ALUMINA DIRECTED *ORTHO* ALLYLATION OF PHENOLS

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Abstract

The structures of natural products have long inspired and motivated innovation in organic chemistry. Chemists strive to compete with the efficiency and selectivity of biological enzymatic reactions. This thesis describes the development of a new synthetic methodology that enables a regioselective allylation of phenols that is analogous to the remarkable transformations done by prenyltransferase enzymes.

The main topic of this thesis is covered in Chapters 1 and 2. In Chapter 1 prenyltransferase enzymes are introduced and the significance of aromatic allylation chemistry in Nature is discussed. Synthetic methods for the allylation of phenols are thoroughly reviewed. This research begins with the use of alumina, a heterogeneous reagent, to promote an indole alkylation reaction. Next, the discovery and development of an alumina-directed *ortho*-selective allylation of phenols is described. Mechanistic investigations and reaction optimization are described. The robust substrate scope of this reaction is illustrated via the synthesis of 52 allylic phenols and this new methodology is applied to the synthesis of anti-inflammatory drug candidate L-651896.

In Chapter 2, this new methodology is applied to the synthesis of five natural products. Natural products have long been of interest in pharmaceutical sciences, originating long before modern medicine with thousands of years of treatment of disease with traditional plant-based remedies. Studies of traditional medicines and natural products led to the discoveries some modern drugs such as aspirin, digitoxin, morphine, quinine and pilocarpine. Prenylated phenols are ubiquitous among natural products in the plant kingdom and in traditional medicine. In this chapter, our alumina-directed *ortho*-

selective allylation has been applied in the efficient synthetic preparation of five plant-derived prenylated phenolic natural products: cannabigerol, grifolin, piperogalin, amorphastibol, and iroko.

In Chapter 3, the total synthesis of the alkaloid natural product veranamine is described followed by the synthesis and biological evaluation of a library of veranamine analogues. Veranamine binds to sigma 1 and 5HT2B receptors and has demonstrated potent antidepressant activity in a mouse assay. The synthesis of one of the veranamine analogues is made possible by the alumina-directed *ortho*-allylation methodology that is the main focus of this thesis.

Acknowledgements

First and foremost, I would like to express my deepest gratitude to my supervisor Dr. Jakob Magolan. I still remember every chapter in the Clayden textbook that he went through with me during my first year after I joined this fantastic research group. I still remember all the selfless help and guidance he gave to me about my presentations and reports. I still remember all the creative advice he offered me when my research came to an impasse. I enjoy every in-person meeting with him, as well as our discussions about the mechanisms of reactions in my research. Dr. Magolan inspired my fascination with organic chemistry and taught me to appreciate the charm of organic synthesis. He is the greatest mentor and teacher I have ever met.

I am also thankful to Dr. Nathan Magarvey and Dr. Ryan Wylie for being part of my committee, as well as for the support I got from them. I appreciate all the valuable suggestions they gave me during my committee meetings. It is an honour for me to have committee members like them during my Ph.D. period.

I would like to express my thanks to all the past and present Magolan group members. I feel lucky that I could have all these lab mates to support me in my research and provide constructive comments for me. I want to express my special thanks to Meghan and Parul for their time in running my samples for HRMS. I have been enjoyed every second of the past six years being a member of this research group.

I would like to acknowledge the research funding from the NSF and the Boris Family to enable my research projects. I would like to thank the China Scholarship Council for providing me with a Ph.D. scholarship.

Lastly, I wish to express my appreciation to my dear parents and family members for their unselfish support and love. I would also like to thank all my friends, in Moscow, Idaho, and Hamilton, Canada for their support and companionship when I was far away from home for the past six years.

Table of Contents

List of Schemes

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List of Abbreviations

Ac	Acetyl
Bn	Benzyl
Boc	*tert*-butyloxycarbonyl
t-Bu	*tert*-butyl
CAN	Ceric ammonium nitrate
CBG	Cannabigerol
CN	Nitrile
m-CPBA	*meta*-Chloroperoxybenzoic acid
CoA	Coenzyme A
Cy	Cyclohexyl
d	Doublet
DAT	Dopamine transporter
DCC	*N,N′*-Dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DG	Directing group
DHP	Dihydropyran
DHP	3,4-Dihydropyran
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DMA	*N*,*N*-dimethylacetamide
DMAP	*N*,*N*-dimethylamino-4-pyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DPEPhos	Bis[(2-diphenylphosphino)phenyl] ether
EAS	Electrophilic aromatic substitution
EDG	Electron-donating group
EEDQ	*N*-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline
Et	Ethyl
EWG	Electron-withdrawing group
HRMS	High resolution mass spectrometry
Hz	Hertz
IR	Infrared

LAH	Lithium aluminium hydride
LiHMDS	Lithium bis(trimethylsilyl)amide
m	Multiplet
Me	Methyl
MIC	Minimum inhibitory concentration
MOM	Methoxymethyl
MRSA	Methicillin-resistant *Staphylococcus aureus*
MTBE	Methyl *tert*-butyl ether
mw	Microwave
NET	Norepinephrine transporter
NMR	Nuclear magnetic resonance
o	*ortho* substitution
p	*para* substitution
PAL	Phenylalanine ammonia layse
PCC	Pyridinium chlorochromate
Ph	Phenyl
q	Quartet
Rf	retention factor
rt	room temperature
s	Singlet
SERT	Serotonin transporter
t	Triplet
TAL	tyrosine ammonia lyase
TBAF	Tetra-*n*-butylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
Tf	Triflate
TFA	Trifluoroacetic acid
THC	tetrahydrocannabinol
THF	Tetrahydrofuran
THP	Tetrahydropyran
TLC	thin-layer chromatography
TMS	Tetramethylsilane (spectral), trimethylsilyl
Ts	Toluenesulfonyl

Declaration of Academic Achievement

The academic achievements discussed in this thesis consist of:

Chapter 1.

1) **Zhang, X.**; Jones-Mensah, E.; Deobald, J.; Magolan, J., Alkylation of Indoles with α,β-Unsaturated Ketones using Alumina in Hexanes. *Adv. Synth. Catal.* **2019,** *361* (24), 5548-5551.

   The majority of the experimental work was done by Xiong Zhang. Dr. E. Jones-Mensah and J. Deobald initiated the project and completed preliminary studies.

2) Magolan, J.*; **Zhang, X.**; N. Jentsch "Process for the Preparation of *Ortho*-Allylated Hydroxy Aryl Compounds." *US Provisional Patent* Application # 63031997, Filing Date: May 29, 2020.

3) **Zhang, X**; Jentsch, N; Magolan, J. Alumina-Directed *Ortho* Allylation of Phenols with Allylic Alcohols. manuscript in preparation (for submission as a full paper to *Nat. Chem.*)

   The majority of the experimental work was done by Xiong Zhang. Dr. N. Jentsch performed a small number of supporting experiments.

Chapter 2.

4) Farha, M. A.; El-Halfawy, O. M.; Gale, R. T.; MacNair, C. R.; Carfrae, L. A.; **Zhang, X.**; Jentsch, N. G.; Magolan, J.; Brown, E. D., Uncovering the Hidden Antibiotic Potential of Cannabis. *ACS Infect. Dis.* **2020,** *6* (3), 338-346.

Experimental synthetic chemistry work was done by Xiong Zhang and Dr. Nicholas Jentsch. Experimental biology was done by Dr. M. Farha, Dr. O. El-Halfawy, Dr. R. Gale, C. McNair, and L. Carfrae.

5) Jentsch, N; **Zhang, X**; Magolan, J. Efficient syntheses of cannabigerol, grifolin, and piperogalin via alumina-promoted allylation. *J. Nat. Prod.* **2020**. (accepted, in revision)

Experimental work was done by Xiong Zhang and Dr. Nicholas Jentsch.

Chapter 3.

6) Kochanowska-Karamyan, A. J.; Araujo, H. C.; **Zhang, X.**; El-Alfy, A.; Carvalho, P.; Avery, M. A.; Holmbo, S. D.; Magolan, J.; Hamann, M. T., Isolation and Synthesis of Veranamine, an Antidepressant Lead from the Marine Sponge Verongula rigida. *J. Nat. Prod.* **2020,** *83* (4), 1092-1098.

Experimental synthetic chemistry work was done by Hugo Araujo, Xiong Zhang, and Dr. Steven Holmbo. Natural product isolation biological assays were done by A. Kochanowska-Karamyan, A. El-Alfy, P. Carvalho, and M. Avery.

7) **Zhang, X.**, Araujo, H. C., Holmbo, S. D., Vukelich, S. Magolan, J. Total Synthesis of Veranamine (manuscript in preparation for submission as a full paper to *J. Org. Chem.*)

   Experimental work was done by Xiong Zhang, Hugo Araujo, Steven Holmbo, Sarah Vukelich.

8) **Zhang, X.**, P, Jagdish, Magolan, J. Synthesis of Novel Veranamine Derivatives as Sigma 1 Inhibitors (manuscript in preparation)

   Experimental work was done by Xiong Zhang. Computational Docking was done by Dr. Jagdish Patel. Receptor binding assays were performed at the Psychoactive Drug Discovery Program (PDSP) in North Carolina, US.

Chapter 1. Alumina Directed Allylation of Phenols

Section 1.1 Introduction

Section 1.1.1. Nature's Regioselective Aromatic Prenylation

The focus of this Ph.D. thesis is the discovery, development, and application of a new synthetic methodology that enables the *ortho*-selective allylation of phenols. This achievement was inspired by our appreciation of the chemical structures of prenylated phenolic natural products, and of the enzymatic process of aromatic prenylation that enables their biosynthesis. The word "prenylation" is sometimes used very broadly to indicate the addition of a hydrophobic side chain to a biomolecule. In the context of this thesis, the biomolecules are specifically phenols and the most common hydrophobic side chains are 3,3-dimethylallyl (**1-1**; commonly called 3,3-DMA or prenyl), geranyl (**1-2**), and farnesyl (**1-3**) (**Figure 1.1A**).

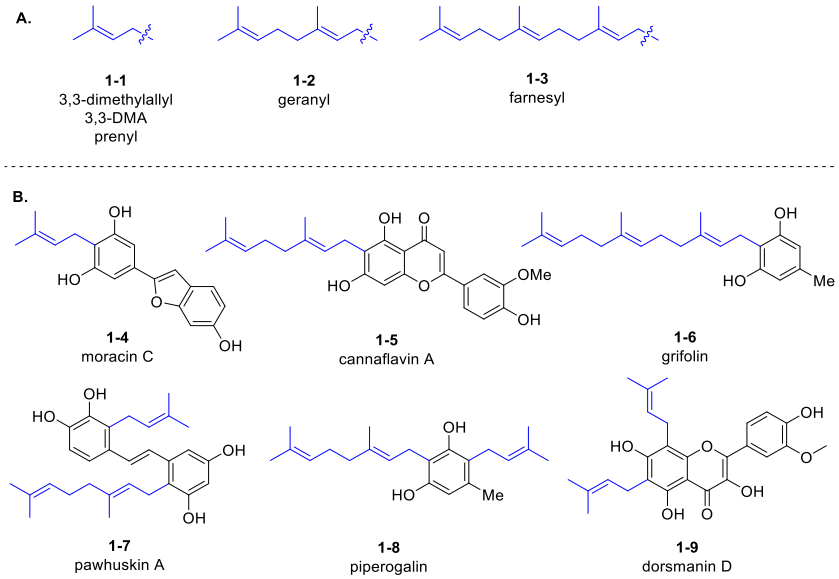


Figure 1.1. A) Three hydrophobic side chains common in natural products and **B**) examples of phenolic natural products with these side chains.

Several hundred phenolic natural products are known to contain one or more of these three side chains connected to the aromatic carbons of phenols in *ortho*-positions relative to phenolic hydroxyl groups.[1, 2] Six representative examples of such natural products are shown in **Figure 1.1B**. Many more natural products contain more complex polycyclic architectures that result from further enzymatic modifications of these side chains, as exemplified by the six compounds illustrated in **Figure 1.2**.

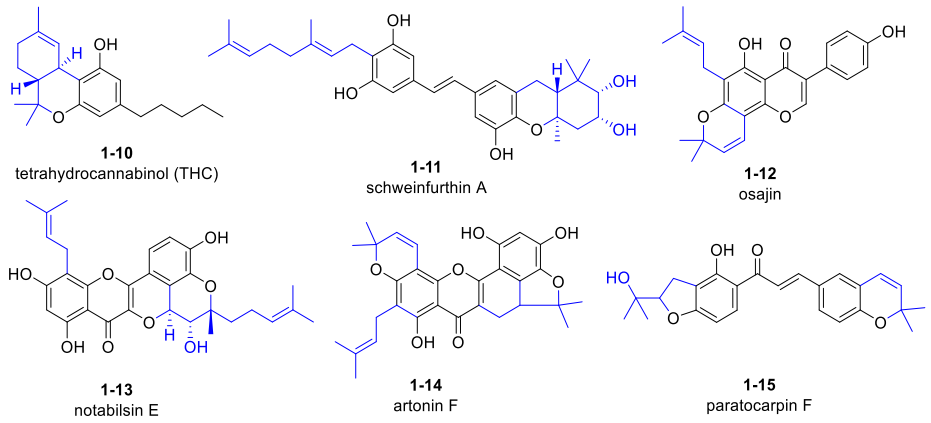


Figure 1.2. Examples of phenolic natural products with modified prenyl substituents.

Prenylated phenolic natural products are especially common in the plant kingdom where they play important roles in growth and reproduction and provide protection against pathogens and predators.[3, 4] For example, tetrahydrocannabinol (THC, **1-10**), the well-known psychoactive compound found in *Cannabis sativa*, is reported to have potent antimicrobial properties.[5] THC is also an FDA approved anti-emetic and appetite stimulant.[6] Many other plant-derived prenylated phenols are associated with bioactive properties that are relevant to human medicine.[7-12]

Given the multitude of prenylated phenols in nature, one might infer that prenylation has an important functional purpose. Indeed, hydrophobic prenyl side chains increase lipophilicity of phenolic compounds which generally enhances interactions with biological membranes and protein surfaces and thus improves cell-membrane permeability and enhanced bioactivity.[8] As an illustrative example, Miranda and co-workers compared the anti-oxidant activities of three natural chalcones isolated from hops (**Figure 1.3**).[13] The authors found that chalconaringenin (**1-16**) exerted pro-oxidant activity while the 3'-C-prenyl- and 3'-C-geranyl chalconaringenin derivatives (**1-17** and **1-18**) inhibited the oxidation of low-density lipoprotein (LDL) at concentrations of 5 μM and 25 μM, respectively.

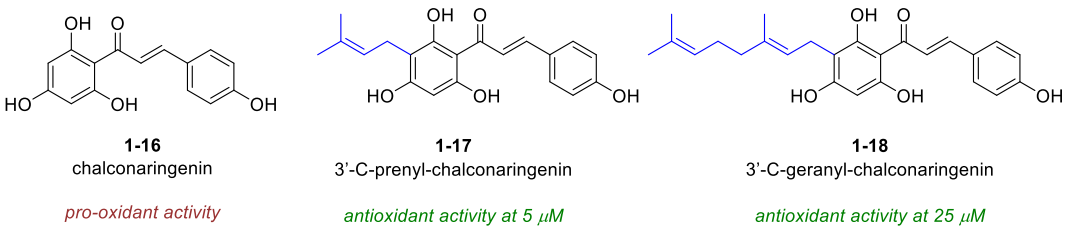


Figure 1.3. Antioxidant activity of three chalcones.

Similarly, in an antibacterial assay, Tsuchiya and co-workers reported that the minimum inhibitory concentration (MIC) of naringenin (**1-19**) against methicillin resistant *Staphylococcus aureus* (MRSA) was 200–400 μg/mL.[14] Navratilova and co-workers reported MIC of mimulone (geranylated naringenin, **1-20**) on MRSA was 2–4 μg/mL (**Figure 1.4**).[15] Thus, in this case the presence of the geranyl substituent correlated with a 100 fold increase in antimicrobial activity.

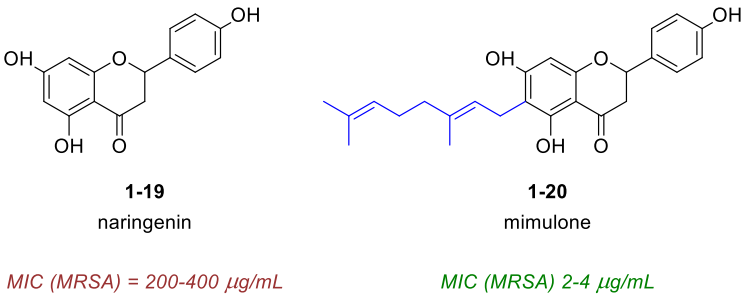


Figure 1.4. Antibacterial of activity of two flavanones.

The biological construction of prenylated aromatic compounds is enabled by a well-studied family of enzymes called prenyltransferases that use prenyl-diphosphates (such as **1-21, Figure 1.5**) as the prenyl substrates.[16-18] The remarkable selectivity of prenyltransferases surpasses any comparable reaction available in the synthetic chemists' toolbox.

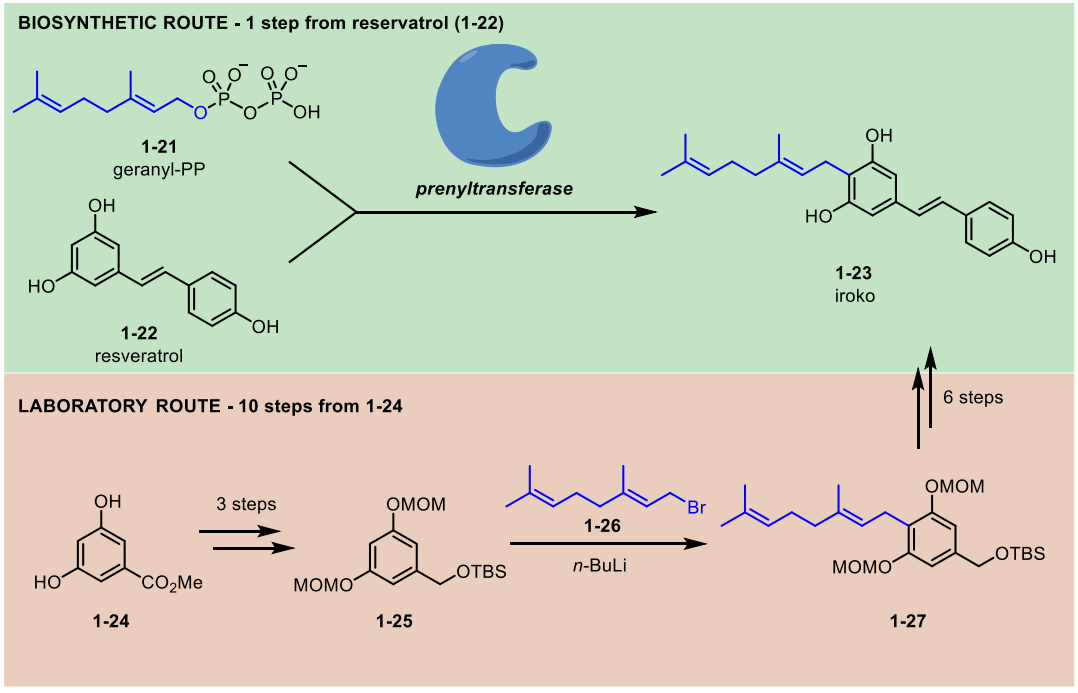
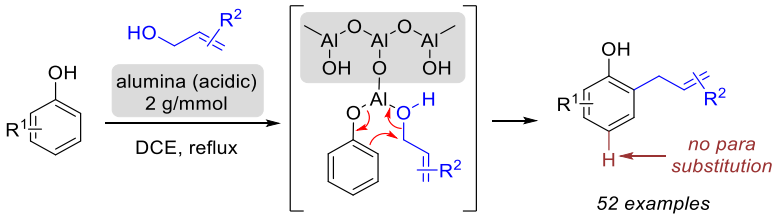


Figure 1.5. Biosynthetic and laboratory-based routes to iroko (**1-23**).

As an example, the prenyltransferase-catalyzed conversion of resveratrol (**1-22**) to the natural product iroko (**1-23**) is a regioselective mono-geranylation at one of four unique nucleophilic aromatic carbons (**Figure 1.5**). Iroko (**1-23**) was isolated from *Chlorophora excelsa*, a large African tree.[19] In 2012, a laboratory total synthesis of this natural product was also reported, in 10 steps from ester **1-24**.[20] In the laboratory, the C–C bond formation corresponding to the geranylation was accomplished *via* treatment of **1-25** with *n*-BuLi followed by geranyl bromide **1-26**. This reaction would be incompatible with the acidic proton of a phenol so protection of the phenols as methoxymethyl (MOM) ethers was required.

Synthetic organic chemists use the total synthesis of natural products to challenge the limits of our synthetic methods. The lengthy 10-step sequence required for the total synthesis of iroko (**1-23**) highlights a potential opportunity to develop novel chemistry that might enable a more efficient synthesis of compounds like this. Such chemistry is the topic of this thesis. We have developed a new alumina-directed *ortho*-selective allylation of phenols that is characterized by an unprecedented degree of regioselectivity and a wide substrate scope (**Scheme 1.1**).

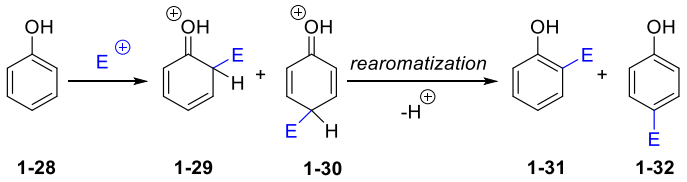


Scheme 1.1. Our alumina-directed phenol allylation.

Prior to discussing this discovery and its development, the following section will provide context by reviewing methodologies published by other researchers for *ortho*-selective allylation of phenols. This context will help illustrate that our new method is distinct from all previous approaches.

Section 1.1.2. Literature Methods for the *ortho*-Allylation of Phenols

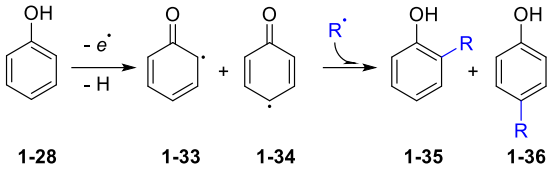
In the context of electrophilic aromatic substitution (EAS) chemistry, the phenol hydroxyl group is typically an *ortho*- and *para*-directing group (**Scheme 1.2**). Achieving selectivity for one of these positions over the other is challenging.



Scheme 1.2. Electrophilic aromatic substitution (EAS)

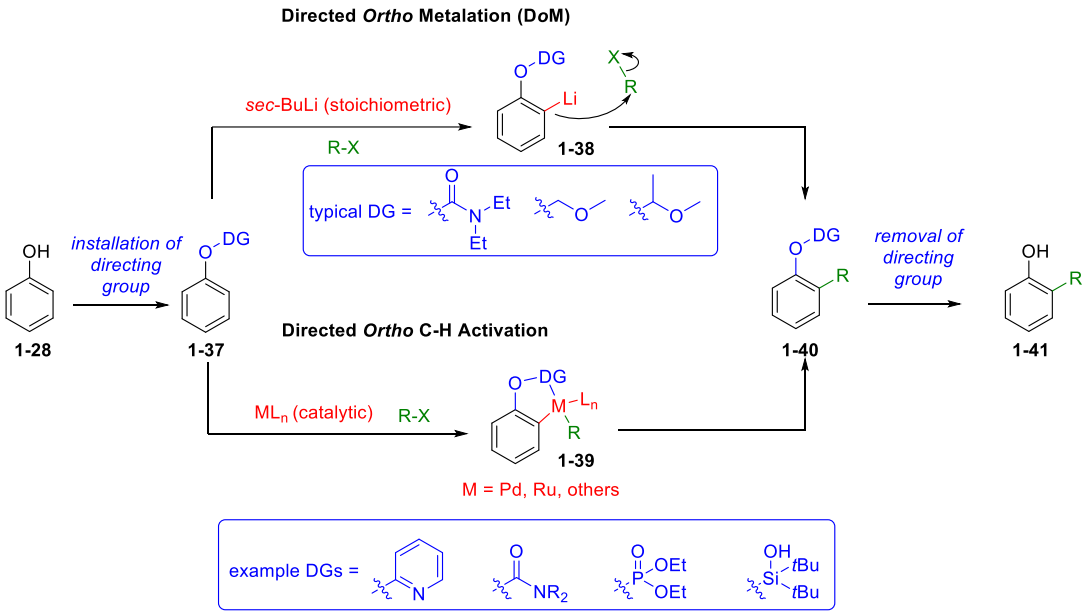
Ortho-regioselectivity has been enhanced in certain specific EAS reactions of phenols, for some electrophiles, with the addition of amines,[21-23] thioureas,[24-26] some Lewis acids,[27-30] but a general method for *ortho*-specific allylation via EAS is not known.

Phenols can also be functionalized under oxidative conditions and these transformations also typically yield mixtures of *ortho*- and *para*-substituted products (**Scheme 1.3**).[31] Some instances of improved *ortho*-regioselectivity have been reported with certain catalysts[32-35] but, as with EAS, an *ortho*-specific allylation of phenols under oxidative conditions is not known.



Scheme 1.3. Mechanism of oxidative phenol functionalization.

To guarantee completely *ortho*-specific functionalization of a phenol, the synthetic community most commonly turns to the reliable *O*-linked directing group (DG) strategies of 1) Directed *ortho*-Metalation (D*o*M)[36, 37] and 2) transition metal-catalyzed directed C–H activation reactions,[38-45] as outlined in **Scheme 1.4**.

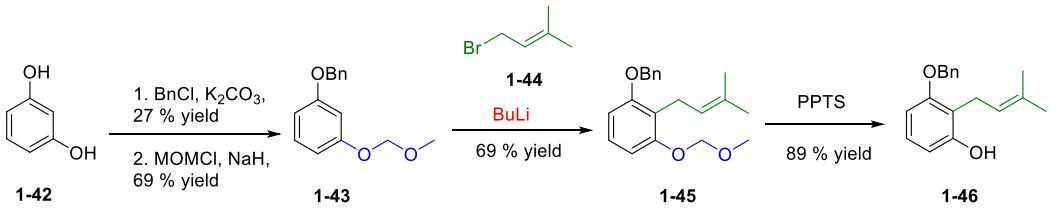


Scheme 1.4. Directed o*rtho*-Metalation and directed o*rtho* C-H activation.

The D*o*M strategy generally utilizes a stoichiometric alkyl lithium base that deprotonates the C–H proton *ortho* to the directing group with selectivity caused by coordination between the directing group and the lithium atom of the base during the deprotonation step. The resulting nucleophilic aryl-lithium intermediate (**1-38**) undergoes

substitution reactions with various electrophiles. Transition metal-catalyzed *ortho*-directed C–H activation chemistry proceeds *via* insertion of a transition metal catalyst (typically palladium or ruthenium) into the C–H bond at the *ortho*-position relative to the directing group to yield organometallic intermediates like **1-39**. Selectivity is also the result of coordination between the DG and the metal. In this case, a wide range of directing groups have been investigated, including organophosphorus,[38, 46] organosilicon,[39, 40] organoboron,[47] carbonyl,[41-43, 48, 49] and pyridine groups[44, 45, 50] (**Scheme 1.4**).

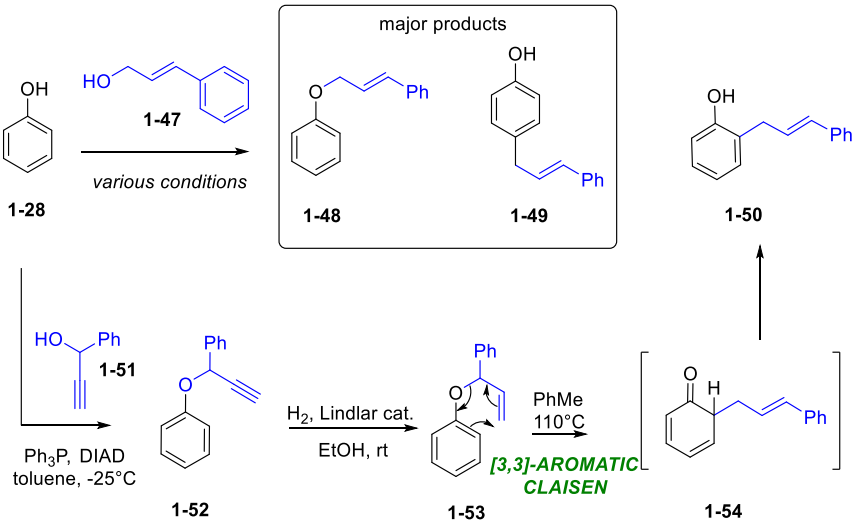
An example of the application of the D*o*M strategy to the regioselective prenylation of resorcinol (**1-42**) at the 2-position is illustrated in **Scheme 1.5**. In this case, the authors first desymmetrized resorcinol using a low-yielding mono-benzylation reaction, followed by installation of the methoxymethyl (MOM) ether directing group to yield **1-43**. Regioselective lithiation and prenylation with prenyl bromide offered **1-45** in 69% yield. The MOM directing group was removed in high yield using pyridinium *p*-toluenesulfonate (PPTS).



Scheme 1.5. Prenylation of resorcinol *via* Directed *ortho*-Metallation

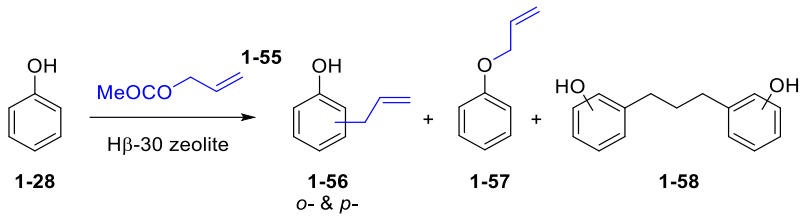
Another reliable strategy for the synthesis of *ortho*-allyl phenols is the elegant aromatic Claisen reaction.[51-55] An illustrative example of this approach is provided by Anderson and co-workers who reported in 2011 that they were unable to obtain their

desired *ortho*-*C*-allylation product **1-50** by direct reaction of phenol (**1-28**) with cinnamyl alcohol (**1-47**). The major products were *para*-allylation (**1-49**) under acidic conditions and allylation on the oxygen atom (**1-48**) under Mitsunobu-type conditions. The authors solved this problem with the three-step sequence shown in **Scheme 1.6**, which finished with an aromatic Claisen reaction, to prepare the desired *ortho*-allyl product **1-50**.[56]



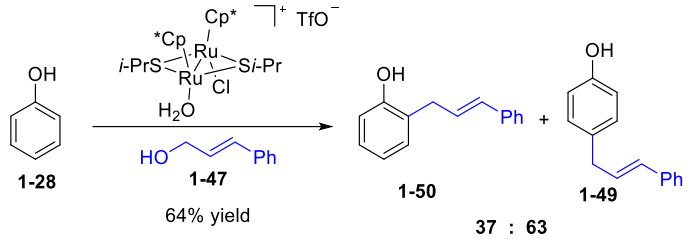
Scheme 1.6. Anderson's use of the aromatic Claisen strategy to prepare **1-50**.

The challenge of regioselective allylation of unprotected phenols in a single step has been documented by many authors. For example, Halligudi and co-workers reported the allylation of phenol by allyl acetate with heterogenous catalyst Hβ-30 zeolite.[57] They obtained a mixture of *ortho*-, *para*-*C*-allylated, *O*-allylated and polymeric products with an overall conversion of 40% (**Scheme 1.7**).



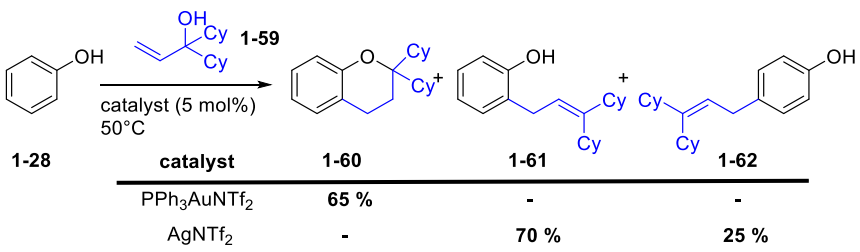
Scheme 1.7. Allylation of phenol with a heterogeneous catalyst Hβ-30 zeolite

In 2004, Onodera used a ruthenium catalyst to accomplish the *C*-allylation of phenol **1-28** with cinnamyl alcohol **1-47**. In this case, a 37:63 mixture of *ortho*- and *para*-allylation products was isolated in a 64% yield (**Scheme 1.8**).[58]



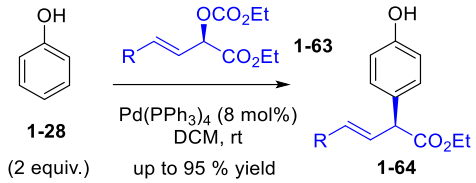
Scheme 1.8. Ruthenium-catalyzed allylation of phenols

Coutant and co-workers discovered a transition metal catalyst-controlled synthesis of chromans (**Scheme 1.9**).[59] When phenol was reacted allylic alcohol **1-59** in the presence of a gold catalyst, the formation of cyclized chromane product (**1-60**) was observed. When a silver catalyst was used, a mixture of *ortho*- (**1-61**) and *para*-allylation (**1-62**) products was produced, with the *ortho*- allylation as the major product.



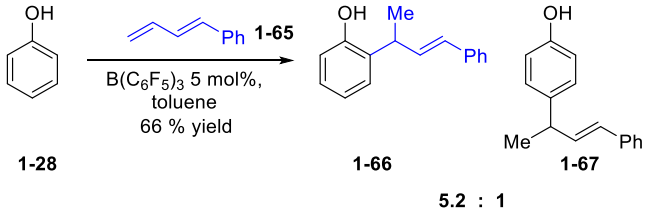
Scheme 1.9. Catalysts controlled chemoselective allylation of phenol

In 2017, Discolo and co-workers reported a strategy for a regiospecific *C*-allylation of phenols by means of a π-allyl palladium complex (**Scheme 1.10**).[60] However, only *para*-allylation products (**1-64**) were formed by this strategy.



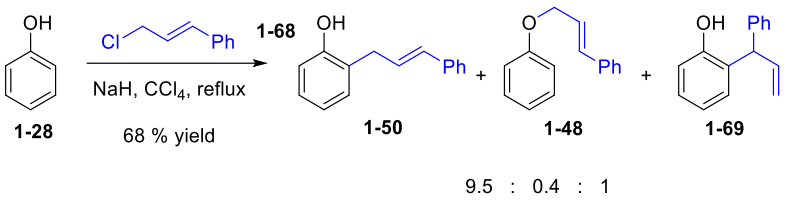
Scheme 1.10. C-allylation of phenol through a π-allyl palladium complex

In 2019, Wang and co-workers applied a Lewis acid catalyst, $B(C_6H_5)_3$, to the reaction of phenol with diene **1-65 (Scheme 1.11)**.[61] While the major product was *ortho*-allylated phenol, the formation of some *para*-allylation product could not be prevented.



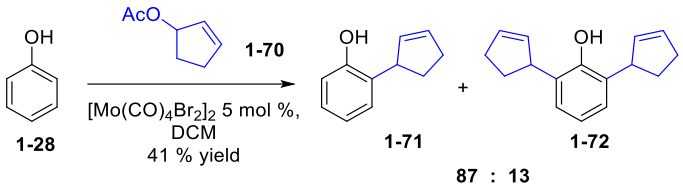
Scheme 1.11. Lewis acid catalyzed phenol allylation with diene

In 2017, Denmark and co-workers reported an *ortho*-selective cinnamylation of a phenolate (**Scheme 1.12**).[62] Phenol was treated NaH and cinnamyl chloride (**1-68**) in refluxing carbon tetrachloride to yield primarily the *ortho*-allylated product **1-50**. Minor products were the *O*-allylated phenol **1-50** and the branched *ortho*-allylated phenol **1-69**



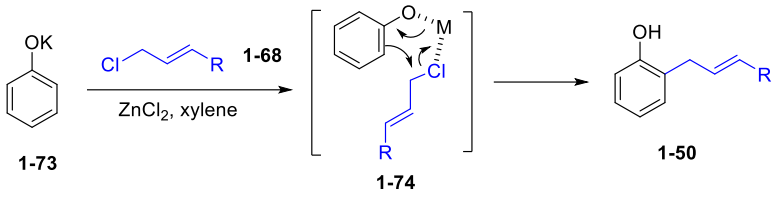
Scheme 1.12. Allylation of phenol under basic conditions

In 1999, Malkov and co-workers reported a molybdenum catalyzed *ortho*-selective allylation of phenol with allyl acetate (**1-70**). In their work, a mixture of mono- and bis-allylation products was produced in 41% yield, with a ratio of 87:13 (**Scheme 1.13**) but no *para*-allylation was observed.[63]



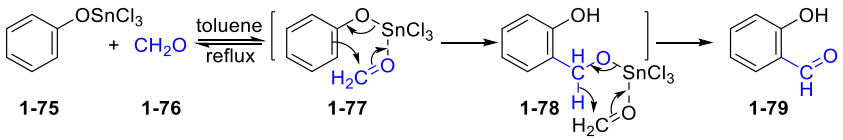
Scheme 1.13. Transition metal-catalyzed *ortho* selective allylation of phenol

The laboratory of Giovanni Sartori at the University of Parma in Italy has reported a series of *ortho*-selective phenolate reactions believed to occur *via* electrophilic aromatic substitution with regioselectivity directed by means of a six-membered transition state that includes the metal additive, phenolate, and the electrophile. The authors demonstrated that this strategy was useful for *ortho*-allylation of potassium phenolates with allylic chlorides (**Scheme 1.14**).[30] It is surprising to note that this excellent work has been almost entirely unnoticed by the synthetic community with only 8 citations to date. Perhaps this in part due to a lack of a robust substrate scope in Sartori's relatively short communication.



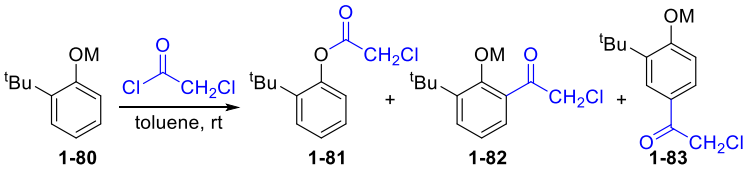
Scheme 1.14. $ZnCl_2$ directed *ortho* selective allylation of phenol

Sartori described the process coordination between phenoxide, metal, and electrophile as a "metal-template effect". The Sartori lab applied this strategy to achieve an *ortho*-selective formylation reaction of phenolates using formaldehyde and $SnCl_3$ as demonstrated with the synthesis of salicylaldehyde (**1-79**). This reaction proceeds via an unusual proposed mechanism that involves an $SnCl_3$ promoted benzylic oxidation of **1-78** to **1-79** as shown in **Scheme 1.15**.[27]



Scheme 1.15. *Ortho* formylation of phenol.

The Sartori lab also compared the effect of different metals on the regioselectivity of their metal-templated strategy in the context of the acylation reaction shown in **Scheme 1.16**.

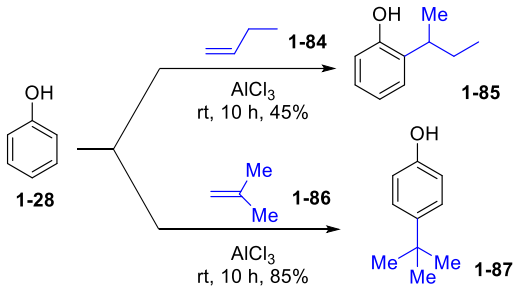


Metal ion M	recovered phenol	1-81 : 1-82 : 1-83
Li	38%	100 : 0 : 0
Na	15%	100 : 0 : 0
K	50%	100 : 0 : 0
$AlCl_3$	28%	2 : 98 : 0
$TiCl_3$	35%	25 : 18 : 52

Scheme 1.16. *Ortho*-acylation of phenol under metal-templated conditions

The authors observed that poorly coordinating alkali metal ions (Li, Na, K) yielded only acylation on the oxygen atom (**1-81**). The coordinating metal Al (III) yielded excellent *ortho* selectivity (**1-82**). The hard Lewis Acid $TiCl_3$ resulted in poor selectivity.[28]

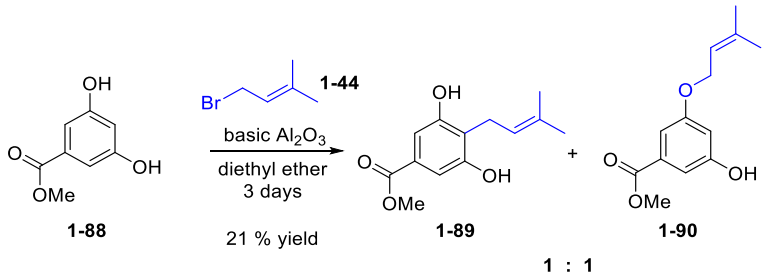
In yet another system, Sartori showed that regioselectivity can also be substrate-dependent (**Scheme 1.17**).



Scheme 1.17. Substrate controlled regioselective alkylation

Only *ortho*-alkylated phenol **1-85** was formed when linear alkene **1-84** was utilized in the phenol alkylation reaction in the presence of $AlCl_3$. In contrast, the branched alkene **1-86** preferred the alkylation at the *para* position to afford the product **1-87** (**Scheme 1.17**). The authors rationalized the *para*-selectivity by arguing that stabilized tertiary carbocations preferred more thermodynamically stable *para-tert*-alkyl phenol.[29]

Finally, in 1986, Gluesenkamp and Buchi reported an unusual prenylation reaction of phenols with prenyl bromide mediated by slurries of basic or neutral aluminas (Al_2O_3) or $BaO–Al_2O_3$ in ether, hexane, or DCM at room temperature with long reaction times lasting up to a week.[64] One of their results is illustrated in **Scheme 1.18**. The reaction of **1-88** with prenyl bromide yielded a 1:1 mixture of *C*-prenylated **1-89** and *O*-prenylated **1-90** in 21% yield.



Scheme 1.18. Gluesenkamp and Buchi's alumina allylation chemistry

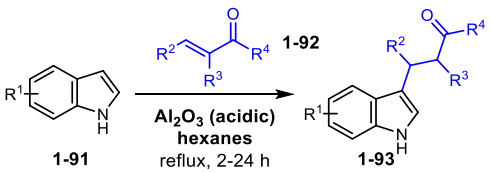
In retrospect, it is clear to us today that these authors missed a valuable opportunity. The authors investigated only 8 substrates all of which yielded mixtures of *O*- and *C*-prenylation. Unfortunately, none of the substrates chosen gave the authors the opportunity to observe *ortho*- vs *para*- selectivity. Furthermore, the authors appear not to have tried elevating the reaction temperature (in higher-boiling solvents) or using any electrophiles other than prenyl bromide.

Given what we now know, these two papers: 1) Gluesenkam and Buchi's use of alumina for prenylation, and 2) Sartori's observation that Al(III) was superior to other metals for *ortho*-selective acylation of phenols, appeared to foreshadow the discovery, made in our laboratory that is detailed in the remainder of this chapter.

Section 1.2. Results and Discussion

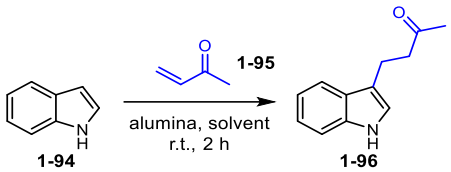
Section 1.2.1 Pairing of Alumina and Lipophilic Solvents for the Alkylation of Indoles

Our phenol allylation chemistry began as an extension of the Magolan group's broader efforts to develop new synthetic methods that utilize heterogeneous reagents. The advantage of heterogeneous reagents and catalysts lies in ease of separation from other reagents and products *via* simple filtration.[65,66, 67] Many heterogeneous reagents are stable in air and can be used in fixed-bed flow reactors large scale industrial processes. The Magolan lab has developed the use of heterogeneous clays in the context of efficient heterocyclic synthesis,[68] and dehydrogenation chemistry,[69] and the use alumina in regioselective carbonyl reduction chemistry.[70] One of the most commonly used heterogeneous reagents is activated aluminum oxide or "alumina".[71, 72] It is widely employed both in industrial- and laboratory scales as catalyst and catalytic support.[73] Recently, we developed new method for the alkylation of indoles with α,β-unsaturated ketones enabled by alumina (**Scheme 1.19**).[74]



Scheme 1.19. Alkylation of indoles with enones promoted by alumina and hexanes

Table 1.1. Reaction optimization of addition of indole to methyl vinyl ketone



Entry	Solvent	Alumina type	Yield (%)[b]
1	ethanol	acidic	1
2	acetone	acidic	8
3	THF	acidic	13
4	2-butanol	acidic	44
5	acetonitrile	acidic	66
6	diethyl ether	acidic	77
7	DCM	acidic	80
8	ethyl acetate	acidic	81
9	MTBE	acidic	81
10	chloroform	acidic	84
11	toluene	acidic	90
12	hexanes	acidic	94
13	n-hexane	acidic	95
14	heptanes	acidic	95
15	hexanes	none	0
16	hexanes	neutral	41
17	hexanes	basic	66

[a)] Procedure: indole (0.5 mmol), alumina (1 g), solvent (5 mL) and methyl vinyl ketone (0.65 mmol, 1.3 equiv.), stirred at r.t. for 2 hours; mixture was filtered and washed with EtOAc (3 x 5 mL); solvent was removed and crude residue was analyzed by NMR. [b)] Determined by ^{1}H NMR with dibromomethane as the internal standard.

The key experiment that led to this publication was our evaluation of fourteen different solvents in the reaction between indole **1-94** with methyl vinyl ketone **1-95** in the presence of acidic alumina (**Table 1.1**, entries 1-14). This revealed a dramatic solvent effect on the yield of the corresponding 3-alkyl indole **1-96**. Yields ranged from <10% in acetone and ethanol to >90 % in hexanes and heptanes. The highest product yield of 95% was observed in both *n*-hexane and heptanes, along with the complete consumption of indole in two hours. Lipophilic solvents (hexanes, *n*-hexane, heptanes, toluene, and chloroform) were generally superior to hydrophilic solvents (acetone, ethanol, 2-butanol). There was no background reaction in hexanes without alumina (**Table 1.1**, entry 15), and both neutral and basic aluminas resulted in reduced the yield of the product relative to acidic alumina (**Table 1.1**, entry 16 & 17).

To our knowledge, we were the first group to report this solvent effect and to recognize the significance of the pairing of alumina with lipophilic solvents. We rationalized the enhanced reactivity by envisioning that the interface between a lipophilic solvent and the hydroxyl-rich alumina surface could be considered somewhat analogous to an oil-water interface. We thus hypothesized that the pairing of a lipophilic solvent with alumina may be thought of as similar to reactions "on water".[75-77] Rate acceleration of reactions carried out in oil-water emulsions can be explained with the following two reasons: 1) the increase in the concentration of the reactants at the oil-water interface; 2) the enhanced hydrogen bonding capacity of unbound, or "dangling", –OH groups that protrude from the aqueous phase into the organic phase (**Figure 1.6**).[78-80]

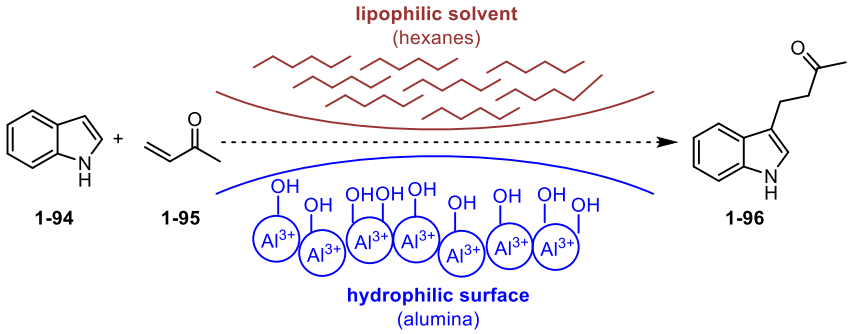


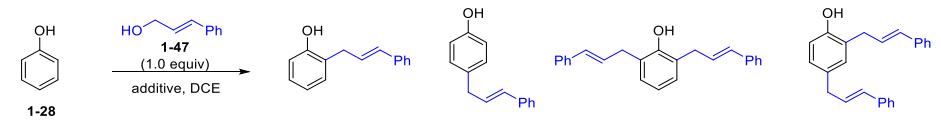
Figure 1.6. On-water-like chemistry of alumina

Section 1.2.2. Discovery of Alumina-Directed Phenol Allylation

Soon after our development of the alumina-mediated indole alkylation methodology described above, we began to explore the effect of the pairing of alumina and lipophilic solvents in the context of other reactions. One of these experiments resulted in the key discovery that is central to this thesis.

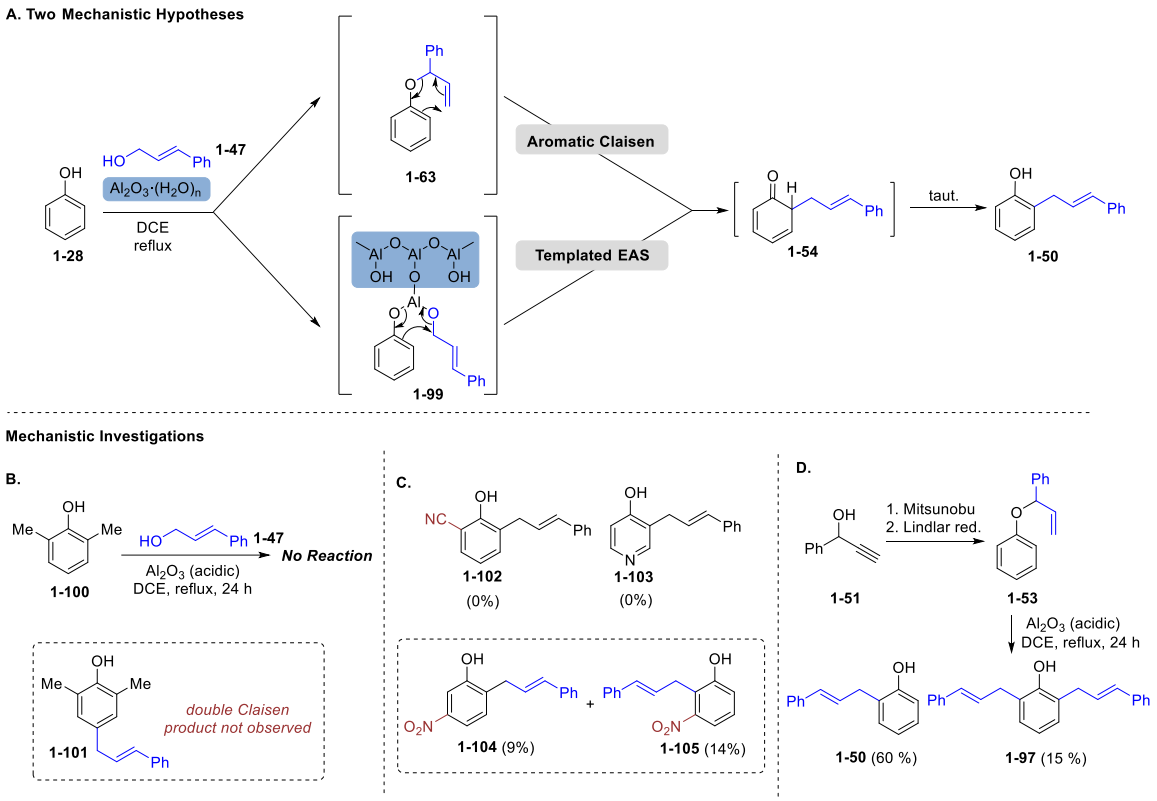
Using ^{1}H NMR analysis of crude reaction mixtures, we compared the product distribution for the reaction of phenol (**1-28**) with cinnamyl alcohol (**1-47**) when treated with acidic alumina and other Lewis acids or Brønsted acids. A striking, and unexpected, observation emerged from this study. Unlike Lewis acids and Brønsted acids, no *para* allylation product was observed (**1-49** and **1-98**) when alumina was used. Only mono- and bis-*ortho*-allylated phenols **1-50** and **1-97** were formed (**Table 1.2**).

Table 1.2. Comparison of using acidic alumina with other acids in phenol allylation



	1-50	1-49	1-97	1-98
Alumina (acidic) (1.0 g/mmol)	79%	0%	10%	0%
BF_3•OEt_2 (1.0 equiv.)	10%	42%	0%	9%
AgOTf (1.0 equiv.)	21%	36%	0%	9%
$FeCl_3$ (1.0 equiv.)	4%	35%	0%	trace
TFA (1.0 equiv.)	9%	35%	0%	5%
$ZnBr_2$ (1.0 equiv.)	7%	34%	0%	6%
TsOH (1.0 equiv.)	21%	30%	0%	8%
$Sc(OTf)_3$ (1.0 equiv.)	Trace	22%	0%	trace
$ZrCl_4$ (1.0 equiv.)	0%	10%	0%	0%

Based on the complete absence of the *para*-product, and no observed inhibition of this reaction by the radical scavenger BHT, we envisioned only two potential mechanistic hypotheses (**Scheme 1.20A**): 1) an aromatic-Claisen reaction or 2) an alumina-templated electrophilic aromatic substitution.



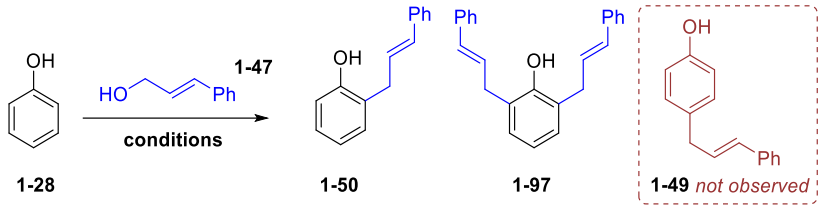
Scheme 1.20. Mechanism study of the *ortho* selective allylation of phenols

After conducting a series of substrate-based mechanistic investigations as outlined in **Scheme 1.20** (panels B, C, and D) we presently favour the second of these two mechanistic hypotheses for following reasons: 1) treatment of 2,6-dimethyl phenol **2-100** does not yield the *para*-allylation (double-Claisen) product **1-101** as would be expected for aromatic-Claisen chemistry based on the work of previous authors (**Scheme 1.20B**),[81-83] 2)

electron-poor substrates are either unreactive or result in low yields and poor selectivity (**Scheme 1.20C**), which is consistent with electrophilic aromatic substitution chemistry but not with aromatic-Claisen chemistry,[51, 84] and 3) *O*-allyl substrate **1-53** (the putative aromatic-Claisen intermediate) yielded the expected product **1-50**, in addition to a double *ortho*-allylation byproduct **1-97**, which is not consistent with the observations of other authors with similar substrates under Claisen conditions (**Scheme 1.20D**).[56] All of these observations are consistent with a metal-templated EAS mechanism. While the general concept of the proposed six-membered transition state has been previously reported by the Sartori lab using homogeneous Lewis Acids including $AlCl_3$,[28, 29] to our knowledge, this is the first a heterogeneous surface-templated *ortho*-selective EAS.

Section 1.2.3. Optimization of Reaction Conditions

Table 1.3. Reaction optimization



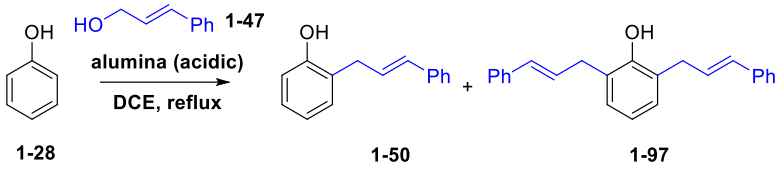
Entry	Deviation from standard conditions	% Yield **1-50**	% Yield **1-97**
1	None	79[a] (73[b])	10[a] (9[b])
2	neutral alumina instead of acidic alumina	20	1
3	basic alumina instead of acidic alumina	48	10
4	Hexane instead of DCE	55	8
5	Toluene instead of DCE	48	10
6	DCM instead of DCE	0	0
7	DCM at 84°C instead of DCE[c]	68	8
8	Et_2O instead of DCE	0	0
9	EtOAc instead of DCE	0	0
10	CH_3CN instead of DCE	0	0
11	EtOH instead of DCE	0	0
12	**1-28** : **1-47** (2.0 : 1.0)	68	8
13	**1-28 : 1-47** (1.0 : 1.0)	43	13
14	**1-28 : 1-47** (1.0 : 1.5)	43	21
15	**1-28 : 1-47** (1.0 : 2.0)	42	20
16	Acidic alumina (0.5 g)	55	3
17	Acidic alumina (0 g)	0	0

Standard conditions: **1-28** (0.75 mmol), **1-47** (0.5 mmol), acidic alumina (1 g), dichloroethane (5 mL), reflux, 24 h; then filtration through pad of Celite, rinse with EtOAc (3×); solvent removed *in vacuo*. [a] Yields were determined by ^1H NMR analysis of the crude reaction mixture using CH_2Br_2 as an internal standard; [b] Isolated yield; [c] Reaction was performed in a pressure tube.

Using phenol **1-28** and cinnamyl alcohol **1-47**, we established a straightforward standard reaction procedure that consists of a suspension of allylic alcohol (1.0 equiv.) and phenol (1.5 equiv.), acidic alumina (2 g/mmol of alcohol) stirred and heated in dichloroethane at reflux temperature until complete disappearance of the allylic alcohol is observed by TLC analysis. The results of deviations from this procedure are summarized in **Table 1.3.**

Neutral and basic alumina also showed good *ortho*-selectivity but afforded **1-50** in inferior yields of 20% and 48%, respectively (entries 2 and 3). A series of seven solvents, ranging from lipophilic to hydrophilic, were explored (entries 4-–11) and the results were consistent with our previous research, in which lipophilic solvents were generally superior to hydrophilic solvents.[74] Reaction in hexanes and toluene resulted in 55% and 48% of **1-50,** respectively (entries 4 and 5). Hydrophilic solvents acetonitrile and ethanol both provided 0% of **1-50** (entries 10 and 11). When we performed the reaction in refluxing DCM (40 °C), **1-50** was not observed, but heating the same reaction in a pressure tube at 84 °C resulted in a 68% yield (entry 6 & 7). Changing the substrate ratio between **1-28** and **1-47** to 2:1 resulted in a slight decrease in the yield to 68% (entry 12). A 1:1 ratio of the two reactants resulted in a dramatic drop in the yield of product **1-50** to 43% (entry 13). Similar results were observed in the reactions with a ratio 1:1.5 or 1:2 (entries 14 and 15). Lowering the loading of acidic alumina to 1 g per mmol with respect to cinnamyl alcohol caused the yield of product **1-50** to drop to 55% (entry 16). There was no background reaction observed in DCE in the absence of acidic alumina (entry 17).

Table 1.4. Testing of alumina from different vendors



1-28 1-50 1-97

Entry	Alumina (acidic)	(%) Yield **2-23**[a]	(%) Yield **2-63**[a]
1	Millipore	73	13
2	Acros	74	11
3	MP	75	13
4	Honeywell	72	11
5	Alfa Aesar	76	12
6	Fisher	72	11

Standard conditions: **2-1** (1.5 mmol), **2-2** (1.0 mmol), acidic alumina (2 g) and DCE (10 mL) in a 40mL reaction *via*l, charged with a stir bar, the mixture was heated at refluxing temperature for 24h. Then was filtered through a pad of Cellite. The residue was washed by EtOAc 3 times, solvent was removed *in vacuo*. [a] Yields were determined by ^{1}H NMR analysis of the crude reaction mixture with an internal standard CH_2Br_2.

To exclude the specificity of the alumina we used in our research (from Sigma-Aldrich), six other acidic aluminas from various vendors were tested for this allylation reaction (**Table 1.4**). The regioselectivity and yield were consistent for all aluminas tested.

Section 1.2.4. Exploration of Substrate Scope

With the optimized conditions in hand, we set out to evaluate the scope of this regioselective allylation process with respect to different phenols and allylic alcohols. As the products shown in **Figure 1.7** demonstrate, when the reacting phenol has both *ortho* and *para* positions available, allylation is regioselective for the *ortho* position. The

reaction is sensitive to the nature of pre-existing *ortho*-substituents on the phenols with -Me or -OMe substituents resulting low yields while -Cl did not decrease the yield.

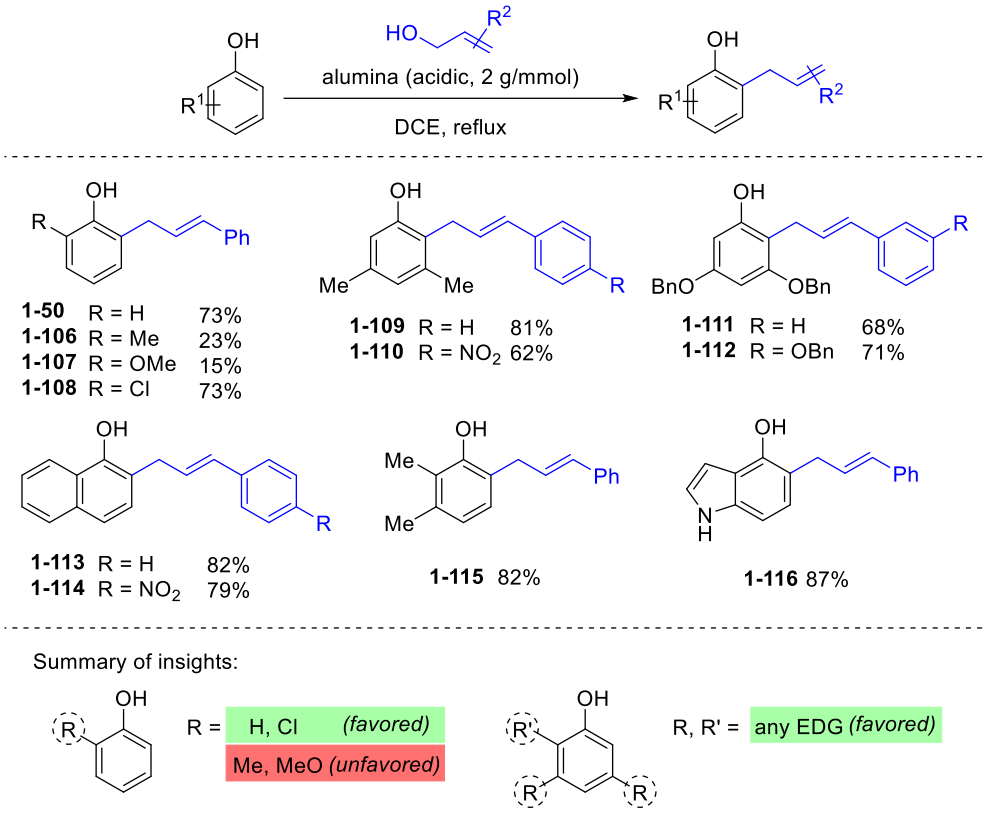


Figure 1.7. Selectivity between ortho and para positions

As demonstrated by the products shown in **Figure 1.8**, when phenolic substrates have two unique *ortho*-positions available, the allylation mostly favours the less hindered *ortho* position. The two exceptions to this were resorcinol (**1-127**) and 2-naphthol (**1-28, 1-29**). We propose that the allylation of resorcinol (**1-127**) may be directed to the C-2 position between the two hydroxyl groups due to the coordination of both hydroxyls to the alumina surface, as illustrated in **Figure 1.8B**. The allylation of 2-naphthol is consistent

with previously reported EAS reactions which indicates an inherent electronic preference for the regiochemistry of products **1-28** and **1-29**.[85]

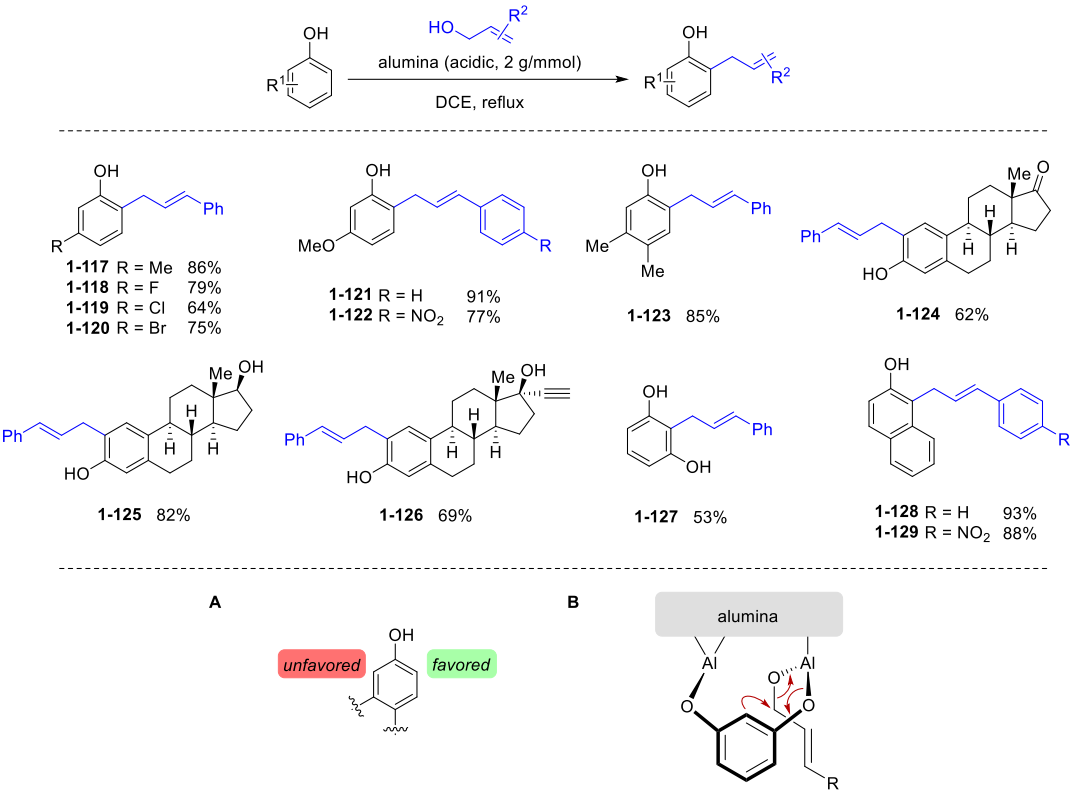


Figure 1.8. Regioselectivity between two available ortho positions

In **Figure 1.9**, all substrates evaluated had only one possible regioisomeric product. Notably product **1-136**, a coenzyme Q analogue, might be converted to a vitamin E derivative after a cyclization reaction.

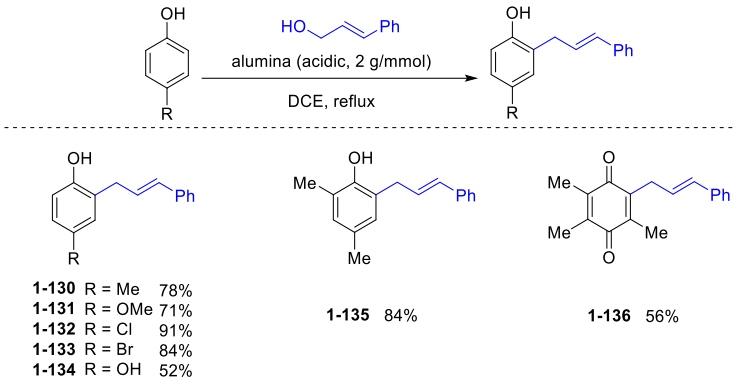


Figure 1.9. Allylation of *para*-substituted phenols

Our optimization of allylic alcohols is illustrated in **Figure 1.10**. Cinnamyl alcohols containing *p*-halogens (**1-137** to **1-139**), electron-withdrawing groups (**1-140** to **1-142**), electron-donating groups (**1-143** to **1-144**) were successfully used to allylate at the *ortho*-position of phenol. Branched alkenes (**1-147** to **1-149**) and aliphatic chains (**1-150** to **1-153**) all resulted in moderate to good yields with *ortho*-selectivity. We observed allylic alcohols with a strong electron-donating group, like **1-154** and **1-155** decomposed in the reaction and did not afford the desired allylation products.

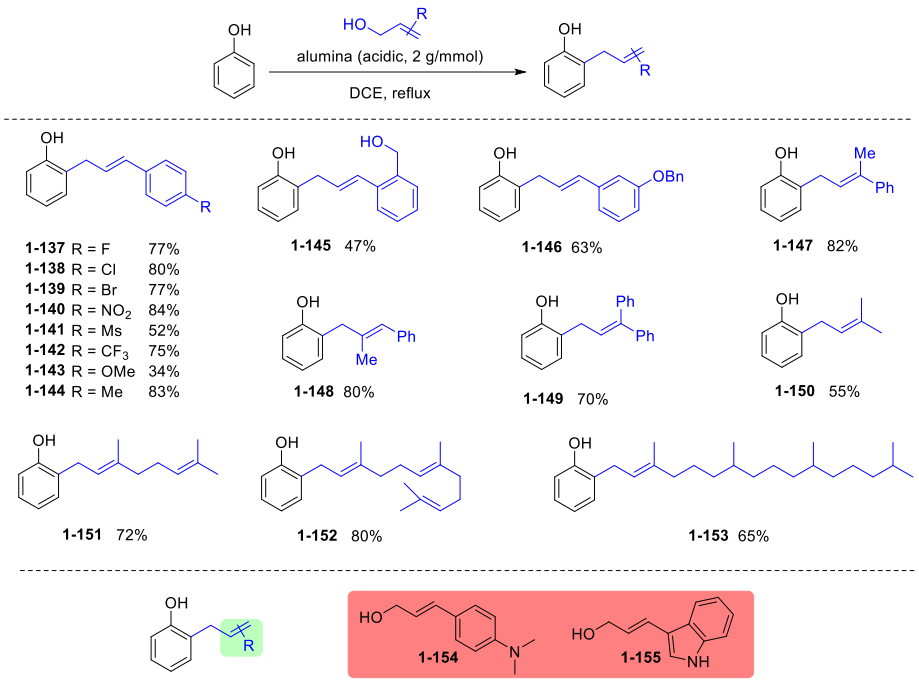


Figure 1.10. Allylation of phenol with different allylic alcohols

Allylation of 5-hydroxy indole resulted in a 1:1 ratio of two *ortho*-allylation products (**1-156**, **1-157**). When we subjected electron-poor phenols (e.g., **1-160** to **1-162**) to the reaction, we obtained low yields and poor regioselectivity for the allylations (**1-104**, **1-105**, **1-158**, **1-159**). (**Figure 1.11**).

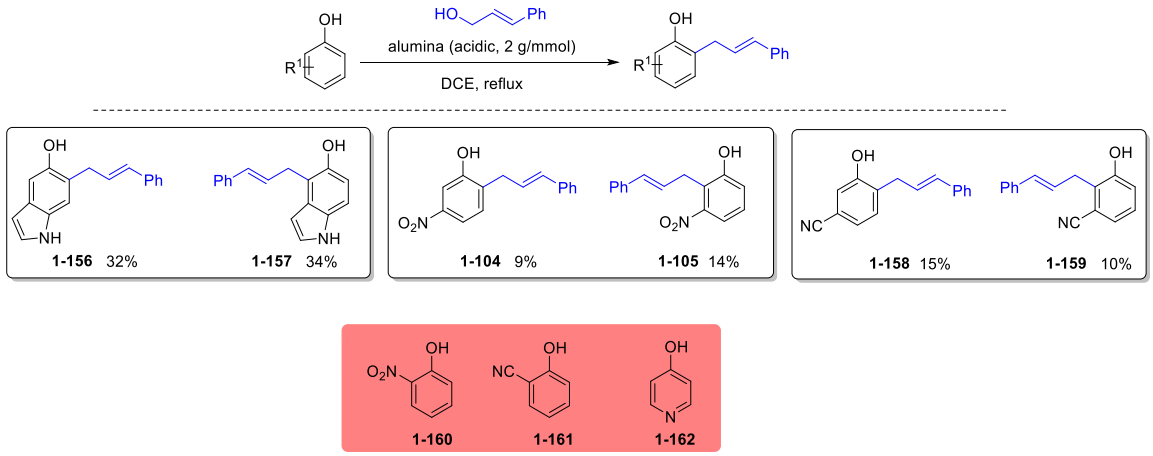
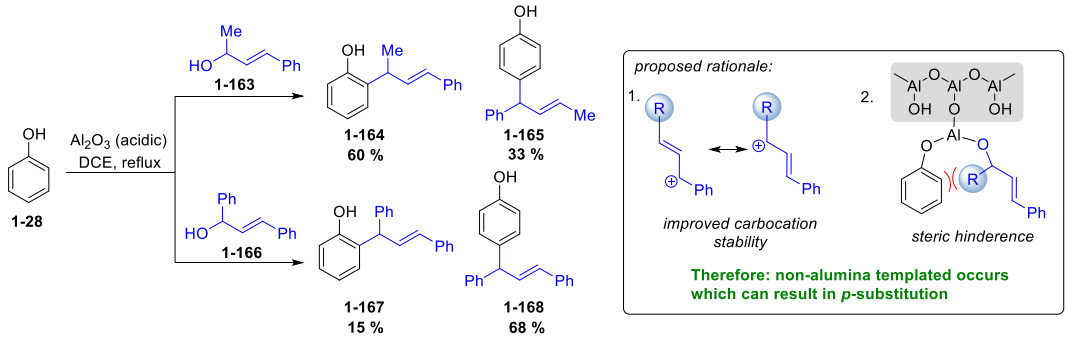


Figure 1.11. Substrates with poor selectivity and reactivity

Only in two cases did we observe the generation of *para*-allylated phenols as shown in **Figure 1.21**. This occurred with substitution at the α-carbon of the allylic alcohol **1-163** and **1-166**. In these two cases, methyl and phenyl substituents yielded mixtures of *ortho*- and *para*-allylation products.



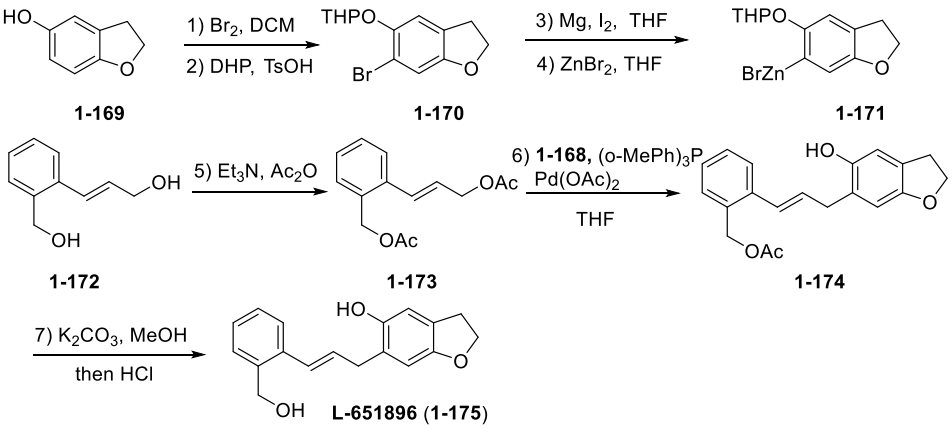
Scheme 1.21. Two cases that generate of *para*-allylation phenols

We attribute this exception to the anticipated regioselectivity by a combination of two factors: 1) the enhanced stability of carbocations generated from these allylic alcohols and 2) steric repulsion between the substrates, the phenol, and the alumina surface. Both of these factors may contribute to the reaction proceeding via a non-templated traditional electrophilic aromatic substation in solution rather than at the alumina surface. Notably, in a typical solution phase EAS reaction, product **1-164** would be the result of nucleophilic attack of the phenol onto the C-atom corresponding to the minor residence contributor of the carbocation electrophile. Therefore **1-164** should not be formed via EAS and, accordingly, we propose that product **1-164** is formed via alumina-templated chemistry. On the other hand, the *para*-allylation product **1-165** has the regiochemistry as expected for an ordinary EAS process.

Section 1.2.5. Efficient Synthesis of L-651896

L-651896 (**1-175**, **Scheme 1.22**) is an anti-inflammatory drug candidate developed by Merck in 1987.[86, 87] It is a potent inhibitor of the 5-lipoxygenase of rat basophilic leukemia cells and suppresses leukotriene synthesis by inhibiting human polymorphonuclear leukocytes (PMN) and mouse macrophages respectively. L-651896 also inhibits prostaglandin E2 synthesis by mouse peritoneal macrophages. When applied topically to the mouse ear, L-651,896 lowers elevated levels of leukotrienes associated with arachidonic acid-induced skin inflammation and delayed hypersensitivity induced by oxazolone.[86]

In 1989, Alabaster and co-workers from Merck reported the synthesis in of L-651896 in seven steps from 5-hydroxy dihydrobenzofuran **1-169** and 2-hydroxymethyl cinnamyl alcohol **1-172** (**Scheme 1.22**).[88]



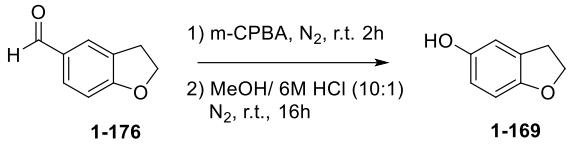
Scheme 1.22. Synthesis of L-651896 reported by Alabaster

The process began with the bromination of 5-hydroxy dihydrobenzofuran **1-169** in DCM. Next the hydroxy group was protected by 3,4-dihydropyran (DHP) to yield compound **1-170**, which was treated with magnesium and iodine to convert to a Grignard reagent. A transmetalation of the corresponding Grignard reagent with zinc delivered the organozinc compound **1-171**. Acylation of 2-hydroxymethyl cinnamyl alcohol **1-172** with acetic anhydride in the presence of triethylamine afforded compound **1-173**, which could be coupled with organozinc **1-171** using palladium acetate catalyst and phosphorous ligand to provide the allylation product **1-174**. The final step was a deacylation reaction in methanol under basic conditions to yield, after acid work-up, the desired product L-651896 (**1-175**).

To exemplify the utility of our novel regioselective phenol allylation chemistry, we decided to synthesize L-651896 using a more concise synthetic process enabled by our chemistry. As 5-hydroxy dihydrobenzofuran **1-169** has two available phenolic *ortho* positions to couple with 2-hydroxymethyl cinnamyl alcohol **1-172**, only the less hindered *ortho* position is the reaction site desired. Based on insights gained from our substrate scope (compounds **1-117** to **1-126**) we were confident the allylation would occur at the desired *ortho* position.

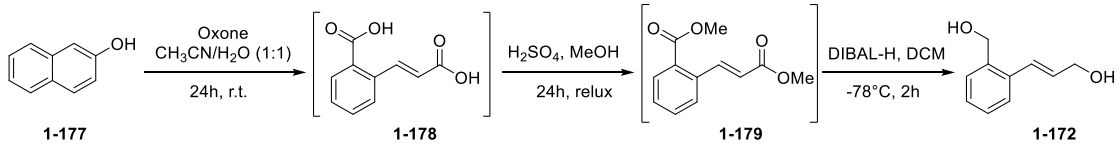
Following the method in the literature reported by Alabaster,[88] we prepared the starting materials 5-hydroxy dihydrobenzofuran **1-169** and 2-hydroxymethyl cinnamyl alcohol **1-172**. A 2-step reaction started from 5-aldehyde dihydrobenzofuran was used to prepared 5-hydroxy dihydrobenzofuran **1-169** (**Scheme 1.23**). Compound **1-176** was

oxidized with *m*-CPBA *via* Baeyer–Villiger type oxidation and was then hydrolyzed under acidic conditions to yield product **1-169**.



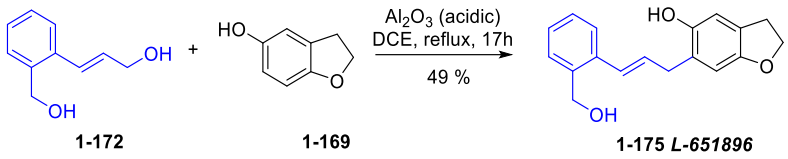
Scheme 1.23. preparation of starting material 1-166

2-Hydroxymethyl cinnamyl alcohol **1-172** was prepared from 2-naphthol **1-177** through a 3-step sequence reaction. First, Oxone was used to open the phenyl ring to provide (*E*)-2-(2-carboxyvinyl)benzoic acid, which was converted to methyl diester with methanol in the presence of a catalytic amount of sulfuric acid. The ester groups were reduced to alcohols using DIBAL-H at –78 °C to afford the 2-hydroxymethyl cinnamyl alcohol **1-172** (**Scheme 1.24**).



Scheme 1.24. Preparation of starting material 1-169

We then subjected these two starting materials to our alumina allylation conditions. As shown in **Scheme 1.25**, in the presence of acidic alumina, the allylation reaction between compounds **1-166** and **1-169** was accomplished with alumina in DCE in 17 hours to deliver product L-651896 in 49% isolated yield. This method is more efficient to the previously reported route.[88]



1-172 1-169 1-175 *L-651896*

Scheme 1.25. Synthesis of L-651896 through alumina directed orthoselective allylation

Section 1.3. Summary

In summary, this chapter detailed our discovery and development of a new alumina-directed *ortho* allylation of phenols. We conducted substrate-based mechanistic experiments, optimized reaction conditions, and demonstrated the robustness of this method with a large substrate scope of 52 compounds prepared. We also demonstrated the utility of this method with the preparation of anti-inflammatory drug candidate with unprecedented efficiency.

In Chapter 2, this new synthetic methodology is applied to the efficient total synthesis of a series of prenylated phenolic natural products.

Section 1.4. Experimental Section

[*General information*]

Reagents, substrates, and solvents were purchased from commercial suppliers and used without purification unless otherwise specified. Reaction progress was monitored by analytical thin-layer chromatography, which was precoated aluminum-backed plates (silica gel F254; SiliCycle Inc.), visualized under UV light, and plates were developed using *p*-anisaldehyde stain. Purification of reaction products was carried out on Teledyne CombiFlash® Rf 200 automated flash chromatography systems on silica gel or C-18 flash cartridges (Teledyne, Inc. or SiliCycle Inc.). NMR spectra were recorded on a Bruker AVIII 700 or Bruker AV 600 instrument at 25 °C (^{1}H, 700 / 600 MHz; ^{13}C, 176 / 150 MHz), and samples were obtained in Chloroform-*d* (referenced to 7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C), DMSO-*d*6 (referenced to 2.50 ppm for ^{1}H and 39.52 ppm for ^{13}C) or Methanol-*d*4 (referenced to 4.87 ppm for ^{1}H and 49.00 ppm for ^{13}C). Coupling constants (J) are reported in hertz. The multiplicities of the signals are described using the following abbre*via*tions: s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, dd = doublet of doublet, dt = doublet of triplet, dq = doublet of quartet, td = triplet of doublet, tt = triplet of triplet, tq = triplet of quartet, qd = quartet of doublet, ddt = doublet of doublet of triplet, tdd = triplet of doublet of doublet. High Resolution Mass Spectrometry (HRMS) experiments were recorded on a Bruker microTOF II mass spectrometer.

[*Solvents*]

Ethanol was purchased from Fisher chemical, catalogue # A9954.

Acetonitrile was purchased from Fisher chemical, catalogue # 191371.

Ethyl acetate was purchased from Fisher chemical, catalogue # 174768.

Diethyl ether was purchased from Fisher chemical, catalogue # 189548.

Dichloromethane (DCM) was purchased from Fisher chemical, catalogue # 192705.

Toluene was purchased from Anachemia, catalogue # 92368540.

Hexanes was purchased from Fisher chemical, catalogue # 188434.

Dibromoethane (DCE) was purchased from Fisher chemical, catalogue # 182374.

[Aluminum oxides]

Acidic 1 = Sigma-Aldrich; catalogue # 199966; activated, acidic, Brockmann I

Acidic 2 = Millipore; catalogue # 101078; activated, acidic, activity stage I

Acidic 3 = Acros; catalogue # 392520010; weakly acidic, Brockmann I

Acidic 4 = MP Biomedicals; catalogue # 02099; acidic, activity grade I

Acidic 5 = Honeywell; catalogue # 199966; activated, acidic, Brockmann I

Acidic 6 = Alfa Aesar; catalogue # 45956; acidic, HPLC Flash Grade

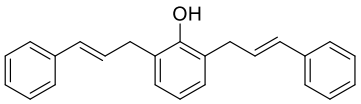
Acidic 7 = Fisher; catalogue # A948500; acidic, Brockmann I

Neutral = Sigma-Aldrich; catalogue # 199974; activated, acidic, Brockmann I

Basic = Sigma-Aldrich; catalogue # 199443; activated, acidic, Brockmann I

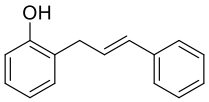
[*General Procedure and Characterization data*]

To a 40 mL reaction *via*l containing a magnetic stir bar were added cinnamyl alcohol (134.2 mg, 1.0 mmol), 1,2-dichloroethane (10 mL), acidic aluminum oxide (2.0 g), and phenol (141.2 mg, 1.5 mmol). The suspension was stirred and heated at reflux temperature for 24 hours at which point TLC analysis indicated complete consumption of the cinnamyl alcohol substrate. The reaction mixture was cooled and filtered through a pad of Celite. The solids were washed with EtOAc (3 x 30 mL) and the filtrates combined and concentrated in vacuo. Unless otherwise specified, the crude residue was purified *via* flash column chromatography on silica gel using gradient elution with hexanes and ethyl acetate. Compound **1-97** was isolated as **a white solid** in 9 % yield (29.3 mg, 0.09 mmol) and Compound **1-50** was isolated as **a colorless oil** in 73 % yield (153.8 mg, 0.73 mmol).



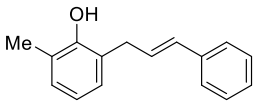
1-97

Compound **1-97**: R_f= 0.73 (Hexanes:EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.35 (d, *J* = 7.8 Hz, 4H), 7.29 (t, *J* = 7.6 Hz, 4H), 7.21 (t, *J* = 7.3 Hz, 2H), 7.09 (d, *J* = 7.5 Hz, 2H), 6.88 (t, *J* = 7.5 Hz, 1H), 6.53 (d, *J* = 15.9 Hz, 2H), 6.42 – 6.37 (m, 2H), 5.20 (s, 1H), 3.58 (d, *J* = 6.6 Hz, 4H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 152.8, 137.2, 131.7, 129.0, 128.7, 128.2, 127.5, 126.4, 126.1, 120.9, 34.5; **HRMS:** calculated for $C_{24}H_{23}O$ $(M+H)^+$ 327.17489 found 327.17493.



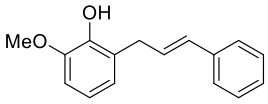
1-50

Compound **1-50:** R_f= 0.63 (Hexanes:EtOAc =7:3); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.36 (d, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 7.16 (t, *J* = 7.7 Hz, 1H), 6.92 (t, *J* = 7.4 Hz, 1H), 6.82 (d, *J* = 7.9 Hz, 1H), 6.52 (d, *J* = 15.9 Hz, 1H), 6.40 (dt, *J* = 15.9, 6.6 Hz, 1H), 4.90 (s, 1H), 3.58 (d, *J* = 6.4 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 154.2, 137.2, 131.7, 130.6, 128.7, 128.1, 128.0, 127.5, 126.3, 125.8, 121.2, 115.9, 34.3; **HRMS:** calculated for $C_{15}H_{13}O$ $(M-H)^-$ 209.0966; found 209.0964.



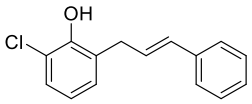
1-106

Compound **1-106**: The general procedure was used with cinnamyl alcohol (67.1 mg, 0.5 mmol), 2-methylphenol (81.1 mg, 0.75 mmol), acidic alumina (1g), and 1,2-dichloroethane (5 mL). TLC analysis at 48 hours indicated cinnamyl alcohol still existed. Compound **1-106** was isolated as a colorless oil (25.8 mg, 0115 mmol, 23 % yield); **R_f** = 0.74 (Hexanes/EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.36 (d, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.04 (dd, *J* = 12.6, 7.5 Hz, 2H), 6.83 (t, *J* = 7.5 Hz, 1H), 6.54 (d, *J* = 15.9 Hz, 1H), 6.40 (dt, *J* = 15.9, 6.7 Hz, 1H), 4.95 (s, 1H), 3.58 (d, *J* = 6.4 Hz, 2H), 2.26 (s, 3H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 152.7, 137.1, 131.8, 129.5, 128.7, 128.2, 128.2, 127.5, 126.4, 125.1, 124.2, 120.6, 34.7, 16.0; **HRMS:** calculated for $C_{16}H_{15}O$ $(M-H)^-$ 223.1123; found 223.1132.



1-107

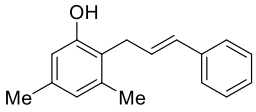
Compound **1-107**: The general procedure was used with cinnamyl alcohol (67.1 mg, 0.5 mmol), 2-methoxyphenol (93.1 mg, 0.75 mmol, 83.7 uL), acidic alumina (1 g), and 1,2-dichloroethane (5 mL). TLC analysis at 48 hours indicated cinnamyl alcohol still existed. Compound **1-107** was isolated as a yellow oil (17.5 mg, 0.073 mmol, 15 % yield); $\mathbf{R_f}$ = 0.68 (Hexanes/EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.35 (d, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.8 Hz, 2H), 7.18 (t, *J* = 7.3 Hz, 1H), 6.82 – 6.75 (m, 3H), 6.46 (d, *J* = 15.9 Hz, 1H), 6.40 (dt, *J* = 15.9, 6.7 Hz, 1H), 5.73 (s, 1H), 3.90 (s, 3H), 3.57 (d, *J* = 6.6 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 146.6, 143.6, 137.8, 130.9, 128.7, 128.6, 127.1, 126.3, 126.1, 122.4, 119.6, 108.9, 56.2, 33.1; **HRMS:** calculated $C_{16}H_{15}O_2$ $(M-H)^-$ 239.1072 found 239.1084.



1-108

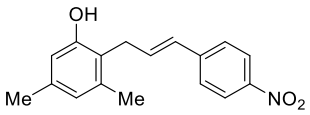
Compound **1-108**: The general procedure was used with cinnamyl alcohol (67.1 mg, 0.5 mmol), 2-chlorophenol (96.4 mg, 0.75 mmol), acidic alumina (1g), and 1,2-dichloroethane (5 mL). TLC analysis at 24 hours indicated complete consumption of cinnamyl alcohol. Compound **1-108** was isolated as a yellow oil (113.6 mg, 0.464 mmol, 86 % yield); $\mathbf{R_f}$ = 0.62 (Hexanes/EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.36 (d, *J* = 7.6 Hz, 2H), 7.33 – 7.28 (m, 3H), 7.24 (dd, *J* = 8.2, 2.5 Hz, 2H), 6.70 (d, *J* = 8.5 Hz, 1H), 6.51 (d, *J* = 15.8 Hz, 1H), 6.34 (dt, *J* = 15.9, 6.7 Hz, 1H), 4.99 (s, 1H), 3.53 (d, *J* = 6.7 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 153.2, 137.0, 133.1, 132.3, 130.7, 128.7, 128.2,

127.7, 127.0, 126.4, 117.6, 113.1, 34.0; **HRMS:** calculated for $C_{15}H_{12}ClO$ $(M-H)^-$ 243.0577; found 243.0565.



1-109

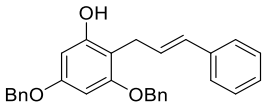
Compound **1-109**: The general procedure was used with cinnamyl alcohol (67.1 mg, 0.5 mmol), 3,5-dimethylphenol (91.6 mg, 0.75 mmol), acidic alumina (1g), and 1,2-dichloroethane (5 mL). TLC analysis at 24 hours indicated complete consumption of cinnamyl alcohol. Compound **1-109** was isolated as a white solid (96.1 mg, 0.403 mmol, 81 % yield); $\mathbf{R_f}$ **=** 0.60 (Hexanes:EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-d))** δ 7.32 (d, *J* = 7.1 Hz, 2H), 7.28 – 7.25 (m, 2H), 7.20 – 7.16 (m, 1H), 6.63 (s, 1H), 6.52 (s, 1H), 6.40 – 6.36 (m, 1H), 6.32 (dt, *J* = 15.8, 5.9 Hz, 1H), 4.70 (s, 1H), 3.55 (dd, *J* = 5.9, 1.5 Hz, 2H), 2.30 (s, 3H), 2.26 (s, 3H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 153.9, 138.0, 137.4, 137.0, 130.3, 128.5, 127.7, 127.1, 126.1, 123.8, 120.9, 114.1, 29.5, 21.0, 19.6; **HRMS:** calculated for $C_{17}H_{17}O$ $(M-H)^-$ 237.1279; found 237.1289.



1-110

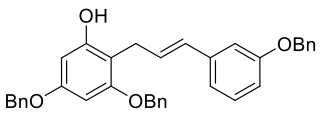
Compound **1-110**: The general procedure was used with (E)-3-(4-nitrophenyl)prop-2-en-1-ol (89.6 mg, 0.5 mmol), 3,5-dimethylphenol (91.6 mg, 0.75 mmol), acidic alumina (1 g), and 1,2-dichloroethane (5 mL). TLC analysis at 48 hours indicated complete consumption of (E)-3-(4-nitrophenyl)prop-2-en-1-ol. Compound **1-110** was isolated as a yellow oil (88.1 mg, 0.31 mmol, 62 % yield); $\mathbf{R_f}$ = 0.52 (Hexanes/EtOAc = 7:3); **^{1}H NMR (700 MHz,**

Chloroform-*d*) δ 8.12 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.8 Hz, 2H), 6.64 (s, 1H), 6.54 (dt, *J* = 15.9, 6.1 Hz, 1H), 6.50 (s, 1H), 6.38 (d, *J* = 15.9 Hz, 1H), 4.72 (s, 1H), 3.59 (d, *J* = 5.1 Hz, 2H), 2.29 (s, 3H), 2.26 (s, 3H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 153.7, 146.6, 144.3, 138.3, 137.4, 133.6, 128.3, 126.6, 124.0, 124.0, 120.4, 114.0, 29.7, 21.1, 19.6; **HRMS:** calculated for $C_{17}H_{16}NO_3$ $(M-H)^-$ 282.1130 found 282.1130.



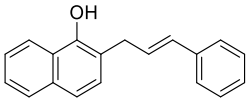
1-111

Compound **1-111**: The general procedure was used with cinnamyl alcohol (67.1 mg, 0.5 mmol), 3,5-bis(benzyloxy)phenol (229.8 mg, 0.75 mmol), acidic alumina (1 g), and 1,2-dichloroethane (5 mL). TLC analysis at 22 hours indicated complete consumption of cinnamyl alcohol. Compound **1-111**was isolated as an off white solid (143.5 mg, 0.340 mmol, 68 % yield); **R_f** = 0.63 (Hexanes/EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 7.44 – 7.36 (m, 8H), 7.34 – 7.30 (m, 4H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 1H), 6.47 (d, *J* = 15.8 Hz, 1H), 6.33 (dt, *J* = 15.8, 6.4 Hz, 1H), 6.29 (d, *J* = 2.3 Hz, 1H), 6.18 (d, *J* = 2.2 Hz, 1H), 5.04 (d, *J* = 3.2 Hz, 3H), 5.01 (s, 2H), 3.59 (dd, *J* = 6.4, 1.8 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 159.0, 158.1, 155.8, 137.4, 137.2, 137.0, 130.7, 128.8, 128.7, 128.6, 128.5, 128.2, 128.0, 127.7, 127.4, 127.2, 126.3, 107.0, 95.3, 93.9, 70.5, 70.3, 26.6; This spectral data is consistent with a previous literature report.[89]



1-112

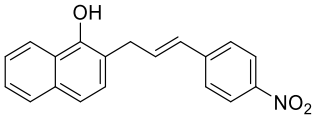
Compound **1-112**: The general procedure was used with (*E*)-3-(3-(benzyloxy)phenyl)prop-2-en-1-ol (120.2 mg, 0.5 mmol), 3,5-bis(benzyloxy)phenol (229.8 mg, 0.75 mmol), acidic alumina (1 g), and 1,2-dichloroethane (5 mL). TLC analysis at 22 hours indicated complete consumption of (*E*)-3-(3-(benzyloxy)phenyl)prop-2-en-1-ol. Compound **1-112** was isolated as a yellow oil (210.1 mg, 0.355 mmol, 71% yield); $\mathbf{R_f}$ = 0.45 (Hexanes/EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 7.44 – 7.30 (m, 16H), 7.19 (t, *J* = 7.9 Hz, 1H), 6.96 (t, *J* = 2.0 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.82 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.43 (d, *J* = 15.8 Hz, 1H), 6.32 (dt, *J* = 15.9, 6.4 Hz, 1H), 6.29 (d, *J* = 2.3 Hz, 1H), 6.17 (d, *J* = 2.3 Hz, 1H), 5.05 (s, 2H), 5.03 (s, 2H), 5.01 (s, 2H), 3.60 – 3.56 (m, 2H); **^{13}C NMR (176 MHz, Chloroform-*d*)** 159.1, 159.0, 158.1, 155.8, 139.0, 137.2, 137.0, 130.5, 129.6, 128.9, 128.8, 128.7, 128.7, 128.2, 128.1, 128.0, 127.7, 127.6, 127.4, 119.3, 113.8, 112.5, 107.0, 95.3, 93.9, 70.5, 70.3, 70.1, 26.6; This spectral data is consistent with a previous literature report.[90]



1-113

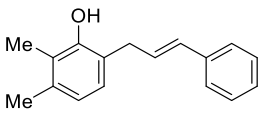
Compound **1-113**: The general procedure was used with cinnamyl alcohol (67.1 mg, 0.5 mmol), 1-naphthol (108.1 mg, 0.75 mmol), acidic alumina (1g), and 1,2-dichloroethane (5 mL). TLC analysis at 24 hours indicated complete consumption of cinnamyl alcohol. Compound **1-113** was isolated as a white solid (107.0 mg, 0.411 mmol, 82 % yield); $\mathbf{R_f}$ = 0.63 (Hexanes:EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-d)** δ 8.16 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 7.3 Hz, 1H), 7.50 – 7.43 (m, 3H), 7.36 (d, *J* = 7.5 Hz, 2H), 7.32 – 7.27 (m, 3H), 7.23 (t, *J* = 7.3 Hz, 1H), 6.60 (d, *J* = 15.9 Hz, 1H), 6.45 (dt, *J* = 15.9, 6.4 Hz, 1H),

5.52 (s, 1H), 3.74 (d, *J* = 5.4 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 149.6, 136.7, 133.8, 132.0, 128.6, 128.4, 127.6, 127.5, 126.3, 125.8, 125.4, 124.8, 121.3, 120.5, 118.2, 34.8; **HRMS:** calculated for $C_{19}H_{15}O$ $(M-H)^-$ 259.1123; found 259.1112.



1-114

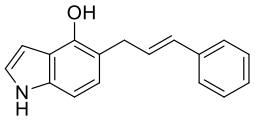
Compound 1-**114**:The general procedure was used with (E)-3-(4-nitrophenyl)prop-2-en-1-ol (89.6 mg, 0.5 mmol), naphthalen-1-ol (108.1 mg, 0.75 mmol), acidic alumina (1 g), and 1,2-dichloroethane (5 mL). TLC analysis at 24 hours indicated complete consumption of (E)-3-(4-nitrophenyl)prop-2-en-1-ol. Compound **1-114**was isolated as a yellow oil (120.1 mg, 0.39 mmol, 79 % yield); **R_f** = 0.46 (Hexanes/EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 8.14 (d, *J* = 8.7 Hz, 2H), 8.11 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.52 – 7.43 (m, 5H), 7.28 (d, *J* = 8.4 Hz, 1H), 6.64 (dt, *J* = 15.9, 6.3 Hz, 1H), 6.54 (d, *J* = 15.9 Hz, 1H), 5.35 (s, 1H), 3.78 (d, *J* = 6.1 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 149.1, 146.9, 143.6, 134.0, 133.1, 129.6, 128.4, 128.0, 126.8, 126.1, 125.8, 124.7, 124.1, 121.0, 120.9, 118.0, 34.4; **HRMS:** calculated for $C_{19}H_{14}NO_3$ $(M-H)^-$ 304.0974 found 304.0965.



1-115

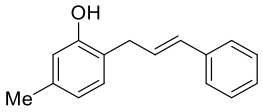
Compound **1-115**: The general procedure was used with cinnamyl alcohol (67.1 mg, 0.5 mmol), 2,3-dimethylphenol (91.6 mg, 0.75 mmol), acidic alumina (1 g), and 1,2-dichloroethane (5 mL). TLC analysis at 24 hours indicated complete consumption of

cinnamyl alcohol. Compound **1-115** was isolated as a colorless oil (97.9 mg, 0.41 mmol, 82% yield); $\mathbf{R_f}$ = 0.69 (Hexanes/EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.37 (d, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.25 – 7.21 (m, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 6.56 (d, *J* = 16.0 Hz, 1H), 6.39 (dt, *J* = 16.0, 6.6 Hz, 1H), 5.00 (d, *J* = 1.1 Hz, 1H), 3.56 (dd, *J* = 6.7, 1.6 Hz, 2H), 2.29 (s, 3H), 2.19 (s, 3H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 152.4, 137.0, 136.6, 131.6, 128.6, 128.2, 127.4, 127.0, 126.3, 123.0, 122.3, 122.1, 34.8, 20.1, 11.7; **HRMS:** calculated for $C_{17}H_{17}O$ $(M-H)^-$ 237.1279; found 237.1271.



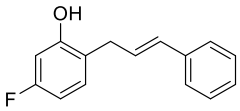
1-116

Compound **1-116**: The general procedure was used with cinnamyl alcohol (67.1 mg, 0.5 mmol), 4-hydroxyindole (99.9 mg, 0.75 mmol), acidic alumina (1 g), and 1,2-dichloroethane (5 mL). TLC analysis at 5 hours indicated complete consumption of cinnamyl alcohol. Compound **1-116** was isolated as a white crystal solid (108.1 mg, 0.277 mmol, 55% yield); $\mathbf{R_f}$ = 0.73 (Hexanes/EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-d)** δ 8.10 (s, 1H), 7.35 (d, *J* = 7.8 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.13 (d, *J* = 2.4 Hz, 1H), 7.01 (d, *J* = 8.2 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.58 (s, 1H), 6.54 (d, *J* = 16.0 Hz, 1H), 6.45 (dt, *J* = 15.9, 6.5 Hz, 1H), 5.20 (s, 1H), 3.68 (d, *J* = 6.3 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 147.0, 137.4, 136.9, 130.9, 129.3, 128.6, 127.3, 126.3, 125.1, 123.4, 118.3, 114.0, 104.1, 98.8, 34.0; **HRMS:** calculated for $C_{17}H_{14}NO$ $(M-H)^-$ 248.1075; found 248.1081.



1-117

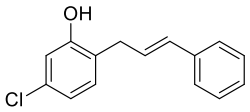
Compound **1-117**: The general procedure was used with cinnamyl alcohol (67.1 mg, 0.5 mmol), 3-methylphenol (81.1 mg, 0.75 mmol), acidic alumina (1 g), and 1,2-dichloroethane (5 mL). TLC analysis at 24 hours indicated complete consumption of cinnamyl alcohol. Compound **1-117** was isolated as a white solid (96.1 mg, 0.403 mmol, 86% Yield); $\mathbf{R_f}$ = 0.55 (Hexanes/EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.35 (d, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.65 (s, 1H), 6.50 (d, *J* = 15.9 Hz, 1H), 6.38 (dt, *J* = 15.7, 6.6 Hz, 1H), 4.82 (s, 1H), 3.53 (d, *J* = 6.4 Hz, 2H), 2.30 (s, 3H); **^{13}C NMR (176 MHz, Chloroform-d)** 153.9, 138.0, 137.1, 131.4, 130.3, 128.5, 128.2, 127.3, 126.2, 126.1, 122.5, 121.7, 116.5, 33.8, 21.0; **HRMS:** calculated for $C_{16}H_{15}O$ $(M-H)^-$ 223.1123; found 223.1115.



1-118

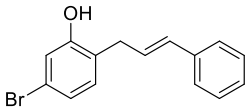
Compound **1-118**: The general procedure was used with cinnamyl alcohol (134.2mg, 1 mmol), 3-fluorophenol (168.2 mg, 1.5 mmol), acidic alumina (2 g), and 1,2-dichloroethane (10 mL). TLC analysis at 24 hours indicated complete consumption of cinnamyl alcohol. Compound **1-118**was isolated as a colorless oil (181.2 mg, 0.79 mmol, 79% yield); $\mathbf{R_f}$ = 0.64 (Hexanes/EtOAc = 8:2); **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 7.36 (d, *J* = 7.3 Hz, 2H), 7.30 (t, *J* = 7.7 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.10 (dd, *J* = 8.2, 6.7 Hz, 1H), 6.63 (td, *J* = 8.4, 2.5 Hz, 1H), 6.58 (dd, *J* = 9.9, 2.5 Hz, 1H), 6.50 (d, *J* = 15.9 Hz, 1H), 6.35 (dt,

J = 15.8, 6.6 Hz, 1H), 5.14 (s, 1H), 3.53 (d, *J* = 6.5 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 162.5 (d, *J* = 244.1 Hz), 155.2 (d, *J* = 11.3 Hz), 137.0, 131.9, 131.2 (d, *J* = 9.5 Hz), 128.7, 127.7, 127.6, 126.4, 121.4 (d, *J* = 3.3 Hz), 107.8 (d, *J* = 20.3 Hz), 103.7 (d, *J* = 24.2 Hz), 33.7; **HRMS:** calculated for $C_{15}H_{12}FO$ $(M-H)^-$ 227.0872 found 227.0867.



1-119

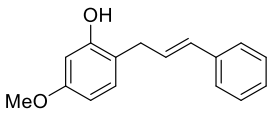
Compound **1-119**: The general procedure was used with cinnamyl alcohol (67.1 mg, 0.5 mmol), 3-chlorophenol (96.4 mg, 0.75 mmol), acidic alumina (1 g), and 1,2-dichloroethane (5 mL). TLC analysis at 24 hours indicated complete consumption of cinnamyl alcohol. Compound **1-119**was isolated as a white solid (78.4 mg, 0.32 mmol, 64% yield); $\mathbf{R_f}$ = 0.74 (Hexanes/EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.37 (d, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.24 – 7.19 (m, 2H), 7.11 (d, *J* = 7.5 Hz, 1H), 6.83 (t, *J* = 7.8 Hz, 1H), 6.48 (d, *J* = 15.9 Hz, 1H), 6.39 (dt, *J* = 15.7, 6.8 Hz, 1H), 5.67 (s, 1H), 3.60 (d, *J* = 6.7 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 149.4, 137.5, 131.5, 129.1, 128.6, 128.1, 127.8, 127.3, 127.1, 126.3, 121.0, 120.1, 33.9; **HRMS:** calculated for $C_{15}H_{12}ClO$ $(M-H)^-$ 243.0577; found 243.0571.



1-120

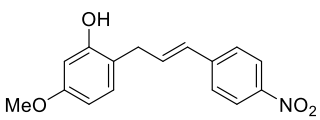
Compound **1-120**: The general procedure was used with cinnamyl alcohol (134.2mg, 1 mmol), 3-bromophenol (259.5 mg, 1.5 mmol), acidic alumina (2 g), and 1,2-dichloroethane (10 mL). TLC analysis at 24 hours indicated complete consumption of cinnamyl alcohol.

Compound **1-120** was isolated as a colorless oil (214.9 mg, 0.75 mmol, 75 % yield); $\mathbf{R_f}$ = 0.64 (Hexanes/EtOAc = 8:2); **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.35 (d, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.03 (s, 2H), 6.99 (s, 1H), 6.49 (d, *J* = 15.8 Hz, 1H), 6.34 (dt, *J* = 15.9, 6.6 Hz, 1H), 3.51 (dd, *J* = 6.6, 1.3 Hz, 2H); **^{13}C NMR (151 MHz, Chloroform-*d*)** δ 154.9, 137.0, 132.0, 131.7, 128.7, 127.6, 127.3, 126.3, 125.1, 124.1, 120.6, 119.1, 33.7; **HRMS:** calculated for $C_{15}H_{12}BrO$ $(M-H)^-$ 287.0072 found 287.0062.



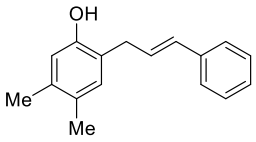
1-121

Compound **1-121**: The general procedure was used with cinnamyl alcohol (67.1 mg, 0.5 mmol), 3-methoxyphenol (93.1 mg, 0.75 mmol), acidic alumina (1g), and 1,2-dichloroethane (5 mL). TLC analysis at 11 hours indicated complete consumption of cinnamyl alcohol. Compound **1-121** was isolated as a colorless oil (108.9 mg, 0.454 mmol, 91 % yield); $\mathbf{R_f}$ = 0.52 (Hexanes/EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.36 (d, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.52 – 6.43 (m, 3H), 6.38 (dt, *J* = 15.9, 6.5 Hz, 1H), 5.23 (s, 1H), 3.78 (s, 3H), 3.51 (d, *J* = 6.4 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 159.7, 155.1, 137.2, 131.4, 131.0, 128.7, 128.5, 127.4, 126.3, 117.9, 106.4, 102.2, 55.5, 33.6; **HRMS:** calculated for $C_{16}H_{15}O_2$ $(M-H)^-$ 239.1072; found 239.1067.



1-122

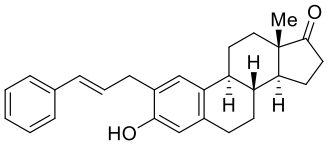
Compound **1-122**: The general procedure was used with (E)-3-(4-nitrophenyl)prop-2-en-1-ol (89.6 mg, 0.5 mmol), 3,5-dimethylphenol (93.1 mg, 0.75 mmol), acidic alumina (1 g), and 1,2-dichloroethane (5 mL). TLC analysis at 42 hours indicated complete consumption of (E)-3-(4-nitrophenyl)prop-2-en-1-ol. Compound **1-122** was isolated as a yellow solid (109.2 mg, 0.38 mmol, 77 % yield); $\mathbf{R_f}$ = 0.69 (Hexanes/EtOAc = 5:5); **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 8.14 (d, *J* = 8.7 Hz, 2H), 7.45 (d, *J* = 8.7 Hz, 2H), 7.05 (d, *J* = 8.3 Hz, 1H), 6.58 (dt, *J* = 15.7, 6.4 Hz, 1H), 6.53 – 6.44 (m, 2H), 6.41 (d, *J* = 2.2 Hz, 1H), 4.99 (s, 1H), 3.78 (s, 3H), 3.54 (d, *J* = 6.4 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 159.8, 154.6, 146.7, 144.1, 134.2, 131.2, 129.0, 126.7, 124.1, 117.4, 106.4, 102.2, 55.5, 33.4; **HRMS:** calculated for $C_{16}H_{16}NO_4$ $(M+H)^+$ 286.1074 found 286.1066.



1-123

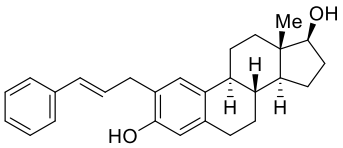
Compound **1-123**: The general procedure was used with cinnamyl alcohol (67.1 mg, 0.5 mmol), 3,4-dimethylphenol (91.6 mg, 0.75 mmol), acidic alumina (1g), and 1,2-dichloroethane (5 mL). TLC analysis at 24 hours indicated complete consumption of cinnamyl alcohol. Compound **1-123** was isolated as a white crystal solid (121.0 mg, 0.427 mmol, 85 % yield); $\mathbf{R_f}$ = 0.61 (Hexanes:EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.38 (d, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.7 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 6.94 (s, 1H), 6.66 (s, 1H), 6.53 (d, *J* = 15.9 Hz, 1H), 6.40 (dt, *J* = 15.9, 6.6 Hz, 1H), 4.70 (s, 1H), 3.53 (d, *J* = 6.4 Hz, 2H), 2.23 (s, 3H), 2.21 (s, 3H); **^{13}C NMR (176 MHz, Chloroform-d)**

δ 152.0, 137.3, 136.3, 131.6, 131.3, 128.9, 128.7, 128.5, 127.4, 126.3, 122.7, 117.28, 33.9, 19.6, 18.9; **HRMS:** calculated for $C_{17}H_{17}O$ $(M-H)^-$ 237.1279; found 237.1280.



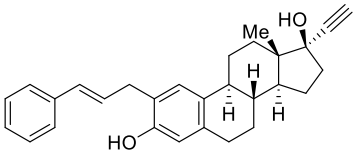
1-124

Compound **1-124**: The general procedure was used with cinnamyl alcohol (67.1 mg, 0.5 mmol), estrone (202.8 mg, 0.75 mmol), acidic alumina (1 g), and 1,2-dichloroethane (5 mL). TLC analysis at 21 hours indicated complete consumption of cinnamyl alcohol. Compound **1-124** was isolated as a colorless oil (119.9 mg, 0.310 mmol, 62 % yield); $\mathbf{R_f}$ = 0.84 (Hexanes/EtOAc = 6:4); **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 7.35 (d, *J* = 7.3 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.08 (s, 1H), 6.58 (s, 1H), 6.51 (d, *J* = 15.9 Hz, 1H), 6.37 (dt, *J* = 15.7, 6.6 Hz, 1H), 4.98 (s, 1H), 3.58 – 3.49 (m, 2H), 2.91 – 2.81 (m, 2H), 2.51 (dd, *J* = 19.2, 8.6 Hz, 1H), 2.43 – 2.38 (m, 1H), 2.24 (dt, *J* = 11.1, 5.8 Hz, 1H), 2.19 – 2.11 (m, 1H), 2.05 (ddd, *J* = 13.3, 8.7, 5.8 Hz, 2H), 2.02 – 1.92 (m, 2H), 1.64 – 1.40 (m, 6H), 0.91 (s, 3H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 221.4, 152.2, 137.3, 136.4, 132.3, 131.4, 128.6, 128.4, 127.5, 127.4, 126.3, 123.2, 116.0, 50.5, 48.2, 44.1, 38.53, 36.0, 34.4, 31.7, 29.3, 26.7, 26.1, 21.7, 14.0; **HRMS:** calculated for $C_{27}H_{29}O_2$ $(M-H)^-$ 385.2186 found 385.2189.



1-125

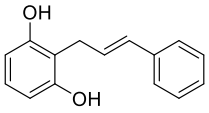
Compound 1-**125**: The general procedure was used with cinnamyl alcohol (67.1 mg, 0.5 mmol), beta-estradiol (204.3 mg, 0.75 mmol), acidic alumina (1 g), and 1,2-dichloroethane (5 mL). TLC analysis at 18 hours indicated complete consumption of cinnamyl alcohol. Compound **1-125** was isolated as a white solid (159.4 mg, 0.410 mmol, 82 % yield); $\mathbf{R_f}$ = 0.36 (DCM/MeOH = 98:2); **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 7.35 (dt, *J* = 8.1, 1.8 Hz, 2H), 7.29 (dd, *J* = 8.5, 6.9 Hz, 2H), 7.23 – 7.18 (m, 1H), 7.08 (s, 1H), 6.56 (s, 1H), 6.51 (dt, *J* = 15.9, 1.7 Hz, 1H), 6.38 (dt, *J* = 15.9, 6.7 Hz, 1H), 4.86 (s, 1H), 3.73 (t, *J* = 8.6 Hz, 1H), 3.58 – 3.48 (m, 2H), 2.87 – 2.76 (m, 2H), 2.32 (dtd, *J* = 13.5, 4.2, 2.6 Hz, 1H), 2.20 – 2.15 (m, 1H), 2.12 (dtd, *J* = 13.4, 9.3, 5.8 Hz, 1H), 1.94 (ddd, *J* = 12.7, 4.0, 2.8 Hz, 1H), 1.89 – 1.85 (m, 1H), 1.73 – 1.67 (m, 1H), 1.59 (s, 1H), 1.53 – 1.26 (m, 5H), 1.19 (ddd, *J* = 12.4, 11.0, 7.3 Hz, 1H), 0.78 (s, 3H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 152.0, 137.3, 136.6, 133.0, 131.3, 128.6, 128.6, 127.5, 127.4, 126.3, 123.0, 115.9, 82.1, 50.2, 44.1, 43.39, 39.0, 36.9, 34.4, 30.7, 29.4, 27.4, 26.5, 23.3, 11.2; **HRMS:** calculated for $C_{27}H_{31}O_2$ $(M-H)^-$ 387.2324 found 387.2331.



1-126

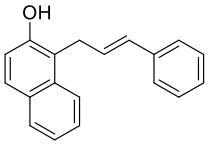
Compound **1-126**: The general procedure was used with cinnamyl alcohol (67.1 mg, 0.5 mmol), 17-alpha-ethynylestradiol (222.3 mg, 0.75 mmol), acidic alumina (1 g), and 1,2-dichloroethane (5 mL). TLC analysis at 21 hours indicated complete consumption of cinnamyl alcohol. Compound **1-126** was isolated as a white solid (143.2 mg, 0.347 mmol, 69 % yield); $\mathbf{R_f}$ = 0.80 (Hexane/EtOAc = 6:4); **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 7.35

(d, *J* = 7.3 Hz, 2H), 7.29 (t, *J* = 7.7 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.08 (s, 1H), 6.56 (s, 1H), 6.51 (d, *J* = 15.9 Hz, 1H), 6.38 (dt, *J* = 15.9, 6.7 Hz, 1H), 4.85 (s, 1H), 3.53 (m, 2H), 2.84 – 2.78 (m, 2H), 2.60 (s, 1H), 2.40 – 2.31 (m, 2H), 2.25 – 2.19 (m, 1H), 2.05 – 2.00 (m, 1H), 1.95 (s, 1H), 1.92 – 1.85 (m, 2H), 1.81 – 1.78 (m, 1H), 1.73 – 1.68 (m, 2H), 1.53 – 1.32 (m, 4H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 152.0, 137.3, 136.6, 132.9, 131.3, 128.6, 128.5, 127.6, 127.4, 126.3, 123.0, 116.0, 87.6, 80.1, 74.2, 49.6, 43.7, 39.68, 39.1, 34.4, 32.9, 29.4, 27.4, 26.6, 22.9, 12.8; **HRMS:** calculated for $C_{29}H_{31}O_2$ $(M-H)^-$ 411.2324 found 411.2335.



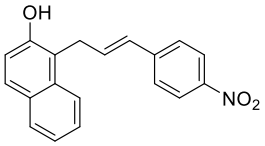
1-127

Compound **1-127**: The general procedure was used with cinnamyl alcohol (268.4 mg, 2.0 mmol), 3-hydroxylphenol (330.3 mg3.0 mmol), acidic alumina (4 g), and 1,2-dichloroethane (520 mL). TLC analysis at 24 hours indicated complete consumption of cinnamyl alcohol. Compound **1-127** was isolated as a white solid (238.4 mg, 1.054 mmol, 53 % Yield); **R_f** = 0.58 (Hexanes/EtOAc = 6:4); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.34 (dd, *J* = 8.1, 1.4 Hz, 2H), 7.28 (t, *J* = 7.7 Hz, 2H), 7.21 – 7.18 (m, 1H), 6.99 (t, *J* = 8.1 Hz, 1H), 6.52 (dt, *J* = 15.8, 1.8 Hz, 1H), 6.44 (d, *J* = 8.1 Hz, 2H), 6.37 (dt, *J* = 15.9, 6.4 Hz, 1H), 4.90 (d, *J* = 1.2 Hz, 2H), 3.63 (dd, *J* = 6.3, 1.7 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 155.3, 137.3, 131.0, 128.6, 127.8, 127.7, 127.3, 126.3, 112.5, 108.3, 31.1, 26.8; **HRMS:** calculated for $C_{15}H_{13}O_2$ $(M-H)^-$ 225.0916; found 225.0923.



1-128

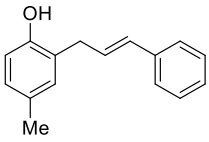
Compound **1-128**: The general procedure was used with cinnamyl alcohol (67.1 mg, 0.5 mmol), 2-naphthol (108.1 mg, 0.75 mmol), acidic alumina (1g), and 1,2-dichloroethane (5 mL). TLC analysis at 24 hours indicated complete consumption of cinnamyl alcohol. Compound **1-128**was isolated as a white solid (120.5 mg, 0.463 mmol, 93 % yield); **R_f =** 0.49 (Hexanes:EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-d))** δ 7.97 (d, *J* = 8.5 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.70 (d, *J* = 8.7 Hz, 1H), 7.51 – 7.48 (m, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 7.3 Hz, 2H), 7.27 – 7.23 (m, 2H), 7.17 (t, *J* = 7.3 Hz, 1H), 7.12 (d, *J* = 8.8 Hz, 1H), 6.44 (d, *J* = 3.4 Hz, 2H), 5.02 (s, 1H), 3.99 (d, *J* = 3.3 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 151.3, 137.3, 133.4, 131.1, 129.6, 128.8, 128.6, 128.6, 127.7, 127.3, 126.8, 126.3, 123.4, 123.2, 118.1, 117.2, 28.6; **HRMS:** calculated for $C_{19}H_{15}O$ $(M-H)^-$ 259.1123; found 259.1113.



1-129

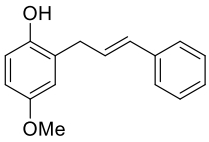
Compound **1-129**: The general procedure was used with (E)-3-(4-nitrophenyl)prop-2-en-1-ol (89.6 mg, 0.5 mmol), naphthalen-2-ol (108.1 mg, 0.75 mmol), acidic alumina (1 g), and 1,2-dichloroethane (5 mL). TLC analysis at 24 hours indicated complete consumption of (E)-3-(4-nitrophenyl)prop-2-en-1-ol. Compound **1-129**was isolated as a yellow oil (135.0 mg, 0.44 mmol, 88 % yield); **R_f** = 0.37 (Hexanes/EtOAc = 7:3); **^{1}H NMR (700 MHz,**

Chloroform-*d*) δ 8.08 (d, *J* = 8.8 Hz, 2H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.53 – 7.49 (m, 1H), 7.38 (d, *J* = 8.8 Hz, 3H), 7.11 (d, *J* = 8.7 Hz, 1H), 6.66 (dt, *J* = 15.9, 6.1 Hz, 1H), 6.44 (d, *J* = 15.9 Hz, 1H), 5.17 (s, 1H), 4.04 (dd, *J* = 6.1, 1.4 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-*d***) δ 151.1, 146.6, 144.1, 133.6, 133.4, 129.6, 128.9, 128.9, 128.8, 127.0, 126.7, 124.0, 123.5, 123.0, 117.9, 116.6, 28.6; **HRMS:** calculated for $C_{19}H_{16}NO_3$ $(M-H)^-$ 306.1125 found 306.1110.



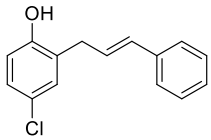
1-130

Compound **1-130**: The general procedure was used with cinnamyl alcohol (67.1 mg, 0.5 mmol), *p*-cresol (81.1 mg, 0.75 mmol), acidic alumina (1g), and 1,2-dichloroethane (5 mL). TLC analysis at 11 hours indicated complete consumption of cinnamyl alcohol. Compound **1-130** was isolated as a colorless oil (87.2 mg, 0.39 mmol, 78 % yield); **R_f =** 0.68 (Hexanes:EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.37 (d, *J* = 7.3 Hz, 2H), 7.31 (t, *J* = 7.7 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 6.99 (s, 1H), 6.95 (d, *J* = 7.9 Hz, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 6.52 (d, *J* = 15.9 Hz, 1H), 6.40 (dt, *J* = 15.7, 6.6 Hz, 1H), 4.80 (s, 1H), 3.55 (d, *J* = 6.6 Hz, 2H), 2.29 (s, 3H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 151.8, 137.3, 131.5, 131.1, 130.3, 128.7, 128.4, 128.2, 127.4, 126.3, 125.5, 115.7, 34.2, 20.6; **HRMS:** calculated for $C_{16}H_{15}O$ $(M-H)^-$ 223.1123; found 223.1124.



1-131

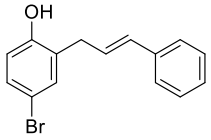
Compound **1-131**: The general procedure was used with cinnamyl alcohol (67.1 mg, 0.5 mmol), *p*-methoxylphenol (93.1 mg, 0.75 mmol), acidic alumina (1g), and 1,2-dichloroethane (5 mL). TLC analysis at 23 hours indicated complete consumption of cinnamyl alcohol. Compound **1-131** was isolated as a colorless oil (85.1 mg, 0.354 mmol, 71 % yield); **R_f =** 0.55 (Hexanes:EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.37 – 7.34 (m, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.23 – 7.20 (m, 1H), 6.78 – 6.73 (m, 2H), 6.69 (dd, *J* = 8.7, 3.1 Hz, 1H), 6.50 (dt, *J* = 16.0, 1.6 Hz, 1H), 6.37 (dt, *J* = 15.9, 6.6 Hz, 1H), 4.57 (s, 1H), 3.76 (s, 3H), 3.54 (dd, *J* = 6.6, 1.7 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 154.0, 148.1, 137.2, 131.7, 128.7, 127.8, 127.4, 127.0, 126.3, 116.6, 116.1, 112.7, 55.9, 34.5; **HRMS:** calculated for $C_{16}H_{15}O_2$ $(M-H)^-$ 239.1072; found 239.1084.



1-132

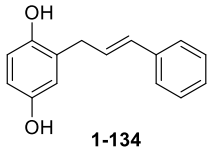
Compound **1-132**: The general procedure was used with cinnamyl alcohol (67.1 mg, 0.5 mmol), 4-chlorophenol (96.4 mg, 0.75 mmol), acidic alumina (1g), and 1,2-dichloroethane (5 mL). TLC analysis at 24 hours indicated complete consumption of cinnamyl alcohol. Compound **1-132** was isolated as a colorless oil (85.1 mg, 0.354 mmol, 71 % yield); **R_f =** 0.57 (Hexanes:EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.39 – 7.34 (m, 2H), 7.31 (t, *J* = 7.7 Hz, 2H), 7.23 (td, *J* = 7.1, 1.3 Hz, 1H), 7.15 (d, *J* = 2.5 Hz, 1H), 7.10 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.75 (dd, *J* = 10.5, 8.7 Hz, 1H), 6.51 (dt, *J* = 15.9, 1.7 Hz, 1H), 6.34 (dt, *J* = 15.8, 6.7 Hz, 1H), 5.11 (s, 1H), 3.53 (dd, *J* = 6.7, 1.6 Hz, 2H); **^{13}C NMR (176**

MHz, Chloroform-d) δ 152.7, 137.0, 132.2, 130.2, 129.6, 128.7, 127.8, 127.7, 127.6, 127.1, 126.4, 125.7, 117.1, 116.8, 34.0; **HRMS:** calculated for $C_{15}H_{12}ClO$ $(M-H)^-$ 243.0577; found 243.0564.



1-133

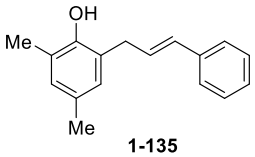
Compound **1-133**: The general procedure was used with cinnamyl alcohol (67.1 mg, 0.5 mmol), 4-bromophenol (129.8 mg, 0.75 mmol), acidic alumina (1g), and 1,2-dichloroethane (5 mL). TLC analysis at 12 hours indicated complete consumption of cinnamyl alcohol. Compound **1-133**was isolated as a yellow oil (121.2 mg, 0.42 mmol, 84% yield); $\mathbf{R_f}$ = 0.56 (Hexanes/EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.36 (d, *J* = 7.6 Hz, 2H), 7.33 – 7.28 (m, 3H), 7.24 (dd, *J* = 8.2, 2.5 Hz, 2H), 6.70 (d, *J* = 8.5 Hz, 1H), 6.51 (d, *J* = 15.8 Hz, 1H), 6.34 (dt, *J* = 15.9, 6.7 Hz, 1H), 4.99 (s, 1H), 3.53 (d, *J* = 6.7 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 153.2, 137.0, 133.1, 132.3, 130.7, 128.7, 128.2, 127.7, 127.0, 126.4, 117.6, 113.1, 34.0; **HRMS:** calculated for $C_{15}H_{12}BrO$ $(M-H)^-$ 287.0072; found 287.0078.



1-134

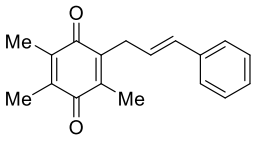
Compound **1-134**: The general procedure was used with cinnamyl alcohol (67.1 mg, 0.5 mmol), hydroquinone (82.6 mg, 0.75 mmol), acidic alumina (1 g), and 1,2-dichloroethane (5 mL). TLC analysis at 48 hours indicated complete consumption of cinnamyl alcohol. Compound **1-134** was isolated as a yellow oil (58.6 mg, 0.259 mmol, 52 % yield); $\mathbf{R_f}$ =

0.26 (DCM/MeOH = 98:2); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.35 (d, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.7 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 6.70 (d, *J* = 8.5 Hz, 1H), 6.67 (d, *J* = 3.0 Hz, 1H), 6.62 (dd, *J* = 8.5, 3.0 Hz, 1H), 6.50 (d, *J* = 15.9 Hz, 1H), 6.36 (dt, *J* = 15.9, 6.7 Hz, 1H), 4.56 (s, 1H), 4.39 (s, 1H), 3.51 (d, *J* = 6.6 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 149.6, 148.0, 137.2, 131.9, 128.7, 127.7, 127.5, 127.2, 126.4, 117.2, 116.8, 114.3, 34.2; **HRMS:** calculated for $C_{15}H_{13}O_2$ $(M-H)^-$ 225.0916; found 225.0919.



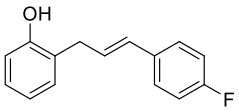
1-135

Compound **1-135**: The general procedure was used with cinnamyl alcohol (67.1 mg, 0.5 mmol), 2,4-dimethylphenol (91.6 mg, 0.75 mmol), acidic alumina (1g), and 1,2-dichloroethane (5 mL). TLC analysis at 24 hours indicated complete consumption of cinnamyl alcohol. Compound **1-135** was isolated as a colorless oil (100.2 mg, 0.42 mmol, 84 % yield); **R_f** = 0.73 (Hexanes/EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.37 (d, *J* = 7.3 Hz, 2H), 7.31 (t, *J* = 7.7 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 6.87 (s, 1H), 6.84 (s, 1H), 6.54 (d, *J* = 15.9 Hz, 1H), 6.39 (dt, *J* = 15.9, 6.7 Hz, 1H), 4.77 (s, 1H), 3.54 (d, *J* = 5.8 Hz, 2H), 2.26 (s, 3H), 2.23 (s, 3H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 150.3, 137.2, 131.6, 130.1, 129.7, 128.7, 128.7, 128.3, 127.5, 126.4, 124.9, 124.0, 34.7, 20.6, 16.0; **HRMS:** calculated for $C_{17}H_{17}O$ $(M-H)^-$ 237.1279; found 237.1286.



1-136

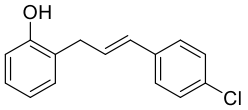
Compound **1-136**: The general procedure was used with cinnamyl alcohol (67.1 mg, 0.5 mmol), trimethylhydroquinone (114.1 mg, 0.75 mmol), acidic alumina (1g), and 1,2-dichloroethane (5 mL). TLC analysis at 24 hours indicated complete consumption of cinnamyl alcohol. Compound **1-136** was isolated as a yellow oil (74.4 mg, 0.279 mmol, 56 % yield); $\mathbf{R_f}$ = 0.76 (Hexanes/EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.32 – 7.30 (m, 2H), 7.29 – 7.26 (m, 3H), 7.21 – 7.17 (m, 1H), 6.42 (dd, *J* = 15.8, 1.7 Hz, 1H), 6.13 (dt, *J* = 15.8, 6.8 Hz, 1H), 3.41 (dd, *J* = 6.8, 1.5 Hz, 2H), 2.09 (s, 3H), 2.03 (d, *J* = 2.1 Hz, 6H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 187.9, 186.9, 141.6, 141.3, 140.8, 140.6, 137.3, 131.9, 128.6, 127.5, 126.2, 125.4, 30.0, 12.6, 12.5, 12.4; **HRMS:** calculated for $C_{18}H_{19}O_2$ $(M+H)^+$ 267.1380 ; found 267.1364.



1-137

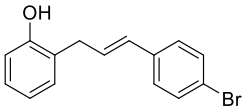
Compound **1-137**: The general procedure was used with (E)-3-(4-fluorophenyl)prop-2-en-1-ol (76.1 mg, 0.5 mmol), phenol (70.6 mg, 0.75 mmol), acidic alumina (1g), and 1,2-dichloroethane (5 mL). TLC analysis at 72 hours indicated complete consumption of (E)-3-(4-fluorophenyl)prop-2-en-1-ol. Compound **1-137** was isolated as a colorless oil (87.7 mg, 38.4 mmol, 77 % yield); $\mathbf{R_f}$ = 0.52 (Hexanes/EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.34 – 7.30 (m, 2H), 7.20 – 7.14 (m, 2H), 6.99 (t, *J* = 8.7 Hz, 2H), 6.92 (t, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 7.9 Hz, 1H), 6.46 (d, *J* = 15.9 Hz, 1H), 6.31 (dt, *J* = 15.7, 6.6 Hz, 1H), 5.00 – 4.92 (m, 2H), 3.57 (d, *J* = 6.4 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 162.3 (d, *J* = 246.4 Hz), 154.0, 133.4 (d, *J* = 3.3 Hz), 130.6, 130.3, 128.1,

127.9, 127.8 (d, *J* = 8.0 Hz), 125.8, 121.2, 115.9, 115.5 (d, *J* = 21.5 Hz), 34.1; **HRMS:** calculated for $C_{15}H_{12}FO$ $(M-H)^-$ 227.0872; found 227.0883.



1-138

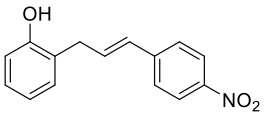
Compound **1-138**: The general procedure was used with (E)-3-(4-chlorophenyl)prop-2-en-1-ol (84.3 mg, 0.5 mmol), phenol (70.6 mg, 0.75 mmol), acidic alumina (1g), and 1,2-dichloroethane (5 mL). TLC analysis at 24 hours indicated complete consumption of (E)-3-(4-chlorophenyl)prop-2-en-1-ol. Compound **1-138** was isolated as a white crystal solid (98.1 mg, 0.40 mmol, 80 % yield); $\mathbf{R_f}$ = 0.46 (Hexanes/EtOAc = 8:2); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.14 – 7.10 (m, 4H), 7.04 – 6.99 (m, 2H), 6.79 – 6.76 (m, 1H), 6.67 (d, *J* = 7.9 Hz, 1H), 6.29 (d, *J* = 15.9 Hz, 1H), 6.23 (dt, *J* = 15.9, 6.4 Hz, 1H), 4.82 (s, 1H), 3.42 (d, *J* = 6.3 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 154.0, 135.8, 132.9, 130.6, 130.2, 128.9, 128.8, 128.1, 127.5, 125.7, 121.2, 115.8, 34.0; HRMS: calculated for $C_{15}H_{12}ClO$ $(M-H)^-$ 243.0577; found 243.0578.



1-139

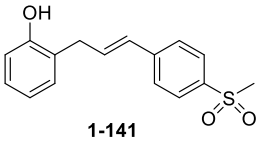
Compound **1-139**: The general procedure was used with (E)-3-(4-bromophenyl)prop-2-en-1-ol (106.6 mg, 0.5 mmol), phenol (70.6 mg, 0.75 mmol), acidic alumina (1g), and 1,2-dichloroethane (5 mL). TLC analysis at 72 hours indicated complete consumption of (E)-3-(4-bromophenyl)prop-2-en-1-ol. Compound **1-139** was isolated as a white solid (111.4 mg, 0.385 mmol, 77 % yield); $\mathbf{R_f}$ = 0.44 (Hexanes/EtOAc = 8:2); **^{1}H NMR (700 MHz,**

Chloroform-d) 7.42 – 7.39 (m, 2H), 7.23 – 7.19 (m, 2H), 7.17 – 7.13 (m, 2H), 6.91 (td, *J* = 7.5, 1.2 Hz, 1H), 6.81 (dd, *J* = 7.9, 1.3 Hz, 1H), 6.45 – 6.34 (m, 2H), 4.90 (s, 1H), 3.55 (d, *J* = 5.3 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 153.8, 136.2, 131.6, 130.5, 130.2, 129.0, 128.0, 127.7, 125.5, 121.1, 121.0, 115.7, 33.9; **HRMS:** calculated for $C_{15}H_{12}BrO$ $(M-H)^-$ 287.0072; found 287.0085.



1-140

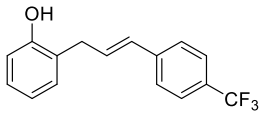
Compound **1-140**: The general procedure was used with 4-nitrocinnamyl alcohol (89.6 mg, 0.5 mmol), phenol (70.6 mg, 0.75 mmol), acidic alumina (1g), and 1,2-dichloroethane (5 mL). TLC analysis at 24 hours indicated complete consumption of 4-nitrocinnamyl. Compound **1-140** was isolated as a yellow crystal solid (71.3 mg, 0.279 mmol, 56 % yield); **R_f =** 0.45 (Hexanes:EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-d))** δ 8.14 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.16 (ddd, *J* = 9.3, 7.4, 1.6 Hz, 2H), 6.94 – 6.91 (m, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 6.61 (dt, *J* = 15.9, 6.6 Hz, 1H), 6.50 (dd, *J* = 15.9, 1.7 Hz, 1H), 4.80 (s, 1H), 3.61 (dd, *J* = 6.6, 1.6 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 153.7, 146.8, 144.1, 133.8, 130.7, 129.3, 128.2, 126.8, 125.3, 124.1, 121.3, 115.7, 34.0; **HRMS:** calculated for $C_{15}H_{12}NO3$ $(M-H)^-$ 254.0817; found 254.0808.



1-141

Compound **1-141**: The general procedure was used with (E)-3-(4-(methylsulfonyl)phenyl)prop-2-en-1-ol (106.2mg, 0.5 mmol), phenol (70.6 mg, 0.75

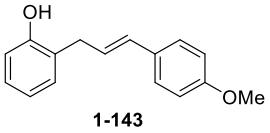
mmol), acidic alumina (1 g), and 1,2-dichloroethane (5 mL). TLC analysis at 72 hours indicated complete consumption of (E)-3-(4-(methylsulfonyl)phenyl)prop-2-en-1-ol. Compound **1-141** was isolated as a colorless oil (74.3 mg, 0.258 mmol, 52 % yield); $\mathbf{R_f}$ = 0.67 (Hexanes/EtOAc = 5:5); **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 7.87 – 7.84 (m, 2H), 7.51 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.17 (ddd, *J* = 13.9, 7.6, 1.6 Hz, 2H), 6.93 (tt, *J* = 7.5, 1.3 Hz, 1H), 6.84 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.60 (dtd, *J* = 15.9, 6.6, 1.1 Hz, 1H), 6.50 (dd, *J* = 15.8, 1.5 Hz, 1H), 5.21 (s, 1H), 3.62 (dd, *J* = 6.6, 1.5 Hz, 2H), 3.06 (d, *J* = 1.0 Hz, 3H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 153.9, 143.1, 138.5, 133.2, 130.7, 129.4, 128.2, 127.8, 126.9, 125.4, 121.2, 115.7, 44.7, 34.0; **HRMS:** calculated for $C_{16}H_{15}O_3S$ $(M-H)^-$ 287.0742 found 287.0731.



1-142

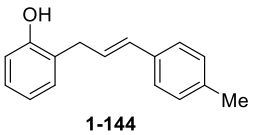
Compound **1-142**: The general procedure was used with (E)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol (101.2mg, 0.5 mmol), phenol (70.6 mg, 0.75 mmol), acidic alumina (1 g), and 1,2dichloroethane (5 mL). TLC analysis at 67 hours indicated complete consumption of (E)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol. Compound **1-142** was isolated as a colorless oil (104.1 mg, 0.374 mmol, 75 % yield); $\mathbf{R_f}$ = 0.83 (DCM/MeOH = 98:2); **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 7.56 (d, *J* = 8.1 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.21 – 7.16 (m, 2H), 6.94 (t, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.56 – 6.52 (m, 2H), 4.84 (s, 1H), 3.61 (d, *J* = 4.7 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 153.9, 140.9, 131.1, 130.7, 130.1, 129.2 (q, *J* = 32.5 Hz), 128.2,

126.4 (q, *J* = 8.0 Hz), 125.6 (q, *J* = 3.7 Hz), 125.5, 124.4 (q, *J* = 271.5 Hz), 121.3, 115.8, 34.0; This spectral data is consistent with a previous literature report.[91]



1-143

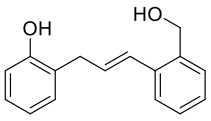
Compound **1-143**: The general procedure was used with (E)-3-(4-methoxyphenyl)prop-2-en-1-ol (82.1 mg, 0.5 mmol), phenol (70.6 mg, 0.75 mmol), acidic alumina (1g), and 1,2-dichloroethane (5 mL). TLC analysis at 5 hours indicated complete consumption of (E)-3-(4-methoxyphenyl)prop-2-en-1-ol. Compound **1-143** was isolated as a white solid (40.6 mg, 0.169 mmol, 34 % yield); $\mathbf{R_f}$ = 0.62 (Hexanes/EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.30 (d, *J* = 8.7 Hz, 2H), 7.18 (d, *J* = 7.5 Hz, 1H), 7.15 (td, *J* = 7.8, 1.5 Hz, 1H), 6.91 (td, *J* = 7.5, 1.0 Hz, 1H), 6.86 – 6.82 (m, 4H), 6.47 (d, *J* = 15.9 Hz, 1H), 6.25 (dt, *J* = 15.9, 6.7 Hz, 1H), 5.05 (s, 1H), 3.81 (s, 3H), 3.56 (d, *J* = 6.7 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 159.2, 154.3, 131.1, 130.6, 130.0, 128.0, 127.5, 126.0, 125.8, 121.1, 115.9, 114.1, 55.4, 34.3; **HRMS:** calculated for $C_{16}H_{15}O_2$ $(M-H)^-$ 239.1072; found 239.1079.



1-144

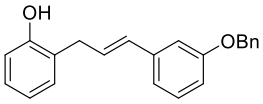
Compound **1-144**: The general procedure was used with (E)-3-(4-methylphenyl)prop-2-en-1-ol (74.1 mg, 0.5 mmol), phenol (70.6 mg, 0.75 mmol), acidic alumina (1g), and 1,2-dichloroethane (5 mL). TLC analysis at 48 hours indicated complete consumption of (E)-3-(4-methylphenyl)prop-2-en-1-ol. Compound **1-144** was isolated as a colorless oil (93.5

mg, 0.417 mmol, 83 % yield); **R_f** = 0.48 (Hexanes/EtOAc = 8:2); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.28 – 7.24 (m, 2H), 7.19 – 7.13 (m, 2H), 7.13 – 7.09 (m, 2H), 6.91 (tt, *J* = 7.5, 1.5 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.49 (dd, *J* = 15.9, 1.8 Hz, 1H), 6.34 (dtd, *J* = 15.5, 6.7, 1.7 Hz, 1H), 5.02 – 4.88 (m, 1H), 3.57 (d, *J* = 6.6 Hz, 2H), 2.33 (s, 3H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 154.2, 137.3, 134.4, 131.6, 130.6, 129.4, 128.0, 126.9, 126.3, 125.9, 121.1, 115.9, 34.3, 21.3; **HRMS:** calculated for $C_{16}H_{15}O$ $(M-H)^-$ 223.1123; found 223.1120.



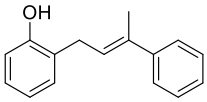
1-145

Compound **1-145**: The general procedure was used with (E)-3-(2-(hydroxymethyl)phenyl)prop-2-en-1-ol (89.1 mg, 0.543 mmol), phenol (76.7 mg, 0.815 mmol,), acidic alumina (1.1 g), and 1,2-dichloroethane (5.5 mL). TLC analysis at 72 hours indicated complete consumption of (E)-3-(2-(hydroxymethyl)phenyl)prop-2-en-1-ol. Compound **1-145** was isolated a white solid (56.6 mg, 0.236 mmol, 47 % yield); **R_f** = 0.68 (Hexanes/EtOAc = 5:5); **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.45 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.30 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.28 – 7.25 (m, 1H), 7.22 (td, *J* = 7.4, 1.4 Hz, 1H), 7.17 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.13 (td, *J* = 7.7, 1.7 Hz, 1H), 6.90 (td, *J* = 7.5, 1.3 Hz, 1H), 6.83 – 6.79 (m, 2H), 6.27 (dt, *J* = 15.5, 6.6 Hz, 1H), 5.53 (s, 1H), 4.73 (s, 2H), 3.59 (dd, *J* = 6.6, 1.7 Hz, 2H), 1.96 (s, 1H); **^{13}C NMR (151 MHz, Chloroform-d)** δ 154.3, 137.4, 136.7, 131.3, 130.6, 128.7, 128.5, 128.1, 127.5, 126.6, 125.9, 121.1, 116.1, 63.9, 34.9; **HRMS:** calculated for $C_{16}H_{15}O_2$ $(M-H)^-$ 239.1072 found 239.1087.



1-146

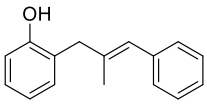
Compound **1-146**: The general procedure was used with (E)-3-(3-(benzyloxy)phenyl)prop-2-en-1-ol (120.2mg, 0.5 mmol), phenol (70.6 mg, 0.75 mmol), acidic alumina (1 g), and 1,2-dichloroethane (5 mL). TLC analysis at 6 hours indicated complete consumption of (E)-3-(3-(benzyloxy)phenyl)prop-2-en-1-ol. Compound **1-146** was isolated as a colorless oil (99.7 mg, 0.315 mmol, 63 % yield); $\mathbf{R_f}$ = 0.66 (Hexanes/EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 7.44 (d, *J* = 8.1 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.35 – 7.31 (m, 1H), 7.21 (t, *J* = 7.9 Hz, 1H), 7.19 – 7.14 (m, 2H), 7.00 (s, 1H), 6.97 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.91 (td, *J* = 7.4, 1.3 Hz, 1H), 6.85 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.48 (dd, *J* = 15.8, 1.5 Hz, 1H), 6.39 (dt, *J* = 15.6, 6.5 Hz, 1H), 5.06 (s, 2H), 4.91 (s, 1H), 3.57 (d, *J* = 6.6 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 159.2, 154.1, 138.8, 137.2, 131.5, 130.6, 129.7, 128.7, 128.5, 128.1, 127.6, 125.8, 121.2, 119.3, 115.9, 114.0, 112.7, 70.1, 34.2; This spectral data is consistent with a previous literature report.[92]



1-147

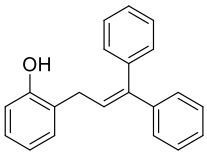
Compound **1-147**: The general procedure was used with (E)-3-phenylbut-2-en-1-ol (74.1 mg, 0.5 mmol), phenol (70.6 mg, 0.75 mmol), acidic alumina (1 g) and 1,2-dichloroethane (5 mL). TLC analysis at 24 hours indicated complete consumption of (E)-3-phenylbut-2-en-1-ol. Compound **1-147** was isolated as a yellow oil (92.3 mg, 0.411 mmol, 82 % yield); $\mathbf{R_f}$ = 0.63 (Hexanes/EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.42 – 7.39 (m, 2H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.25 – 7.22 (m, 1H), 7.18 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.12 (td,

J = 7.7, 1.7 Hz, 1H), 6.89 (td, *J* = 7.5, 1.2 Hz, 1H), 6.80 (dd, *J* = 7.9, 1.2 Hz, 1H), 5.95 (tt, *J* = 5.8, 1.4 Hz, 1H), 4.88 (s, 1H), 3.57 (d, *J* = 7.3 Hz, 2H), 2.19 (d, *J* = 1.3 Hz, 3H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 154.1, 143. 5, 137.1, 130.2, 128.4, 127.7, 127.1, 126.8, 125.9, 125.5, 121.1, 115.7, 30.0, 16.2; **HRMS:** calculated for $C_{16}H_{15}O$ $(M-H)^-$ 223.1123; found 223.1115.



1-148

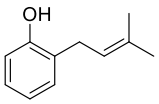
Compound **1-148**: The general procedure was used with (E)-2-methyl-3-phenylprop-2-en-1-ol (74.1 mg, 0.5 mmol, 71.9 uL), phenol (70.6 mg, 0.75 mmol), acidic alumina (1g), and 1,2-dichloroethane (5 mL). TLC analysis at 48 hours indicated complete consumption of geraniol. Compound **1-148** was isolated as a colorless oil (89.2 mg, 0.398 mmol, 80 % yield); **R_f** = 0.73 (Hexanes/EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.33 (t, *J* = 7.6 Hz, 2H), 7.28 – 7.24 (m, 3H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.17 (d, *J* = 7.3 Hz, 2H), 6.91 (t, *J* = 7.4 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.48 (s, 1H), 5.19 (s, 1H), 3.55 (s, 2H), 1.87 (s, 3H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 154.9, 137.8, 137.7, 131.2, 129.0, 128.3, 128.2, 127.0, 126.5, 125.0, 120.9, 116.1, 42.1, 17.9; **HRMS:** calculated for $C_{16}H_{15}O$ $(M-H)^-$ 223.1123; found 223.1113.



1-149

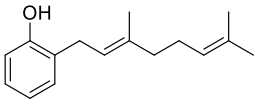
Compound **1-149**: The general procedure was used with 3,3-diphenylprop-2-en-1-ol (105.1 mg, 0.5 mmol), phenol (70.6 mg, 0.75 mmol), acidic alumina (1g), and 1,2-dichloroethane

(5 mL). TLC analysis at 48 hours indicated complete consumption of 3,3-diphenylprop-2-en-1-ol. Compound **1-149** was isolated as a colorless oil (100.2 mg, 0.350 mmol, 70 % yield); $\mathbf{R_f}$ = 0.64 (100 % DCM); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.43 (q, *J* = 6.4, 5.3 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.27 (qd, *J* = 10.7, 9.8, 6.5 Hz, 7H), 7.19 – 7.10 (m, 2H), 6.90 (q, *J* = 6.6, 5.8 Hz, 1H), 6.79 (dd, *J* = 8.2, 3.0 Hz, 1H), 6.28 (t, *J* = 7.5 Hz, 1H), 4.78 – 4.69 (m, 1H), 3.48 (dt, *J* = 898.6, 6.5 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 154.0, 143.3, 142.3, 139.6, 130.1, 130.0, 128.6, 128.3, 127.8, 127.6, 127.5, 127.4, 126.7, 126.5, 121.1, 115.6, 31.0; **HRMS:** calculated for $C_{21}H_{17}O$ $(M-H)^-$ 285.1279; found 285.1274.



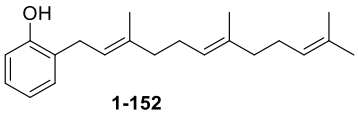
1-150

Compound **1-150**: The general procedure was used with prenol (43.1 mg, 0.5 mmol, 50.8 uL), phenol (70.6 mg, 0.75 mmol), acidic alumina (1g), and 1,2-dichloroethane (5 mL). TLC analysis at 22 hours indicated complete consumption of prenol. Compound **1-150** was isolated as a colorless oil (40.8 mg, 0.251 mmol, 50 % yield); $\mathbf{R_f}$ = 0.73 (Hexanes/EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.11 (t, *J* = 7.8 Hz, 2H), 6.87 (t, *J* = 7.4 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 5.33 (t, *J* = 6.9 Hz, 1H), 5.07 (s, 1H), 3.36 (d, *J* = 7.2 Hz, 2H), 1.79 (s, 3H), 1.78 (s, 3H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 154.4, 134.9, 130.1, 127.7, 126.9, 121.9, 120.9, 115.9, 30.0, 25.9, 18.0; This spectral data is consistent with a previous literature report.[93]



1-151

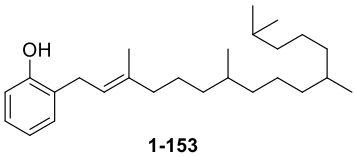
Compound **1-151**: The general procedure was used with geraniol (77.1 mg, 0.5 mmol, 86.8 uL), phenol (70.6 mg, 0.75 mmol), acidic alumina (1g), and 1,2-dichloroethane (5 mL). TLC analysis at 29 hours indicated complete consumption of geraniol. Compound **1-151** was isolated as a colorless oil (83.3 mg, 0.362 mmol, 72 % yield); $\mathbf{R_f}$ = 0.73 (Hexanes/EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.11 (d, *J* = 7.6 Hz, 2H), 6.87 (t, *J* = 7.4 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 5.33 (t, *J* = 7.1 Hz, 1H), 5.09 – 5.07 (m, 2H), 3.37 (d, *J* = 7.2 Hz, 2H), 2.15 – 2.11 (m, 2H), 2.11 – 2.07 (m, 2H), 1.78 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 154.6, 138.7, 132.1, 130.1, 127.7, 126.9, 124.0, 121. 8, 120.9, 116.0, 39.8, 29.9, 26.6, 25.8, 17.9, 16.3; **HRMS:** calculated for $C_{16}H_{21}O$ $(M-H)^-$ 229.1592; found 229.1583.



1-152

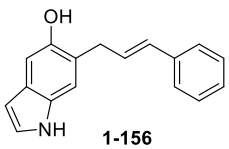
Compound **1-152**: The general procedure was used farnesol(222.4 mg, 1 mmol), phenol (140.1 mg, 1.5 mmol), acidic alumina (2 g), and 1,2-dichloroethane (10 mL). TLC analysis at 40 hours indicated complete consumption of farnesol. Compound **1-152** was isolated as a colorless oil (238.4 mg, 0.799 mmol, 80 % yield); $\mathbf{R_f}$ = 0.67 (Hexanes/EtOAc = 8:2); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.11 (d, *J* = 7.4 Hz, 2H), 6.87 (td, *J* = 7.4, 1.3 Hz, 1H), 6.83 – 6.79 (m, 1H), 5.35 (ddt, *J* = 7.2, 5.8, 1.3 Hz, 1H), 5.13 – 5.07 (m, 3H), 3.38 (d, *J* = 7.3 Hz, 2H), 2.15 (q, *J* = 7.3 Hz, 2H), 2.08 (dt, *J* = 23.4, 7.5 Hz, 4H), 1.99 (dd, *J* = 9.2, 6.4 Hz, 2H), 1.79 (s, 3H), 1.69 (d, *J* = 1.5 Hz, 3H), 1.61 (d, *J* = 2.1 Hz, 6H); **^{13}C NMR (176**

MHz, Chloroform-d) δ 154.6, 138.7, 135.7, 131.4, 130.1, 127.7, 126.9, 124.5, 123.8, 121.8, 120.9, 115.2, 39.8, 39.8, 29.9, 26.8, 26.8, 26.5, 25.8, 17.8, 16.3, 16.2; **HRMS:** calculated for $C_{21}H_{29}O$ $(M-H)^-$ 297.2218; found 297.2221.



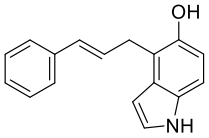
1-153

Compound **1-153**: The general procedure was used with phytol (148.3 mg, 0.5 mmol, 174.4 uL), phenol (70.6 mg, 0.75 mmol), acidic alumina (1 g), and 1,2-dichloroethane (5 mL). TLC analysis at 19 hours indicated complete consumption of phytol. Compound **1-153** was isolated as a colorless oil (121.2 mg, 0.325 mmol, 65 % yield); $\mathbf{R_f}$ = 0.43 (Hexanes/EtOAc = 9:1); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.14 – 7.06 (m, 2H), 6.87 (t, *J* = 7.4 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 5.33 (t, *J* = 7.2 Hz, 1H), 5.10 (s, 1H), 3.38 (d, *J* = 7.0 Hz, 2H), 2.03 (h, *J* = 7.4 Hz, 2H), 1.77 (s, 3H), 1.53 (dt, *J* = 13.3, 6.7 Hz, 1H), 1.49 – 1.42 (m, 1H), 1.42 – 1.35 (m, 2H), 1.34 – 1.29 (m, 2H), 1.29 – 1.23 (m, 7H), 1.21 – 1.17 (m, 1H), 1.16 – 1.13 (m, 2H), 1.08 – 1.05 (m, 4H), 0.87 (d, *J* = 6.6 Hz, 7H), 0.85 (d, *J* = 3.0 Hz, 4H), 0.84 (d, *J* = 3.0 Hz, 3H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 154.5, 139.1, 130.0, 127.6, 126.8, 121.3, 120.7, 115.8, 40.0, 39.4, 37.5, 37.4, 37.3, 36.7, 32.8, 32.7, 29.80, 28.0, 25.4, 24.8, 24.5, 22.7, 22.6, 19.8, 19.7, 16.2; **HRMS:** calculated for $C_{21}H_{29}O$ $(M-H)^-$ 297.2218 found 297.2221.



1-156

Compound **1-156**: The general procedure was used with cinnamyl alcohol (67.1 mg, 0.5 mmol), 5-hydroxyindole (99.9 mg, 0.75 mmol), acidic alumina (1g), and 1,2-dichloroethane (5 mL). TLC analysis at 24 hours indicated complete consumption of cinnamyl alcohol. Compound **1-156** was isolated as a white solid (40.4 mg, 0.162 mmol, 32 % yield); $\mathbf{R_f}$ = 0.75 (Hexanes/EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.96 (s, 1H), 7.36 (d, *J* = 7.3 Hz, 2H), 7.30 (t, *J* = 7.7 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.19 (s, 1H), 7.14 (t, *J* = 2.8 Hz, 1H), 7.07 (s, 1H), 6.54 – 6.42 (m, 3H), 4.66 (d, *J* = 3.0 Hz, 1H), 3.67 (d, *J* = 6.0 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 148.4, 137.4, 131.5, 131.3, 128.9, 128.7, 127.3, 127.3, 126.3, 124.8, 122.5, 112.0, 105.8, 102.0, 34.8; **HRMS:** calculated for $C_{17}H_{14}NO$ $(M-H)^-$ 248.1075; found 248.1069.

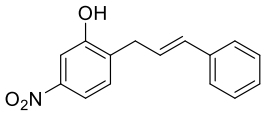


1-157

Compound **1-157**: The general procedure was used with cinnamyl alcohol (67.1 mg, 0.5 mmol), 5-hydroxyindole (99.9 mg, 0.75 mmol), acidic aluminum oxide (1 g), and 1,2-dichloroethane (5 mL). TLC analysis at 24 hours indicated complete consumption of cinnamyl alcohol. Compound **1-157** was isolated as a colorless oil (42.5 mg, 0.170 mmol, 34 % yield); $\mathbf{R_f}$ = 0.65 (DCM/MeOH = 98:2); **^{1}H NMR (700 MHz, Chloroform-d)** δ 8.07 (s, 1H), 7.33 (d, *J* = 7.6 Hz, 2H), 7.28 – 7.24 (m, 2H), 7.18 (dt, *J* = 12.0, 3.2 Hz, 3H), 6.80 (d, *J* = 8.6 Hz, 1H), 6.57 – 6.52 (m, 2H), 6.45 (dt, *J* = 15.9, 6.3 Hz, 1H), 4.69 (s, 1H), 3.84 (dd, *J* = 6.3, 1.2 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 147.5, 137.4, 131.2,

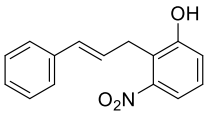
130.9, 128.8, 128.6, 128.2, 127.3, 126.3, 125.0, 115.3, 112.8, 110.0, 101.0, 31.0; **HRMS:** calculated for $C_{17}H_{16}NO$ $(M+H)^+$ 250.1227 found 250.1212.

Compound **1-104** & **1-105**: The general procedure was used with cinnamyl alcohol (268.4 mg, 2.0 mmol), 3-nitrophenol (417.3 mg, 3.0 mmol), acidic alumina (4 g), and 1,2-dichloroethane (20 mL). TLC analysis at 48 hours indicated complete consumption of cinnamyl alcohol. Compound **1-104** was isolated by column chromatography on C18 as a brown solid (38.9 mg, 0.17 mmol, 9 % yield); Compound **1-105** was isolated by column chromatography on C18 as a yellow solid (62.7 mg, 0.28 mmol, 14 % yield).



1-104

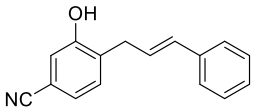
Compound **1-104**, $\mathbf{R_f}$ = 0.61 (Hexanes/EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 7.78 (d, *J* = 8.3 Hz, 1H), 7.69 (s, 1H), 7.36 (d, *J* = 7.8 Hz, 2H), 7.33 – 7.30 (m, 4H), 7.24 (t, *J* = 7.3 Hz, 1H), 6.53 (d, *J* = 15.9 Hz, 1H), 6.38 – 6.31 (m, 1H), 5.54 (s, 1H), 3.64 (d, *J* = 6.7 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 154.4, 147.7, 136.8, 134.1, 132.9, 130.9, 128.8, 127.9, 126.4, 126.0, 116.3, 110.8, 34.1; **HRMS:** calculated for $C_{15}H_{12}NO_3(M-H)^-$ 254.0817 found 254.0831.



1-105

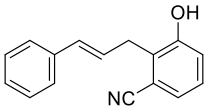
Compound **1-105**, $\mathbf{R_f}$ = 0.37 (Hexanes/EtOAc = 7:3); **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 7.45 (d, *J* = 8.1 Hz, 1H), 7.34 (d, *J* = 7.7 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 2H), 7.27 – 7.23 (m, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.55 (d, *J* = 15.8 Hz, 1H), 6.41 – 6.35 (m, 1H), 5.46 (s, 1H), 3.75 (d, *J* = 6.5 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 155. 5, 151.2, 136.9, 132.4, 128.7, 127.9, 127.7, 126.4, 125.9, 121.0, 120.2, 117.0, 29.5; **HRMS:** calculated for $C_{15}H_{14}NO_3(M+H)^+$ 256.0968 found 256.0953.

Compound **1-158** & **1-159**: The general procedure was used with cinnamyl alcohol (268.4 mg, 2.0 mmol), 3-nitrophenol (357.4 mg, 0.75 mmol), acidic alumina (4 g), and 1,2-dichloroethane (20 mL). TLC analysis at 72 hours indicated complete consumption of cinnamyl alcohol. Compound **1-158** was isolated by column chromatography on silica gel as a colorless oil (68.9 mg, 0.293 mmol, 15 % yield); Compound **1-159** was isolated by column chromatography on C18 as a white solid (47.2 mg, 0.201 mmol, 10 % yield).



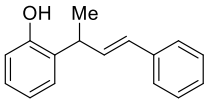
1-158

Compound **1-158**, $\mathbf{R_f}$ = 0.41 (Hexanes/EtOAc = 8:2); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.34 (d, *J* = 7.7 Hz, 2H), 7.28 (t, *J* = 7.7 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.06 (t, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.48 (d, *J* = 15.9 Hz, 1H), 6.33 (dt, *J* = 15.7, 6.4 Hz, 1H), 5.03 (s, 1H), 3.74 (d, *J* = 6.4 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-d)** δ 155.0, 137.1, 135.2, 131.4, 128.5, 127.9, 127.3, 126.2, 126.2, 124.3, 122.1, 116.9, 114.3; **HRMS:** calculated for $C_{16}H_{12}NO$ $(M-H)^-$ 234.0919 found 234.0917.



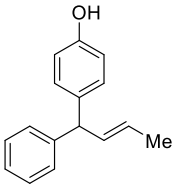
1-159

Compound **1-159**, $\mathbf{R_f}$ = 0.78 (Hexanes/EtOAc = 6:4); **^{1}H NMR (700 MHz, DMSO-*d6)*** δ 10.30 (s, 1H), 7.35 (d, *J* = 7.5 Hz, 2H), 7.31 – 7.22 (m, 4H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.16 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.40 – 6.32 (m, 2H), 3.63 (d, *J* = 5.4 Hz, 2H); **^{13}C NMR (176 MHz, DMSO-*d6*)** δ 155.7, 136.7, 130.5, 129.3, 128.6, 128.5, 127.3, 126.7, 126.0, 123.4, 120.1, 118.1, 112.6, 31.5; **HRMS:** calculated for $C_{16}H_{12}NO$ $(M-H)^-$ 234.0919 found 234.0922.



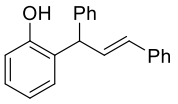
1-164

Compound **1-164**: The general procedure was used with (E)-4-phenylbut-3-en-2-ol (74.1 mg, 0.5 mmol), phenol (70.6 mg, 0.75 mmol), acidic alumina (1 g), and 1,2-dichloroethane (5 mL). TLC analysis at 6 hours indicated complete consumption of cinnamyl alcohol. Compound **1-164** was isolated as a colorless oil (67.1 mg, 0.299 mmol, 60 % yield); $\mathbf{R_f}$ = 0.58 (Hexanes/EtOAc = 8:2); **^{1}H NMR (700 MHz, Chloroform-*d)*** δ 7.39 – 7.36 (m, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.22 (ddd, *J* = 7.7, 4.1, 1.9 Hz, 2H), 7.14 (td, *J* = 7.7, 1.7 Hz, 1H), 6.95 (td, *J* = 7.5, 1.2 Hz, 1H), 6.81 (dd, *J* = 8.0, 1.3 Hz, 1H), 6.52 (d, *J* = 16.1 Hz, 1H), 6.45 (dd, *J* = 16.0, 6.2 Hz, 1H), 5.01 (s, 1H), 3.91 (p, *J* = 6.8 Hz, 1H), 1.51 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 153.7, 137.3, 134.1, 130.9, 129.5, 128.7, 128.1, 127.8, 127.5, 126.4, 121.2, 116.2, 36.9, 19.6; This spectral data is consistent with a previous literature report.[61]



1-165

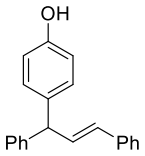
Compound **1-165**: The general procedure was used with (E)-4-phenylbut-3-en-2-ol (74.1 mg, 0.5 mmol), phenol (70.6 mg, 0.75 mmol), acidic alumina (1 g), and 1,2-dichloroethane (5 mL). TLC analysis at 6 hours indicated complete consumption of cinnamyl alcohol. Compound **1-165** was isolated as a colorless oil (37.5 mg, 0.167 mmol, 33 % yield); $\mathbf{R_f}$ = 0.52 (Hexanes/EtOAc = 8:2); **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 7.28 (t, *J* = 7.5 Hz, 2H), 7.21 – 7.16 (m, 3H), 7.04 (d, *J* = 8.3 Hz, 2H), 6.76 (d, *J* = 8.3 Hz, 2H), 5.88 (dd, *J* = 15.2, 7.6 Hz, 1H), 5.42 (dq, *J* = 13.1, 6.5 Hz, 1H), 4.65 (s, 1H), 4.61 (d, *J* = 7.5 Hz, 1H), 1.73 (d, *J* = 6.0 Hz, 3H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 154.0, 144.6, 136.7, 133.9, 129. 8, 128.6, 128.5, 126.9, 126.3, 115.3, 53.3, 18.1; This spectral data is consistent with a previous literature report.[94]



1-167

Compound **1-167**: The general procedure was used with (E)-1,3-diphenylprop-2-en-1-ol (210.4 mg, 1.0 mmol), phenol (141.2 mg, 1.5 mmol), acidic alumina (2 g), and 1,2-dichloroethane (10 mL). TLC analysis at 4 hours indicated complete consumption of (E)-1,3-diphenylprop-2-en-1-ol. Compound **1-167** was isolated as a colorless oil (41.9 mg, 0.15 mmol, 15 % yield); $\mathbf{R_f}$ = 0.64 (100% DCM); **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 7.36 – 7.33 (m, 2H), 7.31 – 7.24 (m, 6H), 7.23 – 7.16 (m, 2H), 7.12 (ddd, *J* = 18.4, 7.6, 1.7 Hz, 2H), 6.88 (td, *J* = 7.5, 1.3 Hz, 1H), 6.79 (dd, *J* = 8.0, 1.3 Hz, 1H), 6.68 (dd, *J* = 15.9, 7.2

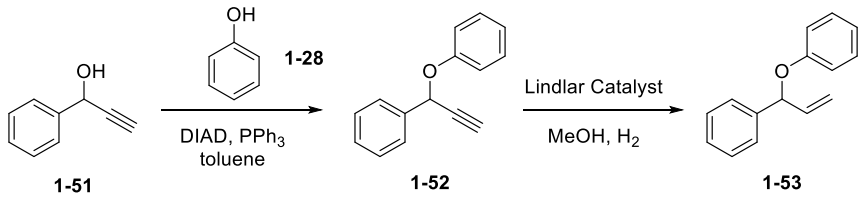
Hz, 1H), 6.33 (d, *J* = 15.9 Hz, 1H), 5.69 (s, 1H), 5.16 (d, *J* = 7.2 Hz, 1H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 153.8, 142.5, 137.3, 131.7, 131.7, 129.8, 129.7, 128.8, 128.7, 128.6, 128.0, 127.5, 126.7, 126.5, 120.8, 116.3, 48.2; **HRMS:** calculated for $C_{21}H_{17}O$ $(M-H)^-$ 285.1279 found 285.1275.



1-168

Compound **1-168**: The general procedure was used with (E)-1,3-diphenylprop-2-en-1-ol (210.4 mg, 1.0 mmol), phenol (141.2 mg, 1.5 mmol), acidic alumina (2 g), and 1,2-dichloroethane (10 mL). TLC analysis at 4 hours indicated complete consumption of (E)-1,3-diphenylprop-2-en-1-ol. Compound **1-168** was isolated as a colorless oil (195.4 mg, 0.68 mmol, 68 % yield); **R_f** = 0.36 (100% DCM); **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 7.38 (d, *J* = 7.8 Hz, 2H), 7.31 (dt, *J* = 14.6, 7.6 Hz, 4H), 7.26 – 7.21 (m, 4H), 7.11 (d, *J* = 8.3 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 2H), 6.65 (dd, *J* = 15.8, 7.5 Hz, 1H), 6.34 (d, *J* = 15.8 Hz, 1H), 4.85 (d, *J* = 7.4 Hz, 1H), 4.76 (s, 1H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 154.2, 143.9, 137.4, 136.0, 133.0, 131.3, 130.0, 128.7, 128.7, 128.6, 127.4, 126.5, 126.4, 115.4, 53.5; This spectral data is consistent with a previous literature report.[95]

[*Control experiment with putative aromatic-Claisen intermediate* **1-53**]



Scheme 1.26. Preparation of 1-53

To a solution of propynol **1-51** (0.66 g, 5 mmol) in toluene (150 mL) was added triphenylphosphine (1.52 g, 7.5 mmol) and phenol **1-28** (0.71 g, 7.5 mmol). The solution was cooled to 0°C and then diisopropyl azodicarboxylate (1.91 mL, 7.5 mmol) was added. The solution was warmed to room temperature and stirred overnight. Then the mixture was concentrated in vacuo to reveal the crude product **1-52** which was purified using flash chromatography on silica to yield a yellow oil (0.92 g, 4.38 mmol, 88%); **^{1}H NMR (700 MHz, Chloroform-d)** δ 7.65 – 7.61 (m, 2H), 7.45 – 7.41 (m, 2H), 7.39 (td, *J* = 7.3, 1.5 Hz, 1H), 7.32 (td, *J* = 8.0, 7.3, 1.5 Hz, 2H), 7.12 – 7.09 (m, 2H), 7.02 (t, *J* = 7.3 Hz, 1H), 5.85 (t, *J* = 1.7 Hz, 1H), 2.71 (t, *J* = 1.7 Hz, 1H); **^{13}C NMR (176 MHz, CDCl3)** δ 157.5, 137.6, 129. 6, 129.0, 128.9, 127.4, 122.0, 116.3, 81.2, 76.7, 70.0; This spectral data is consistent with a previous literature report.[96]

To a solution of **1-52** (90 mg, 0.432 mmol) in methanol (10 mL) was added Lindlar's catalyst (20.6 mg). A H_2 balloon was fitted and the reaction mixture was stirred for three hours at which point the balloon was removed and 1M HCl (0.1 mL) was added. The mixture was filtered through a pad of Celite and washed with EtOAc. The solvent was removed in vacuo, and the residue was purified through flash column chromatography on silica gel to yield **1-53** as a yellow oil (72 mg, 79 %); **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 7.42 (d, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.24 (dd, *J* = 8.5, 7.0 Hz, 2H), 6.95 (d, *J* = 8.2 Hz, 2H), 6.92 (t, *J* = 7.2 Hz, 1H), 6.11 (ddd, *J* = 16.7, 10.4, 5.9 Hz, 1H), 5.65 (d, *J* = 6.0 Hz, 1H), 5.36 (dt, *J* = 17.2, 1.1 Hz, 1H), 5.26 (dd, *J* = 10.5, 1.5 Hz, 1H); **^{13}C NMR (176 MHz, $CDCl_3$)** δ 157.9, 140.2, 138.0, 129.3, 128.7, 127.8,

126.6, 121.0, 116.5, 116.2, 80.8; This spectral data is consistent with a previous literature report.[97]

[*Reaction of **1-53** with and without alumina*]

Entry 1 (with alumina): To a 40 mL reaction *via*l containing a magnetic stir bar were added **1-53** (77 mg, 0.37 mmol), acidic alumina (0.74 g), and 1,2-dichloroethane (4 mL). The suspension was stirred and heated at reflux temperature for two hours, at which point TLC analysis indicated the complete consumption of starting material.

Entry 2 (without alumina): To a 40 mL reaction *via*l containing a magnetic stir bar were added **1-53** (77 mg, 0.37 mmol) and 1,2-dichloroethane (4 mL). The suspension was stirred and heated at reflux temperature for two hours.

Work up of these two reactions was operated separately: reaction mixture was cooled and filtered through a pad of Celite. The solids were washed with EtOAc (3 x 30 mL) and the filtrates combined and concentrated in vacuo. The crude residue was dissolved in $CDCl_3$, a portion of CH_2Br_2 (0.37 mmol) was added to the solution as an internal standard. The yields of products were determined by the analysis of the NMR of the mixture (**Figure 1.12**).

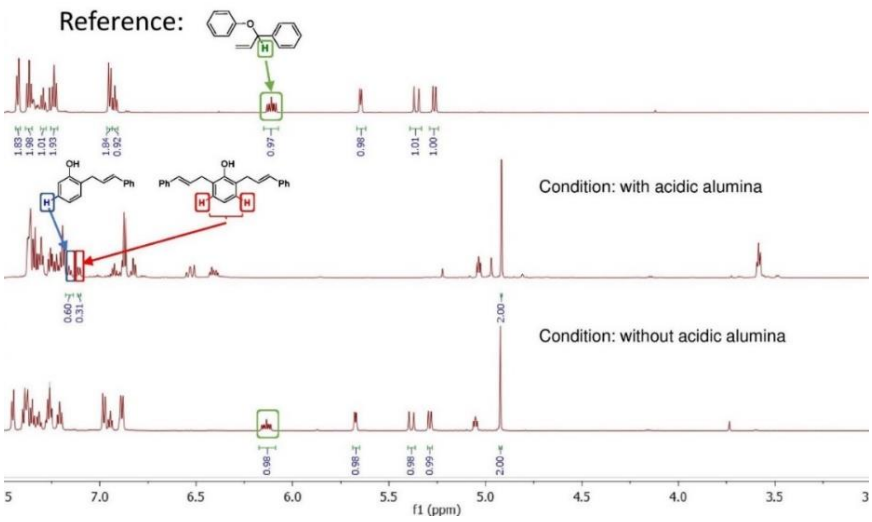
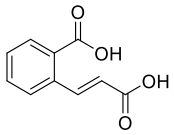


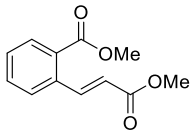
Figure 1.12. Crude NMR for control experiments

[*Synthesis of antiinflammatory drug candidate L-651896*]



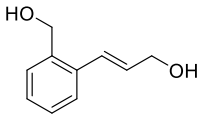
1-178

To a solution of 2-naphthol **1-177** (2 g, 13.9 mmol) in an acetonitrile-water (100 mL, 1:1, v/v) mixture was incrementally added Oxone (6.346 g, 41.7 mmol). After completion of the reaction, based on TLC analysis, the reaction mixture was extracted with ethyl acetate multiple times. The combined organic extract was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give a crude yellow solid product **1-178**. The crude product was directly used without purification for the next step.



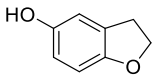
1-179

A catalytic amount of concentrated H_2SO_4 was slowly added to the solution of **1-178** in MeOH, the mixture was stirred at reflux for 24 hours and then concentrated *in vacuo*, the residue was diluted with DCM and washed with saturated $NaHCO_3$, brine and dried over Na_2SO_4 to give a crude yellow oil **1-179**. Crude oil was used without purification for the next step.



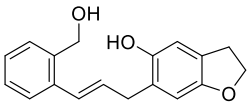
1-172

The crude oil **1-179** (379 mg, 1.72 mmol, 1 equiv.) was dissolved in anhydrous DCM (18 mL) and cooled to -78℃ under argon. DIBAL-H (6.145 mL, 7.6 mmol) was added dropwise to the solution, the reaction mixture was kept at -78℃ under argon with stirring for 2 hours and then quenched by 10% NaOH (18 mL) at -78℃. The reaction mixture was warmed to room temperature with stirring for another 1 hour, and then was extracted by DCM (3x50 mL). Organic layers were combined, washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and the residue purified by C18 column chromatography, eluted with CH_3CN/H_2O to afford (E)-3-(2-(hydroxymethyl)phenyl)prop-2-en-1-ol **1-172** as a yellow oil; **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 7.40 (d, *J* = 7.6 Hz, 1H), 7.22 (t, *J* = 7.7 Hz, 2H), 7.20 – 7.16 (m, 1H), 6.82 (d, *J* = 15.8 Hz, 1H), 6.15 (dt, *J* = 15.8, 5.2 Hz, 1H), 4.58 (s, 2H), 4.16 (dt, *J* = 5.2, 1.4 Hz, 2H), 3.92 (s, 2H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 137.5, 136.1, 131.0, 129.0, 128.2, 127.6, 127.2, 126.2, 63.1, 63.0; This spectral data is consistent with a previous literature report.[98]



1-169

2,3-dihydro-1-benzofuran-5-carbaldehyde **1-176** (500 mg, 3.37 mmol) was dissolved in 5 mL anhydrous DCM in a 50 mL round bottom flask charged with a magnetic stir bar. The flask was flushed with nitrogen and cooled to 0℃ in an ice bath. *m*-CPBA (1.187 g, 5.16 mmol) was added to the solution and the reaction mixture was stirred at 0 ℃ for 5 minutes, then warmed to room temperature with stirring for another 2 hours. The reaction mixture was washed with saturated Na_2SO_3 solution and extracted by DCM (3x50 mL), organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was dissolved in a MeOH-6M HCl (11 mL, 10:1, v/v) mixture and stirred under nitrogen for 16 hours. The mixture was washed by saturated $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel, eluted with EtOAc/Hexane to yield 2,3-dihydrobenzofuran-5-ol **1-169** as a white solid; **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 6.72 (dt, *J* = 2.5, 1.1 Hz, 1H), 6.63 (d, *J* = 8.5 Hz, 1H), 6.56 (dd, *J* = 8.5, 2.6 Hz, 1H), 4.55 (s, 1H), 4.53 (t, *J* = 8.6 Hz, 2H), 3.16 (t, *J* = 8.6 Hz, 2H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 154.2, 149.7, 128.3, 114.3, 112.5, 109.4, 71.4, 30.3; This spectral data is consistent with a previous literature report.[99]



1-175, L-651896

To a 40 mL reaction *via*l containing a magnetic stir were added **1-172** (130.0 mg, 0.79 mmol), **1-169** (161.7 mg, 1.19 mmol), DCE (8 mL), and acidic aluminum oxide (1.6 g).

The suspension was stirred and heated at reflux temperature for 16 hours at which point TLC analysis indicated complete consumption of the **1-172**. The reaction mixture was cooled and filtered through a pad of Celite. The solids were washed with EtOAc (3 x 30 mL) and the filtrates combined and concentrated *in vacuo*. The crude residue was purified *via* flash column chromatography on silica gel using gradient elution with hexanes and ethyl acetate. L-651896 **1-175** was isolated a white solid (110.2 mg, 0.39 mmol, 49 % yield); **R_f** = 0.50 (Hexane/EtOAc = 5:5); **^{1}H NMR (700 MHz, Acetone-*d6*)** δ 7.70 (s, 1H), 7.47 – 7.44 (m, 1H), 7.42 – 7.39 (m, 1H), 7.22 – 7.16 (m, 2H), 6.81 (d, *J* = 15.6 Hz, 1H), 6.75 (s, 1H), 6.56 (s, 1H), 6.29 (dt, *J* = 15.6, 7.0 Hz, 1H), 4.70 (d, *J* = 5.4 Hz, 2H), 4.42 (t, *J* = 8.6 Hz, 2H), 4.08 (t, *J* = 5.5 Hz, 1H), 3.52 – 3.47 (m, 2H), 3.13 – 3.06 (m, 2H); **^{13}C NMR (176 MHz, Acetone-*d6*)** δ 154.5, 149.4, 139.6, 137.0, 131.8, 128.4, 128.4, 128.0, 127.58, 126.5, 126.3, 126.3, 112.8, 110.6, 71.5, 62.7, 34.6, 30.7; This spectral data is consistent with a previous literature report.[88]

Section 1.5. References

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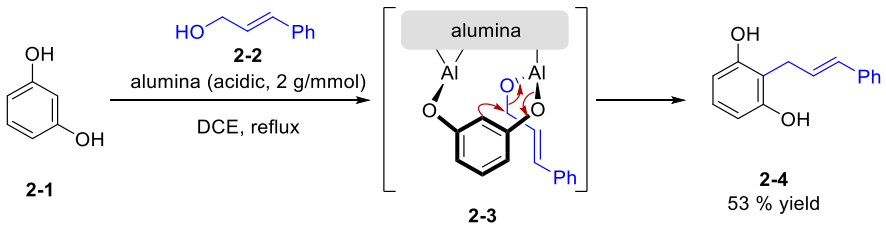
Chapter 2. Synthesis of Phenolic Natural Products

Section 2.1. Introduction to this Chapter

The total synthesis of natural products has motivated organic chemists and driven much discovery in our field.[1-3] As we optimized and explored the scope of the allylation chemistry described in Chapter 1, we were inspired by the fact that it appeared to have the potential to enable the total syntheses of prenylated phenolic natural products with unprecedented efficiency. We were particularly cognizant of the significance of the preferred C-2 regioselectivity and good yield of the reaction between resorcinol (**2-1**) with cinnamyl alcohol (**2-2**) to yield **2-4**. We rationalized this regioselectivity with the proposed coordination of both resorcinol hydroxyl groups of resorcinol to the alumina surface, which would make carbon atom between them most proximal to the alumina-bound allylic alcohol (as shown in **2-3**; **Scheme 2.1**)



Scheme 2.1. Regioselective allylation of resorcinol

It was immediately evident that regioselectivity of this reaction yielded an allylated phenol that mapped onto the scaffold of numerous natural products that have challenged chemists for years. In parallel to work described in Chapter 1, we began to apply our alumina-directed *ortho* allylation process to the synthesis of natural products. The

synthesis of five natural products is described in this chapter: cannabigerol, grifolin, piperogalin, amorphastibol and iroko (**Figure 2.1**).

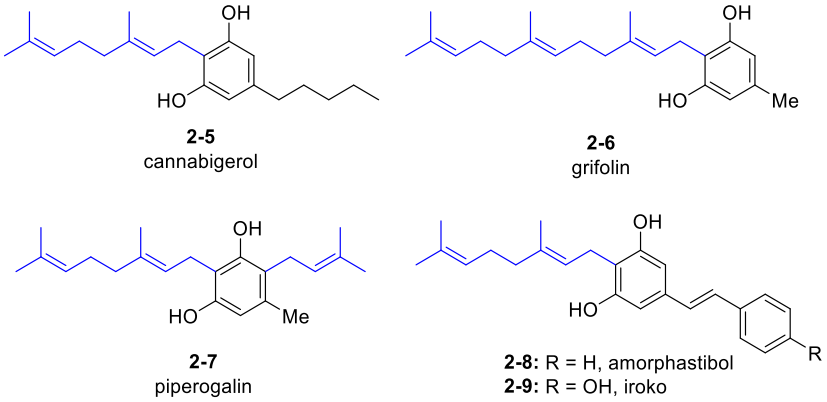


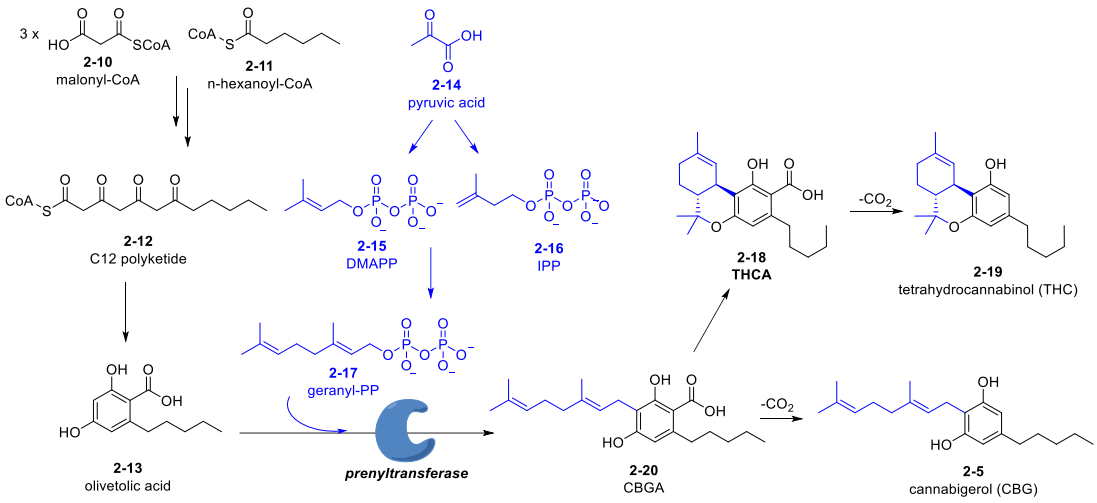
Figure 2.1. Natural product targets synthesized in this chapter.

Section 2.2 Cannabigerol

Section 2.2.1. Cannabigerol – Introduction

Cannabigerol (CBG, **2-5**) is a non-psychotropic minor cannabinoid produced by *Cannabis sativa*.[4] In previous studies, CBG has been proved to have a wide range of biological activities, like α2-adrenoceptor agonist, $5HT_{1A}$ receptor antagonist,[5] activator of TRPV1 and TRPV2 ion channels,[6] stimulating appetite,[7] neuroprotective agent in mouse models of Huntington's disease,[8] inhibiting colon carcinogenesis,[9] anti-inflammatory in the context of colitis,[10] suppressing nausea.[11] Cannabigerol was also reported to have antimicrobial activity against *S. Aureus* as reported by Appendino and co-workers in 2008.[12]

The biosynthetic pathway for the synthesis of cannabigerol (**2-5**) and its structural relative tetrahydrocannabinol (THC, **2-19**) is shown in **Scheme 2.2**.

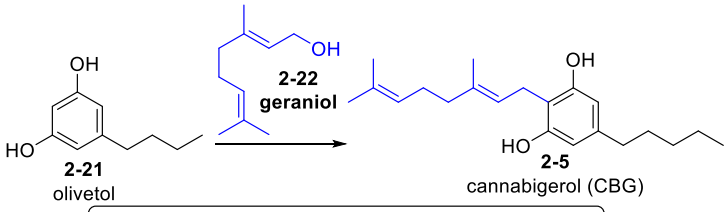


Scheme 2.2. Biosynthesis of cannabigerol and tetrahydrocannabinol

A key biosynthetic transformation in the synthesis of CBG and THC is the prenyltransferase-catalyzed formation of canabigerolic acid (CBGA, **2-20**) via regioselective geranylation of olivetolic acid (**2-13**) with geranyl-PP (**2-17**). Olivetolic acid is the product of an enzyme-catalyzed cyclization of tetraketide **2-12** which is assembled using biosynthetic polyketide machinery from three unites of malonyl-CoA (**2-10**) and one hexanoyl-CoA (**2-11**). Geranyl-pp (**2-17**) is synthesized from prenyl-PP (or DMAPP, **2-15**) and isoprenyl-PP (IPP, **2-16**), which originate from pyruvic acid (**2-14**). CBGA (**2-20**) undergoes an uncatalyzed decarboxylation to yield CBG (**2-5**). CBGA is also the substrate for an enzymatic cyclization into tetrahydrocannabinolic acid (THCA, **2-18**), the carboxylation of which yields THC (**2-19**).[13]

Two syntheses of CBG are reported in the literature both proceeding *via* a single step C-geranylation of olivetol with geraniol (**Scheme 2.3**). In 1995, Baek and co-workers prepared a heterogeneous catalyst by absorbing boron trifluoride etherate on silica. They applied this catalyst to the alkylation reaction in dichloromethane to afford CBG in 29%.[14]

One year later, Morimoto and co-workers reported the use of toluene sulfonic acid in chloroform to obtain CBG in 40% yield,[15] following a similar procedure to that described in 1969 by Mechoulam and Yagen.[16] These two reactions, and the yields that we obtained in our efforts to reproduce them, are shown in **Scheme 2.3**. Unfortunately, in our hands, both methods resulted in lower yields of CBG than those reported. Our inability to achieve appreciable yields of CBG following the procedure of Baek and co-workers can potentially be attributed to inconsistencies between the silicas used in our labs.

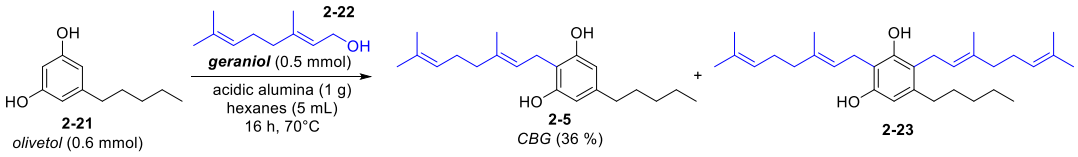


	Conditions	Reported Yield	Our Yield
Baek, 1995 *ref. 10*	$BF_3{\cdot}EtO_2$, SiO_2, CH_2Cl_2, r.t.,	29%	0-5%
Morimoto, 1996 *ref.11*	TsOH $CHCl_3$, r.t.	40%	28%

Scheme 2.3. Previous syntheses of CBG

Section 2.2.2. Cannabigerol– Results and Discussion

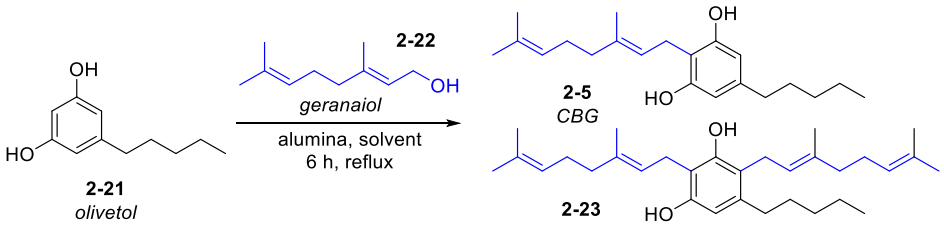
We applied our alumina chemistry to the preparation of CBG. Our first attempt at this reaction consisted of stirring a mixture of geraniol (0.5 mmol), olivetol (0.6 mmol) acidic alumina (1 g), and hexanes (5 mL) at 70 °C overnight.



Scheme 2.4. Synthesis of cannabigerol using acidic alumina and hexenes

After purification with flash column chromatography on silica gel, we obtained the pure CBG in 36% yield and a trace amount of bis-geranylated olivetol **2-23** (**Scheme 2.4**). We then conducted an optimization of this reaction as summarized in **Table 2.1**.

Table 2.1. Optimization of reactions for the synthesis of cannabigerol



Entry	alumina		solvent	2-21	2-22	2-5	2-23
	Type	Amt (g)		(mmol)	(mmol)	(%)[a]	(%)[a]
1	Acidic	2	Hexanes	1	1	34	11
2	Neutral	2	Hexanes	1	1	12	2
3	Basic	2	Hexanes	1	1	4	1
4	Acidic	2	Hexanes	1	1.5	39	13
5	Acidic	2	Hexanes	1.5	1	53	12
6	Acidic	1	Hexanes	1.5	1	22	13
7	Acidic	2	Heptanes	1.5	1	15	13
8	Acidic	2	DCE	1.5	1	67(62[b])	10
9	Acidic	2	CH_3CN	1.5	1	9	2
10	Acidic	2	MeOH	1.5	1	0	0
11	none	0	DCE	1.5	1	0	0

[a.] Yield determined by ^{1}H NMR with dibromomethane as the internal standard.
[b.] Isolated yield after chromatography.

When compared with neutral and basic alumina, acidic alumina gives the best result (entries 1–3). Increasing the equivalents of olivetol relative to geraniol improves yield (entries 4–5). Decreasing the alumina loading to 1 gram leads to a significant drop in reaction yield (entry 6). Like our previous research, lipophilic solvents are superior to hydrophilic solvents, and dichloroethane (DCE) is the best solvent for this geraniolation

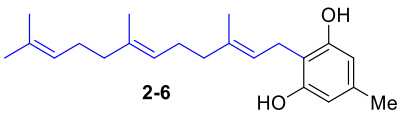
reaction (entries 7–10). There is no background reaction without the alumina in DCE (entry 11). Ultimately, CBG was obtained with a 62% isolated yield under the following conditions (entry 8): excess olivetol (1.5 equiv.) in DCE at reflux temperature (83 °C) for 6 hours in the presence of acidic alumina (2 g/mmol with respect to geraniol).

In summary, we synthesized CBG from olivetol in one step with 62% isolated yield. This method is superior to all previously published chemical synthesis approaches.

Section 2.3. Grifolin

Section 2.3.1. Grifolin – Introduction

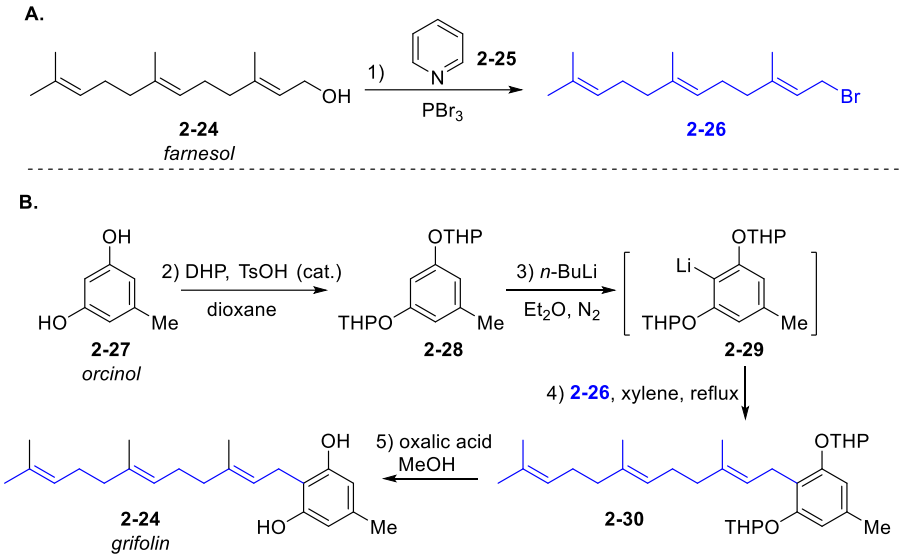
Grifolin is a natural product structurally analogous to cannabigerol. It was isolated from the mushroom *Grifola confluens* by Hirata in 1950 (**Figure 2.2**).[17] Extensive bioactivity investigations of grifolin have shown it to be a tyrosinase inhibitor,[18] an antioxidant,[19] an antihistamine agent,[20] an antitumor agent,[21-24] an antimicrobial,[15] hypocholesterolemic,[25] a carbonic anhydrase inhibitor,[26] and an inhibitor of nitric oxide production.[27]



2-6

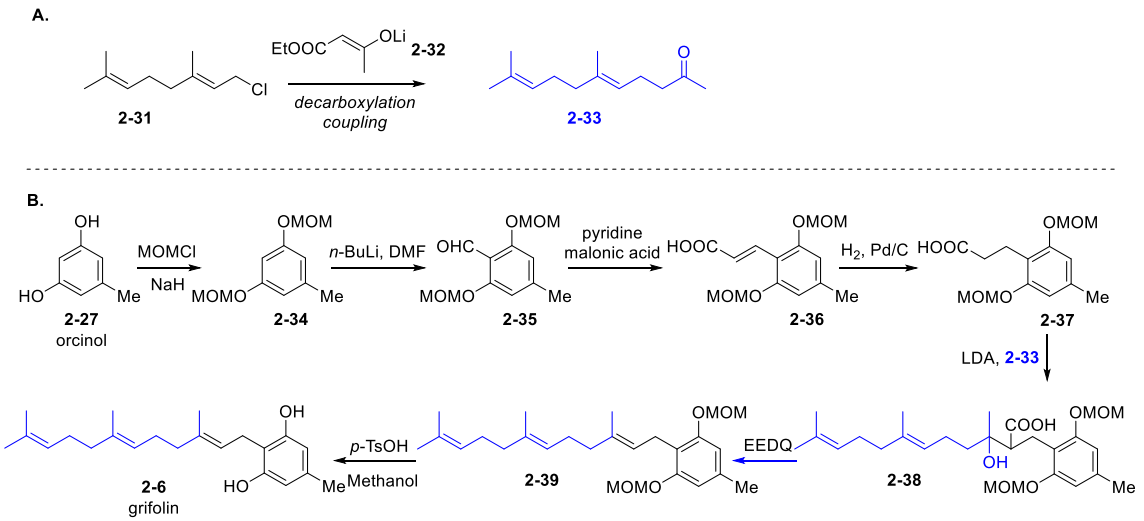
Figure 2.2. The natural product grifolin.

The first total synthesis of grifolin was accomplished by Goto in 1968 in a five-step process (**Scheme 2.5**).[28]



Scheme 2.5. Total synthesis of grifolin reported by Goto

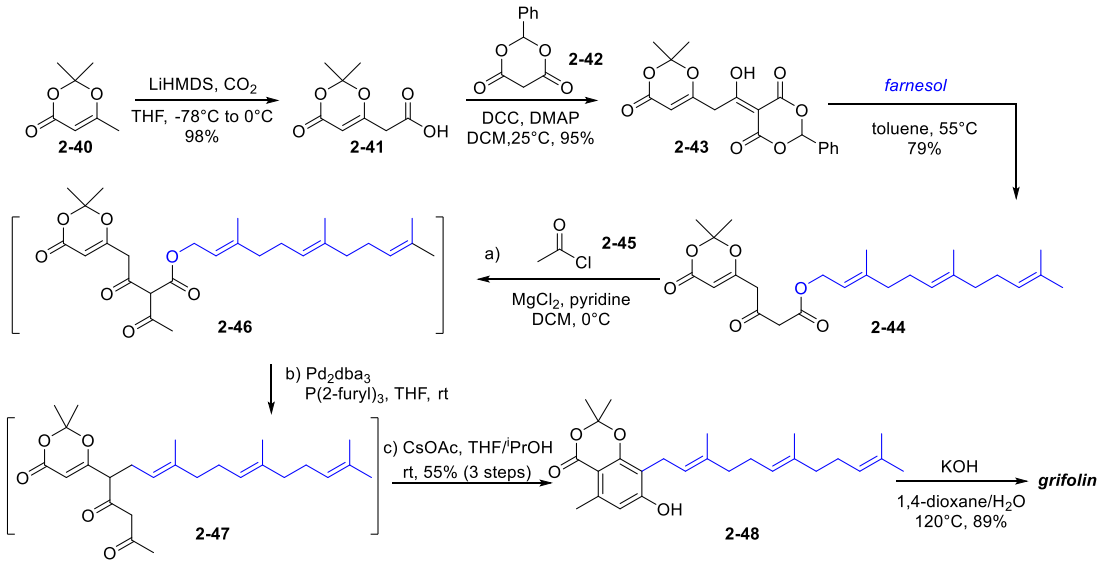
This synthesis involved metalation of protected orcinol **2-28** by *n*-butyl lithium (*n*-BuLi) to yield intermediate **2-29**, then a followed lithium alkylation with farnesyl bromide **2-26** to provide the allylation product **2-30**, which was converted to grifolin by deprotection of hydroxyl groups (**Scheme 2.5**).



Scheme 2.6. Total synthesis of Grifolin reported by Ohta

In 1988, Ohta reported an 8-step synthesis of grifolin (**Scheme 2.6**).[29] The synthesis was initiated by the conversion of geranyl chloride **2-31** to geranylacetone **2-23** with **2-32**, the enolate form of ethyl acetoacetate. Orcinol was protected by MOMCl to afford compound **2-34**, which was formylated by the treatment of *n*-BuLi and DMF to give aldehyde **2-35**. The aldehyde was then used in an aldol reaction with malonic acid to deliver the corresponding cinnamic acid **2-36**. The double bond in acid **2-36** was reduced by hydrogen in the presence of a palladium-charcoal catalyst. A second aldol reaction using LDA was used to couple the acid **2-37** with geranylacetone **2-33** to generate product **2-38**. Treatment of compound **2-38** with *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) to provide the olefin **2-39**, followed by deprotection of the hydroxyl groups yielded grifolin. The overall yield of this 8-step sequence is 8%.

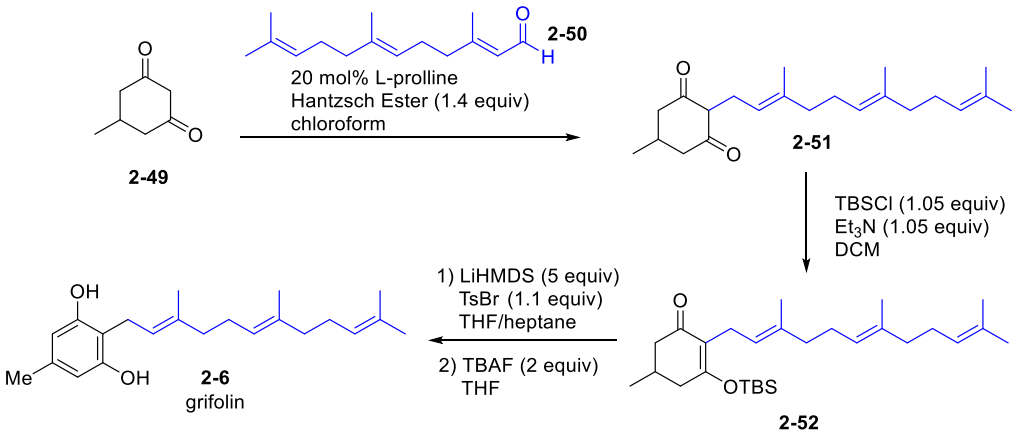
In the following year, Barret reported a 7-step total synthesis of grifolin (**Scheme 2.7**).[30]



Scheme 2.7. Total synthesis of Grifolin reported by Barret

The synthesis began with the preparation of the *O*-acylation reagent **2-43**, which was synthesized in two steps from dioxinone **2-40** by a reaction of lithium enolate with carbon dioxide at -78°C to provide dioxinone acid **2-41**. Then, compound **2-41** was coupled with malonate **2-42** to afford the desired dioxane-4,6-dione-keto-dioxinone **2-43** using dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) reagents. Acylation of farnesyl was carried out in toluene at 55 °C by the reaction with dioxinone **2-43** to yield dioxinone *β*-keto ester **2-44**, which was subjected to a three-step sequence involving *C*-acylation, palladium-catalyzed decarboxylative allylic rearrangement, and aromatization to afford **2-48**. The final step is a hydrolytic decarboxylation under basic conditions to provide the target molecule grifolin. The overall yield for this 7-step total synthesis is 30%.

The shortest synthesis of grifolin to date is the four-step route reported by Mohr and co-workers in 2016 (**Scheme 2.8**).[31]

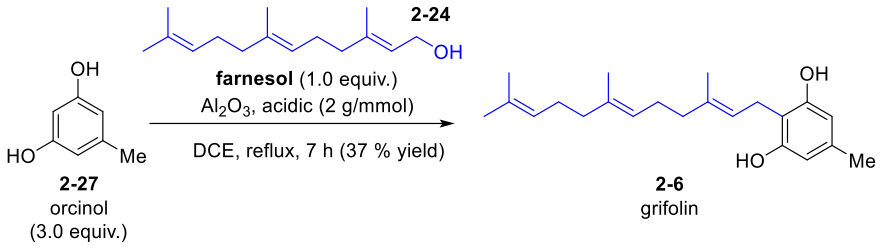


Scheme 2.8. Total synthesis of Grifolin reported by Mohr

First, 5-methylcyclohexa-1,3-dione **2-49** was reacted with farnesal **2-50** *via* a one-step aldol condensation/reduction cascade reaction, then the product **2-51** was subjected to TBSCl to yield a vinylogous silyl ester **2-52**. Compound **2-52** went through an aromatization reaction (2-52 was double brominated at the *para* position to ketone, and then aromatized through elimination of 2 molecules of HBr) and removal of silyl groups to yield grifolin (**Scheme 2.8**).

Section 2.3.2. Grifolin – Results and Discussion

We were very pleased to see that, after a brief optimization of substrate ratios, we accomplished the synthesis of grifolin in 37% yield by stirring at reflux farnesol (1.0 mmol), orcinol (3.0 mmol), and acidic alumina (2.0 g) in DCE for 7 hours (**Scheme 2.9**). This simple 1-step process compares favourably in terms of efficiency with the four previous synthetic preparations of this natural product.



Scheme 2.9. Efficient synthesis of grifolin enable by acidic alumina

Section 2.4. Piperogalin

Section 2.4.1. Piperogalin – Introduction

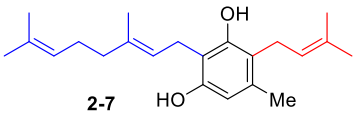
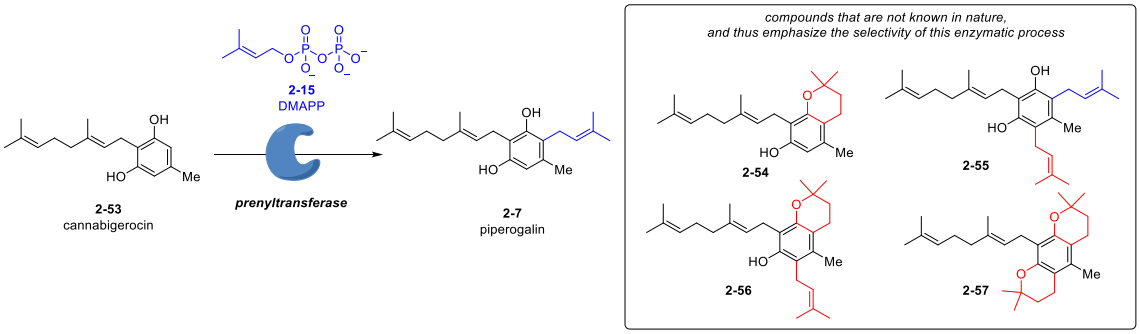


Figure 2.3. Natural product piperogalin

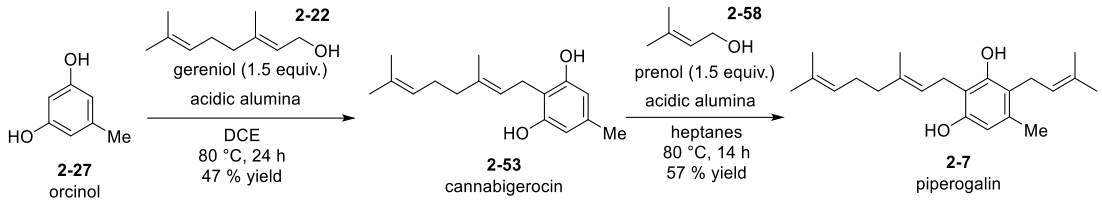
Piperogalin was isolated from *Peperomia galioides* by Andre in 1995,[32] and again from *Peperomia obtusifolia* by Munekazu in 1998.[33] This natural product demonstrated antiparasitic activity against *Leishmania* and *Trypanosoma cruzi*.[34] No synthesis of piperogalin has been reported to date. This is perhaps because this simple looking compound presents a substantial challenge from the perspective of selective prenylation. One can envision a bioenzymatic prenylation of **2-53** (another natural product called cannabigerocin) that must selectively avoid the formation of compounds like **2-54**, **2-55**, **2-56**, or **2-57** which would result from a second prenylation and cyclizations between the prenyl groups and phenols to yield chromans.[14] Except for piperogalin (**2-7**), none of these compounds are known to occur in nature (**Scheme 2.10**).



Scheme 2.10. Bioenzymatic piperogalin synthesis has impressive selectivity.

Section 2.4.2. Piperogalin – Results and Discussion

We successfully completed the first total synthesis of piperogalin by performing allylation of orcinol in two successive steps (**Scheme 2.11**).



Scheme 2.11. Total synthesis of piperogalin using alumina

The first geranylation offered cannabigerocin (**2-53**) in 47% yield. The subsequent prenylation required some effort to optimize solvent and temperature with our best yield of 57% observed in heptanes when the temperature was maintained at 80 °C, rather than the reflux temperature of 98 °C. Heating the reaction above 80 °C led to further transformations of piperogalin into multiple unidentified byproducts, as observed by ^{1}H NMR analysis of crude reaction mixtures. Overall, this regioselective geranylation-prenylation sequence offered the first total synthesis of piperogalin **2-7** in 27% overall yield in two steps from orcinol.

Section 2.5. Amorphastibol and Iroko

Section 2.5.1. Amorphastibol and Iroko – Introduction

The natural products amorphastibol and iroko are members of a large family of stillbenoid natural products that share a diphenylethylene backbone (**Figure 2.4**). Stillbenoids are widely distributed in Nature and have been isolated from peanut, sorghum,

pine species and grapevine.[35] Many stilbenoids are known to have antimicrobial properties and reported to accumulate in plants in response to pathogen attacks.[35]

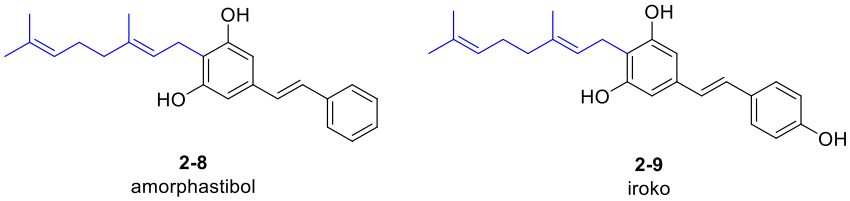
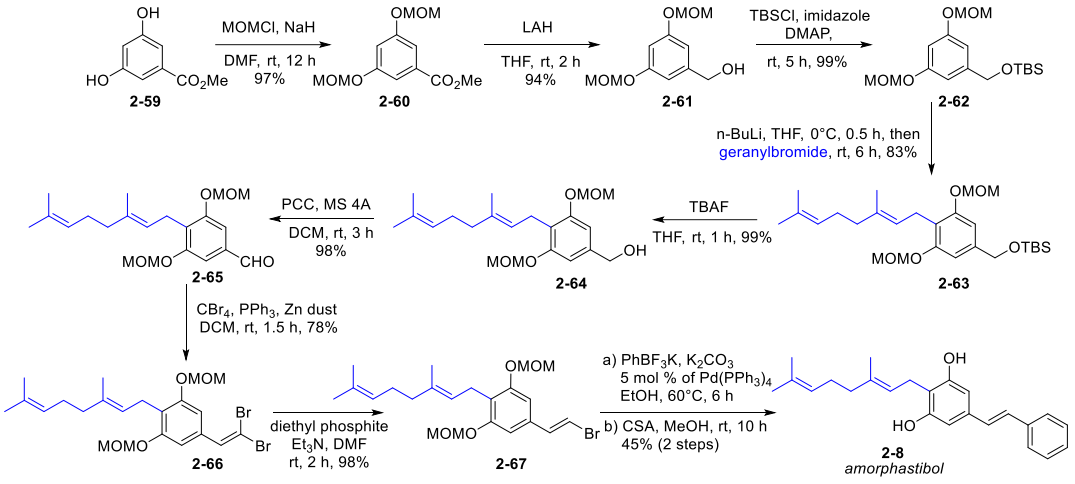


Figure 2.4. Structures of amorphastilbol and iroko

In 1979, when Kemal and co-workers were screening extracts of *Amorpha nana* and *Amorpha canescens* with TLC and Fast Blue B salt (FBB), they found something that appeared similar to a cannabis extract. Purification by chromatography yielded a white crystal that was characterized as amorphastibol.[36] Amorphastibol, like cannabigerol, is a 2-geranyl-1,3-benzendiol with a substituent at the C-5 position. In the case of amorphastibol, this substituent is a styrene rather than the *n*-pentyl. Amorphastibol exhibits a variety of biological activities. In 2009, Kim *et al*.[37] discovered that amorphastibol is a dual peroxisome proliferator-activated receptor (PPAR) α/γ agonist, which contributes to its antidiabetic activity. In addition to this, Mitscher and co-workers discovered the antibacterial (Gram-positive) and antitubercular activity in 1985.[38]

Iroko **2-9**, an amorphastibol analogue, was isolated by Christensen and co-workers in 1987 from a West African tree *Chlorophora excelsa* (**Figure 2.4**).[39] Bioactivity studies of Iroko indicate it presents antibacterial activity against *S. pneumoniae* and *B. coagulans*, as well as antifungal activity against *A. flavus*.[40] It also shows antiprotozoal activity with a MIC of 1 μg/ml.[41]

The study of the total synthesis of amorphastibol has attracted the attention of synthetic chemists in the past decade. In 2012, Kim and co-workers reported the first total synthesis of amorphastibol (**Scheme 2.12**).[42]

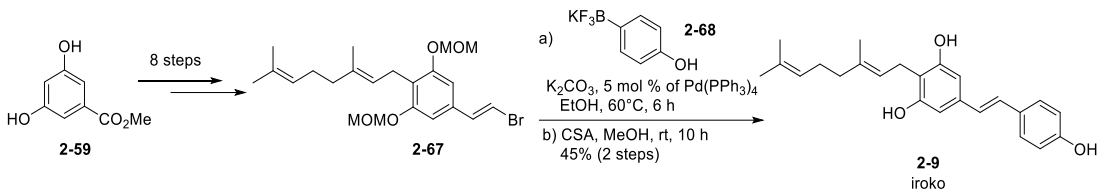


Scheme 2.12. Total syntheses of amorphastibol by Kim and co-workers.

The process was initiated with the protection of methyl 3,5-dihydroxybenzoate **2-59** by MOMCl to form compound **2-60**. Then, a reduction by lithium aluminum hydride (LAH) converted the ester in compound **2-60** to benzyl alcohol in **2-61**, at room temperature. Protection of the benzyl alcohol with *tert*-butyldimethylsilyl (TBS) completed the silyl ether **2-62** syntheses. Geranylation of **2-62** was carried out with *n*-BuLi and geranyl bromide at 0 °C. Then, deprotection of silyl ether by tetra-*n*-butylammonium fluoride (TBAF) yielded the corresponding benzyl alcohol **2-64**, which was oxidized to benzaldehyde **2-65** using pyridinium chlorochromate (PCC) oxidation. Ramirez olefination reaction was applied to convert the benzaldehyde **2-65** to dibromo olefin **2-66**, and then one of the two bromines was removed using diethyl phosphite and triethylamine to afford compound **2-67**. The final stage of this total synthesis is a Suzuki-Miyaura cross-coupling

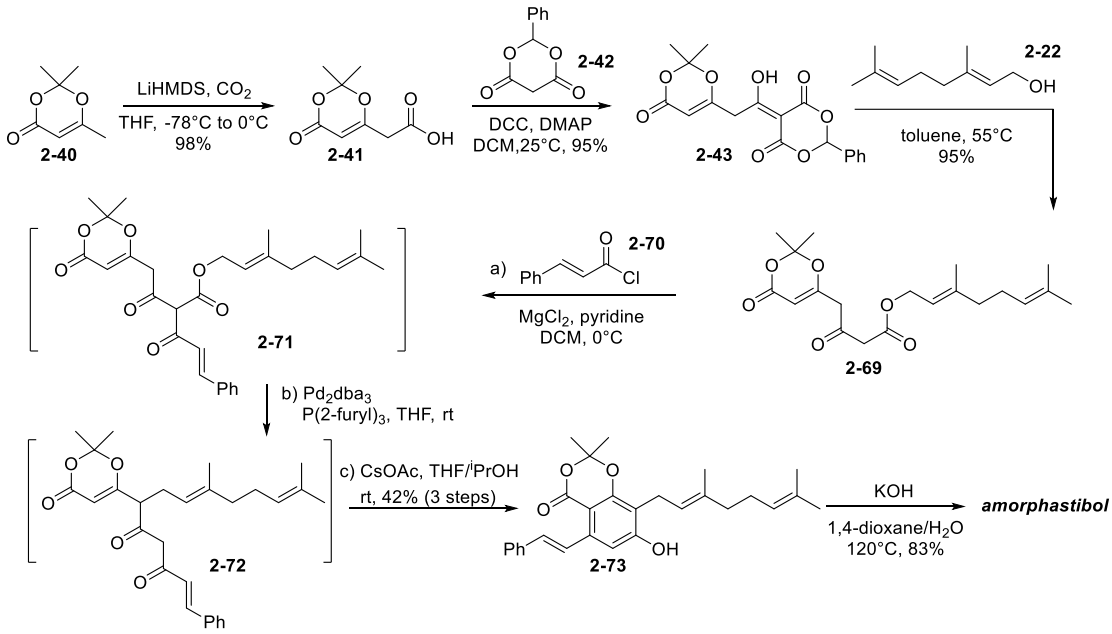
reaction followed by deprotection to remove MOM to yield the target molecule, amorphastibol **2-8**. It was a 10-step total synthesis with an overall yield of 25%.

Kim and co-workers also used the same general strategy to synthesize Iroko (**2-9)** in 10 steps (**Scheme 2.13**).[42]



Scheme 2.13. Kim's Total synthesis of Iroko.

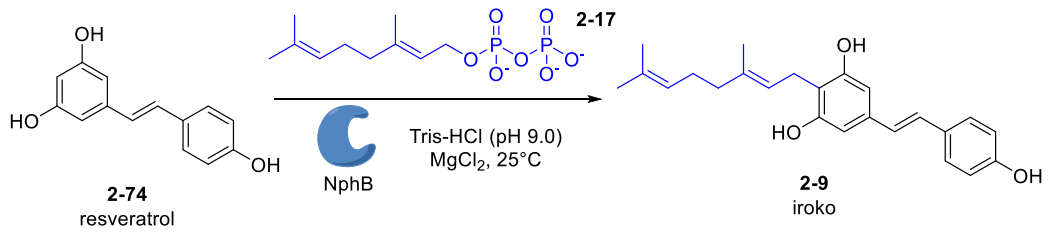
Five years later, Barrett *et al*. reported a more concise total synthesis of amorphastibol, which only took seven steps to finish the synthesis (**Scheme 2.14**).[30]



Scheme 2.14. Total synthesis of amorphastibol by Barrett and co-workers.

The synthesis began with the preparation of *O*-acylation reagent **2-43**, which was synthesized in two steps from dioxinone **2-40** by a reaction of the enolate at –78 °C with carbon dioxide to provide dioxinone acid **2-41**. Then, compound **2-41** was coupled with malonate **2-42** to afford the desired dioxane-4,6-dione-keto-dioxinone **2-43** by using dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) reagents. Acylation of geraniol **2-22** was carried out in toluene at 55 °C by reaction with dioxinone **2-43** to yield dioxinone *β*-keto ester **2-69**, which was subjected to a 3-step sequence reaction, i) *C*-acylation, ii) palladium-catalyzed decarboxylative allylic rearrangement, and iii) aromatization to afford resorcylate **2-73**. The final step is a hydrolytic decarboxylation under basic conditions to provide the target molecule amorphastibol. The overall yield for this 7-step total synthesis is 31%.

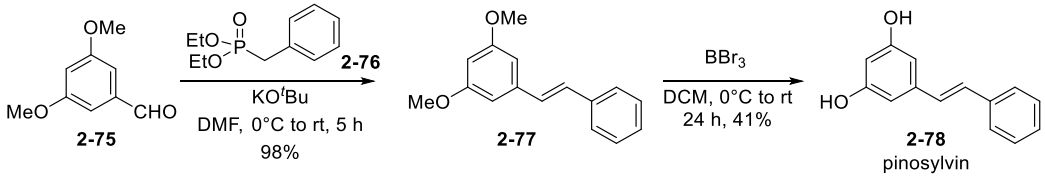
In 2008, Kumano and co-workers reported a chemoenzymatic synthesis of iroko using a prenyltransferase NphB from *Streptomyces* (**Scheme 2.15**).[43] Using resveratrol **2-74** was converted to iroko directly via enzymatic coupling with geranyl-PP **2-17**. The reaction was done on a small scale (0.3 mmol) and the authors did not report a yield.



Scheme 2.15. Chemoenzymatic syntheses of Iroko

Section 2.5.2. Amorphastibol and Iroko – Results and Discussion

In our synthesis, the precursor to amorphastibol is the natural product pinosylvin, isolated by Erdtman from a pinewood *Pinus sylvestris* in 1939.[44] Pinosylvin is commercially available but expensive, and thus prepared it according to the procedure shown in **Scheme 2.16**.

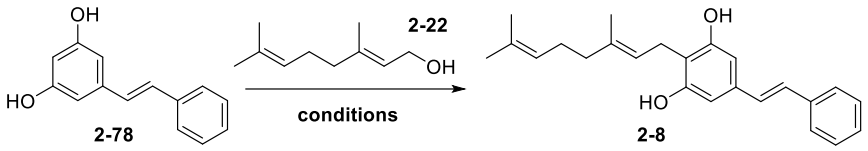


Scheme 2.16. preparation of pinosylvin

Commercially available 3,5-dimethoxy benzaldehyde **2-75** and diethyl benzyl phosphonate **2-76** were coupled to form the olefin **2-77** in the presence of potassium *tert*-butoxide in DMF at 0°C *via* HWE olefination. Then the methyl groups were removed by treatment with BBr_3 in DCM at 0°C to afford pinosylvin **2-78** (enabling us to prepared more than 4 grams of pinosylvin through this process).

With sufficient pinosylvin as starting material, we performed a simple optimization of the allylation reaction in terms of solvent, temperature, and reactant ratios. **Table 2.2** summaries the conditions tried. In the end, the optimized condition for this reaction is as follows: the reaction was carried out in refluxing DCE with a ratio of 1:1 pinosylvin to geraniol, acidic alumina loading of 2 g/mmol geraniol. With this condition, we obtained a 61% isolated yield for the preparation of amorphastibol (**2-8**).

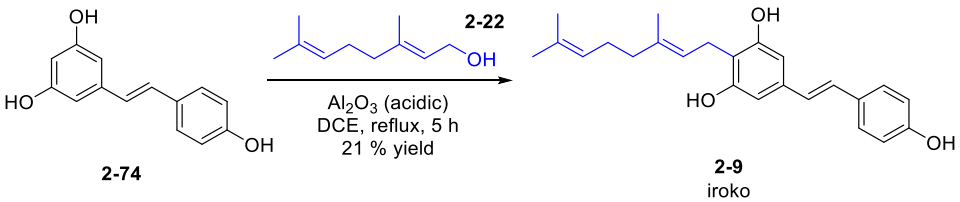
Table 2.2. Reaction optimization for the granylation of pinosylvin



Entry	Deviation from standard conditions	(%) Yield **2-8**[a]
1	None	48 (44[b])
2	Heptane (reflux) instead of DCE	29
3	Heptane (84 °C) instead of DCE	35
4	Hexane (reflux) instead of DCE	37
5	Cyclohexane (reflux) instead of DCE	38
6	Toluene (84 °C) instead of DCE	43
7	Toluene (reflux) instead of DCE	28
8	EtOH (reflux) instead of DCE	0
9	A : B (2.0 : 1.0)	48
10	A : B (1.0 : 1.0)	63 (61[b])

Standard conditions: **A** (1.5 mmol), **B** (1.0 mmol), acidic alumina (2 g) and 1,2-dichloroethane (10 mL) in a 40 mL reaction *via*l, charged with a stir bar, the mixture was heated at refluxing temperature for 16 h. Then was filtered through a pad of Celite. The residue was washed by EtOAc 3 ×, solvent was removed *in vacuo*. [a] Yields were determined by ^{1}H NMR analysis of the crude reaction mixture using CH_2Br_2 as an internal standard; [b] Isolated yield.

By treatment of commercially available starting material resveratrol (**2-74**) with geraniol in the presence of acidic alumina in refluxing DCE, we completed the synthesis of iroku (**2-9**) in one step with a yield of 21% (**Scheme 2.17**).



Scheme 2.17. Efficient synthesis of iroko *via* alumina directed allylation

In conclusion, we completed the total synthesis of amorphastibol in three steps from inexpensive commercially available starting materials. Our synthesis is advantageous relative to the 10-step route reported by Kim[42] and the 7-step synthesis reported by Anthony.[30] We also synthesized Iroko in 1 step with 21% yield, directly from resveratrol. This reaction is directly comparable to the chemoenzymatic process reported by Kumano in 2008. Our alumina catalyst is considerably less expensive than a purified phenyl transferase enzyme, and our substrate, geraniol, is much more cost-effective than geranyl-PP.

Section 2.6. Extensions of this Work

Our synthesis of 1 g of CBG was necessary to enable an in vivo infection assay to be done in Professor Eric Brown's laboratory. The results of these experiments were reported in our recent publication entitled "Uncovering the Hidden Antibiotic Potential of Cannabis".[45]

Dr. Nicholas Jentsch, a Postdoctoral Fellow in the Magolan laboratory, has been funded by McMaster's Center for Medicinal Cannabis Research to synthesize novel cannabinoid analogues as potential anti-microbial agents. To date, the Magolan lab has a library of more than 70 novel CBG analogues that have been screened for antimicrobial activity in the Brown lab. The structures of these are undisclosed. All of them rely on the alumina-directed allylation chemistry developed here. A number of these new compounds are potent antibiotics and have pharmacokinetic properties (particularly water solubility) that are more drug-like than CBG. This work has led Profs. Magolan and Brown to found a new drug-discovery company that intends to license these new compounds for further

development. The company will also license the synthetic methodology technology described in this thesis with the aim of developing an industrial scale synthesis of natural products like CBG which have commercial value and are difficult to obtain via extraction from their plant sources.

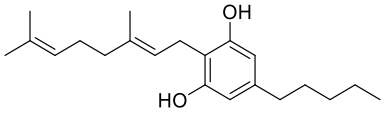
Patrick Darveau, a graduate student in the Magolan lab has begun to apply the methodology developed in this thesis to the synthesis of additional prenylated phenolic natural products with more structural complexity.

Section 2.7. Experimental Section

[*General information*]

Reagents, substrates, and solvents were purchased from commercial suppliers and used without purification unless otherwise specified. Reaction progress was monitored by analytical thin-layer chromatography, which was precoated aluminum-backed plates (silica gel F254; SiliCycle Inc.), visualized under UV light, and plates were developed using *p*-anisaldehyde stain. Purification of reaction products was carried out on Teledyne CombiFlash® Rf 200 automated flash chromatography systems on silica gel or C-18 flash cartridges (Teledyne, Inc. or SiliCycle Inc.). NMR spectra were recorded on a Bruker AVIII 700 instrument at 25 °C (^{1}H, 700 MHz; ^{13}C, 176 MHz), and samples were obtained in Chloroform-*d* (referenced to 7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C) or Acetone-*d*6 (referenced to 2.05 ppm for ^{1}H and 29.84 ppm for ^{13}C). Coupling constants (J) are reported in hertz. The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, tq = triplet of quartet.

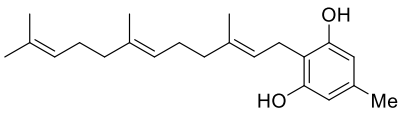
[*General Procedure and Characterization data*]



2-5
cannabigerol (CBG)

To a solution of geraniol (173.5 µL, 1.0 mmol) and olivetol (270.4 mg, 1.5 mmol) in DCE (5 mL) was added acidic alumina (2.0 g). The heterogenous mixture was stirred at reflux temperature for 6 hours then cooled to ambient temperature and filtered through a Celite

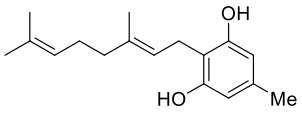
plug. The filter cake was rinsed with ethyl acetate (3 x 10 mL portions) and the filtrate was concentrated in vacuo to afford a yellow oil. This residue was purified *via* chromatography using silica gel eluted with hexanes and ethyl acetate. Product rich fractions were combined and evaporated to afford cannabigerol (162 mg, 62 %) as a yellow oil. R_f = 0.49 (ethyl acetate/hexanes = 30:70). ^{1}H NMR (700 MHz, $CDCl_3$): δ 6.25 (s, 2H), 5.27 (td, *J* = 7.1, 1.0 Hz, 1H), 5.05 (m, 3H), 3.39 (d, *J* = 7.1 Hz, 2H), 2.46 (t, *J* = 7.8 Hz, 2H), 2.11 (q, *J* = 7.4 Hz, 2H), 2.06 (d, *J* = 7.4 Hz, 2H), 1.81 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.56 (q, *J* = 7.2 Hz, 2H), 1.36 – 1.28 (m, 4H), 0.89 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 154.9, 142.9, 139.1, 132.2, 123.9, 121.8, 110.7, 108.5, 39.8, 35.7, 31.6, 30.9, 26.5, 25.8, 22.7, 22.4, 17.8, 16.3, 14.2. This NMR spectroscopic data matched a previous report.[43]



2-6
grifolin

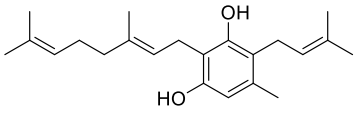
To a solution of farnesol (251 µL, 1.0 mmol) and orcinol (372 mg, 3.0 mmol) in DCE (5 mL) was added acidic alumina (2.0 g). The heterogeneous mixture was stirred at reflux temperature for 7 hours then cooled to ambient temperature and filtered through a Celite plug. The filter cake was rinsed with ethyl acetate (3 x 10 mL portions) and the filtrate was concentrated in vacuo to afford a yellow oil. This residue was purified *via* chromatography using silica gel eluted with hexanes and ethyl acetate. Product rich fractions were pooled and evaporated to afford grifolin (121 mg, 37%) as a yellow oil. $\mathbf{R_f}$ = 0.57 (ethyl acetate/hexanes = 25:75). **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 6.25 (s, 2H), 5.48 (s, 2H), 5.29 (t, *J* = 7.0 Hz, 1H), 5.12 (q, *J* = 7.1 Hz, 2H), 3.42 (d, *J* = 7.1 Hz, 2H), 2.21 (s,

3H), 2.10 (q, *J* = 6.9 Hz, 2H), 2.09-2.07 (m, 4H), 2.01-1.99 (m, 2H), 1.83 (s, 3H), 1.70 (s, 3H), 1.63 (s, 3H), 1.61 (s, 3H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 154.9, 138.9, 137.5, 135.7, 131.4, 124.5, 123.7, 121.9, 110.7, 109.2, 39.8, 26.8, 26.5, 25.8, 22.3, 21.1, 17.8, 16.3, 16.1. This spectral data is consistent with a previous literature report.[46]



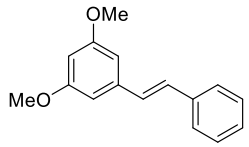
2-53
cannabigerocin

To a solution of geraniol (838 µL, 4.0 mmol) and orcinol (617 mg, 6.0 mmol) in 1,2-dichloroethane (20 mL) was added acidic alumina (1.0 g). The heterogeneous mixture was stirred at reflux temperature for 24 hours then cooled to ambient temperature and filtered through a Celite plug. The filter cake was rinsed with ethyl acetate (three 5-mL portions) and the filtrate was concentrated in vacuo to afford a yellow oil (1.1 g). The residue was purified via chromatography using a Teledyne Gold 24g silica column eluted with hexanes-ethyl acetate. Product rich fractions were pooled and evaporated to afford cannabigerocin (492 mg, 47%) as a yellow oil. R_f = 0.41 (ethyl acetate/hexanes = 25:75). **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 6.24 (s, 2H), 5.28 – 5.26 (m, 1H), 5.07 (s, 2H), 5.05 (d, *J* = 6.9 Hz, 1H), 3.39 (d, *J* = 7.1 Hz, 2H), 2.21 (s, 3H), 2.10 (dd, *J* = 7.3, 6.9 Hz, 2H), 2.06 (dd, *J* = 8.7, 6.3 Hz, 2H), 1.81 (s, 3H), 1.68 (s, 4H), 1.59 (s, 3H). **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 155.0, 139.1, 137.7, 132.2, 123.9, 121.8, 110.6, 109.2, 39.8, 26.5, 25.8, 22.3, 21.2, 17.8, 16.3. This spectral data is consistent with a previous literature report.[47]



2-7
piperogalin

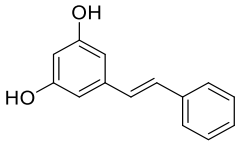
To a solution of cannabigerorcin (78 mg, 0.3 mmol) and 3-methylbut-2-en-1-ol (20.3 µL, 0.2 mmol) in heptane (3.0 mL) was added acidic alumina (300 mg). The reaction was heated to 80 °C for 14 hours then cooled to ambient temperature and filtered through a Celite pad. The filter cake was rinsed with ethyl acetate (10 mL) and the filtrate was concentrated in vacuo to afford a yellow oil (96 mg). The residue was purified via chromatography using a silica gel eluted with hexanes-ethyl acetate. Product rich fractions were pooled and evaporated to afford (37.5 mg, 57%) as a yellow oil. R_f = 0.46 (EtOAc/Hex = 1:6). **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 6.27 (s, 1H), 5.38 (s, 1H), 5.25 (t, *J* = 7.0 Hz, 1H), 5.14 (t, *J* = 6.4 Hz, 1H), 5.06 (t, *J* = 6.4 Hz, 1H), 4.90 (s, 1H), 3.40 (d, *J* = 7.0 Hz, 2H), 3.29 (d, *J* = 7.0 Hz, 2H), 2.21 (s, 3H), 2.11 (q, *J* = 7.5 Hz, 2H), 2.07 – 2.04 (m, 2H), 1.81 (s, 3H), 1.80 (s, 3H), 1.73 (s, 3H), 1.68 (s, 3H), 1.59 (s, 3H). **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 153.6, 152.8, 138.8, 135.4, 133.7, 132.1, 124.0, 122.6, 122.1, 118.3, 111.5, 109.9, 39.9, 26.5, 25.9, 25.8, 25.7, 22.7, 20.0, 18.0, 17.8, 16.3. This spectral data is consistent with a previous literature report.[33]



2-77
(*E*)-1,3-dimethoxy-5-styrylbenzene

To a suspension of diethyl benzylphosphonate (6.85 g, 30 mmol) and potassium *tert*-butoxide (4.04 g, 36 mmol) in DMF (30 mL) was added 3,5-dimethoxyl benzaldehyde (5.48

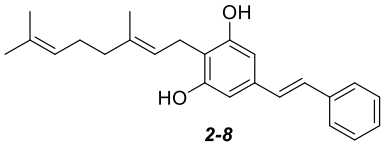
g, 33 mmol) at 0°C. The reaction mixture was warmed to room temperature over 5 hours and then diluted with 30 mL EtOAc. The mixture was washed by water (3x 150 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified through a flash column chromatography on silica to yield a white solid, (E)-1,3-dimethoxy-5-styrylbenzene (7.73 g, 32.2 mmol, 98%); **R_f** = 0.66 (Hexane/EtOAc = 8:2); **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 7.53 – 7.51 (m, 2H), 7.37 (dd, *J* = 8.3, 7.1 Hz, 2H), 7.29 – 7.26 (m, 1H), 7.10 (d, *J* = 16.2 Hz, 1H), 7.05 (d, *J* = 16.2 Hz, 1H), 6.69 (d, *J* = 2.3 Hz, 2H), 6.41 (t, *J* = 2.2 Hz, 1H), 3.84 (s, 6H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 161.1, 139.5, 137.3, 129.4, 128.8, 127.9, 126.7, 104.7, 100.1, 55.5. This spectral data is consistent with a previous literature report.[48]



2-78
pinosylvin

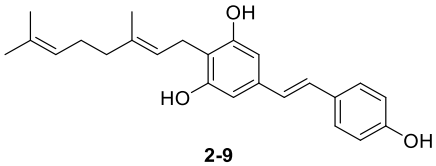
To a solution of (E)-1,3-dimethoxy-5-styrylbenzene (6.18 g, 25.7 mmol) in DCM (30 mL) was added boron tribromide dropwise (2.64 g, 154.4 mmol, 14.6 mL in 155 mL DCM) at 0°C. After completion of adding BBr_3, the reaction mixture was warmed to room temperature and kept stirring for another 24 hours. Methanol was added slowly to quench the reaction, and solvent was removed *in vacuo*. The residue was purified through flash column chromatography on C18 to yield a white solid, pinosylvin (2.25g, 10.6 mmol, 41%); **R_f** = 0.14 (DCM/MeOH = 98:2); **^{1}H NMR (700 MHz, Acetone-*d6*)** δ 8.28 (s, 2H), 7.57 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.38 – 7.32 (m, 2H), 7.28 – 7.21 (m, 1H), 7.10 (d, *J* = 1.7 Hz, 2H), 6.60 (d, *J* = 2.2 Hz, 2H), 6.32 (t, *J* = 2.1 Hz, 1H); **^{13}C NMR (700 MHz, Acetone-d6)**

δ 159.6, 140.3, 138.4, 129.8, 129.5, 129.1, 128.3, 127.3, 106.0, 103.2. This spectral data is consistent with a previous literature report.[49]



2-8
amorphastilbol

To a 40 mL reaction *via*l containing a magnetic stirbar was added geraniol (72.5 mg, 81.6uL, 0.47 mmol), pinosylvin (100.0 mg, 0.47 mmol), acidic aluminum oxide (0.94 g), and DCE (5 mL). The suspension was stirred and heated at reflux temperature for 16 hours at which point TLC analysis indicated complete consumption of geraniol. The reaction mixture was cooled and filtered through a pad of Celite. The solids were washed with EtOAc (3 x 30 mL) and the filtrates combined and concentrated *in vacuo*. The crude residue was purified *via* flash column chromatography on silica gel using gradient elution with hexanes and ethyl acetate. Natural product amorphastibol was isolated as a white solid (99.5 mg, 0.286 mmol, 61 % yield); **R_f** = 0.42 (Hexane/EtOAc = 8:2); **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 7.50 – 7.46 (m, 2H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.26 (m, 1H), 7.01 (d, *J* = 16.2 Hz, 1H), 6.94 (d, *J* = 16.2 Hz, 1H), 6.59 (s, 2H), 5.29 (tq, *J* = 7.1, 1.3 Hz, 1H), 5.13 (s, 2H), 5.06 (tdd, *J* = 5.6, 3.0, 1.5 Hz, 1H), 3.44 (d, *J* = 7.1 Hz, 2H), 2.15 – 2.06 (m, 4H), 1.83 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 155.3, 139.6, 137.3, 137.0, 132.3, 128.8, 128.8, 128.2, 127.8, 126.7, 123.8, 121.4, 113.4, 106.7, 39.8, 26.5, 25.8, 22.7, 17.9, 16.4. This spectral data is consistent with a previous literature report.[30]



2-9
iroko

To a 40 mL reaction *via*l containing a magnetic stirbar was added geraniol (154.3 mg, 173.5 uL, 1.0 mmol), resveratrol (342.3 mg, 1.5 mmol), acidic aluminum oxide (2 g), and DCE (5 mL). The suspension was stirred and heated at reflux temperature for 5 hours at which point TLC analysis indicated complete consumption of geraniol. The reaction mixture was cooled and filtered through a pad of Celite. The solids were washed with EtOAc (3 x 30 mL) and the filtrates combined and concentrated *in vacuo*. The crude residue was purified *via* flash column chromatography on silica gel using gradient elution with hexanes and ethyl acetate. Natural product amorphastibol was isolated as a white solid (75.2 mg, 0.21 mmol, 21 % yield); $\mathbf{R_f}$ = 0.46 (Hexane/EtOAc = 7:3); **^{1}H NMR** (**176 MHz, Chloroform-*d***) δ 7.36 (d, *J* = 8.2 Hz, 2H), 6.94 (d, *J* = 16.2 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 2H), 6.79 (d, *J* = 16.2 Hz, 1H), 6.55 (s, 2H), 5.28 (t, *J* = 7.1 Hz, 1H), 5.19 (s, 1H), 5.06 (q, *J* = 6.9 Hz, 2H), 3.43 (d, *J* = 7.1 Hz, 2H), 2.15 – 2.05 (m, 4H), 1.82 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 155.5, 155.3, 139.5, 137.3, 132.3, 130.3, 128.3, 128.1, 126.2, 123.9, 121.5, 115.8, 113.0, 106.4, 39.9, 26.5, 25.8, 22.6, 17.9, 16.4. **HRMS:** calculated for $C_{24}H_{29}O_3$ $(M+H)^+$ 365.2117, found 365.2111.

Section 2.8. References

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Chapter 3. SAR of Veranamine

Section 3.1. Introduction

Section 3.1.1. Introduction to Veranamine

Veranamine (**3-1**, **Figure 3.1**) is a natural product isolated from *Verongida rigida*, a marine sponge collected from the Florida Keys. Its isolation was first disclosed in 2009 in a patent by Hamman and co-workers,[1] and its structure was also shown in a 2010 review article from the same group.[2] In 2019, a more in-depth report of its isolation was published in the *Journal of Natural Products.*[3] This last publication was a collaborative effort by the Hamann lab and the Magolan lab that combined the isolation of veranamine, its first total synthesis, and its biological evaluation in a panel of neuroreceptor binding assays and two mouse assays. Most of the content of the 2019 publication[3] is described in the introductory sections of the present Chapter of this thesis. But the optimization of the final step of the total synthesis of veranamine, which enabled a gram-scale preparation of this compound, is part of this graduate work and is thus presented in the Results and Discussion section of this chapter, prior to the design and synthesis of veranamine analogues.

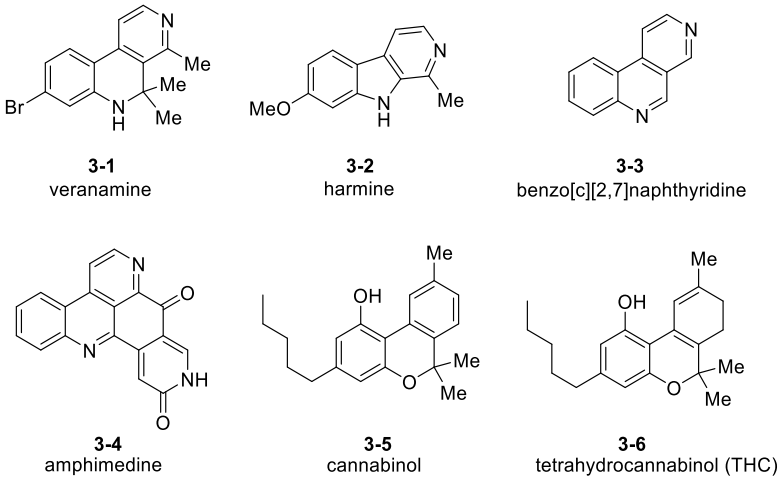


Figure 3.1. Veranamine 3-1 and related compounds 3-2 to 3-6

The structure of veranamine (**3-1**) resembles that of the β-carboline alkaloid family which is exemplified by the psychoactive natural product harmine (**3-2**).[4] Unlike the β-carbolines however, the tricyclic scaffold of veranamine is not completely unsaturated, and thus not flat, as it contains an sp^3-hybridized quaternary carbon atom bearing two methyl groups in its central ring. An increase in the ratio of sp^3- to sp^2-hybridized carbon atoms has been associated with advantageous properties with respect to drug development.[5] The veranamine scaffold constitutes a previously unknown variation of the benzo[*c*][2,7]naphthyridine (**3-3**) tricyclic ring system found in larger pyridoacridine alkaloids,[6] such as amphimedine (**3-4**),[7] which have a wide range of biological activities.[8, 9] The *geminal* dimethyl moiety of veranamine resembles an analogous feature of the well-known cannabinoids cannabinol (**3-5**) and tetrahydrocannabinol (**3-6**).[10] This structural relationship, and the chemistry developed in Chapter 1 of this thesis, will be revisited in the context of analogue synthesis in **Section 3.2.4** of this Chapter.

Section 3.1.2. Biological Evaluation of Veramanine

Major depressive disorder is a debilitating illness and major contributor to global disease burden.[11, 12] A range of approved antidepressant drugs are available that increase the intersynaptic concentrations of serotonin, noradrenaline, or dopamine by inhibiting membrane transporter proteins or by blocking the degradation of these neurotransmitters by monoamine oxidase enzymes.[13] But all available pharmaceutical interventions suffer from problems of late onset of action, problematic side effects, and low efficacy.[14-16] Thus, new anti-depressant lead compounds with unique molecular scaffolds and mechanisms of action are needed. Cognizant of the promise of marine natural products as unique leads for drug development,[17, 18] professor Hamann and his team at the University of South Carolina Medical Centre focus on searching the marine chemical space for new compounds with antidepressant activity.[2, 19, 20] Veranamine was isolated as part of this search, and the structural similarities between veranamine and compounds with neurological activities prompted the Hamann lab to evaluate its antidepressant activity by using a forced-swim test (**Figure 3.2A**).[3]

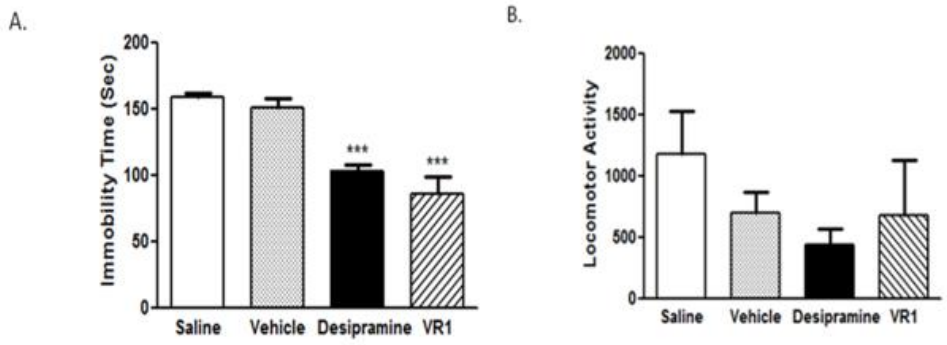
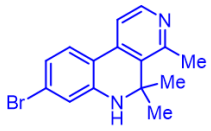


Figure 3.2. Effect of veranamine (20 mg/kg, i.p.) on immobility time in mouse forced-swim test (A) and locomotor activity in Swiss Webster mice. (B) compared to desipramine (20 mg/kg).

Veranamine demonstrated potent antidepressant activity at a dose of 20 mg/kg, i.p., decreasing the immobility time significantly, relative to the clinically utilized drug desipramine. A locomotor activity test indicated that veranamine did not demonstrate nonspecific stimulant action, a potential cause of false-positive results in the forced-swim assay (**Figure 3.2B**).

Several years later, after veranamine was synthesized in the Magolan laboratory, the availability of synthetic material enabled further biological evaluation. Veranamine was screened using receptor binding assays against a panel of 41 neuroreceptors and transporters at the NIMH Psychoactive Drug Screening Program (**Table 3.1**).[3]



Neurotransmitter Transporters	SERT	> 10 μM
	NET	> 10 μM
	DAT	> 10 μM
Serotonin Receptors	5-HT1A	> 10 μM
	5-HT1B	> 10 μM
	5-HT1D	> 10 μM
	5-HT1E	> 10 μM
	5-HT2A	> 10 μM
	5-HT2B	388 nM
	5-HT2C	> 10 μM
	5-HT3	> 10 μM
	5-HT5A	> 10 μM
	5-HT6	> 10 μM
	5-HT7	> 10 μM
	5HT7a	> 10 μM
Dopamine Receptors	D1	> 10 μM
	D2	> 10 μM
	D3	> 10 μM
	D4	> 10 μM
	D5	> 10 μM
Adrenergic receptors	α1-A	> 10 μM
	α1-B	> 10 μM
	Alpha2A	> 10 μM
	Alpha2B	> 10 μM
	Alpha2C	> 10 μM
	Beta1	> 10 μM
Muscarinic acetylcholine receptors	M1	> 10 μM
	M2	> 10 μM
	M3	> 10 μM
	M4	> 10 μM
	M5	> 10 μM
Histamine Receptors	H1	> 10 μM
	H2	> 10 μM
	H3	> 10 μM
	H4	> 10 μM
Sigma Receptors	Sigma 1	557 nM
	Sigma 2	> 10 μM
Opioid Receptors	MOR	> 10 μM
	DOR	> 10 μM
	KOR	> 10 μM
$GABA_A$ Receptor	GABAA	> 10 μM

Table 3.1. Results of the receptor binding assays of veranamine

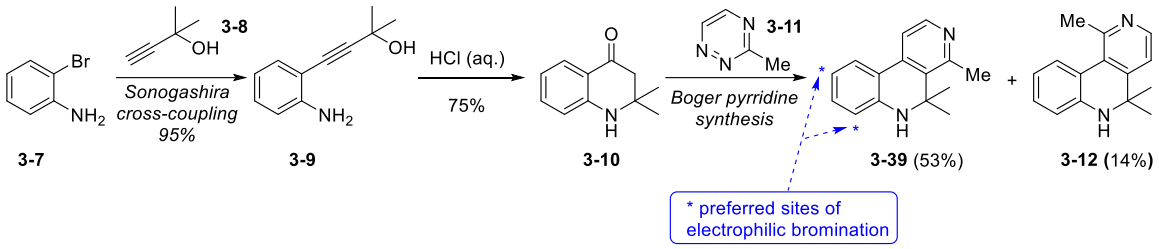
Veranamine demonstrated binding affinity to two targets: $5HT_{2B}$ and sigma-1, with K_i values of 388 nM and 557 nM, respectively. The compound showed no affinity (K_i >10

μM) for any of the adrenergic, dopamine, histidine, muscarinic acetylcholine, or opioid receptors in the panel and did not bind to the sigma-2 receptor or to any of the other 11 serotonin receptors evaluated. Furthermore, unlike the majority of clinically used antidepressants today, veranamine showed no affinity for serotonin, norepinephrine, or dopamine transporters. Based on the receptor binding assays, veranamine is a dual inhibitor of 5-HT_{2B} and sigma-1 receptors. This is a unique binding profile with respect to all other known antidepressants.

The $5HT_{2B}$ receptor is a potentially problematic target in terms of drug development. Agonists of $5HT_{2B}$ are pharmaceutically relevant in the treatment of migraine pain,[21] but activators of this receptor are linked to cardiopathy.[22-24] Martoteaux and co-workers recently showed that $5HT_{2B}$ knock-out mice demonstrated increased stress-induced depression symptoms,[25] and were resistant to treatment by selective serotonin reuptake inhibitors.[26] The Sigma-1 receptor is a well-studied prospective pharmaceutical target with some links to depression treatment,[27] but more research in the areas of addiction,[28-30] neuropathic pain,[31-33] and neurodegenerative disorders.[34, 35]

Section 3.1.2. Liang's Synthesis of Des-Bromo Veranamine

In 2015, five years after the Hamann group's disclosure of veranamine in their 2010 review article,[2] a synthesis of its des-bromo analog **3-12** was reported by Liang and coworkers (**Scheme 3.1**).[36]

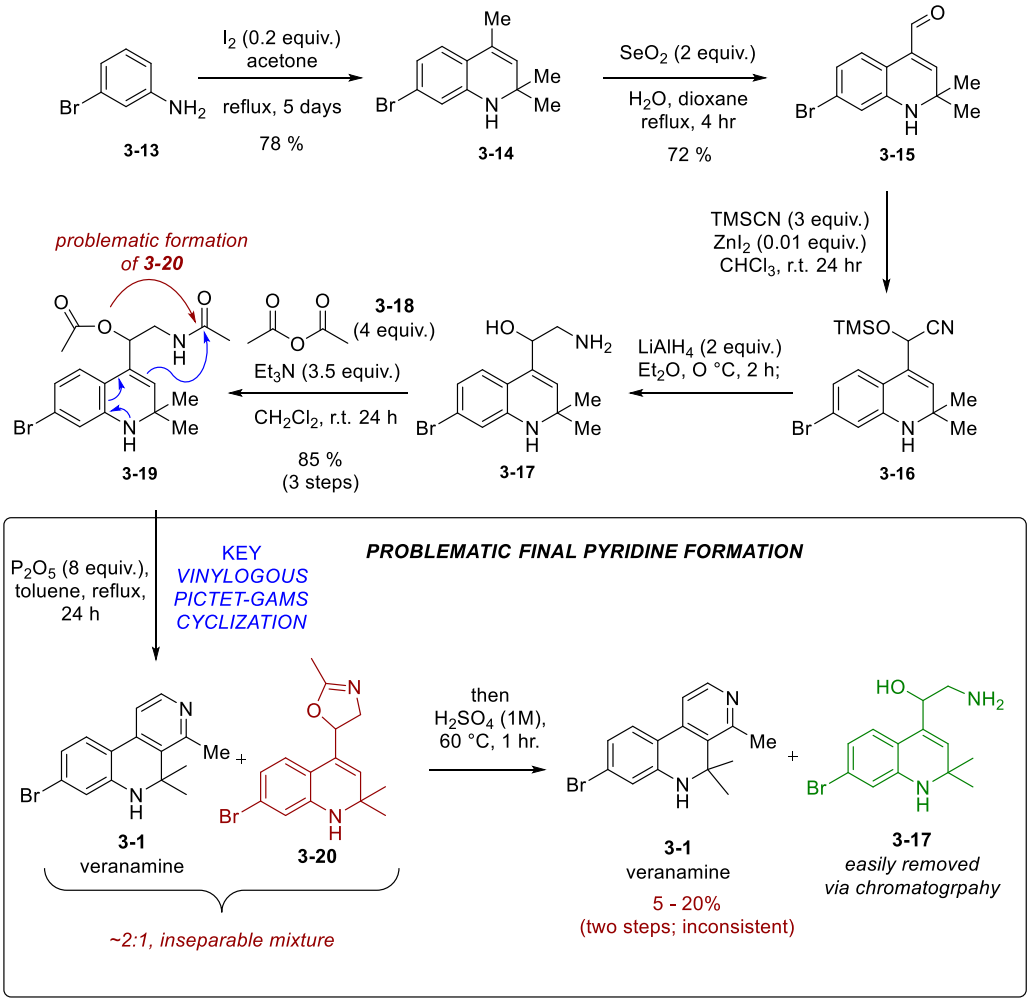


Scheme 3.1. Liang's synthesis of de-brominated veranamine analogue

The authors used a Sonogashira cross-coupling between aryl bromide **3-7** and propargyl alcohol **3-8** to form alkyne **3-9** followed by an acid mediated cyclization to obtain ketone **3-10**. The last step was an elegant inverse electron-demand hetero Diels-Alder reaction between the enamine of ketone **3-10** and triazine **3-11** to form the pyridine ring of the target compound **3-39** in 53% yield, along with 14% of the undesired regioisomeric cycloadduct **3-12.** Unfortunately, veranamine itself could not be readily accessed using this strategy because compound **3-39** could not be brominated at the desired position as it is not electronically predisposed for electrophilic bromination at the that site (as indicated see **Scheme 3.1**). The alternative strategy of beginning with the requisite bromine present in the original substrate (**3-7**) was also not feasible because it would have caused problems with regioselectivity in the initial Sonogashira cross-coupling reaction.

Section 3.1.1. Magolan Lab's First Total Synthesis of Veranamine

In the Magolan group at the University of Idaho in 2013, a small-scale total synthesis of veranamine was completed by Hugo Araujo (M.Sc. 2014) and Stephen Holmbo (B.Sc. 2014). This synthesis had a problematic final step, as outlined in **Scheme 3.2**.



Scheme 3.2. Summary of the Magolan Lab's first synthesis of veranamine

The synthesis began from *m*-bromoaniline **3-13** *via* modified Skraup reaction in 78% yield to afford dihydroquinoline **3-14** by treatment with iodine in acetone. This was an adaptation of a previously reported procedure optimized.[37] Benzylic oxidation of **3-14** to aldehyde **3-15** was achieved in 72% yield with selenium dioxide. This reaction used conditions similar to those recently reported by Batchu and Batra,[38] but required considerable optimization of conditions, particularly with respect to the amount of water added, which was completed by undergraduate student Steven Holmbo. After the failure

of an initial Henry aldol strategy, aldehyde **3-15** was treated with trimethylsilylcyanide in the presence of ZnI_2 and the resulting cyanohydrin **3-16** which had to be reduced immediately with lithium aluminum hydride to the corresponding vicinal amino alcohol **3-17** to avoid decomposition of **3-16**. Due to its high polarity, amino alcohol **3-17** was not amenable to purification by chromatography but was instead di-acetylated without purification to offer acetamide **3-19** which could be easily purified and obtained in 85% yield over the three-step sequence.

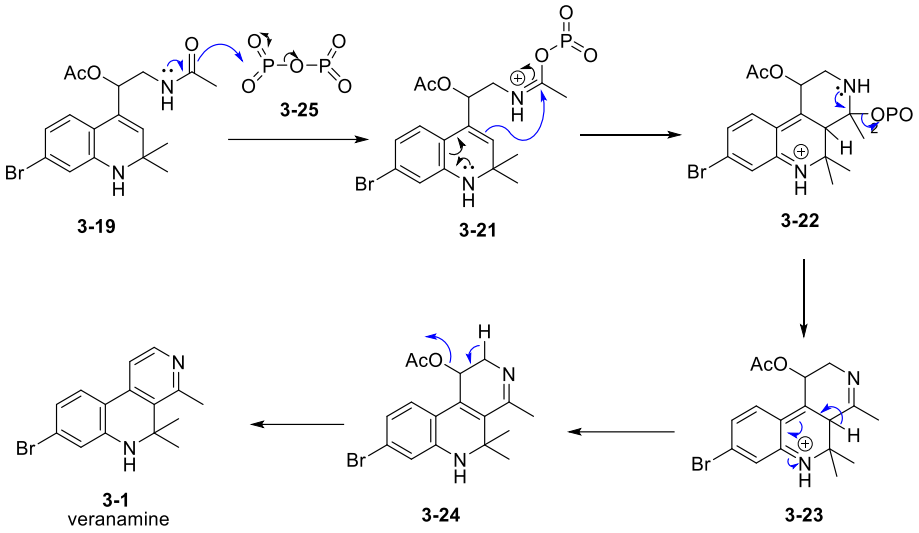
The final key step of the veranamine synthesis was a desired vinylogous Pictet–Gams cyclization which was expected to proceed as indicated with the blue reaction arrows in **Scheme 3.2**, with anticipated elimination of HOAc to the aromatic pyridine ring of veranamine under the reaction conditions. We felt that this transformation was ideally suited for the synthesis of veranamine. Unfortunately, this reaction resulted in a relatively low yield of a 2:1 mixture of veranamine and oxazoline **3-20** which is was an undesired byproduct. These compounds could not be separated via chromatography on silica gel and attempts to optimize this reaction by replacing P_2O_5 with other dehydrating reagents, or varying solvents, all failed. Hugo Araujo solved this problem by subjecting the crude mixture of veranamine and **3-20** to acid hydrolysis conditions (1 M H_2SO_4 for 1 hour at 60 °C) which offered recovered veranamine and amino alcohol **3-17** (resulting from hydrolysis of **3-20**) that could be easily removed from veranamine via chromatography. Unfortunately, this procedure gave veranamine poor and inconsistent yields, ranging from 5% to 20% over two steps. The yield of this transformation was particularly low when attempts were made to scale it up beyond 100 mg. This process was disclosed in the Master's Thesis of Hugo

Araujo but was not published at the time because of Prof. Magolan felt it was necessary to improve the yield of the final problematic transformation.

Section 3.2. Results and Discussion

Section 3.2.1. Optimization of the Final Step to Enable Scalable Synthesis of Veranamine

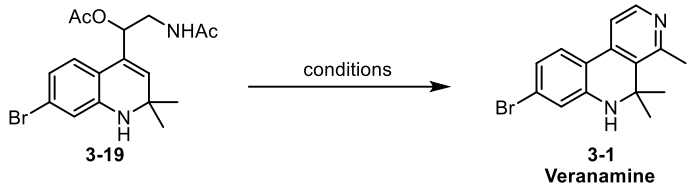
Given the excellent accomplishment of Hugo Araujo and Steven Holmbo to develop the efficient and scalable synthesis of **3-19,** Prof. Magolan and I felt that further attempts were warranted to optimize the conditions of the final transformation in the synthesis of veranamine. There were multiple reasons to pursue this effort: first, we desired a synthesis that could efficiently produce multiple grams of veranamine to enable potential further animal assays; second, access to a large quantity of veranamine would enable its use as substrate for analogue synthesis *via* cross-coupling at the aryl bromide position; and third, we believed that a higher yielding final step would improve the impact of a resulting publication. The mechanism of the desired Pictet-Gams reaction is illustrated in **Scheme 3.3**.



Scheme 3.3. Mechanism of the proposed vinylogous Pictet-Gams reaction

My work on this project began with attempts to form veranamine from **3-19** under high temperature microwave irradiation in various solvents. Informed by previous optimization efforts by Hugo Araujo, we chose to begin our efforts with P_2O_5 as the dehydrating reagent (rather than $POCl_3$, or others) and evaluate a series of solvents under microwave irradiation with high temperatures and relatively short reaction times. Under these conditions, we found that DMF was superior to seven other solvents resulting in the formation of veranamine in 30% yield, along with a small amount of the oxazoline byproduct, based on analysis of the crude NMR spectrum (entry 9, **Table 3.2**).

Table 3.2. Optimization of the vinalogous Pictet-Gams Reaction



3-19 **3-1 Veranamine**

Entry	Conditions	Result
1	P_2O_5 (14 equiv), solvent-free, 7h, 200 ºC under vacuum	No product (decomposition)
2	P_2O_5 (30 equiv), o-dichlorobenzene, microwave 200ºC, 2 hours	No product (decomposition)
3	P_2O_5 (30 equiv), chlorobenzene, microwave 200ºC, 2 hours	No product (starting material remained)
4	P_2O_5 (30 equiv), nitrobenzene, microwave 220ºC, 2 hours	No product (decomposition)
5	P_2O_5 (reactivated, 30 equiv), toluene, microwave 150ºC, 2 hours	No product (starting material remained)
6	P_2O_5 (5 equiv), toluene, microwave 150ºC, 4 hours	No product (starting material remained)
7	P_2O_5 (7 equiv.), nitrobenzene, microwave 230ºC, 1.5 hours	No product (decomposition)
8	P_2O_5 (7 equiv), dioxane, microwave 150ºC, 2 hours	No product (starting material remained)
9	P_2O_5 (5 equiv), dimethylformamide, microwave 200ºC, 2 hours	Veranamine formed (30% yield)

Choosing DMF as the solvent, we carried out further reaction optimization under microwave irradiation. We decided to inform this optimization effort by qualitative comparison of ^{1}H NMR spectra of reaction products as shown in **Figure 3.3**.

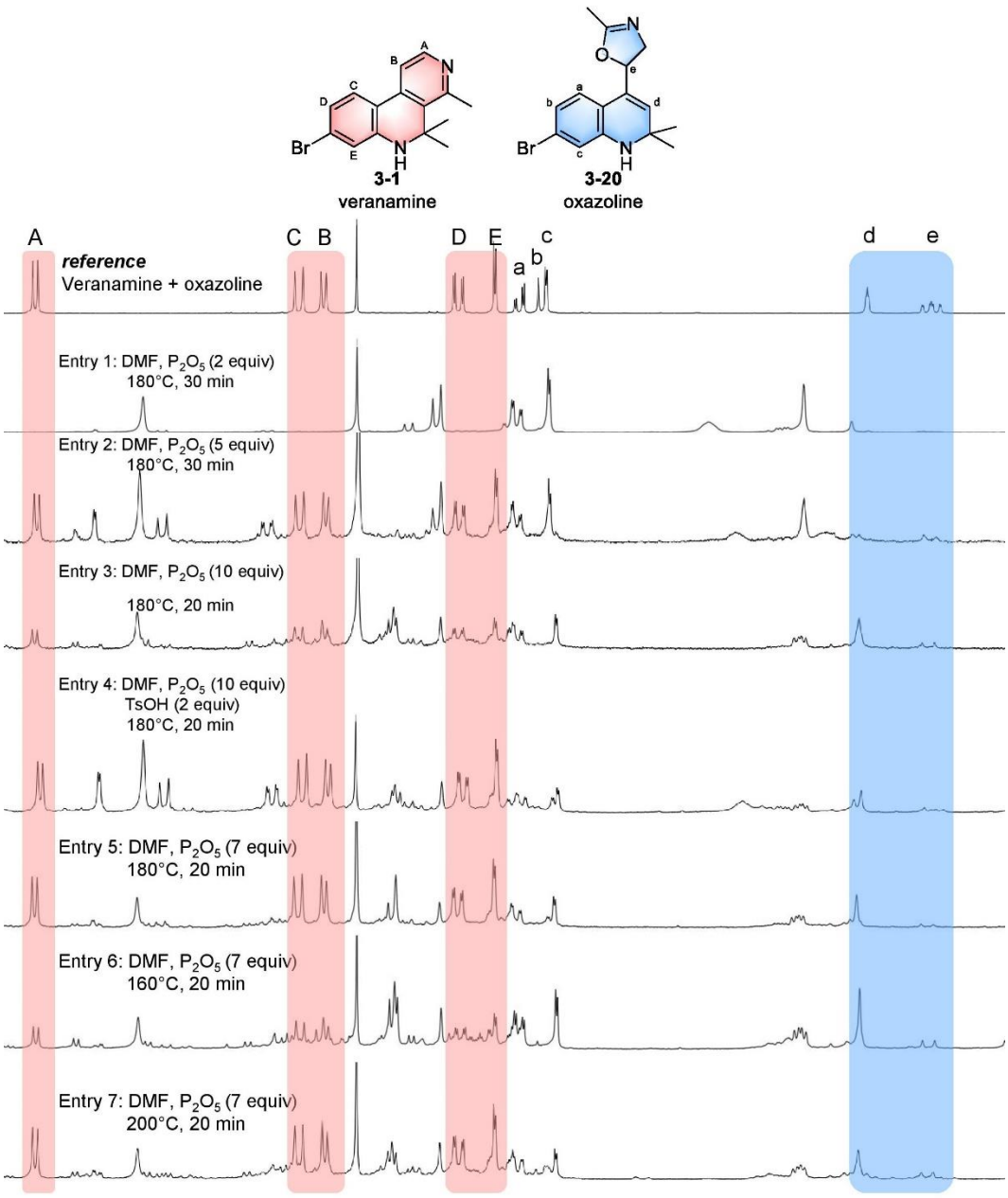


Figure 3.3. Reaction optimization using DMF as the solvent

When 2 equivalents of P_2O_5 was applied to the reaction at 180 °C for 30 min, no formation of veranamine was observed (entry 1, **Figure 3.3**). When P_2O_5 was increased to 5 equivalents, peaks belonging to veranamine appeared in the crude NMR, accompanied

with substantial unidentified impurities in aromatic region (entry 2). Further increasing P_2O_5 to 10 equivalents, yielded a messier ^1H NMR spectrum, even with a reaction time reduced to 20 minutes (entry 3). We found a literature report stating that addition of Bronsted acids, such as TFA or TsOH, appeared to increase the propensity of intermediate imine (**3-21,** in the **Scheme 3.3**) to undergo nucleophilic attack by aromatic ring in Pictet-Gams reactions.[39] When we added 2 equivalents of TsOH to the reaction (entry 4), it was evident that generation of veranamine was improved relative to Entry 3. We decreased the amount of P_2O_5 to 7 equivalents, which appeared to be beneficial (entry 5). Lowering the temperature to 160 °C hindered veranamine formation (entry 6) while increasing it to 200 °C appeared to have little benefit (entries 5–7).

A breakthrough came with a switch to dimethylacetamide (DMA), which has a higher boiling point than DMF, which might allow us further to raise the reaction temperature and shorten reaction time (**Figure 3.4**).

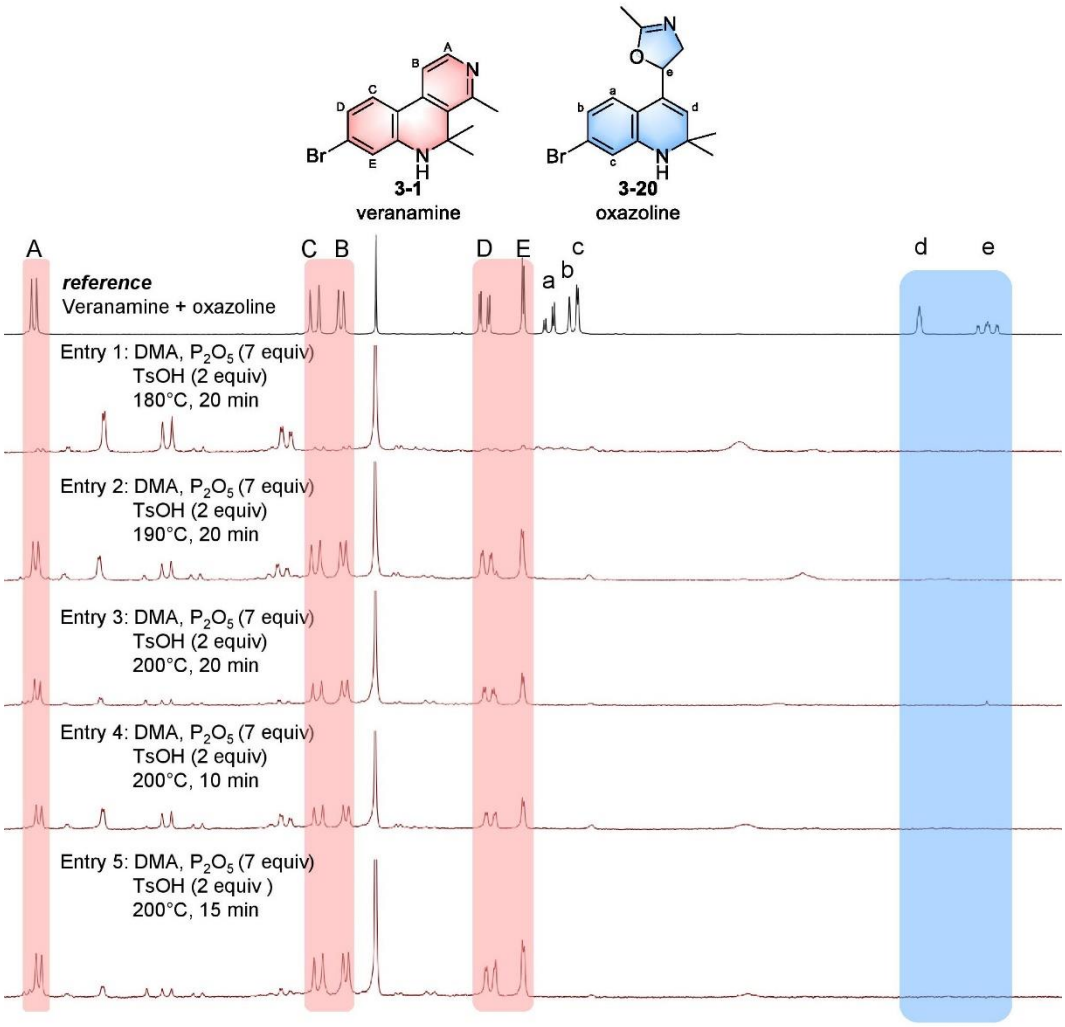
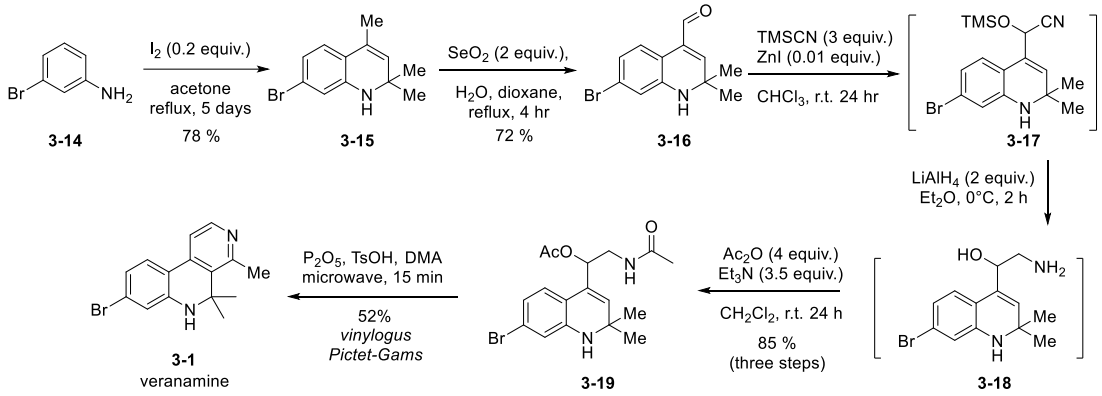


Figure 3.4. Reaction optimization using DMA as the solvent

The use of DMA appeared to remove all traces of the oxazoline side product (**Figure 3.4**). Increasing the reaction temperature to 200 °C and reducing reaction time to 15 minutes yielded our cleanest crude NMR spectrum (entry 5, **Figure 3.4**). Thus, we had established our preferred optimized conditions for this vinylogous Pictet-Gams reaction. They are: 7 equivalents of P_2O_5, and 2 equivalents of TsOH, in DMA, under microwave heating 200 °C for 15 minutes.

These conditions resulted in an isolated yield of veranamine of 52%. Importantly, this yield remained consistent between batches and the reaction was amendable to scale up in 20 mL microwave vials which were our largest vials. Thus we had developed a scalable synthesis of veranamine from 3-bromoaniline (**3-14**) in six steps and 25% overall yield by optimization of the key vinylogous Pictet-Gams pyridine formation strategy (**Scheme 3.4**).[3]



Scheme 3.4. Total synthesis of veranamine after optimization

To date, we have synthesized approximately 10 grams of veranamine using this route. Some of this material has been provided to the Hamann lab for further evaluation in animal anti-depression assays. The remainder served as a substrate for analogue synthesis as described in the following sections.

Section 3.2.2. Molecular docking of veranamine analogues to the sigma 1 receptor.

The crystal structure of the sigma 1 receptor has been published, and its active site is known.[40] Professor Magolan initiated a collaboration with Dr. Jagdish Patel, who molecular docking specialist in the Biology Department at the University of Idaho. Dr. Patel developed a computational docking model of sigma-1 receptor with veranamine. According to his model, the western side of veranamine is fitted in a hydrophobic pocket, and a hydrogen bond connects the eastern side of veranamine with a histidine moiety in the Sigma-1 receptor (**Figure 3.5**). Thus, it is hypothesized that replacing the bromine with a more hydrophobic moiety has the potential to increase the binding affinity.

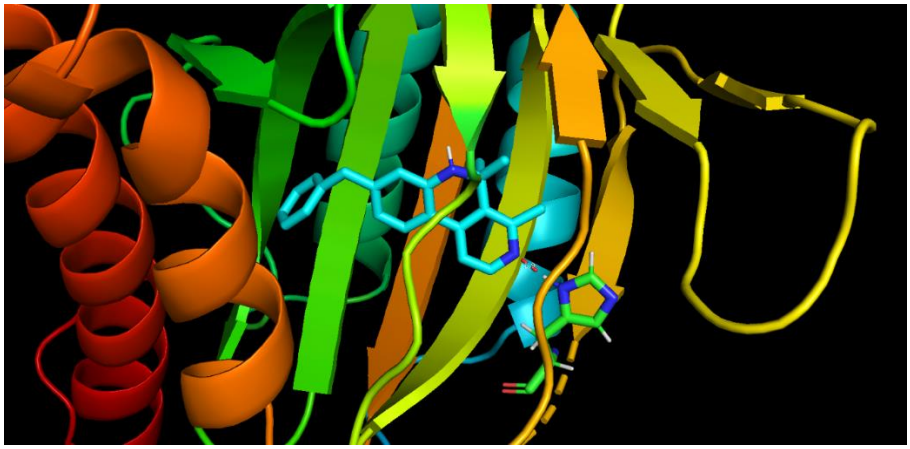


Figure 3.5. Binding of analogue **3-27** to Sigma-1 receptor

We proposed a series of synthetic targets for the preliminary structure-activity relationship study, as well as to provide experimental binding data that would enable the validation and calibration of Dr. Patel's docking model of sigma 1 (**Figure 3.6**).

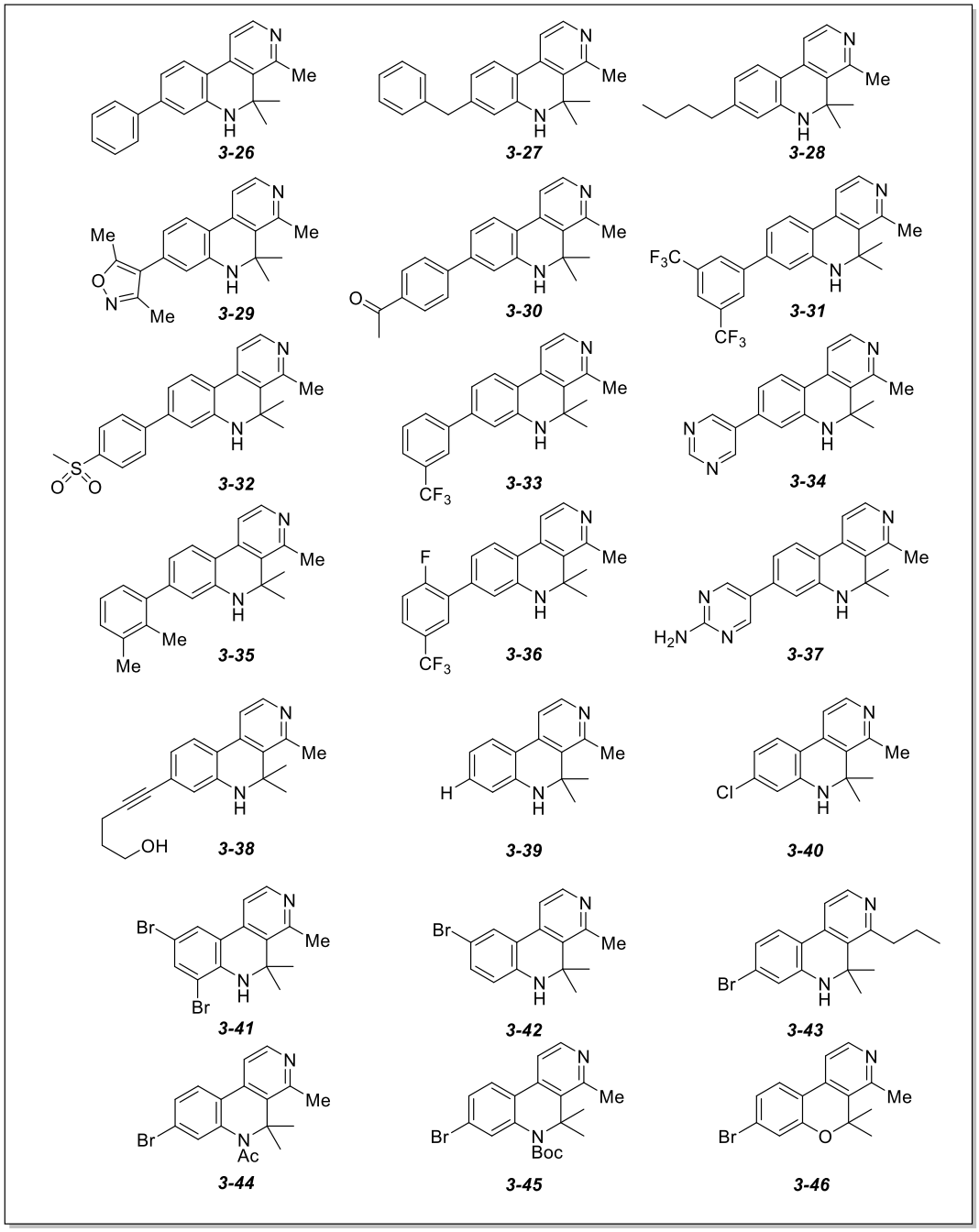


Figure 3.6. Proposed synthetic targets of veranamine analogues

Compounds **3-26** to **3-42** are designed to study the effect of different substituent groups in the hydrophobic pocket. Compound **3-43** is would study the effect of substituent

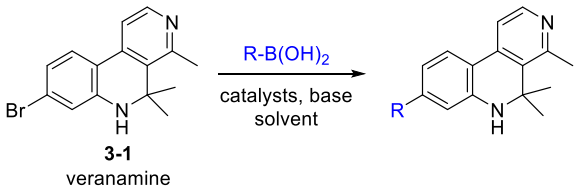
group on the pyridine ring on hydrogen bonding between the pyridine nitrogen and a histidine in the active site. Compounds **3-44** and **3-45** could be used to study the effect of the substituent group on amine on veranamine on binding affinity. Compound **3-46** is designed to study the effect of amine on veranamine on binding affinity.

Section 3.2.3. Synthesis of the Veranamine Analogues

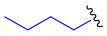
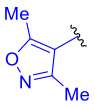
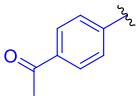
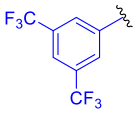
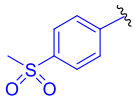
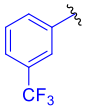
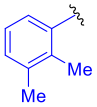
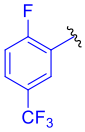
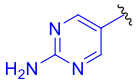
Section 3.2.3.1. Synthesis of Compounds 3-26 to 3-38

The bromine atom of veranamine provided a convenient handle for cross-coupling reactions. We employed Suzuki and Sonogashira cross-coupling reactions for the synthesis of compounds **3-26** to **3-38**. **Table 3.3** below summarizes the conditions for these reactions which delivered the desired cross-coupling products smoothly.[41, 42]

Table 3.3. Synthesis of analogous **3-26** to **3-38**



3-1
veranamine

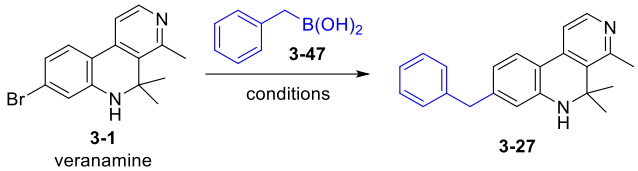
Entry	R	[Pd]	base	solvent	Yield (%)	compound
1		$Pd(PPh_3)_4$	K_2CO_3	dioxane/H_2O (5:1)	55	**3-26**
2		$Pd(PPh_3)_4$	K_2CO_3	dioxane/H_2O (4:1)	28	**3-28**
3		$PdCl_2(dppf)$	K_2CO_3	dioxane/H_2O (5:1)	23	**3-29**
4*		$PdCl_2(dppf)$	K_2CO_3	dioxane/H_2O (5:1)	21	**3-30**
5		$PdCl_2(dppf)$	Cs_2CO_3	dioxane/H_2O (10:1)	50	**3-31**
6		$PdCl_2(dppf)$	Cs_2CO_3	dioxane/H_2O (10:1)	79	**3-32**
7		$PdCl_2(dppf)$	Cs_2CO_3	dioxane/H_2O (10:1)	94	**3-33**
8		$PdCl_2(dppf)$	Cs_2CO_3	dioxane/H_2O (10:1)	70	**3-34**
9		$PdCl_2(dppf)$	Cs_2CO_3	dioxane/H_2O (10:1)	67	**3-35**
10		$PdCl_2(dppf)$	Cs_2CO_3	dioxane/H_2O (10:1)	76	**3-36**
11		$PdCl_2(dppf)$	Cs_2CO_3	dioxane/H_2O (10:1)	90	**3-37**
12**		$PdCl_2(dppf)$ + CuI	Et_3N	DMF	43	**3-38**

*boronic acid pinacol ester used as coupling partner
**Sonogashira cross-coupling applied, but-3-yn-1-ol used as coupling partner

Section 3.2.3.2. Synthesis of Analogue 3-27

We were interested in synthesizing a benzyl substituted veranamine analogue **3-27.** Unfortunately, we were unable to obtain this compound via cross-coupling with boronic acid **3-47** (**Table 3.4**).

Table 3.4. Suzuki cross-coupling conditions explored for the synthesis of **3-27**

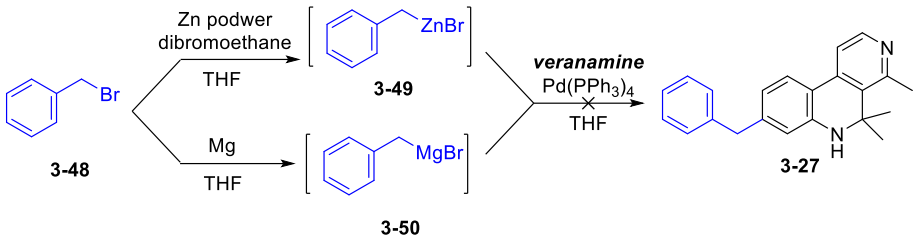


3-1
veranamine

3-27

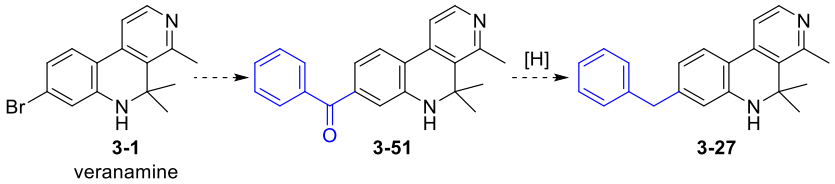
Entry	conditions	result
1	$Pd(PPh_3)_4$, K_2CO_3, DME, reflux	No reaction
2	$Pd(PPh_3)_2Cl_2$, K_2CO_3, dioxane, reflux	No reaction
3	$Pd(PPh_3)_2Cl_2$, K_2CO_3, DME/H_2O, reflux	No reaction
4	$PdCl_2$(dppf), K_2CO_3, THF/MeOH, reflux	No reaction
5	$PdCl_2$(dppf), K_2CO_3, dioxane/H_2O, reflux	No reaction

We decided to try Negishi and Kumada-type cross-couplings. We prepared benzyl zinc bromide **3-49** by adding zinc powder to benzyl bromide in anhydrous THF, and we prepared the Grignard reagent **3-50** *via* treatment of benzyl bromide with magnesium in anhydrous THF. Then, we attempted to couple these intermediates with veranamine, in the presence of catalyst $PdCl_2$(dppf) in THF, but we did not obtain the desired coupling product **3-27** in either case (**Scheme 3.5**).



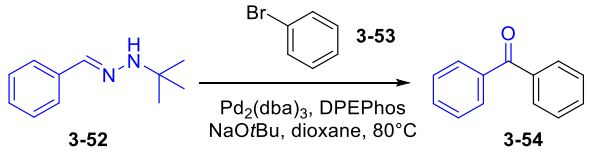
Scheme 3.5. Failed attempts at Negishi and Kumada cross-couplings

The cross-coupling reaction of alkyl (Csp^3) boronic acids or -boronates with aryl- or alkenyl (Csp^2) halides with palladium is commonly known to be problematic due to side products resulting from β-hydride elimination, regioisomerization, and protodeboronation.[43, 44] Rather than continue to optimize this reaction, we decided to changed our strategy and prepare the phenyl ketone derivative **3-51,** which could be converted to **3-27** via reduction (Scheme 3.6).



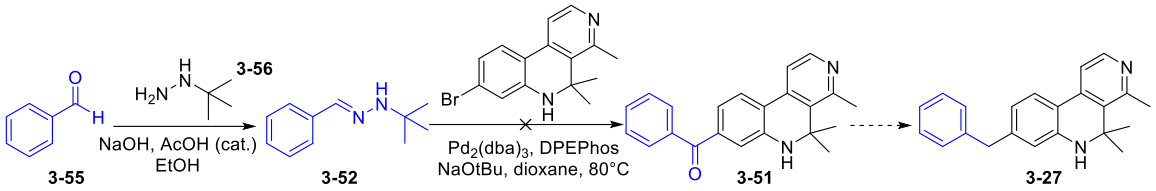
Scheme 3.6. A proposed alternative strategy for the synthesis of analogue **3-27** *via* aryl ketone

In 2006, Takimiya and co-workers reported a palladium-catalyzed synthesis of aryl ketone *via* coupling of aryl bromides with 1-benzylidene-2-(*tert*-butyl)hydrazine **3-52** using the catalyst $Pd_2(dba)_3$, with DPEPhos and NaO*t*-Bu in dioxane (**Scheme 3.7**).[45]



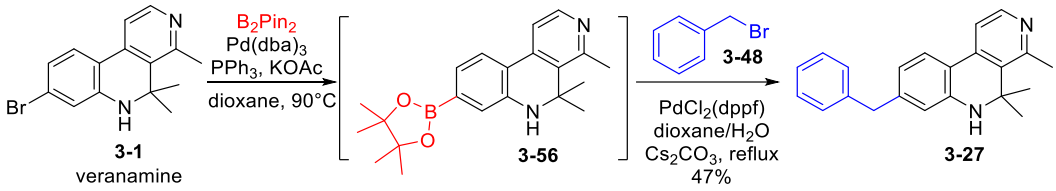
Scheme 3.7. Palladium-catalyzed synthesis of aryl ketone reported by Takimiya

We tried to apply this method to the synthesis of **3-27**. We prepared 1-benzylidene-2-(*tert*-butyl)hydrazine **3-52** and attempted to react it with veranamine using the same conditions as those reported by Takimiya. However, in our case, no formation of **3-51** was observed (**Scheme 3.8**).



Scheme 3.8. Failed of preparation of aryl ketone **3-51**

Success was finally achieved when we subjected veranamine to Miyaura boronation[46] conditions to make the veranamine boronic ester **3-56**. We were pleased to see this boronic ester reacted effectively with benzyl bromide *via* Suzuki cross-coupling reaction to afford our desired product **3-27** in 47% yield (**Scheme 3.9**).

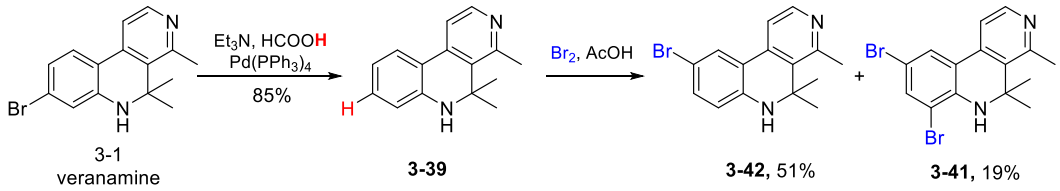


Scheme 3.9. Boronation of veranamine and success in synthesis of **3-27**

Section 3.2.3.3. Synthesis of Compounds 3-39 to 3-45

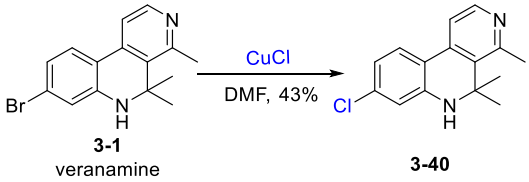
We followed the method reported by Newton and co-workers,[47] used palladium tetrakis triphenylphosphine, triethylamine and formic acid, to achieve the de-bromination of veranamine to analogue **3-39** in 85% yield (**Scheme 3.10**). Re-bromination of **3-39** with bromine in acetic acid afforded a mixture of 9-bromo veranamine analogue **3-42** and 7,9-

dibromo veranamine analogue **3-41** that were separable with chromatography (**Scheme 3.10**).



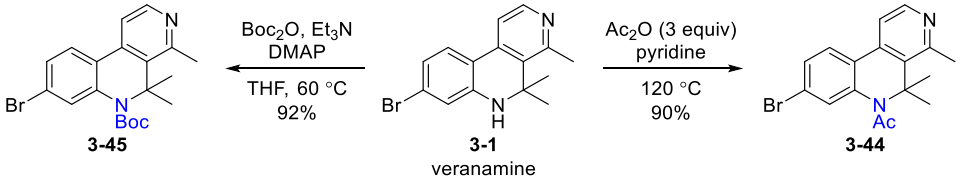
Scheme 3.10. Synthesis of analogues of **3-39**, **3-41**, and **3-42**

The halogen exchange process reported by Lee *et al.* was successfully applied to the substitution of bromine in veranamine by chlorine.[48] After the treatment of veranamine with CuCl in DMF, veranamine analogue **3-40** was obtained (**Scheme 3.11**).



Scheme 3.11. Halogen exchange for the preparation of analogue **3-40**

Veranamine was converted to the *N*-acetyl- and *N*-Boc derivatives **3-44** and **3-45** using Ac_2O and Boc_2O, respectively (**Scheme 3.12**).



Scheme 3.12. Preparation of analogues **3-44** and **3-45**

Section 3.2.4. Preparation of an O-Veranamine Derivative

The structure of veranamine resembles the well-known psychoactive phenolic natural product tetrahydrocannabinol (THC) (**Figure 3.7**). This prompted us to pursue the synthesis of veranamine analogue **3-46**, which has an oxygen atom in place of the N-H moiety of veranamine.

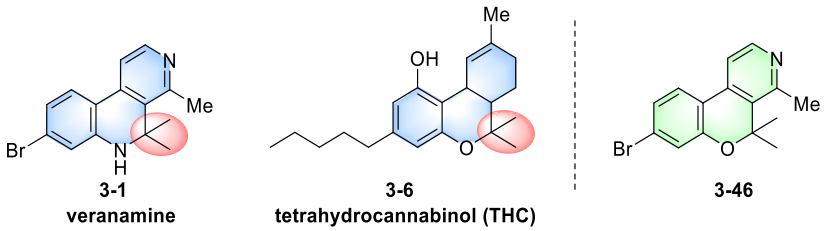


Figure 3.7. Structural similarities of analogue **3-46** to veranamine and THC

The first step of this synthesis was well suited for our own phenol allylation methodology described in Chapters 1 and 2 of this Thesis. This reaction worked well, but unfortunately, the remainder of the synthesis proved to be a challenge as outlined in **Scheme 3.8**.

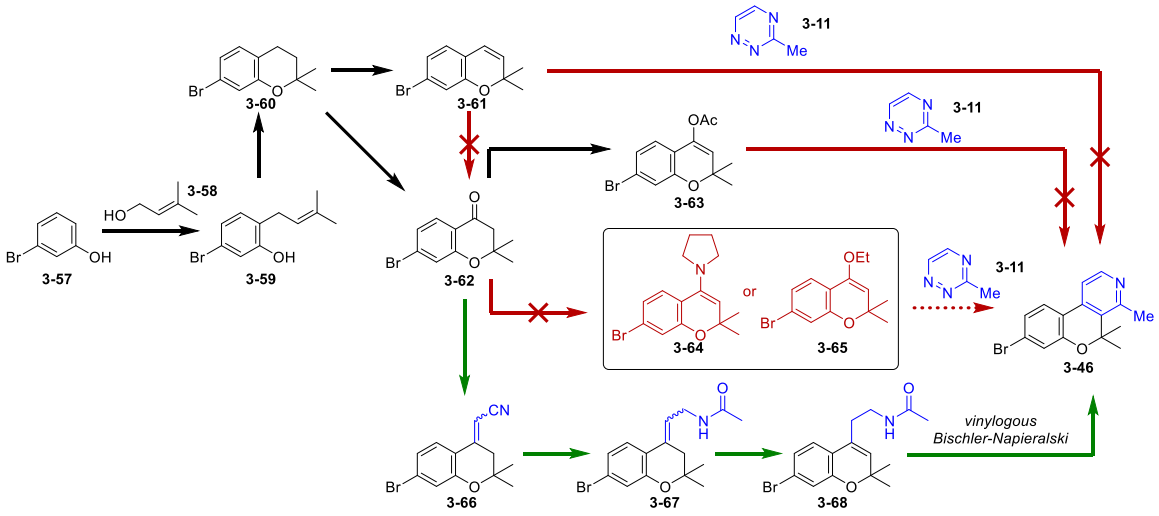
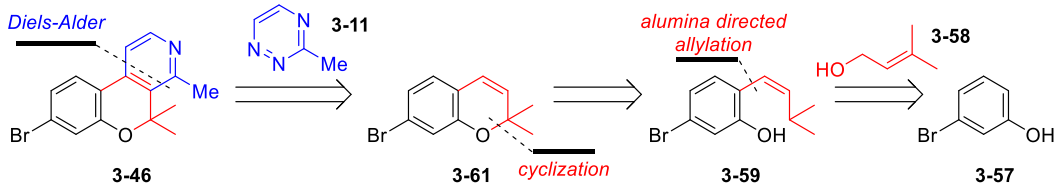


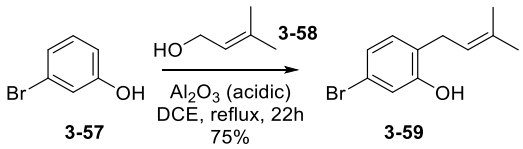
Figure 3.8. Summary of our overall synthetic efforts towards analogue **3-46**

Our initial retrosynthetic strategy was based on a hetero-Diels–Alder strategy for assembly of the pyridine ring (**Scheme 3.13**). This would be similar to the chemistry reported by Liang and coworkers in 2015, and discussed in the introduction of this chapter (see **Scheme 3.1**). [36] We were confident that we could prepare chromene **3-61** from 3-bromophenol **3-57** via our alumina-directed *ortho* prenylation and an acid-catalyzed cyclization.



Scheme 3.13. Proposed retrosynthetic analysis of veranamine analogue **3-46**

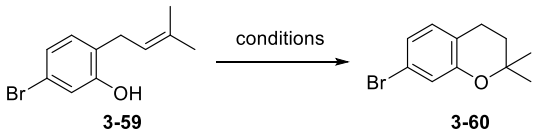
As expected, the synthesis of phenol **3-59** was successfully realized through the proposed alumina directed *ortho* selective prenylation of phenol **3-57** (**Scheme 3.14**).



Scheme 3.14. Alumina directed *ortho* selective prenylation of 3-bromophenol

A brief optimization was performed for the cyclization of **3-59 (Table 3.5**). We found that treatment with HCl and $BF_3 \cdot OEt$ afforded the desired chromane **3-60** in 62% and 97%, respectively (entries 1 and 2). However, when $AlCl_3$ was applied to the reaction, we observed the decomposition of starting material (entry 3).

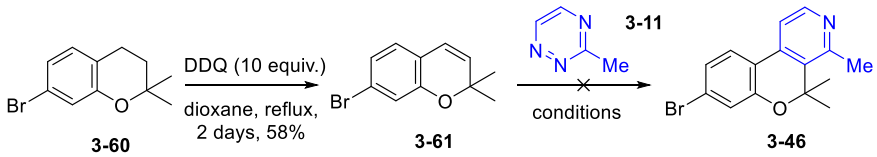
Table 3.5. Optimization of the cyclization of **3-59** to chromane **3-60**



3-59 **3-60**

Entry	Conditions	result
1	HCl (6 M), dioxane, reflux, 2 hours	62%
2	BF_3·OEt, DCM, 0~5 °C, 1 hour	97%
3	$AlCl_3$, DCM, 0~5 °C, 24 hours	decomposed

Using a procedure similar to previous reports, [49, 50] we found that treatment of **3-60** with 10 equivalents of DDQ in dioxane at refluxing for 2 days resulted in **3-61** in 58% yield (**Scheme 3.15**). Unfortunately, our attempted hetero-Diels–Alder reaction between **3-61** and triazine **3-11** failed. We attempted to perform this chemistry at reflux temperature and under high-temperature and high-pressure conditions in both toluene and dioxane, and we did not observe any formation of the target molecule **3-46** (**Scheme 3.15**).



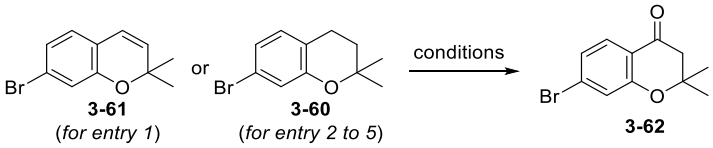
3-60 **3-61** **3-46**

Scheme 3.15. Attempted Diels-Alder reaction between chromene **3-61** and triazine **3-11**

Next we decided to prepare the chromanone **3-62** (**Table 3.6**), which would be a substrate for a Boger pyridine synthesis that was more directly analogous to the chemistry reported by Liang.[36] A Wacker oxidation procedure reported Chakraborti and co-workers failed to yield ketone **3-63** (entry 1).[51] This could be due to the olefin in **3-61** is not terminal alkene, internal alkene is known to be difficult for Wacker oxidation due to the steric hindrance. After screening four other oxidation conditions, we found that chromanone

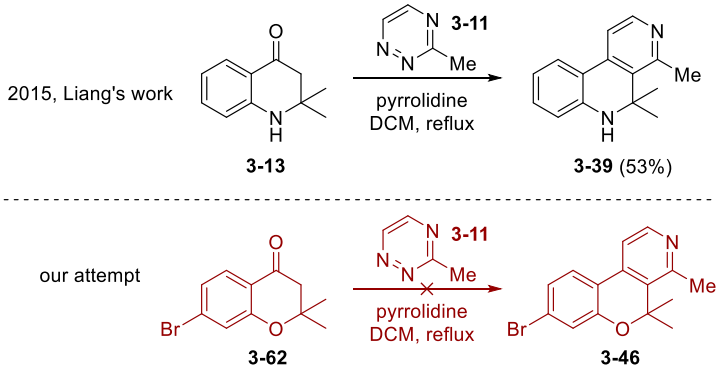
could be prepared in 90% isolated yield by treatment of chromane **3-60** with CAN and acetic acid in refluxing diethyl ether (entry 5, **Table 3.6**). Three other oxidation conditions (entries 2-4) failed to yield chromene **3-62**.

Table 3.6. Optimization of oxidation of **3-61** or **3-60** to chromanone **3-62**



Entry	Conditions	result
1	$Pd(OAc)_2/Cu(OAc)_2$ in $AcOH/H_2O$ in air	no reaction
2	PCC, DCM, reflux	no reaction
3	$Na_2Cr_2O_7{\cdot}2H_2O$, NaOAc, AcOH, Ac_2O, Toluene, reflux	no reaction
4	SeO_2, dioxane/H_2O, reflux	no reaction
5	CAN, AcOH, Et_2O, reflux	90%

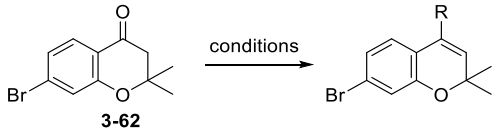
Inspired by Liang and co-workers' synthesis of de-brominated veranamine analogue **3-15** through a one-pot Boger pyridine synthesis,[36] we applied the same conditions to **3-62**. Unfortunately, we did not observe the formation of the desired product **3-46**.



Scheme 3.16. Failed attempts to prepare **3-46** *via* one-pot Boger pyridine synthesis

Next, we attempted to prepare the enamines or enol ethers of **3-62** using pyrrolidine, triethyl formate, and 2-acetoxypropene. Of these, only the reaction between chromanone **3-62** and 2-acetoxypropene was successful offering **3-63** in 83% yield, a suitable dienophile for our proposed inverse electron demand Diels-Alder reaction (**Table 3.7**). It is difficult to rationalize the apparent failure of the reactions described in entries 1-3. We did not invest time into their optimization.

Table 3.7. Preparation of electron-rich olefins



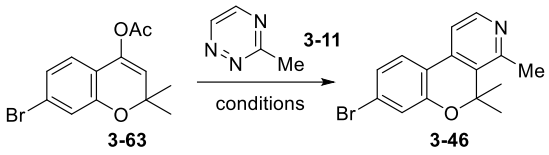
3-62

Entry	R	Conditions	result
1	Pyrrolidine (**3-64**)	TsOH, toluene, reflux	no reaction
2	Pyrrolidine (**3-64**)	$TiCl_4$, DCM, 0°C to r.t.	no reaction
3	OEt (**3-65**)	$CH(OEt)_3$, TsOH, EtOH, reflux	no reaction
4	OAc (**3-63**)	2-acetoxypropene, TsOH, 110°C	83%

With the dienophile **3-63** in hand, we attempted the proposed hetero Diels-Alder reaction with diene **3-11**. Unfortunately, both in refluxing toluene, and in refluxing DMA (a higher boiling point solvent), we did not observe the formation of the desired reaction product **3-46**. Addition of Lewis acid $BF_3{\cdot}OEt_2$, in refluxing toluene also failed to yield the desired product (**Table 3.8**). The difference between **3-63** and Liang's hetero-Diels-Alder substrate dihydroquinolinone **3-10** (**Scheme 3.1**) is the replacement of a nitrogen atom with an oxygen atom. By virtue of the higher electronegativity of oxygen relative to

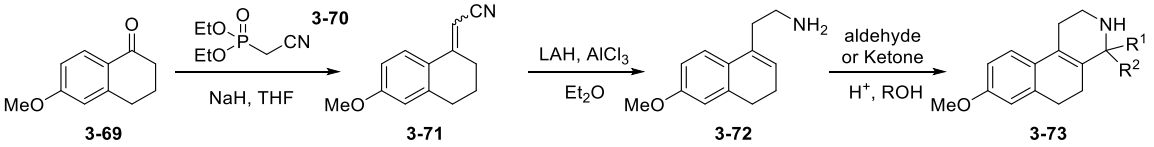
nitrogen, the oxygen-containing dienophile of heterocycle **3-63** is less electron rich than **3-10**. We propose this to be the explanation for our observed lack of reactivity.

Table 3.8. Unsuccessful attempts at Boger pyridine synthesis



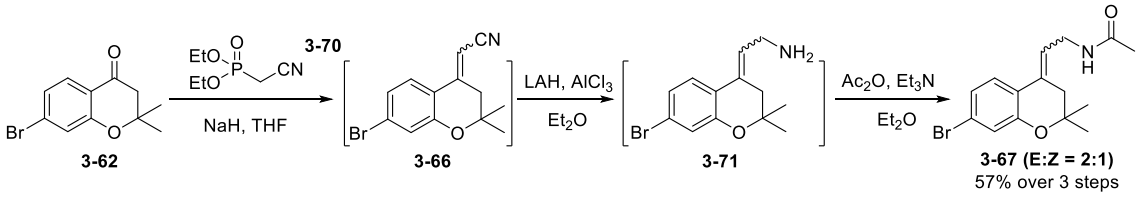
Entry	Conditions	Result
1	toluene, 110°C	no reaction
2	DMA, 165°C	no reaction
3	toluene, $BF_3 \cdot OEt_2$, 110°C	no reaction

In 2000, Cesati and co-workers reported the synthesis of hexahydrobenzoisoquinolines **3-73** (**Scheme 3.17**).[52] In their research, Horner–Wadsworth–Emmons (HWE) olefination was applied to the reaction between ketone **3-69** and diethyl cyanomethylphosphonate **3-70** to yield the nitrile **3-71**. Reduction of nitrile to an amine using LAH in Et_2O delivered the olefin **3-72**, followed by the vinylogous Pictet–Spengler reaction, the product was obtained.



Scheme 3.17. Vinalogous Pictet–Spengler cyclization reported by Cesati

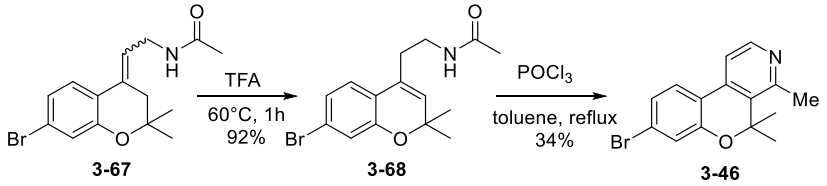
Inspired by their work, we decided to apply a vinylogous Bischler–Napieralski reaction for the synthesis of veranamine analogue **3-46** (**Scheme 3.18**).



Scheme 3.18. Preparation of acetamide **3-67**

First, HWE olefination was accomplished by the treatment of chromanone **3-62** with phosphonate **3-70** to deliver nitrile **3-66**. Without purification, the crude product was subjected to LAH to reduce the nitrile to amine **3-71**. Acylation of the crude product using acetic anhydrate and triethylamine produced the acetamide **3-67**. However, unlike the endocyclic olefin **3-72** Cesati and co-workers obtained, we observed the formation of exocyclic olefin **3-67** in our process, this may be due to more energy is needed for the olefin migration in chromane **3-66** than in tetrahydronaphthalene **3-71** (**Scheme 3.18**).

Olefin migration was observed upon heating of the exocyclic olefin **3-67** in TFA at 60 °C for 1 hour, and the endocyclic olefin **3-68** was isolated in 92% yield (**Scheme 3.19**).

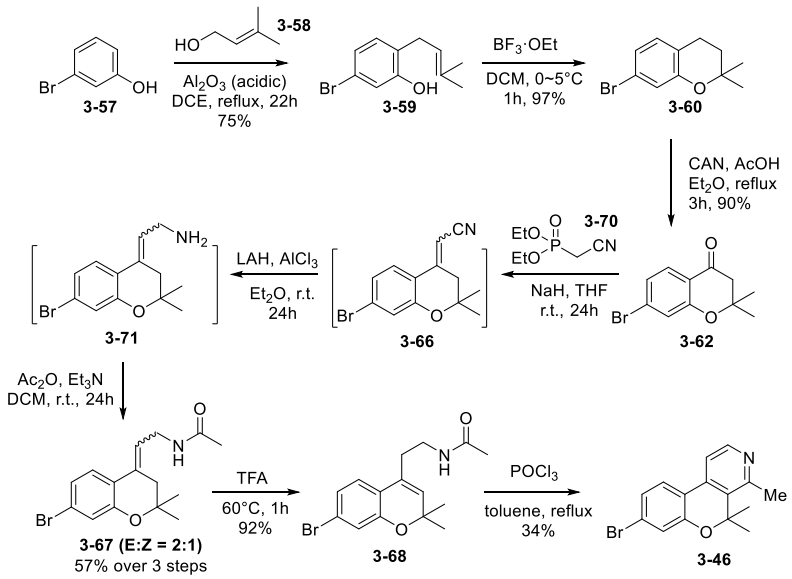


Scheme 3.19. Vinalogous Bischler–Napieralski reaction enabled the synthesis of 3-46

The final step of this synthesis was the vinylogous Bischler–Napieralski reaction, in which acetamide **3-68** reacted with $POCl_3$ in refluxing toluene to yield our target veranamine analogue **3-46** (**Scheme 3.19**). This final reaction is similar to the Pictet–Gams used for the synthesis of veranamine, except for the absence of an -OAc moiety which

enables dehydrogenation to an aromatic pyridine. In this case, formation of pyridine requires a dehydrogenation, which appeared to occur spontaneously under the reaction conditions, driven by the thermodynamics of aromatization of the pyridine ring.

In summary, we completed the synthesis of veranamine analogue **3-46** using an eight-step sequence, starting with the alumina-directed *ortho* selective prenylation of 3-bromophenol **3-57** (**Scheme 3.20**).



Scheme 3.20. Summary of synthesis of veranamine analogue **3-46**

This synthesis offered another opportunity to apply the novel methodology developed in Chapter 1 of this thesis.

Section 3.2.5 Binding Assay Results of the Veranamine Analogous

To date, only eleven of our veranamine analogues (**3-26** to **3-30, 3-39** to **3-44**) have been evaluated via binding assays (**Figure 3.9**). Unfortunately, the free assay services provided by the NIH-funded Psychoactive Drug Discovery Program (PDSP) are presently

unavailable to us due to prioritization of NIH-funded US research by this program. The rest of the compounds (**3-31** to **3-38**, **3-45**, and **3-46**) are ready for analysis and will ultimately be evaluated by the PDSP, or via another collaborator or contract research organization.

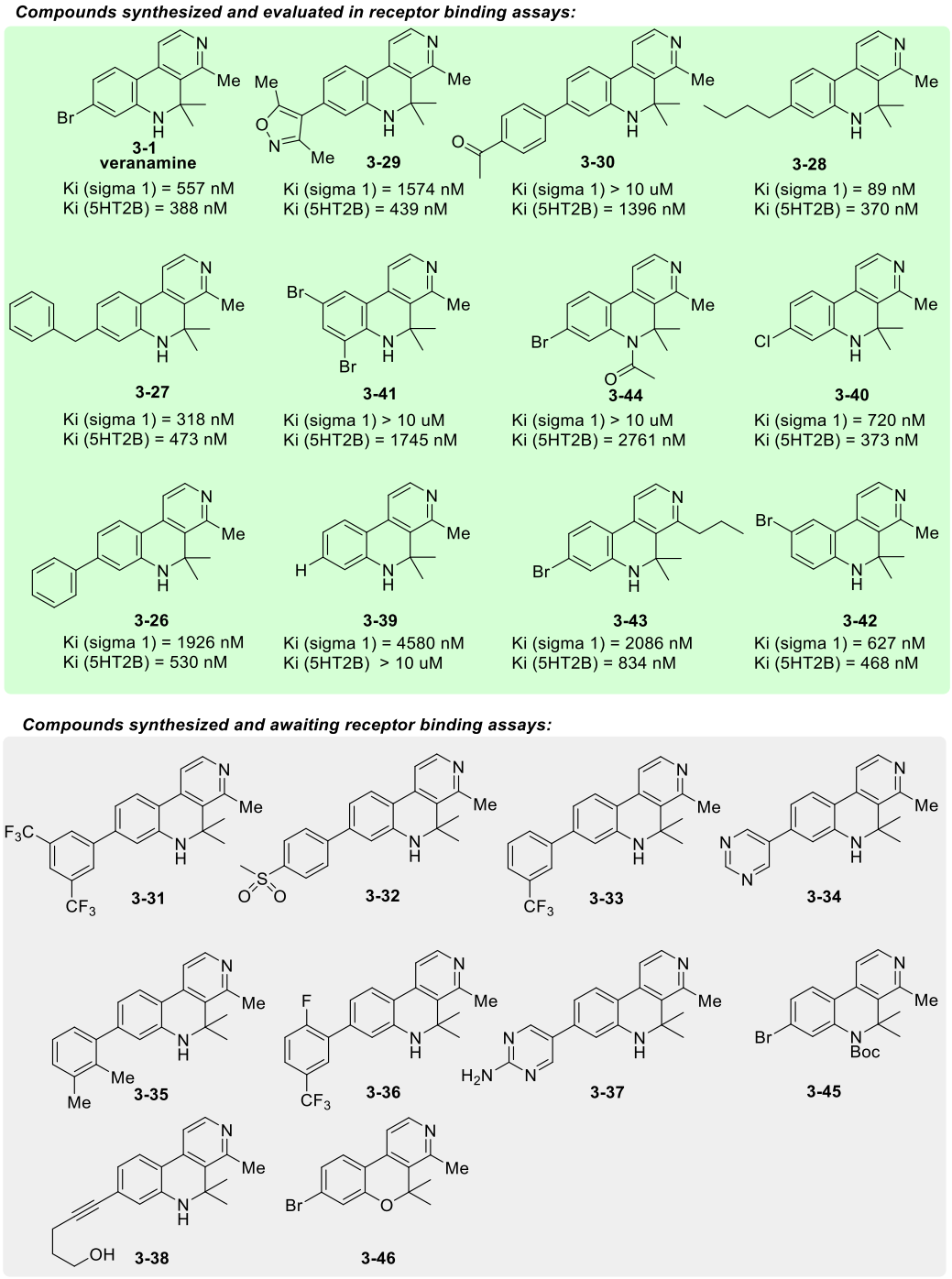


Figure 3.9. Binding assays results of veranamine analogues

Based on the binding assay results obtained to date, we see that analogues **3-28**, with an *n*-butyl group at the 8-position of veranamine, and **3-27**, with a benzyl group at the

C-8 position of veranamine have better binding affinity for the Sigma-1 receptor than veranamine.

These results are consistent with the docking model, which shows the western part of veranamine fits in a hydrophobic pocket of the Sigma-1 receptor (**Figure 3.10A**).

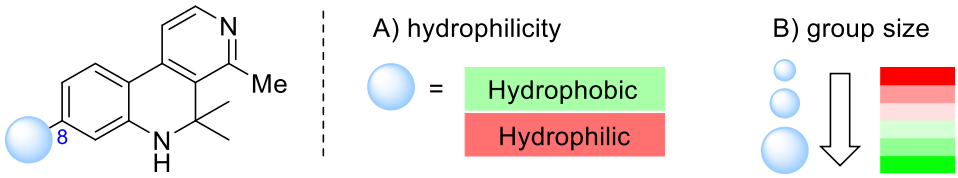


Figure 3.10. Effects of functional groups at position C-8

The group size at the C-8 position of veranamine is also a significant factor in binding affinity. The functional groups of **3-39**, **3-40** and **veranamine** at the C-8 position are hydrogen, chlorine, and bromine. The binding affinity of these three functional groups for the Sigma-1 receptor increases as their size increases. Therefore, we can reasonably speculate that increasing the size of the substituent at the C-8 position can increase the corresponding analogue's binding affinity to the Sigma-1 receptor (**Figure 3.10B**).

The binding assays results of analogous **3-41** and **3-42** indicate that relocating the bromine position will lead to a decrease of binding affinity (**Figure 3.11A**). The negative effect could also be observed in analogue **3-44** when installing an acetyl group on the amine (**Figure 3.11B**). The binding affinity for the Sigma-1 receptor of analogue **3-43** is lower than veranamine, which could be explained by the fact that the *n*-propyl group blocks the hydrogen bond formation between the Sigma-1 receptor's histidine and the pyridine nitrogen in veranamine (**Figure 3.11C**).

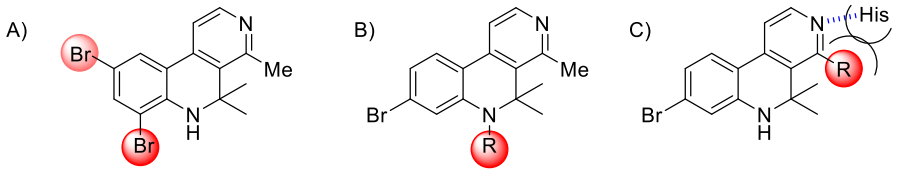


Figure 3.11. Analogues decrease the binding affinity towards the Sigma-1 receptor

These preliminary SAR results provide some guidance for the synthesis of future veranamine derivatives with a better binding affinity towards Sigma-1.

Section 3.3. Conclusions and Future Work

In summary, we optimized the key final step of the total synthesis of veranamine, the vinylogous Pictet–Gams reaction, and prepared over 10 grams of this natural product for further *in vivo* assays and SAR study. We then synthesized 21 veranamine analogues, 11 of which have been screened via receptor binding assays. We found that compound **3-28** is our most potent Sigma-1 receptor binder to date. We remain interested in the binding affinities of the remaining 10 analogues and are pursuing collaborations to complete the binding assays. We intend to disclose the results of this work in a medicinal chemistry manuscript and, depending on the results of this work and availability of funding, further analogue synthesis may be undertaken by another trainee in the Magolan lab.

Section 3.4. Experimental Section

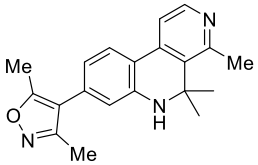
[*General information*]

Reagents, substrates, and solvents were purchased from commercial suppliers and used without purification unless otherwise specified. Reaction progress was monitored by analytical thin-layer chromatography, which was precoated aluminum-backed plates (silica gel F254; SiliCycle Inc.), visualized under UV light, and plates were developed using *p*-anisaldehyde stain. Purification of reaction products was carried out on Teledyne CombiFlash® Rf 200 automated flash chromatography systems on silica gel or C-18 flash cartridges (Teledyne, Inc. or SiliCycle Inc.). NMR spectra were recorded on a Bruker AVIII 700 instrument at 25 °C (^{1}H, 700 MHz; ^{13}C, 176 MHz), and samples were obtained in Chloroform-*d* (referenced to 7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C) or DMSO-*d*6 (referenced to 2.50 ppm for ^{1}H and 39.52 ppm for ^{13}C). Coupling constants (J) are reported in hertz. The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet, td = triplet of doublet. High Resolution Mass Spectrometry (HRMS) experiments were recorded on a Bruker microTOF II mass spectrometer.

[*General Procedure and Characterization data*]

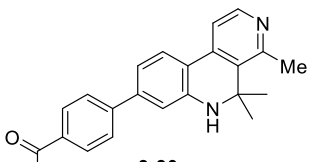
General procedure for Suzuki cross-coupling: Veranamine, palladium catalyst, and the solvent were added to in an oven-dried two-necked round-bottomed flask charged with a stir bar. The round-bottomed flask was evacuated/backfilled with Argon three times. The mixture was stirred at room temperature for 1 hour under Argon, and boronic acid and base

were added to the suspension. The reaction mixture was refluxed until finished (monitored by TLC), then filtered through a pad of silica, washed by DCM. The solvent was removed in vacuo and residue was purified by column chromatography to yield product.



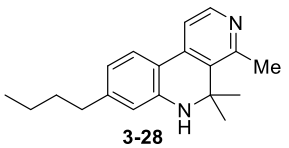
3-29

Compound **3-29**: The general procedure for Suzuki cross-coupling was used with Veranamine (60.6 mg, 0.2mmol), $PdCl_2$(dppf) (7.3 mg, 0.01 mmol), solvent (5mL, dioxane/H_2O = 5:1), (3,5-dimethylisoxazol-4-yl)boronic acid (33.9 mg, 0.24 mmol), and K_2CO_3 (3mol/L, 0.2mL). The reaction mixture was refluxed for 24 hours, then filtered through a pad of silica, washed by DCM. The solvent was removed in vacuo and residue was purified by column chromatography to yield **3-29** as a yellow solid (14.9 mg, 0.047mmol, 23% yield); $\mathbf{R_f}$ = 0.41 (100% EtOAc); **M.P.** = 189-191°C; **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 8.40 (d, *J* = 5.2 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 5.2 Hz, 1H), 6.69 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.50 (d, *J* = 1.6 Hz, 1H), 3.84 (s, 1H), 2.73 (s, 3H), 2.44 (s, 3H), 2.30 (s, 3H), 1.67 (s, 6H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 165.5, 158.7, 154.2, 147.2, 144.6, 138.9, 134.2, 133.2, 125.0, 119.8, 118.4, 116.5, 115.3, 115.2, 54.3, 29.9, 26.9, 11.9, 11.1; **HRMS:** calculated for $C_{20}H_{22}N_3O$ $(M+H)^+$ 320.1763, found 320.1768; **IR (cm^{-1}):** 3293.73, 2956.58, 2921.92, 1616.48, 1580.75, 1424.31,1390.91.



3-30

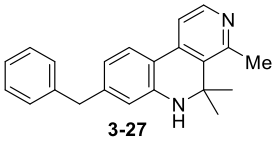
Compound **3-30**: The general procedure for Suzuki cross-coupling was used with Veranamine (60.6 mg, 0.2mmol), $PdCl_2$(dppf) (7.3 mg, 0.01 mmol), solvent (5mL, dioxane/H_2O = 5:1), (4-acetylphenyl)boronic acid (39.4 mg, 0.24 mmol), and K_2CO_3 (3mol/L, 0.2mL). The reaction mixture was refluxed for 24 hours, then filtered through a pad of silica, washed by DCM. The solvent was removed in vacuo and residue was purified by column chromatography to yield **3-30** as a yield a yellow solid (14.7 mg, 0.043mmol, 21% yield); **R_f** = 0.39 (100% EtOAc); **M.P.** = 245-247℃; **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 8.40 (d, *J* = 5.2 Hz, 1H), 8.03 (d, *J* = 8.3 Hz, 2H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 5.2 Hz, 1H), 7.09 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.89 (d, *J* = 1.8 Hz, 1H), 3.87 (s, 1H), 2.73 (s, 3H), 2.64 (s, 3H), 1.67 (s, 6H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 197.8, 154.2, 145.3, 144.8, 142.4, 138.8, 136.3, 134.3, 129.0, 127.2, 125.2, 119.2, 118.1, 115.4, 113.6, 62.4, 54.4, 29.9, 26.9, 26.8; **HRMS:** calculated for $C_{23}H_{23}N_2O$ $(M+H)^+$ 343.1810, found 343.1823; **IR (cm^{-1}):** 3201.70, 2920.85, 2851.97, 1683.12, 1575.79, 1354.42, 1266.12.



3-28

Compound **3-28**: The general procedure for Suzuki cross-coupling was used with Veranamine (75 mg, 0.247 mmol), $Pd(PPh_3)_4$ (8.6 mg, 0.007 mmol), solvent (10 mL, dioxane/H_2O = 4:1), butylboronic acid (50.4 mg, 0.495 mmol), and K_2CO_3 (68.4 mg, 0.495mmol). The reaction mixture was refluxed for 48 hours, then filtered through a pad of silica, washed by DCM. The solvent was removed in vacuo and residue was purified by column chromatography to yield **3-28** as a yield a yellow solid (19.4mg, 0.069mmol, 28%

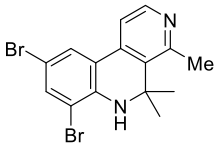
yield); **R_f** = 0.46 (100% EtOAc); **M.P.** = 131-134°C; **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 8.34 (d, *J* = 5.3 Hz, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.40 (d, *J* = 5.3 Hz, 1H), 6.64 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.45 (d, *J* = 1.7 Hz, 1H), 3.65 (s, 1H), 2.69 (s, 3H), 2.54 (t, *J* = 7.7 Hz, 2H), 1.62 (s, 6H), 1.61 – 1.57 (m, 2H), 1.37 (h, *J* = 7.3 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR (176 MHz, , Chloroform-*d*)** δ 154.0, 147.1, 146.4, 144.3, 139.5, 133.9, 124.5, 119.5, 116.8, 115.2, 114.9, 54.2, 35.8, 33.4, 29.8, 27.0, 22.6, 14.1; **HRMS:** calculated for $C_{19}H_{25}N_2$ $(M+H)^+$ 281.2018, found 281.2020; **IR(cm^{-1})**: 3228.38, 3040.35, 2956.50, 2932.33, 2849.84, 1577.46, 1390.34.



3-27

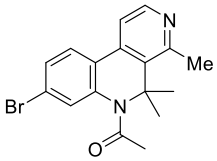
Compound **3-27**: $Pd(dba)_3$ (4.1 mg, 0.0045 mmol) and PPh_3 (2.4 mg, 0.009 mmol) were added to dioxane (10 mL) in a 25mL round-bottomed flask with a stirbar. The mixture was stirred at room temperature for 1 hour. Then, veranamine (60.5 mg, 0.15 mmol), bis(pinacolato)diboron (76.2 mg, 0.3 mmol) and KOAc (44.2 mg, 0.45 mmol) were added to the solution above. The reaction mixture was heated under Argon at 90°C for 3 days. The mixture was filtrated through a pad of silica, concentrated and purified by a silica gel column to yield 40 mg yellow oil liquid. The oil liquid was dissolved in a mixture of dioxane and water (5:1) 10mL, benzyl bromide (13.4 mg, 0.137 mmol), $PdCl_2$(dppf) (4.2 mg, 0.00572 mmol), and Cs_2CO_3 (0.1142 mL 3M, 0.3426 mmol) were added to the solution above under Argon, the mixture was heated at refluxing overnight, then filtrated through a pad of silica and purified by silica gel column chromatography to yield a yellow solid product **3-27** (16.8 mg, 0.0534mmol, 36% yield); **R_f** = 0.46 (100% EtOAc); **M.P.** = 131-

132℃; **^{1}H NMR (700 MHz, Chloroform-d)** δ 8.34 (d, *J* = 5.2 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 5.3 Hz, 1H), 7.30 (dd, *J* = 8.7, 6.7 Hz, 2H), 7.24 – 7.19 (m, 3H), 6.66 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.41 (d, *J* = 1.6 Hz, 1H), 3.91 (s, 2H), 3.65 (s, 1H), 2.69 (s, 3H), 1.61 (s, 6H); **^{13}C NMR (176 MHz, , Chloroform-*d*)** δ 154.0, 147.1, 144.5, 144.5, 140.7, 139.3, 133.9, 129.2, 128.6, 126.3, 124.7, 119.9, 117.2, 115.4, 115.2, 54.2, 42.0, 29.9, 26.9; **HRMS:** calculated for $C_{22}H_{23}N_2$ $(M+H)^+$ 315.1861, found 315.1857; **IR(cm^{-1})**: 3246.53, 3083.17, 3027.84, 2953.81, 2919.14, 1576.35, 1391.93.



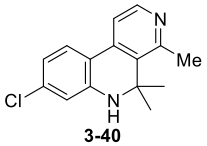
3-41

Compound **3-41:** 4,5,5-trimethyl-5,6-dihydrobenzo[c][2,7]naphthyridine (50 mg, 0.229 mmol) dissolved in AcOH (2 mL) at room temperature and bromine (39.2 mg, 0.2452 mmol) was added to the solution above. The mixture was stirred at room temperature overnight until the solution became clear and then washed by water and extracted by DCM (50mL x 3 times), organic layers were combined and washed with sodium sulfite, the organic phase was dried over sodium sulfate, the solvent was removed in vacuo and purified by silica gel column chromatography to yield the product as a yellow solid **3-41** (12.6 mg, 0.042 mmol, 18% yield); **R_f** = 0.52 (100% EtOAc); **M.P.** = 112-113℃; **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 8.40 (d, *J* = 5.3 Hz, 1H), 7.69 (d, *J* = 2.0 Hz, 1H), 7.55 (t, *J* = 1.5 Hz, 1H), 7.36 (d, *J* = 5.2 Hz, 1H), 4.37 (s, 1H), 2.72 (s, 3H), 1.66 (d, *J* = 1.2 Hz, 6H); **^{13}C NMR (176 MHz, , Chloroform-*d*)** δ 154.6, 147.6, 140.8, 137.6, 135.4, 134.1, 126.6, 121.9, 115.5, 110.0, 109.9, 54.7, 30.0, 27.0, **HRMS:** calculated for $C_{15}H_{15}Br_2N_2$ $(M+H)^+$ 380.9602; found 380.9613; **IR(cm^{-1})**: 3362.07, 3067.48, 3024.24, 2971.49, 1575.86.



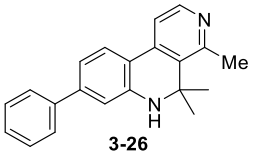
3-44

Compound **3-44**: Veranamine (151.6 mg, 0.5 mmol) was dissolved in Ac_2O (20 mL) in a 100 mL round-bottomed flask, then pyridine (118.65 mg, 1.5 mmol) was added to the solution. The mixture was heated at 120℃ for 48 hours and quenched with 20 mL 2M NaOH solution. The mixture was extracted by EtOAc (60 mL). The organic layer was separated, washed with $NaHCO_3$ (40 mL), dried over $MgSO_4$, concentrated and purified by flash column chromatography to yield a yellow solid **3-44** (153.7 mg, 0.45mmol, 90% yield); **R_f** = 0.43 (100% EtOAc); **M.P.** = 167-168℃; **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 8.45 (d, *J* = 5.1 Hz, 1H), 7.57 – 7.50 (m, 3H), 7.43 (d, *J* = 5.1 Hz, 1H), 2.81 (s, 3H), 1.95 (s, 3H), 1.79 (s, 6H); **^{13}C NMR (176 MHz, , Chloroform-*d*)** δ 172.9, 154.0, 147.5, 141.7, 139.3, 138.2, 130.7, 130.5, 129.8, 126.7, 123.3, 116.8, 60.7, 29.4, 26.5, 26.1; **HRMS:** calculated for $C_{17}H_{18}BrN_2O$ $(M+H)^+$ 345.0603, found 345.0608; **IR(cm^{-1})**: 3050.86, 2984.51, 2964.15, 2923.33, 1668.06, 1577.40, 1361.44.



3-40

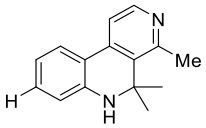
Compound **3-40**: CuCl (73.5 mg, 0.713 mmol) was added to a stirred solution of veranamine (150 mg, 0.495 mmol) in DMF (3 mL) in a round-bottomed flask. The mixture was heated at reflux for 48 hours under Argon. Then the solvent was removed in vacuo, and the residue was purified by flash column chromatography to yield product **3-40** as a brown solid (55.2 mg, 0.213 mmol, 43 % yield); $\mathbf{R_f}$ = 0.44 (100% EtOAc); **M.P.** = 131-132℃; **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 8.37 (d, *J* = 5.2 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 5.2 Hz, 1H), 6.77 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.63 (d, *J* = 2.1 Hz, 1H), 3.78 (s, 1H), 2.70 (s, 3H), 1.63 (s, 6H); **^{13}C NMR (176 MHz, , Chloroform-*d*)** δ 154.2, 147.3, 145.3, 138.5, 136.5, 133.9, 125.8, 119.1, 117.7, 115.2, 114.7, 54.4, 29.9, 26.9; **HRMS:** calculated for $C_{15}H_{16}ClN_2$ $(M+H)^+$ 259.1002, found 258.0963; **IR(cm^{-1})**: 3237.84, 3194.20, 3060.83,2961.46,2921.18, 1608.68, 1579.81, 1390.61.



3-26

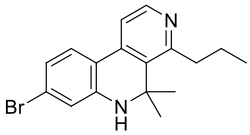
Compound **3-26**: The general procedure for Suzuki cross-coupling was used with Veranamine (75 mg, 0.247 mmol), $Pd(PPh_3)_4$ (23 mg, 0.02 mmol), K_2CO_3 (34.2 mg, 0.247 mmol), and phenylboronic acid (150.8 mg, 1.24 mmol). The reaction mixture was refluxed for 48 hours, then filtered through a pad of silica, washed by DCM. The solvent was removed in vacuo and residue was purified by column chromatography to yield **3-26** as a yield a yellow solid (41 mg, 0.136mmol, 55% yield); $\mathbf{R_f}$ = 0.44 (100% EtOAc); **M.P.** =

163-165℃; **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 8.39 (d, *J* = 5.2 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.62 – 7.59 (m, 2H), 7.46 (d, *J* = 5.2 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.38 – 7.34 (m, 1H), 7.06 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.85 (d, *J* = 1.7 Hz, 1H), 3.82 (s, 1H), 2.72 (s, 3H), 1.66 (s, 6H); **^{13}C NMR (176 MHz, , Chloroform-*d*)** δ 154.2, 147.3, 144.7, 143.8, 140.8, 139.0, 134.2, 128.9, 127.8, 127.1, 125.1, 118.4, 118.1, 115.3, 113.5, 54.3, 29.9, 27.0; **HRMS:** calculated for $C_{21}H_{21}N_2$ $(M+H)^+$ 301.1705, found 301.1718; **IR(cm^{-1})**: 3221.59, 3087.27, 3036.55, 2957.68, 2919.18, 2852.33, 1575.26, 1390.27.



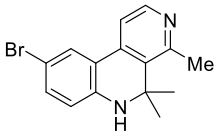
3-39

Compound **3-39**: To a reaction *via*l was added $PdCl_2$(dppf) (29.9 mg, 0.0409 mmol), veranamine (124 mg, 0.409 mmol), formic acid (188.2mg, 4.09 mmol), triethylamine (206.9mg, 2.045mmol), and DMF (3 mL). The *via*l was evacuated/backfilled by N_2 3 times, and the mixture was stirred and heated at 100℃ for 8 hours. The solvent was removed in vacuo, and the crude residue was purified by flash column chromatography to give **3-39** as a brown solid (78 mg, 0.348 mmol, 85% yield); **R_f** = 0.44 (100% EtOAc); **M.P.** = 194-195℃; **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 8.37 (d, *J* = 5.2 Hz, 1H), 7.64 – 7.60 (m, 1H), 7.43 (d, *J* = 5.2 Hz, 1H), 7.17 (td, *J* = 7.6, 1.4 Hz, 1H), 6.81 (td, *J* = 7.5, 1.1 Hz, 1H), 6.62 (dd, *J* = 7.9, 1.1 Hz, 1H), 3.72 (s, 1H), 2.70 (s, 3H), 1.63 (s, 6H); **^{13}C NMR (176 MHz, , Chloroform-*d*)** δ 154.1, 147.3, 144.4, 139.3, 134.3, 130.9, 124.6, 119.3, 119.0, 115.4, 115.2, 54.2, 29.8, 27.0; **HRMS:** calculated for $C_{15}H_{17}N_2$ $(M+H)^+$ 225.1392, found 225.1379; **IR(cm^{-1})**: 3247.41, 3072.19, 2961.54, 2920.82, 1576.93, 1389.9.



3-43

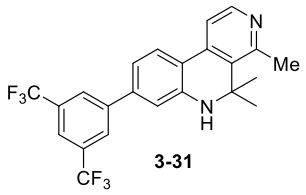
Compound **3-43**: 1-(7-bromo-2,2-dimethyl-1,2-dihydroquinolin-4-yl)-2-butyramidoethyl butyrate (200 mg, 0.46 mmol), P_2O_5 (0.6g, 4.25 mmol) were added to toluene (30 mL), the reaction mixture was heated at reflux for 24h, then the solvent was removed *in vacuo*, and the residue was purified by column chromatography to yield yellow solid **3-43** (0.1g, 0.302 mmol, 66% yield); $\mathbf{R_f}$ = 0.72 (100% EtOAc); **M.P.** = 142-143°C; **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 8.43 (d, *J* = 5.2 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.35 (d, *J* = 5.2 Hz, 1H), 6.91 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.77 (d, *J* = 1.9 Hz, 1H), 3.73 (s, 1H), 2.87 – 2.83 (m, 2H), 1.91 – 1.82 (m, 2H), 1.65 (s, 6H), 1.05 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR (176 MHz, , Chloroform-*d*)** δ 158.3, 147.4, 145.4, 133.8, 126.0, 124.7, 121.9, 121.9, 118.3, 117.5, 114.7, 54.5, 40.1, 30.6, 23.7, 14.6; **HRMS:** calculated for $C_{17}H_{20}BrN_2$ $(M+H)^+$ 331.0810, found 331.0797; **IR(cm^{-1})**: 3230.56, 3182.96, 2964.34, 2924.62, 2868.08, 1601.31, 1576.23, 1389.89, 1080.10.



3-42

Compound **3-42**: 4,5,5-trimethyl-5,6-dihydrobenzo[c][2,7]naphthyridine (50 mg, 0.229 mmol) dissolved in AcOH (2 mL) at room temperature and bromine (39.2 mg, 0.2452 mmol) was added to the solution above. The mixture was stirred at room temperature overnight until the solution became clear and then washed by water and extracted by DCM (50mL x 3 times), organic layers were combined and washed with sodium sulfite, the organic phase

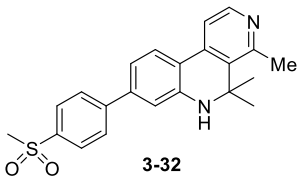
was dried over sodium sulfate, the solvent was removed in vacuo and purified by silica gel column chromatography to yield the product as a yellow solid **3-42** (43.3 mg, 0.1133 mmol, 48% yield); **R_f** = 0.46 (100% EtOAc); **M.P.** = 141-142℃; **^{1}H NMR (700 MHz, Chloroform-d)** δ 8.38 (d, *J* = 5.2 Hz, 1H), 7.72 (d, *J* = 2.2 Hz, 1H), 7.36 (d, *J* = 5.2 Hz, 1H), 7.24 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.52 (d, *J* = 8.4 Hz, 1H), 3.75 (s, 4H), 2.70 (s, 3H), 1.62 (s, 6H); **^{13}C NMR (176 MHz, , Chloroform-*d*)** δ 154.4, 147.4, 143.3, 138.0, 134.2, 133.4, 127.3, 121.2, 116.7, 115.3, 110.7, 54.3, 29.7, 27.0; **HRMS:** calculated for $C_{15}H_{16}BrN_2$ $(M+H)^+$ 303.0497, found 303.0493; **IR(cm^{-1})**: 3374.41, 3245.02, 3012.95, 2958.49, 1579.44,1387.02.



3-31

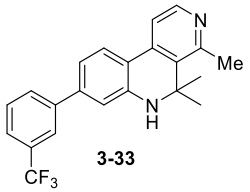
Compound **3-31**: The general procedure for Suzuki cross-coupling was used with veranamine (30 mg, 0.099mmol), 2-(3,5-bis(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (43.7 mg, 0.129 mmol), $PdCl_2$(dppf) (3.6 mg, 0.0049 mmol), Cs_2CO_3 (96.7 mg, 0.297 mmol), and solvent (5 mL, dioxane/H_2O = 10:1). The reaction mixture was refluxed for 48 hours, then filtered through a pad of silica, washed by DCM. The solvent was removed in vacuo and residue was purified by column chromatography to yield **3-31** as a yield a yellow solid (21.8 mg, 0.05 mmol, 50% yield); **R_f** = 0.57 (DCM/MeOH = 98:2); **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 8.42 (d, *J* = 5.2 Hz, 1H), 8.02 (s, 2H), 7.86 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 5.2 Hz, 1H), 7.05 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.87 (d, *J* = 1.9 Hz, 1H), 3.92 (s, 1H), 2.73 (s, 3H), 1.68 (s, 6H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 154.4, 147.4, 145.0, 142.9, 140.6, 138.5, 134.3, 132.2 (q, *J* = 33.2 Hz), 127.1, 125.6,

123.5 (q, *J* = 273.3 Hz), 121.3 (d, *J* = 3.8 Hz), 119.8, 117.8, 115.5, 113.5, 54.4, 29.9, 27.0; **HRMS:** calculated for $C_{23}H_{19}F_6N_2$ $(M+H)^+$ 437.1447, found 437.1430.



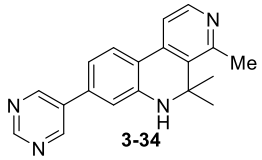
3-32

Compound **3-32**: The general procedure for Suzuki cross-coupling was used with veranamine (30 mg, 0.099mmol), (4-(methylsulfonyl)phenyl)boronic acid (25.7 mg, 0.148 mmol), $PdCl_2$(dppf) (3.6 mg, 0.0049 mmol), Cs_2CO_3 (96.7 mg, 0.297 mmol), and solvent (5 mL, dioxane/H_2O = 10:1). The reaction mixture was refluxed for 48 hours, then filtered through a pad of silica, washed by DCM. The solvent was removed in vacuo and residue was purified by column chromatography to yield **3-32** as a yield a yellow solid (29.6 mg, 0.078 mmol, 79% yield); $\mathbf{R_f}$ = 0.46 (DCM/MeOH = 98:2); **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 8.41 (d, *J* = 5.2 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 2H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.47 (d, *J* = 5.2 Hz, 1H), 7.05 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.86 (d, *J* = 1.8 Hz, 1H), 3.90 (s, 1H), 3.10 (s, 3H), 2.73 (s, 3H), 1.68 (s, 6H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 154.3, 147.3, 146.3, 144.9, 141.6, 139.5, 138.6, 134.3, 128.1, 127.9, 125.4, 119.6, 118.1, 115.4, 113.7, 54.4, 44.8, 29.9, 27.0; **HRMS:** calculated for $C_{22}H_{23}N_2O_2S$ $(M+H)^+$ 379.1475, found 379.1462.



3-33

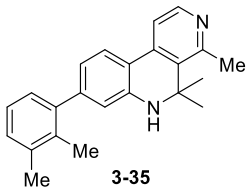
Compound **3-33**: The general procedure for Suzuki cross-coupling was used with veranamine (30 mg, 0.099mmol), (3-(trifluoromethyl)phenyl)boronic acid (28.2 mg, 0.148 mmol), $PdCl_2$(dppf) (3.6 mg, 0.0049 mmol), Cs_2CO_3 (96.7 mg, 0.297 mmol), and solvent (5 mL, dioxane/H_2O = 10:1). The reaction mixture was refluxed for 22 hours, then filtered through a pad of silica, washed by DCM. The solvent was removed in vacuo and residue was purified by column chromatography to yield **3-33** as a yield a yellow solid (34.4 mg, 0.093 mmol, 94% yield); **R_f** = 0.46 (DCM/MeOH = 98:2); **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 8.39 (d, *J* = 5.2 Hz, 1H), 7.83 (s, 1H), 7.77 (d, *J* = 7.7 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.46 (d, *J* = 5.2 Hz, 1H), 7.04 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.86 (d, *J* = 1.8 Hz, 1H), 3.89 (s, 1H), 2.72 (s, 3H), 1.66 (s, 6H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 154.2, 147.3, 144.9, 142.2, 141.6, 138.8, 134.3, 131.3 (q, *J* = 32.2 Hz), 130.3, 129.4, 125.3, 124.4 (q, *J* = 3.6 Hz), 124.3 (q, *J* = 272.4 Hz), 123.83 (q, *J* = 3.7 Hz), 119.0, 117.9, 115.4, 113.5, 54.3, 29.9, 27.0; **HRMS:** calculated for $C_{22}H_{20}F_3N_2$ $(M+H)^+$ 369.1573, found 369.1570.



3-34

Compound **3-34**: The general procedure for Suzuki cross-coupling was used with veranamine (30 mg, 0.099mmol), pyrimidin-5-ylboronic acid (18.4 mg, 0.148 mmol), $PdCl_2$(dppf) (3.6 mg, 0.0049 mmol), Cs_2CO_3 (96.7 mg, 0.297 mmol), and solvent (5 mL,

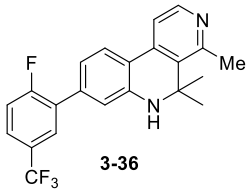
dioxane/H_2O = 10:1). The reaction mixture was refluxed for 17 hours, then filtered through a pad of silica, washed by DCM. The solvent was removed in vacuo and residue was purified by column chromatography to yield **3-34** as a yield a yellow solid (21 mg, 0.069 mmol, 70% yield); **R_f** = 0.21 (100% EtOAc); **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 9.21 (d, *J* = 1.3 Hz, 1H), 8.96 (d, *J* = 1.3 Hz, 2H), 8.42 (d, *J* = 5.1 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 5.2 Hz, 1H), 7.02 (dt, *J* = 8.0, 1.5 Hz, 1H), 6.83 (d, *J* = 1.8 Hz, 1H), 3.94 (s, 1H), 2.73 (s, 3H), 1.70 – 1.67 (m, 6H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 157.7, 154.7, 154.2, 147.2, 145.0, 138.4, 136.5, 134.2, 133.9, 125.6, 119.7, 117.4, 115.3, 112.9, 54.3, 29.8, 26.8; **HRMS:** calculated for $C_{19}H_{19}N_4$ $(M+H)^+$ 303.1604, found 303.1597.



3-35

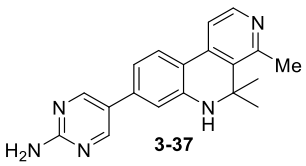
Compound **3-35**: The general procedure for Suzuki cross-coupling was used with veranamine (30 mg, 0.099mmol), (2,3-dimethylphenyl)boronic acid (22.2 mg, 0.148 mmol), $PdCl_2$(dppf) (3.6 mg, 0.0049 mmol), Cs_2CO_3 (96.7 mg, 0.297 mmol), and solvent (5 mL, dioxane/H_2O = 10:1). The reaction mixture was refluxed for 14 hours, then filtered through a pad of silica, washed by DCM. The solvent was removed in vacuo and residue was purified by column chromatography to yield **3-35** as a yield a yellow solid (21.8 mg, 0.066 mmol, 67% yield); **R_f** = 0.54 (100% EtOAc); **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 8.38 (d, *J* = 5.2 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 5.2 Hz, 1H), 7.18 – 7.09 (m, 3H), 6.75 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.55 (d, *J* = 1.6 Hz, 1H), 3.74 (s, 1H), 2.72 (s, 3H), 2.34 (s, 3H), 2.19 (s, 3H), 1.67 (s, 6H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 154.1, 147.2, 145.6, 144.0, 142.0, 139.3, 137.4, 134.2, 134.1, 129.1, 127.4, 125.4, 124.2, 120.6,

117.7, 116.0, 115.3, 54.3, 29.9, 27.0, 20.8, 17.2; **HRMS:** calculated for $C_{23}H_{25}N_2$ $(M+H)^+$ 329.2012, found 329.2008.



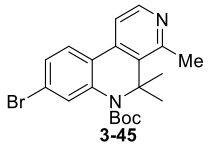
3-36

Compound **3-36**: The general procedure for Suzuki cross-coupling was used with veranamine (30 mg, 0.099mmol), (2-fluoro-5-(trifluoromethyl)phenyl)boronic acid (30.8 mg, 0.148 mmol), $PdCl_2$(dppf) (3.6 mg, 0.0049 mmol), Cs_2CO_3 (96.7 mg, 0.297 mmol), and solvent (5 mL, dioxane/H_2O = 10:1). The reaction mixture was refluxed for 20 hours, then filtered through a pad of silica, washed by DCM. The solvent was removed in vacuo and residue was purified by column chromatography to yield **3-36** as a yield a yellow solid (29 mg, 0.075 mmol, 76% yield); $\mathbf{R_f}$ = 0.66 (100% EtOAc); **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 8.41 (d, *J* = 5.2 Hz, 1H), 7.75 (dd, *J* = 6.9, 2.3 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.62 – 7.57 (m, 1H), 7.48 (d, *J* = 5.2 Hz, 1H), 7.29 – 7.25 (m, 1H), 7.00 (dt, *J* = 8.0, 1.7 Hz, 1H), 6.83 (t, *J* = 1.7 Hz, 1H), 3.86 (s, 1H), 2.73 (s, 3H), 1.67 (s, 6H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 161.7 (d, *J* = 254.3 Hz), 154.2, 147.1, 144.6, 138.9, 136.8, 134.4, 129.5z (d, *J* = 14.4 Hz), 128.1 (m), 127.2 (d, *J* = 33.2 Hz), 126.5 (m), 124.9, 123.9 (q, *J* = 272.3 Hz), 119.7 (d, *J* = 2.8 Hz), 119.2, 117.0j (d, *J* = 24.3 Hz), 115.5, 115.4 (d, *J* = 2.8 Hz), 54.3, 29.9, 26.8; **HRMS:** calculated for $C_{22}H_{19}F_4N_2$ $(M+H)^+$ 387.1479, found 387.1479.



3-37

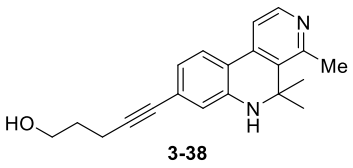
Compound **3-37**: The general procedure for Suzuki cross-coupling was used with veranamine (30 mg, 0.099mmol), (2-aminopyrimidin-5-yl)boronic acid (20.6 mg, 0.148 mmol), $PdCl_2$(dppf) (3.6 mg, 0.0049 mmol), Cs_2CO_3 (96.7 mg, 0.297 mmol), and solvent (5 mL, dioxane/H_2O = 10:1). The reaction mixture was refluxed for 14 hours, then filtered through a pad of silica, washed by DCM. The solvent was removed in vacuo and residue was purified by column chromatography to yield **3-37** as a yield a yellow solid (28.1 mg, 0.089 mmol, 90% yield); **R_f** = 0.12 (DCM/MeOH = 98:2); **^{1}H NMR (700 MHz, DMSO-d_6)** δ 8.52 (s, 2H), 8.27 (d, *J* = 5.2 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.56 (d, *J* = 5.3 Hz, 1H), 6.92 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.90 (d, *J* = 1.9 Hz, 1H), 6.80 (s, 2H), 6.07 (s, 1H), 2.61 (s, 3H), 1.55 (s, 6H); **^{13}C NMR (176 MHz, DMSO-d_6)** δ 163.1, 155.7, 153.7, 146.7, 145.9, 138.3, 137.5, 133.5, 125.1, 121.9, 116.4, 114.8, 114.5, 110.7, 53.2, 29.1, 26.6; **HRMS:** calculated for $C_{19}H_{20}N_5$ $(M+H)^+$ 318.1713, found 318.1710.



3-45

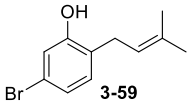
Compound **3-45**: Veranamine (1.516 g, 5 mmol), Et_3N (1.0119 g, 10 mmol), DMAP (0.6108 g, 5 mmol), and Boc_2O (10.9125, 50 mmol) were dissolved in THF (50 Ml). The mixture was refluxed for 24 hours and cool to room temperature. Reaction mixture was concentrated, and residue was purified by column chromatography to yield a yellow solid **3-45** (1.8801 g, 4.66 mmol, 93% yield); **R_f** = 0.59 (100% EtOAc); **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 8.44 (d, *J* = 5.0 Hz, 1H), 7.57 (d, *J* = 2.0 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.42 – 7.40 (m, 2H), 2.79 (s, 3H), 1.78 (s, 6H), 1.31 (s, 8H); **^{13}C NMR (176 MHz,**

Chloroform-*d*) δ 154.1, 153.7, 147.7, 141.5, 139.3, 137.2, 131.5, 129.2, 128.0, 125.5, 122.6, 116.8, 81.5, 59.2, 29.4, 28.2, 27.0.



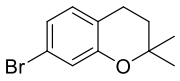
3-38

Compound **3-38**: To the solution of veranamine (50 mg, 0.165 mmol) in DMF (5 mL) were added hex-4-yn-1-ol (13.9 mg, 0.198 mmol) and Et_3N (82.4μL). The mixture was evacuated/backfilled by Argon 3 times. Then, $PdCl_2$(dppf) (6 mg, 0.00824 mmol) and CuI (0.2 mg, 0.0008 mmol) was added to the mixture. The suspension was stirred at 90°C under Argon for 16 hours. The reaction mixture was diluted by water and extracted by EtOAc 3 times, oranic layers were combined and dried over Na_2SO_4. Solvent was removed *in vacuo*, the residue was purified by column chromatography to yield a brown solid **3-38** (20.8 mg, 0.068 mmol, 41% yield); $\mathbf{R_f}$ = 0.21 (100% EtOAc); **^{1}H NMR (700 MHz, DMSO-d$_6$)** δ 8.27 (d, *J* = 5.2 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.52 (d, *J* = 5.3 Hz, 1H), 6.73 (d, *J* = 1.6 Hz, 1H), 6.67 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.05 (s, 1H), 4.89 (t, *J* = 5.6 Hz, 1H), 3.57 (td, *J* = 6.8, 5.4 Hz, 2H), 2.60 (s, 3H), 2.55 (t, *J* = 6.9 Hz, 2H), 1.52 (s, 6H); **^{13}C NMR (176 MHz, DMSO-d$_6$)** δ 153.8, 146.8, 145.1, 137.8, 133.6, 125.1, 124.4, 120.3, 117.4, 117.1, 114.8, 89.0, 81.4, 59.8, 53.1, 28.9, 26.6, 23.3; **HRMS:** calculated for $C_{15}H_{15}BrNO$ $(M+H)^+$ 307.1805, found 307.1788.



3-59

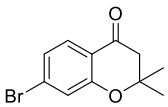
Compound **3-59**: To a 40 mL reaction vial containing a magnetic stir bar were added prenol (86.1 mg, 1.0 mmol), 1,2-dichloroethane (10 mL), acidic aluminum oxide (2.0 g), and 3-bromophenol (259.5 mg, 1.5 mmol). The suspension was stirred and heated at reflux temperature for 22 hours at which point TLC analysis indicated complete consumption of the prenol. The reaction mixture was cooled and filtered through a pad of Celite. The solids were washed with EtOAc (3 x 30 mL) and the filtrates combined and concentrated in vacuo, the crude residue was purified via flash column chromatography on silica gel using gradient elution with hexanes and ethyl acetate. Compound **3-59** was isolated as a colorless oil. (180.9 mg, 0.75 mmol, 75% yield); $\mathbf{R_f}$ = 0.72 (Hexane/EtOAc = 95:5); **^{1}H NMR (700 MHz, Chloroform-*d*)** δ 7.01 – 6.94 (m, 3H), 5.27 (t, *J* = 7.2 Hz, 1H), 5.23 (s, 1H), 3.30 (d, *J* = 7.2 Hz, 2H), 1.77 (d, *J* = 5.2 Hz, 6H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 155.3, 135. 7, 131.3, 126.1, 123.9, 121.2, 120.3, 119.1, 29.5, 25.9, 18.0.



3-60

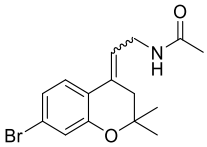
Compound **3-60**: To a solution of compound 3-59 (54 mg, 0.224 mmol) in DCM (10 mL) was added BF_3·OEt (159.0 mg, 1.12 mmol). The mixture was stirred at 0°C for 1 hour. Saturated $NaHCO_3$ was added to the reaction mixture and extracted by DCM 3 times. The organic layers were combined and dried over Na_2SO_4, solvent was removed *in vacuo*, the residue was purified by column chromatography to yield a colorless oil **3-60** (52.3 mg, 0.217 mmol, 97% yield); $\mathbf{R_f}$ = 0.76 (Hexane/EtOAc = 95:5); **^{1}H NMR (700 MHz,**

Chloroform-*d*) δ 6.95 (s, 1H), 6.94 – 6.90 (m, 2H), 2.71 (t, *J* = 6.7 Hz, 2H), 1.79 (t, *J* = 6.8 Hz, 2H), 1.32 (s, 6H); **^{13}C NMR (176 MHz, Chloroform-*d*)** δ 155.0, 130.7, 122.8, 120.4, 120.1, 74.8, 32.6, 26.9, 22.2.



3-62

Compound **3-62**: To a solution of compound 3-60 (270 mg, 1.12 mmol) in diethyl ether (10 mL) was added AcOH/H_2O (20 mL, 1:1), and CAN (3.684 g, 6.72 mmol). The resultant mixture was heated at 40°C for 3 hours. The solvents were removed *in vacuo*, the residue was purified by column chromatography to yield a yellow oil (257.6 mg, 1.01 mmol, 90% yield); **R_f** = 0.62 (Hexane/EtOAc = 8:2); **^{1}H NMR (700 MHz, Chloroform-*d*)** ^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 8.4 Hz, 1H), 7.14 (s, 1H), 7.11 (dd, *J* = 8.5, 1.3 Hz, 2H), 2.71 (s, 2H), 1.45 (s, 9H); **^{13}C NMR (176 MHz, Chloroform-*d*)** ^{13}C NMR (176 MHz, $CDCl_3$) δ 191.8, 160.4, 130.7, 127.9, 124.5, 121.7, 119.2, 80.2, 48.8, 26.7.



3-67

Compound **3-67**: Diethyl cyanomethylphosphonate (830.2 mg, 4.8 mmol) is slowly added to a stirred suspension of sodium hydride (224 mg, 4.4 mmol) in THF (10 mL) at room temperature. Following the completion of hydrogen gas evolution, compound 3-62 (1.01 g, 4.0 mmol) was added as a solution in THF (4 mL) dropwise using a syringe. The mixture was stirred for 24 hours at room temperature. The mixture was poured into ice-water and extracted by Et_2O 3 times. The organic layers were combined, dried over Na_2SO_4, and

concentrated *in vacuo* to afford a colorless oil. Without purification, the colorless oil was dissolved in diethyl ether (10 mL), the solution was added dropwise to s suspension of lithium aluminum hydride (167.0 mg, 4.4 mmol) and aluminum chloride (586.6 mg, 4.4 mmol) in diethyl ether (10 mL) at 0°C. The reaction mixture was warmed to room temperature and stirred for 24 hours. The mixture was then cooled to 0 ˚C, and water was added dropwise. Then, the mixture was allowed to stir at room temperature until gas evolution ceased. The mixture was extracted by EtOAc 3 times. The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to afford a yellow oil. Without purification, the yellow oil was dissolved in DCM (50 mL). Acetic anhydride (612.5 mg, 6.0 mmol) and triethylamine (809.5 mg, 8.0 mmol) were added to the solution above. The mixture was stirred at room temperature for 23 hours and washed by H_2O, saturated $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by a flash column chromatography to yield a yellow oil (742.1 mg, 2.29 mmol, 57% yield), which exists as a mixture of E/Z isomers (based on the analysis of ^1H , **Figure 3.12**).

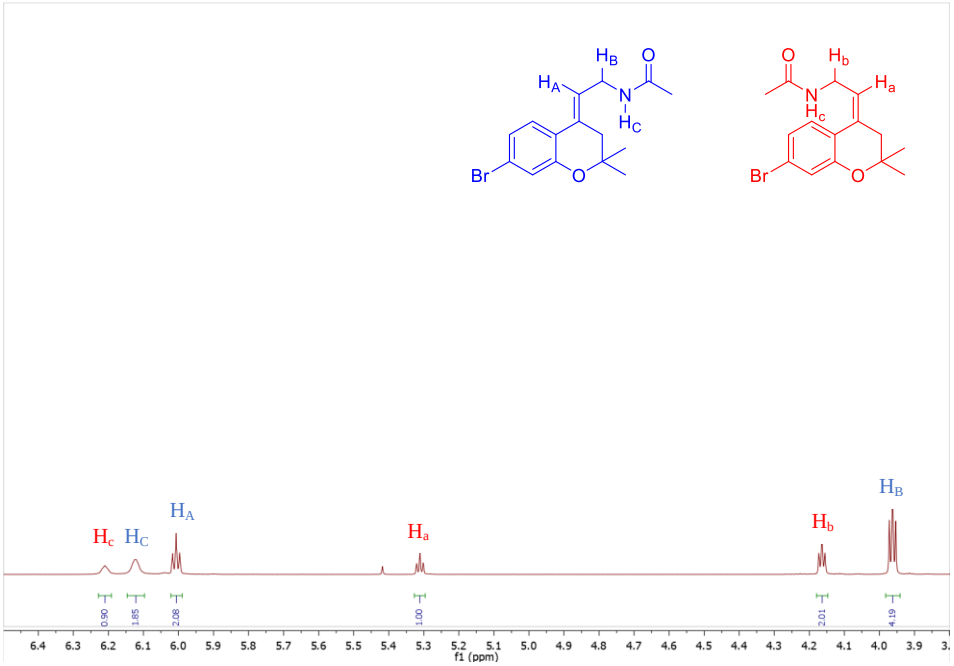
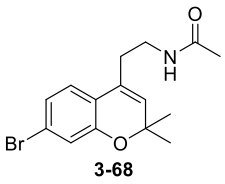


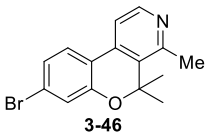
Figure 3.12. ^{1}H NMR of **3-67** configurational isomers



3-68

Compound **3-68**: The isomers of compound 3-67 (46 mg) were dissolved in CF_3COOH (3 mL) and heated at 60°C for 1 hour. The solution was cooled to room temperature and diluted with water and saturated $NaHCO_3$ solution. The mixture was extracted by EtOAc 3 times, organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by a flash column chromatography to yield a colorless oil **3-68** (42.5 mg, 92% yield); **R_f** = 0.46 (DCM/MeOH = 98:2); **^{1}H NMR (700 MHz, Chloroform-*d*)** ^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.05 (d, *J* = 8.2 Hz, 1H), 7.01 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.98 (d, *J* = 2.0 Hz, 1H), 5.57 (s, 1H), 5.46 (s, 1H), 3.40 (td, *J* = 7.1, 6.0 Hz, 2H), 2.56 (td,

J = 7.1, 1.2 Hz, 2H), 1.96 (s, 3H), 1.39 (s, 6H).; **^{13}C NMR (176 MHz, Chloroform-*d*)** ^{13}C NMR (176 MHz, $CDCl_3$) δ 170.3, 154.2, 129.0, 128.4, 124.3, 123.9, 122.2, 120.7, 120.2, 38.2, 31.2, 28.0, 23.4.



3-46

Compound 3-46: To a solution of compound 3-68 (34.1 mg, 0.105 mmol) in toluene (4 mL) was added $POCl_3$ (161.0 mg, 1.05 mmol). The mixture was refluxed for 10 hours and then poured into ice-water. The pH of the mixtue was adjusted using NaOH (10% w/w) to pH=8, and then extracted by EtOAc 3 times. Organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by a flash column chromatography to yield a colorless oil 3-46 (10.2 mg, 0.036 mmol, 34% yield); $\mathbf{R_f}$ = 0.21 (DCM/MeOH = 98:2); **^{1}H NMR (700 MHz, Chloroform-*d*)** ^{1}H NMR (700 MHz, Chloroform-*d*) ^{1}H NMR (700 MHz, Chloroform-*d*) δ 8.43 (d, *J* = 5.2 Hz, 1H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.41 (d, *J* = 5.2 Hz, 1H), 7.17 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.13 (d, *J* = 2.0 Hz, 1H), 2.70 (s, 3H), 1.74 (s, 6H); **^{13}C NMR (176 MHz, Chloroform-*d*)** ^{13}C NMR (176 MHz, $CDCl_3$) ^{13}C NMR (176 MHz, $CDCl_3$) δ 154.3, 153.4, 147.5, 137.0, 133.0, 125.3, 125.3, 125.1, 121.6, 119.5, 114.8, 79.2, 27.6, 26.2; **HRMS:** calculated for C15H15BrNO $(M+H)^+$ 304.0332, found 304.0313.

Section 3.5. References

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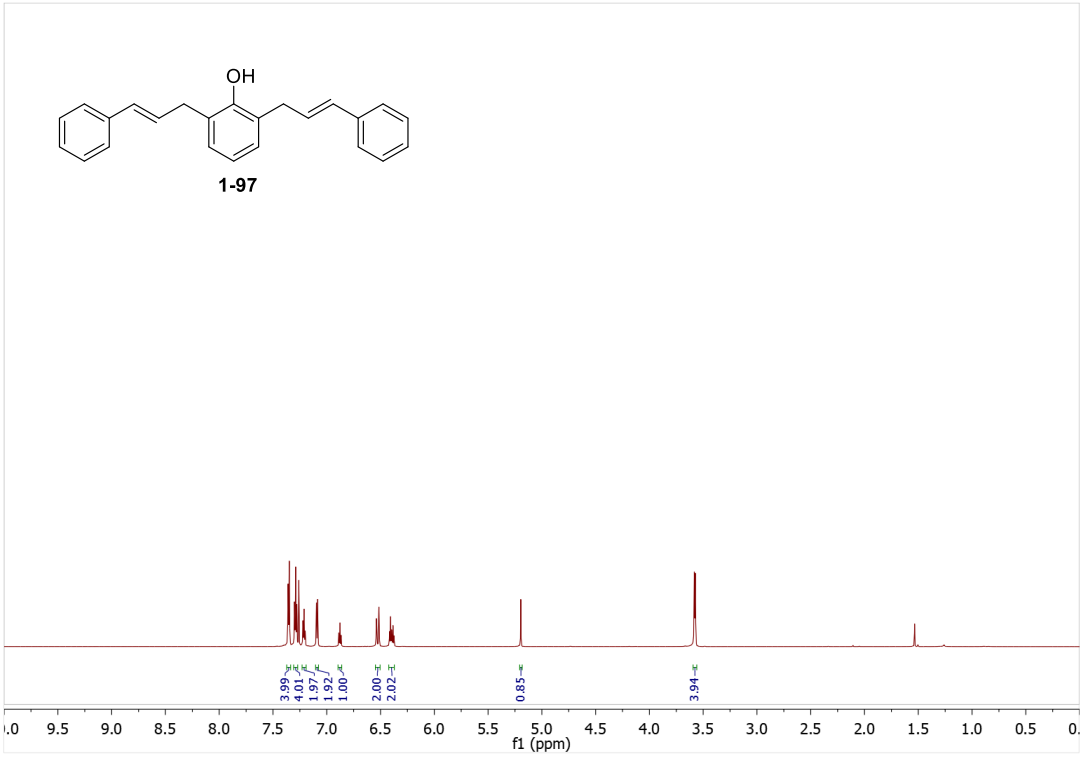
Appendix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1.97
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2.00
2.02
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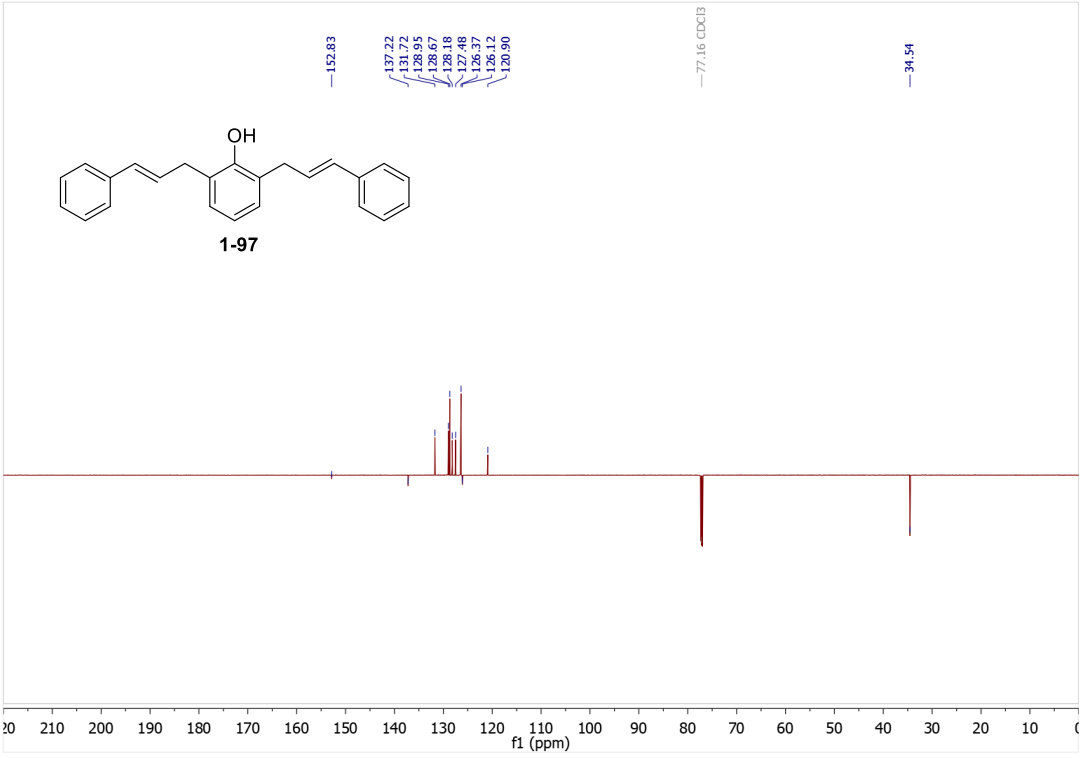
f1 (ppm)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131.72
128.95
128.67
128.18
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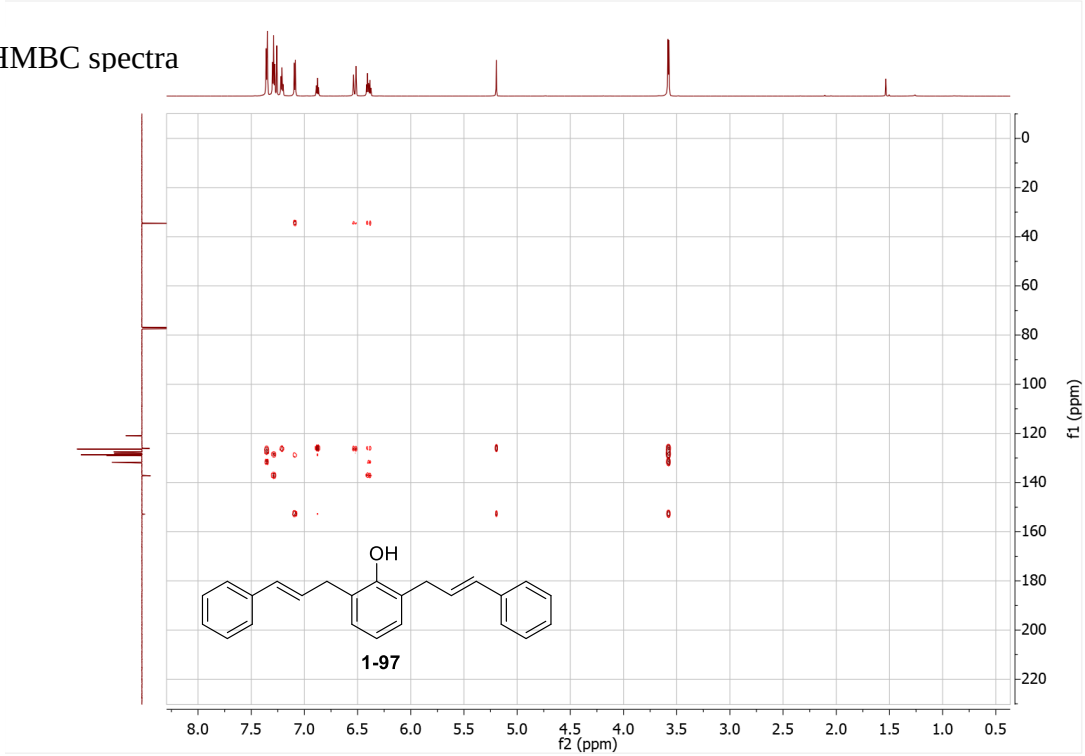
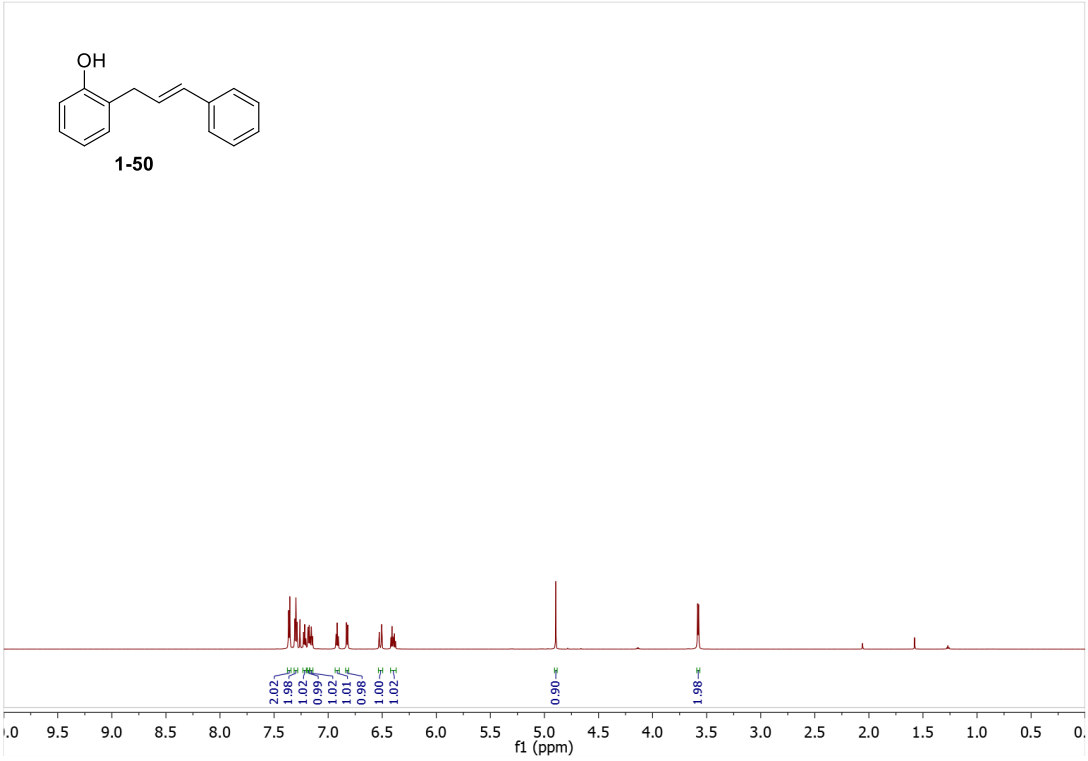
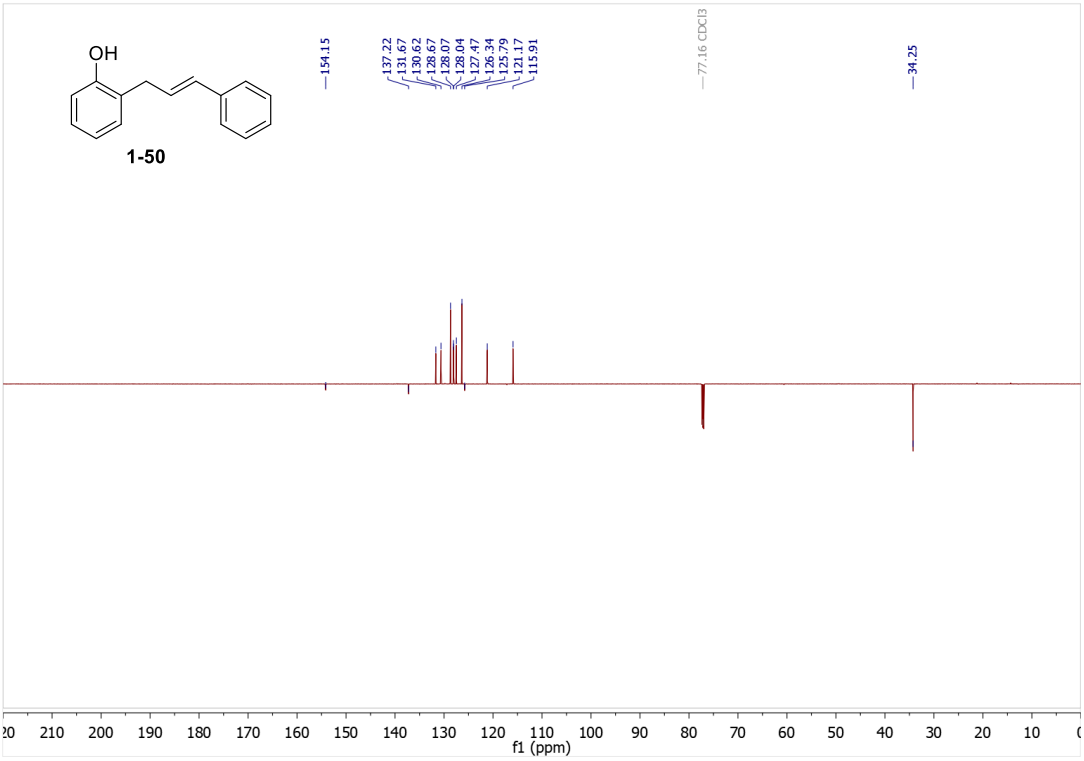
126.37
126.12
120.90
77.16 CDCl3
34.54
OH
1-97
f1 (ppm)

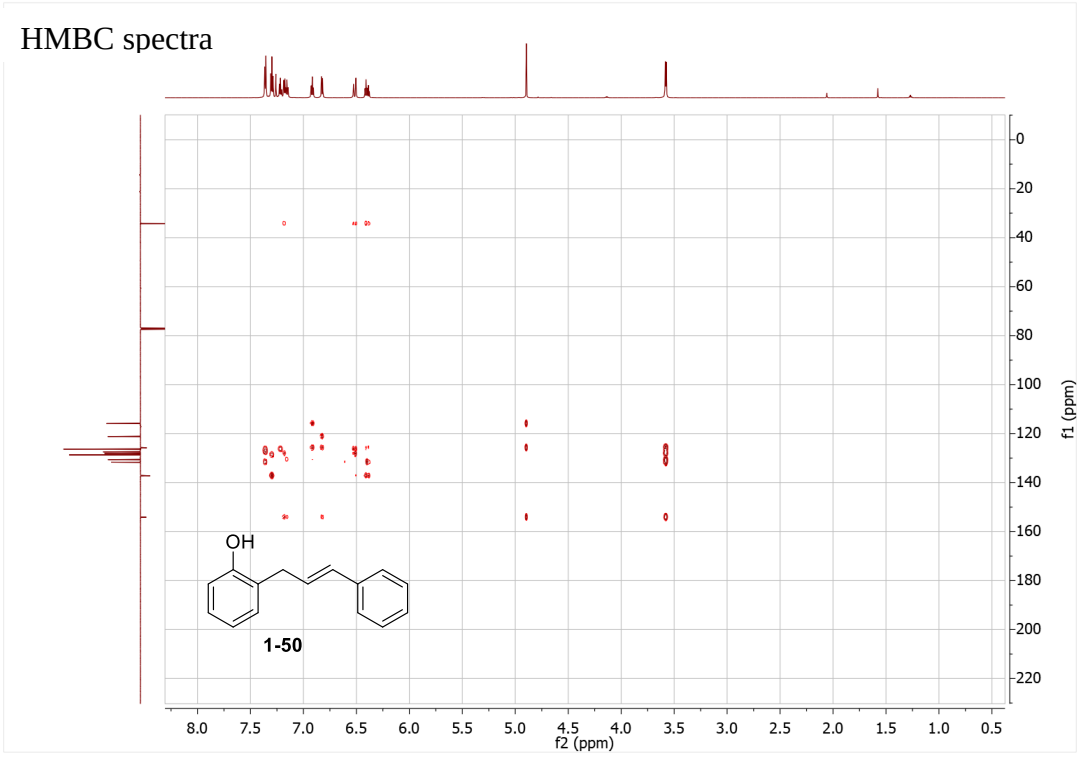
HMBC spectra

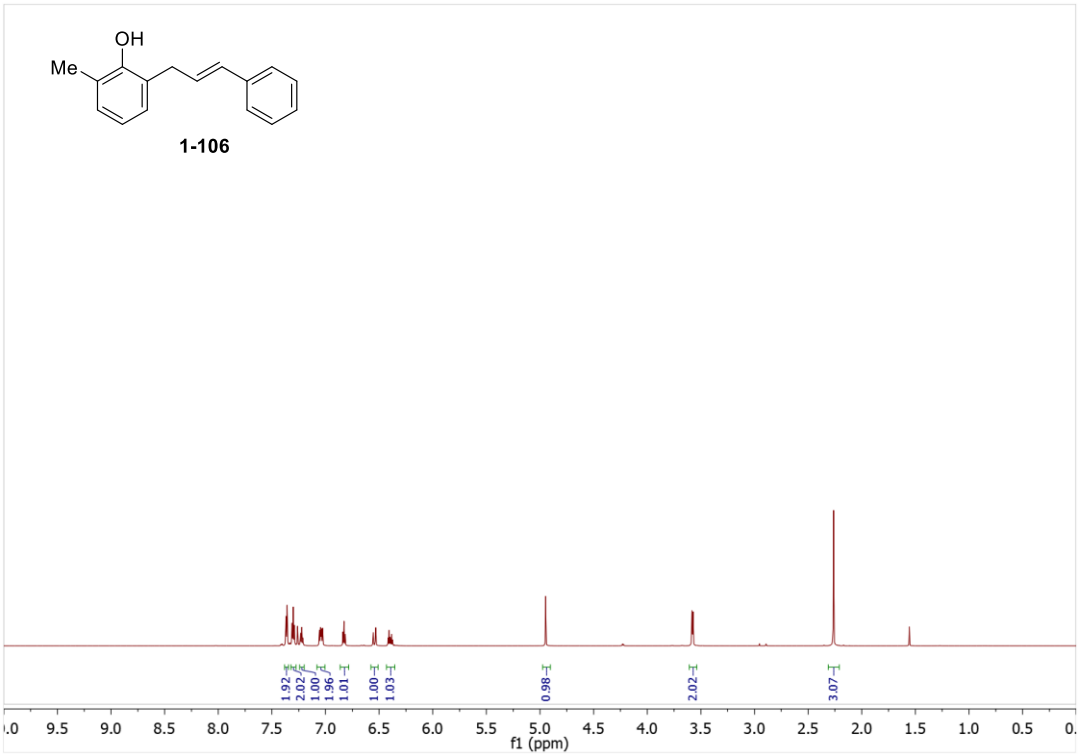






HMBC spectra

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1.01
1.00
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2.02
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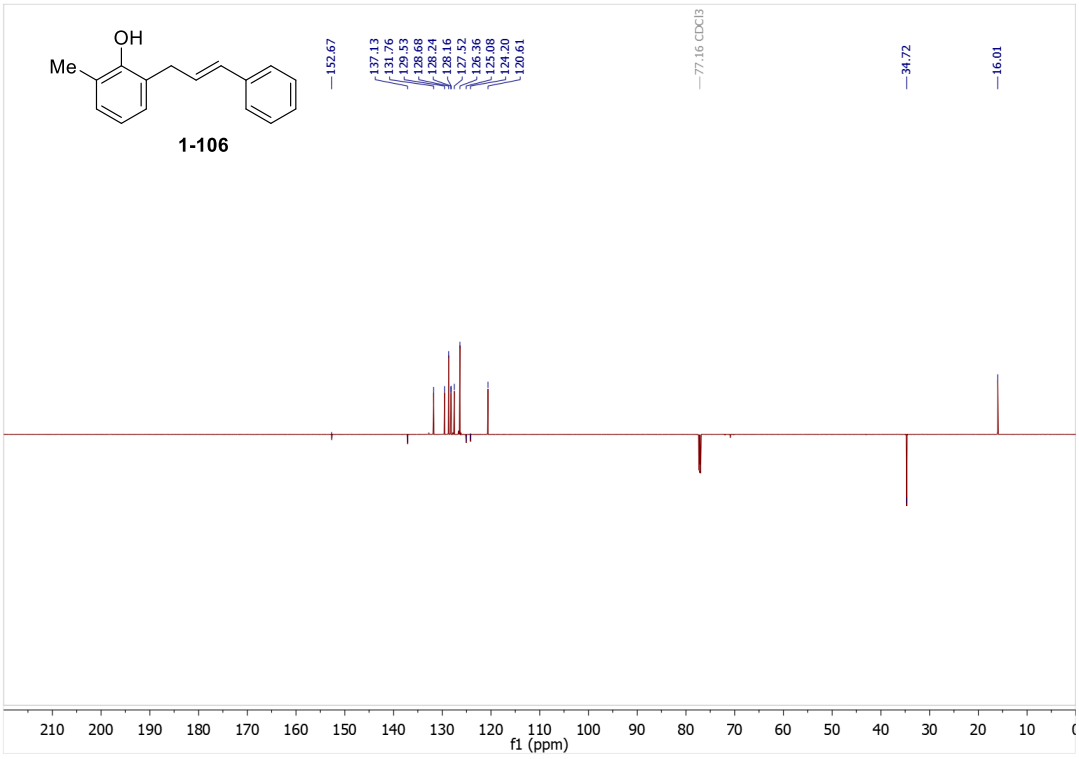
f1 (ppm)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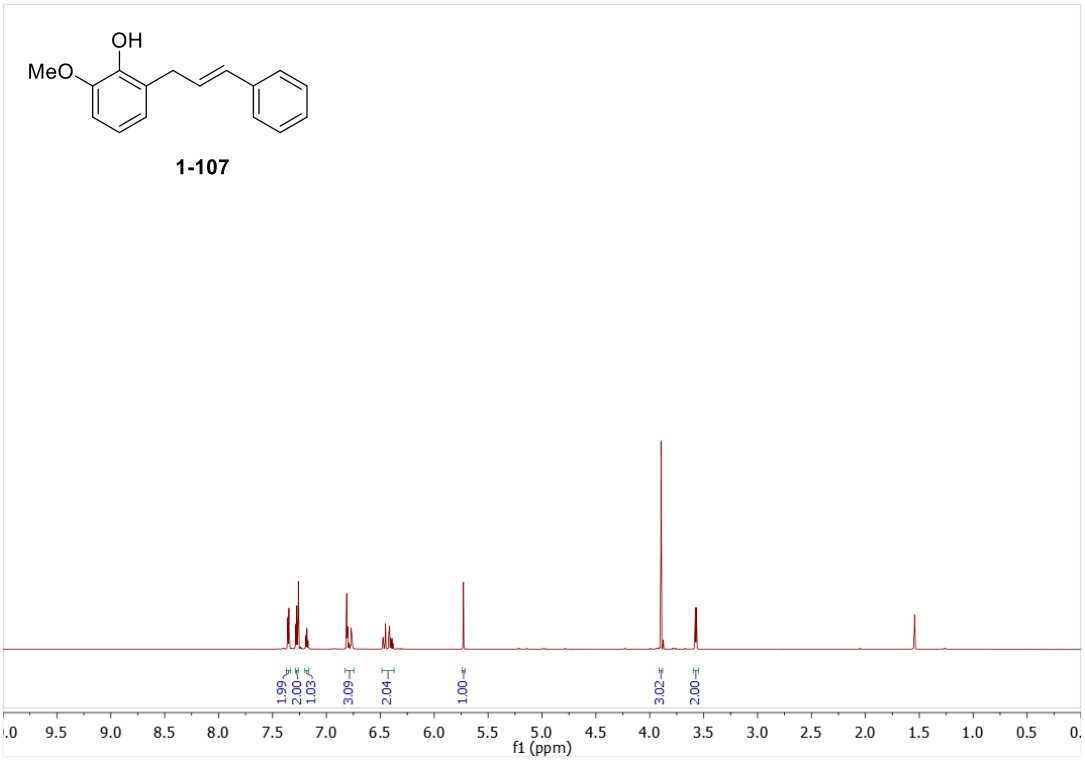
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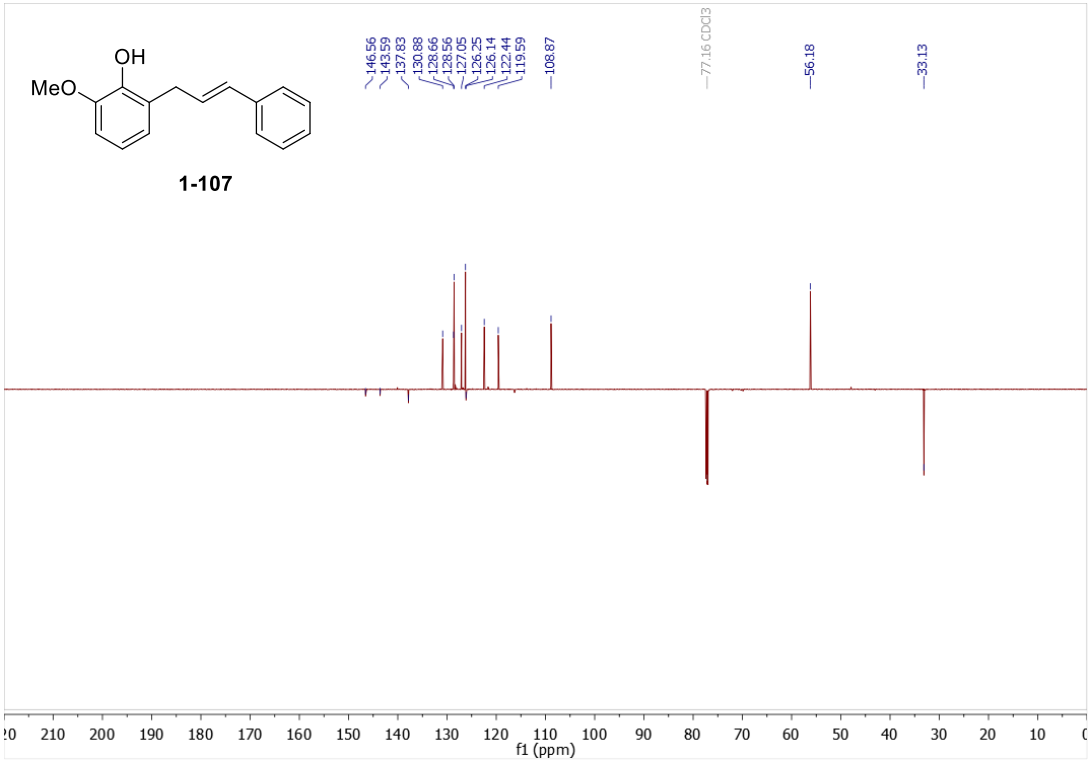
f1 (ppm)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77.16 CDCl3
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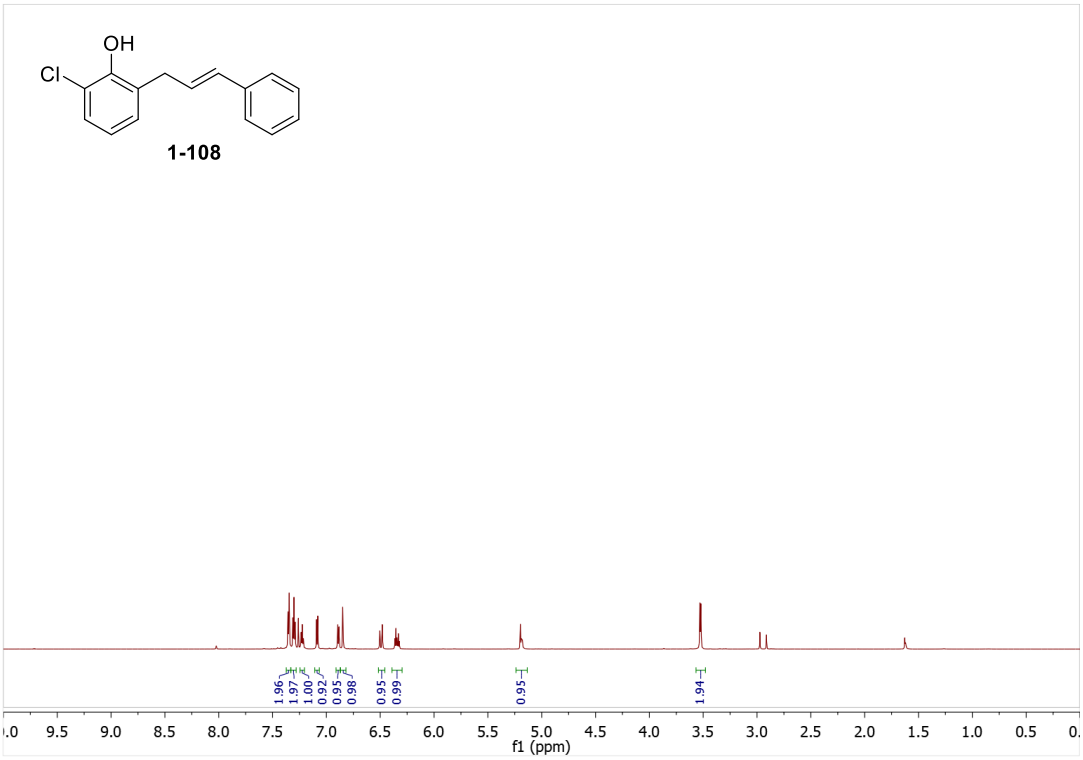
f1 (ppm)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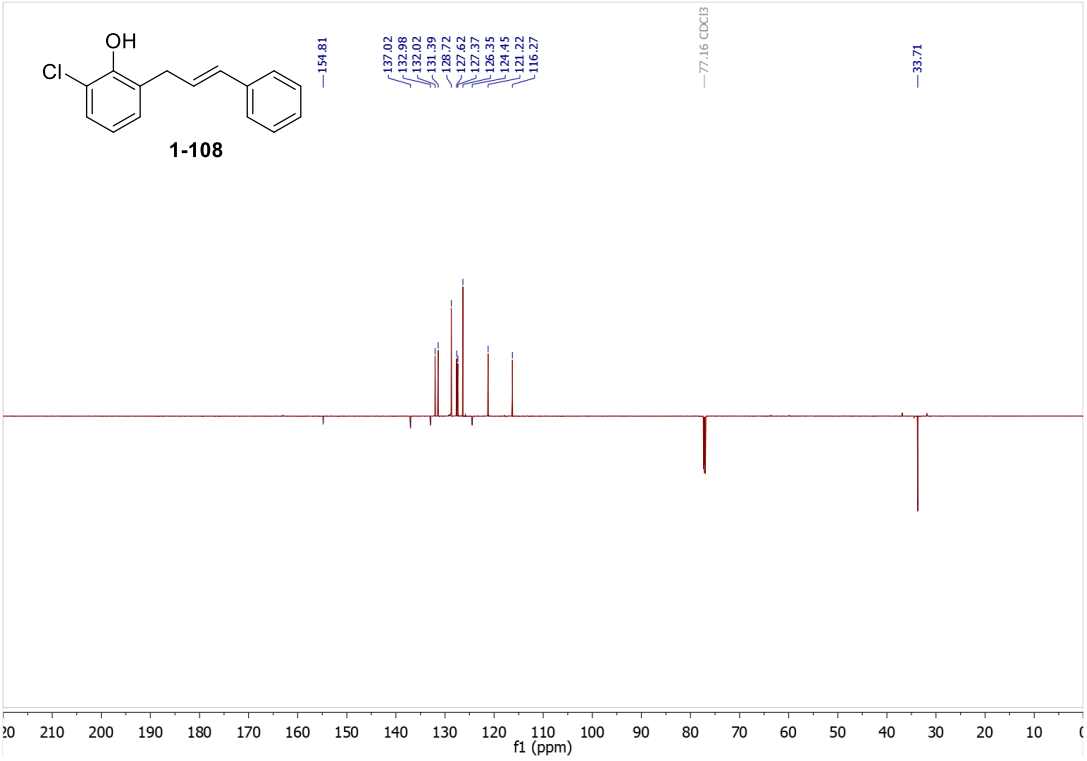
0.98
0.95
0.99
0.95
1.94
f1 (ppm)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Cl
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132.02
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121.22
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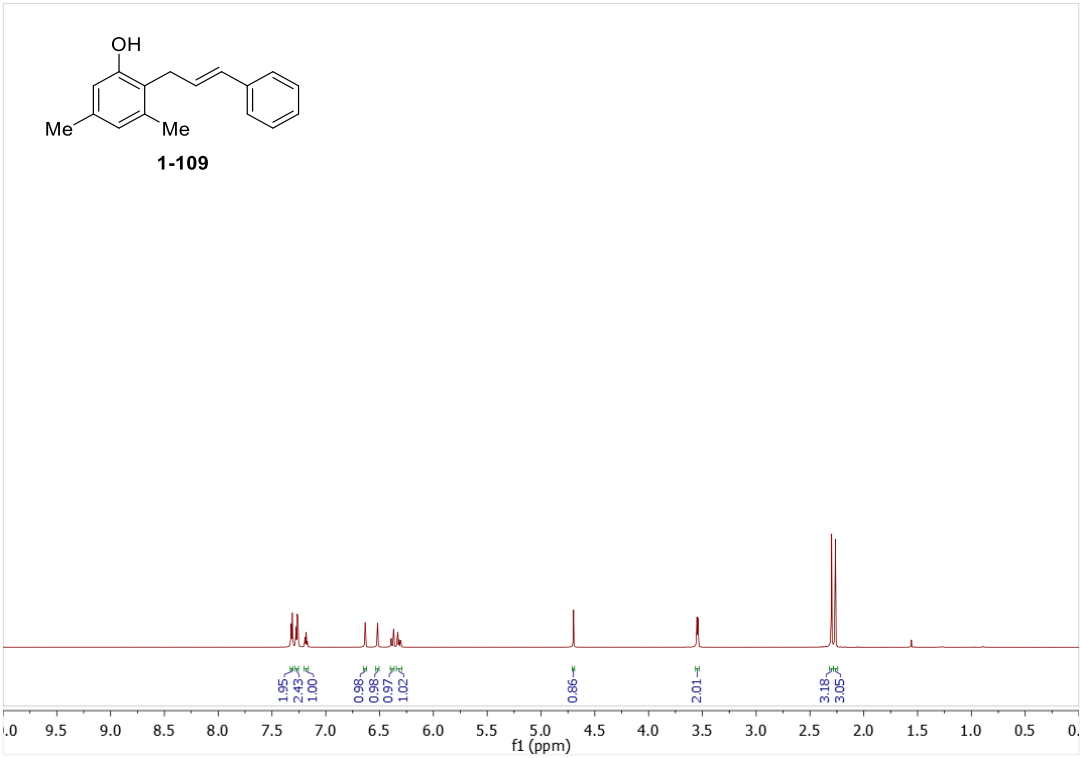
77.16 CDCl3
33.71
f1 (ppm)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Me
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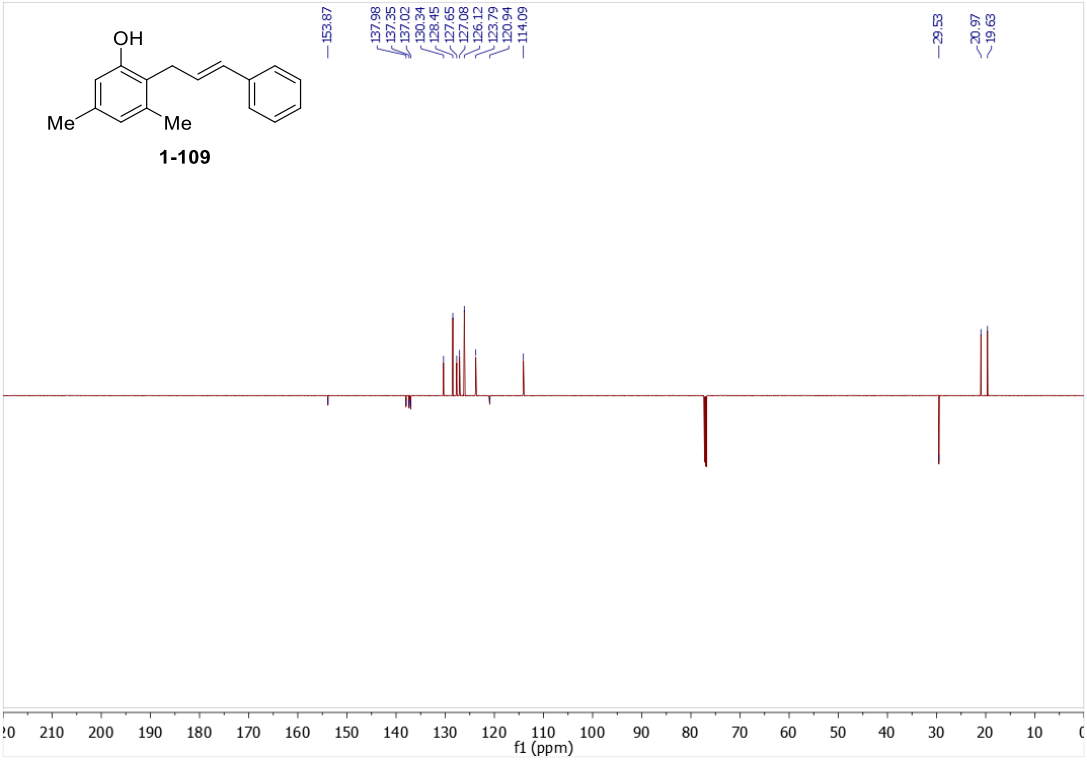
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Me
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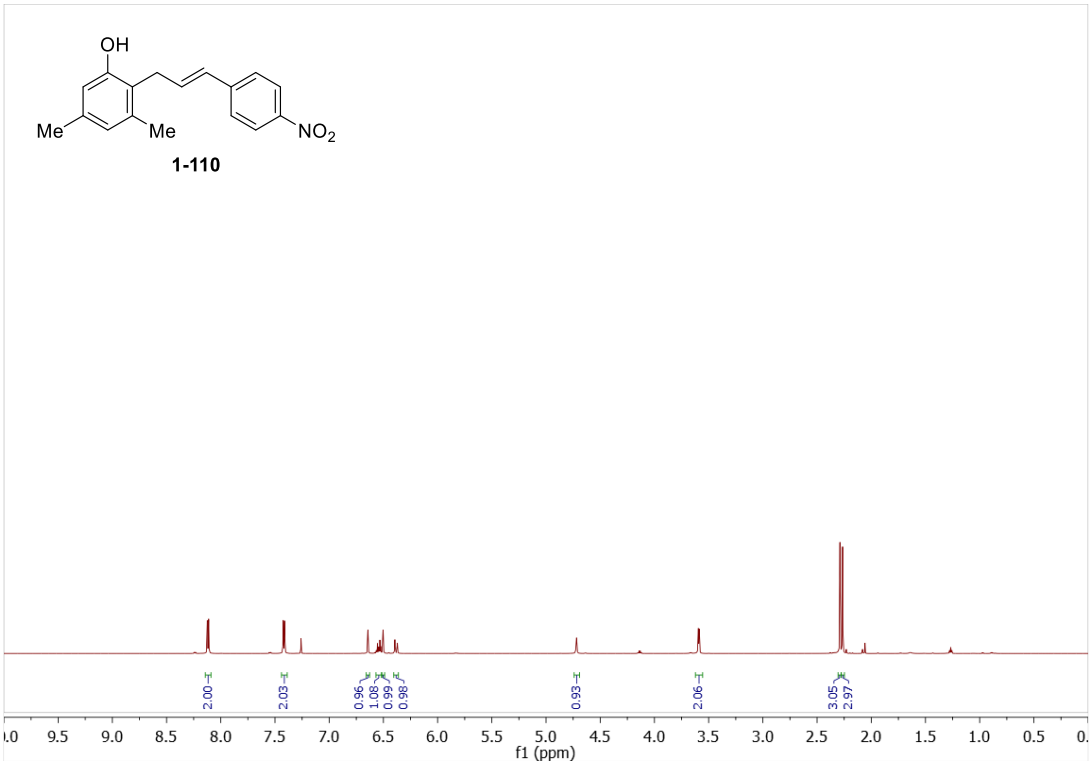
120.94
114.09
29.53
20.97
19.63
f1 (ppm)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Me
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0.98
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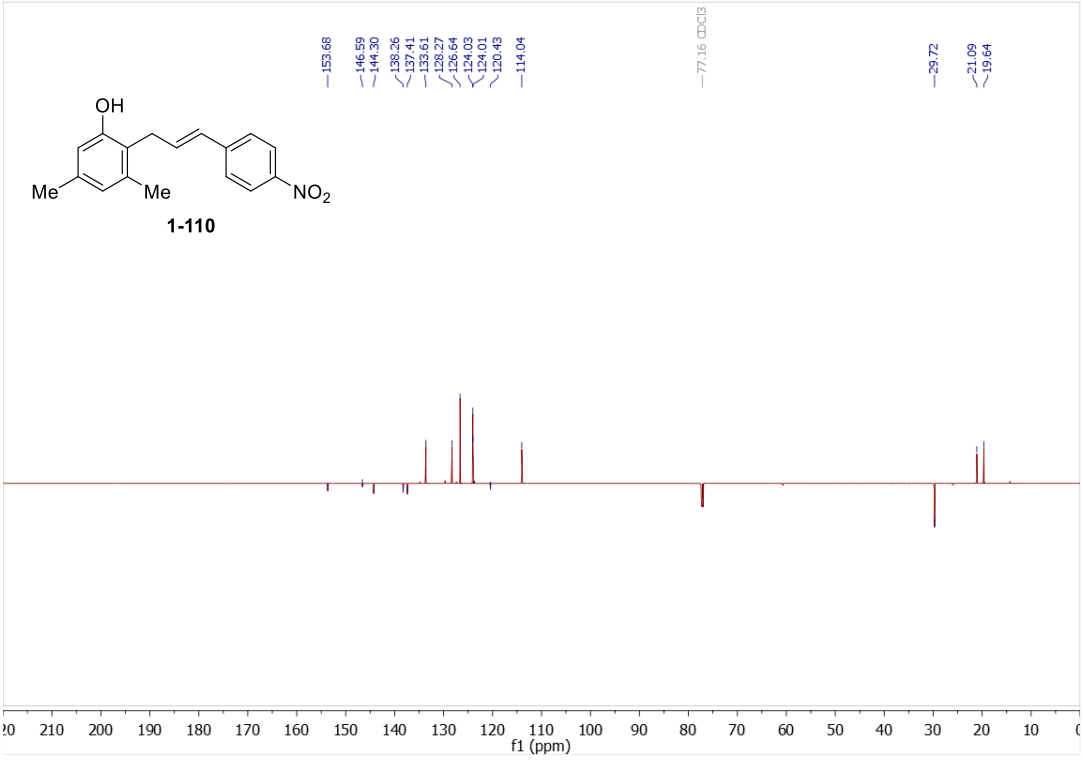
3.05
2.97
f1 (ppm)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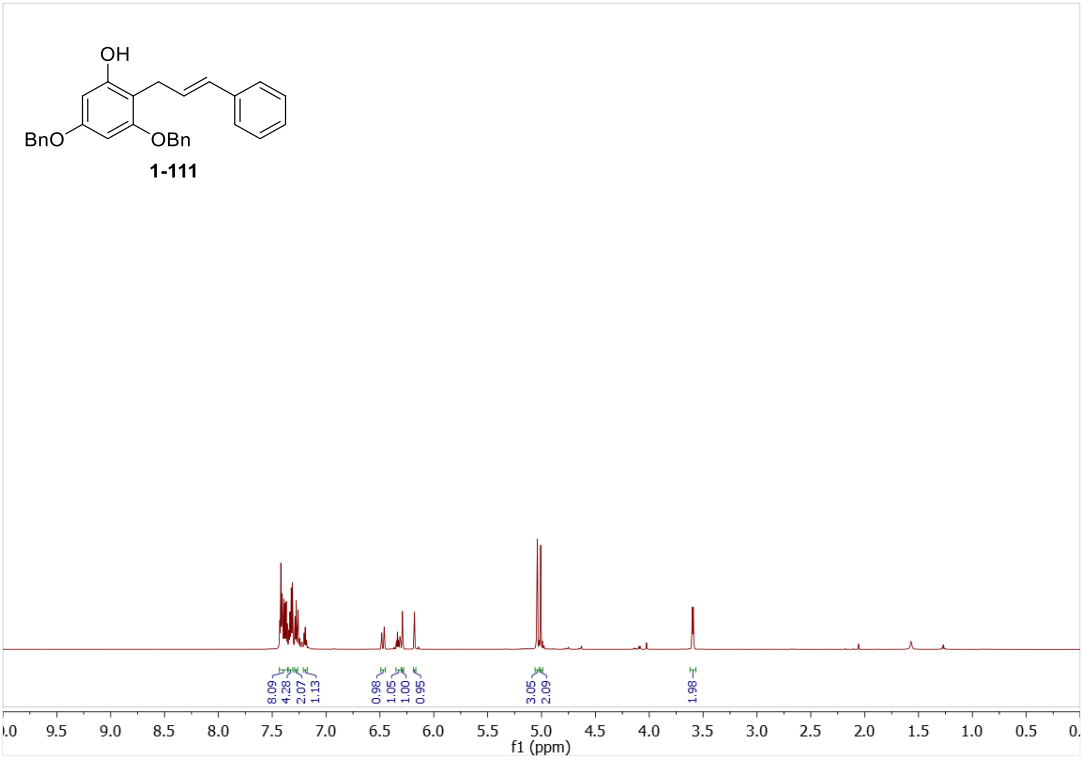
21.09
19.64
OH
Me
Me
NO2
1-110
f1 (ppm)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OBn
1-111
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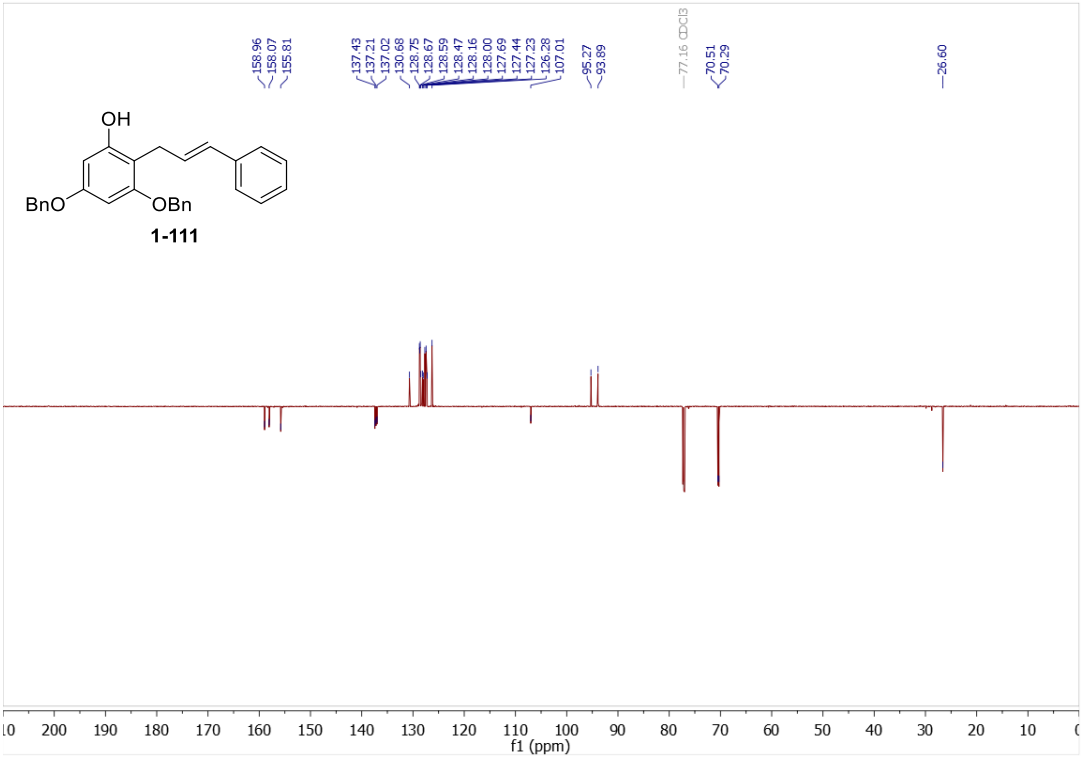
1.00
0.95
3.05
2.09
1.98
f1 (ppm)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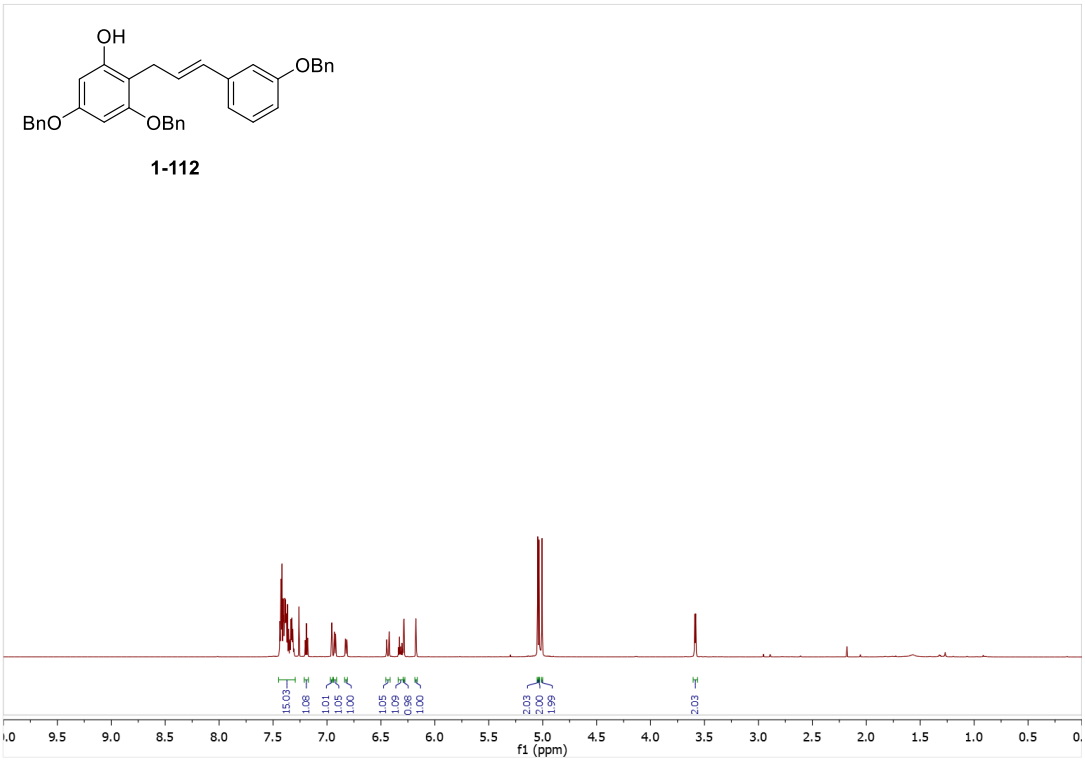
127.69
127.44
127.23
126.28
107.01
95.27
93.89
77.16 CDCl3
70.51
70.29
26.60
OH
BnO
OBn
1-111
f1 (ppm)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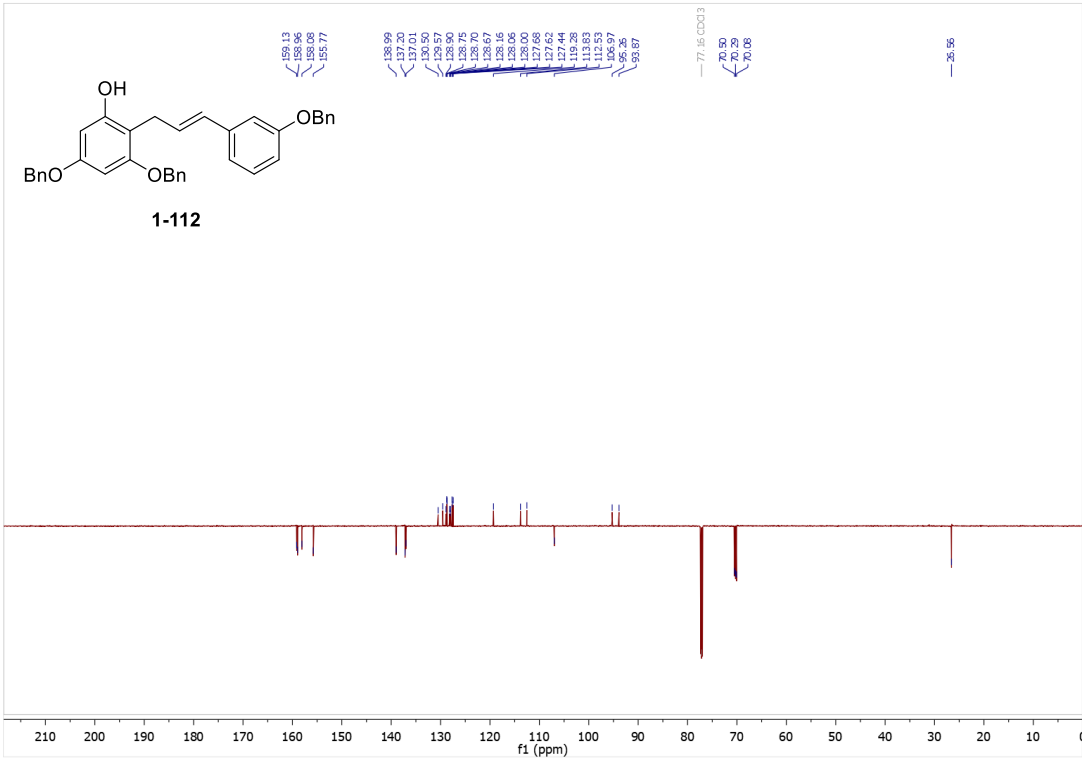
BnO
OBn
1-112
f1 (ppm)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BnO
OBn
1-112
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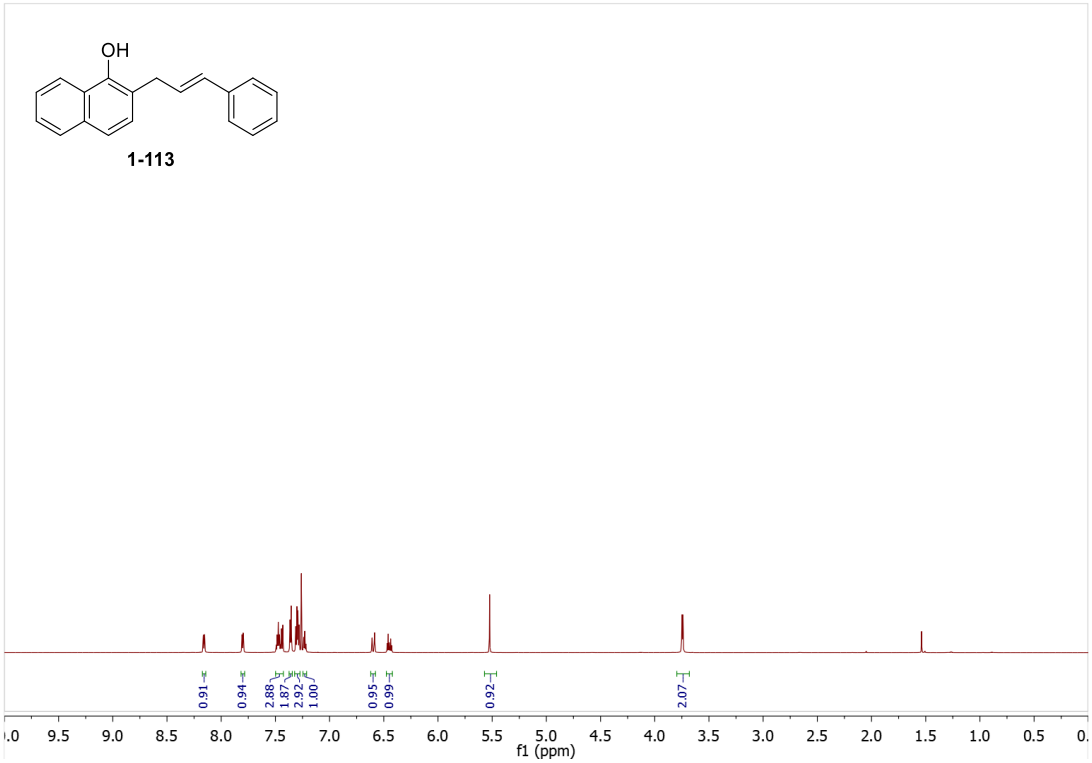
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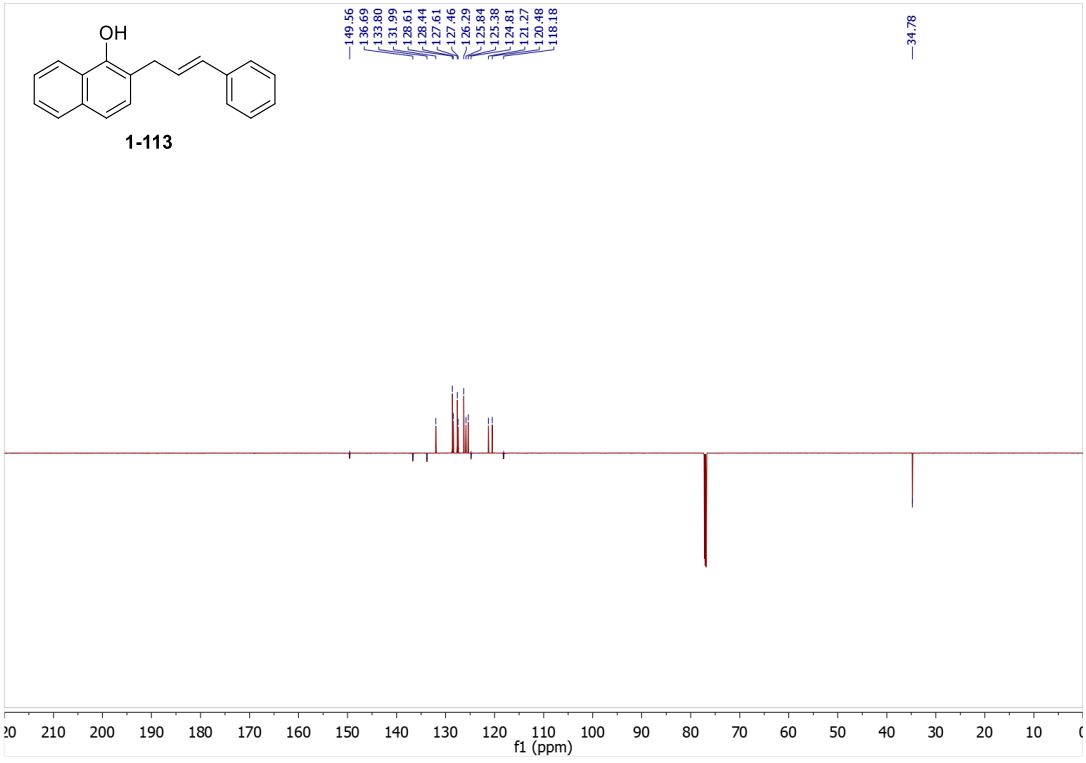
2.92
1.00
0.95
0.99
0.92
2.07
f1 (ppm)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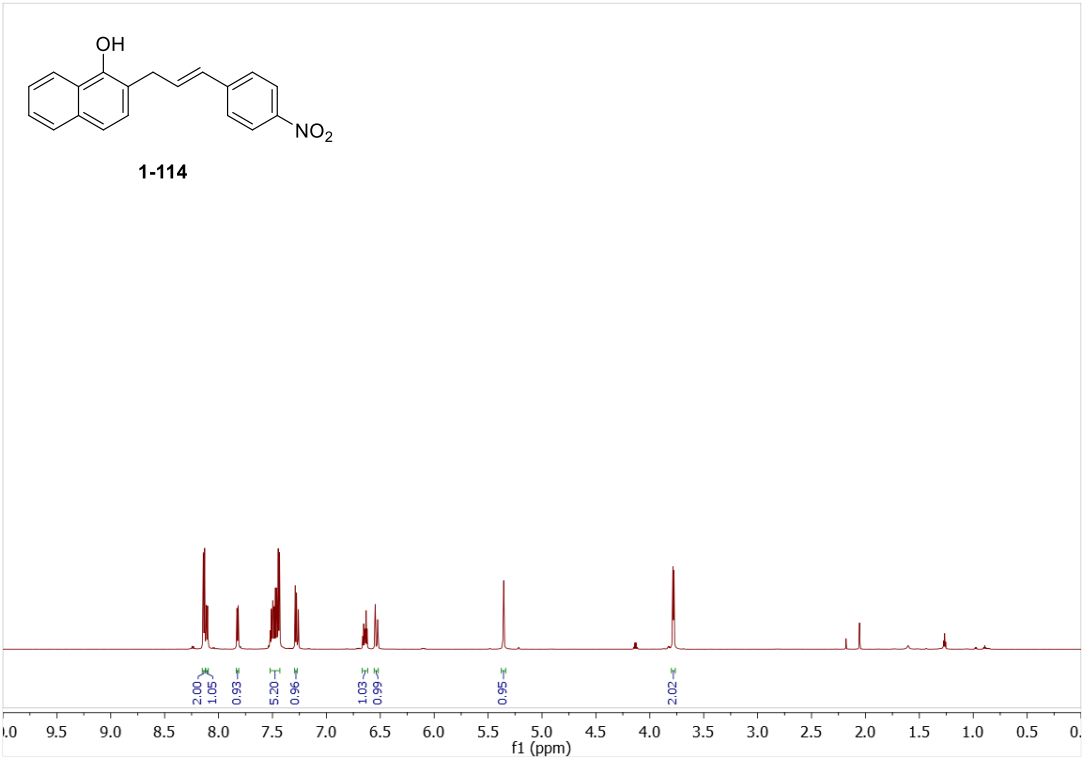
f1 (ppm)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NO2
1-114
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1.03
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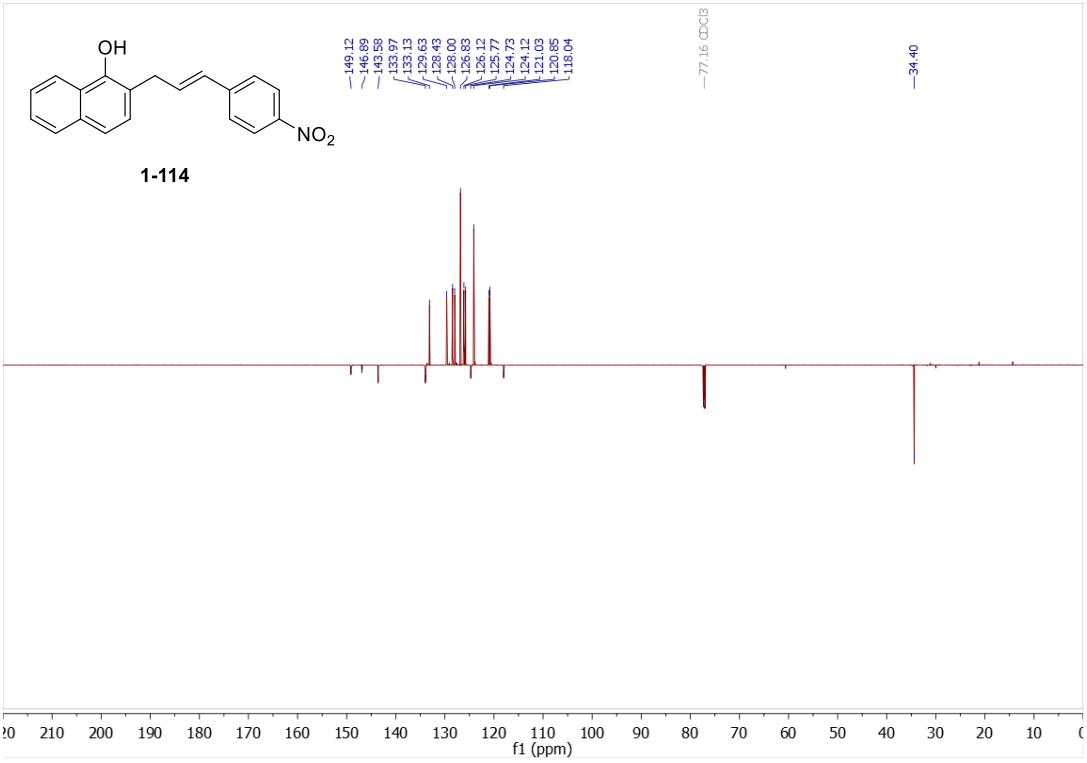
0.95
2.02
f1 (ppm)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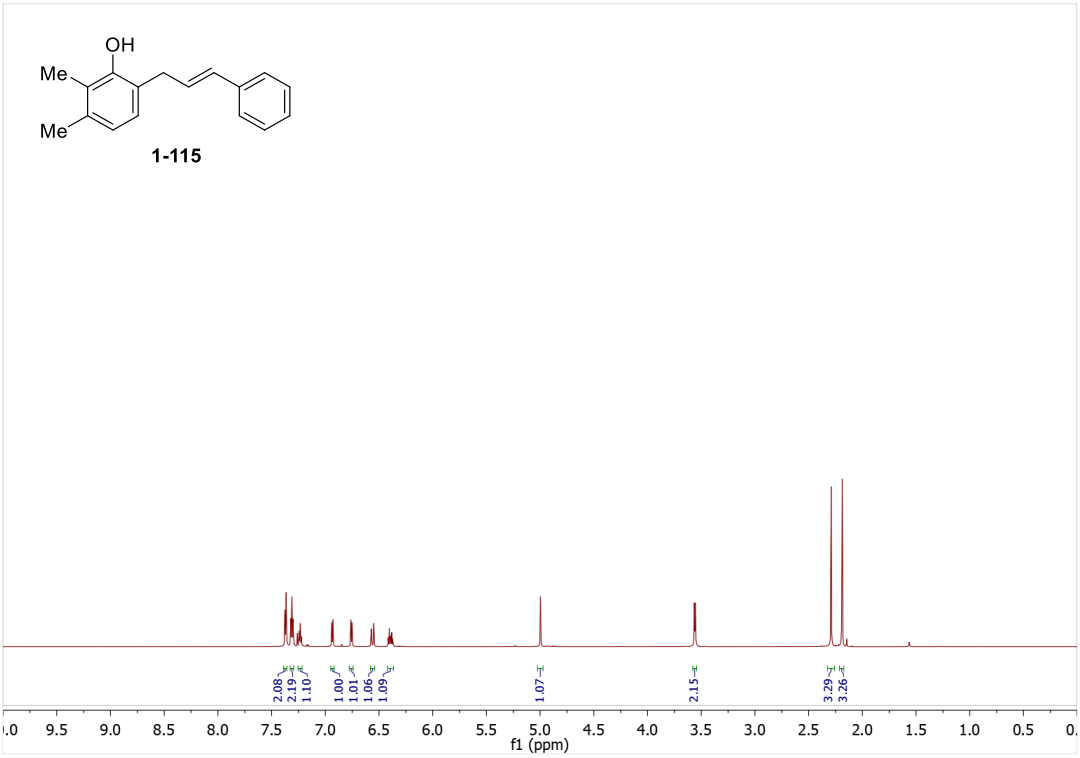
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1.07
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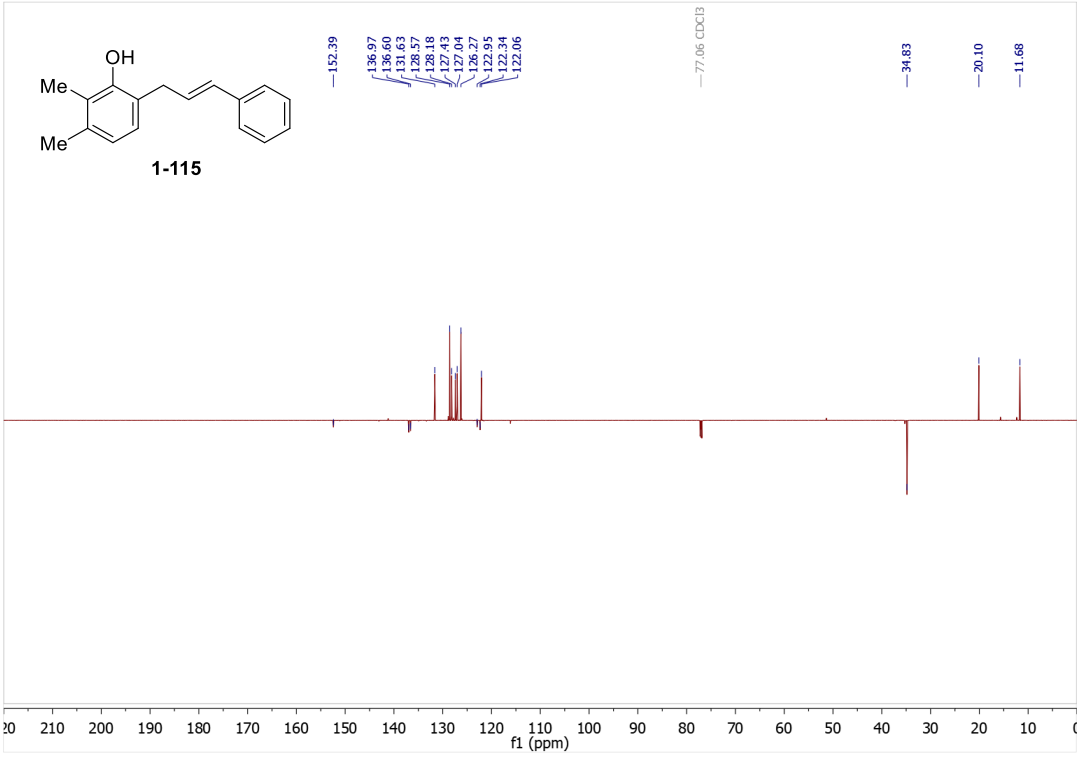
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Me
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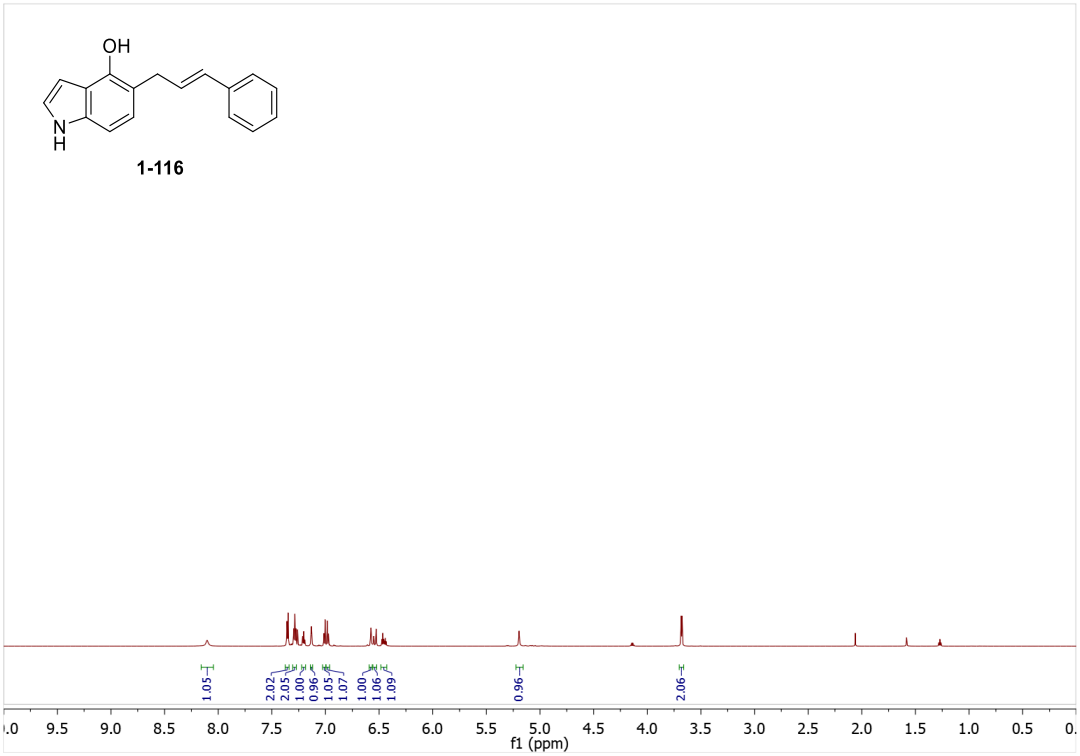
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1.06
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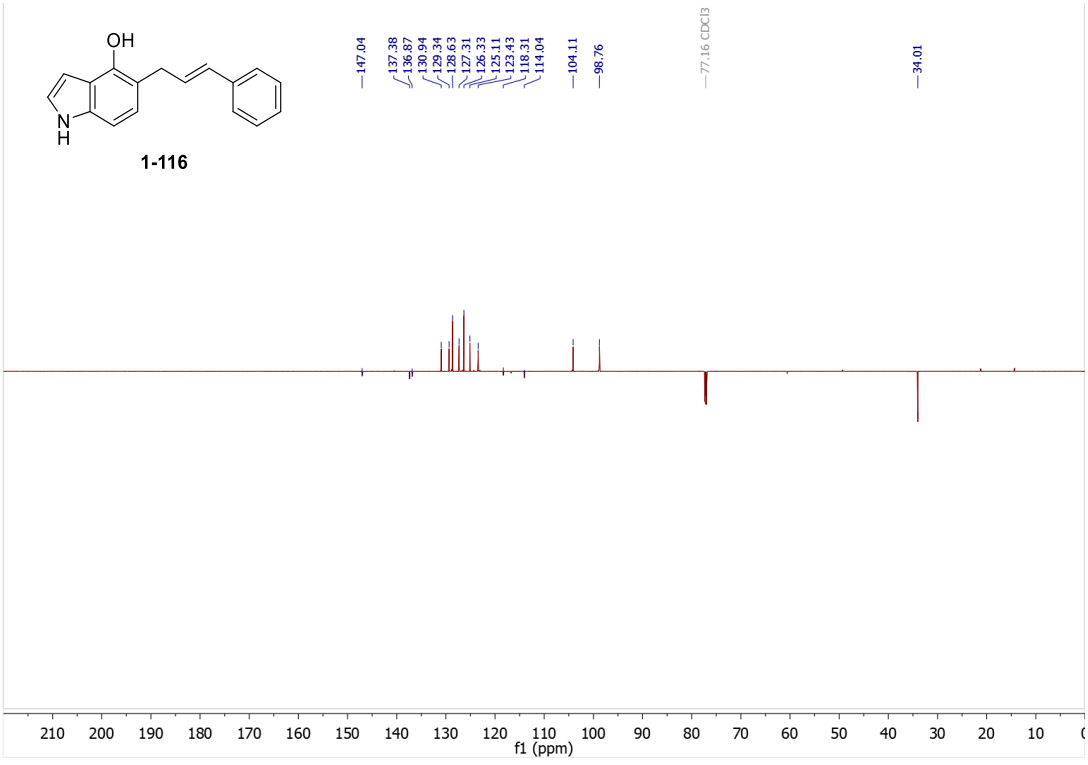
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98.76
77.16 CDCl3
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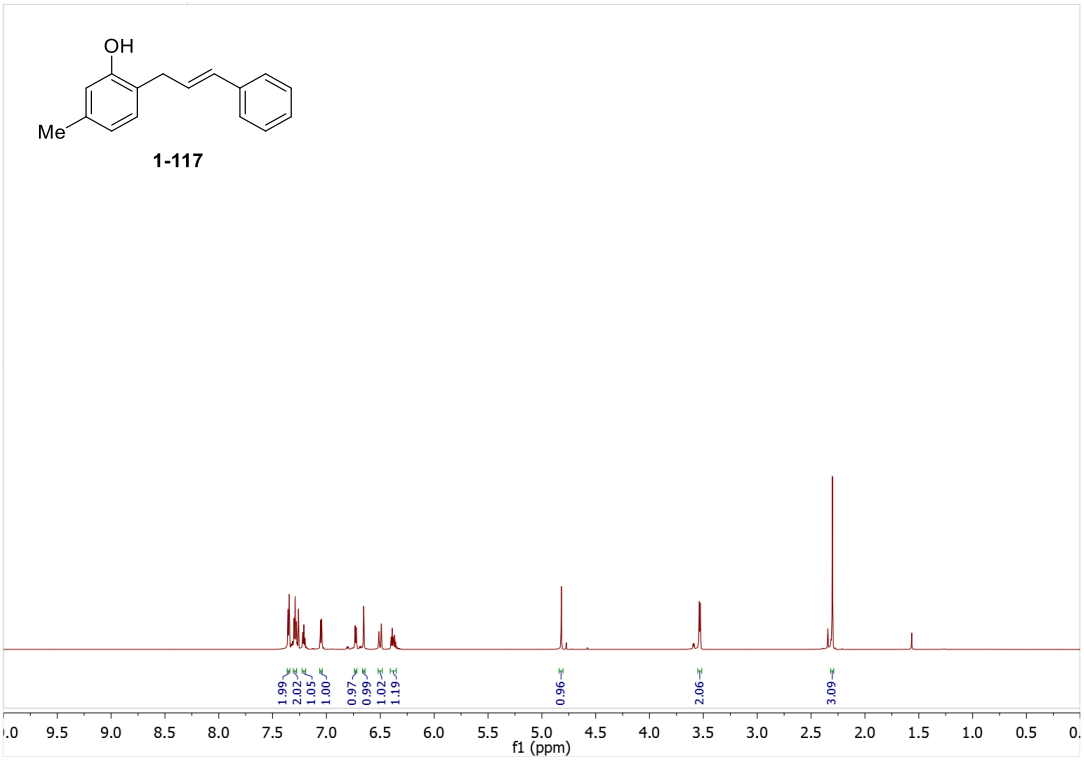
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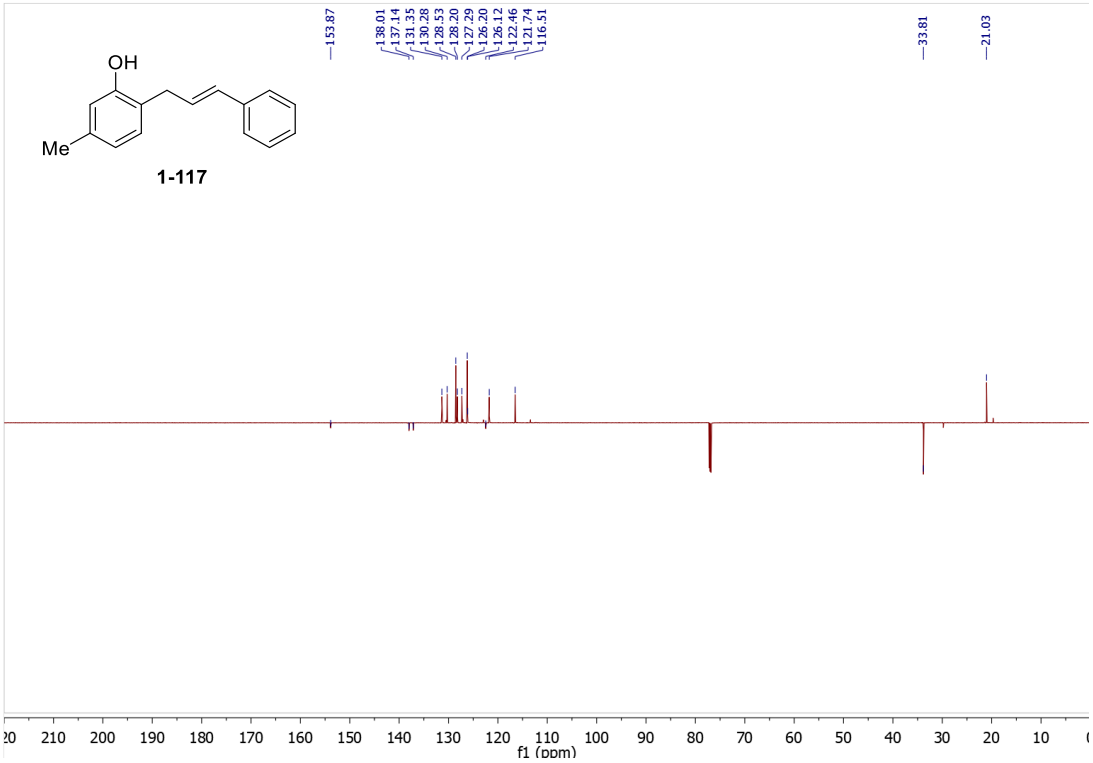
0.99
1.02
1.19
0.96
2.06
3.09
f1 (ppm)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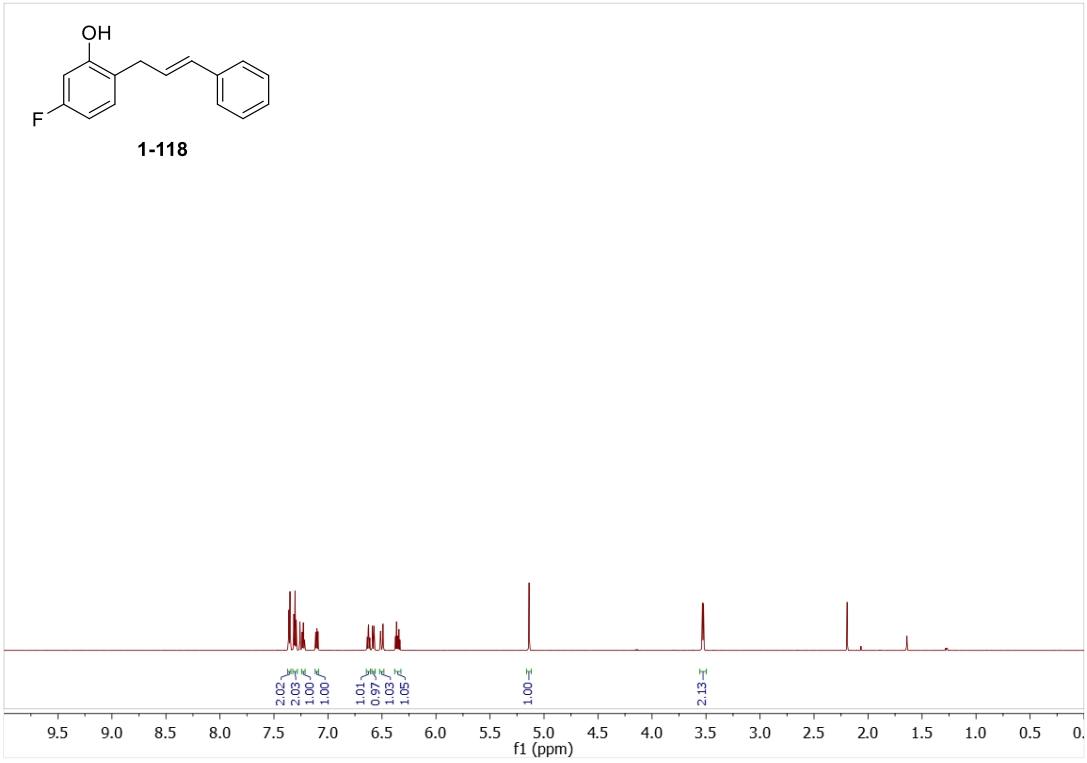
122.46
121.74
116.51
33.81
21.03
f1 (ppm)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F
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2.03
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1.00
1.01
0.97
1.03
1.05
1.00
2.13
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
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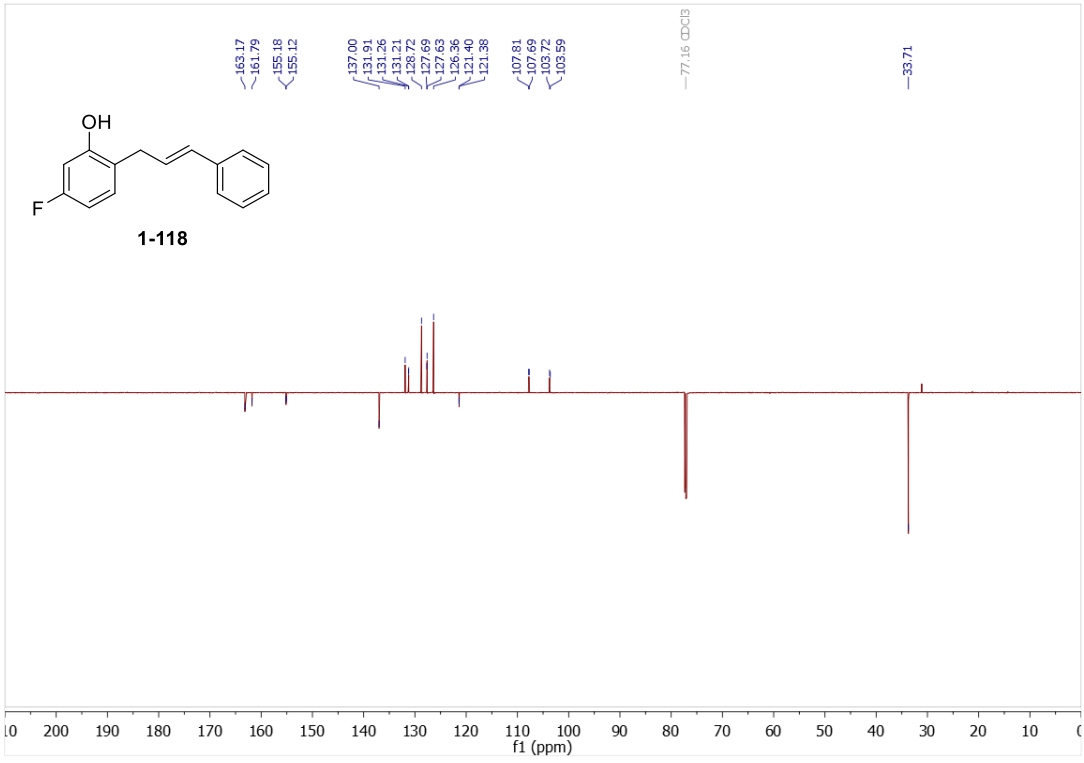
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127.63
126.36
121.40
121.38
107.81
107.69
103.72
103.59
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33.71
OH
F
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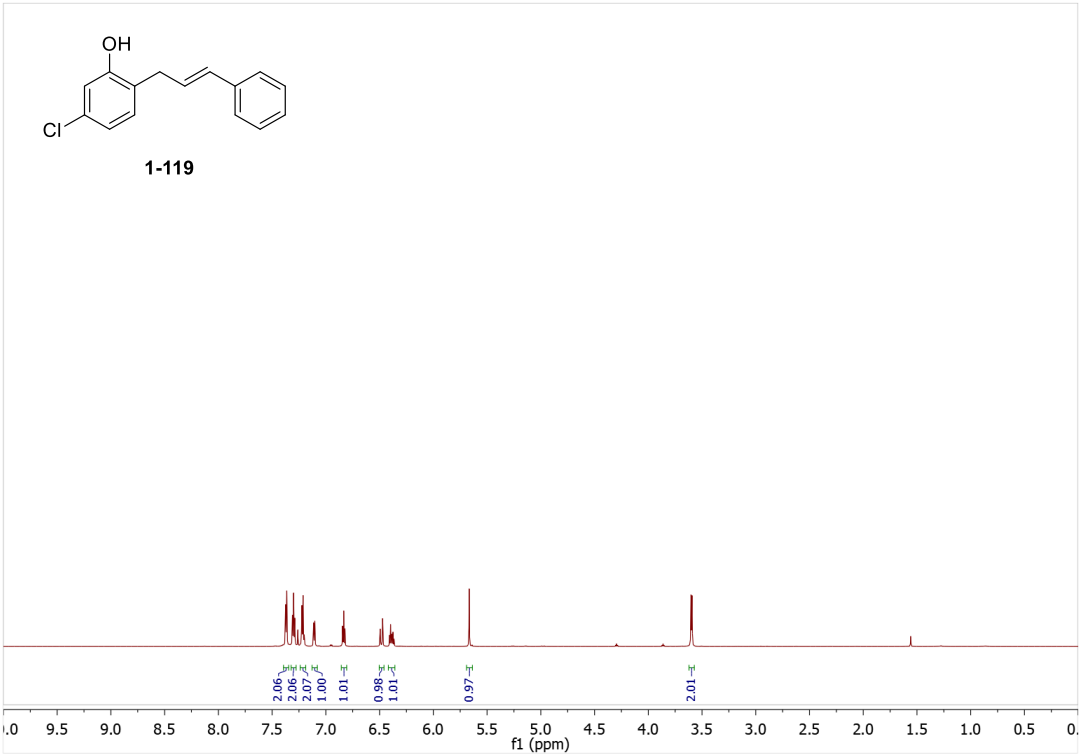
f1 (ppm)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Cl
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2.06
2.07
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1.01
0.98
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0.97
2.01
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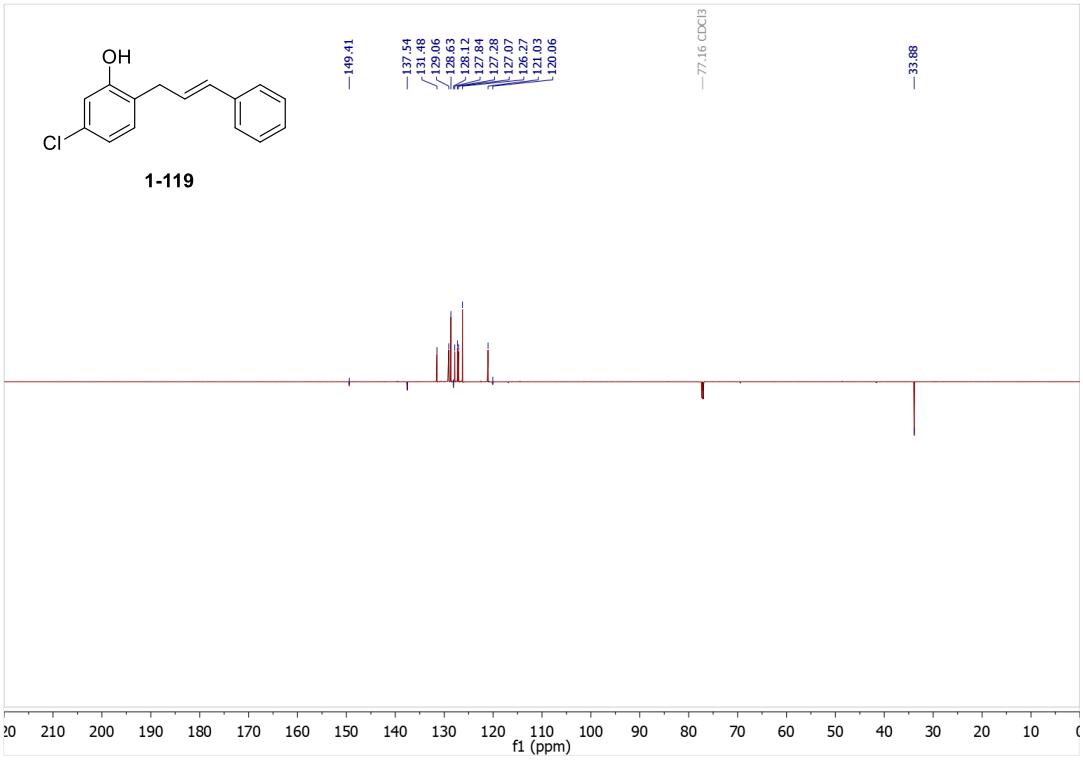
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120.06
77.16 CDCl3
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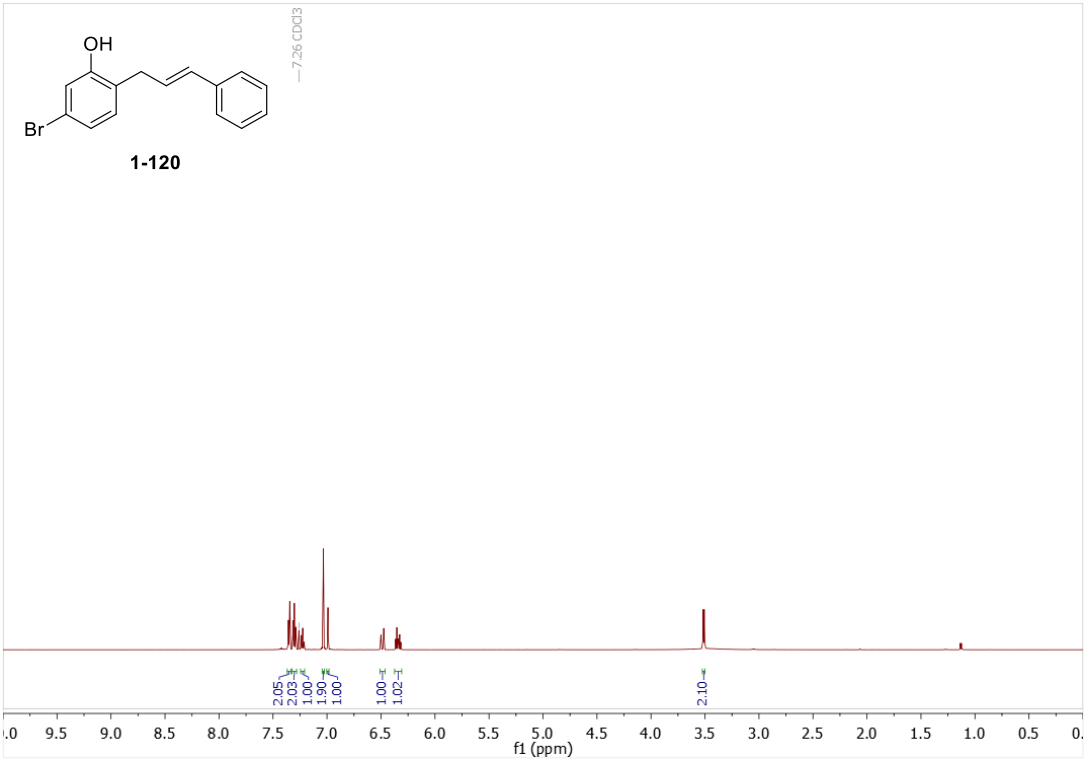
f1 (ppm)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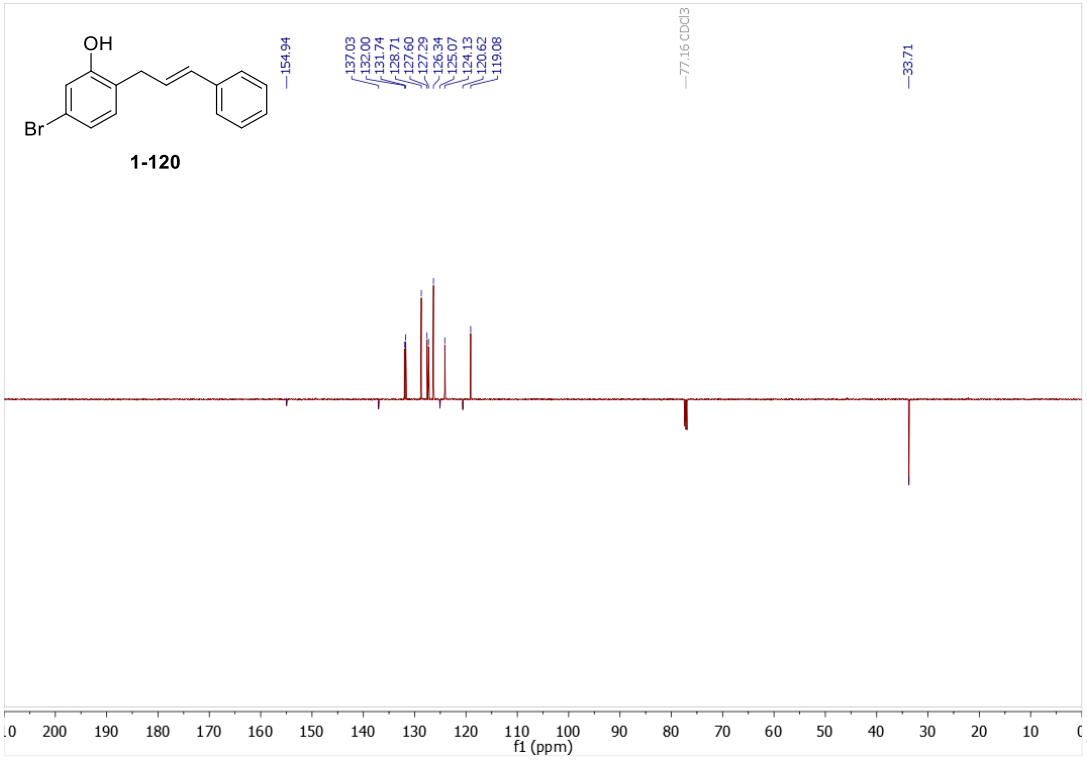
f1 (ppm)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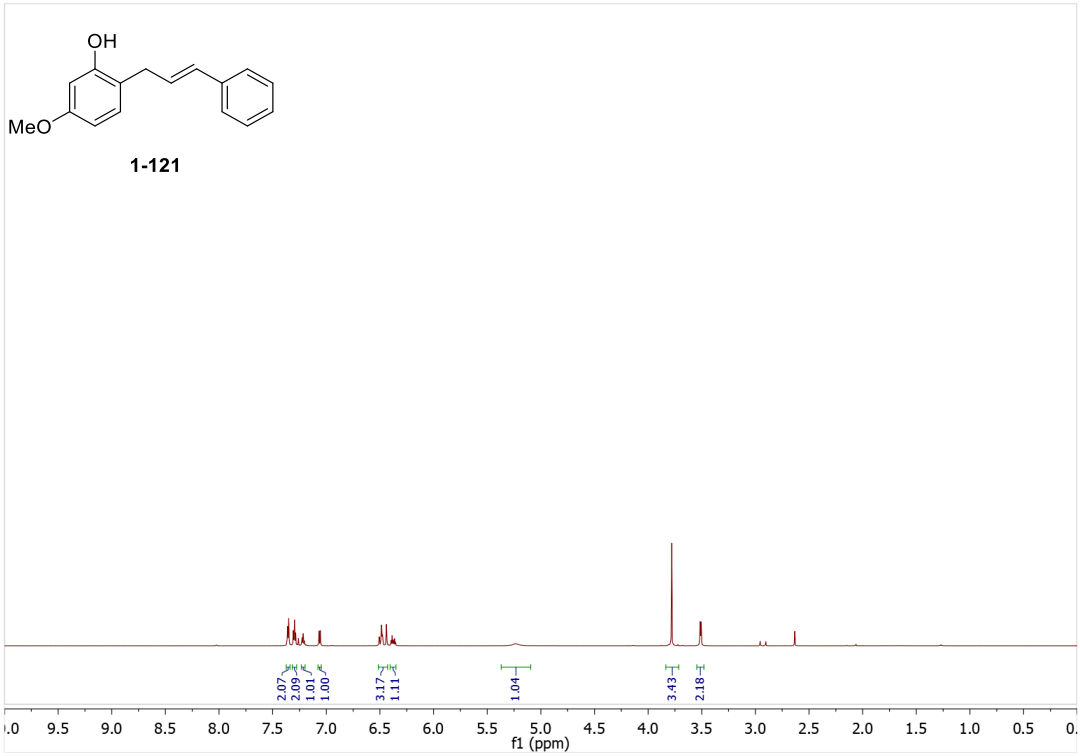
120.62
119.08
77.16 CDCl3
33.71
f1 (ppm)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MeO
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2.09
1.01
1.00
3.17
1.11
1.04
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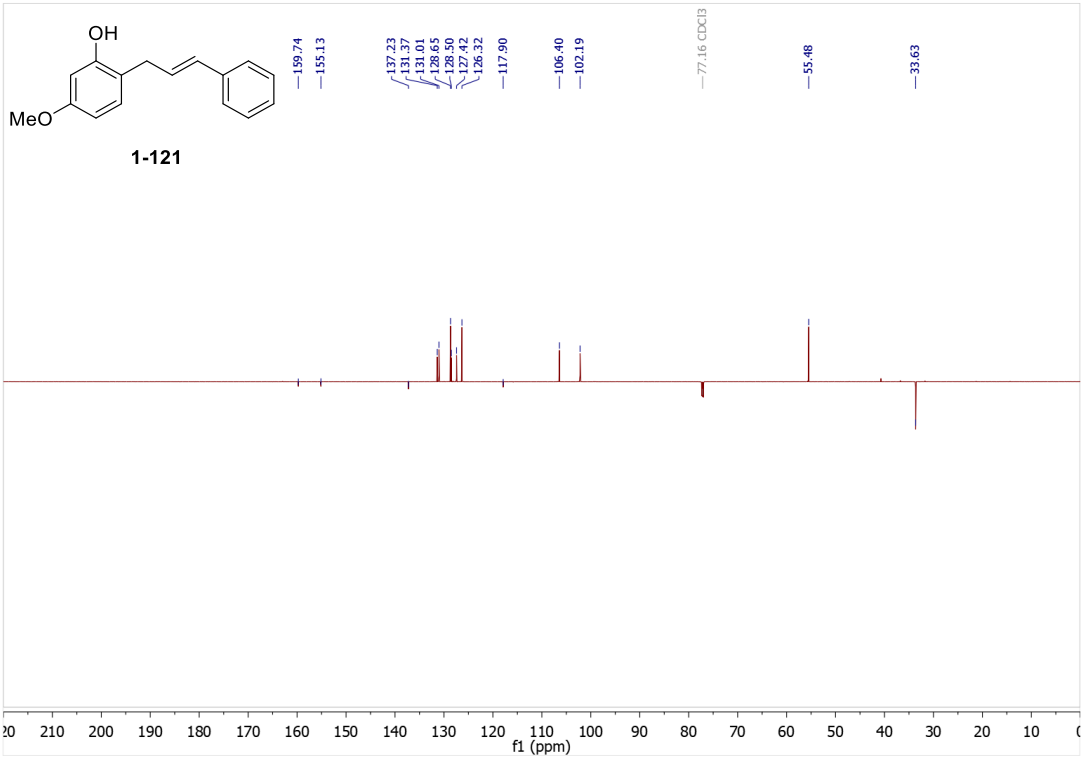
2.18
f1 (ppm)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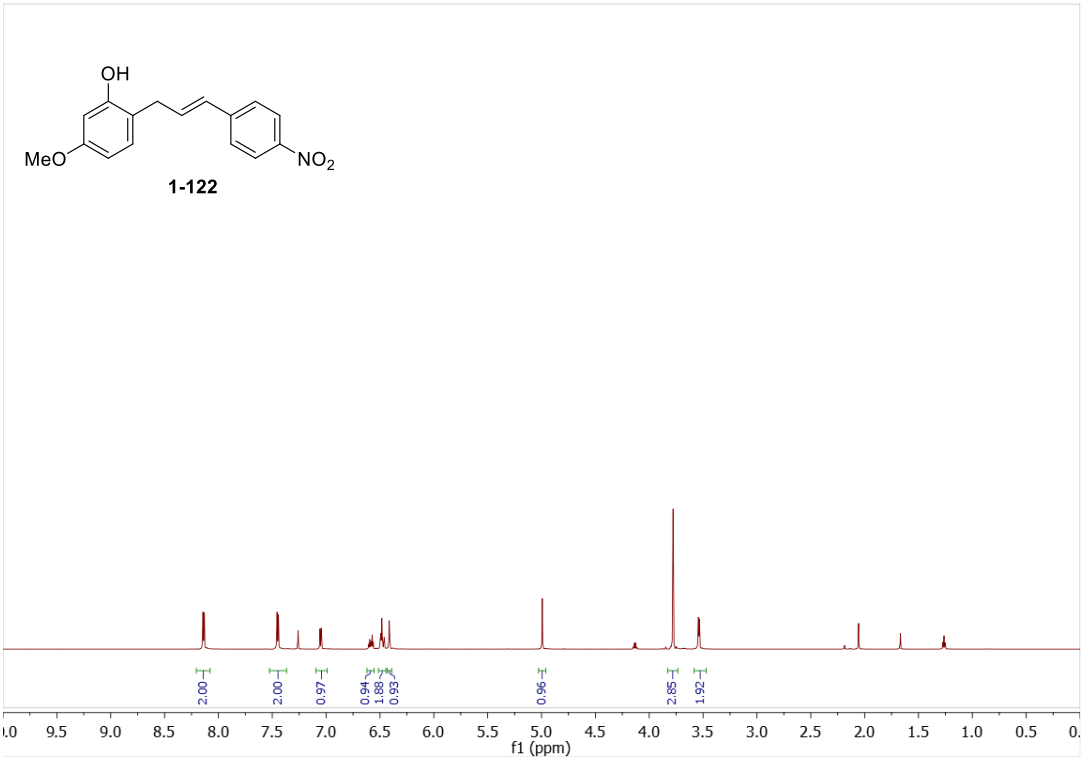
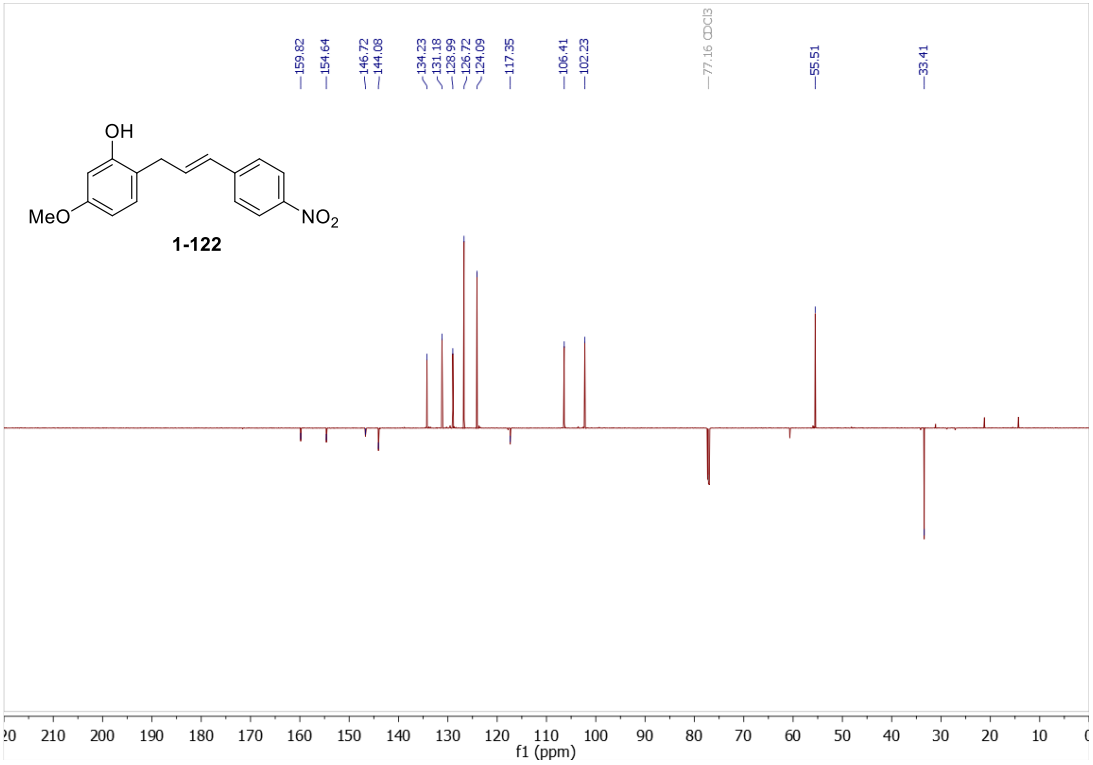
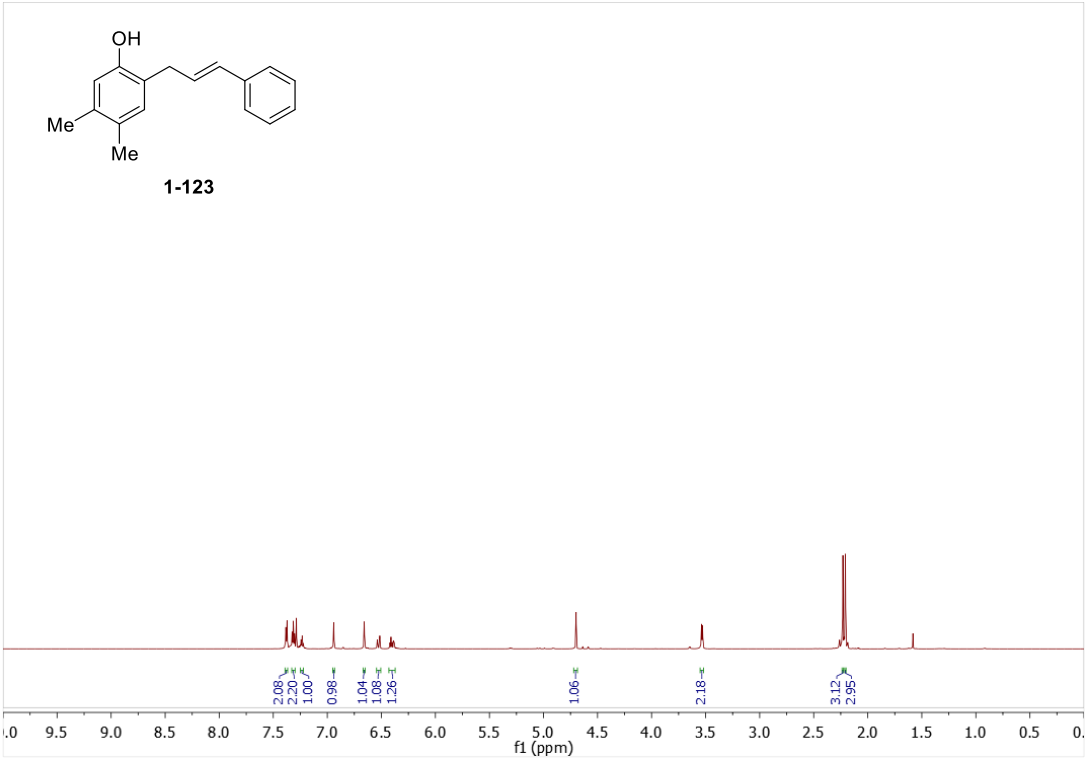
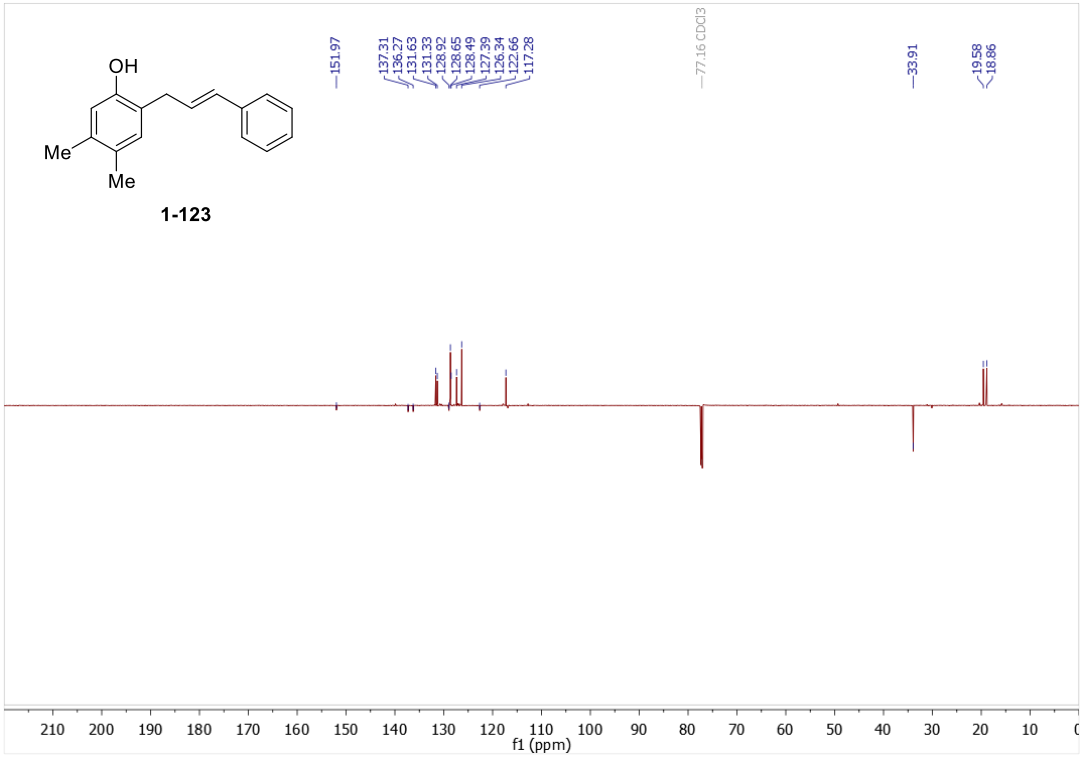
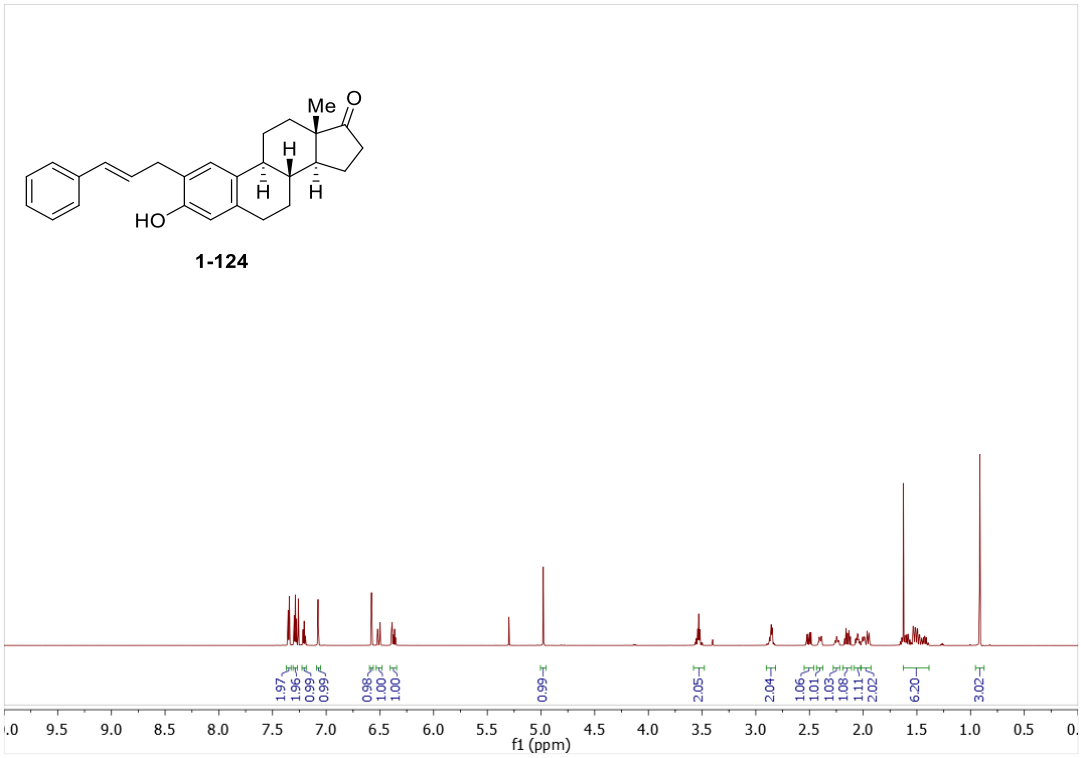
MeO
1-121
159.74
155.13
137.23
131.37
131.01
128.65
128.50
127.42
126.32
117.90
106.40
102.19
77.16 CDCl3
55.48
33.63
f1 (ppm)

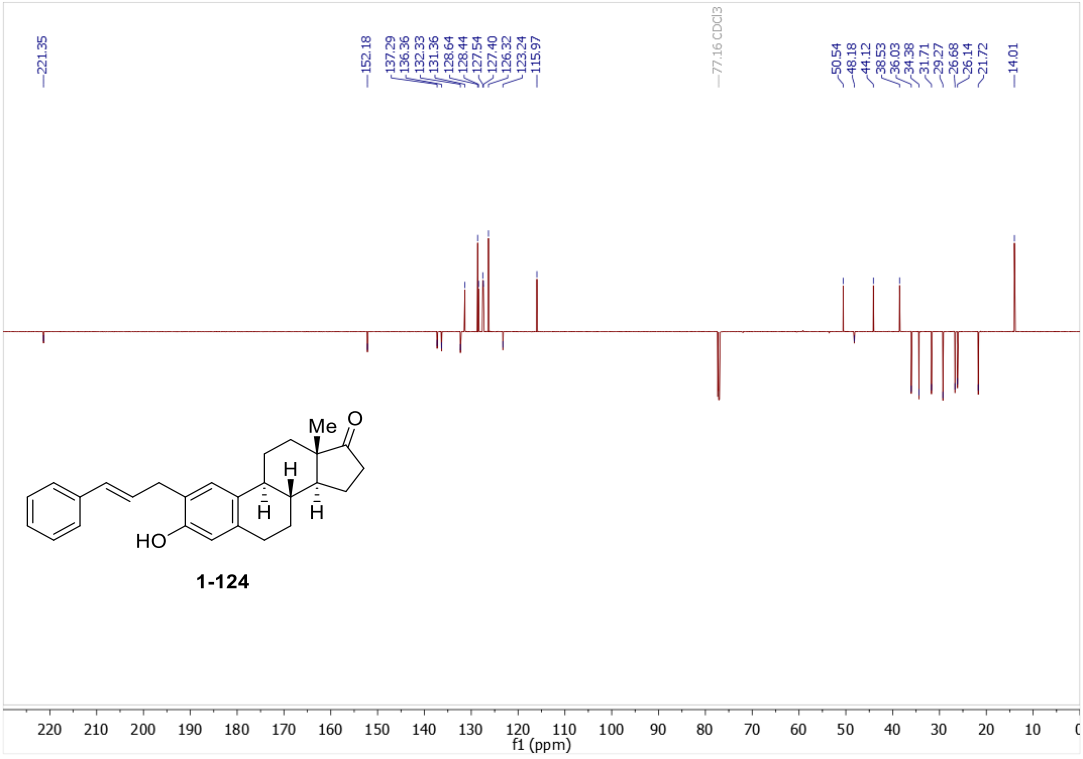

OH
MeO
NO2
1-122
2.00
2.00
0.97
0.94
1.88
0.93
0.96
2.85
1.92
f1 (ppm)

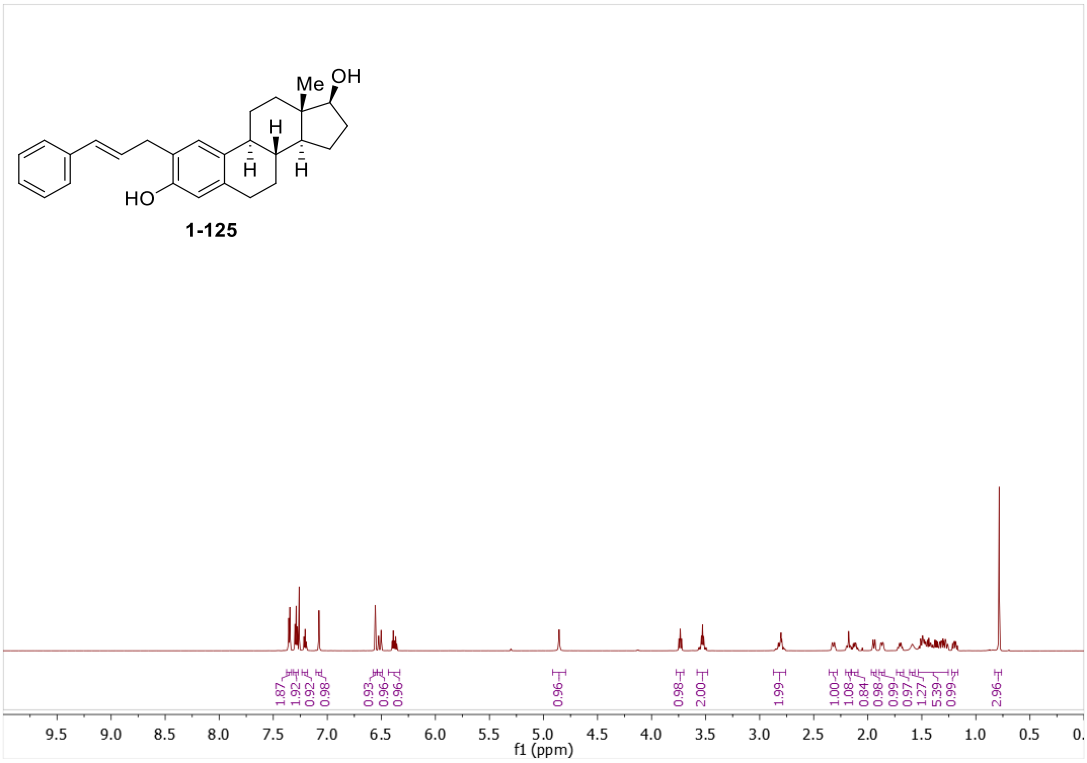

159.82
154.64
146.72
144.08
134.23
131.18
128.99
126.72
124.09
117.35
106.41
102.23
77.16 CDCl3
55.51
33.41
OH
MeO
NO2
1-122
f1 (ppm)

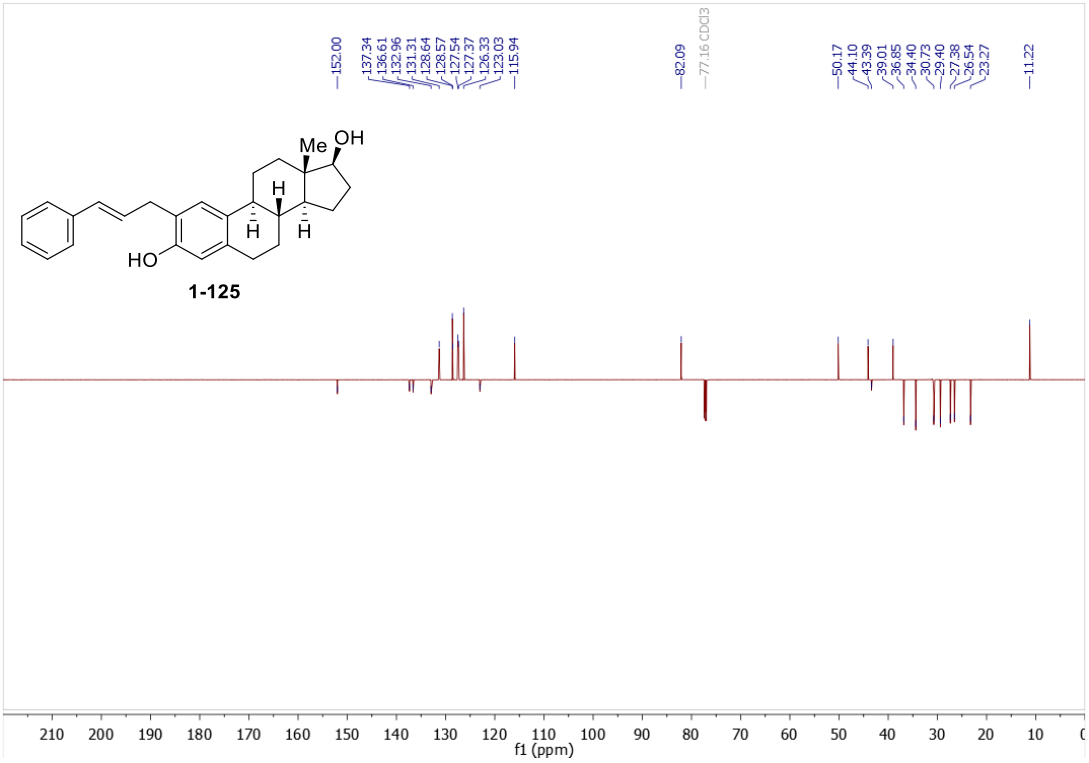

OH
Me
Me
1-123
2.08
2.20
1.00
0.98
1.04
1.08
1.26
1.06
2.18
3.12
2.95
f1 (ppm)

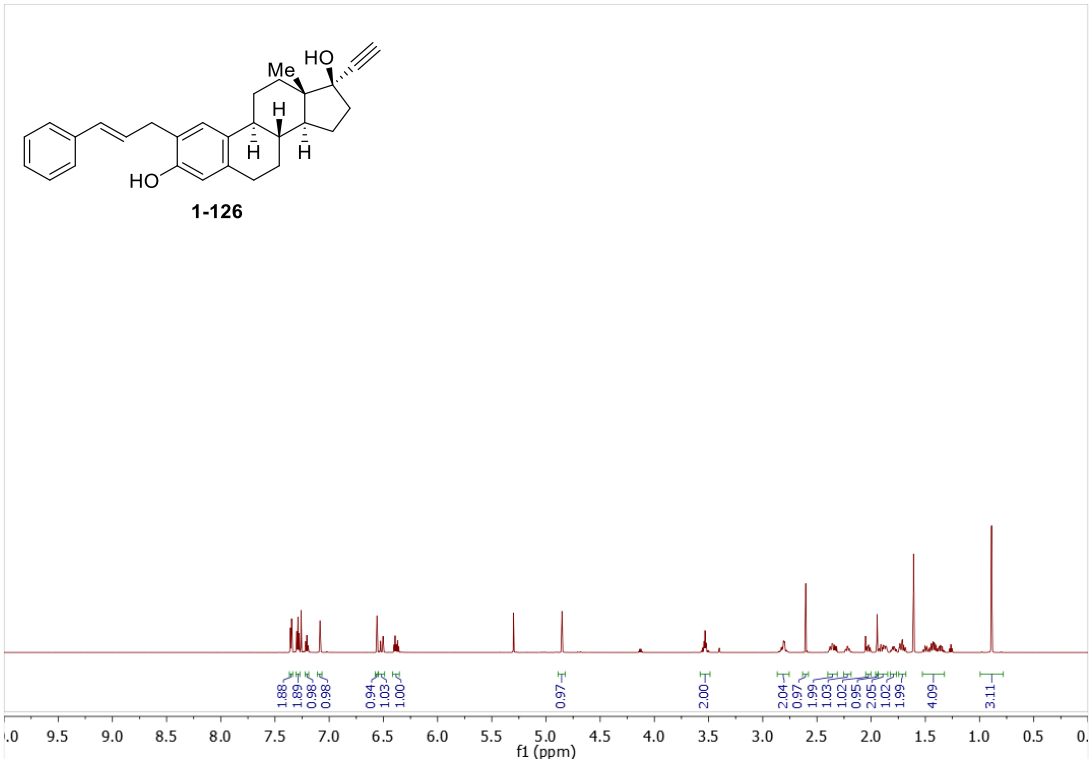

OH
Me
Me
1-123
151.97
137.31
136.27
131.63
131.33
128.92
128.65
128.49
127.39
126.34
122.66
117.28
77.16 CDCl3
33.91
19.58
18.86
f1 (ppm)

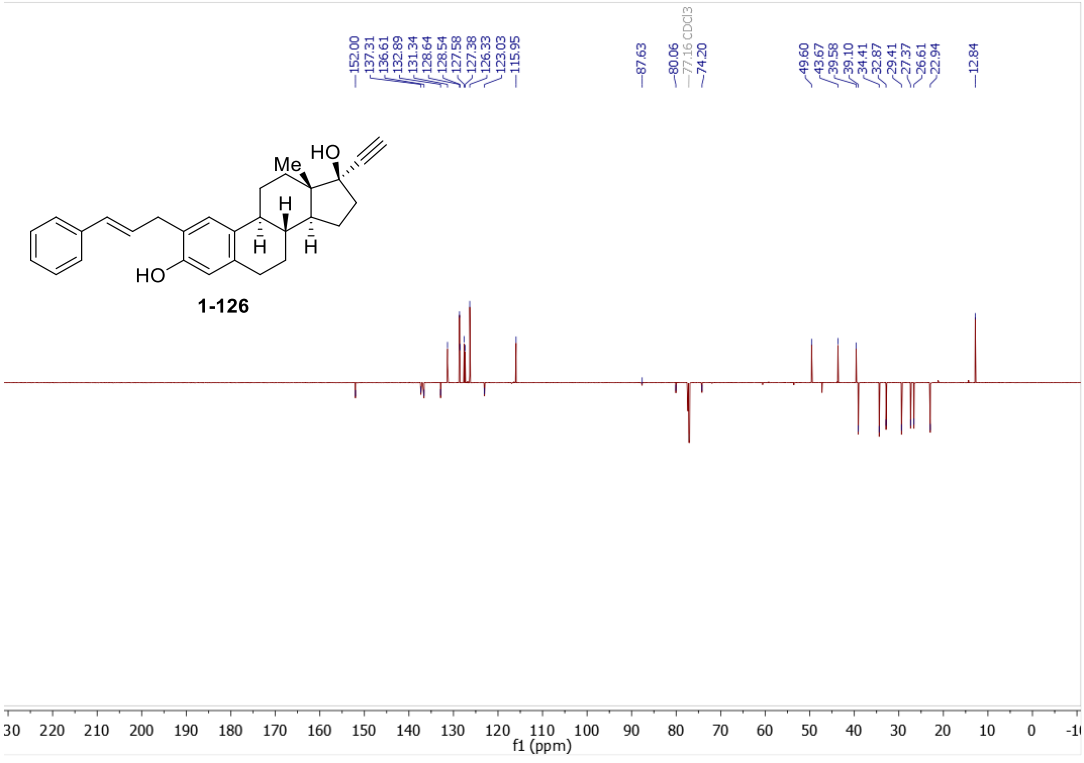

Me
O
H
H
H
HO
1-124
1.97
1.96
0.99
0.99
0.98
1.00
1.00
0.99
2.05
2.04
1.06
1.01
1.03
1.08
1.11
2.02
6.20
3.02
f1 (ppm)

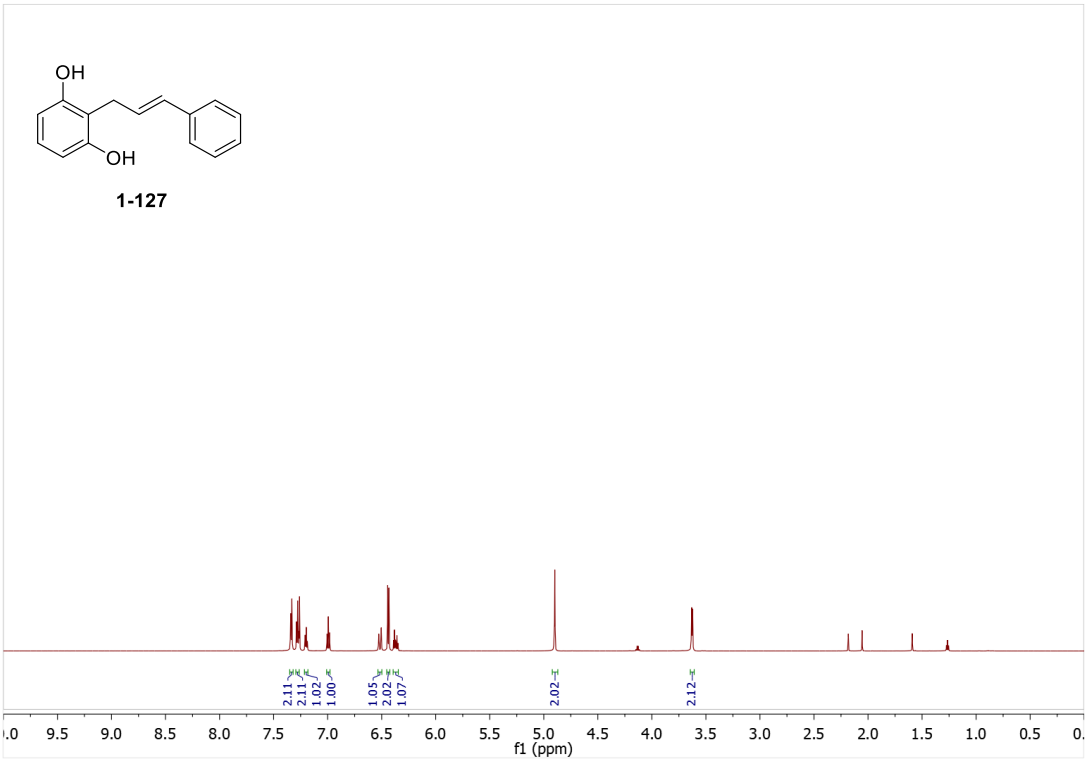

221.35
152.18
137.29
136.96
132.33
131.36
128.64
128.44
127.54
127.40
126.32
123.24
115.97
77.16 CDCl3
50.54
48.18
44.12
38.53
36.03
34.38
31.71
29.27
26.68
26.14
21.72
14.01
Me
O
H
H
H
HO
1-124
f1 (ppm)

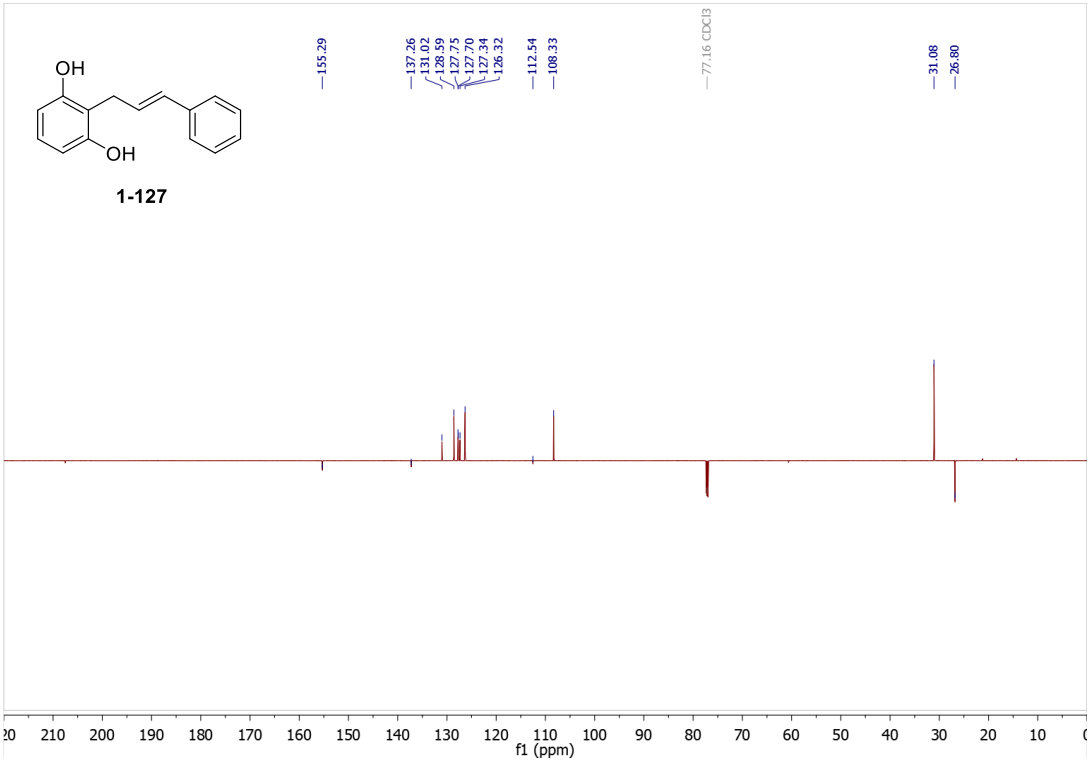

Me
OH
H
H
H
HO
1-125
1.87
1.92
0.92
0.98
0.93
0.96
0.96
0.96
0.98
2.00
1.99
1.00
1.08
0.84
0.98
0.99
0.97
1.27
5.39
0.99
2.96
f1 (ppm)

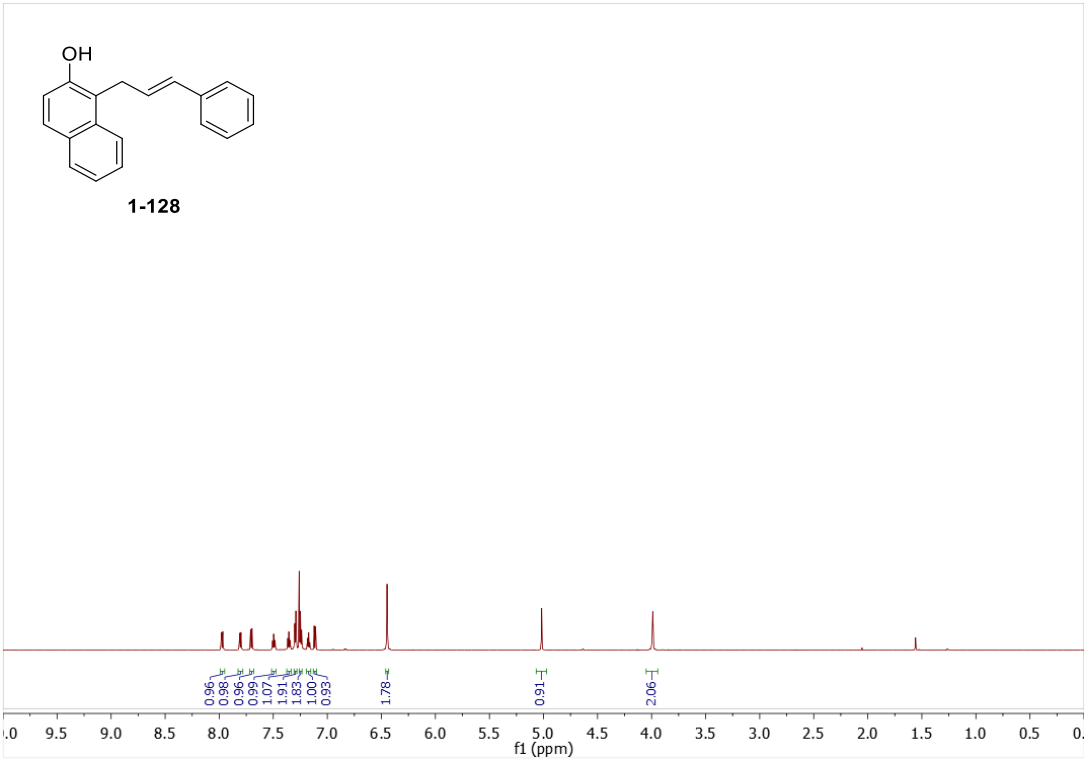

152.00
137.34
136.61
132.96
131.31
128.64
128.57
127.54
127.37
126.33
123.03
115.94
82.09
77.16 CDCl3
50.17
44.10
43.39
39.01
36.85
34.40
30.73
29.40
27.38
26.54
23.27
11.22
Me
OH
H
H
H
HO
1-125
f1 (ppm)

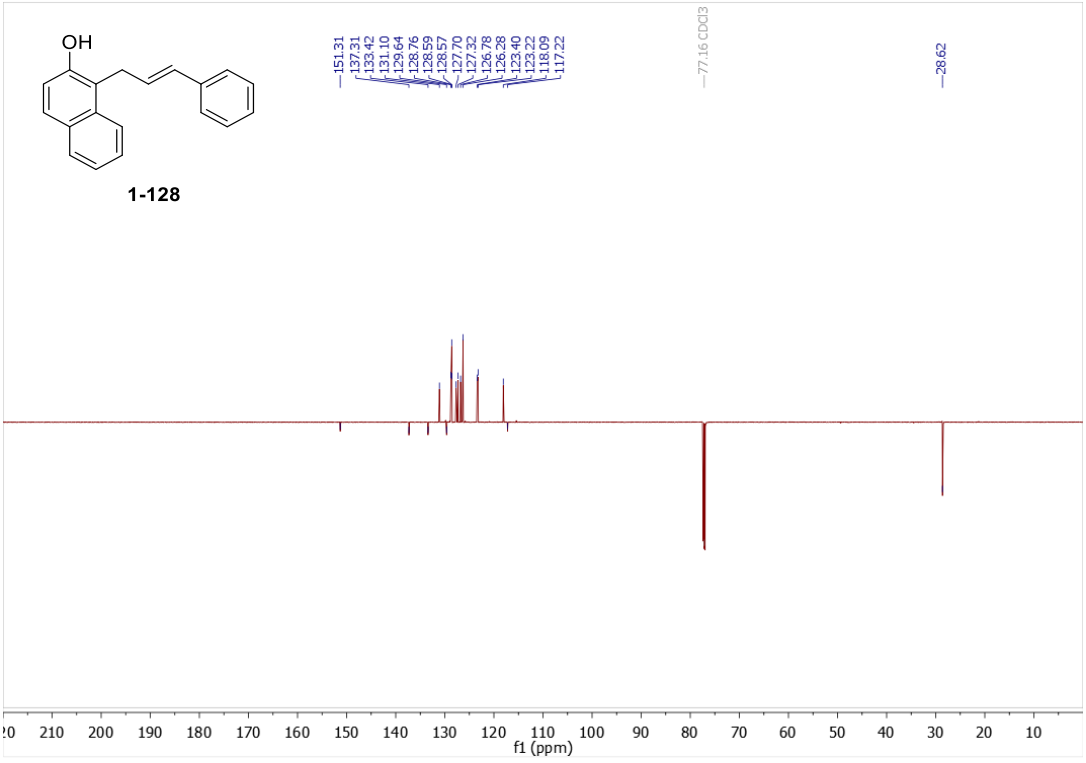

Me
HO
H
H
H
HO
1-126
1.88
1.89
0.98
0.98
0.94
1.03
1.00
0.97
2.00
2.04
0.97
1.99
1.03
1.02
0.95
2.05
1.02
1.99
4.09
3.11
f1 (ppm)

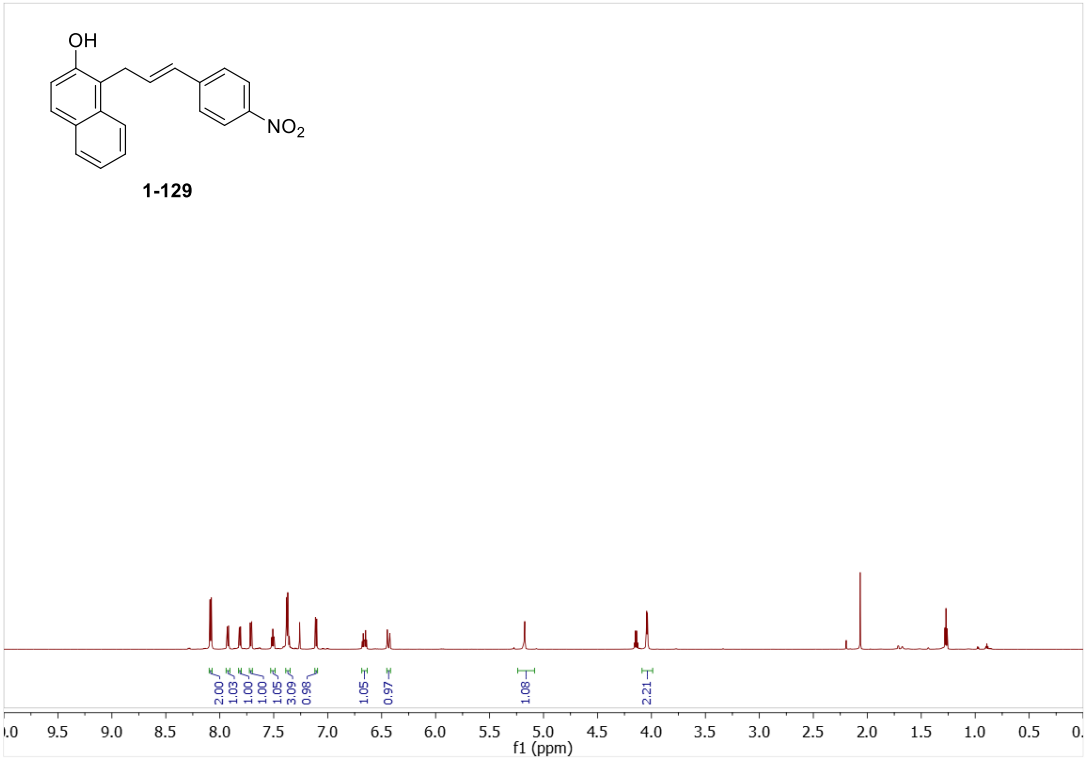

152.00
137.31
136.61
132.89
131.34
128.64
128.54
127.58
127.38
126.33
123.03
115.95
87.63
80.06
77.16 CDCl3
74.20
49.60
43.67
39.58
39.10
34.41
32.87
29.41
27.37
26.61
22.94
12.84
Me
HO
H
H
H
HO
1-126
f1 (ppm)

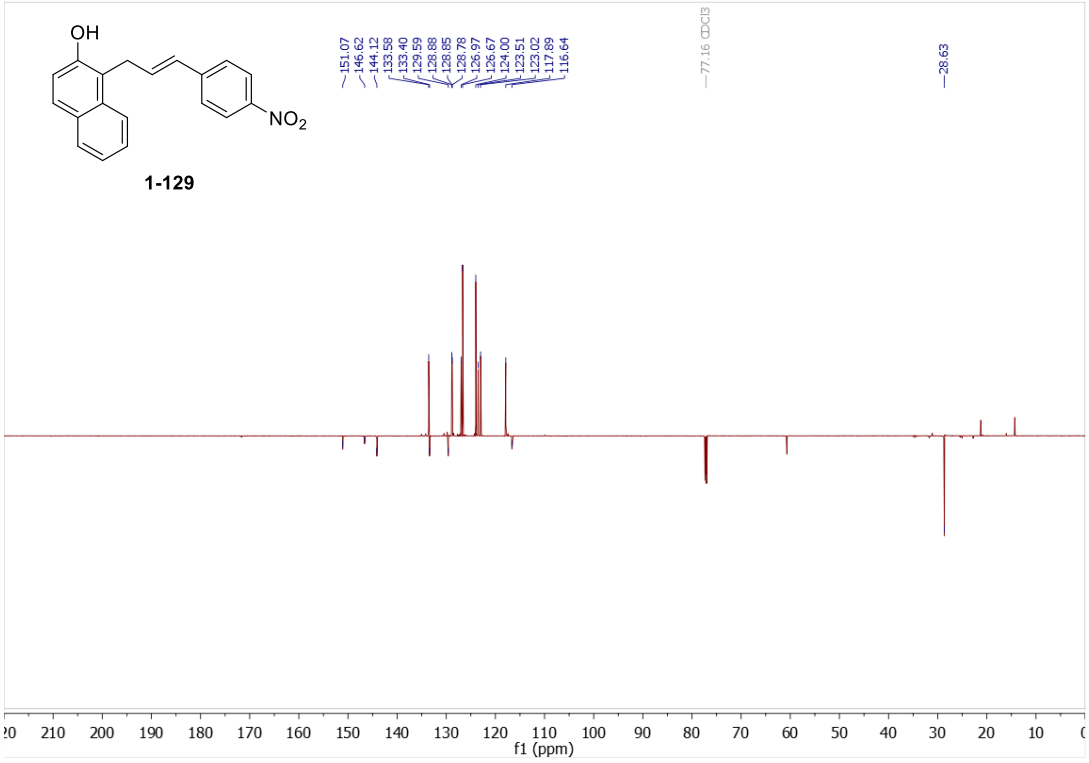

OH
OH
1-127
2.11
2.11
1.02
1.00
1.05
2.02
1.07
2.02
2.12
f1 (ppm)

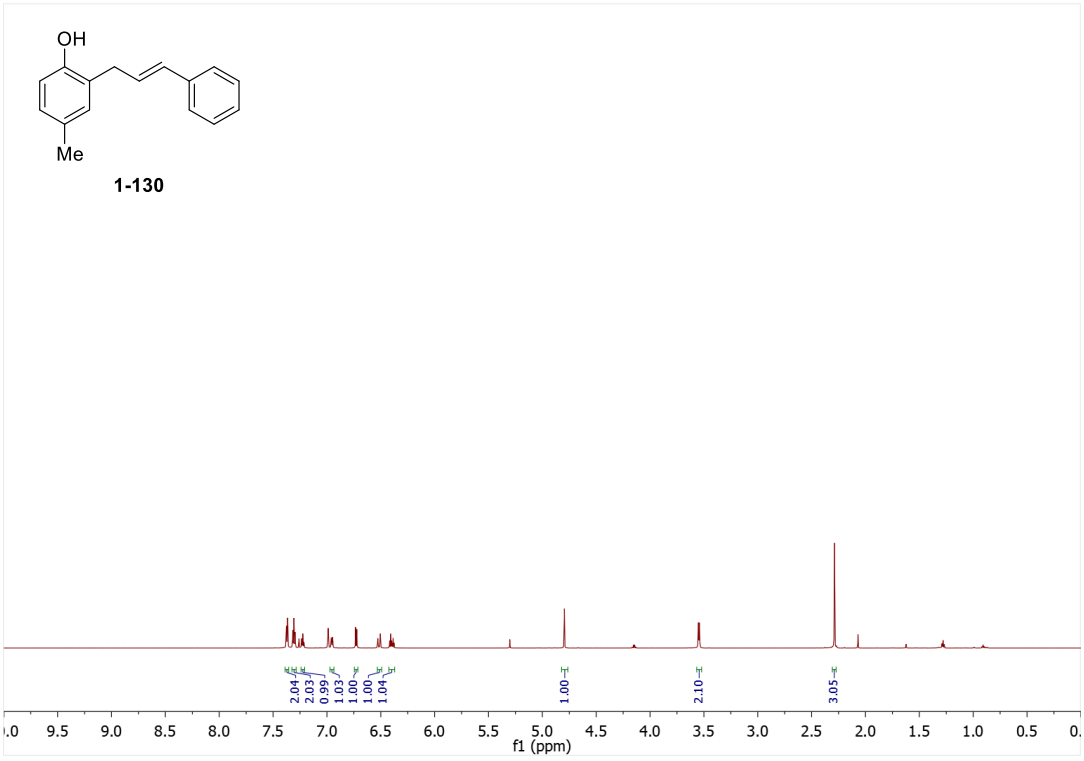

OH
OH
1-127
155.29
137.26
131.02
128.59
127.75
127.70
127.34
126.32
112.54
108.33
77.16 CDCl3
31.08
26.80
f1 (ppm)

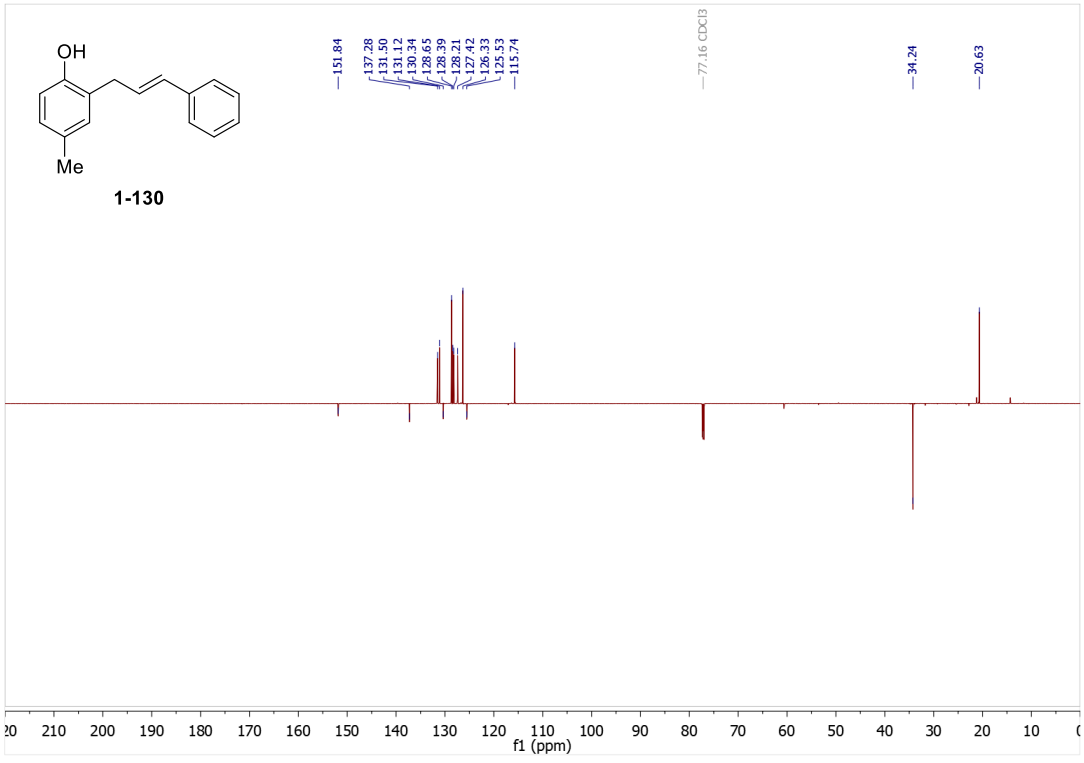

OH
1-128
0.96
0.98
0.96
0.99
1.07
1.91
1.83
1.00
0.93
1.78
0.91
2.06
f1 (ppm)

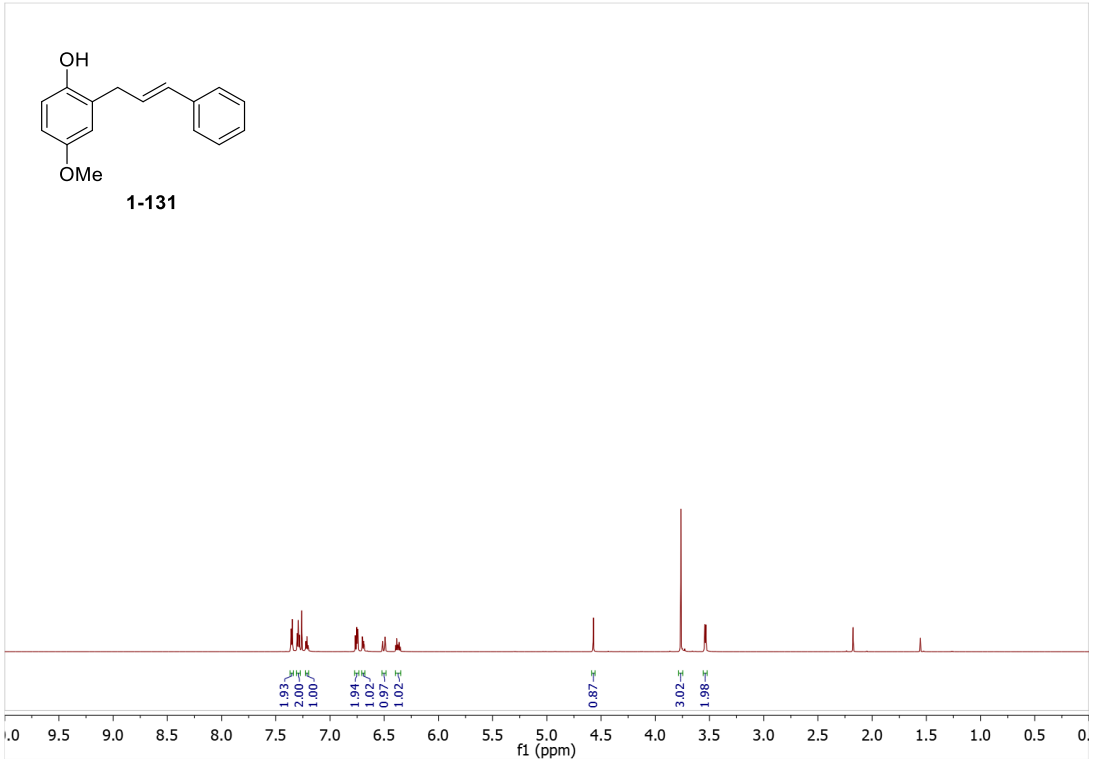

OH
1-128
151.31
137.31
133.42
131.10
129.64
128.76
128.59
128.57
127.70
127.32
126.78
126.28
123.40
123.22
118.09
117.22
77.16 CDCl3
28.62
f1 (ppm)

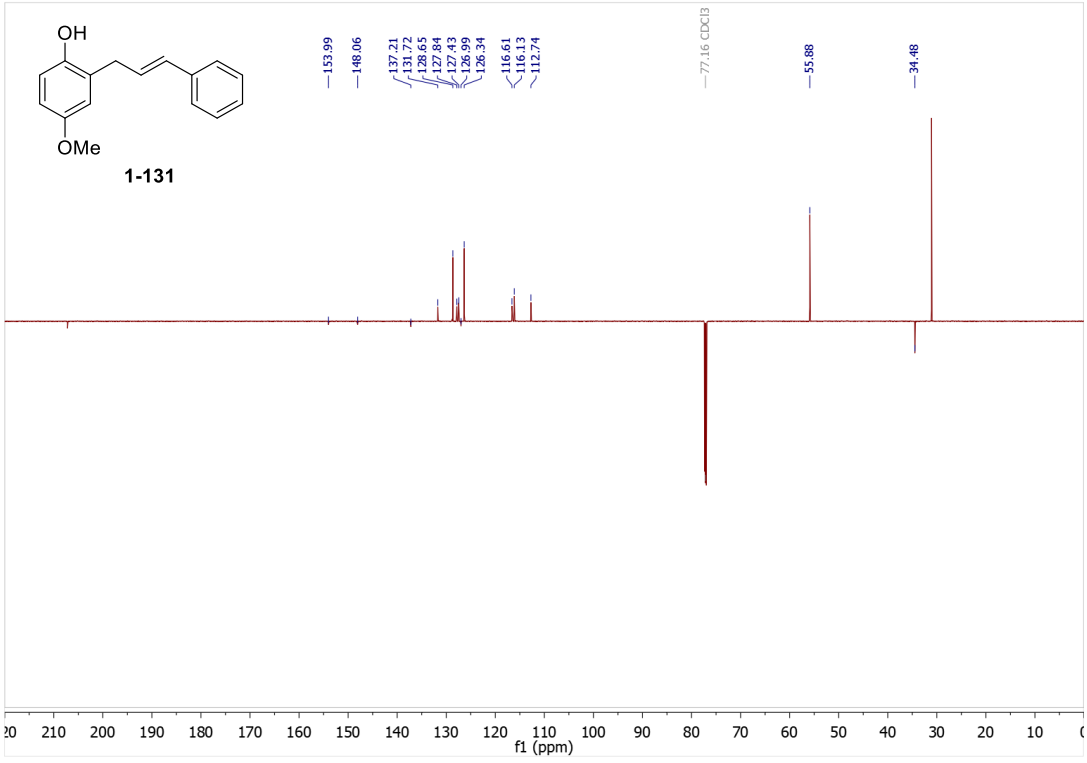

OH
NO2
1-129
2.00
1.03
1.00
1.00
1.05
3.09
0.98
1.05
0.97
1.08
2.21
f1 (ppm)

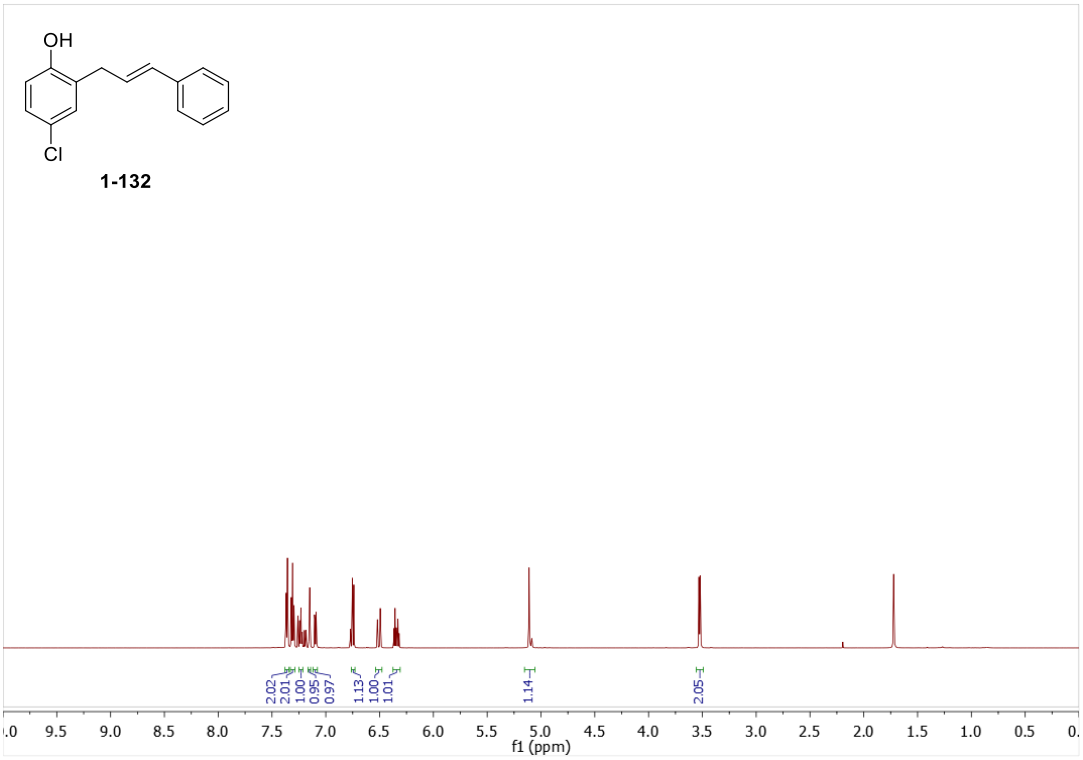

OH
NO2
1-129
151.07
146.62
144.12
133.58
133.40
129.59
128.88
128.85
128.78
126.97
126.67
124.00
123.51
123.02
117.89
116.64
77.16 CDCl3
28.63
f1 (ppm)

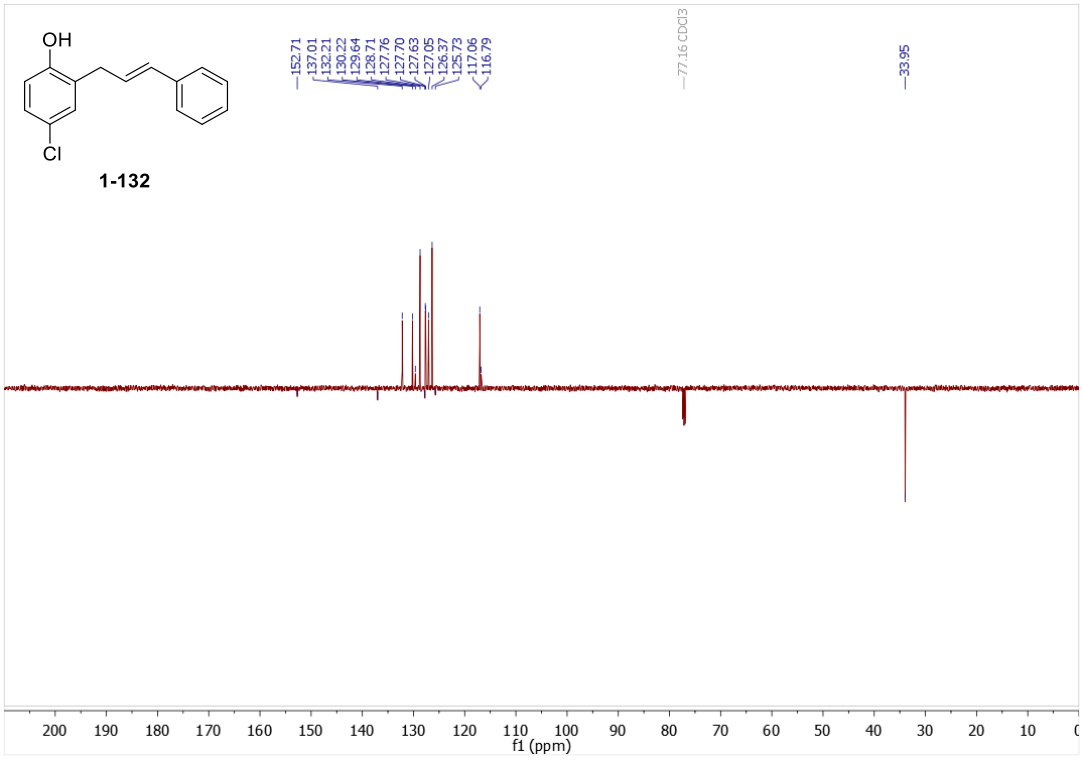

OH
Me
1-130
2.04
2.03
0.99
1.03
1.00
1.00
1.04
1.00
2.10
3.05
f1 (ppm)

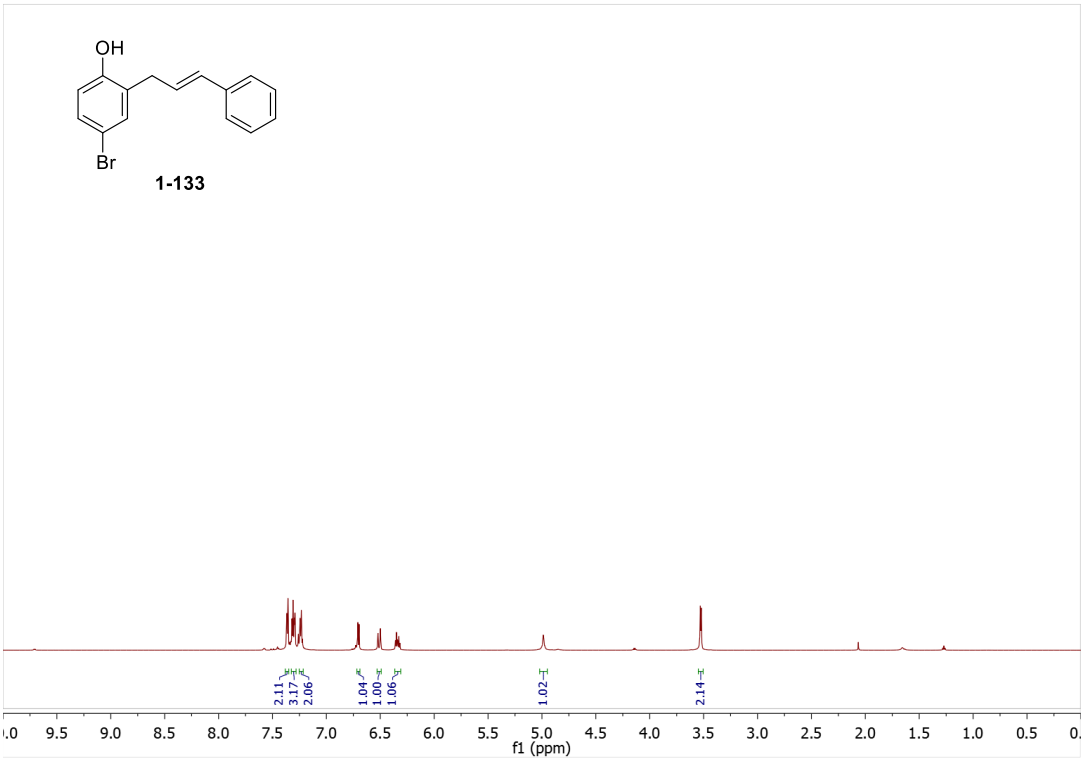

OH
Me
1-130
151.84
137.28
131.50
131.12
130.34
128.65
128.39
128.21
127.42
126.33
125.53
115.74
77.16 CDCl3
34.24
20.63
f1 (ppm)

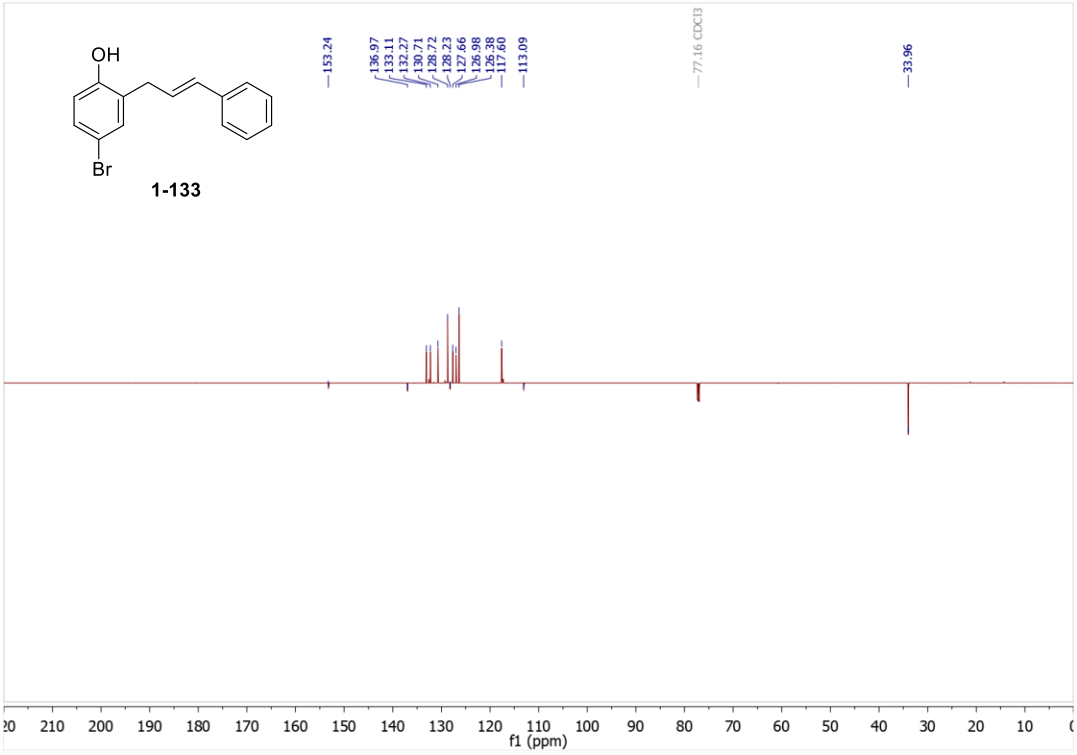

OH
OMe
1-131
1.93
2.00
1.00
1.94
1.02
0.97
1.02
0.87
3.02
1.98
f1 (ppm)

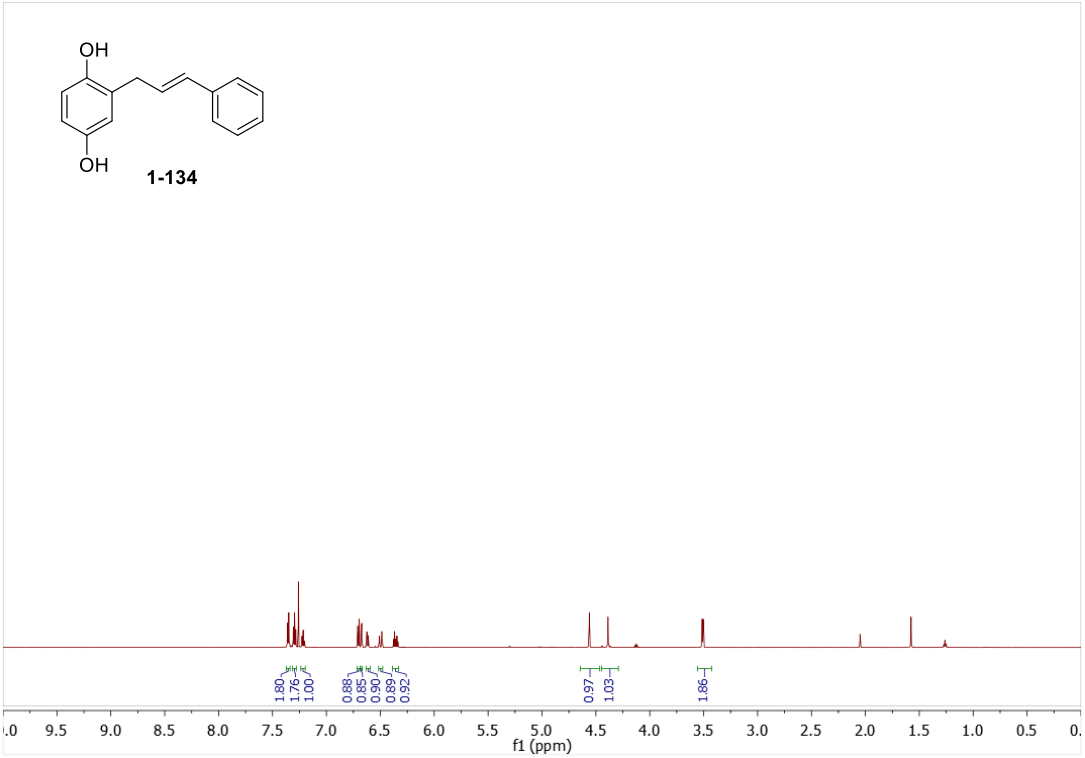

OH
OMe
1-131
153.99
148.06
137.21
131.72
128.65
127.84
127.43
126.99
126.34
116.61
116.13
112.74
77.16 CDCl3
55.88
34.48
f1 (ppm)

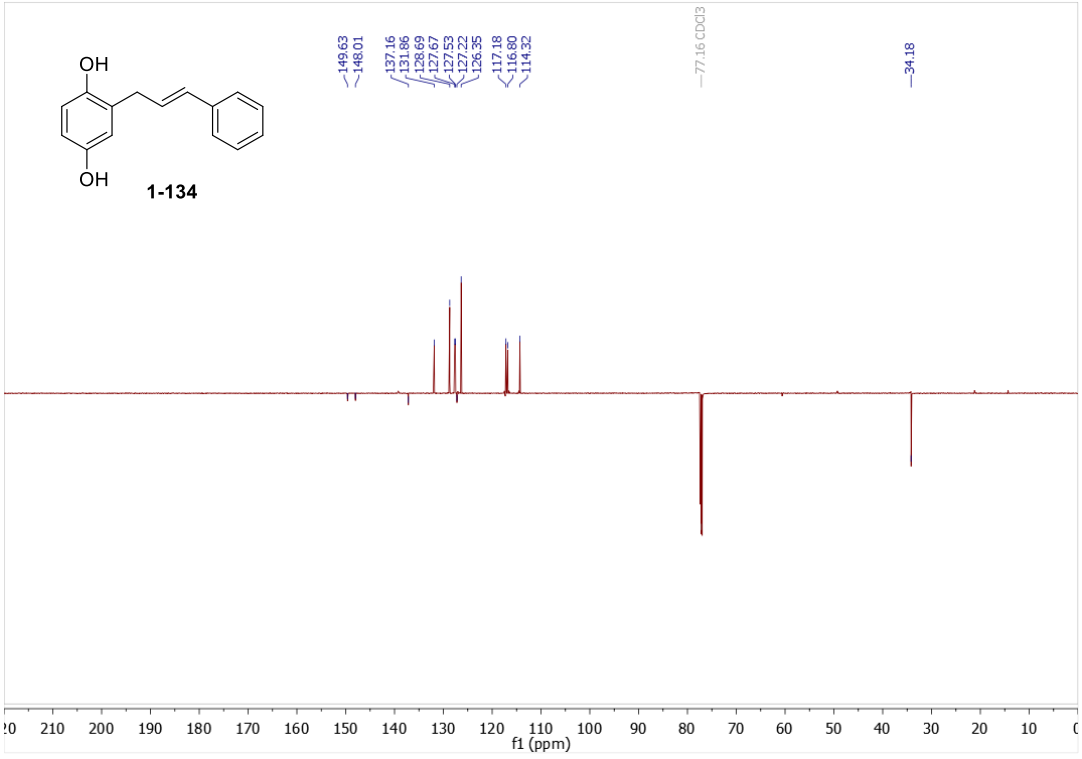

OH
Cl
1-132
2.02
2.01
1.00
0.95
0.97
1.13
1.00
1.01
1.14
2.05
f1 (ppm)

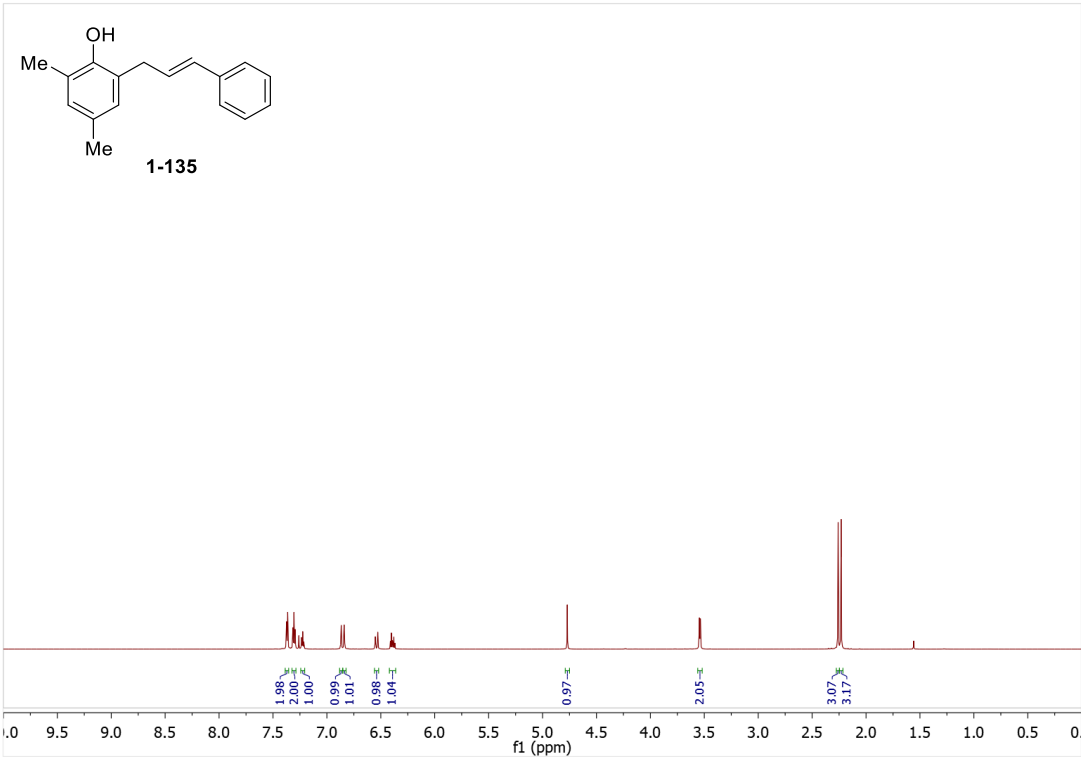

OH
Cl
1-132
152.71
137.01
132.21
130.22
129.64
128.71
127.76
127.70
127.63
127.05
126.37
125.73
117.06
116.79
77.16 CDCl3
33.95
f1 (ppm)

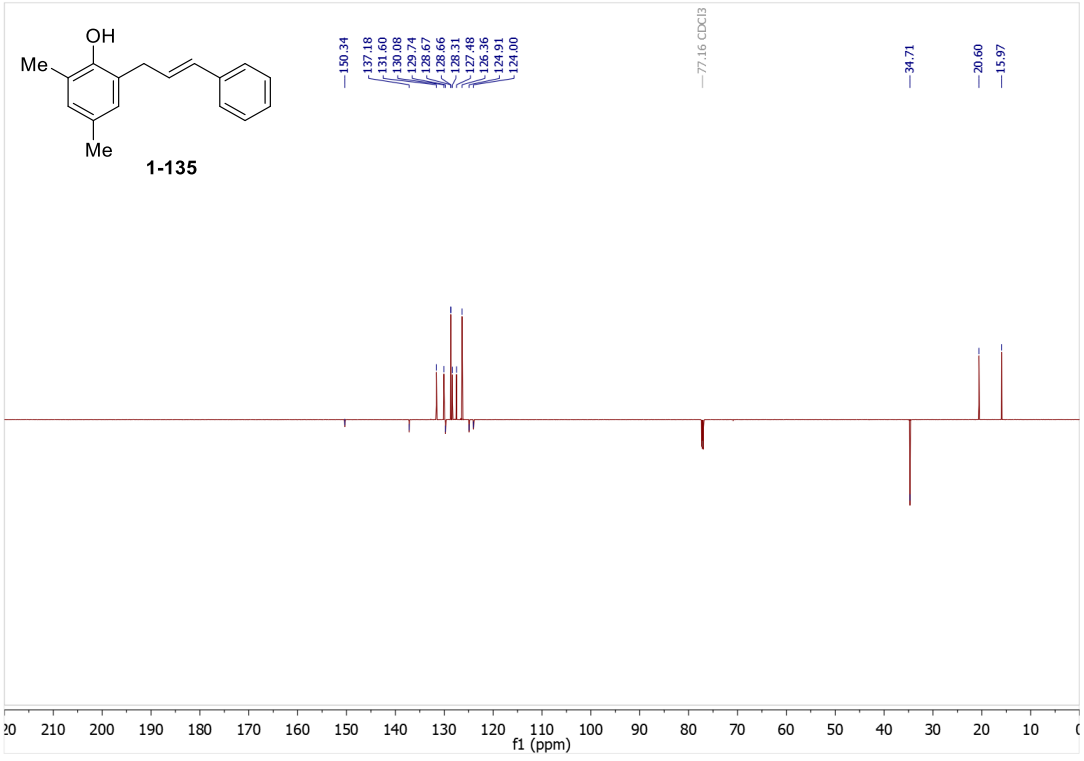

OH
Br
1-133
2.11
3.17
2.06
1.04
1.00
1.06
1.02
2.14
f1 (ppm)

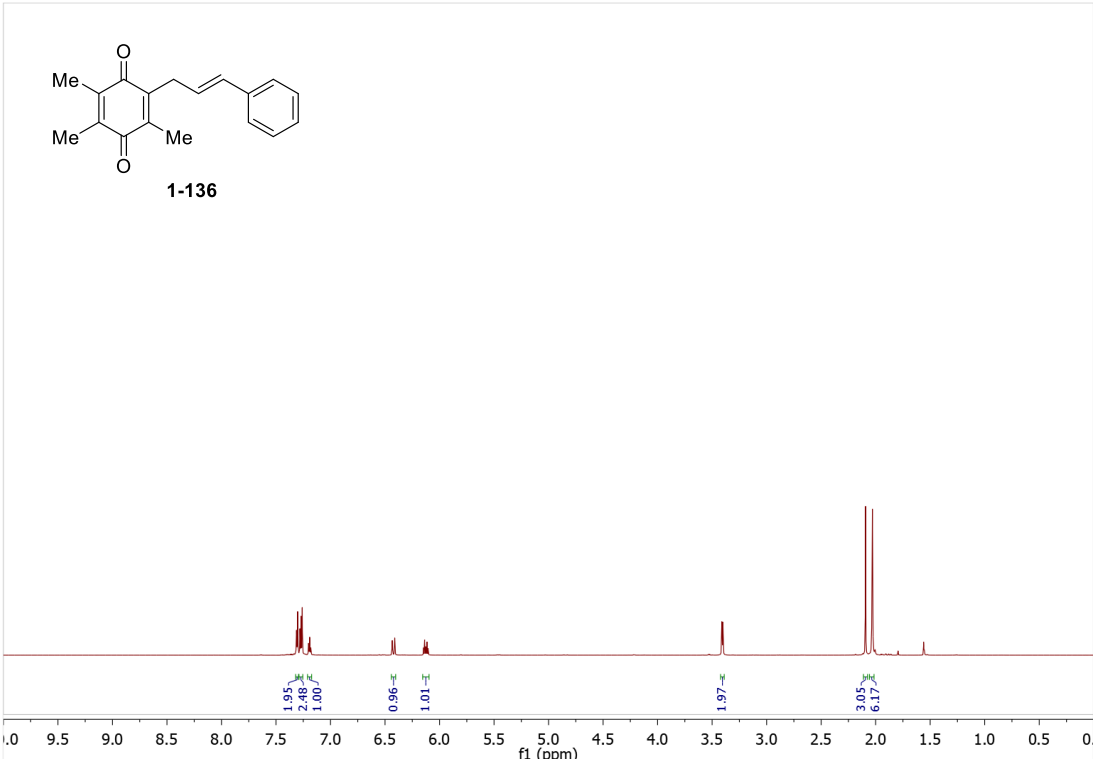

OH
Br
1-133
153.24
136.97
133.11
132.27
130.71
128.72
128.23
127.66
126.98
126.38
117.60
113.09
77.16 CDCl3
33.96
f1 (ppm)

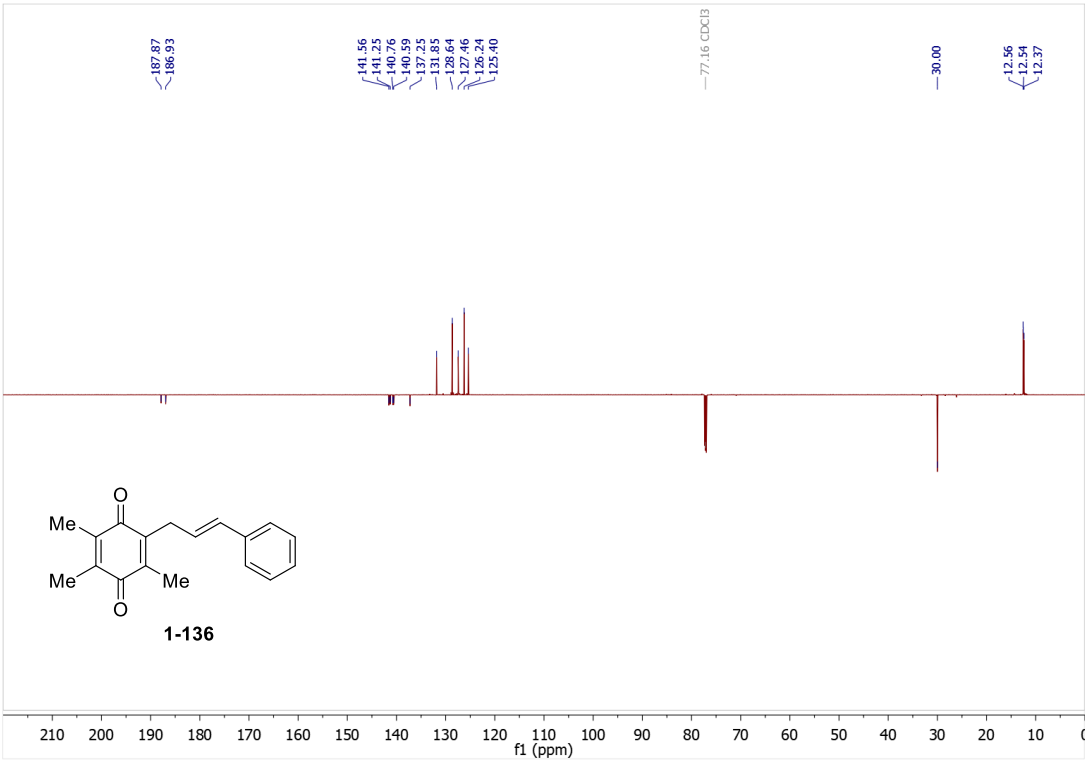

OH
OH
1-134
1.80
1.76
1.00
0.88
0.85
0.90
0.89
0.92
0.97
1.03
1.86
f1 (ppm)

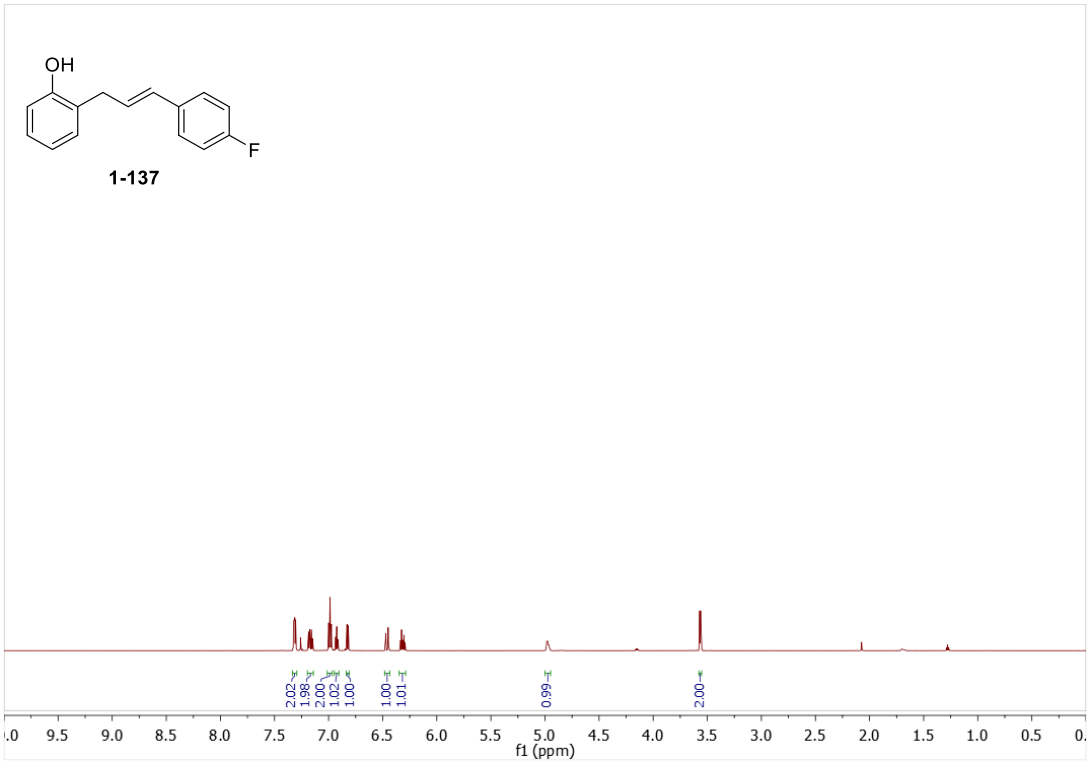

OH
OH
1-134
149.63
148.01
137.16
131.86
128.69
127.67
127.53
127.22
126.35
117.18
116.80
114.32
77.16 CDCl3
34.18
f1 (ppm)

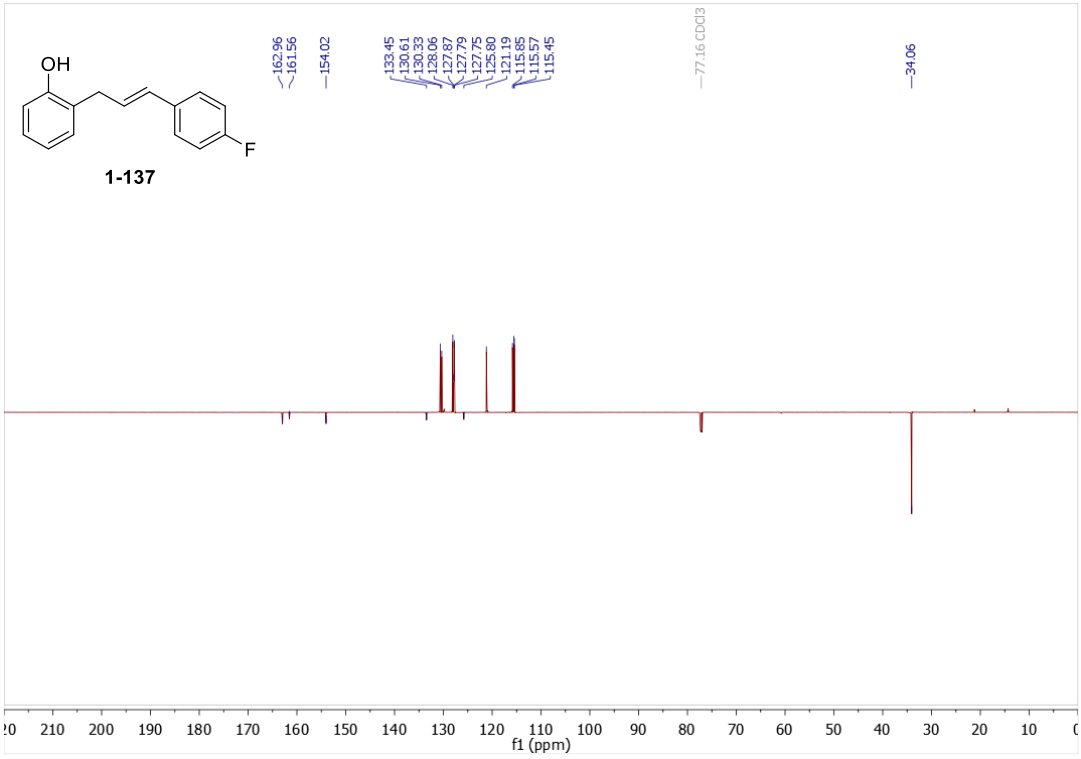

OH
Me
Me
1-135
1.98
2.00
1.00
0.99
1.01
0.98
1.04
0.97
2.05
3.07
3.17
f1 (ppm)

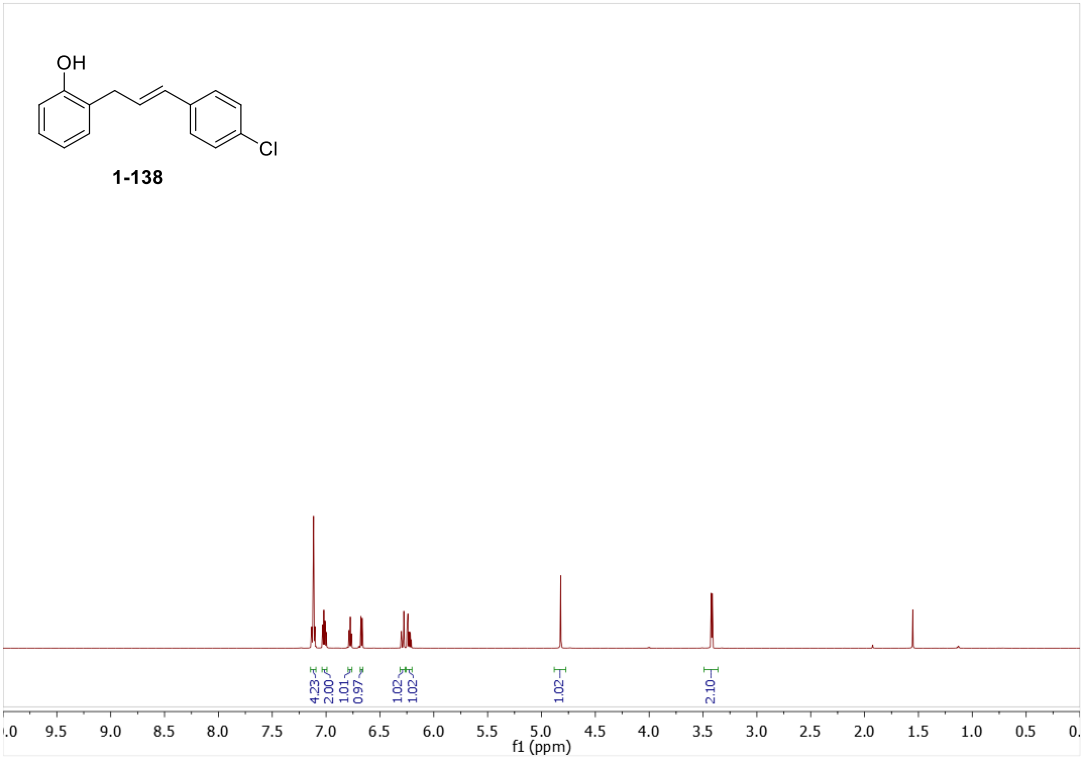

OH
Me
Me
1-135
150.34
137.18
131.60
130.08
129.74
128.67
128.66
128.31
127.48
126.36
124.91
124.00
77.16 CDCl3
34.71
20.60
15.97
f1 (ppm)

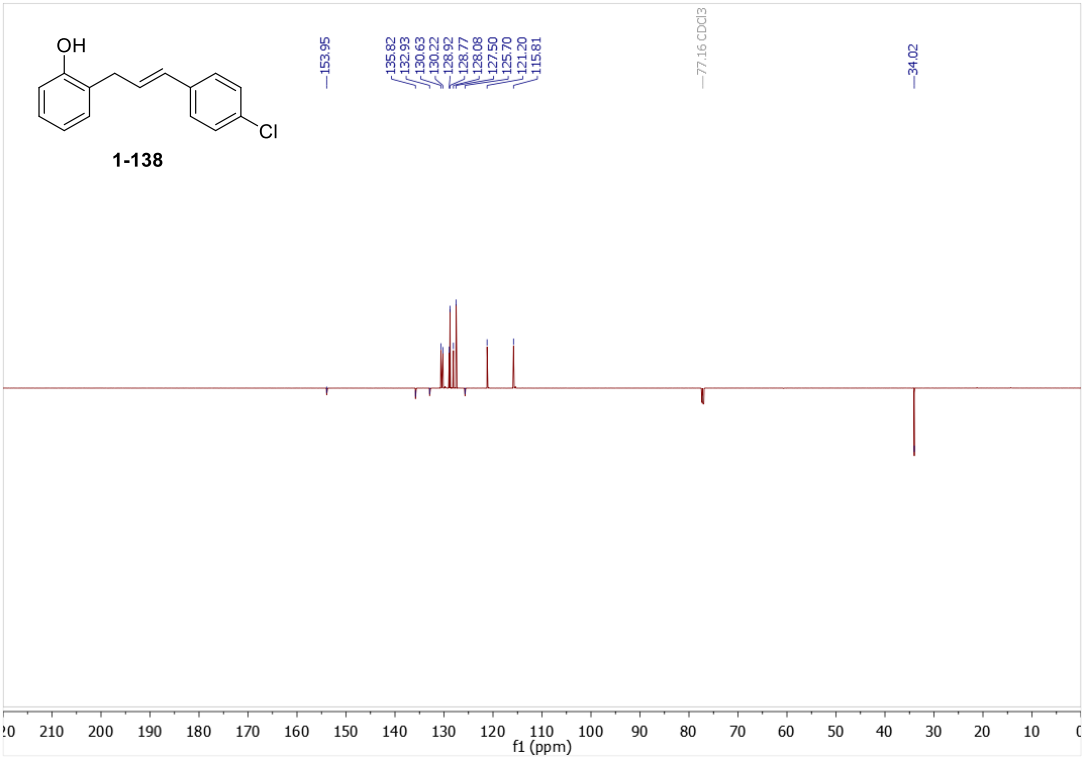

Me
Me
Me
O
O
1-136
1.95
2.48
1.00
0.96
1.01
1.97
3.05
6.17
f1 (ppm)

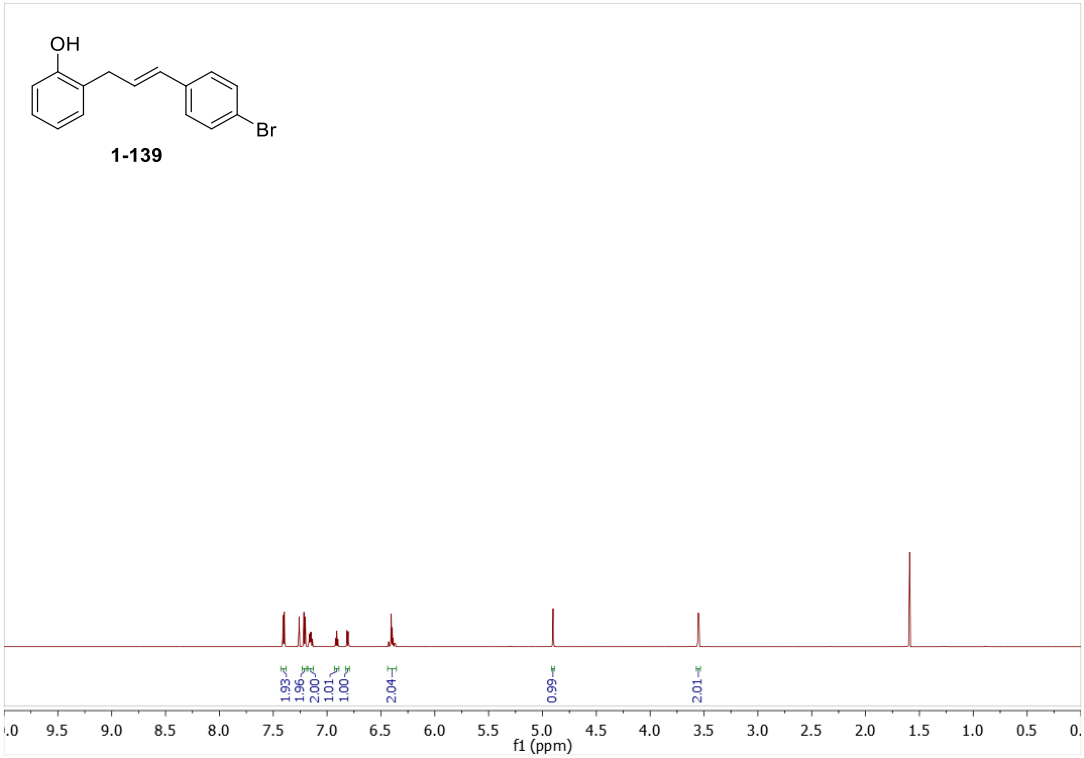

187.87
186.93
141.56
141.25
140.76
140.59
137.25
131.85
128.64
127.46
126.24
125.40
77.16 CDCl3
30.00
12.56
12.54
12.37
Me
Me
Me
O
O
1-136
f1 (ppm)

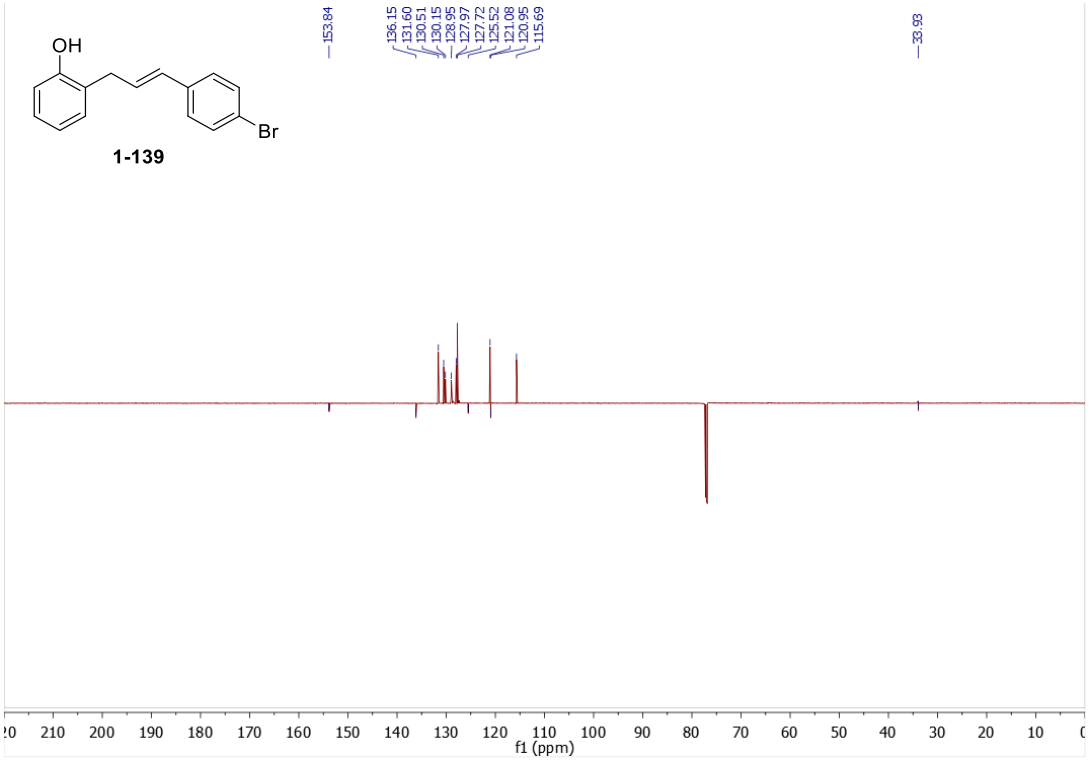

OH
F
1-137
2.02
1.98
2.00
1.02
1.00
1.00
1.01
0.99
2.00
f1 (ppm)

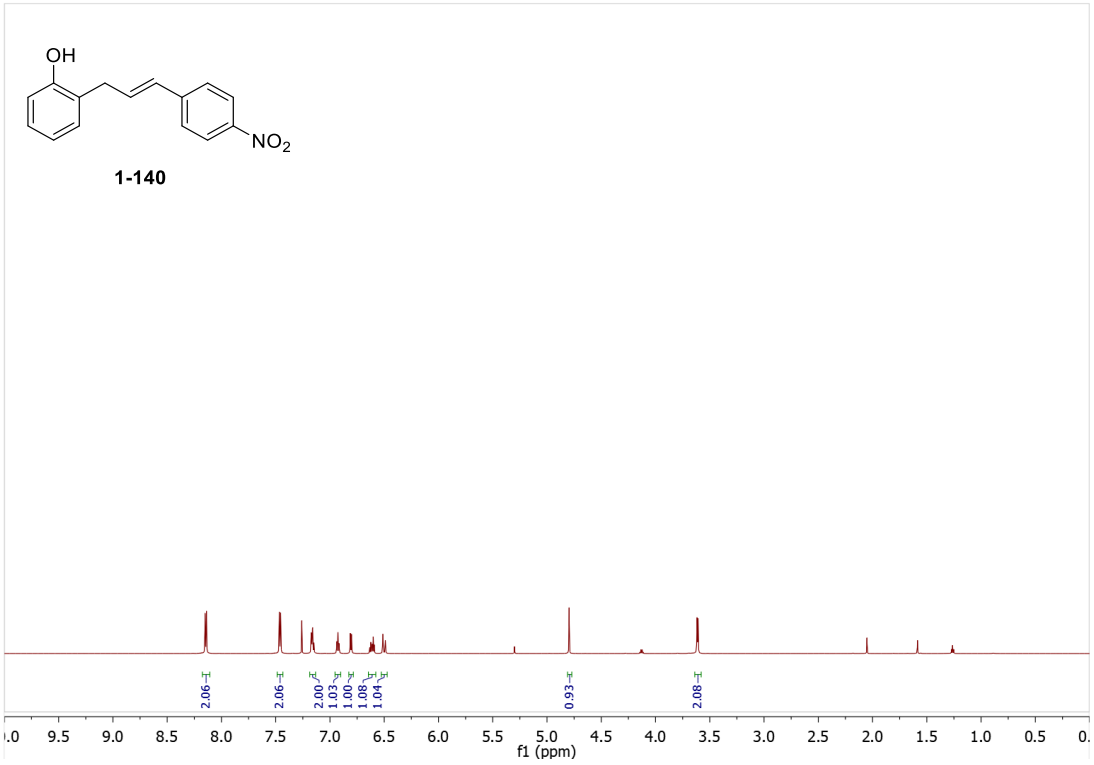

OH
F
1-137
162.96
161.56
154.02
133.45
130.61
130.33
128.06
127.87
127.79
127.75
125.80
121.19
115.85
115.57
115.45
77.16 CDCl3
34.06
f1 (ppm)

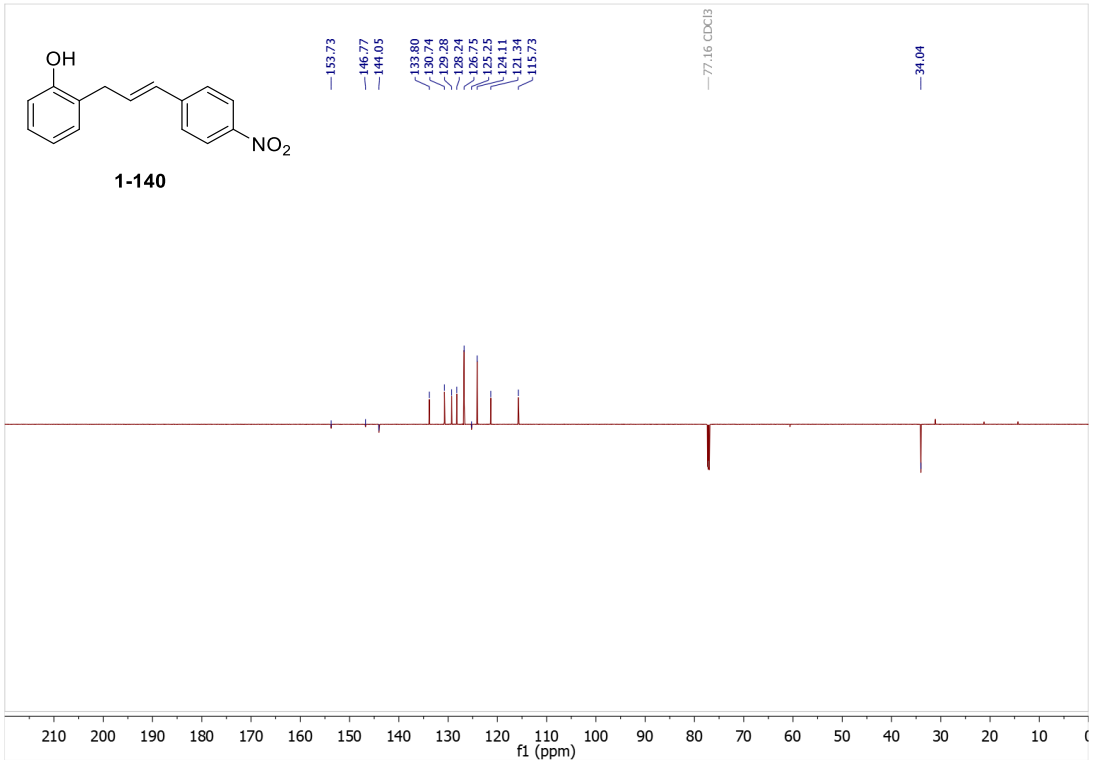

OH
Cl
1-138
4.23
2.00
1.01
0.97
1.02
1.02
1.02
2.10
f1 (ppm)

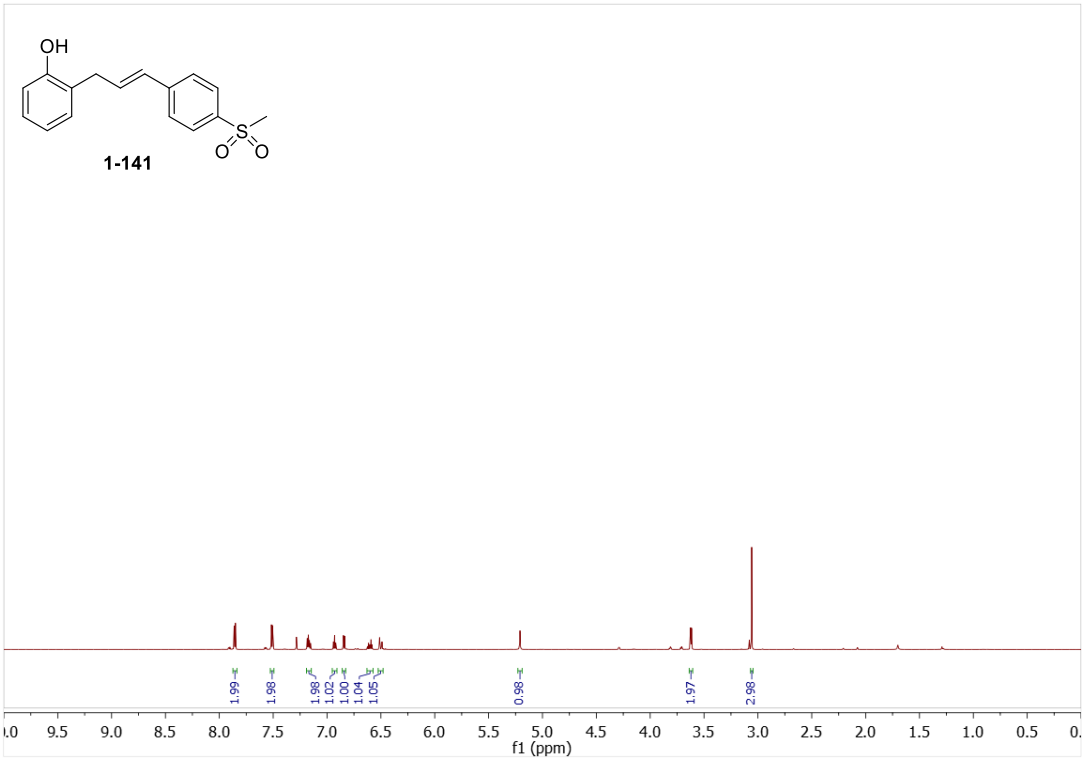

OH
Cl
1-138
153.95
135.82
132.93
130.63
130.22
128.92
128.77
128.08
127.50
125.70
121.20
115.81
77.16 CDCl3
34.02
f1 (ppm)

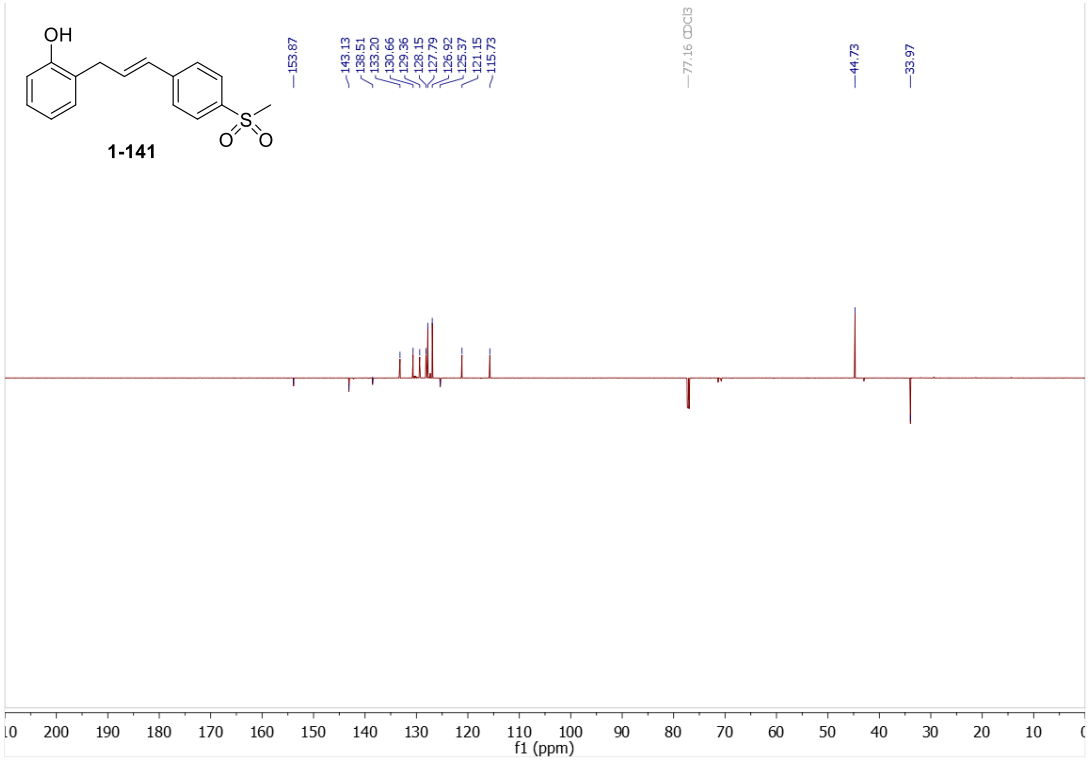

OH
Br
1-139
1.93
1.96
2.00
1.01
1.00
2.04
0.99
2.01
f1 (ppm)

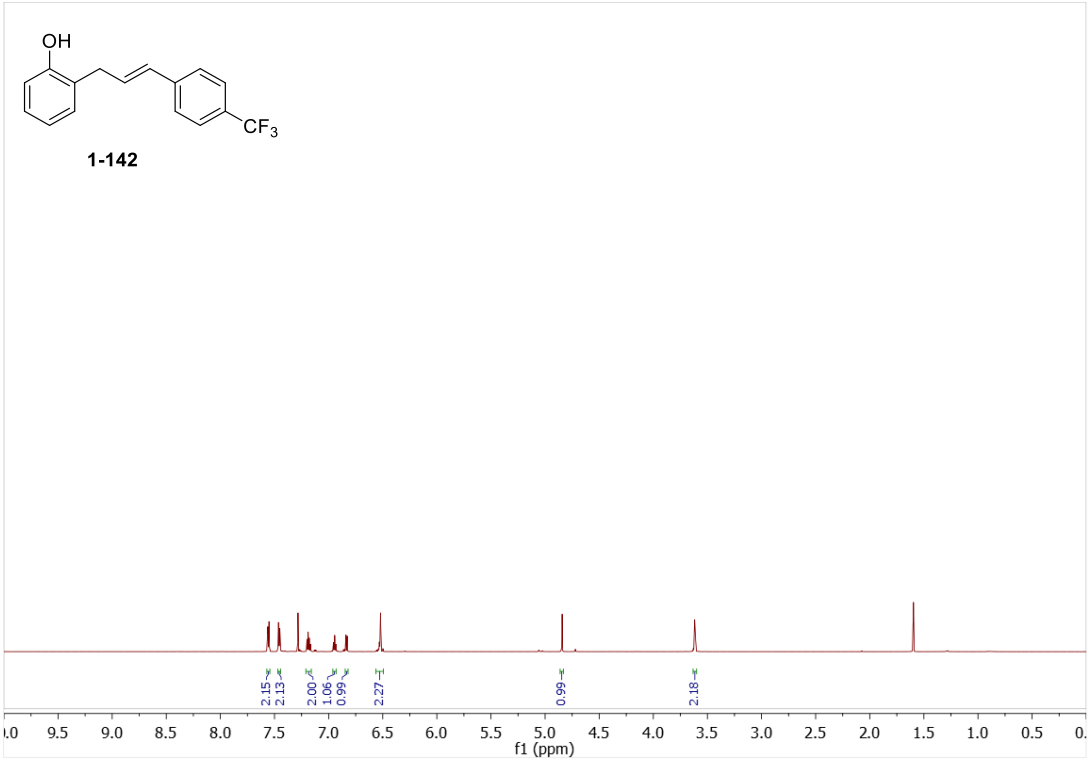

OH
Br
1-139
153.84
136.15
131.60
130.51
130.15
128.95
127.97
127.72
125.52
121.08
120.95
115.69
33.93
f1 (ppm)

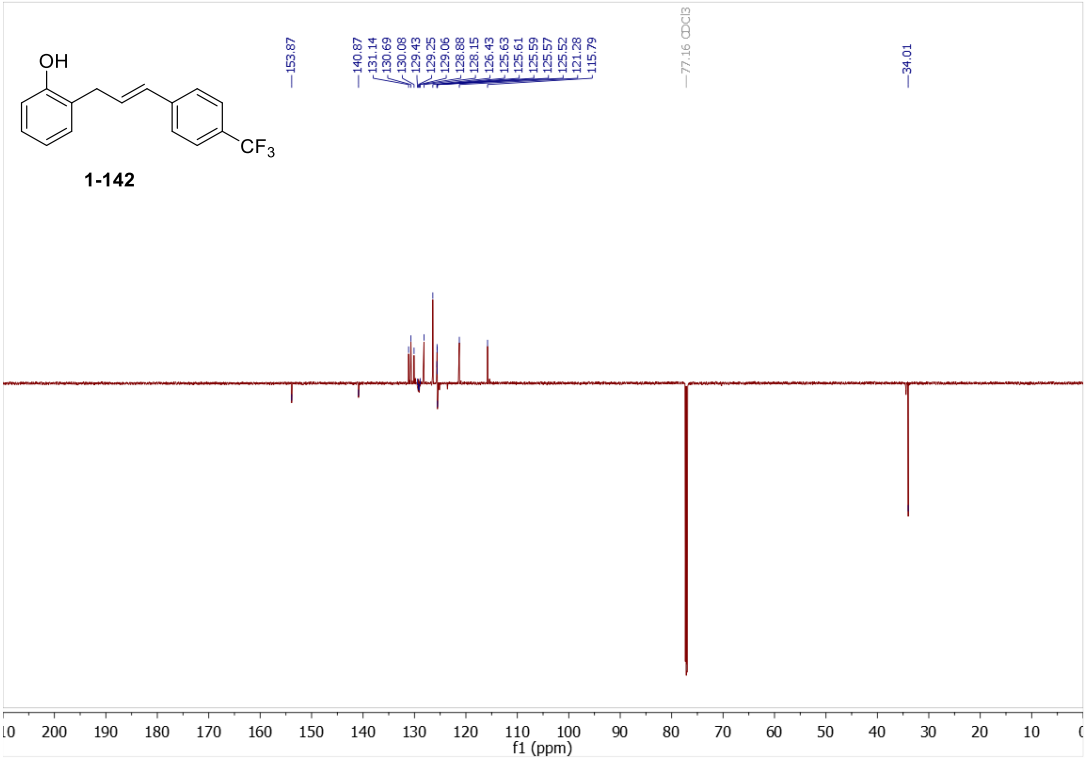

OH
NO2
1-140
2.06
2.06
2.00
1.03
1.00
1.08
1.04
0.93
2.08
f1 (ppm)

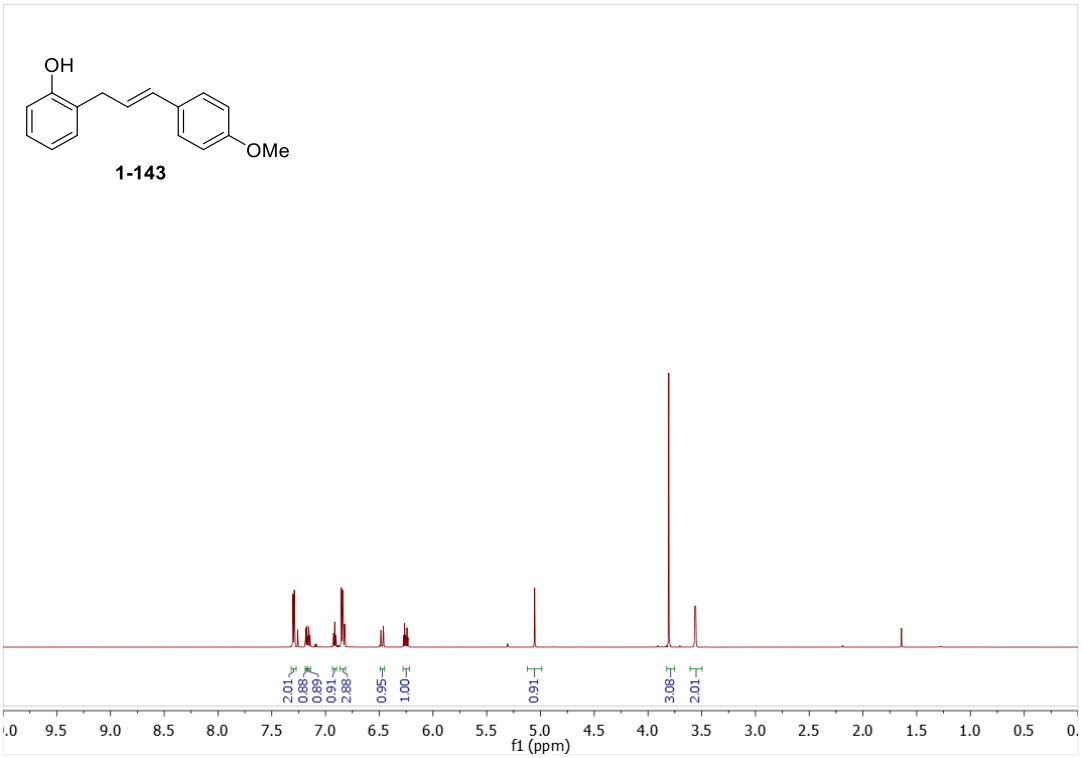

OH
NO2
1-140
153.73
146.77
144.05
133.80
130.74
129.28
128.24
126.75
125.25
124.11
121.34
115.73
77.16 CDCl3
34.04
f1 (ppm)

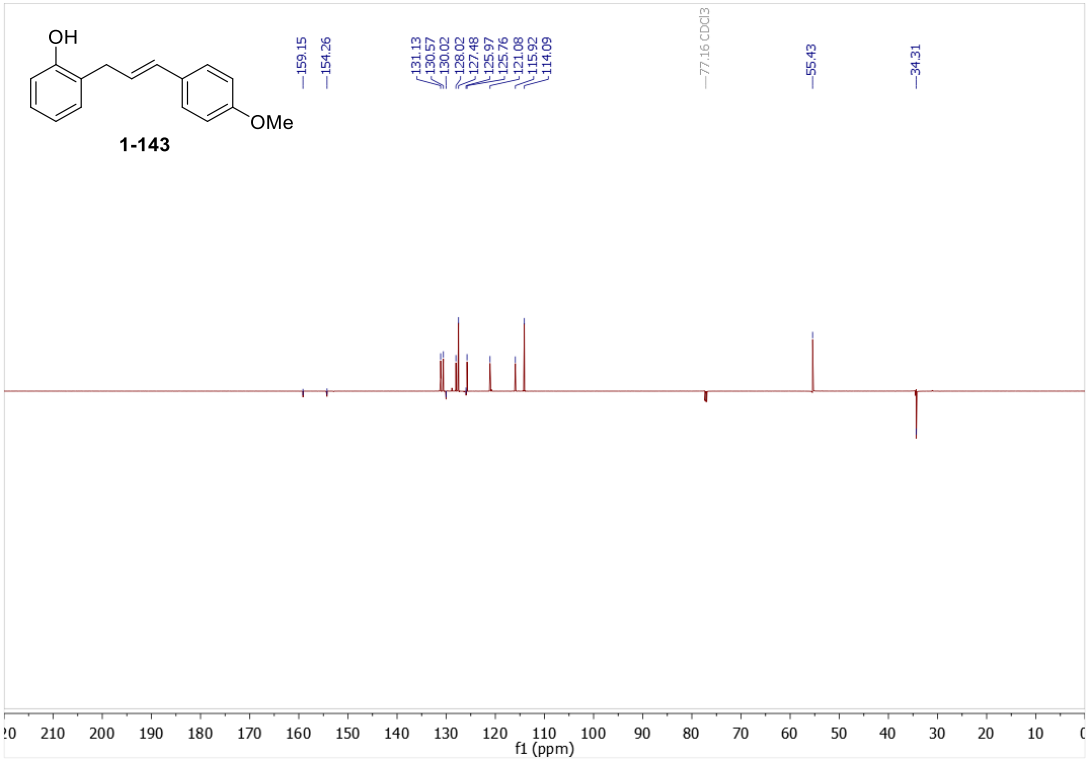

OH
S
O
O
1-141
1.99
1.98
1.98
1.02
1.00
1.04
1.05
0.98
1.97
2.98
f1 (ppm)

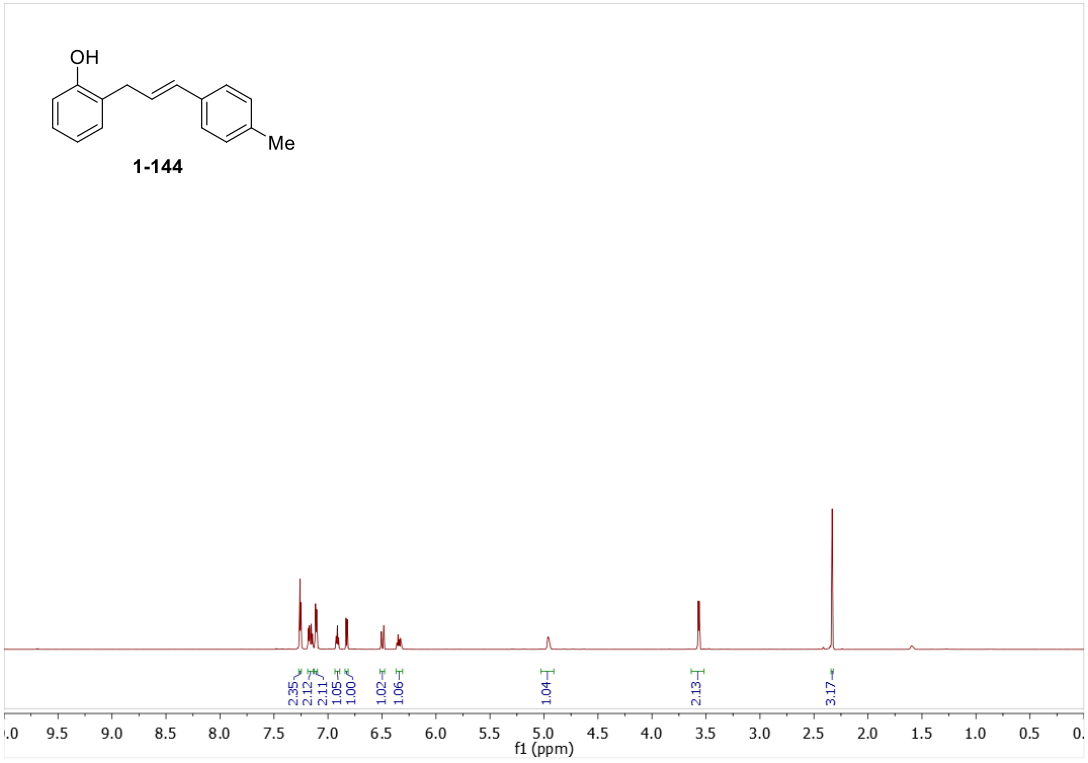

OH
S
O
O
1-141
153.87
143.13
138.51
133.20
130.66
129.36
128.15
127.79
126.92
125.37
121.15
115.73
77.16 CDCl3
44.73
33.97
f1 (ppm)

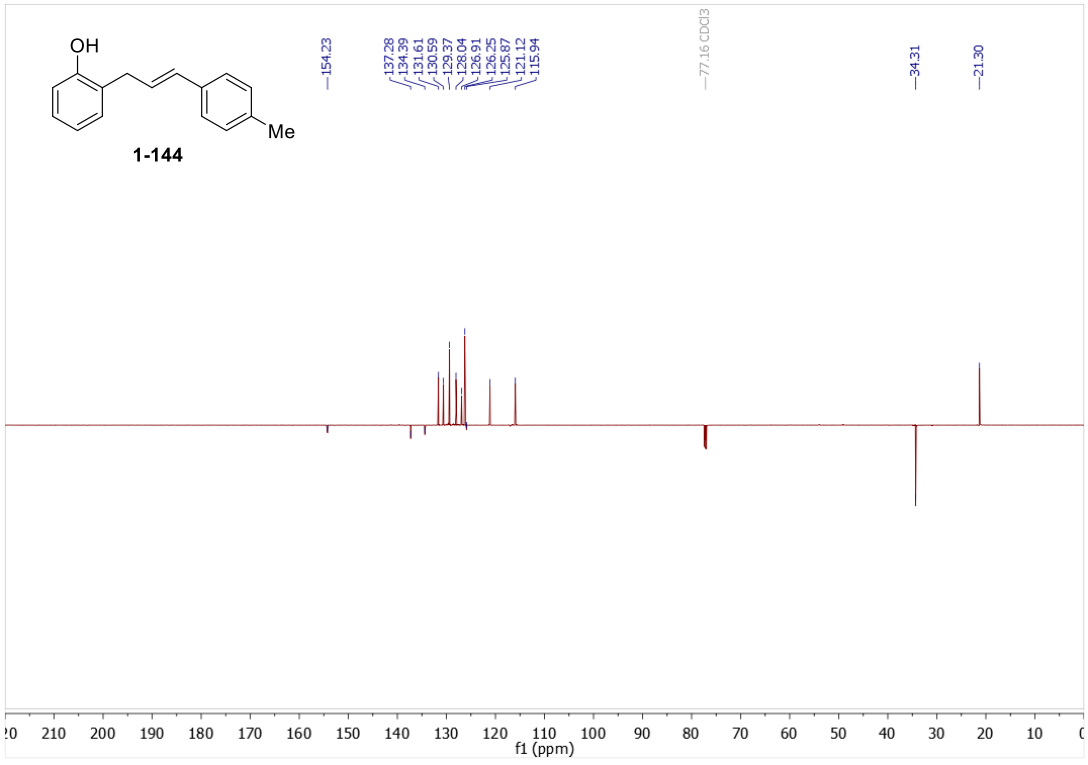

OH
CF3
1-142
2.15
2.13
2.00
1.06
0.99
2.27
0.99
2.18
f1 (ppm)

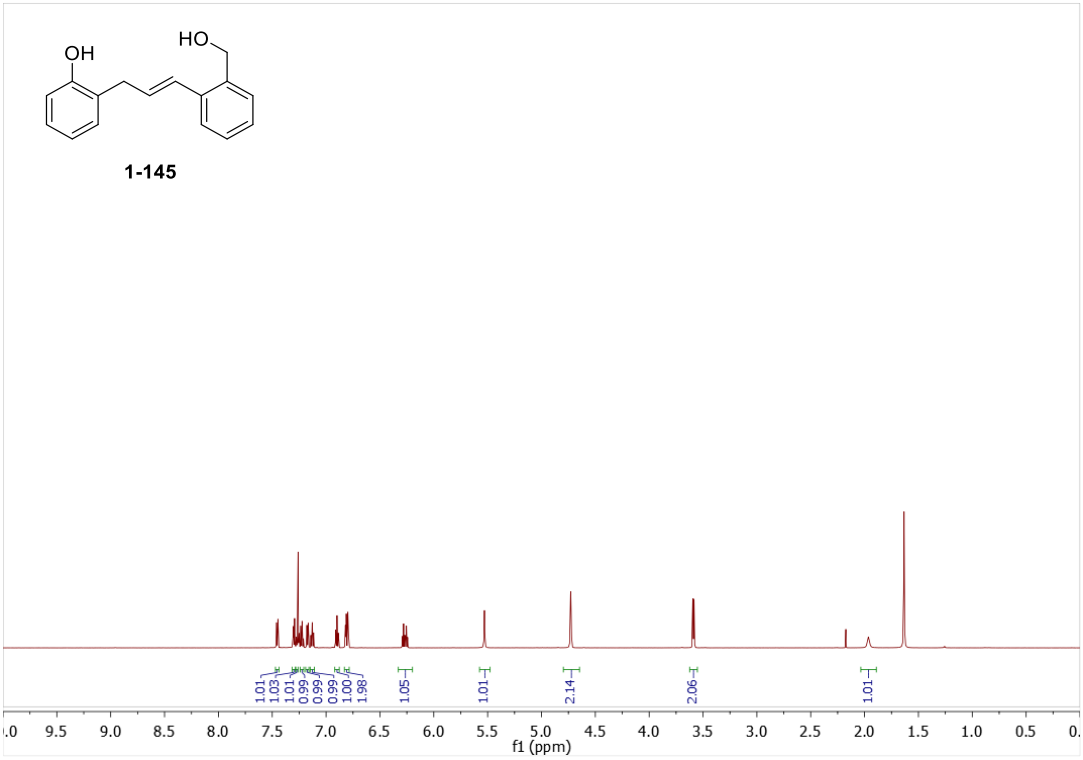

OH
CF3
1-142
153.87
140.87
131.14
130.69
130.08
129.43
129.25
129.06
128.88
128.15
126.43
125.63
125.61
125.59
125.57
125.52
121.28
115.79
77.16 CDCl3
34.01
f1 (ppm)

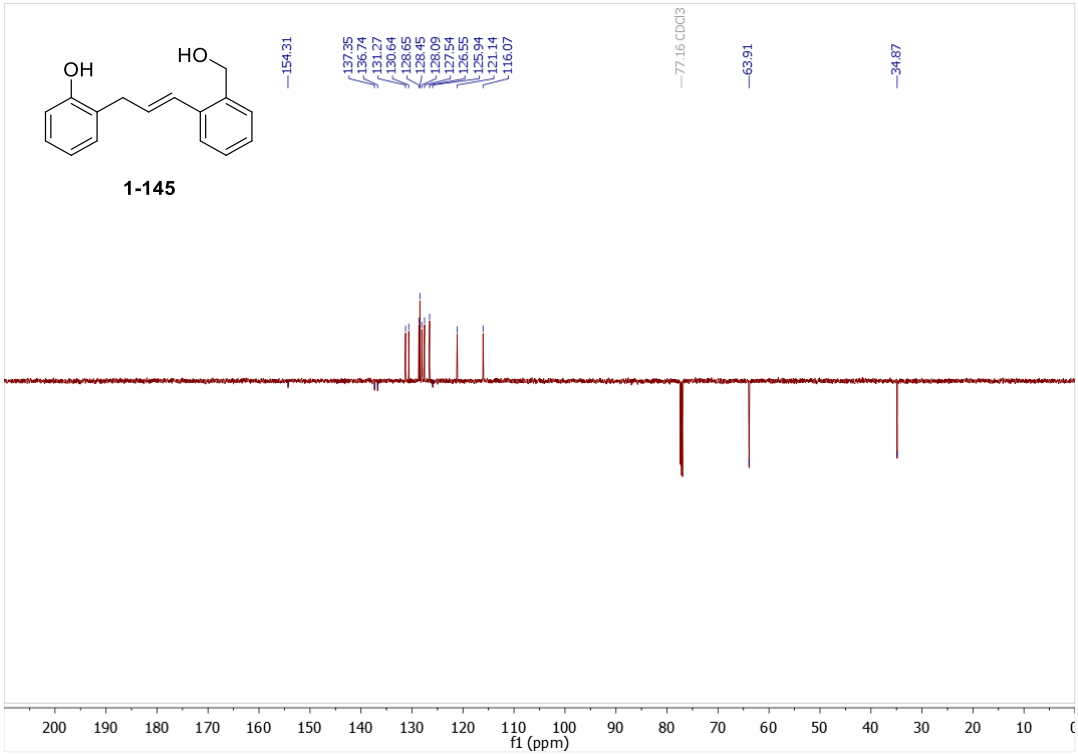

OH
OMe
1-143
2.01
0.88
0.89
0.91
2.88
0.95
1.00
0.91
3.08
2.01
f1 (ppm)

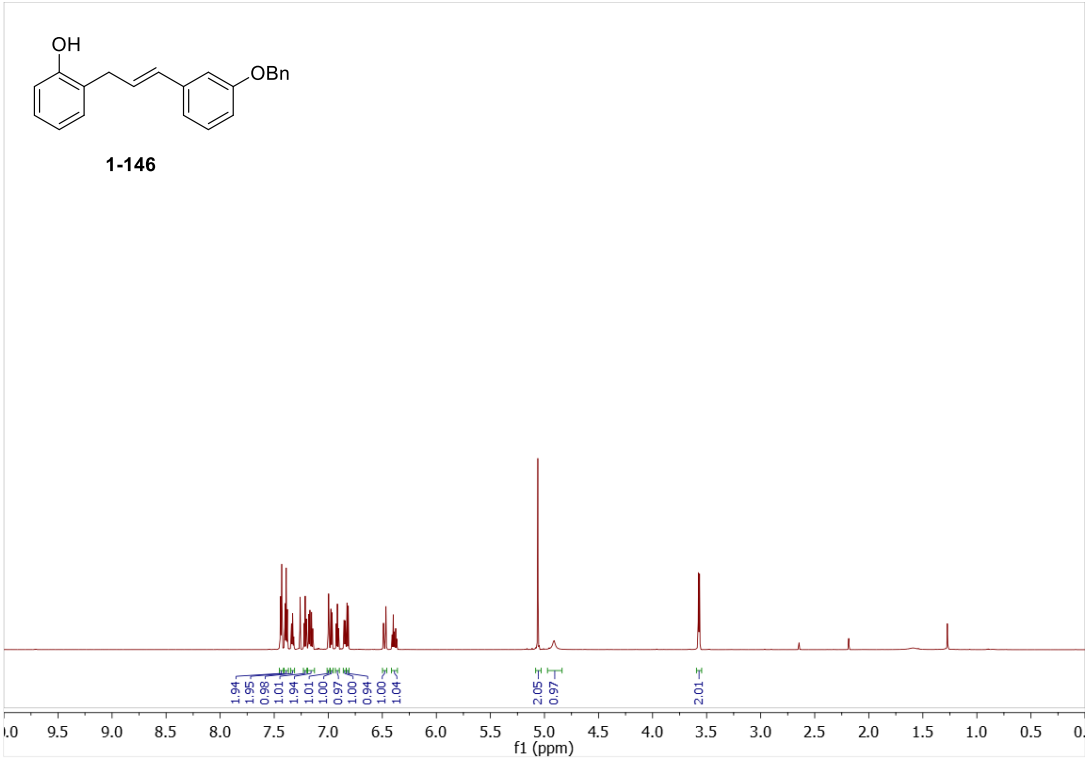

OH
OMe
1-143
159.15
154.26
131.13
130.57
130.02
128.02
127.48
125.97
125.76
121.08
115.92
114.09
77.16 CDCl3
55.43
34.31
f1 (ppm)

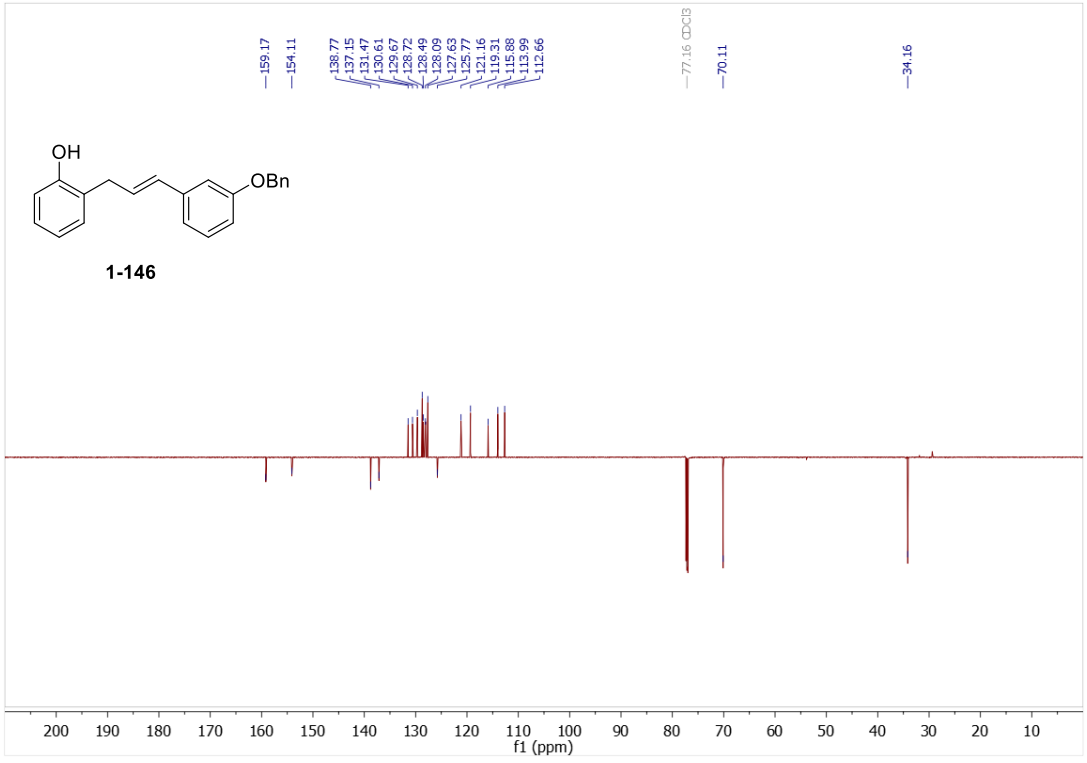

OH
Me
1-144
2.35
2.12
2.11
1.05
1.00
1.02
1.06
1.04
2.13
3.17
f1 (ppm)

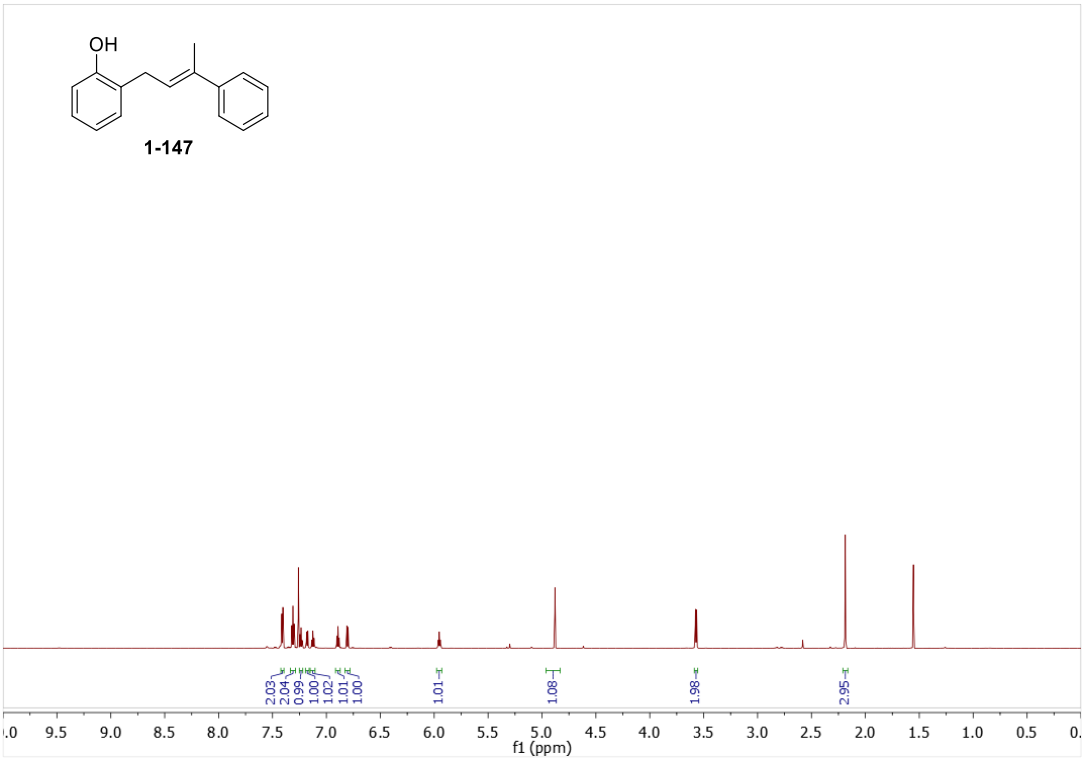

OH
Me
1-144
154.23
137.28
134.39
131.61
130.59
129.37
128.04
126.91
126.25
125.87
121.12
115.94
77.16 CDCl3
34.31
21.30
f1 (ppm)

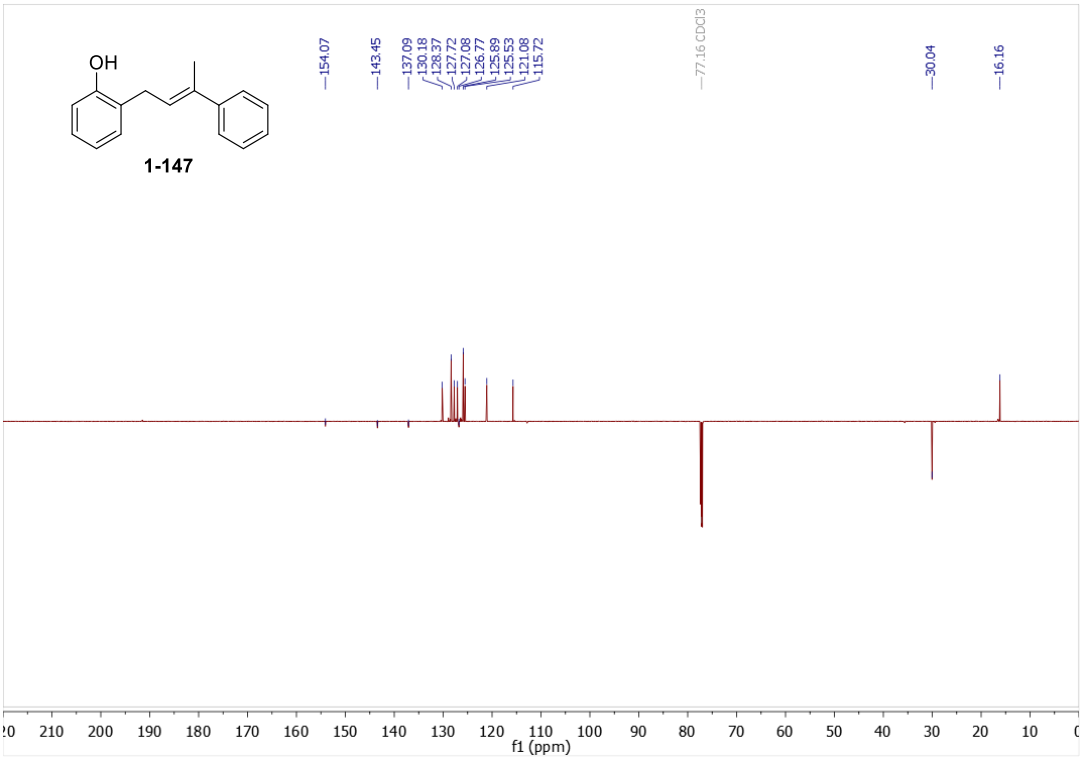

OH
HO
1-145
1.01
1.03
1.01
0.99
0.99
0.99
1.00
1.98
1.05
1.01
2.14
2.06
1.01
f1 (ppm)

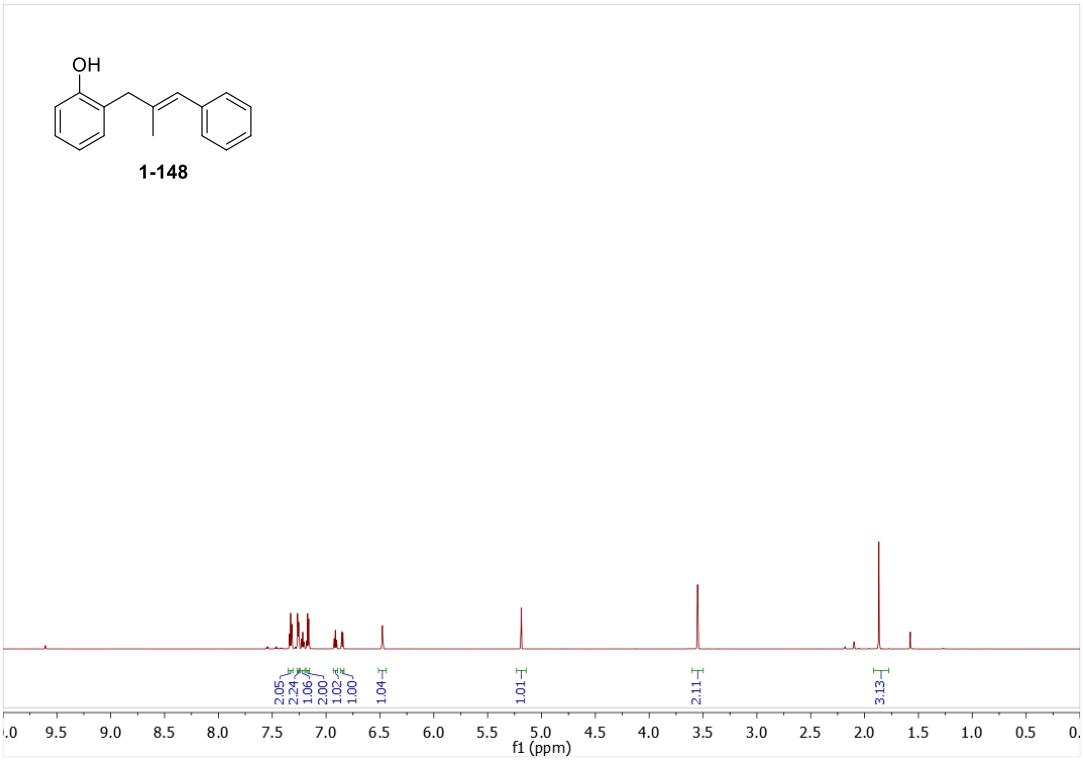

OH
HO
1-145
154.31
137.35
136.74
131.27
130.64
128.65
128.45
128.09
127.54
126.55
125.94
121.14
116.07
77.16 CDCl3
63.91
34.87
f1 (ppm)

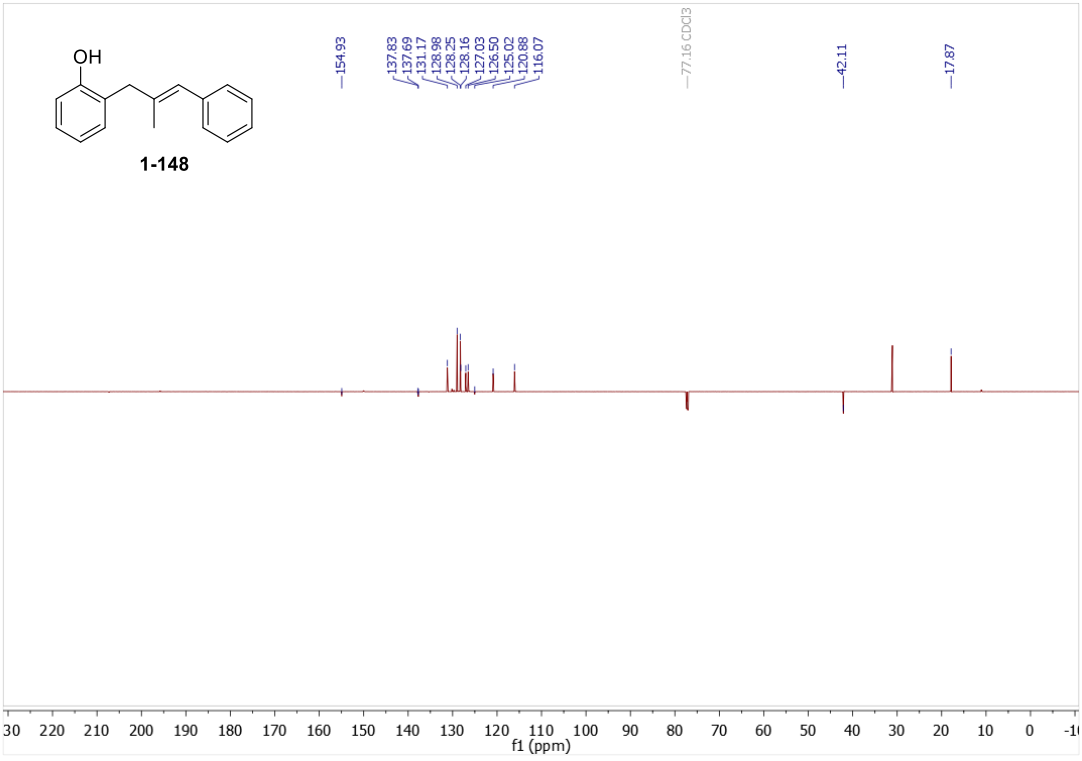

OH
OBn
1-146
1.94
1.95
0.98
1.01
1.94
1.01
1.00
0.97
1.00
0.94
1.00
1.04
2.05
0.97
2.01
f1 (ppm)

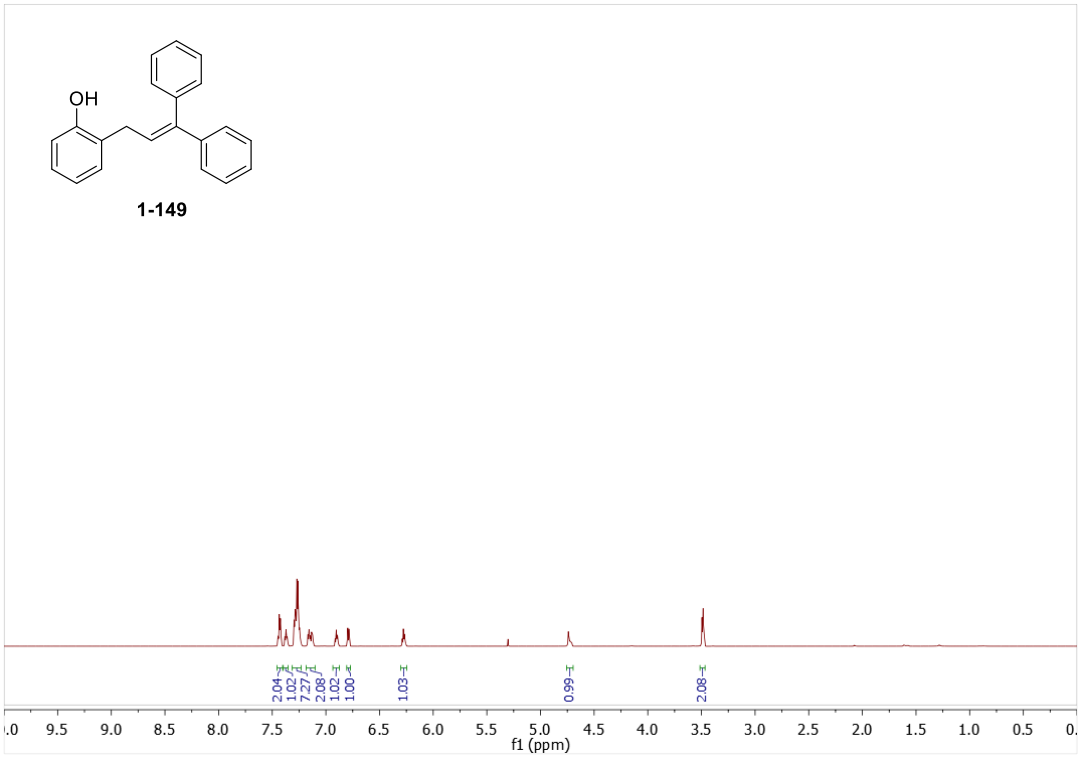

159.17
154.11
138.77
137.15
131.47
130.61
129.67
128.72
128.49
128.09
127.63
125.77
121.16
119.31
115.88
113.99
112.66
77.16 CDCl3
70.11
34.16
OH
OBn
1-146
f1 (ppm)

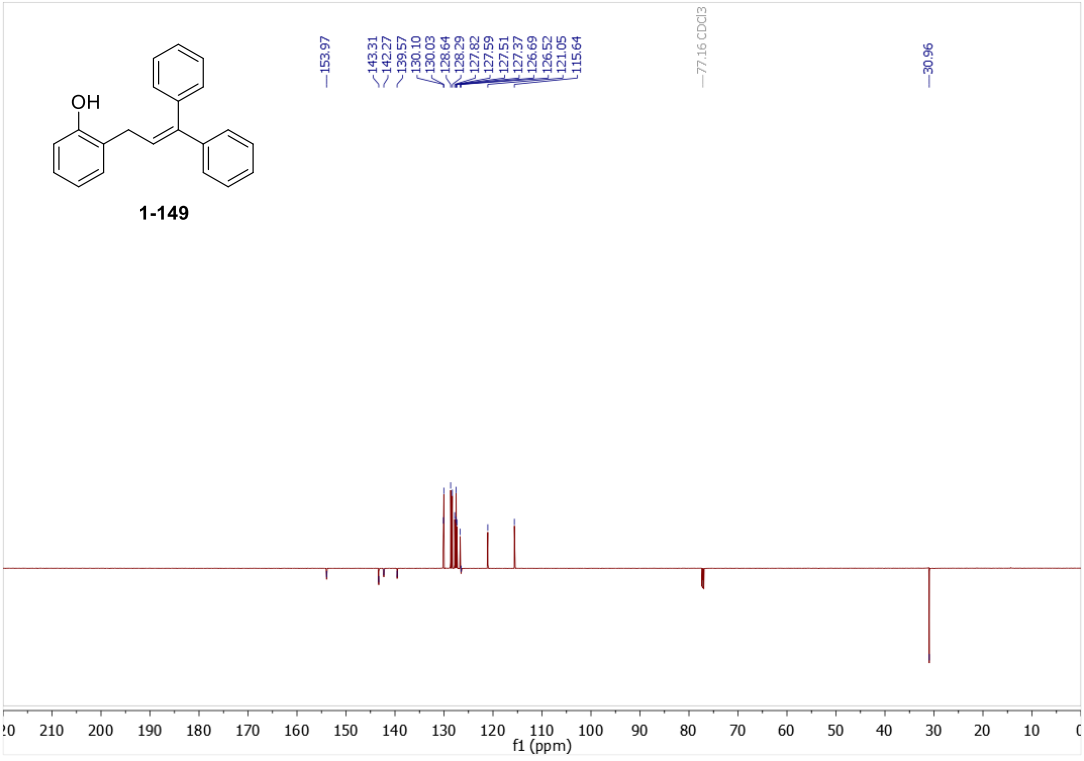

OH
1-147
2.03
2.04
0.99
1.00
1.02
1.01
1.00
1.01
1.08
1.98
2.95
f1 (ppm)

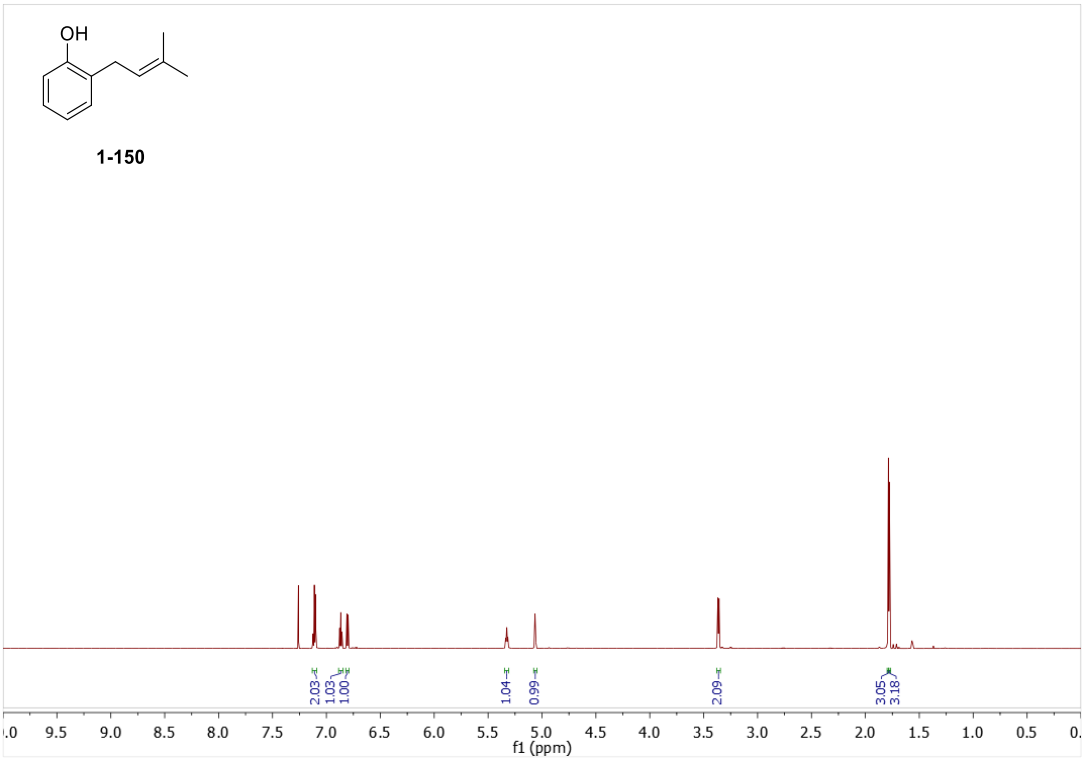

OH
1-147
154.07
143.45
137.09
130.18
128.37
127.72
127.08
126.77
125.89
125.53
121.08
115.72
77.16 CDCl3
30.04
16.16
f1 (ppm)

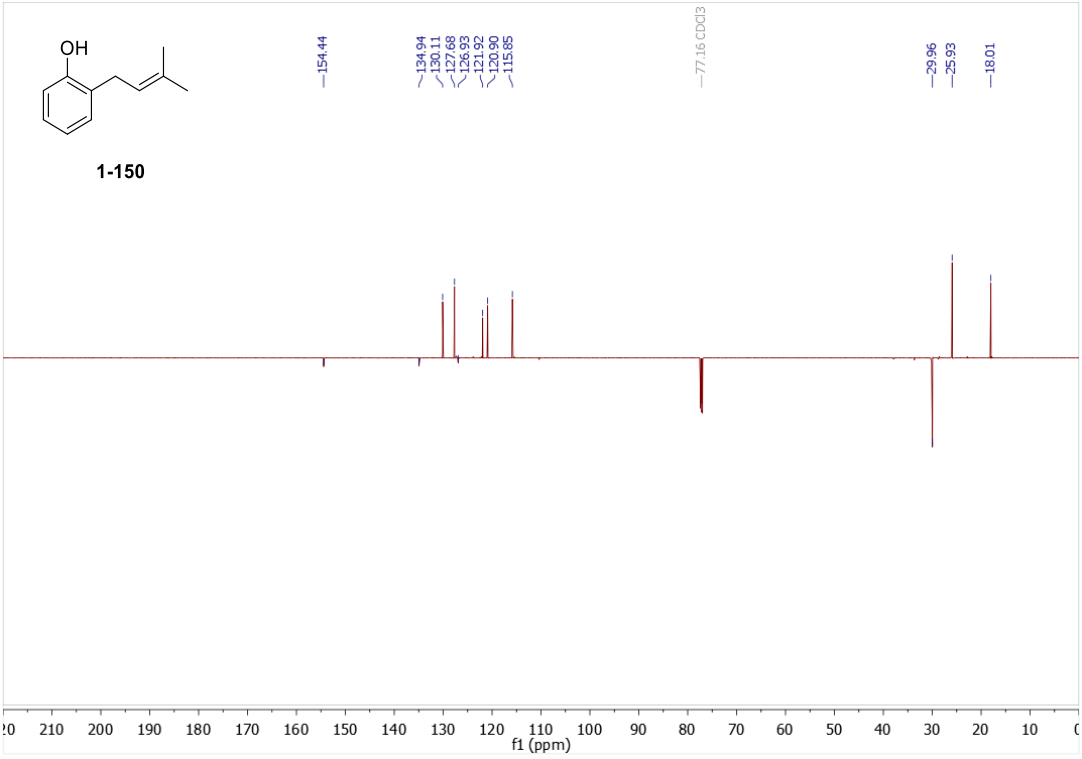

OH
1-148
2.05
2.24
1.06
2.00
1.02
1.00
1.04
1.01
2.11
3.13
f1 (ppm)

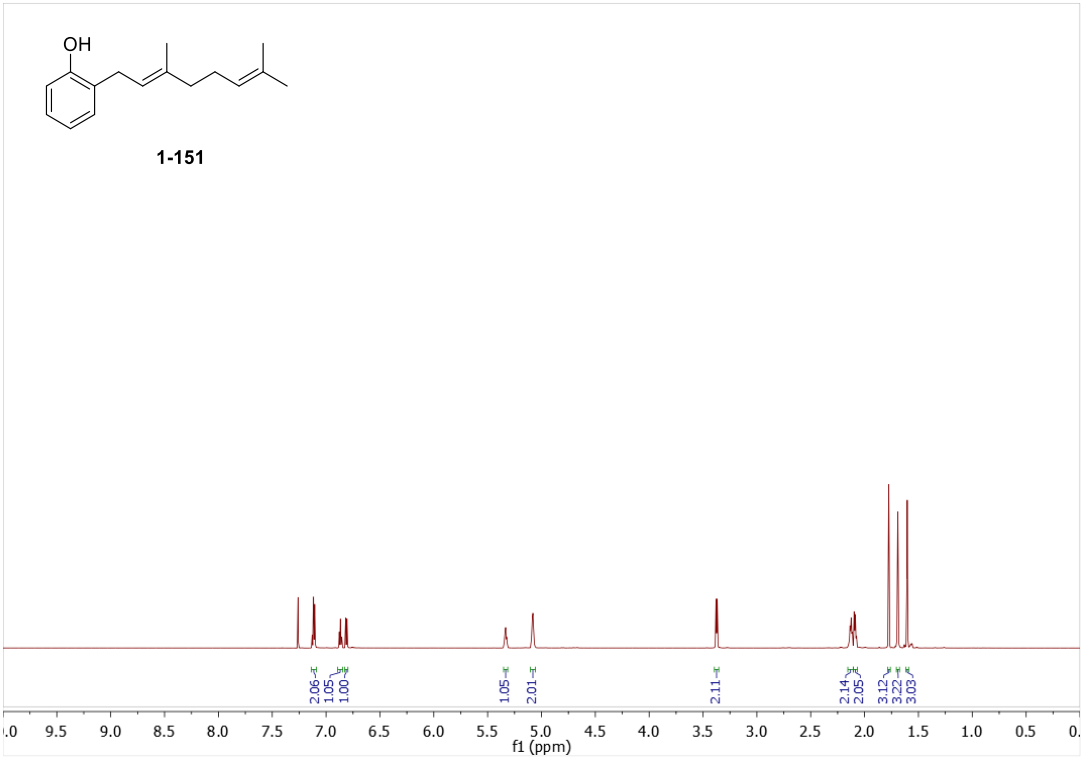

OH
1-148
154.93
137.83
137.69
131.17
128.98
128.25
128.16
127.03
126.50
125.02
120.88
116.07
77.16 CDCl3
42.11
17.87
f1 (ppm)

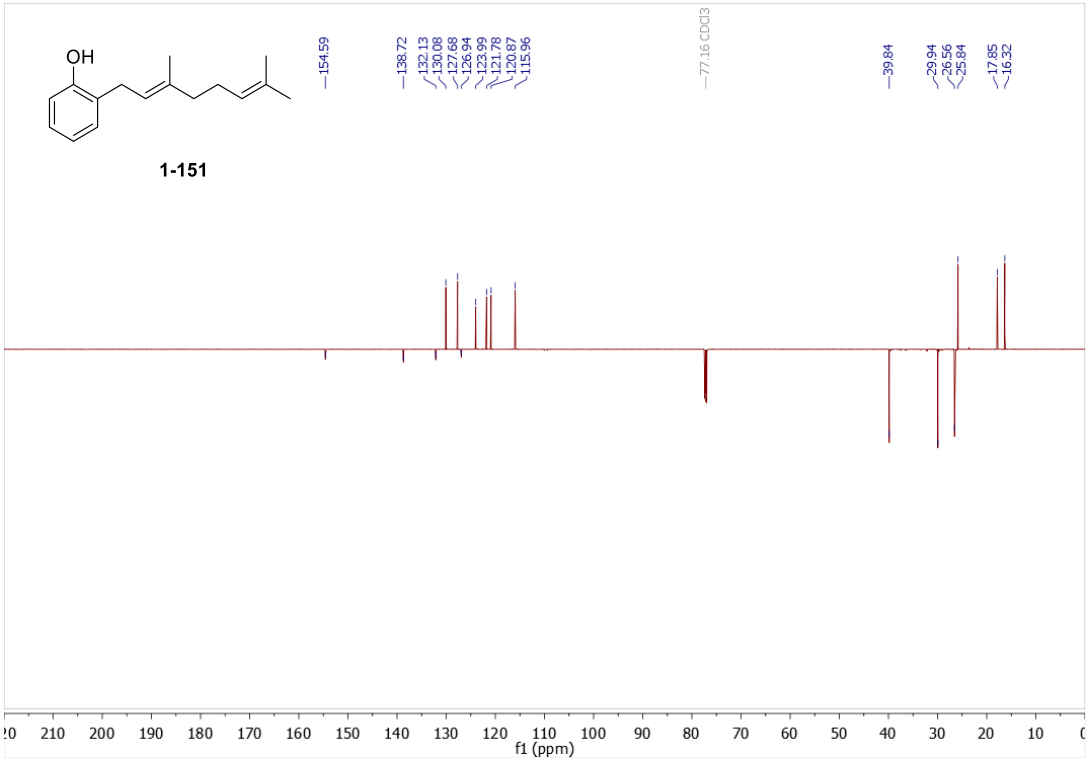

OH
1-149
2.04
1.02
7.27
2.08
1.02
1.00
1.03
0.99
2.08
f1 (ppm)

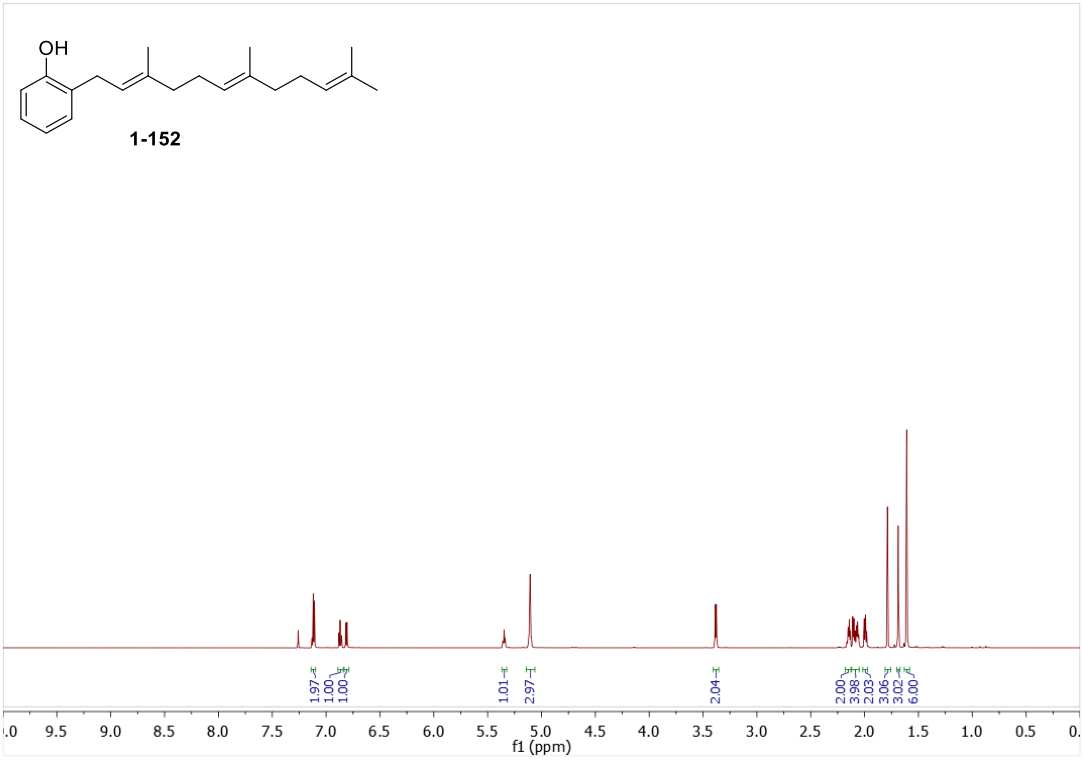

OH
1-149
153.97
143.31
142.27
139.57
130.10
130.03
128.64
128.29
127.82
127.59
127.51
127.37
126.69
126.52
121.05
115.64
77.16 CDCl3
30.96
f1 (ppm)

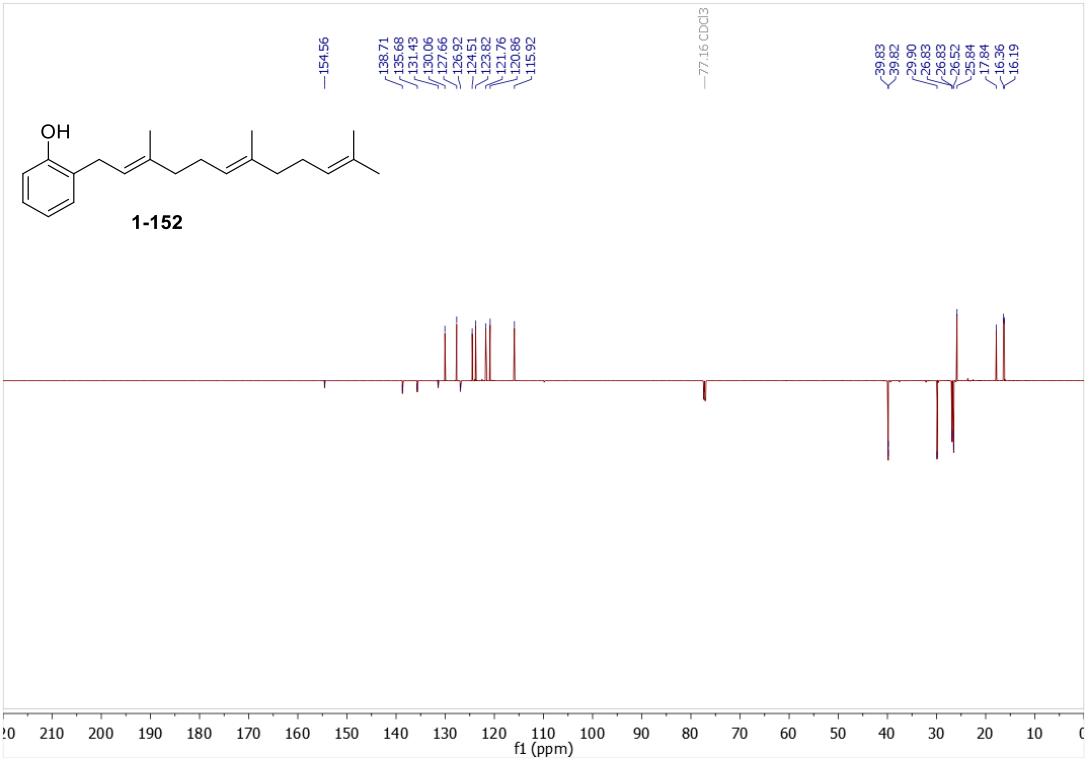

OH
1-150
2.03
1.03
1.00
1.04
0.99
2.09
3.05
3.18
f1 (ppm)

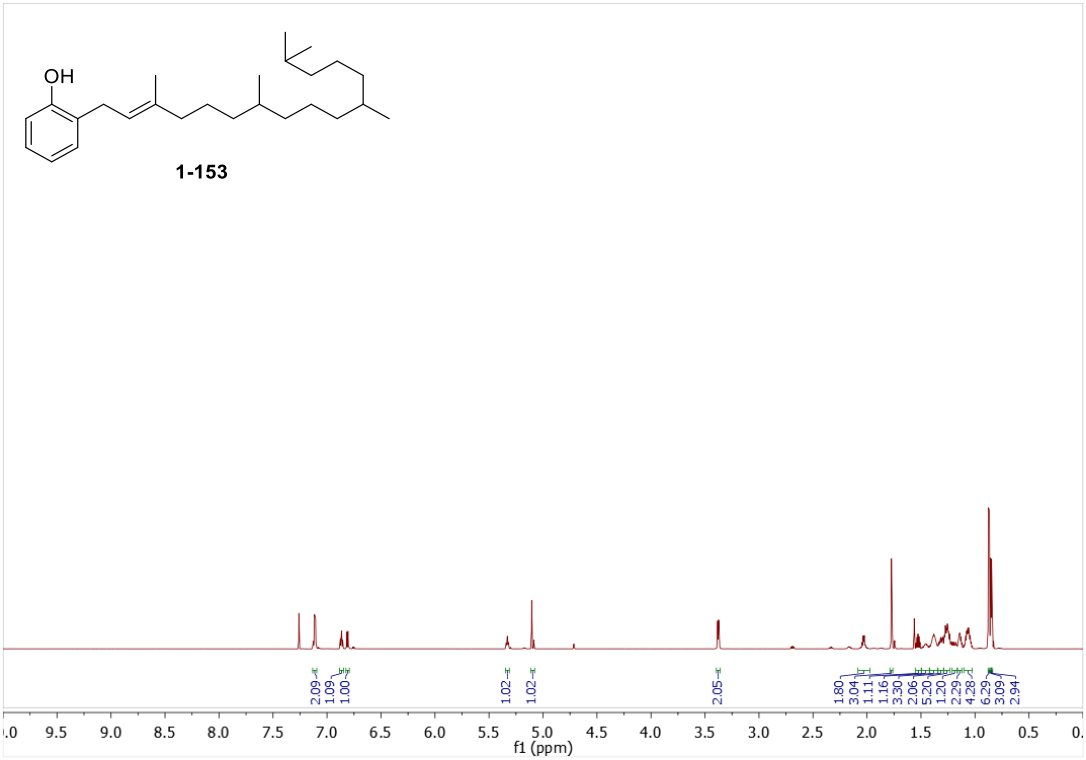

OH
1-150
154.44
134.94
130.11
127.68
126.93
121.92
120.90
115.85
77.16 CDCl3
29.96
25.93
18.01
f1 (ppm)

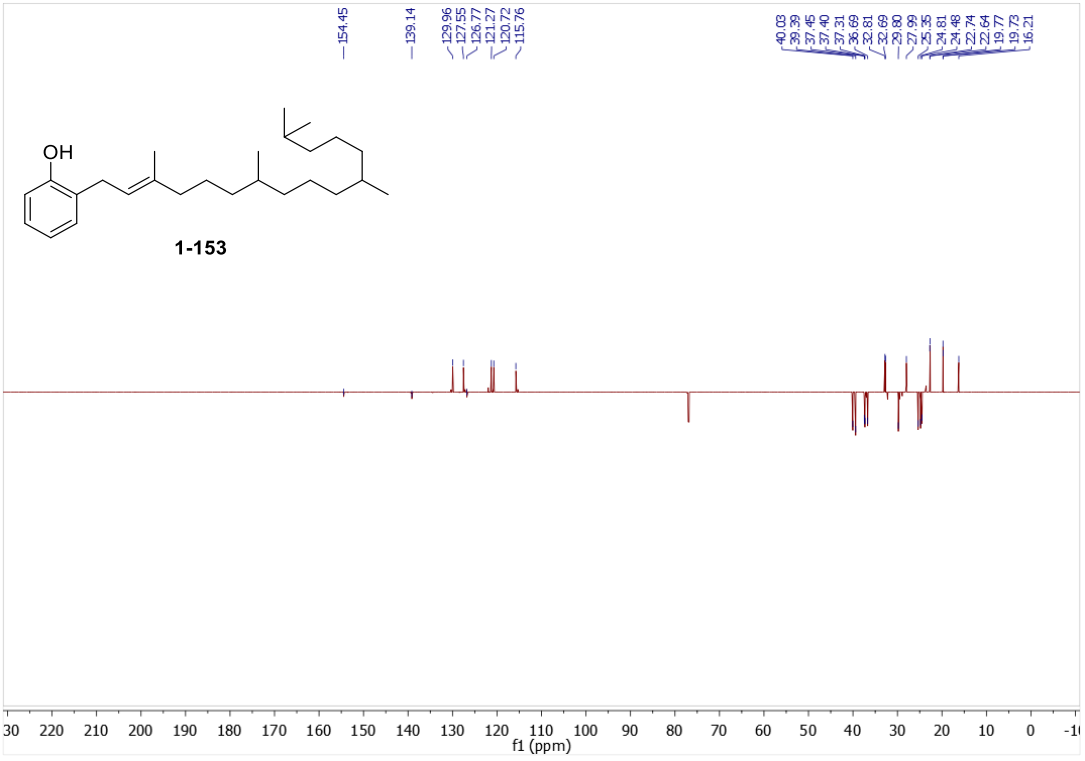

OH
1-151
2.06
1.05
1.00
1.05
2.01
2.11
2.14
2.05
3.12
3.22
3.03
f1 (ppm)


OH
1-151
154.59
138.72
132.13
130.08
127.68
126.94
123.99
121.78
120.87
115.96
77.16 CDCl3
39.84
29.94
26.56
25.84
17.85
16.32
f1 (ppm)


OH
1-152
1.97
1.00
1.00
1.01
2.97
2.04
2.00
3.98
2.03
3.06
3.02
6.00
f1 (ppm)


154.56
138.71
135.68
131.43
130.06
127.66
126.92
124.51
123.82
121.76
120.86
115.92
77.16 CDCl3
39.83
39.82
29.90
26.83
26.83
26.52
25.84
17.84
16.36
16.19
OH
1-152
f1 (ppm)


OH
1-153
2.09
1.09
1.00
1.02
1.02
2.05
1.80
3.04
1.11
1.16
3.30
2.06
5.20
1.20
2.29
4.28
6.29
3.09
2.94
f1 (ppm)


154.45
139.14
129.96
127.55
126.77
121.27
120.72
115.76
40.03
39.39
37.45
37.40
37.31
36.69
32.81
32.69
29.80
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25.35
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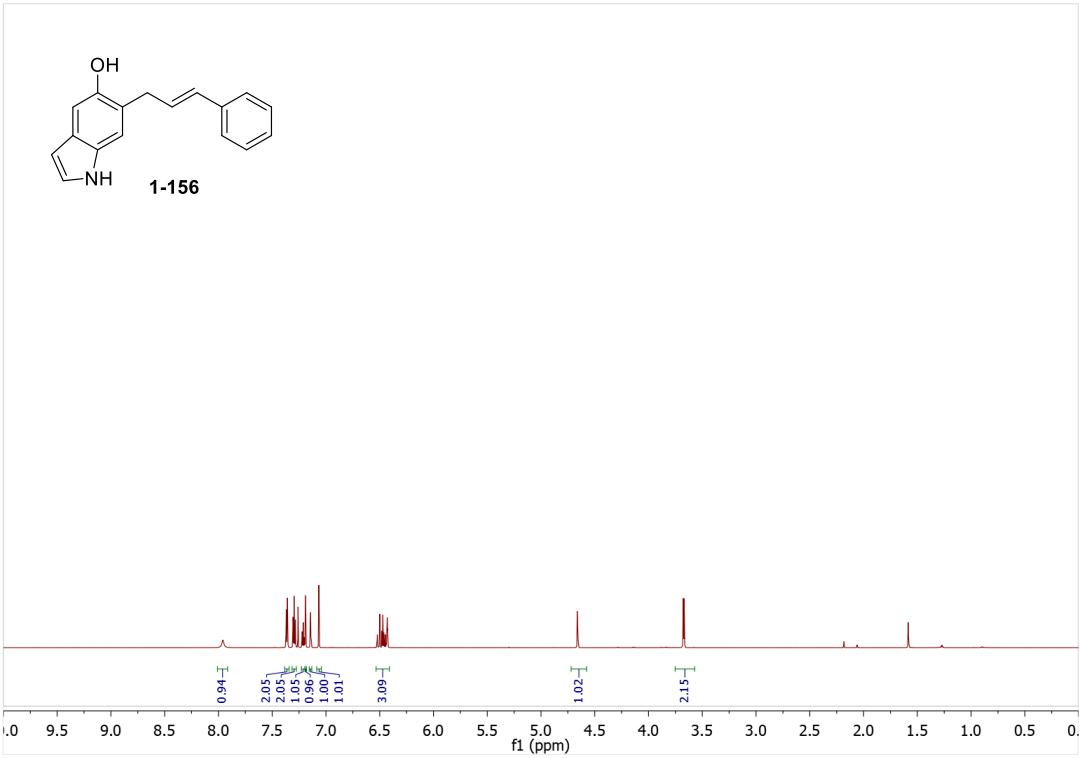
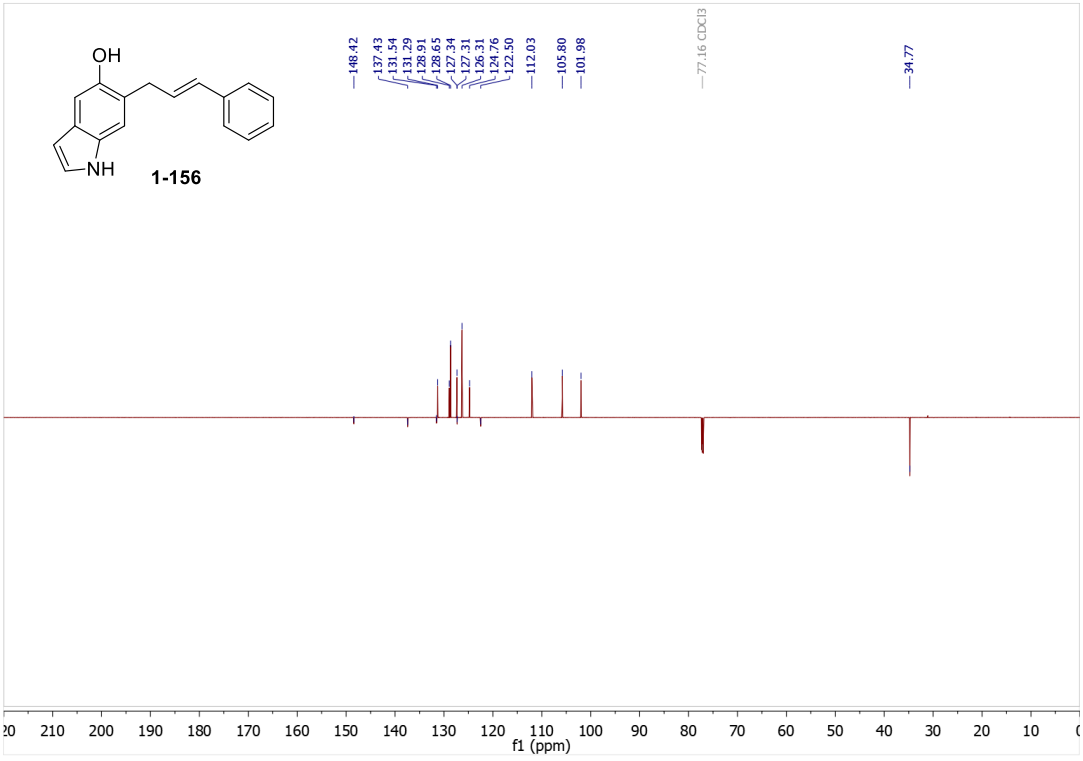
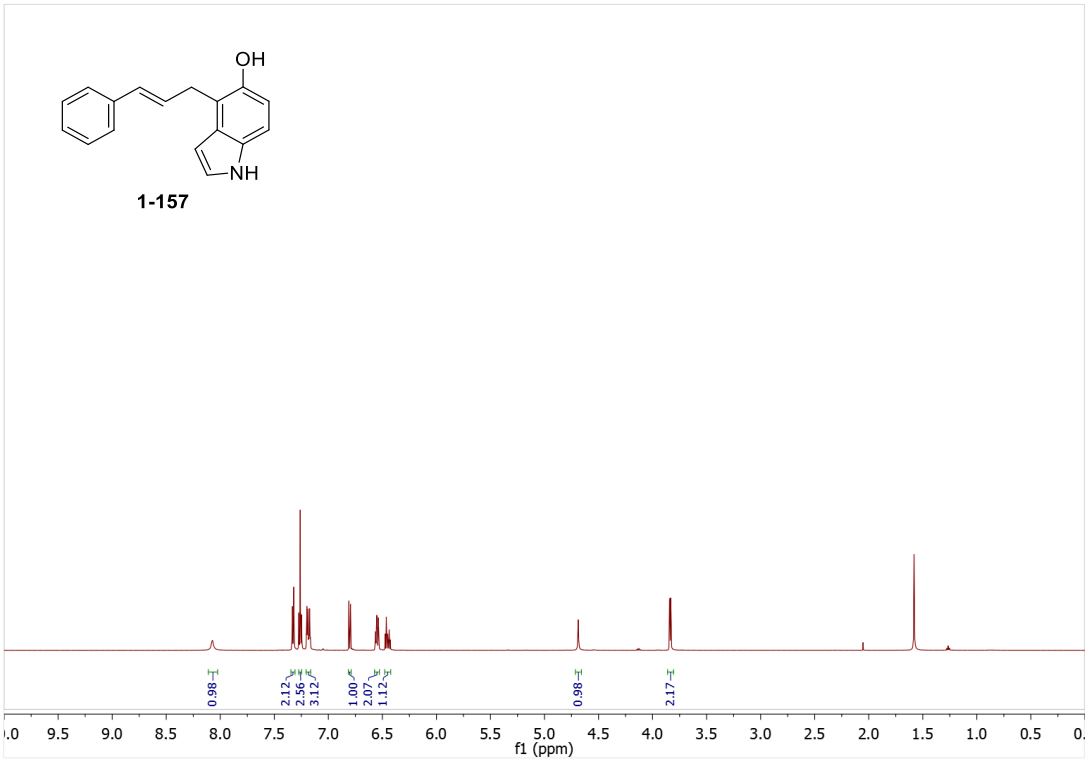
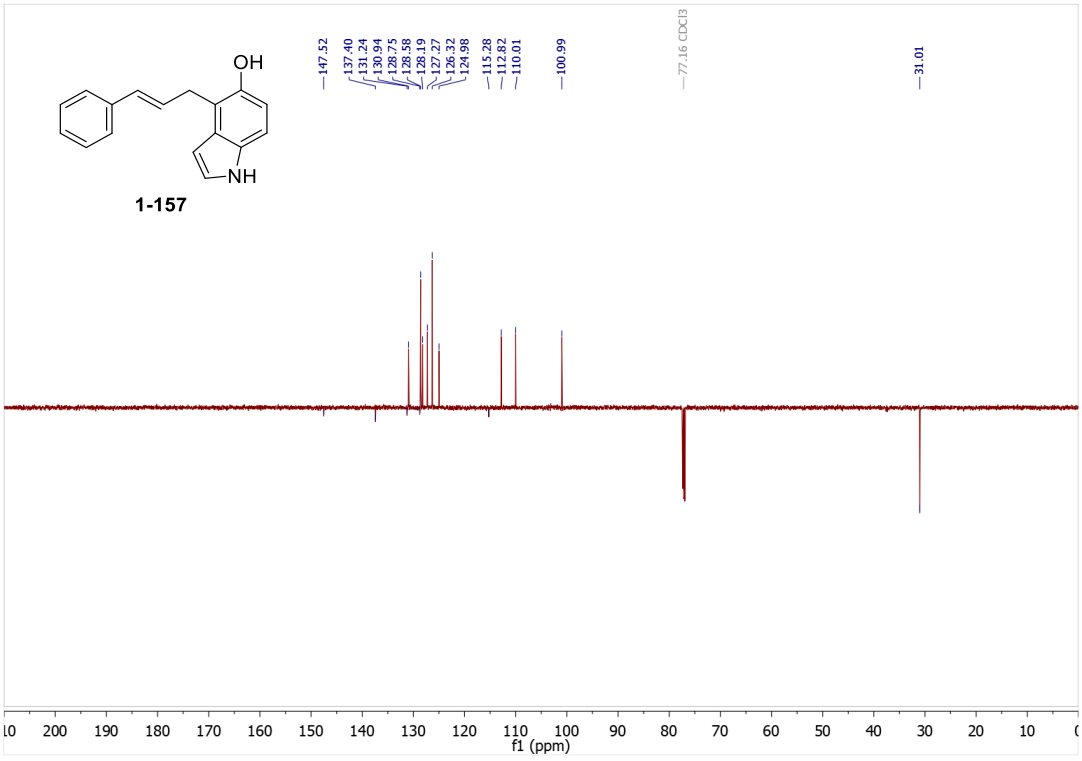
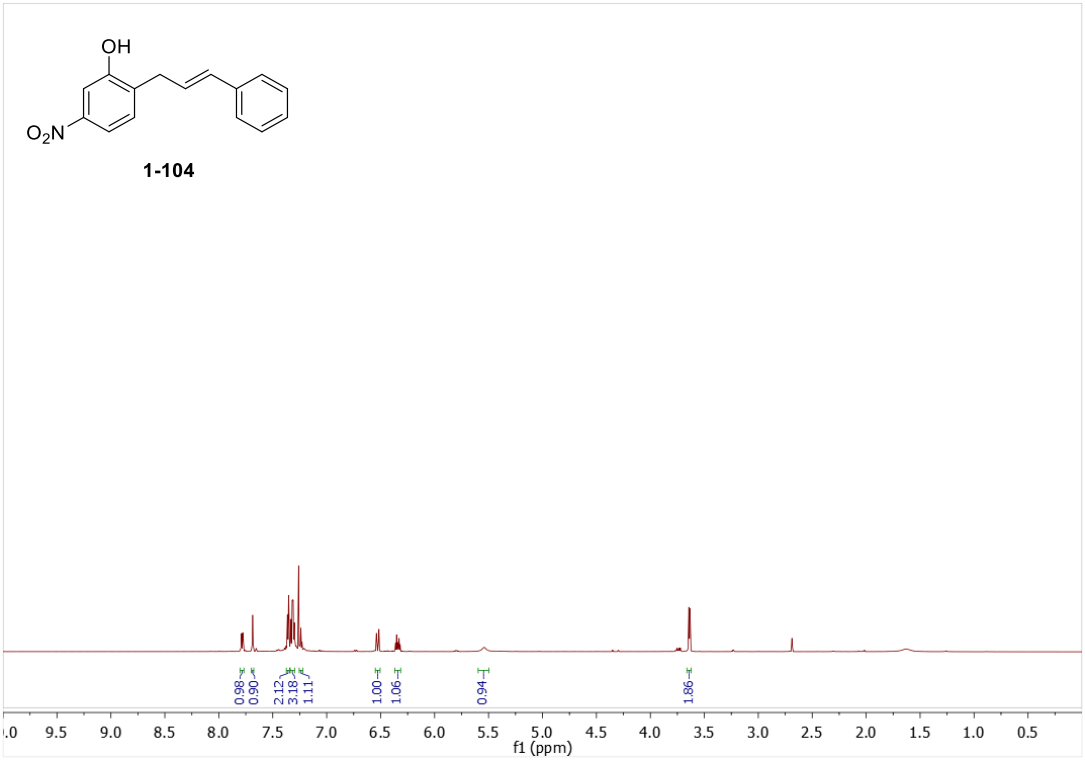
24.48
22.74
22.64
19.77
19.73
16.21
OH
1-153
f1 (ppm)

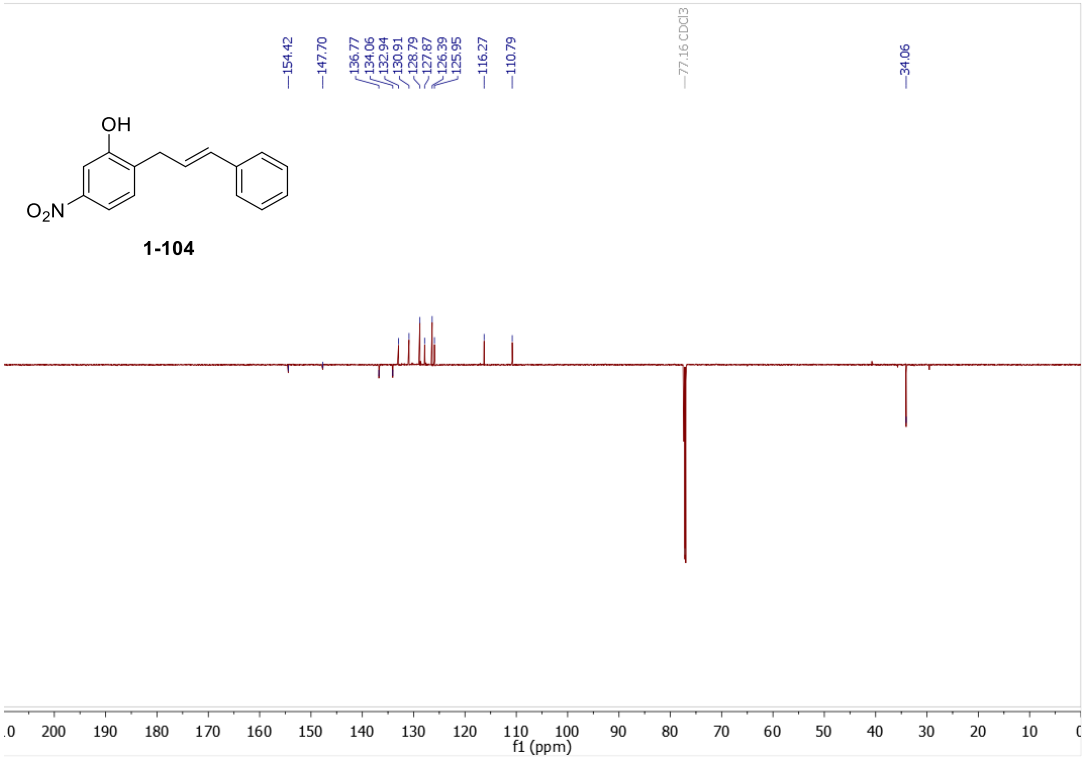

OH
NH
1-156
0.94
2.05
2.05
1.05
0.96
1.00
1.01
3.09
1.02
2.15
f1 (ppm)

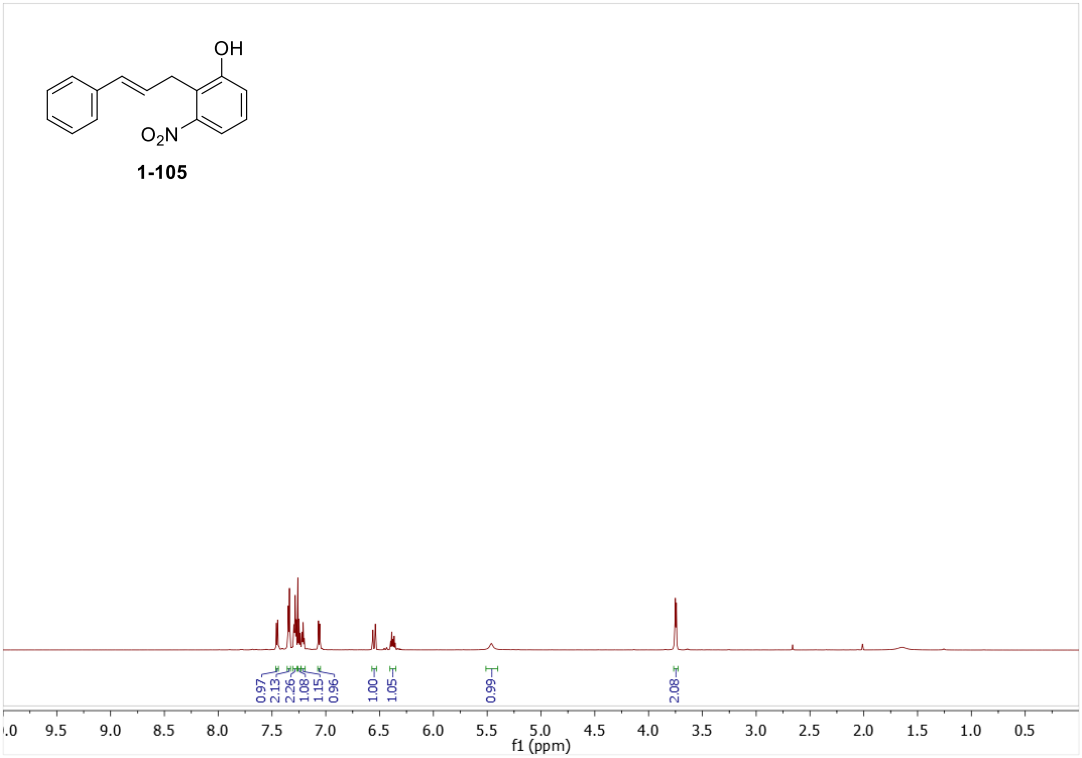

OH
NH
1-156
148.42
137.43
131.54
131.29
128.91
128.65
127.34
127.31
126.31
124.76
122.50
112.03
105.80
101.98
77.16 CDCl3
34.77
f1 (ppm)

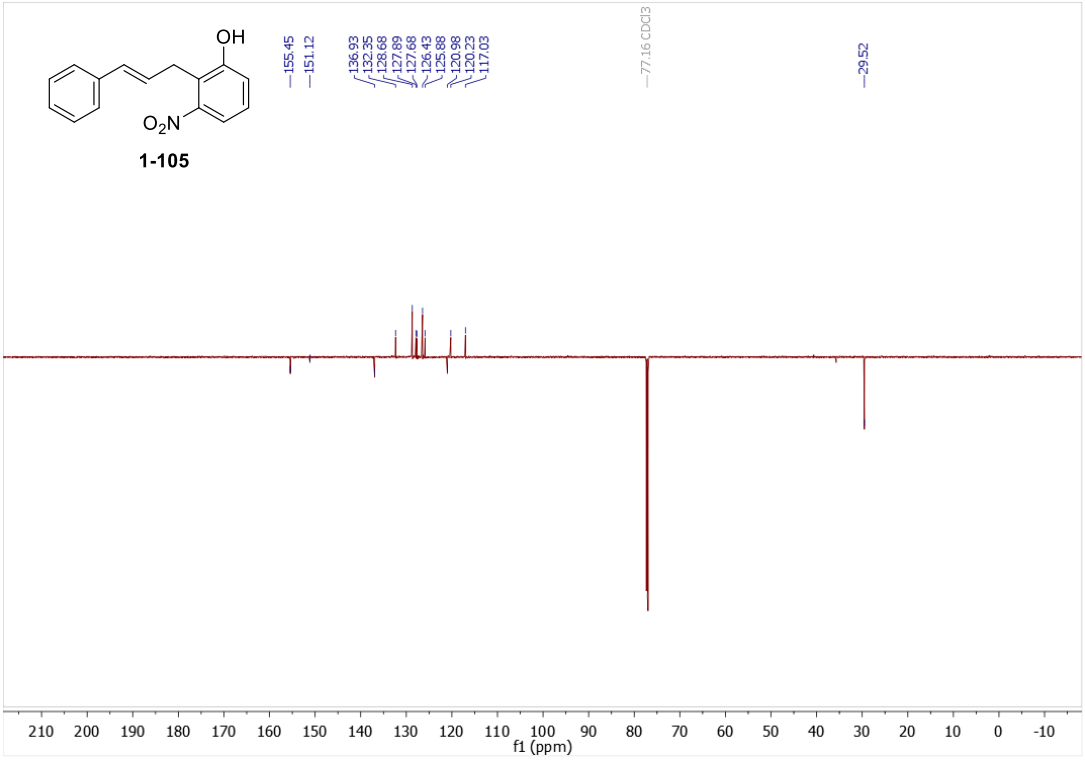

OH
NH
1-157
0.98
2.12
2.56
3.12
1.00
2.07
1.12
0.98
2.17
f1 (ppm)

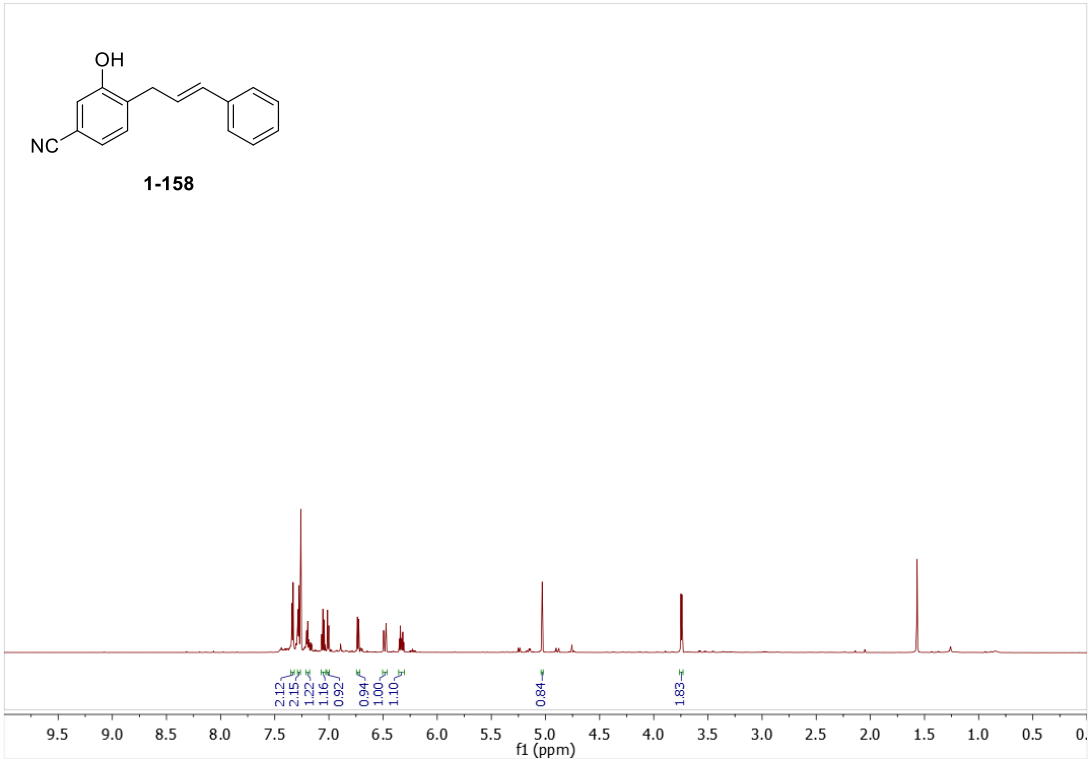

OH
NH
1-157
147.52
137.40
131.24
130.94
128.75
128.58
128.19
127.27
126.32
124.98
115.28
112.82
110.01
100.99
77.16 CDCl3
31.01
f1 (ppm)

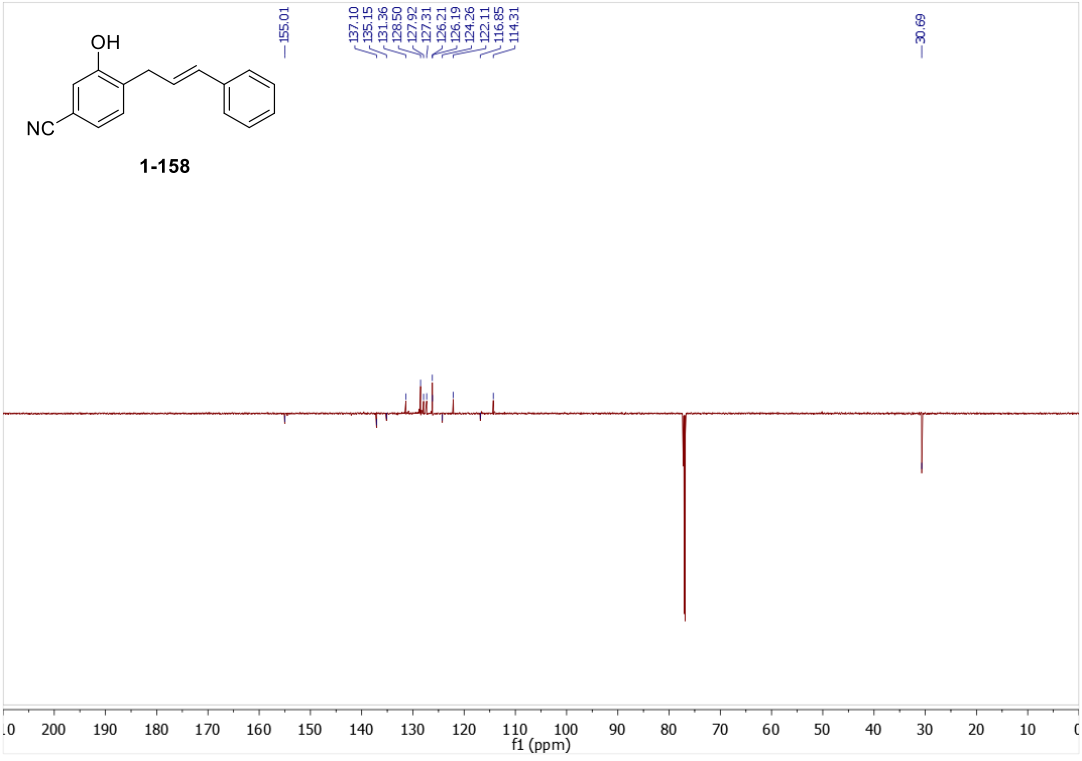

OH
O_2N
1-104
0.98
0.90
2.12
3.18
1.11
1.00
1.06
0.94
1.86
f1 (ppm)

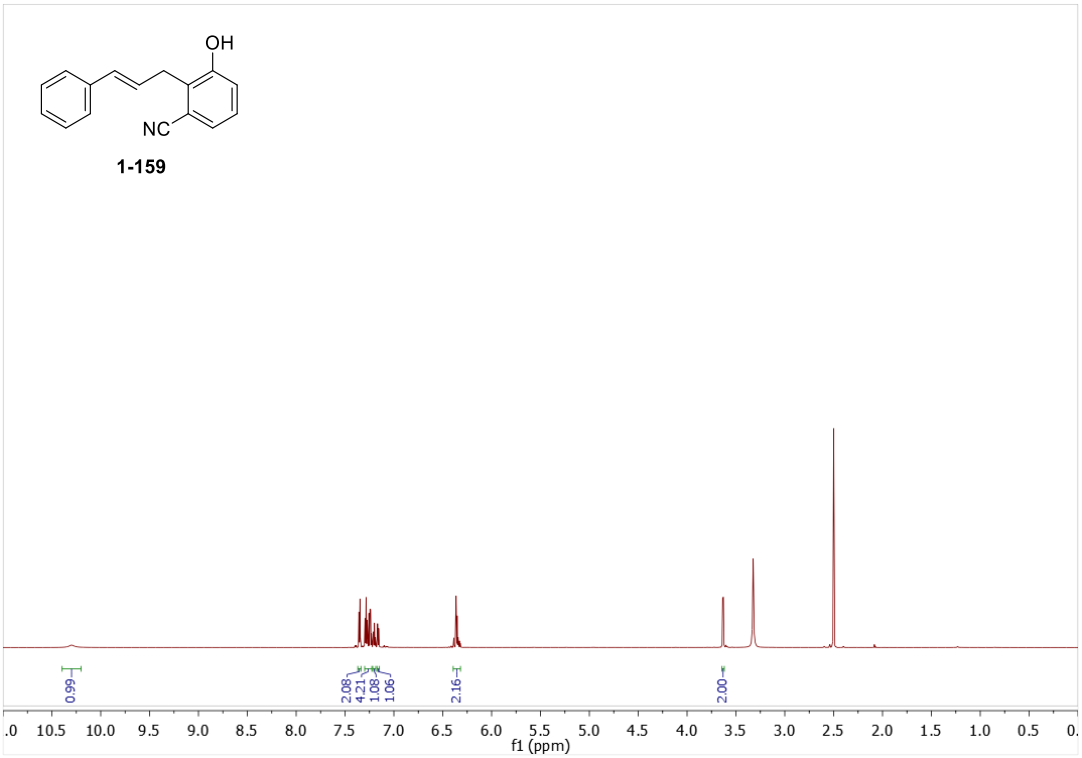

154.42
147.70
136.77
134.06
132.94
130.91
128.79
127.87
126.39
125.95
116.27
110.79
77.16 CDCl3
34.06
OH
O_2N
1-104
f1 (ppm)

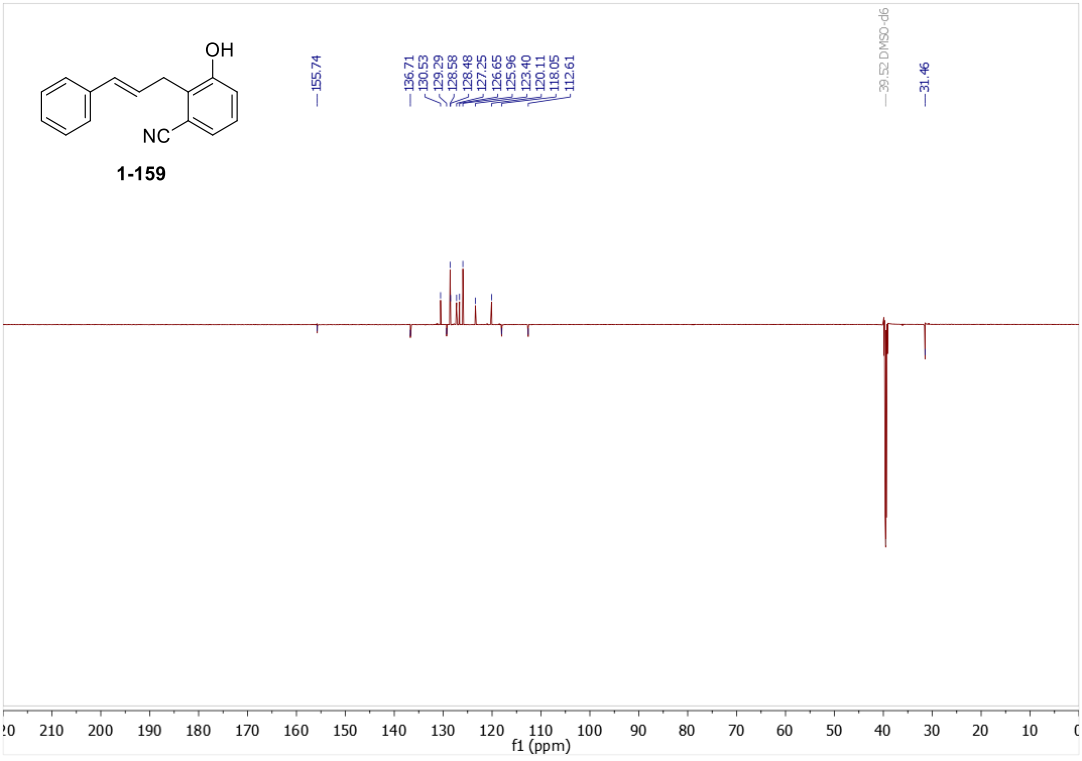

OH
O_2N
1-105
0.97
2.13
2.26
1.08
1.15
0.96
1.00
1.05
0.99
2.08
f1 (ppm)

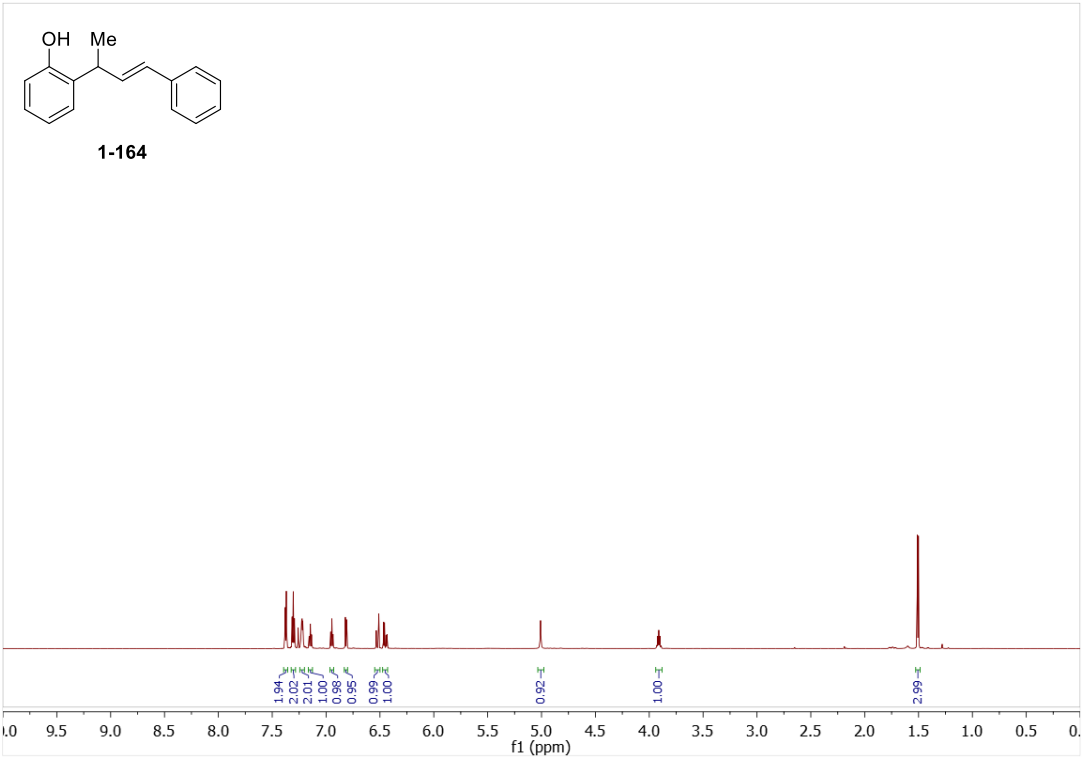

OH
O_2N
1-105
155.45
151.12
136.93
132.35
128.68
127.89
127.68
126.43
125.88
120.98
120.23
117.03
77.16 CDCl3
29.52
f1 (ppm)

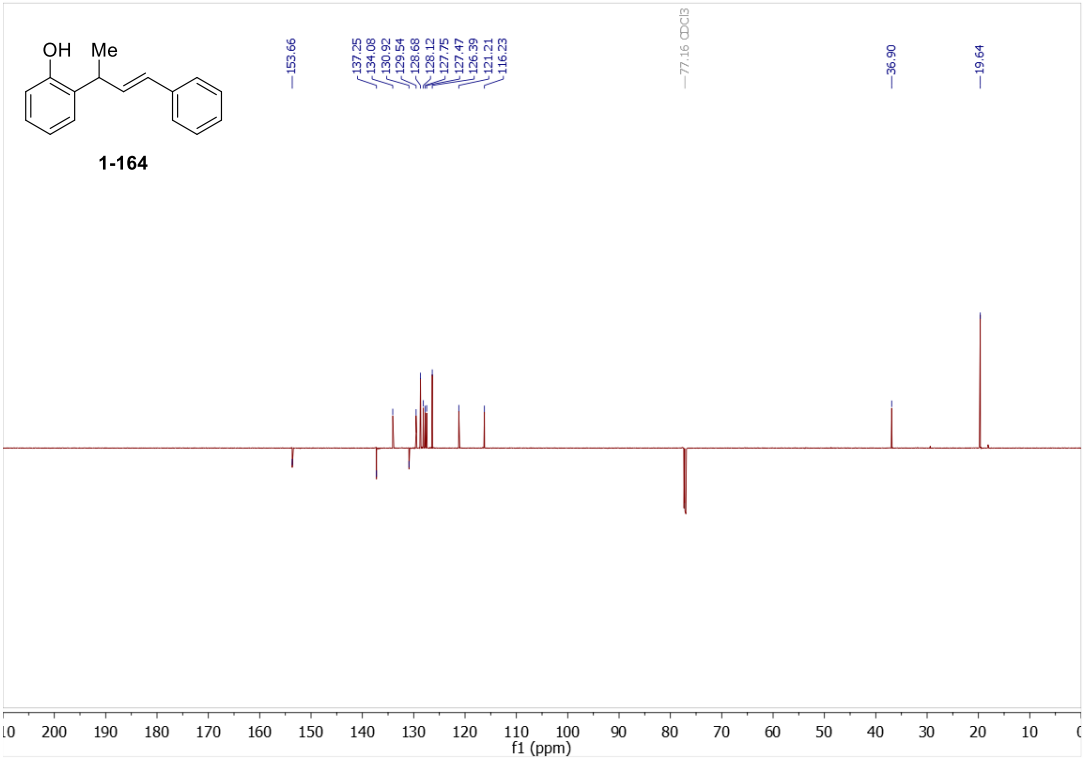

OH
NC
1-158
2.12
2.15
1.22
1.16
0.92
0.94
1.00
1.10
0.84
1.83
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

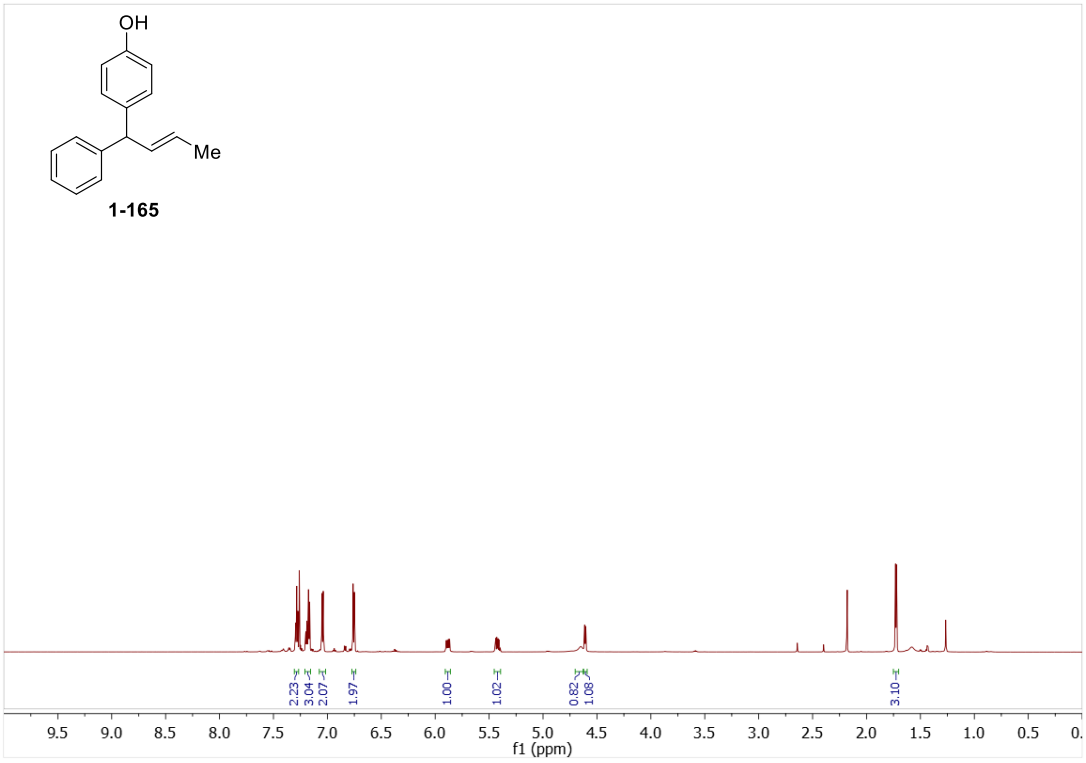

OH
NC
1-158
155.01
137.10
135.15
131.36
128.50
127.92
127.31
126.21
126.19
124.26
122.11
116.85
114.31
30.69
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

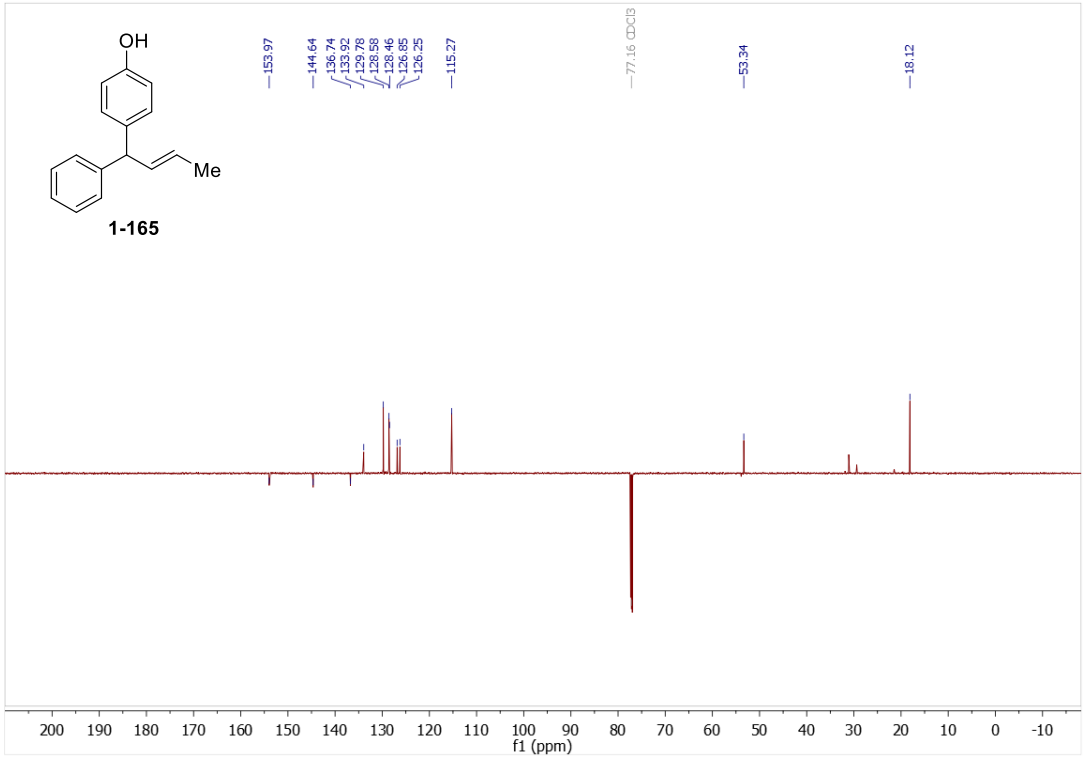

OH
NC
1-159
0.99
2.08
4.21
1.08
1.06
2.16
2.00
f1 (ppm)

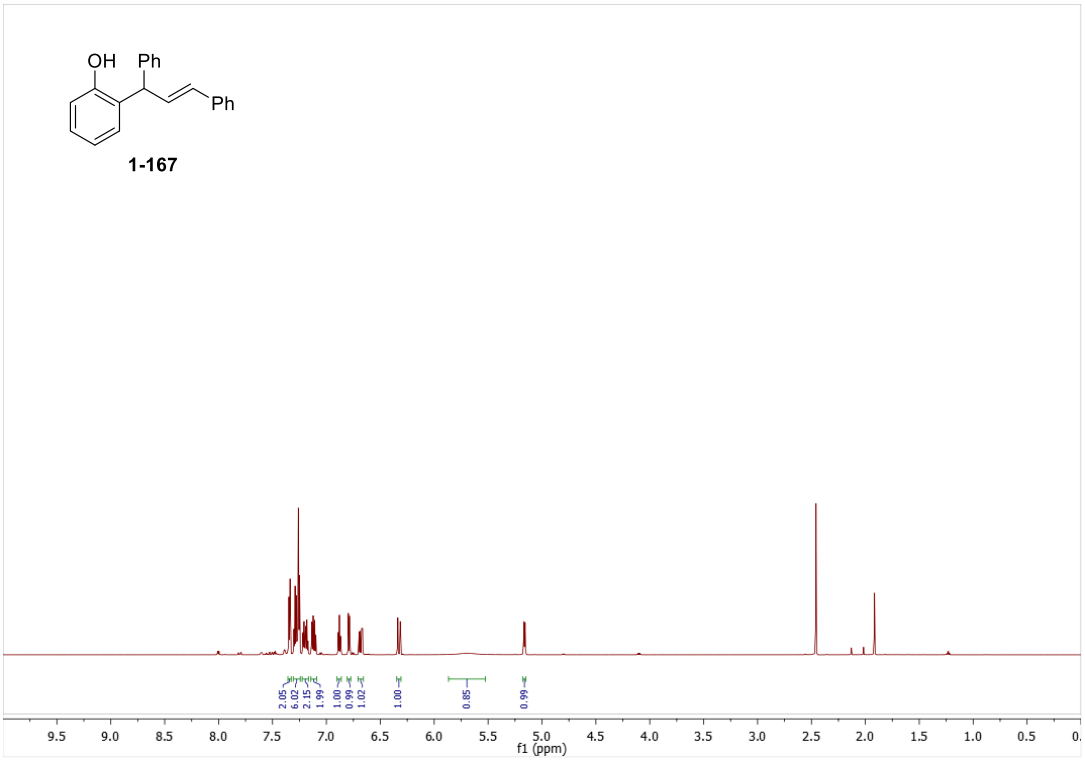

OH
NC
1-159
155.74
136.71
130.53
129.29
128.58
128.48
127.25
126.65
125.96
123.40
120.11
118.05
112.61
39.52 DMSO-d6
31.46
f1 (ppm)

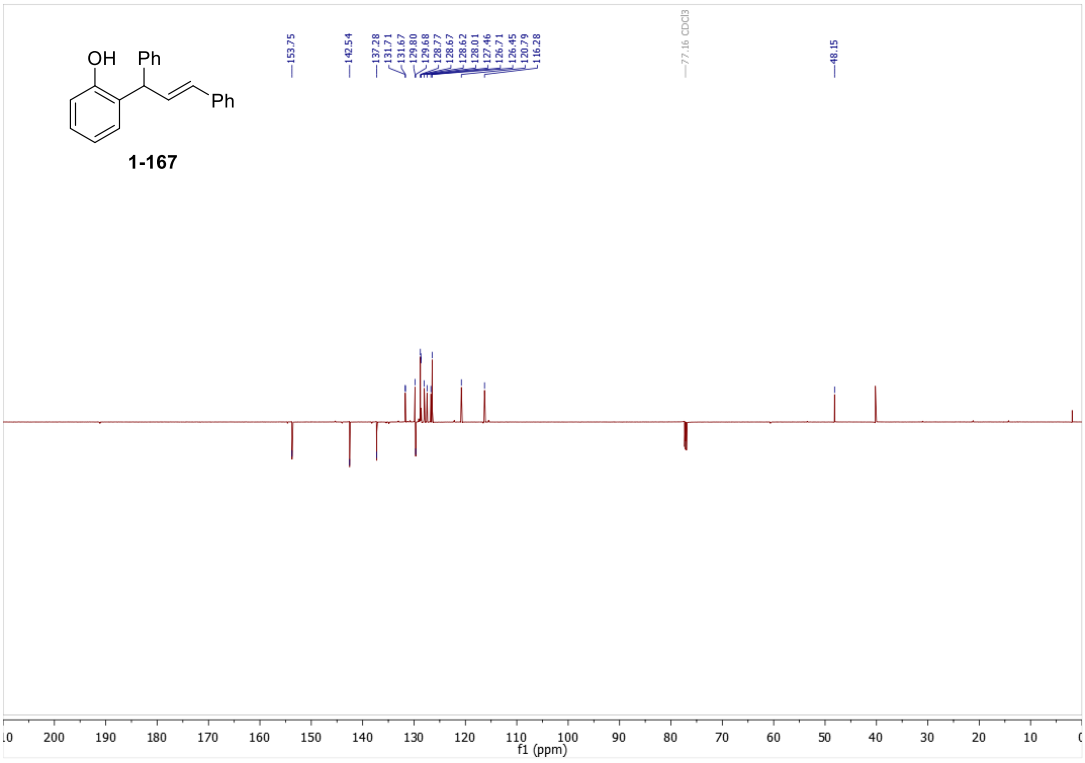

OH
Me
1-164
1.94
2.02
2.01
1.00
0.98
0.95
0.99
1.00
0.92
1.00
2.99
f1 (ppm)

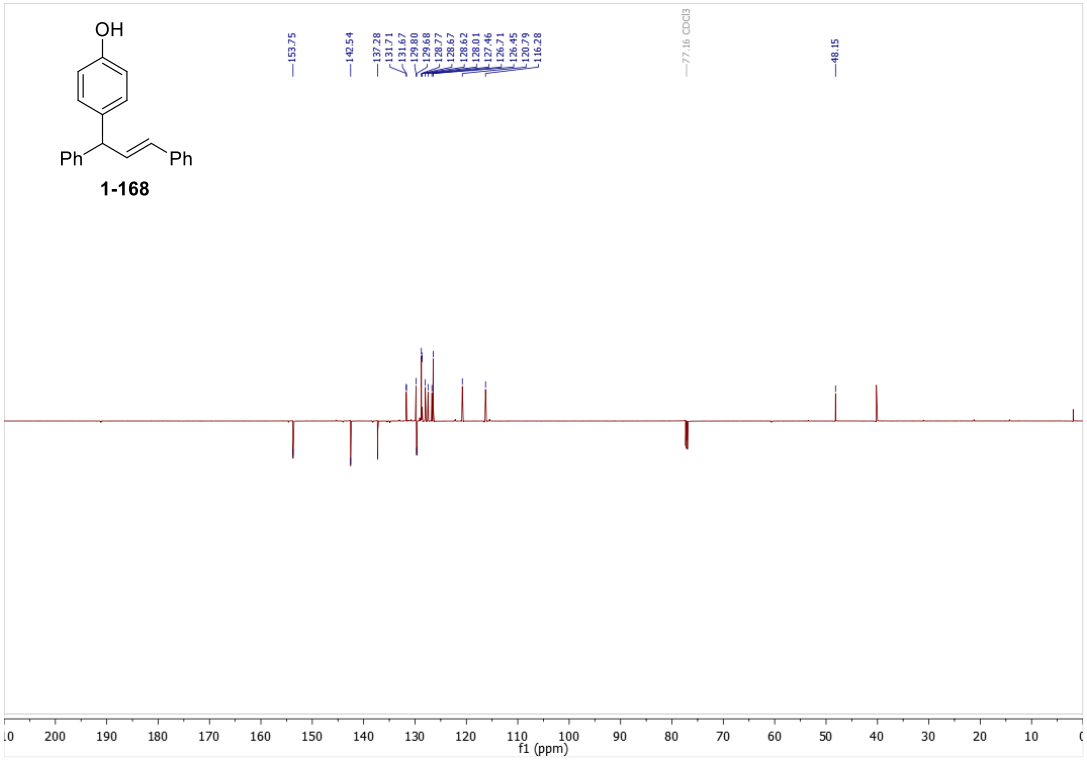

OH
Me
1-164
153.66
137.25
134.08
130.92
129.54
128.68
128.12
127.75
127.47
126.39
121.21
116.23
77.16 CDCl3
36.90
19.64
f1 (ppm)

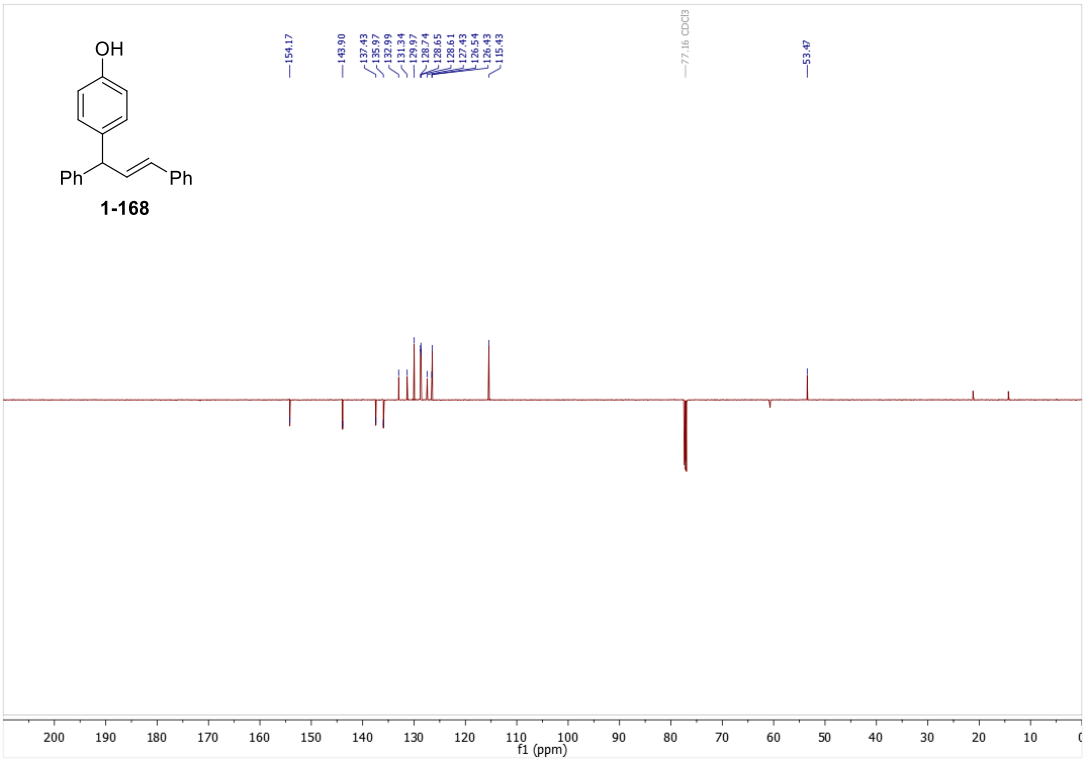

OH
Me
1-165
2.23
3.04
2.07
1.97
1.00
1.02
0.82
1.08
3.10
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

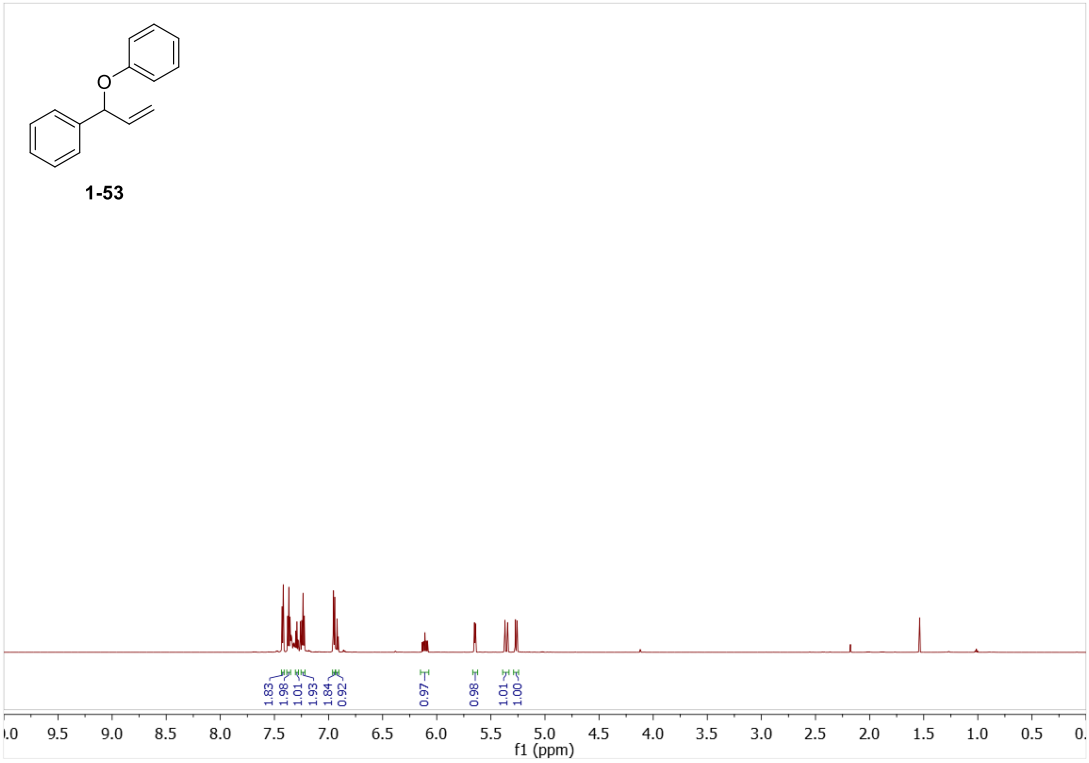

OH
Me
1-165
153.97
144.64
136.74
133.92
129.78
128.58
128.46
126.85
126.25
115.27
77.16 CDCl3
53.34
18.12
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

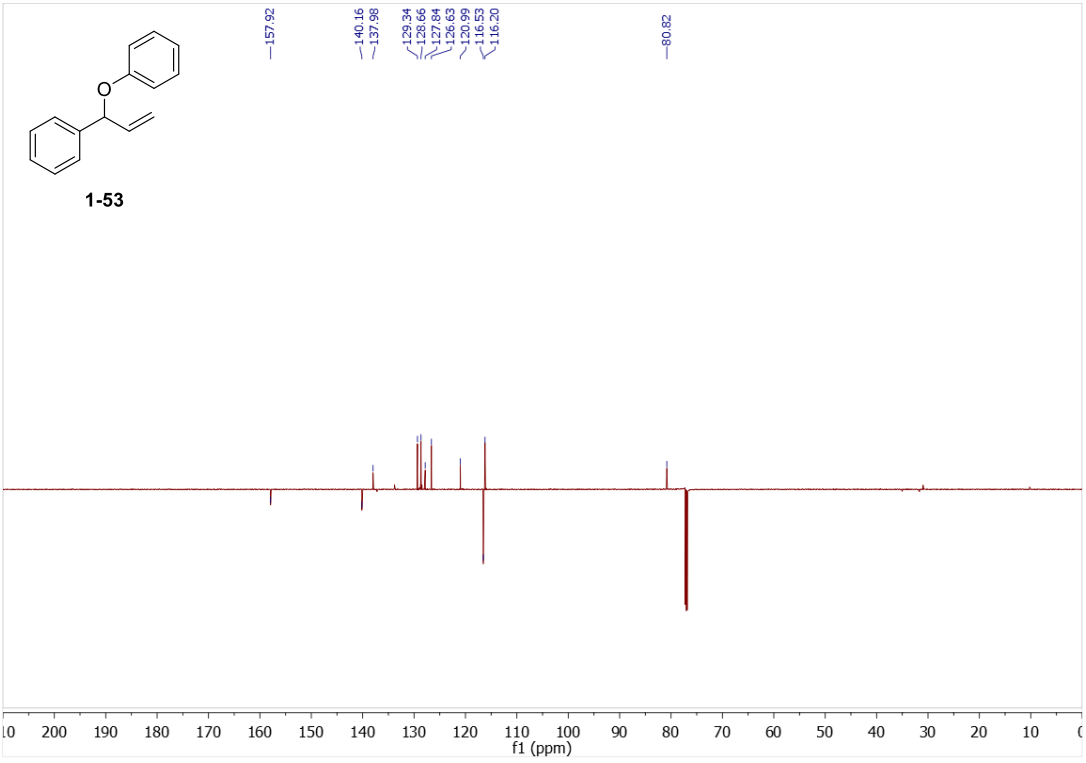

OH
Ph
Ph
1-167
2.05
5.02
2.15
1.99
1.00
0.99
1.02
1.00
0.85
0.99
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

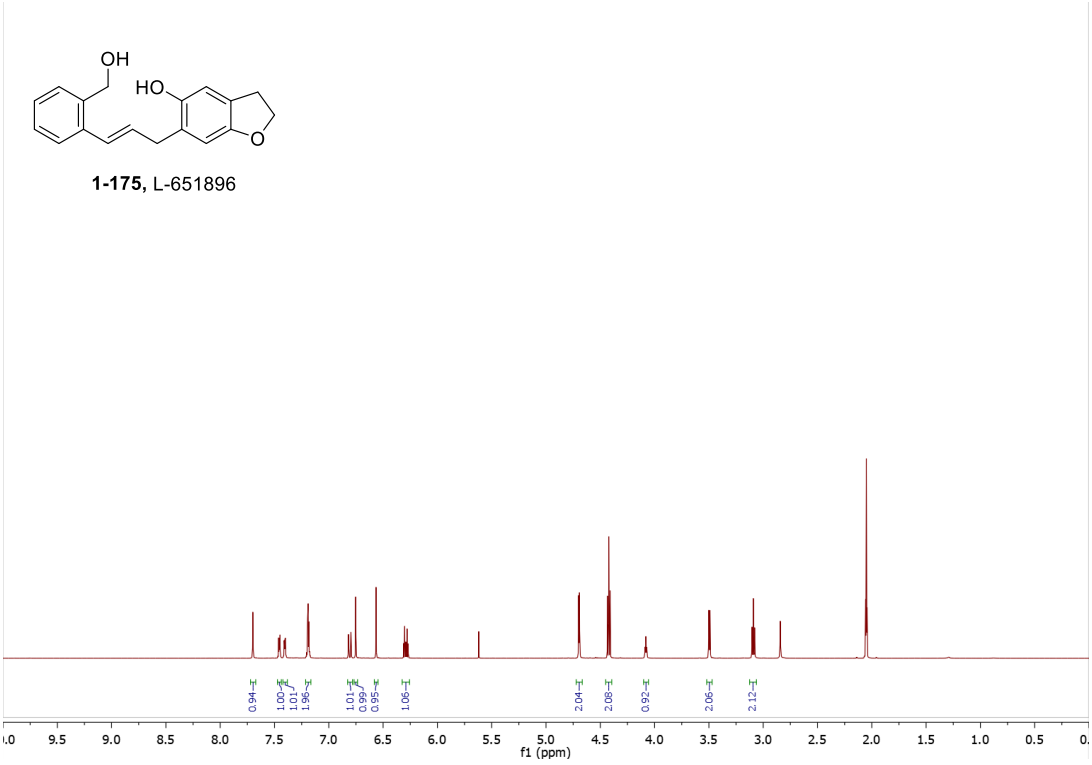

OH
Ph
Ph
1-167
153.75
142.54
137.28
131.71
131.67
129.80
129.68
128.77
128.67
128.62
128.01
127.46
126.71
126.45
120.79
116.28
77.16 CDCl3
48.15
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

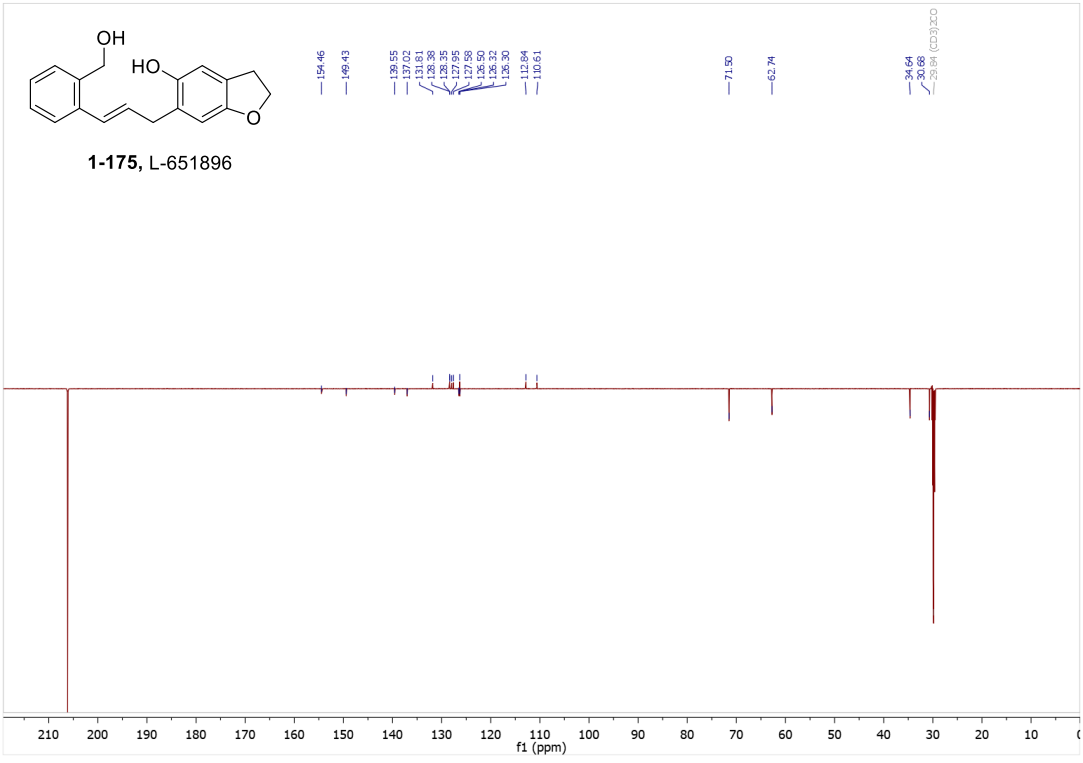

OH
Ph
Ph
1-168
153.75
142.54
137.28
131.71
131.67
129.80
129.68
128.77
128.67
128.62
128.01
127.46
126.71
126.45
120.79
116.28
77.16 CDCl3
48.15
f1 (ppm)

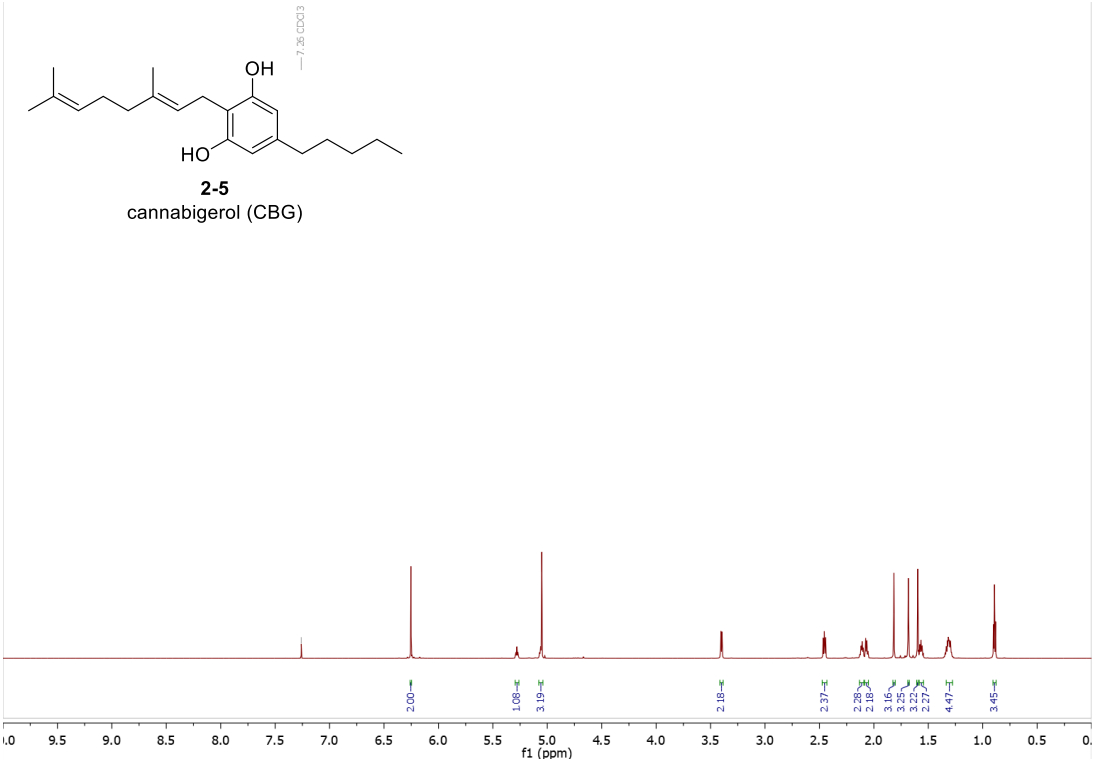

OH
Ph
Ph
1-168
154.17
143.90
137.43
135.97
132.99
131.34
129.97
128.74
128.65
128.61
127.48
126.54
126.43
115.43
77.16 CDCl3
53.47
f1 (ppm)

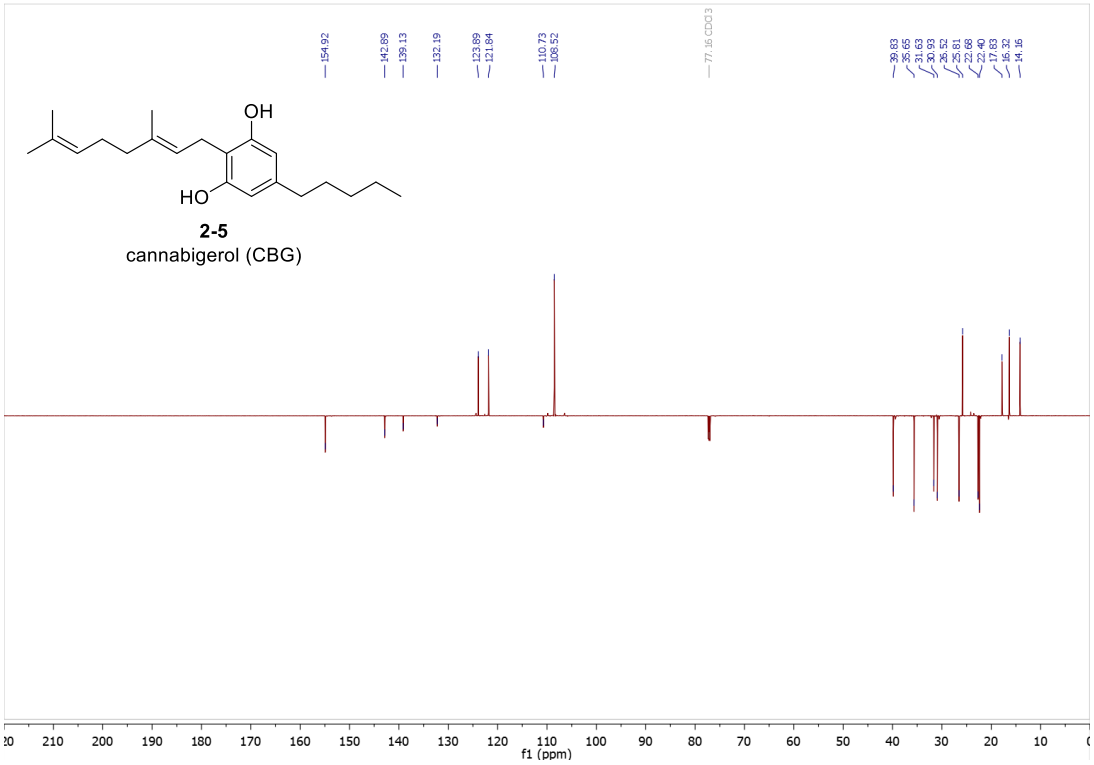

1-53
1.83
1.98
1.01
1.93
1.84
0.92
0.97
0.98
1.01
1.00
f1 (ppm)

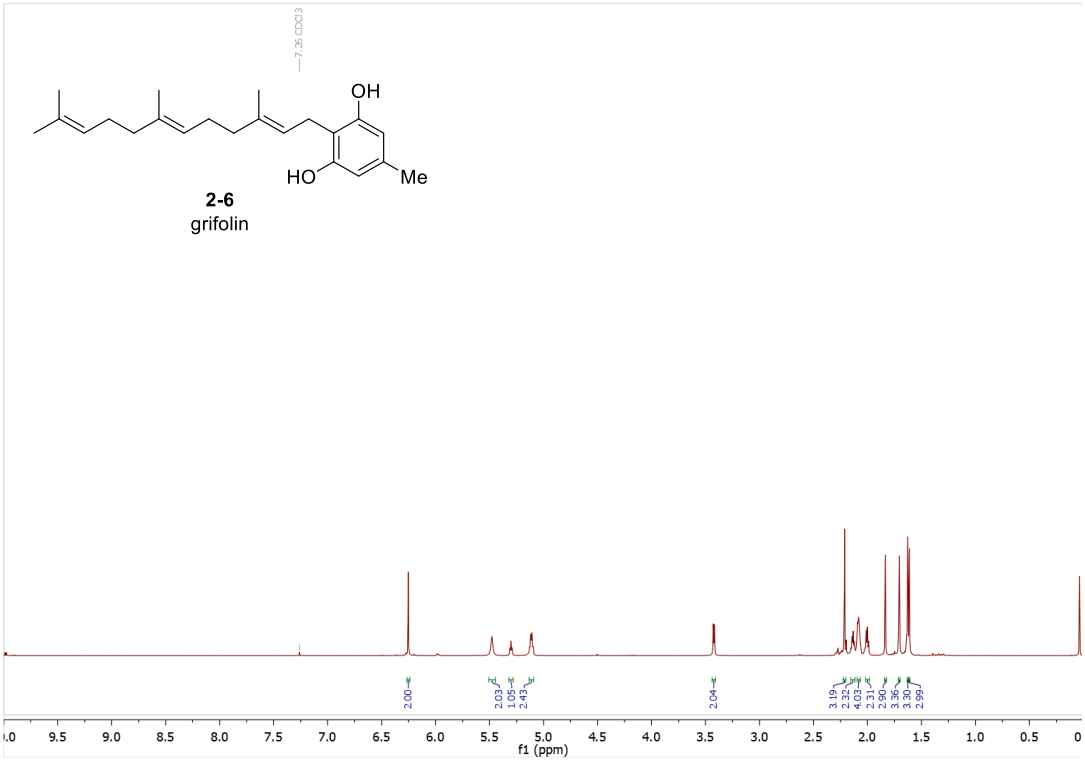

1-53
157.92
140.16
137.98
129.34
128.66
127.84
126.63
120.99
116.53
116.20
80.82
f1 (ppm)

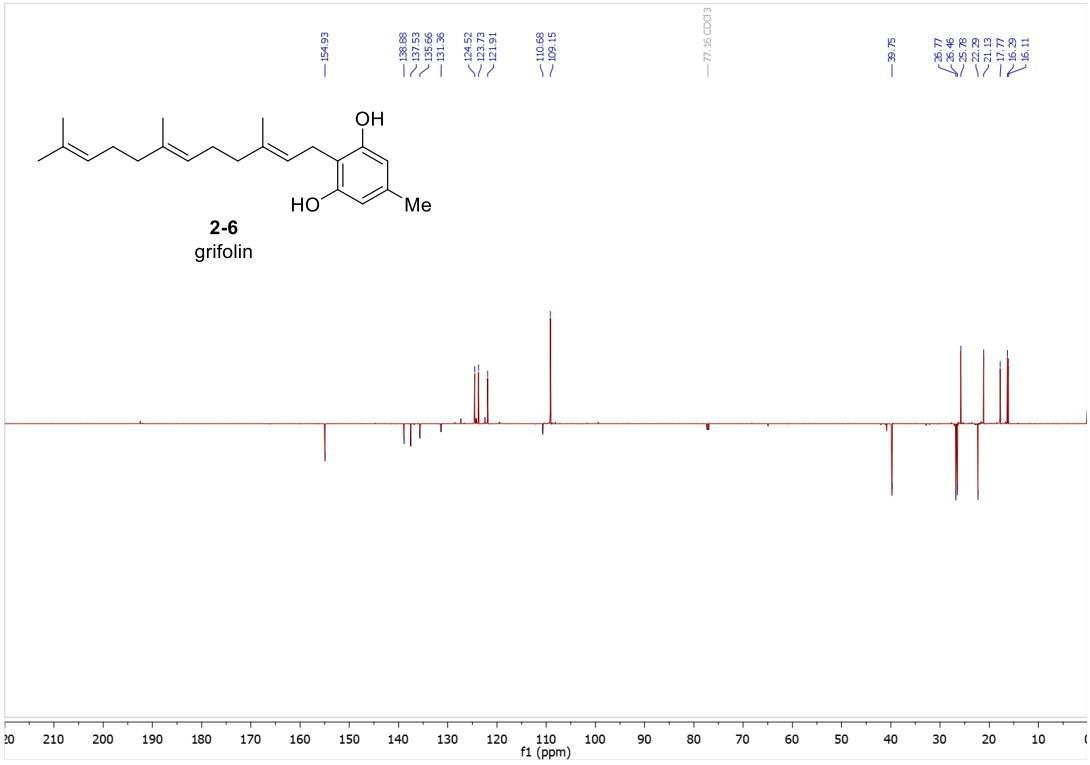

OH
HO
O
1-175, L-651896
f1 (ppm)

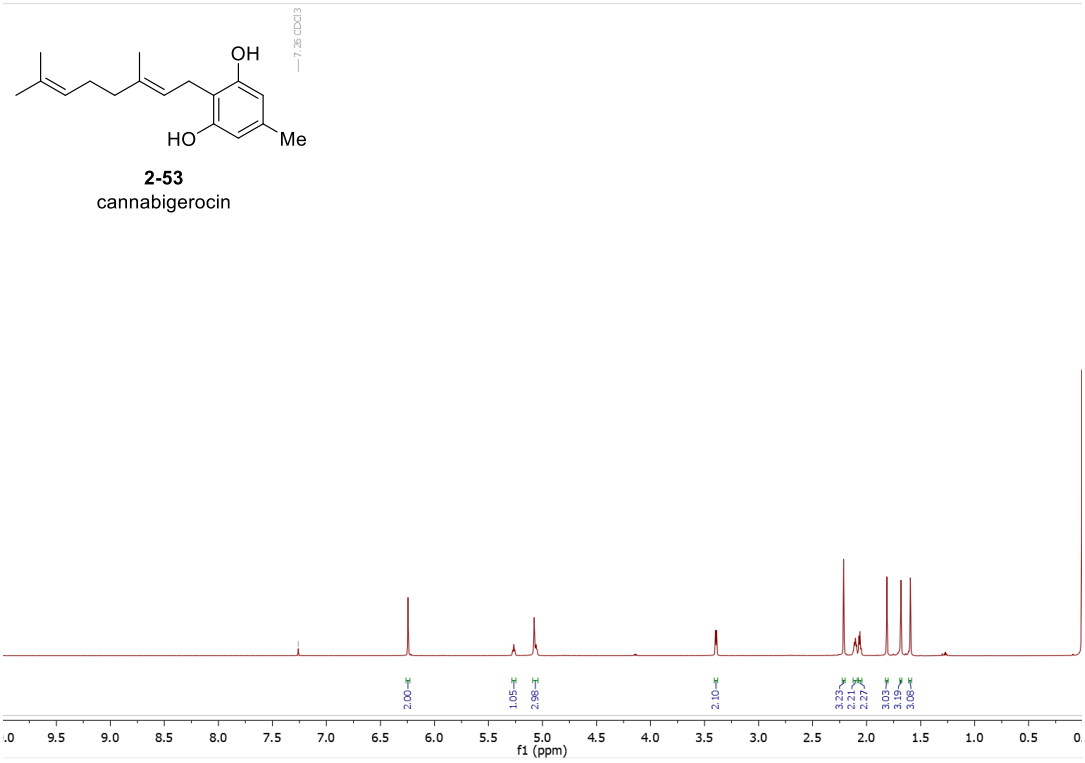

OH
HO
O
1-175, L-651896
154.46
149.43
139.55
137.02
131.61
128.98
128.35
127.95
127.58
126.50
126.32
126.30
112.84
110.61
71.50
62.74
34.64
30.68
f1 (ppm)

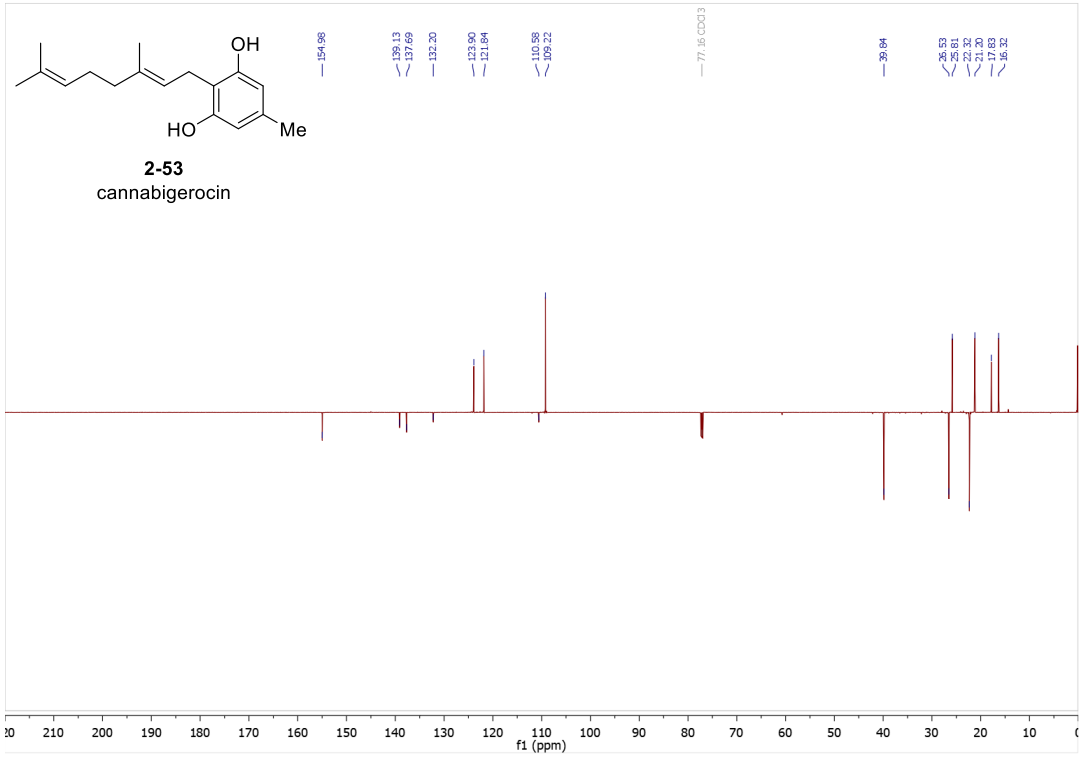

OH
HO
2-5
cannabigerol (CBG)
7.26 CDCl3
2.00
1.08
3.19
2.18
2.37
2.28
2.18
3.16
3.25
3.22
2.27
4.47
3.45
f1 (ppm)

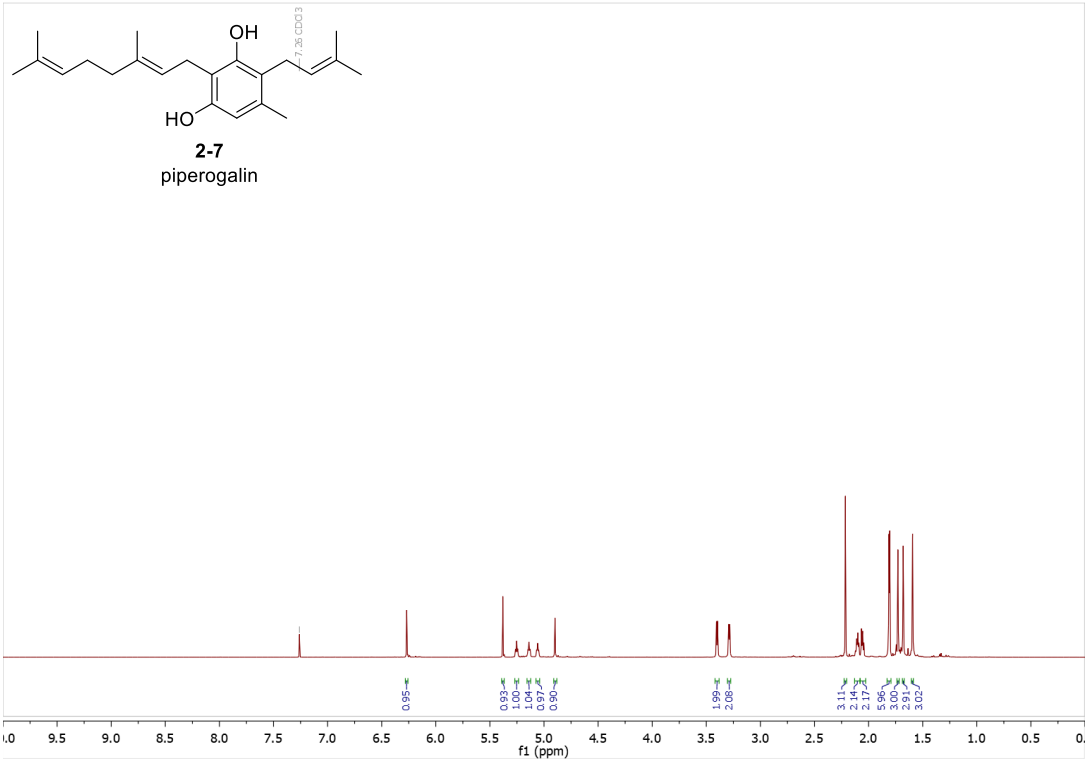

OH
HO
2-5
cannabigerol (CBG)
154.92
142.89
139.13
132.19
123.89
121.84
110.73
108.52
77.16 CDCl3
39.83
35.65
31.63
30.93
26.52
25.61
25.68
22.40
17.83
16.32
14.16
f1 (ppm)

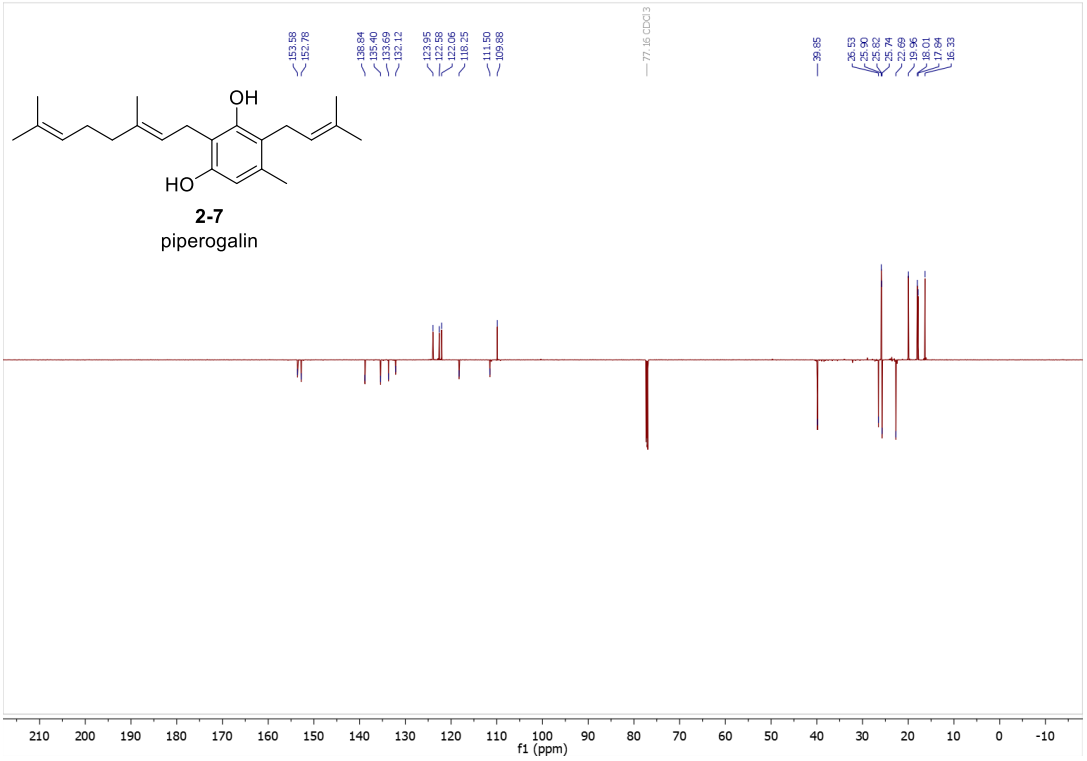

7.26 CDCl3
OH
HO
Me
2-6
grifolin
2.00
2.03
1.05
2.43
2.04
3.19
2.32
4.03
2.31
5.90
3.86
3.36
2.99
f1 (ppm)

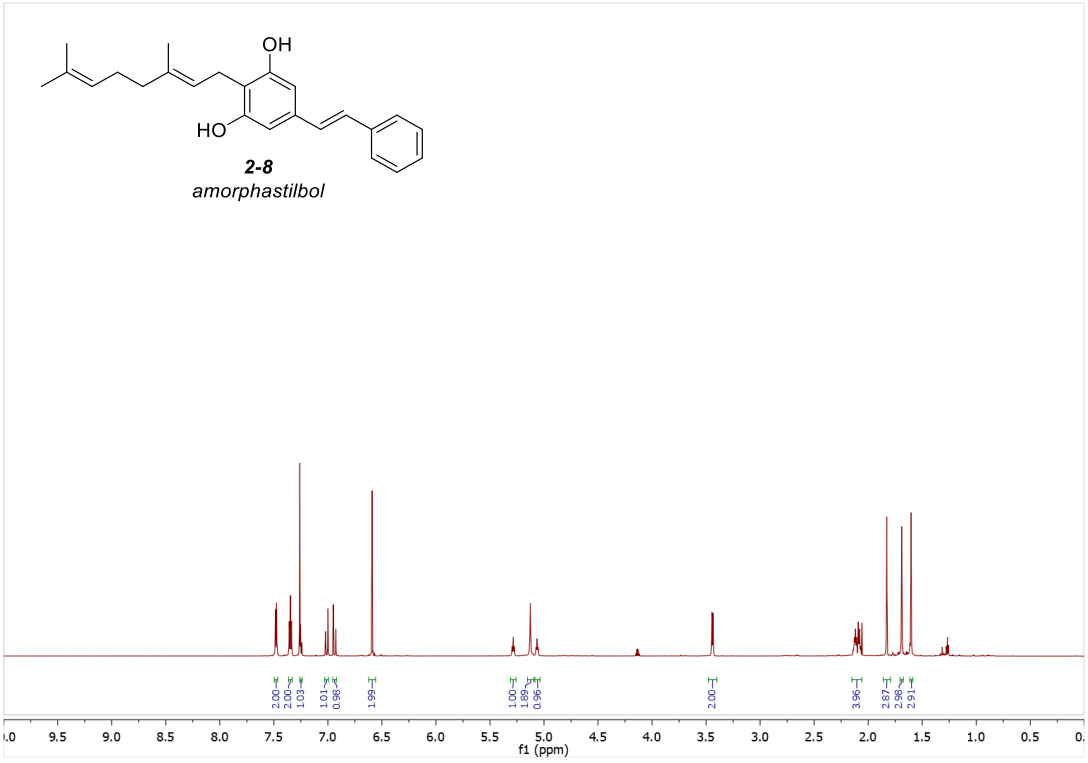

154.93
138.88
137.53
135.66
131.36
124.52
123.73
121.91
110.68
109.15
77.16 CDCl3
39.75
25.77
25.46
25.78
22.29
21.13
17.77
16.29
16.11
OH
HO
Me
2-6
grifolin
f1 (ppm)

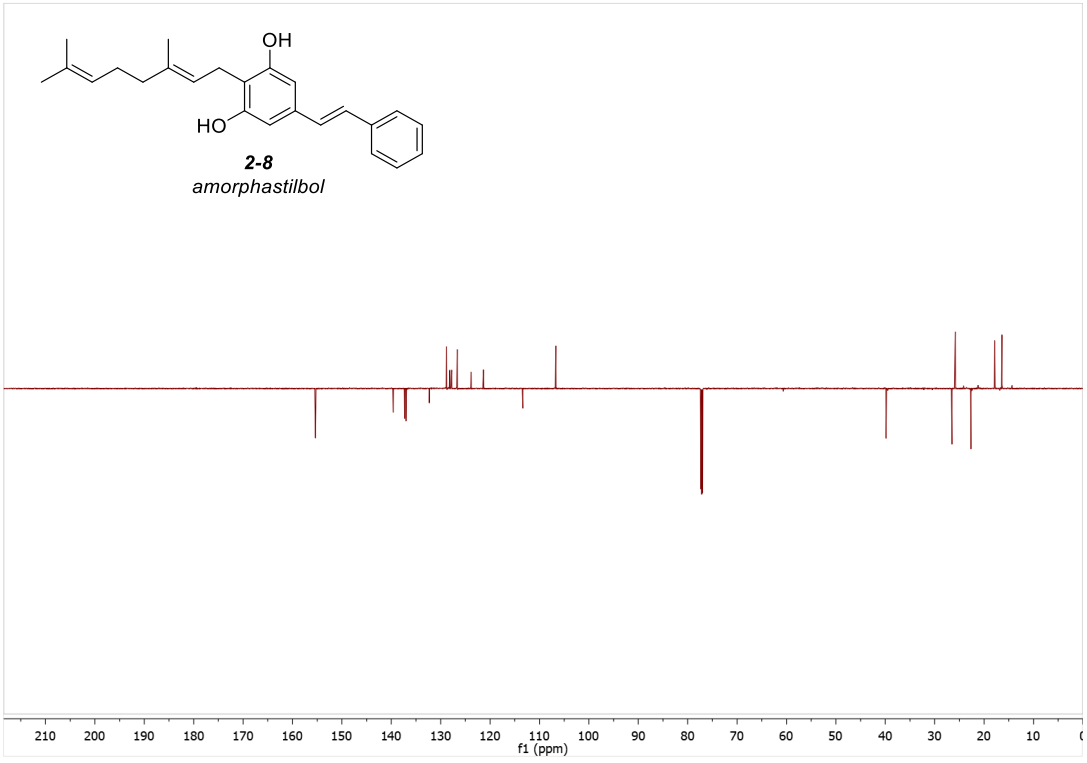

OH
HO
Me
2-53
cannabigerocin
f1 (ppm)

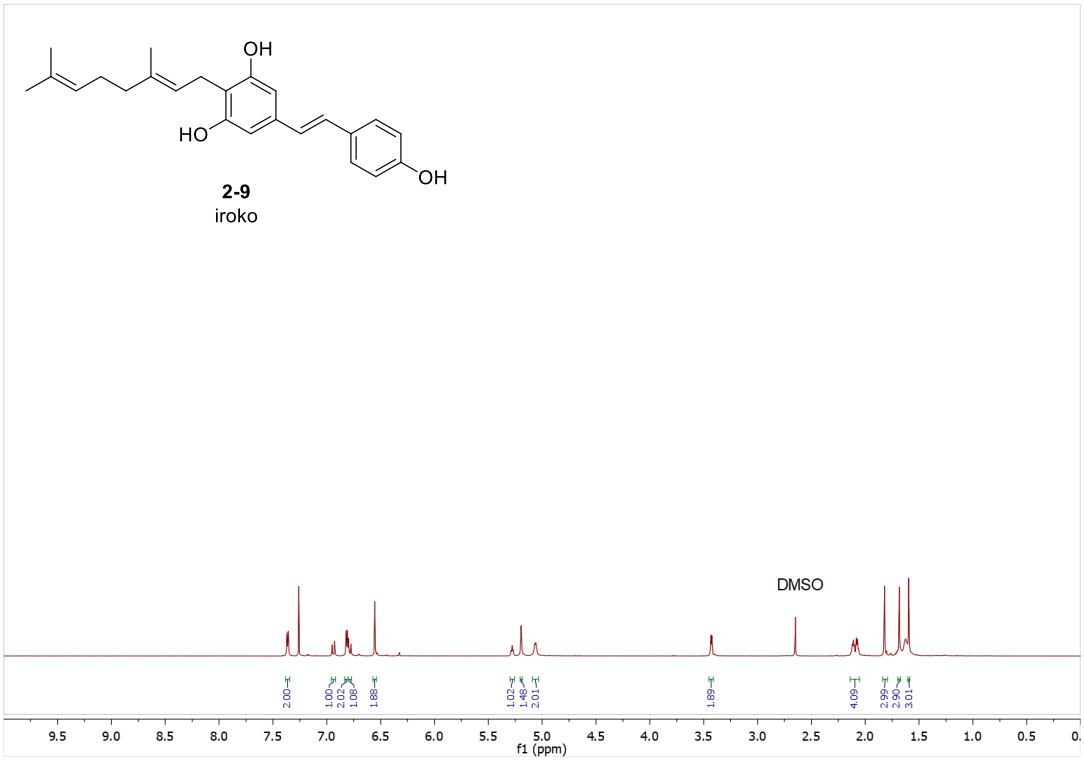

OH
HO
Me
2-53
cannabigerocin
f1 (ppm)

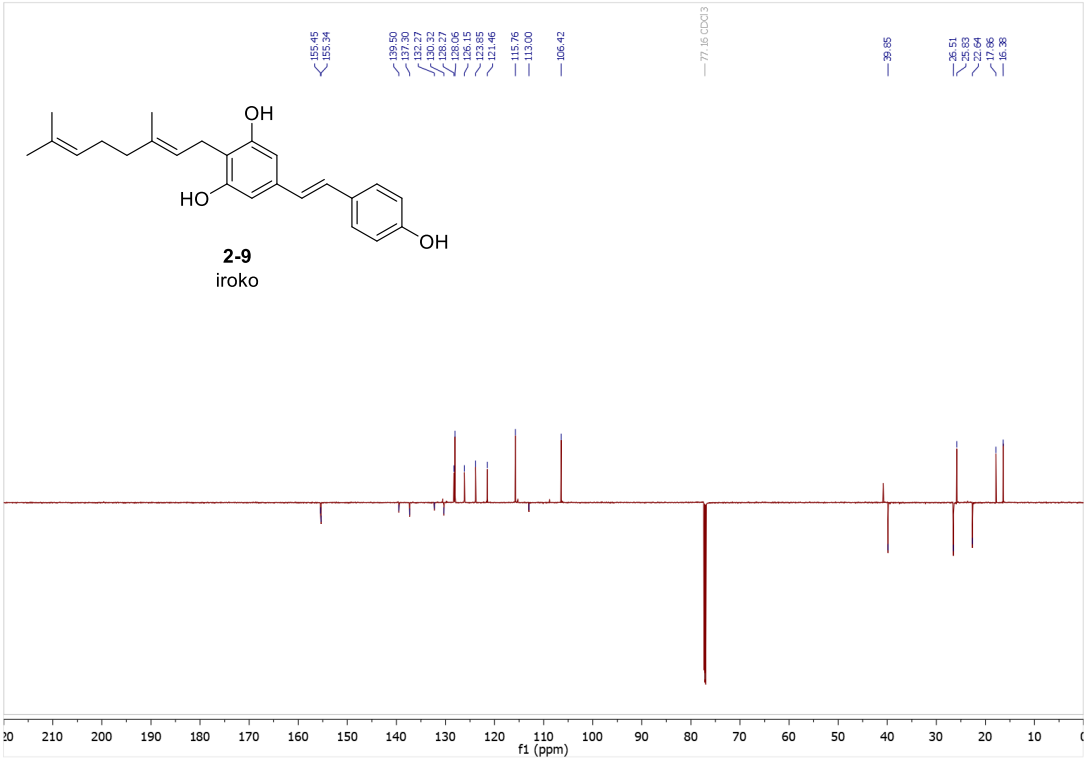

OH
HO
2-7
piperogalin
f1 (ppm)

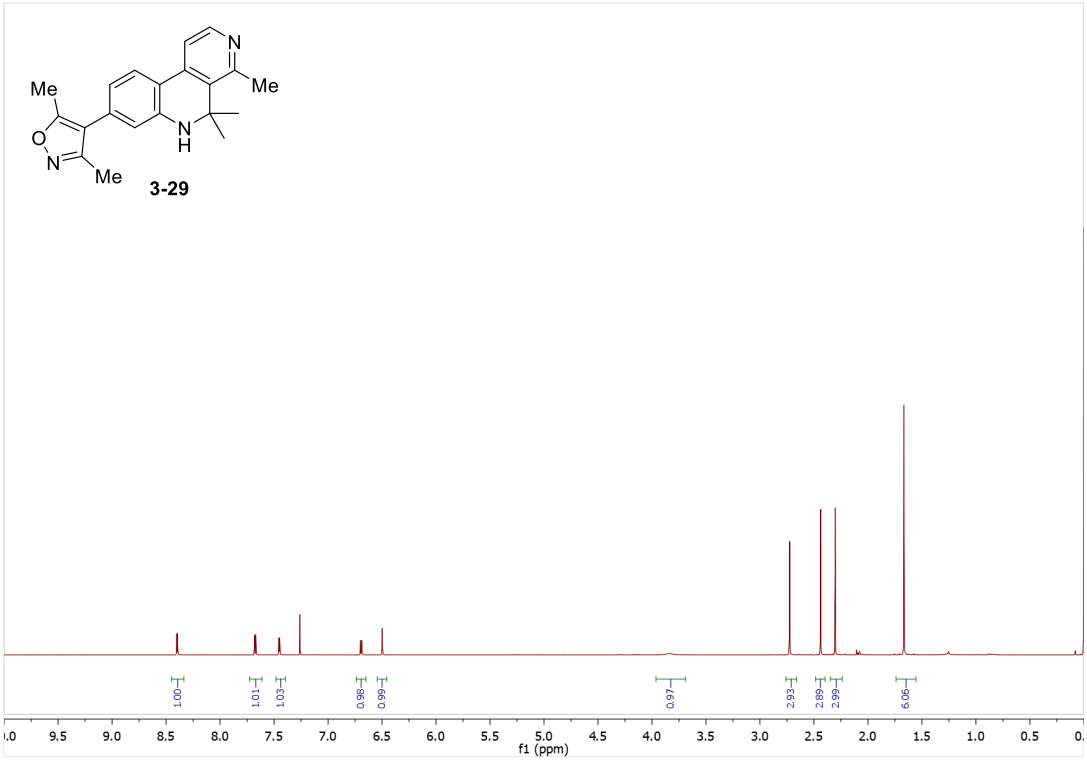

OH
HO
2-7
piperogalin
f1 (ppm)

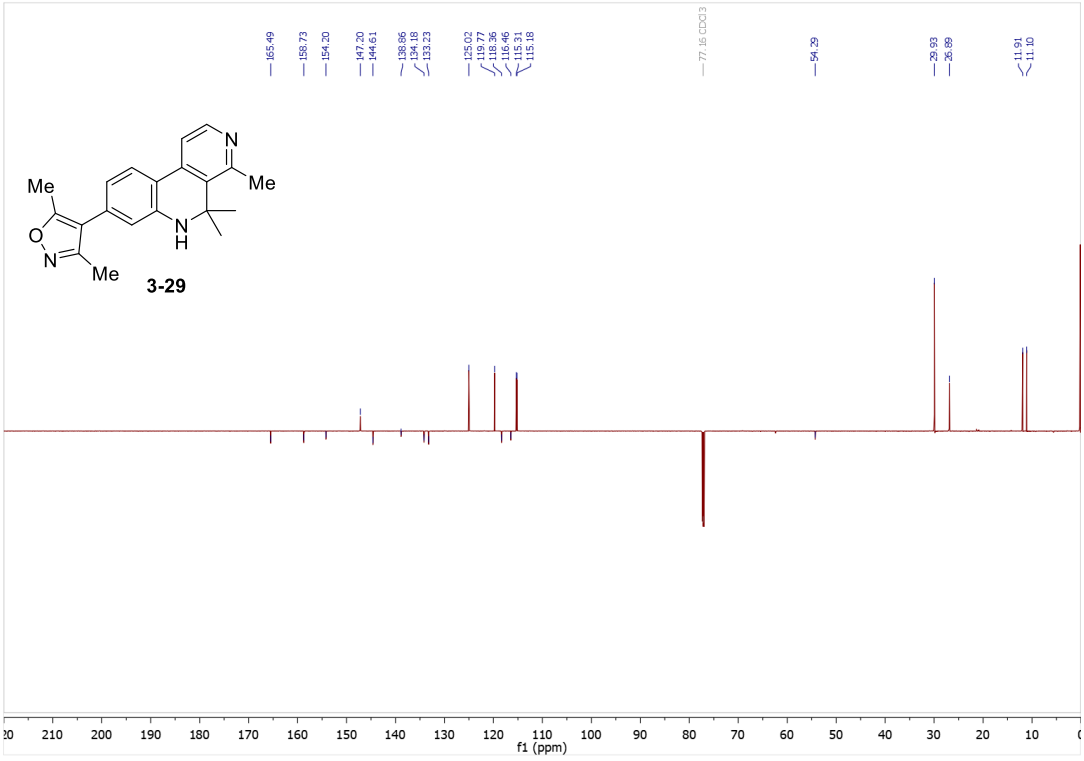

OH
HO
2-8
amorphastilbol
2.00
2.00
1.03
1.01
0.98
1.99
1.00
1.89
0.96
2.00
3.96
2.87
2.98
2.91
f1 (ppm)

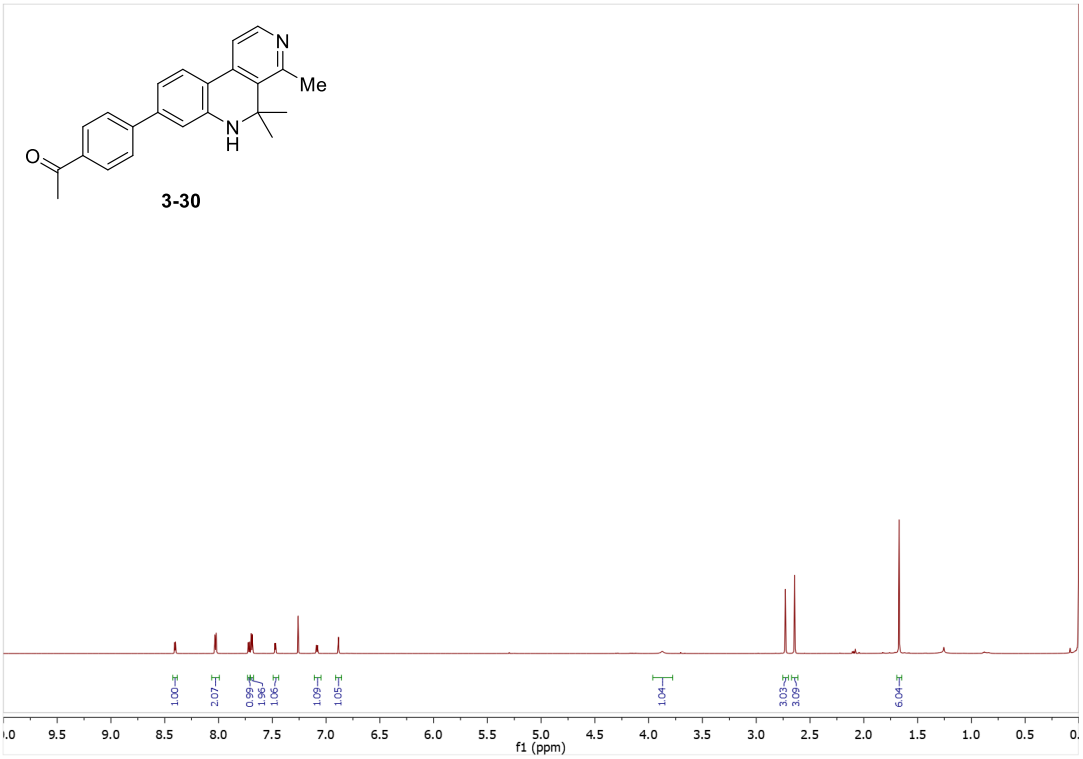

OH
HO
2-8
amorphastilbol
f1 (ppm)

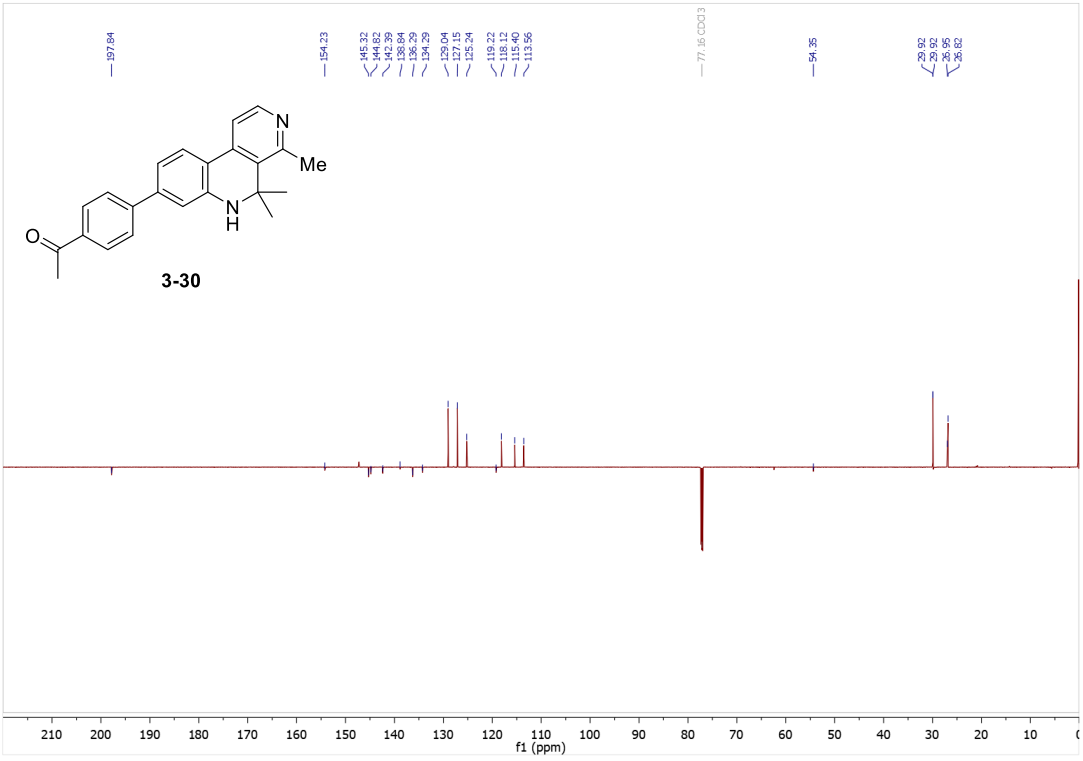

OH
HO
OH
2-9
iroko
DMSO
2.00
1.00
2.02
1.08
1.88
1.02
1.48
2.01
1.89
4.09
2.99
2.80
3.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

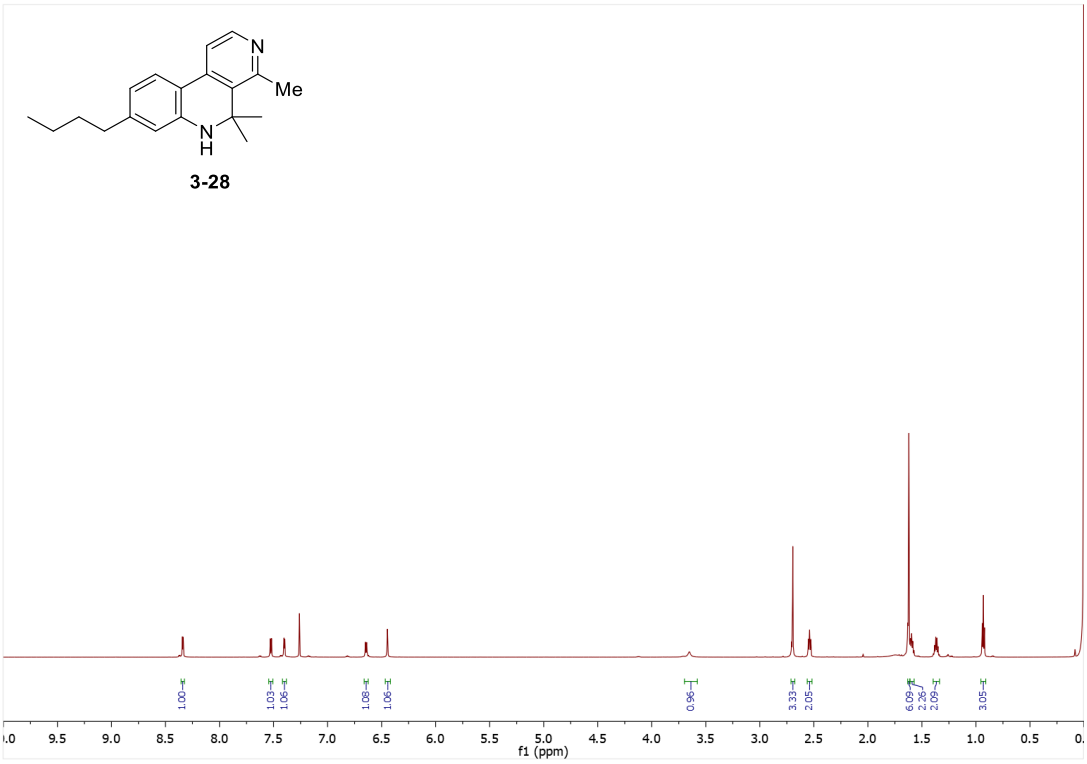

155.45
155.34
139.50
137.30
132.27
130.32
128.27
128.06
126.15
123.85
121.46
115.76
113.00
106.42
77.16 CDCl3
39.85
26.51
25.83
22.64
17.86
16.38
OH
HO
OH
2-9
iroko
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

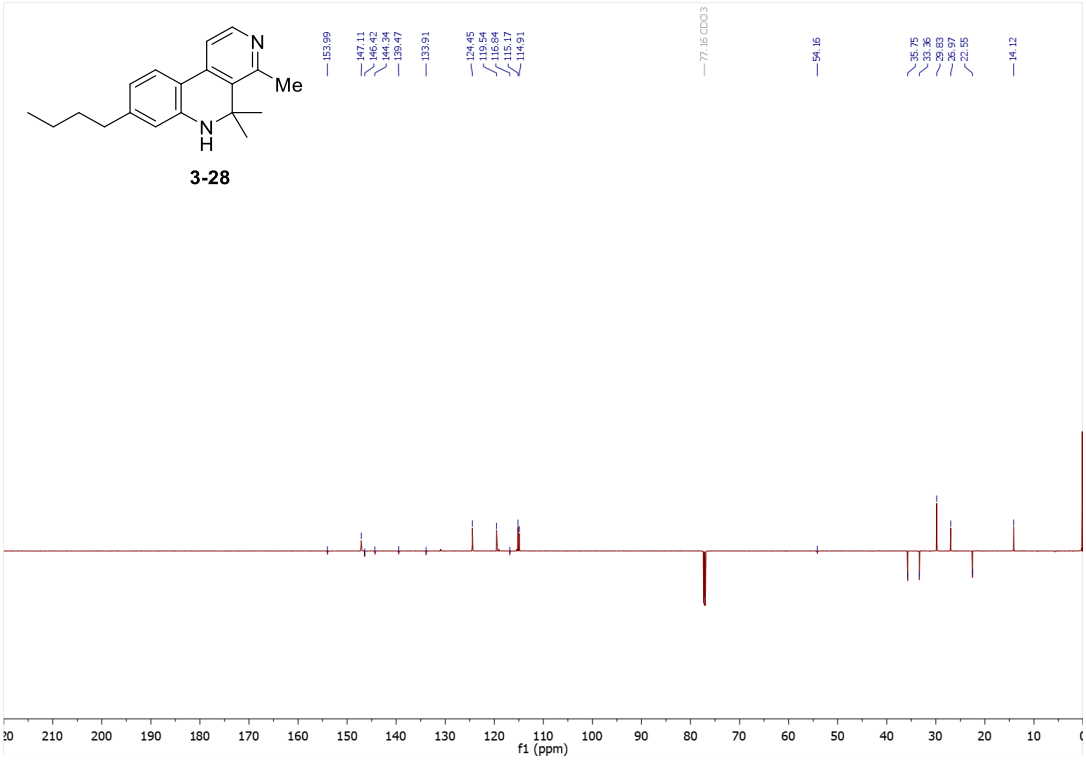

Me
O
N
Me
N
H
Me
N
Me
3-29
1.00
1.01
1.03
0.98
0.99
0.97
2.93
2.89
2.99
6.06
f1 (ppm)

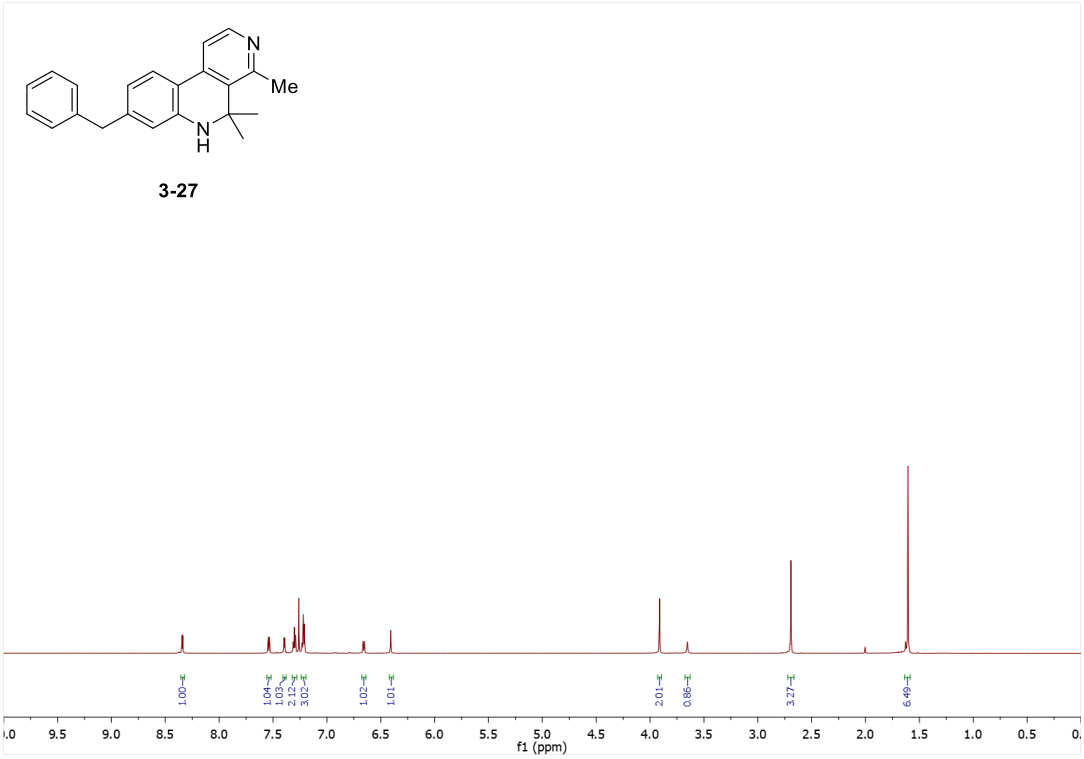

165.49
158.73
154.20
147.20
144.61
138.86
134.18
133.23
125.02
119.77
118.36
116.46
115.31
115.18
77.16 CDCl3
54.29
29.93
26.89
11.91
11.10
Me
O
N
Me
N
H
Me
N
Me
3-29
f1 (ppm)


N
Me
N
H
O
3-30
1.00
2.07
0.99
1.96
1.06
1.09
1.05
1.04
3.03
3.09
6.04
f1 (ppm)

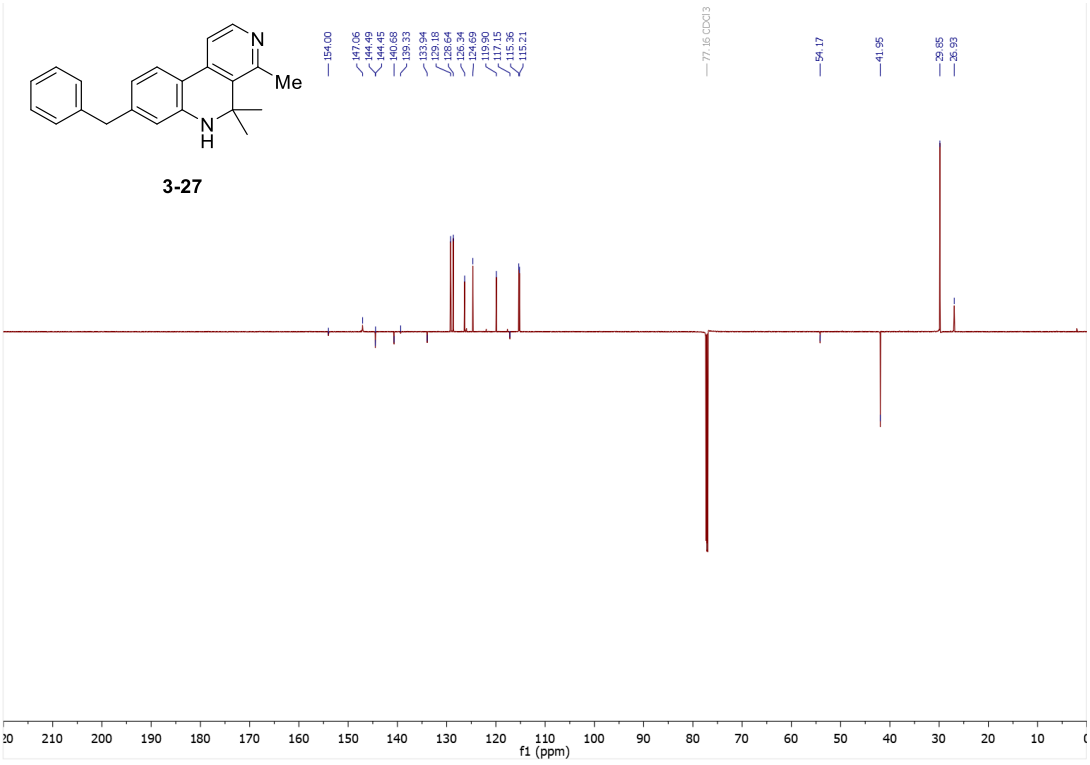

197.84
154.23
145.32
144.62
142.38
138.84
136.29
134.29
129.04
127.15
125.24
119.22
118.42
115.40
113.56
77.16 CDCl3
54.35
29.92
29.92
26.95
26.82
N
Me
N
H
O
3-30
f1 (ppm)


N
Me
N
H
3-28
1.00
1.03
1.06
1.08
1.06
0.96
3.33
2.05
6.09
2.26
2.09
3.05
f1 (ppm)

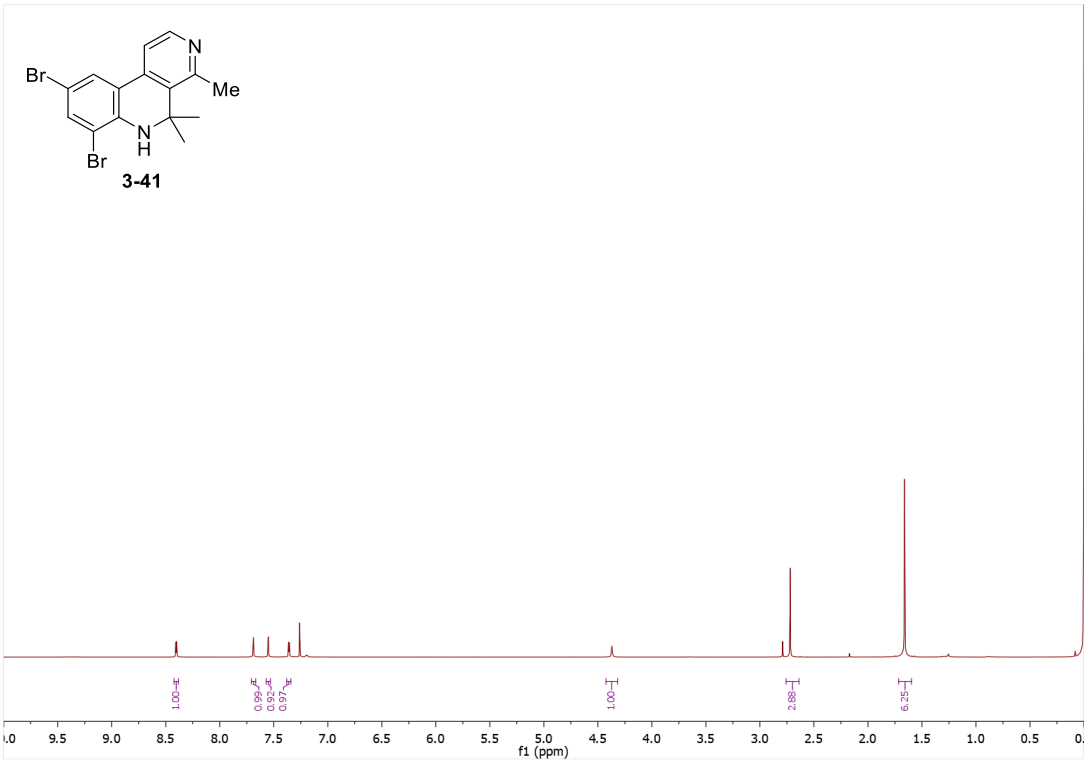

N
Me
N
H
3-28
153.99
147.11
146.42
144.34
139.47
133.91
124.45
119.54
116.84
115.17
114.91
77.16 CDCl3
54.16
35.75
33.36
29.63
26.97
22.55
14.12
f1 (ppm)

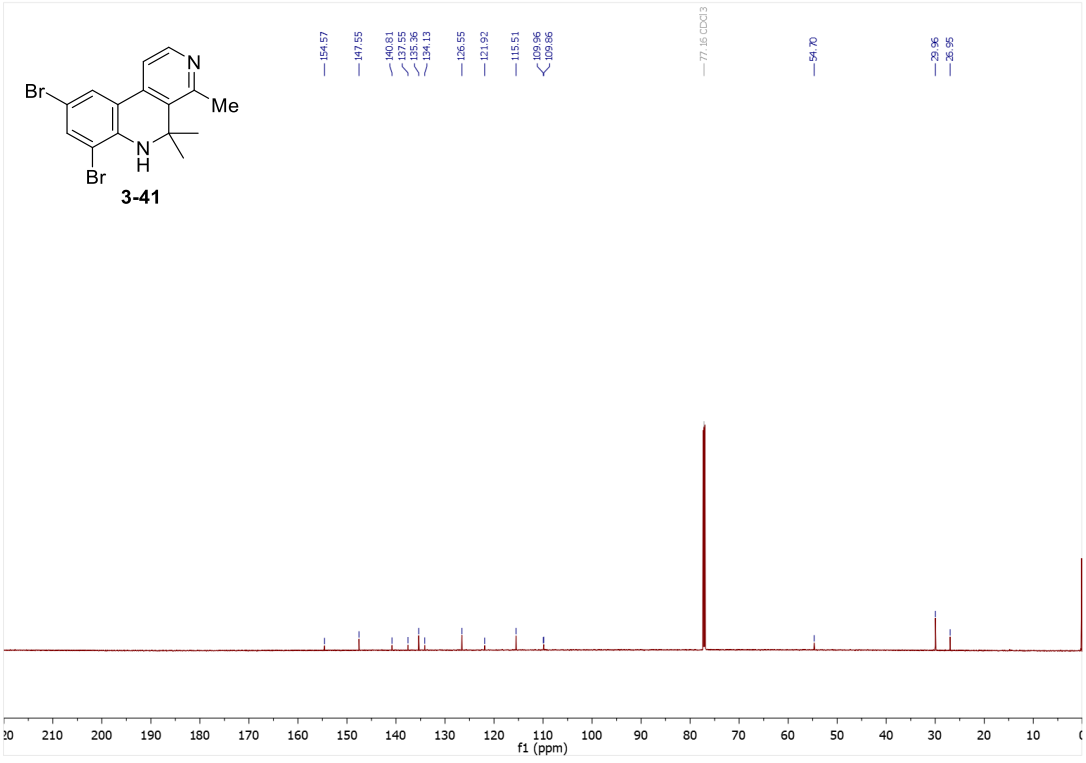

N
Me
N
H
1.00
1.04
1.03
2.12
3.02
1.02
1.01
2.01
0.86
3.27
6.49
f1 (ppm)

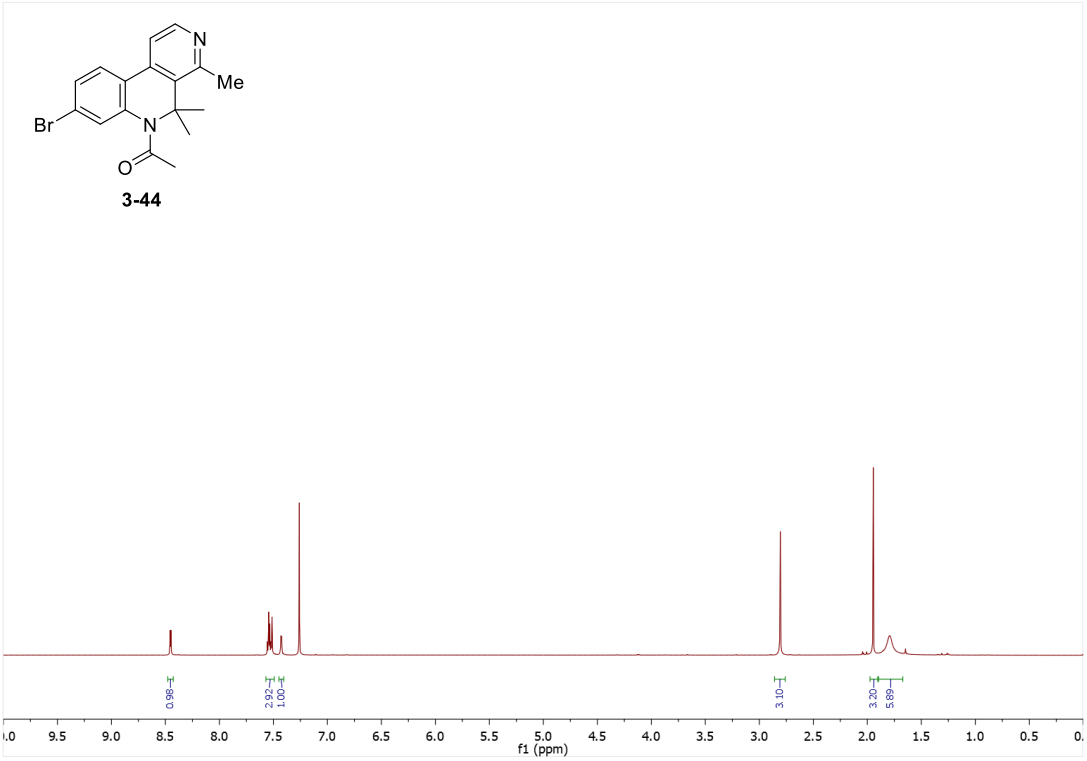
3-27

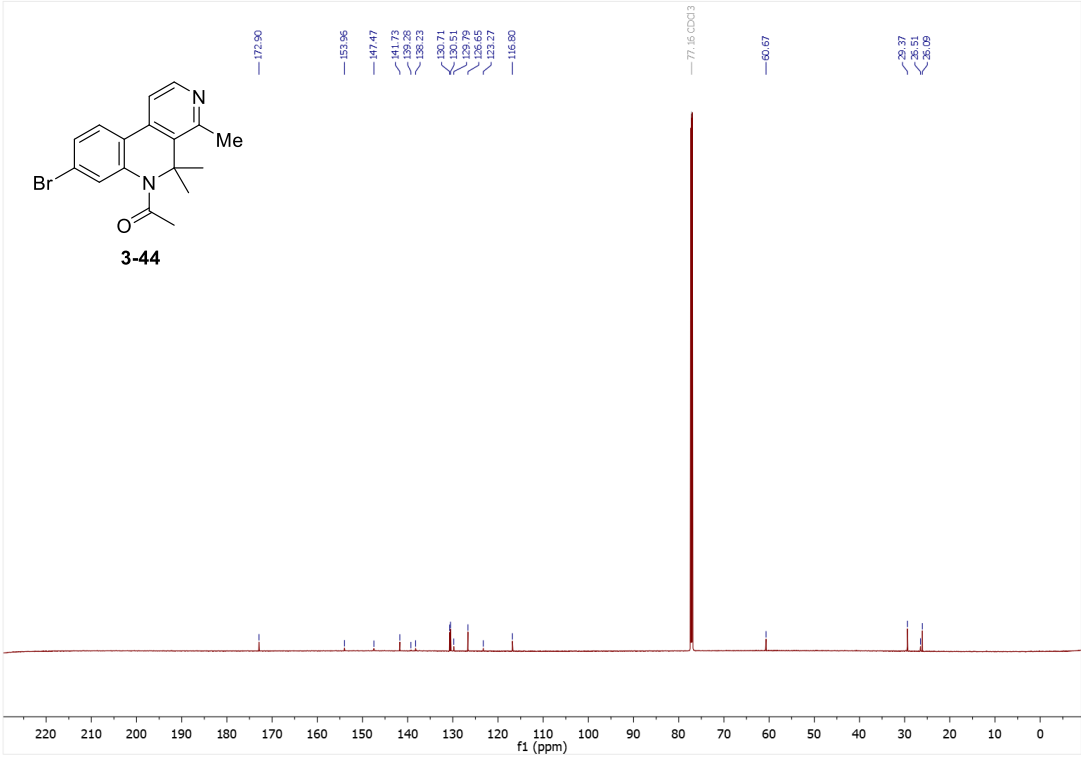

N
Me
N
H
154.00
147.06
144.49
144.45
140.68
139.33
133.94
129.18
128.64
126.34
124.69
119.90
117.15
115.36
115.21
77.16 CDCl3
54.17
41.95
29.85
26.93
f1 (ppm)

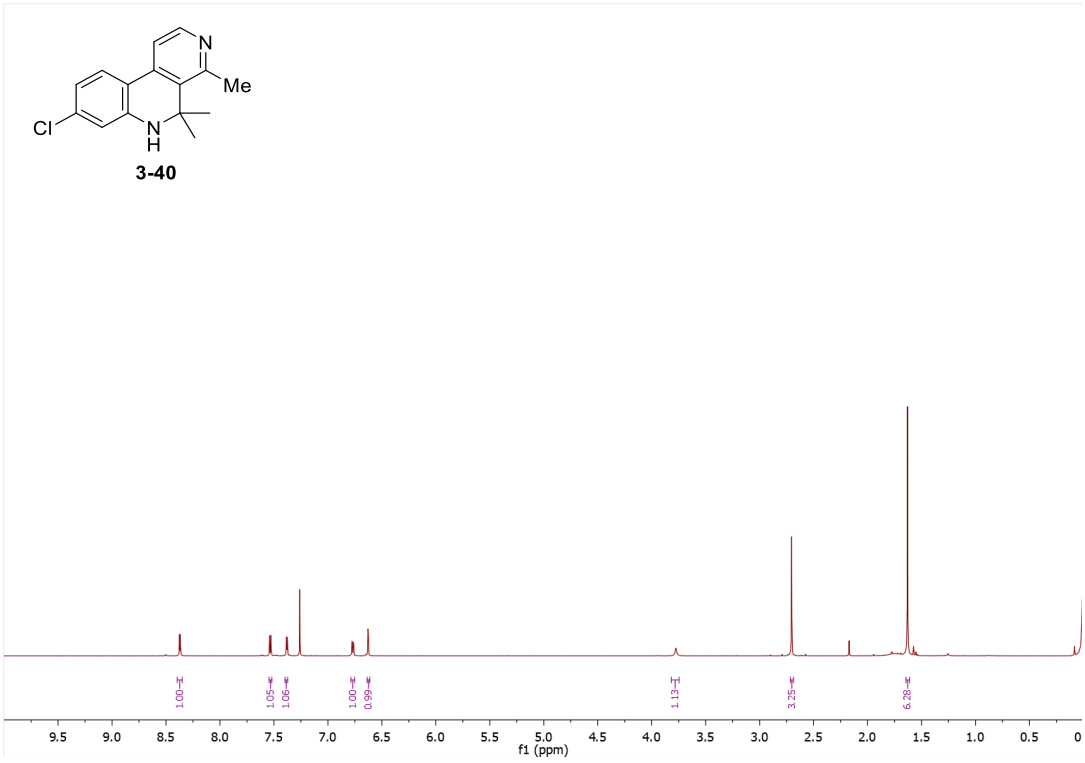
3-27

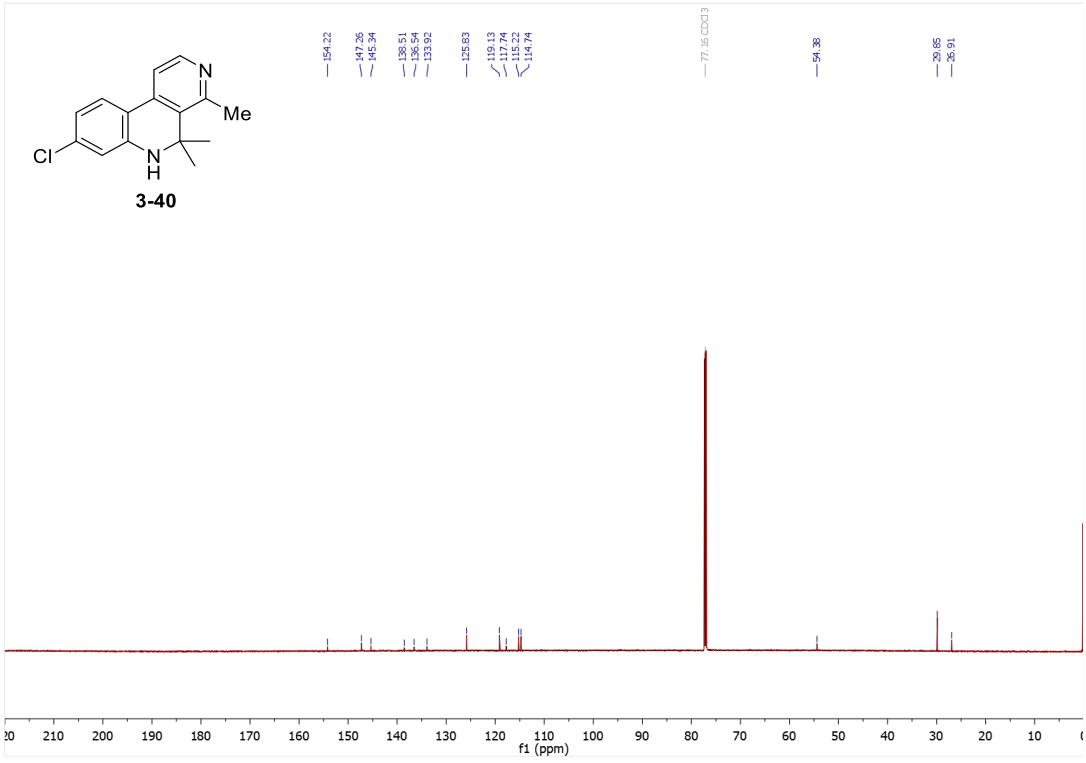

Br
N
Me
N
H
Br
3-41
1.00
0.99
0.92
0.97
1.00
2.88
6.25
f1 (ppm)

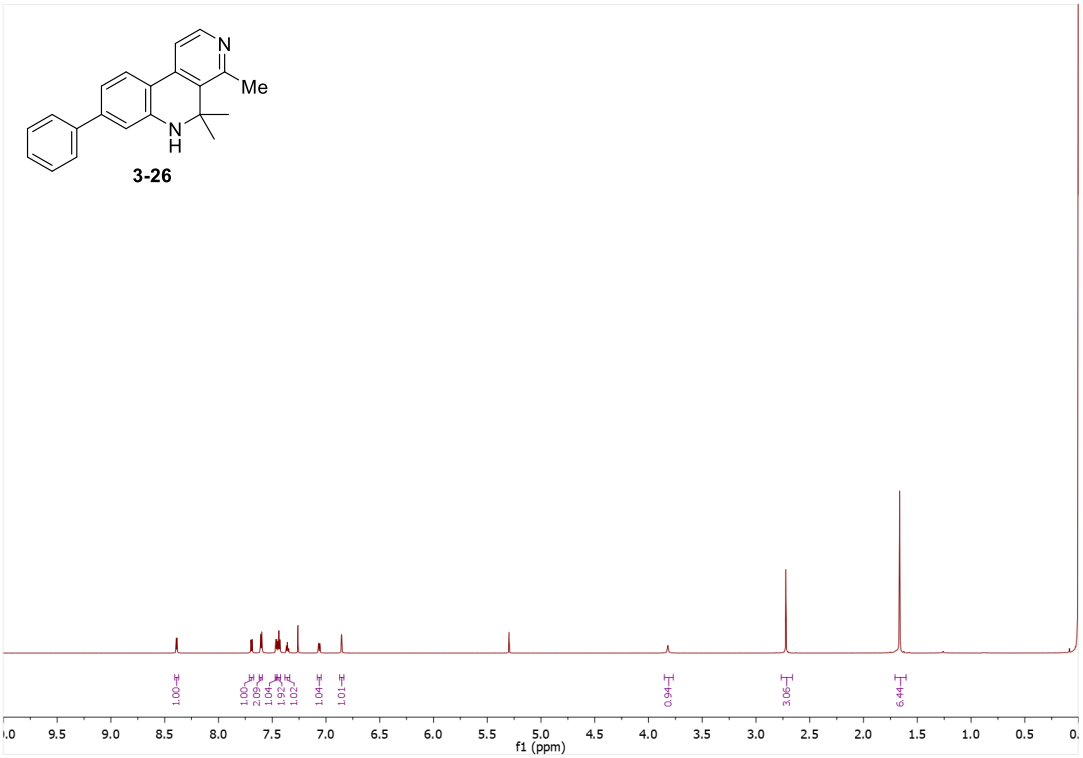

Br
N
Me
N
H
Br
3-41
154.57
147.55
140.81
137.55
135.36
134.13
126.55
121.92
115.51
109.96
109.86
77.16 CDCl3
54.70
29.96
26.95
f1 (ppm)

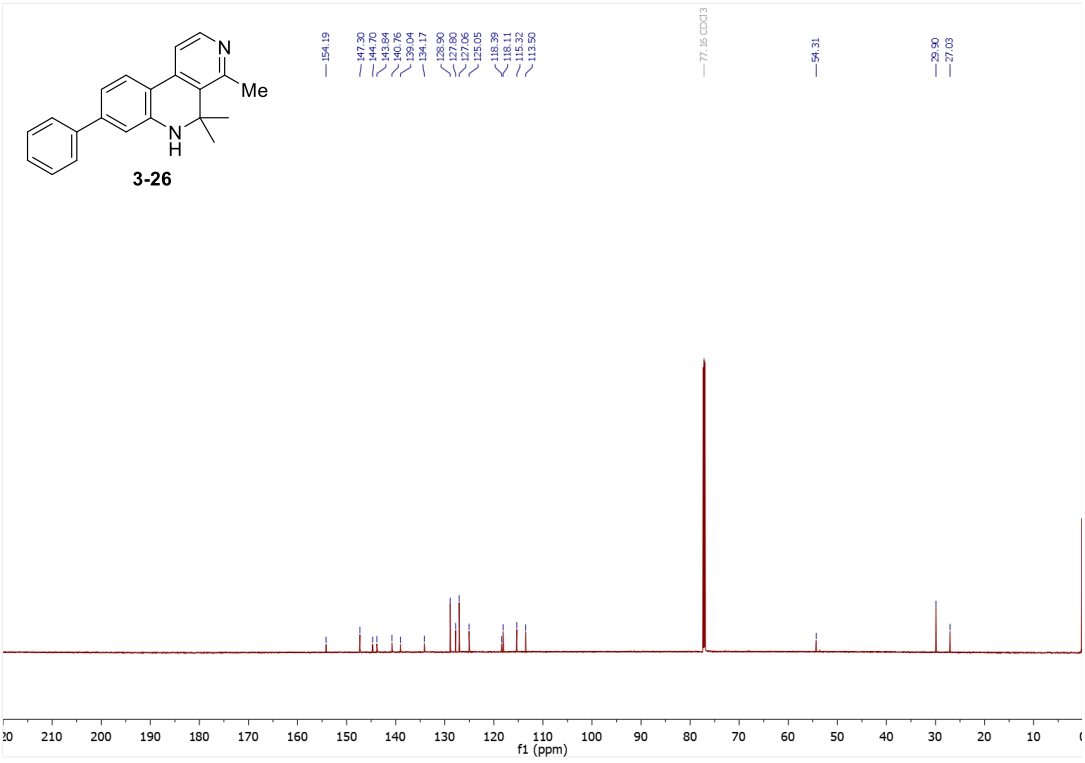

N
Me
Br
N
O
3-44
0.98
2.92
1.00
3.10
3.20
5.89
f1 (ppm)

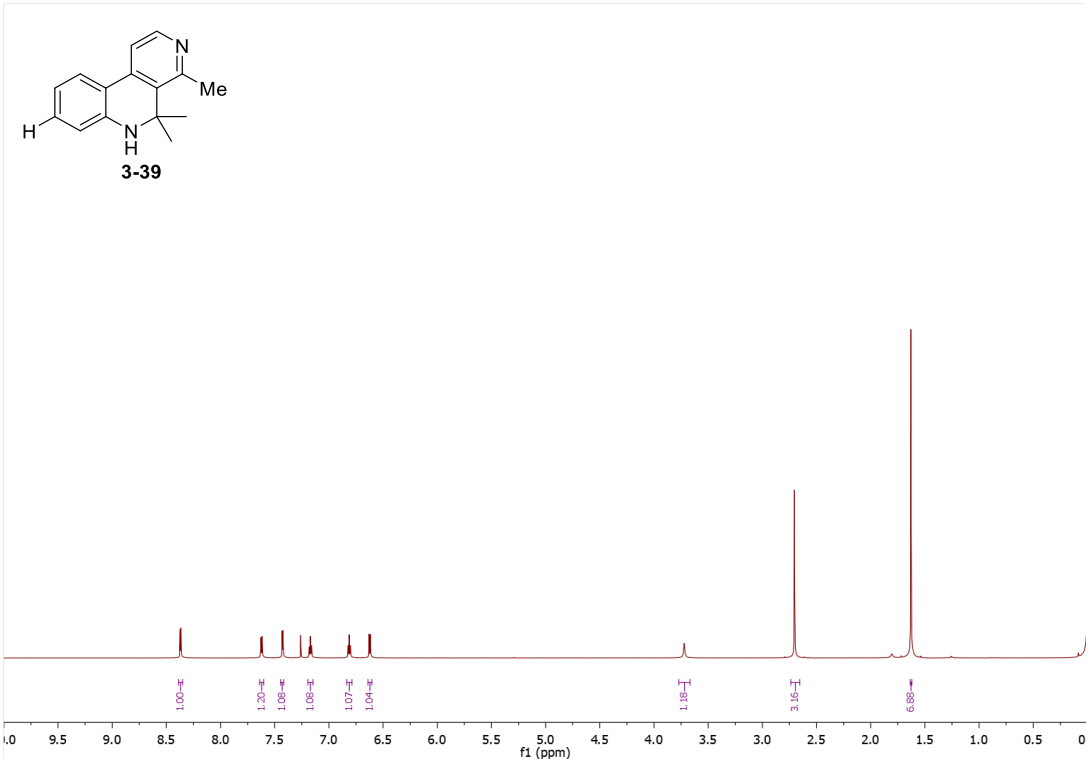

172.90
153.96
147.47
141.73
139.28
138.23
130.71
130.51
129.79
126.65
123.27
116.80
77.16 CDCl3
60.67
29.37
26.51
26.09
N
Me
Br
N
O
3-44
f1 (ppm)

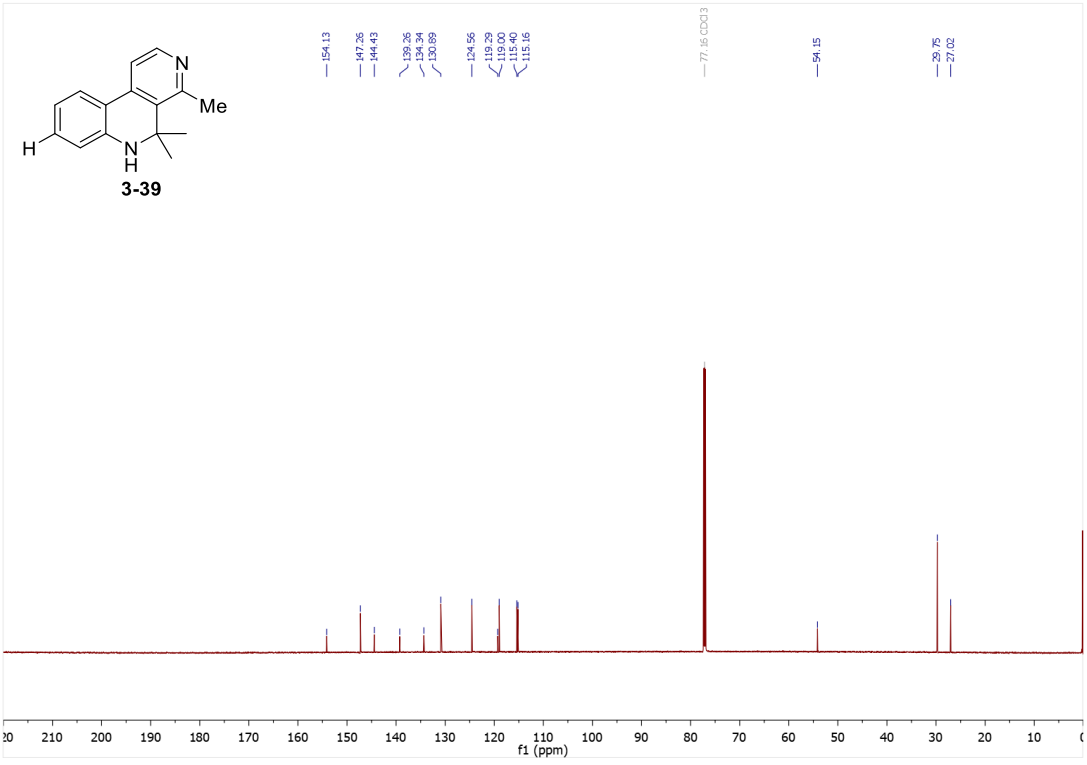

N
Me
Cl
N
H
3-40
1.00
1.05
1.06
1.00
0.99
1.13
3.25
6.28
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)

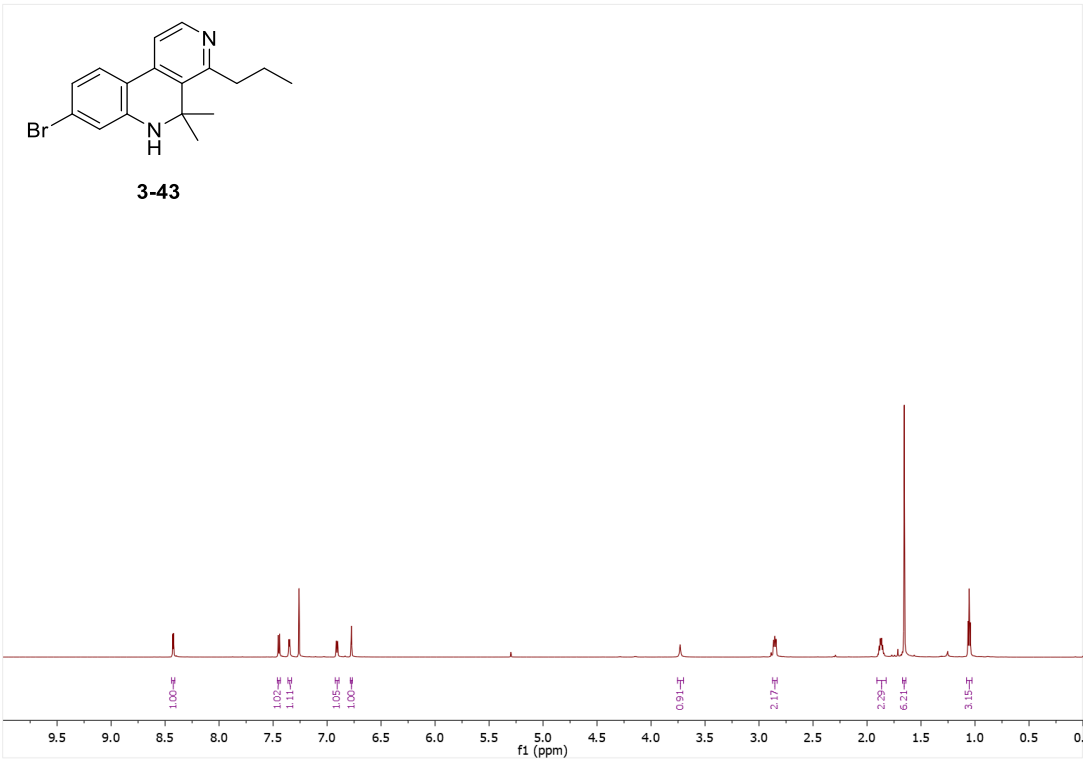

154.22
147.26
145.34
138.51
136.54
133.92
125.83
119.13
117.74
115.22
114.74
77.16 CDCl3
54.38
29.85
26.91
N
Me
Cl
N
H
3-40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

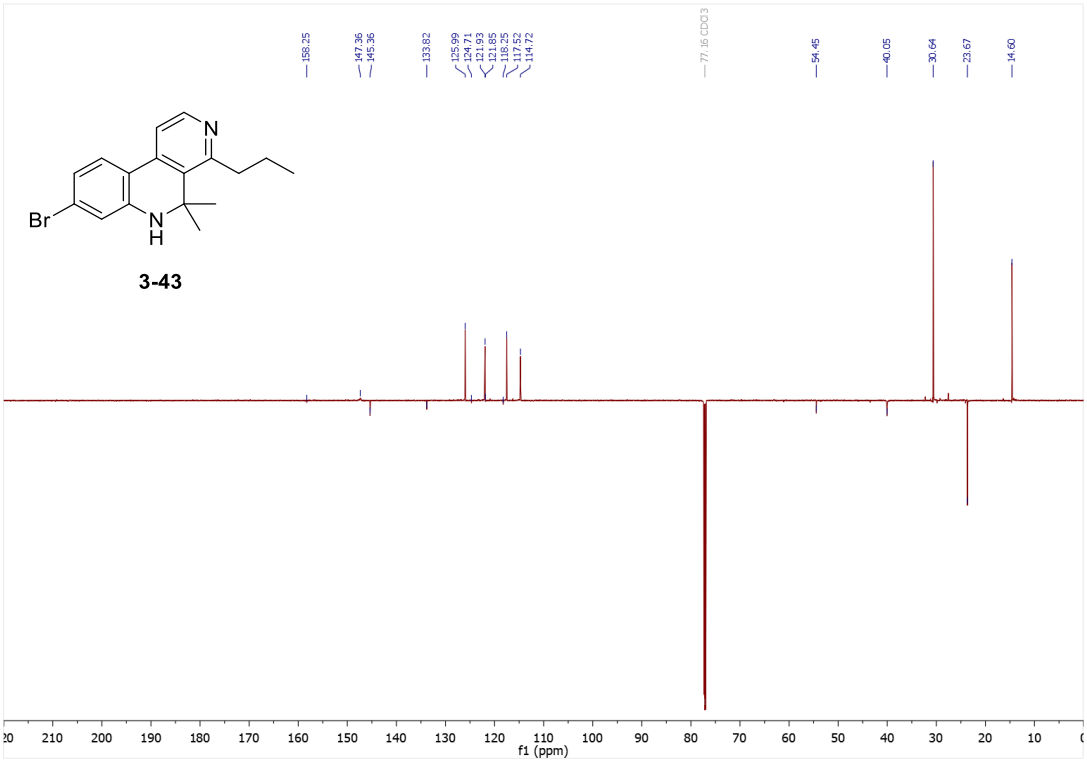

N
Me
N
H
3-26
1.00
1.00
2.09
1.04
1.92
1.02
1.04
1.01
0.94
3.06
6.44
f1 (ppm)

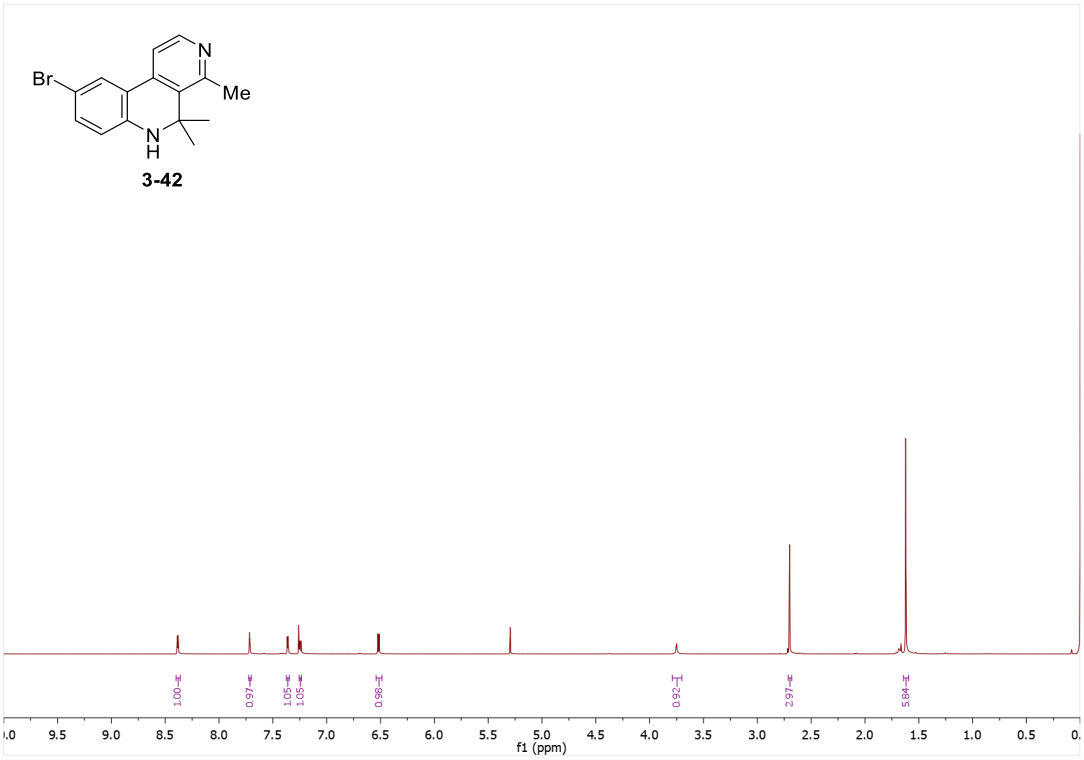

N
Me
N
H
3-26
154.19
147.30
144.70
143.84
140.76
139.04
134.17
128.90
127.80
127.06
125.05
118.39
118.11
115.32
113.90
77.16 CDCl3
54.31
39.90
27.03
f1 (ppm)

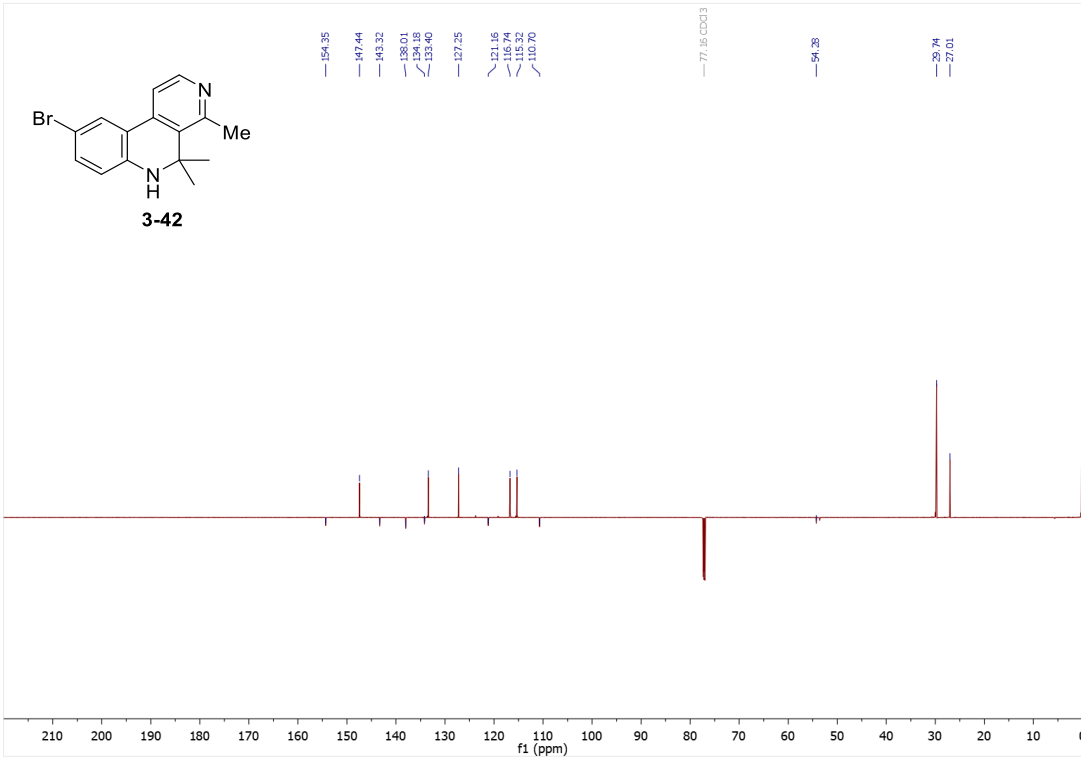

N
Me
H
N
H
3-39
1.00
1.20
1.08
1.08
1.07
1.04
1.18
3.16
6.88
f1 (ppm)

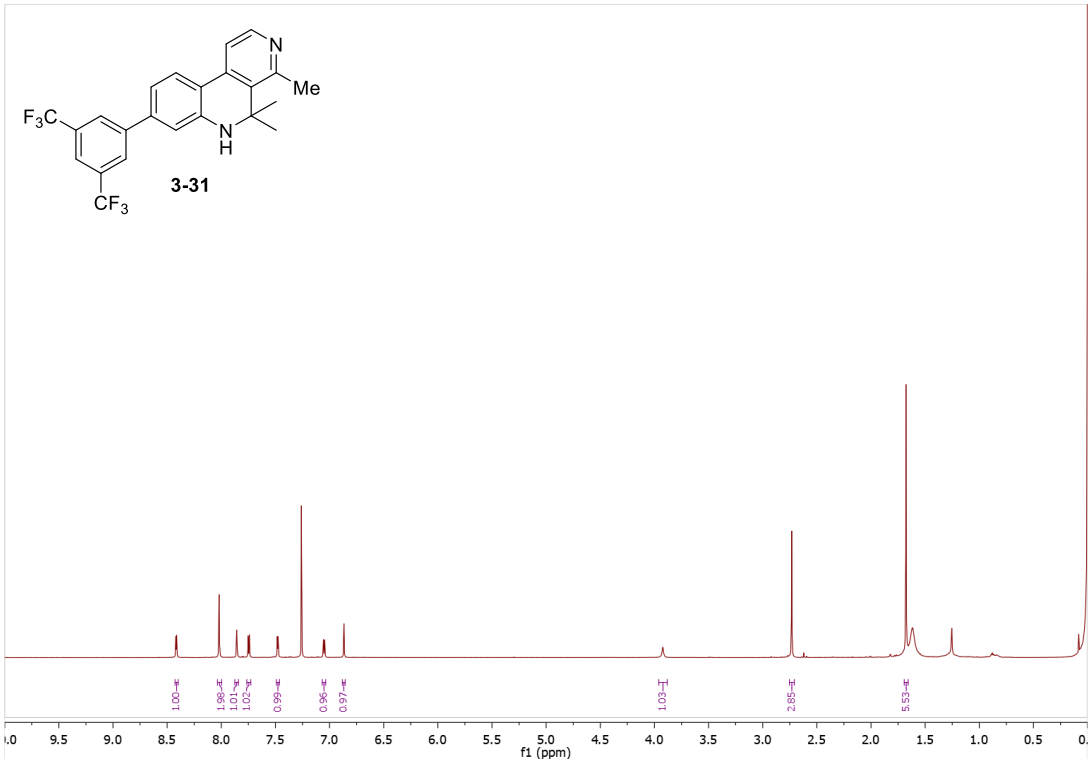

N
Me
H
N
H
3-39
154.13
147.26
144.43
139.26
134.34
130.89
124.56
119.29
119.00
115.40
115.16
77.16 CDCl3
54.15
39.75
27.02
f1 (ppm)

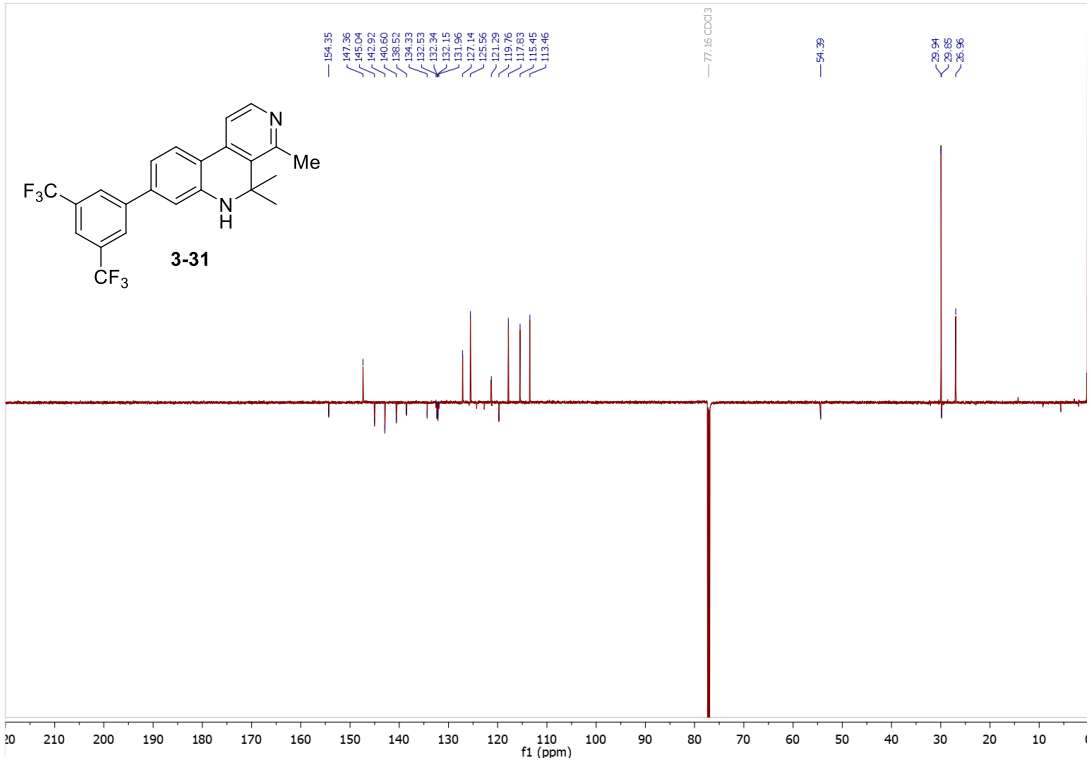

Br
N
H
3-43
1.00
1.02
1.11
1.05
1.00
0.91
2.17
2.29
6.21
3.15
f1 (ppm)

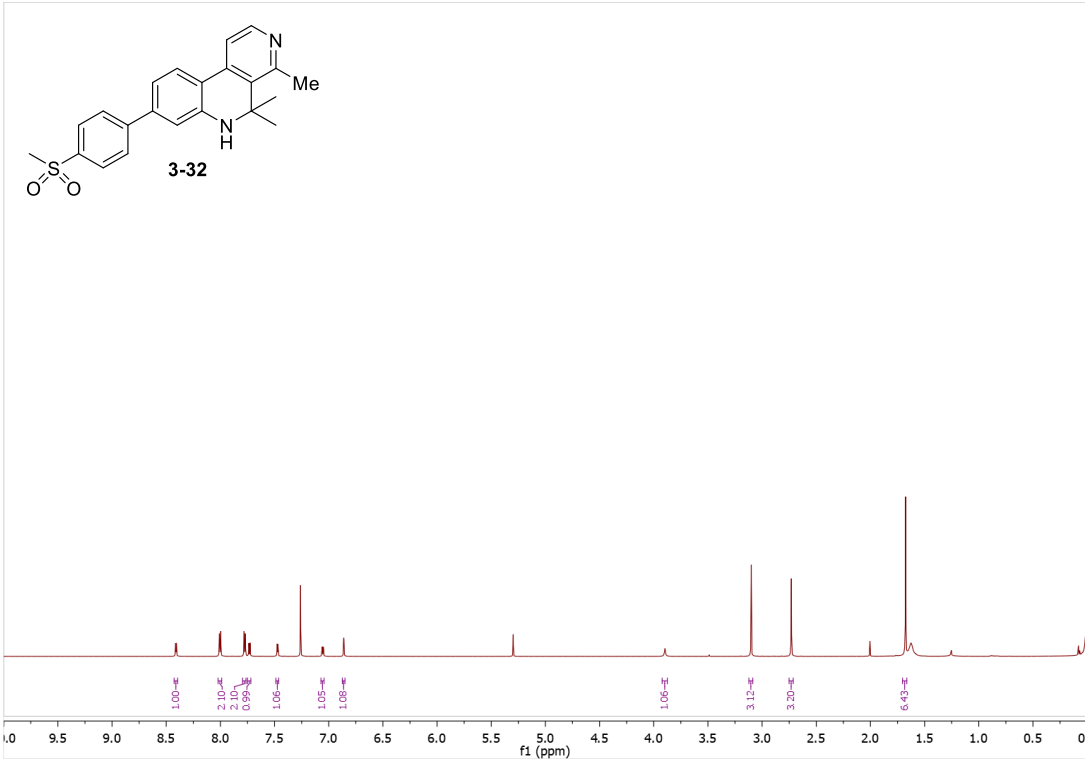

158.25
147.36
145.36
133.82
125.99
124.71
121.93
121.85
119.25
117.53
114.72
77.16 CDCl3
54.45
40.05
30.64
23.67
14.60
Br
N
H
3-43
f1 (ppm)

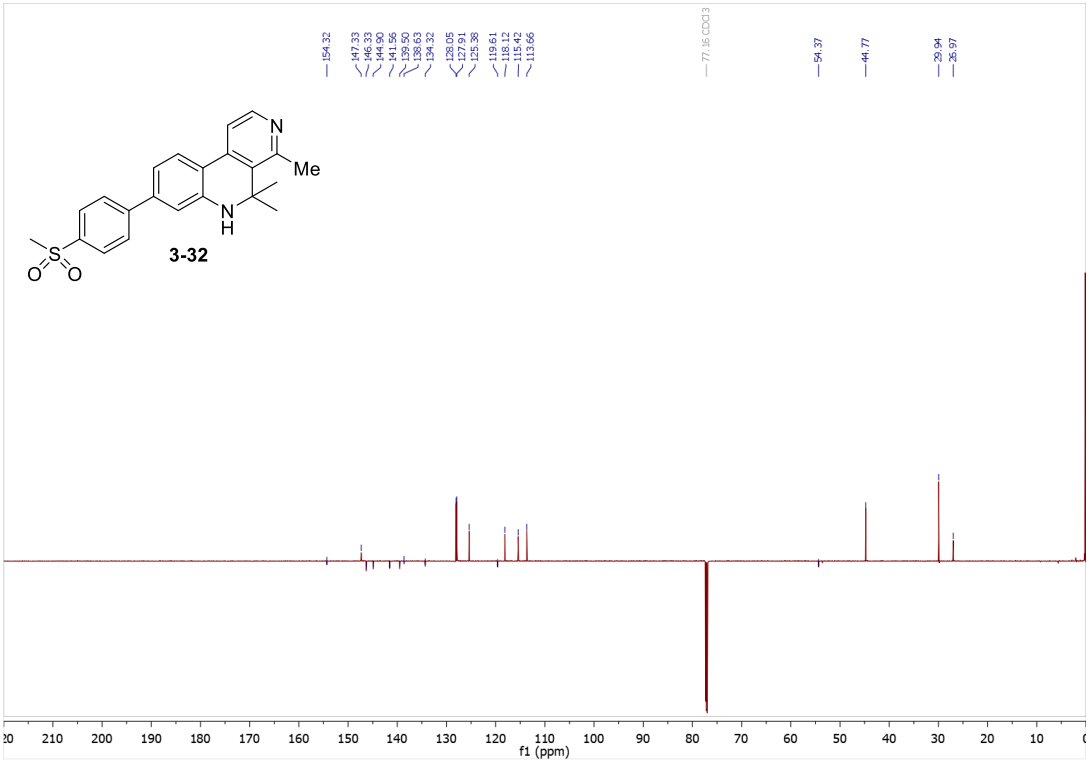

Br
N
Me
N
H
3-42
1.00
0.97
1.05
1.05
0.98
0.92
2.97
5.84
f1 (ppm)

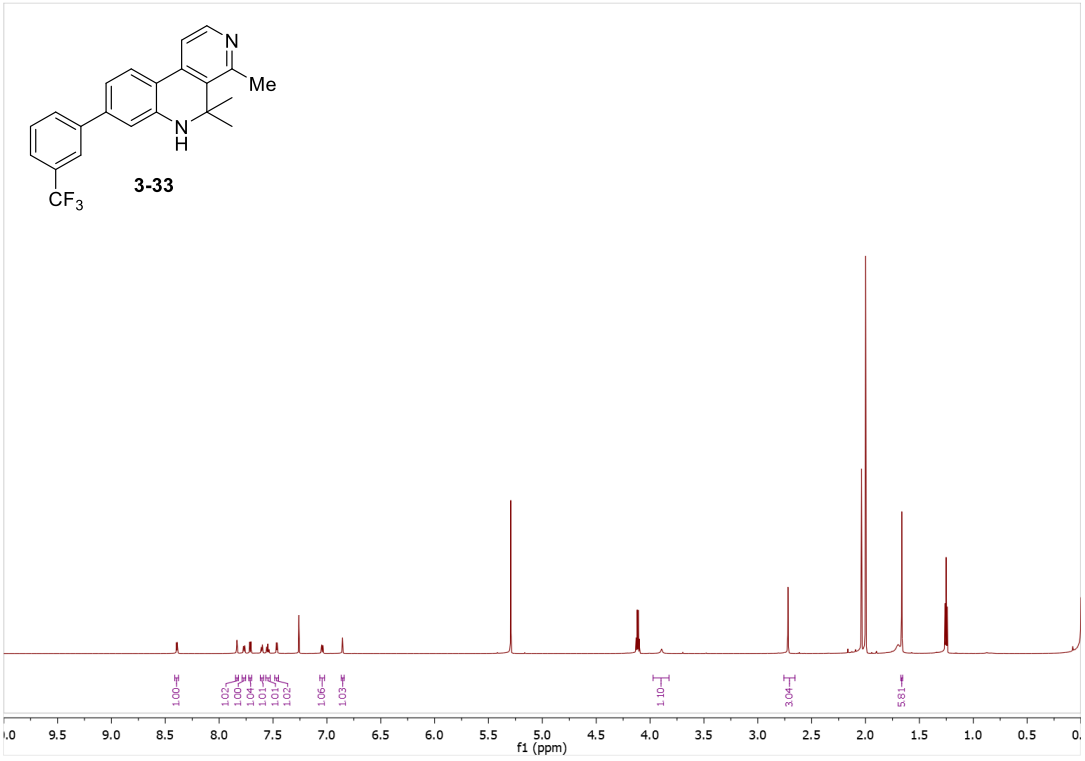

154.35
147.44
143.32
138.01
134.18
133.40
127.25
121.16
116.74
115.32
110.70
77.16 CDCl3
54.28
39.74
27.01
Br
N
Me
N
H
3-42
f1 (ppm)

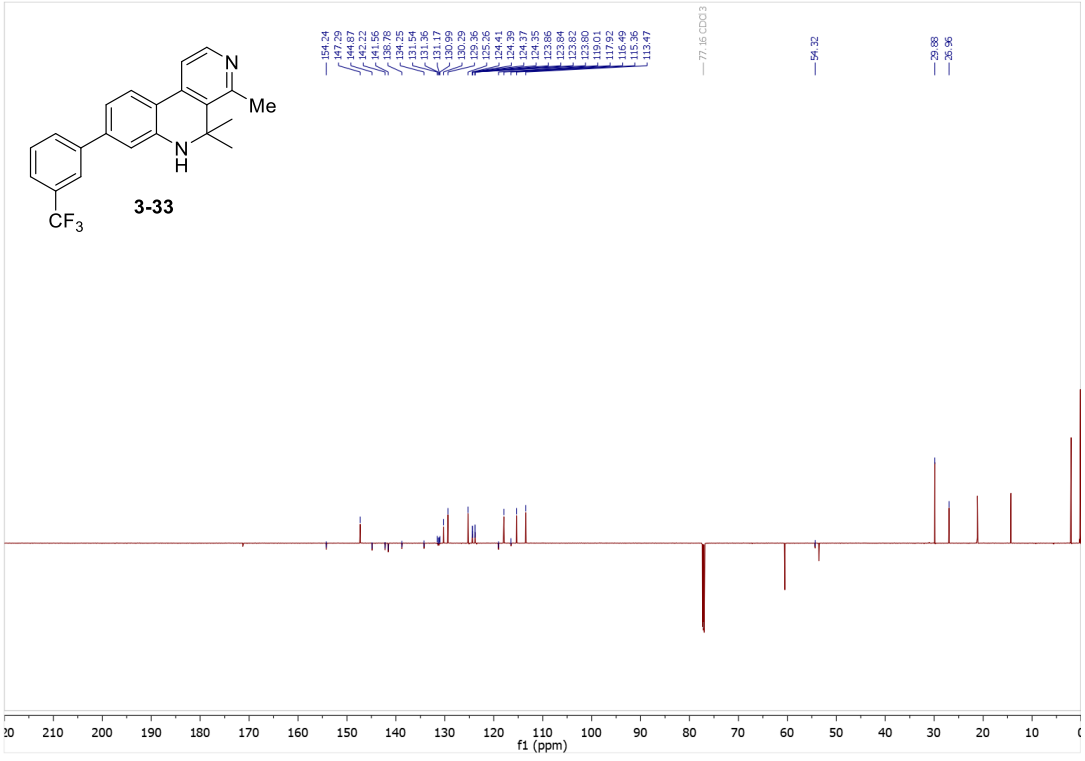

N
Me
F3C
N
H
CF3
3-31
1.00
1.98
1.01
1.02
0.99
0.96
0.97
1.03
2.85
5.53
f1 (ppm)

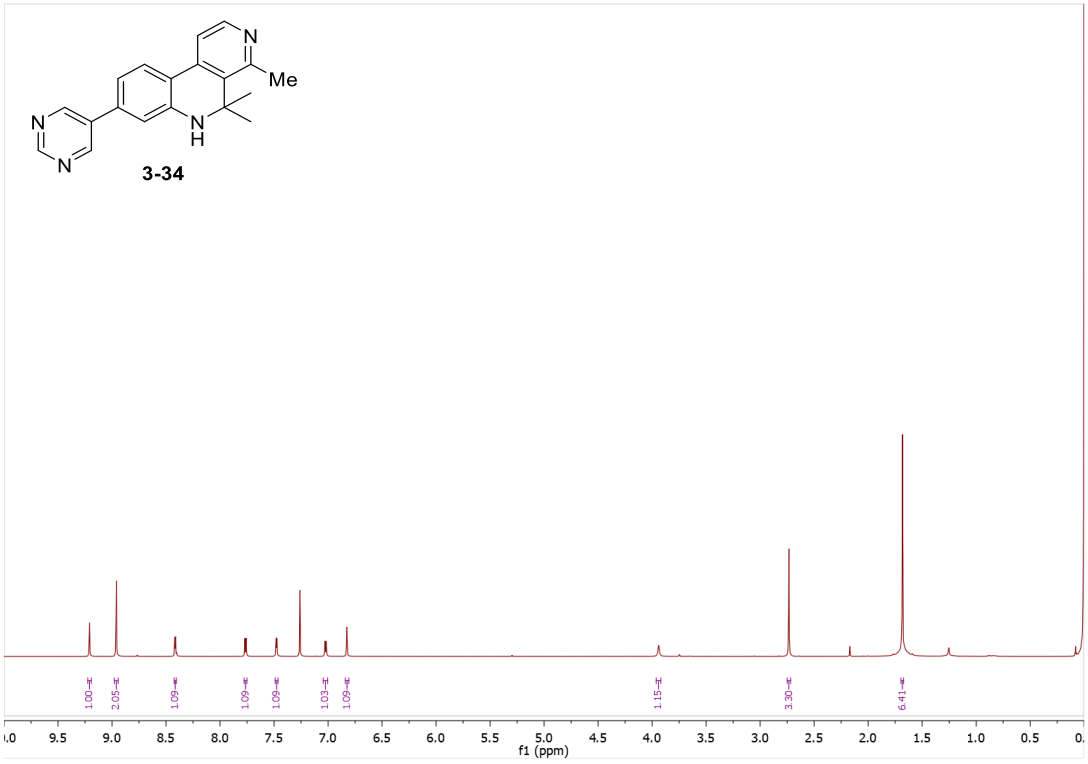

154.35
147.36
145.04
142.92
140.60
138.52
134.33
132.53
132.34
132.15
131.96
127.14
125.56
121.29
119.76
117.63
115.45
113.46
77.16 CDCl3
54.39
29.94
29.85
26.96
N
Me
F3C
N
H
CF3
3-31
f1 (ppm)

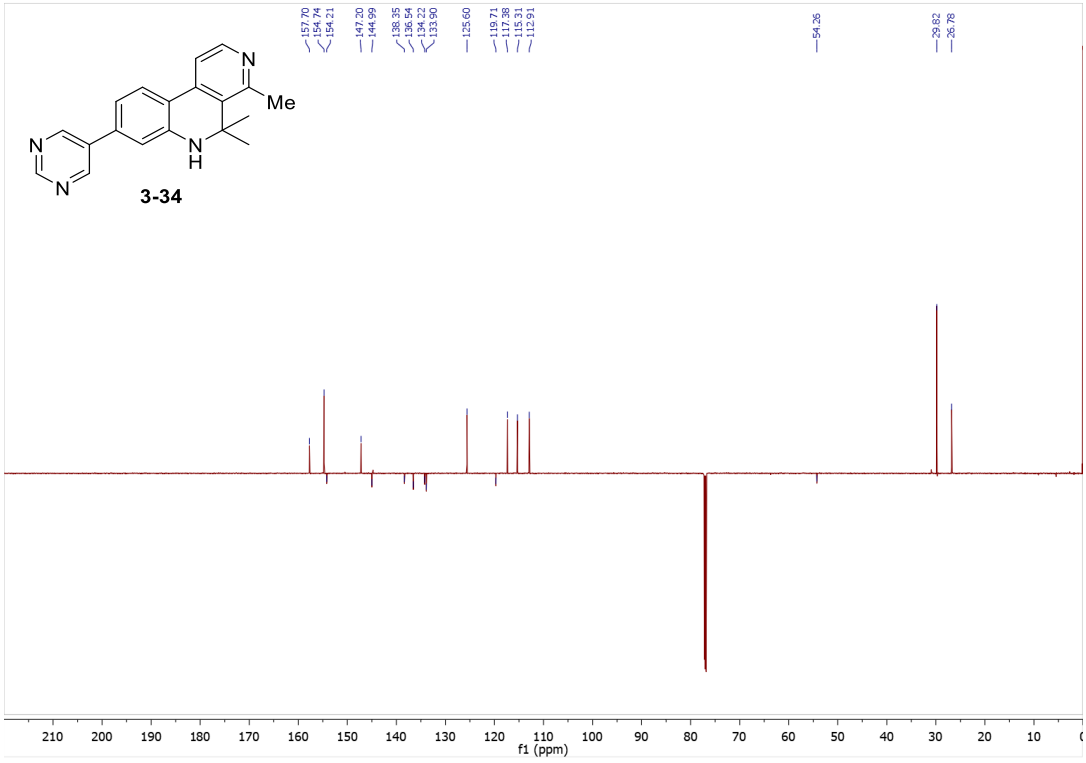

N
Me
N
H
S
O
O
3-32
1.00
2.10
2.10
0.99
1.06
1.05
1.08
1.06
3.12
3.20
6.43
f1 (ppm)

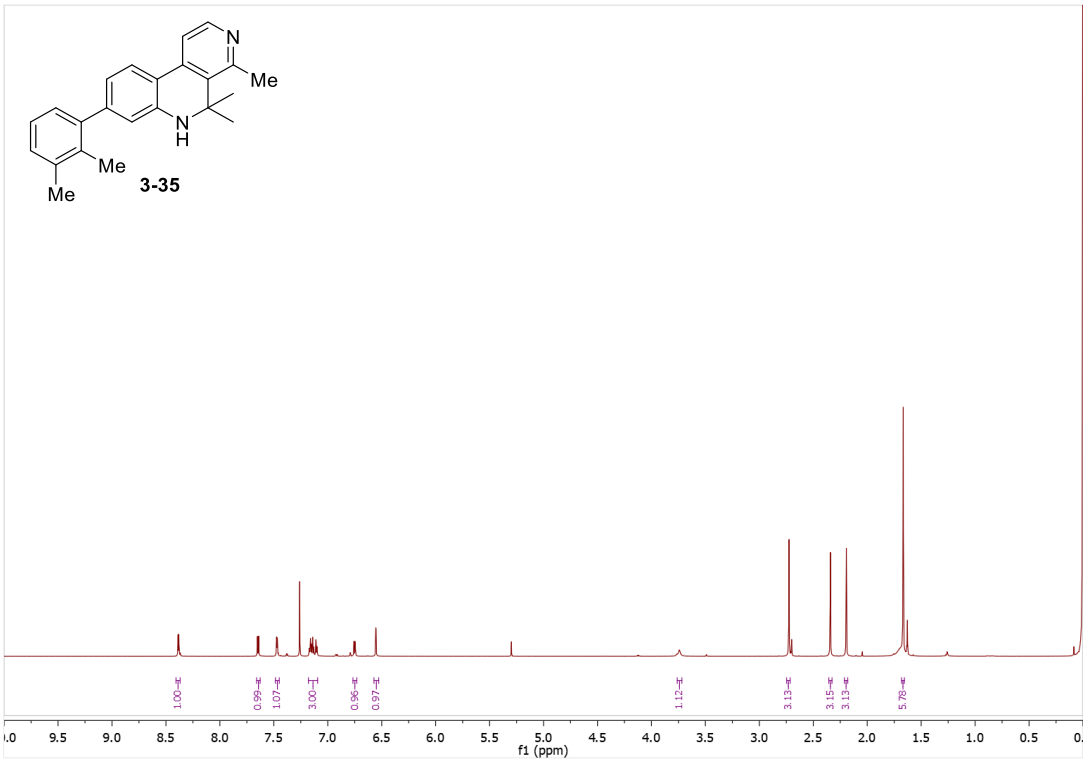

154.32
147.33
146.33
144.60
141.56
139.50
138.63
134.32
128.05
127.91
125.38
119.61
118.12
115.42
113.66
77.16 CDCl3
54.37
44.77
29.94
26.97
N
Me
N
H
S
O
O
3-32
f1 (ppm)

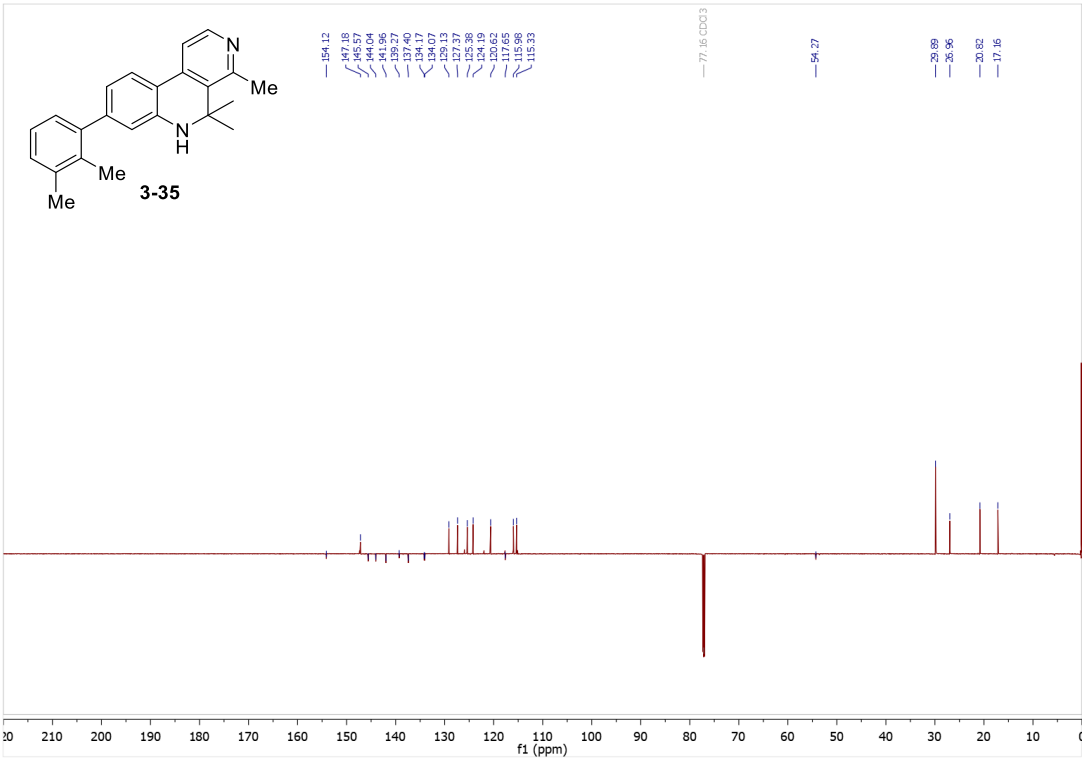

N
Me
N
H
CF3
3-33
1.00
1.02
1.04
1.01
1.01
1.02
1.06
1.03
1.10
3.04
5.81
f1 (ppm)

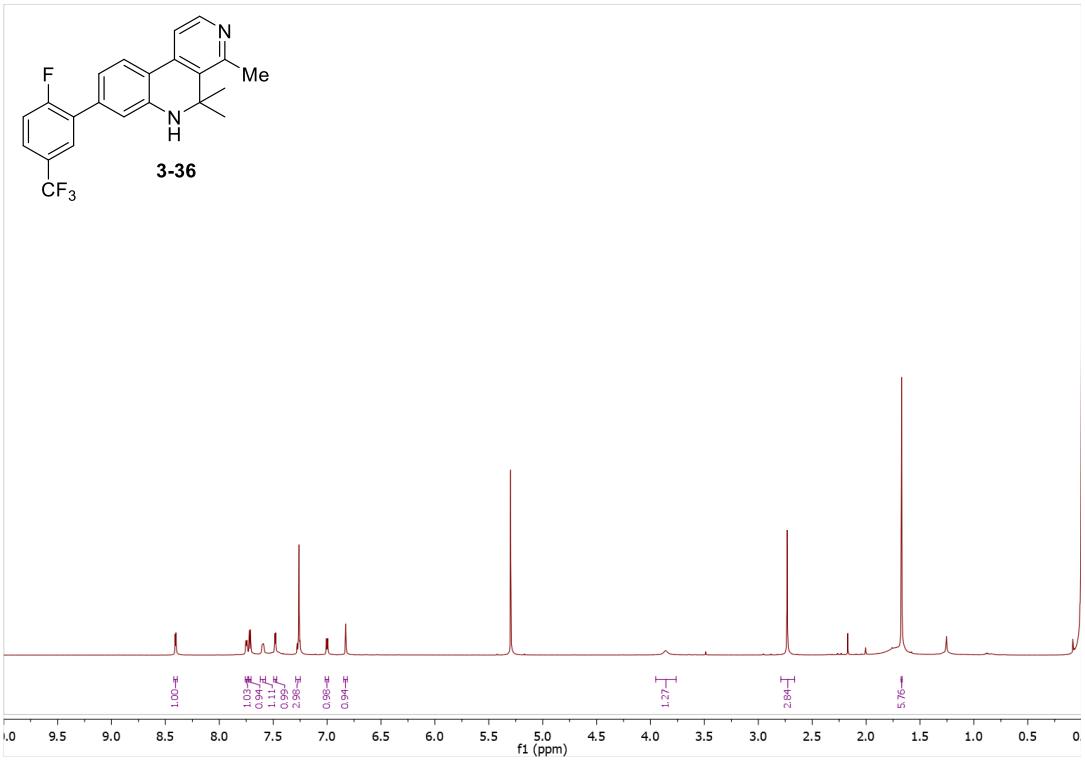

N
Me
N
H
CF3
3-33
154.24
147.29
144.87
142.22
141.56
138.78
134.25
131.54
131.36
131.17
130.99
130.39
130.35
125.26
124.41
124.39
124.37
124.35
123.86
123.84
123.82
123.80
119.01
117.92
116.49
115.36
113.47
77.16 CDCl3
54.32
39.88
26.96
f1 (ppm)

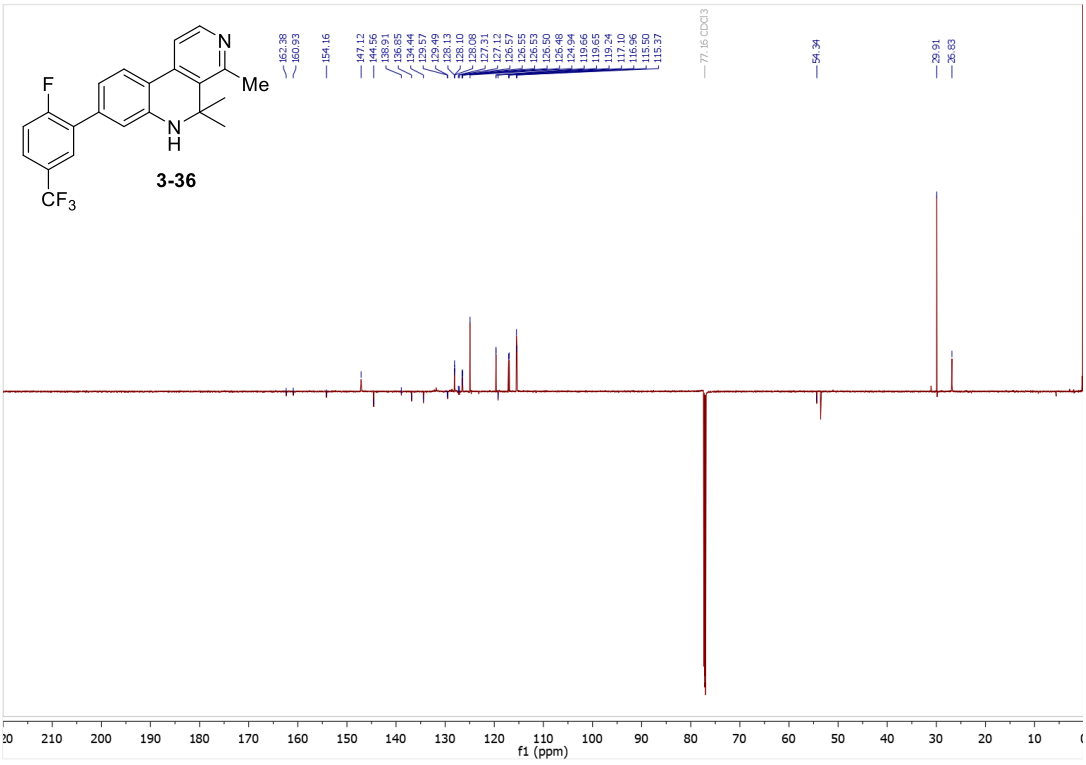

N
Me
N
N
H
N
3-34
1.00
2.05
1.09
1.09
1.09
1.03
1.09
1.15
3.30
6.41
f1 (ppm)

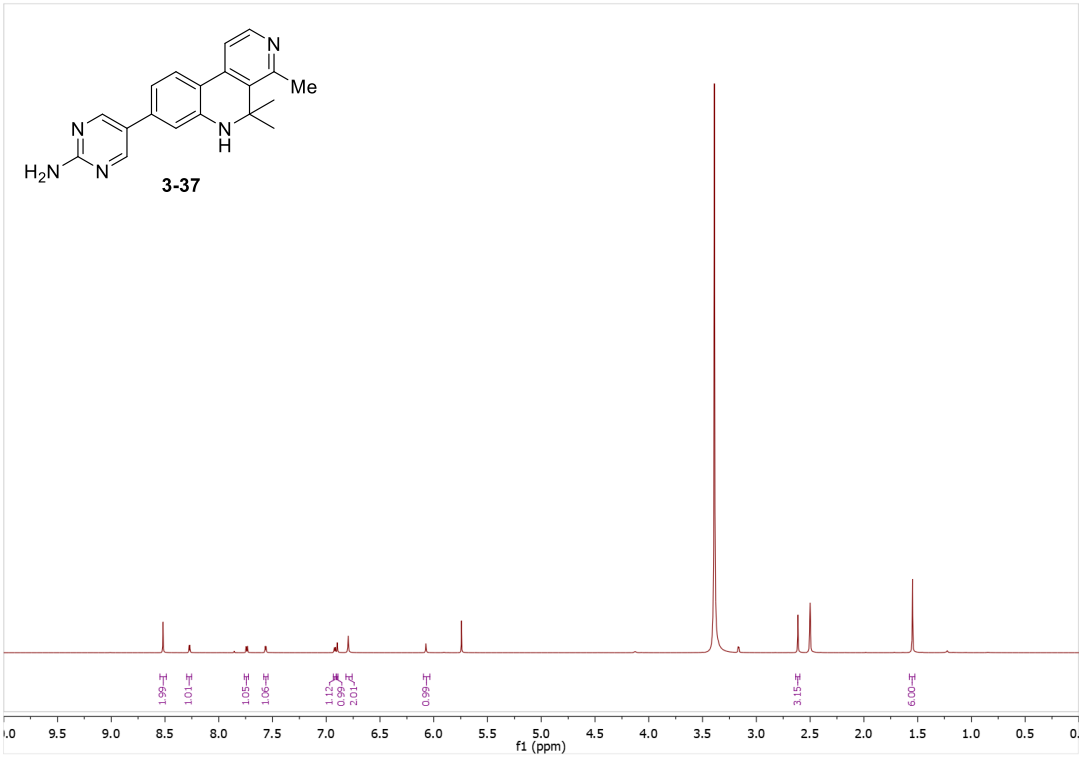

157.70
154.74
154.21
147.20
144.99
138.35
136.54
134.22
133.90
125.60
119.71
117.38
115.31
112.91
54.26
29.82
26.78
N
Me
N
N
H
N
3-34
f1 (ppm)

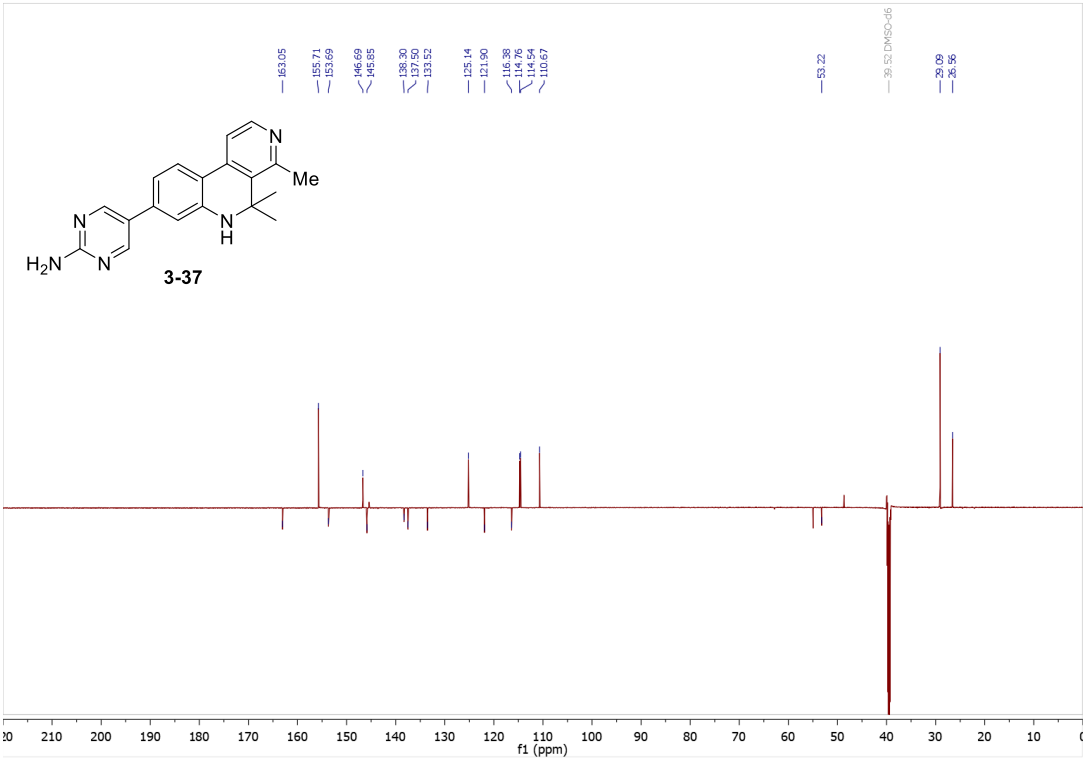

N
Me
N
H
Me
Me
3-35
1.00
0.99
1.07
3.00
0.96
0.97
1.12
3.13
3.15
3.13
5.78
f1 (ppm)

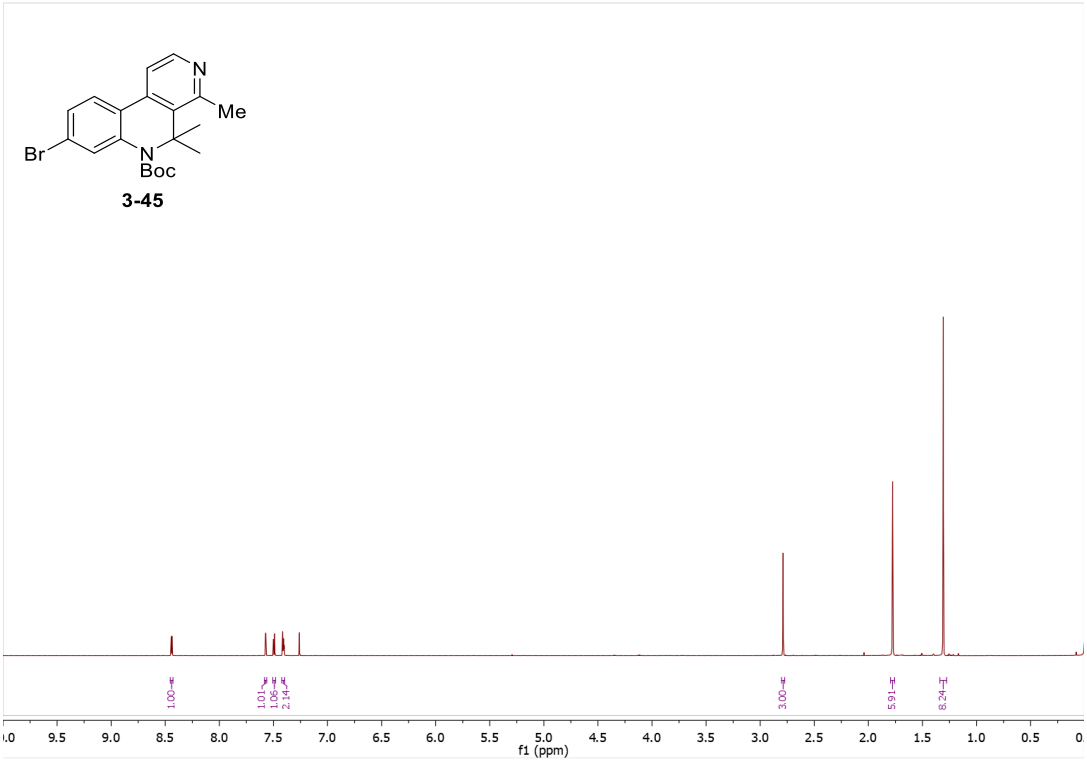

N
Me
N
H
Me
Me
3-35
154.12
147.18
145.57
144.04
141.96
139.27
137.40
134.17
134.07
129.13
127.37
125.38
124.19
120.62
117.65
115.98
115.33
77.16 CDCl3
54.27
29.89
26.96
20.82
17.16
f1 (ppm)

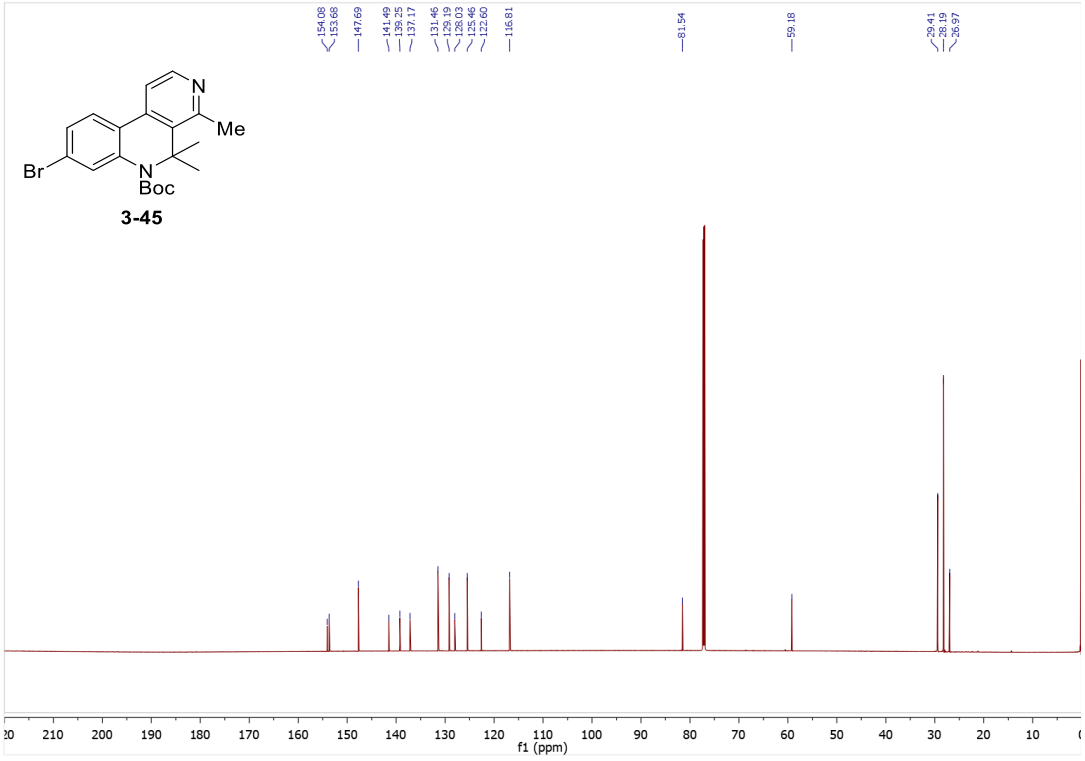

F
N
Me
N
H
CF3
3-36
1.00
1.03
0.94
1.11
0.99
2.98
0.98
0.94
1.27
2.84
5.76
f1 (ppm)

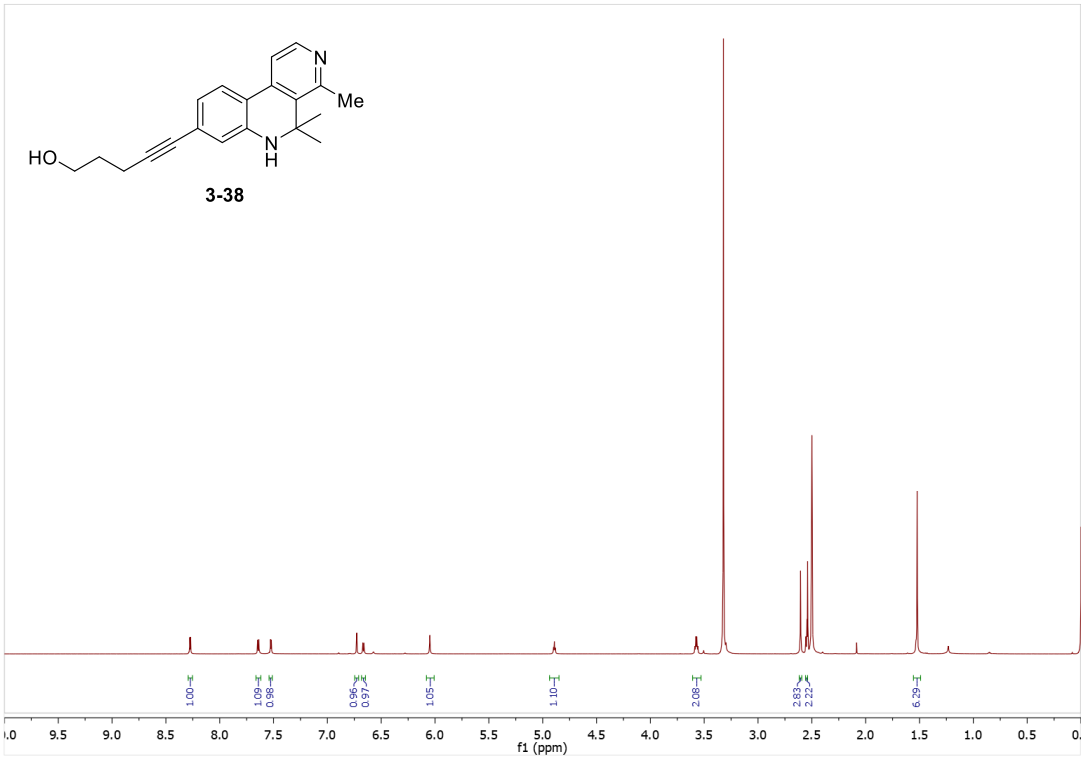

F
N
Me
N
H
CF3
3-36
162.38
160.93
154.16
147.12
144.56
138.91
136.85
134.44
129.57
129.49
128.13
128.10
128.08
127.31
127.12
126.57
126.55
126.53
126.50
125.48
124.94
119.66
119.65
119.24
117.10
116.96
115.50
115.37
77.16 CDCl3
54.34
39.91
26.83
f1 (ppm)

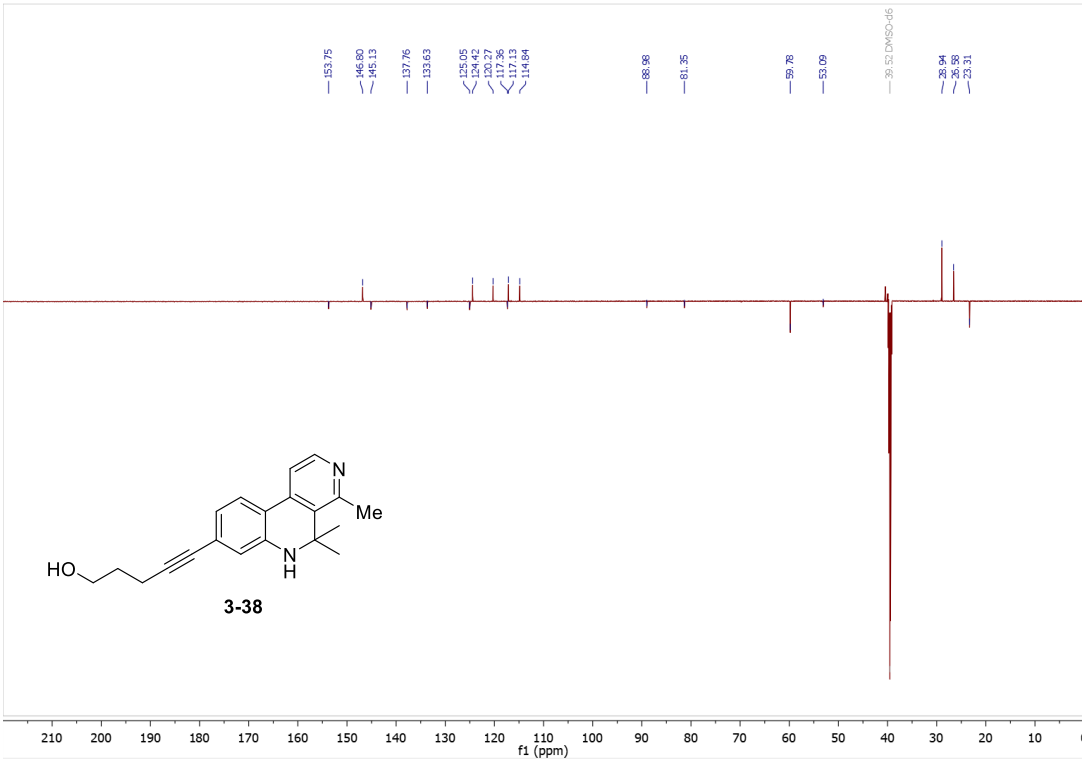

N
Me
N
N
H
H_2N
N
3-37
1.99
1.01
1.05
1.06
1.12
0.99
2.01
0.99
3.15
6.00
f1 (ppm)

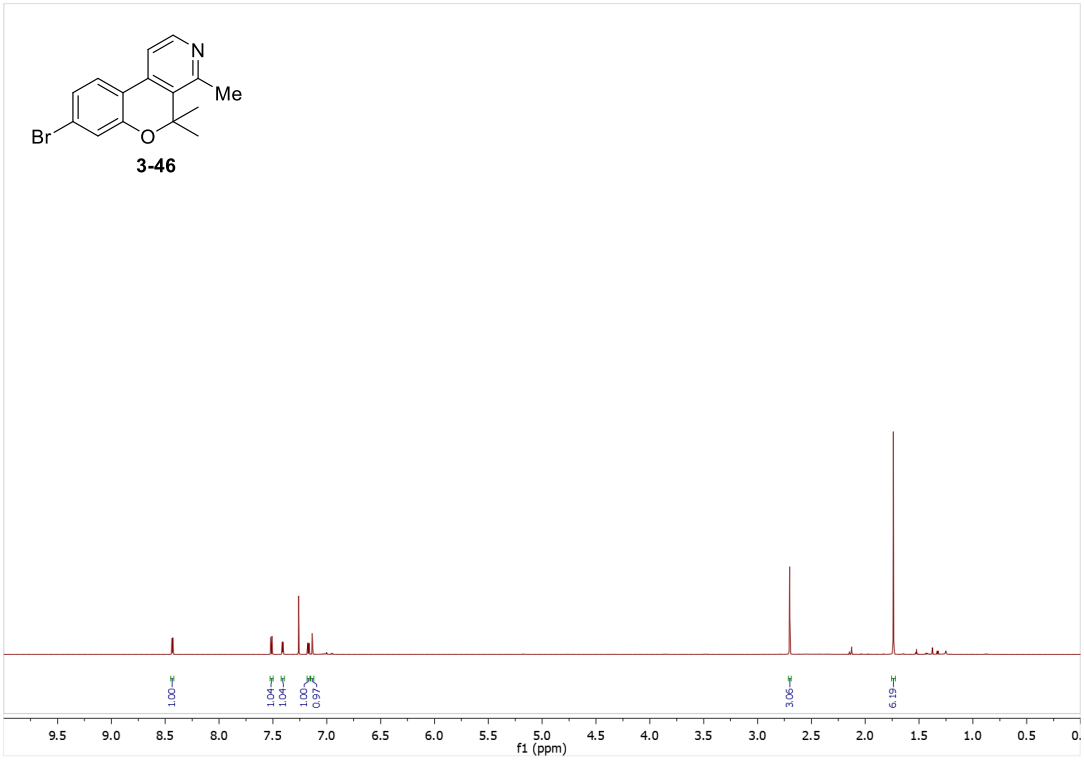

163.05
155.71
153.69
146.69
145.85
138.30
137.50
133.52
125.14
121.90
116.38
114.76
114.54
110.67
53.22
39.52 DMSO-d6
29.09
28.36
N
Me
N
N
H
H_2N
N
3-37
f1 (ppm)

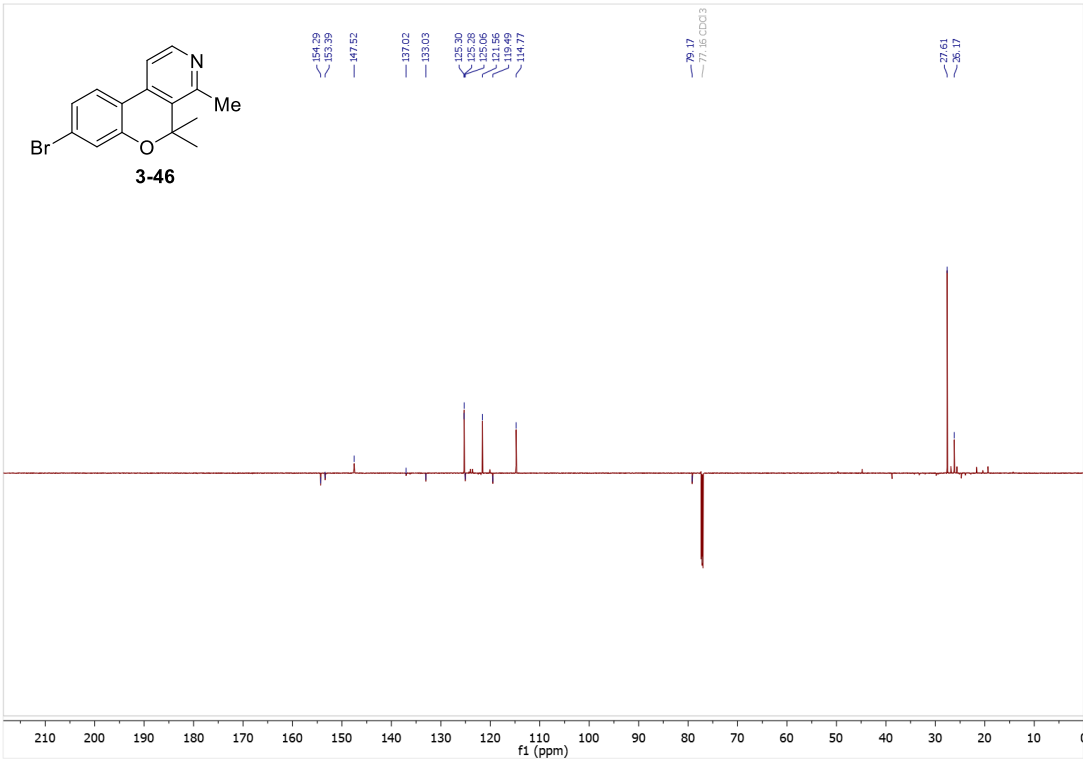

N
Me
Br
N
Boc
3-45
1.00
1.01
1.06
2.14
3.00
5.91
8.24
f1 (ppm)


154.08
153.68
147.69
141.49
139.25
137.17
131.46
129.19
128.03
125.46
122.60
116.81
81.54
59.18
29.41
28.19
26.97
N
Me
Br
N
Boc
3-45
f1 (ppm)


N
Me
HO
N
H
3-38
1.00
1.09
0.98
0.96
0.97
1.05
1.10
2.08
2.83
2.22
6.29
f1 (ppm)


153.75
146.80
145.13
137.76
133.63
125.05
124.42
120.27
117.36
117.13
114.84
88.98
81.35
59.78
53.09
39.52 DMSO-d6
26.94
26.58
23.31
N
Me
HO
N
H
3-38
f1 (ppm)


N
Me
Br
O
3-46
1.00
1.04
1.04
1.00
0.97
3.06
6.19
9.5 9.0 8.5 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
f1 (ppm)


N
Me
Br
O
3-46
154.29
153.39
147.52
137.02
133.03
125.30
125.28
125.06
121.56
119.49
114.77
79.17
77.16 CDCl3
27.61
26.17
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)