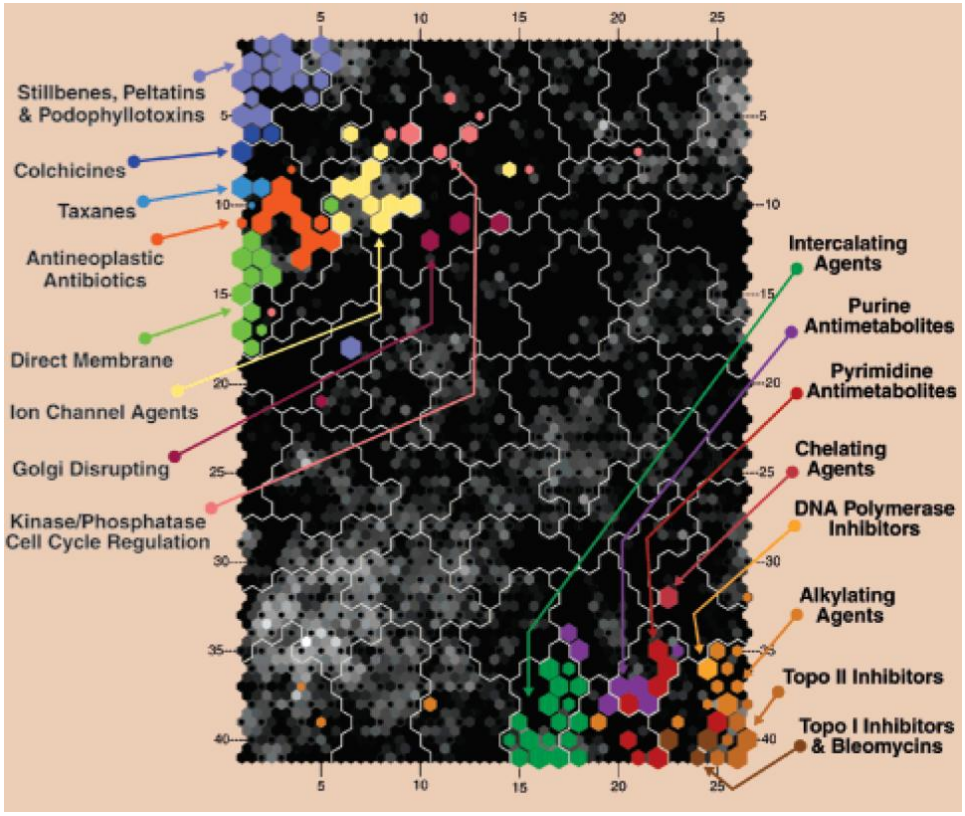
Amoxicillin (**4**)

Penicillin's history is much more brief, but is similarly illustrative of nature's therapeutic arsenal.[1, 2] Penicillin (**3**, Figure 1), a secondary metabolite of various *Penicillium* mold species, was discovered by Sir Alexander Fleming in the 1920's and was shown to demonstrate extraordinary curative properties against bacterial infection. In the decades that followed, antibiotics were developed, arming allied forces in WWII with life-saving drugs to combat infection. The purification and chemical elucidation of penicillin was arguably as vital to the successful D-Day invasions as tanks or planes.[2] Since the discovery of penicillin, other natural antibiotics have been isolated, synthesized, and modified by chemical means to continue to fight resistant bacteria (e.g. amoxicillin **4**, Figure 1).[1, 2]

Although numerous diseases have become curable in the modern era thanks to therapeutic agents and medical advances, other ailments have tested the most modern science and elude successful treatment.[7] Arguably the most devastating class of these diseases is cancer.[8] Cancer continues to be a leading cause of mortality and morbidity in society and it is likely to become the number one killer of Americans by the end of this

decade.[7, 8] Recognizing the far reaching consequences of cancer and a clinical impotency towards treatment, the National Cancer Act was passed in 1971 as a means of funding primary research to better understand the nature of this complicated family of diseases. Since then, researchers have gained considerable fundamental knowledge in the fields of chemistry, cellular biology, molecular biology, and genetics regarding cancer. Of the possible treatments since developed, chemotherapy is a promising notion that has of yet failed to achieve the full realization of its potential.[7]

Figure 2. Self Organizing Map. [9, 10]



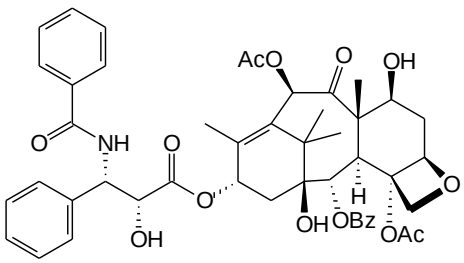
With the goal of identifying unique naturally occurring molecular entities for treating cancer, the National Cancer Institute (NCI) established a high-throughput screen

intended to rapidly identify novel sources of potential chemotherapeutics.[11-14] Since the early 1980's, the NCI has screened extracts from numerous organisms in pursuit of novel anti-proliferative agents. In addition to the evaluation of new synthetic chemotherapeutics, the NCI now uses cellular assays to determine the anti-proliferative activity of any particular extract and then purifies the active component(s) through assay-guided fractionation. Once isolated, the specific active agent(s) can be subjected to the NCI's 60-cell assay (NCI-60) and potency can be determined. As the name implies, the 60-cell line assay screens a compound against 60 different human-derived cancer cell cultures, representing several different cancer types. When this is done at five concentrations, the mean potency of a compound can be determined. The sensitivity or resistance of any particular cell type to the compound can then be ascertained from its deviation from the mean potency. The difference between the most and least sensitive cells is taken as the range, commonly described as differential activity, and is believed to be indicative of therapeutic index.

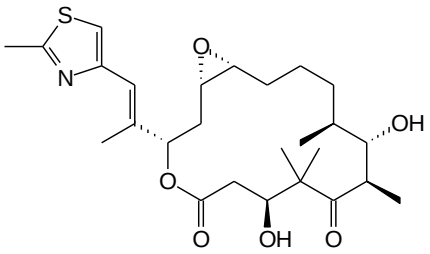
From the NCI-60, a pattern of activity also can be observed across the various cell lines and correlated, by use of various bio-informatics approaches or statistical analysis, to the activity of known chemotherapeutics.[9, 10, 15] The earliest of these methods was the COMPARE algorithm, which was designed to identify agents acting by the same molecular mechanism via statistical correlations.[15-17] Since the initial conception and utilization of the COMPARE algorithm, several other methods have been pioneered by D. G. Covell at the NCI. Contemporary analysis consists of a polydimensional self-organizing map (SOM, Figure 2).[9, 10] Compounds that act on the same molecular target or on the same cellular pathway co-localize on the SOM, providing a hypothesis for an agent's mode of action. If a compound lies in a unique location on the SOM, then it is assumed to act via a unique or unknown mechanism. One example of the utility of this process can be ascertained by examining the history of paclitaxel[18,19] (**5**, Figure 3), a potent and clinically used chemotherapeutic which is itself a natural product isolated by

researchers.[1, 2] When paclitaxel was isolated, its mechanism of action was unknown until Horwitz *et al*. determined that paclitaxel induced polymerization of microtubulin which in turn increases growth of microtubules and stabilizes the resulting polymer.[18, 20] The stability of the polymer arrests the cell cycle, prevents cell division and ultimately results in cell death. After this mechanism was assigned for paclitaxel's cytotoxicity, other natural products were isolated and shown to act on the same biological target with increased potency, including the epothilones and discodermolide (**6** and **7**, Figure 3).[21-24] This effort was greatly expedited by application of the NCI's statistical analysis which correlated these new compounds to the activity pattern of paclitaxel.

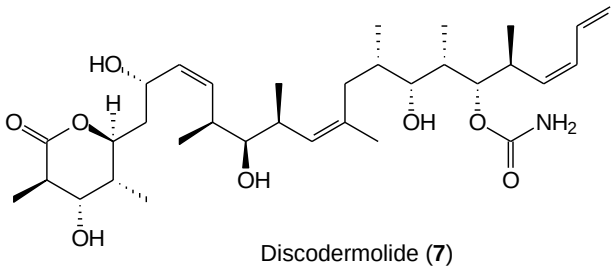
Figure 3. Microtubule-Stabilizing Chemotherapeutics.



Paclitaxel (**5**)



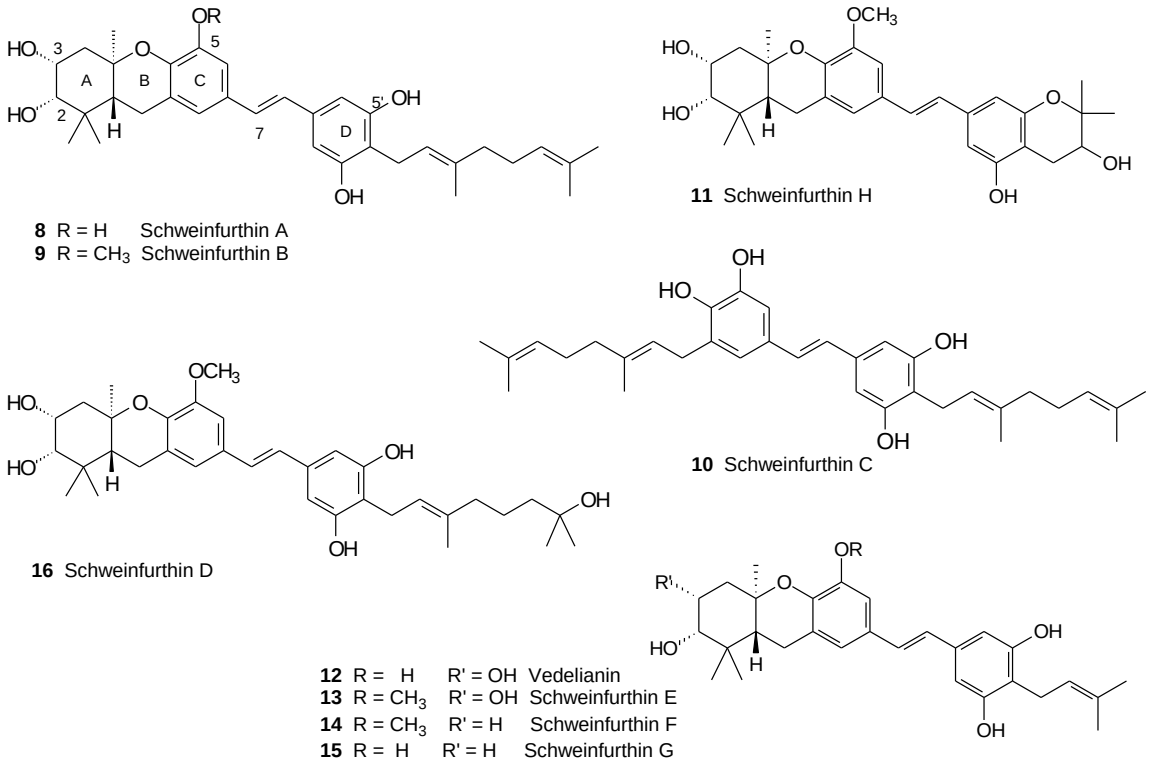
Epothilone A (**6**)



Discodermolide (**7**)

As part of the NCI's program, a collection of leaves from *Macaranga schweinfurthii* was obtained during an expedition to Cameroon by D. W. Thomas in 1987.[25] Extracts from this collection displayed potent activity in the NCI's initial assays.

Figure 4. The Natural Schweinfurthins.



After activity-guided fractionation, conducted by J. A. Beutler, two compounds were isolated which displayed a potent and unique pattern of anti-proliferative activity in the NCI's 60-cell line assay. These compounds were named schweinfurthins A and B (**8** and **9**, Figure 4) and were isolated along with schweinfurthin C (**10**), which was much less potent.[25] Schweinfurthins' 60-cell data (Figure 5) highlights that CNS derived cell lines, most notably the glioblastoma line SF-295, are exceptionally sensitive to schweinfurthin treatment, and that ovarian, melanoma, and lung cancer lines are relatively resistant. Additionally, the schweinfurthins' profiles appear in a unique place on the SOM and do not correlate through statistical analysis to any known mechanism of action.[25] This observation suggests that the schweinfurthins act on a biological pathway or molecular target which is not exploited by contemporary chemotherapy.[14] From nearly 200,000

assayed compounds, the activity of only three other families of natural products correlate to the schweinfurthins profile, the stellettins, the cephalostatins, and OSW-1 (**16**-**18**, Figure 6).[26-28] Given the relative molecular complexity of these three other types of molecules, the schweinfurthins present a unique opportunity to explore and potentially exploit their mode of action for chemotherapy.[14] Unfortunately, the natural source of the schweinfurthins produces only limited quantities of these compounds and several attempts at recollection have led to only meager success.[29] The promising biological profile of the schweinfurthins combined with their scarce and unreliable natural abundance inspired their total synthesis.

Figure 5. NCI's 60 Cell Line Assay Data for Schweinfurthin A.

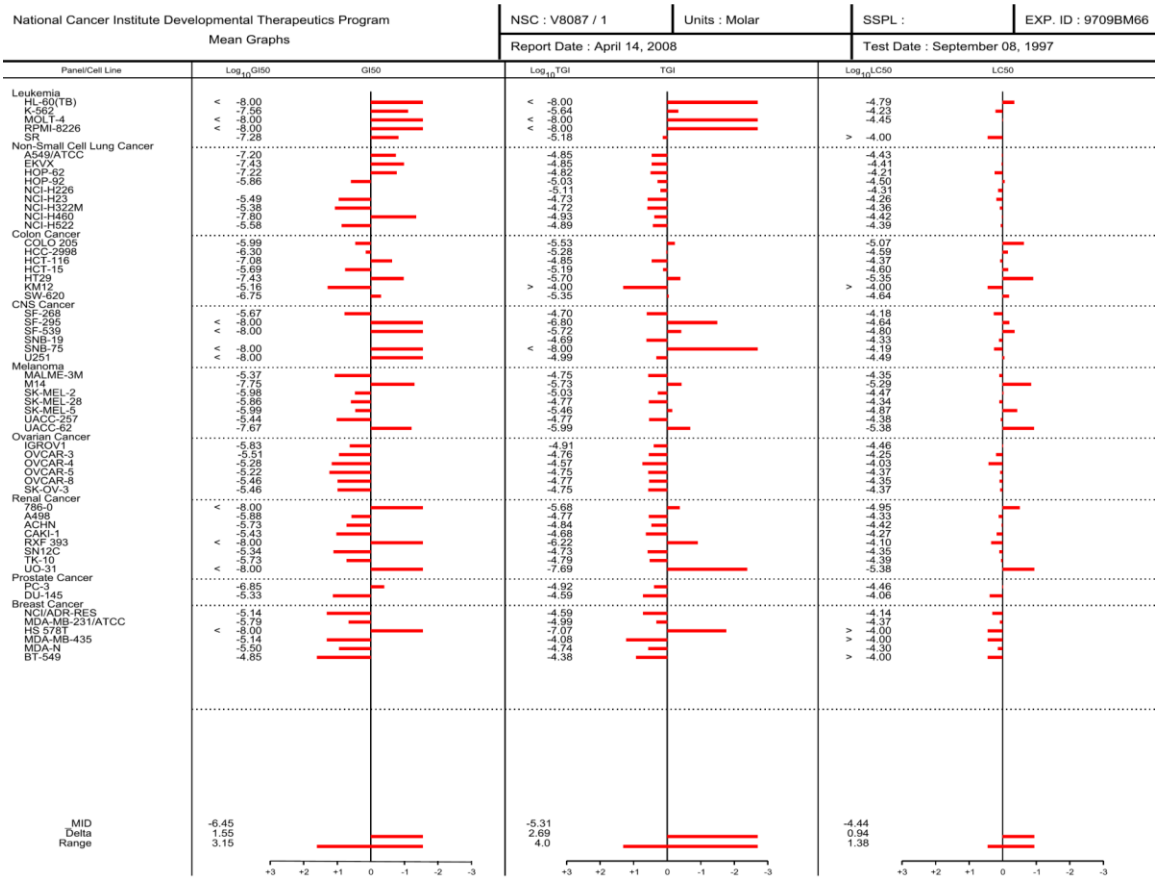
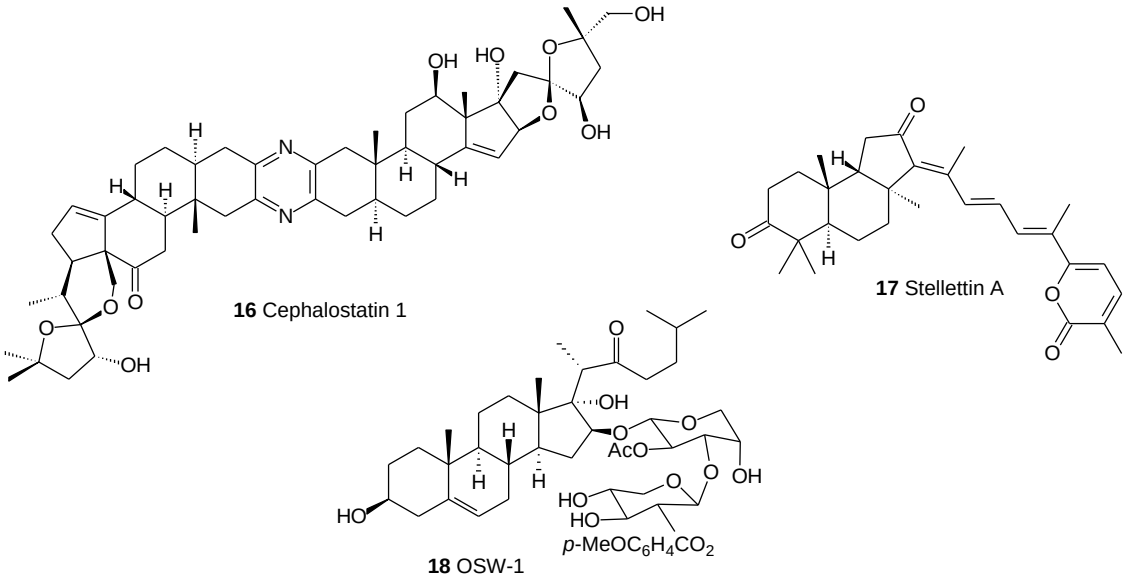


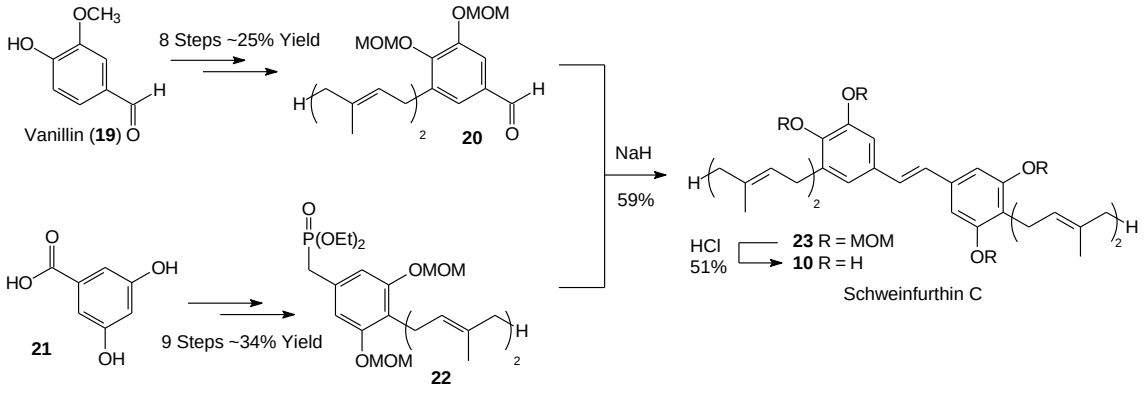
Figure 6. Stellettin A, OSW-1, and Cephalostatin1.



Over 10 years ago, the Wiemer group initiated a program aimed at synthesizing the most potent of the schweinfurthins.[30] Initial efforts by E. M. Treadwell and S. C. Cermak succeeded in the synthesis of schweinfurthin C, as first reported in 1999 (Scheme 1).[30] Although this compound displays poor activity, its synthesis proved the viability of a late-stage condensation to produce the stilbene olefin, a key facet of the Wiemer group's synthetic strategy. Beginning with commercially available vanillin (**19**), aldehyde **20** was obtained in 8 steps with a moderate overall yield. Synthesis of phosphonate **22** was accomplished in 9 steps and better yield from commercial 3,5-dihydroxybenzoic acid (**21**). Of key consideration to a large scale synthesis which would be required of any therapeutic agent, both of these commercial starting materials are available on multi-kilogram quantities and are very inexpensive. An HWE condensation of the requisite precursors afforded stilbene **23** which was deprotected in methonolic HCl to afford the first synthetically available schweinfurthin.[30] Of greater importance than the product, the late-stage HWE proved successful and established a general retrosynthesis

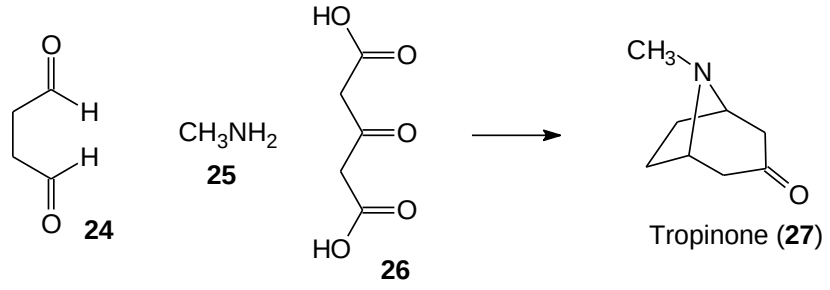
for the remaining schweinfurthins.[31, 32] This disconnection allowed high levels of convergence at the final stages of the synthesis and this approach will be conserved in the forthcoming synthetic efforts reported here.

Scheme 1. Total Synthesis of Schweinfurthin C.



Having synthesized the simplest of the schweinfurthins, the Wiemer group turned their synthetic efforts to the more complicated, and more potent, tetracyclic schweinfurthins. The isolation of schweinfurthin C in conjunction with the other schweinfurthins gives chemists a clue as to the biological origins of the tetracyclic core of schweinfurthins A and B, aiding in synthetic planning. It is not uncommon for chemists to attempt to duplicate the synthetic power of nature in the laboratory by planning synthetic reactions to mimic the biochemistry which may have led to a target's natural existence.[33-36] The first so-called biomimetic synthesis was executed by Sir Robert Robinson in his synthesis of tropinone (Scheme 2), which masterfully crafted the complete bicyclic ring system in a single transformation.[33, 35] Since this initial and triumphant example, biomimetic syntheses have become a keystone strategy in the modern chemists' repertoire[33, 35] and a biomimetic approach has been applied to the synthesis of the schweinfurthins (*vide infra*).

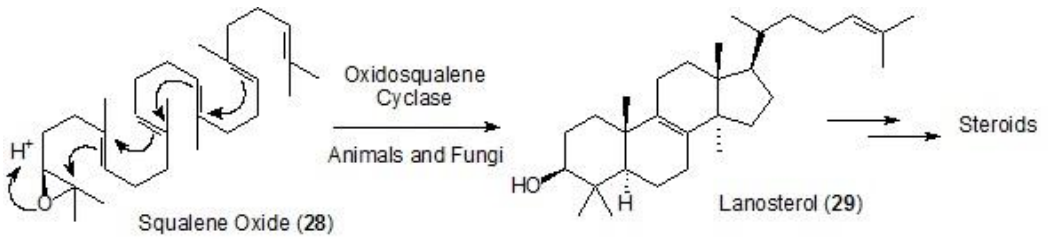
Scheme 2. Robinson's Seminal Biomimetic Synthesis of Tropinone.



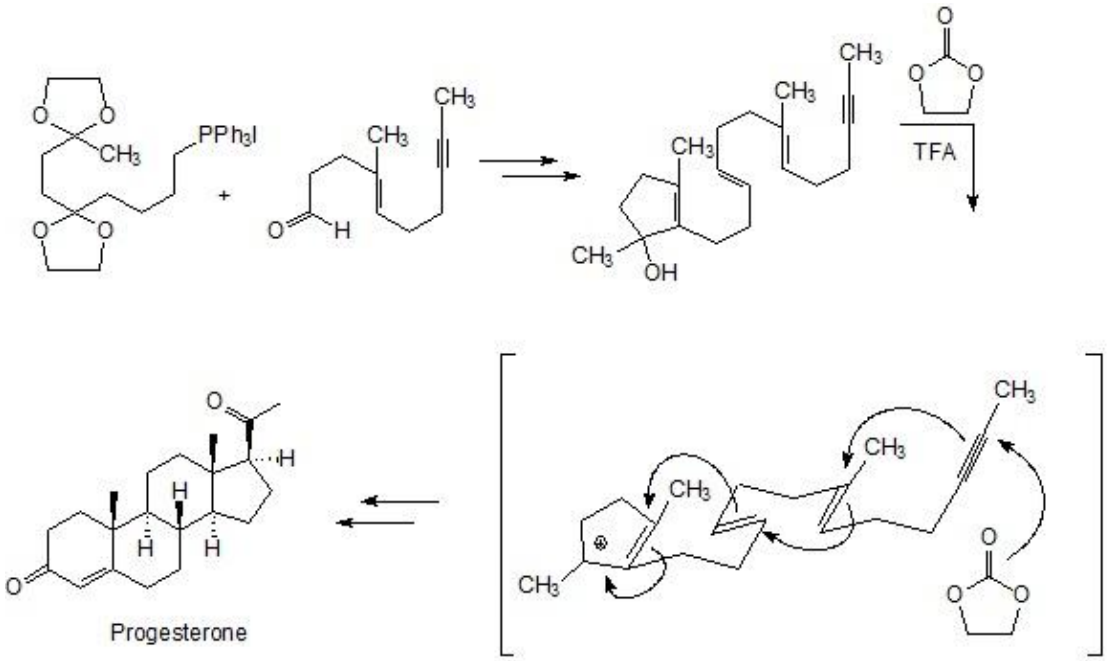
The biosynthesis of the schweinfurthins has not been established in detail, but schweinfurthin C possesses two geranyl chains, each one being a ten-carbon isoprene unit. The other schweinfurthins contain only one acyclic geranyl chain and a tricyclic ring system, presumably derived from the other geranyl chain which matches in methyl group substitution. Based on this observation, it seems likely that the tricyclic core found in the schweinfurthins could arise from a geranyl chain which underwent cyclization. Successive ring closures of isoprenes are a well documented phenomenon, which has been studied in detail since at least the 1950's.[37-39] Pioneering descriptions of this process were set forth by Stork, Woodward, and Eschenmoser as they began to decipher the complex biosynthesis of steroids (e.g., lanosterol **4**) from squalene oxide (**28**, Scheme 3).[37-39] This powerful reaction class, termed polyene cyclization or cascade cyclization, has been studied in great detail since and has been applied to the total synthesis of many natural products.

Historically, the most significant application of this process may be W. S. Johnson's synthesis of progesterone (**34**, Scheme 4), which keenly demonstrated the utility of this process in synthesis.[33, 40, 41] Cascade precursor **32** was rapidly synthesized from trivial fragments **30** and **31**. In Johnson's seminal work, carbocationic intermediate **33**, which is achiral, is transformed into a tetracyclic product that contains six stereogenic centers.

Scheme 3. Naturally Occurring Cascade Cyclization of Squalene Oxide.



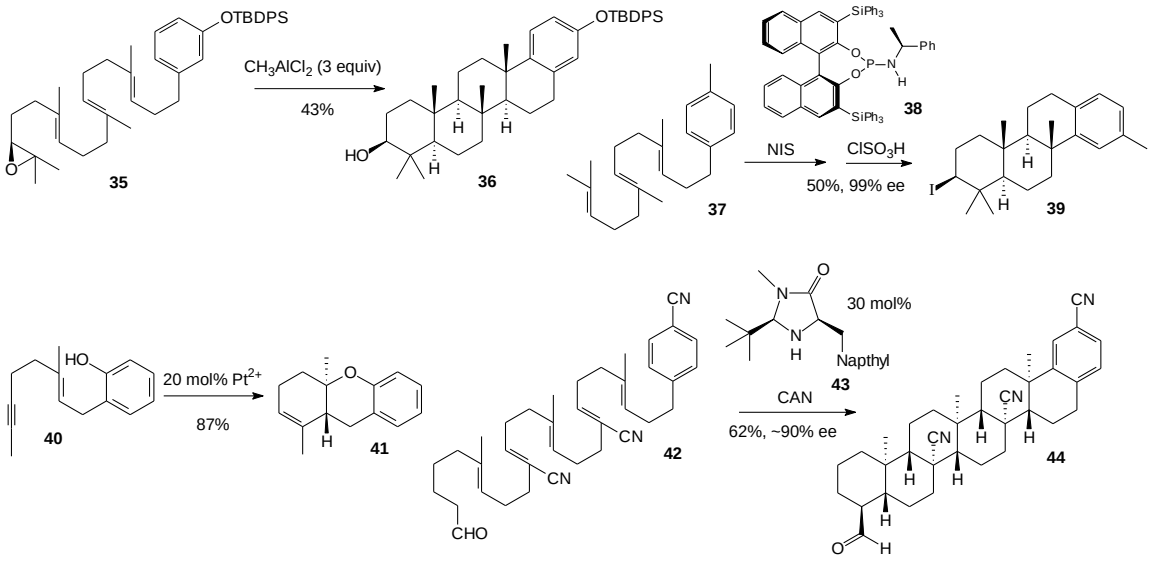
Scheme 4. Outline of W.S. Johnson's Synthesis of Progesterone.



Formation of this many rings and stereocenters in a single step was unprecedented and proceeded with exquisite diastereoselectivity: only one diastereomer was observed of a possible thirty two (although the product was racemic). Chemists' continuing focus on this reaction manifold should underscore the efficiency and appeal of this process.[36, 39, 42] Indeed, contemporary methodologies seem to place an increased emphasis on atom

economy[43-45] and on tandem or cascade reactions which generate ornate molecular architectures during the course of single transformations.[35, 36]

Scheme 5. Selected Cascade Cyclizations.

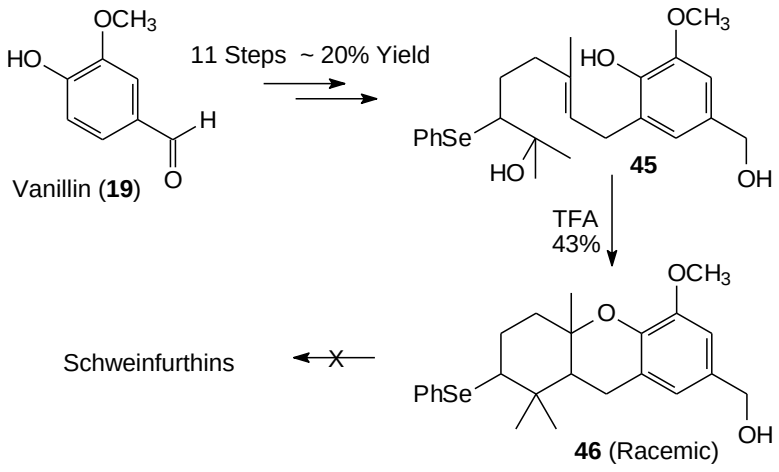


In the decades following Johnson's synthesis of progesterone, many advances have been made in the field of cascade cyclizations. In a typical cascade, an initiating electrophile is generated, ring closure occurs, and the process is extinguished by some terminal nucleophile. Numerous species have since been used to initiate this process and include epoxides,[39, 46] protons,[47-50] halonium ions,[51,52] acetals,[38, 53, 54] transition metal complexes,[55, 56,57] and radical species.[58, 59] To terminate the process, oxygen lone pair electrons, enol ethers, loss of a proton, aromatic rings, and allylic or propargylic silanes are commonly employed.[38, 39, 46]

Several impressive examples of selected classes are known and some are shown in Scheme 5. The first example, formation of compound **36** from epoxide **35**, is from the Corey group and demonstrates the venerability of epoxide-initiated cascade

cyclizations.[46] This type of cyclization is the most parallel to the naturally occurring cyclization of squalene oxide. A novel application of chiral halonium ions[51] was demonstrated in the next example in conversion of compound **37** to **39**, as was the utility of transition metal catalysis in the conversion of compound **40** to **41**.[56] Recently, the MacMillan group[58] established organocatalysis as a premier mode of conducting cascade cyclization. Their impressive cyclization to form compound **44** in high yield and enantiomeric excess from achiral precursor **42** with catalytic amounts of amine **43** via singly occupied molecular orbital catalysis (SOMO) activation[60, 61] will likely stand as a new benchmark for cyclization methodology.

Scheme 6. Selenium Controlled Cascade.



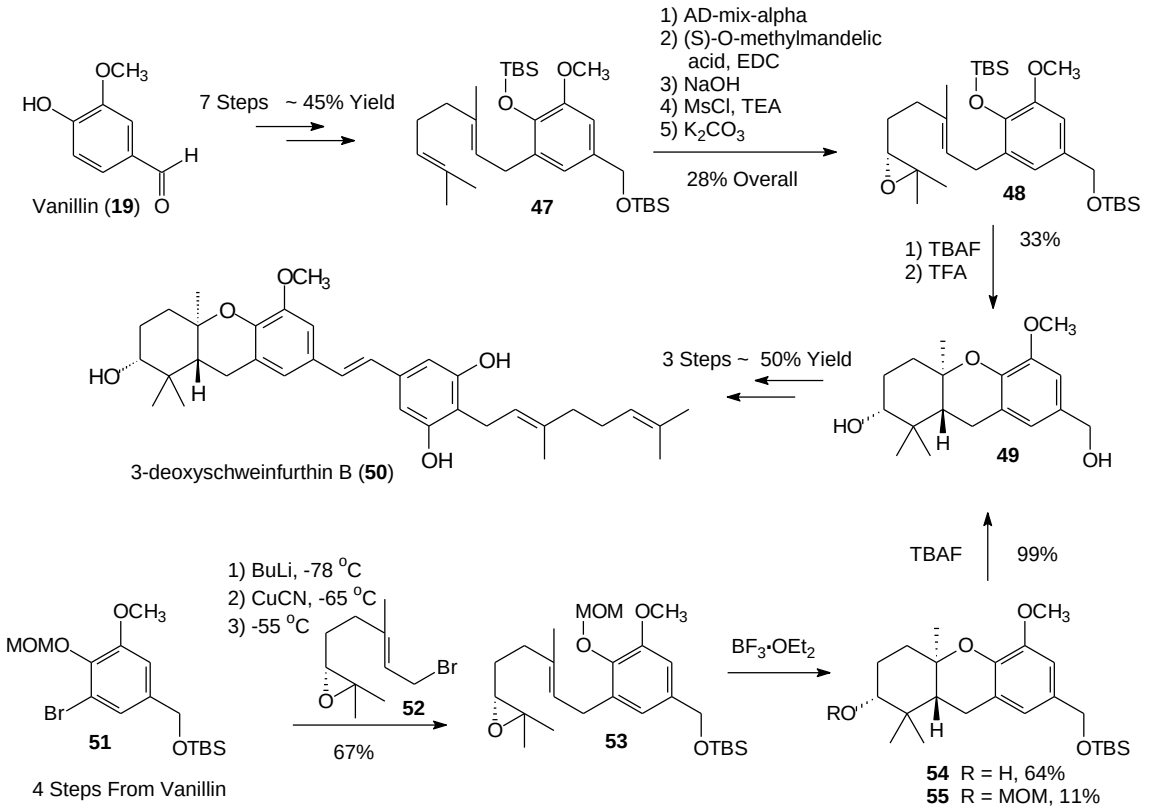
Returning to the schweinfurthins, the tricyclic core of the schweinfurthins was produced via a selenium-controlled cascade cyclization during initial work (Scheme 6).[62] Here cascade precursor **45** was synthesized via a lengthy sequence from vanillin (**19**). Exposure of compound **45** to acid promoted cyclization to selenide **46**. However, selenide **46** could not be converted into the natural products.[31,63] Revision of the

synthetic plan led to the application of an epoxide-initiated cyclization (Scheme 7). The synthesis of cascade precursors proved to be tedious and required a lengthy sequence to obtain epoxide **48**.[31] The first generation synthesis began with vanillin (**19**) and geranyl arene **47** was produced in seven steps. With only one meaningful bond construction during the course of this sequence, the inefficiency of protecting group manipulations should be evident. A five-step sequence then was used to provide epoxide **48** in non-racemic form, after derivation and resolution of diastereomers. Cascade cyclization under protic conditions afforded desired tricycle **49** in poor to moderate yield.[31] Oxidation of this compound to the corresponding aldehyde followed by HWE olefination and deprotection afforded 3-deoxyschweinfurthin B (3dSB, **50**) as the first synthetically prepared tetracyclic schweinfurthin, and it displayed meaningful anti-proliferative activity.[31] Interestingly, 3dSB displays the same pattern of activity as the natural schweinfurthins, albeit with slightly diminished potency.[31, 64] This suggested that the diol motif present in the A-ring of schweinfurthins A and B is not required for cytotoxicity, but does increase both potency and differential activity. This hypothesis was supported by the 60-cell profiles for schweinfurthins F (**14**) and G (**15**), which were reported shortly after the synthesis of 3dSB.[65]

The synthesis of 3dSB marked the beginning of the Wiemer group's program aimed at the synthesis of schweinfurthin analogues. However, it was evident that the existing sequence to key intermediates was too inefficient to produce meaningful quantities of schweinfurthins. Improvements to the existing sequence included the application of an epoxy-bromide coupling between differentially protected arene **51** and bromide **52** (Scheme 7).[32, 66] Although this reaction successfully abbreviated the previous sequence to key epoxide **53**, it is not free of its own drawbacks (see Ch. 2). Additionally, it was discovered that the use of a Lewis acid instead of a protic acid greatly improved the efficiency of the ensuing cascade cyclization to form tricycle **54** in excellent yield.[32, 67] Of key note, MOM-protected phenols proved sufficiently nucleophilic to terminate the

cascade cyclization, eliminating the need for prior deprotection. Trace quantities of acetal **55** were also isolated from this mixture, and this compound must arise from the eliminated MOM group.

Scheme 7. Previous Schweinfurthin Synthesis.



With these improvements, the intermediates utilized in the synthesis of 3dSB and schweinfurthin C were used to synthesize rapidly the other naturally occurring 3-deoxyschweinfurthins as well as numerous analogues.[32, 64, 68, 69,70, 71] Although this work provided a general route to schweinfurthins and an understanding of the schweinfurthins' phamacophore, none of the initially prepared analogues exceeded the potency of the natural products.

Based on these initial efforts, the stage was set to attempt the synthesis of the most potent natural schweinfurthins and to gain a further understanding of the biomimetic cascade cyclization which makes their synthesis possible. The present body of research has accomplished both of these tasks and the following account describes these two aspects in detail.

CHAPTER 2

TOTAL SYNTHESIS OF (+)-SCHWEINFURTHINS B & E[72]

At the onset of this work, significant advancements had been made towards the efficient synthesis of 3-deoxyschweinfurthins[31, 32, 62, 68] and 3-deoxyschweinfurthin analogues.[31, 32, 66,64, 69-71, 73] Nonetheless, a 2,3-dihydroxyschweinfurthin, as in the natural product schweinfurthins A and B, remained elusive and it became the goal of this work to provide schweinfurthins which poseses this motif. Based on previous work, the synthesis of schweinfurthin B could be envisioned to progress via one of two parallel sequences, which vary only in the stage at which further oxidation takes place. One path (Path A, Scheme 8) to compound **58** might proceed by formation of a late stage intermediate like compound **59**, in turn prepared by cascade cyclization of epoxide **60**. Oxidation protocols could then be examined after cyclization to install the missing hydroxyl group and complete aldehyde **58**. In an alternate pathway (Path B), one could imagine installing the hydroxyl prior to cyclization by construction of a more highly oxidized geranyl chain, (compound **61**). Inspection of the possible transition state which might lead to tricycle **61** presented some concern for this later approach (Figure 7). In the requisite chair-like conformation, the C-3 hydroxyl functionality would exist in a pseudo-axial disposition raising the energy barrier for this reaction. Although the A value for most oxygenated substituents is relatively small,[74, 75] the existence of the other axial methyl groups is expected to raise the actual strain in this case. Consideration of this postulate in conjunction with the established routes to intermediates like compound **60**,[31, 32, 66] suggested that it may be more prudent to explore A-ring oxidation after cyclization (Path A).

As described in Chapter 1, the key transformations in the schweinfurthins' synthesis are the implementation of a biomimetic cascade cyclization followed by a convergent HWE olefination. At this juncture, it was decided that further optimization in

Scheme 8. Retrosynthesis of Schweinfurthin B.

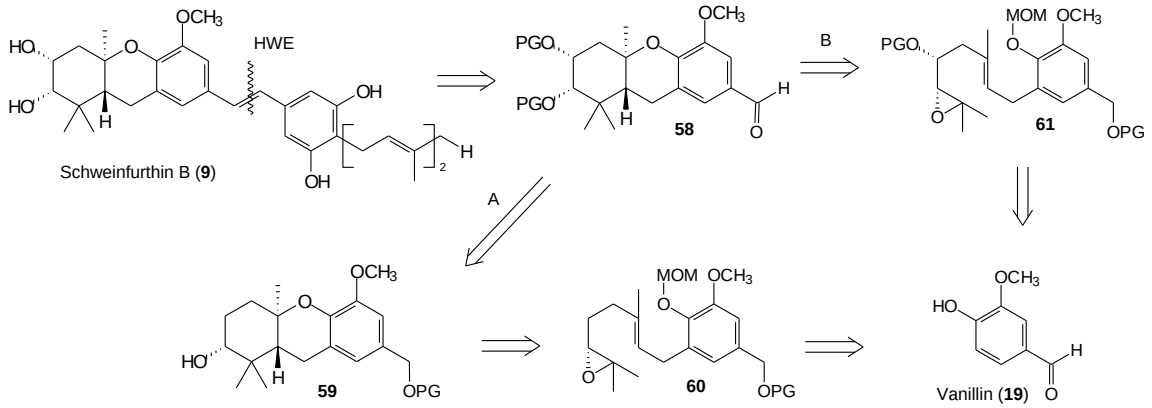
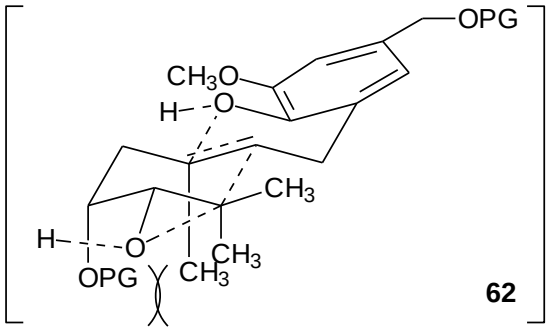


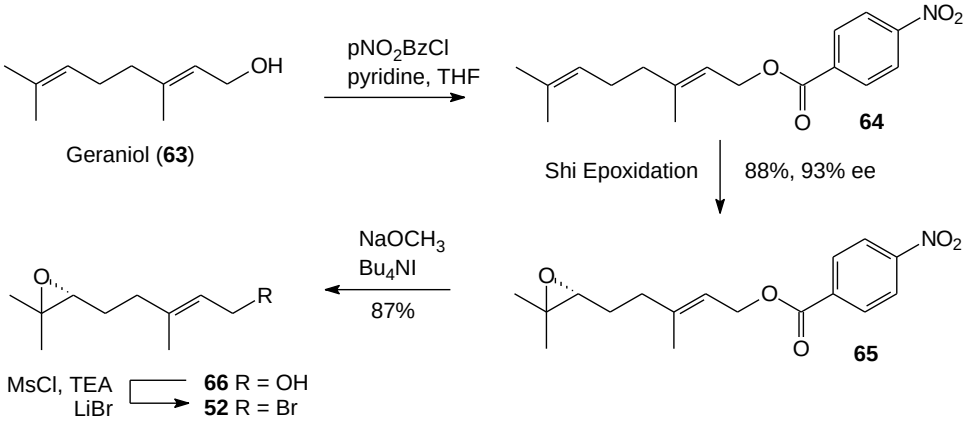
Figure 7. Possible Transition State for Cyclization of Compound **62**.



the synthesis of HWE precursors would be needed to support the synthesis of schweinfurthin B. Although the existing routes to key schweinfurthin intermediates proved reliable, they also proved laborious.[31, 32, 66] Several factors complicated their synthesis. Notably, the key carbon-carbon bond construction relied upon a chemo-selective copper mediated epoxy-bromide coupling (Ch. 1, Scheme 7).[66] This reaction required careful titration of reagents and temperature ramps, which complicate laboratory manipulations.[66] Additionally, successful implementation of this reaction required a four-step synthesis of (*R*)-6,7-epoxygenanylbromide (**52**) from geraniol (**63**) immediately

prior to use (Scheme 9), with two of the four steps in the synthesis of epoxide **52** being superfluous (Scheme 9).[66] Also, the early induction of asymmetry requires large scale use of Shi's catalyst, which could be cost prohibitive. Moreover, protecting group manipulations of the vanillin benzylic position required four additional transformations and installation of the relatively expensive TBS ether early in the synthesis.[32, 66] When taken together, these considerations left open the possibility for further optimization of the synthesis.

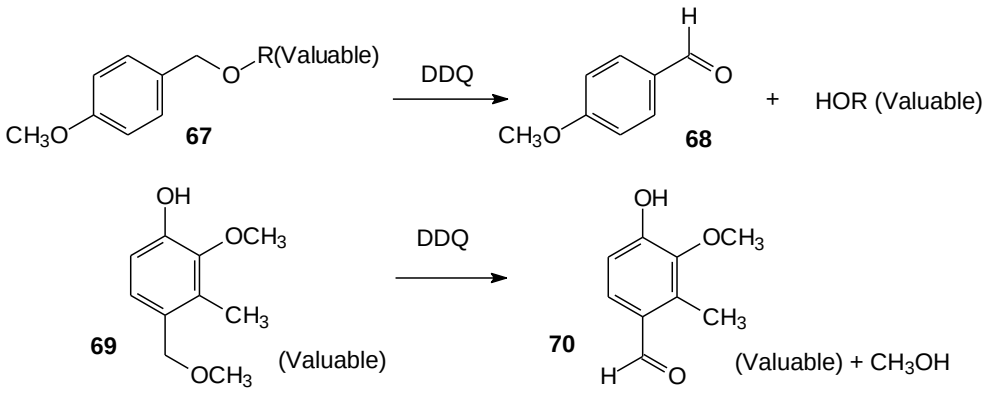
Scheme 9. Published Synthesis of (*R*)-6,7-Epoxygeranyl Bromide.



Most of these issues could be addressed by a simple alteration of the protecting group strategy. One common protecting group for an alcohol is the *para*-methoxybenzyl group (PMB) which can be readily removed by oxidative bond scission to produce a benzaldehyde and the unprotected alcohol (**67** to **68**, Scheme 10).[33, 34, 75] In this example, the valuable fragment is the alcohol but if a disposable alcohol were used, this same transformation would prove valuable in chemo-selective formation of a benzaldehyde late in the synthesis. Literature precedent for the use of a benzyl methyl ether as a latent

benzaldehyde existed, although it was not addressed as such (**69** to **70**, Scheme 10).[76, 77] This concept was adapted to the synthesis of schweinfurthin intermediates.

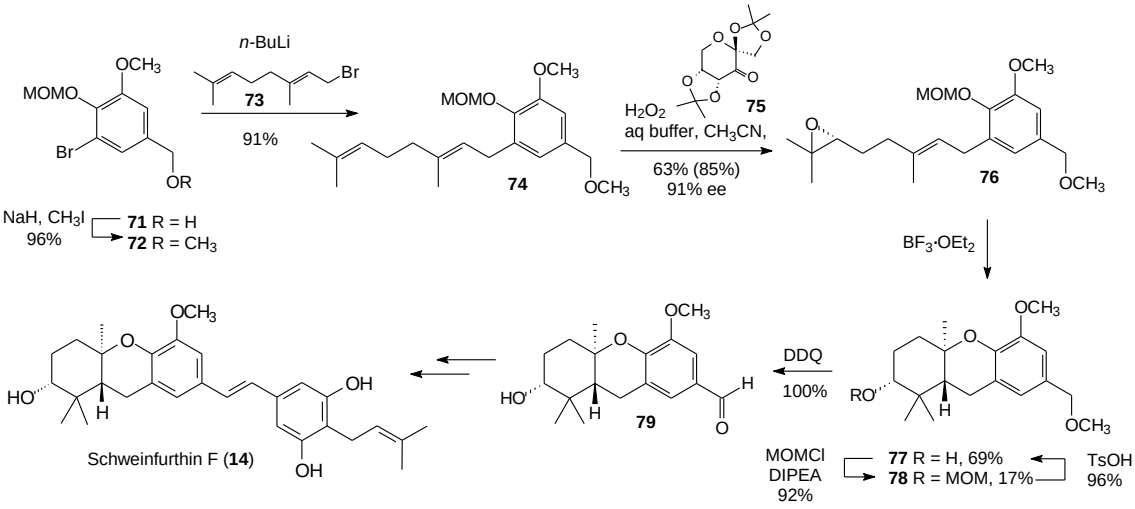
Scheme 10. Previous Work with DDQ.



With this notion in mind, a more efficient path to key aldehyde **79** was examined (Scheme 11). Methylation of the previous intermediate **71**[31, 62] proceeded smoothly via Willimson ether synthesis. Exposure of bromide **72** to *n*-BuLi affected halogen-metal exchange and the resulting aryl lithium species could be directly quenched, without transmetalation to the cuprate, by geranyl bromide (**73**). This afforded compound **74** in excellent yield. Of key note, compound **74** was readily separated from side products via column chromatography as opposed to the TBS-protected counterpart, which required much more tedious purification. Epoxidation under Shi's conditions[78, 79] proceeded smoothly under the previously optimized conditions[66] to provide (*R*)-epoxide **76** in good yield and high enatiomeric excess (typically 85-95% ee) along with a significant amount of recovered starting material. Epoxide formation after C-C bond formation proved much more economical in terms of the amount of Shi's catalyst used. Epoxide **76** was then exposed to the cyclization conditions developed by N. R. Mente which provided tricycle **77** as a separable mixture with acetal **78**.[32] The formation of the A-ring acetal **78**,

although intriguing, is of little consequence since intermediates **77** and **78** can be interconverted in high yield. Additionally, both compounds have been used in the synthesis of schweinfurthins.[32] The key oxidative demethylation of ether **77** proceeded via exposure to DDQ without consequence and the previous path to schweinfurthin F[32] (aldehyde **79**, Scheme 11) was intersected via this easily scaled route.

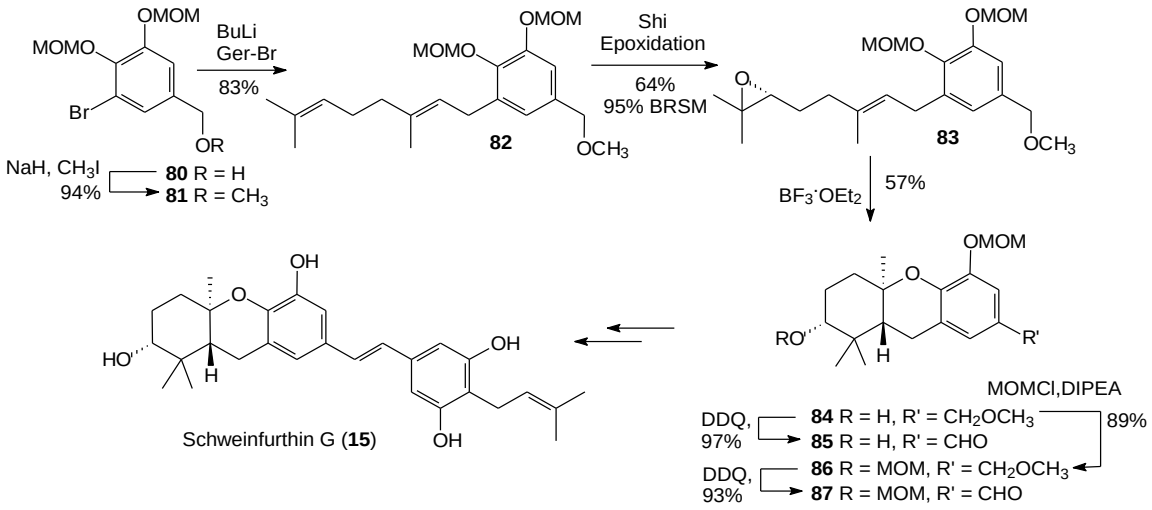
Scheme 11. Formal Synthesis of Schweinfurthin F.



To emphasize the value of this sequence, the same concept was applied to the formal synthesis of schweinfurthin G (**15**, Scheme 12).[30, 32] The previously published intermediate **80**[30] was methylated to afford compound **81**. Bromide **81** could then be converted to tricycle **84** through the intermediate geranyl arene **82** and epoxide **83**, which were synthesized via previously established methodology.[32, 66] Here the mixture of products from the cyclization is slightly more meaningful since hydrolytic conditions removed both acetals from compound **86**, phenolic first, preventing interconversion.[67] Since both of these intermediates have proven useful in the synthesis of schweinfurthins,[32] compound **86** still holds some value although the MOM acetal

prevents elaboration of A-ring functionality (*vide infra*). The DDQ oxidation was again highly successful, producing schweinfurthin G intermediates **85** and **87** in high yield.[32]

Scheme 12. Formal Synthesis of Schweinfurthin G.

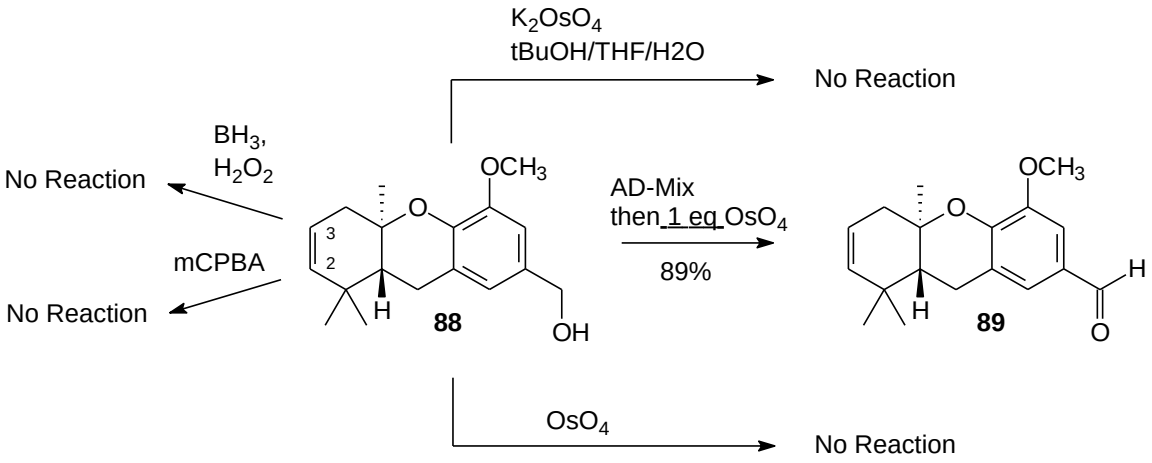


The above described simplifications to the synthesis of tricycles **77** and **85** were able to improve dramatically material throughput and multigram batches of this material could be prepared in less than one week's time. The key points about this path include the cost savings by use of a methyl group over a TBS group, later induction of asymmetry (after carbon-carbon bond formation), and simplification of chromatography. With reliable quantities of this material in hand, various paths to schweinfurthin B could be examined.

Oxidation of the schweinfurthin core to form a cis-2,3-dihydroxyschweinfurthin intermediate has been attempted before. Initial reports from the Wiemer group described efforts to produce a 2,3-cis-diol from a 2,3-olefin.[31, 62, 63] Cis dihydroxylation of an olefin with OsO_4 is a well precedented reaction and is one of the most reliable oxidations in organic chemistry. However, attempts to apply this reaction to the schweinfurthins core

proved futile (compound **88**, Scheme 13). Several different conditions were explored, but only benzylic oxidation, forming aldehyde **89** was observed even after prolonged exposure to *stoichiometric* osmium. Other oxidants were also inspected, but no desirable products were observed. Based on unsuccessful elaboration of olefin **88**, other approaches were inspected.[63]

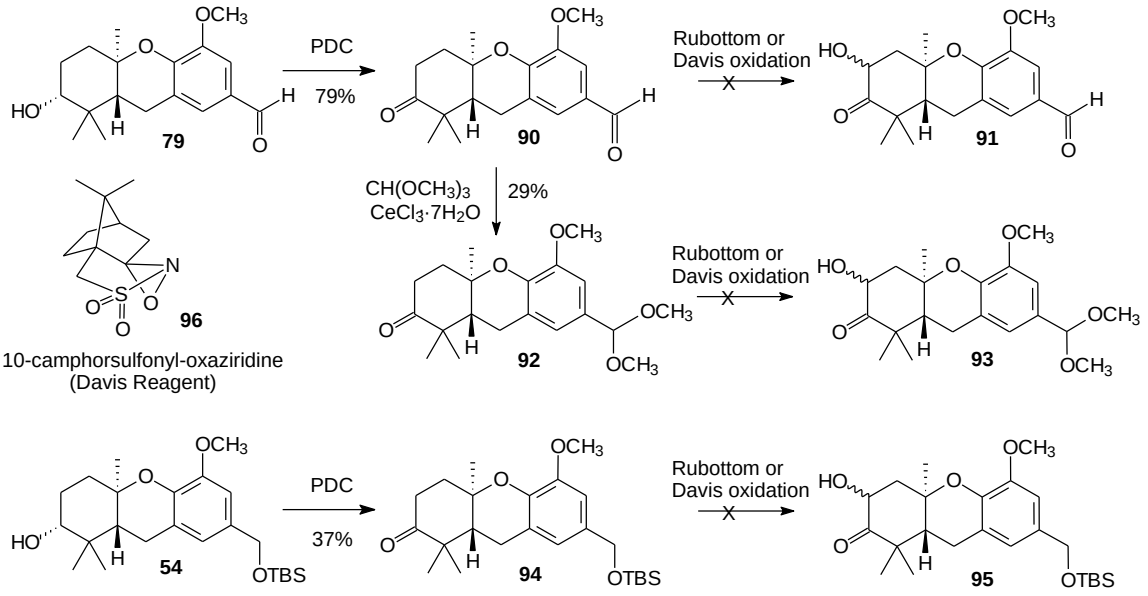
Scheme 13. Previous Attempts at Dihydroxylation.



Previously, J. D. Neighbors attempted to oxidize the C-3 position of the schweinfurthins' A-ring via enolate chemistry (Scheme 14).[63] Several available intermediates, including compounds **54** and **79**, were oxidized with PDC to afford different substrates on which alpha oxidation could be attempted (compounds **90**, **92**, and **94**). Oxidation manifolds to produce acyloins from a silyl enol ether or an enolate have been known for some time. At least two reactions have been developed to effect this transformation and are well documented to proceed in good yield; the Rubottom[80-82] and Davis oxidations.[83-85] Exposure of ketone **90** to various bases, including LHMDS, NHMDS, KHMDS, or LDA, followed by the Davis reagent (**96**) afforded recovered starting material uniformly. Protection of the aldehyde functionality in compound **90**

afforded acetal **92**, which was exposed to KHMDS/TMSCl, followed by *m*-CPBA in an effort to effect Rubottom oxidation. No oxidation was observed. Ketone **94**, prepared from a different intermediate, was exposed to both sets of conditions again to no avail. With these difficulties presented, this approach laid dormant until more reliable quantities of tricycle **77** were made available (*vide supra*).[63]

Scheme 14. Previous Attempts at A-Ring Oxidation.

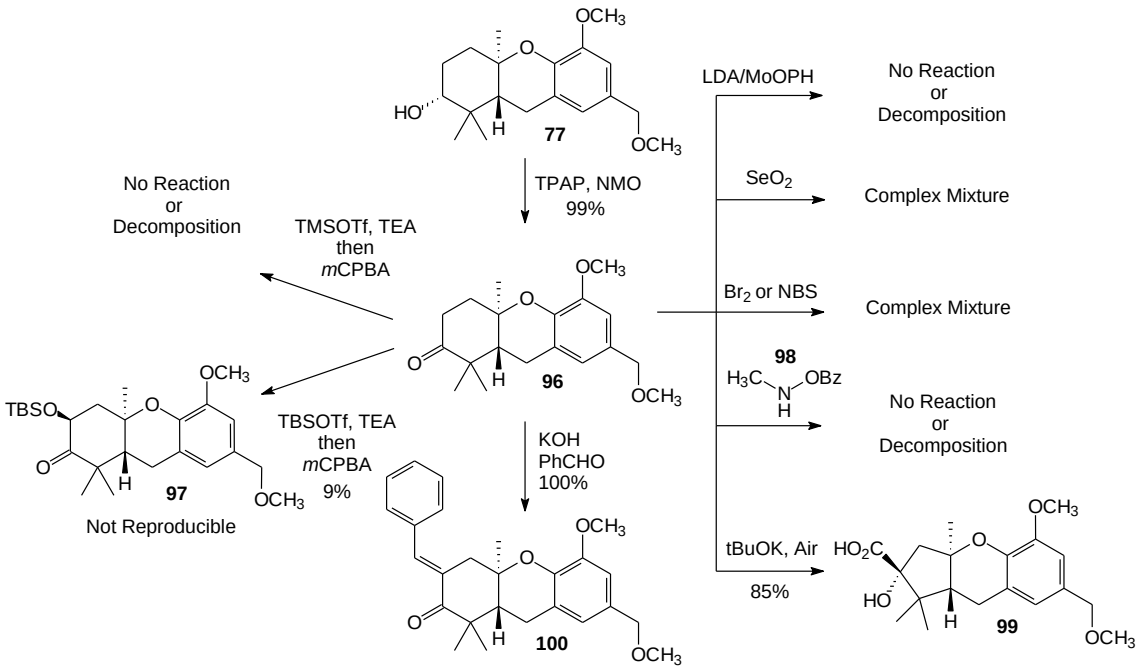


The present effort started by oxidation of intermediate **77**, now available on larger scale, to ketone **96** (Scheme 15). A brief exploration of oxidizing reagents revealed that the conditions developed by S. V. Ley (TPAP/NMO)[86] produced superior results in oxidizing the 2-hydroxy core of the schweinfurthins. Alpha oxidation protocols were then reexamined on ketone **96**. Here, the Rubottom protocol was attempted through use of the more active silylating reagent TMSOTf.[87, 88] Exposure of the crude mixture to excess *m*-CPBA did not afford any detectable quantities of acyloin products. When more

equivalents of either reagent were used, or if the reaction was conducted at higher temperature, decomposition was observed. Recognizing the acid sensitivity of TMS ethers, TBSOTf was used instead of TMSOTf with the intention of establishing a more stable enol ether. Use of TBSOTf did prove superior in this instance because enol ether formation was observed by ^{1}H NMR when the reaction was conducted in CD_2Cl_2. Even with excess TBSOTf, enol ether formation was incomplete and ca. 60% conversion was observed. Exposure of this reaction mixture to excess *m*-CPBA afforded trace quantities of acyloin **97** after separation from a complicated mixture. The isolation of compound **97** is a significant milestone in this project since it marks the first successful functionalization of the C-3 position. This triumph was short celebrated when the ^{1}H NMR spectrum of compound **97** was analyzed. Coupling constants between the C-3 hydrogen and it neighbors showed coupling of 13.5 Hz, indicating an axial disposition of the hydrogen. This implies that the relative stereochemistry of compound **97** is as shown in Scheme 15 and opposite of that desired. Attempts at reproducing or optimizing the preparation of compound **97** failed and it was decided to explore alternative oxidations. The above described frustrations should underscore the intransigence of either a 2,3-olefin or 2,3-enol ether to standard oxidation conditions.

A literature search revealed several possible alternatives to the Rubottom approach (Scheme 15). The molybdenum peroxy species called MoOPH[89] is known to act as an electrophilic oxygen source. Use of this reagent on ketone **96** with LDA failed to produce any detectable amount of acyloin, and instead only starting material was observed. The use of SeO_2 as an oxidant was explored, but only decomposition was observed under the conditions attempted. Attempts at producing an α-halo ketone were unsuccessful because aromatic or benzylic bromination competed with the desired pathway. The recently reported application of compound **98** to α-oxidation was explored.[90] Here initial enamine formation followed by sigmatropic rearrangement should produce an α-benzoate. Because this reaction progresses through a different

Scheme 15. Attempts at Oxidation of the C-3 Position.



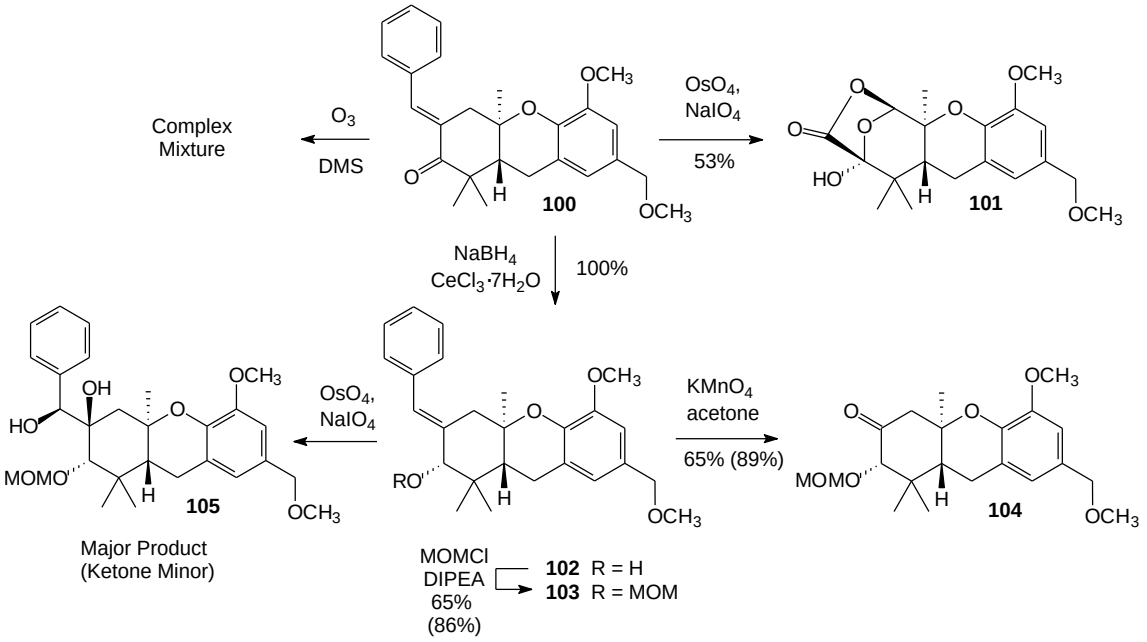
mechanism, the desired stereochemistry might have been obtained, but only starting material was recovered. When the reaction was heated to temperatures well above the published conditions, decomposition was observed. It should be noted that this reaction proceeded quantitatively on model systems and is a promising alternative to the other approaches described. Finally, reports which utilized tBuOK and air as an oxidizing medium were applied.[91, 92] From the reaction conditions attempted, only a very polar compound was isolated. Careful monitoring by TLC did not reveal the presence of any long-lived intermediates. Spectroscopic analysis of the major product suggested that the A-ring had undergone ring contraction and comparison to literature examples led to the structural assignment of this material as compound **99**.[93] The formation of compound **99** is likely to occur via initial oxidation to the 2,3-diketone, the desired product, followed by tautomerization to the 3-enol and then Favorski-like rearrangement. Given the facile

nature of this reaction sequence, one might assume that desired diketone would be unstable to basic conditions.

Having exhausted the most promising and direct literature procedures, a more meandering solution was sought. The classic aldol condensation proceeds with formal oxidation of the alpha position through production of an enone. If this reaction could be applied to the schweinfurthin core, oxidation of the exocyclic olefin would afford a 3-keto schweinfurthin intermediate. Literature precedent suggested that reduction of a C-3 ketone would provide the desired stereochemistry.[91, 92, 94] A brief exploration of aldehydes and reaction conditions was fruitful as enone **100** could be formed quantitatively in less than 20 min at room temperature in the presence of benzaldehyde and base! A certain irony must be acknowledged given this system's reluctance to react in the desired manner via modern α-oxidation reactions, but gracious surrender to fundamental and historic reactivity. With reproducible and scalable quantities of a C-3 functionalized schweinfurthin core available, further oxidation of this enone was explored.

Enone **100** first was exposed to ozone in an attempt to produce the 2,3-diketone whose synthesis was attempted earlier (Scheme 16). Under both standard and modified[95] ozonolysis conditions, complete decomposition was observed. Exposure of enone **100** to OsO_4 and $NaIO_4$ should have provided the same intermediate,[96] but compound **101** was isolated instead. The formation of this intermediate can be explained by initial formation of the desired diketone, followed by tautomerization to the enol form of the C-3 ketone. Dihydroxylation of this enol followed by $NaIO_4$ oxidation would afford an intermediate tricarbonyl compound. Successive ring closures of this intermediate under the basic conditions would afford hemiacetal **101**. Spectroscopic data of this compound coalesces nicely with the same motif present in other systems.[97, 98] The isolation of acetal **101** suggests a reason why ozonolysis of enone **100** would afford a mixture, since several of the intermediates along this path can react further with ozone.

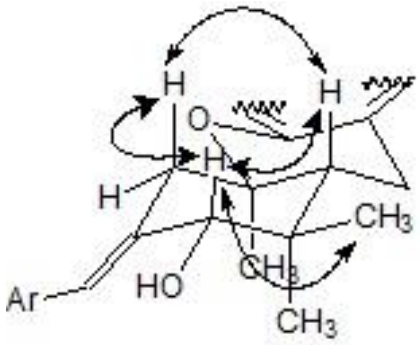
Scheme 16. Oxidation of Enone **100**.



At this juncture, enone **100** was reduced under Luche's conditions[99, 100] to afford allylic alcohol **102**. The relative configuration of the newly generated stereocenter was established based on nOe correlations (Figure 8). This assignment is also in agreement with the parallel reduction from the 3-deoxy series[63] and with that predicted based on hand-held models. Exposure of alcohol **102** to ozonolysis again produced a complex mixture. Wrongfully fearing unselective oxidation under other conditions (*vide infra*), alcohol **102** was protected as MOM acetal **103**. This protection was sluggish and numerous equivalents of MOMCl were required to drive the reaction to completion. Some experimentation revealed that the yield could be improved by increasing the reaction concentration to be 1:1 v/v CH_2Cl_2 and DIPEA (10 eq) followed by slow addition of MOMCl. The limited reactivity of this alcohol is not surprising given the extreme steric congestion about this position. Exposure of acetal **103** to OsO_4 and $NaIO_4$ provided trace amounts of the desired C-2 ketone along with significant quantities of diol

105. Increased reaction time or added equivalents of $NaIO_4$ did little to increase the formation of ketone **104**. With little recourse, $KMnO_4$ was explored as an oxidant.[101] Gratifyingly, numerous equivalents of this harsh oxidant were found to be effective in the formation of ketone **104**. It should be noted that portion-wise addition of $KMnO_4$, several equivalents at a time, and complete quenching of excess oxidant by 2-propanol provided the most reproducible results.

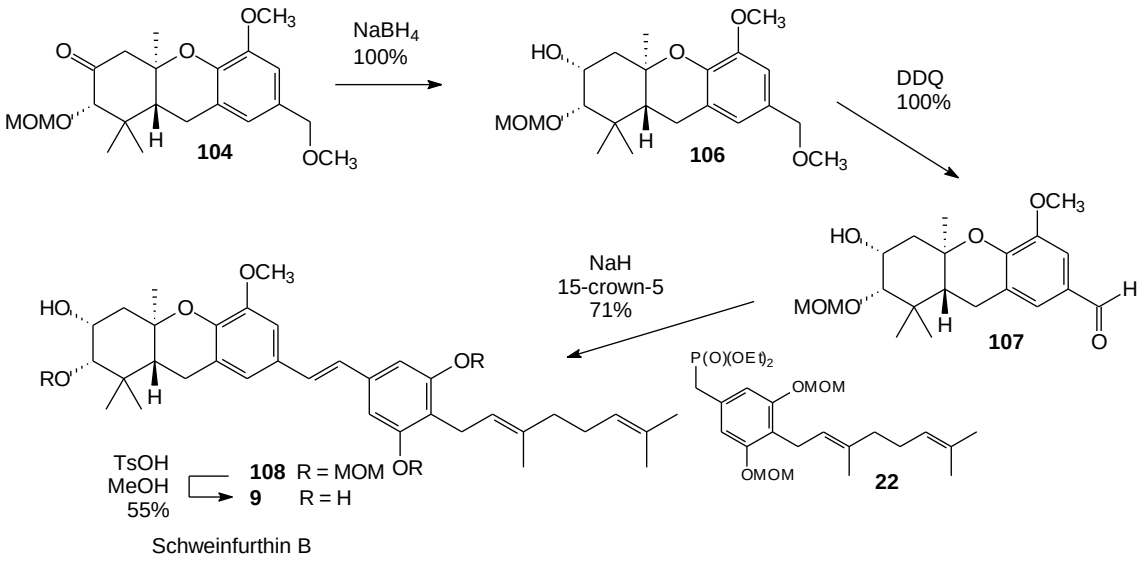
Figure 8. Key nOe Correlations for Compound **102**.



With a 3-keto schweinfurthin intermediate in hand, the completion of this synthesis could be pursued (Scheme 17). Reduction of ketone **104** under standard conditions afforded alcohol **106** whose relative configuration was evident by analysis of coupling constants (ddd, J = 3.2, 3.2, 3.2 Hz), which were in good agreement with those reported for schweinfurthin B. [25] Oxidation of the benzyl methyl ether with DDQ faithfully afforded aldehyde **107** in quantitative yield. This aldehyde then served as a key point of divergence from which numerous schweinfurthins could be produced. Condensation of aldehyde **107** with known phosphonate **22**,[30] prepared by N. R. Mente, afforded stilbene **108**. Concurrent acidic hydrolysis of all three MOM acetals under established conditions afforded schweinfurthin B (**9**), the first synthetically prepared 2,3-

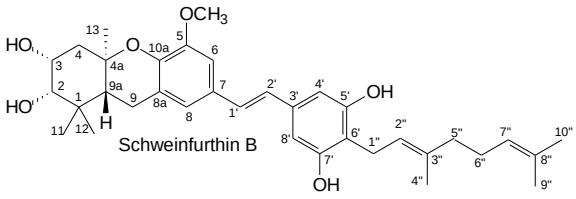
dihydroxy schweinfurthin. Material prepared in this manner provided spectroscopic data in excellent agreement with that published for the natural product (Table 1).[25] Additionally, both synthetic schweinfurthin B ([α] = +40.2, 92% ee by HPLC) and natural schweinfurthin B ([α] = +44.7)[25] rotated plane polarized light in the same direction and magnitude, which allows assignment of the absolute stereochemistry of the natural material as (+)-(2*S*, 3*R*, 4a*R*, 9aR)-schweinfurthin B. Furthermore, synthetically prepared (+)-schweinfurthin B was shown to be a potent anti-proliferative agent based on analysis in the NCI's 60 cell line assay (Figure 9).

Scheme 17. Total Synthesis of Schweinfurthin B.



In a similar fashion, aldehyde **107** was allowed to condense with phosphonate **108**,[68] again provided by N. R. Mente, under HWE conditions to provide stilbene **109** in excellent yield (Scheme 18). Deprotection of stilbene **109** afforded (+)-schweinfurthin E (**13**), which was found to be identical to the natural material in all respects (Table 2)[65] including optical rotation (observed [α] = +40.5, 92% ee by HPLC; literature[65] [α] =

Table 1. NMR Data for Schweinfurthin B.



^{1}H NMR of Schweinfurthin B				^{13}C NMR of Schweinfurthin B			
Signal	Literature	Observed	Δδ	Signal	Literature	Observed	Δδ
H-6	6.91 (d, J = 2.0 Hz, 1H)	6.91 (d, J = 2Hz, 1H)	0	C-5', 7'	157.2	157.2	0
H-1'	6.87 (d, J = 16 Hz, 1H)	6.87 (d, J = 16.0, 1H)	0	C-5	150.1	150.1	0
H-8	6.83 (d, J = 2.0 Hz, 1H)	6.83 (s, 1H)	0	C-3'	143.3	143.2	0.1
H-2'	6.77 (d, J = 16 Hz, 1H)	6.77 (d, J = 16.4, 1H)	0	C-10a	137.5	137.4	0.1
H-4', 8'	6.47 (s, 2H)	6.47 (s, 2H)	0	C-3"	134.8	134.7	0.1
H-2"	5.25 (tq, J = 7.2 Hz, 1.2 Hz, 1H)	5.25 (tq, J = 7.2, 1.2 Hz, 1H)	0	C-8"	131.9	131.9	0
H-7"	5.07 (tq, J = 7.2, 1.4, 1H)	5.07 (m, 1H)	0	C-7	130.6	130.6	0
H-3	4.14 (q, J = 3.4 Hz, 1H)	4.14 (ddd, J = 3.6, 1H)	0	C-1'	128.5	128.4	0.1
OCH_3	3.83 (s, 3H)	3.83 (s, 3H)	0	C-2'	127.6	127.6	0
H-2	3.30 obscured	3.30 (m, 1H, obscured)	0	C-7"	125.6	125.5	0.1
H-1"	3.30 obscured	3.30 (obscured)	0	C-2"	124.5	124.5	0
H-9	2.75 (m, 2H)	2.77 – 2.73 (m, 2H)	0	C-8a	124.3	124.2	0.1
H-4	2.34 (dd, J = 13.9, 3.3 Hz, 1H)	2.34 (dd, J = 14 Hz, 3.2 Hz, 1H)	0	C-8	121.7	121.6	0.1
H-6"	2.05 (m, 2H)	2.06 – 2.04 (m, 2H)	0	C-6'	115.9	115.8	0.1
H-4a, 5"	1.94 (m, 3H)	1.96 – 1.93 (m, 3H)	0	C-6	108.3	108	0.3
H-4"	1.76 (3H, s)	1.76 (d, J = 1.2 Hz, 3H)	0	C-4', 8'	105.8	105.6	0.2
H-9a	1.74 (m, 1H)	1.72 (dd, J = 12.2, 6.2 1H)	-0.02	C-2	78.7	78.7	0
H-10"	1.62 (s, 3H)	1.62 (d, J = 1.2 Hz, 3H)	0	C-4a	78	78	0
H-9"	1.56 (s, 3H)	1.56 (s, 3H)	0	C-3	71.7	71.7	0
H-13	1.40 (s, 3H)	1.40 (s, 3H)	0	OCH_3	56.4	56.3	0.1
H-12	1.10 (s, 3H)	1.09 (s, 3H)	-0.01	C-9a	48.6	48.6	0
H-11	1.08 (s, 3H)	1.08 (s, 3H)	0	C-4	44.7	44.7	0
				C-5"	40.9	41	0.1
				C-1	39.1	39.1	0.1
				C-12	29.3	29.3	0
				C-6"	27.7	27.7	0
				C-10"	25.8	25.8	0
				C-9	23.9	23.9	0
				C-1"	23.2	23.2	0.7
				C-13	21.9	21.9	0
				C-9"	17.7	17.6	0.1
				C-4"	16.5	16.5	0
				C-11	16.2	16.2	0

Figure 9. Synthetic Schweinfurthin B's 60 Cell Line Data.

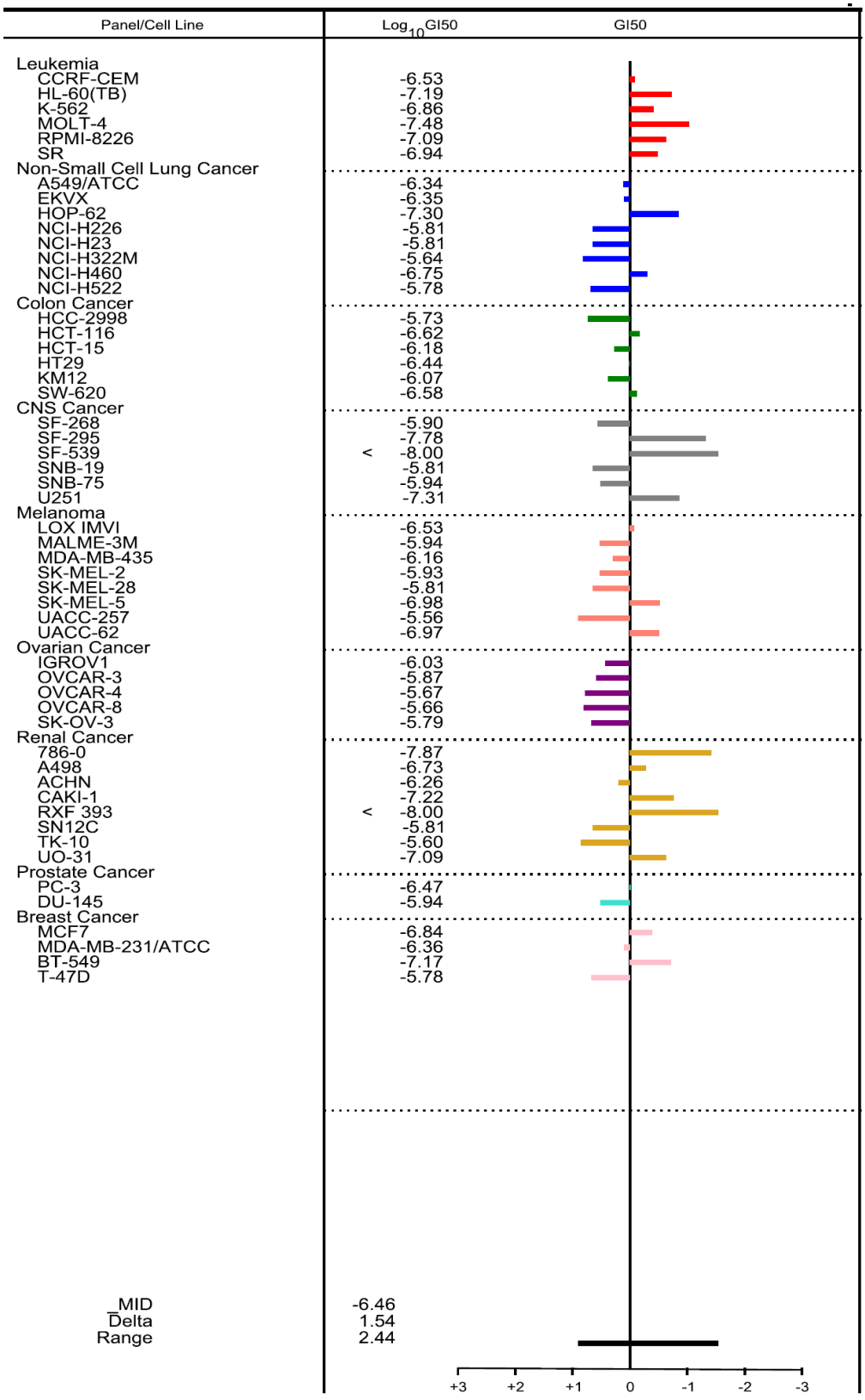
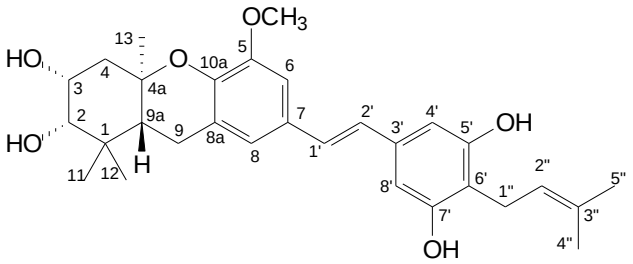
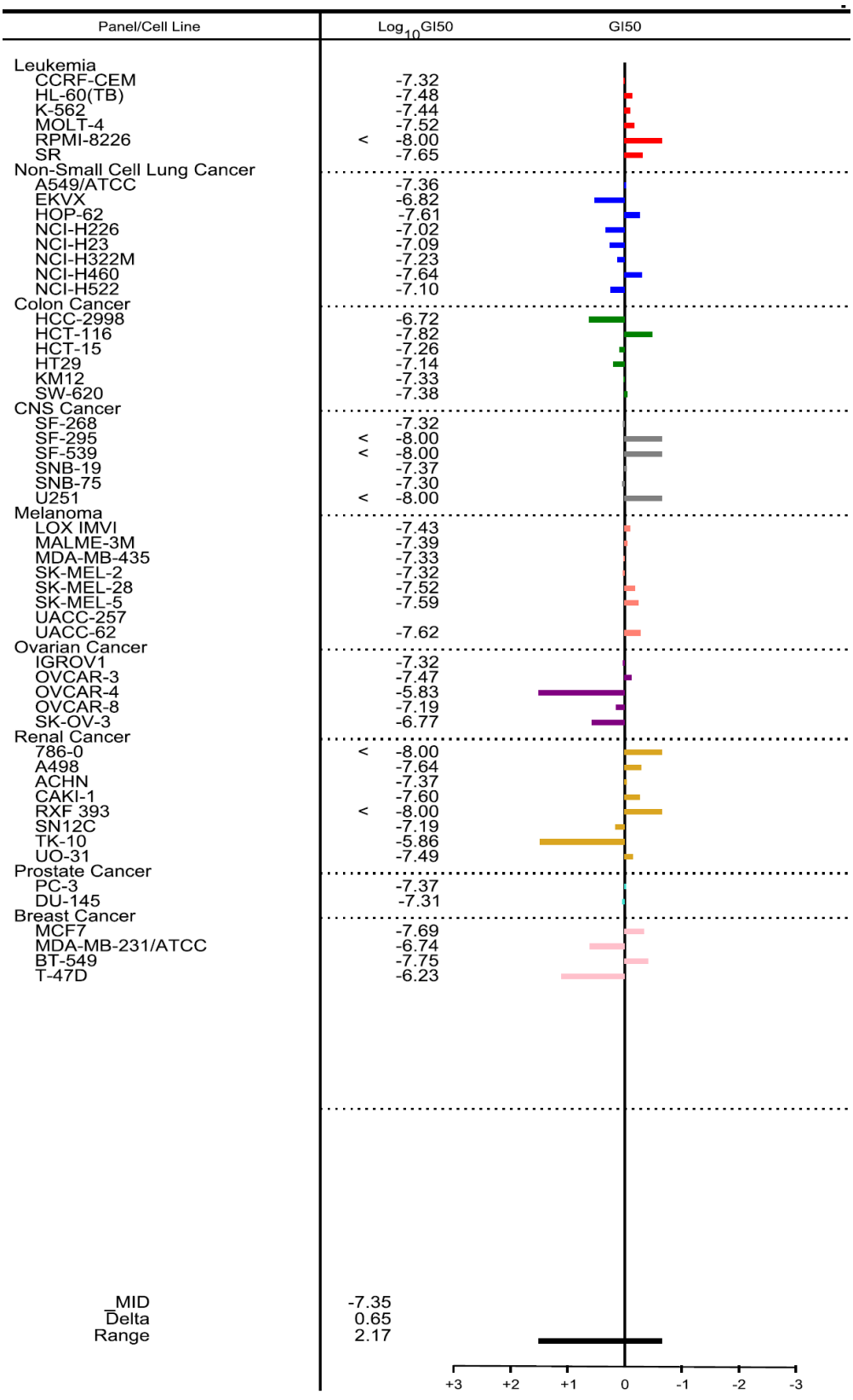


Table 2. NMR Data for Schweinfurthin E.



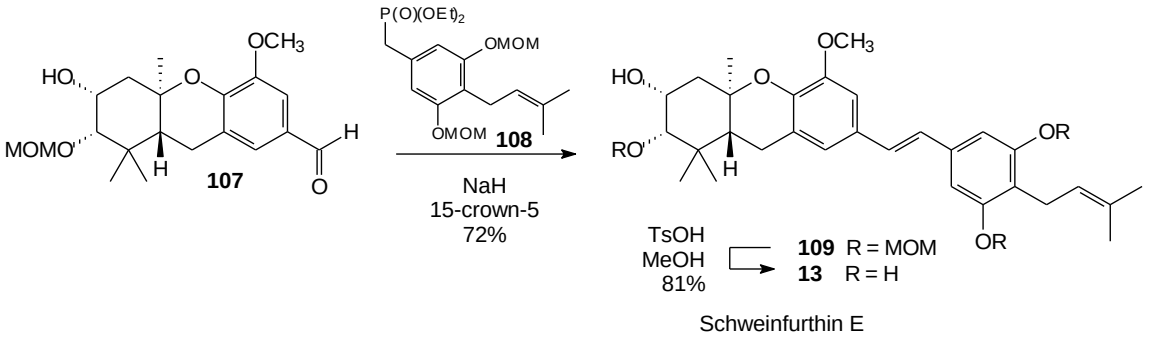
^{1}H NMR of Schweinfurthin E				^{13}C NMR of Schweinfurthin E			
Signal	Literature	Observed	Δδ	Signal	Literature	Observed	Δδ
H-6	6.91 (d, J = 1.5 Hz, 1H)	6.91 (s, 1H)	0	C-5', 7'	157.3	157.3	0
H-1'	6.87 (d, J = 16 Hz, 1H)	6.86 (d, J = 16.4, 1H)	-0.01	C-5	150.2	150.2	0
H-8	6.84 (d, J = ?? Hz, 1H)	6.83 (s, 1H)	-0.01	C-10a	143.4	143.3	-0.1
H-2'	6.77 (d, J = 16.5 Hz, 1H)	6.77 (d, J = 16.4, 1H)	0	C-3'	137.6	137.5	-0.1
H-4', 8'	6.46 (s, 2H)	6.46 (s, 2H)	0	C-3"	131.1	131.1	0
H-2"	5.23 (tq, J = 7 Hz, 1.5 Hz, 1H)	5.24 – 5.20 (m, 1H)	0	C-7	130.8	130.7	-0.1
H-3	4.14 (q, J = 3.5 Hz, 1H)	4.14 (ddd, J = 3.2, 1H)	0	C-1'	128.6	128.5	-0.1
OCH3	3.84 (s, 3H)	3.83 (s, 3H)	-0.01	C-2'	127.7	127.7	0
H-2, 1"	3.30 obscured	3.30 (m, 1H, obscured)	0	C-2"	124.6	124.6	0
1"	3.30 obscured	3.27 (d, J = 7.2, 2H)	-0.03	C-8a	124.4	124.3	-0.1
H-9	2.76 (m, 2H)	2.76 (m, 2H)	0	C-8	121.7	121.7	0
H-4	2.34 (dd, J = 14 Hz, 3 Hz, 1H)	2.34 (dd, J = 14 Hz, 3.2 Hz, 1H)	0	C-6'	116	115.9	-0.1
H-4	1.93 (dd, J = 13.5, 3.5 Hz, 1H)	1.92 (dd, J = 14 Hz, 3.2 Hz, 1H)	-0.01	C-6	108.3	108.2	-0.1
H-4"	1.76 (3H, s)	1.76 (d, J = 0.8 Hz, 3H)	0	C-4', 8'	105.8	105.7	-0.1
H-9a	1.74 (dd, J = 12.5, 6 Hz, 1H)	1.72 (d, J = 12 Hz, 6.4 HZ, 1H)	-0.02	C-2	78.8	78.8	0
H-5"	1.65 (s, 3H)	1.65 (d, J = 0.8 Hz, 3H)	0	C-4a	78.1	78	-0.1
H-13	1.40 (s, 3H)	1.40 (s, 3H)	0	C-3	71.8	71.8	0
H-12	1.10 (s, 3H)	1.09 (s, 3H)	-0.01	OCH3	56.5	56.4	-0.1
H-11	1.09 (s, 3H)	1.08 (s, 3H)	-0.01	C-9a	48.5	48.7	0.2
				C-4	44.8	44.8	0
				C-1	39.2	39.2	0
				C-12	29.4	29.4	0
				C-5"	26	26	0
				C-9	24	24	0
				C-1"	23.3	23.3	0
				C-13	22	22	0
				C-4"	17.9	17.9	0
				C-11	16.5	16.6	0.1

Figure 10. Synthetic Schweinfurthin E's 60 Cell Line Data.



+49.2). Synthetic schweinfurthin E also was subjected to the NCI's 60 cell line assay and was found to be a potent anti-proliferative agent with greater activity than schweinfurthin B (Figure 10).

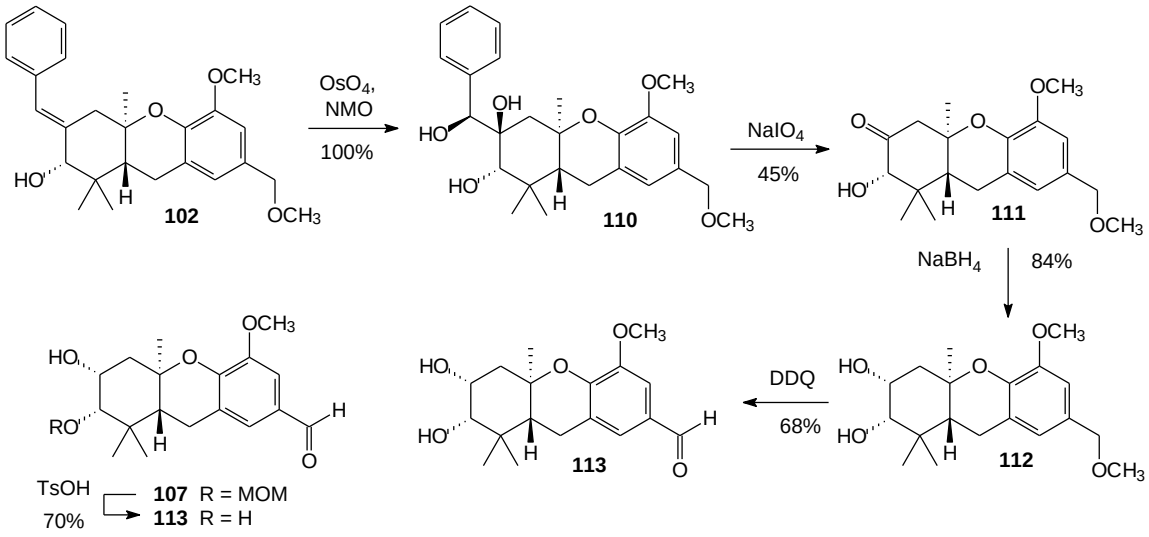
Scheme 18. Total Synthesis of Schweinfurthin E.



In an effort to optimize the original synthesis of a 2,3-dihydroxy schweinfurthin intermediate, it was discovered that the synthetic sequence could be abbreviated (Scheme 19). In the previously described sequence, intermediate **102** was protected as a MOM acetal to avoid competing oxidations. It was subsequently discovered that if the enone oxidations were performed sequentially, they were highly selective for the exocyclic diol. Here allylic alcohol **102** was exposed to OsO_4 under Upjohn[102] conditions to afford triol **110**. Triol **110** then was subjected to $NaIO_4$ oxidation in a separate flask to effect bond cleavage, which was highly selective for the desired bond to afford ketone **111**. Dihydroxylation and $NaIO_4$ cleavage of compound **102** was much more facile under these conditions than with the corresponding MOM-protected counterpart **103**. This increase in reaction rate could be attributed to reduced steric crowding, but is more likely the effect of complexation and delivery.[74] Reduction of ketone **111** was accomplished by exposure to $NaBH_4$ to provide diol **113**. Because complexation and delivery is likely at play in this system, one could imagine that an alternate diastereomer was formed during

the course of this reduction. To corroborate that the desired C-3 epimer was formed during the course of reduction, aldehyde **107** was hydrolyzed in the presence of acid. The product of this reaction was identical to that prepared via reduction. Although this path was not optimized, it did provide proof of principle in that the A-ring need not be protected to afford 2, 3-dihydroxyschweinfurthin intermediates, information that may be valuable in the synthesis of schweinfurthin A.

Scheme 19. Alternate path to A-Ring Diol.



In summary, the synthesis of schweinfurthins B and E has been accomplished. The above-described path to these natural schweinfurthins provided the natural products in 16 scalable steps proceeding in ~6% overall yield from vanillin. If the overall yield is corrected for various intermediates which were recovered as starting material, the yield can be represented as an astounding 18%. Optimization of the previously established intermediates provided increased material throughput so that oxidation protocols could be examined. Although oxidation of the schweinfurthins A-ring proved highly troublesome,

a rather classical solution was found which surmounted the limitations of more contemporary methodology. Elaboration of these intermediates to key aldehyde **107** was accomplished and the absolute stereochemistry of schweinfurthins B and E was established. Of critical importance, the biological activity of the synthetically prepared material matched that of the natural material in NCI-60 cell line assay.

CHAPTER 3

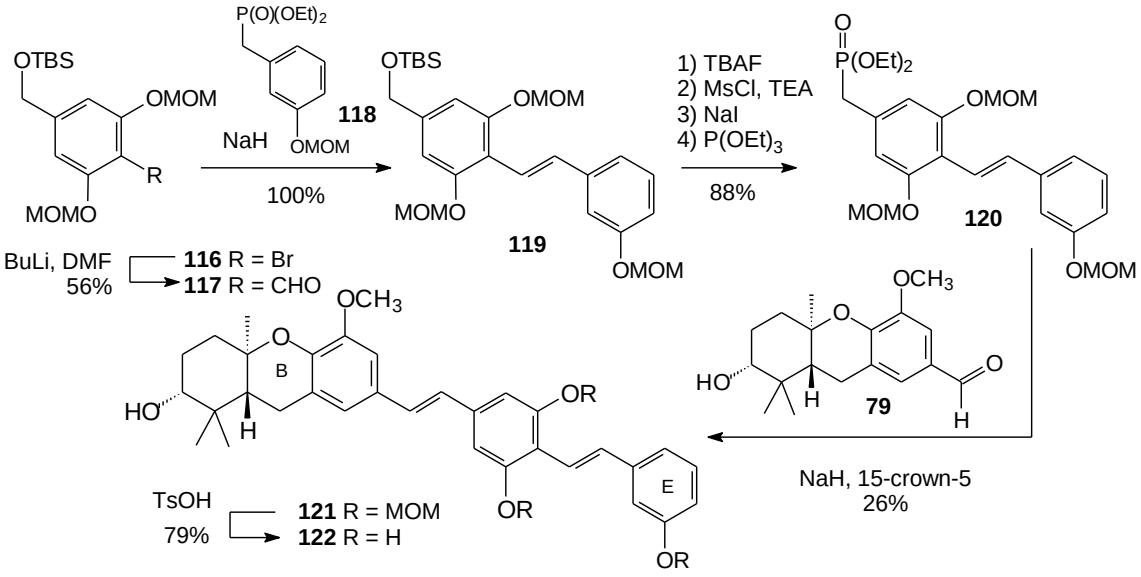
THE SYNTHESIS OF FLOURESCENT SCHWEINFURTHINS

The schweinfurthins exhibit potent and differential cytotoxicity (Chapter 1). They also display a unique pattern of activity across the NCI-60 cell line assay.[25] Attempts at ascribing the observed biological activity to a known mechanism of action via statistical analysis were unsuccessful, which probably indicates a novel mode of anti-proliferative activity.[31] Additionally, the cell lines which are most sensitive to the schweinfurthins (central nervous system cells) represent a class of incurable cancers.[7] Glioblastoma multiforme is likely the most aggressive of these cancers and the prognosis of those diagnosed typically does not exceed 12 months even with rigorous treatment.[103] The high potency of the schweinfurthins against these cell lines makes them an attractive lead agent for drug development.[14] However, the identification of an agent's mechanism of action or determination of its molecular target is a key step in securing approval for clinical trials. With this consideration, several schweinfurthins were designed so that they could be used as tools in the identification of the schweinfurthins' molecular target(s).

The Wiemer group's ongoing efforts at describing the schweinfurthins pharmacophore[64, 68-70] proved invaluable in the design of mechanistic probes. Previous work indicated that the D-ring of the schweinfurthins could contain a variety of alkyl chains without loss of potency.[70] Given that the *trans*-stilbene core of the schweinfurthins must be conserved for cytotoxicity,[67, 70] it was hypothesized by J. D. Neighbors that extending the conjugation of this system to a third arene would lead to highly fluorescent schweinfurthin analogues. This hypothesis was based on the weak fluorescence that the natural schweinfurthin core displays and the first such analogue was rapidly prepared by J. D. Neighbors (Scheme 20).[73] The synthesis began with bromide **116,**[32, 67] which was converted to aldehyde **117** through the intermediate aryl lithium.

Aldehyde **117** then was condensed with phosphonate **118** to form stilbene **119**, which was converted to stilbene phosphonate **120**. Union of phosphonate **120** with tricyclic aldehyde **79**[31] yielded bis-stilbene **121**, which was deprotected to afford the target analogue **122**. Compound **122** did display more favorable fluorescent properties (absorption max at 330 nm, emission max at 416 nm) then the parent schweinfurthin F (absorption max at 330 nm, emission max at 390 nm) and was biologically active (MTT assay, EC_{50} ~800 nM against SF-295), although not as potent as schweinfurthin F (MTT assay, EC_{50} < 80 nM against SF-295). Unfortunately, the emission maximum for this compound overlapped with background emission from SF-295 cells and this analogue was not stable to prolonged irradiation. [73]

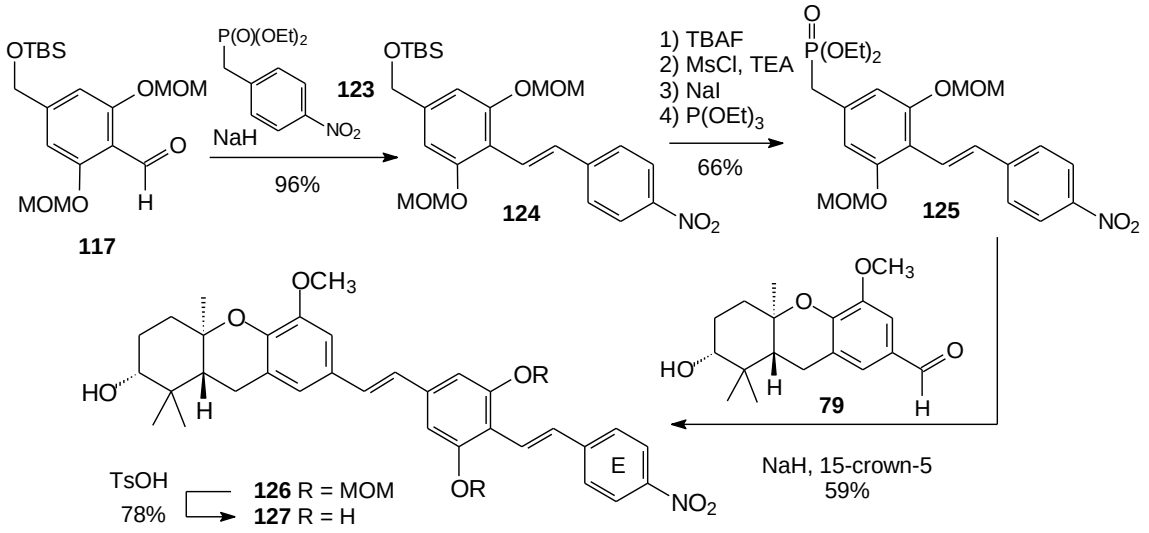
Scheme 20. Synthesis of First fluorescent Analogue **122**.



The weak activity and marginally enhanced fluorescence of compound **122** dictated that additional analogues be synthesized. Several factors were considered in the design of second generation targets. Recognition of the B-ring oxygen's electron

donating character led to the postulate that an electron withdrawing group would be complementary and shrink the HOMO/LUMO gap of any resulting schweinfurthin analogue. Reduction of the HOMO/LUMO gap is recognized as one way to increase fluorescence.[104, 105] To better transmit any electronic effects present on the E-ring of the bis-stilbene core, the substitution pattern on the terminal arene was altered. Placing substituents on the para position allows direct communication to the B-ring oxygen through resonance.[74] These combined factors lead J. D. Neighbors to synthesize compound **127** (Scheme 21). The synthesis began with aldehyde **117**. Condensation of aldehyde **117** with phosphonate **123**,[106, 107] which is available directly from the commercially available benzylic bromide, afforded stilbene **124**. Manipulations of the benzylic position required four steps, but afforded phosphonate **125** in good yield. Condensation of phosphonate **125** provided protected schweinfurthin **126**, which upon exposure to hydrolytic conditions provided the desired schweinfurthin **127**.

Scheme 21. Synthesis Schweinfurthin **127**.



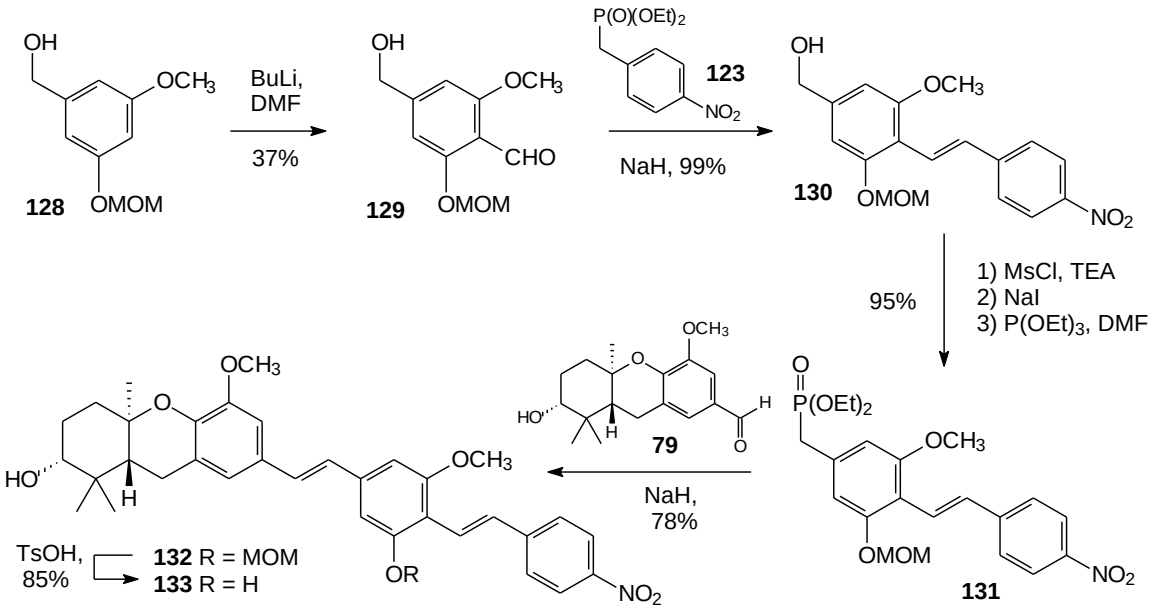
The properties of schweinfurthin **127** were more desirable than those of compound **122**, but they were still less than ideal. As postulated, compound **127** displayed an emission maximum which was red shifted (emmisson max at 575 nm) compared to analogue **122**, and also possessed a greater Stokes shift (absorbtion max at 430 nm). The biological activity of compound **127** (MTT assay, EC_{50} ~50 nM against SF-295) also was improved and it was slightly more potent then schweinfurthin F. Regretfully, this analogue also showed poor shelf and photo stability and as such, further analogues were needed.

In the Wiemer group's previous work, it was shown that one of the two D-ring phenols could be masked as a methyl ether without significant loss of potency.[67, 68] From a qualitative perspective, the addition of a methyl group also increased the stability of the resulting schweinfurthins.[68] Given the rapid decomposition of schweinfurthin **127**, we sought to incorporate a methyl group onto the D-ring of fluorescent analogues to increase stability. Also, during the course of this work, the total synthesis of schweinfurthin B (Chapter 2)[72] marked a key milestone in accessing schweinfurthis analogues because it made aldehyde **107** available for condensation with a variety of phosphonates. Because the schweinfurthins with an A-ring diol display greater potency and differential activity,[25, 31] it appeared prudent at this juncture to synthesize fluorescent analogues which contained an A-ring diol motif.

With these considerations in mind, several additional schweinfurthin analogues were prepared. To advance the present studies, monomethoxy phosphonate **131** was synthesized (Scheme 22). Benzyl alcohol **128**, available in four steps from previous work,[68] was subjected to multiple equivalents of BuLi. The resulting dianion could then be quenched with DMF to afford directly aldehyde **129**. Although the yield for this step is low, large quantities of starting material can be recovered. Exposure of aldehyde **129** to excess NaH and phosphonate **123** allowed the direct synthesis of benzyl alcohol **130**.

The brevity with which alcohol **130** was synthesized represents a significant improvement over the previous sequence (Scheme 20).

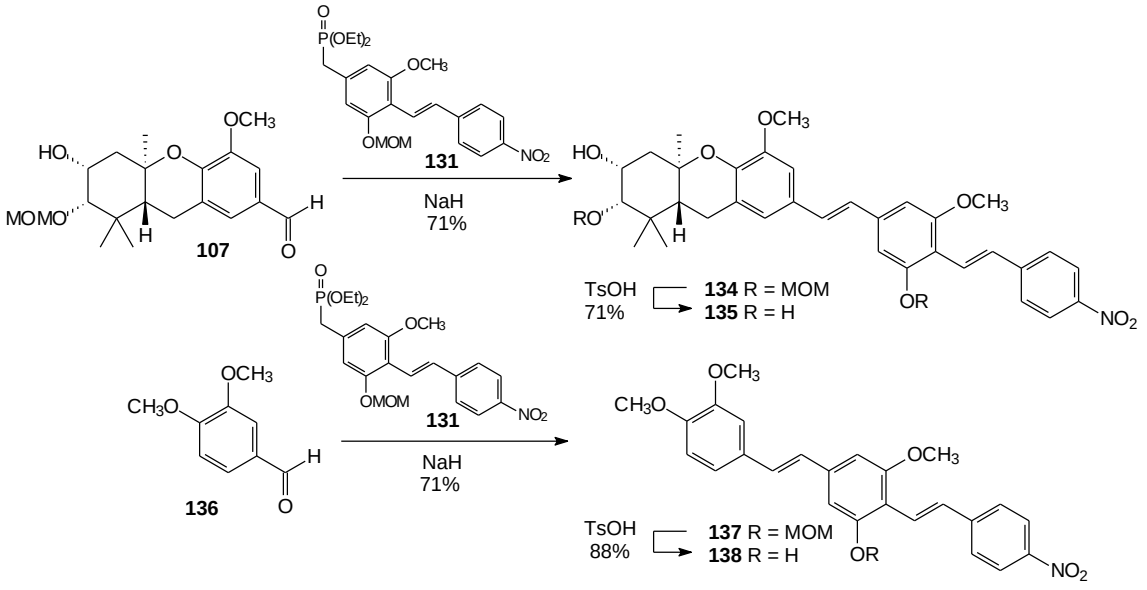
Scheme 22. Synthesis of 5'-Methoxy Schweinfurthin **133**.



Conversion of benzyl alcohol **130** to the corresponding phosphonate proceeded through three standard transformations. Here the use of a more polar solvent for the final Arbuzov reaction was key to high and reproducible conversion and is recommended as a general solution for sluggish reactions of this type. Phosphonate **131** then was employed with aldehyde **79**[31] in an HWE olefination to produce stilbene **132**. Deprotection of this compound under hydrolytic conditions provided fluorescent schweinfurthin **133**. Schweinfurthin **133** displayed fluorescent properties nearly identical to compound **127** and was almost as potent (MTT assay, EC_{50} ~ 100 nM against SF-295). Of greater significance, analogue **133** also was much more stable and has since been employed in microscopy experiments (*vide infra*).

Key phosphonate **131** then stood as a point of divergence (Scheme 23). Schweinfurthin B analogue **135** was synthesized by condensation of aldehyde **107**, available from the total synthesis of schweinfurthin B,[72] with phosphonate **131**. This afforded bis-stilbene **134** in moderate yield. Removal of both MOM groups proceeded smoothly under acidic conditions to afford analogue **135**. This compound displayed fluorescence equivalent to compound **133** and was more than twice as potent as its deoxy counterpart (MTT assay, EC_{50} ~40 nM against SF-295). Schweinfurthin **135** is also the first analogue prepared which contains an A-ring diol.

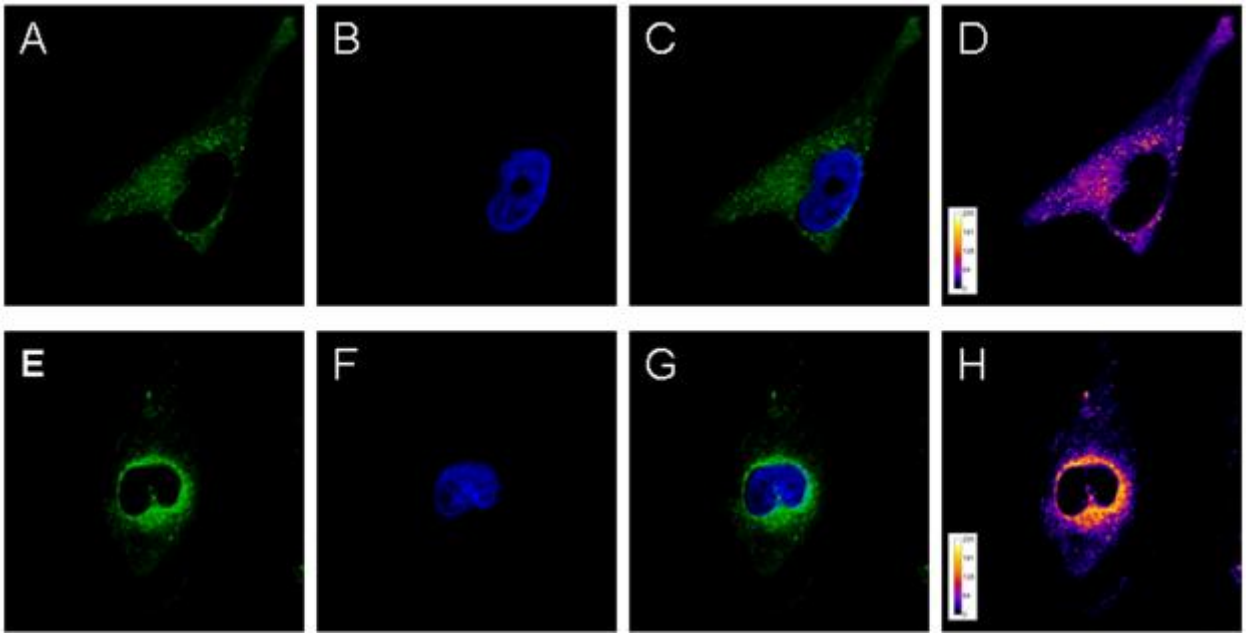
Scheme 23. Assembly of Fluorescent Schweinfurthin B Analogue **135** and Control Compound **138**.



To increase the significance of ensuing microscopy work, control experiments would be necessary. To aid in this regard, compound **138** was synthesized by condensation of commercially available aldehyde **136** with phosphonate **131** to provide

bis-stilbene **137**. Hydrolysis of the MOM acetal then afforded compound **138**. The fluorescent properties of compounds **127**, **133** and **135** where conserved in this control compound, but it showed no anti-proliferative activity at relevant concentrations.

Figure 11. Microscopy Experiments.



SF-295 cells were treated with compound **133** (500 nM) (A-D) or compound **138** (500 nM) (E-H) for 24 hours. Images depict intracellular localization of compound **133** (A) or compound **138** (E) alone, nuclear labeling of treated cell with DAPI (B and F), merged images of DAPI with compound **133** (C) or compound **138** (G), or fluorescence brightness distribution images of compound **133** (D) or **138** (H).

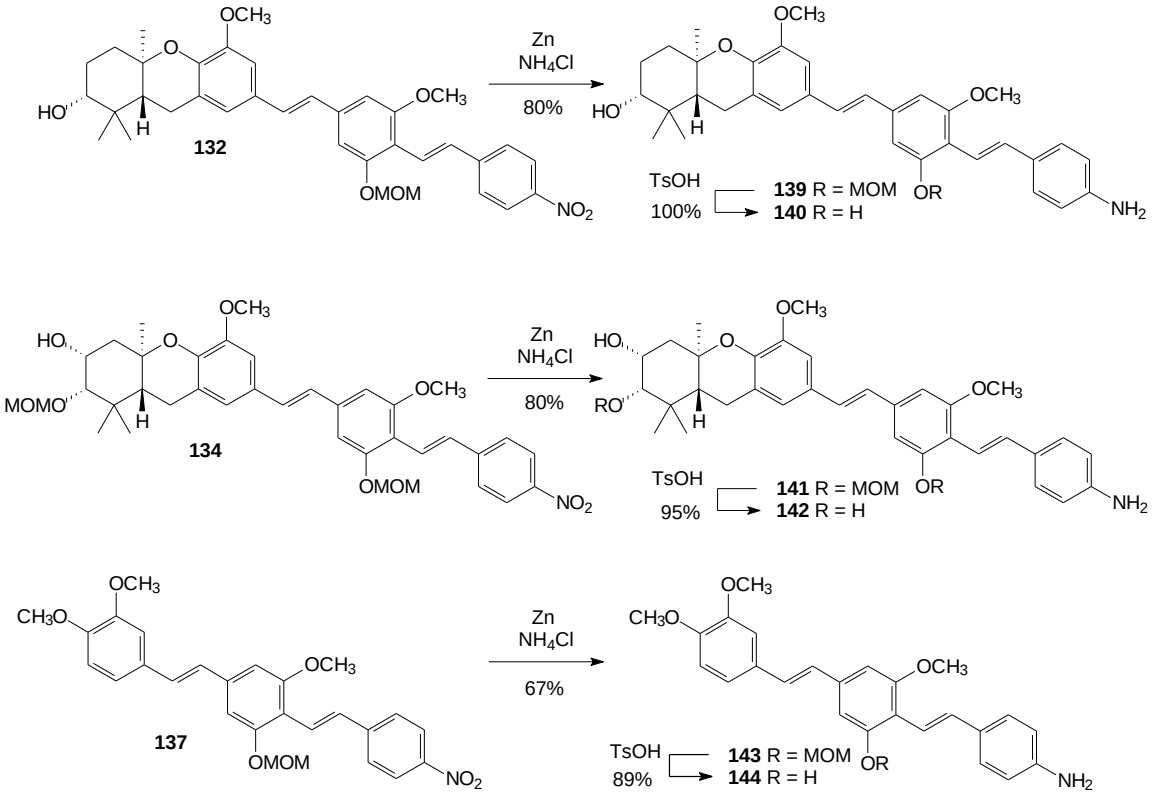
Numerous microscopy experiments utilizing compounds **133** and **137** have since been conducted. Dr. C. H. Kuder has spent significant effort determining the sub-cellular localization of the schweinfurthins and the time course of schweinfurthin exposure which leads to cell death. As can be seen in Figure 11, clear differences in localization exist

between active schweinfurthin **133** and control compound **137**. The existence of discrete fluorescence near the periphery of schweinfurthin-treated cells is one distinguishing characteristic and might help explain the morphological changes cells undergo when exposed to schweinfurthins or chephalostatin.[108, 109] Additionally, monitoring schweinfurthin-treated cells over longer durations has revealed that significant amounts of schweinfurthin accumulate at the tips of structurally degraded cells.

The above described microscopy experiments have generated a wealth of knowledge regarding the cellular localization of the schweinfurthins and the time course of schweinfurthin activity, and provided clues on modes of action. However, these experiments cannot directly identify the schweinfurthins' target. To identify specific binding partners, most likely a protein or proteins, other assays and protocols will be needed. The most common and popular of these experiments involves the utilization of affinity based chromatography.[110-112] In these experiments, an active agent is attached to a solid support and loaded onto a column. Cell lysate is then passed down the column and the target(s) is allowed to bind to the active agent. After thorough washing, detergents can be sent down the column to detach binding partners. Molecules eluted from the column can then be separated by gel electrophoresis and can then be analyzed via various methods, most commonly MALDI-MS-MS. To implement this concept in the present work, a chemical means for attaching a schweinfurthin to a column must be generated. Therefore, the nitro group in schweinfurthins **132** and **135** was chemoselectively reduced to afford compounds **139** and **141** (Scheme 24).[113] Removal of the MOM groups in compounds **139** and **141** proceeded under standard conditions to afford schweinfurthins **140** and **142** in excellent yield. In a similar fashion, bis-stilbene **137** was reduced to compound **143** and deprotected, yielding compound **144** as another control compound. These compounds presented diminished fluorescent properties when compared to the nitro-containing compounds and were found to be slightly less potent against SF-295 cells in MTT assay. Fortunately, condensation of the amino functionality

with aldehyde-functionalized beads followed by reduction afforded a schweinfurthin labeled solid phase, which is now employed in studies that use affinity-based chromatography to elucidate schweinfurthin binding partners.[114]

Scheme 24. Synthesis of Aniline Derivatives.



The synthesis of these schweinfurthin analogues should provide a set of tools that may allow discovery of the schweinfurthins' mechanism of action. Both microscopy and affinity chromatography can be utilized in this elucidation. These experiments also validate the enhanced activity of schweinfurthins with an A-ring diol.

CHAPTER 4

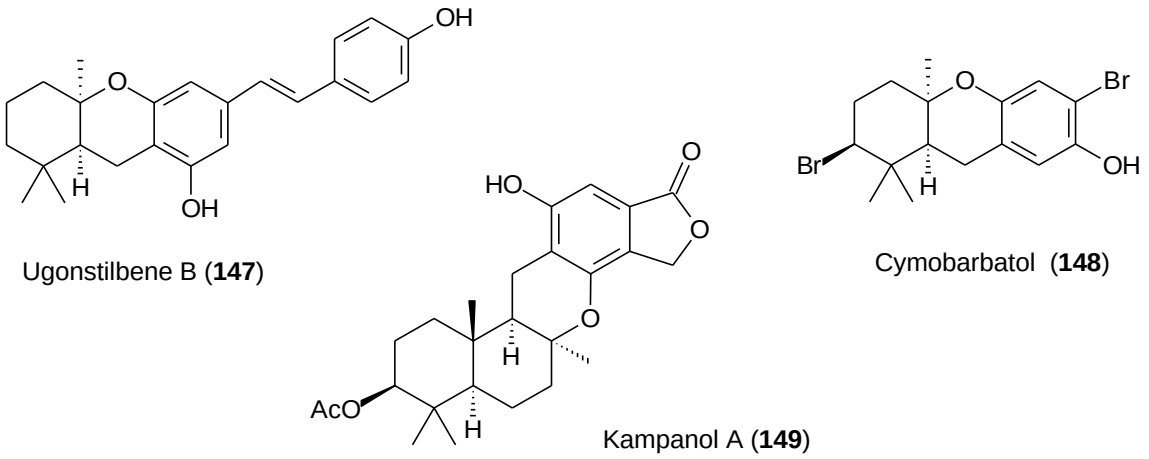
SYNTHESIS OF A CIS FUSED HEXAHYDROXANTHENE

The schweinfurthins contain a terpenoid-based ring system which is a found occasionally in natural prenylated aromatic compounds. As discussed above (chapter 1), there is strong evidence that this substructure originates through a cascade cyclization of a linear C-10 isoprene chain. Although there are several examples of natural products which contain this ring system, most display a *trans* ring fusion. A *cis* fused ring system of this type is rare although a few have been reported (Figure 12)[115-118] Perhaps most notable is kampanol A (**149**) which is an inhibitor of farnesyl:protein transferase.[119] The Wiemer group's interest in this enzyme[120, 121] and the notion that the ring system of kampanol might arise synthetically from a cascade cyclization[32, 122] make this an exciting target for the Wiemer group to pursue. Given the complexity of kampanol A, a model system was sought so that the sterochemical course of a cascade cyclization could be evaluated. Noting the successful formation of the schweinfurthins' ring system based on the cyclization of a geranyl epoxide onto a vanillin core,[32, 72] this substructure was chosen for model studies. Choosing vanillin as a model system also held the dual purpose of providing a novel schweinfurthin analogue, through which the schweinfurthins' pharmacophore could continue to be mapped.

Cascade cyclizations are known to proceed through chair like-transitions states, which faithfully preserve the sterochemical information encoded into the olefin geometry.[37, 38, 40] Examples exist where cyclization of both olefin isomers in the isoprene chain have been studied and the isomers yield sterioisomeric products (Scheme 25). The first example given, was generated to address the possibility of a concerted cascade mechanism and involves the cyclization of norgeranic acid (**150**) to form acid **151**.[42] When the other olefin isomer **152** was used, ring closure formed the epimeric product **153**. This observation of selectivity was later confirmed when mono-cyclization of

farnesol derivatives, compounds **154** and **156** to compounds **155** and **157**, was accomplished in zeolites.[123, 124] Another example recently was provided with the use of a gold catalyzed cyclization to provide lactones **159** and **161** from the linear precursors **158** and **160**.[57]

Figure 12. Natural Cyclaized Prenylated Aromatics with Cis-Ring Fusion.



Ugonstilbene B (**147**)

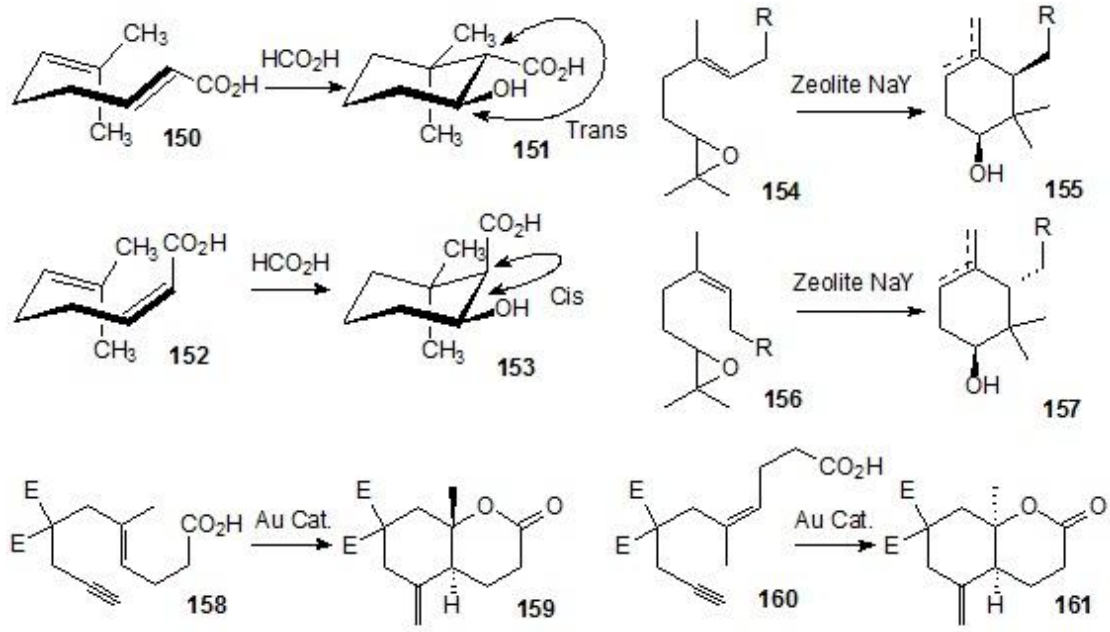
Kampanol A (**149**)

Cymobarbatol (**148**)

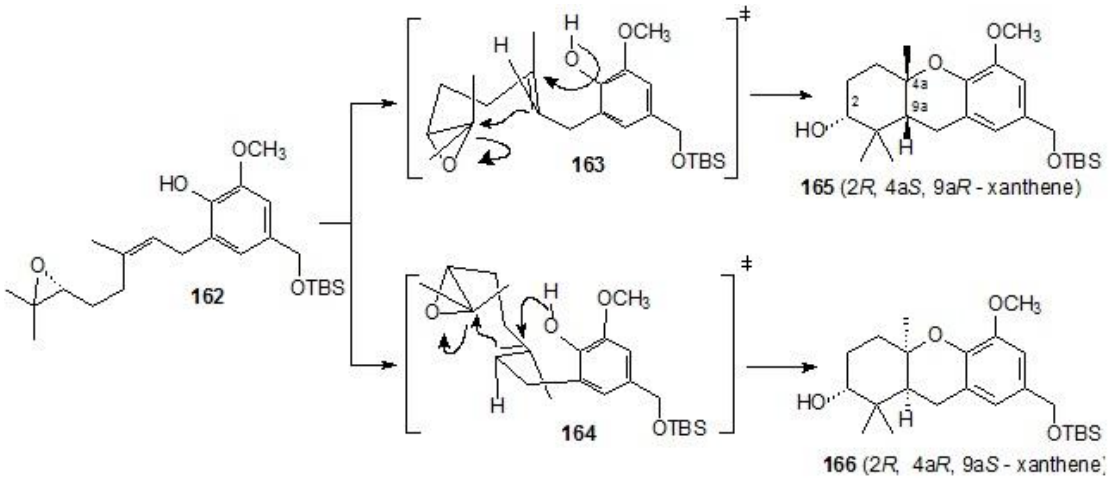
We hypothesized that altering the olefin geometry present in the cascade precursor used for schweinfurthin synthesis, from geranyl (*E*) to neryl (*Z*), would provide the *cis*-fused stereochemistry. A cascade cyclization of neryl epoxide **162** could conceivably proceed to form one or both of the diastereomers depicted (**165** and **166**, Scheme 26) which differ in the relative arrangement of the A-ring alcohol. The isolation of cymobarbatol suggested that compound **165** might be favored in the natural course of cyclization and the equatorial disposition of the bromide seemed to follow the observed pattern in the *trans* case. With these hypotheses generated, efforts to synthesize a *cis*-fused analogue of 3dSB were undertaken.

The synthesis of the requisite neryl epoxide **172** began with differentially protected arene **51**, which was available from previous work (Scheme 27).[32] Exposure to

Scheme 25. Diastereomeric Cyclization Outcomes Based on Olefin Geometry.



Scheme 26. Possible Stereochemical Outcomes from a Neryl Cascade.



Scheme 27. Initial Synthesis of Epoxide **172**.

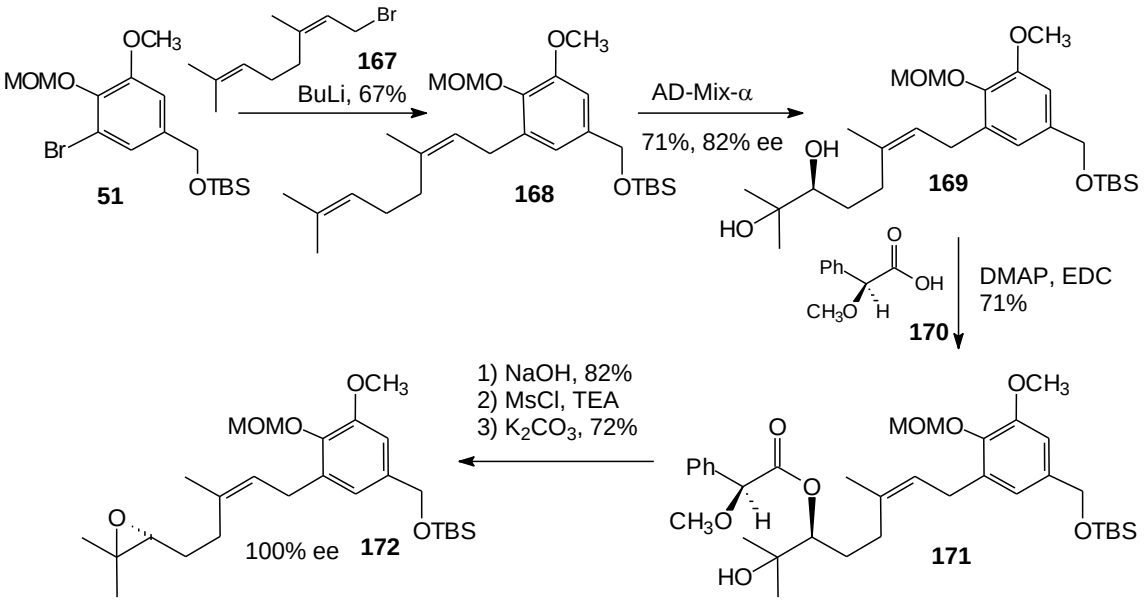
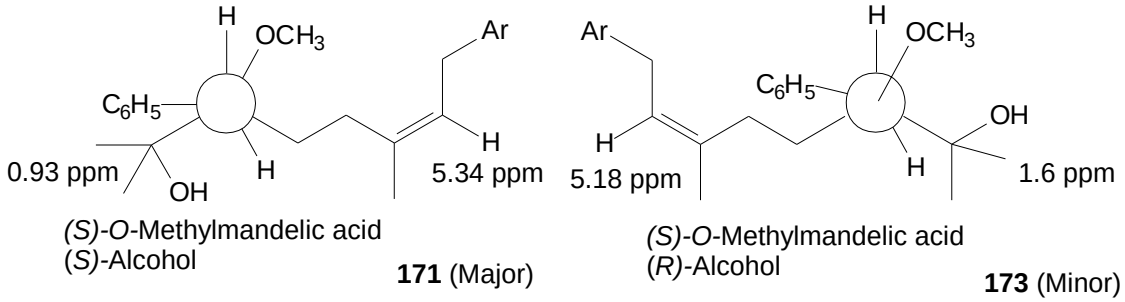


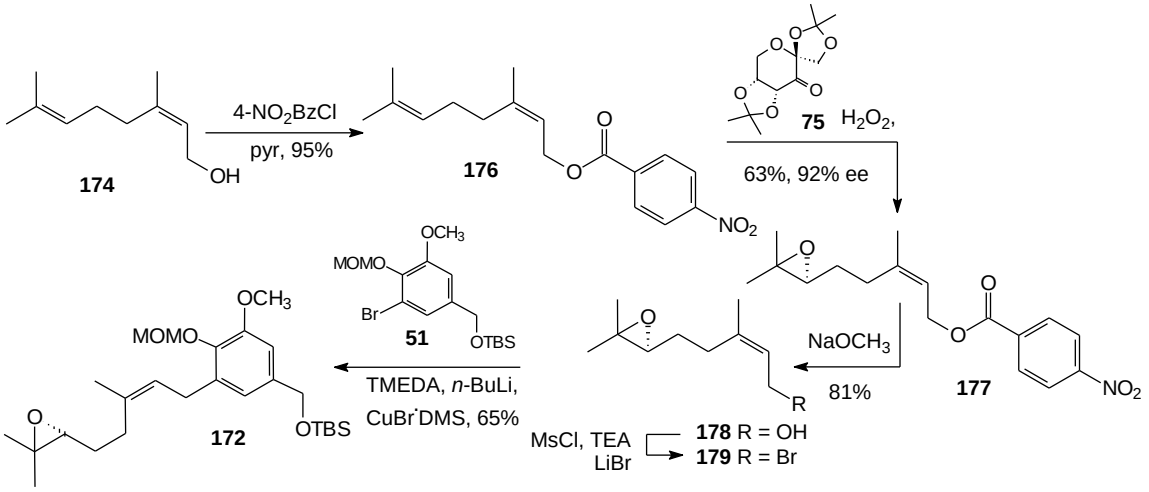
Figure 13. Mosher Trost Analysis of Mandalate **171**.



BuLi promoted halogen-metal exchange and the resulting anion was quenched with freshly prepared neryl bromide (**167**) to afford compound **168** in good yield. Dihydroxylation of the terminal olefin in compound **168** was conducted under the asymmetric conditions developed by Sharpless to afford diol **169** in an enatioenriched form.[125] The ee of this material was found to be approximately 82% based on the isolation and characterization of more advanced intermediates. Esterification of diol **169**

to form the mandelate **171** allowed chromatographic separation of the resulting diastereomers. Total resolution was possible and as such the pair was subjected to Mosher-Trost analysis (Figure 13).[126, 127] Key resonances in the ^{1}H NMR spectrum showed upfield shifts and thus the absolute stereochemistry of diol **169** was assigned as the *S* configuration, which was expected based on the dihydroxylation model provided by Sharpless.[125] Subsequent hydrolysis of mandelate **171** provided diol **169** as a single enateomer. Selective conversion of the secondary hydroxyl group to the mesylate followed by base promoted ring closure resulted in epoxide **172.**[31]

Scheme 28. Alternate Synthesis of Epoxide **172**.



During the course of these studies, several advances were made concerning the synthesis of the corresponding geranyl epoxide.[66] Based on these advances, the synthesis of epoxide **172** was shortened (Scheme 28). Using previous work as a guide, nerol (**174**) was esterified to form 4-nitrobenzoate **176**.[66, 128] This group was chosen because if allows for greater levels of regioselectivity in the subsequent Shi epoxidation. Epoxidation under Shi's conditions[78, 79] provided epoxide **177** in good yield and high

enantioselectivity. Removal of the benzoate proceeded smoothly in the presence of methoxide to afford (*R*)-6,7-epoxynerol with a specific rotation that corresponded in magnitude to literature data for the opposite enantiomer.[129] Conversion of alcohol **178** to allylic bromide **179** was accomplished in one pot by mesylate formation followed by treatment with LiBr. Bromide **179** was used immediately in the following coupling reaction. Exposure of compound **51** to *n*-BuLi, transmetalation of the aryl lithium to the presumed cuprate, and subsequent addition of allylic bromide **179** afforded epoxide **172** directly in improved overall yield.[66, 130]

With significant quantities of enatioenriched epoxide **172** in hand, the ensuing cascade cyclization was explored (Scheme 29). Exposure of epoxide **172** to our standard $BF_3{\cdot}OEt_2$ mediated conditions produced the desired tricycle **173** in poor yield along with significant quantities of polymeric material. Efforts to optimize this key transformation proceeded with meager success providing tricycle **173** in modest yield. With the aid of J. D. Neighbors, numerous protic and Lewis acids where screened. Of those inspected, $BF_3{\cdot}OEt_2$ was found to provide the highest yields of the desired material. Stronger Lewis acids increased the amount of polymeric material formed, whereas weaker Lewis acids, such as $In(OTf)_3$, promoted alternate epoxide rearrangements to form either alcohol **175** or ketone **174** in varying ratios (Scheme 29). The cis ring fusion of tricycle **173** was evident from the ^1H NMR spectrum. When compared to the *trans*-fused counterpart, there were several distinguishing resonances. One of the methyl groups showed a significant upfield shift to below 0.7 ppm and the benzylic spin system on C-9, which shows up as an overlapping multiplet for the *trans* case, was well resolved and displayed clear germinal coupling ($J \sim 20$ Hz). Although these observations supported the *cis* ring fusion, no conclusive evidence defined the relative disposition of the C-2 stereocenter.

The scant quantities of tricycle made available from $BF_3{\cdot}OEt_2$ mediated cascade cyclization was advanced to the final schweinfurthin (Scheme 30). Desilyation of compound **173** was conducted upon exposure to TBAF to provide alcohol **176**.

Scheme 29. Cyclization Of Epoxide **172**.

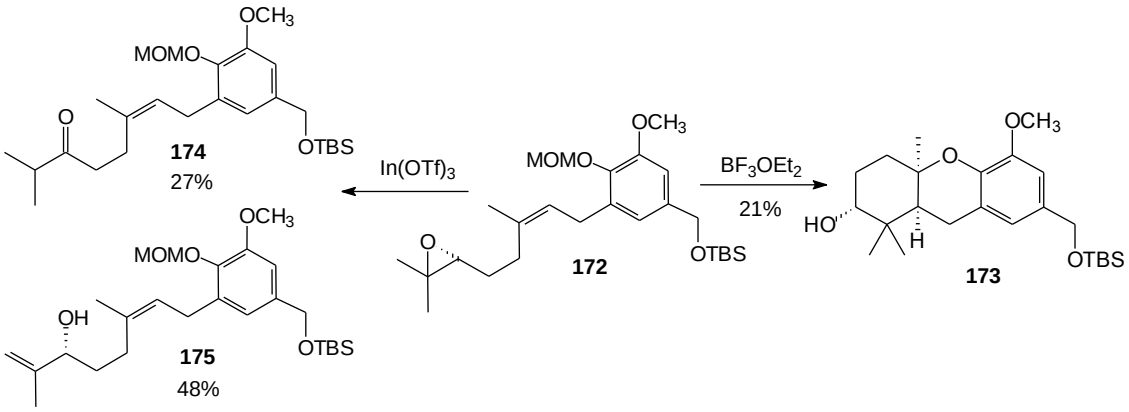
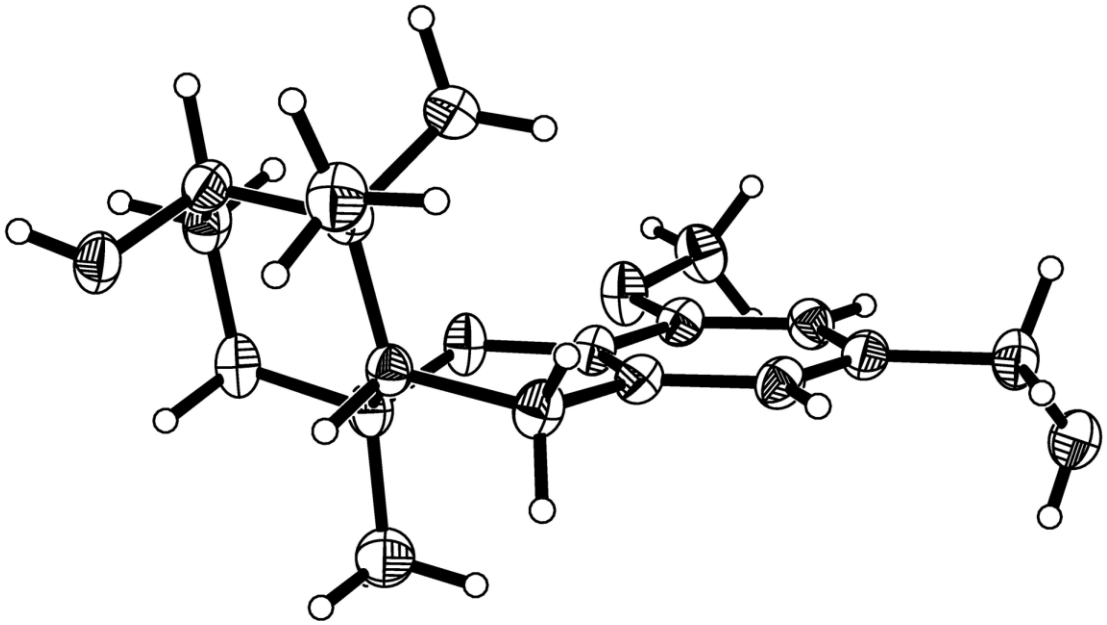


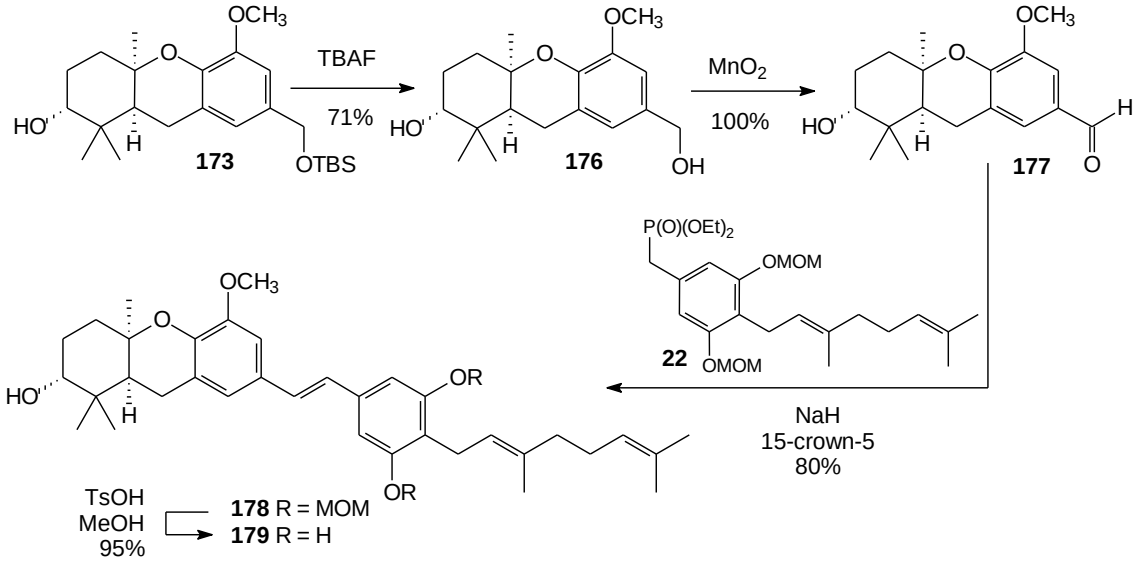
Figure 14. ORTEP Representation of the Single Crystal Analysis of Alcohol **176**.



Fortuitously, this alcohol proved to be crystalline and provided a crystal suitable for X-ray diffraction analysis. Dr. D. C. Swenson analyzed the provided crystal and an ORTEP

representation of this structure can be seen in Figure 14. This analysis provides support that the transition state leading to the *cis* fused product is substantially higher in energy then for the *trans* case based on the large degree of conformation distortion requiered. Additionally, the large upfield shift observed for the resonance of the C-1 methyl group can be explained by its position in the shielding zone of the arene core. The X-ray structure of compound **176** also established the relative configuration of the A-ring alcohol to be that depicted, a point which had been debatable based strictly on simple ^{1}H NMR data. In combination with the known absolute stereochemistry of the epoxide precursor, compound **176** can be assigned as (2*R*, 4a*R*, 9a*S*)-compound **176**. Astonishingly, this relative configuration is opposite of that observed in the cymobarbatol series with respect to the A-ring substituent (also assigned by X-ray diffraction analysis).[116] Elaboration of alcohol **176** preceded through chemoselective MnO_2 oxidation to provide aldehyde **177** in quantitative yield. Condensation of aldehyde **177** with phosphonate **22**[30] provided stilbene **178**. Final deprotection of stilbene **178** provided the target schweinfurthin analogue **179** in excellent yield.[69]

Scheme 30. Synthesis of Epi-3dSB.



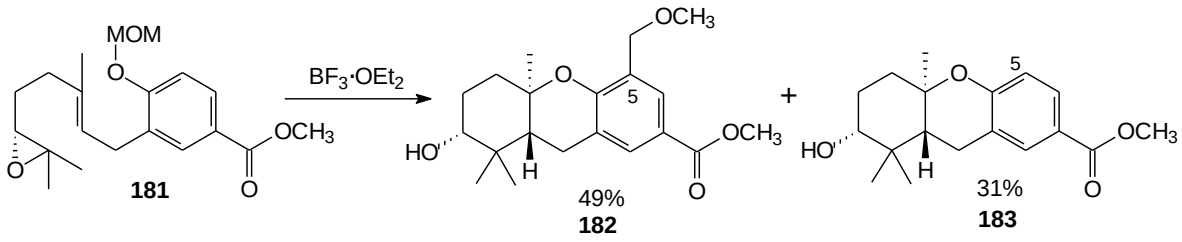
The new schweinfurthin analogue **179** was submitted to the NCI to be assayed in the 60-cell line screen. The biological activity of the *cis* fused schweinfurthin (mean GI_{50} ~2.9 μM) was inferior to the *trans* fused counterpart (3dSB, mean GI_{50} ~870 nM), and this compound showed decreased differential activity. These observations, which are not surprising given the difference in three dimensional structures of the two stereoisomers, supports the hypothesis that schweinfurthins bind to a specific cellular target. Although the lack of biological activity is disappointing, it is possible that this compound could be considered as a control agent in cellular experiments or that it may be isolated as a metabolite from a *Macaranga* species.

CHAPTER 5

EXPLORATION OF CASCADE CYCLIZATIONS TERMINATED VIA TANDEM ELECTROPHILIC AROMATIC SUBSTITUTION

During the course of studies directed at exploration of the schweinfurthins' pharmacophore, an expansion of cascade cyclization methodology was discovered serendipitously. The work of Dr. M. P. Callahan was designed to yield schweinfurthin analogues containing different functionality at the C-5 position (Scheme 31) and as such a cascade cyclization of the appropriate precursor was attempted.[131] Previous work indicated that prior deprotection of the MOM acetal was unnecessary for cyclization to procede.[32] Thus it was anticipated that cyclization of epoxide **181** would yield compound **183**, however compound **182** was obtained as the major product! Evidently, the MOM group expelled during cyclization functioned as a potent electophile and aromatic substitution took place.

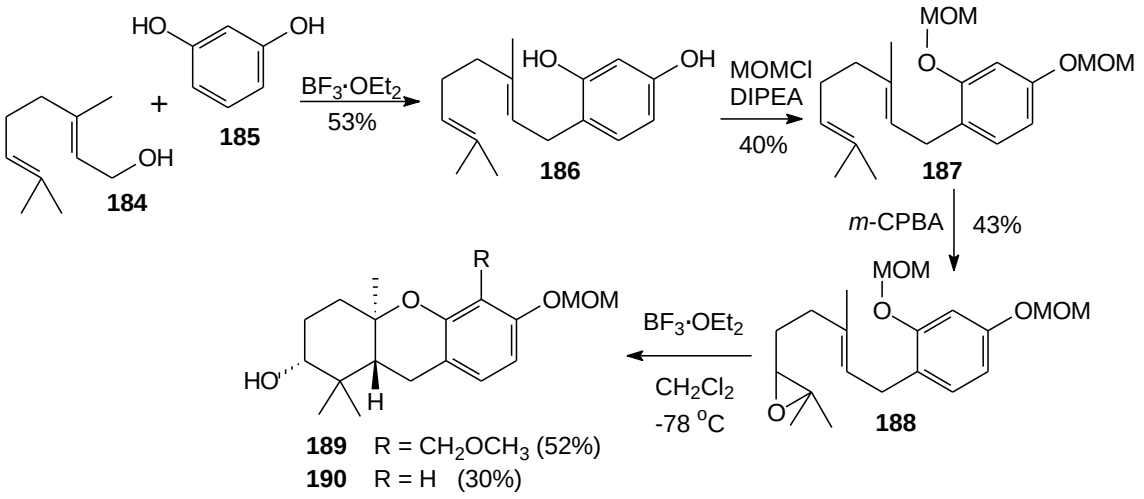
Scheme 31. Observation of CEAS.



To explore the potential utility of any transient MOM-based electrophile, a readily accessible cascade precursor was desired. A substituted resorcinol core was chosen for these studies because it can be synthesized rapidly on a large scale at minimal cost and

because both the *ortho* and *para* positions on the aromatic core are free to undergo aromatic substitution. Additionally, the second activating group should aid in the capture of any electrophilic species generated during cyclization.

Scheme 32. Model System for CEAS.



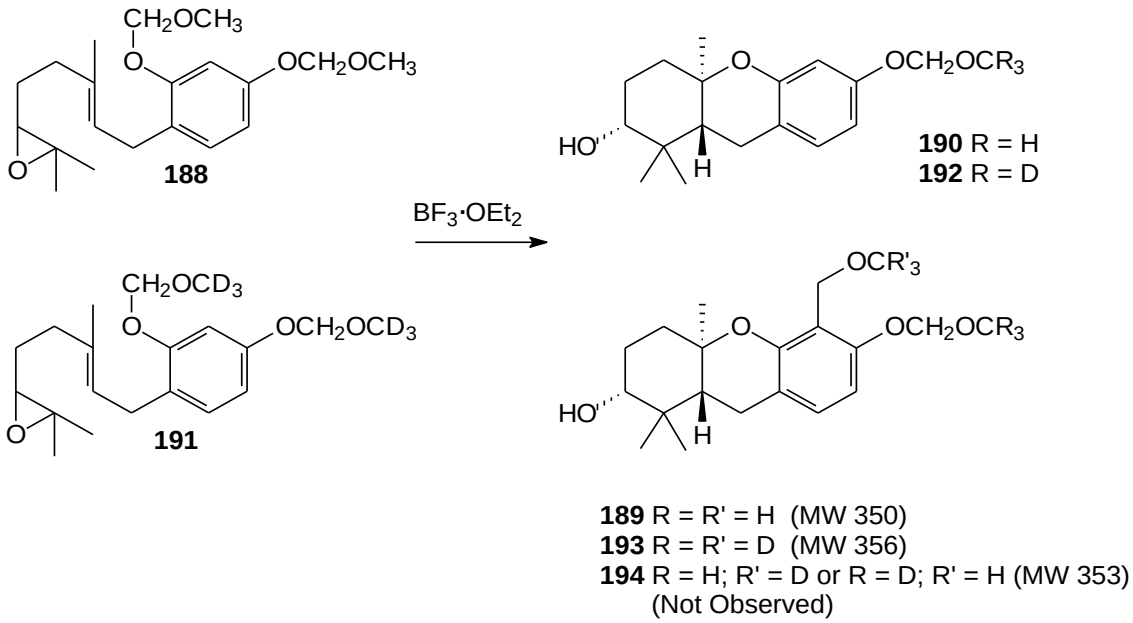
The synthesis of the key substrate began with the addition of a geranyl chain to resorcinol (Scheme 32). Highly activated systems can undergo aromatic substitution directly from an alcohol under Lewis acid mediated conditions.[132] Here, exposure of resorcinol (**185**) to $BF_3 \cdot OEt_2$ in dioxane followed by slow addition of geraniol (**184**) afforded the desired product **186** in modest yield. Slow addition of geraniol, via syringe pump, was essential for reproducible yields. The regiochemistry of this reaction was evident by the asymmetric product, and by evaluation of the coupling constants which revealed a clear 1,2,4-substitution pattern.

Standard protection of compound **186** as the MOM acetal afforded compound **187** in moderate yield. Compound **187** then could be epoxidized by reaction with *m*-CPBA to afford cascade precursor **188**, which was separated from the regioisomeric epoxide.

Gratifyingly, brief exposure of this compound to multiple equivalents of $BF_3 \cdot OEt_2$ in dilute CH_2Cl_2 under cryogenic conditions afforded compound **189** as the major product.[122] Compound **189** had clearly trapped a MOM-based electrophile and then had undergone aromatic substitution at C-2. The regiochemistry of this reaction was clearly evident from the ^{1}H NMR spectrum of the product since an *ortho* coupling (J = 8.4 Hz) clearly persisted. This regiochemistry is curious given that resorcinol is known to undergo aromatic substitution at the C-4 position,[133-135] not between the phenolic carbons (C-2), and keenly highlights the unique attributes this process might confer over traditional methodologies. This process is formally a cascade cyclization terminated via tandem electrophilic aromatic substitution (hereafter referred to as CEAS), and highlights an exceptional extension of cascade cyclization beyond ring closure. Compound **190** also was isolated from this reaction mixture as a minor product, one which had undergone cyclization, but had failed to trap the MOM-derived electrophile.

Given the unique regiochemistry observed for this cascade cyclization and the novelty displayed, the mechanism of this reaction was investigated (Scheme 33). A crossover experiment was performed to determine if a free MOM^+ ion was responsible for the formation of compound **189**. Tri-deutero MOMCl was previously known[136, 137] and was chosen as the basis of the crossover experiment. It was synthesized by Dr. M. P. Callahan and K. D. Boss from NMR grade CD_3OD. Exposure of compound **186** to standard conditions with CD_3OCH_2Cl afforded d_6-compound **187**. Near complete incorporation of deuterium was evidenced by the absence of methoxy signals in the ^{1}H NMR spectrum and by the appropriate high resolution mass spectrum. This material then was mixed with varying ratios of d_0-compound **187** and epoxidized with *m*-CPBA. The ratio of d_0 to d_6 material was determined from both integration of the ^{1}H NMR spectrum and from GC-MS experiments. For the two trials analyzed, this ratio was 1:1 and 2:1 d_0:d_6.

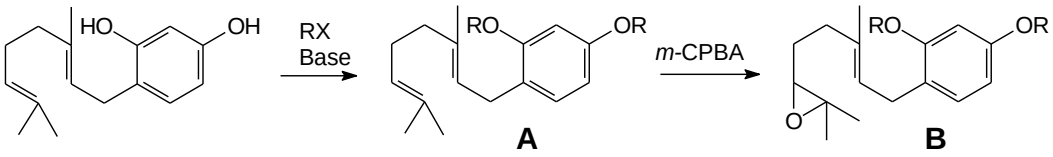
Scheme 33. Crossover Experiment of CEAS with d_0 and d_6 MOM Acetals.



Exposure of a mixture of epoxides **188** and **191**, which varied only in the level of deuterium incorporation, to cyclization conditions afforded a mixture of products which was purified by column chromatography. The products which had not undergone aromatic substitution (compound **190** and **192**) were isolated as a mixture and used as a control to indicate that the ratio of deuterium labeled compounds matched that of the starting material. The ratio of compounds **190**:**192** was determined by GC-MS analysis with the aid of the UI Mass Spectrometry Lab. Because the ratio of compounds **190**:**192** was found to be within experimental error of the starting material, either ~1:1 or ~2:1, it was assumed that analytical difficulties arising from partial resolution of the isotopically labeled compound or because of preferential ionization of one of the compounds were negligible. The mixture of compounds which had undergone tandem aromatic substitution was then analyzed via the same method. The GC-MS analysis of the mixture which had undergone aromatic substitution showed strong peaks for d_0 (**189**, *m/z* = 350) and d_6 (**193**, *m/z* = 356) compounds, however no d_3 (**194**, *m/z* = 353) peak was observed

above background, indicating that no crossover had taken place. This crossover experiment was conclusive showing that the reaction proceeds via intramolecular transfer of the MOM group.

Table 3. Synthesis of CEAS Precursors.



Entry	Halide	Base	% yield A	% yield B
1	MOMCl	DIPEA	40 (**195**)	31 (**208**)
2	MEMCl	K_2CO_3	47 (**196**)	7 (**209**)
3	pClPhOCH$_2$Cl	DIPEA	81 (**197**)	22 (**210**)
4	SEMCl	DIPEA	90 (**198**)	38 (**211**)
5	TESCl	Imid	95 (**199**)	28 (**212**)
6	DHP	PPTS	97 (**200**)	56 (**213**)
7	MeI	K_2CO_3	76 (**201**)	34 (**214**)
8	AllylBr	K_2CO_3	73 (**202**)	40 (**215**)
9	BnBr	K_2CO_3	99 (**203**)	22 (**216**)
10	*o*BrBnBr	K_2CO_3	87 (**204**)	28 (**217**)
11	AcCl	K_2CO_3	99 (**205**)	71 (**218**)
12	Bz_2O	K_2CO_3	37 (**206**)	58 (**219**)
13	$^tBOC_2O$	NaH	99 (**207**)	56 (**220**)

Given the novelty of CEAS and its potential synthetic applications, the scope of this reaction was explored. Geranyl resorcinol was used as a platform for divergence since it could be routinely synthesized in multi-gram batches and because it already had demonstrated its ability to undergo CEAS. Numerous CEAS substrates were synthesized

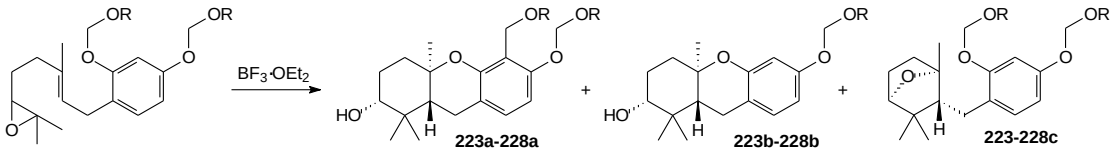
in a manner parallel to compound **188** (Table 3). Alkylation of the phenols in compound **186** was readily accomplished by exposure to the appropriate halide and base, which was followed by epoxidation with *m*-CPBA to provide epoxides **208**-**220** (Table 3).

Once access to a variety of CEAS precursors was established, the scope of this reaction was evaluated (Table 4) with the aid of Dr. J. G. Kodet (contribution denoted with * and included here for continuity). Because that the MOM group could form a stabilized MOM^+ ion due to the adjacent heteroatom,[74] other oxymethyl groups were screened. Several other acetal groups were found to provide the desired CEAS product as the major product (Table 4, entrees 1-4). These results indicate that this process is general for providing differentially protected benzylic positions and confirms the speculation that other groups with adjacent heteroatoms will undergo this process. Although not yet tested, it is hypothesized that both *p*-methoxybenzyloxymethyl and allyloxymethyl[131] groups would also be suitable for CEAS, which would expand the number of benzylic ethers made available by this process.

It was later discovered that some oxymethyl substituents did not undergo CEAS (Table 4). The pivoyl substituted acetal (entry 5) was not suitable for CEAS and instead formed the A-ring bridged ether **227c**. Mechanistically, this product can be explained by epoxide opening and subsequent quenching of the tertiary carbocation by the A-ring oxygen. Indeed, this substructure has been identified as a product from similar cyclizations.[123, 138-142] Conceivably, the electron withdrawing nature of the acyl group would diminish the stability of the POM-based cation and this could be responsible for the failure of the POM group to undergo CEAS. Of significance, the cyclization involving the 4-chlorophenoxymethyl group, which arose from the commercially available chloroacetal, provided compound **228b** as the major product and no product of the A type was isolated. This behavior is unique among the groups surveyed in Table 4 since all other substituents preferred to form either product A or C as the major product. The utility of this observation is that this group could be used deliberately to leave the

ortho position of the product unsubstituted as was desired in the preparation of numerous schweinfurthin analogues.[131]

Table 4. Cyclizations of Alkoxymethyl-substituted Phenols.



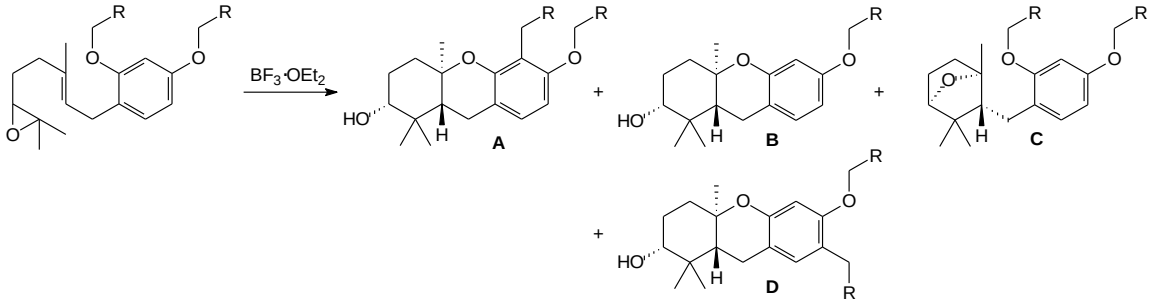
entry	substrate (R =)	common abbreviation	**a** % yield	**b** % yield	**c** % yield
1	CH_3 (**208**)	MOM	52 (**223a**)	30 (**223b**)	
2*	Bn (**221**)	BOM	62 (**224a**)		
3	CH_2CH_2TMS (**211**)	SEM	57 (**225a**)		
4	$CH_2CH_2OCH_3$ (**209**)	MEM	53 (**226a**)	28 (**226b**)	
5*	$C(O)C(CH_3)_3$ (**222**)	POM			47 (**227c**)
6	C_6H_4Cl (**210**)			56 (**228b**)	37 (**228c**)

Emboldened by the successful CEAS reactions from the oxymethyl groups, substituents lacking a stabilizing oxygen were investigated (Table 5). The first group examined was a methoxy substituent. Methyl ether **214** did not undergo CEAS presumably because a methyl cationic species is too high in energy, and ether **233c** was isolated as the major product. An allyl substituted phenol was found to undergo CEAS although ether **234c** was the predominant product (entry 2). Although an allyl CEAS product is significantly useful in its own right, it also marks the minimum stabilization that a group must have in order to undergo CEAS as evidenced by the mixture of products. To confirm speculations regarding carbocation stability, substituted benzyl groups were investigated to generate a qualitative Hammet plot.[143] As expected, the

strongly withdrawing nitro group prevented CEAS in compound **229** and ether **235c** was generated preferentially. An electronically neutral benzyl group favored the CEAS product in excellent yield along with trace quantities of material which had undergone aromatic substitution at C-4 (**236d**, entry 4). This is the first observation of less than flawless regioselectivity in the course of the cascade and is potentially of mechanistic importance (*vide infra*). An *o*-bromobenzyl group was investigated and found to provide bridged ether **237c** as the predominant product. Although bromine is formally a withdrawing group, the stark change in product distribution between benzyl and *o*-bromobenzyl is more likely due to the steric influence of the bromine atom (*vide infra*). The common *p*-methoxybenzyl group (PMB) faithfully afforded the CEAS product as might be expected based on the stabilizing nature of the methoxy group. Unfortunately, the more stabilized electrophile was less regioselective and a ~3:2 ratio of regioisomers was isolated in favor of the C-2 substituted product **238a** (entry 6). The highly stabilized 3,4,5-trimethoxybenzyl group was inspected and found to provide a CEAS product which had undergone substitution only at the C-4 (**239d**) position along with large amounts of the unsubstituted product **239b**. A trace amount of material which had formed an A-ring ether, analogous to that observed in the schweinfurthin B series (Chapter 2), also was isolated for the PMB and 3,4,5-trimethoxy benzyl groups, indicating at least partial formation of a solvated cation in these two cases. Lastly, a heteroaromatic ring was used in this process. The furan containing epoxide **232** was subjected to CEAS conditions and formed product **240a**, which demonstrates that other ring systems can be used in CEAS.

Given the Wiemer group's long standing interest in prenylated aromatics[30, 31, 132, 144] and the ability of the ally group to undergo CEAS (Table 5), other allylic or propargylic groups were investigated as CEAS participants (Table 6). In an attempt to generate a more stable allylic cation, a crotyl group was investigated. Surprisingly, when crotyl containing compound **241** was subjected to CEAS conditions (entry 1) the predominant product had undergone aromatic substitution with concurrent allylic

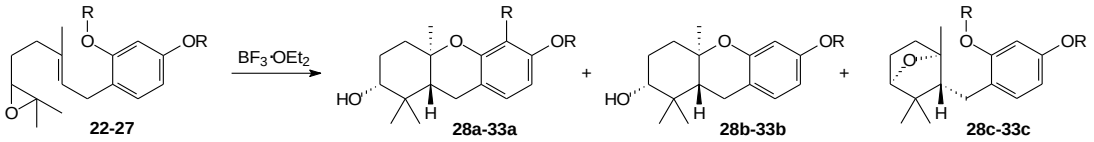
Table 5. Additional Examples of Cascade Cyclization/Aromatic Substitution.



Entry	Substrate (R =)	**a**	**b**	**c**	**d**
		% yield	% yield	% yield	% yield
1	H (**214**)			72 (**233c**)	
2	$CH{=}CH_2$ (**215**)	32 (**234a**)		8 (**234c**)	
3*	$C_6H_4NO_2$ (**229**)			20 (**235c**)	
4	C_6H_5 (**216**)	43 (**236a**)	18 (**236b**)		2 (**236d**)
5	2-bromophenyl (**217**)			49 (**237c**)	
6*	$C_6H_4OCH_3$ (**230**)	33 (**238a**)	12 (**238b**)		19 (**238d**)
7*	3,4,5-trimethoxyphenyl (**231**)		41 (**239b**)		28 (**239d**)
8	3-furyl (**232**)	49 (**240a**)			

transposition. Amazingly, the newly formed benzylic stereocenter was formed with a diastereomeric ratio identical to that of the E/Z ratio of the crotyl group. To determine if this indicated sterospecificity, the pure *E* crotyl isomer was synthesized by Dr. J. G. Kodet and again subjected to the reaction conditions. The product ratio resulting from CEAS of the pure *E* isomer matched that from the previous cyclization indicting that the stereochemistry of the olefin does not translate to the relative configuration of the new center.

Table 6. Cyclizations of Alkoxymethyl-substituted Phenols.



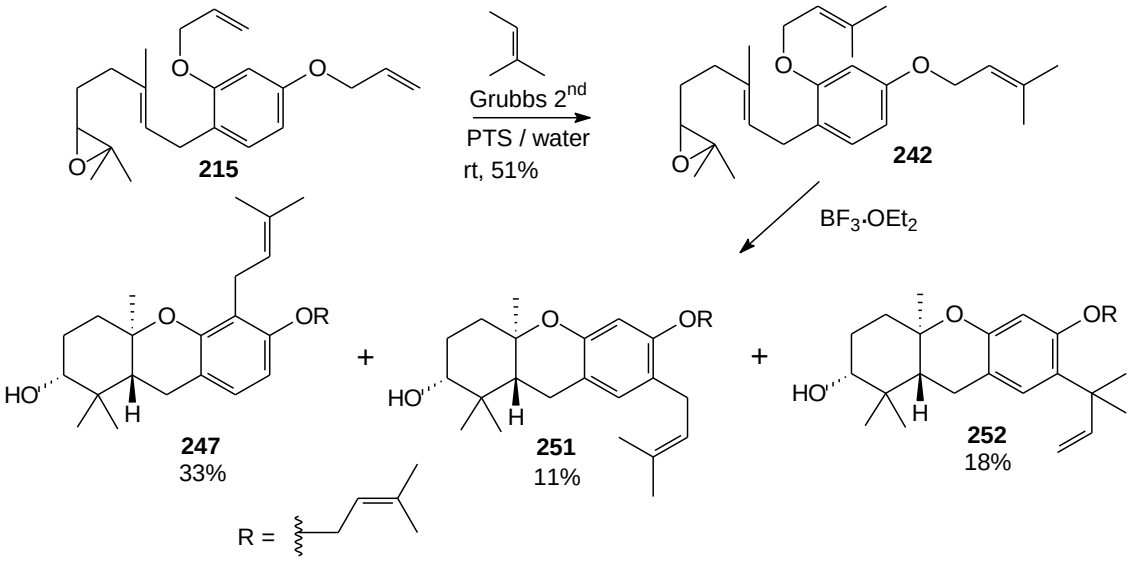
entry	substrate (R =)	**a**	**b**	**c**
		% yield	% yield	% yield
1	Allyl (**215**)	8 (**234a**)		32 (**234c**)
2*	Crotyl (**241**)	61† (**246a**)		
3	Prenyl (**242**)	31† (**247a**)		
4*	Inverted Prenyl (**243**)			12 (**248c**)
5*	Propargyl (**244**)			47 (**249c**)
6*	$C(CH_3)_2CCH$ (**245**)		14 (**250b**)	47 (**250c**)

† see narrative

A phenolic prenyl chain was synthesized (Scheme 34) through cross metathesis with allyl ether **215**. When this compound was subjected to CEAS conditions, a mixture of regioisomers resulted in high overall yield. Additionally, the product which was substituted at the C-2 position was found only as the normal prenyl compound **247**. The products which underwent substitution at C-4 (**251** and **252**) existed as an inseparable mixture of prenyl and inverted prenyl (or 1,1-dimethylallyl) isomers. The selectivity for placement of a normal prenyl group at the C-2 position and the formation of a mixture at the C-4 position adds an additional level of mechanistic curiosity to this process. To inspect if an inverted prenyl chain affords the same product distribution, because it would form the same putative allyl cationic intermediate, compound **243** was synthesized and subjected to CEAS. Remarkably, epoxide **243** provided only ether **248c** from the reaction mixture. The inability of the inverted prenyl group to undergo CEAS may have more to do with increased steric bulk about the ring closing conformation than on the

process itself, and the inability of the *o*-bromobenzyl group to undergo CEAS would support this notion. A propargyl analogue **244** was subjected to CEAS conditions and it was found to provide bridged ether **249c**. The dimethyl propargyl group present in the intermediate used in the synthesis epoxide **242** also was found to provide predominantly the bridged ether (epoxide **245**, entry 6).

Scheme 34. Synthesis and Cyclization of Prenyl Group.



Finally, it was desired to attempt generation of an acetophenone via CEAS for the synthesis of angelichalcone (*vide infra*).[122] Unfortunately, subjection of requisite acetate **218** to CEAS conditions yielded exclusively the crystalline bridged ether **254b** (Table 7). Given our difficulty in determining the relative configuration of this product by NMR spectroscopy, compound **254b** was subjected to single crystal X-ray diffraction. An ORTEP representation of the crystal structure, provided by Dr. D. Swenson, is shown as Figure 15 and allows assignment of the configuration in compound **254c**. Attempts at utilizing other acyl groups were equally unsuccessful. Thus both benzoyl and *t*-

butylcarbonate epoxides also afforded the bridged ethers C as the major product. In an attempt to circumvent the limitations of acyl substituents, secondary acetals were examined. Given the success in DDQ based oxidations of activated benzylic positions,[72] an ethoxyethyl acetal was inspected, hypothesizing that the product might lead to an acetophenone after oxidative loss of ethanol. Exposure of acetal **253** to cyclization conditions resulted in a complex mixture without any isolatable quantity of the desired ring system. In an effort to simplify the product distribution, the crude mixture was exposed to methanolic acid to hydrolyze the remaining acetal group. From this reaction, a trace quantity of compound **257b** could be isolated as the only hexahydroxanthene. Given this setback, THP acetals were inspected and again were found to behave poorly under these conditions. Complexation of a Lewis acid to the secondary acetal and formation of a more stable oxocarbonium ion may prohibit the desired reaction pathway. Indeed, oxocarbonium ions arising from secondary acetals have been utilized to initiate cascade cyclization.[38,40]

Figure 15. ORTEP of Compound **254b**.

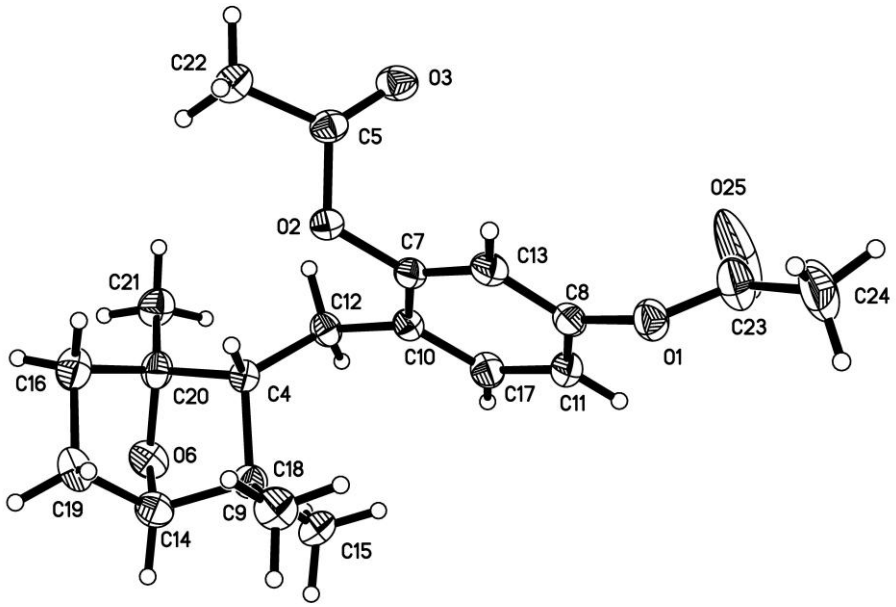
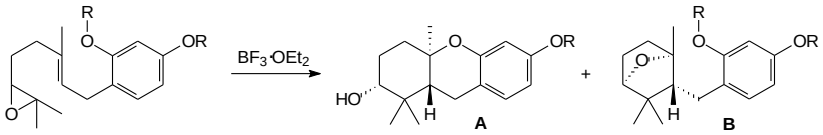


Table 7. Efficacy of CEAS.

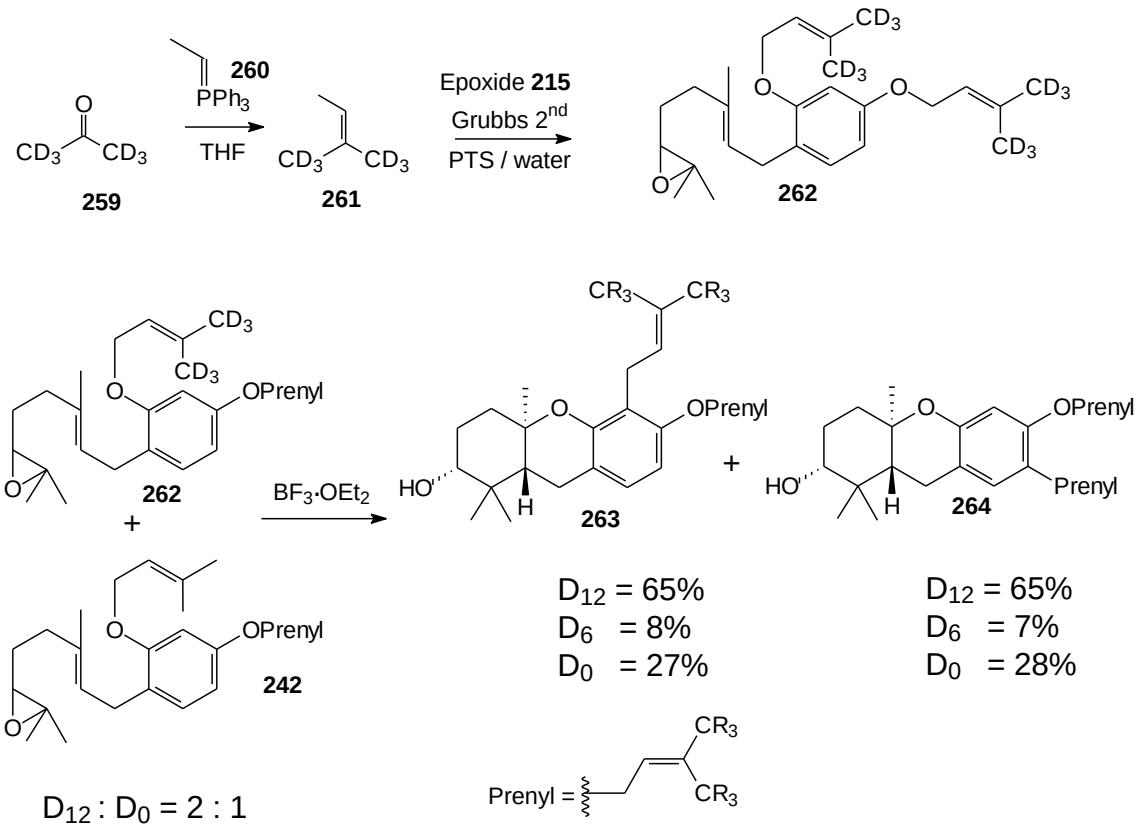


entry	substrate (R =)	**a** % yield	**b** % yield
1	Ac (**218**)		46 (**254b**)
2	Bz (**219**)		49 (**255b**)
3	tBoC (**220**)		57 (**256b**)
4	EOE (**253**)	14 (**257a**, R = H)	
5	THP (**213**)	8 (**258a**, R = H)	

Given the perfect regioselectivity presented by the class of oxymethyl groups in CEAS and the poor selectivity of the prenyl and PMB groups, it was hypothesized that a change in mechanism might be responsible for the apperent inconsistency. If substitution at C-2 is the result of an intramolecular pathway, as demonstrated by the MOM crossover experiment, then it is possible that the substitution observed at C-4 might be the result of an intermolecular pathway. Given the highly stabilized nature of the prenyl or PMB carbocations, it is possible that they might have appreciable half-lives in solution and the intermolecular pathway may be viable. Resorcinol's propensity to undergo substitution at the C-4 position seems to encourage this notion and the mixture of C-4 allylic isomers from the prenyl cyclization was also supportive.

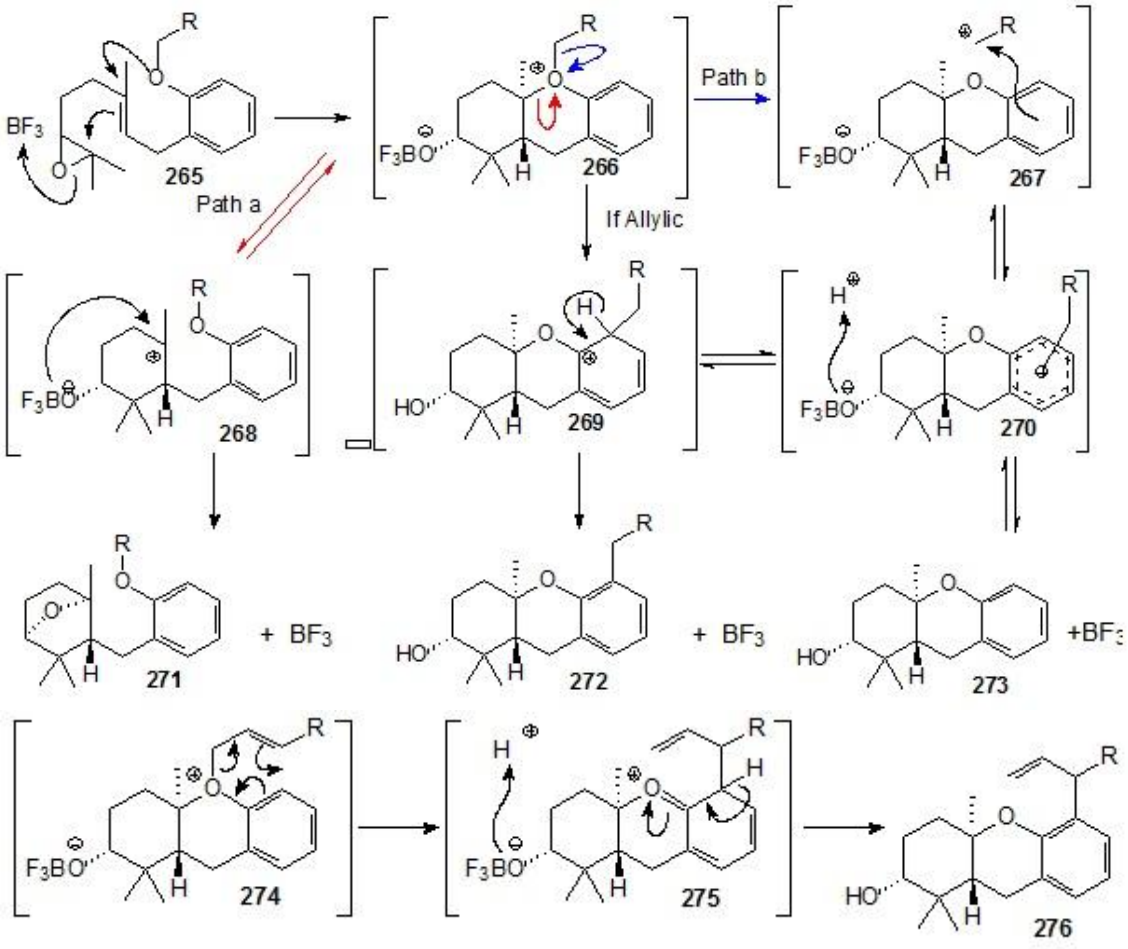
To explore possible changes in mechanism, another crossover experiment was undertaken. If this hypothesis is valid, then the CEAS product with C-2 substitution would show no crossover and the C-4 CEAS product would show crossover. The prenyl group was chosen for the second crossover because the cross metathesis provided a means for late stage deuterium incorporation. The deuterium labeled substrate was synthesized from allyl epoxide **215** (Scheme 35). Hexadeutero-3-methyl-2-butene (**261**)

Scheme 35. Prenyl Crossover Experiment.



is known[145] and this reagent was synthesized by condensation of ethylidine phosphorane (**260**) with NMR grade acetone (**259**).[146] The crude reaction mixture then was fitted with a distillation apparatus, gently heated, and the desired reagent was co-distilled as a solution in THF (~1:2, **261**:THF). Direct use of the mixture of **261** in THF in the subsequent cross-metathesis proceeded as previously reported[147] without incident to provide d_{12} epoxide **262**. Mixing d_0 and d_{12} epoxides **242** and **262** in a 2:1 ratio allowed the crossover experiment. Exposure of this mixture to $BF_3{\cdot}OEt_2$ under our standard conditions afforded compounds **263** and **264** after chromographic purification. These compounds were subjected to GC-MS analysis similar to that for the MOM crossover experiment described above. Analysis showed that only trace crossover product was

Scheme 36. Mechanistic Proposal of CEAS.



observed for either the C-2 or the C-4 product. These results indicate that alkylation at both positions is the result of a predominantly intramolecular process and strongly implicates closely associated ion pairs instead of free carbocations in the mechanism.

Based on the observations listed above, a mechanistic picture of CEAS can be formed (Scheme 36). Initial complexation of BF_3 to the epoxide oxygen could result in cascade cyclization to form oxonium ion **266** in the B-ring of the hexahydroxanthene system. If the alkyl group, which was originally on the phenol, cannot form a stabilized carbocation (e.g. methyl) then this oxonium ion could reversibly open to form tertiary

carbocation **268** (Path a). Attack of the A-ring oxygen onto this carbocation would then explain the formation of ether **271**. Alternatively, the phenolic alkyl group might be too bulky to promote a ring closing conformation, which would also result in this product (e.g. *o*-bromobenzyl group). If the initial oxonium ion decomposed with loss of a stabilized carbocation, then the adjacent arene could immediately serve as a Lewis base and complex to the carbocation to form intermediate **270** (Path b). Simple dissociation of this complex would result in the formation of unsubstituted products **273**. If the Lewis base complex resulted in ipso or sigma complex **269** then electophilic aromatic substitution can occur to afford CEAS product **272**. More stabilized cations, such as that derived from a prenyl group, should form weaker Lewis acid/base complexes and this would allow for rearrangement to form various regiosiomers from a tightly associated and poorly solvated ion pair.

One alternative mechanistic possibility exists for allylic substrates that undergo CEAS (Scheme 36). In the case of allylic substrates, a concerted pericyclic process via a Claisen rearrangement is possible. If oxonium ion **274** rearranges to the quinone like structure **275**, then loss of a proton would complete the sequence to yield CEAS product **276**. Although Claisen rearrangements usually require high temperatures, the highly electron deficient nature of the oxonium ion should decrease the HOMO/ LUMO gap and accelerate this process, similar to that observed under standard Lewis acid catalysis. This concept is merely speculative, but it would explain the unique regioselectivity observed for the crotyl case. The formation of a normal prenyl group that did not undergo allylic rearrangement via this mechanism might indicate a subtle balance between possible transition states that favored the ionic EAS pathway due to steric hindrance.

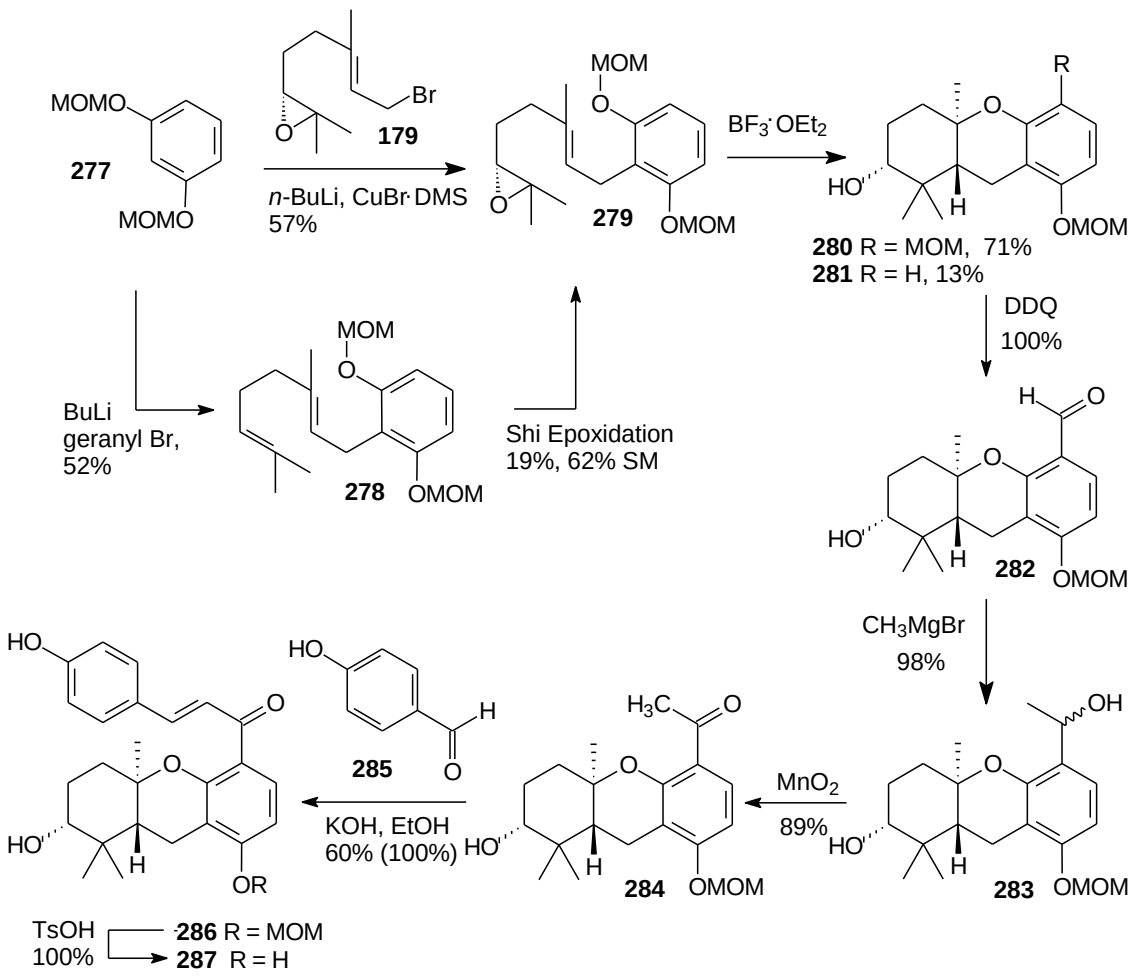
With the scope of CEAS better defined and a working mechanistic proposal defined, this strategy was applied to the first total synthesis of (+)-angelichalcone (**287**, Scheme 37).[122, 148] Angelichalcone was reported as an isolate from *Angelica keiskei*. This plant species was of interest due to its use in traditional Japanese medicine and as result

of these studies, numerous geranylated chalcones have been identefied.[149, 150] Exploration of the biological properties of angelichalcone indicated that it might be a lead agent for treatment of osteoporosis.[148] The two dimensional structure of angelichalcone was assigned based on ^{1}H NMR, ^{13}C NMR and HRMS data. The original authors made no significant effort to identify either the relative stereochemistry or the absolute stereochemistry of angelichalcone,[148] however previous experience from the Wiemer group suggested that the relative stereochemistry was very likely to be identical to that of schweinfurthin F. Most indicatively, the geminal hydrogen adjacent to the A-ring hydroxyl group displayed a doublet of doublets with coupling constants in good agreement with previous work (J = ~11, ~4 Hz) and the benzylic hydrogens displayed a very narrowly split system with no coupling constants larger than 14 Hz.[69] Unfortunately, the specific rotation for angelichalcone was not provided in the original description so it would not be possible to identify the absolute stereochemistry. Nonetheless it appeared likely that a highly efficient synthesis of non-racemic material could be achieved through CEAS, and with the aid of Dr. M. P. Callahan, this has been accomplished.

The synthesis of angelichalcone began with MOM-protected resorcinol **277**. Exposure of this intermediate to *n*-BuLi resulted in *ortho*-metalation. Geranylation could be accomplished by transmetalation and subsequent quenching of the presumed cuprate with geranyl bromide to yield compound **278**. Subsequent Shi epoxidation[78, 79] afforded epoxide **279** in moderate yield and high enantiomeric excess. Alternatively, direct coupling with epoxy-bromide **179** was made viable from the previously established procedure and was optimized on this substrate by Dr. J. D. Neighbors.[66, 130] Treatment of epoxide **279** with $BF_3 \cdot OEt_2$ resulted in facile CEAS cyclization to afford the desired product **280** in an astonishing 71% yield along with trace amounts of the unsubstituted product **281**. The high yield for this reaction can be attributed to the symmetric nature of the epoxide which results in degenerate cyclization conformations. Additionally, the

ortho position of this substructure is activated by both phenols, which should make aromatic substitution facile.

Scheme 37. Total Synthesis of (+)-Angelichalcone (**287**).



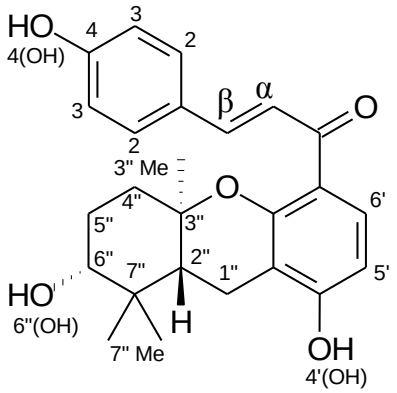
Elaboration of CEAS product **280** was accomplished by exposure to DDQ,[72] which resulted in quantitative oxidation to benzaldehyde **282**. A two-step homologation was accomplished by exposure of aldehyde **282** to excess CH_3MgCl to afford a ~1:1 mixture of diasteromers **283**. These diastereomers were not easily separable, but converged to acetophenone **284** by treatment with MnO_2. Claisen-Schmidt condensation

was accomplished by exposure of this intermediate to ethanolic base and *p*-hydroxybenzaldehyde (**285**). This condensation was sluggish, but could be accomplished without protection of the phenol to afford chalcone **286** in moderate yield. It should be stated that the mass balance of unreacted starting material could be recovered. The final step of the synthesis was accomplished by heating chalcone **286** under hydrolytic conditions which afforded (+)-angelichalcone (**287**) in quantitative yield. This efficient synthesis affords the target in just seven atom-economical[43, 44] transformations and ~35% overall yield!

The ^{1}H NMR, ^{13}C NMR, and HRMS data of synthetic angelichalcone were found to be in excellent agreement with that originally reported (Table 8). This indicates that the correct relative stereochemistry of angelichalcone is as depicted in Scheme 37. Regretfully, no comment can be made if the (+) antipode of angelichalcone is the naturally occurring enantiomer. However the absolute stereochemistry of the synthetically prepared material can be assigned as (+)-(*2R, 4aR, 9aR*)-angelichalcone based on the known stereochemistry of epoxide **179**.[66]

In summary, epoxide initiated polyene cascade cyclizations terminated with tandem electrophilic aromatic substitution (CEAS) offers a unique and highly efficient means of carbon-carbon bond construction. The large degree of molecular complexity that this single transformation generates should make it an attractive protocol. The scope of this process has been explored and CEAS seems to be general for any semi-stabilized carbocation. Most significantly, this process has proven efficient in installing a differentially protected benzylic alcohol from an oxymethyl ether. The mechanism of this process has been explored via crossover experiments and a functioning mechanistic proposal has been developed. Furthermore, CEAS has been applied to a succinct total synthesis of (+)-angelichalcone.

Table 8. NMR Data for Angelichalcone.



^{1}H NMR of Target Compound				^{13}C NMR of Target Compound			
Signal	Natural	Synthetic	Δδ	Signal	Natural	Synthetic	Δδ
4'(OH)	10.22 (1H, br-s)	10.20 (br-s, 1H)	0.02	C=O	189.8	189.4	0.4
4(OH)	9.97 (1H, br-s)	9.96 (br-s, 1H)	0.01	4'	160.6	160.2	0.4
2	7.51 (2H, d, J = 8.4Hz)	7.50 (d, J = 8.4 Hz, 2H)	0.01	4	160.3	159.9	0.4
Alpha	7.48 (1H, d, J = 15.6 Hz)	7.47 (d, J = 16.2 Hz, 1H)	0.01	2'	154.9	154.5	0.4
Beta	7.42 (1H, d, J = 15.6 Hz)	7.44 (d, J = 15.6 Hz, 1H)	0.02	β	141.2	140.9	0.3
6'	7.39 (1H, d, J = 8.4 Hz)	7.39 (d, J = 8.4 Hz, 1H)	0	2	130.8	130.4	0.4
3	6.83 (2H, d, J = 8.4 Hz)	6.83 (d, J = 8.4 Hz, 2H)	0	6'	130.2	129.8	0.4
5'	6.47 (1H, d, J = 8.4 Hz)	6.47 (d, J = 8.4 Hz, 1H)	0	1	127.1	126.7	0.4
6" (OH)	4.65 (1H, d, J = 4.8, Hz)	4.64 (d, J = 5.4 Hz, 1H)	0.01	α	125.2	124.9	0.3
6"	3.27 (1H, m)	3.27 (ddd, J = 11.4 Hz, 4.8 Hz, 4.8 Hz, 1H)	0	1'	120.8	120.4	0.4
1"	2.67 (1H, dd, J = 4.8, 16.8 Hz)	2.67 (dd, J = 16.8 Hz, 4.8 Hz, 1H)	0	3	116.8	116.4	0.4
1"	2.34 (1H, dd, J = 13.2, 16.8 Hz)	2.34 (dd, J = 17.4 Hz, 13.8 Hz, 1H)	0	3'	110.4	110	0.4
4"	1.87 (1H, m)	1.87 (ddd, J = 12 Hz, 3.6 Hz, 3.6 Hz, 1H)	0	5'	107.7	107.3	0.4
4"	1.75 (1H, m)	1.77 – 1.74 (m, 1H)	-	3"	77.9	77.5	0.4
5"	1.71 (1H, m)	1.72 – 1.69 (m, 1H)	-	6"	76.8	76.4	0.4
2"	1.61 (1H, dd, J = 4.8, 13.2 Hz)	1.61 (dd, J = 13.6 Hz, 4.8 Hz, 1H)	0	2"	46.4	46.0	0.4
5"	1.54 (1H, m)	1.55 – 1.53 (m, 1H)	-	7"	38.9	38.6	0.3
3" Me	1.25 (3H, s)	1.23 (s, 3H)	0.02	4"	38.3	37.9	0.4
7" Me	1.03 (3H, s)	1.03 (s, 3H)	0	5"	28.9	28.5	0.4
7" Me	0.81 (3H, s)	0.81 (s, 3H)	0	7" Me	28.1	27.7	0.4
				3" Me	20.7	20.3	0.4
				1"	18.8	18.4	0.4
				7" Me	15.3	14.9	0.4

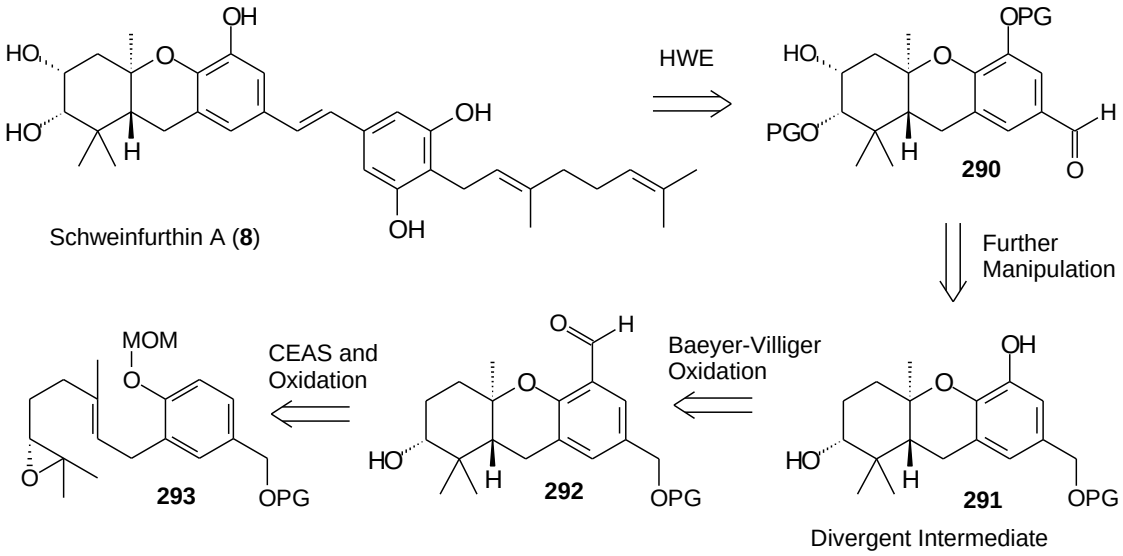
CHAPTER 6
FORMAL SYNTHESIS OF SCHWEINFURTHINS VIA CEAS & THE FIRST TOTAL SYNTHESIS OF SCHWEINFURTHIN A & VEDELIANIN

The Wiemer group's SAR program has made significant progress in describing the elements of the schweinfurthins structure that are important for biological activity.[32, 64, 68, 70, 72, 73] Key to the success of this program is the late stage divergence of intermediate aldehydes via HWE olefination with various phosphonates. In a similar vein, if a late stage intermediate could be used to provide numerous aldehydes, the permutations of schweinfurthins available for SAR work would be greatly enhanced. Unfortunately, no synthetic avenue is currently available that allows both schweinfurthin F and schweinfurthin G aldehydes (compounds **79** and **85** respectively) to be synthesized from the same late stage intermediate. At the onset of this work, two individual but parallel synthetic sequences were required for their synthesis (Chapter 2). Additionally, if reliable quantities of a key divergent intermediate were made available, then the synthesis of schweinfurthin A, the most potent of the natural schweinfurthins[25] could be pursued while simultaneously continuing SAR work.

The genesis of this venture was the notion of exploiting CEAS to circumvent the limitations of late stage C-ring divergence in schweinfurthin synthesis. To accomplish this task, a retrosynthesis was devised (Scheme 38) by simplification of schweinfurthin A to late stage aldehyde **290**. Aldehyde **290** could arise from an intermediate such as phenol **291** by a reaction sequence parallel to that used to synthesize schweinfurthin B.[72] Phenol **291** possesses all of the characteristics necessary to serve as the key divergent intermediate. Application of the Baeyer-Villiger oxidation synthon[76, 77, 151] reveals aldehyde **292** which is itself the synthon for CEAS cyclization.[122] These simplifications

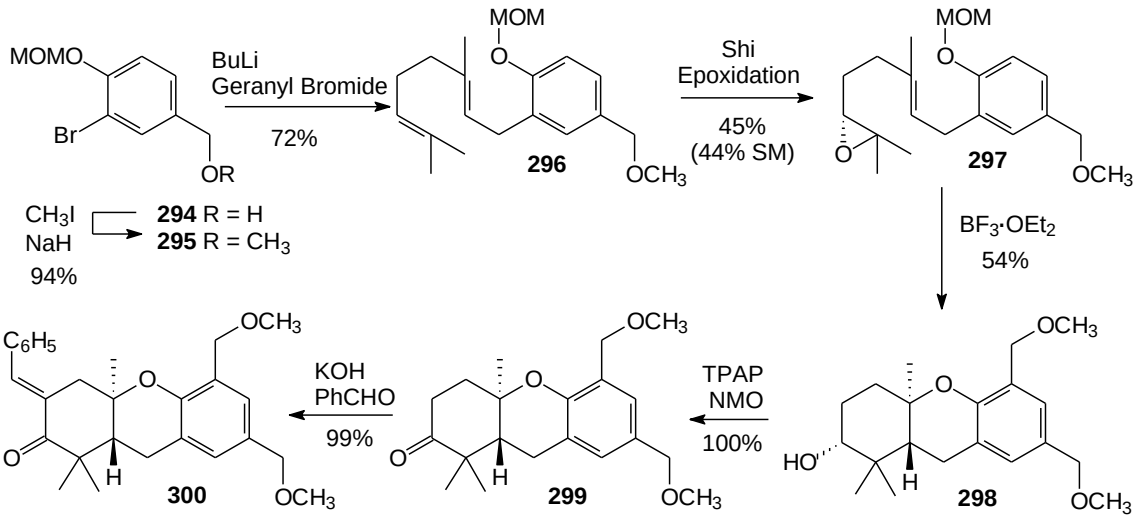
provide epoxide **293** as an appropriate sub-target at which synthetic efforts could be directed.

Scheme 38. Retrosynthesis of Schweinfurthin A via CEAS.



The present effort began by methylation of benzyl alcohol **294** by standard Williamson ether synthesis (Scheme 39). Geranylation of this intermediate was accomplished through halogen-metal exchange followed by exposure to geranyl bromide which afforded intermediate **296** in good yield. Epoxidation under Shi's conditions afforded compound **297** in moderate yield and high enantiomeric excess (86 – 93% ee).[66, 78, 79] This reaction was more sensitive to over-epoxidation than the parallel reaction in the schweinfurthin B series, presumably because of diminished bulk about the C-5 position. This propensity for over-oxidation necessitated that the epoxidation reaction be quenched prior to complete conversion and recovered starting material was successively recycled. Exposure of epoxide **297** to $BF_3 \cdot OEt_2$ resulted in CEAS reaction and compound **298** was isolated as the major product.

Scheme 39. Synthesis of Compound **300**.

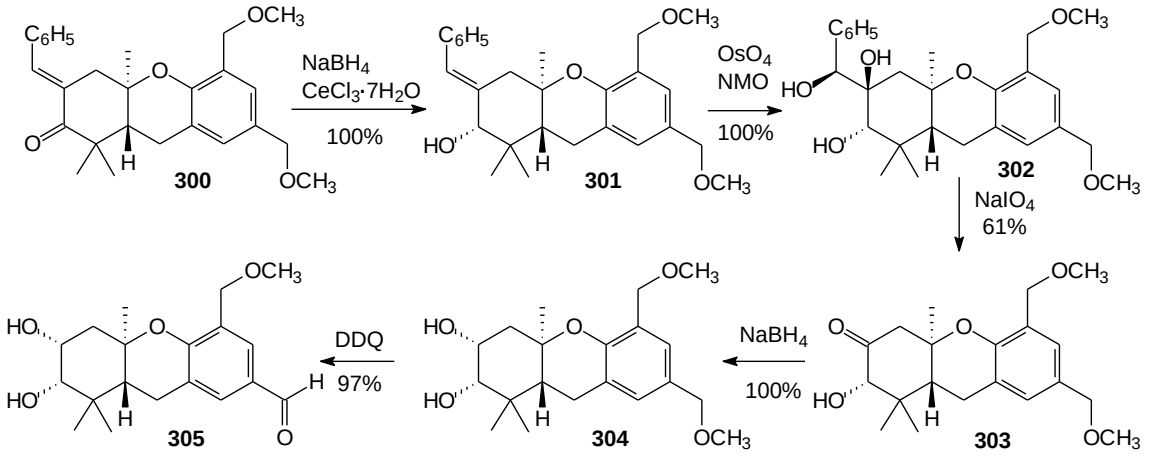


Given the direct route to compound **298**, it was decided to pursue the synthesis of schweinfurthin A by incorporation of the C-3 hydroxyl group. Further elaboration of this intermediate proceeded via TPAP mediated oxidation to yield ketone **299**. Benzylidine **300** was obtained by exposure of ketone **299** to base and benzaldehyde. Ketone **300** (Scheme 40) then was subjected to Luche reduction,[99] which faithfully afforded alcohol **301** in excellent yield as a single diastereomer. Application of the protecting group free sequence developed for olefinic cleavage (Chapter 2) was accomplished by Upjohn dihydroxylation[102] to yield triol **302** as a crystalline solid. Glycolytic cleavage was then accomplished in a separate flask by treatment with $NaIO_4$ to provide ketone **303**. Reduction of ketone **303** with $NaBH_4$ provided diol **304** which required immediate purification via column chromatography to minimize decomposition.

Unfortunately, exposure of diol **304** to DDQ provided aldehyde **305** as the sole and undesired regioisomer (Scheme 40). Attempts at differentiating the benzylic positions to obtain the desired regiochemistry via other means were also unsuccessful. Exposure of intermediate **304** to cerium ammonium nitrate as an alternate oxidant

provided aldehyde **305** in decreased yield. Hydrolysis of compound **304** was conducted in dioxane/water with excess TsOH. The crude product was exposed to MnO_2 so that the regiochemistry of the product could be determined and it was identified as the undesired regioisomer **305**. Excess cerium chloride was used in dichloroethane under reflux conditions to assist in hydrolysis, but no product was formed after several days. Addition of Lewis acids to the DDQ-mediated oxidation did little to sway the regioselectivity and carbocation formation, upon exposure to trityl tetraflouroborate, also was unsuccessful in yielding the desired product. These failures required that alternative approaches for the synthesis of a C-5 phenol be inspected.

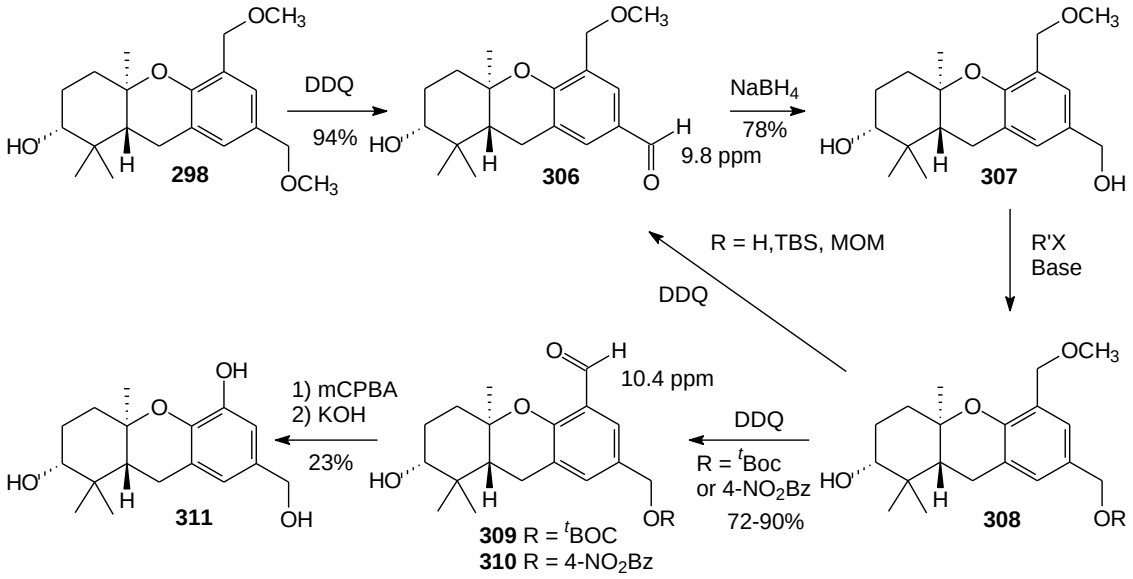
Scheme 40. Synthesis of Aldehyde **305**.



Based on the unfortunate regioselectivity presented by the DDQ oxidation of compound **304**, various substituents were screened with the intention of reversing this selectivity (Scheme 41). Because the C-7 benzylic protecting group was installed early in the synthesis, one could imagine that a different group might bias the selectivity of the reaction based either on steric or electronic factors. With this goal in mind, CEAS product **298** was exposed to DDQ which provided aldehyde **306** (Scheme 41). Reduction

of aldehyde **306** was accomplished upon exposure to $NaBH_4$, which afforded alcohol **307**. This alcohol was exposed to DDQ which regenerated benzaldehyde **306**.

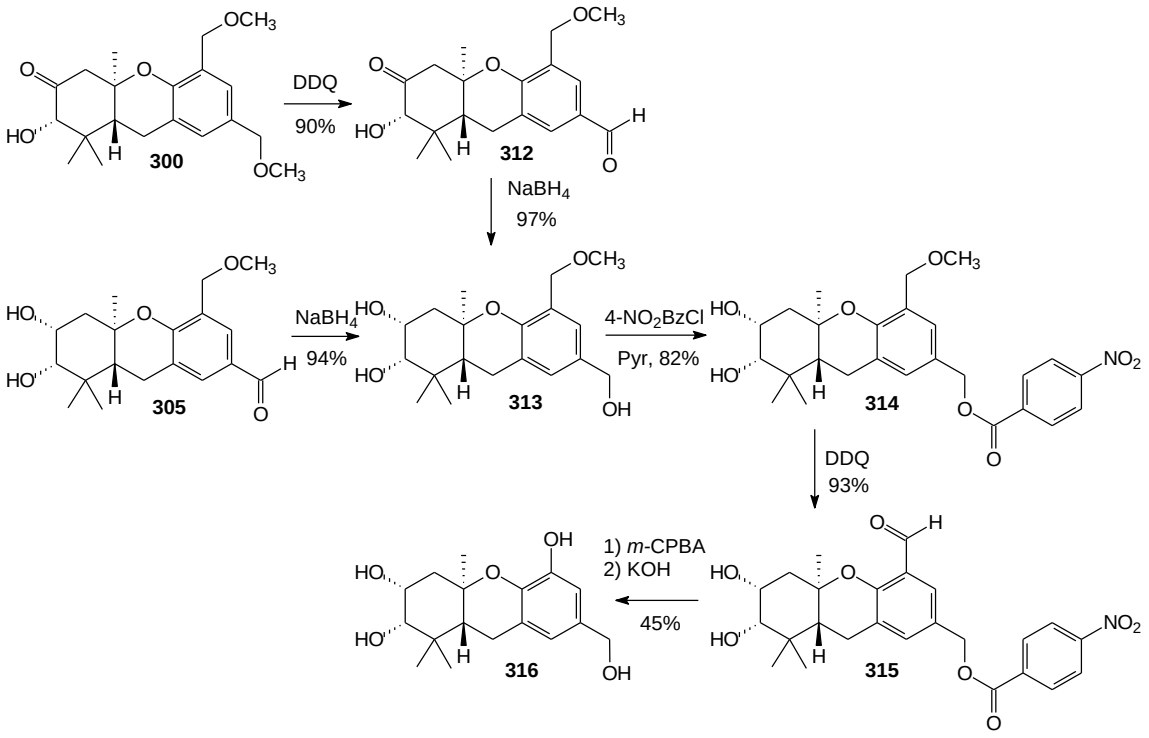
Scheme 41. Synthesis of Phenol **311**.



Various groups then were installed onto benzylic alcohol **307**. The first group screened was a MOM-acetal, which was selectively cleaved by DDQ to regenerate aldehyde **306**. A TBS group also was removed by oxidation to yield the same aldehyde. Finally a *t*-BOC group was installed, and this product was exposed to DDQ. Delightfully, this substrate provided the desired regioisomeric aldehyde **309**, which was plainly evident based on the ^{1}H NMR spectrum. The aldehyde hydrogen for compounds **306** and **309** appear at 9.8 ppm and 10.4 ppm respectively. Also inspected was the *p*-nitrobenzoate ester, which successfully yielded aldehyde **310** after DDQ oxidation. These observations indicate that an electron withdrawing substituent will alter the regioselectivity in this DDQ oxidation, and that electronic factors have a larger impact than steric bulk (e.g. the OTBS compound yielded aldehyde **306**). With limmited

quantities of aldehyde **310** in hand, the crucial Baeyer-Villiger oxidation was attempted. Exposure of aldehyde **310** to *m*-CPBA followed by addition of KOH afforded phenol **311** in moderate yield. The isolation of phenol **311** served as a proof of principle and validates the key step in the sequence.

Scheme 42. Synthesis of Alcohol **316**.

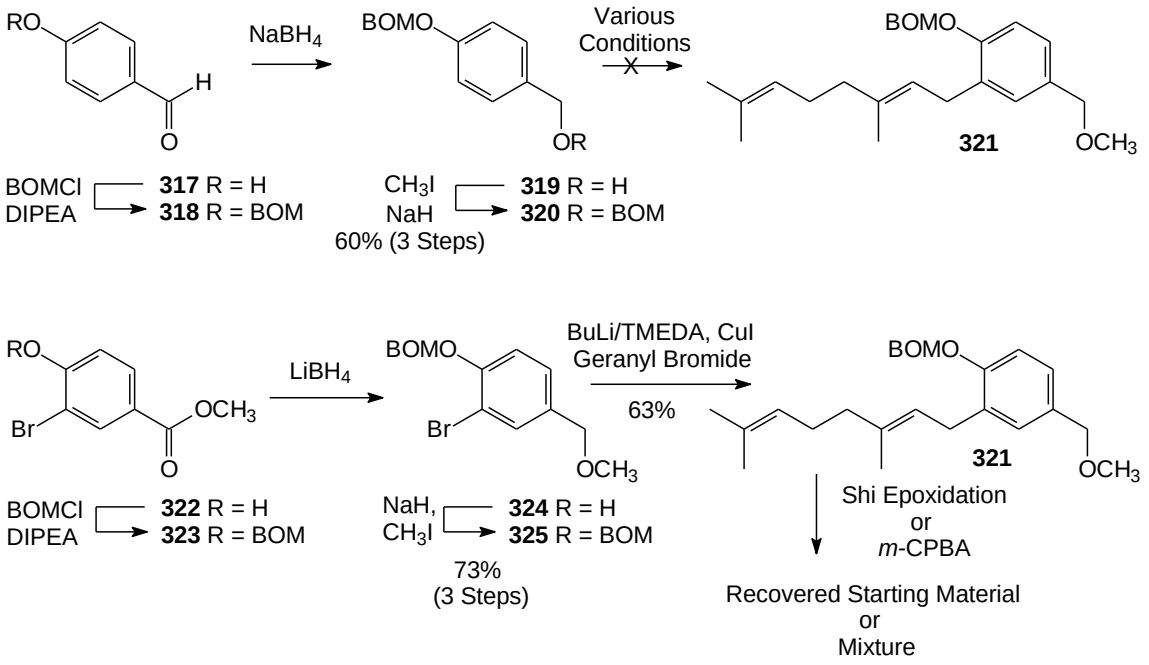


With the problem of regioselective oxidation addressed, attention was refocused on intermediate **305** and the synthesis of schweinfurthin A. Given that acyl groups were able to sway the selectivity of DDQ oxidation but that they are unstable to the alkyl lithium intermediates used in the preparation of compound **305**, it was decided that a protecting group exchange would be attempted late in the synthesis. Thus benzaldehyde **305** was reduced to benzyl alcohol **313** (Scheme 42). To shorten the synthesis of this

intermediate, ketone **300** was exposed to DDQ which resulted in the formation of benzaldehyde **312**. The double reduction of keto-aldehyde **312** yielded alcohol **313** via this abridged path. Derivatization of alcohol **313** as the *p*-nitrobenzoate was accomplished with the corresponding acid chloride. This yielded benzoate **314** which was oxidized with DDQ to yield C-5 aldehyde **315**. Baeyer-Villiger oxidation was attempted on aldehyde **315** and phenol **316** was isolated in moderate yield after base-mediated hydrolysis of both the benzoate and formate. The yield of this transformation is problematic given its placement in the late stage of the synthesis. To probe the reason for this modest yield, the reaction was performed in CD_2Cl_2, which revealed that the Baeyer-Villiger reaction was complete within minutes at room temperature as evidenced by disappearance of the signal at 10.4 ppm. This suggested that the low yield was the result of the hydrolysis/work up procedure. Nonetheless, it was decided to explore alternate pathways to this target due to the length of the sequence. The necessity of late stage protection/deprotection and oxidation/reduction sequences made this approach far from practical, which would discourage its application to schweinfurthin synthesis.

To address the difficulties encountered in the application of CEAS to schweinfurthin synthesis a different oxymethyl acetal was chosen as the migrating group. Of those previously screened (Chapter 5), the commercial availability of BOMCl in conjunction with its potential removal through reaction with H_2 and Pd/C made it an appealing choice. Additionally, attempts were made to shorten the previous sequence by employing directed ortho metalation[144, 152] instead of halogen-metal exchange. As such, *p*-hydroxybenzaldehyde (**317**) was treated with BOMCl to form BOM acetal **318** (Scheme 43). Reduction of this intermediate yielded alcohol **319,** which was methylated under standard conditions to afford compound **320**. Exposure of compound **320** to various ortho metalation protocols resulted only in complex mixtures with no dominant product. It is likely that metalation occurred, but the numerous benzylic and vinylic protons in compound **320** lead to unselective lithiation/alkylation.

Scheme 43. Problematic Synthesis of BOM Epoxide.



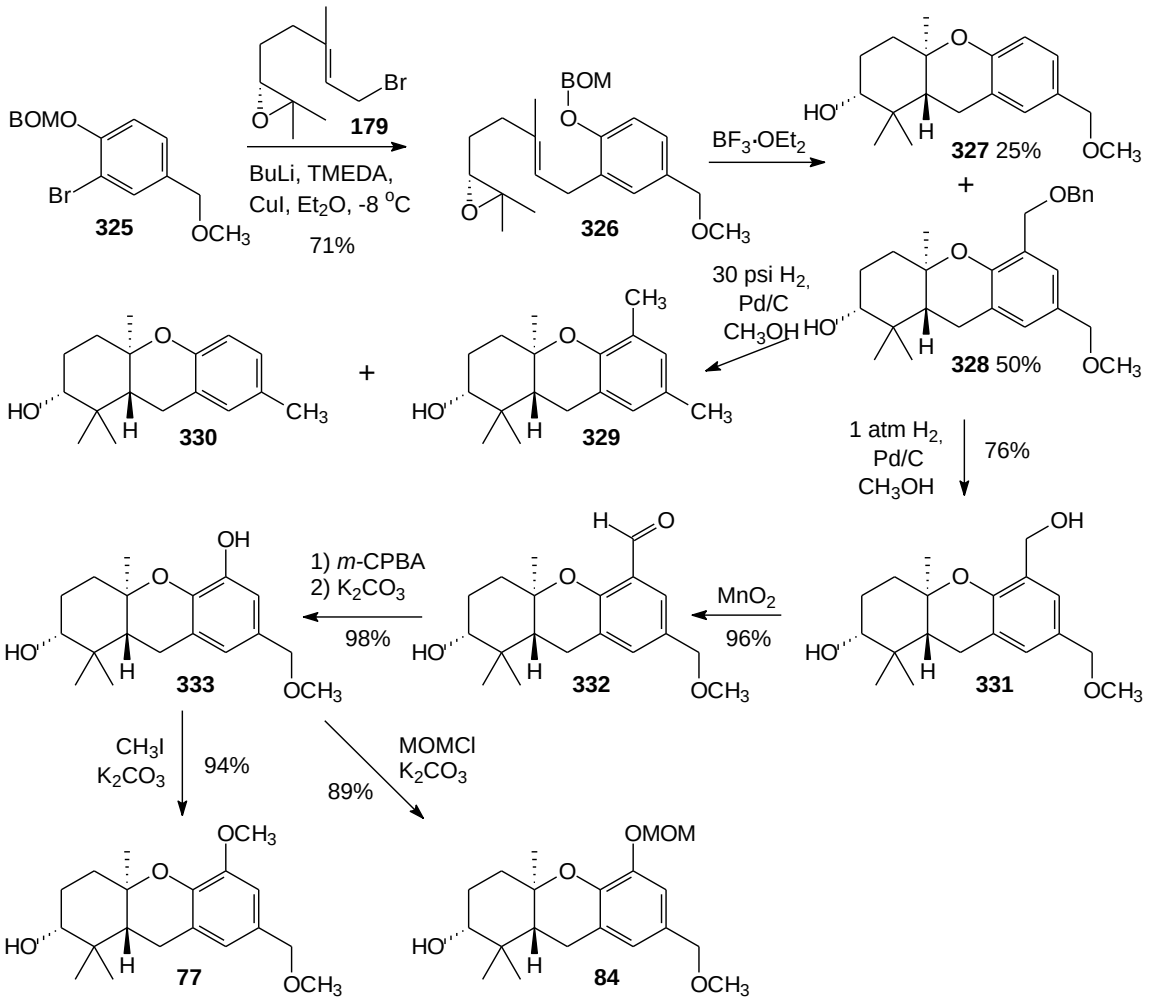
To circumvent this setback, a halogen-metal exchange approach was investigated on a BOM protected substrate. The BOM acetal **323** was synthesized from bromide **322** and BOMCl (Scheme 43). Reduction of the ester was originally accomplished through reaction with DIBAL, however quenching this reaction on a large scale was tedious. Lithium aluminum hydride was apparently too strong of a reducing agent and reduced a substantial amount of the C-Br bond. Thus lithium borohydride was utilized as an alternate reducing agent and this reagent cleanly afforded benzyl alcohol **324**. Standard ether formation yielded compound **325**. It is of note that compound **325** could be prepared in batches exceeding fifty grams without incident or decrease in yield. Halogen-metal exchange under standard conditions provided geranyl arene **321**, illustrating the utility of this protocol over ortho metalation on this system. Regretfully, attempts at epoxidation of the terminal olefin present in compound **321** were problematic under Shi's conditions and only trace product was formed. Exposure of compound **321**

to *m*-CPBA provided the requisite epoxide, however this product was obtained as a ~1:1 mixture of nearly inseparable regioisomers. With these difficulties in mind, other alkylation reactions were examined.

The Wiemer group has previously utilized a direct epoxy bromide alkylation to synthesize cyclization precursors and this strategy was adapted for this research.[66, 130] Exposure of bromide **325**[66] to a mixture of *n*-BuLi and TMEDA resulted in halogen metal exchange (Scheme 44). Transmetalation of the resultant lithiate was accomplished by treatment with CuI and this nucleophile was quenched by addition of epoxy bromide **179**.[66] After some optimization, this reaction sequence afforded CEAS precursor **326** in excellent yield typically on a multi-gram scale. The CEAS reaction was conducted under our standard conditions to afford the desired tricycle **328** which was contaminated by unsubstituted product **327**. Although these compounds could not be readily separated by column chromatography, their ratio could be determined by integration of the different benzylic hydrogens in the ^{1}H NMR spectrum.

Extensive experimentation was required to develop conditions for selective hydrogenolysis of the benzyl ether in compound **328**. Initial attempts at hydrogenolysis utilized a Parr apparatus, which was pressurized to 30 psi of H_2, with catalytic palladium on carbon in methanol. The only products which arose from this reaction, compounds **329** and **330**, were reduced at all benzylic positions. The solvent was changed to EtOAc or acetone and no reaction occurred under otherwise identical conditions even after several days. The pressure of H_2 utilized in methanol was reduced to 1 atm (balloon) and under these conditions only trace conversion to the desired product resulted. More productive conditions were found serendipitously by allowing the reaction in methanol to concentrate to near dryness under a stream of hydrogen and then the resultant slurry was stirred under 1 atm of H_2. Under these conditions, the reaction still required a significant duration, but was sufficiently selective that an acceptable yield of benzyl alcohol **331** was obtained.

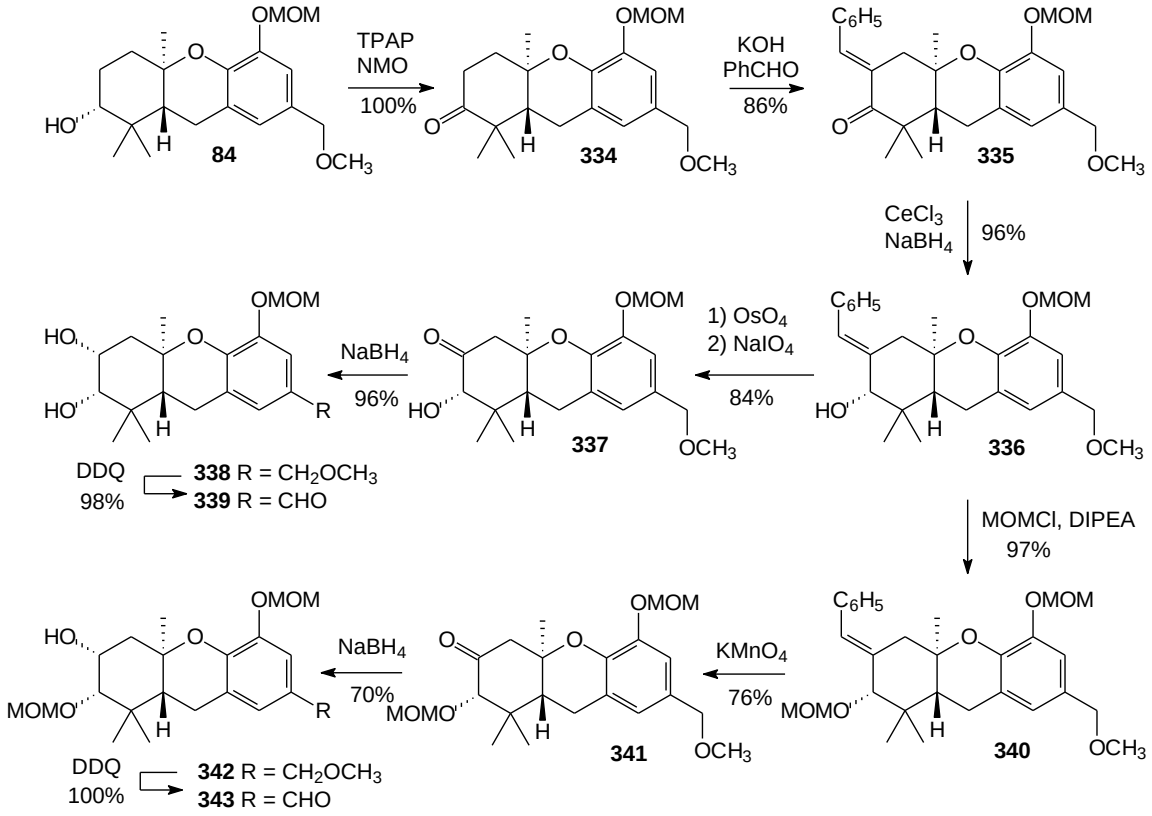
Scheme 44. Formal Synthesis of Schweinfurthins via CEAS.



With a reliable avenue to alcohol **331** mapped, a formal synthesis of the schweinfurthins fell nicely into place (Scheme 44). Selective oxidation of the benzylic position in compound **331** was accomplished upon exposure to excess MnO_2 to provide aldehyde **332**. Treatment of this benzaldehyde with *m*-CPBA resulted in facile Baeyer-Villiger oxidation. After the resultant formate was observed in the ^1H NMR spectrum of the initial product, it was not isolated but instead was hydrolyzed by treatment with aqueous K_2CO_3 to afford phenol **333** in excellent yield. The use of a milder base for this hydrolysis increased the yield when compared to KOH, which was used in earlier work

(Scheme 42). Phenol **333** then served as the long sought point of late stage divergence. Alkylation of phenol **333** with methyl iodide provided intermediate **77**, which has been utilized in the synthesis of schweinfurthins B, E, and F as well as lead agent 3dSB.[31, 68, 72] Protection of the phenol as the MOM acetal provided intermediate **84** which has been engaged as an intermediate in the synthesis of schweinfurthin G and 3dSA.[32, 67] Both of these alkylations proceeded with excellent chemoselectivity and only the phenolic oxygen was alkylated.[67] When taken together, this path allows any of the currently synthesized schweinfurthins to be synthesized from a single, readily prepared, intermediate.

Scheme 45. Synthesis of Key Aldehydes.



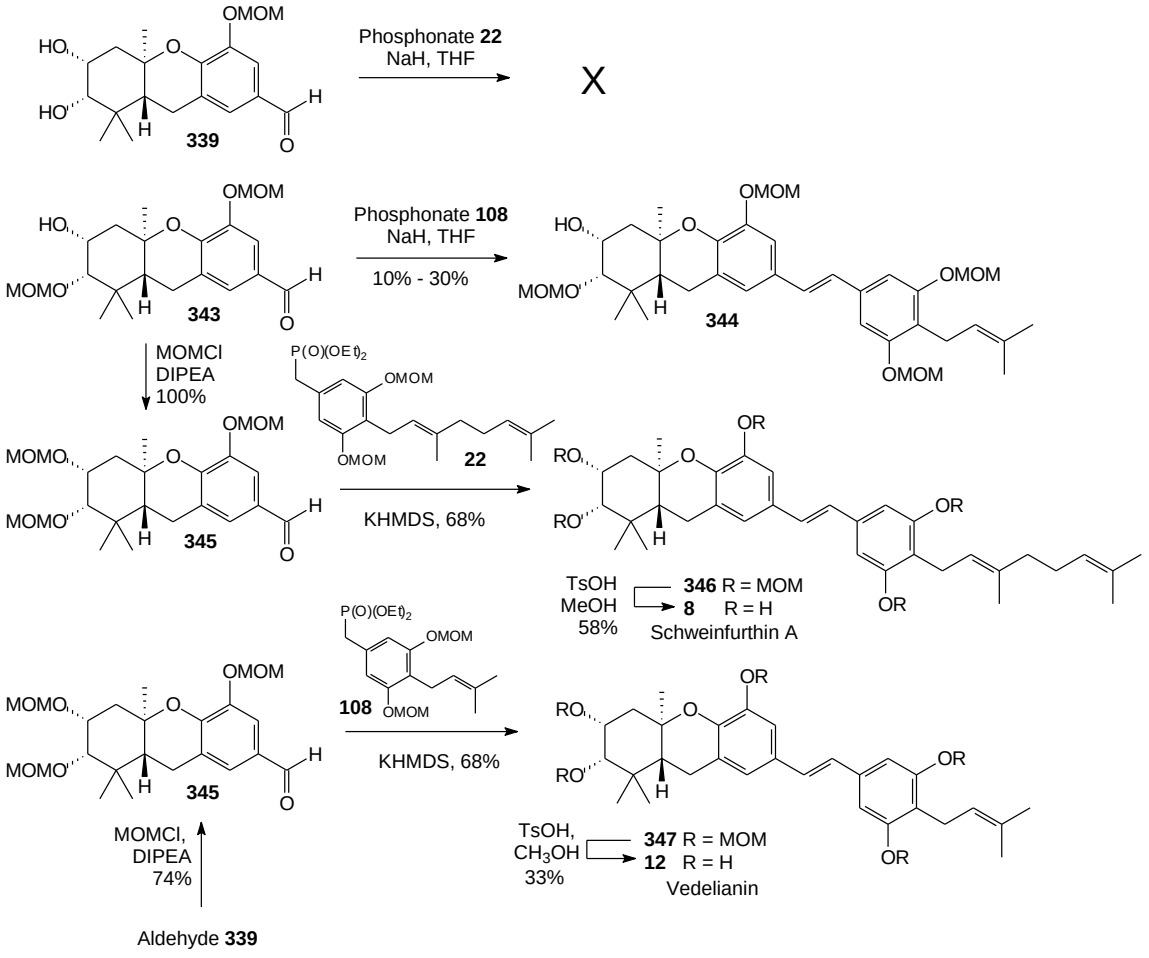
With access to intermediate **84** established, the synthesis of schweinfurthin A was pursued (Scheme 45). Hexahydroxanthene **84** was oxidized to ketone **334** under Ley's conditions.[86] Claisen-Schmidt condensation was executed under the conditions optimized for schweinfurthin B to yield compound **335**. Reduction under the mediation of cerium chloride afforded allylic alcohol **336**, which was dihydroxylated upon exposure to catalytic OsO_4 and further oxidized with sodium periodate in a separate flask to afford ketone **337** in excellent overall yield. Reduction of ketone **337** afforded diol **338** as the sole diastereomer whose relative configuration was evident based on coupling constants. Oxidation of diol **338** with DDQ provided aldehyde **339** in excellent yield.

In an alternate sequence (scheme 45), allyllic alcohol **336** could be protected as MOM acetal **340**. Exposure of acetal **340** to potassium permanganate afforded ketone **341**, which could be reduced to alcohol **342** with sodium borohydride. Treatment of alcohol **342** with DDQ provided aldehyde **343** in quantitative yield.

Having synthesized the requisite aldehydes **339** and **343**, the penultimate HWE condensation was explored. Unfortunately, initial attempts at olefination under standard conditions lead to disappointing results (Scheme 46). Subjecting a mixture of aldehyde **339** and phosphonate **22**, prepared by Dr. N. R. Mente, to standard HWE condensation conditions resulted in a very poor yield. Given this setback, it was suggested that the A-ring diol motif may be complicating the desired condensation. Thus, the C-2 MOM protected aldehyde **343** was subjected to olefination conditions. Again poor results were obtained with both phosphonates **22** and **108**. Although this substructure is directly analogous to that used in the schweinfurthin B series, no productive HWE olefination resulted and only trace quantities of stilbene **344** could be isolated. Due to these setbacks, the C-3 hydroxyl group was protected as a MOM acetal. This could be accomplished from either aldehyde **339** or **343** to provide the fully protected aldehyde **345**. Again, only trace stilbene formation was observed when NaH was used as base. A brief exploration of the reaction conditions revealed that when KHMDS was used as the

base, HWE olefination between aldehyde **345** and phosphonate **22** was complete in less than 10 min at rt to provide a good yield of stilbene **346**. Concurrent hydrolysis of the five MOM groups present in stilbene **346** afforded synthetic schweinfurthin A (**8**) in good yield.

Scheme 46. Total Synthesis of Schweinfurthin A and Vedelianin.



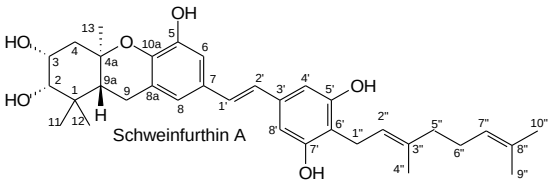
Comparison of natural schweinfurthin A's published NMR data to the spectra obtained for the synthetic material revealed slight discrepancies in the aliphatic region of the ^{1}H NMR spectrum (Table 9, key differences highlighted). To confirm that

schweinfurthin A had indeed been synthesized, an authentic sample of the natural material was obtained from Dr. J. A. Beutler from NCI. Direct comparison of this material to the synthetic material confirmed our assignment and the first total synthesis of schweinfurthin A. Additionally, the synthetic material showed a specific rotation of the same sign and magnitude as that reported for the natural product [($[\alpha]^{25}_{D}$ = +47 (c 1.0, EtOH); from epoxide of 90% ee; lit ($[\alpha]^{25}_{D}$ = +51.8 (c 2.0, EtOH)].[25] Therefore, the natural antipode of schweinfurthin A can now be assigned as (+)-(2*S*, 3*R*, 4a*R*, 9aR)-schweinfurthin A (**8**).

With the total synthesis of schweinfurthin A accomplished, it appeared prudent to synthesize vedelianin, the most potent member of the natural family of schweinfurthins. Aldeyde **346** was exposed to KHMDS and phosphonate **108**, prepared by Dr. N. M. Mente, which resulted in facile formation of stilbene **347** (Scheme 46). Acidic hydrolysis of the MOM acetals provided vedelianin (**12**) in low yield along with significant amounts of partially hydrolyzed material (another ~35%). The NMR spectra of synthetically prepared vedelianin were identical to the published data[153] (Table 10) and the specific rotation of the synthetically prepared material matches both the sign and magnitude reported for natural vedelianin (lit +37 (c 2.9, MeOH); observed $[\alpha]^{25}_{D}$ = +35 (c 1.4, MeOH) for material of 90% ee by HPLC). These comparisons indicate that the naturally occurring antipode has been synthesized and can be assigned as (+)-(2*S*, 3*R*, 4a*R*, 9aR)-vedelianin.

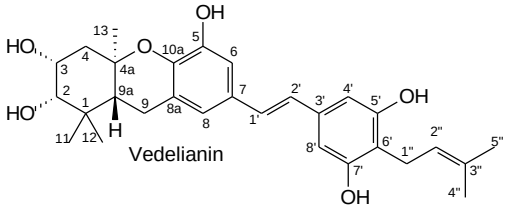
In conclusion, the formal synthesis of schweinfurthins B, E, F, and G has been accomplished by application of CEAS. Although application of a MOM based cascade cyclization tandem substitution sequence was found to be highly problematic, the use of a BOM acetal solved many of these limitations and provided intermediates **77** and **84**. Additionally, the intermediates prepared through this reaction were used in the first total synthesis of (+)-schweinfurthin A and (+)-vedelianin the most potent members of the natural family.

Table 9. NMR Data for Schweinfurthin A.



^{1}H NMR of Schweinfurthin A			^{13}C NMR of Schweinfurthin A			
Signal	Literature	Observed	Signal	Literature	Observed	Δδ
H-6	6.80 (d, J = 2, 1H)	6.79 (s, 1H)	C-5', 7'	157.2	157.3	0.1
H-1'	6.82 (d, J = 16, 1H)	6.77 (d, J = 16.4 Hz, 1H)	C-5	147.0	147.1	0.1
H-8	6.69 (d, J = 2, 1H)	6.72 (s, 1H)	C-3'	141.9	141.9	0.0
H-2'	6.71 (d, J = 16, 1H)	6.72 (d, J = 16.4 hz, 1H)	C-10a	137.6	137.5	0.1
H-4', 8'	6.46 (s, 2H),	6.44 (s, 2H)	C-3"	134.9	134.8	0.1
H-2"	5.25 (tq, J = 7.1, 1.2, 1H)	5.24 (t, J = 7.2 Hz, 1H)	C-8"	131.9	132.0	0.1
H-7"	5.07 (t pent, J = 7.1, 1.4, 1H)	5.07 (t, J = 7.2 Hz, 1H)	C-7	130.8	130.9	0.1
H-3	4.13 (d, J = 2.4, 1H)	4.14 (q, J = 3.6 Hz, 1H)	C-1'	128.7	128.6	-0.1
H-2	3.35 (m, 1H)	3.30 obscured	C-2'	127.4	127.4	0.0
H-1"	3.35 (m, 2H)	3.30 obscured	C-7"	125.6	125.5	-0.1
H-9	2.71 (m, 2H)	2.75 (m, 2H)	C-2"	124.6	124.6	0.0
H-4	1.94 (m, 1H)	2.36 (dd, J = 13.8, 3.0 Hz, 1H) 1.94 (m, 1H) (same m as 5")	C-8a	124.2	124.2	0.0
H-6"	2.04 (t, J = 7.3, 2H)	2.06 – 2.02 (m, 2H)	C-8	120.5	120.4	-0.1
H-4a, 5"	1.95 (t, J = 7.3, 2H); 2.35 (d, J = 13.0, 1H)	1.94 (m, 2H) H-4a	C-6'	115.9	115.8	-0.1
H-4"	1.07 (s, 3H)	1.76 (s, 3H)	C-6	111.1	111.0	-0.1
H-9a	3.35 (m)	1.77 – 1.73 (m, 1H)	C-4', 8'	105.7	105.6	-0.1
H-10"	1.62 (s, 3H)	1.62 (s, 3H)	C-2	78.8	78.8	0.0
H-9"	1.56 (s, 3H)	1.56 (s, 3H)	C-4a	78.2	78.1	-0.1
H-13	1.40 (s, 3H)	1.41 (s, 3H)	C-3	71.7	71.8	0.1
H-12	1.08 (s, 3H)	1.10 (s, 3H)	C-9a	48.8	48.9	0.1
H-11	1.76 (s, 3H)	1.08 (s, 3H)	C-4	44.6	44.7	0.1
			C-5"	40.9	41.0	0.1
			C-1	39.1	39.2	0.1
			C-12	29.4	29.4	0.0
			C-6"	27.8	27.8	0.0
			C-10"	25.8	25.9	0.1
			C-9	23.9	23.9	0.0
			C-1"	23.2	23.2	0.0
			C-13	22.0	22.0	0.0
			C-9"	17.7	17.7	0.0
			C-4"	13.5	16.6	3.1
			C-11	16.3	16.3	0.0

Table 10. NMR Data for Vedelianin.



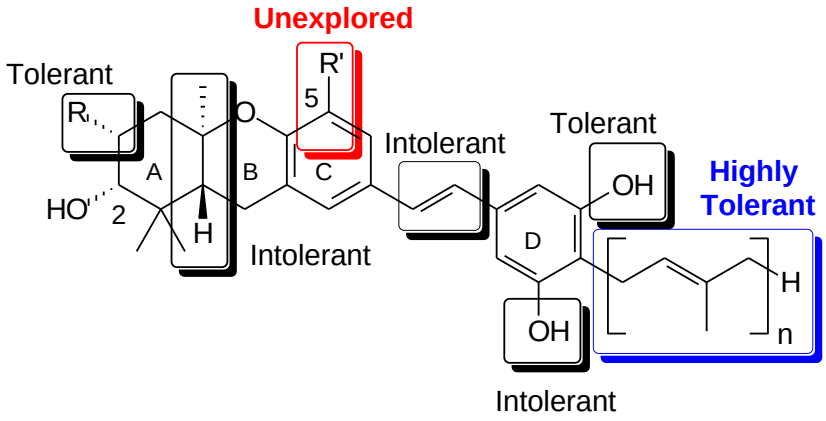
^{1}H NMR of Vedelianin				^{13}C NMR of Vedelianin			
Signal	Literature	Observed	Δδ	Signal	Literature	Observed	Δδ
H-6	6.78 (d, J = 2.0, 1H)	6.80 (s, 1H)	0.02	C-5', 7'	157.1	157.0	0.1
H-1'	6.76 (d, J = 16, 1H)	6.78 (d, J = 16.4 Hz, 1H)	0.02	C-5	146.8	146.8	0.0
H-8	6.70 (d, J = 2.0, 1H)	6.71 (s, 1H)	0.01	C-3'	141.8	141.6	0.2
H-2'	6.73 (d, J = 16, 1H)	6.70 (d, J = 16.4 Hz, 1H)	0.03	C-10a	137.6	137.2	0.4
H-4', 8'	6.5 (s, 2H)	6.44 (s, 2H)	0.01	C-3"	131.3	130.7	0.4
H-2"	5.24 (t, J = 7, 1H)	5.22 (m, 1H)	0.02	C-7	130.7	130.5	0.2
H-3	4.16 (br d, J = 3, 1H)	4.15 (q, J = 3.2 Hz, 1H)	0.01	C-1'	128.8	128.2	0.6
H-2	3.3 (d, J = 3, 1H)	3.35 (m, 1H)	0.0	C-2'	127.3	127.1	0.2
H-1"	3.3 (d, J = 7, 2H)	3.26 (d, J = 7.2, 2H)	0.0	C-2"	124.5	124.3	0.2
H-9	2.72 (m, 2H)	2.77 – 2.73 (m, 2H)	0.02	C-8a	124.1	123.8	0.3
H-4	2.37 (dd, 14.0, 3.0, 1H)	2.37 (dd, J = , 1H)	0.0	C-8	120.5	120.0	0.5
	2.00 (dd, J = 14, 2.0, 1H)	1.95 (dd, J = , 1H)	0.05				
H-4a, 5"	1.78 (s, 3H)	1.75 (s, 3H)	0.03	C-6'	115.9	115.5	0.4
H-4"	1.69 (s, 3H)	1.65 (s, 3H)	0.04	C-6	111.0	110.7	0.3
H-9a	1.75 (dd, J = 12, 5, 1H)	1.75 (m, 1H)	0.0	C-4', 8'	105.9	105.3	0.6
H-13	1.45 (s, 3H)	1.41 (s, 3H)	0.04	C-2	78.7	78.5	0.2
H-12	1.15 (s, 3H)	1.10 (s, 3H)	0.05	C-4a	78.0	77.7	0.3
H-11	1.15 (s, 3H)	1.08 (s, 3H)	0.07	C-3	71.7	71.5	0.2
				C-9a	48.6	48.6	0.0
				C-4	44.5	44.4	0.1
				C-5"	17.9	17.6	0.3
				C-1	39.0	38.8	0.2
				C-12	29.3	29.1	0.2
				C-9	23.8	23.6	0.2
				C-1"	23.3	23.0	0.3
				C-13	22.0	21.7	0.3
				C-4"	25.9	25.7	0.2
				C-11	16.2	16.2	0.0

CHAPTER 7

THE SYNTHESIS OF C-5 SCHWEINFURTHIN ANALOUGES

The Wiemer group has been interested not only in the total synthesis of the natural schweinfurthins but also in exploring the portions of the schweinfurthins' structure that are essential for biological activity. These studies might uncover more potent analogues that could be accessed through synthesis. Considerable effort has been allocated to mapping the schweinfurthins pharmacophore through SAR work and a summary of this work is provided below (Figure 16). [32, 64, 68, 69,70, 71] Much of this effort has been focused on the right half of the schweinfurthins' stilbene core due to the ease in which achiral phosphonates can be synthesized and then condensed with the same hexahydroxanthene aldehyde. By comparison, relatively little work has addressed how modification to the schweinfurthins' tricyclic core will influence activity.

Figure 16. The Schweinfurthin Pharmacophore.



Synthesis of schweinfurthins with varied hexahydroxanthene cores would appear to be a worthwhile endeavor based on variations present within the natural family. The

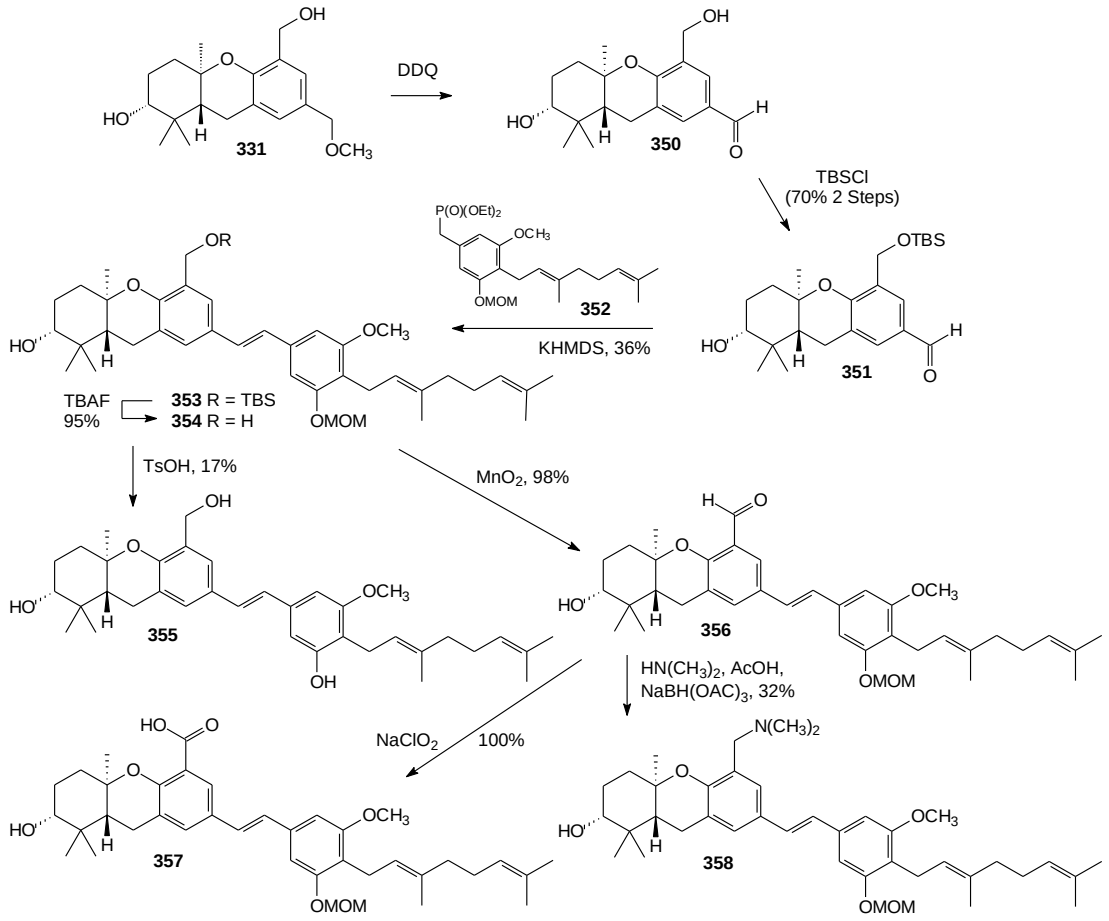
natural products schweinfurthin F and G show that the C-3 hydroxyl group is not essential for activity, and the synthetic 3-deoxyschweinfurthins (e.g. 3dSB) only lose 2-3 fold activity relative to their 2,3-dihydroxy counterparts, schweinfurthin E and vedelianin respectively. Additionally, the natural family shows variation at the C-5 position which presents as either a phenol or a methoxy group (e.g. schweinfurthin A vs. schweinfurthin B). Within the natural family, schweinfurthins containing a free phenol are about 2-3 times more potent and have enhanced differential activity relative to those that contain a methoxy group. Thus, we sought to incorporate a variety of substituents onto the schweinfurthins' C-5 position to further map the schweinfurthins' pharmocophore.

This work began with advanced benzyl alcohol **331** (Scheme 47) which was made available from the CEAS reaction en route to other schweinfurthin intermediates (Chapter 6). Exposure of alcohol **331** to DDQ provided aldehyde **350**. The chemoselectivity displayed by DDQ in this reaction is noteworthy because it reacts with the benzyl ether instead of the free benzyl alcohol which underscores the natural selectivity present in this system (Chapter 6).

The subsequent HWE olefination did not proceed on compound **350**. Therefore, protection of aldehyde **350** through reaction with excess TBSCl and imidazole resulted in silyl ether **351**. First attempts by J. D. Inbarasu at HWE condensation between aldehyde **351** and phosphonate **352**, initially prepared by Dr. M. P. Callahan and later by J. D. Inbarasu, were unsuccessful. Later efforts employing KHMDS as base were found to provide a higher yield than NaH and provided a moderate yield of stilbene **353**. Exposure of this stilbene to TBAF resulted in smooth desilylation, and stilbene **354** was isolated. Initial attempts at acidic hydrolysis of the MOM acetal under standard conditions resulted in a complicated mixture where the major product was less polar than stilbene **354**. Isolation of the less polar material, along with trace amounts of compound **355**, proved that etherification had occurred at the C-5 position in acidic methanol. The assignment of a C-5 methoxymethyl group was corroborated by comparison to the

authentic material prepared by a CEAS reaction with a MOM acetal.[131] Attempts at preventing etherification by addition of water to the reaction resulted in recovered starting material.

Scheme 47. Synthesis of C-5 Schweinfurthin Analogues.

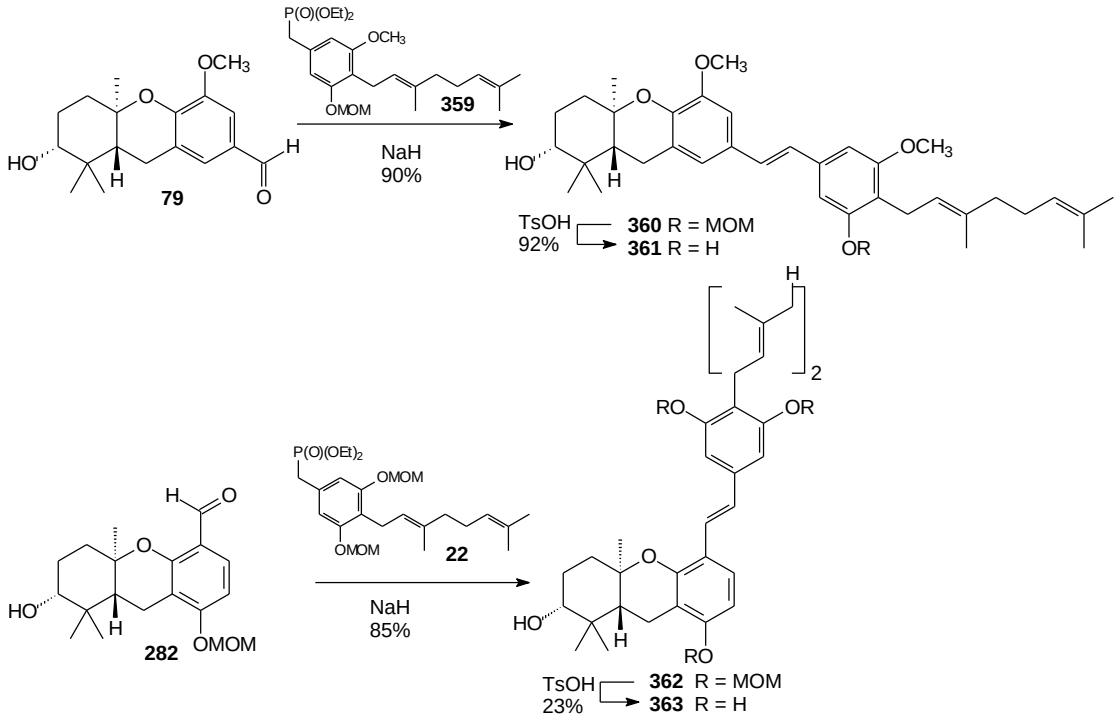


Even in light of the problematic hydrolysis, compound **354** was taken forward. Further elaboration of alcohol **354** (Scheme 47) was accomplished upon exposure to MnO_2, which resulted in formation of aldehyde **356**. A sample of aldehyde **356** was

oxidized to the carboxylic acid **357**, while reductive amination of aldehyde **356** with dimethylamine, $NaBH(OAc)_3$, and molecular sieves which provided amine **358**.

When taken together, this family of compounds possesses quite varied functionality at the C-5 position. The amine should be cationic under buffered conditions of physiological pH whereas the acid would likely be anionic. The incorporation of one or more ionized functional groups may be advantageous in schweinfurthin analogues since it would allow for salt formation. Salt formation would lower the Log D of the schweinfurthin, and aid in any attempts at formulation. Furthermore, the aldehyde could form Schiff bases under physiological conditions which may allow covalent linkage to the schweinfurthins' target(s). Additionally, most of these compounds are only hydrogen bond acceptors in contrast to the hydrogen bond donating and accepting abilities of benzylic alcohol **355**. Determination of the biological activity of this set of compounds may clarify which of these characteristics are favorable in a schweinfurthin.

Scheme 48. Synthesis of Schweinfurthins **361** and **363**.



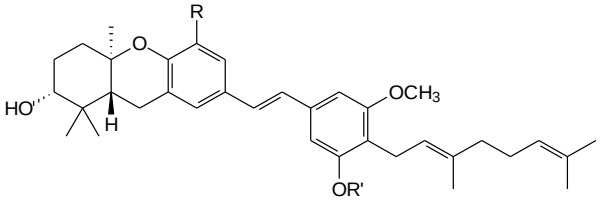
To act as a control compound, aldehyde **79** was condensed with phosphonate **352** to provide stilbene **360** (Scheme 48) and the MOM group was hydrolyzed. This afforded schweinfurthin **361** as a 3dSB analogue with a D-ring methyl group. Additionally, aldehyde **282**, available from the synthesis of angelichalcone (Chapter 5), was allowed to react with phosphonate **22** in the presence of base to provide stilbene **362**. Removal of the three MOM acetals afforded schweinfurthin **363** in acceptable yield. Schweinfurthin **363** is a constitutional isomer of 3-deoxyschweinfurthin A about the C ring.

Once this family of C-5 schweinfurthin analogues was in hand, they were submitted for biological assay. An MTT assay of the above described schweinfurthins was performed by Dr. C. H. Kuder and the results are summarized in Table 11. The schweinfurthins were screened against two cell lines chosen from the NCI's 60-cell line panel to represent a sensitive cell line (SF-295) and a resistant cell line (A-549). Although the NCI's 60-cell line assay provides a wealth of information (representing over 300 individual assays), turnaround time frequently exceeds 6 months making more rapid assay alternatives appealing. Choosing a resistant cell line and a sensitive cell line for a two cell assay allows determination of the potency of these compounds against the sensitive cell line but also indicates if the unique pattern of schweinfurthin activity is preserved by demonstrating that the resistant line is unaffected at elevated doses.

The results from the two cell assay indicate several key points (Table 11). First, even though most of the schweinfurthins were submitted with a D-ring MOM group intact, they still display biological activity. A direct comparison of this feature can be seen in entries 1 and 2. This indicates that the D-ring MOM group is likely metabolized within the cell during the assay to afford an active schweinfurthin. Further evidence for this hypothesis comes from the observation that D-ring dimethylschweinfurthins show poor activity.[64] This was hypothesized to be because the dimethyl analogues are incapable of acting as hydrogen bond donors about the D-ring. Also of note is that the addition of an amine to the C-5 position (**358**) makes the schweinfurthins toxic to both of

the cell lines assayed. Acid **357** showed very poor activity in the 2-cell line screen. Given the less than desirable profile, schweinfurthins **357** and **358** were not submitted for further assay.

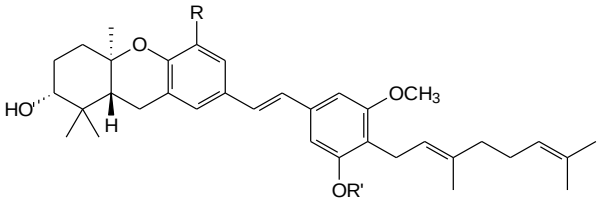
Table 11. Results from MTT Assay of C-5 Modified schweinfurthins.



Entry	Schweinfurthin	R =	R' =	SF-295 GI_{50} (uM)	A-549 GI_{50} (uM)
1	**354**	CH_2OH	MOM	1.0	>100
2	**355**	CH_2OH	H	0.4	14
3	**356**	CHO	MOM	4.0	>100
4	**357**	CO_2H	MOM	20	>10
5	**358**	$CH_2N(CH_3)_2$	MOM	2.0	2.0

Several of the more interesting compounds listed above were pooled with schweinfurthins prepared by other individuals and submitted to the NCI for assay in the NCI-60. The results of that analysis are shown in Table 12. The full NCI data indicates that the C-5 OH, which is present in schweinfurthin A and vedelianin, remains the most potent and selective motif. The addition of either a methyl group (schweinfurthin **361**), or a benzylic carbon and a MOM group (schweinfurthin **354**) somewhat decreases the potency and the differential activity. Any of the other tested modifications to the C-5 position were less well tolerated. Thus it would appear that a hydrogen bond donor at the C-5 position is important for activity. One might speculate that the C-5 O-methyl group in schweinfurthin B is metabolized *in vivo* to afford schweinfurthin A, and that the diminished activity of schweinfurthin B, relative to schweinfurthin A reflects only partial metabolism at this site.

Table 12. NCI-60 Assay of C-5 Modified schweinfurthins.



Entry	Schweinfurthin	R =	R' =	Mean GI_{50} (uM)	Differential (log units)	SF-295 GI_{50} (uM)	A-549 GI_{50} (uM)
1*	**364**	H	H	10	1.6	1.7	13
2*	**365**	F	H	6.2	1.4	5.01	2.1
3*	**366**	SCH_3	H	8.0	1.6	3.80	6.0
4*	**367**	OH	H	0.53	2.9	0.023	0.95
5	**361**	OCH_3	H	1.7	1.6	0.19	2.5
6	**354**	CH_2OH	MOM	2.1	2.5	0.15	0.98
7	**356**	CHO	MOM	6.3	2.5	1.20	7.8

In conclusion, several C-5 modified schweinfurthin analogues have been prepared by application of CEAS and the biological activity of these compounds has shed additional light on the schweinfurthins' pharmacophore.

CHAPTER 8

CONCLUSIONS AND FUTURE DIRECTIONS

Humanity has had a long and rich history in utilizing natural substances for their curative properties. However it is only in the last century that mankind has had the capability, and the audacity, to modify the individual chemical entities in nature for medical applications. One of the largest fields which exploits this notion is oncology where the prognosis for those afflicted with cancer is in need of continual improvement. As part of a national program aimed at alleviating cancer-induced suffering and mortality, the National Cancer Institute uncovered the structure of a small family of natural terpenoids which exhibit remarkable anti-proliferative properties and named them the schweinfurthins. Subsequently, the Wiemer group has had a long interest in synthesizing and evaluating these natural products as potential treatments for cancer. Initially, this work yielded syntheses of schweinfurthins C, F, and G as well as a number of analogues.

The work disclosed herein has summarized the successful synthesis of the most potent naturally occurring schweinfurthins, those which contain an A-ring diol. Further optimization of key hexahydroxanthene intermediates' synthesis has made the preparation of 3-deoxy schweinfurthins commonplace and provided material so that the synthesis of the other schweinfurthins could be pursued. Oxidation of the schweinfurthins' C-3 position to introduce the natural hydroxyl group was exceptionally problematic, but a classical solution to his problem was developed which lead to the first total synthesis of (+)-schweinfurthin B and (+)-schweinfurthin F. The intermediates used in this synthesis were then utilized to prepare a handful of fluorescent schweinfurthins which are currently under investigation by our collaborators in both affinity chromatography and microscopy experiments.

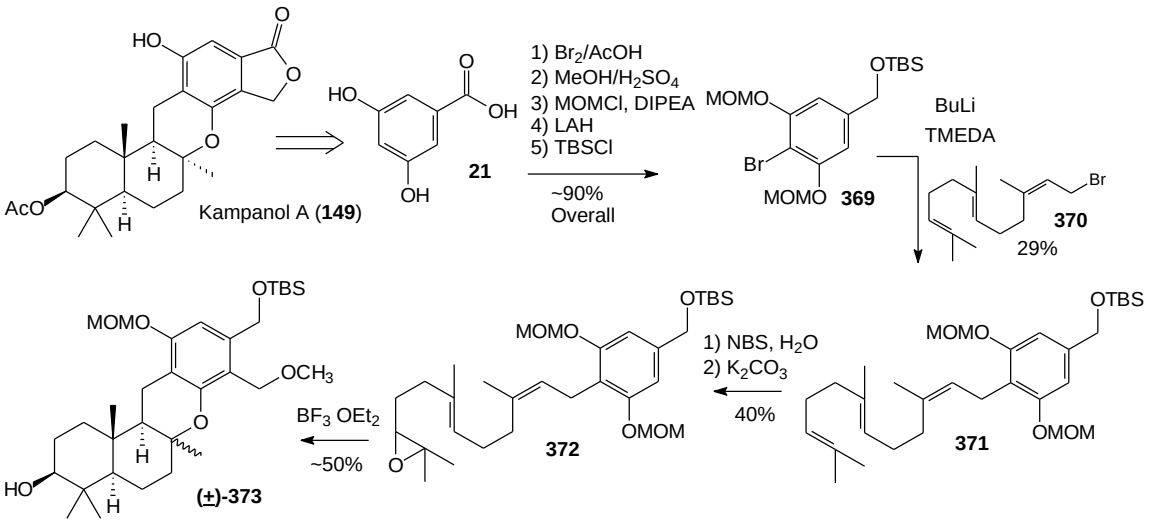
The synthesis of the *cis*-fused hexahydroxanthene schweinfurthin core was accomplished by a modified cascade cyclization and the relative configuration of this product was unambiguously assigned by X-ray analysis. Biological evaluation of this schweinfurthin demonstrated the importance of the *trans* ring fusion in active schweinfurthins.

As part of synthetic efforts aimed at schweinfurthin analogues, an unprecedented extension of cascade cyclization methodology was discovered. When a phenolic MOM substituent was utilized, it lead to aromatic substitution and the incorporation of a CH_2OCH_3 substituent into the adjacent arene. Exploration of this process revealed that it shows considerable generality and that other oxymethyl groups and semi-stabilized electrophiles can undergo this process with excellent regioselectivity. A series of crossover experiments then confirmed that transfer of the electrophile to the arene is intramolecular, which provided mechanistic insight. This cascade sequence then was applied to the succinct total synthesis of (+)-angelichalcone and a formal synthesis of numerous schweinfurthins and schweinfurthin analogues. Intermediates obtained in this work were used to complete the first total synthesis of (+)-schweinfurthin A and (+)-vedelianin as well as a family of C-5 modified schweinfurthin analogues.

This work has accomplished many of the keystone goals presented by the Wiemer group's schweinfurthin program, but the synthesis of other related natural products continues to be pursued. One agent identified as a synthetic target is kampanol A (Chapter 4, **149**) which might be synthesized by cascade cyclization terminated with tandem aromatic substitution. The synthetic work of Dr. N. R. Mente (Scheme 49) afforded late stage kampanol intermediate **373** and identified several synthetic hurdles to be overcome in any efficient kampanol synthesis. First, construction of farnesyl epoxide **372** proved troublesome both in C-C bond formation and in asymmetric oxidation. Although bromide **369** could be prepared in large batches in high yield, alkylation with bromide **370** was difficult to reproduce. When conditions for the synthesis of compound

371 where developed, it was discovered that regio- and stereoselective epoxidation was tedious. This work did however demonstrate that the key cascade sequence could be accomplished in excellent yield when one considered the level of molecular complexity generated, and intermediate **373** was synthesized as a racemic mixture of epimers.

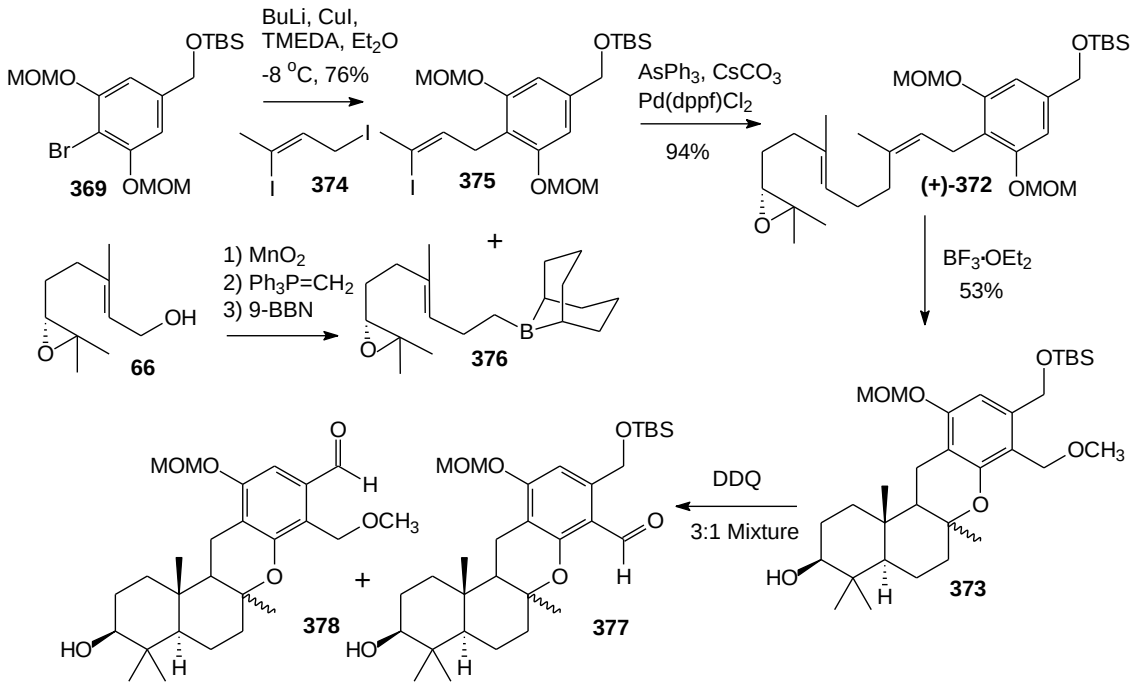
Scheme 49. Contributions of Dr. N. R. Mente to the synthesis of (±)-Kampanol A.



To overcome these limitations, an application of a β–alkyl Suzuki coupling[154, 155] was envisioned to provide the requisite epoxide in a much abridged sequence where the established chiral alcohol **66** was utilized (Scheme 50). Coupling bromide **369** to diiodide **374**[156] was accomplished through halogen-metal exchange and the vinylic iodide was then used in a Pd-mediated cross coupling with 9-BBN derivative **376**, prepared from the corresponding diene.[157] Cyclization of the resultant epoxide **372**, now prepared as a single enantiomer on a larger scale, confirmed previous observations that a mixture of diasteriomes was obtained. Careful inspection of the ^{1}H NMR spectrum of this mixture indicates that the diastereomers are likely the two possible *cis*-fused isomers

(Chapter 4), based on the benzylic hydrogen spin systems and methyl groups' chemical shifts.

Scheme 50. Contributions to the Synthesis of Kampanol A.



To corroborate this, it would appear prudent to synthesize epi-*trans*-*trans*-kampanol A which would likely form as a single diastereomer upon cyclization. All-*trans* polyenes are known to provide the *trans* polycycle in high yield (Chapter 1). The all *trans* compound would likley feature a methyl group of higher chemical shift than the *cis* isomer (Chapter 4) and the benzylic spin system would not show the large coupling present in the *cis* compounds. Because the all-*trans* cyclization should proceed to form only a single diastereomer, that product could be used for comparative purposes in assigning the relative stereochemistry of the cascade product **373**, and in exploring synthetic endgame tactics, and its biological activity could be evaluated. To circumvent

lengthy benzylic manipulations, compound **373** was treated with DDQ and a mixture of aldehydes resulted in a near 3:1 ratio (tentatively assigned as compounds **377** and **378**). This mixture indicates that if properly orchestrated, it should be possible to elaborate a bis-benzyl ether like compound **373** to the corresponding lactone in a single transformation under the guidance of DDQ. These improvements should provide the basis of a concise synthesis of kampanol A.

In closing, the most potent schweinfurthins now have succumbed to total synthesis and the synthetic avenue developed can provide enough of the key intermediates to support further SAR work. A CEAS cyclization has been developed that allows divergence to multiple schweinfurthins from the same late stage intermediate. This CEAS-based strategy has already been applied to the synthesis of several natural products including (+)-schweinfurthins A, B, E, F, and G, (+)-vedelianin, and (+)-angelichalcone. Additionally, progress towards the synthesis of kampanol A has been made by a variation of this methodology. The sum of this work is significant both for its contributions to the methodology of synthetic organic chemistry and for advancing our understanding of the biological activity and medicinal properties of the schweinfurthins.

CHAPTER 9

EXPERIMENTAL SECTION

General Conditions. All commercially available reagents and catalysts were used without further purification. Both THF and Et_2O were freshly distilled from sodium/benzophenone, while CH_2Cl_2 and Et_3N were freshly distilled from CaH. All reactions in non-aqueous solvents were conducted in oven dried glassware under a positive pressure of argon with magnetic stirring. All commercial reagents were used without further purification unless otherwise stated. Thin-layer chromatography (TLC) was routinely used to monitor the progress of the reactions. TLC was performed using pre-coated plastic plates with 230-400 mesh silica gel impregnated with a fluorescent indicator (250 nm) eluting with EtOAc in Hex. Visualization was achieved using UV light, potassium permangenate, or phosphomolybdic acid. Flash chromatography was performed on glass flash chromatography columns using EtOAc in Hex as a default solvent system. Organic solutions were concentrated by rotary evaporation below 60 ^{o}C at 25 torr. All NMR spectra were recorded on Bruker instruments at 300 MHz for ^{1}H, and 75 MHz for ^{13}C or higher field strength with $CDCl_3$ as solvent and $(CH_3)_4Si$ (^{1}H, 0.00 ppm) or $CDCl_3$ (^{1}H, 7.26 ppm or ^{13}C, 77.0 ppm) as internal standards unless otherwise noted. Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad singlet), integration, and coupling constant in Hertz (Hz). Elemental analyses were performed by an outside facility. Analyses of enantiomeric purity were performed using a chiral HPLC column with photodiode array UV-Vis analysis using a Diacel Chiralcel OD-H (0.46 cm x 25 cm) column on a Waters 2695 Alliance HPLC eluting with IPA in Hex. High resolution TOF mass spectrometry utilizing electrospray ionization or magnetic sector mass spectrometry utilizing electron impact ionization in positive mode was performed to confirm the

identity of the compounds by the U-Iowa Mass Spec. Lab. The X-Ray diffraction analyses were performed by the U-Iowa X-Ray facility.

Methyl Ether 72. To a solution of the known benzyl alcohol **71**[66] (4.42 g, 15.9 mmol) in THF at 0 ^{o}C was added NaH (1.2 g, 60% in oil, 30 mmol) followed by CH_3I (1.5 mL, 24 mmol). After 3 hr the reaction was quenched by addition of water. The resulting solution was extracted with EtOAc, and the organic extract was washed with brine. After the organic phase was dried ($MgSO_4$) and concentrated in vacuo, final purification by column chromatography (3:1 Hex/EtOAc) afforded methyl ether **72** (4.84 g, 96%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.06 (s, 1H), 6.82 (s, 1H), 5.12 (s, 2H), 4.31 (s, 2H), 3.80 (s, 3H), 3.60 (s, 3H), 3.33 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 153.6, 142.8, 135.8, 124.1, 117.7, 111.0, 98.8, 73.9, 58.4, 58.1, 56.2; HRMS (EI) *m/z* calcd for $C_{11}H_{15}O_4Br$ (M^+) 290.0154, found 290.0157.

Geranyl Arene 74. To a solution of methyl ether **72** (2.0 g, 6.9 mmol) in THF at – 78 ^{o}C was added *n*-BuLi (3.0 mL, 2.5 M in Hex) over 5 min. After 28 min geranyl bromide (**73**, 1.5 mL, 7.9 mmol) was added drop wise. The solution was kept cold for 50 min and quenched by addition of water. The resulting solution was extracted with EtOAc, and the combined organic phases were washed with brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (9:1 Hex/EtOAc) afforded arene **74** (2.2 g, 91%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 6.78 (s, 1H), 6.73 (s, 1H), 5.32 (t, *J* = 7.2 Hz, 1H), 5.13 – 5.10 (m, 1H), 5.07 (s, 2H), 4.37 (s, 2H), 3.84 (s, 3H), 3.59 (s, 3H), 3.43 (d, *J* = 7.2 Hz, 2H), 3.38 (s, 3H), 2.12 – 2.02 (m, 4H), 1.71 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.1, 143.3, 136.0, 135.5, 134.0, 131.2, 124.2, 122.6, 121.0, 109.3, 98.8, 74.6, 58.0, 57.3, 55.6, 39.6, 28.2, 26.5, 25.6, 17.6, 16.0; HRMS (EI) *m/z* calcd for $C_{21}H_{32}O_4$ (M^+) 348.2301, found 348.2309.

Epoxide 76. To a solution of arene **74** (2.8 g, 8.0 mmol) and Shi's catalyst (**75**, 590 mg, 2.1 mmol) in aq buffer (30 mL, 2 M K_2CO_3 and 4 mM EDTA) and organic phase (50 mL, 1:1:1 CH_2Cl_2/MeCN/EtOH) at 0 ^oC was added hydrogen peroxide (7 mL, 30%) over 7 hr. After an additional 2 hr the reaction was quenched by addition of aq Na_2SO_3. The resulting solution was extracted with EtOAc, and the combined organic phases were washed with brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (4:1 Hex/EtOAc) afforded recovered starting material (0.62 g, 22%) and epoxide **78** (1.84 g, 63%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 6.75 (s, 1H), 6.69 (s, 1H), 5.34 (t, *J* = 7.1 Hz, 1H), 5.04 (s, 2H), 4.34 (s, 2H), 3.81 (s, 3H), 3.55 (s, 3H), 3.40 (d, *J* = 7.1 Hz, 2H), 3.35 (s, 3H), 2.68 (t, *J* = 6.3 Hz, 1H), 2.31 – 2.08 (m, 2H), 1.71 (s, 3H), 1.68 – 1.63 (m, 2H), 1.24 (s, 3H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.0, 143.2, 135.2, 135.0, 134.0, 123.1, 120.8, 109.3, 98.7, 74.5, 64.0, 58.2, 58.0, 57.3, 55.5, 36.2, 28.2, 27.2, 24.7, 18.6, 16.0; HRMS (EI) *m/z* calcd for $C_{21}H_{32}O_5$ (M^+) 364.2250, found 364.2262.

Tricyclic Ether 77. To a solution of epoxide **76** (958 mg, 2.6 mmol) in CH_2Cl_2 (350 mL) at -78 ^oC was added $BF_3{\cdot}OEt_2$ (2.0 mL, 16 mmol). After 7 min the reaction was quenched by addition of TEA (4.1 mL, 29 mmol). The resulting solution was concentrated in vacuo, dissolved in CH_2Cl_2 (30 ml), and washed with water then brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (1:1 Hex/EtOAc) afforded desired tricyclic ether **77** (583 mg, 69%) as a yellow oil: $[\alpha]^{26.4}_D$ = +122º (c 1.3, CH_3OH, 92% ee by HPLC); ^1H NMR ($CDCl_3$) δ 6.69 (s, 1H), 6.67 (s, 1H), 4.33 (s, 2H), 3.83 (s, 3H), 3.38 (s, 3H), 3.38 – 3.33 (m, 1H), 2.70 – 2.67 (m, appears as d, *J* = 9.3 Hz, 2H), 2.13 – 2.04 (m, 1H), 1.87 – 1.76 (m, 3H), 1.68 – 1.57 (m, 2H), 1.24 (s, 3H), 1.06 (s, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.7, 142.1, 129.0, 122.3, 121.3, 109.0, 77.8, 76.7, 74.9, 58.0, 55.9, 46.6, 38.3, 37.6, 28.2, 27.3, 23.0, 19.7, 14.2; HRMS (EI) *m/z* calcd for $C_{19}H_{28}O_4$ (M^+) 320.1988, found

320.1991. The MOM acetal **78** (140 mg, 17%) also was isolated from this reaction mixture.

MOM Acetal 78. $[\alpha]^{26.4}_{D}$ = +34.8º (c 1.56, CH_3OH, 92% ee by HPLC); ^{1}H NMR ($CDCl_3$) δ 6.67 (s, 1H), 6.66 (s, 1H), 4.74 (d, *J* = 6.8 Hz, 1H), 4.61 (d, *J* = 6.9 Hz, 1H), 4.31 (s, 2H), 3.82 (s, 3H), 3.40 (s, 3H), 3.36 (s, 3H), 3.24 (dd, *J* = 11.5, 4.2 Hz, 1H), 2.68 – 2.65 (m, appears as d, *J* = 9.3 Hz, 2H), 2.12 – 2.07 (m, 1H), 1.98 – 1.93 (m, 1H), 1.78 – 1.53 (m, 3H), 1.21 (s, 3H), 1.05 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.6, 142.0, 128.9, 122.2, 121.1, 108.9, 96.0, 83.9, 76.6, 74.8, 57.8, 55.8, 55.5, 46.8, 38.1, 37.4, 27.2, 25.1, 22.9, 19.6, 15.0; HRMS (EI) *m/z* calcd for $C_{21}H_{32}O_5$ (M^+) 364.2250, found 364.2256.

Known Aldehyde 79. To a solution of tricyclic ether **77** (36 mg, 0.11 mmol) in CH_2Cl_2/water (10:1) at rt was added DDQ (67 mg, 0.30 mmol), and after 75 min the reaction was quenched by addition of $NaHCO_3$. The resulting solution was extracted with CH_2Cl_2, and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography (1:1 Hex/EtOAc) afforded tricyclic aldehyde **79** (34 mg, 100%) as a yellow wax. The spectroscopic data and reactivity of this material were identical to aldehyde **79** prepared via different methods.[31]

A-Ring MOM Tricycle 78. To a solution of tricycle **77** (60 mg, 0.89 mmol) in CH_2Cl_2 at rt was added DIPEA (0.25 mL, 1.5 mmol) followed by MOMCl (0.1 mL, 1.3 mmol). After 4 hr, the reaction was quenched by addition of water, the resulting solution was extracted with CH_2Cl_2, and the combined organic phases were washed with 1N HCl and brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (3:2 Hex/EtOAc) afforded tricycle **78** (62 mg,

92%) as a colorless oil. Both the physical and spectroscopic properties of this material were identical to those of the same material described above.

Compound 77. To a solution of the compound **78** (110 mg, 0.30 mmol) in MeOH at rt was added TsOH (195 mg, 1.1 mmol). After 84 hr the reaction was quenched by the addition of $NaHCO_3$. The resulting solution was concentrated in vacuo and then extracted with EtOAc. The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography (1:1 Hex/EtOAc) afforded tricycle **77** (95 mg, 96%) as a yellow oil. Both the physical and spectroscopic properties of this material were identical to those of the same material described above.

Methyl Ether 81. To a solution of benzyl alcohol **80** (1.76 g, 5.7 mmol) in THF (30 mL) in an ice bath was added NaH (550 mg, 60% in oil, 14 mmol) followed by MeI (0.75 mL, 12 mmol). After 15 h the reaction was quenched by addition of water, the resulting solution was extracted with EtOAc, and the combined organic phases were washed with brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (30% EtOAc in Hex) afforded methyl ether **81** (1.73 g, 94%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.16 (m, 1H), 7.05 (m, 1H), 5.16 (s, 2H), 5.14 (s, 2H), 4.31 (s, 2H), 3.62 (s, 3H), 3.45 (s, 3H), 3.36 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 151.2, 143.6, 136.0, 125.5, 117.9, 115.1, 99.0, 95.4, 73.8, 58.4, 58.1, 56.5; HRMS (EI) *m/z* calcd for $C_{12}H_{17}O_5Br$ (M^+) 320.0259, found 320.0248.

Arene 82. To a solution of methyl ether **81** (1.70 g, 5.3 mmol) in THF (20 mL) at –78 ^{o}C was added *n*-BuLi (2.5 mL, 2.3 M in Hex) over 5 min. After an additional 5 min, geranyl bromide (2.00 g, 9.2 mmol) was added dropwise over 5 min. The solution was keep cold for 1 hr and then it was allowed to warm slowly to rt. After 18 hr the reaction was quenched by addition of water, the resulting solution was extracted with EtOAc, and

the combined organic extracts were washed with brine. After the organic phase was dried ($MgSO_4$), and concentrated in vacuo, final purification by column chromatography (10% EtOAc in Hex) afforded arene **82** (1.65 g, 83%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 6.98 (s, 1H), 6.81 (s, 1H), 5.32 (t, *J* = 7.1 Hz, 1H), 5.18 (s, 2H), 5.11 – 5.01 (m, 1H), 5.10 (s, 2H), 4.34 (s, 2H), 3.58 (s, 3H), 3.48 (s, 3H), 3.43 (d, *J* = 7.2 Hz, 2H) 3.34 (s, 3H), 2.12 – 2.03 (m, 4H), 1.73 (s, 3H), 1.71 (s, 3H), 1.56 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 149.5, 144.0, 135.9, 135.7, 134.0, 131.0, 124.1, 122.4, 121.1, 113.3, 98.8, 94.9, 74.3, 57.8, 57.1, 55.9, 39.4, 28.2, 26.4, 25.4, 17.4, 15.9; HRMS (EI) *m/z* calcd for $C_{22}H_{34}O_5$ (M^+) 378.2406, found 378.2418.

Epoxide 83. To a solution of arene **82** (5.40 g, 14.3 mmol) and Shi catalyst (**75**, 1.05 mg, 3.75 mmol) in aq buffer (120 mL, 2 M K_2CO_3 and 4 mM EDTA) and organic phase (200 mL, 2:1:1 CH_2Cl_2/MeCN/EtOH) on ice was added hydrogen peroxide (8.0 mL, 30%) over 16 hr by syringe pump (0.5 mL/hr). After addition of peroxide was complete, the reaction was quenched by addition of Na_2SO_3. The resulting solution was extracted with EtOAc, and the combined organic phases were washed with brine. After the organic phase was dried ($MgSO_4$) and concentrated in vacuo, final purification by column chromatography (25% EtOAc in Hex) afforded recovered starting material (1.8 g, 33%) and epoxide **7** (3.47 g, 62%, 90% ee based on HPLC analysis of compound **83** derived from this material) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 6.95 (s, 1H), 6.77 (s, 1H), 5.33 (t, *J* = 7.1 Hz, 1H), 5.16 (s, 2H), 5.06 (s, 2H), 4.31 (s, 2H), 3.55 (s, 3H), 3.56 (s, 3H), 3.41 (d, *J* = 7.1 Hz, 2H), 3.33 (s, 3H), 2.68 (t, *J* = 6.2 Hz, 1H), 2.18 – 2.10 (m, 2H), 1.70 (s, 3H), 1.67 – 1.54 (m, 2H), 1.27 (s, 3H), 1.23 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 149.5, 144.0, 135.5, 135.0, 134.0, 123.0, 122.1, 113.3, 98.9, 94.8, 74.3, 63.9, 58.1, 57.9, 57.3, 56.0, 36.2, 28.3, 27.2, 24.6, 18.5, 16.0; HRMS (EI) *m/z* calcd for $C_{22}H_{34}O_6$ (M^+) 394.2355, found 394.2362.

Hexahydroxanthenes 84 and 86. To a solution of epoxide **83** (206 mg, 0.52 mmol) in CH_2Cl_2 (180 mL) at –78 ^oC was added $BF_3 \cdot OEt_2$ (0.4 mL, 3.2 mmol). After 8 min the reaction was quenched by addition of TEA (0.75 mL, 5.4 mmol). The resulting solution was concentrated in vacuo, extracted with EtOAc, and the combined organic extracts were washed with 1N HCl followed by brine. The organic phase was dried ($MgSO_4$), and concentrated in vacuo. Final purification of the residue by column chromatography (50% EtOAc in Hex) afforded acetal **86** (41 mg, 20%) along with alcohol **84** (68 mg, 37%), both as yellow oils. For alcohol **84**: ^1H NMR ($CDCl_3$) δ 6.91 (s, 1H), 6.76 (s, 1H), 5.17 (d, *J* = 6.3 Hz, 1H), 5.13 (d, *J* = 6.5 Hz, 1H), 4.30 (s, 2H), 3.49 (s, 3H), 3.34 (s, 3H), 3.38–3.30 (m, 1H), 2.70 (m, 2H), 2.08–1.57 (m, 6H), 1.20 (s, 3H), 1.05 (s, 3H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 145.7, 143.5, 129.0, 123.3, 123.0, 115.6, 95.8, 77.7, 76.7, 74.6, 57.9, 56.1, 46.6, 38.2, 37.7, 28.1, 27.2, 23.1, 19.7, 14.2; HRMS (EI) *m/z* calcd for $C_{20}H_{30}O_5$ (M^+) 350.2093, found 350.2098.

For Acetal 86: ^1H NMR ($CDCl_3$) δ 6.92 (s, 1H), 6.78 (s, 1H), 5.19 (d, *J* = 6.5 Hz, 1H), 5.15 (d, *J* = 6.5 Hz, 1H), 4.77 (d, *J* = 6.8 Hz, 1H), 4.64 (d, *J* = 6.7 Hz, 1H), 4.31 (s, 2H), 3.50 (s, 3H), 3.39 (s, 3H), 3.36 (s, 3H), 3.27 (dd, *J* = 11.2, 3.9 Hz, 1H), 2.70 (m, 2H), 2.10 – 1.55 (m, 5H), 1.22 (s, 3H), 1.08 (s, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 145.8, 142.9, 129.2, 123.3, 123.1, 115.5, 96.1, 95.9, 84.0, 76.6, 74.7, 58.0, 56.2, 55.6, 47.0, 38.2, 37.6, 27.3, 25.2, 23.1, 19.8, 15.1; HRMS (EI) *m/z* calcd for $C_{22}H_{34}O_6$ (M^+) 394.2355, found 394.2348.

Preparation of acetal 86 from alcohol 84. To a solution of compound **84** (35 mg, 0.1 mmol) in CH_2Cl_2 (5 mL) at rt was added DIPEA (0.2 mL, 1.2 mmol) followed by MOMCl (0.08 mL, 1.1 mmol). After 3 hr, the reaction was quenched by addition of water. The resulting solution was extracted with CH_2Cl_2, and the combined organic extracts were washed with 1N HCl followed by brine. After the organic phase was dried

($MgSO_4$) and concentrated in vacuo, final purification by column chromatography (35% EtOAc in Hex) afforded acetal **86** (35 mg, 89%) as a colorless oil. This material was identical to that obtained during the cyclization described above by comparison of the ^1H NMR spectra.

Preparation of alcohol 84 from acetal 86. To a solution of compound **86** (23 mg, 0.06 mmol) in MeOH (1 mL) at rt was added TsOH (63 mg, 0.2 mmol). After 72 hr, the reaction was quenched by addition of $NaHCO_3$ and the resulting solution was extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The oil was dissolved in acetone (1 mL) and solid K_2CO_3 (73 mg, 0.45 mmol) was added followed by MOMCl (0.05 mL, 0.3 mmol). After 2 hr, the reaction was quenched by addition of water. The resulting solution was extracted with EtOAc, and the combined organic phases were washed with brine. After the organic phase was dried ($MgSO_4$) and concentrated in vacuo, final purification by column chromatography (25% EtOAc in Hex) compound **84** (15 mg, 73%) as a yellow oil. This material was identical to the material prepared by cyclization of epoxide **83** based on comparison of the ^1H NMR spectra.

Aldehyde 85. To a solution of compound **84** (21 mg, 0.06 mmol) in CH_2Cl_2 (5 mL) and water (0.5 mL) at rt was added DDQ (31 mg, 0.14 mmol). After 10 min the reaction was quenched by addition of $NaHCO_3$ and the resulting solution was extracted with CH_2Cl_2. The combined organic extracts were washed with water (1mL) followed by brine. The organic phase then was dried ($MgSO_4$) and concentrated in vacuo to afford compound **85** (20 mg, 97%), which was used in the next step without further purification. This material was identical to material prepared via other methods based on comparison of the ^1H NMR and ^{13}C NMR spectra.

Aldehyde 87. According to the method described above for preparation of aldehyde **85**, compound **86** (14 mg, 0.35 mmol) was treated with DDQ (17 mg, 0.06 mmol) in CH_2Cl_2 (1 mL), and water (0.2 mL) at rt for 17 min. Standard work up afforded aldehyde **87** (12 mg, 97%), which was used without further purification. This material was identical to the material prepared via other methods based on comparison of the ^{1}H NMR spectra.

Ketone 96. To a solution of tricycle **77** (119 mg, 0.28 mmol) in CH_2Cl_2 at rt was added TPAP (9 mg, 0.03 mmol) and NMO (49 mg, 0.41 mmol). After 18.5 hr the reaction mixture was diluted with EtOAc, filtered through celite, and concentrated in vacuo. Final purification by column chromatography (2:3 Hex/EtOAc) afforded ketone **96** (117 mg, 99%) as a colorless oil: $[\alpha]^{26.4}_D$ = +92º (c 1.1, CH_3OH, 92% ee by HPLC); ^{1}H NMR ($CDCl_3$) δ 6.72 (s, 1H), 6.70 (s, 1H), 4.34 (s, 2H), 3.85 (s, 3H), 3.39 (s, 3H), 2.81 (dd, *J* = 16.0, 13.6 Hz, 1H), 2.73 – 2.63 (m, 2H), 2.48 (ddd, *J* = 18.5, 4.7, 3.2 Hz, 1H), 2.37 (ddd, *J* = 13.1, 5.7, 3.2, 1H), 2.16 (dd, *J* = 14.4, 4.7 Hz, 1H), 2.07 (dd, *J* = 13.0, 4.9 Hz, 1H), 1.43 (s, 3H), 1.20 (s, 3H), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 213.6, 148.8, 141.8, 129.6, 121.5, 121.0, 109.2, 75.6, 74.8, 58.0, 55.9, 47.4, 46.4, 38.0, 35.2, 24.5, 23.7, 20.8, 19.0; HRMS (EI) *m/z* calcd for $C_{19}H_{26}O_4$ (M^+) 318.1831, found 318.1812.

Silyloxy Ketone 97. To a solution of ketone **96** (42 mg, 0.13 mmol) in CH_2Cl_2 at rt was added TEA (0.1 mL, 0.72 mmol) followed by TBSOTf (0.06 mL, 0.26 mmol). After 1.5 hr at rt, *m*CPBA (223 mg, 70%, 0.90 mmol) was added. After an additional 17 hr, the reaction mixture was quenched by addition of $NaHCO_3$, extracted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography (3:1 Hex/EtOAc) afforded silyloxy ketone **97** (5 mg, 9%): ^{1}H NMR ($CDCl_3$) δ 6.73 (s, 1H), 6.69 (s, 1H), 4.55 (dd, *J* = 13.5, 5.8 Hz, 1H), 4.35 (s, 2H), 3.86 (s, 3H), 3.39 (s, 3H), 2.82 (dd, *J* = 16.0, 13.2 Hz, 1H), 2.70 – 2.63 (m, 2H), 2.22 (dd,

J = 13.2, 13.2 Hz, 1H), 2.03 (dd, *J* = 13.0, 5.0 Hz, 1H), 1.54 (s, 3H), 1.25 (s, 3H), 1.16 (s, 3H), 0.91 (s, 9H), 0.17 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 211.5, 149.0, 141.5, 129.8, 121.3, 121.0, 109.3, 75.2, 74.8, 71.0, 58.0, 56.0, 47.9, 47.8, 45.8, 25.7 (3C), 24.5, 23.8, 21.1, 20.1, 18.6, -4.7, -5.7; HRMS (EI) *m/z* calcd for $C_{25}H_{40}O_5Si$ (M^+) 448.2645, found 448.2640.

Acidic Tricycle 99. To a solution of tricyclic ketone **96** (84 mg, 0.26 mmol) in *t*–BuOH was added *t*-BuOK (1.11 g, 9.9 mmol). This solution was heated in an oil bath to 40 ^{o}C and a stream of air was introduced to the vigorously stirred solution. After 40 min the reaction was quenched by addition of 1N HCl. The resulting solution was extracted with EtOAc, and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography (6:1 $CHCl_3$/MeOH) afforded acid **98** (78 mg, 85%) as colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.72 (s, 1H), 6.68 (s, 1H), 4.36 (s, 2H), 3.84 (s, 3H), 3.38 (s, 3H), 2.98 (d, *J* = 13.8, 1H), 2.74 – 2.52 (m, 2H), 2.24 (d, *J* = 13.8, 1H), 2.14 (dd, *J* = 13.5, 4.8, 1H), 1.38 (s, 3H), 1.08 (s, 3H), 1.00 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 179.4, 149.2, 143.4, 129.0, 122.5, 122.0, 109.4, 84.3, 81.2, 74.8, 57.8, 55.8, 52.4, 49.0, 45.4, 27.2, 24.1, 20.0, 19.4.

Enone 100. To a solution of ketone **96** (152 mg, 0.48 mmol) in ethanol at rt was added benzaldehyde (0.2 mL, 1.7 mmol) followed by KOH (209 mg, 3.7 mmol). After 2 hr the reaction was quenched by addition of NH_4Cl, the resulting solution was extracted with EtOAc, and the combined organic extract was washed with brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Final purification of the residue by column chromatography (3:1 Hex/EtOAc) afforded enone **100** (194 mg, 100%) as colorless oil: $[\alpha]^{26.4}_D$ = +201º (c 1.0, $CHCl_3$, 92% ee by HPLC); ^{1}H NMR ($CDCl_3$) δ 7.63 (d, *J* = 3.2 Hz, 1H), 7.45 – 7.33 (m, 5H), 6.74 (d, *J* = 1.2 Hz, 1H), 6.71 (m, 1H), 4.35 (s, 2H), 3.39 (s, 3H), 3.55 (d, *J* = 15.6 Hz, 1H), 3.39 (s, 3H), 3.00 (dd, *J* = 15.6 Hz, 2.8 Hz,

1H), 2.81 – 2.71 (m, 2H), 2.35 (dd, *J* = 12.4 Hz, 5.2 Hz, 1H), 1.32 (s, 3H), 1.21 (s, 3H), 1.17 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 205.0, 148.5, 141.5, 138.6, 135.0, 132.3, 130.0 (2C), 129.5, 128.6, 128.3 (2C), 121.2, 120.8, 109.3, 75.4, 74.6, 57.8, 55.9, 45.9, 45.3, 41.7, 28.7, 24.2, 22.3, 19.0; HRMS (EI) *m/z* calcd for $C_{26}H_{30}O_4$ (M^+) 406.2144, found 406.2135.

Acetal 101. To a solution of enone **100** (128 mg, 0.32 mmol) in 1,4-dioxane/water (4 mL, 3:1) at rt was added 2,6-lutidine (0.1 mL, 0.86 mmol), OsO_4 (0.6 mL, 0.02M in ^{t}BuOH, 0.01mmol), and $NaIO_4$ (335 mg, 1.6 mmol). After 10 min the black solution had turned white and after 18 hrs additional 1,4-dioxane/water (4 mL, 3:1) was added. After an additional 4 hr the mixture was diluted with EtOAc and water, the phases were[158] separated and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification of the residue by column chromatography (2:1 Hex/EtOAc) afforded acetal **101** (57 mg, 53%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 6.73 (s, 1H), 6.68 (s, 1H), 5.81 (s, 1H), 4.35 (s, 2H), 3.83 (s, 3H), 3.37 (s, 3H), 2.76 – 2.72 (m, 2H), 2.06 (dd, *J* = 11.6, 5.6 Hz, 1H), 1.64 (bd, 1H), 1.41 (s, 3H), 1.15 (s, 3H), 1.13 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.4, 149.2, 141.3, 130.3, 121.5, 121.1, 109.8, 102.1, 101.3, 76.9, 74.4, 58.0, 56.0, 41.0, 38.3, 22.2, 22.1, 17.5, 14.7; HRMS (EI) *m/z* calcd for $C_{19}H_{24}O_7$ (M^+) 364.1522, found 364.1516.

Alcohol 102. To a solution of ketone **100** (1.75 g, 4.3 mmol) in CH_3OH at rt was added $CeCl_3 \cdot 7H_2O$ (1.81 g, 4.9 mmol) followed by $NaBH_4$ (300 mg, 7.9 mmol). After 20 min, the reaction was quenched by addition of water and concentrated in vacuo. The resulting solution was extracted with EtOAc, and the combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo, to afford alcohol **102** (1.75 g, 100%) as white crystals. This material was used in the next step without further

purification: $[\alpha]^{26.4}_D$ = +45.3º (c 1.0, $CHCl_3$, 92% ee by HPLC); ^{1}H NMR ($CDCl_3$) δ 7.33 – 7.21 (m, 5H), 6.77 (s, 1H), 6.68 – 6.67 (m, 2H), 4.32 (s, 2H), 3.91 (s, 1H), 3.81 (s, 3H), 3.39 (s, 3H), 3.36 (d, *J* = 7.2 Hz, 1H), 2.72 – 2.60 (m, 2H), 2.29 (d, *J* = 12.8 Hz, 1H), 1.90 (dd, *J* = 11.6 Hz, 5.6 Hz, 1H), 1.19 (s, 3H), 1.04 (s, 3H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.7, 142.2, 138.2, 137.4, 129.2, 128.8 (2C), 128.2 (2C), 126.4, 124.0; 122.2, 121.3, 109.1, 80.0, 78.1, 74.9, 58.0; 55.9; 47.2; 41.2; 39.7; 27.3; 23.2; 19.8; 14.2; HRMS (EI) *m/z* calcd for $C_{26}H_{32}O_4$ (M^+) 408.2301, found 408.2295. Images of the NOESY and COSY spectra have been included at the end of the apendix.

MOM-Arene 103. To a solution of alcohol **102** (236 mg, 0.58 mmol) in CH_2Cl_2 at rt was added DIPEA (0.4 mL, 2.3 mmol) followed by MOMCl (0.1 mL, 1.3 mmol). After 15 hr, the reaction was quenched by addition of water. The resulting solution was extracted with CH_2Cl_2, and the combined organic phases were washed with 1N HCl followed by brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (4:1 Hex/EtOAc) afforded recovered starting material (42 mg, 18%) and the MOM acetal **103** (262 mg, 68%) as a colorless oil: $[\alpha]^{26.4}_D$ = +21.7º (c 1.1, $CHCl_3$, 92% ee by HPLC); ^{1}H NMR ($CDCl_3$) δ 7.34 – 7.19 (m, 5H), 6.68 – 6.67 (m, 3H), 4.78 (d, *J* = 6.8 Hz, 1H), 4.70 (d, *J* = 7.2 Hz, 1H), 4.33 (s, 2H), 3.99 (d, *J* = 1.2 Hz, 1H), 3.82 (s, 3H), 3.45 (s, 3H), 3.40 (d, *J* = 10.8 Hz, 1H), 3.38 (s, 3H), 2.73 – 2.67 (m, 2H), 2.29 (d, *J* = 12.4 Hz, 1H), 1.95 (dd, *J* = 12.4, 5.6 Hz, 1H), 1.21 (s, 3H), 1.01 (s, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.7, 142.2, 137.3, 135.1, 129.3, 128.8 (2C), 128.2 (2C), 126.4, 124.9, 122.3, 121.2, 109.0; 96.2, 85.6, 78.2, 74.8, 58.0, 56.4, 55.9, 47.4, 41.4, 39.6, 27.3, 23.2, 19.6, 15.0; HRMS (EI) *m/z* calcd for $C_{28}H_{36}O_5$ (M^+) 452.2563, found 452.2561.

Ketone 104. To a solution of compound **103** (35 mg, 0.08 mmol) in acetone was added $NaHCO_3$ (14 mg, 0.17 mmol) followed by $KMnO_4$ (23 mg, 0.15 mmol). After 20

hours at rt, additional $NaHCO_3$ (70 mg, 0.83 mmol) and $KMnO_4$ (20 mg, 0.13 mmol) was added. After an additional 24 hr at rt, the reaction mixture was filtered through celite, washed with acetone, and concentrated in vacuo. Final purification by column chromatography (3:1 Hex/EtOAc) afforded recovered starting material (8 mg, 23%) and ketone **103** (19 mg, 65%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.73 (s, 1H), 6.71 (s, 1H), 4.73 (d, *J* = 7.2 Hz, 1H), 4.70 (d, *J* = 7.2 Hz, 1H), 4.36 (s, 2H), 4.14 (s, 1H), 3.86 (s, 3H), 3.44 (s, 3H), 3.40 (s, 3H), 3.00 – 2.78 (m, 4H), 2.34 (dd, *J* = 12.4, 5.6 Hz, 1H), 1.26 (s, 3H), 1.21 (s, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 206.4, 150.0, 142.8, 131.2, 122.9, 122.2, 110.5, 97.4, 87.4, 79.6, 75.9, 59.2, 57.8, 57.4, 55.0, 48.4, 42.0, 28.3, 24.4, 21.8, 16.8; HRMS (EI) *m/z* calcd for $C_{21}H_{30}O_6$ (M^+) 378.2049, found 378.2042.

Diol 105. To a solution of enone **103** (1.05 mg, 2.32 mmol) in 1,4-dioxane/water (10 mL, 3:1) at rt was added 2,6-lutidine (0.60 mL, 5.2 mmol), OsO_4 (3.5 mL, 0.02M in ^{t}BuOH, 0.07 mmol), and $NaIO_4$ (3.2 mg, 15 mmol). After 10 min the black solution had turned white and after 23 hrs the mixture was diluted with EtOAc and water, the phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification of the residue by column chromatography (3:1 Hex/EtOAc) afforded ketone **104** (245 mg, 34%) and diol **105** white solid (291 mg, 26%): ^{1}H NMR ($CDCl_3$) δ 7.49 (d, *J* = 7.2 Hz, 2H), 7.35 – 7.26 (m, 3H), 6.66 – 6.64 (m, 2H), 5.01 (d, *J* = 1.6 Hz, simplifies to s upon D_2O exchange, 1H), 4.90 (d, *J* = 6.4 Hz, 1H), 4.77 (d, *J* = 6.0 Hz, 1H), 4.32 (s, 2H), 4.23 (d, *J* = 2.4 Hz, exchanges with D_2O, 1H), 3.76 (s, 3H), 3.61 (s, 1H), 3.53 (s, 3H), 3.36 (s, 3H), 3.26 (s, exchanges with D_2O, 1H), 2.72 – 2.67 (m, 2H), 2.23 (d, *J* = 15.3 Hz, 1H), 2.15 (dd, *J* = 12.4, 5.6 Hz, 1H), 1.74 (d, *J* = 15.2 Hz, 1H), 1.33 (s, 3H), 1.22 (s, 3H), 1.12 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.6, 141.9, 139.2, 129.1 (2C), 129.0, 128.2 (2C), 127.9, 122.2, 121.1, 109.1, 100.7, 92.7, 77.1, 76.8, 75.7, 74.8, 57.9, 56.8,

55.8, 46.0, 44.0, 37.9, 31.1, 23.3, 22.0, 18.6; HRMS (EI) *m/z* calcd for $C_{28}H_{38}O_7$ (M^+) 486.2618, found 486.2612.

Alcohol 106. To a solution of ketone **104** (18 mg, 0.05 mmol) in CH_3OH at rt was added $NaBH_4$ (24 mg, 0.66 mmol). After 10 min, the reaction was quenched by addition of water and concentrated in vacuo. The resulting solution was extracted with EtOAc, and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. This afforded alcohol **106** (18 mg, 100%) as white solid, which was used in the subsequent step without further purification: $[\alpha]^{26.4}_D$ = +22.2º (c 1.1, CH_3OH, 92% ee by HPLC); ^1H NMR ($CDCl_3$) δ 6.70 (s, 1H), 6.68 (s, 1H), 4.82 (d, *J* = 6.4 Hz, 1H), 4.70 (d, *J* = 7.2 Hz, 1H), 4.34 (s, 2H), 4.31 (ddd, *J* = 3.2, 3.2, 3.2 Hz, 1H), 3.85 (s, 3H), 3.45 (s, 3H), 3.38 (s, 3H), 3.26 (d, *J* = 3.2 Hz, 1H), 2.77 – 2.60 (m, 2H), 2.54 (dd, *J* = 14.0, 3.6 Hz, 1H), 2.36 (br, 1H), 1.96 (dd, *J* = 14.4, 3.6 Hz, 1H), 1.77 (dd, J = 12.8, 5.2 Hz, 1H), 1.45 (s, 3H), 1.10 (s, 3H), 1.04 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.9, 141.8, 129.1, 122.6, 121.2, 109.2, 96.9, 84.9, 76.2, 74.9, 68.7, 57.9, 56.1, 56.0, 47.1, 42.3, 37.8, 28.7, 22.9, 21.4, 16.6; HRMS (EI) *m/z* calcd for $C_{21}H_{32}O_6$ (M^+) 380.2199, found 380.2183.

Aldehyde 107. To a solution of methyl ether **106** (50 mg, 0.13 mmol), in CH_2Cl_2/water (4:1) at rt was added DDQ (34 mg, 0.15 mmol). After 80 min the reaction was quenched by addition of brine and $NaHCO_3$. The resulting solution was extracted with CH_2Cl_2, and the combined organic phases were washed with a small amount of water followed by brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Aldehyde **107** (48 mg, 100%) was obtained as a faintly yellow wax that was used without further purification: $[\alpha]^{26.4}_D$ = +41.6º (c 1.0, CH_3OH, 92% ee by HPLC); ^1H NMR ($CDCl_3$) δ 9.80 (s, 1H), 7.25 (s, 1H), 7.24 (s, 1H), 4.83 (d, *J* = 6.6 Hz, 1H), 4.73 (d, *J* = 6.6 Hz, 1H), 4.32 (ddd, *J* = 3.6, 3.6, 3.6 Hz, 1H), 3.90 (s, 3H), 3.47 (s, 3H), 3.27 (d, *J*

= 3.6 Hz, 1H), 2.86 – 2.79 (m, 2H), 2.59 (dd, *J* = 14.4, 3.6 Hz, 1H), 2.39 (br, 1H), 1.98 (dd, *J* = 14.4, 3.6 Hz, 1H), 1.79 (dd, *J* = 13.2, 5.4 Hz, 1H), 1.49 (s, 3H), 1.13 (s, 3H), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 191.0, 149.7, 148.5, 128.8, 127.2, 122.7, 107.5, 97.0, 84.7, 78.0, 68.6, 56.2, 56.1, 46.9, 42.1, 38.0, 28.8, 22.9, 21.8, 16.7; HRMS (EI) *m/z* calcd for $C_{20}H_{28}O_6$ (M^+) 364.1886, found 364.1896.

Stilbene 108. To a solution of aldehyde **107** (23 mg, 0.063 mmol) and phosphonate **22**[30] (50 mg, 0.1 mmol) in THF at rt was added 15-crown-5 (0.01 mL) followed by NaH (44 mg, 60% in oil, 1.1 mmol). After 3.5 hr the reaction was quenched by addition of water, the resulting solution was extracted with EtOAc, and the combined organic phases were washed with brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Final purification by preparative thin layer chromatography (2:8 Hex/EtOAc) afforded stilbene **108** (31 mg, 71%) as a yellow wax: ^{1}H NMR ($CDCl_3$) δ 6.97 – 6.86 (m, 6H), 5.22 (s, 4H), 5.23 – 5.22 (m, 1H), 5.07 – 5.06 (m, 1H), 4.83 (d, *J* = 6.4 Hz, 1H), 4.72 (d, *J* = 6.8 Hz, 1H), 4.32 (ddd, *J* = 3.2, 3.2, 3.2 Hz, 1H), 3.90 (s, 3H), 3.50 (s, 6H), 2.46 (s, 3H), 3.40 (d, *J* = 7.2 Hz, 2H), 3.27 (d, *J* = 2.8 Hz, 1H), 2.79 – 2.74 (m, 2H), 2.56 (dd, J = 14.4, 3.2 Hz, 1H), 2.36 (bd, 1H), 2.06 – 1.94 (m, 5H), 1.79 (s, 3H), 1.81 – 1.77 (m, 1H), 1.65 (s, 3H), 1.57 (s, 3H), 1.47 (s, 3H), 1.12 (s, 3H), 1.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.9 (2C), 149.0, 142.3, 136.7, 134.6, 131.2, 128.9, 128.3, 126.4, 124.4, 122.8, 122.6, 120.5, 119.5, 107.0 (2C), 106.0, 96.9, 94.5 (2C), 84.9, 76.5, 68.7, 56.1 (2C), 56.0, 55.9, 47.2, 42.3, 39.8, 37.9, 28.8, 26.7, 25.6, 23.0, 22.7, 21.5, 17.6, 16.7, 16.1; HRMS (EI) *m/z* calcd for $C_{41}H_{58}O_9$ (M^+) 694.4081, found 694.4077.

Schweinfurthin B (9). To a solution of compound **108** (12 mg, 0.017 mmol), in CH_3OH was added TsOH (24 mg, 0.13 mmol) and the resultinh solution was stirred at rt. After 46 hr, the reaction was quenched by addition of $NaHCO_3$ and concentrated in vacuo. The resulting solution was extracted with EtOAc, and the combined organic

phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. After final purification by preparative thin layer chromatography (1:9 Hex/EtOAc), schweinfurthin B (**9**, 5.3 mg, 55%) was obtained as colorless wax: $[\alpha]^{26.4}_D$ = +40º (c 0.41, EtOH, 92% ee by HPLC); lit[25] $[\alpha]^{26.4}_D$ = +45º (c 1.0, EtOH); the ^1H and ^{13}C NMR spectra were found to be identical to the literature spectra.[25] HRMS (EI) *m/z* calcd for $C_{35}H_{46}O_6$ (M^+) 562.3294, found 562.3287.

Stilbene 109. To a solution of aldehyde **107** (21 mg, 0.058 mmol) and phosphonate **108**[65] (38 mg, 0.09 mmol) in THF (5 mL) at rt was added 15-crown-5 (0.01 mL) followed by NaH (60 mg, 60% in oil, 1.5 mmol), and after 4 hr the reaction was quenched by addition of water. The resulting solution was extracted with EtOAc, and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography (3:7 Hex/EtOAc) afforded stilbene **109** (26 mg, 72%) as a white wax: ^1H NMR ($CDCl_3$) δ 6.97 – 6.87 (m, 6H), 5.21 (s, 4H), 5.24 – 5.19 (m, 1H), 4.83 (d, *J* = 6.8 Hz, 1H), 4.72 (d, *J* = 6.8 Hz, 1H), 4.31 (ddd, *J* = 3.2, 3.2, 3.2 Hz, 1H), 3.90 (s, 3H), 3.50 (s, 6H), 3.46 (s, 3H), 3.39 (d, *J* = 7.2 Hz, 2H), 3.27 (d, *J* = 3.2 Hz, 1H), 2.80 – 2.74 (m, 2H), 2.56 (dd, *J* = 14.4, 3.2 Hz, 1H), 2.36 (bd, 1H), 1.98 (dd, *J* = 14.4, 3.2 Hz, 1H), 1.81 – 1.77 (m, 1H), 1.79 (s, 3H), 1.66 (s, 3H), 1.48 (s, 3H), 1.12 (s, 3H), 1.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.5, 155.8 (2C), 149.0, 142.3, 136.7, 131.0, 128.9, 128.3, 126.4, 122.8, 120.4, 119.4, 107.0, 105.9 (2C), 96.9, 94.5 (2C), 84.9, 76.5, 68.7, 56.1, 56.0, 56.0 (2C), 47.2, 42.3, 37.9, 28.8, 25.8, 22.9, 22.8, 21.5, 17.7, 16.6; HRMS (EI) *m/z* calcd for $C_{36}H_{50}O_9$ (M^+) 626.3455, found 626.3466.

Schweinfurthin E (13). Stilbene **109** was treated with TsOH in CH_3OH as described for compound **108**. After standard workup and final purification by preparative thin layer chromatography (1:9 Hex/EtOAc), schweinfurthin E (**13**, 7.6 mg, 81%) was obtained as colorless oil: $[\alpha]^{26.4}_D$ = +41º (c 0.67, CH_3OH; 92% ee by HPLC); lit[65] $[\alpha]^{26.4}_D$

= +49.2º (c 0.13, CH_3OH); the ^1H and ^{13}C NMR spectra were identical to literature spectra.[65] HRMS (EI) *m/z* calcd for $C_{30}H_{38}O_6$ (M^+) 494.2668, found 494.2670.

Triol 110. To a solution of alcohol **102** (158 mg, 0.39 mmol) in dioxane (2 mL) and water (0.5 mL), catalytic OsO_4 (0.2 mL, 0.02 M in ^tBuOH, 0.004 mmol, 1 mol%) was added followed by NMO (73 mg, 0.63 mmol) at rt. After 17 hr, water was added and the resulting solution was extracted with EtOAc. The combined organic phase was washed with brine and dried ($MgSO_4$) and concentrated in vacuo to afford triol **110** (170 mg, 100%) as a crystalline solid which was used without further purification: ^1H NMR ($CDCl_3$) δ 7.43 – 7.40 (m, 2H), 7.26 – 7.20 (m, 3H), 6.59 (s, 1H), 6.57 (s, 1H), 4.99 (s, 1H), 4.24 (s, 2H), 3.66 (s, 3H), 3.56 (s, 1H), 3.29 (s, 3H), 2.61 (d, *J* = 8.8 Hz, 2H), 2.14 (d, *J* = 14.4 Hz, 1H), 1.89 (t, *J* = 9.0 Hz, 1H), 1.67 (d, *J* = 14.4 Hz, 1H), 1.18 (s, 3H), 1.06 (s, 3H), 0.97 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.5, 141.6, 139.4, 129.1 (2C), 128.8, 128.1 (2C), 128.0, 122.3, 121.1, 108.9, 84.2, 77.5, 76.8, 75.2, 74.7, 57.8, 55.6, 45.7, 45.2, 37.6, 30.2, 23.1, 21.6, 16.7; HRMS (EI) *m/z* calcd for $C_{26}H_{34}O_6$ (M^+) 442.2355, found 442.2351.

Ketone 111. To a solution of diol **110** (170 mg, 0.39 mmol) in CH_2Cl_2 (5 mL) and water (0.5 mL) $NaIO_4$ (530 mg, 2.4 mmol) was added at rt. After 18 hr, excess water was added and the resulting solution was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (40% EtOAc in Hex) afforded ketone **111** (53 mg, 45%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 6.72 (s, 1H), 6.70 (s, 1H), 4.34 (s, 2H), 4.03 (s, 1H), 3.84 (s, 3H), 3.44 (s, 1H), 3.38 (s, 3H), 3.06 – 2.97 (m, 2H), 2.87 – 2.73 (m, 2H), 2.33 – 2.30 (m, 1H), 1.25 (s, 3H), 1.20 (s, 3H), 0.73 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 207.5, 148.7, 141.3, 130.0, 121.8, 120.9, 109.1, 82.4, 78.7, 74.6, 58.0, 55.8, 52.4, 46.2,

41.4, 27.2, 23.1, 20.9, 15.0; HRMS (EI) *m/z* calcd for $C_{19}H_{26}O_5$ (M^+) 334.1780, found 334.1784.

Diol 112. To a solution of ketone **111** (51 mg, 0.15 mmol) in CH_3OH (2 mL), $NaBH_4$ (25 mg, 0.66 mmol) was added at rt. After 30 min, the reaction was quenched with 1N HCl and the resulting solution was extracted with EtOAc. The combined organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to afford diol **112** (43 mg, 84%) as colorless oil: ^{1}H NMR (CD_3OD + $CDCl_3$) δ 6.50 (s, 1H), 6.49 (s, 1H), 4.15 (s, 2H), 3.96 (brd s, 1H) 3.66 (s, 3H), 3.17 (s, 3H), 3.09 (br, 1H), 2.57 – 2.52 (m, 2H), 2.22 (d, *J* = 14 Hz, 1H), 1.75 (d, *J* = 13.6 Hz, 1H), 1.53 (dd, *J* = 13.0, 5.6 Hz, 1H), 1.21 (s, 3H), 0.88 (s, 3H), 0.86 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.2, 141.4, 128.3, 122.4, 121.2, 108.8, 77.1, 76.3, 74.4, 70.0, 57.2, 56.3, 46.6, 42.9, 37.5, 28.3, 22.5, 20.8, 15.3; HRMS (EI) *m/z* calcd for $C_{19}H_{28}O_5$ (M^+) 336.1937, found 333.1940.

Aldehyde 113. To a solution of diol **112** (40 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) and water (0.5 mL) DDQ (52 mg, 0.23 mmol) was added at rt. After 30 min, the reaction was quenched by addition of aqueous $NaHCO_3$ and the resulting solution was extracted with CH_2Cl_2, washed with brine. The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo to afford aldehyde **113** (26 mg, 68%) as yellow oil: ^{1}H NMR ($CDCl_3$) δ 9.78 (s, 1H), 7.25 (s, 1H), 7.23 (s, 1H), 5.29 (s, 1H), 4.26 (ddd, *J* = 3.2, 3.2, 3.2 Hz, 1H), 3.89 (s, 3H), 3.38 (d, *J* = 3.2 Hz, 1H), 2.89 – 2.78 (m, 2H), 2.45 (dd, J = 14.0, 3.2 Hz, 1H), 2.46 (brd, 1H), 2.01 (dd, *J* = 14.0, 3.2 Hz, 1H), 1.76 (dd, *J* = 12.4, 5.6 Hz, 1H), 1.47 (s, 3H), 1.12 (s, 3H), 1.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 192.4, 150.6, 149.5, 129.7, 128.5, 123.8, 108.4, 79.2, 71.6, 57.1, 47.7, 44.3, 39.2, 30.0, 24.0, 22.8, 17.1; ^{13}C NMR (CD_3OD) δ 193.1, 150.8, 149.9, 130.0, 128.4, 124.4, 108.6, 79.5, 78.5, 71.5, 56.3, 48.1, 44.5, 39.1, 29.3, 23.8, 22.2, 16.6; HRMS (EI) *m/z* calcd for $C_{18}H_{24}O_5$ (M^+) 320.1624, found 320.1629.

Benzyl Alcohol 130. To a solution of aldehyde **129** (128 mg, 0.57 mmol) in THF (12 mL) at rt was added 15-crown-5 (0.01 mL), diethyl 4-nitrobenzylphosphonate (**123**, 203 mg, 0.74 mmol), followed by NaH (220 mg, 5.5 mmol, 60% in oil), which resulted in the rapid appearance of a maroon color. After 8 min, the reaction was quenched by slow addition of water. The resulting solution was extracted with EtOAc, and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography (6:4 Hex/THF) afforded compound **130** (191 mg, 98%) as an orange solid: ^{1}H NMR δ 8.20 – 8.18 (m, 2H), 7.64 – 7.61 (m, 4H), 6.80 (s, 1H), 6.69 (s, 1H), 5.29 (s, 2H), 4.70 (s, 2H), 3.94 (s, 3H), 3.53 (s, 3H); ^{13}C NMR δ 159.2, 156.6, 145.9, 142.9, 129.8, 126.6 (2C), 124.5, 124.3, 124.0 (2C), 113.8, 105.5, 103.1, 94.8, 65.2, 56.4, 55.8; HRMS (EI) calcd for $C_{18}H_{19}NO_6$ (M^+) 345.1212 found 345.1216.

Phosphonate 131. To a solution of benzyl alcohol **130** (193 mg, 0.56 mmol) in THF at rt was added TEA (0.2 mL, 1.4 mmol) followed by MsCl (0.1 mL, 1.3 mmol). After 50 min, the reaction was quenched by addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried ($MgSO_4$), and concentrated in vacuo. This material was used immediately without further purification. The residue from the above step was dissolved in anhydrous acetone (8 mL) and NaI (210 mg, 1.4 mmol) was added at rt in the dark. After 1 h, the reaction was quenched by addition of water, the resulting solution was extracted with EtOAc, and was washed with brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo in the dark. This material was used immediately in the next step without further purification. The residue from the above step was dissolved in DMF (3 mL), $P(OEt)_3$ (0.4 mL, 2.3 mmol) was added, and the mixture was heated to 115 ºC. After 17 h, an additional portion of $P(OEt)_3$ (0.4 mL, 2.3 mmol) was added. The reaction was allowed to cool to rt after an additional 3.5 h and concentrated in vacuo. Final purification by column chromatography (1% MeOH, 20%

Hex, 79% EtOAc) afforded the desired phosphonate **131** (245 mg, 95% over 3 steps) as a bright yellow oil: ^{1}H NMR δ 8.20 – 8.17 (m, 2H), 7.63 – 7.61 (m, 4H), 6.75 (s, 1H), 6.63 (s, 1H), 5.27 (s, 2H), 4.11 – 4.01 (m, 4H), 3.92 (s, 3H), 3.51 (s, 3H), 3.13 (d, J_{HP} = 22 Hz, 2H), 1.28 (t, J = 7.1 Hz, 6H); ^{13}C NMR δ 158.8 (d, J_{CP} = 3.8 Hz), 156.4 (d, J_{CP} = 3.4 Hz), 146.3, 146.0, 133.5 (d, J_{CP} = 9.1 Hz), 129.7, 126.6 (2C), 124.5 (d, J_{CP} = 1.8 Hz), 124.0 (2C), 123.0, 109.1 (d, J_{CP} = 7.1 Hz), 106.5 (d, J_{CP} = 6.6 Hz), 94.9, 62.2, 62.1, 56.1 (d, J_{CP} = 34 Hz, 2C), 34.5 (d, J_{CP} = 138 Hz), 16.4 (d, J_{CP} = 6.0 Hz, 2C); ^{31}P NMR δ 26.3; HRMS (EI) calcd for $C_{22}H_{28}NO_8P$ (M^+) 465.1553 found 465.1552.

Protected stilbene 132. To a solution of aldehyde **79** (80 mg, 0.26 mmol) and phosphonate **131** (100 mg, 0.25 mmol) in THF at rt was added 15-crown-5 (0.01 mL) followed by NaH (63 mg, 1.6 mmol, 60% in oil), and after 75 min the reaction was quenched by addition of water. The resulting solution was extracted with EtOAc and the combined organic phases were washed with brine. After the organic phase was dried ($MgSO_4$) and concentrated in vacuo, final purification by column chromatography (1:1 Hex/EtOAc) afforded recovered phosphonate **131** (12 mg, 12%) and compound **132** (94 mg, 71%) as an orange solid: ^{1}H NMR δ 8.22–8.18 (m, 2H), 7.67 – 7.63 (m, 4H), 7.09 – 7.04 (m, 1H), 6.97 – 6.90 (m, 4H), 6.78 – 6.74 (m, 1H), 5.36 (s, 2H), 4.00 (s, 3H), 3.92 (s, 3H), 3.58 (s, 3H), 3.48 – 3.44 (m, 1H), 2.78 – 2.73 (m, 2H), 2.19 – 2.13 (m, 1H), 1.92 – 1.82 (m, 2H), 1.73 – 1.54 (m, 3H), 1.28 (s, 3H), 1.13 (s, 3H), 0.91 (s, 3H); ^{13}C NMR δ 159.1, 156.8, 149.0, 146.2, 146.1, 143.0, 139.1, 129.8, 129.4, 128.4, 126.5 (2C), 125.8, 124.6, 124.0 (2C), 122.7, 120.9, 113.8, 106.9, 105.4, 102.4, 94.8, 77.9, 77.2, 56.4, 56.0, 55.8, 46.7, 38.4, 37.6, 28.2, 27.3, 23.1, 19.8, 14.3; HRMS (EI) calcd for $C_{36}H_{41}NO_8$ (M^+) 615.2832, found 615.2837.

Nitro schweinfurthin 133. To a solution of compound **132** (16 mg, 0.03 mmol), in CH_3OH (2.5 mL) and EtOAc (0.5 mL) was added $TsOH{\cdot}H_2O$ (32 mg, 0.16 mmol).

After 24 h, the reaction was quenched by addition of $NaHCO_3$ and concentrated in vacuo. The resulting solution was extracted with EtOAc, and the combined organic phase was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography (1:1 Hex/EtOAc) afforded compound **133** (13 mg, 85%) as a dark orange solid: UV (EtOH) λ_{max} (log ε) 429 (4.25); λ_{em} 557; ^{1}H NMR δ 8.20 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 16.8 Hz, 1H), 7.54 (d, *J* = 16.8 Hz, 1H), 7.01 (d, *J* = 16.0 Hz, 1H), 6.89 (s, 1H), 6.88 (s, 1H), 6.85 (d, *J* = 16.0 Hz, 1H), 6.65 (s, 1H), 6.63 (s, 1H), 5.50 (br d, 1H), 3.97 (s, 3H), 3.91 (s, 3H), 3.46 – 3.44 (m, 1H), 2.75 – 2.72 (m, 2H), 2.17 – 2.14 (m, 2H), 1.90 – 1.69 (m, 4H), 1.27 (s, 3H), 1.11 (s, 3H), 0.90 (s, 3H); ^{13}C NMR δ 159.2, 155.0, 149.0, 146.3, 145.5, 143.1, 139.1, 129.9, 129.2, 128.4, 126.6 (2C), 125.4, 124.8 124.0 (2C), 122.7, 120.9, 111.8, 106.9, 106.5, 101.5, 78.0, 77.7, 56.0, 55.8, 46.7, 38.4, 37.6, 28.3, 27.3, 23.1, 19.9, 14.3; HRMS (EI) *m/z* calcd for $C_{34}H_{37}NO_7$ (M^+) 571.2570, found 571.2567.

Compound 134. To a solution of aldehyde **107** (25 mg, 0.07 mmol) and phosphonate **131** (50 mg, 0.11 mmol) in THF (4 mL) at rt was added 15-crown-5 (0.01 mL) followed by NaH (51 mg, 1.3 mmol, 60% in oil). After 35 min, the reaction was quenched by addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (4:6 Hex/EtOAc) afforded compound **134** (36 mg, 78%) as an orange solid: ^{1}H NMR δ 8.19 (d, *J* = 8.8 Hz, 2H), 7.66 – 7.62 (m, 4H), 7.06 (d, *J* = 16.4 Hz, 1H), 6.96 (s, 1H), 6.95 – 6.90 (m, 3H), 6.77 (s, 1H), 5.35 (s, 2H), 4.83 (d, *J* = 6.8 Hz, 1H), 4.73 (d, *J* = 6.8 Hz, 1H), 4.32 (ddd, *J* = 3.2, 3.2, 3.2 Hz, 1H), 3.99 (s, 3H), 3.92 (s, 3H), 3.57 (s, 3H), 3.47 (s, 3H), 3.28 (d, *J* = 3.6 Hz, 1H), 2.81 – 2.75 (m, 2H), 2.57 (dd, *J* = 14.2, 3.0 Hz, 1H), 2.34 (br d, 1H), 1.98 (dd, *J* = 14.0, 2.8 Hz, 1H), 1.80 (dd, *J* = 12.5, 5.2 Hz, 1H), 1.49 (s, 3H), 1.12 (s, 3H), 1.10 (s, 3H); ^{13}C NMR δ 159.1, 156.8, 149.0, 146.1, 146.1, 142.6, 139.1, 129.8, 129.3, 128.4, 126.5 (2C), 125.8, 124.6, 124.0 (2C), 122.8,

120.8, 113.7, 106.8, 105.3, 102.4, 96.8, 94.8, 84.7, 76.6, 68.6, 56.3, 56.1, 55.9, 55.7, 47.0, 42.2, 37.8, 28.7, 22.9, 21.5, 16.6; HRMS (EI) *m/z* calcd for $C_{38}H_{45}NO_{10}$ (M^+) 675.3043, found 675.3040.

Compound 135. According to the procedure for compound **132**, compound **134** (16 mg, 0.024 mmol), in CH_3OH and EtOAc was treated with $TsOH \cdot H_2O$ (60 mg, 0.32 mmol) and after final purification by column chromatography (3:7 Hex/EtOAc) afforded schweinfurthin **135** (10 mg, 71%) as a dark orange wax: ^{1}H NMR δ 8.20 (d, *J* = 8.8 Hz, 2H), 7.67 – 7.61 (m, 3H), 7.55 (d, *J* = 16.4 Hz, 1H), 7.01 (d, *J* = 16.0 Hz, 1H), 6.89 (s, 1H), 6.88 (s, 1H), 6.85 (d, *J* = 16.0 Hz, 1H), 6.64 (s, 2H), 4.26 (ddd, *J* = 3.2, 3.2, 3.2 Hz, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 3.39 (d, *J* = 3.6 Hz, 1H), 2.82 – 2.76 (m, 2H), 2.52 (dd, *J* = 14.4, 2.8 Hz, 1H), 2.30 (dd, *J* = 14.4, 3.2 Hz, 1H), 1.79 (dd, *J* = 12.8, 5.2 Hz, 1H), 1.47 (s, 3H), 1.13, (s, 3H), 1.09 (s, 3H); ^{13}C NMR δ 159.2, 155.3, 149.0, 146.2, 145.7, 142.6, 139.1, 129.8, 129.2, 128.4, 126.6 (2C), 125.5, 124.8, 124.0 (2C), 122.9, 120.9, 111.9, 107.0, 106.5, 101.4, 77.5, 76.8, 70.7, 56.0, 55.8, 46.8, 43.3, 38.0, 28.9, 23.0, 21.6, 16.0; HRMS (EI) *m/z* calcd for $C_{34}H_{37}NO_8$ (M^+) 587.2519, found 587.2518.

Stilbene 137. To a solution of 3,4-dimethoxybenzaldehyde (**136**, 50 mg, 0.26 mmol) and phosphonate **131** (100 mg, 0.25 mmol) in THF (4 mL) at rt was added 15-crown-5 (0.01 mL) followed by NaH (57 mg, 1.4 mmol, 60% in oil), and after 65 min the reaction was quenched by addition of water. The resulting solution was extracted with EtOAc, and the combined organic phases were washed with brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (3:1 Hex/EtOAc to EtOAc) afforded recovered phosphonate **131** (27 mg, 27%) and compound **137** (94 mg, 71%) as an orange solid: ^{1}H NMR δ 8.19 (d, *J* = 8.8 Hz, 2H), 7.66 (s, 2H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.11 – 7.07 (m, 3H), 6.96 (s, 1H), 6.96 (s, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.78 (s, 1H), 5.34 (s, 2H), 3.99 (s, 3H), 3.96 (s,

3H), 3.91 (s, 3H), 3.56 (s, 3H); ^{13}C NMR δ 159.1, 156.8, 149.1, 149.0, 146.1, 146.1, 138.9, 129.9, 129.5, 129.5, 126.6 (2C), 126.3, 124.6, 124.0 (2C), 120.2, 113.9, 111.1, 108.5, 105.4, 102.4, 94.8, 56.4, 55.9, 55.8, 55.7; HRMS (EI) *m/z* calcd for $C_{27}H_{27}NO_7$ (M^+) 477.1788, found 477.1771.

Compound 138. To a solution of compound **137** (20 mg, 0.042 mmol), in CH_3OH (4 mL) and EtOAc (2 mL) was added $TsOH \cdot H_2O$ (54 mg, 0.28 mmol) and the solution was stirred at rt. After 18.5 h, the reaction was quenched by addition of $NaHCO_3$ and concentrated in vacuo. The resulting solution was extracted with EtOAc, and the combined organic phases were washed with brine. After the organic phase was dried ($MgSO_4$) and concentrated in vacuo, final purification by column chromatography (6:4 Hex/EtOAc to 4:6 Hex/EtOAc) afforded compound **138** (16 mg, 88%) as a dark orange solid: UV (EtOH) λ_{max} (log ε) 431 (4.39); λ_{em} 579; ^{1}H NMR ($(CD_3)_2CO$) δ 8.22 (d, *J* = 9.2 Hz, 2H), 7.81 (s, 2H), 7.76 (d, *J* = 9.2 Hz, 2H), 7.25 (d, *J* = 2.0 Hz, 1H), 7.19 (d, *J* = 16.0 Hz, 1H), 7.00 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.04 (d, *J* = 16.4 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 1.2 Hz, 1H), 6.81 (d, *J* = 1.2 Hz, 1H), 4.00 (s, 3H), 3.87 (s, 3H), 3.83 (3H); ^{13}C NMR ($(CD_3)_2CO$) δ 160.5, 158.1, 150.7, 150.6, 147.4, 147.1, 140.3, 131.2, 130.3, 129.3, 127.4 (2C), 127.1, 126.0, 124.8 (2C), 121.1, 112.7, 110.4, 107.6, 104.5, 101.5, 56.2, 56.1, 56.1; HRMS (EI) *m/z* calcd for $C_{25}H_{23}NO_6$ (M^+) 433.1525, found 433.1522.

Protected amine 139. To a solution of compound **132** (33 mg, 0.05 mmol) in acetone (3 mL) was added sat. NH_4Cl (1 mL) followed by Zn^0 dust (67 mg, 1.0 mmol) and the mixture was heated to reflux. After 70 min, the solution was allowed to cool and decanted into a separatory funnel. The resulting solution was extracted with EtOAc, and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography (4:6 Hex/EtOAc to 99:1

EtOAc/MeOH) afforded amine **139** (25 mg, 80%) as an orange oil: ^{1}H NMR δ 7.51 (d, *J* = 16.4 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 16.4 Hz, 1H), 7.01 (d, *J* = 16.4 Hz, 1H), 6.92 – 6.88 (m, 4H), 6.76 (d, *J* = 0.8 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 2H), 5.30 (s, 2H), 3.94 (s, 3H), 3.90 (s, 3H), 3.54 (s, 3H), 3.42 (dd, *J* = 11.8, 4.0 Hz, 1H), 2.72 (m, 2H), 2.16 – 2.11 (m, 1H), 1.88 – 1.81 (m, 3H), 1.73 – 1.60 (m, 2H), 1.25 (s, 3H), 1.10 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 158.4, 156.0, 148.9, 145.6, 142.6, 136.8, 132.4, 129.9, 128.7, 128.5, 127.5 (2C), 126.2, 122.6, 120.6, 116.3, 115.7, 115.1 (2C), 106.7, 105.9, 102.7, 94.9, 77.9, 77.0, 56.2, 55.9, 55.7, 46.7, 38.3, 37.6, 28.2, 27.3, 23.1, 19.8, 14.3; HRMS (EI) *m/z* calcd for $C_{36}H_{43}NO_6$ (M^+) 585.3090, found 585.3088.

Amine 140. To a solution of amine **139** (22 mg, 0.036 mmol), in CH_3OH (2 mL) and EtOAc (0.5 mL) was added $TsOH \cdot H_2O$ (43 mg, 0.13 mmol). After 23 h, the reaction was quenched by addition of $NaHCO_3$ and concentrated in vacuo. The resulting solution was extracted with EtOAc, and the combined organic phases were washed with brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. This afforded schweinfurthin **140** (20 mg, 100%) without further purification as a dark orange solid: UV (EtOH) λ_{max} (log ε) 377 (4.53); λ_{em} 493; ^{1}H NMR δ 7.33 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 16.8 Hz, 1H), 7.12 (d, *J* = 16.8 Hz, 1H), 6.95 (d, *J* = 16.8 Hz, 1H), 6.87 – 6.81 (m, 3H), 6.67 – 6.65 (m, 3H), 6.59 (s, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.41 (dd, *J* = 11.8, 3.4 Hz, 1H), 2.71 (m, 2H), 2.14 – 2.10 (m, 1H), 1.87 – 1.83 (m, 2H), 1.71 – 1.58 (m, 2H), 1.24 (s, 3H), 1.09 (s, 3H), 0.87 (s, 3H); ^{13}C NMR δ 159.5, 155.6, 150.0, 147.0, 143.8, 138.4, 133.3, 130.1, 129.9, 129.8, 128.7 (2C), 127.3, 123.8, 121.8, 117.9, 116.3 (2C), 114.4, 108.1, 107.7, 102.2, 79.0, 78.2, 57.1, 56.8, 47.8, 39.4, 38.7, 29.3, 28.4, 24.2, 20.9, 15.3; HRMS (EI) *m/z* calcd for $C_{34}H_{39}NO_5$ (M^+) 541.2828, found 541.2835.

Amine 141. According to the procedure described for compound **139**, compound **134** (16 mg, 0.024 mmol), sat. NH_4Cl (1 mL) and Zn^0 dust (26 mg, 0.4 mmol) gave after

final purification by column chromatography (4:6 Hex/EtOAc to 99:1 EtOAc/MeOH) amine **141** (12 mg, 80%) as an orange oil: ^{1}H NMR δ 7.52 (d, *J* = 16.8 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 16.0 Hz, 1H), 7.01 (d, *J* = 16.0 Hz, 1H), 6.93 – 6.88 (m, 4H), 6.76 (s, 1H), 6.70 (d, 8.0 Hz, 2H), 5.30 (s, 2H), 4.84 (d, *J* = 6.8 Hz, 1H), 4.73 (d, *J* = 6.8 Hz, 1H), 4.32 (ddd, *J* = 2.8, 2.8, 2.8 Hz, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.55 (s, 3H), 3.47 (s, 3H), 3.28 (d, *J* = 2.8 Hz, 1H), 2.84 – 2.71 (m, 2H), 2.57 (dd, *J* = 13.6, 2.4 Hz, 1H), 1.98 (dd, *J* = 11.2, 2.6 Hz, 1H), 1.80 (dd, *J* = 12.6, 5.0 Hz, 1H), 1.49 (s, 3H), 1.12 (s, 3H), 1.10 (s, 3H); ^{13}C NMR δ 158.5, 156.1, 149.1, 145.2, 142.5, 136.9, 132.4, 130.4, 128.8, 128.7, 127.6 (2C), 126.3, 122.8, 120.6, 116.6, 115.8, 115.5 (2C), 107.0, 106.0, 102.8, 96.9, 95.0, 84.9, 76.5, 68.7, 56.3, 56.1, 56.0, 55.8, 47.2, 42.3, 37.9, 28.8, 23.0, 21.6, 16.7; HRMS (EI) *m/z* calcd for $C_{38}H_{47}NO_8$ (M^+) 645.3302, found 645.3312.

Amine 142. According to the procedure for compound **140**, compound **141** (11 mg, 0.017 mmol), in CH_3OH was treated with $TsOH{\cdot}H_2O$ (25 mg, 0.13 mmol), and gave after final purification by column chromatography (EtOAc) schweinfurthin **142** (9 mg, 95%) as a dark orange wax: UV (EtOH) λ_{max} (log ε) 375 (4.63); λ_{em} 481; ^{1}H NMR (CD_3OD) δ 7.50 (d, *J* = 16.4 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 16.4 Hz, 1H), 7.01 – 6.88 (m, 4H), 6.69 (d, *J* = 8.4 Hz, 2H), 6.66 (d, *J* = 1.2 Hz, 1H), 6.64 (s, 1H), 4.14 (ddd, *J* = 3.6, 3.6, 3.6 Hz, 1H), 3.91 (s, 3H), 3.85 (s, 3H), 3.30 (obscured by solvent, 1H), 2.78 – 2.76 (m, 2H), 2.35 (dd, *J* = 13.8, 3.0 Hz, 1H), 1.92 (dd, *J* = 13.4, 3.0 Hz, 1H), 1.73 (dd, *J* = 11.8, 6.2 Hz, 1H), 1.41 (s, 3H), 1.10 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (CD_3OD) δ 160.1, 157.4, 150.3, 147.9, 143.6, 138.3, 131.3, 130.6, 129.5, 128.1 (2C), 127.4, 124.4, 122.0, 117.5, 116.7 (2C), 115.8, 114.6, 108.5, 107.5, 101.9 78.8, 78.1, 71.8, 56.5, 56.2, 48 (obscured by solvent), 44.8, 39.2, 29.4, 24.0, 22.0, 16.6; HRMS (EI) *m/z* calcd for $C_{34}H_{39}NO_6$ (M^+) 557.2777, found 557.2784.

Compound 143. According to the procedure described for compound **139**, compound **137** (20 mg, 0.04 mmol), sat. NH_4Cl (1 mL), and Zn^0 dust (30 mg, 0.46 mmol) gave after final purification by column chromatography (4:6 Hex/EtOAc) amine **143** (12 mg, 67%) as orange solid: ^{1}H NMR δ 7.53 (d, *J* = 16.8 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 16.8 Hz, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 7.06 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.04 (d, *J* = 16.4 Hz, 1H), 6.94 (d, *J* = 1.2 Hz, 1H), 6.93 (d, *J* = 16.4 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.77 (d, *J* = 0.8 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 2H), 5.31 (s, 2H), 3.96 (s, 3H), 3.95 (s, 3H), 3.91 (s, 3H), 3.55 (s, 3H); ^{13}C NMR δ 158.4, 156.0, 149.0, 148.9, 145.7, 136.6, 132.5, 130.3, 129.9, 128.3, 127.6 (2C), 126.8, 119.9, 116.3, 115.8, 115.2 (2C), 111.1, 108.5, 106.0, 102.7, 94.9, 56.3, 55.9, 55.8, 55.7; HRMS (EI) *m/z* calcd for $C_{27}H_{29}NO_5$ (M^+) 447.0246, found 447.2051.

Compound 144. According to the procedure described for compound **140,** compound **143** (10 mg, 0.02 mmol), in CH_3OH and EtOAc was treated with $TsOH{\cdot}H_2O$ (60 mg, 0.31 mmol), and after final purification by column chromatography (4:6 Hex/EtOAc) afforded compound **144** (8 mg, 89%) as a dark orange solid: UV (EtOH) λ_{max} (log ε) 377 (4.63); λ_{em} 512; ^{1}H NMR ($(CD_3)_2CO$) δ 7.56 (d, *J* = 16.8 Hz, 1H), 7.29 – 7.22 (m, 3H), 7.10 – 6.92 (m, 6H), 6.76 (d, *J* = 2.8 Hz, 1H), 6.65 (d, *J* = 8.4 Hz, 2H), 4.69 (brd, 1H), 3.92 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H); ^{13}C NMR ($(CD_3)_2CO$) δ 159.6, 156.9, 150.6, 150.4, 148.7, 137.6, 132.8, 131.5, 129.3, 128.9, 128.0 (2C), 127.5, 120.8, 116.4, 115.3 (2C), 112.8, 110.3, 107.7, 104.5, 101.6, 56.1, 56.1, 56.0; HRMS (EI) *m/z* calcd for $C_{25}H_{25}NO_4$ (M^+) 403.1784, found 403.1779.

Compound 168. To a solution of arene **51** (6.2 g, 15.9 mmol) in THF (75 mL) at –78 ^{o}C was added *n*-BuLi (10 mL, 2.3 M in Hex). After 30 min neryl bromide (3.80 g, 17.5 mmol) was added via syringe. The solution was allowed to warm to rt and after 17.5 hr, the reaction was quenched by the addition of water. The resulting solution was

extracted with EtOAc and the combined organic phases were washed with brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (25:1 to 9:1 Hex/EtOAc) afforded compound **168** (4.78 g, 67%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.81 (s, 1H), 6.75 (s, 1H), 5.37 (t, *J* = 7.2 Hz, 1H), 5.20 – 5.15 (m, 1H), 5.10 (s, 2H), 4.70 (s, 2H), 3.84 (s, 3H), 3.61 (s, 3H), 3.45 (d, *J* = 7.0 Hz, 2H), 2.20 – 2.09 (m, 4H), 1.77 (s, 3H), 1.70 (s, 3H), 1.64 (3H), 0.98 (s, 9H), 0.13 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 151.6, 142.3, 136.9, 135.8, 135.1, 131.1, 123.9, 123.0, 118.5, 107.4, 98.5, 64.4, 57.0, 55.2, 31.7, 27.8, 26.3, 25.6 (3C), 25.3, 23.1, 18.0, 17.3, –5.6 (2C); HRMS (EI) *m/z* calcd for $C_{26}H_{44}O_4Si$ (M^+) 448.3009, found 448.3008.

Diol 169. To a solution of AD-mix-α (1.45 g) and methanesulfonamide (110 mg) in water/t-BuOH (1:1, 20 mL) was added diene **168** (475 mg, 1.06 mmol). After 18 hr, the reaction was quenched by addition of $NaSO_3$ and the resulting solution was washed with water, extracted with EtOAc and the combined organic layers were washed with brine. The resulting organic phase was dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (3:2 Hex/EtOAc) afforded the diol **169** (364 mg, 71%) as a yellow oil: $[\alpha]^{26.4}_D$ = – 5.35 (c 1.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.77 (d, *J* = 1.8 Hz, 1H), 6.73 (d, *J* = 1.9 Hz, 1H), 5.38 (t, *J* = 3.8 Hz, 1H), 5.07 (s, 2H), 4.67 (s, 2H), 3.82 (s, 3H), 3.59 (s, 3H), 3.42 (d, *J* = 9.0 Hz, 2H), 3.32 – 3.27 (m, 1H), 2.71 (br, 1H, exchanges with D_2O), 2.37 – 2.21 (m, 3H, 2H upon exchange with D_2O), 1.73 (d, *J* = 1.3 Hz, 3H), 1.64 – 1.54 (m, 1H), 1.42 – 1.31 (m, 1H), 1.16 (s, 3H), 1.11 (s, 3H), 0.94 (s, 9H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 154.6, 145.1, 140.2, 138.8, 138.1, 126.7, 121.5, 110.5, 101.7, 80.7, 75.6, 67.4, 60.3, 58.3, 32.3, 31.5, 30.8, 28.9, 28.6 (3C), 26.1, 25.9, 21.1, -2.5 (2C); HRMS (ESI) *m/z* calcd for $C_{26}H_{46}O_6NaSi$ (M^++Na) 505.2961, found 505.2973.

(*S,S*)-Mandelate Ester 171. To a solution of diol **169** (520 mg, 1.08 mmol) in CH_2Cl_2 (10 mL) was added EDC (357 mg, 1.86 mmol), DMAP (186 mg, 1.51 mmol), and (*S*)-(+)-α methoxyphenylacetic acid (**170**, 244 mg, 1.47 mmol). After 4 hr, the reaction mixture was quenched by addition of water, extracted with CH_2Cl_2, and the extract was washed with brine. The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (9:1 to 1:1 Hex/EtOAc) afforded the ester **171** (430 mg, 63%) as a clear oil and the (*R,S*) diastereomer **171** (46 mg, 8%) as a yellow oil. For ester **(*S, S*)-171**: ^{1}H NMR ($CDCl_3$) δ 7.49–7.31 (m, 5H), 6.79 (d, *J* = 1.9 Hz, 1H), 6.67 (d, *J* = 1.9 Hz, 1H), 5.31 (t, *J* = 6.3 Hz, 1H), 5.07 (s, 2H), 4.85–4.79 (m, 2H), 4.67 (s, 2H), 3.83 (s, 3H), 3.57 (s, 3H), 3.41 (s, 3H), 3.36 (d, *J* = 7.2 Hz, 2H), 2.10–2.03 (m, 2H), 1.75 – 1.58 (m, 2H), 1.7 (s, 3H), 0.95 (s, 9H), 0.92 (s, 3H), 0.90 (s, 3H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 170.2, 151.6, 142.2, 137.0, 136.2, 135.1, 134.8 (2C), 128.6, 128.4, 126.9 (2C), 123.5, 118.4, 107.5, 98.5, 82.1, 80.5, 71.8, 64.3, 57.1, 56.9, 55.2, 28.2, 27.7, 27.6, 25.6 (3C), 25.3, 24.3, 23.1, 18.0, –5.6 (2C); HRMS (EI) *m/z* calcd for $C_{35}H_{54}O_8Si$ (M^+) 630.3588, found 630.3575.

For (*R,S*)-Mandelate Ester 171: ^{1}H NMR ($CDCl_3$) δ 7.52 – 7.24 (m, 5H), 6.78 (d, *J* = 1.8 Hz, 1H), 6.56 (d, *J* = 1.8 Hz, 1H), 5.08 (t, *J* = 7.1, Hz, 1H), 5.04 (s, 2H), 4.83 – 4.81 (m, 2H), 4.65 (s, 2H), 3.82 (s, 3H), 3.57 (s, 3H), 3.42 (s, 3H), 3.13 (d, brd, *J* = 5.3 Hz, 1H), 1.85 – 1.77 (m, 2H), 1.57 – 1.48 (m, 2H), 1.41 (s, 3H) 1.16 (s, 3H), 1.15 (s, 3H), 0.94 (s, 9H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 170.6, 151.6, 142.2, 136.9, 135.9, 134.8, 134.6, 128.5, 128.3 (2C), 126.7 (2C), 123.6, 118.7, 107.5, 98.5, 82.3, 80.5, 72.0, 64.4, 57.1, 57.0, 55.2, 27.8, 27.7, 27.7, 26.0, 25.6 (3C), 24.5, 22.9, 18.0, –5.59 (2C); HRMS (EI) *m/z* calcd for $C_{35}H_{54}O_8{}^{28}Si$ (M^+) 630.3588, found 630.3597.

(–)-(*S*)-Diol 169. To a solution of ester **171** (430 mg, 0.68 mmol) in ethanol (15 mL) was added NaOH (0.46 mL, 3N, 1.38 mmol). After 4.5 hr water (2 mL) was added

and after an additional 2.5 hr the reaction was quenched by addition of HCl (1.4 mL, 1N, 1.4 mmol). The resulting solution was washed with water, extracted with EtOAc, and the extract was washed with brine. The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (1:1 Hex/EtOAc) afforded the diol **17** (269 mg, 82%) as a clear oil: $[\alpha]^{26.4}_D = -5.45^o$ (c 1.4, $CHCl_3$). The ^1H NMR spectrum was identical to that of the enantioenriched material given above.

Epoxide 172. An ice cold solution of the (*S*)-(–)-diol **169** (324 mg, 0.68 mmol) in CH_2Cl_2 (10 mL) was treated with triethylamine (0.3 mL, 2.2 mmol), and after 5 min mesyl chloride (0.06 mL, 0.8 mmol) was added. The resulting solution was allowed to warm to rt after 1 hr and a suspension of K_2CO_3 (1.03 g, 7.3 mmol) in MeOH (10 mL) was added. The reaction was quenched after 20 hr by addition of water, the resulting solution was filtered, washed with water, extracted with EtOAc and, the organic extracts were washed with brine. The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (4:1 Hex/EtOAc) afforded the epoxide **172** (223 mg, 72%) as a clear oil. The ^1H NMR spectrum matched that of epoxide **172** prepared via a different method.

Neryl- 4-Nitrobenzoate (176). To a solution of nerol (5.18 g, 32.5 mmol) in THF (75 mL) was added *p*-nitrobenzoyl chloride (8.14 g, 43.9 mmol) and pyridine (3.1 mL, 39 mmol) at rt. After 15 hr, additional pyridine (1 mL, 12 mmol) and p-nitrobenzoyl chloride (0.75 g, 4.0 mmol) was added. After 2 hr at rt, the reaction was quenched by addition of water and the resulting solution was extracted with EtOAc and washed with brine. The combined organic phase was dried ($MgSO_4$) and concentrated. Purification by recrystalization afforded yellow crystals of the desired ester **176** (9.43 g, 95%): ^1H NMR ($CDCl_3$) δ 8.26 – 8.18 (m, 4H), 5.48 (t, J = 6.9 Hz, 1H), 5.10 (t, J = 7.1 Hz, 1H), 4.84 (d, J = 7.3 Hz, 2H), 2.22–2.08 (m, 4H), 1.80 (s, 3H), 1.65 (s 3H), 1.59 (s, 3H); ^{13}C

NMR ($CDCl_3$) δ 164.6, 150.3, 143.6, 135.8, 130.6 (2C), 123.4 (2C), 123.3, 118.5, 62.4, 32.1, 26.5, 25.6, 23.5, 17.6.

(*R*)-6'-Epoxy-Neryl-4-Nitrobenzoate (177). To a solution of ester **176** (4.97 g, 16.4 mmol) and Shi catalyst **75** (1.31 g, 4.85 mmol) in acetonitrile (20 mL) and aqueous buffer (9 mL of 2 M K_2CO_3 and 4 mM EDTA), hydrogen peroxide (8 mL, 30%, 75 mmol) was added over 48 hr at –15 ^oC. The reaction was quenched after an additional 24 hr by addition of $NaSO_3$ and the resulting solution was extracted with EtOAc, and washed with brine. The combined organic phase was dried ($MgSO_4$) and concentrated. Final purification by column chromatography (8:1 to 2:1 Hex/EtOAc) afforded the epoxide **177** (1.4 g, 23%) as pale yellow crystals: ^1H NMR ($CDCl_3$) δ 8.28 – 8.17 (m, 4H), 5.53 (t, *J* = 7.3 Hz, 1H), 4.88 (d, *J* = 7.3 Hz, 2H), 2.72 (t, *J* = 6.3 Hz, 1H), 2.35 (td, *J* = 7.0 Hz, 2.5 Hz, 2H), 1.82 (s, 3H), 1.70 –1.63 (m, 2H), 1.29 (s, 3H), 1.26 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.6, 150.2, 142.7, 135.8, 130.7 (2C), 123.4 (2C), 119.2, 63.6, 62.2, 58.3, 28.9, 27.5, 24.8, 23.4, 18.7. Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63. Found: C, 63.82; H, 6.62.

(*R*)-6,7-Epoxynerol (178). To a solution of ester **177** (0.99 g, 3.09 mmol) in MeOH (20 mL) and Hex (2 mL) was added tetrabutylamonium iodide (1.18 g, 3.19 mmol), and After 10 min, sodium methoxide (1.21 g, 22.4 mmol) was added. The reaction was quenched after 3 hr by addition of water and the resulting solution was extracted with EtOAc and washed with brine. The combined organic phase was dried ($MgSO_4$) and concentrated. Final purification by column chromatography (4:1 to 1:1 Hex/EtOAc) afforded the epoxide **12** (430 mg, 81%) as a clear oil: $[\alpha]^{26.4}_D$ = +19.4º (c 2.2, $CHCl_3$). (92% ee based on the literature rotation of $[\alpha]^{25}_D$ = 14.7º (c 1.6, $CHCl_3$) for material of 70% ee).[18] The ^1H NMR spectrum matched literature data.

(*R*)-6,7-Epoxynerol Bromide (179). Triethylamine (0.75 mL, 5.38 mmol) was added to a solution of alcohol **178** (400 mg, 2.35 mmol) in THF (10 mL) in an ice bath. After 10 min, mesyl chloride (0.33 mL, 3.38 mmol) was added and the solution was stirred for 1.5 hr. Solid LiBr (0.28 g, 3.22 mmol) was added and after an additional hr the reaction was washed with water, extracted with Hex, filtered through basic alumina, dried ($MgSO_4$), and concentrated in vacuo. Bromo epoxide **179** was used in the next step without further purification.

Epoxide 172. To a solution of arene **51** (5.50 g, 14.1 mmol) in THF (75 mL) at –40^oC was added *n*-BuLi (6.0 mL, 2.5 M in Hex). After 30 min, CuBr as its DMS complex (3.38 g, 16 mmol) was added, and after an additional 50 min bromide **13** (2.90 g, 12.4 mmol) was added via canula. After 15 hr, the reaction was quenched by the addition of water. The resulting solution was extracted with EtOAc, and the combined organic phases were washed with brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (9:1 to 6:1 Hex/EtOAc) afforded compound **172** (3.76 g, 65%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ ^{1}H NMR ($CDCl_3$) δ 6.78 (s, 1H), 6.71 (s, 1H), 5.36 (t, *J* = 7.2 Hz, 1H), 5.07 (s, 2H), 4.67 (s, 2H), 3.82 (s, 3H), 3.58 (s, 3H), 3.43 (d, *J* = 7.4 Hz, 2H) 2.74 (t, *J* = 6.6 Hz, 1H), 2.39 – 2.25 (m, 2H), 1.76 (s, 3H), 1.76 – 1.52 (m, 2H), 1.30 (s, 3H), 1.27 (s, 3H), 0.94 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 152.0, 142.6, 137.4, 135.2, 135.0, 124.0, 118.8, 107.9, 98.5, 64.7, 64.0, 58.3, 57.4, 55.6, 28.5, 28.1, 27.4, 25.9 (3C), 24.9, 23.4, 18.7, 18.4, –5.3 (2C); HRMS (EI) *m/z* calcd for $C_{26}H_{44}O_5Si$ (M^+) 464.2958, found 464.2961.

Tricycle 173. To a solution of epoxide **172** (125 mg, 0.27 mmol) in CH_2Cl_2 (40 mL) at –78 ^oC was added $BF_3{\cdot}OEt_2$ (0.17 mL, 1.4 mmol). After 15 min the reaction was quenched by addition of TEA (0.4 mL, 2.9 mmol) and concentrated in vacuo. The residue was dissolved in EtOAc and washed with water, 1N HCl, and brine. The organic

phase was then dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (7:3 Hex/EtOAc) afforded tricycle **173** (23 mg, 21%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.69 (s, 1H), 6.62 (s, 1H), 4.64 (s, 2H), 3.83 (s, 3H), 3.49 (br, 1H), 3.07 (dd, *J* = 17.9, 8.1 Hz, 1H), 2.66 (d, *J* = 17.9 Hz, 1H), 2.31 – 2.20 (m, 1 H), 2.07 – 1.93 (m, 3H), 1.86 (d, *J* = 7.9 Hz, 1H), 1.24 (s, 3H), 1.04 (s, 3H), 0.94 (s, 9H), 0.67 (s, 3H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 149.0, 142.8, 132.4, 122.6, 118.8, 108.0, 76.4, 75.6, 65.3, 56.3, 38.5, 38.1, 32.0, 27.2, 26.8, 26.2 (3C), 25.2, 23.4, 22.2, 18.6, –5.0 (2C); HRMS (EI) *m/z* calcd for $C_{24}H_{40}O_4Si$ (M^+) 420.2696, found 420.2702.

Diol 176. To a solution of TBS ether **173** (136 mg, 0.32 mmol) in THF (10 mL) at rt was added TBAF (0.4 mL, 1M in THF). After 2 hr the reaction was quenched by addition of water. The resulting solution was extracted with EtOAc, and the combined organic phases were washed with brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (1:1 Hex/EtOAc) afforded compound **176** (69 mg, 71%) as a crystalline solid: ^{1}H NMR (MeOD) δ 6.70 (s, 1H), 6.65 (s, 1H), 4.43 (s, 2H), 3.76 (s, 3H), 3.33 (br, 1H), 2.97 (dd, *J* = 17.2, 8.2 Hz, 1H), 2.70 (d, *J* = 17.7 Hz, 1H), 2.20 – 2.08 (m, 1H), 2.03 – 1.91 (m, 1H), 1.82 – 1.78 (m, 2H), 1.52 – 1.47 (m, 1H), 1.14 (s, 3H), 0.97 (s, 3H), 0.57 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 150.0, 144.3, 133.9, 124.1, 121.2, 110.1, 77.0, 77.0, 65.5, 56.6, 39.7, 39.1, 33.1, 27.8, 27.1, 25.9, 24.2, 22.7; HRMS (EI) *m/z* calcd for $C_{18}H_{26}O_4$ (M^+) 306.1831, found 306.1820.

Aldehyde 177. To a solution of alcohol **176** (24 mg, 0.08 mmol) in CH_2Cl_2 (5 mL) at rt was added MnO_2 (231 mg, 2.3 mmol). After 15 hr, the reaction mixture was filtered through Celite, and the pad was rinsed with MeOH, EtOAc, and CH_2Cl_2. The filtrate was concentrated in vacuo to afford aldehyde **177** (24 mg, 100%) as colorless crystals without further purification: ^{1}H NMR ($CDCl_3$) δ 9.80 (s, 1H), 7.26 (s, 1H), 7.24

(s, 1H), 3.90 (s, 3H), 3.51 (s, 1H), 3.17 (dd, *J* = 17.8, 8.3 Hz, 1H), 2.79 (d, *J* = 17.5 Hz, 1H), 2.26–1.59 (m, 7H), 1.29 (s, 3H), 1.07 (s, 3H), 0.64 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 191.2, 150.0, 149.6, 128.7, 126.4, 122.8, 107.6, 77.3, 75.9, 56.1, 38.0, 37.9, 31.6, 26.94, 26.93, 24.9, 23.0, 21.9; HRMS (EI) *m/z* calcd for $C_{18}H_{24}O_4$ (M^+) 304.1675, found 304.1683.

Bis-MOM-Cis-3DSB (178). To a solution of aldehyde **177** (23 mg, 0.08 mmol) and phosphonate **22** (67 mg, 0.14 mmol) in THF (10 mL) on ice was added 15-crown -5 (0.1 mL) and NaH (63 mg, 1.6 mmol). After 5 hr, the reaction was quenched by addition of water. The resulting solution was extracted with EtOAc, and the combined organic extracts were washed with brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (1:1 Hex/EtOAc) afforded compound **178** (38 mg, 80%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.95 – 6.85 (m, 6H), 5.23 – 5.20 (m, 1H), 5.23 (s, 4H), 5.07 (tt, *J* = 7.0, 1.3 Hz, 1H), 3.89 (s, 3H), 3.50 (s, 6H), 3.40 (d, J = 7.3 Hz, 2H), 3.09 (dd, J = 17.7, 8.0 Hz, 1H), 2.69 (d, J = 17.8 Hz, 1H), 2.32 – 2.19 (m, 1H), 2.10 – 1.92 (m, 6H), 1.88 (d, *J* = 7.8 Hz, 1H), 1.79 (s, 3H), 1.70 – 1.54 (m, 3H), 1.65 (s, 3H), 1.57 (s, 3H),1.27 (s, 3H), 1.05 (s, 3H), 0.68 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.9 (2C), 149.1, 143.9, 136.8, 134.6, 131.2, 128.7, 128.4, 126.2, 124.4, 122.7, 122.6, 120.1, 119.4, 107.0, 105.9 (2C), 94.5 (2C), 76.2, 75.8, 56.2, 56.0 (2C), 39.8, 38.3, 37.9, 31.8, 27.0, 26.8, 26.7, 25.6, 25.0, 23.2, 22.7, 22.0, 17.6, 16.0; HRMS (EI) *m/z* calcd for $C_{39}H_{54}O_7$ (M^+) 634.3870, found 634.3873.

(2*R, 4aR, 9aS*)-3-Deoxyschweinfurthin B (179). To a solution of compound **178** (9.1 mg, 0.014 mmol) in MeOH (5 mL) at rt was added TsOH (7.5 mg, 0.042 mmol). The reaction was quenched by addition of $NaHCO_3$ after 5 days. The resulting solution was extracted with EtOAc, and the combined organic extracts were washed with brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Final purification by

preparative TLC (1:1 Hex/EtOAc) afforded compound **179** (7.4 mg, 95%) as a colorless oil:^{1}H NMR ($CDCl_3$) δ 6.92 – 6.75 (m, 4H), 6.55 (s, 2H), 5.28 (t, *J* = 6.5 Hz, 1H), 5.06 (t, *J* = 6.8 Hz, 1H), 3.88 (s, 3H), 3.50 (bd, 1H), 3.43 (d, *J* = 6.8 Hz, 2H), 3.09 (dd, *J* = 18.0, 8.1 Hz, 1H), 2.93 (d, *J* = 17.8 Hz, 1H), 2.27 – 2.21 (m, 1H), 2.12 – 1.95 (m, 7H), 1.88 (d, *J* = 7.8 Hz, 1H), 1.82 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.26 (s, 3H), 1.05 (s, 3H), 0.68 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.2 (2C), 149.0, 143.9, 139.3, 137.2, 132.1, 128.7, 128.5, 125.5, 123.7, 122.9, 121.3, 120.1, 112.6, 107.1, 106.1 (2C), 76.2, 75.9, 56.2, 39.3, 38.3, 37.9, 31.8, 27.0, 26.8, 26.6, 25.7, 24.9, 23.2, 22.6, 22.0, 17.7, 16.2; HRMS (EI) *m/z* calcd for $C_{35}H_{46}O_5$ (M^+) 546.3345, found 546.3349.

4-Geranylresorcinol (186). To a solution of resorcinol (**185**, 14.0 g, 127 mmol) in dioxane (150 mL) at 50 °C was added $BF_3{\cdot}Et_2O$ (6.5 mL, 51 mmol), and then geraniol (**184**, 11.2 mL, 63 mmol) in dioxane (20 mL) was added over 1hr. The resulting solution was allowed to stir for 30 min, and then the reaction was quenched by addition of water. The product was extracted into Et_2O, and the combined organic layers were washed with dilute NaOH (0.1 M), water, and brine. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (20% EtOAc in Hex) afforded compound **186** (8.3 g, 53%) as a thick oil which rapidly browned: ^{1}H NMR δ 6.94 (d, *J* = 8.6 Hz, 1H), 6.40 – 6.36 (m, 2H), 6.18 (br s, 1H), 5.80 (br s, 1H), 5.32 (t, *J* = 7.1 Hz, 1H), 5.11 (t, *J* = 7.0 Hz, 1H), 3.29 (d, *J* = 7.3 Hz, 2H), 2.15 – 2.07 (m, 4H), 1.75 (s, 3H), 1.71 (s, 3H), 1.62 (s, 3H); ^{13}C NMR δ154.9, 154.7, 138.0, 131.8, 130.5, 123.9, 122.0, 119.5, 107.7, 103.4, 39.6, 28.6, 26.4, 25.6, 17.6, 16.0; HRMS (EI) *m/z* calcd for $C_{16}H_{22}O_2$ (M^+) 246.1620, found 246.1625.

Resorcinol 187. To a solution of compound **186** (389 mg, 1.6 mmol) in CH_2Cl_2 at rt was added DIPEA (1.1 mL, 11 mmol) followed by MOMCl (0.4 mL, 4.7 mmol) and after 16 hr the reaction was quenched by addition of water. The resulting solution was

extracted with CH_2Cl_2. The combined organic phases were washed with 1N HCl, and brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography (10% EtOAc in Hex) afforded compound **187** (209 mg, 40%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.08 (d, *J* = 8.1 Hz, 1H), 6.83 (d, *J* = 2.1 Hz, 1H), 6.68 (dd, *J* = 8.1, 2.4 Hz, 1H), 5.35 (t, *J* = 7.2 Hz, 1H), 5.19 (s, 2H), 5.16 (s, 2H), 5.18 – 5.15 (m, 1H), 3.51 (s, 3H), 3.50 (s, 3H), 3.33 (d, *J* = 6.9 Hz, 2H), 2.16 – 2.08 (m, 4H), 1.75 (s, 3H), 1.72 (s, 3H), 1.64 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.4, 155.5, 135.6, 131.2, 129.6, 124.3, 124.2, 122.7, 108.7, 103.4, 94.6, 94.4, 55.8, 55.8, 39.7, 27.8, 26.6, 25.6, 17.6, 15.9; HRMS (ESI) *m/z* calcd for $C_{20}H_{30}O_4$ $(M + H)^+$ 334.2145, found 334.2144.

Epoxide 188. To a solution of compound **187** (198 mg, 0.6 mmol) in CH_2Cl_2 at – 20 °C was added *m*CPBA in three portions (77% max by mass, 141 mg, 0.63 mmol). After 1 hr the reaction was quenched with $NaHCO_3$ and the resulting solution was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography (20% EtOAc in Hex) afforded epoxide **188** (88 mg, 43%) as colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.01 (d, *J* = 8.4 Hz, 1H), 6.74 (d, *J* = 2.4 Hz, 1H), 6.63 (dd, *J* = 8.4, 2.5 Hz, 1H), 5.36 – 5.31 (m, 1H), 5.17 (s, 2H), 5.12 (s, 2H), 3.48 (s, 3H), 3.46 (s, 3H), 3.33 (d, *J* = 7.2 Hz, 2H), 2.70 (t, *J* = 6.3 Hz, 1H), 2.18 – 2.12 (m, 2H), 1.72 (s, 3H), 1.70 – 1.57 (m, 2H), 1.27 (s, 3H), 1.24 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.4, 155.5, 135.7, 129.6, 124.0, 123.4, 108.7, 103.5, 94.6, 94.4, 64.1, 58.2, 55.9, 55.9, 36.3, 27.9, 27.4, 24.7, 18.7, 16.0; HRMS (EI) *m/z* calcd for $C_{20}H_{30}O_5$ (M^+) 350.2093, found 350.2083.

Compound 189. To a solution of epoxide **188** (62 mg, 0.18 mmol) in CH_2Cl_2 (40 mL) at -78 ^{o}C was added $BF_3{\cdot}OEt_2$ (0.13 mL, 1.0 mmol). After 10 min the reaction was quenched by addition of TEA (0.25 mL, 1.8 mmol) and concentrated in vacuo. The residue was disolved in EtOAc and washed with water, 1N HCl, and brine. The organic

phase was then dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (30% EtOAc in Hex) afforded compound **190** (20 mg, 30%) along with CEAS product **189** (32 mg, 52%) as colorless oils. For compound **189**: ^{1}H NMR ($CDCl_3$) δ 6.96 (d, *J* = 8.4 Hz, 1H), 6.63 (d, *J* = 8.4 Hz, 1H), 5.17 (s, 2H), 4.54 (d, *J* = 10.5 Hz, 1H), 4.49 (d, *J* = 10.2 Hz, 1H), 3.47 (s, 3H), 3.39 (dd, *J* = 11.1, 3.6 Hz, 1H), 3.34 (s, 3H), 2.66 – 2.62 (m, 2H), 2.04 – 1.61 (m, 6H), 1.19 (s, 3H), 1.06 (s, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.2, 152.6, 129.7, 115.6, 114.9, 106.5, 94.8, 77.9, 76.4, 62.6, 57.8, 56.0, 46.7, 38.3, 37.7, 28.2, 27.2, 22.6, 20.0, 14.2. Anal. calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63 Found: C, 68.48; H, 8.68.

Compound 190. ^{1}H NMR ($CDCl_3$) δ 6.96 (d, *J* = 8.0, 1H), 6.54 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.48 (d, *J* = 2.4), 5.13 (s, 2H), 3.46 (s, 3H), 3.39 (dd, *J* = 11.4, 4.3 Hz, 1H), 2.66 – 2.62 (m, 2H), 2.04 – 1.61 (m, 6H), 1.21 (s, 3H), 1.09 (s, 3H), 0.86 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.6, 153.7, 130.0, 115.4, 108.6, 104.7, 94.6, 78.1, 76.4, 55.9, 47.0, 38.3, 37.8, 28.2, 27.3, 22.6, 20.0, 14.3; HRMS (EI) *m/z* calcd for $C_{18}H_{26}O_4$ (M^+) 306.1831, found 306.1824.

***d*$_6$-Resorcinol 187.** Compound **186** (166 mg, 0.68 mmol) was treated with d_3-MOMCl[136, 137] (0.2 mL, 2.2 mmol) and DIPEA (1 mL) in CH_2Cl_2 as described for compound **7**. After standard workup and final purification by column chromatography, d_6-compound **7** (71 mg, 31%) was obtained as a colorless oil. The ^{1}H NMR spectrum of d_6-compound **7** was found to be identical to that of compound **7** except that it lacked the two methoxy signals at 3.51 and 3.50 ppm.

Mixture of epoxides 188 and 191. A mixture of compound **187** (20 mg, 0.08 mmol) and d_6-compound **187** (19 mg, 0.08 mmol) was treated with *m*-CPBA (23 mg, 0.13 mmol) in CH_2Cl_2 as described for compound **188**. After standard workup and final

purification by column chromatography, the expected mixture of compounds **188** and **191** was obtained as colorless oil (13 mg, 30%). The ^{1}H NMR spectrum of this mixture was found to be identical to that of compound **188** except that it showed decreased intensity in the two methoxy signals at 3.48 and 3.46 ppm. The integrations of these signals have been included in the spectrum of this mixture (SI 25) and confirm that the ratio of compound **188**:**191** is ca. 1:1.

Crossover experiment. A mixture of epoxides **188** and **191** (12 mg, **188**:**191** ca. 1:1 by ^{1}H NMR, 0.05 mmol) in CH_2Cl_2 (20 mL) at -78 ^{o}C was treated with $BF_3{\cdot}OEt_2$ (0.05 mL, 0.4 mmol). After 10 min the reaction was quenched by addition of excess TEA and concentrated in vacuo. The residue was dissolved in EtOAc and washed with water, 1N HCl, and brine. The organic phase was then dried ($MgSO_4$) and concentrated in vacuo. Final purification by thin layer chromatography (30% EtOAc in Hex) afforded a mixture of deuterium labeled products. This mixture was analyzed by ^{1}H NMR and displayed a spectrum identical to that observed for compound **189** except that it showed decreased intensity in the two methoxy signals at 3.47 and 3.34 ppm. The integrations of these signals have been included in the spectrum of this mixture (SI 26) and confirm a ca. 1:1 ratio of labeled to unlabeled material. This mixture was analyzed by GC-MS using authentic compound **189** as a retention time standard. For compound **193**: HRMS (EI) *m/z* calcd for $C_{20}H_{24}D_6O_5$ (M^+) 356.2470, found 356.2484.

Compounds 195 – 264. The vast majority of these compounds have been previously reported.[159, 160] For the specific compounds which have not been described, full details are given immeediety below. For the compounds which have been described, the genral procedure given for compounds **187** – **189** was followed.[159, 160]

Prenyl epoxide 242.[147] To a suspension of epoxide **215**[161] (85 mg, 0.25 mmol) in PTS (0.6 mL, 2.5% w/v in water) in a screw-cap vial at rt was added 2-methyl-2-butene (0.16 ml, 1.5 mmol) followed by Grubb's 2nd generation catalyst (14 mg, 0.016 mmol). After 19 hr, the reaction mixture was diluted with EtOAc and filtered through celite. The filtrate was concentrated in vacuo and final purification of the residue by column chromatography (12% EtOAc in Hex) afforded epoxide **242** (52 mg, 53%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.00 (d, *J* = 8.2 Hz, 1H), 6.47 (d, *J* = 2.4 Hz, 1H), 6.41 (dd, *J* = 8.2, 2.4 Hz, 1H), 5.47 (m, 2H), 5.33 (t, *J* = 7.2 Hz, 1H), 4.47 (d, *J* = 6.6 Hz, 4H), 3.26 (d, *J* = 7.3 Hz, 2H), 2.71 (t, *J* = 6.3 Hz, 1H), 2.20 – 2.12 (m, 2H), 1.79 (s, 3H), 1.78 (s, 3H), 1.74 (s, 3H), 1.72 (s, 3H), 1.72 (s, 3H), 1.69 – 1.60 (m, 2H), 1.27 (s, 3H), 1.25 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.1, 157.3, 138.0, 137.1, 134.4, 129.3, 123.7, 122.4, 120.1, 119.7, 104.6, 100.2, 64.9, 64.7, 64.2, 58.3, 36.3, 27.8, 27.4, 25.8, 25.7, 24.8, 18.7, 18.2, 18.1, 16.0; HRMS (EI) *m/z* calcd for $C_{26}H_{38}O_3$ (M^+) 398.2821, found 398.2816.

Prenyl Arene 247. According to the general procedure, a solution of epoxide **242** (81 mg, 0.20 mmol) in CH_2Cl_2 (25 mL) at – 78 °C was treated with $BF_3{\cdot}OEt_2$ (0.20 mL, 1.6 mmol). After 10 min, the reaction was quenched, and standard work-up gave compound **247** (25 mg, 31%) along with a mixture of compounds **251** and **252** (23 mg, 28% total, 3:2 **252**:**253**). For compound **247**: ^{1}H NMR ($CDCl_3$) δ 6.84 (d, *J* = 8.4 Hz, 1H), 6.44 (d, *J* = 8.4 Hz, 1H), 5.48 (t, *J* = 6.4 Hz, 1H), 5.20 (t, *J* = 7.4 Hz, 1H), 4.47 (d, *J* = 6.5 Hz, 2H), 3.42 (dd, *J* = 11.5, 7.4 Hz, 1H), 3.28 (d, *J* = 7.4 Hz, 2H), 2.65 – 2.62 (m, 2H), 2.00 (dt, *J* = 12.2, 3.2 Hz, 1H), 1.87 – 1.82 (m, 1H), 1.79 – 1.69 (m, 4H), 1.77 (s, 3H), 1.77 (s, 3H), 1.71 (s, 3H), 1.64 (s, 3H), 1.17 (s, 3H), 1.08 (s, 3H), 0.86 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.6, 151.2, 136.6, 130.3, 126.6, 123.1, 120.7, 118.1, 114.4, 104.4, 78.2, 75.8, 65.5, 46.9, 38.3, 37.9, 28.3, 27.3, 25.9, 25.7, 22.7, 22.4, 20.0, 18.2, 17.9, 14.2; HRMS (EI) *m/z* calcd for $C_{26}H_{38}O_3$ (M^+) 398.2821, found 398.2825.

Mixture Compounds of 251 and 252. ^{1}H NMR ($CDCl_3$) δ 6.92 (s, 1H), 6.79 (s, 0.7H), 6.31 (s, 1H), 6.31 (s, 0.7H), 6.21 (dd, *J* = 14.8, 10.7 Hz, 1H), 5.50 (m, 1.7H), 5.29 (m, 0.7H), 4.96 (dd, *J* = 14.0 Hz, 1.6 Hz, 1H), 4.92 (dd, *J* = 7.0, 1.6 Hz, 1H), 4.42 (m, 3.4H), 3.41 (dd, *J* = 11.2, 4.2 Hz, 1.7H), 3.23 (d, *J* = 7.3 Hz, 1.4H), 2.61 (m, 3.4H), 1.99 (m, 1.7H), 1.84 (m, 1.7H), 1.75 – 1.65 (m, 6.8H), 1.78 (s, 5.1H), 1.74 (s, 2.1H), 1.70 (s, 5.1H), 1.68 (s, 2.1H), 1.43 (s, 6H), 1.22 (s, 3H), 1.21 (s, 2.1H), 1.09 (s, 3H), 1.08 (s, 2.1H), 0.87 (s, 3H), 0.86 (s, 2.1H); ^{13}C NMR ($CDCl_3$) δ 156.7, 155.7, 151.7, 151.4, 148.5, 136.9, 136.4, 131.7, 129.6, 128.5, 127.8, 123.2, 122.1, 120.3, 112.8, 112.2, 109.4, 101.5, 100.6, 78.1, 78.1, 76.3, 76.2, 65.1, 65.0, 47.3, 47.2, 40.0, 38.4, 38.3, 37.8, 28.2, 27.7, 27.4, 27.4, 27.3, 27.2, 25.9, 25.7, 25.6, 22.5, 22.3, 20.0, 19.9, 18.1, 17.7, 14.3, 14.2; HRMS (EI) *m/z* calcd for $C_{26}H_{38}O_3$ (M^+) 398.2821, found 398.2815.

1,1,1-Trideuetero-2-(1,1,1-trideuteromethyl)-2-butene (261). To a suspension of $EtP(Ph_3)_3Br$ (7.4 g, 20 mmol) in THF (30 mL) cooled in an ice bath was added PhLi (12 mL, 1.6 M in Bu_2O, 19 mmol). The ice bath was removed for 5 min to allow anion formation and then the reaction was cooled with an ice bath. After 5 min, $(CD_3)_2CO$ (0.9 ml, 12 mmol) was added and the reaction flask was fitted with a distillation apparatus. After 5 min, the ice bath was removed and the reaction was slowly heated to 33 ^{o}C. This afforded 1.75 g of distillate in the receiving flask which was a 1:8 mixture of compound **261**[145, 146] (210 mg, 23%) and THF by ^{1}H NMR analysis. This mixture was used in the subsequent reaction without further purification: ^{1}H NMR ($CDCl_3$) δ 5.10 (q, *J* = 6.8 Hz, 1H), 1.47 (d, *J* = 6.8 Hz, 3H).

Deuterium-Labeled Epoxide 262. To suspension of epoxide **215** (62 mg, 0.18 mmol) in PTS (0.5 mL, 2.5% w/v in water) in a screw-capped vial at rt was added labeled 2-methyl-2-butene (**261**, 690 mg of an 8:1 THF:**261** mixture, 83 mg) followed by Grubb's 2nd generation catalyst (11 mg, 0.013 mmol). After 19 hr, the reaction mixture

was diluted with EtOAc and filtered through celite. After the filtrate was concentrated in vacuo, final purification by column chromatography (8% EtOAc in Hex) afforded epoxide **262** (39 mg, 53%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.00 (d, *J* = 8.4 Hz, 1H), 6.48 (d, *J* = 2.4 Hz, 1H), 6.42 (dd, *J* = 8.0, 2.4 Hz, 1H), 5.52 – 5.46 (m, 2H), 5.34 – 5.32 (m, 1H), 4.47 (d, *J* = 6.4 Hz, 2H), 4.46 (d, *J* = 6.8 Hz, 2H), 3.26 (d, *J* = 7.2 Hz, 2H), 2.71 (t, *J* = 6.8 Hz, 1H), 2.22 – 2.08 (m, 2H), 1.71 (s, 3H), 1.74 – 1.62 (m, 2H), 1.27 (s, 3H), 1.25 (s, 3H); HRMS (EI) *m/z* calcd for $C_{26}H_{26}D_{12}O_3$ (M^+) 410.3574, found 410.3578.

Cross-over Experiment. To a solution of epoxide **242** (8 mg, 0.020 mmol) and deuterated epoxide **262** (12 mg, 0.029 mmol) in CH_2Cl_2 (40 mL) at – 78 ^{o}C was added $BF_3{\cdot}OEt_2$ (0.10 mL, 0.8 mmol). After 10 min, the reaction was quenched by addition of triethylamine (0.25 mL), diluted with HCl, and extracted with CH_2Cl_2. The organic phase was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Final purification by column chromatography (20% EtOAc in Hex) afforded a mixture of deuterium labeled products. This mixture was analyzed by ^{1}H NMR and displayed a spectrum identical to that observed for compounds **247**, **251** and **252** except that it showed decreased intensity in the methyl region. This mixture was analyzed by GC-MS using authentic samples of compounds **247**, **251** and **252** as standards. For the mixture of compounds **247** and **263,** GC-MS analysis showed 27% D_0, 8% D_6, and 65% D_{12}. For the mixture of compounds **251** and **252** and their labeled analogues, GC-MS analysis showed 29% D_0, 8% D_6, and 63% D_{12}, corresponding to a process ≥96% intramolecular. This experiment was repeated with epoxide **242** (10 mg, 0.025 mmol) and labeled epoxide **262** (15 mg, 0.37 mmol) in a slightly different ratio. Analysis of the resulting mixtures by GC-MS indicated 27% D_0, 10% D_6, and 63% D_{12} for compounds **247** and **263**, and 28% D_0, 7% D_6, and 65% D_{12} for the mixture of compounds **251** and **252** with their deuterated analogues.

Hexahydroxanthene 280. To a solution of epoxide **279** (130 mg, 0.37 mmol) in freshly distilled CH_2Cl_2 (50 mL) at – 78 ^oC was added $BF_3 \cdot OEt_2$ (0.25 mL, 2.0 mmol). After 15 min, the reaction was quenched by addition of TEA (0.5 mL, 3.6 mmol). The resulting solution was concentrated in vacuo to near dryness and extracted with EtOAc. The combined organic phases were washed with 1N HCl, and brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography (30% EtOAc in Hex) afforded compound **281** (17 mg, 13%) and compound **280** (92 mg, 71%) as colorless oils. For compound **280**: $[\alpha]^{26}_D$ = +39 (c 4.1, $CHCl_3$, 76% ee by HPLC); ^1H NMR ($CDCl_3$) δ 7.07 (d, *J* = 8.0 Hz, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 5.20 (s, 2H), 4.39 (d, *J* = 11.6 Hz, 1H), 4.36 (d, *J* = 12.0 Hz, 1H), 3.49 (s, 3H), 3.40 – 3.36 (m, 1H), 3.36 (s, 3H), 2.78 (dd, *J* = 16.8, 4.4 Hz, 1H), 2.40 (dd, *J* = 17.2, 13.6 Hz, 1H), 2.01 – 1.96 (m, 2H), 1.85 – 1.81 (m, 1H), 1.77 (dd, *J* = 16.8, 4.0 Hz, 1H), 1.65 – 1.58 (m, 2H), 1.17 (s, 3H), 1.10 (s, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.1, 151.5, 127.1, 119.5, 111.5, 104.4, 94.4, 78.0, 75.8, 69.0, 57.9, 56.0, 46.2, 38.3, 37.6, 28.1, 27.2, 19.8, 18.1, 14.1; HRMS (EI) *m/z* calcd for $C_{20}H_{30}O_5$ (M^+) 350.2093, found 350.2090.

Compound 281. $[\alpha]^{26}_D$ = +21 (c 1.2, $CHCl_3$, 81% ee by HPLC); ^1H NMR ($CDCl_3$) δ 7.02 (dd, *J* = 8.4, 8.4 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 6.46 (d, *J* = 8.4 Hz, 1H), 5.21 (s, 2H), 3.50 (s, 3H), 3.42 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.80 (dd, *J* = 17.1, 5.1 Hz, 1H), 2.41 (dd, *J* = 16.9, 13.2 Hz, 1H), 2.00 (dt, *J* = 12.3, 2.9 Hz, 1H), 1.90 – 1.84 (m, 1H), 1.74 – 1.57 (m, 4H), 1.21 (s, 3H), 1.13 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.2, 153.5, 126.7, 111.5, 110.3, 104.5, 94.1, 77.7, 75.6, 55.7, 46.1, 38.1, 37.3, 27.9, 27.0, 19.3, 17.7, 13.8; HRMS (EI) *m/z* calcd for $C_{18}H_{26}O_4$ (M^+) 306.1831, found 306.1828.

Aldehyde 282. To a solution of compound **281** (354 mg, 1.01 mmol) in CH_2Cl_2 (40 mL) and water (4 mL) at rt was added solid DDQ (504 mg, 2.22 mmol) in one

portion. After 2 hr, the reaction was quenched by addition of sat. $NaHCO_3$. The resulting solution was extracted with CH_2Cl_2 and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography (40% EtOAc in Hex) afforded aldehyde **282** (352 mg, 100%) as a colorless oil: $[\alpha]^{26}_D$ = +34 (c 3.4, $CHCl_3$, 76% ee by HPLC); ^{1}H NMR ($CDCl_3$) δ 10.28 (s, 1H), 7.67 (d, *J* = 8.6 Hz, 1H), 6.69 (d, *J* = 8.8 Hz, 1H), 5.27 (s, 2H), 3.51 (s, 3H), 3.45 (dd, *J* = 11.4, 3.9 Hz, 1H), 2.79 (dd, *J* = 17.1, 4.8 Hz, 1H), 2.41 (dd, *J* = 17.1, 13.2 Hz, 1H), 2.18 (d, *J* = 3.2 Hz, 1H), 2.06 (m, 1H), 1.93 – 1.62 (m, 4H), 1.27 (s, 3H), 1.15 (s, 3H), 0.93 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 188.7, 160.3, 156.9, 126.9, 118.9, 111.5, 104.8, 93.7, 77.8, 77.3, 56.0, 45.5, 38.1, 37.1, 27.7, 26.9, 19.5, 17.6, 13.8; HRMS (EI) *m/z* calcd for $C_{19}H_{26}O_5$ (M^+) 334.1780, found 334.1784.

Alcohols 283. To an ice cold solution of aldehyde **282** (67 mg, 0.19 mmol) in THF was added CH_3MgBr (0.8 ml, 3M in Et_2O, 2.4 mmol). After 1.5 hr, the reaction was quenched by addition of sat. NH_4Cl. The resulting solution was extracted with EtOAc and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography (40% EtOAc in Hex) afforded a mixture of epimeric alcohols **283** (66 mg, 98%) as a colorless oil: HRMS (EI) *m/z* calcd for $C_{20}H_{30}O_5$ (M^+) 350.2093, found 350.2086.

Ketone 284. To a solution of epimeric alcohols **283** (26 mg, 0.07 mmol) in CH_2Cl_2 at rt was added MnO_2 (210 mg, 2.4 mmol, 88%). After 17 hr, the reaction mixture was diluted with CH_2Cl_2, allowed to settle, filtered through celite, and rinsed with excess solvent. After the filtrate was concentrated in vacuo, final purification by column chromatography (50% EtOAc in Hex) afforded ketone **284** (23 mg, 89%) as a colorless oil: $[\alpha]^{26}_D$ = +65 (c 2.1, $CHCl_3$, 76% ee by HPLC); ^{1}H NMR ($CDCl_3$) δ 7.66 (d, *J* = 8.8 Hz, 1H), 6.65 (d, *J* = 8.8 Hz, 1H), 5.24 (s, 2H), 3.49 (s, 3H), 3.45 (dd, *J* = 11.2,

4.0 Hz, 1H), 2.79 (dd, *J* = 17.6, 5.2 Hz, 1H), 2.54 (s, 3H), 2.42 (dd, *J* = 17.2, 13.2 Hz, 1H) 2.08 – 2.03 (m, 1H), 1.91 – 1.86 (m, 1H), 1.81 (dd, *J* = 12.8, 4.0 Hz, 1H), 1.75 – 1.62 (m, 3H, 2H upon D_2O exchange), 1.26 (s, 3H), 1.13 (s, 3H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 198.4, 159.0, 154.4, 129.5, 111.7, 104.8, 103.6, 94.1, 78.0, 77.1, 56.3, 45.8, 38.4, 37.7, 32.2, 28.2, 27.2, 20.0, 18.2, 14.3; HRMS (EI) *m/z* calcd for $C_{20}H_{28}O_5$ (M^+) 348.1937, found 348.1929.

Angelichalcone 287. To a solution of chalcone **286** (11 mg, 0.02 mmol) in CH_3OH was added $TsOH{\cdot}H_2O$ (34 mg, 0.18 mmol) and the reaction mixture was heated to 65 ºC. After 3 hr, the reaction was allowed to cool to rt and quenched by addition of $NaHCO_3$. The resulting solution was concentrated in vacuo, extracted with EtOAc, the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography (60% EtOAc in Hex) afforded chalcone **287** (9 mg, 92%) as a yellow solid: $[\alpha]^{26}_D$ = +30 (c 1.0, EtOH); The ^{1}H and ^{13}C spectra and M^+ were found to be identical to that reported for the natural material[148] but have been reproduced here for convenience: ^{1}H NMR (DMSO) δ 10.20 (br s, 1H), 9.96 (br s, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 16.2 Hz, 1H), 7.44 (d, *J* = 15.6 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 2H), 6.47 (d, *J* = 8.4 Hz, 1H), 4.64 (d, *J* = 5.4 Hz, 1H), 3.27 (ddd, *J* = 11.4, 4.8, 4.8 Hz, 1H), 2.67 (dd, *J* = 16.8, 4.8 Hz, 1H), 2.34 (dd, *J* = 17.4, 13.8 Hz, 1H), 1.87 (ddd, *J* = 12, 3.6, 3.6 Hz, 1H), 1.77 – 1.74 (m, 1H), 1.72 – 1.69 (m, 1H), 1.61 (dd, *J* = 13.6, 4.8 Hz, 1H), 1.55 – 1.53 (m, 1H), 1.23 (s, 3H), 1.03 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (DMSO) 189.4, 160.2, 159.9, 154.5, 140.9, 130.4 (2C), 129.8, 126.7, 124.9, 120.4, 116.4 (2C), 110.0, 107.3, 77.5, 76.4, 46.0, 38.6, 37.9, 28.5, 27.7, 20.3, 18.4, 14.9; HRMS (EI) *m/z* calcd for $C_{25}H_{28}O_5$ (M^+) 408.1937, found 408.1946.

Arene 295. To a solution of methyl 3-bromo-4-methoxymethylbenxylalcohol (8.6 g, 35 mmol) in THF in an ice bath was added NaH (3.0 g, 60% in oil, 75 mmol). After hydrogen evolution had ceased, CH_3I (2.6 mL, 42 mmol) was added. The reaction was allowed to slowly warm to rt and after 12 h was quenched by addition of water. The resulting mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography (20% EtOAc in Hex) afforded ether **295** (8.6 g, 94%) as colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.54 (d, *J* = 2.4 Hz, 1H), 7.21 (dd, *J* = 8.0, 2.4 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 5.24 (s, 2H), 4.36 (s, 2H), 3.51 (s, 3H), 3.36 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 153.1, 133.1, 132.7, 127.8, 115.8, 112.6, 94.9, 73.4, 58.0, 56.2; HRMS (EI) *m/z* calcd for $C_{10}H_{13}O_3Br$ (M^+) 260.0048, found 260.0052.

Arene 296. To a solution of TMEDA (7.5 mL, 50 mmol) in Et_2O (200 mL) in a brine bath, *n*-BuLi (20 mL, 2.4 M in Hex, 48 mmol) was added. After 5 min, bromide **294** (10.1 g, 39 mmol) in Et_2O (50 mL) was added via canula. After an additional 10 min, neat geranyl bromide (10.8 mL, 54 mmol) was added slowly over 15 min. The reaction was allowed to proceed for 1.5 h and then was quenched by addition of aqueous NH_4Cl. The resulting solution was extracted with EtOAc, and the combined organic phase was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography (15% EtOAc in Hex) afforded arene **296** (9.1 g, 74%) as yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.13 (d, *J* = 2.0 Hz, 1H), 7.10 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 5.31 (tq, *J* = 6.0, 1.2 Hz, 1H), 5.18 (s, 2H), 5.11 (tq, *J* = 6.0, 1.2 Hz, 1H), 4.36 (s, 2H), 3.46 (s, 3H), 3.35 (s, 3H), 3.35 (m, 2H), 2.11 – 2.01 (m, 4H), 1.71 (d, *J* =

1.2 Hz, 3H), 1.67 (d, *J* = 1.2 Hz, 3H), 1.59 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 154.4, 135.8, 131.2, 131.1, 130.7, 129.3, 126.5, 124.2, 122.3, 113.6, 94.2, 74.4, 57.7, 55.7, 39.7, 28.5, 26.5, 25.6, 17.5, 16.0; HRMS (EI) *m/z* calcd for $C_{20}H_{30}O_3$ (M^+) 318.2195, found 318.2190.

Epoxide 297. To a solution of the corresponding olefin **296** (6.2 g, 19 mmol) and Shi's catalyst (**75**, 1.4 g, 5.0 mmol) in aq buffer (80 mL, 2 M K_2CO_3 and 4 mM EDTA) and organic phase (100 mL, 1:1:1 CH_2Cl_2/MeCN/EtOH) at 0 ^{o}C was added hydrogen peroxide (7 mL, 30%) via syringe pump over 20 h. The reaction was then quenched by addition of aq Na_2SO_3. The resulting solution was extracted with EtOAc, and the organic phase was washed with brine. After the organic phase was dried ($MgSO_4$), and concentrated *in vacuo*, final purification by column chromatography (20% EtOAc in Hex) afforded recovered starting material (2.8 g, 44%) and epoxide **297** (2.9 g, 44%, ee ranged from 88% - 92%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.11 – 7.08 (m, 2H), 7.01 (d, *J* = 8.0 Hz, 1H), 5.35 (m, 1H), 5.19 (s, 2H), 4.35 (s, 2H), 3.45 (s, 3H), 3.34 (s, 3H), 3.35 (m, 2H), 2.69 (t, *J* = 6.4 Hz, 1H), 2.19 – 2.11 (m, 2H), 1.73 (s, 3H), 1.68 – 1.60 (m, 2H), 1.25 (s, 3H), 1.23 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 154.4, 134.8, 131.1, 130.4, 129.3, 126.6, 123.0, 113.6, 94.2, 74.3, 64.0, 58.2, 57.8, 55.8, 36.3, 28.5, 27.3, 24.7, 18.6, 16.0; HRMS (EI) *m/z* calcd for $C_{20}H_{30}O_4$ (M^+) 334.2144, found 334.2135.

Ether 298. To a solution of epoxide **297** (1.15 g, 3.4 mmol) in CH_2Cl_2 (350 mL) at –78 ^{o}C was added $BF_3{\cdot}OEt_2$ (2.2 mL, 20 mmol). After 9 min, the reaction was quenched by addition of excess Et_3N (5 mL). The resulting solution was concentrated *in*

vacuo and the resulting oil was dissolved in EtOAc which was washed with 1N HCl followed by brine. The organic phase was dried ($MgSO_4$), and concentrated *in vacuo*. Final purification by column chromatography (30% EtOAc in Hex) afforded the cyclized product without a C-5 substituent[40](229 mg, 23%) along with ether **298** (620 mg, 54%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.12 (s, 1H), 6.97 (s, 1H), 4.40 (s, 2H), 4.30 (s, 2H), 3.38 (s, 3H), 3.34 (s, 3H), 3.09 (dd, *J* = 11.2, 4.0 Hz, 1H), 2.85 (br, 1H), 2.66 – 2.62 (m, 2H), 1.93 – 1.89 (m, 1H), 1.72 – 1.52 (m, 4H), 1.13 (s, 3H), 0.97 (s, 3H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 150.0, 128.7, 128.5, 126.3, 125.7, 121.2, 77.1, 76.2, 74.5, 68.9, 58.1, 57.7, 46.5, 37.9, 37.5, 27.9, 27.0, 22.8, 19.8, 14.0; HRMS (EI) *m/z* calcd for $C_{20}H_{30}O_4$ (M^+) 334.2144, found 334.2134.

Ketone 299. To a solution of tricycle **298** (670 mg, 2.0 mmol) in CH_2Cl_2 (10 mL) in the presence of molecular sieves at rt was added TPAP (67 mg, 0.19 mmol) followed by NMO (253 mg, 2.2 mmol). After 6 hr at rt, the reaction was diluted with EtOAc (25 mL) and filtered through a plug of celite on top of silica, which was thoroughly washed with EtOAc. The resulting solution was concentrated in vacuo to afford ketone **299** (663 mg, 100%) as a colorless oil which was of sufficient purity to be used is subsequent transformations without further purification. A sample was purified by column chromatography (24% EtOAc in Hex): ^{1}H NMR ($CDCl_3$) δ 7.12 (s, 1H), 6.99 (s, 1H), 4.39 (s, 2H), 4.30 (s, 2H), 3.36 (s, 3H), 3.31 (s, 3H), 2.82 – 2.59 (m, 3H), 2.40 (ddd, *J* = 19.8, 5.2, 5.2 Hz, 1H), 2.20 (ddd, *J* = 17.2, 6.2, 4.0 Hz, 1H), 2.07 – 1.98 (m, 2H), 1.34 (s, 3H), 1.11 (s, 3H), 1.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 213.1, 149.5, 129.1, 128.2, 126.3, 126.0, 120.3, 74.9, 74.2, 68.8, 58.0, 57.6, 47.1, 46.1, 37.8, 34.8, 24.1, 23.3, 20.4, 19.0; HRMS (EI) *m/z* calcd for $C_{20}H_{28}O_4$ (M^+) 332.1988, found 332.1992.

Benzylidine 300. To a solution of ketone **299** (584 mg, 1.8 mmol) in EtOH (8 mL) at rt was added benzaldehyde (0.90 mL, 9.3 mmol) followed by solid KOH (525 mg, 9.4 mmol). After 3 hr, the reaction was diluted with water and the resulting solution was extracted with EtOAc. The combined organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo which afforded benzylidine **300** (657 mg, 77%) as yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.63 (d, *J* = 2.8 Hz, 1H), 7.44 – 7.28 (m, 5H), 7.20 (d, *J* = 1.6 Hz, 1H), 7.04 (d, *J* = 1.6 Hz, 1H), 4.47 (s, 2H), 4.35 (s, 2H), 3.40 (s, 3H), 3.35 (s, 3H), 3.35 (m, 1H), 2.93 (dd, *J* = 15.4, 2.6 Hz, 1H), 2.78 – 2.73 (m, 2H), 2.31 (dd, *J* = 12.6, 5.8 Hz, 1H), 1.30 (s, 3H), 1.21 (s, 3H), 1.12 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 204.6, 149.1, 138.2, 134.7, 131.9, 129.7 (2C), 129.0, 128.4, 128.1 (2C), 127.9, 126.1, 125.6, 120.0, 74.8, 74.1, 68.7, 57.9, 57.4, 45.3, 45.0, 41.5, 28.3, 23.8, 21.9, 19.1; HRMS (EI) *m/z* calcd for $C_{27}H_{32}O_4$ (M^+) 420.2301, found 420.2297.

Alylic Alcohol 301. To a solution of benzylidine **300** (543 mg, 1.29 mmol) in CH_3OH (5 mL) at rt was added $CeCl_3 \cdot 7\ H_2O$ (523 mg, 1.4 mmol) followed by $NaBH_4$ (50 mg, 1.3 mmol). After 30 min, the reaction was quenched with 1N HCl and the resulting solution was extracted with EtOAc. The combined organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (24% EtOAc in Hex) afforded alylic alcohol **301** (378 mg, 69%) as yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.36 (m, 2H), 7.25 – 7.20 (m, 3H), 7.15 (d, *J* = 1.6 Hz, 1H), 7.00 (d, *J* = 2.4 Hz, 1H), 6.77 (s, 1H), 4.39 (s, 2H), 4.32 (s, 2H), 3.58 (s, 1H), 3.38 (s, 3H), 3.37 (s, 3H), 3.18 (d, *J* = 12.4 Hz, 1H), 3.04 (d, *J* = 4.0 Hz, 1H), 2.69 – 2.64 (m, 2H), 2.10 (d, *J* = 12.8 Hz, 1H), 1.80 (dd, *J* = 12.2, 5.8 Hz, 1H), 1.09 (s, 3H), 1.00 (s, 3H), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 150.1, 138.0, 137.5, 128.8, 128.7 (2C), 128.1 (2C), 126.7, 126.4, 126.1, 125.8, 123.8, 121.2, 79.2, 77.5, 74.6, 68.9, 58.2, 57.9, 47.1, 41.1, 39.4, 27.0, 23.0, 20.0, 14.1; HRMS (EI) *m/z* calcd for $C_{27}H_{34}O_4$ (M^+) 422.2451, found 422.2451.

Triol 302. To a solution of alcohol **301** (375 mg, 0.89 mmol) in Dioxane (5 mL) and water (0.5 mL) at rt was added OsO4 (0.7 mL, 0.02 M in ^{t}BuOH, 0.014 mmol) followed by NMO (158 mg, 1.3 mmol). After 5 hr, the reaction was quenched by addition of Na_2SO_3 and the resulting solution was extracted with EtOAc. The combined organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo which afforded triol **302** (405 mg, 100%) as an oil which was of sufficient purity to warrant no further purification: ^{1}H NMR ($CDCl_3$) δ 7.50 – 7.48 (m, 2H), 7.35 – 7.26 (m, 3H), 7.09 (s, 1H), 6.98 (d, *J* = 1.6 Hz, 1H), 5.19 (brd s, 1H), 5.02 (s, 1H), 4.82 (br, 1H), 4.30 (s, 2H), 4.28 – 4.24 (m, 2H), 3.70 (brd s, 1H), 3.47 (s, 1H), 3.32 (s, 3H), 3.28 (s, 3H), 2.67 – 2.64 (m, 2H), 2.02 (d, *J* = 14.4 Hz, 1H), 1.88 (dd, *J* = 11.6, 6.0 Hz, 1H), 1.62 (d, *J* = 14.4, 1H), 1.22 (s, 3H), 1.06 (s, 3H), 1.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 149.7, 139.4, 129.1 (2C), 128.6, 128.5, 127.9 (2C), 126.6, 126.5, 125.8, 121.3, 84.6, 77.6, 76.3, 74.7, 74.4, 68.8, 58.1, 57.7, 45.9, 45.5, 37.6, 29.9, 23.0, 21.9, 16.3; HRMS (EI) *m/z* calcd for $C_{27}H_{36}O_6$ (M^+) 456.2512, found 456.2518.

Ketone 303. To a solution of triol **302** (237 mg, 0.52 mmol) in CH_2Cl_2 (3 mL) and water (0.3 mL) at rt was added $NaIO_4$ (502 mg, 2.3 mmol). After 50 hr at rt, TLC analysis showed a significant amount of starting material and more $NaIO_4$ (495 mg, 2.3 mmol) was added. After an additional 49 hr, the reaction was diluted with water and the resulting solution was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (25% EtOAc in Hex) afforded ketone **303** (110 mg, 61%) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.17 (d, *J* = 1.6 Hz, 1H), 7.05 (d, *J* = 1.2 Hz, 1H), 4.42 (d, *J* = 12.4 Hz, 1H), 4.35 (d, *J* = 12.8 Hz, 1H), 4.35 (s, 2H), 4.04 (d, *J* = 4.8 Hz, 1H), 3.48 (d, *J* = 4.4 Hz, 1H), 3.40 (s, 3H), 3.37 (s, 3H), 2.93 (s, 2H), 2.87 (dd, *J* = 16.4, 5.2 Hz, 1H), 2.76 (m, 1H), 2.34 (dd, *J* = 12.8, 5.2 Hz, 1H), 1.25 (s, 3H), 1.15 (s, 3H), 0.73 (s, 3H); ^{13}C NMR

($CDCl_3$) δ 207.6, 149.5, 129.8, 128.6, 126.8, 126.3, 121.0, 82.6, 78.5, 74.4, 69.1, 58.4, 58.0, 52.4, 46.2, 41.5, 27.3, 23.1, 21.2, 15.1; HRMS (EI) *m/z* calcd for $C_{20}H_{28}O_5$ (M^+) 348.1937, found 348.1936.

Cis-Diol 304. To a solution of ketone **303** (40 mg, 0.11 mmol) in CH_3OH (1 mL) at rt was added $NaBH_4$ (15 mg, 0.39 mmol). After 10 min, the reaction was quenched with 1N HCl and the resulting solution was extracted with EtOAc. The combined organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo which afforded diol **304** (40 mg, 100%) as an oil which was of sufficient purity to warrant no further purification: ^{1}H NMR (CD_3OD) δ 7.08 (d, *J* = 1.6 Hz, 1H), 7.00 (d, *J* = 2 Hz, 1H), 4.40 (s, 2H), 4.32 (s, 2H), 4.12 (ddd, *J* = 3.2, 3.2, 3.2 Hz, 1H), 3.35 (s, 3H), 3.32 (s, 3H), 3.25 (d, *J* = 3.2 Hz, 1H), 2.77 – 2.73 (m, 2H), 2.27 (dd, *J* = 14.0, 3.2 Hz, 1H), 1.88 (dd, *J* = 13.6, 3.2 Hz, 1H), 1.70 (dd, *J* = 11.6, 6.4, 1H), 1.36 (s, 3H), 1.07 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (CD_3OD) δ 151.5, 130.3, 129.9, 128.1, 126.8, 123.3, 78.7, 77.5, 75.6, 71.7, 70.3, 58.4, 57.9, 48.5, 44.8, 39.0, 29.4, 24.0, 22.1, 16.5; HRMS (EI) *m/z* calcd for $C_{20}H_{30}O_5$ (M^+) 350.2093, found 350.2100.

Aldehyde 305. To a solution of diol **304** (38 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) and water (0.5 mL) at rt was added DDQ (30 mg, 0.13 mmol). After 10 min at rt, the reaction was quenched with aqueous $NaHCO_3$ and the resulting solution was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo which afforded aldehyde **305** (35 mg, 97%) as an oil which was of sufficient purity to warrant no further purification:: ^{1}H NMR ($CDCl_3$) δ 9.82 (s, 1H), 7.72 (d, *J* = 2.0 Hz, 1H), 7.59 (d, *J* = 1.6 Hz, 1H), 4.44 (s, 2H), 4.23 (ddd, *J* = 3.2, 3.2, 3.2, Hz, 1H), 3.44 (s, 3H), 3.36 (d, *J* = 2.8 Hz, 1H), 2.84 – 2.80 (m, 2H), 2.56 (brd s , 2H), 2.40 (dd, *J* = 14.2, 3.0 Hz, 1H), 1.94 (dd, *J* = 14.2, 3.0 Hz, 1H), 1.75 (dd, *J* = 11.6, 6.8, 1H), 1.42 (s, 3H), 1.10 (s, 3H), 1.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 191.4, 155.9, 130.7, 128.7,

128.6, 127.2, 122.3, 77.7, 77.4, 70.5, 68.9, 58.6, 46.6, 43.1, 38.0, 28.8, 22.8, 22.0, 15.9; HRMS (EI) *m/z* calcd for $C_{19}H_{26}O_5$ (M^+) 334.1780, found 334.1783.

Aldehyde 306. To a solution of benzyl ether **298** (400 mg, 1.2 mmol) in CH_2Cl_2 (10 mL) and water (1.0 mL) at rt was added DDQ (308 mg, 1.4 mmol). After 2 hr, the reaction was quenched by addition of $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2. The organic phases were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* afforded aldehyde **306** as orange oil which was advanced to the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 9.79 (s, 1H), 7.70 (d, *J* = 1.2 Hz, 1H), 7.56 (d, *J* = 1.2 Hz, 1H), 4.46 (s, 2H), 3.41 (s, 3H), 3.40 (m, 1H), 2.76 – 2.71 (m, 2H), 2.25 (br, 1H), 2.01 (ddd, *J* = 12.4, 3.6, 3.6 Hz, 1H), 1.84 (dq, *J* = 12.8, 3.6 Hz, 1H), 1.73 (dd, *J* = 13.0, 3.8 Hz, 1H), 1.65 (dd, *J* = 11.8, 5.8 Hz, 1H), 1.59 (m, 1H), 1.19 (s, 3H), 1.07 (s, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 191.3, 156.1, 130.7, 128.5, 128.4, 127.0, 122.1, 78.0, 77.5, 68.7, 58.5, 46.3, 38.3, 37.4, 27.9, 27.1, 22.8, 20.2, 14.2; HRMS (EI) *m/z* calcd for $C_{19}H_{26}O_4$ (M^+) 318.1831, found 318.1813.

Benzyl Alcohol 307. The residue from the previous step was dissolved in CH_3OH (5 mL), the solution was placed in an ice bath, and $NaBH_4$ (100 mg, 2.6 mmol) was added in one portion. After 1 h, the reaction was quenched by slow addition of 1N HCl. The resulting solution was extracted with EtOAc, and the combined organic phases were washed with brine. After the organic phase was dried ($MgSO_4$), and concentrated in vacuo, final purification by column chromatography (40% EtOAc in Hex) afforded alcohol **307** (225 mg, 59% over 2 steps) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.13 (s, 1H), 6.99 (d, *J* = 1.2 Hz, 1H), 4.49 (s, 2H), 4.40 (m, 2H), 3.38 (s, 3H), 3.04 (dd, *J* = 11.2,

4.0 Hz, 1H), 2.67 – 2.62 (m, 2H), 1.93 – 1.90 (m, 1H), 1.72 – 1.48 (m, 4H), 1.13 (s, 3H), 0.97 (s, 3H), 0.78 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 149.9, 131.8, 128.1, 125.8, 125.6, 121.3, 77.3, 76.2, 67.0, 64.7, 58.2, 46.6, 38.0, 37.5, 27.9, 27.0, 22.9, 19.9, 14.1; HRMS (EI) *m/z* calcd for $C_{19}H_{28}O_4$ (M^+) 320.1988, found 320.1985.

MOM Acetal 308a. ^{1}H NMR ($CDCl_3$) δ 7.16 (s, 1H), 7.02 (s, 1H), 4.68 (s, 2H), 4.47 (s, 2H), 4.42 (s, 2H), 3.41 (s, 3H), 3.40 (s, 3H), 3.26 (dd, *J* = 11.4, 3.8 Hz, 1H), 2.70 – 2.66 (m, 2H), 2.19 (br, 1H), 1.99 – 1.95 (m, 1H), 1.80 – 1.57 (m, 4H), 1.16 (s, 3H), 1.03 (s, 3H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 150.2, 128.7, 128.3, 126.5, 126.0, 121.4, 95.3, 77.5, 76.3, 69.1, 69.0, 58.2, 55.1, 46.6, 38.2, 37.8, 28.0, 27.1, 22.9, 19.9, 14.1; HRMS (EI) *m/z* calcd for $C_{21}H_{32}O_5$ (M^+) 364.2250, found 364.2264.

Boc Carbonate 308b. To a solution of alcohol **307** (179 mg, 0.56 mmol) in THF in an ice bath, was added NaH (190 mg, 60% in oil, 4.8 mmol) followed by Boc anhydride (153 mg, 0.70 mmol). After 12 hr, the reaction was quenched with water and the resulting solution was extracted with EtOAc, and the combined organic phases were washed with brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (40% EtOAc in Hex) afforded carbonate **308b** (102 mg, 43 %) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.17 (d, *J* = 2Hz, 1H), 7.03 (d, *J* = 1.6 Hz, 1H), 4.97 (s, 2H), 4.39 (s, 2H), 3.39 (s, 3H), 3.39 – 3.33 (m, 1H), 2.69 – 2.65 (m, 2H), 2.09 (bd, 1H), 1.96 (dt, *J* = 12.8, 3.4 Hz, 1H), 1.81 (dq, *J* = 8.8, 3.6 Hz, 1H), 1.72 (dd, *J* = 14.0, 4.0 Hz, 1H), 1.63 (dd, *J* = 12.0, 6.4 Hz, 1H), 1.58 – 1.50 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 156.4, 153.4, 150.7, 129.4, 127.0, 126.2, 121.6, 81.9, 77..7, 76.4, 69.0, 68.8, 58.3, 46.5, 38.2, 37.6, 28.0, 27.7, 27.2, 22.9, 19.9, 14.1; HRMS (EI) *m/z* calcd for $C_{24}H_{36}O_6$ (M^+) 420.2512, found 420.2507.

Nitro Benzoate 308c. To a solution of alcohol **307** (222 mg, 0.69 mmol) in THF (10 mL) at rt was added 4-nitrobenzoyl chloride (160 mg, 0.86 mmol) followed by pyr (0.12 mL, 1.5 mmol). After 3.5 hr, the reaction was quenched by addition of water and the resulting mixture extracted with EtOAc. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (30% to 50% EtOAc in Hex) afforded benzoate **308c** (209 mg, 64%) as colorless oil: ^{1}H NMR (MeOD+$CDCl_3$) δ 8.20 – 8.05 (m, 4 H), 7.19 (d, *J* = 1.6 Hz, 1H), 7.06 (d, *J* = 2.0 Hz, 1H), 5.2 (s, 2 H), 4.94 (s, bd, 1H), 4.35 (d, *J* = 12.4 Hz, 1H), 4.30 (d, *J* = 12.4 Hz, 1H), 3.34 (s, 3H), 3.30 – 3.27 (m, 1H), 2.65 – 2.62 (m, 2H), 1.94 – 1.91 (m, 1H), 1.78 – 1.50 (m, 4H), 1.11 (s, 3H), 1.02 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (MeOD+$CDCl_3$) δ 165.6, 152.0, 151.5, 136.5, 131.6 (2C), 130.8, 128.2, 127.1, 124.3, 123.0, 78.3, 77.7, 70.0, 68.6, 58.7, 47.7, 39.2, 38.7, 28.7, 27.8, 23.9, 20.4, 14.8; HRMS (EI) *m/z* calcd for $C_{26}H_{31}NO_7$ (M^+) 469.2101, found 469.2096.

Aldehyde 309. To a To a Solution of carbonate **308b** (95 mg, 0.23 mmol) in CH_2Cl_2 (5 mL) and water (0.5 mL) at rt was added DDQ (110 mg, 0.48 mmol). After 2 hr, the reaction was quenched by addition of $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated in vacuo afforded aldehyde **309** (71 mg, 78%) as orange oil: ^{1}H NMR ($CDCl_3$) δ 10.37 (s, 1H), 7.64 (d, *J* = 1.6 Hz, 1H), 7.34 (d, *J* = 2.0 Hz, 1H), 4.98 (s, 2H,), 3.44 (dd, *J* = 11.2, 4.4 Hz, 1H), 2.75 – 2.71 (m, 2H), 2.07 – 2.04 (m, 1H), 1.48 (s, 9H), 1.25 (s, 3H), 1.07 (s, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 189.8, 156.2, 153.3, 136.3, 126.8, 126.3, 124.2, 123.8, 82.4, 80.0, 77.7, 68.0, 46.3, 38.3, 37.4, 28.1, 27.7 (3C), 27.2, 22.8, 20.1, 14.2; HRMS (EI) *m/z* calcd for $C_{23}H_{32}O_6$ (M^+) 404.2199, found 404.2192.

Aldehyde 310. To a Solution of benzoate **308c** (204 mg, 0.43 mmol) in CH_2Cl_2 (5 mL) and water (0.5 mL) at rt was added DDQ (150 mg, 0.66 mmol). After 2 hr, the reaction was quenched by addition of $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated in vacuo afforded aldehyde **310** (140 mg, 71%) as orange oil: ^{1}H NMR ($CDCl_3$) δ 10.38 (s, 1H), 8.24 (d, *J* = 8.6, 2H), 8.18 (d, *J* = 8.6 Hz, 2H), 7.71 (d, *J* = 2.4 Hz, 1H), 7.41 (d, *J* = 2.0 Hz, 1H), 5.28 (s, 2H), 3.42 (dd, *J* = 11.6, 4.4 Hz, 1H), 2.77 – 2.74 (m, 2H), 2.05 (dt, *J* = 12.8, 3.2 Hz, 1H), 1.89 (dq, *J* = 12.8, 3.2 Hz, 1H), 1.78 (dd, *J* = 13.2, 3.6 Hz, 1H), 1.64 – 1.60 (m, 1H), 1.23 (s, 3H), 1.10 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 189.7, 164.4, 156.3, 150.4, 136.4, 135.3, 130.7 (2C), 126.4, 126.4, 124.2, 124.0, 123.4 (2C), 78.1, 77.5, 66.9, 46.2, 38.3, 37.4, 28.0, 27.1, 22.8, 20.1, 14.2; HRMS (EI) *m/z* calcd for $C_{25}H_{27}NO_7$ (M^+) 453.1788, found 453.1782.

Keto Aldehyde 312. To a solution of ketone **300** (110 mg, 0.32 mmol) in CH_2Cl_2 (5 mL) and water (0.5 mL) at rt was added DDQ (91 mg, 0.40 mmol). After 90 min at rt, the reaction was quenched with aqueous $NaHCO_3$ and the resulting solution was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo which afforded keto aldehyde **312** (94 mg, 90%) as an oil which was of sufficient purity to warrant no further purification: ^{1}H NMR ($CDCl_3$) δ 9.82 (s, 1H), 7.73 (s, 1H), 7.59 (s, 1H), 4.41 (s, 3H), 4.05 (d, *J* = 5.2 Hz, 1H), 3.49 (d, *J* = 4.4 Hz, 1H), 3.42 (s, 3H), 2.97 – 2.90 (m, 3H), 2.81 (dd, *J* = 16.4, 13.2 Hz, 1H), 2.34 (dd, *J* = 12.8, 5.2 Hz, 1H), 1.26 (s, 3H), 1.18 (s, 3H), 0.73 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 206.9, 191.0, 155.1, 130.6, 129.3, 128.7, 127.4, 121.6, 82.4, 79.6, 68.7, 58.6, 52.1, 45.8, 41.4, 27.2, 22.9, 21.4, 15.1; HRMS (EI) *m/z* calcd for $C_{19}H_{24}O_5$ (M^+) 332.1624, found 332.1614.

Triol 313. To a solution of keto aldehyde **312** (94 mg, 0.28 mmol) in CH_3OH (3 mL) at rt was added $NaBH_4$ (28 mg, 0.74 mmol). After 10 min, the reaction was quenched with 1N HCl and the resulting solution was extracted with EtOAc. The combined organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo which afforded triol **313** (92 mg, 97%) as an oil which was of sufficient purity to warrant no further purification. An analytical sample was purified by column chromatography (90% EtOAc in Hex): ^{1}H NMR (CD_3OD) δ 7.11 (d, J = 2.0 Hz, 1H), 7.02 (d, J = 1.2 Hz, 1H), 4.47 (s, 2H), 4.40 (s, 2H), 4.10 (ddd, J = 3.2, 3.2, 3.2 Hz, 1H), 3.36 (s, 3H), 3.21 (d, J = 4.0 Hz, 1H), 2.77 – 2.73 (m, 2H), 2.26 (dd, J = 13.6, 3.2 Hz, 1H), 1.86 (dd, J = 13.6, 3.4 Hz, 1H), 1.68 (dd, J = 11.8, 6.6 Hz, 1H), 1.36 (s, 3H), 1.06 (s, 6H); ^{13}C NMR (CD_3OD) δ 151.2, 133.3, 129.4, 127.3, 126.7, 123.2, 78.7, 77.4, 71.7, 70.4, 65.1, 58.4, 48.6, 44.8, 39.0, 29.4, 24.0, 22.1, 16.5; HRMS (EI) *m/z* calcd for $C_{19}H_{28}O_5$ (M^+) 336.1937, found 336.1936.

Ester 314. To a solution of alcohol **313** (44 mg, 0.13 mmol) in THF (3 mL) in an ice bath was added pyridine (0.7 mL, 0.87 mmol) followed by 4-nitrobenzoyl chloride (63 mg, 0.34 mmol). After 45 min, the reaction was quenched by addition of water and the resulting solution was extracted with EtOAc. The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography (60% EtOAc in Hex) afforded *p*-nitrobenzoate **314** (52 mg, 82%) as colorless oil: ^{1}H NMR ($CDCl_3$) δ 8.28 – 8.20 (m, 4H), 7.28 (d, *J* = 1.6 Hz, 1H), 7.12 (d, *J* = 1.6 Hz, 1H), 5.29 (s, 2H), 4.44 (s, 2H), 4.22 (ddd, *J* = 3.2, 3.2, 3.2 Hz, 1H), 3.44 (s, 3H), 3.35 (d, *J* = 3.2 Hz, 1H), 2.70 – 2.72 (m, 2H), 2.37 (dd, *J* = 14.4, 2.8 Hz, 1H), 1.93 (dd, *J* = 14.0, 3.2 Hz, 1H), 1.75 (dd, *J* = 11.8, 5.8 Hz, 1H), 1.39 (s, 3H), 1.08 (s, 3H), 1.06 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.6, 150.5, 150.4, 135.7, 130.8 (2C), 129.6, 127.1, 126.5, 125.9, 123.4 (2C), 121.9, 77.5, 76.2, 70.6, 69.1, 67.8, 58.5, 46.7, 43.2, 37.9,

28.8, 22.9, 21.8, 15.9; HRMS (EI) *m/z* calcd for $C_{26}H_{31}NO_8$ (M^+) 485.2050, found 485.2037.

Aldehyde 315. To a solution of methyl ether **314** (51 mg, 0.11 mmol), in CH_2Cl_2/water (6:1 3.5 mL) at rt was added DDQ (55 mg, 0.24 mmol). After 4 hr the reaction was quenched by addition of brine and $NaHCO_3$. The resulting solution was extracted with CH_2Cl_2, and the combined organic phases were washed with a small amount of water followed by brine. After, the organic phase was dried ($MgSO_4$) and concentrated in vacuo, aldehyde **315** (45 mg, 93%) was obtained as a faintly yellow wax that was used without further purification: ^{1}H NMR ($CDCl_3$) δ 10.40 (s, 1H), 8.28 – 8.20 (m, 4H), 7.74 (d, *J* = 2.0 Hz, 1H), 7.42 (d, *J* = 1.6 Hz, 1H), 5.31 (s, 2H), 4.27 (ddd, *J* = 3.2, 3.2, 3.2 Hz, 1H), 3.40 (d, *J* = 3.2 Hz, 1H), 2.85 – 2.81 (m, 2H), 2.45 (dd, *J* = 14.4, 2.8 Hz, 1H), 2.45 (brd s, 2H), 1.98 (dd, *J* = 14.0, 3.6 Hz, 1H), 1.80 (dd, *J* = 11.8, 5.8 Hz, 1H), 1.49 (s, 3H), 1.12 (s, 3H), 1.09 (s, 3H); ^{1}H NMR (Acetone-d_6) δ 10.38 (s, 1H), 8.34 – 8.24 (m, 4H), 7.68 (d, *J* = 1.6 Hz, 1H), 7.57 (d, *J* = 2.0 Hz, 1H), 5.35 (s, 2H), 4.17 (ddd, *J* = 3.2, 3.2, 3.2 Hz, 1H), 3.36 (d, 3.2 Hz, 1H), 2.87 – 2.84 (m, 2H), 2.37 (dd, *J* = 13.6, 3.2 Hz, 1H), 2.00 (m, 1H), 1.82 (dd, *J* = 10.8, 7.2 Hz, 1H), 1.48 (s, 3H), 1.11 (s, 3H), 1.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 189.8, 164.5, 156.1, 150.5, 136.4, 135.3, 130.8 (2C), 126.6, 126.5, 124.4, 124.2, 123.5 (2C), 77.9, 70.5, 67.0, 46.4, 43.1, 38.1, 28.8, 22.8, 21.9, 15.9; ^{13}C NMR (Acetone-d_6) δ 189.4, 165.1, 156.9, 151.5, 137.2, 136.4, 131.6 (2C), 127.9, 126.6, 125.7, 125.2, 124.5 (2C), 79.0, 77.6, 71.0, 67.5, 47.3, 43.9, 38.8, 29.1, 23.3, 22.2, 16.4; HRMS (EI) *m/z* calcd for $C_{25}H_{27}NO_8$ (M^+) 469.1719, found 469.1724.

Phenol 316. To a solution of aldehyde **315** (27 mg, 0.06 mmol) in CH_2Cl_2 (1 mL) at rt was added *m*-CPBA (30 mg, 77% max, 0.13 mmol). After 3 hr $NaOCH_3$ (51 mg, 0.94 mmol) was added. After an additional 15 hr, the reaction was acidified with

excess HCl and the resulting solution was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography (80% EtOAc in Hex) afforded phenol **316** (8 mg, 45%) as colorless oil: ^{1}H NMR (CD_3OD) δ 6.62 (d, *J* = 1.2 Hz, 1H), 6.58 (s, 1H), 4.41 (s, 2H), 4.12 (ddd, *J* = 3.2, 3.2, 3.2 Hz, 1H), 3.26 (d, *J* = 3.2 Hz, 1H), 2.74 – 2.71 (m, 2H), 2.34 (dd, *J* = 14.0, 3.2 Hz, 1H), 1.92 (dd, *J* = 14.0, 3.2 Hz, 1H), 1.72 (dd, *J* = 11.6, 6.4 Hz, 1H), 1.38 (s, 3H), 1.07 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (CD_3OD) δ 146.8, 141.3, 133.9, 124.0, 120.3, 113.1, 78.8, 77.7, 71.8, 65.3, 48.9, 44.7, 39.1, 29.4, 23.9, 21.9, 16.5; HRMS (EI) *m/z* calcd for $C_{17}H_{24}O_5$ (M^+) 308.1624, found 308.1634.

Acetal 318. To a solution of 4-hydroxybenzaldehyde **317** (5.0 g, 41 mmol) in CH_2Cl_2 (50 mL), was added DIPEA (10 mL, 57 mmol) followed by BOMCl (6.5 mL, 0.46 mmol). After 3 hr at rt, the reaction was quenched by addition of water and extracted with CH_2Cl_2. The resulting solution was washed with 1N HCl. The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo which afforded compound **318** (7.3 g, 74%) as a white crystals: ^{1}H NMR ($CDCl_3$) δ 9.85 (s, 1H), 7.80 (d, *J* = 8.8 Hz, 2H), 7.33 – 7.29 (m, 5H), 7.17 (d, *J* = 8.4 Hz, 2H), 5.33 (s, 2H), 4.70 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 190.4, 161.8, 136.5, 131.4 (2C), 130.3, 128.1 (2C), 127.6, 127.6 (2C), 155.9 (2C), 91.5, 69.9; HRMS (EI) *m/z* calcd for $C_{15}H_{14}O_3$ (M^+) 242.0943, found 242.0946.

BOM Alcohol 319. To a solution of aldehyde **318** (7.3 g, 30 mmol) in CH_3OH (2 mL) and THF (120 mL) at rt was added $NaBH_4$ (1.5 g, 40 mmol). After 30 min, the reaction was quenched by addition of 1N HCl. The resulting solution was extracted with EtOAc, and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to afford alcohol **319** in sufficient purity for direct use in the

following reaction: ^{1}H NMR ($CDCl_3$) δ 7.38 – 7.26 (m, 7H), 7.09 (d, *J* = 8.8 Hz, 1H), 5.30 (s, 2H), 4.74 (s, 2H), 4.65 (s, 2H), 1.89 (brd, 1H); ^{13}C NMR ($CDCl_3$) δ 156.9, 137.2, 134.5, 128.5 (2C), 128.5 (2C), 128.0, 127.8 (2C), 116.4 (2C), 92.4, 70.0, 64.9; HRMS (EI) *m/z* calcd for $C_{15}H_{16}O_3$ (M^+) 244.1099, found 244.1102.

Methyl Ether 320. The crystals obtained above (ca. 30 mmol) were dissolved in THF (120 mL), the solution was cooled to 0 ^{o}C, and NaH (2.0 g, 60% in oil, 50 mmol) was added in small portions. After evolution of hydrogen subsided (ca. 10 min), CH_3I (2.5 mL, 40 mmol) was added slowly. After an additional 2 hr, the reaction was slowly quenched by addition of water and the resulting solution was extracted with EtOAc. The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography (25% EtOAc in Hex) afforded ether **320** (6.4g, 73% over 83% steps) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.43 – 7.39 (m, 5H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 1H), 5.36 (s, 2H), 4.80 (s, 2H), 4.48 (s, 2H), 3.45 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.7, 137.1, 131.4, 129.0 (2C), 128.2, (2C), 127.7 (2C), 127.6, 116.0 (2C), 92.1, 74.0, 69.7, 57.6; HRMS (EI) *m/z* calcd for $C_{16}H_{18}O_3$ (M^+) 258.1256, found 258.1252.

Geranyl Arene 321. To a solution of TMEDA (0.6 mL, 4.0 mmol) in ether (30 mL) cooled in a brine bath was added BuLi (1.6 mL, 2.4 M in Hex, 3.7 mmol) followed by neat bromide **325** (1.0 g, 3.1 mmol). After 15 min, solid CuI (703 mg, 3.7 mmol) was added in one portion. After 10 min, neat geranyl bromide then was added over a period of 5 min. After an additional 3 hr, the reaction was quenched by addition of NH_4Cl, and the resulting solution was extracted with EtOAc. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (8% EtOAc in Hex) afforded compound **321** (760 mg, 63%) as a

colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.23 – 7.13 (m, 5H), 7.05 – 7.01 (m, 3H), 5.26 (m, 1H), 5.19 (s, 2H), 5.03 – 5.00 (m, 1H), 4.60 (s, 2H), 4.26 (s, 2H), 3.27 (d, *J* = 7.2 Hz, 2H), 3.25 (s, 3H), 2.02 – 1.92 (m, 2H), 1.62 (s, 3H), 1.56 (s, 3H), 1.49 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 154.5, 137.2, 135.8, 131.2, 131.2, 130.7, 129.3, 128.3 (2C), 127.9 (2C), 127.7, 126.6, 124.2, 122.4, 113.7, 92.2, 74.4, 69.8, 57.7, 39.7, 28.5, 26.6, 25.6, 17.6, 16.0; HRMS (EI) *m/z* calcd for $C_{26}H_{34}O_3$ (M^+) 394.2508, found 394.2505.

BOM Acetal 323. To a solution of methyl 4-hydroxybenzoate (32 g, 210 mmol) in CH_2Cl_2 (260 mL) was added Br_2 (11 mL, 225 mmol) at rt. After 24 h, the reaction was concentrated under a stream of air, resulting in acidic fumes. The crude solid obtained was dissolved in CH_2Cl_2, cooled to 0 ^{o}C, and DIPEA (110 mL, 630 mmol) was added followed by BOMCl (40 mL, 285 mmol). After 20 h, the reaction was quenched by addition of water followed by 1N HCl. The resulting mixture was extracted with CH_2Cl_2. The organic phase was washed with 2N NaOH, brine, dried ($MgSO_4$), and concentrated in vacuo. Ester **323** crystallized from the reaction mixture as white crystals in sufficient purity to warrant no further purification: ^{1}H NMR ($CDCl_3$) δ 8.27 (d, *J* = 2.0 Hz, 1H), 7.95 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.37 – 7.30 (m, 5H), 7.23 (d, *J* = 8.8 Hz, 1H), 5.41 (s, 2H), 4.75 (s, 2H), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.4, 157.2, 136.4, 134.7, 130.2, 128.3 (2C), 128.0, 127.9 (2C), 124.7, 114.6, 112.2, 92.4, 70. 4, 52.0; HRMS (EI) *m/z* calcd for $C_{16}H_{15}O_4Br$ (M^+) 350.0157, found 350.0160.

Benzyl Alcohol 324. To a solution of ester **323** (assumed quantitative reaction from above) in ether (300 mL) was cooled to 0 ^{o}C and $LiBH_4$ (9.0 mL, 413 mmol) was slowly added in small portions over 30 min. After 20 h, the reaction was quenched by slow addition of water, and the resulting mixture was extracted with EtOAc. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated in vacuo, which afforded

alcohol **324** as colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.56 (d, *J* = 2.0 Hz, 1H), 7.38 – 7.30 (m, 5 H), 7.21 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 5.35 (s, 2H), 4.77 (s, 2H), 4.55 (d, *J* = 4.0 Hz, 1H), 2.43 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 153.0, 136.8, 136.0, 132.0, 128.4 (2C), 128.0 (2C), 127.9, 127.1, 116.1, 112.8, 92.8, 70.2, 63.9; HRMS (EI) *m/z* calcd for $C_{15}H_{15}O_3Br$ (M^+) 322.0205, found 322.0213.

Methyl Ether 325. To a solution of the parent alcohol (ca. 210 mmol from above) in THF (250 mL) cooled to 0 ^{o}C was added NaH (18 g, 60% in oil, 600 mmol) in small portions. After evolution of hydrogen ceased (ca. 10 min), CH_3I (17 mL, 272 mmol) was added slowly. After an additional 5 hr, the reaction was slowly quenched by addition of water. The resulting solution was extracted with EtOAc. The organic phases were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Final purification by column chromatography (25% EtOAc in Hex) afforded compound **325** (51 g, 73% over 4 steps) as colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.61 (s, 1H), 7.38 – 7.37 (m, 5H), 7.24 – 7.23 (m, 2H), 5.37 (s, 2H), 4.79 (s, 2H), 4.39 (s, 2H), 3.39 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.95, 136.7, 133.1, 132.5, 128.2, (2C), 127.8 (2C), 127.7, 127.7, 115.7, 112.5, 92.6, 73.1, 70.0, 57.7; HRMS (EI) *m/z* calcd for $C_{16}H_{17}O_3Br$ (M^+) 336.0361, found 336.0362.

Epoxide 326. To a solution of TMEDA (3 mL, 20 mmol) in ether (40 mL) cooled in a brine bath was added BuLi (7.5 mL, 2.3 M in Hex, 17.3 mmol). After 5 min, bromide **325** (4.86 g, 14.4 mmol) was added in ether (20 mL) via canula. After an additional 15 min, CuI (3.0 g, 16 mmol) was added as a solid in one portion, resulting in a slow blackening of the solution. After an additional 15 min at the same temperature, freshly prepared (*R*)-6,7-epoxy geranyl bromide, prepared from the corresponding alcohol (**179**, 3.74g, 22 mmol, 93% ee), was added via canula as a solution in ether (5 mL). The reaction was allowed to warm slowly to rt and then was quenched by addition of NH_4Cl after an additional 4 h. The resulting mixture was extracted with EtOAc, and

the organic phases were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Final purification by column chromatography (18% EtOAc in Hex) afforded epoxide **326** (4.2 g, 71%) as colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.31 – 7.22 (m, 5H), 7.13 (s, 1H), 7.09 (m, 2H), 5.38 (t, *J* = 7.2 Hz, 1H), 5.26 (s, 2H), 4.67 (s, 2H), 4.33 (s, 2H), 3.37 (d, *J* = 7.2 Hz, 2H), 3.32 (s, 3H), 2.66 (t, *J* = 6.2 Hz, 1H), 2.20 – 2.12 (m, 2H), 1.74 (s, 3H), 1.67 – 1.60 (m, 2H), 1.23 (s, 3H), 1.21 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 154.3, 137.0, 134.6, 131.0, 130.1, 129.0, 128.1 (2C), 127.6 (2C), 127.4, 126.4, 122.9, 113.5, 92.0, 74.1, 69.6, 63.6, 57.8, 57.5, 36.1, 28.4, 27.1, 24.5, 18.4, 15.8; HRMS (EI) *m/z* calcd for $C_{26}H_{34}O_4$ (M^+) 410.2457, found 410.2462.

Compound 327. ^{1}H NMR ($CDCl_3$) δ 7.04 – 6.99 (m, 2H), 6.70 (d, *J* = 8.0 Hz, 1H), 4.31 (s, 2H), 3.35 (s, 3H), 3.15 – 3.10 (m, 1H), 2.67 – 2.64 (m, 2H), 1.92 (dt, *J* = 12.0, 3.0 Hz, 1H), 1.75 – 1.51 (m, 5H), 1.16 (s, 3H), 1.00 (s, 3H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.6, 129.6, 129.0, 127.3, 121.6, 116.7, 77.2, 76.2, 74.5, 57.8, 46.7, 38.0, 37.6, 27.9, 27.1, 22.8, 19.7, 14.1; HRMS (EI) *m/z* calcd for $C_{18}H_{26}O_3$ (M^+) 290.1882, found 290.1894.

Hexahydroxanthene 328. To a solution of epoxide **326** (774 mg, 1.89 mmol) in CH_2Cl_2 (200 mL) at –78 ^{o}C was added $BF_3{\cdot}OEt_2$ (1.0 mL, 8.0 mmol). After 8 min, the reaction was quenched by addition of Et_3N (2 mL), allowed to warm to rt, and concentrated *in vacuo*. Purification of the initial oil by column chromatography (30% EtOAc in Hex) afforded compounds **327** and **328** as an inseparable mixture (520 mg, 1:2 **327**: **328** corresponding to compound **328** (384 mg, 50%) and compound **327** (136 mg, 25%)) as a colorless oil: For compound **328**, HRMS (EI) *m/z* calcd for $C_{26}H_{34}O_4$ (M^+) 410.2457, found 410.2450.

Compound 329. ^{1}H NMR ($CDCl_3$) δ 6.81 (s, 1H), 6.77 (s, 1H), 3.44 (dd, *J* = 11.4, 4.2 Hz, 1H), 2.70 – 2.68 (m, 2H), 2.26 (s, 3H), 2.16 (s, 3H), 2.03 (dt, *J* = 12.8, 3.2 Hz, 1H), 1.89 – 1.62 (m, 5H), 1.21 (s, 3H), 1.12 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.9, 129.0, 128.1, 127.3, 125.7, 120.8, 78.1, 75.6, 47.0, 38.2, 37.8, 28.2, 27.3, 23.1, 20.4, 20.0, 15.9, 14.2; HRMS (EI) *m/z* calcd for $C_{18}H_{26}O_2$ (M^+) 274.1933, found 274.1938.

Compound 330. A mixture of compounds **327** and **328** was dissolved in CH_3OH (10 mL) in a high pressure vessel and 10% Pd/C (75 mg) was added. The reaction vessel was placed in a Parr shaker and pressurized to 30 psi at rt. After 15 h, the pressure was released, the reaction mixture was diluted with EtOAc, filtered over celite, and concentrated in vacuo. Final purification by column chromatography (25% EtOAc in Hex) afforded compound **329** (110 mg) and compound **330** (44 mg) as a colorless oil. For compound **330**: ^{1}H NMR ($CDCl_3$) δ 6.90 – 6.88 (m, 2H), 6.66 (d, *J* = 8.8 Hz, 1H), 3.43 (dd, *J* = 11.2, 4.0 Hz, 1H), 2.69 – 2.66 (m, 2H), 2.26 (s, 3H), 2.00 (dt, *J* = 12.4, 3.6 Hz, 1H), 1.87 – 1.56 (m, 5 H), 1.22 (s, 3H), 1.10 (s, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 150.7, 129.9, 128.9, 127.8, 121.5, 116.7, 78.1, 76.0, 47.0, 38.3, 37.8, 28.2, 27.3, 23.0, 20.4, 19.8, 14.2; HRMS (EI) *m/z* calcd for $C_{17}H_{24}O_2$ (M^+) 260.1776, found 260.1771.

Benzyl Alcohol 331. A mixture of compound **337** and compound **338** (185 mg, 2:1 **337** to **338**) was dissolved in CH_3OH (0.5 mL) and 10% Pd/C (30 mg) was added. The reaction vessel was sealed and purged with H_2 at rt. A stream of H_2 then was provided to maintain 1 atm of H_2, which resulted in the slow concentration of the solution to near dryness. After 23 hr, the resulting mixture was diluted with CH_3OH, filtered through celite, and concentrated *in vacuo*. Final purification by column chromatography (50% EtOAc in Hex) afforded alcohol **331** (81 mg, 76%) as colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.03 (m, 2H), 4.63 (d, *J* = 12.8 Hz, 1H), 4.57 (d, *J* = 12.8, 1H), 4.34 (s, 2H),

3.41 (dd, *J* = 11.6, 4.0 Hz, 1H), 3.37 (s, 3H), 2.73 – 2.68 (m, 2H), 2.02 (dt, *J* = 12.8, 3.4 Hz, 1H), 1.88 – 1.60 (m, 4 H), 1.22 (s, 3H), 1.09 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$) δ150.7, 129.4, 129.0, 128.5, 126.4, 121.8, 77.9, 74.5, 62.4, 58.0, 46.8, 38.4, 37.8, 28.2, 27.3, 22.9, 20.1, 14.2; ^{13}C NMR (MeOD) δ 151.3, 130.1, 130.0, 129.8, 126.8, 122.8, 78.8, 77.7, 75.8, 60.3, 57.9, 39.4, 39.0, 29.0, 27.9, 24.0, 20.3, 14.8; HRMS (EI) *m/z* calcd for $C_{19}H_{28}O_4$ (M^+) 320.1988, found 320.1990.

Aldehyde 332. To a solution of alcohol **331** (13 mg, 0.04 mmol) in CH_2Cl_2 at rt was added activated MnO_2 (95 mg, 0.87 mmol). After 20 h at rt, the solution was diluted with EtOAc, filtered through celite, and concentrated *in vacuo* which afforded aldehyde **332** (13 mg, 96%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 10.40 (s, 1H), 7.58 (d, *J* = 2.0 Hz, 1H), 7.33 (d, *J* = 2.0 Hz, 1H), 4.35 (s, 2H), 3.42 (dd, *J* = 11.6, 3.6 Hz, 1H), 3.37 (s, 3H), 2.76 – 2.73 (m, 2H), 2.05 (dt, *J* = 12.6, 3.2 Hz, 1H), 1.90 – 1.60 (m, 5H), 1.26 (s, 3H), 1.10 (s, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 190.0, 155.8, 135.7, 129.5, 125.6, 125.1, 123.7, 77.8, 77.8, 74.0, 58.1, 46.4, 38.4, 37.5, 28.2, 27.2, 22.9, 20.1, 14.2; HRMS (EI) *m/z* calcd for $C_{19}H_{26}O_4$ (M^+) 318.1831, found 318.1839.

Phenol 333. To a solution of aldehyde **332** (18 mg, 0.056 mmol) in CH_2Cl_2 (2 mL) was added *m*-CPBA (35 mg, 77% maximum, 0.14 mmol) at rt. After 2 hr, the reaction was diluted with CH_3OH (3mL) and solid K_2CO_3 (65 mg, 0.47 mmol) was added. After an additional 20 hr, the reaction was quenched by addition of 1N HCl and Na_2SO_3. The resulting mixture was neutralized by addition of $NaHCO_3$ and extracted with CH_2Cl_2. After the organic phases were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*, final purification by column chromatography (30% to 50% EtOAc in Hex) afforded phenol **333** (17 mg, 98%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.73 (d, *J* = 1.6 Hz, 1H), 6.63 (d, *J* = 1.6, 1H), 5.46 (s, 1H), 4.31 (s, 2H), 3.40 (dd, *J* = 11.2, 3.6 Hz, 1H), 3.36 (s, 3H), 2.71 – 2.66 (m, 2H), 2.01 (dt, *J* = 12.8, 3.6 Hz, 1H), 1.89 – 1.59

(m, 5H), 1.22 (s, 3H), 1.09 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 145.0, 139.6, 130.0, 121.9, 120.1, 112.0, 77.9, 77.7, 74.7, 57.9, 47.2, 38.4, 37.7, 28.2, 27.3, 22.7, 20.1, 14.3; HRMS (EI) *m/z* calcd for $C_{18}H_{26}O_4$ (M^+) 306.1831, found 306.1837.

Schweinfurthin B intermediate 77. To a solution of phenol **333** (9 mg, 0.03 mmol) in acetone (2 mL) was added K_2CO_3 (60 mg, 0.43 mmol) followed by CH_3I (0.06 mL, 0.96 mmol) and this solution was heated to reflux. After 2 hrs, the solution was allowed to cool to rt, quenched by addition of water and extracted with CH_2Cl_2. The organic phases were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford compound **77** (9 mg, 94%) as a colorless oil in sufficient purity for further use. The ^{1}H MNR spectrum of this material was identical to that prepared via different methods.

Schweinfurthin G intermediate 84. To a solution of phenol **333** (13 mg, 0.04 mmol) in CH_2Cl_2 (2mL), was added DIPEA (0.1 mL, 0.57 mmol) followed by MOMCl (0.02 mL, 0.26 mmol). After 2 h at rt, the reaction was quenched by addition of water and extracted with CH_2Cl_2. The resulting solution was washed with 1N HCl. The organic phase was dried ($MgSO_4$), and concentrated *in vacuo* to afford compound **84** (13 mg, 89%) as a yellow oil. The ^{1}H NMR spectrum of this material was identical to that prepared via different methods.

Ketone 334. To a solution of hexahydroxanthene **84** (680 mg, 1.9 mmol) in CH_2Cl_2 at rt was added catalytic TPAP (73 mg, 0.21 mmol) and NMO (284 mg, 2.4 mmol). After 26 hr, the reaction mixture was diluted with EtOAc, filtered through celite and silica, and concentrated *in vacuo*. Final purification by column chromatography (50% EtOAc in Hex) afforded ketone **334** (675 mg, 100%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.81 (s, 1H), 6.66 (s, 1H), 5.04 (d, J = 6.4 Hz, 1H), 5.02 (d, J = 6.8 Hz, 1H), 4.18 (s,

2H), 3.36 (s, 3H), 3.22 (s, 3H), 2.73 – 2.65 (m, 1H), 2.60 – 2.52 (m, 2H), 2.33 – 2.28 (m, 1H), 2.22 – 2.17 (m, 1H), 2.01 – 1.90 (m, 2H), 1.29 (s, 3H), 1.02 (s, 3H), 0.96 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 212.5, 145.3, 142.7, 129.2, 122.4, 121.5, 115.2, 95.2, 74.9, 73.8, 57.3, 55.5, 46.9, 45.8, 37.5, 34.5, 23.9, 23.1, 20.2, 18.5; HRMS (EI) *m/z* calcd for $C_{20}H_{28}O_5$ (M^+) 348.1937, found 348.1940.

Enone 335. To a solution of ketone **334** (140 mg, 0.40 mmol) in ethanol at rt was added benzaldehyde (0.2 mL, 1.7 mmol) followed by KOH (177 mg, 3.2 mmol). After 25 min, the reaction was quenched by addition of NH_4Cl, the resulting solution was extracted with EtOAc, and the organic extracts were washed with brine. After the organic phase was dried ($MgSO_4$) and concentrated *in vacuo*, final purification of the residue by column chromatography (25% EtOAc in Hex) afforded enone **335** (148 mg, 86%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.63 (d, *J* = 2.4 Hz, 1H), 7.45 – 7.32 (m, 5H), 6.96 (d, *J* = 2.0 Hz, 1H), 6.79 (d, *J* = 1.6 Hz, 1H), 5.20 (d, *J* = 6.8 Hz, 1H), 5.15 (d, *J* = 6.8 Hz, 1H), 4.32 (s, 2H), 3.49 (s, 3H), 3.50 – 3.40 (m, 1H), 3.36 (s, 3H), 2.98 (dd, *J* = 15.2, 2.8 Hz, 1H), 2.84 – 2.70 (m, 2H), 2.34 (dd, *J* = 12.6, 5.6, 1H), 1.31 (s, 3H), 1.20 (s, 3H), 1.16 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 205.0, 145.5, 142.8, 138.6, 135.0, 132.2, 130.0 (2C), 129.5, 128.7, 128.3 (2C), 122.6, 121.8, 115.4, 95.6, 75.4, 74.3, 57.8, 56.0, 45.7, 45.3, 41.7, 28.6, 24.2, 22.1, 19.1; HRMS (EI) *m/z* calcd for $C_{27}H_{32}O_5$ (M^+) 436.2250, found 436.2257.

Alcohol 336. To a solution of ketone **335** (115 mg, 0.26 mmol) in CH_3OH at rt was added $CeCl_3 \cdot 7H_2O$ (108 mg, 0.27 mmol) followed by $NaBH_4$ (12 mg, 0.32 mmol). After 2 hr, the reaction was quenched by addition of water and concentrated *in vacuo*. The resulting solution was extracted with EtOAc, and the extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Final purification by column chromatography (20% EtOAc in Hex) afforded alcohol **336** (110 mg, 96%) as white

crystals: ^{1}H NMR ($CDCl_3$) δ 7.37 – 7.22 (m, 5H), 6.94 (d, *J* = 2.0 Hz, 1H), 6.80 (m, 2H), 5.19 (d, *J* = 6.6 Hz, 1H), 5.14 (d, *J* = 6.6 Hz, 1H), 4.33 (s, 2H), 3.91 (s, 1H), 3.41 (s, 3H), 3.39 (s, 3H), 2.75 – 2.70 (m, 2H), 2.29 (m, 2H), 1.92 (dd, *J* = 12.2, 5.8 Hz, 1H), 1.20 (s, 3H), 1.06 (s, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 145.8, 143.5, 138.0, 137.4, 129.2, 128.8 (2C), 128.2 (2C), 126.3, 123.9, 123.2, 122.8, 115.3, 95.6, 79.8, 78.0, 74.6, 58.0, 56.0, 47.1, 41.2, 39.7, 27.2, 23.2, 19.8, 14.2; HRMS (EI) *m/z* calcd for $C_{27}H_{34}O_5$ (M^+) 438.2406, found 438.2408.

Triol 336a. To a solution of alcohol **336** (115 mg, 0.26 mmol) in dioxane (2 mL) and water (0.1 mL) at rt was added OsO_4 (0.2 mL, 0.002 M in tBuOH, 0.004 mmol) followed by NMO (68 mg, 0.58 mmol). After 17 hr, the reaction was diluted with water and extracted with EtOAc. The extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*, which afforded triol **336a** as a crystalline solid: ^{1}H NMR ($CDCl_3$) δ 7.50 – 7.48 (m, 2H), 7.34 – 7.26 (m, 3H), 6.86 (s, 1H), 6.75 (s, 1H), 5.07 (s, 1H), 5.03 (s, 2H), 4.64 (br s, 1H), 4.36 (br s, 1H), 4.28 (s, 2H), 3.61 (br s, 1H), 3.40 (s, 3H), 3.36 – 3.30 (m, 1H), 3.33 (s, 3H), 2.69 – 2.66 (m, 2H), 2.14 (d, *J* = 14.4 Hz, 1H), 1.94 (dd, *J* = 10.8, 7.2 Hz, 1H), 1.72 (d, *J* = 14.4 Hz, 1H), 1.26 (s, 3H), 1.12 (s, 3H), 1.06 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 145.8, 143.2, 139.4, 129.1 (2C), 129.1, 128.2 (2C), 128.1, 123.2, 123.0, 115.8, 95.8, 84.8, 77.8, 76.7, 75.1, 74.5, 57.9, 56.0, 46.0, 45.5, 37.8, 30.1, 23.2, 21.7, 16.5; HRMS (EI) *m/z* calcd for $C_{27}H_{36}O_7$ (M^+) 472.2461, found 472.2467.

Ketone 337. To a solution of partially purified triol **336a** (ca. 0.26 mmol) in CH_2Cl_2 (5mL) and water (0.1 mL) at rt was added $NaIO_4$ (720 mg, 3.3 mmol) and the resulting mixture was *vigorously* stirred. After 24 hr, the reaction was diluted with water and extracted with CH_2Cl_2 and the extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Final purification by column chromatography (30% EtOAc in Hex) afforded ketone **337** (81 mg, 84% over 2 steps) as a colorless oil: ^{1}H NMR ($CDCl_3$)

δ 6.95 (d, *J* = 1.6 Hz, 1H), 6.80 (s, 1H), 5.18 (d, *J* = 6.4 Hz, 1H), 5.15 (d, *J* = 6.4 Hz, 1H), 4.33 (s, 2H), 4.05 (d, *J* = 3.6 Hz, 1H), 3.50 (s, 3H), 3.46 (d, *J* = 4.4 Hz, 1H), 3.38 (s, 3H), 3.03 – 2.99 (m, 2H), 2.85 (dd, *J* = 16.4, 3.6 Hz, 1H), 2.77 (m, 1H), 2.34 (dd, *J* = 12.8, 5.2 Hz, 1H), 1.25 (s, 3H), 1.20 (s, 3H), 0.74 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 207.5, 146.0, 142.8, 130.2, 122.9, 122.5, 115.4, 95.8, 82.6, 78.8, 74.5, 58.1, 56.2, 52.5, 46.3, 41.5, 27.3, 23.2, 21.0, 15.1; HRMS (EI) *m/z* calcd for $C_{20}H_{28}O_6$ (M^+) 364.1886, found 364.1883.

Diol 338. To a solution of ketone **337** (81 mg, 0.22 mmol) in CH_3OH (0.3 mL) and THF (3 mL) at rt was added $NaBH_4$ (18 mg, 0.47 mmol). After 15 min, the reaction was quenched by addition of 1N HCl. The resulting solution was extracted with EtOAc, and the organic phases were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Immediate purification by column chromatography (80% EtOAc in Hex) afforded diol **338** (78 mg, 96%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.92 (d, *J* = 1.6 Hz, 1H), 6.77 (s, 1H), 5.18 (d, *J* = 6.0 Hz, 1H), 5.14 (d, *J* = 6.4 Hz, 1H), 4.31 (s, 2H), 4.15 (q, *J* = 3.2 Hz, 1H), 3.51 (s, 3H), 3.38 (s, 3H), 3.39 – 3.36 (m, 1H), 3.16 (brd, 1H), 2.77 – 2.69 (m, 3H), 2.42 (dd, *J* = 14.2, 3.0 Hz, 1H), 1.93 (dd, *J* = 14.4, 3.6 Hz, 1H), 1.70 (dd, *J* = 12.2, 5.4 Hz, 1H), 1.41 (s, 3H), 1.05 (s, 3H), 1.04 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 145.9, 143.3, 129.1, 123.4, 123.2, 115.9, 95.9, 77.3, 76.3, 74.7, 70.8, 58.0, 56.2, 46.9, 43.3, 37.9, 28.8, 23.0, 21.5, 15.9; HRMS (EI) *m/z* calcd for $C_{20}H_{30}O_6$ (M^+) 366.2042, found 366.2041.

Aldehyde 339. To a solution of methyl ether **338** (116 mg, 0.32 mmol), in CH_2Cl_2/water (15:1) at rt was added DDQ (90 mg, 0.40 mmol). After 15 min, the reaction was quenched by addition of brine and $NaHCO_3$. The resulting solution was extracted with CH_2Cl_2, and the organic extracts were washed with a small amount of water followed by brine. After the organic phase was dried ($MgSO_4$) and concentrated *in vacuo*, aldehyde **339** (109 mg, 98%) was obtained as a faintly yellow wax that was used

without further purification: ^{1}H NMR ($CDCl_3$) δ 9.79 (s, 1H), 7.46 (d, *J* = 1.6 Hz, 1H), 7.35 (d, *J* = 2.0 Hz, 1H), 5.23 (d, *J* = 6.4 Hz, 1H), 5.21 (d, *J* = 6.4 Hz,1 H), 4.26 (q, *J* = 3.2 Hz, 1H), 3.56 (s, 3H), 3.40 (m, 1H), 2.86 – 2.82 (m, 2H), 2.51 (dd, *J* = 14.2, 3.0 Hz, 1H), 2.25 (m, 2H), 2.03 (dd, *J* = 14.8, 3.4, Hz, 1H), 1.78 (dd, *J* = 11.8, 5.8 Hz, 1H), 1.47 (s, 3H), 1.13 (s, 3H), 1.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 190.9, 149.6, 146.6, 128.8, 127.1, 123.5, 115.3, 95.7, 78.0, 77.4, 70.7, 56.3, 46.6, 43.2, 38.1, 28.9, 23.0, 21.8, 16.0; HRMS (EI) *m/z* calcd for $C_{19}H_{26}O_6$ (M^+) 350.1729, found 350.1736.

Acetal 340. To a solution of alcohol **336** (119 mg, 0.27 mmol) in CH_2Cl_2 (2 mL) at rt was added DIPEA (1.0 mL, 5.7 mmol) followed by MOMCl (0.3 mL, 3.9 mmol). After 4 hr, additional MOMCl (0.2 mL, 2.6 mmol) was added, and after another 15 hr the reaction was quenched by addition of water. The resulting solution was extracted with CH_2Cl_2, and the combined organic extracts were washed with 1N HCl followed by brine. After the organic phase was dried ($MgSO_4$) and concentrated in vacuo, final purification by column chromatography (30% EtOAc in Hex) afforded acetal **340** (126 mg, 97%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.26 – 7.11 (m, 5H), 6.82 (d, *J* = 1.6 Hz, 1H), 6.68 (d, *J* = 1.2 Hz, 1H), 6.59 (s, 1H), 5.07 (d, *J* = 6.4 Hz, 1H), 5.04 (d, *J* = 6.8 Hz, 1H), 4.71 (d, *J* = 7.2 Hz, 1H), 4.61 (d, *J* = 6.8 Hz, 1H), 4.22 (s, 2H), 3.91 (s, 1H), 3.40 (s, 3H), 3.38 (s, 3H), 3.27 (s, 3H), 3.31 – 3.27 (m, 1H), 2.68 – 2.59 (m, 2H), 2.19 (d, *J* = 12.4 Hz, 1H), 1.87 (dd, *J* = 12.8, 5.6 Hz, 1H), 1.13 (s, 3H), 0.92 (s, 3H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 145.8, 143.4, 137.3, 135.0, 129.3, 128.7 (2C), 128.2 (2C), 126.3, 124.8, 122.9, 122.8, 115.2, 96.1, 95.6, 85.4, 78.1, 74.5, 57.9, 56.4, 56.0, 47.4, 41.5, 39.6, 27.1, 23.2, 19.6, 14.9; HRMS (EI) *m/z* calcd for $C_{29}H_{38}O_6$ (M^+) 482.2668, found 482.2672.

Ketone 341. To a solution of compound **340** (93 mg, 0.19 mmol) in acetone (2.5 mL) was added solid $NaHCO_3$ (340 mg, 4.0 mmol) followed by solid $KMnO_4$ (163 mg, 1.0 mmol). After 3 hours at rt, additional $KMnO_4$ (54 mg, 0.34 mmol) was added, and

after an additional 5 hr at rt the reaction was quenched by addition of 2-propanol. After 20 min, the mixture was filtered through celite, the celite was washed with acetone, and the filtrate was concentrated in vacuo. Final purification of the residue by column chromatography (30% EtOAc in Hex) afforded recovered starting material (18 mg, 19%) and ketone **341** (60 mg, 76%) as colorless oils: ^{1}H NMR ($CDCl_3$) δ 6.93 (d, *J* = 1.2 Hz, 1H), 6.79 (s, 1H), 5.17 (d, *J* = 6.8 Hz, 1H), 5.13 (d, *J* = 6.8 Hz, 1H), 4.71 (d, *J* = 7.2 Hz, 1H), 4.68 (d, *J* = 6.8 Hz, 1H), 4.31 (s, 2H), 4.13 (s, 1H), 3.48 (s, 3H), 3.42 (s, 3H), 3.36 (s, 3H), 2.96 – 2.76 (m, 4H), 2.32 (dd, *J* = 12.8, 5.6 Hz, 1H), 1.24 (s, 3H), 1.18 (s, 3H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 205.1, 146.0, 142.9, 130.1, 122.8, 122.4, 115.5, 96.2, 95.8, 86.2, 78.4, 74.4, 58.1, 56.2, 56.1, 53.9, 47.2, 40.9, 27.2, 23.3, 20.6, 15.7; HRMS (EI) *m/z* calcd for $C_{22}H_{32}O_7$ (M^+) 408.2148, found 408.2151.

Alcohol 342. To a solution of ketone **341** (57 mg, 0.15 mmol) in CH_3OH (0.5 mL) and THF (3.0 mL) at rt was added $NaBH_4$ (20 mg, 0.53 mmol). After 20 min, the reaction was quenched by addition of water and concentrated in vacuo. The resulting solution was extracted with EtOAc, and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography (60% EtOAc in Hex) afforded alcohol **342** (40 mg, 70%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 6.92 (d, *J* = 1.6 Hz, 1H), 6.77 (d, *J* = 1.6 Hz, 1H), 5.20 (d, *J* = 6.8 Hz, 1H), 5.14 (d, *J* = 6.4 Hz, 1H), 4.81 (d, *J* = 6.8 Hz, 1H), 4.71 (d, *J* = 6.4 Hz, 1H), 4.30 (s, 2H), 4.29 (m, 1H), 3.51 (s, 3H), 3.45 (s, 3H), 3.36 (s, 3H), 3.26 (d, *J* = 3.2 Hz, 1H), 2.77 – 2.72 (m, 2H), 2.49 (dd, *J* = 14.8, 3.0 Hz, 1H), 2.37 (s, 1H), 1.93 (dd, *J* = 14.8, 3.2 Hz, 1H), 1.76 (dd, *J* = 11.8, 5.8 Hz, 1H), 1.43 (s, 3H), 1.08 (s, 3H), 1.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 145.9, 143.3, 129.2, 123.2, 123.1, 115.7, 96.9, 95.9, 84.8, 76.1, 74.6, 68.6, 57.9, 56.1, 56.1, 47.1, 42.3, 37.8, 28.7, 22.9, 21.5, 16.6; HRMS (EI) *m/z* calcd for $C_{22}H_{34}O_7$ (M^+) 410.2260, found 410.2296.

Aldehyde 343. To a solution of methyl ether **342** (73 mg, 0.18 mmol), in CH_2Cl_2/water (10:1) at rt was added DDQ (70 mg, 0.31 mmol). After 20 min, the reaction was quenched by addition of brine and $NaHCO_3$. The resulting solution was extracted with CH_2Cl_2, and the combined organic extracts were washed with a small amount of water followed by brine. After the organic phase was dried ($MgSO_4$) and concentrated in vacuo, aldehyde **343** (70 mg, 100%) was obtained as a light yellow wax that was used without further purification: ^{1}H NMR ($CDCl_3$) δ 9.77 (s, 1H), 7.44 (d, *J* = 1.6 Hz, 1H), 7.34 (d, *J* = 1.2 Hz, 1H), 5.22 (d, *J* = 6.4 Hz, 1H), 5.19 (d, *J* = 6.4 Hz, 1H), 4.82 (d, *J* = 7.2 Hz, 1H), 4.72 (d, *J* = 6.8 Hz, 1H), 4.31 (q, *J* = 3.4 Hz, 1H), 3.51 (s, 3H), 3.46 (s, 3H), 3.27 (d, *J* = 3.6 Hz, 1H), 2.84 – 2.77 (m, 2H), 2.55 (dd, *J* = 14.4, 3.2 Hz, 1H), 2.40 (s, 1H), 1.95 (dd, *J* = 14.2, 3.0 Hz, 1H), 1.78 (dd, *J* = 12.0, 5.6 Hz, 1H), 1.47 (s, 3H), 1.11 (s, 3H), 1.10 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 190.9, 149.7, 146.6, 128.7, 127.0, 123.5, 115.3, 96.9, 95.7, 84.6, 77.9, 68.5, 56.3, 56.1, 46.8, 42.1, 37.9, 28.7, 22.9, 21.8, 16.6; HRMS (EI) *m/z* calcd for $C_{21}H_{30}O_7$ (M^+) 394.1992, found 394.1982.

Aldehyde 345. To a solution of alcohol **343** (23 mg, 0.058 mmol) in CH_2Cl_2 (0.5 mL) at rt was added DIPEA (0.3 mL, 1.7 mmol) followed by slow addition of MOMCl (0.1 mL, 1.3 mmol) over 5 min. After 23 hr, the reaction was quenched by addition of water, the resulting solution was extracted with CH_2Cl_2, and the combined organic extracts were washed with 1N HCl followed by brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to afford aldehyde **345** in quantitative yield as a yellow oil, which was used in the subsequent reaction HWE condensation without further purification. This material was identical to the material prepared via other methods[5l] based on comparison of the ^{1}H NMR spectra.

Tris-MOM Aldehyde 345. To a solution of diol **339** (40 mg, 0.11 mmol) in CH_2Cl_2 (0.5 mL) at rt was added DIPEA (0.8 mL, 7.3 mmol) followed by slow addition

of MOMCl (0.2 mL, 2.6 mmol) over 20 min. After 5 hr, the reaction was quenched by addition of water, the resulting solution was extracted with CH_2Cl_2, and the organic phases were washed with 1N HCl followed by brine. The organic phase was dried ($MgSO_4$), and concentrated *in vacuo*. Final purification by column chromatography (45% EtOAc in Hex) afforded aldehyde **345** (37 mg, 74%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 9.78 (s, 1H), 7.46 (d, *J* = 1.6 Hz, 1H), 7.35 (d, *J* = 1.2 Hz, 1H), 5.24 (d, *J* = 6.4 Hz, 1H), 5.20 (d, *J* = 6.8 Hz, 1H), 4.85 (d, *J* = 6.8 Hz, 1H), 4.70 (s, 2H), 4.64 (d, *J* = 6.8 Hz, 1H), 4.21 (q, *J* = 3.4 Hz, 1H), 3.50 (s, 3H), 3.45 (s, 3H), 3.40 (s, 3H), 3.32 (d, *J* = 3.2 Hz, 1H), 2.84 – 2.81 (m, 2H), 2.50 (dd, *J* = 14.4, 3.6 Hz, 1H), 1.91 (dd, *J* = 14.0, 3.2 Hz, 1H), 1.78 (dd, *J* = 11.2, 6.8 Hz, 1H), 1.44 (s, 3H), 1.12 (s, 3H), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 190.9, 149.5, 146.6, 128.7, 127.1, 123.6, 115.0, 96.2, 95.9, 95.5, 82.7, 78.1, 72.9, 56.3, 56.2, 55.6, 47.1, 41.5, 38.3, 28.7, 22.9, 21.3, 16.2; HRMS (EI) *m/z* calcd for $C_{23}H_{34}O_8$ (M^+) 438.2254, found 438.2250.

Stilbene 346. To a solution of diisopropyl amine (0.05 mL, 0.36 mmol) in THF (0.3 mL) in an ice bath was added BuLi (2.4M in Hex, 0.05 mL, 0.12 mmol). To this solution, phosphonate **22** (68 mg, 0.14 mmol) in THF (0.5 mL) was added via canula. After 5 min, aldehyde **345** (21 mg, 0.05 mmol) in THF (0.5 mL) was added via canula. After 2 hr, TLC analysis showed little reaction progress and additional base was added (KHMDS, 0.5 M in toluene, 0.3 mL, 0.15 mmol). After an additional 2 hr, the reaction was complete by TLC and the reaction was quenched by addition of NH_4Cl. The resulting solution was extracted with EtOAc, and the organic phases were washed with 1N HCl followed by brine. After the organic phase was dried ($MgSO_4$), and concentrated *in vacuo*, final purification by column chromatography (50% EtOAc in Hex) afforded stilbene **346** (25 mg, 68%) as colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.16 (d, *J* = 1.6 Hz, 1H), 6.96 (s, 1H), 6.94 – 6.89 (m, 4H), 5.27 (d, *J* = 6.8 Hz, 1H), 5.25 (s, 4H), 5.23 (d, *J* = 7.2 Hz, 1H), 5.20 (t, *J* = 5.2 Hz, 1H), 5.05 (t, *J* = 5.2 Hz, 1H), 4.87 (d, *J* = 6.8 Hz, 1H), 4.73

(d, *J* = 6.8 Hz, 1H), 4.68 (d, *J* = 7.2 Hz, 1H), 4.66 (d, *J* = 7.2 Hz, 1H), 4.20 (q, *J* = 3.2 Hz, 1H), 3.54 (s, 3H), 3.49 (s, 6H), 3.46 (s, 3H), 3.41 (s, 3H), 3.37 (d, *J* = 6.4 Hz, 2H), 3.35 (d, *J* = 3.6 Hz, 1H), 2.78 – 2.75 (m, 2H), 2.51 (dd, *J* = 14.0, 2.8 Hz, 1H), 2.06 – 1.88 (m, 6H), 1.78 (s, 3H), 1.64 (s, 3H), 1.56 (s, 3H), 1.43 (s, 3H), 1.11 (s, 3H), 1.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.4 (2C), 146.1, 142.9, 136.3, 134.7, 131.4, 128.7, 127.6, 126.2, 124.1, 123.2, 122.1, 121.7, 118.9, 112.3, 105.3 (2C), 95.9, 95.4, 95.3, 93.9 (2C), 82.3, 77.2, 72.9, 56.2, 56.2, 55.9 (2C), 55.6, 46.9, 41.2, 39.7, 38.1, 28.6, 26.5, 25.7, 22.9, 22.4, 21.0, 17.6, 16.2, 16.0; HRMS (EI) *m/z* calcd for $C_{44}H_{64}O_{11}$ (M^+) 768.4449, found 768.4452.

Schweinfurthin A (8). To a solution of stilbene **346** (12 mg, 0.016 mmol) in methanol (1 mL) at rt was added TsOH (16 mg, 0.08 mmol). After 48 hr, the reaction was quenched by addition of $NaHCO_3$ and the resulting solution was extracted with EtOAc. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Final purification by preparative thin layer chromatography (70% EtOAc in Hex) afforded schweinfurthin A (**8**, 5 mg, 58%) as a yellow wax: $[\alpha]^{25}_D$ = +47 (c 1.0, EtOH, 90% ee by HPLC); ^{1}H NMR (MeOD) δ 6.79 (s, 1H), 6.77 (d, *J* = 16.4 Hz, 1H), 6.72 (s, 1H), 6.72 (d, *J* = 16.4 Hz, 1H), 6.44 (s, 2H), 5.24 (t, *J* = 7.2 Hz, 1H), 5.07 (t, *J* = 7.2 Hz, 1H), 4.14 (q, *J* = 3.6 Hz, 1H), 3.30 (m, 3H), 2.75 (m, 2H), 2.36 (dd, *J* = 13.8, 3.0 Hz, 1H), 2.06 – 2.02 (m, 2H), 1.96 – 1.93 (m, 3H), 1.76 (s, 3H), 1.77 – 1.73 (m, 1H), 1.62 (s, 3H), 1.56 (s, 3H), 1.41 (s, 3H), 1.10 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (MeOD) δ 157.3 (2C), 147.1, 141.9, 137.5, 134.8, 132.0, 130.9, 128.6, 127.4, 125.5, 124.6, 124.2, 120.4, 115.8, 111.0, 105.6 (2C), 78.8, 78.1, 71.8, 48.9, 44.7, 41.0, 39.2, 29.4, 27.8, 25.9, 23.9, 23.2, 22.0, 17.7, 16.6, 16.3; HRMS (EI) *m/z* calcd for $C_{34}H_{44}O_6$ (M^+) 548.3138, found 548.3145.

Stilbene 347. To a solution of aldehyde **345** (13 mg, 0.03 mmol) and phosphonate **108** (35 mg, 0.08 mmol) in THF (1.5 mL) in an ice bath was added KHMDS

(0.5 M in toluene, 0.2 mL, 0.1 mmol). After 30 min, the reaction appeared to be complete by TLC analysis, so it was quenched by addition of NH_4Cl. The resulting solution was extracted with EtOAc, and the combined organic extracts were washed with 1N HCl followed by brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (50% EtOAc in Hex) afforded stilbene **347** (14 mg, 68%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.13 (d, *J* = 2.4 Hz, 1H), 6.96 – 6.85 (m, 5H), 5.23 (s, 4H), 5.22 (d, *J* = 6.8 Hz, 1H), 5.19 (d, *J* = 6.8 Hz, 1H), 5.23 – 5.18 (m, 1H), 4.86 (d, *J* = 6.8 Hz, 1H), 4.71 (d, *J* = 6.4 Hz, 1H), 4.70 (d, *J* = 6.8 Hz, 1H), 4.65 (d, *J* = 6.8 Hz, 1H), 4.21 (q, *J* = 3.0 Hz, 1H), 3.54 (s, 3H), 3.50 (s, 6H), 3.46 (s, 3H), 3.41 (s, 3H), 3.38 (d, *J* = 6.4 Hz, 2H), 3.33 (d, *J* = 3.2 Hz, 1H), 2.79 – 2.76 (m, 2H), 2.47 (dd, J = 14.0, 3.2 Hz, 1H), 1.90 (dd, J = 14.0, 2.4 Hz, 1H), 1.80 (m, 1H), 1.78 (s, 3H), 1.66 (s, 3H), 1.43 (s, 3H), 1.12 (s, 3H), 1.10 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.8 (2C), 146.2, 143.5, 136.7, 131.0, 129.0, 128.0, 126.6, 123.5, 122.7, 122.0, 119.4, 113.4, 105.9 (2C), 96.2, 96.0, 95.8, 94.4 (2C), 83.0, 77.2, 73.1, 56.2, 56.2, 56.0 (2C), 55.6, 47.4, 41.6, 38.3, 28.7, 25.8, 23.1, 22.7, 21.1, 17.8, 16.2; HRMS (EI) *m/z* calcd for $C_{39}H_{56}O_{11}$ (M^+) 700.3823, found 700.3815.

Vedelianin (12). To a solution of stilbene **347** (13 mg, 0.018 mmol) in methanol (1 mL) at rt was added TsOH (27 mg, 0.14 mmol). After 48 hr, the reaction was quenched by addition of $NaHCO_3$ and the resulting solution was extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Final purification by preparative thin layer chromatography (80% EtOAc in Hex) afforded partially hydrolyzed material (4.2 mg, ca. 40%) along with vedelianin (**12**, 3 mg, 33%) as a yellow wax: $[\alpha]^{25}_D$ = +35 (c 1.4, MeOH, 90% ee by HPLC); ^{1}H NMR (MeOD) δ 6.80 (d, *J* = 16.4 Hz, 1H), 6.79 (s, 1H), 6.71 (s, 1H), 6.70 (d, *J* = 16.4 Hz, 1H), 6.44 (s, 2H), 5.23 (m, 1H), 4.14 (q, *J* = 3.2 Hz, 1H), 3.30 (m, 1H), 3.26 (d, *J* = 7.2 Hz, 2H), 2.77 – 2.73 (m, 2H), 2.36 (dd, *J* = 13.6, 2.8 Hz, 1H), 1.94 (dd, *J* = 14.6, 3.4 Hz, 1H), 1.78 (m, 1H),

1.75 (s, 3H), 1.65 (s, 3H), 1.41 (s, 3H), 1.10 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (MeOD) δ 157.0 (2C), 146.8, 141.6, 137.2, 130.7, 130.5, 128.2, 127.1, 124.3, 123.8, 120.0, 115.5, 110.7, 105.3 (2C), 78.5, 77.7, 71.5, 48.6, 44.4, 38.8, 29.1, 25.7, 23.6, 23.0, 21.7, 17.6, 16.2.

Aldehyde 350. To a solution of methyl ether **331** (350 mg, 1.1 mmol), in CH_2Cl_2/water (10:1) at rt was added DDQ (320 mg, 1.4 mmol). After 15 min, the reaction was quenched by addition of brine and $NaHCO_3$. The resulting solution was extracted with CH_2Cl_2, and the combined organic extracts were washed with a small amount of water followed by brine. After the organic phase was dried ($MgSO_4$) and concentrated in vacuo, aldehyde **350** was obtained as a faintly yellow wax that was used without further purification: ^{1}H NMR δ 9.76 (s, 1H), 7.65 (d, *J* = 1.6 Hz, 1H), 7.54 (d, *J* = 2.0 Hz, 1H), 5.26 (s, 1H), 4.64 (d, *J* = 13.2 Hz, 1H), 4.60 (d, *J* = 13.6 Hz, 1H), 3.38 (dd, *J* = 11.4, 4.2 Hz, 1H), 2.79–2.67 (m, 2H), 2.34 (br, 1H), 2.04–1.99 (m, 1H), 1.87–1.57 (m, 4H), 1.20 (s, 3H), 1.07 (s, 3H), 0.85 (s, 3H); ^{13}C NMR δ 191.2, 156.2, 131.3, 129.6, 128.6, 127.7, 122.2, 78.4, 77.5, 60.7, 46.4, 38.3, 37.5, 27.9, 27.1, 22.7, 20.2, 14.2; HRMS (EI) calcd for $C_{18}H_{24}O_4$ (M^+) 304.1675, found 304.1668.

Silyl Ether 351. To a solution of alcohol **350**, in CH_2Cl_2 at rt was added TBSCl (485 mg, 3.2 mmol) followed by imidazole (394 mg, 5.8 mmol). After 45 min, the reaction was quenched by addition of water. The resulting solution was extracted with CH_2Cl_2, and the combined organic extracts were washed with a small amount of water followed by brine. After which the organic phase was dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (30% EtOAc in Hex) afforded aldehyde **351** (321 mg, 70% over 2-steps) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 9.82 (s, 1H), 7.78 (d, *J* = 1.2 Hz, 1H), 7.55 (d, *J* = 1.8 Hz, 1H), 4.70 (d, *J* = 14.4 Hz, 1H), 4.62 (d, *J* = 14.1 Hz, 1H), 3.40 (dd, *J* = 11.4, 3.9 Hz, 1H), 2.77–2.72 (m, 2H), 2.07–2.00 (m, 1H),

1.89–1.62 (m, 4H), 1.20 (s, 3H), 1.09 (s, 3H), 0.94 (s, 9H), 0.87 (s, 3H), -0.11 (s, 6H); ^{13}C NMR δ 191.5, 155.3, 130.1, 130.0, 128.6, 127.4, 121.6, 77.9, 77.6, 59.7, 46.4, 38.3, 37.5, 28.0, 27.1, 25.9 (3C), 22.8, 20.2, 18.4, 14.2, –5.4 (2C); HRMS (EI) calcd for $C_{24}H_{38}O_4Si$ (M^+–*t*Bu) 362.1869, found 362.1861.

Stilbene 353. Under the general conditions for HWE condensations, aldehyde **351** (320 mg, 0.76 mmol) phosphonate **352** (560 mg, 1.23 mmol), and KHMDS (0.5 M in toluene, 5 mL, 2.5 mmol) were allowed to react in THF (10 mL) for 10 min. Final purification by column chromatography (30% EtOAc in Hex) afforded stilbene **353** (195 mg, 36%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.44 (d, *J* = 0.8 Hz, 1H), 7.14 (d, *J* = 1.6 Hz, 1H), 6.96 (d, *J* = 16.0 Hz, 1H), 6.90 (*J* = 16.0 Hz, 1H), 6.86 (d, *J* = 0.8 Hz, 1H), 6.71 (d, *J* = 0.8 Hz, 1H), 5.23 (s, 2H), 5.20 (t, *J* = 6.8 Hz, 1H), 5.07 (t, *J* = 6.8 Hz, 1H), 4.70 (d, *J* = 13.6 Hz, 1H), 4.63 (d, *J* = 13.6 Hz, 1H), 3.87 (s, 3H), 3.50 (s, 3H), 3.43 (dd, *J* = 11.6, 4.4 Hz, 1H), 3.37 (d, *J* = 6.8 Hz, 2H), 2.73–2.70 (m, 2H), 2.06–1.84 (m, 8H), 1.78 (s, 3H), 1.72–1.68 (m, 2H), 1.65 (s, 3H), 1.57 (s, 3H), 1.20 (s, 3H), 1.10 (s, 3H), 0.98 (s, 9H), 0.88 (s, 3H), –0.13 (s, 6H); ^{13}C NMR δ 158.2, 155.8, 149.6, 136.8, 134.6, 131.2, 129.4, 128.8, 128.4, 126.3, 126.3, 124.4, 123.4, 122.7, 121.1, 118.6, 105.3, 102.6, 94.5, 78.0, 76.5, 60.2, 56.0, 55.7, 46.8, 39.8, 38.3, 37.8, 28.2, 27.3, 26.7, 26.0, 25.7 (3C), 23.0, 22.4, 20.1, 18.5, 17.6, 16.0, 14.2, –5.2 (2C); HRMS (EI) calcd for $C_{44}H_{66}O_6Si$ (M^+) 718.4629, found 718.4631.

Alcohol 354. To a solution of silyl ether **353** (195 mg, 0.27 mmol) in THF at rt was added TBAF (0.5 mL, 1 M in THF, 0.5 mmol). After 4 h, the reaction was quenched by addition of water, the resulting solution was extracted with EtOAc, and the combined organic phases were washed with brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo, which provided nonracemic alcohol **354** (193 mg, 100% yield, 89% ee by HPLC) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.27 (d, *J* = 1.2 Hz, 1H), 7.18

(d, *J* = 1.2 Hz, 1H), 6.97 (d, *J* = 16.0 Hz, 1H), 6.92 (d, *J* = 16.0 Hz, 1H), 6.84 (s, 1H), 6.71 (s, 1H), 5.23 (s, 2H), 5.22 (m, 1H), 5.08 (t, *J* = 6.2 Hz, 1H), 4.66 (d, *J* = 13.2 Hz, 1H), 4.59 (d, *J* = 13.2 Hz, 1H), 3.87 (s, 3H), 3.50 (s, 3H), 3.40–3.37 (m, 3H), 2.75–2.64 (m, 2H), 2.08–1.95 (m, 5H), 1.86–1.80 (m, 2H), 1.79 (s, 3H), 1.75–1.67 (m, 3H), 1.66 (s, 3H), 1.58 (s, 3H), 1.22 (s, 3H), 1.10 (s, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.1, 155.7, 150.5, 136.5, 134.4, 130.9, 129.0, 128.7, 127.7, 127.2, 126.6, 124.3, 124.2, 122.6, 121.8, 118.7, 105.3, 102.6, 94.4, 77.6, 77.1, 61.8, 55.8, 55.6, 46.7, 39.7, 38.2, 37.7, 28.0, 27.2, 26.6, 25.6, 22.8, 22.4, 20.1, 17.5, 15.9, 14.2; HRMS (EI) *m/z* calcd for $C_{38}H_{52}O_6$ (M^+) 604.3764, found 604.3751.

Schweinfurthin analogue 355. Under the general conditions for MOM hydrolysis, stilbene **354** (14 mg, 0.025 mmol), methanol (1 mL), and *p*-TsOH·H_2O (68 mg, 0.37 mmol) were allowed to react for 24 h to provide analogue **355** (2 mg, 17%) as a white solid after purification by thin layer chromatography (50% EtOAc in Hex): ^{1}H NMR ($CDCl_3$) δ 7.26 (s, 1H), 7.18 (s, 1H), 6.95 (d, *J* = 16.0 Hz, 1H), 6.86 (d, *J* = 16.0 Hz, 1H), 6.63 (s, 1H), 6.60 (s, 1H), 5.23 (m, 1H), 5.06 (m, 1H), 4.67 (d, *J* = 12.4 Hz, 1H), 4.60 (d, *J* = 12.4 Hz, 1H), 3.85 (s, 3H), 3.46–3.40 (m, 3H), 2.76 (m, 2H), 2.09–1.88 (m, 8H), 1.80 (s, 3H), 1.75–1.70 (m, 2H), 1.66 (s, 3H), 1.59 (s, 3H), 1.25 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); HRMS (EI) *m/z* calcd for $C_{36}H_{48}O_5$ (M^+) 560.3502, found 560.3508.

Aldehyde 356. To a solution of alcohol **354** (50 mg, 0.10 mmol) in CH_2Cl_2 at rt was added activated MnO_2 (250 mg, 2.3 mmol). After 22 h at rt, the solution was diluted with EtOAc, filtered through celite, and concentrated in vacuo which afforded aldehyde **356** (49 mg, 98%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 10.41 (s, 1H), 7.78 (s, 1H), 7.47 (s, 1H), 6.96 (s, 2H), 6.87 (s, 1H), 6.70 (s, 1H), 5.20 (s, 2H), 5.19 (m, 1H), 5.06 (m, 1H), 3.86 (s, 3H), 3.49 (s, 3H), 3.44 (dd, *J* = 11.4, 3.4 Hz, 1H), 3.37 (d, *J* = 6.8 Hz, 2H), 2.77–2.73 (m, 2H), 2.08–1.82 (m, 8H), 1.77 (s, 3H), 1.74–1.70 (m, 2H), 1.64 (s, 3H), 1.50 (s,

3H), 1.28 (s, 3H), 1.12 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 189.9, 158.2, 155.8, 155.6, 136.0, 134.6, 133.6, 131.1, 129.2, 128.0, 126.6, 124.4, 124.4, 123.8, 123.7, 122.5, 119.2, 105.4, 102.7, 94.5, 78.0, 77.7, 55.9, 55.7, 46.5, 39.7, 38.4, 37.4, 28.1, 27.2, 26.7, 25.6, 22.9, 22.4, 20.2, 17.6, 16.0, 14.2; HRMS (EI) *m/z* calcd for $C_{38}H_{50}O_6$ (M^+) 602.3607, found 602.3616.

Acid 357. To a solution of aldehyde **356** (17 mg, 0.028 mmol) in $(CH_3)_3COH$ (1 mL) at rt was added 2-methyl-2-butene (0.3 mL). Dropwise addition of NaH_2PO_4 (40 mg) and $NaClO_2$ (34 mg, 0.38 mmol) as an aqueous solution (0.3 mL) resulted in a darkening of the reaction solution. After 45 min, the reaction was quenched by addition of 1N HCl. The resulting solution was extracted with EtOAc, and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to afford acid **357** (18 mg, 100%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.23 (d, *J* = 2.4 Hz, 1H), 7.55 (d, *J* = 1.8 Hz, 1H), 7.09 (d, *J* = 16.8 Hz, 1H), 7.05 (d, *J* = 16.6 Hz, 1H), 6.97 (d, *J* = 0.8 Hz, 1H), 6.79 (d, *J* = 1.2 Hz, 1H), 5.30 (s, 2H), 5.27 (m, 1H), 5.15 (t, *J* = 5.1 Hz, 1H), 3.95 (s, 3H), 3.58 (s, 3H), 3.56 (m, 1H), 3.45 (d, *J* = 7.2 Hz, 2H), 2.92–2.87 (m, 2H), 2.20–1.88 (m, 8H), 1.85 (s, 3H), 1.81–1.74 (m, 2H), 1.72 (s, 3H), 1.65 (s, 3H), 1.44 (s, 3H), 1.23 (s, 3H), 1.00 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.7, 158.3, 155.9, 151.1, 135.8, 134.7, 132.8, 131.2, 130.9, 129.5, 129.1, 126.0, 124.4, 123.4, 122.5, 119.5, 117.4, 105.6, 102.9, 94.6, 81.3, 77.2, 56.0, 55.7, 46.4, 39.8, 38.5, 37.5, 28.0, 27.1, 26.7, 25.6, 22.9, 22.4, 20.3, 17.6, 16.0, 14.2; HRMS (EI) *m/z* calcd for $C_{38}H_{50}O_7$ (M^+) 618.3557, found 618.3560.

Amine 358. Aldehyde **356** (7.5 mg, 0.012 mmol) was dissolved in dimethylamine (2 M solution in THF, 1 mL, 2 mmol) at rt and molecular sieves were added. After 2 h, additional dimethylamine (1 mL, 2 mmol) was added along with AcOH (0.05 mL). After an additional 5 h, $NaBH(OAc)_3$ (58 mg, 0.4 mmol) was added in one portion. After 15 h, the reaction was quenched by addition of 1N NaOH. The resulting

solution was extracted with EtOAc, and the combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Final purification by preparative thin layer chromatography on a base-washed plate (75% EtOAc and 5% TEA in Hex) afforded amine **358** (2.5 mg, 33%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.34 (s, 1H), 7.30 (s, 1H), 6.95 (s, 2H), 6.86 (s, 1H), 6.70 (s, 1H), 5.22 (s, 2H), 5.19 (m, 1H), 5.05 (m, 1H), 3.88 (s, 3H), 3.64 (s, 2H), 3.50 (s, 3H), 3.44 (dd, *J* = 11.4, 7.6 Hz, 1H), 3.36 (d, *J* = 7.6 Hz, 2H), 2.76–2.73 (m, 2H), 2.59 (s, 6H), 2.06–2.03 (m, 6H), 1.97–1.88 (m, 2H), 1.81 (s, 3H), 1.73–1.68 (m, 2H), 1.67 (s, 3H), 1.59 (s, 3H), 1.24 (s, 3H), 1.11 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.4, 156.9, 152.6, 137.3, 135.7, 132.2, 130.6, 130.3, 129.9, 129.7, 128.7, 128.6, 128.0, 125.5, 123.7, 120.2, 106.6, 103.8, 95.6, 78.9, 78.2, 71.6, 57.0, 56.8, 48.0, 43.9, 40.9 (2C), 39.5, 38.9, 29.3, 28.4, 27.8, 26.7, 24.3, 23.5, 21.3, 18.7, 17.1, 15.4; HRMS (EI) *m/z* calcd for $C_{40}H_{57}NO_5$ (M^+) 631.4237, found 631.4232.

Stilbene 360. Under the general conditions for HWE condensations, aldehyde **79** (98 mg, 0.32 mmol), phosphonate **359** (172 mg, 0.38 mmol), and NaH (130 mg, 3.2 mmol, 60% in oil) were allowed to react in THF (6.2 mL) for 15 h. Final purification by column chromatography (1:1 Hex/EtOAc) afforded stilbene **360** (175 mg, 90%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.00–6.72 (m, 6H), 5.23 (s, 2H), 5.23–5.21 (m, 1H), 5.08 (t, *J* = 8.5 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.50 (s, 3H), 3.46–3.37 (m, 3H), 2.73 (d, *J* = 9.2 Hz, 2H), 2.17–1.51 (m, 10H), 1.78 (s, 3H), 1.65 (s, 3H), 1.58 (s, 3H), 1.26, (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H);^{13}C NMR ($CDCl_3$) δ 158.2, 155.8, 148.9, 142.5, 136.5, 134.6, 131.1, 128.9, 128.0, 126.6, 124.4, 122.59, 122.56, 120.5, 118.7, 106.8, 105.3, 102.5, 94.4, 77.9, 77.1, 55.94, 55.92, 55.7, 46.7, 39.8, 38.3, 37.6, 28.2, 27.3, 26.7, 25.6, 23.1, 22.4, 19.8, 17.6, 16.0, 14.2; HRMS (EI) *m/z* calcd for $C_{38}H_{52}O_6$ (M^+) 604.3764, found 604.3754.

3-Deoxyschweinfurthin B Analogue 361. Under the general conditions for MOM hydrolysis given for schweinfurthin B, stilbene **360** (80 mg, 0.13 mmol), MeOH (35 mL), and *p*-TsOH (75 mg, 0.42 mmol) were allowed to react for 4 days. Final purification by column chromatography (1:1 Hex/EtOAc) afforded compound **361** (68 mg, 92%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.00–6.60 (m, 6H), 5.28–5.24 (m, 1H), 5.07–5.05 (m, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.43–3.37 (m, 3H), 2.73 (d, *J* = 9.2 Hz, 2H), 2.17–1.51 (m, 10H), 1.80 (s, 3H), 1.68 (s, 3H), 1.59 (s, 3H), 1.26, (s, 3H), 1.11 (s, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.0, 155.6, 148.8, 142.5, 137.7, 136.8, 131.7, 128.9, 128.2, 126.3, 123.9, 122.6, 121.9, 120.5, 114.7, 106.79, 106.77, 101.2, 77.9, 77.0, 55.94, 55.7, 46.7, 39.7, 38.3, 37.6, 28.2, 27.3, 26.4, 25.6, 23.1, 22.2, 19.8, 17.6, 16.1, 14.2; HRMS (EI) *m/z* calcd for $C_{36}H_{48}O_5$ (M^+) 560.3502, found 560.3481.

Bis-MOM-Schweinfurthin 362. Under the general HWE conditions given for comound **108**; aldehyde **282** (43 mg, 0.13 mmol), phosphonate **22** (59 mg, 0.12 mmol), THF (5 mL), and NaH (98 mg, 2.5 mmol, 60% in oil) were allowed to react for 2.5 hr standard work up and final purification by column chromatography (1:1 Hex/EtOAc) afforded bis-MOM-schweinfurthin **362** (69 mg, 85%) as colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.31 (d, *J* = 8.7 Hz, 1H), 7.23 (d, *J* = 16.5 Hz, 1H), 6.97 (d, *J* = 16.2 Hz, 1H), 6.89 (s, 2H), 6.62 (d, *J* = 8.7 Hz, 1H), 5.22 (s, 6H), 5.22 – 5.19 (m, 1H), 5.10 – 5.07 (m, 1H), 3.50 (s, 3H), 3.49 (s, 6H), 3.47 – 3.37 (m, 3H), 2.80 (dd, *J* = 17.1, 4.8 Hz, 1H), 2.42 (dd, *J* = 17.1, 13.5 Hz, 1H), 2.08 – 1.72 (m, 10H), 1.78 (s, 3H), 1.65 (s, 3H), 1.57 (s, 3H), 1.22 (s, 3H), 1.12 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.8 (2C), 155.1, 151.3, 137.6, 134.4, 131.1, 127.1, 124.6, 124.4 (2C), 123.9, 122.8, 120.0, 119.4, 111.7, 106.2, 105.0, 94.6 (2C), 94.4, 78.1, 76.2, 56.1, 55.9 (2C), 46.2, 39.8, 38.4, 37.6, 28.2, 27.3, 26.7, 25.6, 22.6, 19.9, 18.2, 17.6, 16.0, 14.1; HRMS (EI) *m/z* calcd for $C_{40}H_{56}O_8$ (M^+) 664.3975, found 664.3969.

Schweinfurthin 363. Under the general conditions for MOM hydrolysis given for schweinfurthin B, stilbene **362** (18 mg, 0.027 mmol), methanol (1 mL), TsOH (16 mg, 0.08 mmol), 72 hr. Final purification by preparative thin layer chromatography (40% EtOAc in Hex) afforded schweinfurthin **363** (3.5 mg, 24%) as a yellow wax: ^{1}H NMR ($CDCl_3$) δ 7.26 – 7.20 (m, 2H), 6.82 (d, *J* = 16.2 Hz, 1H), 6.55 (s, 2H), 6.35 (s, *J* = 8.4 Hz, 1H), 5.28 (t, *J* = 6.6 Hz, 1H), 5.12 (s, 2H, exchanges with D_2O), 5.07 – 5.05 (m, 1H), 4.90 (s, 1H, exchanges with D_2O), 3.46 (dd, *J* = 16.2, 4.2 Hz, 1H), 4.42 (d, *J* = 7.2 Hz, 2H), 2.75 (dd, *J* = 16.3, 5.0 Hz, 1H), 2.44 (dd, *J* = 16.2, 13.2 Hz, 1H), 2.12 – 2.05 (m, 6H), 1.87 – 1.65 (m, 4H), 1.82 (s, 3H), 1.70 (s, 3H), 1.60 (s, 3H), 1.25 (s, 3H), 1.30 (s, 3H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.1 (2C), 153.7, 151.7, 139.2, 138.1, 132.1, 125.8, 124.6, 123.9, 123.7, 121.4, 118.9, 112.4, 109.4, 106.5, 106.2 (2C), 78.2, 76.4, 46.2, 39.7, 38.4, 37.7, 28.3, 27.3, 26.4, 25.7, 22.5, 20.0, 17.9, 17.7, 16.2, 14.2; HRMS (EI) *m/z* calcd for $C_{34}H_{44}O_5$ (M^+) 532.3189, found 532.3177.

Iodide 375. To a solution of TMEDA (0.5 mL, 3.3 mmol) in Et_2O (10 mL) in a brine bath *n*-BuLi (0.8 mL, 2.4 M in Hex, 1.9 mmol) was added. After 3 min, bromide **369** (617 mg, 1.5 mmol) was added in Et_2O (1 mL) via canula. After an additional 15 min at this temperature, solid CuI (670 mg, 3.5 mmol) was added in one portion. The resulting solution darkened slowly over the course of a few min, and after a total of 10 additional min, neat diiodide **347**[156] (910 mg, 3.0 mmol) was added slowly, quenching the dark color. This solution was allowed to warm to rt slowly and after a total of 2 additional hr, the reaction was quenched by addition of aqueous NH_4Cl. The resulting solution was extracted with EtOAc and washed with brine. The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (5% EtOAc in Hex) afforded iodide **375** (580 mg, 76%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.80 (s, 2H), 5.45 (m, 1H), 5.20 (s, 4H), 4.71 (s, 2H), 3.51 (s, 6H), 3.51 – 3.47 (m, 2H), 2.48 (q, *J* = 1.2 Hz, 3H), 0.96 (s, 9H), 0.12 (s, 6H); ^{13}C NMR

($CDCl_3$) δ 155.6 (2C), 141.4, 134.2, 115.9, 105.3 (2C), 99.6, 94.3 (2C), 64.7, 55.9 (2C), 33.5, 31.4, 25.8 (3C), 18.3, -5.3 (2C); HRMS (EI) *m/z* calcd for $C_{21}H_{35}O_5Si$ (M^+) 522.1299, found 522.1302.

Epoxide 372. To a solution of epoxydiene **66a** (65 mg, 0.39 mmol) at rt in THF (0.5 mL), 9-BBN (0.9 mL, 0.5 M in THF, 0.45 mmol) was slowly added to form compound **376** *in situ*. After 2.5 hr at rt, this solution was added to the reaction described below via canula and the canula was rinsed with THF (0.2 mL).

In a separate flask, iodide **375** (95 mg, 0.18 mmol) was dissolved in DMF (1.5 mL) at rt. To this solution, water (0.05 mL), Cs_2CO_3 (190 mg, 0.58 mmol), $AsPh_3$ (8 mg, 0.03 mmol), and $PdCl_2$(dppf) (9 mg, 0.01 mmol) were respectively added. Immediately after these additions were compleate, the above described solution of the presumed 9-BBN derivative was added via canula. After 1.5 additional hr, the reaction was diluted with water and the resulting solution was extracted with EtOAc. The combined organic phase was washed with brine and dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (13% EtOAc in Hex) afforded epoxide **372** (96 mg, 94%) as colorless oil. This material matched the ^1H and ^{13}C NMR spectra previously reported for this compound.[67]

Compound 373. This compound was prepared as previously described.[67] To a solution of epoxide **372** (47 mg, 0.083 mmol) in CH_2Cl_2 (20 mL) at –78 ^oC was added $BF_3{\cdot}OEt_2$ (0.07 mL, 0.40 mmol). After 8 min, the reaction was quenched by addition of Et_3N (0.2 mL), allowed to warm to rt, and concentrated *in vacuo*. Purification of the initial oil by column chromatography (20% EtOAc in Hex) afforded compound **373** (25 mg, 52%) as a colorless oil. A similar yield and mixture of compounds as reported[67] was obtained, which matched the reported ^1H and ^{13}C NMR spectra.[67]

Compounds 377 and 378. To a solution of compound **373** (25 mg, 0.044 mmol) in CH_2Cl_2 (5 mL) and water (0.5 mL) was added DDQ (15 mg, 0.066 mmol). After 70 min, the reaction was quenched by addition of saturated $NaHCO_3$ and the resulting solution was extracted with CH_2Cl_2. The combined organic phases were washed with a small amount of water followed by brine. After, the organic phase was dried ($MgSO_4$) and concentrated in vacuo ^1H NMR analysis ($CDCl_3$) of the residue indicated the formation of two new aldehydes which were tentatively assigned as compounds **377** and **378** based on the integration of their respective protecting groups (3:1, **377**:**378**).

REFERENCES

(1) Corey, E. J.; Czako, B.; Kurti, L. *Molecules and Medicine;* Wiley: New York, **2008**; p 254.

(2) Nicolaou, K. C.; Montagnon, T. *Molecules That Changed the World*; Wiley: New York, **2008**; p 385.

(3) Pollan, M. *In Defense of Food: An Eater's Manifesto;* Penguin: New York, **2008**; p 256.

(4) Adlercreutz, H. *Scand. J. Clin. Lab. Invest. Suppl.* **1990**, *201*, 3-23.

(5) Adlercreutz, H.; Mousavi, Y.; Hockerstedt, K. *Acta Oncol.* **1992**, *31*, 175-181.

(6) Rose, D. P. *Annu. Rev. Public Health* **1993**, *14*, 1-17.

(7) Faguet, G. B. *The War on Cancer: An Anatomy of Failure, a Blueprint for the Future*; Springer: New York, **2006**; p 227.

(8) Begley, S. *Newsweek* **2008**, *Sept 15th*, 42-58.

(9) Keskin, O.; Bahar, I.; Jernigan, R. L.; Beutler, J. A.; Shoemaker, R. H.; Sausville, E. A.; Covell, D. G. *Anti-Cancer Drug Design* **2000**, *15*, 79-98.

(10) Rabow, A. A.; Shoemaker, R. H.; Sausville, E. A.; Covell, D. G. *J. Med. Chem.* **2002**, *45*, 818-840.

(11) Teicher, B. A.; Andrews, P. A. *Anticancer drug development guide: preclinical screening, clinical trials, and approval*; Humana Press: New York, **2004**; p 430.

(12) Erickson, K. L.; Beutler, J. A.; Cardellina, J. H.; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8188-8192.

(13) Niederhuber, J. E. *Current therapy in oncology;* B. C. Decker: St. Louis, **1993**, p 832.

(14) Beutler, J. A.; Jato, J. l. C., G.; Wiemer, D. F.; Neighbors, J. D.; Salnikova, M. S.; Hollingshead, M.; Scudiero, D. A.; McCloud, T. G. In *The Schweinfurthins: Issues in Development of a Plant-Derived Anticancer Lead.* Bogers, R. J.; Medicinal and Aromatic Plants; Springer: **2006**; p 301 - 309.

(15) Paull, K. D.; Shoemaker, R. H.; Hodes, L.; Monks, A.; Scudiero, D. A.; Rubinstein, L.; Plowman, J.; Boyd, M. R. *J. Nat. Cancer Inst.* **1989**, *81*, 1088-1092.

(16) Zhou, B.; Hoch, J. M.; Johnson, R. K.; Mattern, M. R.; Eng, W.; Ma, J.; Hecht, S. M.; Newman, D. J.; Kingston, D. G. I. *J. Nat. Prod.* **2000**, *63*, 1273-1276.

(17) Deng, J.; Newman, D. J.; Hecht, S. M. *J. Nat. Prod.* **2000**, *63*, 1269-1272.

(18) Parness, J.; Horwitz, S. B. *Journal of Cell Biology* **1981**, *91*, 479-487.

(19) Kingston, D. G. I. *J. Org. Chem.* **2008**, *73*, 3975-3984.

(20) Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature* **1979**, *277*, 665-667.

(21) Vielle, S.; Raimbaud, E.; Bertrand, P.; Quintard, D.; Renard, P.; Pfeiffer, B.; Gesson, J. *Tetrahedron Lett.* **2002**, *43*, 9213-9216.

(22) Danishefsky, S. J. *J. Org. Chem.* **1999**, *64*, 8434-8456.

(23) Wilson, R. M.; Danishefsky, S. J. *J. Org. Chem.* **2006**, *71*, 8329-8351.

(24) Wilson, R. M.; Danishefsky, S. J. *Chem. Soc. Rev.* **2007**, *8*, 1207-1226.

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

(26) McCormick, J. L.; McKee, T. C.; Cardellina, J. H.; Leid, M.; Boyd, M. R. *J. Nat. Prod.* **1996**, *59*, 1047-1050.

(27) McKee, T. C.; Bokesch, H. R.; McCormick, J. L.; Rashid, M. A.; Spielvogel, D.; Gustafson, K. R.; Alavanja, M. M.; Cardellina, J. H.; Boyd, M. R. *J. Nat. Prod.* **1997**, *60*, 431-438.

(28) Moser, B. R. *J. Nat. Prod.* **2008**, *71*, 487-491.

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

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

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

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

(33) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis: Targets, Strategies, Methods;* Wiley: New York, **1996**; p 821.

(34) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II: More Targets, Strategies, Method;* Wiley: New York, **2003**; p 658.

(35) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551-564.

(36) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134-7186.

(37) Johnson, W. S. *Acc. Chem. Res.* **1968**, *1*, 1-8.

(38) Johnson, W. S. *Tetrahedron* **1991**, *47*, xi-l.

(39) Fish, P. V.; Sudhakar, A. R.; Johnson, W. S. *Tetrahedron Lett.* **1993**, *34*, 7849-7852.

(40) Johnson, W. S.; Li, T.; Harbert, C. A.; Bartlett, W. R.; Herrin, T. R.; Staskun, B.; Rich, D. H. *J. Am. Chem. Soc.* **1970**, *92*, 4461-4463.

(41) Johnson, W. S.; Gravestock, M. B.; McCarry, B. E. *J. Am. Chem. Soc.* **1971**, *93*, 4332-4334.

(42) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730-4756.

(43) Trost, B. M. *Science* **1991**, *254*, 1471-1477.

(44) Trost, B. M. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259-281.

(45) Trost, B. M.; Dong, G. *Nature* **2008**, *456*, 485-488.

(46) Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 8865-8869.

(47) Ishibashi, H.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 11122-11123.

(48) Uyanik, M.; Ishibashi, H.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 1601-1604.

(49) Uyanik, M.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2006**, *8*, 5649-5652.

(50) Kumazawa, K.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2004**, *6*, 2551-2554.

(51) Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900-903.

(52) Snyder, S. A.; Treitler, D. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 7899-7903.

(53) Zhao, Y.; Loh, T. *Org. Lett.* **2008**, *10*, 2143-2145.

(54) Zhao, Y.; Loh, T. *J. Am. Chem. Soc.* **2008**, *130*, 10024-10029.

(55) Mullen, C. A.; Gagne, M. R. *J. Am. Chem. Soc.* **2007**, *129*, 11880-11881.

(56) Nelsen, D. L.; Gagne, M. R. *Organometallics* **2009**, *28*, 950-952.

(57) Fürstner, A.; Morency, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 5030-5033.

(58) Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027-5029.

(59) Gonzalez, M. A.; Molina-Navarro, S. *J. Org. Chem.* **2007**, *72*, 7462-7465.

(60) Beeson, T. D.; Mastracchio, A.; Hong, J.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582-585.

(61) MacMillan, D. W. C. *Nature* **2008**, *455*, 304-308.

(62) Treadwell, E. M.; Neighbors, J. D.; Wiemer, D. F. *Org. Lett.* **2002**, *4*, 3639-3642.

(63) Neighbors, J. D. *Synthetic Studies on the Schweinfurthin Family of Anticancer Compounds*, Ph.D. Thesis, University of Iowa, Iowa City IA, **2004**.

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

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

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

(67) Mente, N. R. *Cascade Cyclizations in Synthesis of Isoprenoid Natural Products*, Ph.D. Thesis, University of Iowa, Iowa City, IA, **2008**.

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

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

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

(71) Wiemer, D. F.; Neighbors, J. D.; Beutler, J. A. PCT Int. Appl. *Preparation of Schweinfurthin analogues.* **2005** WO2005092878A220051006 CAN143:347317 AN2005:1075787.

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

(73) Kuder, C. H.; Neighbors, J. D.; Hohl, R. J.; Wiemer, D. F. *Bioorg. Med. Chem.* **2009**, *17*, 4718-4723.

(74) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry: Part A: Structure and Mechanisms;* Springer: New York, **2007**; 5th ed., p 1199.

(75) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry: Part B: Reaction and Synthesis;* Springer: New York, **2007**; 5th ed., p 1322.

(76) Cook, S. P.; Danishefsky, S. J. *Org. Lett.* **2006**, *8*, 5693-5695.

(77) Cook, S. P.; Gaul, C.; Danishefsky, S. J. *Tetrahedron Lett.* **2005**, *46*, 843-847.

(78) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488-496.

(79) Wang, Z.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 3099-3104.

(80) Rubottom, G. M.; Marrero, R. *J. Org. Chem.* **1975**, *40*, 3783-3784.

(81) Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599-1602.

(82) Rubottom, G. M.; Mott, R. C.; Juve, H. D. *J. Org. Chem.* **1981**, *46*, 2717-2721.

(83) Davis, F. A.; Haque, M. S. *J. Org. Chem.* **1986**, *51*, 4083-4085.

(84) Davis, F. A.; Sheppard, A. C. *J. Org. Chem.* **1987**, *52*, 954-955.

(85) Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919-934.

(86) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639-666.

(87) Deng, Y.; Snyder, J. K. *J. Org. Chem.* **2002**, *67*, 2864-2873.

(88) Zhu, C.; Tang, P.; Yu, B. *J. Am. Chem. Soc.* **2008**, *130*, 5872-5873.

(89) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188-196.

(90) Beshara, C. S.; Hall, A.; Jenkins, R. L.; Jones, K. L.; Jones, T. C.; Killeen, N. M.; Taylor, P. H.; Thomas, S. P.; Tomkinson, N. C. O. *Org. Lett.* **2005**, *7*, 5729-5732.

(91) Urban, M.; Sarek, J.; Klinot, J.; Korinkova, G.; Hajduch, M. *J. Nat. Prod.* **2004**, *67*, 1100-1105.

(92) Urban, M.; Sarek, J.; Tislerova, I.; Dzubak, P.; Hajduch, M. *Bioorg. Med. Chem.* **2005**, *13*, 5527-5535.

(93) Liu, H.; Siegel, D. R.; Danishefsky, S. J. *Org. Lett.* **2006**, *8*, 423-425.

(94) Wen, X.; Xia, J.; Cheng, K.; Zhang, L.; Zhang, P.; Liu, J.; Zhang, L.; Ni, P.; Sun, H. *Biorg. Med. Chem. Lett.* **2007**, *17*, 5777-5782.

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

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

(97) Sejbal, J.; Homolova, M.; Tislerova, I.; Krecek, V. *Collect. Czech. Chem. C.* **2000**, *65*, 1339-1356.

(98) Hanson, J. R. *Tetrahedron* **1966**, *22*, 1453-1460.

(99) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226-2227.

(100) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454-5459.

(101) Cope, A. C.; Berchtold, G. A.; Peterson, P. E.; Sharman, S. H. *J. Am. Chem. Soc.* **1960**, *82*, 6366-6369.

(102) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973-1976.

(103) Norden, A. D.; Wen, P. Y. *Neurologist* **2006**, *12*, 297-298.

(104) Meier, H. *Angew. Chem. Int. Ed.* **2005**, *44*, 2482-2506.

(105) Gompper, R.; Wagner, H. *Angew. Chem. Int. Ed.* **1988**, *27*, 1437-1455.

(106) Kagan, F.; Birkenmeyer, R. D.; Strube, R. E. *J. Am. Chem. Soc.* **1959**, *81*, 3026-3031.

(107) Wadsworth, D. H.; Schupp, O. E.; Seus, E. J.; Ford, J. A. *J. Org. Chem.* **1965**, *30*, 680-685.

(108) Rudy, A.; López-Antón, N.; Dirsch, V. M.; Vollmar, A. M. *J. Nat. Prod.* **2008**, *71*, 482-486.

(109) Moser, B. R. *J. Nat. Prod.* **2008**, *71*, 487-491.

(110) Cuatrecasas, P. *J. Biological Chemistry* **1970**, *245*, 3059-3065.

(111) Leslie, B. J.; Hergenrother, P. J. *Chem. Soc. Rev.* **2008**, *37*, 1347-1360.

(112) Terstappen, G. C.; Schlupen, C.; Raggiaschi, R.; Gaviraghi, G. *Nature Reviews Drug Discovery* **2007**, *6*, 891-903.

(113) Miljanic, S.; Frkanec, L.; Meic, Z.; Zinic, M. *Langmuir* **2005**, *21*, 2754-2760.

(114) Kuder, C. H.; Neighbors, J. D.; Hohl, R. J.; Wiemer, D. F. *Bioorg. Med. Chem.* **2009**, *17*, 4718-4723.

(115) Singh, S. B.; Zink, D. L.; Williams, M.; Polishook, J. D.; Sanchez, M.; Silverman, K. C.; Lingham, R. B. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2071-2076.

(116) Wall, M. E.; Wani, M. C.; Manikumar, G.; Taylor, H.; Hughes, T. J.; Gaetano, K.; Gerwick, W. H.; McPhail, A. T.; McPhail, D. R. *J. Nat. Prod.* **1989**, *52*, 1092-1099.

(117) Chen, C. C.; Huang, Y. L.; Yeh, P. Y.; Ou, J. C. *Planta Med.* **2003**, *69*, 964-967.

(118) Hinkley, S. F.; Fettinger, J. C.; Dudley, K.; Jarvis, B. B. *J. Antibiot.* **1999**, *52*, 988-997.

(119) Singh, S. B.; Zink, D. L.; Williams, M.; Polishook, J. D.; Sanchez, M.; Silverman, K. C.; Lingham, R. B. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2071-2076.

(120) Hohl, R. J.; Lewis, K. A.; Cermak, D. M.; Wiemer, D. F. *Lipids* **1998**, *33*, 39-46.

(121) Holstein, S. A.; Cermak, D. M.; Wiemer, D. F.; Lewis, K.; Hohl, R. J. *Bioorg. Med. Chem.* **1998**, *6*, 687-694.

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

(123) Tsangarakis, C.; Arkoudis, E.; Raptis, C.; Stratakis, M. *Org. Lett.* **2007**, *9*, 583-586.

(124) Tsangarakis, C.; Lykakis, I. N.; Stratakis, M. *J. Org. Chem.* **2008**, *73*, 2905-2908.

(125) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M. *J. Org. Chem.* **1992**, *57*, 2768-2771.

(126) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370-2374.

(127) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512-519.

(128) Winstein, S.; Valkanas, G.; Wilcox, C. F. *J. Am. Chem. Soc.* **1972**, *94*, 2286-2290.

(129) Cuerva, J. M.; Campaña, A. G.; Justicia, J.; Rosales, A.; Oller-López, J. L.; Robles, R.; Cárdenas, D. J.; Buñuel, E.; Oltra, J. E. *Angew. Chem. Int. Ed.* **2006**, *45*, 5522-5526.

(130) Gansauer, A.; Justicia, J.; Rosales, A.; Rinker, B. *Synlett* **2005**, *12*, 1954-1956.

(131) Callahan, M. P. *Stereocontrolled Synthesis of Functionalized Hexahydroxanthenes*, Ph.D. Thesis, University of Iowa, Iowa City, IA, **2009**.

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

(133) Bellucci, G.; Bianchini, R.; Chiappe, C.; Marioni, F.; Spagna, R. *J. Am. Chem. Soc.* **1988**, *110*, 546-552.

(134) Paul, S.; Nanda, P.; Gupta, R.; Loupy, A. *Synthesis* **2003**, *18*, 2877-2881.

(135) Selvam, J. J. P.; Suresh, V.; Rajesh, K.; Reddy, S. R.; Venkateswarlu, Y. *Tetrahedron Lett.* **2006**, *47*, 2507-2509.

(136) Reggelin, M.; Doerr, S. *Synlett* **2004**, *6*, 1117.

(137) Buschek, J. M.; Holmes, J. L.; Terlouw, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 7321-7325.

(138) Janusz, J. M.; Gardlik, J. M.; Young, P. A.; Burkes, R. V.; Stoll, S. J.; Estelle, A. F.; Riley, C. M. *J. Med. Chem.* **1990**, *33*, 1052-1061.

(139) Aziz, M.; Rouessac, F. *Tetrahedron* **1988**, *44*, 101-110.

(140) Yamada, Y.; Sanjoh, H.; Iguchi, K. *J. Chem. Soc. Chem. Commun.* **1976**, 997-998.

(141) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Mar Herrador, M.; Alvarez-Manzaneda, R.; Quilez, J.; Chahboun, R.; Linares, P.; Rivas, A. *Tetrahedron Lett.* **1999**, *40*, 8273-8276.

(142) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Palomino, P. L. *Tetrahedron* **1994**, *50*, 13239-13250.

(143) Isaacs, N. *Physical Organic Chemistry;* Wiley: New York, **1995**; 2nd Ed., p 877.

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

(145) Atkinson, J. G.; Fisher, M. H.; Horley, D.; Morse, A. T.; Stuart, R. S.; Synnes, E. *Can. J. Chem.* **1965**, *43*, 1612-1622.

(146) Stephenson, L. M.; Speth, D. R. *J. Org. Chem.* **1979**, *44*, 4683-4689.

(147) Lipshutz, B. H.; Aguinaldo, G. T.; Ghorai, S.; Voigtritter, K. *Org. Lett.* **2008**, *10*, 1325-1328.

(148) Ohnogi, H.; Sugiyama, K.; Muraki, N.; Sagawa, H.; Kato, I. US Patent US20060039998, **2006**.

(149) Akihisa, T.; Tokuda, H.; Ukiya, M.; Iizuka, M.; Schneider, S.; Ogasawara, K.; Mukainaka, T.; Iwatsuki, K.; Suzuki, T.; Nishino, H. *Cancer Lett.* **2003**, *201*, 133-137.

(150) Aoki, N.; Muko, M.; Ohta, E.; Ohta, S. *J. Nat. Prod.* **2008**, *71*, 1308-1310.

(151) Baeyer, A.; Villiger, V. *Chem. Ber.* **1899**, *32*, 3625-3633.

(152) Townsend, C. A.; Davis, S. G.; Christensen, S. B.; Link, J. C.; Lewis, C. P. *J. Am. Chem. Soc.* **1981**, *103*, 6885-6888.

(153) Thoison, O.; Hnawia, E.; Gueritte-Voegelein, F.; Sevenet, T. *Phytochemistry* **1992**, *31*, 1439-1442.

(154) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Sato, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314-321.

(155) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4544-4568.

(156) Manickam, G.; Siddappa, U.; Li, Y. *Tetrahedron Lett.* **2006**, *47*, 5867-5868.

(157) Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 8865-8869.

(158) Wiemer, D. F.; Neighbors, J. D.; Beutler, J. A. US Patent WO2005092878; US20080015232, **2005**.

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

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

APPENDIX

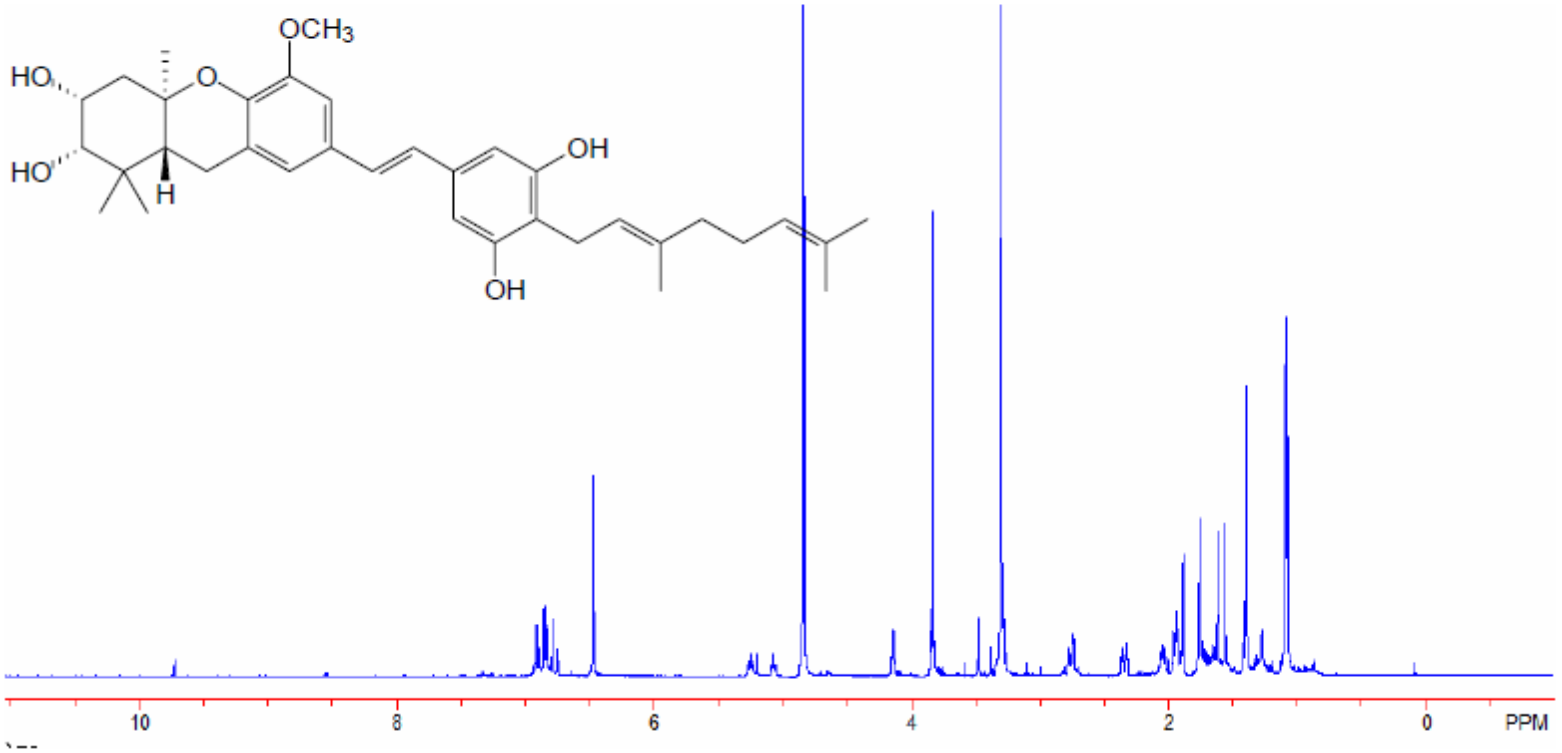


Figure A1. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Schweinfurthin B (**9**)

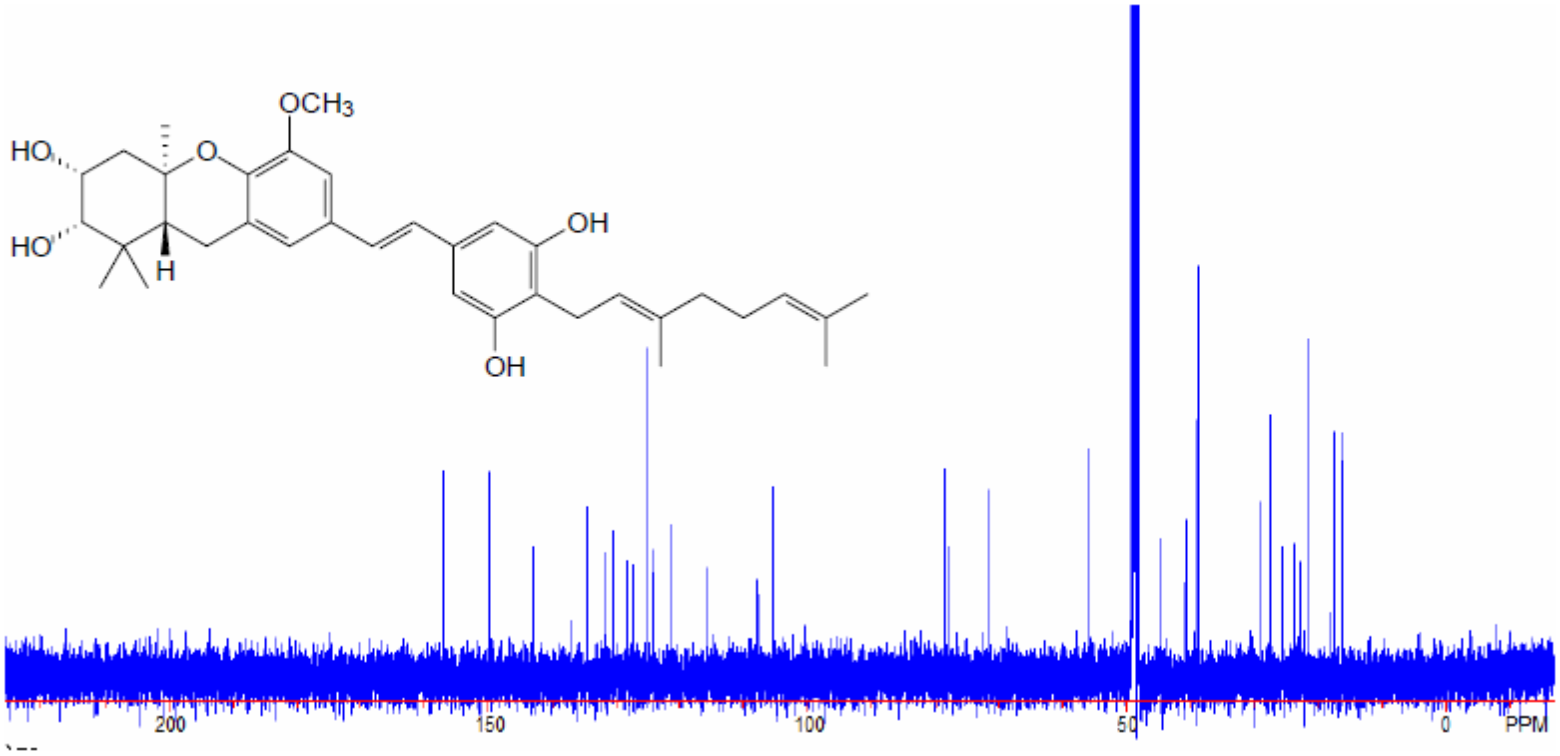


Figure A2. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Schweinfurthin B (**9**)

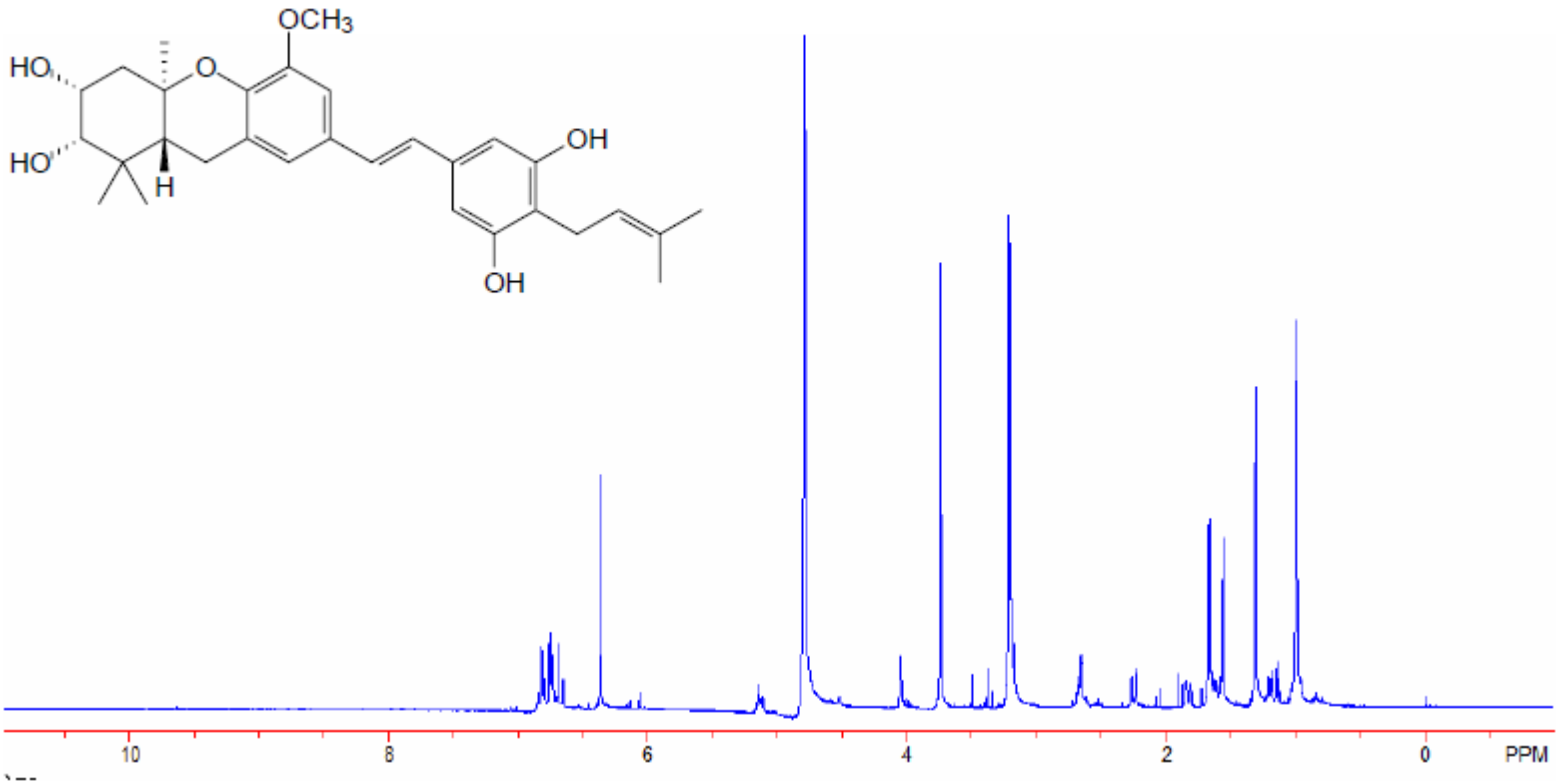


Figure A3. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Schweinfurthin E (**13**)

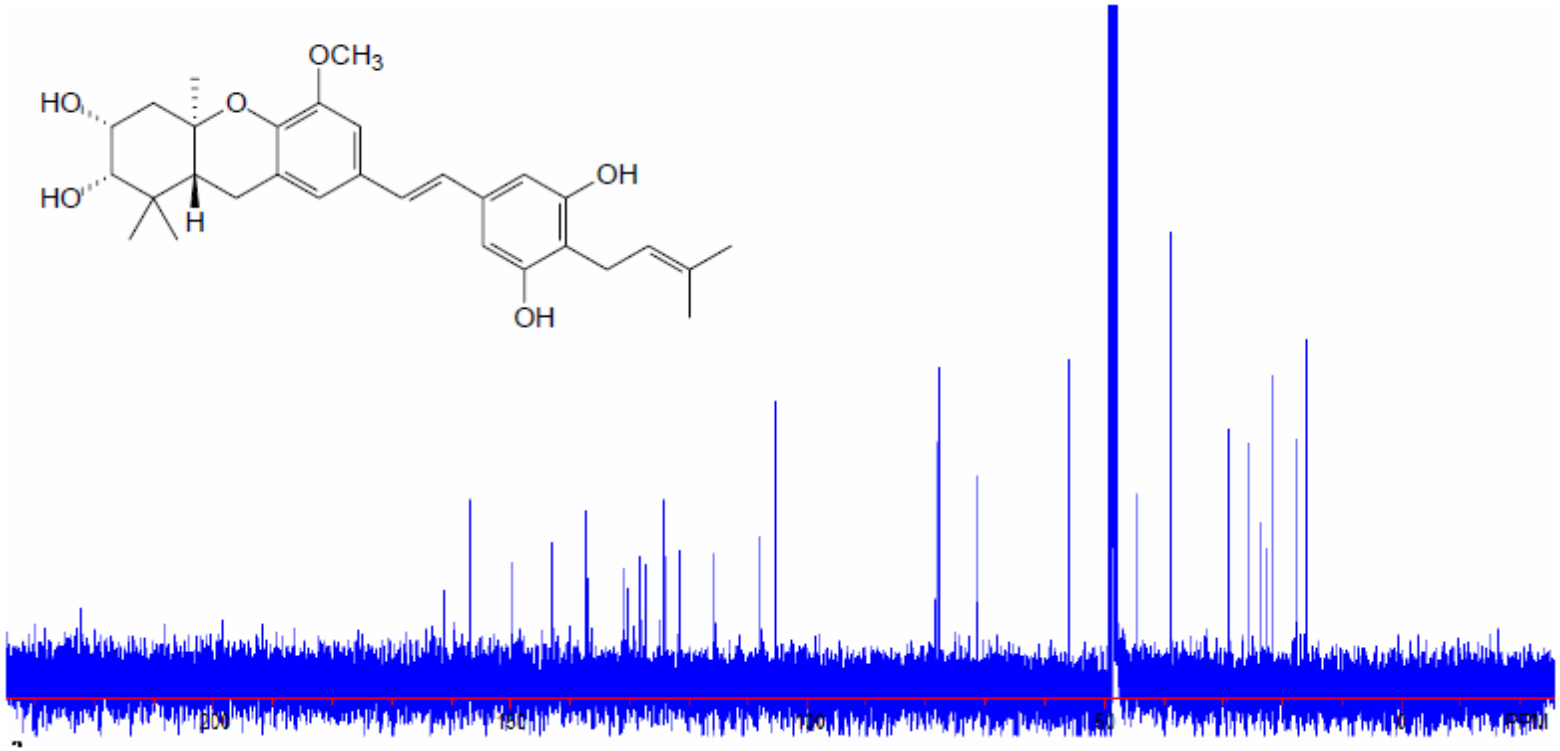


Figure A4. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Schweinfurthin E (**13**)

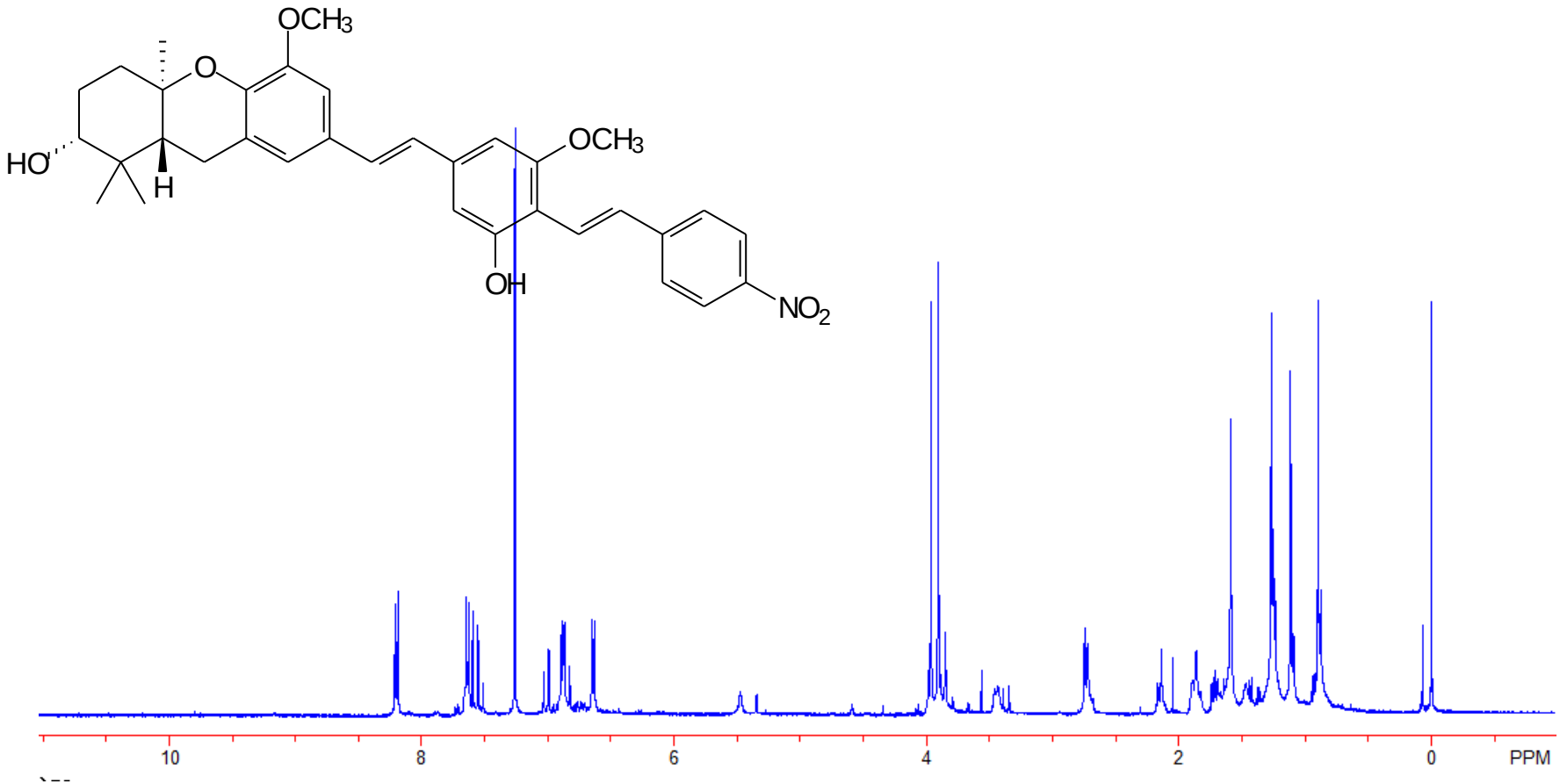


Figure A5. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Compound **133**

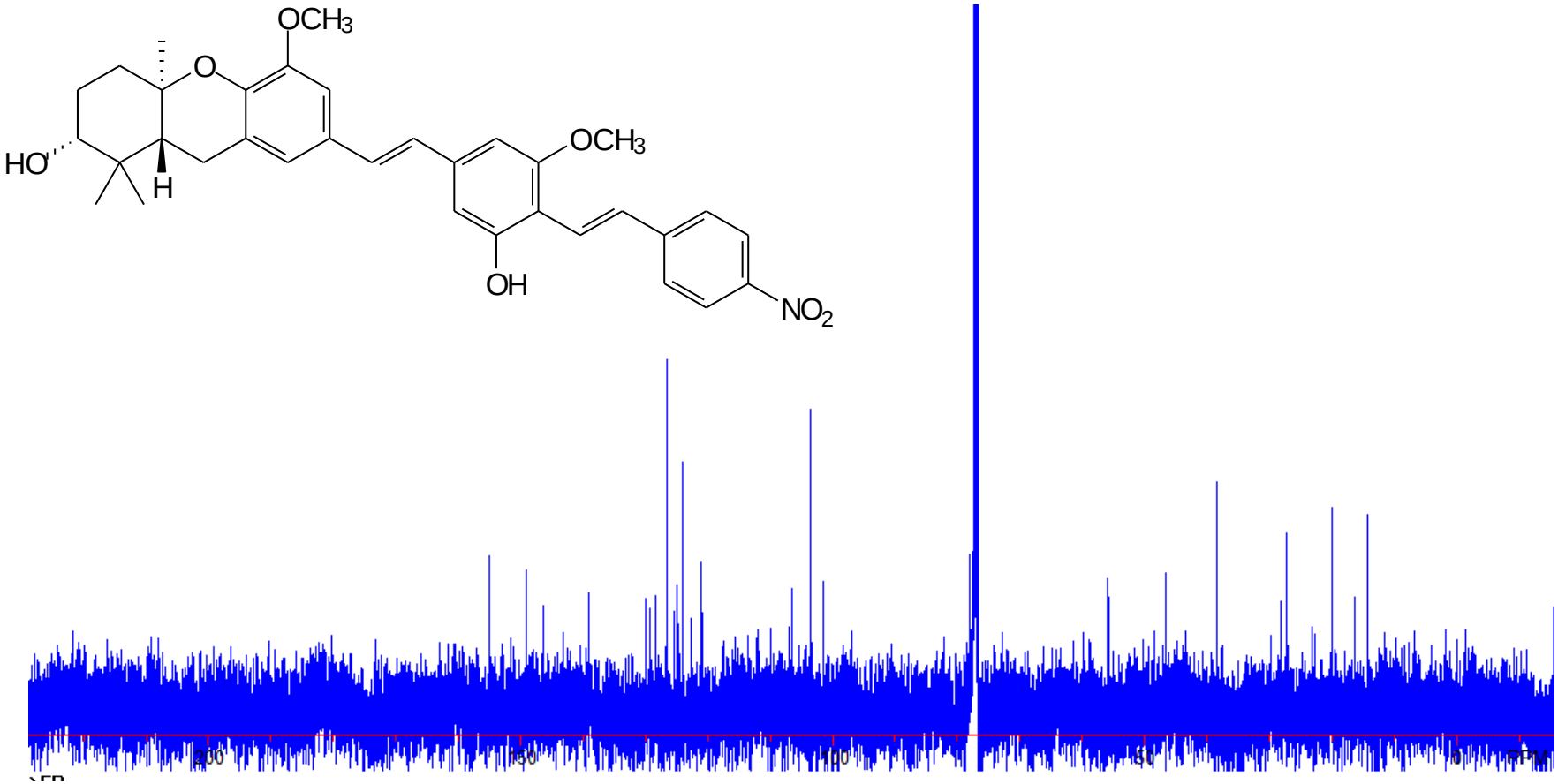


Figure A6. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Compound **133**

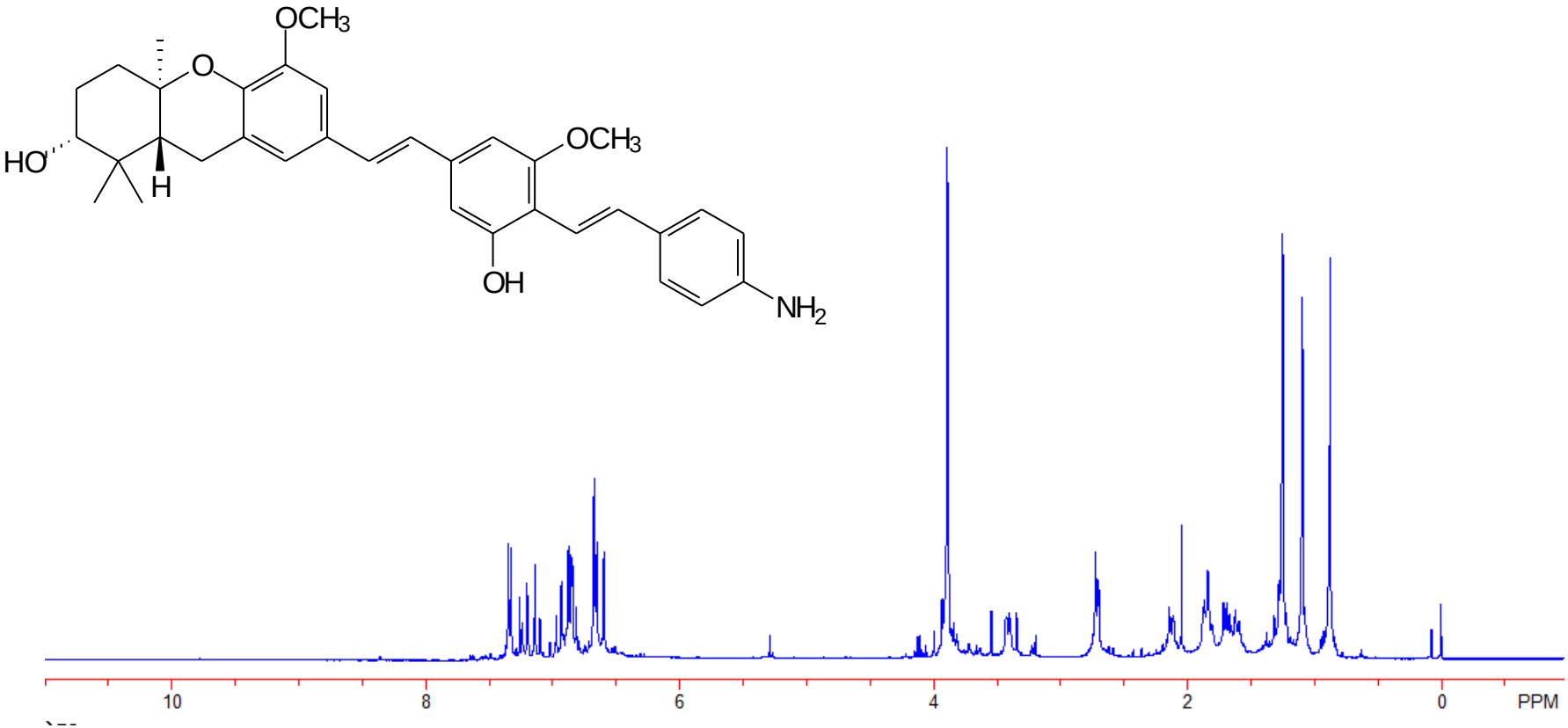


Figure A7. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Compound **140**

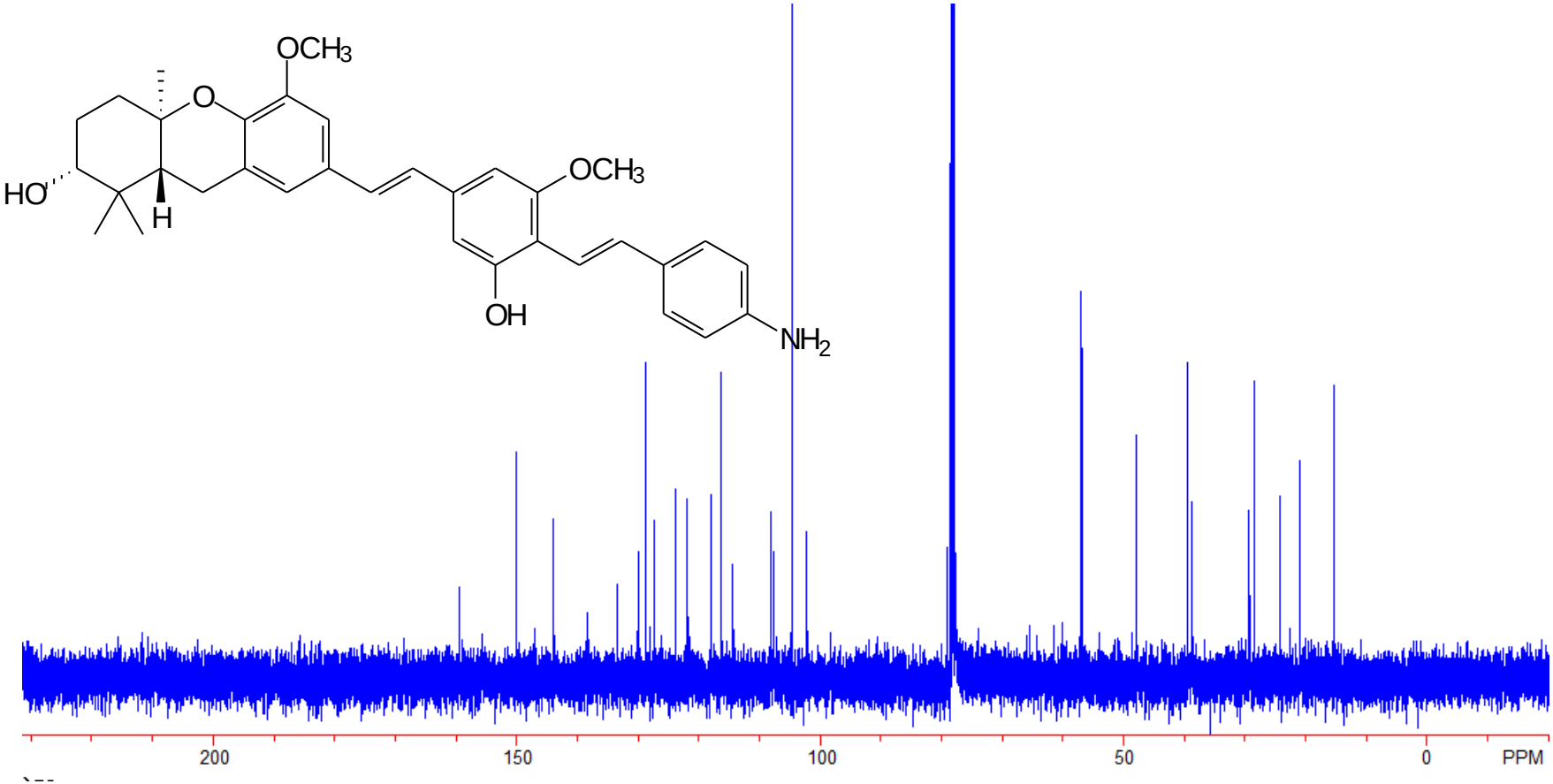


Figure A8. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Compound **140**

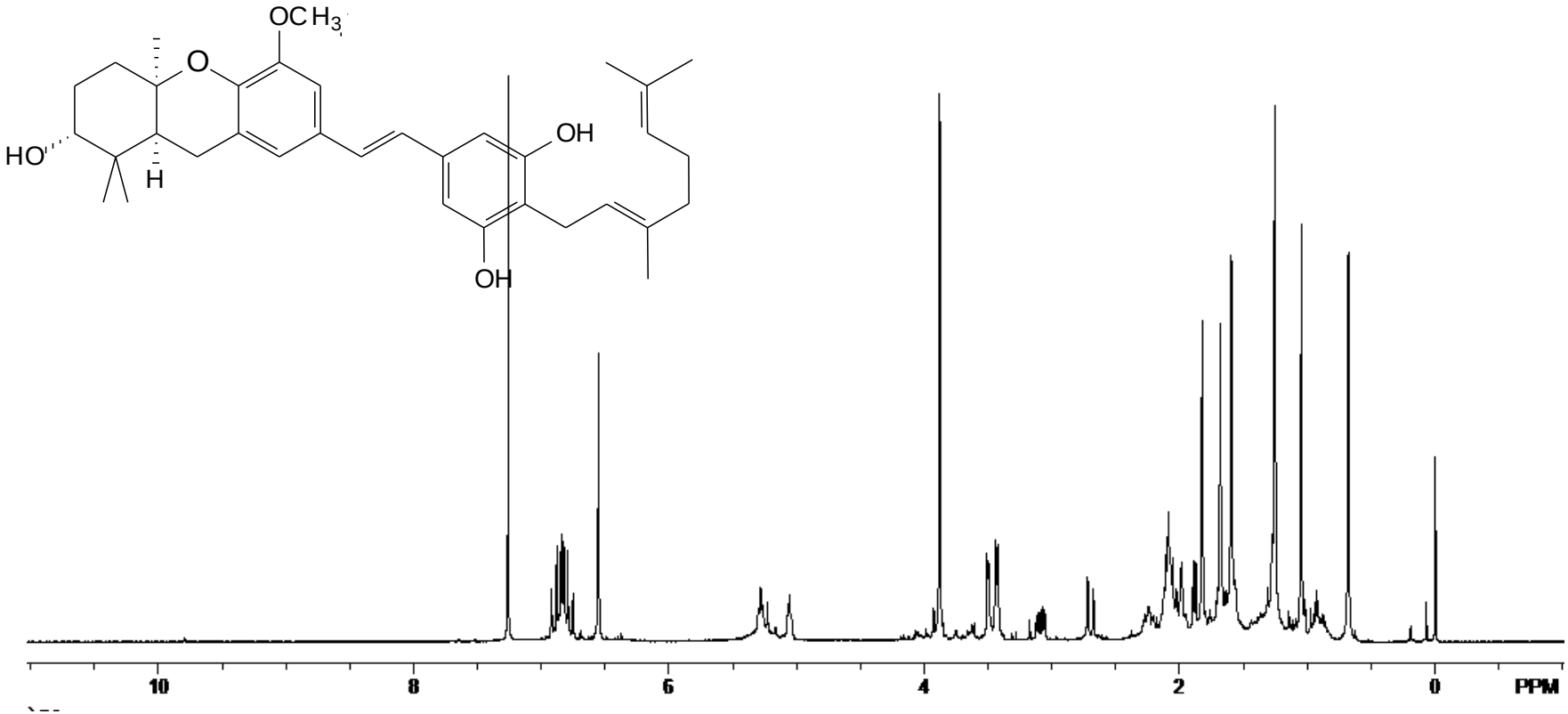


Figure A9. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) Spectrum of Compound **179**

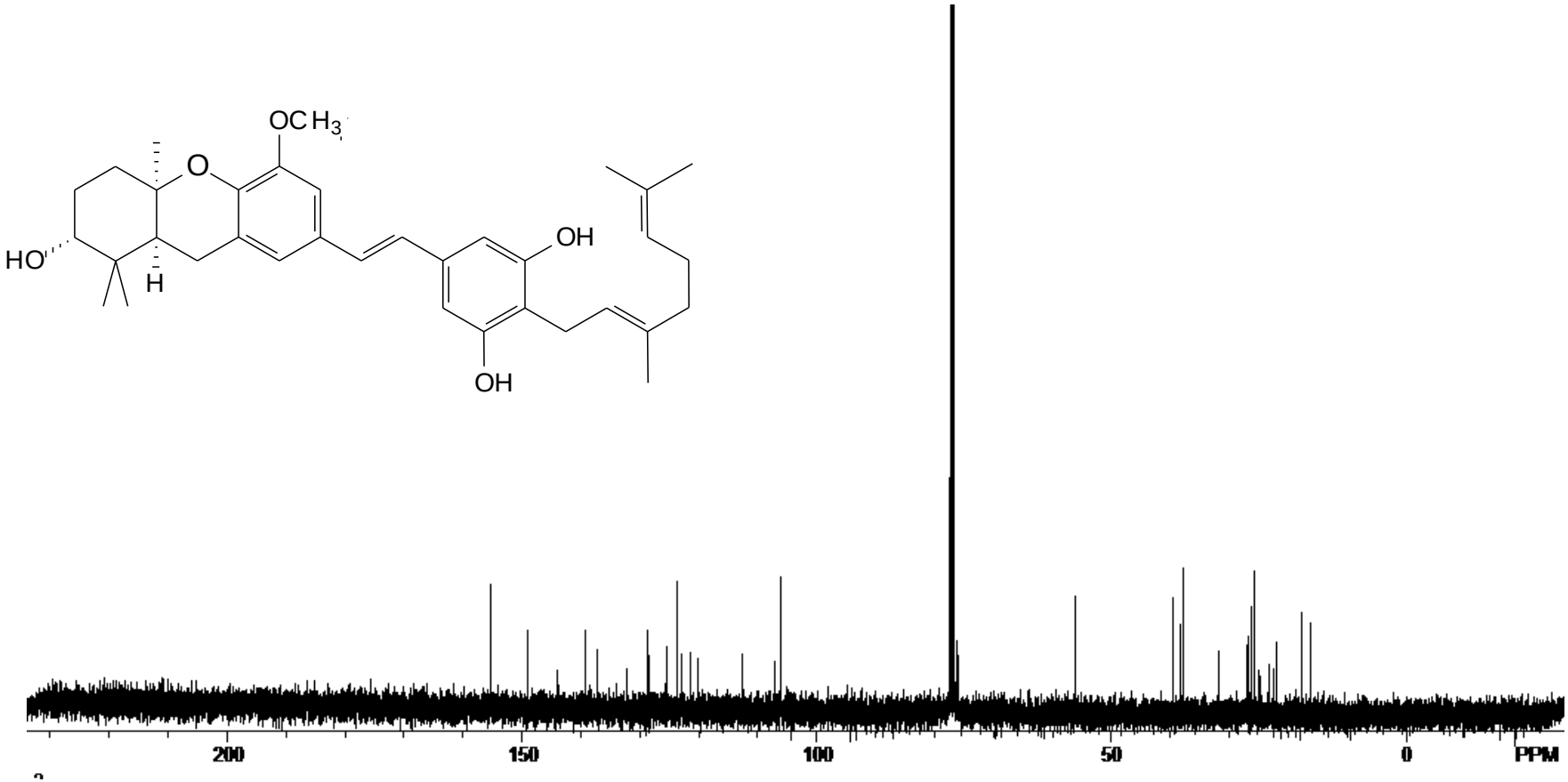


Figure A10. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) Compound **179**

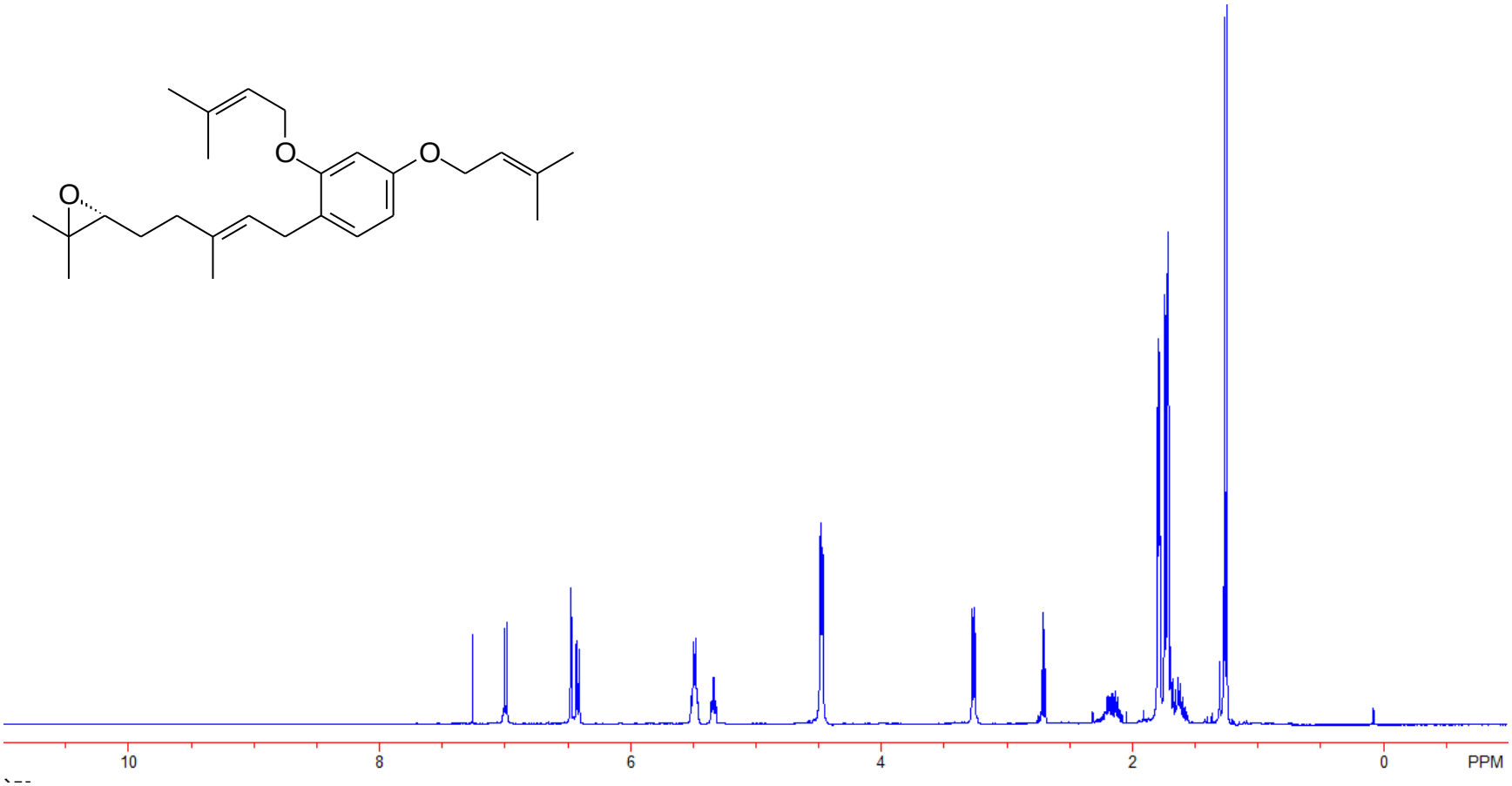


Figure A11. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Compound **242**

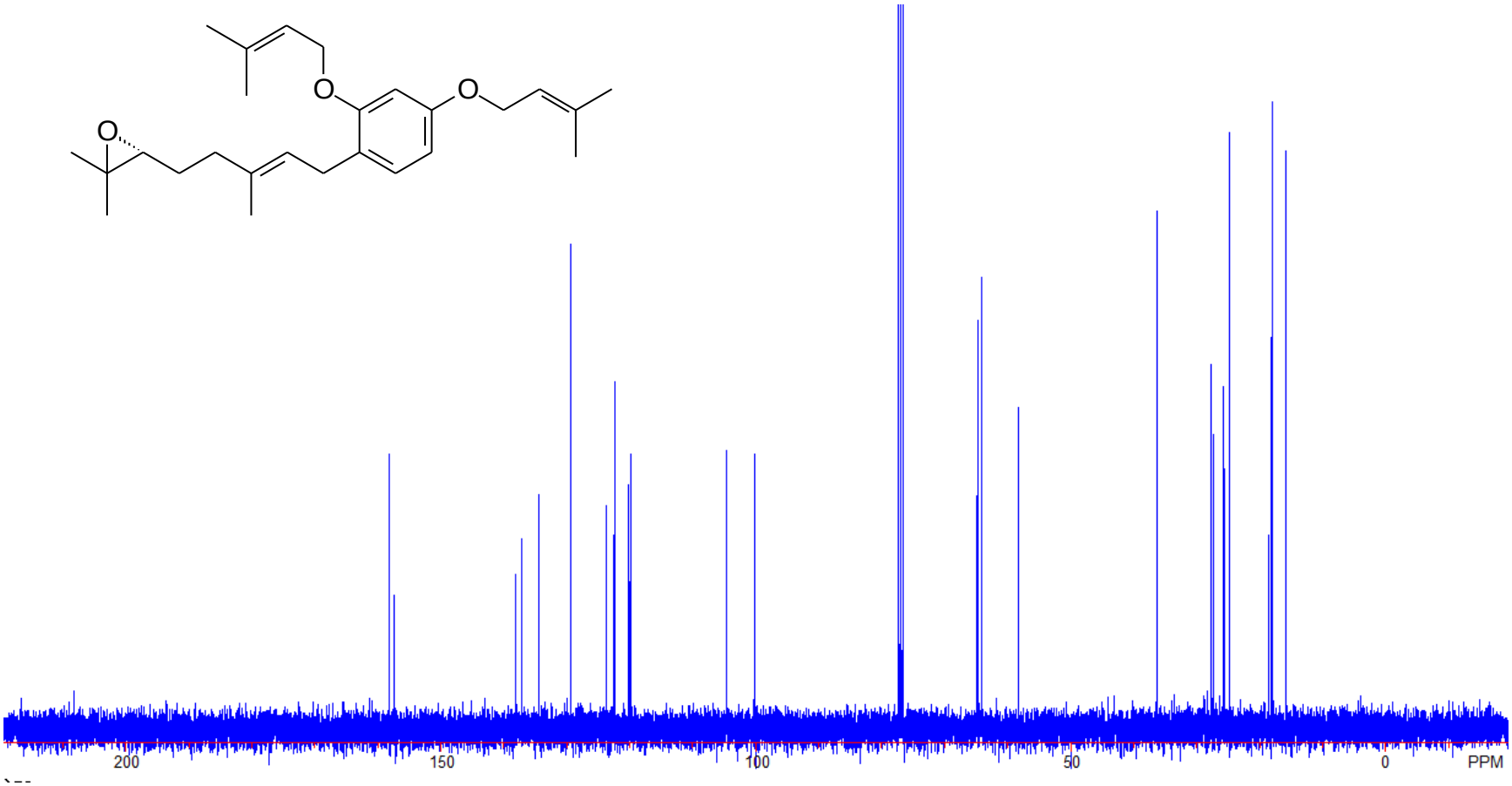


Figure A12. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Compound **242**

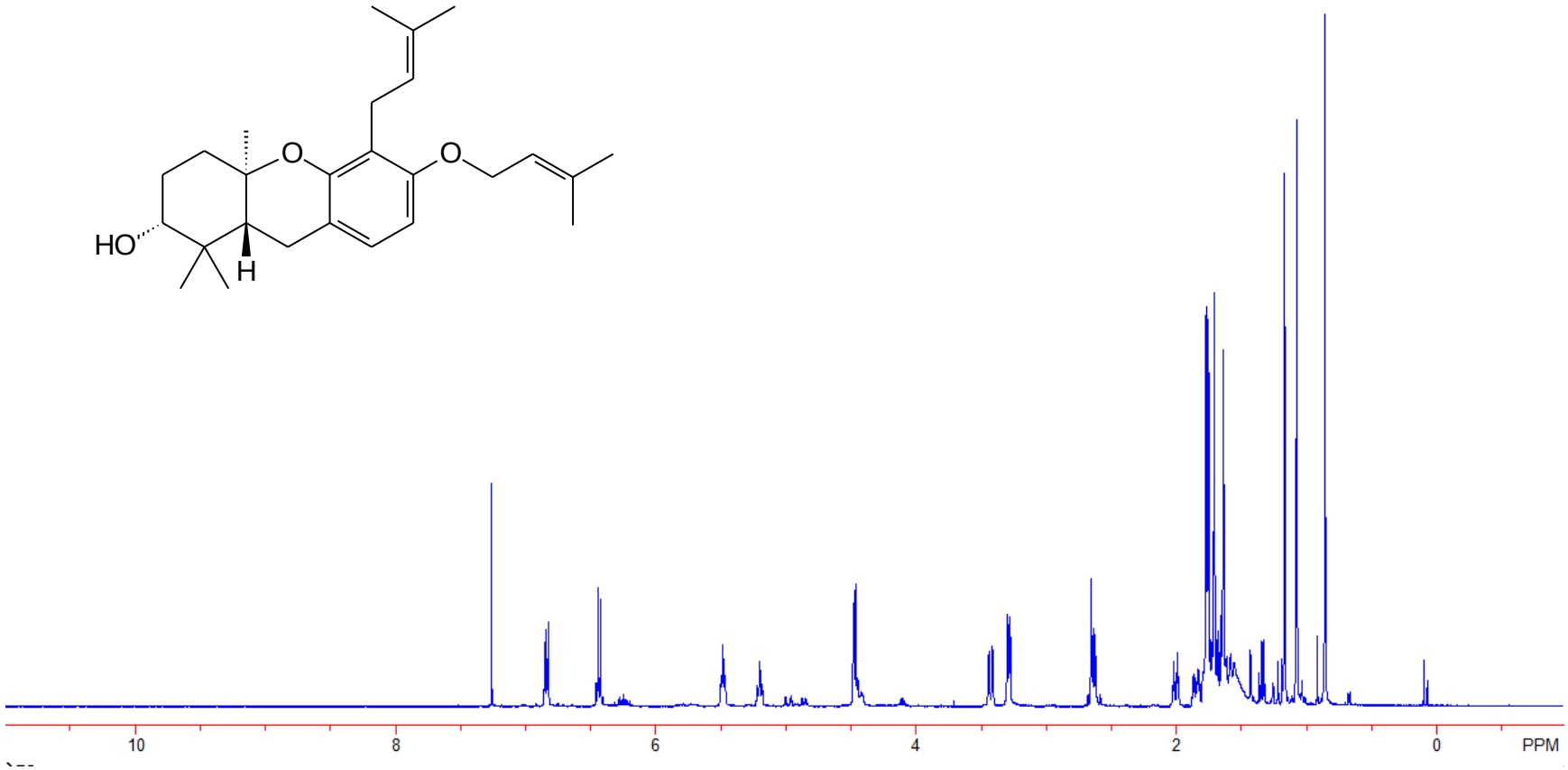


Figure A13. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Compound **247**

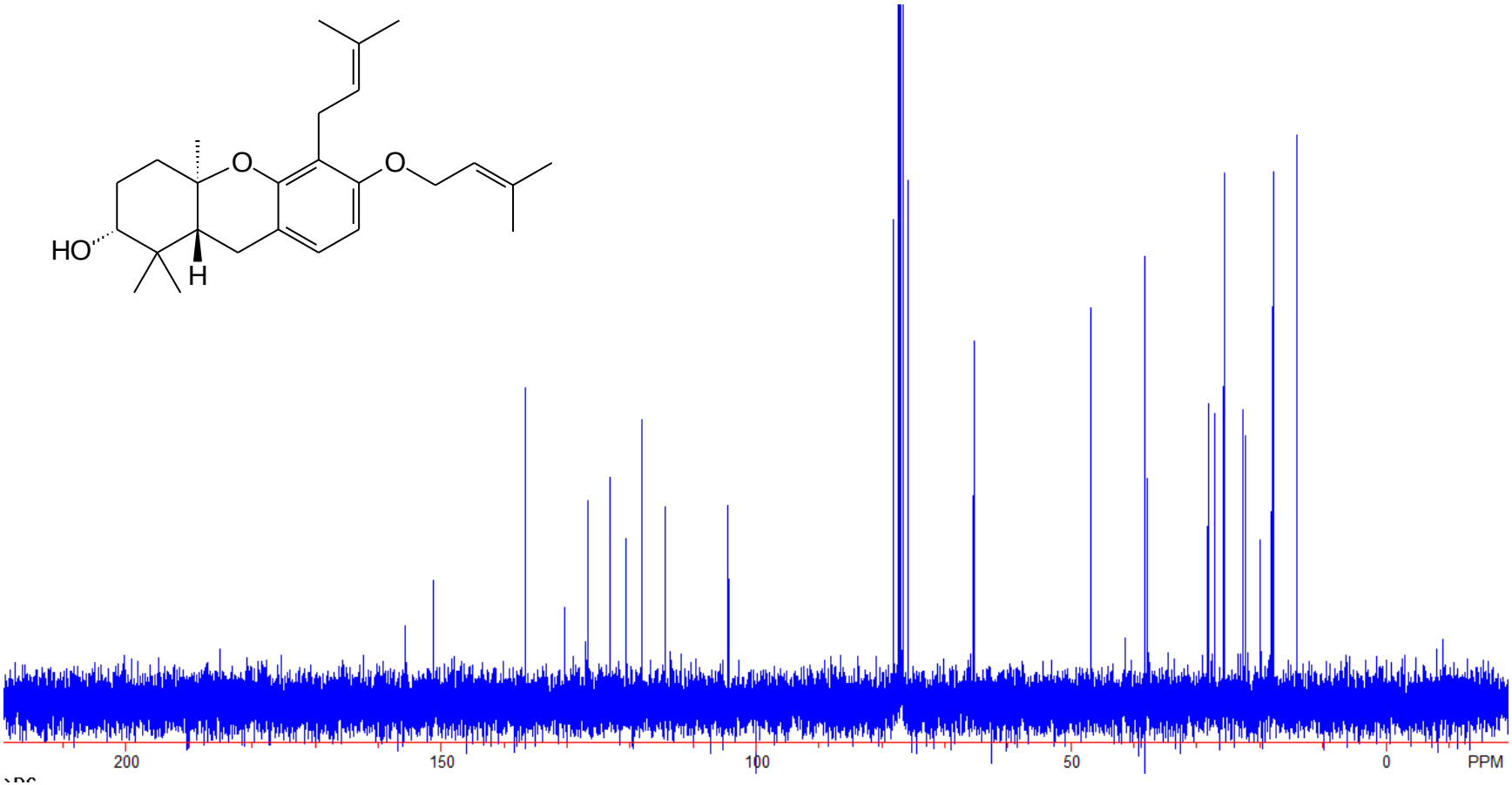


Figure A14. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Compound **247**

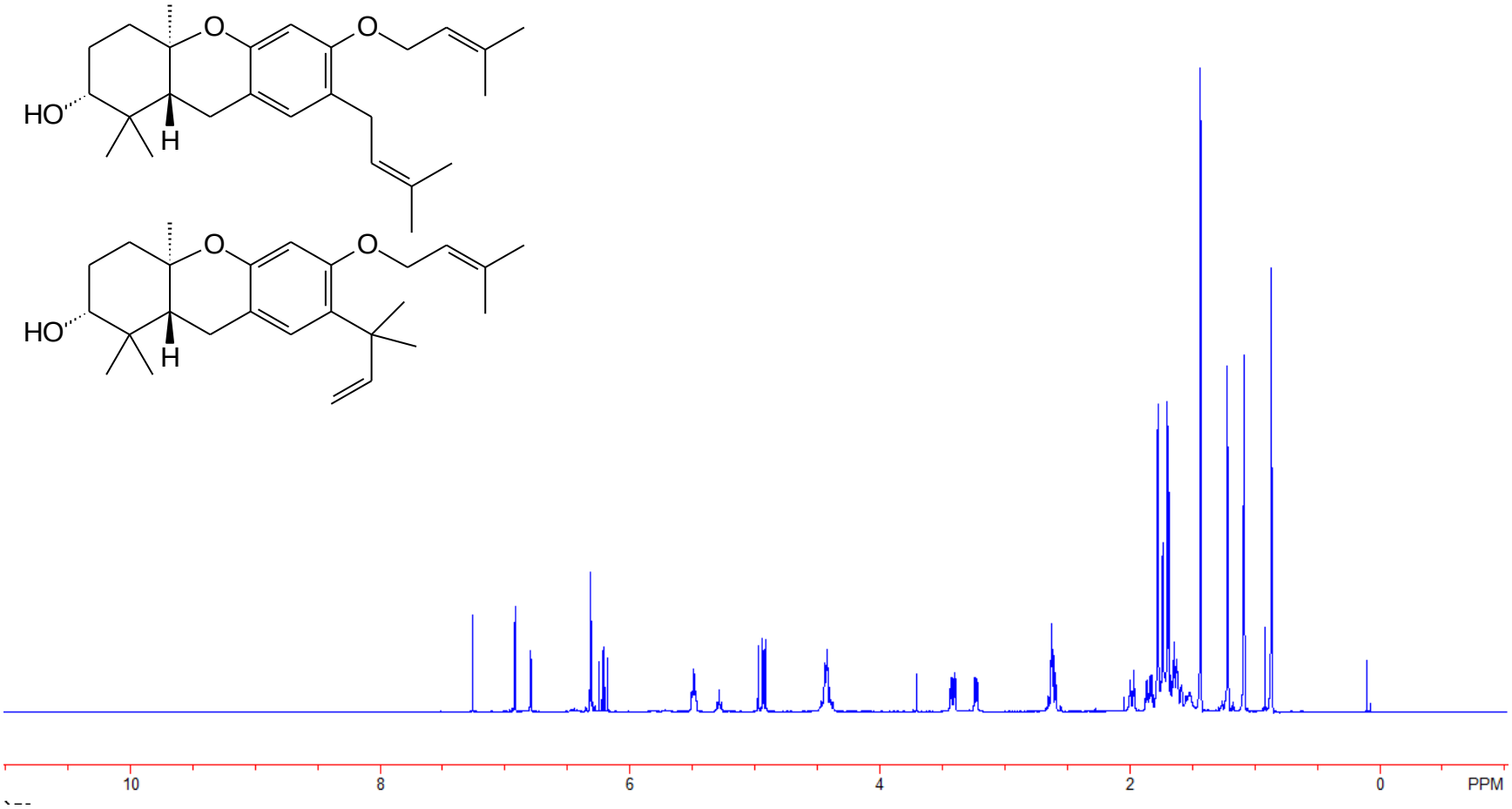


Figure A15. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Compounds **251** and **252**

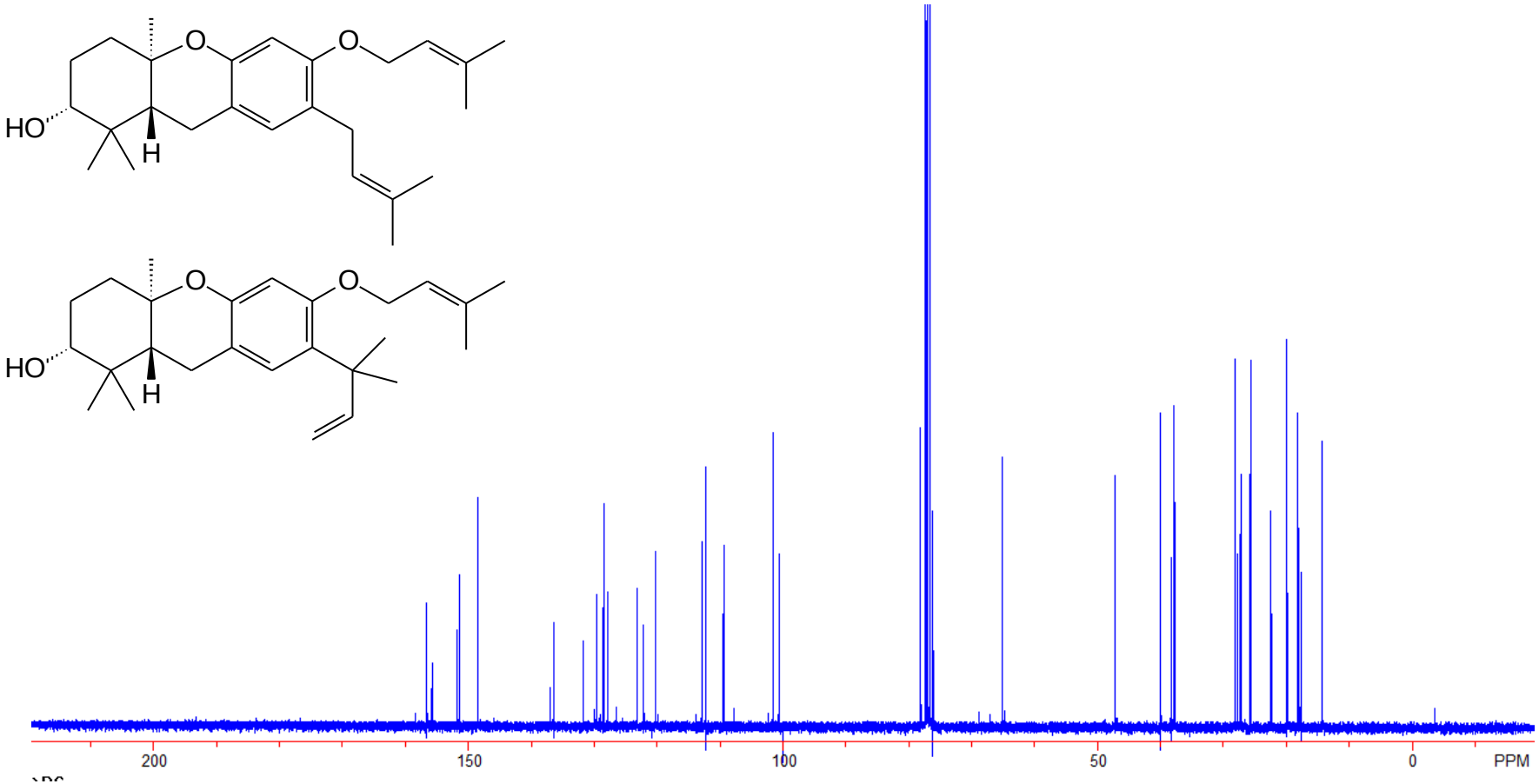


Figure A16. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Compounds **251** and **252**

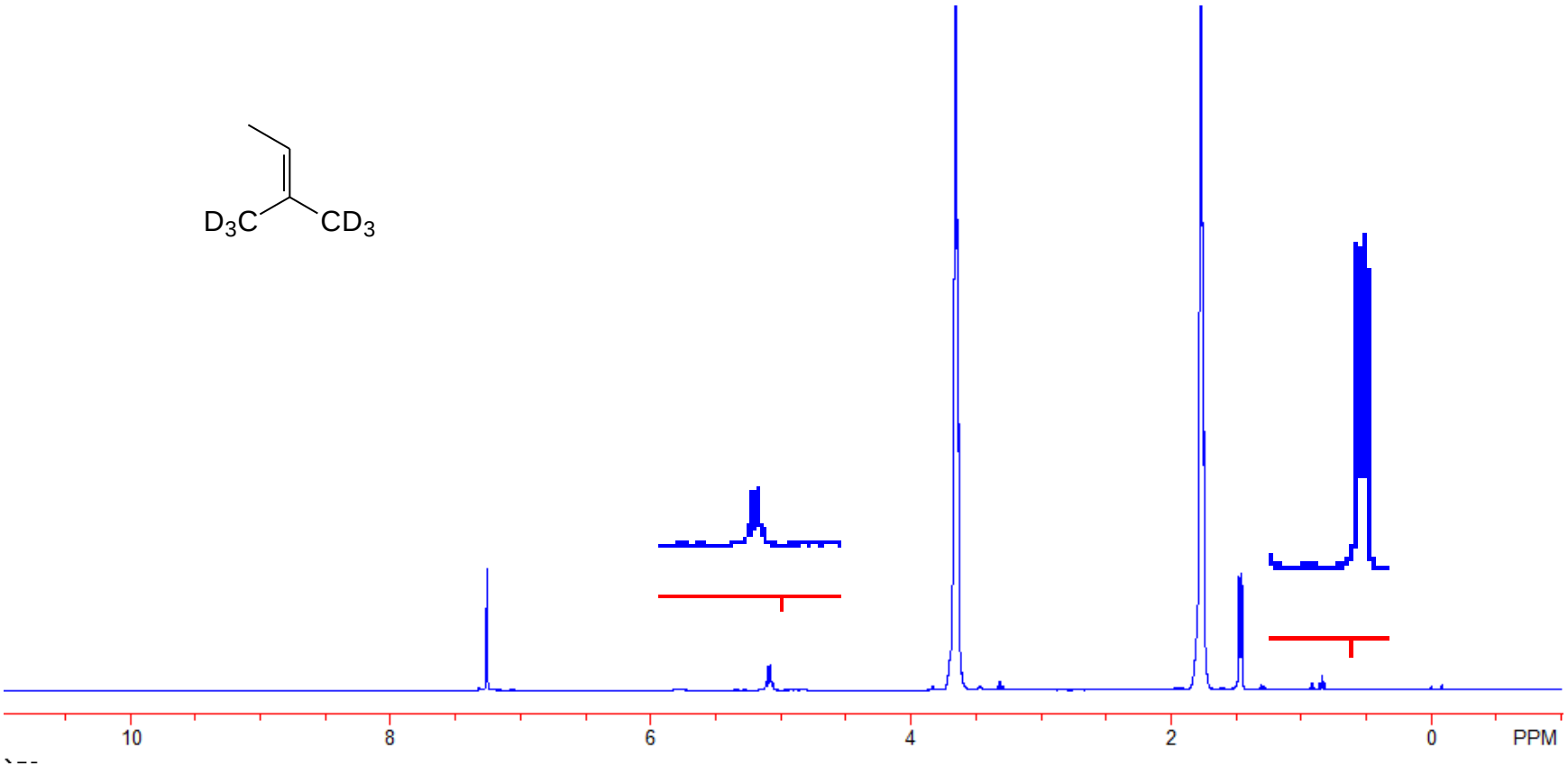


Figure A17. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Compound **261** as a solution in THF

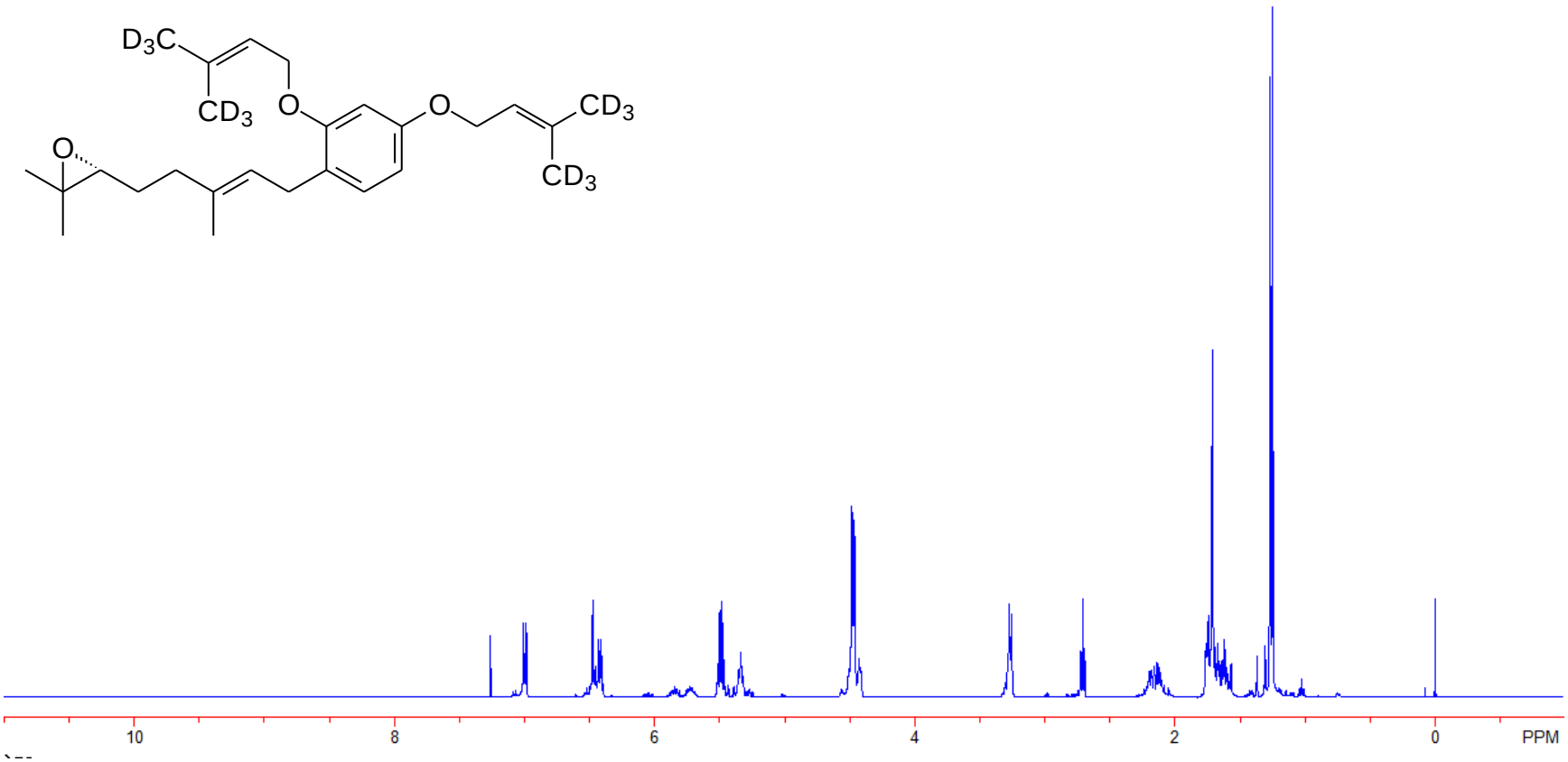


Figure A18. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Compound **262**

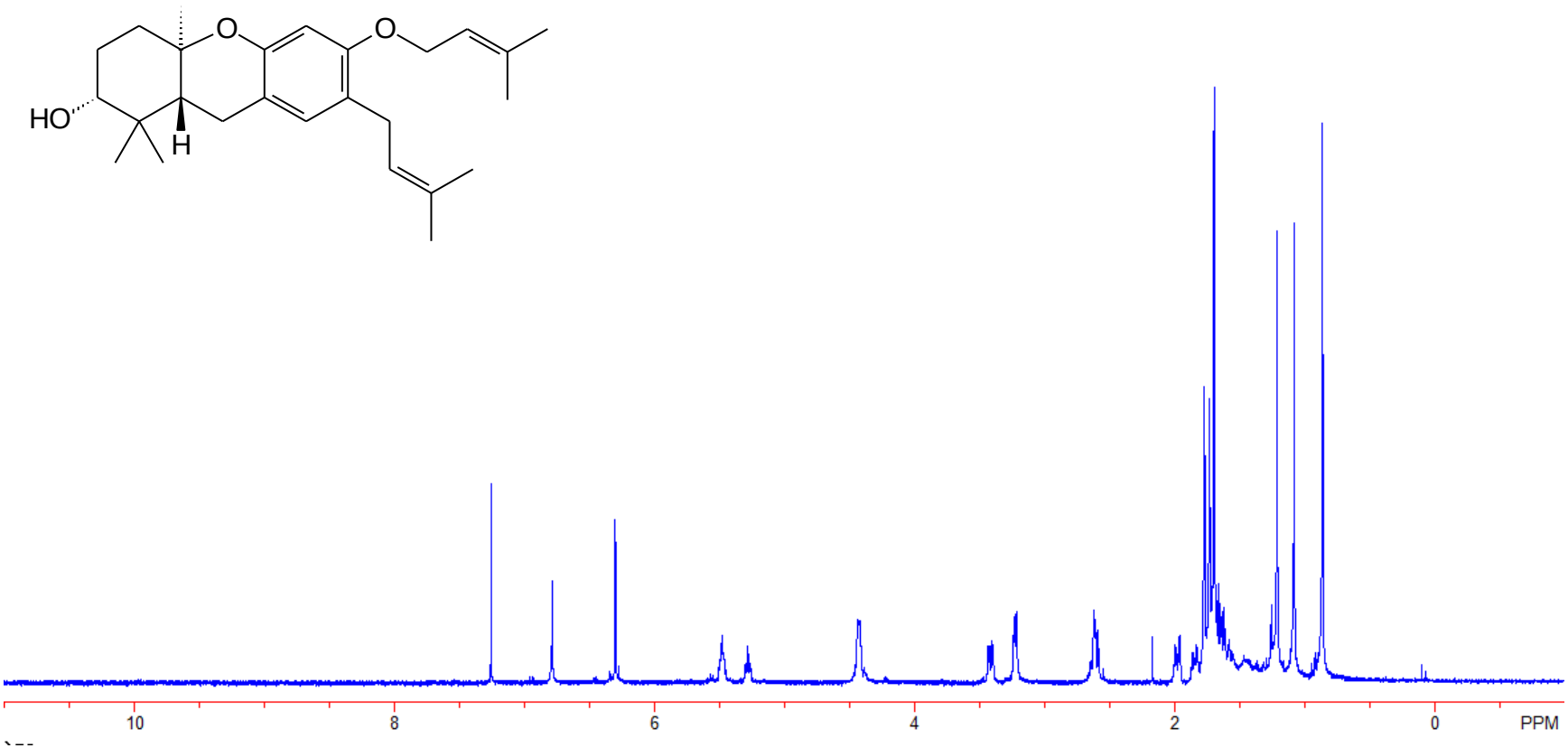


Figure A19. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Compound **251**

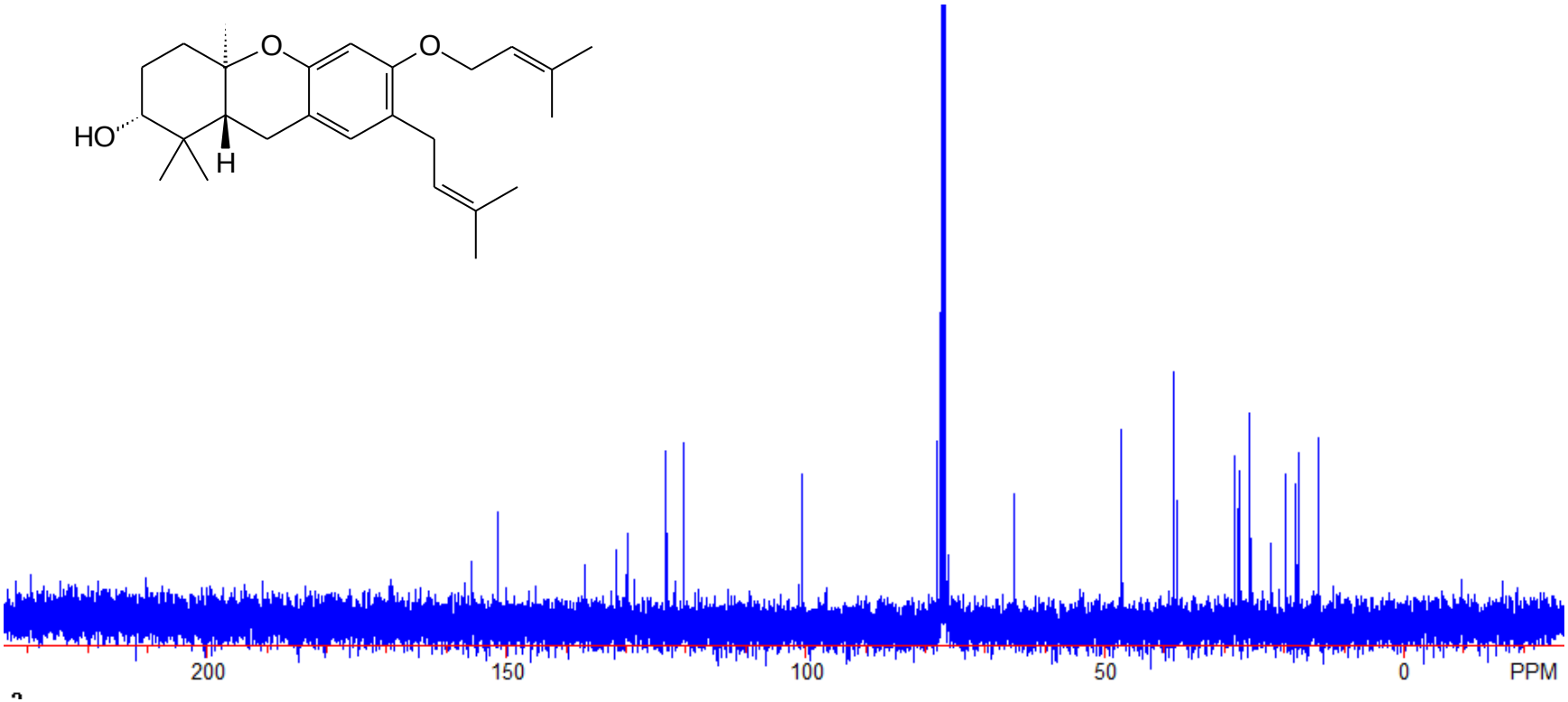


Figure A20. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Compound **251**

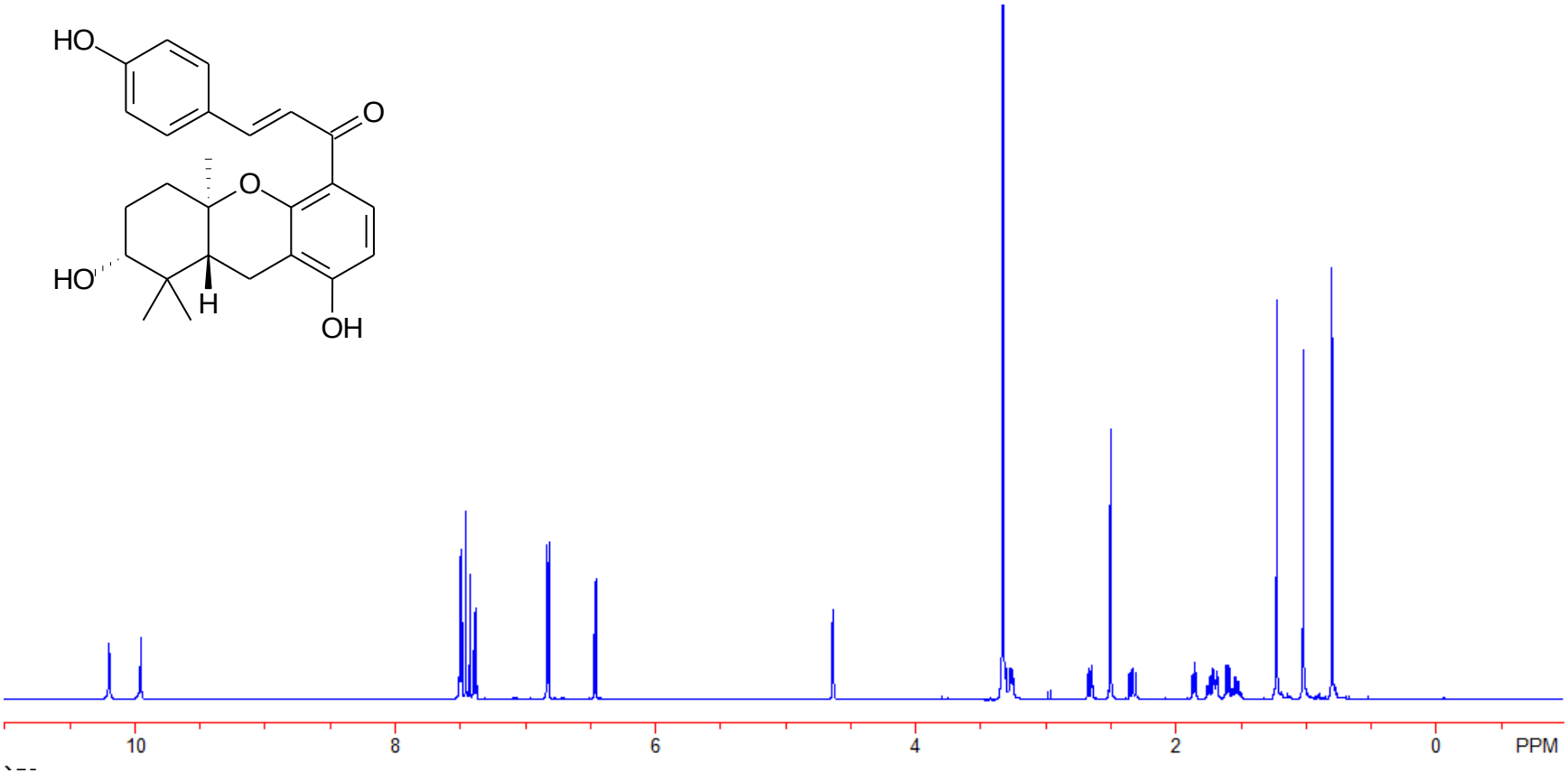


Figure A21. 600 MHz ^{1}H NMR Spectrum (DMSO) of angelichalcone (**287**)

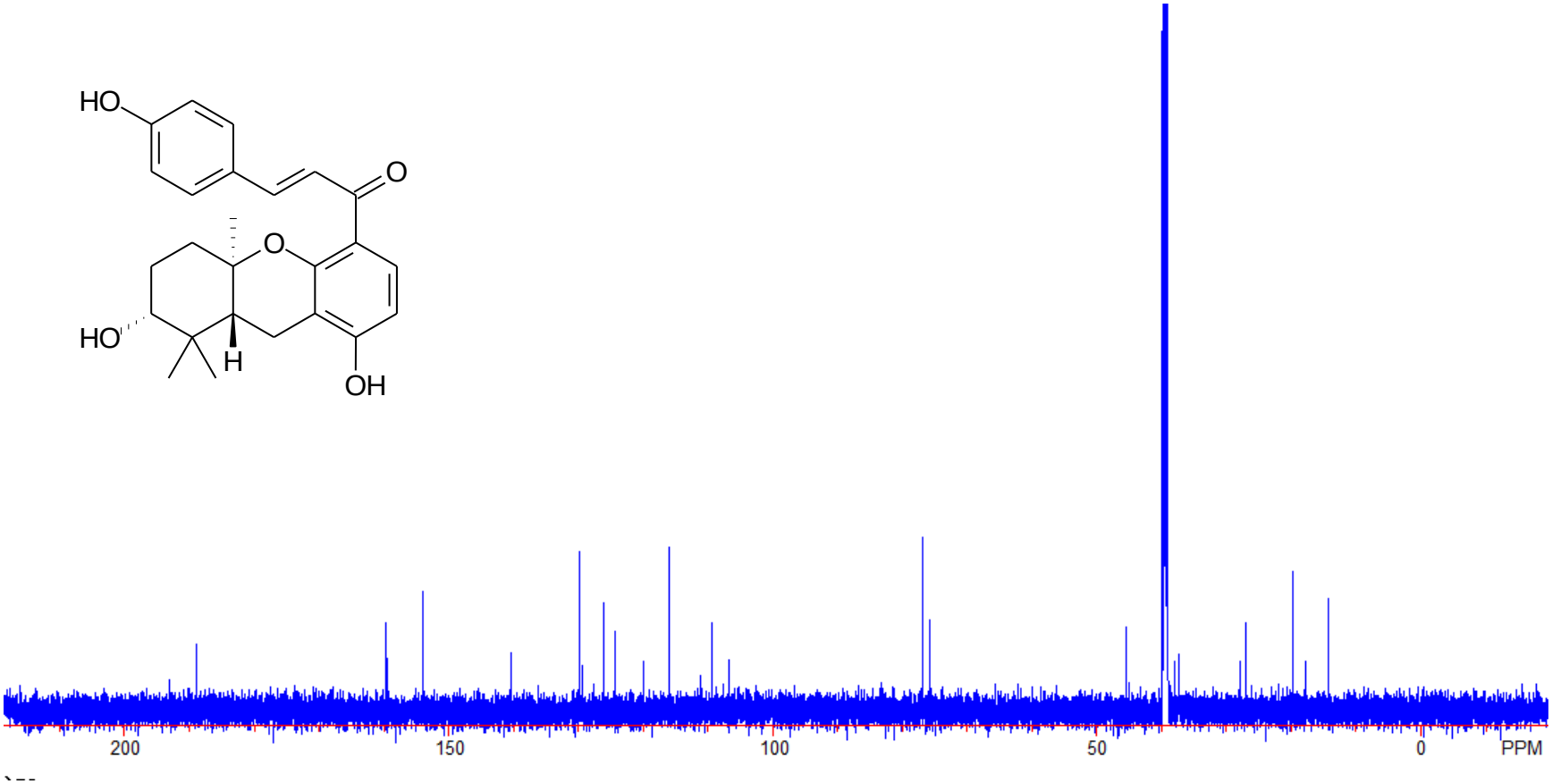


Figure A22. 150 MHz ^{13}C NMR Spectrum (DMSO) of angelichalcone (**287**)

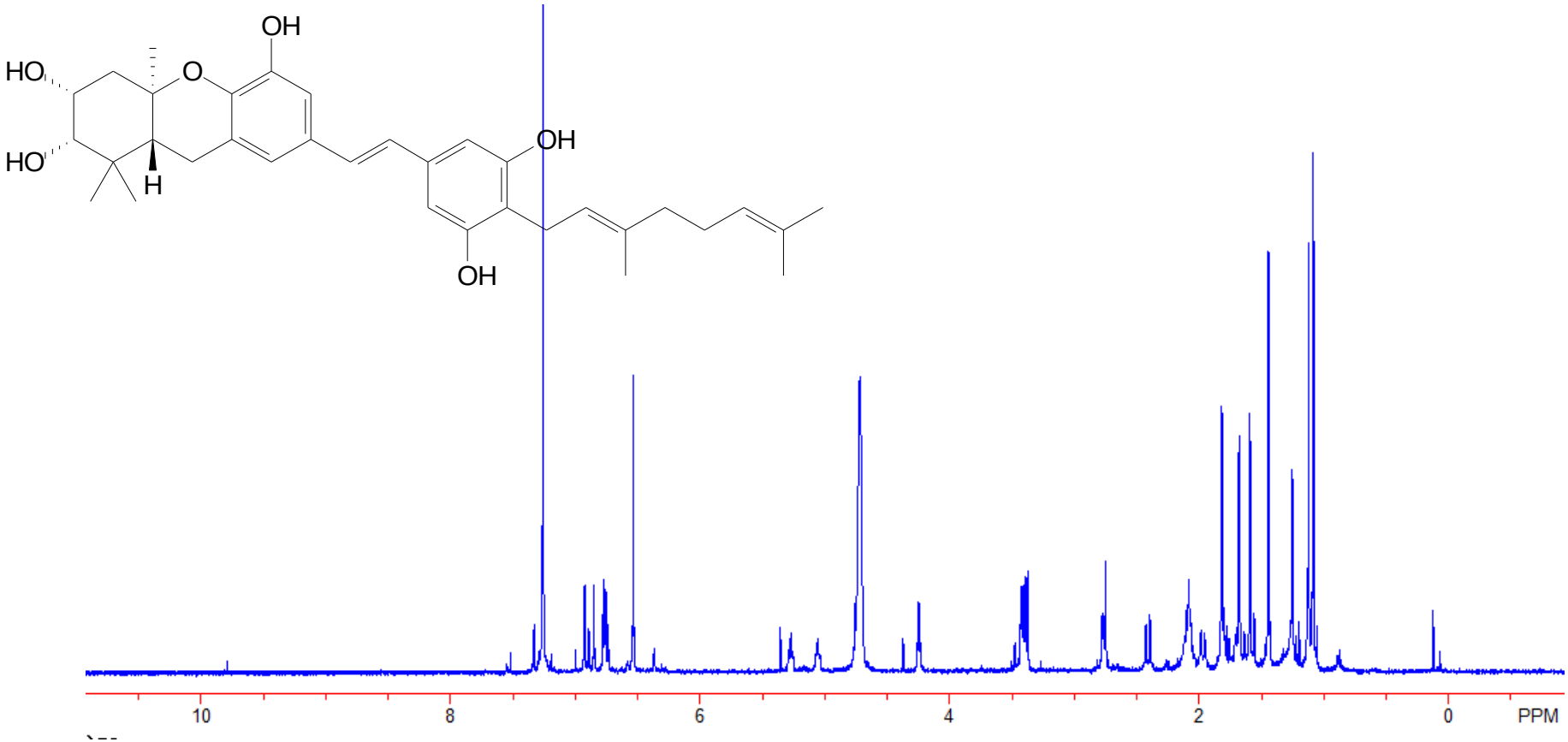


Figure A23. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Schweinfurthin A (**8**)

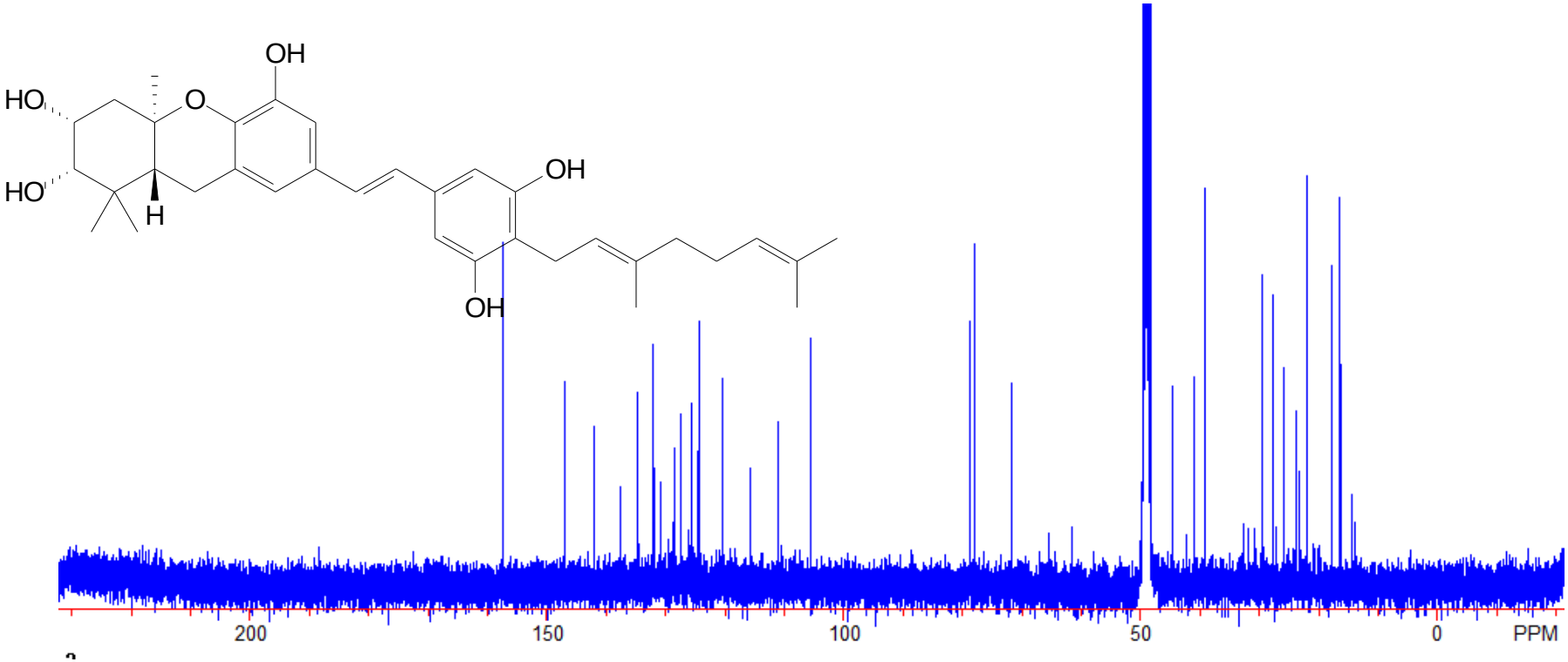


Figure A24. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Schweinfurthin A (**8**)

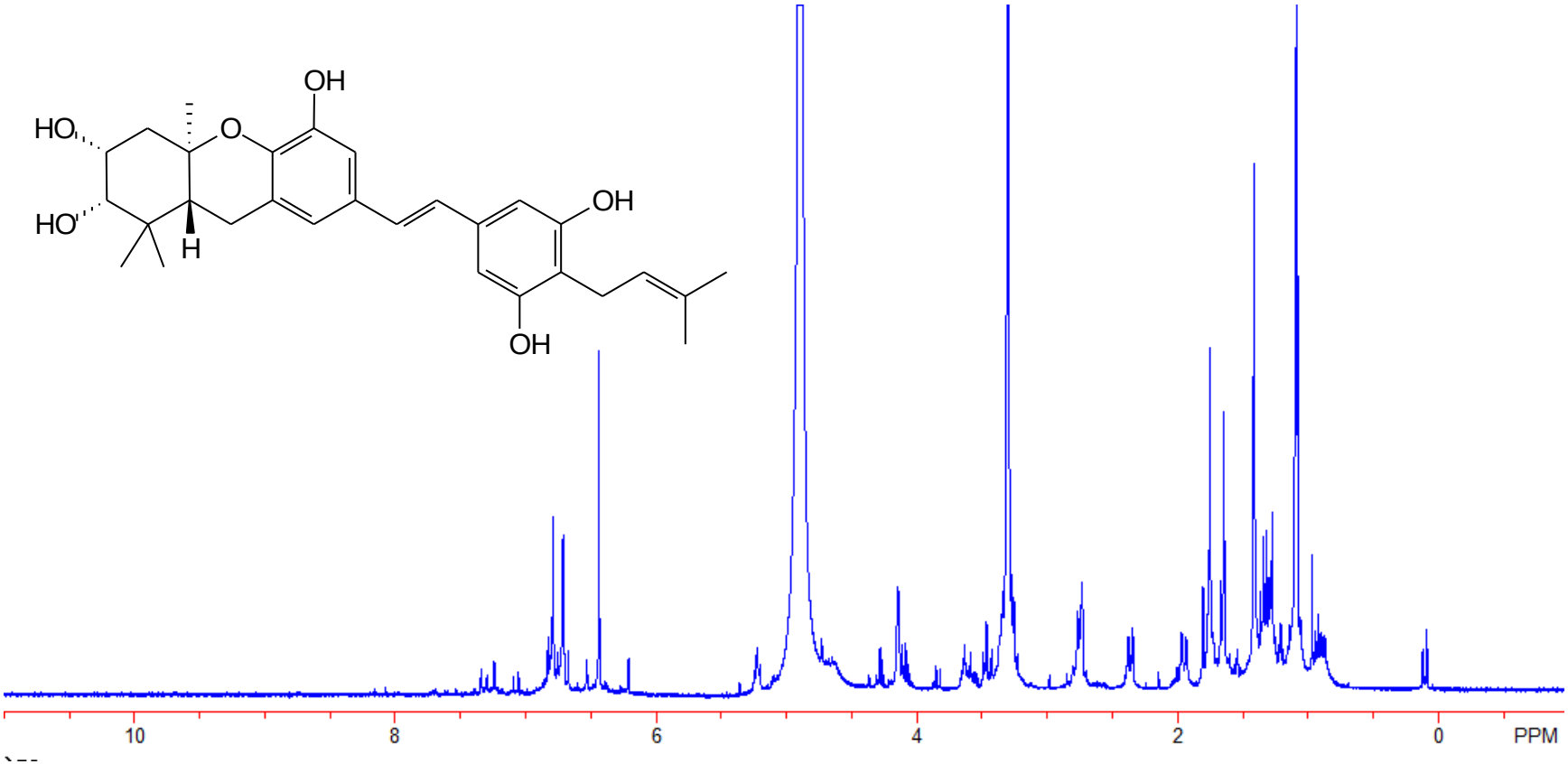


Figure A25. 400 MHz ^{1}H NMR Spectrum (MeOD) of Vedelianin (**12**)

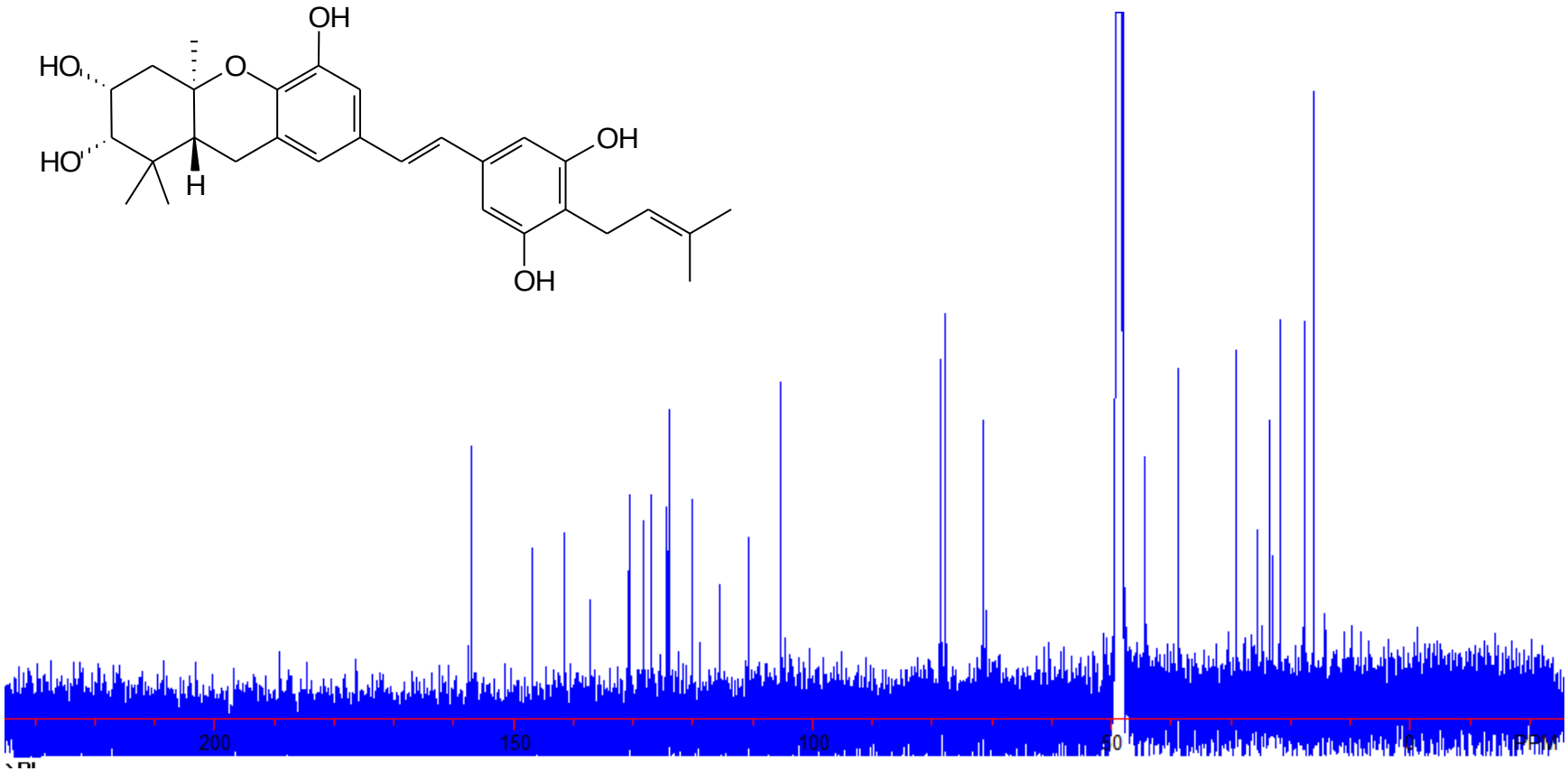


Figure A26. 100 MHz ^{13}C NMR Spectrum (MeOD) of Vedelianin (**12**)

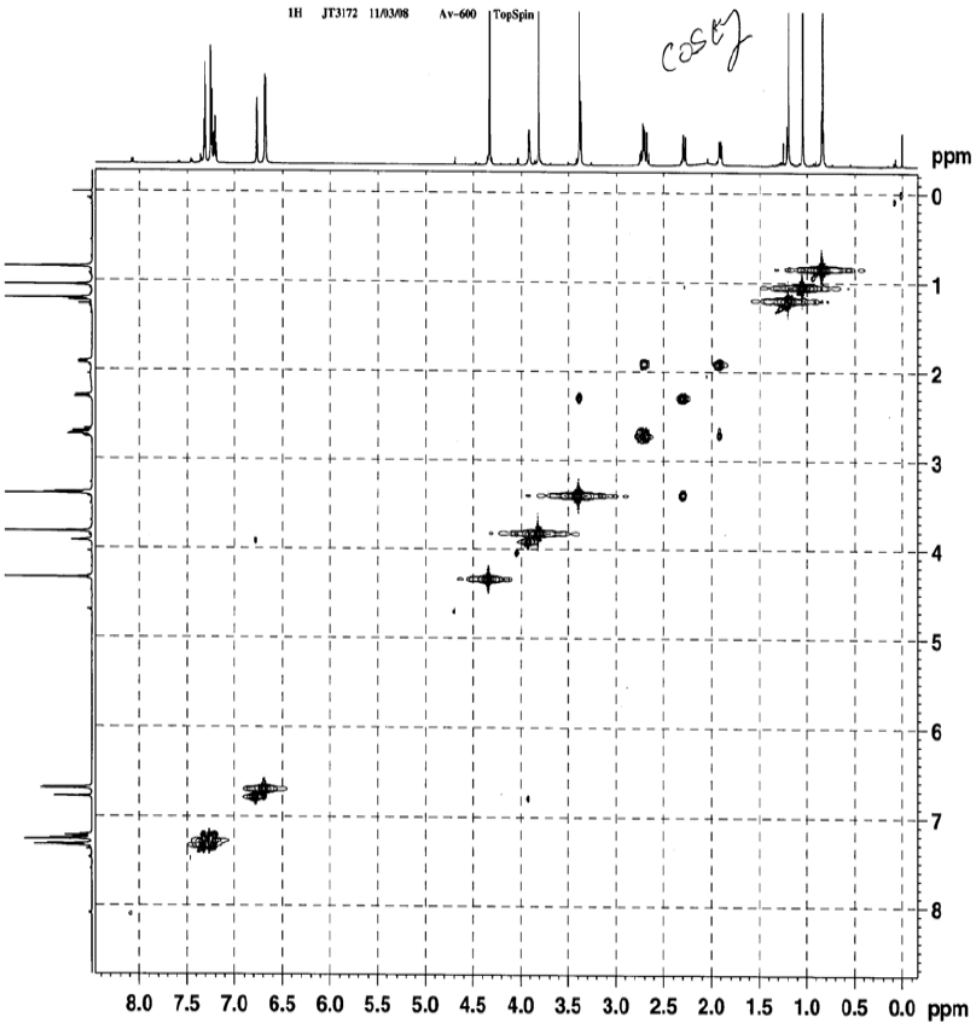


Figure A27. ^{1}H COSY NMR of Compound **102**

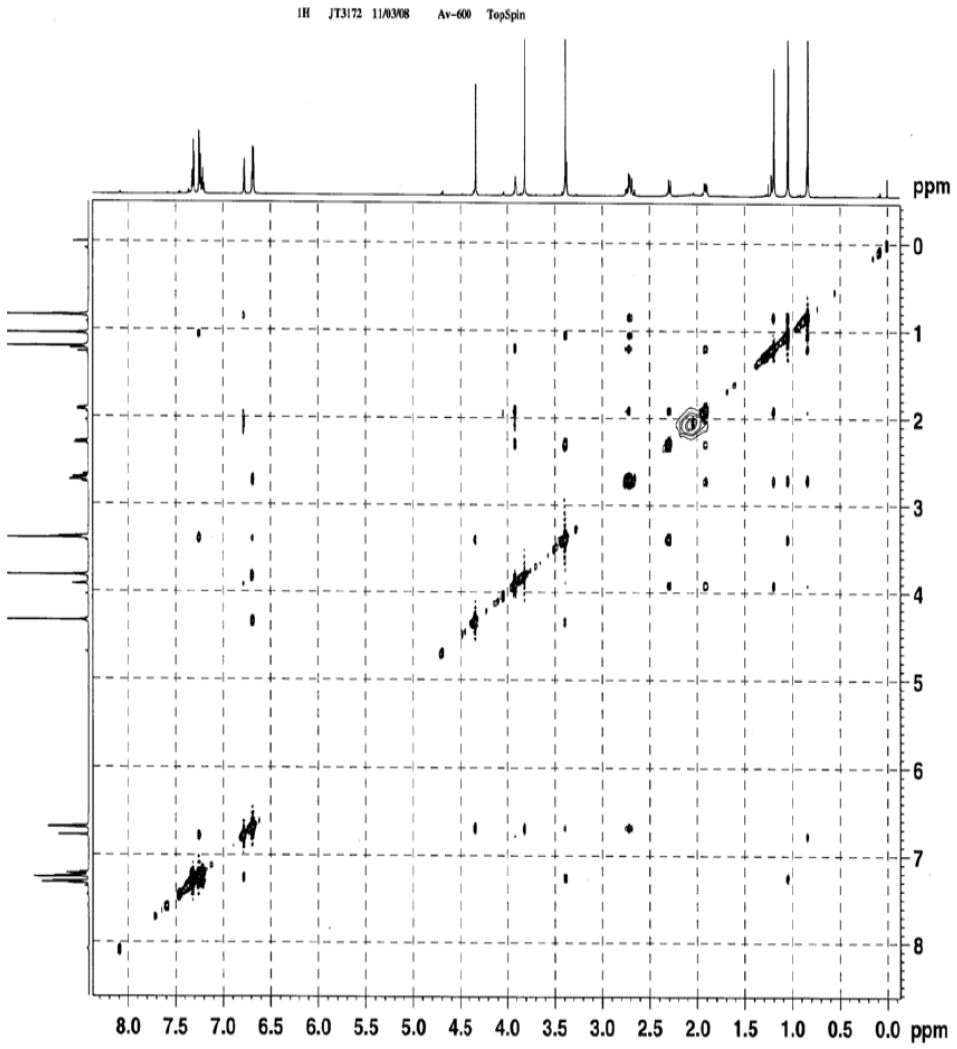


Figure A28. ^{1}H NOESY NMR of Compound **102**