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Studies on heteroaromatic schweinfurthin analogues

John Gordon Kodet
University of Iowa

STUDIES ON HETEROAROMATIC SCHWEINFURTHIN ANALOGUES

by

John Gordon Kodet

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

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Thesis Supervisor: Professor David F. Wiemer

ABSTRACT

Natural products are a rich source of lead compounds for treatment of cancer as well as other diseases. Researchers at the National Cancer Institute, as part of their continuing effort to discover anticancer agents from natural sources, created the 60 human tumor cell-line anticancer screen to test natural products for their potential against various types of cancer. Through this screening process a family of natural products called schweinfurthins was discovered to possess potent and differential activity. Of potentially great significance, the pattern of activity that the schweinfurthins displayed in the screen does not correlate with any currently used anticancer drug, indicating that the schweinfurthins likely act via a previously unknown mechanism or on a novel target. Our group has synthesized many of the natural schweinfurthins as well as numerous analogues in an effort to probe the pharmacophore and gain understanding of the key features that are important for potency as well as differential activity. During the course of these studies, it was discovered that the right-half of the molecule is most amenable for modifications.

One potential modification to the schweinfurthins is to replace the resorcinol substructure seen in the right-half of the natural product with a heteroaromatic moiety such as a benzofuran or indole system. This change may produce analogues that are potentially more active, that contain motifs that are seen in many therapeutic drugs, and that have improved chemical stability relative to the natural products. With this goal in mind benzofuran and indole containing schweinfurthin analogues were synthesized. Once these compounds were prepared, it was found that such modifications were well-tolerated, and in the case of the indole analogues activity in the 60 cell-line screen was

equivalent to the corresponding natural product. In an effort to improve that activity, prenyl and geranyl side chains were added to the indole system, at both the C-2 and C-3 positions, to better match the structure of the natural schweinfurthins. In addition, analogues methylated selectively on the indole nitrogen or phenol were synthesized to improve stability. The impact of those modifications on the activity was tested, and potent compounds were found.

The left-half of the schweinfurthins is prepared via a Lewis acid mediated cascade of a geranyl epoxide. The protecting group that is typically employed on the terminating phenol, a methoxymethyl ether or MOM group, is cleaved during the reaction. In the past preparation of an analogue that lacked a substituent at the C-5 position, it was found that the MOM cation released during the cyclization would participate in an electrophilic aromatic substitution reaction at the neighbouring position which resulted in the formation of a benzyl methyl ether. In order to probe the scope of this reaction and its potential utility in the synthesis of natural products, several geranyl epoxides with various "protecting groups" on the phenol were prepared and subjected to the cyclization conditions. These investigations have established that stabilization of the liberated cation determines the likelihood and regioselectivity of a tandem electrophilic aromatic substitution reaction.

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

PH.D. THESIS

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

John Gordon Kodet

has been approved by the Examining Committee
for the thesis requirement for the Doctor of Philosophy
degree in Chemistry at the December 2010 graduation.

Thesis Committee:

David F. Wiemer, Thesis Supervisor

Gregory K. Friestad

Chris Pigge

Lei Geng

Michael W. Duffel

The important thing is not to stop questioning.
Curiosity has its own reason for existing.

Albert Einstein

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Natural products are a rich source of lead compounds for treatment of cancer as well as other diseases. Researchers at the National Cancer Institute, as part of their continuing effort to discover anticancer agents from natural sources, created the 60 human tumor cell-line anticancer screen to test natural products for their potential against various types of cancer. Through this screening process a family of natural products called schweinfurthins was discovered to possess potent and differential activity. Of potentially great significance, the pattern of activity that the schweinfurthins displayed in the screen does not correlate with any currently used anticancer drug, indicating that the schweinfurthins likely act via a previously unknown mechanism or on a novel target. Our group has synthesized many of the natural schweinfurthins as well as numerous analogues in an effort to probe the pharmacophore and gain understanding of the key features that are important for potency as well as differential activity. During the course of these studies, it was discovered that the right-half of the molecule is most amenable for modifications.

One potential modification to the schweinfurthins is to replace the resorcinol substructure seen in the right-half of the natural product with a heteroaromatic moiety such as a benzofuran or indole system. This change may produce analogues that are potentially more active, that contain motifs that are seen in many therapeutic drugs, and that have improved chemical stability relative to the natural products. With this goal in mind benzofuran and indole containing schweinfurthin analogues were synthesized. Once these compounds were prepared, it was found that such modifications were well-tolerated, and in the case of the indole analogues activity in the 60 cell-line screen was

equivalent to the corresponding natural product. In an effort to improve that activity, prenyl and geranyl side chains were added to the indole system, at both the C-2 and C-3 positions, to better match the structure of the natural schweinfurthins. In addition, analogues methylated selectively on the indole nitrogen or phenol were synthesized to improve stability. The impact of those modifications on the activity was tested, and potent compounds were found.

The left-half of the schweinfurthins is prepared via a Lewis acid mediated cascade of a geranyl epoxide. The protecting group that is typically employed on the terminating phenol, a methoxy methyl ether or MOM group, is cleaved during the reaction. In the past preparation of an analogue that lacked a substituent at the C-5 position, it was found that the MOM cation released during the cyclization would participate in an electrophilic aromatic substitution reaction at the neighbouring position which resulted in the formation of a benzyl methyl ether. In order to probe the scope of this reaction and its potential utility in the synthesis of natural products, several geranyl epoxides with various "protecting groups" on the phenol were prepared and subjected to the cyclization conditions. These investigations have established that stabilization of the liberated cation determines the likelihood and regioselectivity of a tandem electrophilic aromatic substitution reaction.

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LIST OF ABBREVIATIONS

3dSA	3–deoxyschweinfurthin A
3dSB	3–deoxyschweinfurthin B
Å	Angstrom
A549	Human–Derived Lung Adenocarcinoma Cell Line
Ac	Acetate
Anal.	Analysis
Aq.	Aqueous
Boc	*t*-Butoxycabonyl
br	Broad
Bu	Butyl
C	Celsius
calcd	Calculated
CNS	Central Nervous System
COMPARE	NCI Based Computer Algorithm
d	Doublet
DBU	1,8-diazabicyclo[5.4.0] undec-7-ene
dd	Doublet of doublets
DEPT	Distortionless Enhancement for Polarization Transfer (NMR)
DIPEA	Diisopropylethylamine
DMF	Dimethylformamide
dt	Doublet of Triplets
ee	Enantiomeric Excess
EI	Electron Impact
Et	Ethyl
g	Gram

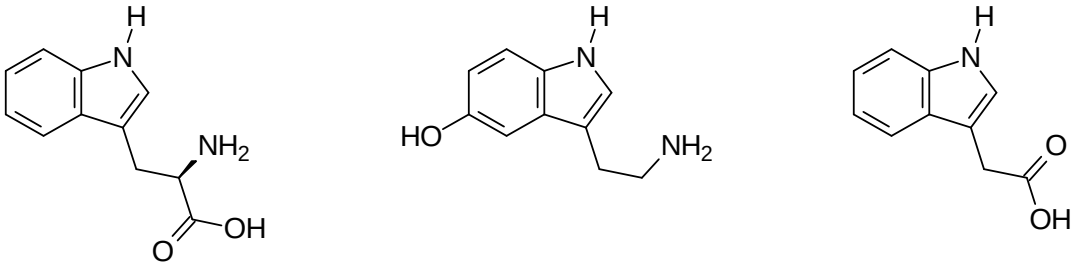
GI_{50}	Growth Inhibition at 50%
h	Hour
HMPA	Hexamethylphosphoramide
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectroscopy
HWE	Horner–Wadsworth–Emmons
Hz	Hertz
i-Pr	Isopropyl
J	Coupling Constant
LDA	Lithium Diisopropyl Amide
cLogP	Octanol–water Partition Coefficient
m	Multiplet
M	Molar
m-CPBA	*meta*–Chloroperbenzoic Acid
Me	Methyl
mg	Milligram
mL	Milliliter
mmol	Millimole
MOM	Methoxymethyl
Ms	Methanesulfonyl
m/*z*	Mass/Charge
n-BuLi	*n*-Butyl Lithium
NP	Natural Product
NBS	*N*–bromosuccinimide
NCI	National Cancer Institute
NMR	Nuclear Magnetic Resonance
q	Quartet

rt	Room Temperature
s	Singlet
SA	schweinfurthin A
sat	Saturated
SB	schweinfurthin B
SC	schweinfurthin C
SE	schweinfurthin E
sep	septet
SF	schweinfurthin F
SF–295	CNS Cancer Cell Line
SF–539	CNS Cancer Cell Line
SG	schweinfurthin G
t	Triplet
TBAF	Tetrabutylammonium Fluoride
TBS	*tert*–Butyldimethylsilyl
Tf	Triflate
TFAA	Trifluoroacetic anhydride
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
tol	Toluene
Ts	*p*–Toluene Sulfonyl
TsOH	*p*–Toluene Sulfonic Acid

CHAPTER 1

INDOLE CONTAINING COMPOUNDS IN MEDICINE

The indole structure has a long and rich history in chemistry beginning with the study of dyes in the mid 19th century. Adolf von Baeyer in his study of the blue dye indigo first synthesized indole by the reduction of oxindole with Zn dust in 1866.[1] Later that decade he proposed the initial structure of indole.[2] In the early 20th century the indole moiety was determined to be a feature of the amino acid tryptophan (**1**, Figure 1). [3] With the amino acid tryptophan as an ubiquitous source of starting material, it is no wonder that many natural products have been found to contain an indole or indole-derived structure. Small indole-containing compounds have many important biological functions. For example, indoles such as the neurotransmitter serotonin (**2**) are used for cellular signaling and regulate numerous neuropsychological processes,[4] and the auxin indole 3-acidic acid (IAA, **3**) regulates plant cell division and growth.[5]



1 **2** **3**

Figure 1. Small indole-containing natural products

The indole moiety also is found in many natural products and compromises a major subset for the alkaloid class of compounds. Perhaps because of their similarities to

serotonin (**2**), many indole-containing natural products have very potent neurochemical effects. A few examples of these are 4-hydroxy-*N*,*N*-dimethyltryphamine (**4**, Figure 2), or psilocin, which is found as the active component in psychedelic or "magic" mushrooms,[6] and the ergot alkaloids which cause ergot poisoning and have been postulated as the root of the behavior that lead to the Salem witch trials.[7] One of the more infamous ergot alkaloids is lysergic acid (**5**) whose derivative lysergic acid diethylamide (**6**, LSD) is widely known for its very powerful psychedelic effects.

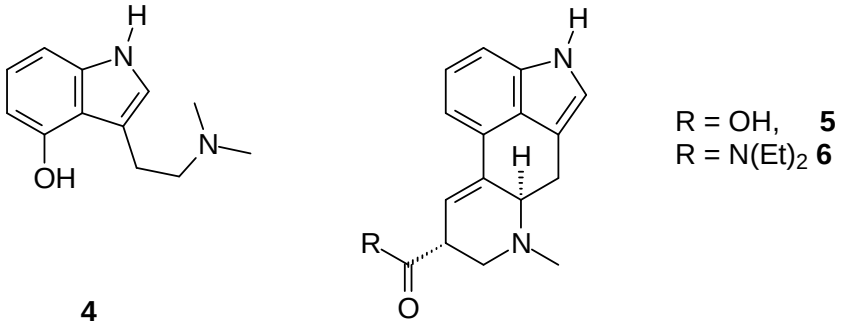


Figure 2. Mind-altering indole compounds

Beyond the potentially dangerous nature of indole-containing compounds, others have clinically beneficial properties. The natural products vinblastine (**7**) and vincristine (**8**), isolated from *C. roseus*,[8] are active against a variety of leukemia, lymphoma, breast, and lung cancer cell types (Figure 3).[9] Analogues of these compounds are in current use to treat a variety of cancers.[10] Numerous other indole-containing compounds have been shown to possess anti-cancer activity as well as a myriad of other clinical uses.[11-13] Because of the prevalence of the indole moiety in biologically active compounds, it is

considered a “privileged structure” and that makes it a logical motif to incorporate or retain in a synthetic molecule to improve biological activity.[14]

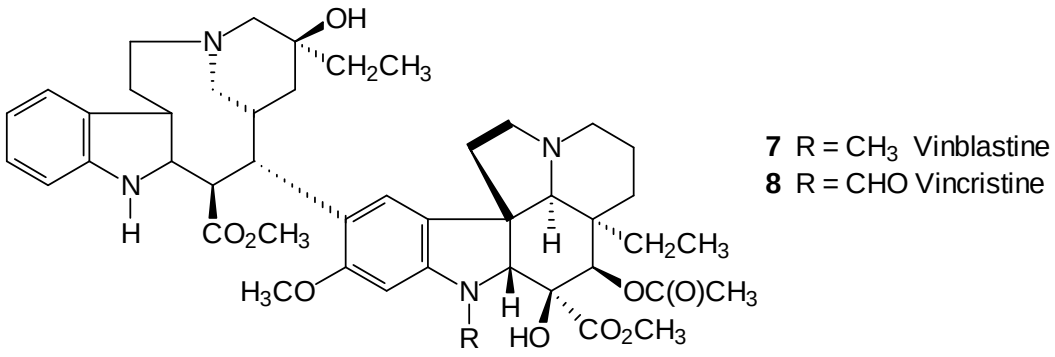


Figure 3. Indole containing natural products with anti-cancer activity

Cancer is one of the leading causes of death in the United States. Currently there are over 1,000,000 new cases each year, and over 500,000 (or 1 in 4) deaths per year occur from cancer.[15] Because of these grim statistics, the development of cancer treatments has been a priority for many years. In 1937 Congress established the National Cancer Institute (NCI) with a mission to fund and maintain cancer therapy efforts through a range of independent entities.[16] Then in the 1950’s the NCI developed the Cancer Chemotherapy National Service Center (CCNSC), which was involved in the screening, pre-clinical testing, and clinical studies of potential anticancer drugs.[17]

As part of the NCI’s mission to search for compounds with potential cytotoxic activity, the NCI has screened more than 500,000 compounds.[17] Initially researchers used transplantable murine tumors as a method to screen compounds for cytotoxic activity, but unfortunately it was found that the pattern of activity seen in the mouse

tumor cell lines did not necessary translate to activity against human cancer cells.[18] In addition, this testing process was expensive. In an effort to improve the efficiency of the process, NCI began to develop a human cancer cell assay in the mid 1980's. After some setup experiments, screening of compounds for potential anticancer activity began in earnest in 1989.[19-21] The assay contains a panel of approximately 60 human tumor derived cell lines, to screen effectively against a variety of cancer cell types. This approach has allowed over 10,000 compounds to be tested annually. With all the assay results generated, a method to effectively analyze the data was necessary, so the NCI developed a computer algorithm (COMPARE) to analyze the data generated from the 60 cell-line assay and to identify compounds which display similar patterns of activity.[22] If compounds display high correlations to one another, it can be inferred that these compounds act via a similar mechanism of action, perhaps on the same molecular target or in the same molecular pathway.

This screening process has allowed many natural products to be tested for anticancer activity. One of the unique family of natural products isolated at NCI and tested in this assay was the schweinfurthins. In 1987, D. W. Thomas of the Missouri Botanical Garden collected the leaves of the plant *Macaranga schweinfurthii* during a visit to Korup National Park, Cameroon.[23] The leaves were subsequently dried and placed in storage. Over a decade later, Dr. John A. Beutler and coworkers at NCI–Frederick examined the extract of the dried leaves (425 g) for activity against the human-derived CNS (Central Nervous System) cell lines SF-295 and SF-539. After activity was observed in these two cell lines, schweinfurthins A and B (SA, **9**, 50 mg; SB, **10**, 38 mg), along with the less active schweinfurthin C (SC, **11**, 25 mg) were isolated (Figure 4)

through bioassay-guided fractionation. When SA and SB were tested in NCI's 60 cell-line assay, they displayed potent and selective anti-proliferative activity (mean GI_{50} = 0.36 and 0.81 μM, respectively). The modified schweinfurthin D (**12**) was isolated in 2000 and showed similar activity to SB.[24] In 2007, Kingston and coworkers reported the isolation of schweinfurthins E-H (**13**–**16**, SE mean GI_{50} = 0.19 μM).[25] Very recently schweinfurthins I (**17**) and J (**18**) were isolated.[26]

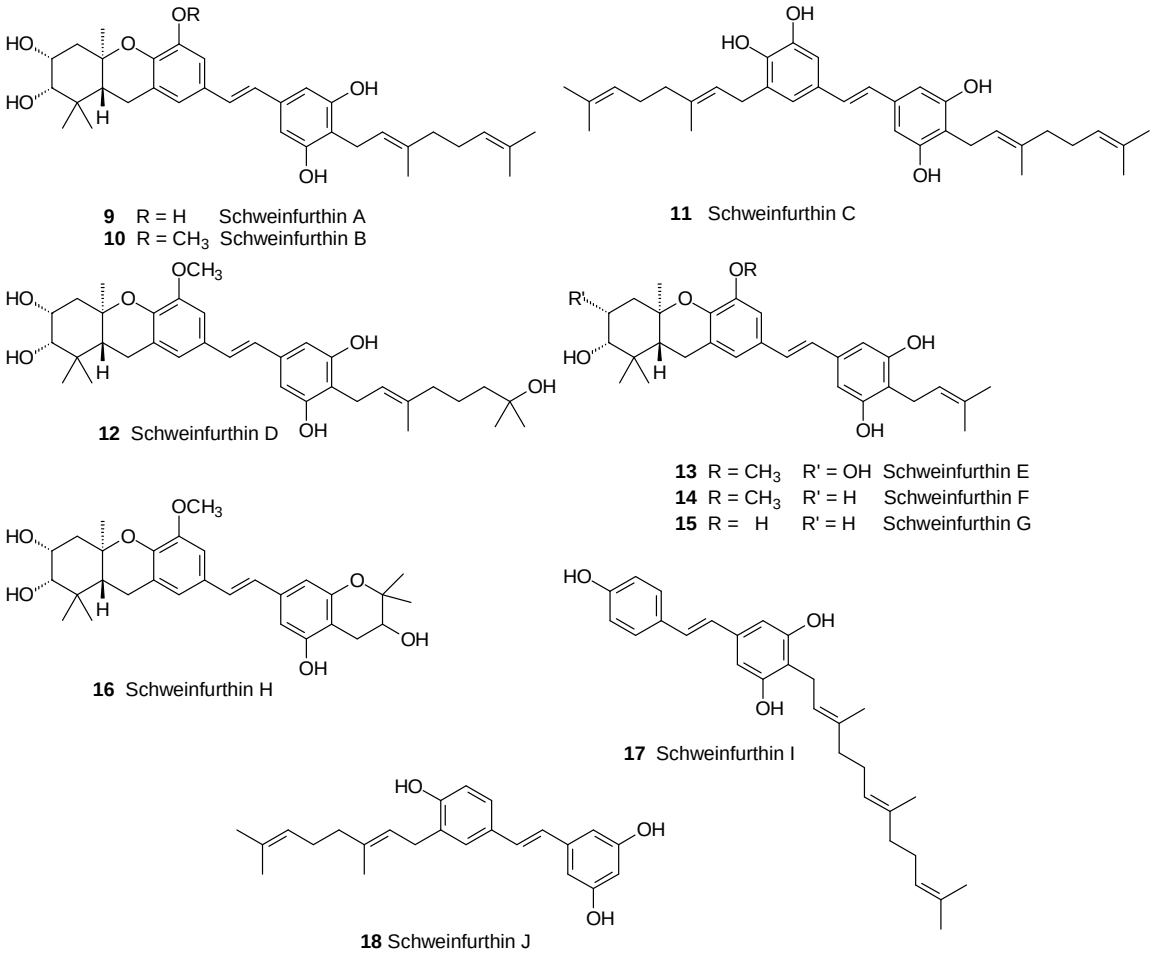


Figure 4. Naturally occurring schweinfurthins

When the pattern of activity for the schweinfurthins in the 60 cell-line assay was compared to clinically used anticancer agents through the COMPARE program, no correlation was found.[23] This suggests that schweinfurthins act via a novel and unexplored molecular pathway or pathways to target cancer cells, which make them an attractive subject for cancer research. When the COMPARE analysis was expanded to include all the natural products in the NCI database, the schweinfurthins were found to display high correlation to a few structurally unrelated natural products: the cephalostatins (eg. Cephalostatin 1, **19**),[18, 27, 28] the stellettins (eg. Stellettin A, **20**),[29-32] and OSW–1 (**21**, Figure 5).[33]

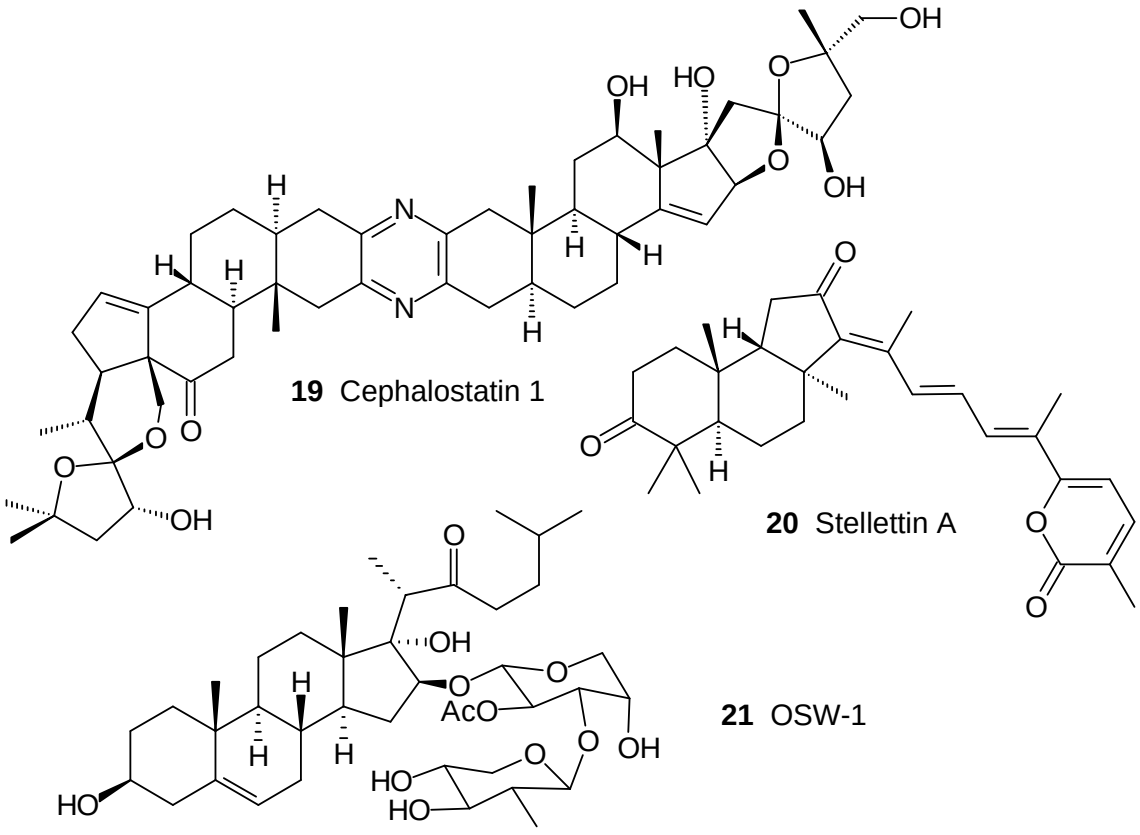


Figure 5. Natural products with high correlations to the schweinfurthins

The structural complexity of cephalostatin makes it very difficult to synthesize and develop it as a drug for clinical use. However, despite its structural complexity several groups have worked to synthesize this molecule. The synthesis of cephalostatin 1 (**19**) was accomplished by the Fuchs group in 65 steps to afford ~2 mg of product in less than a 1% yield.[27, 34] Stellettin A (**20**) features a polyene structure that unfortunately makes it photolabile and no total synthesis has been reported at this time. The total synthesis of OSW–1 has been reported by a several groups.[35-39]

Because of our group's background with isoprenylated aryl systems and Horner-Wadsworth-Emmons (HWE) reactions,[40] we decided to focus our efforts on the synthesis of the schweinfurthins. This work began over a decade ago with the convergent synthesis of schweinfurthin C (**11**) via a late stage HWE coupling between aldehyde **22** and phosphonate **23** (Figure 6).[41] This strategy has served as a blueprint for the synthesis of other schweinfurthins.

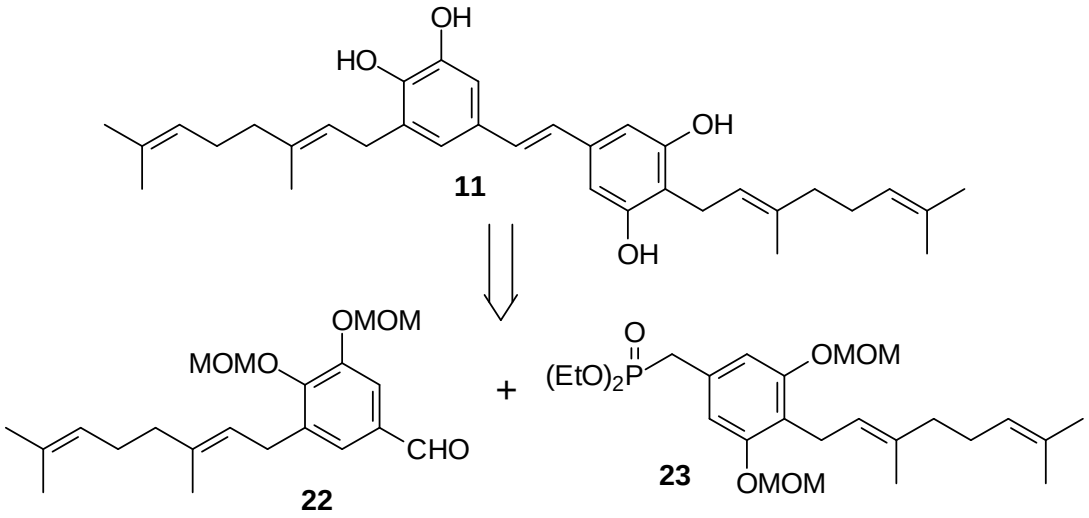
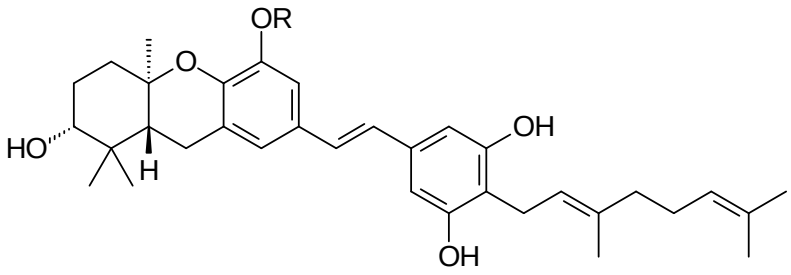


Figure 6. Convergent synthesis of schweinfurthin C (**11**)

Preparation of compounds with a cyclized geranyl chain in the left-half first was accomplished to produce the analogue 3-deoxyschweinfurthin B (3dSB, **24**, Figure 7), which lacks a hydroxyl group at the C-3 position of SB (**10**).[42] Soon afterward the syntheses of SF (**14**), 3-deoxyschweinfurthin A (3dSA, **25**) and SG (**15**) were reported.[43-45] Initially the synthesis produced only a limited quantity of the final target. As more research was performed, the total number of steps required was reduced and efficiency was improved, thus allowing greater quantities of the products to be obtained. This allowed experimentation into methods to install the hydroxyl group at the 3-position and ultimately syntheses of schweinfurthin B (**10**) and E (**13**)[46] were accomplished. Very recently the total synthesis of (+)-schweinfurthin A (**9**) has been completed.[47]



24 R = CH_3 3-deoxyschweinfurthin B
25 R = H 3-deoxyschweinfurthin A

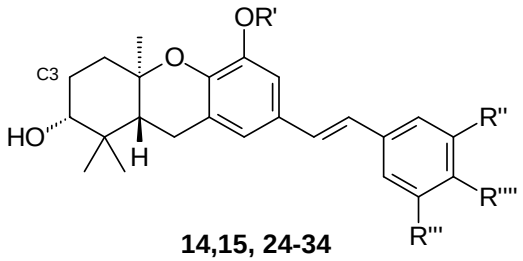
Figure 7. 3-deoxyschweinfurthin analogues

With improvements in the synthesis, several analogues were targeted in an effort to elucidate the pharmacophore of the molecule and to study which areas are amenable to modifications.[43, 45, 48-50] Structure-activity analysis of the analogues reveals modifications that are well-tolerated and maintain good activity and others that are not well-tolerated

(Table 1). When the C-3 hydroxyl group was removed from Schweinfurthin B (SB, **10**) the analogue **24** (3dSB) showed good activity with a mean GI_{50} across the 60 cell lines of 0.2 μM. When both phenols were protected as the methyl ether, the analogue **26** demonstrated diminished activity (mean GI_{50} of 6.6 μM) indicating that at least one phenol is important for activity. This view was confirmed when removal of the phenols from the D-ring in analogue **27** or replacement with fluorides in analogue **28** also was found to lead to a dramatic reduction in activity of the analogues (mean GI_{50} of 19 μM and 43 μM respectively). When both phenols and the D-ring side chain were removed as in analogue **29**, the activity also dropped substantially (16 μM). Removing the D-ring side chain gave an analogue **30** with diminished activity (7.8 μM), but when one additional phenol was removed, analogue **31** showed a somewhat better activity (3.2 μM). When one phenol was protected as the methyl ether to improve the stability, the resulting analogue **32** showed only a slight reduction in activity (0.87 μM) in comparison to schweinfurthin F (**14** mean GI_{50} of 0.41 μM). The pattern also holds for schweinfurthin G (**15**) and analogue **33**, as well as for 3dSA (**25**) in comparison to **34**.

These studies indicate that the best-tolerated places for modification were in the right-half of the molecule, provided that at least one phenol group was maintained on the D-ring. Considering the ubiquity of the "privileged"[14, 51] indole structure in bioactive compounds, it was envisioned that modification of the right-half of the schweinfurthin from a resorcinol substructure, which is prone to chemical instability, to an indole may produce analogues with improved activity, greater stability, and better drug-like properties.[52, 53] In this thesis, the studies which led to the synthesis of these new indole analogues, and those studies utilizing methods developed in the syntheses of these

compounds, will be presented, along with the cytotoxic activities of several of the newly prepared compounds.



14,15, 24-34

Compound	R’	R’’	R’’’	R’’’’	GI_{50} (μM)	Range (Log units)	clogP (Cal)
24	CH_3	OH	OH	Geranyl	0.2	3.26	8.19
26	CH_3	OCH_3	OCH_3	Geranyl	6.6	2.52	8.48
27	CH_3	H	H	Geranyl	19	0.79	8.79
28	CH_3	F	F	Geranyl	43	1.63	9.08
29	CH_3	H	H	H	16	1.20	5.40
30	CH_3	OH	OH	H	7.8	2.41	4.80
31	CH_3	OH	H	H	3.2	1.94	5.10
14	CH_3	OH	OH	Prenyl	0.41	4.0	6.53
32	CH_3	OH	OCH_3	Prenyl	0.87	3.05	6.67
15	H	OH	OH	Prenyl	0.10	3.15	6.38
33	H	OH	OCH_3	Prenyl	0.18	2.70	6.54
25	H	OH	OH	Geranyl	0.32	3.26	8.04
34	H	OH	OCH_3	Geranyl	0.52	2.88	8.19

Table 1. Structural and biological properties of some schweinfurthins and analogues

CHAPTER 2

INDOLE CONTAINING SCHWEINFURTHIN ANALOGUES

The initial target for synthesis would be the indole analogues of the schweinfurthins for several reasons. The natural schweinfurthins are predicted to have poor bioavailability due to their calculated partition coefficients (Chapter 1), and potential instability due to the resorcinol substructure. Incorporating an indole ring system should improve the bioavailability by lowering the partition coefficient.[52, 53] The lower partition coefficient indicates that the drug would have increased water solubility, which would allow better absorption and increased bioavailability. Secondarily the indole motif is seen in numerous pharmologically active natural products and synthetic drugs, and is considered a privileged structure[14, 54] in drug development.

The general method used in the synthesis of schweinfurthin analogues has included an HWE (Horner-Wadsworth-Emmons) condensation to form the central stilbene olefin (Figure 8). Because several schweinfurthin analogues already have been synthesized this way, with this approach it would not be necessary to develop a novel synthetic approach to the "left-halves" of the new indole analogues. Typically the aldehyde is placed on the left-half intermediate while the phosphonate is on the right-half. However, in a few reported syntheses the phosphonate has been placed in the left-half intermediate and the aldehyde has been part of the right-half.[43] The syntheses of the indole schweinfurthin analogues **40** and **41** were envisioned through an HWE condensation of our previously reported left-half aldehydes **42** and **43**[45] and an indole phosphonate **44** (Figure 1). The phosphonate should be readily available from alcohol **45**. The indole alcohol **45** would be available in turn from the parent indole core **46** via

the installation of the appropriate protecting groups and reduction of the ester. The indole core would arise from readily available diethyl succinate (**47**) and 2-pyrrole carboxaldehyde (**48**) through a Stobbe condensation followed by a cyclization/ aromatization and deprotection using established methodologies[55]

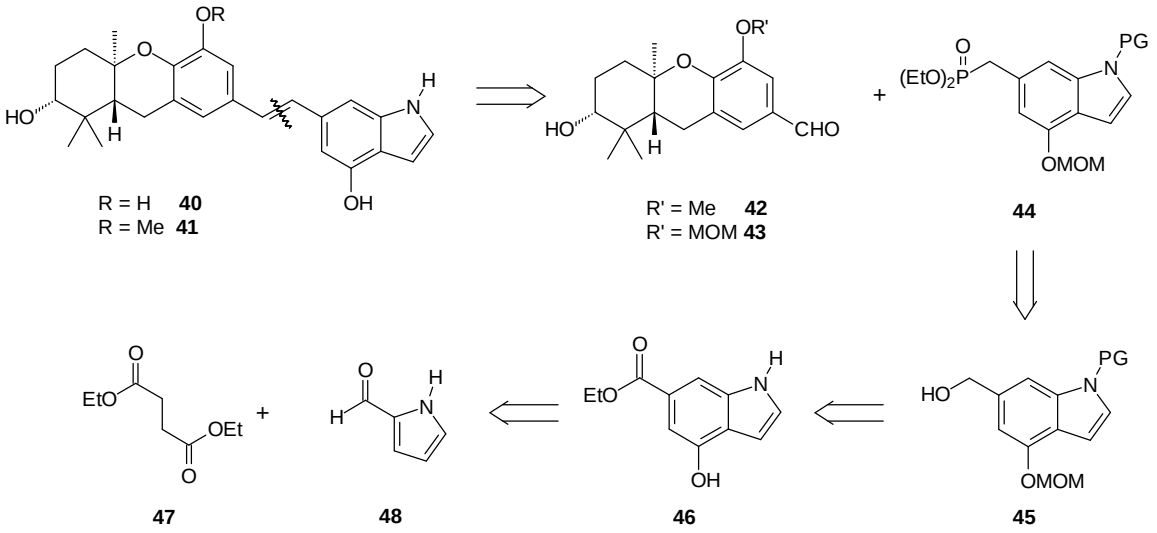


Figure 8. Retrosynthetic analysis

The synthesis of the desired indole phosphonates began with the Stobbe condensation of diethyl succinate (**47**) with 2-pyrrole carboxaldehyde (**48**) to give the intermediate acid. The intermediate acid was treated with a 6:1 mixture of acetic anhydride and acetic acid in toluene, and then brought to reflux to induce cyclization and form the acetate-protected indole core. Removal of the acetate from the phenol was achieved upon treatment with K_2CO_3 in refluxing ethanol to afford the free phenol **46** (Figure 9). Performing all three steps without purification of the intermediates offered a better overall yield and reduced the time required for preparation of intermediate **46**.

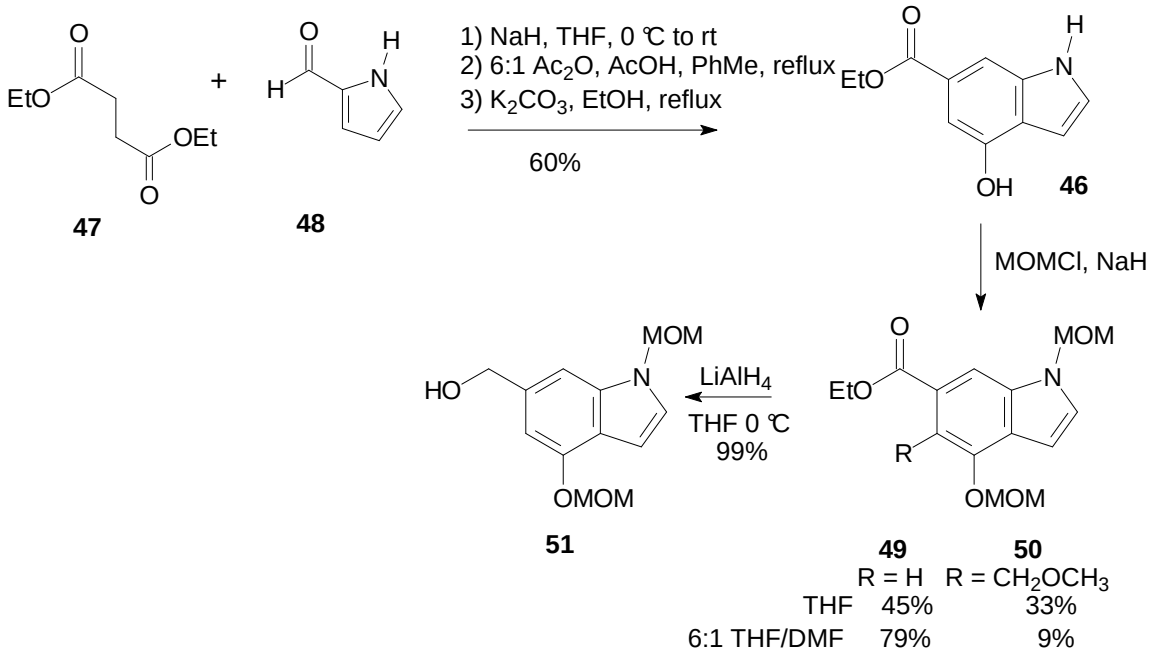


Figure 9. Synthesis of indole alcohol **51**

In the typical schweinfurthin synthesis, the phenols are protected with methoxymethyl (MOM) groups that can be cleaved as the final step of the sequence. In keeping with this tradition, the indole phenol and nitrogen were both protected with MOM groups. Treatment of compound **46** with NaH in THF followed by addition of MOMCl gave a mixture of the desired MOM-protected indole **49** as well as a substantial amount of the C-alkylated compound **50** (Figure 9). Adding DMF to the solvent system greatly improved the ratio of desired to undesired products and the overall yield as well. The final reduction of ester **49** to alcohol **51** proceeded cleanly and in quantitative yield.

Conversion of alcohol **51** to the phosphonate proved somewhat challenging. In our previous analogue syntheses, the benzylic alcohol was converted to a mesylate then to the iodide through reaction with NaI. The final step involved dissolving the iodide in

$(EtO)_3P$ and then heating the reaction mixture to reflux to allow conversion to the phosphonate via an Arbuzov reaction.[56] Attempts to use this method with alcohol **51** proved unsuccessful as the iodide appeared to polymerize upon removal of the solvent to form a paper-like film that was insoluble (Table 2, Entry 1). Synthesis of the phosphonate using CBr_4 and PPh_3 in THF to form the intermediate bromide[57] followed by an Arbuzov reaction in toluene with triethylphosphite afforded the desired compound, but only in a 12% yield (Entry 2). Switching the solvent to neat triethylphosphite only improved the yield to 14% (Entry 3).

Entry	Conditions	Yield
1	1) Et_3N, MsCl, CH_2Cl_2 2) NaI, acetone, 3) $(EtO)_3P$ reflux	Failed
2	1) CBr_4, PPh_3, THF, 2) $(EtO)_3P$, toluene, reflux	12%
3	1) CBr_4, PPh_3, THF, 2) $(EtO)_3P$, reflux	14%
4	1) Et_3N, MsCl, CH_2Cl_2 2) NaI, acetone 3) $(EtO)_3P$, reflux	25%
5	1) Et_3N, MsCl, CH_2Cl_2 2) LiBr, acetone 3) $(EtO)_3P$, toluene, reflux	39%
6	1) LiBr,Et_3N, MsCl, THF, 2), $(EtO)_3P$, reflux	13%
7	1) LiBr, Et_3N, MsCl, THF, –78 °C to 0 °C, 2) $(EtO)_3P$, THF, reflux	25%

Table 2. Synthesis of indole phosphonate **52**

Because of the limited success of the CBr_4 approach, use of an iodide intermediate was revisited. The TLC analysis of the reaction in entry 1 indicated that the some iodide had formed after treatment of the mesylate with NaI. Instead of removing all the solvent from the intermediate iodide during workup, concentration of the ether solution to a small volume, ~0.5 mL without heating, followed by addition of $(EtO)_3P$

and then removal of the remaining ether allowed the phosphonate to be isolated in an improved yield of 25% (Entry 4). Replacing the NaI with LiBr in the second step, followed by reaction with $(EtO)_3P$ in toluene, allowed the synthesis of the phosphonate **52** to proceed in 39% (Entry 5) but this was only accomplished on a small scale (7 mg). From this reaction it appeared that intermediate bromide was more stable than the iodide, as might be expected.

To make the synthesis more efficient, conversion of the alcohol to the bromide in a single step was attempted. Switching the solvent from CH_2Cl_2 to THF for formation of the mesylate would allow conversion to the bromide without the need for an intermediate workup. The literature offers several methods to perform this reaction. It can either be done sequentially, in which conversion to the mesylate is allowed to go to completion and then the LiBr is added, or the mesylate can be formed *in situ* in the presence LiBr and immediately converted to the bromide.[58] The latter reaction was chosen since it would be more efficient. Addition of the alcohol **51** as a THF solution to a mixture of the LiBr and Et_3N at 0 °C in THF, followed by dropwise addition of MsCl allowed the formation of the bromide, which was then converted to the phosphonate in low yield (13%, Entry 6). Adjusting the conditions to those Kajiwara[59] followed by careful workup with THF as the co-solvent, allowed formation of the desired phosphonate **52** in a 25% yield and on a useful scale (112 mg, Entry 7).

Phosphonate **52** then was coupled with left-half aldehyde **43**[45] to afford protected analogue **53** (Figure 10). Attempted removal of the MOM groups by treatment with TsOH was successful for hydrolysis of the two phenolic MOM protecting groups to give compound **54**, but did not remove the MOM group from the indole nitrogen.

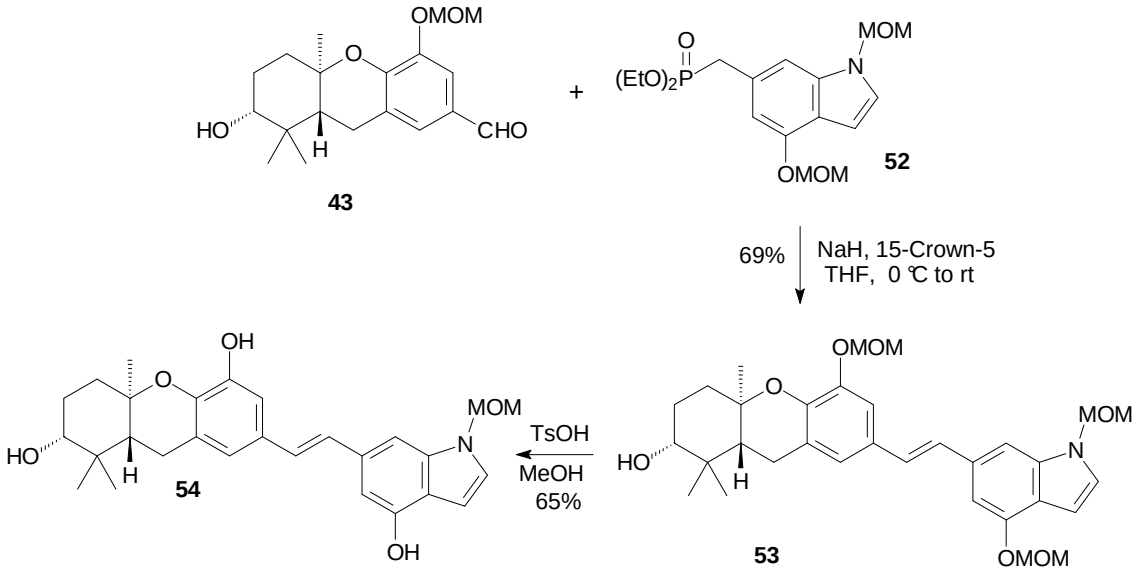


Figure 10. HWE and partial MOM hydrolysis

Attempted hydrolysis of the MOM group from the stilbene **54** under more forceful conditions[60] by treatment with HCl at reflux in THF (Figure 11) gave only decomposition of the compound. Other conditions for the removal of N–linked MOM groups, such as TfOH,[61] or BBr_3 to remove the terminal methyl followed by NaOH[62] on the precursor **51**, were unsuccessful, and resulted only in decomposition of the starting material (Figure 11).

After this setback a new strategy that involved installation of a different protecting group on the indole nitrogen was pursued. Selective MOM protection of the phenol **46** using DIPEA in CH_2Cl_2 gave indole **55** in acceptable yield (Figure 12), although a small amount of the product **56** was detected, a parallel reaction of the indole nitrogen has been seen during a selective protection of a phenol on an indole ring.[63] Once the phenol was masked, a better protecting group for the indole nitrogen was needed. The indole protecting group would have to be stable to the subsequent reaction steps yet easily

cleaved. One of the major difficulties in the synthesis of the indole phosphonate **52** above was the instability of the intermediate halide. If the protecting group also could address this issue it would make the synthesis significantly higher yielding and more practical. A survey of indole derivatives that contained a bromomethylene unit revealed that in most cases there was an electron-withdrawing group on the nitrogen,[64-69] and most of those that did not had an electron-withdrawing group elsewhere on the indole.[70] Protection of the indole nitrogen with an electron withdrawing group should allow formation of a bromide that was more stable but still useful in formation of the phosphonate. Based on the available literature precedent, an attractive choice appeared to be the Boc group,[64-68] so the use of this group was explored.

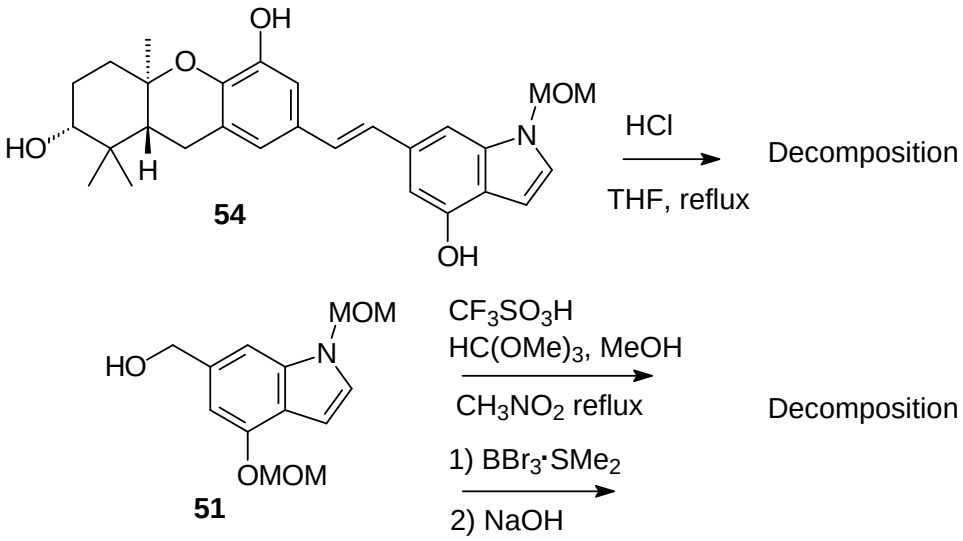


Figure 11. Attempts to remove the *N*–MOM group

Protection of indole **55** by reaction with NaH followed by Boc_2O afforded the *N*–protected indole **57**. Because the Boc group would be reactive with $LiAlH_4$, a different

reducing agent was needed to accomplish a selective reduction of the ester in the presence of the Boc group. Selective reduction with DIBAL–H gave alcohol **58**. Conversion to the bromide occurred via a one-flask procedure through the intermediate mesylate,[58] and after workup the bromide was converted to the phosphonate **60**. Interestingly the main product of the Arbuzov reaction with triethylphosphite, compound **59**, also had lost the Boc protecting group. This result can be attributed to the temperature of refluxing $P(OEt)_3$ (165 °C), which is higher than the temperature needed to remove the Boc group.[71] Fortunately reinstallation of the Boc group went cleanly to afford phosphonate **60**. Reducing the temperature for the reaction in $P(OEt)_3$ to 95 °C, allowed formation of the phosphonate without the removal of the Boc group and gave compound **60** in 60% yield.

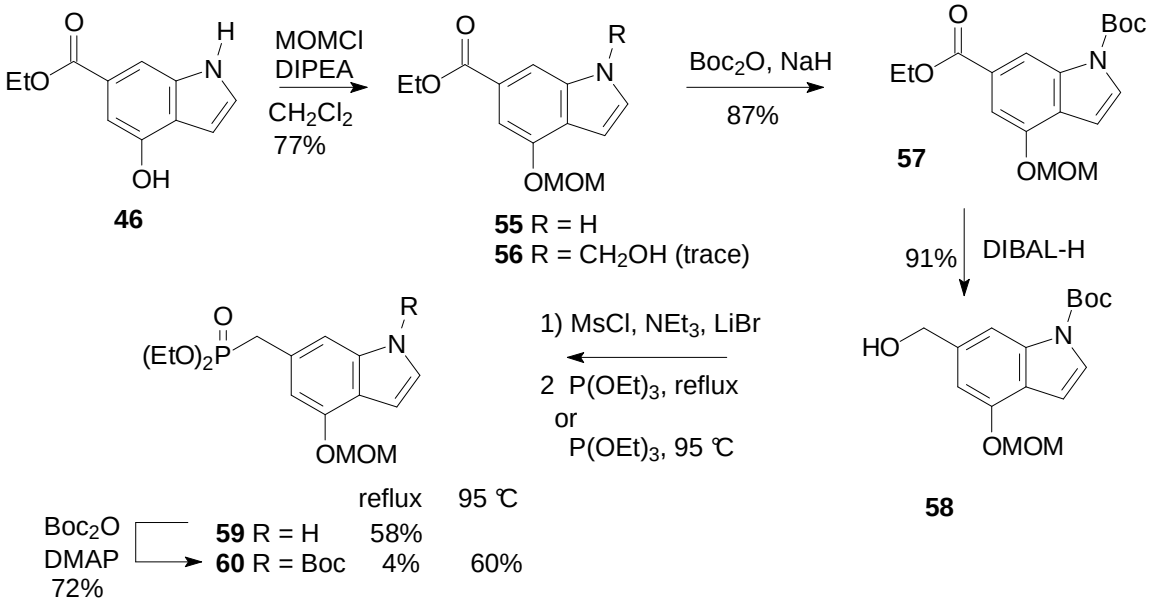


Figure 12. Synthesis of differentially protected indole phosphonate **60**

If phosphonate **59** would undergo an HWE reaction, it would be potentially useful since the stilbene product would not require a deprotection at a later stage. Because the pKa of an indole is approximately 21,[72] while that of the benzylic phosphonate is approximately 28,[72] treatment with a base strong enough to deprotonate the benzylic position would also deprotonate the nitrogen and result in formation of a dianion. To determine if the dianion would undergo an HWE reaction a brief model study was undertaken. Fortunately coupling under standard conditions with a model aldehyde, ansialdehyde (**61**), gave the desired stilbene **62** in good yield (71%). Gentle heating to increase the reaction rate gave the expected product in an improved yield (94%, Figure 13). With this promising result in hand the HWE condensation was attempted with both left-half aldehydes **42** and **43,** but unfortunately both reactions were unsuccessful and only gave trace amounts of stilbene products. A second model study was attempted using aldehyde **63**,[41] an intermediate in the synthesis of left-half aldehyde **42**, but again the reaction was without success. For some as yet undetermined reason, the HWE condensation reaction worked with aldehyde **61** in the model study, but with systems substituted like the schweinfurthins the reactions were problematic.

Because of these results, the HWE reaction next was attempted with the Boc-protected indole phosphonate **60**, but also without success (Figure 14). The TLC analysis of the reaction indicated that the Boc group was cleaved quickly during the reaction. This resulted in the free indole which was shown above to give only trace amounts of a condensation product in attempted HWE reactions. Experiments in which the base was changed to *n*-BuLi did not lead to formation of a recoverable product.

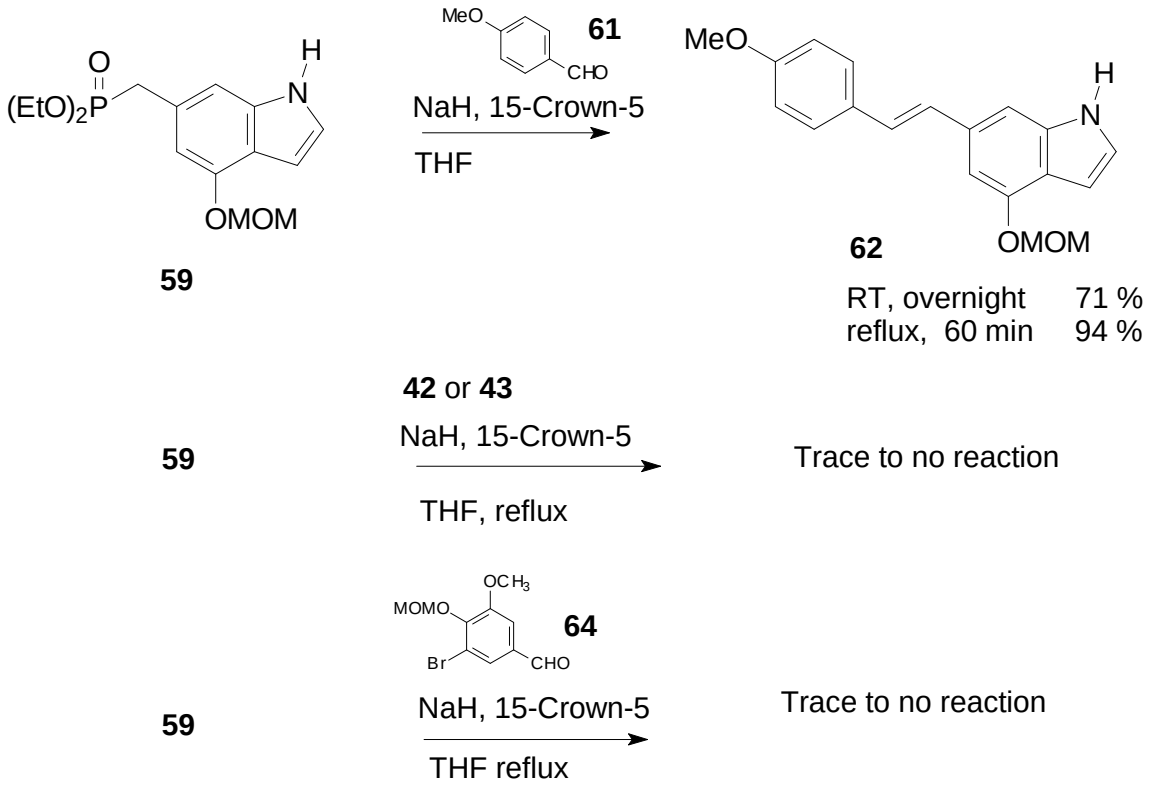


Figure 13. Attempted HWE reactions with **59**

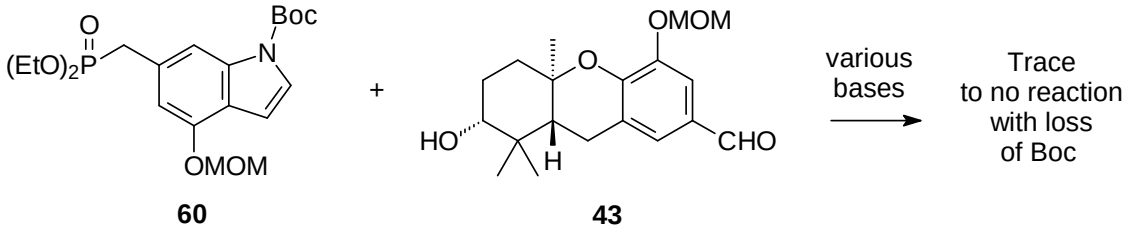


Figure 14. Attempted HWE reactions with **60**

Still another alternative nitrogen protecting group was needed, one that would be more robust during the HWE reaction but still be removable at a later stage. Use of a sulfonyl protecting group now appeared to be the logical choice. After protection of

indole **55** as the tosyl derivative and selective reduction of the carboxylic acid ester using DIBAL–H, alcohol **64** was obtained. Conversion of alcohol **64** to the bromide followed by conversion to the phosphonate **65** also proceeded in a much improved yield (Figure 15) relative to the Boc-protected substrate **60**. In addition, TLC analysis and subsequent NMR analysis did not indicate loss of the tosyl group during the formation of phosphonate **65**. The HWE condensation of **65** with aldehyde **43**, starting at 0 °C and allowing the reaction mixture to warm to room temperature overnight gave a coupled product with the initially assigned structure of **66**.

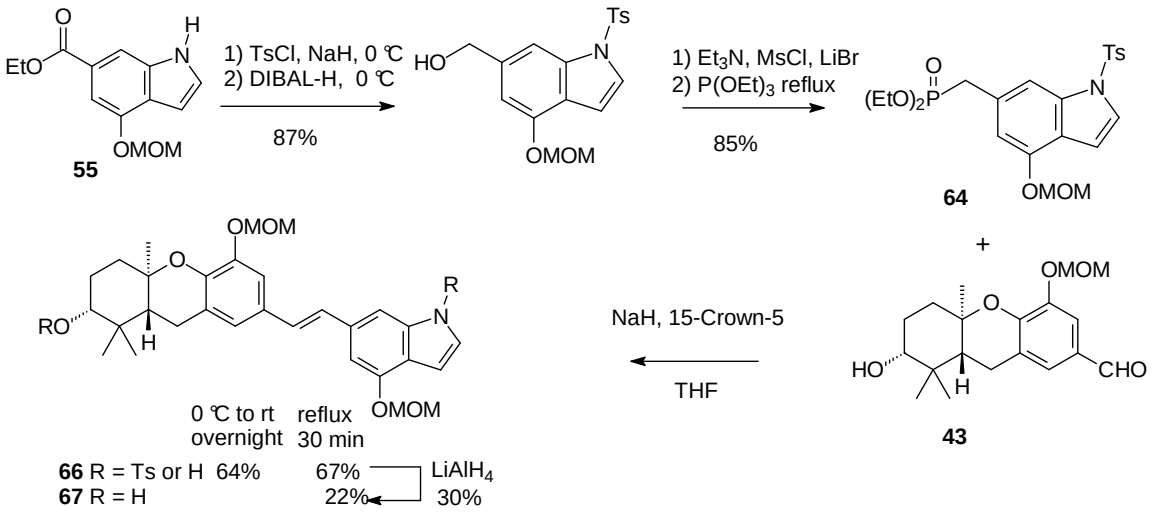


Figure 15. Synthesis using the Ts protected indole

Cursory analysis of the NMR showed that HWE reaction proceeded and the tosyl group was still present. Attempts to improve the yield by heating the HWE reaction increased overall yield with the additional presence of stilbene **67**. The NMR analysis revealed compound **67** to be the coupled product with the *N*–tosyl group lost.

Removal of the tosylate from compound **66** was attempted using a common tosyl removing procedure of Mg in MeOH with NH_4Cl added to accelerate the reaction[73, 74] (Figure 16). The reaction was a success in terms of removal of the tosylate but unexpectedly also reduced the stilbene olefin to afford **68**. Extensive literature research into this result revealed that Mg in MeOH had been reported to reduce stilbene olefins. [75] Therefore, the tosylate removal was attempted through basic hydrolysis[76-78] with bases such as KOH, NaOH, or K_2CO_3 in either MeOH or EtOH. All such attempts were unsuccessful in removing the tosylate. Next use of $LiAH_4$ was explored to remove the tosylate by reduction.[79] This method proved successful but the yield was inconsistent. Lastly removal of the tosylate was attempted by treatment with TBAF[80] but this also was unsuccessful.

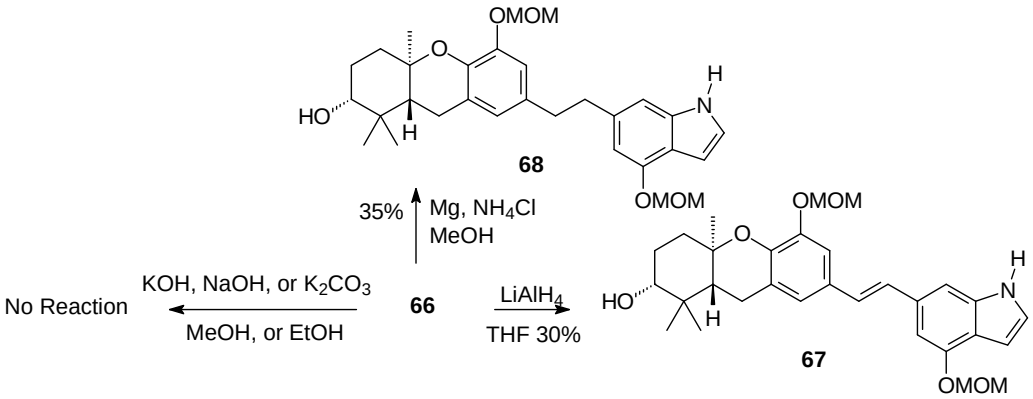
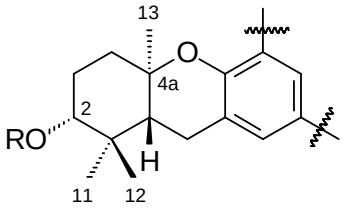


Figure 16. Attempts to remove the tosyl group

With so many problems in the removal of the presumed indole tosylamide, the NMR spectrum of compound **66** was reexamined to determine if the desired compound

had indeed been made. An in-depth comparison of the NMR spectra of compound **66** and **67** revealed some interesting results. First, the shifts for the aromatic signals appeared to be very similar when those attributed to the tosyl group were excluded. Because the tosyl group is strongly withdrawing, it would be expected to affect the shifts of the adjacent signals. In addition an extra signal in the aromatic region was observed. This led to the conclusion that the tosyl group was no longer on the indole nitrogen but was somewhere else on the molecule, and the extra signal could be attributed to the unprotected indole nitrogen. This resonance disappeared when the ^{1}H NMR spectrum was run in CD_3OD which verified the presence of the N–H. Comparison of the assigned shifts of schweinfurthin G to those of compound **66** and **67** leads to the conclusion that the tosylate group is attached to the A-ring oxygen. The best evidence for this may be the downfield shift of the H–2 proton but the C-2 carbon is shifted from 78.8 ppm to 84.6 ppm indicating that it is a derivatized alcohol (Table 3). In addition, one of the methyl group resonances is shifted in the ^{1}H spectrum. Based on this analysis the structure of compound **66** assigned to have the tosyl group on the C–2 oxygen as shown in compound **66A** (Figure 17). This structure also would explain why it was so difficult to remove the tosyl group and why attempts to do so only were successful upon treatment with $LiAlH_4$.[81, 82] Fortunately, treatment of compound **67** with TsOH in MeOH was effective in removing the MOM group to afford the desired analogue **40** (Figure 17).



Peak	SG **15** (CD_3OD) R = H (in ppm)	**66A** ($CDCl_3$) R = Ts (in ppm)	**67** ($CDCl_3$) R = H (in ppm)
H–2	3.30	4.33	3.43
H–11	0.88	0.90[a]	0.89
H–12	1.10	0.91[a]	1.11
H–13	1.23	1.22	1.25
C–2	78.8	88.4	78.0
C-4a	78.2	76.0	76.9

[a] Assignment may be interchanged

Table 3. Comparison of ^{1}H and ^{13}C NMR shifts.

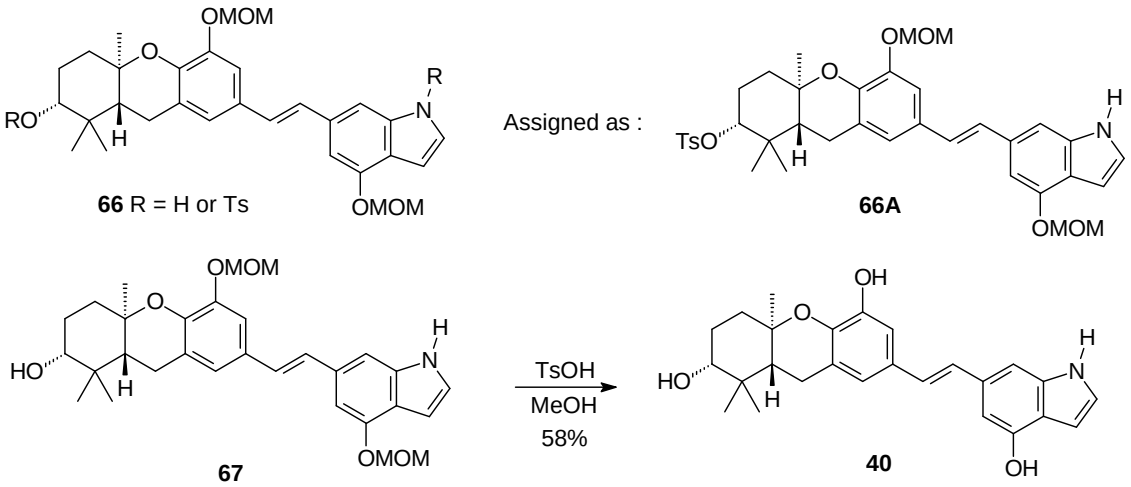


Figure 17. Assignment and removal of the protecting group

With the first indole schweinfurthin analogue in hand, the next logical analogue to prepare would be a Schweinfurthin F analogue through the use of a different aldehyde in the HWE reaction. Coupling of phosphonate **65** with aldehyde **43** under reflux conditions, afforded only the A-ring tosylated product **69** in 56% yield. Removal of the tosyl group again proved difficult and the best yield achieved for compound **70** was just 43% (Figure 18).

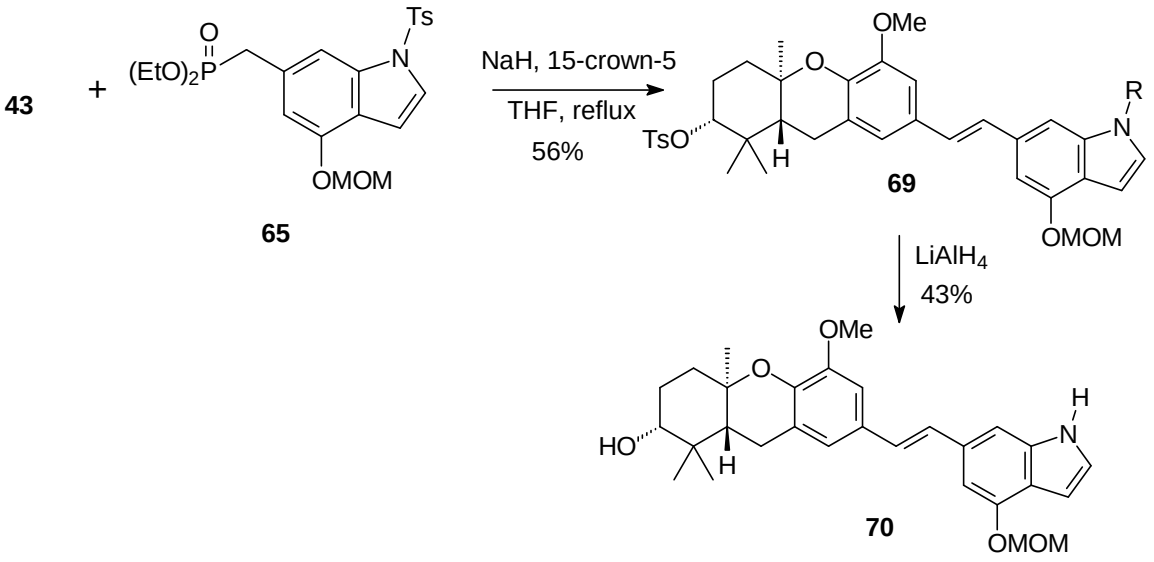


Figure 18. Synthesis of indole analogue **70**

New conditions for the HWE reaction to mitigate transfer of the tosyl group would be very attractive. It was found that maintaining the HWE reaction temperature at 0 °C with regular monitoring, and quenching the reaction when TLC analysis indicated that aldehyde **43** had been consumed, limited the amount of A-ring tosylate formed. Purification yielded two pairs of spots. The pair with the higher R_f value was the A ring

tosylate with some of the indole nitrogen protected and some not, compounds **69** and **71**. A lower pair of spots also was observed in which the A-ring alcohol was unprotected with a mixture of protected and unprotected indole nitrogen, compounds **70** and **72** (Figure 19).

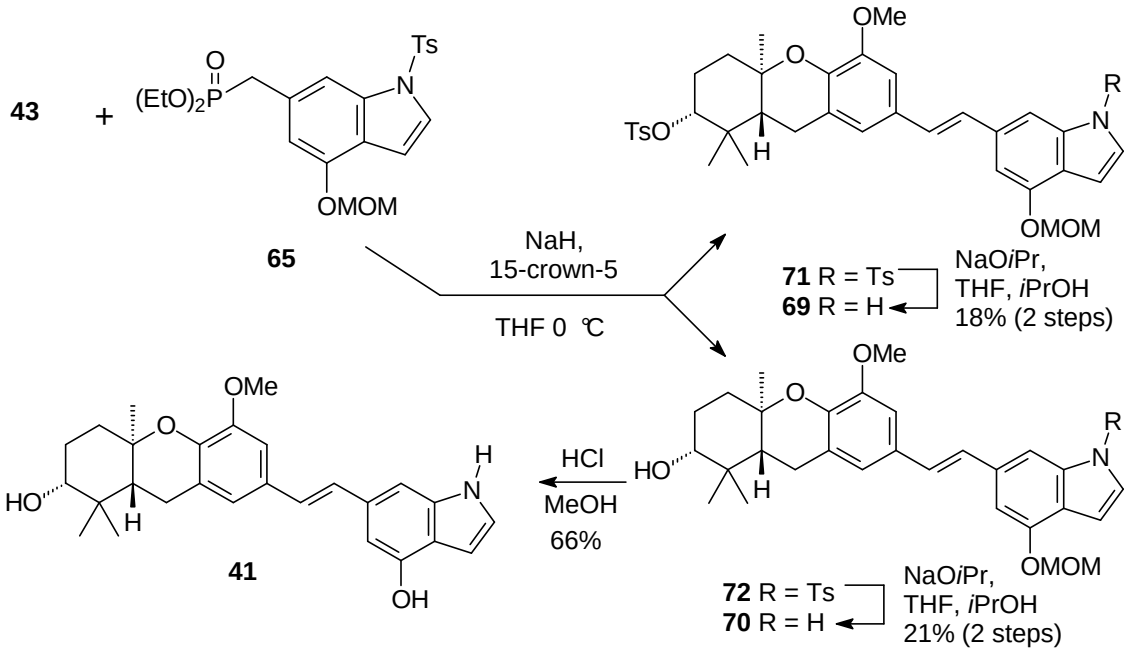


Figure 19. Revised HWE conditions

In order to remove the remaining tosyl protecting group from the indole in analogue **72**, basic hydrolysis was employed. Considering that during the HWE it appeared that excess NaH would deprotonate the alcohol leading to attack at sulfur and displacement of the indole, it was reasoned that a structurally similar base would give the same reaction. When a mixture of compounds **70** and **72** was dissolved in 1:1 THF and *i*-PrOH, and NaH was added to form the base NaO*i*-Pr *in situ*, these conditions allowed

clean removal of the remaining *N*–tosyl group to give alcohol **70**. This base would cleave all the indole tosyl group in a matter of hours at room temperature whereas a more commonly used base such as NaOMe[83] required heating or longer reaction times to accomplish the same results. To secure a proof of concept, the mixture of A-ring tosylate compounds **69** and **71** also was subjected to the same conditions. This experiment also was effective in removing the tosyl group from the indole but it failed to remove the A-ring tosylate, giving compound **69** solely. Removal of the MOM protecting group from stilbene **70** afforded the Schweinfurthin F indole analogue **41**. These new conditions for the HWE coupling and tosyl cleavage should allow a much more consistent coupling and deprotection to form other indole analogues.

With the synthesis of the first analogues accomplished, biological testing was pursued to determine if the new analogues were active. Comparison to the pattern of activity in the 60 cell-line assay versus the natural schweinfurthins would demonstrate if the structural change was desirable, tolerable, or unacceptable, but this assay is time-consuming. To test the new analogues more quickly and to gauge their toxicity, they were tested in a local 2 cell-line assay with SF-295 and A559 cells.[49] The results show (Table 4) that stilbene **40** has a calculated EC_{50} of 0.2 μM and compound **41** has an EC_{50} value of 2.5 μM against SF-295 cells. (The EC_{50} is the value where with 50% of the cell growth is inhibited.) Against A549 cells a non-small cell lung cancer cell line which is generally insensitive to the schweinfurthins, a calculated EC_{50} of 3 μM and >10 μM for compounds **40** and **41** was observed.

Compound	EC_{50} in SF-295 (μM)	EC_{50} in A549 (μM)
40	0.2	3
41	2.5	>10

Table 4. Two cell-line assay results

These two indole analogues also were submitted to the National Cancer Institute (NCI) for screening in their 60 cell-line assay. These assay results are shown in Figure 20 for indole **40** and in Figure 21 for indole **41**.

The 60 cell-line assays gave much more encouraging results than those of the two cell-line assay. Analogue **40** had a GI_{50} of 0.62 μM with a range of 3.37 log units, or a 2340 fold difference between the GI_{50} of the most sensitive and most resistant cell-lines (Figure 20). Analogue **41** has a GI_{50} of 0.69 μM with a range of 2.31 log units or a 204 fold difference between the concentration of the most sensitive and most resistant cell-lines (Figure 21). Some comparisons of the assay results to synthetic schweinfurthin F (SF, **14**) and schweinfurthin G (SG, **15**) are given in Table 5. As shown in this table the new indoles display activity very similar to that of the corresponding schweinfurthins.

Compound	GI_{50} (μM)	Range (log units)	cLogP (calculated)
SF (**14**)	0.41	4.0	6.53
SG (**15**)	0.10	3.15	6.38
40	0.62	3.37	5.05
41	0.69	2.31	5.20

Table 5. Comparison of 60 cell-line assay results

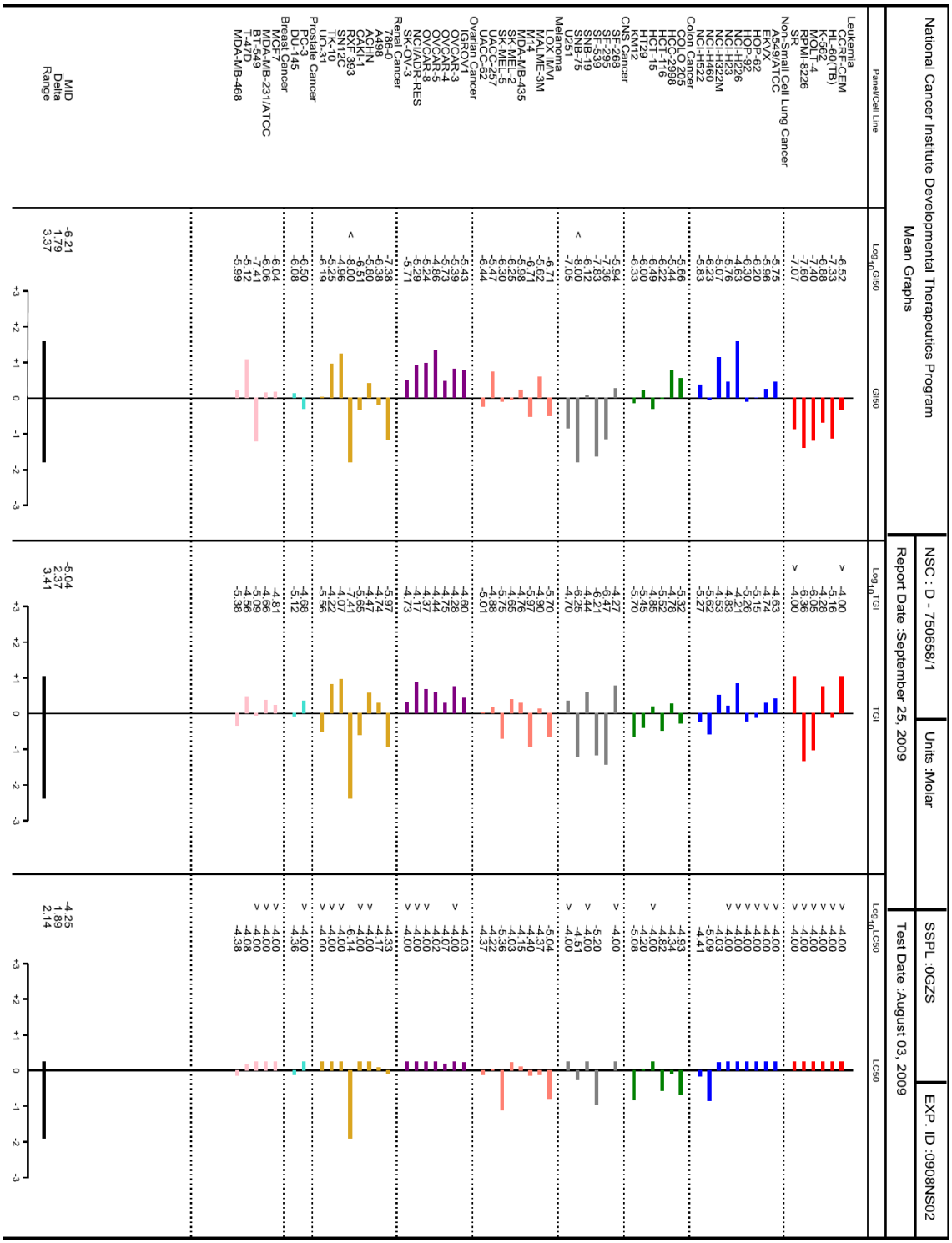


Figure 20. The 60 cell-line assay results for compound **40**

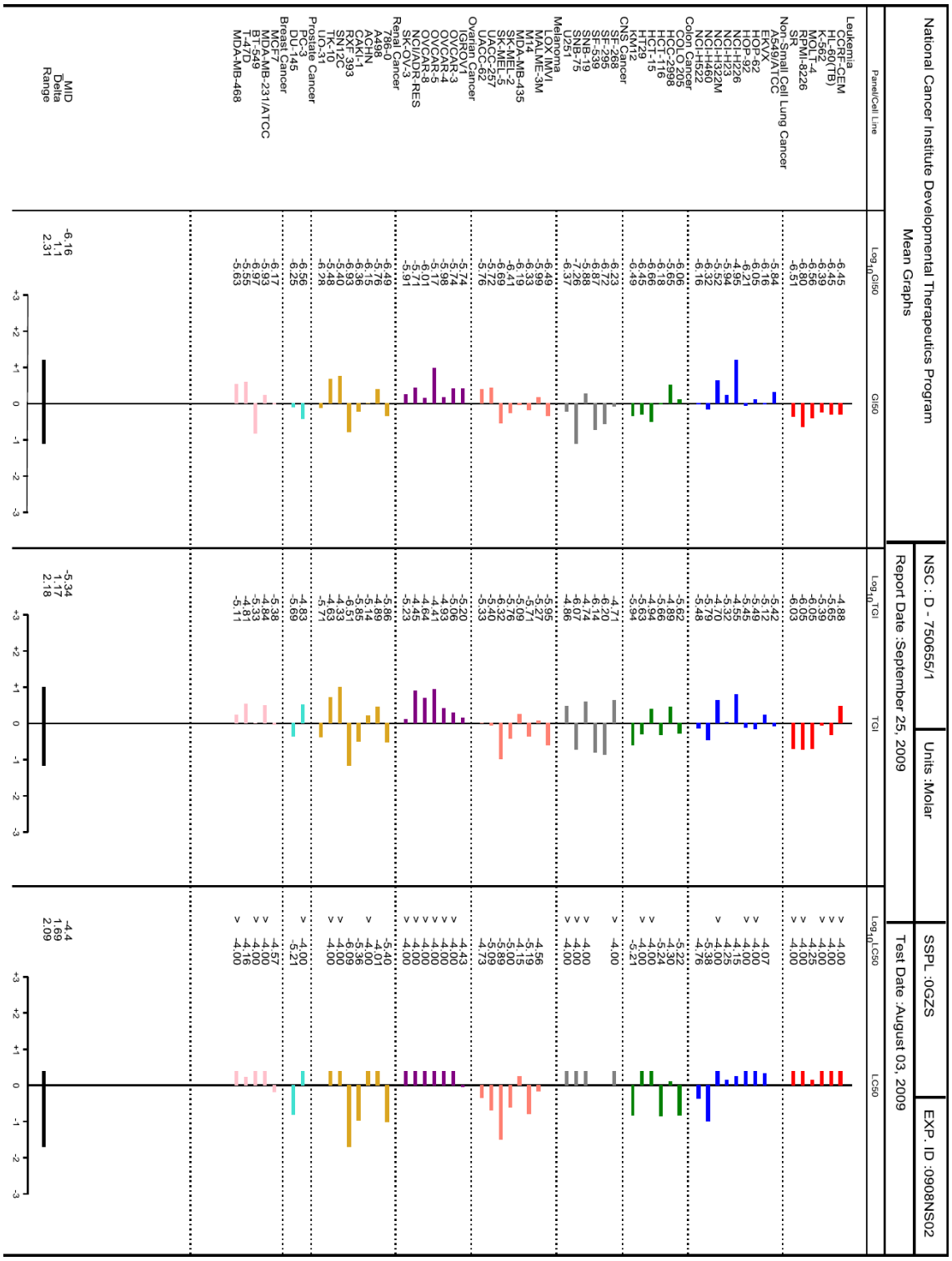


Figure 21. The 60 cell-line assay data for compound **41**

Comparison of the mean GI_{50} data from all the cell lines with a Pearson correlation shows if the new analogues display "schweinfurthin like" activity. The correlations for **14**, **15**, **40**, and **41** are given in Table 6. These Pearson correlations indicate that the new analogues show good correlation to the natural schweinfurthins, confirming that they indeed demonstrate "schweinfurthin-like" behavior. Thus modification of the right-half resorcinol to an indole motif is a well-tolerated change. These results led to the conclusion that attachment of side chains to prepare analogues that more closely resemble the schweinfurthins should be pursued.

	SF (**14**)	SG (**15**)	**40**	**41**
SF (**14**)	1.00			
SG (**15**)	0.42	1.00		
40	0.67	0.83	1.00	
41	0.61	0.70	0.88	1.00

Table 6. Pearson correlations.

CHAPTER 3

PRENYLATED AND GERANYLATED INDOLE. SCHWEINFURTHIN ANALOGUES

With the initial indole schweinfurthin analogues in hand (Chapter 2), the synthesis of indole analogues with an isoprenoid side chain to parallel more closely the biologically active natural schweinfurthins[23, 43, 84] was envisioned. A side chain attached at either the C-2 or C-3 position of the indole core would yield interesting analogues (Figure 22).

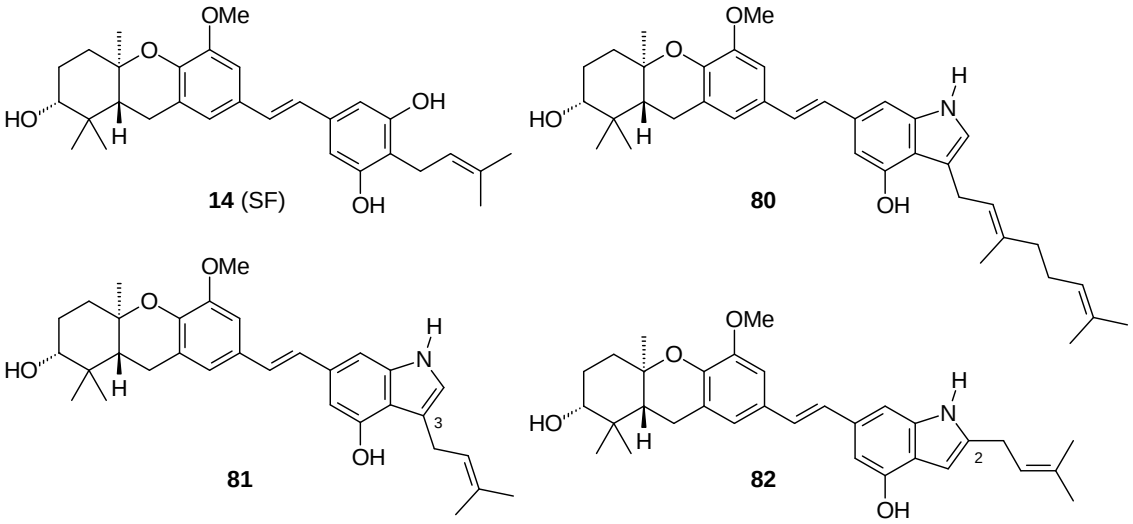


Figure 22. Proposed new indole schweinfurthins

Because of the additional ring of the indole, the isoprenoid chain would be slightly out of alignment relative to the natural products in either case. Attachment at C-3 would render it one carbon out of position while attachment at C-2 would extend the isoprenoid chain a bit further out of the natural position. However past studies indicate

some variations on the nature of the chain are well tolerated,[49] and so it is reasonable to question whether either, or both, alkyl derivatives would enhance the activity of the indole schweinfurthins. To address these questions the initial targets were the C-3 geranyl- and prenyl-substituted analogues **80** and **81**. To determine the influence that the position of the side chain has on activity, the C-2 prenyl analogue **82** also was of interest.

The similarity of prenyl and geranyl groups should allow installation of either group on the indole core by analogous procedures. Installation of either side chain must be both highly regioselective with respect to the indole and not produce a significant amount of an S_N2' bi-product. Due to the prevalence of prenylated indole compounds, several methodologies have been developed for the synthesis of a 3-prenyl indole substructure.[85-94] One of the more attractive methods in terms of both regioselectivity and minimizing S_N2' product, was reported by Ganesan and Zhu in 2002.[94] In an attempt to improve the synthesis of 3-alkylated indoles, these chemists screened a series of metal triflates for their effectiveness at selective prenylation.[94] They found that $Zn(OTf)_2$ gave the highest yield along with a 10:1 ratio of the desired S_N2 product to the S_N2' (or inverse prenyl) product. Changing the base to DIPEA and converting the electrophile to the iodide via an *in situ* Finkelstein reaction with TBAI, increased the selectivity to >70 to 1. These optimized conditions allowed installation of prenyl, geranyl, and farnesyl chains as well as the corresponding terminal epoxides in acceptable yields without any detection of the S_N2' product. The only drawback was that in order to minimize di-subsitution two equivalents of indole were needed for every equivalent of the halide.

The method of Ganesan appeared to be well suited for incorporation of a prenyl or geranyl chain onto the indole substructure of the right-half synthon and should only add one step to the reaction sequence. However due to the increased structural complexity of indole **55** compared to indole itself, the same selectivity was not assured. Fortunately use of the optimized conditions as outlined[94] on indole **55**, allowed synthesis of the geranylated indole **83** in a reasonable yield (62%, Figure 23). The H^1 NMR spectrum of the product indicated the desired C-3 geranylated indole was obtained with no evidence of the S_N2' bi-product. Loss of the ortho coupling in the aromatic region was clear, which indicates that either the C-2 or C-3 analogue had been synthesized. The resonance of the most upfield peak in the aromatic region at 6.96 ppm indicated formation of the C-3 derivative,[89] as opposed to a value of < 6.5 ppm which would be indicative of the C-2 derivative.[95]

Preparation of the tosyl derivative of indole **83** proceeded noticeably slower once the geranyl side chain was present in relationship to the unsubsituted indole. This may be attributed to steric interference of the rather large side chain. As before (Chapter 2), treatment of intermediate ester **84** with DIBAL–H allowed for selective reduction of the carboxylic acid ester to afford alcohol **85**, which was readily converted to the phosphonate **86**. Using the standard conditions for the HWE condensation of phosphonate **86** and aldehyde **42** provided protected schweinfurthin analogues **87** without any evidence in the ^{1}H NMR for loss of the tosyl group that would afford analogue **88**. Unfortunately there was a small amount of the aldehyde **42** remaining.

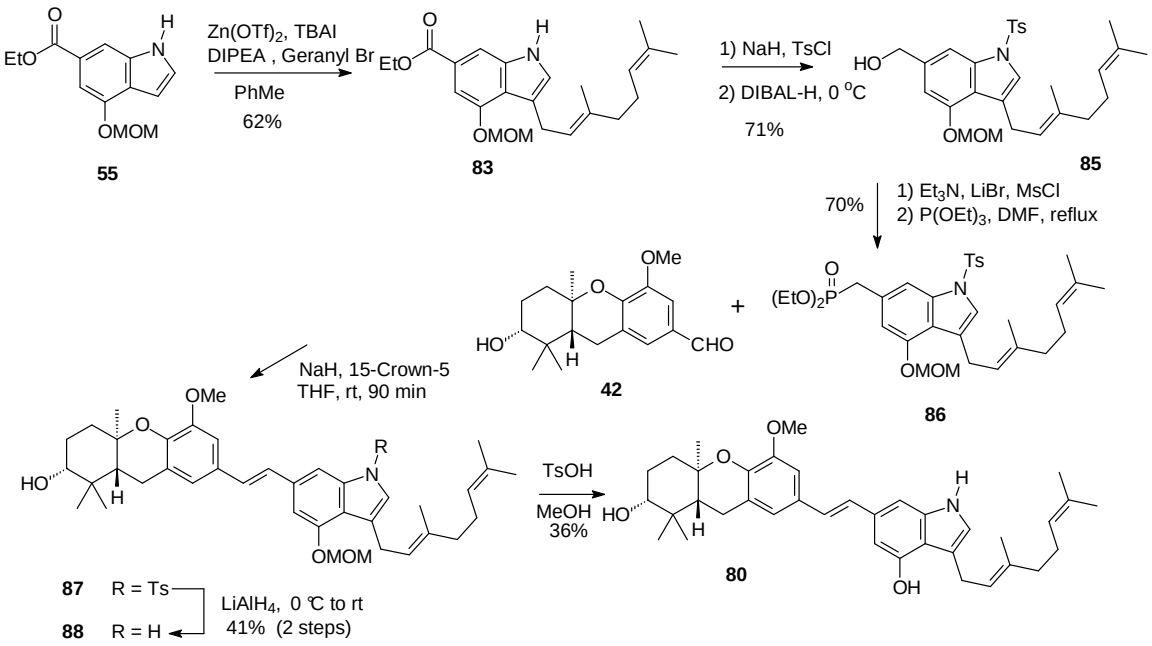


Figure 23. Synthesis of a C-3 geranyl indole-schweinfurthin

Reduction with $LiAlH_4$ was used to remove the tosyl group from the indole nitrogen of compound **87** to afford the desired product **88** in an acceptable 2 step yield (41%). When the reaction was repeated the ^1H NMR spectrum did not indicate any remaining aldehyde **42** but there was a slight amount of free indole product **88** mixed with compound **87** in an approximately 12:1 ratio. When the mixture of compounds **87** and **88** was treated with NaO*i*-Pr in THF and *i*-PrOH the tosyl group from compound **87** was removed to afford compound **88** in a somewhat lower 2 step yield (23%) for the single instance tried. Removal of the MOM protecting group proceeded in modest yield to afford analogue **80**. With the side chain present, MOM hydrolysis appears to be slightly more problematic and side products appeared with longer reaction times. Careful

monitoring of the reaction progress by TLC allowed quenching of the reaction before side-products became dominant.

With the 3-geranyl analogue **80** now available, our focus turned to the preparation of the 3-prenyl analogue. Schweinfurthins E, F, and G and vedalianin, as well as several previously synthesized prenylated analogues, have been shown to possess high potency in the 60 cell-line assay. In many cases, the activity of the prenyl compounds is superior to that of the geranylated counterparts, and thus there was reason to believe a prenylated indole would possess good activity.

During installation of the geranyl chain onto indole **55**, the reaction mixture exhibited a biphasic appearance. This was attributed to its low solubility in the reaction solvent (toluene), although this did not seem to be detrimental to the yield. Addition of CH_2Cl_2 to the solvent system as reported for the prenylation of 5-nitroindole[94] removed the biphasic appearance in the reaction of indole **55** with prenyl bromide and allowed the synthesis of 3-prenyl indole compound **89** in 65% yield (Figure 24). Protection of the indole nitrogen as the tosyl derivative proceeded cleanly. When the reaction was judged complete by TLC analysis, DIBAL–H was added to reduce selectively the carboxylic acid ester and give alcohol **90**. Conversion to phosphonate **91** via the bromide proceeded smoothly, and an HWE reaction with the aldehyde **42** gave (after partial purification of the reaction mixture) the stilbene products **92** and **93**. Removal of the remaining tosyl group from the indole nitrogen of stilbene **92** via basic hydrolysis proceeded smoothly and the penultimate product **93** was isolated in 44% yield for 2 steps. Removal of the MOM protecting group by acidic hydrolysis proceeded in modest yield and gave the desired analogue **81**.

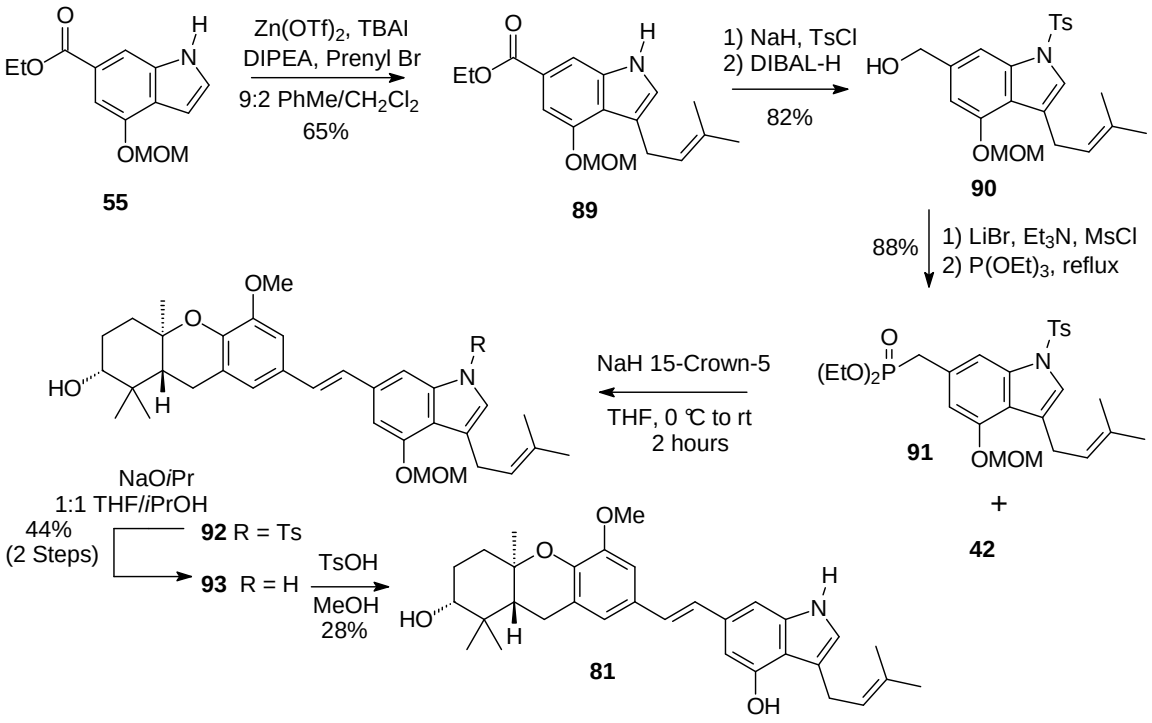


Figure 24. Synthesis of 3-prenyl indole schweinfurthin

To determine if the activity of indole-containing schweinfurthin analogues was influenced by the regiochemistry of the prenyl side chain, the C-2 analogue **82** also was desired. Selective C-2 alkylation of indoles is well established.[95-98] In 1953, Shirley and Koussel treated *N*–methyl indole with *n*-BuLi and exposure of the resulting anion to various alkylating agents showed that substitutions occurred at the C-2 position exclusively.[96] Due to difficultly in removing an alkyl group from the indole nitrogen, subsequent work done by Sundberg and Russell showed that protection of the nitrogen with either the MOM or phenylsulfonyl groups followed by treatment with *t*-BuLi allowed alkylation at the C-2 position of indole in decent yields.[97] Recently *N*–Boc and tosyl protected indoles [95, 98] were shown to provide the 2-substituted products upon

treatment with base and an alkyl bromide. Based on these results the currently favored tosyl protecting group should allow selective C-2 alkylation and afford the 2-prenyl analogue without the need to modify the protecting group strategy.

To pursue this new target, the previously synthesized alcohol **64** was protected as the *tert*-butyldimethysilyl (TBS) ether in almost quantitative yield to give indole **94** (Figure 25). Treatment with *n*–BuLi followed by addition of prenyl bromide afforded 2-prenyl indole **95** in reasonable yield along with some recovered starting material **94**. After treatment with TBAF to remove of the TBS protecting group, alcohol **96** was obtained. Standard conditions were used to prepare the phosphonate **97**. The HWE reaction of phosphonate **97** with aldehyde **42** was monitored by TLC until consumption of the aldehyde was complete. Partial purification of the reaction mixture by flash column chromatography afforded the mixed stilbene products **98** and **99**. Basic hydrolysis of the remaining tosyl group from the indole nitrogen of stilbene **98** was achieved by treatment with NaO*i*-Pr in a mixed THF/*i*-PrOH solution and afforded stilbene **99** as the sole product. A final acidic hydrolysis of the MOM protecting group afforded the desired analogue **82**.

With the desired analogues synthesized, submission for biological screening to determine their potency first was undertaken locally. Screening of the indole analogues was done in a 2 cell-line assay using SF-295 and A549 cancer cell-lines to test the toxicity and selectivity of the schweinfurthin analogues, and to determine if addition of a prenyl or geranyl chain to the indole schweinfurthins improved or diminished activity. The activity against the schweinfurthin-sensitive SF-295 cells should show if the new analogues are potent. The comparison of the activity in SF-295 against A549 cells

should gauge the selectivity of the analogues. A summary of these assay results is shown in Table 7.

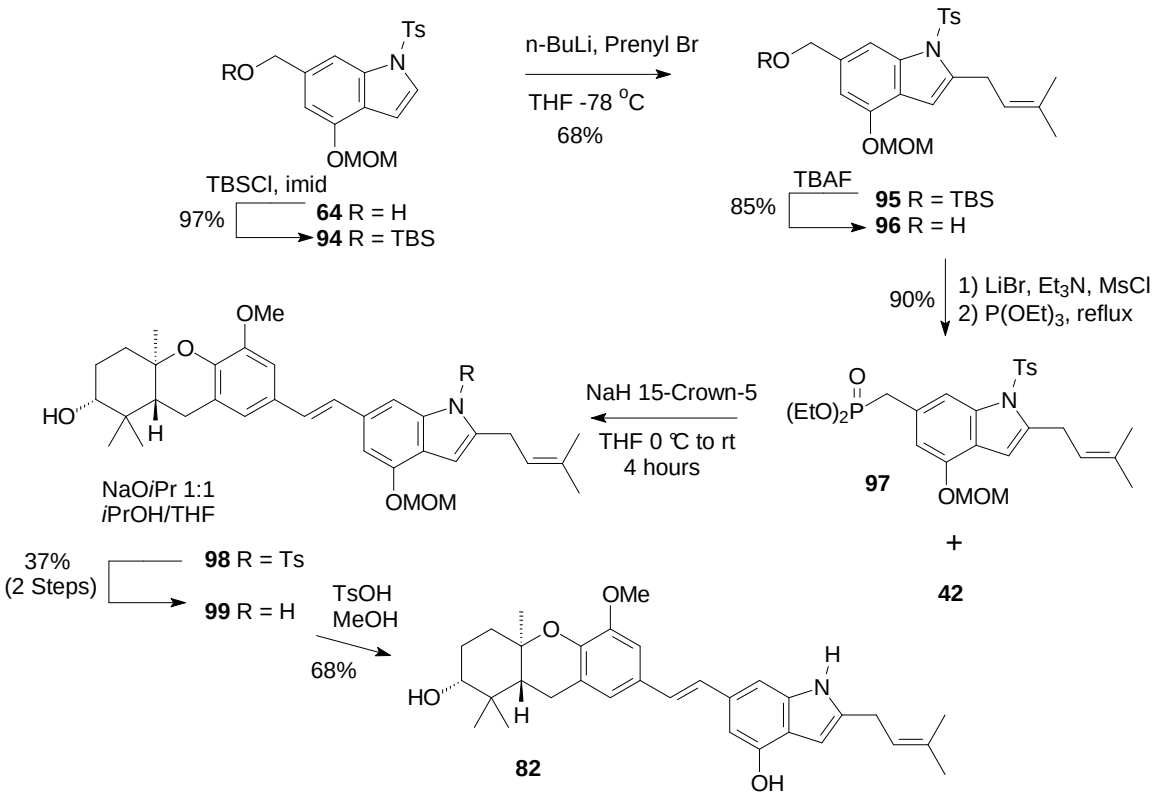
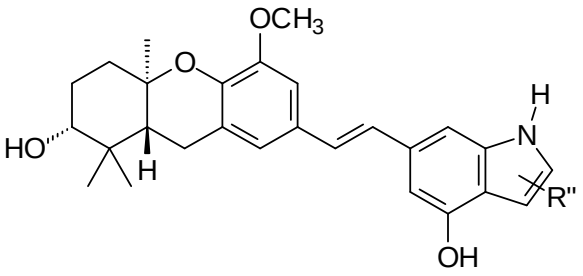


Figure 25. Synthesis of 2-prenyl indole schweinfurthin **82**

Both the 3-geranyl and 3-prenyl analogues **80** and **81** show similar results against SF-295 cells, with EC_{50} values of 0.3 and 0.2 μM respectively. The 2-prenyl analogue **82** shows an almost 10-fold diminished potency as compared to its 3-prenyl counterpart **81**. This suggests that the position of the prenyl chain affects activity in a noticeable manner. Against the schweinfurthin-resistant A549 cells, the analogue **81** showed an EC_{50} of 1.2 μM while compound **82** showed an EC_{50} of greater than 10 μM. This

difference is similar to that seen previously against SF-295 cells. These results suggest that the impact of the prenyl substituent is related to the shape of the analogue, and is not a simple function of the hydrophobicity of the compound.



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Compound	R	SF-295 (μM)	A549 (μM)
80	3-geranyl	0.3	ND
81	3-prenyl	0.2	1.2
82	2-prenyl	2.2	>10

Table 7. Two cell assay results for isoprenylated indole schweinfurthin analogues

The three new analogues also were submitted for screening in the NCI's 60 cell-line assay and the results are shown for analogues **80** (Figure 26), **81** (Figure 27) and **82** (Figure 28). For comparison, the assay results for 3dSB (**24**) and SF (**14**) are provided in the Appendix.

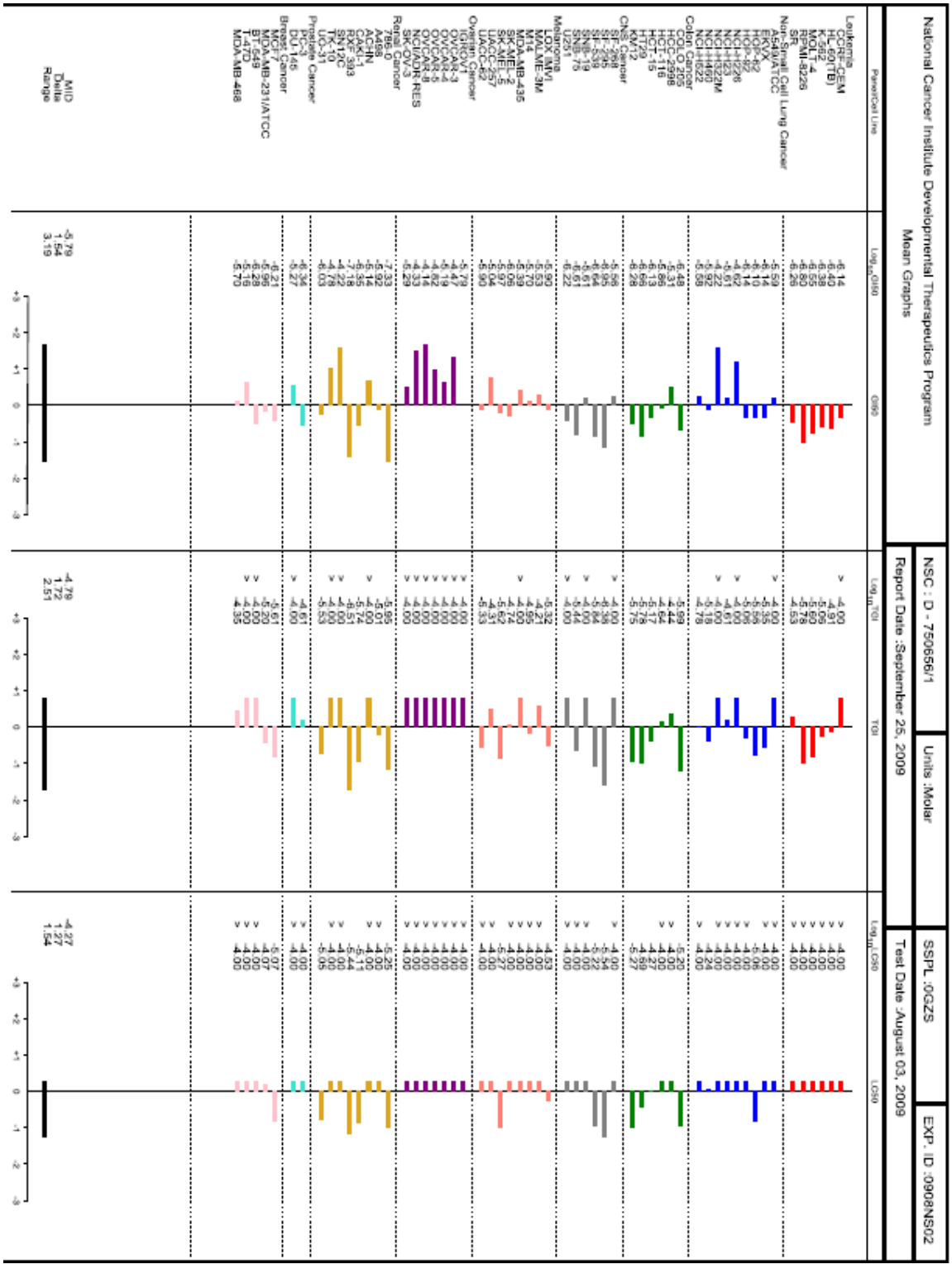


Figure 26. 60 cell-line assay results for analogue **80**

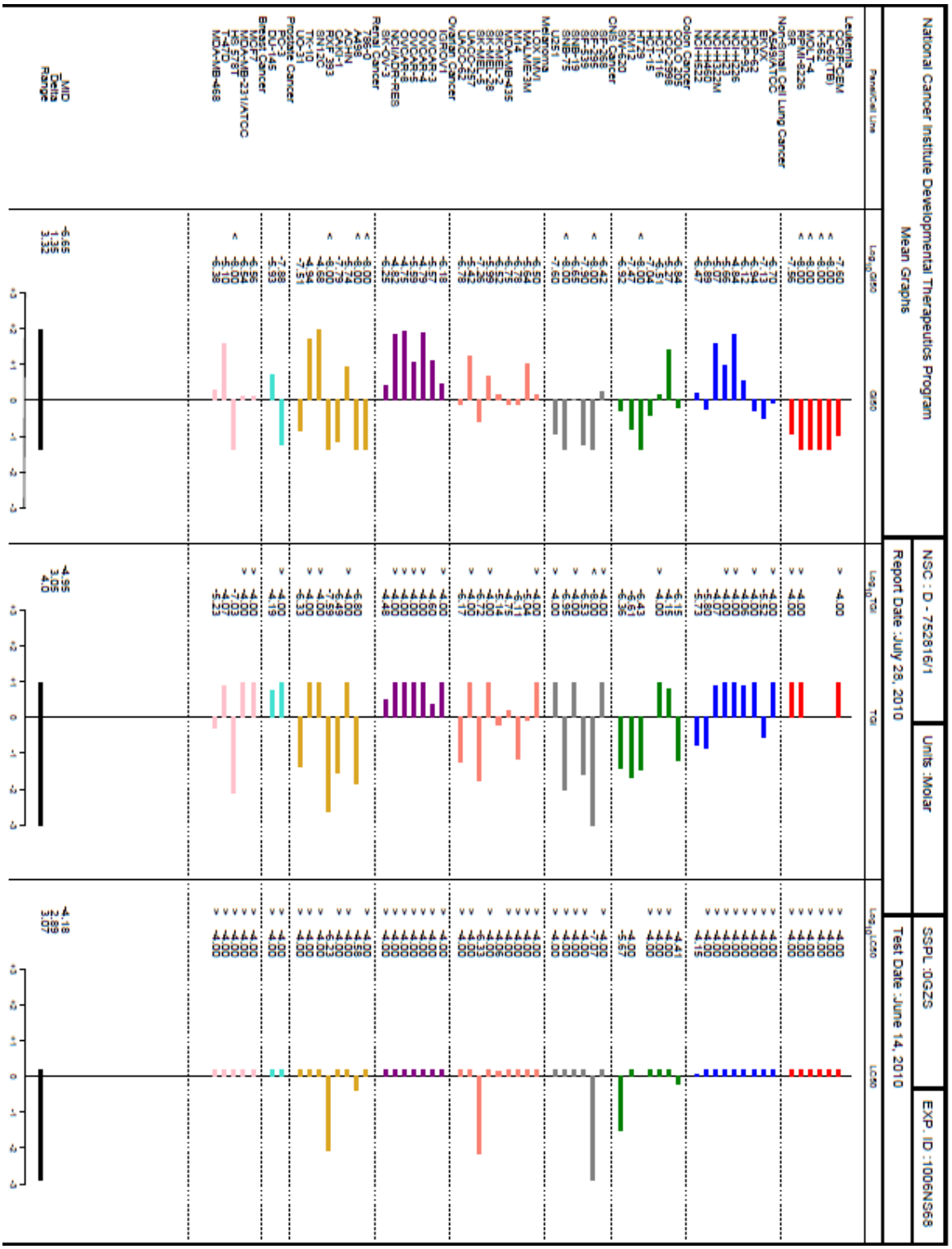


Figure 27. 60 cell-line assay results for analogue **81**

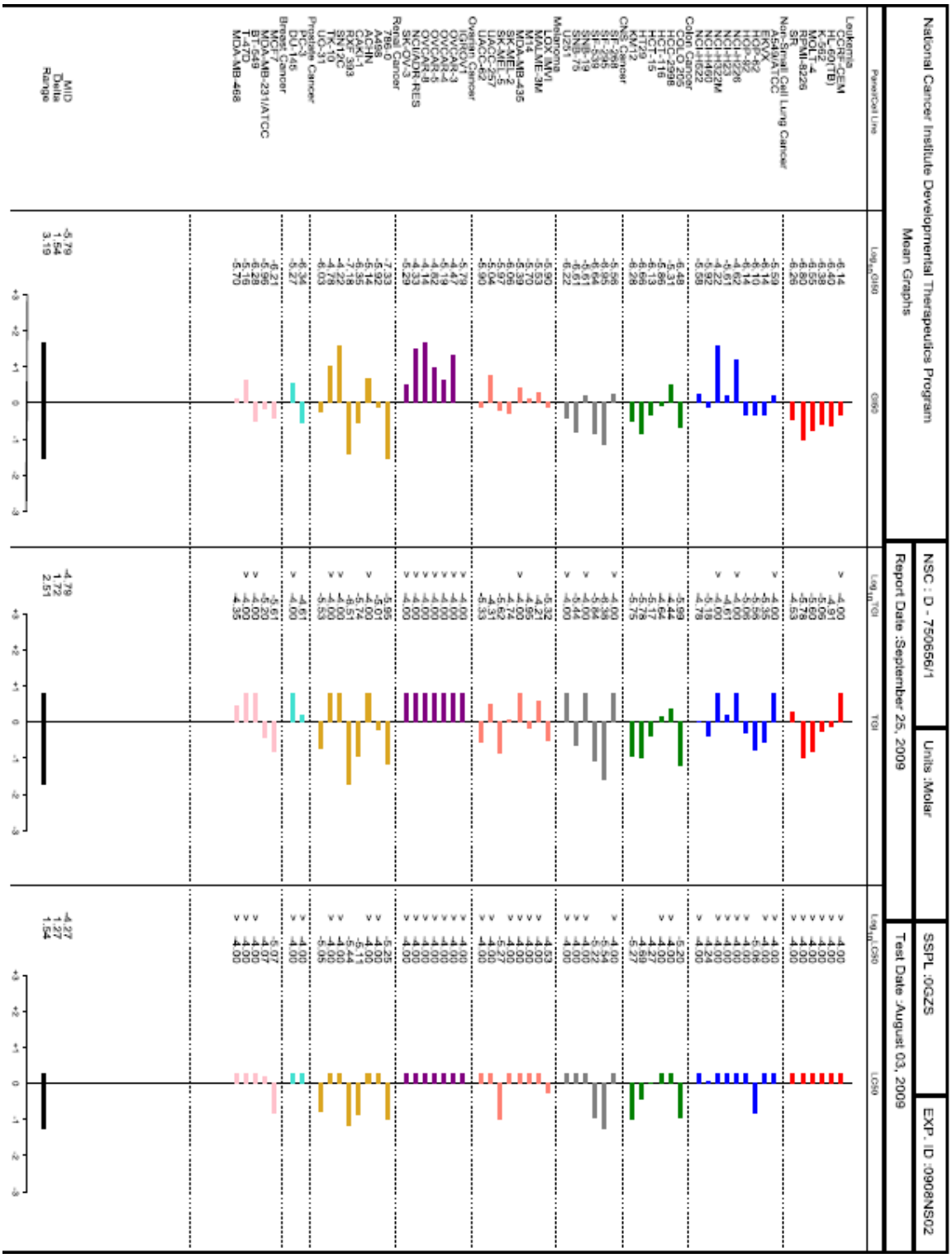


Figure 28. 60 cell-line assay results for analogue **82**

A summary of the 60 cell-line assay results is shown in Table 8. All three analogues display good differential activity with a range > 3 log units, or greater than a 1000-fold difference between the most sensitive and most resistant cell lines. For the 3-geranyl compound (**80**) and the 2-prenyl compound (**82**), the mean GI_{50} values are diminished slightly in comparison to the natural schweinfurthins, with GI_{50} values of 1.63 and 2.40 μM respectively. However the 3-prenyl analogue shows an excellent mean GI_{50} of 0.22 μM in addition to an excellent range. The difference in the mean GI_{50}'s between the 3-prenyl (**81**) and 2-prenyl (**82**) compounds is about 10-fold, which is similar to that seen in the two cell-line assay (Table 7). This offers further indication that the position of the side chain influences potency but does not have a great impact on the differential activity. In comparison to SF and 3dSB, the indole analogue **81** has roughly 2- and 4-fold greater potency, respectively.

Compound	R'	Mean GI_{50} (μM)	Range (log units)	GI_{50} SF-295 (μM)	clogP (Calculated)
80	3-geranyl	1.63	3.19	0.11	8.59
81	3-prenyl	0.22	3.32	<0.01	6.93
82	2-prenyl	2.40	3.38	0.195	6.69
SF (**14**)		0.41	4.0	<0.01	6.53
3dSB (**24**)		0.87	3.25	0.018	8.19

Table 8. Summary of 60 cell-line assay results

Visual analysis of the 60 cell-line assay data indicates a schweinfurthin-like pattern. This is seen in the sensitivity of the CNS, leukemia and several of renal cancer cell lines to the schweinfurthins, and the insensitivity of the ovarian subpanel, a pattern which is typical for the schweinfurthins.[23, 84] Pearson correlations of the GI_{50}'s of the 60 cell lines between the analogues and the structurally similar compounds SF and 3dSB were preformed (Table 9). The data indicates that the analogues display excellent correlation to one another and also to 3dSB. Surprisingly in comparison to SF the correlation is not quite as strong, but it is similar to that between SF and 3dSB.

	80	**81**	**82**	SF (**14**)	3dSB (**24**)
80	1.0				
81	0.90	1.0			
82	0.85	0.81	1.0		
SF (**14**)	0.63	0.56	0.45	1.0	
3dSB (**24**)	0.77	0.74	0.73	0.58	1.0

Table 9. Pearson correlations of isoprenylated indole schweinfurthins.

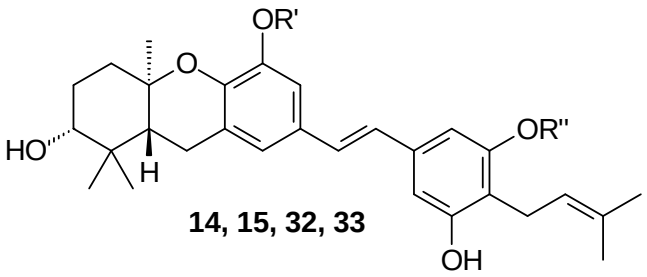
In conclusion the synthesis of the desired isoprenoid substituted indole schweinfurthins has been accomplished. Biological assays show that the analogues display both good selectivity and activity. The mean GI_{50}'s in the 60 cell-line assay were only slightly diminished in comparison to the natural schweinfurthins for analogues **82** and **80**. Analogue **81** shows increased activity in comparison to the structurally similar

natural product SF. With the high potency of analogue **81** it may be desirable to view it as lead compound to synthesize additional and, hopefully, still more potent analogues.

CHAPTER 4

METHYLATION OF INDOLE ANALOGUES AND AFFECTS ON ACTIVITY

Once preparation of the indole schweinfurthin analogues was accomplished (Chapter 2 and 3) it was questioned whether addition of a D-ring methyl group to improve stability would be tolerated. Our group previously prepared several mono-methylated D-ring schweinfurthin analogues in an effort to improve the chemical stability of the schweinfurthins, and tested their relative potency.[43, 99] A summary of the 60 cell-line assay data in comparison to the parent phenols is shown in Table 10. These results indicate that when a single methyl group is attached to the D-ring oxygen the activity is only slightly diminished. An additional benefit is that the methylated compounds would not require deprotection at the respective position to give the desired compound, which might shorten the synthesis and/or improve the overall yield.

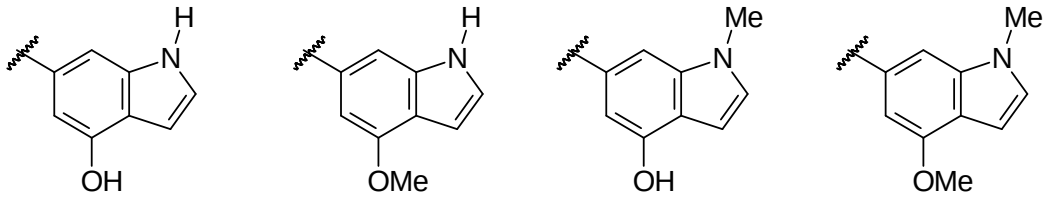


14, 15, 32, 33

Number	R’	R”	Mean GI_{50} (μM)	Range (log units)
SF (**14**)	CH_3	H	0.41	4.00
32	CH_3	CH_3	0.87	3.05
SG (**15**)	H	H	0.10	3.15
33	H	CH_3	0.18	2.70

Table 10. Affects of one additional methyl group on the activity of selected schweinfurthins

Unlike the case with schweinfurthin F and G (SF, **14** and SG, **15**, respectively) in which the D-ring phenols are equivalent by symmetry, the schweinfurthin indoles could be uniquely mono-methylated at either the phenol (**110**) or the indole nitrogen (**111**) (Figure 29). Both compounds appeared to be worthy targets. Furthermore, previous assays on a dimethoxy 3dSB analogue (**24**)[50] indicate that protecting both phenols on the D-ring created an analogue that displayed diminished activity. To determine if this held true for indole analogues the dimethylated indole analogue (**112**) also was targeted.



41 **110** **111** **112**

Figure 29. Protection of the indole functional groups with methyl groups

The synthesis of the methoxy indole **110** commenced with the selective protection of the phenol in the presence of the free nitrogen. Selective protection using K_2CO_3 in DMF at 0 °C with MeI[55] proceeded smoothly for the ethyl ester **46** and gave the desired methoxy indole **113** (Figure 30). Protection of the indole nitrogen with a tosyl group followed by DIBAL–H reduction of the ester gave benzylic alcohol **114** in an 81% yield for these two steps. Conversion to phosphonate **115** through the intermediate bromide proceeded without incident. The HWE coupling of the left-half aldehyde **42** and phosphonate **115** at 0 °C for one hour gave a mixture of four products because some

tosylate formation was observed at the C-2 position under the reaction conditions. Provided the reaction was monitored and quenched when aldehyde **42** was consumed, free A-ring alcohols usually represented the major products and were purified easily to afford a pair of compounds (**116** and **110**), but the indole tosyl compound **116** and the free indole **110** were difficult to separate. In a similar sense, the A-ring tosylate was obtained as a mixture of the indole tosyl compound **117** and the free indole **118**. Without further separation, the major products (**116** and **110**) could be treated with NaH in 2-propanol and THF to give the desired target **110** (39% yield, 2 steps).

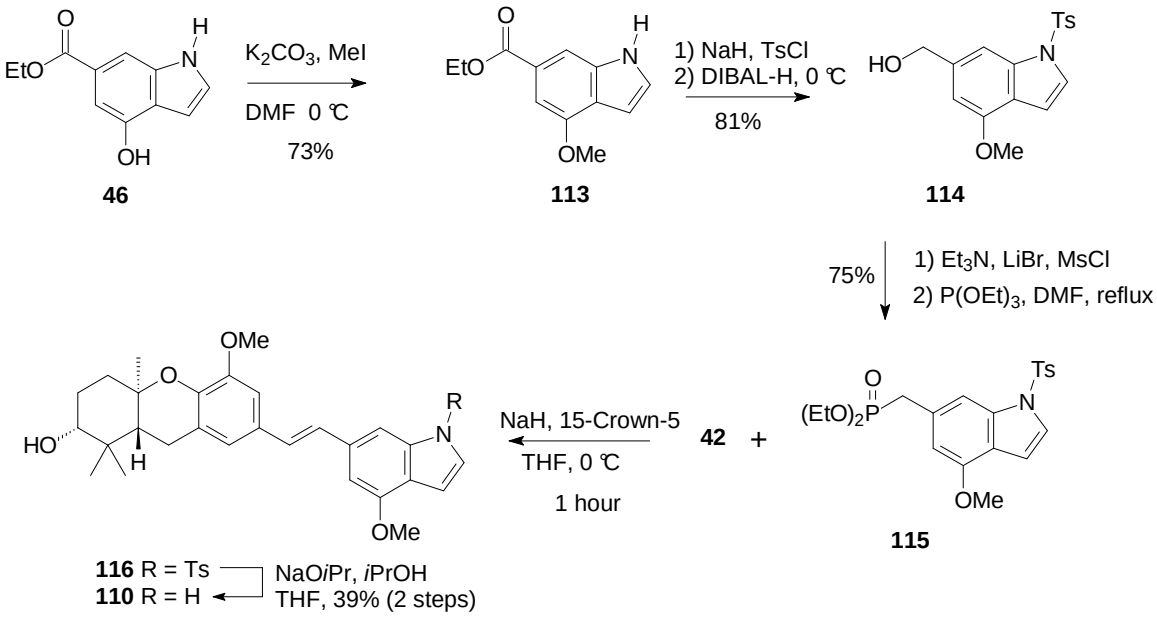


Figure 30. Synthesis of analogue **110**

The next target was the *N*–methyl analogue **111**. Methylation of the indole nitrogen of compound **55** and subsequent reduction of the ester with $LiAlH_4$ gave the benzylic alcohol **119** (Figure 31). Attempted conversion of the alcohol to the

phosphonate **120** was unsuccessful because the intermediate bromide proved to be very unstable. Workup of the bromide and concentration to 1 mL, followed by attempted conversion to the phosphonate gave material that only had a trace of the appropriate resonance in the ^{31}P NMR spectrum of the reaction mixture. The attempt to purify the crude product to afford the desired phosphonate met with no success.

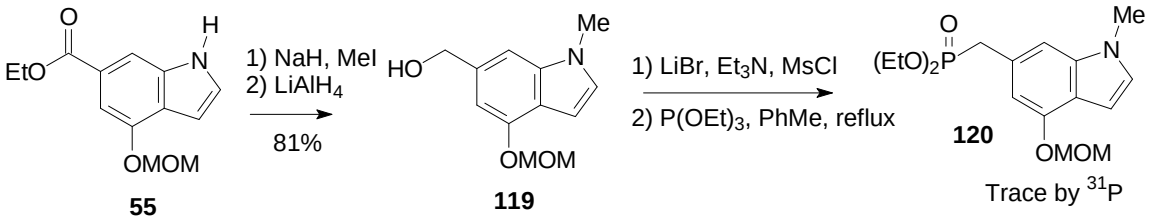


Figure 31. Attempted synthesis of phosphonate **120**

Because introduction of a protecting group compatible with generation of the phosphonate, removing it, and subsequent *N*–methylation, seemed impractical, it was decided revise the synthesis of the *N*–Me analogue by reversing the phosphonate and aldehyde components of the HWE reaction. Fortunately the left-half phosphonates had been prepared and had been used in alternative syntheses of 3dSB (**24**) and 3dSA (**34**).[45] To obtain the complementary reagent for an HWE condensation, MnO_2 oxidation of benzylic alcohol **119** gave aldehyde **121** (Figure 32). The HWE coupling of right-half aldehyde **121** and phosphonate **122**,[45] which was accessed from aldehyde **123** in an improved yield of 69%, was successful and gave stilbene **124**. Hydrolysis of the MOM protecting groups afforded the desired analogue **111** along with some of the partially deprotected A-ring MOM analogue **125**.

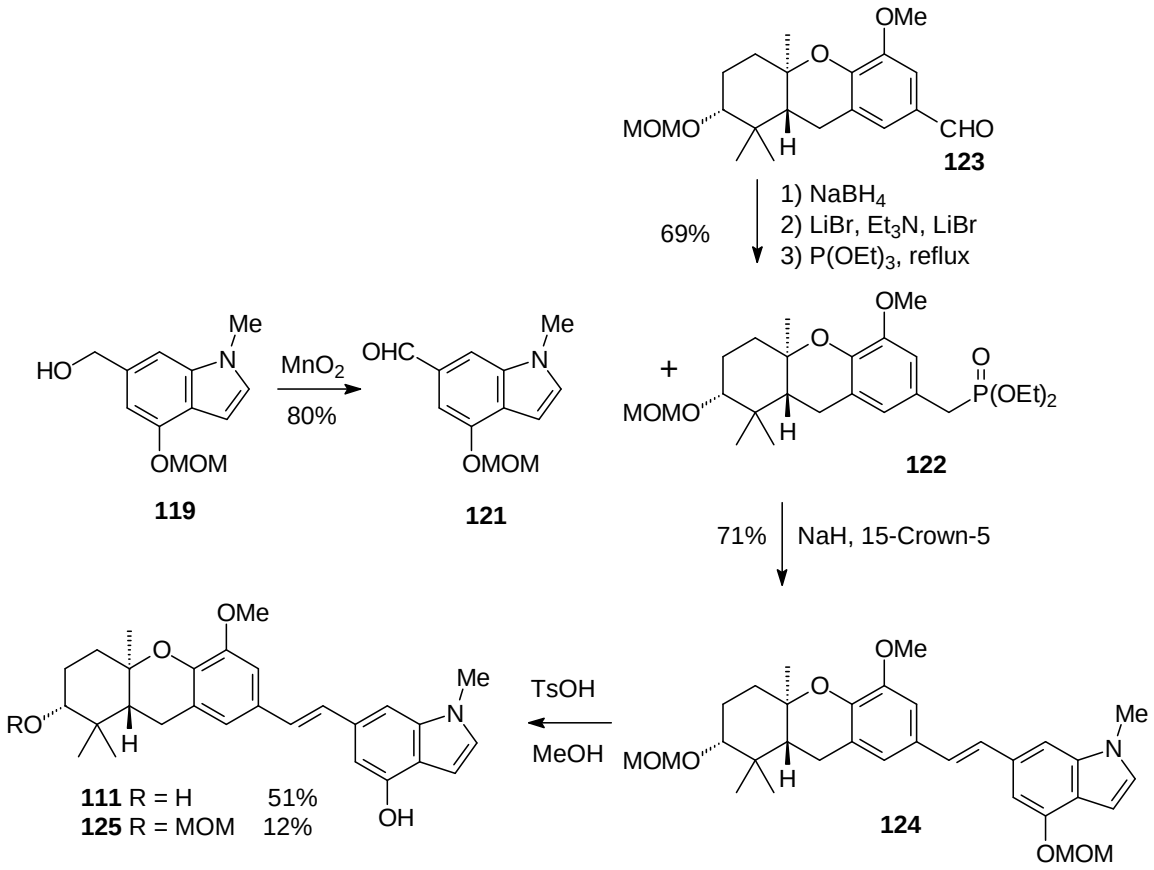


Figure 32. Synthesis of analogue **111**

The next target among the indole schweinfurthin analogues was the dimethylated compound **112**. During the preparation of methoxy indole **113** (Figure 30) a small amount of the di-methylated side product **126** was isolated but that reaction gave a quantity insufficient for further development. In the initial attempt to synthesize compound **126** using THF as the solvent, the reaction did not appear to proceed well, but when DMF was added the reaction quickly went to completion to give the desired product **126** in 66% yield. To favor formation of dimethylated indole **126**, ester **46** was dissolved in a 5:1 THF/DMF solution, NaH was added to deprotonate the indole, and,

after the reaction was allowed to stir for 30 min, MeI was added (Figure 33) and afforded **126** in an 81% yield. Reduction of the ester with $LiAlH_4$ afforded alcohol **127**. As before, the attempt to synthesize the phosphonate was unsuccessful because the bromide proved to be unstable. It turned into a paper-like film when the solvent was removed completely, and the attempt to dissolve this material and obtain phosphonate **128** was unsuccessful.

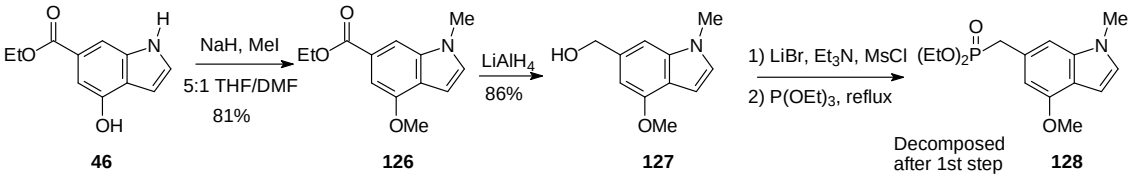


Figure 33. Attempted synthesis of phosphonate **128**

To circumvent these issues, the reversed HWE approach was used. In this case, the necessary aldehyde was prepared by reduction of ester **126** and oxidization with MnO_2 to afford aldehyde **129** (84% yield, 2 steps) without purification of the intermediate alcohol **127** (Figure 34). Because there was a methoxy group rather than a MOM-protected phenol on the right-half aldehyde **129**, hydrolysis of the MOM group from the A-ring alcohol prior to the HWE was attractive. This approach would not increase the total number of steps in the reaction sequence but would conserve the indole intermediates. Deprotection of the A-ring MOM of phosphonate **122** using EtOH as the solvent (to avoid the possibility of trans-esterification of the phosphonate) and TsOH, the reaction went smoothly and afforded the phosphonate **130** in an 85% yield. The HWE coupling between phosphonate **130** and aldehyde **129** was observed in an acceptable

(51%) but un-optimized, yield and gave the desired analogue **112** without the need for subsequent deprotection.

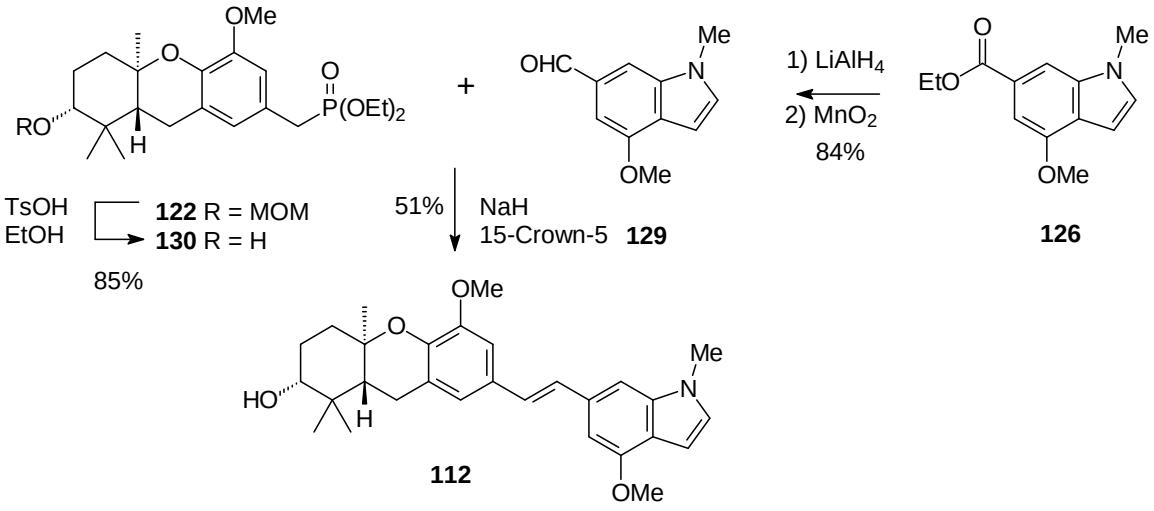


Figure 34. Preparation of analogue **112**

To determine the effect of the methoxy group on the activity of analogues with a side chain present, the syntheses of 3-geranylated and 3-prenylated methoxy indole analogues **131** and **132** also were pursued. The installation of the geranyl chain on indole **113** was pursued through reaction with $Zn(OTf)_2$ and geranyl bromide in a mixed toluene and CH_2Cl_2 solvent system. As in previous C-3 alkylation's, traces of side products were observed but not isolated, and separation of the product (**133**) from the starting material was straightforward. Protection of the indole nitrogen as the sulfonamide went smoothly, with extra time needed until complete protection as judged by TLC compared to the unsubstituted indole. This was consistent with previous protection of the geranylated indole **83** (Chapter 3). Immediately after protection was judged complete by TLC,

DIBAL–H was added to the reaction mixture and the ester was reduced to give benzylic alcohol **134**. This alcohol subsequently was converted to phosphonate **135** through standard methods and in good yields. An HWE coupling with left half aldehyde **42** and phosphonate **135** afforded the tosyl protected indole analogue **136** in modest yield. Like the installation of the tosyl group on the indole, removal of the tosyl group also was slow in the case of compound **136**. This may be reason that compound **136** could be isolated without noticeable formation of the A-ring tosylate. In this case, the ^{1}H NMR spectrum did not indicate any noticeable presence of deprotected nitrogen. Removal of the tosyl went in a reasonable yield upon treatment with sodium isopropoxide to provide the desired analogue **131**.

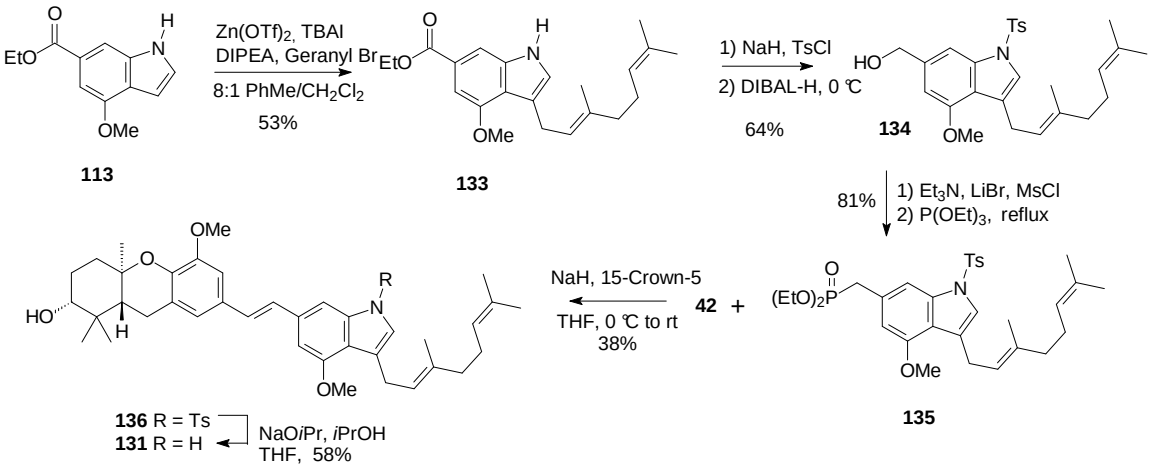


Figure 35. Synthesis of analogue **131**

The 3-prenyl analogue **132** also was of interest because the free phenol **81** (Chapter 3) had shown potent activity. If compound **132** showed activity, it would further demonstrate that the methoxy group is beneficial. The preparation of this

analogue (Figure 36) and is similar to the preparation of the 3-geranyl analogue (Figure 35), and compound **132** was obtained in 7 steps and approximately 14% yield from indole **113**.

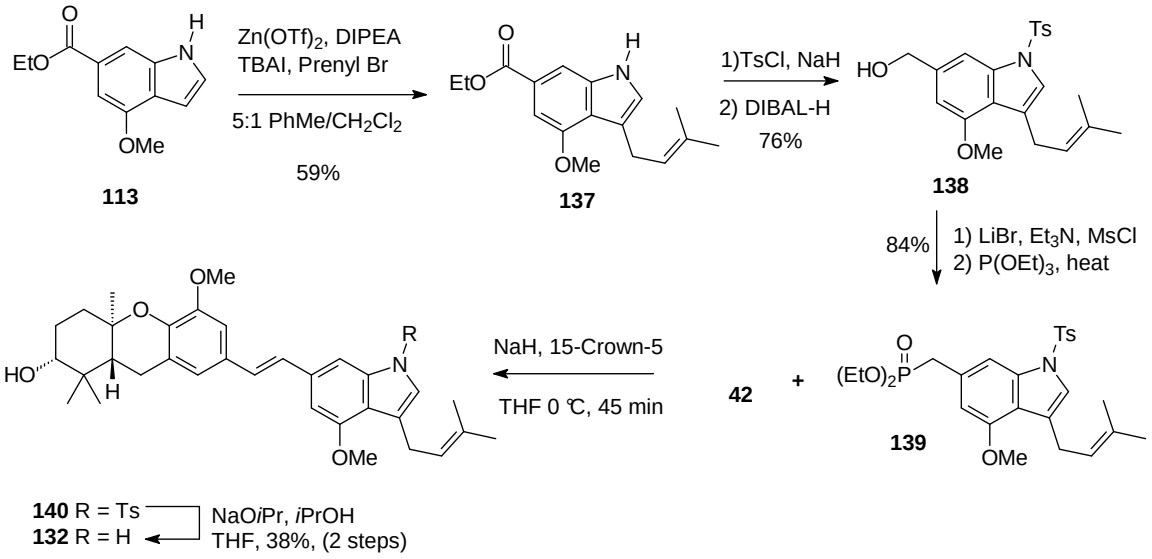


Figure 36. Synthesis of analogue **132**

Comparison of the mean GI_{50}'s of the natural schweinfurthins suggests that having a phenol at the C-5 position instead of a methoxy group leads to increased activity. With these C-5 methoxy analogues synthesized, it was decided to prepare some C-5 phenol analogues to gauge the impact of substituting a phenol for the methoxy group at this position in indole schweinfurthins. Initial assay results against SF-295 showed that compound **112** was the most active of the new methylated compounds (Table 11), and so the C-5 phenol **141** was targeted. This synthesis started with the HWE coupling of left-half phosphonate **142**,[45] here prepared in an improved yield of 90% from alcohol

143, and aldehyde **129** to afford stilbene **145** (Figure 37) in modest yield. Subsequent deprotection by reaction with TsOH in a 1:1 THF/MeOH solution afforded the desired analogue **141** in acceptable yield (60%).

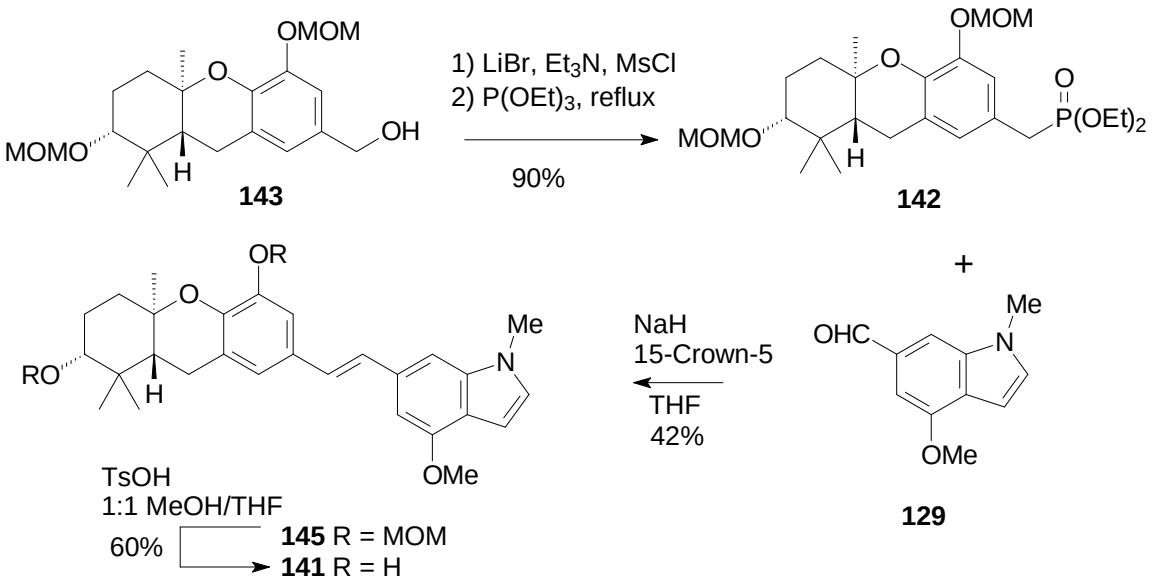


Figure 37. Synthesis of analogue **141**

The phenol analogue **146** (Figure 38) also was targeted because of the activity found in compounds **81** and **132**. To access this target, the phosphonate **139** was coupled with aldehyde **147** under typical HWE conditions to give a mixture tosyl-protected indole **148** and free indole **149**. This aldehyde was chosen with the A-ring MOM group because this would prevent any possible transfer of the tosyl group to the A-ring. After aldehyde **147** was consumed based on TLC analysis, 2-propanol and additional NaH was added to the reaction mixture. This allowed removal of the tosyl protecting group and gave compound **149** in a 51% yield over the two steps without the need for isolation of the

intermediate. Removal of the MOM protecting groups afforded the desired analogue **146** in acceptable yield.

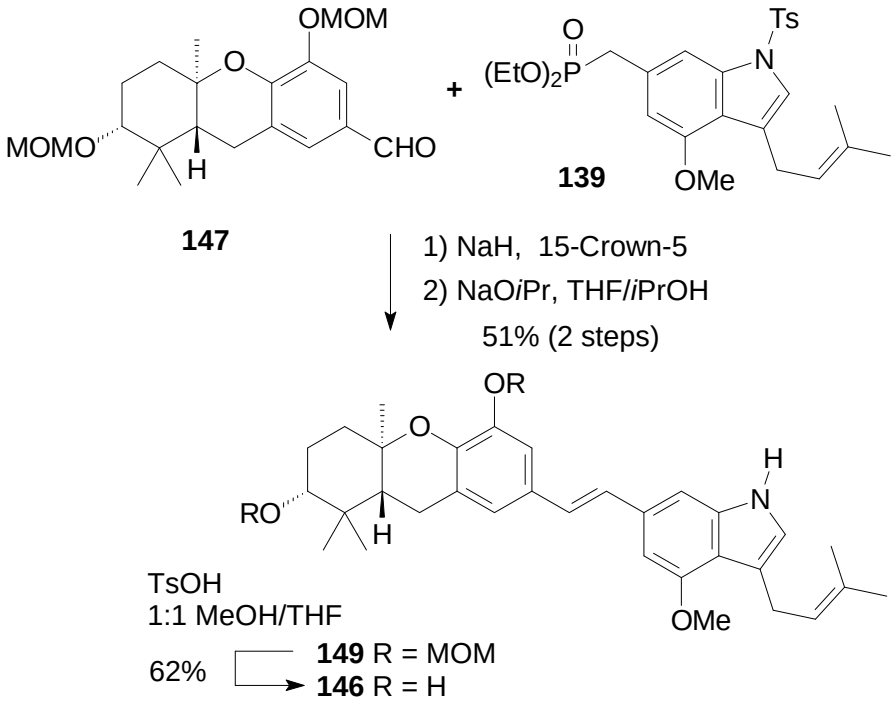


Figure 38. Synthesis of analogue **146**

With this set of 7 new compounds synthesized, they were submitted for the two cell-line assay described in Chapter 2. A summary of the results is shown below (Table 11). Addition of a single methyl group to the compounds gave products that showed improved potency, while there was little difference between the *O*–methyl compound **110** and *N*–methyl analogue **111**. These materials had calculated EC_{50} values for SF-295 cells of 0.6 and 0.5 μM respectively. In the A549 cell-line there was a slightly more noticeable difference of 6.5 versus >10 μM EC_{50}'s respectively. The dimethylated analogue **112**

displayed an EC_{50} value of 0.2 μM against SF-295 indicating that a dimethylated indole had increased potency, which is counter to the previously studied analogues with the dimethylated resorcinol structure. The geranylated analogue **131** did not show promising results, with an EC_{50} value of 1.3 μM. In contrast, the prenylated analogue **132** displayed a calculated EC_{50} of 0.2 μM

The C-5 phenol analogues **141** and **146** both displayed excellent EC_{50} values, in both cases below 0.1 μM. The calculated EC_{50} value for compound **141** was 0.02 μM or 20 nM. As an added bonus, the A549 cell-line showed little sensitivity to **141** and had an EC_{50} value of over 10 μM, representing a differential of at least 500 between these two cell-lines. For the phenol **146** the EC_{50} value also was 0.02 μM in the SF-295 cell line.

Compound	SF-295 EC_{50} (μM)	A549 EC_{50} (μM)
110	0.6	6.5
111	0.5	>10
112	0.2	>10
131	1.9	>10
132	0.2	1.3
141	0.02	>10
146	0.02	0.8

Table 11. 2 cell-line assay results for methylated indole analogues

To test further the potency of the analogues they were submitted to the NCI's 60 cell-line assay. The results of the complete assays are summarized in Table 12. The

assay results for compound **141**, the most active of those tested, are provided in Figure 39. The other 60 cell-line assay results are provided in the appendix.

Compound	GI_{50} (μM)	Range (log units)	SF-295 (μM)	cLog P (calcd)
110	0.38	2.41	0.06	5.35
111	1.12	2.62	0.43	5.42
112	1.12	2.49	0.15	5.57
131	1.07	2.54	0.20	8.37
141	0.24	2.77	<0.01	5.52

Table 12. The 60 cell-line assay data for methylated indole schweinfurthin analogues

The NCI assay results show that the compounds have good activity. Analogue **110** displayed a mean GI_{50} of 0.38 μM and a differential activity of 2.41 log units. This is superior to the previously synthesized (Chapter 2) non-methylated analogue **41**, which had a GI_{50} of 0.69 μM and differential of 2.31. It also showed a GI_{50} of 60 nm in this assay against the specific cell line SF-295. The *N*–methylated indole analogue **111** showed a slightly decreased activity with an average GI_{50} of 1.1 μM and a very similar differential activity of 2.62 log units. The dimethylated indole **112** also displayed a mean GI_{50} of 1.1 μM with a comparable differential activity. Against SF-295 cells, compound **112** had a GI_{50} of 0.15 μM and analogue **111** had a GI_{50} of 0.43 μM. This data indicates that the compounds that performed the best in the 2 cell-line assay did not necessarily correspond to the best compounds in the full 60 cell-line assay. The data also shows that there is a difference between the methoxy analogues and the *N*–methyl analogues. Once

the indole nitrogen is protected there seemed to be little difference between the protected and unprotected indole phenol.

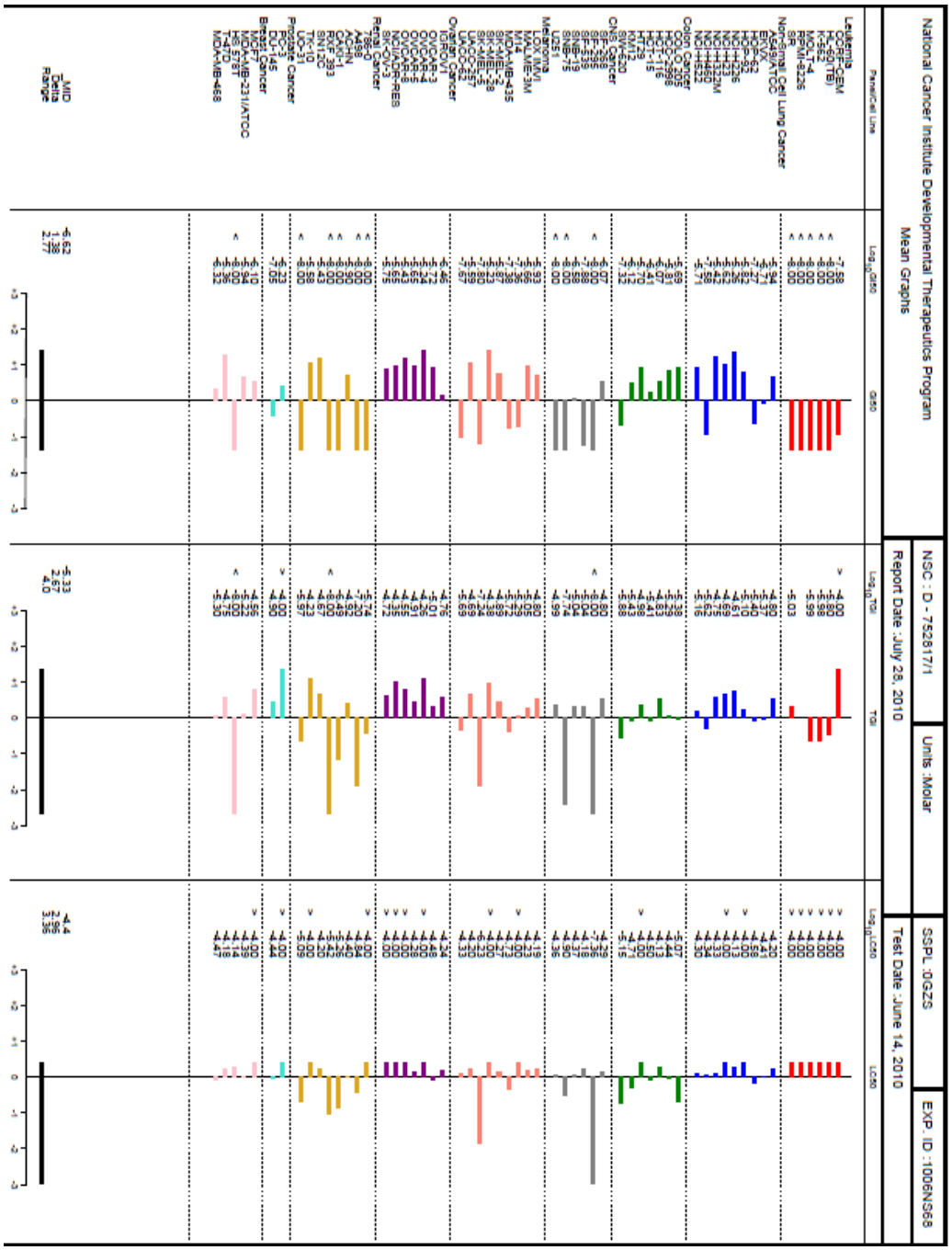


Figure 39. 60 cell-line assay results for **141**

Analogue **131**, with the attached geranyl chain, shows a mean GI_{50} of 1.07 μM in the 60 cell-line assay, which is slightly lower in comparison to the non-geranylated indole analogue but with comparable differential activity. When it is compared to the geranyl phenol analogue **80** (Chapter 3), compound **131** displayed a lower GI_{50} of 1.07 versus 1.63 μM, but with only a slightly diminished range (2.54 versus 3.19 log units). Interestingly, in both cases the methoxy analogue shows a better mean GI_{50} than the phenol counterpart, unlike the mono-methoxy analogues for SF and SG (Table 10).

The C-5 phenol analogue **141** displayed an excellent mean GI_{50} of 0.24 μM, with a range at least 2.7, because in several of the cell lines the GI_{50} was below the lowest concentration tested (10 nM). In this series changing from the 5-methoxy to the 5-phenol analogue (**141**) does indeed afford compounds that are more potent, and this is consistent with the assay results seen with the natural schweinfurthins.

To determine if the new analogues were behaving like the early indole schweinfurthins, a Pearson correlation of these indoles was conducted (Table 13). This analysis should reveal if the methyl groups affect the pattern of activity in comparison to the early indoles and other previously synthesized schweinfurthin analogues.

The correlations of the geranylated analogue **80**, the methoxy geranylated analogue **131**, and 3dSB to the unsubstituted indole counterparts **41** and **110** are all good, indicating that the addition of the methyl groups does not affect the pattern of activity when a geranyl side chain is present (Table 14).

To summarize, these studies have shown that protection of the indole phenol with a methyl group gives analogues that are more stable, easier to make, and have better activity while still showing the schweinfurthin-like pattern of anti-proliferative activity.

	40	**41**	**110**	**111**	**112**	**141**
40	1					
41	0.88	1				
110	0.84	0.76	1			
111	0.85	0.78	0.81	1		
112	0.82	0.67	0.85	0.85	1	
141	0.81	0.64	0.73	0.65	0.79	1.0

Table 13. Pearson correlation of methyl groups on indole analogues

	3dSB (**24**)	**41**	**80**	**110**	**131**
3dSB (**24**)	1.0				
41	0.63	1			
80	0.77	0.77	1		
110	0.70	0.76	0.86	1	
131	0.71	0.76	0.87	0.90	1

Table 14. Pearson correlations of methylated indole analogues to previous analogues

While the addition of a methyl group to the phenol of the indole improves the activity of the compounds, addition of a methyl to the nitrogen of the indole leads to a decrease in the activity. The compounds that have a phenol at the C-5 position show increased activity vis-à-vis the corresponding methyl ether. Analogues with a

methyoxyindole and a C-ring phenol might benefit from both modifications and have even more impressive activity, but this will require further study.

CHAPTER 5

D-RING SCHWEINFURTHIN ANALOGUES

During our group's previous studies of the schweinfurthins, several analogues and natural products were prepared in an effort to elucidate the pharmocophore(s) responsible for their differential activity.[42, 43, 45, 50] This prompted an investigation into the role of the D-ring substituent on the activity of the schweinfurthins, as well as the role that the electronics of the stilbene moiety had on the biological activity.

One strategy envisioned to modify the schweinfurthins was the addition of an E-ring to form a benzofuran (**160**) or dihydrobenzofuran (**161**) substructure (Figure 40). These modifications might improve the chemical stability of the resorcinol while preserving most of its features. A second unexplored area for modification was the stilbene olefin. Reduction of the stilbene would allow synthesis of the Schweinfurthin F analogues **162** and **163**. To gauge the influence of olefin reduction on activity, analogue **164** also was prepared because it differs from the known analogue **165**[50] only by loss of the stilbene olefin. Some dimethylated schweinfurthin F analogue (**166** and **167**) also were targeted to test the activity of dimethylated prenyl analogues. Still other analogues to test the effects of the hydrophobic properties of the D-ring tail were prepared by Natalie Ulrich, and an analogue to test the impact of a cis-stilbene was synthesized by Nolan Mente. These syntheses have been reported elsewhere (Figure 41).[49]

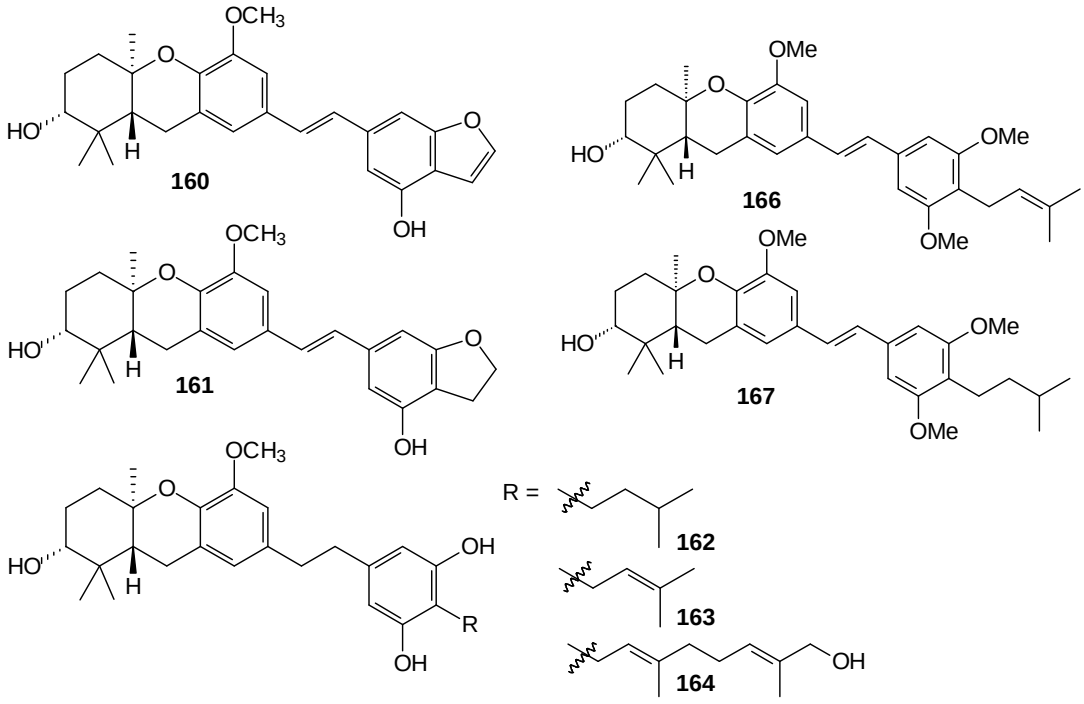


Figure 40. Targeted schweinfurthin F analogues

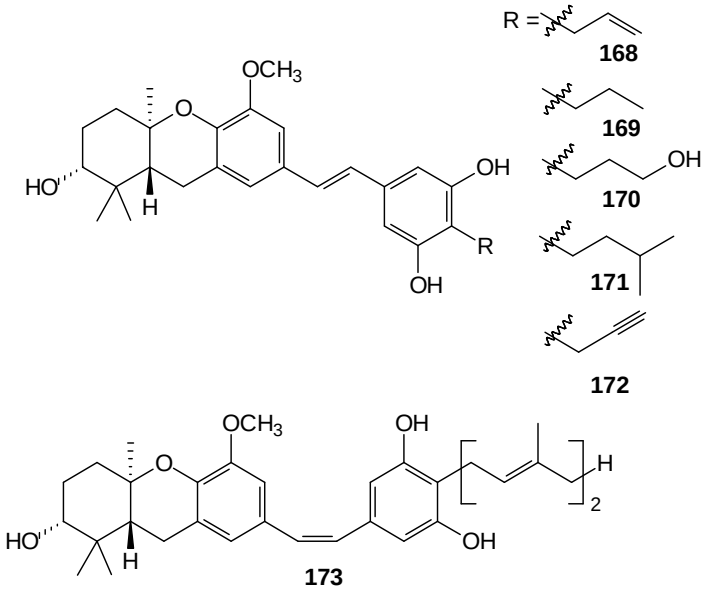


Figure 41. Known schweinfurthin analogues[49]

The synthesis of the benzofuran analogue **160** could be approached from the known benzofuran **175**. Unfortunately, in our hands synthesis by shortest described route[100] only gave the product in 1.3% yield (Figure 42). Further inspection of the published experimental information suggested that the reported yield (30% for the same 3 steps) was suspect.

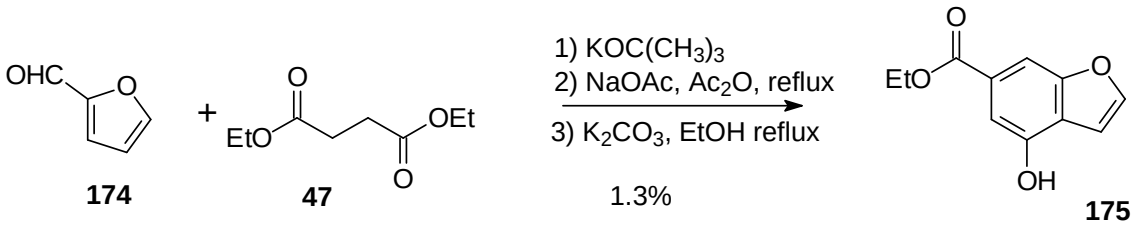


Figure 42. Preparation of benzofuran **175**[100]

To overcome this disappointing yield, an alternate method to access the benzofuran core was sought. Instead of forming the acid **180** by a Stobbe condensation, an alternative method for preparation of the benzofuran was explored. [101] One previously employed strategy involves an HWE reaction between phosphonate **178**,[102] itself prepared by condensation of commercially available phosphonate **176** and bromide **177**, and aldehyde **174** to give the mixed ester **179**. The condensation was followed by selective removal of the *tert-b*utyl group using trifluoroacetic acid to obtain acid **180** (Figure 43). Cyclization under the same conditions as before[100] gave acetate **181** smoothly, and removal of the acetate afforded phenol **175** in a much better overall yield (60%).

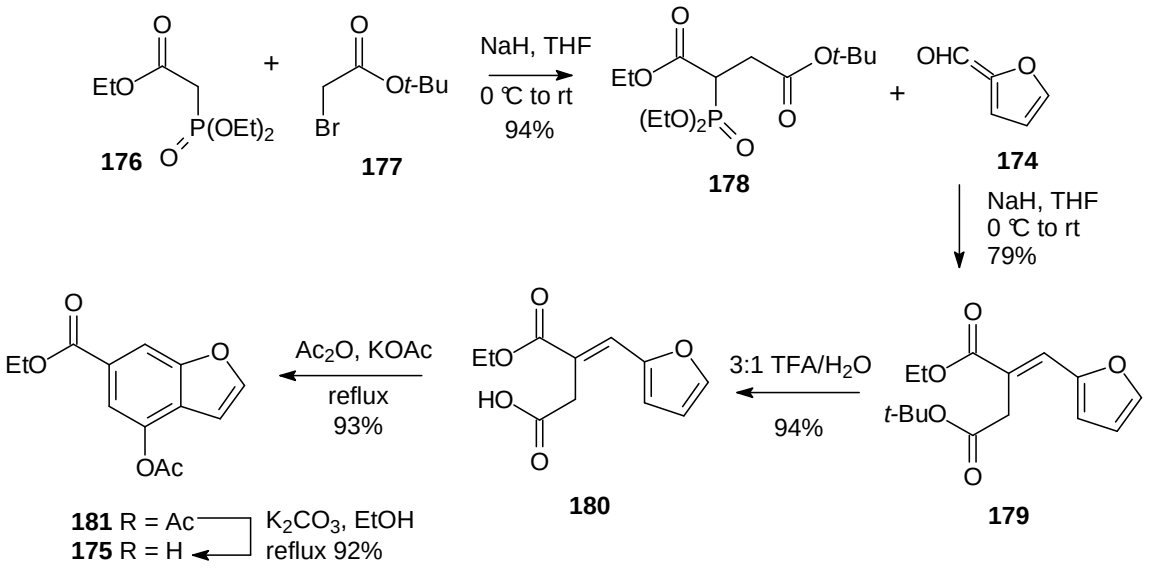


Figure 43. Alternate route to benzofuran **175**

As noted above, the synthesis of the phosphonate mixed ester **178** had been reported via a carbon-carbon bond formation reaction. Alternatively it might be prepared via a carbon-phosphorus bond formation reaction.[103] To prepare the same phosphonate would require the mixed ester, ethyl, *t*-butyl succinate which is apparently not known. However the very similar methyl, *t*-butyl succinate ester **182** is commercially available, and was used to study this strategy.

Treatment of ester **182** with freshly prepared LDA generated the ester anion which can be quenched by addition of $ClP(OEt)_2$ and oxidized to afford the phosphonate(s) (Figure 44). After purification, the NMR data revealed that there were two regioisomeric phosphonates that could be assigned the structures **183** and **184** in a 10.5:1 ratio (Table 15, entry 1), but separation of these isomers proved elusive. Based on the similarity of the spectroscopic data to that of the ethyl analogue,[102] the major product

tentatively was assigned as phosphonate **183**. To confirm this assignment, an authentic sample of phosphonate **183** was prepared via a carbon-carbon bond formation reaction starting with phosphonate **185** and bromide **177**. Material prepared in this way matched the spectra of dominant product from the phosphorylation sequence.

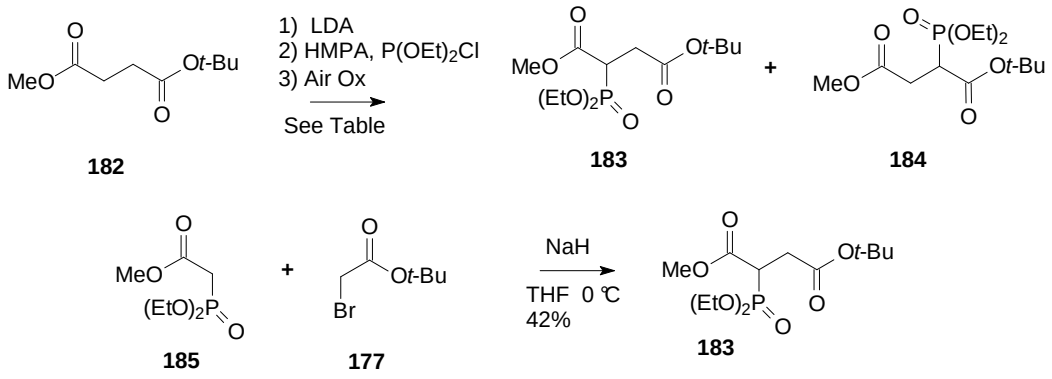


Figure 44. Synthesis of mixed ester phosphonates

Entry	Conditions	**183**:**184** Product ratio by ^{31}P NMR	Yield
1	–78 °C, 80 min	10.5:1	27%
2	–78 °C, 30 min	8.8:1	28%
3	–78 °C, 90 min	7.9:1	ND
4	–78 °C, 20 min, warm 40 min then –78 °C, 20 min	>100:1	ND

Table 15. Regioselective Phosphorylation

To determine if the product ratio could be altered, the length of time that the anion was allowed to form before quenching with $ClP(OEt)_2$ was varied, but this did not significantly alter the product ratio (entry 2 and 3). However, if after formation of the anion, the reaction temperature was allowed to increase by removing the reaction flask from the dry ice–acetone bath for 40 min and then cooled again to –78 °C before addition of the phosphite, a product ratio of over 100:1 was obtained (entry 4). This suggests that the anion distribution is affected by the reaction temperature, with equilibration favoring formation of the enolate leading to phosphonate **183**. Unfortunately the yields obtained via C-P bond formation did not approach that of the alternate route based on carbon-carbon bond formation, so this strategy was not pursued further.

With ester **175** in hand, conversion to the benzylic phosphonate to allow an HWE coupling was desired. After protection of the phenol as the TBS ether, reduction of the ester (**186**) under standard conditions afforded alcohol **187** (Figure 45). Attempts to convert alcohol **187** to the corresponding phosphonate via standard methodology proved unsuccessful. Conversion to the phosphonate next was attempted with a MOM protected phenol. In this case, protection of benzofuran **175** as the MOM ether followed by reduction of the ester gave alcohol **188** in good yield. However, under standard conditions conversion of alcohol **188** to the corresponding phosphonate unfortunately proved unsuccessful.

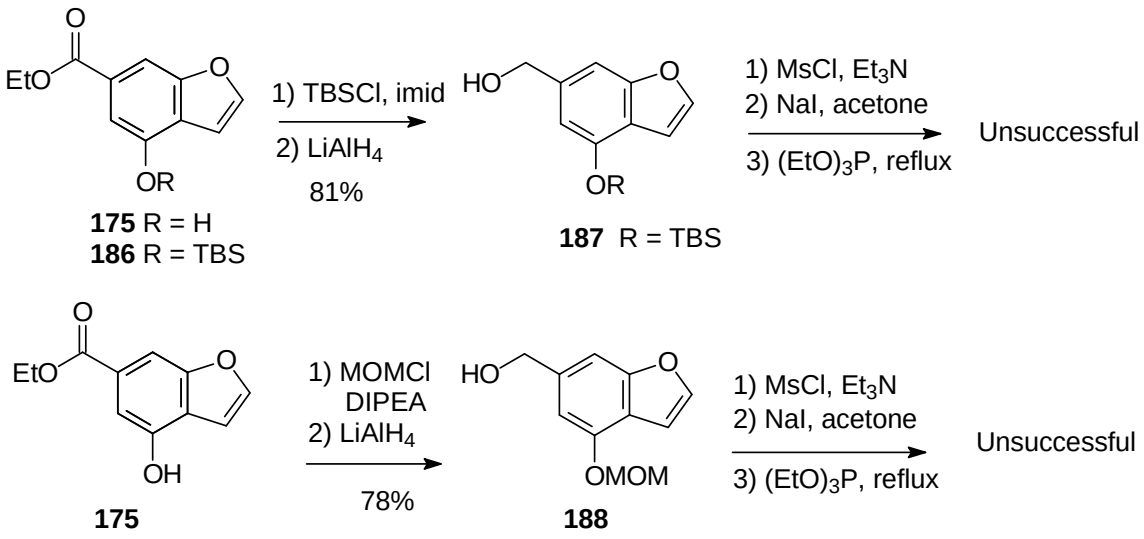


Figure 45. Attempts to synthesize the benzofuran phosphonates

To overcome the difficulty in the preparation of phosphonates from alcohols **187** and **188**, the benzofuran schweinfurthin analogue was approached by reversing the HWE coupling strategy. Conversion of alcohol **188** to aldehyde **189** and condensation with phosphonate **122**[45] afforded stilbene **190**, which was then treated with TsOH to remove the protecting groups and afford analogue **160** (Figure 46). The dihydrobenzofuran analogue **161** was prepared by hydrogenation of alcohol **188** by treatment with H_2 over Pd/C to afford alcohol **191**. The addition of 0.5 equivalents of NH_4OAc to the reaction solution mitigated the possibility of reduction of the benzylic alcohol.[104] Fortunately conversion of alcohol **191** to phosphonate **192** was successful under standard conditions in this case, and gave phosphonate **192** in a reasonable yield. Standard HWE coupling of phosphonate **191** with aldehyde **42** followed by deprotection gave the desired analogue **161**.

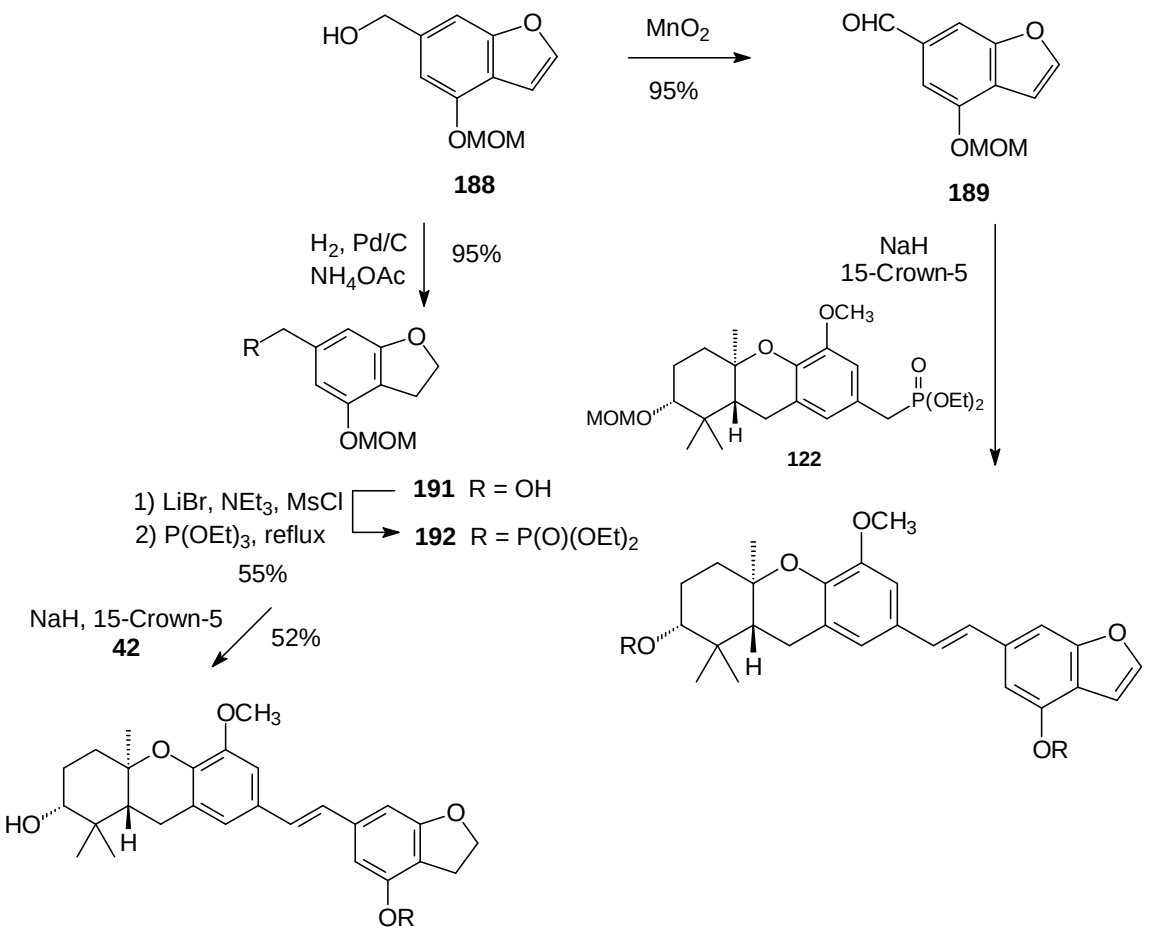


Figure 46. Synthesis of analogues **161** and **160**

To determine the impact of the *trans*-stilbene olefin on activity, analogues were prepared where this moiety was replaced by a simple alkyl chain. The global hydrogenation of the known stilbene **194**[43] over Pd/C gave the fully saturated analogue **196**, and MOM hydrolysis provided one desired target, compound **162** (Figure 47). To remove the stilbene selectively in presence of the isoprenoid olefins, compounds **194** and **195** were treated with Mg^0 and NH_4Cl in methanol.[75] This was followed by standard deprotection of the products **197** and **198** to provide analogues **163** and **164**, respectively.

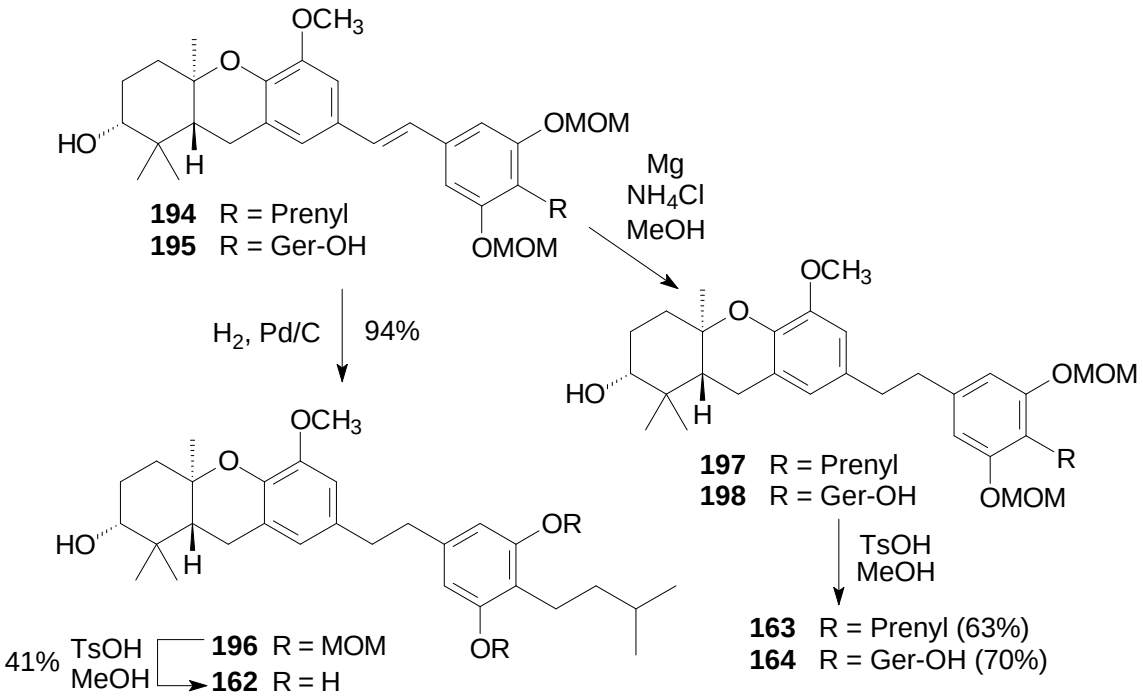


Figure 47. Synthesis of analogues **162**, **163**, and **164**

In a previously tested analogue which carried a geranyl chain on the D-ring, when both D-ring phenols were converted to the methoxy groups the product exhibited poor activity.[50] Comparison of the activity of geranyl versus prenyl D-ring natural products showed that prenyl-containing compounds displayed greater activity. Because of this, it was questioned if the same diminished activity would be observed with a dimethoxy right-half bearing a prenyl substituent. To address this question, reduction of commercially available ester **199** was followed by a directed *ortho* metallation/transmetallation/alkylation protocol[105] to afford alcohol **200** (Figure 48). Conversion to the phosphonate gave compound **201**. To provide an additional analogue for testing, reduction of the prenyl olefin on phosphonate **201** was accomplished by

treatment with H_2 over Pd/C to afford phosphonate **202**. The HWE condensation of phosphonates **201** and **202** with aldehyde **42** afford analogues **166** and **167** respectively.

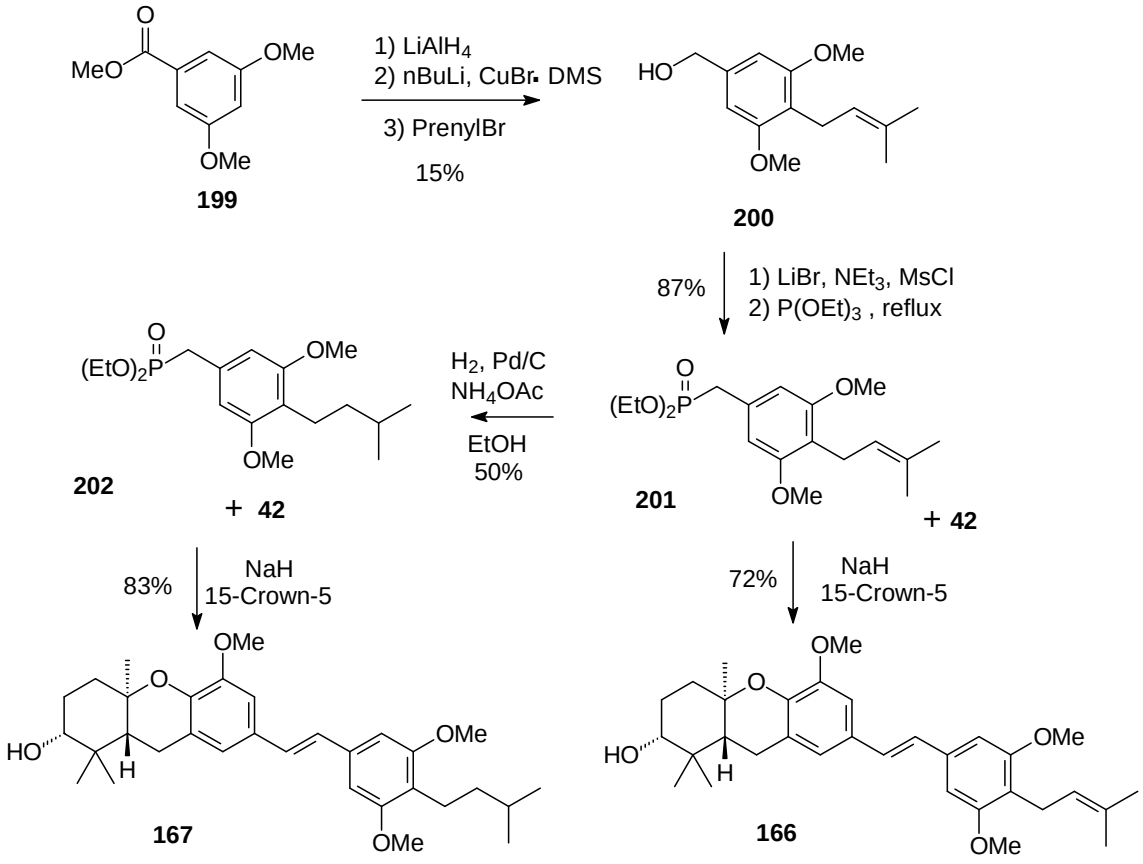


Figure 48. Synthesis of analogues **166** and **167**

All of these compounds, including stilbenes **160**, **161**, **166**, and **167**, and reduced stilbenes **162**, **163**, **164**, along with others prepared by Natalie Ulrich and Nolan Mente (see page 65), were submitted to the two-cell assay for biological analysis. compounds can be grouped into several subsets. One subset includes analogues **168, 171, 169, 170, 172** with various substituents on the D-ring. All five of these compounds showed activity

in the low or sub-micromolar range when tested against SF-295 cells (Table 16), and all showed substantially less activity when tested in the A549 cells. In this subset the most potent compound was the isopentyl compound **171** (EC_{50} = 0.4 μM), which suggests that the presence of an olefin in the sidechain is unnecessary for activity in the SF-295 cell assay. The least active analogue in this subset, compound **170**, displayed an EC_{50} of 2.5 μM which suggests that the addition of the hydroxyl moiety leads to decreased activity.

The two heterocyclic compounds can be viewed as a second subset. Benzofuran **160** and its dihydro counterpart **161** showed activity in the low micromolar range against the SF-295 cell line, with dihydrobenzofuran **161** being somewhat more active. This result is in agreement with findings observed in a similar study.[106]

Assays on the third subset, the reduced stilbene compounds, suggest that reduction of the *trans*-stilbene olefin diminishes activity. Analogues **162**, **163**, and **164**, all showed micromolar activity against SF-295. Comparison of the cis olefin **173**[49] to 3dSB (**24**) showed that isomerization caused a dramatic negative impact on activity with EC_{50}'s of 6.4 and 0.45 for the cis and trans olefins respectively in this assay. Given the varied potencies observed in cis and trans analogues of medicinally important stilbenes such as resveratrol[107] and combretastatin,[108] this result is interesting. It clearly indicates that the E-stilbene is important for the potency of the schweinfurthin system. Assays on the methylated analogues **166** and **167** revealed that both had only modest activity with slightly greater activity in the isopentyl analogue **167**. Clearly methylation of the D-ring phenols results in diminished activity in this series.

Compound	clogP	SF-295 EC_{50} (μM)	A549 EC_{50} (μM)
160	5.11	4.8	>10
161	4.84	2.9	>10
162	6.98	2.8	>10
163	6.58	2.9	>10
164	6.95	>10	>10
166	6.82	>10	>10
167	7.22	5.3	>10
168	5.75	1.7	>10
169	6.05	0.9	>10
170	4.62	2.5	>10
171	6.79	0.4	4.2
172	5.16	1.3	>10
173	8.04	>10	>10

Table 16. Activity of synthetic schweinfurthins in a two-cell screen

Several of the analogues that were prepared were submitted for 60 cell-line assay, and those results are given in Figure 49, Figure 50, and in the Appendix. A summary of the results of these assays, as well as some structurally similar compounds for comparison, is given in Table 17.

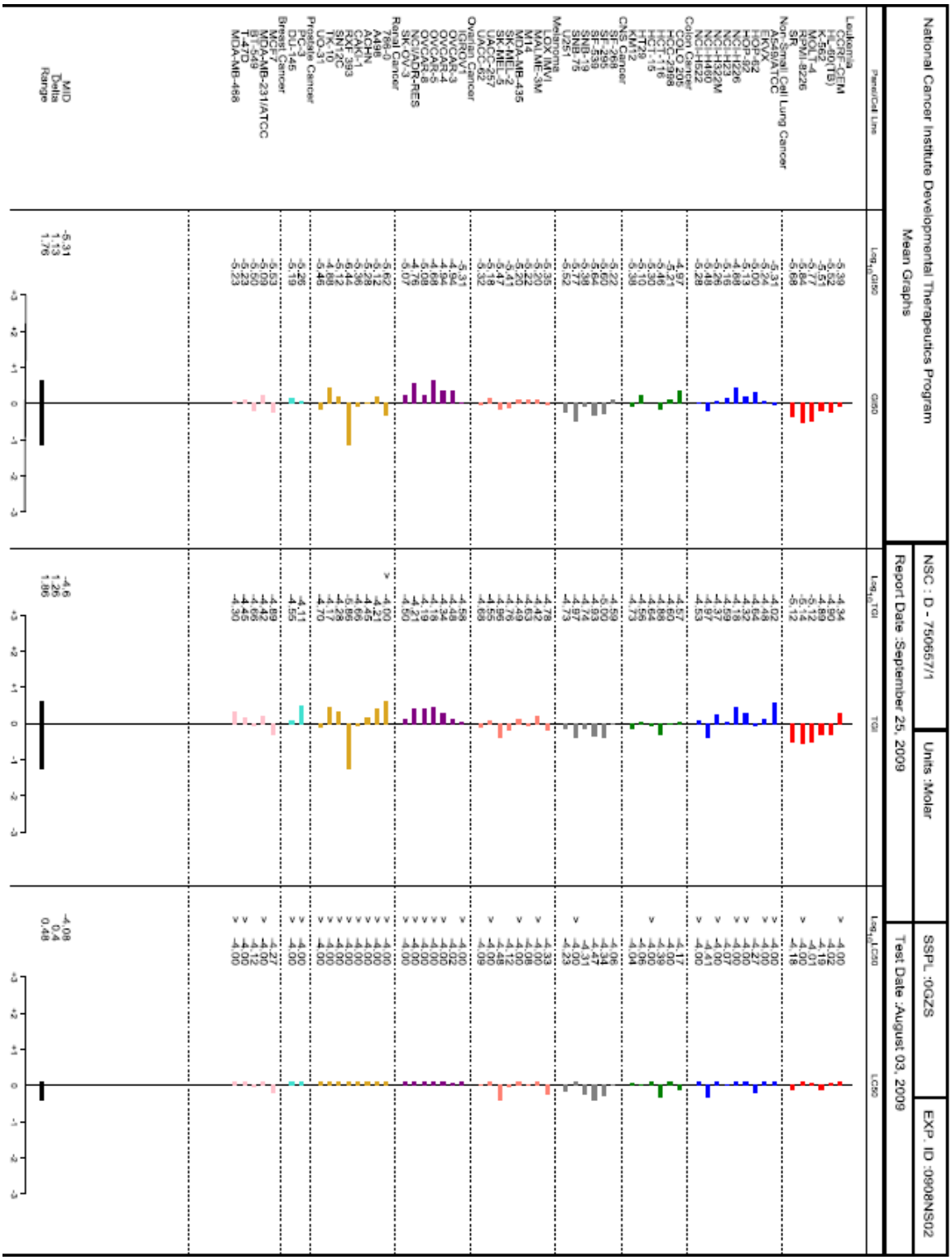


Figure 49. 60 cell-line assay for compound **164**

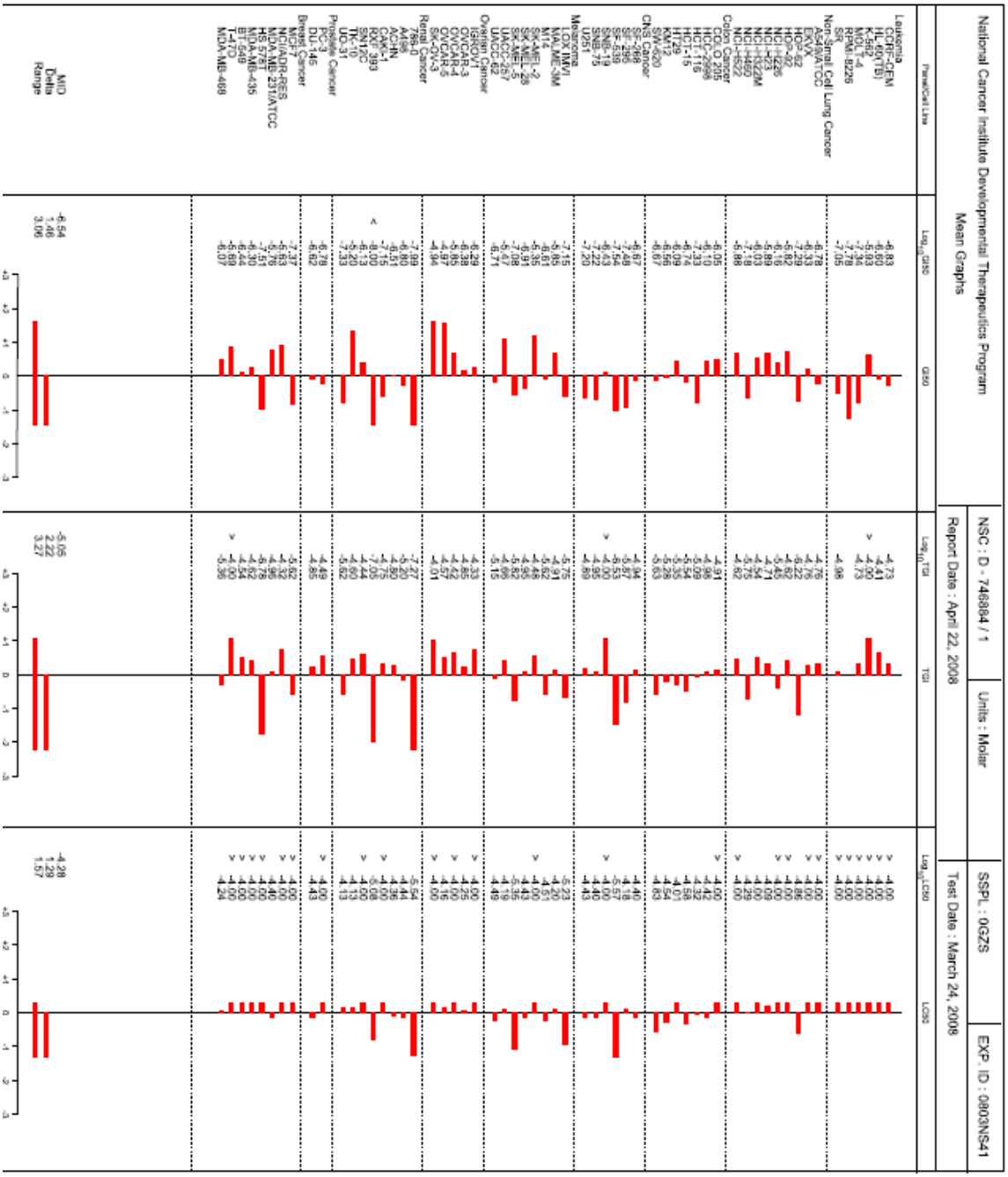
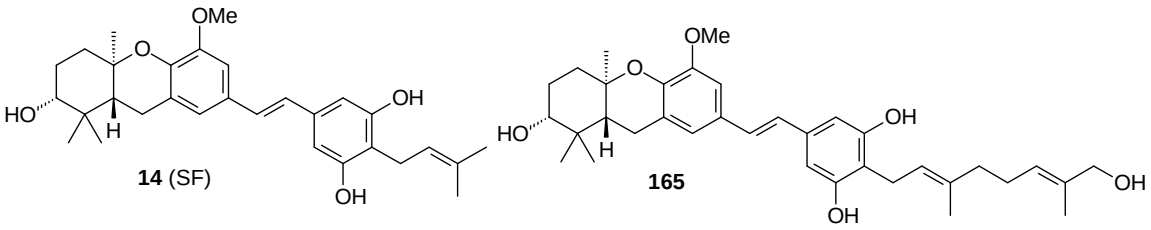


Figure 50. 60 cell-line assay for compound **171**



Compound	GI_{50} (μM)	Range	SF295 (μM)
SF (**14**)	0.41	4.0	< 0.01
160	3.0	1.58	0.83
161	2.4	1.59	1.4
162	1.3	2.35	0.23
163	3.0	1.74	1.7
164	4.9	1.76	2.5
165	1.0	2.39	ND[a]
171	0.29	3.06	0.033

[a] Not determined

Table 17. Summary of 60 cell-line assay data

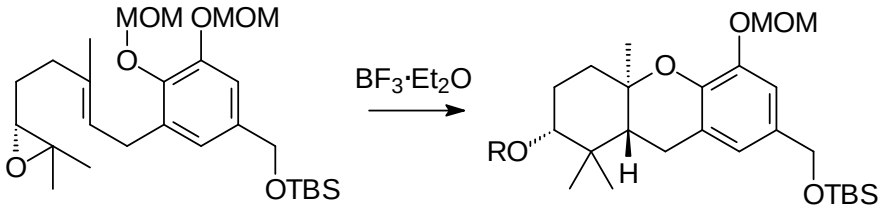
Of the new analogues tested in the two-cell assay, compound **171** demonstrated the greatest potency against SF-295 cells, along with a 10-fold difference in activity. When this compound was tested in the 60-cell line assay at the NCI,[49] it also showed significant potency. The average GI_{50} across the 60 cell lines was 0.29 μM, and the GI_{50} in the SF-295 cell line was ~33 nM. This potency exceeds that of several of the natural products (e.g. SA and SB), as well as SF (**14**), from which it differs only by the reduction of the prenyl chain.

The benzofuran **160** and dihydrobenzofuran **161** were only weakly cytotoxic and exhibited low differential activity in the 60 cell-line. Compound **164** proved to be one of the least active compounds tested in the two-cell assay and when tested in the NCI's 60-cell line assay its average GI_{50} was 4.9 μM. It also showed little differential activity with a range of just 1.76 log units. Compared to its stilbene counterpart **165**,[50] it has both reduced activity and little differential activity. In pairwise comparisons of stilbenes SF (**14**)[43] and **171** with the reduced stilbene analogues **163** and **162** respectively, both reduced stilbenes showed little activity and limited differential activity. This provides further evidence that the stilbene olefin is important to the schweinfurthin pharmacophore. The isopentyl analogue **162** showed better activity than its prenyl counterpart **163**, which was consistent with the results seen with compound **171**. Because of the lower activity of the benzofuran analogues, further modification such as installation of a side chain was not pursued. However, based on these results further insight into the pharmacophore of the schweinfurthins was achieved, which was the objective of these efforts.

CHAPTER 6

MIGRATION OF "PROTECTING GROUPS" DURING THE CASCADE CYCLIZATION REACTION

An epoxide initiated cascade cyclization has been utilized in the synthesis of the schweinfurthin left-half. In the synthesis of Schweinfurthin G (**15**), in addition to the expected product **211**, the MOM protecting group liberated during cyclization was partially transferred to the A-ring hydroxyl group to afford compound **212** (Figure 51).[45] The mechanistic rationale for the product **212** is that the MOM group forms a transient electrophilic species which then is quenched by the A-ring hydroxyl group. When there is a hydrogen substituent at the C-5 position, an electrophilic aromatic substitution of the MOM carbocation was observed which resulted in new carbon-carbon bond formation (Figure 52).[109] After recognizing that this reaction could be utilized in the controlled construction of carbon-carbon bonds, this tandem cyclization and electrophilic substitution was utilized in an efficient synthesis of (+)-angelichalcone (Figure 53).[110]



210

211 R = H (52%)
212 R = MOM (30%)

Figure 51. Migration of the MOM group in the cascade reaction

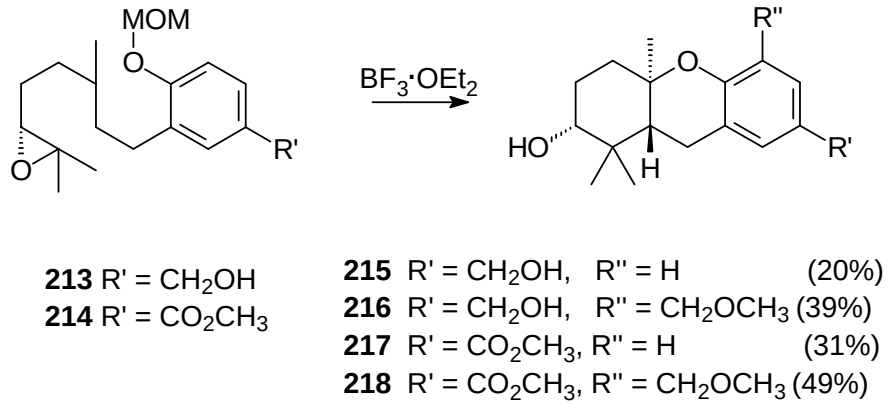


Figure 52. Cyclization with ortho electrophilic aromatic substitution

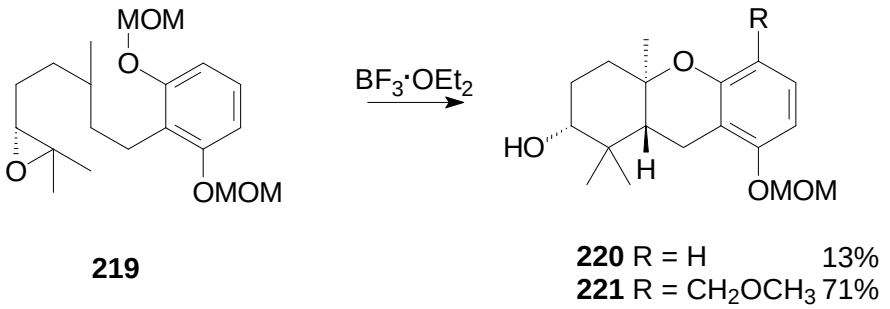
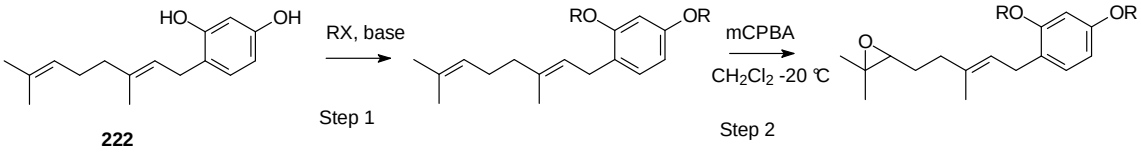


Figure 53. Cyclization en route to angelichalcone

With the utility of the MOM ether migration demonstrated, it became of interest to determine if other protecting groups would undergo cyclization with or without electrophilic aromatic substitution. To study how various "protecting" groups react, 4-geranylresorcinol (**222**) was prepared.[110] It then was protected with a variety of different groups and each product was epoxidized to give a substrate appropriate for cyclization. This aromatic system was selected for this study in part because the aromatic substitution pattern of the product should be easily interpretable from the ^{1}H NMR spectrum.

The first set of substituents studied were those most similar to the MOM group, namely acetal-containing protecting groups. A summary of the preparation of these epoxides is shown in Table 18. Additional epoxides for this study were prepared and cyclized by Joseph Topczewski to provide a more extensive body of information.[47] The epoxides were subjected to cyclization conditions ($BF_3 \cdot OEt_2$, –78 °C) parallel to those previously reported for the MOM protected resorcinol,[110] and the results of these reactions are summarized in Table 19.



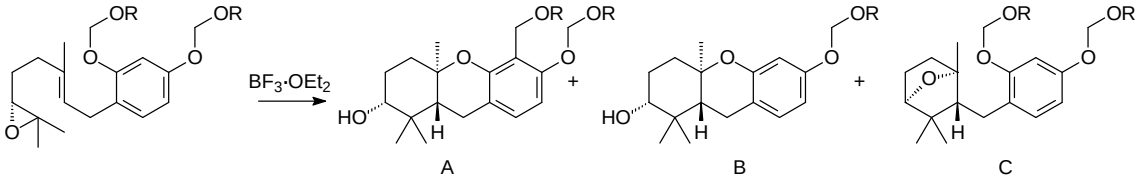
222

Entry	R =	Abv	Step 1 Yield	Compound	Step 2 Yield	Compound
1	$BnOCH_2$	BOM	63%	**223**	31%	**224**
2	$(CH_3)_3CCO_2CH_2$	POM	39%	**225**	28%	**226**

Table 18. Preparation of geranyl epoxides

Compound **227** (entry 1) underwent cyclization with substitution to give a 52% yield of the ortho-substituted product **231A** along with the unsubstituted product **231B** in a 30% yield. Other common protecting groups including the BOM, SEM, and MEM compounds (entries 2-4) all gave the ortho substituted product in yields comparable to those of the MOM cyclization. The unsubsituted product **234B** (compound B) was isolated again during the cyclization of the MEM-protected resorcinol. When *p*-

chlorophenoxylmethyl protected phenol **230** was cyclized (entry 5), it provided the unsubstituted product **235B** as the major product with no detectable amount of the ortho-substituted compound. In addition, a bridged ether product (**235C**) was obtained from this reaction. Cyclization of the POM-protected phenol (**226**, entry 6) also yielded the bridged ether as the only product (**236C**). The ether's structure was deduced by analysis of the ^{1}H and ^{13}C NMR spectra and comparison to natural products with the same bridged-ether motif attached to an aromatic ring system.[111, 112]



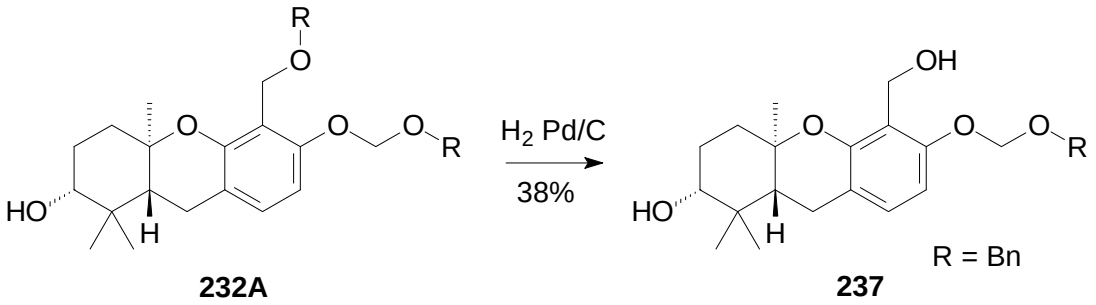
Entry	Substrate (R=)	Abbr	% Yield A[a]	% Yield B[a]	%Yield C[a]
1[b]	CH_3 (**227**)	MOM	52 **231A**	30 **231B**	
2	Bn (**224**)	BOM	62 **232A**		
3[c]	CH_2CH_2TMS (**228**)	SEM	57 **233A**		
4[c]	$CH_2CH_2OCH_3$ (**229**)	MEM	53 **234A**	28 **234B**	
5[c]	$pClC_6H_4$ (**230**)	AOM		56 **235B**	37 **235C**
6	$C(O)C(CH)_3$ (**226**)	POM			48 **236C**

[a] Isolated Yields [b]Previously reported[110] [c]Prepared and cyclized by Joseph Topczewski

Table 19. Migration of acetyl protecting groups

With the new benzylic ether **232A** formed, the ability to manipulate the functional group selectively was desired. It has been demonstrated that the benzyl methyl ether

resulting from the MOM migration can be transformed to the corresponding aldehyde upon treatment with DDQ.[110, 113] If other protecting groups could migrate and be cleaved to give the alcohol directly, it would provide a convenient strategy to allow further synthetic manipulation. An alcohol formed through ester hydrolysis would be one possible route to obtain the desired target. Unfortunately, the POM protecting group did not undergo electrophilic aromatic substitution. An alternative route to obtain an alcohol would be the cleavage of the benzyl ether **232A** from the migrated BOM group by hydrogenolysis to afford alcohol **237**. Preliminary testing revealed that cleavage of the benzyl group by treatment with H_2 in EtOAc at 40 psi resulted in a partial cleavage of the benzyl group in a modest yield (Figure 54). Even though the reaction was allowed to proceed for 2 days, there were still noticeable amounts of starting material remaining without any other detectable side product. This may be due to the large substituents nearby, resulting in steric hindrance for cleavage of the benzyl group. Further optimization of the benzyl cleavage has allowed a formal synthesis of schweinfurthins B, E, F and G, and the synthesis of (+)-schweinfurthin A.[47]



232A **237**

Figure 54. Removal of the benzyl group to alcohol **237**

If a secondary acetal protecting group such as an ethoxylethyl group were to undergo cyclization and electrophilic aromatic substitution (EAS) successfully, the expected product could be oxidized to the acetophenone using DDQ.[113] With this in mind, an ethoxyethyl protected phenol was prepared (Figure 55), and then subjected to cyclization conditions (Table 20, Entry 1).

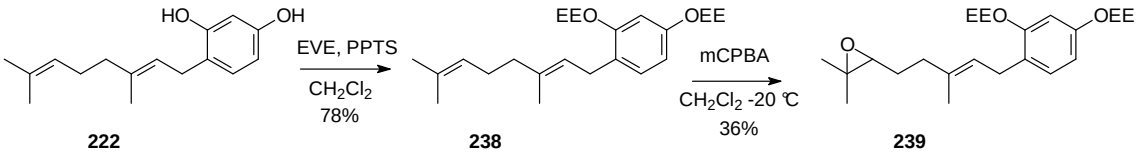
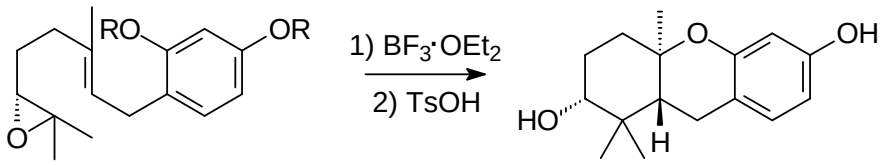


Figure 55. Preparation of ethoxyethyl protected phenol **239**

Unfortunately the cyclization afforded a complex mixture of products. In an effort to simplify the product distribution, the initial material was exposed to TsOH to hydrolyze the ethoxyethyl protecting group from the phenol. This gave compound **241** as the only isolable product, but in just 14% yield. Identification of this product indicated that the hexahydroxanthene was formed, but that the protecting group did not participate in electrophilic aromatic substitution. Repeating the cyclization and deprotection did not afford any recoverable material. The similarly constructed THP acetal **240** also was investigated and showed similar behavior. The poor results of these secondary acetals might be explained by formation of a more stable oxocarbonium ion which impedes the desired reaction pathways.



241

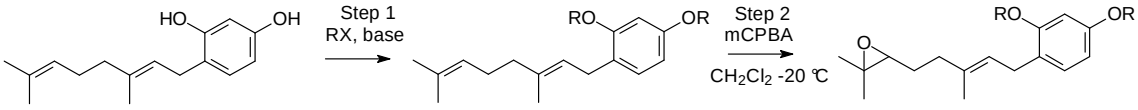
entry	Number	Substrate	Yield (%)
1	**239**	Ethoxyethyl	14
2	**240**[a]	THP	8

[a]Prepared and cyclized by Joseph Topczewski

Table 20. Cyclization and deprotection of secondary acetyls

Based on the information gained from these trials, the success of the cyclization/aromatic substitution reaction seemed to be affected by the ability of the protecting group to form a stabilized carbocation. A stronger electron-withdrawing protecting group destabilizes the carbocation and results in formation of the bridged ether. This was seen with the ester protecting groups that all produced bridged ethers.[47] The more electron donating protecting groups allowed formation of a tricycle, and the liberated carbocation then underwent electrophilic aromatic substitution on the adjacent site. Of note, no bridged ether with cleavage of the protecting group was ever detected.

To explore further the effects that electronics have on the cascade reaction, a series of geranyl epoxides with adjacent benzylic protected phenols was synthesized using standard conditions (Table 21). Variation of the substituents on the phenyl ring allows some control of the electron density of the “protecting” group.



222

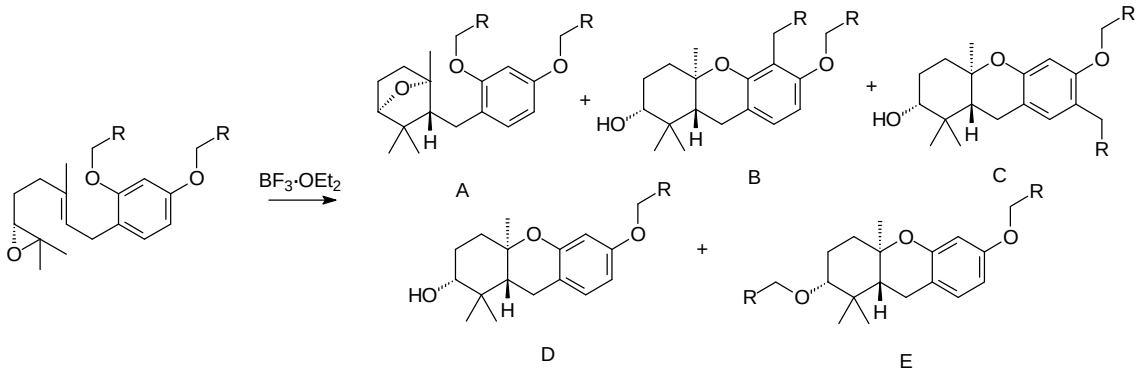
Entry	R	Step 1 Yield	Compound	Step 2 Yield	Compound
1	4-NO_2Bn	43%	**242**	34%	**243**
2	4-MeOBn	68%	**244**	36%	**245**
3	3,4,5-MeOBn	65%	**246**	34%	**247**
4	2-furyl	49%	**248**	41%[a]	**251**

[a] Reaction performed by Joseph Topczewski.

Table 21. Preparation of benzylic protected phenols

Under the standard reaction conditions, cyclization of the parent unsubstituted benzyl group (Table 22, entry 1) led to the product where the benzyl group underwent EAS at the ortho position (**252B**) along with a trace amount of the para-substituted product **252C** as well as some unsubsituted tricycle **252D**. This para-substituted product was not detected with the acetyl type protecting groups. More electron deficient groups such as the 4-nitro- (entry 2) or the 2-bromophenyl compounds (entry 3) led to the bridged ether products, **253A** and **254A**. Addition of electron donating groups to the phenyl ring leads to the tricycle product in good yield but with less control over the EAS regiochemistry. For example, the PMB group (*p*-methoxybenzyl, entry 4) undergoes substitution at the ortho position (**255B**) in a 33% yield along with considerable amounts (19%) of the para product **255C**. Also observed in this case was the A-ring protected alcohol **255E** in 12% yield. To produce an analogue with even more electron density in the phenol system the 2,4-dimethoxybenzyl group was studied. Unfortunately, this effort

was without success due to the tendency of the benzyl halides to undergo polymerization.[114] To circumvent this difficulty, the slightly less electron donating 3,4,5-trimethoxybenzyl analogue **247** was prepared. As expected, the cyclization (entry 5) preceded well but the major products were the unsubsituted compound **256D** along with a nearly equal amount of the para-subsituted compound **256C**. As before there was a small amount of the A-ring protected product **256E**.



Entry	Substrate (R =)	Yield[a] A (%)	B (%)	C (%)	D (%)	E (%)	Number
1	C_6H_5[b] **249**		42	2	18		**252B-D**
2	*p*-$NO_2C_6H_4$ **243**	20					**253A**
3	*o*-BrC_6H_4[b] **250**	49					**254A**
4	*p*-$OCH_3C_6H_4$ **245**		33	19		12	**255B,C,E**
5	3,4,5-$MeOC_6H_2$ **247**			28	32	9	**256C-E**
6	3-furyl[b] **251**		49				**257B**

[a] Isolated yields. [b] Cyclized by Joseph Topczewski

Table 22. Cascade cyclization with benzyl protecting groups

Formation of the para-substituted product and especially the A-ring product indicate that when the electron density of the benzyl group is increased, the resulting carbocation has sufficient stability to migrate to more distant positions. This suggests that the process is not a concerted reaction, and that the carbocation exists as distinct, albeit transient, species. Because the para-position is typically the preferred reaction site for substitution,[115-117] the stabilized carbocation allows the electrophile a longer lifetime and thus there are more possible positions for substitution.

A 3-furyl protected phenol (entry 6) also was studied and it produced the ortho substituted product **257** in 49% yield. The 3-furyl group can be viewed as a representative case of a heteroaryl system. Furthermore, this group is found in numerous natural terpenoids, which may increase the applicability of this reaction.

Once it was shown that cyclization with electrophilic aromatic substitution is possible with a variety of "protecting groups", it was decided to explore a cyclization that could terminate at either of two different sites. Construction of a geranyl epoxide with differently protected phenols at both ortho positions should allow determination of the more favored group for termination of the cascade reaction. The simplest comparison would be between a free phenol and a protected phenol. The protecting group must be one that is known to undergo EAS, such as a MOM ether.

Construction of a test case started with partial MOM protection of resorcinol (**258**, Figure 56). Separation of the mono-protected acetal from unprotected and di-protected materials was followed by protection of the remaining phenol as a THP ether to afford the known compound **259**.[118] Directed-ortho metalation with *n*-BuLi followed by trans-metalation with CuI presumably formed the cuprate.[119] This anion was allowed to

react with geranyl bromide to afford the geranylated arene **260** with the desired regiochemistry. Selective removal of the THP protecting group gave compound **261**, which subsequently was epoxidized to afford compound **262**. Subjection of this epoxide to the cyclization conditions afforded compound **220** as the only detectable product but in a poor isolated yield (15%). Structural confirmation was accomplished by comparison to the ^{1}H NMR and ^{13}C NMR spectra of the same compound obtained as a side product during the synthesis of angelichalcone.[110] Nevertheless, this indicates that cyclization to the free phenol is favored over reaction at the MOM acetal.

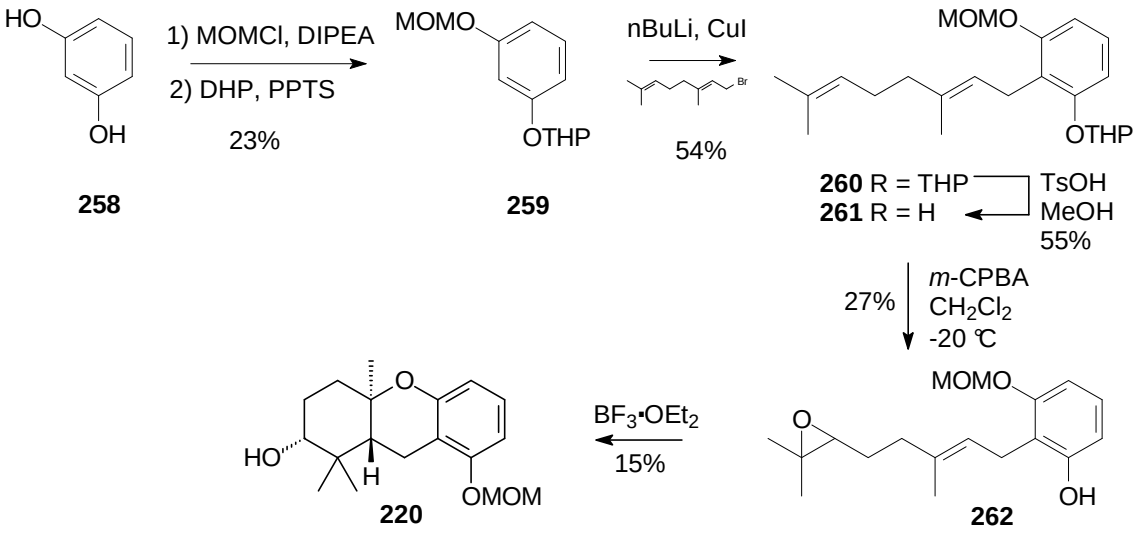


Figure 56. Cyclization of a mono-MOM protected analogue

After the success of the benzyl group in the tandem cascade-EAS reaction migration, attention was turned to cyclizations involving olefin or other unsaturated groups. Successful cyclization with electrophilic aromatic substitution of these groups should produce a new carbon-carbon bond, and the new olefin then can serve as a site for

further synthetic manipulation. The installations of the required groups for the allyl, crotyl, and propargyl cases were accomplished by treating the diphenol **222** with base and then adding the allyl or propargyl halide, followed by treatment with *m*-CPBA to form the epoxide (Figure 57). While the epoxidation reactions were not high-yielding, perhaps because of the numerous sites that might compete for oxidation, sufficient epoxide was obtained in each case for the desired study.

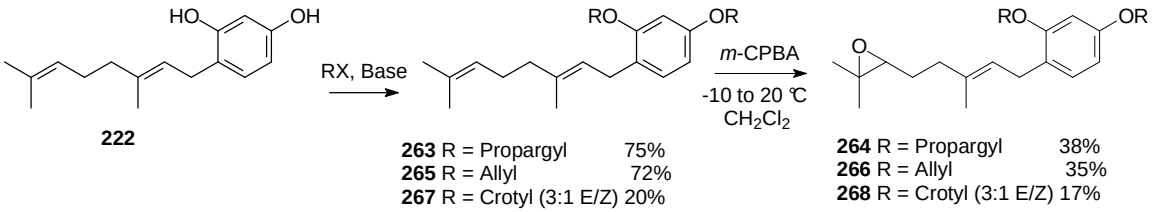


Figure 57. Preparation of olefin containing protecting groups

Analysis of the ^{1}H NMR spectrum for the crotyl product **267** indicated that it was formed as a mixture of E- and Z-olefin isomers in approximately a 3:1 ratio. This was attributed to the commercial crotyl bromide, which was obtain and used as a mixture of isomers. Attempts to separate the isomers by flash chromatography proved unrewarding, so pure E-crotyl bromide (**270**) was prepared from E-crotyl aldehyde (**269**, Figure 58).[120, 121] Alkylation of resorcinol **222** with pure isomer **270** in the presence of K_2CO_3 in acetone led to a low yield (16%) of the desired compound **271**, along with noticeable amounts of the mono-alkylation products. Attempts to increase the yield through the use of NaH in DMF at 0 °C did improve the yield to 51%, but there also was evidence of partial C-alkylation at the C-5 position to afford compound **272**. Unfortunately, the di-

ether **272** was not easily separated from the desired product **271**. Epoxidation of compound **271** afforded epoxide **273** in a 24% yield.

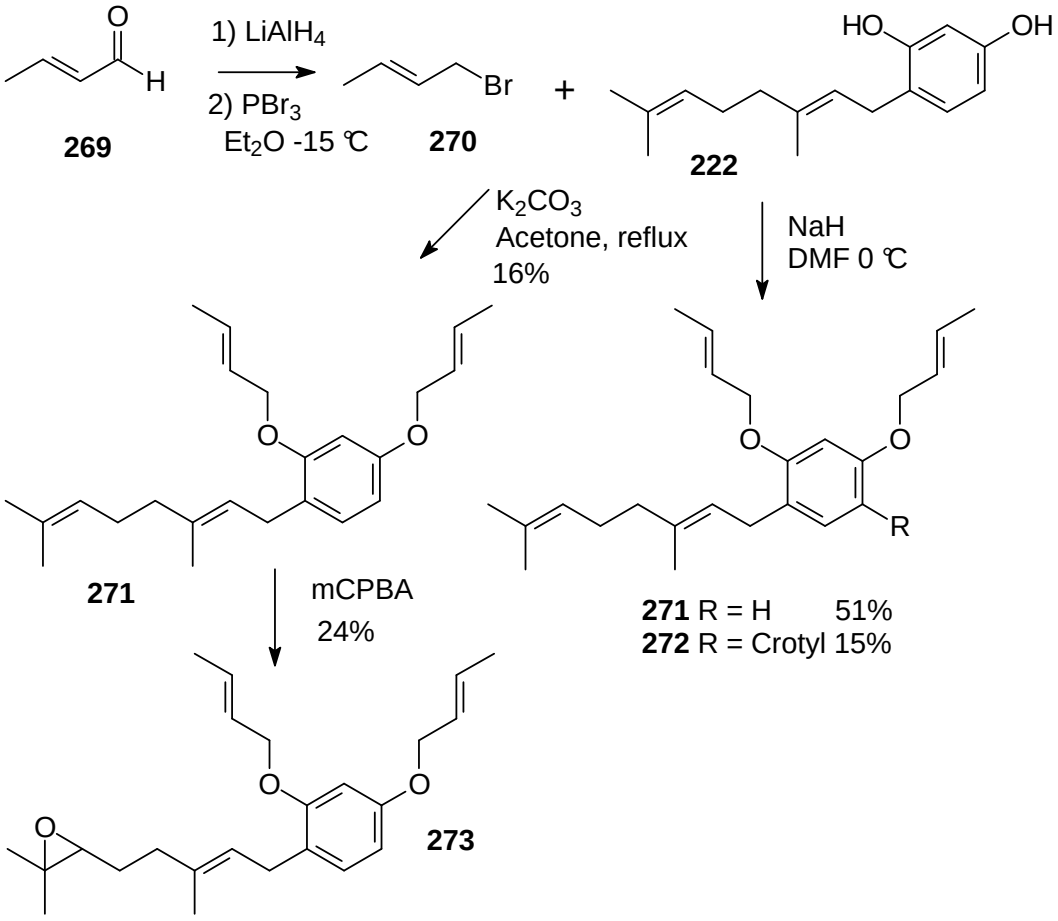


Figure 58. Preparation of pure (E)-crotyl bromide and resorcinol alkylation

Preparation of the "reverse" prenyl epoxide **278** was somewhat more difficult (Figure 59). This synthesis started with installation of the 1,1-dimethylpropargyl groups by conversion of the alcohol **274** to the trifluoroacetate **275** and then alkylation of the phenol **222** with this ester.[122] This procedure went in a very modest yield, and there was

a noticeable but undetermined additional product which was difficult to remove. Fortunately partial separation afforded a small amount of pure sample that was confirmed as the desired compound **276** by NMR analysis. Because complete separation remained elusive, the mixed material was subjected to epoxidation conditions and then the products were separated after this step to afford the desired epoxide **277** albeit in a low 2-step yield. Treatment of compound **277** with H_2 at 1 atmosphere in the presence of Lindlar's catalyst[123] and quinoline afforded the desired "reverse" prenyl epoxide **278** in 76% yield.

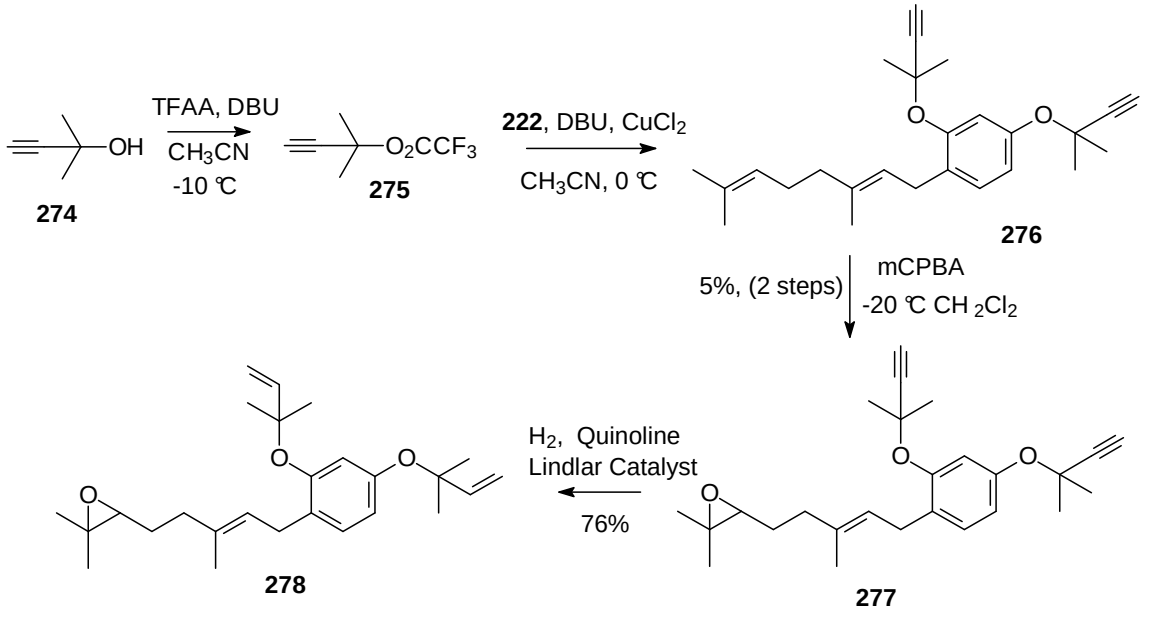
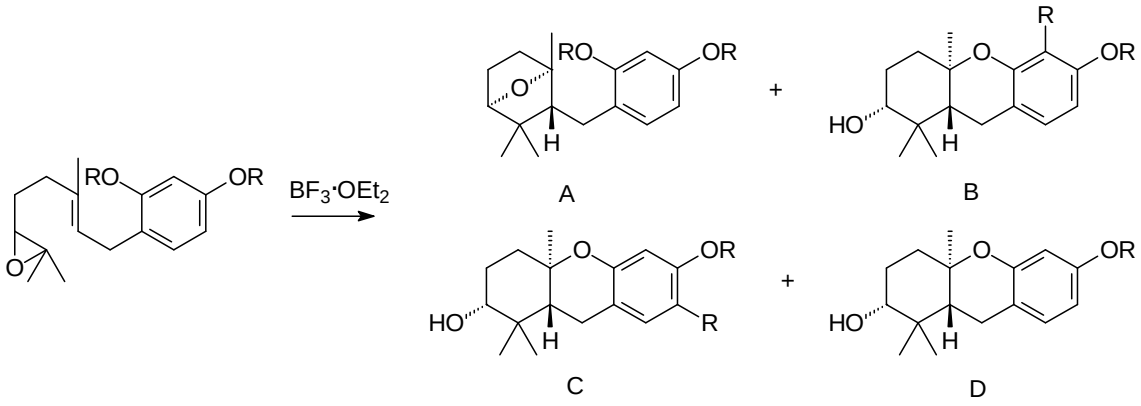


Figure 59. Preparation of epoxides **278** and **277**

A set of compounds consisting of eight epoxides was treated with $BF_3 \cdot OEt_2$ under standard conditions to induce the cascade cyclizations. The results are given in Table 23.



Entry	Substrate (R =)	Yield [a]				Number
		A (%)	B (%)	C (%)	D (%)	
1	CH_3 [b] (**279**)	74				**281A**
2	$CH_2C{\equiv}CH$ **(264)**	47				**282A**
3	$C(CH_3)_2C{\equiv}CH$ (**277)**	47			14	**283A**,**D**
4	$CH_2CH{=}CH_2$ (**266**)	32	8			**284A**,**B**
5	$C(CH_3)_2CH{=}CH_2$ (**278)**	12[c]				**285A**
6	$CH_2CH{=}CHCH_3$ (3:1 E:Z) **(268)**		61[d]			**286B**
7	$CH_2CH{=}CHCH_3$ (E) (**273)**		58[d]			**287B**
8	$CH_2CH{=}C(CH_3)_2$ [b](**280**)		31	29[e]		**288B**,**C**

[a] Isolated Yields, [b] Prepared and cyclized by Joseph Topczewski [c] Several cyclized product(s) were indicated by TLC but isolation was elusive [d] Inversion [e] 2:3 prenyl to reverse prenyl

Table 23. Cyclization with olefin substituents

The methyl protected phenol (entry 1) cyclized only to an A-ring ether in good yield (74%), and did not close a B-ring or undergo electrophilic aromatic substitution to any detectable extent. Attempted cyclization of the propargyl phenol **264** (entry 2) also gave an A-ring bridged ether (**282A**) as the only detectable product. Attempted cyclization with the more substituted 1,1-dimethylpropargyl moiety (entry 3) also gave the bridged ether **283A** product but in addition the unsubsituted tricycle **283D** was detected indicating a cascade cyclization. The allyl group (entry 4) also demonstrated partial cyclization, with 32% of the A-ring bridged ether detected **284A** as well the ortho substituted product **284B** in an 8% yield. The reverse prenyl epoxide **278** (entry 5) gave the bridged ether product **285A** in just 12% yield. While TLC analysis of the reaction mixture indicated the presence of multiple products with Rf values suggestive of the formation of hexahydroxanthenes, isolation was problematic.

Cyclization of the crotyl compound (entry 6) proved particularly interesting. For the crotyl epoxide of mixed olefin stereochemistry, the ortho product **286B** was obtained in 61% yield. The crotyl group had inverted during this reaction to give a terminal olefin. This was apparent from olefinic region of the ^{1}H NMR spectrum and a DEPT analysis of the ^{13}C NMR spectrum that showed a terminal methylene group above 100 ppm. This reaction also resulted in formation of an additional stereocenter. The cyclization of the mixed *E*- and *Z*-crotyl epoxides gave the diastereomers in roughly a 2.5:1 ratio, which was similar to the (3:1) E/Z ratio of starting olefins suggesting that the diastereomeric ratio possibly could be influenced by the olefin geometry. To test the hypothesis that the E/Z geometry of the crotyl group translated into the diastereomeric ratio, pure E-crotyl epoxide **273** was cyclized and compound **287B** was isolated in a comparable 58% yield.

Inspection of the ^{1}H NMR spectrum indicated that the diastereomeric ratio was still roughly 2.1:1. This indicates that the ratio was not directly controlled by the E/Z ratio of the starting olefin, but the difference also may suggest that there is some influence.

The cyclization of the prenyl phenol (**280**, Entry 8) gave the ortho product **288B** as the dominant hexahydroxanthene in 31% yield without inversion of the prenyl group. Also obtained was the para-substituted product **288C**, but this material was isolated as a mixture of the prenyl and reverse prenyl products in a 2:3 ratio and a total yield of 29%. The lack of inversion at the ortho position may suggest that the attack of a tertiary carbocation at this position is impeded by steric bulk.

These results indicate that the ability of various groups to undergo cyclization with EAS is influenced by the stability of the carbocation formed when the phenolic group is lost. Groups that would contain more electron-withdrawing characteristics would require formation of a carbocation that is not easily lost, and the result is a bridged A-ring ether product instead. As the ability of the phenolic group to stabilize a positive charge increases, partial cyclization is seen with some substitution at the ortho position. Further increasing the cation-stabilizing characteristics of the protecting group leads to the detection of both the A-ring product and the para-subsituted product. This can reach the point that the protecting group no longer undergoes substitution at the ortho position and instead is found only at the para position. A more stable carbocation is less reactive and more selective during electrophilic aromatic substitution, and seems to favor reaction at the para position which is typically preferred.[116, 117] The trend with the olefinic groups is also representative of the stability of the respective carbocation, with tertiary and secondary allylic carbocations being more stable and thus more likely to form a tricycle

than primary carbocations. Carbocations adjacent to an olefin are more stable than those adjacent to an acetylene unit, [124] and can more easily undergo cyclization with electrophilic aromatic substitution. This observation is consistent with the relative stabilities of the allyl and propargyl carbocations.[124]

CHAPTER 7

SUMMARY AND FUTURE DIRECTIONS

During the course of these studies, many new analogues have been prepared to better understand the pharmacophore of the schweinfurthins. Modification of the right-half of the molecule to contain an indole has produced many novel analogues. These new compounds show both good activity and differential range, demonstrating that modification of the schweinfurthin structure to include an indole system is a desirable change.

The choice of the appropriate protecting group(s) in the preparation of the indole analogues is critical. Without an appropriate protecting group, conversion to the phosphonate proved challenging as seen with the *N*–MOM indole phosphonate **52**. When this protecting group proved resistant to removal, the Boc and tosyl protecting groups were utilized and both allowed conversion to the phosphonate in a more consistent manor. These phosphonates represent the first B-ring indole phosphonates since previously only C-2 or C-3 indole phosphonates have been reported. The Boc protecting group proved too labile toward the HWE reaction conditions and its rapid removal prevented successful coupling with the necessary aldehyde. During the HWE reaction, a tosyl protecting group on the indole nitrogen was found to transfer to the A-ring alcohol. Removal of the tosyl protecting group from this position proved quite difficult and typical conditions were unreliable. If an approach was employed based on frequent monitoring of the reaction progress by TLC analysis and quenching the reaction mixture immediately after the aldehyde had been consumed, the transfer of the tosyl protecting

group was minimized. This proved to be a more reliable route to access the final product(s).

To access analogues that are more reminiscent of the structure of the natural schweinfurthins, isoprenoid side chains were added to the indole. Because the effect of the position of the side chain on the activity of the indole analogues initially was unclear, both the C-2 and C-3 substituted analogues were targeted. Electrophilic aromatic substitution (which is favored at C-3 of indole itself)[125] could be employed to obtain compound **81**. Since both the C-6 and C-4 groups that might impact reactivity were required, it was uncertain if the direct approach using the methodology of Ganesan[94] which relies upon $Zn(OTf)_2$ could be applied to access the substituted indole required. Fortunately this method proved successful and allowed the rapid synthesis of analogue **81**. An anion approach, which can be directed to C-2 in *N*–substituted indoles, was explored to provide compound **82**. Even with the di-substituted indole system, alkylation proceeded selectivity and in an acceptable yield. Using the methods developed in the synthesis of the parent indole, compounds **40** and **41** allowed the successful synthesis of analogues **81** and **82** as well as the C-3 geranyl analogue **80**.

The C-3 prenyl analogue **81**, displayed both potent activity and good differential activity, while the C-2 prenyl analogue **82** displayed activity diminished by a factor of 10, but maintained a similar level of differential activity. This was seen in both the local two cell-line assay with SF-295 and A549 cells, and the full 60 cell-line assay at NCI. The C-3 geranyl analogue **80** had activity that was slightly diminished in comparison to the unsubsituted analogue **41** in NCI's 60 cell-line assay. This indicates that it is more

desirable to have a prenyl length side chain than the geranyl length side chain. The relative potency of the C-3 analogues based on substituent is prenyl > H > geranyl.

Protection of functional groups on the indole with a methyl group(s) to improved stability proved interesting. When the indole phenol was protected with a methyl group to give analogue **110**, the resulting compound showed increased activity relative to the indole phenol **41**. In the preparation of *N*–methyl indole analogues, difficulty was encountered in the formation of to the indole phosphonate. Because of this, the components for the HWE reaction were reversed from the standard left-half aldehyde and right-half phosphonate to a left-half phosphonate and a right-half aldehyde. The analogue **111** showed a similar level of activity to compound **100** in the SF-295 cell-line assay, but in the full 60 cell-line assay the mean activity was diminished by about a factor of three. The *N*,*O*–dimethylated indole **112** showed excellent activity in the 2 cell-line assay, but this did not directly translate into the full screen as it displayed a very similar mean activity to analogue **111** at NCI.

Alkylation of the *O*-methyl indole compound **113** at the C-3 position again was successful and allowed the synthesis of isoprenylated analogues **131** and **132**. When the methyl protected C-3 geranyl analogue **131** was assayed, it showed better activity in the full 60-cell line assay than its non-methylated counterpart **80**. The prenyl analogue **132** also showed a similar level of activity in the 2-cell line assay to compound **81** but at this time the full 60-cell line assay results are unavailable. Changing the C-ring methoxy group to a phenol substituent leads to analogues with increased activity, with both analogues **141** and **146** having an EC_{50} value under 50 nm against SF-295. In the standard schweinfurthins, the addition of a methyl group to the D-ring substituent leads to

a slight decrease in activity but in the indole containing analogues this change leads to a slight increase in activity. A Pearson correlation of the 60 cell-line assay results indicates that the indole containing schweinfurthin analogues still display a "schweinfurthin-like" pattern of activity. Some of the more potent indole analogues have activity that makes them attractive targets for further synthetic development and in depth testing of their biological activities.

Other studies involving schweinfurthin F analogues have shown that the incorporation of a benzofuran moiety into the schweinfurthin structure leads to analogues with slightly diminished activity. The reduction or isomerization of the stilbene olefin leads to analogues with diminished activity in the SF-295 cell-line and also in the full 60 cell-line assay. Modification to the side chain appears to be well tolerated provided that its hydrophobic nature is maintained. Reduction of the prenyl side chain to an isopentyl group gives analogues with a slightly increased activity.

In general the two-cell line assay developed locally is effective at rapidly screening new analogues for potency. Compounds that show good activity in the 2 cell-line assay also show good activity in the full 60 cell-line assay and those that show poor activity show poor results in the full screen. However, the relative order of potency is not exact, so it is important test several or all of the more active compounds so as not to miss those that might potentially show a higher activity in the full screen. The two cell-line assay can been viewed as a "first pass" assay to identify which compounds have sufficient activity to warrant further testing and synthetic investigation.

Future work on the heteroaromatic schweinfurthin analogues can be envisioned. With the left-half aldehydes for schweinfurthin A and B now accessible, it may be

interesting to prepare more heteroaromatic analogues that utilize these substrates. Phosphonates at all positions on the indole B-ring could targeted to explore their reactivity, especially if the indole nitrogen protecting group is absent, during the HWE reaction with a variety of aldehyde or ketones. Given the biological activity of the indole analogues it may be interesting to determine if removal of the phenol or methoxy group diminishes activity and if other substitution patterns are tolerable. Side chain modification such as reduction to create an isopentyl side chain or incorporation of an amine functional group could be explored. Given the improved activity of the dihydrobenzofuran analogue **161** relative to the benzofuran analogue **160** it may be intriguing to prepare an indoline analogue for biological testing. Other heteroaromatic analogues could be targeted such as those that contain a benzothiophene or quinoline substructure.

Finally studies were performed on the ability of various "protecting" groups to undergo an EAS reaction during the cascade cyclization that leads to the schweinfurthin left half. It was found that functional groups that have difficulty in stabilizing a cation give products that have a bridged A-ring ether structure. As the ability of the "protecting" group to stabilize a cation is increased, the group is seen to undergo electrophilic aromatic substitution at the ortho position. As the ability of the "protecting" group to stabilize a cation is increased even further, substitution at the para-position and the A-ring alcohol is observed, which provides evidence that the reaction is not a concerted process and that the intermediate cation has a significant lifetime. Cationic stabilization can reach the point that substitution at the ortho position is no longer observed. The combined cascade reaction with electrophilic aromatic substitution may

provide a route to synthesize chemical structures that are difficult to access via other methods. Further study into tandem cascade reaction with electrophilic aromatic substitution by varying the solvent, Lewis acid, temperature, and substitution pattern may provide better insight into the scope of the reaction.

CHAPTER 8

EXPERIMENTAL PROCEDURES

General experimental conditions. Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone; methylene chloride, triethylamine, toluene, and diisopropyl amine were distilled from calcium hydride immediately before use. Butyl lithium solutions were purchased from a commercial source and their titer was determined by titration with diphenyl acetic acid before use. All other reagents and solvents were purchased from commercial sources and used without further purification. All reactions in anhydrous solvents were conducted in flame–dried glassware under a positive pressure of argon and with magnetic stirring. NMR spectra were obtained at 300 MHz for ^{1}H and 75 MHz for ^{13}C with $CDCl_3$ as solvent and $(CH_3)_4Si$ (^{1}H, 0.00 ppm) or $CDCl_3$ (^{13}C, 77.0 ppm) as internal standards unless otherwise noted. Chemical shifts for ^{31}P NMR were reported in ppm relative to 85% H_3PO_4 (external standard). High resolution mass spectra were obtained at the University of Iowa Mass Spectrometry Facility. Elemental analyses were performed by an outside facility. Silica gel (60 Å, 0.040–0.063 mm) was used for flash chromatography. Left–half aldehydes **42** and **43** both had over a 90% ee, as determined by HPLC.

Indole 46. To diethyl succinate (**47**, 7.64 mL, 45.6 mmol) and aldehyde **48** (3.10 g, 32.6 mmol) in THF (22 mL) at 0 °C was added NaH (2.74 g, 68.5 mmol, 60% dispersion in oil) in small batches and then the reaction mixture was allowed to warm to rt. The following day the reaction mixture was quenched by addition of H_2O, acidified, and extracted with EtOAc. The combined organic extracts were then extracted with 10% KOH. After the aqueous extracts were acidified and extracted with EtOAc, the combined

organic extracts were washed with brine, dried ($MgSO_4$), and filtered and the solvent was removed *in vacuo.* To the resulting crude brown solid (5.70 g) was added toluene (250 mL), Ac_2O (16.9 mL, 179 mmol) and glacial AcOH (1.76 mL, 30.7 mmol) and the resulting mixture was slowly heated to reflux while stirring. The following day the reaction mixture was allowed to cool to rt and quenched by addition of $NaHCO_3$ (sat) and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the solvent was removed *in vacuo*. The resulting solid was dissolved in EtOH (300 mL), K_2CO_3 was added (4.20 g, 30.4 mmol) and the resulting mixture was heated to reflux while stirring until the reaction was judged complete by TLC analysis. The reaction mixture was allowed to cool, filtered through celite, and then concentrated *in vacuo*. The resulting residue was partitioned between EtOAc and H_2O, acidified and extracted with EtOAc. The organic extracts were washed with $NaHCO_3$ (sat), brine, dried ($MgSO_4$), and filtered and the solvent was removed *in vacuo* to afford indole **46** (4.01 g, 60%) as light brown solid; ^{1}H NMR ($(CD_3)_2CO$) δ 10.5 (br s, 1H), 8.60 (br s, 1H), 7.76 (t, *J* = 1.2 Hz, 1H), 7.42 (dd, *J* = 3.2, 2.5 Hz, 1H), 7.18 (d, *J* = 1. 3 Hz, 1H), 6.67 (m, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 167.8, 150.9, 138.2, 127.2, 125.5, 122.8, 107.0, 104.5, 100.1, 60.9, 14.7. A small sample was further purified by column chromatography for elemental analysis (20% EtOAc in hexanes). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N 6.83. Found: C, 64.39; H, 5.49, N 6.66.

Preparation of indoles 49 and 50. Indole **46** (201 mg, 0.98 mmol) was added to a suspension of NaH (125 mg, 3.25 mmol, 60% dispersion in oil) in THF at 0 °C, followed by MOMCl, (0.2 mL, 2.63 mmol). After 40 min the reaction mixture was

quenched by addition of H_2O and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$), filtered, and then concentrated *in vacuo*. Final purification by flash column chromatography (25% to 50% Et_2O in hexanes) afforded indole **49** (128 mg, 45%) and **50** (107 mg, 33%). For **49**: ^{1}H NMR δ 7.94 (t, *J* = 0.9 Hz, 1H), 7.47 (d, *J* = 1.1 Hz, 1H), 7.25 (d, *J* = 3.3 Hz, 1H), 6.69 (dd, *J* =3.2, 0.8 Hz, 1H), 5.47 (s, 2H), 5.38 (s, 2H), 4.40 (q, *J* = 7.2 Hz, 2H), 3.55 (s, 3H), 3.25 (s, 3H), 1.44 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 167.3, 150.0, 137.1, 129.8, 125.4, 124.0, 106.8, 104.6, 100.2, 94.7, 77.4, 60.8, 56.2, 55.9, 14.4. Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; Found: C, 61.59; H, .6.62. For **50**: ^{1}H NMR δ 7.82 (d, *J* = 0.6 Hz, 1H), 7.25 (d, *J* = 3.3 Hz, 1H), 6.68 (dd, *J* = 3.3, 0.8 Hz, 1H), 5.46 (s, 2H), 5.28 (s, 2 H), 4.93 (s, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.66 (s, 3H), 3.39 (s, 3H), 3.22 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR δ 168.4, 150.0, 136.7, 130.1, 126.9, 124.6, 121.1, 109.1, 100.9, 99.5, 77.4, 65.7, 61.0, 58.0, 57.4, 56.0, 14.3. Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15; Found: C, 60.40; H, .7.00; N 4.00.

Alternate route to 49 and 50. To a stirring suspension of NaH (800 mg, 20 mmol, 60% dispersion in oil) in a 6:1 solution of THF and DMF (35 mL) at 0 °C was added indole **46** (1.612 g, 7.86 mmol) as a THF solution. Next MOMCl (1.5 mL, 20 mmol) was added dropwise and the reaction mixture was allowed to stir for 50 min. Following the workup procedure described above yielded **49** (1.82 g, 79%) and **50** (227 mg, 9%) whose NMR spectra were consistent with those obtained for material prepared via the alternate method.

Alcohol 51. To ester **49** (668 mg, 2.28 mmol) in THF at 0 °C was added $LiAlH_4$ (190 mg, 5.0 mmol) and the resulting mixture was allowed to stir for 2 hours. The

reaction mixture was then quenched by addition of H_2O, acidified, and extracted with Et_2O. The combined organic extracts were washed with water, dried ($MgSO_4$), and filtered, and then concentrated *in vacuo.* Final purification by flash column chromatography (50% EtOAc in hexanes) afforded alcohol **51** (0.566 mmol, 99%) as a while solid: ^{1}H NMR δ 7.17 (s, 1H), 7.09 (d, *J* = 3.3 Hz, 1H), 6.80 (d, *J* = 0.9 Hz, 1H), 6.63 (dd, *J* = 3.2, 0.7 Hz, 1H), 5.39 (s, 2H), 5.32 (s, 2 H), 4.75 (s, 2H), 3.53 (s, 3H), 3.22 (s, 3H), 2.02 (br s, 1H); ^{13}C NMR δ 150.7, 137.9, 136.6, 127.3, 119.9, 103.7, 102.8, 99.8, 94.7, 77.5, 66.1, 56.1, 55.8; HRMS (EI^+) calcd for $C_{13}H_{17}NO_4$ [M^+] 251.1158; found 251.1152.

Phosphonate 52. To alcohol **51** (12 mg, 0.048 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added Et_3N (0.05 mL, 0.38 mmol) and MsCl (0.02 mmol, 0.24 mmol) and the reaction was allowed to warm to rt. The following day the reaction was quenched by addition of NH_4Cl (sat) and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and then concentrated *in vacuo.* The resulting residue was dissolved in acetone (5 mL) at rt, LiBr, (33 mg, 0.38 mmol) was added, and the reaction mixture was allowed to stir overnight. The following day the reaction mixture was poured into Et_2O and quenched by addition of H_2O and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and then concentrated *in vacuo*. The resulting residue was dissolved in $P(OEt)_3$ (0.5 mL) and toluene (3mL) and the solution was heated to reflux overnight. The following day the solution was allowed to cool to rt, poured into Et_2O, and then quenched by addition of H_2O and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered and finally concentrated *in vacuo.* Final

purification by flash column chromatography (80% EtOAc in hexanes) afford phosphonate **52** (7 mg, 39% yield) as a oil: ^{1}H NMR δ 7.12 (d, *J* = 3.2 Hz, 1H), 7.07 (dd, *J* = 3.2 Hz, 1.0 Hz, 1H), 6.75 (dd, *J* = 1.7, 1.3 Hz, 1H), 6.61 (dd, *J* = 3.2 Hz, 0.7 Hz, 1H), 5.40 (s, 2H), 5.32 (s, 2H), 4.06 – 3.96 (m, 4H), 3.53 (s, 3H), 3.25 (d, J_{HP} = 21.3 Hz, 2H), 3.23 (s, 3H), 1.26 (td, *J* = 7.1, 0.3 Hz, 6H); ^{13}C NMR δ 150.4 (d, J_{CP} = 2.8 Hz) , 138.0 (d, J_{CP} = 3.0 Hz), 127.0 (d, J_{CP} = 1.2 Hz), 126.4 (d, J_{CP} = 9.2 Hz), 119.3 (d, J_{CP} = 2.9 Hz), 106.5 (d, J_{CP} = 5.9 Hz), 105.5 (d, J_{CP} = 7.7 Hz), 99.7 (d, J_{CP} = 1.5 Hz), 94.7, 77.4, 62.0 (d, J_{CP} = 6.6 Hz, 2C), 56.1, 55.8, 34.2 (d, J_{CP} = 138 Hz), 16.3 (d, J_{CP} 6.1 Hz, 2C); ^{31}P NMR 27.4; HRMS (EI^{+}) calcd for $C_{12}H_{26}NO_6P$ [M^{+}] 371.1498; found 371.1497.

Stilbene 53. To a suspension of NaH (45 mg, 1.13 mol, 60% dispersion in oil) in THF at 0 °C was added phosphonate **52** (37 mg, 0.10 mmol) as a THF solution followed by aldehyde **43**[45] (17.6 mg, 0.052 mmol) as a THF solution and the reaction was allowed to warm slowly warm to rt. The following day the reaction mixture was quenched by addition of H_2O and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and then concentrated *in vacuo*. Final purification by flash column chromatography (50% to 70% EtOAc in hexanes) afforded stilbene **53** (16 mg, 55%) as an oil: ^{1}H NMR δ 7.24 (s, 1H), 7.16 (d, *J* = 1.9 Hz, 1H), 7.43 (d, *J* = 3.2 Hz, 1H), 7.03 – 6.97 (m 4H), 6.62 (d, *J* = 3.2 Hz, 1H), 5.44 (s, 2H), 5.39 (s, 2H), 5.25 (d, *J* = 6.5 Hz, 1H), 5.21 (d, *J* = 6.6 Hz, 1H), 3.57, (s, 3H) 3.55 (s, 3H), 3.47 – 3.42 (m, 1H), 3.27 (s, 3H), 2.75 – 2.72 (m, 2H), 2.13 – 2.08 (m, 1H), 1.91 – 1.64 (m, 5H), 1.25 (s, 3H), 1.12 (s, 3H), 0.90 (s, 3H); ^{13}C NMR δ 150.8, 146.2, 143.6, 138.2, 133.5, 129.5, 127.7, 127.0,125.5, 123.1, 121.9, 120.1, 113.4, 102.9, 102.5, 100.0, 95.9, 94.8,

78.0, 77.6, 76.9, 56.2, 56.2, 55.9, 46.8, 38.4, 37.7, 28.3, 27.3, 23.2, 19.9, 14.3; HRMS (EI^+) calcd for $C_{32}H_{41}NO_7$ [M^+] 551.2883 found 551.2891.

Analogue 54. To trisMOM protected analogue **53** (16 mg, 0.029 mmol) in MeOH (3 mL) was added $TsOH \cdot H_2O$ (80 mg, 0.42 mmol) and was allowed to stir. The next day the solution was quenched by addition of NH_4Cl (sat) diluted with H_2O and extracted with EtOAc. The combined organics extracts were washed with H_2O, dried ($MgSO_4$), filtered and, concentrated *in vacuo*. Final purification by flash column chromatography (50% EtOAc in hexanes), afforded schweinfurthin analogue **54** (9 mg, 67%), as a yellow oil: ^1H NMR (CD_3OD) δ 7.16 (d, *J* = 3.3 Hz, 1H), 7.11 (m, 1H), 6.98 (d, *J* = 16.0 Hz, 1H), 6.91 (d, *J* = 16.4 Hz, 1H), 6.86 (d, *J* = 1.9 Hz, 1H), 6.77 (d, *J* = 1.8 Hz, 1H), 6.73 (d, *J* = 1.0 Hz, 1H), 6.55 (dd, *J* = 3.3, 0.7 Hz, 1H), 5.47 (s, 2H), 3.40 – 3.35 (m, 1H), 3.25 (s, 3H), 2.75 – 2.71 (m, 2H), 2.09 – 2.04 (m, 1H), 1.85 – 1.63 (m, 4H), 1.24 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 151.6, 147.0, 142.1, 140.1, 134.9, 131.4, 128.6, 128.4, 128.0, 124.0, 120.3, 120.2, 111.1, 103.3, 102.2, 100.5, 78.8, 78.3, 78.2, 56.0, ~49*, 39.5, 38.9, 29.0, 27.9, 24.0, 20.3, 14.8; HRMS (EI^+) calcd for $C_{28}H_{33}NO_5$ [M^+] 463.2359 found 463.2353. *Obscured by solvent.

Preparation of indole 55 and alcohol 56. To a suspension of phenol **46** (1.18 g, 5.74 mmol) in CH_2Cl_2 (100 mL) at rt was added DIPEA (4.0 mL, 23.0 mmol) and MOMCl (0.7 mL, 9.2 mmol), the flask was wrapped in foil, and the reaction mixture was allowed to stir overnight. The reaction was quenched by addition of H_2O and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and then concentrated *in vacuo*. Final purification by flash column chromatography (15% to 25% EtOAc in hexanes) afforded indole **55** (1.10 g, 77%) as a

light yellow solid: ^{1}H NMR δ 8.95 (br s, 1H), 7.89 (t, *J* = 1.0 Hz, 1H), 7.43 (d, *J* = 1.1 Hz, 1H), 7.26 (dd, *J* = 3.1, 2.5 Hz, 1H), 6.69 (m, 1H), 5.38 (s, 2H), 4.38 (q, *J*= 7.1 Hz, 2H), 3.54 (s, 3H), 1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 167.7, 149.9, 136.5, 126.4, 124.7, 123.0, 108.4, 103.8, 100.0, 94.7, 60.8, 56.2, 14.3. Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N 5.62. Found: C, 62.83; H, 6.12, N 5.42.

For alcohol **56:** ^{1}H NMR δ 7.86 (m, 1H), 7.36 (d, *J* = 1.1 Hz, 1H), 7.20 (d, *J* = 3.2 Hz, 1H), 6.61 (m, *J* = 3.9 Hz, 1H), 5.45 (s, 2H), 5.32 (s, 2H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.50 (s, 3H), 1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 167.9, 150.0, 136.4, 129.5, 124.9, 124.3, 106.8, 104.5, 100.3, 94.7, 69.8, 61.1, 56.3, 14.4.

Indole 57. To indole **55** (1.00 g, 4.01 mmol) in THF (20 mL) at 0 °C was added NaH (200 mg, 5 mmol, 60% dispersion in oil) and Boc_2O (960 mg, 4.40 mmol). An additional amount of THF was added (8 mL) and after 1 h the reaction mixture was quenched by addition of NH_4Cl (sat) and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered and finally the solvent was removed *in vacuo*. Final purification by flash column chromatography (12.5 to 15% Et_2O in hexanes) afforded indole **57** (1.23 g, 87%): ^{1}H NMR δ 8.54 (br s, 1H), 7.67 (d, *J* = 3.7 Hz, 1H), 7.57 (d, *J* = 1.2 Hz, 1H), 6.74 (dd, *J* = 3.7, 0.7 Hz, 1H), 5.36 (s, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.53 (s, 3H), 1.70 (s, 9H), 1.41 (t, *J* = 7.1 Hz, 3H) ^{13}C NMR 167.0, 149.8, 149.4, 135.7, 127.5, 127.4, 125.4, 111.6, 107.5, 104.2, 94.8, 84.4, 60.9, 56.3, 28.1 (3C), 14.4. Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64; N 4.01. Found: C, 62.00; H, 6.68, N 4.02.

Benzylic alcohol 58. To ester **57** (434 mg, 1.24 mmol) in THF (30 mL) at 0 °C was added DIBAL–H (4.1 mL, 1M in THF). When judged complete by TLC analysis,

the reaction was quenched by addition of NH_4Cl (sat), poured into EtOAc, acidified and then extracted with EtOAc. The combined organic extracts were washed with $NaHCO_3$ (sat), brine, dried ($MgSO_4$), and filtered, and then concentrated *in vacuo.* Final purification by flash column chromatography (25% EtOAc in hexanes) afforded alcohol **58** (345 mg, 91%) as a colorless oil: ^{1}H NMR δ 7.84 (s, 1H), 7.48 (d, *J* = 3.8 Hz, 1H), 6.93 (d, *J* = 0.9 Hz, 1H), 6.67 (dd, *J* = 3.8, 0.7 Hz, 1H), 5.30 (s, 2H), 4.75 (s, 2H), 3.51 (s, 3H), 2.16 (br s, 1H), 1.66 (s, 9H); ^{13}C 150.3, 149.7, 138.7, 136.6, 124.8, 121.0, 108.0, 106.3, 104.1, 94.7, 83.7, 66.0, 56.1, 28.1 (3C). Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N 4.56. Found: C, 62.30; H, 7.13, N 4.56.

Preparation of phosphonates 59 and 60. To LiBr (450 mg, 5.18 mmol) and Et_3N (0.43 mL, 3.09 mmol) in THF at 0 °C was added benzylic alcohol **58** (312 mg, 1.02 mmol) as a THF solution. The solution was stirred for 5 min and then MsCl (0.16 mL, 2.07 mmol) was added dropwise. The reaction mixture was allowed to stir for 1 h and more LiBr (400 mg, 4.61 mmol) was added. After the reaction was judged complete by TLC analysis it was quenched by addition of $NaHCO_3$ (sat), diluted with H_2O, and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered and then concentrated *in vacuo*. To the resulting residue was added $P(OEt)_3$ (4 mL) and the solution was allowed to reflux overnight. The next day the solution was allowed to cool to rt and then poured into water and extracted with EtOAc. The organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and then concentrated *in vacuo*. Final purification by flash column chromatography (50 to 70% EtOAc in hexanes) afforded indole phosphonate **60** (18 mg, 4%): ^{1}H NMR δ 7.78 (br s, 1H), 7.48 (d, *J* = 3.5 Hz, 1H), 6.88 (m, 1H), 6.66 (d, *J* = 3.7 Hz, 1H), 5.30 (s, 2H), 4.09 –

4.00 (m, 4H), 3.51 (s, 3H), 3.26 (d, J_{PH} = 21.6 Hz, 2H), 1.66, (s 9H), 1.27 (t, J = 7.1 Hz, 6H); ^{13}C NMR δ 150.0 (d, J_{CP} = 2.9 Hz), 149.6, 128.7 (d, J_{CP} = 9.5 Hz), 124.6, 120.3, 110.7 (d, J_{CP} = 7.9 Hz), 108.9 (d, J_{CP} = 5.7 Hz), 104.0 (d, J_{CP} =1.6 Hz), 94.7, 83.6, 62.0 (d, J_{CP} = 6.6 Hz, 2C), 56.3, 34.3 (d, J_{CP} = 138 Hz), 28.1 (3C), 16.3 (d, J_{CP} = 6.3 Hz, 2C); ^{31}P NMR δ 27.3; HRMS (EI$^+$) calcd for $C_{20}H_{30}NO_7P$ [M$^+$] 427.1760; found 429.1760.

The unprotected indole phosphonate **59** (194 mg, 58%) also was isolated from this reaction: ^{1}H NMR δ 9.61 (s, 1H), 7.05 (d, J = 2.9 Hz, 1H), 6.99 (t, J = 2.3 Hz, Hz, 1H), 6.66 (s 1H), 6.54, (t, J = 2.2 Hz, 1H), 5.29 (s, 2H), 4.44 – 3.96 (m, 4H), 3.50 (s, 3H), 3.21 (d, J_{PH} = 21.1, 2H), 1.24 (t, J = 7.0 Hz, 6H); ^{13}C NMR δ 150.2 (d, J_{CP} = 2.7 Hz), 137.7 (d, J_{CP} = 2.9 Hz), 124.8 (d, J_{CP} = 9.4 Hz), 123.5, 118.2 (d, J_{CP} = 2.7 Hz), 107.1 (d, J_{CP} = 7.4 Hz), 105.6 (d, J_{CP} = 5.8 Hz), 98.7, 94.7, 62.1 (d, J_{CP} = 6.8 Hz, 2C), 55.9, 33.9 (d, J_{CP} = 138 Hz), 16.2 (d, J_{CP} = 6.1 Hz, 2C); ^{31}P NMR δ 28.2; HRMS (EI$^+$) calcd for $C_{15}H_{22}NO_5P$ [M$^+$] 327.1236; found 327.1229.

Alternative route to phosphonate 60. To phosphonate **59** (194 mg, 0.593 mmol) in CH_2Cl_2 (10 mL) was added DMAP (8 mg, 0.065 mmol) and Boc_2O (150 mg, 0.687 mmol). The reaction was allowed to stir for 2 hours then checked by TLC. After an additional amount of Boc_2O (50 mg, 0.229 mmol) was added, the reaction was allowed to proceed for another hour. It was quenched by addition of H_2O, extracted with CH_2Cl_2, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (80% EtOAc in hexanes) afforded Boc protected indole **60** (183 mg, 72%) whose ^{1}H and ^{13}C NMR were consistent with data from material prepared via previous route.

Preparation of 60 at reduced temperature. To alcohol **58** (147 mg, 0.48 mmol) in THF (10 mL) was added LiBr (250 mg, 2.9 mmol) and Et_3N (0.2 mL, 1.4 mmol), the solution was cooled to 0 °C, and then the solution was allowed to stir. After 10 min, MsCl (0.08 mL, 2.07 mmol) was added dropwise and the reaction mixture was allowed to stir for 2 hours, then quenched by addition of NH_4Cl (sat), diluted with H_2O, and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), and filtered, and then concentrated *in vacuo*. To the resulting residue was added $P(OEt)_3$ and the resulting solution was heated to 95 °C and allowed to stir overnight. The next day the solution was allowed to cool to room temperature, and then concentrated *in vacuo*. Final purification by flash column chromatography (1.5% EtOH in Et_2O) afforded indole phosphonate **60** (125 mg, 61%) as an oil whose ^1H and ^{31}P NMR spectra were consistent with those via the previous route.

Stilbene 62. To NaH (40 mg, 1 mmol, 60% dispersion in oil) in THF (4 mL) was added phosphonate **59** (19.0 mg, 0.058 mmol) and anisaldehyde (**61**), (0.02 mL, 0.16 mmol) followed by 15-Crown-5 (2 drops). The solution was heated to reflux and after 1 hour it was allowed to cool to rt and quenched by addition of NH_4Cl (sat), then diluted with water, and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (25 % EtOAc in hexanes) afforded indole **62**(17 mg, 93%): ^1H NMR δ 8.15 (br s, 1H), 7.46, (d, J = 8.8 Hz, 2H), 7.15 (s, 1H), 7.13 (dd, J = 3.1, 2.4 Hz, 1H), 7.05 (s, 2H), 7.01 (d, J = 1.0 Hz, 1H), 6.90 (d, J = 8.8 Hz, 2H), 6.64 (m, 1H), 5.40 (s, 2H), 3.83 (s, 3H), 3.57 (s, 3H);. ^{13}C NMR δ 158.9, 150.8, 137.7,

133.2, 130.5, 127.8, 127.5 (2C), 126.5, 123.5, 119.1, 114.1 (2C), 104.1, 101.9, 100.2, 94.8, 56.2, 55.3; HRMS (EI^+) calcd for $C_{19}H_{19}NO_3$ [M^+] 309.1365; found 309.1361.

Alcohol 64. To indole **55** (805 mg, 3.23 mmol) in THF (30 mL) at 0 °C was added NaH (170 mg, 4.2 mmol, 60% dispersion in oil) followed after 10 min by TsCl (700 mg, 3.61 mmol). After 30 min DIBAL–H (1.45 mL, 8.1 mmol) was added, the reaction mixture was allowed to stir for an additional 30 min and then was quenched by addition of NH_4Cl (sat), poured into EtOAc, acidified, and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered and then concentrated *in vacuo.* Final purification by flash column chromatography (50% EtOAc in hexanes) afforded benzylic alcohol **64** (1.018 mg, 87% for 2 steps): ^{1}H NMR ($(CD_3)_2CO$) δ 7.84 (d, *J* = 8.3 Hz, 2H), 7.78 (s, 1H), 7.59 (d, *J* = 3.6 Hz, 1H), 7.22, (d, *J* =8.5 Hz, 2H), 6.99 (s, 1H), 6.81, (dd, *J* = 3.7, 0.7 Hz, 1H), 5.27 (s, 2H), 4.78 (s, 2H), 4.53 (br s, 1H), 3.41 (s, 3H), 2.23 (s, 3H); ^{13}C NMR δ 151.2, 146.0, 141.8, 136.9, 135.8, 130.7 (2C), 127.5 (2C), 126.0, 121.5, 107.2, 106.7, 105.9, 95.2, 65.0, 56.2, 21.3; HRMS (EI^+) calcd for $C_{18}H_{19}NO_5S$ [M^+] 361.0984; found 361.0992.

Phosphonate 65. To alcohol **64** (118 mg, 0.33 mmol) in THF (10 mL) at 0 °C was added LiBr (226 mg 2.62 mmol) and Et_3N (0.18 mL, 1.30 mmol). The reaction was allowed to stir for 5 min and then MsCl (0.06 mL, 0.78 mmol) was added dropwise. The reaction was allowed to warm to rt and after 3 hours, it was quenched by addition of $NaHCO_3$ (sat) and extracted with EtOAc. The organic extracts were washed with brine, dried ($MgSO_4$), and filtered and then concentrated in vacuo. The resulting residue was dissolved in $P(OEt)_3$ (3 mL) and heated to reflux. The next day the reaction was allowed to cool to rt, poured into water, and extracted with EtOAc. The organic extracts were

washed with brine, dried (Mg SO_4), and filtered and then concentrated *in vacuo*. Final purification by flash column chromatography (2.5 to 3% EtOH in Et_2O) afforded indole phosphonate **65** (133 mg, 85%) as a white solid: ^{1}H NMR δ 7.78 (d, J = 8.3 Hz, 2H), 7.62 (d, J = 2.8 Hz, 1H), 7.44 (dd, J = 3.7 , 0.9 Hz , 1H), 7.22, (d, J = 8.0 Hz, 2H), 6.86 (m, 1H), 6.73 (d, J = 3.7 Hz, 1H), 5.25 (s, 2H), 4.05 – 3.95 (m, 4H), 3.47 (s, 3H), 3.25 (d, J_{PH} = 21.5, 2H), 2.33 (s, 3H), 1.24 (t, J = 7.1 Hz, 6H); ^{13}C NMR δ 150.2 (d, J_{CP} = 2.9 Hz), 144.8, 136.1 (d, J_{CP} = 3.1 Hz), 135.1, 129.7 (2C), 129.3 (d, J_{CP} = 9.2 Hz), 126.8 (2C), 125.0 (d, J_{CP} = 1.4 Hz), 120.6 (d, J_{CP} = 3.1 Hz), 109.3 (d, J_{CP} = 6.0 Hz), 108.6 (d, J_{CP} = 7.5 Hz), 105.8 (d, J_{CP} = 1.5 Hz), 94.6, 62.0 (d, J_{CP} = 6.7 Hz, 2C), 56.2, 34.2 (d, J_{CP} = 138.1 Hz), 21.5, 16.3 (d, J_{CP} = 6.1 Hz, 2C); ^{31}P NMR δ 27.3; HRMS (EI^+) calcd for $C_{22}H_{28}NO_7PS$ [M^+] 481.1324; found 481.1315.

Preparation of analogues 66 and 67. To phosphonate **65** (40 mg, 0.83 mmol) and aldehyde **43**[45] (18 mg, 0.54 mmol) in THF (3 mL) at rt was added NaH (60 mg, 1.5 mmol, 60% dispersion in oil) and 15-Crown-5 (3 drops) and was the resulting solution heated to reflux. After 30 min the reaction mixture was allowed to cool to rt and quenched by addition of NH_4Cl (sat), diluted with H_2O and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and then concentrated *in vacuo*. Final purification by flash column chromatography (20% to 40% EtOAc in hexanes) afforded analogue **66A** (24 mg, 67%) as well as analogue **67** (5 mg, 22%). For **66A**: ^{1}H NMR δ 8.24 (br s, 1H), 7.82 (d J = 8.3 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H) 7.14 – 7.11 (m, 3H), 6.98 – 6.92 (m, 4H) 6.63 (m, 1H), 5.38 (s, 2H), 5.23 (d, J = 6.6 Hz, 1H), 5.19 (d, J = 6.6 Hz, 1H), 4.33 (dd, J = 10.6, 4.8 Hz, 1H), 3.57 (s, 3H), 3.53 (s 3H), 2.69 – 2.66 (m, 2H), 2.45 (s, 3H), 2.10 – 2.04 (m, 1H), 1.82 – 1.60 (m, 4H), 1.22 (s,

3H), 0.91 (s, 3H). 0.90 (s, 3H); ^{13}C NMR δ 150.8, 146.1, 144.7, 143.3, 137.7, 134.3, 133.1, 129.8 (3C) 127.9, 127.7 (2C), 126.5, 123.5, 122.6, 121.7, 119.1, 113.4, 104.1, 101.9, 100.1, 95.9, 94.8, 88.4, 76.0, 56.2, 56.2, 47.0, 38.2, 37.4, 27.0, 25.8, 23.1, 21.6, 19.8, 15.1; HRMS $(M+H)^+$ calcd for $C_{37}H_{44}NO_8S$ $[M^+]$ 662.2788; found 662.2797.

For **67**: ^{1}H NMR δ 8.30 (br s, 1H), 7.15 – 7.11 (m, 3H), 7.05 – 6.92 (m, 4H), 6.64 (m, 1H), 5.39 (s, 2H), 5.24 (d, *J* = 6.4 Hz, 1H), 5.20 (d, *J* = 6.5 Hz, 1H), 3.57 (s, 3H), 3.35 (s, 3H), 3.43 (dd, *J* = 11.5, 3.8 Hz, 1H), 2.75 – 2.71 (m, 2H), 2.11 – 2.04 (m, 1H), 1.90 – 1.54 (m, 5H), 1.25 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 150.8, 146.1, 143.6, 137.7, 133.2, 129.6, 127.8, 126.7, 123.5, 123.2, 121.9, 119.1, 113.5, 104.1, 102.0, 100.1, 96.0, 94.8, 78.0, 76.9. 56.2, 56.2, 46.8, 38.4, 37.7, 28.3, 27.3, 23.2, 19.9, 14.2; HRMS (EI^+) calcd for $C_{30}H_{37}NO_6$ $[M^+]$ 507.2621; found 507.2620.

Alternative preparation of analogue 66A. To phosphonate **65** (35 mg, 0.073 mmol) and aldehyde **43** (14.5 mg, 0.043 mmol) in THF at rt was added NaH (40 mg, 1.0 mmol, 60% dispersion in oil) and 15-Crown-5 (2 drops) and the resulting mixture was allowed to stir overnight. The following day the reaction mixture was allowed to warm to rt and quenched by addition of NH_4Cl (sat), diluted with H_2O, and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and then concentrated *in vacuo*. Final purification by flash column chromatography (20% to 50% EtOAc in hexanes) afforded analogue **66A** (18.4 mg, 64%) as an oil whose ^{1}H and ^{13}C NMR matched those obtained from material prepared by the alternative route.

Analogue 68. To Mg turnings (20 mg) and NH_4Cl (20 mg) in anhydrous MeOH was added protected analogue **66A** (13.8 mg, 0.021 mmol). The reaction was allowed to stir for 1 hour, then poured into NH_4Cl (sat), and extracted with EtOAc. The combined

organic layers were dried ($MgSO_4$) and filtered, and the filtrated was concentrated *in vacuo*. Final purification by preparative TLC gave indole **68** (3.7 mg, 35%): ^{1}H NMR δ 8.07 (br s, 1H), 7.09 (dd, *J* = 3.1, 2.4 Hz, 1H). 6.90, (s, 1H), 6.78 (d, *J* = 1.9 Hz, 1H), 6.66–6.61 (m, 3H), 5.33 (s, 2H), 5.15 (d, *J* = 6.5 Hz, 1H), 5.11 (d, *J* = 6.5 Hz, 1H), 3.55 (s, 3H), 3.49 (s, 3H), 3.47 – 3.40 (m, 1H), 2.98 – 2.92 (m, 2H), 2.87 – 2.80 (m, 2H) 2.70 – 2.67 (m, 2H), 2.11 – 2.05 (m, 1H), 1.89 – 1.62 (m, 5H), 1.23 (s, 3H), 1.09 (s, 3H), 0.87 (s, 3H).

Alternative route to compound 67. To the protected analogue **66A** (19.0 mg, 0.03 mmol) in THF (3 mL) at 0 °C was added $LiAlH_4$ (14 mg, 0.40 mmol) and the reaction mixture was allowed to warm to rt overnight. The following morning the reaction was quenched by addition of NH_4Cl (sat), diluted with water, and extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Final purification by preparative TLC (70% EtOAc in hexanes) afforded the desired deprotected indole **67** (4.4 mg, 30%) along with recovered starting material (2.7 mg, 14%). The ^{1}H NMR spectra was consistent with that prepared via the alternative route.

Analogue 40. To a MeOH solution of protected indole **67** (6mg, 0.012 mmol) at 0 °C was added TsOH (25 mg, 0.145 mmol) and the reaction was allowed to stir overnight. The reaction was quenched by addition of water, and extracted with EtOAc. The combined organic extracts were dried (Mg_2SO_4), filtered, and concentrated *in vacuo*. Final purification by preparative TLC (70% EtOAc in hexanes) afforded schweinfurthin analog **40** (2.9 mg, 58%):^{1}H NMR (CD_3OD) δ 7.09 (d, *J* = 3.3 Hz, 1H), 7.00 (s, 1H), 6.95 (d, *J* = 16.2 Hz, 1H), 6.87 (d, *J* = 16.2 Hz, 1H), 6.84 (d, *J* = 1.6 Hz, 1H), 6.75 (d, *J* = 1.6

Hz, 1H), 6.66, (d, *J* = 1.0 Hz, 1H), 6.50 (dd, *J* = 3.2, 0.9 Hz, 1H), 3.43 (dd, *J* = 11.5. 3.8 Hz, 1H), 2.74 – 2.71 (m, 2H), 2.09 – 2.04 (m, 1H), 1.83 – 1.63 (m, 4H), 1.24 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 151.2, 147.0, 141.9, 139.8, 133.9, 131.5, 128.9, 127.2, 124.4, 124.0, 120.2, 119.3, 111.0, 103.8, 101.8, 99.7, 78.8, 78.2, 39.5, 38.9, 29.0, 27.9, 24.0, 20.3, 14.9; HRMS (EI$^+$) calcd for $C_{26}H_{29}NO_4$ [M$^+$] 419.2097; found 419.2096.

Analogue 69. To aldehyde **42**[42, 45] (63 mg, 0.21 mmol) and phosphonate **65** (156 mg, 0.323) in THF (5 mL) at rt was added NaH (80 mg, 2.0 mmol, 60% dispersion in oil) and 15-Crown-5 (3 drops). The reaction mixture was slowly heated to reflux for 40 min and then allowed to cool to room temperature. The reaction was quenched by addition of $NaHCO_3$ (sat), diluted with H_2O, and extracted with EtOAc. The combined organics extracts were washed with brine, dried ($MgSO_4$), and filtered, and then concentrated *in vacuo*. Final purification by flash column chromatography (30% EtOAc in hexanes) afforded tosyl protected alcohol **69** (73 mg, 56%): ^{1}H NMR δ 8.25 (br s, 1H), 7.82 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.14 (s, 1H), 7.12 (dd, *J* = 3.2, 2.4, 1H), 7.03 (d, *J* = 16.2 Hz, 1H), 6.99 (d, *J* = 1.1 Hz, 1H), 6.95 (d, *J* = 16.3 Hz, 1H), 6.90 (d, *J* = 1.8 Hz, 1H), 6.83 (d, *J* = 1.6 Hz, 1H), 6.63 (m, 1H), 5.39 (s, 2H), 4.32 (m 1H), 3.89 (s, 3H) 3.57 (s, 3H), 2.70–2.66 (m, 2H), 2.45 (s, 3H) 2.12 – 2.10 (m, 1H), 2.01 – 1.95 (m, 1H), 1.81 – 1.67 (m, 3H), 1.23 (s, 3H), 0.91 (m, 6H); ^{13}C δ 150.8, 148.9, 144.6, 142.0, 137.7, 134.3, 133.1, 129.8 (2C), 129.6, 127.8, 127.7 (2C), 126.8, 123.6, 122.0, 120.1, 119.2, 107.0, 104.0, 102.0, 100.1, 94.8, 88.5, 76.0, 56.2, 56.0, 47.0, 38.2, 37.3, 27.1, 25.7, 23.1, 21.6, 19.7, 15.1; HRMS (EI$^+$) calcd for $C_{36}H_{42}NO_7S$ [M$^+$H] 632.2682; found 632.2684.

Analogue 70. To tosyl protected alcohol **69** (73 mg, 0.116 mmol) in THF (3 mL) was added $LiAlH_4$ (45 mg, 1.18 mmol) and the reaction mixture was allowed to stir

overnight. The reaction mixture was then quenched by addition of NH_4Cl (sat), and extracted with Et_2O. The combined organics layers were washed with brine, dried ($MgSO_4$), and filtered and then concentrated *in vacuo*. Final purification by flash column chromatography (30 to 50% EtOAc in hexanes) yielded deprotected alcohol **70** (24 mg, 43%): ^{1}H NMR δ 8.25 (br s, 1H), 7.15 (s, 1H), 7.12 (dd, *J* = 3.1, 2.5 Hz, 1H), 7.04 (d, *J* = 16.2 Hz, 1H), 7.00 (s, 1H), 6.97 (d, *J* = 16.2 Hz, 1H), 6.91 (d, *J* = 2.3 Hz, 1H), 6.88 (d, *J* = 2.3 Hz), 6.63 (m, 1H), 5.39 (s, 2H), 3.90 (s, 3H), 3.58 (s, 3H), 3.45 – 3.40 (m, 1H), 2.74 – 2.71 (m, 2H), 2.15 – 2.10 (m, 1H), 1.90 – 1.80 (m, 2H), 1.74 – 1.50 (m, 3H), 1.26 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 150.8, 148.9, 142.3, 137.7, 133.2, 129.4, 127.6, 127.0, 123.5, 122.6, 120.2, 119.1, 106.9, 104.0, 102.0, 100.1, 94.8, 78.0, 77.0, 56.2, 56.0, 46.8, 38.4, 37.7, 28.3, 27.3, 23.2, 19.9, 14.3; HRMS (EI^+) calcd for $C_{29}H_{35}NO_5$ [M^+] 477.2515; found 477.2512.

Alternative preparation of compound 69. To phosphonate **65** (65 mg, 0.14 mmol) and aldehyde **42** (33 mg, 0.11 mmol) in THF (2 mL) at 0 °C was added NaH (50 mg, 1.25 mmol, 60% dispersion oil) and 15-Crown-5 (3 drops), and the reaction mixture was allowed to stir and monitored by TLC. When all the aldehyde was consumed by TLC analysis the reaction mixture was quenched by addition of NH_4Cl (sat), diluted with water, and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered and the solvent was removed *in vacuo*. Purification by flash column chromatography (20% to 50% EtOAc in hexanes) afforded a mixture of A-ring tosylate products **69** and **71** (29 mg) and a mixture of free hydroxyl products **70** and **72** (37mg). The mixed A-ring tosylate products were dissolved in a 1:1 mixture of THF and *i*-PrOH (4 mL), NaH (120 mg, 3 mmol, 60% dispersion oil) was added, and the reaction

solution was allowed to stir overnight. The next day the reaction mixture was quenched by addition of H_2O and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (20% EtOAc in hexanes) afforded stilbene **69** (12 mg. 18%) as an oil whose NMR spectrum was consistent with that of material prepared via the alternative route.

Alternative preparation of analogue 70. To the mixed A-ring hydroxyl products **70** and **72** (37 mg) dissolved in 1:1 THF and 2-propanol (4 mL) was added NaH (160 mg, 4 mmol, 60% dispersion oil), and the reaction solution was allowed to stir overnight. The next day the reaction mixture was quenched by addition of water and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (50% EtOAc in hexanes) afforded to deprotected indole **70** (11mg, 21%) as an oil, whose NMR spectrum was consistent with that from material prepared via the alternative route.

Analogue 41. To MOM protected indole **70** (16.0 mg, 0.033 mmol) in MeOH (3 mL) and wrapped in foil was added HCL (0.15 mL, 6M). The reaction was stirred in a warm water bath for 8.5 hours, quenched by dropwise addition of $NaHCO_3$ (sat), and then extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered through basic alumina, and then concentrated *in vacuo*. Final purification by preparative TLC (70% EtOAc in hexanes) afford unprotected indole **41** (9 mg, 62%); ^{1}H NMR δ 8.2 (br s, 1H), 7.13 (dd, J = 3.1, 2.5 Hz, 1H), 7.07 (s, 1H), 7.00 (d, J = 16.2 Hz, 1H), 6.94 (d, J = 16.4 Hz, 1H), 6.90 (d, J = 1.8 Hz, 1H), 6.85 (d, J = 1.7 Hz,

1H), 6.77 (d, *J* = 0.9 Hz, 1H), 6.59 – 6.57 (m, 1H), 5.22 (br s, 1H), 3.90 (s, 3H), 3.43 (dd, *J* = 11.5, 3.7 Hz, 1H), 2.75 – 2.72 (m, 2H), 2.16 – 2.10 (m, 1H), 1.90 – 1.80 (m, 2H), 1.75 – 1.60 (m, 3H), 1.26 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); ^{13}C δ 149.0, 148.9, 142.4, 138.0, 133.4, 129.4, 127.3, 127.2, 123.5, 122.7, 120.4, 117.4, 106.9, 103.1, 102.1, 99.2, 78.1, 77.0, 56.0, 46.8, 38.4, 37.6, 28.3, 27.4, 23.2, 19.9, 14.3; HRMS (EI^+) calcd for $C_{27}H_{31}NO_4$ [M^+] 433.2253; found 433.2245.

Gernaylated indole 83. To indole **55** (1.11 g, 4.44 mmol), TBAI (820 mg, 2.22 mmol), and $Zn(OTf)_2$ (968 mg, 2.66 mmol) in toluene (15 mL) at rt was added DIPEA (0.86 mL, 4.88 mmol) and the reaction mixture was allowed to stir for 15 min. Geranyl bromide (481 mg, 2.22 mmol) was added dropwise, the reaction was allowed to proceed for 3 hours and then quenched by addition of NH_4Cl (sat) and extracted with Et_2O. The combined organic layers were washed with H_2O, dried (Na_2SO_4), concentrated, and purified by column chromatography (17.5% to 20% EtOAc in hexanes) to afford geranylated indole **83** (524 mg, 62%) as a colorless oil along with recovered starting material **55** (553 mg): ^{1}H NMR δ 8.72 (br s, 1H), 7.81 (d, *J* = 0.9 Hz, 1H), 7.35 (d, *J* = 0.9 Hz, 1H), 6.96 (m, 1H), 5.49 (m, 1H), 5.35 (s, 2H), 5.12 (m, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.67 (d, *J* = 7.1 Hz, 2H), 3.53 (s, 3H), 2.16 – 2.03 (m, 4H), 1.72 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H) 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR 167.7, 151.3, 137.3, 135.1, 131.2, 124.3, 124.3, 123.9, 123.5, 121.2, 116.4, 108.3, 102.6, 94.1, 60.7, 56.1, 39.6, 26.6, 25.6, 25.2, 17.6, 15.9, 14.3. Anal. Calcd for $C_{23}H_{31}NO_4$: C, 71.66; H, 8.11; N 3.63. Found: C, 71.43; H, 8.19, N 3.77.

Alcohol 85. To indole **83** (397 mmol, 1.04 mmol) in THF at 0 °C was added NaH (55 mg, 1.38 mmol, 60% dispersion in oil) and the solution was allowed to stir for 10

min. Tosyl chloride (235 mg, 1.23 mmol) was added and the solution was allowed to warm to rt. When the reaction was judged complete by TLC analysis for compound **84** the reaction mixture was cooled to 0 °C, then DIBAL–H (0.54 mL, 2.63 mmol) was added. After 30 min the solution was quenched by addition of NH_4Cl (sat), poured into EtOAc, acidified, and extracted with EtOAc. The combined organic extracts were washed with Na_2CO_3 (sat), brine, dried ($MgSO_4$), and filtered, and then concentrated *in vacuo*. Final purification by flash column chromatography (35% EtOAc in hexanes) afforded benzylic alcohol **85** (366 mg, 71%) as an oil: ^{1}H NMR δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.61 (s, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.13 (s, 1H), 6.86 (s, 1H), 5.41 (m, 1H), 5.22 (s, 2H), 5.12 (m, 1H), 4.71 (s, 2H), 3.53 (d, *J* = 7.0 Hz, 2H), 3.47 (s, 3H), 2.29, (m, 4H), 2.14 – 2.05 (m, 4H), 1.68 (m, 6H), 1.61 (s, 3H); ^{13}C δ 151.9, 144.6, 139.1, 137.1, 136.6, 135.3, 131.5, 129.7 (2C), 126.6 (2C), 124.1, 122.7, 121.9, 121.7, 120.3, 106.0, 105.8, 94.2, 65.5, 56.1, 39.6, 26.6, 25.6, 25.5, 21.4, 17.6, 16.1. Anal. Calcd for $C_{28}H_{35}NO_5S$: C, 67.58; H, 7.09; N 2.81. Found: C, 67.81; H, 7.19, N 2.83.

Phosphonate 86. To alcohol **85** (366 mg, 0.74 mmol) in THF (20 mL) was added LiBr (510 mg 5.87 mmol) and Et_3N (0.41 mL, 2.94 mmol) and the solution was cooled to 0 °C. After 20 min, MsCl (0.14 mL, 1.8 mmol) was added dropwise. The reaction was allowed to stir and slowly warm to rt. When complete by TLC analysis it was quenched by addition of saturated $NaHCO_3$ and extracted with Et_2O. The organic layers were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. The resulting residue was dissolved in DMF (3 mL) and $P(OEt)_3$ (0.4 mL) was added and the solution was heated at reflux overnight. The next day the solution was allowed to cool to room temperature, then poured into water, and extracted with EtOAc.

The organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification by flash column chromatography (2.5% EtOH in Et_2O) afforded phosphonate **86** (320 mg, 70%) as a light yellow oil: ^{1}H NMR δ 7.74 (d, J = 8.3 Hz, 2H), 7.59 (m, 1H), 7.20 (d, J = 8.4 Hz, 2H), 7.09, (d, J = 1.1 Hz, 1H), 6.81 (m, 1H), 5.41 (m, 1H), 5.23 (s, 2H), 5.13 (m, 1H), 4.06 – 3.95 (m, 4H), 3.52 (d, J = 7.2 Hz, 2H), 3.47 (s, 3H), 3.22 (d, J_{PH} = 21.5 Hz, 2H), 2.32 (s, 3H), 2.14 – 2.07 (m, 4H), 1.70 (s, 3H), 1.68 (s, 3H), 1.62 (s, 3H) 1.25 (t, J = 7.1 Hz, 6H); ^{13}C NMR δ 151.6 (d, J_{CP} = 2.8 Hz,) 144.4, 137.1 (d, J_{CP} = 2.9 Hz), 136.5, 135.3, 131.4, 129.6 (2C), 129.2 (d, J_{CP} = 9.3 Hz), 126.7 (2C), 124.0, 122.7 (d, J_{CP} = 1.6 Hz), 121.7, 121.6, 119.7 (d, J_{CP} = 3.2 Hz), 108.9 (d, J_{CP} = 5.6 Hz), 108.7 (d, J_{CP} = 7.7 Hz), 94.3, 61.9 (d, J_{CP} = 6.7 Hz, 2C), 56.0, 39.5, 34.1 (d, J_{CP} = 138.1 Hz), 26.5, 25.5, 25.4, 21.3, 17.5, 16.2 (d, J_{CP} = 6.0 Hz, 2C), 15.9; ^{31}P δ 26.9; HRMS (EI^+) calcd for $C_{32}H_{44}NO_7PS$ [M^+] 617.2576; found 617.2562.

Analogue 87. To phosphonate **86** (84 mg, 0.14 mmol) and aldehyde **42** (32 mg, 0.10 mmol) in THF (5mL) at rt was added NaH (60 mg, 1.50 mmol, 60% dispersion in oil) followed by 15-Crown-5 (3 drops). The reaction mixture was allowed to stir for 90 min, then quenched by addition of Na_2CO_3 (sat), and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and then concentrated *in vacuo*. Final purification by flash column chromatography (35% to 40% EtOAc in hexanes) afforded analogue **87** (53%, 43 mg): ^{1}H NMR δ 7.75 – 7.73 (m, 3H), 7.21 (d, J = 8.0 Hz, 2H), 7.11 (s, 1H), 7.04 – 7.02 (m 3H), 6.93 (m 1H), 6.91 (m, 1H), 5.44 – 5.40 (m, 1H), 5.28, (s, 2H), 5.15 – 5.11 (m, 1H), 3.93 (s, 3H), 3.53 – 3.51 (m, 2H), 3.51 (s, 3H), 3.46 – 3.42 (m, 1H), 2.75 – 2.73 (m, 2H), 2.33 (s, 3H), 2.17 – 2.08 (m, 5H), 1.92 – 1.60 (m, 5H), 1.70 (s, 3H), 1.69 (s, 3H), 1.62 (s, 3H), 1.27 (s, 3H), 1.12 (s, 3H),

0.91 (s, 3H); ^{13}C NMR δ 152.0, 149.0, 144.6, 142.7, 137.5, 136.7, 135.7, 135.3, 131.5, 129.7 (2C), 128.9, 128.5, 126.7, 126.7 (2C), 124.1, 123.1, 122.6, 122.1, 121.7, 120.5, 120.3, 106.9, 105.9, 104.8, 94.3, 78.0, 77.0, 56.2, 56.0, 46.8, 39.7, 38.4, 37.7, 28.3, 27.3, 26.6, 25.7, 25.6, 23.1, 21.5, 19.8, 17.7, 16.1, 14.2; HRMS (EI$^+$) calcd for $C_{46}H_{57}NO_7S$ [M^+] 767.3856; found 767.3853.

Analogue 88. To schweinfurthin analogue **87** (43 mg, 0.056 mmol) in THF (5 mL) at 0 °C was added $LiAlH_4$ (45 mg, 1.06 mmol) and then the mixture was allowed to warm to rt. The following day, the reaction mixture was quenched by addition of NH_4Cl (sat), poured into H_2O, and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried ($MgSO_4$), and filtered and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (30 to 40% EtOAc in hexanes) afforded indole **88** (27 mg, 78%) as a light yellow oil: ^{1}H NMR δ 7.92 (br s, 1H), 7.07 (m, 1H), 7.02 (d, *J* = 16.2 Hz, 1H), 6.95 (d, *J* = 16.3 Hz, 1H), 6.92, (d, *J* = 0.7 Hz, 1H), 6.90 (d, *J* = 1.7 Hz, 1H), 6.87 (d, *J* = 1.4 Hz, 1H), 6.80 (m, 1H), 5.50 (m, 1H), 5.36 (s, 2H), 5.13 (m, 1H), 3.90 (s, 3H), 3.64 (d, *J* = 7.3 Hz, 2H) 3.57 (s, 3H), 3.41 (m, 1H), 2.74 – 2.71 (m, 2H), 2.11 – 2.04, (m, 6H), 1.89 – 1.84 (m, 2H), 1.72 (d, *J* = 0.6 Hz, 3H), 1.72 – 1.57 (m, 2H), 1.69 (d, *J* = 0.8 Hz, 3H), 1.60 (s, 3H), 1.26 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); ^{13}C NMR 152.2, 148.9, 142.3, 138.6, 135.0, 133.0, 131.3, 129.4, 127.6, 126.7, 124.4, 123.8, 122.6, 121.0, 120.2, 117.6, 116.7, 106.9, 103.8, 100.9, 94.3, 78.1, 77.0, 56.0, 56.0, 46.8, 39.8, 38.4, 37.7, 28.3, 27.3, 26.7, 25.7, 25.5, 23.2, 19.8, 17.7, 16.0, 14.3; HRMS (EI$^+$) calcd for $C_{39}H_{51}NO_5$ [M^+] 613.3763; found 613.3754.

Analogue 80. To protected schweinfurthin analogue **88** (21 mg, 0.034 mmol) in MeOH (2 mL) was added TsOH (40 mg, 0.21 mmol) in two proportions 3 hours apart the

solution and was allowed to stir. The next day the solution was quenched by addition of $NaHCO_3$ (sat), diluted with H_2O and extracted with EtOAc. The combined organics extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (50% EtOAc in hexanes) afforded schweinfurthin analogue **80** (7 mg, 36%) as a light yellow oil: ^{1}H NMR (CD_3OD) δ 6.96 – 6.93 (m, 3H), 6.92 (m, 1H), 6.85 (m, 1H), 6.73 (d, *J* = 0.9 Hz, 1H), 6.61 (m, 1H), 5.54 – 5.49 (m, 1H), 5.16 – 5.11 (m, 1H), 3.61 (d, *J* = 7.1 Hz, 2H), 3.38 – 3.33 (m, 1H), 3.31* (m, 2H), 3.25 (s, 3H), 2.74 – 2.71 (m, 2H), 2.15 – 2.01 (m, 5H), 1.83 – 1.59 (m, 4H), 1.72 (s, 3H), 1.68 (s, 3H), 1.61 (s, 3H), 1.22 (s, 3H), 1.09 (s, 3H), 0.87 (s, 3H); ^{13}C NMR δ 153.2, 150.1, 143.2, 140.7, 135.4, 133.6, 132.1, 131.4, 129.2, 126.9, 125.8, 125.6, 124.0, 121.8, 121.4, 118.0, 116.6, 108.0, 103.8, 101.4, 78.7, 77.1, 56.4, ~49*, 40.9, 39.5, 38.5, 38.9, 29.0, 27.9, 27.7, 26.4, 26.0, 24.1, 20.2, 17.8, 16.1, 14.9; HRMS (EI^+) calcd for $C_{37}H_{47}NO_4$ [M^+] 569.3505 found 569.3504. *Obscured by solvent

Synthesis of 89. To indole **55** (1.00 g, 4.01 mmol), TBAI (739 mg, 2.00 mmol), and $Zn(OTf)_2$ (878 mg, 2.41 mmol) in a 9:2 mixture of toluene and CH_2Cl_2 (22 mL) at rt was added DIPEA (0.77 mL, 4.41 mmol) and the reaction mixture was allowed to stir for 10 min. Prenyl bromide (298 mg, 2.00 mmol) was added dropwise. After 3 hours the reaction mixture was quenched by addition of NH_4Cl (sat) and extracted with EtOAc. The combined organic extracts were washed with H_2O, dried ($MgSO_4$), and filtered, and the filtrate concentrated *in vacuo*. Final purification by flash column chromatography (10% to 15% EtOAc in hexanes) afforded prenylated indole **89** (415 mg 65%) along with recovered starting material **55** (540 mg): ^{1}H NMR δ 8.47 (br s, 1H), 7.79 (d, *J* = 1.2 Hz,

1H), 7.34 (d, *J* = 1.1 Hz, 1H), 6.96 (m, 1H), 5.46 (m, 1H), 5.35 (s, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.65 (d, *J* = 6.6 Hz, 2H), 3.53 (s, 3H) 1.74 (d, *J* = 1.0 Hz, 3H), 1.72 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C δ 167.6, 151.4, 137.4, 131.5, 124.6, 123.8, 123.7, 121.3, 116.7, 108.2, 102.8, 94.2, 60.7, 56.2, 25.7, 25.4, 17.7, 14.4; HRMS (EI^+) calcd for $C_{18}H_{23}NO_4$ [M^+] 317.1627; found 317.1631.

Alcohol 90. To indole **89** (315 mmol, 0.99 mmol) in THF at 0 °C was added NaH (50 mg, 1.25 mmol, 60% dispersion oil) and the reaction mixture was allowed to stir for 10 min. After TsCl (230 mg, 1.21 mmol) was added, the solution was stirred for 30 min and DIBAL–H (0.71 mL, 4.0 mmol) was added dropwise. After an additional 30 min the reaction was quenched with NH_4Cl (sat) acidified with HCl, and extracted with EtOAc. The combined organic extracts were washed with Na_2CO_3 (sat), brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Purification by flash column chromatography (34% EtOAc in hexanes) afforded benzylic alcohol **90** (348 mg, 82%): ^{1}H NMR δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.60 (s, 1H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.13 (m, 1H), 6.85 (d, *J* = 0.6 Hz, 1H), 5.41 – 5.39 (m, 1H), 5.22 (s, 2H), 4.71 (s, 2H), 3.51 (d, *J* = 7.1 Hz, 2H) 3.46 (s, 3H) 2.37 (br s, 1H), 2.30 (s, 3H), 1.76 (d, *J* = 0.8 Hz, 3H), 1.68 (s, 3H); ^{13}C NMR δ 151.8, 144.6, 139.1, 137.0, 135.2, 132.9, 129.7 (2C), 126.6 (2C), 122.7, 121.9, 121.8, 120.2, 105.9, 105.7, 94.1, 65.5, 56.1, 25.7, 25.6, 21.4, 17.7; HRMS (EI^+) calcd for $C_{23}H_{27}NO_5S$ [M^+] 429.1610; found 429.1609.

Indole phosphonate 91. To alcohol **90** (332 mg) in THF (15 mL) at 0 °C was added LiBr (537 mg, 6.18 mmol) and Et_3N (0.43 mL, 3.09 mmol). The solution was stirred for 5 min and then MsCl (0.18 mL, 2.32 mmol) was added dropwise. The reaction was allowed to warm to rt, and after 2 hours it was quenched by addition of saturated

$NaHCO_3$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. The resulting residue was dissolved in $P(OEt)_3$ (3 mL) and was heated to reflux. The next day the solution was allowed to cool to rt then poured into water and extracted with EtOAc. The organic extracts was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification by flash column chromatography (2% EtOH in Et_2O) afforded indole phosphonate **91** (374 mg, 88%) as a white waxy solid: ^{1}H NMR δ 7.75 (d, J = 8.4 Hz, 2H), 7.57 (m, 1H), 7.21 (d, J = 8.1 Hz, 2H), 7.10, (d, J = 1.1 Hz, 1H), 6.80 (m, 1H), 5.41 – 5.36 (m, 1H), 5.23 (s, 2H), 4.00 (m, 4H), 3.51 – 3.47 (m, 5H), 3.22 (d, J_{PH} = 21.5 Hz, 2H), 2.33 (s, 3H), 1.77 (s, 3H), 1.68 (s, 3H), 1.25 (t, J = 7.0 Hz, 6H); ^{13}C NMR δ 151.6 (d, J_{CP} = 2.9 Hz) 144.8, 137.1 (d, J_{CP} = 3.1 Hz), 135.4, 133.0, 129.7 (2C), 129.2 (d, J_{CP} = 9.3 Hz), 126.8 (2C), 122.7 (d, J_{CP} = 1.6 Hz), 121.8, 121.7 (d, J_{CP} = 1.8 Hz), 119.7 (d, J_{CP} = 3.2 Hz), 108.9 (d, J_{CP} = 5.9 Hz), 108.7 (d, J_{CP} = 7.6 Hz), 94.3, 62.1 (d, J_{CP} = 6.7 Hz, 2C), 56.1, 34.2 (d, J_{CP} = 138.3 Hz), 25.7, 25.6, 21.4, 17.7, 16.3 (d, J_{CP} = 6.0 Hz, 2C); ^{31}P NMR δ 26.9; HRMS (EI^+) calcd for $C_{27}H_{36}NO_7PS$ [M^+] 549.1950; found 549.1959.

Protected analogue 93. To aldehyde **42** (44 mg, 0.15 mmol) and phosphonate **91** (100 mg, 0.182 mmol) in THF (4 mL) at 0 °C was added NaH (80mg, 2.0 mmol, 60% dispersion oil) and 15-Crown-5 (2 drops). The reaction mixture was allowed to stir for 2 hours. It was then quenched by addition of NH_4Cl (sat) and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered and the filtrate was concentrated *in vacuo*. Purification by flash column chromatography (50% EtOAc in hexanes) afforded a mixture of *N*–Ts protected analogue **92** and unprotected indole analogue **93** (55 mg) as an oil. The resulting mixed residue was dissolved in a 1:1

mixture of THF and 2-propanol (5 mL) at 0 °C and to it was added NaH (150 mg, excess) and the reaction mixture was allowed to warm to rt. The following day the reaction mixture was quenched by addition of water and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (50% EtOAc in hexanes) afforded analogue **93** (35 mg, 0.064 mmol) as an oil: ^{1}H NMR δ 7.95 (br s, 1H), 7.07 (s, 1H), 6.99 – 6.98 (m, 2H), 6.92 – 6.90 (m, 2H), 6.87 (m, 1H), 6.81 (s, 1H), 5.51 – 5.46 (m, 1H), 5.36 (s, 2H), 3.90 (s, 3H), 3.62 (d, *J* = 7.0 Hz, 2H), 3.57 (s, 3H), 3.43 (dd, *J* = 11.6, 3.8 Hz, 1H), 2.74 – 2.71 (m, 2H), 2.15 – 2.10 (m, 1H), 1.89 – 1.56 (m, 11H), 1.26 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 152.1, 148.9, 142.3, 138.6, 133.0, 131.2, 129.4, 127.6, 126.8, 124.1, 122.6, 120.9, 120.2, 117.5, 116.7, 106.9, 103.8, 100.9, 94.3, 78.0, 77.0, 56.1, 56.0, 46.8, 38.4, 37.7, 28.3, 27.3, 25.7, 25.6, 23.2, 19.8, 17.7, 14.3; HRMS (EI$^+$) calcd for $C_{34}H_{43}NO_4$ [M^+] 545.3141; found 545.3135.

Analogue 81. To analogue **93** (31 mg, 0.057 mmol) in MeOH (2 mL) at rt was added TsOH (75 mg, 0.39 mmol) and the reaction flask was wrapped in foil. After 10 hours the reaction was quenched by pouring into $NaHCO_3$ (sat) and extracted with EtOAc. The combined organic extracts were washed with Na_2CO_3 (sat), brine, and dried ($MgSO_4$), filtered, and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (50% EtOAc in hexanes) afforded analogue **81** (8 mg, 28%) as a light yellow oil: ^{1}H NMR δ 7.90 (br s 1H), 6.99 – 6.96 (m, 3H), 6.89 – 6.85 (m, 3H), 6.74 (s, 1H), 5.91 (br s, 1H), 5.54 (m, 1H), 3.90 (s, 3H), 3.58 (d, *J* = 6.6 Hz, 2H), 3.44 (dd, *J* = 11.6, 3.7 Hz, 1H), 2.75 – 2.72 (m, 2H), 2.16 – 2.10 (m, 1H), 1.90 – 1.55 (m, 5H), 1.84 (s, 3H), 1.82 (s, 3H), 1.26 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 150.1,

148.9, 139.2, 135.1, 133.6, 129.8, 129.4, 127.3, 127.1, 125.1, 122.6, 121.0, 120.3, 116.4, 115.2, 106.9, 102.8, 102.8, 78.1, 56.0, 46.8, 38.4, 37.7, 28.3, 27.4, 25.8, 25.7, 23.2, 19.8, 17.7, 14.3; HRMS (EI^+) calcd for $C_{32}H_{39}NO_4$ [M^+] 501.2879; found 501.2874.

Silyl protected alcohol 94. To alcohol **64** (1.09 g, 3.01 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added imidazole (502 mg, 7.53 mmol) and TBSCl (500 mg, 3.31 mmol) and then the solution was allowed to warm to rt. The next day the reaction was quenched by addition of NH_4Cl (sat), and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (8% EtOAc in hexanes) afforded silyl protected alcohol **94** (1.39 g, 97%): ^{1}H NMR δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.63 (m, 1H), 7.45 (d, *J* = 3.7 Hz, 1H), 7.20, (dd, *J* = 8.5, 0.6 Hz, 2H), 6.88 (m, 1H), 6.73 (dd, *J* = 3.7, 0.8 Hz, 1H), 5.24 (s, 2H), 4.81 (s, 2H), 3.47 (s, 3H), 2.33 (s, 3H), 0.97 (s, 9H), 0.12 (s, 6H); ^{13}C δ 150.3, 144.8, 139.8, 136.1, 135.3, 129.8 (2C), 168.8 (2C), 124.9, 120.7, 105.8, 105.9, 104.9, 94.7, 65.2, 56.1, 25.9 (3C), 21.5, 18.3, -5.2 (2C); HRMS (EI^+) calcd for $C_{29}H_{41}NO_5SSi$ [M^+] 475.1849; found 475.1856.

Prenylated indole 95. To silyl protected indole **94** (724 mmol, 1.52 mmol) in THF was added a few 4 Å molecular sieves and the mixture was cooled to –78 °C. After *n*-BuLi (0.75ml, 2.3M in hexanes) was added, the mixture was stirred for 20 min and prenyl bromide (420 mmol, 2.82 mmol) was added. The next day the reaction mixture was quenched by addition of NH_4Cl (sat), and extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, and the filtrated was concentrated *in vacuo*. Final purification by flash column chromatography (5% EtOAc in hexanes) afforded prenyl indole **95** (560 mg, 68%) as well as recovered starting material

(76 mg, 10%): ^{1}H NMR δ 7.91 (d, *J* = 0.8 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.25, (d, *J* = 8.5 Hz, 2H), 6.99 (s, 1H), 6.52 (d, *J* = 0.8 Hz, 1H), 5.47 (m, 1H), 5.31 (s, 2H), 4.90 (s, 2H), 3.74 (d, *J* = 7.2 Hz, 2H), 3.55 (s, 3H), 2.40 (s, 3H), 1.86 (s, 3H), 1.71 (s, 3H) 1.05 (s, 9H), 0.20 (s, 6H); ^{13}C NMR δ 149.5, 144.5, 139.9, 138.7, 138.6, 136.5, 134.5, 129.7 (2C), 126.3 (2C), 119.8, 119.6, 106.5, 106.3, 105.3, 94.8, 65.5, 56.0, 27.9, 25.9 (3C), 25.7, 21.4, 18.3, 17.7, -5.2 (2C); HRMS (EI^{+}) calcd for $C_{29}H_{41}NO_5SSi$ [M^{+}] 543.2475; found 543.2476.

Alcohol 96. To silyl protected alcohol **95** (682 mg, 1.26 mmol) in THF (20 mL) at rt was added TBAF (1.88 mL, 1.0 M in THF). After 2 hours the reaction was quenched with H_2O and extracted with EtOAc. The combined organics were washed with brine, dried ($MgSO_4$), and filtered, and the solvent was removed *in vacuo*. Purification by flash column chromatography (30 to 45% EtOAc in hexanes) afforded alcohol **96** (461 mg, 85%): ^{1}H NMR δ 7.84 (s, 1H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.17, (d, *J* = 8.4 Hz, 2H), 6.93 (s, 1H), 6.44 (s, 1H), 5.38 (m, 1H), 5.24 (s, 2H), 4.74 (s, 2H), 3.64 (d, *J* = 7.1 Hz, 2H), 3.46 (s, 3H), 2.60 (br s, 1H), 2.31 (s, 3H), 1.78 (s, 3H), 1.61 (s, 3H); ^{13}C δ 149.5, 144.6, 140.1, 138.5, 138.1, 136.2, 134.7, 129.7 (2C), 126.2 (2C), 119.9, 119.5, 107.2, 106.7, 105.2, 94.5, 65.7, 56.1, 27.8, 25.7, 21.4, 17.6; HRMS (EI^{+}) calcd for $C_{23}H_{27}NO_5S$ [M^{+}] 317.1627; found 317.1631.

Phosphonate 97. To benzylic alcohol **96** (333 mg, 0.775 mmol) in THF was added LiBr (540 mg, 6.20 mmol) and Et_3N (0.44mL, 3.10 mmol) and the solution was cooled to 0 °C. After 15 min MsCl (0.19 mL, 2.46 mmol) was added dropwise. The reaction was allowed to stir and slowly warm to rt. After 2 hours, when complete by TLC analysis, it was quenched by addition H_2O and extracted with Et_2O. The organic

extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. To the resulting residue was added $P(OEt)_3$ (3 mL) and the solution was heated at reflux overnight. The next day the solution was allowed to cool to rt and then poured into water and extracted with EtOAc. The organic extract was washed with brine, dried ($MgSO_4$), and filtered and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (50 to 70% EtOAc in hexanes) afforded indole phosphonate **97** (384 mg, 90%): ^{1}H NMR δ 7.82 (d, J = 2.8 Hz, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.5 Hz, 2H), 6.87 (s, 1H), 6.43 (s, 1H), 5.40 – 5.35 (m, 1H), 5.25 (s, 2H), 4.07 – 3.94 (m, 4H), 3.64 (d, J = 7.2 Hz, 2H), 3.48 (s, 3H), 3.26 (d, J_{PH} = 21.3 Hz, 2H), 2.34 (s, 3H), 1.78 (s, 3H), 1.62 (s, 3H), 1.26 (t, J = 7.1 Hz, 6H); ^{13}C NMR δ 149.3 (d, J_{CP} = 3.1 Hz) 144.6, 140.0 (d, J_{CP} = 1.9 Hz), 138.5 (d, J_{CP} = 3.1 Hz), 136.2, 134.7, 129.9 (2C), 128.1 (d, J_{CP} = 9.3 Hz), 126.3 (2C), 119.5, 119.4 (d, J_{CP} = 3.1 Hz), 109.9 (d, J_{CP} = 7.4 Hz), 109.5 (d, J_{CP} = 6.1 Hz), 105.2, 94.8, 62.2 (d, J_{CP} = 6.9 Hz, 2C), 56.2, 34.2 (d, J_{CP} = 137.7 Hz), 27.8, 25.6, 21.4, 17.7, 16.2 (d, J_{CP} = 5.9 Hz, 2C); ^{31}P NMR δ 27.3; HRMS (EI^+) calcd for $C_{27}H_{36}NO_7PS$ [M^+] 549.1950; found 549.1943.

Protected analogue 99. To phosphonate **97** (74 mg, 0.14 mmol) and aldehyde **42** (30 mg, 0.10 mmol) in THF (2mL) at 0 °C was added NaH (50 mg, 1.25 mmol, 60% dispersion oil) and 15-Crown-5 (3 drops). The reaction mixture was allowed to stir for 4 hours, then quenched by addition of NH_4Cl (sat) and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and then concentrated *in vacuo*. Purification by flash column chromatography (50% EtOAc in hexanes) afforded a mixture of *N*–tosyl indole **98** and unprotected indole **99**. To the mixed residue in 1:1 THF and 2-propanol (3 mL) at 0 °C was added NaH (120 mg, 3

mmol) and the reaction mixture allowed to warm to rt overnight. The next day the reaction mixture was quenched by addition of NH_4Cl (sat), diluted with H_2O, and extracted with EtOAc. The combined organic extracts were washed with water, brine, and dried ($MgSO_4$), filtered, and then the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (50% EtOAc in hexanes) afforded indole **99** (20 mg, 37% (2 steps)) as an oil: ^{1}H NMR δ 7.92 (br s, 1H), 7.08 (m, 1H), 7.02 (d, *J* = 16.1 Hz, 1H), 6.96 (m, 1H), 6.94 (d, *J* = 16.1 Hz, 1H), 6.89 (m, 1H), 6.86 (m, 1H), 6.31 (m, 1H), 5.40 (m, 1H) 5.36 (s, 2H), 3.90 (s, 3H), 3.56 (s, 3H), 3.49 – 3.39 (m, 3H), 2.74 – 2.71 (m, 2H), 2.18 – 2.10 (m, 1H), 1.90 – 1.60 (m, 5H), 1.79 (s, 3H), 1.74 (s, 3H), 1.26 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 150.1, 148.9, 142.3, 138.3, 137.5, 134.6, 132.1, 129.5, 127.8, 126.4, 122.6, 120.1, 120.1, 119.9, 107.1, 106.9, 103.5, 102.3, 95.0, 78.1, 77.0, 56.1, 56.0, 46.8, 38.4, 37.7, 28.3, 27.4, 27.1, 25.7, 23.2, 19.9, 17.8, 14.3; HRMS (EI^+) calcd for $C_{34}H_{43}NO_5$ [M^+] 545.3141; found 545.3135.

Analogue 82. To analogue **99** (8mg, 0.015 mmol) in MeOH (0.8 mL) in a foil-wrapped flask was added TsOH (25 mg, 0.13 mmol) and the reaction was allowed to stir. After 10 hours the reaction was quenched by addition of $NaHCO_3$ (sat) and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Final purification by radial chromatography (50% EtOAc in hexanes) afforded compound **82** (5mg, 68%) as a light yellow oil: ^{1}H NMR (CD_3OD) δ 6.99 (d, *J* = 16.4 Hz, 1H), 6.95 (m, 2H), 6.90 (d, *J* = 16.2 Hz, 1H), 6.82 (m, 1H), 6.63 (s, 1H), 6.17 (s, 1H), 5.46 – 5.41 (m, 1H), 3.85 (s, 3H), 3.44 (d, *J* = 7.3 Hz, 2H), 3.37 (dd, *J* = 10.8, 3.9 Hz, 1H), 2.76 – 2.73 (m, 2H), 2.07 – 2.02 (m, 1H), 1.85–1.60 (m, 4H), 1.79 (s, 3H), 1.75 (s, 3H), 1.23 (s, 3H), 1.11 (s, 3H), 0.88 (s,

3H); ^{13}C NMR δ 150.5, 150.1, 143.2, 140.1, 139.4, 134.3, 132.9, 131.4, 129.3, 126.6, 124.0, 122.2, 121.4, 119.4, 108.0, 103.4, 102.0, 96.7, 78.7, 78.1, 56.4, ~49*, 39.5, 38.9, 29.0, 28.0, 27.9, 25.9, 24.1, 20.2, 17.8, 14.9; HRMS (EI$^+$) calcd for $C_{32}H_{39}NO_6$ [M$^+$] 502.2957; found 502.2956. * Obscured by solvent.

Procedure to methoxyindole 113 and dimethylindole 126. Following Vedejs[55] procedure, to phenol **46** (1.05 g, 5.12 mmol) in DMF (28 mL) was added K_2CO_3 (2.12 g, 15.4 mmol), the reaction mixture was cooled to 0 °C, and after 20 min MeI (0.32 mL, 5.12 mmol) was added dropwise. The reaction was maintained at 0 °C overnight, then quenched by addition of 1M HCl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and then concentrated *in vacuo.* Final purification by flash column chromatography (20% to 25% EtOAc in hexanes) afforded methoxyindole **113** (824 mg, 73%) as a white solid: ^{1}H NMR δ 8.66 (br s, 1H), 7.85 (t, *J* = 0.9 Hz, 1H), 7.26 (dd, *J* = 3.3, 2.5 Hz, 1H), 7.22 (d, *J* = 1.0 Hz, 1H), 6.69 (m, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.00 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H); ^{13}C δ 167.8, 152.7, 136.2, 125.9, 124.9, 122.3, 107.5, 100.2, 99.9, 60.8, 55.4, 14.4; HRMS (EI$^+$) calcd for $C_{12}H_{13}NO_3$ [M$^+$] 219.0895; found 219.0904.

Also recovered was dimethylated indole **126** (31 mg, 3%) as a white solid: ^{1}H NMR δ 7.77 (t, *J* = 0.9 Hz, 1H), 7.21 (d, *J* = 1.0 Hz, 1H), 7.11 (d, *J* = 3.0 Hz, 1H), 6.60 (dd, *J* = 0.8, 3.1 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.01 (s, 3H), 3.83 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR δ 167.7, 152.7, 137.1, 130.3 124.4, 122.7, 105.8, 99.6, 98.7, 60.8, 55.4, 33.2, 14.5; HRMS (EI$^+$) calcd for $C_{13}H_{15}NO_3$ [M$^+$] 233.1052; found 233.1056.

Benzylic indole alcohol 114. To indole **113** (436 mg, 1.99 mmol) in THF (10 mL) at 0 °C was added NaH (100 mg, 2.5 mmol, 60% dispersion in oil), followed by

TsCl (430 mg, 2.25 mmol). Once the reaction was judged complete by TLC analysis, DIBAL–H (1.07 mL, 6.0 mmol) was added dropwise. After 1 hour the reaction mixture was quenched by addition of NH_4Cl (sat), diluted with EtOAc, acidified with 1M HCl to dissolve the solids, and extracted with EtOAc. The combined organic extracts were washed with $NaHCO_3$ (sat), brine, dried ($MgSO_4$), and filtered, and then the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (35% EtOAc in hexanes) afforded alcohol **114** (533 mg, 81%) as a white solid: ^{1}H NMR δ 7.72 (d, *J* = 8.4, Hz, 2H), 7.57 (s, 1H), 7.43 (d, *J* = 3.6 Hz, 1H), 7.16 (d, *J* = 8.5 Hz, 2H), 6.72 (dd, *J* = 3.7, 0.8 Hz, 1H), 6.67 (s, 1H), 4.74 (s, 2H), 3.85 (s, 3H), 2.32 (br s, 1H), 2.29 (s, 3H); ^{13}C δ 153.0, 144.9, 139.2, 135.8, 135.0, 129.8 (2C), 126.7 (2C), 124.9, 120.4, 105.9, 104.7, 102.7, 65.8, 55.3, 21.4; HRMS (EI^+) calcd for $C_{17}H_{17}NO_4S$ [M^+] 331.0878; found 331.0873.

Phosphonate 115. To benzylic alcohol **114** (517 mg, 1.56 mmol) in THF (15 mL) was added LiBr (1.09 g, 12.5 mmol) and the solution was cooled to 0 °C. Next Et_3N (0.87 mL, 6.2 mmol) and, after 10 min, MsCl (0.36 mL, 1.73 mmol) were added and the reaction mixture was allowed to stir for 2.5 h. The reaction mixture was quenched by addition of NH_4Cl (sat) and extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, and then the filtrate was concentrated *in vacuo*. After the resulting oil was dissolved in DMF (6mL), and $P(OEt)_3$ (2 mL) was added, the solution was heated at reflux. The next day the reaction was allowed to cool to rt and poured into Et_2O, washed with H_2O, brine, dried ($MgSO_4$), and filtered and then the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (2.5 to 3% MeOH in Et_2O) afforded phosphonate **115** (529 mg, 75%) as

a light yellow solid: ^{1}H NMR δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 2.9 Hz, 1H), 7.42 (dd, *J* = 3.7, 1.3 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 3.6, 1H), 6.65 (s, 1H), 4.03–3.93 (m, 4H), 3.88 (s, 3H), 3.25 (d, J_{HP} = 21.5 Hz, 2H), 2.33 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 6H); ^{13}C δ 152.8 (d, J_{CP} = 2.8 Hz), 144.8, 136.0 (d, J_{CP} = 3.1 Hz), 135.3, 129.7 (2C), 129.4 (d, J_{CP} = 9.2 Hz), 126.7 (2C), 124.8 (d, J_{CP} = 1.7 Hz), 120.0 (d, J_{CP} = 3.3 Hz), 107.7 (d, J_{CP} = 7.9 Hz), 106.0 (d, J_{CP} = 1.7 Hz), 105.6 (d, J_{CP} = 5.7 Hz), 62.1 (d, J_{CP} = 6.7 Hz, 2C), 55.4, 34.4 (d, J_{CP} = 138.3 Hz), 21.4, 16.3 (d, J_{CP} = 5.9 Hz, 2C); ^{13}P δ 26.2; HRMS (EI^{+}) calcd for $C_{21}H_{26}NO_6PS$ [M^{+}] 451.1218; found 451.1216.

Schweinfurthin analogue 110. To aldehyde **42** (40 mg, 0.13 mmol) and phosphonate **115** (72 mg, 0.16 mmol) in THF (1.2 mL) was added NaH (50 mg, 1.25 mmol, 60% dispersion in oil) and 15-Crown-5 (3 drops). After 1 h the reaction was quenched by addition of NH_4Cl (sat) and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and then concentrated *in vacuo.* Purification by flash column chromatography (35% EtOAc in hexanes) afforded a mixture of tosyl protected indole **116** and the free indole **110** (36 mg). The resulting mixture in THF (5 mL) was added dropwise to a solution of NaH (115 mg, 2.88 mmol, 60% dispersion in oil) in 2-propanol (2 mL). The solution was allowed to stir overnight and then quenched by addition of H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo.* Final purification by flash column chromatography (40% EtOAc in hexanes) afforded schweinfurthin analogue **110** (23 mg, 39% for 2 steps) as a colorless oil: ^{1}H NMR δ 8.17 (br s, 1H), 7.11 (m, 2H), 7.06 (d, *J* = 16.3, Hz, 1H), 6.99 (d, *J* = 16.3 Hz), 6.91 – 6.89 (m, 2H), 6.74 (s, 1H), 6.63 (t, *J* = 2.4 Hz, 1H), 4.02 (s, 3H), 3.91 (s, 3H),

3.44 (dd, *J* = 11.6, 4.0 Hz, 1H), 2.76–2.73 (m, 2H), 2.16 – 2.11 (m, 1H), 1.90 – 1.56 (m, 5H), 1.27 (s, 3H), 1.11 (s, 3H), 0.90 (s, 3H); ^{13}C δ 153.5, 149.1, 142.5, 137.6, 133.3, 129.6, 128.0, 127.0, 123.3, 122.8, 120.4, 118.7, 107.1, 103.5, 100.4, 97.9, 78.2, 56.2, 55.5, 47.0, 38.6, 37.8, 28.5, 27.5, 23.4, 20.0, 14.4; HRMS (EI^+) calcd for $C_{28}H_{33}NO_4$ [M^+] 447.2410; found 447.2413.

Alcohol 119. To indole **55** (202 mg, 0.81 mmol) in THF (10 mL) at 0 °C was added NaH (49 mg, 1.2 mmol, 60% dispersion in mineral oil) followed after 5 min by MeI (0.06 mL, 0.96 mmol), and the reaction mixture was allowed to stir for 2 hours. After $LiAlH_4$ (92 mg, 2.42 mmol) was added, the solution was allowed to stir for 1 h and then quenched with NH_4Cl (sat) and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (40% EtOAc in hexanes) afforded benzylic alcohol **119** (146 mg, 81%, 2 steps) as a light yellow solid: ^{1}H NMR δ 6.96 (s, 1H), 6.91 (d, *J* = 3.2 Hz, 1H), 6.70 (s, 1H), 6.53 (d, *J* = 3.1 Hz, 1H), 5.27 (s, 2H), 4.69 (s, 2H), 3.65 (s, 3H), 3.48 (s, 3H), 2.68 (br s 1H); ^{13}C NMR δ 150.3, 138.1, 135.7, 127.8, 118.9, 102.6, 102.2, 97.9, 94.4, 65.8, 56.0, 32.8; HRMS (EI^+) calcd for $C_{12}H_{15}NO_3$ [M^+] 221.1052; found 221.1042.

Failed Synthesis of phosphonate 120. To alcohol **119** (73 mg, 0.33 mmol) in THF (4 mL) at 0 °C was added LiBr (229 mg, 2.64 mmol) and Et_3N (0.19 mL, 1.32 mmol) followed by MsCl (0.07 mL, 0.82 mmol), the reaction flask was wrapped in foil, and the reaction mixture was allowed to stir for 3 hours. The reaction then was quenched by addition of H_2O and extracted with Et_2O. The combined organics were washed with brine, dried ($MgSO_4$), and filtered and the filtrate was concentrated *in vacuo* to about 1

mL. Toluene (2 mL) and $P(OEt)_3$ (1 mL) were added, and the flask was placed back on the rotary evaporator to remove the remaining Et_2O. The reaction was then heated to reflux overnight. After it was allowed to cool to rt, the solvent was removed *in vacuo*. Attempted purification of the residue by flash column chromatography (2% EtOH in Et_2O) failed to recover the desired compound **120**.

Aldehyde 121. To alcohol **119** (73 mg, 0.33 mmol) in CH_2Cl_2 (10 mL) at rt was added MnO_2 (430 mg, 4.9 mmol) and the resulting mixture was allowed to stir for 4 hours, then filtered through celite, and washed with EtOAc. The solvent was removed *in* vacuo to afford aldehyde **121** (58 mg, 80%) as a light yellow solid: ^{1}H NMR δ 9.98 (s, 1H), 7.55 (s, 1H), 7.27 (s, 1H), 7.19 (d, *J* = 2.9 Hz, 1H), 6.65 (d, *J* = 2.8 Hz, 1H), 5.38, (s, 2H), 3.85 (s, 3H), 3.54 (s, 3H); ^{13}C NMR δ 192.2, 150.7, 137.4, 131.8, 131.7, 124.8, 108.5, 102.0, 99.2, 94.5, 56.2, 33.2; HRMS (EI^+) calcd for $C_{12}H_{13}NO_3$ [M^+] 219.0895; found 219.0889.

Phosphonate 122. To aldehyde **123** (116 mg, 0. 33 mmol) in MeOH at 0 °C was added $NaBH_4$ (15 mg, 0.38 mmol), the reaction was allowed to stir for 30 min, and then was quenched by addition of water and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. The resulting residue was dissolved in THF (5 mL) and cooled to 0 °C. Next LiBr (231 mg, 2.7 mmol) and Et_3N (0.18 mL, 1.3 mmol) were added. After 5 min MsCl (0.07 mL, 0.83 mmol) was added and the reaction mixture was allowed to warm to rt and stir for 2 hours. The reaction mixture was quenched by addition of NH_4Cl (sat), and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. The resulting

residue was dissolved in $P(OEt)_3$ (2 mL) and then heated to reflux overnight. The next day the reaction mixture was allowed to cool to rt and then concentrated *in vacuo*. Final purification by flash column chromatography (2.5 % EtOH in Et_2O) afforded phosphonate **122** (107 mg, 69%) as an oil whose ^1H and ^{31}P NMR spectrum was consistent with that of material prepared previously.[45]

Stilbene 124. To aldehyde **121** (11 mg, 0.05 mmol) and phosphonate **122** (27 mg, 0.06 mmol) in THF (1.5 mL) at rt was added NaH (40 mg, 1.0 mmol, 60% dispersion in oil). After the reaction mixture was allowed to stir for 6 hours, it was quenched by addition of NH_4Cl (sat) and then extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (50% Et_2O in hexanes) afforded stilbene **124** (19 mg, 71%) as a light yellow oil: ^1H NMR δ 7.11 (d, *J* = 16.1 Hz, 1H), 7.10 (s, 1H), 7.01 (d, *J* = 16.2 Hz, 1H), 7.00 (s, 1H), 6.98 (d, *J* = 3.1 Hz, 1H), 6.92 (s, 1H), 6.89 (s, 1H), 6.56 (d, *J* = 3.0 Hz, 1H), 5.39 (s, 2H), 4.78 (d, *J* = 6.9 Hz, 1H), 4.66 (d, *J* = 6.9 Hz, 1H), 3.92 (s, 3H), 3.72 (s, 3H), 3.57 (s, 3H), 3.42 (s, 3H), 3.29 (dd, *J* = 11.5, 4.0, Hz, 1H), 2.74 – 2.71 (m, 2H), 2.17 – 2.12 (m, 1H), 1.87 – 1.57 (m, 4H), 1.25 (s, 3H), 1.10 (s, 3H), 0.92 (s, 3H); ^{13}C NMR δ 150.7, 148.9, 142.3, 138.4, 132.7, 129.3, 128.2, 127.7, 126.8, 122.6, 120.2, 119.5, 106.7, 102.3, 101.5, 98.4, 96.1, 94.8, 76.9, 56,1, 55.7, 55.6, 47.0, 38.2, 37.6, 33.0, 30.3, 29.7, 25.3, 23.1, 19.8, 15.1; HRMS (EI^+) calcd for $C_{32}H_{41}NO_6$ [M^+] 535.2934; found 535.2919.

Analogue 111. To stilbene **124** (19 mg 0.035 mmol) in a 1:1 mixture of THF and MeOH (2 mL) was added TsOH (30 mg, 0.16 mmol) and the resulting solution was allowed to stir at rt overnight. It was then quenched by addition of $NaHCO_3$ (sat) and

extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered and then concentrated *in vacuo*. Final purification by flash column chromatography (40% EtOAc in hexanes) afforded analogue **111** (8 mg, 51%) as a light yellow oil along with MOM protected analogue **125** (2 mg, 12%). For analogue **111**: ^{1}H NMR δ 7.05 (d, *J* = 16.1 Hz, 1H), 7.00 (s, 1H), 6.98 (d, *J* = 3.1 Hz, 1H), 6.97 (d, *J* = 16.5 Hz, 1H), 6.91 (s, 1H), 6.87 (s, 1H), 6.77 (s, 1H), 6.50 (d, *J* = 3.1 Hz, 1H), 5.24 (br s, 1H), 3.91 (s, 3H), 3.79 (s, 3H), 3.44 (dd, *J* = 11.6, 3.8 Hz, 1H), 2.75 – 2.72 (m, 2H), 2.17 – 2.11 (m 1H), 1.90 – 1.55 (m 5H), 1.25 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 148.9, 148,9, 142.3, 138.8, 132.9, 129.3, 128.2, 127.5, 127.0, 122.6, 120.3, 117.8, 106.6, 101.6, 101.5, 97.4, 78.0, 56,0, 46.7, 38.4, 37.6, 33.1, 29.7, 28.2, 27.3, 19.8, 14.3; HRMS (EI^+) calcd for $C_{28}H_{33}NO_4$ [M^+] 447.2410; found 447.2422.

Alternative route to dimethyl indole 126. To indole **46** (500 mg, 2.43 mmol) in a mixture of THF and DMF (5:1) at 0 °C was added NaH (224 mg, 5.6 mmol, as a 60% dispersion in oil), followed after 20 min by MeI (0.34 mL, 5.35 mmol). The reaction was allowed to stir for 3 hours, then quenched by addition of NH_4Cl (sat), and finally extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (20% EtOAc in hexanes) afforded indole **126** (460 mg, 81%) as a white solid with ^{1}H and ^{13}C NMR spectra identical to those of material previously synthesized via an alternate route.

Alcohol 127. To ester **126** (47 mg, 0.20 mmol) in THF (5 mL) at 0 °C was added $LiAlH_4$ (40 mg, 0.8 mmol) in two proportions 20 min apart, and after another 20 min the reaction was quenched by addition of NH_4Cl (sat) and extracted with EtOAc. The

combined organics extracts were washed with brine, dried ($MgSO_4$), filtered and then concentrated *in vacuo*. Final purification by flash column chromatography (50% EtOAc in hexanes) afforded alcohol **127** (33 mg, 86%) as a white solid: ^{1}H NMR δ 6.95–6.94 (m, 2H), 6.55 (d, *J* = 3.0 Hz, 1H), 6.52 (s, 1H), 4.76 (s, 2H), 3.94 (s, 3H), 3.73 (s, 3H), 1.93 (br s, 1H); ^{13}C NMR δ 153.3, 137.9, 135.6, 127.6, 118.4, 101.4, 98.7, 98.1, 66.4, 55.3, 33.0; HRMS (EI^+) calcd for $C_{11}H_{13}NO_2$ [M^+] 191.0946; found 191.0932.

Failed Synthesis of phosphonate 128. To benzylic alcohol **127** (28 mg, 0.15 mmol) in THF (3 mL) at 0 °C was added LiBr (101 mg, 1.2 mmol) followed by Et_3N (0.08 mL, 0.58 mmol), and then MsCl (0.03 mL, 0.37 mmol). The reaction was allowed to stir for 3 hours, then quenched by addition of NH_4Cl (sat) and then extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and then concentrated *in vacuo* to yield a paper-like film. Addition of $P(OEt)_3$ to the residue and heating to reflux did not dissolve the material or afford phosphonate **128**.

Aldehyde 129. To indole **126** (54 mg, 0.24 mmol) in THF (5 mL) at 0 °C was added $LiAlH_4$ (28 mg, 0.73 mmol), and the reaction was allowed to warm to rt over 50 min. It was then quenched by addition by NH_4Cl (sat) and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, and the solvent was removed *in vacuo*. The resulting residue was then dissolved in CH_2Cl_2 (10 mL) and MnO_2 (315 mg, 3.62 mmol) was added. After the reaction mixture was allowed to stir for 4 hours, it was filtered through celite and the solvent was removed *in vacuo* to afford aldehyde **129** (38 mg, 84%, for 2 steps) as a light yellow solid: ^{1}H NMR δ 9.98 (s, 1H), 7.48 (s, 1H), 7.17 (d, *J* = 2.9 Hz, 1H), 7.05 (s, 1H), 6.64 (d, *J* = 2.7 Hz, 1H), 4.00 (s,

3H), 3.85 (s, 3H); ^{13}C NMR δ 192.2, 153.5, 137.0, 132.0, 131.4, 124.2, 109.3, 99.4, 97.1, 55.4 33.2; HRMS (EI$^+$) calcd for $C_{11}H_{11}NO_2$ [M$^+$] 189.0790; found 189.0787.

Phosphonate 130. To phosphonate **122**[45] (81 mg, 0.17 mmol) in EtOH (3 mL) was added TsOH (80 mg, 0.42 mmol) and the reaction flask was wrapped in foil. The solution was allowed to stir for 2 days, then quenched by addition of $NaHCO_3$ (sat), and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, and then concentrated *in vacuo*. Final purification by flash column chromatography (3% EtOH in Et_2O) afforded phosphonate **130** (62 mg, 85%) as a colorless oil whose ^{1}H and ^{13}C NMR spectra were in agreement with those of material prepared by another route.[126]

Analogue 112. To phosphonate **130** (31 mg, 0.073 mmol) and aldehyde **129** (12 mg, 0.063 mmol) in THF (1 mL) was added NaH (40 mg, 1.0 mmol, 60% dispersion in oil) and 15-Crown-5 (1 drop). The solution was allowed to stir overnight, then quenched by addition of NH_4Cl (sat) and finally extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (45% EtOAc in hexanes) afforded analogue **112** (15 mg, 51%) as a yellow oil: ^{1}H NMR δ 7.11 (d, *J* = 16.1 Hz, 1H), 7.04 – 6.99 (m, 2H), 6.96 (d, *J* = 3.2 Hz, 1H), 6.93 (d, *J* = 1.6 Hz, 1H), 6.90 (d, *J* = 1.5 Hz, 1H), 6.75 (s, 1H), 6.55 (d, *J* = 2.9 Hz, 1H), 4.02 (s, 3H), 3.92 (s, 3H), 3.79 (s, 3H), 3.44 (dd, *J* = 11.7, 4.0 Hz, 1H), 2.75 – 2.72 (m, 2H), 2.17 – 2.12 (m 1H), 1.90 – 1.60 (m, 5H), 1.27 (s, 3H), 1.11 (s, 3H), 0.90 (s, 3H); ^{13}C NMR δ 153.3, 148.9, 142.3, 138.3, 132.6, 129.4, 128.0, 127.9, 126.6, 122.6, 120.2, 118.8, 106.7, 101.8, 98.5,

97.2, 78.0, 77.0, 56,0, 55.3, 46.7, 38.4, 37.6, 33.1, 28.3, 27.4, 23.2, 19.8, 14.3; HRMS (EI^+) calcd for $C_{29}H_{35}NO_4$ [M^+] 461.2566; found 461.2569.

Geranyl indole 133. According to the procedure of Zhu and Ganesan,[94] to indole **113** (824 mg, 3.76 mmol), TBAI (663 mg, 1.80 mmol), and $Zn(OTf)_2$ (745 mg, 2.05 mmol) were allowed to react in a mixture of toluene (16 mL), and CH_2Cl_2 (2 mL) and DIPEA (0.66 mL, 3.76 mmol). After stirring for 15 min geranyl bromide (371mg, 1.71 mmol) was added dropwise and after an additional 2.5 h the reaction mixture was quenched by addition of NH_4Cl (sat), and finally extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered and then concentrated *in vacuo*. Final purification by flash column chromatography (17% EtOAc in hexanes) afforded the geranylated indole **133** (325 mg, 53%) as a colorless oil along with recovered starting indolel (436 mg): ^{1}H NMR δ 8.18 (br s, 1H), 7.74 (d, *J* = 0.9 Hz, 1H), 7.15 (d, *J* = 1.0, 1H), 6.94 (m, 1H), 5.46 (m, 1H), 5.13 (m, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 3.96 (s, 3H), 3.64 (d, *J* = 7.2 Hz, 2H), 2.14 – 2.04 (m, 4H), 1.71, (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR δ 167.7, 154.5, 137.1, 135.3, 131.3, 124.7, 124.7, 123.5, 123.2, 120.9, 117.2, 107.4, 99.8, 60.7, 55.3, 39.7, 26.7, 25.7, 25.3, 17.7, 16.0, 14.4; HRMS (EI^+) calcd for $C_{22}H_{29}NO_3$ [M^+] 355.2147; found 355.2152.

Benzylic alcohol 134. To indole **133** (325 mg, 0.91 mmol) in THF (10 mL) at 0 °C was added NaH (44 mg, 1.1 mmol, 60% dispersion in oil) followed by TsCl (183 mg, 0.96 mmol). When the reaction was judged complete by TLC, DIBAL–H (0.53 mL, 2.97 mmol) was added dropwise. After 1 additional hour the solution was quenched by addition of NH_4Cl (sat), diluted with EtOAc, acidified with 1M HCl to dissolve the solids, and finally extracted with EtOAc. The combined organic layers were washed with

$NaHCO_3$ (sat), brine, dried ($MgSO_4$), and filtered and then concentrated *in vacuo*. Final purification by flash column chromatography (35% EtOAc in hexanes) afforded alcohol **134** (273 mg, 64%) as a colorless oil: ^{1}H NMR δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.54 (s 1H), 7.12 (d, *J* = 8.2 Hz, 2H), 7.09 (s, 1H), 6.62 (s, 1H), 5.41 – 5.37 (m, 1H), 5.15 – 5.11 (m, 1H), 4.71 (s, 2H), 3.79 (s, 3H), 3.50 (d, *J* = 7.0 Hz, 2H), 2.74 (br s, 1H), 2.26 (s, 3H), 2.14 – 2.04 (m, 4H), 1.67 (s, 3H), 1.67 (s, 3H), 1.61 (s, 3H); ^{13}C NMR δ 154.6, 144.5, 139.0, 136.9, 136.5, 135.2, 131.4, 129.6 (2C), 126.5 (2C), 124.0, 123.1, 121.7, 121.4, 119.8, 104.8, 102.8, 65.6, 55.1, 39.6, 26.5, 25.6, 25.5, 21.3, 17.6, 15.9; HRMS (EI^+) calcd for $C_{27}H_{33}NO_4S$ [M^+] 467.2130; found 467.2135.

Phosphonate 134. To benzylic alcohol **134** (269mg, 0.58 mmol) in THF (10 mL) was added LiBr (400 mg, 4.60 mmol) and the solution was cooled to 0 °C. Next Et_3N (0.32 mL, 2.3 mmol) followed after 10 min by MsCl (0.13 mL, 1.73 mmol) were added, and the reaction mixture was allowed to stir for 2 h. The reaction mixture was then quenched by addition of NH_4Cl (sat) and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. The resulting oil was dissolved in $P(OEt)_3$ (2 mL) and heated at reflux. The next day the reaction was allowed to cool to rt, then poured into Et_2O, washed with H_2O, brine, dried ($MgSO_4$), and filtered, and finally the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (2.5 to 3% MeOH in Et_2O) afforded phosphonate **134** (273 mg, 81%) as a colorless oil; ^{1}H NMR δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.50 (dd, *J* = 3.0, 1.1 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.07 (m, 1H), 6.62 (m, 1H), 5.38 (m, 1H), 5.13 (m, 1H), 4.02 – 3.96 (m, 4H), 3.84 (s, 3H), 3.49 (d, *J* = 7.2 Hz, 2H), 3.23 (d, J_{PH} = 21.4 Hz, 2H), 2.33 (s, 3H), 1.70 (d, *J* = 0.8 Hz, 3H), 1.67

(d, J = 1.0 Hz, 3H), 1.62 (s 3H), 1.24 (t, J = 7.1 Hz, 6H); ^{13}C NMR δ 154.3 (d, J_{CP} = 3.0 Hz), 144.4, 137.0 (d, J_{CP} = 3.1 Hz), 136.5, 135.4, 131.4, 129.6 (2C), 129.1 (d, J_{CP} = 9.1 Hz), 126.6 (2C), 124.1, 123.1 (d, J_{CP} = 1.6 Hz) 121.6, 121.4 (d, J_{CP} = 1.3 Hz), 119.3 (d, J_{CP} = 3.2 Hz), 107.8 (d, J_{CP} = 7.9 Hz), 105.8 (d, J_{CP} = 5.5 Hz), 62.1 (d, J_{CP} = 6.6 Hz, 2C), 55.2, 39.6, 34.3 (d, J_{CP} = 138.1 Hz), 26.6, 25.6, 25.5, 21.4, 17.6, 16.3 (d, J_{CP} = 5.9 Hz, 2C) 16.0; ^{13}P NMR δ 26.2; HRMS (EI$^+$) calcd for $C_{31}H_{42}NO_6PS$ [M^+] 587.2470; found 587.2481.

Geranylated analogue 136. To phosphonate **135** (100 mg, 0.17 mmol) and aldehyde **42** (40 mg, 0.13 mmol) in THF (1.0 mL) at 0 °C was added NaH (60mg, 1.0 mmol, 60% oil dispersion) and 15-Crown-5 (1 drop). When the aldehyde had disappeared as judged by TLC, the reaction was quenched by addition of NH_4Cl (sat), and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$), and filtered, and then concentrated *in vacuo*. Final purification by flash column chromatography (30% EtOAc in hexanes) afforded analogue **136** (37 mg, 38%) as an oil which was used directly in the next step : ^{1}H NMR δ 7.73 (d, J = 8.3 Hz, 2H), 7.68 (d, J = 0.9 Hz, 1H), 7.20 (d, J = 8.1 Hz, 2H), 7.09 (t, J = 1.1 Hz, 1H), 7.03 (m, 2H), 6.93 (m, 1H), 6.92 (m, 1H), 6.79 (s, 1H), 5.39 (m, 1H), 5.13 (m, 1H), 3.93 (s, 3H), 3.90, (s, 3H), 3.51–3.42 (m, 3H), 2.76–2.73 (m, 2H), 2.17 – 2.04 (m, 5H), 1.91 – 1.82 (m, 3H), 1.75 – 1.59 (m, 11 H), 1.27 (s, 3H), 1.11 (s, 3H), 0.90 (s, 3H); ^{13}C NMR δ 154.6, 149.0, 144.6, 142.7, 137.5, 136.6, 135.7, 135.4, 131.5, 129.7 (2C), 128.9, 128.2, 127.0, 126.7 (2C), 124.2, 123.5, 122.7, 121.8, 121.7, 120.5, 120.0, 106.9, 105.4, 101.4, 78.0, 77.1, 56.0, 55.2, 46.8, 39.7, 38.4, 37.7, 28.3, 27.3, 26.6, 25.7, 25.6, 23.2, 21.5, 19.8, 17.7, 16.0, 14.3.

Analogue 131. Stilbene **136** (37 mg, 0.05 mmol) in THF (2 mL) was added to a solution of NaH (150 mg, 3.75 mmol, 60% dispersion in oil) in 2-propanol (2mL) and the solution was allowed to stir overnight. The reaction mixture was then quenched by addition of H_2O and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and then concentrated *in vacuo*. Final purification by flash column chromatography (45% EtOAc in hexanes) afforded schweinfurthin analogue **131** (17 mg, 58%) as a colorless oil: ^{1}H NMR δ 7.91 (br s, 1H), 7.02 – 6.99 (m, 3H), 6.90 (m, 1H). 6.88 (m 1H), 6.78 (s, 1H), 6.68 (s, 1H), 5.48 (m, 1H), 5.14 (m, 1H), 3.97 (s, 3H), 3.90 (s, 3H), 3.63 (d, *J* = 7.2 Hz, 2H), 3.44 (m, 1H), 2.75 – 2.71 (m, 2H), 2.16 – 2.06 (m, 5H), 1.90 – 1.61 (m, 14H), 1.26 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 155.0, 148.9, 142.3, 138.4, 135.0, 132.9, 131.3, 129.5, 127.9, 126.5, 124.5, 123.8, 122.6, 120.6, 120.2, 117.2, 117.0, 106.9, 103.3, 97.4, 78.0, 56.0, 55.1, 46.8, 39.8, 38.4, 37.7, 28.3, 27.4, 26.8, 25.7, 25.5, 23.2, 19.8, 17.7, 16.0, 14.3; calcd for $C_{38}H_{49}NO_4$ [M^+] 583.3662; found 587.2672.

Prenylated indole 137. To indole **113** (388 mg, 1.77 mmol), TBAI (360 mg, 0.98 mmol), and $Zn(OTf)_2$ (436 mg, 1.2 mmol) in a 5:1 mixture of toluene and CH_2Cl_2 (12 mL) at rt was added DIPEA (0.38 mL, 2.2 mmol) and the reaction mixture was allowed to stir for 10 min. Prenyl bromide (126 mg, 0.88 mmol) was added dropwise. After 2 hours the reaction mixture was quenched by addition of NH_4Cl (sat) and extracted with EtOAc. The combined organic extracts were washed with H_2O, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (10% to 15% EtOAc in hexanes) afforded prenylated indole **137** (209 mg, 59%) along with recovered indole **113** as expected[94] (149 mg): ^{1}H NMR δ 8.31 (br s,

1H), 7.74 (d, *J* = 1.0 Hz, 1H), 7.15 (d, *J* = 0.5 Hz, 1H), 6.93 (m, 1H), 5.47 – 5.42 (m, 1H), 4.39 (q, *J* = 7.1 Hz, 1H), 3.95 (s, 3H), 3.63 (d, *J* = 7.2 Hz, 2H), 1.75 (s, 3H), 1.72 (s, 3H), 1.40 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 167.8, 154.4, 137.1, 131.5, 124.6, 123.7, 123.2, 120.8, 117.1, 107.4, 99.8, 60.7, 55.3, 25.7, 25.4, 17.7, 14.4; HRMS (EI^+) calcd for $C_{17}H_{21}NO_3$ [M^+] 287.1521; found 287.1523.

Alcohol 138. To a solution of indole **137** (18 mg, 0.06 mmol) in THF (3 mL) at rt was added NaH (5 mg, 0.13 mmol, 60% dispersion oil) and the reaction mixture was allowed to stir for 10 min. After TsCl (15 mg, 0.08 mmol) was added, the solution was stirred for 2 hours and then DIBAL–H (0.05 mL, 0.44 mmol) was added dropwise. After an additional 30 min, the reaction was quenched by addition of NH_4Cl (sat), poured into EtOAc, acidified with 1M HCl, and extracted with EtOAc. The combined organic extracts were washed with $NaHCO_3$ (sat), and brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo.* Final purification by flash column chromatography (35% EtOAc in hexanes) afforded the benzylic alcohol **138** (19 mg, 76%): ^{1}H NMR δ 7.70 (d, *J* = 8.1 Hz, 2H), 7.53 (s, 1H), 7.15 (d, *J* = 8.3 Hz, 2H), 7.10 (s, 1H), 6.64 (s, 1H), 5.39 – 5.35 (m, 1H), 4.72 (s, 2H), 3.82 (s, 3H), 3.49 (d, *J* = 7.1 Hz, 2H), 2.29 (s, 3H), 1.76 (s, 3H), 1.68 (s, 3H); ^{13}C NMR δ 154.7, 144.6, 139.0, 136.9, 135.2, 132.9, 129.7 (2C), 126.6, (2C), 123.1, 121.8, 121.5, 119.8, 104.9, 102.9, 65.7, 55.2, 25.7, 25.6, 21.4, 17.7; HRMS (EI^+) calcd for $C_{22}H_{25}NO_4S$ [M^+] 399.1504; found 399.1508.

Phosphonate 139. To alcohol **138** (102 mg, 0.25 mmol) in THF (5 mL) at 0 °C was added LiBr (133 mg, 1.53 mmol) and Et_3N (0.11 mL, 0.79 mmol). The solution was stirred for 5 min, MsCl (0.05 mL, 0.65 mmol) was added dropwise, and the reaction was allowed to warm to rt. After 2 hours it was quenched by addition of NH_4Cl (sat),

extracted with Et_2O, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. To the resulting residue was added $P(OEt)_3$ (2 mL) and the solution was heated to 130 °C and allowed to stir overnight. The next day the solution was allowed to cool to rt and the solvent was removed *in vacuo*. Final purification by flash column chromatography (2% EtOH in Et_2O) afforded indole phosphonate **139** (111 mg, 84%) as a colorless oil: ^{1}H NMR δ 7.72 (d, J = 8.4 Hz, 2H), 7.50 (d, J_{HP} = 2.3 Hz, 1H), 7.19 (d, J = 8.2 Hz, 2H), 7.07 (d, J = 1.1 Hz, 1H), 6.62 (s, 1H), 5.40 – 5.34 (m, 1H), 4.06 – 3.92 (m, 4H), 3.84 (s,3H), 3.48 (d, J = 7.1 Hz, 2H), 3.23 (d, J_{HP} = 21.5 Hz, 2H), 2.32 (s, 3H), 1.76 (s, 3H), 1.67 (s, 3H), 1.24 (t, J = 7.1 Hz, 6H); ^{13}C NMR δ 154.3 (d, J_{CP} = 2.9 Hz), 144.4, 136.9 (J_{CP} = 2.9 Hz), 135.2, 132.9, 129.7 (2C), 129.1 (J_{CP} = 9.8 Hz), 126.7 (2C), 123.1 (d, J_{CP} = 1.7 Hz), 121.7, 121.3 (d, J_{CP} = 1.6 Hz), 119.3 (d, J_{CP} = 3.2 Hz), 107.8 (d, J_{CP} = 7.8 Hz), 105.8 (d, J_{CP} = 5.6 Hz), 62.0 (d, J_{CP} = 2.9 Hz, 2C), 55.2, 34.2 (d, J_{CP} = 138.2 Hz), 25.7, 25.6, 21.4, 17.7, 16.3 (d, J_{CP} = 6.0 Hz, 2C); ^{31}P NMR δ 26.2; HRMS (EI^+) calcd for $C_{26}H_{34}NO_6PS$ [M^+] 519.1844; found 519.1843.

Analogue 132. To phosphonate **139** (45 mg, 0.089 mmol) and aldehyde **42** (21 mg, 0.069 mmol) in THF (1mL) at 0 °C was added NaH (40 mg, 1.0 mmol, 60% dispersion oil) and 15-Crown-5 (2 drops). The reaction mixture was allowed to stir for 45 min, then quenched by addition of NH_4Cl (sat), and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and then the filtrate was concentrated *in vacuo*. Purification by flash column chromatography (20% to 50% EtOAc in hexanes) afforded a mixture of protected and unprotected indole (26 mg). This mixture was treated with NaO*i*-Pr in THF (3 mL), generated *in situ* from NaH (160 mg, 4 mol, 60% dispersion oil) and *i*-PrOH, and the reaction mixture was

allowed to stir overnight. The next day the reaction mixture was quenched by addition of H_2O and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (45% EtOAc in hexanes) afforded indole **132** (13.5 mg, 38% (2 steps)) as a light yellow oil: ^{1}H NMR δ 7.90 (br s, 1H), 7.03 (d, *J* = 16.0 Hz, 1H), 7.01 (s, 1H), 6.96 (d, *J* = 16.2 Hz, 1H), 6.91 (m, 1H), 6.88 (m, 1H), 6.79 – 6.78 (m, 1H), 6.68 (s, 1H) 5.49 – 5.44 (m, 1H), 3.97 (s, 3H), 3.90 (s, 3H), 3.61 (d, *J* = 7.2 Hz, 2H), 3.46 – 3.41 (m, 1H), 2.75 – 2.72 (m, 2H), 2.17 – 2.10 (m, 1H), 1.91 – 1.59 (m, 5H), 1.75 (s, 3H), 1.73 (s, 3H), 1.26 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 155.0, 148.9, 142.3, 138.3, 132.9, 131.2, 129.5, 127.9, 126.5, 124.0, 122.6, 120.5, 120.2, 117.2, 117.0, 106.9, 103.3, 97.4, 78.1, 77.0, 56.0. 55.1, 46.8, 38.3, 37.7, 28.3, 27.3, 25.8, 25.6, 23.3, 19.8, 17.7, 14.3; HRMS (EI^+) calcd for $C_{33}H_{41}NO_4$ [M^+] 515.3036; found 515.3040.

Phosphonate 142. To alcohol **142**[45] (204 mg, 0.66 mmol) in THF (10 mL) at 0 °C was added LiBr (400 mg, 4.6 mmol) and Et_3N (0.37 mL, 2.65 mmol) and then after 5 min MsCl (0.13 mL, 1.65 mmol) was added., After 90 min, the reaction mixture was quenched by addition of water and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. The resulting residue was dissolved in $P(OEt)_3$ (3 mL) and the solution was heated to reflux overnight. The next day the solution was allowed to cool to rt and then concentrated *in vacuo*. Final purification by flash column chromatography (2% EtOH in Et_2O) afforded phosphonate **142** (297 mg, 90%) as an oil whose ^{1}H and ^{13}C NMR spectra were consistent with those from previously prepared materials.[45].

Analogue 145. To aldehyde **129** (15 mg, 0.08 mmol) and phosphonate **142** (48 mg, 0.10 mmol) in THF (3 mL) at 0 °C was added NaH (40 mg, 1.0 mmol, 60% dispersion oil) and 15-Crown-5 (2 drops) and the reaction mixture was allowed to warm to rt. The following day the reaction mixture was quenched by addition of NH_4Cl (sat) and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (20% EtOAc in hexanes) afforded analogue **145** (18 mg, 42%) as a light yellow oil: ^{1}H NMR δ 7.17 (d, *J* = 1.7 Hz, 1H), 7.08 (d, *J* = 16.8 Hz, 1H), 7.03 (s, 1H), 6.99 (d, *J* = 16.4 Hz, 1H), 6.98 (d, *J* = 1.4 Hz, 1H), 6.94 (d, *J* = 3.1 Hz, 1H), 6.73 (s, 1H), 6.54 (d, *J* = 2.9 Hz, A1H), 5.25 (d, *J* = 6.7 Hz, 1H), 5.21 (d, *J* = 6.5 Hz, 1H), 4.78 (d, *J* = 6.9 Hz, 1H), 4.65 (d, *J* = 6.8 Hz, 1H), 4.01 (s, 3H), 3.78 (s, 3H), 3.55 (s, 3H), 3.41 (s, 3H), 3.29 (dd, *J* = 11.5, 3.9 Hz, 1H), 2.75 – 2.72 (m, 2H), 2.13 – 1.97 (m, 2H), 1.80 – 1.57 (m, 3H), 1.26 (s, 3H), 1.10 (s, 3H), 0.91 (s, 3H); ^{13}C NMR δ 153.3, 146.2, 143.6, 138.3, 132.7, 129.6, 128.2, 127.8, 126.4, 123.2, 121.7, 118.9, 113.4, 101.8, 98.5, 97.3, 96.2, 95.9, 84.0, 76.9, 56.2, 55.6, 55.3, 47.1, 38.3, 37.7, 33.0, 27.3, 25.3, 23.2, 19.9, 15.1; HRMS (EI$^+$) calcd for $C_{32}H_{41}NO_6$ [M^+] 535.2934; found 535.2933.

Analogue 141. To di-MOM protected analogue **145** (18 mg, 0.034 mmol) in 1:1 MeOH:THF (0.8 mL) protected from ambient light was added TsOH (50 mg, excess) and the resulting solution was allowed to stir overnight. The reaction mixture was quenched by addition of NH_4Cl (sat) and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (50% EtOAc in hexanes) afforded analogue **141** (9 mg, 60%) as a light green oil: ^{1}H NMR δ 7.08 (d, *J* = 16.2 Hz,

1H), 7.02 (s, 1H), 7.00 – 6.95 (m, 2H), 6.94 (d, *J* = 3.0 Hz, 1H), 6.82 (d, *J* = 1.5 Hz, 1H), 6.73 (s, 1H), 6.54 (d, *J* = 2.6 Hz, 1H), 5.46 (br s, 1 OH), 4.01 (s, 3H), 3.78 (s, 3H), 3.45 (dd, *J* = 11.3, 4.0 Hz, 1H), 2.74 – 2.70 (m, 2H), 2.06 – 2.01 (m, 1H), 1.91 – 1.60 (m, 4H), 1.55 (br s, 1 OH), 1.26 (s, 3H), 1.12 (s, 3H), 0.90 (s, 3H); ^{13}C NMR δ 153.3, 145.2, 139.7, 138.4, 132.7, 130.3, 128.3, 127.9, 126.5, 122.0, 119.2, 118.9, 119.4, 101.8, 98.5, 97.3, 77.9, 77.9, 55.3, 47.2, 38.5, 37.7, 33.0, 28.2, 27.3, 22.7, 20.2, 14.3; HRMS (EI$^+$) calcd for $C_{28}H_{33}NO_4$ [M^+] 447.2410; found 447.2404.

Analogue 149. To phosphonate **139** (45 mg, 0.089 mmol) and aldehyde **147** (25.7 mg, 0.068 mmol) in THF (3mL) at 0 °C was added NaH (50 mg, 1.25 mmol, 60% dispersion oil) and 15-Crown-5 (2 drops). The reaction was allowed to warm to rt and then allowed to stir for 4 hours. To the reaction mixture was added 2-propanol (3 mL) and NaH (40 mg, 1.0 mmol, 60% dispersion oil) and the solution was allowed to stir. After 20 hours the reaction was quenched by addition of $NaHCO_3$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (40% EtOAc in hexanes) afforded indole **149** (20 mg, 51% for 2 steps) as a light yellow oil: ^{1}H NMR δ 7.89 (br s, 1H), 7.15 (d, *J* = 1.4 Hz, 1H), 7.00 (s, 1H), 6.99 (s, 1H), 6.97 (m, 2H), 6.78 (d, *J* = 1.1 Hz, 1H), 6.68 (s, 1H), 5.49 – 5.44 (m, 1H), 5.25 (d, *J* = 6.6 Hz, 1H), 5.20 (d, *J* = 6.6 Hz, 1H), 4.78 (d, *J* = 6.9 Hz, 1H), 4.65 (d, *J* = 6.9 Hz, 1H), 3.97 (s, 3H), 3.61 (d, *J* = 7.2 Hz, 2H), 3.55 (s, 3H), 3.41 (s, 3H), 3.29 (dd, *J* = 11.6, 3.9 Hz, 1H), 2.75 – 2.71 (m, 2H), 2.13 – 1.94 (m, 2H), 1.75 – 1.55 (m, 3H), 1.75 (s, 3H), 1.73 (s, 3H), 1.26 (s, 3H), 1.10 (s, 3H), 0.91 (s, 3H); ^{13}C NMR δ 155.0, 146.2, 143.6, 138.3, 132.9, 131.2, 129.6, 128.0, 126.3, 124.7, 123.3, 121.7, 120.5, 117.2, 117.0,

113.4, 103.4, 97.4, 96.2, 95.9, 84.0, 76.9, 56.2, 55.6, 55.1, 47.1, 38.3, 37.7, 27.4, 25.8, 25.6, 25.3, 23.2, 19.9, 17.7, 14.3; HRMS (EI^+) calcd for $C_{36}H_{47}NO_6$ [M^+] 589.3426; found 589.3416.

Analogue 146. To protected analogue **149** (12.2 mg, 0.021 mmol) was added 1:1 THF/MeOH (2 mL) and TsOH (35 mg, 0.184 mmol) and the reaction mixture was allowed to stir overnight. The next day the reaction mixture was quenched by addition of NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (25% to 50% EtOAc in hexanes) afforded analogue **146** (6.4 mg, 62%) as an oil: ^{1}H NMR δ 7.89 (br s, 1H), 7.01 (d, *J* = 16.1 Hz, 1H), 7.00 (s, 1H), 6.97 (d, *J* = 1.9 Hz, 1H), 6.93 (d, *J* = 16.2 Hz, 1H), 6.80 – 6.78 (m, 2H), 6.67 (s, 1H), 5.49 – 5.44 (m, 2H), 3.97 (s, 3H), 3.61 (d, *J* = 7.2 Hz, 2H), 3.45 (dd, *J* = 11.2, 4.0 Hz, 1H), 2.78 – 2.63 (m, 2H), 2.06 – 2.00 (m, 1H), 1.93 – 1.58 (m, 5H), 1.75 (s, 3H), 1.73 (s, 3H), 1.25 (s, 3H), 1.12 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 155.0, 145.2, 139.7, 138.3, 132.9, 131.2, 130.3, 128.2, 126.4, 124.1, 122.0, 120.5, 119.2, 117.2, 117.1, 109.4, 103.4, 97.4, 77.9, 77.8, 55.1, 47.2, 38.5, 37.7, 28.2, 27.3, 25.8, 25.6, 22.7, 20.2, 17.7, 14.3; HRMS (EI^+) calcd for $C_{32}H_{39}NO_4$ [M^+] 501.2879; found 501.2881.

Phosphonate 178. A dispersion of NaH in oil (606 mg, 15.2 mmol) was washed twice with hexanes. After THF (120 mL) was added, it was cooled to 0 °C. Phosphonate **176** (2.25 mL, 11.2 mL) was dissolved in THF (20 mL) and added dropwise to the reaction flask. After one hour bromide **177** (2.0 mL, 13.5 mmol) in THF (20 mL), was added dropwise to the reaction, and it was allowed to stir overnight while it warmed to rt. After addition of HCL (1 M), the solution was extracted with EtOAc. The combined

organic layers were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Final purification by column chromatography, (30 to 50%, EtOAc in hexanes) afforded phosphonate **178** (3.56 g, 94%) as colorless oil. Both the ^{1}H NMR and ^{13}C NMR matched previously reported data.[102]

Diester 179. A 60% dispersion of NaH in oil ((160 mg, 4.0 mmol) was washed twice with hexanes, then THF was added, and the suspension was cooled to 0 °C. Phosphonate **178** (1.01 g, 2.98 mmol) was dissolved in THF and added dropwise to the reaction flask. After one hour aldehyde **174** (0.3 mL, 3.6 mmol) in THF (1 mL) was added dropwise to the reaction flask. The solution was allowed to warm to rt and allowed to stir overnight. The reaction mixture was quenched by addition of water and extracted with ether. The combined organic layers were combined, washed with brine, dried ($MgSO_4$), and filtered and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (30% EtOAc in hexanes) afforded known diester **179**[101] (659 mg, 79%) as a bright yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.45 – 7.44 (m, 2H), 6.56 (d, *J* = 3.3 Hz, 1H), 6.40 (dd *J* = 3.5, 1.8 Hz, 1H), 4.17 (q, *J* = 7.1H, 2H), 3.68 (s, 2H), 1.35 (s, 9H), 1.24 (t, *J* =7.1 Hz, 3H)); ^{13}C NMR δ 170.2, 167.6, 151.1, 144.5, 127.1, 122.2, 116.0, 112.0, 80.5, 60.9, 34.7, 27.9 (3C), 14.2.

Acid 180. A solution of diester **179** (869 mg, 3.10 mmol) in 3:1 TFAA/H_2O (4 mL) was allowed to stir for 2 hours and the solvent was removed under a stream of air. The residue was dissolved in EtOAc and extracted with $NaHCO_3$ (sat). The combined aqueous extracts were acidified with HCl (6 M) and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered and the filtrate was concentrated *in vacuo* to yield known acid **180**[101] (94%, 653 mg) as a light

brown solid: ^{1}H NMR δ 8.17 (br s, 1H), 7.55–7.54 (m, 2H), 6.68 (d, *J* = 3.4 Hz, 1H), 6.49 (dd, *J* = 3.4, 1.8 Hz, 1H), 4.27 (q, *J* = 7.1Hz, 2H), 3.90 (s, 2H), 1.30 (t, *J* =7.1 Hz, 3H); ^{13}C NMR δ 177.0, 167.6, 150.8, 145.1, 127.8, 120.6, 117.0, 112.0, 61.3, 33.4, 14.2.

Benzofuran 181. To acid **180** (653 mg, 2.91 mmol) was added Ac_2O (15 mL) and KOAc (445 mg, 4.53 mmol) and was the solution was heated at reflux for 2 hours. After the solvent was removed under a stream of air, the residue was partitioned between EtOAc and Na_2CO_3 (sat), and the aqueous layer was further extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (10% to 20% EtOAc in hexanes) afforded known benzofuran **181**[101] (674 mg, 93%) as a yellow solid: ^{1}H NMR δ 8.12 (dd, *J* = 1.1, 1.1 Hz, 1H), 7.73 (d, *J* = 2.1 Hz, 1H), 7.71 (d, *J* = 1.1 Hz, 1H), 6.71 (dd, *J* = 2.2, 1.0 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 2.40 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 168.7, 165.9, 155.5, 147.7, 143.2, 127.3, 125.3, 116.6, 111.1, 104.2, 61.3, 20.9, 14.3.

Benzofuran 175. To a solution of acetate **181** (674 mg, 2.72 mmol) in EtOH (10 mL) was added K_2CO_3 (565 mg, 4.1 mmol) and the resulting reaction mixture was heated to reflux for 100 min, allowed to cool and the solvent was removed under a stream of air. To the residue was added water and HCL (1M) was added until slightly acidic and was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, and then the filtrate was concentrated *in vacuo* to afford benzofuran **175** (514 mg, 92%) as a light yellow solid: ^{1}NMR δ 7.83 – 7.82 (m, 1H), 7.67 (d, *J* = 2.3 Hz, 1H), 7.56 (d, *J* = 1.2 Hz, 1H), 6.93 (dd, *J* = 2.3, 0.9 Hz, 1H), 6.77 (br s, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 167.4, 156.0, 149.5,

146.4, 127.1, 121.3, 108.9, 106.2, 104.0, 61.4, 14.3. The ^{1}H NMR data was consistent with previously reported spectra.[100]

Phosphonate 183 by C-C bond formation. To an oil dispersion of NaH (40 mg, 1 mmol) in THF (10 mL) was added phosphonate **185** (100 mg, 0.48 mmol), the reaction was allowed to stir for 5 min and then bromide **177** (0.8 mL, 0.52 mmol) was added and the solution was allowed to stir for an additional 2 hours. The reaction then was quenched by addition of water, and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrated was concentrated *in vacuo*. Final purification by flash column chromatography (70% EtOAc in hexanes) afforded phosphonate **180** (65 mg, 40%) as a light yellow oil: ^{1}H NMR δ 4.14 – 4.03 (m, 4H), 3.70 (d, J_{HP} = 0.6 Hz, 3H), 3.35 (ddd, J_{HP} = 24.0 Hz, J = 11.5, 3.5 Hz, 1H), 2.89 (ddd, J = 17.4, 11.5 Hz, J_{HP} = 7.1 Hz, 1H), 2.66 (ddd, J = 17.4, 3.5 Hz, J_{HP} = 9.1 Hz, 1H), 1.36 (s, 9H), 1.28 (td, J = 7.1 Hz, J_{HP} = 0.4 Hz, 3H), 1.26 (td, J = 7.1 Hz, J_{HP} = 0.3 Hz, 3H); ^{13}C NMR δ 170.0 (d, J_{CP} = 19.2 Hz), 168.8 (d, J_{CP} = 5.4 Hz), 81.4, 62.9 (d, J_{CP} = 6.4 Hz), 62.8 , (d, J_{CP} = 6.7 Hz), 52.5. 41.2(d, J_{CP} = 131.5 Hz), 32.5 (d, J_{CP} = 2.7 Hz), 27.9 (3C), 16.2 (d, J_{CP} = 6.0 Hz), 16.2 (d, J_{CP} = 6.1 Hz); ^{31}P NMR 21.9; HRMS (TOF ES^{+}) calcd for $C_{13}H_{25}O_7NaP$ [M+Na^{+}] 347.1236; found 347.1250.

Phosphonate 183 and 184 via C-P bond formation. To the mixed diester **182** (641 mg, 3.17 mmol) in ether at –78 °C was added freshly prepared LDA (3.79 mmol) and the solution was was allowed to stir for 80 min. Next HMPA was added (0.66 mL, 3.79 mmol) and then after 5 min $ClP(OEt)_2$ (0.65 mL, 4.5 mmol) was added and the solution was allowed to stir for 4 hours. The reaction was quenched by addition of AcOH (1M) in ether, filtered through celite, and the solvent was removed *in vacuo*. The

crude product was allowed to stir open to air overnight. Final purification by flash column chromatography(50% to 100% EtOAc in hexanes) afforded phosphonates **183** and **184** (289 mg, 27%) as a mixtures of regioisomers (10.9:1) as a light yellow oil. The ^{1}H and ^{13}C spectra for the major component (**183**) were consistent with that prepared via an alternative route. For phosphonate **184**: ^{1}H NMR δ 4.14 – 4.03 (m, 4H), 3.63 (s, 3H), 3.30 (ddd, J_{HP} = 24.0 Hz, J = 8.6, 3.5 Hz, 1H), 3.00 – 2.85 (m, 1H), 2.78 – 2.63 (m, 1H), 1.41 (s, 9H), 1.31 – 1.24 (m, 6H); ^{13}C NMR δ 171.5 (d, J_{CP} = 19.4 Hz), 166.9 (d, J_{CP} = 5.6 Hz), 82.0, 62.7 (d, J_{CP} = 6.4 Hz), 62.6 , (d, J_{CP} = 6.7 Hz), 51.9, 41.9 (d, J_{CP} = 131.4 Hz), 31.1 (d, J_{CP} = 2.4 Hz), 27.7 (3C), ~16.2 (obscured by major peak) 16.0 (d, J_{CP} = 6.6 Hz); ^{31}P NMR δ 22.4.

Alcohol 186. Phenol **175** (581 mg, 2.82 mmol) was treated with TBSCl (1.2g, 8.0 mmol), and imidazole (1.23g, 18.1 mmol) in CH_2Cl_2 (10 mL) and the solution was allowed to stir overnight. The next day it was quenched by addition of H_2O and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered and the filtrate was concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc in hexanes) afforded protected TBS phenol **186** (820 mg, 91%) as a solid which was used directly in the next step: ^{1}H NMR δ 7.87 (t, J = 1.1 Hz, 1H), 7.64 (d, J = 2.1 Hz, 1H), 7.37 (d, J = 1.1 Hz, 1H), 6.82 (dd, J = 2.2, 1.0 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H), 1.05 (s, 9H), 0.26 (s, 6H); ^{13}C NMR δ 166.6, 155.8, 148.9, 146.2, 127.4, 125.0, 113.2, 107.0, 104.5, 61.0, 25.7 (3C), 18.2, 14.3, –4.4 (2C).

Alcohol 187. To ester **186** (820 mg, 2.56 mmol), in THF (30mL) at 0 °C was added $LiAlH_4$ (162 mg, 4.27 mmol), the resulting reaction solution was allowed to stir for

one hour, and then quenched by addition of water and acidified and then extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (15% to 20% EtOAc in hexanes) afforded alcohol **187** (421 mg, 59%) as a light yellow oil: ^{1}H NMR δ 7.50 (d, *J* = 2.2 Hz, 1H), 7.15 (s, 1H), 6.75 (dd, *J* = 2.2, 0.8 Hz, 1H), 6.60 (d, *J* = 0.6 Hz, 1H), 4.70 (s, 2H), 1.90 (br s, 1H), 1.04 (s, 9H), 0.23 (s, 6H); ^{13}C NMR δ 156.6, 149.2, 143.8, 138.4, 120.1, 111.4, 104.2, 103.6, 65.5, 25.6 (3C), 18.2, –4.4 (2C); HRMS (EI^+) calcd for $C_{15}H_{22}O_3Si$ [M^+] 278.1338; found 278.1332.

Alcohol 200. To ester **199** (800 mg, 4.21 mmol) in THF (30 mmol) at 0 °C was added $LiAlH_4$ (400 mg, 10.5 mmol) and the reaction mixture was allowed to stir for 30 min and quenched by addition of NH_4Cl solution (sat). After the solution was and diluted with water and extracted with EtOAc, the combined organic extracts were washed with water, brine, dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The resulting alcohol was then dissolved in THF (20 mL), cooled to –20 °C and, after 10 min *n*-BuLi (4.0 mL, 2.2 M in THF) was added. The reaction mixture was allowed to warm to 0 °C and stir for 30 min, then cooled to –20 °C, CuBr·DMS (1.80 g, 8.8 mmol), was added, and the reaction was allowed to stir for 40 min and, then prenyl bromide (690 mg, 4.63 mmol) was added. After the reaction was allowed to warm to room temperature over the course of 2 hours, it was quenched by addition of NH_4Cl solution (sat), diluted with H_2O, and extracted with EtOAc. The combined organics were washed with water, dried ($MgSO_4$) filtered and concentrated *in vacuo*. Final purification by flash column chromatography (15% EtOAc in Hexanes) afforded alcohol **200** (146 mg, 15%) as white solid: ^{1}H NMR δ 6.54 (s, 2H), 5.16 (m, 1H), 4.61 (s, 2H), 3.80 (s, 6H), 3.32 (d, *J* = 7.1

Hz, 2H), 2.08 (br s, 1H), 1.76, (s, 3H), 1.65 (s, 3H); ^{13}C NMR δ 158.0 (2C), 139.8, 131.1, 122.7, 117.4 102.4 (2C), 65.6, 55.7, 25.8, 22.1, 17.6; HRMS (EI$^+$) calcd for $C_{14}H_{20}O_3$ [M$^+$] 236.1412; found 236.1412.

Phosphonate 201. To alcohol **200** (146 mmol, 0.62 mmol) in THF (6 mL) at 0 °C was added LiBr (429 mg, 4.94 mmol), followed by Et_3N (0.34 mL, 2.47 mmol). After 5 min MsCl (0.12 mL, 1.55 mmol) was added dropwise and the solution was allowed to warm to rt. After 1 hour the reaction was quenched by addition of NH_4Cl solution (sat) and then extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$) filtered and the filtrate was concentrated *in vacuo*. The resulting oil was dissolved in $P(OEt)_3$ and then slowly heated to reflux and allowed go while stirring overnight. The reaction was allowed to cool to rt and then concentrated *in vacuo*. Final purification by flash column chromatography (2.5 % EtOH in Et_2O) afforded phosphonate **201** (192, 87%) as an oil: ^{1}H NMR δ 6.49 (d, J = 2.4 Hz, 2H), 5.17–5.13 (m, 1H), 4.09 – 3.99 (m, 4H), 3.80 (s, 6H), 3.30 (d, J = 7.0 Hz, 2H), 3.11 (d, J = 21.5 Hz, 2H), 1.75, (s, 3H), 1.65 (s, 3H), 1.27 (t, J = 7.1 Hz, 6H); ^{13}C NMR δ 157.8 (d, J_{CP} = 3.2 Hz, 2C), 131.0, 129.5 (d, J_{CP} = 8.9 Hz),122.8 (d, J_{CP} = 2.1 Hz), 116.8 (d, J_{CP} = 4.0 Hz), 105.4 (d, J_{CP} = 6.8 Hz, 2C), 62.0 (d, J_{CP} = 6.6 Hz, 2C), 55.7 (2C), 34.0 (d, J_{CP} = 138.2 Hz) 25.8, 22.0, 17.6, 16.4 (d, J_{CP} = 6.1 Hz, 2C); ^{31}P NMR 26.7; HRMS (EI$^+$) calcd for $C_{18}H_{29}O_3P$ [M$^+$] 356.1753; found 356.1747.

Stilbene 166. To aldehyde **42** (15 mg, 0.049 mmol) and phosphonate **201** (24 mg, 0.064 mmol) in THF (0.8 mL) at rt was added NaH (40mg, 1.0 mmol, 60% dispersion oil) and 15-Crown-5 (1 drop). After the reaction mixture was allowed to stir for 3 hours and more THF (1.0 mL) was added and the reaction was allowed to stir

overnight. The next day the reaction was quenched by addition of NH_4Cl solution (sat) and then extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Final purification by flash column chromatography (40% EtOAc in Hexanes) afforded stilbene **166** (18 mg, 72%), as a light yellow oil; ^{1}H NMR δ 6.95 –9.93 (m, 2H), 6.89 –6.88 (m, 2H), 6.68 (s, 2H), 5.21 – 5.16 (m, 1H), 3.90 (s, 3H), 3.87 (s, 6H), 3.44 (dd, *J* =11.6, 3.7 Hz, 1H), 3.34 (d, *J* = 7.1 Hz, 2H), 2.74 – 2.71 (m, 2H). 2.17 –2.12 (m, 1H), 1.91 –1.60 (m, 5H), 1.77, (s, 3H), 1.66 (s, 3H), 1.26 (s, 3H), 1.10 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 158.1 (2C), 148.9, 142.5, 136.4, 131.2, 128.9, 127.9, 126.8, 122.7, 122.6,120.4, 117.8, 106.8, 102.0 (2C), 80.0, 77.0, 56.0, 55.7 (2C), 46.7, 38.4, 37.6, 28.3, 27.3, 25.9, 23.2, 22.3, 19.8, 17.7, 14.3; HRMS (EI^+) calcd for $C_{32}H_{42}O_5$ [M^+] 506.3032; found 506.3032.

Phosphonate 202. To phosphonate **201** (96 mg, 0.27 mmol) in EtOH (2 mL) was added 10% Pd/C (10 mg) and NH_4OAc (10 mg, 0.13 mmol) and the reaction mixture was hydrogenated overnight on a Parr apparatus. The resulting suspension was filtered through celite and washed with EtOAc, and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (2.5% EtOH in Et_2O) afforded phosphonate **202** (48 mg, 50% as an colorless oil; ^{1}H NMR δ 6.48 (d, *J* = 2.6 Hz, 2H), 4.08 – 3.98 (m, 4H), 3.79 (s, 6H), 3.11 (d, *J* = 21.5 Hz, 2H), 2.61 – 2.56 (m, 2H), 1.54 (sep, J = 6.6 Hz, 1H), 1.32 – 1.23 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 6H), 0.92 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR δ 158.4 (d, J_{CP} = 3.2 Hz, 2C), 129.9 (d, J_{CP} = 8.9 Hz), 118.7 (d, J_{CP} = 4.0 Hz), 105.7 (d, J_{CP} = 6.7 Hz, 2C), 62.4 (d, J_{CP} = 6.7 Hz, 2C), 56.0 (2C), 38.7 (d, J_{CP} = 2.1 Hz), 34.4 (d, J_{CP} = 138.4 Hz), 28.5, 22.9 (2C), 21.1 (d, J_{CP} = 1.0 Hz), 16.8 (d, J_{CP} = 6.1 Hz, 2C); ^{31}P NMR δ 26.8; HRMS (EI^+) calcd for $C_{18}H_{31}O_3P$ [M^+] 358.1909; found 358.1912.

Stilbene 167. To aldehyde **42** (15mg, 0.049 mmol) and phosphonate **202** (24mg, 0.067 mmol) in THF (1.5 mL) at rt was added NaH (40mg, 1.0 mmol, 60% dispersion oil) and 15-Crown-5 (1 drop) and the solution was allowed to stir overnight. The next day the reaction was quenched by addition of NH_4Cl solution (sat) and then extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (40% EtOAc in Hexanes) afforded stilbene **167** (21 mg, 83%), as a light yellow oil; ^{1}H NMR δ 6.90 (d *J* = 16.1 Hz, 1H), 6.93 – 6.88 (m, 3H), 6.67 (s, 2H), 3.90 (s, 3H), 3.86 (s, 6H), 3.44 (dd, *J* = 11.7, 3.9 Hz, 1H), 2.74 – 2.71 (m, 2H). 2.64 – 2.60 (m, 2H), 2.16 – 2.12 (m, 1H), 1.90 – 1.82 (m, 2H), 1.74 – 1.54 (m, 4H), 1.37 – 1.32 (m, 2H), 1.26 (s, 3H), 1.11 (s, 3H), 0.94 (d, *J* = 6.6 Hz, 6H), 0.89 (s, 3H); ^{13}C NMR δ 158.3 (2C), 148.9, 142.6, 136.1, 129.0, 127.8, 126.9, 122.6, 120.4, 119.5, 106.9, 101.9 (2C), 78,0, 77.0, 56.0, 55.7 (2C), 46.8, 38.5, 38.4, 37.6, 28.3 (2C), 27.3, 23.2, 22.3 (2C), 21.0, 19.8, 14.3; HRMS (EI^+) calcd for $C_{32}H_{44}O_5$ [M^+] 508.3189; found 506.3190.

BOM Acetal 223. To 4-geranylresorcinol (675 mg, 2.74 mmol) in DMF (20 mL) at 0 °C was added NaH (329 mg, 8.22 mmol, 60% dispersion oil) and NaI (82 mg, 0.55 mmol) and the solution was allowed to stir for 20 min. Next BOMCl (1.07 g, 6.85 mmol) was added dropwise, the reaction was allowed to stir for 2 hours, and then was quenched by addition of water and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Final purification by flash column chromatography (6% EtOAc in hexanes) afforded protected arene **223** (835 mg, 63%) as a colorless oil: ^{1}H NMR δ; 7.36 – 7.27 (m, 10H), 7.06 (d, *J* = 8.3 Hz, 1H), 6.93 (d, *J* = 2.3 Hz, 1H), 6.71 (dd, *J* = 8.3, 2.3 Hz, 1H), 5.31 – 5.29 (m, 1H), 5.29 (s,

2H), 5.24 (s, 2H), 5.11 (t, *J* = 6.1 Hz, 1H), 4.72 (s, 2H), 4.71 (s, 2H), 3.31 (d, *J* = 7.3 Hz, 2H), 2.14 – 2.02 (m, 4H), 1.71 (s, 3H), 1.67 (s, 3H), 1.59 (s, 3H); ^{13}C NMR δ 156.4, 155.6, 137.3, 137.2, 135.8, 131.4, 129.7, 128.4 (4C), 128.0 (2C), 127.9 (2C), 127.7 (2C), 124.3, 124.2, 122.6, 108.8, 103.5, 92.5, 92.2, 69.9, 69.7, 39.7, 27.8, 26.6, 25.7, 17.7, 16.0; HRMS (EI$^+$) calcd for $C_{32}H_{38}O_4$ [M$^+$] 486.2770; found 486.2776.

BOM Epoxide 224. To geranylated arene **223** (411 mg, 0.88 mmol) in CH_2Cl_2 (15 mL) at –20 °C was added *m*-CPBA (200 mg, 0.89 mmol) slowly. The reaction was allowed to stir for 1 hour and then quenched by addition of Na_2SO_3 (satd.) and extracted with CH_2Cl_2. The combined organic extracts were washed with 0.5 M NaOH, brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Final purification by flash column chromatography (4% to 5% EtOAc in hexanes) afforded the external epoxide **224** (131 mg, 31%) as a colorless oil: ^{1}H NMR δ 7.33 – 7.27 (m, 10H), 7.04 (d, *J* = 8.3 Hz, 1H), 6.93 (d, *J* = 2.3 Hz, 1H), 6.71 (dd, *J* = 8.3, 2.3 Hz, 1H), 5.36 (t, *J* = 7.3 Hz, 1H), 5.29 (s, 2H), 5.24 (s, 2H), 4.72 (s, 2H), 4.71 (s, 2H), 3.32 (d, *J* = 7.3 Hz, 2H), 2.71 (t, *J* = 6.3 Hz, 1H), 2.22 – 2.12 (m, 2H), 1.74 (s, 3H), 1.74 – 1.61 (m, 2H), 1.27 (s, 3H), 1.24 (s, 3H); ^{13}C NMR δ 156.5, 155.5, 137.2, 137.2, 134.7, 129.7, 128.4 (2C), 128.4 (2C), 127.9 (2C), 127.9 (2C), 127.8, 127.7, 123.9, 123.3, 108.8, 103.5, 92.4, 92.2, 69.9, 69.7, 64.2, 58.4, 36.3, 27.9, 27.3, 24.8, 18.7, 16.1; HRMS (EI$^+$) calcd for $C_{32}H_{38}O_5$ [M$^+$] 502.2719; found 502.2716.

POM Acetal 225. To POMCl (1.01 g, 7 mmol) in acetone (40 mL) in the dark was added NaI (1.12 g, 7.5 mmol) and the reaction mixture was allowed to stir overnight. The next day K_2CO_3 (830 mg, 6 mmol) was added, followed by 4-geranylresorcinol (600 mg, 2.4 mmol). The reaction was allowed to stir at rt for 4 hours, and then heated at

reflux overnight. The next day an additional amount of POMCl (0.5 mL, 3.5 mmol) was added and the reaction was allowed to reflux for another day. The reaction then was allowed to cooled to rt, quenched by addition of NH_4Cl (satd.), and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Final purification by flash column chromatography (5% EtOAc in hexanes) afforded protected phenol **225** (461 mmol, 39%) as a colorless oil: ^{1}H NMR δ; 7.07 (d, *J* = 8.5 Hz, 1H), 6.78 (d, *J* = 2.2 Hz, 1H), 6.68 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.75 (s, 2H), 5.73 (s, 2H), 5.25 (t, *J* = 7.0 Hz, 1H), 5.10 (t, *J* = 6.1 Hz, 1H), 3.27 (d, *J* = 7.3 Hz, 2H), 2.15 – 1.95 (m, 4H), 1.68 (s, 6H), 1.60 (s, 3H), 1.22 (s, 18H); ^{13}C NMR δ 177.3, 177.2, 156.1, 155.5, 136.3, 131.3, 129.9, 125.5, 124.3, 122.1, 109.3, 103.4, 86.1, 86.0, 39.7, 38.8, 38.8, 27.5, 26.9 (6C), 26.5, 25.7, 17.6, 15.9; HRMS (EI^+) calcd for $C_{28}H_{42}O_6$ [M^+] 474.2981; found 474.2984.

POM Epoxide 226. To geranylated arene **225** (461 mg, 0.97 mmol) in CH_2Cl_2 (25 mL) at –20 °C was added *m*-CPBA (229 mg, 1.02 mmol) slowly. The reaction was allowed to stir for 1 hour and then quenched by addition of Na_2SO_3 (satd.) and extracted with CH_2Cl_2. The combined organic extracts were washed with 0.5 M NaOH, brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Final purification by flash column chromatography (5% EtOAc in hexanes) afforded epoxide **226** (134 mg, 28%) as a colorless oil: ^{1}H NMR δ; 7.06 (d, *J* = 8.4 Hz, 1H), 6.78 (d, *J* = 2.4 Hz, 1H), 6.68 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.75 (s, 2H), 5.73 (s, 2H), 5.32 – 5.27 (m, 1H), 3.28 (d, *J* = 7.3 Hz, 2H), 2.71 (t, *J* = 6.3 Hz, 1H), 2.23 – 2.10 (m, 2H), 1.75 – 1.61 (m, 2H), 1.72 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H), 1.22 (s, 18H); ^{13}C NMR δ 177.8, 177.3, 159.2, 155.4, 135.2, 130.0,

125.2, 122.8, 109.2, 103.4, 86.0 (2C), 64.1, 58.4, 38.8, 38.8, 36.3, 27.7, 27.3, 26.9 (6C), 24.8, 18.7, 16.0; HRMS (EI^+) calcd for $C_{28}H_{42}O_7$ [M^+] 490.2931; found 490.2935.

Benzyl Ether 232A. To epoxide **224** (121 mg, 0.24 mmol) in CH_2Cl_2 (50 mL) at –78 °C was added $BF_3{\cdot}OEt_2$ (0.15 mL, 1.19 mmol). After 8 min the reaction was quenched by addition of Et_3N, diluted with water, and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Final purification by flash column chromatography (30% EtOAc in hexanes) afforded compound **232A** (75 mg, 62%) as a colorless oil: ^{1}H NMR δ 7.39–7.21 (m, 10H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 5.28 (s, 2H), 4.70 (s, 2H), 4.65 (d, *J* = 10.0 Hz, 1H), 4.61 (d, *J* = 9.9 Hz, 1H), 4.58 (s, 2H), 3.41 (dd, *J* = 11.5, 4.1 Hz, 1H), 2.67–2.64 (m, 2H), 2.04–1.97 (m, 1H), 1.85–1.75 (m, 2H), 1.70 – 1.56 (m, 3H), 1.20 (s, 3H), 1.08 (s, 3H), 0.86 (s, 3H); ^{13}C NMR δ 155.4, 152.6, 139.3, 137.4, 129.8, 128.4 (2C), 128.1 (2C), 127.9 (2C), 127.7, 127.2 (2C), 127.2, 115.6, 115.0, 106.6, 92.7, 78.1, 76.4, 72.0, 69.9, 60.8, 46.7, 38.3, 37.7, 28.2, 27.3, 22.7, 20.0, 14.2; HRMS (EI^+) calcd for $C_{32}H_{38}O_5$ [M^+] 502.2719; found 502.2721.

POM Ether 236C. To epoxide **226** (134 mg, 0.27 mmol) in CH_2Cl_2 (55 mL) at –78 °C was added $BF_3{\cdot}OEt_2$ (0.17 mL, 1.4mmol). After 8 min the reaction was quenched by addition of Et_3N, diluted with water, and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Final purification by flash column chromatography (10% to 15% EtOAc in hexanes) afforded ether **236C** (63 mg, 47%) as a colorless oil: ^{1}H NMR δ 7.12 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 2.5 Hz, 1H), 6.66, (dd, *J* = 8.4, 2.4 Hz, 1H), 5.78 – 5.72 (m, 4H), 3.74 (d, *J* = 5.4 Hz, 1H), 2.59 – 2.57 (m, 2H), 1.97 – 1.85 (m, 2H), 1.77 – 1.63 (m, 1H),

1.58 – 1.42 (m, 2H), 1.28 (s, 3H), 1.21 (s, 18H), 0.98 (s, 3H), 0.94 (s, 3H); ^{13}C NMR δ 177.4, 177.2, 155.8, 155.4, 130.4, 125.6, 108.8, 103.0, 86.8, 86.1, 85.9, 85.4, 54.3, 45.6, 38.9, 38.9, 38.8, 26.9 (3C), 26.9 (3C), 26.7, 25.9, 25.7, 23.8, 18.9; HRMS (EI$^+$) calcd for $C_{28}H_{42}O_7$ [M$^+$] 490.2931; found 490.2924.

Alcohol 237. To tricycle **232A** (31 mg, 0.06 mmol) in EtOAc (1.5 mL) was added Pd/C (9 mg) and the reaction mixture was treated with H_2 at 40 psi for 2 days. More EtOAc (2 mL) was added and the reaction was continued for another 2 days. The reaction was then filtered through celite and the filtrated was concentrated *in vacuo.* Final purification by flash column chromatography (50% EtOAc in hexanes) afforded recovered starting material **232A** (7 mg, 23%) as well as benzylic alcohol **237** (10 mg, 39%) as a colorless oil: ^{1}H NMR δ 7.35 – 7.29 (m, 5H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.73 (d, *J* = 8.5 Hz, 1H), 5.29 (s, 2H), 4.77 – 4.73 (m, 2H), 4.73 (s, 2H), 3.44 (dd, *J* = 11.2, 4.1 Hz, 1H), 2.69 – 2.65 (m, 2H), 2.05 – 2.00 (m, 1H), 1.90 – 1.59 (m, 6H), 1.24 (s, 3H), 1.10 (s, 3H), 0.87 (s, 3H); ^{13}C NMR δ 154.1, 151.8, 137.2, 129.3, 128.4 (2C), 128.0 (2C), 127.9, 117.5, 115.8, 106.9, 92.9, 78.0, 76.9, 70.2, 55.3, 46.7, 38.3, 37.8, 28.2, 27.3, 22.5, 20.1, 14.2; HRMS (EI$^+$) calcd for $C_{25}H_{32}O_5$ [M$^+$] 412.2250; found 412.2241.

Acetal 238. 4-Geranylresorcinol (682 mmol, 2.77 mmol) was dissolved in CH_2Cl_2 (15 mL) at rt and ethyl vinyl ether (0.8 mL, 8.31 mmol) was added followed by solid PPTS (12 mg). The reaction was allowed to stir for 4 hours, then quenched by the addition of NH_4Cl (satd.) and finally extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Final purification by flash column chromatography (5% EtOAc in hexanes) afforded protected arene **238** (846 mg, 78%) as a colorless oil : ^{1}H NMR δ 7.03 (d, *J* = 8.3 Hz, 1H), 6.72 (d,

J = 2.2 Hz, 1H), 6.57 (dd, *J* = 8.3, 2.2 Hz, 1H), 5.40 – 5.31 (m, 2H), 5.29 (t, *J* = 7.4 Hz, 1H), 5.11 (t, *J* = 6.5 Hz, 1H), 3.85 – 3.72 (m, 2H), 3.59 – 3.48 (m, 2H), 3.28 (d, *J* = 7.3 Hz, 2H), 2.11 – 2.01 (m, 4H), 1.70 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.50 (t, *J* = 5.5 Hz, 6H), 1.24 – 1.19 (m, 6H);^{13}C NMR δ (mixture of diasteromers)155.9, 155.3, 155.3, 135.7, 131.3, 129.6, 124.6, 124.3, 122.7, 109.5, 109.5, 105.2, 99.7, 99.7, 99.5, 99.4, 61.4, 61.3, 61.2, 39.7, 27.7, 26.6, 25.7, 20.3, 20.3, 20.3 17.6, 16.0, 15.2; HRMS (EI$^+$) calcd for $C_{24}H_{38}O_4$[M$^+$] 390.2770; found 390.2767.

Epoxide 239. To geranylated arene **238** (289 mg, 0.74 mmol) in CH_2Cl_2 (20 mL) at –20 °C was added *m*-CPBA (166 mg, 0.74 mmol) slowly. The reaction was allowed to stir for 1 hour and then quenched by addition of Na_2SO_3 (satd.) and extracted with CH_2Cl_2. The combined organic extracts were washed with 0.5 M NaOH, brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Final purification by flash column chromatography (5% EtOAc in hexanes) afforded recovered starting material **238** (43 mg, 15%) as well as epoxide **239** (107 mg, 36%) as a colorless oil: ^{1}H NMR δ 7.01 (d, *J* = 8.4 Hz, 1H), 6.72 – 6.71 (m, 1H), 6.58 – 6.55 (m, 1H), 5.40 – 5.31 (m, 3H), 3.85 – 3.71 (m, 2H), 3.59 – 3.48 (m, 2H), 3.29 (d, *J* = 7.2 Hz, 2H), 2.71 (t, *J* = 6.2 Hz, 1H), 2.29–2.07 (m, 2H), 1.73 (s, 3H), 1.73–1.60 (m, 2H), 1.49 (t, *J* = 5.3 Hz, 6H), 1.27 (s, 3H), 1.25 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR δ (mixture of diasteromers) 155.9, 155.2, 155.2, 134.5, 134.5, 129.5, 124.3, 123.5, 123.4, 109.5, 109.5, 105.1, 99.6, 99.6, 99.4, 99.4, 99.4, 64.1, 61.3, 61.3, 61.2, 58.3, 58.3, 36.3, 27.8, 27.3, 24.7, 20.2, 20.2, 20.2, 18.6, 16.0, 15.1, 15.1. Anal. Calcd for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 70.78; H, 9.53.

Phenol 241. To epoxide **239** (100 mg, 0.25 mmol) in CH_2Cl_2 (49 mL) at –78 °C was added $BF_3{\cdot}OEt_2$ (0.15 mL, 1.23 mmol). After 8 min the reaction was quenched by

addition of Et_3N, diluted with water and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. TLC analysis of the crude reaction mixture showed an abnormally large number of products. In an attempt to simplify the mixture, the remaining acetal was hydrolyzed. The resulting oil was dissolved in 1:1 THF/MeOH (4 mL) and to it was added $TsOH \cdot H_2O$ (40 mg, 0.21 mmol) and the reaction was allowed to stir overnight. The following day the reaction was quenched by addition of $NaHCO_3$ (satd.) and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. Final purification by flash column chromatography (30% EtOAc in hexanes) afforded compound **240** (9 mg, 14%) as the only identifiable major product as a colorless oil: ^{1}H NMR (CD_3OD) δ; 6.86 (d, *J* = 8.2 Hz, 1H), 6.28 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.03 (d, *J* = 2.4 Hz, 1H), 3.36 – 3.32 (m, 1H), 2.62 – 2.59 (m, 2H),1.95 – 1.91 (m, 1H), 1.80 – 1.56 (m, 4H), 1.18 (s, 3H), 1.07 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (CD_3OD) δ 157.5, 155.0, 131.1, 114.4, 108.8, 104.3, 78.8, 77.3, 48.8, 39.5, 39.2, 29.0, 27.9, 23.5, 20.2, 14.9 HRMS (EI^+) calcd for $C_{16}H_{22}O_3$ [M^+] 262.1569; found 262.1567.

Nitro Ether 242. To 4-geranylresorcinol (630 mg, 2.56 mmol) in DMF (20 mL) at 0 °C was added NaH (307 mg, 7.68 mol, 60% dispersion oil) and NaI (77 mg, 0.5 mmol) and the resulting mixture was allowed to stir for 20 min. Next pNO_2BnCl (1.38 g, 6.5 mmol) was added, the reaction was allowed to stir for 2 hours, and then quenched by pouring into water. The reaction mixture was extracted with EtOAc and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Final purification by flash column chromatography (17% EtOAc in hexanes) afforded the protected arene **242** (568 mg, 43%) as a light yellow solid: ^{1}H NMR δ 8.25

(d, *J* = 8.8 Hz, 2H), 8.24 (d, *J* = 8.8 Hz, 2H), 7.62 – 7.58 (m, 4H), 7.09 (d, *J* = 8.3 Hz, 1H), 6.53 (d, *J* = 2.4 Hz, 1H), 6.49 (dd, *J* =8.3, 2.4 Hz, 1H), 5.33 – 5.29 (m, 1H), 5.16 (s, 2H), 5.13 (s, 2H), 5.12 – 5.08 (m, 1H), 3.35 (d, *J* = 7.3 Hz, 2H), 2.11 – 2.04 (m, 4H), 1.67 (m, 6H), 1.59 (s, 3H); ^{13}C NMR δ 157.5, 156.7, 147.5, 147.5, 144.5 (2C), 136.3, 131.5, 130.0, 127.6 (2C), 127.4 (2C), 124.2, 123.8 (4C), 123.7, 122.3, 105.5, 100.5, 68.8, 68.6, 39.7, 27.9, 26.6, 25.7, 17.7, 16.1; HRMS (EI$^+$) calcd for $C_{30}H_{32}N_2O_6$ [M$^+$] 516.2260; found 516.2257.

Nitro Epoxide 243. To geranylated arene **242** (142 mg, 0.27 mmol) in CH_2Cl_2 (15 mL) at –20 °C *m*-CPBA (62 mg, 0.27 mmol) was added slowly. The reaction was allowed to stir for 1 hour at –20 °C and then quenched by addition of Na_2SO_3 (satd.) and extracted with CH_2Cl_2. The combined organic extracts were washed with 0.5 M NaOH, brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Final purification by flash column chromatography (20% EtOAc in hexanes) afforded external epoxide **243** (49 mg, 34%) as a light yellow solid: ^{1}H NMR δ 8.25 (d, *J* = 8.7 Hz, 2H), 8.24 (d, *J* = 8.7 Hz, 2H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.08 (d, *J* = 8.3 Hz, 1H), 6.54 (d, *J* = 2.3 Hz, 1H), 6.49 (dd, *J* = 8.3, 2.3 Hz, 1H), 5.38 – 5.34 (m, 1H), 5.17 (s, 2H), 5.13 (s, 2H), 3.36 (d, *J* = 7.2 Hz, 2H), 2.72 (t, *J* = 6.2 Hz, 1H), 1.24 – 2.09 (m, 2H), 1.71 – 1.59 (m, 2H), 1.70 (s, 3H), 1.28 (s, 3H), 1.25 (s, 3H); ^{13}C NMR δ 157.5, 156.6, 147.5 (2C), 144.4, 144.4, 135.2, 130.0, 127.6 (2C), 127.3 (2C), 123.8 (2C), 123.8 (2C), 123.4, 123.0, 105.3, 100.4, 68.8, 68.5, 64.1, 58.4, 36.3, 27.9, 27.4, 24.8, 18.7, 16.1; HRMS (EI$^+$) calcd for $C_{30}H_{32}N_2O_7$ [M$^+$] 532.2210; found 532.2217.

PMB Ether 244. To 4-geranylresorcinol (600 mg, 2.44 mmol) in DMF (20 mL) at 0 °C was added NaH (244 mg, 6.1 mmol, 60% dispersion oil) and the mixture was

allowed to stir for 30 min. Next PMBCl (0.73 mL, 5.36 mmol) was added dropwise and the reaction was allowed to warm to rt overnight. The following day it was quenched by addition of NH_4Cl (satd.) and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Final purification by flash column chromatography (12% EtOAc in hexanes) afforded protected phenol **244** (806 mg, 68%) as a colorless oil: ^{1}H NMR δ 7.34 – 7.32 (m, 4H), 7.04 (d, *J* = 8.2 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.57 (d, *J* = 2.0 Hz, 1H), 6.49 (dd, *J* =8.1, 2.1 Hz, 1H), 5.30 (t, *J* = 7.2 Hz, 1H), 5.11 (t, *J* = 6.0 Hz, 1H), 4.94 (s, 2H), 4.92 (s, 2H), 3.79 (s, 6H), 3.29 (d, *J* = 7.3 Hz, 2H), 2.10 – 2.03 (m, 4H), 1.68 (s, 3H), 1.63 (s, 3H), 1.59 (s, 3H); ^{13}C NMR δ 159.3, 159.2, 158.1, 157.2, 135,7, 131.3, 129.4, 129.2 (2C), 129.2, 129.1, 128.8 (2C), 124.4, 122.9, 122.7, 113.9 (2C), 113.8 (2C), 105.0, 100.4, 69.8, 69.6, 55.2, 55.2, 39.7, 27.7, 26.6, 25.7, 17.7, 15.9; HRMS (EI$^+$) calcd for $C_{32}H_{38}O_4$ [M^+] 486.2770; found 486.2767.

PMB Epoxide 245. To geranylated arene **244** (806 mg, 1.66 mmol) in CH_2Cl_2 (60 mL) at –20 °C was added slowly *m*-CPBA (372 mg, 1.66 mmol). The reaction was allowed to stir for 1 hour at –20 °C and then quenched by addition of Na_2SO_3 (satd.) and extracted with CH_2Cl_2. The combined organic extracts were washed with 0.5 M NaOH, brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Final purification by flash column chromatography (8% to 15% EtOAc in hexanes) afforded epoxide **245** (301 mg, 36%) as a colorless oil and recovered starting material (138 mg, 17%): ^{1}H NMR δ 7.35 (d, *J* = 8.6 Hz, 2H), 7.33 (d, *J* = 8.6 Hz, 2H), 7.02 (d, *J* = 8.3 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.58 (d, *J* = 2.5 Hz, 1H), 6.50 (dd, *J* =2.4, 8.3 Hz, 1H), 5.36-5.31 (m, 1H), 4.95 (s, 2H), 4.94 (s, 2H), 3.82 (m, 6H), 3.29 (d, *J* = 7.3 Hz, 2H), 2.70

(t, *J* = 6.3 Hz, 1H), 2.19-2.08 (m, 2H),1.73-1.55 (m, 2H), 1.64 (s, 3H), 1.26 (s, 3H), 1.24 (s, 3H); ^{13}C NMR δ 159.4, 159.2, 158.2, 157.2, 134.6, 129.5, 129.3 (2C), 129.2, 129.1, 128.9 (2C), 123.5, 122.7, 113.9 (2C), 113.8 (2C), 105.1, 100.5, 69.9, 69.6, 64.2, 58,4, 55.3, 55.3, 36.3, 27.9, 27.4, 24.8, 18.7, 16.0; HRMS (EI^+) calcd for $C_{32}H_{38}O_5$ [M^+] 502.2719; found 502.2712.

Benzyl ether 246. To 4-geranylresorcinol (510 mg, 2.07 mmol) in 2:1 THF:DMF (30 mL) at 0 °C was added NaH (190 mg, 4.75 mmol, 60% dispersion in mineral oil) followed by 15-Crown-5 (0.1 mL) and the reaction mixture was allowed to stir for 30 min. After 3,4,5-trimethoxybenzylbromide (1.35 g, 5.18 mmol) was added, the reaction was allowed to warm to room temperature. The following day the reaction mixture was quenched by addition of NH_4Cl (sat), diluted with water, and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, and then the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (25% EtOAc in hexanes) afforded **246** (816 mg, 65%) as a light yellow oil: ^{1}H NMR δ 7.08 (d, *J* = 8.4 Hz, 1H), 6.67 (s, 2H), 6.67 (s, 2H), 6.60 (d, *J* = 2.3 Hz, 1H), 6.53 (dd, *J* = 8.3, 2.3 Hz, 1H), 5.38 – 5.32 (m, 1H), 5.12 – 5.07 (m, 1H), 4.98 (s, 2H), 4.95 (s, 2H), 3.87 (s, 6H), 3.86 (s, 6H), 3.86 (s, 3H), 3.85 (s, 3H), 3.34 (d *J* = 7.4 Hz, 2H), 2.10 – 2.03 (m, 4H), 1.67 (s, 3H), 1.66 (s, 3H), 1.59 (s, 3H); ^{13}C NMR δ 158.0, 157.1, 153.3 (2C), 153.3 (2C), 137.6, 137.3, 135.9, 132.8, 132.8, 131.4, 129.5, 124.2, 123.1, 122.5, 105.1, 104.6 (2C), 104.0 (2C), 100.6, 70.5, 70.0, 60.8, 60.8, 56.0 (2C), 56.0 (2C), 39.8, 27.7, 26.6, 25.7, 17.6, 15.9. Anal. Calcd for $C_{36}H_{46}O_8$: C, 71.26; H, 7.64; Found: C, 70.98; H, 7.63.

Benzyl epoxide 247: To geranylated arene **246** (816 mg, 1.34 mmol), in CH_2Cl_2 (20 mL) at –10 °C was added *m*-CPBA (301 mg, 1.34 mmol, 77% max by weight). After the reaction mixture was allowed to stir for one hour, it was quenched by addition of Na_2SO_3 (sat), diluted with water, and extracted with CH_2Cl_2. The organic extracts were washed with 0.2 M NaOH, brine, dried ($MgSO_4$), and filtered and then the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (25% to 30% EtOAc in hexanes) afforded epoxide **247** (284 mg, 34%) as a colorless oil: ^{1}H NMR δ 7.06 (d, *J* = 8.3 Hz, 1H), 6.66 (s, 4H), 6.60 (d, *J* = 2.2 Hz, 1H), 6.53 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.41 – 5.36 (m, 1H), 4.98 (s, 2H), 4.94 (s, 2H), 3.88 (s, 6H), 3.87 (s, 6H), 3.86 (s, 3H), 3.85 (s, 3H), 3.34 (d *J* = 7.3 Hz, 2H); 2.70 (t, *J* = 6.3 Hz, 1H), 2.25 – 2.06 (m, 2H), 1.68 (s, 3H), 1.68 – 1.60 (m, 2H), 1.27 (s, 3H), 1.24 (s, 3H); ^{13}C NMR δ 158.1, 157.1, 153.4 (2C), 153.3 (2C), 137.6, 137.4, 134.9, 132.8, 132.5, 129.6, 123.3, 122.9, 105.2, 104.7 (2C), 104.1 (2C), 100.6, 70.5, 70.1, 64.1, 60.9, 60.8, 58.4, 56.1 (2C), 56.1 (2C), 36.4, 27.8, 27.4, 24.8, 18.7, 16.0; HRMS (EI$^+$) calcd for $C_{36}H_{46}O_9$ [M^+] 622.3142; found 622.3148.

Furyl ether 248: To 4-geranylresorcinol (420 mg, 1.70 mmol) in DMF (20 mL) at 0 °C was added NaH (156 mg, 3.91 mmol, 60% dispersion in oil) and the reaction mixture was allowed to stir for 15 min. To it was added 0.82 g of freshly prepared (3-furyl)bromomethane (820 mg, 5.1 mmol) and the solution was allowed to warm to room temperature overnight. The next day the reaction mixture was quenched by addition of NH_4Cl (sat), diluted with H_2O, and extracted with EtOAc. The combined organic layers were washed with 2N NaOH, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (4% EtOAc in

hexanes) afforded protected arene **248** (338 mg, 49%) as a light yellow oil: ^{1}H NMR δ 7.49 – 7.47 (m, 2H), 7.43–7.41 (m, 2H), 7.05 (d, *J* = 8.2 Hz, 1H), 6.56 (d, *J* = 8.2 Hz, 1H), 6.52 – 6.46 (m, 3H), 5.31 – 5.26 (m, 1H), 5.13 – 5.08 (m, 1H), 4.90 (s, 2H), 4.89 (s, 2H), 3.27 (d, *J* = 7.3 Hz, 2H), 2.10 – 2.00 (m, 4H), 1.68 (s, 3H), 1.65 (s, 3H), 1.59 (s, 3H); ^{13}C NMR δ 157.8, 157.0, 143.5, 143.3, 140.8, 140.4, 135.8, 131.3, 129.5, 124.3, 123.2, 122.6, 121.5, 121.3, 110.2, 110.0, 105.1, 100.4, 62.1, 61.9, 39.7, 27.7, 26.6, 25.7, 17.7, 16.0; HRMS (EI^{+}) calcd for $C_{26}H_{30}O_4$ [M^{+}] 406.2144; found 406.2145.

Bridged Ether 253A. To epoxide **242** (49 mg, 0.09 mmol) in CH_2Cl_2 (20 mL) at –78 °C was added $BF_3{\cdot}OEt_2$ (0.07 mL, 0.55 mmol). After 8 min the reaction was quenched by addition of Et_3N, diluted with water, and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Final purification by flash column chromatography (15% to 30% EtOAc in hexanes) afforded ether **253A** (10 mg, 20%) as a light yellow solid: ^{1}H NMR δ 8.27 (d, *J* = 8.8 Hz, 2H), 8.25 (d, *J* = 8.7 Hz, 2H), 7.61 (d, *J* = 8.9 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 8.3 Hz, 1H), 6.53 – 6.48 (m, 2H), 5.16 (s, 2H), 5.13 (s, 2H), 3.74 (d, *J* = 5.3 Hz, 1H), 2.67 – 2.65 (m, 2H), 1.96 – 1.90 (m, 2H), 1.75 – 1.63 (m, 1H), 1.56 – 1.40 (m, 2H), 1.30 (s, 3H), 1.01 (s, 3H), 0.90 (s, 3H); ^{13}C NMR δ 157.2, 156.8, 147.5, 147.5, 144.4, 144.3, 130.3, 127.6 (2C), 127.5 (2C), 123.9 (2C), 123.8 (2C), 123.7, 105.1, 100.5, 86.8, 86.1, 68.8, 68,8, 54.0, 46.9, 45.6, 38.9, 26.7, 25.9, 23.8, 19.1; HRMS (EI^{+}) calcd for $C_{30}H_{32}N_2O_7$ [M^{+}] 532.2210; found 532.2207.

PMB Ether 255B, 255C and 255E. To epoxide **244** (150 mg, 0.3 mmol) in CH_2Cl_2 (60 mL) at –78 °C was added $BF_3{\cdot}OEt_2$ (0.19 mL, 1.49 mmol). After 8 min the reaction was quenched by addition of Et_3N, diluted with water, and extracted with

CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Final purification by flash column chromatography (20% EtOAc in hexanes) afforded compounds **255E** (18 mg, 12%) as a white solid, **255B** (49 mg, 33%) as a colorless oil, and **255C** (29mg, 19%) as a colorless oil. For **255E**: ^{1}H NMR (400 MHz) δ 7.33 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.49 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.40 (d, *J* = 2.5 Hz, 1H), 4.93 (d, *J* = 11.2 Hz, 1H), 4.89 (d, *J* = 11.2 Hz, 1H), 4.62 (d, *J* = 11.4 Hz, 1H), 4.40 (d, *J* = 11.4 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.09 (dd, *J* = 11.4, 3.7 Hz, 1H), 2.62 – 2.60 (m, 2H), 2.05 – 1.98 (m, 2H) 1.68 – 1.62 (m, 2H), 1.56 – 1.49 (m, 1H), 1.22 (s, 3H), 1.07 (s, 3H), 0.90 (s, 3H); ^{13}C NMR δ 159.3, 159.0, 158.3, 153.8, 131.2, 130.0, 129.2, 129.2 (2C), 129.0 (2C), 114.3, 113.9 (2C), 113.7 (2C), 107.7, 102.6, 85.2, 76.5, 71.4, 69.7, 55.3, 55.3, 47.5, 38.5, 37.7, 27.5, 24.0, 22.3, 19.9, 15.3; HRMS (EI^+) calcd for $C_{32}H_{38}O_5$ [M^+] 502.2719; found 502.2712.

PMB Ether 225B: ^{1}H NMR δ 7.28 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 1H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.49 (d, *J* = 8.4 Hz, 1H), 4.96 (s, 2H), 3.93 (d, *J* = 13.5 Hz, 1H), 3.85 (d, *J* = 14.2 Hz, 1H), 3.81 (s, 3H), 3.74 (s, 3H), 3.42 (dd, *J* = 11.3, 3.9 Hz, 1H), 2.65 – 2.61 (m, 2H), 2.03 – 1.98 (m, 1H), 1.87 – 1.53 (m, 5H), 1.08 (s, 3H), 1.07 (s, 3H), 0.84 (s, 3H); ^{13}C NMR δ 159.1, 157.2, 155.4, 151.4, 134.5, 129.9 (2C), 129.6, 128.9 (2C), 127.1, 118.2, 114.6, 113.7 (2C), 113.1 (2C), 104.2, 78.1, 76.1, 70.0, 55.2, 55.2, 46.8, 38.3, 37.8, 28.3, 28.0, 27.2, 22.7, 19.9, 14.2; HRMS (EI^+) calcd for $C_{32}H_{38}O_5$ [M^+] 502.2719; found 502.2713.

PMB Ether 255C: ^{1}H NMR (CD_3OD) δ 7.17 (d, *J* = 8.7 Hz, 2H), 7.02 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.76 (s, 1H), 6.75 (d, *J* = 8.5 Hz, 2H), 6.32 (s, 1H),

4.82 (s, 2H), 3.79 (s, 3H), 3.75 (s, 2H), 3.73 (s, 3H), 3.32 – 3.30 (m, 1H), 2.57 – 2.55 (m, 2H), 1.94 – 1.90 (m 1H), 1.78 – 1.53 (m, 4H), 1.16 (s, 3H), 1.04 (s, 3H), 0.83 (s, 3H); ^{13}C NMR δ 160.7, 159.1, 156.9, 153.3, 135.2, 131.9, 130.8, 130.8 (2C), 130.1 (2C), 123.5, 114.7 (2C), 114.5 (2C), 102.0, 78.8, 77.4, 70.8, 55.6, 55.6, 48.7, 39.4, 39.1, 35.7, 28.9, 27.0, 23.4, 20.3, 14.9; HRMS (EI$^+$) calcd for $C_{32}H_{38}O_5$ [M$^+$] 502.2719; found 503.2726.

Preparation of compounds 256C, 256D, and 256E. To epoxide **246** (145 mg, 0.23 mmol) in CH_2Cl_2 (46 mL) at –78 °C was added $BF_3{\cdot}OEt_2$ (0.15 mL, 1.2 mmol). And the solution was allowed to stir for 10 min and then quenched by addition of Et_3N (0.4 mL). After the solvent was removed *in vacuo*, final purification by flash column chromatography (25% to 40% EtOAc in hexanes) afforded protected A-ring alcohol **256E** (13 mg, 9%) as a colorless oil, compound **256D** (33 mg, 32%) as a colorless oil and substituted arene **256C** (40 mg, 28%) as a colorless oil. **For 256E**: ^{1}H NMR δ 6.88 (d, *J* = 8.4 Hz, 1H), 6.65 (s, 2H), 6.60 (s, 2H), 6.52 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.42 (d, *J* = 2.5 Hz, 1H), 4.92 (s, 2H), 4.63 (d, *J* = 11.7 Hz, 1H), 4.43 (d, *J* = 11.8 Hz, 1H), 3.87 (s, 12 H), 3.85 (s, 3H), 3.84 (s, 3H), 3.13 (dd, *J* = 11.3, 3.5 Hz, 1H), 2.66 – 2.62 (m, 2H), 2.07 - 1.52 (m, 5H), 1.24 (s, 3H), 1.13 (s, 3H), 0.94 (s, 3H); ^{13}C NMR δ 158.1, 153.7, 153.3 (2C), 153.1 (2C), 137.5, 137.1, 134.7, 132.7, 130.1, 114.4, 107.7, 104.5 (2C), 104.2, (2C), 102.6, 85.5, 76.5, 71.8, 70.3, 60.9, 60.8, 56.1 (2C), 56.0 (2C), 47.4, 38.5, 37.6, 27.6, 23.9, 22.3, 19.8, 15.3; HRMS (EI$^+$) calcd for $C_{36}H_{46}O_9$[M$^+$] 622.3142; found 622.3152.

For ether 256D: ^{1}H NMR δ 6.98 (d, *J* = 8.3 Hz, 1H), 6.64 (s, 2H), 6.52 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.42 (d, *J* = 2.6 Hz, 1H), 4.91 (s, 2H), 3.87 (s, 6 H), 3.85 (s, 3H), 3.42 (dd, *J* = 11.2, 3.9 Hz, 1H), 2.66 – 2.62 (m, 2H), 2.03 - 1.63 (m, 5H), 1.58, (br s, 1H), 1.22

(s, 3H), 1.09 (s, 3H), 0.87 (s, 3H); ^{13}C NMR δ 158.1, 153.7, 153.3 (2C), 137.4, 132.6, 130.1, 114.4, 107.6, 104.5 (2C), 102.5, 78.0, 76.4, 70.2, 60.8, 56.0 (2C), 46.9, 38.3, 37.7, 28.1, 27.3, 22.3, 19.8, 14.3; HRMS (EI$^+$) calcd for $C_{26}H_{34}O_6$[M$^+$] 442.2355; found 442.2344.

For ether 256C: ^{1}H NMR δ 6.81 (s, 1H), 6.60 (s, 2H), 6.44 (s, 2H), 6.40 (s, 1H), 4.95 (d, *J* = 11.6 Hz, 1H), 4.89 (d, *J* = 11.6 Hz, 1H), 3.88 – 3.86 (m, 2H), 3.84 (s, 3H), 3.81, (s, 9H), 3.74 (s, 3H), 3.42 (dd, *J* = 11.1, 3.9 Hz, 1H), 2.63 – 2.59 (m, 2H), 2.03 - 1.59 (m, 6H), 1.22 (s, 3H), 1.09 (s, 3H), 0.87 (s, 3H); ^{13}C NMR δ 155.4, 153.2 (2C), 152.9 (2C), 152.1, 137.3, 137.1, 135.8, 132.8, 130.7, 121.3, 113.6, 105.7 (2C), 104.0, (2C), 100.7, 78.0, 76.4, 70.0, 60.8, 60.8, 56.0 (2C), 55.8 (2C), 47.0, 38.3, 37.7, 36.0, 28.1, 27.3, 22.3, 19.8, 14.3; HRMS (EI$^+$) calcd for $C_{36}H_{46}O_9$[M$^+$] 622.3142; found 622.3145.

Protected phenol 259. To resorcinol **258** (1.38 g, 12.5 mmol) in CH_2Cl_2 (30 mL) at 0 °C and was added DIPEA (5.4 mL, 31.3 mmol) followed by MOMCl (1.5 mL, 18.8 mmol) and the solution was allowed to warm to rt. The next day the reaction solution was quenched by addition of NH_4Cl (sat), diluted with water, and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (15% to 20% EtOAc in hexanes) afforded the mono-MOM protected phenol (649 mg, 34%) as a colorless oil. whose ^{1}H and ^{13}C NMR was consistent with the previously reported spectra.[118] To this phenol (649 mg, 4.21 mmol) in CH_2Cl_2 (20 mL) was added DHP (0.45 mL, 5.0 mmol) followed by PPTS (15 mg, cat.), and the solution was allowed to stir for 5 hours at rt. The reaction solution was then quenched by addition

of NH_4Cl (sat) and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (10% to 15 % EtOAc in hexanes afforded the THP protected phenol **259** (682 mg, 68%, or 23% overall for 2 steps) as a colorless oil whose ^1H and ^{13}C NMR was consistent with the previously reported spectra.[118]

Geranylated Arene 260. To arene **259** (1.75 g, 7.42 mmol) in THF (20 mL) at 0 °C was added *n*-BuLi (3.22 mL, 2.3 M) and the solution was allowed to stir for 15 min, after CuI (1.55 g, 8.17 mmol) was added to the reaction solution, it was allowed to stir for an additional 40 min. Freshly prepared geranyl bromide (1.74 g, 8.0 mmol) was added dropwise and the resulting solution was allowed to warm to room temperature. The following day the reaction mixture was quenched by addition of NH_4Cl (sat), diluted with water, and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (4% EtOAc in hexanes) afforded geranylated arene **260** (1.49 g, 54%) as a colorless oil: ^1H NMR δ 7.07 (t, *J* = 8.3 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.74 (d, *J* = 8.2 Hz, 1H), 5.43 (t, *J* = 3.0 Hz, 1H), 5.28 – 5.23 (m, 1H), 5.19 (s, 2H), 5.09 – 5.05 (m, 1H), 3.89 (td, *J* = 10.6, 2.8 Hz, 1H), 3.63 – 3.57 (m, 1H), 3.47 (s, 3H), 3.47 – 3.41 (m, 2H), 2.06 – 1.93 (m, 5H), 1.89 – 1.85 (m, 2H), 1.79 (s, 3H), 1.72 – 1.60 (m, 3H), 1.64 (s, 3H), 1.54 (s, 3H); ^{13}C NMR δ 155.6, 155.5, 134.3, 131.2, 126.6, 124.4, 123.0, 119.9, 110.1, 107.5, 96.0, 94.4, 61.7, 55.9, 39.7, 30.4, 26.6, 25.6, 25.3, 22.6, 18.7, 17.6, 16.1. Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15; Found: C, 73.73; H, 9.29.

Phenol 261. To the THP protected phenol **260** (1.44 g, 3.84 mmol) in MeOH (40 mL) was added TsOH (800 mg, 4.2 mmol). After the reaction solution was allowed to stir for one hour, the reaction was quenched by addition of $NaHCO_3$ (sat), diluted with water, and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and then the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (10% EtOAc in hexanes) afforded phenol **261** (423 mg, 38%) as a colorless oil: ^{1}H NMR δ 7.02 (t, *J* = 8.2 Hz, 1H), 6.67 (d, *J* = 8.2 Hz, 1H), 6.51 (d, *J* = 8.2 Hz, 1H), 5.40 (s, 1H), 5.27 – 5.22 (m, 1H), 5.18 (s, 2H), 5.07 – 5.03 (m, 1H), 3.48 (s, 3H), 3.45 (d, *J* = 7.1 Hz, 2H), 2.10–2.00 (m, 4H), 1.81 (s, 3H), 1.67 (s, 3H), 1.58 (s, 3H); ^{13}C NMR δ 155.5, 155.5, 137.8, 131.8, 127.1, 123.8, 121.8, 116.4, 109.8, 106.6, 94.6, 56.0, 39.7, 26.4, 25.6, 22.4, 17.6, 16.1; HRMS (EI^+) calcd for $C_{18}H_{26}O_3$[M] 290.1882; found 290.1888.

Epoxide 262. To arene **261** (423 mg, 1.46 mmol) in CH_2Cl_2 (20 mL) at –10 °C was added *m*-CPBA (326 mg, 1.46 mmol, 77% max by weight). After one hour, the reaction mixture was quenched by addition of Na_2SO_3 (sat), diluted with H_2O, and extracted with CH_2Cl_2. The combined organic extracts were washed with $NaHCO_3$ (sat), dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (15% EtOAc in hexanes) afforded epoxide **262** (104 mg, 23%) as a colorless oil: ^{1}H NMR δ 7.02 (d, *J* = 8.2 Hz, 1H), 6.67 (dd, *J* = 8.3 Hz, 0.9 Hz, 1H), 6.50 (dd, *J* = 8.1, 0.9 Hz, 1H), 5.31 – 5.26 (m, 1H), 5.18 (s, 2H), 3.47 (s, 3H), 3.44 (d, *J* = 7.2 Hz, 2H), 2.67 (t, *J* = 6.3 Hz, 1H), 2.23 – 2.09 (m, 2H), 1.83 (d, *J* = 1.0 Hz, 3H), 1.67 – 1.60 (m, 2H), 1.26 (s, 3H), 1.24 (s, 3H); ^{13}C NMR δ 155.6, 155.2, 136.2,

127.1, 122.6, 116.6, 109.8, 106.7, 94.7, 64.2, 58.5, 56.0, 36.4, 27.2, 24.7, 22.4, 18.7, 16.2; HRMS (EI^+) calcd for $C_{18}H_{26}O_4$[M] 306.1831; found 306.1831.

Compound 220. To epoxide **262** (91 mg, 0.30 mmol) in CH_2Cl_2 (60 mL) at –78 °C was added $BF_3 \cdot OEt_2$ (0.19 mL, 1.5 mmol). After 10 min the reaction solution was quenched by addition of Et_3N (0.5 mL) and the solvent was removed *in vacuo*. Final purification by flash column chromatography (15% EtOAc in hexanes) afforded compound **220** (14 mg, 15%) as a colorless oil whose ^1H and ^{13}C NMR where consistent with those that were previously reported.[110]

Ether 263. To 4-geranylrescorinol (500 mg, 2.03 mmol) in DMF (30 mL) at 0 °C was added NaH (180 mg, 4.5 mmol, 60% dispersion in mineral oil) and 15-Crown-5 (3 drops, cat.) and the reaction mixture was allowed to stir for 30 min. After propargyl bromide (760 mg, 5.1 mmol, 80% by weight in toluene) was added, the solution was allowed to warm slowly to room temperature and then quenched by addition of NH_4Cl (sat), diluted with water, and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (4% EtOAc in hexanes) afforded ether **263** (494 mg, 75%) as a colorless oil: ^1H NMR δ 7.06 (d, *J* = 8.3 Hz, 1H), 6.63 (d, *J* = 2.3 Hz, 1H), 6.53 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.31 – 5.25 (m, 1H), 5.13 – 5.08 (m, 1H), 4.67 (d, *J* = 2.4 Hz, 1H), 4.66 (d, *J* = 2.4 Hz, 1H), 3.27 (d, *J* = 7.3 Hz, 2H), 2.52 (t, *J* = 2.4 Hz, 1H), 2.50 (t, *J* = 2.3 Hz, 1H), 2.11 – 2.01 (m, 4H), 1.68 (m, 6H), 1.60 (s, 3H) ^{13}C NMR δ 156.6, 156.0, 136.0, 131.3, 129.5, 124.3, 123.8, 122.3, 105.9, 100.7, 78.6 (2C), 75.4, 75.4, 56.0, 55.9, 39.7, 27.5, 26.6, 25.7, 17.7, 16.0. Anal. Calcd for $C_{22}H_{26}O_2$: C, 81.95; H, 8.13; Found: C, 82.05; H, 8.28.

Expoxide 264. To arene **263** (494 mg, 1.53 mmol) in CH_2Cl_2 (20 mL) at –10 °C was added *m*-CPBA (376 mg, 1.68 mmol, 77% max by weight), and the reaction mixture was allowed to stir for one hour. After the reaction mixture was quenched by addition of Na_2SO_3 (sat), it was diluted with water and extracted with CH_2Cl_2. The combined organic extracts were washed with 0.5 M NaOH, brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (7% EtOAc in hexanes) afforded epoxide **264** (195 mg, 38%) as a colorless oil: ^{1}H NMR δ 7.04 (d, *J* = 8.2 Hz, 1H), 6.63 (d, *J* = 2.4 Hz, 1H), 6.53 (dd, *J* = 8.3, 2.5 Hz, 1H), 5.35 – 5.30 (m, 1H), 4.68, (d, *J* = 2.5 Hz, 1H), 4.66 (d, *J* = 2.4 Hz, 1H), 3.29 (d, *J* = 7.3 Hz, 2H), 2.71 (t, *J* = 6.3 Hz, 1H), 2.53 (t, *J* = 2.4 Hz, 1H), 2.51 (t, *J* = 2.3 Hz, 1H), 2.25 – 2.07 (m, 2H), 1.74 – 1.57 (m, 2H), 1.72 (m, 3H), 1.26 (s, 3H), 1.25 (s, 3H); ^{13}C NMR δ 156.7, 156.0, 134.9, 129.6, 123.6, 123.1, 105.9, 100.7, 78.6, 78.5, 75.4 (2C), 64.1, 58.4, 55.9, 55.9, 39.3, 27.7, 27.3, 24.8, 18.7, 16.0. Anal. Calcd for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74; Found: C, 78.02; H, 7.80.

Crotyl ether 267. To 4-geranylrescorinol (927 mg, 3.76 mmol) in acetone (15 ml) was added K_2CO_3 (1.45 g, 10.5 mmol) followed by crotyl chloride (815 mg, 9.0 mmol), and the reaction mixture was heated to reflux overnight. The reaction mixture then was allowed to cool to rt and quenched by the addition of $NaHCO_3$ (sat), and extracted with EtOAc. The organic extracts were washed with H_2O, brine, dried ($MgSO_4$) and then filtered, and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (4% EtOAc in hexanes) afforded epoxide **267** (265 mg, 20%) as a colorless oil: ^{1}H NMR δ 7.02 – 6.99 (m, 1H), 6.47 – 6.39 (m, 2H), 5.88 – 5.68 (m, 4H), 5.32 – 5.27 (m, 1H), 5.13 – 5.09 (m, 1H), 4.57 – 4.55 (m) (cis), 4.43 – 4.41 (m),

(trans) 1:3 ratio, 4H), 3.26 (d, *J* =7.5 Hz, 2H), 2.11 – 2.03 (m, 4H), 1.76 – 1.73 (m, 6H), 1.68 (m, 6H), 1.60 (s, 3H); ^{13}C NMR δ 157.9, 157.2, 135.7, 131.3, 130.5, 129.4, 129.2, 126.3, 126.2, 124.4, 122.8, 122.7, 104.8, 100.2, 68.8, 68.7, 39.8, 27.6, 26.6, 25.7, 17.9, 17.8, 17.7, 16.0; HRMS (EI$^+$) calcd for $C_{24}H_{34}O_2$ [M$^+$] 354.2559; found 354.2551.

Epoxide 268. To arene **267** (438 mg, 1.24 mmol), in CH_2Cl_2 (25 mL) at –20 °C was added *m*-CPBA (277 mg, 0.124 mmol, 77% max by weight). After the reaction mixture was allowed to stir for one hour, it was quenched by addition of Na_2SO_3 (sat) and extracted with CH_2Cl_2. The combined organic extracts were washed with 0.5 M NaOH, brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (4% EtOAc in hexanes) afforded epoxide **268** (76 mg, 17%) as a light yellow oil: ^{1}H NMR δ 7.01 – 6.91 (m, 1H), 6.47 – 6.39 (m, 2H), 5.87 – 5.67 (m, 4H), 5.34 – 5.32 (m, 1H), (4.56 – 4.54 (m) (cis), 4.43 – 4.40 (m), (trans) 1:3 ratio, 4H) , 3.27 (d, *J* = 7.9 Hz, 2H), 2.73 (t, *J* = 6.3 Hz, 1H), 2.24 – 2.07 (m, 2H), 1.76 (m, 3H), 1.74 (m, 3H), 1.71 (s, 3H), 1.70 – 1.57 (m, 2H), 1.26 (s, 3H), 1.25 (s, 3H); ^{13}C NMR δ 158.3, 157.5, 134.9, 130.9, 129.8, 129.7, 126.6, 125.5, 124.0, 122.8, 105.1, 100.6, 69.1, 69.0, 64.6, 58.7, 36.7, 28.1, 27.7, 25.2, 19.1, 18.2, 18.2, 16.4; HRMS (EI$^+$) calcd for $C_{24}H_{34}O_3$[M$^+$] 370.2508; found 370.2617.

Ether 271. To 4-geranylrescorinol (486 mg, 1.97 mmol), in acetone (15 mL) was added K_2CO_3 (1.36 g, 9.85 mmol) and the reaction mixture was heated to reflux for 30 min and then crotyl bromide **270** (400 mg, 2.96 mmol) was added was added to the hot reaction mixture. After another 30 min and additional amount of crotyl bromide[121] (400 mg, 2.96 mmol) was added and the reaction mixture was allowed to reflux for four hours. The solution was allowed to cool to room temperature, filtered and concentrated *in*

vacuo. Final purification by flash column chromatography (2.5% EtOAc in hexanes) afforded the pure E ether compound **271** (110 mg, 16%) as an oil: ^{1}H NMR δ 7.00 (d, *J* = 8.3 Hz, 1H), 6.45 (d, *J* = 2.4 Hz, 1H), 6.40 (d, *J* = 8.3, 2.3 Hz, 1H), 5.89 – 5.78 (m, 2H), 5.76 – 5.67 (m, 2H), 5.32 – 5.28 (m, 1H), 5.13 – 5.09 (m, 1H), 4.43 – 4.39 (m, 4H), 3.27 (d, *J* = 7.3 Hz, 2H), 2.13 – 2.02 (m, 4H), 1.75 – 1.73 (m, 6H), 1.68 (m, 6H), 1.59 (3H); ^{13}C NMR δ 157.9, 157.1, 135.6, 131.2, 130.4, 129.3, 129.2, 126.3, 126.2, 124.4, 122.8, 122.7, 104.7, 100.2, 68.7, 68.6, 39.7, 27.6, 26.6, 25.7, 17.8, 17.8, 17.6, 15.9.

Alternative route to ethers 271 and 272. To 4-geranylrescorinol (1.02 g, 4.14 mmol) in DMF (20 mL) at 0 °C was added NaH (200 mg, 5 mmol, 60 % dispersion oil) and then bromide **270** (675 mg, 5 mmol) was added and after 30 min and addition amount of NaH (200 mg, 5 mmol) and bromide **270** (810 mg, 6 mmol). After 30 min the reaction progress was checked by TLC and then an additional amount of NaH (200 mg, 5 mmol) and bromide **270** (610 mg, 4.5 mmol). After another 30 min the reaction mixture was quenched by the addition of NH_4Cl (sat), and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and then the solvent was removed *in vacuo*. Final purification by flash column chromatography (2% EtOAc in hexanes) afforded ethers **271** and **272** (1.001 g total , 1:0.3 mol ratio, 51%:15%) as an oil that was an inseparable mixture. For **272**: ^{1}H NMR (400 MHz) δ 6.93 (s, 1H), 6.49 (s, 1H), 5.95 – 5.84 (m, 2H), 5.82 – 5.73 (m, 2H), 5.68 – 5.60 (m, 1H), 5.57 – 5.48 (m, 1H), 5.38 – 5.34 (m, 1H), 5.19 – 5.17 (m, 1H), 4.48 – 4.45 (m, 4H), 3.34 – 3.32 (m, 2H), 3.30 – 3.29 (m, 2H), 2.17 – 2.08 (m, 4H), 1.82 – 1.79 (m, 6H), 1.76 (s, 3H), 1.74 (s, 6H), 1.65 (s, 3H); ^{13}C NMR (100 MHz) δ 155.2, 154.9, 135.2, 131.1, 130.2,

130.2, 130.0, 129.2, 129.1, 125.2, 123.1, 122.2, 121.6, 98.6, 69.3, 69.3, 39.8, 32.5, 27.7, 26.7, 17.9, 27.6, 16.0. (some peaks are overlapping with the major component **271**).

Epoxide 273. To arene **271** (110 mg, 0.31 mmol) in CH_2Cl_2 (10 mL) at –15 °C was added *m*-CPBA (70 mg, 0.31 mmol, 77% max by weight), and the reaction mixture was allowed to stir for one hour. After the reaction was quenched by addition of Na_2SO_3 (sat), it was diluted with water and extracted with CH_2Cl_2. The combined organic extracts were washed with 0.5 M NaOH, brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (3% EtOAc in hexanes) afforded epoxide **273** (27 mg, 24%) as a colorless oil: ^{1}H NMR (400 MHz) δ 6.98 (d, *J* = 8.2 Hz, 1H), 6.45 (d, *J* = 2.4 Hz, 1H), 6.40 (dd, *J* = 8.3, 2.5 Hz, 1H), 5.89 – 5.79 (m, 2H), 5.76 – 5.67 (m, 2H), 5.36 – 5.32 (m, 1H), 4.43 – 4.40 (m, 4H), 3.27 (d, *J* = 7.3 Hz, 2H), 2.70 (t, *J* = 6.3 Hz, 1H), 2.23 – 2.08 (m, 2H), 1.76 – 1.74 (m, 6H), 1.71 (s, 3H), 1.69 – 1.56 (m, 2H), 1.26 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (100 MHz) δ 157.9, 157.1, 134.4, 130.4, 129.4, 129.3, 126.2, 126.1, 123.6, 122.4, 104.7, 100.2, 68.7, 68.6, 64.1, 58.3, 36.3, 27.7, 27.3, 24.8, 18.6, 17.8, 17.8, 16.0.

Ether 276. To a solution of the propargylic alcohol (**274**) (1.5 mL, 15.3 mmol) in CH_3CN (20 mL) cooled to 0 °C was added DBU (2.65 mL, 17.7 mmol), then TFAA (1.97 mL, 14.2 mmol) was added dropwise and the reaction was allowed to stir for 1 hour to afford triflate **275**. To phenol **222** (1.45 g, 5.90 mmol) in CH_3CN (20 mL) at 0 °C was added DBU (2.3 mL, 15.3 mmol) and $CuCl_2$ (10 mg, cat), followed by the freshly prepared triflate ester **275** solution via canula. The reaction mixture was allowed to stir for 4 hours at 0 °C, then was quenched by the addition of NH_4Cl (sat), and finally was extracted with EtOAc. The combined organic extracts were washed with brine, dried

($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Purification by flash column chromatography lead to a mixture of the desired compound **276** as a yellow oil and an unknown contaminate. This mixture was used the next step without further purification. For **276**: ^{1}H NMR δ 7.48 (d, *J* = 2.2 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.77 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.28 (t, *J* = 7.7 Hz, 1H), 5.11 (t, *J* = 6.6 Hz, 1H), 3.26 (d, *J* = 7.3 Hz, 2H), 2.56 (s, 1H), 2.53 (s, 1H), 2.12 – 2.01 (m, 4H), 1.68 (m, 6H),1.67 (s, 6H), 1.63 (s, 6H), 1.60 (s, 3H); ^{13}C NMR δ 153.6, 153.6, 135.6, 131.4, 129.0, 128.0, 124.4, 123.1, 115.5, 112.3, 86.5, 86.5, 73.4 (2C), 72.3, 71.9, 39.7, 29.7 (2C), 29.6 (2C), 28.1, 26.6, 25.7, 17.7, 16.1; HRMS (EI^+) calcd for $C_{26}H_{34}O_2$ [M^+] 378.2559; found 378.2558.

Epoxide 277. To the mixture of compound **276** (384 mg) from the previous reaction in CH_2Cl_2 (20 mL) at –20 °C *m*-CPBA (227 mg, 1.01 mmol) was slowly added. The reaction was allowed to stir for 1 hour and then quenched by addition of Na_2SO_3 (satd.) and extracted with CH_2Cl_2. The combined organic extracts were washed with 0.5 M NaOH, brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (5% EtOAc in hexanes) afforded epoxide **277** (51 mg, 5%) over 2 steps as a light yellow oil: ^{1}H NMR δ 7.48 (d, *J* = 2.2 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.76 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.35 – 5.30 (m, 1H), 3.27 (d, *J* = 7.2 Hz, 2H), 2.71 (t, *J* = 6.2 Hz, 1H), 2.56 (s, 1H), 2.54 (s, 1H), 2.26 – 2.08 (m, 2H), 1.72 (s, 3H), 1.69 – 1.60 (m, 2H), 1.67 (s, 6H), 1.63 (s, 6H), 1.26 (s, 3H), 1.25 (s, 3H); ^{13}C NMR δ 153.7, 153.5, 134.5, 129.0, 127.7, 123.8, 115.4, 112.3, 86.4, 86.4, 73.4, 73.4, 72.3, 71.8, 64.1, 58.3, 36.4, 29.7, 29.6, 29.6 (2C), 28.3, 27.4, 24.8, 18.7, 16.1; HRMS (EI^+) calcd for $C_{26}H_{34}O_3$[M^+] 394.2508; found 394.2597.

Epoxide 278. To epoxide **277** (95 mg, 0.24 mmol), in MeOH (3 mL) at 0 °C was added Lindlar catalyst (7mg) and quinoline (2 drops) and the reaction mixture was allowed to stir under one atmosphere of H_2. After 130 min the reaction mixture was filtered through celite, the pad was washed with EtOAc and the filtrate was concentrated *in vacuo*. Final purification of the residue by flash column chromatography (4% EtOAc in hexanes) afforded epoxide **278** (73 mg, 76%) as a colorless oil: ^{1}H NMR δ 6.92 (d, *J* = 8.3 Hz, 1H), 6.72 (d, *J* = 2.2 Hz, 1H), 6.51 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.17 – 6.03 (m, 2H), 5.36 – 5.31 (m, 1H), 5.21 – 5.07 (m, 4H), 3.26 (d, *J* = 7.3 Hz, 2H), 2.71 (t, *J* = 6.3 Hz, 1H), 2.21 – 2.12 (m, 2H), 1.76 – 1.60 (m, 2H), 1.72 (s, 3H), 1.45 (s, 6H), 1.39 (s, 6H), 1.26 (s, 3H), 1.24 (s, 3H); ^{13}C NMR δ 153.9 (2C) 144.7, 144.4 134.2, 128.7, 126.8, 124.0, 114.9, 113.0, 112.9, 112.6, 79.3, 79.1, 64.1, 58.3, 36.3, 28.2, 27.3, 27.2, 27.1, 26.8 (2C) 24.8, 18.7, 16.1; HRMS (EI$^+$) calcd for $C_{26}H_{38}O_3$ [M$^+$] 398.2821; found 398.2811.

Ether 282A. To epoxide **268** (89 mg, 0.26 mmol) in CH_2Cl_2 (53 mL) at –78 °C was added $BF_3{\cdot}OEt_2$ (0.17 mmol, 1.3 mmol). The reaction mixture was allowed to stir for 10 min and then quenched by addition of Et_3N (0.4 mL). After concentration *in vacuo*, final purification by flash column chromatography (15% EtOAc in hexanes) afforded **282A** (42 mg, 47%) as a colorless oil: ^{1}H NMR δ 7.10 (d, *J* = 8.4 Hz, 1H), 6.60 (d, *J* = 2.4 Hz, 1H), 6.52 (dd, *J* = 8.3, 2.5 Hz, 1H), 4.68 – 4.66 (m, 4H), 3.74 (d, *J* = 5.3 Hz, 1H), 2.59 – 2.57 (m, 2H), 2.54 (t, *J* = 2.3 Hz, 1H), 2.50 (t, *J* = 2.4 Hz 1H), 1.97 – 1.47 (m, 5H), 1.30 (s, 3H), 1.00 (s, 3H), 0.97 (s, 3H); ^{13}C NMR δ 156.4, 156.1, 130.1, 124.1, 105.6, 100.6, 86.9, 86.0, 78.6, 78.5, 75.5, 75.4, 55.9, 55.8, 54.2, 45.6, 38.9, 36.6, 25.9, 25.7, 23.8, 19.0; HRMS (EI$^+$) calcd for $C_{22}H_{26}O_3$[M$^+$] 338.1882; found 338.1882.

Ether 283A and Arene 283D. To epoxide **277** (51 mg, 0.13 mmol) in CH_2Cl_2 (26 mL) cooled to –78 °C was added $BF_3{\cdot}Et_2O$ (0.08 mL, 0.645 mmol) dropwise. After 10 min the reaction solution was quenched by addition of Et_3N, allowed to warm to rt, washed with 1M HCl and brine, dried ($MgSO_4$), and filtered and the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (10% to 20% EtOAc in hexanes) afforded bridged-ether **283A** (24 mg, 47%) as a colorless oil and tricycle **283D** (6 mg, 14%) as a colorless oil. For **283A**: ^{1}H NMR δ 7.46 (d, *J* = 2.4 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.74 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.73 (d, *J* = 5.3 Hz, 1H), 2.59 – 2.55 (m, 2H), 2.56 (s, 1H), 2.54 (s, 1H), 1.95 – 1.90 (m, 2H), 1.72 – 1.65 (m, 1H), 1.68 (s, 6H), 1.63 (s, 6H), 1.58 – 1.51 (m, 1H), 1.47 – 1.42 (m, 1H), 1.28 (s, 3H), 1.00 (s, 3H), 0.93 (s, 3H); ^{13}C NMR δ 153.7, 153.5, 129.5, 127.7, 114.9, 112.0, 89.9, 86.4, 86.2, 86.1, 73.5, 73.4, 72.3, 71.7, 54.0, 45.6, 39.0, 29.7, 29.6, 29.6, 29.5, 27.5, 25.9, 25.8, 23.8, 19.1; HRMS (EI^+) calcd for $C_{26}H_{34}O_3$ [M^+] 394.2508; found 394.2504.

For **283D**: ^{1}H NMR δ 6.95 (d, *J* = 8.3 Hz, 1H), 6.70 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.66 (d, *J* = 2.4 Hz, 1H), 3.42 (dd, *J* = 11.5, 4.2 Hz, 1H), 2.67 – 2.63 (m, 2H), 2.55 (s, 1H), 2.01 – 1.97 (m, 1H), 1.87 – 1.82 (m, 1H), 1.78 – 1.60 (m, 4H), 1.62 (s, 3H), 1.61 (s, 3H), 1.27 (s, 3H), 1.09 (s, 3H), 0.87 (s 3H); ^{13}C NMR δ 154.7, 153.2, 129.5, 116.5, 113.7, 110.0, 86.3, 78.1, 76.3, 73.6, 72.2, 47.0, 38.4, 37.8, 29.6, 29.6, 28.3, 27.3, 22.6, 19.9, 14.3; HRMS (EI^+) calcd for $C_{21}H_{28}O_3$ [M^+] 328.2038; found 328.2034.

Allyl Arene 284a. To epoxide **277** (127 mg, 0.37 mmol) in CH_2Cl_2 (74 mL) at –78 °C was added $BF_3{\cdot}Et_2O$ (0.23 mL, 1.8 mmol) and the solution was allowed to stir for 8 min. The reaction was quenched by addition of Et_3N and allowed to warm room temperature, washed with 0.1 M HCl, brine, dried ($MgSO_4$), and filtered, and the filtrate

was concentrated *in vacuo*. Final purification by flash column chromatography (5% to 10% EtOAc in hexanes) afforded bridged allyl ether **284A** (41 mg, 32%) as a colorless oil along with compound **284B** (10 mg, 8%) as a colorless oil. For **284B**: ^{1}H NMR δ 6.87 (d, *J* = 8.4 Hz, 1H), 6.42 (d, *J* = 8.4 Hz, 1H), 6.10 – 5.85 (m, 2H), 5.45 – 5.37 (m, 1H), 5.26 – 5.21 (m, 1H), 5.03 – 4.96 (m, 1H), 4.92 – 4.88 (m, 1H), 4.51 – 4.49 (m, 2H), 3.43 (dd, *J* = 11.4, 4.0 Hz, 1H), 3.37 (d, *J* = 6.5 Hz, 2H), 2.67 – 2.63 (m, 2H), 2.00 (dt, *J* = 12.3, 3.1 Hz, 1H), 1.88 – 1.61 (m, 4H), 1.58 (br s, 1H), 1.17 (s, 3H), 1.08 (s, 3H), 0.86 (s, 3H); ^{13}C NMR δ 155.3, 151.4, 137.0, 133.9, 127.0, 116.5, 116.2, 114.6, 114.0, 104.3, 78.2, 75.9, 69.1, 46.8, 38.3, 37.8, 28.2, 27.5, 22.7, 20.0, 14.2; HRMS (EI^+) calcd for $C_{22}H_{30}O_3$ [M^+] 342.2195; found 342.2180.

Ether 285A. To epoxide **278** (65 mg, 0.16 mmol) in CH_2Cl_2 (32 mL) at –78 °C was added $BF_3{\cdot}Et_2O$ (0.1 mL, 0.8 mmol) and the reaction solution was allowed to stir for 8 min. The reaction then was quenched by addition of Et_3N and allowed to warm room temperature, washed with 0.1 M HCl, brine, dried ($MgSO_4$), and filtered. After the filtrate was concentrated *in vacuo*, final purification by flash column chromatography (5% to 10% EtOAc in hexanes) afforded **285A** (8 mg, 12%) as a colorless oil: ^{1}H NMR δ 6.98 (d, *J* = 8.5 Hz, 1H), 6.69 (d, *J* = 2.4 Hz, 1H), 6.49 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.12 (dd, *J* = 10.9, 4.9 Hz, 1H), 6.06 (dd, *J* = 10.9, 4.9 Hz, 1H), 5.20 – 5.07 (m, 4H), 3.72 (d, *J* = 5.2 Hz, 1H), 2.63 – 2.48 (m, 2H), 1.98 – 1.88 (m, 2H), 1.76 – 1.52 (m, 3H), 1.46 (m, 6H), 1.39 (s, 6H), 1.28 (s, 3H), 1.00 (s, 3H), 0.91 (s, 3H); ^{13}C NMR δ 154.1, 153.6, 144.7, 144.5, 129.3, 126.9, 114.5, 113.0, 113.0, 112.5, 86.9, 86.1, 79.3, 79.2, 53.9, 45.6, 39.0, 27.7, 27.3, 27.2, 26.9, 26.8, 25.9, 25.8, 23.8, 19.1; HRMS (EI^+) calcd for $C_{26}H_{38}O_3$ [M^+] 398.2821; found 398.2820.

Compound 286B. Following the standard procedure BF_3OEt_2 (0.13 mL, 1.0 mmol) was added to epoxide **266** (76 mg, 0.20 mmol) in CH_2Cl_2 (41 mL) was added. After standard work-up, final purification by flash column chromatography (15% to 20% EtOAc in hexanes) afforded **286B** (46 mg, 61%) as a colorless oil: ^{1}H NMR δ 6.84 (d, *J* = 8.4 Hz, 1H), 6.43 (d, *J* = 8.4 Hz, 1H), 6.31 – 6.19 (m, 1H), 5.85 – 5.65 (m, 2H), 5.02 – 4.95 (m, 1H), 4.89 – 4.83 (m, 1H), 4.54 (d, *J* = 4.4 Hz): 4.40 (d, *J* = 5.4 Hz) (1:3 cis: trans 2H), 4.15 – 4.08 (m, 1H), 3.43 (dd, *J* = 11.2, 3.9 Hz, 1H), 2.66 – 2.62 (m, 2H), 2.03 – 1.98 (m, 1H), 1.88 – 1.81 (m, 1H), 1.76 – 1.57 (m, 6H), 1.48 (br s, 1H), 1.37 – 1.32 (m, 3H), 1.19:1.17 (s, 3H) (1:2.5 ratio), 1.07 (s, 3H), 0.85 (s, 3H); ^{13}C NMR δ 155.4, 151.6, 143.4, 129.0, 127.1, 126.8, 126.4, 114.9, 111.8, 105.4, 78.2, 75.9, 69.8, 46.7, 38.3, 37.8, 33.6, 28.2, 27.2, 22.2, 19.8, 18.4, 17.8, 14.2; HRMS (EI^+) calcd for $C_{24}H_{34}O_3$[M] 370.2508; found 370.2504.

Compound 287B. Following the standard procedure, $BF_3{\cdot}OEt_2$ (0.195 mL, 1.55 mmol) was added to epoxide **273** (114 mg, 0.31 mmol) in CH_2Cl_2 (60 mL). After standard work-up, final purification by flash column chromatography (15% EtOAc in hexanes) afforded compound **287** (66 mg, 58%) as a colorless oil as a mixture of diasteromers in a 2.1:1 ratio. For the major component: ^{1}H NMR δ (400 MHz) 6.83 (dd, *J* = 8.5, 0.9 Hz, 1H), 6.43 (d, *J* = 8.4 Hz, 1H), 6.25 (ddd, *J* = 17.2, 10.1, 6.9 Hz, 1H), 5.85 – 5.76 (m, 1H), 5.74 – 5.66 (m, 1H), 4.99 (ddd, *J* = 17.3, 2.0, 1.6 Hz, 1H), 4.87 (ddd, *J* = 10.2, 2.1, 1.4 Hz, 1H), 4.41 – 4.39 (m, 2H), 4.16 – 4.08 (m, 1H), 3.42 (dd, *J* = 11.6, 4.1 Hz, 1H), 2.67 – 2.62 (m, 2H), 2.01 (dt, *J* = 12.6, 3.2 Hz, 1H), 1.87 – 1.58 (m, 7H), 1.53 (br s, 1H), 1.34 (d, *J* = 7.2 Hz, 3H), 1.17 (s, 3H), 1.07 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (100 MHz) δ 155.3, 151.6, 143.4, 129.0, 127.1, 126.8, 121.8, 114.9, 111.8, 105.3, 78.1,

75.9, 69.7, 46.7, 38.2, 37.7, 33.5, 28.2, 27.2, 22.8, 19.8, 18.4, 17.9, 14.2. For the minor component: ^{1}H NMR δ (400 MHz) 6.83 (dd, *J* = 8.5, 0.9 Hz, 1H), 6.43 (d, *J* = 8.4 Hz, 1H), 6.26 (ddd, *J* = 17.1, 10.1, 7.4 Hz, 1H), 5.85 – 5.76 (m, 1H), 5.74 – 5.66 (m, 1H), 4.98 (ddd, *J* = 17.2, 2.1, 1.4 Hz, 1H), 4.85 (ddd, *J* = 10.1, 2.1, 1.1 Hz, 1H), 4.41 – 4.39 (m, 2H), 4.16 – 4.08 (m, 1H), 3.42 (dd, *J* = 11.6, 4.1 Hz, 1H), 2.67 – 2.62 (m, 2H), 2.01 (dt, *J* = 12.6, 3.2 Hz, 1H), 1.87 – 1.58 (m, 7H), 1.53 (br s, 1H), 1.36 (d, *J* = 7.2 Hz, 3H), 1.19 (s, 3H), 1.07 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (100 MHz) δ 155.3, 151.4, 143.2, 129.0, 127.1, 126.8, 121.7, 114.9, 111.9, 105.4, 78.1, 75.9, 69.7, 46.7, 38.2, 37.8, 33.8, 28.2, 27.2, 22.8, 19.6, 18.7, 17.9, 14.2.

APPENDIX

RESULT FOR FULL 60 CELL-LINE ASSAY AND SELECTED NMR SPECTRA

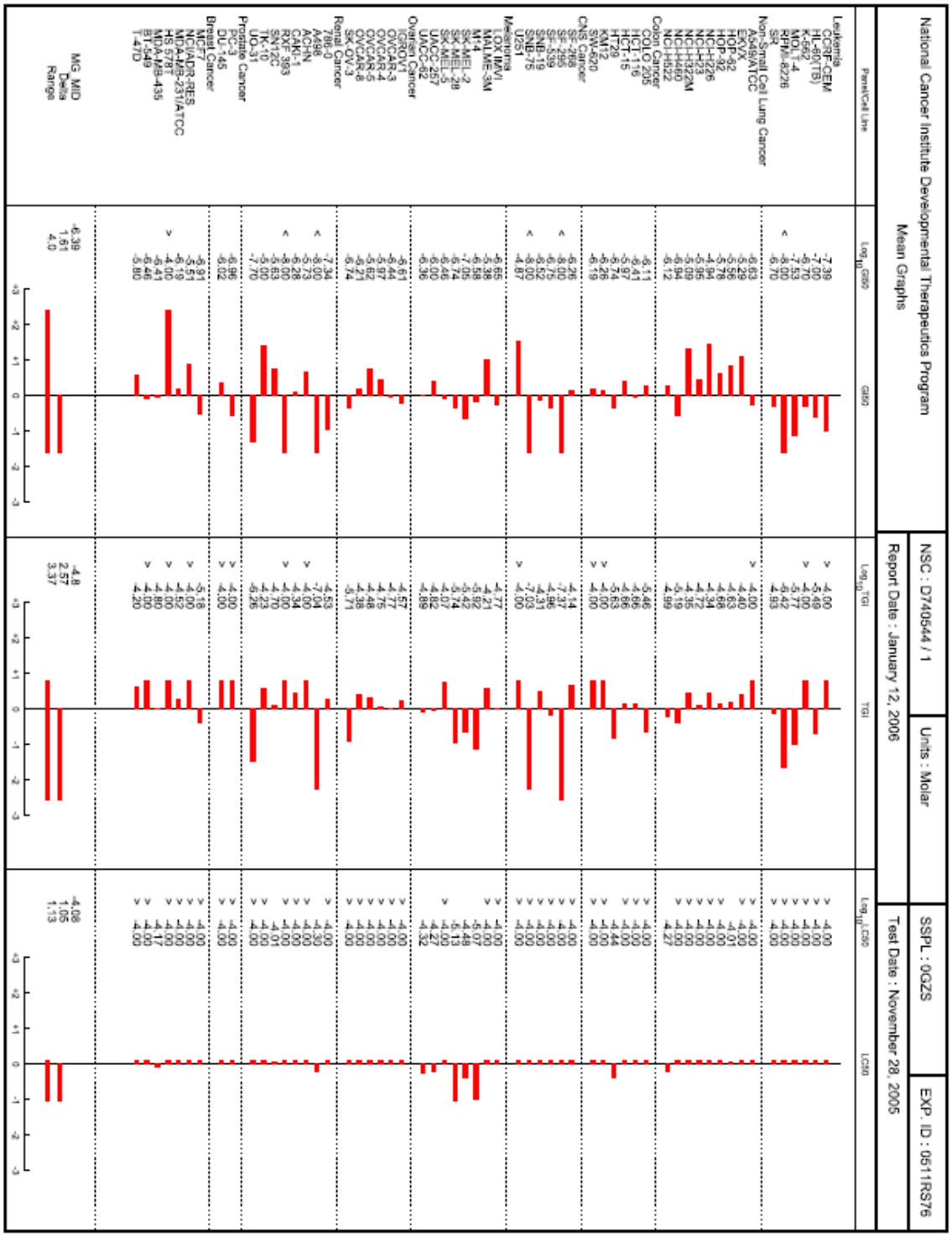


Figure A1. 60 cell-line assay results for SF (**14**)

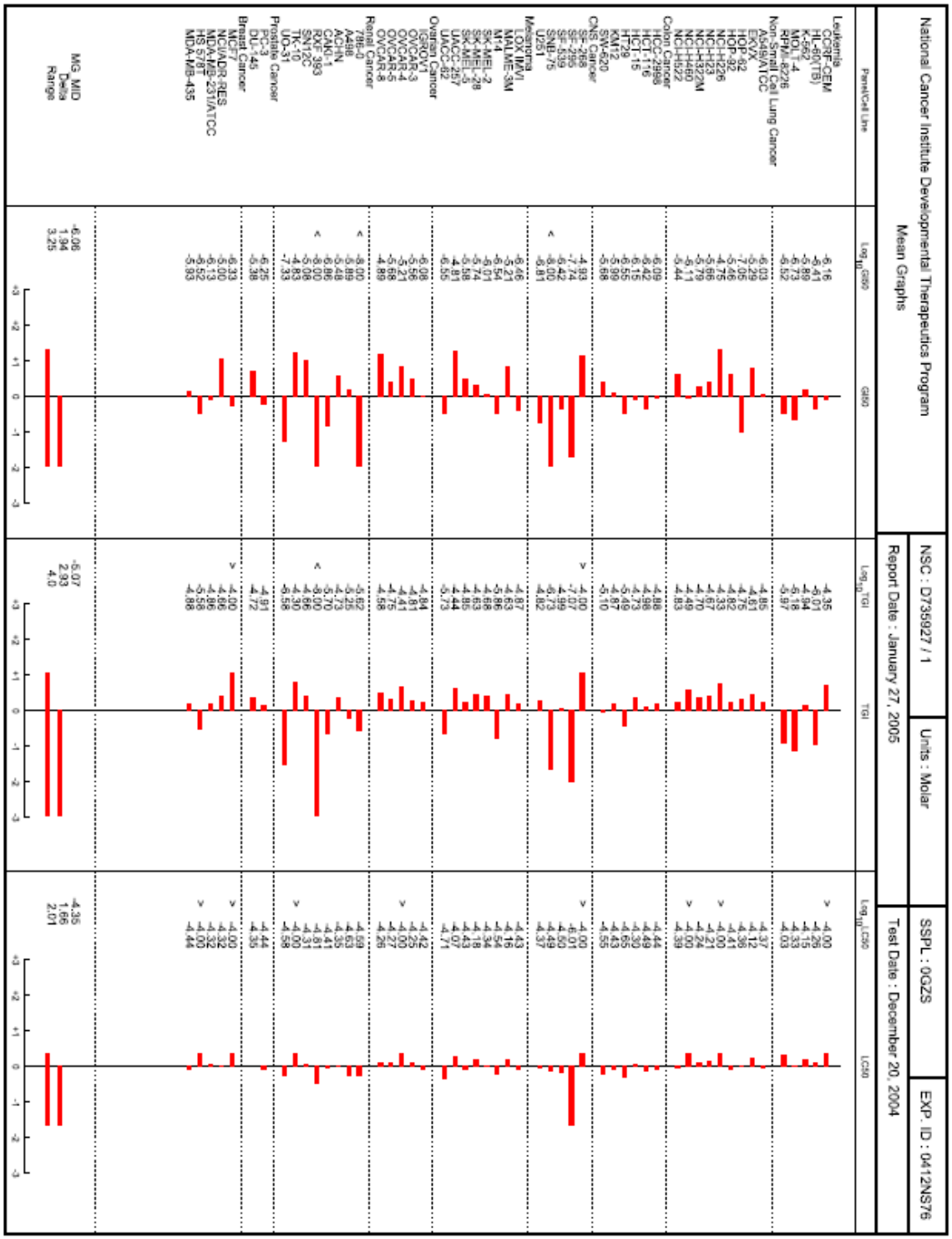


Figure A2. 60 cell-line assay results for 3dSB (**24**)

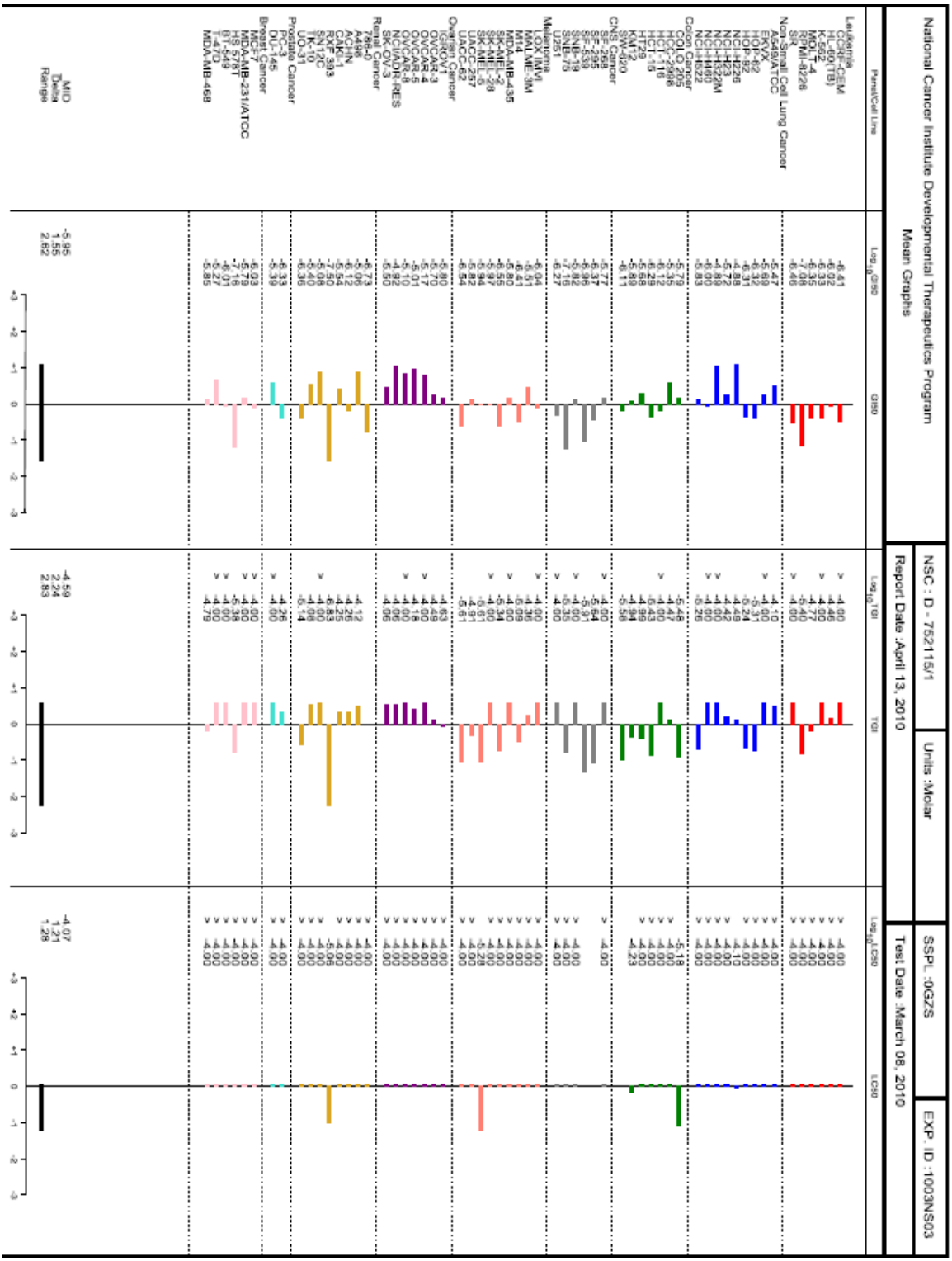


Figure A3. 60 cell-line assay results for compound **111**

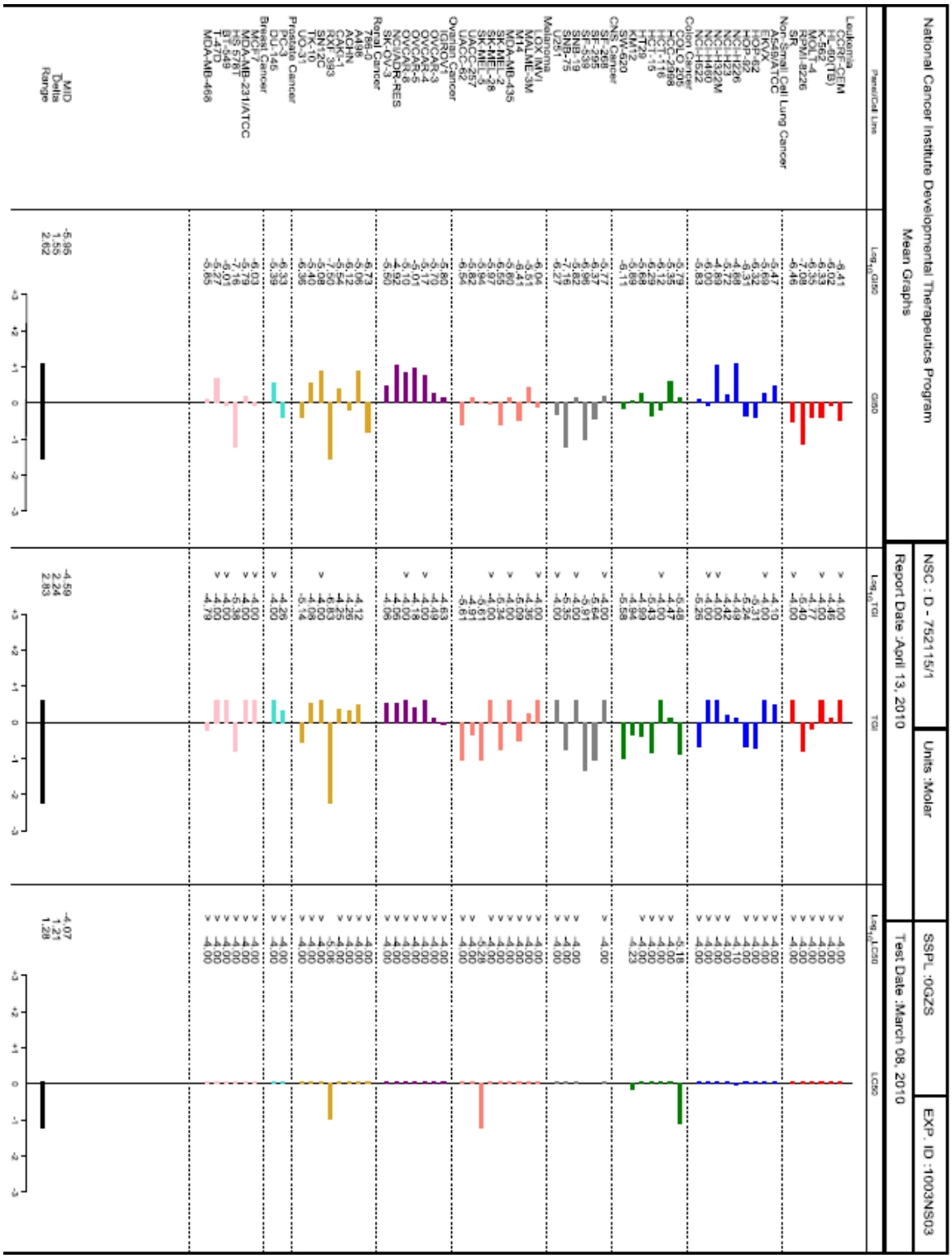


Figure A4. 60 cell-line assay results for compound **112**

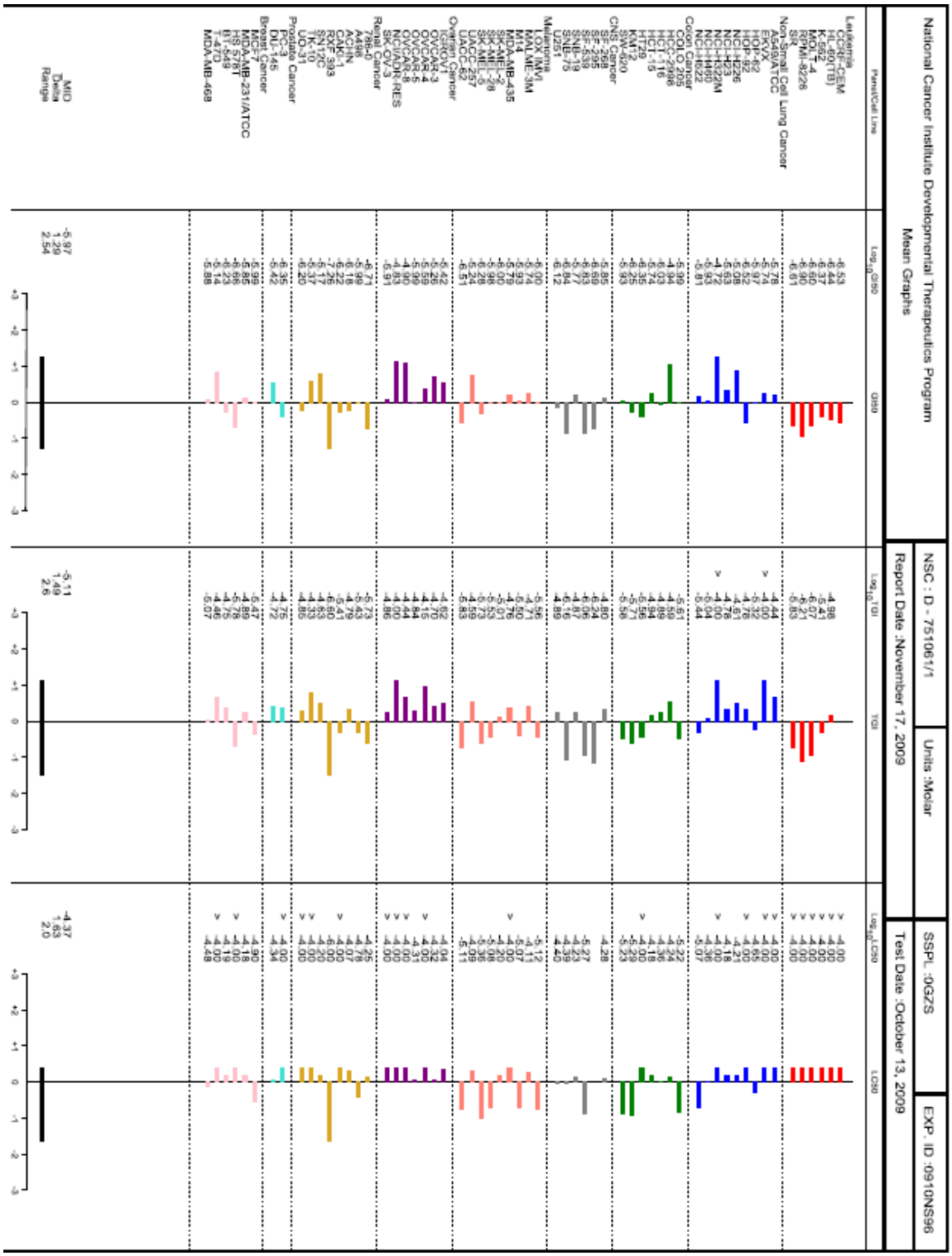


Figure A5. 60 cell-line assay results for compound **131**

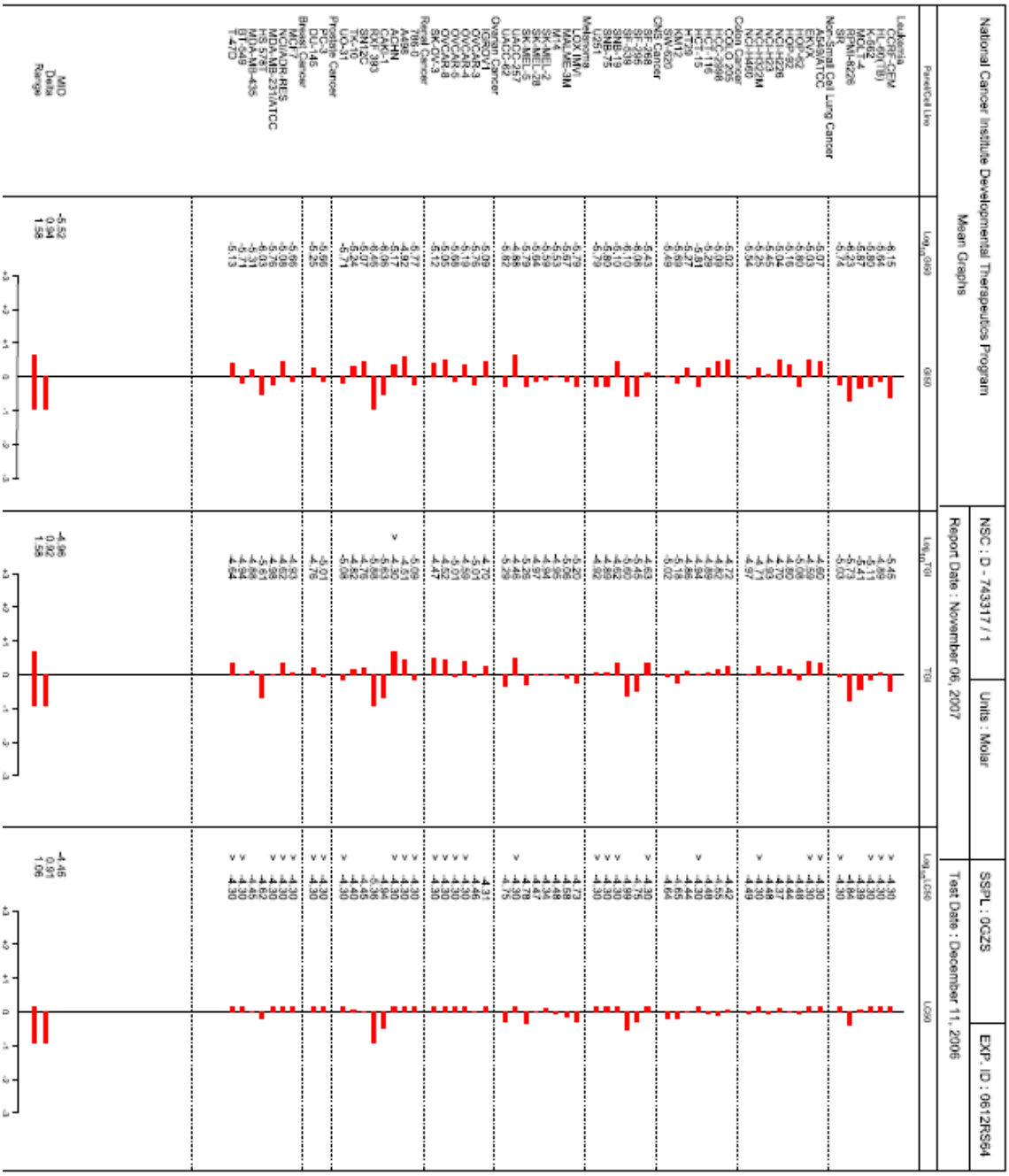


Figure A6. 60 cell-line assay results for compound **160**

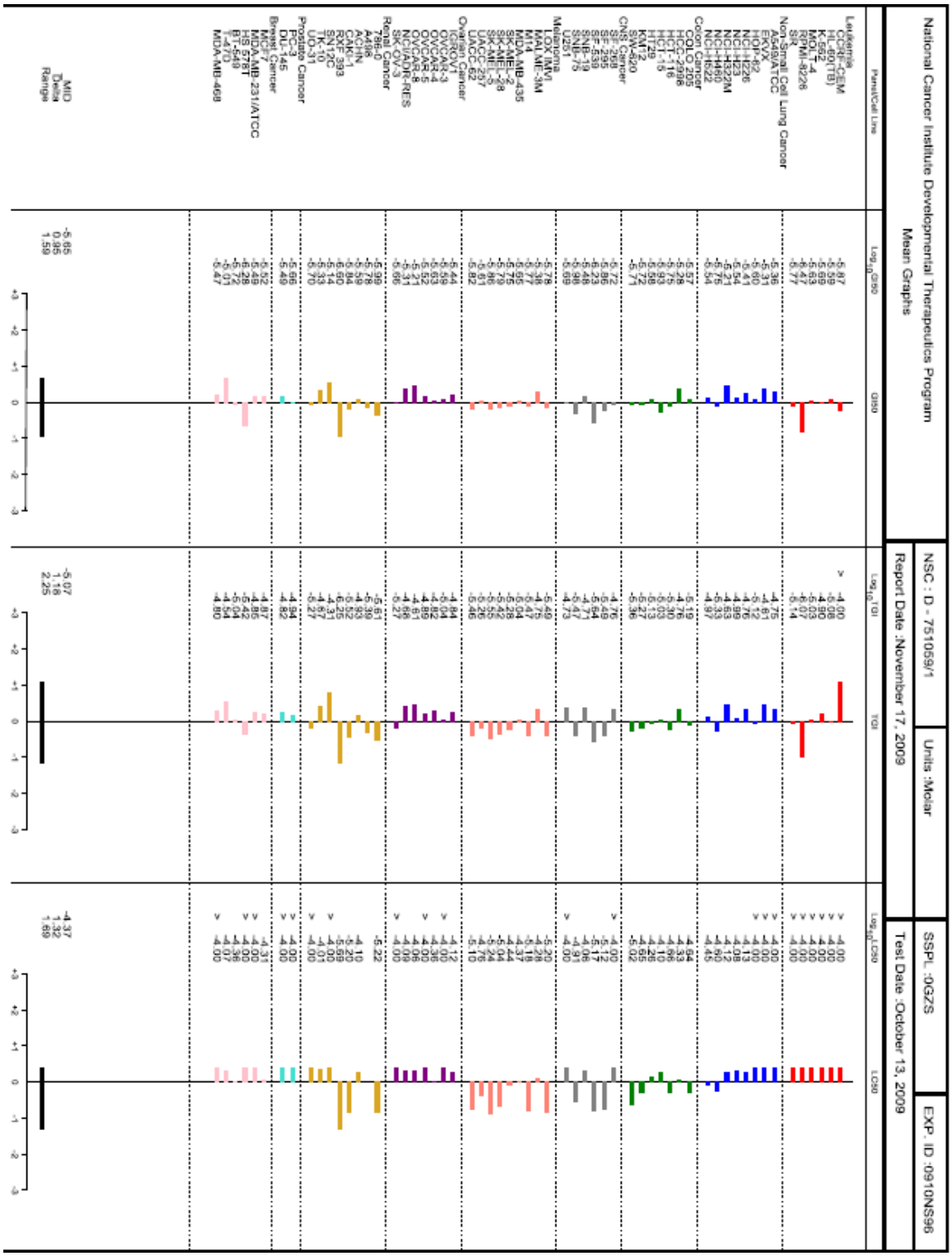


Figure A7. 60 cell-line assay results for compound **161**

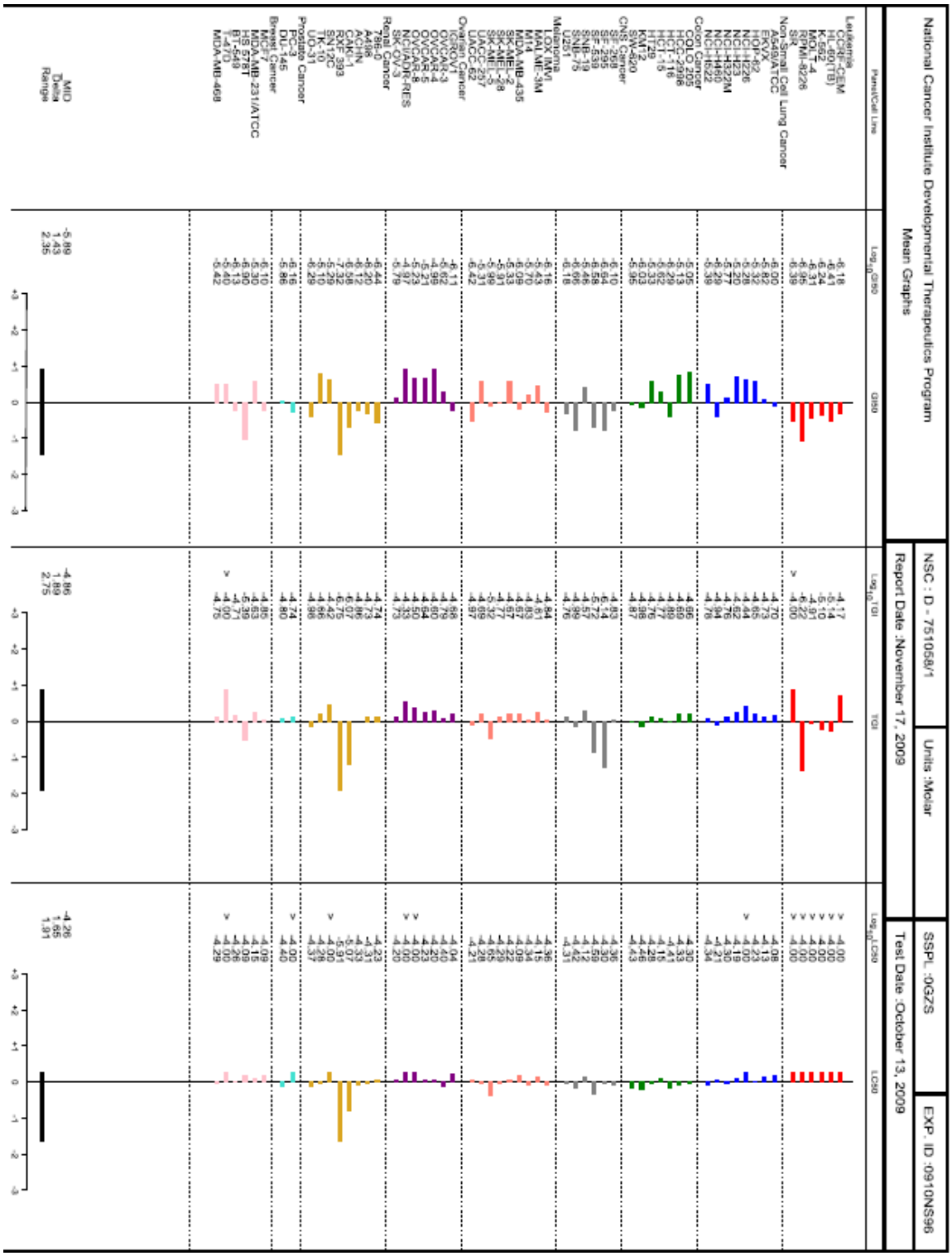


Figure A8. 60 cell-line assay results for compound **162**

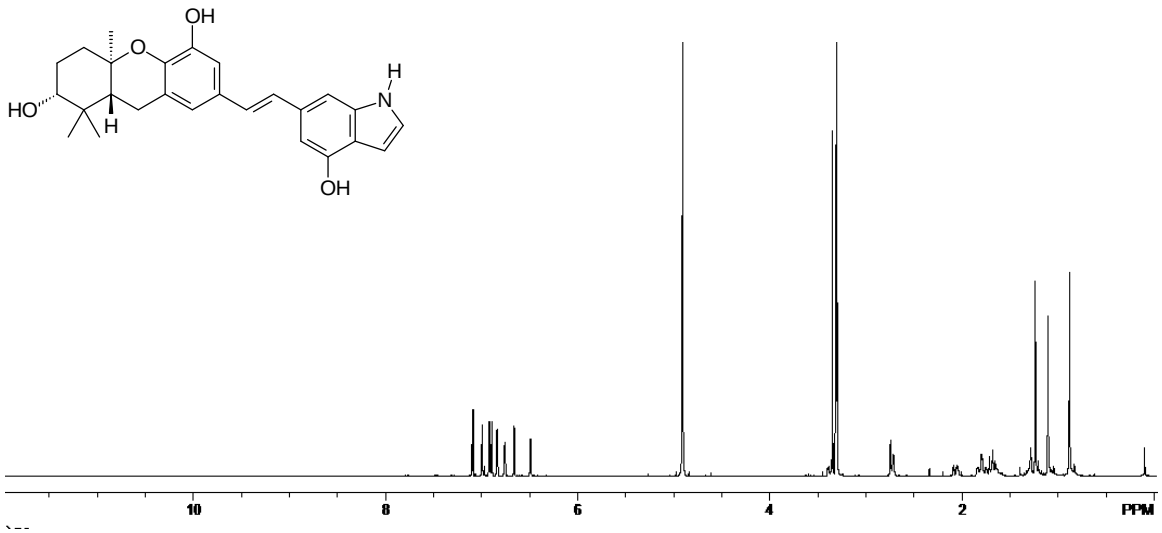


Figure A9. ^{1}H NMR spectrum for analogue **40**

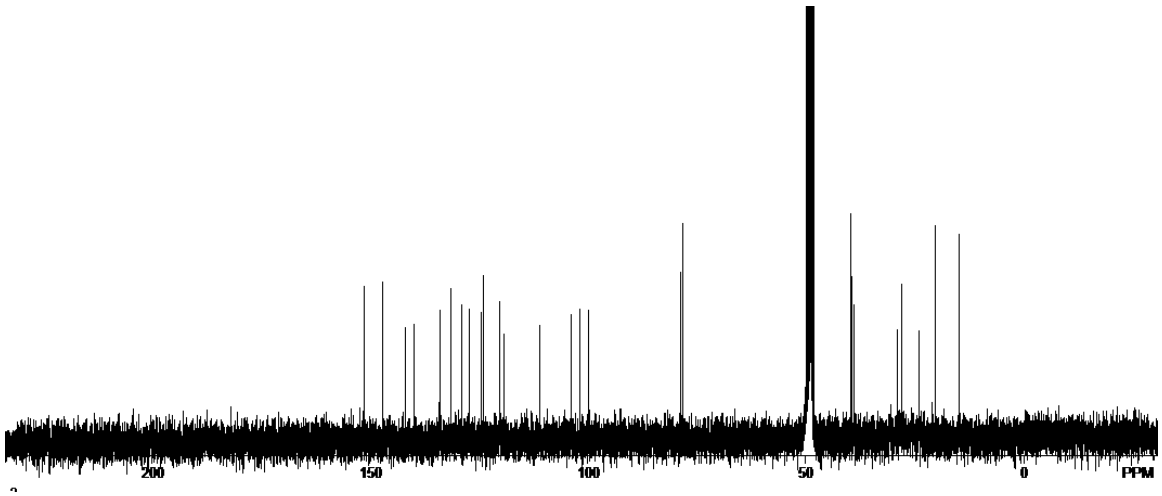


Figure A10. ^{13}C NMR spectrum for analogue **40**

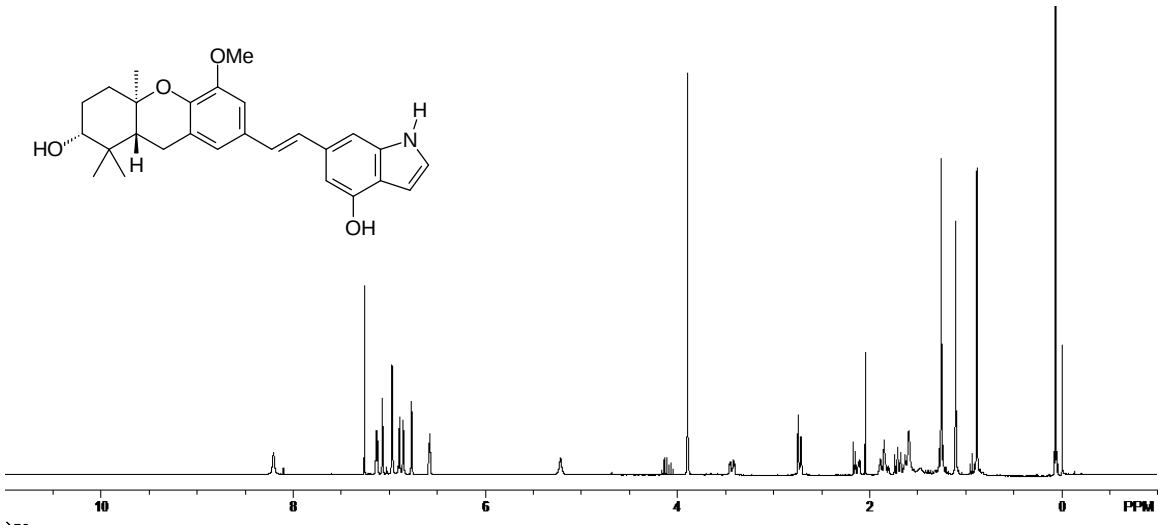


Figure A11. ^{1}H NMR spectrum for analogue **41**

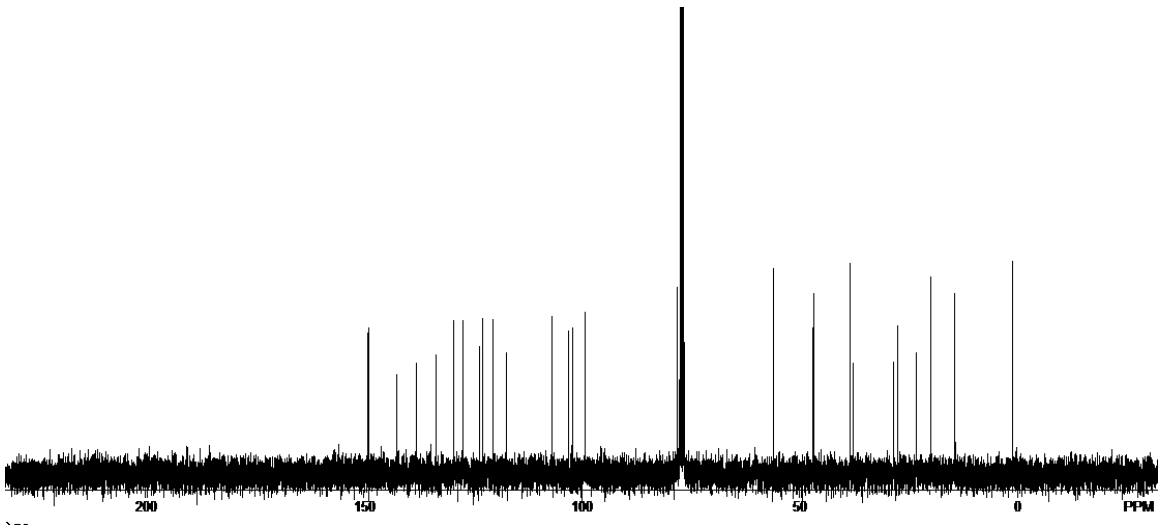


Figure A12. ^{13}C NMR spectrum for analogue **41**

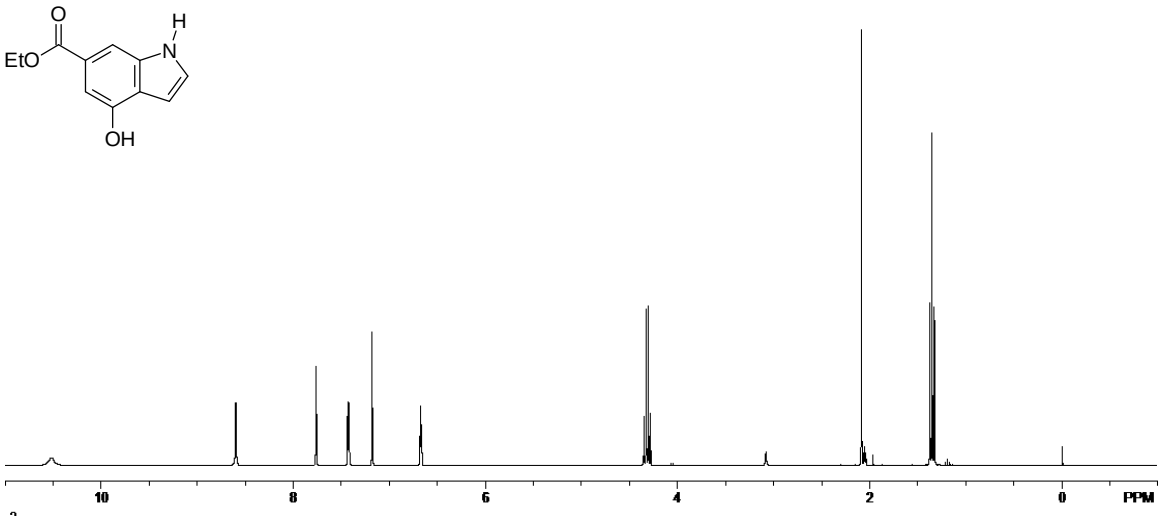


Figure A13. ^{1}H NMR spectrum for analogue **46**

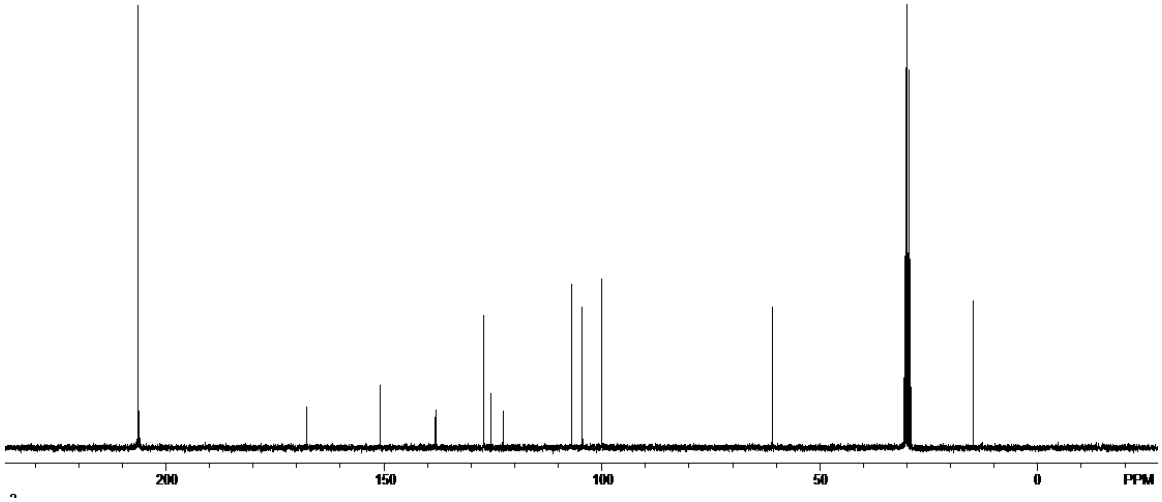


Figure A14. ^{13}C NMR spectrum for analogue **46**

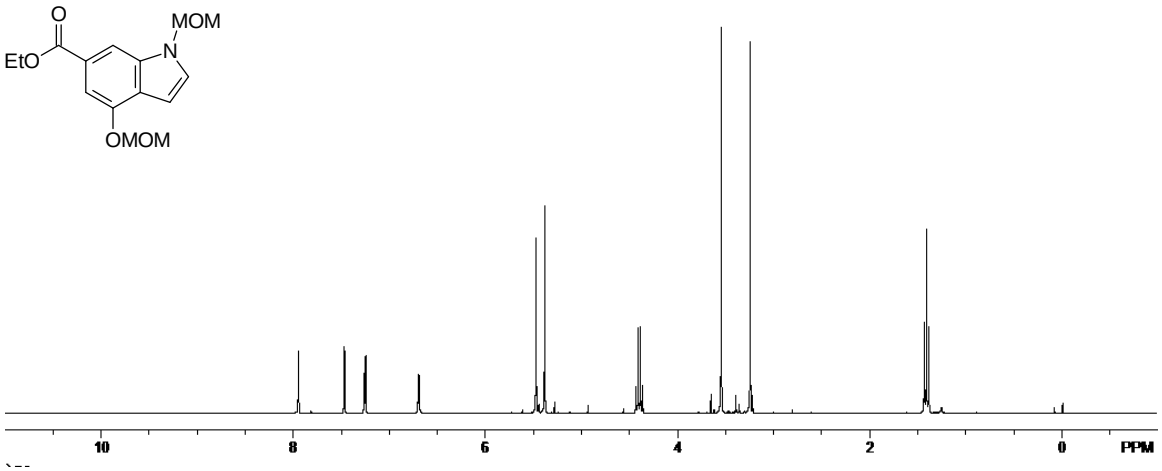


Figure A15. ^{1}H NMR spectrum for analogue **49**

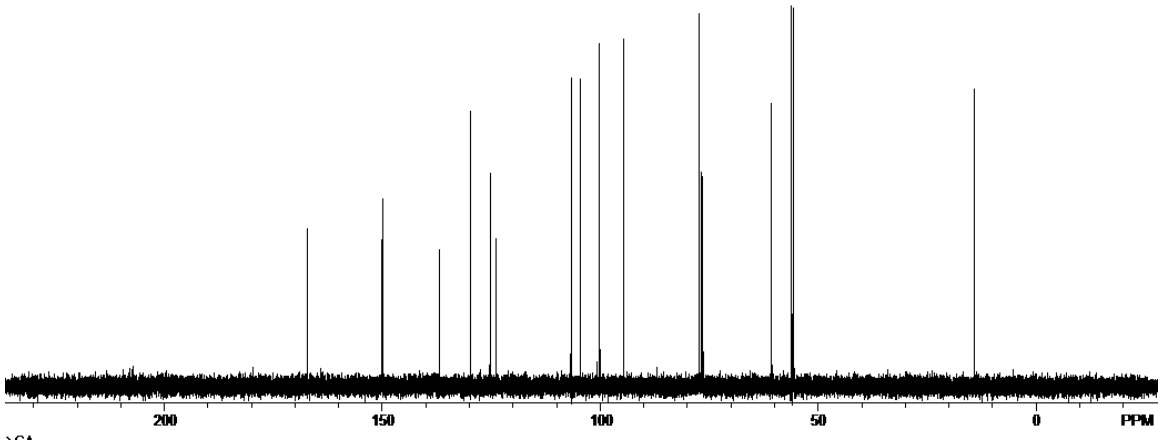


Figure A16. ^{13}C NMR spectrum for analogue **49**

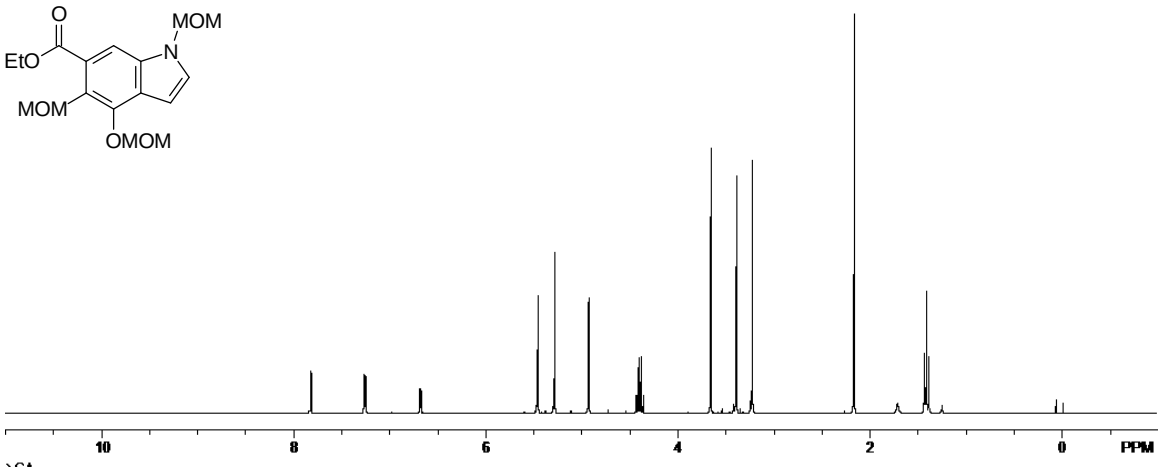


Figure A17. ^{1}H NMR spectrum for analogue **50**

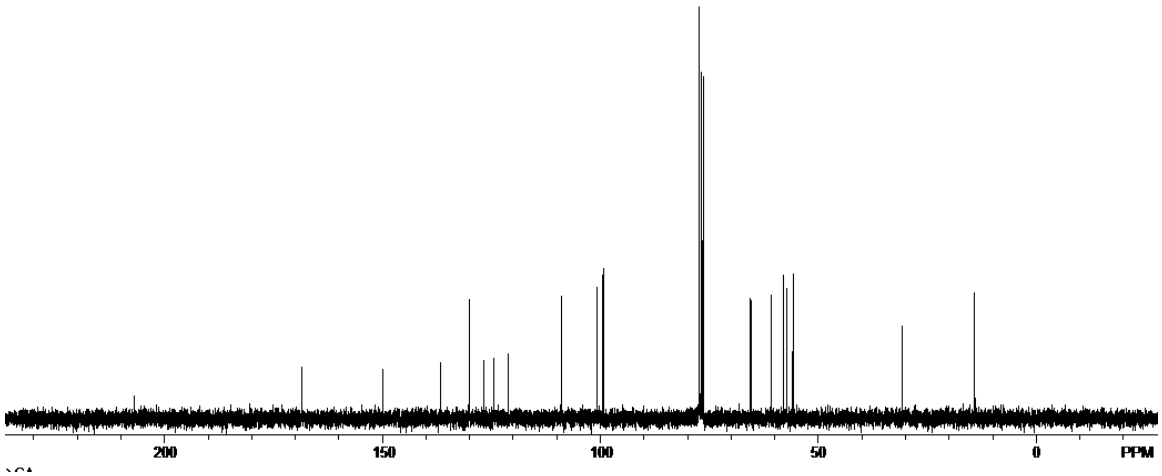


Figure A18. ^{13}C NMR spectrum for analogue **50**

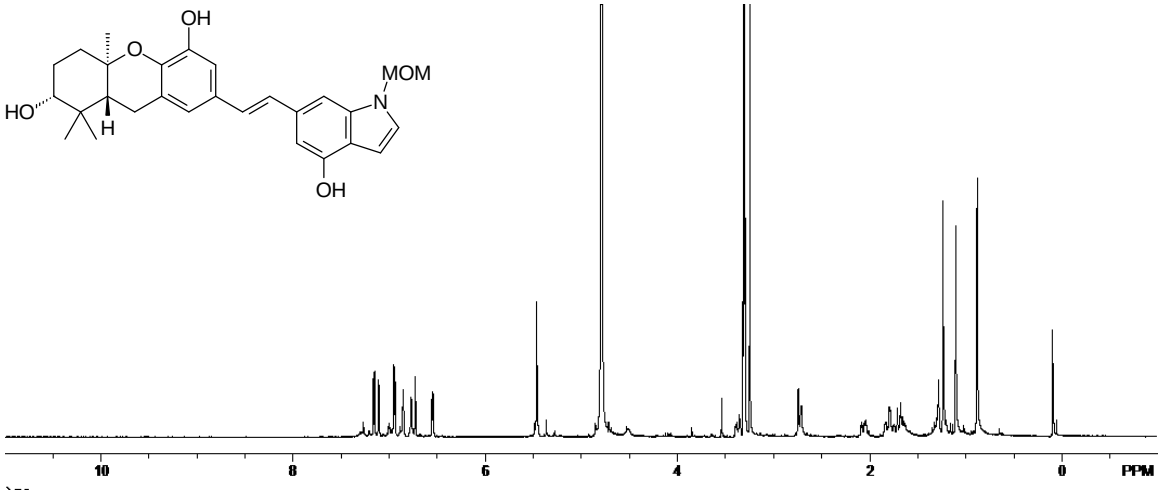


Figure A19. ^{1}H NMR spectrum for analogue **54**

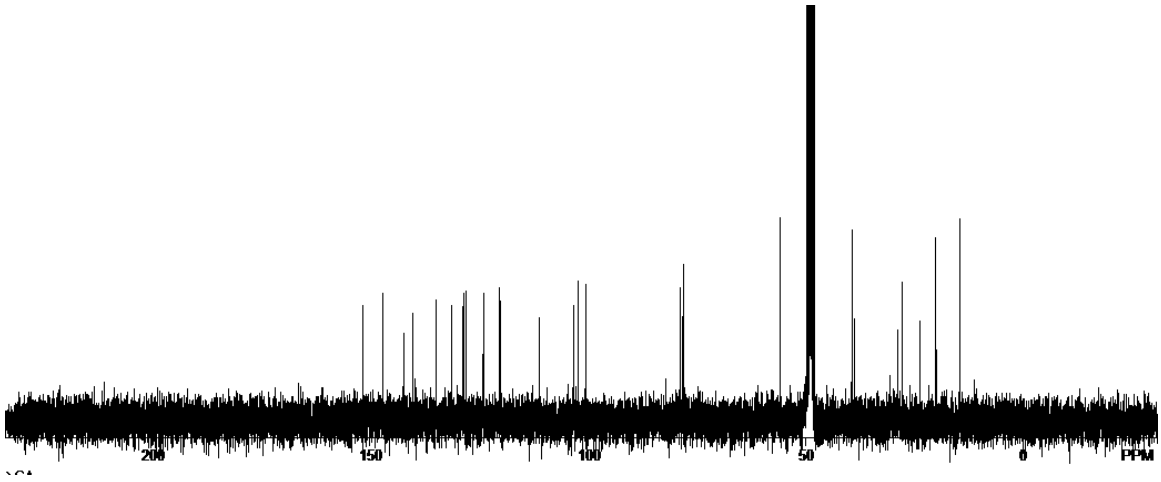


Figure A20. ^{13}C NMR spectrum for analogue **54**

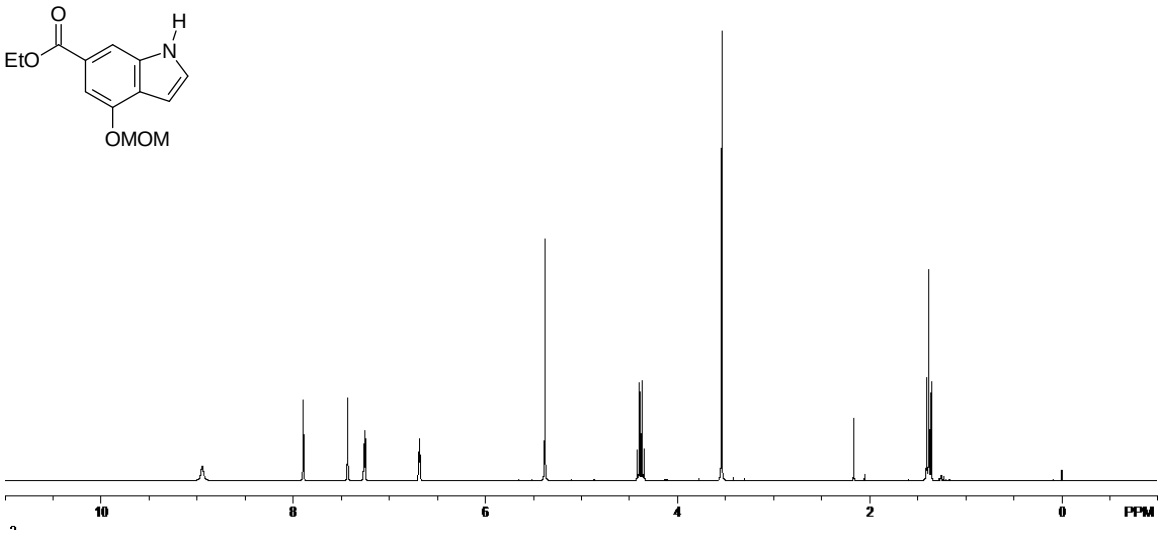


Figure A21. ^{1}H NMR spectrum for analogue **55**

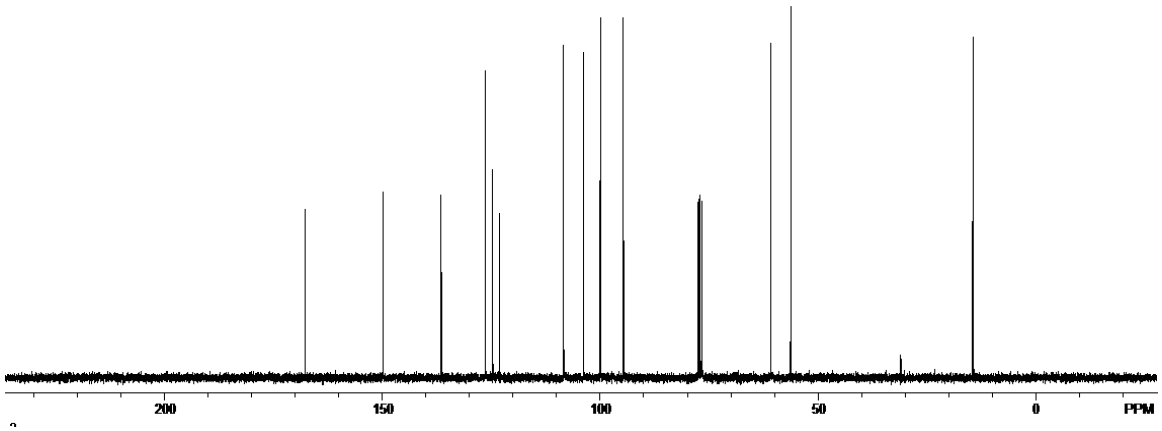


Figure A22. ^{13}C NMR spectrum for analogue **55**

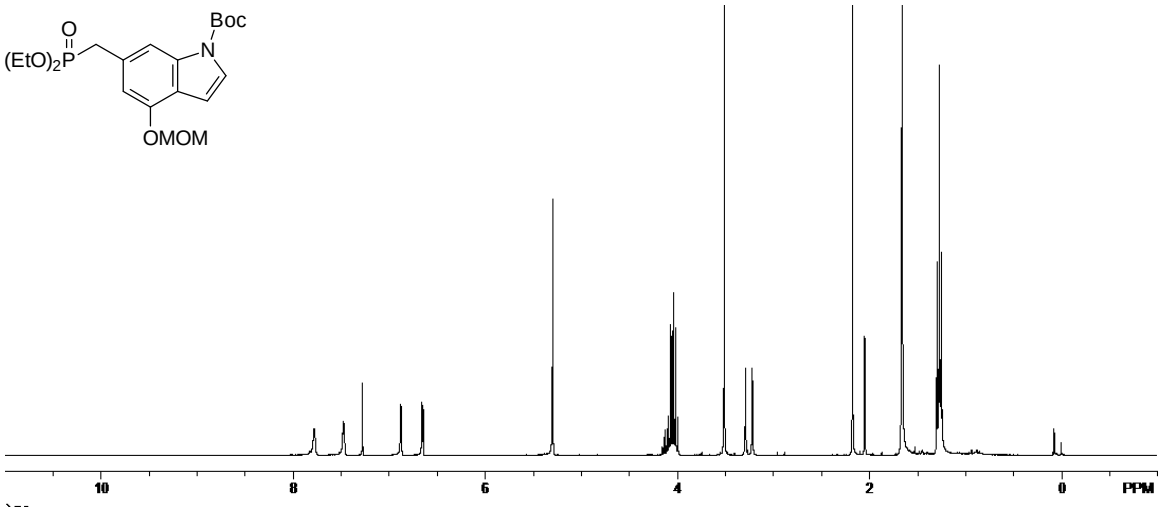


Figure A23. ^{1}H NMR spectrum for analogue **60**

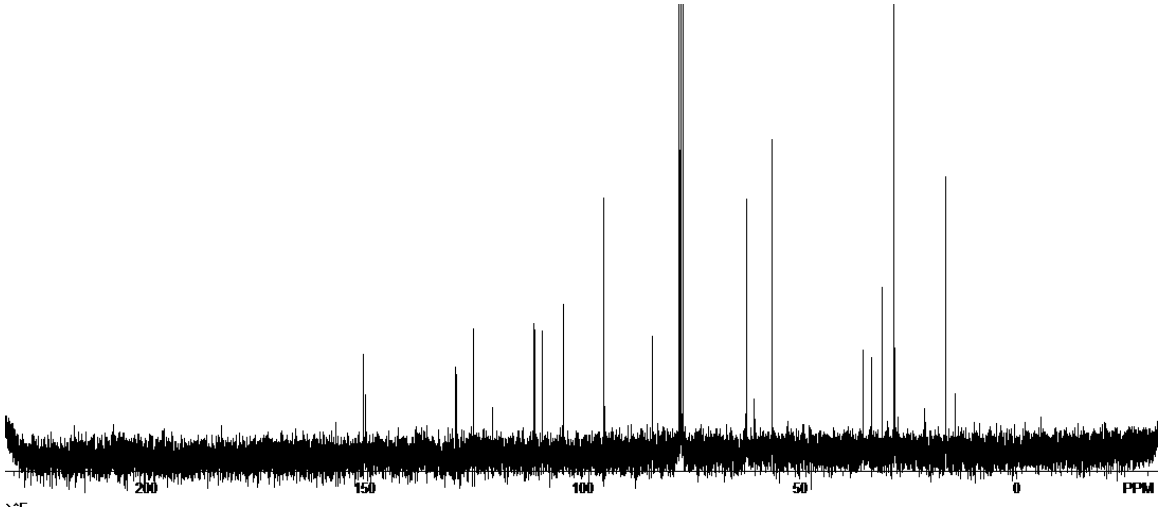


Figure A24. ^{13}C NMR spectrum for analogue **60**

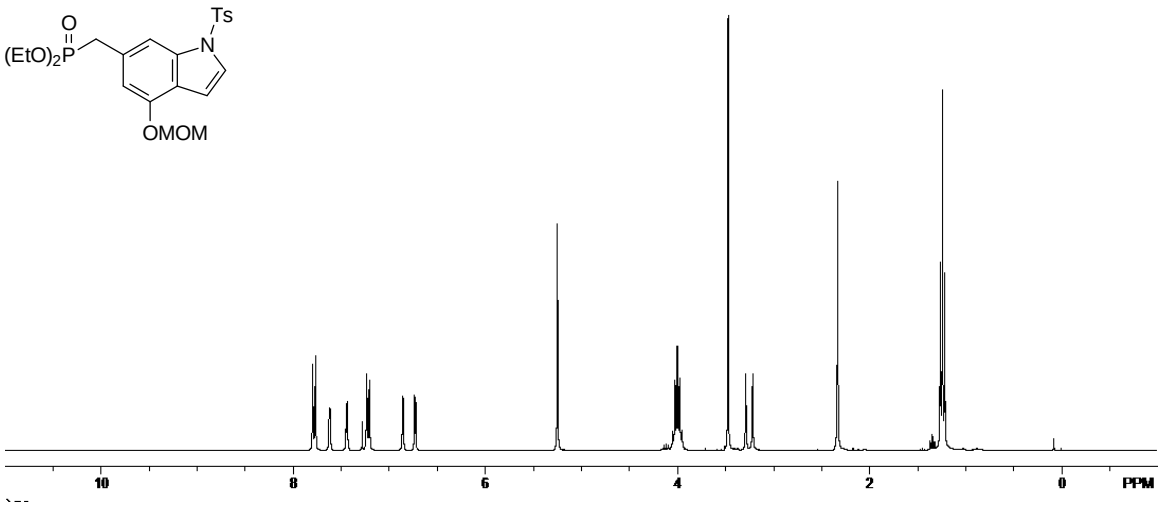


Figure A25. ^{1}H NMR spectrum for analogue **65**

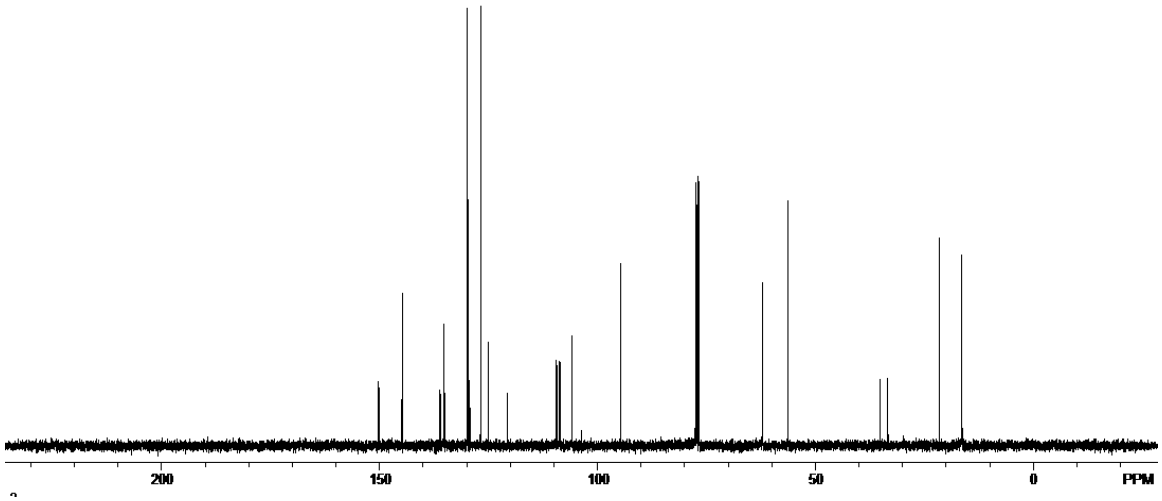


Figure A26. ^{13}C NMR spectrum for analogue **65**

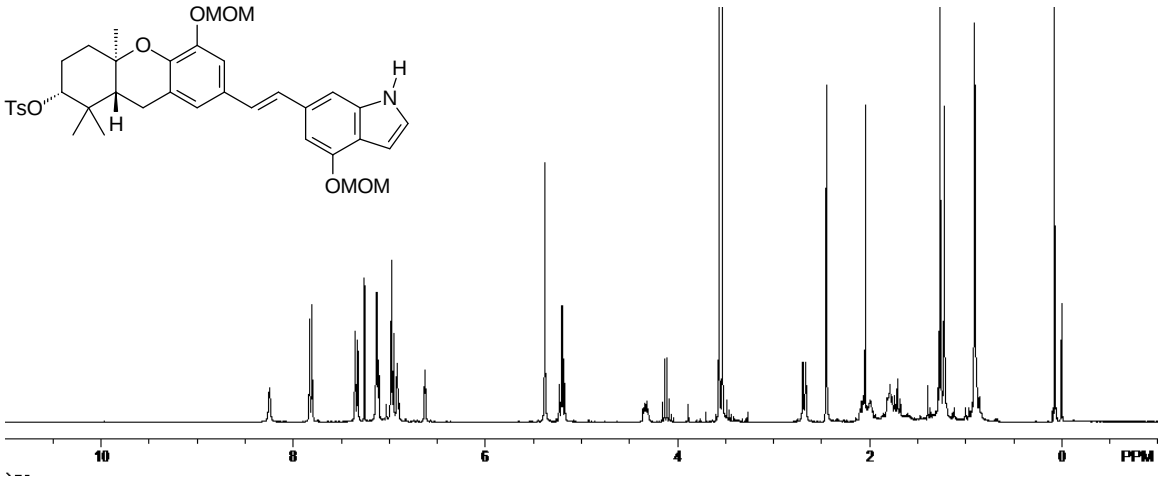


Figure A27. ^{1}H NMR spectrum for analogue **66A**

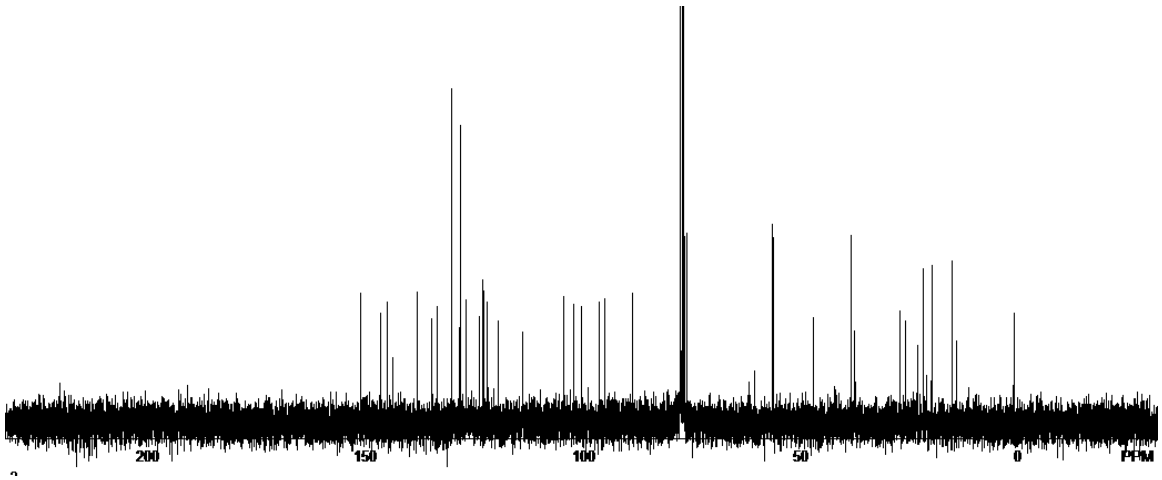


Figure A28. ^{13}C NMR spectrum for analogue **66A**

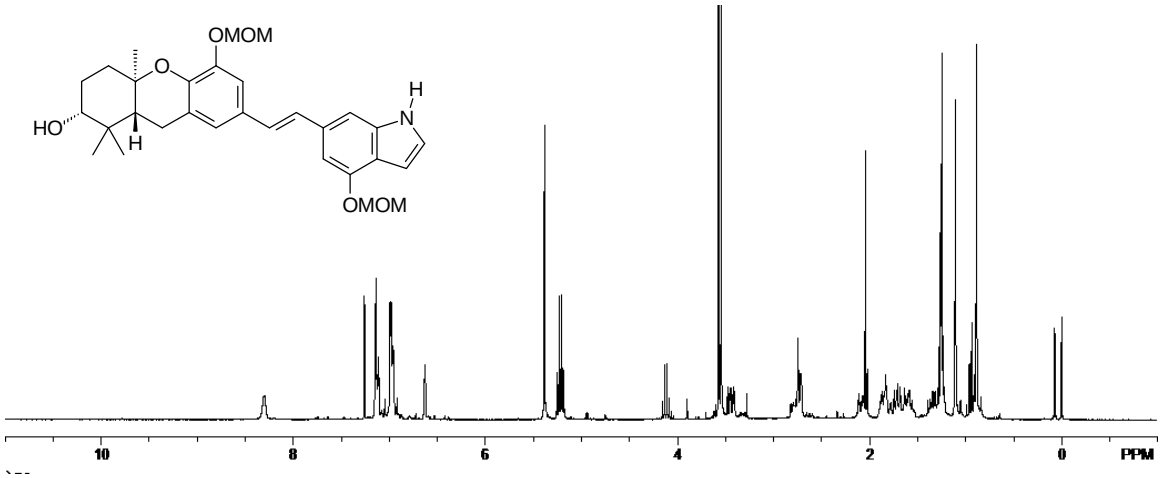


Figure A29. ^{1}H NMR spectrum for analogue **67**

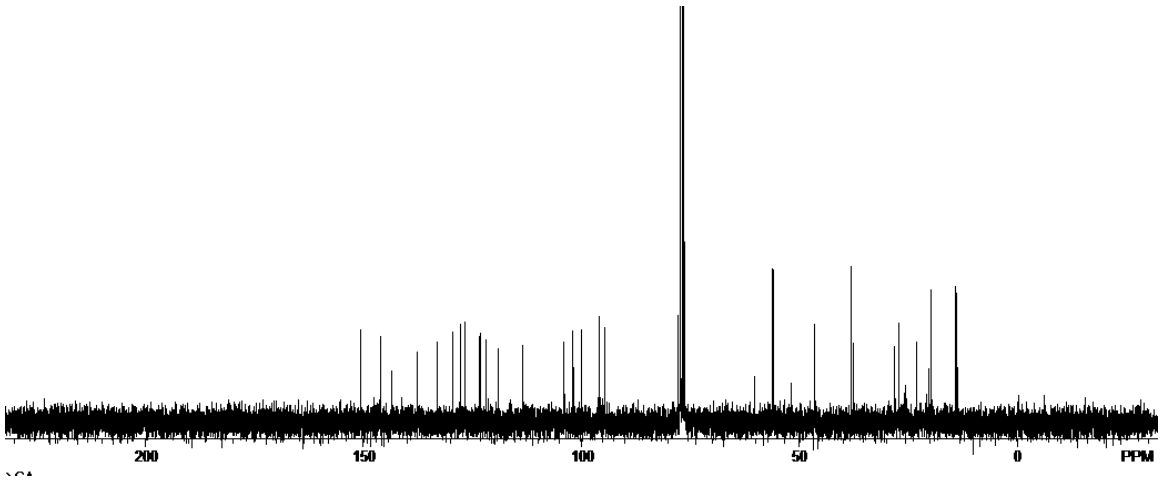


Figure A30. ^{13}C NMR spectrum for analogue **67**

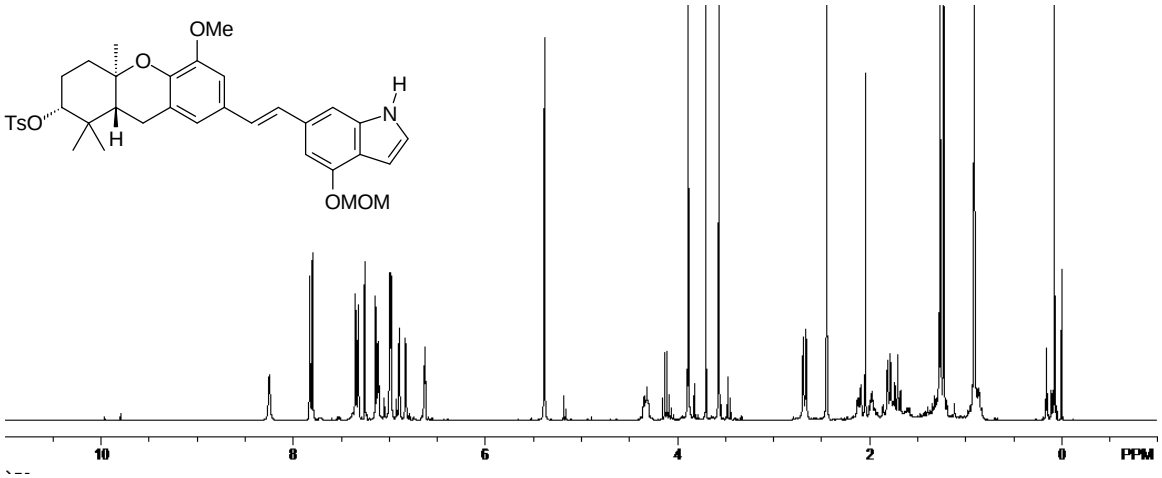


Figure A31. ^{1}H NMR spectrum for analogue **69**

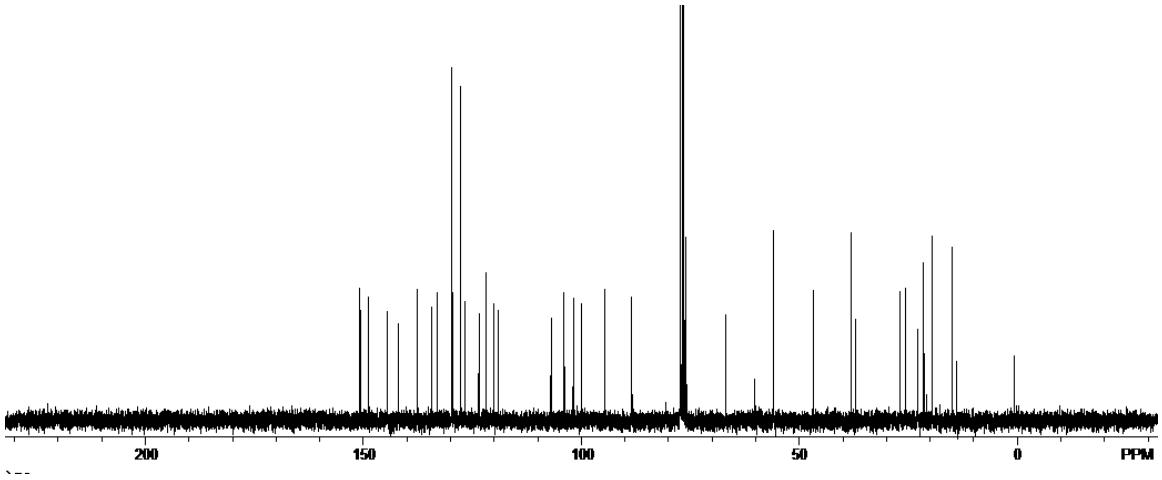


Figure A32. ^{1}H NMR spectrum for analogue **69**

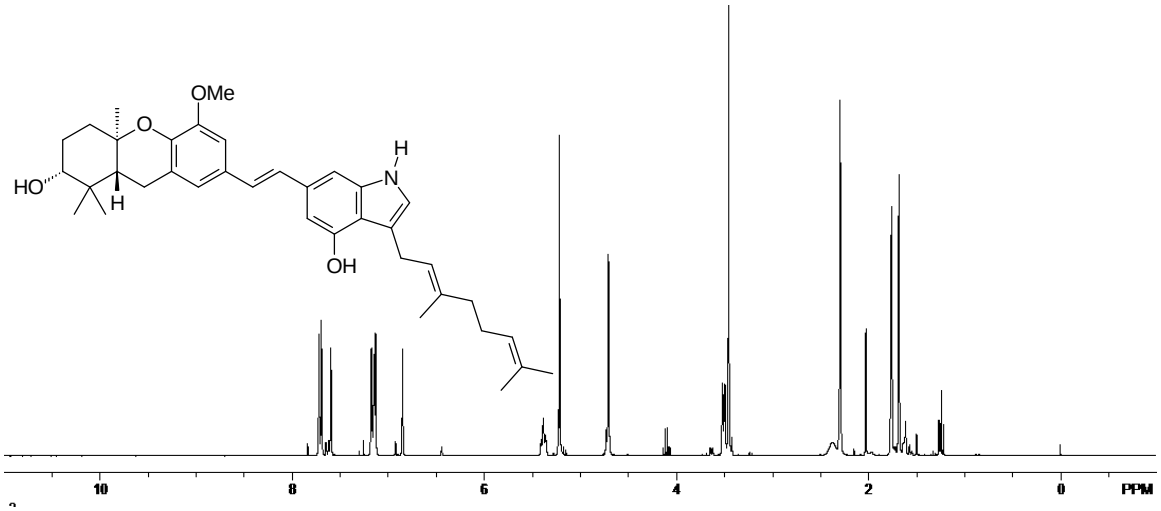


Figure A33. ^{1}H NMR spectrum for analogue **80**

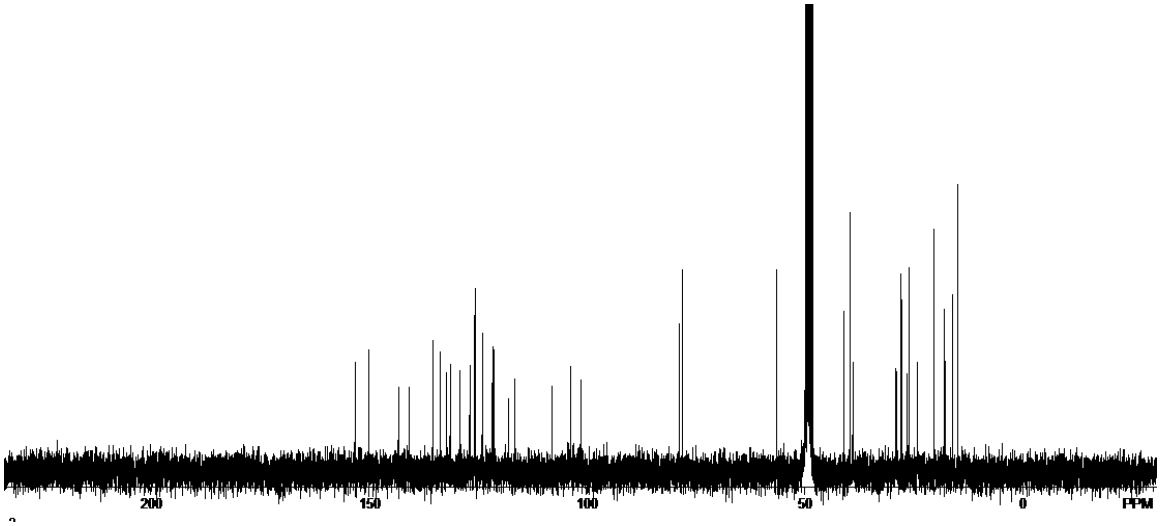


Figure A34. ^{13}C NMR spectrum for analogue **80**

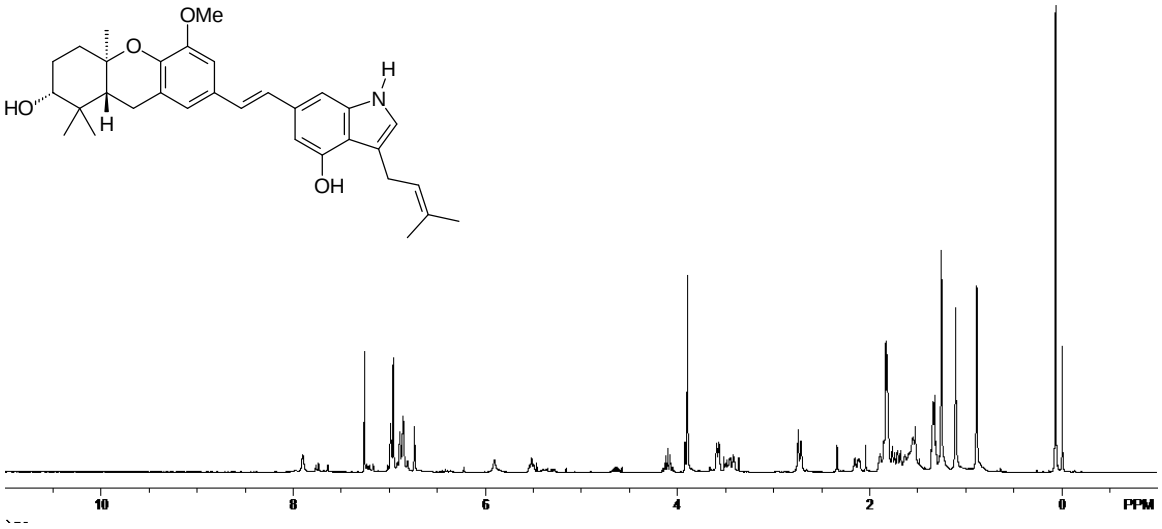


Figure A35. ^{1}H NMR spectrum for analogue **81**

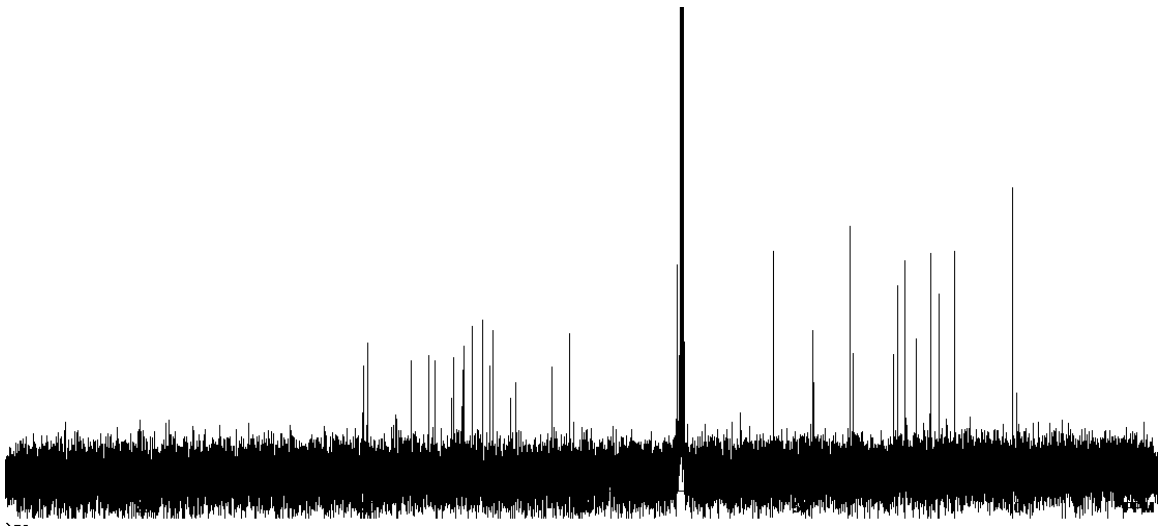


Figure A36. ^{13}C NMR spectrum for analogue **81**

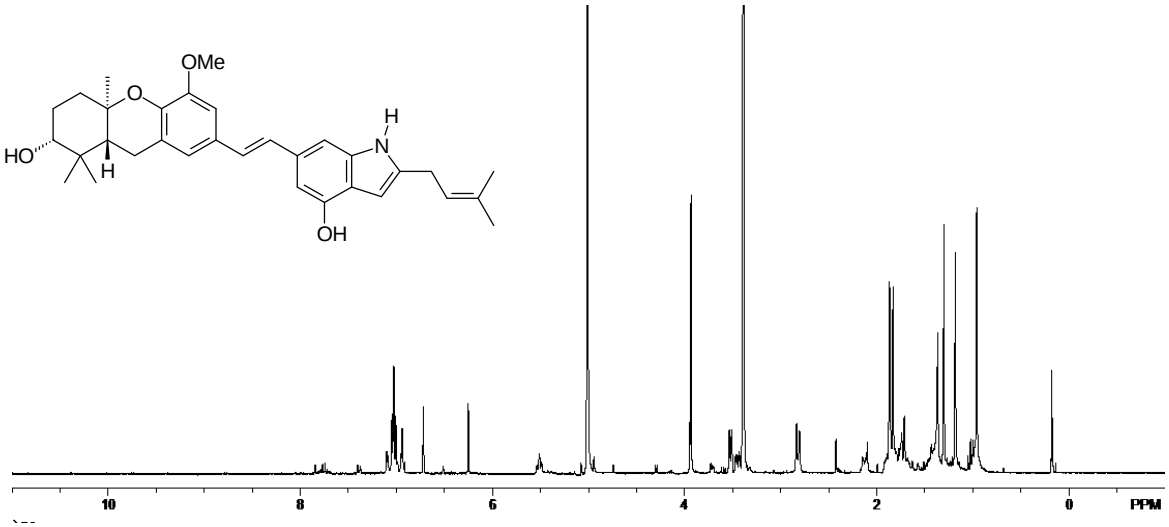


Figure A37. ^{1}H NMR spectrum for analogue **82**

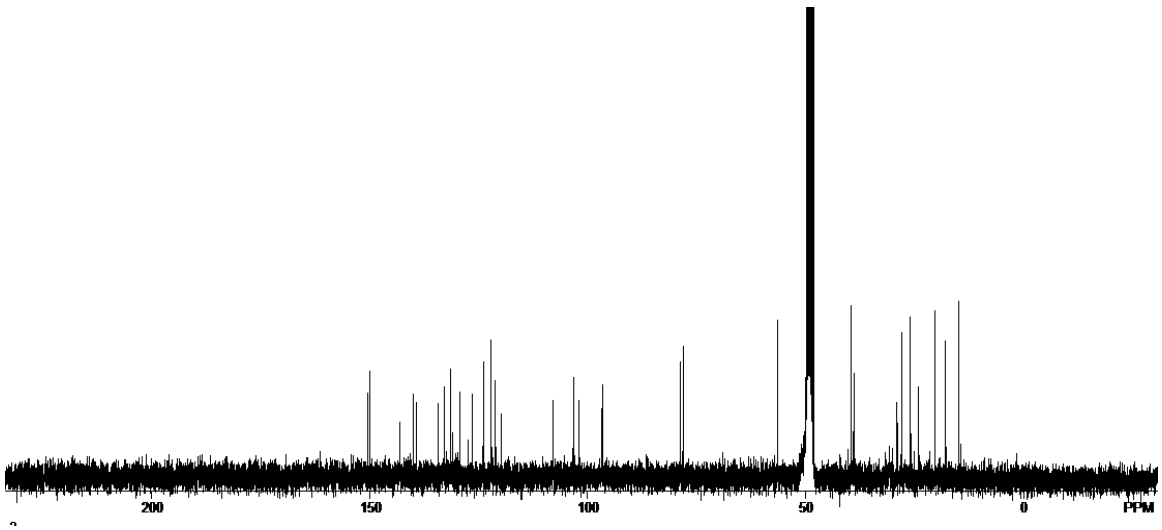


Figure A38. ^{13}C NMR spectrum for analogue **82**

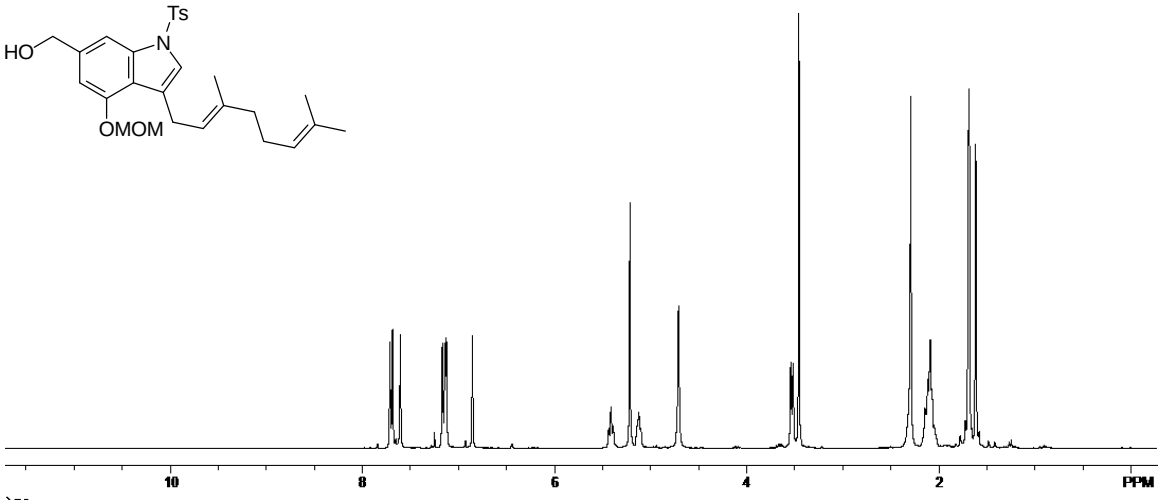


Figure A39. ^{1}H NMR spectrum for analogue **85**

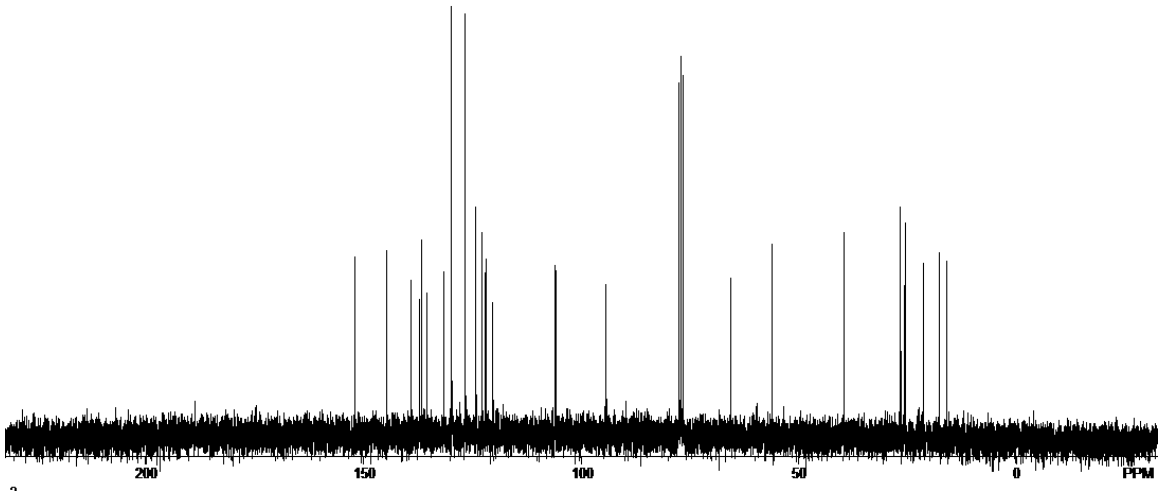


Figure A40. ^{13}C NMR spectrum for analogue **85**

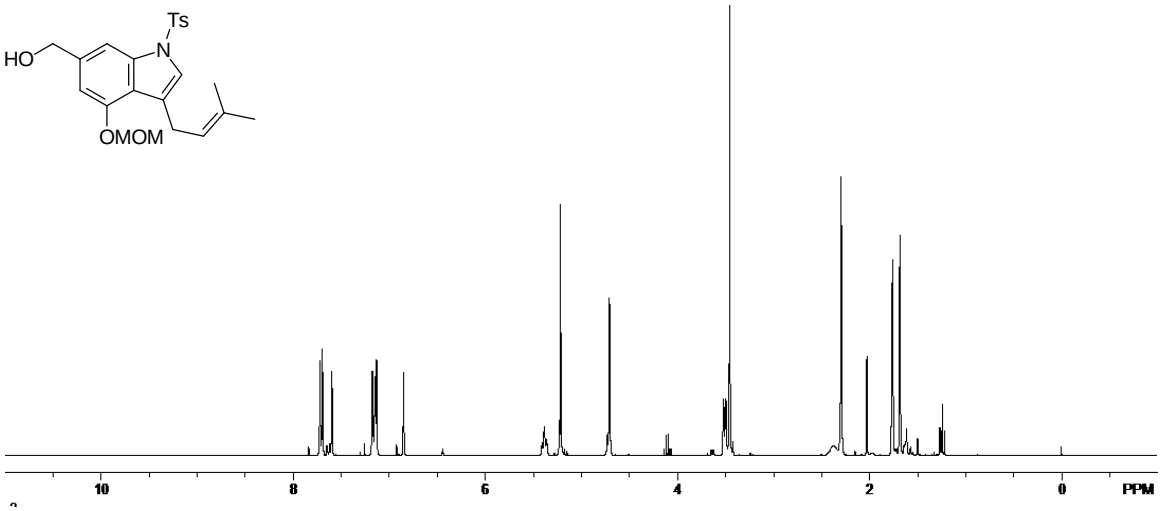


Figure A41. ^{1}H NMR spectrum for analogue **90**

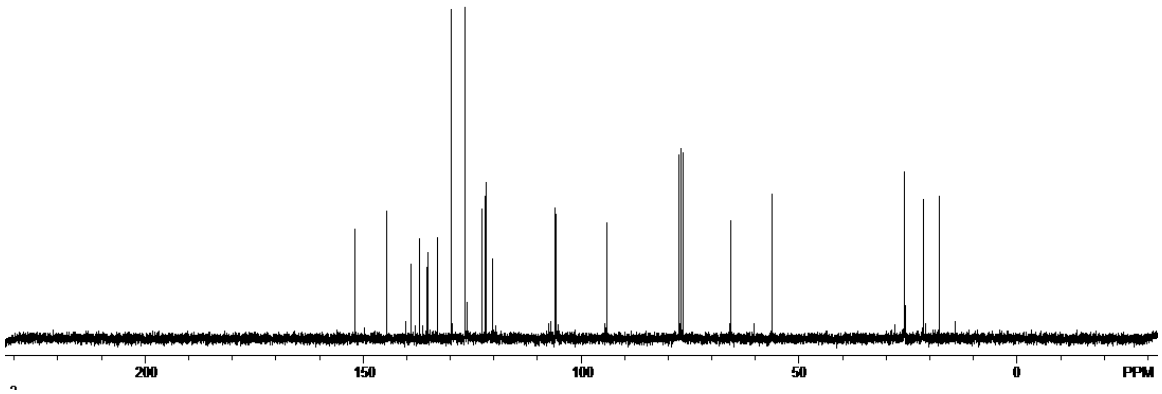


Figure A42. ^{13}C NMR spectrum for analogue **90**

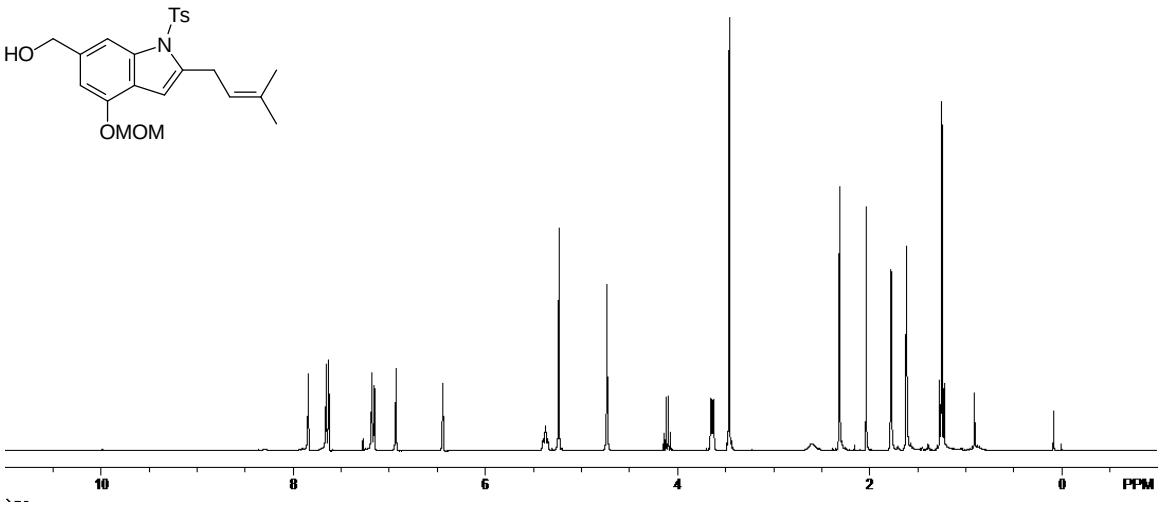


Figure A43. ^{1}H NMR spectrum for analogue **96**

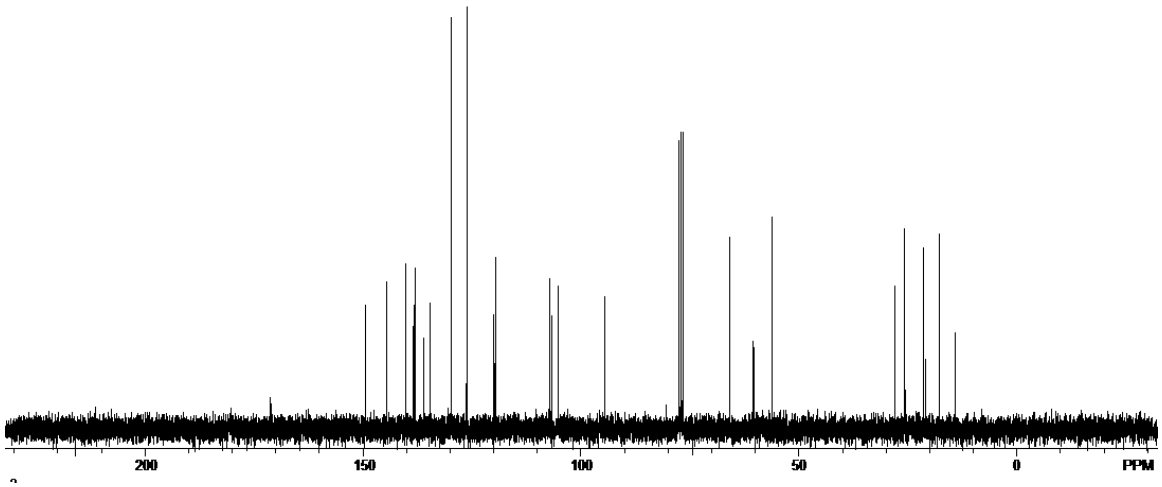


Figure A44. ^{13}C NMR spectrum for analogue **96**

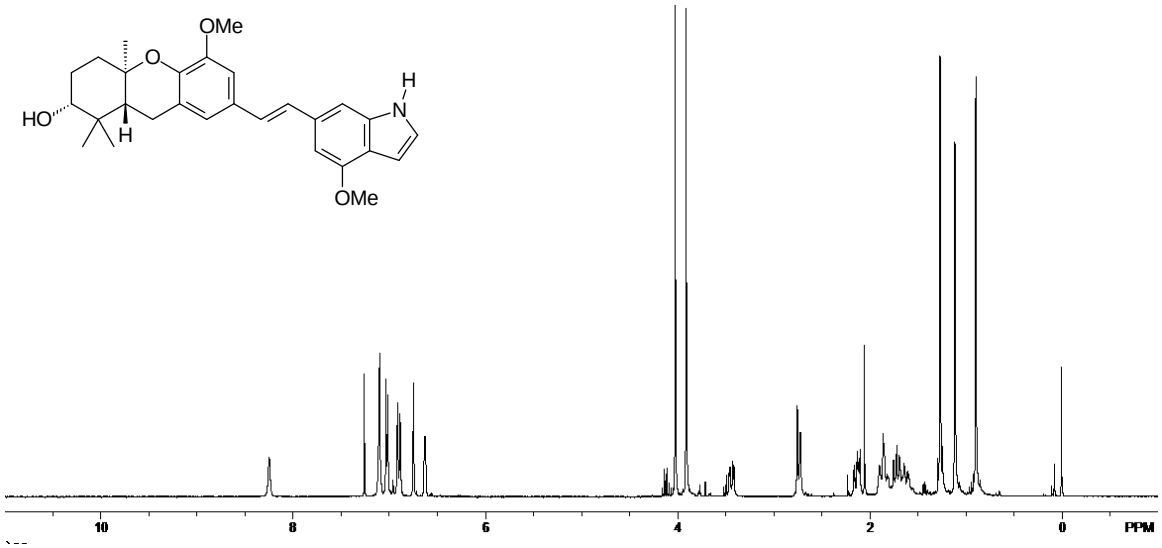


Figure A45. ^{1}H NMR spectrum for analogue **110**

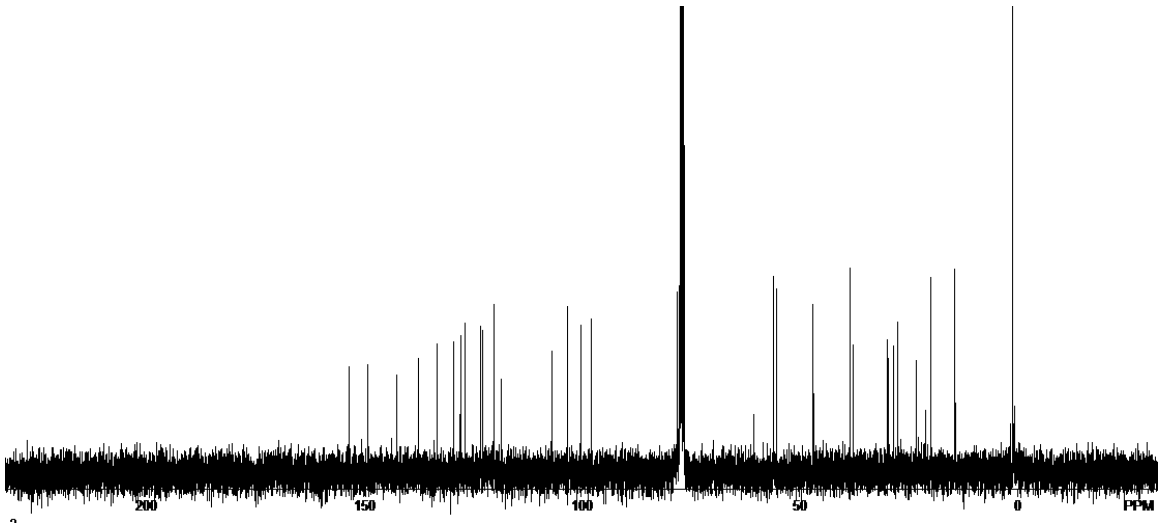


Figure A46. ^{13}C NMR spectrum for analogue **110**

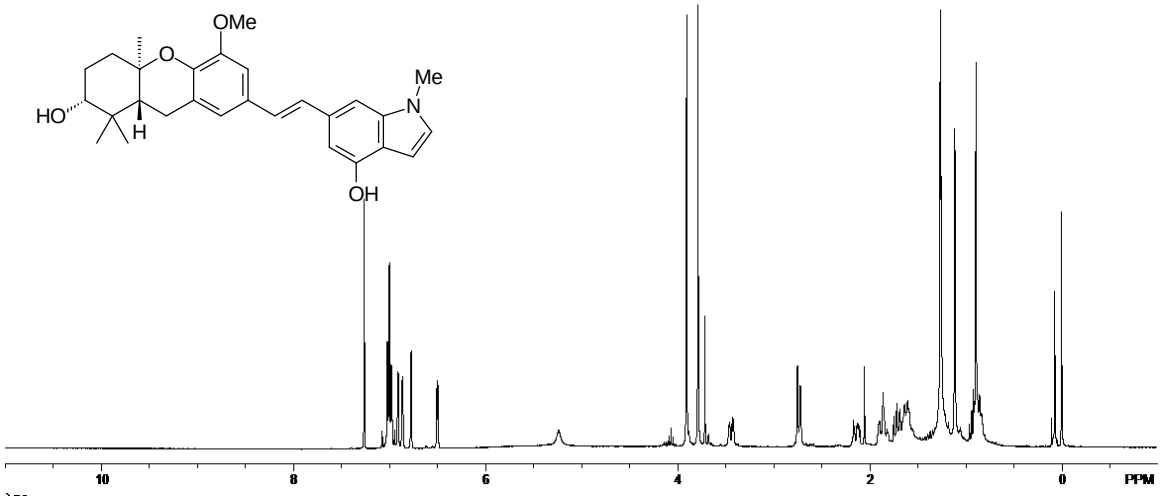


Figure A47. ^{1}H NMR spectrum for analogue **111**

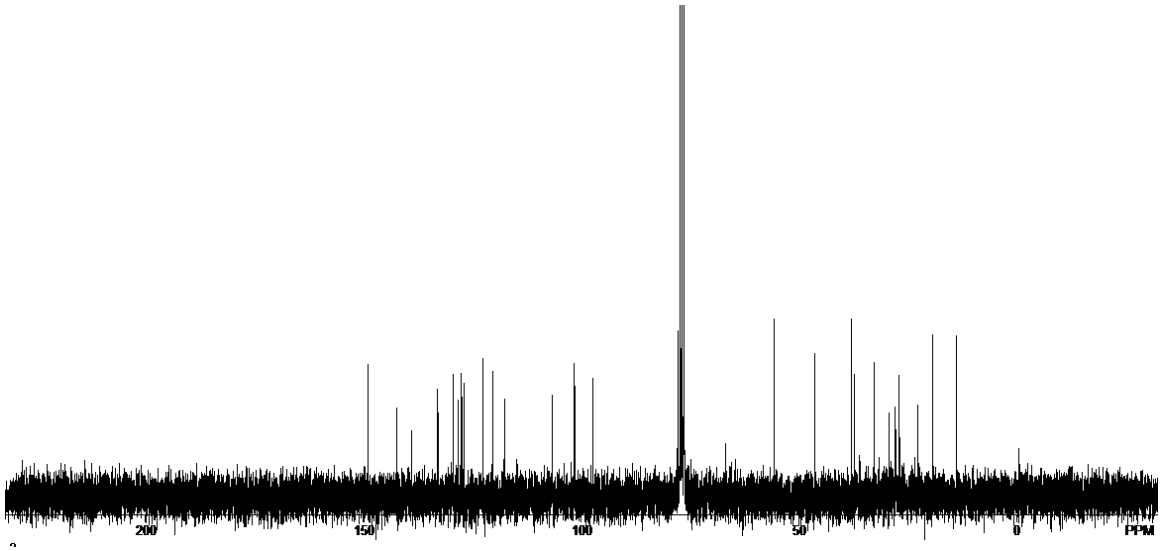


Figure A48. ^{13}C NMR spectrum for analogue **111**

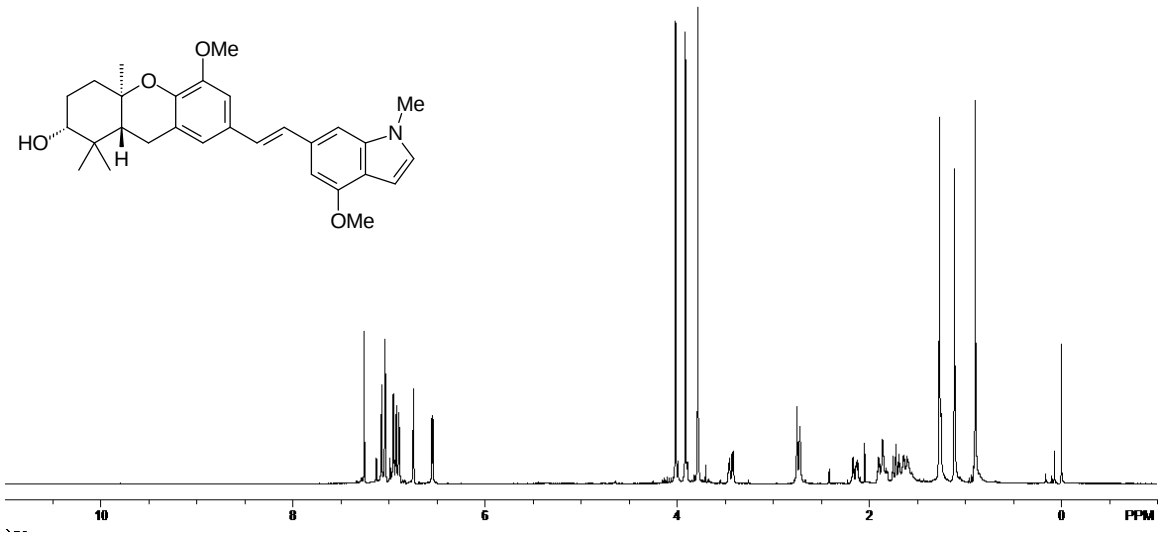


Figure A49. ^{1}H NMR spectrum for analogue **112**

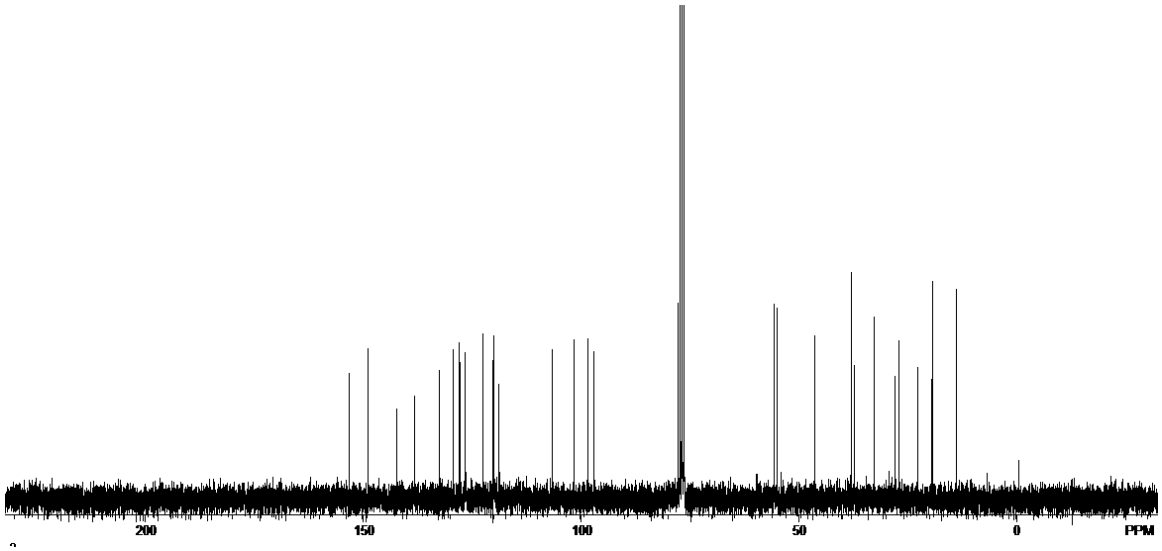


Figure A50. ^{13}C NMR spectrum for analogue **112**

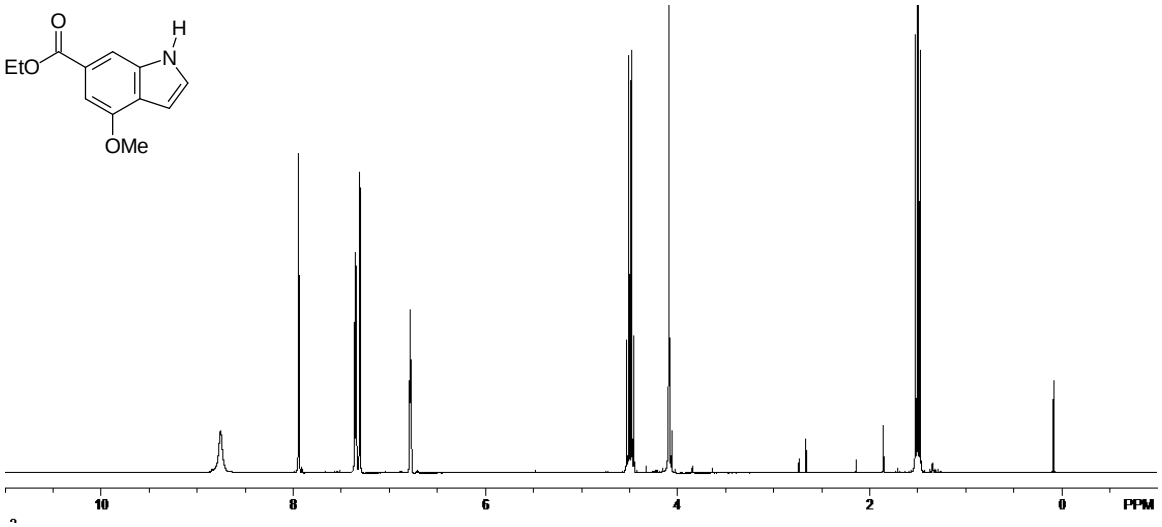


Figure A51. ^{1}H NMR spectrum for analogue **113**

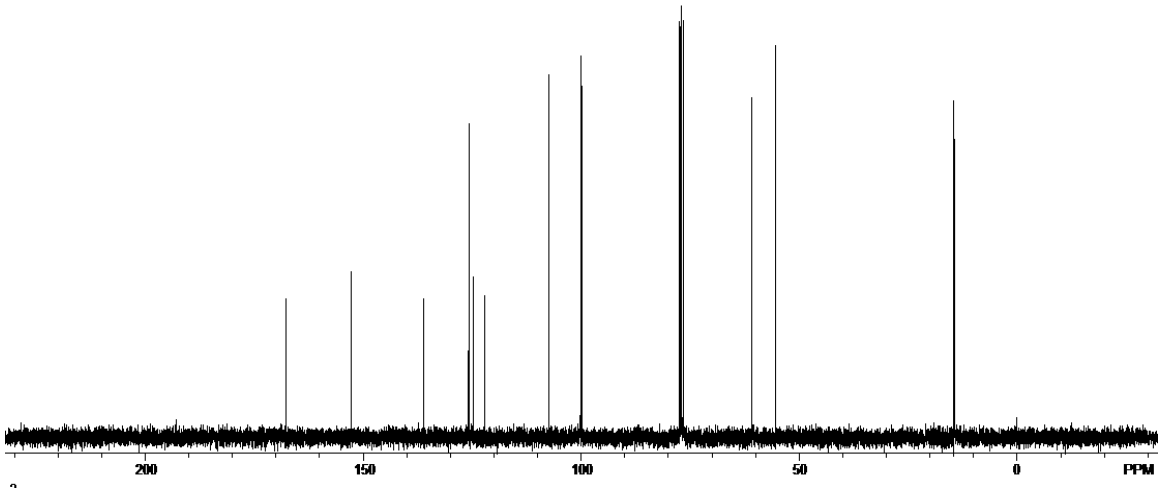


Figure A52. ^{13}C NMR spectrum for analogue **113**

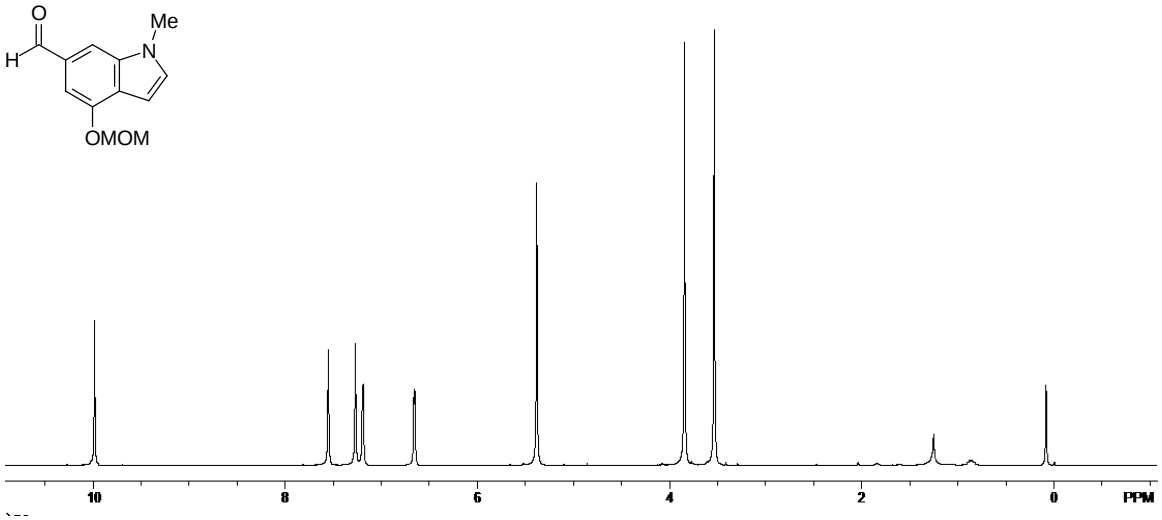


Figure A53. ^{1}H NMR spectrum for analogue **121**

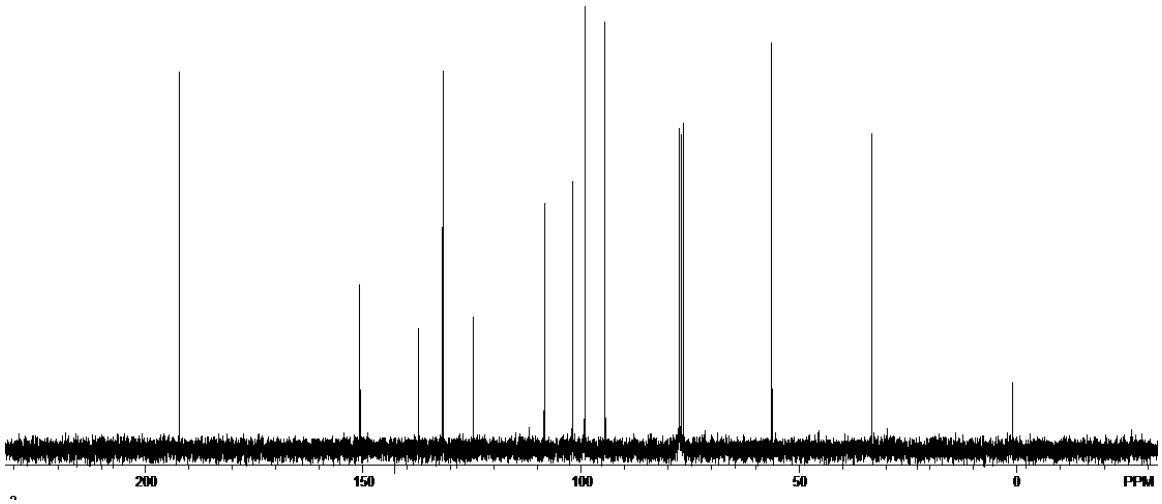


Figure A54. ^{13}C NMR spectrum for analogue **121**

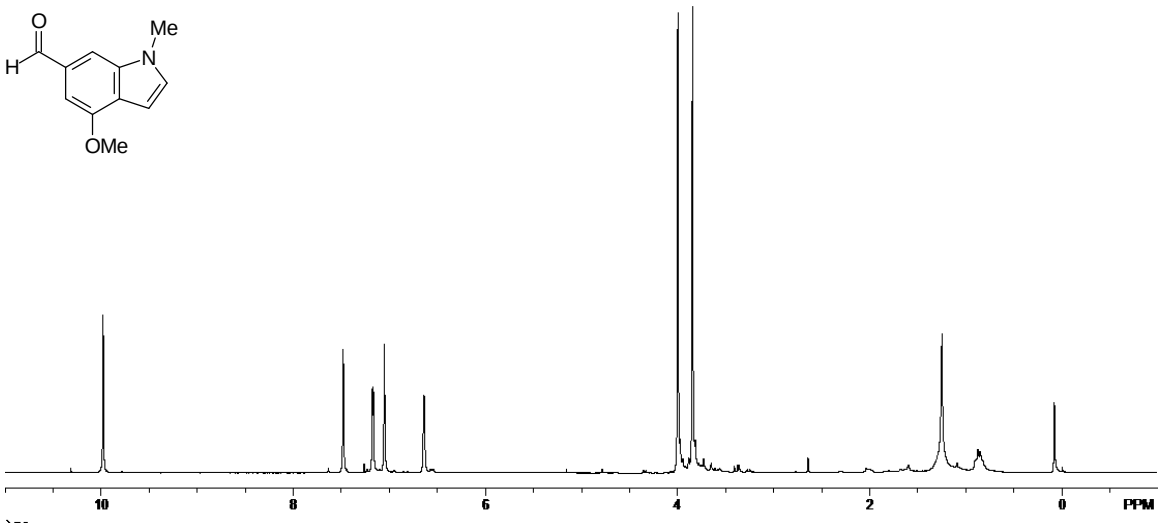


Figure A55. ^{1}H NMR spectrum for analogue **129**

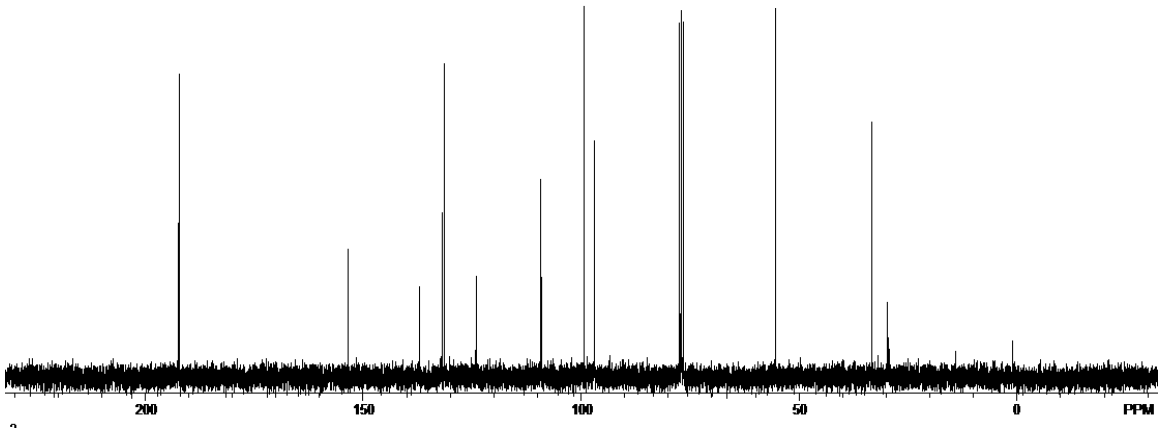


Figure A56. ^{13}C NMR spectrum for analogue **129**

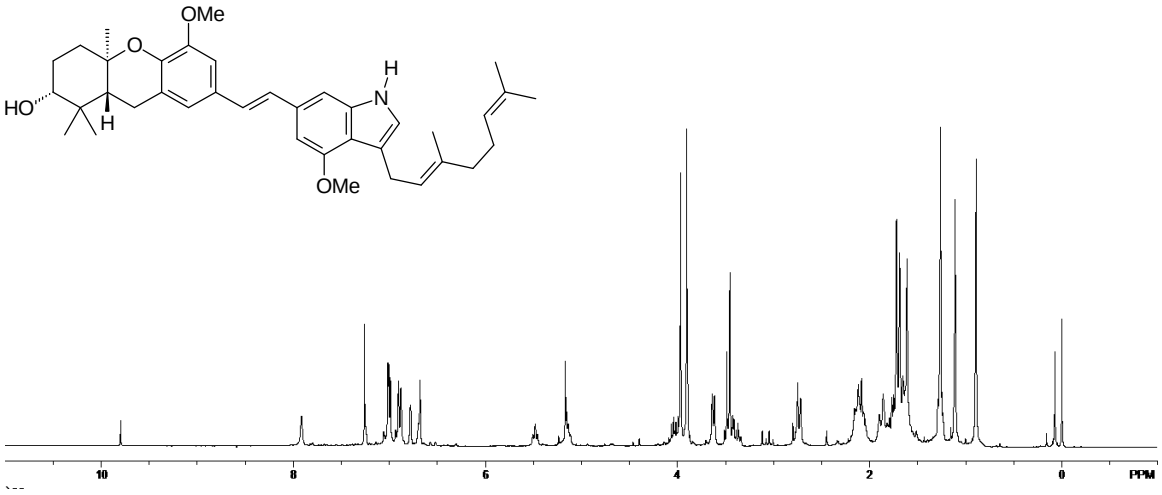


Figure A57. ^{1}H NMR spectrum for analogue **131**

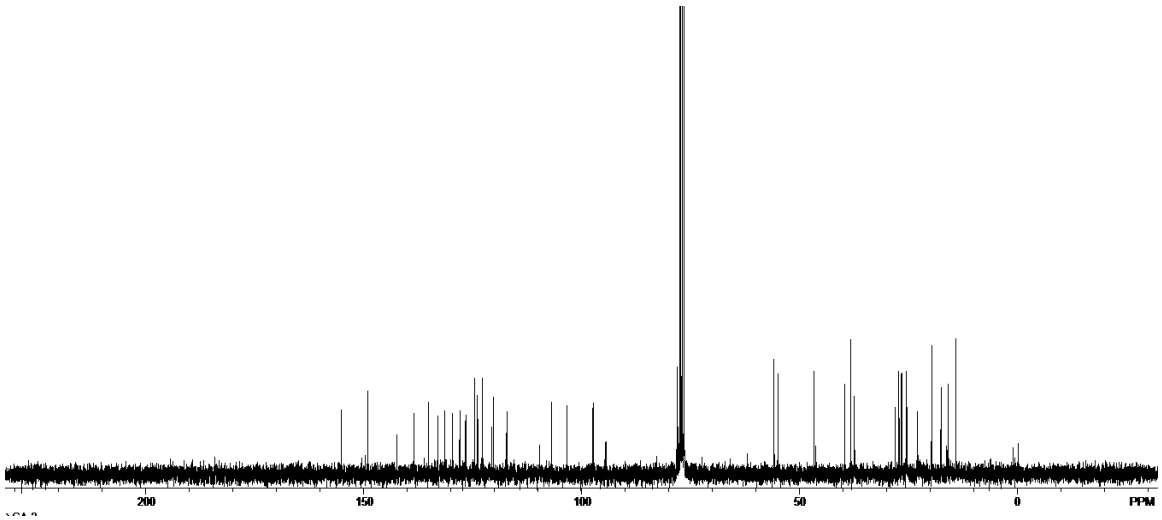


Figure A58. ^{13}C NMR spectrum for analogue **131**

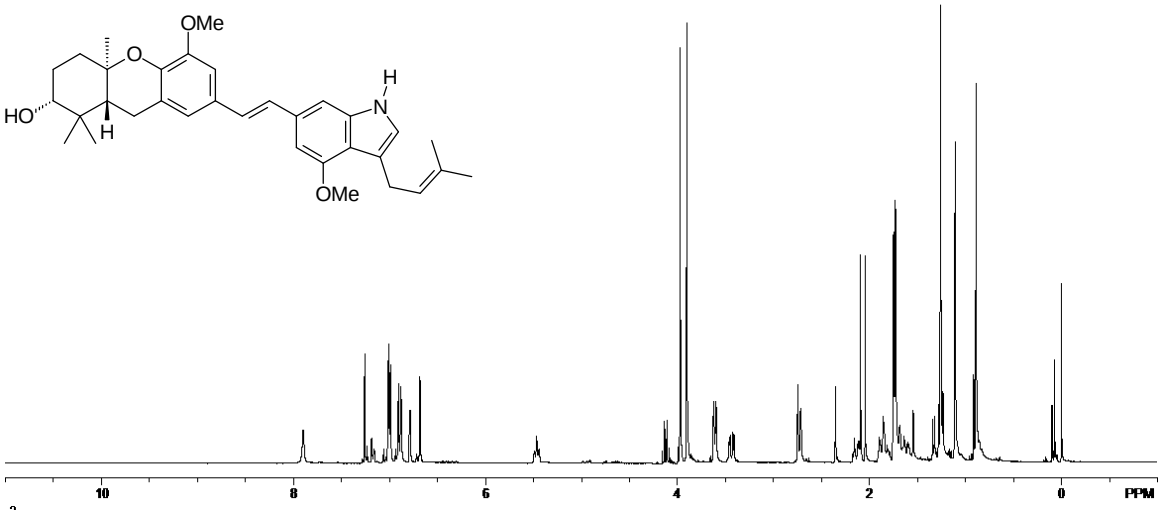


Figure A59. ^{1}H NMR spectrum for analogue **132**

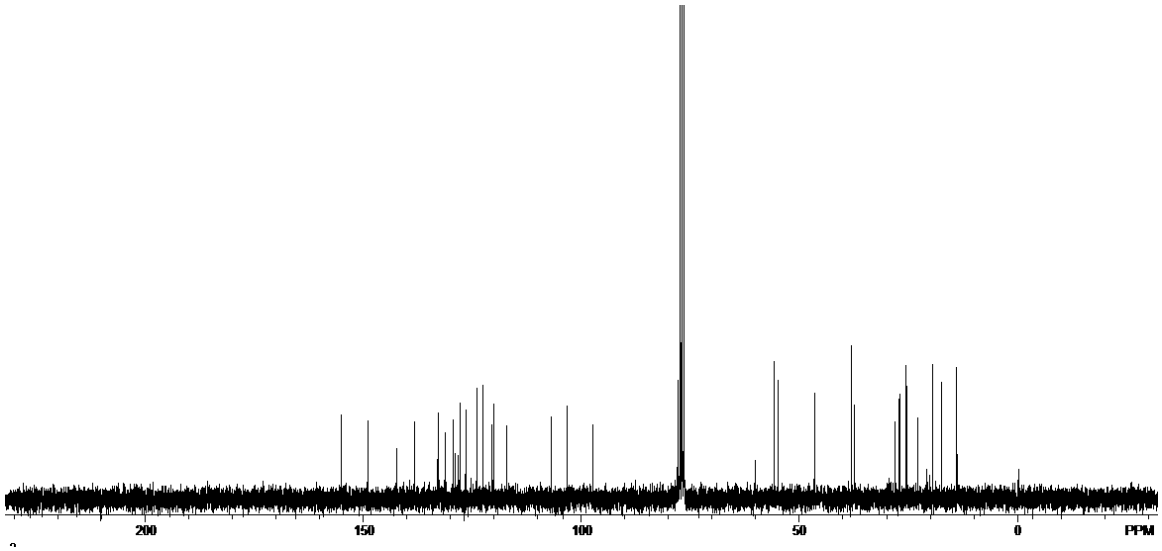


Figure A60. ^{13}C NMR spectrum for analogue **132**

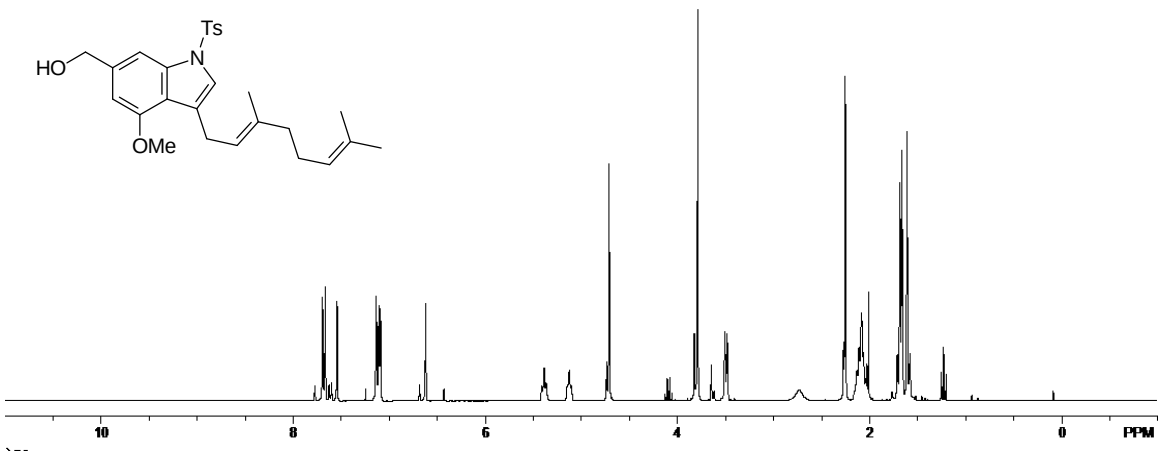


Figure A61. ^{1}H NMR spectrum for analogue **134**

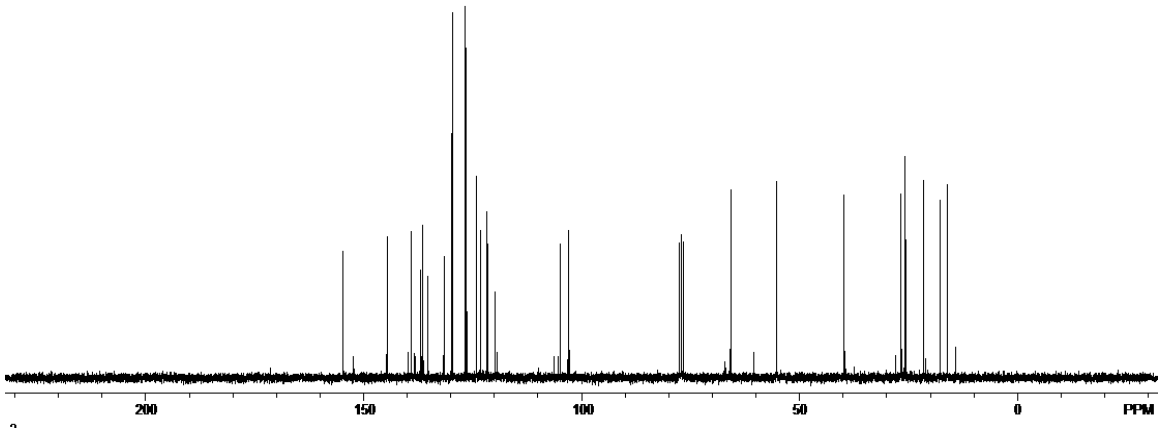


Figure A62. ^{13}C NMR spectrum for analogue **134**

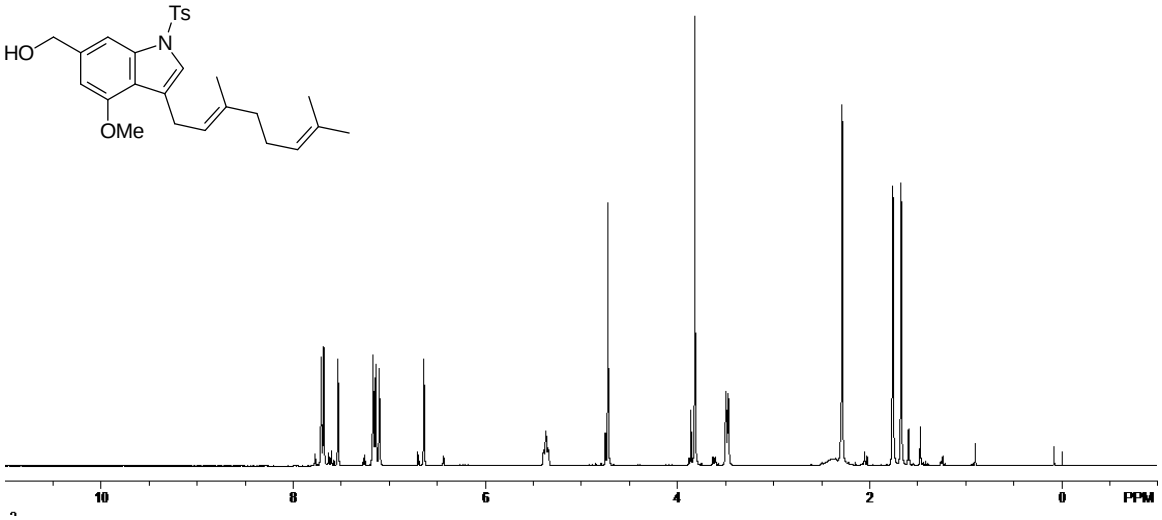


Figure A63. ^{1}H NMR spectrum for analogue **138**

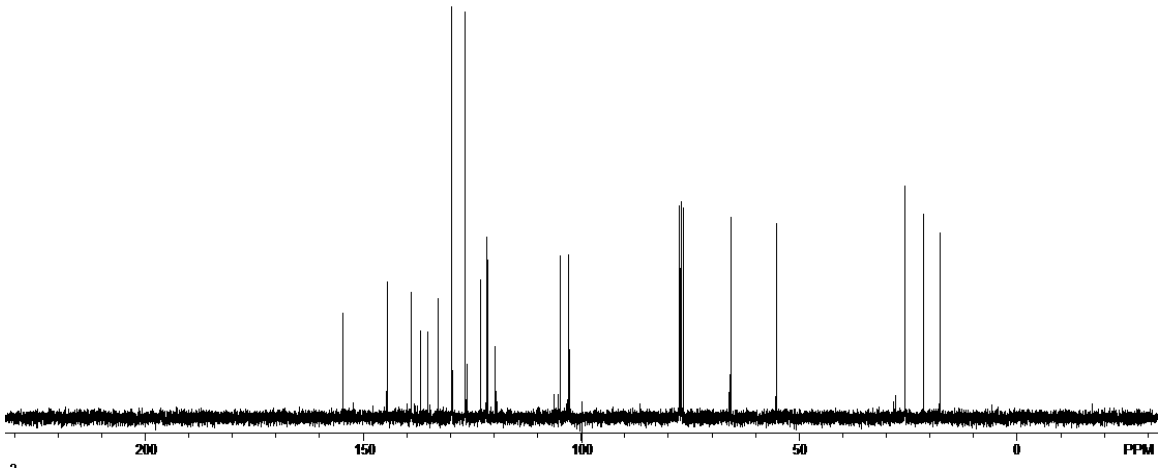


Figure A64. ^{13}C NMR spectrum for analogue **138**

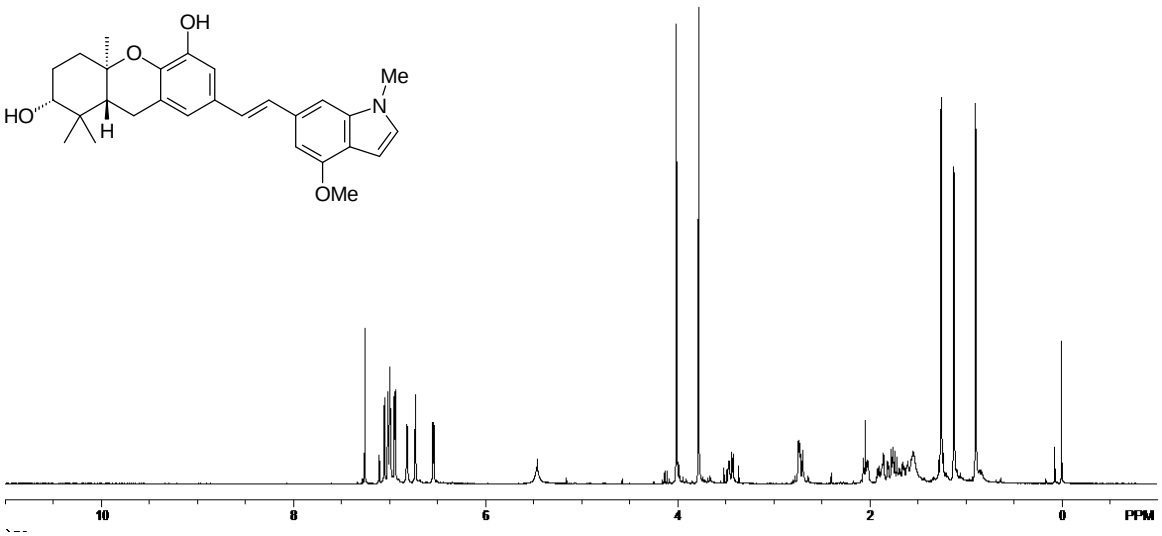


Figure A65. ^{1}H NMR spectrum for analogue **141**

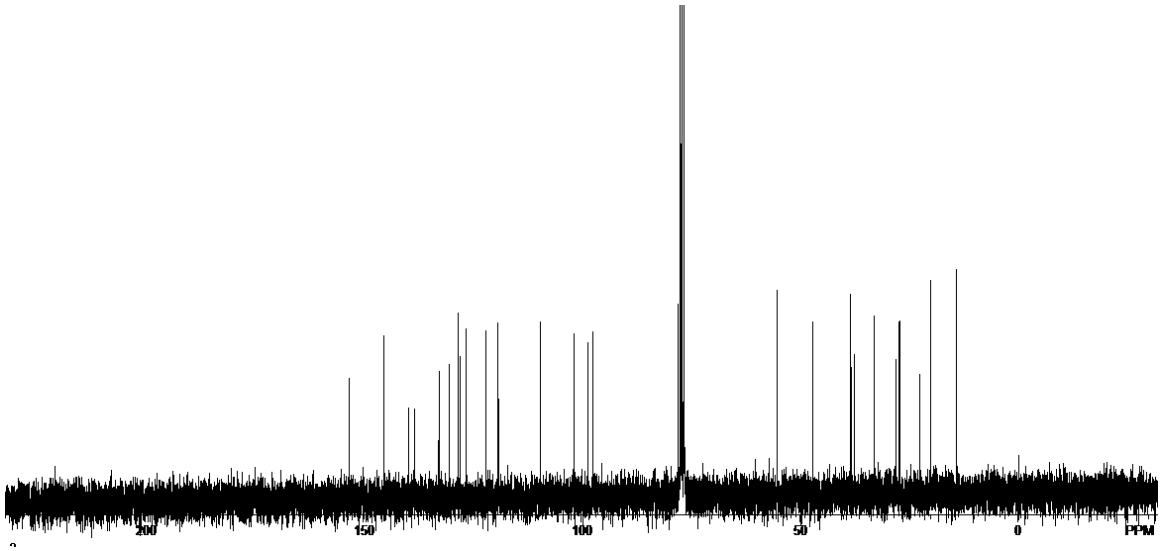


Figure A66. ^{13}C NMR spectrum for analogue **141**

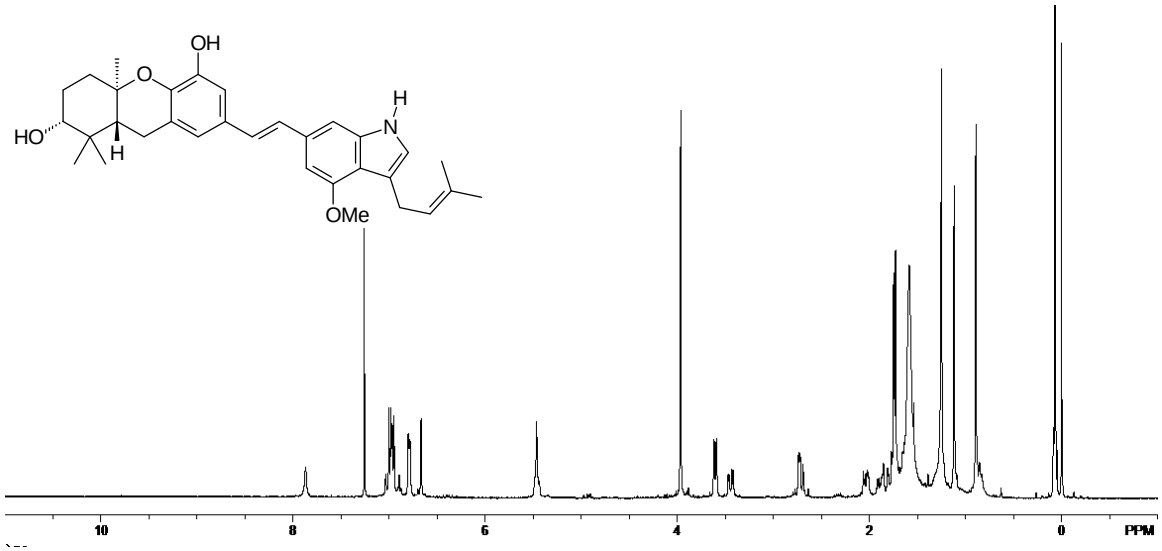


Figure A67. ^{1}H NMR spectrum for analogue **146**

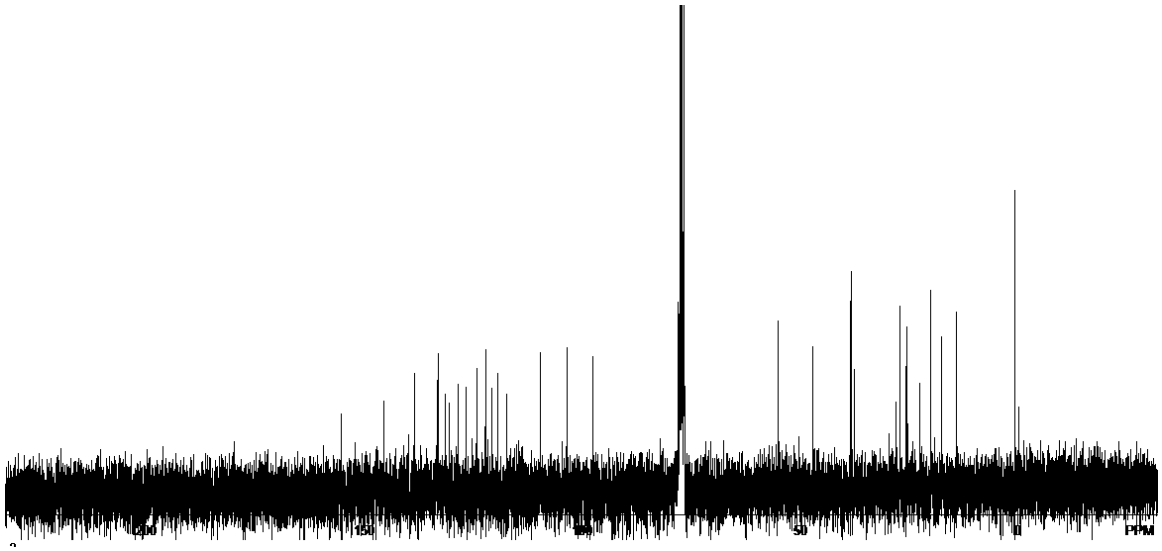


Figure A68. ^{13}C NMR spectrum for analogue **146**

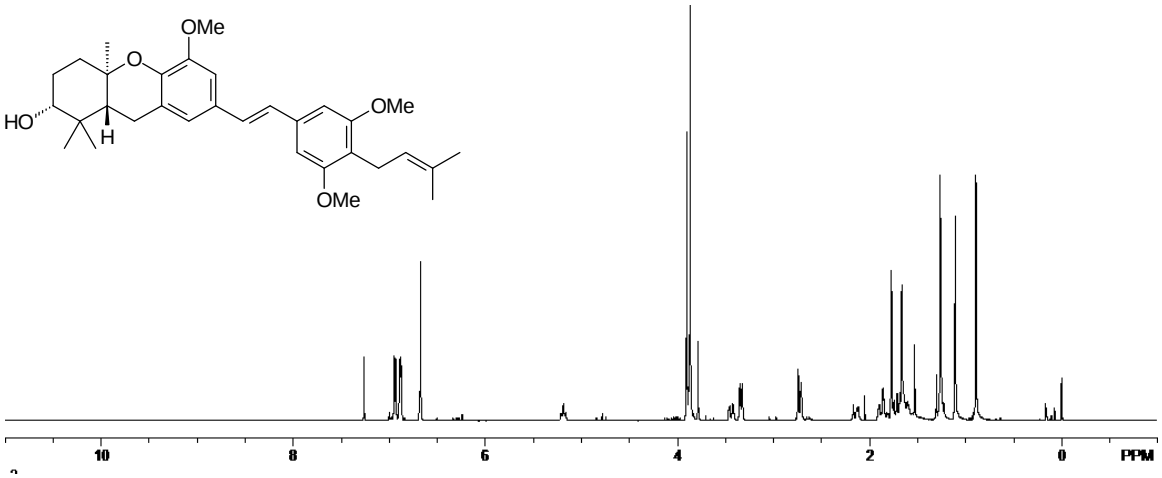


Figure A69. ^{1}H NMR spectrum for analogue **166**

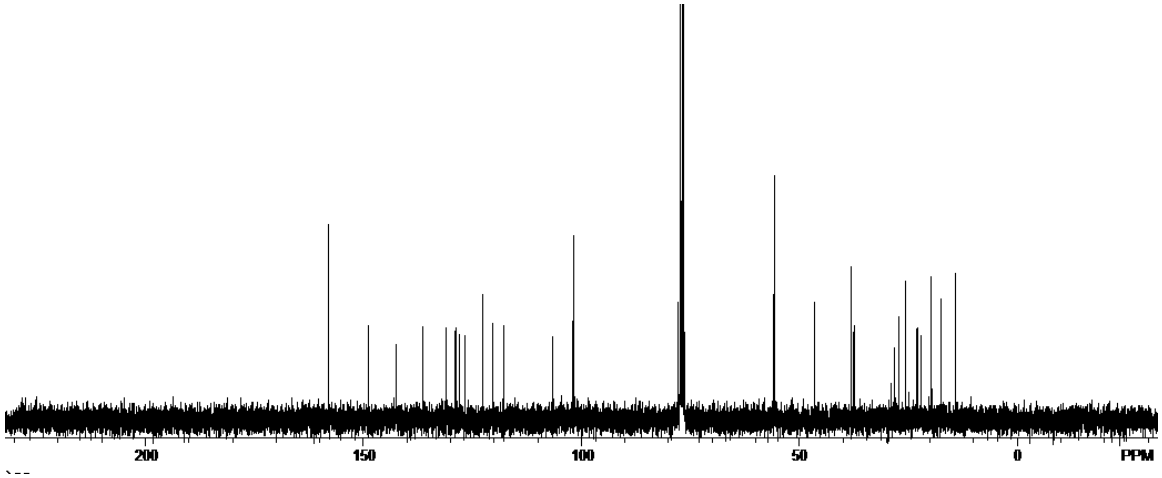


Figure A70. ^{13}C NMR spectrum for analogue **166**

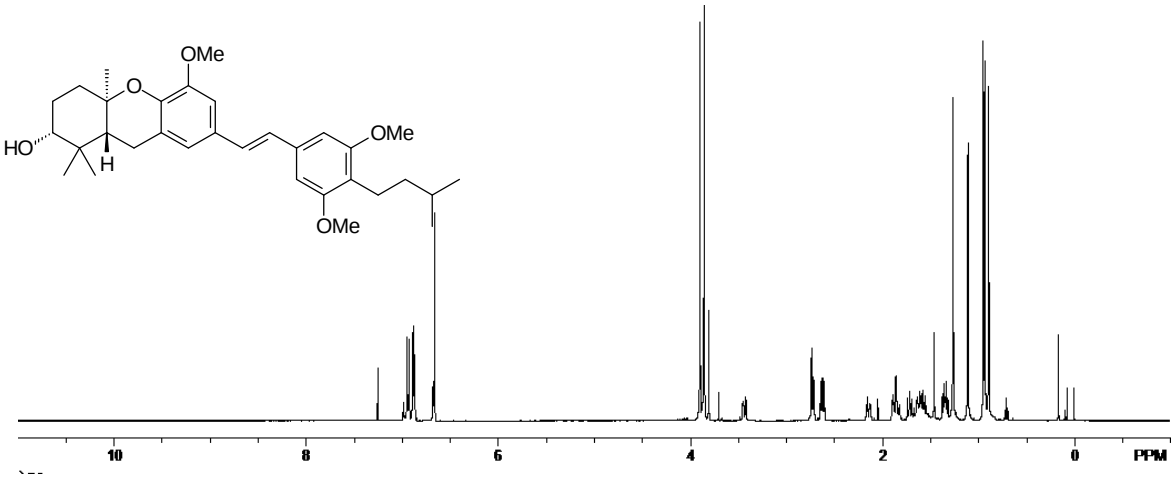


Figure A71. ^{1}H NMR spectrum for analogue **171**

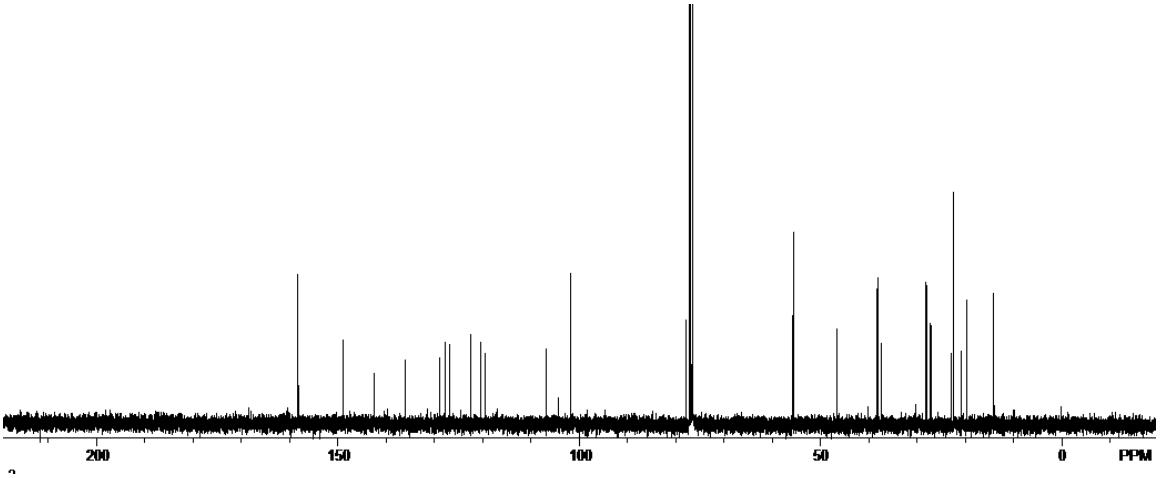


Figure A72. ^{13}C NMR spectrum for analogue **167**

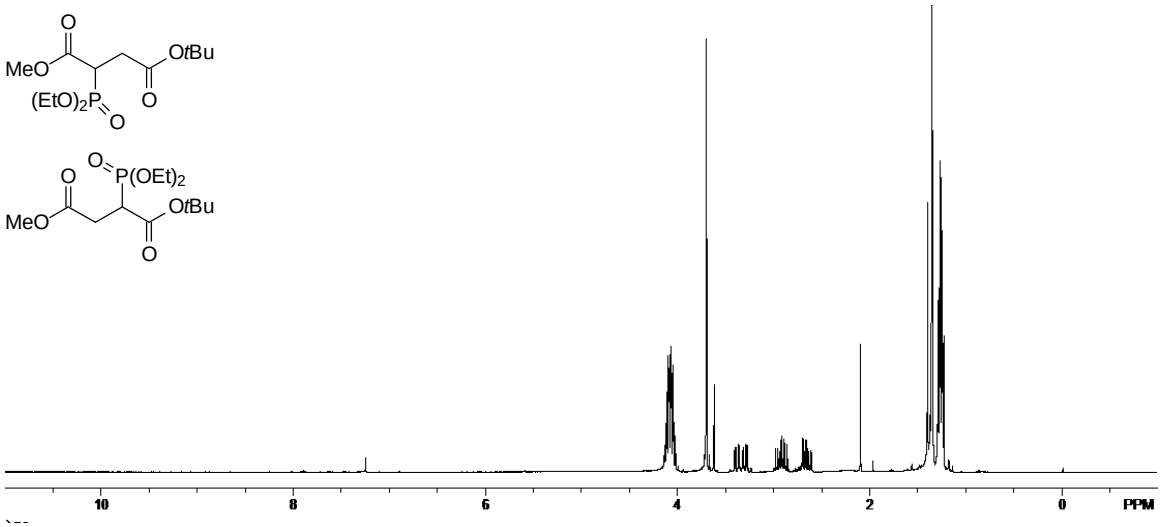


Figure A73. ^{1}H NMR spectrum for analogues **183** and **184**

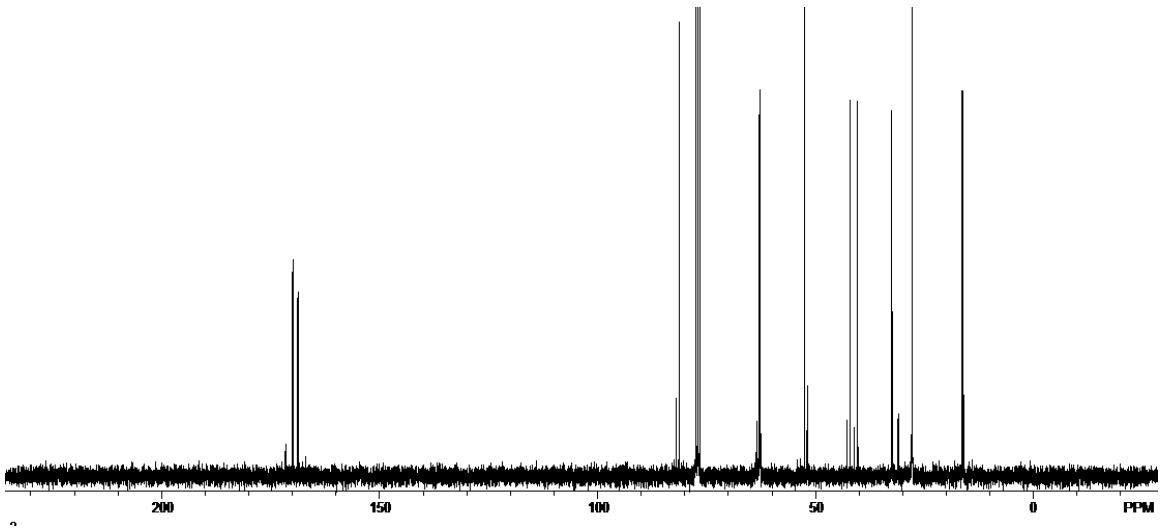


Figure A74. ^{13}C NMR spectrum for analogues **183** and **184**

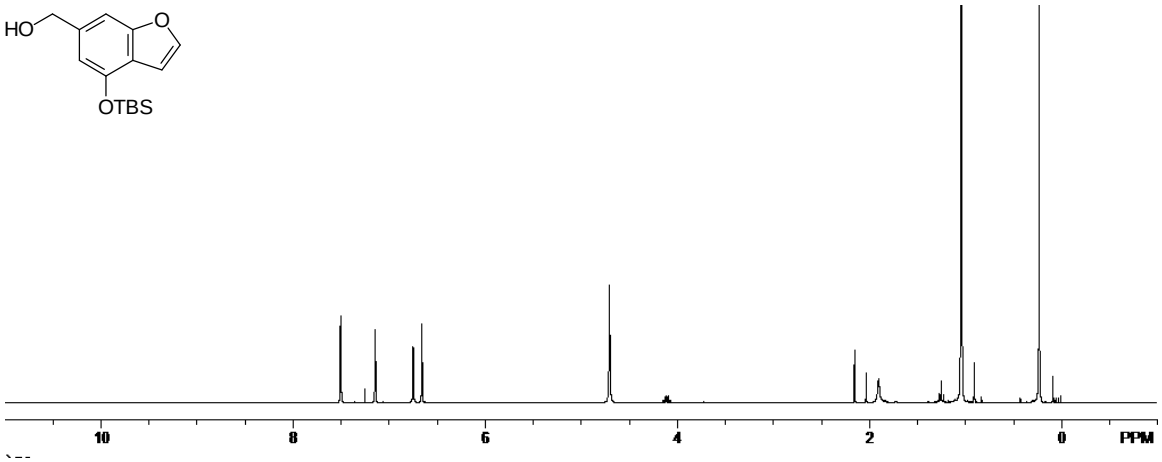


Figure A75. ^{1}H NMR spectrum for analogue **187**

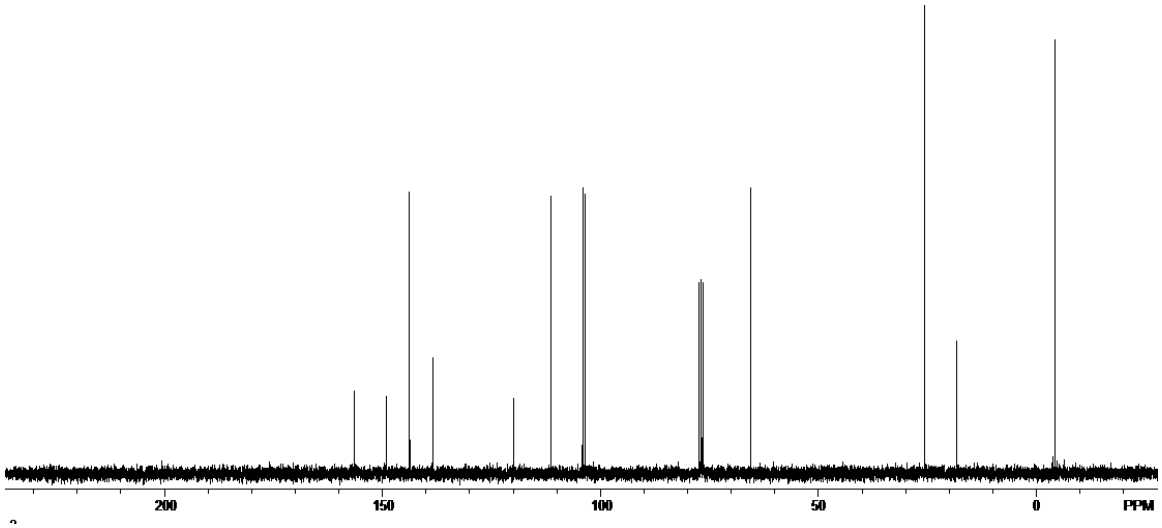


Figure A76. ^{13}C NMR spectrum for analogue **187**

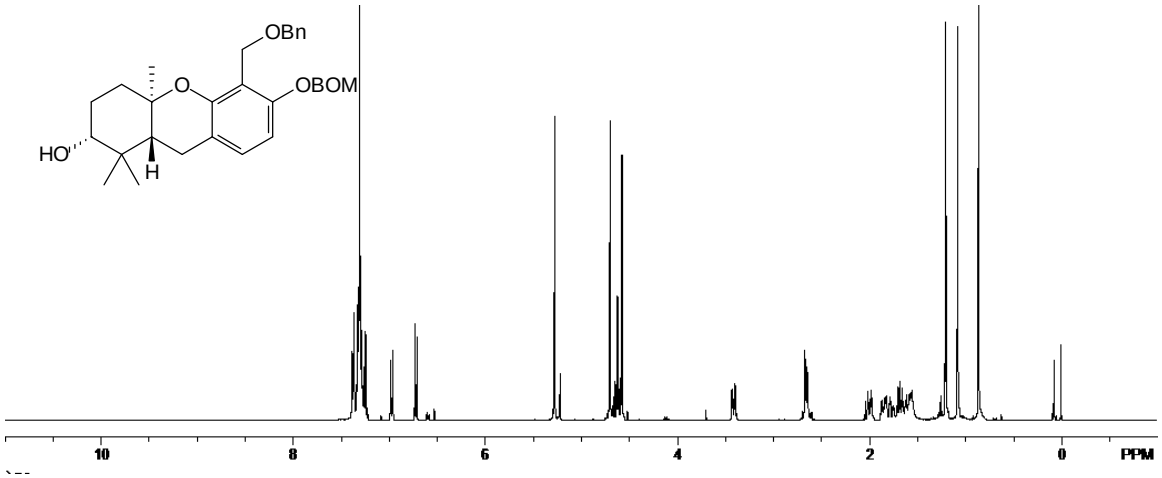


Figure A77. ^{1}H NMR spectrum for analogue **232A**

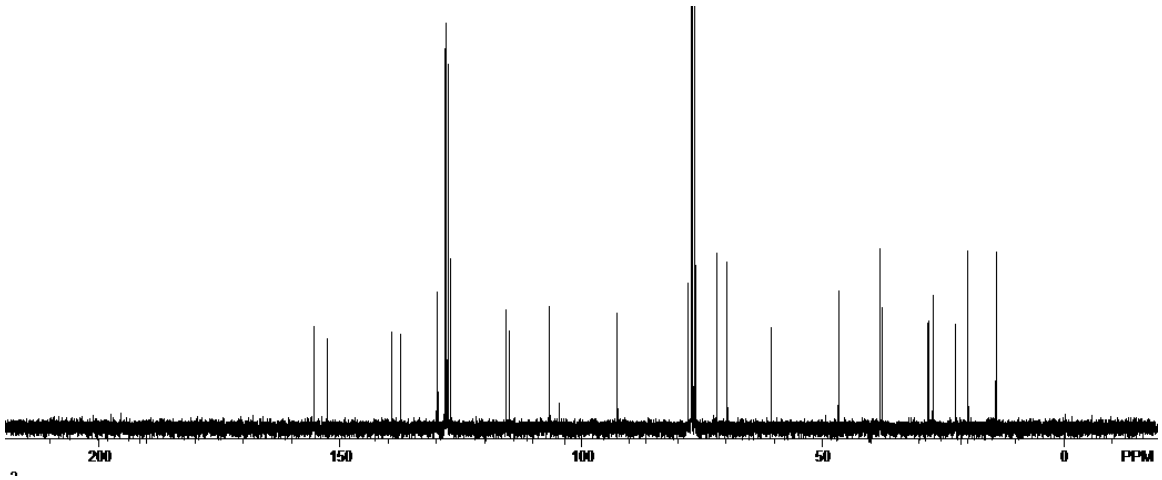


Figure A78. ^{13}C NMR spectrum for analogue **232A**

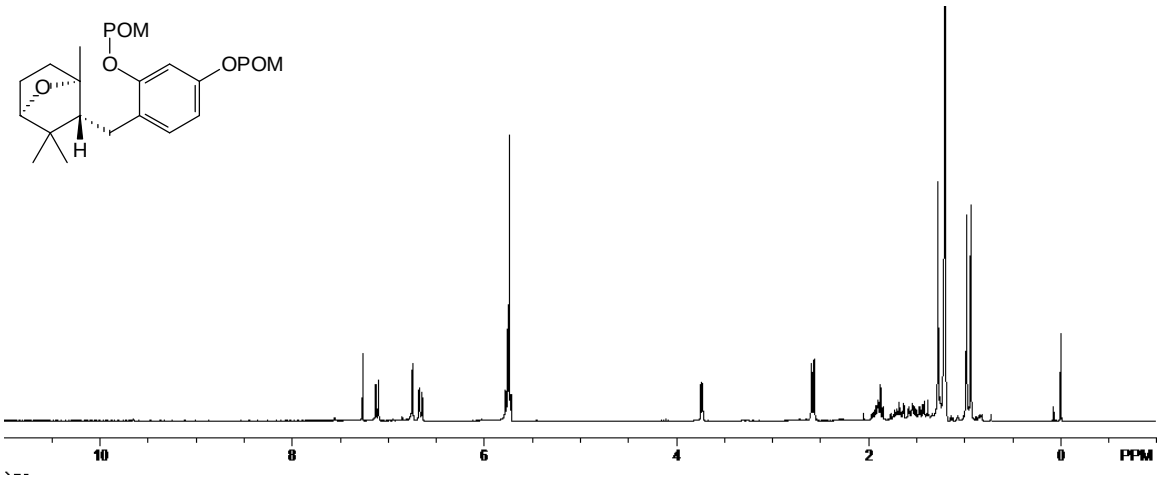


Figure A79. ^{1}H NMR spectrum for analogue **236C**

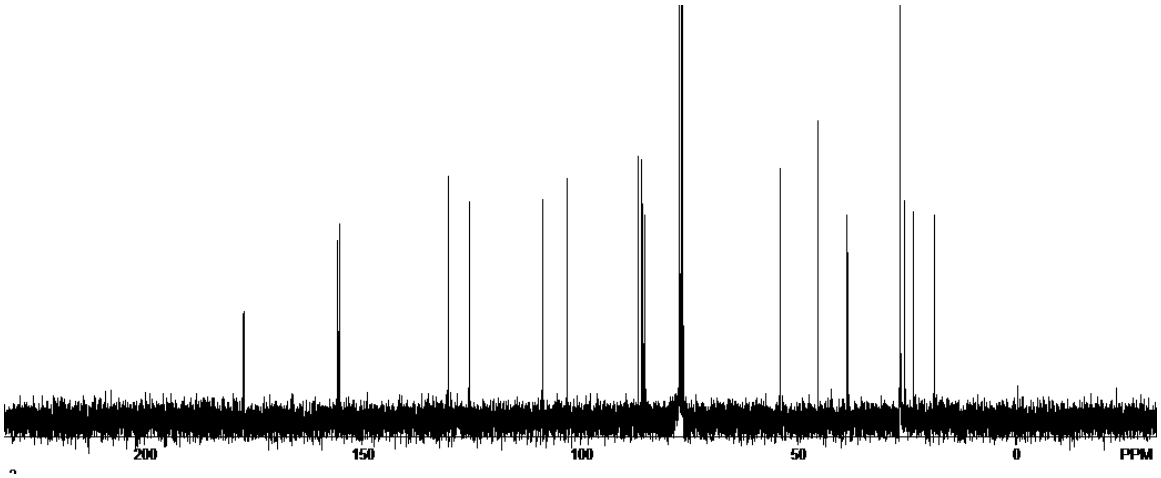


Figure A80. ^{13}C NMR spectrum for analogue **236C**

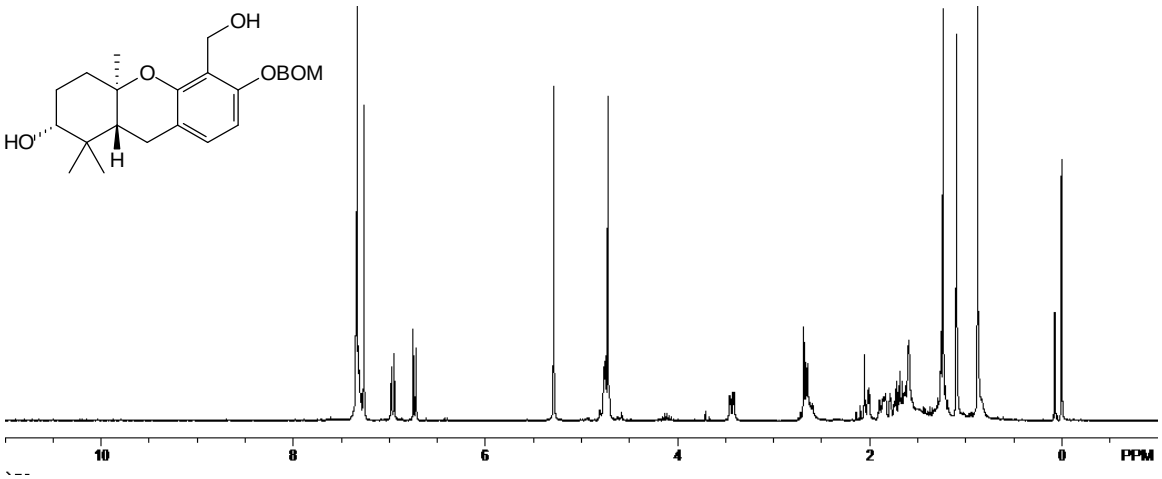


Figure A81. ^{1}H NMR spectrum for analogue **237**

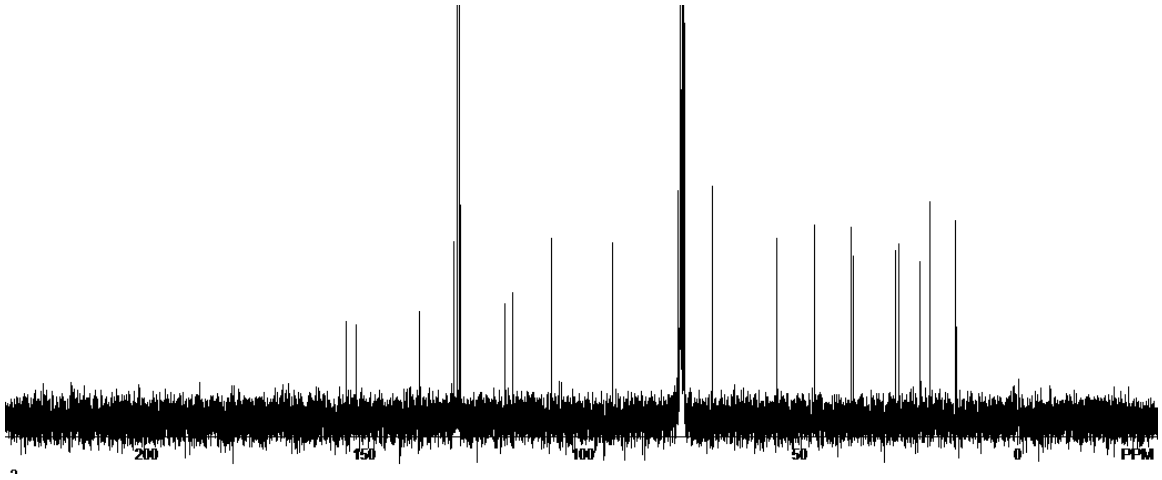


Figure A82. ^{13}C NMR spectrum for analogue **237**

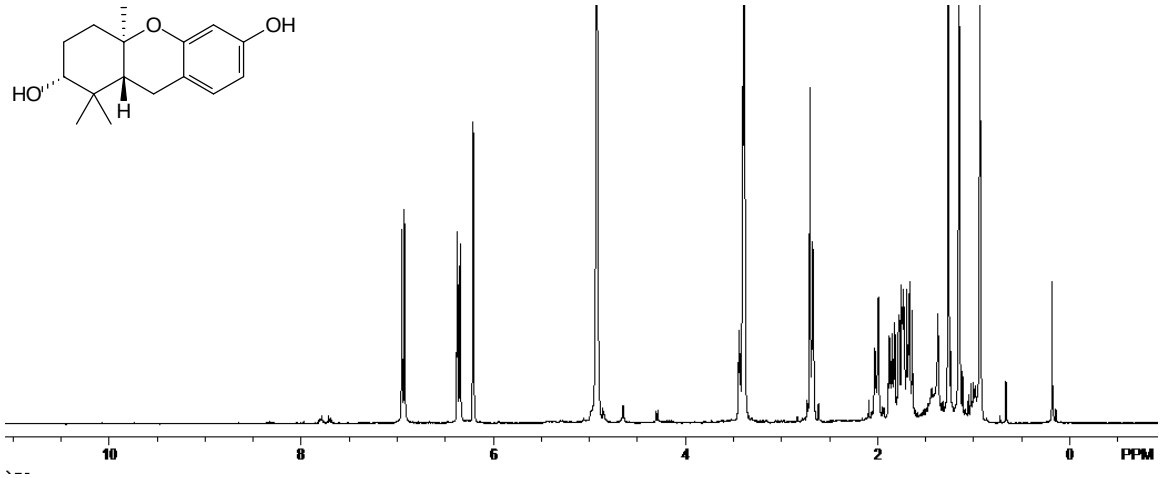


Figure A83. ^{1}H NMR spectrum for analogue **241**

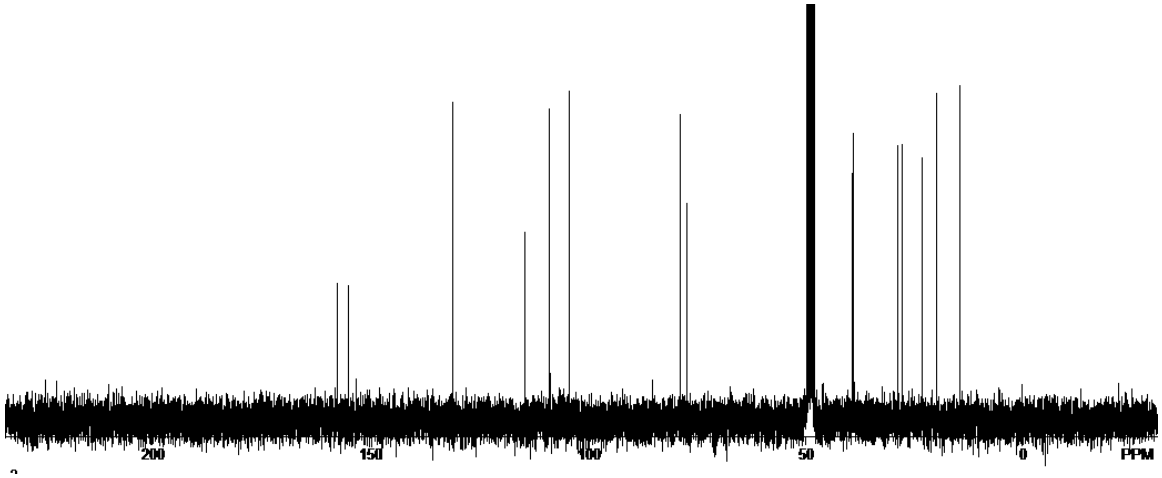


Figure A84. ^{13}C NMR spectrum for analogue **241**

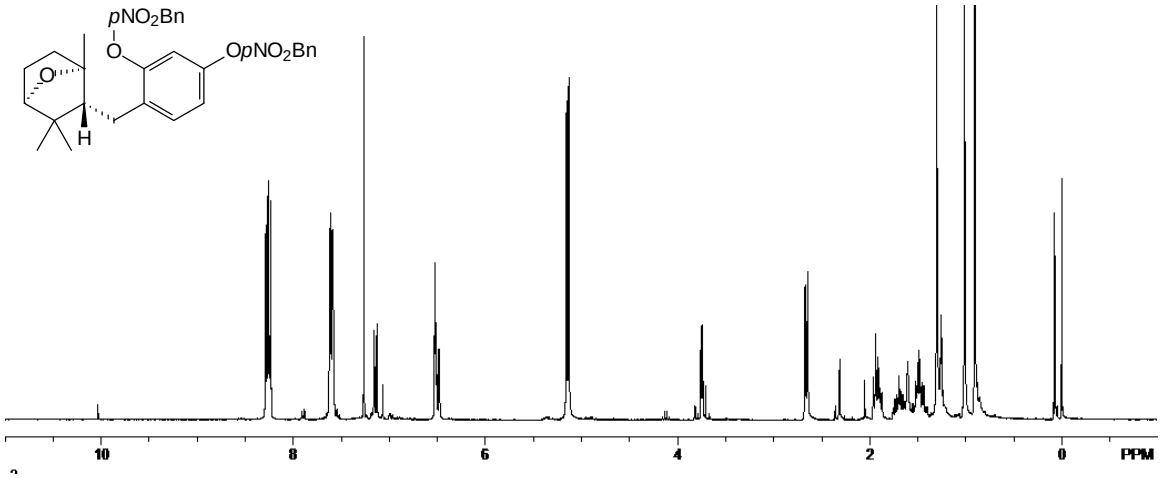


Figure A85. ^{1}H NMR spectrum for analogue **253A**

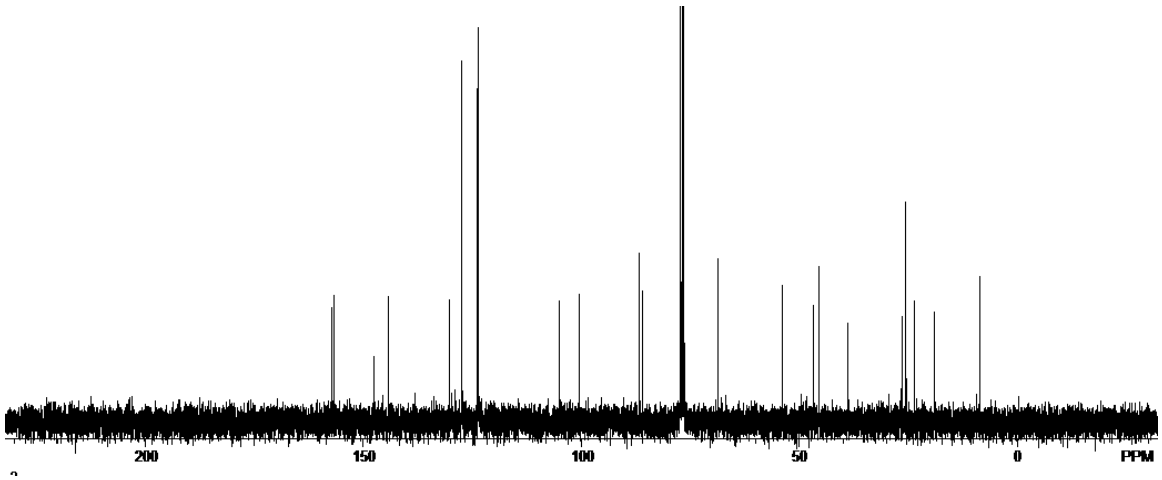


Figure A86. ^{13}C NMR spectrum for analogue **253A**

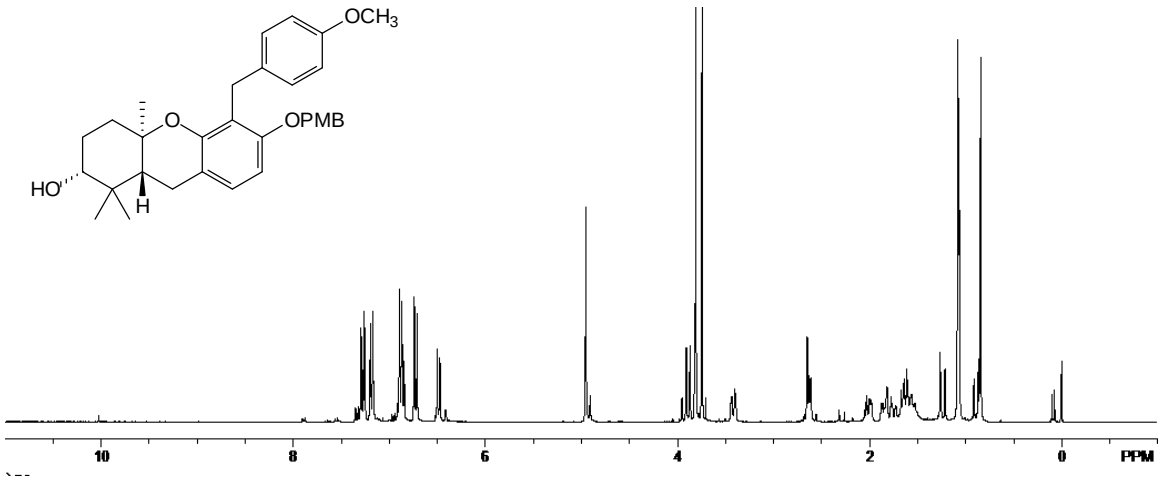


Figure A87. ^{1}H NMR spectrum for analogue **255B**

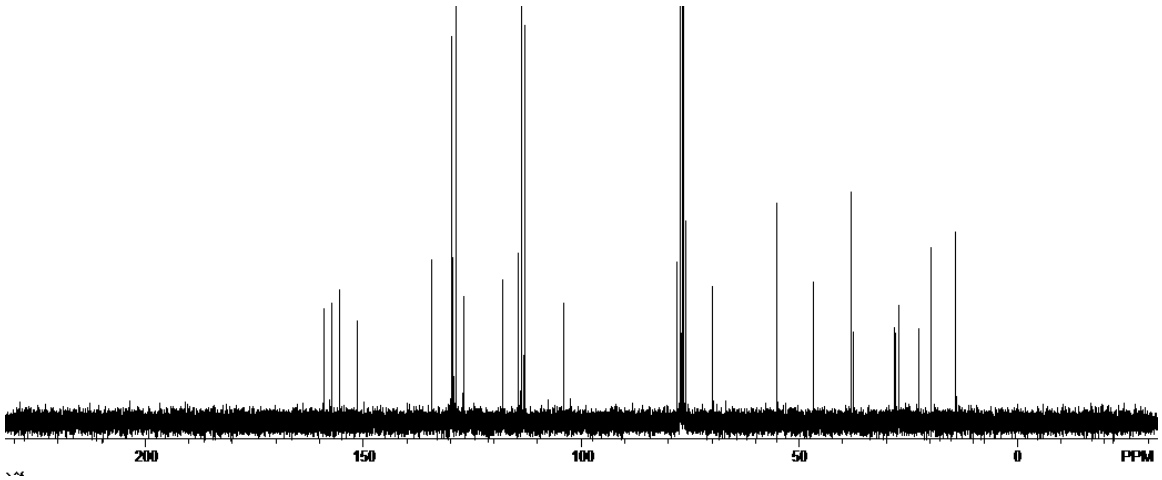


Figure A88. ^{13}C NMR spectrum for analogue **255B**

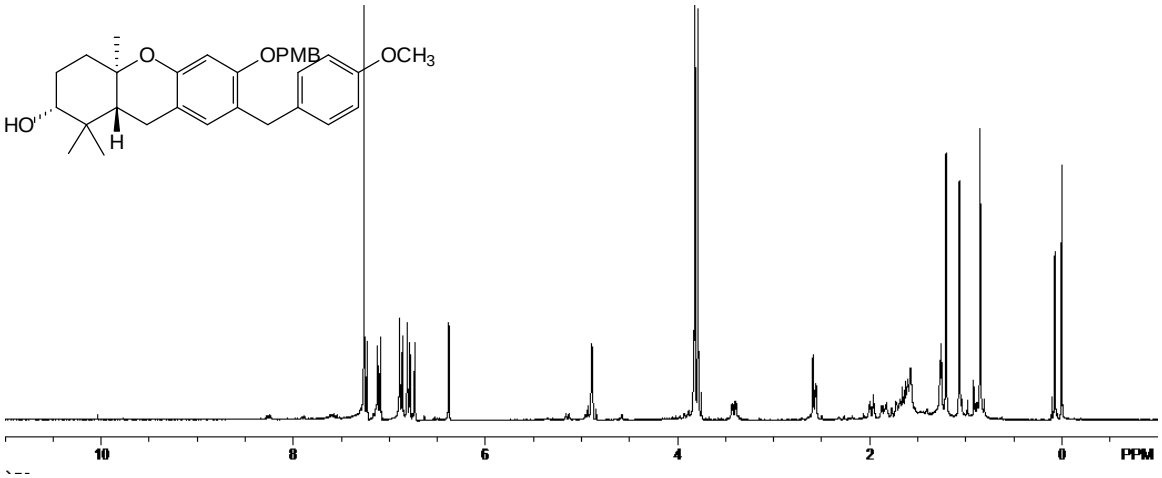


Figure A89. ^{1}H NMR spectrum for analogue **255C**

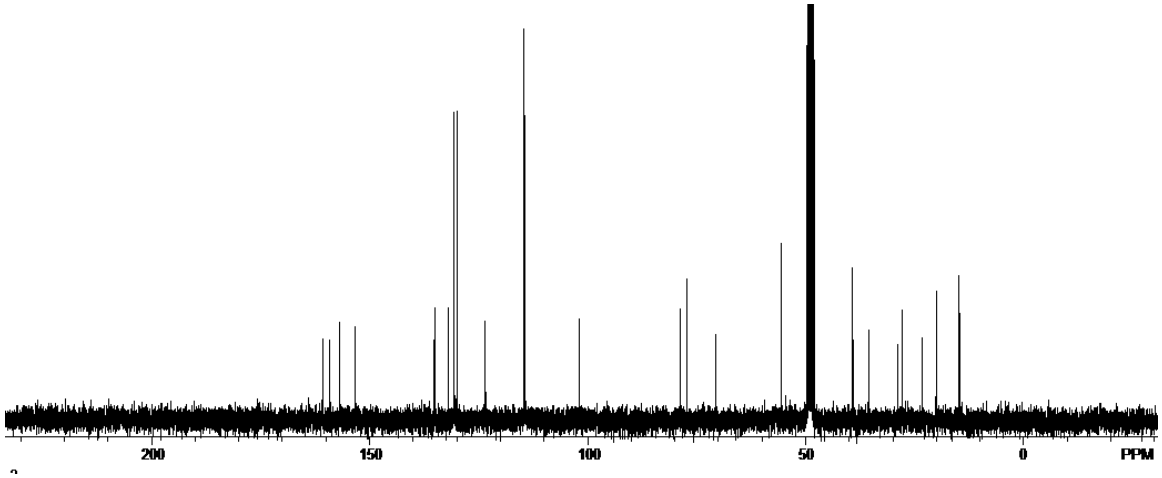


Figure A90. ^{13}C NMR spectrum for analogue **255C**

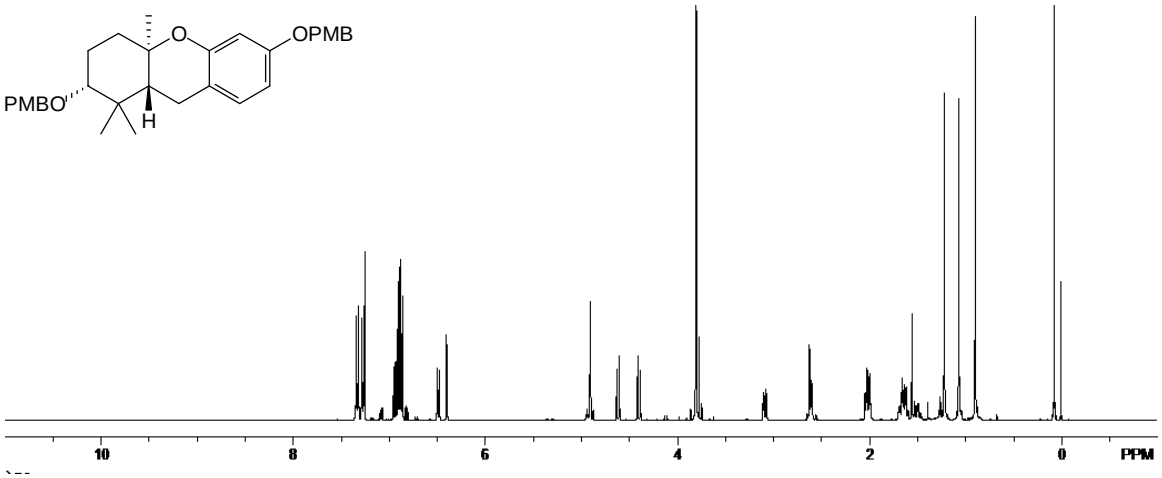


Figure A91. ^{1}H NMR spectrum for analogue **255E**

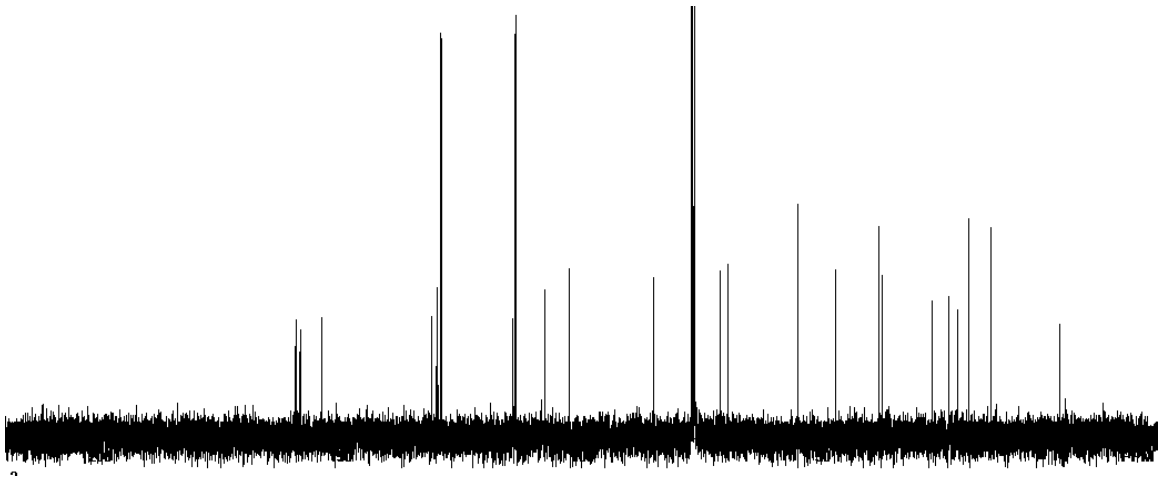


Figure A92. ^{13}C NMR spectrum for analogue **255E**

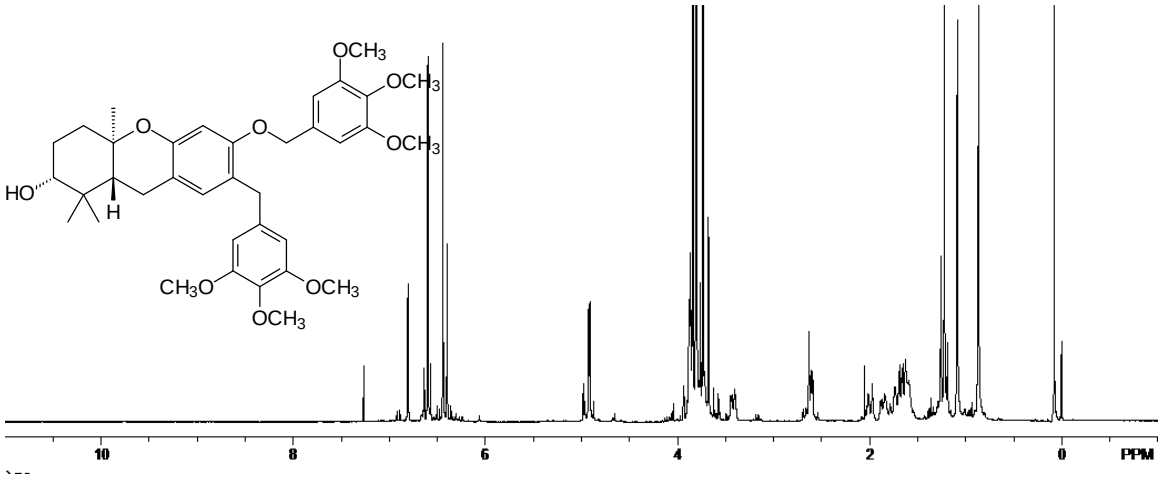


Figure A93. ^{1}H NMR spectrum for analogue **256C**

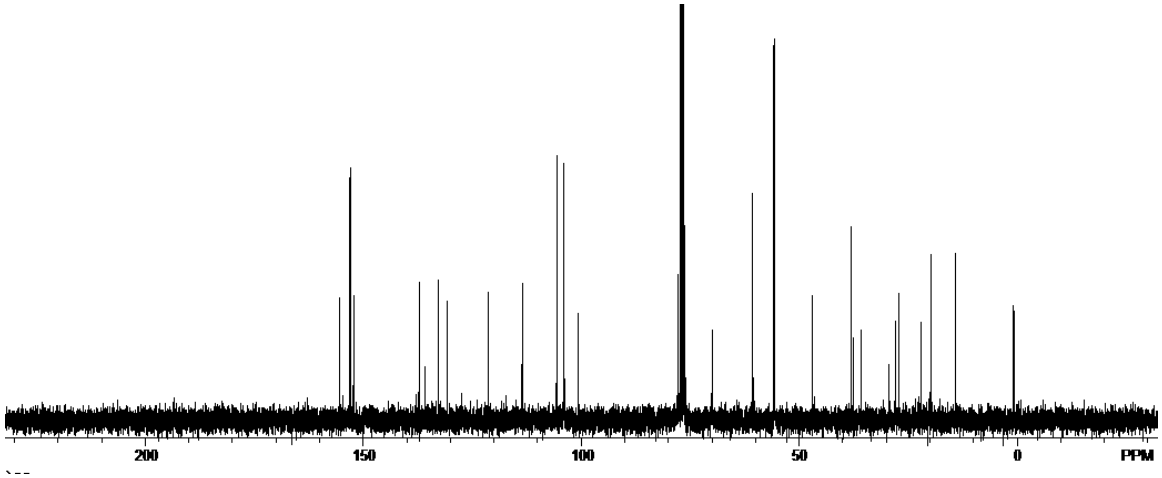


Figure A94. ^{13}C NMR spectrum for analogue **256C**

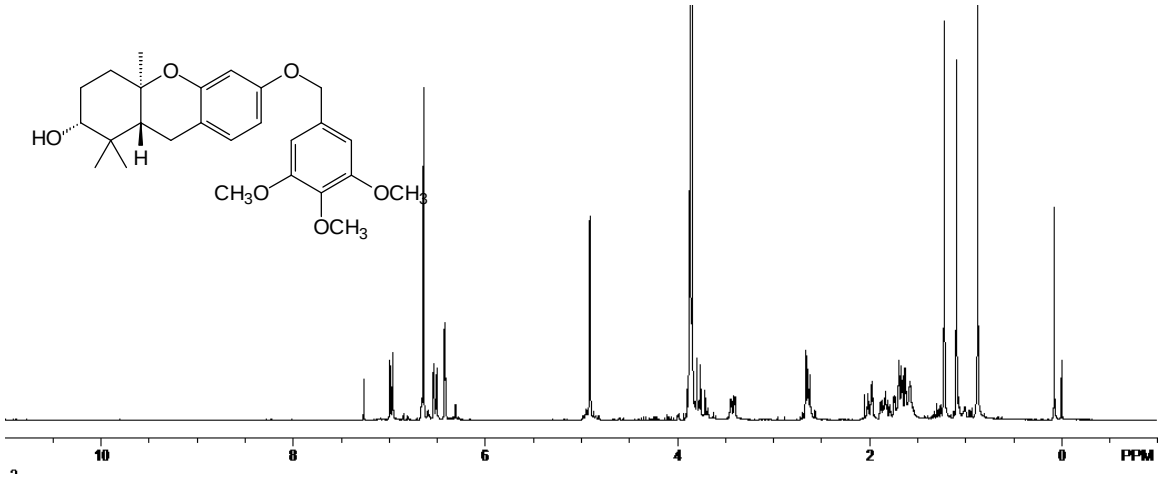


Figure A95. ^{1}H NMR spectrum for analogue **256D**

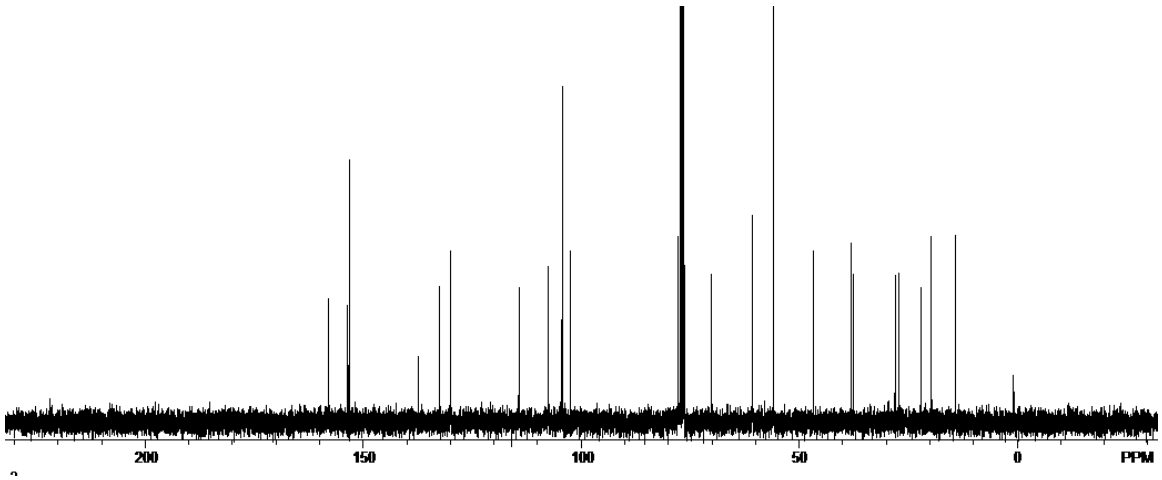


Figure A96. ^{13}C NMR spectrum for analogue **256D**

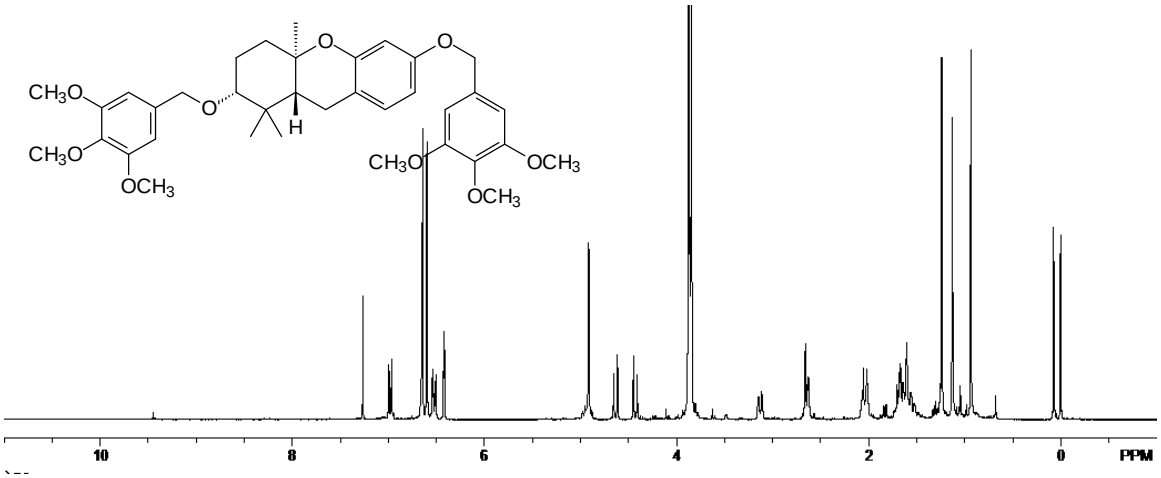


Figure A97. ^{1}H NMR spectrum for analogue **256E**

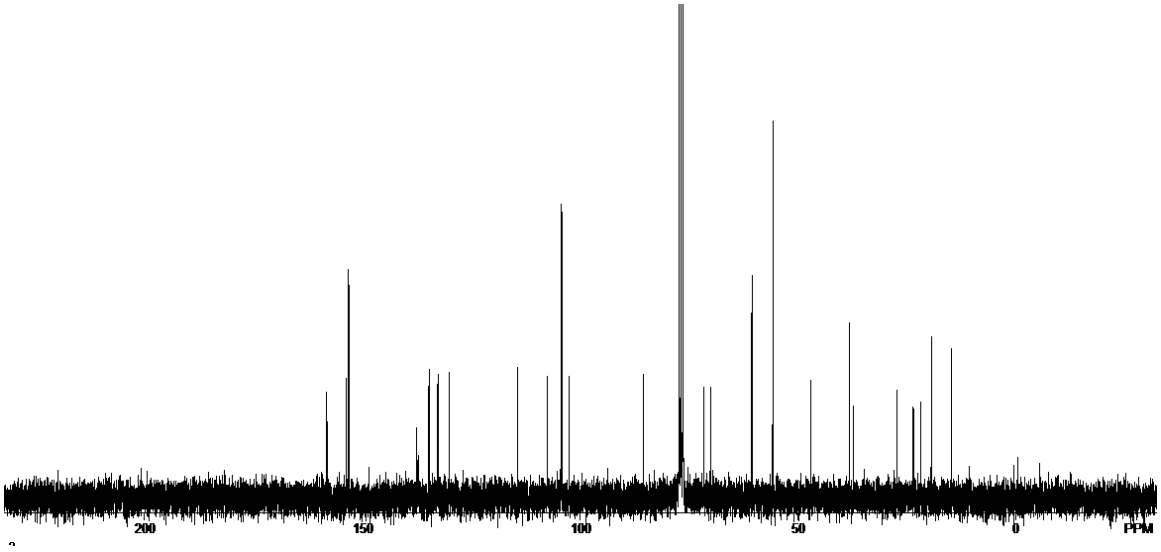


Figure A98. ^{13}C NMR spectrum for analogue **256E**

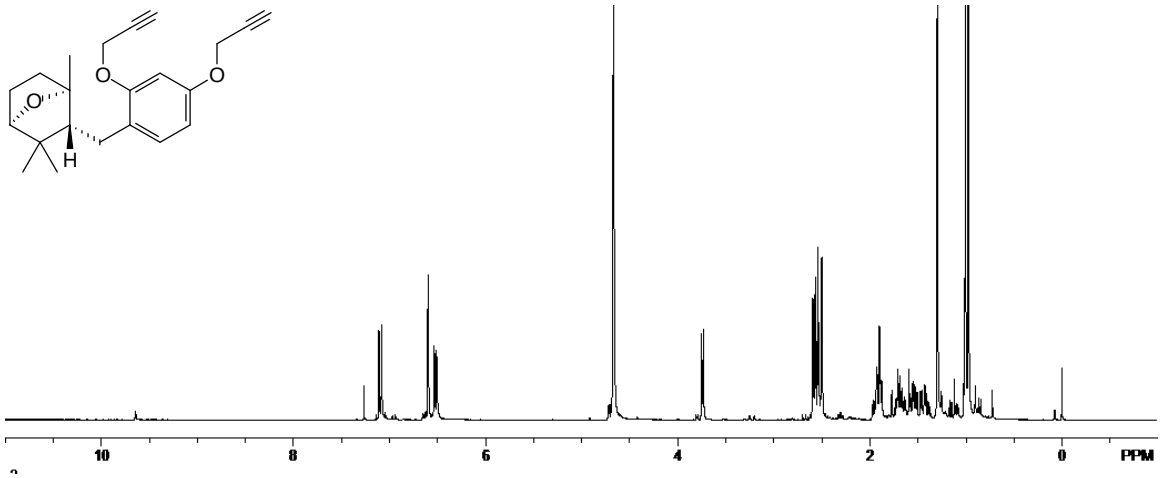


Figure A99. ^{1}H NMR spectrum for analogue **282A**

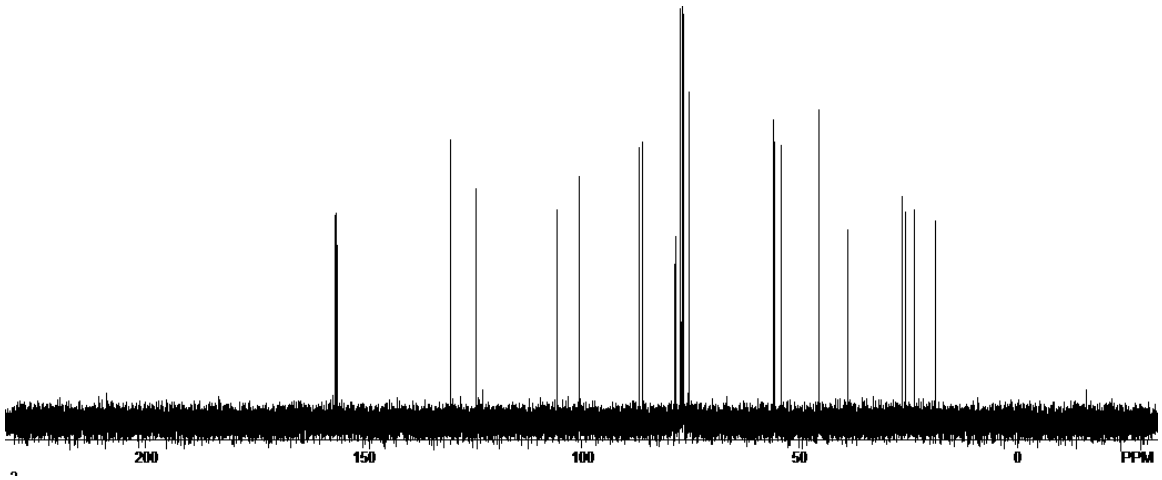


Figure A100. ^{13}C NMR spectrum for analogue **282A**

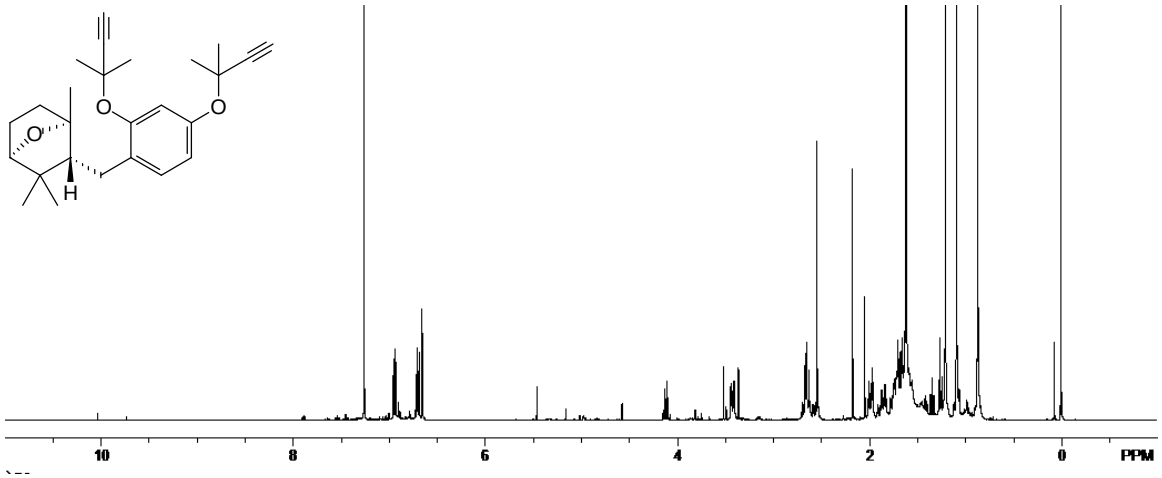


Figure A101. ^{1}H NMR spectrum for analogue **283A**

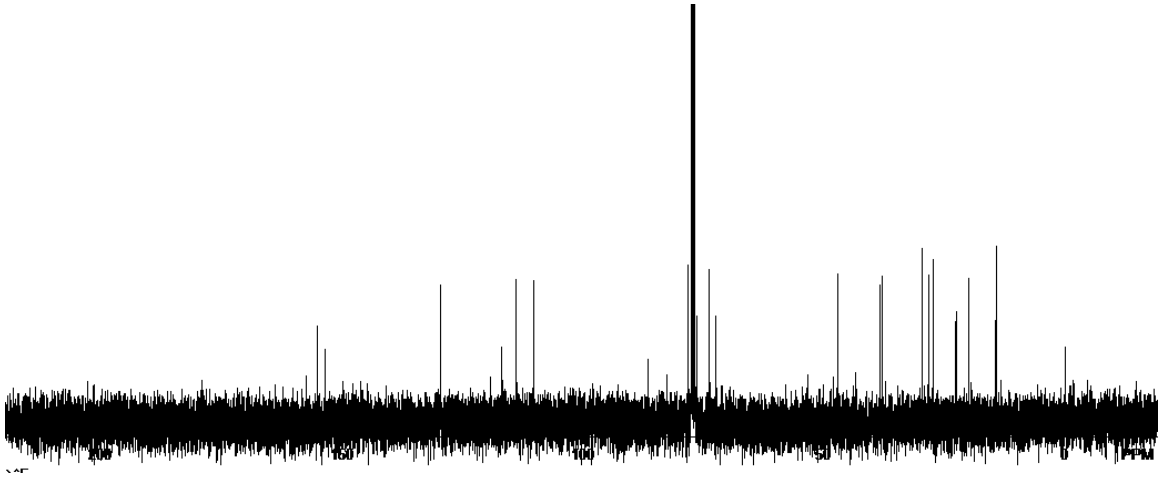


Figure A102. ^{13}C NMR spectrum for analogue **283A**

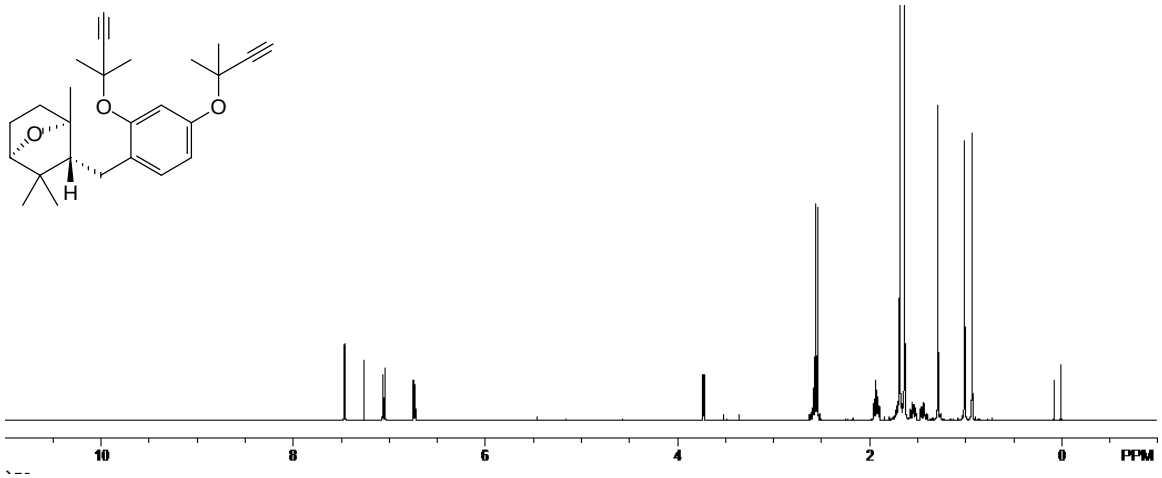


Figure A103. ^{1}H NMR spectrum for analogue **283D**

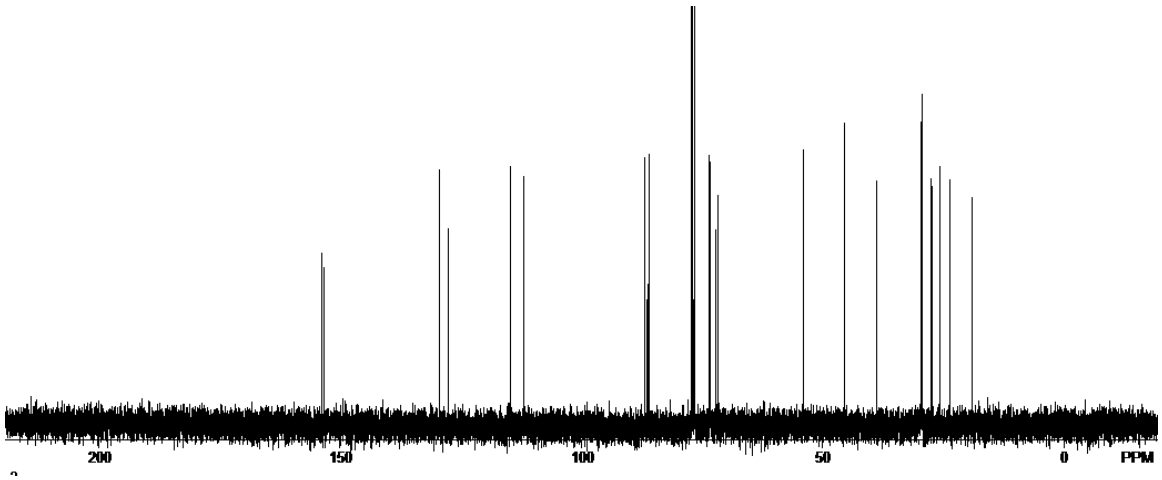


Figure A104. ^{13}C NMR spectrum for analogue **283D**

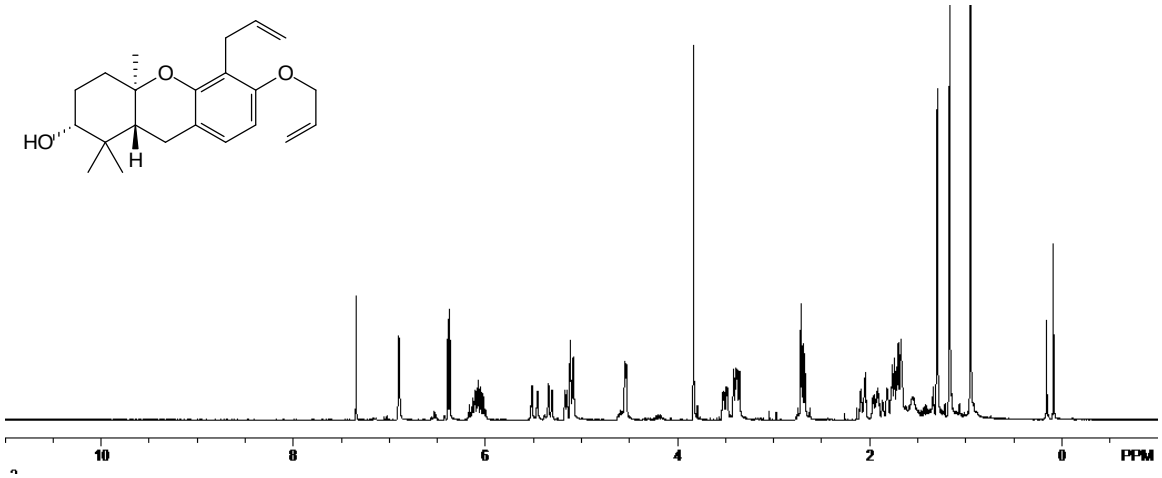


Figure A105. ^{1}H NMR spectrum for analogue **284B**

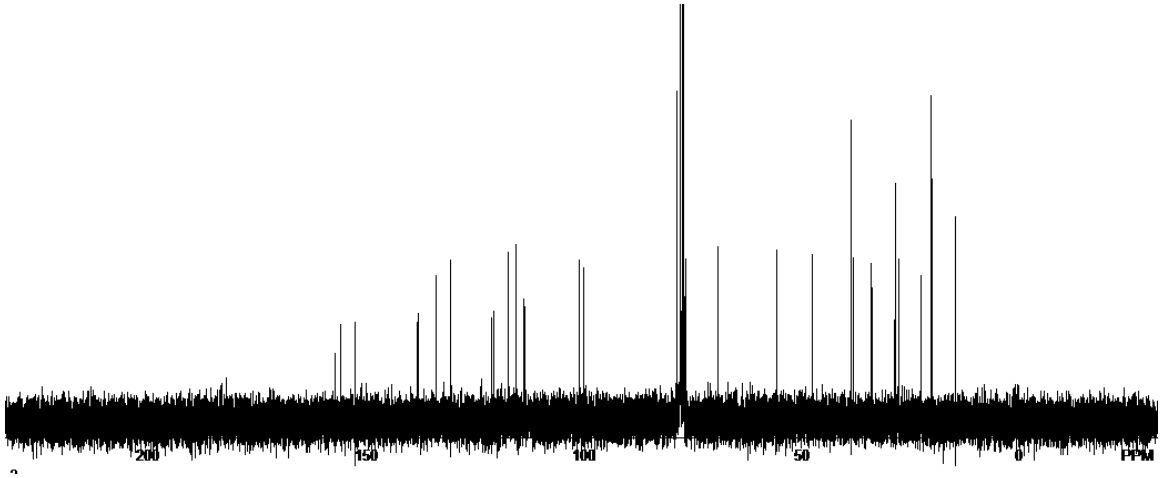


Figure A106. ^{13}C NMR spectrum for analogue **284B**

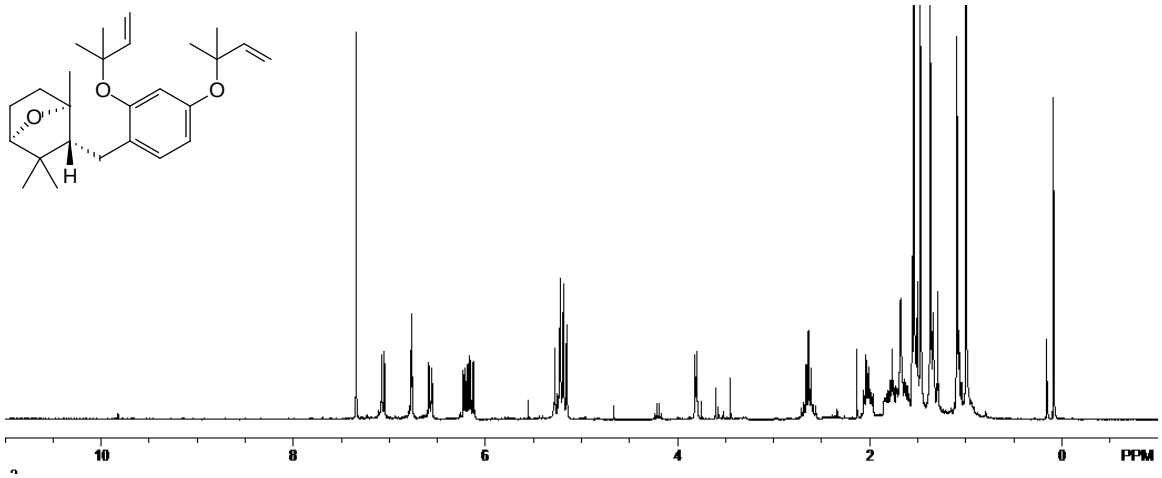


Figure A107. ^{1}H NMR spectrum for analogue **285A**

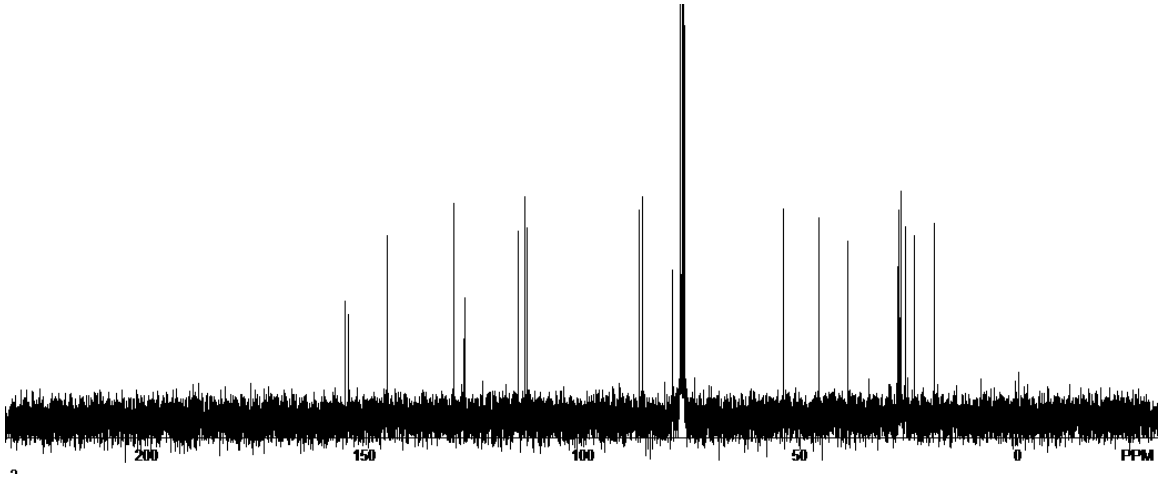


Figure A108. ^{13}C NMR spectrum for analogue **285A**

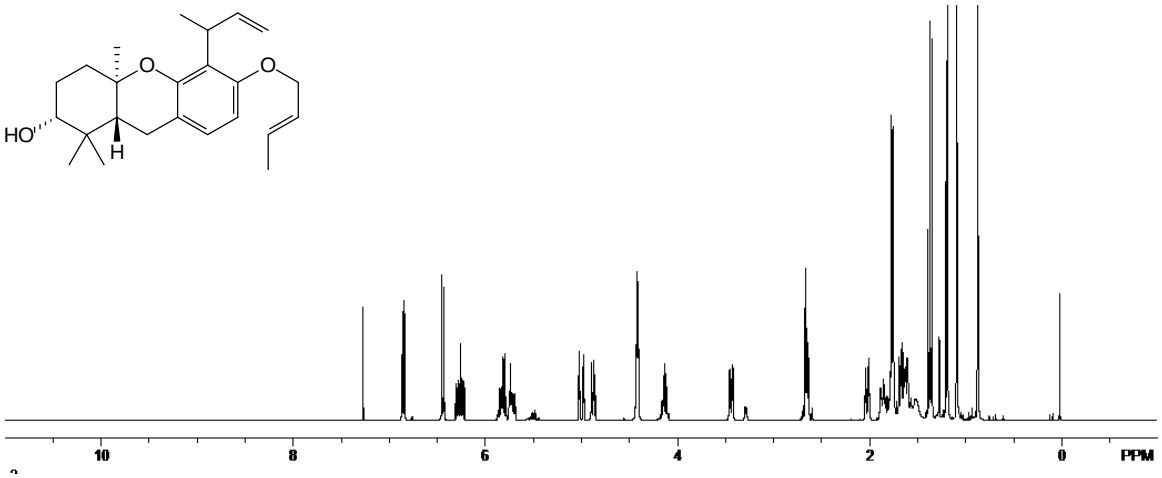


Figure A109. ^{1}H NMR spectrum for analogue **287B**

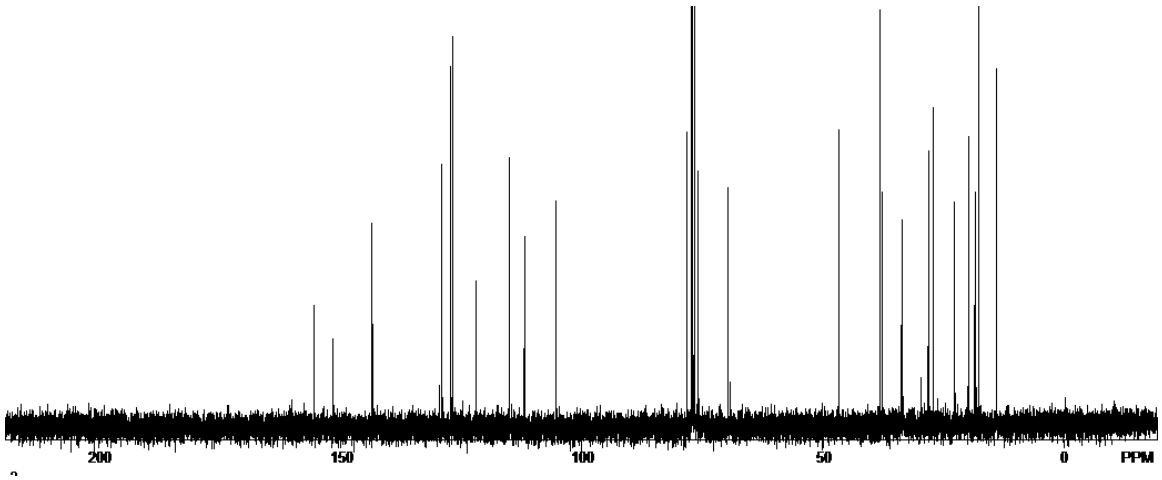


Figure A110. ^{13}C NMR spectrum for analogue **287B**

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