SYNTHETIC EFFORTS TOWARD THE TOTAL SYNTHESIS OF PREMNALATIFOLIN A

&

MONOMERIC UNNATURAL ICETEXANE ANALOGS

by

Ali Amiri Naeini

A dissertation submitted to the Faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry and Biochemistry

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2D	two dimensional
3D	three dimensional
A–431	epidermal cell line
A–549	human lung cancer cell line
Ac	acetyl
ACHN	Renal cancer cell line
AIBN	azobisisobutyronitrile
Anis	*p*–anisaldehyde
app	apparent
aq	aqueous
B.	bacillus
B–16F10	murine melanoma cell line
br	broadened
Bu	butyl
BHT	2,6–di–*tert*–butyl–4– methylphenol
BINAP	2,2'–bis(diphenylphosphino)–1,1'–binaphtyl
Bn	benzyl
°C	degrees Celsius
^{13}C	carbon–13 nuclear magnetic resonance
Calcd	calculated

CAM	ceric ammonium molybdate
cat.	catalytic
CBS	corey–bakshi–shibata
CC_{50}	50% cytotoxic concntration
cm^{-1}	reciprocal centimeters
CRC	colorectal cancer
d	doublet
DBU	1,8–diazabicyclo[5.4.0]undec–7–ene
dd	doublet of doublets
ddd	doublet of doublet of doublets
DCE	1,2–dichloroethane
DDQ	2,3–dichloro–5,6–dicyano–1,4–benzoquinone
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL–H	Diisobutylaluminium hydride
DIPA	diisopropylamine
DMAP	4–dimethylaminopyridine
DMP	dess–martin periodinane
DPPH	2,2–dipheyl–1–picrylhydrazil
dt	doublet of triplets
DME	1,2–dimethoxyethane
DMF	*N,N*–dimethylformamide
DMPU	*N,N'*–dimethylpropyleneurea
DMS	dimethyl sulfide

DMSO	Dimethyl sulfoxide
DNA	deoxyribonucleic acid
E.	enterococcus
ED_{50}	median effective dose
EDC	1–ethyl–3– (3–dimethylaminopropyl)carbodiimide
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
equiv	equivalent(s)
EtOAc	ethyl acetate
FRSA	DPPH radical scavenging activity
g	gram(s)
Gen.	generation
^1H	proton nuclear magnetic resonance
h	hour(s)
HBeAg	hepatitis B e–antigen
HBsAg	hepatitis B's surface antigen
HBV	hepatitis B virus
HeLa	human ephithelial cells
Hep–2	human epidermoid carcinoma #2
Hep 3B	hepatocellular carcinoma
HepG2	liver cancer cell line
HFIP	hexafluoroisopropanol
HL–60	human eukemia cell line

HMBC	heteronuclear multiple–bond correlation spectroscopy
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
HSQC	heteronuclear single–bond correlation spectroscopy
HT–29	colon cancer cell line
Hz	hertz
IBX	2–iodobenzoic acid
IC_{50}	half maximal inhibitory concentration
FTIR	fourier–transform infrared spectroscopy
^{i}Pr	isopropyl
J	coupling constant
L	liter(s)
L.	leishmania
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LIFDI	liquid injection field desorption/ionization
LPS	lipopolysaccharide
m	meta
m	multiplet; or milli (10^{-3}); or meter
M	molar (mol L^{-1}); or metal
M^{+}	molecular ion (positive)
^{m}CPBA	*meta*–chloroperoxybenzoic acid
MCF–7	breast cancer cell line

MHz	megahertz
MIC	minimum inhibitory activity
min	minute(s)
mol	mole
MOM	methoxymethyl
MRSA	methicillin–resistant staphylococcus aureus
MS	mass spectrometry; or molecular sieves
Ms	methanesulfonyl
MW	microwave
m/z	mass to charge ratio
n	Nano (10^{-9})
N	normal (concentration)
N.A.	not available
NEt_3	triethylamine
NHC	*N*–heterocyclic carbine
NBS	*N*–bromosuccinimide
NBSH	2–nitrobenzenesulfonylhydrazide
NIS	*N*–iodosuccinimide
NMR	nuclear magnetic resonance
NMO	*N*–methylmorpholine *N*–oxide
NOE	nuclear overhauser effect spectroscopy
NOESY	2D nuclear overhauser effect spectroscopy
Nu	nucleophile
OQM	*ortho*–quinone methide

p	para
P.	plasmodium
p–TSA	*para*–toluenesulfonic acid
PC–3	human prostate cancer cell line
PCC	pyridinium chlrochromate
PG	protecting group
Ph	phenyl
PMP	*para*–methoxy phenyl
PPA	polyphosphoric acid
ppm	parts per million
PPTS	pyridinium *para*–toluenesulfonate
Pr	propyl
pyr	pyridine
q	quartet
quant.	quantitative
RCM	ring closing metathesis
R_f	retention factor
RSM	recovered starting material
RT	room temperature
s	second(s); in NMR: singlet
S.	staphylococcus
SAR	structure–activity relationship
SC_{50}	50% of the maximum stimulation
SSMC–7721	human hepatocellular cell line

SW–480	colorectal cancer cell line
t	triplet
t	tertiary
T.	Trypanosoma
T. b.	Trypanosoma brucei
TBAF	tetrabutylammonium fluoride
TBHP	*tert*–butyl hydroperoxide
TBS	*tert*–butyldimethylsilyl
td	triplet of doublets
Tf	triflate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMAF	tetramethylammonium fluoride
TMEDA	*N, N, N', N'*–tetramethylethylenediamine
TMP	2,2,6,6–tetramethylpiperidine
TMS	trimethylsilyl
TPA	12–O–tetradecanoylphorbol–13–acetate
Ts	4–toluenesulfonyl
UPLC	ultra–performance liquid chromatography
VRE	vancomycin–resistant enterococcus
wt. %	weight percent
Å	Ångström

δ	chemical shift
μ	Micro (10^{-6})

ABSTRACT

Icetexanes are a family of natural products with a wide array of biological activities and complex structure, which has encouraged synthesis chemists to approach them with different strategies over the past decade. Chapter 1 outlines the different types of icetexanes and then takes a closer look at the newly discovered icetexanes—since 2009—and their biological activities. Chapter 1 is then concluded with a discussion around the last decade of development on the synthesis of icetexane natural products and their core structure.

Chapter 2 outlines the prior and current effort on synthesis of icetexanes and their core 6–7–6 structures. Inspired by the remarkable works of Mr. Daniel J. Moon and Dr. Mohammad Al–Amin in the Chain Laboratory, chapter 2 is focused on development of a small library of inverted icetexanes. During this chapter the capability of the Richie formylation in generating *para* methoxy benzaldehydes as well as a new tandem formylation–cyclization reaction to synthesize both dihydrobenzofurans and dihydrobenzopyrans was demonstrated.

Chapter 3 focuses on the synthesis of conventional unnatural icetexane analogs. Additionally, chapter 3 outlines the path toward completion of premnalatifolin A's monomers and in due course, the natural product premnalatifolin A itself.

Chapter 1

ICETEXANES: SYNTHESIS AND BIOLOGICAL ACTIVITY

1.1 Introduction to Icetexanes

Icetexanes[1] are a family of diterpenoid natural products with a fascinating 6–7–6 tricyclic framework that exhibit a wide array of biological activity—anti–microbial activity of **1.1**,[2] antibacterial activity of **1.2**,[3] trypanocidal activity of **1.3**,[4] and cytotoxicity of **1.4**[5] are just a few examples of the potential of icetexanes as new drug leads. Since the extraction of Icetexone **1.5** from aerial parts of *Salvia Ballotaeflora* in 1976,[6] more than 90 novel icetexanes have been isolated and described (Figure 1.1).

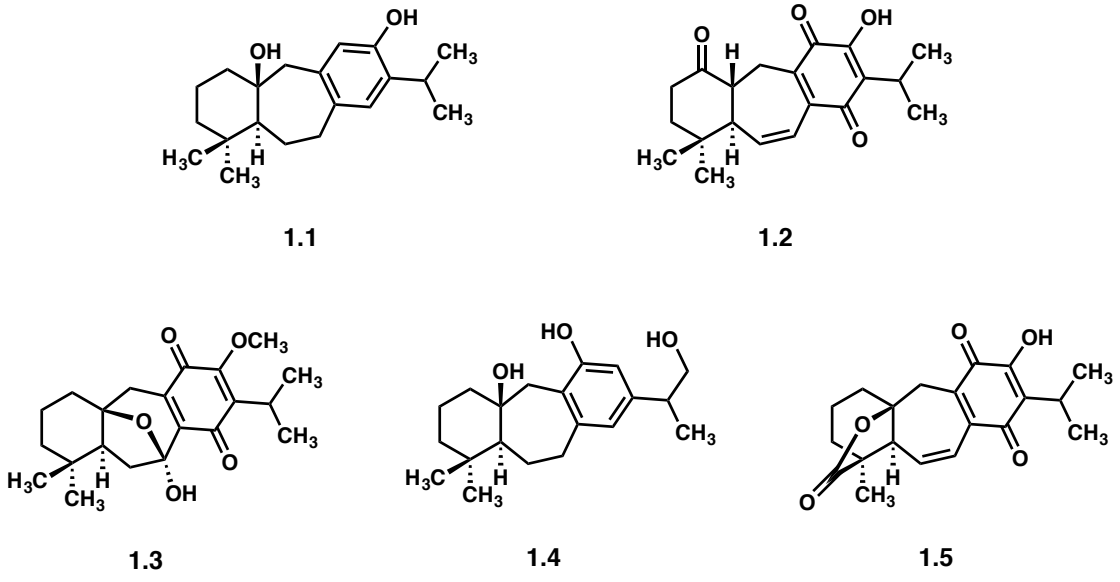


Figure 1.1 Structure of biologically active icetexanes (**1.1** to **1.4**) and icetexone (**1.5**)

Matsumoto and coworkers reported the first total synthesis of an icetexane in 1986[7]. This racemic synthesis of pisiferin was initiated with a Wittig reaction between the phosphonium ylide **1.6** and the racemic aldehyde **1.7** followed by a selective hydrogenation of the resulting styrene to produce the trisubstituted aromatic **1.8**. Epoxidation of **1.8** with ^{m}CPBA followed by epoxide opening with $LiNEt_2$ resulted in alcohol **1.9**. PCC oxidation of alcohol **1.9** resulted in the corresponding enone which was gone through an intramolecular cyclization upon heating at 80–85 °C with polyphosphoric acid to generate a mixture of epimeric ketones **1.10** and **1.11**. Ketone **1.10** then was reduced upon treating with $LiAlH_4$ followed by demethylation of resulting phenyl methyl ether to produce alcohol **1.12**, demethylation of phenol here has been proved essential to prevent a dearomatization event further down the line. Regioselective dehydration of **1.12** was achieved through bismesylation followed by heating in 2,4–lutidine to give the trisubstituted alkene **1.13,** which was then demesylated under the action of $LiAlH_4$ to generate racemic pisiferin **1.14** (Figure 1.2).

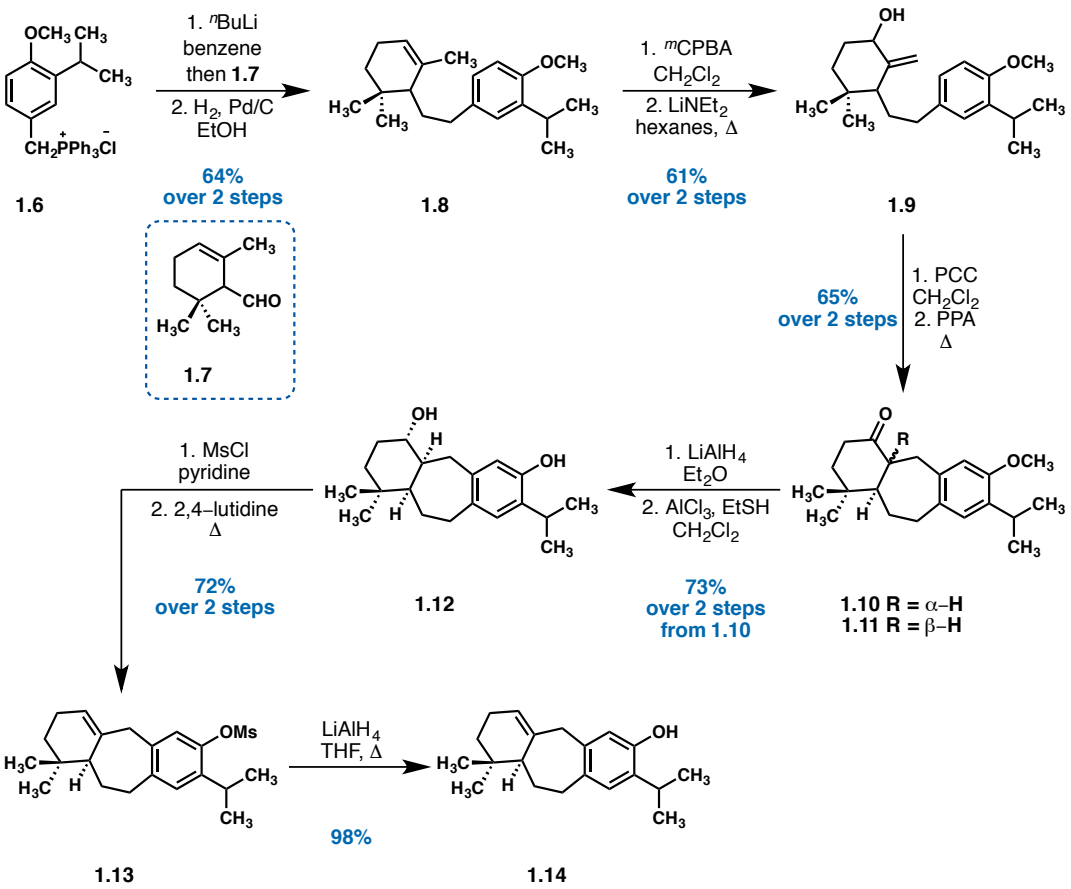


Figure 1.2 Racemic total synthesis of pisiferin

The first ever, asymmetric total synthesis of an icetexane was reported in 2007 by Majetich and his group.[8, 9] The synthesis begins with a three–step esterification–regioselective nucleophilic aromatic *para*–methoxy substitution reaction[10] of the benzoic acid **1.15**. Transesterification of the triethylcarbinyl ester **1.16** with methanol followed by a NBS mediated mono–bromination furnishes **1.17**. The bromobenzene **1.17** is treated with copper(I) chloride and sodium methoxide to result in the corresponding aryl methyl ether which is then reduced and brominated under the action of PBr_3 to afford the benzyl bromide **1.18** (Figure 1.3).

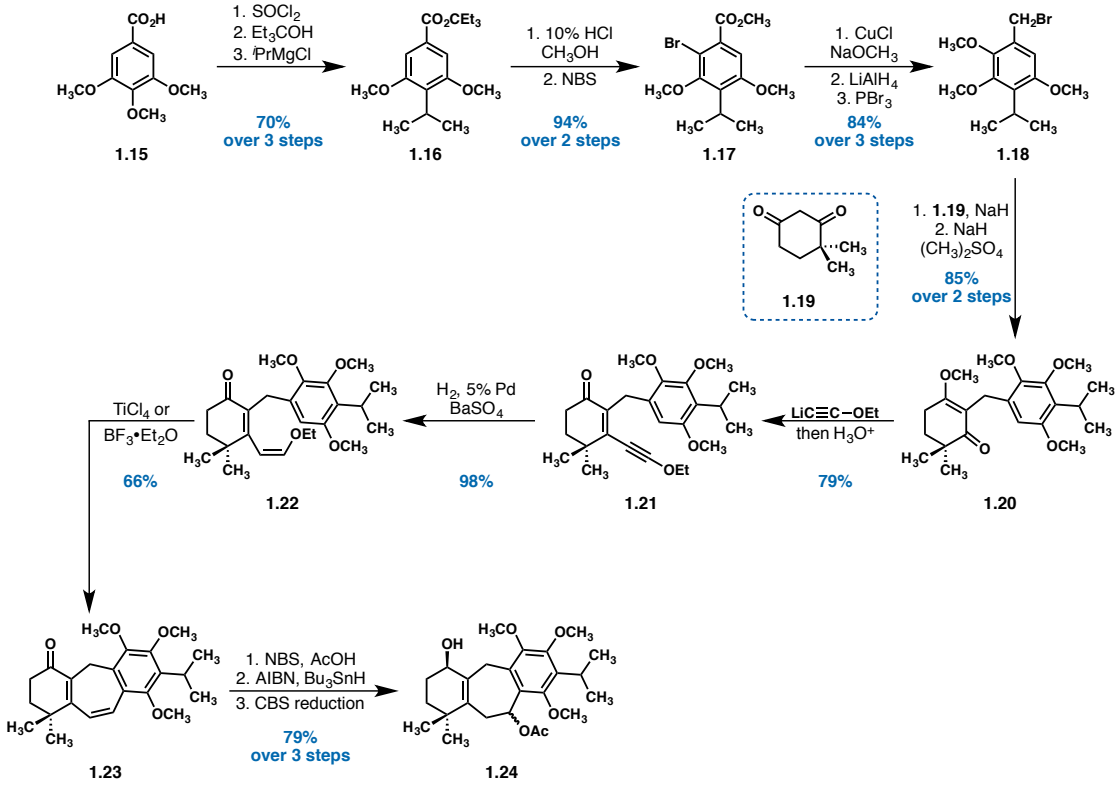


Figure 1.3 Enantioselective total synthesis of (+)–komaroviquinone, Part 1

A two–step alkylation–methyl enolate formation results in the enone **1.20** which then goes through a tandem Isler alkynylation[11]–Stork–Danheiser transposition to generate the enynone **1.21**. Stereoselective reduction of **1.21** then generates the conjugated dienone **1.22**, which upon treatment with excess Lewis acid gives the cyclized product **1.23**. Bromination of **1.23** with NBS in acetic acid followed by a radical dehalogenation and a stereoselective CBS reduction of the enone generates **1.24** as a 1:1 diastereomeric mixture (Figure 1.3). **1.24** goes through a Myers allylic transposition and then an acetate cleavage–oxidation to furnish **1.26**. Introducing NBS in wet acetone to alkene **1.26** followed by radical dehalogenation generates **1.27** which

upon treatment with silver(II) oxide in 7N nitric acid oxidizes **1.27** into (+)–komaroviquinone **1.28** (Figure 1.4).[12]

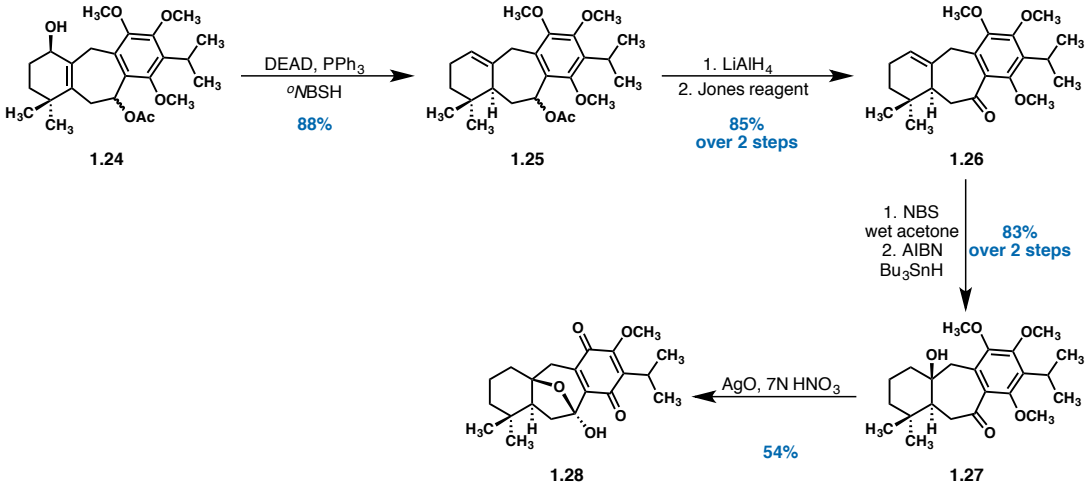


Figure 1.4 Enantioselective total synthesis of (+)–komaroviquinone, Part 2

1.2 Biosynthetic Pathway

Icetexane natural products are most commonly extracted from plants that also produce abietane natural products (comprised of a 6–6–6 tricyclic framework) as secondary metabolites. Consequently, it is believed that icetexanes are products of a rearrangement in the skeleton of abietanes and hence the formal name 9(10→20)–abeo–abietane with the name "icetexane" was proposed by Rodriguez–Hahn and coworkers in 1989.[13] In 1983, the first synthetic link between an icetexane and an abietane was observed during the structural elucidation of barbatusol **1.34** (Figure 1.5).[14]

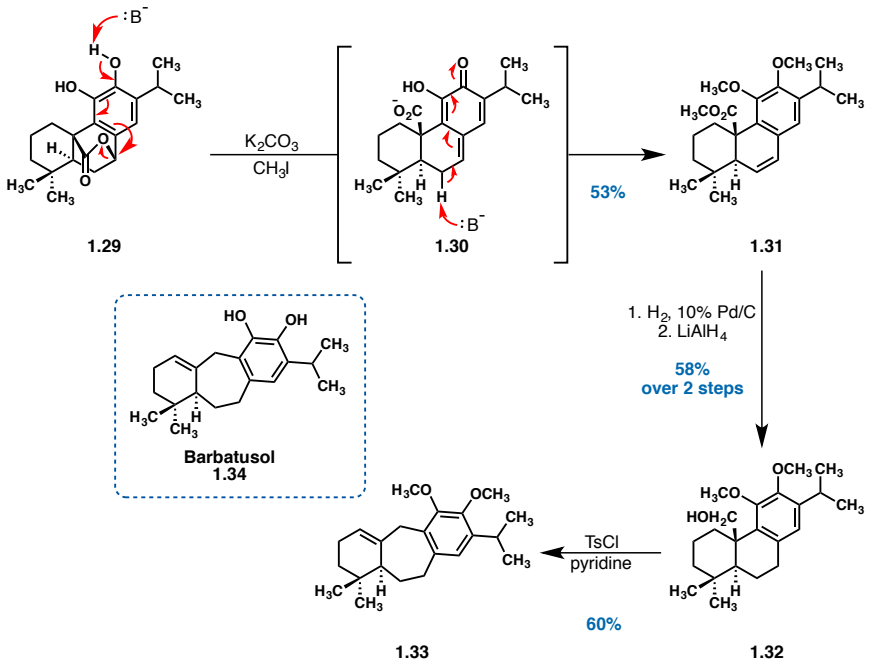


Figure 1.5 Synthesis of Barbatusol from Abietane **1.29**

It was discovered that treating the abietane **1.29** with potassium carbonate and iodomethane in wet acetone results in the opening of the lactone moiety and formation of a C(6)–C(7) double bond to generate the ester **1.31**. Sequential hydrogenation and reduction furnished the primary alcohol **1.32**, which upon treatment with excess amount of TsCl in pyridine generated Barbatusol dimethyl ether **1.33** (Figure 1.5).

Gonzalez and coworkers proposed a general biosynthetic pathway from abietanes to icetexanes.[15] Beginning from **1.35**, it was proposed that an enzymatic protonation–dehydration of C(20) furnishes the intermediate **1.36** which undergoes a Wagner–Meerwein rearrangement to produce the central 7–member ring of the icetexanes. **1.38** is then produced through trapping the carbocation **1.37** by water. It has also been reported that the C(20) activated abietane **1.36** could be a result of

enzymatic hydride abstraction from the C(20) methyl group of the abietane **1.39** (Figure 1.6).[16]

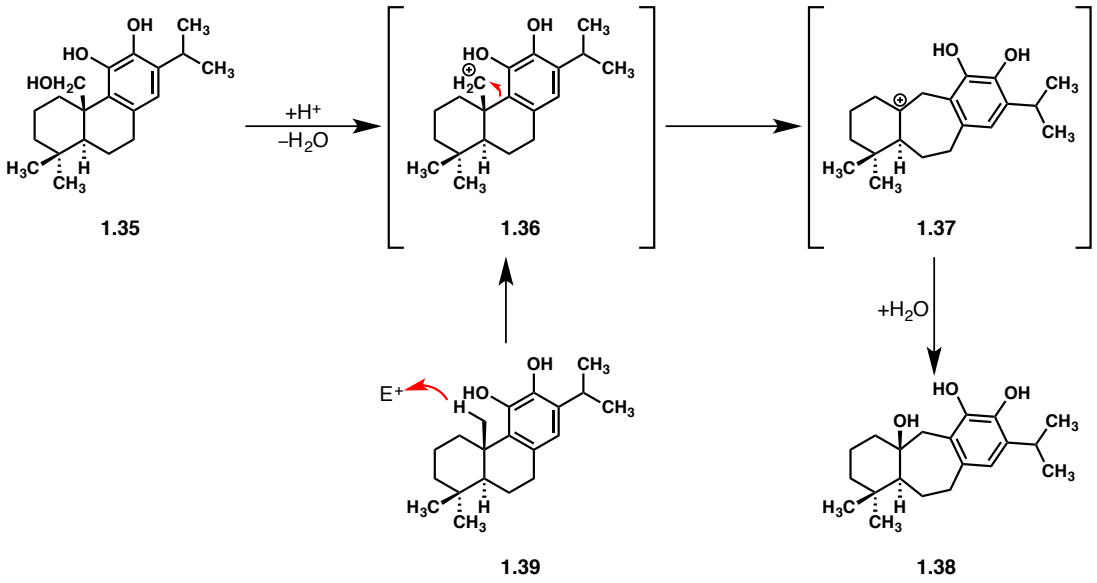


Figure 1.6 Biosynthetic pathways of icetexanes from abietanes

1.3 Classification of Icetexanes

Icetexanes described to date are widely varied in degree of oxygenation as well as the regiochemistry of oxygenation. Simmons and Sarpong proposed a method of classification for icetexanes, which accounts for both the location and number of oxygenations within the natural product scaffold (Figure 1.7).[1]

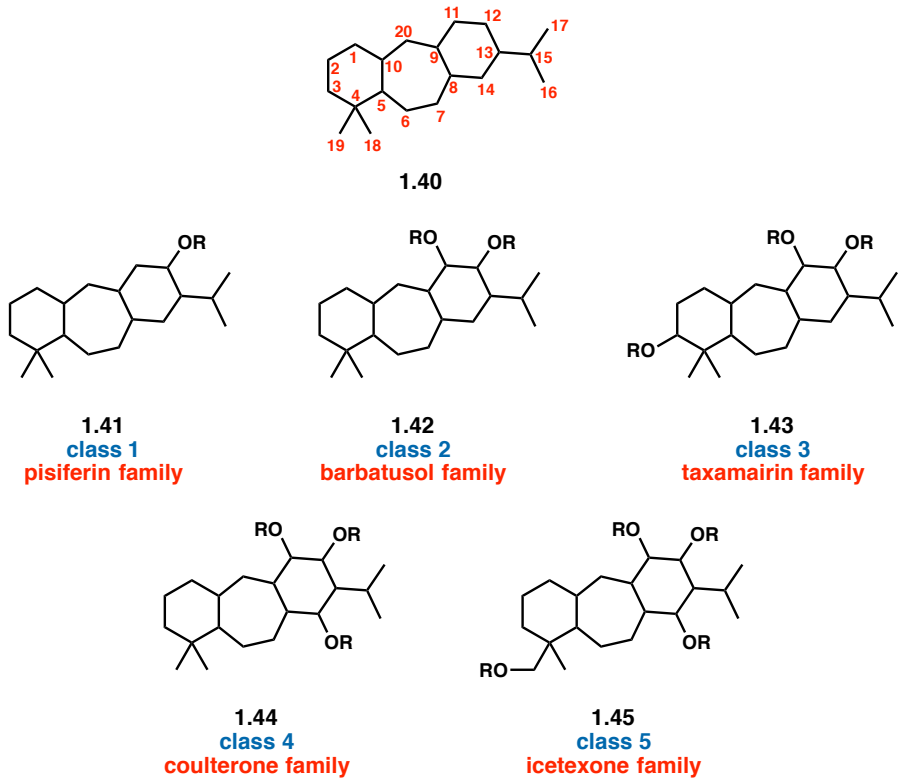


Figure 1.7 Classification of icetexanes

The first icetexane class **1.41** is oxygenated at C(12) and lacks oxygenation at the other positions. The parent member of this class is the natural product pisiferin **1.46** (Figure 1.8), which was first extracted from leaves of *Chamaecyparis pisifera*.[17] However, the structure of this compound was originally proposed as the 7–6–6 tricyclic framework **1.47** and was later revised to **1.46** after a second independent isolation from the seeds of *Chamaecyparis pisifera* (Figure 1.7).[18]

The second icetexane class **1.42** is oxygenated at both C(11) and C(12) and lacks oxygenations at other positions. The parent member of this class is the natural product barbatusol **1.34** (Figure 1.8), which was first extracted from the bark and heartwood of *Coleus barbatus*. As mentioned above, the structure elucidation of

barbatusol was one of the first chemical experiments showing the relationship between icetexanes and abietanes[1.2] (Figure 1.7).

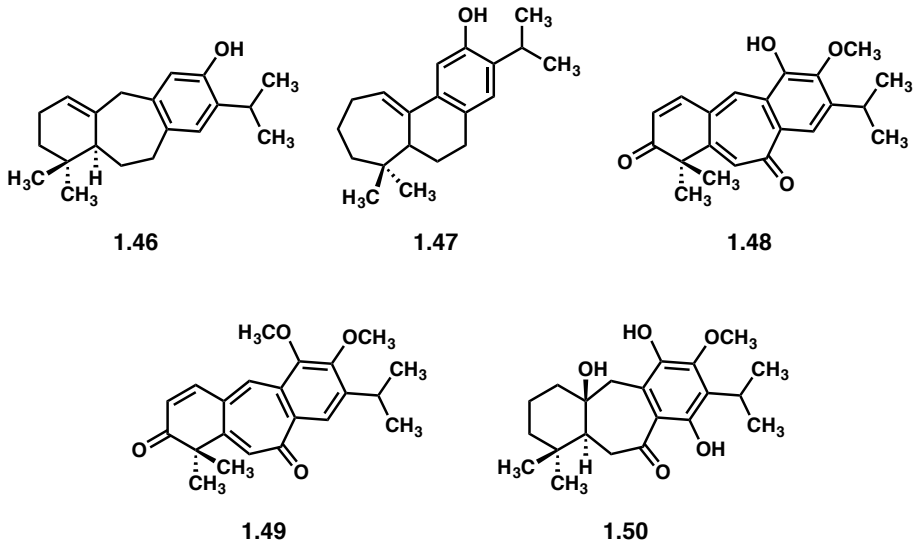


Figure 1.8 Parents of icetexanes classes

The third icetexane class **1.43** is oxygenated at C(3), C(11) and C(12) and lacks oxygenations at other positions. The parent members of this class are the natural products taxamairin A **1.48** and taxamairin B **1.49** (Figure 1.8). Both of these icetexanes were isolated from bark of *Taxus mairei* (Figure 1.7).[19]

The fourth icetexane class **1.44** is oxygenated at C(11), C(12) and C(14) and lacks oxygenations at other positions. The parent member of this class is the natural product coulterone **1.50**, which was first isolated from roots of *Salvia coulteri* (Figure 1.7).[20]

The fifth icetexane class **1.45** is oxygenated at C(11), C(12), C(14) and C(19) and lacks oxygenation at C(3). The parent member of this class is the natural product

icetexone **1.5**. As was mentioned above, it was the first icetexane to be discovered and was extracted from aerial parts of *Salvia Ballotaeflora* (Figure 1.7).Watson, W. H.; Taira, Z. *Tetrahedron Lett.* **1976**, *29*, 2501–2502.[6]

It is very important to point out that members of each of these icetexane classes can bear further oxygenation at non–specified positions. For example, oxygenation at C(1), C(10) or C(16) are very common—**1.1** to **1.4** are examples of natural products with such oxygenation patterns.

Simmons and Sarpong listed all of the discovered icetexanes in their 2009 review,[1] and since that time more than 50 novel icetexanes have been described which along with their known biological activities are the subject of this review.

1.4 Newly Discovered Pisiferins and Barbatusols

Zhao and co–workers extracted Fokihodgin J **1.51** from twigs and leaves of *Fokienia hodginsii* along with nine other newly discovered diterpenoids in 2013 (Figure 1.9).[21] Fokihodgin J was expected to have some activity against human cancer cell lines based on other similar members of this icetexane family and was screened against five different cancer cell lines—human myeloid leukemia (HL–60), hepatocellular carcinoma (SMMC–7721), lung cancer (A–549), breast cancer (MCF–7), and colon cancer (SW–480). Unfortunately, the natural product was found to be inactive against all of them ($IC_{50} > 40\ \mu M$, *cis*–platin as positive control).

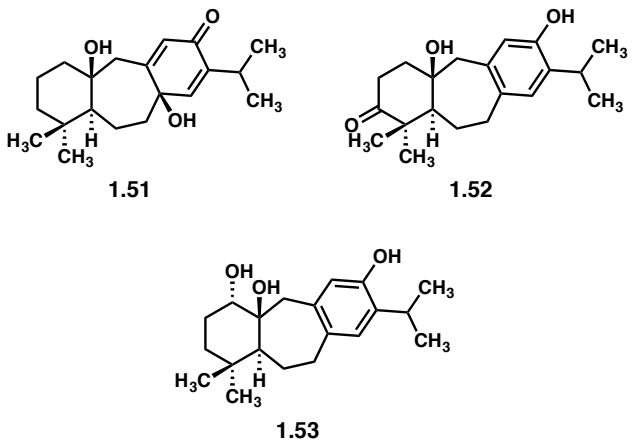


Figure 1.9 The pisiferins

Yue and co–workers isolated 3–oxopisiferanol **1.52** from powdered twigs of *Podocarpus imbricatus* along with 13 other newly discovered diterpenoids (Figure 1.9).[22] As part of their study, they screened four of these diterpenoids for activity relevant to Zika virus, however **1.52** was not among those selected for detailed testing.

The ethanolic extract of the perennial shrub *Pervoskia atriplicifolia* yielded one new pisiferin—1α–hydroxypisiferanol **1.53**—and 4 new barbatusols—perovskatone B **1.54**, 1α–hydroxybrussonol **1.55**, perovskatone C **1.56**, and perovskatone D **1.57** in a study described by Jiang and co–workers (Figure 1.10).[23] Demethylsalvicanol quinone **1.58** was also extracted from the same source for the first time, although it is a known compound and has been previously synthesized in 1996[24] and 2008.[25] Two previously known natural products—przewalskin E **1.59**,[26] and brussonol **1.60**[27]—were isolated as well.

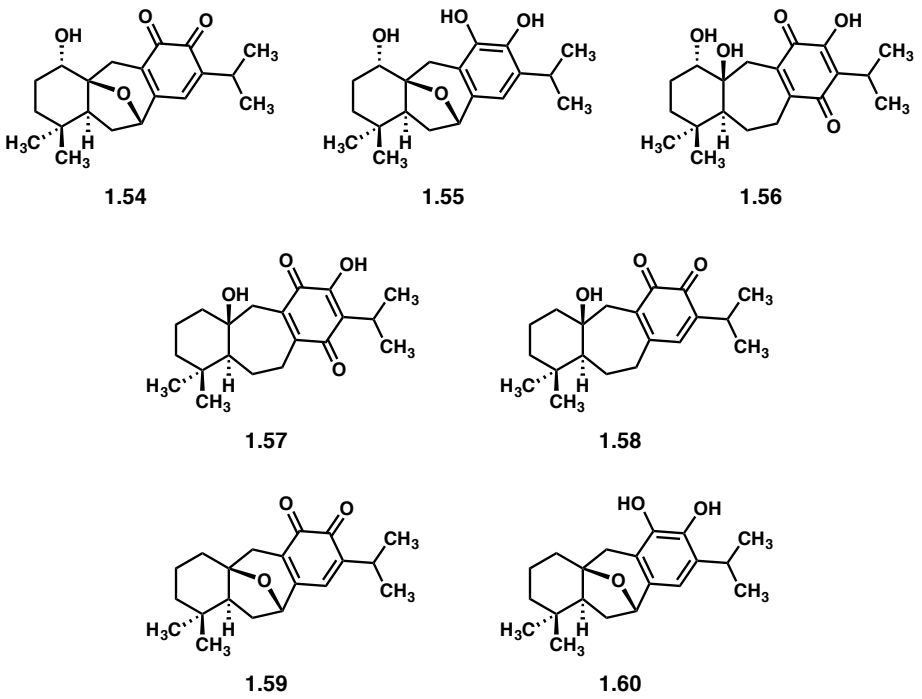


Figure 1.10 Barbatusols from *Pervoskia atriplicifolia*

Icetexanes **1.53** to **1.60** were tested for their inhibitory activities toward hepatitis–B virus in the HepG 2.2.15 cell line. Based on the results (Table 1.1**)** Jiang and co–workers showed noteworthy anti–hepatitis B activity *in vitro* for **1.54** and **1.55**.

		HBsAg		HBeAg		Inhibitory HBV DNA replication	
	CC_{50} (mM)	IC_{50} (mM)	SI	IC_{50} (mM)	SI	IC_{50} (mM)	SI
1.53	1.85	2.45	–	3.82	–	NT	NT
1.54	>2.13	1.03	>2.06	1.97	>1.08	13.8	154.3
1.55	2.85	0.59	4.83	1.42	2.00	20.7	137.7
1.56	2.13	1.54	1.38	3.67	–	NO	–
1.57	2.78	0.92	3.02	4.01	–	NT	NT
1.58	>2.13	4.08	–	3.68	–	NO	–
1.59	1.44	2.23	–	1.72	–	NO	–
1.60	>3.54	1.39	>2.55	4.72	–	NO	–
3TC[a]	29.96	23.50	1.27	28.19	1.06	1.12	26750.0

All values are mean of two independent experiment; SI = CC_{50}/IC_{50}.
[a] 3TC: Lamivudine, positive control.
NT: not been tested for their trace amount
NO: IC_{50} values was not obtained at the highest tested concentration

Table 1.1 *In vitro* anti–hepatitis B activities of **1.53** to **1.60**

Moujir and co–workers determined the MIC of **1.58** against six different bacteria[24]—*Staphylococcus aureus*, *Staphylococcus albus*, *Staphylococcus epidermidis*, *Micrococcus luteus*, *Bacillus subtilis*, and *Bacillus pumilus*. Results are summarized in Table 1.2. (**1.58** was inactive against Escherichia coli, Pseudomonas aeruginosa, and Candida albicans at a level of 20 μg/mL)

Test Organism	1.58 MIC, μg/mL	cephotaxime MIC, μg/mL
Staphylococcus aureus	> 20	2–5
Staphylococcus albus	> 20	1
Staphylococcus epidermidis	> 20	5
Micrococcus luteus	> 20	1
Bacillus subtilis	17	2–5
Bacillus pumilus	> 20	>10

Table 1.2 MIC of **1.58** against bacteria

Cytotoxic activity of **1.58** against HeLa and Hep–2 cancer cell lines *in vitro* are summarized in Table 1.3.

	HeLa IC_{50}, μg/mL	Hep–2 IC_{50}, μg/mL
1.58	1.3±0.6	>50
Mercaptopurine	0.1±0.01	0.6±0.02

Table 1.3 In vitro cytotoxicity of **1.58** against HeLa and Hep–2

Kashiwada and co–workers isolated **1.58** from extracts of aerial parts of *Pervskia scrophulariifolia* and screened for inhibitory activity on 1L–1β production from LPS–simulated microglial cells; **1.58** shows an inhibitory activity of 44.8% at 25 μM with no cytotoxicity.[28]

Zhao and co–workers discovered two new icetexane from barbatusol family from the acetone extraction of Chinese plant *Salvia przewalskii*—przewalskin C **1.61** and przewalskin D **1.62** (Figure 1.11).[29]

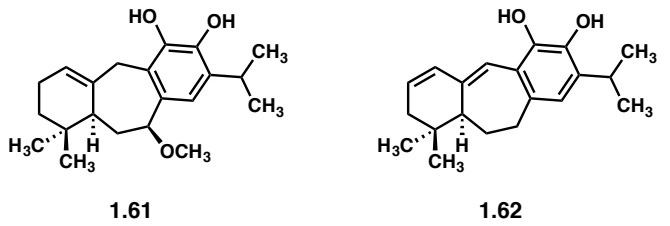


Figure 1.11 Barbatusols from *Salvia przewalskii*

Karalai and co–workers[30] isolated the barbatusol type icetexane **1.63** for the first time from twigs and roots of *Premna obtusifolia* alongside three previously known icetexanes; **1.64**, and **1.66**[31] from *Salvia aspera* and **1.65**[32] from *Rosmarinus officinalis* (Figure 1.12).

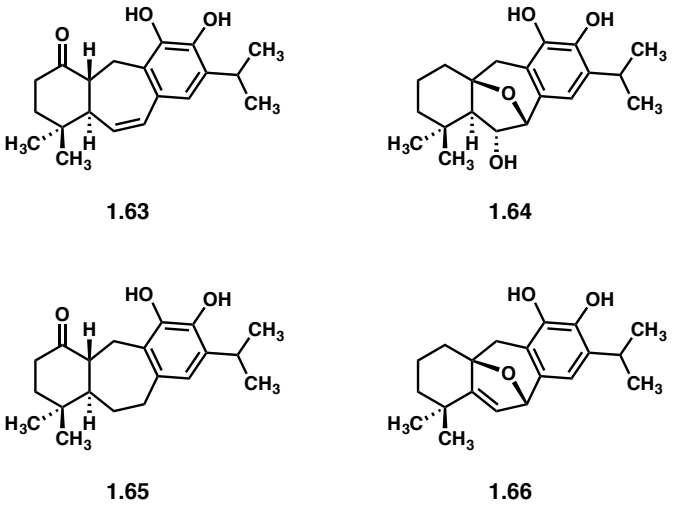


Figure 1.12 Barbatusol type icetexanes from *Premna obtusifolia*

Anti–bacterial activity of compounds **1.63**, **1.64**, and **1.66** against five different gram–positive bacteria and three gram–negative bacteria is summarized in Table 1.4.

The icetexane **1.66** is significantly active against *S. sonei* and moderately active against *B. subtilis, E. faecalis,* MRSA, and VRE with **1.64** being moderately active against MRSA. In addition, anti–NO activity of icetexanes **1.63** to **1.66** were evaluated with the results summarized in Table 1.5.

	B. subtilis[a]	*S. aureus*[a]	*E. faecalis*[a]	MRSA[a]	VRE[a]	*S. typhi*[b]	*S. sonei*[b]	*P. aeruginosa*[b]
1.63	75	75	75	75	75	75	37.5	150
1.64	37.5	75	75	9.37	75	75	18.75	>300
1.66	9.37	18.75	9.37	9.37	9.37	37.5	2.34	>300
Vancomycin	<2.34	<2.34	<2.34	<2.34	<2.34	<2.34	<2.34	<2.34

Antibacterial activity (MIC, μg/ml)
[a] Gram–positive bacteria
[b] Gram–negative bacteria

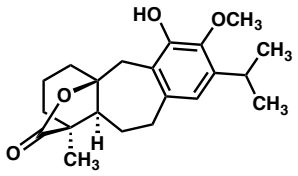
Table 1.4 Antibacterial activity of icetexanes **1.63**, **1.64**, and **1.65**

	0	2	10	30	100	IC_{50}(M)
1.63	0.0±8.8		13.4±1.0	48.8±2.0**	94.7±1.3**	29.1
1.64	0.0±6.1		6.9±0.9	33.2±1.0**	96.0±1.1**	35.0
1.65	0.0±6.1		6.9±1.3	59.4±1.1**	97.6±1.0**	27.6
1.66	0.0±6.1		6.9±0.9	52.8±0.9**	96.9±1.1**	29.3
L Nitroarginine (L NA)	0.0±9.9	11.7±4.6	20.2±0.2	34.7±0.4**	71.6±1.2**	61.8
Caffeic acid phenethylester (CAPE)	0.0±9.9	30.7±3.2*	68.6±1.2**	98.7±1.2**	98.9±2.1**	5.6

Inhibitory effect on NO production of compounds 1.63 to 1.66 at various concentrations(μM)
Statistical significance *p<0.05, **p<0.001
each value represents mean ± SEM of four determinations

Table 1.5 Inhibitory effects of NO production of icetexanes **1.63** to **1.66**

Quijano and co–workers discovered clinopodiolide D **1.67** from extracts of the leaves of *Salvia clinopodioides*.[33] As part of their study investigating novel radical scavengers and antioxidants, clinopodiolide D **1.67** was evaluated in several assays including a thiobarbituric acid–reactive substances screen (TBARS) with modest results (Figure 1.13).



1.67

	DPPH (IC_{50}), μM	TBARS (IC_{50}), μM
1.67	Not Active	40.9±2.7
BHT(n=5)		1.2±0.4
quercetin(n=3)	10.9±0.5	1.5±0.0
α-tocopherol(n=4)	31.7±1.0	6.8±2.2

values represent the mean±SD, n=3, NA = not active
BHT, quercetin, α–tocopherol: positive control

Figure 1.13 Antioxidant activity of clinopodiolide D **1.67**

Fun and co–workers extracted the barbatusol type icetexane **1.68** from the roots of *Premna obtusifolia* and elucidated its structure using X–ray crystallography techniques (Figure 1.14).[34]

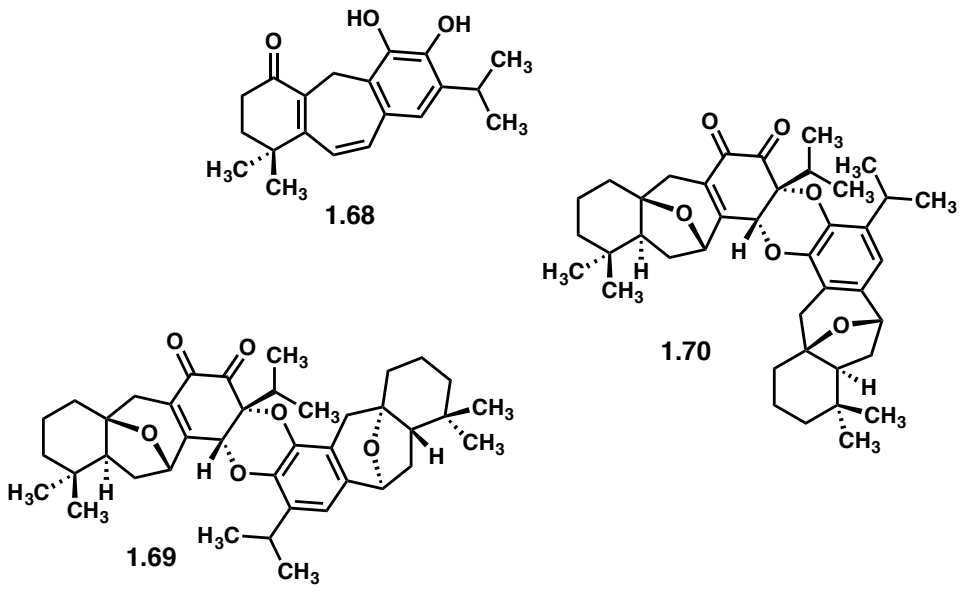
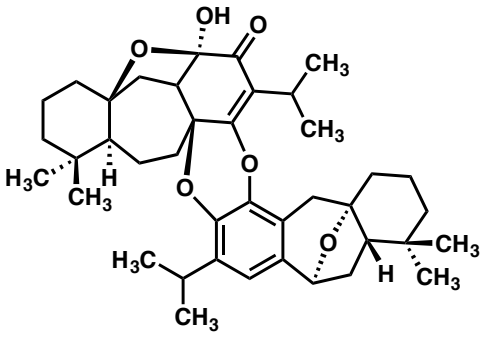


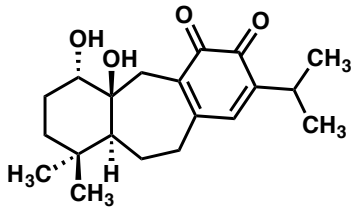
Figure 1.14 Icetexanes **1.68** to **1.70** from *Premna obtusifolia*

Salae and Boonnak reported the discovery of obtusinone D **1.69** and obtusinone E **1.70** from the root extracts of *Premna obtusifolia*.[35] **1.69** and **1.70** are constitutional hetero–dimeric isomers of each other with 2 units of przewalskin E **1.59** acting as monomers, fused by putative hetero–Diels–Alder event in either a linear or angular manner, respectively (Figure 1.14).

Jiang and co–workers reported isolation of biperovskatone B **1.71** and 1α–hydroxyl demethylsalvicanol quinine **1.72** from ethanolic extract of cultured *Perovskia atriplicifolia* (Figure 1.15).[36]



1.71



1.72

Figure 1.15 Icetexanes **1.71** and **1.72** from *Perovskia atriplicifolia*

Biperovskatone B **1.71** is a hetero–dimeric barbatusol type icetexane (Figure 1.15) that alongside **1.72** shows noteworthy activity against the hepatitis B virus (HBV) by inhibiting replication of HBV DNA (results summarized in Table 1.6).

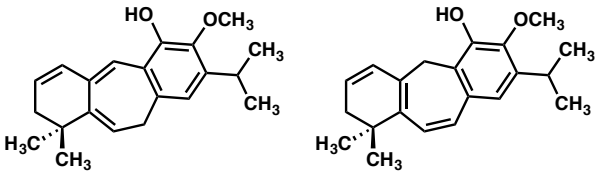
		HBsAg		HBeAg		Inhibitory HBV DNA replication	
	CC_{50} (mM)	IC_{50} (mM)	SI	IC_{50} (mM)	SI	IC_{50} (mM)	SI
1.71	>2.08	1.36	>1.53	1.85	>1.12	10.78	192.95
1.72	1.15	0.84	1.35	>2.08	–	8.61	133.57
3TC[a]	28.32	22.62	1.25	28.17	1.01	1.15	24626.09

All values are mean of two independent experiment; SI = CC_{50}/IC_{50}.
[a] 3TC: Lamivudine, positive control.

Table 1.6 In vitro anti–hepatitis B activities of **1.71** to **1.72**

Li and co–workers reported isolation of two new barbatusol type icetexanes—Salprzeside A **1.73** and Salprzeside B **1.74**—from extract of *Salvia przewalskii*.[37] The

results of an anti–angiogenic study of **1.73** and **1.74** against human umbilical vascular endothelial cells (HUVECs) by using the MTT assay are summarized in Figure 1.16.



1.73 **1.74**

	$IC_{50}(\mu M)$
1.73	13.49±1.16
1.74	39.31±2.17
Vatalanib	9.28±0.93

Data are expressed as mean ± SEM
of three independent experiments
Vatalanib: positive control

Figure 1.16 Anti–angiogenic activities of **1.73** to **1.74**

Aisa and co–workers reported the isolation of four new icetexanes—Salviadenone A **1.75**, Salviadenone B **1.76**, Salviadenone C **1.77**, and Salviadenone D **1.78**—from root extracts of *Salvia deserta* (Figure 1.17).[38] Interestingly, three of these new icetexanes **1.76** to **1.78** have a C(20) carbonyl functional group which has previously been observed only in taxamairin H **1.79**,[39] a class 3 icetexane.

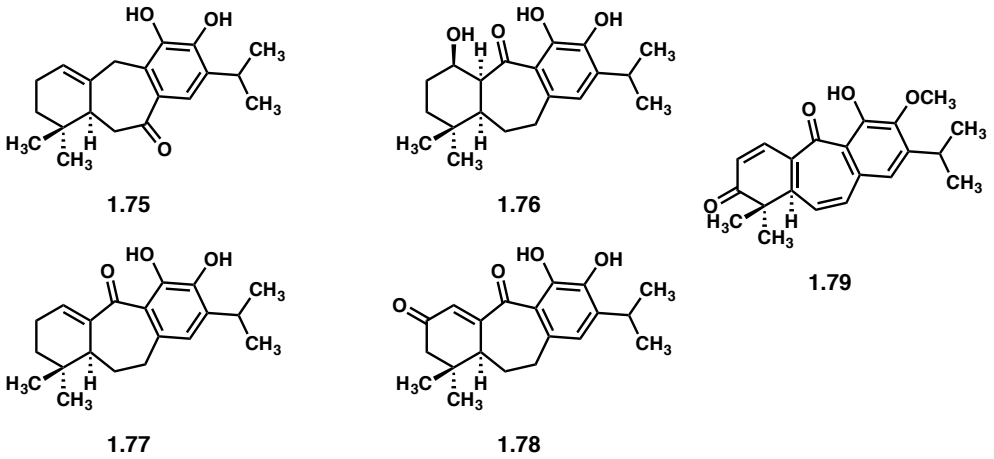


Figure 1.17 Icetexanes **1.75** to **1.78** from *Salvia deserta* and taxamairin H **1.79**

The cytotoxic activity of **1.75** to **1.78** was evaluated against five different cancer cell lines—human myeloid leukemia (HL–60), hepatocellular carcinoma (SMMC–7721), lung cancer (A–549), breast cancer (MCF–7), and colon cancer (SW–480)—and a noncancerous cell line (BEAS–2B), the results of which are summarized in Table 1.7. Only **1.75** showed significant activity in this study.

Compound	IC_{50} (μM) A–549	IC_{50} (μM) SMMC–7721	IC_{50} (μM) HL–60	IC_{50} (μM) MCF–7	IC_{50} (μM) SW480	IC_{50} (μM) BEAS–2B	Highest index of selectivity[a]
1.75	>40	31.98±3.09	17.70±0.83	26.9±1.52	28.79±2.67	30.73±0.45	>1.72
1.76	>40	>40	>40	>40	>40	>40	N/A
1.77	>40	>40	>40	>40	>40	>40	N/A
1.78	>40	>40	>40	>40	>40	>40	N/A
***cis*–platin**[b]	13.84±0.47	7.82±0.62	2.47±0.12	13.46±0.49	10.06±0.30	>40	>16.19

values are expressed as the means ± SD, n = 3
[a] Highest index of selectivity is the ratio of the IC_{50} value for the Beas–2B cell line over the lowest cancer cell IC_{50} value
[b] *Cis*–platin: positive control

Table 1.7 *In vitro* cytotoxicity of **1.75** to **1.78**

Xu and co–workers reported the isolation of przewalskone **1.80** from root extracts of *Salvia przewalskii* (Figure 1.18).[40] Przewalskone **1.80** is a very interesting natural product, as it appears to be the result of a putative hetero–Diels–Alder event between przewalskin E **1.59** and a danshenol type C_{23} terpenoid. Danshenol A (**1.81**) is the parent member of this family of natural products (Figure 1.18).[41]

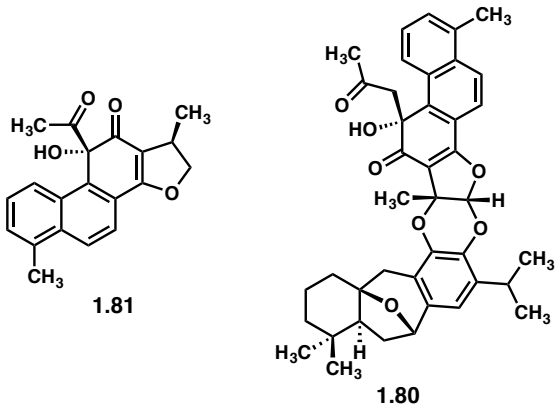


Figure 1.18 Icetexane **1.80** and danshenol A **1.81**

Cytotoxic activity of **1.80** was evaluated against five different cancer cell lines—human myeloid leukemia (HL–60), hepatocellular carcinoma (SMMC–7721), lung cancer (A–549), breast cancer (MCF–7), and colon cancer (SW–480)—and a noncancerous cell line (BEAS–2B). The natural product shows significant activity against all five cell lines in the study and outperformed *cis*–platin as the positive control; the results of this study are summarized in Table 1.8.

Cell lines	przewalskone	Cisplatin
(IC_{50}, μM) HL–60	0.69	1.10
(IC_{50}, μM) SMMC–7721	2.35	14.75
(IC_{50}, μM) A–549	1.82	13.39
(IC_{50}, μM) MCF–7	0.90	12.99
(IC_{50}, μM) SW–480	0.72	12.61
(IC_{50}, μM) Beas–2B	21.26	14.84

Cisplatin: positive control

Table 1.8 *In vitro* cytotoxicity of **1.80**

Zhang and co–workers isolated phyllane A **1.82** from twigs and leaves of *Isodon phyllopodus* along with another newly discovered diterpenoid in 2021 (Figure 1.19).[42] It is interesting to note the C(19) oxygenation of this barbatusol type icetexane which has previously only been seen in the icetexone family of icetexanes. Phyllane A (**1.82**) showed anti–HIV activity with an IC_{50} of 15.7 μM using an assay described in 2017 by Zhang and co–workers.[43]

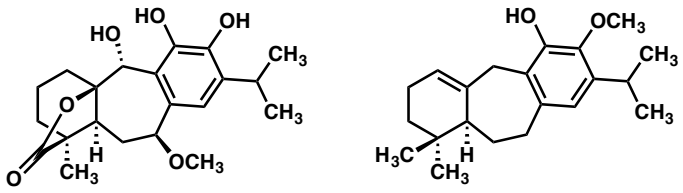


Figure 1.19 Phyllane A **1.82** and 12–methoxybarbatusol **1.83**

Hamburger and co–workers discovered 12–methoxybarbatusol **1.83** from extracts of aerial parts of *Perovskia abrotanoides*.[44] The results of anti–protozoal activity of **1.83** are summarized in Table 1.9.

Compound	1.83	Positive control
T. b. rhodesiense (IC_{50}, μM)[a]	45.8 (43.6, 48.0); 1.7[b]	0.04[c]
T. cruzi (IC_{50}, μM)[a]	111.5 (134.8, 88.2); 0.7[b]	5.7[d]
L. donovani (IC_{50}, μM)[a]	34.8 (17.8, 51.9); 2.3[b]	0.9[e]
P. falciparum (IC_{50}, μM)[a]	10.7 (9.8, 11.6); 7.4[b]	0.01[f]
L6 cells (IC_{50}, μM)[a]	79.4 (54.0, 104.8)	0.009[g]

[a] Each value corresponds to the mean of two independent assays, with individual values indicated in brackets
[b] Selectivity index, [c] Melarsoprol
[d] Benznidazole, [e] Miltefosine
[f] Chloroquine, [g] Phodophyllotoxin

Table 1.9 *In vitro* anti–protozoal activity of **1.83**

Rao and co–workers reported the isolation of four new icetexanes from stem–bark of *Premna tomentosa*.[45] Two of these icetexanes—icetexane–1 **1.84** and

icetexane–4 **1.85**—are barbatusol type icetexanes; the other two will be discussed in [1.6] (Figure 1.20). **1.84** and **1.85** are very interesting due to the fact that they are the first ever isolated icetexanes that are oxygenated at C(16). Until today the only other examples of such oxygenation on an icetexane have been isolated exclusively from genus *Premna*—either *Premna tomentosa* or *Premna Latifolia*. Rao and co–workers tested cytotoxicity of **1.84** against 5 different cancer cell lines the results of which are summarized in (Table 1.15).

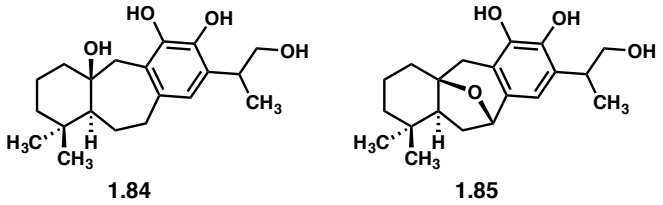


Figure 1.20 icetexane–1 **1.84** and icetexane–4 **1.85**

In 2011 Babu and co–workers in 2 different publications reported isolation of 4 new barbatusol type icetexanes—latifolionol **1.86**, dihydrolatifolionol **1.87**, latiferanol **1.88**, and premnalatifolin A **1.89** (Figure 1.21).[46, 47] These four icetexanes are the first ever examples that introduce a dihydrobenzofuran cycle to the family. Premnalatifolin A is a heterodimeric icetexane which is specially interesting since it is the only example of such a dimer with monomers being linked through a C—O—C bond.

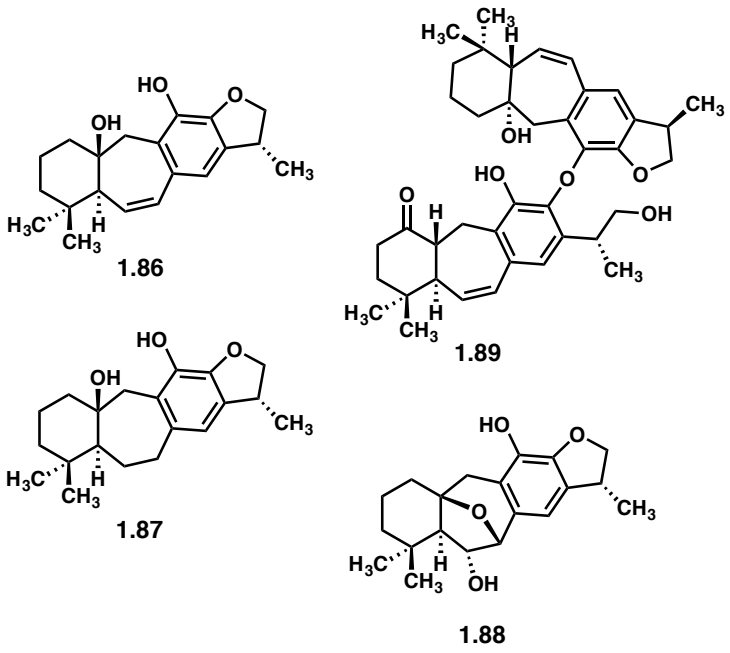


Figure 1.21 icetexanes **1.86** to **1.89** from *Premna latifolin*

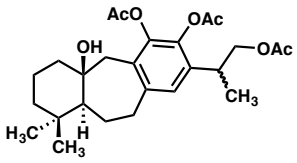
Icetexanes **1.86** to **1.89** were tested against 8 different cancer lines the results of which are summarized in Table 1.10.

	HT–29[a]	MCF–7[a]	Hep–G2[a]	A–549[a]	A–431[a]	PC–3[a]	B–16F10[a]	ACHN[a]
1.86	0.04±0.02	1.11±0.23	2.13±1.92	6.05±0.71	33.40±1.95	3.24±0.38	6.41±5.47	4.83±0.32
1.87	2.17±0.71	6.02±0.00	0.18±0.06	58.24±6.8	10.14±1.39	3.77±0.18	5.71±0.28	0.40±0.04
1.88	15.25±0.54	11.49±0.53	18.92±0.99	9.85±0.54	21.22±0.74	9.27±0.67	19.65±0.69	24.50±0.9
1.89	12.15±2.29	1.11±0.23	13.29±0.64	12.21±0.32	22.55±0.30	17.38±0.4	22.91±0.53	1.40±0.13
doxorubicin	21.54±0.29	2.01±0.03	1.63±0.04	2.68±0.28	4.23±0.20	1.71±0.11	21.22±0.74	1.29±0.02

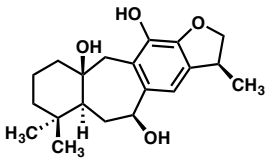
doxorubicin: positive control
[a] IC_{50}, μg/mL

Table 1.10 *In vitro* cytotoxicity of **1.86** to **1.89**

Ayinampudi and co–workers reported the isolation of 2 new barbatusol type icetexanes—icetexatriene–1 **1.90** and icetexatriene–2 **1.91**—from the extracts of dried roots of *Premna Tomentosa* (Figure 1.22).[48] The exact stereochemistry of icetexatriene–1 at C(15) is not determined. Both icetexatriene–1 **1.90** and icetexatriene–2 **1.91** were screened for rat intestinal *α*–glucosidase inhibitory and free radical scavenging potentials, the results of which are summarized in Figure 1.22.



1.90



1.91

Compound	α-glucosidase inhibition (IC_{50}, μg/mL)	FRSA (SC_{50}, DPPH, μg/mL)
1.90	22.58±0.61	24.80±0.98
1.91	9.59±0.319	7.01±0.118
Trolox	–	15.94±0.04
1-deoxynoji rimycin	50.00±0.91	–

Trolox: positive control, 1-deoxynoji rimycin: positive control

Figure 1.22 *α*–glucosidase inhibitory and DPPH scavenging potentials for **1.90**, **1.91**

1.5 Newly Discovered Taxamairins and Icetexones

In 2011 Gan and co–workers reported the isolation of a new taxamairin type icetexane, amentonone **1.92**[49] alongside brevitaxin[50] **1.93** a previously known taxamairin from barks of *Amentotaxus formosana* (Figure 1.23).

	A–549 (ED_{50} μg/mL)	Hep 3B (ED_{50} μg/mL)	HT–29 (ED_{50} μg/mL)	MCF–7 (ED_{50} μg/mL)
1.92	19.1±2.9		15±2.3	
1.93	5.1±0.9	6.1±0.6	2.72±0.1	0.08±0.05
5–fluorouracil	3.1±0.2	0.6±0.3	0.6±0.1	1.5±0.1

5–fluorouracil: positive control
for significant activity an $ED_{50} \leq 4.0$ μg/mL is required

Table 1.11 *In vitro* cytotoxicity of amentonone **1.92** and brevitaxin **1.93**

Hu and co–workers reported the isolation of 3 new taxamairin type icetexanes—amentotaxin N **1.94**, amentotaxin O **1.95**, and amentotaxin P **1.96**—from leaves and twigs of *Amentotaxus argotaenia* alongside amentonone **1.92** and previously described demethylsalvicanol **1.38** (Figure 1.24).[51]

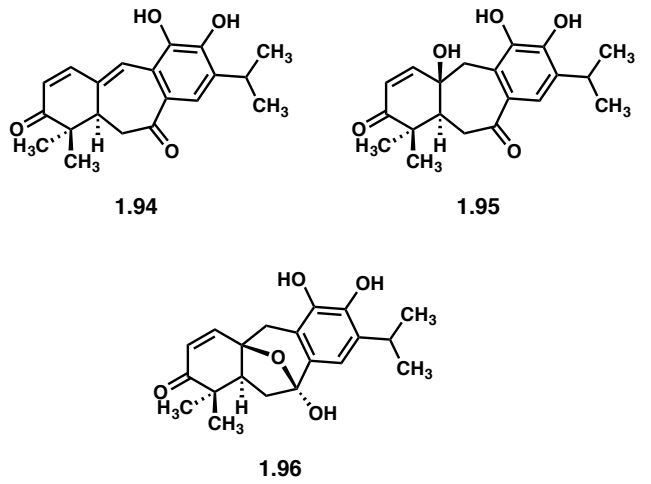


Figure 1.24 amentotaxin N to P **1.94** to **1.96**

Newest members of icetexone **1.5** class of icetexanes were extracted from aerial parts of *Salvia ballotiflora*—ballotiquinone **1.97**, 6,7–anhydroballotiquinone **1.98**, 7α–acetoxy–6,7–dhydroicetexone **1.99**, and 6,7,11,14–tetrahydro–7–oxo–icetexone **1.100**—by Quijano and co–workers (Figure 1.25).[52]

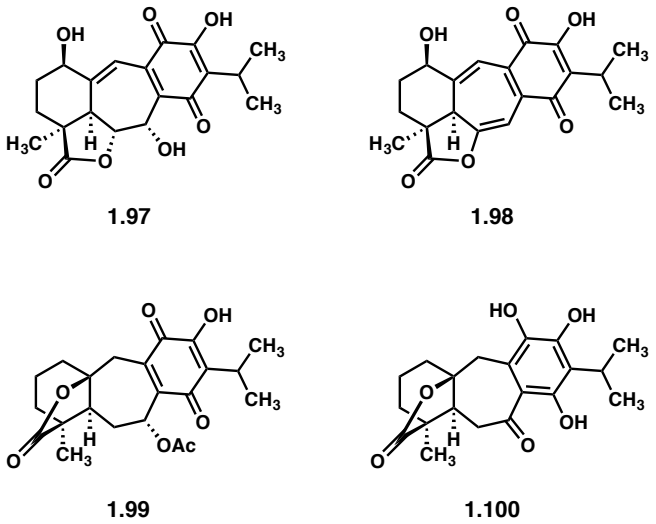


Figure 1.25 icetexone type icetexanes **1.97** to **1.100**

Additionally, Quijano and co–workers reported isolation of 4 previously known icetexanes, Icetexone **1.5**, anastomosine **1.101**[53], 7,20–dihydroanastomosine **1.102**[54], and unnamed icetexane **1.103**[55] (Figure 1.26).

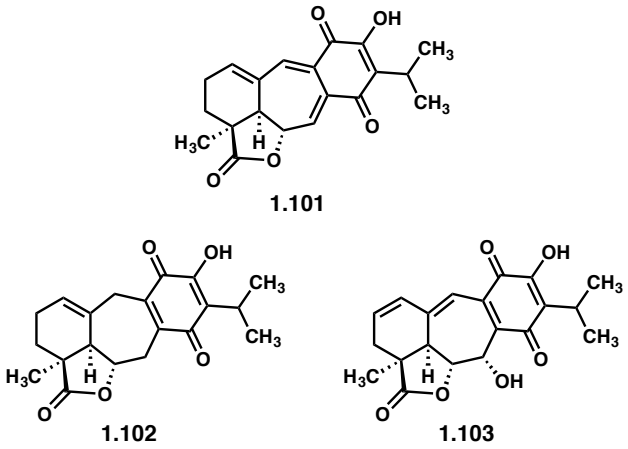


Figure 1.26 icetexone type icetexanes **1.101** to **1.103**

Results of *in vitro* cytotoxicity activity of icetexone **1.5**, 7α–acetoxy–6,7–dhydroicetexone **1.99**, anastomosine **1.101**, and 7,20–dihydroanastomosine **1.102** are summarized in Table 1.12.

Compound	IC_{50} (μM)(SI) U251	IC_{50} (μM)(SI) SKLU–1	IC_{50} (μM)(SI) COS–7	IC_{50} (μM)(SI) K562	IC_{50} (μM)(SI) MCF–7
1.5	Nd	Nd	Nd	17.0±1.4	28.7±1.6
1.99	1.4±0.03 (1.2)	0.82±0.06 (2.0)	1.62±0.1	Nd	Nd
1.101	0.27±0.08 (2.3)	0.46±0.05 (1.3)	0.61±0.007	Nd	Nd
1.102	Nd	Nd	Nd	31.2±1.1	33.24±1.2
Adriamicyn	0.08±0.003 (3.1)	0.05±0.003 (5.0)	0.25±0.009	0.20±0.02	0.23±0.02

Results represent the mean ± SD of at least 3 different experiments, Nd = Not determined
SI = selective index calculated at the quotient of IC_{50} of COS–7/IC_{50} of cancer cell lines.
For **1.99** and **1.101** IC_{50} was determined at four concentrations in a range of 1.0 to 0.18 μM
75.0 to 12.5 μM for **1.102**, and 50.0 to 6.25 μM for **1.5**
Adriamicyn: positive control

Table 1.12 *In vitro* cytotoxicity of **1.5**, **1.99**, **1.101**, **1.102**

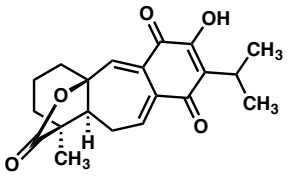
Icetexanes—7α–acetoxy–6,7–dihydroicetexone **1.99**, anastomosine **1.101**, and 7,20–dihydroanastomosine **1.102** were evaluated on the TPA model of induced acute inflammation, and the results are summarized in Table 1.13.

Compound	Edema (mg)	Inhibition of Edema (%)
1.99	9.87±0.44**	37.42±2.77**
1.101	15.97±0.61	NA
1.102	15.50±0.76	NA
Control (TPA)	15.77±0.78	
Indometacin	2.88±0.73**	78.76±7.68**
Celecoxib	6.94±1.56*	54.34±10.28

Effects on ear edema of female mice CD–1; doses (1.0 μmol ear^{-1});
each value represents the mean of three–seven animals ± SEM;
The results were analyzed with the Dunnett test;
The values at p≤0.05(*) and p≤0.01(**) were considered as significant differences with respect to the control group. NA = Non–active

Table 1.13 Inhibitory effect of icetexanes on TPA–induced inflammation in a mouse model

von Poser and co–workers reported isolation of isoicetexone **1.104**, from extrct of aerial parts of *Salvia uliginosa* alongside 2 previously isolated icetexanes—icetexone **1.5**, and 7α–acetoxy–6,7–dihydroicetexone **1.99**—all three, class 5 icetexanes (Figure 1.27).[56]



1.104

Figure 1.27 icetexone type icetexane **1.104**

The ability of **1.104** and **1.5** to inhibit the PMNs migration *in vitro* was investigated to evaluate their potential anti–inflammatory activity. Results of this investigation are summarized in Table 1.14.

Compound	Concentration (M)	Migration (M)	Migration inhibition (%)
1.104	14.61	NM	100***###
	2.92	NM	100***###
	0.29	NM	100***###
	0.029	18.4±1.3	42.9***###
	0.0029	25.3±1.8	21.8***###
1.5	14.61	NM	100***###
	2.9	NM	100***###
	0.29	17.8±1.9	45.0***###
	0.029	18.9±1.5	31.5***###
	0.0029	20.3±1.3	37.3***###
Negative control	–	100	0
Indomethancin	27.9	31.6±6.4	60.9***

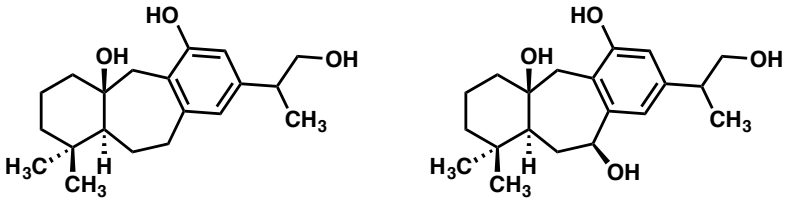
Chemotaxis expressed as mean ± SEM, deviation of leukocyte migration.
***### < 0.001 indicate the levels of significance in relation to
the negative control and indomethacin, respectively.
NM: no migration

Table 1.14 Effects of *Salvia uliginosa* isolated compounds on the chemotaxis of PMNs

1.6 A New Class of Icetexanes

Rao and co–workers isolated four new icetexanes two of which have been already discussed, **1.84** and **1.85**. Two other icetexanes that have been isolated from

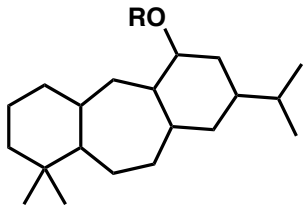
stem bark of *Premna tomentosa* do not match oxygenation pattern of any of the previously proposed classes.



1.105 **1.106**

Figure 1.28 Icetexanes **1.105** and **1.106**

Icetexane–2 **1.105** and icetexane–3 **1.106** are both oxygenated at C(11) so they cannot be considered as a member of pisiferin family, neither they are oxygenated at C(12) so they cannot be a member of barbatusol family (Figure 1.28).[45] Here we propose these two natural products to be considered the first members of a new class of icetexanes named deoxo–barbatusol **1.107** illustrated in Figure 1.29.



1.107
class 6
deoxo–barbatusol family

Figure 1.29 deoxo–barbatusol family of icetexanes

Study of *in vitro* cytotoxicity activity of icetexane–1 **1.84**, icetexane–2 **1.105**, and icetexane–3 **1.106** on 5 different cancer cell lines are summarized in Figure **1.44**.

Compound	IC_{50}, (μg/mL) HT–29	IC_{50}, (μg/mL) MCF–7	IC_{50}, (μg/mL) Hep–G2	IC_{50}, (μg/mL) A–549	IC_{50}, (μg/mL) A–431
Hexane extract	41.04±6.08	75.77±1.61	45.01±0.60	61.65±0.04	123.1±14.7
1.84	16.21±0.00	15.96±0.21	18.63±0.73	18.62±0.02	NA
1.105	NA	80.75±4.65	NA	43.65±0.32	NA
1.106	14.57±0.69	15.84±0.37	34.41±0.46	21.37±0.10	NA

NA: not active.

Table 1.15 *In vitro* cytotoxicity of **1.84**, **1.105**, **1.106**

1.7 Recent Synthesis Efforts Toward Icetexanes

Brutoloso and co–workers in 2010 reported their efforts toward the synthesis of core structure of brussonol **1.60** using an epoxide ring–opening approach.[57] Epoxide **1.109** was synthesized through utilizing a Corey–Chaykovsky epoxidation reaction on **1.108**. An epoxide ring–opening using lithobenzene **1.110** and subsequent trapping of resulted alkoxide with TMSCl then generated **1.111**. Aldehyde **1.112**, which was generated through a carbon–carbon double bond cleavage using Lemieux–Johnson oxidation protocol, was treated with a Lewis acid to get to the desired product **1.114** by a Marson–type Friedel–Crafts cyclization reaction in just four steps (Figure 1.30).

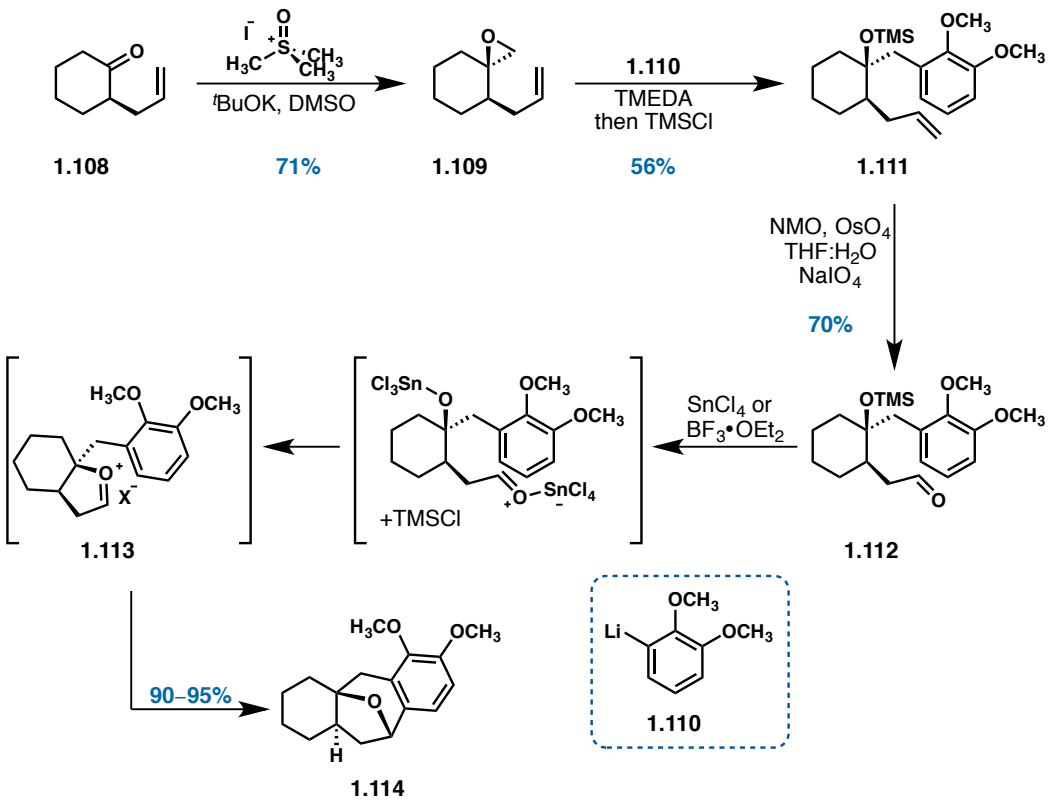


Figure 1.30 Brutoloso's synthesis of an analogue of (±)–brussonol **1.114**

Brutoloso and co–workers indeed tried to utilize their approach toward a synthesis of (±)–brussonol **1.60**,[58] however as was reported previously by Jennings and co–workers the epoxide ring–opening reaction between **1.115** and **1.116** to furnish product **1.117** proved to be a failure (Figure 1.31).[59]

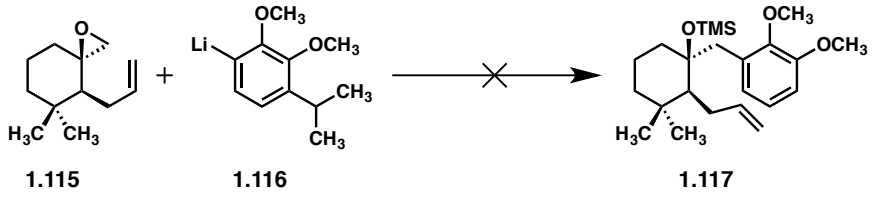


Figure 1.31 Epoxide ring–opening reaction

Although the epoxide ring–opening using a lithiobenzene was unsuccessful, employing a cross–electrophile coupling with epoxide **1.118** and aryl halide **1.119** catalyzed by nickel proved successful in constructing hemi–acetal **1.121**. Friedel–Crafts cyclization with BF_3 etherate furnished **1.122**, which after universal deprotection produced brusonnol **1.60** (Figure 1.32).

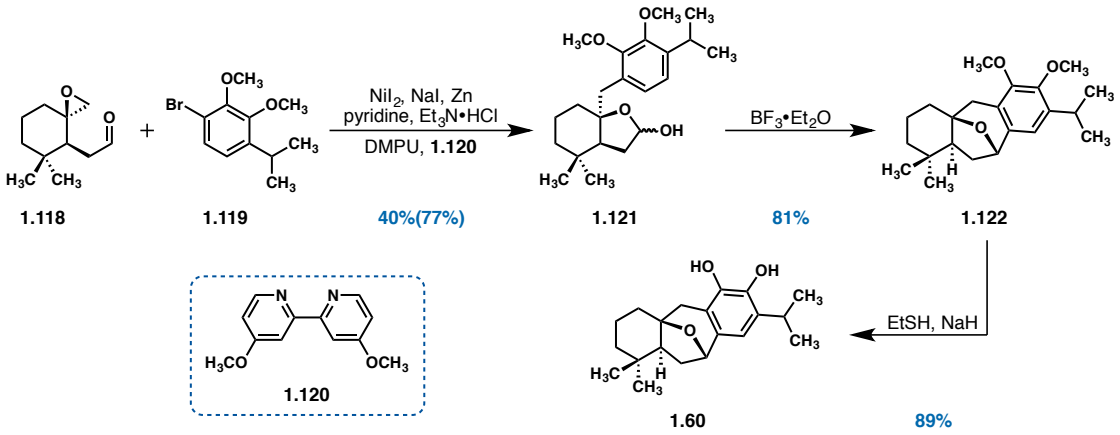


Figure 1.32 Brutoloso's synthesis of (±)–brussonol **1.60**

Employing the same approach, Brutoloso group, was able to access the natural product komaroviquinone **1.28**. The same type of cross–electrophile coupling this time with aryl halide **1.123** furnished **1.124** which was further oxidized using Fetizon reagent to generate lactone **1.125**. Iodination of **1.125** resulted in fully substituted benzene ring **1.126**, which after a modified Suto intramolecular nucleophilic cyclization converted to the icetexane **1.27**—which is in equilibrium with its corresponding hemi–acetal. Finally, treating **1.27** with the previously reported silver(II) oxide in nitric acid afforded komaroquninone **1.28** (Figure 1.33).

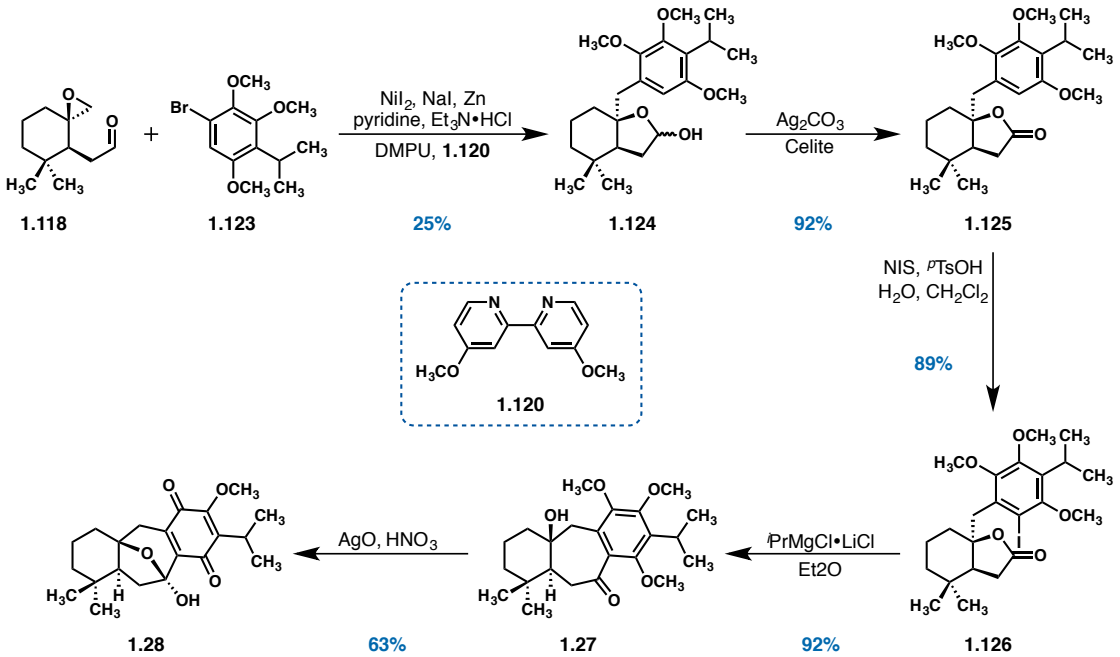


Figure 1.33 Brutoloso's synthesis of (±)–komaroviquinone **1.28**

Sarpong and co–workers in 2010 reported their formal synthesis of icetexone **1.5** with a Ga(III)–catalyzed cyclo–isomerization reaction as their key step.[60] Claisen condensation of prepared indanone **1.127** and dimethyl carbonate generated the corresponding β–ketoester that after alkylation with prepared alkyl iodide **1.128** afforded alkyne **1.129**. Alkyne **1.129** then was pushed through a sequence of saponification–decarboxylation that resulted in **1.131**. Alkyne **1.131** was the envisioned intermediate for the cyclo–isomerization key step that was achieved by using $GaCl_3$ as the catalyst and furnished **1.132** (Figure 1.34).

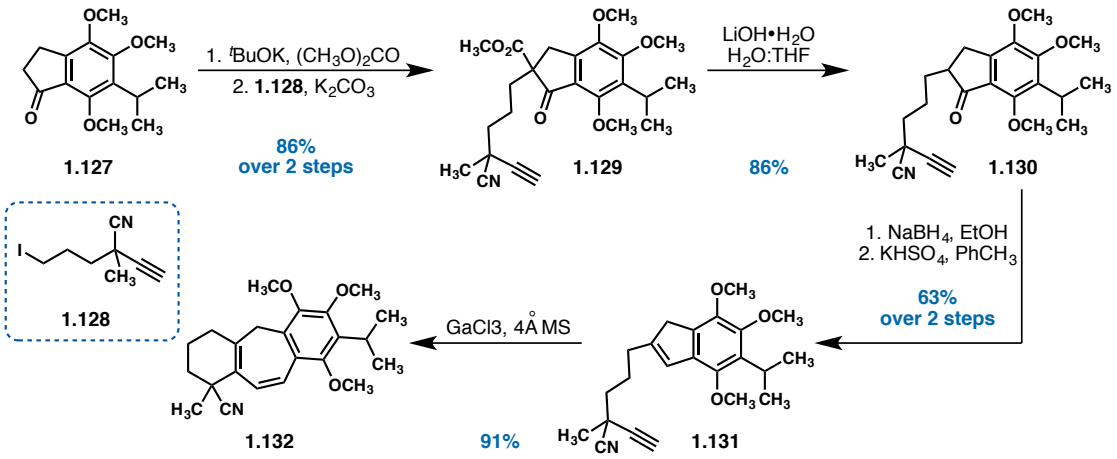


Figure 1.34 Sarpong's formal synthesis of 5–epi–icetexone and icetexone **1.5** Part 1

With icetexane core structure **1.132** in hand the functionalization of diene moiety was investigated and it was shown that using Ghaffar and Parkins' phosphonito complex resulted in primary amide **1.133**,[61] which upon subsequent diastereoselective epoxidation generated **1.134**. Treatment of **1.134** with camphorsulfonic acid and tosylhydrazide in benzene generated a 2.5:1 mixture of **1.136** and **1.135** while treating **1.134** with camphorsulfonic acid in wet dichloromethane followed by subsequent treatment with camphorsulfonic acid and tosylhydrazide in benzene favored **1.135** over icetexone **1.136** (>10:1 dr). Sarpong and co–workers in 2013 published an enantioselective formal synthesis of 5–epi–icetexone and icetexone **1.5** that relied on early enantioselective synthesis of **1.128** using a rhodium catalyst (Figure 1.35).[62]

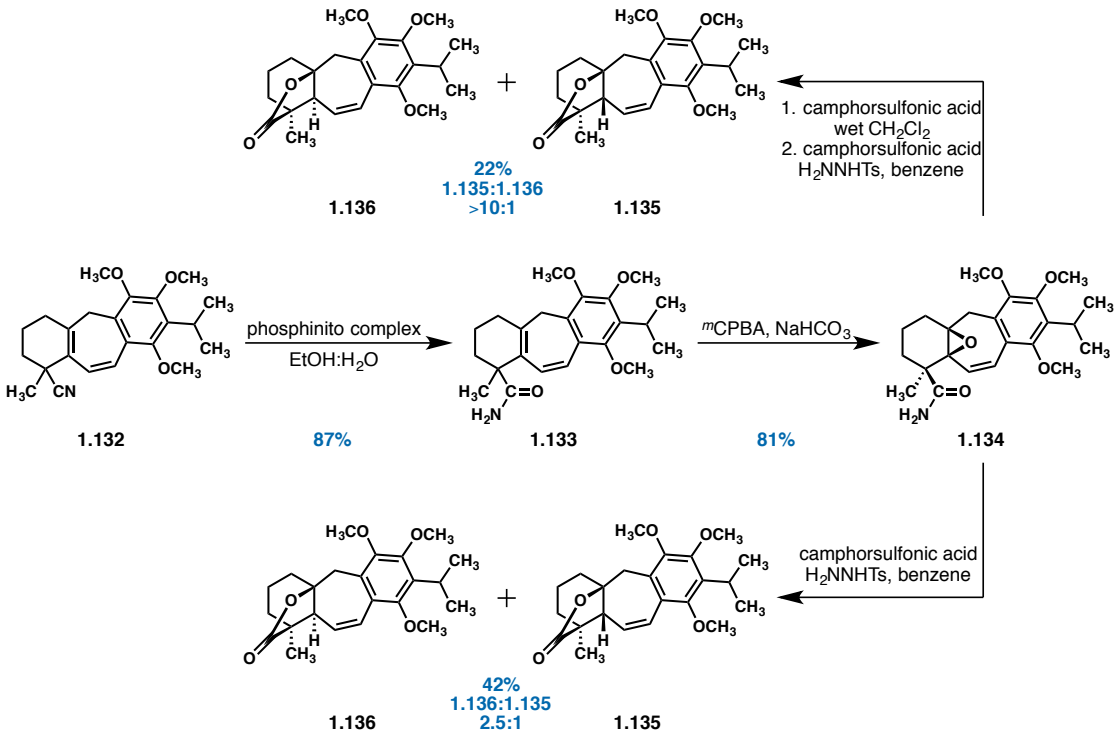


Figure 1.35 Sarpong's formal synthesis of 5–epi–icetexone and icetexone **1.5** Part 2

In 2011 Wang and co–workers reported a synthesis of icetexane core **1.142**.[63] Starting from tetra–substituted benzene ring **1.137** with an ozonolysis followed by reduction to generate the corresponding alcohol which was iodinated following Appel protocol to generate **1.138**. Treating **1.138** with LDA followed by a Mannich–type reaction with imine **1.139** furnished ketone **1.140** which went through a Wittig reaction followed by revealing the corresponding aldehyde **1.141** from protected enol. Treating **1.141** with sodium methoxide increased the ratio of trans isomer comparing to cis isomer, which was later treated with hydrochloric acid to complete the synthesis of core structure of icetexane **1.142** (Figure 1.36).

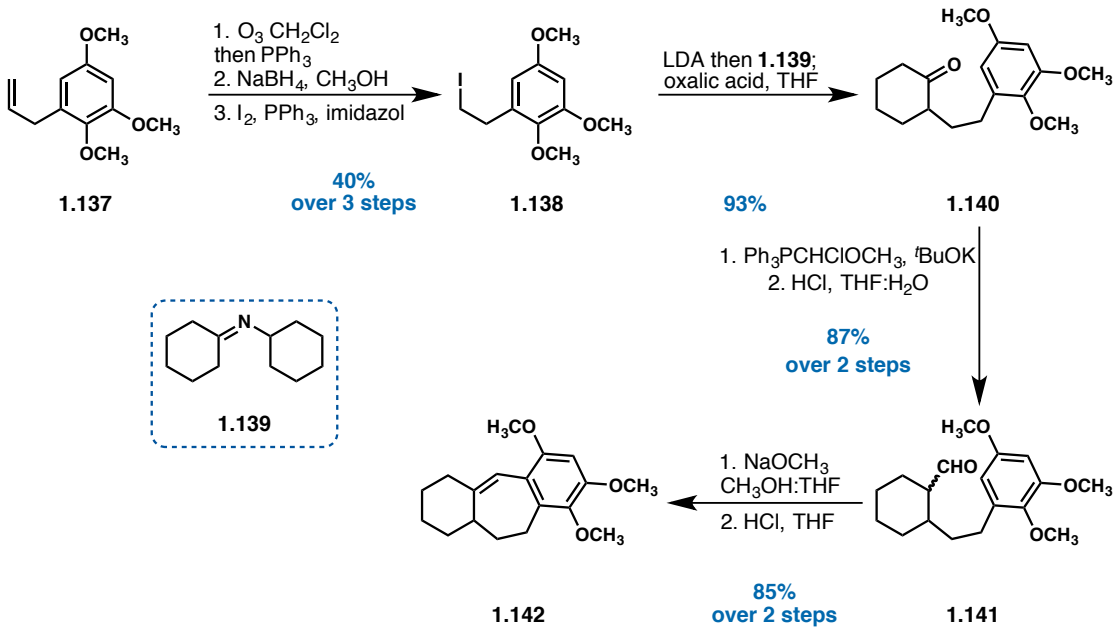


Figure 1.36 Wang's synthesis of icetexane core **1.142**

In 2011 Green and co–worker reported use of the Nicholas reaction in synthesizing the tricyclic core of icetexanes.[64] Prepared allylic acetate complexes **1.143** were treated with BF_3 etherate to furnish the icetexane core structure **1.144** in 40 to 90% yields. They showcased their ability to cleave $Co_2(CO)_6$ by treating **1.144a** with Isobe conditions followed by in situ protodesilylation with TFA generating **1.145a** (Figure 1.37).[65]

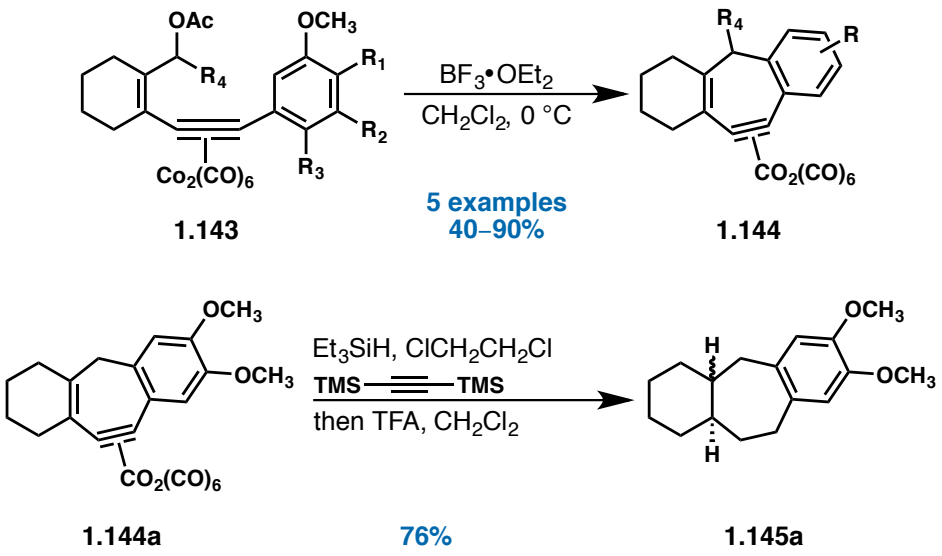


Figure 1.37 Green's synthesis of icetexane core **1.144**

In 2015 Green and co–workers published a new work with more successful examples of their methodology and a new method for cleaving the cobalt complex.[66] They discovered that a stepwise hydrosilylation and then protodesilylation instead of previous one–pot protocol that they used, furnishes **1.147a** without over reduction. Alternatively they got positive results from use of $NaH_2PO_2{\cdot}H_2O$ and 2–methoxyethanol (Figure 1.38).

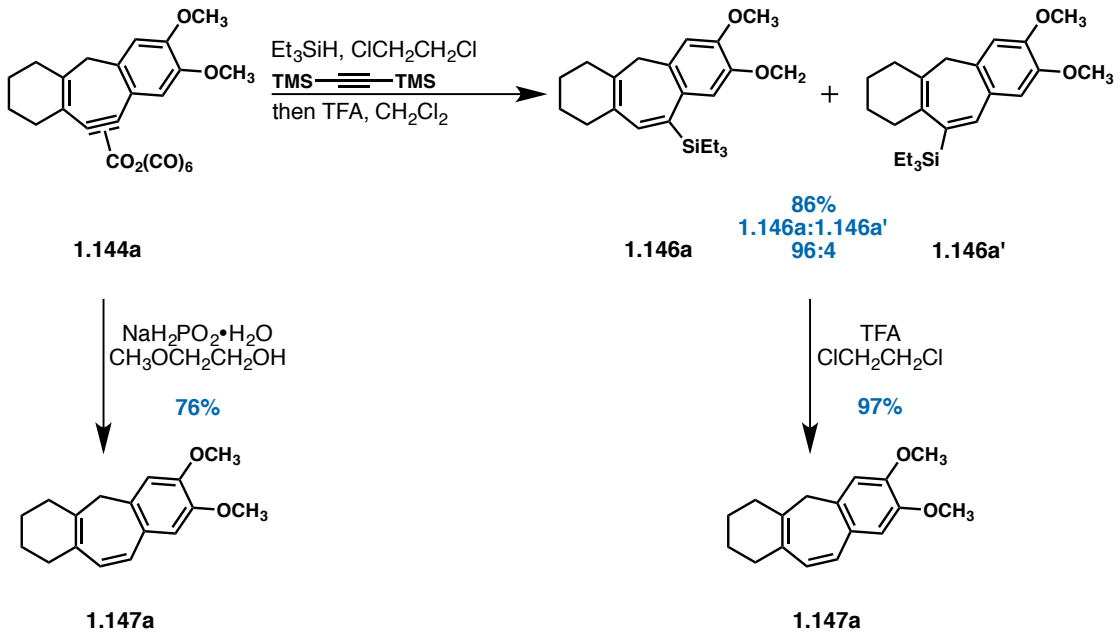


Figure 1.38 reductive–decomplexation of **1.144a**

They also reported synthesis of an unnatural pisiferin **1.149** using their methodology. Cobalt complex of **1.148** proved to be unstable. As a result, they decided to employ a one–pot complexation–Nicholas reaction and decomplexation tactic which resulted in **1.149** (Figure 1.39).

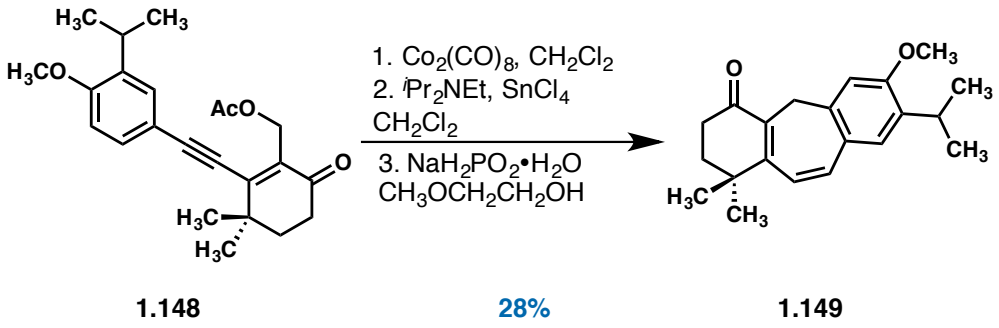


Figure 1.39 Synthesis of an unnatural pisiferin **1.149**

In 2016 Matsushita and co–workers reported synthesis of three different barbatusol type icetexanes—barbatusol **1.34**, demethylsalvicanol **1.38**, rosmaridiphenol **1.65**—from their corresponding pisiferin type icetexanes with an ortho–selective oxygenation reaction.[67] Synthesis of MOM–protected pisiferin **1.151** was accomplished by a modified reaction condition previously described by Kametani and co–workers (Figure 1.40).[68]

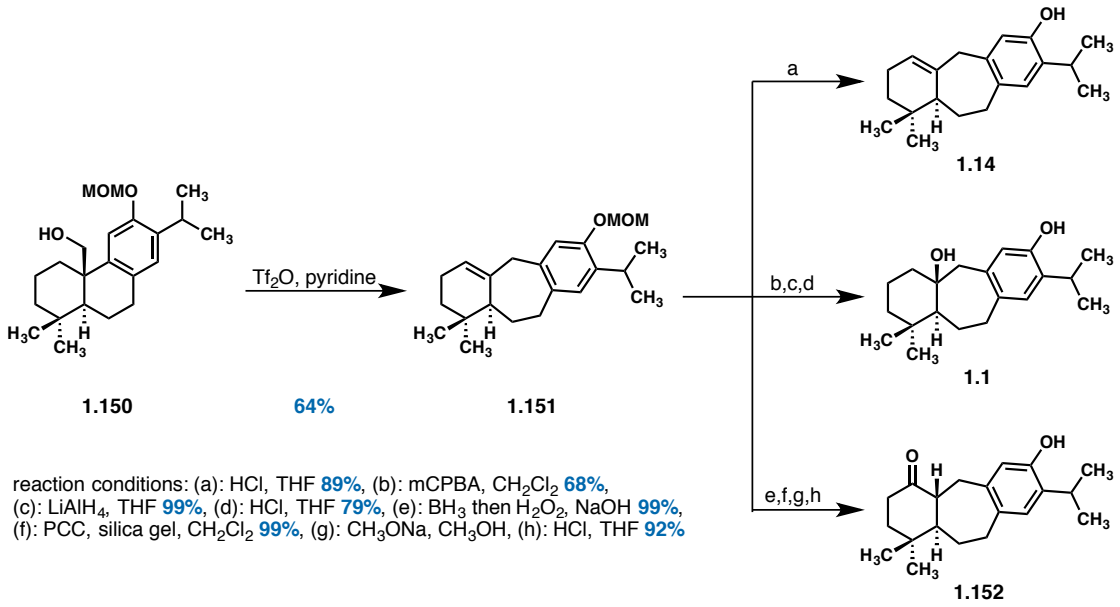


Figure 1.40 Synthesis of pisiferins from **1.151**

They then relied on the work of Tada and co–workers to selectively oxygenate C(11) using SIBX which is a mixture of IBX, benzoic acid and isophtalic acid (Figure 1.41).[69]

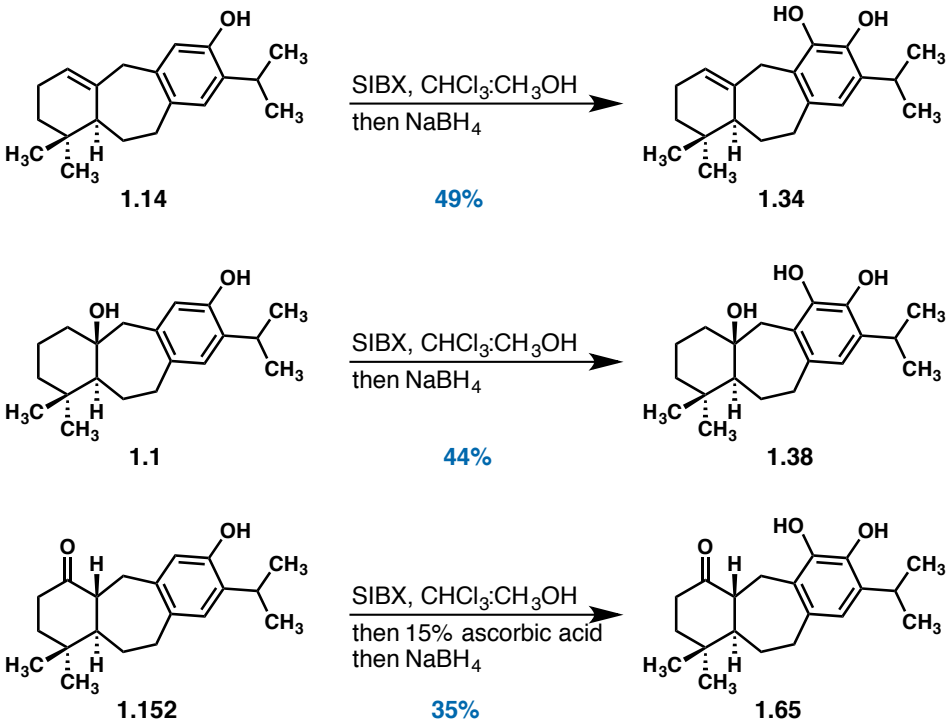


Figure 1.41 Synthesis of barbatusol **1.34**, demethylsalvicanol **1.38**, rosmaridiphenol **1.65**

In 2017 Gademann and co–workers showed the first experimental support for the non–enzymatic mechanism for the attack of water molecule to intermediate **1.154** and thus showing the *β*–face selectivity, despite what Dreiding models has shown before.[70] A selective demethylation of **1.155** furnished salvicanol **1.156**, a barbatusol type icetexane (Figure 1.42).

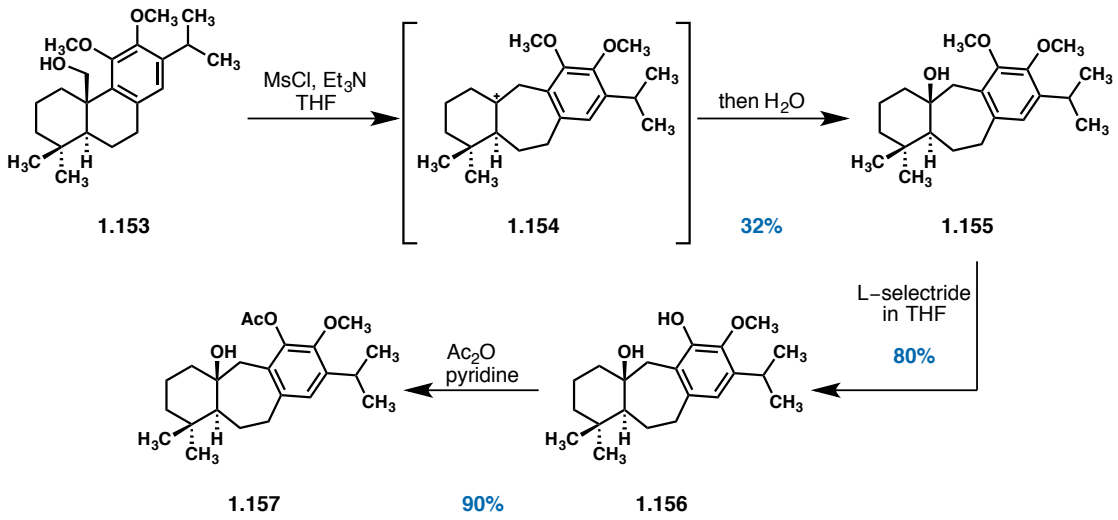


Figure 1.42 β–face selectivity and synthesis of salvicanol **1.156**

Acetate **1.157** was oxidized at C(7) under a modified Hirao protocol using $RuCl_3$ to icetexane **1.158** which was then deacetylated and further oxidized to produce komaroviquinone **1.28**.[71] Komaroviquinone was then reduced in an aqueous ethereal solution of sodium thiosulfate to furnish coulterone **1.50**. Additionally, komaroviquinone **1.28** was subjected to photolysis to furnish cyclocoulterone **1.159** and the rearranged icetexane komarovispirone **1.160** (Figure 1.43).

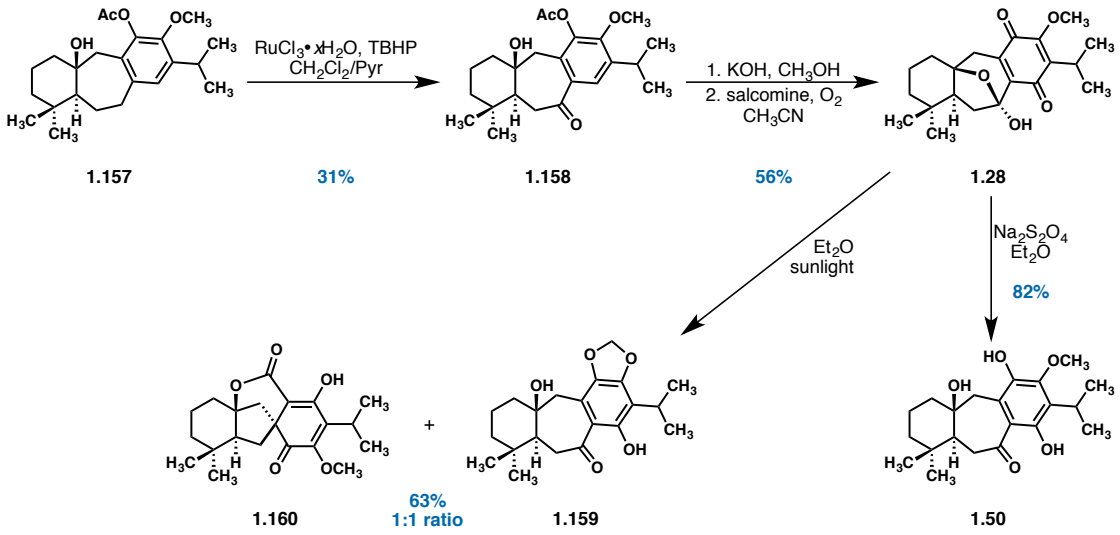


Figure 1.43 Synthesis of icetexanes **1.28**, **1.50**, **1.159** and rearranged icetexane **1.160**

Salvicanol **1.156** was oxidized with DDQ in acetone to obtain demethylsalvicanol quinone **1.58**. Gademann and his group realized that letting **1.58** to sit on silica would yield a mixture of przewalskin E **1.59** and brussonol **1.60**. Interestingly enough, leaving **1.58** on silica gel and open to air with frequent mixing resulted in przewalskin E **1.59** in 50% yield without any detectable formation of brussonol **1.60**. Przewalskin E **1.59** and brussonol **1.60** are convertible to each other with oxidizing–reducing events. Although, the spectral data of synthesized brussonol **1.60** matched with the natural product, however, the spectral data of synthesized przewalskin E **1.59** and the natural product deviate from each other on both ^{1}HNMR chemical shifts and FTIR absorption bands, a discrepancy that has not been resolved up to date. (Figure 1.44).[72]

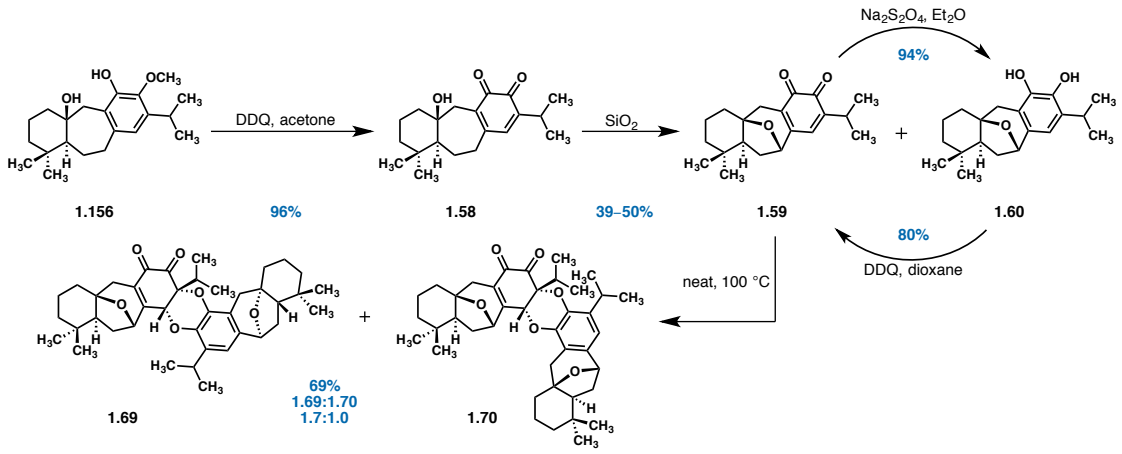


Figure 1.44 Synthesis of icetexanes **1.58**, **1.59**, **1.60**, **1.69**, and **1. 70**

Having przewalskin E **1.59** in hand Gademann and his group decided to utilize modified Takeya conditions to synthesize both obtusinone D **1.69** and obtusinone E **1.70**.[73] The spectral data of synthesized obtusinone D **1.69** and obtusinone E **1.70** matched those of the natural products. However, after obtaining a crystal structure of obtusinone D **1.69**, Gademann and his group realized that the configurations at C(13) and C(14) are different than those of reported by Salae and Boonnak—which was reported based on a NOESY experiment (Figure 1.44).[35] Consequently, Gademann and co–workers suggested that the configuration of C(13) and C(14) for obtusinone E **1.70** should be revised as well (Figure 1.45).

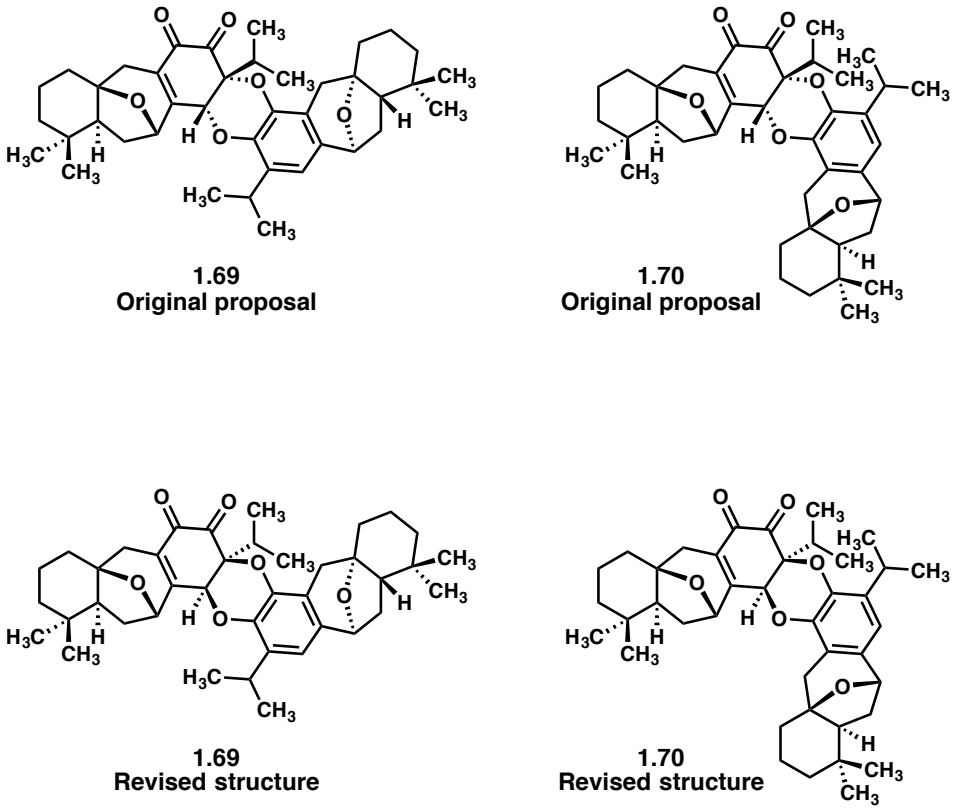


Figure 1.45 Structure of obtusinone D **1.69** and obtusinone E **1.70**

Deng and co–workers, in 2021, reported synthesizing a group of icetexanes using a biomimetic approach.[74] The alcohol **1.35** was treated with triphenyl phosphine and DIAD to construct the rearranged core structure of barbatusol **1.34** (Figure 1.46).

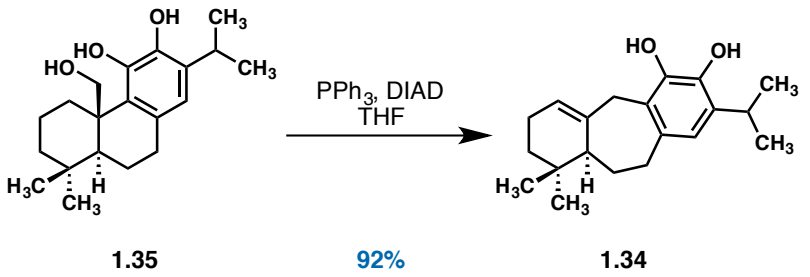


Figure 1.46 Deng and co–workers' biomimetic approach

Having barbatusol **1.34** provided an opportunity for synthesizing other icetexanes. Barbatusol was universally acetylated and then was treated with ^{m}CPBA to generate the epoxide **1.162**, which was then treated with $LiAlH_4$ to construct demethylsalvicanol **1.38**. Two step epoxide–diene conversion produced przewalskin D **1.62** (Figure 1.47).[75]

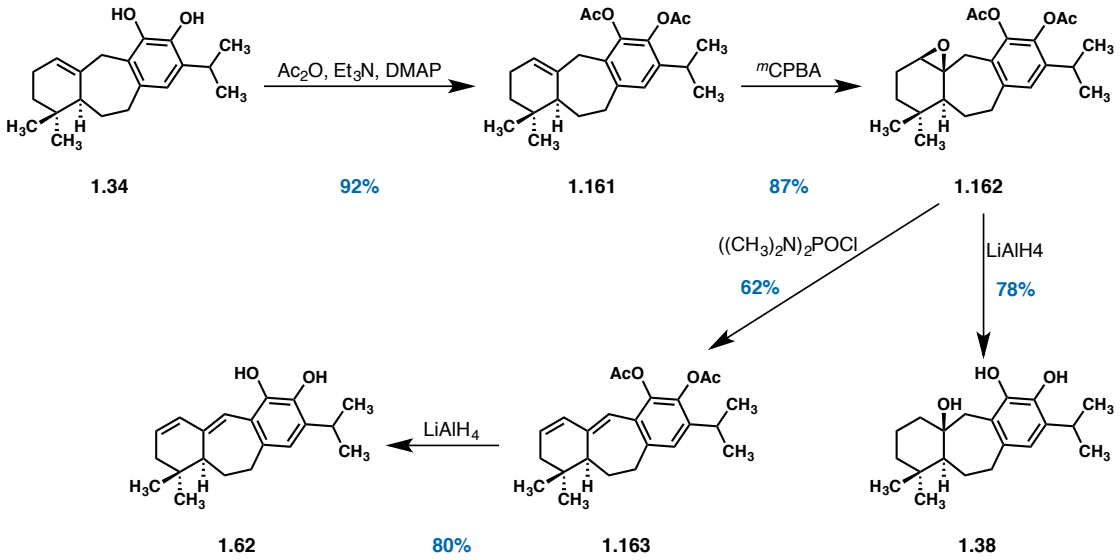


Figure 1.47 Deng's synthesis of demethylsalvicanol **1.38** and przewalskin D **1.62**

Demethylsalvicanol **1.38** was oxidized with silver(I) oxide to construct demethylsalvicanol quinone **1.58** which was dimerized upon heating at 100 °C to furnish grandione **1.164**—with brussonol **1.60** as a minor product.[73, 76] Additionally, treating demethylsalvicanol quinone **1.58** with silica produces przewalskin E **1.59** (Figure 1.48).

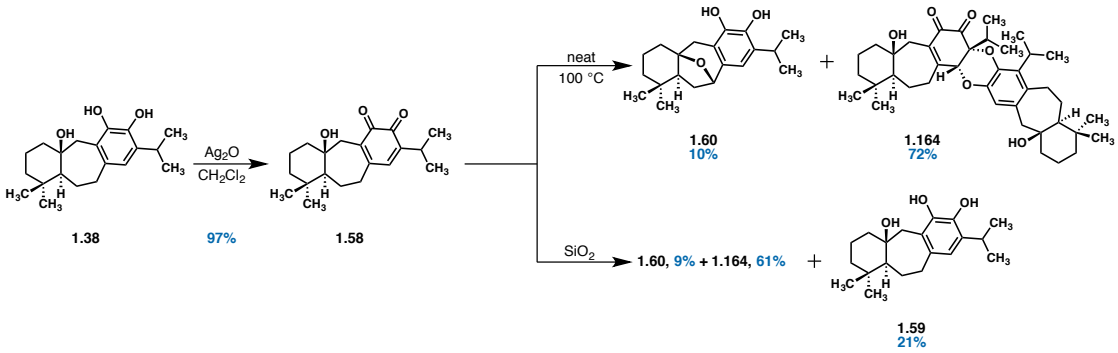


Figure 1.48 Deng's synthesis of grandion **1.164**

Nine of the synthesized icetexanes were screened against HCT–116, COLO–205, and Caco–2 using the 3–(4,5–dimethylthiazol–2–yl)–2,5–diphenyltetrazolium bromide (MTT) assay with anti–colorectal drug 5–fluorouracil as the positive control. The results are summarized in Table 1.16.

Compound	IC_{50} (μM)[b] HCT–116	IC_{50} (μM)[b] COLO–205	IC_{50} (μM)[b] Caco–2
1.34	>20.87	>20.87	13.71±1.36
1.38	18.77±1.39	11.15±1.07	3.07±1.52
1.58	2.93±1.08	3.18±0.95	2.71±1.10
1.59	13.33±1.57	10.42±1.38	3.86±0.98
1.60	>20.23	>20.23	>20.23
1.62	10.58±2.01	7.81±1.74	7.20±1.56
1.161	18.55±2.33	18.52±2.52	10.42±2.64
1.162	11.07±1.92	7.52±1.19	13.81±1.82
1.164	2.70±0.73	3.39±1.45	2.69±1.08
5–FU[a]	7.38±0.83	5.29±0.32	7.77±1.24

[a] 5–Fluorouracil (5–FU) was used as the positive control
[b] An average of three determinations was reported

Table 1.16 Deng's study on cytotoxicity of his icetexanes

In 2018 Chain and co–workers attempted to use their OQM methodology to construct the core structure of icetexanes.[77, 78] Exposure of a mixture of the silyl enol ether **1.165A** and the silyloxybenzyl chloride **1.166A** with TMAF was successful in diastereoselective alkylation reaction, however addition of the phenyl to the carbonyl functional group generated the robust, under both acidic and basic conditions, hemi–acetal **1.168**. Chain and his group solved this problem with using a more conventional alkylation reaction conditions. Methyl lithium was employed to reveal the enolate from silyl enol ether **1.165B**, which was then treated with **1.166B** to generate **1.169**. The icetexane core **1.170** was then constructed upon treating **1.169** with 2nd generation Grubbs catalyst followed by a desilylation reaction (Figure 1.49).

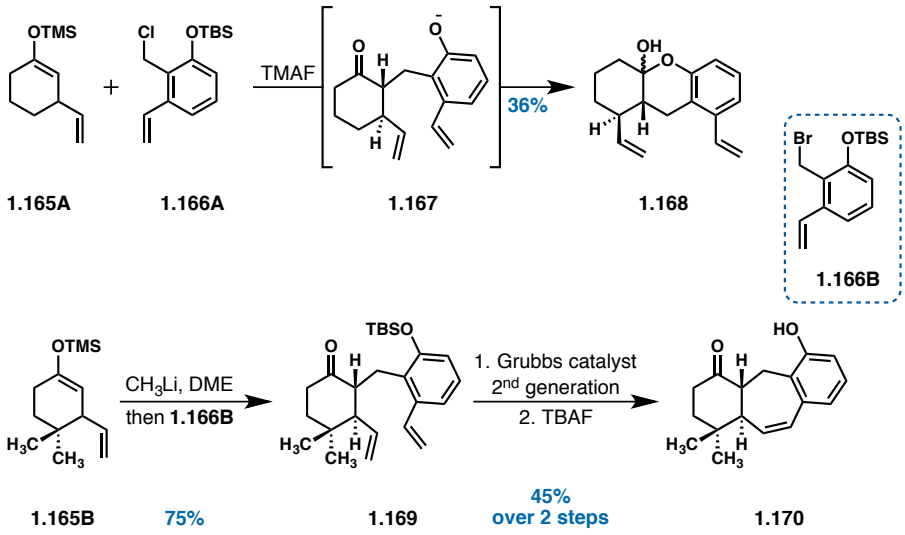


Figure 1.49 Chain's synthesis of icetexane core

In 2019 Oh and co–workers reported their Heck strategy for synthesis of taxamairin B **1.49**.[79] The cyclohexanone **1.171** was converted to the corresponding lithium enolate with ^{n}butyl lithium and then was treated with the ^{o}bromobenzylbromide **1.172** to furnish the ^{o}bromobenzyl cyclohexanone **1.173**. Then a 1,2–addition of an allyl group, employing a Barbier reaction generated a mixture of diastereomeric tertiary alcohols **1.174**.[80] Intramolecular Heck reaction was employed to generate **1.175**, which was then pushed through an oxidative cleavage of exocyclic double bond using a modified OsO_4–$NaIO_4$.[81] **1.176** was then dehydrated using 6N HCl in acetone to produce **1.177** and then was treated with DDQ to generate taxamairin **1.49** (Figure 1.50).

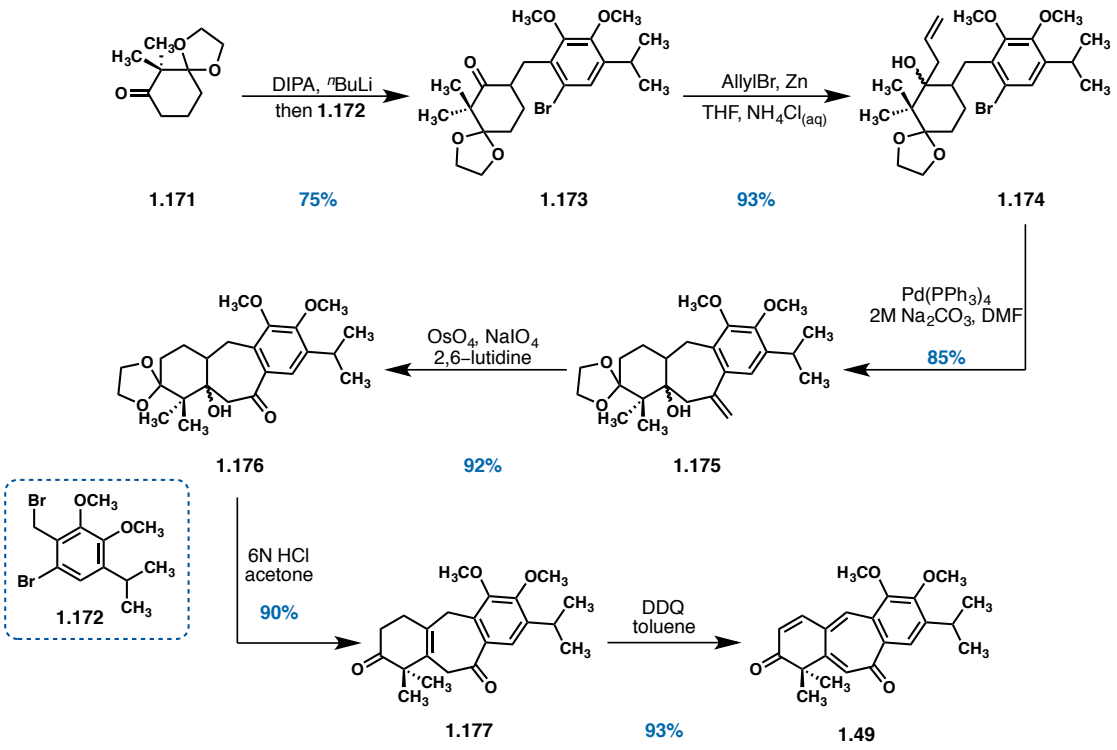


Figure 1.50 Oh's Heck strategy for synthesis of taxamairin B **1.49**

In 2020 Oh and co–workers reported their synthesis of taxamairin B **1.49** and rosmaridiphenol **1.65**.[82] They employed their gold catalyzed cycloisomerization of diynals and enynals toward complex 6–7–n tricyclic systems.[83] After testing different reaction conditions, it was discovered that treating compound **1.178** with $AuBr_3$ in 1,2–dichloroethane as the solvent would result in the tricyclic structure of icetexane **1.179** which is an intermediate toward the synthesis of rosmaridiphenol **1.65**. Hydrogenation of **1.179** generated a mixture of cis and trans **1.180** which was converted to trans **1.180** upon treating with potassium *t*butoxide. Demethylation of **1.180** produced rosmaridiphenol **1.65** (Figure 1.51).

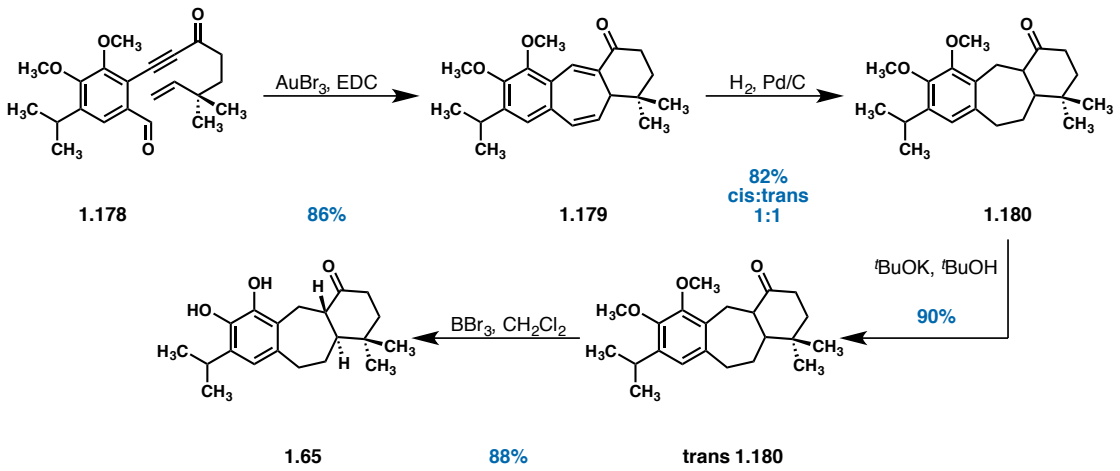


Figure 1.51 Oh's synthesis of rosmaridiphenol **1.65**

Treating **1.181** with COAuCl furnished **1.182**, which has the 6–7–6 core structure of icetexanes and is an intermediate toward synthesis of taxamairin B **1.49**. A mild oxidation of **1.182** using IBX resulted in diketone **1.183** which was converted to **1.184** upon treating with DDQ. Further treatment of **1.184** with DDQ generated taxamairin B **1.49** (Figure 1.52).

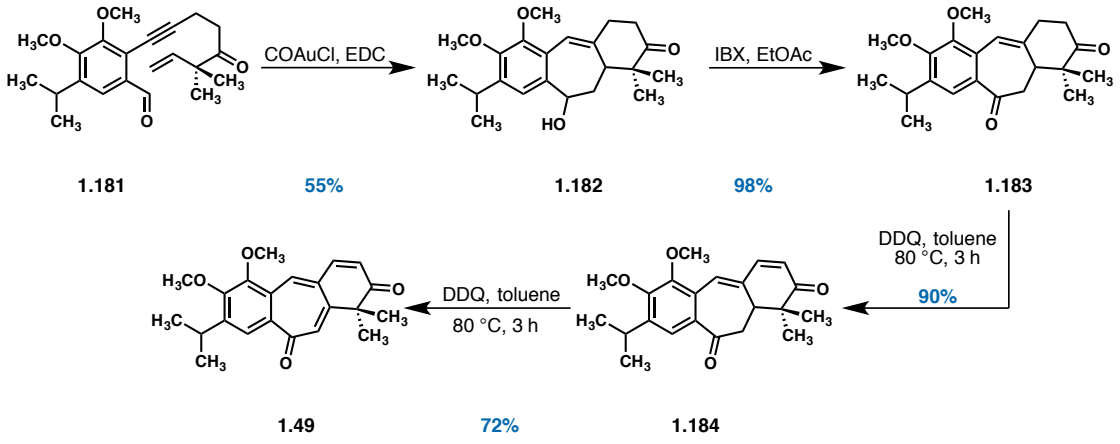


Figure 1.52 Oh's cycloisomerization strategy for synthesis of taxamairin B **1.49**

In 2020 Qiu and co–workers reported their synthesis of brussonol **1.60** and rosmaridiphenol **1.65**.[84] They employed a tandem [5+2]/Diels–Alder to convert intermediate **1.185** to **1.187** and construct the core structure of icetexane in one step. A sequential hydroboration and oxidation followed by a DBU mediated elimination furnished **1.188**, which was aromatized upon treatment with selenium dioxide. Protecting the phenol **1.189** with methyl iodide and reduction of the ketone functional group using sodium borohydride generated **1.190**. Natural icetexane euolutchuol E **1.192** was prepared after a radical deoxygenation followed by thioethoxide mediated demethylation reaction (Figure 1.53).[85]

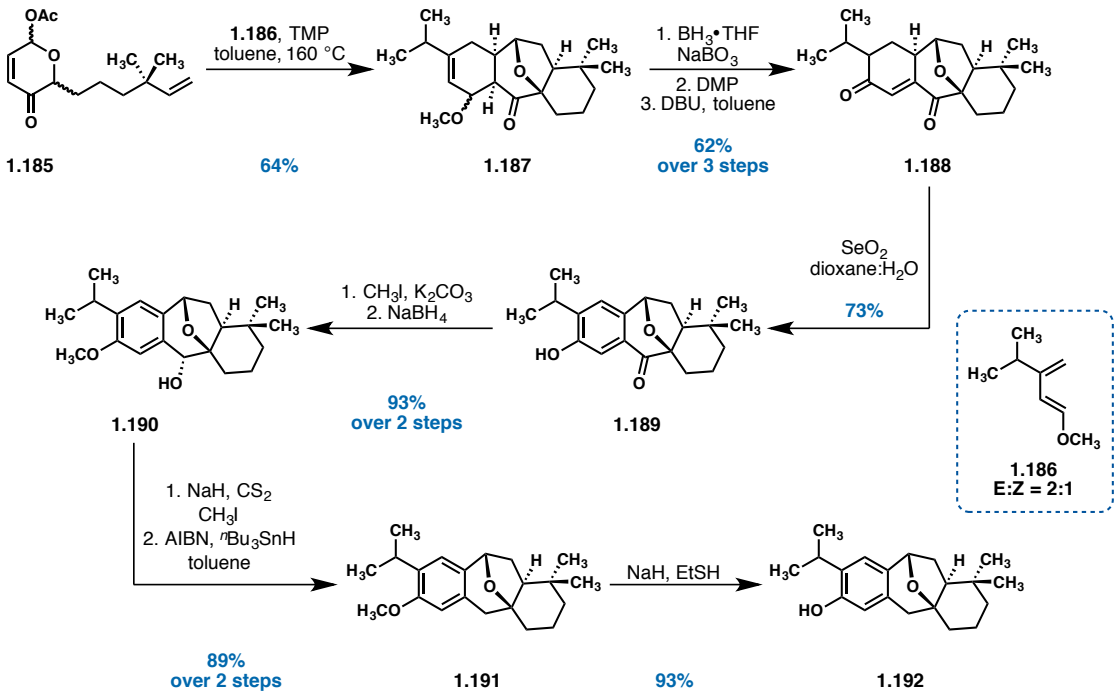


Figure 1.53 Qiu's synthesis of euolutchuol E **1.192**

Ortho–selective oxygenation of **1.192** furnished przewalskin E **1.59**, which was reduced to brussonol **1.60** using sodium thiosulfate (Figure 1.54).

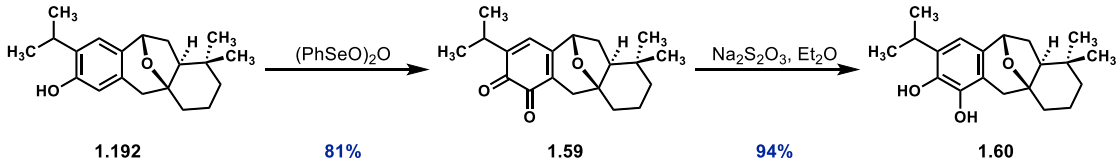


Figure 1.54 Qiu's synthesis of przewalskin E **1.59** and brussonol **1.60**

In 2021 Gao and co–workers reported a new method of constructing icetexane core.[86] An asymmetric photoenolizaion/Diels–Alder reaction between the fully substituted benzene **1.194** and the enone **1.193** furnished the tricyclic system **1.196** which was oxidized to generate ketone **1.197**. Removal of the benzyl group followed by selective reduction of aldehyde functionality was followed by an Appel reaction using quinolone as base to produce iodide **1.198**. The final step of constructing the icetexane core was a radical–mediated ring expansion reaction, which generated **1.199** (Figure 1.55).

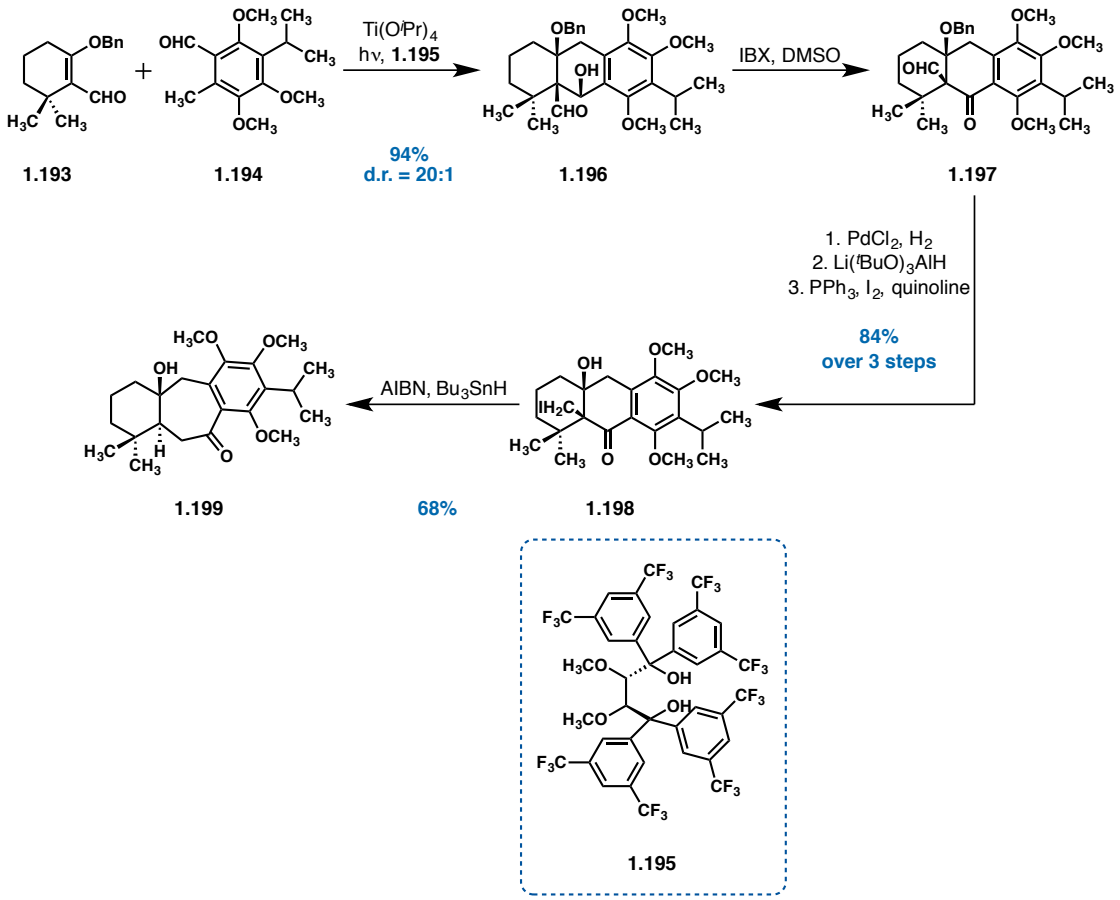


Figure 1.55 Gao's construction of icetexane core

1.8 Summary

Icetexanes are a family of natural products with a wide array of biological activities and complex structure, which has encouraged synthesis chemists to approach them with different strategies over the past decade. Since 2009, there has been more than 50 newly discovered icetexanes and with more than a dozen of new strategies for their synthesis which have all been shown in this chapter.

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Chapter 2

PREMNALATIFOLIN A: EFFORTS TOWARD THE SYNTHESIS OF INVERTED ICETEXANE STRUCTURES

2.1 Introduction: Prior Efforts Toward a Model System for Premnalatifolin A

Premnalatifolin A **2.1** was first described in 2011 by Babu and co–workers and originated from the hexane extract of dry stem–bark of *Premna latifolia*, a familiar plant to traditional medicine system of India (Figure 2.1).[1] It is a heterodimeric icetexane, which is especially interesting since it is the only example of such a dimer featuring a C–O–C diaryl ether bond linkage. Additionally, Babu and his group discovered three monomeric icetexanes that are structurally related to the northern monomer of premnalatifolin A **2.1**—latifolionol **2.2**, dihydrolatifolionol **2.3**, and latiferanol **2.4** (Figure 2.1).[2]

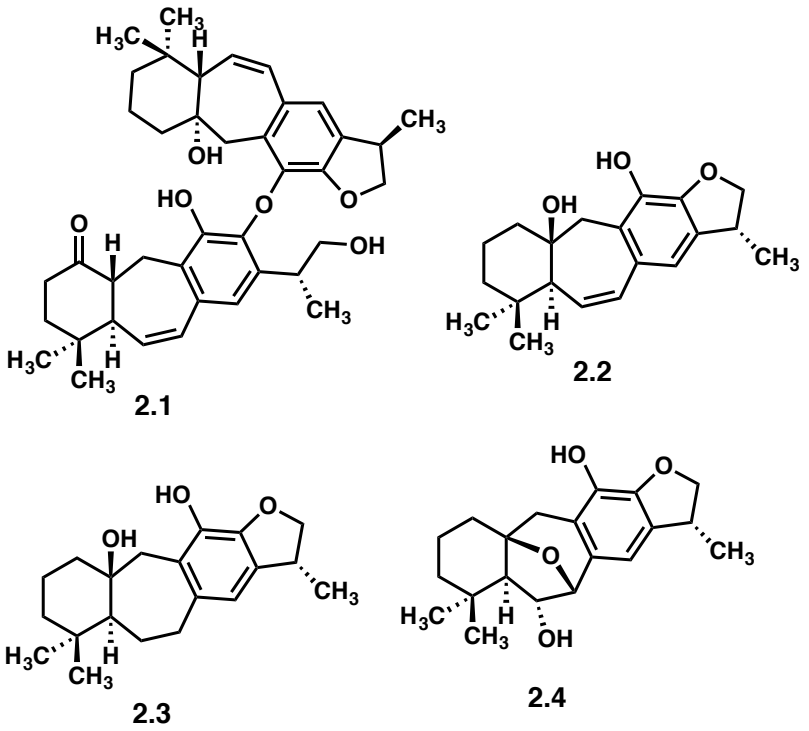

Figure 2.1 icetexanes **2.1** to **2.4** from *Premna latifolin*

All four of these icetexanes were evaluated for their cytotoxicity against eight different cancer cell lines. Premnalatifolin A **2.1** was shown to have growth inhibitory effects toward both MCF–7 (breast) and HT–29 (colon) cancer cell lines with an IC_{50} of 1.77 μM and 19.4 μM, respectively. Latifolionol **2.2** (the northern monomer of premnalatifolin A **2.1**) has also shown cytotoxic activity against the same cancer cell lines (MCF–7, IC_{50} = 3.53 μM and HT–29, IC_{50} = 127 nM).[2.31, 2.32]

The current standard of care for the chemotherapeutic intervention in breast cancer patients is doxorubicin (commercially branded as Adriamycin®), with an IC_{50} of 3.70 μM against MCF–7 cancer cell lines, despite the fact that its mechanism of action is not perfectly understood.[3] Doxorubicin is notorious for its destructive side

effects and high mortality rate, hence the unfortunate nickname “the red death”.[4] As a result, it is clear that there is an immediate need for new chemotherapeutics for the treatment of patients suffering from breast cancer. Results of *in vitro* cytotoxicity of premnalatifolin A **2.1** show it to be a promising target for a new, less toxic cure.

Both the northern and the southern monomers (**2.2** and **2.5**, respectively) of premnalatifolin A **2.1** are barbatusol type icetexanes with one difference in their oxidation pattern. The northern monomer **2.2** is oxygenated at C(10) with the southern monomer **2.5** bearing a carbonyl group at C(1). Our long term goal has been the development of a synthetic route toward the southern monomer **2.5** and then adjustment of the oxidation pattern to produce **2.2** (Figure 2.2).[5]

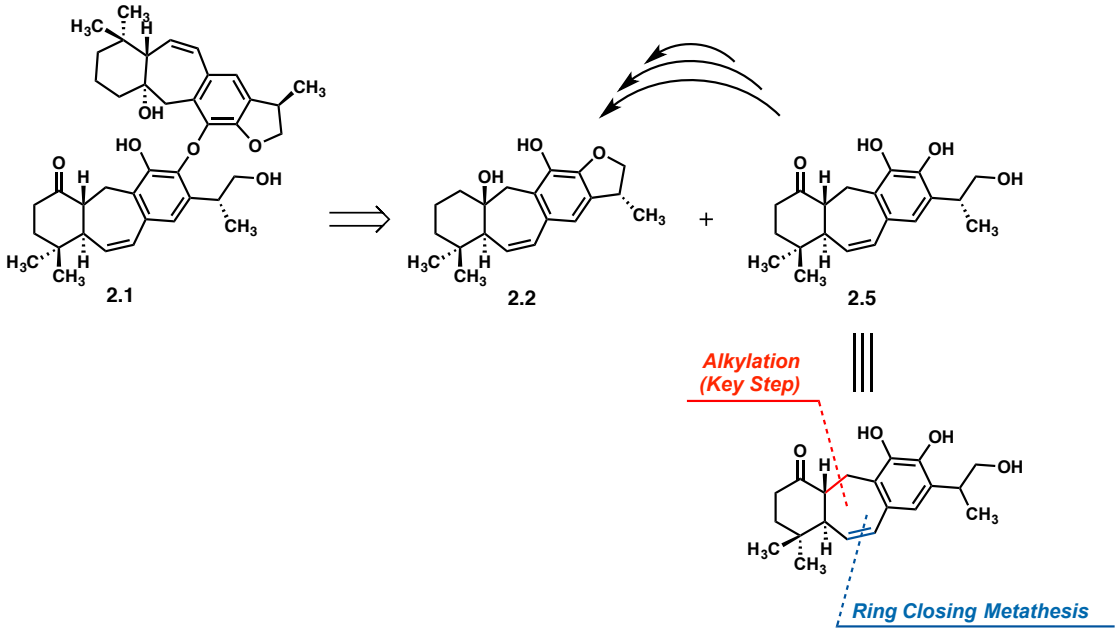

Figure 2.2 Retrosynthetic analysis of premnalatifolin A **2.1**

We decided to first synthesize a simplified model system of the monomeric icetexanes to identify the possible unforeseen synthetic problems that might arise with the alkylation reaction (key step) and the RCM. To that end, target **2.7** was chosen which contains the C(1) carbonyl group and is oxygenated at C(11) (Figure 2.3). It was envisioned that an alkylation reaction would be employed to generate **2.8**, which is a great candidate for a ring closing metathesis reaction to form the seven–membered ring in the heart of the icetexanes. Synthesis of silyl enol ether **2.9** was completed in one step—a conjugate addition of vinyl cuprate to the commercially available enone **2.11** followed by *in situ* trapping of the resultant enolate with chlorotrimethylsilane.[6]

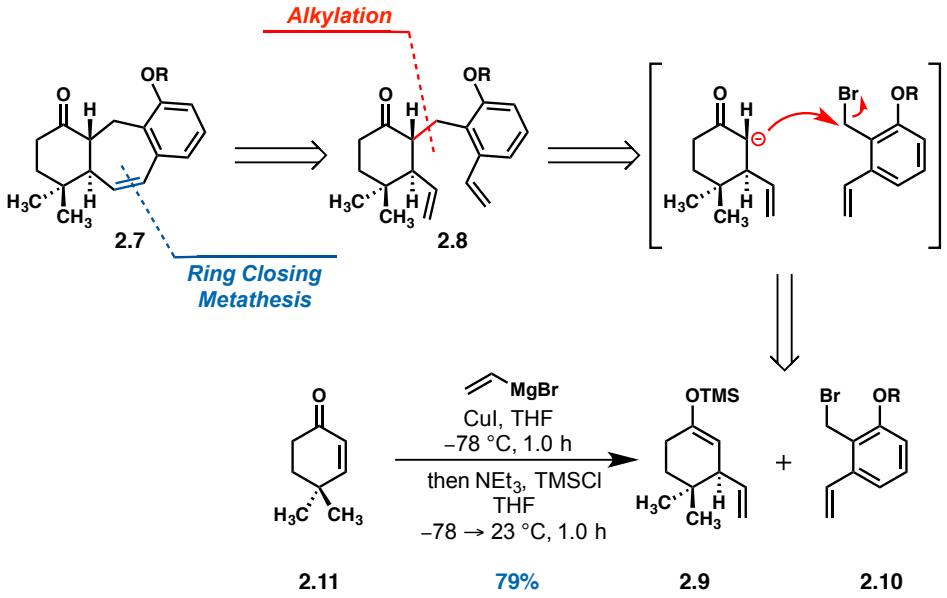

Figure 2.3 Retrosynthetic analysis of the model system **2.7**

Commercially available benzaldehyde **2.12** was treated with potassium hydroxide to displace fluoride by a nucleophilic aromatic substitution reaction to

afford the phenol **2.13**. Then a Suzuki–Miyaura coupling was employed to convert **2.13** to **2.14** under wet conditions.[7] These cross–coupling conditions are unusual but well suited to phenolic substrates. The phenol **2.14** was then protected as the silyl ether by treatment with TBSCl to produce **2.15**, which was reduced with sodium borohydride in wet methanol to furnish benzyl alcohol **2.16**. Finally, the bromination of **2.16** under the action of PBr_3 generated the desired benzyl bromide **2.10** (Figure 2.4).

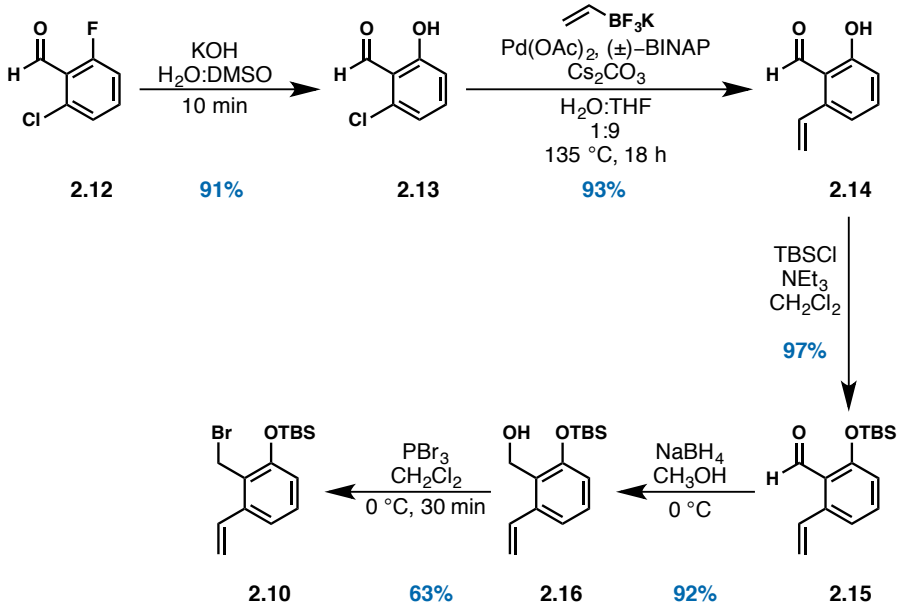

Figure 2.4 Synthesis of the benzyl bromide **2.10**

The convergent synthesis of model system **2.7** was completed with an alkylation reaction[8] to generate **2.8** followed by a ring–closing metathesis using the 2nd generation Grubbs catalyst (Figure 2.5).[9]

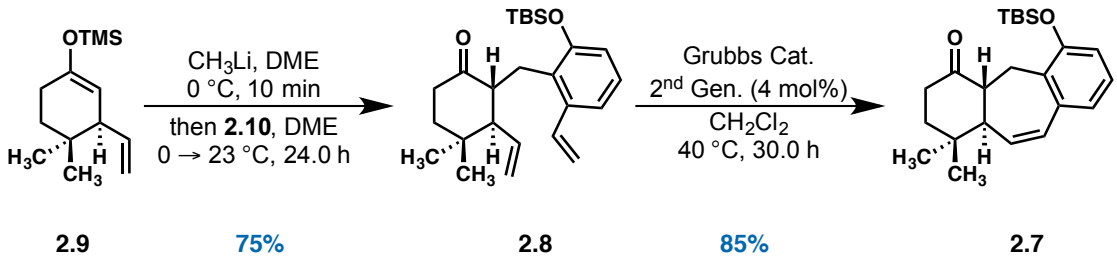

Figure 2.5 Completing the divergent synthesis of the model system

2.2 Synthesis of Inverted Icetexane Structures

As was discussed in the first chapter, the core structure of icetexanes **2.17** include an isopropyl unit at C(13) which is not oxygenated in most of the known members of this family of natural products.[10] However, the icetexanes discovered from *Premna latifolia*[2.31,2.32] are oxygenated at C(16). Given this fact, we have decided to study the importance of the isopropyl group and the functional groups installed on it on the cytotoxic activity of icetexanes by diversifying the type of installed functional groups as well as the position of isopropyl group on core structure. To that end, we have attempted to synthesize a number of inverted icetexanes **2.18** with isopropyl unit at C(11) instead of C(13) (Figure 2.6).

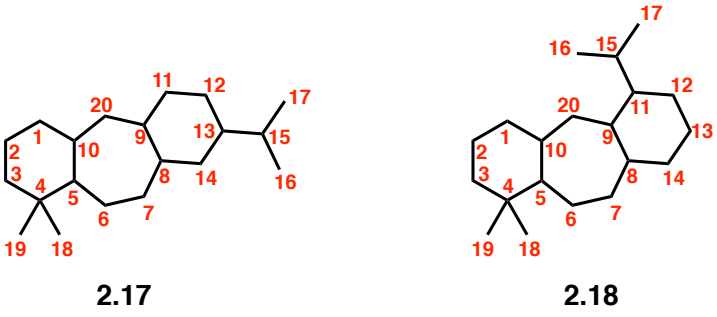

Figure 2.6 Core structure of icetexanes **2.17** and inverted icetexanes **2.18**

2.2.1 Synthesis of Inverted Icetexane 2.19

The inverted icetexane **2.19** was the first target that we pursued since it bears the dihydrofuran moiety, which is a common feature of the icetexanes extracted from *Premna latifolia* (Figure 2.7).

The dihydrobenzofuran **2.20** is an essential intermediate en route to the inverted icetexane **2.19** (Figure 2.7). The synthesis begins with a Wittig reaction following the protocol of Harayama and co–workers to furnish the conjugated ester **2.22**.[11] A 1.4–addition of methyl cuprate to **2.22** in the presence of chlorotrimethylsilane afforded the phenol **2.23**, which was protected as the corresponding benzyl ether by treatment with benzyl bromide in basic acetone, and the methyl ester was saponified using sodium hydroxide in dichloromethane and methanol to generate the carboxylic acid **2.24**.

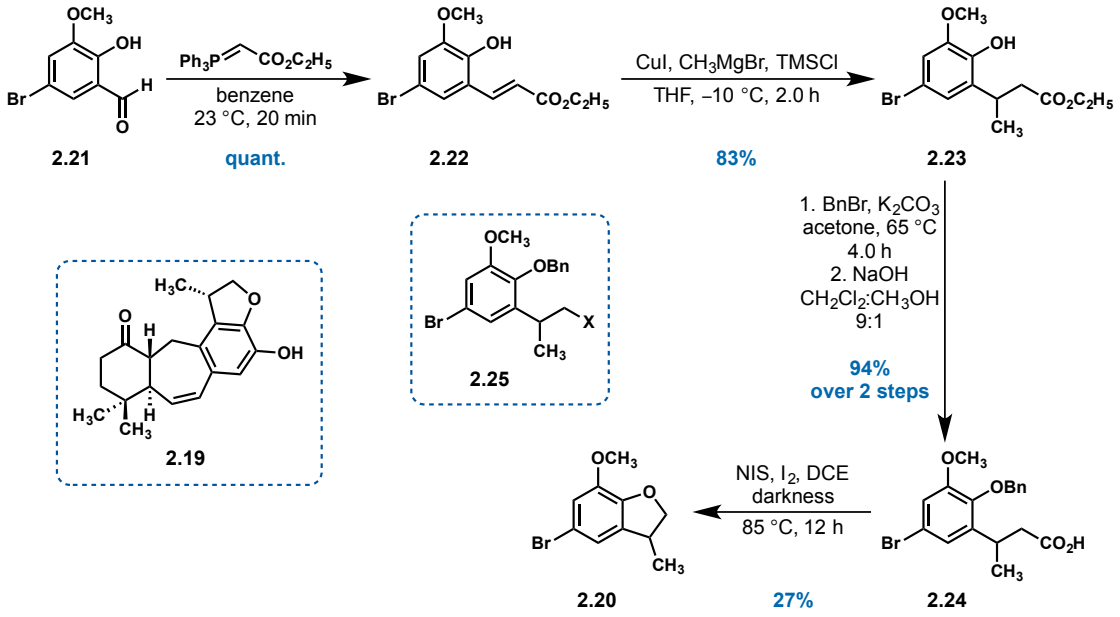

Figure 2.7 Inverted icetexane **2.19**, 1st generation synthesis of dihydrobenzofuran **2.20**

We envisioned an oxidative decarboxylation of **2.24** to generate alkyl halide **2.25**,[12] however upon treatment of **2.24** with *N*–iodosuccinimide and iodine, dihydrobenzofuran **2.20** was prepared in one step (Figure 2.7).[13]

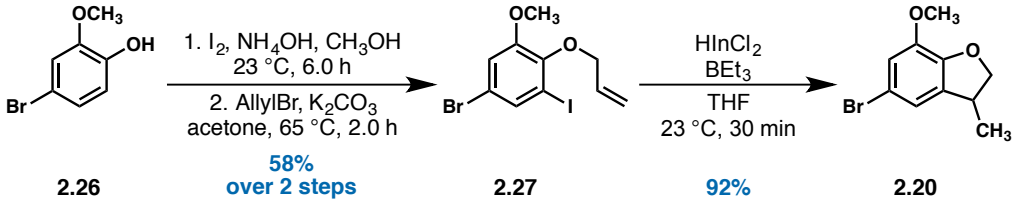

Figure 2.8 2nd generation synthesis of dihydrobenzofuran **2.20**

The first generation synthesis of **2.20** was fruitful, however the lengthy sequence suffered too many steps with a low overall yield, which encouraged us to think about a new pathway toward **2.20** starting from the phenol **2.26** (Figure 2.8). The 2nd generation synthesis begins with an *ortho* iodination reaction followed by an allylation to generate allyloxybenzene **2.27**.[14] Dihydrobenzofuran **2.20** was then furnished through a radical mediated cyclization of **2.27** upon treatment with *in situ* generated $HInCl_2$.[15]

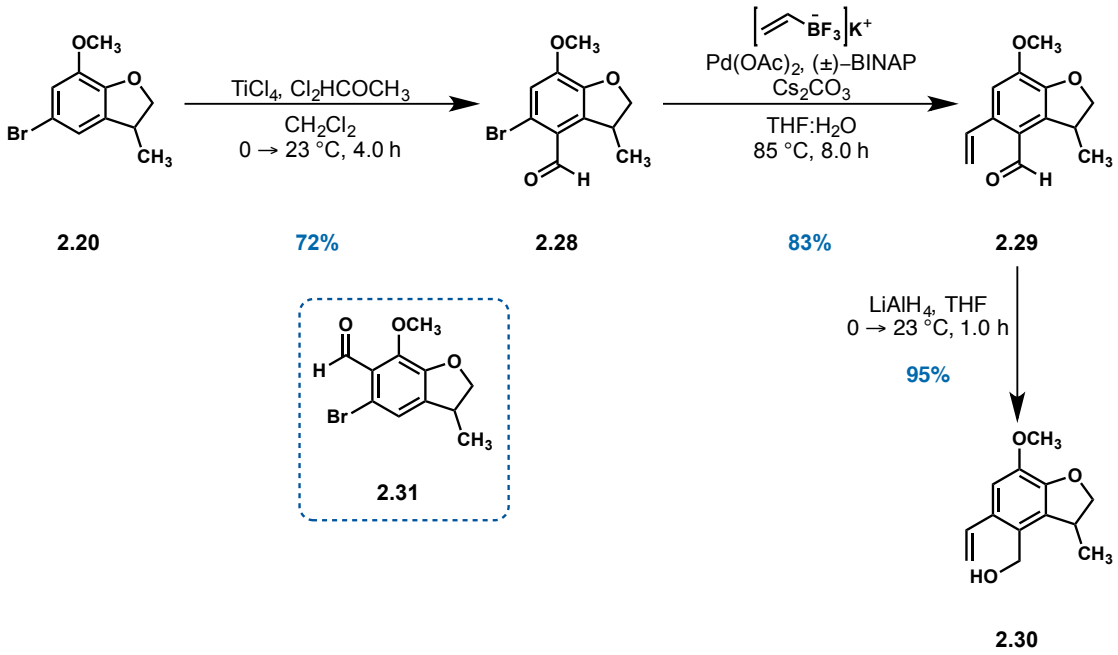

Figure 2.9 Synthesis of benzyl alcohol **2.30**

At this stage it was decided to employ the Rieche formylation,[16] a titanium(IV) chloride–mediated process that employs a halogenated dimethyl ether as a source of electrophilic formyl equivalent. Based on the previous reports from Albercio and co–workers we were expecting to observe *ortho* methoxy benzaldehyde **2.31**, however the resultant product proved to be *para* methoxy benzaldehyde **2.28** (Figure 2.9).[17] While unexpected, this afforded the opportunity for analog chemical space that is completely unexplored in the icetexane literature. The Suzuki–Miyaura coupling we perfected in model studies was employed to convert **2.28** to **2.29** under wet conditions followed by a reduction under the action of lithium aluminum hydride to furnish the desired pentasubstituted aromatic **2.30**.

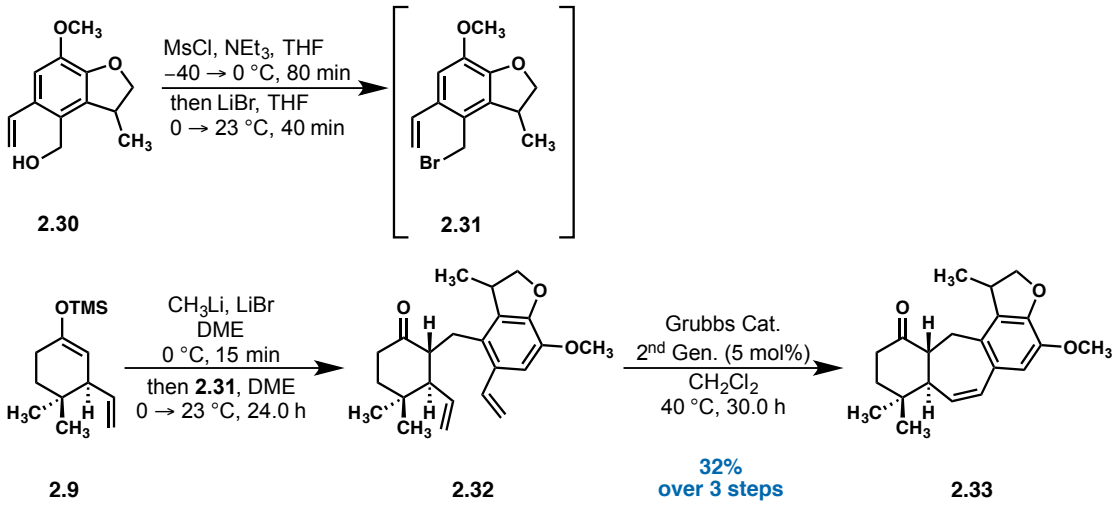

Figure 2.10 Constructing the central seven–membered ring of inverted icetexane **2.33**

Displacing the hydroxyl group on **2.30** with bromine to afford the corresponding benzyl bromide proved to be a deceptively challenging process. Conventional bromination methods—the Appel reaction,[18] and PBr_3 mediated bromination to name a few—proceeded with low conversions. Ultimately, a one–pot two–step process in which the alcohol is converted to the corresponding methylsulfonate under the action of methanesulfonyl chloride followed by displacement of the mesylate with lithium bromide afforded us the benzyl bromide **2.31** (Figure 2.10).[19]

The alkylation protocol that was employed before for the synthesis of **2.8** proved to be unsuccessful for the more complex target **2.32**Figure **2.5]**.**Error! Bookmark not defined.** After screening different reaction conditions we found that addition of halide to the enolate reaction mixture (1.50 equiv of LiBr) improved the yield of the alkylation significantly, presumably by influencing the aggregation state

of the reaction components.[20] The final ring closing metathesis step of the synthesis proceeded smoothly, however, to construct inverted icetexane **2.33** (Figure 2.10).

2.2.2 Synthesis of inverted icetexane 2.34

With the ester **2.23** in hand (Figure 2.7), we started to explore the idea of synthesizing an icetexane with an ester functional group to diversify the library of our molecules. Protection of the free phenol as the corresponding methyl ether by treatment with iodomethane in basic acetone furnished **2.35**, which was formylated using Richie protocol (again with regiochemistry we encountered above) to generate **2.36**[2.316] followed by a Suzuki–Miyaura coupling under our optimized conditions to generate the styrene **2.37** (Figure 2.11).

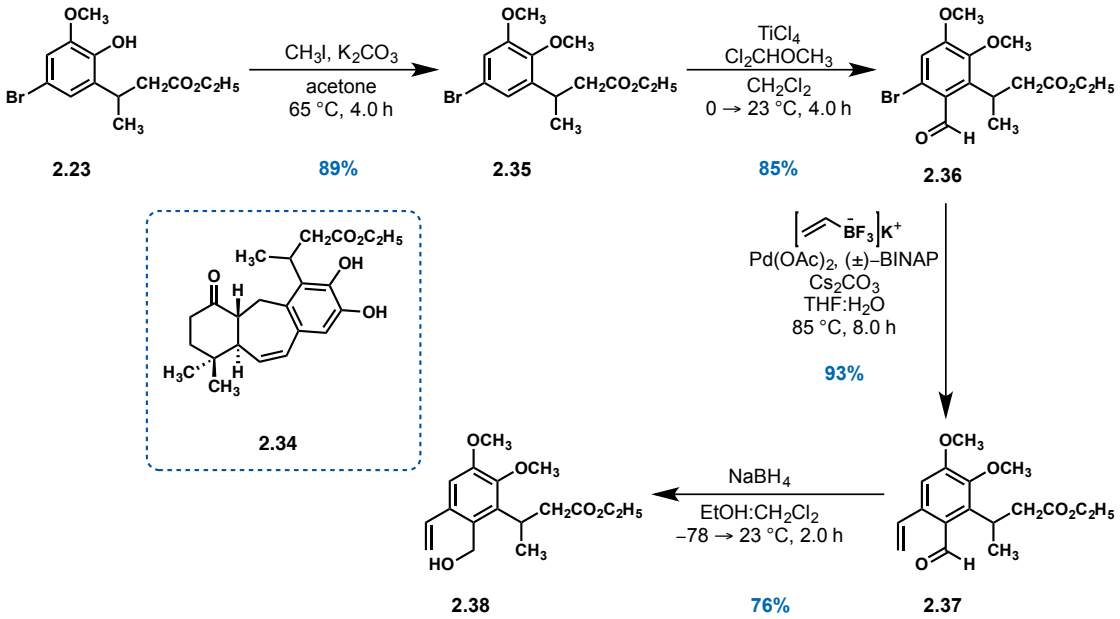

Figure 2.11 Synthesis of benzyl alcohol **2.38**

Reduction of benzaldehyde **2.37** with $LiAlH_4$ as we had achieved in other contexts would be fruitless as **2.37** bears an ester function, however reduction with $NaBH_4$ in a mixed $EtOH/CH_2Cl_2$ solution chemoselectively reduced the aldehyde with the ester intact to afford the desired pentasubstituted aromatic **2.38** (Figure 2.11).

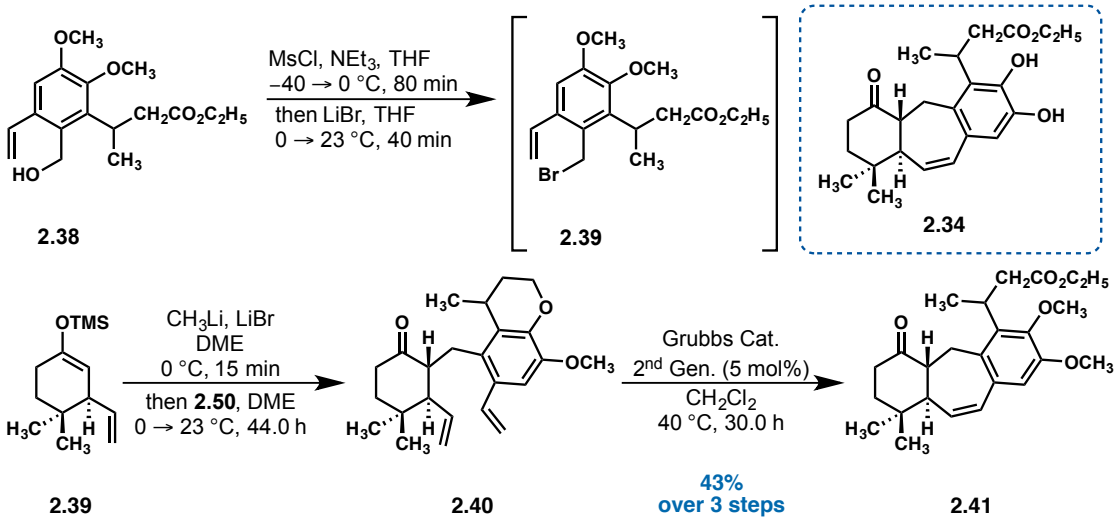

Figure 2.12 Constructing the central seven member ring of inverted icetexane **2.41**

Displacing hydroxyl group on **2.38** with bromine was completed employing the optimized one–pot, two–step reaction conditions described above (Figure 2.11),[2.318] and then the LiBr–doped alkylation protocol was employed to generate the desired product **2.40**. The final step of the synthesis, ring closing metathesis reaction, was done smoothly to construct inverted icetexane **2.41** (Figure 2.12).

2.2.3 Synthesis of Inverted Icetexane 2.52

To further diversify our icetexane library and explore unnatural aromatic alkyl appendanges, we constructed the inverted icetexane **2.42**, which has a hydroxylated

sec–butyl substitute on C(11) instead of a hydroxylated isopropyl group (Figure 2.13). The ester **2.23** was reduced with $LiAlH_4$ and the resultant dihydroxylated compound **2.43** was globally protected as the corresponding methyl ethers by treatment with iodomethane and sodium hydride in warm THF to furnish the aryl bromide **2.44**.

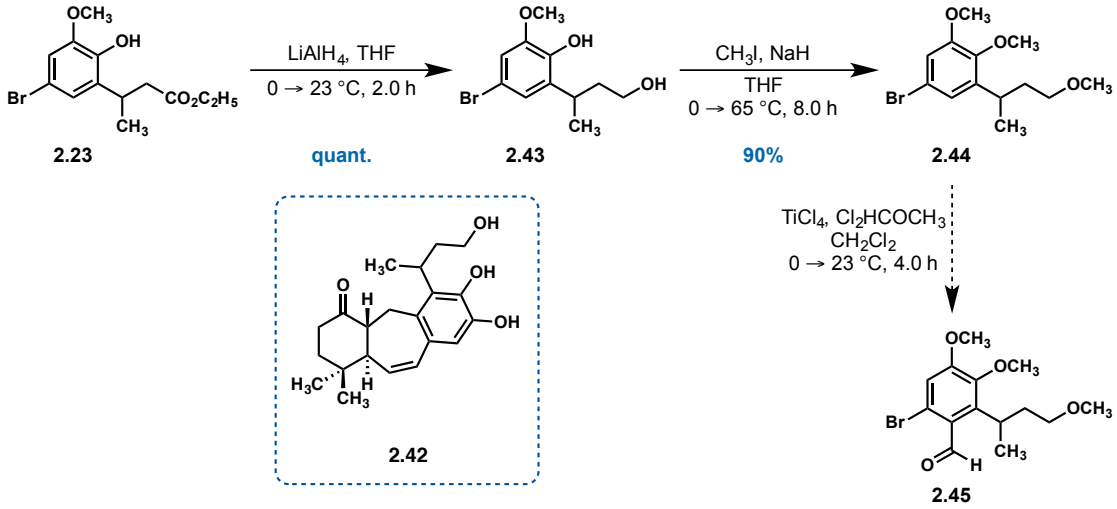

Figure 2.13 Attempts to synthesize benzaldehyde **2.45**

At this stage we attempted to selectively formylate the aryl bromide **2.44** by employing the same Richie protocol that we have used previously and expected to obtain the benzaldehyde **2.45**, however to our surprise we not only formylated compound **2.44** at the position between the bromide and appendage functions, but also cyclized the material to generate the dihydrobenzopyran system **2.46** (Figure 2.14).

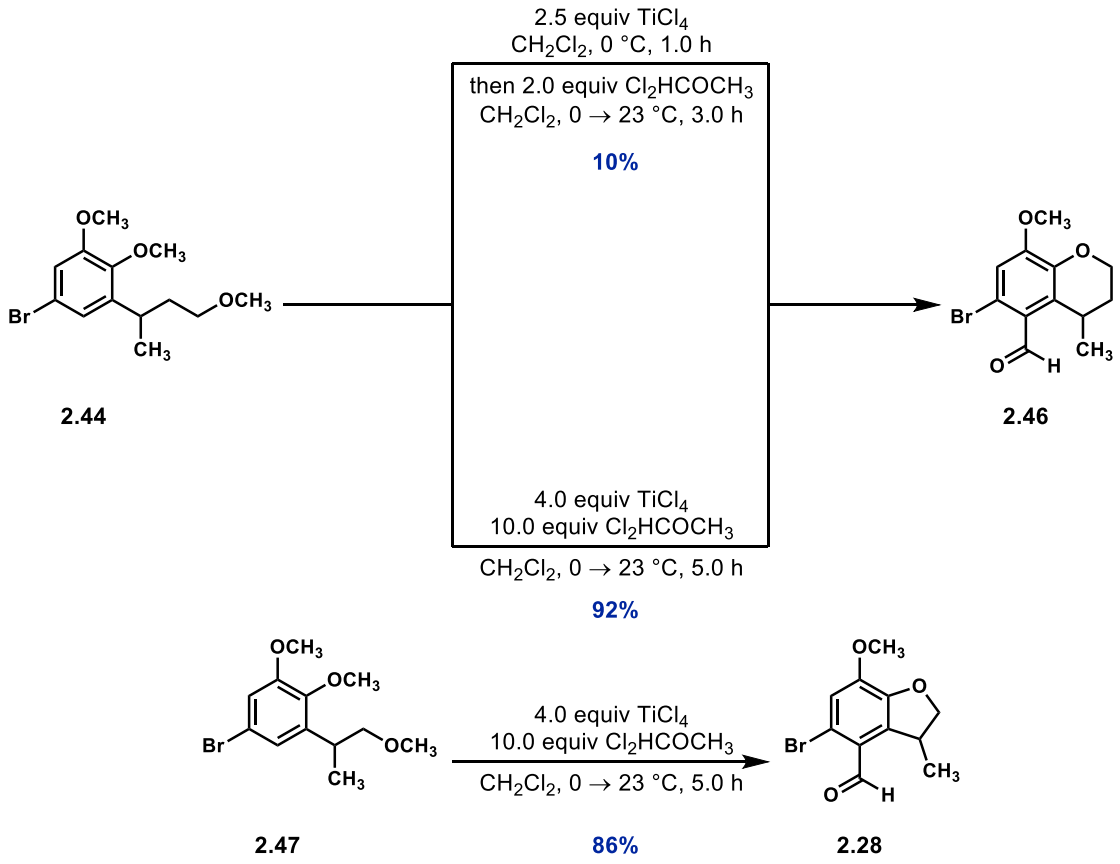

Figure 2.14 Tandem formylation–cyclization reaction

The substrate undergoes a selective aryl methyl ether deprotection, presumably under the action of the Lewis acidic titanium(IV) chloride, followed by a displacement of the alkyl ether in an intramolecular substitution reaction. Complexation or other consumption of the titanium reagent in this manner diminishes the efficiency of the desired formylation. After unsuccessfully searching for conditions to carry out the selective formylation of the aryl bromide, we elected to focus on the tandem formylation–cyclization. Increasing the amount of both titanium(IV) chloride and dichloromethyl methyl ether in addition to modifying the order of addition of each

reagent allowed us to to improve the yield of the tandem reaction significantly, affording **2.46** in 92% overall yield (Figure 2.14). We were also to employ this reaction to synthesize the dihydrobenzofuran system **2.28** in addition to the dihydrobenzopyran **2.46**.

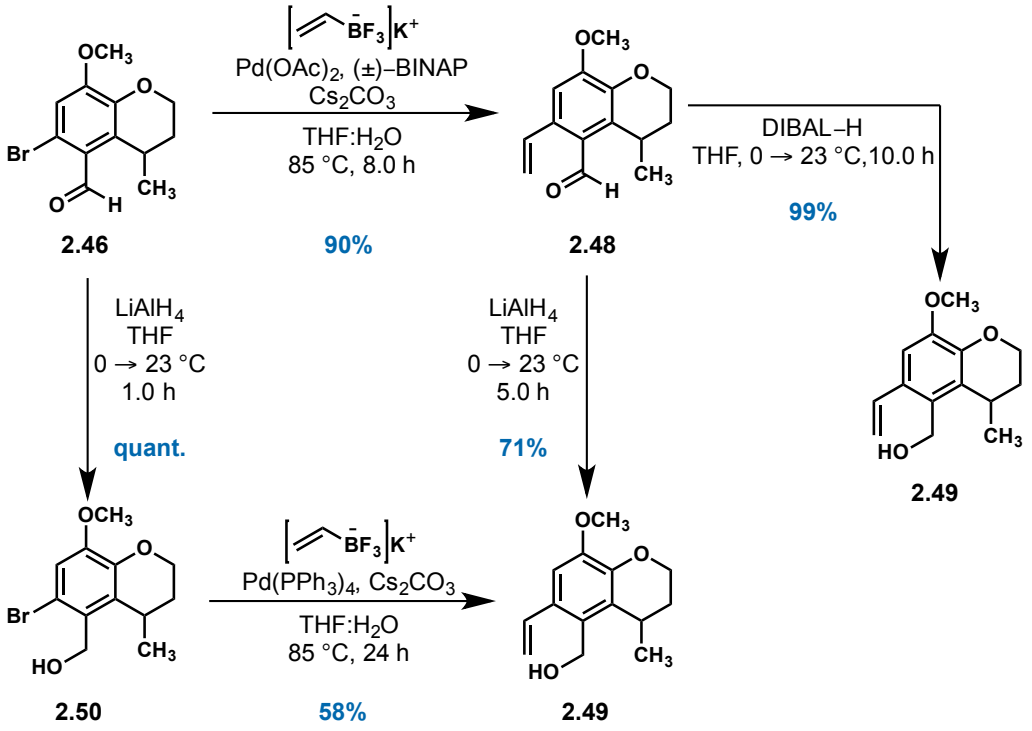

Figure 2.15 Synthesis of pentasubstituted benzene **2.49**

The optimized Suzuki–Miyaura coupling was employed to generate the styrene **2.48**, and subsequent $LiAlH_4$ reduction furnishes **2.49** in a disappointing 71% yield. The reduction reaction routinely returned the starting material **2.48** unchanged after the workup (Figure 2.15). We hypothesized that the steric hindrance around the formyl group with both of *ortho* positions substituted is the cause of the reaction inefficiency.

In order to address this problem, we decided to invert the order of reactions by first completing reduction from **2.46** to give **2.50** followed by a Suzuki reaction to afford **2.49**. In this manner, we were able to solve the diminished yield of the reduction reaction, however this route ultimately compromised the yield of Suzuki reaction. The ultimate solution to this problem was reducing **2.48** under the action of electrophilic DIBAL–H, which afforded **2.49** in high yield (Figure 2.15).

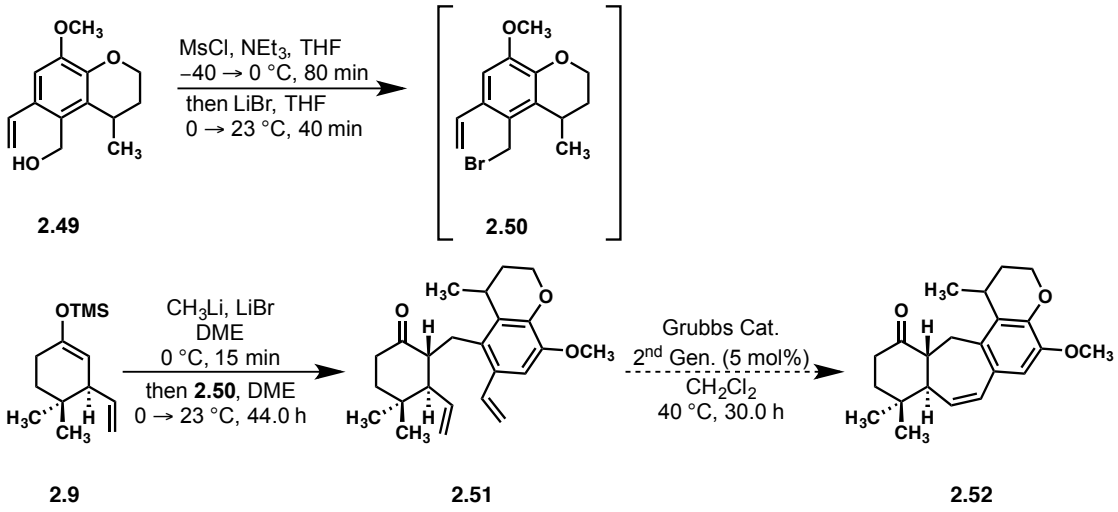

Figure 2.16 Efforts to construct inverted icetexane **2.52**

Unfortunately, the alcohol **2.49** has presented a new challenge in the bromination sequence to access the benzyl bromide **2.50**. We applied the same protocol that we employed for our other substrates and while **2.50** is formed in the reaction mixture, the isolation of **2.50** has proven problematic despite extensive effort. We have noted that the bromide **2.50** undergoes reversion to the alcohol **2.49** by reaction with moisture upon workup or exposure to silica gel or alumina for

chromatographic purification. Efforts to telescope the bromination procedure with the alkylation protocol have also proven inefficient to generate the desired product. That being the case, to date we have not successfully synthesized **2.51** (Figure 2.16).

2.3 Summary

The necessity of finding a new chemotherapeutic treatment for patients suffering from breast cancer and the captivating diverse structures of icetexanes encouraged us to work on developing a new methodology capable of synthesizing different icetexanes. Inspired by the remarkable works of Mr. Daniel J. Moon and Dr. Mohammad Al–Amin in the Chain Laboratory,[5] I worked to develop a small library of inverted icetexanes including **2.19**, **2.34**, **2.42**, and **2.53**.

During this work, we demonstrated the capability of the Richie formylation in generating *para* methoxy benzaldehydes as well as a new tandem formylation–cyclization reaction to synthesize both dihydrobenzofurans and dihydrobenzopyrans.

Experimental Procedures

General Information: These experimental procedures have been published previously in its current or a substantially similar form and I have obtained permission to republish it.[1] All reactions were performed in single-neck oven- or flame-dried round bottom flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless-steel cannula. Organic solutions were concentrated by rotary evaporation at or below 35 °C at 10 Torr (diaphragm vacuum pump) unless otherwise noted. Compounds were isolated using flash column chromatography[2] with silica gel (60-Å pore size, 40–63μm, standard grade, Silicycle). Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25 mm, 60-Å pore size, 5–20 μm, Silicycle) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV), then were stained by submersion in aqueous ceric ammonium molybdate solution (CAM), acidic ethanolic *p*-anisaldehyde solution (anisaldehyde), or aqueous

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[1] (a) Wu, Z.; Suppo, J. S.; Tumova, S.; Strope, J.; Bravo, F.; Moy, M.; Weinstein, E. S.; Peer, C. J.; Figg, W. D.; Chain, W. J.; Echavarren, A. M.; Beech, D. J.; Beutler, J. A., *ACS Med. Chem. Lett.* **2020,** *11*, 1711-1716. (b) Reed, H.; Paul, T. R.; Chain, W. J., *J. Org. Chem.* **2018,** *83*, 11359-11368. (c) Bush, T. S.; Yap, G. P. A.; Chain, W. J., *Org. Lett.* **2018,** *20*, 5406-5409. (d) Lewis, R. S.; Garza, C. J.; Dang, A. T.; Pedro, T. K.; Chain, W. J., *Org. Lett.* **2015,** *17*, 2278-2281. (e) Li, Z.; Nakashige, M.; Chain, W. J., *J. Am. Chem. Soc.* **2011,** *133*, 6553-6556.

[2] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978,** *43,* 2923–2925.

methanolic iron(III) chloride ($FeCl_3$), followed by brief heating on a hot plate (215 °C, 10–15 s).

Materials: Commercial reagents and solvents were used as received with the following exceptions. Triethylamine, dichloromethane, diethyl ether, tetrahydrofuran, and 1,2-dimethoxyethane were purified by the method of Pangborn, et al.[3] 2-Chloropropanoate, 3-methyl-2-butanone, hexamethyldisilazide, and *N,N*-diisopropylamine were distilled from calcium hydride under an atmosphere of argon at 760 Torr. Hexamethylphosphoramide (HMPA) and *N,N*-dimethylformamide (DMF) were distilled from calcium hydride under reduced pressure (0.1 Torr) and stored under argon. The molarity of solutions of $_n$- butyllithium was determined by titration against diphenylacetic acid as an indicator (average of three determinations).[4] Where noted, solvents were deoxygenated before use a minimum of five freeze-pump-thaw cycles.

Instrumentation: Proton (^1H), carbon (^{13}C), fluorine (^{19}F), and silicon (^{29}Si) nuclear magnetic resonance (NMR) spectra were recorded on Bruker AV400 CryoPlatform QNP or Bruker AVIII600 SMART NMR spectrometers at 23 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26, CD_3COCD_2H: δ 2.05). Carbon chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the

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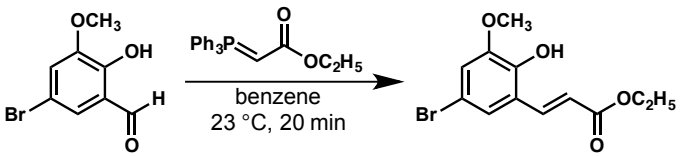
[3] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. Organometallics 1996, 15, 1518–1520.

[4] Kofron, W. G.; Baclawski, L. M. J. Org. Chem. 1976, 41, 1879.

carbon resonance of the NMR solvent ($CDCl_3$: δ 77.16, CD_3COCD_3: δ 29.84). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent), integration, and coupling constant (*J*) in Hertz (Hz). Accurate mass measurements were obtained using an Agilent 1100 quaternary LC system coupled to an Agilent 6210 LC/MSD-TOF fitted with an ESI or an APCI source, or Thermo Q-Exactive Orbitrap using electrospray ionization (ESI) or a Waters GCT Premier spectrometer using chemical ionization (CI).

Synthesis of Conjugated Ester 2.22:



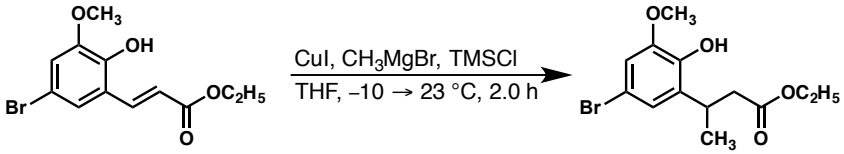
2.21 quant. **2.22**

(Carbethoxymethylene)triphenylphosphorane (6.62 g, 19.0 mmol, 1.10 equiv) was added to a stirred solution of 5–bromo–2–hydroxy–3–methoxybenzaldehyde **2.21** (4.00 g, 17.3 mmol, 1 equiv) in benzene (60.0 mL) under an air atmosphere. The resultant brown mixture was stirred for 20 min at 23 °C whereupon excess phosphorane was quenched by the addition of 1.0 N aqueous hydrochloric acid solution (60.0 mL). The resultant biphasic mixture was extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant oily residue was purified by flash column chromatography (silica gel, 30% ethyl acetate−hexanes) to afford ethyl 5–bromo–2–hydroxy–3–methoxycinnamate **2.22** (5.20 g, 17.3 mmol, quant.) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	7.85 (d, J = 16.1 Hz, 1H), 7.22 (d, J = 2.1 Hz, 1H), 6.95 (d, J = 2.1 Hz, 1H), 6.55 (d, J = 16.1 Hz, 1H), 6.08 (s, 1H), 4.26 (q, J = 7.1 Hz, 2H), 3.91 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	167.2, 147.5, 144.4, 138.0, 123.1, 122.3,

	120.5, 114.9, 111.7, 60.7, 56.6, 14.5.
FTIR (KBr, thin film), cm^{-1}:	3323, 1702, 1630.
HRMS: ES^+ $[M+H]^+$:	Calcd for $C_{12}H_{14}O_4Br$: 301.0070 Found: 301.0070.
TLC:	20% ethyl acetate−hexanes, R_f = 0.24 (UV, CAM, $KMnO_4$).

Synthesis of Phenol 2.23:



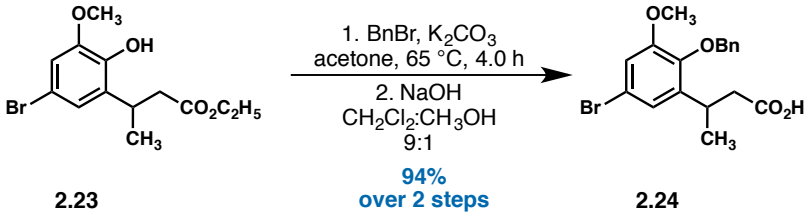
2.22 **83%** **2.23**

Methylmagnesium bromide (3.00 M in Et_2O, 6.80 mL, 6.10 equiv) was added dropwise to a stirred suspension of copper(I) iodide (1.90 g, 10.0 mmol, 3.00 equiv) in THF (15 mL) at −10 °C. The resultant green mixture was stirred at −10 °C for 50 min whereupon a solution of ethyl 5–bromo–2–hydroxy–3–methoxycinnamate 2.22 (1.00 g, 3.32 mmol, 1 equiv) and chlorotrimethylsilane (3.00 mL, 23.2 mmol, 7.0 equiv) in THF (5.00 mL) was added via cannula. The resultant mixture was stirred at –10 °C for 10 min then was warmed to 23 °C and was stirred for 2 h. The reaction mixture was cooled to −10 °C and excess methylmagnesium bromide was quenched by the addition of saturated aqueous ammonium chloride solution (20.0 mL). The resultant biphasic mixture was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant oily residue was purified by flash column chromatography (silica gel, 20% ethyl acetate−hexanes) to afford ethyl–3–(5–bromo–2–hydroxy–3–methoxyphenyl)butanoate **2.23** (0.947 g, 2.99 mmol, 90%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.90 (d, J = 2.2 Hz, 1H), 6.84 (d, J = 2.2 Hz, 1H), 5.79 (s, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.87 (s, 3H), 3.63−3.53 (m, 1H),

	2.68 (dd, J_1 = 15.3 Hz, J_2 = 6.8 Hz, 1H), 2.52 (dd, J_1 = 15.3 Hz, J_2 = 8.1 Hz, 1H), 1.28 (d, J = 7.0 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	172.7, 147.3, 142.4, 133.0, 122.5, 122.2, 111.5, 60.5, 56.4, 14.3.
FTIR (KBr, thin film), cm^{-1}:	3435, 2975, 1730.
HRMS: ES^+ $[M+H]^+$:	Calcd for $C_{13}H_{18}O_4Br$: 317.0383 Found: 317.0380.
TLC:	20% ethyl acetate−hexanes, R_f = 0.36 (UV, CAM, $KMnO_4$).

Synthesis of Carboxylic Acid 2.24:



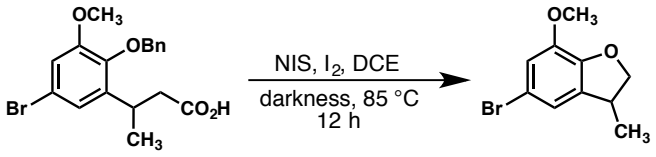
2.23 **2.24**

Benzyl bromide (1.15 mL, 12.0 mmol, 4.01 equiv) was added to a stirred solution of ethyl–3–(5–bromo–2–hydroxy–3–methoxyphenyl)butanoate 2.23 (0.947 g, 2.99 mmol, 1 equiv) and potassium carbonate (1.66 g, 12.0 mmol, 4.02 equiv) in acetone (10 mL). The reaction mixture was heated at 65 °C for 4 h, then was cooled to 23 °C and was quenched by the addition of water (30 mL). The resultant mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant oily residue was purified by flash column chromatography (silica gel, 8% ethyl acetate−hexanes) to afford a pale yellow oil. The pale yellow oil was then dissolved in dichloromethane:methanol (9:1, 9 mL CH_2Cl_2:1 mL CH_3OH) whereupon sodium hydroxide (600 mg, 15.0 mmol, 5.02 equiv) was added and the resultant mixture was heated at reflux for 2 h. The reaction mixture was cooled to 23 °C and was concentrated. The resulting residue was dissolved in water (50 mL) and the resultant solution was cautiously acidified by the addition of 1.0 N aqueous hydrochloric acid solution (final solution pH = 2). The resultant mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant oily residue was purified by

flash column chromatography (silica gel, 40% ethyl acetate−hexanes) to afford 3–(5–bromo–2–hydroxy–3–methoxyphenyl)butanoic acid **2.24** (1.06 g, 2.80 mmol, 94%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	7.50–7.40 (m, 2H), 7.40–7.28 (m, 3H), 6.94 (d, J = 2.3 Hz, 1H), 6.91 (d, J = 2.3 Hz, 1H), 5.01 (app d, J = 2.5 Hz, 2H), 3.87 (s, 3H), 3.72–3.61 (m, 1H), 2.53 (dd, J_1 = 15.9 Hz, J_2 = 6.3 Hz, 1H), 2.44 (dd, J_1 = 15.9 Hz, J_2 = 8.6 Hz, 1H), 1.17 (d, J = 6.9 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	178.6, 153.6, 144.2, 141.3, 137.4, 128.5, 128.2, 121.6, 116.8, 114.0, 74.9, 56.1, 41.4, 29.1, 21.1.

Synthesis of Dihydrobenzofuran 2.20:



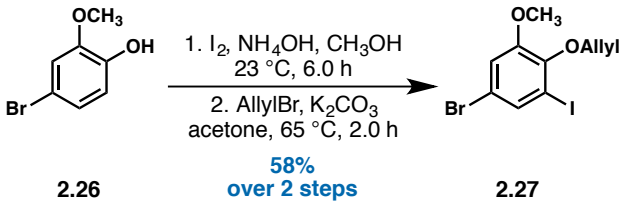
2.24 **27%** **2.20**

N–Iodosuccinimide (1.89 g, 8.40 mmol, 3.00 equiv) and iodine (711 mg, 2.80 mmol, 1.00 equiv) were added to a stirred solution of 3–(5–bromo–2–hydroxy–3–methoxyphenyl)butanoic acid **2.24** (1.06 g, 2.80 mmol, 1 equiv) in dichloromethane (28 mL) protected from light. The resultant mixture was heated at 85 °C and stirred for 12 h. The reaction mixture then was cooled to 23 °C and was quenched by the addition of saturated aqueous sodium thiosulfate solution (20 mL). The resultant biphasic mixture was extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant oily residue was purified by flash column chromatography (silica gel, 15% ethyl acetate−hexanes) to afford 5–bromo–7–methoxy–3–methyl–2,3–dihydrobenzofuran **2.20** (183 mg, 0.75 mmol, 27%) as a pale solid.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	6.96−6.87 (m, 1H), 6.85 (d, J = 1.8 Hz, 1H), 4.73 (t, J = 8.9 Hz, 1H), 4.14 (dd, J_1 = 8.7 Hz, J_2 = 7.5 Hz, 1H), 3.85 (s, 3H), 3.61−3.49 (m, 1H), 1.30 (d, J = 6.9 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	147.3, 145.1, 135.1, 119.2, 114.5, 112.3,

	79.5, 56.3, 32.3, 19.3.
FTIR (KBr, thin film), cm^{-1}:	2963, 2878, 2835.
HRMS: ES^+ $[M+H]^+$:	Calcd for $C_{10}H_{12}O_2Br$: 243.0021. Found: 243.0018.
TLC:	10% ethyl acetate−hexanes, R_f = 0.32 (UV, CAM, $KMnO_4$).

Synthesis of Allyloxybenzene 2.27:

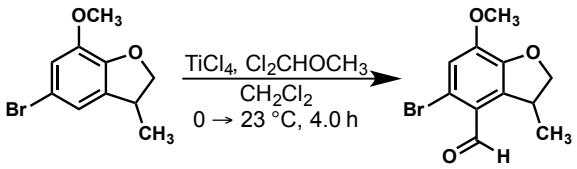


Aqueous solution of ammonium hydroxide (20% w/v, 2.50 mL, 1.43 mmol, 1.43 equiv) was added to a stirred solution of 4−bromo−2−methoxyphenol **2.26** (203 mg, 1.00 mmol, 1 equiv) in methanol (2.50 mL). The resultant colorless solution was stirred for 15 min whereupon a solution of iodine (300 mg, 1.18 mmol, 1.18 equiv) in methanol (2.50 mL) was added dropwise to the reaction solution. The heterogeneous brown mixture was stirred for 6 h and then was quenched by the addition of 1.0 N aqueous hydrochloric acid solution (3.00 mL). The resultant mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was dissolved in acetone (10 mL). Potassium carbonate (80 mg, 0.581 mmol, 1.00 equiv), and allyl bromide (0.06 mL, 0.726 mmol, 1.25 equiv) were added to the resultant brown solution respectively. The resultant solution was heated at reflux for 2 h, then was cooled to 23 °C and quenched by the addition of 1.0 N aqueous hydrochloric acid solution (2.00 mL). The resultant mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (10% ethyl acetate−hexanes) to afford

2−(allyloxy)−5−bromo−1−iodo−3−methoxybenzene **2.27** (214 mg, 0.579 mmol, 58%) as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	7.48 (d, J = 2.1 Hz, 1H), 6.99 (d, J = 2.1 Hz, 1H), 6.19−6.08 (m, 1H), 5.39 (dq, J_1 = 17.2 Hz, J_2 = 1.6 Hz, 1H), 5.25 (dq, J_1 = 10.4 Hz, J_2 = 1.2 Hz, 1H), 4.49 (dt, J_1 = 5.9 Hz, J_2 = 1.3 Hz, 2H), 3.83 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	153.0, 147.3, 133.6, 132.5, 118.6, 117.5, 116.2, 93.6, 74.0, 56.3.
FTIR (KBr, thin film), cm^{-1}:	3080, 1646.
HRMS: ES^+ $[M+H]^+$:	Calcd for $C_{10}H_{11}O_2BrI$: 368.8982. Found: 368.8979.
TLC:	20% ethyl acetate−hexanes, R_f = 0.59 (UV, CAM, $KMnO_4$).

Synthesis of *p*−Methoxy Benzaldehyde 2.28:



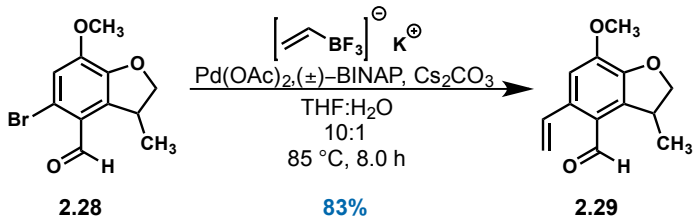
2.20 **72%** **2.28**

Titanium tetrachloride (90.0 µL, 0.819 mmol, 1.99 equiv) was added dropwise to a stirred solution of 5−bromo−7−methoxy−3−methyl−2,3−dihydrobenzofuran **2.20** (100 mg, 0.411 mmol, 1 equiv) in dichloromethane (1.30 mL) at 0 °C. The resultant dark red solution was stirred at 0 °C for 1 h whereupon dichloromethyl methyl ether (70 µL, 0.774 mmol, 1.88 equiv) was added. The resultant solution was warmed up to 23 °C and stirred for 4 h and then was quenched by the addition of 1.0 N aqueous hydrochloric acid solution (1.30 mL) and then the resultant biphasic solution was stirred for 1 h. The resultant mixture was extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 10% ethyl acetate−hexanes) to afford 5−bromo−4−carbaldehyde−7−methoxy−3−methyl−2,3−dihydrobenzofuran **2.28** (80.6 mg, 0.297 mmol, 72%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 10.28 (s, 1H), 6.99 (s, 1H), 4.60 (t, J = 8.5 Hz, 1H), 4.39 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1H), 4.08−3.99 (m, 1H), 3.95 (s, 3H), 1.25 (d, J = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$), δ:	192.2, 149.3, 148.0, 136.5, 122.8, 120.1, 116.0, 80.2, 56.6, 37.5, 20.1.
FTIR (KBr, thin film), cm^{-1}:	2968, 2895, 1686.
HRMS: ES^+ $[M+H]^+$:	Calcd for $C_{10}H_{11}O_2BrI$: 368.8982. Found: 368.8979.
TLC:	15% ethyl acetate−hexanes, R_f = 0.53 (UV, CAM, $KMnO_4$).

Synthesis of Styrene 2.29:



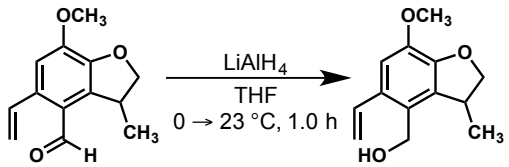
2.28 **83%** **2.29**

A solution of potassium vinyltrifluoroborate (86.0 mg, 0.649 mmol, 1.76 equiv), palladium(II) acetate (8.27 mg, 0.037 mmol, 10.0 mol%), 2,2'−bis(diphenylphosphino)−1,1'−binaphthyl (45.9 mg, 0.0738 mmol, 20.0 mol%), cesium carbonate (361 mg, 1.11 mmol, 3.00 equiv), and 5−bromo−4−carbaldehyde−7−methoxy−3−methyl−2,3−dihydrobenzofuran 2.28 (100 mg, 0.369 mmol, 1 equiv) in tetrahydrofuran:water (10:1, 1.5 mL THF:0.15 mL H_2O) in a 10 mL glass pressure reactor was degassed by bubbling with argon for 15 min. The reactor was sealed and the reaction mixture was heated at 85 °C for 8 h. The reaction mixture was cooled down to 23 °C and quenched by the addition of water (2 mL). The resultant biphasic mixture was extracted with dichloromethane (3 × 5 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant oily residue was purified by flash column chromatography (silica gel, 10% ethyl acetate−hexanes) to afford 4−carbaldehyde−7−methoxy−3−methyl−5−vinyl−2,3−dihydrobenzofuran **2.29** (66.6 mg, 0.305 mmol, 83%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 10.32 (s, 1H), 7.36 (dd, J_1 = 17.2 Hz, J_2 = 10.9 Hz, 1H), 6.85 (s, 1H), 5.54 (dd, J_1 =

	17.2 Hz, J_2 = 1.2 Hz, 1H), 5.44 (dd, J_1 = 10.9 Hz, J_2 = 1.2 Hz, 1H), 4.62 (t, J = 8.4 Hz, 1H), 4.40 (dd, J_1 = 8.6 Hz, J_2 = 2.5 Hz, 1H), 4.02−3.94 (m, 1H), 3.96 (s, 3H), 1.27 (d, J = 6.9 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	190.2, 148.9, 148.1, 137.7, 135.5, 133.6, 122.7, 118.6, 110.0, 80.2, 56.1, 37.4, 20.7.
FTIR (KBr, thin film), cm^{-1}:	1677, 1621.
HRMS: LIFDI$^+$ $[M]^+$:	Calcd for $C_{13}H_{14}O_3$: 218.0943. Found: 218.0951.
TLC:	20% ethyl acetate−hexanes, R_f = 0.43 (UV, CAM, Anis).

Synthesis of Pentasubstituted Benzene 2.30:



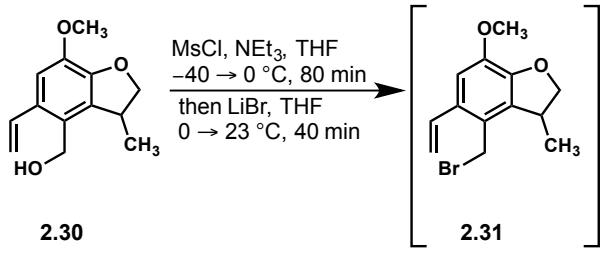
2.29 **95%** **2.30**

A solution of 4−carbaldehyde−7−methoxy−3−methyl−5−vinyl−2,3−dihydrobenzofuran **2.29** (89.9 mg, 0.412 mmol, 1.00 equiv) in tetrahydrofuran (2.00 mL) was transferred to a suspension of lithium aluminum hydride (23.3 mg, 0.614 mmol, 1.50 equiv) in tetrahydrofuran (1.50 mL) at 0 °C through a cannula. The resultant mixture was then warmed up to 23 °C and was stirred for 1 h. The reaction mixture was then cooled down to 0 °C and quenched by slow and careful addition of 1.0 N aqueous hydrochloric acid solution (1.00 mL). The resultant mixture was extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 30% ethyl acetate−hexanes) to afford 4−hydroxymethyl−7−methoxy−3−methyl−5−vinyl−2,3−dihydrobenzofuran **2.30** (85.8 mg, 0.390 mmol, 95%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.04 (dd, J_1 = 17.3 Hz, J_2 = 10.9 Hz, 1H), 6.96 (s, 1H), 5.58 (dd, J_1 = 17.3 Hz, J_2 = 1.2 Hz, 1H), 5.29−5.22 (m, 1H), 4.73−3.59 (m, 3H), 4.30 (dd, J_1 = 8.7 Hz,

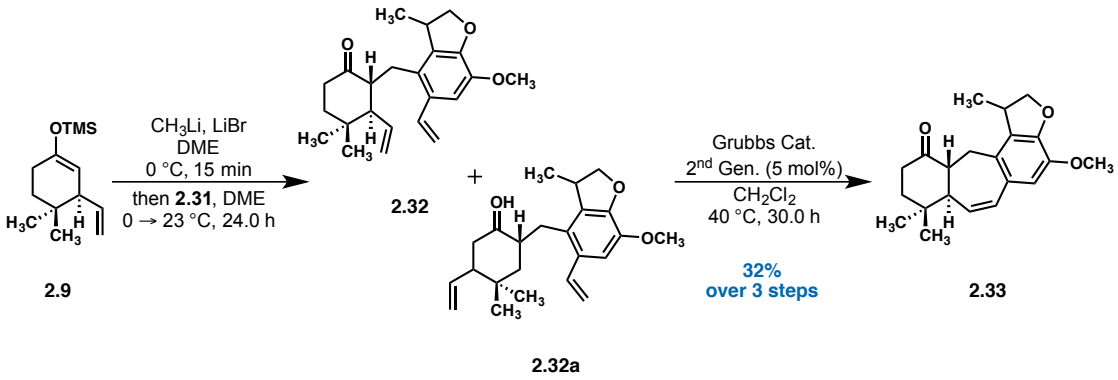
	J_2 = 3.2 Hz, 1H), 3.90 (s, 3H), 3.64−3.53 (m, 1H), 1.59−1.49 (br s, 1H), 1.33 (d, J = 6.9 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	147.6, 144.5, 133.9, 133.3, 131.3, 126.3, 114.6, 109.2, 79.7, 59.2, 56.0, 36.6, 21.5.
FTIR (KBr, thin film), cm^{-1}:	3398, 1605.
HRMS: ES^+ $[M-H_2O+H^+]^+$:	Calcd for $C_{13}H_{15}O_3$: 203.1072. Found: 203.1070.
TLC:	20% ethyl acetate−hexanes, R_f = 0.11 (UV, CAM, Anis).

Synthesis of Inverted Icetexane 2.33:



2.30 **2.31**

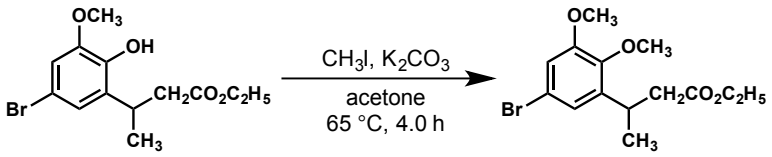
4−hydroxymethyl−7−methoxy−3−methyl−5−vinyl−2,3−dihydrobenzofuran **2.30** (200 mg, 0.91 mmol, 1 equiv) in tetrahydrofuran (6.0 mL) was cooled down to −40 °C. After 15 min triethylamine (0.85 mL, 6.08 mmol, 6.70 equiv) and methanesulfonyl chloride (0.45 mL, 5.81 mmol, 6.40 equiv) were added to the −40 °C solution respectively. After stirring for 50 min in the same temperature, the reaction solution's temperature was raised to 0 °C and was stirred for extra 30 min at 0 °C. A solution of lithium bromide (780 mg, 8.98 mmol, 9.89 equiv) in tetrahydrofuran (6.0 mL) was transferred to the reaction flask through a cannula and then the reaction mixture was stirred at 0 °C for another 10 min. The reaction mixture's temperature then was raised to 23 °C and was stirred for 30 min and then it was quenched by the slow addition of saturated aqueous solution of sodium bicarbonate (10 mL). The resultant mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was passed through a short column of basic alumina to afford 4−bromomethyl−7−methoxy−3−methyl−5−vinyl−2,3−dihydrobenzofuran **2.31**.



Methyllithium (1.60 M in diethyl ether, 0.80 mL, 1.28 mmol, 1.40 equiv) was added to a 0 °C suspension of ((4,4−dimethyl−3−vinylcyclohex−1−en−1−yl)oxy)trimethylsilane (305 mg, 1.36 mmol, 1.50 equiv) and lithium bromide (118 mg, 1.36 mmol, 1.50 equiv) in 1,2−dimethoxyethane (4.0 mL). The resultant heterogeneous yellow mixture was stirred at 0 °C for 10 min, whereupon solution of 4−bromomethyl−7−methoxy−3−methyl−5−vinyl−2,3−dihydrobenzofuran **2.31** from the previous experiment in 1,2−dimethoxyethane (4.0 mL) was added dropwise. The heterogeneous yellow mixture was then slowly warmed to 23 °C and stirred at that temperature for 24 h, then was filtered through a 5.0 cm celite pad. The pad was washed with diethyl ether (20 mL) and the combined filtrates were concentrated. The resultant residue was then purified by flash column chromatography (silica gel, 20% diethyl ether−hexanes) to afford a combined mixture of **2.32** and its structural isomer (149 mg). This mixture was dissolved in dichloromethane (10.0 mL) and then the 2nd generation Grubbs catalyst (18.0 mg, 0.021 mmol, 5 mol%) was added to the solution at 23 °C. The resultant red solution was heated at 45 °C for 30 h, was then cooled to 23 °C and concentrated and the resultant residue was purified by flash column chromatography (silica gel, 5% ethyl acetate−hexanes) to afford **2.33** (95 mg, 0.29 mmol, 32% over 3 steps) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	6.59 (s, 1H), 6.44 (dd, J_1 = 12.7 Hz, J_2 = 2.4 Hz, 1H), 5.72 (dd, J_1 = 12.7 Hz, J_2 = 3.4 Hz, 1H), 4.58 (t, J = 8.4 Hz, 1H), 4.30 (dd, J_1 = 8.7 Hz, J_2 = 2.6 Hz, 1H), 3.85 (s, 3H), 3.60 (br d, J = 14.7 Hz, 1H), 3.53−3.43 (m, 1H), 2.61 (dd, J_1 = 12.7 Hz, J_2 = 8.1 Hz, 1H), 2.54−2.32 (m, 4H), 1.81−1.65 (m, 2H), 1.29 (d, J = 6.9 Hz, 3H), 1.14 (s, 3H), 1.03 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	211.2, 146.6, 142.3, 132.2, 130.9, 129.1, 129.1, 128.9, 114.6, 79.7, 58.0, 56.1, 51.0, 41.2, 38.5, 36.7, 35.1, 29.8, 27.6, 21.2, 20.0.
FTIR (KBr, thin film), cm^{-1}:	2924, 1712, 1596.
HRMS: LIFDI$^+$ $[M]^+$:	Calcd for $C_{21}H_{26}O_3$: 326.1882. Found: 326.1867.
TLC:	20% ethyl acetate−hexanes, R_f = 0.32 (UV, CAM).

Synthesis of Ester 2.35:



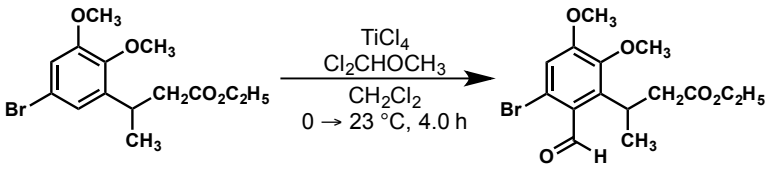
2.23 **89%** **2.35**

Ethyl−3−(5−bromo−2−hydroxy−3−methoxyphenyl)butanoate **2.23** (950 mg, 3.00 mmol, 1 equiv) was dissolved in acetone (5 mL), potassium carbonate (1.24 g, 9.00 mmol, 3.00 equiv) and methyl iodide (0.93 mL, 15.0 mmol, 5.00 equiv) were added to the yellow solution respectively. The resultant solution was warmed up to 65 °C and then was stirred for 4 h and then it was cooled down to 23 °C. The resultant solution then was quenched with the addition of H_2O (25 mL). The resultant mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 15% ethyl acetate−hexanes) to afford ethyl−3−(5−bromo−2,3−dimethoxyphenyl)butanoate **2.35** (884 mg, 2.67 mmol, 89%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.90 (d, J = 2.3 Hz, 1H), 6.89 (d, J = 2.3 Hz, 1H), 4.08 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.69−3.58 (m, 1H), 2.60 (dd, J_1 = 15.3 Hz, J_2 = 6.9 Hz, 1H), 2.50 (dd, J_1 = 15.3 Hz, J_2 = 8.2 Hz, 1H), 1.23 (d, J = 7.0 Hz, 3H), 1.20 (t, J = 7.1

	Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	172.3, 153.6, 145.8, 141.2, 121.8, 116.6, 113.9, 61.0, 60.5, 56.1, 41.6, 29.9, 21.4, 14.3.
FTIR (KBr, thin film), cm^{-1}:	2975, 1734, 1686.
HRMS: ES^+ $[M+H]^+$:	Calcd for $C_{14}H_{20}O_4Br$: 331.0539 Found: 331.0527.

Synthesis of *p*−Methoxy Benzaldehyde 2.36:



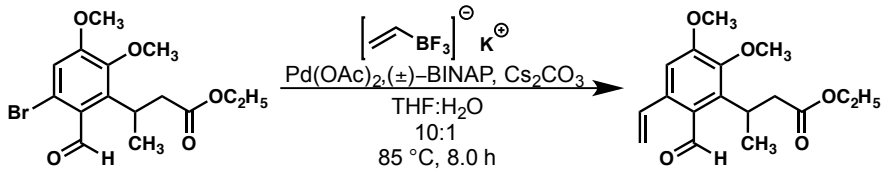
2.35 **85%** **2.36**

Ethyl−3−(5−bromo−2,3−dimethoxyphenyl)butanoate **2.35** (940 mg, 2.84 mmol, 1 equiv) was dissolved in dichloromethane (5.00 mL) and the resultant solution was cooled down to 0 °C. To the resultant solution, titanium tetrachloride (0.800 mL, 7.10 mmol, 2.50 equiv) was added dropwise and was stirred at 0 °C for 1 h. To the dark red solution, dichloromethyl methyl ether (0.51 mL, 5.68 mmol, 2.00 equiv) was added. The resultant solution was warmed up to 23 °C and stirred for 4 h and then was quenched by the addition of 1.0 N aqueous hydrochloric acid solution (10 mL) and was stirred for 1 h. The resultant mixture was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 15% ethyl acetate−hexanes) to afford ethyl−3−(5−bromo−6−carbaldehyde−2,3−dimethoxyphenyl)butanoate **2.36** (866 mg, 2.41 mmol, 85%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 10.34 (s, 1H), 7.04 (s, 1H), 4.30−4.22 (m, 1H), 4.01 (q, J = 7.2 Hz, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 2.87 (dd, J_1 = 15.8 Hz, J_2 = 8.4 Hz, 1H), 2.68 (dd, J_1 = 15.8 Hz,

	J_2 = 6.9 Hz, 1H), 1.35 (d, J = 7.0 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	194.5, 172.86, 156.2, 148.4, 141.5, 127.1, 122.2, 115.5, 60.9, 60.3, 56.2, 40.1, 29.2, 20.0, 14.3.
FTIR (KBr, thin film), cm^{-1}:	2980, 1732, 1693.
HRMS: ES^+ $[M+H]^+$:	Calcd for $C_{15}H_{20}O_5Br$: 359.0489 Found: 359.0474.
TLC:	20% ethyl acetate−hexanes, R_f = 0.40 (UV, CAM, $KMnO_4$).

Synthesis of Styrene 2.37:



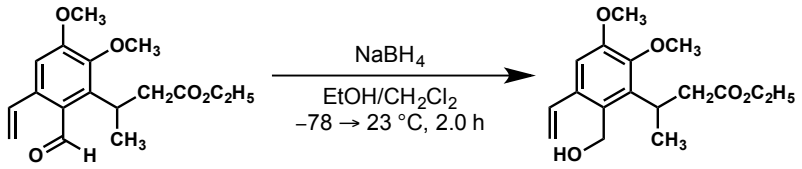
2.36 **93%** **2.37**

A solution of potassium vinyltrifluoroborate (584 mg, 4.41 mmol, 1.76 equiv), palladium(II) acetate (56.2 mg, 0.25 mmol, 10 mol%), 2,2'−bis(diphenylphosphino)−1,1'−binaphthyl (311 mg, 0.50 mmol, 20 mol%), cesium carbonate (2.45 g, 7.54 mmol, 3.00 equiv), and ethyl−3−(5−bromo−6−carbaldehyde−2,3−dimethoxyphenyl)butanoate **2.36** (900 mg, 2.51 mmol, 1 equiv) in tetrahydrofuran:water (10:1, 10 mL THF:1 mL H_2O) in a 50 mL glass pressure reactor was degassed by bubbling with argon for 15 min. The reactor was sealed and the reaction mixture was heated at 85 °C for 8 h. The reaction mixture was cooled down to 23 °C and was quenched by the addition of water (10 mL). The resultant mixture was extracted with dichloromethane (3 × 15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 10% ethyl acetate−hexanes) to afford ethyl−3−(6−carbaldehyde−2,3−dimethoxy−5−vinylphenyl)butanoate **2.37** (715 mg, 2.33 mmol, 93%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 10.49 (s, 1H), 7.15 (dd, J_1 = 17.2 Hz, J_2 = 10.9 Hz, 1H), 6.87 (s, 1H), 5.50 (d, J =

	17.2 Hz, 1H), 5.38 (d, J = 10.9 Hz, 1H), 4.19−4.11 (m, 1H), 4.02 (q, J = 7.1 Hz, 2H), 3.93 (s, 3H), 3.89 (s, 3H), 2.90 (dd, J_1 = 15.8 Hz, J_2 = 7.9 Hz, 1H), 2.76 (dd, J_1 = 15.8 Hz, J_2 = 7.2 Hz, 1H) 1.39 (d, J = 7.0 Hz, 3H), 1.14 (t, J = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	193.5, 172.9, 156.0, 147.9, 140.1, 137.8, 135.6, 127.0, 117.9, 109.7, 60.9, 60.4, 55.8, 40.5, 29.3, 20.3, 14.3.
FTIR (KBr, thin film), cm^{-1}:	2979, 1731, 1703.
HRMS: ES^+ $[M+H]^+$:	Calcd for $C_{17}H_{23}O_5$: 307.1540 Found: 307.1527.
TLC:	20% ethyl acetate−hexanes, R_f = 0.33 (UV, CAM, Anis).

Synthesis of Pentasubstituted Benzene 2.38:



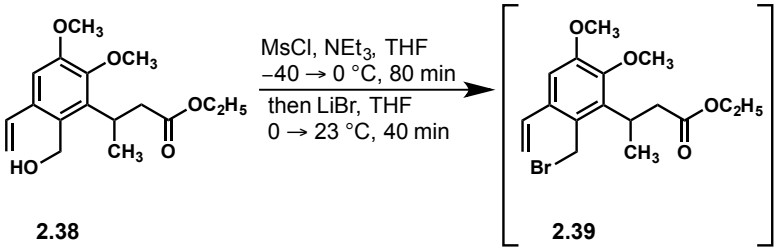
2.37 **76%** **2.38**

Ethyl−3−(6−carbaldehyde −2,3−dimethoxy−5−vinylphenyl)butanoate **2.37** (715 mg, 2.33 mmol, 1 equiv) was dissolved in ethanol:dichloromethane (1:1, 5 mL EtOH:5 mL CH_2Cl_2) and then the resultant solution was cooled down to −78 °C. Sodium borohydride (132 mg, 3.49 mmol, 1.5 equiv) was added to the reaction mixture under air. The reaction mixture was then warmed up to 23 °C and then was stirred at that temperature and under air for 2 h. The reaction solution then was quenched by the slow addition of 1.0 N aqueous hydrochloric acid solution (10 mL). The resultant biphasic mixture was extracted with dichloromethane (3 × 15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 20% ethyl acetate−hexanes) to afford ethyl−3−(6−hydroxymethyl−2,3−dimethoxy−5−vinylphenyl)butanoate **2.38** (546 mg, 1.77 mmol, 76%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.16 (dd, J_1 = 17.3 Hz, J_2 = 10.9 Hz, 1H), 6.92 (s, 1H), 5.57 (dd, J_1 = 17.3 Hz, J_2 = 1.4 Hz, 1H), 5.31 (dd, J_1 = 10.9 Hz, J_2 = 1.4 Hz, 1H), 4.76−4.58 (m, 2H),

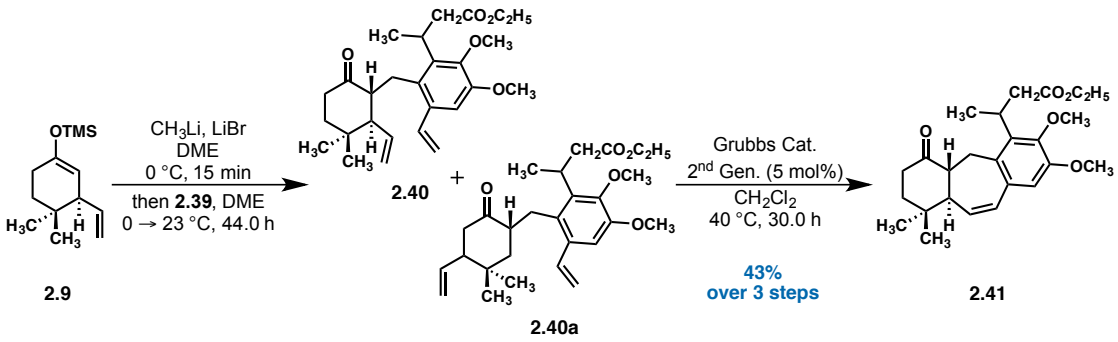
	4.06−3.92 (m, 1H), 3.90−3.78(m, 7H), 3.74−3.61 (m, 1H), 2.26 (dd, J_1 = 17.2 Hz, J_2 = 4.4 Hz, 1H), 1.36 (d, J = 7.1 Hz, 3H) 1.10 (t, J = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	174.6, 152.4, 148.0, 136.7, 135.7, 134.3, 129.3, 116.2, 111.68, 109.0, 60.8, 60.7, 58.6, 55.6, 39.7, 30.7, 20.5, 14.1.
HRMS: ES^+ $[M+H]^+$:	Calcd for $C_{17}H_{25}O_5$: 309.1697 Found: 309.1696.
TLC:	20% ethyl acetate−hexanes, R_f = 0.26 (UV, CAM, Anis).

Synthesis of Inverted Icetexane 2.41:



2.38 **2.39**

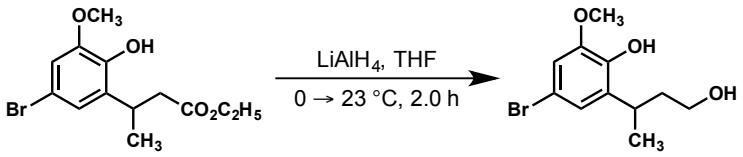
A solution of ethyl−3−(6−hydroxymethyl−2,3−dimethoxy−5−vinylphenyl)butanoate **2.38** (200 mg, 0.65 mmol, 1 equiv) in tetrahydrofuran (5.0 mL) was cooled down to −40 °C. After 15 min triethylamine (0.61 mL, 4.35 mmol, 6.70 equiv) and methanesulfonyl chloride (0.32 mL, 4.16 mmol, 6.40 equiv) were added to the −40 °C solution respectively. After stirring for 50 min in the same temperature, the reaction solution's temperature was raised to 0 °C and was stirred for extra 30 min at 0 °C. A solution of lithium bromide (559 mg, 6.43 mmol, 9.89 equiv) in tetrahydrofuran (5.0 mL) was transferred to the reaction flask through a cannula and then the reaction mixture was stirred at 0 °C for another 10 min. The reaction mixture's temperature then was raised to 23 °C and was stirred for 30 min and then it was quenched by the slow addition of saturated aqueous solution of sodium bicarbonate (8 mL). The resultant mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was passed through a short column of basic alumina to afford ethyl−3−(6−bromomethyl−2,3−dimethoxy−5−vinylphenyl)butanoate **2.39**.



Methyllithium (1.60 M in diethyl ether, 0.57 mL, 0.91 mmol, 1.40 equiv) was added to a 0 °C suspension of ((4,4−dimethyl−3−vinylcyclohex−1−en−1−yl)oxy)trimethylsilane (305 mg, 1.36 mmol, 1.50 equiv) and lithium bromide (85 mg, 0.98 mmol, 1.50 equiv) in 1,2−dimethoxyethane (3.0 mL). The resultant heterogeneous yellow mixture was stirred at 0 °C for 10 min, whereupon solution of ethyl−3−(6−bromomethyl−2,3−dimethoxy−5−vinylphenyl)butanoate **2.39** from the previous experiment in 1,2−dimethoxyethane (3.0 mL) was added dropwise. The heterogeneous yellow mixture was then slowly warmed to 23 °C and stirred at that temperature for 24 h, then was filtered through a 5.0 cm celite pad. The pad was washed with diethyl ether (20 mL) and the combined filtrates were concentrated. The resultant residue was then purified by flash column chromatography (silica gel, 20% diethyl ether−hexanes) to afford a combined mixture of **2.40** and its structural isomer **2.40a** (165 mg). This mixture was dissolved in dichloromethane (7.0 mL) and then the 2nd generation Grubbs catalyst (16.3 mg, 0.019 mmol, 5 mol%) was added to the solution at 23 °C. The resultant red solution was heated at 45 °C for 30 h, was then cooled to 23 °C and concentrated and the resultant residue was purified by flash column chromatography (silica gel, 5% ethyl acetate−hexanes) to afford **2.41** (116 mg, 0.28 mmol, 43% over 3 steps) as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	6.62−6.57 (m, 1H), 6.52−6.42 (m, 1H), 5.92−5.81 (m, 1H), 4.17−3.76 (m, 11H), 2.89−2.58 (m, 4H), 2.51−2.40 (m, 1H), 2.37−2.28 (m, 2H), 1.75−1.59 (m, 2H), 1.38−1.32 (m, 2H), 1.17−1.02 (m, 9H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	210.7, 173.1, 150.5, 132.6, 132.5, 131.6, 130.8, 130.8, 60.8, 60.0, 59.9, 55.7, 55.7, 41.2, 40.4, 38.4, 38.4, 29.7, 29.7, 29.5, 27.0, 22.9, 22.8, 20.4, 20.0, 14.3, 14.2.
HRMS: ES^+ $[M+H]^+$:	Calcd for $C_{25}H_{35}O_5$: 415.2479 Found: 415.2484.

Synthesis of Di–hydroxylated Compound 2.43:



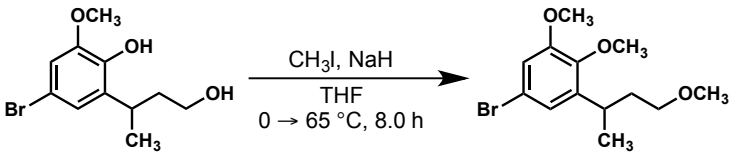
2.23 quant. **2.43**

Lithium aluminum hydride (180 mg, 4.73 mmol, 1.50 equiv), was dissolved in tetrahydrofuran (10 mL) at 0 °C then a solution of ethyl–3–(5–bromo–2–hydroxy–3–methoxyphenyl)butanoate **2.23** (1.00 g, 3.15 mmol, 1 equiv) in tetrahydrofuran (20.0 mL) was transferred to the reaction flask through a cannula. The reaction mixture was warmed up to 23 °C and was stirred for 2 h. The reaction mixture was then cooled down to 0 °C and quenched by slow and careful addition of 1.0 N aqueous hydrochloric acid solution (10 mL). The resultant mixture was extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 30% ethyl acetate−hexanes) to afford (5–bromo–2–hydroxy–3–methoxyphenyl)butanol **2.43** (867 mg, 3.15 mmol, quant.) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.92 (d, J = 2.2 Hz, 1H), 6.84 (d, J = 2.2 Hz, 1H), 5.92 (br s, 1H), 3.88 (s, 3H), 3.60−3.53 (m, 1H), 3.45−3.31 (m, 2H), 1.92 (dt, J_1 = 9.2 Hz, J_2 = 5.5 Hz, 1H), 1.69−1.58 (m, 1H), 1.27 (d, J = 7.02 Hz,

	1H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	147.0, 142.2, 133.7, 122.1, 112.1, 111.9, 60.9, 56.4, 40.7, 27.9, 20.9.
FTIR (KBr, thin film), cm^{-1}:	3368, 2961.
HRMS: ES^+ $[M+H]^+$:	Calcd for $C_{11}H_{16}O_3Br$: 275.0277 Found: 275.0273.
TLC:	20% ethyl acetate−hexanes, R_f = 0.10 (UV, CAM).

Synthesis of Compound 2.44:



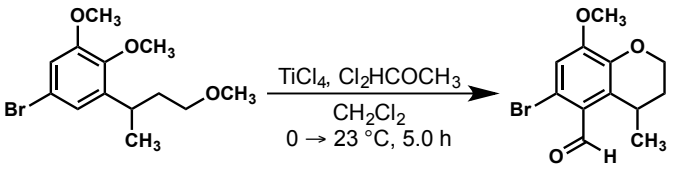
2.43 **90%** **2.44**

Sodium hydride (60% in mineral oil, 189 mg, 4.73 mmol, 1.50 equiv), was dissolved in tetrahydrofuran (5 mL) at 0 °C then a solution of (5–bromo–2–hydroxy–3–methoxyphenyl)butanol **2.43** (867 mg, 3.15 mmol, 1 equiv) in tetrahydrofuran (25.0 mL) was transferred to the reaction flask through a cannula. The reaction mixture was warmed up to 65 °C and was stirred for 8 h. The reaction mixture was then cooled down to 0 °C and quenched by slow and careful addition of 1.0 N aqueous hydrochloric acid solution (15 mL). The resultant mixture was extracted with diethyl ether (3 × 25 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 5% ethyl acetate−hexanes) to afford (5–bromo–2,3–dimethoxyphenyl)butyl methyl ether **2.44** (860 mg, 2.84 mmol, 90%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	6.91 (d, J = 2.2 Hz, 1H), 6.87 (d, J = 2.2 Hz, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 3.39−3.16 (m, 3H), 3.27 (s, 3H), 1.82 (q, J = 6.9 Hz, 2H), 1.19 (d, J = 7.0 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	153.5, 146.0, 142.5, 121.9, 116.7, 113.4,

	71.0, 61.0, 58.7, 56.0, 37.1, 29.1, 22.2.
FTIR (KBr, thin film), cm^{-1}:	2922, 1681.
HRMS: ES^+ $[M+H]^+$:	Calcd for $C_{13}H_{20}O_3Br$: 303.0590 Found: 303.0587.
TLC:	20% ethyl acetate−hexanes, R_f= 0.50 (UV, CAM).

Synthesis of Dihydrobenzopyran 2.46:



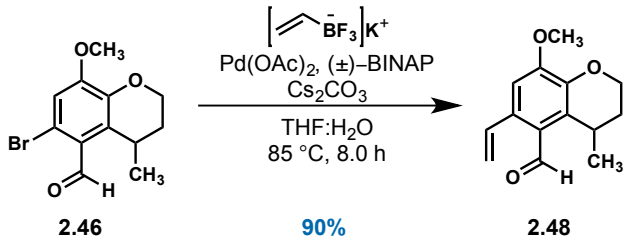
2.44 **92%** **2.46**

(5–bromo–2,3–dimethoxyphenyl)butyl methyl ether **2.44** (500 mg, 1.65 mmol, 1 equiv) was dissolved in dichloromethane (10.0 mL) and was cooled down to 0 °C. To the resultant solution, titanium tetrachloride (0.73 mL, 6.60 mmol, 4.00 equiv) and dichloromethyl methyl ether (1.50 mL, 16.5 mmol, 10.0 equiv) were added dropwise and then the dark red solution was warmed up to 23 °C and stirred for 5 h and then was quenched by the addition of 1.0 N aqueous hydrochloric acid solution (15.0 mL) and then the resultant biphasic solution was stirred for 1 h. The resultant mixture was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (basic alumina, 5% ethyl acetate−hexanes) to afford 6−bromo−5−carbaldehyde−8−methoxy−4−methyl−3,4−dihydrobenzopyran **2.46** (433 mg, 1.52 mmol, 92%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 10.38 (s, 1H), 7.00 (s, 1H), 4.45−4.39 (m, 1H), 4.28 (ddd, J_1 = 13.0 Hz, J_2 = 10.9 Hz, J_3 = 2.5 Hz, 1H), 4.02−3.88 (m, 1H), 3.94 (s, 3H), 2.04 (tt, J_1 = 13.5 Hz, J_2 =

	4.8 Hz, 1H), 1.74 (dq, J_1 = 14.0 Hz, J_2 = 2.4 Hz, 1H), 1.28 (d, J = 6.8 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	193.9, 153.0, 143.1, 131.5, 123.3, 122.5, 114.2, 62.4, 56.5, 27.9, 24.7, 22.6.
FTIR (KBr, thin film), cm^{-1}:	2922, 1681.
HRMS: ES^+ $[M+H]^+$:	Calcd for $C_{12}H_{14}O_3Br$: 285.0121 Found: 285.0119.
TLC:	20% ethyl acetate−hexanes, R_f = 0.36 (UV, CAM).

Synthesis of Styrene 2.48:



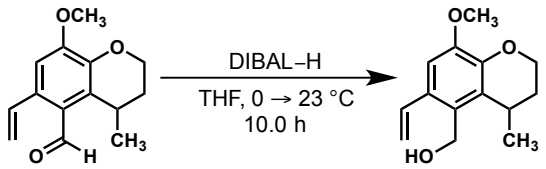
2.46 **90%** **2.48**

A solution of potassium vinyltrifluoroborate (355 mg, 2.68 mmol, 1.76 equiv), palladium(II) acetate (33.7 mg, 0.15 mmol, 10 mol%), 2,2'−bis(diphenylphosphino)−1,1'−binaphthyl (187 mg, 0.30 mmol, 20 mol%), cesium carbonate (1.48 g, 4.56 mmol, 3.00 equiv), and 6−bromo−5−carbaldehyde−8−methoxy−4−methyl−3,4−dihydrobenzopyran **2.46** (433 mg, 1.52 mmol, 1 equiv)in tetrahydrofuran:water (10:1, 7 mL THF:0.7 mL H_2O) in a 15 mL glass pressure reactor was degassed by bubbling with argon for 15 min. The reactor was sealed and the reaction mixture was heated at 85 °C for 8 h. The reaction mixture was cooled down to 23 °C and was quenched by the addition of water (10 mL). The resultant mixture was extracted with dichloromethane (3 × 15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 10% ethyl acetate−hexanes) to afford 5−carbaldehyde−8−methoxy−4−methyl−6−vinyl−3,4−dihydrobenzopyran **2.48** (318 mg, 1.37 mmol, 90%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 10.41 (s, 1H), 7.30 (dd, J_1 = 17.3 Hz, J_2 = 10.9 Hz, 1H), 6.82 (s, 1H), 5.50 (dd, J_1 =

	17.3 Hz, J_2 = 1.3 Hz, 1H), 5.43 (dd, J_1 = 10.9 Hz, J_2 = 1.3 Hz, 1H), 4.47−4.40 (m, 1H), 4.30 (ddd, J_1 = 12.9 Hz, J_2 = 11.0 Hz, J_3 = 2.5 Hz, 1H), 3.96 (s, 3H), 3.89−3.77 (m, 1H), 2.12 (tt, J_1 = 13.3 Hz, J_2 = 4.8 Hz, 1H), 1.77 (dq, J_1 = 14.0 Hz, J_2 = 2.4 Hz, 1H), 1.34 (d, J = 6.9 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	191.9, 152.6, 143.0, 137.2, 135.2, 129.8, 123.9, 118.4, 108.3, 62.2, 56.1, 28.3, 24.8, 23.4.
FTIR (KBr, thin film), cm^{-1}:	2963, 1678.
HRMS: ES^+ $[M+H]^+$:	Calcd for $C_{14}H_{17}O_3$: 233.1172 Found: 233.1171.
TLC:	20% ethyl acetate−hexanes, R_f = 0.26 (UV, CAM, Anis).

Synthesis of Pentasubstituted Benzene 2.49:



2.48 **99%** **2.49**

5−carbaldehyde−8−methoxy−4−methyl−6−vinyl−3,4−dihydrobenzopyran **2.48** (318 mg, 1.37 mmol, 1 equiv) was dissolved in tetrahydrofuran (15 mL), then the resultant reaction solution was cooled down to 0 °C. A solution of diisobutylaluminium hydride (1.00 M in hexanes, 2.10 mL, 2.10 mmol, 1.53 equiv) was added slowly to the reaction solution. The resultant pale yellow solution was warmed up to 23 °C and was stirred for 10 h. The reaction solution then was quenched by the addition of 1.0 N aqueous hydrochloric acid solution (10.0 mL). The resultant mixture was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 20% ethyl acetate−hexanes) to afford 5−hydroxymethyl−8−methoxy−4−methyl−6−vinyl−3,4−dihydrobenzopyran **2.49** (318 mg, 1.36 mmol, 99%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.12 (dd, J_1 = 17.3 Hz, J_2 = 10.9 Hz, 1H), 6.93 (s, 1H), 5.59 (dd, J_1 = 17.3 Hz, J_2 = 1.3 Hz, 1H), 5.29 (dd, J_1 = 10.9 Hz, J_2 = 1.3 Hz), 4.74 (app d, J = 2.3 Hz, 2H),

	4.45−4.39 (m, 1H), 4.26 (ddd, J_1 = 13.2 Hz, J_2 = 11.0 Hz, J_3 = 2.4 Hz, 1H), 3.90 (s, 3H), 3.32−3.22 (m, 1H), 2.12 (tt, J_1 = 13.6 Hz, J_2 = 4.8 Hz, 1H), 1.77 (dq, J_1 = 13.8 Hz, J_2 = 2.2 Hz, 1H), 1.34 (d, J = 7.0 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	148.5, 143.4, 134.5, 130.1, 128.3, 126.8, 115.2, 106.9, 61.7, 57.5, 55.9, 28.6, 25.3, 23.3.
FTIR (KBr, thin film), cm^{-1}:	2963, 1678.
HRMS: ES^+ $[M+H]^+$:	Calcd for $C_{14}H_{19}O_3$: 235.1329 Found: 235.1331.

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Chapter 3

PREMNALATIFOLIN A: EFFORTS TOWARD THE SYNTHESIS OF NEW ICETEXANES

3.1 Introduction: Prior Efforts Toward a Model System for Premnalatifolin A

Premnalatifolin A **3.1** was first discovered in 2011 by Babu and co–workers from the hexane extract of the dry stem–bark of *Premna latifolia*, a plant familiar to traditional medicine systems of India (Figure 3.1).[1] It is a heterodimeric icetexane, and is especially interesting as it is the only example of such a dimer with the monomeric units joined through a C–O–C diaryl ether bond linkage. Additionally, Babu and his group discovered three monomeric icetexanes that are structurally related to the northern monomer of premnalatifolin A **3.1**—latifolionol **3.2**, dihydrolatifolionol **3.3**, and latiferanol **3.4** (Figure 3.1).[2]

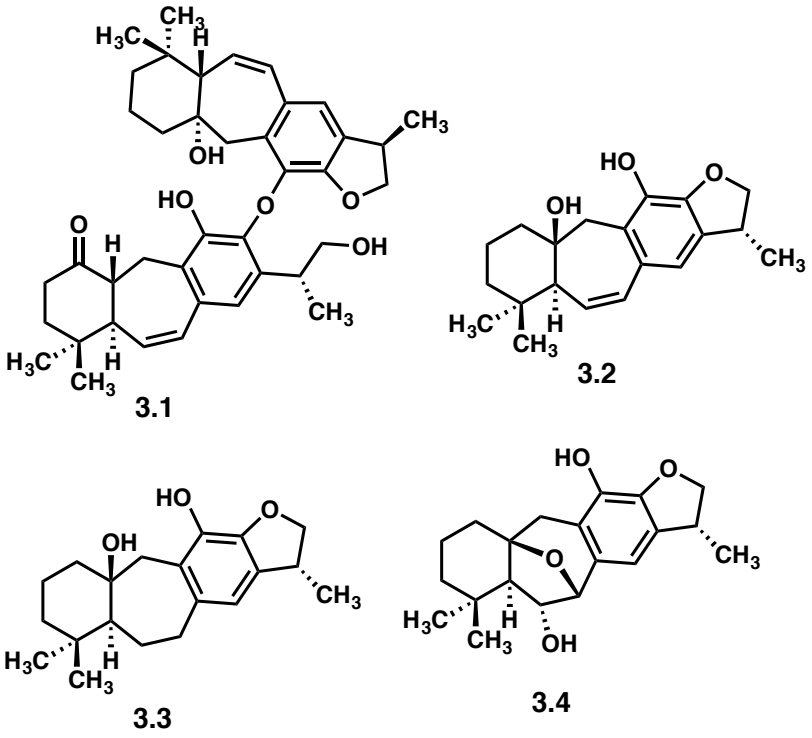


Figure 3.1 Icetexanes **3.1** to **3.4** from *Premna latifolia*

All four of these icetexanes were evaluated for their cytotoxicity against eight different cancer cell lines. Premnalatifolin A **3.1** was shown to have growth inhibitory effects toward both MCF–7 (breast) and HT–29 (colon) cancer cell lines with IC_{50} values of 1.77 μM and 19.4 μM, respectively. Latifolionol **3.2** (the northern monomer of premnalatifolin A **3.1**) also showed cytotoxic against the same cancer cell lines (MCF–7, IC_{50} = 3.53 μM and HT–29, IC_{50} = 127 nM).[3.52]**Error! Bookmark not defined.**

The current standard of care for chemotherapuetic intervention in patients who suffer from breast cancer is doxorubicin, commercially branded as Adriamycin®, with IC_{50} = 3.70 μM against MCF–7 cancer cell lines. The mechanism of action of

doxorubicin in the context of cancer treatment is not perfectly understood,[3] and moreover doxorubicin is notorious for its destructive side effects and high mortality rate, hence the unfortunate nickname "the red death".[4] As a result, there is an immediate need for new chemotherapeutics for the treatment of patients suffering from breast cancer. Results of *in vitro* cytotoxicity screening of premnalatifolin A **3.1** show it to be a promising new lead compound for the treatment of human cancers.

Both the northern and the southern monomers (**3.2** and **3.5** respectively) of premnalatifolin A **3.1** are barbatusol type icetexanes with one key difference in their oxidation pattern. The northern monomer **3.2** is oxygenated at C(10) with the southern monomer **3.5** bearing a carbonyl group at C(1). Our goal has been the development of a synthetic route toward the southern monomer **3.5** and then adjustment of the oxidation pattern to generate **3.2** (Figure 3.2).[5]

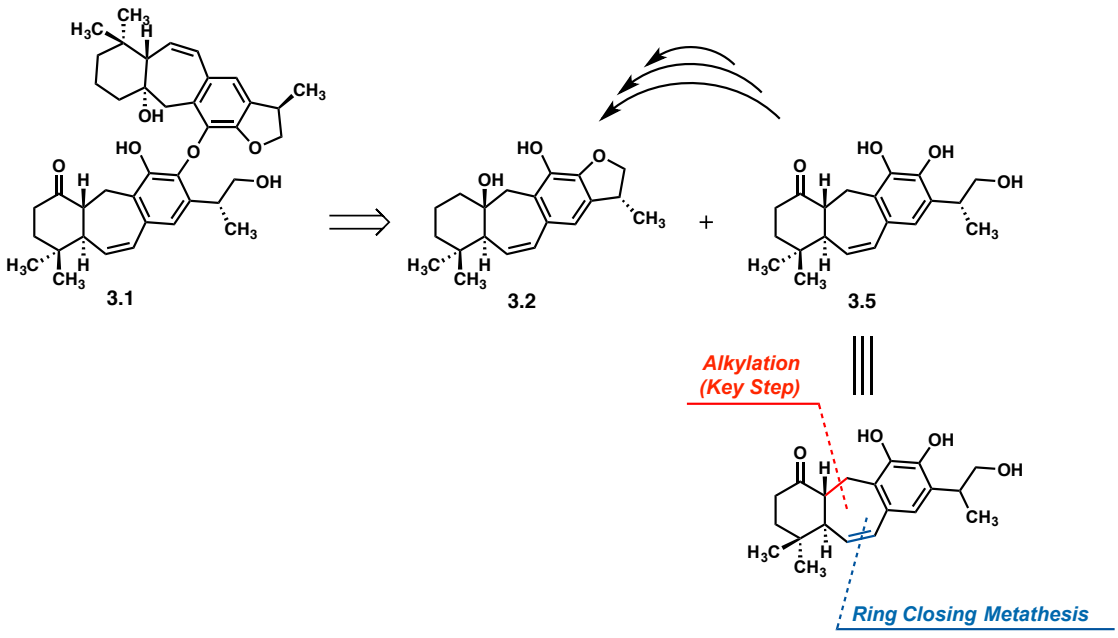


Figure 3.2 Retrosynthetic analysis of premnalatifolin A **3.1**

3.2 Synthesis of Icetexane Analog Structures

In the previous chapter, I described our method for constructing the core structure of icetexanes and our efforts toward the synthesis of a library of inverted icetexanes. In the current chapter, I first describe our efforts toward the synthesis of a library that includes conventional unnatural icetexane analogs—diol **3.7** ([3.2.1]) and dihydrobenzopyran **3.14** (part [3.2.2]).

Next we focus on our journey to find a formylation reaction well–suited to our needs to finish the synthesis of premnalatifolin A (part [3.3.1]).

At the conclusion of this chapter we discuss our efforts toward the synthesis of southern monomer (part [3.3.2] &[3.3.3]) and the northern monomer of premnalatifolin A (part [0]).

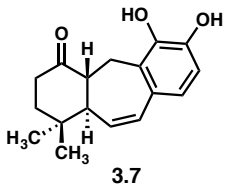
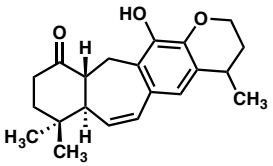
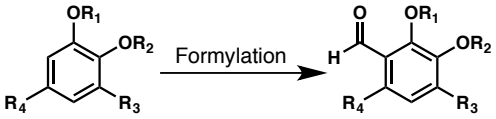
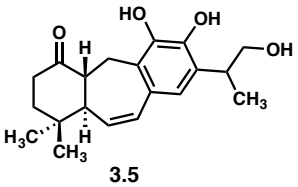
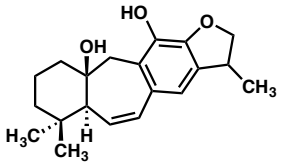
Goal	Chapter	Scheme
Synthesis of conventional unnatural icetexane 3.7	3.2.1	 3.7
Synthesis of conventional unnatural icetexane 3.14	3.2.2	 3.14
Formylation Reaction	3.3.1	
Synthesis of southern monomer of premnalatifolin A 3.5	3.3.2 & 3.3.3	 3.5
Synthesis of northern monomer of premnalatifolin A 3.2	3.4	 3.2

Table 3.1 Summary of challenges faced in chapter 3

3.2.1 Synthesis of Icetexane 3.7

In previous work, the Chain group completed the synthesis of **3.6** as a model system and explored the bioactivity of simplified icetexanes scaffolds,[5] and thus we embarked upon the syntheses of more complex unnatural analogs and natural icetexanes beginning with the diol **3.7** (Figure 3.3). The diol **3.7** was identified as a

simple means of increasing the water solubility of new analogs, which was a major liability in simplified scaffolds.[5]

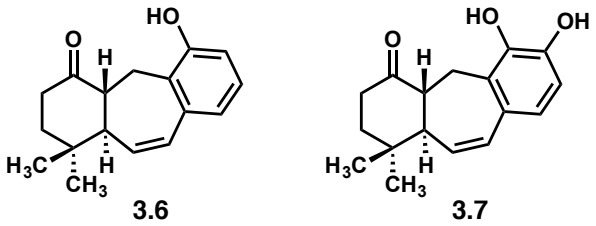


Figure 3.3 Structure of icetexanes **3.6** and **3.7**

The synthesis of the tetrasubstituted aromatic **3.9** from 2,3–dihydroxybenzaldehyde has been previously described.[6] Building on this work, a Suzuki–Miyaura coupling was employed to convert **3.9** to the styrene **3.10** under wet conditions (Figure 3.4).[7]

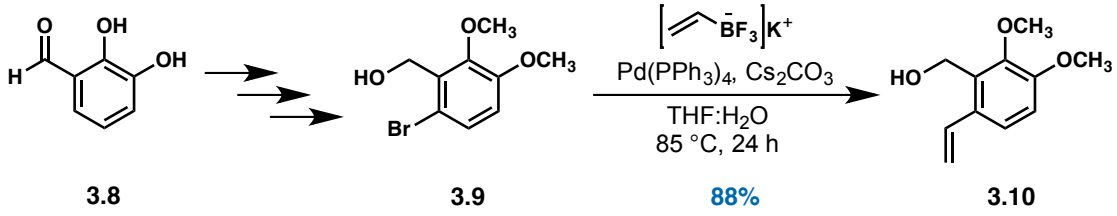


Figure 3.4 Synthesizing of the styrene **3.10**

Conversion of the hydroxyl group of the benzyl alcohol **3.10** to the corresponding bromide was completed employing the optimized one–pot, two–step protocol described in chapter 2. Following that operation, the LiBr–doped alkylation

protocol was employed to generate the desired adduct **3.12**. As in our previous work, the final ring closing metathesis reaction smoothly afforded the icetexane **3.13** (Figure 3.5).

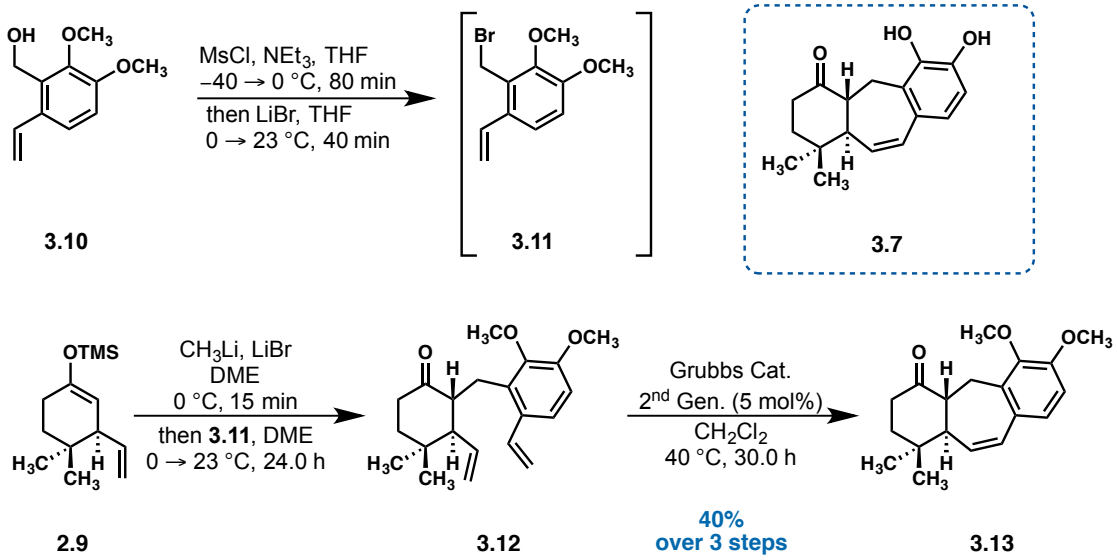


Figure 3.5 Constructing the central seven–membered ring of icetexane **3.7**

Conversion of the hydroxyl group of the benzyl alcohol **3.10** to the corresponding bromide was completed employing the optimized one–pot, two–step protocol described in chapter 2. Following that operation, the LiBr–doped alkylation protocol was employed to generate the desired adduct **3.12**. As in our previous work, the final ring closing metathesis reaction smoothly afforded the icetexane **3.13** (Figure 3.5).

3.2.2 Synthesis of icetexane 3.14

During our efforts to generate the southern monomer of premnalatifolin A **3.5** (Figure 3.6), we discovered a pathway to access the dihydropyran icetexane analog **3.14** (see Figure 3.9). The plan was to employ a [3,3]–sigmatropic rearrangement (Claisen) to produce the pentasubstituted aromatic **3.17** from the crotyl phenyl ether **3.16** (Figure 3.6).

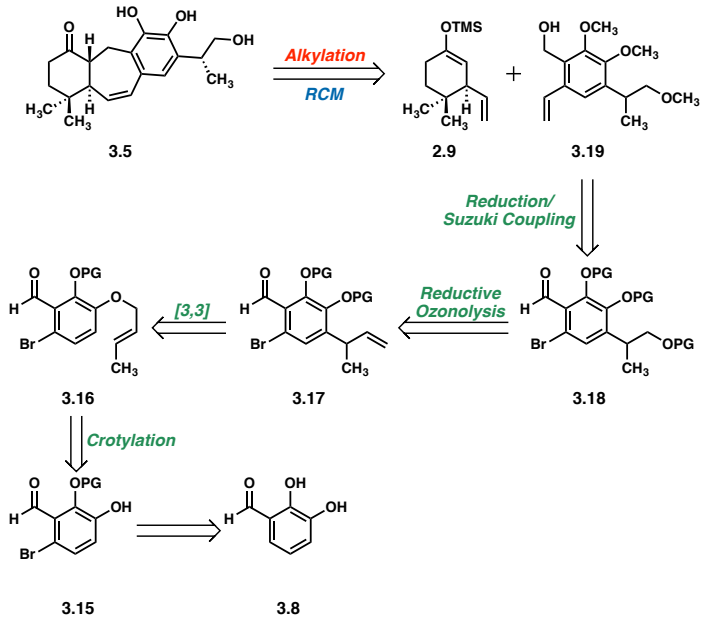


Figure 3.6 Proposed retrosynthetic synthesis of southern monomer of Premnalatifolin A

The synthesis of the tetrasubstituted aromatic **3.15** from 2,3–dihydroxybenzaldehyde has been previously described (Figure 3.7).[8]

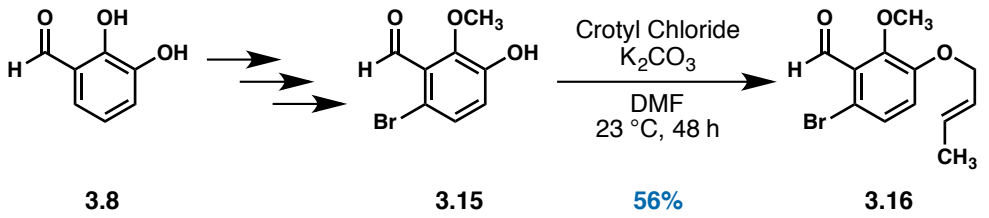
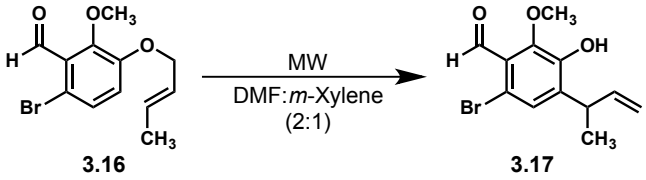


Figure 3.7 Synthesis of the crotyl phenyl ether **3.16**

Building upon this work, the crotyl phenyl ether **3.16** was generated in 56% yield by straightforward alkylation with crotyl chloride, whereupon the ether underwent the [3,3]–sigmatropic rearrangement,[9] the results of which are summarized below in Figure 3.8. The optimized yield for this transformation in our hands was 35% (entry 3) and was only achievable in small scale reactions. As a result, this pathway was abandoned for the synthesis of premnalatifolin A but was utilized for production of the icetexane analog **3.14** (Figure 3.10).



	Temperature (°C)	Time (h)	Scale (mmol)	Result
1	220	2.0	0.35	**Decomposed**
2	140	2.0	0.35	**RSM**
3	180	2.0	0.35	**35%**
4	180	3.0	0.35	**21%**
5	180	4.0	0.35	**Decomposed**
6	180	2.0	0.70	**26%**

Figure 3.8 Claisen rearrangement optimization

The direct hydroboration of **3.17** was problematic. For example, treatment of **3.17** with borane dimethylsulfide complex resulted in hydroboration of the alkene, however reduction of the benzaldehyde function was competitive with that process. As a result, a two–step sequence with **3.17** was employed; the aldehyde function was reduced to the corresponding benzyl alcohol under the action of DIBAL–H to give the benzalcohol **3.20** which was then was hydroborated and cyclized using the Mitsunobu protocol[10] to furnish **3.21**. Finally, a Suzuki–Miyaura coupling was employed to convert the aryl bromide **3.21** to the styrene **3.22** (Figure 3.9).

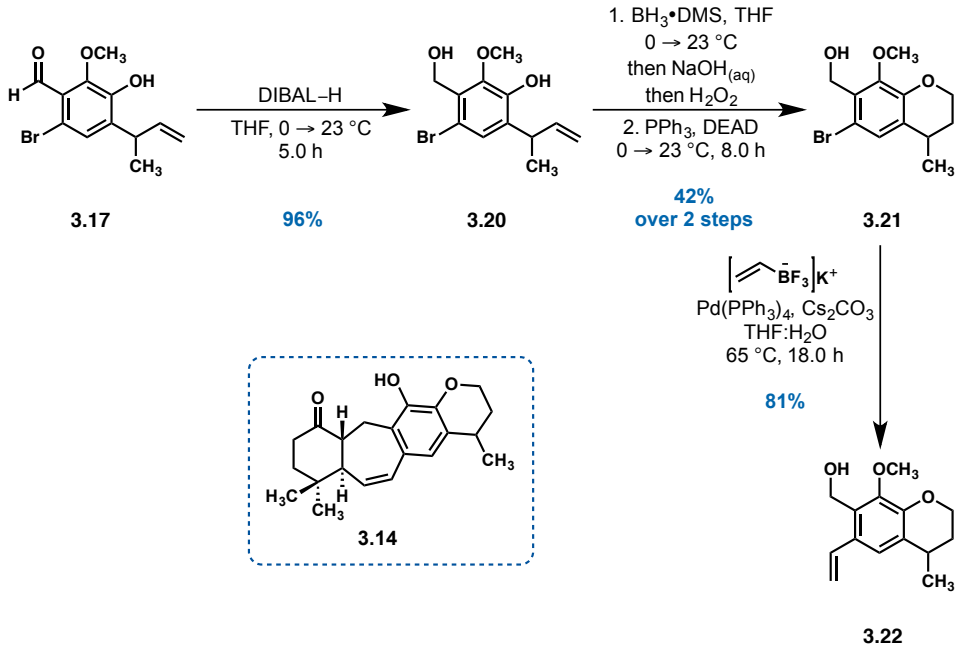


Figure 3.9 Synthesizing pentasubstituted benzalcohol **3.22**

With the styrene **3.22** in hand, the path to the icetexane analog **3.14** is straightforward. Synthesis of the icetexane analog **3.14** will be completed by new

personnel. Conversion of the benzyl alcohol **3.22** into the corresponding benzyl bromide will again be achieved via the one–pot, two–step reaction conditions described above (Figure 3.10) and then the LiBr–doped alkylation protocol will be employed to generate the desired product **3.24**. The final ring closing metathesis process will complete the construction of the icetexane analog **3.25**.

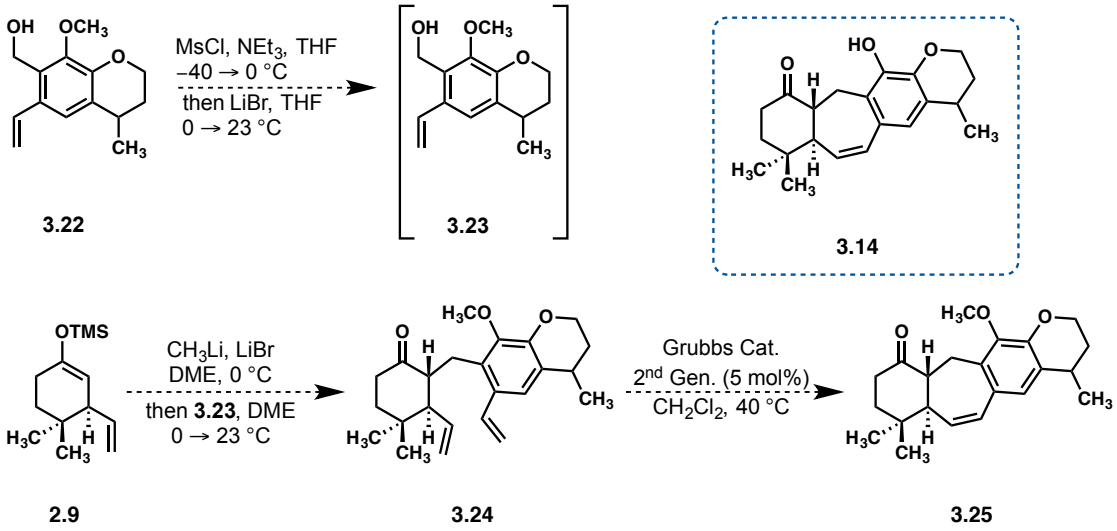
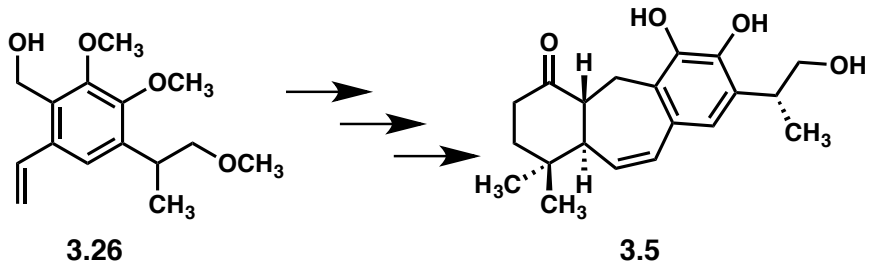


Figure 3.10 Constructing the central seven–member ring of icetexane

3.3 Synthesis of the Southern Monomer of Premnalatifolin A

Our synthetic strategy toward the icetexanes features a highly diastereoselective alkylation reaction joining a 3,4,4–trisubstituted cyclohexanone enolate nucleophile with highly functionalized benzyl halide electrophile. We have successfully demonstrated the feasibility of this strategy and the major obstacle in the way of generating both monomeric units of premnalatifolin A is preparing the appropriate pentasubstituted aromatics such as **3.26** (Figure 3.11).

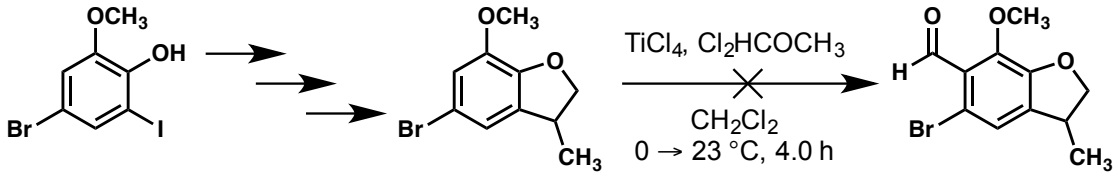


3.26 **3.5**

Figure 3.11 The key intermediate, pentasubstituted **3.26**

3.3.1 Formylation Challenge

In the previous chapter, we generated the dihydrobenzofuran **3.28** in the hope of conducting a Rieche formylation to furnish the pentasubstituted benzaldehyde **3.29**, thus installing the one carbon appendage that will eventually become the required benzylic electrophile (Figure 2.9). The Rieche protocol ultimately did not afford us with the desired product, despite extensive effort to productively formylate either **3.27** or **3.28**.



3.27 **3.28** **3.29**

Figure 3.12 Failed attempt of Rieche formylation

3.3.1.1 Efforts toward formylation, Vilsmeier–Haack reaction

One of the most widely known classical formylation reactions is the Vilsmeier–Haack protocol that is employed typically with electron–rich aromatic compounds.[11] The phenol **3.27** was demethylated to generate the electron rich catechol

3.30 (Figure 4.5) which we envisioned as an ideal substrate for the Vilsmeier–Haack protocol.

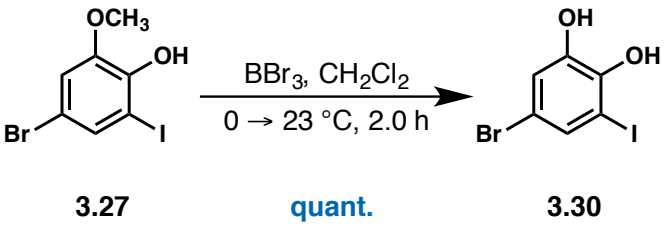
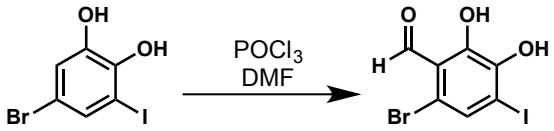


Figure 3.13 Producing the highly electron–rich alcohol

Upon treatment of **3.27** with the Vilsmeier reagent—generated *in situ* from DMF under the action of $POCl_3$—we were surprised to observe no conversion to the desired aldehyde and instead recovered starting material unchanged. Exhaustive modifications of the Vilsmeier–Haack reaction parameters (addition orders, equivalents of each reagent, temperature profiles) failed to generate any detectable formylated product (Figure 3.14).

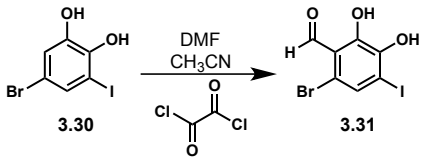


3.30 3.31

	$POCl_3$ (equiv)	DMF (equiv)	Temperature	Time (h)	Order of Addition	Results
1	1.5	1.5	0 → 40 °C	4	POCl3 First	RSM
2	1.5	1.5	0 → 40 °C	8	POCl3 First	RSM
3	2.6	12.3	0 → 100 °C	4	POCl3 First	RSM
4	2.6	12.3	0 → 100 °C	8	POCl3 First	RSM
5	1.5	1.5	0 → 40 °C	4	Mix all Together	RSM
6	1.5	1.5	0 → 40 °C	8	Mix all Together	RSM
7	2.6	12.3	0 → 100 °C	4	Mix all Together	RSM
8	2.6	12.3	0 → 100 °C	8	Mix all Together	RSM

Figure 3.14 Vilsmeier–Haack reaction employing $POCl_3$ as the activating agent

Alternative activating agents such as oxalyl chloride in place of $POCl_3$ also failed to produce the desired formylated product, again returning starting material unchanged (Figure 3.15).



	$(COCl)_2$ (equiv)	DMF (equiv)	Temperature	Time (h)	Results
1	1.1	1.2	0 °C	2.0	RSM
2	1.1	1.2	0 → 23 °C	2.0	RSM
3	1.1	1.2	0 → 23 °C	12.0	RSM
4	1.1	1.2	0 → 60 °C	12.0	RSM

Figure 3.15 Vilsmeier–Haack reaction employing oxalyl chloride as the activating agent

With **3.30** failing to undergo Vilsmeier–Haack formylation, we turned our eyes toward using **3.28** as the electron–rich aromatic nucleophile, but unfortunately this substrate did not successfully engage the Vilsmeier reagent and the starting material was recovered unchanged (Figure 3.16).

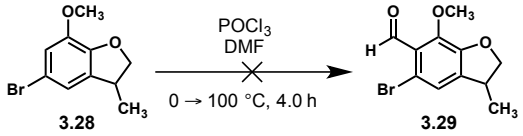


Figure 3.16 Attempted Vilsmeier–Haack reaction with **3.28** and $POCl_3$ activating agent

3.3.1.2 Efforts toward an alternatice formylation protocol

The Rieche formylation of **3.28** did not produce the desired product; as a result, we decided to attempt the same protocol with the phenol **3.32**. Treating **3.32** with $TiCl_4$ and dichloromethyl methyl ether yielded no detectable amount of the desired product. In addition to that, we attempted to formylate **3.32** using $MgCl_2$ and

formaldehyde—a method described by Skattebøl and co–workers in 1999[12]—however this protocol also failed to generate the benzaldehyde **3.33** (Figure 3.17).

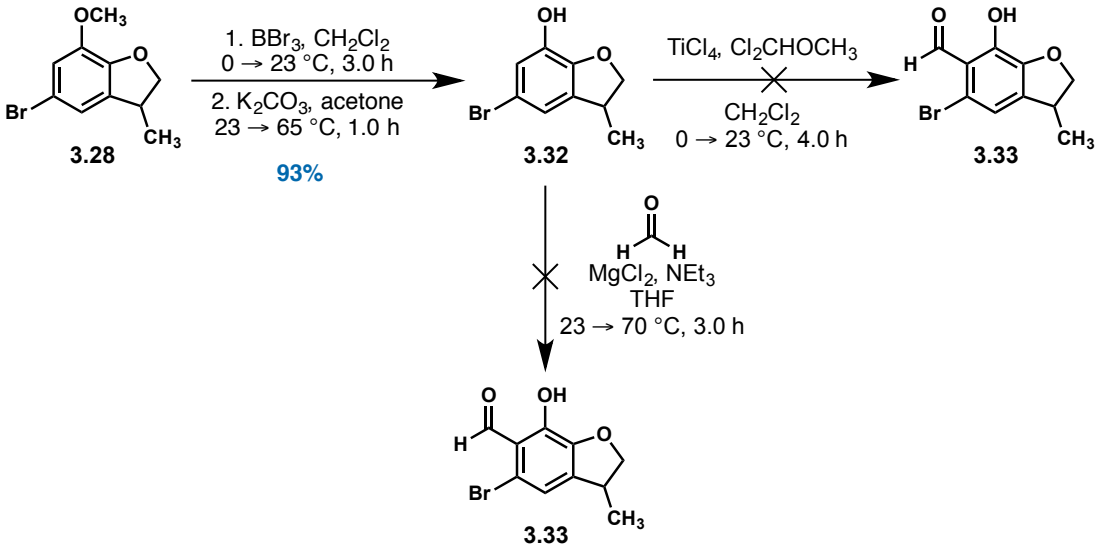
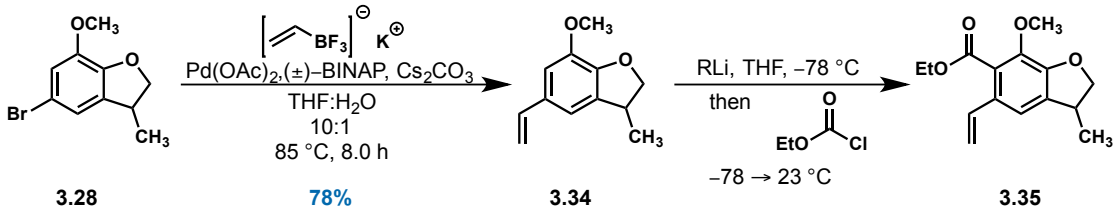


Figure 3.17 Efforts toward formylation of **3.32**

Next, we envisioned taking advantage of the C(7) methoxy group as a directing group for the ortho metallation of the aromatic ring, and capture of that nucleophile with a formyl electrophile.[13] To that end, we conducted a Suzuki–Miyaura coupling under wet conditions to afford the styrene **3.34**, thus avoiding any complications that might arise from the aryl bromide via lithium–halogen exchange.[14] With **3.34** in hand, we screened both *n*–butyllithium and *t*–butyllithium to lithiate the aromatic ring at C(6), and then we treated the resultant species with chloroformic acid ethyl ester. Unfortunately, we were not successful in isolating the ester **3.35** or other acylated products. (Figure 3.18).



	RLi	Results
1	^{n}BuLi	RSM
2	^{t}BuLi	RSM

Figure 3.18 Directed *ortho*–metallation of **3.34**

We reasoned that perhaps the C(7) methoxy group did not facilitate the quantitative metallation of the aromatic system, and thus we decided to install a cleavable carbamate group as a stronger directing group. To that end, the phenol **3.32** was converted to styrene **3.36** again through a Suzuki–Miyaura coupling under wet conditions, and upon treatment of **3.36** with diethylcarbamic chloride, the carbamate **3.37** was formed in good yield (Figure 3.19).

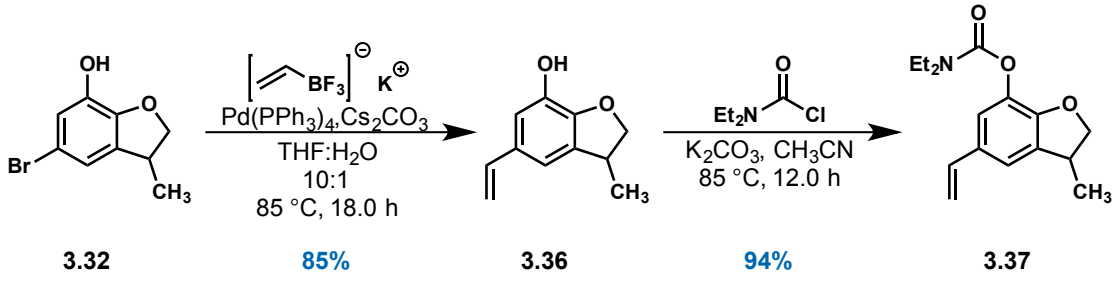
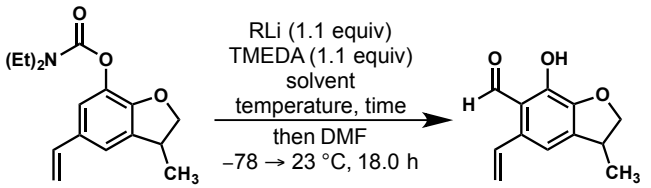


Figure 3.19 Producing carbamate **3.37**

Optimization of the one–pot three–step lithiation–formylation–dicarbamation reaction is summarized in Figure 3.20. The optimal reaction conditions employed *sec*–BuLi as the alkyl lithium in 1,2–dimethoxyethane as solvent with *N,N,N',N'*–tetramethylethylenediamine as the additive; the desired benzaldehyde **3.38** was isolated in 51% yield on a 3 mmol scale (entries 8 and 9).



3.37 **3.38**

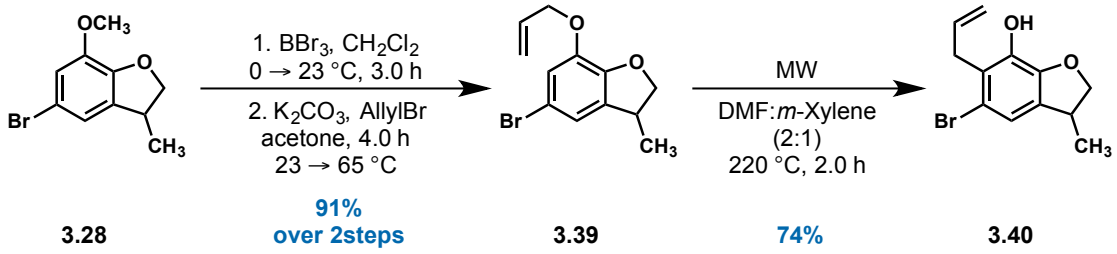
	RLi (equiv)	TMEDA (equiv)	Solvent	Scale (mmol)	Yield
1	*s*-BuLi (2.16)	1.20	THF	0.25	**31%**
2	*t*-BuLi (2.16)	1.20	THF	0.25	**15%**
3	*s*-BuLi (2.16)	1.20	Et_2O	0.25	**41%**
4	*s*-BuLi (2.16)	1.20	Et_2O	3.94	**29%**
5	*s*-BuLi (2.16)	1.20	DME	0.25	**40%**
6[a]	*s*-BuLi (2.16)	1.20	DME	0.25	**19%**
7	*s*-BuLi (2.16)	1.20	DME	0.64	**43%**
8	*s*-BuLi (4.32)	2.40	DME	0.25	**57%**
9	*s*-BuLi (4.32)	2.40	DME	3.44	**51%**

a: start at T = –40 °C instead of T = –78 °C

Figure 3.20 Optimization of the generation of **3.38**

In work complementary to the use of *ortho*–metallation to install the required formyl group or equivalent, we pursued the classical idea of the Claisen rearrangement

to install the required carbon atom at C(6) – the [3,3]–sigmatropic rearrangement to relay a three–carbon unit onto the aromatic platform (Figure 3.21).[14] The sequential demethylation–allylation of the dihydrobenzofuran **3.28** furnished **3.39**, which is a promising candidate for a Claisen rearrangement. Heating **3.39** at 220 °C in a microwave reactor smoothly afforded the desired rearranged product **3.40**.



3.28 **3.39** **3.40**

Figure 3.21 Claisen [3,3]–sigmatropic rearrangement route for the generation of **3.40**

With two methods to functionalize at C(6) of the dihydrobenzofuran **3.28**, we are in a good position to complete the synthesis of icetexane **3.5a**. However, in order to accomplish the synthesis of the icetexane **3.5** it is necessary that we generate the pentasubstituted aromatic **3.26** (Figure 3.22). To that end, we sought to apply one of the formylation methods described above to the substrate **3.41** (or a similar variant).

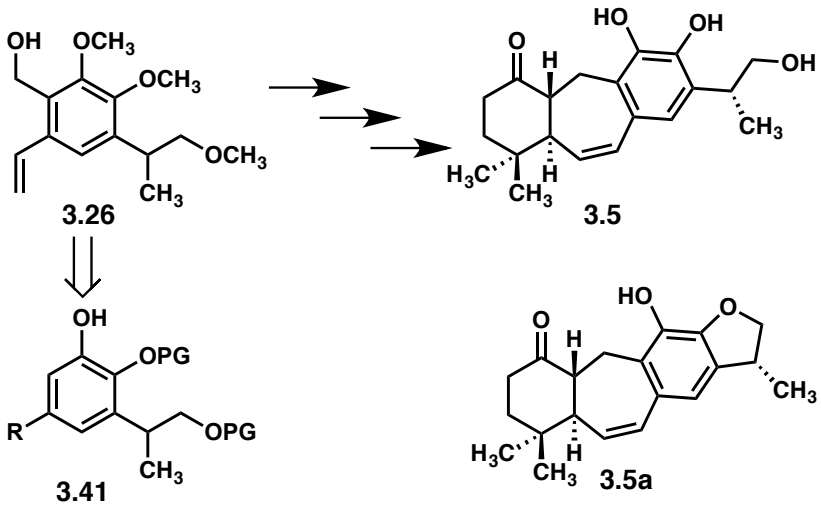


Figure 3.22 Icetexane **3.5** and **3.5a**

To that end, we began with a chemoselective Suzuki–Miyaura coupling—engaging the aryl iodide over the bromide, thus converting **3.27** to **3.42**. A hydroboration–oxidation reaction was employed to prepare **3.43**, which was converted to the styrene **3.24** through a second Suzuki–Miyaura coupling followed by global alcohol protection as the corresponding TBS ethers to furnish **3.45** (Figure 3.23).

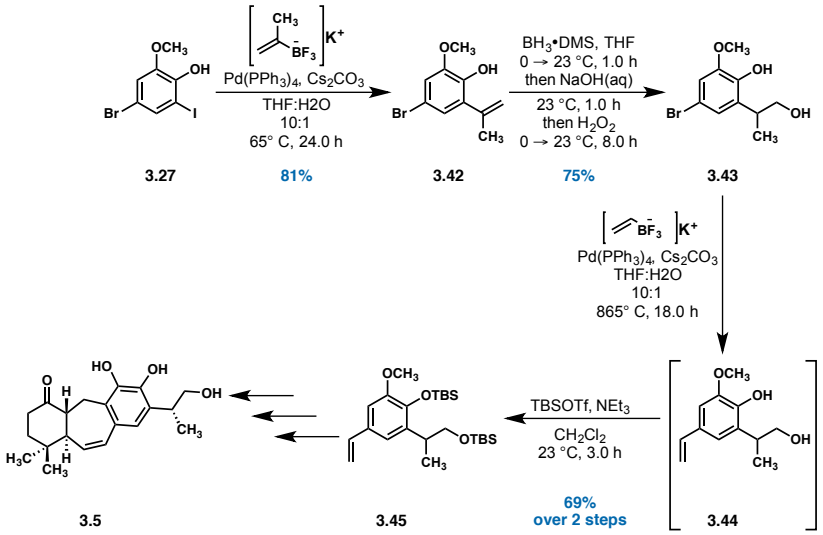
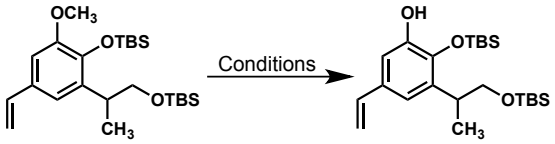


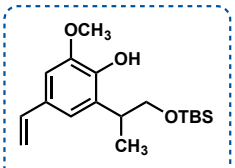
Figure 3.23 Synthesizing **3.45**

Both C(6) functionalization strategies described rely upon demethylation of the C(6) methoxy group; the Claisen rearrangement requires an allyl ether and the metalation requires a carbamate function. Unfortunately, exhaustive screening of deprotection conditions failed to afford the phenol **3.46** (Figure 3.24), returning starting material unchanged or various other products that presented other challenges.

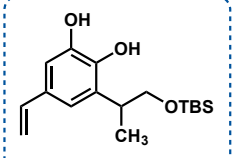


3.45 3.46

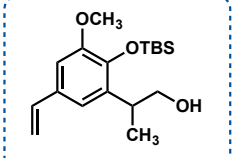
	Additive (equiv)	Solvent	Temperature	Time (h)	Result
1	BBr_3 (1.1)	CH_2Cl_2	–78 °C	3.0	RSM
2	BBr_3 (1.1)	CH_2Cl_2	–40 °C	3.0	RSM
3	BBr_3 (1.1)	CH_2Cl_2	0 °C	3.0	3.46a
4	BBr_3 (1.1)	CH_2Cl_2	23 °C	3.0	3.46b
5	BCl_3 (1.1)	CH_2Cl_2	–78 °C	5.0	RSM
6	BCl_3 (1.1)	CH_2Cl_2	23 °C	5.0	3.46b
7	$ZnBr_2$ (0.5)	CH_2Cl_2	23 °C	2.0	3.46c
8	$AlCl_3$ (1.0)	EtSH	23 °C	1.0	3.46a
9	$ZnBr_2$ (0.5), EtSH (1.0)	CH_2Cl_2	23 °C	1.0	3.46c
10	$NaSCH_3$ (3.0)	CH_2Cl_2	40 °C	5.0	RSM
11	PPh_2Li (5.0)	THF	23 °C	4.0	RSM
12	PPh_2Li (5.0)	THF	66 °C	4.0	Decomposed



3.46a



3.46b



3.46c

Figure 3.24 Synthesizing **3.46**

3.3.2 The answer to formylation

Without an efficient means of selectively deprotecting **3.46**, our attention was turned to an alternate strategy beginning from the benzaldehyde **3.47**. Shuffling the methyl group from one phenol function to the other furnished **3.48**. The benzaldehyde **3.48** was oxidized using the Tollens' oxidation protocol[16] and the corresponding carboxylic acid was esterified under acidic conditions to produce **3.49**. Subjecting **3.49** to excess methyl magnesium bromide afforded the tertiary alcohol **3.50**. Dehydration of **3.50** produced the styrene **3.51** which after a hydroboration–oxidation sequence generated the primary alcohol **3.52**. The hydroboration reaction also affords us the

opportunity for stereochemical control of the methyl–bearing center on the three–carbon appendage in future work. Exploiting the difference in pK_a between a phenol and a primary alcohol, we were able to selectively allylate the phenolic hydroxyl to afford **3.53** which was then exhaustively methylated to generate **3.54** (Figure 3.25).

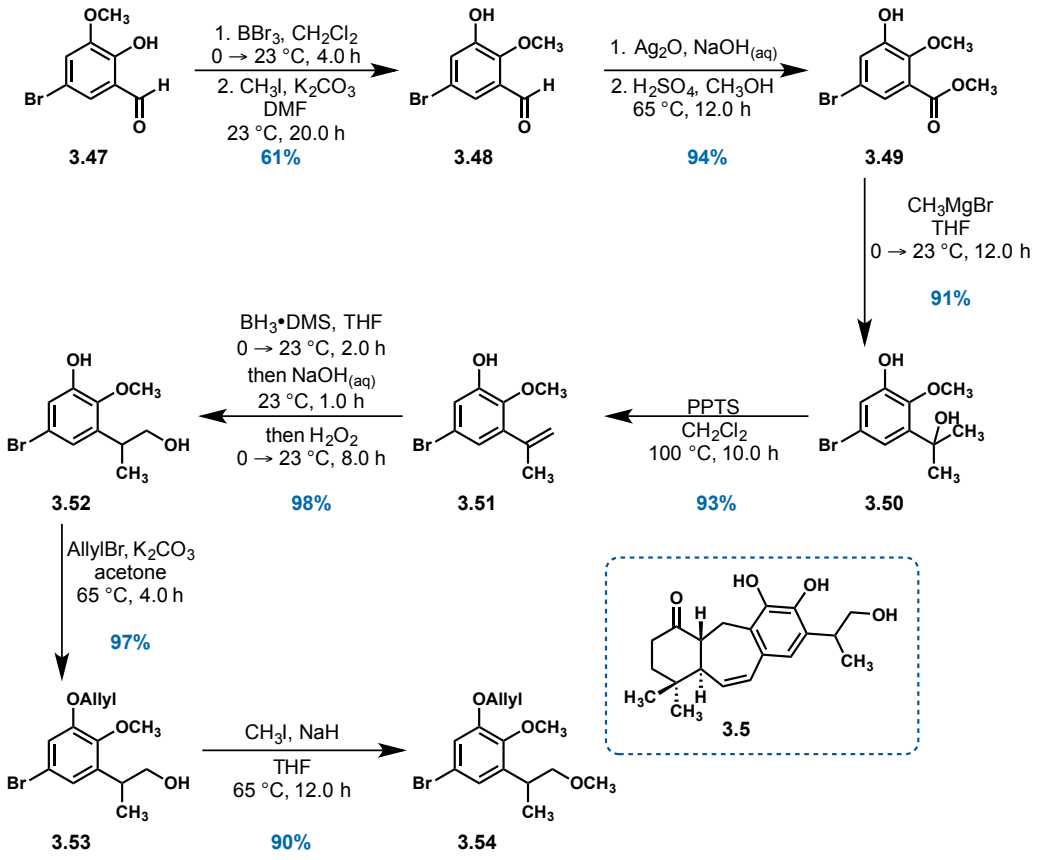
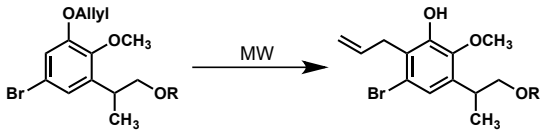


Figure 3.25 Synthesizing **3.54**

Both **3.53** and **3.54** are candidates for the Claisen [3,3]–sigmatropic rearrangement and indeed both of them afforded the desired product; while **3.54** produces the desired rearrangement product exclusively, the ether **3.53** however does

afford a small amount of *para* Claisen rearrangement product, presumably as a result of a rate–competitive Cope [3,3]–sigmatropic rearrangement (Figure 3.26).[17]



3.53: R=H
3.54: R=CH_3

3.55a: R=H
3.55: R=CH_3

	Solvent	R	Temperature (°C)	Time (h)	Scale(mmol)	Yield (%) **3.55a**	Yield (%) **3.55**
1	DMF:*m*Xylene 1:2	**H**	220	2	0.66	–	89
2	DMF:*m*Xylene 1:2	**CH_3**	200	2	0.63	87	–
3	*m*Xylene	**CH_3**	200	2	0.63	91	–
4	*m*Xylene	**CH_3**	200	1	0.63	72	–
5	*m*Xylene	**CH_3**	180	2	0.63	60	–
6	*m*Xylene	**CH_3**	200	2	3.17	79	–
7	DMF:*m*Xylene 1:10	**CH_3**	200	2	6.35	90	–

Figure 3.26 Optimization of Claisen [3,3]–sigmatropic rearrangement

The allylbenzene **3.55** was then isomerized upon treatment with potassium *tert*–butoxide to the corresponding 1–propenylbenzene which was immediately treated with iodomethane and potassium carbonate to produce **3.56** (Figure 3.27). Oxidative–ozonolysis of **3.56** resulted in the benzaldehyde **3.57** in excellent yield—in our optimized procedure, the ozonolysis was quenched by the addition of triphenylphosphine, which proved far superior in that role to either dimethyl sulfide or sodium borohydride. Our Suzuki–Miyaura coupling under wet conditions generated

styrene **3.58**, which was reduced upon treatment with DIBAL–H to the benzalcohol **3.59**.

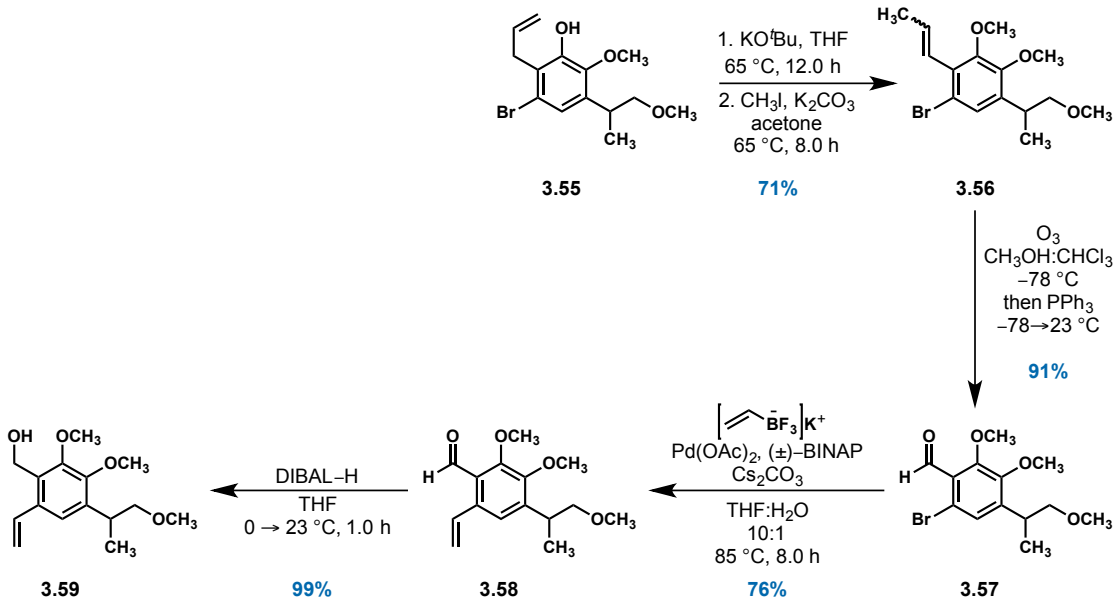


Figure 3.27 Synthesis path toward benzalcohol **3.59**

Conversion of the hydroxyl group on **3.59** to the corresponding bromide was again trouble–free, and cleanly afforded the benzyl bromide **3.60** using our one–pot two–step process—conversion of the alcohol to the corresponding methanesulfonate under the action of methanesulfonyl chloride followed by displacement of the mesylate with lithium bromide—proved to be a trouble–free transformation. Following that sequence, the LiBr–doped alkylation protocol was employed to generate the desired product **3.61**. The final step of the synthesis, ring closing metathesis reaction, proceeded smoothly to construct sought after icetexane **3.62** (Figure 3.28).

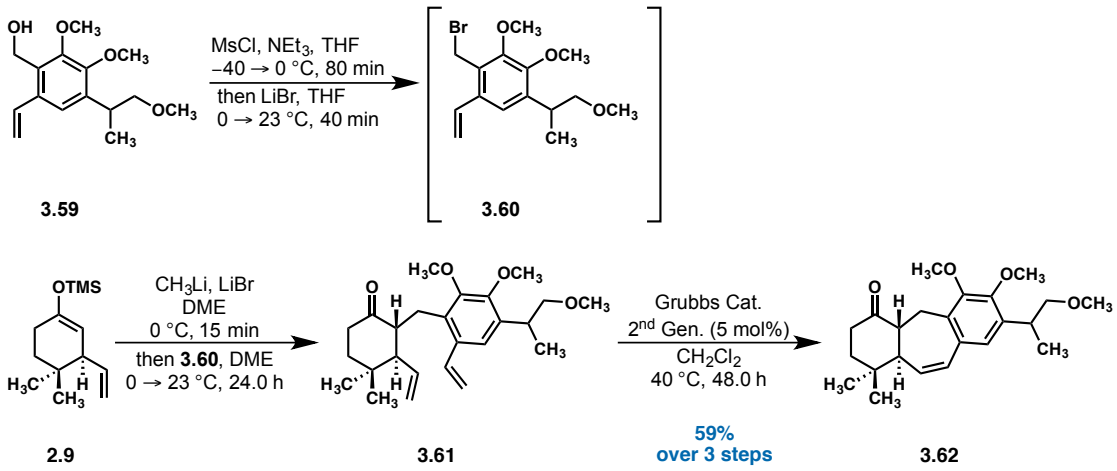


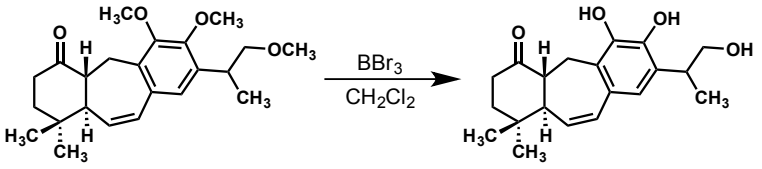
Figure 3.28 Constructing the central seven–membered ring of icetexane **3.62**

3.3.3 Deprotection

To protect hydroxyl groups there are quite a number of different methods—etheric protecting groups, silyl ethers, esters, carbamates, and phosphinates to name a few.[18] Formation of robust methyl ethers is among the most abundantly employed protecting group methods. The robustness of methyl ethers is both very helpful during synthetic operations, but does come at the cost of forcing deprotection conditions when the time comes.

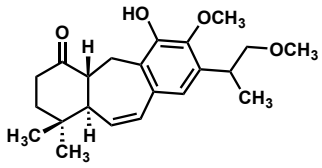
In the icetexane literature, one of the most frequently used methods to cleave the methyl ethers is use of sodium thioethoxide in refluxing DMF.[19, 20] In our work, we prefer the application of boron tribromide, which is among the most widely used methods for demethylation of methyl ethers, for two primary reasons; first of all, the use of sodium thioethoxides on aliphatic methyl ethers (such as those at C(16) of our substrates) is not well–established. Moreover, it is more convenient to achieve the much needed deprotection in low temperatures (usually in the range of –78 °C to 25 °C) comparing to the boiling point of DMF.

Treatment of icetexane **3.62** with boron tribromide was studied in different temperatures with results being summarized in Figure 3.29. The demethylation reactions at low temperatures result in mono demethylation **3.62b**—at one of the two phenyl methyl ethers, which we suspect to be at C(11) based on the existing literature and careful spectroscopic analysis of our products. Increasing the reaction temperature furnishes the fully demethylated product, though that deprotection does come at the cost of displacing the aliphatic alcohol to afford the bromide **3.62a** (Figure 3.29). While undesired, such a transformation has been reported previously in literature,[21] and does afford the opportunity for manipulation at C(16) should future analog and tool compound synthesis require.



3.62 **3.5** **3.62a**

	Temperature (°C)	Time (h)	Product	Yield (%)
1	23	3.0	**3.62a**	54
2	0	2.0	**3.62a**	71
3	–40	2.0	**3.62b**	93
4	–78	2.0	**3.62b**	65



3.62b

Figure 3.29 Demethylation of **3.62**

To date, we have not successfully isolated **3.5**, however we do not expect this to be an issue as we can generate alternative options such as **3.62a** and **3.62b**, both of which are useful in our work toward the desired icetexane monomers.

3.4 Synthesis of the northern monomer of premnalatifolin A

With the synthesis of southern monomer of premnalatifolin A nearing conclusion, we have turned our focus to the synthesis of the northern monomer.

3.4.1 Retrosynthetic analysis

As was explained previously, [3.1] premnalatifolin A **3.1** is a heterodimer with minor oxygenation pattern differences within a conserved carbocyclic framework of each monomer. The first structural distinction between the two monomers appears within the aromatic ring substitution pattern. While **3.5** has a C(12) hydroxyl and a C(13) 2–(1–hydroxyl)propyl substitution, icetexane **3.2** consists of a dihydrobenzofuran ring—presumably from a ring–closure event from the open monomer. The second important distinction is about the oxygenation pattern within the cyclohexane moiety; the heterodimer **3.2** has a bridgehead hydroxyl group on C(10), while **3.5** has a carbonyl group on C (1) (Figure 3.30).

We plan to generate the dihydrobenzofuran moiety of **3.2** via a Mitsunobu–type cyclization from our monomer **3.5**, which is a known strategy in the literature (Figure 3.30).

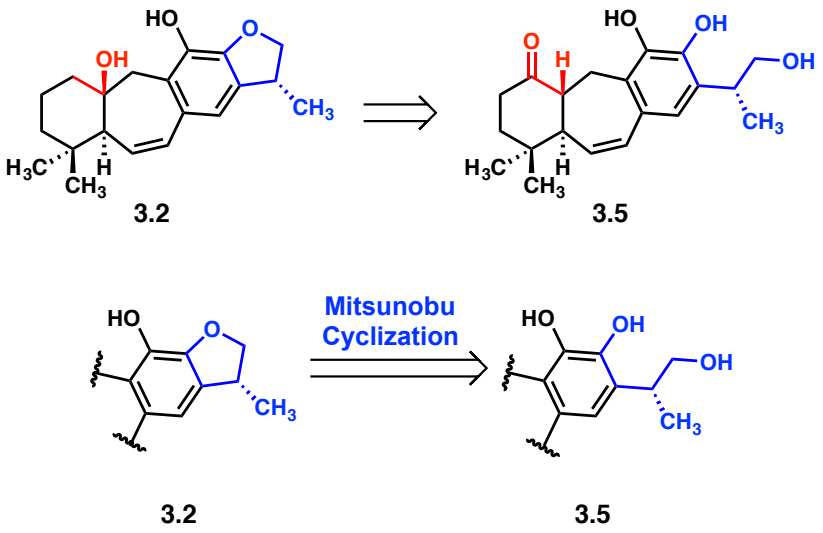


Figure 3.30 Relationship between **3.2** and **3.5**

In order to achieve the transposition of the oxygen, we have designed a synthesis inspired by the biosynthetic pathway of icetexane's core structure functionalization. It has been proposed that both C(1) carbonyl and C(10) hydroxyl groups are the result of opening of the same epoxide ring (Figure 3.31).

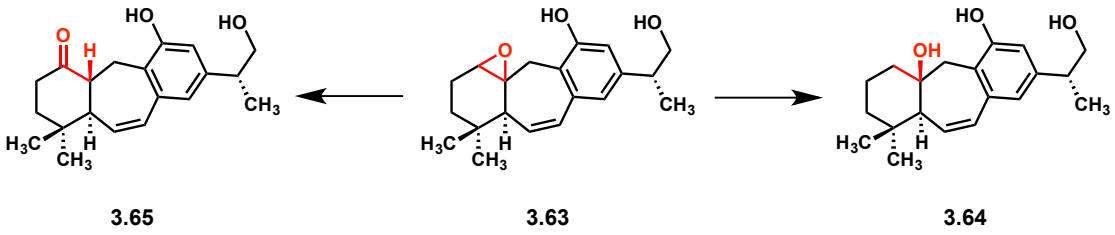


Figure 3.31 Biosynthetic pathway

The first key step of the retrosynthetic analysis is the dehydration reaction from **3.66** to **3.67**, which should be performed in a regioselective manner to produce

desired Zaitsev product (Figure 3.32). The second key step is the epoxidation of **3.67**, which should be chemoselective and diastereoselective by the virtue of the 3D shape of the molecule.

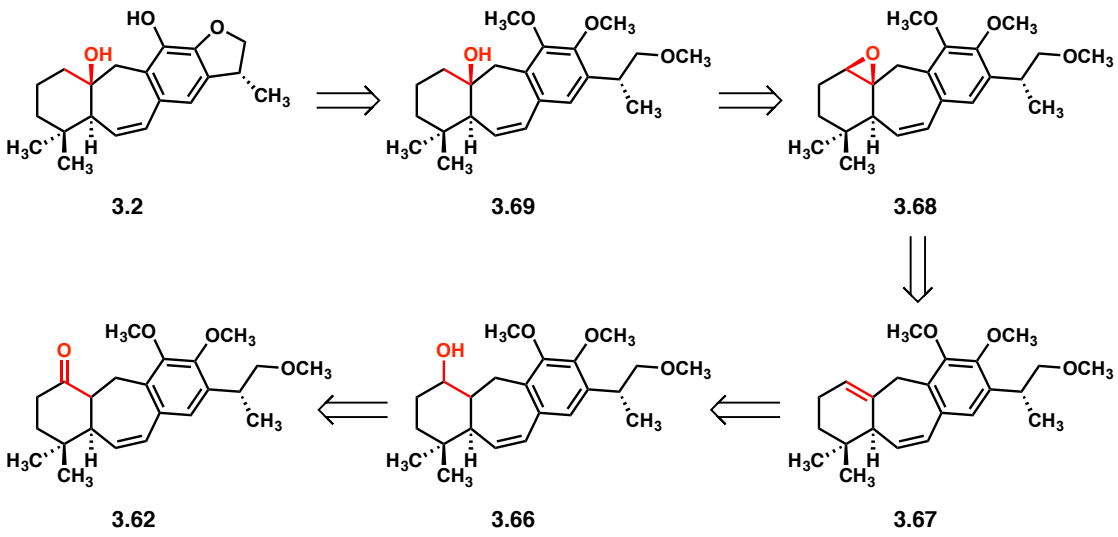


Figure 3.32 Retrosynthetic analysis of **3.2**

3.4.2 Model system

We have validated the proposed synthetic plan for the transposition of oxygen atom utilizing the simplified icetexane **3.13** as a model system. The synthesis began with the reduction of **3.13** with lithium aluminum hydride, which resulted in the expected mixture of diastereomers **3.70a** and **3.70b** (Figure 3.33).

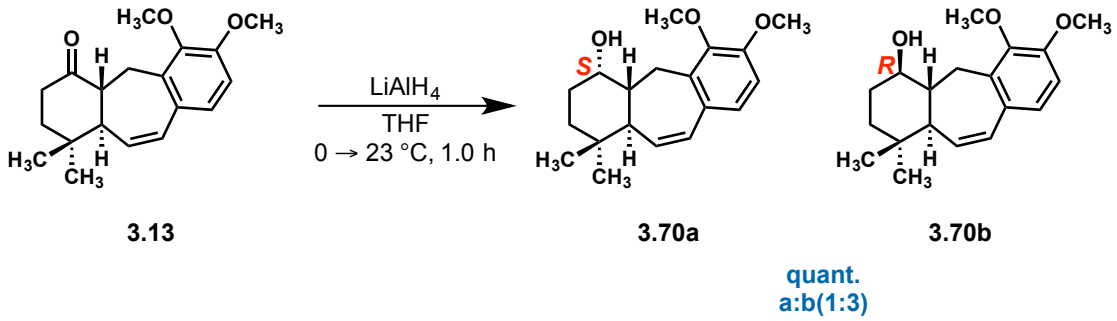


Figure 3.33 Reduction of **3.13**

The chromatographic separation of **3.70a** and **3.70b** via conventional column chromatography is tedious, but achievable. After the separation of the diastereomers, we attempted a dehydration previously reported in literature[22] featuring mesylation of the alcohol in pyridine and subsequent heating of that methanesulfonate electrophile in 2,4–lutidine (Figure 3.34). The (*1s*) diastereomer undergoes the desired elimination (a formal dehydration reaction) to give the desired diene **3.71** in 19% yield. Other alkene products were present; however, these can be separated by conventional column chromatography utilizing silver–impregnated silica gel. A small amount of the alkyl chloride **3.72** is also generated in this process, which undoubtedly arises from adventitious chloride in the mesylation process. Treating **3.70b** with the same procedure yielded **3.71** in a slightly higher yield; however, we are still working to optimize this process.

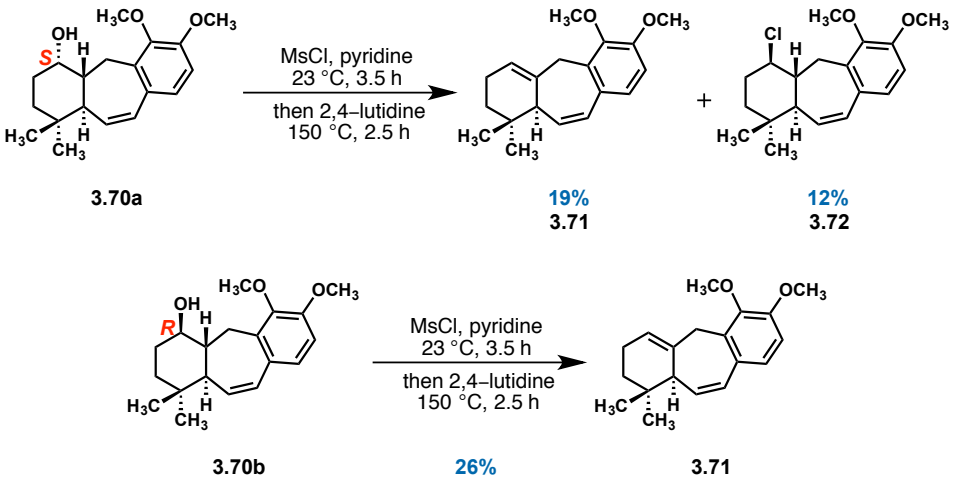


Figure 3.34 Dehydration of **3.70a** and **3.70b**

In parallel to the two–step mesylation–elimination procedure, we explored another literature elimination reaction employing the Burgess reagent (Figure 3.35).[23] The mechanism of this elimination process is distinctly different from that of the E2–type elimination of the methanesulfonate, however this procedure successfully afforded **3.71** in 15% yield directly. We are still exploring elimination reaction conditions but we have been able to move forward with the diene **3.71** in hand.

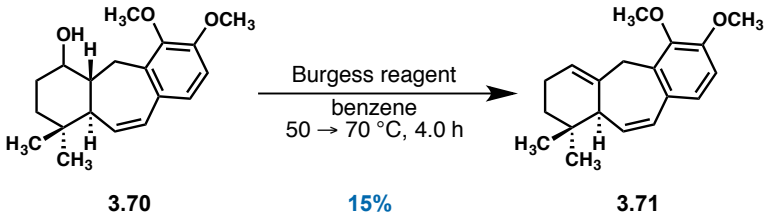


Figure 3.35 Dehydration of **3.70** using Burgess reagent

The second key reaction in this route is the epoxidation reaction, which was performed using ^{m}CPBA to generate **3.72** (Figure 3.36). The chemoselectivity of **3.72** has been confirmed by NMR spectroscopy but the stereochemistry of the product is still under study. Finally, the reductive epoxide ring opening of **3.72** was successfully performed under the action of lithium aluminum hydride in warm THF, generating the alcohol **3.73** in 22% yield in our first attempt.

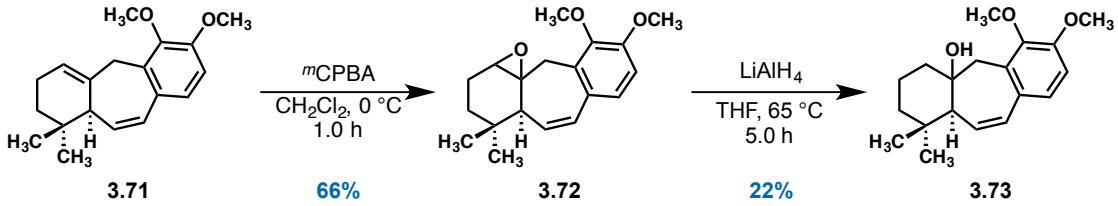


Figure 3.36 Synthesis of **3.73**

3.5 Summary

The necessity of finding a new chemotherapeutic treatment for patients suffering from breast cancer and the captivating diverse structures of icetexanes encouraged us to work on developing a new methodology capable of synthesizing different icetexanes. Inspired by the remarkable works of Mr. Daniel J. Moon and Dr. Mohammad Al–Amin in the Chain Laboratory, I worked to enlarge the library of synthesized icetexanes in Chain lab, including **2.19**, **2.34**, **2.42**, and **2.53** from chapter 2.

During this work, the synthesis of icetexanes **3.13**, **3.42** and **3.73** was completed, and we are poised to complete the syntheses of the icetexanes **3.14**, **3.5**, **3.64**, and in due course, the natural product premnalatifolin A. We will evaluate all

our materials against a panel of human breast cancer cell lines and identify new lead compounds for human cancer chemotherapeutic agents.

Experimental Procedures

General Information: These experimental procedures have been published previously in its current or a substantially similar form and I have obtained permission to republish it.[4] All reactions were performed in single-neck oven- or flame-dried round bottom flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless-steel cannula. Organic solutions were concentrated by rotary evaporation at or below 35 °C at 10 Torr (diaphragm vacuum pump) unless otherwise noted. Compounds were isolated using flash column chromatography[5] with silica gel (60-Å pore size, 40–63μm, standard grade, Silicycle). Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25 mm, 60-Å pore size, 5–20 μm, Silicycle) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV), then were stained by submersion in aqueous ceric ammonium molybdate solution (CAM), acidic ethanolic *p*-anisaldehyde solution (anisaldehyde), or aqueous

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[4] (a) Wu, Z.; Suppo, J. S.; Tumova, S.; Strope, J.; Bravo, F.; Moy, M.; Weinstein, E. S.; Peer, C. J.; Figg, W. D.; Chain, W. J.; Echavarren, A. M.; Beech, D. J.; Beutler, J. A., *ACS Med. Chem. Lett.* **2020,** *11*, 1711-1716. (b) Reed, H.; Paul, T. R.; Chain, W. J., *J. Org. Chem.* **2018,** *83*, 11359-11368. (c) Bush, T. S.; Yap, G. P. A.; Chain, W. J., *Org. Lett.* **2018,** *20*, 5406-5409. (d) Lewis, R. S.; Garza, C. J.; Dang, A. T.; Pedro, T. K.; Chain, W. J., *Org. Lett.* **2015,** *17*, 2278-2281. (e) Li, Z.; Nakashige, M.; Chain, W. J., *J. Am. Chem. Soc.* **2011,** *133*, 6553-6556.

[5] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978,** *43,* 2923–2925.

methanolic iron(III) chloride (FeCl3), followed by brief heating on a hot plate (215 °C, 10–15 s).

Materials: Commercial reagents and solvents were used as received with the following exceptions. Triethylamine, dichloromethane, diethyl ether, tetrahydrofuran, and 1,2-dimethoxyethane were purified by the method of Pangborn, et al.[6] 2-Chloropropanoate, 3-methyl-2-butanone, hexamethyldisilazide, and *N,N*-diisopropylamine were distilled from calcium hydride under an atmosphere of argon at 760 Torr. Hexamethylphosphoramide (HMPA) and *N,N*-dimethylformamide (DMF) were distilled from calcium hydride under reduced pressure (0.1 Torr) and stored under argon. The molarity of solutions of *n*- butyllithium was determined by titration against diphenylacetic acid as an indicator (average of three determinations).[4] Where noted, solvents were deoxygenated before use a minimum of five freeze-pump-thaw cycles.

Instrumentation: Proton (^{1}H), carbon (^{13}C), fluorine (^{19}F), and silicon (^{29}Si) nuclear magnetic resonance (NMR) spectra were recorded on Bruker AV400 CryoPlatform QNP or Bruker AVIII600 SMART NMR spectrometers at 23 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26, CD_3COCD_2H: δ 2.05). Carbon chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the

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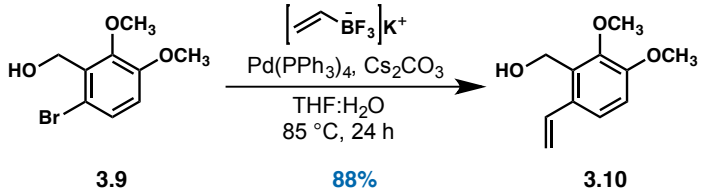
[3] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. Organometallics 1996, 15, 1518–1520.

[4] Kofron, W. G.; Baclawski, L. M. J. Org. Chem. 1976, 41, 1879.

carbon resonance of the NMR solvent ($CDCl_3$: δ 77.16, CD_3COCD_3: δ 29.84). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent), integration, and coupling constant (*J*) in Hertz (Hz). Accurate mass measurements were obtained using an Agilent 1100 quaternary LC system coupled to an Agilent 6210 LC/MSD-TOF fitted with an ESI or an APCI source, or Thermo Q-Exactive Orbitrap using electrospray ionization (ESI) or a Waters GCT Premier spectrometer using chemical ionization (CI).

Synthesis of Styrene 3.10:



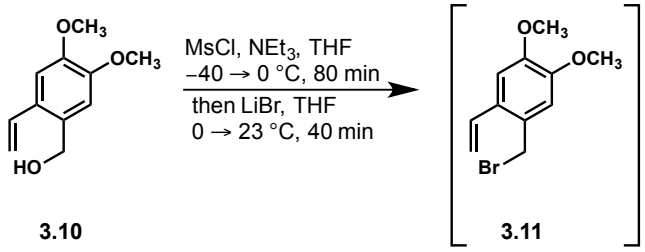
3.9 **88%** **3.10**

A solution of potassium vinyltrifluoroborate (955 mg, 7.10 mmol, 1.76 equiv), tetrakis(triphenylphosphane)palladium(0) (239 mg, 0.21 mmol, 5 mol%), cesium carbonate (4.09 g, 12.50 mmol, 3.10 equiv), and 6−bromo−2,3−dimethoxybenzyl alcohol **3.9** (1.00 g, 4.05 mmol, 1 equiv) in tetrahydrofuran:water (10:1, 25 mL tetrahydrofuran:2.5 mL H_2O) in a 100 mL glass pressure reactor was degassed by bubbling with argon for 15 min. The reactor was sealed and the reaction mixture was heated at 85 °C for 24 h. The reaction mixture was cooled down to 23 °C and quenched by the slow addition of water (50 mL). The resultant mixture was extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (40 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 20% ethyl acetate−hexanes) to afford 2,3−dimethoxy−6−vinylbenzyl alcohol **3.10** (691 mg, 3.56 mmol, 88%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.25 (d, J = 8.5 Hz, 1H), 7.01 (dd, J_1 = 17.3 Hz, J_2 = 10.9 Hz, 1H), 6.88 (d, J = 8.5 Hz, 1H), 5.58 (dd, J_1 = 17.3 Hz, J_2 = 1.4 Hz, 1H), 5.28 (dd, J_1 = 10.9 Hz, J_2 =

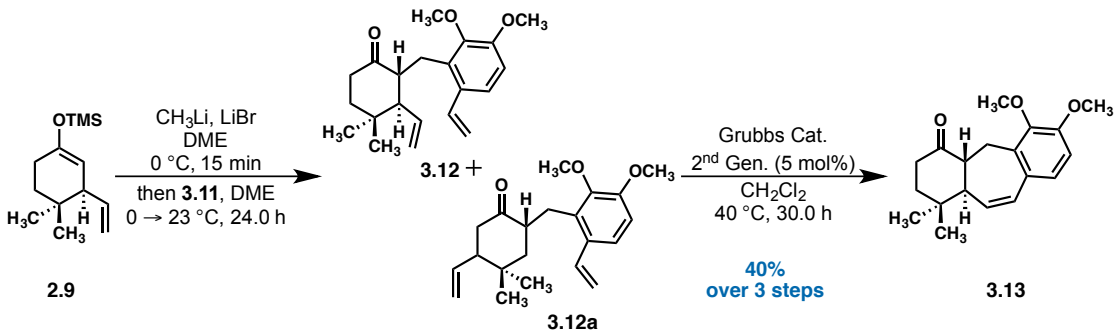
	1.4 Hz, 1H), 4.79 (s, 2H), 3.94−3.83 (m, 6H), 2.08−2.00 (br s, 1H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	152.2, 147.5, 133.8, 131.8, 131.0, 122.2, 115.7, 112.3, 61.5, 57.1, 56.0.
FTIR (KBr, thin film), cm^{-1}:	3418, 2940, 1624.
HRMS ES^+ $[M+H]^+$:	Calcd for $C_{11}H_{15}O_3$: 195.1021. Found: 195.1013.
TLC:	20% ethyl acetate–hexanes, R_f = 0.17 (Anis, CAM).

Synthesis of Icetexane 3.13:



3.10 **3.11**

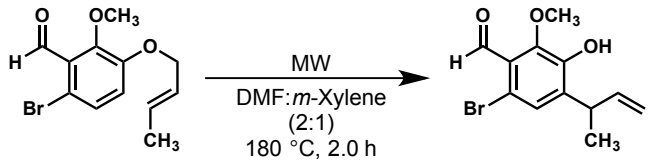
Triethylamine (2.10 mL, 15.03 mmol, 6.50 equiv) and methanesulfonyl chloride (1.14 mL, 14.7 mmol, 6.36 equiv) were added respectively to a stirred solution of 2,3−dimethoxy−6−vinylbenzyl alcohol (450 mg, 2.32 mmol, 1 equiv) in tetrahydrofuran (18.0 mL) at −40 °C. The resultant yellow mixture was stirred at −40 °C for 50 min whereupon the solution's temperature was raised to 0 °C and was stirred for extra 30 min. A solution of lithium bromide (1.98 g, 22.8 mmol, 9.84 equiv) in tetrahydrofuran (18.0 mL) was transferred to the reaction flask through a cannula and then the reaction mixture was stirred at 0 °C for another 10 min. The reaction mixture's temperature then was raised to 23 °C and was stirred for 40 min and then it was quenched by the slow addition of saturated aqueous solution of sodium bicarbonate (30 mL). The resultant mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was passed through a short column of basic alumina to afford 2,3−dimethoxy−6−vinylbenzyl bromide **3.11**.



Methyllithium (1.60 M in diethyl ether, 1.79 mL, 2.86 mmol, 1.40 equiv) was added to a stirred suspension of ((4,4−dimethyl−3−vinylcyclohex−1−en−1−yl)oxy)trimethylsilane **2.9** (673 mg, 3.00 mmol, 1.47 equiv) and lithium bromide (266 mg, 3.06 mmol, 1.50 equiv) in 1,2−dimethoxyethane (6.0 mL) at 0 °C. The resultant heterogeneous yellow mixture was stirred at 0 °C for 10 min, whereupon a solution of 2,3−dimethoxy−6−vinylbenzyl bromide **3.11** from the previous experiment in 1,2–dimethoxyethane (6.0 mL) was added dropwise. The heterogeneous yellow mixture was then slowly warmed to 23 °C and stirred at that temperature for 24 h, then was filtered through a 5.0 cm celite pad. The pad was washed with diethyl ether (30 mL) and the combined filtrates were concentrated. The resultant residue was then purified by flash column chromatography (silica gel, 20% diethyl ether−hexanes) to afford a combined mixture of **3.12** and its structural isomer (489 mg). This mixture was dissolved in dichloromethane (15.0 mL) and then the Grubbs second–generation catalyst (62.9 mg, 0.074 mmol, 0.05 equiv) was added to the solution at 23 °C. The resultant red solution was heated at reflux for 30 h, was then cooled to 23 °C and concentrated. Purification of the residue by flash column chromatography (silica gel, 5% ethyl acetate−hexanes) to afford **3.13** (289 mg, 0.96 mmol, 40% over 3 steps) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	6.88 (d, J = 8.4 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.47 (dd, J_1 = 12.7 Hz, J_2 = 2.4 Hz, 1H), 5.75 (dd, J_1 = 12.6 Hz, J_2 = 3.5 Hz, 1H), 4.08 (dd, J_1 = 14.8 Hz, J_2 = 1.5 Hz, 1H), 3.85 (s, 3H), 3.77 (s, 3H), 2.58 (ddt, J_1 = 12.8 Hz, J_2 = 7.6 Hz, J_3 = 1.2 Hz, 1H), 2.52−2.41 (m, 2H), 2.35 (ddd, J_1 = 13.9 Hz, J_2 = 4.6 Hz, J_3 = 3.0 Hz, 1H), 2.26 (dd, J_1 = 14.8 Hz, J_2 = 7.7 Hz, 1H), 1.78−1.67 (m, 2H), 1.13 (s, 3H), 1.02 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	210.8, 152.2, 146.0, 134.4, 130.5, 129.7, 129.4, 126.3, 109.5, 61.3, 57.8, 55.9, 51.0, 41.3, 38.6, 34.9, 29.8, 23.7, 20.0.
FTIR (KBr, thin film), cm^{-1}:	2959, 1713, 1596.
HRMS LIFDI^{+} $[M]^{+}$:	Calcd for $C_{19}H_{24}O_3$: 300.1725. Found: 300.1730.
TLC:	20% ethyl acetate–hexanes, R_f = 0.31 (UV, CAM).

Synthesis of Pentasubstituted Aromatic 3.17:



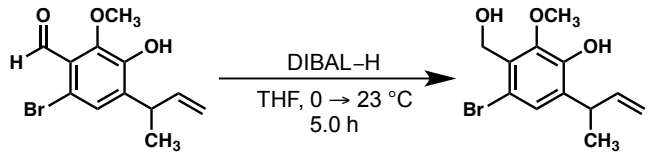
3.16 **35%** **3.17**

(4−Bromo−3−carbaldehyde−2−methoxy)phenyl crotyl ether **3.16** (100 mg, 0.35 mmol, 1 equiv) was dissolved in DMF:*m*xylene (1:2, 1 mL DMF:2 mL *m*xylene) in a 10 mL reaction vial and then was sealed under air. The reaction mixture was then heated in a microwave reactor at 180 °C for 2 h. It was then cooled down to 23 °C. The resultant mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 5% ethyl acetate−hexanes) to afford 3−(4−carbaldehyde−5−bromo−2−hydroxy−3−methoxyphenyl)−1−butene **3.17** (35 mg, 0.12 mmol, 35%) as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	10.31 (s, 1H), 7.21 (s, 1H), 6.08 (s, 1H), 5.99 (ddd, J_1 = 16.1 Hz, J_2 = 10.0 Hz, J_3 = 6.1 Hz, 1H), 5.19−5.14 (m, 1H), 5.10 (dt, J_1 = 4.5 Hz, J_2 = 1.5 Hz, 1H), 3.92 (s, 3H), 3.98−3.82 (m, 1H), 1.35 (d, J = 7.0 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	191.2, 148.1, 146.9, 140.4, 139.8, 128.5,

	124.3, 116.6, 114.9, 63.5, 36.6, 18.9.
HRMS ES^+ $[M+H]^+$:	Calcd for $C_{12}H_{14}O_3Br$: 285.0121. Found: 285.0120.
TLC:	30% ethyl acetate−hexanes, R_f = 0.46 (UV, CAM).

Synthesis of Benzalcohol 3.20:



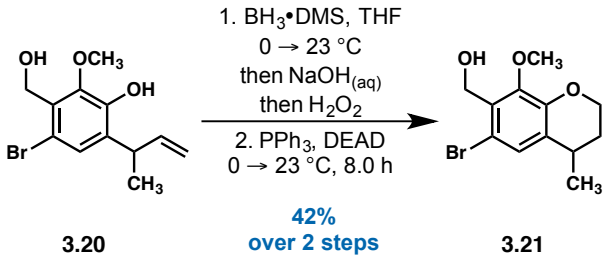
3.17 **96%** **3.20**

A solution of 3−(4−carbaldehyde−5−bromo−2−hydroxy−3−methoxyphenyl)−1−butene **3.17** (100 mg, 0.35 mmol, 1 equiv) in tetrahydrofuran (3 mL) was cooled down to 0 °C. After 15 min diisobutylaluminium hydride (1.0 M in hexane, 0.40 mL, 0.40 mmol, 1.14 equiv) was slowly added to the solution and then the resultant reaction mixture was warmed up to 23 °C. After stirring for 1.5 h in the same temperature, the reaction mixture's temperature was cooled down to 0 °C and was quenched by the slow addition of 1.0 N aqueous hydrochloric acid solution (2 mL). The resultant mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (5 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 25% ethyl acetate−hexanes) to afford 3−(5−bromo−4−hydroxymethyl−2−hydroxy−3−methoxyphenyl)−1−butene **3.20** (96.5 mg, 0.34 mmol, 96%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.12 (s, 1H), 6.05−5.95 (m, 1H), 5.76 (s, 1H), 5.12 (dt, J_1 = 6.7 Hz, J_2 = 1.5 Hz, 1H), 5.08 (d, J = 1.5 Hz, 1H), 4.76 (br s, 2H), 3.91 (s, 3H), 3.87−3.78 (m, 1H),

	2.22 (br s, 1H), 1.32 (d, J = 7.0 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	146.6, 146.2, 141.4, 134.1, 130.6, 127.3, 114.4, 114.2, 63.4, 60.0, 36.3, 19.2.
HRMS ES$^+$ [M−OH]$^+$:	Calcd for $C_{12}H_{14}O_2Br$: 269.0172. Found: 269.0172.
TLC:	30% ethyl acetate−hexanes, R_f = 0.22 (UV, CAM).

Synthesis of Dihydrobenzopyran 3.21:



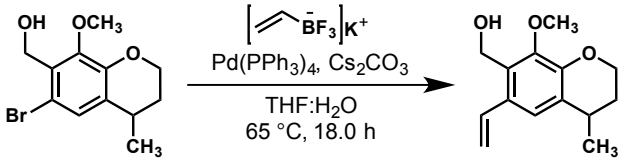
3.20 **3.21**

3−(5−bromo−4−hydroxymethyl−2−hydroxy−3−methoxyphenyl)−1−butene **3.20** (96.5 mg, 0.34 mmol, 1 equiv) was dissolved in tetrahydrofuran (4 mL). The reaction solution was cooled down to 0 °C and then a solution of boron dimethyl sulfide complex (2.0 M in tetrahydrofuran, 0.43 mL, 0.86 mmol, 2.53 equiv) was slowly added to the solution and then the resultant reaction mixture was warmed up to 23 °C and was stired for 2 h. A 4.0 N aqueous NaOH solution (0.43 mL, 1.72 mmol, 5.06 equiv) then was added dropwise to the reaction solution followed by stirring for 1 h, at that point the reaction mixture was cooled down to 0 °C and hydrogen peroxide (30%w/w, 0.43 mL, 4.18 mmol, 12.3 equiv) was added dropwise to the reaction mixture. The resultant reaction mixture then was warmed up to 23 °C and was stirred for 8 h. The reaction mixture was quenched by dropwise addition of 1.0 N aqueous hydrochloric acid solution (5 mL). The resultant mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (5 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 25% ethyl acetate−hexanes) to afford 3−(5−bromo−4−hydroxymethyl−2−hydroxy−3−methoxyphenyl)−1−butanol (80 mg). Triphenylphosphine (88.8 mg, 0.34 mmol, 1.00 equiv) was then added to a solution of

the resultant residue in tetrahydrofuran (4 mL) at 0 °C followed by addition of diethyl azodicarboxylate (0.08 mL, 0.51 mmol, 1.50 equiv). The resultant pale orange solution was warmed up to 23 °C and then stirred for 8 h. The reaction mixture was quenched by dropwise addition of 1.0 N aqueous hydrochloric acid solution (5 mL). The resultant mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (5 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 10% ethyl acetate−hexanes) to afford 6−bromo−5−hydroxymethyl−8−methoxy−4−methyl−3.4−dihydrobenzopyran **3.21** (40.5 mg, 0.14 mmol, 42% over 2 steps) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	7.13 (br s, 1H), 4.78 (s, 2H), 4.30−4.18 (m, 2H), 3.87 (s, 3H), 2.97−2.87 (m, 1H), 2.30 (br s, 1H), 2.12 (m, 1H), 1.76−1.66 (m, 1H), 1.31 (d, J = 7.0 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	147.9, 147.3, 131.6, 130.7, 127.5, 113.8, 64.3, 61.8, 60.4, 29.9, 28.6, 22.1.
TLC:	20% ethyl acetate−hexanes, R_f = 0.13 (UV, CAM).

Synthesis of Styrene 3.22:



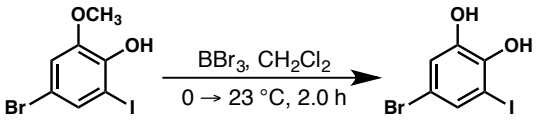
3.21 **81%** **3.22**

A solution of potassium vinyltrifluoroborate (33.6 mg, 0.25 mmol, 1.79 equiv), tetrakis(triphenylphosphane)palladium(0) (8.00 mg, 7.00 μmol, 5 mol%), cesium carbonate (144 mg, 0.44 mmol, 3.14 equiv), and 6−bromo−5−hydroxymethyl−8−methoxy−4−methyl−3.4−dihydrobenzopyran **3.21** (40.5 mg, 0.14 mmol, 1 equiv) in tetrahydrofuran:water (10:1, 3.0 mL tetrahydrofuran:0.3 mL H_2O) in a 10 mL glass pressure reactor was degassed by bubbling with argon for 15 min. The reactor was sealed and the reaction mixture was heated at 85 °C for 18 h. The reaction mixture was cooled down to 23 °C and quenched by the slow addition of water (50 mL). The resultant mixture was extracted with dichloromethane (3 × 5 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (4 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 15% ethyl acetate−hexanes) to afford 5−hydroxymethyl−8−methoxy−4−methyl−6−vinyl−3.4−dihydrobenzopyran **3.22** (26.8 mg, 0.11 mmol, 81%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.11 (s, 1H), 6.99 (dd, J_1 = 17.3 Hz, J_2 = 10.8 Hz, 1H), 5.56 (dd, J_1 = 17.3 Hz, J_2 =

	1.5 Hz, 1H), 5.25 (dd, J_1 = 10.8 Hz, J_2 = 1.5 Hz, 1H), 4.75 (s, 2H), 4.31−4.21 (m, 2H), 3.86 (s, 3H), 3.01−2.90 (m, 1H), 2.14−2.06 (m, 1H), 1.78−1.69 (s, 1H), 1.62 (br s, 1H), 1.35 (d, J = 7.0 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	147.3, 146.7, 134.0, 129.6, 129.5, 129.2, 121.6, 115.2, 64.2, 61.5, 57.0, 30.2, 28.6, 22.3.
TLC:	20% ethyl acetate−hexanes, R_f = 0.13 (UV, CAM, Anis).

Synthesis of Catechol 3.30:

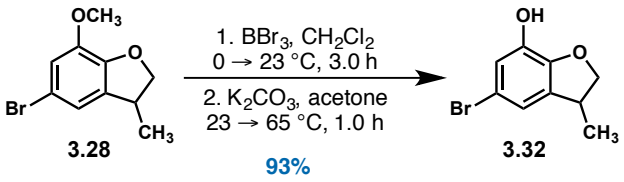


3.27 quant. **3.30**

A solution of boron tribromide (1.0 M in dichloromethane, 4.60 mL, 4.60 mmol, 1.51 equiv) was added dropwise to an ice–cooled solution of 4–bromo–6–iodo–2–methoxy–phenol **3.27** (1.00 g, 3.04 mmol, 1 equiv) in dichloromethane (15 mL). The resultant red solution was warmed to 23 °C and was stirred at that temperature for 2 h. The reaction solution then was cooled to 0 °C and excess boron tribromide was quenched by the cautious addition of water (20 mL) followed by the addition of 1.0 N aqueous hydrochloric acid solution (10 mL). The resultant biphasic mixture was extracted with dichloromethane (3 × 15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant oily residue was purified by flash column chromatography (silica gel, 25% ethyl acetate−hexanes) to afford 5–bromo–3–iodocatechol **3.30** (1.00 g, 3.04 mmol, quant.) as an orange solid.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	7.24 (d, J = 2.3 Hz, 1H), 6.89 (d, J = 2.3 Hz, 1H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	147.0, 146.9, 132.0, 119.1, 112.5, 84.6.

Synthesis of Phenol 3.32:

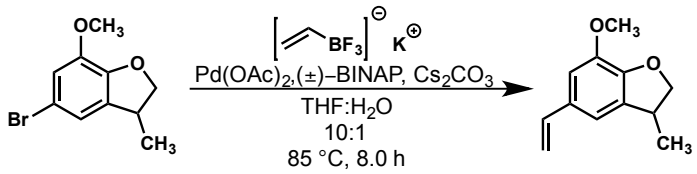


5–Bromo–7–methoxy–3–methyl–2,3–dihydrobenzofuran **3.28** (1.00 g, 4.11 mmol, 1 equiv) was dissolved in dichloromethane (20 mL) and was cooled down to 0 °C. A solution of boron tribromide (1.0 M in dichloromethane, 6.20 mL, 6.20 mmol, 1.51 equiv) was added dropwise. The resultant red solution was then warmed up to 23 °C and was stirred for 3 h. The reaction solution then was cooled down to 0 °C and the excess boron tribromide was quenched with the slow addition of water (20 mL) followed by addition of 1.0 N aqueous hydrochloric acid solution (15 mL). The resultant biphasic mixture was extracted with dichloromethane (3 × 15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant oily residue was dissolved in acetone (20 mL). Potassium carbonate (851 mg, 6.16 mmol, 1.50 equiv) was added to the reaction solution and the resultant heterogeneous mixture was warmed up to 65 °C and was stirred for 1 h. The reaction solution then was cooled down to 23 °C and the excess potassium carbonate was quenched with the slow addition of water (5 mL) followed by addition of 1.0 N aqueous hydrochloric acid solution (20 mL). The resultant mixture was extracted with ethyl acetate (3 × 40 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant oily residue was purified by flash column chromatography (silica gel, 15%

ethyl acetate−hexanes) to afford 5–bromo–7–hydroxy–3–methyl–2,3–dihydrobenzofuran **3.32** (876 mg, 3.83 mmol, 93%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	6.90 (d, *J* = 1.9 Hz, 1H), 6.87–6.80 (m, 1H), 5.18 (s, 1H), 4.74 (t, *J* = 8.8 Hz, 1H), 4.13 (app t, *J* = 8.4 Hz, 1H), 3.63–3.51 (m, 1H), 1.31 (d, *J* = 6.9 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	145.8, 141.0, 134.9, 119.0, 118.3, 112.7, 79.7, 37.5, 19.1.

Synthesis of Styrene 3.34:



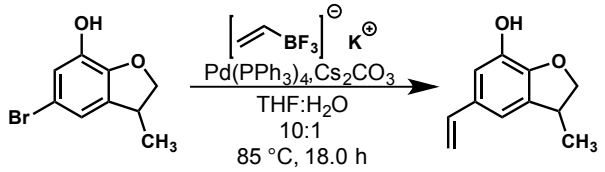
3.28 **78%** **3.34**

A solution of potassium vinyltrifluoroborate (958 mg, 7.23 mmol, 1.76 equiv), palladium(II) acetate (91.6 mg, 0.41 mmol, 10.0 mol%), 2,2'−bis(diphenylphosphino)−1,1'−binaphthyl (510 mg, 0.82 mmol, 20.0 mol%), cesium carbonate (4.00 g, 12.3 mmol, 3.00 equiv), and 5–bromo–7–methoxy–3–methyl–2,3–dihydrobenzofuran **3.28** (1.00 g, 4.11 mmol, 1 equiv) in tetrahydrofuran:water (10:1, 10 mL THF:1 mL H_2O) in a 25 mL glass pressure reactor was degassed by bubbling with argon for 15 min. The reactor was sealed and the reaction mixture was heated at 85 °C for 8 h. The reaction mixture was cooled down to 23 °C and quenched by the addition of water (30 mL). The resultant biphasic mixture was extracted with dichloromethane (3 × 40 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant oily residue was purified by flash column chromatography (silica gel, 15% ethyl acetate−hexanes) to afford 7–methoxy–3–methyl–5–vinyl–2,3–dihydrobenzofuran **3.34** (610 mg, 3.21 mmol, 78%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.86 (br s, 1H), 6.82 (d, J = 1.5 Hz, 1H), 6.65 (dd, J_1 = 17.5 Hz, J_2 = 10.8 Hz, 1H), 5.59 (dd, J_1 = 17.5 Hz, J_2 = 0.9 Hz, 1H),

	5.11 (dd, J_1 = 10.8 Hz, J_2 = 0.9 Hz, 1H), 4.75 (d, J = 8.8 Hz, 1H), 4.15 (dd, J_1 = 8.7 Hz, J_2 = 7.3 Hz, 1H), 3.89 (s, 3H), 3.60−3.49 (m, 1H), 1.33 (d, J = 6.9 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	148.1, 144.5, 136.9, 133.7, 131.7, 114.4, 111.4, 109.4, 79.6, 56.1, 37.1, 19.4.

Synthesis of Styrene 3.36:



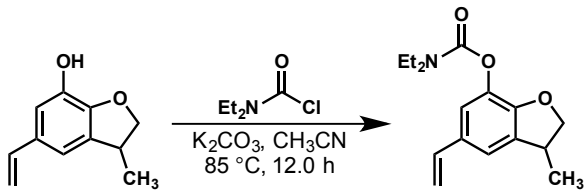
3.32 **85%** **3.36**

A solution of potassium vinyltrifluoroborate (509 mg, 3.84 mmol, 1.76 equiv), tetrakis(triphenylphosphane)palladium(0) (250 mg, 0.22 mmol, 10.0 mol%), cesium carbonate (2.13 g, 6.54 mmol, 3.00 equiv), and 5–bromo–7–hydroxy–3–methyl–2,3–dihydrobenzofuran **3.32** (500 mg, 2.18 mmol, 1 equiv) in tetrahydrofuran:water (10:1, 10 mL THF:1 mL H_2O) in a 25 mL glass pressure reactor was degassed by bubbling with argon for 15 min. The reactor was sealed and the reaction mixture was heated at 85 °C for 18 h. The reaction mixture was cooled down to 23 °C and quenched by the addition of water (30 mL). The resultant biphasic mixture was extracted with dichloromethane (3 × 40 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant oily residue was purified by flash column chromatography (silica gel, 15% ethyl acetate−hexanes) to afford 7–hydroxy–3–methyl–5–vinyl –2,3–dihydrobenzofuran **3.36** (328 mg, 1.86 mmol, 85%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.85 (d, J = 1.8 Hz, 1H), 6.82 (br s, 1H), 6.61 (dd, J_1 = 17.6 Hz, J_2 = 10.9 Hz, 1H), 5.58 (dd, J_1 = 17.6 Hz, J_2 = 0.9 Hz, 1H), 5.38 (br s, 1H), 5.10 (dd, J_1 = 10.9 Hz, J_2

	= 0.9 Hz, 1H), 4.75 (t, J = 8.8 Hz, 1H), 4.14 (dd, J_1 = 8.6 Hz, J_2 = 7.6 Hz, 1H), 3.62–3.51 (m, 1H), 1.33 (d, J = 6.9 Hz, 1H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	146.4, 140.2, 136.7, 133.5, 132.1, 113.9, 113.2, 111.7, 79.8, 37.3, 19.2.

Synthesis of Carbamate 3.37:



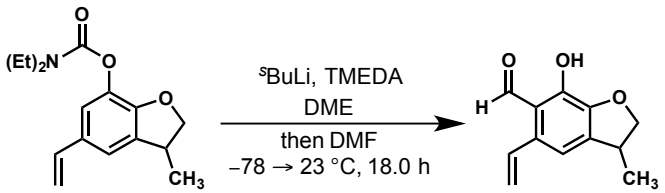
3.36 **94%** **3.37**

Diethylcarbamic chloride (0.50 mL, 3.95 mmol, 3.87 equiv) was added to a stirred solution of 7–hydroxy–3–methyl–5–vinyl –2,3–dihydrobenzofuran **3.36** (180 mg, 1.02 mmol, 1 equiv) and potassium carbonate (500 mg, 3.62 mmol, 3.55 equiv) in acetonitrile (6 mL). The reaction mixture was heated at 85 °C for 12 h, then it was concentrated. The resultant residue was extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant oily residue was purified by flash column chromatography (silica gel, 10% ethyl acetate−hexanes) to afford **3.37** as a yellow oil (264 mg, 0.96 mmol, 94%).

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.06 (br s, 1H), 6.99 (d, J = 1.8 Hz, 1H), 6.61 (dd, J_1 = 17.5 Hz, J_2 = 10.9 Hz, 1H), 5.57 (dd, J_1 = 17.6 Hz, J_2 = 0.8 Hz, 1H), 5.10 (dd, J_1 = 10.9 Hz, J_2 = 0.8 Hz, 1H), 4.76 (t, J = 8.8 Hz, 1H), 4.13 (dd, J_1 = 8.6 Hz, J_2 = 7.8 Hz, 1H), 3.63−3.51 (m, 1H), 3.50−3.32 (m, 4H), 1.34 (d, J = 6.9 Hz,

	3H), 1.29−1.16 (m, 6H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	153.9, 151.2, 136.4, 135.1, 135.0, 131.6, 120.6, 118.6, 111.9, 79.9, 42.5, 42.2, 37.0, 19.3, 14.4, 13.6.

Synthesis of Benzaldehyde 3.38:



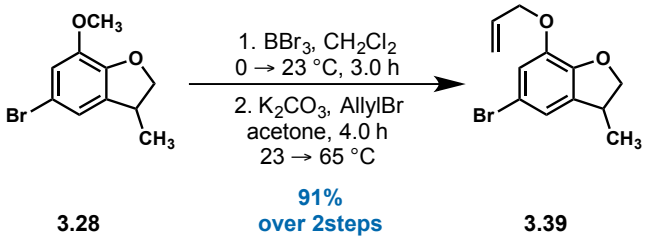
3.37 **51%** **3.38**

Tetramethylethylenediamine (1.24 mL, 8.26 mmol, 2.40 equiv) was added to a solution of **3.37** (947 mg, 3.44 mmol, 1 equiv) in dimethoxyethane (10 mL) at –78 °C. *s*−Butyl lithium (1.4 M in cyclohexane, 10.6 mL, 14.8 mmol, 4.32 equiv) was added dropwise to the resultant solution and then the resultant reaction mixture was warmed up to 23 °C and was stirred for 18 h. The excess *s*−butyl lithium was then quenched by the addition of water (5 mL) followed by addition of 1.0 N aqueous hydrochloric acid solution (15 mL).. The resultant biphasic mixture was extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant oily residue was purified by flash column chromatography (silica gel, 10% ethyl acetate−hexanes) to afford 6–carbaldehyde–7–hydroxy–3–methyl–5–vinyl –2,3–dihydrobenzofuran **3.38** (358 mg, 1.75 mmol, 51%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 11.74 (s, 1H), 10.26 (s, 1H), 7.16 (dd, J_1 = 17.2 Hz, J_2 = 10.9 Hz, 1H), 6.83 (s, 1H), 5.57 (dd, J_1 = 17.2 Hz, J_2 = 1.2 Hz, 1H), 5.47 (dd, J_1 = 10.9 Hz, J_2 = 1.2 Hz,

	1H), 4.80 (t, J = 9.0 Hz, 1H), 4.20 (dd, J_1 = 8.8 Hz, J_2 = 7.5 Hz, 1H), 3.64–3.53 (m, 1H), 1.36 (t, J = 6.9 Hz, 1H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	195.5, 147.1, 146.7, 141.4, 136.5, 132.1, 119.6, 117.6, 113.7, 79.2, 37.6, 18.8.

Synthesis of allyl phenyl ether 3.39:



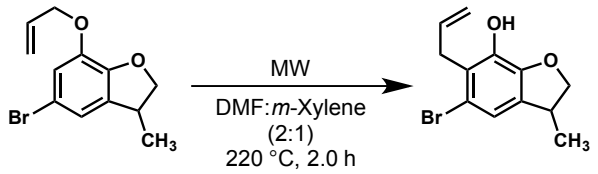
3.28 **3.39**

5–Bromo–7–methoxy–3–methyl–2,3–dihydrobenzofuran **3.28** (1.00 g, 4.11 mmol, 1 equiv) was dissolved in dichloromethane (20 mL) and was cooled down to 0 °C. A solution of boron tribromide (1.0 M in dichloromethane, 6.20 mL, 6.20 mmol, 1.51 equiv) was added dropwise. The resultant red solution was then warmed up to 23 °C and was stirred for 3 h. The reaction solution then was cooled down to 0 °C and the excess boron tribromide was quenched with the slow addition of water (20 mL) followed by addition of 1.0 N aqueous hydrochloric acid solution (15 mL). The resultant biphasic mixture was extracted with dichloromethane (3 × 15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant oily residue was dissolved in acetone (20 mL). potassium carbonate (851 mg, 6.16 mmol, 1.50 equiv) was added to the reaction solution followed by addition of allyl bromide (0.57 mL, 6.58 mmol, 1.60 equiv) and the resultant heterogeneous mixture was warmed up to 65 °C and was stirred for 4 h. The reaction solution then was cooled down to 23 °C and the excess Potassium carbonate was quenched with the slow addition of water (5 mL) followed by addition of 1.0 N aqueous hydrochloric acid solution (20 mL). The resultant mixture was extracted with ethyl acetate (3 × 40 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL) and then were dried over

anhydrous sodium sulfate. The dried solution was concentrated, and the resultant oily residue was purified by flash column chromatography (silica gel, 10% ethyl acetate−hexanes) to afford 5–bromo–7–allyloxy–3–methyl–2,3–dihydrobenzofuran **3.39** (1.01 g, 3.74 mmol, 91%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	6.94–6.88 (m, 1H), 6.86 (d, J = 1.8 Hz, 1H), 6.05 (ddt, J_1 = 17.3 Hz, J_2 = 10.5 Hz, J_3 = 5.5 Hz, 1H), 5.40 (dq, J_1 = 17.2 Hz, J_2 = 1.6 Hz, 1H), 5.29 (dq, J_1 = 10.4 Hz, J_3 = 1.3 Hz, 1H), 4.73 (t, J = 8.9 Hz, 1H), 4.58 (dt, J_1 = 5.5 Hz, J_2 = 1.5 Hz, 2H), 4.14 (dd, J_1 = 8.7 Hz, J_2 = 7.5 Hz, 1H), 3.61–3.47 (m, 1H), 1.30 (d, J = 6.8 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	147.7, 144.0, 135.4, 132.9, 119.6, 118.5, 116.5, 112.1, 79.4, 70.2, 37.2, 19.3.

Synthesis of 3.40:

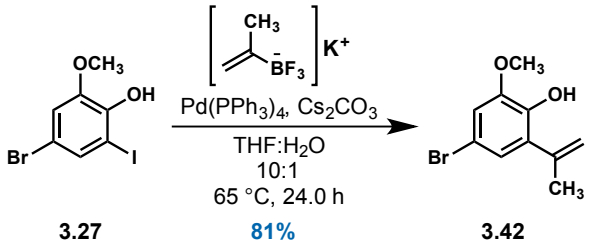


3.39 **74%** **3.40**

5–Bromo–7–allyloxy–3–methyl–2,3–dihydrobenzofuran **3.39** (200 mg, 0.35 mmol, 1 equiv) was dissolved in DMF:*m*xylene (1:2, 1 mL DMF:2 mL *m*xylene) in a 10 mL reaction vial and then was sealed under air. The reaction mixture was then heated in a microwave reactor at 220 °C for 2 h. It was then cooled down to 23 °C. The resultant mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 5% ethyl acetate−hexanes) to afford 6–allyl–5–bromo–7–hydroxy–3–methyl–2,3–dihydrobenzofuran **3.40** (148 mg, 0.55 mmol, 74%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	6.95 (app d, J = 1.0 Hz, 1H), 5.95 (ddt, J_1 = 17.1 Hz, J_2 = 10.1 Hz, J_3 = 6.1 Hz, 1H), 5.12–5.03 (m, 2H), 5.03 (s, 1H), 4.73 (t, J = 8.7 Hz, 1H), 4.12 (dd, J_1 = 8.6 Hz, J_2 = 7.5 Hz, 1H), 3.62–3.52 (m, 3H), 1.30 (d, J = 6.9 Hz, 1H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	146.2, 139.2, 134.9, 132.3, 125.4, 119.3, 115.7, 115.5, 79.8, 37.5, 33.9, 19.2.

Synthesis of 3.42



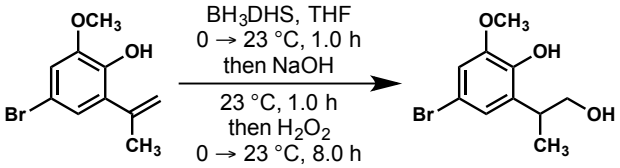
3.27 **81%** **3.42**

A solution of potassium isopropenyltrifluoroborate (792 mg, 5.35 mmol, 1.76 equiv), tetrakis(triphenylphosphane)palladium(0) (341 mg, 0.30 mmol, 10.0 mol%), cesium carbonate (2.97 g, 9.12 mmol, 3.00 equiv), and 4−bromo−6−iodo−2−methoxy−phenol **3.27** (1.00 g, 3.04 mmol, 1 equiv) in tetrahydrofuran:water (10:1, 15 mL THF:1.5 mL H_2O) in a 50 mL glass pressure reactor was degassed by bubbling with argon for 15 min. The reactor was sealed and the reaction mixture was heated at 65 °C for 24 h. The reaction mixture was cooled down to 23 °C and quenched by the addition of water (30 mL). The resultant biphasic mixture was extracted with dichloromethane (3 × 40 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant oily residue was purified by flash column chromatography (silica gel, 10% ethyl acetate−hexanes) to afford 4−bromo−6−isopropenyl−2−methoxy−phenol **3.42** (599 mg, 2.46 mmol, 81%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.97 (d, J = 2.2 Hz, 1H), 6.90 (d, J = 2.2 Hz, 1H), 5.81 (s, 1H), 5.27−5.23 (m, 1H), 5.23−5.19 (m, 1H), 3.89 (s, 3H), 2.12 (d, J = 1.1 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$), δ:	147.3, 142.0, 141.4, 130.7, 123.9, 116.6, 112.9, 111.2, 56.5, 23.1.

Synthesis of 3.43



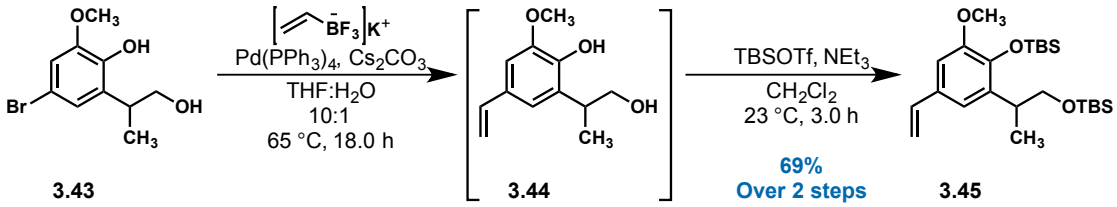
3.42 **75%** **3.43**

4−bromo−6−isopropenyl−2−methoxy−phenol **3.42** (599 mg, 2.46 mmol, 1 equiv) was dissolved in THF (10 mL) and was cooled down to 0 °C and then a solution of boron dimethyl sulfide complex (2.0 M in tetrahydrofuran, 3.08 mL, 6.16 mmol, 2.50 equiv). The reaction mixture then was then warming up to 23 °C and stirred for 2 h. Then a 4.0 N aqueous NaOH solution (3.07 mL, 12.3 mmol, 5.00 equiv) was added dropwise to the reaction. The reaction solution then was stirred for 1 h and then was cooled down to 0 °C and a 30%w/w hydrogen peroxide (3.10 mL, 30.3 mmol, 12.3 equiv) was added dropwise to the reaction mixture. The reaction solution then was warmed up to 23 °C and was stirred for 8 h. The reaction solution then was quenched by the addition of 1.0 N aqueous hydrochloric acid solution (40 mL). The resultant biphasic mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant oily residue was purified by flash column chromatography (silica gel, 20% ethyl acetate−hexanes) to afford 2−(5−bromo−3−methoxy−2−hydroxyphenyl)−1−propanol **3.43** (483 mg, 1.85 mmol, 75%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.92 (d, J = 2.2 Hz, 1H), 6.87 (d, J = 2.2

	Hz, 1H), 6.04 (br s, 1H), 3.87 (s, 3H), 3.73 (d, *J* = 7.0 Hz, 2H), 3.40−3.29 (m, 1H), 1.25 (d, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	147.4, 142.9, 131.4, 122.7, 112.4, 111.7, 67.7, 56.4, 35.8, 16.3.

Synthesis of 3.45:



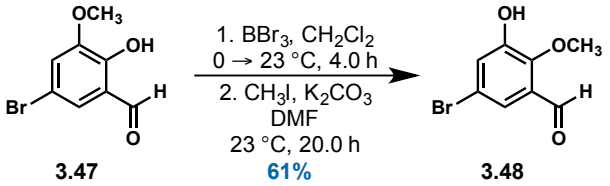
A solution of potassium vinyltrifluoroborate (432 mg, 3.26 mmol, 1.76 equiv), tetrakis(triphenylphosphane)palladium(0) (216 mg, 0.19 mmol, 10.0 mol%), cesium carbonate (1.81 g, 5.55 mmol, 3.00 equiv), and 2−(5−bromo−3−methoxy−2−hydroxyphenyl)−1−propanol **3.43** (483 mg, 1.85 mmol, 1 equiv) in tetrahydrofuran:water (10:1, 10 mL THF:1 mL H_2O) in a 25 mL glass pressure reactor was degassed by bubbling with argon for 15 min. The reactor was sealed and the reaction mixture was heated at 85 °C for 18 h. The reaction mixture was cooled down to 23 °C and quenched by the addition of water (20 mL). The resultant biphasic mixture was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant oily residue was purified by flash column chromatography (silica gel, 10% ethyl acetate−hexanes) to afford 2−(5−vinyl−3−methoxy−2−hydroxyphenyl)−1−propanol **3.44** (385 mg).

Triethylamine (1.40 mL, 10.01 mmol, 3.07 equiv) was added to a solution of **3.44** (385 mg) and dimethyl(2−methyl−2−propanyl)silyl trifluoromethanesulfonate (1.47 g, 5.55 mmol, 3.00 equiv) in dichloromethane (30 mL). The reaction solution then was stirred for 3 h and then was quenched by the addition of 1.0 N aqueous hydrochloric acid solution (40 mL). The resultant biphasic mixture was extracted with

dichloromethane (3 × 40 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (40 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant oily residue was purified by flash column chromatography (silica gel, 5% ethyl acetate−hexanes) to afford **3.45** (559 mg, 1.28 mmol, 69% over 2 steps) as a yellow viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	6.86 (d, J = 2.1 Hz, 1H), 6.81 (d, J = 2.0 Hz, 1H), 6.64 (dd, J_1 = 17.5 Hz, J_2 = 10.8 Hz, 1H), 5.60 (dd, J_1 = 17.5 Hz, J_2 = 1.0 Hz, 1H), 5.13 (dd, J_1 = 10.8 Hz, J_2 = 0.9 Hz, 1H), 3.81 (s, 3H), 3.75−3.68 (m, 1H), 3.52−3.43 (m, 2H), 1.25 (d, J = 6.3 Hz, 3H), 1.02 (s, 9H), 0.88 (s, 9H), 0.20 (app d, J = 6.1 Hz, 6H), −0.01 (app d, J = 3.5 Hz, 6H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	149.9, 142.6, 137.2, 135.5, 130.3, 118.2, 111.5, 106.4, 67.9, 54.8, 34.4, 26.3, 26.0, 19.1, 18.4, 17.3, −3.7, −3.7, −5.3, −5.3.

Synthesis of Benzaldehyde 3.48:

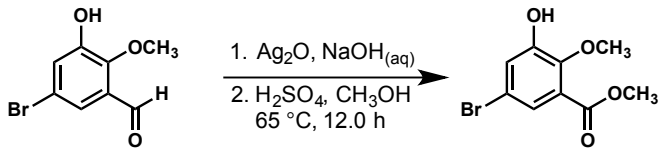


5−Bromo−2−hydroxy−3−methoxybenzaldehyde **3.47** (10.7 g, 46.4 mmol, 1 equiv) was dissolved in dichloromethane (150 mL) and then the resultant dark brown solution was cooled down to 0 °C and boron tribromide (1.0 M in dichloromethane, 57 mL, 57 mmol, 1.23 equiv) was added dropwise from a dropping funnel to it. The resultant dark red solution was warmed up to 23 °C and was stirred for 4 h. The solution was then cooled down to 0 °C and was quenched with the slow addition of water (70 mL) followed by addition of 1.0 N aqueous hydrochloric acid solution (105 mL). The resultant mixture was extracted with dichloromethane (3 × 250 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 20% ethyl acetate−hexanes) to afford a yellow solid (10.0 g) which was dissolved in *N,N*−dimethylformamide (100 mL) alongside potassium carbonate (6.21 g, 44.9 mmol, 0.97 equiv). To the resultant dark green suspension methyl iodide (3.10 mL, 49.8 mmol, 1.08 equiv) was added dropwise and then the resultant mixture was stirred at 23 °C for 20 h. The excess of potassium carbonate then was quenched with the slow addition of 1.0 N aqueous hydrochloric acid solution (100 mL). The resultant solution was extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with saturated aqueous sodium chloride

solution (100 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 10% ethyl acetate−hexanes) to afford 5−bromo−3−hydroxy−2−methoxybenzaldehyde **3.48** (6.51 g, 28.2 mmol, 61%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	10.20 (s, 1H), 7.49 (d, *J* = 2.4 Hz, 1H), 7.36 (d, *J* = 2.4 Hz, 1H), 5.86 (s, 1H), 3.97 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	188.1, 150.5, 148.7, 130.0, 124.8, 124.1, 117.9, 64.4.
FTIR (KBr, thin film), cm^{-1}:	3270, 1666.
HRMS: ES+ [M+H]+:	Calcd for $C_8H_8O_3Br$: 230.9651 Found: 230.9645.
TLC:	20% ethyl acetate–hexanes, R_f = 0.18 (UV, CAM, $KMnO_4$).

Synthesis of 3.49:

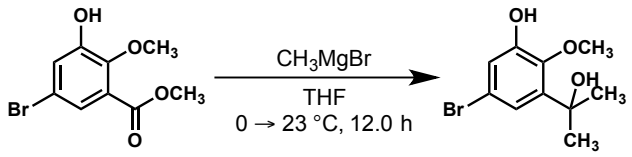


3.48 **94%** **3.49**

Silver oxide (13.2 g, 57.0 mmol, 2.02 equiv) was added to a solution of 5–bromo–3–hydroxy–2–methoxybenzaldehyde **3.48** (6.51 g, 28.2 mmol, 1 equiv) in 4.0 N aqueous NaOH solution (50 mL). The resultant suspension then was stirred at 23 °C for 10 h under air. The suspension then was filtered through a Büchner funnel and the filtrate was acidified with a 1.0 N aqueous hydrochloric acid solution (210 mL). The resultant suspension then was extracted with ethyl acetate (3 × 250 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the remaining residue was dissolved in methanol (150 mL) and was cooled down to 0 °C. Concentrated sulfuric acid (10 mL) was added over 15 min to the cold solution and then it was heated at 65 °C for 12 h. The reaction solution was cooled down to 23 °C and was diluted with addition of water (150 mL). The resultant mixture was extracted with diethyl ether (3 × 150 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (150 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 20% ethyl acetate−hexanes) to afford methyl 5−bromo−3−hydroxy−2−methoxybenzoate **3.49** (6.89 g, 26.4 mmol, 94%) as a dark yellow oily solid.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	7.52 (d, *J* = 2.4 Hz, 1H), 7.29 (d, *J* = 2.4 Hz, 1H), 6.00 (s, 1H), 3.92 (s, 3H), 3.90 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	164.7, 150.8, 146.7, 125.5, 124.7, 122.7, 116.8, 62.7, 52.7.
HRMS: ES+ [M+H]+:	Calcd for $C_9H_{10}O_4Br$: 260.9757 Found: 260.9760.
TLC:	20% ethyl acetate−hexanes, R_f = 0.29 (UV, CAM, $KMnO_4$).

Synthesis of Tertiary Alcohol 3.50:



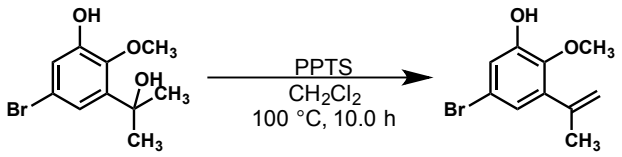
3.49 **91%** **3.50**

Methylmagnesium bromide (3.0 M in tetrahydrofuran, 35.0 mL, 105 mmol, 3.98 equiv) was added dropwise to a solution of methyl 5−bromo−3−hydroxy−2−methoxybenzoate **3.49** (6.89 g, 26.4 mmol, 1.00 equiv) in tetrahydrofuran (100 mL) at 0 °C. The resultant suspension then was warmed up to 23 °C and was stirred for 12 h. The resultant solution then was cooled down to 0 °C and the excess methylmagnesium bromide was quenched with slow addition of water (50 mL) followed by addition of 1.0 N aqueous hydrochloric acid solution (100 mL). The resultant mixture was extracted with ethyl acetate (3 × 150 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 15% ethyl acetate−hexanes) to afford 2−(5−bromo−3−hydroxy−2−methoxyphenyl)−2−propanol **3.50** (6.24 g, 23.9 mmol, 91%) as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	7.03 (d, J = 2.4 Hz, 1H), 6.99 (d, J = 2.4 Hz, 1H), 5.67 (s, 1H), 3.91 (s, 3H), 3.70 (s, 1H), 1.60 (s, 6H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	150.1, 144.7, 142.8, 121.4, 119.2, 117.1,

	73.1, 61.7, 31.0.
HRMS: LIFDI $[M]^+$:	Calcd for $C_{10}H_{13}O_3Br$: 260.0048 Found: 260.0053.
TLC:	20% ethyl acetate−hexanes, R_f = 0.21 (UV, CAM, $KMnO_4$).

Synthesis of Styrene 3.51:



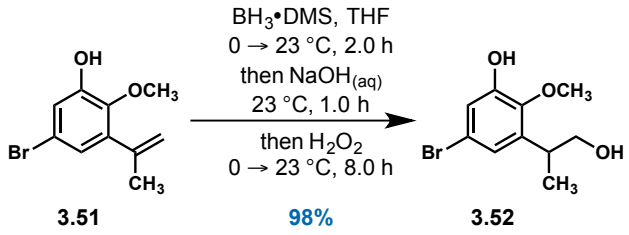
3.50 **93%** **3.51**

Pyridinium *p*–toluenesulfonate (13.8 g, 55.0 mmol, 2.30 equiv) was added to a mixture of 2−(5−bromo−3−hydroxy−2−methoxyphenyl)−2−propanol **3.50** (6.24 g, 23.9 mmol, 1 equiv) in dichloromethane (150 mL) in a 500 mL glass pressure reactor. The reactor was sealed and the resultant yellow reaction solution was heated at 100 °C for 10 h. The reaction solution was cooled down to 0 °C and then was quenched with the addition of water (150 mL). The resultant mixture was extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 10% ethyl acetate−hexanes) to afford 2−(5−bromo−3−hydroxy−2−methoxyphenyl)propene **3.51** (5.43 g, 22.3 mmol, 93%) as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	7.03 (d, J = 2.5 Hz, 1H), 6.87 (d, J = 2.5 Hz, 1H), 5.86−5.83 (br s, 1H), 5.23−5.18 (m, 2H), 3.74 (s, 3H), 2.10 (t, J = 1.2 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	149.8, 143.4, 141.7, 137.6, 123.7, 117.5, 116.9, 116.8, 60.9, 22.7.

FTIR (KBr, thin film), cm^{-1}:	3492, 2972, 1635.
HRMS: ES^+ $[M+H]^+$:	Calcd for $C_{10}H_{12}O_2Br$: 243.0015 Found: 243.0013.
TLC:	20% ethyl acetate−hexanes, R_f = 0.47 (UV, CAM, Anis).

Synthesis of Primary Alcohol 3.52:

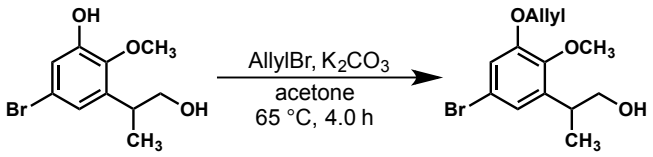


Boron dimethyl sulfide complex (2.0 M in tetrahydrofuran, 28.0 mL, 56.0 mmol, 2.51 equiv) was added to a solution of 2−(5−bromo−3−hydroxy−2−methoxyphenyl)propene **3.51** (5.43 g, 22.3 mmol, 1 equiv) in tetrahydrofuran (75 mL) at 0 °C. The resultant mixture then was warmed up to 23 °C and was stirring for 2 h whereupon a 4.0 N aqueous NaOH solution (28 mL, 112 mmol, 5.02 equiv) was added dropwise followed by stirring for 1 h. The reaction mixture then was cooled down to 0 °C and a 30%w/w hydrogen peroxide (28.0 mL, 274 mmol, 12.3 equiv) was added dropwise to it and then the resultant mixture was warmed up to 23 °C followed by stirring for 8 h. The reaction mixture was quenched by dropwise addition of 1.0 N aqueous hydrochloric acid solution (50 mL) and then it was extracted with ethyl acetate (3 × 150 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 20% ethyl acetate−hexanes) to afford 2−(5−bromo−3−hydroxy−2−methoxyphenyl)−1−propanol **3.52** (5.72 g, 21.9 mmol, 98%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.99 (d, J = 2.3 Hz, 1H), 6.88 (d, J = 2.3 Hz, 1H), 5.89 (s, 1H), 3.77 (s, 3H),

	3.74−3.63 (m, 2H), 3.38−3.28 (m, 1H), 1.23 (d, J = 7.0 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	150.1, 144.9, 139.1, 121.6, 117.9, 117.6, 68.1, 62.0, 34.9, 17.7.
HRMS: ES^+ $[M+H]^+$:	Calcd for $C_{10}H_{14}O_3Br$: 261.0121 Found: 261.0123.
TLC:	60% ethyl acetate−hexanes, R_f = 0.38 (UV, CAM, $KMnO_4$).

Synthesis of Phenyl Allyl Ether 3.53:



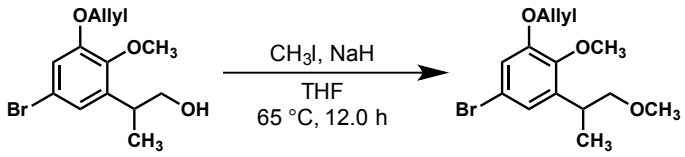
3.52 **97%** **3.53**

Allyl bromide (2.50 mL, 28.9 mmol, 1.32 equiv) was added to a solution of 2−(5−bromo−3−hydroxy−2−methoxyphenyl)−1−propanol **3.52** (5.72 g, 21.9 mmol, 1 equiv) and potassium carbonate (3.63 g, 26.3 mmol, 1.20 equiv) in acetone (100 mL). The resulted yellow solution then was heated at 65 °C for 4 h. The reaction mixture was then cooled down to 23 °C and the excess potassium carbonate was quenched by the dropwise addition of water (50 mL) and subsequent addition of 1.0 N aqueous hydrochloric acid solution (30 mL). The resultant solution then was extracted with ethyl acetate (3 × 100 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL) and were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 10% ethyl acetate−hexanes) to afford 2−(3−allyloxy−5−bromo−2−methoxyphenyl)−1−propanol **3.53** (6.39 g, 21.2 mmol, 97%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.95 (d, J = 2.3 Hz, 1H), 6.92 (d, J = 2.3 Hz, 1H), 6.11−6.00 (m, 1H), 5.44 (dq, J_1 = 17.3 Hz, J_2 = 1.6 Hz, 1H), 5.31 (dq, J_1 = 10.6 Hz, J_2 = 1.4 Hz, 1H), 4.55 (dt, J_1 = 5.2 Hz, J_2 = 1.6 Hz, 2H), 3.83 (s, 3H),

	3.73−3.63 (m, 2H), 3.44−3.34 (m, 1H), 1.57 (s, 1H), 1.22 (d, *J* = 7.0 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	152.5, 146.8, 139.5, 132.7, 122.4, 118.1, 116.7, 115.5, 69.7, 68.1, 61.1, 35.4, 17.3.
HRMS: ES^+ $[M+H]^+$:	Calcd for $C_{13}H_{18}O_3Br$: 301.0434 Found: 301.0432.
TLC:	20% ethyl acetate−hexanes, R_f = 0.16 (UV, CAM, $KMnO_4$).

Synthesis of 3.54:



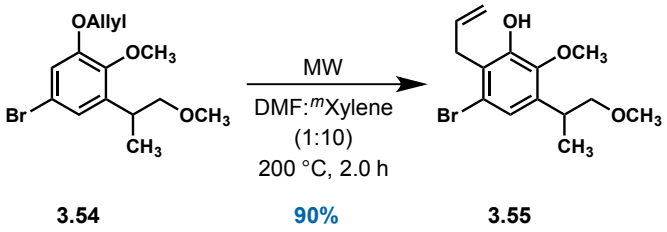
3.53 **90%** **3.54**

On sodium hydride (1.02 g, 25.5 mmol, 1.20 equiv) was added a 0 °C solution of 2−(3−allyloxy−5−bromo−2−methoxyphenyl)−1−propanol **3.53** (6.39 g, 21.2 mmol, 1 equiv) in tetrahydrofuran (100 mL) through a cannula. Methyl iodide (1.70 mL, 27.3 mmol, 1.29 equiv) was added to the reaction mixture and the resultant suspension then was heated at 65 °C for 12 h. The reaction mixture was then cooled down to 0 °C and the excess sodium hydride was quenched by dropwise addition of water (50 mL) and subsequent addition of 1.0 N aqueous hydrochloric acid solution (30 mL). It was then extracted with diethyl ether (3 × 100 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL) and were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 10% ethyl acetate−hexanes) to afford 2−(3−allyloxy−5−bromo−2−methoxyphenyl)−1−propanyl methyl ether **3.54** (6.02 g, 19.1 mmol, 90%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.93 (d, J = 2.3 Hz, 1H), 6.89 (d, J = 2.3 Hz, 1H), 6.11−6.01 (m, 1H), 5.44 (dq, J_1 = 17.2 Hz, J_2 = 1.6 Hz, 1H), 5.30 (dq, J_1 = 10.5 Hz, J_2 = 1.4 Hz, 1H), 4.54 (dt, J_1 = 5.2 Hz, J_2 = 1.6 Hz, 2H), 3.82 (s, 3H),

	3.53−3.35 (m, 3H), 3.32 (s, 3H), 1.21 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	152.4, 146.5, 140.1, 132.8, 122.5, 118.0, 116.5, 115.3, 77.8, 69.7, 61.0, 59.0, 32.7, 18.1.
FTIR (KBr, thin film), cm^{-1}:	2967, 1649.
HRMS: ES^+ $[M+H]^+$:	Calcd for $C_{14}H_{20}O_3Br$: 315.0590 Found: 315.0584.
TLC:	20% ethyl acetate−hexanes, R_f = 0.54 (UV, CAM, $KMnO_4$).

Synthesis of 3.55:



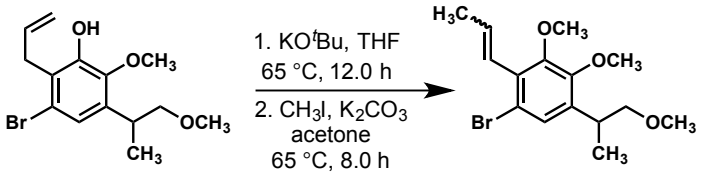
3.54 **90%** **3.55**

2−(3−Allyloxy−5−bromo−2−methoxyphenyl)−1−propanyl methyl ether **3.54** (2.00 g, 6.35 mmol, 1 equiv) was dissolved in *N,N*−dimethylformamide:*m*xylene (1:10, 3 mL DMF:30 mL *m*xylene) in a 100 mL reaction vial and then was sealed under air. The resultant reaction mixture was then heated in a microwave reactor at 200 °C for 2 h. It was then cooled down to 23 °C and was extracted with ethyl acetate (3 × 50 mL) from water (15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 15% ethyl acetate−hexanes) to afford 2−(4−allyl−5−bromo−3−hydroxy−2−methoxyphenyl)−1−propanyl methyl ether **3.55** (1.80 g, 5.71 mmol, 90%) as a pale yellow oil.

1H NMR (400 MHz, $CDCl_3$), δ:	6.96 (s, 1H), 6.00−5.90 (m, 1H), 5.78 (s, 1H), 5.13−5.01 (m, 2H), 3.78 (s, 3H), 3.62−3.51 (m, 2H), 3.51−3.23 (m, 6H), 1.22 (d, J = 6.7 Hz, 3H).
13C NMR (100 MHz, $CDCl_3$), δ:	148.0, 144.3, 140.0, 134.8, 124.5, 122.0, 120.6, 115.7, 78.0, 62.1, 59.1, 34.3, 32.4, 18.6.

FTIR (KBr, thin film), cm-1:	2967, 1649
HRMS: ES+ [M+H]+:	Calcd for $C_{14}H_{20}O_3Br$: 315.0590 Found: 315.0588.
TLC:	20% ethyl acetate−hexanes, R_f = 0.45 (UV, CAM, $KMnO_4$).

Synthesis of 3.56:



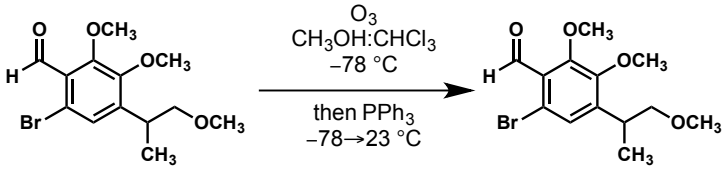
3.55 **71%** **3.56**

Potassium ^{t}butoxide (3.21 g, 28.6 mmol, 5.01 equiv) was added to a solution of 2−(4−allyl−5−bromo−3−hydroxy−2−methoxyphenyl)−1−propanyl methyl ether **3.55** (1.80 g, 5.71 mmol, 1 equiv) in tetrahydrofuran (40 mL). The resultant suspension was heated at 65 °C for 12 h. It was then cooled down to 23 °C and the excess potassium ^{t}butoxide was quenched with the dropwise addition of 1.0 N aqueous hydrochloric acid solution (35 mL). It was then extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL) and were dried over anhydrous sodium sulfate. The dried solution was concentrated and then was dissolved in acetone (30 mL) alongside potassium carbonate (1.18 g, 8.54 mmol, 1.50 equiv). Methyl iodide (0.64 mL, 10.3 mmol, 1.80 equiv) was added to the resultant reaction mixture. The resultant solution was heated at 65 °C for 5 h. It was then cooled down to 23 °C and the excess potassium carbonate was quenched with the dropwise addition of 1.0 N aqueous hydrochloric acid solution (20 mL). The resultant solution was then extracted with ethyl acetate (3 × 75 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL) and were dried over anhydrous sodium sulfate. The dried solution was concentrated and purified by flash column chromatography (silica gel, 15% ethyl acetate−hexanes) to afford

2−(5−bromo−2,3−dimethoxy−4−propenylphenyl)−1−propanyl methyl ether **3.56** (1.33 g, 4.04 mmol, 71%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	7.16 (s, 1H), 6.47−6.30 (m, 2H), 3.84 (s, 3H), 3.77 (s, 3H), 3.46−3.29 (m, 6H), 1.93 (d, *J* = 4.6 Hz, 3H), 1.21 (d, *J* = 4.6 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	152.0, 151.1, 138.1, 132.8, 130.6, 126.6, 125.8, 118.2, 77.8, 61.0, 60.0, 59.0, 32.7, 19.6, 18.1.
HRMS: ES^+ $[M+H]^+$:	Calcd for $C_{15}H_{22}O_3Br$: 329.0747 Found: 329.0744.
TLC:	20% ethyl acetate−hexanes, R_f = 0.55 (UV, CAM, $KMnO_4$).

Synthesis of Benzaldehyde 3.57:



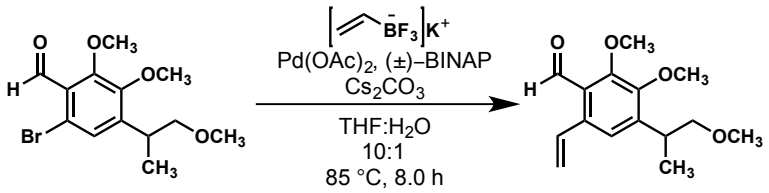
3.56 **91%** **3.57**

A constant stream of ozone was passed through the pale yellow solution of 2−(5−bromo−2,3−dimethoxy−4−propenylphenyl)−1−propanyl methyl ether **3.56** (1.33 gr, 4.04 mmol, 1.00 equiv) in methanol:dichloromethane (1:3, 10 mL CH_3OH:30 mL CH_2Cl_2) under air at −78 °C until the color of solution was turned into a persistent blue at which point the stream of ozone would be exchanged for a stream of oxygen until the blue color was dispersed. The reaction mixture was then quenched with the addition of triphenylphosphine (2.55 gr, 9.74 mmol, 2.41 equiv). The resultant suspension was then warmed up to 23 °C and was stirred for 4 h. It was then concentrated and the resultant residue was purified by flash column chromatography (5% ethyl acetate−hexanes) to afford 2−(5−bromo−4−formyl−2,3−dimethoxyphenyl)−1−propanyl methyl ether **3.57** (1.17 gr, 3.69 mmol, 91%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	10.29 (s, 1H), 7.26 (s, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 3.53−3.40 (m, 3H), 3.32 (s, 3H), 1.22 (d, J = 6.3 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	190.4, 156.0, 151.4, 146.2, 128.2, 127.0, 118.2, 77.2, 62.1, 61.2, 59.1, 33.2, 17.8.
HRMS: ES$^+$ $[M+H]^+$:	Calcd for $C_{13}H_{18}O_4Br$: 317.0383 Found:

	317.0384.
TLC:	20% ethyl acetate−hexanes, R_f = 0.40 (UV, CAM, $KMnO_4$).

Synthesis of Styrene 3.58:

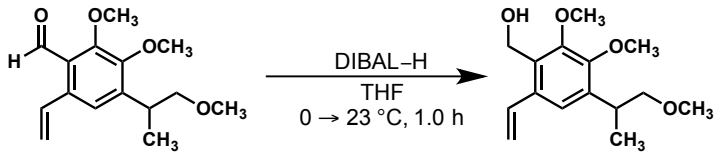


A solution of potassium vinyltrifluoroborate (693 mg, 5.17 mmol, 1.40 equiv), palladium(II) acetate (23.0 mg, 0.102 mmol, 2.76 mol%), triphenylphosphine (148 mg, 0.564 mmol, 15.3 mol%), cesium carbonate (4.24 gr, 13.0 mmol, 3.52 equiv), and 2−(5−bromo−4−formyl−2,3−dimethoxyphenyl)−1−propanyl methyl ether **3.57** (1.17 gr, 3.69 mmol, 1.00 equiv) in tetrahydrofuran:water (10:1, 15 mL THF:1.5 mL H_2O) in a 75 mL glass pressure reactor was degassed by bubbling with argon for 15 min. The reactor was sealed and the reaction mixture was heated at 85 °C for 8 h. The reaction mixture was cooled down to 23 °C and quenched by the addition of water (20 mL). The resultant mixture was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 10% ethyl acetate−hexanes) to afford 2−(4−formyl−2,3−dimethoxy−5−vinylphenyl)−1−propanyl methyl ether **3.58** (859 mg, 3.25 mmol, 88%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 10.48 (s, 1H), 7.44 (dd, J_1 = 17.4 Hz, J_2 = 10.9 Hz, 1H), 7.15 (s, 1H), 5.56 (dd, J_1 = 17.4 Hz, J_2 = 1.4 Hz, 1H), 5.32 (dd, J_1 =

	10.9 Hz, J_2 = 1.4 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 3.55−3.42 (m, 3H), 3.32 (s, 3H), 1.26 (d, J = 6.4 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	192.0, 156.8, 150.7, 145.5, 135.8, 135.5, 125.7, 121.4, 116.8, 77.6, 62.0, 61.0, 59.0, 33.4, 17.9.
HRMS: LIFDI$^+$ $[M]^+$:	Calcd for $C_{15}H_{20}O_4$: 264.1362. Found: 264.1369.
TLC:	20% ethyl acetate−hexanes, R_f = 0.40 (UV, CAM, Anis).

Synthesis of Benzalcohol 3.59:



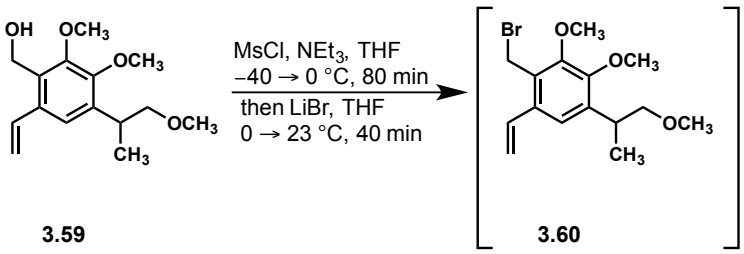
3.58 **99%** **3.59**

Diisobutylaluminium hydride (1.0 M in hexane, 5.00 mL, 5 mmol, 1.54 equiv) was slowly added to the solution of 2−(4−formyl−2,3−dimethoxy−5−vinylphenyl)−1−propanyl methyl ether **3.58** (859 mg, 3.25 mmol, 1 equiv) in tetrahydrofuran (15 mL) at 0 °C and then the resultant reaction mixture was warmed up to 23 °C and was stirred for 1.5 h. The resultant solution was then cooled down to 0 °C and was quenched by the slow addition of 1.0 N aqueous hydrochloric acid solution (10 mL). The resultant mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 20% ethyl acetate−hexanes) to afford 2−(4−hydroxymethyl−2,3−dimethoxy−5−vinylphenyl)−1−propanyl methyl ether **3.59** (858 mg, 3.22 mmol, 99%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.11 (s, 1H), 7.02 (dd, J_1 = 17.4 Hz, J_2 = 11.0 Hz, 1H), 5.60 (dd, J_1 = 17.4 Hz, J_2 = 1.4 Hz, 1H), 5.31 (dd, J_1 = 11.0 Hz, J_2 = 1.4 Hz, 1H), 4.73 (app d, J = 4.9 Hz, 2H),

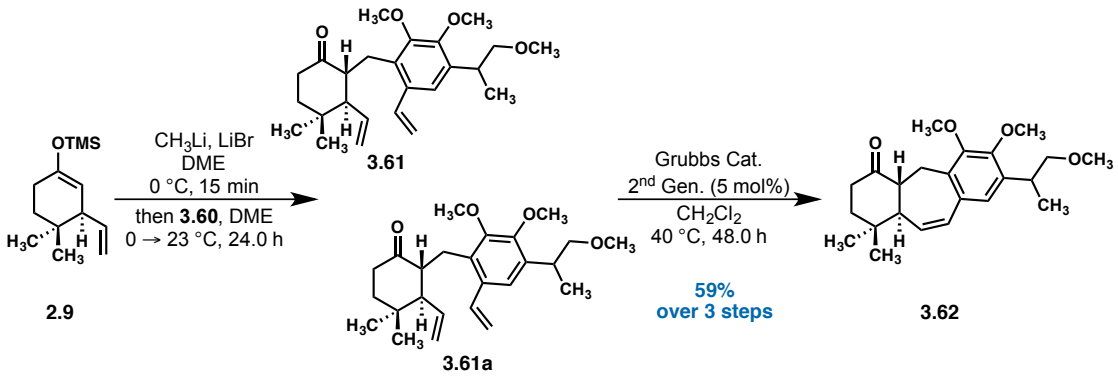
	3.89 (s, 3H), 3.84 (s, 3H), 3.53−3.39 (m, 3H), 3.33 (s, 3H), 2.16 (app t, J = 5.6 Hz, 1H), 1.25 (d, J = 6.3 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	151.6, 150.6, 138.6, 134.1, 133.8, 130.0, 120.3, 116.4, 78.0, 61.1, 60.8, 58.9, 56.9, 32.8, 18.2.
HRMS: LIFDI$^+$ $[M]^+$:	Calcd for $C_{15}H_{22}O_4$: 266.1518. Found: 266.1512.
TLC:	20% ethyl acetate−hexanes, R_f = 0.19 (UV, CAM, Anis).

Synthesis of Icetexane 3.62:



3.59 **3.60**

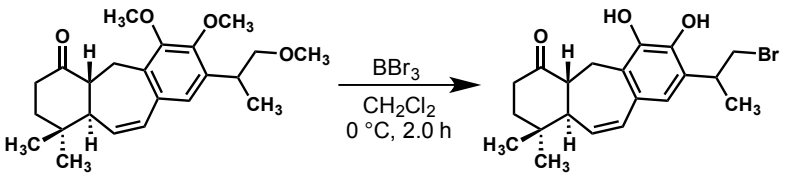
A solution 2−(4−hydroxymethyl−2,3−dimethoxy−5−vinylphenyl)−1−propanyl methyl ether **3.59** (450 mg, 1.69 mmol, 1 equiv) in tetrahydrofuran (15.0 mL) was cooled down to −40 °C. After 15 min triethylamine (1.54 mL, 11.0 mmol, 6.51 equiv) and methanesulfonyl chloride (0.83 mL, 10.7 mmol, 6.33 equiv) were added to the −40 °C solution respectively. After stirring for 50 min in the same temperature, the solution's temperature was raised to 0 °C and was stirred for extra 30 min at 0 °C. A solution of lithium bromide (1.44 g, 16.6 mmol, 9.84 equiv) in tetrahydrofuran (15.0 mL) was transferred to the reaction flask through a cannula and then the reaction mixture was stirred at 0 °C for another 10 min. The reaction mixture's temperature then was raised to 23 °C and was stirred for 40 min and then it was quenched by the slow addition of saturated aqueous solution of sodium bicarbonate (30 mL). The resultant mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was passed through a short column of basic alumina to afford 2−(4−bromomethyl−2,3−dimethoxy−5−vinylphenyl)−1−propanyl methyl ether **3.60**.



Methyllithium (1.60 M in diethyl ether, 1.48 mL, 2.37 mmol, 1.40 equiv) was added to a 0 °C suspension of ((4,4−dimethyl−3−vinylcyclohex−1−en−1−yl)oxy)trimethylsilane **2.9** (556 mg, 2.48 mmol, 1.47 equiv) and lithium bromide (221 mg, 2.54 mmol, 1.50 equiv) in 1,2−dimethoxyethane (4.0 mL). The resultant heterogeneous yellow mixture was stirred at 0 °C for 10 min, whereupon solution of 2−(4−bromomethyl−2,3−dimethoxy−5−vinylphenyl)−1−propanyl methyl ether **3.60** from the previous experiment in 1,2–dimethoxyethane (4.0 mL) was added dropwise. The heterogeneous yellow mixture was then slowly warmed to 23 °C and stirred at that temperature for 24 h, then was filtered through a 5.0 cm celite pad. The pad was washed with diethyl ether (30 mL) and the combined filtrates were concentrated. The resultant residue was then purified by flash column chromatography (silica gel, 20% diethyl ether−hexanes) to afford a combined mixture of **3.61** and its structural isomer (455 mg). This mixture was dissolved in dichloromethane (15.0 mL) and then the Grubbs second–generation catalyst (50.2 mg, 0.059 mmol, 0.05 equiv) was added to the solution at 23 °C. The resultant red solution was heated at reflux for 30 h, was then cooled to 23 °C and concentrated. Purification of the residue by flash column chromatography (silica gel, 5% ethyl acetate−hexanes) to afford **3.62** (371 mg, 1.00 mmol, 59% over 3 steps) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	6.75 (app d, J = 1.8 Hz, 1H), 6.46 (dd, J_1 = 12.6 Hz, J_2 = 2.4 Hz, 1H), 5.80 (dd, J_1 = 12.5 Hz, J_2 = 3.5 Hz, 1H), 3.99 (br d, J = 4.9 Hz, 1H), 3.85 (br s, 3H), 3.79 (s, 3H), 3.53−3.47 (m, 1H), 3.45−3.32 (m, 2H), 3.34 (app d, J = 5.8 Hz, 3H), 2.64−2.56 (m, 1H), 2.53−2.40 (m, 2H), 2.35 (ddd, J_1 = 13.9 Hz, J_2 = 4.5 Hz, J_3 = 3.0 Hz, 1H), 2.26 (ddd, J_1 = 14.9 Hz, J_2 = 7.6 Hz, J_3 = 1.6 Hz, 1H), 1.80−1.64 (m, 2H), 1.23 (app t, J = 6.1 Hz, 3H), 1.13 (s, 3H), 1.04 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	210.9, 150.4, 150.1, 150.1, 135.5, 135.5, 132.4, 132.3, 132.3, 132.3, 130.9, 130.3, 124.6, 124.6, 78.2, 61.0, 61.0, 60.9, 58.9, 57.7, 57.7, 51.2, 51.1, 41.3, 38.6, 34.9, 32.7, 32.6, 29.8, 23.6, 20.2, 20.2, 18.3, 18.2.

Synthesis of Icetexane 3.62a:



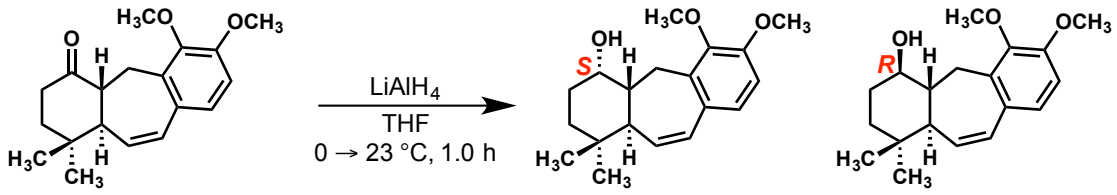
3.62 **71%** **3.62a**

Boron tribromide (1.0 M in dichloromethane, 0.35 mL, 0.35 mmol, 4.34 equiv) was added to a solution of **3.62** (30.0 mg, 0.08 mmol, 1 equiv) in dichloromethane (2 mL) at 0 °C. The resultant dark red solution was stirred for 4 h. The excess amount of boron tribromide was then quenched with the slow addition of water (1 mL) followed by addition of 1.0 N aqueous hydrochloric acid solution (3 mL). The resultant mixture was extracted with dichloromethane (3 × 5 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 15% ethyl acetate−hexanes) to afford **3.62a** (22.5 mg, 57.8 μmol, 71%) as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.06 (s, 1H), 6.61 (app ddd, J_1 = 10.3 Hz, J_2 = 4.2 Hz, J_3 = 1.8 Hz, 1H), 6.52 (s, 1H), 5.92 (dd, J_1 = 10.3 Hz, J_2 = 6.1 Hz, 1H), 5.86 (s, 1H), 4.55−4.41 (m, 1H), 3.39−3.29 (m, 2H), 3.22−2.96 (m, 3H), 2.55 (br td, J_1 = 13.9 Hz, J_2 = 6.7 Hz, 1H), 2.36−2.27 (m, 2H), 1.91−1.83 (m, 1H),

	1.76−1.65 (m, 4H), 1.26 (s, 3H), 0.90 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	216.8, 143.2, 143.2, 140.9, 140.9, 131.7, 131.6, 130.3, 130.3, 129.5, 129.5, 124.4, 122.6, 122.5, 122.4, 122.3, 60.3, 51.9, 51.9, 50.4, 49.8, 42.3, 42.2, 41.7, 41.7, 38.3, 32.8, 26.2, 25.9, 24.6, 20.1.
HRMS: LIFDI$^+$ $[M]^+$:	Calcd for $C_{20}H_{25}O_3Br$: 392.0987. Found: 392.0994.

Synthesis of epimers 3.70a and 3.70b:



3.13 **3.70a** **3.70b**

quant.
a:b(1:3)

Lithium aluminum hydride (25.0 mg, 0.659 mmol, 1.65 equiv), was dissolved in tetrahydrofuran (2.00 mL) at 0 °C. Then a solution of **3.13** (121 mg, 0.399 mmol, 1 equiv) in tetrahydrofuran (4.00 mL) was transferred to the reaction flask through a cannula. The reaction mixture was warmed up to 23 °C and was stirred for 1 h. The reaction mixture was then cooled down to 0 °C and quenched by slow and careful addition of 1.0 N aqueous hydrochloric acid solution (1.00 mL). The resultant mixture was extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 5% ethyl acetate−hexanes) to afford **3.70a** (32 mg, 0.106 mmol, 27%) as an oily solid and **3.70b** (95 mg, 0.314 mmol, 73%) as an oily solid.

3.70b:

^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.86 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.45 (dd, J_1 = 11.5 Hz, J_2 = 2.2

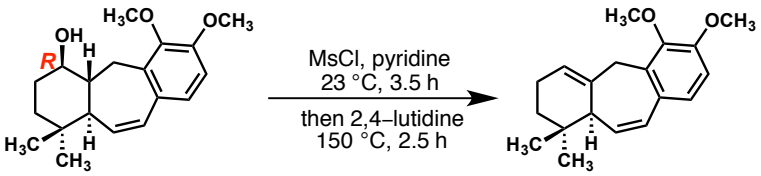
	Hz, 1H), 5.93 (dd, J_1 = 11.6 Hz, J_2 = 4.9 Hz, 1H), 4.09 (app q, J = 2.9 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 2.95 (dd, J_1 = 13.9 Hz, J_2 = 5.0 Hz, 1H), 2.63 (dd, J_1 = 13.9 Hz, J_2 = 4.6 Hz, 1H), 2.36 (ddd, J_1 = 12.6 Hz, J_2 = 5.0 Hz, J_3 = 2.3 Hz, 1H), 2.06−1.97 (m, 1H), 1.74−1.56 (m, 3H), 1.26 (br s, 1H), 1.16−1.07 (m, 1H), 0.96 (s, 3H), 0.86 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	151.4, 145.4, 134.7, 132.5, 131.4, 129.1, 124.9, 109.5, 72.5, 61.1, 55.8, 47.1, 46.4, 34.7, 33.6, 30.9, 30.3, 29.2, 19.6.

3.70b:

^{1}H NMR (400 MHz, $CDCl_3$), δ:	6.87 (d, J = 8.4 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 6.49 (dd, J_1 = 11.5 Hz, J_2 = 2.1 Hz, 1H), 5.88 (dd, J_1 = 11.4 Hz, J_2 = 5.0 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.32 (td, J_1 = 10.6 Hz, J_2 = 4.6 Hz, 1H), 2.91 (dd, J_1 = 13.7 Hz, J_2 = 4.3 Hz, 1H), 2.81 (dd, J_1 = 13.7 Hz, J_2 = 4.2 Hz, 1H), 1.96−1.87 (m, 1H), 1.86−1.79 (m, 1H), 1.68 (ddd, J_1 = 12.0 Hz, J_2 = 5.0 Hz, J_3 = 2.2 Hz, 1H), 1.55−1.46 (m, 1H),

	1.45−1.37 (m, 1H), 1.29−1.22 (m, 1H), 0.90 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	151.3, 146.3, 133.8, 131.8, 131.8, 129.7, 124.6, 109.5, 73.5, 61.0, 55.8, 52.0, 51.1, 39.6, 33.3, 31.3, 30.7, 26.4, 20.5.

Synthesis of diene 3.71:



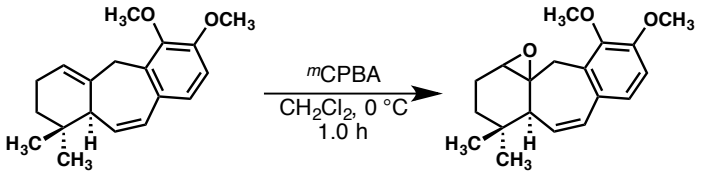
3.70b **26%** **3.71**

Methanesulfonyl chloride (0.03 mL, 0.39 mmol, 2.42 equiv) was added to a solution of **3.70b** (50 mg, 0.16 mmol, 1 equiv) in pyridine (2.00 mL) and was stirred for 3.5 h. The resultant reaction mixture was poured into the 1.0 N aqueous hydrochloric acid solution (5.00 mL). The resultant biphasic mixture was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated and the resultant residue was dissolved in 2,4−lutidine (3.00 mL). The resultant reaction solution was warmed up to 150 °C and was stirred for 2.5 h. The resultant residue was cooled down to 23 °C and was quenched by the addition of 1.0 N aqueous hydrochloric acid solution (5.00 mL). The resultant biphasic mixture was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated and the resultant residue was purified by flash column chromatography (silica gel impregnated with 5% silver nitrate, 5% ethyl acetate−hexanes) to afford **3.71** (12 mg, 0.043 mmol, 26%) as an oily solid.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.86 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.49 (dd, J_1 = 11.9 Hz, J_2 = 2.2

	Hz, 1H), 5.90 (dd, J_1 = 11.9 Hz, J_2 = 5.1 Hz, 1H), 5.51−5.46 (m, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.68 (d, J = 13.2 Hz, 1H), 3.17 (d, J = 13.1 Hz, 1H), 2.89−2.83 (m, 1H), 2.05−1.92 (m, 2H), 1.46−1.34 (m, 2H), 1.03 (s, 3H), 0.76 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	151.8, 145.6, 140.9, 133.8, 130.8, 130.3, 129.7, 124.9, 121.4, 109.4, 61.3, 55.8, 52.0, 37.6, 34.3, 32.9, 29.9, 22.9, 20.9.

Synthesis of epoxide 3.72:



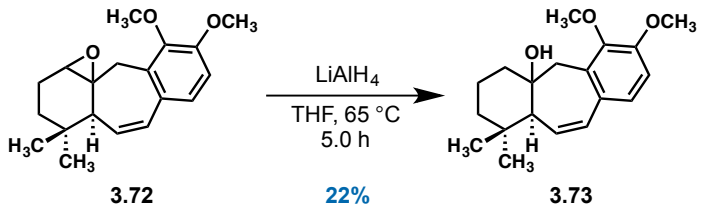
3.71 3.72

Meta−chloroperoxybenzoic acid (24 mg, 0.139 mmol, 1.10 equiv), was added to a solution of **3.71** (36 mg, 0.126 mmol, 1 equiv) in tetrahydrofuran (4.00 mL) under air at 0 °C and the resultant solution was then stirred for 1 h. The reaction mixture was quenched by addition of saturated aqueous sodium thiosulfate solution (1.00 mL) followed by addition of saturated aqueous sodium carbonate solution (1.00 mL). The resultant biphasic mixture was extracted with dichloromethane (3 × 7 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 5% ethyl acetate−hexanes) to afford **3.72** (25 mg, 0.083 mmol, 66%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.87 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 6.58 (d, J = 12.0 Hz, 1H), 5.94 (dd, J_1 = 11.9 Hz, J_2 = 7.1 Hz, 1H), 3.87 (s, 3H), 3.77 (s, 3H), 3.17 (t, J = 2.0 Hz, 1H), 3.04 (d, J = 12.5 Hz, 1H), 2.83 (d, J = 12.5 Hz, 1H), 2.52 (d, J = 7.1 Hz, 1H), 1.91 (dd, J_1 = 15.1 Hz, J_2 = 5.0 Hz, 1H),

	1.73−1.63 (m, 1H), 1.39 (td, J_1 = 13.0 Hz, J_2 = 5.3 Hz, 1H), 1.04−0.96 (m, 1H), 0.91 (s, 3H), 0.37 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	151.7, 146.6, 130.9, 130.7, 129.8, 128.7, 123.8, 110.3, 64.9, 61.1, 59.9, 55.8, 52.0, 35.0, 33.4, 33.2, 30.0, 21.6, 20.7.

Synthesis of alcohol 3.73:



3.72 **3.73**

Lithium aluminum hydride (4.0 mg, 0.105 mmol, 1.27 equiv), was dissolved in tetrahydrofuran (1.00 mL) at 0 °C then a solution of **3.72** (25 mg, 0.083 mmol, 1 equiv) in tetrahydrofuran (4.00 mL) was transferred to the reaction flask through a cannula. The reaction mixture was warmed up to 65 °C and was stirred for 5 h. The reaction mixture was then cooled down to 0 °C and quenched by slow and careful addition of 1.0 N aqueous hydrochloric acid solution (1.00 mL). The resultant mixture was extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and then were dried over anhydrous sodium sulfate. The dried solution was concentrated, and the resultant residue was purified by flash column chromatography (silica gel, 5% ethyl acetate−hexanes) to afford **3.73** (5.5 mg, 0.018 mmol, 22%) as an oily solid.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.92 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.50 (dd, J_1 = 11.0 Hz, J_2 = 1.7 Hz, 1H), 5.97 (dd, J_1 = 11.0 Hz, J_2 = 6.2 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.12 (d, J = 13.8 Hz, 1H), 2.48 (d, J = 13.8 Hz, 1H), 1.82−1.72 (m, 3H), 1.59−1.46 (m, 2H), 1.36−1.25 (m, 3H), 1.10 (s, 3H),

	0.85 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	151.6, 147.3, 132.9, 132.0, 131.4, 129.3, 124.3, 110.1, 83.0, 61.0, 55.9, 54.6, 41.3, 37.7, 37.0, 33.2, 30.1, 29.9, 29.5, 18.5.
HRMS: LIFDI$^+$ $[M]^+$:	Calcd for $C_{19}H_{26}O_3$: 302.1884. Found: 302.1882.

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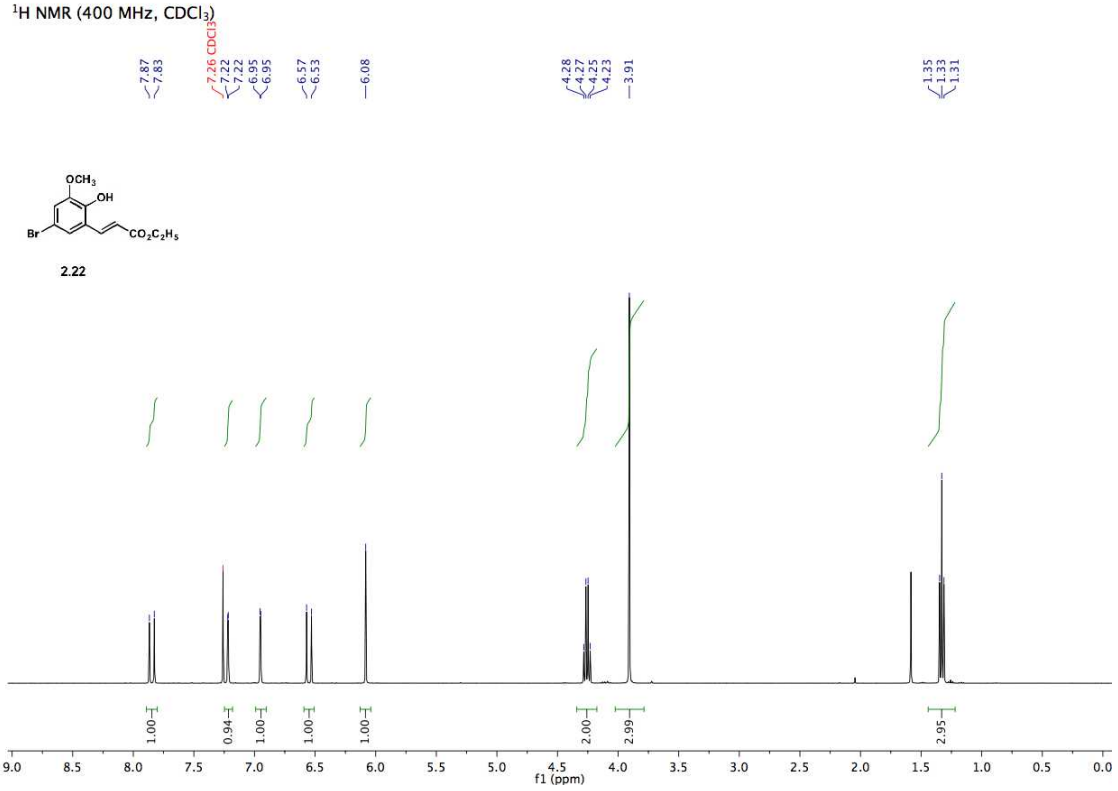
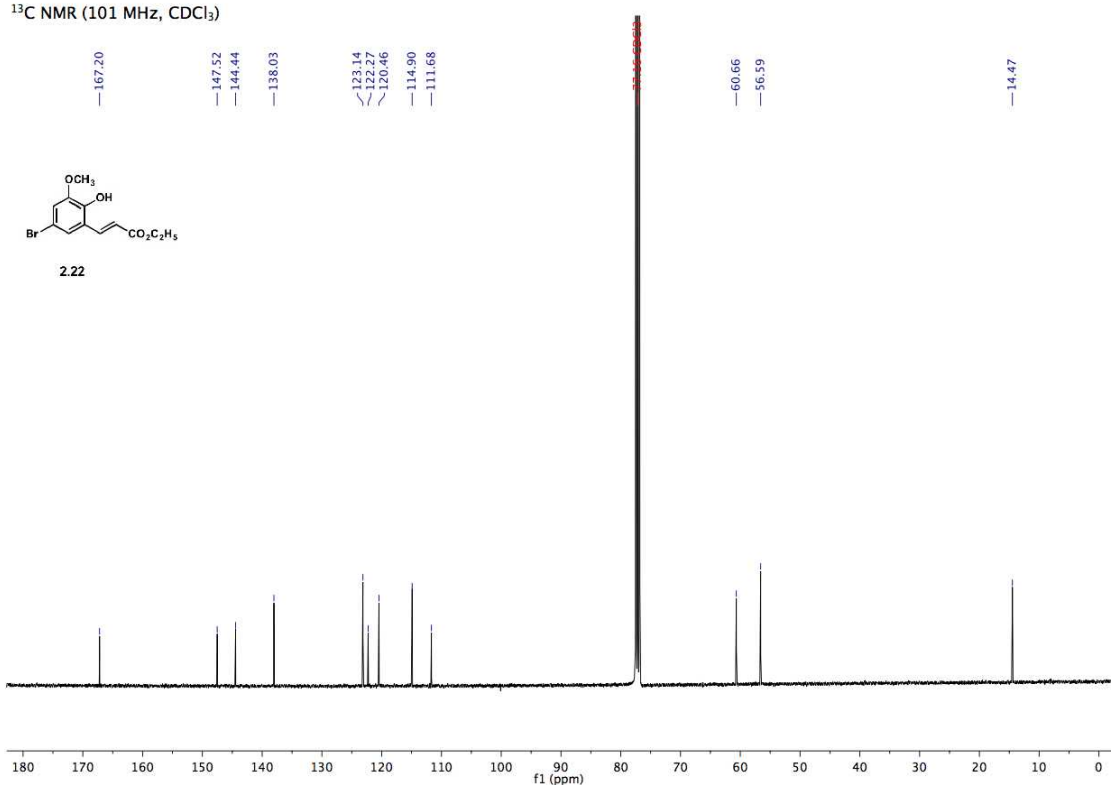
Appendix A

CATALOG OF SPECTRA

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)



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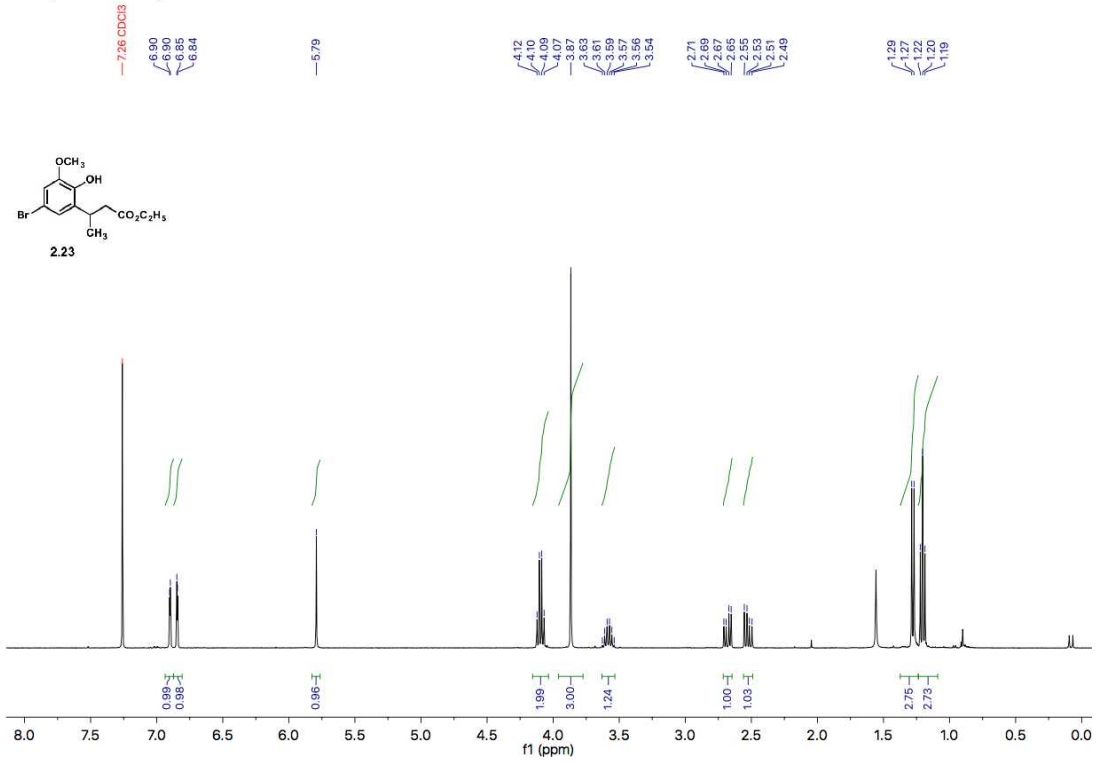

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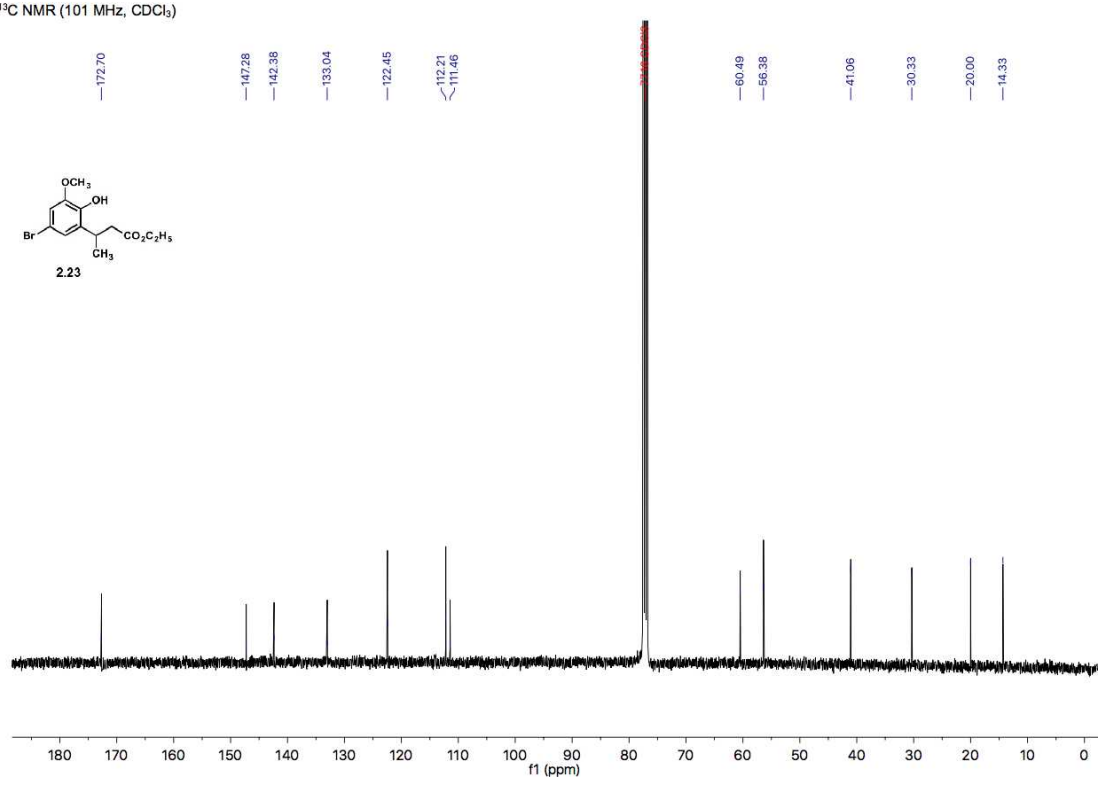

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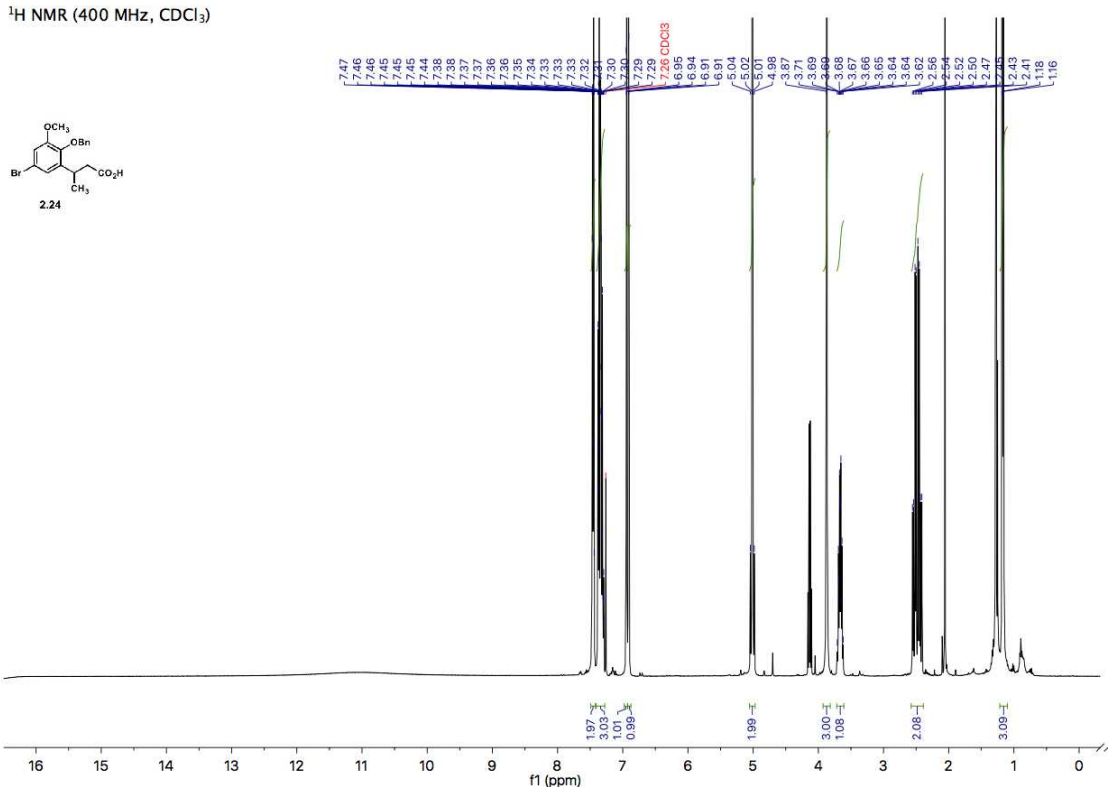

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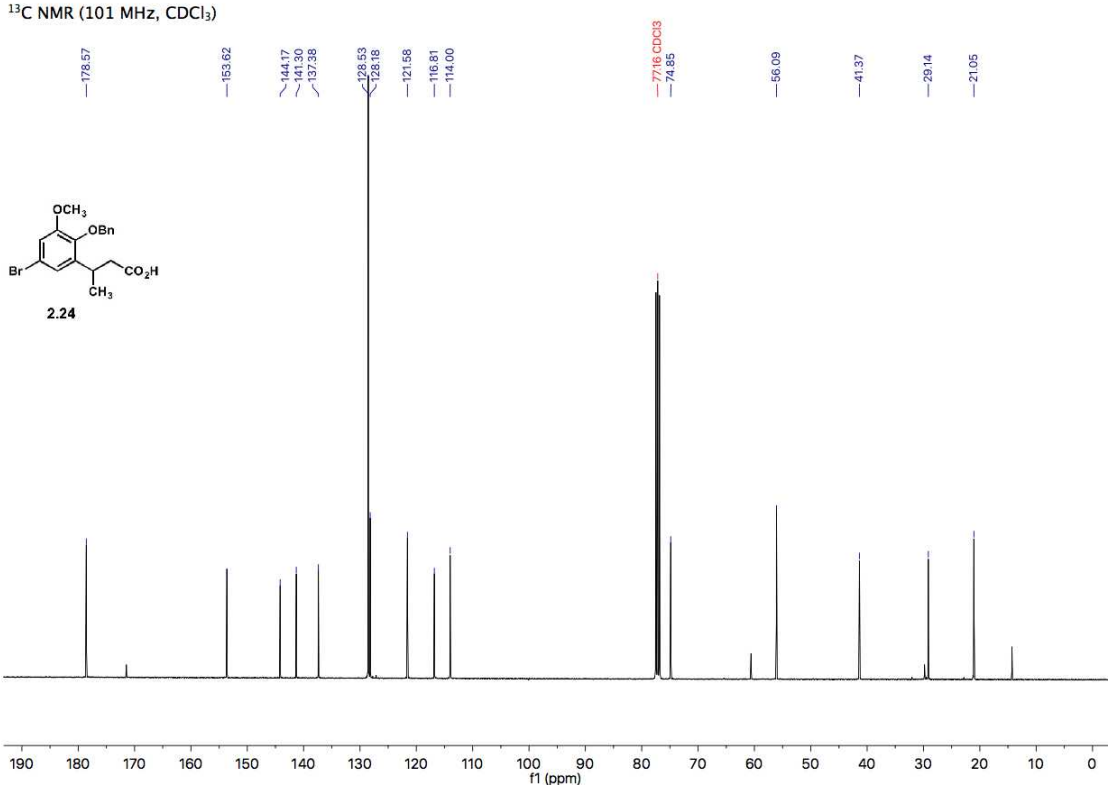

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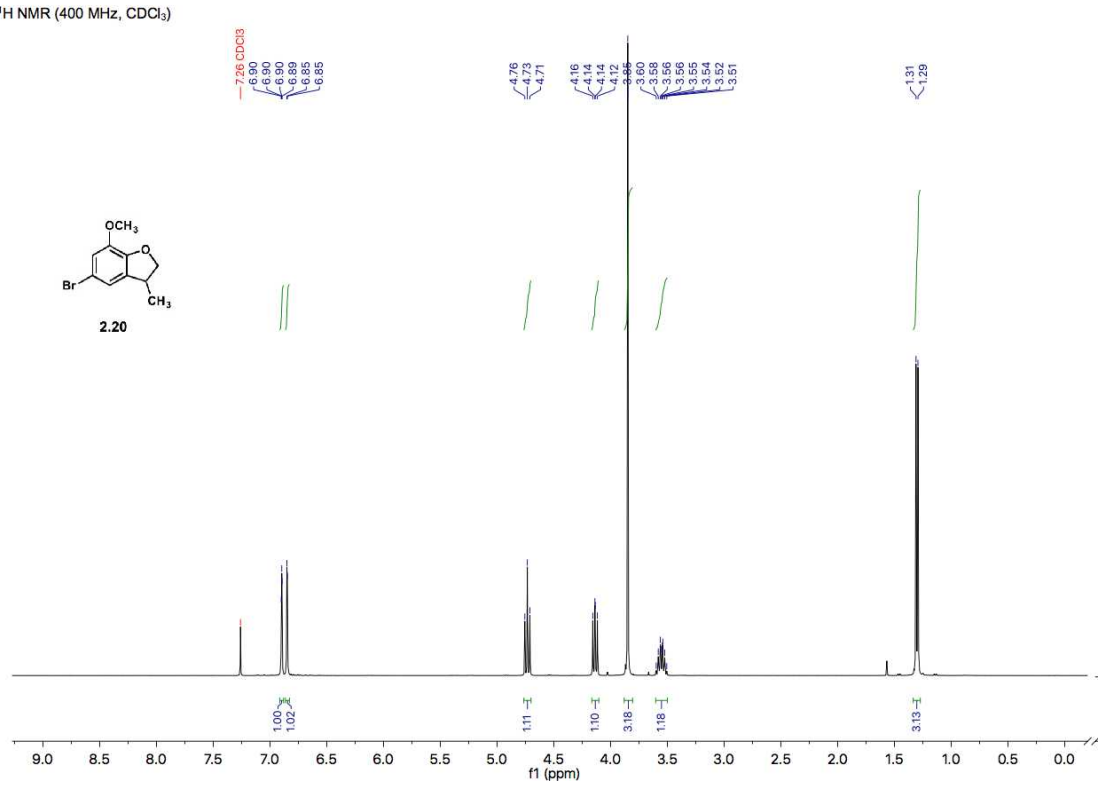

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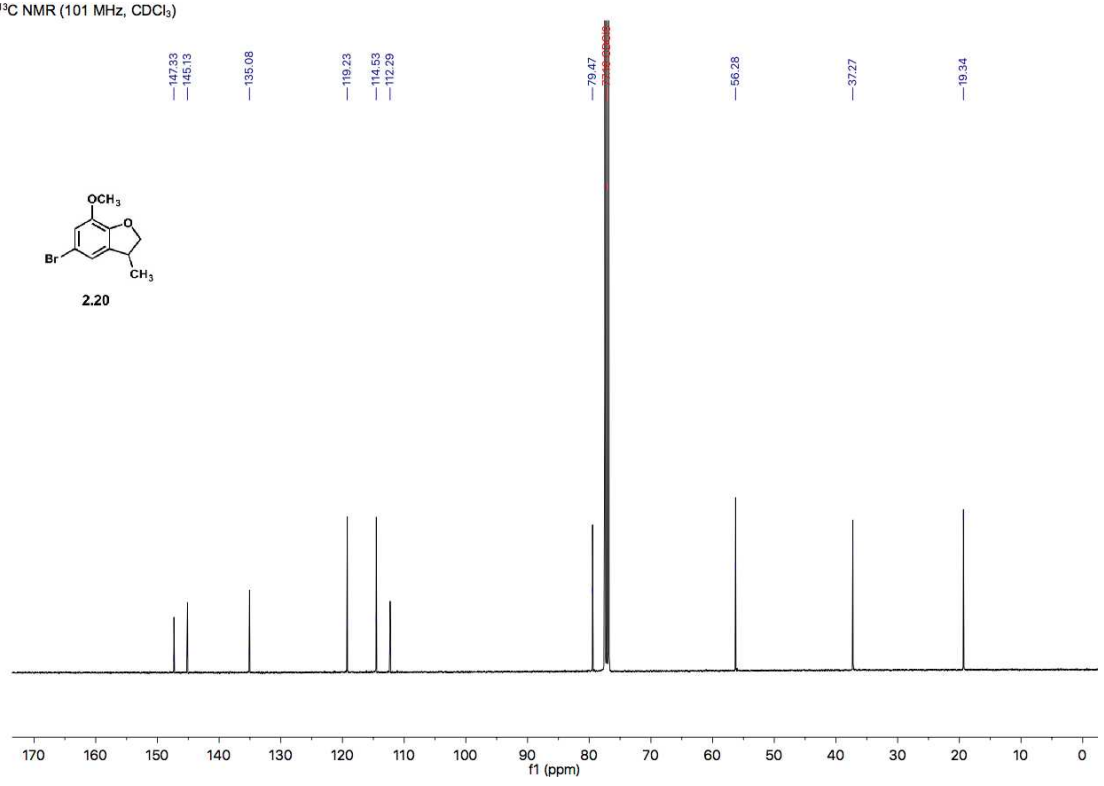

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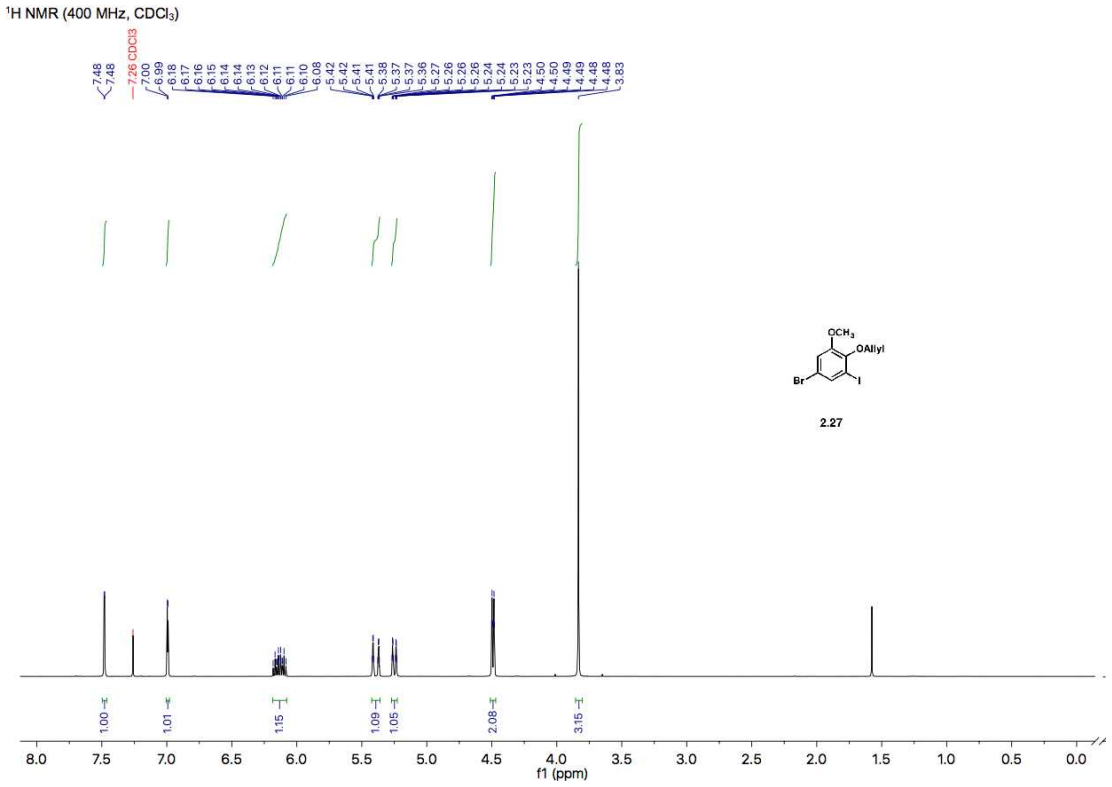

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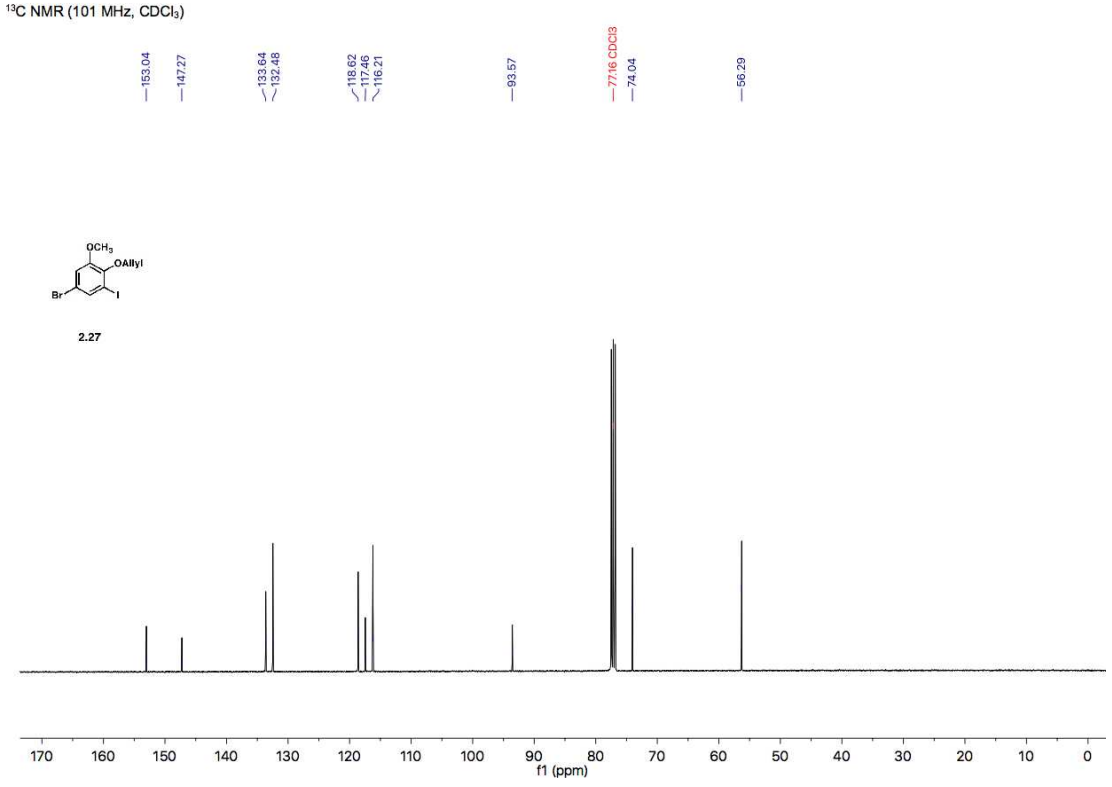

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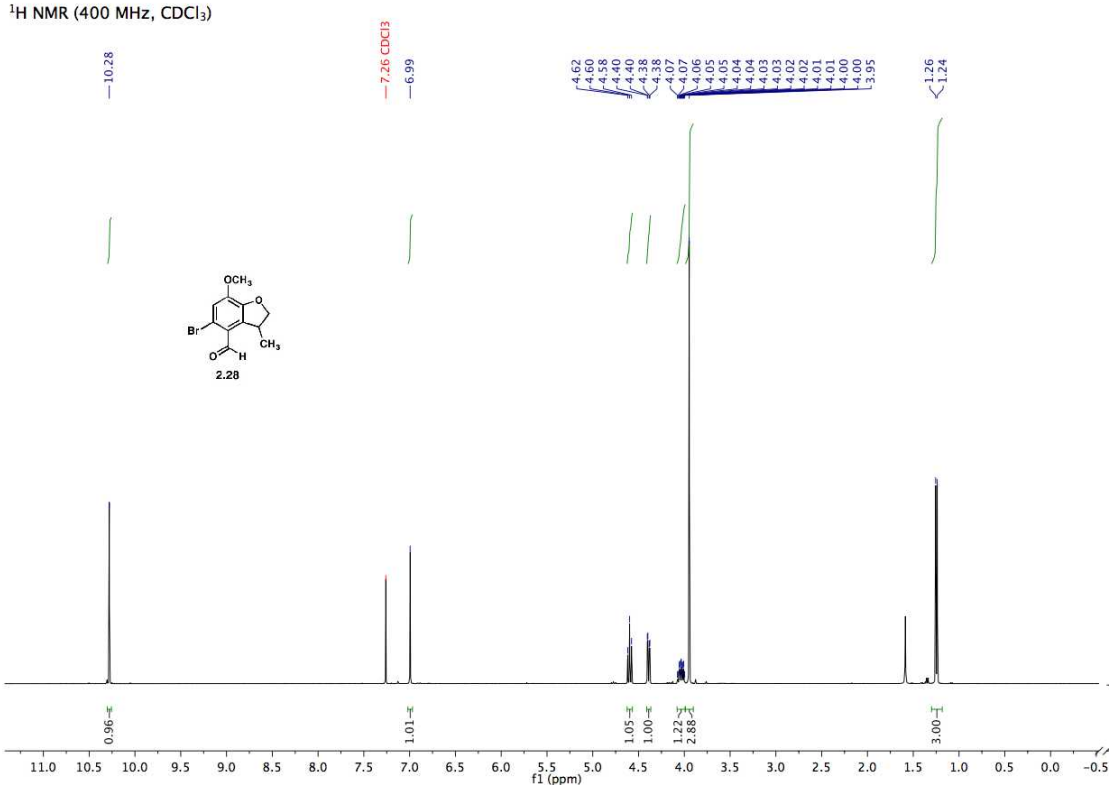

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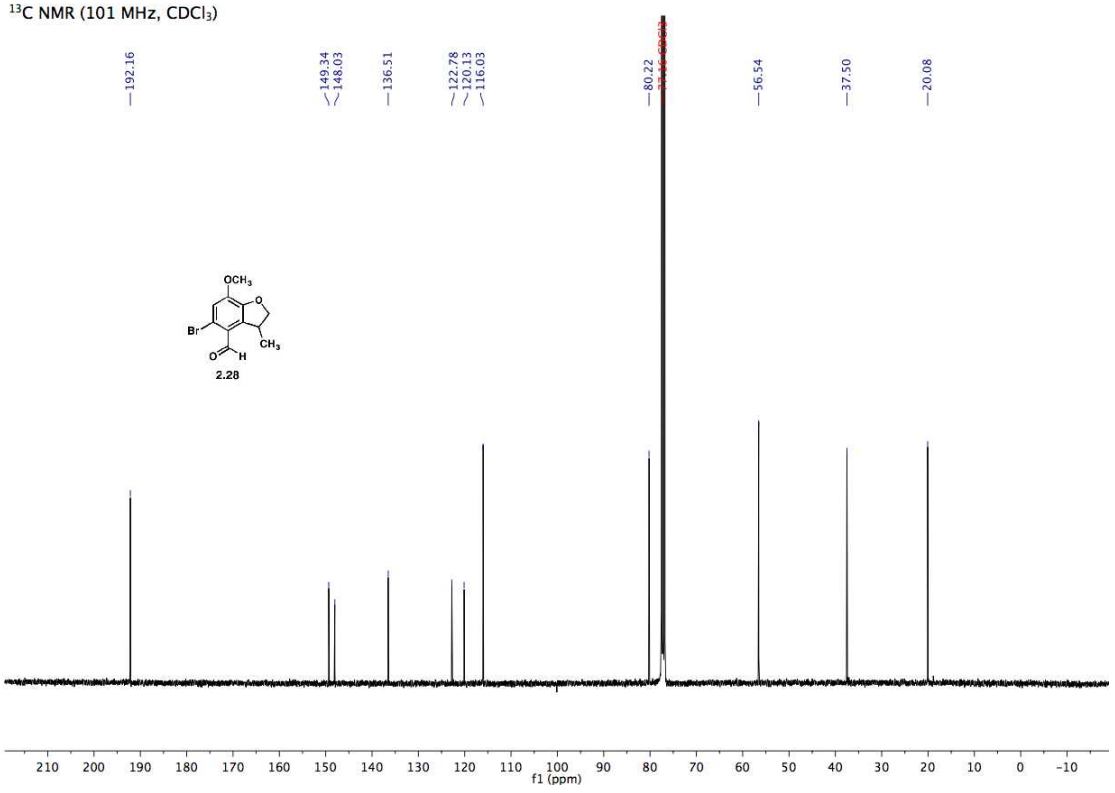

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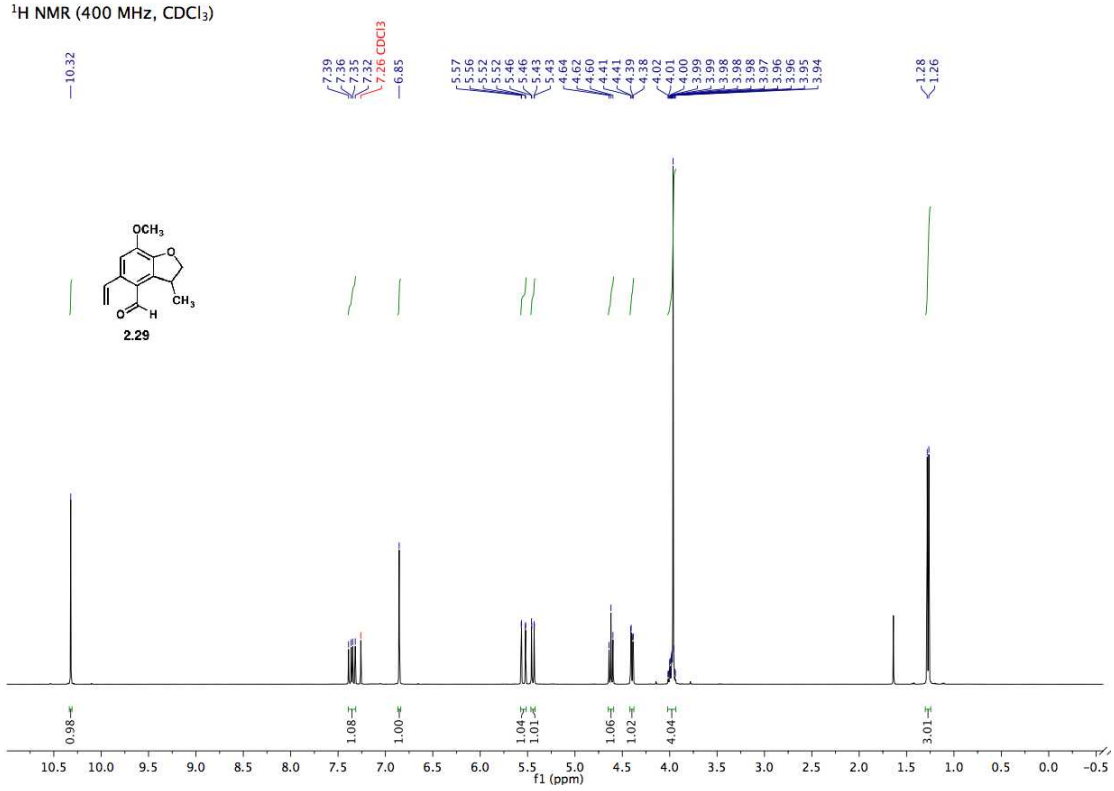

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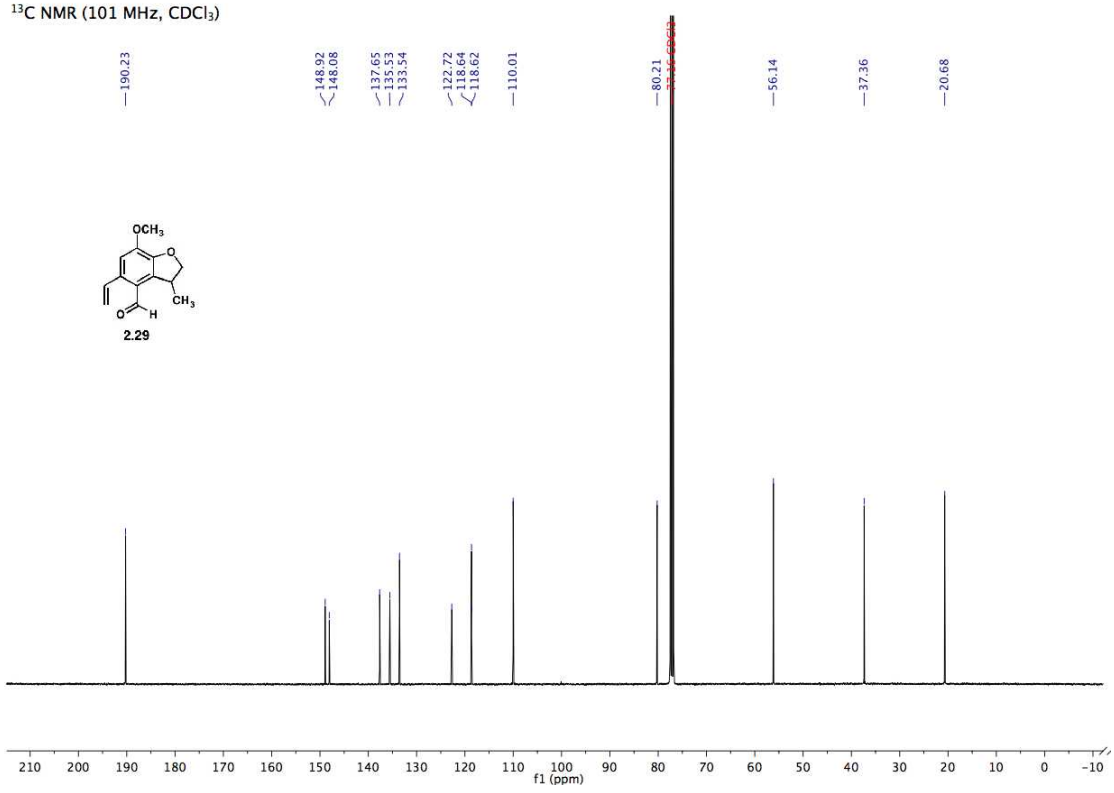

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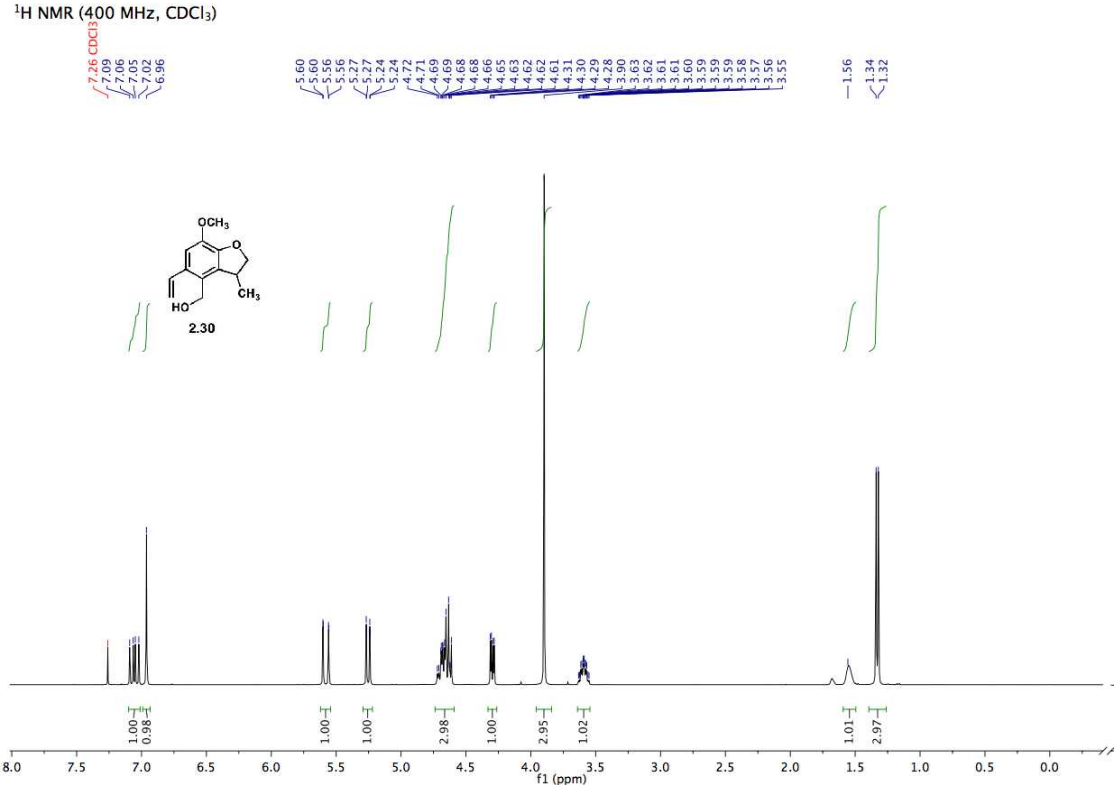

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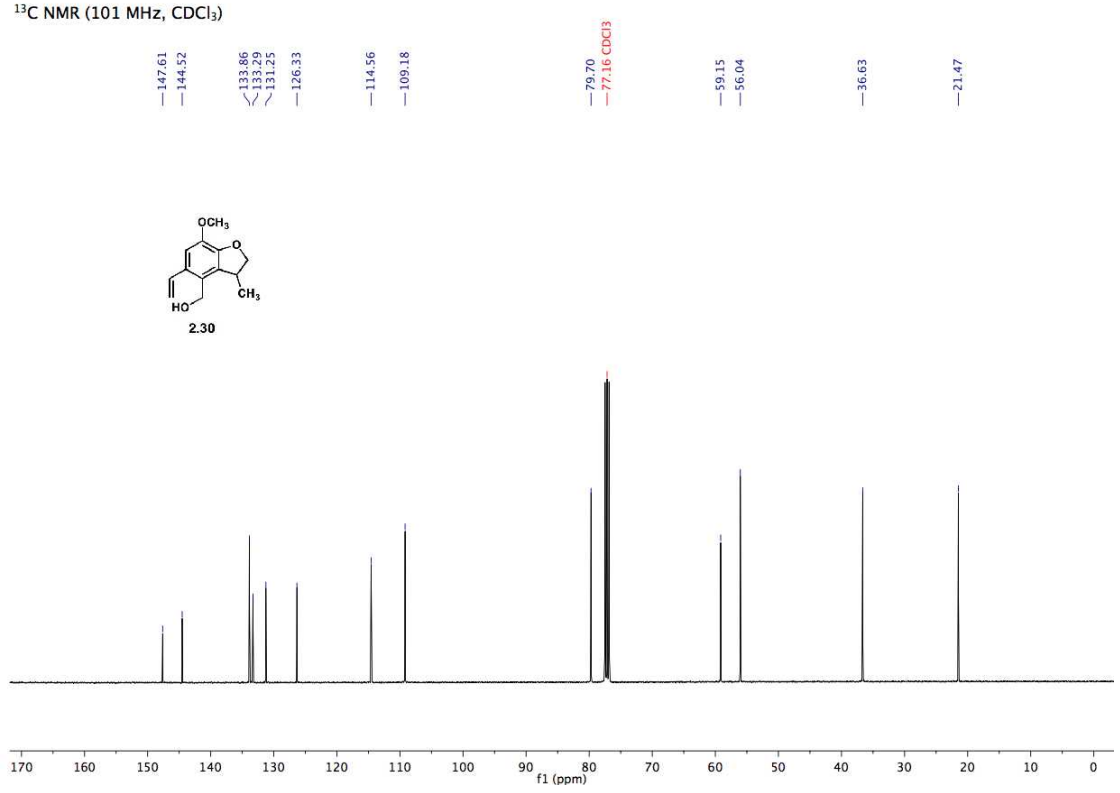

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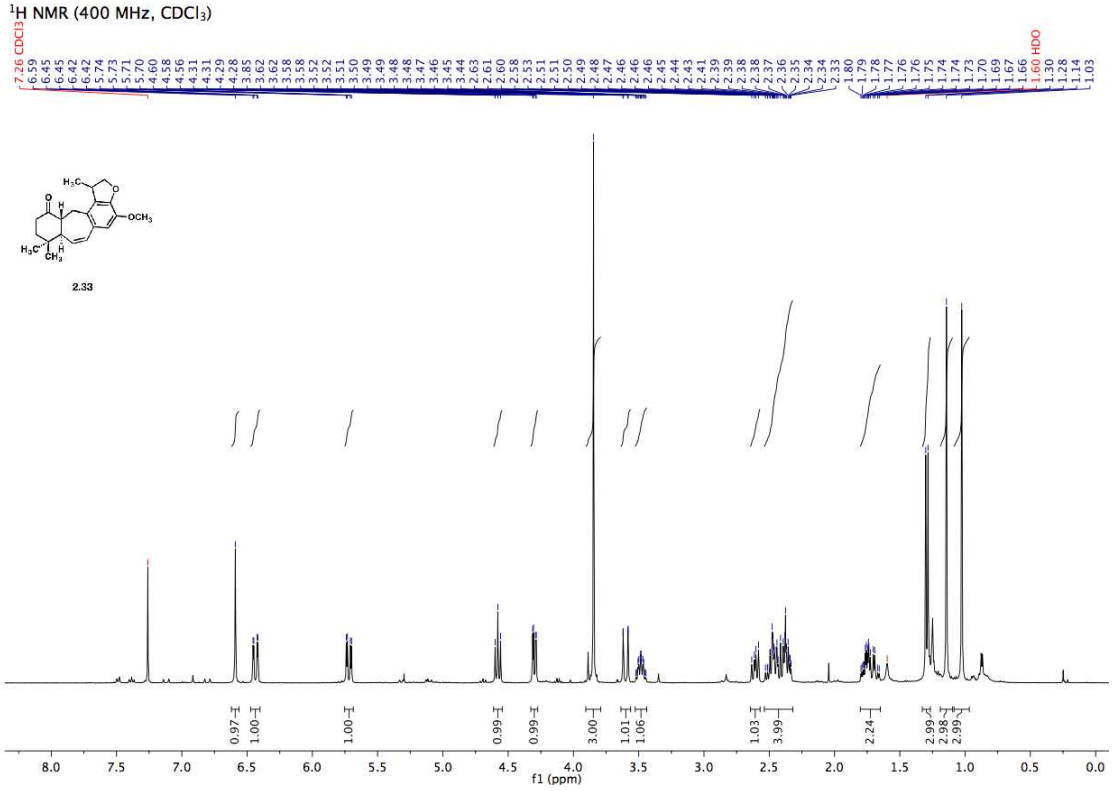

2.33

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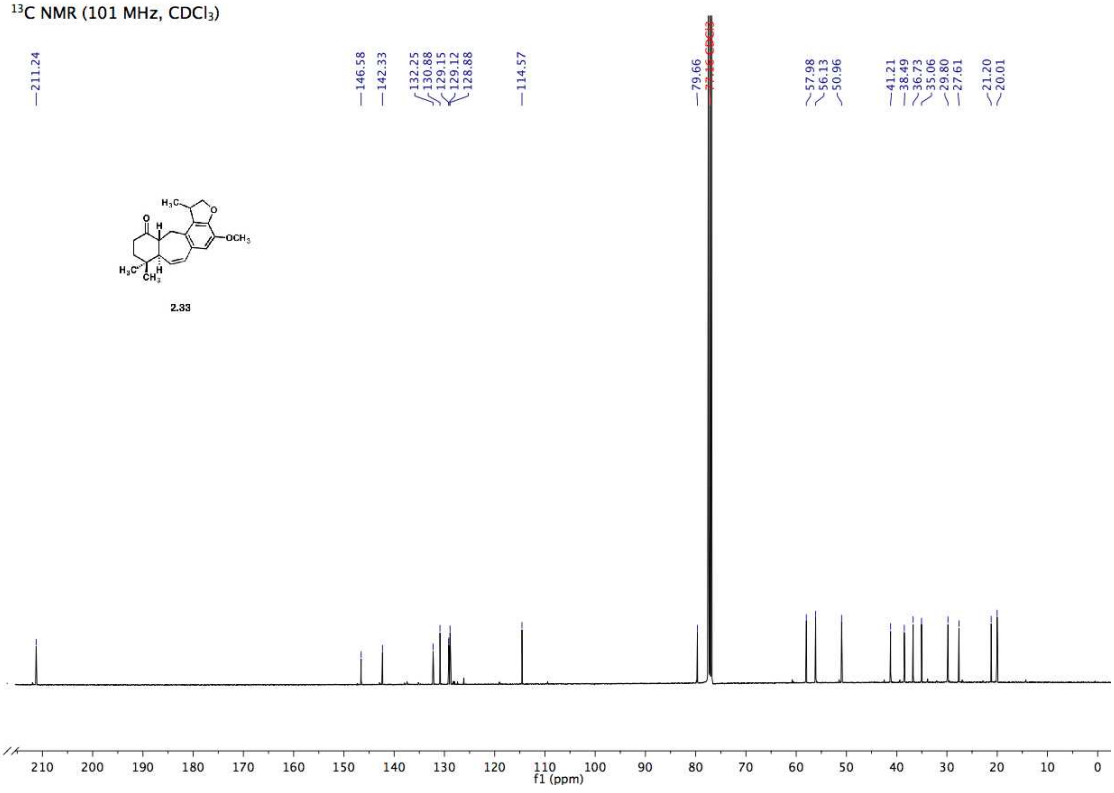

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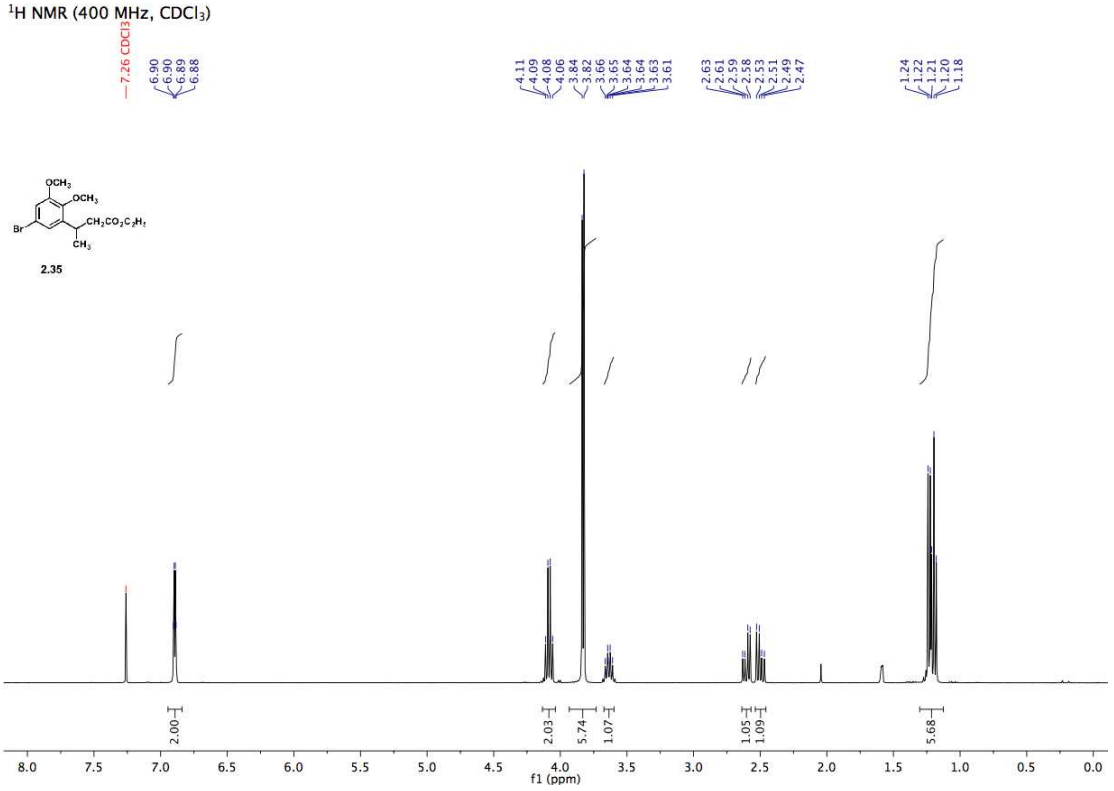

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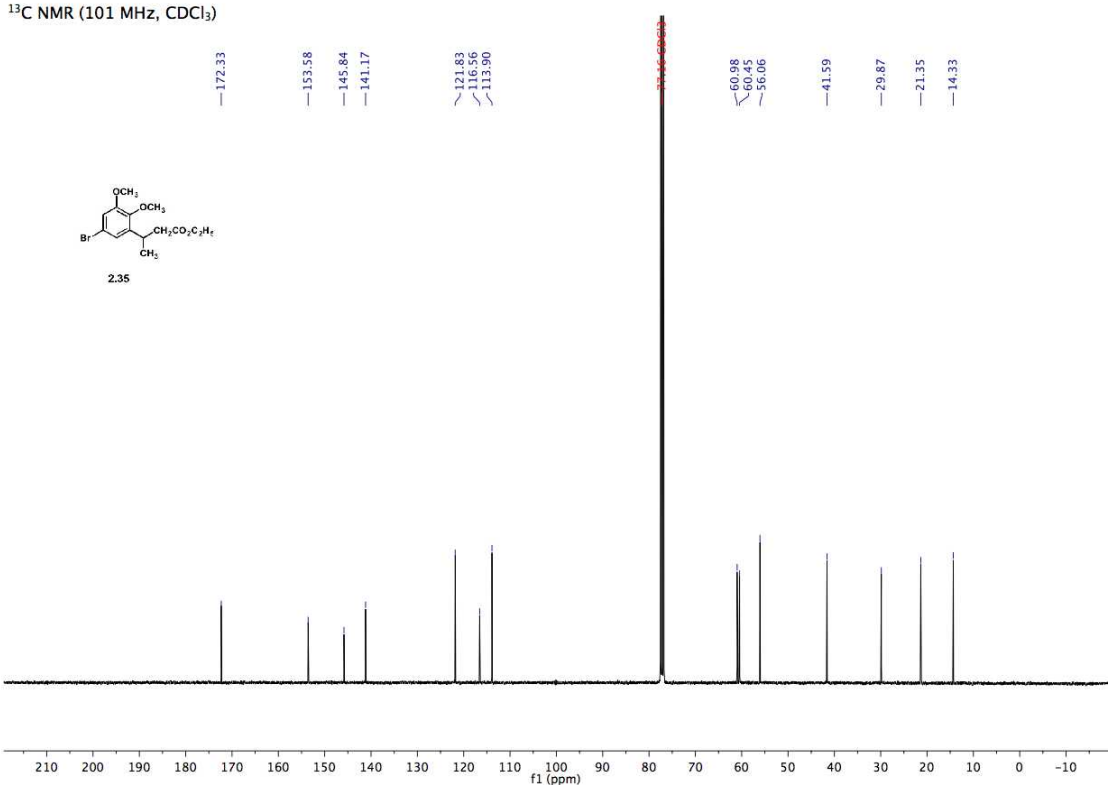

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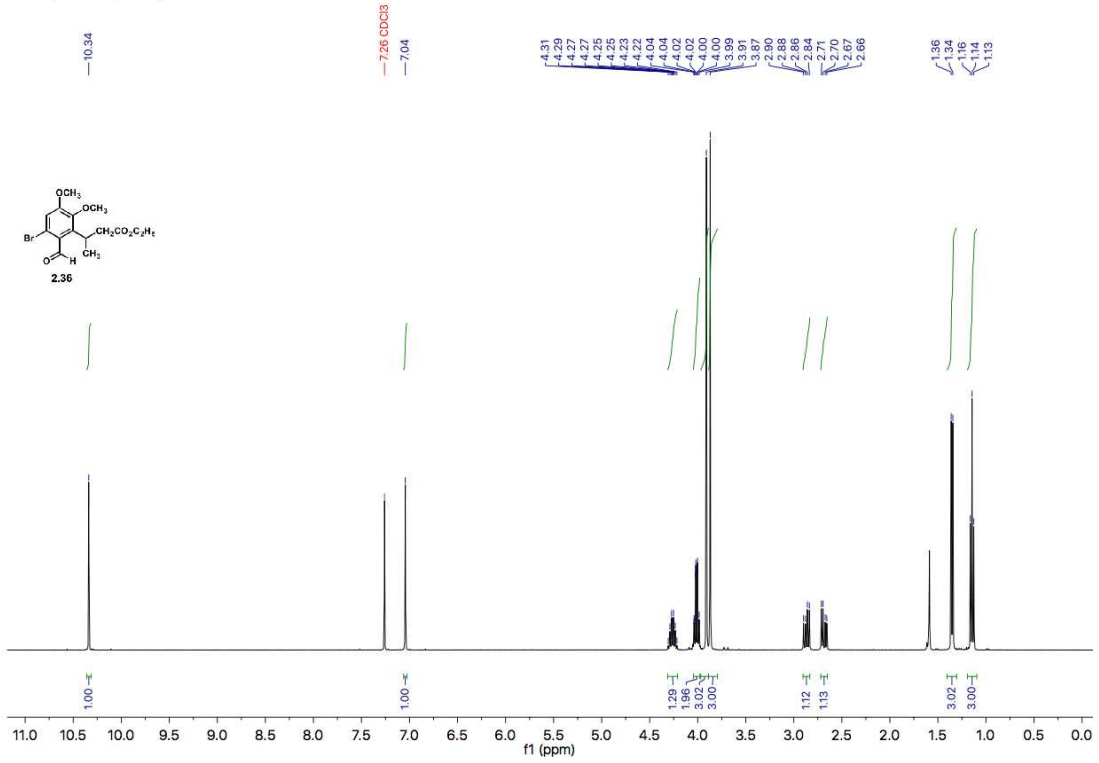

2.36

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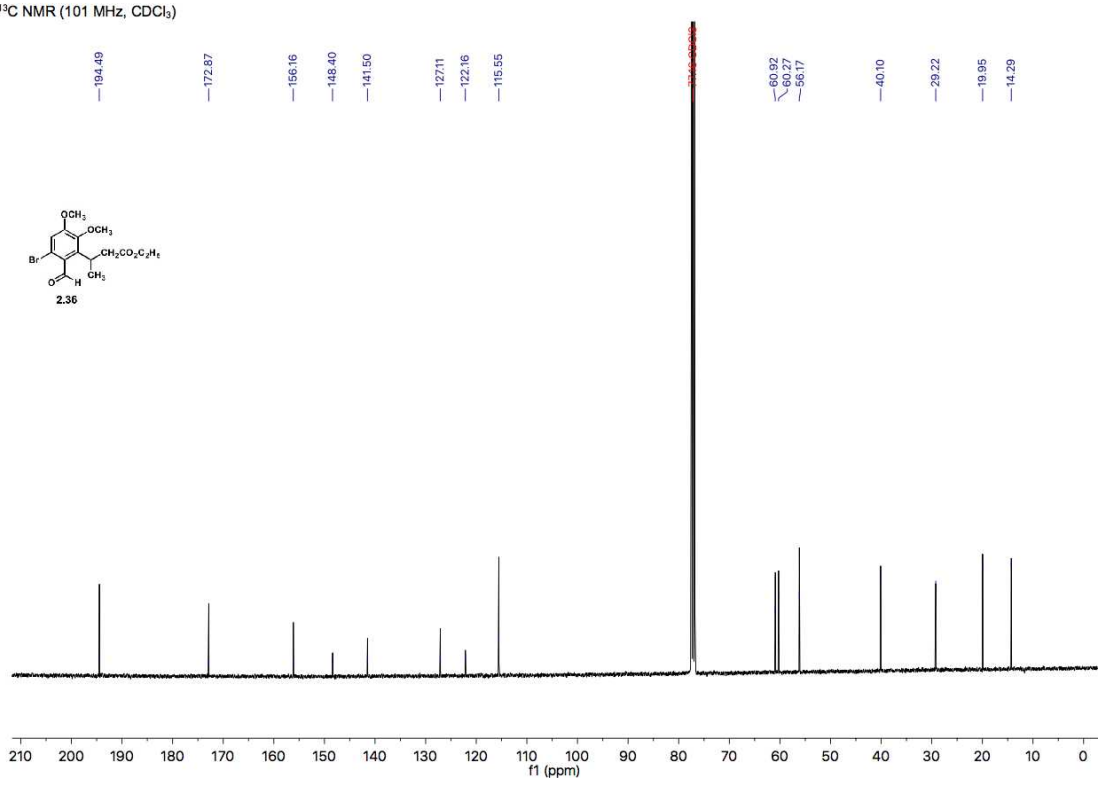

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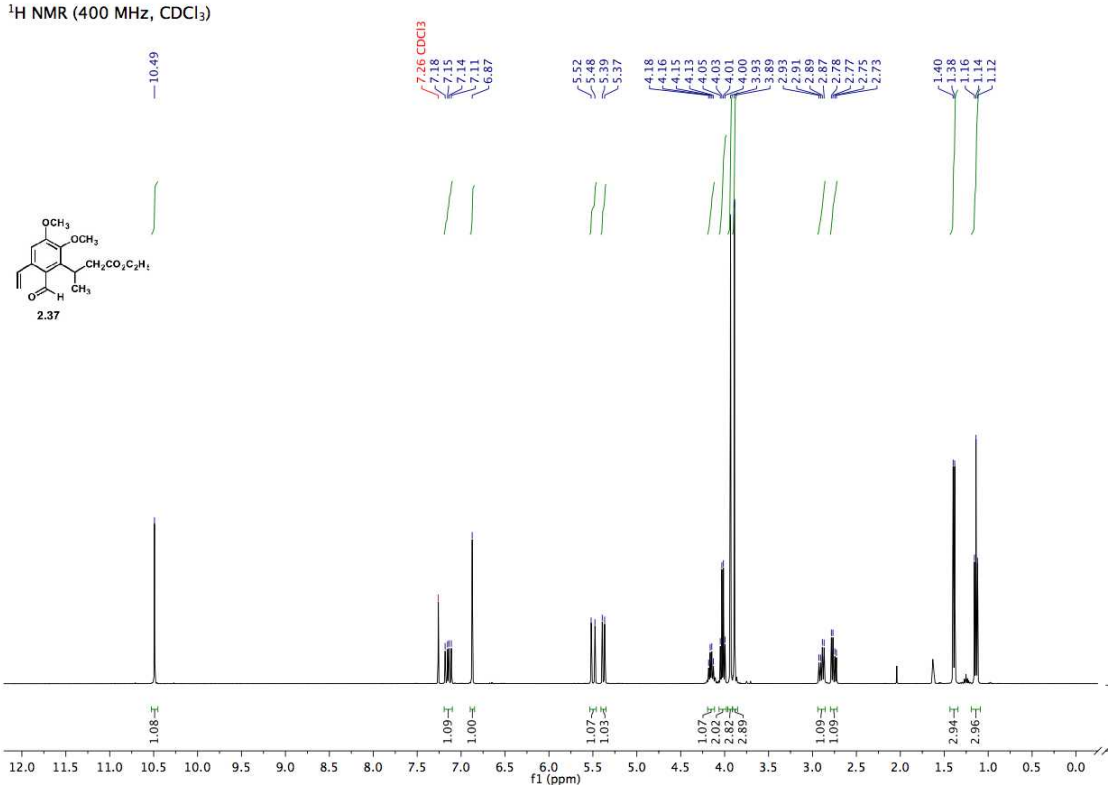
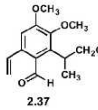
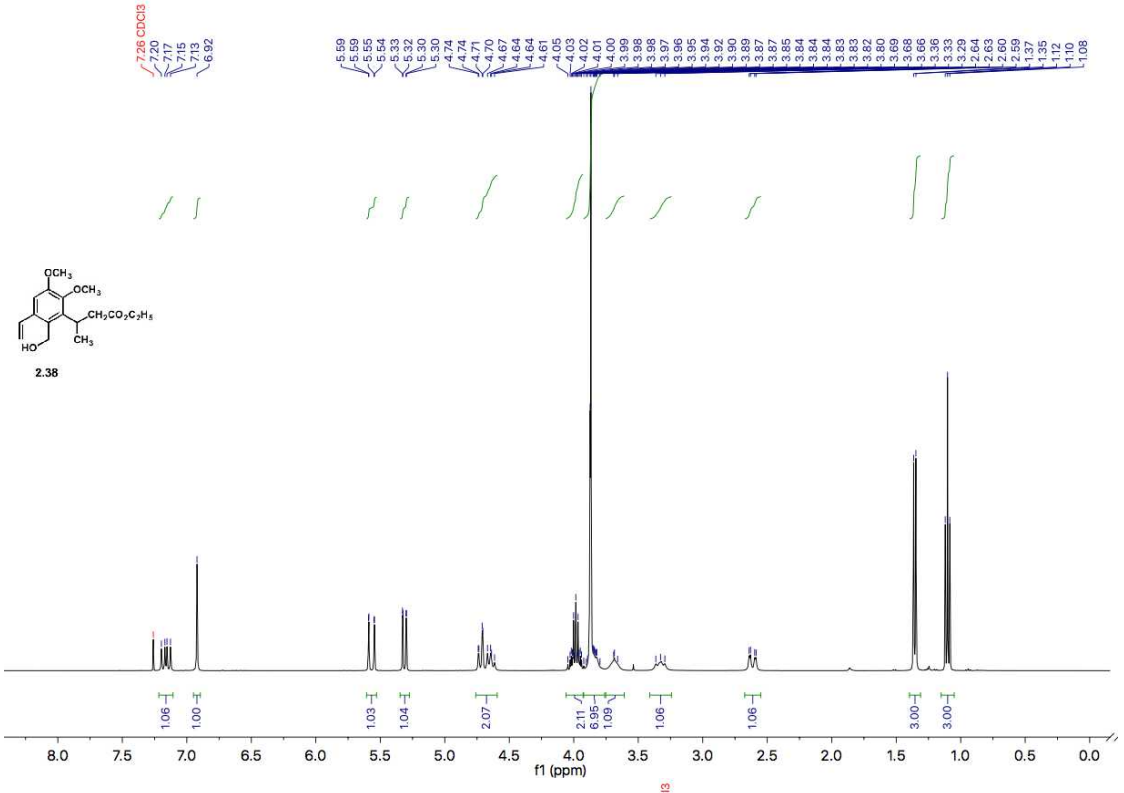




2.37

^{13}C NMR (101 MHz, $CDCl_3$)

2.37


7.26 CDCl3
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7.13
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4.71
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4.67
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3.82
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CH3
HO
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1.09
1.06
1.06
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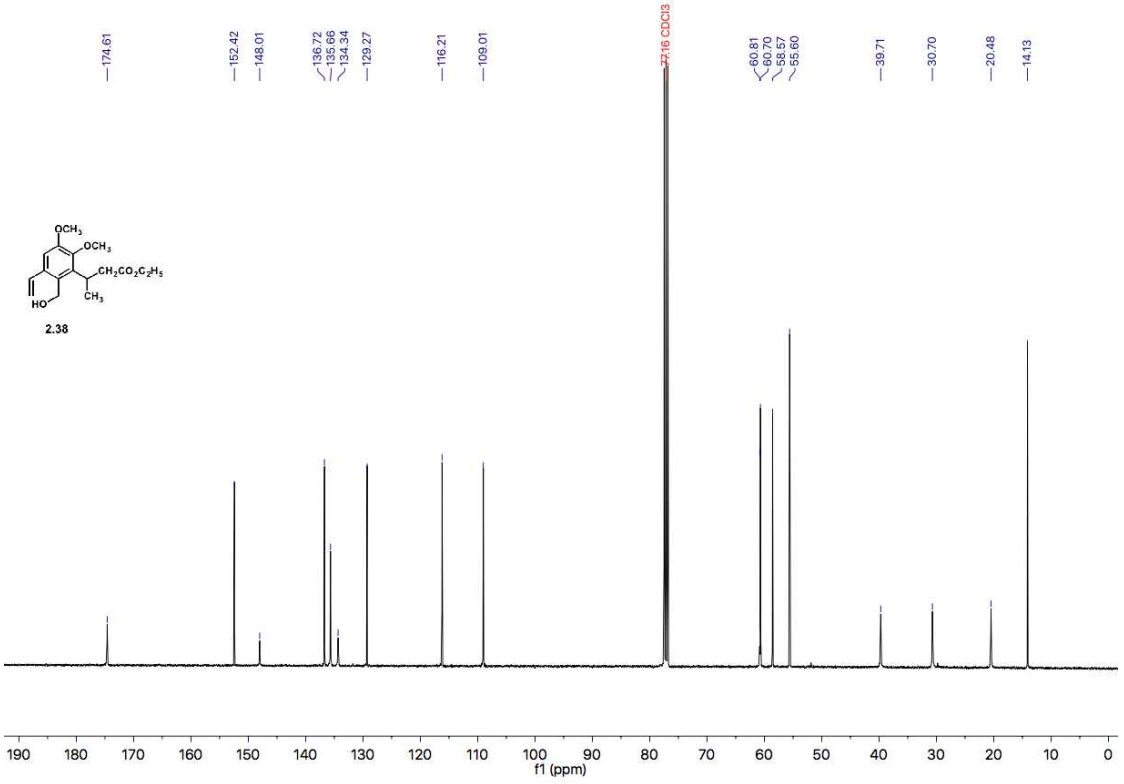
3.00
f1 (ppm)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77.16 CDCl3
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60.70
58.57
55.60
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30.70
20.48
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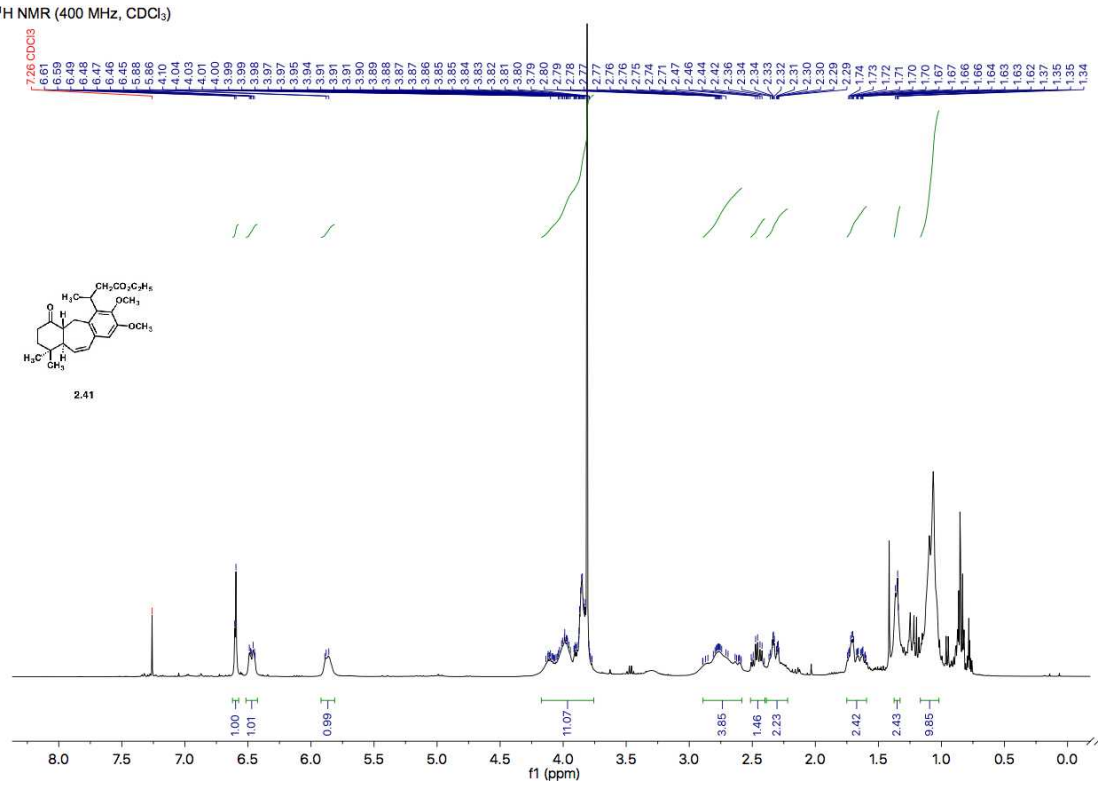
f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)



2.41

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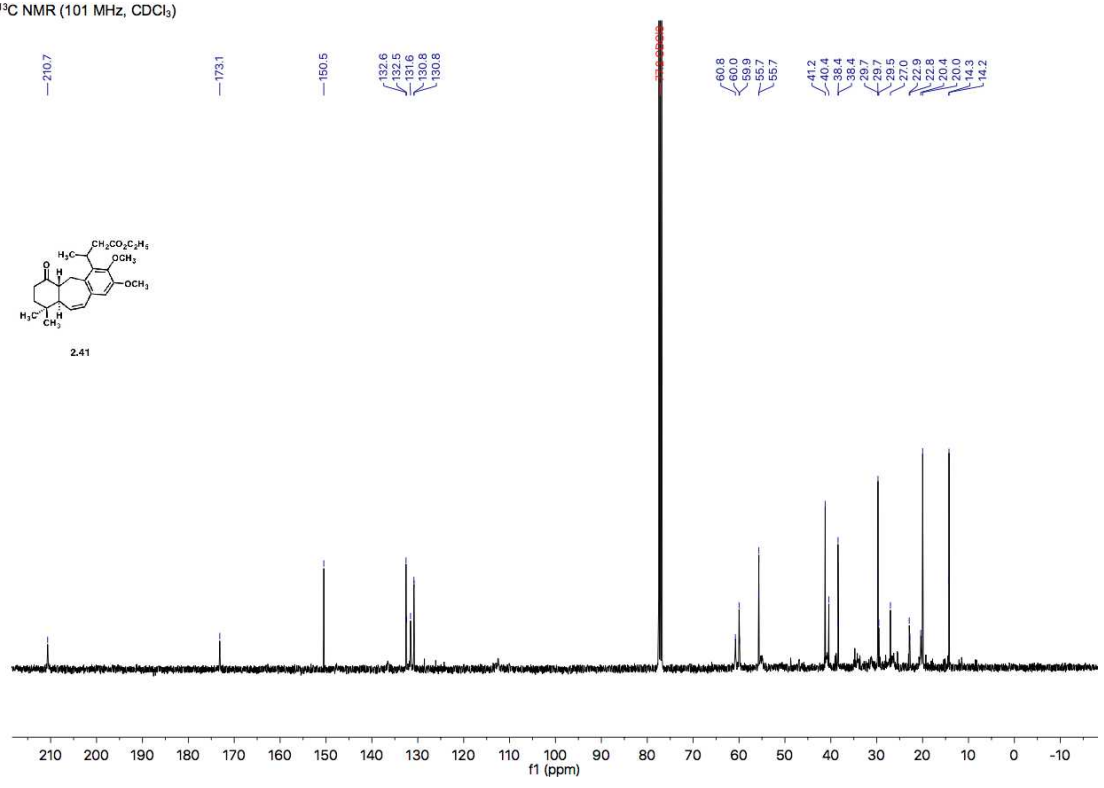

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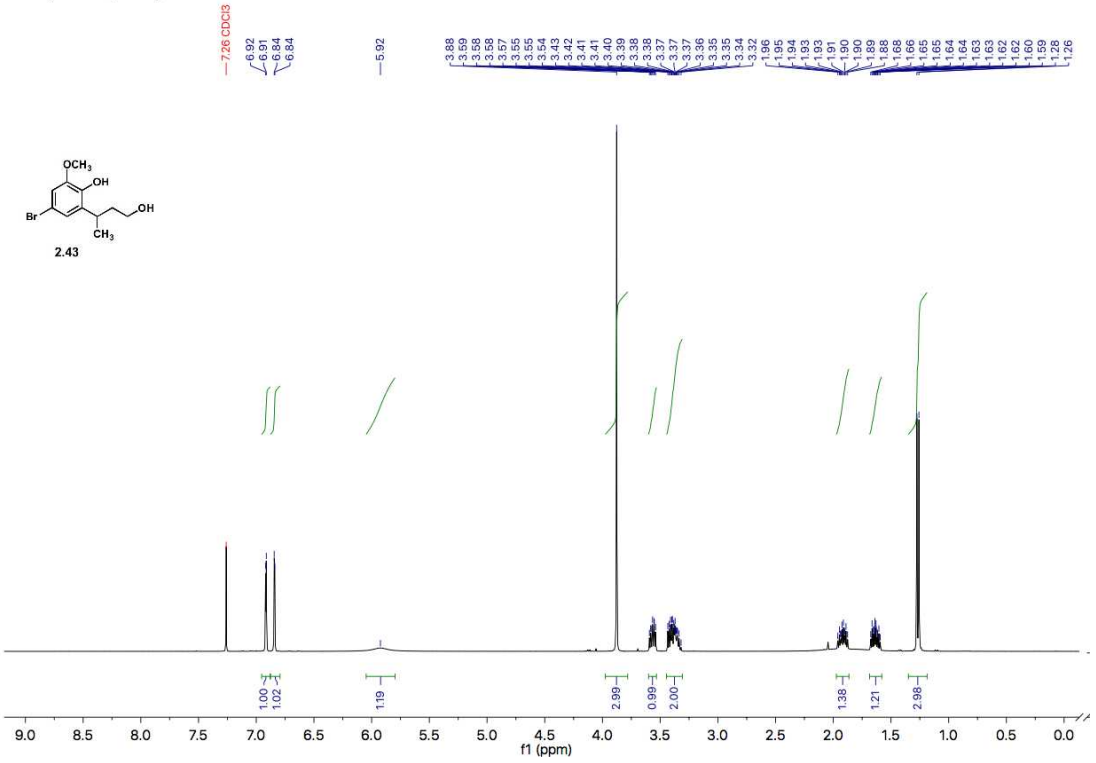

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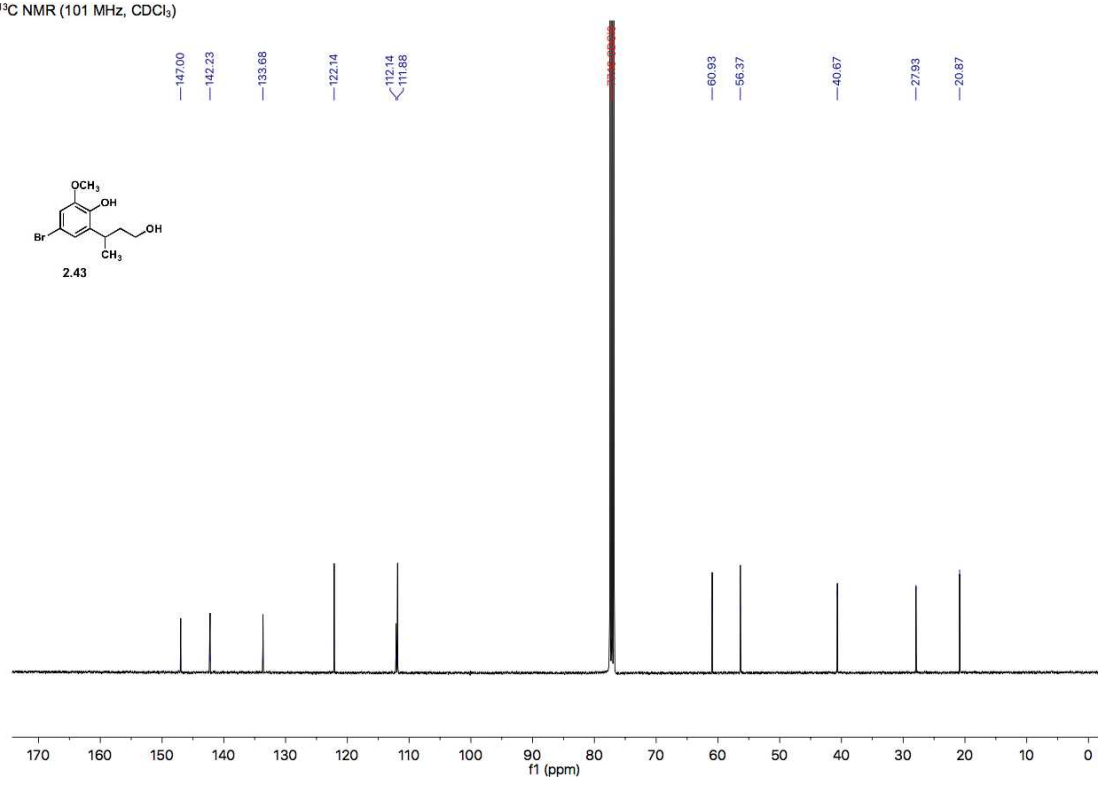

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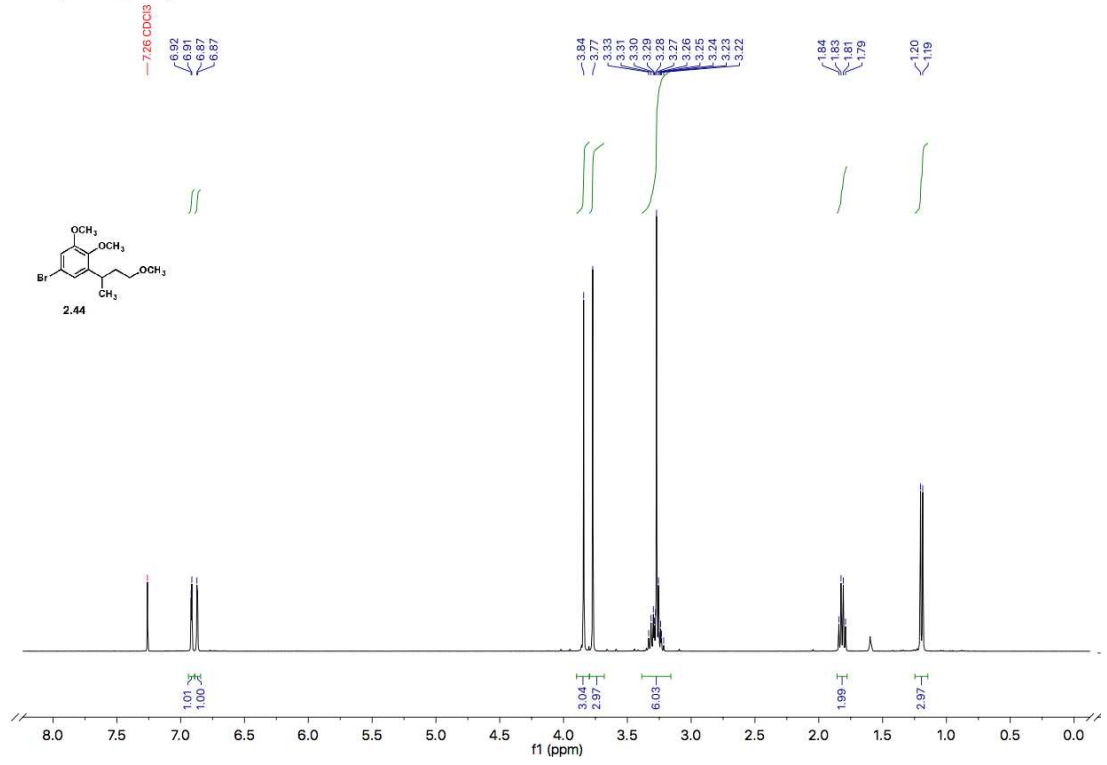

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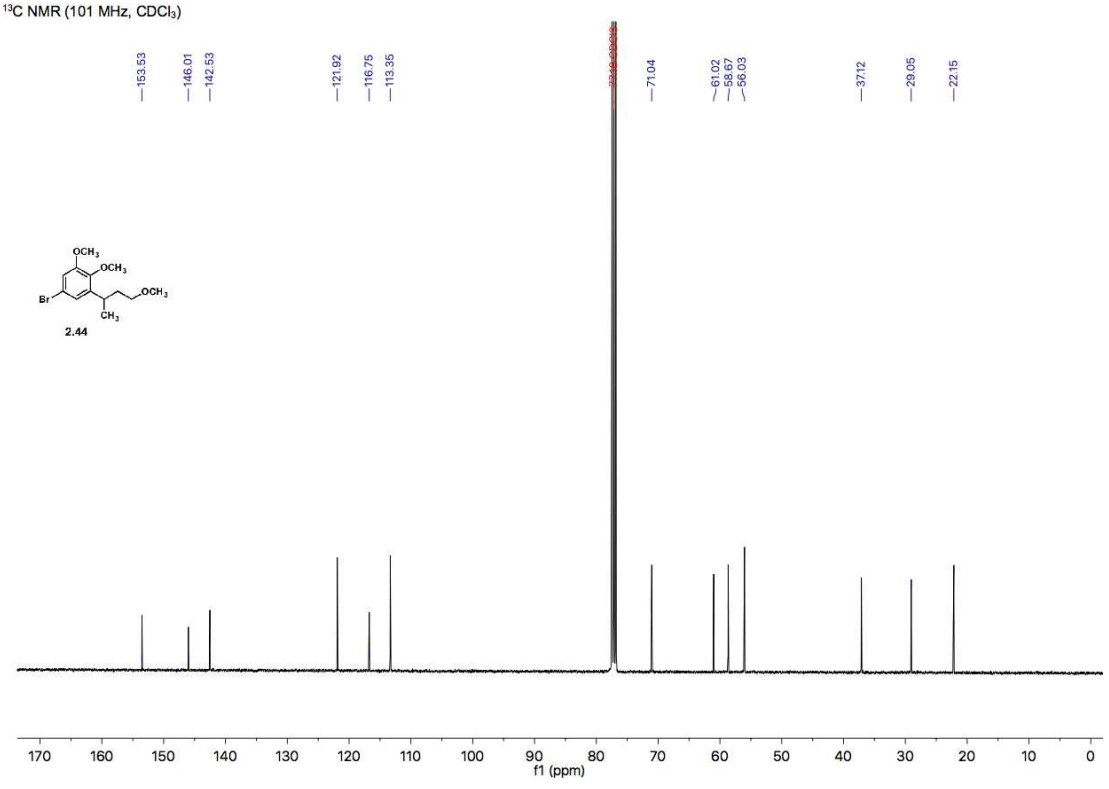

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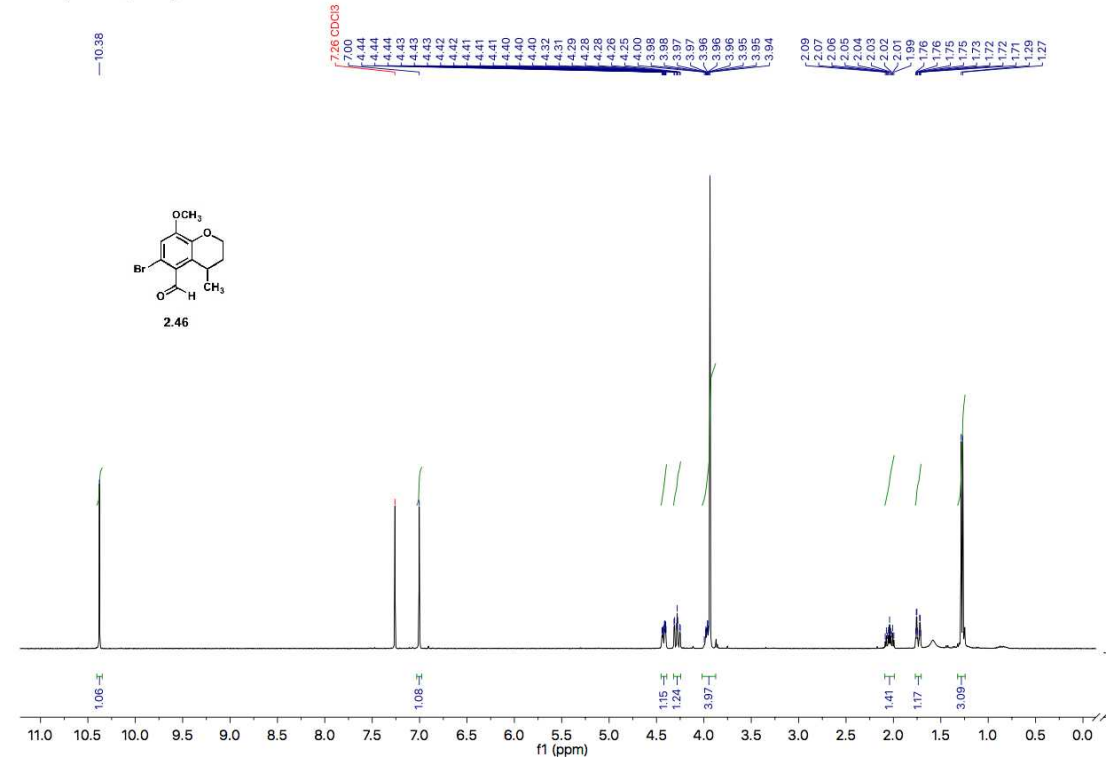

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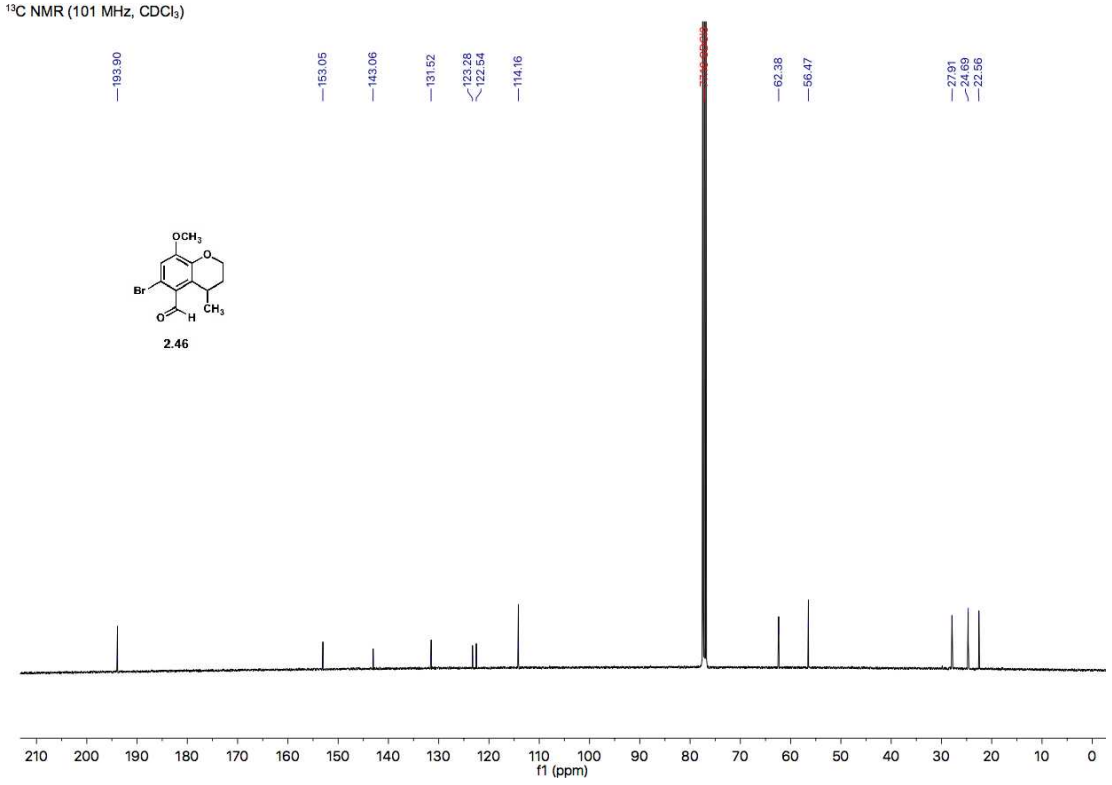

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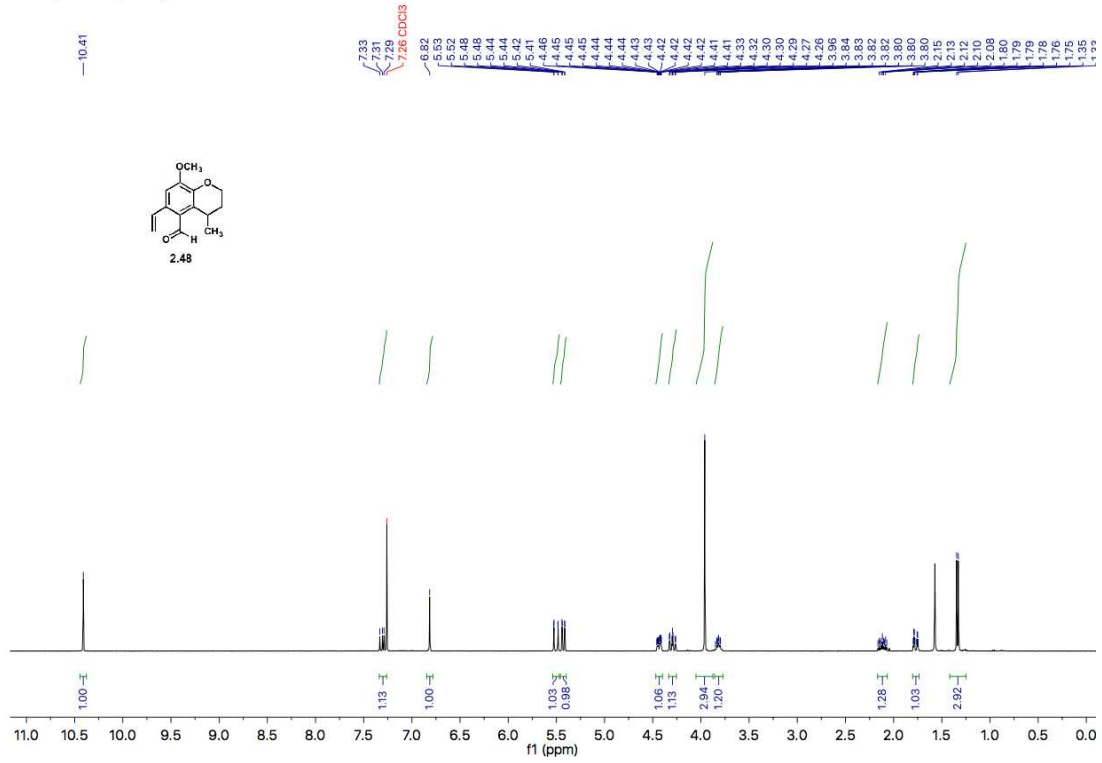

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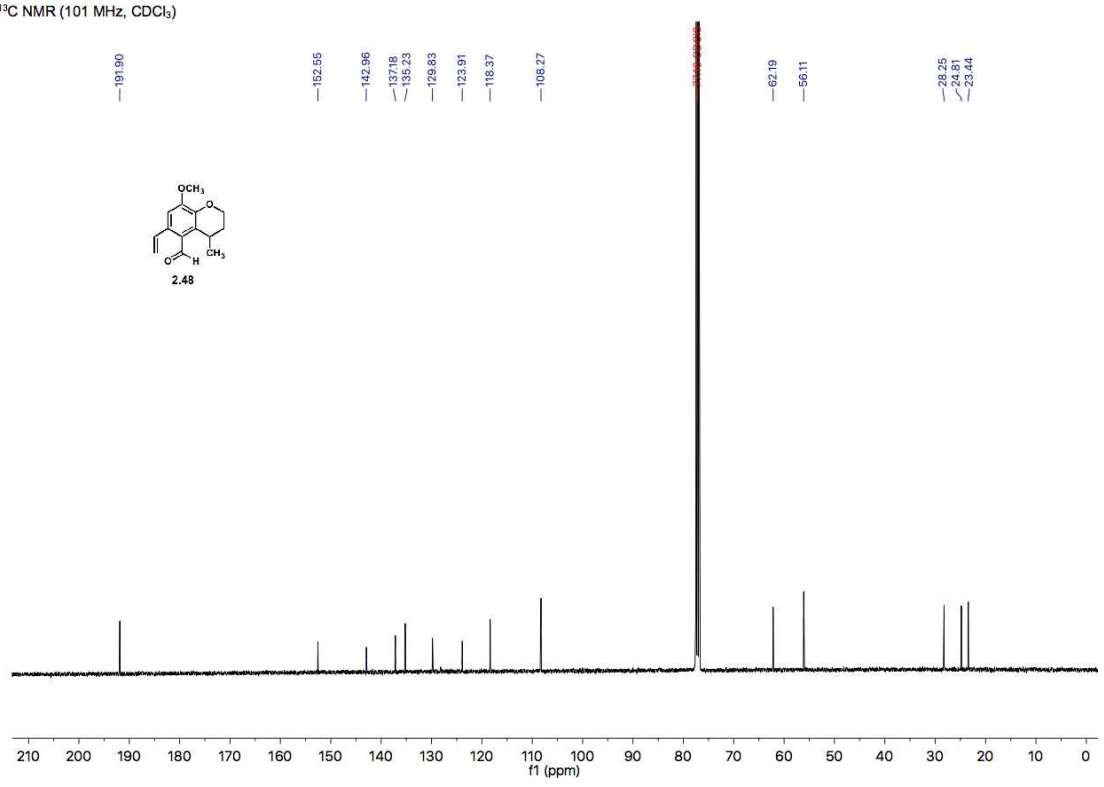

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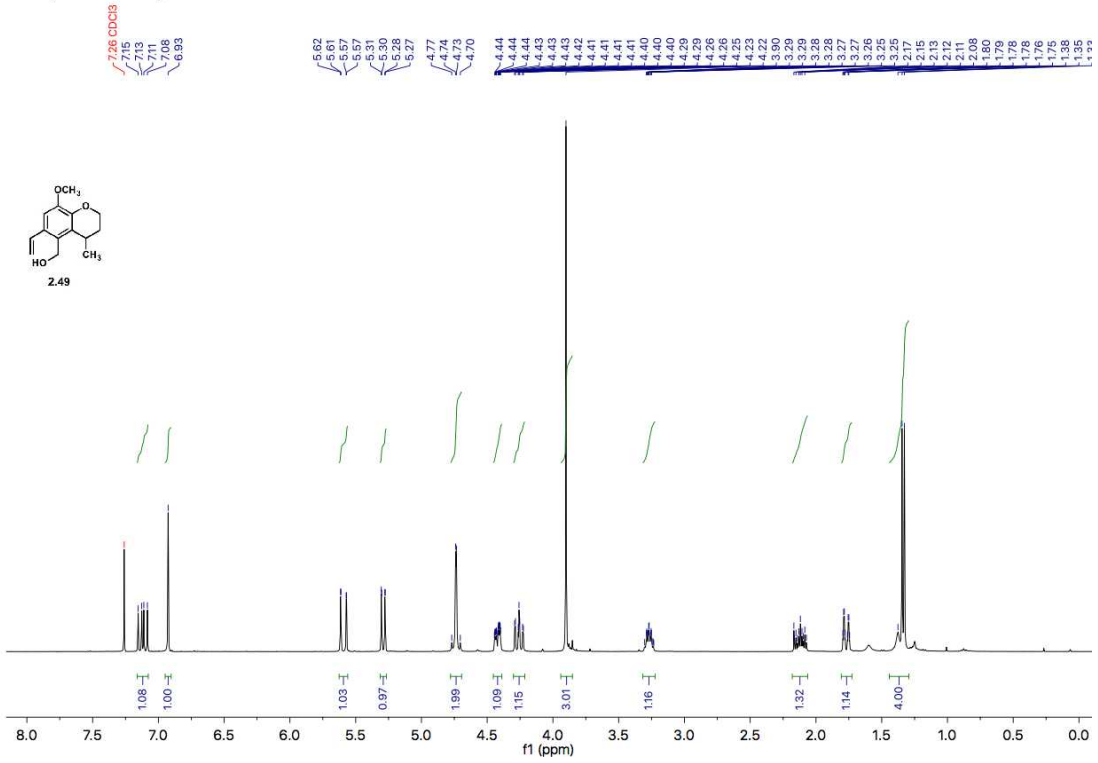

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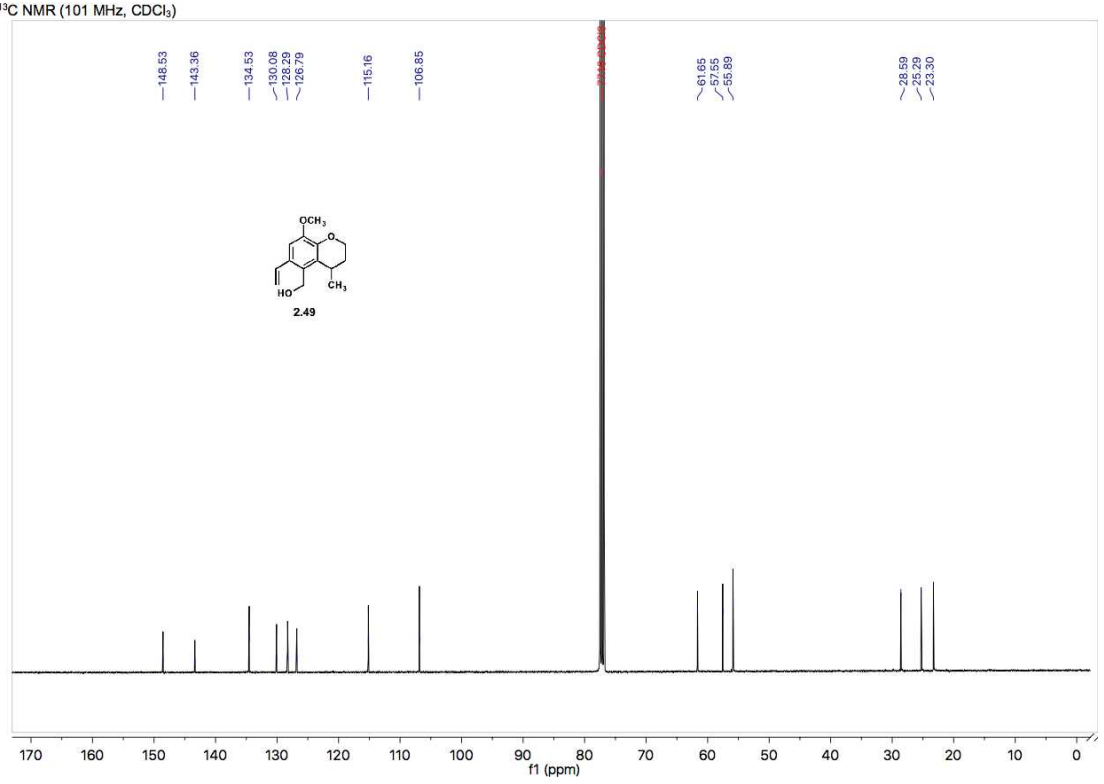

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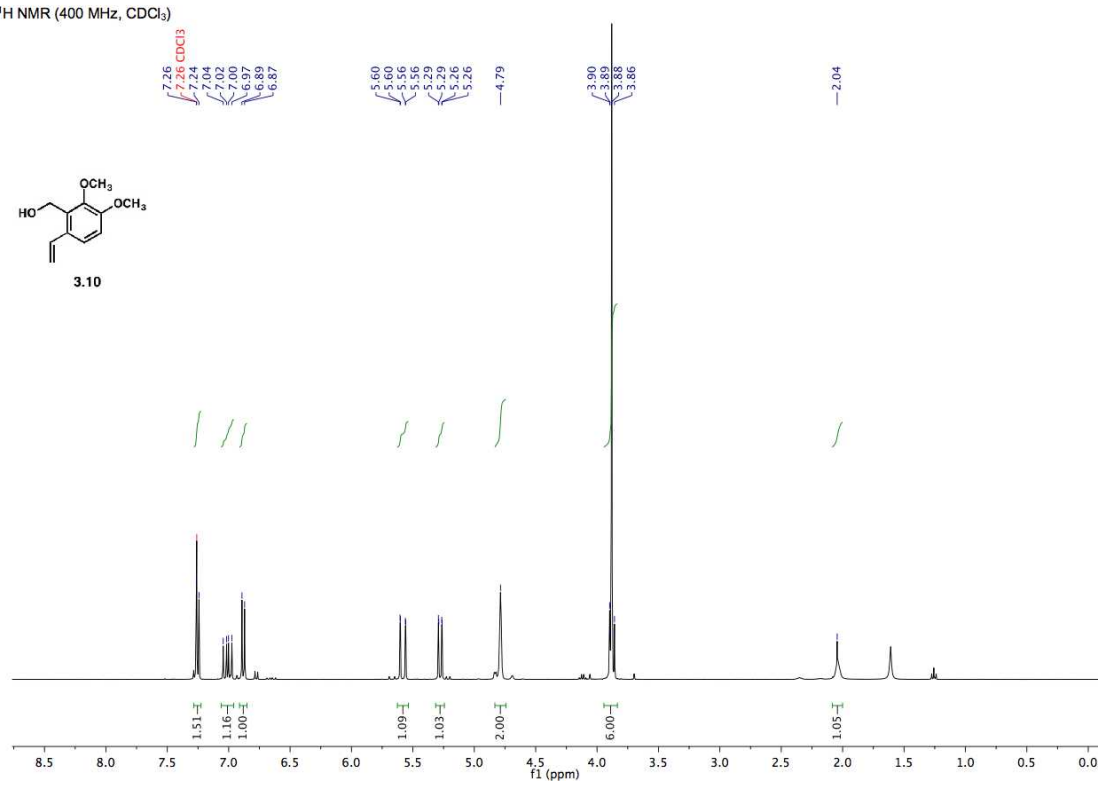
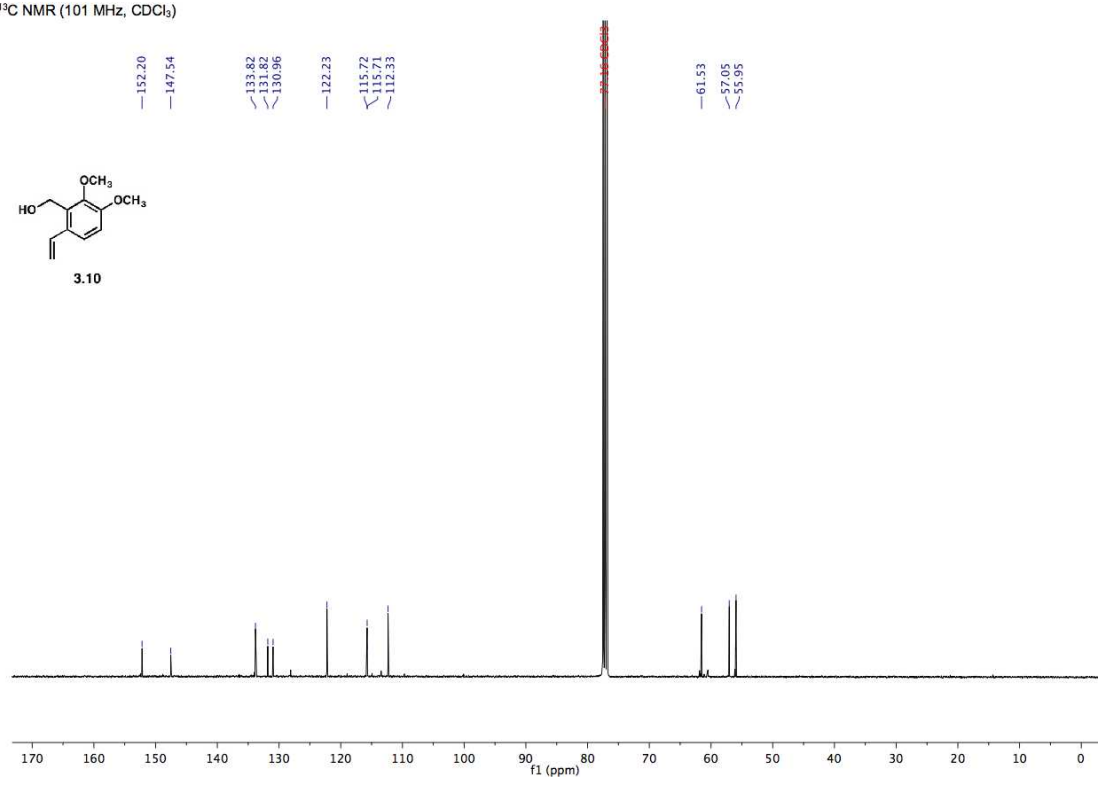


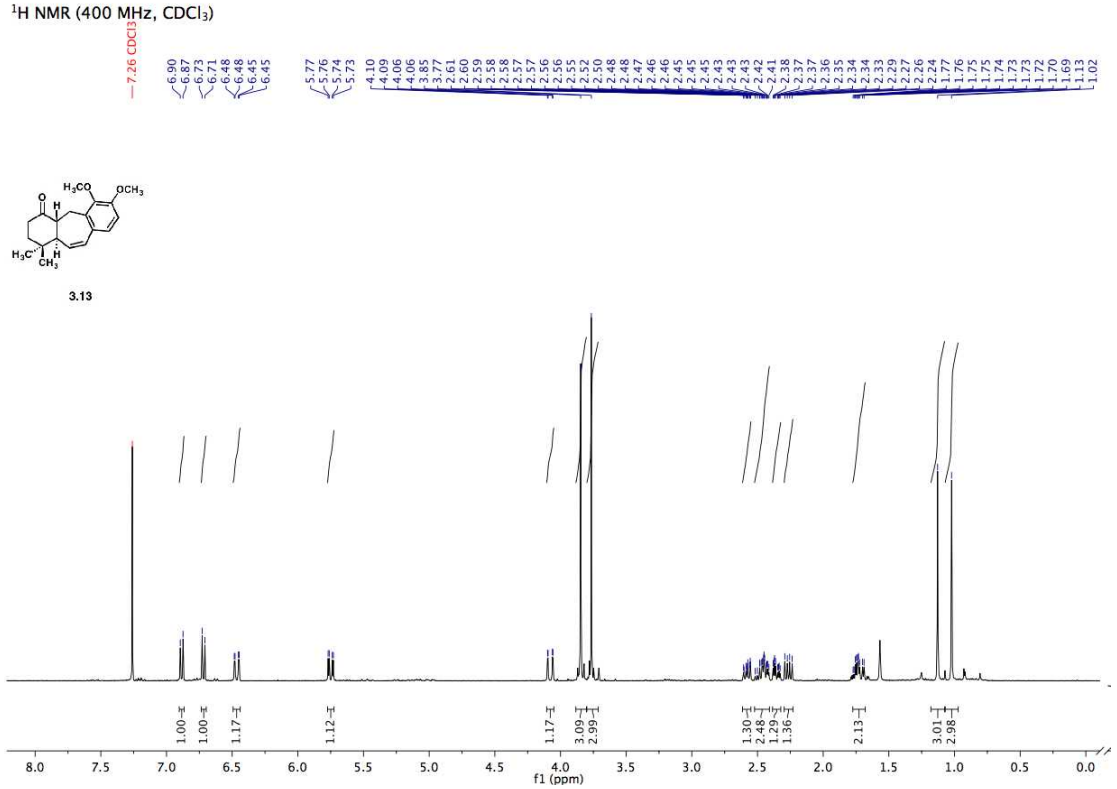
3.10

^{13}C NMR (101 MHz, $CDCl_3$)

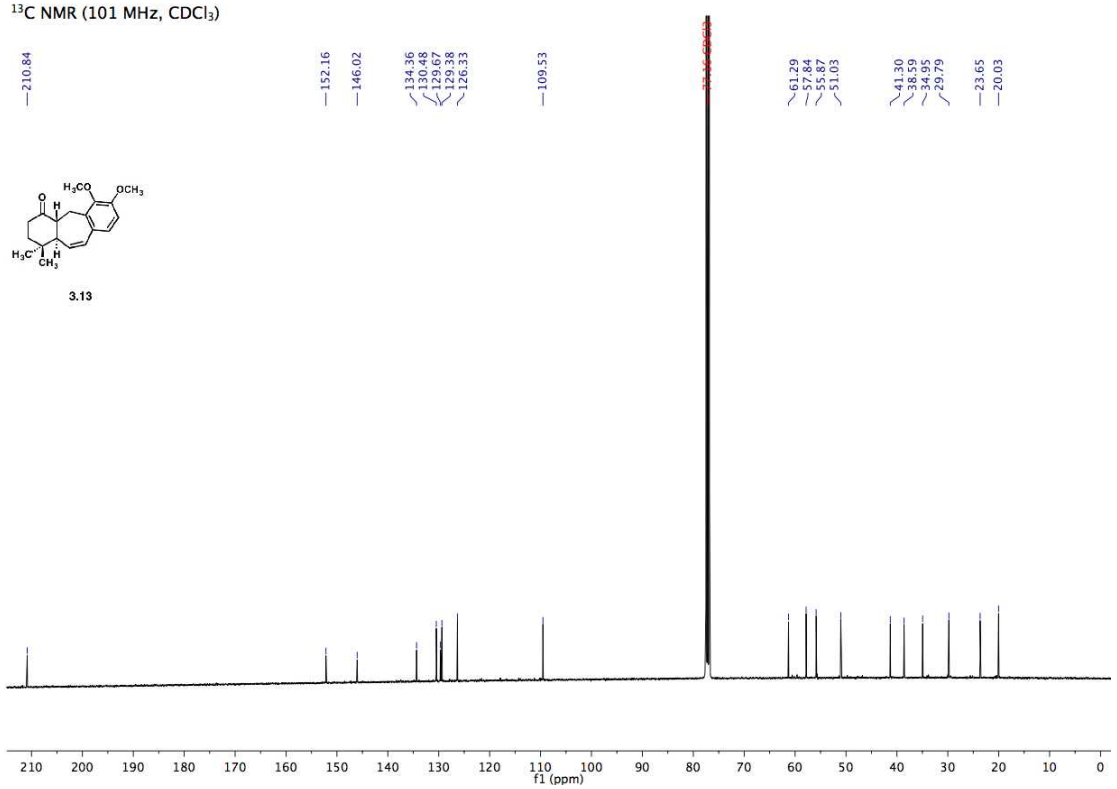


3.10

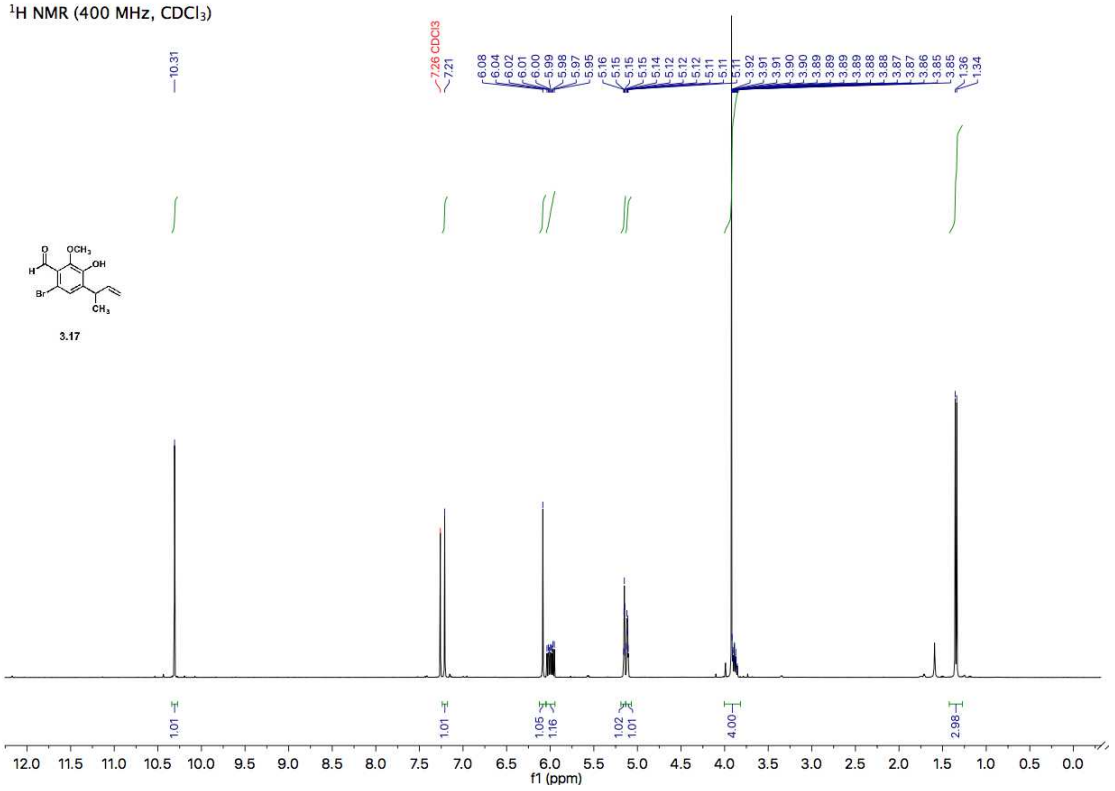
^{1}H NMR (400 MHz, $CDCl_3$)



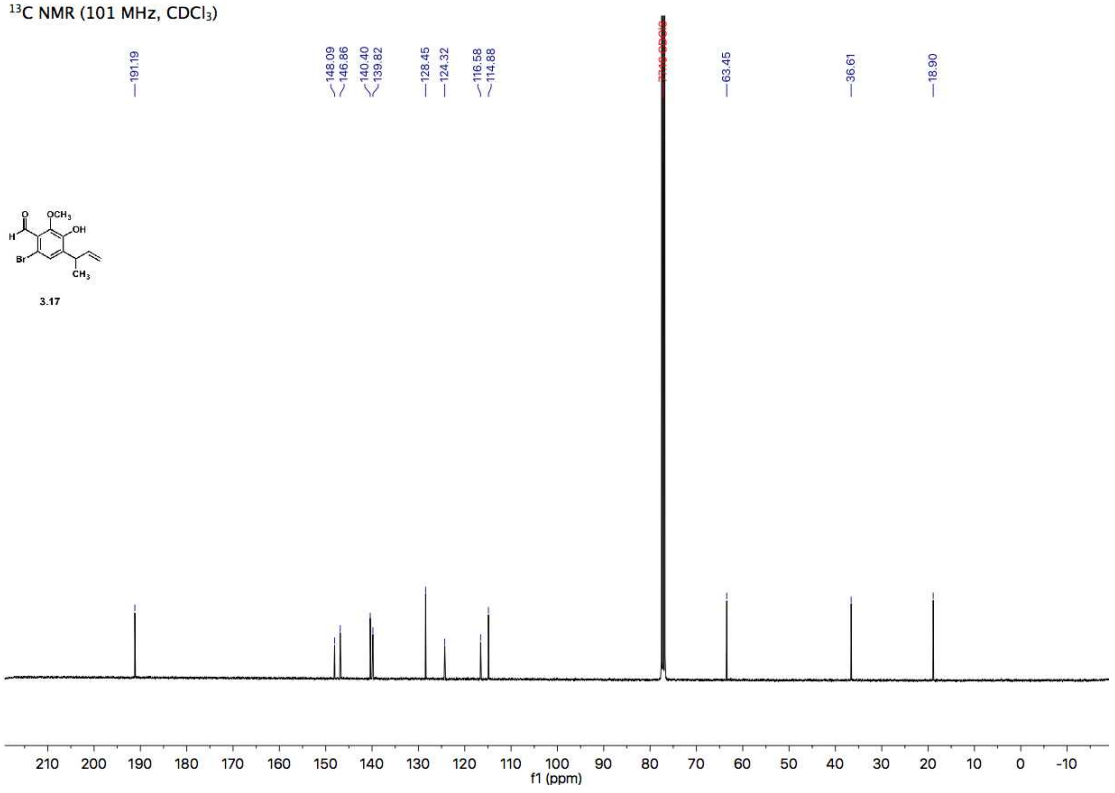
^{13}C NMR (101 MHz, $CDCl_3$)

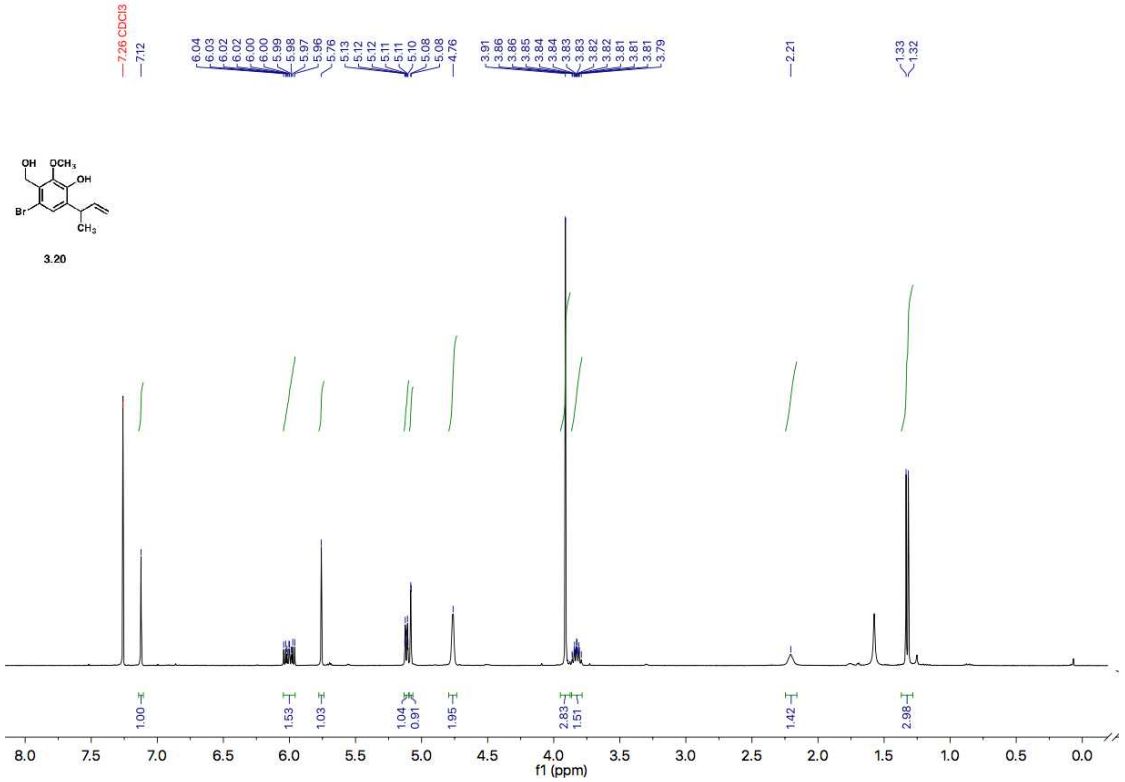


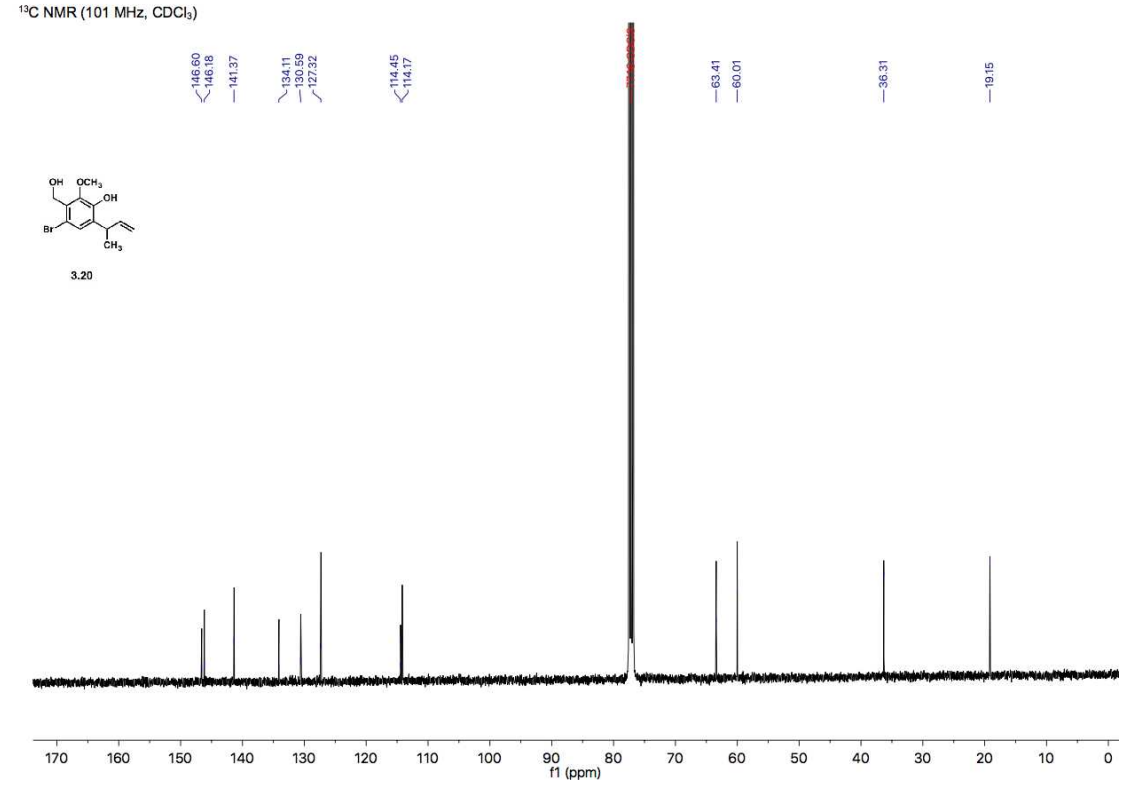
^{1}H NMR (400 MHz, $CDCl_3$)



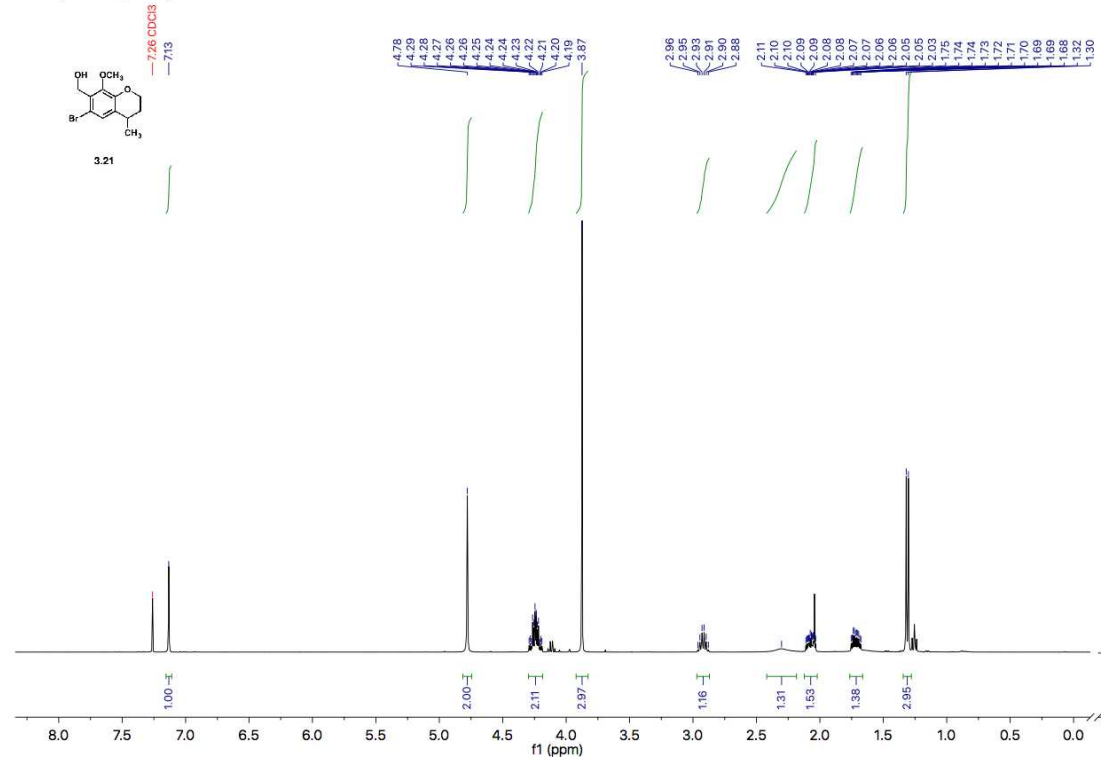
^{13}C NMR (101 MHz, $CDCl_3$)



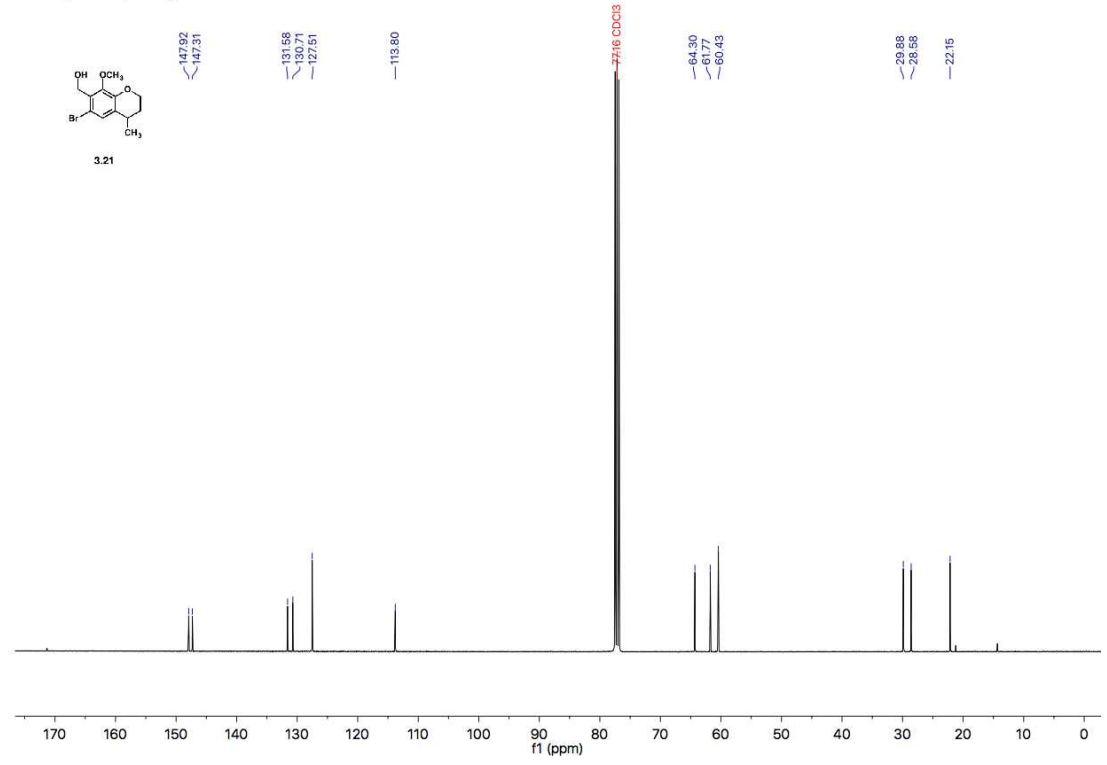

7.26 CDCl3
7.12
6.04
6.03
6.02
6.02
6.00
6.00
5.99
5.98
5.97
5.96
5.76
5.13
5.12
5.12
5.11
5.11
5.10
5.08
5.08
4.76
3.91
3.86
3.86
3.85
3.84
3.84
3.83
3.83
3.82
3.82
3.81
3.81
3.81
3.79
2.21
1.33
1.32
OH
OCH3
OH
Br
CH3
3.20
1.00
1.53
1.03
1.04
0.91
1.95
2.83
1.51
1.42
2.98
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


13C NMR (101 MHz, CDCl3)
146.60
146.18
141.37
134.11
130.59
127.32
114.45
114.17
63.41
60.01
36.31
19.15
OH
OCH3
OH
Br
CH3
3.20
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

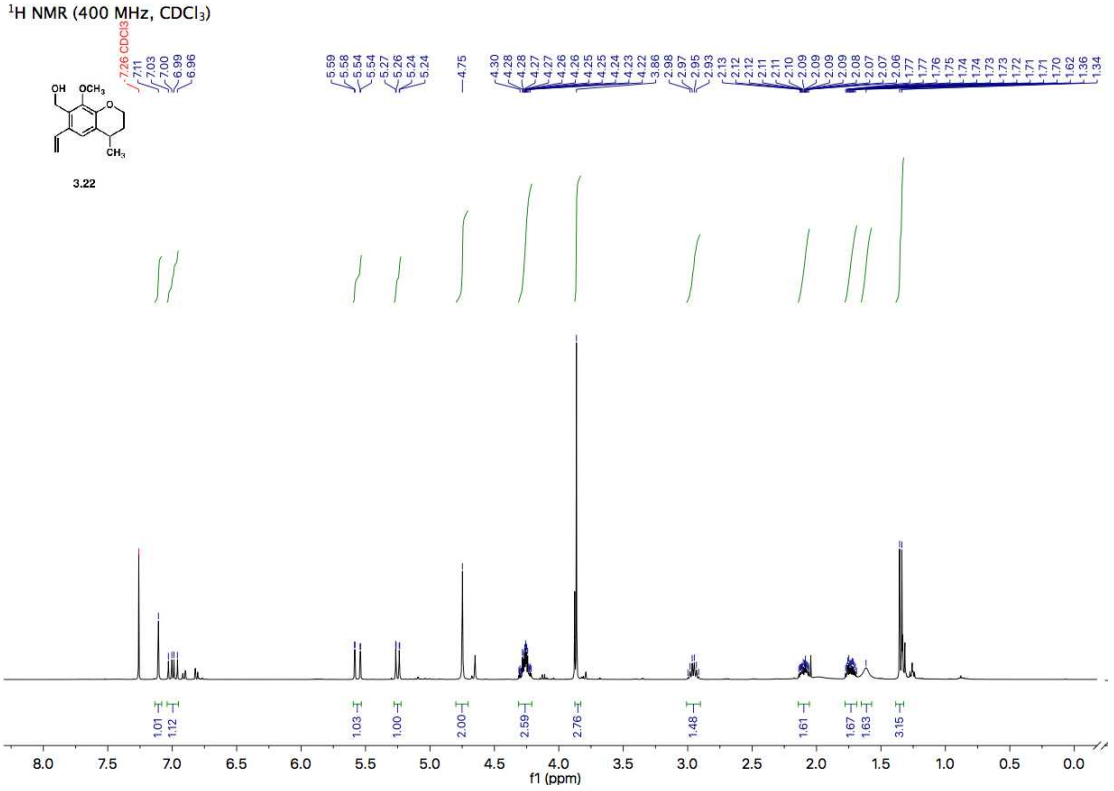
^{1}H NMR (400 MHz, $CDCl_3$)



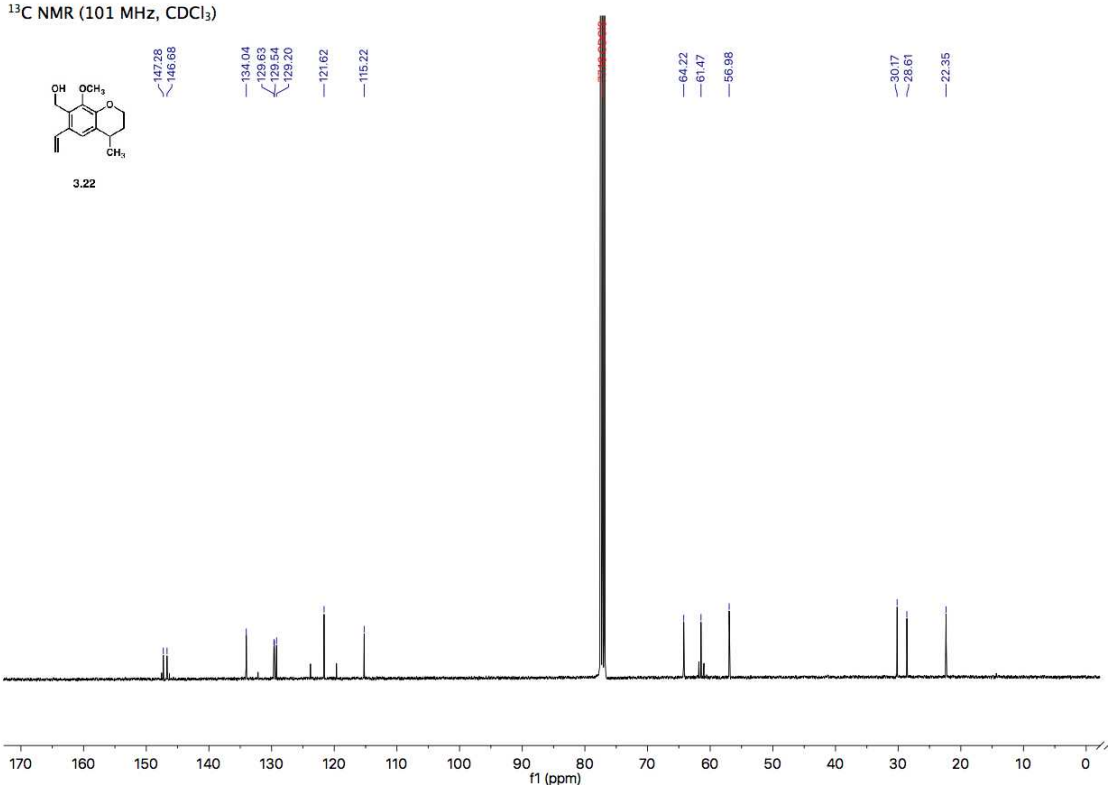
^{13}C NMR (101 MHz, $CDCl_3$)



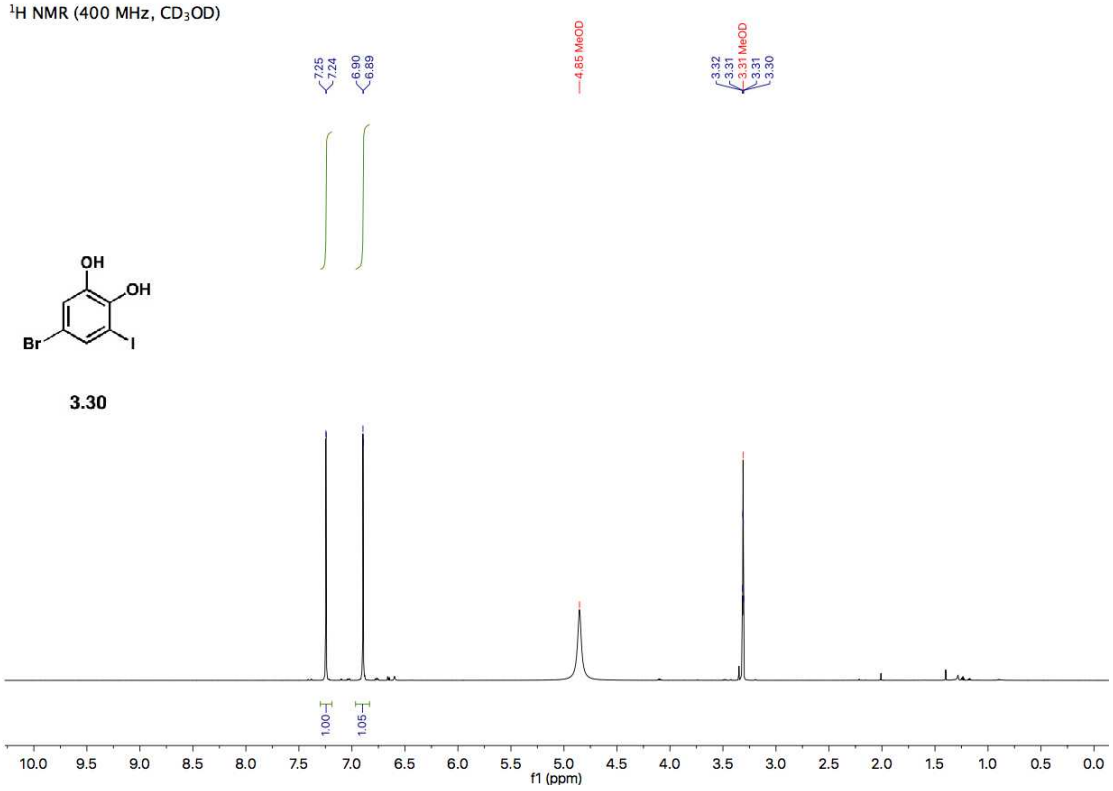
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

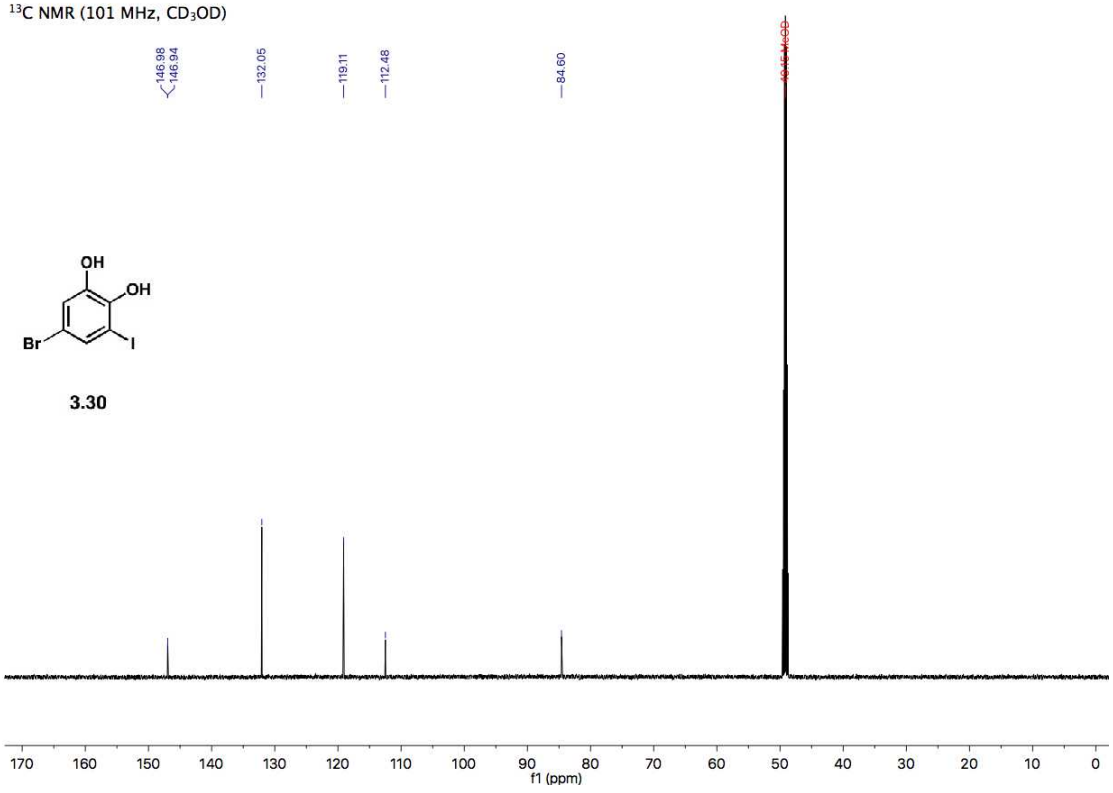


^{1}H NMR (400 MHz, CD_3OD)



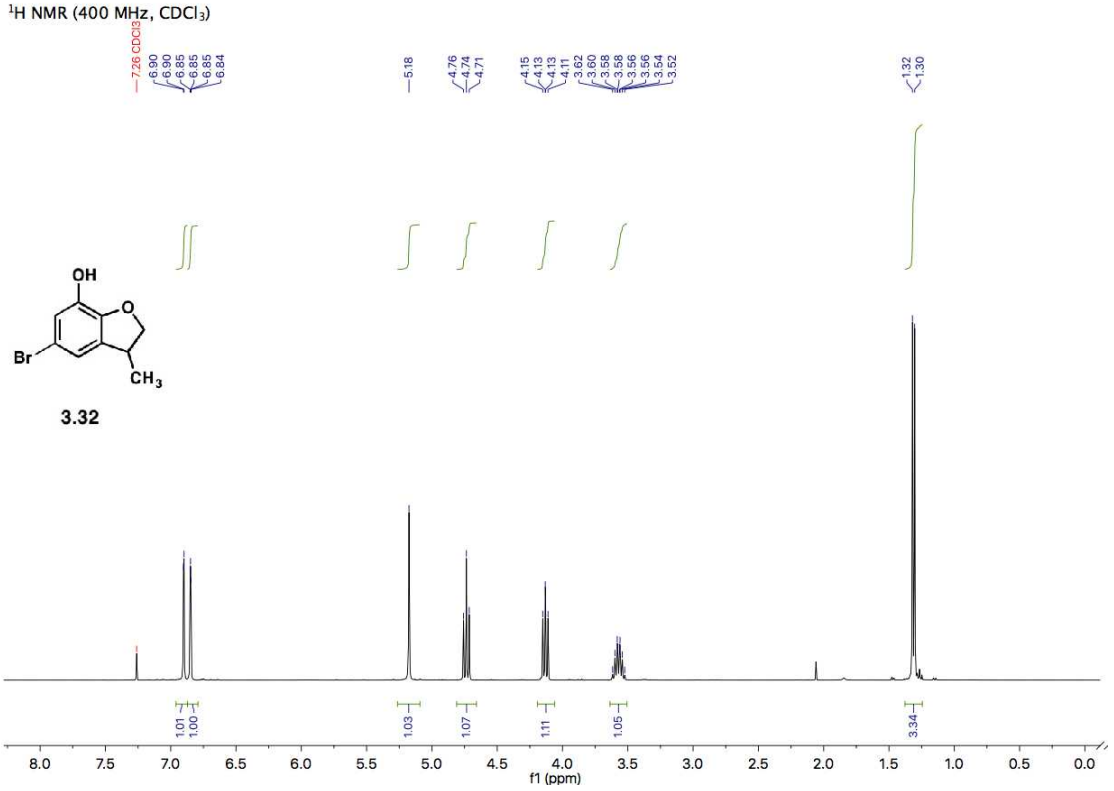
3.30

^{13}C NMR (101 MHz, CD_3OD)



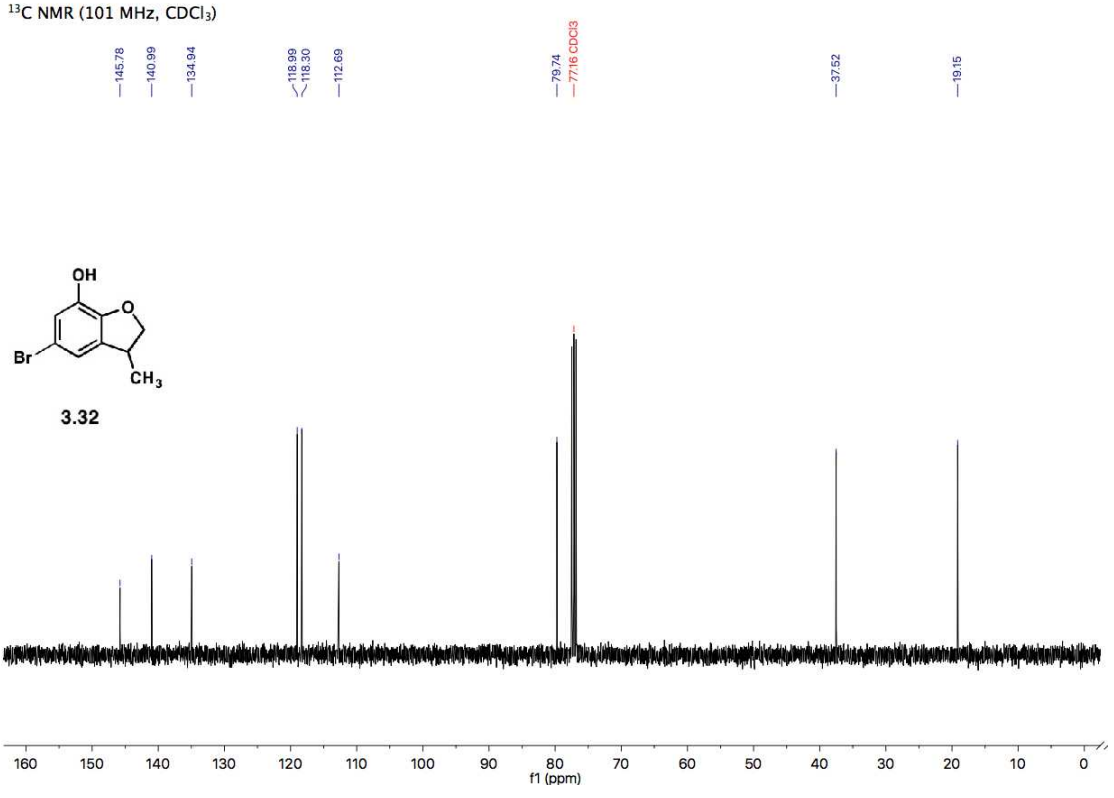
3.30

^{1}H NMR (400 MHz, $CDCl_3$)



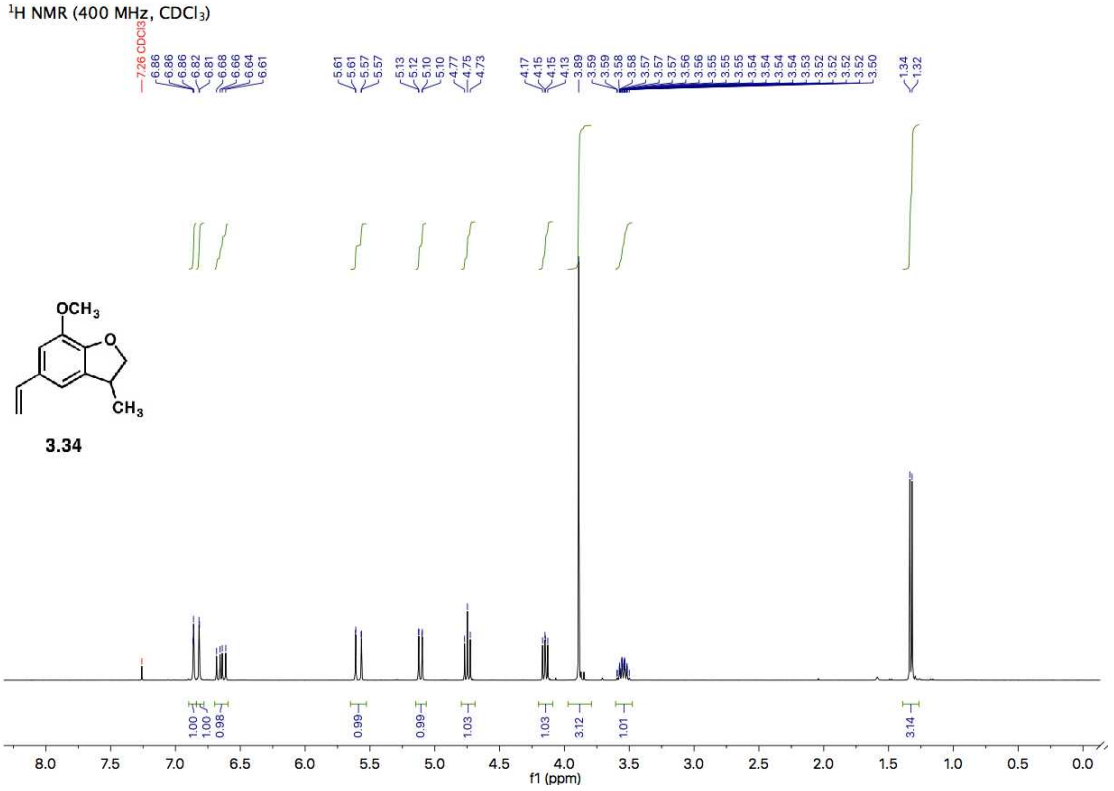
3.32

^{13}C NMR (101 MHz, $CDCl_3$)



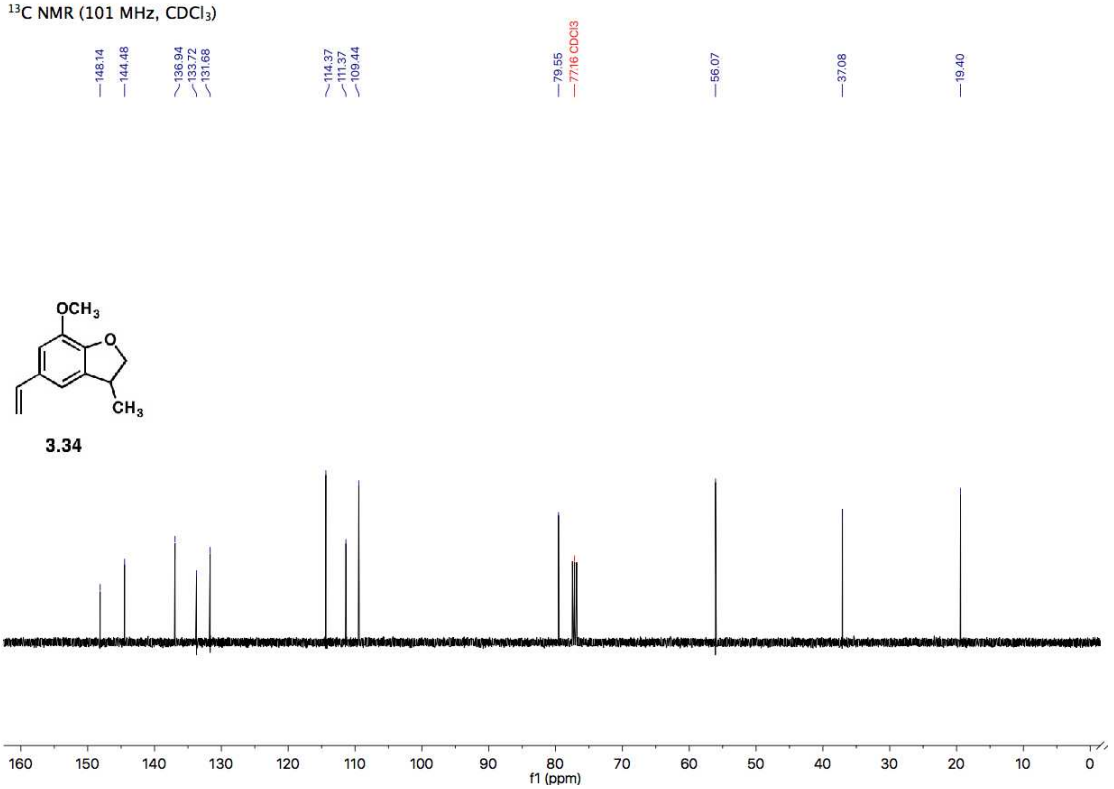
3.32

^{1}H NMR (400 MHz, $CDCl_3$)



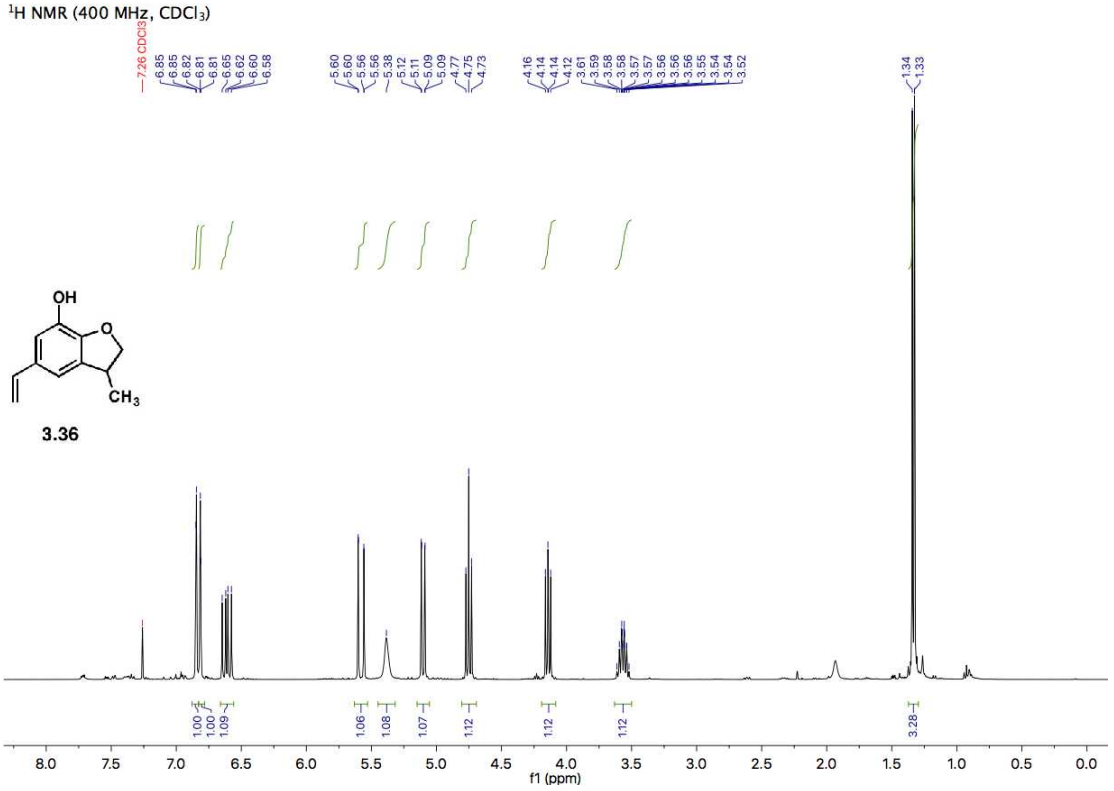
3.34

^{13}C NMR (101 MHz, $CDCl_3$)



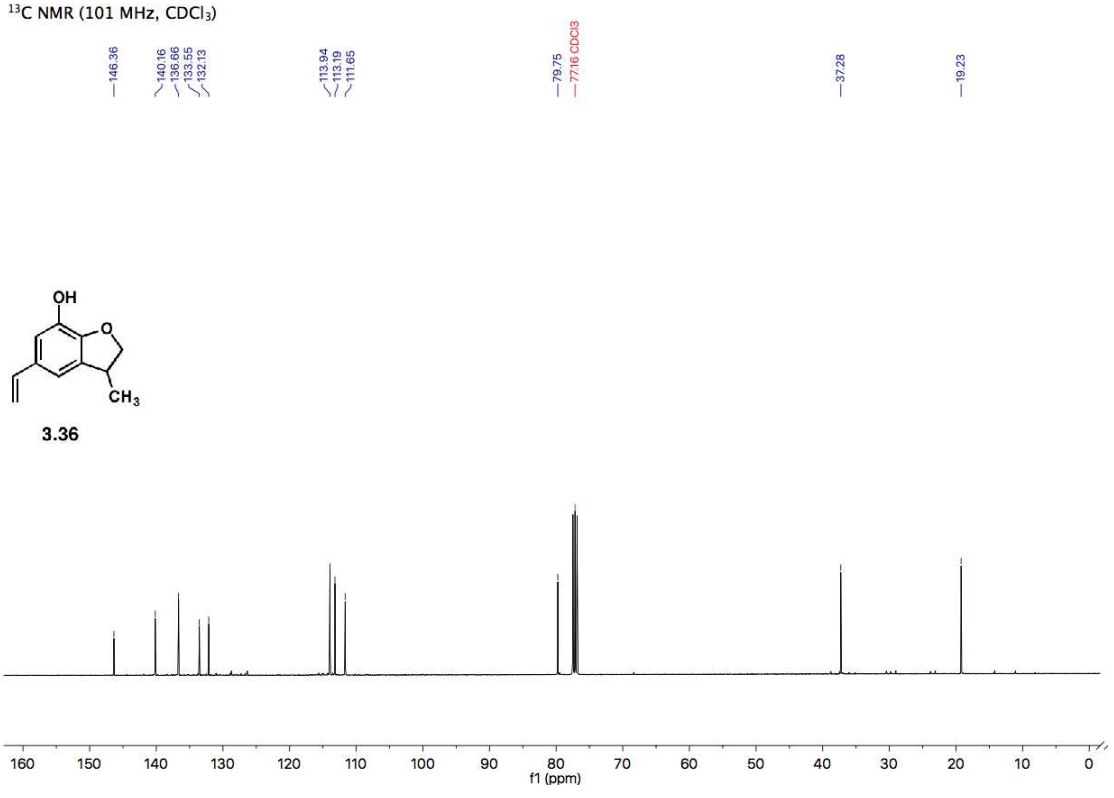
3.34

^{1}H NMR (400 MHz, $CDCl_3$)



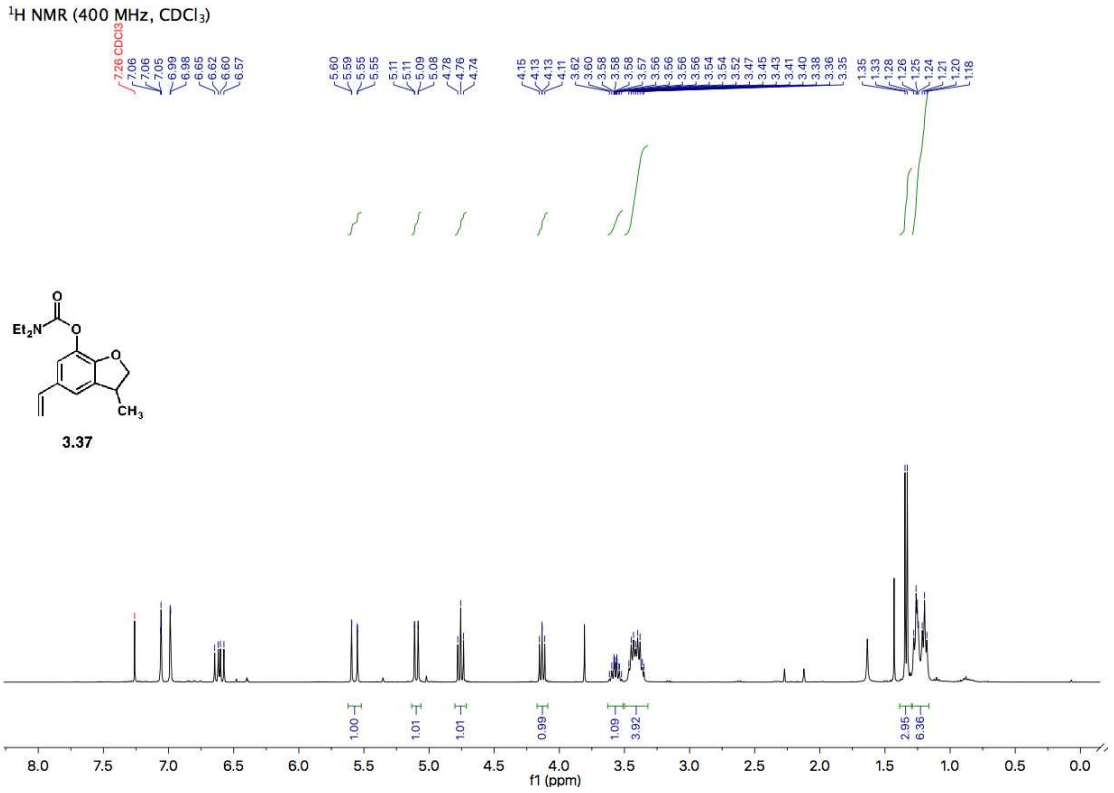
3.36

^{13}C NMR (101 MHz, $CDCl_3$)

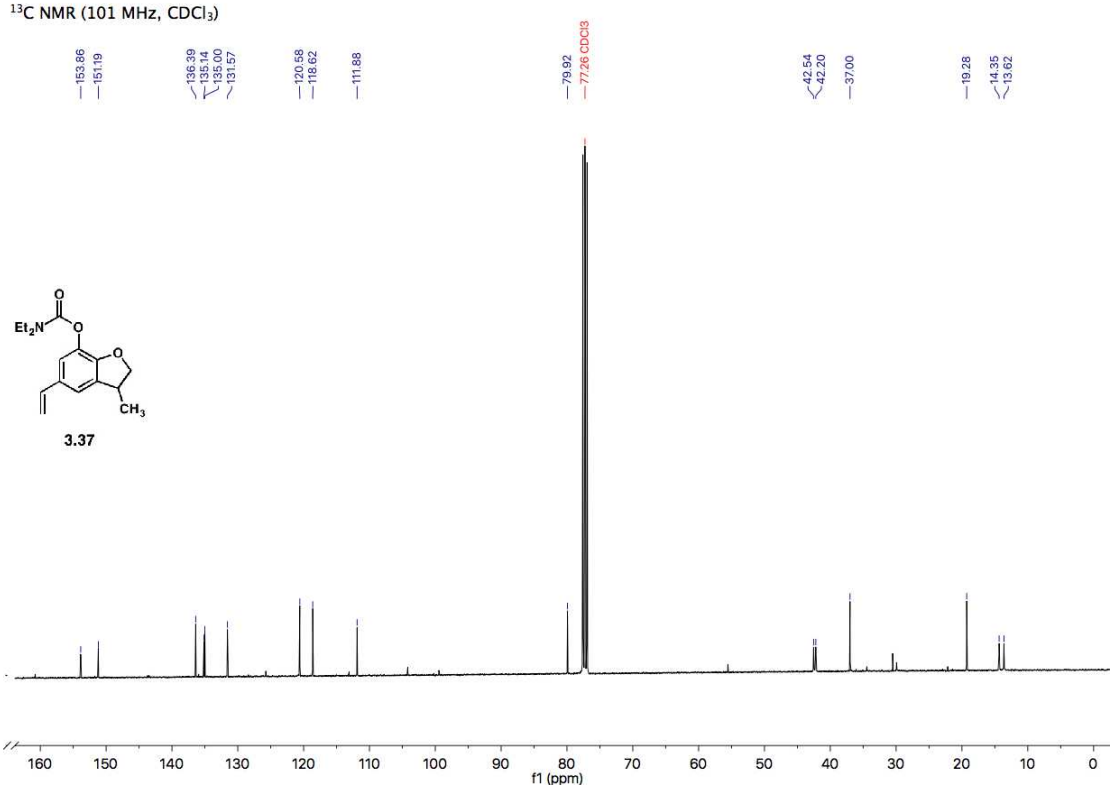


3.36

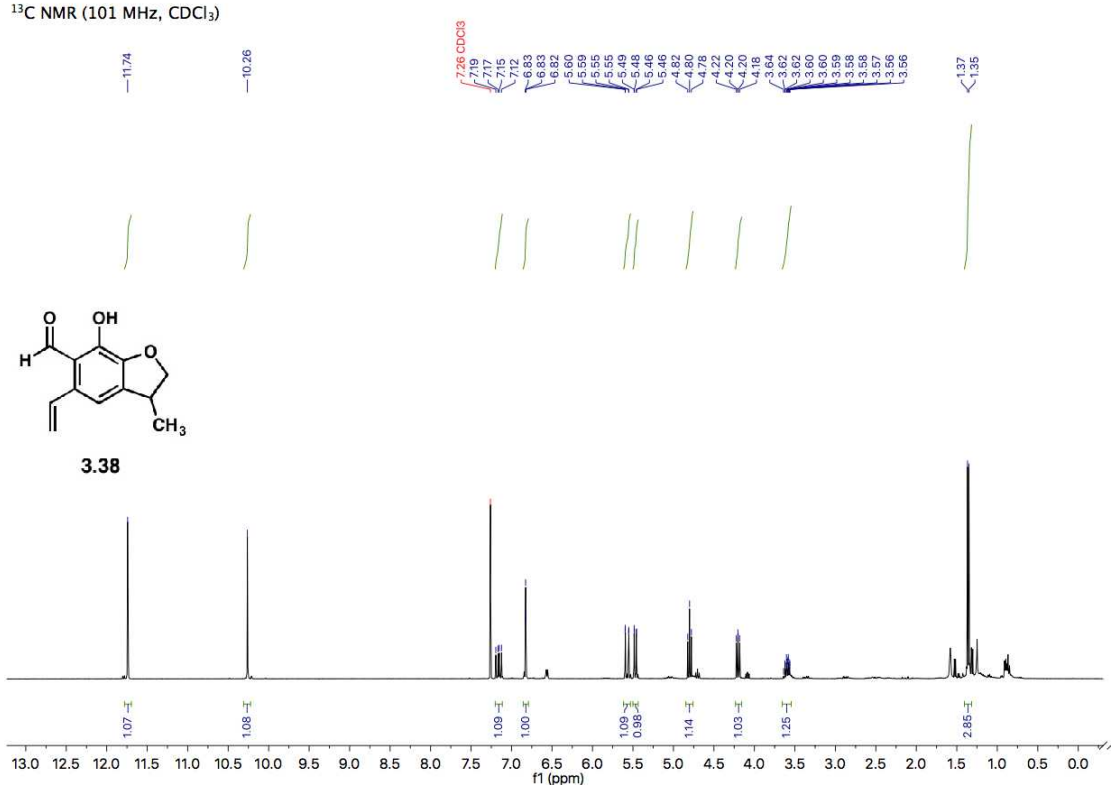
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

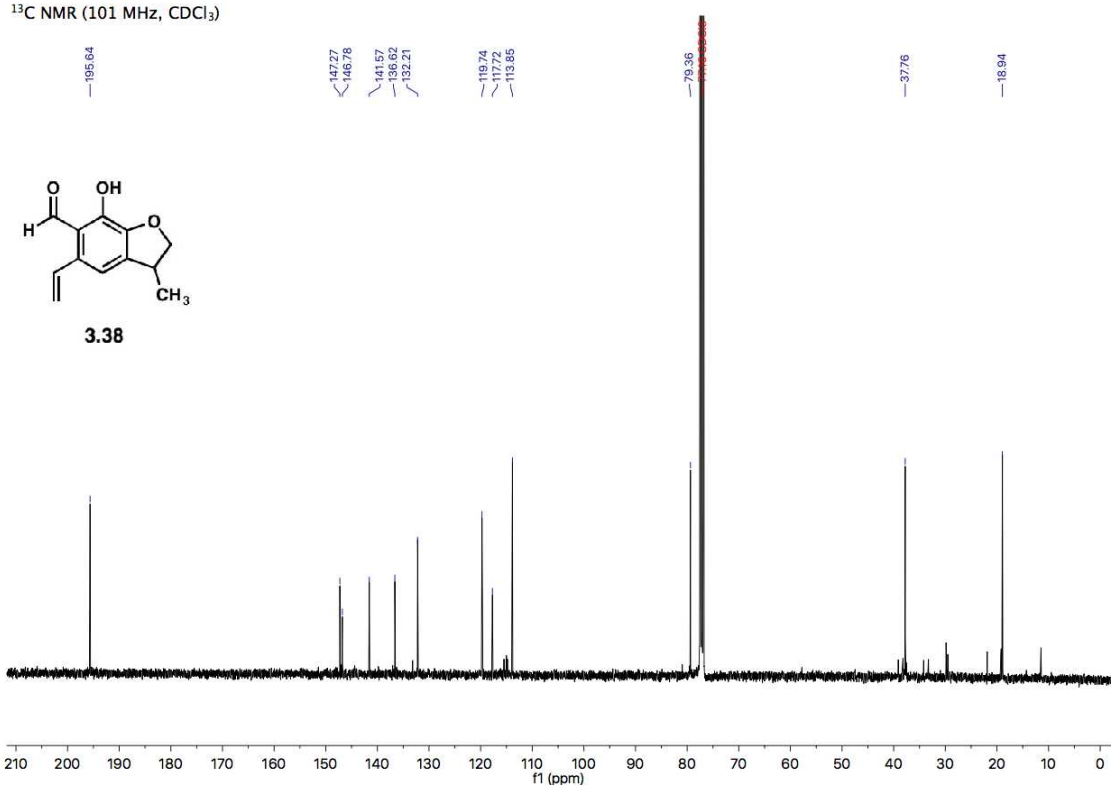


^{13}C NMR (101 MHz, $CDCl_3$)



3.38

^{13}C NMR (101 MHz, $CDCl_3$)

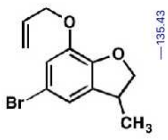


3.38

^{1}H NMR (400 MHz, $CDCl_3$)

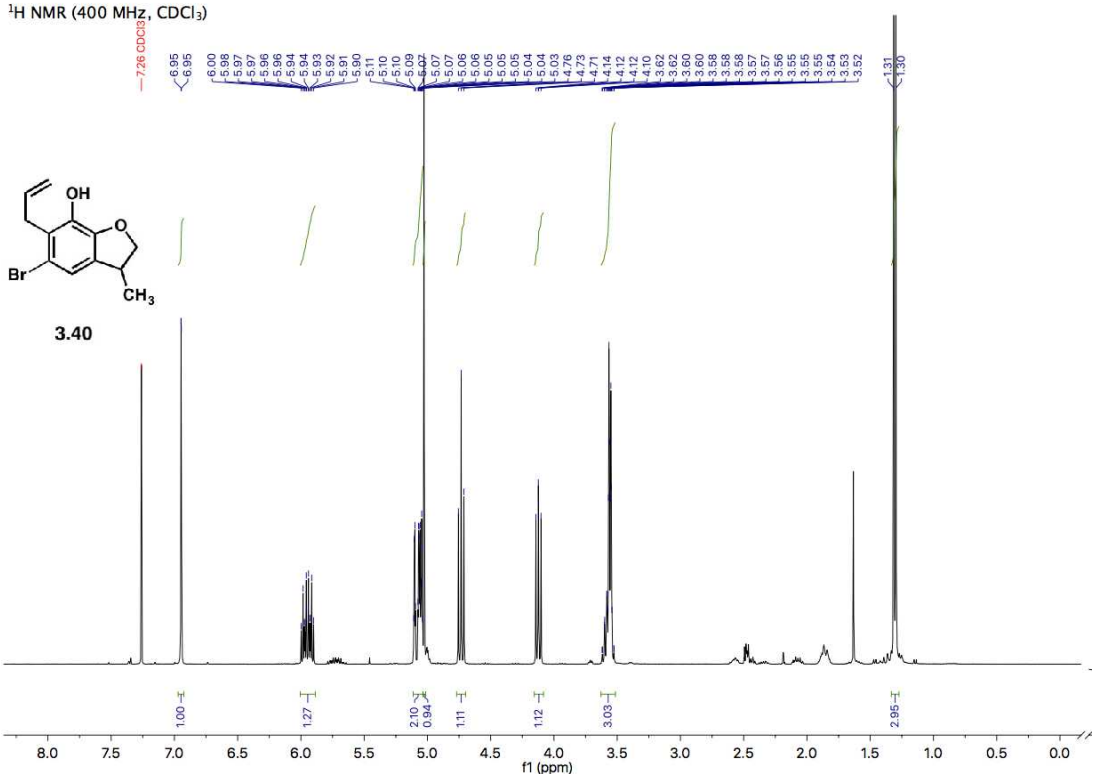
3.39

^{13}C NMR (101 MHz, $CDCl_3$)

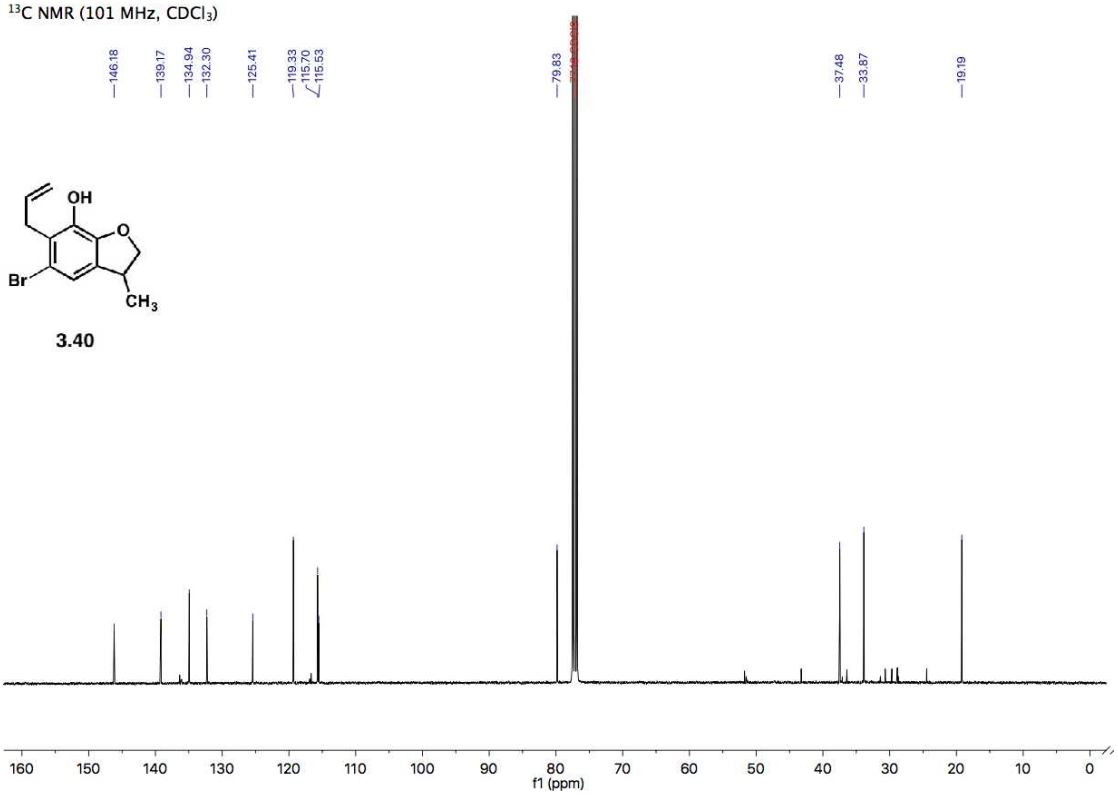


3.39

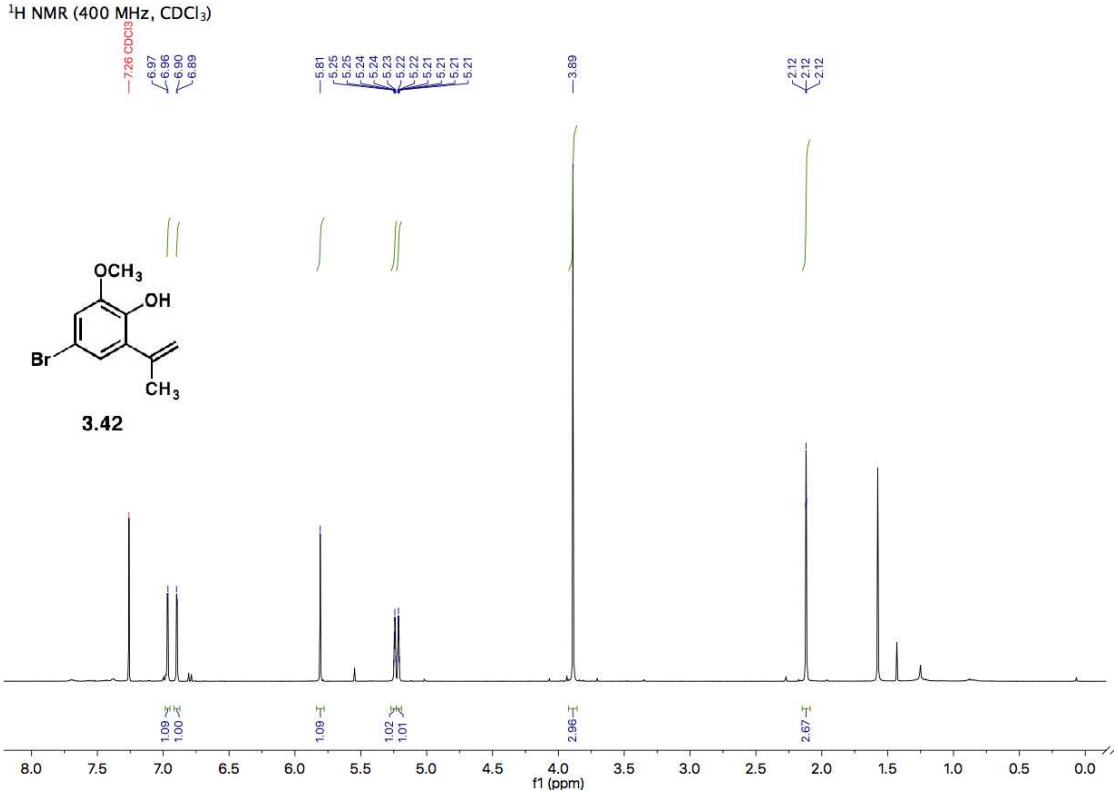
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

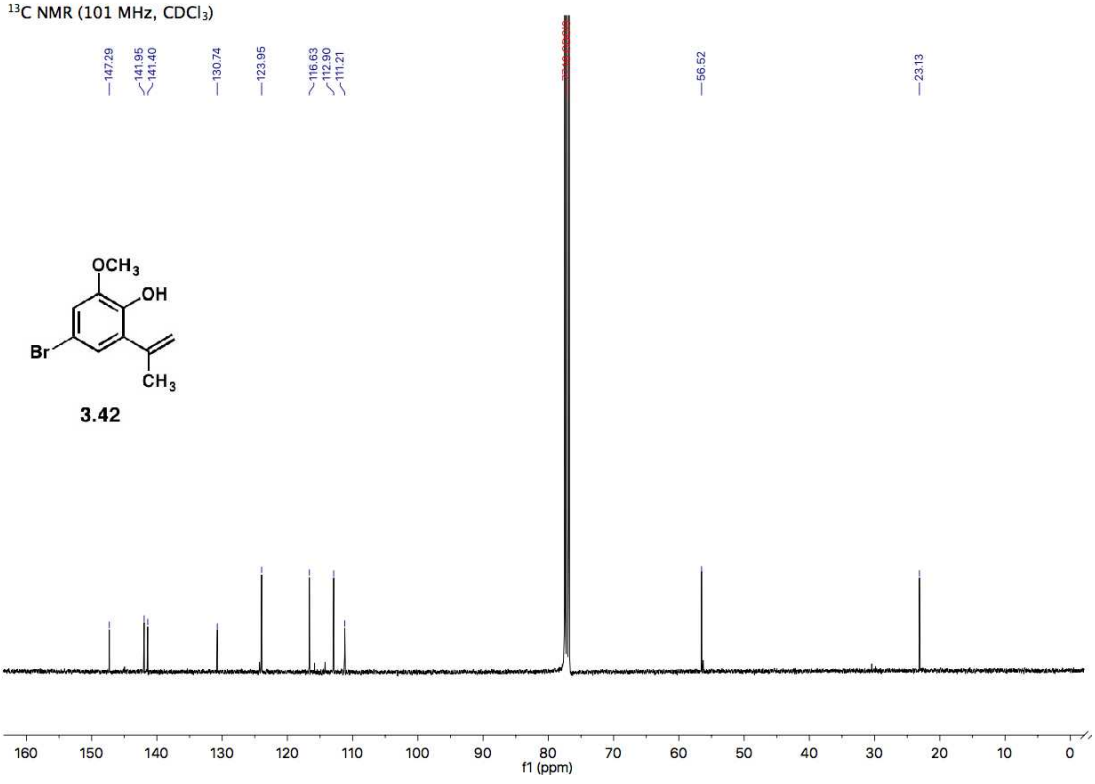


^{1}H NMR (400 MHz, $CDCl_3$)



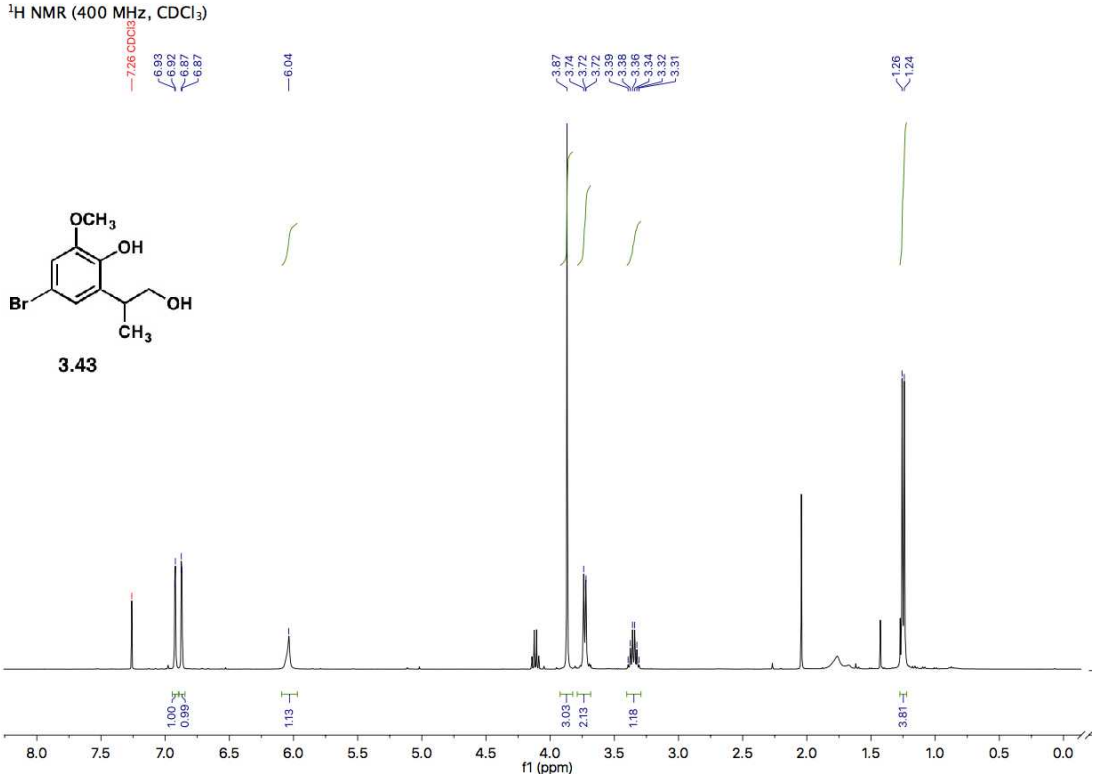
3.42

^{13}C NMR (101 MHz, $CDCl_3$)



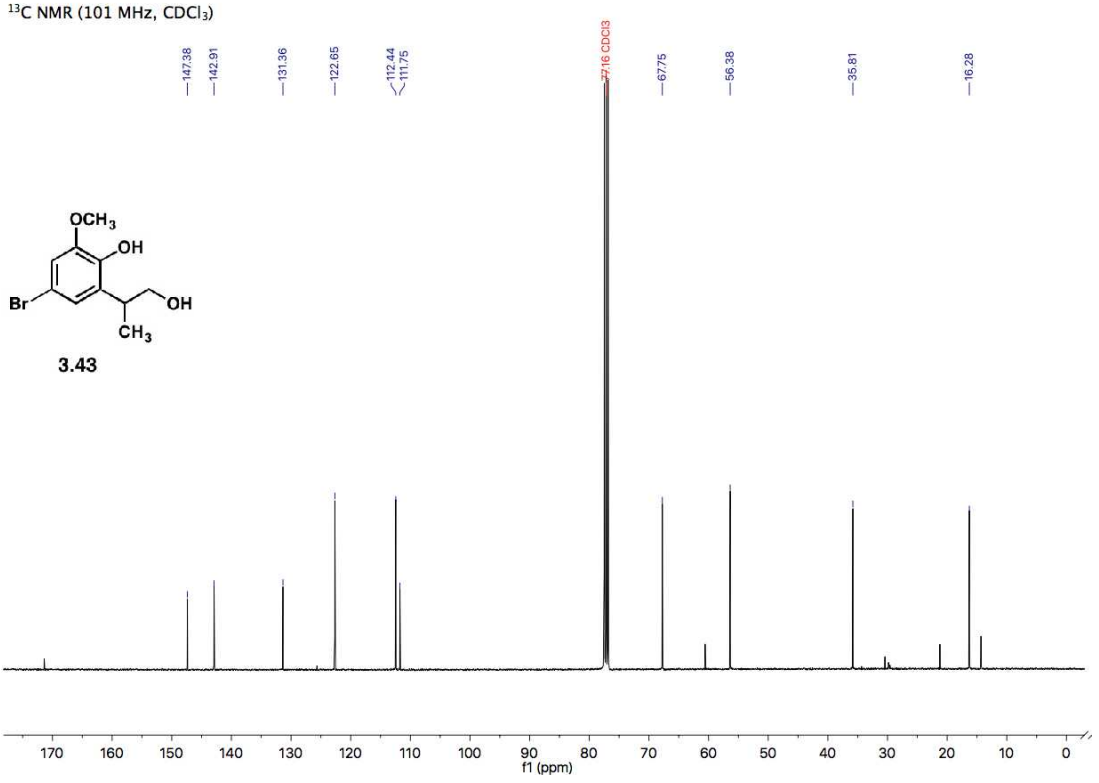
3.42

^{1}H NMR (400 MHz, $CDCl_3$)



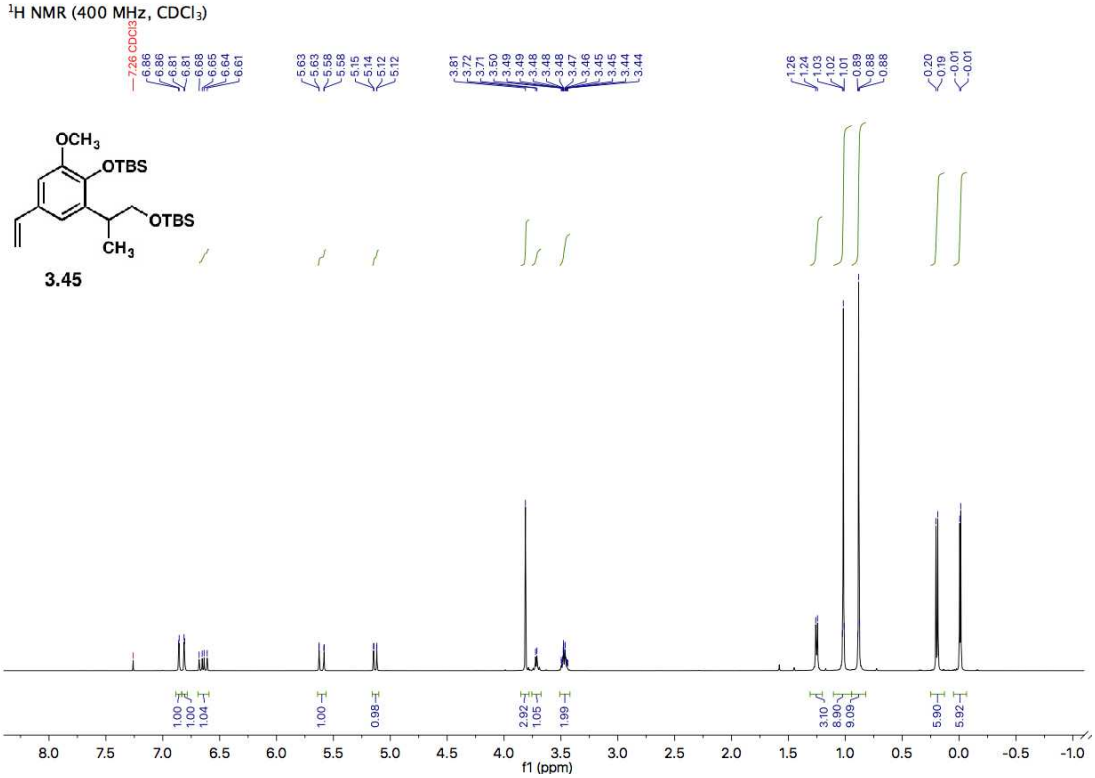
3.43

^{13}C NMR (101 MHz, $CDCl_3$)

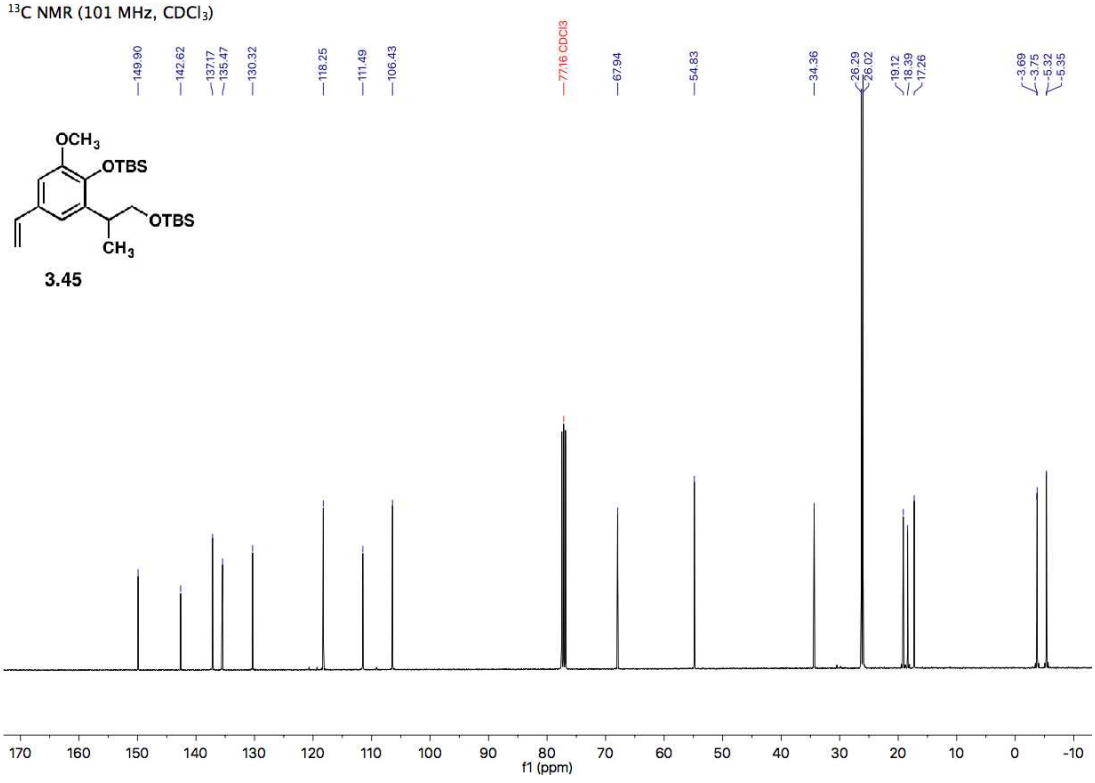


3.43

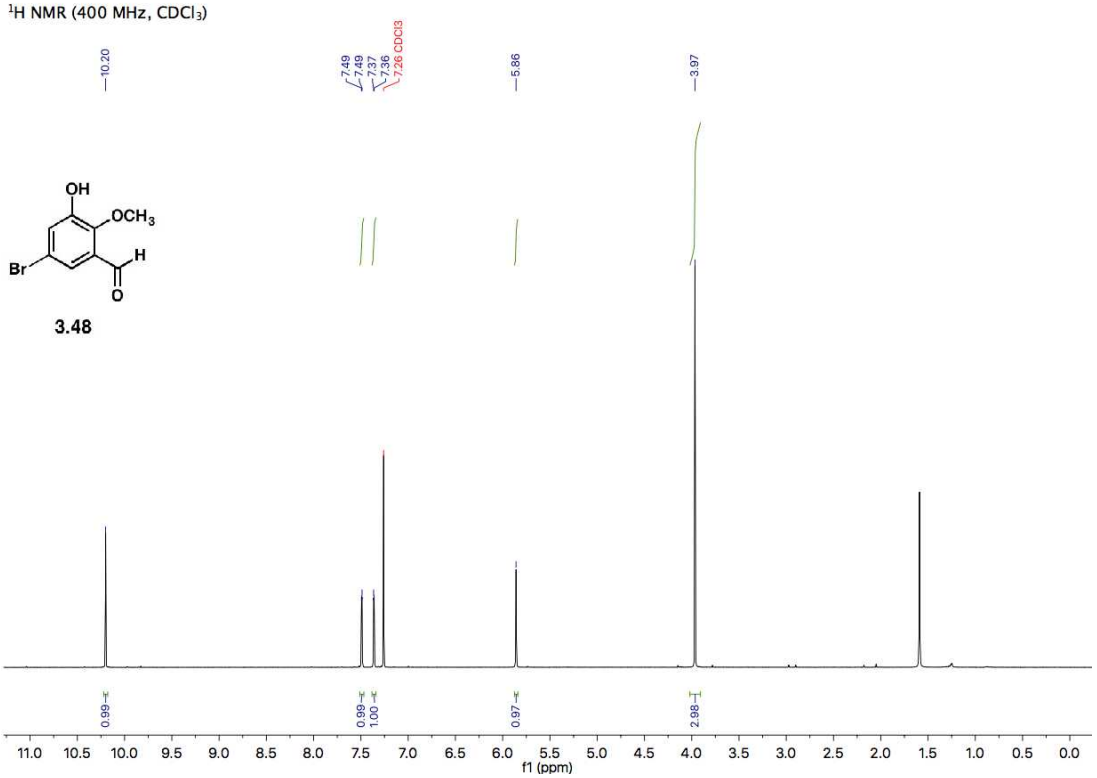
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

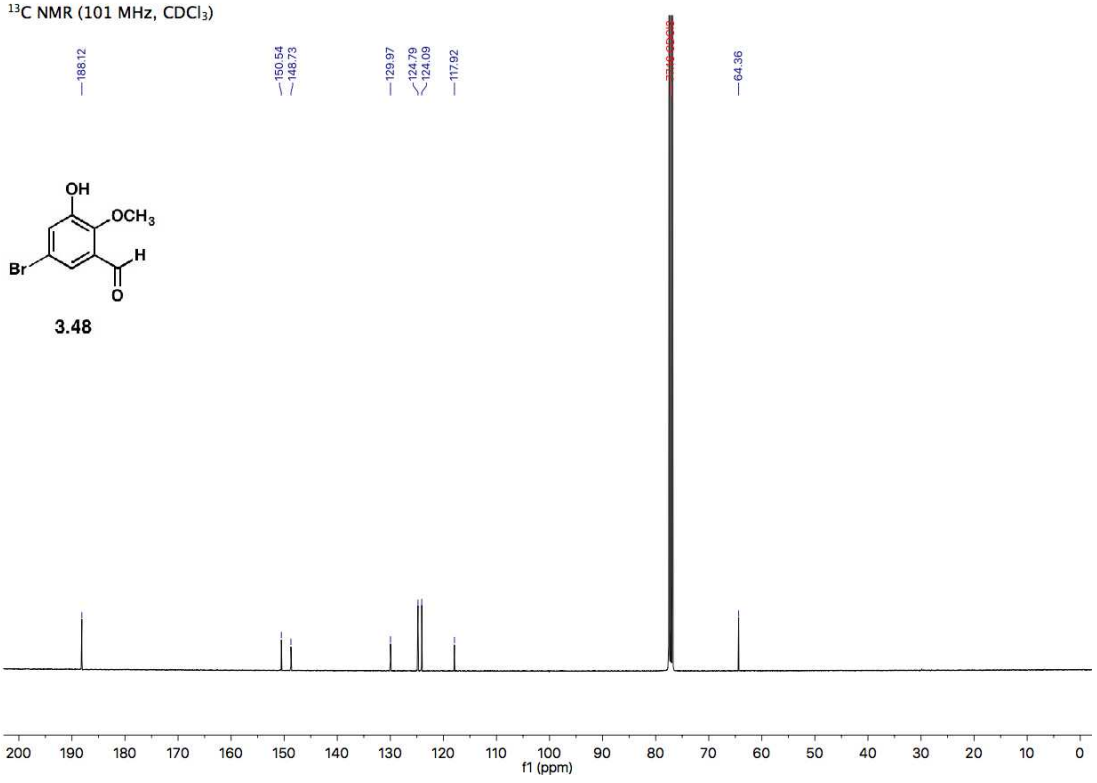


^{1}H NMR (400 MHz, $CDCl_3$)



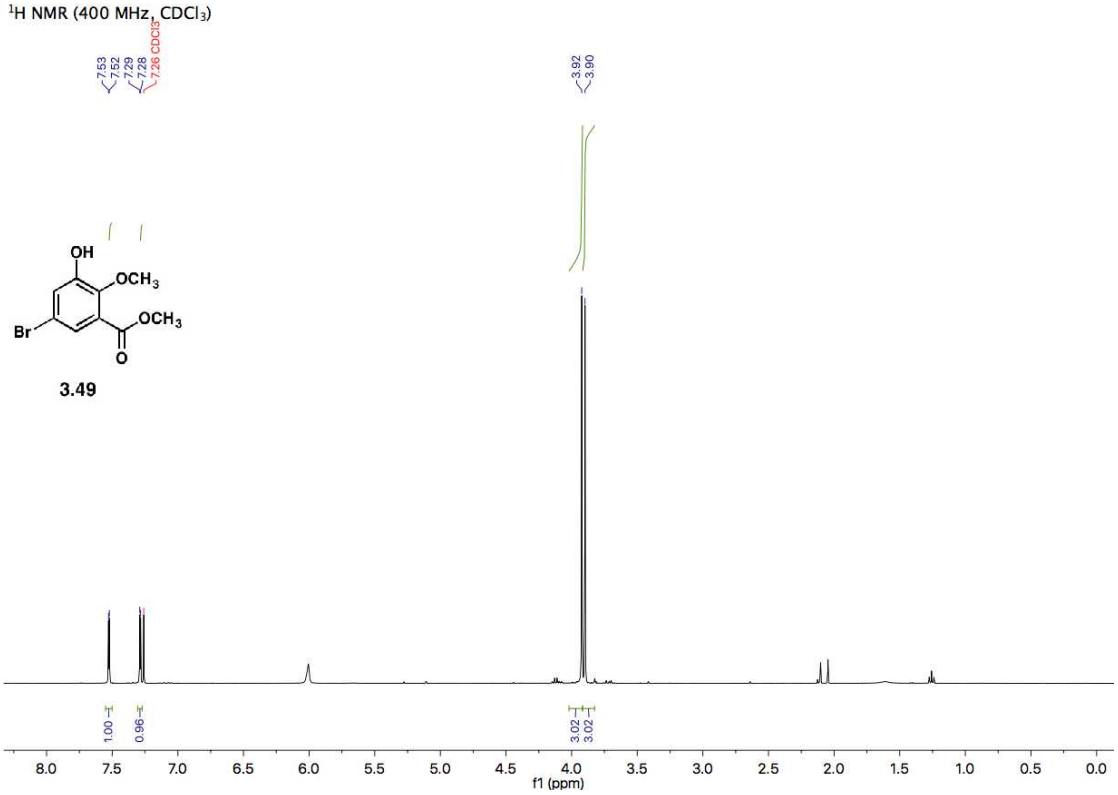
3.48

^{13}C NMR (101 MHz, $CDCl_3$)



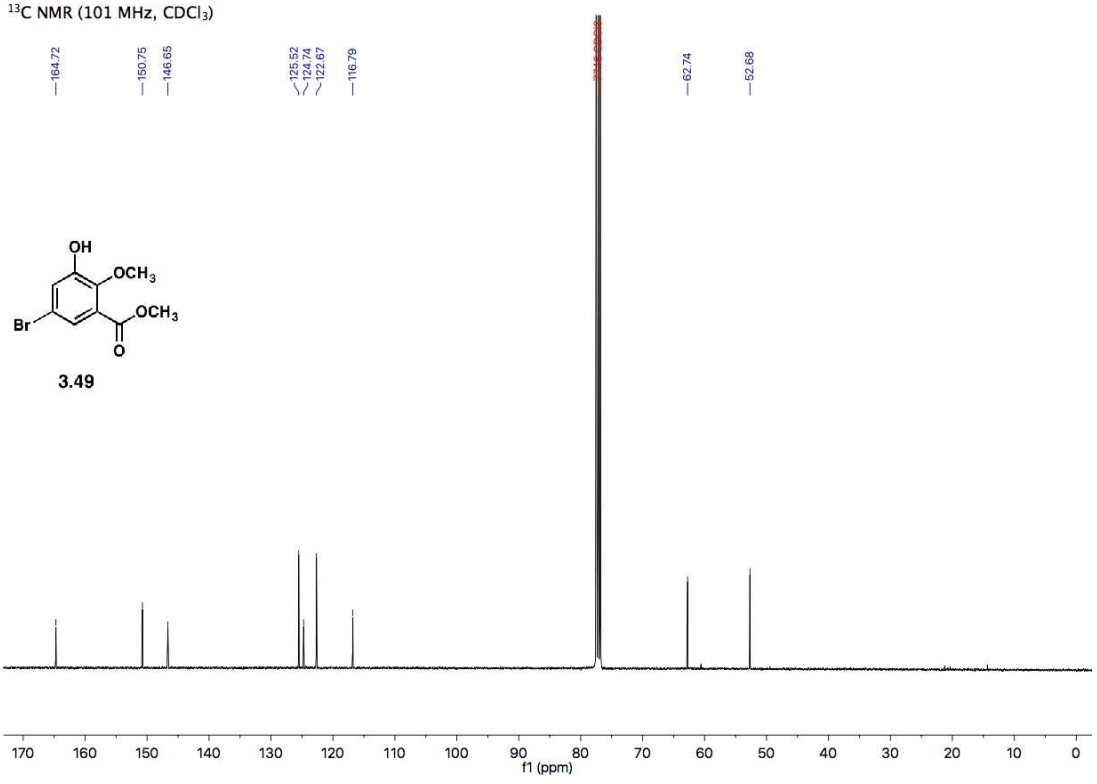
3.48

^{1}H NMR (400 MHz, $CDCl_3$)



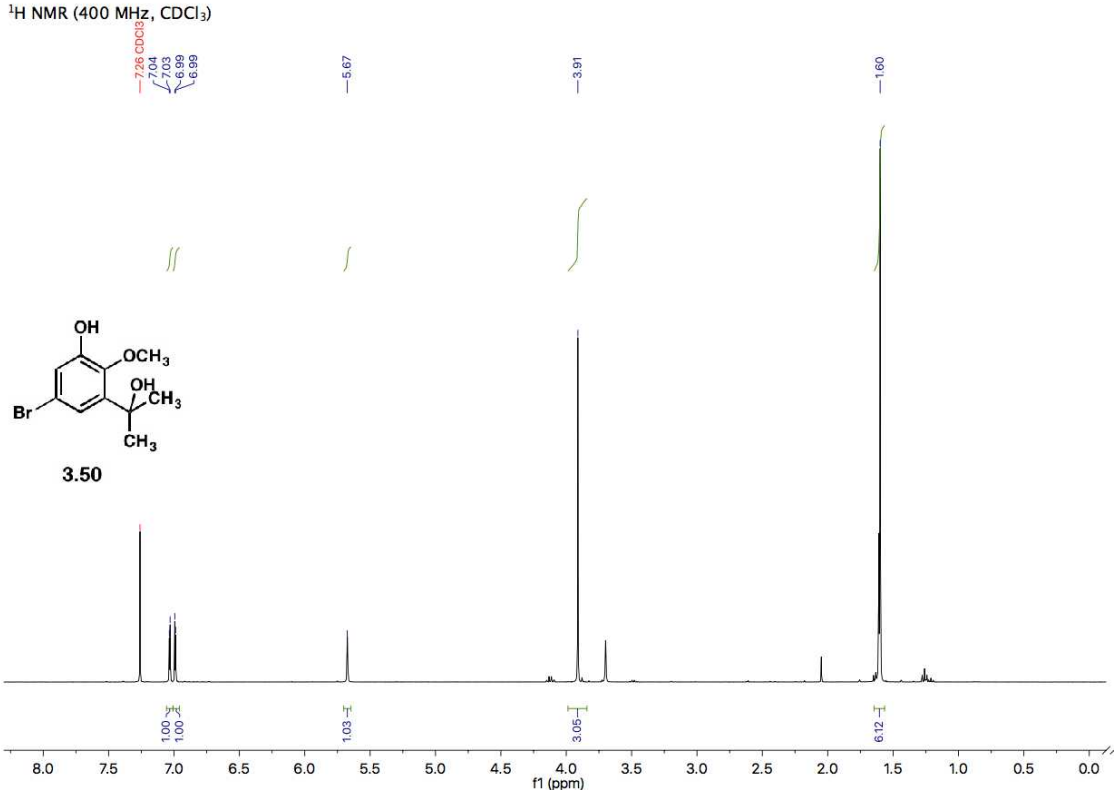
3.49

^{13}C NMR (101 MHz, $CDCl_3$)



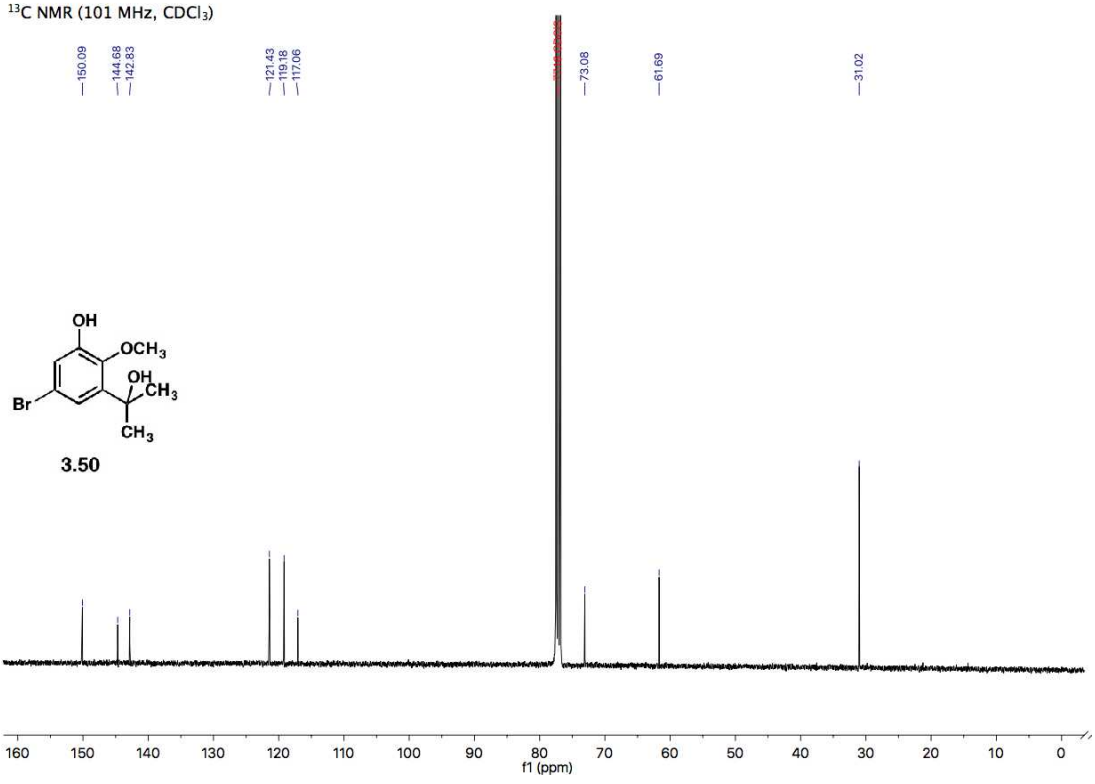
3.49

^{1}H NMR (400 MHz, $CDCl_3$)



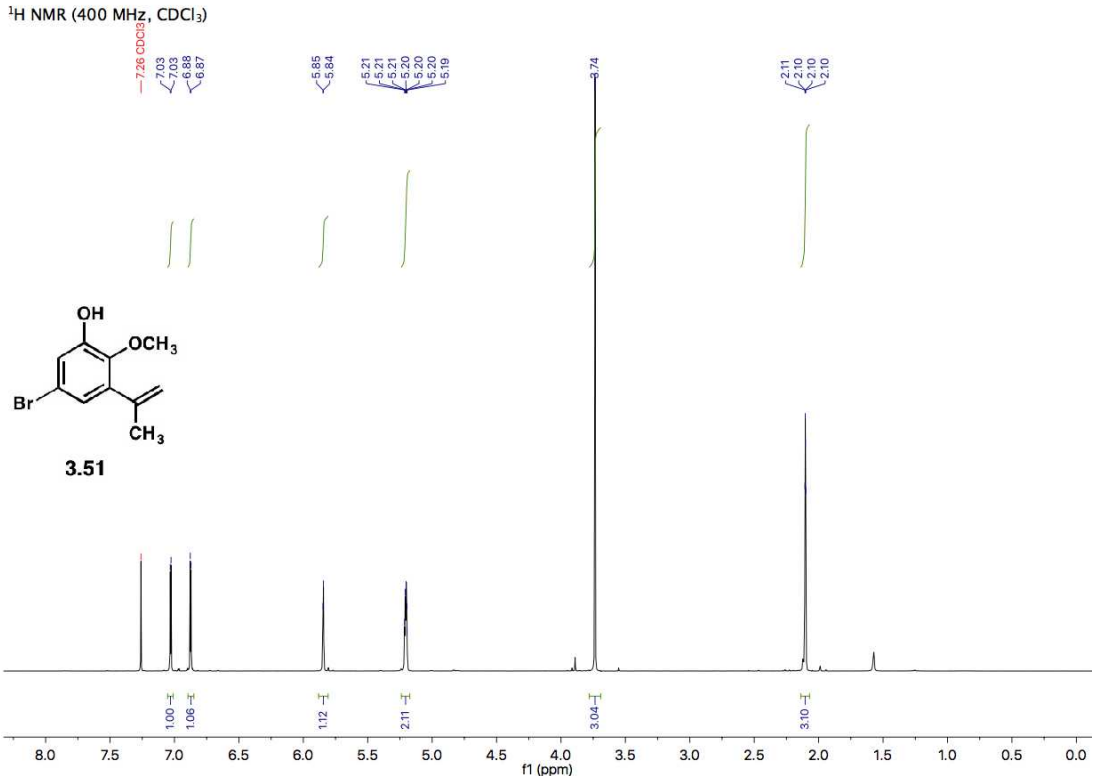
3.50

^{13}C NMR (101 MHz, $CDCl_3$)



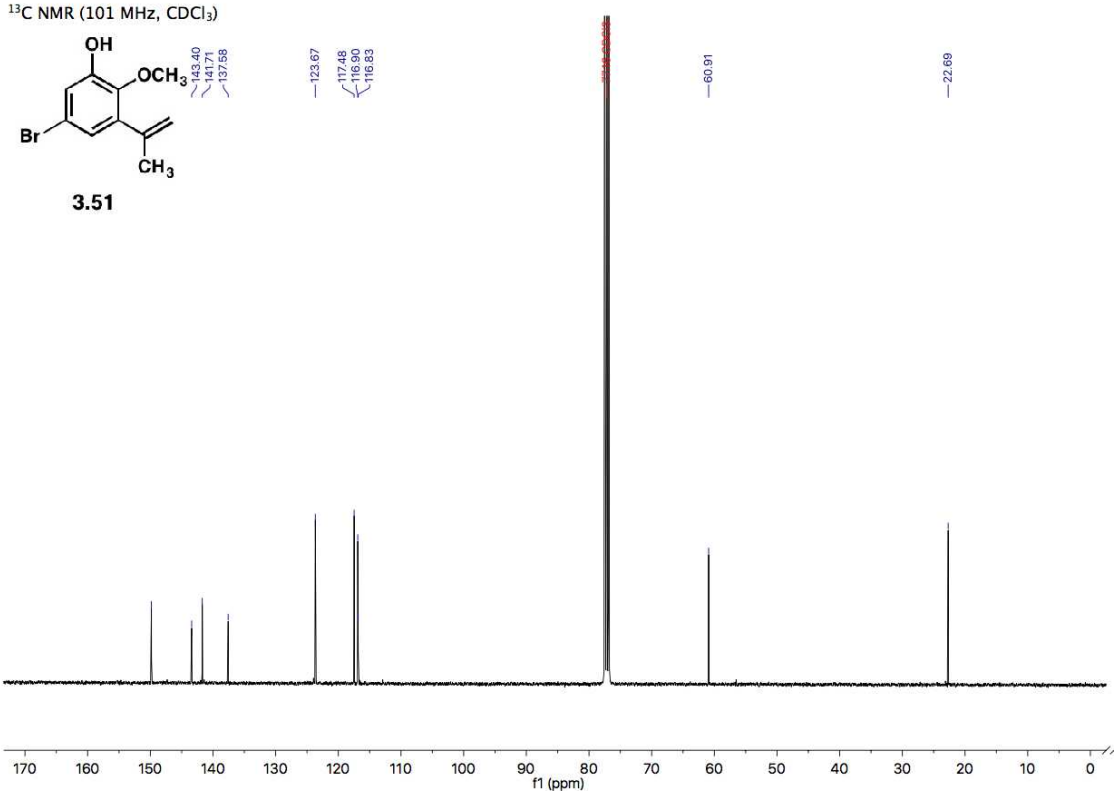
3.50

^{1}H NMR (400 MHz, $CDCl_3$)



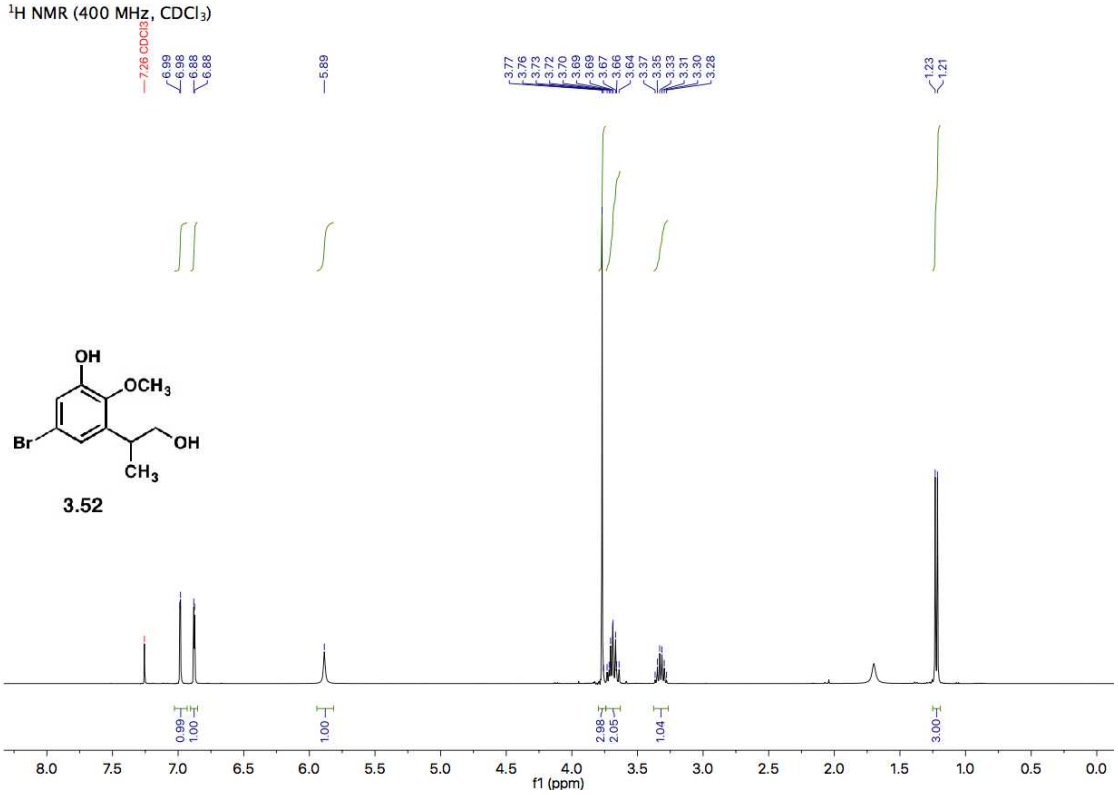
3.51

^{13}C NMR (101 MHz, $CDCl_3$)



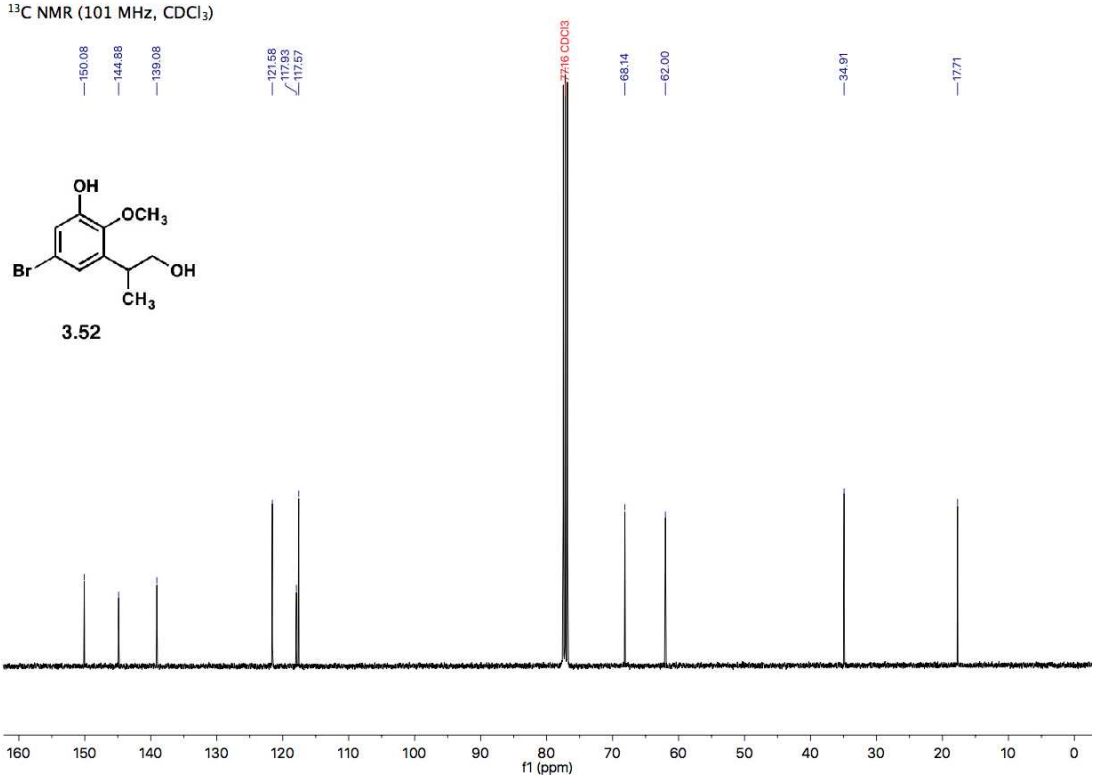
3.51

^{1}H NMR (400 MHz, $CDCl_3$)



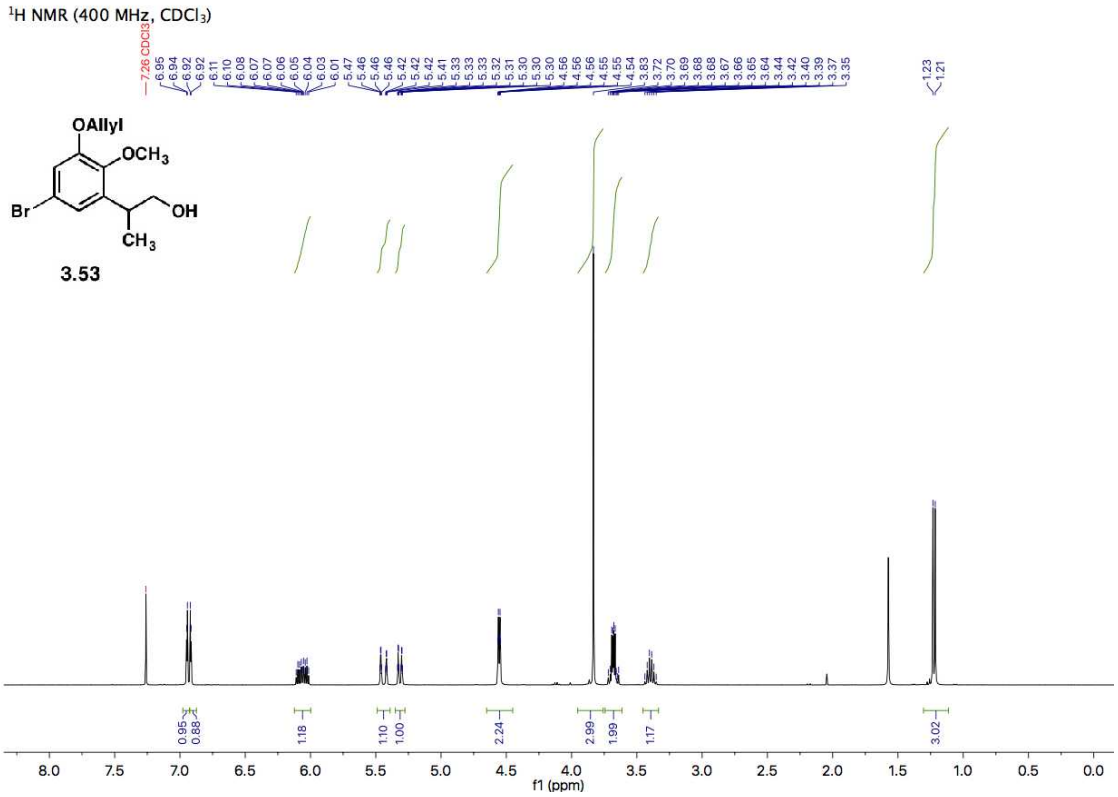
3.52

^{13}C NMR (101 MHz, $CDCl_3$)

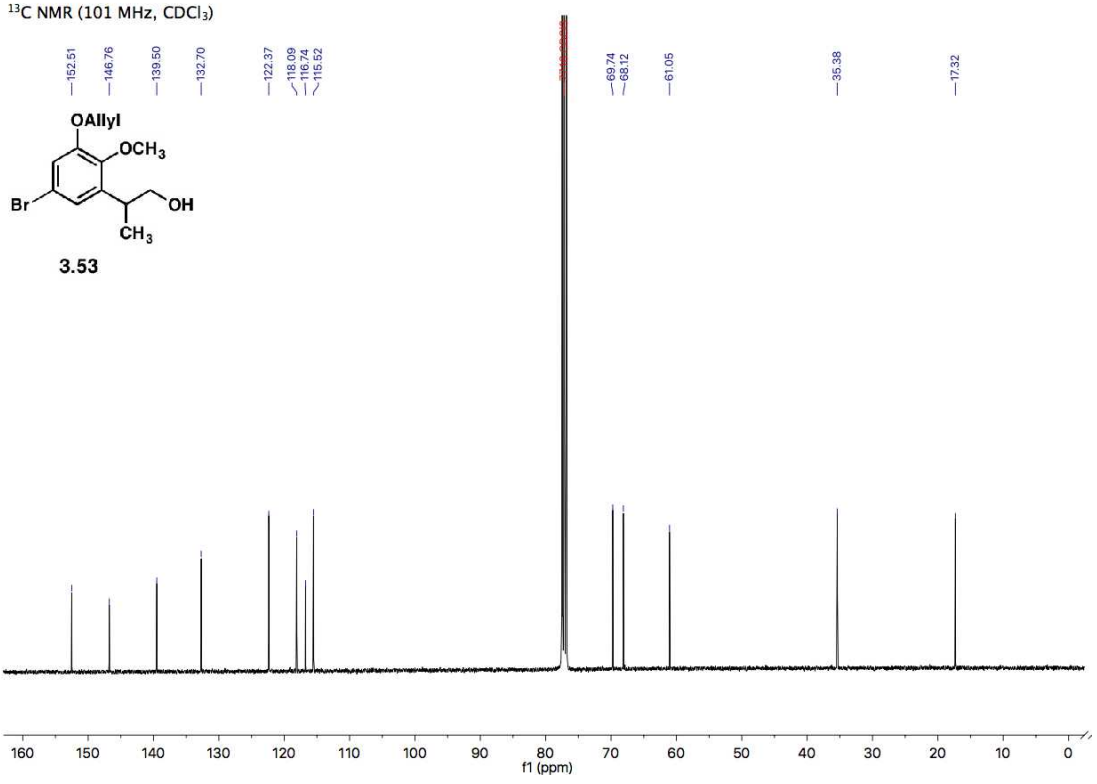


3.52

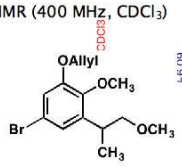
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

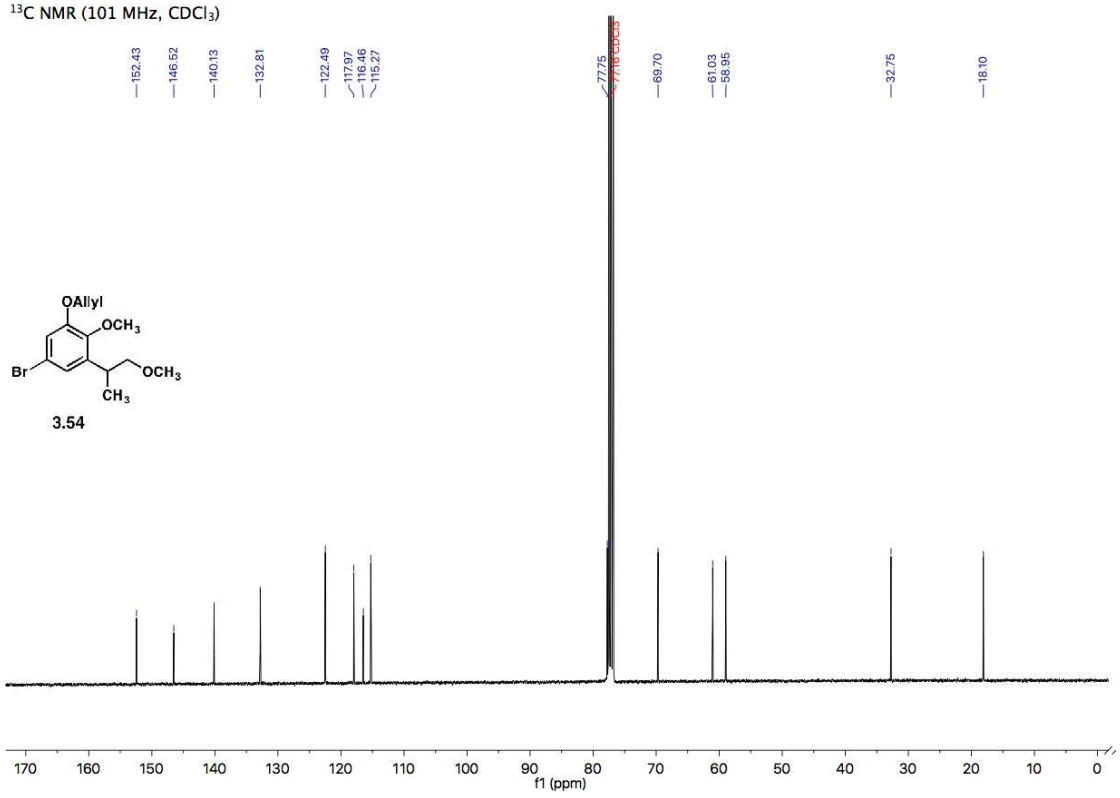


^{1}H NMR (400 MHz, $CDCl_3$)



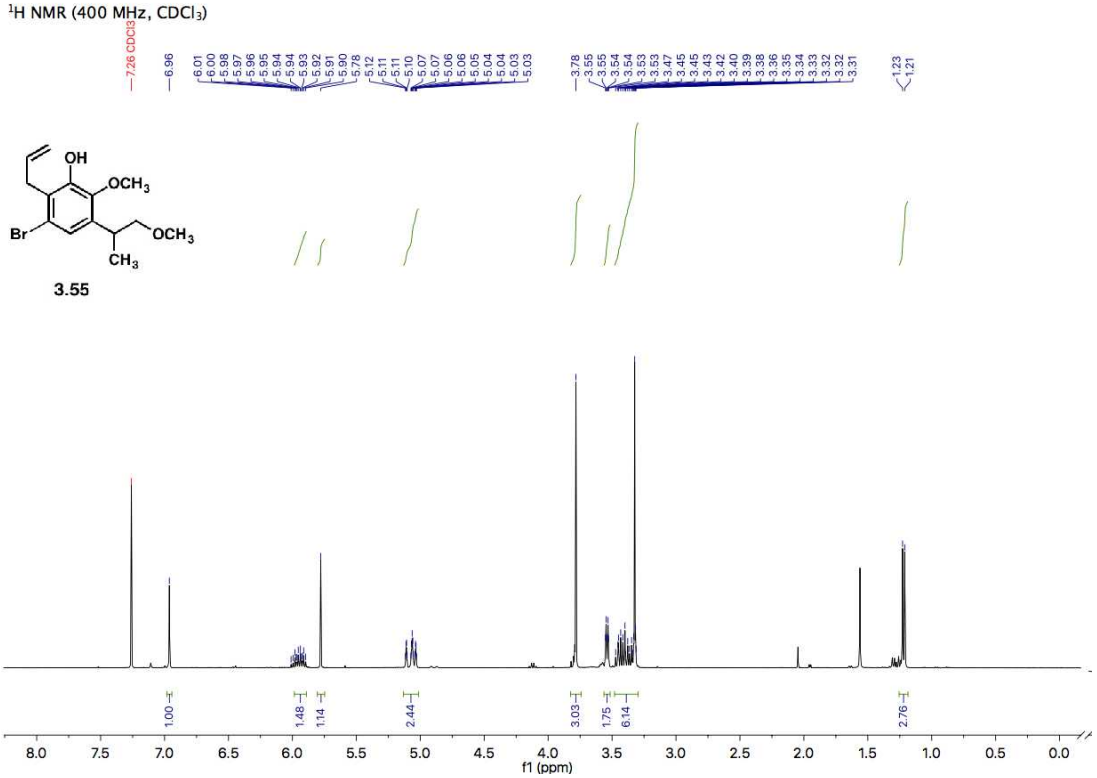
3.54

^{13}C NMR (101 MHz, $CDCl_3$)



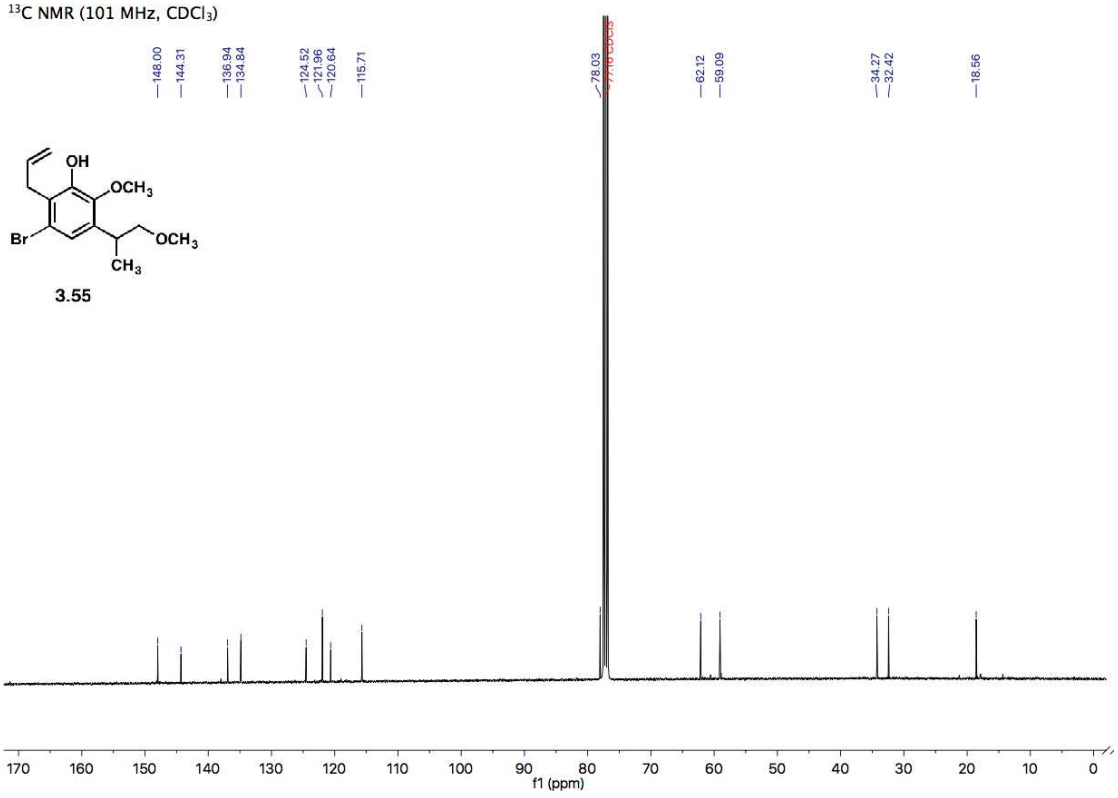
3.54

^{1}H NMR (400 MHz, $CDCl_3$)



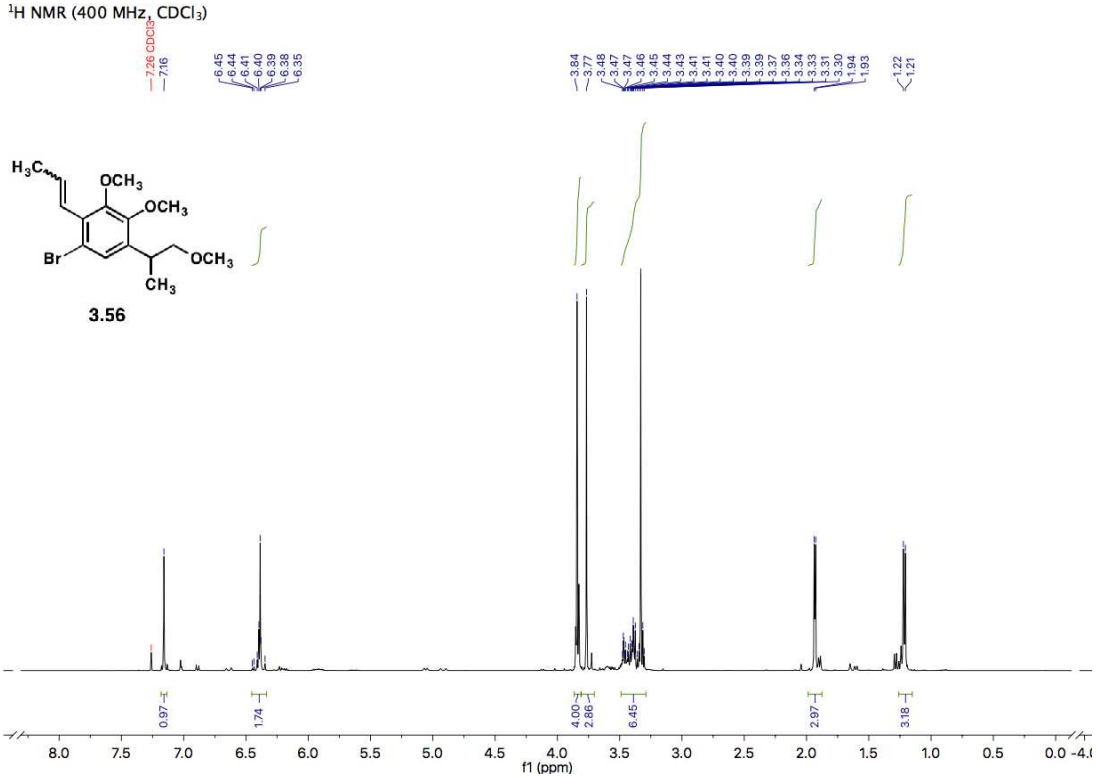
3.55

^{13}C NMR (101 MHz, $CDCl_3$)



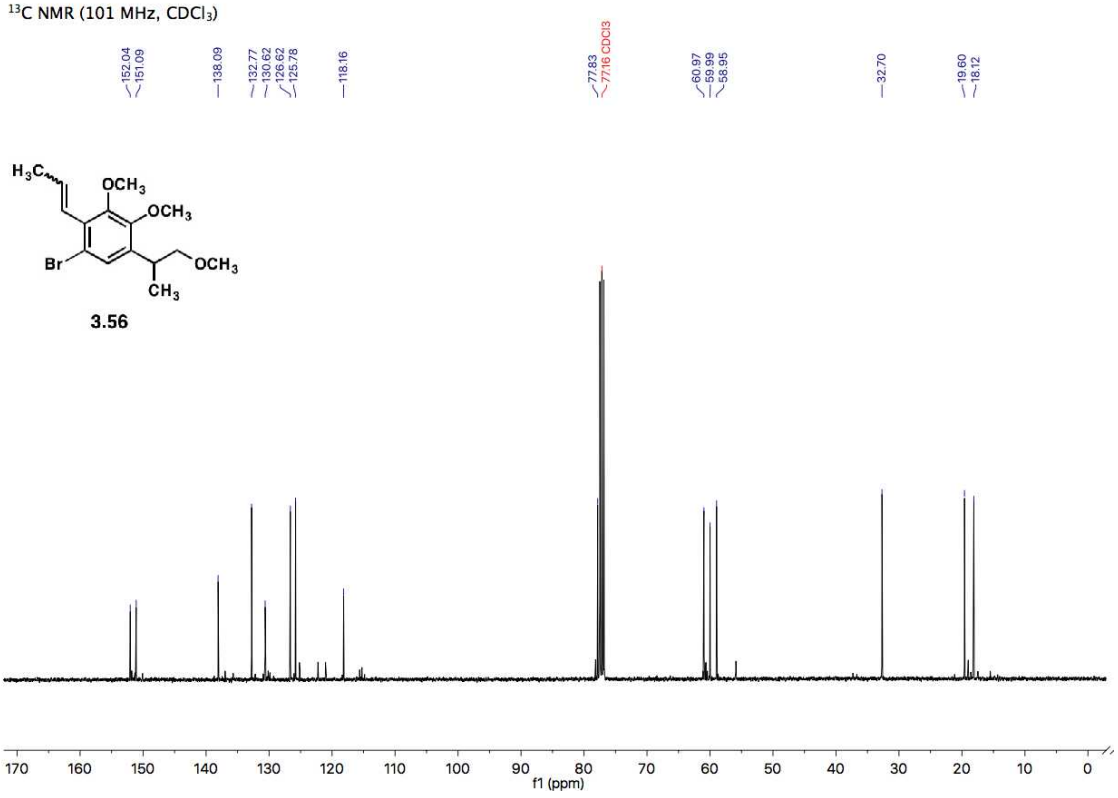
3.55

^{1}H NMR (400 MHz, $CDCl_3$)



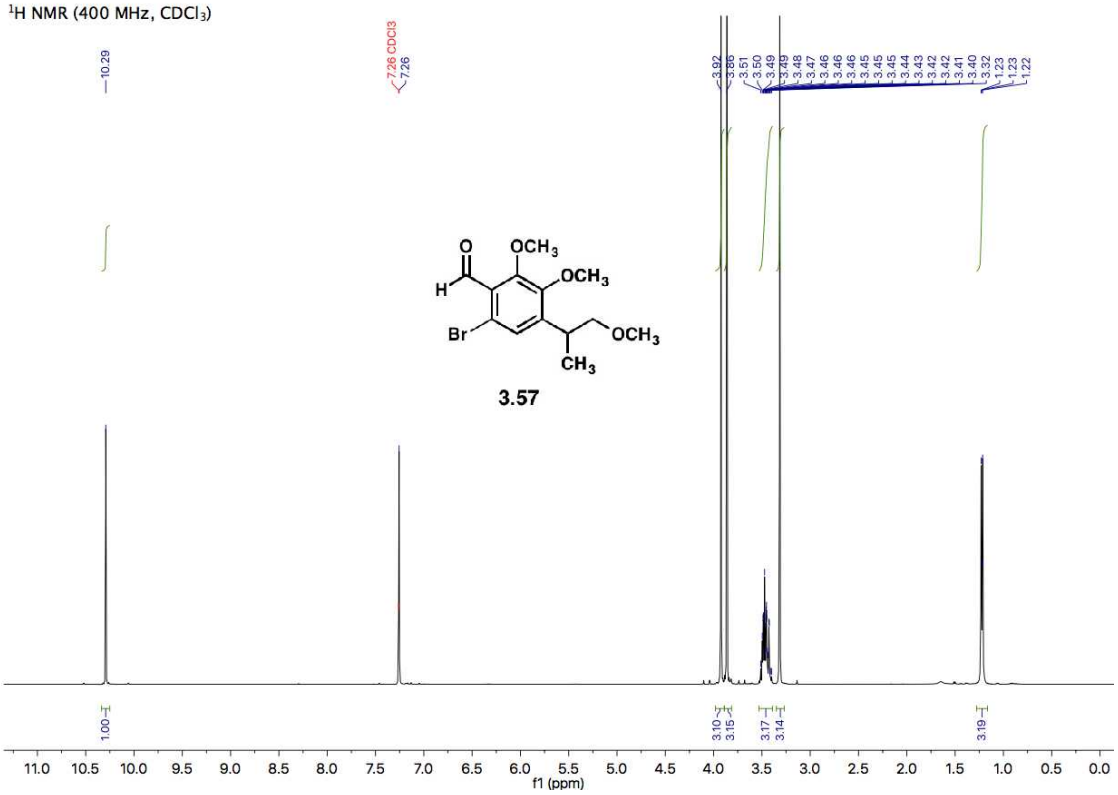
3.56

^{13}C NMR (101 MHz, $CDCl_3$)



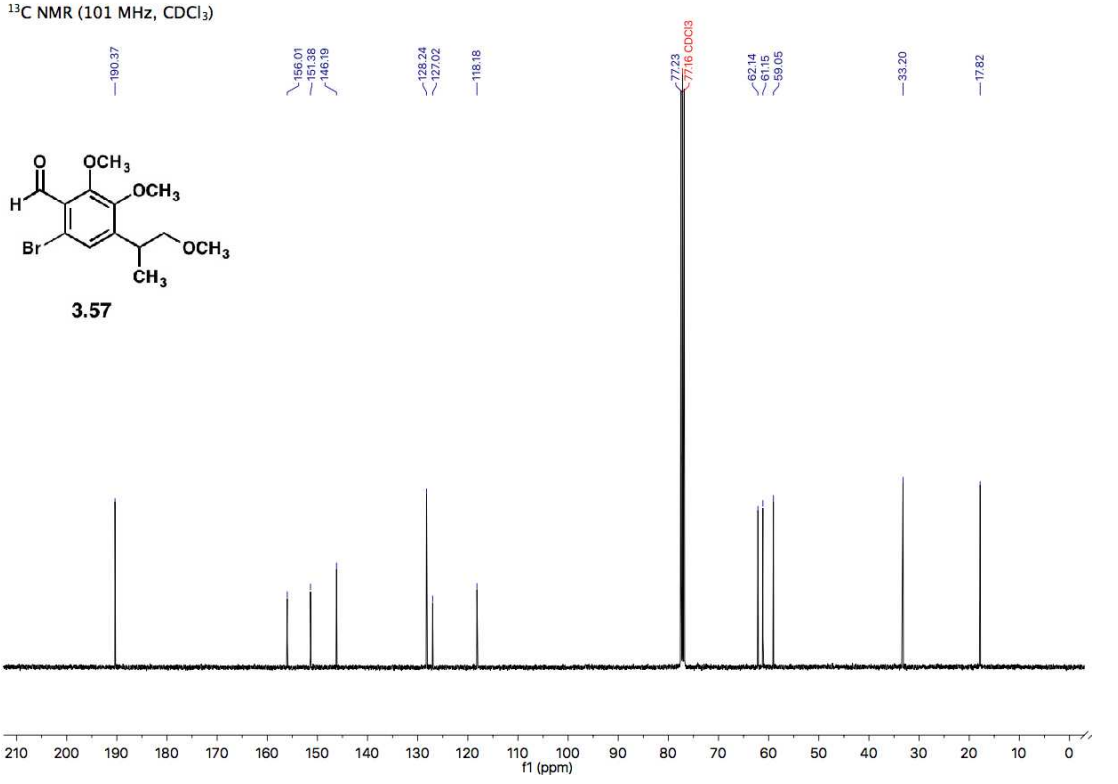
3.56

^{1}H NMR (400 MHz, $CDCl_3$)



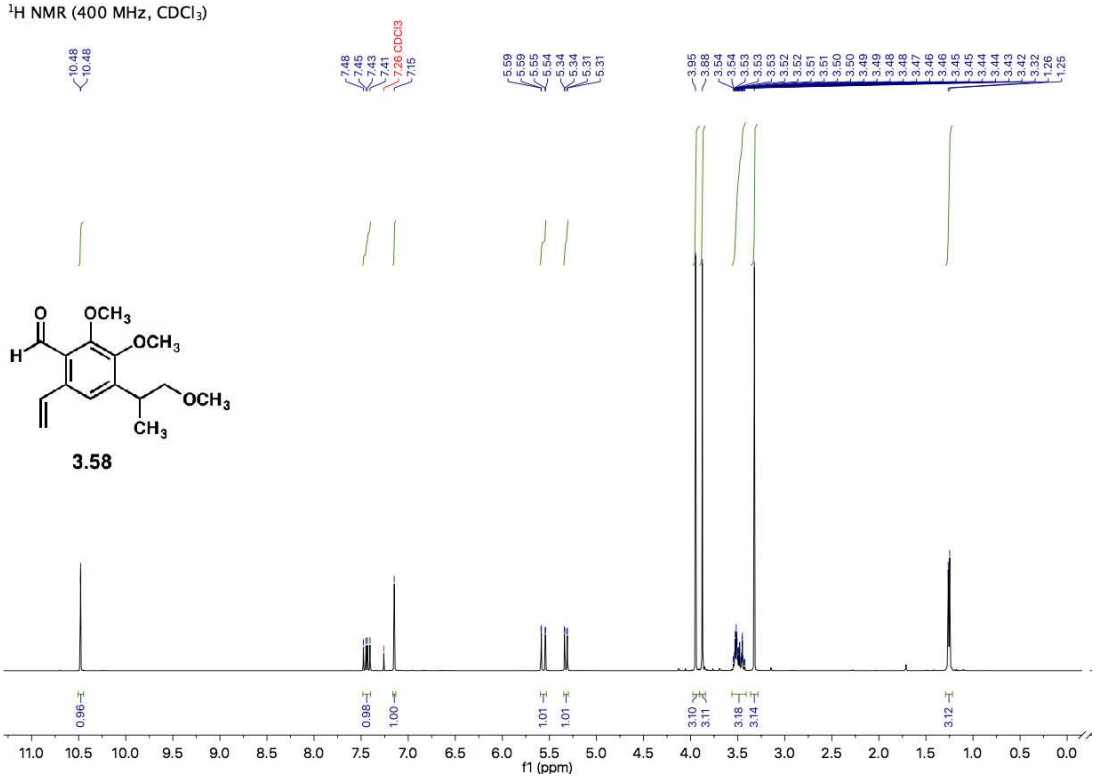
3.57

^{13}C NMR (101 MHz, $CDCl_3$)



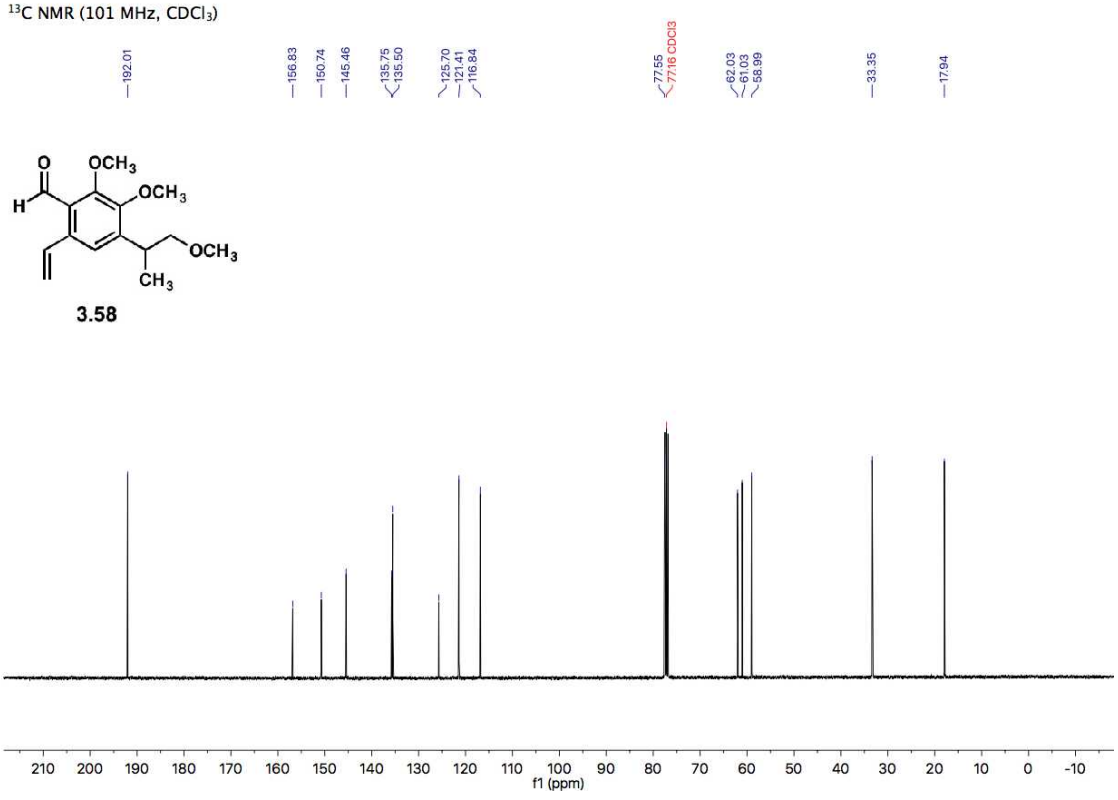
3.57

^{1}H NMR (400 MHz, $CDCl_3$)



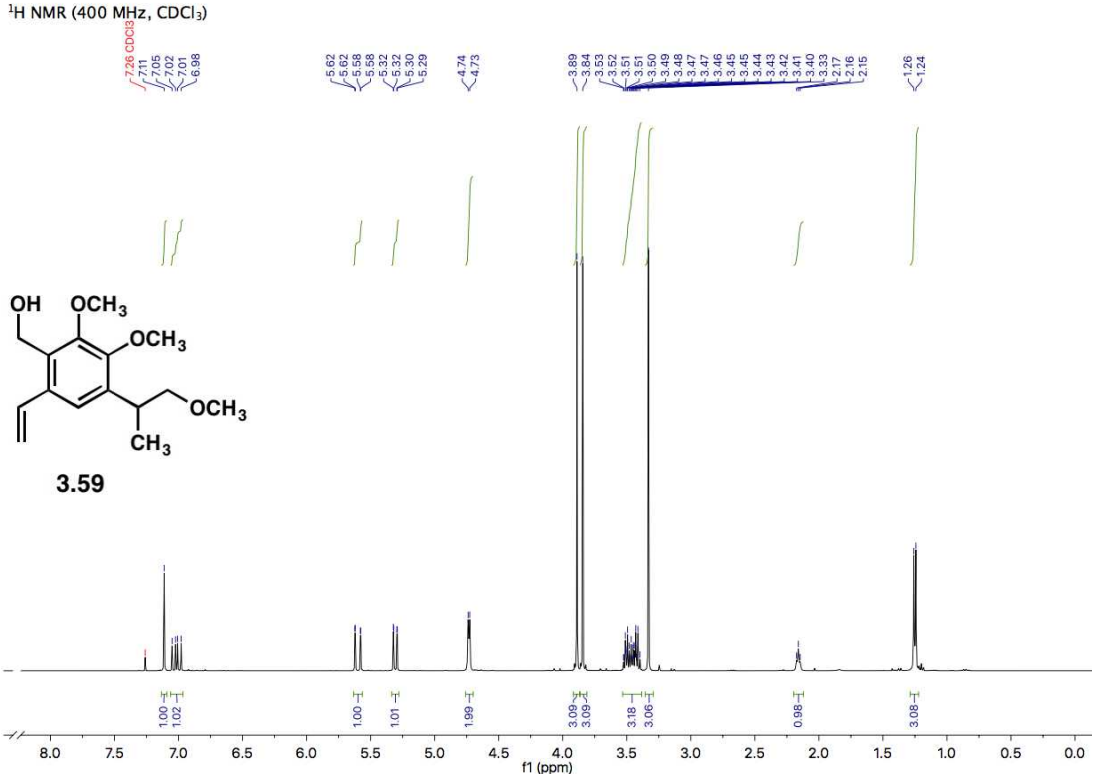
3.58

^{13}C NMR (101 MHz, $CDCl_3$)



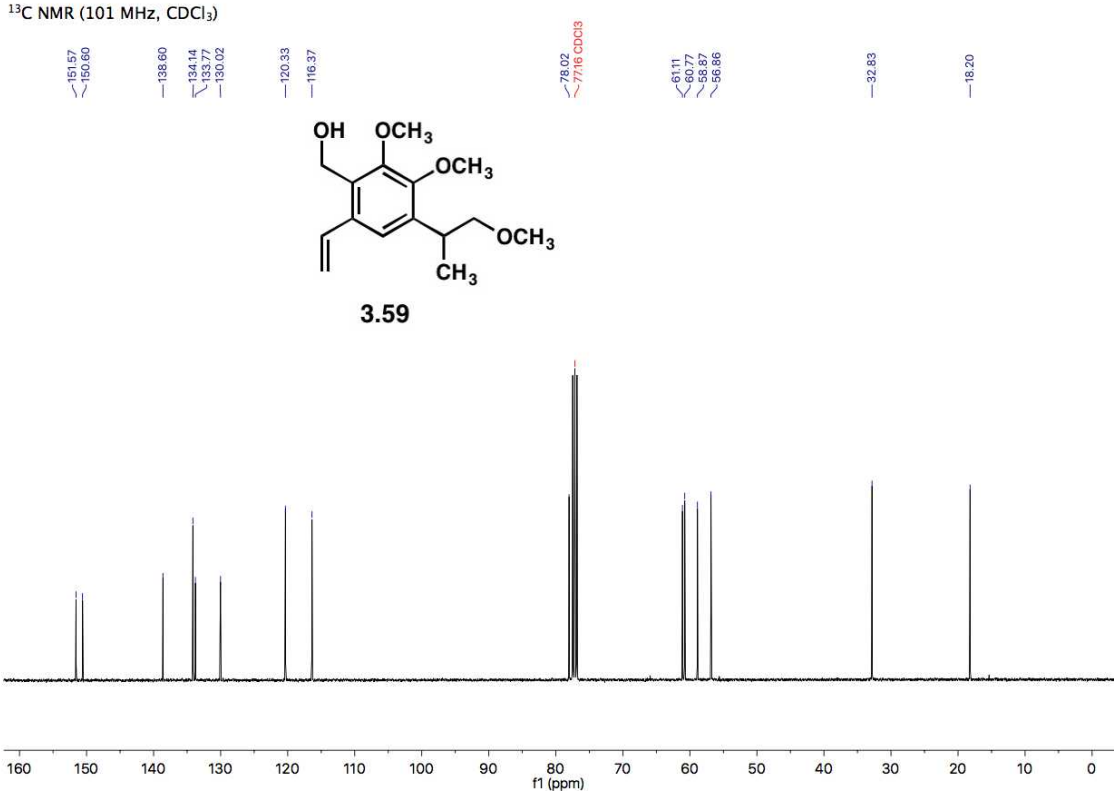
3.58

^{1}H NMR (400 MHz, $CDCl_3$)



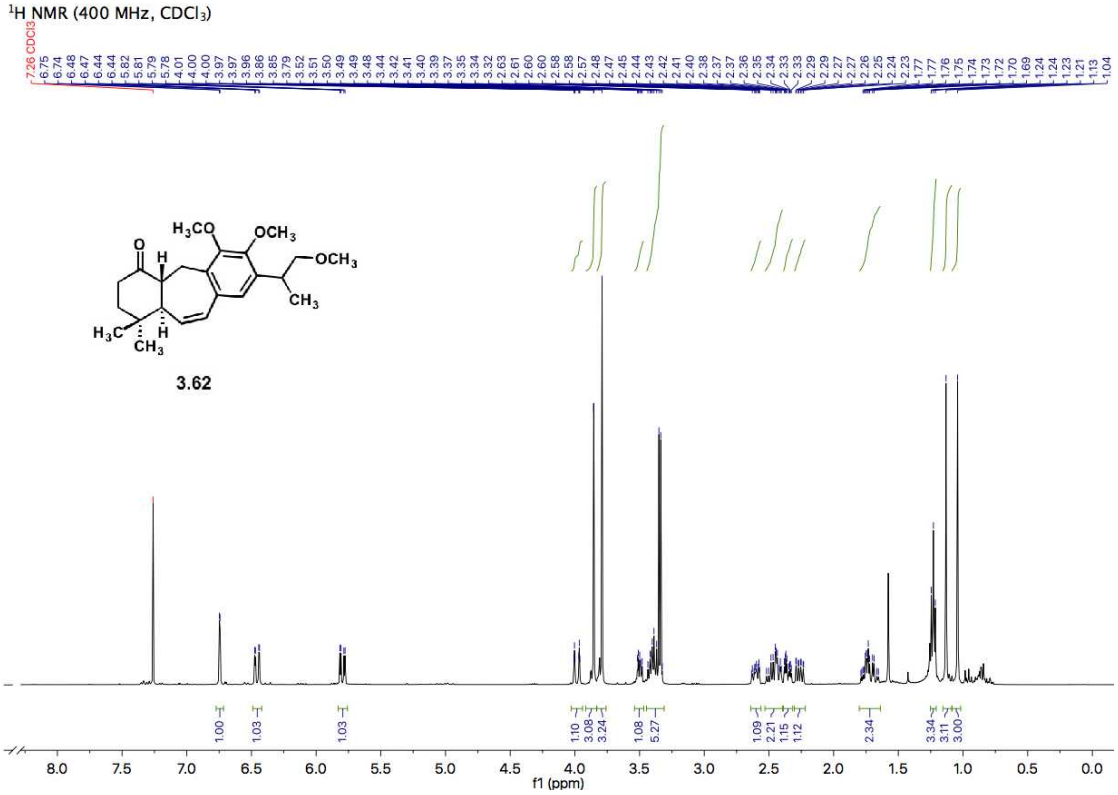
3.59

^{13}C NMR (101 MHz, $CDCl_3$)

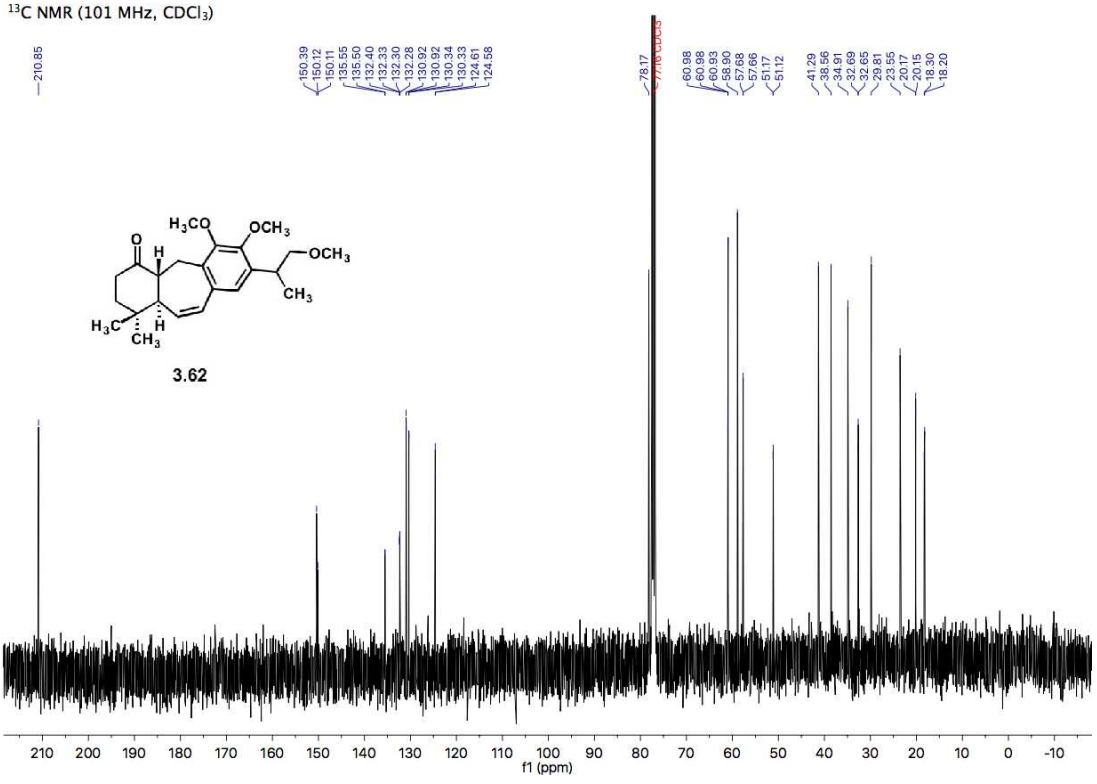


3.59

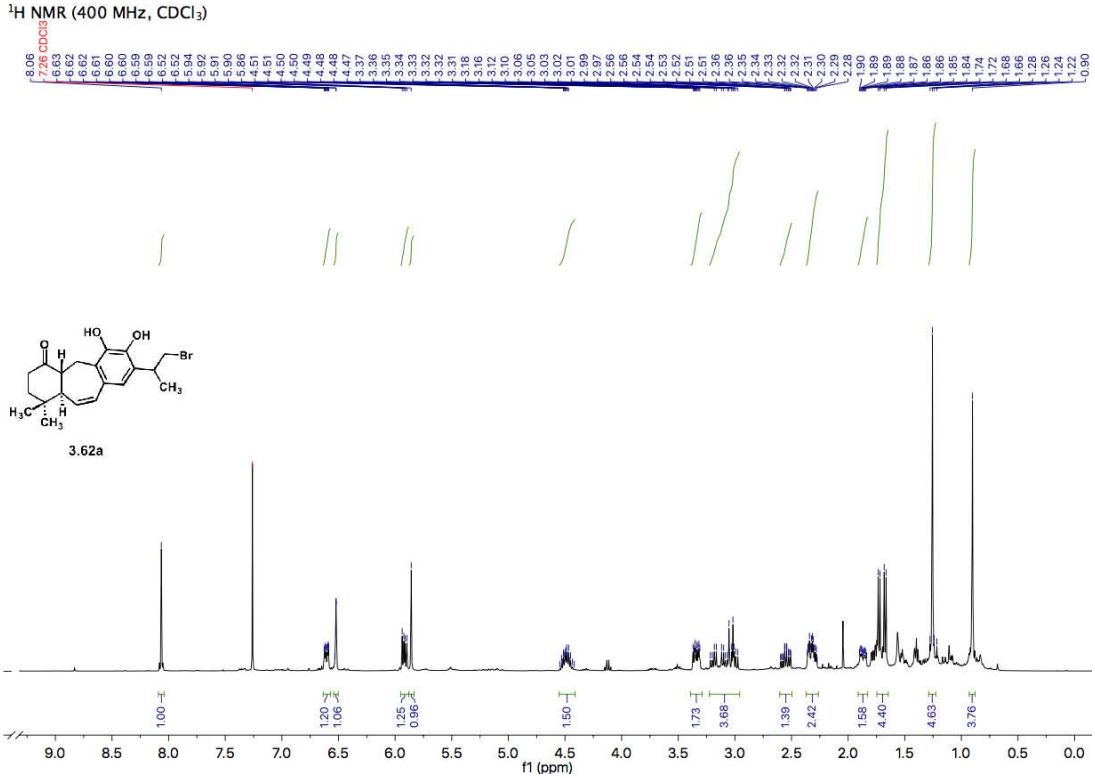
^{1}H NMR (400 MHz, $CDCl_3$)



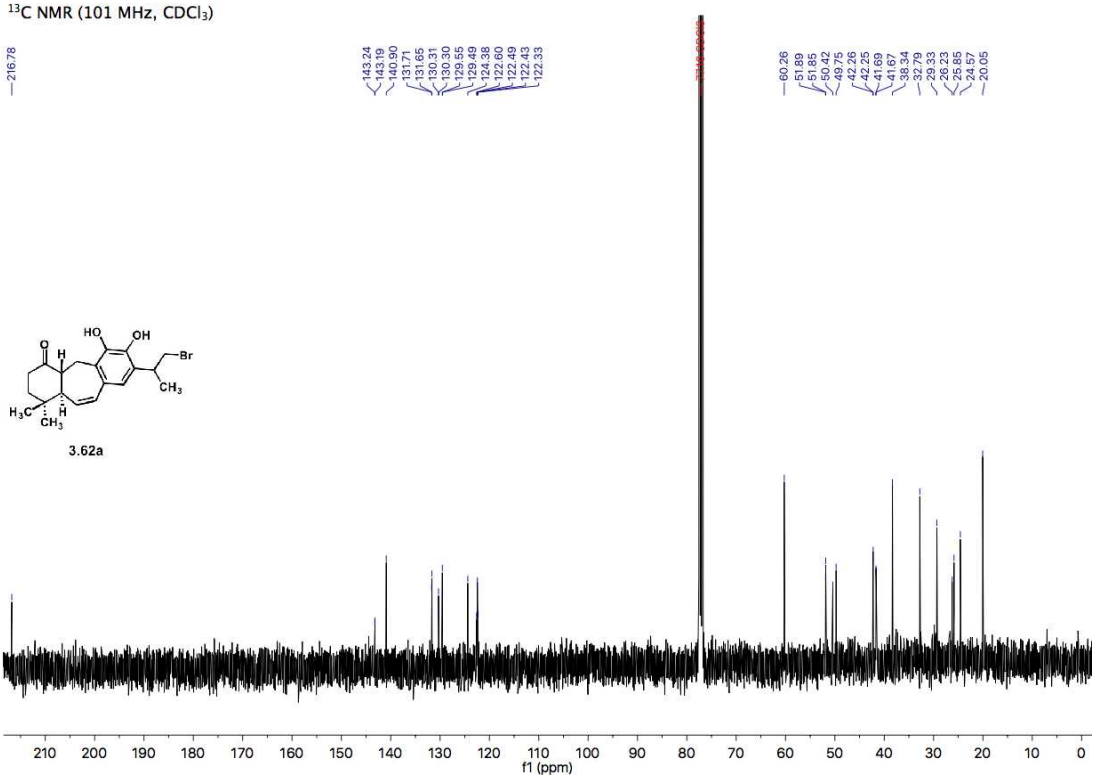
^{13}C NMR (101 MHz, $CDCl_3$)



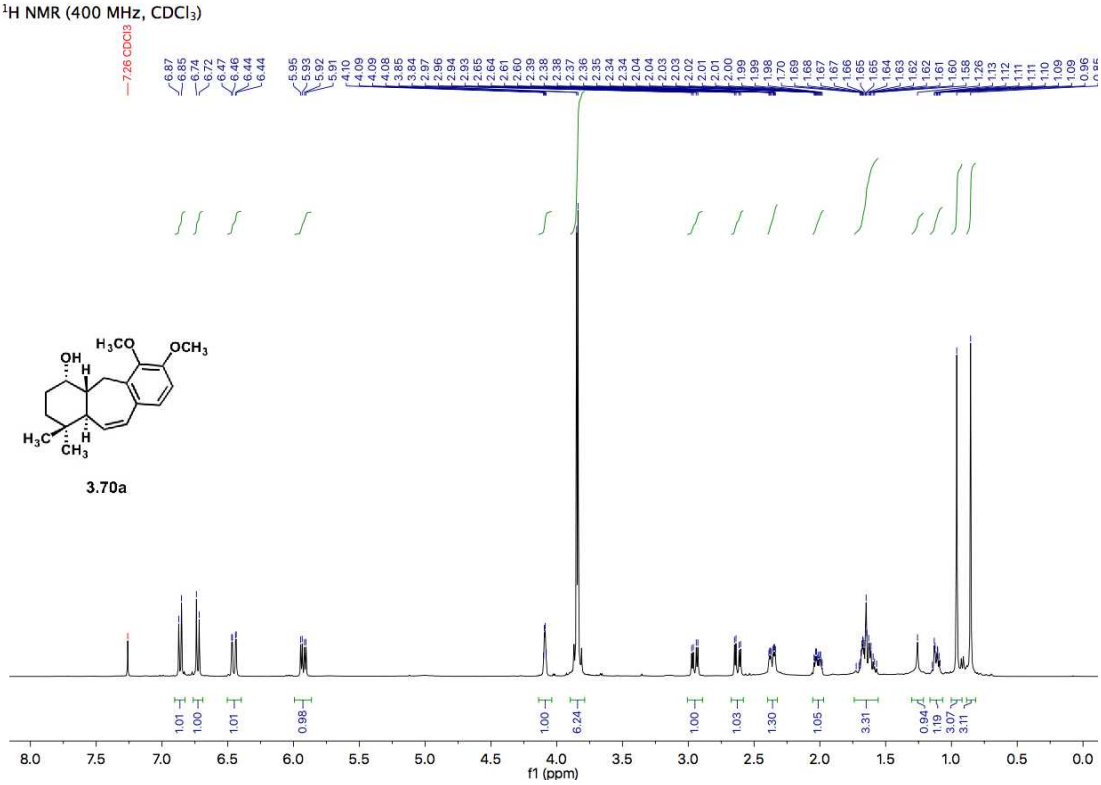
^{1}H NMR (400 MHz, $CDCl_3$)



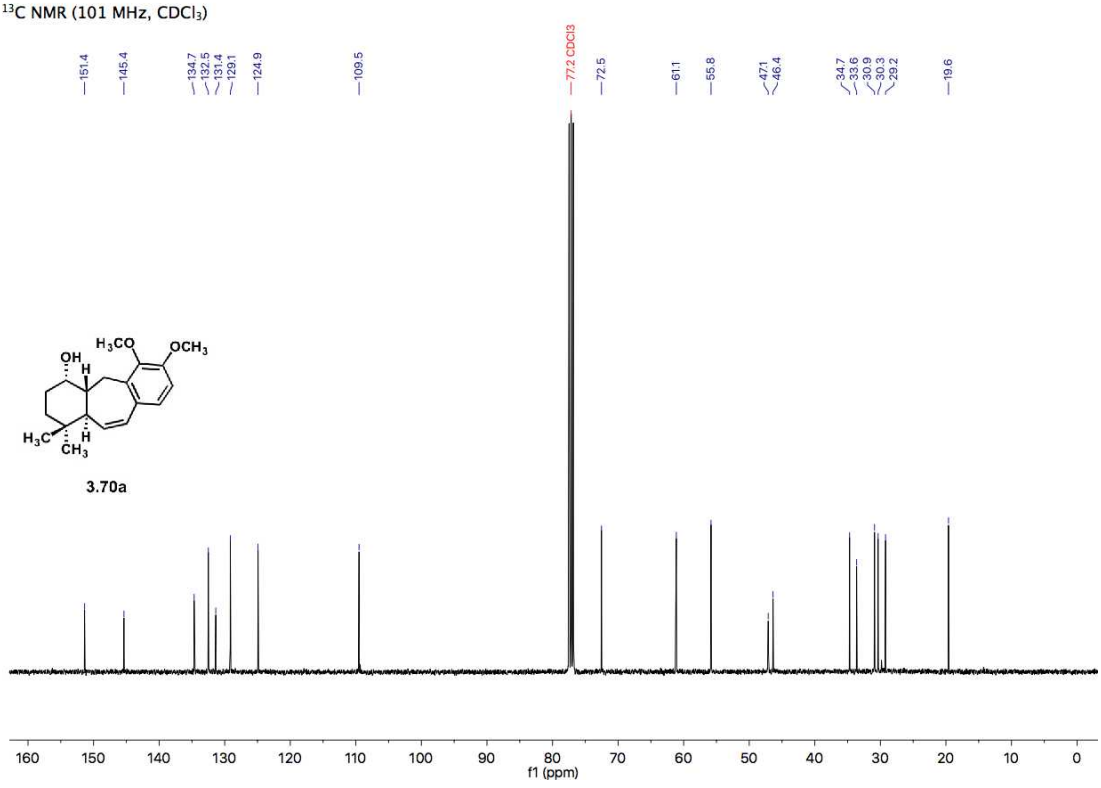
^{13}C NMR (101 MHz, $CDCl_3$)



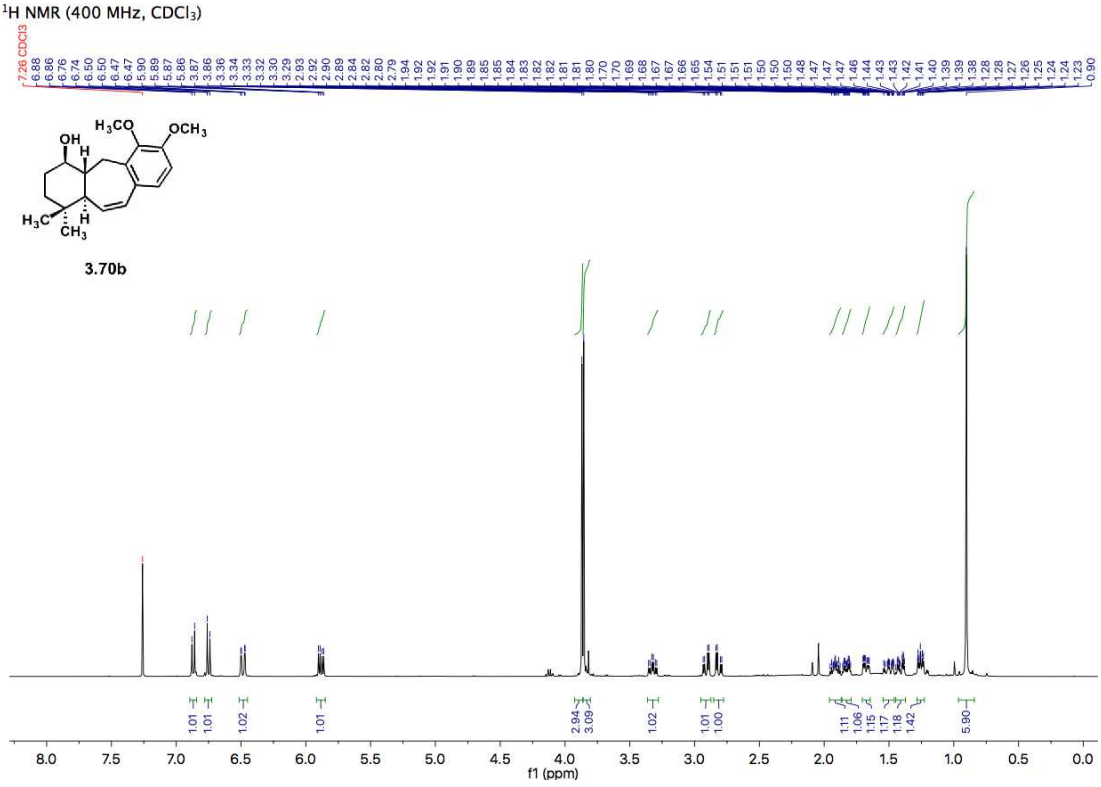
^{1}H NMR (400 MHz, $CDCl_3$)



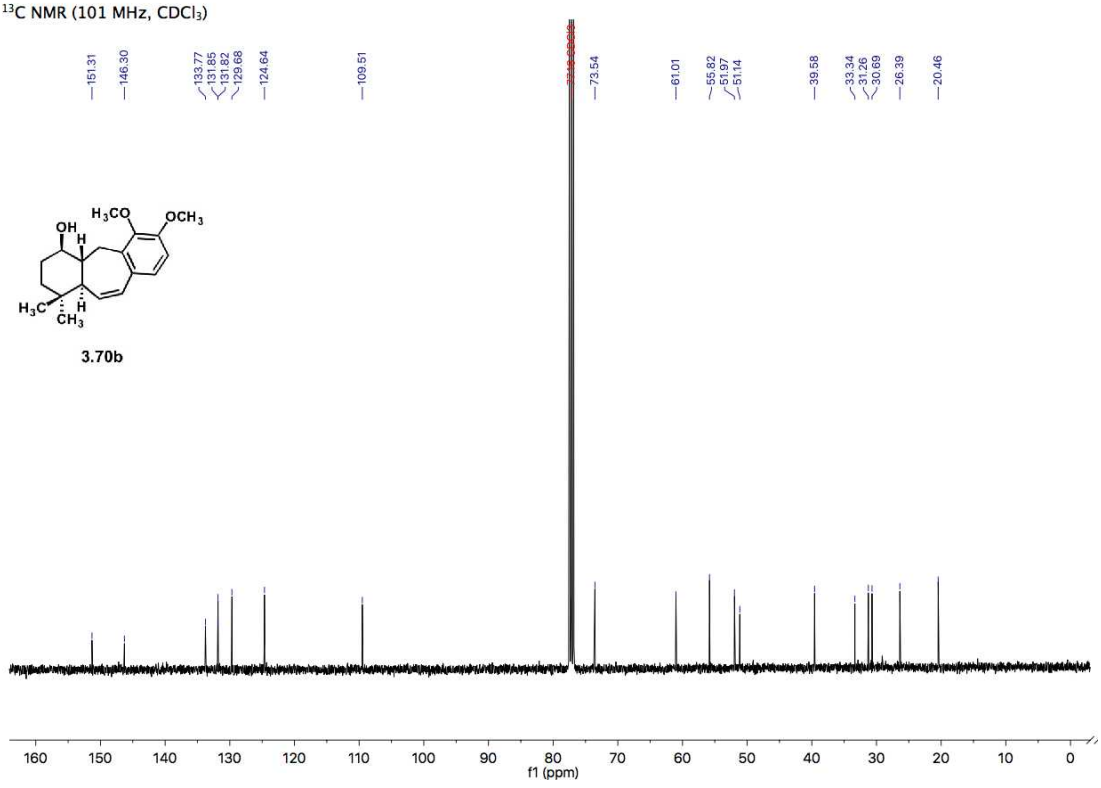
^{13}C NMR (101 MHz, $CDCl_3$)



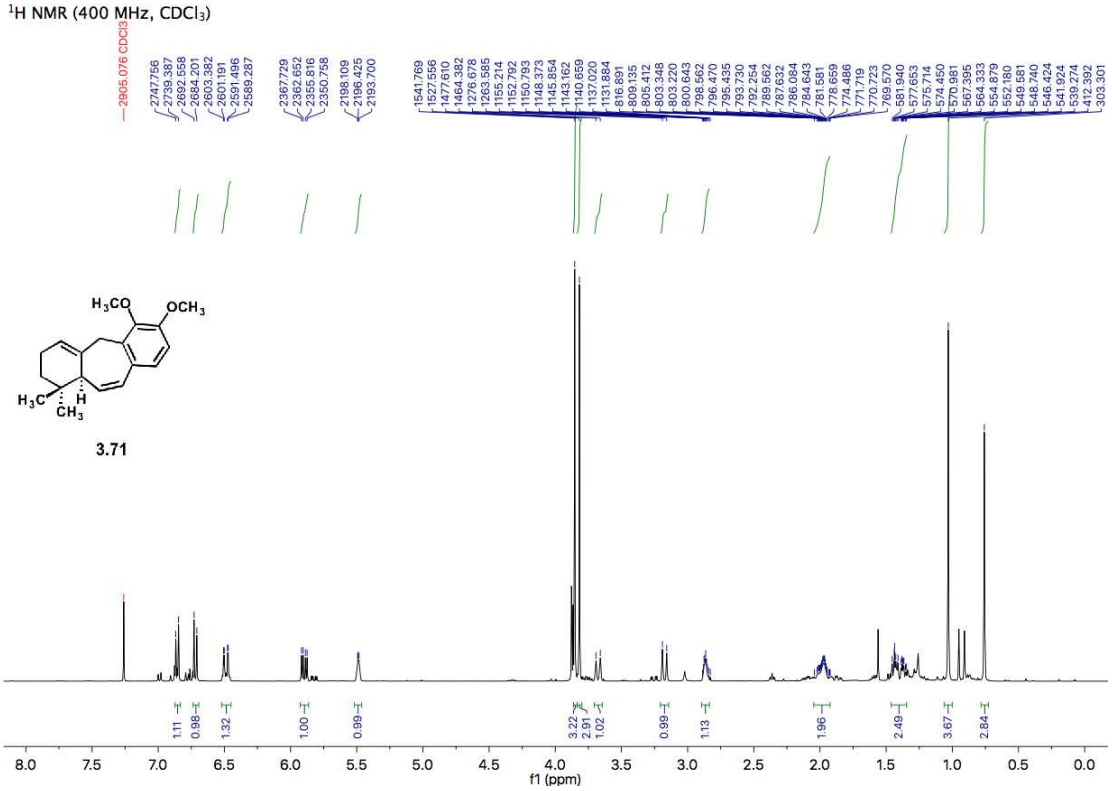
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

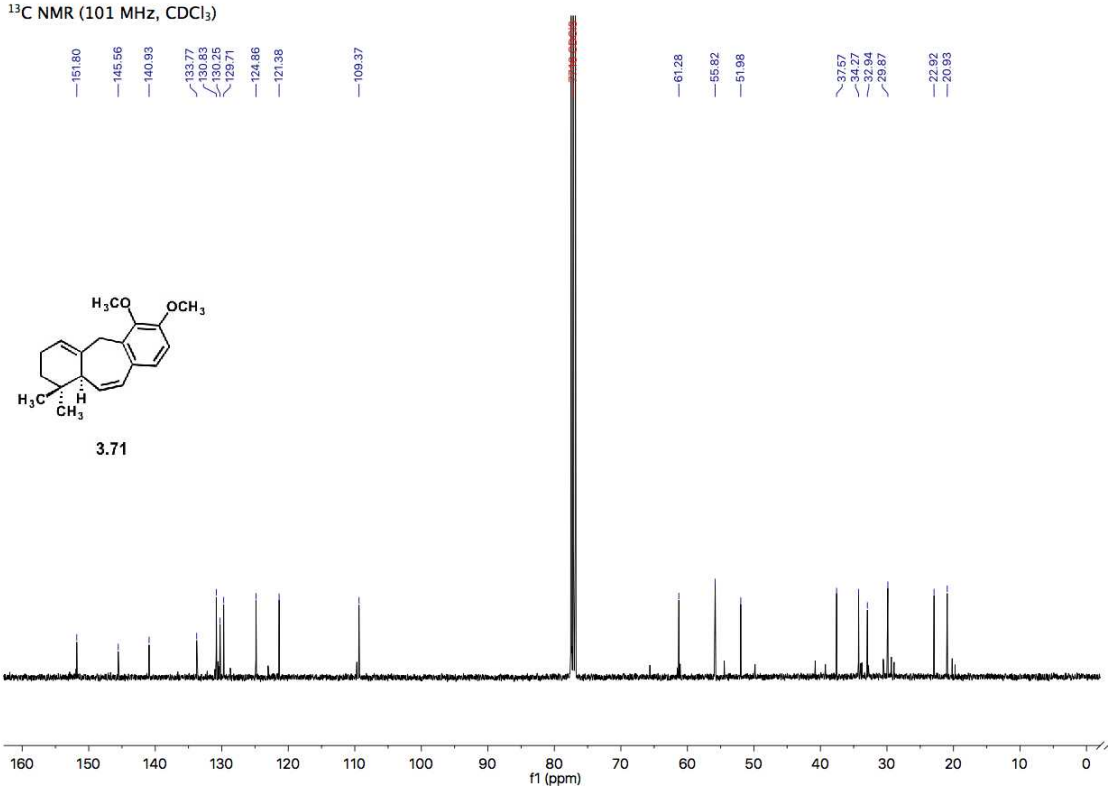


^{1}H NMR (400 MHz, $CDCl_3$)



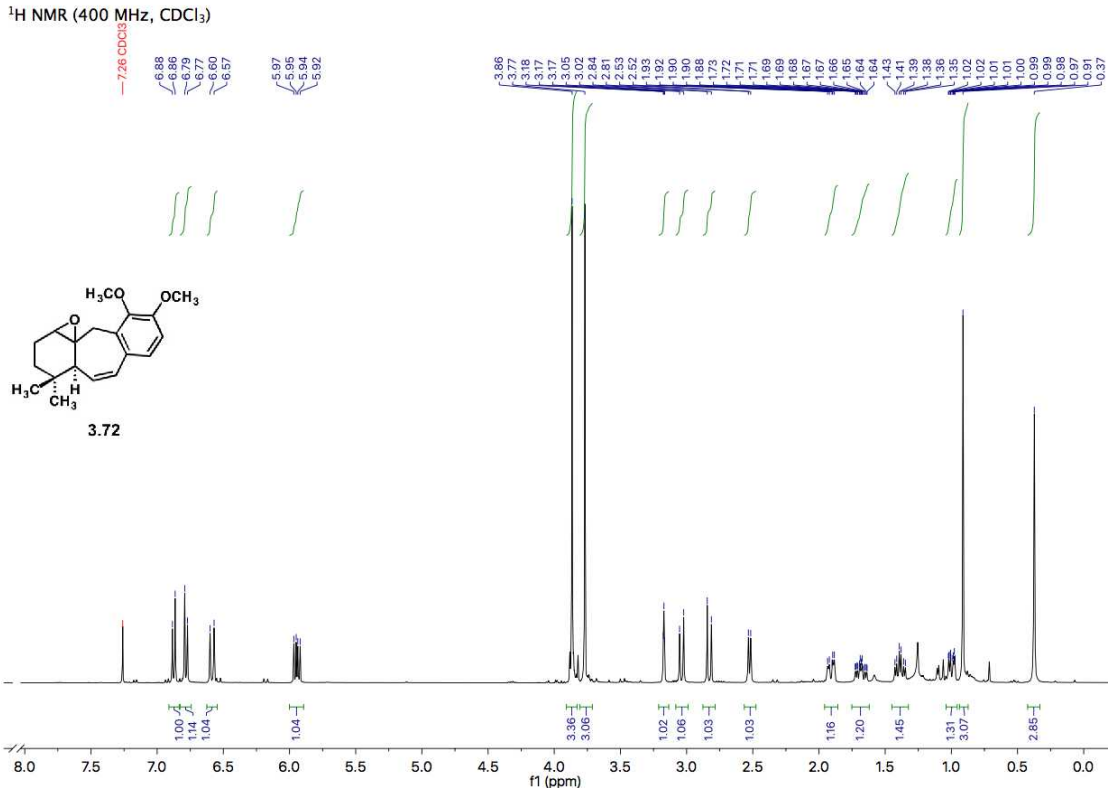
3.71

^{13}C NMR (101 MHz, $CDCl_3$)



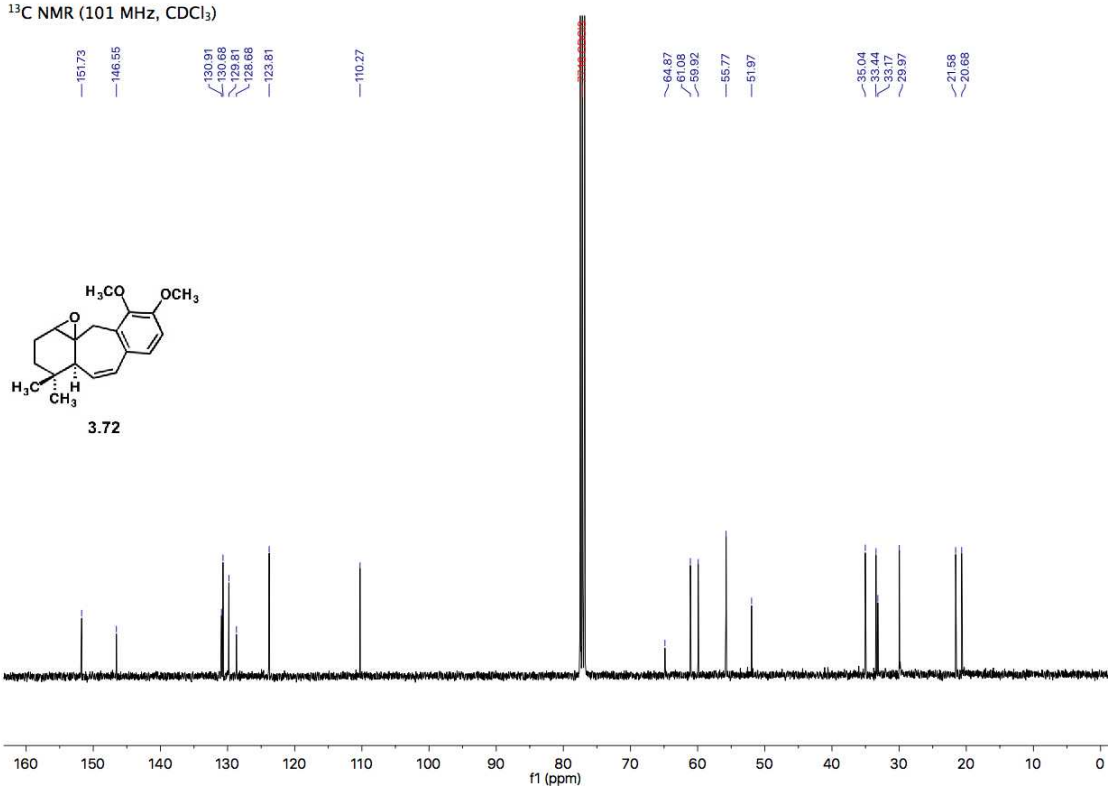
3.71

^{1}H NMR (400 MHz, $CDCl_3$)



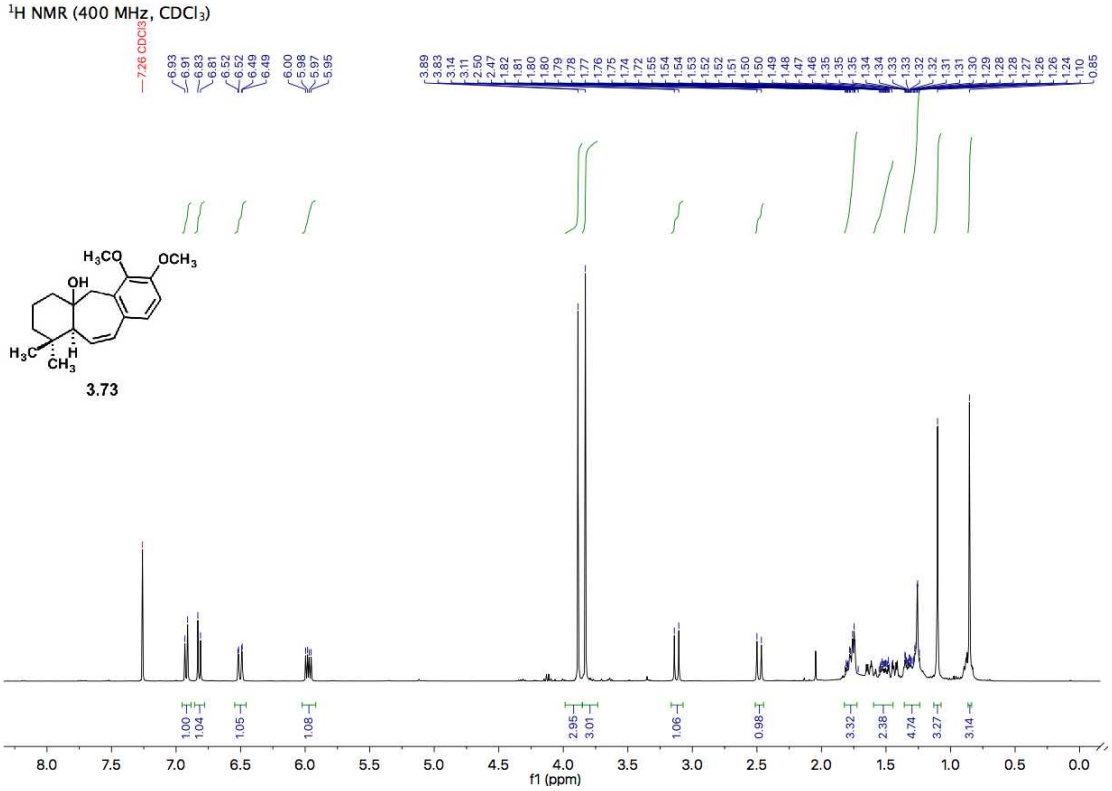
3.72

^{13}C NMR (101 MHz, $CDCl_3$)

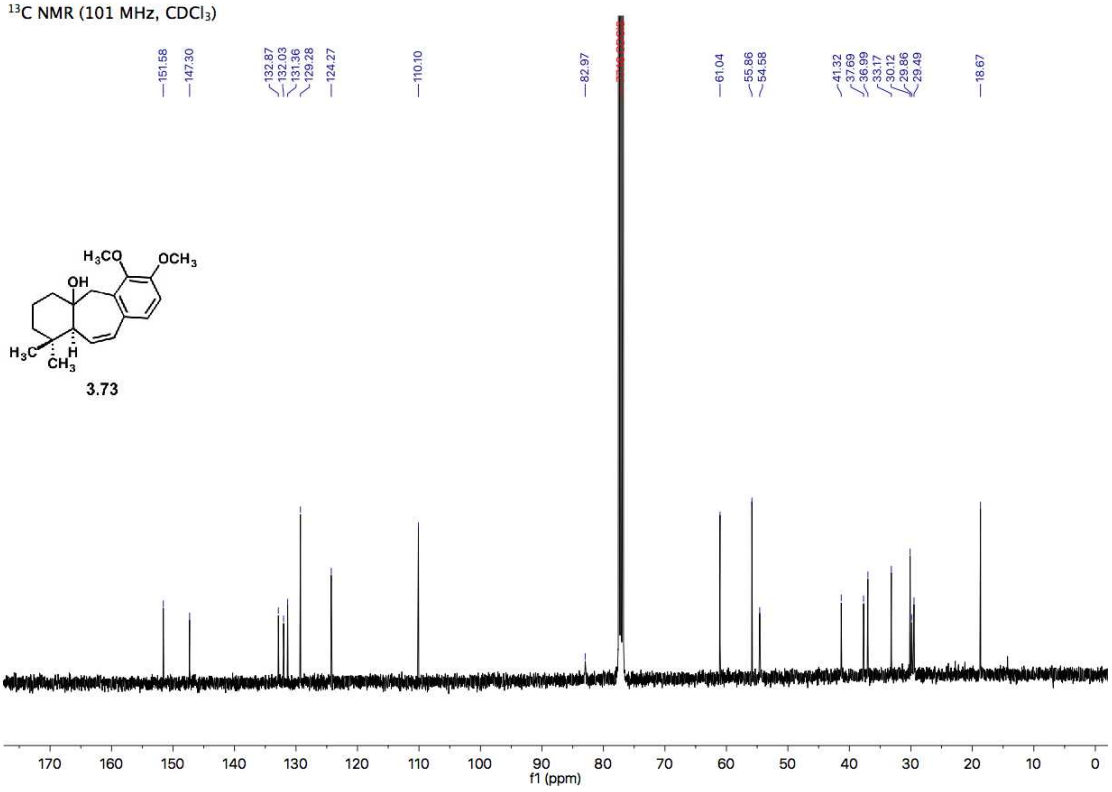


3.72

^{1}H NMR (400 MHz, $CDCl_3$)



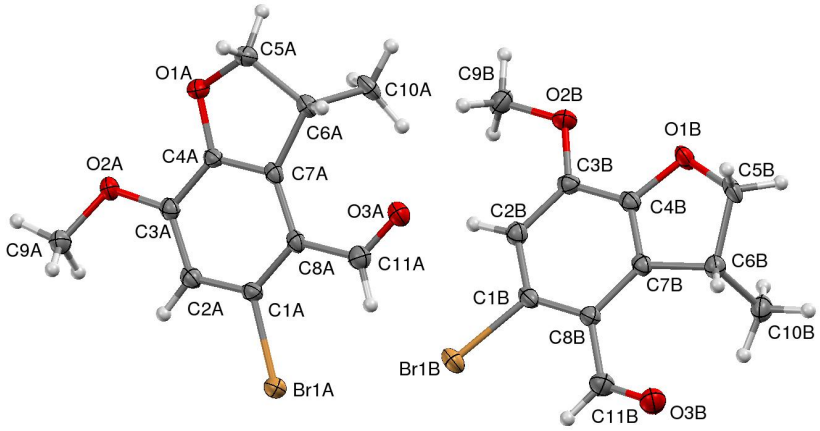
^{13}C NMR (101 MHz, $CDCl_3$)



Appendix B

CRYSTAL STRUCTURE DATA

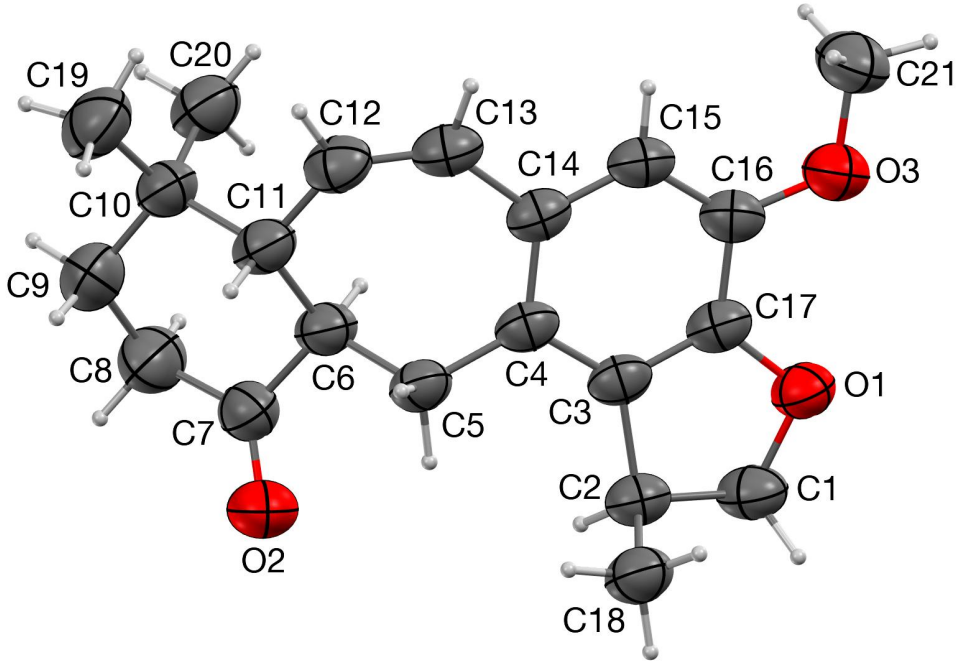
Crystal structure for 2.28:



Empirical Formula	$C_{11}H_{11}BrO_3$
Formula Weight, g/mol	271.11
Temperature, K	100 (2)
Wavelength, Å	0.71073
Crystal system	Triclinic
Space group	P1
Cell dimensions:	
a, Å	4.4849 (9)
b, Å	9.3120 (18)
c, Å	12.797 (3)
alpha, °	83.685 (3)
beta, °	87.265 (3)
gamma, °	80.628 (3)
Volume, $Å^3$	523.88 (18)

Z	2
ρ_{calc} mg/m^3	1.719
absorption coefficient, mm^{-1}	3.906
F(000)	272
Crystal Size	$0.213 \times 0.127 \times 0.074\ mm$
Theta range for data collection, °	2.229 to 28.585
Limiting indices	–6<=h<=5, –12<=k<=12, –17<=l<=17
Reflections collected / unique	10539 / 5274 [R(int) = 0.0294]
Completeness to theta = 25.242	99.9 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.7457 and 0.6089
Refinement method	Full–matrix least–squares on F^2
Data / restraints / parameters	5274 / 3 / 275
Goodness–of–fit on F^2	1.029
Final R indices [I>2sigma(I)]	R1 = 0.0360, wR2 = 0.0760
R indices (all data)	R1 = 0.0468, wR2 = 0.0797
Absolute structure parameter	–0.013(7)
Largest diff. peak and hole	0.733 and –0.726 e.A^{-3}

Crystal structure for 2.33:



Empirical Formula	$C_{21}H_{26}O_3$
Formula Weight, g/mol	326.42
Temperature, K	200 (2)
Wavelength, Å	1.54178
Crystal system	Trigonal
Space group	R–3
Cell dimensions:	
a, Å	31.1408 (12)
b, Å	31.1408 (12)
c, Å	10.2694 (5)
alpha, °	90

beta, °	90
gamma, °	120
Volume, $Å^3$	8624.5 (8)
Z	18
ρ_{calc} mg/m^3	1.131
absorption coefficient, mm^{-1}	0.588
F(000)	3168
Crystal Size	$0.635 \times 0.540 \times 0.288\, mm$
Theta range for data collection, °	2.838 to 75.623
Limiting indices	–39<=h<=38, –36<=k<=38, –12<=l<=12
Reflections collected / unique	42514 / 3959 [R(int) = 0.0729]
Completeness to theta = 25.242	100.0 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.7539 and 0.5776
Refinement method	Full–matrix least–squares on F^2
Data / restraints / parameters	3959 / 0 / 221
Goodness–of–fit on F^2	1.089
Final R indices [I>2sigma(I)]	R1 = 0.0830, wR2 = 0.2078
R indices (all data)	R1 = 0.1187, wR2 = 0.2491
Largest diff. peak and hole	0.336 and –0.230 $e.A^{-3}$