

**METHODOLOGY UTILIZING TRIPHOSGENE TO PROMOTE
CYCLIZATION OF EPOXY KETONES TO PYRANOSIDE
DERIVATIVES VIA PROPOSED EPOXONIUM IONS**

A Thesis

Submitted to the Graduate Faculty of the
Louisiana State University and
Agricultural and Mechanical College
in partial fulfillment of the
Requirements for the degree of
Master of Science

in

The Department of Chemistry

by
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B.S., State University of New York at Plattsburgh, 2018
August 2021

This work is dedicated to my parents;

Roberto and Renata Dos Reis

ACKNOWLEDGEMENTS

Throughout my life I've been fortunate to have many amazing teachers and role models. First and foremost, I must thank my parents for always being supportive of me in whatever I've wanted to pursue in life. Thank you for instilling a work ethic in me that has helped me get to where I am today. It has been almost three years since I've began my graduate studies here in Baton Rouge and each year presented its own set of challenges. Without the support and encouragement from friends and family I would not have been able to accomplish this.

My interest in chemistry began in high school when I took chemistry with a couple of wonderful teachers, Mrs. Miller and Mr. Pavlich. Before then my interest had not been grabbed by anything in school. Their enthusiasm towards the subject is very apparent and it led me on a path to pursue chemistry at the State University of New York at Plattsburgh. While at Plattsburgh, I had the pleasure of taking organic chemistry with two amazing professors, both of whom had a strong impact on me. Dr. Criss and Dr. Sunasee made what I thought was going to be a dreadful experience into one that was quite enjoyable, albeit difficult. Thank you to both of you for guiding me through my education, research, and graduate school applications while at Plattsburgh.

My time here at LSU has been a great experience and it's all thanks to my wonderful lab mates and friends: Alex, Josh, Josh, Moshood, Binod, Fatimat, Christian, and Satish. You have all made the lab a place that I looked forward to coming into every day. Special thanks to Dr. Alex Cleveland and Moshood Ganiu for teaching me all of the lab techniques and answering all of my many questions. I want to thank my advisor Rendy Kartika for being an understanding and patient mentor to me. You pushed me to become a better scientist and I have learned so much during my time here because of you. I hope the best for all of you! Lastly, thank you to the NIH (R01GM127649) for funding the research that I was a part of for the past three years.

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LIST OF ABBREVIATIONS

$[\alpha]^{23}_D$	absolute optical rotation
$^{\circ}\text{C}$	degrees Celsius
α	alpha
β	beta
^1H	proton NMR
^{13}C	carbon NMR
\AA	angstrom
Ac	acetate
AcOH	acetic acid
b	broad
$\text{BF}_3 \cdot \text{OEt}_2$	boron trifluoride diethyl etherate
$\text{BH}_3 \cdot \text{SMe}_2$	boron dimethylsulfide
Bn	benzyl
Boc	tert-butoxycarbonyl
Bu_2SnO	dibutyltin oxide
Bu	butyl
Bs	besylate
CDCl_3	deuterated chloroform
cm^{-1}	per centimeter
CSA	camphorsulfonic acid
d	doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dd	doublet of doublets
ddd	doublet of doublet of doublets
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DME	1,2-dimethoxyethane
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
EtOH	ethanol
EtOAc	ethyl acetate
f	wavenumber
FT-IR	Fourier-transform infrared
g	gram
$h\nu$	light
Hz	Hertz
<i>i</i> Pr	isopropyl
<i>i</i> PrOH	isopropanol

J	coupling constant
LA	Lewis acid
LDA	lithium diisopropylamide
LiI	lithium iodide
LiAlH ₄	lithium aluminum hydride
m	multiplet
M	molarity
M ⁺	molecular ion
MBSA	methoxybenzene sulfo nate
<i>m</i> -CPBA	meta-chloroperoxybenzoic acid
Me	methyl
MeOH	methanol
mg	milligram
mL	milliliter
mmol	millimol
Ms	mesyl
MS	molecular sieves
<i>m/z</i>	mass-to-charge ratio
NaBH ₄	sodium borohydride
NCS	N-chlorosuccinimide
NMQPF ₆	<i>N</i> -methylquinolinium hexafluorophosphate
NMR	nuclear magnetic resonance
Nuc	nucleophile
<i>p</i> TsOH	para-toluenesulfonic acid
Ph	phenyl
Ph ₃ P	triphenylphosphine
ppm	parts per million
<i>p</i> TsCl	para-toluenesulfonyl chloride
Py	pyridine
Py•MBSA	pyridinium para-methoxybenzene sulfonate
Py•TfOH	pyridinium triflate
Py•TsOH	pyridinium para-toluenesulfonate
R _f	retention factor
s	singlet
SEM	trimethylsilylethoxymethyl
t	triplet
TBDPS	tert-butyldiphenyl silyl
TBS	tert-butyldimethylsilyl
<i>t</i> Bu	tert-butyl
Tf	triflate
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	tosyl
UV	ultraviolet

ABSTRACT

The development of new methodologies in organic chemistry is of great importance. In fact, the discovery and creation of new reactions frequently uncovers new chemical reactivities and creates new areas of chemistry. The purpose of this thesis is to present the development of new synthetic reactions that were discovered through previous findings. Additionally, the main theme of this work relies on the intermediacy of a cationic reactive intermediate: epoxonium ions. Chapter 1 provides a brief review of bicyclic epoxonium ions and methods for their generation, as well as their utility in the synthesis of interesting heterocycles. Furthermore, Chapter 1 illustrates our attempts at applying the information we gained from our group's previous projects utilizing triphosgene and pyridinium acids for the chemoselective cyclization of epoxides to novel chlorinated pyranoside heterocycles. Ultimately through this study we were able to uncover the unprecedented chemoselective activation of an epoxyketone with triphosgene, as well as discover a novel counterion based selectivity during the ionization of epoxyketones.

Chapter 1. A Review of Epoxonium Ions and their Application for the Synthesis of Chlorine Substituted Pyranosides

1.1. Purpose

The purpose of this chapter is to review methodologies for the generation of bicyclic epoxonium ions from medium ring ether heterocycles and acyclic epoxides and showcase their value in synthesis. Baldwin's Rules for ring closure will be reviewed as they are important in demonstrating how the reactivities of epoxonium ions differ from common acid or base promoted epoxide cyclizations. Approaches for the cyclization of acyclic, terminal epoxides developed by Murai, McDonald and Floreancig will be discussed. Finally, the successful cyclization of unactivated epoxyketones to pyranoside heterocycles promoted by pyridinium acid in combination with triphosgene will be presented. Mechanistic analyses supporting the formation of a transient epoxonium ion will be discussed, as well as a model illustrating a novel counterion biased chemoselectivity.

1.2. Baldwin's Rules for Ring Closure

The synthesis of a target molecule usually begins with forming a retrosynthetic plan. Retrosynthetic analysis¹ is a powerful method wherein the synthetic chemist imagines working backwards starting with the target molecule and breaking it down into smaller fragments. These fragments are known as synthons and can further be broken down into smaller and smaller components of the target molecule until the chemist arrives at either commercially available materials or ones that can be synthesized from commercial sources. As powerful of a tool this is, retrosynthetic analyses wouldn't be possible without fundamental knowledges of chemical reactivity, specifically whether a reaction is going to produce the correct regioisomer, stereoisomer, or react with multiple functional groups. This process of working backwards from a

target molecule has become a less intimidating task with the development of chemical models and rules to help predict reaction outcomes.

A specific set of rules that have been developed to help with the retrosynthesis of target molecules and has found extensive utility are Baldwin's Rules for Ring Closure.²⁻⁴ These empirical rules were developed by Sir Jack Baldwin in the late 1970s to help predict the outcome of a cyclization reaction of a carbocyclic system. The success of the cyclization reaction is classified as either disfavored (D) meaning not likely to produce the desired product; or *favored* (F) which is likely to produce the desired cyclized product. Yet deviations do occur, as these rules are more like guidelines rather than law. These rules provide a model for the attack of a carbon-leaving group bond ($\bullet\text{--Y}$) by heteroatom, carbon or radical nucleophile (X) (Table 1.1). One of the limitations of Baldwin's rules is that they do not predict the reactivities of electrocyclic reactions.

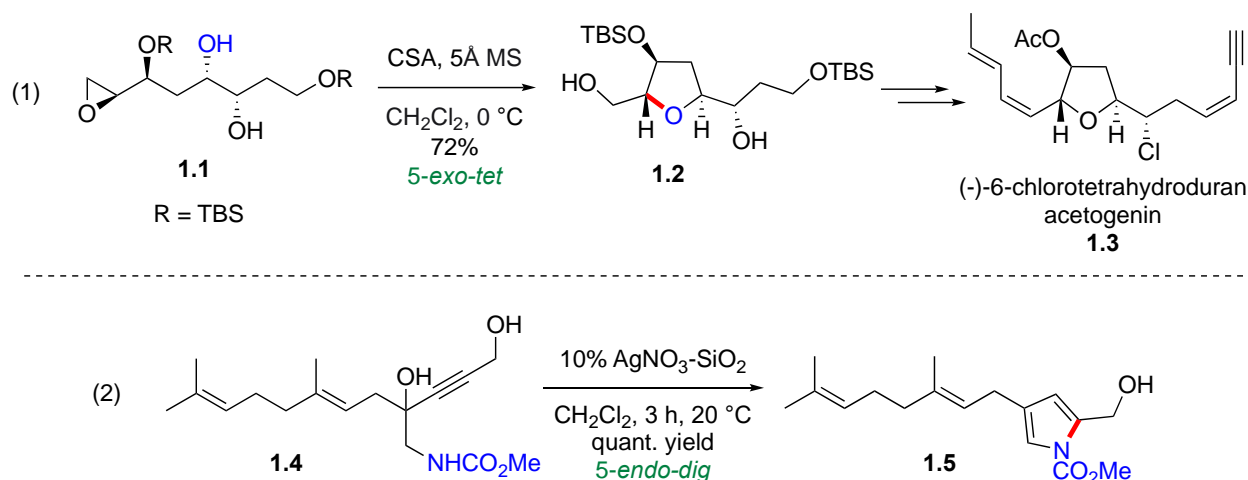
Table 1.1. Baldwin's Rules for Ring Closure

Ring Size	Exo-dig	Exo-trig	Exo-tet	Endo-dig	Endo-trig	Endo-tet
3	D	F	F	F	D	-
4	D	F	F	F	D	-
5	F	F	F	F	D	D
6	F	F	F	F	F	D
7	F	F	F	F	F	-

D = Disfavored cyclization; F = Favored Cyclization

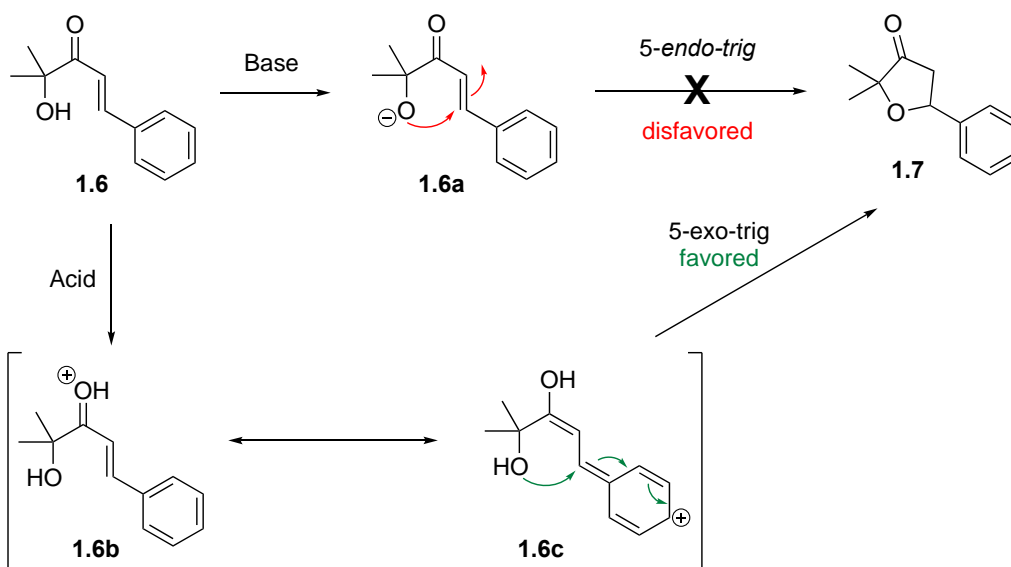
Baldwin's Rules use the following descriptors to predict if a ring closure reaction will be favored or disfavored: 1) The number of atoms in the newly formed ring (3-7 atoms). 2) Whether the bond broken is *exocyclic* or *endocyclic* to the newly formed ring. 3) The hybridization of the carbon atom that is attacked, *i.e.* sp , sp^2 , or sp^3 . The last descriptor also provides information about the angle of trajectory of the incoming nucleophile determined by Bürgi and Dünitz.⁵ These descriptors are represented using the following nomenclature *n-endo/exo-hybridization*, *n* being the number of atoms in the newly formed ring to represent the corresponding cyclization reaction. As already mention, this nomenclature governs: 1) The size of the newly formed ring (*n*). 2) Whether the broken bond is outside of the ring formed (*exo*) or inside the ring formed (*endo*). 3) The hybridization of the carbon atom attacked during ring closure, which are tetragonal (*tet*) for sp^3 -hybridized atoms, trigonal (*trig*) for sp^2 -hybridized atoms, and digonal (*dig*) for sp -hybridized atoms.

Scheme 1.1 *eqn. 1* illustrates a favored exocyclic ring-formation used toward the first total synthesis of two possible diastereomers of natural product 6-chlorotetrahydrofuran acetogenin.⁶ Takamura and co-workers were able to compare the ^1H and ^{13}C NMR data and specific rotations of these diastereomers with those of the isolated natural product and concluded that the correct stereochemistry of (-)-6-chlorotetrahydrofuran acetogenin is **1.3**. To achieve the furan ring of the natural product, diol **1.1** underwent 5-*exo-tet* cyclization in the presence of camphorsulfonic acid (CSA) and 5Å molecular sieves to give product **1.2** in 72% yield. With the furan ring set, they went on to complete the synthesis natural product **1.3**. This is a favored cyclization, and the descriptor is 5 for the size of the newly formed ring, *exo* because the bond broken is outside of the newly formed ring, and *tet* due to the sp^3 -hybridization of the electrophilic carbon of **xx** that was attacked.



Scheme 1.1. Examples of Baldwin's Rules for Ring Closure

A second example shows a favored endocyclic cyclization (Scheme 1.1, *eqn. 2*) that was used *en route* to a novel total synthesis of Pyrrolostatin by Knight and co-workers.⁷ To achieve the pyrrole ring of Pyrrolostatin, diol **1.4** underwent 5-*endo-dig* cyclization when exposed to AgNO₃-SiO₂, affording 2-pyrrolymethanol **1.5**, which was then converted to natural product Pyrrolostatin in a few more steps. Again, 5 is the size of the newly formed ring, *endo* because the bond broken is a part of the newly formed ring and *dig* due to the electrophilic carbon that gets attacked being *sp*-hybridized. Also, Baldwin's Rules can help explain reaction mechanisms when supported by experimental observations.⁸ For example, starting with α -hydroxyenone **1.6** you get two different results when treating it with either acidic or basic conditions (Scheme 1.2). When treated with basic conditions, it fails to produce any product as this would have to go through a 5-*endo-trig* cyclization, which is disfavored under Baldwin's rules. However, when acidic conditions are applied to **1.6** there is formation of the desired furanone product **xx** that presumably goes through a favored 5-*exo-trig* cyclization.



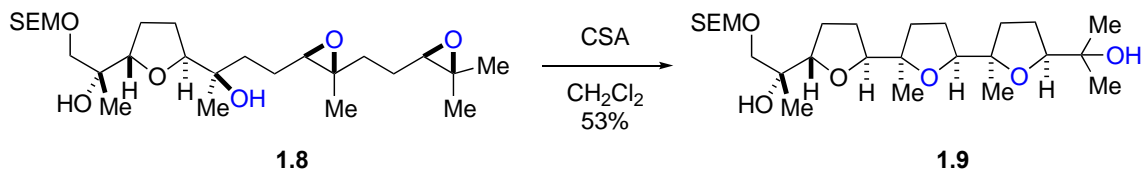
Scheme 1.2. 5-endo-trig vs 5-exo-trig Cyclizations

It is important to note that Baldwin's Rules are just a model used to help predict whether or not a desired cyclization is likely to occur. They help to give an idea of the necessary trajectories a nucleophile must have in order for good orbital overlap to occur, which is needed for the formation of a chemical bond. The 5-endo-dig cyclization is disfavored because the alkoxide attacking the enone (**1.6a** → **1.7**) does not possess enough orbital overlap to result in bond formation. In the case of the acidic conditions, delocalizing the π -conjugation by one carbon atom leads to more orbital overlap and less strain (**1.6b** → **1.6c**). Baldwin's Rules are not laws, and while there are some exceptions and limitations⁹⁻¹³, they will usually predict the appropriate reactivity of a given ring closing reaction.

1.3. Strategies for the Generation of Epoxonium Ions

Epoxides are three-membered oxygen containing heterocycles that are highly strained due to its roughly 20-24 kcal/mol of ring strain energy.¹⁴⁻¹⁵ Due to this ring strain, the two α -carbons of an epoxide are rather electrophilic, which is taken advantage of in synthesis quite often in

synthesis. An example of this is the well-known reactivity of epoxides that involves the cyclization of alcohols onto epoxides, producing cyclic ether products. For instance, Morimoto exploited an epoxide-opening cascade *en route* to the total synthesis of the natural product enshuol.¹⁶ In this synthesis, Morimoto and co-workers generated diepoxy alcohol **1.8** and then subjected it to activation with stoichiometric CSA, which led to a favored 5-*exo-tet* cyclization producing **1.9**. This resulted in the formation of two more tetrahydrofuran rings on the compound in a 53% yield on the way to their total synthesis of enshuol. This reactivity of epoxides is commonly used to the advantage of synthetic chemists to produce heterocycles as the oxygen atom of epoxides is easily activated by various acid sources.¹⁷⁻¹⁹



Scheme 1.3. Morimoto's Epoxide-Opening Cascade

This type of acid activation of the epoxide forms these oxonium intermediates **1.10a** or **1.10b** (Figure 1.1) that are known as monocyclic epoxonium ions. In Morimoto's synthesis of enshuol, activation of one of the epoxides with CSA supposedly generates a monocyclic epoxonium ion that is then attacked by the free alcohol via an *S_N2* mechanism, thus forming the observed ring system. There is, however, a different strategy for activating epoxides that involves reversing its inherent electrophilicity and instead utilizing them as nucleophiles. This umpolung strategy relies on the oxygen atom of the epoxide to attack an electrophilic species, forming what is called a bicyclic epoxonium ion **1.11** (Figure 1.1). These intermediates are very strained, unstable electrophiles that are formed through the same cyclization process as previously discussed

or through ring expansion medium ring oxygen containing heterocycles.²⁰⁻²² Interestingly, these intermediates involve a deviation from Baldwin's Rules as attack of epoxonium ions can lead to either endocyclic or exocyclic products depending on the reaction conditions and starting materials employed.

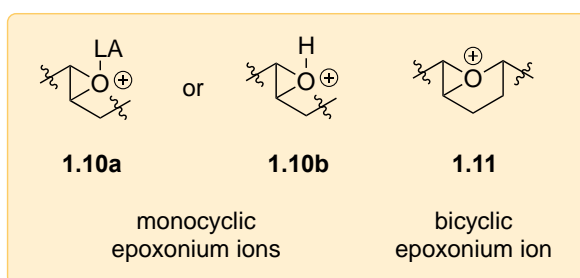
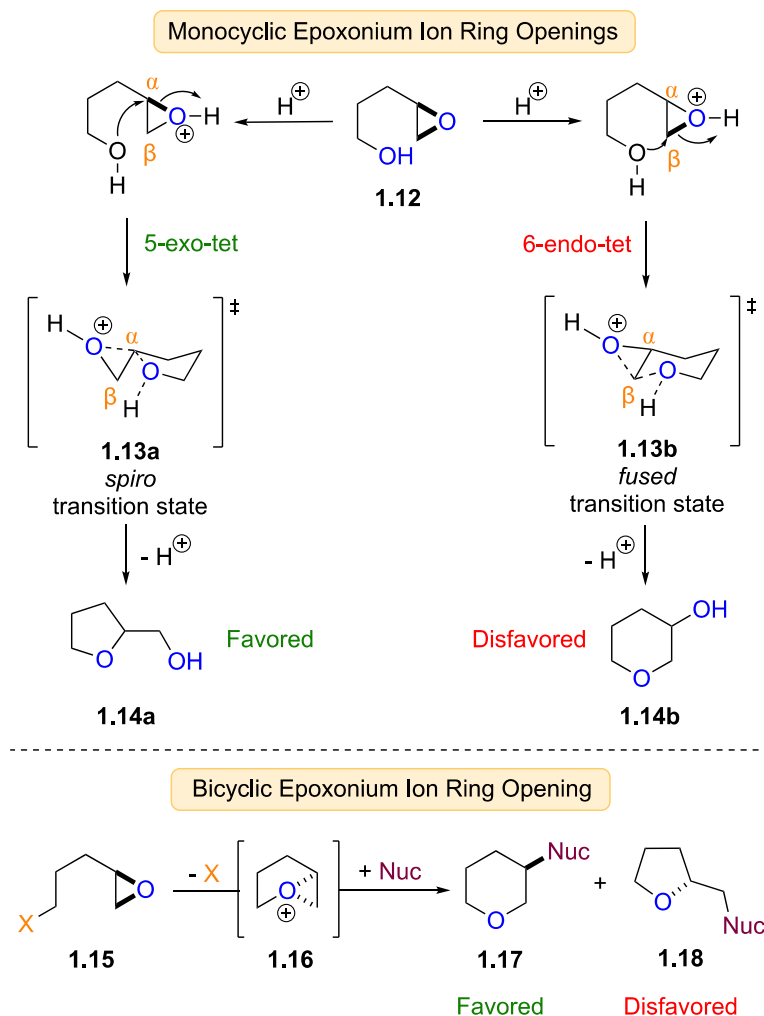


Figure 1.1. Epoxonium ions

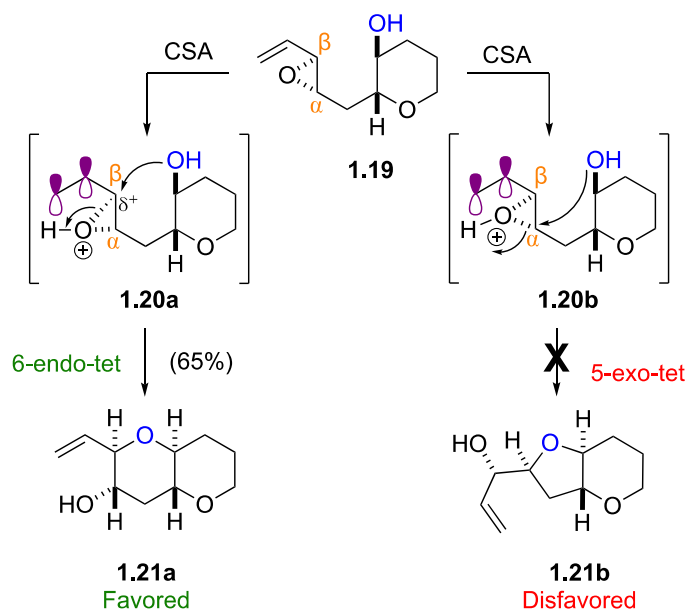
Ring opening of epoxides typically occur via the favored *n-exo-tet* cyclization pathway, forming the smaller ring system instead of the larger (Scheme 1.4). In this example, activation of epoxyalcohol **1.12** with either an acid or a base will make the α -position or β -position of the epoxide more electrophilic. Attack of the α -carbon will occur via a *spirocyclic* transition state **1.13a**. This pathway has the least amount of angle strain in the transition state resulting in 5-*exo-tet* cyclization, forming the favored five-membered tetrahydrofuranol **1.14a**. Alternatively, attack at the β -position of **1.12** is disfavored as this mode of attack proceeds through a *fused* transition state **1.13b**, which would form the tetrahydropyranol product **1.14b**. This pathway (6-*endo-tet*) to form the endocyclic product is disfavored because of the increase in angle strain in the transition state. It is important to note that both of these cyclization pathways are technically *exocyclic* since the bond being broken is outside of the ring formed, thus to avoid confusion it is preferred to use the terms “*spiro*” and “*fused*” for *exocyclic* and *endocyclic* products respectively. If the *fused* product is desired, then simple acid or base catalyzed methods will usually be unable to yield the

desired result. To produce the *fused* product in a system in which a monocyclic epoxonium ion intermediate is present, then it is required to either stabilize the *fused* transition state or destabilize the *spiro* transition state. An alternative method to forming the *fused* product is to design a system that encourages the formation of bicyclic epoxonium ions that result in the larger ring system being formed. The generation of bicyclic epoxonium ions circumvents the constrained *fused* transition state of these types of reactions and results in the formation of the *fused* products which are typically disfavored according to Baldwin's Rules.



Scheme 1.4. Ring Openings of Epoxides

Interestingly, in 1985 the Nicolaou research group were able to overcome this natural preference for the undesired 5-*exo-tet* cyclization of alcohols onto epoxides without having to design a system that generates bicyclic epoxonium ions (Scheme 1.5).⁹ They were able to do this by placing an alkene adjacent to the epoxide of compound **1.19**. Although this reaction is presumed to proceed via a monocyclic epoxonium ion, hydroxy epoxide **1.19** treated with CSA underwent 6-*endo-tet* cyclization to afford bispyran moiety **1.21a** rather than the 5-*exo-tet* product **1.21b**. This reversal of ring selectivity is attributed to the stabilization of the nearby π orbital to the developing electron deficient β -carbon in transition state **1.20a**, leading to bispyran **1.21a** exclusively. This stabilization to the α -carbon in the hypothetical transition state **1.20b** towards the formation of 5-*exo-tet* product **1.21b** is not present, making it disfavored in this situation. This was the first reported stereo- and regioselective synthesis of pyrans involving the opening of epoxides with a hydroxy group and was used *en route* to the Nicolaou group's eventual total synthesis of marine polyether biotoxin Brevetoxin B.²³



Scheme 1.5. 6-*endo-tet* Hydroxy Epoxide Opening via Monocyclic Epoxonium Ion

Both of these cyclization processes that go through bicyclic or monocyclic epoxonium ions are believed to be how marine polyether natural products, like Brevetoxin B, are formed in nature.¹⁸⁻¹⁹ These *trans*-fused compounds typically consist of repeating tetrahydropyranyl and oxepanyl ethers that are substituted with hydroxyl and methyl groups which possess various stereochemistries. These natural products can be toxic to marine life and we can see their impact during large algal blooms also known as “red tide” algal blooms, which occur all over the world. Florida, for instance, experiences these outbreaks almost every year. The brevetoxin producing dinoflagellate *Karenia Brevis* is responsible for the toxicity of these “red tide” algal blooms and have been seen to cause the death of marine animals and massive fish kills.²⁴ Furthermore, many species of fish consume these toxin-producing dinoflagellates, which in turn can be passed onto human when they consume the seafood, resulting in sickness. The majority of these polyether natural products are neurotoxins which can affect humans through the activation of voltage-sensitive ion channels.²⁵ Interestingly, some of these ladder polyether compounds have been found to possess antifungal activities.²⁶ It is for these reasons that there have been Herculean efforts made to be able to synthesize these stunning structures.

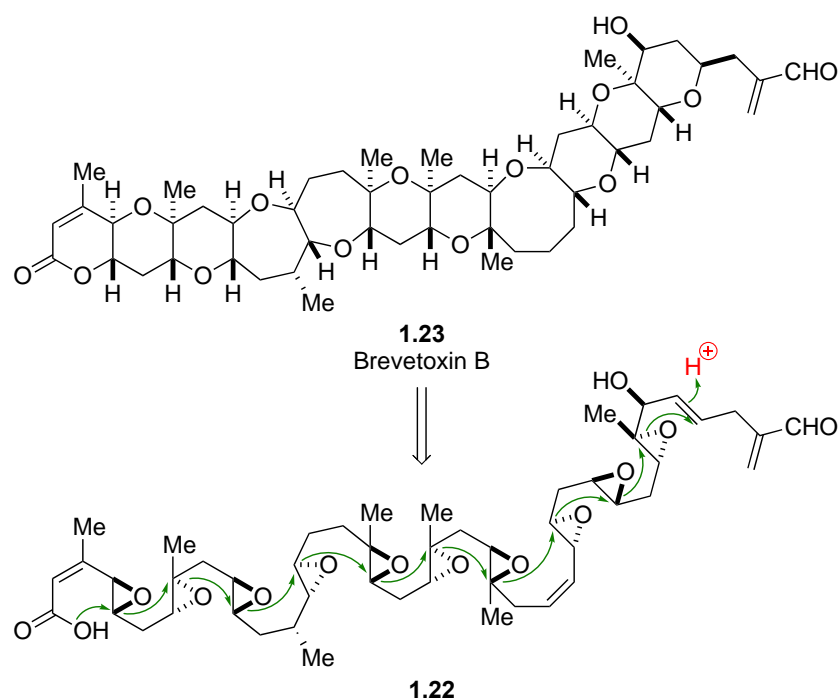
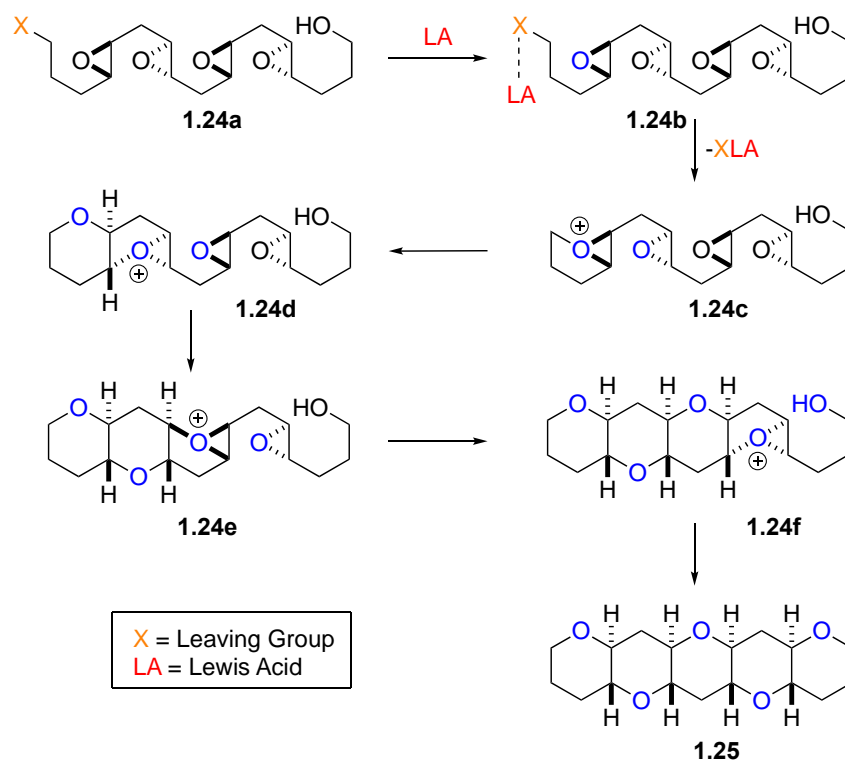


Figure 1.2. Nakanishi's Hypothesis for Polyepoxide Cascade Cyclization

The discovery of the structure of Brevetoxin B²⁷ **1.23** (Figure 1.2) in 1981 helped spark the interest in searching for new synthetic methods for the construction of these unique ladder polyether substrates. Soon after this report, Nakanishi and co-workers reported a hypothesis for how Brevetoxin B is produced in nature, which involves polyepoxide precursor **1.22** undergoing a zip-type cascade reaction to produce the biotoxin.²⁸⁻²⁹ There is presumed to be an enzymatic process in *Karenia Brevis* that assists this hypothetical reaction take place, but in the absence of enzymes this method is not considered feasible in the laboratory. One reason for this is the natural preference for the smaller (*spiro*) ring to be formed during these cyclizations according to Baldwin's Rules as mentioned previously. Secondly, a big restriction on performing this reaction in a lab was the lack of methods available to synthesize these polyepoxide precursors. There is some debate about whether this proposed biosynthetic mechanism goes through normal ring-opening of monocyclic epoxonium ions or through the formation of bicyclic epoxonium ions and

subsequent capture, but some scientists believe it might be a combination of both.³⁰ However, the immense control needed for all the rings to be *fused* in this situation provides some support for a bicyclic epoxonium ion mechanism.



Scheme 1.6. Model Epoxonium Cascade

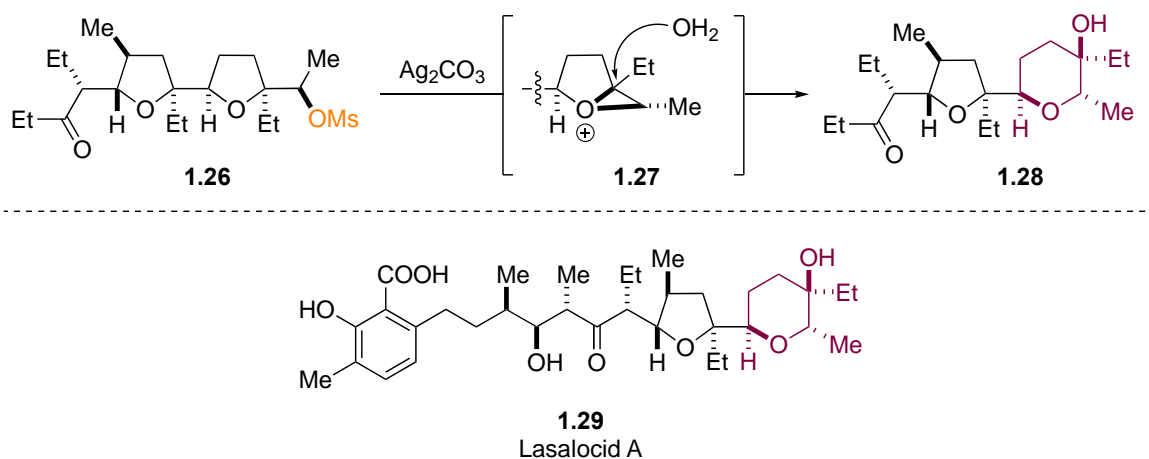
These cascades presumably undergo tandem ring-opening/cyclization of the epoxide which occur until the desired compound is formed. The regioselectivity of these cascades are problematic because of the inherent preference to form the smaller ring system, so the most plausible pathway would be the formation of a tandem bicyclic epoxonium ion followed by nucleophilic attack of the nearby epoxide. Scheme 1.6 details a proposed epoxide cascade process where tetraepoxide **1.24a** undergoes activation of a leaving group with an acid source.²⁰ This allows for nucleophilic substitution, generating bicyclic epoxonium ion **1.24c**. The nearby epoxide can then attack the

epoxonium ion via an analogous process and form **1.24d**. This process continues until the final *trans*-fused product **1.25** is formed. This example is oversimplified considering these natural products can contain a mix of five-, six-, and seven-membered rings within their structures; however, it is suggested that this is the reason for the selectivity of the typically disfavored *fused* pathway.

The generation of bicyclic epoxonium ions is known to occur through two methods. The first way is attack of a leaving group by the oxygen atom of a medium ring ether, forming the bicyclic epoxonium ion. Addition of a nucleophile at the endocyclic position then gives a ring expanded product. Another method is the direct cyclization of an epoxide onto an activated leaving group, forming a bicyclic epoxonium ion. The latter method is more common in literature and is largely applicable to polyepoxide cascade cyclizations towards marine ladder natural products.

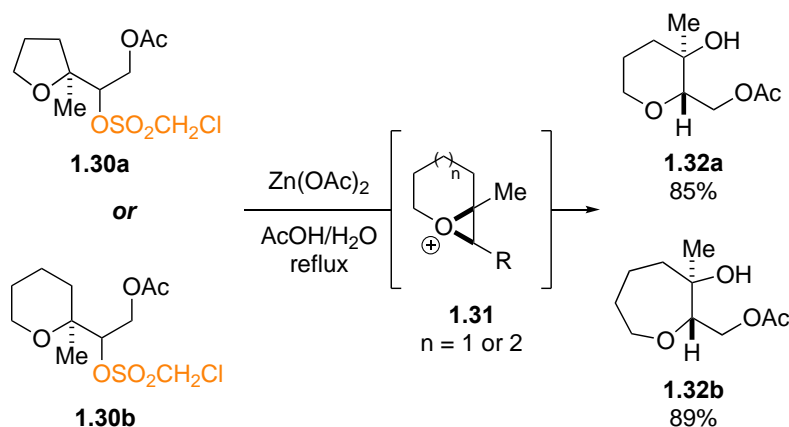
1.3.1 Ring Expansion via Capture of Bicyclic Epoxonium Ion

One of the first examples of ring expansion via nucleophilic capture of a bicyclic epoxonium ion was reported by Kishi and co-workers in 1978. In their attempt to produce natural product Lasalocid A **1.29** they found that they were able to construct the six membered ring at the end of the molecule via this method (Scheme 1.7).³¹ They reported that the mesyl group on compound **1.26** was activated by Ag₂CO₃, resulting in attack of the nearby oxygen atom at the β-carbon. It was hypothesized that bicycle epoxonium ion **1.27** was then formed and subsequent regioselective nucleophilic capture at the *endocyclic* position produced the ring expanded product **1.28** in a 65% yield. Nucleophilic capture at the *exocyclic* position in this case would have resulted in the non-ring expanded product.



Scheme 1.7. Kishi's Ring Expansion Strategy

Nakata, A former student of Kishi, gained inspiration while working on the synthesis of Lasalocid A to further study the ring expansion of heterocycles via bicyclic epoxonium ion intermediates. Utilizing a similar strategy to Kishi, Nakata and co-workers offered an improved strategy by using a different protecting group, monochloromethanesulfonate (monochlate), as opposed to a methanesulfonate (mesylate).³²⁻³³ Monochlate protected medium ring ethers **1.30a** and **1.30b** were treated with $\text{Zn}(\text{OAc})_2$ and it was found that the monochlate was a superior leaving group in this case as ring expanded products **1.32a** and **1.32b** were produced in excellent yields (Scheme 1.8). Activation of the leaving group with $\text{Zn}(\text{OAc})_2$ supposedly results in the formation of bicyclic epoxonium ion **1.31** that is ready for nucleophilic capture at the *endocyclic* position.

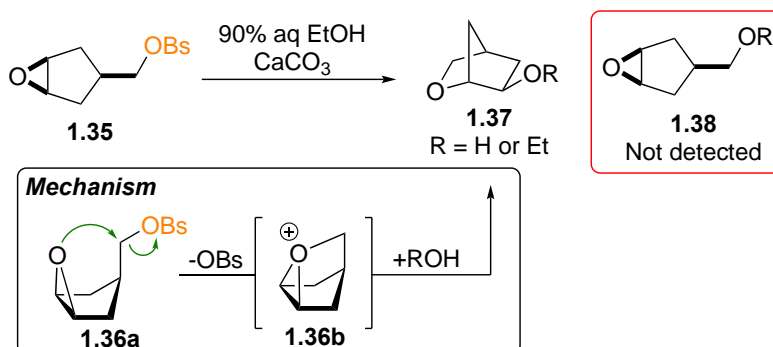


Scheme 1.8. Nakata's Ring Expansion Strategy

1.3.2 Bicyclic Epoxonium Ion Formation via Acyclic Epoxides

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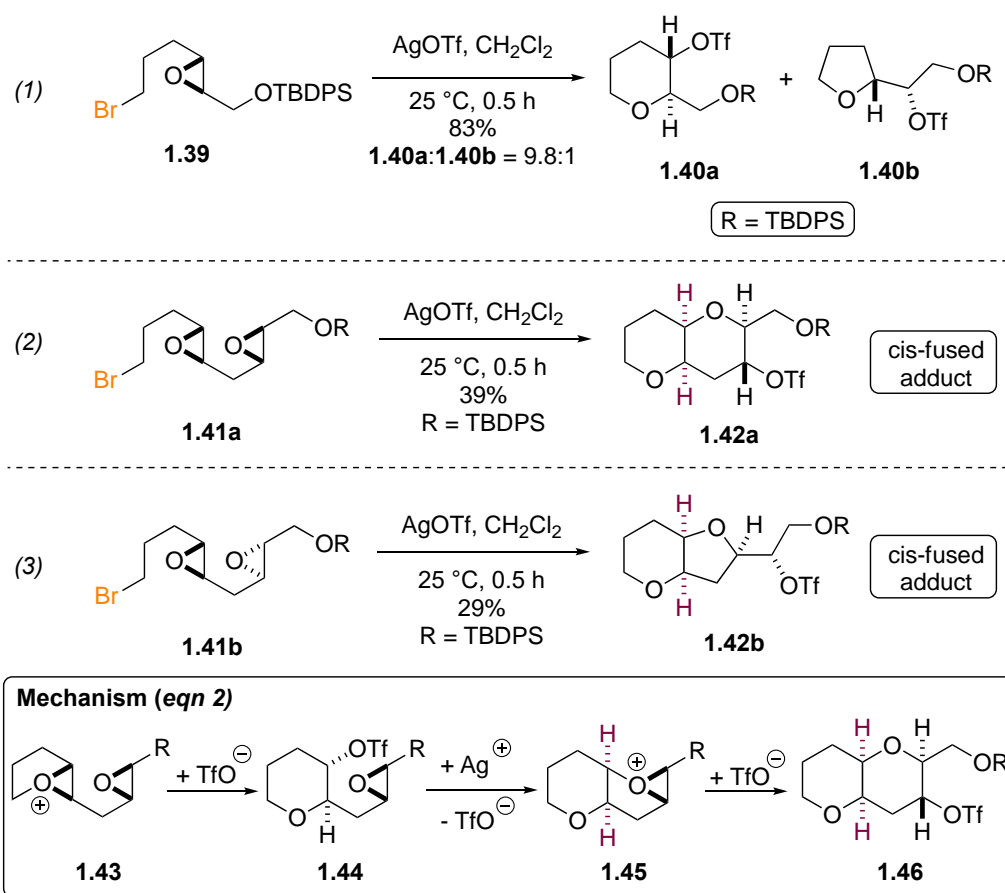
product mixture. This interesting result led to more scientists attempting to use epoxides as precursors to bicyclic epoxonium ion intermediates.



Scheme 1.10. David's Solvolysis Experiment

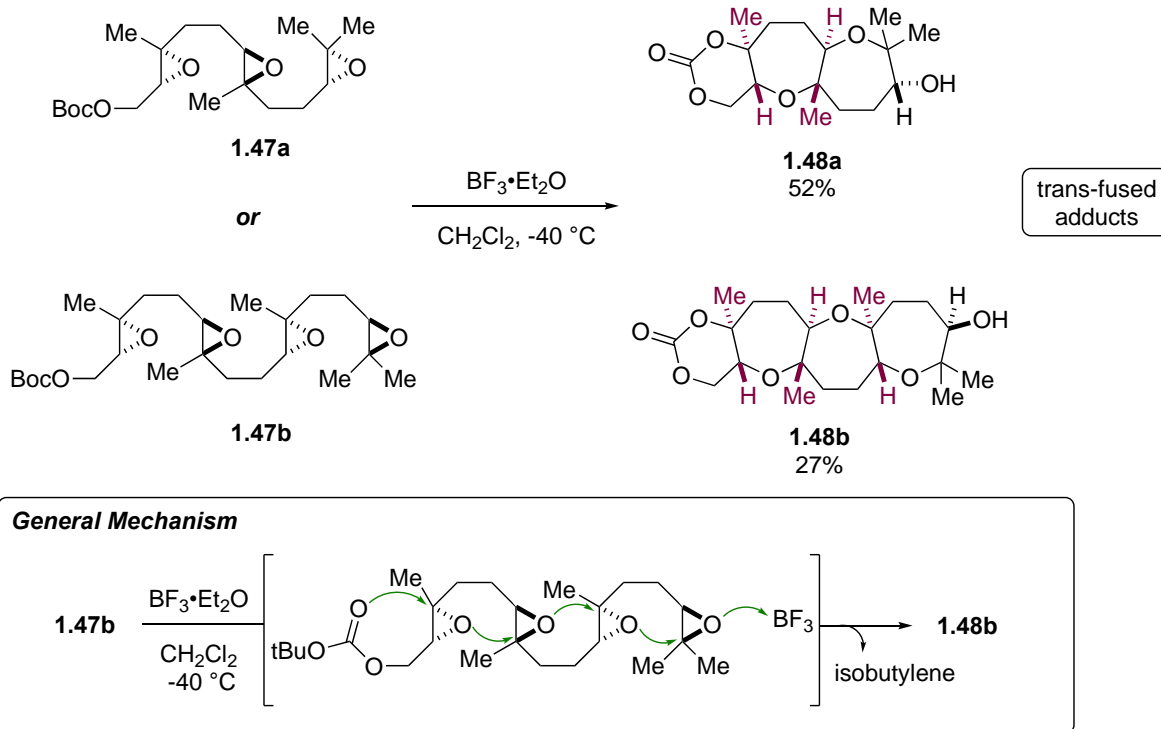
Inspired by the work of David as well as Nakanishi's hypothesis on the synthesis of marine polyether natural products, Murai and his team set out to explore this reactivity of acyclic epoxides.³⁷ Their goal was to find a method suitable for forming predominantly the *endo* product, as well as forming trans-fused ring systems similar to those that many marine ladder polyethers possess. Murai found that treatment of bromoepoxide **1.39** with AgOTf in CH₂Cl₂ generated about a 10:1 mixture *endo:exo* (**1.40a:1.40b**) products in a yield of 83% (Scheme 1.11, *eqn 1*). After further studies, it was shown that **1.40a** and **1.40b** lie in equilibrium and that **1.40a** is the thermodynamically favored product. When the same reaction of **1.39** was ran at -15 °C for 30 minutes it was found that the *exo* product **1.40b** was kinetically favored in a 1:16 ratio, but when the reaction was allowed to spin for another 5 hours, **1.40a** was formed in a 16:1 ratio. Murai and co-workers then set out to apply this methodology toward a cascade process. Upon activation of *cis*-diepoxide **1.41a** with AgOTf in CH₂Cl₂ produced *cis*-fused ether **1.42a** in 39% yield (scheme 1.11 *eqn 2*). *Trans*-diepoxide **1.41b** was also subjected to the same conditions and a similar *cis*-

fused adduct was formed (Scheme 1.11 *eqn 3*). Forming the *cis*-fused product in both cases was not what Murai was expecting. They were hoping to form trans-fused adducts similar to those seen in many of the marine polyether natural products such as Brevetoxin B. Murai proposed that after formation of the first bicyclic epoxonium ion **1.43**, addition of triflate ion beats out the cyclization of the adjacent epoxide. This forms compound **1.44** which was able to be isolated by quenching the reaction early. They then treated **1.44** with AgOTf which allowed for cyclization upon attack of the epoxide to give the *cis*-fused product **1.46**.



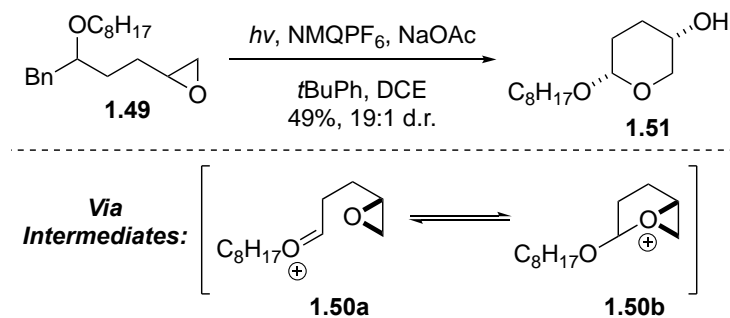
Scheme 1.11. Murai's Epoxide Cyclization Strategy

Following the works of Murai, McDonald and his team developed a number of strategies for forming *trans*-fused polyether products from polyepoxide cascade cyclizations.³⁸⁻⁴⁰ McDonald and his team were the first to report a cascade reaction that formed *trans*-fused bisoxepane systems via *endo*-selective epoxide ring opening. Triepoxide **1.47a** and tetraepoxide **1.47b** were activated with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in CH_2Cl_2 at $-40\text{ }^\circ\text{C}$ and generated *trans*-fused tricycle **1.48a** and *trans*-fused tetracycle **1.48b** in 52% and 27% yield respectively (Scheme 1.12). It is presumed that this mechanism begins with activation of the terminal epoxide that is distal to the carbonate group with $\text{BF}_3 \cdot \text{Et}_2\text{O}$, forming a monocyclic epoxonium ion. The neighboring epoxide can then attack the epoxonium ion, leading to a bicyclic epoxonium ion which is primed for nucleophilic attack by another neighboring epoxide, thus resulting in a cascade reaction. The *tert*-butoxy group acts as a terminating nucleophile and caps the last cationic intermediate, consequently terminating the reaction and releasing isobutylene in the process. The use of *tert*-butoxy ester as a terminating nucleophile led to the *trans*-fused heterocycles, which suggests that the trapping of epoxonium ions are all occurring intramolecularly. This is different to the situation in Murai's case discussed before where there was addition of a triflate ion to the epoxonium ion, resulting in the *cis*-fused system. It was seen that as the number of epoxides in the polyepoxide precursor increased, there was a decrease in yield. A possible reason for this could be the inability of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to activate all of the epoxides in these larger systems.



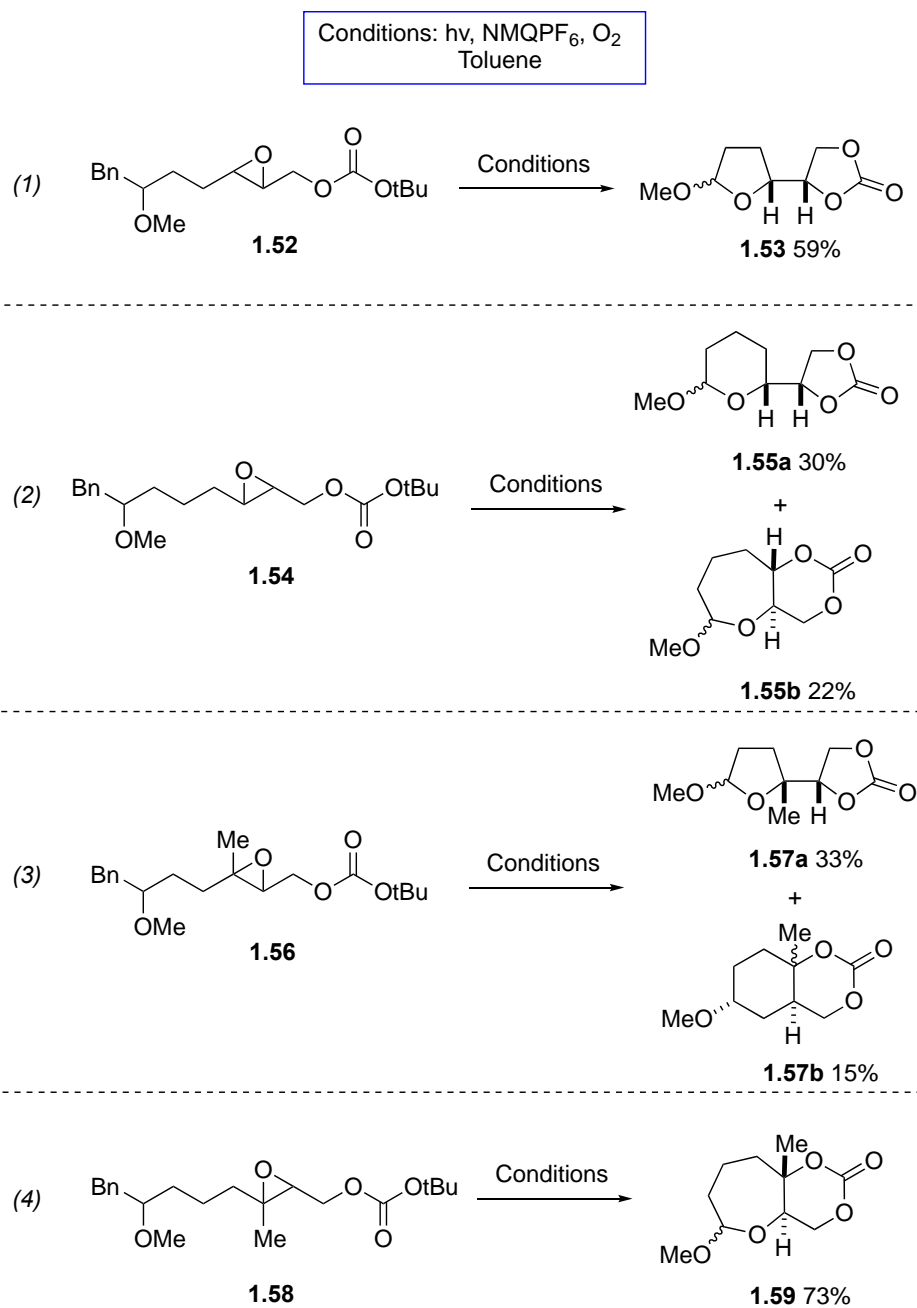
Scheme 1.12. McDonalds Polyepoxide Cyclization Strategy

The lab of Paul Floreancig has also been a large contributor to this area of study.⁴¹⁻⁴³ In 2005, they reported that the oxidation of epoxide **1.49** with $h\nu$ and NMQPF₆ afforded tetrahydropyran **1.51** in 49% yield at a 19:1 diastereomeric ratio (Scheme 1.13).⁴² Upon oxidation, oxonium ion **1.50a** is presumably generated. This intermediate then can be captured by the neighboring epoxide, forming bicyclic epoxonium ion **1.50b**. Ring opening with H₂O then led to the generation of *endocyclic* product **1.51**.



Scheme 1.13. Floreancig's Epoxonium Ion Cyclization

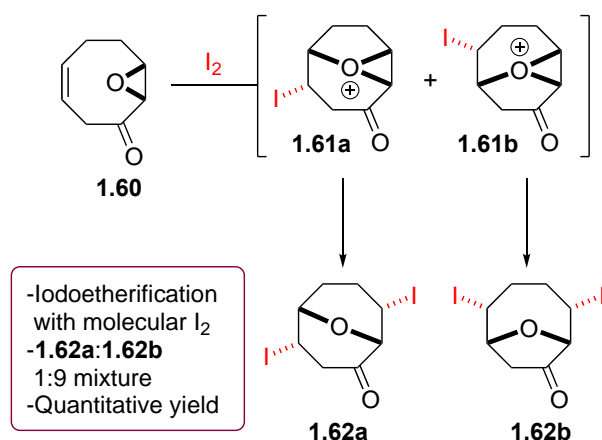
Later in 2007, Floreancig and co-workers set out to apply a similar methodology to di- and trisubstituted epoxides.⁴³ Necessary components in these photochemical reactions were NMQPF₆ as a catalytic oxidant, Oxygen from air as a terminal oxidant and toluene as a cosensitizer. Disubstituted epoxide **1.52** generated exocyclic product **1.53** as a mixture of anomers in a 59% yield (Scheme 1.14, *eqn 1*). Homologated disubstituted epoxide **1.54** generated a mixture of *exocyclic* product **1.55a** and *endocyclic* product **1.55b** in a 30% and 22% yield respectively (Scheme 1.14, *eqn 2*). The formation of endocyclic product **1.55b** was interesting because the only difference between the reactions of epoxides **1.55a** and **1.55b** is that the initial cyclization of **1.55a** proceeds through a bicyclo[3.1.0] epoxonium ion, while **1.55b** proceeds through a bicyclo[4.1.0] epoxonium ion. This type of *endo*-cyclization proceeding through a bicyclo[4.1.0] epoxonium ion has been seen by McDonald and co-workers.⁴⁴ Trisubstituted epoxide **1.56** produced also produced a mixture of the exocyclic product **1.57a** and endocyclic product **1.57b** in a 33% and 15% yield respectively, which was determined based on NMR analysis of the product mixture (Scheme 1.14, *eqn 3*). The methyl group added to the epoxide helped stabilize the cationic intermediate enough to help the regioselectivity of the reaction modestly, but it was still not enough to form mostly the *endocyclic* product. It should also be noted that endocyclic product **1.57b** is a mixture of the *trans*- and *cis*-fused products. Gratifyingly, Homologous trisubstituted epoxide **1.58** generated solely the *trans*-fused endocyclic product **1.59** in a 73% yield (Scheme 1.14, *eqn 4*). This showed that the combined impact of the methyl substituent on the epoxide, and the generation of a bicyclo[4.1.0] epoxonium ion intermediate led to a complete reversal of the *exo*-cyclization preference that was observed in the reaction of epoxide **1.52**. These experimental results as well as computational studies done by the Houk lab showed that the outcome of these cyclizations is largely dependent on the structure of the starting epoxide.



Scheme 1.14. Cyclization of [3.1.0] vs [4.1.0] Bicyclic Epoxonium ions

1.4. Nucleophilic Capture of Bicyclic Epoxonium Ions by Halogen Nucleophiles

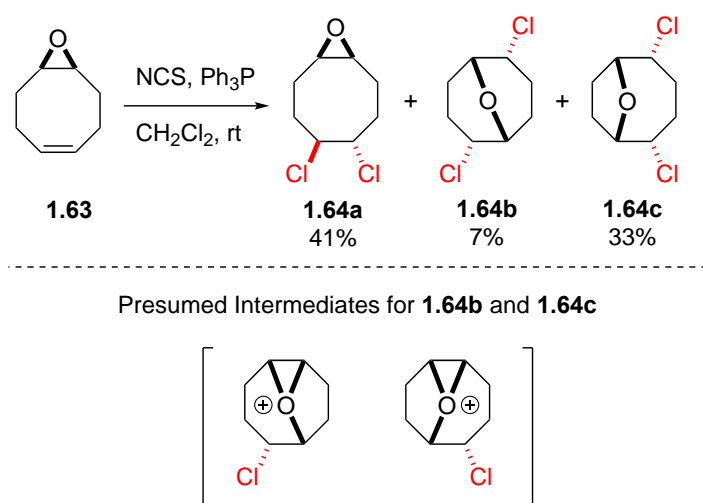
Much of the literature on capture of bicyclic epoxonium ions has the cationic intermediate captured by a neighboring epoxide. However, an interesting avenue for the capture of these epoxonium ions is the use of halogen nucleophiles. The Martín group were one of the first labs to report on this type of reactivity.⁴⁵⁻⁴⁶ Epoxyketone **1.60** was treated with I₂ in CH₂Cl₂ and generated bicyclic ketones **1.61a** and **1.62b** in a 1:9 ratio respectively (Scheme 1.15).⁴⁶ It is presumed that after the iodonium intermediate is formed across the olefin that capture with the epoxide occurs, forming possible epoxonium ions **1.60a** and **1.60b**. Subsequent attack by iodine forms the products seen.



Scheme 1.15. Martín's Iodetherification via Bicyclic Epoxonium ion

Yoshimitsu discovered a similar reactivity while exploring the dichlorination of olefins using mixtures of NCS/Ph₃P in the presence of epoxides.⁴⁷ Interestingly, it was found that the reaction of epoxide **1.63** generated expected dichloride **1.64a**, as well as unexpected bicycles **1.64b** and **1.64c** in low yields (Scheme 1.16). Yoshimitsu and co-workers did not conduct any further mechanistic studies but comparing the results of this reaction with that of Martín's discussed before shows an interesting trend. In Martín's work we see that the bicyclo[2.1.4] octane **1.62b**

was favored over bicyclo[3.1.3] octane **1.62a** in a 9:1 ratio. Similarly in Yoshimitsu's work, we see bicyclo[2.1.4] octane **1.64c** formed in a 33% yield versus bicyclo[3.1.3] octane **1.64b** formed in only a 7% yield. These results show that the reaction observed by Yoshimitsu probably goes through analogous epoxonium intermediates as describes by Martín. The [2.1.4] bicyclic compounds appear to be the thermodynamically favored products in these situations due to reduced ring strain in the product.

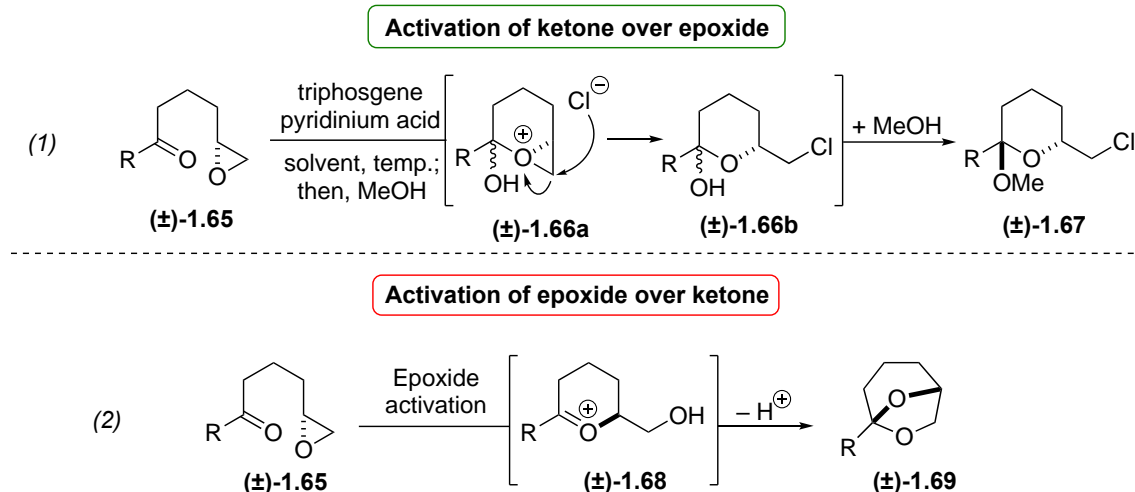


Scheme 1.16. Yoshimitsu's Epoxonium Ion Encounter

The works of Martín and Yoshimitsu help demonstrate the potential for regioselective capture of epoxonium ions with halogen nucleophiles. Martín also demonstrated the usefulness of the halogenated products in generating more complex molecules with the utility of the added iodine. Our group then became interested in the possibility of generating a bicyclic epoxonium ion via the cyclization of an acyclic epoxide, followed by attack of a chlorine nucleophile. To our knowledge, no examples of this have been reported. Given our groups established triphosgene-amine base chlorination methodologies,⁴⁸⁻⁵² we began exploring these modes of reactivity.

1.5. Chemoselective Cyclization of 1,5-Epoxyketones Enabling Regioselective Ring Opening of Epoxonium Ions with Chloride Ions

As shown previously, Literature examples of ring opening of epoxonium ions typically involves the use of oxygen nucleophiles. Our group surmised that we could find a use for our known triphosgene-pyridine technology in this field of reactivity. Specifically, the use of chloride ions as nucleophiles for the capture of bicyclic epoxonium ions has limited examples shown in literature. It was envisioned that 1,5-epoxyketone (\pm)-**1.65** could be activated chemoselectively at the carbonyl oxygen with a pyridinium Brønsted acid (Py•HX) enabling cyclization to form bicyclic epoxonium ion (\pm)-**1.66a** (Scheme 1.17, *eqn* 1). Subsequent chloride ions generated *in situ* upon degradation of triphosgene by either pyridine or X⁻ could then act as a nucleophile towards the regioselective ring opening of bicyclic epoxonium ion (\pm)-**1.66a** at the *exo* position, leading to unstable hemiketal (\pm)-**1.66b**. Methanolic quench and subsequent work up would then ideally generate chlorine substituted pyranoside (\pm)-**1.67**. It was important to consider the vulnerability of the 1,5-epoxyketone starting material being subject to intramolecular ketalization under acidic conditions.⁵³ This process generally proceeds through activation of the epoxide over the ketone. Looking at our model epoxyketone (\pm)-**1.65**, activation of the epoxide with either Brønsted or Lewis acids could result in 6-*exo-tet* cyclization from the ketone (Scheme 1.17, *eqn* 2). Oxocarbenium ion (\pm)-**1.68** can be intercepted by the nearby hydroxyl group, generating bicyclic ketal (\pm)-**1.69** after proton transfer. It was hypothesized that the choice of pyridinium acid used could allow for chemoselective activation of the ketone over the epoxide.



Scheme 1.17. Cyclization Strategy with 1,5-Epoxyketones

As reported previously, we synthesized our model epoxyketone (±)-**1.71** via epoxidation of ketoalkene (±)-**1.70** with *m*-CPBA (Table 1.2). Our concerns about the acid sensitivity of the 1,5-epoxyketone were substantiated as the use of 1.5 equiv of *m*-CPBA in CH₂Cl₂ generated the desired epoxide, but bicyclic ketal (±)-**1.72** was also produced in nearly equimolar amounts (entry 1). This most likely occurred via unintentional protonation of the epoxide moiety of (±)-**1.71** by *m*-CPBA, undergoing an analogous mechanism as shown in Scheme 1.17, eqn 2. Gratifyingly, simply switching the solvent to Et₂O led to a dramatic change in reactivity as epoxyketone (±)-**1.71** was generated in a 47% yield with 39% of unreacted starting material (entry 2). In an attempt to consume more of the starting material, the use of 2.0 equiv of *m*-CPBA was employed but this led to generation of the Baeyer-Villiger product (±)-**1.73** in 75% yield (entry 3). When reducing the amount of *m*-CPBA back to 1.5 equiv we saw inconsistent results, so we attempted to lower it to 0.75 equiv. This led to more consistent results, as it generated epoxyketone (±)-**1.65** in 64% yield based on 44% of recovered starting material (±)-**1.70** (entry 4). The epoxyketone proved to

be very acid sensitive, as a buffered column with Et₃N was necessary during purification in preventing unwanted cyclization to the bicyclic ketal.

Table 1.2. Synthesis of Model 1,5-Epoxyketone

Reaction scheme: **1.70** (Bn-C(=O)-CH₂-CH₂-CH=CH₂) reacts with *m*-CPBA in solvent (0.25 M) at rt to yield **(±)-1.71** (Bn-C(=O)-CH₂-CH₂-CH(O)₂-CH₃), **(±)-1.72** (bicyclic ketal), and **(±)-1.73** (BnO-C(=O)-CH₂-CH₂-CH(O)₂-CH₃).

Entry	Equiv of <i>m</i> -CPBA	Solvent	1.70	(±)-1.71	(±)-1.72	(±)-1.73
1	1.50	CH ₂ Cl ₂	0%	50%	50%	0%
2	1.50	Et ₂ O	39%	47%	0%	0%
3	2.00	Et ₂ O	0%	0%	0%	75%
4	0.75	Et₂O	44%	64%	0%	0%

^[a] Isolated yield after column chromatography.

With the model epoxyketone in hand, reaction optimization began by exposing **(±)-1.71** to mixtures of triphosgene and different pyridinium sulfonates (Table 1.3). Given the relative basicity of the ketone and epoxide functionalities, it was hypothesized that by biasing the relative electronics of sulfonate counterion there could be selective protonation of the ketone over the epoxide. The pilot study was done by treating **(±)-1.71** with Py•TsOH in 1,4-dioxane with 4Å MS at room temperature. This resulted in a 2:1 ratio of pyranoside **(±)-1.74** and bicyclic ketal **(±)-1.72** in 37% yield after methanolic quench (entry 1). Switching the acid to Py•TfOH reversed the selectivity in favor of unwanted ketal **(±)-1.72** (entry 2). Py•TsOH was then used with a series of polar aprotic solvent (entries 3-5). Ultimately, 1,2-DME was chosen as **(±)-1.72** was favored in a 5:1 ratio in a 60% yield at room temperature (entry 5). Given the results of entries 1-5, it was surmised that a more electron rich pyridinium sulfonic acid would more favor the generation of pyranoside **(±)-1.72**. A novel pyridinium sulfonic acid was then designed and generated,

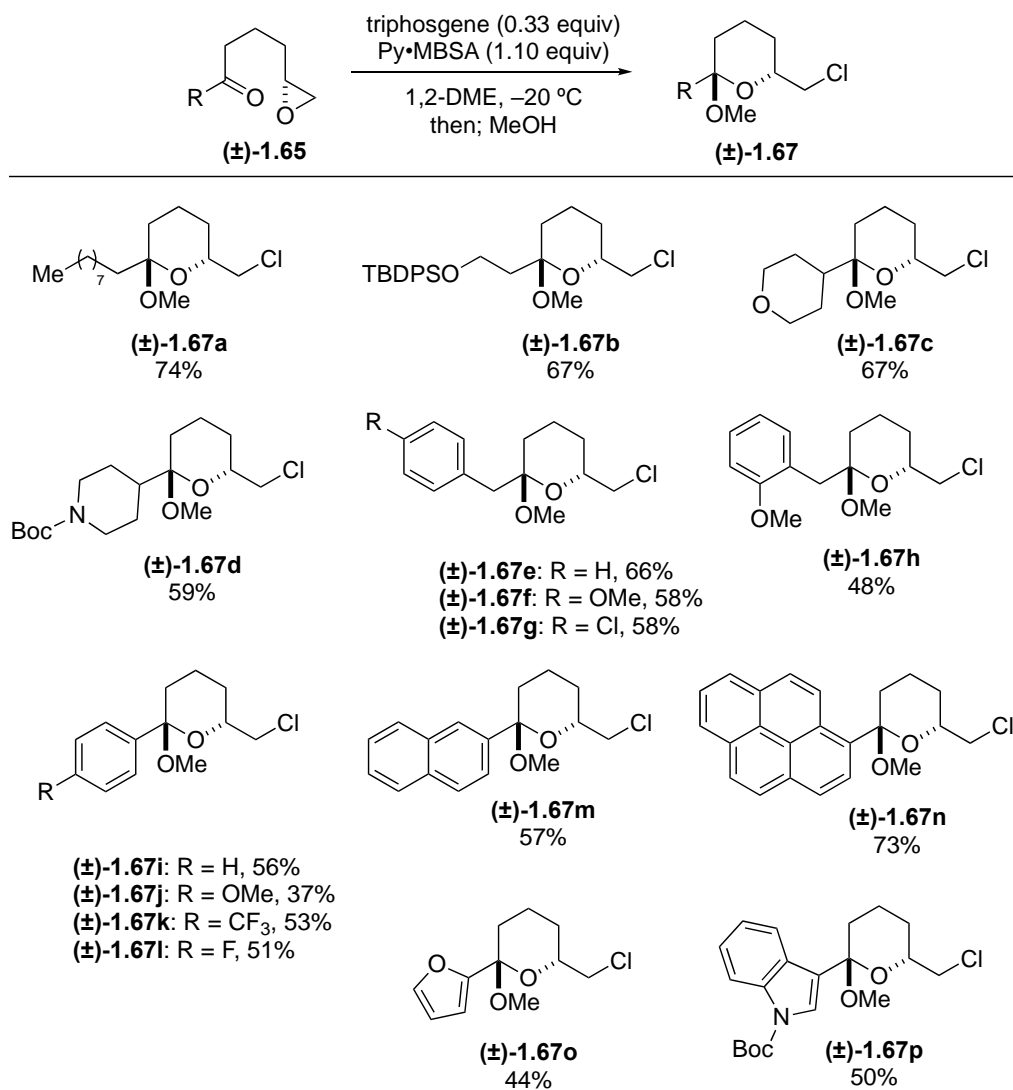
pyridinium *para*-methoxybenzenesulfonate (Py•MBSA), via sulfonation of anisole, followed by neutralization with pyridine and subsequent recrystallization to give a white solid. Initial attempts at using Py•MBSA generated (±)-**1.74** in a 6:1 ratio, but in only 38% yield (entry 6). Subsequent cooling down of the reaction to -20 °C led to afford the target pyranoside in a 20:1 ratio in a 73% yield (entry 8). To see if the reduced temperature would produce better results with the other pyridinium sulfonates, entries 9-10 were conducted with Py•TfOH and Py•TsOH. The use of Py•TfOH at -20 °C generated a 2:3 mixture in favor of ketal (±)-**1.72** (entry 9) and Py•TsOH at -20 °C generated a 20:1 mixture in favor of pyranoside (±)-**1.74** (entry 10), although in a low yield of 20%. Ultimately, entry 8 with Py•MBSA at -20 °C proved to be the optimal conditions. The loading of triphosgene was kept at 0.33 equiv, as this in theory should deliver only 1 equiv of chloride ions. Increased loading of triphosgene led to decreased yields of pyranoside (±)-**1.74**. A crystal structure for pyranoside (±)-**1.74** was able to be obtained via X-Ray Crystallographic analysis. From this it was determined that the relative configuration of (±)-**1.74** to be 2,6-*syn* across the ring.

Table 1.3. Reaction Optimization

Entry	Pyridinium Acid	Solvent	Temp.	(±)- 1.74 :(±)- 1.72 ^[b]	Yield (%) ^[a]
1	Py•TsOH	1,4-dioxane	rt	2:1	37
2	Py•TfOH	1,4-dioxane	rt	1:2	61
3	Py•TsOH	THF	rt	3:1	37
4	Py•TsOH	Et ₂ O	rt	-	- ^[c]
5	Py•TsOH	1,2-DME	rt	5:1	60
6	Py•MBSA	1,2-DME	rt	6:1	38
7	Py•MBSA	1,2-DME	0 °C	12:1	51
8	Py•MBSA	1,2-DME	-20 °C	20:1	73
9	Py•TfOH	1,2-DME	-20 °C	2:3	45
10	Py•TsOH	1,2-DME	-20 °C	20:1	20

^[a] Isolated yield after column chromatography. ^[b] Ratios determined via ¹H-NMR on crude mixtures. ^[c] Intractable slurry formed. Py•MBSA – pyridinium 4-methoxybenzenesulfonate

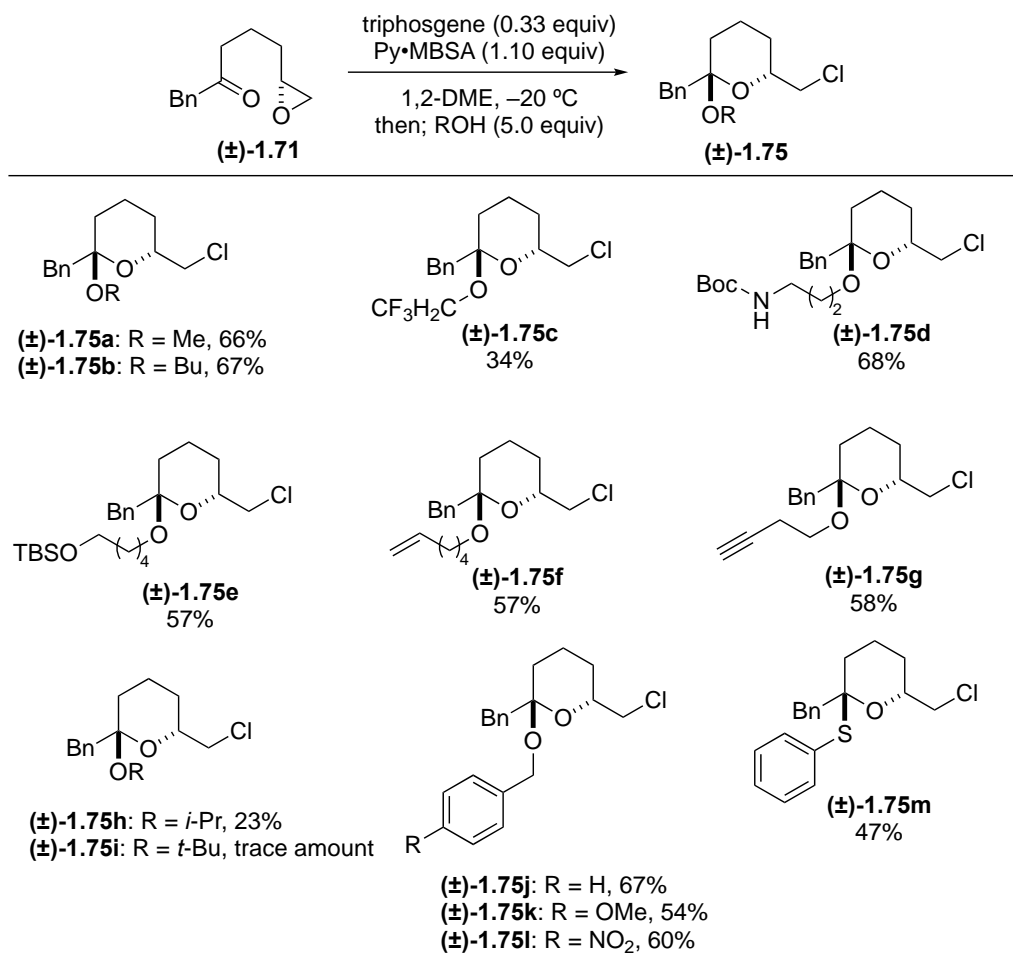
With completion of the reaction optimization, our investigation continued by examining the utility of this transformation through a scope of substrate study (Scheme 1.18). While we were producing these substrates, we noticed that the use of 4Å MS wasn't necessary as we saw very little change in yields with them versus without them included in the reaction. Thus, we decided to not include molecular sieves in the reaction conditions going further. To this end, substrate (±)-**1.65** was treated with 1.10 equiv of Py•MBSA in the presence of 0.33 equiv of triphosgene at -20 °C in 1,2-dimethoxyethane at a concentration of 0.25 M based on the starting material. This is subsequently followed by a methanolic quench to generate the desired pyranoside (±)-**1.67**. The use of simple and TBS-protected aliphatic epoxyketones generated the desired pyranosides (±)-**1.67a** and (±)-**1.67b** in 74% and 67% yield respectively. Nonaromatic heterocycles such as tetrahydropyran and Boc-protected piperidine epoxyketones furnished the corresponding pyranosides (±)-**1.67c** and (±)-**1.67d** in 67% and 59% yield respectively. Substituted aromatic homobenzylic epoxyketones produced the requisite methyl pyranosides (±)-**1.67e** – (±)-**1.67h** in moderate to good yields of 48% to 66%. Substituted phenyl epoxyketones produced their respective methyl pyranosides (±)-**1.67i** – (±)-**1.67l** in yields of 37% to 56%. Larger aromatic groups on epoxyketones such as naphthyl and pyrene produced methyl pyranosides (±)-**1.67m** and (±)-**1.67n** in 57% and 73% yield respectively. Lastly, aromatic heterocycles such as Boc-protected indole and furan epoxyketones gave (±)-**1.67o** and (±)-**1.67p** in 50% and 44% yields respectively. Gratifyingly, all products shown in Scheme 1.17 were generated as single diastereomers and all relative stereochemistries were assigned based on analogy with (±)-**1.74**.



[a] Isolated yields after column chromatography. [b] All products isolated in >20:1 d.r.

Scheme 1.18. Scope of Substrate Study

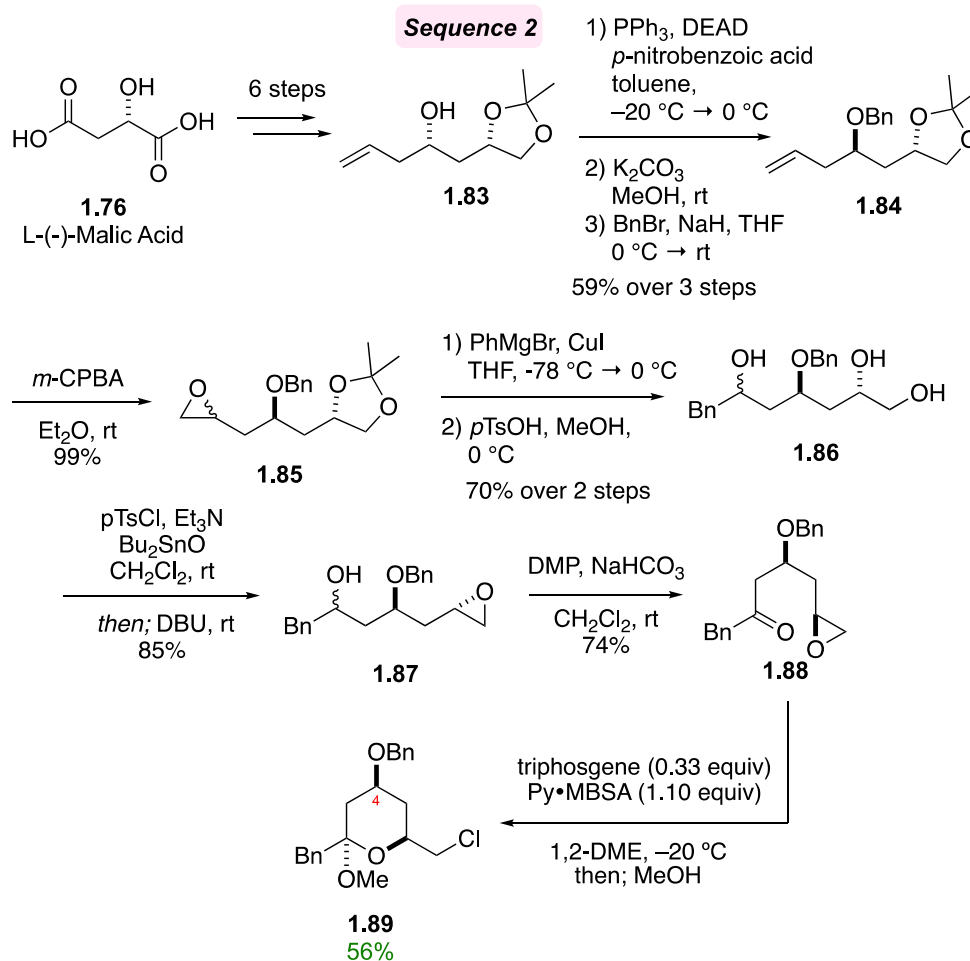
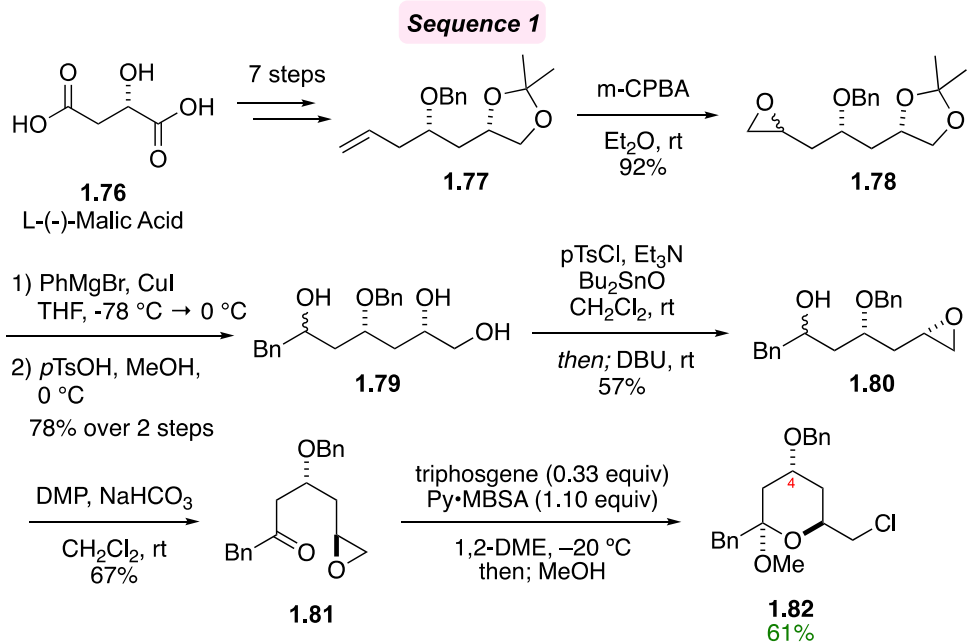
Next, we wanted to display a scope of various quenching nucleophiles that could be used to capture the bicyclic epoxonium ion to produce different substituted pyranosides (\pm)-**1.75** (Scheme 1.19). During methanolic quenching we added a large excess of methanol due to its ease of being removed via rotary evaporation; however, this was not the case with different nucleophiles. With that being said, it was found that 5.0 equiv of the corresponding nucleophiles was needed, as using less resulted in diminished yields. Our starting material for this study is homobenzylic epoxyketone **1.71** that was used for reaction optimization. Our study began with the use of butanol as a quenching agent which afforded expected pyranoside (\pm)-**1.75b** in 67% yield. Trifluoroethanol generated pyranoside (\pm)-**1.75c** in a low yield of 34%, presumably because of the lack of nucleophilic character of the alcohol. Aliphatic alcohols with terminal Boc-protected amines TBS-protected alcohol produced pyranosides (\pm)-**1.75d** and (\pm)-**1.75e** in good yields of 68% and 57% respectively. Aliphatic alcohols with terminal alkene and alkyne groups also formed the expected products (\pm)-**1.75f** and (\pm)-**1.75g** in similar yields of 57% and 58% respectively. Next, we tested the use of simple secondary and tertiary alcohols as isopropanol and *tert*-butanol were employed. Isopropanol yielded the expected pyranoside (\pm)-**1.75h**, albeit in a low yield of 23%, while *tert*-butanol produced pyranoside (\pm)-**1.75i** in trace amounts. Benzyl alcohol and substituted benzyl alcohols were employed and generated pyranosides (\pm)-**1.75j** – (\pm)-**1.75l** in good yields of 54% to 67% yields. Lastly, the use of thiophenol as a nucleophilic quencher proved to be successful at producing pyranoside (\pm)-**1.75m** in 47% yield.



[^a] Isolated yields after column chromatography. [^b] All products isolated in >20:1 d.r.

Scheme 1.19. Scope of Quenching Nucleophile Study

We then set our attention towards synthesizing an enantiopure epoxyketone to see if there would be retention of stereochemistry following treatment with our optimized conditions. Our synthesis began with alkene **1.77** which we made in seven steps from L-(-)-malic acid **1.76** according to literature procedure (Scheme 1.20, *sequence 1*).⁵⁴ Epoxidation of **1.77** with *m*-CPBA gave epoxide **1.78**. Opening of the epoxide with PhMgBr, followed by deprotection of the acetonide gave us triol **1.79**. The terminal 1,2-diol was then converted into an epoxide via a two-step, one pot reaction in which the primary alcohol was first protected with a tosyl group, followed by subsequent cyclization of the pendant alkoxide after addition of DBU, giving us epoxy alcohol **1.80**. Subsequent oxidation with DMP yielded us enantiopure epoxyketone **1.81**. Treatment of **1.81** with triphosgene and Py•MBSA at -20 °C, followed by methanolic quenching generated the expected pyranoside **1.82** in 61% yield. We also wanted to generate the pyranoside with stereochemistry at carbon 4 flipped, and that process began in a similar way as before. We began with alcohol **1.83** which we generated in six steps from L-(-)-malic acid **1.76** (Scheme 20, *sequence 2*). **1.83** underwent a Mitsunobu reaction in order flip the stereochemistry of the alcohol,⁵⁵⁻⁵⁶ followed by benzyl protected to give us alkene **1.84**. All subsequent steps remained the same as the previous synthesis and gave us enantiopure epoxyketone **1.88**. Treatment of this epoxyketone with our optimized conditions generated expected pyranoside **1.89** in 56% yield.



Scheme 1.20. Synthesis of Enantiopure epoxides and Subsequent Cyclizations

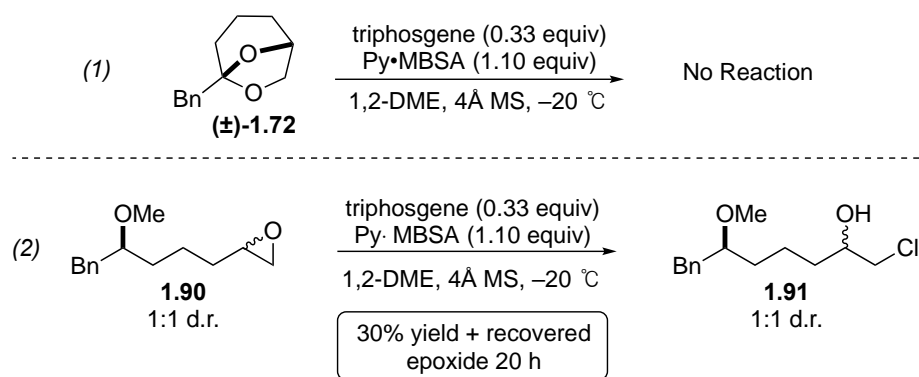
In an effort to get a better idea of the mechanism taking place for the conversion of epoxyketone (\pm)-**1.71** to pyranoside (\pm)-**1.74**, the optimized conditions were modified to discern the role of triphosgene and to probe the observed counter-ion dependency (Table 1.4). Entry 2 examines the reaction with no triphosgene used, which yielded no pyranoside or bicyclic ketal (\pm)-**1.72**. No formation of the ketal was surprising given the acid sensitivity of the epoxyketone. Entry 3 examined the reaction with no Py•MBSA used, which surprisingly generated a 1:1 mixture of pyranoside and ketal in quantitative yield. Our study continued by further probing the role of triphosgene as a source of chloride ions. Organic chloride source Et₄NCl was added instead of triphosgene and no reaction occurred after 24 hours (entry 4). Next, phosgene was used in place of triphosgene and pyranoside (\pm)-**1.74** was formed in 36% yield after 2 hours as an 18:1 mixture in favor of the pyranoside. This suggests that triphosgene decomposes, releasing chloride ions as well as phosgene gas (entry 5). Epoxyketone (\pm)-**1.71** was then combined with Py•HCl instead of Py•MBSA and in the absence of triphosgene, but this yielded no reaction (entry 6). Interestingly, when a combination of Py•HCl and triphosgene was used, pyranoside (\pm)-**1.74** was generated in 46% yield as an 8:1 mixture favoring the pyranoside (entry 7). Entries 4-7 allude to the role of triphosgene being more than just a source of chloride ions and entry 7 specifically highlights the importance of the triphosgene-pyridine combination.

Table 1.4. Deviation from Optimized Conditions

Entry	Deviation from optimized conditions	(±)-1.74:(±)-1.72	Yield (%) ^[a]	Time (hr)
1	no change	20:1	73	1
2	no triphosgene	–	NR	–
3	no Py•MBSA	1:1	99	26
4	Et ₄ NCl instead of triphosgene	–	NR	–
5	phosgene instead of triphosgene	18:1	36	2
6	Py•HCl instead of Py•MBSA, no triphosgene	–	NR	–
7	Py•HCl instead of Py•MBSA	8:1	46	1

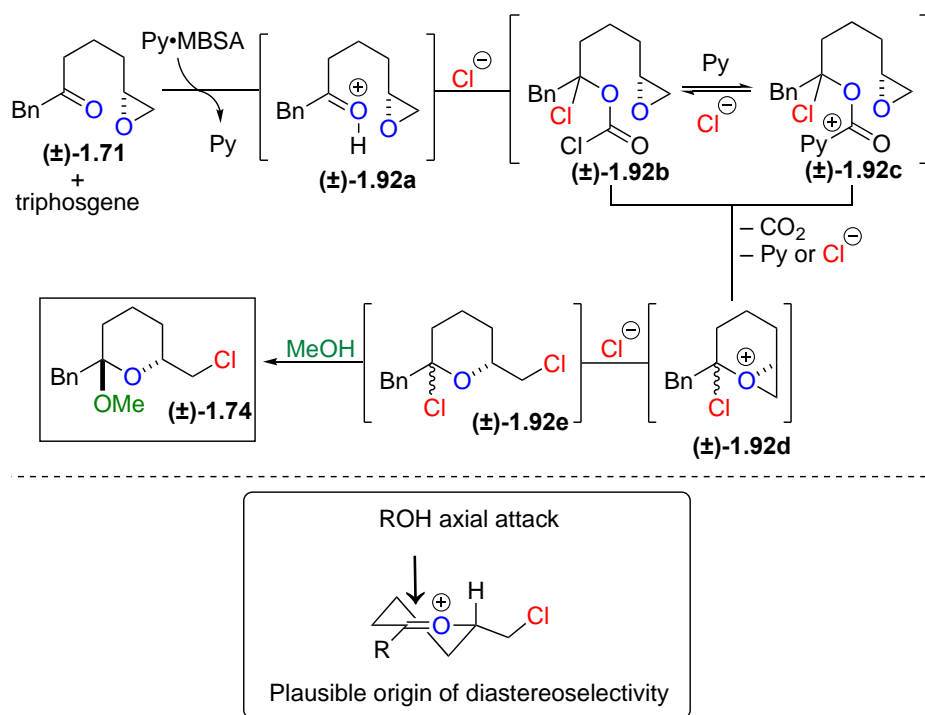
^[a] Isolated yields after column chromatography. ^[b] (±)-1.74 and (±)-1.72 are inseparable.

As reported previously, some further control experiments were done to probe the mechanism further. Bicyclic ketal (±)-1.72 was treated with the optimized conditions and yielded no reaction after 24 hours (Scheme 1.21, *eqn 1*). This result indicates that ketal (±)-1.72 is not a reactive intermediate as is simply a byproduct produced via a separate process. The intermediacy of a chlorohydrin intermediate was also examined. Ether **1.90** was combined with Py•MBSA and triphosgene at -20 °C and after 20 hours, chlorohydrin **1.91** was formed in only 30% yield with unreacted starting material still present (Scheme 1.21, *eqn 2*). This would suggest that formation of the chlorohydrin is disfavored. Comparing this result to epoxyketone (±)-1.71, it is entirely possible that chlorohydrin formation followed by cyclization is a potential mechanism towards forming pyranoside (±)-1.74; however, we believe this is a minor mechanistic process.



Scheme 1.21. Mechanistic Controls

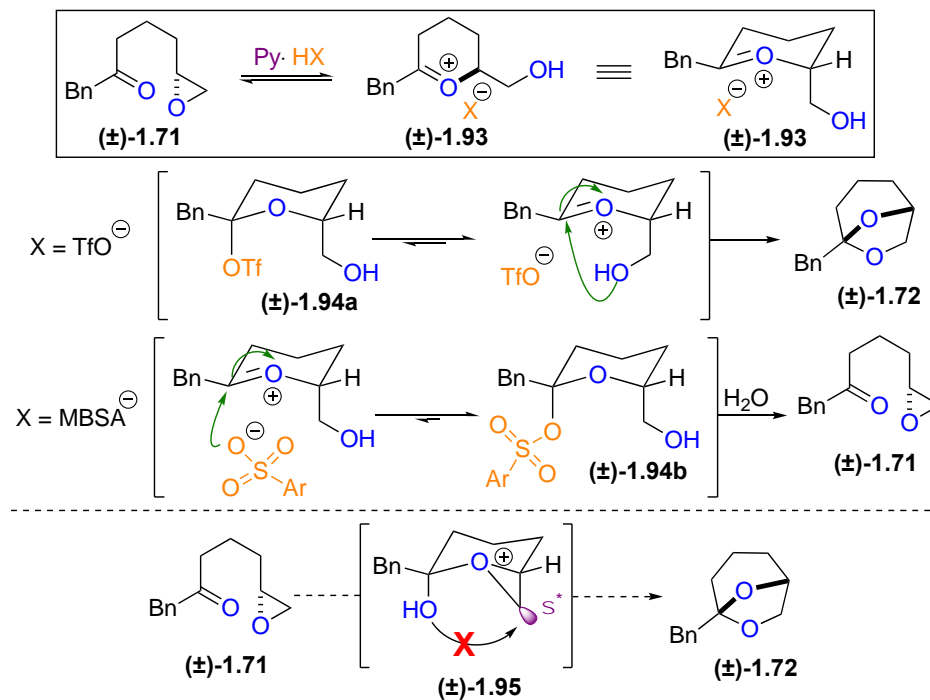
These findings finally led us to the following proposed mechanism (Scheme 1.22). We predict that chemoselective protonation of the ketone of (±)-**1.71** leads to oxonium ion intermediate (±)-**1.92a**. This step also releases an equivalent of pyridine which is then able to aid in the decomposition of triphosgene, releasing chloride ions. Attack of (±)-**1.92a** by chloride ions reveals α-chloro chloroformate (±)-**1.92b** analogous to our chlorovinylolation chemistry.⁵⁰ This intermediate can exist in equilibria with pyridinium carbamate (±)-**1.92c**, and both of these species can presumably undergo self-decomposition liberating CO₂ and chloride or pyridine en route to bicyclic epoxonium ion (±)-**1.92d**. Regioselective attack of the bicyclic epoxonium ion with chloride ion at the *exocyclic* position most likely forms chlorine substituted α-chloropyranoside (±)-**1.92e**. Methanolic quench then generates the observed pyranoside product (±)-**1.74**.



Scheme 1.22. Proposed Mechanism

The following model is proposed in an attempt to explain the observed counterion effects which cause the formation of the bicyclic ketal over the pyranoside (Scheme 1.23). As mentioned previously, 1,5-epoxyketone (±)-1.71 in the presence of an acid source can rearrange to bicyclic ketal (±)-1.72. It is likely that this transformation occurs via oxocarbenium ion intermediate (±)-1.93 which is associated with the conjugate base of the pyridinium acid through ionic interaction. As shown in Table 1.3, the use of Py•TfOH instead of Py•MBSA favors the generation of bicyclic ketal (±)-1.72, presumably through activation of the ketone of (±)-1.71 over the epoxide moiety. We believe that upon formation of oxocarbenium ion (±)-1.93 that triflate ion can attack at the anomeric carbon, forming α -sulfonated pyranoside (±)-1.94a. While triflate ions are weakly nucleophilic, they have been reported to add to anomeric carbons of glycosyl donors to generate glycosyl triflate intermediates. Crich and co-workers have observed and characterized these glycosyl triflate intermediates via low temperature (-78 °C) NMR studies.⁵⁷⁻⁵⁸ Given that the

reactions we are running are at -20 °C and the weakly nucleophilic nature of triflate ions, we believe that intermediate (±)-**1.94a** is able to decompose back to its respective contact ion pairs leaving (±)-**1.93** primed for intramolecular capture by the nearby alcohol generating ketal (±)-**1.72**. Conversely, we believe that Py•MBSA primarily activates the ketone of **1.71**; however, if activation of the epoxide were to occur then the more nucleophilic *para*-methoxybenzenesulfonate ion can add to the anomeric carbon of oxocarbenium ion (±)-**1.93**. Inspired by the works of Schuerch and co-workers,⁵⁹ we believe this α-sulfonated pyranoside (±)-**1.94b** is more stable than its triflate-substituted counterpart (±)-**1.93a**, leaving the anomeric position blocked from attack of the pendant alcohol. (±)-**1.94b** is very moisture sensitive and decomposes rapidly upon aqueous workup, making attempts at its isolation unsuccessful. Lastly, we believe that formation of bicyclic ketal **1.72** is only possible through activation of the epoxide followed by 6-*exo-tet* cyclization by the ketone. If ketal formation were to occur via bicyclic epoxonium ion intermediate (±)-**1.95**, the hemiketal hydroxyl would require significant torsional strain in order to capture it, making this unlikely.



Scheme 1.23. Model to Account for Counterion Bias

1.6. Conclusion

This chapter has served to summarize the utility of monocyclic and bicyclic epoxonium ions. Their utilization has primarily been in ring expansion of medium ring ethers to large heterocycles and as intermediates in polyepoxide cascade processes towards ladder polyether natural products. The capture of bicyclic epoxonium ions with halogen nucleophiles has not been reported often in literature, which makes us very excited about our contributions to this area. Specifically, we have reported the cyclization of acyclic terminal epoxides onto ketones. These ketones were chemoselectively activated with the use of a novel pyridinium acid source and subsequent regioselective capture of the ensuing bicyclic epoxonium ion at the *exocyclic* position with chloride ions afforded us a variety of pyranosides. Our study is near complete and will be published in a peer reviewed journal in due course.

Chapter 2. Experimental Procedures

2.1. General Information

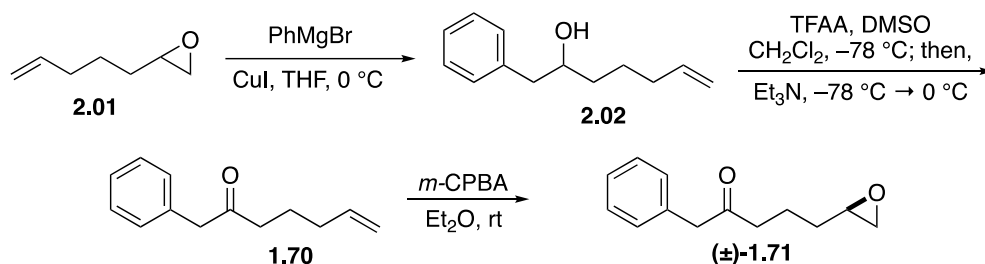
Unless otherwise noted, all materials were used as received from commercial suppliers without further purification. All anhydrous reactions were performed using oven-dried or flame-dried glassware, which was then cooled under vacuum and purged with nitrogen gas. Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), acetonitrile, toluene, and diethyl ether (Et_2O) were filtered through activated 3Å molecular sieves under nitrogen contained in an M-Braun Solvent Purification System. All reactions were monitored by EMD analytical thin layer chromatography (TLC Silica Gel 60 F₂₅₄, Glass Plates) and analyzed with 254 nm UV light and / or anisaldehyde – sulfuric acid or potassium permanganate treatment. Silica gel for column chromatography was purchased from Dynamic Adsorbents, Inc. or Sigma Aldrich (Flash Silica Gel 32-63u).

Unless otherwise noted, all ^1H and ^{13}C NMR spectra were recorded in CDCl_3 using a Bruker Ascend 400 spectrometer operating at 400 MHz for ^1H and 100 MHz for ^{13}C or Bruker Ascend 500 spectrometer operating at 500 MHz for ^1H and 125 MHz for ^{13}C . Chemical shifts (δ) are reported in ppm relative to residual CHCl_3 as an internal reference (^1H : 7.26 ppm, ^{13}C : 77.23 ppm). Coupling constants (J) are reported in Hertz (Hz). Peak multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), (septet), h (heptet), b (broad), and m (multiplet). FT-IR spectra were recorded on Bruker Tensor 27 spectrometer and OPUS 6.5 Data Collection Program, and absorption frequencies were reported in reciprocal centimeters (cm^{-1}). High Resolution Mass Spectrometry – Electron Spray Ionization (HRMS-ESI) analyses were performed by the Louisiana State University Mass Spectrometry Facility using an Agilent 6210 Instrument. X-ray structure analyses were performed by the Louisiana State University X-ray Structure Facility using a Bruker APEX-II CCD diffractometer. Thermo Scientific TG-SQC GC

Column (15m x 0.25mm x 0.25 μ m) using a modified gradient of 40 °C to 300 °C over 29 minutes using helium as the carrier gas. The detector utilized was a Thermo Scientific ISQD QD mass spectrometer with the mass range limit set from 60 – 400 amu and with the ion source temperature set at 200 °C. Solvent delay was set to 5.00 minutes for each trial.

2.2. Experimental Procedures

5-(oxiran-2-yl)-1-phenylpentan-2-one ((\pm)-**1.71**)



1-phenylhept-6-en-2-ol (**2.02**)

CuI (1.24 g, 6.50 mmol) was added to a 250-mL round-bottom flask while still hot and vacuum purged with N₂ while gradually cooling to room temperature. THF (100 mL) was added and the resulting slurry was cooled to 0 °C. After 5 minutes, PhMgBr (14.1 mL, 3 M in Et₂O) was added dropwise. After 10 minutes epoxide **2.01** (3.64 g, 32.5 mmol) was added via cannula in THF (60 mL). The resulting solution was stirred at 0 °C. After 3 hours, the reaction was determined to be complete by TLC analysis and quenched with saturated NH₄Cl (20 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x20 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording **2.02** and a clear oil in 73% yield (4.52 g, 23.8 mmol).

¹H NMR (500 MHz, CDCl₃) δ 7.32 (t, *J* = 7.5 Hz, 2H), 7.27 – 7.21 (m, 3H), 5.82 (ddt, *J* = 17.0, 10.4, 6.7 Hz, 1H), 5.05 – 5.00 (m, 1H), 4.99 – 4.94 (m, 1H), 3.86 – 3.80 (m, 1H), 2.84 (dd, *J* = 13.5, 4.2 Hz, 1H), 2.65 (dd, *J* = 13.6, 8.5 Hz, 1H), 2.14 – 2.05 (m, 2H), 1.68 – 1.40 (m, 5H).

¹³C NMR (126 MHz, CDCl₃) δ 138.7, 138.5, 129.4, 128.6, 126.5, 114.6, 72.5, 44.1, 36.2, 33.7, 25.0.

1-phenylhept-6-en-2-one (1.70)

TFAA (2.2 mL, 15.6 mmol) and CH₂Cl₂ (10 mL) were combined in 250-mL round-bottom flask. The resulting solution was cooled to –78 °C for 10 minutes before DMSO (2.2 mL, 31.2 mmol) was added as a solution in CH₂Cl₂ (20 mL) slowly, dropwise. After 1 hour alcohol **2.02** (2.47 g, 13.0 mmol) was added via cannula in CH₂Cl₂ (35 mL). After 1 hour the reaction was determined to be complete by TLC analysis and Et₃N (9.1 mL, 65.0 mmol) was added slowly. The reaction was slowly warmed to room temperature over 30 minutes. Further reaction monitoring by TLC analysis determined that the reaction was complete. The reaction was then cooled to 0 °C and quenched by the addition of 2M HCl (20 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording **1.70** and a clear oil in 87% yield (2.12 g, 11.3 mmol).

¹H NMR (400 MHz, CDCl₃) δ 5.72 (ddt, *J* = 17.2, 10.2, 6.7 Hz, 1H), 5.01 – 4.92 (m, 2H), 3.67 (s, 2H), 2.46 (t, *J* = 7.2 Hz, 2H), 2.01 (q, *J* = 6.9 Hz, 2H), 1.66 (p, *J* = 7.4 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 208.1, 137.8, 134.2, 129.3, 128.6, 126.9, 115.1, 50.1, 41.0, 32.9, 22.6.

Ketone **1.70** (1.10 g, 5.84 mmol) was added to a 100-mL round-bottom flask and dissolved in Et₂O (24 mL). *m*-CPBA (1.01 g, 4.38 mmol, 75 wt %) was added and the reaction was stirred at room temperature. After 24 hours the reaction was quenched with saturated NaHCO₃ (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording recovered ketone **1.70** as a clear oil (571 mg, 3.03 mmol). Further elution with a 20% gradient of EtOAc in hexanes afforded epoxyketone (±)-**1.71** as a clear oil in 64% yield based on recovered starting material (370 mg, 1.81 mmol).

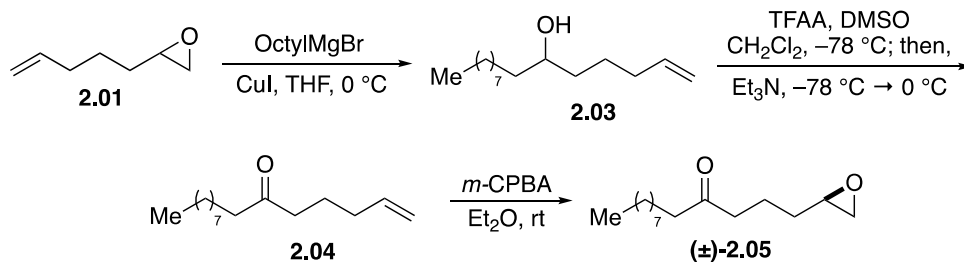
¹H NMR (500 MHz, CDCl₃) δ 7.37 – 7.33 (m, 2H), 7.31 – 7.27 (m, 1H), 7.24 – 7.21 (m, 2H), 3.71 (s, 2H), 2.90 – 2.84 (m, 1H), 2.73 (dd, *J* = 5.0, 2.8 Hz, 1H), 2.55 (td, *J* = 7.3, 1.4 Hz, 2H), 2.43 (dd, *J* = 5.0, 2.7 Hz, 1H), 1.79 – 1.72 (m, 2H), 1.64 – 1.54 (m, 1H), 1.47 – 1.39 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 207.9, 134.2, 129.4, 128.7, 127.0, 52.0, 50.2, 46.8, 41.2, 31.7, 20.1.

IR (cm⁻¹): *f* = 3030, 2838, 1712, 1495, 1453, 1409, 1366, 1260, 1116, 1031, 922, 834, 733, 700, 475.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ = 205.12231 calculated for C₁₃H₁₇O₂, experimental 205.12284.

1-(oxiran-2-yl)tridecan-4-one ((±)-**2.05**)



pentadec-1-en-6-ol (2.03)

CuI (360 mg, 1.89 mmol) was added to a 100-mL round-bottom flask while still hot and vacuum purged with N₂ while gradually cooling to room temperature. THF (15 mL) was added and the resulting slurry was cooled to 0 °C. After 5 minutes, OctylMgBr (5.6 mL, 2 M in THF) was added dropwise. After 10 minutes epoxide **2.01** (1.06 g, 9.46 mmol) was added via cannula in THF (15 mL). The resulting solution was stirred at 0 °C. After 30 minutes the reaction was determined to be complete by TLC analysis and quenched with saturated NH₄Cl (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording **2.03** as a clear oil in 94% yield (2.01 g, 8.88 mmol).

¹H NMR (400 MHz, CDCl₃) δ 5.81 (ddt, *J* = 17.3, 10.3, 6.6 Hz, 1H), 5.01 (dq, *J* = 17.2, 1.7 Hz, 1H), 4.98 – 4.93 (m, 1H), 3.63 – 3.56 (m, 1H), 2.11 – 2.04 (m, 2H), 1.57 – 1.39 (m, 6H), 1.33 – 1.23 (m, 12H), 0.87 (t, *J* = 6.6 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 138.7, 114.5, 71.9, 37.5, 36.9, 33.7, 31.9, 29.7, 29.6, 29.6, 29.3, 25.6, 24.9, 22.7, 14.1.

pentadec-1-en-6-one (2.04)

Alcohol **2.03** (2.01 g, 8.88 mmol) was combined with CH₂Cl₂ (30 mL) in a 100-mL round-bottom flask. The solution was cooled to 0 °C followed by the addition of Dess-Martin Periodinane (5.64 g, 13.3 mmol) and NaHCO₃ (2.23 g, 26.6 mmol). The ice bath was removed after 10 minutes and the reaction was allowed to warm to room temperature. After stirring for 3 hours, the reaction was determined to be complete by TLC analysis and cooled to 0 °C prior to

being quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL). Upon separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude oil was then filtered through a silica plug using a 10% EtOAc in hexanes gradient affording **2.04** as a clear oil in 89% (1.77 g, 7.89 mmol).

^1H NMR (400 MHz, CDCl_3) δ 5.77 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 5.04 – 4.95 (m, 2H), 2.39 (q, J = 7.7 Hz, 2H), 2.09 – 2.02 (m, 2H), 1.68 (p, 2H), 1.60 – 1.52 (m, 2H), 1.32 – 1.22 (m, 13H), 0.90 – 0.86 (m, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 211.3, 138.0, 115.1, 42.9, 41.8, 33.1, 31.9, 29.4, 29.4, 29.3, 23.9, 22.8, 22.6, 14.2, 14.1.

1-(oxiran-2-yl)tridecan-4-one ((\pm)-2.05)

Ketone **2.04** was added to a 100-mL round-bottom flask and dissolved in Et_2O (31 mL). *m*CPBA (2.91 g, 11.8 mmol, 70 wt %) was added and the reaction was stirred at room temperature. After 19 hours the reaction was determined to be complete by TLC analysis and quenched with 1M NaOH (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording (\pm)-**2.05** and a white solid in 39% yield (733 mg, 3.05 mmol).

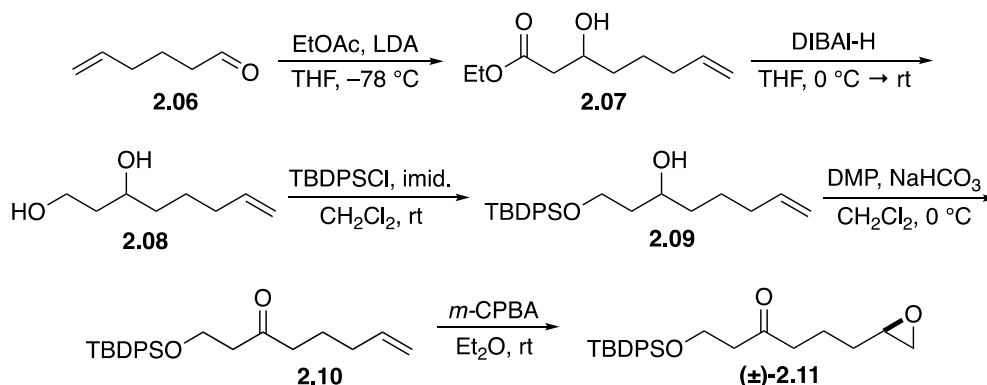
^1H NMR (500 MHz, CDCl_3) δ 2.92 – 2.88 (m, 1H), 2.74 (t, J = 4.5 Hz, 1H), 2.51 – 2.45 (m, 3H), 2.39 (t, J = 7.4 Hz, 2H), 1.74 (p, J = 7.7 Hz, 2H), 1.65 – 1.53 (m, 4H), 1.50 – 1.43 (m, 1H), 1.32 – 1.22 (m, 14H), 0.87 (t, J = 6.7 Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 210.8, 77.2, 52.0, 46.8, 42.9, 42.1, 31.9, 31.8, 29.4, 29.4, 29.3, 23.9, 22.7, 20.2, 14.1.

IR (cm^{-1}): ν = 2923, 2854, 1712, 1460, 1410, 1374, 1259, 1130, 1070, 921, 834, 723, 426, 408.

HRMS (ESI-TOF) m/z : ($\text{M}+\text{H}^+$) = 241.21621 calculated for $\text{C}_{15}\text{H}_{29}\text{O}_2$, experimental 241.21604.

Synthesis of 1-((*tert*-butyldiphenylsilyl)oxy)-6-(oxiran-2-yl)hexan-3-one ((\pm)-**2.11**)



ethyl 3-hydroxyoct-7-enoate (**2.07**)

To a 100-mL round-bottom flask was added $i\text{Pr}_2\text{NH}$ (2.1 mL, 15.0 mmol) and THF (20 mL). The resulting solution was then cooled to 0°C and $n\text{BuLi}$ (6.0 mL, 2.5 M in hexanes) was added dropwise. After 30 minutes the solution of LDA was cooled to -78°C and EtOAc (1.5 mL, 15.0 mmol) was added as a solution in THF (10 mL) dropwise. After 30 minutes aldehyde **2.06** was added via cannula in THF (10 mL). The reaction was stirred at -78°C for 2 hours when the reaction was determined to be complete by TLC analysis and quenched with saturated NH_4Cl (10 mL) then warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with Et_2O (3x15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording **2.07** as a clear oil in 60% yield, over two steps (1.12 g, 6.01 mmol).

¹H NMR (400 MHz, CDCl₃) δ 5.80 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.01 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.97 – 4.93 (m, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.04 – 3.97 (m, 1H), 2.96 (d, *J* = 4.0 Hz, 1H), 2.50 (dd, *J* = 16.5, 3.1 Hz, 1H), 2.40 (dd, *J* = 16.5, 9.1 Hz, 1H), 2.11 – 2.05 (m, 2H), 1.61 – 1.41 (m, 4H), 1.28 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 173.1, 138.5, 114.7, 67.8, 60.7, 41.3, 35.8, 33.5, 24.7, 14.2.

oct-7-ene-1,3-diol (2.08)

To a 100-mL round-bottom flask was added β-hydroxy ester **2.07** (700 mg, 3.76 mmol) and THF (12 mL). The resulting solution was cooled to 0 °C and DIBAL-H (12 mL, 1 M in heptane) was added dropwise. After 2 hours the reaction was determined to be complete by TLC analysis and quenched with saturated Rochelle's salt (5 mL) and 2M HCl (5 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x15 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of MeOH in CH₂Cl₂ affording **2.08** as a clear oil in 84% yield (458 mg, 3.17 mmol).

¹H NMR (500 MHz, CDCl₃) δ 5.80 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.01 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.97 – 4.94 (m, 1H), 3.91 – 3.80 (m, 3H), 2.57 – 2.49 (m, 2H), 2.11 – 2.05 (m, 2H), 1.79 – 1.62 (m, 2H), 1.57 – 1.40 (m, 4H).

¹³C NMR (126 MHz, CDCl₃) δ 114.7, 72.1, 61.8, 38.2, 37.2, 33.6, 24.8.

IR: $f(\text{cm}^{-1})$ = 3331, 3077, 2933, 2861, 2212, 2155, 1640, 1437, 1372, 1332, 1183, 1054, 995, 909, 828, 640.

HRMS (ESI-TOF) *m/z*: (*M*+*H*⁺) = 145.12231 calculated for C₈H₁₇O₂, experimental 145.12242.

1-((*tert*-butyldiphenylsilyl)oxy)oct-7-en-3-ol (2.09)

Diol **2.08** (458 mg, 3.17 mmol) was combined with imidazole (323 mg, 4.75 mmol) in a 50-mL round-bottom flask. CH₂Cl₂ (11 mL) added and the solution was cooled to 0 °C. TBDPSCl (866 µL, 3.33 mmol) was added dropwise. After stirring overnight, the reaction was determined to be complete by TLC analysis and quenched by the addition of 2 M HCl (5 mL). Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude oil was then purified by column chromatography using a 1% EtOAc in hexanes gradient affording **2.09** as a clear oil in 41% (496 mg, 1.30 mmol).

¹H NMR (500 MHz, CDCl₃) δ 7.70 – 7.66 (m, 4H), 7.46 – 7.37 (m, 6H), 5.82 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.02 (dq, *J* = 17.0, 1.6 Hz, 1H), 4.97 – 4.93 (m, 1H), 3.93 – 3.82 (m, 2H), 3.25 – 3.20 (m, 1H), 2.12 – 2.06 (m, 2H), 1.75 – 1.62 (m, 2H), 1.59 – 1.50 (m, 2H), 1.50 – 1.41 (m, 2H), 1.06 (s, 9H).

¹³C NMR (126 MHz, CDCl₃) δ 138.8, 135.6, 135.5, 134.8, 133.0, 132.9, 129.8, 129.8, 127.8, 114.5, 71.7, 63.6, 38.3, 37.0, 33.8, 26.8, 26.6, 24.9.

IR: *f* (cm⁻¹) = 3406, 3071, 2930, 2857, 1640, 1470, 1427, 1389, 1188, 1109, 997, 909, 859, 822, 737, 701, 611, 431.

HRMS (ESI-TOF) *m/z*: (M+H⁺) = 383.24008 calculated for C₂₄H₃₅O₂Si, experimental 383.24032.

1-((*tert*-butyldiphenylsilyl)oxy)oct-7-en-3-one (2.10)

Alcohol **2.09** (496 mg, 1.30 mmol) was combined with CH₂Cl₂ (6.5 mL) in a 100-mL round-bottom flask. The solution was cooled to 0 °C followed by the addition of Dess-Martin

Periodinane (823 mg, 1.94 mmol) and NaHCO₃ (324 mg, 3.89 mmol). The ice bath was removed after 10 minutes and the reaction was allowed to warm to room temperature. After stirring for 2 hours, the reaction was determined to be complete by TLC analysis and cooled to 0 °C prior to being quenched with saturated Na₂S₂O₃ (10 mL). Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude oil was then filtered through a silica plug using a 5% EtOAc in hexanes gradient affording **2.10** as a clear oil in 82% (408 mg, 1.07 mmol).

¹H NMR (500 MHz, CDCl₃) δ 7.67 – 7.64 (m, 4H), 7.45 – 7.37 (m, 6H), 5.76 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.04 – 4.99 (m, 1H), 4.99 – 4.96 (m, 1H), 3.94 (t, *J* = 6.4 Hz, 2H), 2.61 (t, *J* = 6.1 Hz, 2H), 2.47 (t, *J* = 7.3 Hz, 2H), 2.09 – 2.03 (m, 2H), 1.69 (p, *J* = 7.3 Hz, 2H), 1.03 (s, 9H).

¹³C NMR (126 MHz, CDCl₃) δ 209.7, 138.0, 135.5, 134.8, 133.4, 129.7, 127.7, 127.7, 115.2, 59.8, 45.5, 42.9, 33.1, 26.8, 22.5, 19.1.

1-((*tert*-butyldiphenylsilyl)oxy)-6-(oxiran-2-yl)hexan-3-one ((±)-2.11)

Ketone **2.10** (408 mg, 1.07 mmol) was added to a 50-mL round-bottom flask and dissolved in Et₂O (4.3 mL). *m*CPBA (397 mg, 1.61 mmol, 70 wt %) was added and the reaction was stirred at room temperature. After 12 hours the reaction was quenched with 1M NaOH (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording recovered ketone **2.10** as a clear oil (264 mg, 0.694 mmol). Further elution with a 10% gradient of EtOAc in

hexanes afforded epoxyketone (\pm)-**2.11** as a clear oil in 92% yield based on recovered starting material (138 mg, 0.348 mmol).

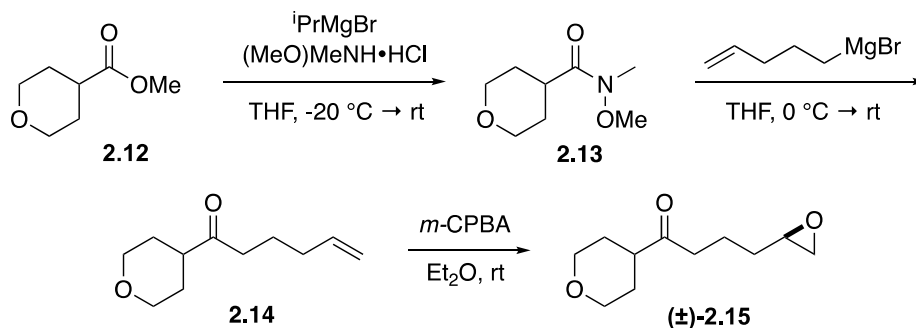
^1H NMR (400 MHz, CDCl_3) δ 7.68 – 7.63 (m, 4H), 7.46 – 7.35 (m, 6H), 3.94 (t, J = 6.2 Hz, 2H), 2.92 – 2.87 (m, 1H), 2.73 (dd, J = 5.0, 4.1 Hz, 1H), 2.63 (t, J = 6.2 Hz, 1H), 2.54 (t, J = 7.2 Hz, 2H), 2.45 (dd, J = 5.0, 2.6 Hz, 1H), 1.80 – 1.71 (m, 2H), 1.65 – 1.57 (m, 1H), 1.53 – 1.44 (m, 1H), 1.03 (s, 9H).

^{13}C NMR (126 MHz, CDCl_3) δ 209.1, 135.5, 133.4, 129.7, 127.6, 59.7, 51.9, 46.7, 45.4, 43.0, 31.7, 26.7, 19.9, 19.1.

IR: $f(\text{cm}^{-1})$ = 2931, 2857, 1714, 1472, 1428, 1109, 823, 740, 703, 613, 505.

HRMS (ESI-TOF) m/z : ($\text{M}+\text{H}^+$) = 397.21935 calculated for $\text{C}_{24}\text{H}_{33}\text{O}_3\text{Si}$, experimental 397.21857.

4-(oxiran-2-yl)-1-(tetrahydro-2H-pyran-4-yl)butan-1-one ((\pm)-**2.15**)



N-methoxy-*N*-methyltetrahydro-2H-pyran-4-carboxamide (**2.13**)

Methyltetrahydro-2H-pyran-4-carboxylate **2.12** (1.85 mL, 13.87 mmol) was combined with THF (46.2 mL) in a 250-mL round-bottom flask and the solution was cooled to - 20 °C. This was followed by the addition of *N,O*-Dimethylhydroxylamine hydrochloride (2.03 g, 20.81 mmol) and a dropwise addition of isopropylmagnesium bromide (10.4 mL, 31.21 mmol). The reaction

was stirred at - 20 °C overnight. After the reaction was determined to be complete by TLC analysis, it was quenched with NH₄Cl (20 mL). Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording recovered ester **xx** as a colorless liquid (669 mg, 4.64 mmol). Further elution with a 20% to 50% gradient of EtOAc in hexanes afforded Weinreb amide **2.13** as a colorless oil in quantitative yield based on recovered starting material (1.60 g, 9.24 mmol).

Rf: 0.16 in 50:50 (Hexanes: EtOAc)

¹H NMR (400 MHz, CDCl₃) δ 4.04 – 4.02 (m, 1H), 4.01 – 4.00 (m, 1H), 3.71 (s, 3H), 3.46 (td, *J* = 11.8, 2.1 Hz, 2H), 3.19 (s, 3H), 2.94 – 2.88 (m, 1H), 1.87 (qd, *J* = 12.1, 4.4 Hz, 2H), 1.67 – 1.66 (m, 1H), 1.64 – 1.63 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 67.3, 61.6, 37.3, 32.3, 28.6.

IR (cm⁻¹): *f* = 2956, 2845, 1658, 1445, 1385, 1352, 1309, 1240, 1176, 1120, 1089, 1014, 993, 872, 823, 633, 560, 435.

1-(tetrahydro-2*H*-pyran-4-yl)hex-5-en-1-one (2.14)

Freshly ground Mg turnings (225 mg, 9.24 mmol) were added to a 100-mL three-neck round-bottom flask, with a pressure-equalizing addition funnel and condenser attached. Catalytic I₂ (1–2 crystals) was added and the apparatus was heated gently to sublime the I₂ and coat the Mg turnings. Once coated THF (10 mL) was added to cover the Mg. 5-bromo-1-pentene (1.2 mL, 9.70 mmol) was subsequently added to the addition funnel and dissolved in THF (20 mL). The solution of alkyl halide was slowly added to the slurry of magnesium turnings over 10 minutes.

After complete addition of 5-bromo-1-pentene, the translucent solution was refluxed for an additional 3 hours to consume the remaining Mg. Weinreb amide **2.13** (800 mg, 4.62 mmol) was added to a separate 100-mL round-bottom flask, and THF (20 mL) was then added. After cooling the reaction to 0 °C, the solution of pent-4-en-1-ylmagnesium bromide was added dropwise via a cannula. The resulting solution was allowed to warm to room temperature and stirred overnight. After completion of reaction as determined by TLC, the reaction was cooled to 0 °C and quenched with saturated 1 M HCl (10 ml). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x20 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% to 15% gradient of EtOAc in hexanes affording **2.14** as a yellow oil in 89% yield (747 mg, 4.10 mmol).

Rf: 0.47 in 70:30 (Hexanes: EtOAc)

¹H NMR (400 MHz, CDCl₃) δ 5.75 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.03 – 4.95 (m, 2H), 4.00 (dd, *J* = 3.8, 2.6 Hz, 1H), 3.98 – 3.97 (m, 1H), 3.41 (td, *J* = 11.2, 2.9 Hz, 2H), 2.56 – 2.49 (m, 1H), 2.45 (t, *J* = 7.3 Hz, 2H), 2.07 (d, *J* = 7.0 Hz, 1H), 2.03 (d, *J* = 7.2 Hz, 1H), 1.75 – 1.65 (m, 6H).

¹³C NMR (100 MHz, CDCl₃) δ 211.9, 138.0, 115.3, 67.3, 47.6, 39.3, 33.1, 28.2, 22.5.

IR (cm⁻¹): *f* = 3076, 2947, 2844, 1706, 1640, 1444, 1410, 1384, 1274, 1239, 1092, 1018, 912, 859, 634, 559.

4-(oxiran-2-yl)-1-(tetrahydro-2H-pyran-4-yl)butan-1-one ((±)-2.15)

Ketone **2.14** (470 mg, 2.58 mmol) was added to a 50-mL round-bottom flask and dissolved in Et₂O (10.3 mL). *m*CPBA (593 mg, 2.58 mmol, 70 wt %) was added and the reaction was stirred at room temperature. After 13 hours the reaction was quenched with 1M NaOH (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x10 mL), dried

over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording recovered ketone **3.14** as a yellow oil (281 mg, 1.54 mmol). Further elution with a 10% to 35% gradient of EtOAc in hexanes afforded epoxyketone (±)-**2.15** as a yellow oil in quantitative yield based on recovered starting material (206 mg, 1.04 mmol).

Rf: 0.13 in 70:30 (Hexanes: EtOAc)

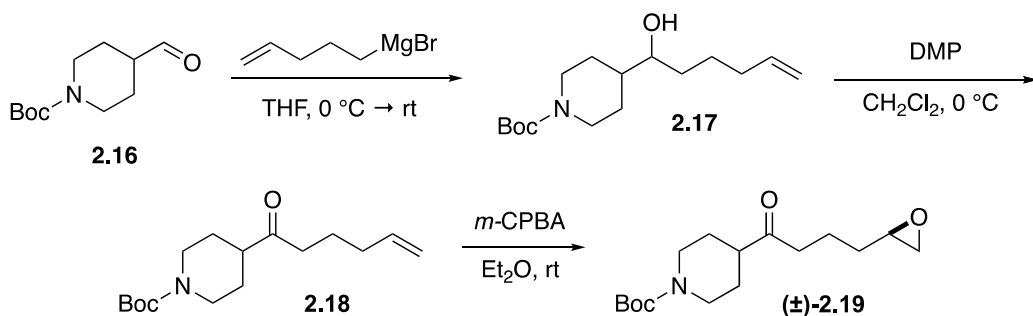
¹H NMR (400 MHz, CDCl₃) δ 4.01 – 3.97, (m, 2H), 3.41 (td, *J* = 11.5, 2.7 Hz, 2H), 2.91 – 2.88 (m, 1H), 2.74 – 2.73 (m, 1H), 2.56 – 2.52 (m, 3H), 2.45 (dd, *J* = 5.0, 2.7 Hz, 1H), 1.78 – 1.61 (m, 8H), 1.46 – 1.39 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 211.5, 67.2, 52.0, 47.6, 46.7, 39.6, 31.7, 28.2, 20.1.

IR (cm⁻¹): *f* = 2949, 2846, 1706, 1445, 1384, 1240, 1092, 1018, 833, 560.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ = 199.13287 calculated for C₁₁H₁₉O₃; experimental 199.13299.

***tert*-butyl-4-(4-(oxiran-2-yl)butanoyl)piperidine-1-carboxylate ((±)-**2.19**)**



***tert*-butyl-4-(1-hydroxyhex-5-en-1-yl)piperidine-1-carboxylate (**2.17**)**

Freshly ground Mg turnings (228 mg, 9.38 mmol) were added to a 100-mL three-neck round-bottom flask, with a pressure-equalizing addition funnel and condenser attached. Catalytic I₂ (1–2 crystals) was added and the apparatus was heated gently to sublime the I₂ and coat the Mg turnings. Once coated THF (10 mL) was added to cover the Mg. 5-bromo-1-pentene (1.2 mL,

9.85 mmol) was subsequently added to the addition funnel and dissolved in THF (20 mL). The solution of alkyl halide was slowly added to the slurry of magnesium turnings over 10 minutes. After complete addition of 5-bromo-1-pentene, the translucent solution was refluxed for an additional 3 hours to consume the remaining Mg. *Tert*-butyl-4-formylpiperidine-1-carboxylate **2.16** (1.0 g, 4.69 mmol) was added to a separate 100-mL round-bottom flask, and THF (20 mL) was then added. After cooling the reaction to 0 °C, the solution of pent-4-en-1-ylmagnesium bromide was added dropwise via a cannula. The resulting solution was allowed to warm to room temperature and stirred overnight. After completion of reaction as determined by TLC, the reaction was cooled to 0 °C and quenched with saturated NH₄Cl (10 ml). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x20 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% to 25% gradient of EtOAc in hexanes affording **2.17** as a yellow oil in 96% yield (1.28 g, 4.50 mmol).

Rf: 0.32 in 70:30 (Hexanes: EtOAc)

¹H NMR (400 MHz, CDCl₃) δ 5.80 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.04 – 4.99 (m, 1H), 4.97 – 4.94 (m, 1H), 4.16 – 4.13 (m, 2H), 3.41 – 3.37 (m, 1H), 2.69 – 2.62 (m, 2H), 2.11 – 2.04 (m, 2H), 1.76 (dt, *J* = 13.1, 5.1 Hz, 1H), 1.61 – 1.51 (m, 5H), 1.44 (s, 9H), 1.43 – 1.37 (m, 3H), 1.31 – 1.16 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 154.8, 138.6, 114.8, 79.3, 75.1, 42.1, 33.7, 33.5, 28.5, 28.3, 25.0.

IR (cm⁻¹): *f* = 3444, 2932, 2858, 1693, 1671, 1426, 1366, 1279, 1236, 1169, 968, 909, 867, 768.

***tert*-butyl-4-(hex-5-enoyl)piperidine-1-carboxylate (2.18)**

Alcohol **2.17** (928 mg, 3.27 mmol) was combined with CH₂Cl₂ (16.4 mL) in a 100-mL round-bottom flask. The solution was cooled to 0 °C followed by the addition of Dess-Martin Periodinane (1.53 g, 3.60 mmol). The reaction was left in ice bath and stirred overnight. After the reaction was determined to be complete by TLC analysis, it was filtered over celite and subsequently diluted with H₂O (15 mL). Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL) and washed with NaHCO₃ (10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% to 20% gradient of EtOAc in hexanes affording **2.18** as a colorless oil in 96% yield (879 mg, 3.13 mmol).

Rf: 0.60 in 70:30 (Hexanes: EtOAc)

¹H NMR (500 MHz, CDCl₃) δ 5.79 – 5.71 (m, 1H), 5.02 – 4.96 (m, 2H), 4.11 – 4.09 (m, 2H), 2.76 (t, *J* = 12.2 Hz, 2H), 2.46 – 2.41 (m, 3H), 2.08 – 2.03 (m, 2H), 1.79 – 1.77 (m, 2H), 1.67 (t, *J* = 7.3 Hz, 2H), 1.57 – 1.48 (m, 4H), 1.45 (s, 9H).

¹³C NMR (126 MHz, CDCl₃) δ 212.1, 154.7, 137.9, 115.3, 79.6, 48.7, 43.3, 39.6, 33.1, 28.4, 27.5, 22.5.

IR (cm⁻¹): *f* = 2932, 1692, 1421, 1365, 1277, 1235, 1169, 1133, 1010, 912.

***tert*-butyl-4-(4-(oxiran-2-yl)butanoyl)piperidine-1-carboxylate ((±)-2.19)**

Ketone **2.18** (491 mg, 1.75 mmol) was added to a 100-mL round-bottom flask and dissolved in Et₂O (7 mL). *m*CPBA (402 mg, 1.75 mmol, 70 wt %) was added and the reaction was stirred at room temperature. After 15 hours the reaction was quenched with 1M NaOH (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O

(3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording recovered ketone **2.18** as a colorless oil (357 mg, 1.27 mmol). Further elution with a 15% to 35% gradient of EtOAc in hexanes afforded epoxyketone (±)-**2.19** as a colorless oil in 58% yield based on recovered starting material (83 mg, 0.28 mmol).

Rf: 0.40 in 50:50 (Hexanes: EtOAc)

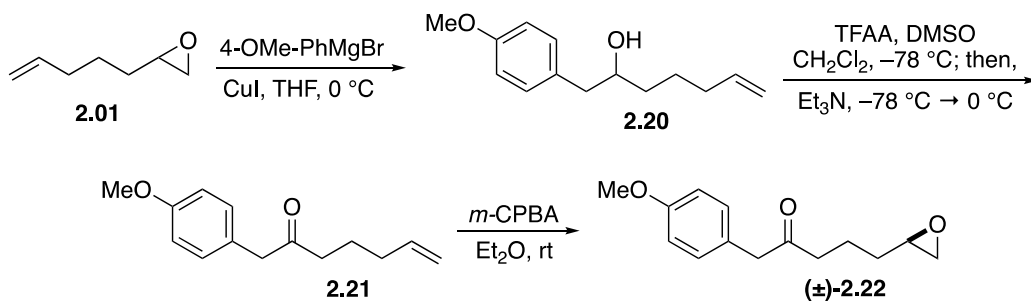
¹H NMR (400 MHz, CDCl₃) δ 4.14 – 4.09 (m, 2H), 2.89 (td, *J* = 6.8, 4.1 Hz, 1H), 2.78 (d, *J* = 12.3 Hz, 1H), 2.73 (t, *J* = 4.6 Hz, 1H), 2.53 (t, *J* = 7.1 Hz, 2H), 2.49 – 2.42 (m, 2H), 1.80 – 1.71 (m, 4H), 1.68 – 1.61 (m, 1H), 1.56 – 1.48 (m, 3H), 1.45 (s, 9H).

¹³C NMR (100 MHz, CDCl₃) δ 211.7, 154.7, 79.6, 52.0, 48.6, 46.7, 39.9, 31.8, 28.4, 27.5, 20.1.

IR (cm⁻¹): *f* = 2929, 1689, 1420, 1365, 1277, 1235, 1167, 1133, 1013, 769.

HRMS (ESI-TOF) *m/z*: (M+Na)⁺ = 320.18323 calculated for C₁₆H₂₇NNaO₄; experimental 320.18295.

1-(4-methoxyphenyl)-5-(oxiran-2-yl)pentan-2-one ((±)-**2.22**)



1-(4-methoxyphenyl)hept-6-en-2-ol (**2.20**)

CuI (240 mg, 1.26 mmol) was added to a 100-mL round-bottom flask while still hot and vacuum purged with N₂ while gradually cooling to room temperature. THF (15 mL) was added and the resulting slurry was cooled to 0 °C. After 5 minutes, 4-MeO-PhMgBr (7.5 mL, 1 M in

THF) was added dropwise. After 10 minutes epoxide **2.01** (698 mg, 6.23 mmol) was added via cannula in THF (15 mL). The resulting solution was stirred at 0 °C. After 1 hour, the reaction was determined to be complete by TLC analysis and quenched with saturated NH₄Cl (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording **2.20** and a clear oil in 81% yield (1.11 g, 5.04 mmol).

¹H NMR (500 MHz, CDCl₃) δ 7.13 (d, *J* = 9.0 Hz, 2H), 6.86 (d, *J* = 8.2 Hz, 2H), 5.82 (ddt, *J* = 16.5, 9.8, 6.7 Hz, 1H), 5.01 (d, *J* = 17.1 Hz, 1H), 4.96 (d, *J* = 9.8 Hz, 1H), 3.81 – 3.77 (m, 4H), 2.78 (dd, *J* = 13.8, 4.2 Hz, 1H), 2.58 (dd, *J* = 13.6, 8.5 Hz, 1H), 2.13 – 2.05 (m, 2H), 1.63 – 1.46 (m, 4H).

¹³C NMR (126 MHz, CDCl₃) δ 158.3, 138.7, 130.4, 130.3, 114.6, 114.0, 72.6, 55.2, 43.1, 36.1, 33.7, 25.1.

1-(4-methoxyphenyl)hept-6-en-2-one (2.21)

TFAA (1.2 mL, 8.14 mmol) and CH₂Cl₂ (6 mL) were combined in 250-mL round-bottom flask. The resulting solution was cooled to –78 °C for 10 minutes before DMSO (1.2 mL, 16.3 mmol) was added as a solution in CH₂Cl₂ (15 mL) slowly, dropwise. After 1 hour alcohol **2.20** (1.63 g, 7.40 mmol) was added via cannula in CH₂Cl₂ (20 mL). After 1 hour the starting material had been completely consumed as judged by TLC analysis and Et₃N (5.2 mL, 37.0 mmol) was added slowly. The reaction was slowly warmed to room temperature over 30 minutes. Further reaction monitoring by TLC analysis determined that the reaction was complete. The reaction was then cooled to 0 °C and quenched by the addition of 2M HCl (10 mL). Upon complete separation

of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x15 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording **2.21** and a clear oil in 89% yield (1.44 g, 6.60 mmol).

¹H NMR (500 MHz, CDCl₃) δ 7.13 – 7.09 (m, 2H), 6.89 – 6.84 (m, 2H), 5.72 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H), 4.99 – 4.93 (m, 2H), 3.80 (s, 3H), 3.61 (s, 2H), 2.44 (t, *J* = 7.4 Hz, 2H), 2.03 – 1.98 (m, 2H), 1.65 (p, *J* = 7.4 Hz, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 208.6, 158.6, 137.9, 130.4, 126.3, 115.1, 114.1, 55.2, 49.3, 40.9, 33.0, 22.7.

1-(4-methoxyphenyl)-5-(oxiran-2-yl)pentan-2-one ((±)-2.22)

Ketone **2.21** (1.33 g, 6.11 mmol) was added to a 100-mL round-bottom flask and dissolved in Et₂O (24 mL). *m*CPBA (2.26 g, 9.16 mmol, 70 wt %) was added and the reaction was stirred at room temperature. After 19 hours the reaction was quenched with 1M NaOH (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording recovered ketone **2.21** as a clear oil (778 mg, 3.56 mmol). Further elution with a 10% gradient of EtOAc in hexanes afforded epoxyketone (±)-**2.22** as a clear oil in 52% yield based on recovered starting material (309 mg, 1.32 mmol).

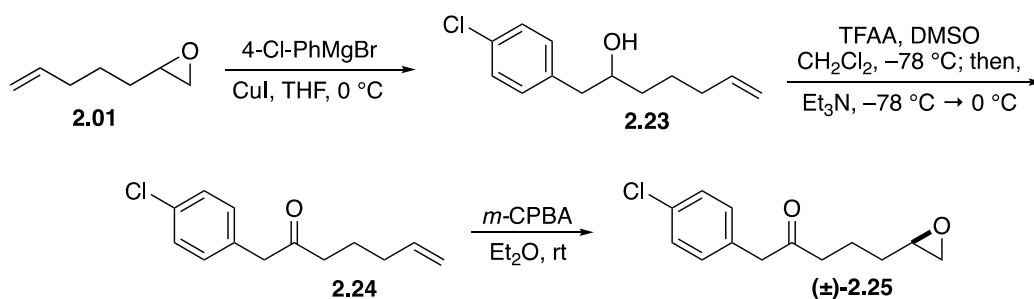
¹H NMR (400 MHz, CDCl₃) δ 7.13 – 7.09 (m, 2H), 6.88 – 6.84 (m, 2H), 3.79 (s, 3H), 3.62 (s, 2H), 2.87 – 2.82 (m, 1H), 2.70 (dd, *J* = 4.8, 4.3 Hz, 1H), 2.51 (t, *J* = 7.1 Hz, 2H), 2.41 (dd, *J* = 5.0, 2.7 Hz, 1H), 1.76 – 1.67 (m, 2H), 1.61 – 1.52 (m, 1H), 1.46 – 1.36 (m, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 208.2, 158.6, 130.3, 126.2, 114.1, 55.2, 51.9, 49.3, 46.8, 41.1, 31.7, 20.1.

IR (cm^{-1}): f = 2935, 2836, 1710, 1611, 1583, 1511, 1461, 1409, 1366, 1300, 1246, 1178, 1112, 1033, 924, 829, 519.

HRMS (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 235.13287$ calculated for $\text{C}_{14}\text{H}_{19}\text{O}_3$, experimental 235.13316.

1-(4-chlorophenyl)-5-(oxiran-2-yl)pentan-2-one ((\pm)-**2.25**)



1-(4-chlorophenyl)hept-6-en-2-ol (**2.23**)

CuI (187 mg, 0.982 mmol) was added to a 100-mL round-bottom flask while still hot and vacuum purged with N₂ while gradually cooling to room temperature. THF (8 mL) was added and the resulting slurry was cooled to 0 °C. After 5 minutes, 4-Cl-PhMgBr (5.9 mL, 1 M in Et₂O) was added dropwise. After 10 minutes epoxide **2.01** (550 mg, 4.91 mmol) was added via cannula in THF (8 mL). The resulting solution was stirred at 0 °C. After 1 hours, the reaction was determined to be complete by TLC analysis and quenched with saturated NH₄Cl (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording **2.23** as a white solid in 91% yield (1.00 g, 4.45 mmol).

¹H NMR (400 MHz, CDCl₃) δ 7.29 – 7.26 (m, 2H), 7.16 – 7.13 (m, 2H), 5.80 (ddt, *J* = 16.7, 10.2, 6.5 Hz, 1H), 5.04 – 4.99 (m, 1H), 4.99 – 4.93 (m, 1H), 3.84 – 3.76 (m, 1H), 2.79 (dd, *J* = 13.5, 4.1 Hz, 1H), 2.63 (dd, *J* = 13.5, 8.4 Hz, 1H), 2.13 – 2.05 (m, 2H), 1.62 – 1.45 (m, 3H), 1.45 – 1.42 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 138.5, 137.0, 132.3, 130.7, 128.6, 114.7, 72.4, 43.3, 36.2, 33.6, 25.0.

1-(4-chlorophenyl)hept-6-en-2-one (2.24)

TFAA (1.0 mL, 7.19 mmol) and CH₂Cl₂ (5 mL) were combined in 100-mL round-bottom flask. The resulting solution was cooled to –78 °C for 10 minutes before DMSO (745 μL, 10.5 mmol) was added as a solution in CH₂Cl₂ (7 mL) slowly, dropwise. After 1 hour alcohol **2.23** (1.08 g, 4.79 mmol) was added via cannula in CH₂Cl₂ (12 mL). After 1 hour the starting material had been completely consumed as judged by TLC analysis and Et₃N (3.3 mL, 24.0 mmol) was added slowly. The reaction was slowly warmed to room temperature over 30 minutes. Further reaction monitoring by TLC analysis determined that the reaction was complete. The reaction was then cooled to 0 °C and quenched by the addition of 2M HCl (5 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording **2.24** and a clear oil in 88% yield (945 mg, 4.24 mmol).

¹H NMR (400 MHz, CDCl₃) δ 7.31 – 7.27 (m, 2H), 7.15 – 7.10 (m, 2H), 5.72 (ddt, *J* = 16.7, 9.9, 6.7 Hz, 1H), 5.00 – 4.96 (m, 1H), 4.96 – 4.93 (m, 1H), 3.65 (s, 2H), 2.47 (d, *J* = 7.3 Hz, 2H), 2.05 – 1.99 (m, 2H), 1.67 (p, *J* = 7.4 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 137.8, 132.9, 132.6, 130.7, 128.8, 115.3, 49.2, 41.3, 32.9, 22.6.

1-(4-chlorophenyl)-5-(oxiran-2-yl)pentan-2-one ((±)-2.25)

Ketone **2.24** (1.69 g, 7.59 mmol) was added to a 100-mL round-bottom flask and dissolved in Et₂O (30 mL). *m*CPBA (2.81 g, 11.4 mmol, 70 wt %) was added and the reaction was stirred at room temperature. After 19 hours the reaction was quenched with 1M NaOH (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording recovered ketone **2.24** as a clear oil (529 mg, 2.37 mmol). Further elution with a 10% gradient of EtOAc in hexanes afforded epoxyketone (±)-**2.25** as a clear oil in 47% yield based on recovered starting material (584 mg, 2.45 mmol).

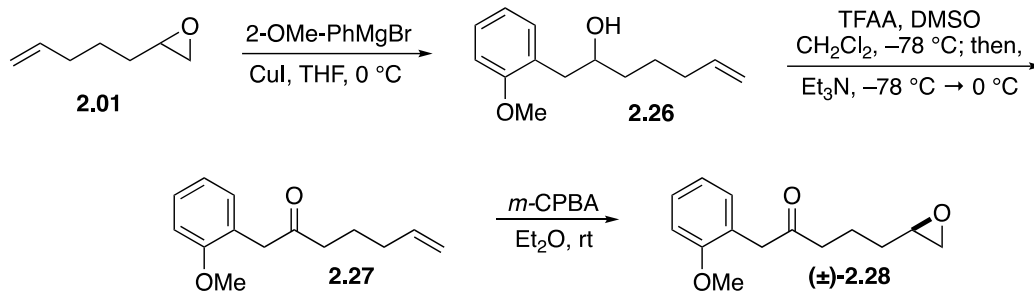
¹H NMR (500 MHz, CDCl₃) δ 3.66 (s, 2H), 2.86 (dtd, *J* = 6.8, 4.2, 2.7 Hz, 1H), 2.72 (dd, *J* = 5.0, 3.9 Hz, 1H), 2.53 (dd, *J* = 7.7, 6.9 Hz, 2H), 2.42 (dd, *J* = 5.0, 2.7 Hz, 1H), 1.77 – 1.70 (m, 2H), 1.60 (dddd, *J* = 12.0, 8.6, 5.1, 3.5 Hz, 1H), 1.43 – 1.37 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 207.2, 133.0, 132.6, 130.7, 128.8, 51.9, 49.2, 46.7, 41.5, 31.6, 20.1.

IR (cm⁻¹): *f* = 3048, 2933, 1712, 1491, 1408, 1367, 1333, 1260, 1190, 1089, 1015, 924, 828, 671, 619, 493, 427.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ = 239.08333 calculated for C₁₃H₁₆ClO₂, experimental 239.08314.

1-(2-methoxyphenyl)-5-(oxiran-2-yl)pentan-2-one ((±)-2.28)



1-(2-methoxyphenyl)hept-6-en-2-ol (2.26)

CuI (400 mg, 2.10 mmol) was added to a 100-mL round-bottom flask while still hot and vacuum purged with N_2 while gradually cooling to room temperature. THF (20 mL) was added and the resulting slurry was cooled to $0\text{ }^{\circ}\text{C}$. After 5 minutes, 2-OMe-PhMgBr (13 mL, 1 M in Et_2O) was added dropwise. After 10 minutes epoxide **2.01** (1.18 g, 10.5 mmol) was added via cannula in THF (15 mL). The resulting solution was stirred at $0\text{ }^{\circ}\text{C}$. After 3 hours, the reaction was determined to be complete by TLC analysis and quenched with saturated NH_4Cl (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et_2O (3x15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording **2.26** as a white solid in 94% yield (2.18 g, 9.89 mmol).

^1H NMR (500 MHz, CDCl_3) δ 7.23 (t, $J = 7.6\text{ Hz}$, 1H), 7.15 (d, $J = 7.8\text{ Hz}$, 1H), 6.94 – 6.86 (m, 2H), 5.83 (ddt, $J = 16.8, 10.2, 6.8\text{ Hz}$, 1H), 5.01 (d, $J = 17.4\text{ Hz}$, 1H), 4.95 (d, $J = 10.6\text{ Hz}$, 1H), 3.88 – 3.81 (m, 4H), 2.90 (dd, $J = 14.0, 3.7\text{ Hz}$, 1H), 2.69 (dd, $J = 13.1, 8.2\text{ Hz}$, 1H), 2.12 – 2.02 (m, 2H), 1.65 – 1.57 (m, 1H), 1.54 – 1.47 (m, 2H).

^{13}C NMR (126 MHz, CDCl_3) δ 138.9, 131.3, 127.8, 127.1, 120.7, 114.4, 110.4, 71.7, 55.3, 38.7, 36.6, 33.7, 25.1.

IR: $f(\text{cm}^{-1}) = 3400, 3073, 2998, 2933, 2858, 2836, 1639, 1600, 1586, 1492, 1438, 1289, 1240, 1113, 1050, 996, 864, 729, 611, 478.$

HRMS (ESI-TOF) m/z : $(M+H^+) = 221.15361$ calculated for $C_{14}H_{21}O_2$, experimental 221.15427.

1-(2-methoxyphenyl)hept-6-en-2-one (2.27)

TFAA (1.5 mL, 10.8 mmol) and CH_2Cl_2 (10 mL) were combined in 250-mL round-bottom flask. The resulting solution was cooled to $-78\text{ }^\circ\text{C}$ for 10 minutes before DMSO (1.5 mL, 21.7 mmol) was added as a solution in CH_2Cl_2 (20 mL) slowly, dropwise. After 1 hour alcohol **2.26** (2.18 g, 9.89 mmol) was added via cannula in CH_2Cl_2 (20 mL). After 1 hour the reaction was determined to be complete by TLC analysis and Et_3N (6.9 mL, 49.5 mmol) was added slowly. The reaction was slowly warmed to room temperature over 30 minutes. Further reaction monitoring by TLC analysis determined that the reaction was complete. The reaction was then cooled to $0\text{ }^\circ\text{C}$ and quenched by the addition of 2M HCl (20 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording **2.27** and a clear oil in 85% yield (1.84 g, 8.41 mmol).

^1H NMR (400 MHz, CDCl_3) δ 7.28 – 7.23 (m, 1H), 7.12 (dd, $J = 7.4, 1.6$ Hz, 1H), 6.92 (td, $J = 7.4, 1.0$ Hz, 1H), 6.87 (d, $J = 8.3$ Hz, 1H), 5.75 (ddt, $J = 17.0, 10.0, 6.7$ Hz, 1H), 5.01 – 4.93 (m, 2H), 3.80 (s, 3H), 3.66 (s, 2H), 2.44 (t, $J = 7.4$ Hz, 2H), 2.03 (q, $J = 7.0$ Hz, 2H), 1.68 (p, $J = 7.4$ Hz, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ 208.7, 157.3, 138.1, 131.2, 128.4, 123.7, 120.6, 115.0, 110.4, 55.3, 44.7, 41.0, 33.0, 22.8.

IR: $f(\text{cm}^{-1}) = 3074, 2937, 2837, 1784, 1722, 1600, 1493, 1439, 1408, 1363, 1290, 1175, 1115, 1028, 911, 833, 751, 636, 453.$

HRMS (ESI-TOF) m/z : $(M+H^+) = 219.13796$ calculated for $C_{14}H_{19}O_2$, experimental 219.13820.

1-(2-methoxyphenyl)-5-(oxiran-2-yl)pentan-2-one ((\pm)-2.28**)**

Ketone **2.27** (945 mg, 4.33 mmol) was added to a 50-mL round-bottom flask and dissolved in Et_2O (17 mL). *m*CPBA (1.60 g, 6.49 mmol, 70 wt %) was added and the reaction was stirred at room temperature. After 12 hours the reaction was quenched with 1M NaOH (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et_2O (3x10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording recovered ketone **2.27** as a clear oil (358 mg, 1.64 mmol). Further elution with a 20% gradient of EtOAc in hexanes afforded epoxyketone (\pm)-**2.28** as a clear oil in 63% yield based on recovered starting material (395 mg, 1.68 mmol).

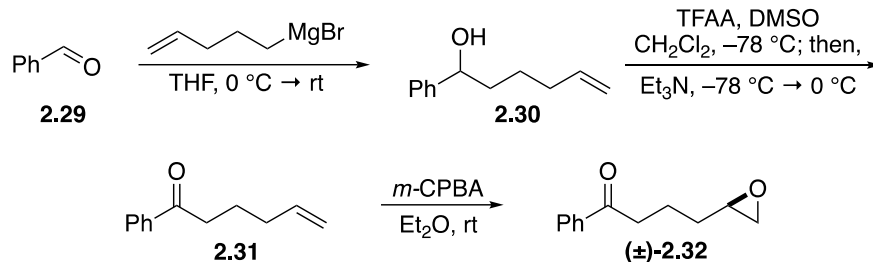
^1H NMR (500 MHz, CDCl_3) δ 7.27 – 7.23 (m, 1H), 7.12 (dd, $J = 7.3, 1.1$ Hz, 1H), 6.92 (t, $J = 7.5$ Hz, 1H), 6.87 (d, $J = 8.1$ Hz, 1H), 3.80 (s, 3H), 3.66 (s, 2H), 2.89 – 2.84 (m, 1H), 2.72 (t, $J = 5.0$ Hz, 1H), 2.50 (td, $J = 7.3, 1.4$ Hz, 2H), 2.43 (dd, $J = 4.9, 2.6$ Hz, 1H), 1.77 – 1.70 (m, 2H), 1.59 – 1.53 (m, 1H), 1.50 – 1.43 (m, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 208.3, 157.3, 131.2, 128.5, 123.5, 120.6, 110.4, 55.3, 52.0, 46.8, 44.8, 41.1, 31.7, 20.1.

IR: $f(\text{cm}^{-1}) = 2937, 2838, 1712, 1600, 1494, 1461, 1440, 1408, 1365, 1290, 1245, 1177, 1114, 1049, 925, 834, 754, 557, 495, 454.$

HRMS (ESI-TOF) m/z : $(M+H^+) = 235.13287$ calculated for $C_{14}H_{19}O_3$, experimental 235.13343

4-(oxiran-2-yl)-1-phenylbutan-1-one ((±)-2.32)



1-phenylhex-5-en-1-ol (2.30)

Freshly ground Mg turnings (1.37 g, 56.5 mmol) were added to a 500-mL three-neck round-bottom flask, with a pressure-equalizing addition funnel and condenser attached. Catalytic I₂ (1–2 crystals) was added and the apparatus was heated gently to sublime the I₂ and coat the Mg turnings. Once coated THF (25 mL) was added to cover the Mg. 5-bromo-1-pentene (6.7 mL, 56.5 mmol) was subsequently added to the addition funnel and dissolved in THF (25 mL). The solution of alkyl halide was slowly added to the slurry of magnesium turnings over 30 minutes. After complete addition of 5-bromo-1-pentene, the translucent solution was refluxed for an additional 1 hour to consume the remaining Mg. Once all of the Mg had been consumed, the solution of 4-pentenylmagnesium bromide (~ 1 M) was cooled to room temperature and diluted with an additional 50 mL of THF, before being cooled to 0 °C. After approximately 15 minutes, benzaldehyde **2.29** (4.8 mL, 47.1 mmol) was added to the addition funnel, diluted with THF (50 mL) and added slowly to the solution containing the Grignard reagent. After complete addition of **7.30** the reaction was allowed to warm to room temperature. After 30 minutes the reaction was determined to be complete by TLC analysis and quenched with the addition of saturated NH₄Cl (30 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x50 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil

was purified by flash column chromatography using a 5% to 10% gradient of EtOAc in hexanes affording **2.30** as a clear oil in 94% yield (7.82 g, 44.4 mmol).

¹H NMR (400 MHz, CDCl₃) δ 7.29 – 7.25 (m, 4H), 7.23 – 7.17 (m, 1H), 5.70 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H), 4.91 (dq, *J* = 17.1, 1.5 Hz, 1H), 4.88 – 4.84 (m, 1H), 4.60 (dd, *J* = 7.5, 5.9 Hz, 1H), 1.99 (q, *J* = 7.2 Hz, 2H), 1.79 – 1.60 (m, 3H), 1.45 (dddd, *J* = 5.2, 7.6, 10.7, 17.0 Hz, 1H), 1.36 – 1.26 (m, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 144.8, 138.5, 128.4, 127.5, 125.8, 114.7, 74.5, 38.5, 33.6, 25.1.

1-phenylhex-5-en-1-one (2.31)

TFAA (2.2 mL, 15.3 mmol) and CH₂Cl₂ (20 mL) were combined in 250-mL round-bottom flask. The resulting solution was cooled to –78 °C for 10 minutes before DMSO (2.2 mL, 30.6 mmol) was added as a solution in CH₂Cl₂ (20 mL) slowly, dropwise. After 1 hour alcohol **2.30** (2.45 g, 13.9 mmol) was added via cannula in CH₂Cl₂ (20 mL). After 1 hour the reaction was determined to be complete by TLC analysis and Et₃N (9.7 mL, 69.5 mmol) was added slowly. The reaction was slowly warmed to room temperature over 30 minutes. Further reaction monitoring by TLC analysis determined that the reaction was complete. The reaction was then cooled to 0 °C and quenched by the addition of 2M HCl (15 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x15 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording **2.31** and a clear oil in 79% yield (1.91 g, 11.0 mmol).

¹H NMR (500 MHz, CDCl₃) δ 7.97 – 7.95 (m, 2H), 7.55 (tt, *J* = 7.5, 1.3 Hz, 1H), 7.48 – 7.44 (m, 2H), 5.82 (ddt, *J* = 17, 10.2, 6.7 Hz, 1H), 5.05 (dq, *J* = 17.1, 1.8 Hz, 1H), 5.01 – 4.98 (m, 1H), 2.98 (t, *J* = 7.3 Hz 2H), 2.16 (q, *J* = 6.9 Hz 2H), 1.86 (p, *J* = 7.5 Hz 2H).

¹³C NMR (126 MHz, CDCl₃) δ 200.2, 138.0, 137.0, 132.9, 128.5, 128.0, 115.3, 37.7, 33.2, 23.3.

4-(oxiran-2-yl)-1-phenylbutan-1-one ((±)-2.32)

Ketone **2.31** (1.91 g, 11.0 mmol) was added to a 100-mL round-bottom flask and dissolved in Et₂O (44 mL). *m*CPBA (4.04 g, 16.4 mmol, 70 wt %) was added and the reaction was stirred at room temperature. After 20 hours the reaction was quenched with 1M NaOH (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording recovered ketone **2.31** as a clear oil (774 mg, 4.44 mmol). Further elution with a 10% gradient of EtOAc in hexanes afforded epoxyketone (±)-**2.32** as a clear oil in 64% yield based on recovered starting material (792 mg, 4.16 mmol).

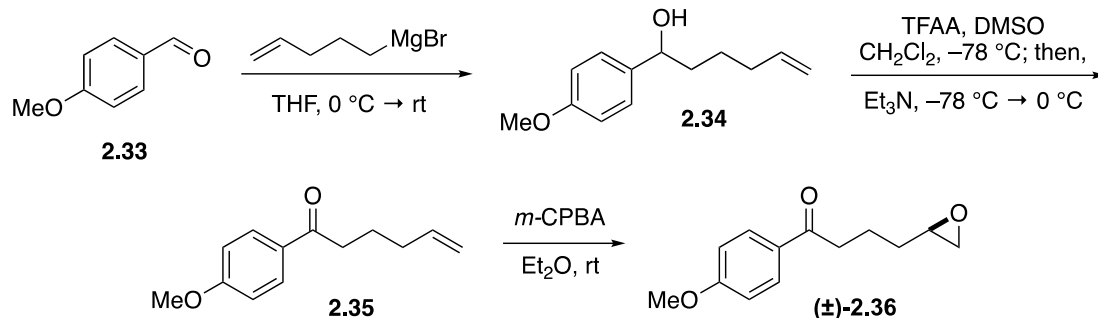
¹H NMR (500 MHz, CDCl₃) δ 7.96 (d, *J* = 7.8 Hz, 2H), 7.56 (t, *J* = 7.1 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 3.08 – 3.04 (m, 2H), 2.98 – 2.94 (m, 1H), 2.78 – 2.75 (m, 1H), 2.50 – 2.48 (m, 1H), 1.96 – 1.89 (m, 2H), 1.76 – 1.69 (m, 1H), 1.62 – 1.53 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 199.7, 136.9, 133.0, 128.6, 128.0, 52.1, 46.8, 37.9, 31.9, 20.6.

IR (cm⁻¹): *f* = 3054, 2934, 1681, 1596, 1482, 1370, 1320, 1251, 1133, 1101, 1023, 973, 918, 869, 747, 691, 569, 492, 429.

HRMS (ESI-TOF) *m/z*: (M+H⁺) = 191.10666 calculated for C₁₂H₁₅O₂, experimental 191.10682.

1-(4-methoxyphenyl)-4-(oxiran-2-yl)butan-1-one ((±)-2.36)



1-(4-methoxyphenyl)hex-5-en-1-ol (**2.34**)

Freshly ground Mg turnings (357 mg, 14.68 mmol) were added to a 100-mL three-neck round-bottom flask, with a pressure-equalizing addition funnel and condenser attached. Catalytic I_2 (1–2 crystals) was added and the apparatus was heated gently to sublime the I_2 and coat the Mg turnings. Once coated THF (10 mL) was added to cover the Mg. 5-bromo-1-pentene (1.8 mL, 15.42 mmol) was subsequently added to the addition funnel and dissolved in THF (20 mL). The solution of alkyl halide was slowly added to the slurry of magnesium turnings over 10 minutes. After complete addition of 5-bromo-1-pentene, the translucent solution was refluxed for an additional 2 hours to consume the remaining Mg. 4-Methoxybenzaldehyde **2.33** (1.0 g, 7.34 mmol) was added to a separate 100-mL round-bottom flask, and THF (20 mL) was then added. After cooling the reaction to $0\text{ }^{\circ}\text{C}$, the solution of pent-4-en-1-ylmagnesium bromide was added dropwise via a cannula. The resulting solution was allowed to warm to room temperature and stirred overnight. After completion of reaction as determined by TLC, the reaction was cooled to $0\text{ }^{\circ}\text{C}$ and quenched with saturated NH_4Cl (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et_2O (3x20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% to 15% gradient of EtOAc in hexanes affording **2.34** as a yellow solid in quantitative yield (1.52 g, 7.34 mmol).

Rf: 0.41 in 70:30 (Hexanes: EtOAc)

¹H NMR (400 MHz, CDCl₃) δ 7.28 – 7.27 (m, 1H), 7.25 – 7.24 (m, 1H), 6.90 – 6.89 (m, 1H), 6.88 – 6.86 (m, 1H), 5.78 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 5.02 – 4.96 (m, 1H), 4.95 – 4.92 (m, 1H), 4.64 – 4.60 (m, 1H), 3.81 (s, 3H), 2.09 (d, J = 7.4 Hz, 1H), 2.05 (d, J = 7.3 Hz, 1H), 1.86 – 1.75 (m, 2H), 1.74 – 1.65 (m, 1H), 1.56 – 1.45 (m, 1H), 1.40 – 1.31 (m, 1H).

¹³C NMR (100 MHz, CDCl₃) δ 159.1, 138.6, 137.0, 127.1, 114.6, 113.8, 74.1, 55.3, 38.4, 33.6, 25.2.

IR (cm⁻¹): ν = 3389, 2933, 1611, 1511, 1459, 1301, 1244, 1174, 1034, 910, 831, 554.

1-(4-methoxyphenyl)hex-5-en-1-one (2.35)

TFAA (1.4 mL, 9.86 mmol) and CH₂Cl₂ (10 mL) were combined in 250-mL round-bottom flask. The resulting solution was cooled to –78 °C for 10 minutes before DMSO (1.4 mL, 19.73 mmol) was added as a solution in CH₂Cl₂ (10 mL) slowly, dropwise. After 1 hour alcohol **2.34** (1.85 g, 8.97 mmol) was added via cannula in CH₂Cl₂ (30 mL). After 1 hour the reaction was determined to be complete by TLC analysis and Et₃N (6.3 mL, 44.85 mmol) was added slowly. The reaction was slowly warmed to room temperature overnight. Further reaction monitoring by TLC analysis determined that the reaction was complete. The reaction was then cooled to 0 °C and quenched by the addition of 2M HCl (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x15 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% to 10% gradient of EtOAc in hexanes affording **2.35** as a colorless liquid in 79% yield (1.45 g, 7.10 mmol).

Rf: 0.63 in 70:30 (Hexanes: EtOAc)

¹H NMR (400 MHz, CDCl₃) δ 7.96 – 7.95 (m, 1H), 7.93 – 7.92 (m, 1H), 6.95 – 6.94 (m, 1H), 6.92 – 6.91 (m, 1H), 5.82 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.04 (dd, *J* = 17.0, 1.6 Hz, 1H), 4.99 (dd, *J* = 10.2, 1.0 Hz, 1H), 3.87 (s, 3H), 2.92 (t, *J* = 7.4 Hz, 2H), 2.17 (d, *J* = 7.1 Hz, 1H), 2.13 (d, *J* = 7.2 Hz, 1H), 1.84 (p, *J* = 7.5 Hz, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 198.9, 163.4, 138.1, 130.3, 130.2, 115.2, 113.7, 55.4, 37.4, 33.3, 23.6.

1-(4-methoxyphenyl)-4-(oxiran-2-yl)butan-1-one ((±)-2.36)

Ketone **2.35** (1.45 g, 7.10 mmol) was added to a 100-mL round-bottom flask and dissolved in Et₂O (28.4 mL). *m*CPBA (1.63 g, 7.10 mmol, 70 wt %) was added and the reaction was stirred at room temperature. After 20 hours the reaction was quenched with 1M NaOH (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording recovered ketone **2.35** as a colorless liquid (569 mg, 2.79 mmol). Further elution with a 10% to 20% gradient of EtOAc in hexanes afforded epoxyketone (±)-**2.36** as a white solid in 87% yield based on recovered starting material (821 mg, 3.73 mmol).

Rf: 0.30 in 70:30 (Hexanes: EtOAc)

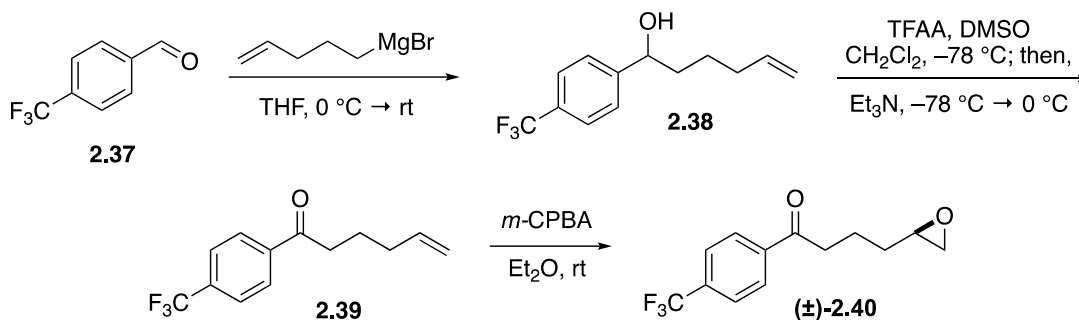
¹H NMR (400 MHz, CDCl₃) δ 7.96 – 7.94 (m, 1H), 7.93 – 7.92 (m, 1H), 6.94 – 6.93 (m, 1H), 6.92 – 6.91 (m, 1H), 3.86 (s, 3H), 3.01 – 2.97 (m, 2H), 2.96 – 2.95 (m, 1H), 2.74 (t, *J* = 4.9 Hz, 1H), 2.48 (dd, *J* = 4.9, 2.7 Hz, 1H), 1.90 (p, *J* = 7.2 Hz, 2H), 1.74 – 1.66 (m, 1H), 1.62 – 1.52 (m, 1H).

¹³C NMR (100 MHz, CDCl₃) δ 198.4, 163.4, 130.3, 130.1, 113.7, 55.4, 52.1, 46.8, 37.6, 32.0, 20.9.

IR (cm⁻¹): ν = 2936, 1674, 1599, 1575, 1510, 1459, 1417, 1367, 1311, 1254, 1207, 1170, 1028, 919, 829, 606.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 221.11722 calculated for C₁₃H₁₇O₃; experimental 221.11753, (M+Na)⁺ = 243.09917 calculated for C₁₃H₁₆NaO₃; experimental 243.09889.

4-(oxiran-2-yl)-1-(4-(trifluoromethyl)phenyl)butan-1-one ((±)-2.40)



1-(4-(trifluoromethyl)phenyl)hex-5-en-1-ol (2.38)

Freshly ground Mg turnings (279 mg, 11.48 mmol) were added to a 100-mL three-neck round-bottom flask, with a pressure-equalizing addition funnel and condenser attached. Catalytic I₂ (1–2 crystals) was added and the apparatus was heated gently to sublime the I₂ and coat the Mg turnings. Once coated THF (10 mL) was added to cover the Mg. 5-bromo-1-pentene (1.4 mL, 12.06 mmol) was subsequently added to the addition funnel and dissolved in THF (20 mL). The solution of alkyl halide was slowly added to the slurry of magnesium turnings over 10 minutes. After complete addition of 5-bromo-1-pentene, the translucent solution was refluxed for an additional 2 hours to consume the remaining Mg. 4-(trifluoromethyl)benzaldehyde **2.37** (0.8 mL, 5.74 mmol) was added to a separate 100-mL round-bottom flask, and THF (20 mL) was then added. After cooling the reaction to 0 °C, the solution of pent-4-en-1-ylmagnesium bromide was added dropwise via a cannula. The resulting solution was allowed to warm to room temperature and stirred overnight. After completion of reaction as determined by TLC, the reaction was cooled

to 0 °C and quenched with saturated NH₄Cl (10 ml). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x20 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% to 10% gradient of EtOAc in hexanes affording **2.38** as a yellow liquid in 91% yield (1.33 g, 5.43 mmol).

Rf: 0.58 in 70:30 (Hexanes: EtOAc)

¹H NMR (500 MHz, CDCl₃) δ 7.61 – 7.59 (m, 2H), 7.47 – 7.45 (m, 2H), 5.78 (dd, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.00 (dd, *J* = 17.2, 1.6 Hz, 1H), 4.96 (dd, *J* = 10.2, 0.9 Hz, 1H), 4.77 – 4.74 (m, 1H), 2.10 (d, *J* = 7.2 Hz, 1H), 2.07 (d, *J* = 7.1 Hz, 1H), 1.93 – 1.89 (m, 1H), 1.83 – 1.77 (m, 1H), 1.76 – 1.69 (m, 1H), 1.58 – 1.49 (m, 1H), 1.45 – 1.36 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 148.7, 138.3, 129.8, 129.6, 126.1, 125.4, 125.4, 125.4, 125.4, 125.2, 123.1, 114.9, 73.9, 38.6, 33.5, 24.8.

IR (cm⁻¹): *f* = 3354, 2937, 1641, 1620, 1417, 1324, 1163, 1123, 1067, 1016, 913, 841, 606.

1-(4-(trifluoromethyl)phenyl)hex-5-en-1-one (2.39)

TFAA (0.9 mL, 5.98 mmol) and CH₂Cl₂ (5 mL) were combined in 250-mL round-bottom flask. The resulting solution was cooled to –78 °C for 10 minutes before DMSO (0.9 mL, 11.95 mmol) was added as a solution in CH₂Cl₂ (5 mL) slowly, dropwise. After 1 hour alcohol **2.38** (1.32 g, 5.43 mmol) was added via cannula in CH₂Cl₂ (20 mL). After 1 hour the reaction was determined to be complete by TLC analysis and Et₃N (3.8 mL, 27.15 mmol) was added slowly. The reaction was slowly warmed to room temperature overnight. Further reaction monitoring by TLC analysis determined that the reaction was complete. The reaction was then cooled to 0 °C and quenched by the addition of 2M HCl (15 mL). Upon complete separation of the two layers,

the aqueous layer was extracted with CH₂Cl₂ (3x15 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording **2.39** and a yellow oil in 91% yield (1.19 g, 4.91 mmol).

Rf: 0.74 in 70:30 (Hexanes: EtOAc)

¹H NMR (400 MHz, CDCl₃) δ 8.06 – 8.04 (m, 2H), 7.74 – 7.71 (m, 2H), 5.82 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.05 (d, *J* = 17.2, 1.6 Hz, 1H), 5.01 (d, *J* = 10.4, 0.9 Hz, 1H), 3.00 (t, *J* = 7.3 Hz, 2H), 2.19 (d, *J* = 7.1 Hz, 1H), 2.15 (d, *J* = 7.1 Hz, 1H), 1.87 (p, *J* = 7.4 Hz, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 199.2, 139.7, 137.8, 134.4, 134.1, 128.3, 126.7, 125.7, 125.7, 125.7, 125.6, 124.7, 122.5, 115.5, 38.0, 33.1, 23.0.

4-(oxiran-2-yl)-1-(4-(trifluoromethyl)phenyl)butan-1-one ((±)-2.40)

Ketone **2.39** (1.19 g, 4.91 mmol) was added to a 100-mL round-bottom flask and dissolved in Et₂O (19.6 mL). *m*CPBA (1.13 g, 4.91 mmol, 70 wt %) was added and the reaction was stirred at room temperature. After 99 hours the reaction was quenched with 1M NaOH (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording recovered ketone **2.39** as a yellow oil (535 mg, 2.21 mmol). Further elution with a 10% gradient of EtOAc in hexanes afforded epoxyketone (±)-**2.40** as a yellow oil in 84% yield based on recovered starting material (584 mg, 2.26 mmol).

Rf: 0.47 in 70:30 (Hexanes: EtOAc)

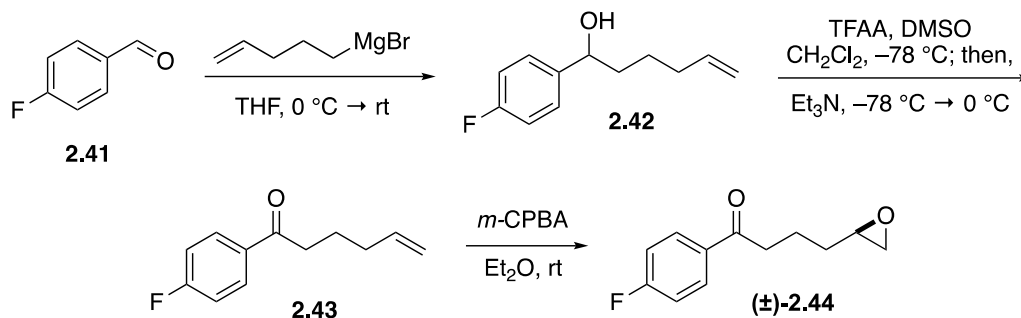
^1H NMR (500 MHz, CDCl_3) δ 8.07 – 8.05 (m, 2H), 7.74 – 7.72 (m, 2H), 3.10 – 3.07 (m, 2H), 2.95 (ddt, J = 6.8, 4.2, 2.8 Hz, 1H), 2.77 – 2.75 (m, 1H), 2.48 (dd, J = 5.0, 2.7 Hz, 1H), 1.95 (p, J = 7.3 Hz, 2H), 1.80 – 1.74 (m, 1H), 1.58 – 1.51 (m, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 198.7, 139.6, 134.5, 134.2, 128.3, 126.1, 125.7, 125.7, 125.7, 125.6, 122.5, 52.0, 46.7, 38.2, 31.7, 20.5.

IR (cm^{-1}): ν = 2932, 1691, 1511, 1409, 1324, 1167, 1127, 1065, 1015, 920, 828, 603.

HRMS (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 259.09404$ calculated for $\text{C}_{13}\text{H}_{14}\text{F}_3\text{O}_2$; experimental 259.09406.

1-(4-fluorophenyl)-4-(oxiran-2-yl)butan-1-one ((\pm)-**2.44**)



1-(4-fluorophenyl)hex-5-en-1-ol (**2.42**)

Freshly ground Mg turnings (392 mg, 16.12 mmol) were added to a 100-mL three-neck round-bottom flask, with a pressure-equalizing addition funnel and condenser attached. Catalytic I_2 (1–2 crystals) was added and the apparatus was heated gently to sublime the I_2 and coat the Mg turnings. Once coated THF (10 mL) was added to cover the Mg. 5-bromo-1-pentene (2.0 mL, 16.92 mmol) was subsequently added to the addition funnel and dissolved in THF (20 mL). The solution of alkyl halide was slowly added to the slurry of magnesium turnings over 10 minutes. After complete addition of 5-bromo-1-pentene, the translucent solution was refluxed for an additional 2 hours to consume the remaining Mg. 4-Fluorobenzaldehyde **2.41** (0.9 mL, 8.06 mmol)

was added to a separate 100-mL round-bottom flask, and THF (20 mL) was then added. After cooling the reaction to 0 °C, the solution of pent-4-en-1-ylmagnesium bromide was added dropwise via a cannula. The resulting solution was allowed to warm to room temperature and stirred overnight. After completion of reaction as determined by TLC, the reaction was cooled to 0 °C and quenched with saturated NH₄Cl (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x20 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% to 10% gradient of EtOAc in hexanes affording **2.42** as a colorless liquid in quantitative yield (1.62 g, 8.06 mmol).

Rf: 0.55 in 70:30 (Hexanes: EtOAc)

¹H NMR (500 MHz, CDCl₃) δ 7.32 – 7.29 (m, 2H), 7.04 – 7.01 (m, 2H), 5.77 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 4.99 (dd, *J* = 17.2, 1.3 Hz, 1H), 4.95 (dd, *J* = 10.2, 1.0 Hz, 1H), 4.68 – 4.65 (m, 1H), 2.09 (d, *J* = 6.5 Hz, 1H), 2.06 (d, *J* = 6.4 Hz, 1H), 1.82 – 1.76 (m, 1H), 1.73 – 1.66 (m, 1H), 1.55 – 1.46 (m, 1H), 1.41 – 1.32 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 163.2, 161.2, 140.5, 138.4, 127.5, 127.5, 115.3, 115.2, 114.8, 73.9, 38.6, 33.5, 25.0.

IR (cm⁻¹): *f* = 3349, 2934, 1640, 1604, 1509, 1223, 1156, 995, 912, 835, 572, 548.

1-(4-fluorophenyl)hex-5-en-1-one (2.43)

TFAA (1.5 mL, 10.37 mmol) and CH₂Cl₂ (10 mL) were combined in 250-mL round-bottom flask. The resulting solution was cooled to –78 °C for 10 minutes before DMSO (1.5 mL, 20.75 mmol) was added as a solution in CH₂Cl₂ (20 mL) slowly, dropwise. After 1 hour alcohol **2.42** (1.83 g, 9.43 mmol) was added via cannula in CH₂Cl₂ (30 mL). After 1 hour the reaction was

determined to be complete by TLC analysis and Et₃N (6.6 mL, 47.15 mmol) was added slowly. The reaction was slowly warmed to room temperature overnight. Further reaction monitoring by TLC analysis determined that the reaction was complete. The reaction was then cooled to 0 °C and quenched by the addition of 2M HCl (15 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x15 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording **2.43** and a yellow oil in 97% yield (1.76 g, 9.14 mmol).

Rf: 0.77 in 70:30 (Hexanes: EtOAc)

¹H NMR (400 MHz, CDCl₃) δ 8.00 – 7.98 (m, 1H), 7.97 – 7.96 (m, 1H), 7.14 – 7.09 (m, 2H), 5.82 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.04 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.00 (dd, *J* = 10.7, 0.9 Hz, 1H), 2.94 (t, *J* = 7.3 Hz, 2H), 2.17 (d, *J* = 7.1 Hz, 1H), 2.14 (d, *J* = 7.1 Hz, 1H), 1.85 (p, *J* = 7.4 Hz, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 198.6, 166.7, 164.6, 138.0, 133.5, 133.5, 130.7, 130.6, 128.5, 115.9, 115.7, 115.5, 115.4, 37.6, 33.2, 24.4, 23.3.

1-(4-fluorophenyl)-4-(oxiran-2-yl)butan-1-one ((±)-2.44)

Ketone **2.43** (1.75 g, 9.09 mmol) was added to a 100-mL round-bottom flask and dissolved in Et₂O (36.4 mL). *m*CPBA (2.09 g, 9.09 mmol, 70 wt %) was added and the reaction was stirred at room temperature. After 99 hours the reaction was quenched with 1M NaOH (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording recovered

ketone **2.43** as a yellow oil (970 mg, 5.05 mmol). Further elution with a 10% gradient of EtOAc in hexanes afforded epoxyketone (\pm)-**2.44** as a yellow oil in quantitative yield based on recovered starting material (950 mg, 4.56 mmol).

Rf: 0.43 in 70:30 (Hexanes: EtOAc)

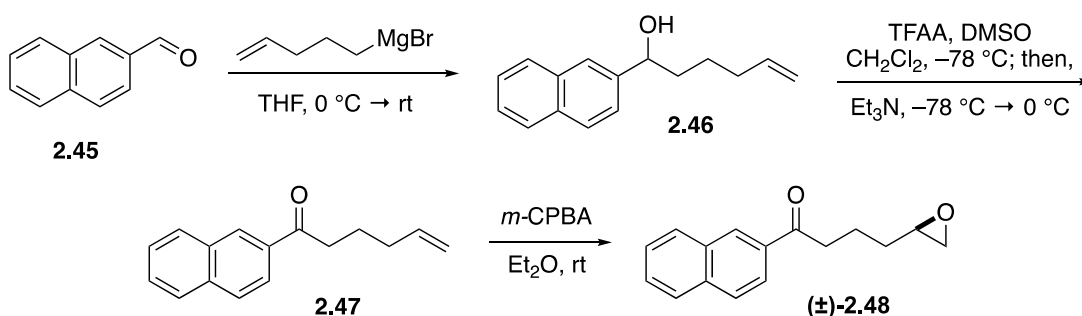
^1H NMR (500 MHz, CDCl_3) δ 8.00 – 7.99 (m, 1H), 7.98 – 7.97 (m, 1H), 7.14 – 7.13 (m, 1H), 7.12 – 7.11 (m, 1H), 3.02 (td, $J = 7.2, 1.5$ Hz, 2H), 2.95 (ddt, $J = 6.8, 4.2, 2.9$ Hz, 1H), 2.76 – 2.74 (m, 1H), 2.48 (dd, $J = 5.0, 2.7$ Hz, 1H), 1.92 (p, $J = 7.4$ Hz, 2H), 1.77 – 1.70 (m, 1H), 1.59 – 1.52 (m, 1H).

^{13}C NMR (100 MHz, CDCl_3) δ 198.1, 166.7, 164.7, 133.4, 130.6, 130.6, 115.7, 115.6, 52.0, 46.7, 37.9, 31.8, 20.7.

IR (cm^{-1}): $\nu = 2933, 1683, 1597, 1505, 1409, 1369, 1229, 1202, 1157, 1099, 978, 919, 830, 598, 566$.

HRMS (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 209.09723$ calculated for $\text{C}_{12}\text{H}_{14}\text{FO}_2$; experimental 209.09771.

1-(naphthalen-2-yl)-4-(oxiran-2-yl)butan-1-one ((\pm)-**2.48**)



1-(naphthalen-2-yl)hex-5-en-1-ol (**2.46**)

Freshly ground Mg turnings (467 mg, 19.20 mmol) were added to a 100-mL three-neck round-bottom flask, with a pressure-equalizing addition funnel and condenser attached. Catalytic I_2 (1–2 crystals) was added and the apparatus was heated gently to sublime the I_2 and coat the Mg

turnings. Once coated THF (5 mL) was added to cover the Mg. 5-bromo-1-pentene (2.4 mL, 20.17 mmol) was subsequently added to the addition funnel and dissolved in THF (10 mL). The solution of alkyl halide was slowly added to the slurry of magnesium turnings over 10 minutes. After complete addition of 5-bromo-1-pentene, the translucent solution was refluxed for an additional 2 hours to consume the remaining Mg. 2-Naphthaldehyde **2.45** (1.50 g, 9.60 mmol) was added to a separate 100-mL round-bottom flask, and THF (20 mL) was then added. After cooling the reaction to 0 °C, the solution of pent-4-en-1-ylmagnesium bromide was added dropwise via a cannula. The resulting solution was allowed to warm to room temperature. After completion of reaction as determined by TLC, the reaction was cooled to 0 °C and quenched with saturated NH₄Cl (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x20 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% to 10% gradient of EtOAc in hexanes affording **2.46** as a white solid in quantitative yield (2.17 g, 9.60 mmol).

Rf: 0.63 in 70:30 (Hexanes:EtOAc)

¹H NMR (400 MHz, CDCl₃) δ 7.85 – 7.82 (m, 3H), 7.78 (s, 1H), 7.51 – 7.44 (m, 3H), 5.78 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.02 – 4.97 (m, 1H), 4.96 – 4.93 (m, 1H), 4.86 (t, *J* = 6.6 Hz, 1H), 2.11 (d, *J* = 7.4 Hz, 1H), 2.08 (d, *J* = 7.3 Hz, 1H), 1.95 – 1.78 (m, 3H), 1.62 – 1.51 (m, 1H), 1.32 – 1.26 (m, 1H).

¹³C NMR (100 MHz, CDCl₃) δ 142.2, 138.5, 133.3, 133.0, 128.3, 127.9, 127.7, 126.2, 125.8, 124.6, 124.1, 114.8, 74.7, 38.4, 33.6, 25.1.

IR (cm⁻¹): *f* = 3366, 3057, 2933, 2858, 1639, 1601, 1508, 1438, 1365, 1270, 1125, 1019, 995, 910, 856, 818, 747, 657, 478.

1-(naphthalen-2-yl)hex-5-en-1-one (2.47)

TFAA (1.4 mL, 10.04 mmol) and CH_2Cl_2 (10 mL) were combined in 250-mL round-bottom flask. The resulting solution was cooled to $-78\text{ }^\circ\text{C}$ for 10 minutes before DMSO (1.4 mL, 20.06 mmol) was added as a solution in CH_2Cl_2 (10 mL) slowly, dropwise. After 30 mins alcohol **2.46** (2.19 g, 9.12 mmol) was added via cannula in CH_2Cl_2 (25 mL). After 2 hours the reaction was determined to be complete by TLC analysis and Et_3N (6.4 mL, 45.60 mmol) was added slowly. The reaction was slowly warmed to room temperature over 30 minutes. Further reaction monitoring by TLC analysis determined that the reaction was complete. The reaction was then cooled to $0\text{ }^\circ\text{C}$ and quenched by the addition of 2M HCl (15 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 1% to 2% gradient of EtOAc in hexanes affording **2.47** as a yellow solid in 82% yield (1.79 g, 7.99 mmol).

Rf: 0.73 in 70:30 (Hexanes: EtOAc)

^1H NMR (400 MHz, CDCl_3) δ 8.47 (s, 1H), 8.04 (dd, $J = 8.6, 1.7\text{ Hz}$, 1H), 7.97 (d, $J = 8.0\text{ Hz}$, 1H), 7.91 – 7.87 (m, 2H), 7.62 – 7.58 (m, 1H), 7.57 – 7.53 (m, 1H), 5.86 (ddt, $J = 17.0, 10.2, 6.7\text{ Hz}$, 1H), 5.08 (dd, $J = 17.1, 3.4\text{ Hz}$, 1H), 5.04 – 5.01 (m, 1H), 3.12 (t, $J = 7.2\text{ Hz}$, 2H), 2.23 (d, $J = 7.1\text{ Hz}$, 1H), 2.19 (d, $J = 7.2\text{ Hz}$, 1H), 1.92 (p, $J = 7.6\text{ Hz}$, 2H)

^{13}C NMR (126 MHz, CDCl_3) δ 200.2, 138.1, 135.6, 134.4, 132.6, 129.6, 129.6, 128.4, 128.4, 127.8, 126.7, 123.9, 115.3, 37.8, 33.3, 23.5.

1-(naphthalen-2-yl)-4-(oxiran-2-yl)butan-1-one ((±)-2.48)

Ketone **2.47** (865 mg, 3.63 mmol) was added to a 100-mL round-bottom flask and dissolved in Et₂O (14.5 mL). *m*CPBA (895 mg, 3.63 mmol, 70 wt %) was added and the reaction was stirred at room temperature. After 24 hours the reaction was quenched with 1M NaOH (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x20 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 2% gradient of EtOAc in hexanes affording recovered ketone **2.47** as a yellow solid (476 mg, 2.12 mmol). Further elution with a 5% to 20% gradient of EtOAc in hexanes afforded epoxyketone (±)-**2.48** as a white solid in 85% yield based on recovered starting material (355 mg, 1.04 mmol).

Rf: 0.26 in 70:30 (Hexanes: EtOAc)

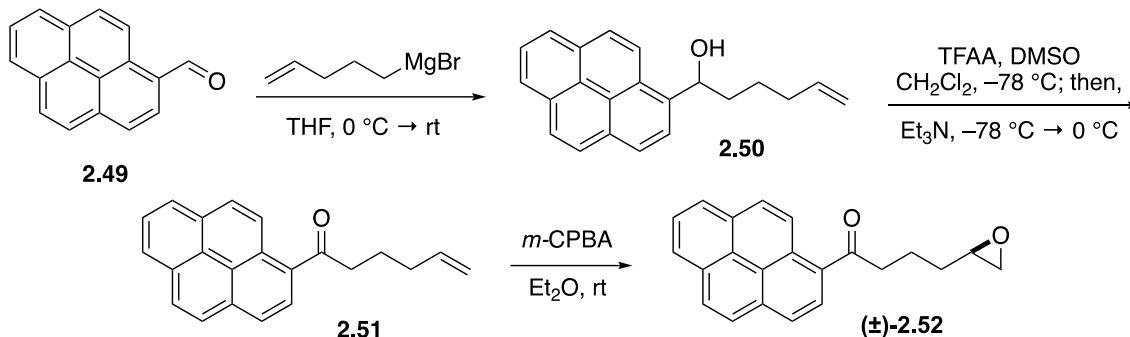
¹H NMR (500 MHz, CDCl₃) δ 8.48 (s, 1H), 8.05 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.89 (t, *J* = 9.0 Hz, 1H), 7.62 – 7.54 (m, 2H), 3.25 – 3.15 (m, 2H), 3.01 – 2.97 (m, 1H), 2.78 (t, *J* = 4.7 Hz, 1H), 2.51 (dd, *J* = 5.0, 2.7 Hz, 1H), 1.99 (t, *J* = 7.3 Hz, 2H), 1.81 – 1.74 (m, 1H), 1.65 – 1.58 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 199.7, 135.6, 134.3, 132.6, 129.6, 129.6, 128.5, 128.4, 127.8, 126.8, 123.9, 52.2, 46.9, 38.0, 32.0, 20.9.

IR (cm⁻¹): *f* = 3057, 2930, 2195, 2161, 2025, 1948, 1679, 1627, 1595, 1468, 1409, 1371, 1277, 1183, 1124, 919, 821, 751.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ = 241.12231 calculated for C₁₆H₁₇O₂; experimental 241.12242.

4-(oxiran-2-yl)-1-(pyren-1-yl)butan-1-one ((±)-2.52)



1-(pyren-1-yl)hex-5-en-1-ol (2.50)

Freshly ground Mg turnings (316 mg, 13.02 mmol) were added to a 100-mL three-neck round-bottom flask, with a pressure-equalizing addition funnel and condenser attached. Catalytic I₂ (1–2 crystals) was added and the apparatus was heated gently to sublime the I₂ and coat the Mg turnings. Once coated THF (5 mL) was added to cover the Mg. 5-bromo-1-pentene (1.6 mL, 13.68 mmol) was subsequently added to the addition funnel and dissolved in THF (10 mL). The solution of alkyl halide was slowly added to the slurry of magnesium turnings over 10 minutes. After complete addition of 5-bromo-1-pentene, the translucent solution was refluxed for an additional 2 hours to consume the remaining Mg. Pyrene-1-carbaldehyde **2.49** (1.50 g, 6.51 mmol) was added to a separate 100-mL round-bottom flask, and THF (20 mL) was then added. After cooling the reaction to 0 °C, the solution of pent-4-en-1-ylmagnesium bromide was added dropwise via a cannula. The resulting solution was allowed to warm to room temperature. After completion of reaction as determined by TLC, the reaction was cooled to 0 °C and quenched with saturated NH₄Cl (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x20 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% to 10% gradient of EtOAc in hexanes affording **2.50** as a yellow solid in 79% yield (1.54 g, 5.14 mmol).

Rf: 0.58 in 70:30 (Hexanes: EtOAc)

¹H NMR (400 MHz, CDCl₃) δ 8.36 – 8.33 (m, 1H), 8.20 – 8.18 (m, 3H), 8.12 – 8.10 (m, 1H), 8.05 (s, 1H), 8.01 (t, J = 7.6 Hz, 1H), 5.85 – 5.75 (m, 2H), 5.03 – 4.98 (m, 1H), 4.96 – 4.93 (m, 1H), 2.16 – 2.11 (m, 3H), 2.09 – 2.03 (m, 2H), 1.74 – 1.64 (m, 1H), 1.61 – 1.50 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 138.6, 138.3, 131.4, 130.7, 130.6, 127.6, 127.5, 127.5, 127.2, 125.9, 125.3, 125.1, 125.0, 125.0, 124.9, 123.3, 122.5, 114.8, 71.2, 38.5, 33.7, 25.5.

IR (cm⁻¹): ν = 3369, 3041, 2932, 1639, 1600, 1415, 1183, 1065, 994, 909, 756, 717, 681, 628.

HRMS (ESI-TOF) m/z : (M-OH)⁺ = 281.14813 calculated for C₂₂H₁₉; experimental 283.14807.

1-(pyren-1-yl)hex-5-en-1-one (2.51)

TFAA (0.8 mL, 5.40 mmol) and CH₂Cl₂ (7 mL) were combined in 250-mL round-bottom flask. The resulting solution was cooled to -78 °C for 10 minutes before DMSO (0.8 mL, 10.80 mmol) was added as a solution in CH₂Cl₂ (7 mL) slowly, dropwise. After 30 mins alcohol **2.50** (1.54 g, 4.91 mmol) was added via cannula in CH₂Cl₂ (20 mL). After 2 hours the reaction was determined to be complete by TLC analysis and Et₃N (3.4 mL, 24.55 mmol) was added slowly. The reaction was slowly warmed to room temperature over 30 minutes. Further reaction monitoring by TLC analysis determined that the reaction was complete. The reaction was then cooled to 0 °C and quenched by the addition of 2M HCl (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x15 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 1% to 5% gradient of EtOAc in hexanes affording **2.51** as a yellow solid in 76% yield (1.16 g, 3.90 mmol).

Rf: 0.75 in 70:30 (Hexanes: EtOAc)

¹H NMR (400 MHz, CDCl₃) δ 8.88 (d, *J* = 9.4 Hz, 1H), 8.31 (d, *J* = 8.0 Hz, 1H), 8.25 (dd, *J* = 7.6, 2.7 Hz, 2H), 8.21 (d, *J* = 9.4 Hz, 1H), 8.18 (d, *J* = 3.5 Hz, 1H), 8.16 (d, *J* = 4.4 Hz, 1H), 8.08 – 8.04 (m, 2H), 5.87 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.08 (dd, *J* = 17.1, 3.4 Hz, 1H), 5.03 – 5.01 (m, 1H), 3.23 (t, *J* = 7.4 Hz, 2H), 2.26 (d, *J* = 7.1 Hz, 1H), 2.23 (d, *J* = 7.0 Hz, 1H), 1.99 (p, *J* = 7.5 Hz, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 205.1, 138.1, 133.6, 132.9, 131.1, 130.6, 129.5, 129.4, 129.3, 127.1, 126.4, 126.2, 126.0, 125.0, 124.8, 124.4, 124.0, 115.4, 41.8, 33.3, 24.0.

IR (cm⁻¹): *f* = 3042, 2929, 1672, 1640, 1595, 1539, 1506, 1452, 1413, 1383, 1327, 1249, 1224, 1179, 1121, 1073, 993, 959, 911, 843, 819, 758, 716, 682, 622, 547, 455.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ = 299.14304 calculated for C₂₂H₁₉O; experimental 299.14293.

4-(oxiran-2-yl)-1-(pyren-1-yl)butan-1-one ((±)-2.52)

Ketone **2.51** (1.16 g, 3.89 mmol) was added to a 100-mL round-bottom flask and dissolved in Et₂O (14.9 mL). *m*CPBA (856 mg, 3.72 mmol, 70 wt %) was added and the reaction was stirred at room temperature. After 24 hours the reaction was quenched with 1M NaOH (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording recovered ketone **2.51** as a yellow solid (915 mg, 3.07 mmol). Further elution with a 10% to 30% gradient of EtOAc in hexanes afforded epoxyketone (±)-**2.52** as a yellow solid in 97% yield based on recovered starting material (254 mg, 0.81 mmol).

Rf: 0.24 in 70:30 (Hexanes: EtOAc)

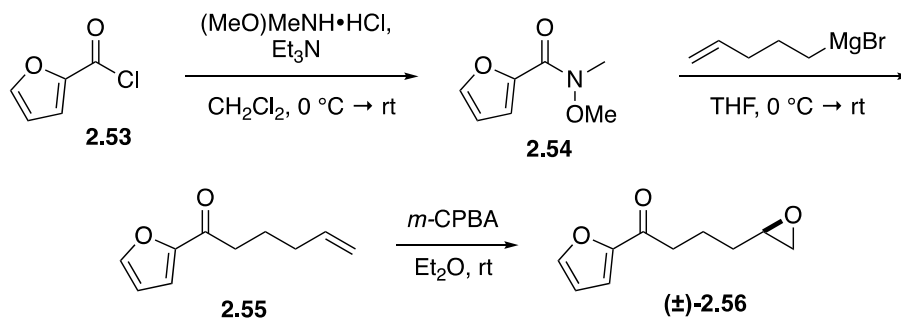
¹H NMR (500 MHz, CDCl₃) δ 8.89 (d, *J* = 9.4 Hz, 1H), 8.34 – 8.32 (m, 1H), 8.26 – 8.15 (m, 6H), 8.09 – 8.04 (m, 2H), 3.32 – 3.29 (m, 2H), 3.02 – 2.99 (m, 1H), 2.78 (t, *J* = 4.8 Hz, 1H), 2.52 (dd, *J* = 5.0, 2.7 Hz, 1H), 2.07 (p, *J* = 7.3 Hz, 2H), 1.84 – 1.77 (m, 1H), 1.71 – 1.64 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 204.5, 133.7, 132.6, 131.1, 130.6, 129.6, 129.5, 129.3, 127.1, 126.4, 126.3, 126.1, 126.0, 125.1, 124.7, 124.4, 124.1, 52.1, 46.9, 41.9, 32.0, 21.3.

IR (cm⁻¹): *f* = 3043, 2930, 1673, 1595, 1539, 1506, 1454, 1410, 1383, 1328, 1250, 1215, 1180, 1123, 1071, 990, 959, 919, 845, 760, 717.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ = 315.13796 calculated for C₂₂H₁₉O₂; experimental 315.13801, (M+Na)⁺ = 337.1199 calculated for C₂₂H₁₈NaO₂; experimental 337.12036

1-(furan-2-yl)-4-(oxiran-2-yl)butan-1-one ((±)-**2.56**)



N-methoxy-*N*-methylfuran-2-carboxamide (**2.54**)

N,O-Dimethyl hydroxylamine hydrochloride (747 mg, 7.66 mmol) was combined with CH₂Cl₂ (10.2 mL) in a 100-mL round-bottom flask. The solution was cooled to 0 °C followed by the addition of 2-Furoyl chloride **2.53** (0.8 mL, 7.66 mmol) and triethylamine (2.2 mL, 15.32 mmol). The ice bath was removed after 10 minutes, and the reaction was stirred at room temperature overnight. After the reaction was determined to be complete by TLC analysis, it was quenched with NaHCO₃ (10 mL). Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered,

and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% to 40% gradient of EtOAc in hexanes affording **2.54** as a yellow oil in quantitative yield (1.25 g, 7.66 mmol).

Rf: 0.17 in 70:30 (Hexanes: EtOAc)

¹H NMR (400 MHz, CDCl₃) δ 7.59 (dd, J = 1.7, 0.8 Hz, 1H), 7.14 (dd, J = 3.5, 0.7 Hz, 1H), 6.51 (dd, J = 3.5, 1.7 Hz, 1H), 3.76 (s, 3H), 3.35 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 159.2, 145.7, 145.2, 117.4, 111.6, 61.4, 33.2.

1-(furan-2-yl)hex-5-en-1-one (2.55)

Freshly ground Mg turnings (447 mg, 18.40 mmol) were added to a 100-mL three-neck round-bottom flask, with a pressure-equalizing addition funnel and condenser attached. Catalytic I₂ (1–2 crystals) was added and the apparatus was heated gently to sublime the I₂ and coat the Mg turnings. Once coated THF (10 mL) was added to cover the Mg. 5-bromo-1-pentene (2.3 mL, 19.31 mmol) was subsequently added to the addition funnel and dissolved in THF (20 mL). The solution of alkyl halide was slowly added to the slurry of magnesium turnings over 10 minutes. After complete addition of 5-bromo-1-pentene, the translucent solution was refluxed for an additional 1 hour to consume the remaining Mg. Weinreb amide **2.54** (1.43 g, 9.20 mmol) was added to a separate 100-mL round-bottom flask, and THF (20 mL) was then added. After cooling the reaction to 0 °C, the solution of pent-4-en-1-ylmagnesium bromide was added dropwise via a cannula. The resulting solution was allowed to warm to room temperature and stirred overnight. After completion of reaction as determined by TLC, the reaction was cooled to 0 °C and quenched with saturated 1 M HCl (10 ml). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x20 mL), dried over Na₂SO₄ and concentrated under reduced pressure.

The resulting crude oil was purified by flash column chromatography using a 5% to 10% gradient of EtOAc in hexanes affording **2.55** as a yellow oil in 88% yield (1.34 g, 8.14 mmol).

Rf: 0.67 in 70:30 (Hexanes: EtOAc)

¹H NMR (500 MHz, CDCl₃) δ 7.57 (dd, *J* = 1.7, 0.7 Hz, 1H), 7.17 (dd, *J* = 3.6, 0.7 Hz, 1H), 6.52 (dd, *J* = 3.6, 1.7 Hz, 1H), 5.81 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.06 – 5.01 (m, 1H), 5.01 – 4.97 (m, 1H), 2.83 (t, *J* = 7.4 Hz, 2H), 2.14 (q, *J* = 7.1 Hz, 2H), 1.83 (p, *J* = 7.6 Hz, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 189.5, 152.8, 146.2, 137.9, 116.8, 115.3, 112.1, 37.6, 33.2, 23.3.

1-(furan-2-yl)-4-(oxiran-2-yl)butan-1-one ((±)-2.56)

Ketone **2.55** (932 mg, 5.68 mmol) was added to a 100-mL round-bottom flask and dissolved in Et₂O (22.7 mL). *m*CPBA (1.31 g, 5.68 mmol, 70 wt %) was added and the reaction was stirred at room temperature. After 17 hours the reaction was quenched with 1M NaOH (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording recovered ketone **2.55** as a yellow oil (487 mg, 2.97 mmol). Further elution with a 10% to 20% gradient of EtOAc in hexanes afforded epoxyketone (±)-**2.56** as a yellow oil in 71% yield based on recovered starting material (348 mg, 1.93 mmol).

Rf: 0.30 in 70:30 (Hexanes: EtOAc)

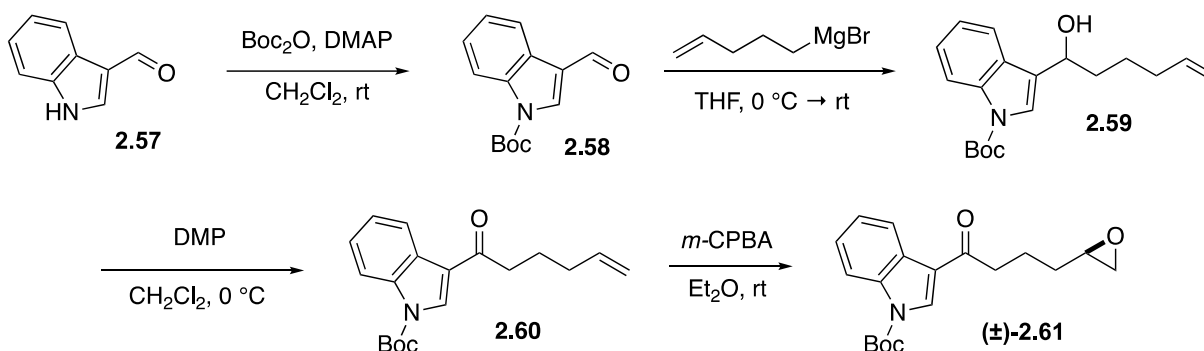
¹H NMR (400 MHz, CDCl₃) δ 7.57 (dd, *J* = 1.6, 0.6 Hz, 1H), 7.19 (dd, *J* = 3.5, 0.6 Hz, 1H), 6.52 (dd, *J* = 3.6, 1.7 Hz, 1H), 2.96 – 2.92 (m, 1H), 2.90 (t, *J* = 7.1 Hz, 2H), 2.75 (t, *J* = 4.8 Hz, 1H), 2.48 (dd, *J* = 5.0, 2.7 Hz, 1H), 1.90 (p, *J* = 7.0 Hz, 2H), 1.73 – 1.65 (m, 1H), 1.56 (td, *J* = 14.2, 7.6 Hz, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 189.0, 152.7, 146.3, 116.9, 112.2, 52.0, 46.8, 37.8, 31.9, 20.6.

IR (cm^{-1}): ν = 3129, 2929, 1672, 1567, 1468, 1395, 1260, 1227, 1162, 1083, 1014, 905, 883, 866, 834, 765, 596, 494.

HRMS (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 181.08592$ calculated for $\text{C}_{10}\text{H}_{13}\text{O}_3$; experimental 181.08568, $(\text{M}+\text{Na})^+ = 203.06787$ calculated for $\text{C}_{10}\text{H}_{12}\text{NaO}_3$; experimental 203.06713.

***tert*-butyl-3-(4-(oxiran-2-yl)butanoyl)-1*H*-indole-1-carboxylate ((\pm))-2.61**



***tert*-butyl-3-formyl-1*H*-indole-1-carboxylate (2.58)**

1*H*-indole-3-carbaldehyde **2.57** (1.0 g, 6.89 mmol) was added to a 100-mL round-bottom flask, and CH_2Cl_2 (34.5 mL) was then added. This was followed by the addition of Boc_2O (1.7 mL, 7.23 mmol) and DMAP (84 mg, 0.69 mmol). The solution was stirred at room temperature overnight. After completion of reaction as determined by TLC, the reaction was quenched with 1 M HCl (10 mL). Upon separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were then dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting aldehyde **2.58** was obtained clean in quantitative yield (1.68 g, 6.89 mmol) as a white solid.

Rf: 0.60 in 70:30 (Hexanes: EtOAc)

¹H NMR (400 MHz, CDCl₃) δ 10.11 (s, 1H), 8.29 (dd, *J* = 7.3, 1.6 Hz, 1H), 8.24 (s, 1H), 8.15 (d, *J* = 7.9 Hz, 1H), 7.42 (td, *J* = 7.3, 1.4 Hz, 1H), 7.37 (td, *J* = 7.7, 1.5 Hz, 1H), 1.71 (s, 9H).

¹³C NMR (126 MHz, CDCl₃) δ 185.8, 148.8, 136.5, 136.0, 126.1, 126.1, 124.6, 122.2, 121.6, 115.2, 85.7, 28.1.

***tert*-butyl-3-(1-hydroxyhex-5-en-1-yl)-1*H*-indole-1-carboxylate (2.59)**

Freshly ground Mg turnings (337 mg, 13.88 mmol) were added to a 100-mL three-neck round-bottom flask, with a pressure-equalizing addition funnel and condenser attached. Catalytic I₂ (1–2 crystals) was added and the apparatus was heated gently to sublime the I₂ and coat the Mg turnings. Once coated THF (10 mL) was added to cover the Mg. 5-bromo-1-pentene (1.7 mL, 14.57 mmol) was subsequently added to the addition funnel and dissolved in THF (10 mL). The solution of alkyl halide was slowly added to the slurry of magnesium turnings over 10 minutes. After complete addition of 5-bromo-1-pentene, the translucent solution was refluxed for an additional 2 hours to consume the remaining Mg. Aldehyde **2.58** (1.70 g, 6.94 mmol) was added to a separate 100-mL round-bottom flask, and THF (20 mL) was then added. After cooling the reaction to 0 °C, the solution of pent-4-en-1-ylmagnesium bromide was added dropwise via a cannula. The resulting solution was allowed to warm to room temperature and stirred overnight. After completion of reaction as determined by TLC, the reaction was cooled to 0 °C and quenched with saturated NH₄Cl (10 ml). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x20 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% to 10% gradient of EtOAc in hexanes affording **2.59** as a yellow oil in quantitative yield (2.18 g, 6.94 mmol).

Rf: 0.55 in 70:30 (Hexanes: EtOAc)

¹H NMR (400 MHz, CDCl₃) δ 8.14 (d, *J* = 8.1 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.53 (s, 1H), 7.34 – 7.30 (m, 1H), 7.24 – 7.22 (m, 1H), 5.80 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.04 – 4.99 (m, 1H), 4.98 – 4.95 (m, 2H), 2.12 (q, *J* = 7.2 Hz, 2H), 1.98 (d, *J* = 7.5 Hz, 1H), 1.94 (d, *J* = 6.6 Hz, 1H), 1.79 – 1.77 (m, 1H), 1.67 (s, 9H), 1.63 – 1.45 (m, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 138.5, 124.5, 124.1, 122.6, 122.4, 119.9, 115.4, 114.8, 83.8, 68.0, 36.6, 33.6, 28.2, 25.2.

IR (cm⁻¹): *f* = 3405, 2977, 2933, 1731, 1640, 1607, 1568, 1476, 1452, 1370, 1307, 1252, 1223, 1156, 1086, 1018, 909, 856, 766, 745, 588, 473, 423.

***tert*-butyl 3-(hex-5-enoyl)-1*H*-indole-1-carboxylate (2.60)**

Alcohol **2.59** (1.11 g, 3.52 mmol) was combined with CH₂Cl₂ (17.6 mL) in a 100-mL round-bottom flask. The solution was cooled to 0 °C followed by the addition of Dess-Martin Periodinane (1.64 g, 3.87 mmol). The reaction was left in the ice bath and stirred overnight. After the reaction was determined to be complete by TLC analysis, it was filtered over celite and subsequently diluted with H₂O (15 mL). Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL) and washed with NaHCO₃ (10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording **2.60** as a white solid in 82% yield (903 mg, 2.88 mmol).

Rf: 0.71 in 70:30 (Hexanes: EtOAc)

¹H NMR (400 MHz, CDCl₃) δ 8.40 – 8.38 (m, 1H), 8.24 (s, 1H), 8.12 – 8.10 (m, 1H), 7.39 – 7.33 (m, 2H), 5.84 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.06 (dd, *J* = 17.1, 1.4 Hz, 1H), 5.01 (d, *J* = 10.2 Hz, 1H), 2.90 (t, *J* = 7.4 Hz, 2H), 2.18 (q, *J* = 7.0 Hz, 2H), 1.89 (p, *J* = 7.4 Hz, 2H), 1.71 (s, 9H).

¹³C NMR (126 MHz, CDCl₃) δ 196.6, 149.3, 138.1, 135.5, 131.8, 127.6, 125.5, 124.4, 122.8, 120.3, 115.3, 114.9, 85.4, 39.0, 33.2, 28.1, 23.7.

IR (cm⁻¹): $f = 2978, 2934, 1742, 1667, 1545, 1478, 1450, 1369, 1333, 1308, 1268, 1239, 1141, 1099, 1018, 909, 854, 749, 474, 422.$

***tert*-butyl-3-(4-(oxiran-2-yl)butanoyl)-1*H*-indole-1-carboxylate ((±)-2.61)**

Ketone **2.60** (900 mg, 2.87 mmol) was added to a 50-mL round-bottom flask and dissolved in Et₂O (11.5 mL). *m*CPBA (661 mg, 2.87 mmol, 70 wt %) was added and the reaction was stirred at room temperature. After 19 hours the reaction was quenched with 1M NaOH (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording recovered ketone **2.60** as a white solid (675 mg, 2.16 mmol). Further elution with a 10% to 20% gradient of EtOAc in hexanes afforded epoxyketone (±)-**2.61** as a white solid in 93% yield based on recovered starting material (220 mg, 0.67 mmol).

Rf: 0.39 in 70:30 (Hexanes: EtOAc)

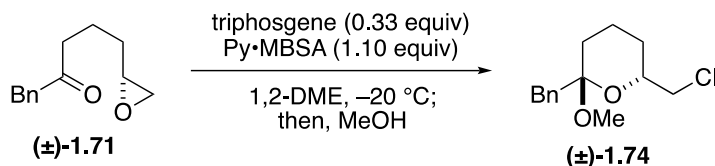
¹H NMR (500 MHz, DMSO-*d*₆) δ 8.55 (s, 1H), 8.26 – 8.25 (m, 1H), 8.09 – 8.08 (m, 1H), 7.42 – 7.39 (m, 1H), 7.37 – 7.34 (m, 1H), 3.05 – 3.02 (m, 2H), 2.97 – 2.92 (m, 1H), 2.67 (t, $J = 4.5$ Hz, 1H), 2.46 – 2.44 (m, 1H), 1.79 – 1.73 (m, 3H), 1.67 (s, 9H), 1.63 – 1.47 (m, 3H).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 196.7, 149.1, 135.4, 133.5, 127.5, 125.8, 124.7, 122.5, 119.8, 115.3, 85.9, 51.9, 46.5, 39.0, 31.8, 28.1, 21.0.

IR (cm⁻¹): $f = 2924, 1742, 1667, 1545, 1450, 1368, 1308, 1270, 1239, 1140, 1098, 914, 838, 750, 426.$

HRMS (ESI-TOF) m/z : $(M+H)^+ = 330.16998$ calculated for $C_{19}H_{24}NO_4$; experimental 330.17037, $(M+Na)^+ = 352.15193$ calculated for $C_{19}H_{23}NNaO_4$; experimental 352.15192.

2-benzyl-6-(chloromethyl)-2-methoxytetrahydro-2H-pyran ((±)-1.74)



Epoxyketone **(±)-1.71** (122 mg, 0.597 mmol) was combined with 1,2-DME (2.4 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to $-20\text{ }^{\circ}\text{C}$ for at least 10 minutes. Triphosgene (58.5 mg, 0.197 mmol) was added and the solution was stirred at $-20\text{ }^{\circ}\text{C}$ for another 5 minutes before Py•MBSA (176 mg, 0.657 mmol) was added. After stirring at $-20\text{ }^{\circ}\text{C}$ for 1 hour the reaction was determined to be complete by TLC analysis and quenched with MeOH (1.2 mL) while still at $-20\text{ }^{\circ}\text{C}$. After 10 minutes saturated NaHCO_3 (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording **(±)-1.74** as a white solid in 66% yield as a single diastereomer (100 mg, 0.393 mmol).

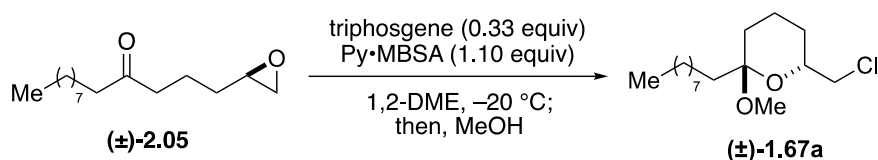
^1H NMR (400 MHz, CDCl_3) δ 7.30 – 7.27 (m, 1H), 7.27 – 7.20 (m, 4H), 3.81 (dddd, $J = 11.5, 7.0, 5.5, 2.3$ Hz, 1H), 3.56 – 3.47 (m, 2H), 3.41 (s, 3H), 3.01 (d, $J = 14.0$ Hz, 1H), 2.87 (d, $J = 14.1$ Hz, 1H), 1.84 – 1.71 (m, 1H), 1.65 – 1.59 (m, 1H), 1.58 – 1.51 (m, 1H), 1.49 – 1.42 (m, 1H), 1.31 (td, $J = 13.5, 4.7$ Hz, 1H), 1.17 (qd, $J = 12.6, 4.0$ Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 136.8, 130.2, 128.0, 126.3, 99.9, 70.5, 47.7, 42.2, 31.9, 28.0, 18.3.

IR: $f(\text{cm}^{-1}) = 2943, 1712, 1495, 1453, 1217, 1092, 975, 903, 828, 734, 698, 657, 521, 477$.

HRMS (ESI-TOF) m/z : ((M–MeOH)+H⁺) = 223.08842 calculated for C₁₃H₁₆ClO, experimental 223.08839.

6-(chloromethyl)-2-methoxy-2-nonyltetrahydro-2H-pyran ((±)-1.67a)



Epoxyketone (**(±)-2.05**) (115 mg, 0.478 mmol) was combined with 1,2-DME (1.9 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to -20 °C for at least 10 minutes. Triphosgene (46.9 mg, 0.158 mmol) was added and the solution was stirred at -20 °C for another 5 minutes before Py•MBSA (141 mg, 0.526 mmol) was added. After stirring at -20 °C for 1 hour the reaction was determined to be complete by TLC analysis and quenched with MeOH (1.0 mL) while still at -20 °C. After 10 minutes saturated NaHCO₃ (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording (**(±)-1.67a**) as a white solid in 74% yield as a single diastereomer (103 mg, 0.355 mmol).

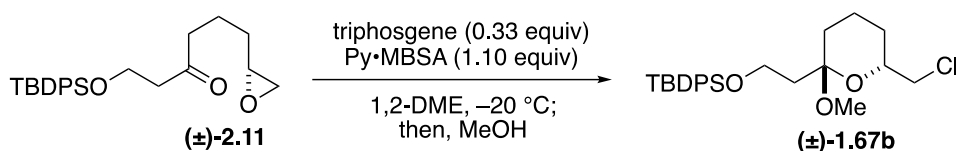
¹H NMR (500 MHz, CDCl₃) δ 3.77 (dddd, J = 11.5, 6.8, 4.8, 2.1 Hz, 1H), 3.49 (dd, J = 11.2, 6.5 Hz, 1H), 3.45 (dd, J = 11.2, 4.9 Hz, 1H), 3.19 (s, 3H), 1.86 – 1.72 (m, 3H), 1.69 – 1.60 (m, 2H), 1.46 – 1.32 (m, 2H), 1.32 – 1.21 (m, 17H), 0.88 (t, J = 6.9 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 100.0, 100.0, 70.2, 47.8, 47.4, 36.3, 32.3, 31.9, 29.8, 29.5, 29.5, 29.3, 28.4, 23.2, 22.7, 18.5, 14.1.

IR: $f(\text{cm}^{-1}) = 2923, 2853, 1722, 1460, 1377, 1201, 1123, 1096, 1028, 974, 934, 903, 857, 824, 740, 474$.

HRMS (ESI-TOF) m/z : $((M - \text{MeOH}) + \text{H}^+) = 259.18232$ calculated for $\text{C}_{15}\text{H}_{28}\text{ClO}$, experimental 259.18261.

***tert*-butyl(2-(6-(chloromethyl)-2-methoxytetrahydro-2*H*-pyran-2-yl)ethoxy)diphenylsilane
(\pm)-**1.67b**)**



Epoxyketone (\pm)-**2.11** (45 mg, 0.113 mmol) was combined with 1,2-DME (0.45 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to $-20\text{ }^{\circ}\text{C}$ for at least 10 minutes. Triphosgene (11 mg, 0.037 mmol) was added and the solution was stirred at $-20\text{ }^{\circ}\text{C}$ for another 5 minutes before Py•MBSA (33 mg, 0.124 mmol) was added. After stirring at $-20\text{ }^{\circ}\text{C}$ for 1 hour, the reaction was determined to be complete by TLC analysis and quenched with MeOH (0.2 mL) and stirred for an additional 10 minutes. Saturated NaHCO_3 (1 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording (\pm)-**1.67b** as a clear oil in 67% yield as a single diastereomer (34 mg, 0.0761 mmol).

^1H NMR (500 MHz, CDCl_3) δ 7.70 – 7.66 (m, 4H), 7.44 – 7.35 (m, 7H), 3.79 – 3.67 (m, 3H), 3.46 (dd, $J = 11.1, 6.5\text{ Hz}$, 1H), 3.42 (dd, $J = 11.2, 4.8\text{ Hz}$, 1H), 3.08 (s, 3H), 2.05 (ddd, $J = 14.1, 8.3$,

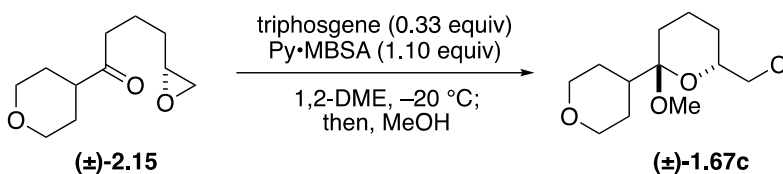
5.9 Hz, 1H), 1.90 – 1.84 (m, 1H), 1.77 (ddd, $J = 17.3, 8.6, 4.0$ Hz, 1H), 1.71 – 1.62 (m, 2H), 1.61 – 1.53 (m, 1H), 1.41 (td, $J = 13.6, 4.6$ Hz 1H), 1.21 (qd, $J = 12.8, 4.1$ Hz, 1H), 1.05 (s, 9H).

^{13}C NMR (126 MHz, CDCl_3) δ 135.6, 135.6, 133.8, 129.6, 129.6, 127.6, 99.0, 70.2, 59.7, 47.7, 47.4, 39.0, 33.0, 28.2, 26.8, 19.1, 18.4.

IR: $f(\text{cm}^{-1}) = 3071, 3049, 2955, 2932, 2890, 2857, 1589, 1472, 1427, 1390, 1109, 1084, 1029, 823, 739, 702, 612, 505$.

HRMS (ESI-TOF) m/z : $((\text{M}-\text{OMe})^+) = 415.18546$ calculated for $\text{C}_{24}\text{H}_{32}\text{ClO}_2\text{Si}^+$; Found 415.18579.

6-(chloromethyl)-2-methoxyoctahydro-2*H*,2'*H*-2,4'-bipyran ((\pm)-1.67c)



Epoxyketone (\pm)-2.15 (102 mg, 0.51 mmol) was combined with 1,2-DME (2.1 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to $-20\text{ }^\circ\text{C}$ for at least 10 minutes. Triphosgene (50 mg, 0.17 mmol) was added and the solution was stirred at $-20\text{ }^\circ\text{C}$ for another 5 minutes before Py•MBSA (152 mg, 0.57 mmol) was added. After stirring at $-20\text{ }^\circ\text{C}$ for 1 hour the reaction was determined to be complete by TLC analysis and quenched with MeOH (1.0 mL) while still at $-20\text{ }^\circ\text{C}$. After 10 minutes saturated NaHCO_3 (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5%

gradient of EtOAc in hexanes affording (\pm)-**1.67c** as a colorless oil in 67% yield as a single diastereomer (85 mg, 0.34 mmol).

Rf: 0.50 in 70:30 (Hexanes: EtOAc)

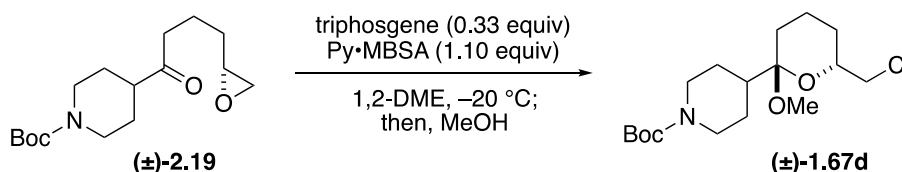
^1H NMR (400 MHz, CDCl_3) δ 4.02 (d, J = 3.8 Hz, 1H), 3.99 (d, J = 3.4 Hz, 1H), 3.81 – 3.75 (m, 1H), 3.47 (d, J = 5.3 Hz, 1H), 3.40 (dd, J = 11.7, 2.1 Hz, 1H), 3.35 (dd, J = 11.2, 2.4 Hz, 1H), 3.20 (s, 3H), 1.99 (tt, J = 12.0, 3.6 Hz, 1H), 1.83 (qt, J = 12.8, 3.9 Hz, 1H), 1.70 – 1.63 (m, 3H), 1.55 – 1.35 (m, 5H), 1.29 – 1.19 (m, 1H).

^{13}C NMR (100 MHz, CDCl_3) δ 100.7, 70.4, 68.4, 68.2, 47.9, 46.7, 39.8, 28.3, 27.9, 27.4, 26.9, 18.2.

IR: $f(\text{cm}^{-1})$ = 2949, 2844, 1444, 1373, 1284, 1235, 1204, 1090, 1030, 984, 957, 910, 854, 828, 735, 557.

HRMS (ESI-TOF) m/z : ((M-MeOH)+H) $^+$ = 217.09898 calculated for $\text{C}_{11}\text{H}_{18}\text{ClO}_2$; experimental 217.09937.

***tert*-butyl-4-(6-(chloromethyl)-2-methoxytetrahydro-2*H*-pyran-2-yl)piperidine-1-carboxylate ((\pm)-**1.67d**)**



Epoxyketone (\pm)-**2.19** (68 mg, 0.23 mmol) was combined with 1,2-DME (1.0 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to $-20\text{ }^\circ\text{C}$ for at least 10 minutes. Triphosgene (23 mg, 0.08 mmol) was added and the solution was stirred at $-20\text{ }^\circ\text{C}$ for another 5 minutes before Py•MBSA (67 mg, 0.25 mmol) was added. After stirring at $-20\text{ }^\circ\text{C}$ for 1 hour the

reaction was determined to be complete by TLC analysis and quenched with MeOH (0.5 mL) while still at $-20\text{ }^{\circ}\text{C}$. After 10 minutes saturated NaHCO_3 (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% to 10% gradient of EtOAc in hexanes affording (\pm)-**1.67d** as a colorless oil in 59% yield as a single diastereomer (47 mg, 0.14 mmol).

Rf: 0.59 in 70:30 (Hexanes: EtOAc)

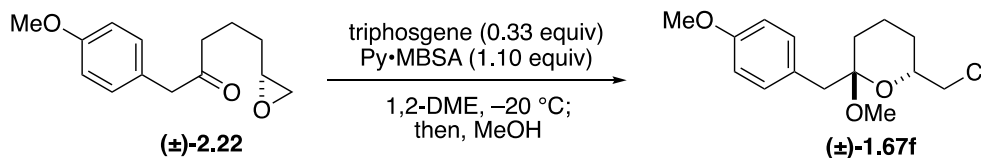
^1H NMR (400 MHz, CDCl_3) δ 4.24 – 4.10 (m, 2H), 3.80 – 3.75 (m, 1H), 3.48 – 3.47 (m, 2H), 3.20 (s, 3H), 2.67 (d, $J = 12.8\text{ Hz}$, 1H), 2.61 (d, $J = 13.1\text{ Hz}$, 1H), 1.90 – 1.76 (m, 3H), 1.65 – 1.63 (m, 2H), 1.58 – 1.54 (m, 3H), 1.46 (s, 9H), 1.25 – 1.17 (m, 4H).

^{13}C NMR (126 MHz, CDCl_3) δ 154.8, 100.8, 79.3, 70.4, 47.9, 46.7, 40.8, 28.5, 28.3, 27.5, 27.0, 26.0, 18.2.

IR: $f(\text{cm}^{-1}) = 2881, 2274, 1776, 1738, 1563, 1384, 1334, 1289, 1261, 1220, 1140, 1112, 1055, 994, 972, 887, 801, 697, 507, 477, 467, 433, 417$.

HRMS (ESI-TOF) m/z : $(\text{M}+\text{Na})^+ = 370.17556$ calculated for $\text{C}_{17}\text{H}_{30}\text{ClNNaO}_4$; experimental 370.17490.

6-(chloromethyl)-2-methoxy-2-(4-methoxybenzyl)tetrahydro-2H-pyran ((\pm)-1.67f**)**



Epoxyketone (\pm)-**2.22** (99 mg, 0.422 mmol) was combined with 1,2-DME (1.7 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to $-20\text{ }^{\circ}\text{C}$ for at least 10 minutes.

Triphosgene (41 mg, 0.139 mmol) was added and the solution was stirred at $-20\text{ }^{\circ}\text{C}$ for another 5 minutes before Py•MBSA (124 mg, 0.465 mmol) was added. After stirring at $-20\text{ }^{\circ}\text{C}$ for 1 hour the reaction was determined to be complete by TLC analysis and quenched with MeOH (0.8 mL) while still at $-20\text{ }^{\circ}\text{C}$. After 10 minutes saturated NaHCO_3 (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording (\pm)-**1.67f** as a white solid in 58% yield as a single diastereomer (70 mg, 0.245 mmol).

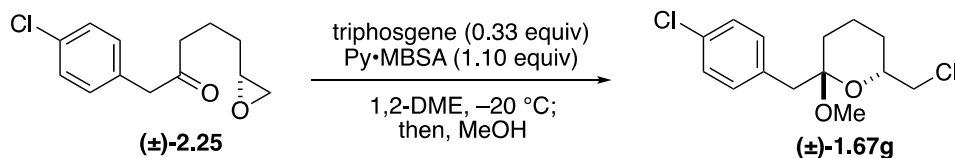
^1H NMR (500 MHz, CDCl_3) δ 7.15 (d, $J = 8.2$ Hz, 2H), 6.82 (d, $J = 8.6$ Hz, 2H), 3.83 – 3.77 (m, 4H), 3.55 – 3.48 (m, 2H), 3.39 (s, 3H), 2.94 (d, $J = 14.0$ Hz, 1H), 2.80 (dd, $J = 14.0$ Hz, 1H), 1.77 (qt, $J = 13.4, 3.7$ Hz, 1H), 1.64 – 1.58 (m, 1H), 1.57 – 1.51 (m, 1H), 1.47 – 1.42 (m, 1H), 1.30 (td, $J = 13.5, 4.6$ Hz, 1H), 1.17 (dd, $J = 12.4, 4.0$ Hz, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 158.1, 131.1, 128.8, 113.4, 100.0, 70.5, 55.2, 47.8, 47.7, 41.3, 31.9, 28.0, 18.3.

IR: $f(\text{cm}^{-1}) = 2939, 2833, 1612, 1459, 1350, 1243, 1119, 1064, 977, 905, 737, 626, 523, 473$.

HRMS-ESI: $((\text{M}-\text{MeOH})+\text{H}^+) = 253.09898$ calculated for $\text{C}_{14}\text{H}_{18}\text{ClO}_2$, experimental 253.09840.

2-(4-chlorobenzyl)-6-(chloromethyl)-2-methoxytetrahydro-2H-pyran ((\pm)-**1.67g**)



Epoxyketone (\pm)-**2.25** (89 mg, 0.376 mmol) was combined with 1,2-DME (1.5 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to $-20\text{ }^{\circ}\text{C}$ for at least 10 minutes.

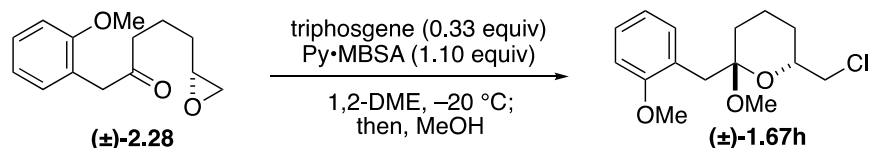
Triphosgene (37 mg, 0.124 mmol) was added and the solution was stirred at $-20\text{ }^{\circ}\text{C}$ for another 5 minutes before Py•MBSA (111 mg, 0.414 mmol) was added. After stirring at $-20\text{ }^{\circ}\text{C}$ for 1 hour the reaction was determined to be complete by TLC analysis and quenched with MeOH (0.8 mL) while still at $-20\text{ }^{\circ}\text{C}$. After 10 minutes saturated NaHCO_3 (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording (\pm)-**1.67g** as a white solid in 58% yield as a single diastereomer (63 mg, 0.217 mmol).

^1H NMR (500 MHz, CDCl_3) δ 7.25 – 7.22 (m, 2H), 7.18 – 7.16 (m, 2H), 3.80 (dtd, $J = 11.3, 5.4, 2.3$ Hz, 1H), 3.51 (d, $J = 5.5$ Hz, 2H), 3.38 (s, 3H), 2.91 (d, $J = 14.1$ Hz, 1H), 2.87 (d, $J = 14.1$ Hz, 1H), 1.77 (qt, $J = 13.3, 4.0$ Hz, 1H), 1.63 – 1.59 (m, 1H), 1.58 – 1.52 (m, 1H), 1.47 – 1.41 (m, 1H), 1.26 (td, $J = 13.5, 4.6$ Hz, 1H), 1.16 (qd, $J = 12.5, 4.0$ Hz, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 135.3, 132.2, 131.6, 128.1, 99.7, 70.6, 47.8, 47.8, 41.6, 31.8, 27.9, 18.3.

IR: $f(\text{cm}^{-1}) = 2942, 2831, 1492, 1435, 1374, 1320, 1267, 1119, 1025, 969, 940, 871, 810, 737, 686, 623, 490, 456$.

6-(chloromethyl)-2-methoxy-2-(2-methoxybenzyl)tetrahydro-2H-pyran ((\pm)-**1.67h**)



Epoxyketone (\pm)-**2.28** (91 mg, 0.388 mmol) was combined with 1,2-DME (1.6 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to $-20\text{ }^{\circ}\text{C}$ for at least 10 minutes.

Triphosgene (38 mg, 0.128 mmol) was added and the solution was stirred at $-20\text{ }^{\circ}\text{C}$ for another 5 minutes before Py•MBSA (114 mg, 0.427 mmol) was added. After stirring at $-20\text{ }^{\circ}\text{C}$ for 1 hour the reaction was determined to be complete by TLC analysis and quenched with MeOH (0.8 mL) while still at $-20\text{ }^{\circ}\text{C}$. After 10 minutes saturated NaHCO_3 (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording (\pm)-**1.67h** as a white solid in 58% yield as a single diastereomer (53 mg, 0.186 mmol).

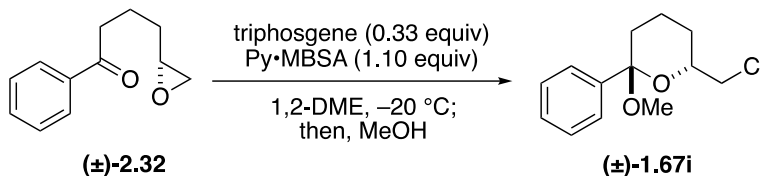
^1H NMR (400 MHz, CDCl_3) δ 7.27 (d, $J = 7.5$ Hz, 2H), 7.19 (t, $J = 7.8$, 1.7 Hz, 1H), 6.89 (t, $J = 7.5$ Hz, 1H), 6.85 (d, $J = 8.2$ Hz, 1H), 3.83 – 3.76 (m, 4H), 3.53 (dd, $J = 11.2$, 6.5 Hz, 1H), 3.48 (dd, $J = 11.1$, 4.9 Hz, 1H), 3.41 (s, 3H), 3.08 (d, $J = 14.0$ Hz, 1H), 2.94 (d, $J = 14.0$ Hz, 1H), 1.77 (qt, $J = 13.7$, 4.0 Hz, 1H), 1.66 – 1.59 (m, 1H), 1.57 – 1.48 (m, 1H), 1.37 (td, $J = 13.6$, 4.7 Hz, 1H), 1.17 (qd, $J = 12.7$, 3.9 Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 157.9, 131.7, 127.4, 125.3, 120.2, 110.3, 100.4, 70.6, 55.3, 47.8, 47.8, 34.4, 31.3, 28.1, 18.4.

IR: $f(\text{cm}^{-1}) = 2940, 2834, 1600, 1493, 1438, 1348, 1323, 1289, 1201, 1174, 1123, 1094, 1024, 944, 848, 811, 657, 557, 518, 474$.

HRMS (ESI-TOF) m/z : ((M–MeOH)+ H^+) = 253.09898 calculated for $\text{C}_{14}\text{H}_{18}\text{ClO}_2$, experimental 253.09976.

6-(chloromethyl)-2-methoxy-2-phenyltetrahydro-2H-pyran ((±)-1.67i)



Epoxyketone **(±)-2.32** (100 mg, 0.526 mmol) was combined with 1,2-DME (2.1mL) in a 15-mL pressure vessel. The resulting mixture was cooled to -20 °C for at least 10 minutes. Triphosgene (51 mg, 0.170 mmol) was added and the solution was stirred at -20 °C for another 5 minutes before Py•MBSA (155 mg, 0.577 mmol) was added. After stirring at -20 °C for 1 hour the reaction was determined to be complete by TLC analysis and quenched with MeOH (1 mL) while still at -20 °C. After 10 minutes saturated NaHCO₃ (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording **(±)-1.67i** as a white solid in 56% yield as a single diastereomer (71 mg, 0.294 mmol).

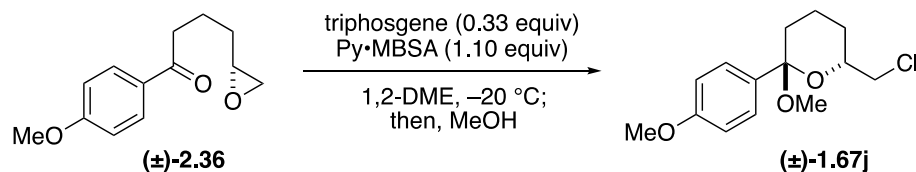
¹H NMR (500 MHz, CDCl₃) δ 7.50 (dd, *J* = 8.6, 1.5 Hz, 2H), 7.38 – 7.34 (m, 2H), 7.30 (tt, *J* = 7.2, 1.4 Hz, 1H), 4.00 (dddd, *J* = 11.2, 5.5, 2.3 Hz, 1H), 3.66 (dd, *J* = 11.2, 6.1 Hz, 1H), 3.62 (dd, *J* = 11.2, 4.7 Hz, 1H), 3.03 (s, 3H), 2.08 – 1.98 (m, 2H), 1.79 – 1.69 (m, 2H), 1.52 – 1.45 (m, 1H), 1.45 – 1.36 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 142.5, 128.1, 127.6, 125.8, 99.9, 70.4, 49.0, 47.9, 37.1, 27.9, 19.2.

IR: *f* (cm⁻¹) = 2942, 2830, 1491, 1376, 1250, 1121, 1071, 1027, 946, 900, 853, 760, 700, 602, 519.

HRMS-ESI: ((M-MeOH)+H⁺) = 209.07277 calculated for C₁₂H₁₄ClO, experimental 209.07276.

6-(chloromethyl)-2-methoxy-2-(4-methoxyphenyl)tetrahydro-2H-pyran ((±)-1.67j)



Epoxyketone (±)-**2.36** (110 mg, 0.50 mmol) was combined with 1,2-DME (2.0 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to -20 °C for at least 10 minutes. Triphosgene (49 mg, 0.17 mmol) was added and the solution was stirred at -20 °C for another 5 minutes before Py•MBSA (147 mg, 0.55 mmol) was added. After stirring at -20 °C for 1 hour the reaction was determined to be complete by TLC analysis and quenched with MeOH (1.0 mL) while still at -20 °C. After 10 minutes saturated NaHCO₃ (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording (±)-**1.67j** as a colorless oil in 37% yield as a single diastereomer (50 mg, 0.18 mmol).

Rf: 0.72 in 70:30 (Hexanes: EtOAc)

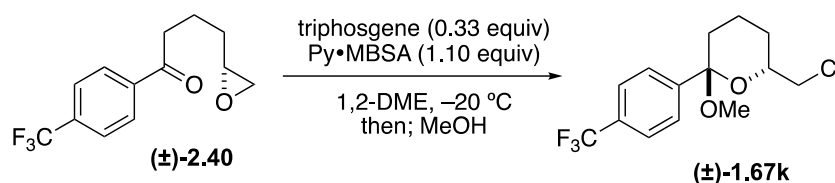
¹H NMR (500 MHz, CDCl₃) δ 7.42 – 7.41 (m, 2H), 6.89 – 6.87 (m, 2H), 4.00 – 3.95 (m, 1H), 3.81 (s, 3H), 3.65 (dd, *J* = 11.2, 6.2 Hz, 1H), 3.61 (dd, *J* = 11.2, 4.8 Hz, 1H), 3.00 (s, 3H), 2.04 – 1.97 (m, 2H), 1.76 – 1.68 (m, 2H), 1.46 (td, *J* = 14.5, 5.6 Hz, 1H), 1.43 – 1.35 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 159.1, 134.9, 127.1, 113.4, 99.8, 70.4, 55.2, 48.9, 47.9, 37.2, 27.9, 19.2.

IR: *f* (cm⁻¹) = 2950, 1676, 1608, 1510, 1440, 1303, 1244, 1173, 1147, 1101, 1056, 1030, 996, 939, 831, 736, 606.

HRMS (ESI-TOF) m/z : ((M–MeOH)+H)⁺ = 239.08333 calculated for C₁₃H₁₆ClO₂; experimental 239.08225.

6-(chloromethyl)-2-methoxy-2-(4-(trifluoromethyl)phenyl)tetrahydro-2H-pyran ((±)-1.67k)



Epoxyketone (±)-**2.40** (119 mg, 0.461 mmol) was combined with 1,2-DME (1.9 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to –20 °C for at least 10 minutes. Triphosgene (45.1 mg, 0.152 mmol) was added and the solution was stirred at –20 °C for another 5 minutes before Py•MBSA (135.5 mg, 0.507 mmol) was added. After stirring at –20 °C for 35 minutes the reaction was determined to be complete by TLC analysis and quenched with methanol (0.95 mL) while still at –20 °C. After 10 minutes saturated NaHCO₃ (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 2% gradient of EtOAc in hexanes affording ((±)-**1.67k**) as a colorless oil in 53% yield as a single diastereomer (74.7 mg, 0.242 mmol).

Rf: 0.75 in 30:70 (Hexanes : EtOAc).

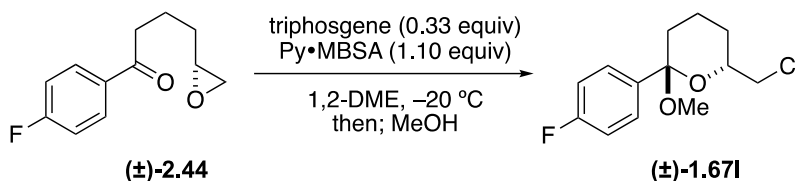
¹H NMR (500 MHz, CDCl₃) δ 7.62 (s, 4 H), 4.03 – 3.98 (m, 1 H), 3.68 – 3.61 (m, 2 H), 3.02 (s, 3 H), 2.09 – 1.97 (m, 2 H), 1.78 – 1.72 (m, 2 H), 1.47 – 1.37 (m, 2 H).

¹³C NMR (126 MHz, CDCl₃) δ 146.5, 126.4, 125.3, 125.2, 125.2, 125.1, 125.1, 99.6, 70.6, 49.2, 47.7, 37.0, 27.8, 19.1.

IR: $f(\text{cm}^{-1}) = 2952, 1620, 1439, 1409, 1325, 1251, 1163, 1126, 1068, 1036, 841, 741, 616, 435$.

HRMS (ESI-TOF) m/z : $((M-\text{MeOH})+\text{H})^+ = 277.06015$ calculated for $\text{C}_{13}\text{H}_{13}\text{ClF}_3\text{O}^+$; Found 277.06349

6-(chloromethyl)-2-(4-fluorophenyl)-2-methoxytetrahydro-2H-pyran ((±)-1.67I)



Epoxyketone (±)-**2.44** (113 mg, 0.543 mmol) was combined with 1,2-DME (2.2 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to $-20\text{ }^{\circ}\text{C}$ for at least 10 minutes. Triphosgene (53.2 mg, 0.179 mmol) was added and the solution was stirred at $-20\text{ }^{\circ}\text{C}$ for another 5 minutes before Py•MBSA (157 mg, 0.587 mmol) was added. After stirring at $-20\text{ }^{\circ}\text{C}$ for 35 minutes the reaction was determined to be complete by TLC analysis and quenched with methanol (1.1 mL) while still at $-20\text{ }^{\circ}\text{C}$. After 10 minutes saturated NaHCO_3 (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 2% gradient of EtOAc in hexanes affording (±)-**1.67I** as a white solid in 51% yield as a single diastereomer (71 mg, 0.275 mmol).

Rf: 0.78 in 30:70 (Hexanes : EtOAc).

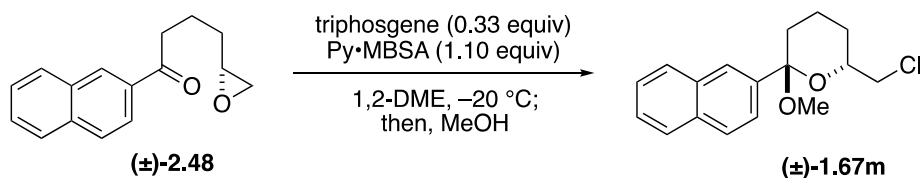
^1H NMR (500 MHz, CDCl_3) δ 7.48 – 7.45 (m, 2 H), 7.03 (tt, $J = 9.7, 2.9$ Hz, 2 H), 4.01 – 3.96 (m, 1 H), 3.66 – 3.60 (m, 2 H), 3.00 (s, 3 H), 2.07 – 1.96 (m, 2 H), 1.77 – 1.68 (m, 2 H), 1.48 – 1.39 (m, 2 H).

^{13}C NMR (126 MHz, CDCl_3) δ 163.3, 161.3, 138.5, 138.4, 127.7, 127.7, 115.0, 114.8, 99.6, 70.5, 48.9, 47.8, 37.2, 27.8, 19.1.

IR: $f(\text{cm}^{-1})$ = 2949, 1606, 1508, 1439, 1406, 1351, 1252, 1225, 1154, 1033, 836, 587, 564.

HRMS (ESI-TOF) m/z : $((\text{M}-\text{MeOH})+\text{H})^+ = 227.06335$ calculated for $\text{C}_{12}\text{H}_{13}\text{ClFO}^+$; Found 227.06424

6-(chloromethyl)-2-methoxy-2-(naphthalen-2-yl)tetrahydro-2H-pyran ((\pm)-1.67m**)**



Epoxyketone (\pm)-**2.48** (103 mg, 0.43 mmol) was combined with 1,2-DME (1.7 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to $-20\text{ }^\circ\text{C}$ for at least 10 minutes. Triphosgene (42 mg, 0.14 mmol) was added and the solution was stirred at $-20\text{ }^\circ\text{C}$ for another 5 minutes before $\text{Py}\cdot\text{MBSA}$ (126 mg, 0.47 mmol) was added. After stirring at $-20\text{ }^\circ\text{C}$ for 1 hour the reaction was determined to be complete by TLC analysis and quenched with MeOH (0.9 mL) while still at $-20\text{ }^\circ\text{C}$. After 10 minutes saturated NaHCO_3 (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 2% gradient of EtOAc in hexanes affording (\pm)-**1.67m** as a colorless oil in 57% yield as a single diastereomer (71 mg, 0.24 mmol).

Rf: 0.78 in 70:30 (Hexanes: EtOAc)

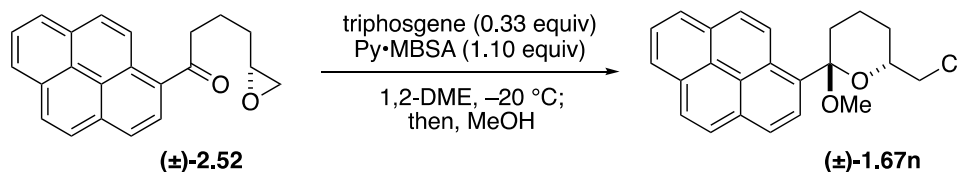
¹H NMR (500 MHz, CDCl₃) δ 8.01 (s, 1H), 7.89 – 7.88 (m, 1H), 7.85 – 7.83 (m, 2H), 7.60 – 7.58 (m, 1H), 7.50 – 7.46 (m, 2H), 4.09 – 4.04 (m, 1H), 3.73 (dd, *J* = 11.2, 6.2 Hz, 1H), 3.68 (dd, *J* = 11.2, 4.7 Hz, 1H), 3.06 (s, 3H), 2.14 – 2.04 (m, 2H), 1.82 – 1.73 (m, 2H), 1.57 – 1.51 (m, 1H), 1.45 (qd, *J* = 12.9, 4.1 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 140.0, 133.1, 132.9, 128.4, 127.9, 127.6, 126.0, 125.9, 125.1, 123.9, 100.1, 70.6, 49.2, 47.9, 37.1, 28.0, 19.3.

IR: *f* (cm⁻¹) = 3057, 2941, 1600, 1506, 1437, 1349, 1318, 1272, 1228, 1201, 1179, 1144, 1126, 1097, 1076, 1055, 1030, 965, 939, 905, 858, 820, 745, 686, 661, 630, 596, 519, 479.

HRMS (ESI-TOF) *m/z*: ((M-MeOH)+H)⁺ = 259.0884 calculated for C₁₆H₁₆ClO; experimental 259.0880.

6-(chloromethyl)-2-methoxy-2-(pyren-1-yl)tetrahydro-2*H*-pyran ((±)-1.67n)



Epoxyketone (±)-**2.52** (103 mg, 0.33 mmol) was combined with 1,2-DME (1.3 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to -20 °C for at least 10 minutes. Triphosgene (32 mg, 0.11 mmol) was added and the solution was stirred at -20 °C for another 5 minutes before Py•MBSA (97 mg, 0.36 mmol) was added. After stirring at -20 °C for 1 hour the reaction was determined to be complete by TLC analysis and quenched with MeOH (0.7 mL) while still at -20 °C. After 10 minutes saturated NaHCO₃ (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x10 mL), dried over Na₂SO₄ and concentrated under reduced

pressure. The resulting crude oil was purified by flash column chromatography using a 2% gradient of EtOAc in hexanes affording (±)-**1.67n** as a white fluffy solid in 73% yield as a single diastereomer (87 mg, 0.24 mmol).

Rf: 0.77 in 70:30 (Hexanes: EtOAc)

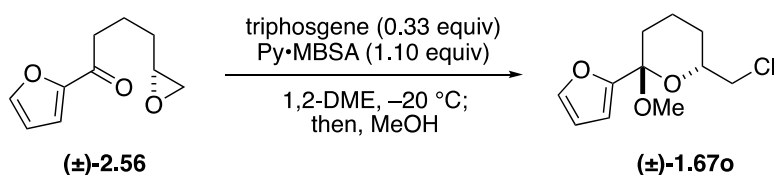
¹H NMR (400 MHz, CDCl₃) δ 8.99 (d, *J* = 9.5 Hz, 1H), 8.49 (d, *J* = 8.2 Hz, 1H), 8.20 – 8.17 (m, 3H), 8.10 (d, *J* = 9.6 Hz, 1H), 8.07 (s, 2H), 8.00 (t, *J* = 7.6 Hz, 1H), 4.30 – 4.24 (m, 1H), 3.84 – 3.75 (m, 2H), 3.13 (s, 3H), 2.61 (d, *J* = 13.9 Hz, 1H), 2.27 (qt, *J* = 13.2, 3.8 Hz, 1H), 1.88 (dd, *J* = 12.6, 2.1 Hz, 1H), 1.80 (dd, *J* = 13.2, 2.9 Hz, 1H), 1.70 (td, *J* = 13.6, 4.3 Hz, 1H), 1.59 (qd, *J* = 12.2, 3.7 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 135.7, 131.3, 131.3, 130.5, 128.0, 127.5, 127.5, 127.4, 125.8, 125.5, 125.2, 125.2, 125.0, 124.9, 124.9, 124.9, 101.4, 70.4, 49.4, 48.2, 36.9, 28.2, 19.3.

IR: *f* (cm⁻¹) = 3041, 2939, 1584, 1437, 1378, 1346, 1320, 1247, 1204, 1141, 1095, 1071, 1050, 1024, 998, 966, 906, 849, 829, 758, 726, 683, 633, 553, 503, 480.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ = 365.13028 calculated for C₂₃H₂₂ClO₂; experimental 365.13071, ((M-MeOH)+H)⁺ = 333.10407 calculated for C₂₂H₁₈ClO; experimental 333.10397.

6-(chloromethyl)-2-(furan-2-yl)-2-methoxytetrahydro-2H-pyran ((±)-**1.67o**)



Epoxyketone (±)-**2.56** (111 mg, 0.62 mmol) was combined with 1,2-DME (1.5 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to -20 °C for at least 10 minutes. Triphosgene (61 mg, 0.20 mmol) was added and the solution was stirred at -20 °C for another 5

minutes before Py•MBSA (181 mg, 0.68 mmol) was added. After stirring at $-20\text{ }^{\circ}\text{C}$ for 1 hour the reaction was determined to be complete by TLC analysis and quenched with MeOH (1.2 mL) while still at $-20\text{ }^{\circ}\text{C}$. After 10 minutes saturated NaHCO_3 (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 2% gradient of EtOAc in hexanes affording (\pm)-**1.67o** as a white solid in 44% yield as a single diastereomer (62 mg, 0.27 mmol).

Rf: 0.75 in 70:30 (Hexanes: EtOAc)

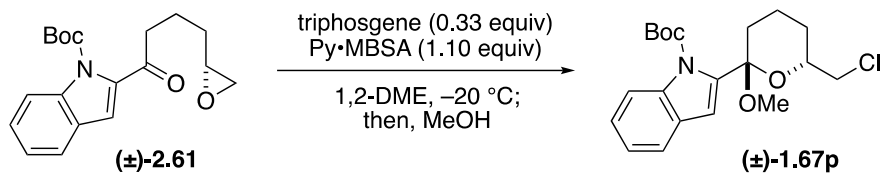
^1H NMR (500 MHz, CDCl_3) δ 7.38 (dd, $J = 1.8, 0.9\text{ Hz}$, 1H), 6.40 (dd, $J = 3.2, 0.8\text{ Hz}$, 1H), 6.34 (dd, $J = 3.2, 1.8\text{ Hz}$, 1H), 3.94 (dddd, $J = 11.4, 6.7, 4.8, 2.0\text{ Hz}$, 1H), 3.60 (dd, $J = 11.2, 6.6\text{ Hz}$, 1H), 3.54 (dd, $J = 11.2, 4.8\text{ Hz}$, 1H), 3.09 (s, 3H), 2.19 – 2.15 (m, 1H), 1.98 (qt, $J = 14.5, 5.0\text{ Hz}$, 1H), 1.78 – 1.70 (m, 2H), 1.62 (td, $J = 13.5, 4.6\text{ Hz}$, 1H), 1.41 – 1.33 (m, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 154.0, 141.9, 109.9, 107.5, 97.2, 70.5, 49.4, 47.5, 33.9, 28.1, 18.5.

IR: $f(\text{cm}^{-1}) = 2943, 1438, 1350, 1257, 1202, 1148, 1098, 1038, 1000, 961, 911, 877, 815, 737, 599, 472$.

HRMS (ESI-TOF) m/z : $((\text{M}-\text{MeOH})+\text{H})^+ = 199.05203$ calculated for $\text{C}_{10}\text{H}_{12}\text{ClO}_2$; experimental 199.05237.

***tert*-butyl-2-(6-(chloromethyl)-2-methoxytetrahydro-2*H*-pyran-2-yl)-1*H*-indole-1-carboxylate ((±)-1.67p)**



Epoxyketone (**(±)-2.61**) (102 mg, 0.31 mmol) was combined with 1,2-DME (1.2 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to $-20\text{ }^{\circ}\text{C}$ for at least 10 minutes. Triphosgene (30 mg, 0.10 mmol) was added and the solution was stirred at $-20\text{ }^{\circ}\text{C}$ for another 5 minutes before Py•MBSA (91 mg, 0.34 mmol) was added. After stirring at $-20\text{ }^{\circ}\text{C}$ for 1 hour the reaction was determined to be complete by TLC analysis and quenched with MeOH (0.6 mL) while still at $-20\text{ }^{\circ}\text{C}$. After 10 minutes saturated NaHCO_3 (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording (**(±)-1.67p**) as a white fluffy solid in 50% yield as a single diastereomer (59 mg, 0.16 mmol).

Rf: 0.77 in 70:30 (Hexanes: EtOAc)

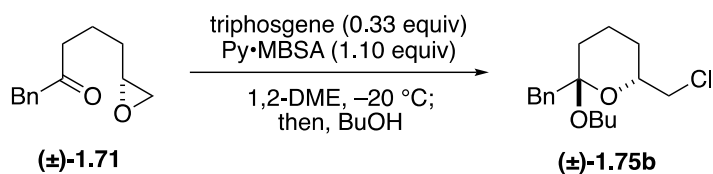
^1H NMR (400 MHz, DMSO-d_6) δ 8.07 (d, $J = 8.3\text{ Hz}$, 1H), 7.75 (d, $J = 7.8\text{ Hz}$, 1H), 7.51 (s, 1H), 7.35 – 7.31 (m, 1H), 7.26 – 7.23 (m, 1H), 3.97 – 3.93 (m, 1H), 3.83 (dd, $J = 11.4, 3.5\text{ Hz}$, 1H), 3.74 (dd, $J = 11.4, 6.4\text{ Hz}$, 1H), 3.01 (s, 3H), 2.18 – 2.15 (m, 1H), 1.99 – 1.89 (m, 1H), 1.73 – 1.67 (m, 2H), 1.63 (s, 9H), 1.59 – 1.51 (m, 1H), 1.47 – 1.38 (m, 1H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 149.5, 135.4, 127.7, 124.9, 124.1, 123.4, 122.9, 121.2, 115.3, 98.7, 84.6, 70.3, 49.2, 48.5, 35.9, 28.1, 27.6, 18.9.

IR: $f(\text{cm}^{-1}) = 2925, 1742, 1664, 1545, 1450, 1369, 1308, 1238, 1139, 1105, 853, 750$.

HRMS (APCI-TOF) m/z : $(\text{M}+\text{H})^+ = 380.16231$ calculated for $\text{C}_{20}\text{H}_{27}\text{ClNO}_4$; experimental 380.16160, $((\text{M}-\text{MeOH})+\text{H})^+ = 348.13610$ calculated for $\text{C}_{19}\text{H}_{23}\text{ClNO}_3$; experimental 348.13514.

2-benzyl-2-butoxy-6-(chloromethyl)tetrahydro-2H-pyran ((\pm)-1.75b)



Epoxyketone (\pm)-**1.71** (103 mg, 0.50 mmol) was combined with 1,2-DME (2.0 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to $-20\text{ }^{\circ}\text{C}$ for at least 10 minutes. Triphosgene (49 mg, 0.16 mmol) was added and the solution was stirred at $-20\text{ }^{\circ}\text{C}$ for another 5 minutes before Py•MBSA (149 mg, 0.55 mmol) was added. After stirring at $-20\text{ }^{\circ}\text{C}$ for 1 hour the reaction was determined to be complete by TLC analysis and quenched with 1-BuOH (0.23 mL) while still at $-20\text{ }^{\circ}\text{C}$. After 10 minutes saturated NaHCO_3 (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 1% gradient of EtOAc in hexanes affording (\pm)-**1.75b** as a colorless viscous oil in 67% yield as a single diastereomer (100 mg, 0.34 mmol).

Rf: 0.81 in 70:30 (Hexanes: EtOAc)

^1H NMR (400 MHz, CDCl_3) δ 7.29 – 7.27 (m, 1H), 7.25 – 7.19 (m, 4H), 3.86 – 3.80 (m, 1H), 3.64 (t, $J = 6.7\text{ Hz}$, 12H), 3.54 – 3.46 (m, 2H), 3.00 (d, $J = 14.0\text{ Hz}$, 1H), 2.91 (d, $J = 14.0\text{ Hz}$, 1H), 1.81

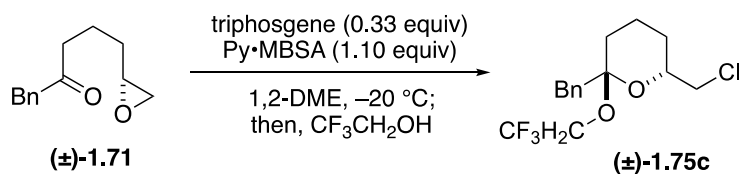
(qt, $J = 13.2, 3.8$ Hz, 1H), 1.62 (p, $J = 7.5$ Hz, 3H), 1.55 – 1.40 (m, 4H), 1.28 (td, $J = 13.3, 4.4$ Hz, 1H), 1.15 (qd, $J = 13.0, 3.9$ Hz, 1H), 0.97 (t, $J = 7.3$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 137.1, 130.2, 128.0, 126.2, 99.7, 70.5, 59.5, 47.9, 43.0, 32.2, 32.1, 28.2, 19.8, 18.4, 14.1.

IR: $f(\text{cm}^{-1}) = 2933, 2870, 1495, 1454, 1377, 1319, 1216, 1100, 1026, 988, 910, 823, 738, 699, 652, 477$.

HRMS (APCI-TOF) m/z : $((\text{M}-\text{BuOH})+\text{H})^+ = 223.08842$ calculated for $\text{C}_{13}\text{H}_{16}\text{ClO}$; experimental 223.08886.

2-benzyl-6-(chloromethyl)-2-(2,2,2-trifluoroethoxy)tetrahydro-2H-pyran ((±)-1.75c)



Epoxyketone (±)-1.71 (114 mg, 0.56 mmol) was combined with 1,2-DME (2.2 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to $-20\text{ }^\circ\text{C}$ for at least 10 minutes. Triphosgene (55 mg, 0.019 mmol) was added and the solution was stirred at $-20\text{ }^\circ\text{C}$ for another 5 minutes before Py•MBSA (164 mg, 0.61 mmol) was added. After stirring at $-20\text{ }^\circ\text{C}$ for 1 hour the reaction was determined to be complete by TLC analysis and quenched with $\text{CF}_3\text{CH}_2\text{OH}$ (0.2 mL) while still at $-20\text{ }^\circ\text{C}$. After 10 minutes saturated NaHCO_3 (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 2%

gradient of EtOAc in hexanes affording (\pm)-**1.75c** as a colorless oil in 34% yield as a single diastereomer (61 mg, 0.19 mmol).

Rf: 0.75 in 70:30 (Hexanes: EtOAc)

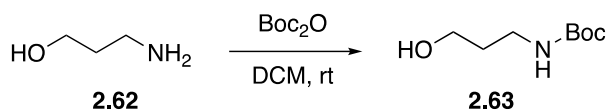
^1H NMR (500 MHz, CDCl_3) δ 7.30 – 7.27 (m, 2H), 7.25 – 7.23 (m, 3H), 4.11 – 4.04 (m, 1H), 4.02 – 3.94 (m, 1H), 3.88 – 3.82 (m, 1H), 3.53 – 3.50 (m, 2H), 2.99 (d, J = 14.1 Hz, 1H), 2.86 (d, J = 14.0 Hz, 1H), 1.82 (qt, J = 13.2, 3.4 Hz, 1H), 1.63 – 1.55 (m, 3H), 1.33 (td, J = 11.0, 4.6 Hz, 1H), 1.14 (qd, J = 13.1, 3.9 Hz, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 135.9, 130.3, 128.2, 126.7, 100.7, 71.2, 59.1, 58.8, 58.5, 58.3, 47.5, 43.4, 31.3, 27.7, 18.0.

IR: $f(\text{cm}^{-1})$ = 2949, 1496, 1418, 1377, 1283, 1216, 1158, 1123, 1094, 1073, 1032, 974, 908, 860, 752, 700, 662, 631, 549, 517, 477.

HRMS (APCI-TOF) m/z : $((\text{M}-\text{CF}_3\text{CH}_2\text{OH})+\text{H})^+ = 223.08842$ calculated for $\text{C}_{13}\text{H}_{16}\text{ClO}$; experimental 223.08851.

***tert*-butyl (3-hydroxypropyl)carbamate (**2.63**)**



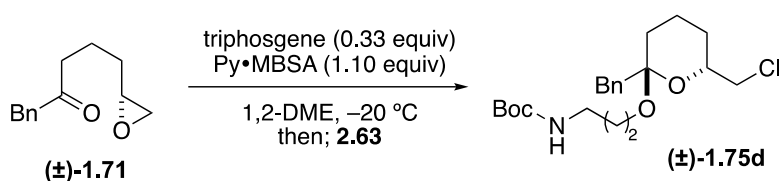
Procedure: 3-amino-1-propanol **2.62** (500 mg, 6.66 mmol) was combined with DCM (33 mL) in a round-bottom flask at room temperature. Di-*tert*-butyl-dicarbonate (1.6 g, 7.32 mmol) was added and the solution was stirred for 24 hours, at which point the reaction was determined to be complete by TLC analysis. Upon complete separation of the two layers, the aqueous layer was washed with DI water (3x20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 50% gradient of EtOAc in hexanes affording **2.63** as a clear oil in 91% yield. (1.06 g, 6.05 mmol).

Rf: 0.13 in 30:70 (Hexanes : EtOAc).

¹H NMR (500 MHz, CDCl₃) δ 4.80 (s, 1 H), 3.65 (q, *J* = 6.20 Hz, 2 H), 3.28 (q, *J* = 6.80 Hz, 2 H), 3.01 (s, 1 H), 1.65 (p, *J* = 6.30 Hz, 2 H), 1.44 (s, 9 H).

¹³C NMR (126 MHz, CDCl₃) δ 157.2, 79.6, 59.2, 36.8, 32.9, 28.3.

***tert*-butyl (3-(2-benzyl-6-(chloromethyl)tetrahydro-2*H*-pyran-2-yl)oxy)propylcarbamate ((±)-**1.75d**)**



Procedure: Epoxyketone **1.71** (109.7 mg, 0.537 mmol) was combined with 1,2-DME (2.2 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to -20 °C for at least 10 minutes. Triphosgene (52.6 mg, 0.177 mmol) was added and the solution was stirred at -20 °C for another 5 minutes before Py•MBSA (157.9 mg, 0.591 mmol) was added. After stirring at -20 °C for 1 hour the reaction was determined to be complete by TLC analysis and quenched with amino alcohol **2.63** (470 mg, 2.69 mmol) while still at -20 °C. After 10 minutes saturated NaHCO₃ (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 7.5% gradient of EtOAc in hexanes affording **1.75d** as a colorless oil in 68% yield as a single diastereomer (144.5 mg, 0.363 mmol).

Rf: 0.56 in 30:70 (Hexanes : EtOAc).

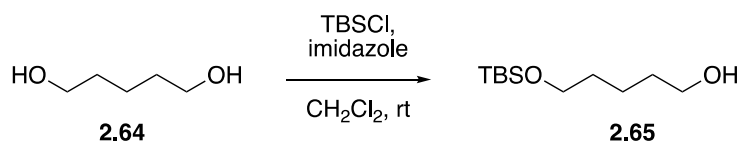
¹H NMR (400 MHz, CDCl₃) δ 7.28 – 7.20 (m, 5 H), 4.86 (s, 1 H), 3.80 – 3.73 (m, 1 H), 3.71 (t, *J* = 5.96 Hz, 2 H), 3.53 – 3.46 (m, 2 H), 3.28 (dd, *J* = 12.6, 6.72 Hz, 2 H), 2.95 (dd, *J* = 17.5, 14.1 Hz, 2 H), 1.85 – 1.73 (m, 3 H), 1.62 – 1.49 (m, 2 H), 1.44 (s, 9 H), 1.34 – 1.10 (m, 3 H).

¹³C NMR (126 MHz, CDCl₃) δ 156.0, 136.8, 130.2, 128.0, 126.3, 99.9, 70.7, 58.1, 47.8, 42.9, 38.9, 32.0, 29.7, 28.4, 28.0, 18.3.

IR: *f* (cm⁻¹) = 3357, 2928, 1701, 1497, 1454, 1366, 1248, 1169, 1102, 1030, 996, 736, 700, 478.

HRMS (ESI-TOF) *m/z*: ((M+Na)⁺) = 420.19121 calculated for (C₂₁H₃₂ClNO₄+Na)⁺; Found 420.19092

5-((*tert*-butyldimethylsilyl)oxy)pentan-1-ol (**2.65**)



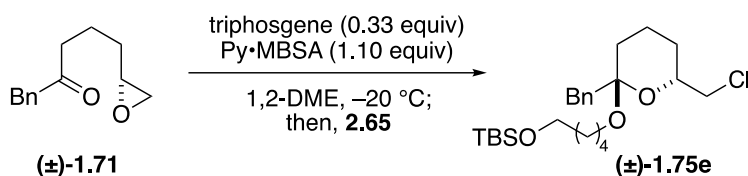
Pentane-1,5-diol **2.64** (1 g, 9.62 mmol) was dissolved in dry CH₂Cl₂. Imidazole (653 mg, 9.62 mmol) and TBSCl (1.45 g, 9.62 mmol) were added. The mixture was stirred at room temperature overnight after which it was diluted with H₂O (20 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x20 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The concentrate was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording di-protected product as a colorless oil (700 mg, 2.10 mmol). Further elution with a 10% to 15% gradient of EtOAc in hexanes afforded alcohol **2.65** as a colorless oil in 41% yield based on converted starting material (787 mg, 3.61 mmol), with spectroscopic data in agreement with literature values.

R_f: 0.44 in 70:30 (Hexanes: EtOAc)

¹H NMR (500 MHz, CDCl₃) δ 3.66 – 3.61 (m, 4H), 1.62 – 1.52 (m, 5H), 1.44 – 1.37 (m, 2H), 1.34 (s, 1H), 0.89 (s, 9H), 0.05 (s, 6H).

¹³C NMR (126 MHz, CDCl₃) δ 63.1, 63.0, 32.5, 26.0, 22.0, 18.4, -5.3.

(2-((2-benzyl-6-(chloromethyl)tetrahydro-2H-pyran-2-yl)oxy)ethoxy)(tert-butyl)dimethylsilane ((±)-1.75e)



Epoxyketone (±)-**1.71** (105 mg, 0.51 mmol) was combined with 1,2-DME (2.1 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to –20 °C for at least 10 minutes. Triphosgene (50 mg, 0.17 mmol) was added and the solution was stirred at –20 °C for another 5 minutes before Py•MBSA (151 mg, 0.57 mmol) was added. After stirring at –20 °C for 1 hour, the reaction was determined to be complete by TLC analysis and quenched with a solution of alcohol **2.65** (556 mg, 2.55 mmol) in 1 mL DME while still at –20 °C. After 10 minutes saturated NaHCO₃ (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 2% gradient of EtOAc in hexanes affording (±)-**1.75e** as a colorless oil in 57% yield as a single diastereomer (129 mg, 0.29 mmol).

Rf: 0.81 in 70:30 (Hexanes: EtOAc)

¹H NMR (500 MHz, CDCl₃) δ 7.28 – 7.26 (m, 1H), 7.25 – 7.21 (m, 5H), 3.82 (dddd, *J* = 11.2, 6.9, 4.8, 2.3 Hz, 1H), 3.67 – 3.59 (m, 4H), 3.53 – 3.46 (m, 2H), 2.99 (d, *J* = 14.0 Hz, 1H), 2.91 (d, *J* =

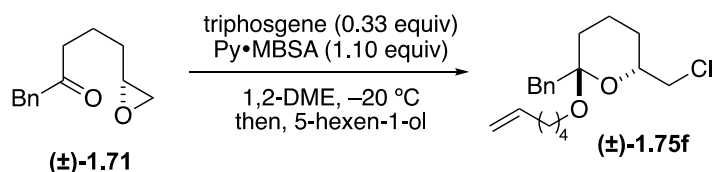
14.1 Hz, 1H), 1.80 (qt, $J = 13.2, 3.8$ Hz, 1H), 1.68 – 1.40 (m, 10H), 1.28 (td, $J = 13.3, 4.4$ Hz, 1H), 1.15 (qd, $J = 13.0, 3.9$ Hz, 1H), 0.90 (s, 9H), 0.06 (s, 6H).

^{13}C NMR (126 MHz, CDCl_3) δ 137.1, 130.3, 128.0, 126.2, 99.7, 70.5, 63.1, 59.7, 47.9, 43.0, 32.8, 32.1, 29.8, 28.1, 26.0, 22.9, 18.4, 5.3.

IR: $f(\text{cm}^{-1}) = 2930, 2856, 1456, 1385, 1253, 1094, 1029, 907, 833, 774, 735, 699, 660, 478$.

HRMS (APCI-TOF) m/z : $((\text{M}-\text{C}_{11}\text{H}_{26}\text{O}_2\text{Si})+\text{H})^+ = 223.08842$ calculated for $\text{C}_{13}\text{H}_{16}\text{ClO}$; experimental 223.08817.

2-benzyl-6-(chloromethyl)-2-(hex-5-en-1-yloxy)tetrahydro-2H-pyran (\pm)-**1.75f**



Epoxyketone (\pm)-**1.71** (111 mg, 0.543 mmol) was combined with 1,2-DME (2.2 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to $-20\text{ }^\circ\text{C}$ for at least 10 minutes. Triphosgene (53.2 mg, 0.179 mmol) was added and the solution was stirred at $-20\text{ }^\circ\text{C}$ for another 5 minutes before Py•MBSA (160 mg, 0.597 mmol) was added. After stirring at $-20\text{ }^\circ\text{C}$ for 1 hour the reaction was determined to be complete by TLC analysis and quenched with 5-hexen-1-ol (0.32 mL, 2.72 mmol) while still at $-20\text{ }^\circ\text{C}$. After 10 minutes saturated NaHCO_3 (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 2.5% gradient of EtOAc in hexanes affording **1.75f** as a light-yellow oil in 57% yield as a single diastereomer (101.4 mg, 0.314 mmol).

Rf: 0.8 in 30:70 (Hexanes : EtOAc)

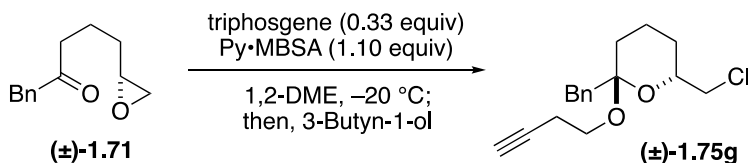
¹H NMR (400 MHz, CDCl₃) δ 7.29 – 7.21 (m, 5 H), 5.84 (ddt, J = 16.9, 10.1, 6.9 Hz, 1 H), 5.04 (dq, J = 17.1, 1.6 Hz, 1 H), 4.99 – 4.96 (m, 1 H), 3.81 (dddd, J = 11.3, 8.4, 4.9, 2.3 Hz, 1 H), 3.64 (t, J = 6.6 Hz, 1 H), 3.50 (ddd, J = 16.0, 11.2, 6.3 Hz, 2 H), 2.95 (dd, J = 35.1, 14.0 Hz, 2 H), 2.12 (q, J = 7.3 Hz, 2 H), 1.80 (qt, J = 13.2, 3.8 Hz, 1 H), 1.69 – 1.59 (m, 3 H), 1.57 – 1.47 (m, 4 H), 1.28 (td, J = 13.1, 4.2 Hz, 1 H), 1.15 (qd, J = 13.1, 3.9 Hz, 1 H).

¹³C NMR (126 MHz, CDCl₃) δ 138.8, 137.0, 130.2, 127.9, 126.2, 114.5, 99.7, 70.6, 59.5, 47.8, 42.9, 33.6, 32.1, 29.4, 28.1, 25.8, 18.3.

IR: $f(\text{cm}^{-1})$ = 3062, 3028, 2936, 2870, 1649, 1243, 1640, 1496, 1454, 1216, 1102, 1028, 990, 910, 737, 700, 655, 464.

HRMS (ESI-TOF) m/z : ((M-OC₆H₁₁)⁺) = 223.08842 calculated for C₁₃H₁₆ClO⁺; Found 223.08837

2-benzyl-2-(but-3-yn-1-yloxy)-6-(chloromethyl)tetrahydro-2H-pyran ((±)-1.75g)



Epoxyketone **(±)-1.71** (119 mg, 0.58 mmol) was combined with 1,2-DME (2.3 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to $-20\text{ }^{\circ}\text{C}$ for at least 10 minutes. Triphosgene (57 mg, 0.19 mmol) was added and the solution was stirred at $-20\text{ }^{\circ}\text{C}$ for another 5 minutes before Py•MBSA (172 mg, 0.64 mmol) was added. After stirring at $-20\text{ }^{\circ}\text{C}$ for 1 hour the reaction was determined to be complete by TLC analysis and quenched with 3-Butyn-1-ol (0.22 mL, 2.90 mmol) while still at $-20\text{ }^{\circ}\text{C}$. After 10 minutes saturated NaHCO₃ (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers,

the reaction was determined to be complete by TLC analysis and quenched with isopropanol (0.21 mL, 2.70 mmol) while still at $-20\text{ }^{\circ}\text{C}$. After 10 minutes saturated NaHCO_3 (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 2.5% gradient of EtOAc in hexanes affording (\pm)-**1.75h** as a colorless oil in 23% yield as a single diastereomer (35.1 mg, 0.124 mmol).

Rf: 0.69 in 30:70 (Hexanes : EtOAc).

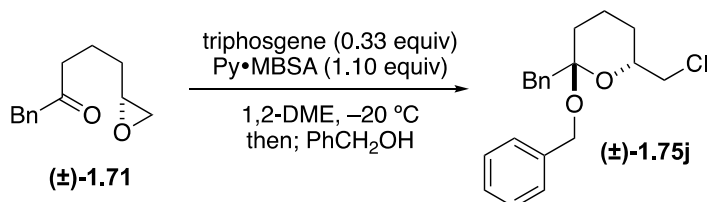
^1H NMR (500 MHz, CDCl_3) δ 7.30 – 7.24 (m, 4 H), 7.22 – 7.19 (m, 1 H), 4.35 (he, 1 H), 3.98 – 3.95 (m, 1 H), 3.52 – 3.45 (m, 2 H), 3.22 (d, $J = 13.6$ Hz, 1 H), 2.73 (d, $J = 13.6$ Hz, 1 H), 1.81 (qt, $J = 13.9, 4.3$ Hz, 1 H), 1.57 – 1.46 (m, 3 H), 1.28 – 1.21 (m, 7 H), 1.00 (qd, $J = 13.0, 3.9$ Hz, 1 H).

^{13}C NMR (126 MHz, CDCl_3) δ 137.6, 130.6, 127.8, 126.1, 100.5, 70.7, 62.6, 47.9, 45.3, 31.9, 28.0, 25.0, 24.5, 18.3.

IR: $f(\text{cm}^{-1}) = 2932, 1496, 1454, 1381, 1219, 1114, 997, 905, 732, 700, 649$.

HRMS (ESI-TOF) m/z : $((\text{M}-\text{OC}_3\text{H}_7)^+)$ = 223.08842 calculated for $\text{C}_{13}\text{H}_{16}\text{ClO}^+$; Found 223.08782

2-benzyl-2-(benzyloxy)-6-(chloromethyl)tetrahydro-2H-pyran ((\pm)-1.75j**)**



Epoxyketone (\pm)-**1.71** (115.8 mg, 0.567 mmol) was combined with 1,2-DME (2.3 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to $-20\text{ }^{\circ}\text{C}$ for at least 10 minutes.

Triphosgene (55.6 mg, 0.187 mmol) was added and the solution was stirred at $-20\text{ }^{\circ}\text{C}$ for another 5 minutes before Py•MBSA (167 mg, 0.624 mmol) was added. After stirring at $-20\text{ }^{\circ}\text{C}$ for 1 hour the reaction was determined to be complete by TLC analysis and quenched with benzyl alcohol (0.28 mL, 2.84 mmol) while still at $-20\text{ }^{\circ}\text{C}$. After 10 minutes saturated NaHCO_3 (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 2.5% gradient of EtOAc in hexanes affording (\pm)-**1.75j** as a white solid in 67% yield as a single diastereomer (126 mg, 0.380 mmol).

Rf: 0.8 in 30:70 (Hexanes : EtOAc).

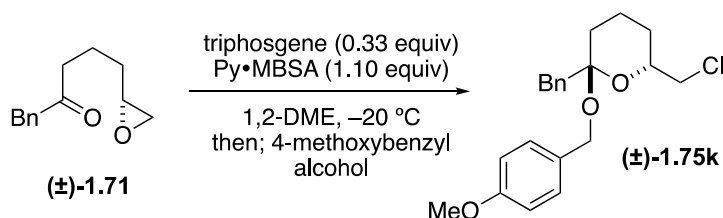
^1H NMR (400 MHz, CDCl_3) δ 7.44 – 7.35 (m, 4 H), 7.31 – 7.20 (m, 6 H), 4.75 (dd, J = 18.5, 11.8 Hz, 2 H), 3.91 – 3.84 (m, 1 H), 3.55 – 3.48 (m, 2 H), 3.08 (dd, J = 18.8, 14.1 Hz, 2 H), 1.87 (qt, J = 13.5, 3.88 Hz 1 H), 1.63 – 1.53 (m, 3 H), 1.36 (td, J = 13.6, 4.48 Hz, 1 H), 1.24 – 1.13 (m, 1 H).

^{13}C NMR (126 MHz, CDCl_3) δ 138.8, 136.8, 130.3, 128.4, 128.0, 127.4, 127.2, 126.3, 100.3, 70.8, 61.9, 47.9, 43.3, 32.0, 28.0, 18.4.

IR: $f(\text{cm}^{-1})$ = 3062, 3029, 2949, 2870, 1739, 1603, 1496, 1454, 1216, 1101, 1022, 732, 698, 481.

HRMS (ESI-TOF) m/z : ((M–OC₇H₆)⁺) = 223.08842 calculated for C₁₃H₁₆ClO⁺; Found 223.08864

2-benzyl-6-(chloromethyl)-2-((4-methoxybenzyl)oxy)tetrahydro-2H-pyran ((\pm)-1.75k**)**



Epoxyketone (\pm)-**1.71** (109.6 mg, 0.537 mmol) was combined with 1,2-DME (2.2 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to $-20\text{ }^{\circ}\text{C}$ for at least 10 minutes. Triphosgene (52.6 mg, 0.177 mmol) was added and the solution was stirred at $-20\text{ }^{\circ}\text{C}$ for another 5 minutes before Py•MBSA (158 mg, 0.591 mmol) was added. After stirring at $-20\text{ }^{\circ}\text{C}$ for 1 hour the reaction was determined to be complete by TLC analysis and quenched with 4-methoxybenzyl alcohol (0.33 mL, 2.69 mmol) while still at $-20\text{ }^{\circ}\text{C}$. After 10 minutes saturated NaHCO_3 (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 2.5% gradient of EtOAc in hexanes affording (\pm)-**1.75k** as a light-yellow oil in 54% yield as a single diastereomer (104.5 mg, 0.290 mmol).

Rf: 0.78 in 30:70 (Hexanes : EtOAc).

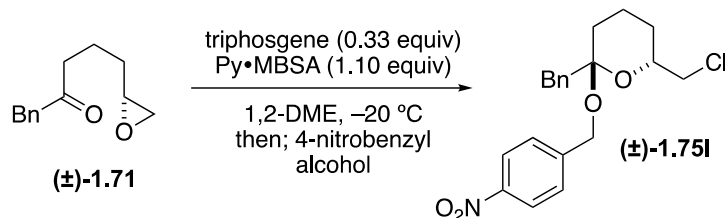
^1H NMR (500 MHz, CDCl_3) δ 7.34 (dd, $J = 8.7, 2.3\text{ Hz}$, 2 H), 7.29 – 7.27 (m, 4 H), 7.24 – 7.20 (m, 1 H), 6.92 – 6.90 (m, 2 H), 4.68 (qd, $J = 11.3, 2.2\text{ Hz}$, 2 H), 3.91 – 3.86 (m, 1 H), 3.82 (s, 1 H), 3.56 – 3.49 (m, 2 H), 3.07 (qd, $J = 14.1, 2.2\text{ Hz}$, 2 H), 1.87 – 1.79 (m, 1 H), 1.60 – 1.52 (m, 3 H), 1.34 (tq, $J = 13.7, 2.1\text{ Hz}$, 1 H), 1.17 (qt, $J = 11.7, 2.3\text{ Hz}$, 1 H).

^{13}C NMR (126 MHz, CDCl_3) δ 158.9, 136.9, 130.9, 130.3, 129.0, 128.0, 126.3, 113.8, 100.3, 70.7, 61.7, 55.3, 47.9, 43.3, 32.0, 28.1, 18.3.

IR: $f(\text{cm}^{-1}) = 2950, 1613, 1514, 1454, 1379, 1302, 1247, 1102, 1033, 976, 822, 734, 701, 530$.

HRMS (ESI-TOF) m/z : $((\text{M}-\text{O}_2\text{C}_8\text{H}_8)^+)$ = 223.08842 calculated for $\text{C}_{13}\text{H}_{16}\text{ClO}^+$; Found 223.08588

2-benzyl-6-(chloromethyl)-2-((4-nitrobenzyl)oxy)tetrahydro-2H-pyran ((±)-1.75I)



Epoxyketone **(±)-1.71** (113.7 mg, 0.557 mmol) was combined with 1,2-DME (2.2 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to $-20\text{ }^{\circ}\text{C}$ for at least 10 minutes. Triphosgene (54.5 mg, 0.184 mmol) was added and the solution was stirred at $-20\text{ }^{\circ}\text{C}$ for another 5 minutes before Py•MBSA (163.8 mg, 0.613 mmol) was added. After stirring at $-20\text{ }^{\circ}\text{C}$ for 1 hour the reaction was determined to be complete by TLC analysis and quenched with 4-nitrobenzyl alcohol (427 mg, 2.79 mmol) while still at $-20\text{ }^{\circ}\text{C}$. After 10 minutes saturated NaHCO_3 (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 2.5% gradient of EtOAc in hexanes affording **(±)-1.75I** as a yellow solid in 60% yield as a single diastereomer (125.9 mg, 0.335 mmol).

Rf: 0.61 in 30:70 (Hexanes : EtOAc).

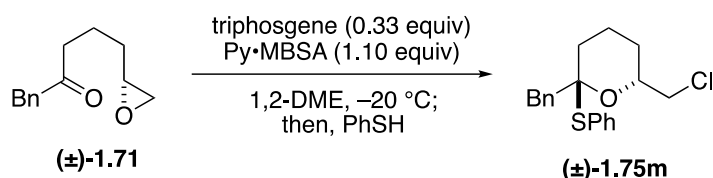
^1H NMR (500 MHz, CDCl_3) δ 8.22 (dt, $J = 9.15, 2.25\text{ Hz}$, 2 H), 7.57 (d, $J = 8.85\text{ Hz}$, 2 H), 7.29 – 7.22 (m, 5 H), 4.85 (dd, $J = 29.3, 13.5\text{ Hz}$, 2 H), 3.77 – 3.72 (m, 1 H), 3.53 – 3.46 (m, 2 H), 3.05 (s, 1 H), 1.85 (qt, $J = 12.6, 3.55\text{ Hz}$, 1 H), 1.68 – 1.59 (m, 3 H), 1.41 (td, $J = 13.4, 4.35\text{ Hz}$, 1 H), 1.22 – 1.14 (m, 1 H).

^{13}C NMR (126 MHz, CDCl_3) δ 147.2, 146.6, 136.4, 130.3, 128.1, 127.4, 126.5, 123.6, 100.6, 71.3, 60.8, 47.7, 43.5, 31.9, 27.9, 18.4.

IR: $f(\text{cm}^{-1}) = 2950, 1604, 1519, 1495, 1454, 1344, 1215, 1103, 1029, 975, 907, 857, 736, 700$.

HRMS (ESI-TOF) m/z : ((M-OC₇H₅NO₂)⁺) = 223.08842 calculated for C₁₃H₁₆ClO⁺; Found 223.08867

2-benzyl-6-(chloromethyl)-2-(phenylthio)tetrahydro-2H-pyran ((±)-1.75m)



Epoxyketone (±)-**1.71** (107 mg, 0.52 mmol) was combined with 1,2-DME (2.1 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to $-20\text{ }^{\circ}\text{C}$ for at least 10 minutes. Triphosgene (51 mg, 0.17 mmol) was added and the solution was stirred at $-20\text{ }^{\circ}\text{C}$ for another 5 minutes before Py•MBSA (154 mg, 0.58 mmol) was added. After stirring at $-20\text{ }^{\circ}\text{C}$ for 1 hour the reaction was determined to be complete by TLC analysis and quenched with thiophenol (0.27 mL, 2.60 mmol) while still at $-20\text{ }^{\circ}\text{C}$. After 10 minutes saturated NaHCO₃ (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% to 50% gradient of CH₂Cl₂ in hexanes affording (±)-**1.75m** as a colorless viscous oil in 47% yield as a single diastereomer (81 mg, 0.24 mmol).

Rf: 0.71 in 70:30 (Hexanes: EtOAc)

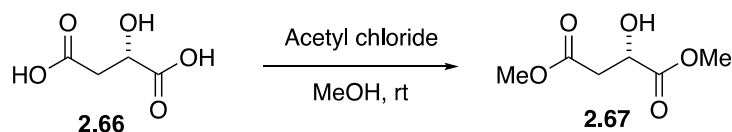
¹H NMR (500 MHz, CDCl₃) δ 7.61 – 7.60 (m, 2H), 7.36 – 7.31 (m, 3H), 7.24 – 7.17 (m, 5H), 4.58 (ddt, J = 11.5, 5.2, 2.3 Hz, 1H), 3.60 (dd, J = 11.3, 5.6 Hz, 1H), 3.57 (dd, J = 9.8, 3.3 Hz, 1H), 3.06 (d, J = 14.0 Hz, 1H), 3.00 (d, J = 14.0 Hz, 1H), 1.97 (qt, J = 13.2, 3.9 Hz, 1H), 1.75 – 1.58 (m, 4H), 1.18 (qd, J = 12.9, 3.6 Hz, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 136.7, 134.7, 132.9, 131.0, 128.7, 127.8, 127.7, 126.4, 92.0, 71.1, 47.9, 47.6, 32.8, 28.1, 19.3.

IR: $f(\text{cm}^{-1})$ = 3060, 2947, 1582, 1495, 1475, 1438, 1347, 1266, 1206, 1078, 1046, 1028, 925, 860, 780, 745, 700, 554, 505, 478.

HRMS (APCI-TOF) m/z : $(\text{M}+\text{H})^+ = 333.10744$ calculated for $\text{C}_{19}\text{H}_{22}\text{ClOS}$; experimental 333.10755, $((\text{M}-\text{PhSH})+\text{H})^+ = 223.08842$ calculated for $\text{C}_{13}\text{H}_{16}\text{ClO}$; experimental 223.08842.

(S)-Dimethyl-2-hydroxysuccinate (2.67)



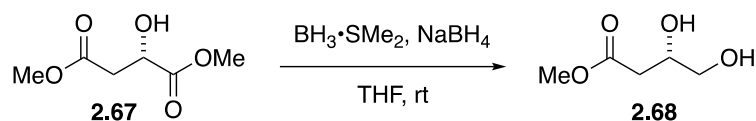
Acetyl chloride (6.4 mL, 89.50 mmol) and MeOH (112 mL) were combined in 250-mL round-bottom flask. The solution was cooled to 0 °C for 10 minutes before L-(-)-Malic acid **2.66** (15.0 g, 111.87 mmol) was added in one portion. The mixture was allowed to warm to room temperature and stirred overnight before the volatile components were evaporated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 1% to 5% gradient of MeOH in CH_2Cl_2 affording **2.67** as a pale-yellow oil in quantitative yield (18.14 g, 111.87 mmol).

Rf: 0.29 in 95:5 (CH_2Cl_2 : MeOH)

^1H NMR (400 MHz, CDCl_3) δ 4.50 (dd, $J = 10.2, 5.7$ Hz, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 3.20 (d, $J = 5.4$ Hz, 1H), 2.87 (dd, $J = 16.4, 4.4$ Hz, 1H), 2.79 (dd, $J = 16.4, 6.1$ Hz, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 173.7, 171.0, 67.3, 52.9, 52.0, 38.4.

(S)-Methyl-3,4-dihydroxybutanoate (2.68)



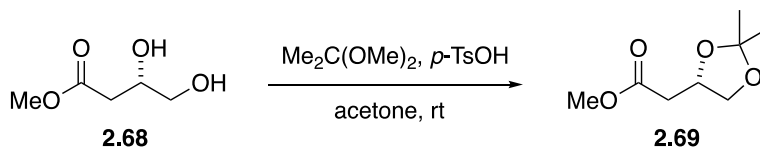
Diester **2.67** (14.1 g, 86.96 mmol) and THF (87 mL) were combined in 250-mL round-bottom flask. The solution was cooled to 0 °C for 10 minutes before borane-dimethyl sulfide (9.0 mL, 86.96 mmol) was added dropwise. The reaction was warmed to room temperature and stirred for 1 hr. The solution was re-cooled to 0 °C and sodium borohydride (658 mg, 17.39 mmol) was added. The reaction was stirred for an additional 30 min, followed by the addition of MeOH (60 mL). Following 30 min of continued stirring, the reaction mixture was concentrated in vacuo. The concentrate was purified by flash column chromatography using a 5% gradient of MeOH in EtOAc affording **2.68** as a colorless oil in 66% yield (7.70 g, 57.41 mmol), with spectroscopic data in agreement with literature values.

Rf: 0.40 in 95:5 (EtOAc: MeOH)

^1H NMR (500 MHz, CDCl_3) δ 4.15 - 4.11 (m, 1H), 3.72 (s, 3H), 3.70 – 3.67 (m, 1H), 3.53 (dd, J = 11.3, 6.2 Hz, 1H), 2.57 (dd, J = 16.8, 8.7 Hz, 1H), 2.51 (dd, J = 16.5, 4.0 Hz, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 173.1, 68.4, 65.7, 51.9, 37.4.

(S)-Methyl-2-(2,2-dimethyl-1,3-dioxolan-4-yl)acetate (2.69)



To a stirring solution of diol **2.68** (7.70 g, 57.37 mmol) in acetone (82 mL), 2,2-dimethoxypropane (14 mL) at 0 °C was added p -TsOH (1.09 g, 5.74 mmol). The reaction mixture was left in the ice-bath and stirred overnight. The reaction was subsequently quenched with

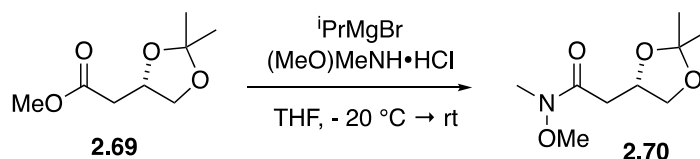
saturated NaHCO₃ (20 ml). Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x40 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The concentrate was purified by flash column chromatography using a 1% to 2% gradient of MeOH in CH₂Cl₂ affording **2.69** as a colorless oil in 87% yield (8.71 g, 50.00 mmol).

Rf: 0.70 in 95:5 (CH₂Cl₂: MeOH)

¹H NMR (500 MHz, CDCl₃) δ 4.47 (p, *J* = 6.4 Hz, 1H), 4.16 (dd, *J* = 8.4, 6.0 Hz, 1H), 3.70 (s, 3H), 3.65 (dd, *J* = 8.4, 6.4 Hz, 1H), 2.72 (dd, *J* = 15.9, 6.4 Hz, 1H), 2.53 (dd, *J* = 15.9, 7.0 Hz, 1H), 1.41 (s, 3H), 1.36 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 171.1, 109.3, 72.0, 69.2, 51.8, 38.8, 26.9, 25.5.

(S)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)-N-methoxy-N-methylacetamide (2.70)



Ester **2.69** (2.81 g, 16.13 mmol) was combined with THF (54 mL) in a 250-mL round-bottom flask and the solution was cooled to -20 °C. This was followed by the addition of *N,O*-Dimethylhydroxylamine hydrochloride (1.97 g, 20.16 mmol) and a dropwise addition of isopropylmagnesium bromide (10.8 mL, 32.26 mmol). The reaction was stirred at -20 °C overnight and was subsequently quenched with NH₄Cl (20 mL). Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The concentrate was purified by flash column chromatography using a 20% gradient of EtOAc in hexanes affording recovered ester **2.69** as a colorless oil (1.63 g, 9.38 mmol). Further elution with a 30% to 50%

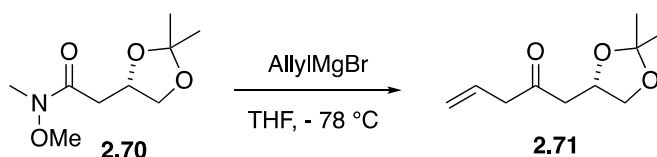
gradient of EtOAc in hexanes afforded Weinreb amide **2.70** as a yellow oil in 95% yield based on recovered starting material (1.31 g, 6.43 mmol).

Rf: 0.32 in 50:50 (Hexanes: EtOAc)

¹H NMR (400 MHz, CDCl₃) δ 4.52 (dt, *J* = 13.7, 6.1 Hz, 1H), 4.22 (dd, *J* = 8.4, 6.1 Hz, 1H), 3.69 (s, 3H), 3.65 (dd, *J* = 8.3, 6.7 Hz, 1H), 3.17 (s, 3H), 2.99 (dd, *J* = 16.2, 5.4 Hz, 1H), 2.55 (dd, *J* = 16.2, 7.8 Hz, 1H), 1.42 (s, 3H), 1.36 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 171.4, 108.7, 72.3, 69.6, 61.3, 36.7, 31.9, 26.9, 25.4.

(S)-1-(2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-en-2-one (2.71)



Weinreb amide **2.70** (5.95 g, 29.28 mmol) was added to a 250-mL round-bottom flask, and THF (100 mL) was then added. After cooling the solution to -78 °C, Allylmagnesium bromide (35.1 mL, 35.13 mmol) was added dropwise. After stirring for 1 hour, the reaction was determined to be complete by TLC analysis and was quenched with saturated NH₄Cl (30 mL). Upon separation of the two layers, the aqueous layer was extracted with Et₂O (3 x 30 mL). The combined organic layers were then dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The concentrate was then purified by flash column chromatography using a 40% - 50% Et₂O in petroleum ether gradient, to afford ketone **2.71** in 98% yield (5.29 g, 28.69 mmol) as a yellow oil.

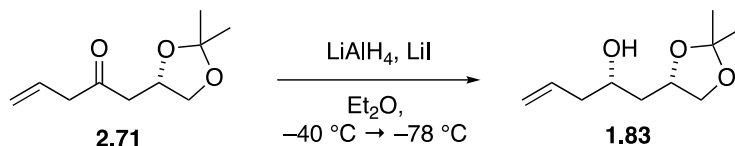
Rf: 0.65 in 60:40 (Petroleum ether: Et₂O)

¹H NMR (400 MHz, CDCl₃) δ 5.96 – 5.84 (m, 1H), 5.21 (dd, *J* = 10.2, 1.2 Hz, 1H), 5.16 (dd, *J* = 17.1, 1.4 Hz, 1H), 4.45 (p, *J* = 6.6 Hz, 1H), 4.18 (dd, *J* = 8.3, 6.0 Hz, 1H), 3.53 (dd, *J* = 8.3, 6.7

Hz, 1H), 3.21 (d, $J = 7.0$ Hz, 2H), 2.93 (dd, $J = 17.0, 6.0$ Hz, 1H), 2.60 (dd, $J = 17.0, 7.1$ Hz, 1H), 1.40 (s, 3H), 1.34 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 206.4, 130.0, 119.3, 108.9, 71.7, 69.4, 48.3, 46.4, 26.9, 25.4.

(S)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-en-2-ol (1.83)



Ketone **2.71** (4.54 g, 24.64 mmol) was added to a 1000-mL round-bottom flask and dissolved in Et_2O (500 mL). LiI (16.5 g, 123.22 mmol) was added and the mixture was stirred at $-40\text{ }^\circ\text{C}$ for 10 minutes. The resulting solution was then cooled to $-78\text{ }^\circ\text{C}$ and LiAlH_4 (4.68 g, 123.22 mmol) was added. After stirring for 1 hour, the reaction was determined to be complete by TLC analysis. DI H_2O (5 mL), 3M NaOH (5 mL), and DI H_2O (12 mL) were sequentially added to the reaction mixture for quench. The slurry was warmed to room temperature, filtered through a pad of celite, and the filtrate was subsequently diluted with H_2O (100 mL). Upon separation of the two layers, the aqueous layer was extracted with Et_2O (2 x 100 mL). The combined organic layers were then dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting alcohol **1.83** was obtained clean in 92% yield (4.25 g, 22.82 mmol) as a yellow oil.

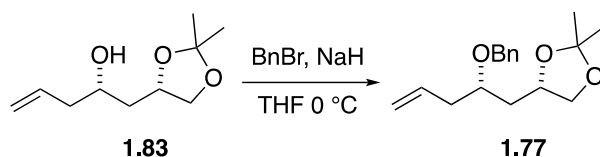
Rf: 0.25 in 60:40 (Petroleum ether: Et_2O)

^1H NMR (400 MHz, CDCl_3) δ 5.84 (ddt, $J = 17.4, 10.5, 7.1$ Hz, 1H), 5.16 – 5.09 (m, 2H), 4.31 – 4.24 (m, 1H), 4.09 (dd, $J = 8.1, 6.0$ Hz, 1H), 3.91 – 3.85 (m, 1H), 3.60 – 3.55 (m, 1H), 3.02 (s, 1H), 2.30 (dd, $J = 13.9, 7.0$ Hz, 1H), 2.26 – 2.20 (m, 1H), 1.74 (dt, $J = 14.2, 3.5$ Hz, 1H), 1.69 – 1.61 (m, 1H), 1.42 (s, 3H), 1.36 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 134.6, 117.8, 109.4, 75.7, 70.2, 69.7, 41.9, 39.7, 26.9, 25.8.

$[\alpha]_D^{23} = +9.77$ (c 1.0, CHCl_3)

(S)-4-((S)-2-(benzyloxy)pent-4-en-1-yl)-2,2-dimethyl-1,3-dioxolane (1.77)



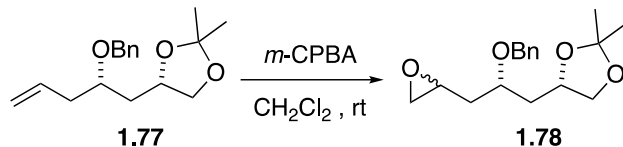
Alcohol **1.83** (798 mg, 4.29 mmol) was combined with THF (21 mL) in a round-bottom flask and cooled to 0 °C. Sodium hydride (308 mg, 12.9 mmol) was added, followed by benzyl bromide (0.63 mL, 6.42 mmol). The solution was stirred for 24 hours, at which point the reaction was determined to be complete by TLC analysis. The reaction was quenched with methanol (10 mL) and upon complete separation of the two layers, the aqueous layer was washed with CH_2Cl_2 (3x15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording **1.77** as a clear oil in 81% yield. (959 mg, 3.47 mmol).

Rf: 0.56 in 20:80 (Hexanes : EtOAc).

^1H NMR (500 MHz, CDCl_3) δ 7.36 – 7.33 (m, 4 H), 7.31 – 7.26 (m, 1 H), 5.85 (ddt, $J = 17.3, 10.3, 7.10$ Hz, 1 H), 5.14 – 5.08 (m, 2 H), 4.59 (d, $J = 11.6$ Hz, 1 H), 4.47 (d, $J = 11.6$ Hz, 1 H), 4.23 (p, $J = 6.45$ Hz, 1 H), 3.94 (dd, $J = 7.90, 5.90$ Hz, 1 H), 3.55 (p, $J = 5.75$ Hz, 1 H), 3.50 (t, $J = 7.70$ Hz, 1 H), 2.39 (t, $J = 6.40$ Hz, 2 H), 1.99 (p, $J = 6.45$ Hz, 1 H), 1.74 – 1.69 (m, 1 H), 1.40 (s, 3 H), 1.35 (s, 3 H).

^{13}C NMR (126 MHz, CDCl_3) δ 138.5, 134.3, 128.4, 127.8, 127.6, 117.5, 108.5, 75.5, 73.1, 70.8, 69.5, 38.1, 37.4, 27.0, 25.7.

(4S)-4-((2S)-2-(benzyloxy)-3-(oxiran-2-yl)propyl)-2,2-dimethyl-1,3-dioxolane (1.78)



Alkene **1.77** (881 mg, 3.19 mmol) was combined with CH₂Cl₂ (13 mL) in a round-bottom flask. Meta-chloroperoxybenzoic acid (75% w/w) (1.10 g, 4.78 mmol) was added and the solution was stirred for 24 hours, at which point the reaction was determined to be complete by TLC analysis. The reaction was quenched with 1 M NaOH (10 mL) and upon complete separation of the two layers, the aqueous layer was washed with CH₂Cl₂ (3x15 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 30% gradient of EtOAc in hexanes affording **1.78** as a clear oil in 92% yield as a mixture of diastereomers. (834 mg, 2.85 mmol).

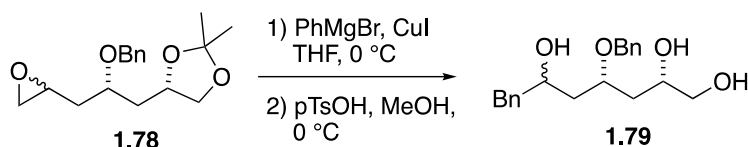
Rf: 0.28 in 20:80 (Hexanes : EtOAc).

¹H NMR (500 MHz, CDCl₃) δ 7.37 – 7.33 (m, 4 H), 7.31 – 7.27 (m, 1 H), 4.59 – 4.50 (m, 2 H), 4.26 – 4.19 (m, 1 H), 3.98 (dd, J = 7.95, 5.95 Hz, 1 H), 3.79 – 3.71 (m, 1 H), 3.52 (dd, J = 15.4, 7.70 Hz, 1 H), 3.10 – 3.05 (m, 1 H), 2.78 (dt, J = 25.6, 4.45 Hz, 1 H), 2.50 (dq, J = 15.0, 2.70 Hz, 1 H), 2.07 – 1.99 (m, 1 H), 1.93 – 1.66 (m, 3 H), 1.40 (s, 3 H), 1.34 (s, 3 H).

¹³C NMR (126 MHz, CDCl₃) δ 138.3, 138.2, 128.4, 128.4, 127.8, 127.7, 127.7, 127.7, 108.7, 108.6, 74.2, 74.1, 72.8, 72.7, 71.4, 70.7, 69.6, 69.5, 49.6, 49.2, 47.6, 46.7, 38.0, 37.7, 37.4, 36.4, 27.0, 25.7.

IR: $f(\text{cm}^{-1})$ = 3032, 2985, 2934, 2896, 1454, 1370, 1249, 1213, 1159, 1094, 1059, 847, 739, 698.

(2*S*,4*S*)-4-(benzyloxy)-7-phenylheptane-1,2,6-triol (1.79)



CuI (54.3 mg, 0.285 mmol) was combined with THF (5 mL) in a round-bottom flask and the resulting solution was cooled to 0 °C. Phenylmagnesium bromide (1.9 mL, 5.71 mmol) was added and the solution was stirred for 10 minutes. Epoxide **1.78** (834 mg, 2.85 mmol) was dissolved in THF (5 mL) and then added to the cooled reaction mixture slowly via syringe. The reaction stirred for 3 hours, at which point the reaction was determined to be complete by TLC analysis. The reaction was quenched with saturated NH₄Cl (10 mL) and DI H₂O (10 mL). Upon complete separation of the two layers, the aqueous layer was washed with CH₂Cl₂ (3x20 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford the crude alcohol as a yellow oil (R_f = 0.31 in 30% EtOAc in hexanes). The resulting crude material was carried onto the next step without further purification.

The crude alcohol was dissolved in methanol (14 mL) and the resulting solution was cooled to 0 °C. Tosylic acid (225 mg, 1.18 mmol) was added and the solution stirred for 18 hours, at which point the reaction was determined to be complete by TLC analysis. The reaction was quenched with saturated NaHCO₃ (15 mL) and upon complete separation of the two layers, the aqueous later was washed with CH₂Cl₂ (3x20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of MeOH in CH₂Cl₂, affording **1.79** as a viscous white oil in 78% over two steps as a mixture of diastereomers (743 mg, 2.25 mmol).

Rf: 0.24 in 5 : 95 (MeOH : CH₂Cl₂).

¹H NMR (500 MHz, CDCl₃) δ 7.36 – 7.30 (m, 7 H), 7.25 – 7.19 (m, 3 H), 4.64 – 4.50 (m, 2 H), 4.13 – 4.09 (m, 1 H), 3.99 – 3.93 (m, 1 H), 3.85 – 3.81 (m, 1 H), 3.61 – 3.54 (m, 1 H), 3.46 – 3.40 (m, 1 H), 3.25 – 3.19 (m, 1 H), 2.79 – 2.72 (m, 2 H), 2.51 – 2.43 (m, 1 H), 2.08 – 2.03 (m, 1 H), 1.92 – 1.69 (m, 3 H), 1.62 – 1.59 (m, 1 H).

¹³C NMR (126 MHz, CDCl₃) δ 138.2, 138.1, 137.6, 129.4, 129.4, 128.7, 128.6, 128.6, 128.5, 128.2, 128.1, 128.0, 128.0, 128.0, 126.6, 126.5, 77.4, 76.4, 76.4, 71.4, 70.7, 70.6, 70.6, 70.5, 69.7, 66.8, 44.6, 44.4, 40.3, 39.8, 37.2, 37.0.

IR: $f(\text{cm}^{-1}) = 3380, 3086, 3062, 3028, 2939, 2869, 1740, 1601, 1495, 1453, 1365, 1212, 1084, 1063, 1028, 905, 853, 737, 700, 649, 612.$

(4S)-4-(benzyloxy)-5-((S)-oxiran-2-yl)-1-phenylpentan-2-ol (1.80)



Triol **1.79** (743 mg, 2.25 mmol) was dissolved in dry CH₂Cl₂ (45 mL). Et₃N (0.63 mL, 4.50 mmol) was added to the solution, followed by *p*-TsCl (858 mg, 4.50 mmol) and dibutyltin (IV) oxide (56 mg, 0.23 mmol). The mixture was stirred for 24 hours. Upon complete consumption of **xx** as monitored by TLC, DBU (1.12 mL, 7.49 mmol) was added, and the mixture was stirred for 10 hours. Once the epoxide formation was completed as monitored by TLC, the reaction mixture was concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography using a 10% to 20% gradient of EtOAc in hexanes affording **1.80** as a yellow oil in 57% yield as a mixture of diastereomers (397 mg, 1.27 mmol).

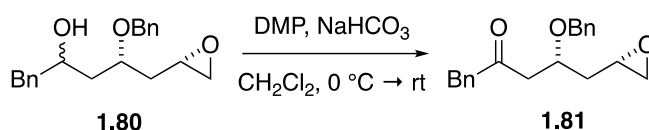
Rf: 0.44 in 50 : 50 (EtOAc : Hexanes).

¹H NMR (500 MHz, CDCl₃) δ 7.36 – 7.28 (m, 14 H), 7.24 – 7.20 (m, 6 H), 4.64 – 4.47 (m, 4 H), 4.14 – 4.01 (m, 2 H), 3.96 – 3.85 (m, 2 H), 3.02 – 2.95 (m, 2 H), 2.82 – 2.69 (m, 6 H), 2.48 – 2.41 (m, 4 H), 1.97 – 1.69 (m, 8 H).

¹³C NMR (126 MHz, CDCl₃) δ 138.5, 138.4, 138.1, 137.7, 129.5, 129.4, 128.6, 128.5, 128.5, 128.5, 127.9, 127.9, 127.9, 126.5, 126.4, 74.7, 72.1, 71.4, 70.9, 69.5, 49.3, 48.9, 46.9, 46.8, 44.3, 44.2, 40.4, 40.2, 36.6, 36.5, 29.7.

IR: $f(\text{cm}^{-1}) = 3456, 3028, 2920, 2855, 1602, 1496, 1454, 1352, 1090, 1067, 1029, 835, 756, 700.$

(R)-4-(benzyloxy)-5-((S)-oxiran-2-yl)-1-phenylpentan-2-one (1.81)



Epoxy alcohol **1.80** (377 mg, 1.21 mmol) was combined with CH₂Cl₂ (12 mL) in a round-bottom flask. The resulting mixture was cooled to 0 °C. Dess-Martin periodinane (772 mg, 1.82 mmol) was added, followed by NaHCO₃ (305 mg, 3.63 mmol). The resulting mixture was allowed to gradually warm to room temperature. After stirring for 24 hours, the reaction was determined to be complete by TLC analysis. The reaction mixture was cooled to 0 °C and quenched with saturated sodium thiosulfate (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 15% gradient of EtOAc in hexanes affording **1.81** as a light-yellow oil in 67% yield. (252 mg, 0.813 mmol).

R_f: 0.75 in 50:50 (Hexanes : EtOAc).

¹H NMR (400 MHz, CDCl₃) δ 7.35 – 7.24 (m, 8 H), 7.18 (d, *J* = 7.28 Hz, 2 H), 4.51 (dd, *J* = 17.4, 11.3 Hz, 2 H), 4.15 (p, *J* = 5.36 Hz, 1 H), 3.73 (s, 2 H), 3.04 (se, *J* = 3.84 Hz, 1 H), 2.91 (dd, *J* = 16.6, 7.08 Hz, 1 H), 2.72 (m, 2 H), 2.43 (dd, *J* = 5.07, 2.63 Hz, 1 H), 1.90 (dt, *J* = 14.6, 4.69 Hz, 1 H), 1.63 (m, 1 H).

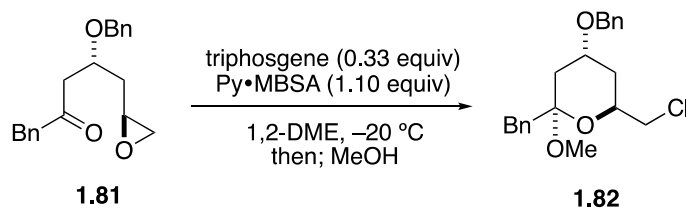
¹³C NMR (126 MHz, CDCl₃) δ 206.7, 138.2, 133.8, 129.5, 128.7, 128.4, 127.8, 127.7, 127.1, 73.5, 71.6, 51.1, 48.9, 46.5, 46.4, 36.7.

IR: *f* (cm⁻¹) = 3029, 2918, 1715, 1497, 1454, 1350, 1088, 1066, 833, 739, 699.

HRMS (ESI-TOF) *m/z*: ((*M*+*H*)⁺) = 311.16417 calculated for (C₂₀H₂₂O₃+H)⁺; Found 311.16459.

[α]_D²³ = -9.01 (c 1.0, CHCl₃)

(2*S*,4*R*,6*S*)-2-benzyl-4-(benzyloxy)-6-(chloromethyl)-2-methoxytetrahydro-2*H*-pyran (1.82)



Epoxyketone **1.81** (105.4 mg, 0.338 mmol) was combined with 1,2-DME (1.4 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to -20 °C for at least 10 minutes. Triphosgene (33.1 mg, 0.112 mmol) was added and the solution was stirred at -20 °C for another 5 minutes before Py•MBSA (99.3 mg, 0.372 mmol) was added. After stirring at -20 °C for 30 minutes the reaction was determined to be complete by TLC analysis and quenched with methanol (0.70 mL) while still at -20 °C. After 10 minutes saturated NaHCO₃ (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a

2.5% gradient of EtOAc in hexanes affording **1.82** as a yellow oil in 61% yield as a single diastereomer (74.6 mg, 0.207 mmol).

Rf: 0.61 in 30:70 (Hexanes : EtOAc).

¹H NMR (400 MHz, CDCl₃) δ 7.31 – 7.20 (m, 10 H), 4.57 (dd, *J* = 12.1 Hz, 1 H), 4.36 (dd, *J* = 12.1 Hz, 1 H), 4.30 – 4.25 (m, 1 H), 3.71 – 3.66 (m, 1 H), 3.61 – 3.53 (m, 2 H), 3.44 (s, 3 H), 3.01 – 2.91 (m, 2 H), 1.92 – 1.78 (m, 2 H), 1.55 – 1.38 (m, 2 H).

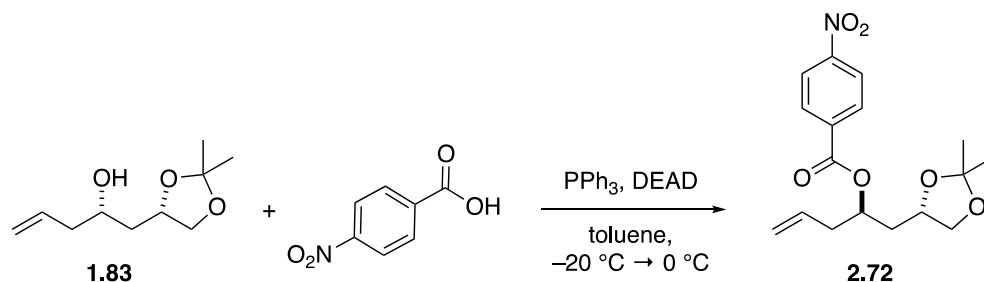
¹³C NMR (126 MHz, CDCl₃) δ 138.8, 136.8, 130.3, 128.3, 128.1, 127.5, 127.4, 126.4, 100.2, 69.8, 69.7, 65.4, 47.9, 42.5, 34.2, 32.2, 29.7.

IR: *f* (cm⁻¹) = 3030, 2956, 1604, 1496, 1453, 1431, 1331, 1302, 1208, 1102, 1029, 908, 735, 698.

HRMS (ESI-TOF) *m/z*: ((*M*+*Na*)⁺) = 383.13844 calculated for (C₂₁H₂₅ClO₃+*Na*)⁺; Found 383.13851

[*α*]_D²³ = +19.8 (c 1.0, CHCl₃)

(*R*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-en-2-yl 4-nitrobenzoate (2.72**)**



Triphenylphosphine (3.38 g, 12.89 mmol) and *p*-nitrobenzoic acid (2.15 g, 12.89 mmol) were added to a 250-mL round-bottom flask and dissolved in toluene (35 mL). The mixture was cooled to -20 °C and a solution of alcohol **1.83** (2.0 g, 10.74 mmol) in toluene (10 mL) was added. After stirring for 30 minutes, a solution of diethyl azodicarboxylate (2.0 mL, 12.89 mmol) in toluene (20 mL) was added dropwise over 5 minutes to the vigorously stirred mixture during which

the temperature was maintained at -20 °C. When the addition was complete, the mixture was allowed to warm gradually to 0 °C over 1 hour 30 minutes. After the reaction was determined to be complete by TLC analysis, it was quenched with saturated NaHCO₃ (40 mL). Upon separation of the two layers, the aqueous layer was extracted with Et₂O (3 x 30 mL). The combined organic layers were then dried over Na₂SO₄, filtered, and concentrated under reduced pressure. To the residue was added Et₂O (25 mL) and hexanes (75 mL), whereupon the bulk of triphenylphosphine oxide was filtered off. Concentration of the filtrate gave a viscous oil which was purified by flash column chromatography using a 10% - 30% Et₂O in hexanes gradient, to afford ester **2.72** in 60% yield (2.15 g, 6.42 mmol) as a white solid.

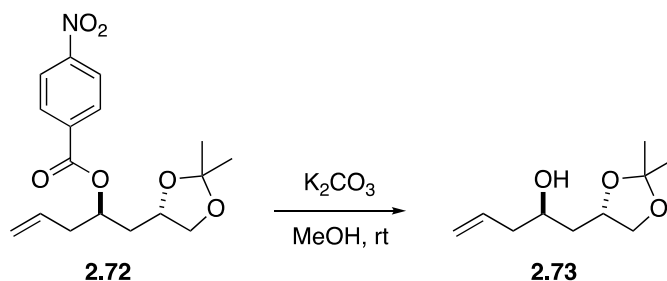
Rf: 0.55 in 70:30 (Hexanes: EtOAc)

¹H NMR (400 MHz, CDCl₃) δ 8.30 – 8.28 (m, 2H), 8.20 – 8.18 (m, 2H), 5.81 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H), 5.40 – 5.33 (m, 1H), 5.15 – 5.12 (m, 1H), 5.11 – 5.09 (m, 1H), 4.21 – 4.15 (m, 1H), 4.02 (dd, *J* = 8.0, 5.9), 3.56 (t, *J* = 7.6 Hz, 1H), 2.59 – 2.47 (m, 2H), 2.05 – 1.91 (m, 2H), 1.39 (s, 3H), 1.31 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 164.1, 150.6, 135.8, 132.7, 130.7, 123.6, 118.7, 109.0, 72.9, 72.8, 69.6, 39.1, 37.9, 27.0, 25.7

[α]²¹_D = -19.8 (c 2.5, CHCl₃)

(*R*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-en-2-ol (2.73**)**



Ester **2.72** (2.04 g, 6.08 mmol) was added to a 100-mL round-bottom flask and dissolved in MeOH (30.4 mL). K_2CO_3 (1.68 g, 12.15 mmol) was added and the reaction was stirred at room temperature. After stirring at room temperature for 20 hours the reaction was determined to be complete by TLC analysis and was quenched with NH_4Cl (20 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting alcohol **2.73** was obtained clean in 99% yield (1.13 g, 6.07 mmol) as a yellow oil.

Rf: 0.38 in 70:30 (Hexanes: EtOAc)

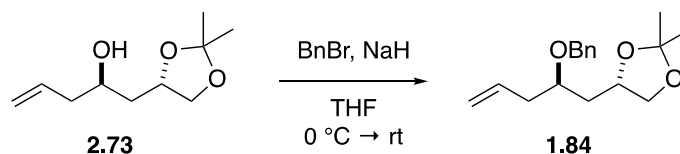
1H NMR (500 MHz, $CDCl_3$) δ 5.86 – 5.78 (m, 1H), 5.15 – 5.12 (m, 2H), 4.37 – 4.31 (m, 1H), 4.09 (dd, J = 8.1, 6.1 Hz, 1H) 3.92 – 3.87 (m, 1H), 3.58 (t, J = 7.9 Hz, 1H), 2.33 – 2.28 (m, 1H), 2.26 – 2.20 (m, 1H), 1.77 (qd, J = 14.3, 7.4, 2.9 Hz, 1H), 1.71 – 1.65 (m, 1H), 1.42 (s, 3H), 1.36 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 134.5, 118.3, 108.8, 73.6, 69.5, 67.9, 42.3, 39.5, 26.9, 25.7.

IR: f (cm^{-1}) = 3444, 2984, 2937, 1641, 1371, 1216, 1157, 1057, 915, 873, 826, 519.

$[\alpha]^{21}_D$ = -4.29 (c 2.6, $CHCl_3$)

(S)-4-((R)-2-(benzyloxy)pent-4-en-1-yl)-2,2-dimethyl-1,3-dioxolane (1.84)



Alcohol **2.73** (1.07 g, 5.72 mmol) was added to a 100-mL round-bottom flask, and THF (29 mL) was then added. After cooling the solution to 0 °C, neat NaH (686 mg, 28.60 mmol) was added in one portion. After the cessation of gas evolution, Benzyl bromide (0.62 mL, 6.29 mmol) was added slowly, dropwise. The solution was allowed to warm to room temperature and stirred overnight. After completion of the reaction as determined by TLC, the reaction was cooled to 0 °C

and quenched with saturated MeOH (10 mL) and DI H₂O (20 mL). Upon separation of the two layers, the aqueous layer was extracted with Et₂O (3 x 20 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The concentrate was then purified by flash column chromatography using a 5% - 10% Et₂O in Petroleum ether gradient, to afford **1.84** in quantitative yield (1.57 g, 5.72 mmol) as a yellow oil.

Rf: 0.82 in 60:40 (Petroleum ether: Et₂O)

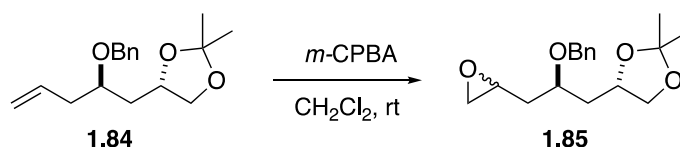
¹H NMR (400 MHz, CDCl₃) δ 7.34 – 7.33 (m, 4H), 7.31 – 7.28 (m, 1H), 5.84 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.13 – 5.11 (m, 1H), 5.09 – 5.08 (m, 1H), 4.64 (d, *J* = 11.3 Hz, 1H), 4.48 (d, *J* = 11.3 Hz, 1H), 4.28 – 4.22 (m, 1H), 4.04 (dd, *J* = 8.0, 5.9 Hz, 1H), 3.72 – 3.66 (m, 1H), 3.51 (t, *J* = 7.8 Hz, 1H), 2.41 (dd, *J* = 14.2, 5.4 Hz, 1H), 2.34 (dd, *J* = 14.5, 7.3 Hz, 1H), 1.79 (qd, *J* = 14.1, 7.7, 3.2 Hz, 1H), 1.73 – 1.66 (m, 1H), 1.39 (s, 3H), 1.35 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 138.6, 134.2, 128.4, 127.8, 127.6, 117.6, 108.4, 76.0, 73.6, 71.5, 70.0, 38.8, 38.7, 27.0, 25.9.

IR: *f* (cm⁻¹) = 3066, 3031 2983, 2925, 2868, 2223, 2039, 1640, 1496, 1455, 1370, 1245, 1215, 1159, 1062, 996, 914, 871, 829, 735, 697, 511, 464, 409.

[α]_D²³ = -21.8 (c 1.0, CHCl₃)

(4*S*)-4-((2*R*)-2-(benzyloxy)-3-(oxiran-2-yl)propyl)-2,2-dimethyl-1,3-dioxolane (1.85**)**



Alkene **1.84** (1.74 g, 6.35 mmol) was added to a 100-mL round-bottom flask and dissolved in CH₂Cl₂ (25.4 mL). *m*CPBA (2.19 g, 9.53 mmol, 70 wt %) was added and the reaction was stirred at room temperature. After 20 hours the reaction was quenched with 1M NaOH (15 mL).

Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x15 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% to 20% EtOAc in hexanes gradient, to afford epoxide **1.85** as a colorless liquid in 99% yield as a 1:1 mixture of diastereomers (1.81 g, 6.20 mmol).

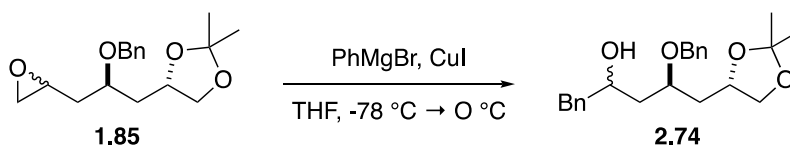
Rf: 0.52 in 70:30 (Hexanes: EtOAc)

¹H NMR (500 MHz, CDCl₃) δ 7.35 – 7.32 (m, 8H), 7.30 – 7.28 (m, 2H), 4.63 (dd, *J* = 17.5, 11.3 Hz, 2H), 4.58 – 4.50 (m, 2H), 4.30 – 4.24 (m, 2H), 4.07 – 4.03 (m, 2H), 3.88 – 3.82 (m, 2H), 3.52 (dd, *J* = 14.7, 7.6 Hz, 2H), 3.07 – 3.03 (m, 2H), 2.78 (dt, *J* = 15.8, 4.4 Hz, 2H), 2.50 (dq, *J* = 14.7, 5.0, 2.7 Hz, 2H), 1.88 – 1.80 (m, 6H), 1.79 – 1.71 (m, 2H), 1.40 (s, 6H), 1.35 (s, 6H).

¹³C NMR (100 MHz, CDCl₃) δ 138.3, 128.5, 128.4, 127.9, 127.8, 127.7, 127.7, 74.7, 74.6, 73.4, 73.2, 72.2, 71.6, 70.0, 69.9, 49.4, 49.1, 47.4, 46.8, 39.5, 39.2, 38.1, 37.3, 27.0, 25.9.

IR: *f* (cm⁻¹) = 2954, 2923, 2853, 1461, 1376.

(4*R*)-4-(benzyloxy)-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-phenylpentan-2-ol (2.74)



Copper Iodide (118 mg, 0.62 mmol) was added to a 100-mL round-bottom flask while still hot and vacuum purged with N₂ while gradually cooling to room temperature. THF (15 mL) was added and the resulting slurry was cooled to -78 °C. After 10 minutes, Phenylmagnesium bromide (4.1 mL, 12.40 mmol) was added dropwise. After 30 minutes epoxide **1.85** (1.81 g, 6.20 mmol) was added via cannula in THF (10 mL). The resulting solution was stirred at 0 °C. After 2 hours, the reaction was determined to be complete by TLC analysis and quenched with saturated NH₄Cl

(20 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x20 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% to 25% gradient of EtOAc in hexanes affording **2.74** as a yellow oil in 77% yield as a mixture of diastereomers (1.76 g, 4.75 mmol).

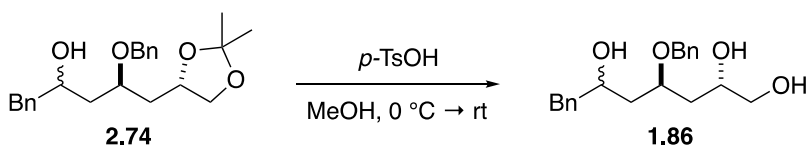
Rf: 0.44 in 70:30 (Hexanes: EtOAc)

¹H NMR (400 MHz, CDCl₃) δ 7.36 – 7.20 (m, 10H), 7.24 – 7.20 (m, 4H), 4.65 – 4.51 (m, 3H), 4.24 – 4.12 (m, 2H), 4.07 – 4.00 (m, 2H), 3.96 – 3.90 (m, 1H), 3.86 – 3.75 (m, 0.5H), 3.54 – 3.47 (m, 1H), 2.82 – 2.71 (m, 3H), 1.90 – 1.63 (m, 7H), 1.39 – 1.38 (m, 4H), 1.34 – 1.33 (m, 4H).

¹³C NMR (126 MHz, CDCl₃) δ 138.4, 138.1, 129.5, 129.4, 128.5, 128.5, 128.5, 128.0, 127.9, 127.9, 127.8, 126.4, 108.7, 108.6, 76.5, 75.0, 73.3, 73.2, 72.2, 71.5, 71.3, 70.0, 69.9, 69.5, 44.4, 44.4, 41.1, 40.1, 38.8, 38.7, 27.0, 27.0, 25.8.

IR: $f(\text{cm}^{-1}) = 3460, 3028, 2983, 2925, 1602, 1495, 1453, 1370, 1212, 1157, 1055, 865, 744, 698, 601, 499.$

(2*S*,4*R*)-4-(benzyloxy)-7-phenylheptane-1,2,6-triol (1.86)



To a stirring solution of alcohol **2.74** (1.52 g, 4.10 mmol) in methanol (20.5 mL) at 0 °C was added *p*-TsOH (234 mg, 1.23 mmol). The reaction mixture was left in the ice-bath and stirred overnight. The reaction was subsequently quenched with saturated NaHCO₃ (20 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x20 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 1% gradient of MeOH in CH₂Cl₂ affording recovered

alcohol **xx** as a yellow oil (272 mg, 0.73 mmol). Further elution with a 2% to 5% gradient of MeOH in CH₂Cl₂ afforded triol **1.86** as a yellow oil in 91% yield based on recovered starting material, as a mixture of diastereomers (1.01 g, 3.06 mmol).

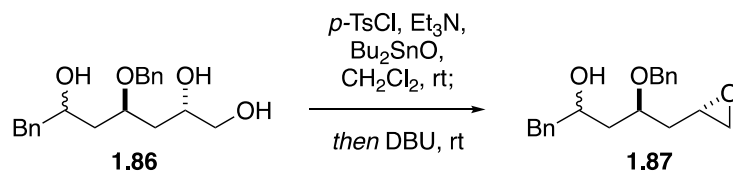
Rf: 0.16 in 95:5 (CH₂Cl₂:MeOH)

¹H NMR (500 MHz, CDCl₃) δ 7.37 – 7.29 (m, 7H), 7.25 – 7.19 (m, 3H), 4.65 – 4.54 (m, 2H), 4.11 – 4.03 (m, 1H), 4.00 – 3.95 (m, 2H), 3.62 – 3.58 (m, 1H), 3.44 – 3.41 (m, 1H), 2.78 – 2.77 (m, 1H), 2.75 – 2.71 (m, 1H), 1.95 – 1.86 (m, 1H), 1.83 – 1.71 (m, 2H), 1.66 – 1.55 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 138.2, 129.4, 129.4, 128.6, 128.6, 128.2, 128.1, 128.1, 126.5, 76.2, 74.6, 72.0, 71.3, 71.0, 69.6, 69.1, 69.1, 67.0, 44.5, 40.2, 40.0, 36.9.

IR: $f(\text{cm}^{-1}) = 3363, 3028, 2922, 1495, 1454, 1376, 1083, 849, 745, 699, 493, 427$.

(4R)-4-(benzyloxy)-5-((S)-oxiran-2-yl)-1-phenylpentan-2-ol (1.87)



Triol **1.86** (1.0 g, 3.03 mmol) was dissolved in dry CH₂Cl₂ (60.7 mL). Et₃N (0.85 mL, 6.07 mmol) was added to the solution, followed by *p*-TsCl (1.16 g, 6.07 mmol) and dibutyltin(IV) oxide (75 mg, 0.30 mmol). The mixture was stirred for 18 hours. Upon complete consumption of **xx** as monitored by TLC, DBU (2.0 mL, 13.40 mmol) was added, and the mixture was stirred for 28 hours. Once the epoxide formation was completed as monitored by TLC, the reaction mixture was concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography using a 10% to 50% gradient of EtOAc in hexanes affording **1.87** as a colorless oil in 85% yield as a mixture of diastereomers (801 mg, 2.57 mmol).

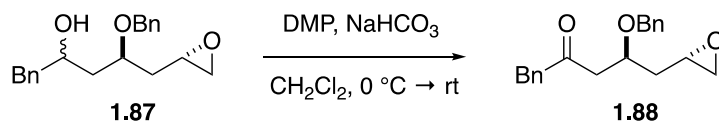
Rf: 0.21 in 70:30 (Hexanes: EtOAc)

¹H NMR (500 MHz, CDCl₃) δ 7.35 – 7.29 (m, 9H), 7.24 – 7.20 (m, 4H), 4.67 – 4.58 (m, 2H), 4.54 – 4.47 (m, 1H), 4.13 – 4.12 (m, 1H), 4.03 – 3.95 (m, 1H), 3.89 – 3.89 (m, 0.6H), 3.04 – 2.99 (m, 1H), 2.81 – 2.72 (m, 2H), 2.50 – 2.40 (m, 2H), 1.97 – 1.92 (m, 1H), 1.89 – 1.72 (m, 4H), 1.66 – 1.61 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 138.4, 138.1, 129.5, 129.4, 128.6, 128.5, 128.5, 128.0, 127.9, 127.9, 126.5, 77.2, 75.0, 72.1, 71.4, 69.4, 49.6, 49.2, 47.4, 47.3, 44.3, 40.6, 37.5.

IR: $f(\text{cm}^{-1})$ = 3457, 3028, 2921, 1601, 1495, 1453, 1355, 1258, 1176, 1067, 1028, 916, 830, 744, 699, 601, 554, 503.

(S)-4-(benzyloxy)-5-((S)-oxiran-2-yl)-1-phenylpentan-2-one (1.88)



Alcohol **1.87** (783 mg, 2.51 mmol) was combined with CH₂Cl₂ (25.1 mL) in a 100-mL round-bottom flask. The solution was cooled to 0 °C followed by the addition of Dess-Martin Periodinane (1.28 g, 3.01 mmol) and NaHCO₃ (633 mg, 7.53 mmol). The reaction was left in the ice bath and stirred overnight. After the reaction was determined to be complete by TLC analysis, it was filtered over celite and the filtrate was concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography using a 10% to 20% Hexanes in EtOAc gradient affording **1.88** as a colorless oil in 74% yield as a single diastereomer (575 mg, 1.85 mmol).

Rf: 0.26 in 70:30 (Hexanes: EtOAc)

¹H NMR (500 MHz, CDCl₃) δ 7.34 – 7.31 (m, 4H), 7.29 – 7.27 (m, 4H), 7.18 – 7.17 (m 2H), 4.56 (d, *J* = 11.2 Hz, 1H), 4.52 (d, *J* = 11.3 Hz, 1H), 4.21 – 4.15 (m, 1H), 3.71 (s, 2H), 2.98 (td, *J* = 7.1, 4.1 Hz, 1H), 2.86 (dd, *J* = 16.5, 7.1 Hz, 1H), 2.75 (t, *J* = 4.8 Hz, 1H), 2.65 (dd, *J* = 16.5, 5.1 Hz, 1H), 2.44 (dd, *J* = 5.0, 2.7 Hz, 1H), 1.87 (qd, *J* = 14.3, 7.0, 4.4 Hz, 1H), 1.58 (qd, *J* = 14.1, 7.1, 5.6 Hz, 1H).

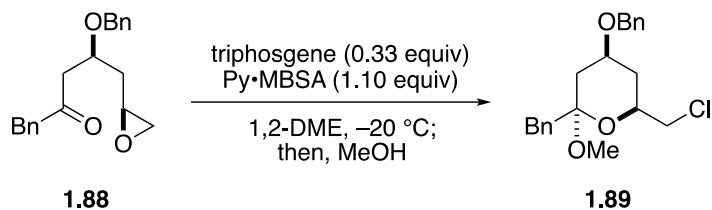
¹³C NMR (126 MHz, CDCl₃) δ 206.4, 138.2, 133.8, 129.5, 128.8, 128.4, 127.8, 127.7, 127.1, 73.6, 72.2, 51.1, 49.3, 47.2, 47.2, 37.6

IR: *f* (cm⁻¹) = 2954, 2953, 2853, 1715, 1495, 1456, 1376, 1068, 1027, 848, 740, 700, 472.

HRMS (ESI-TOF) *m/z*: (*M*+*H*)⁺ = 311.16417 calculated for C₂₀H₂₃O₃; experimental 311.16347, (*M*+*K*)⁺ = 349.12005 calculated for C₂₀H₂₂KO₃; experimental 349.12086.

[*α*]_D²⁵ = +2.75 (c 1.0, CHCl₃)

(2*S*,4*S*,6*S*)-2-benzyl-4-(benzyloxy)-6-(chloromethyl)-2-methoxytetrahydro-2*H*-pyran (1.89)



Epoxyketone **1.88** (94 mg, 0.30 mmol) was combined with 1,2-DME (1.2 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to -20 °C for at least 10 minutes. Triphosgene (29 mg, 0.10 mmol) was added and the solution was stirred at -20 °C for another 5 minutes before Py•MBSA (89 mg, 0.33 mmol) was added. After stirring at -20 °C for 1 hour the reaction was determined to be complete by TLC analysis and quenched with MeOH (0.6 mL) while still at -20 °C. After 10 minutes saturated NaHCO₃ (5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted

with CH₂Cl₂ (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 2% gradient of EtOAc in hexanes affording **1.89** as a white solid in 56% yield as a single diastereomer (61 mg, 0.17 mmol).

Rf: 0.55 in 70:30 (Hexanes:EtOAc)

¹H NMR (500 MHz, CDCl₃) δ 7.32 – 7.27 (m, 6H), 7.26 – 7.22 (m, 4H), 4.48 (d, *J* = 11.6 Hz, 1H), 4.45 (d, *J* = 11.6 Hz, 1H), 3.87 – 3.77 (m, 2H), 3.60 (dd, *J* = 11.3, 6.5 Hz, 1H), 3.55 (dd, *J* = 11.3, 4.7 Hz, 1H), 3.37 (s, 3H), 3.02 (d, *J* = 14.1 Hz, 1H), 2.94 (d, *J* = 14.1 Hz, 1H), 2.11 (dt, *J* = 12.1, 2.1 Hz, 1H), 1.99 – 1.95 (m, 1H), 1.31 – 1.26 (m, 2H), 1.23 – 1.16 (m, 1H).

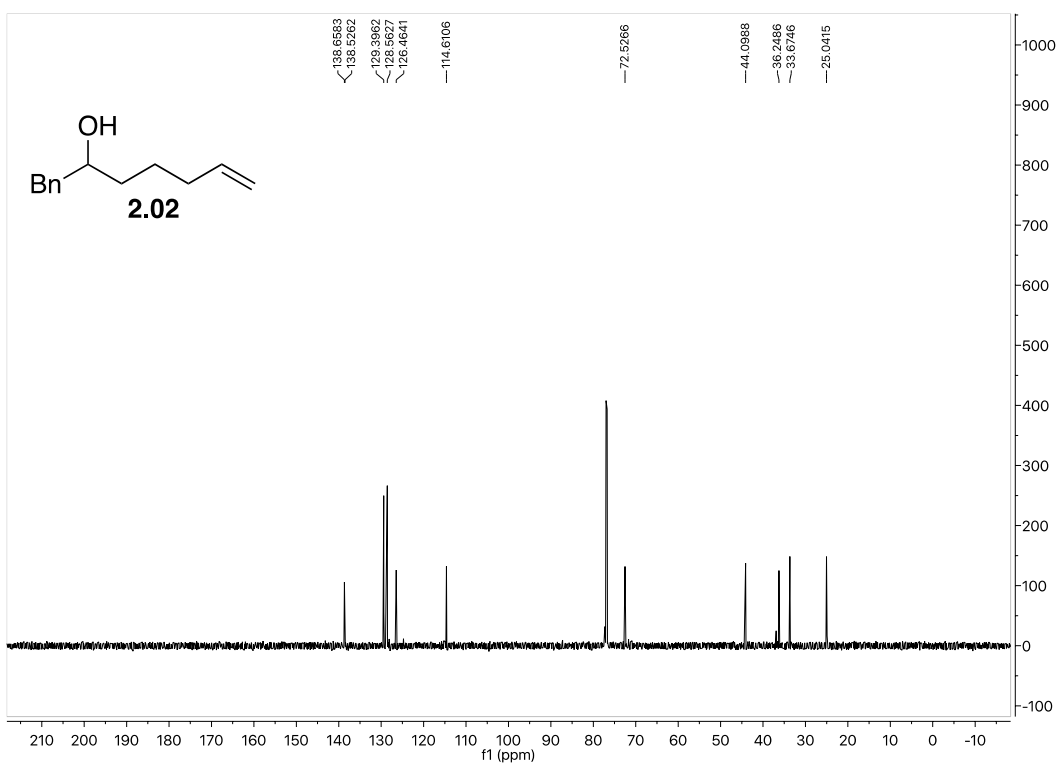
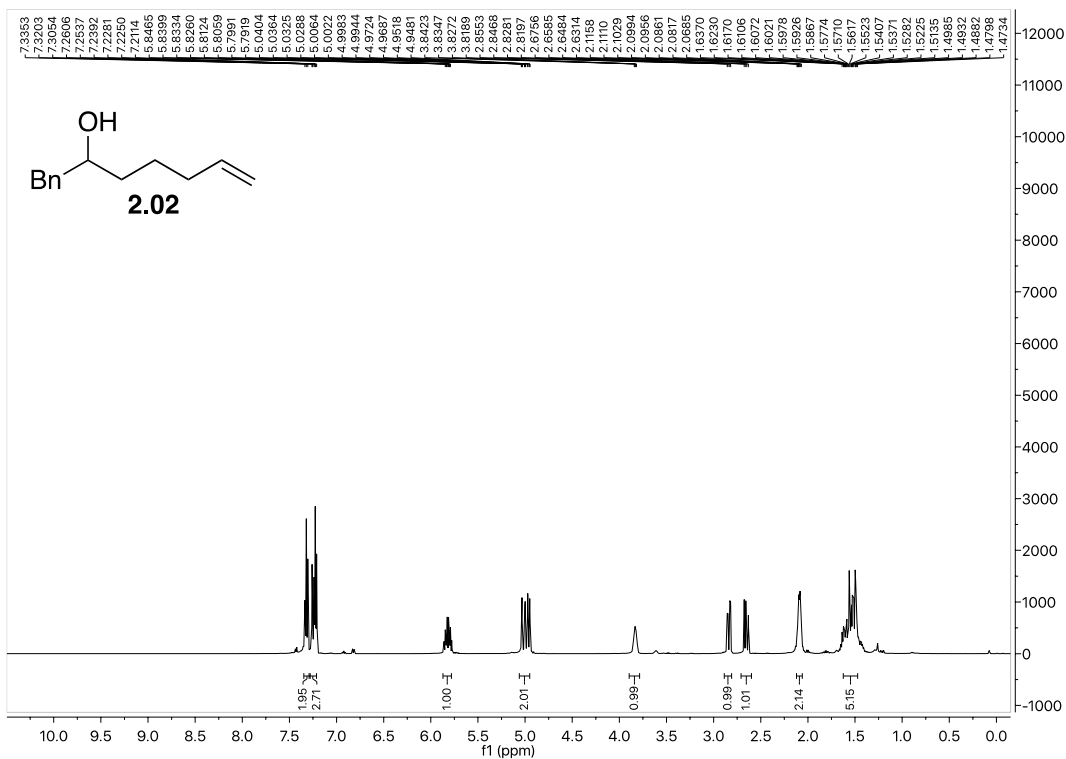
¹³C NMR (126 MHz, CDCl₃) δ 138.5, 136.2, 130.3, 128.4, 128.2, 128.1, 127.6, 126.5, 101.7, 71.7, 70.1, 69.5, 47.8, 47.3, 42.0, 38.8, 34.8.

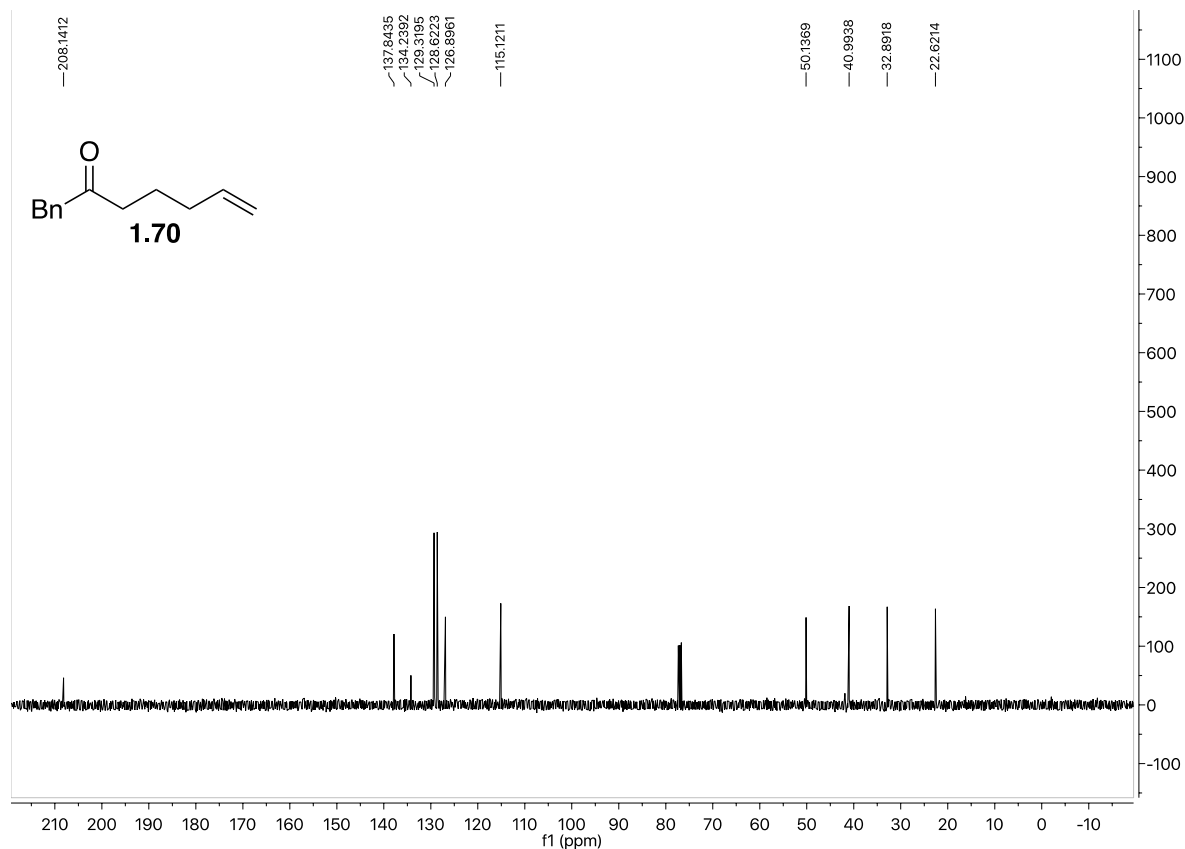
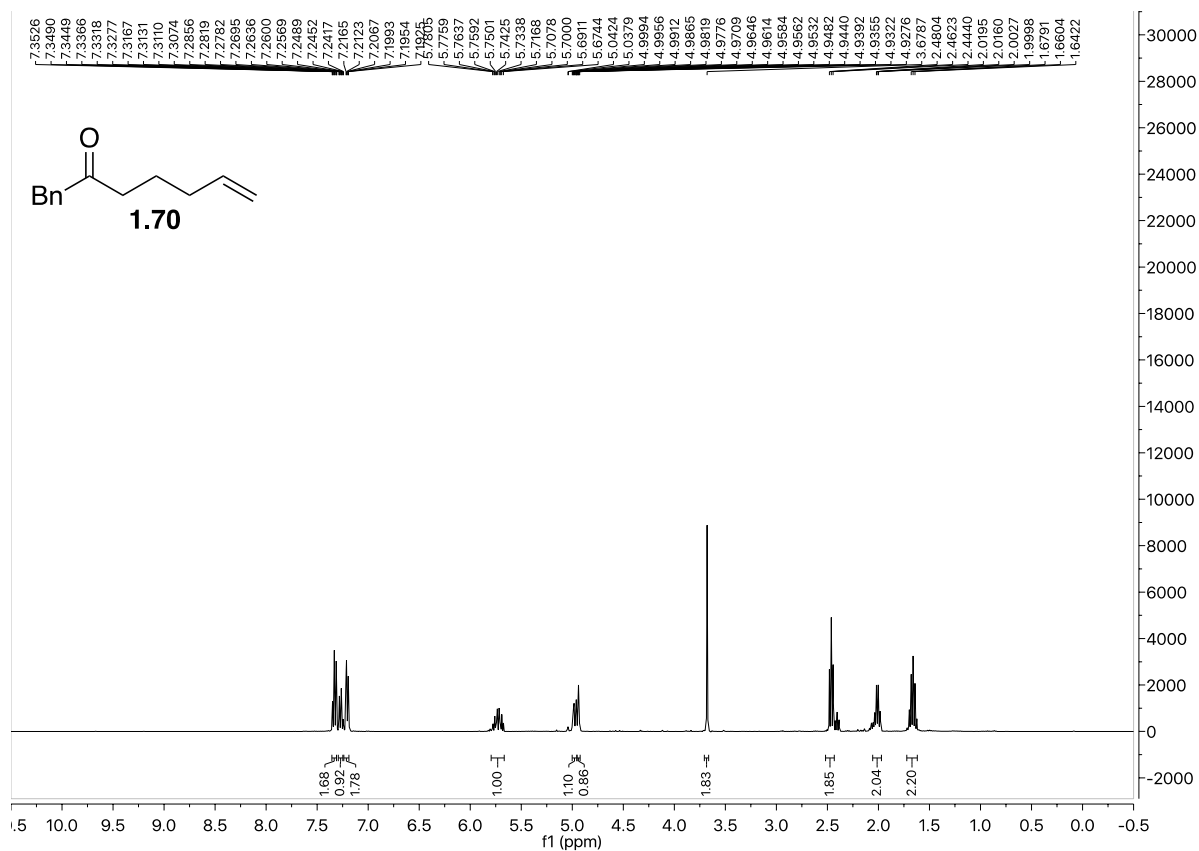
IR: *f* (cm⁻¹) = 3029, 2926, 1719, 1496, 1453, 1357, 1209, 1153, 1113, 1037, 983, 738, 699, 468.

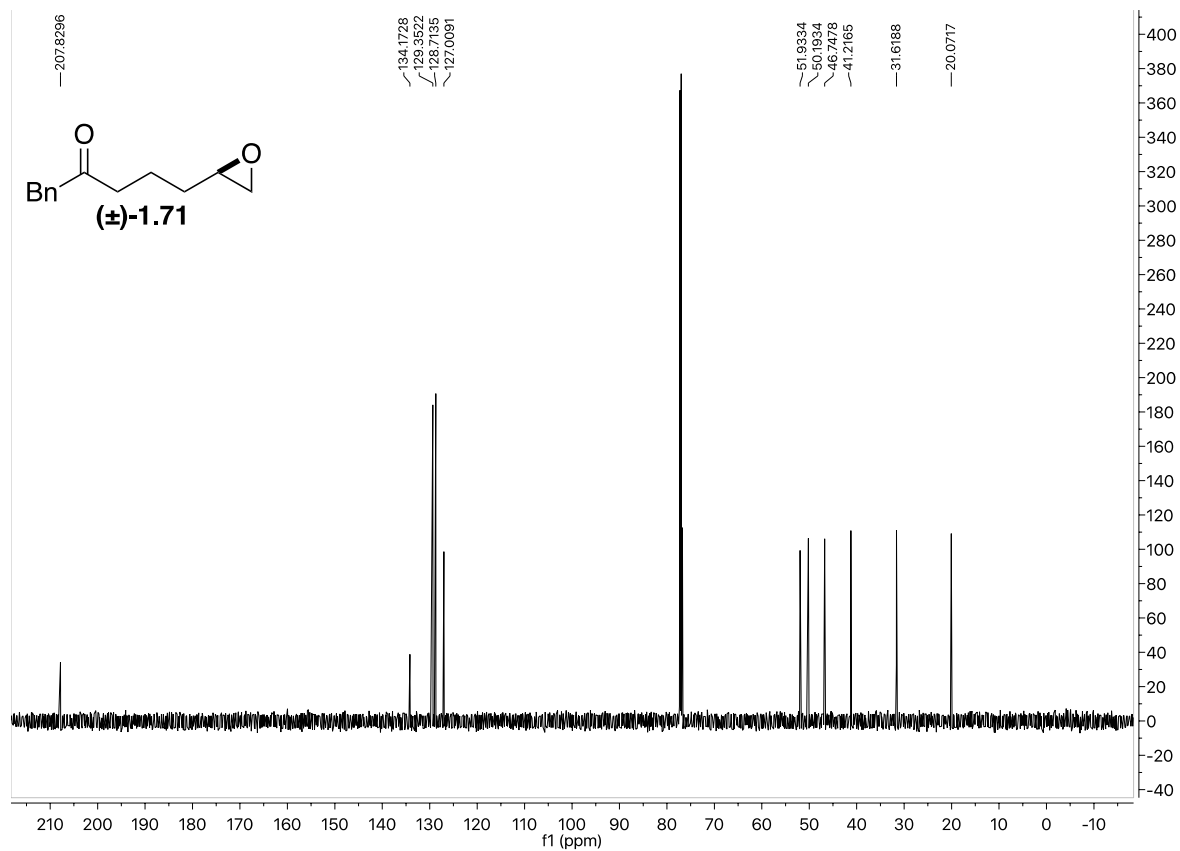
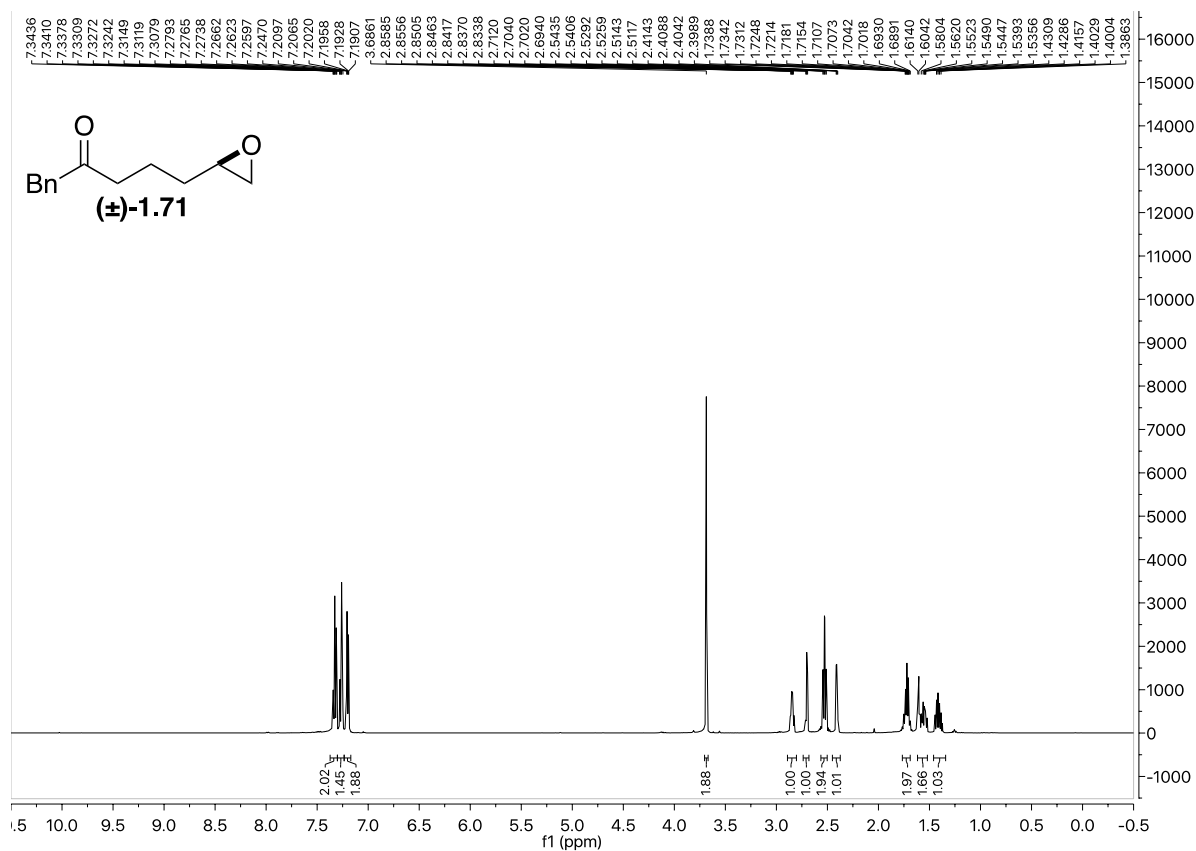
HRMS (ESI-TOF) *m/z*: (M+Na)⁺ = 383.13844 calculated for C₂₁H₂₅ClNaO₃; experimental 383.13800, (M+K)⁺ = 399.11238 calculated for C₂₁H₂₅ClKO₃; experimental 399.11259, ((M-MeOH)+H)⁺ = 329.13028 calculated for C₂₀H₂₂ClO₂; experimental 329.12948.

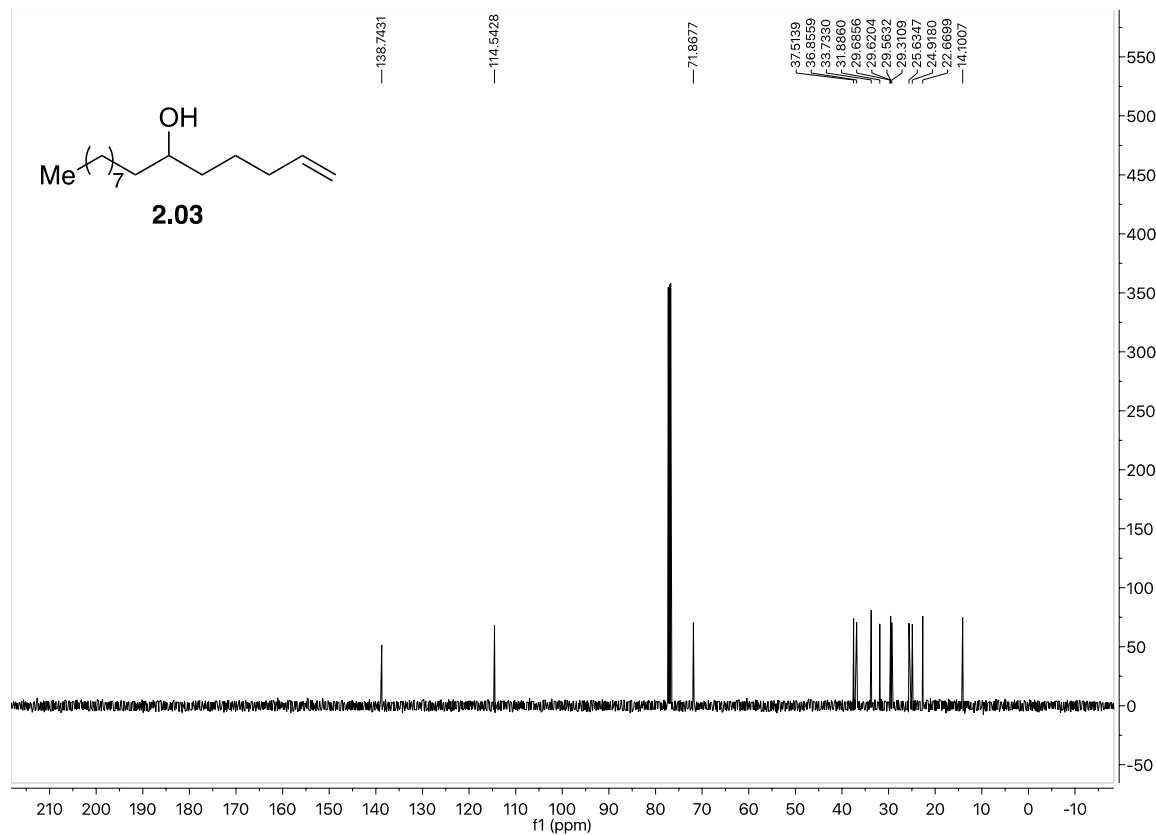
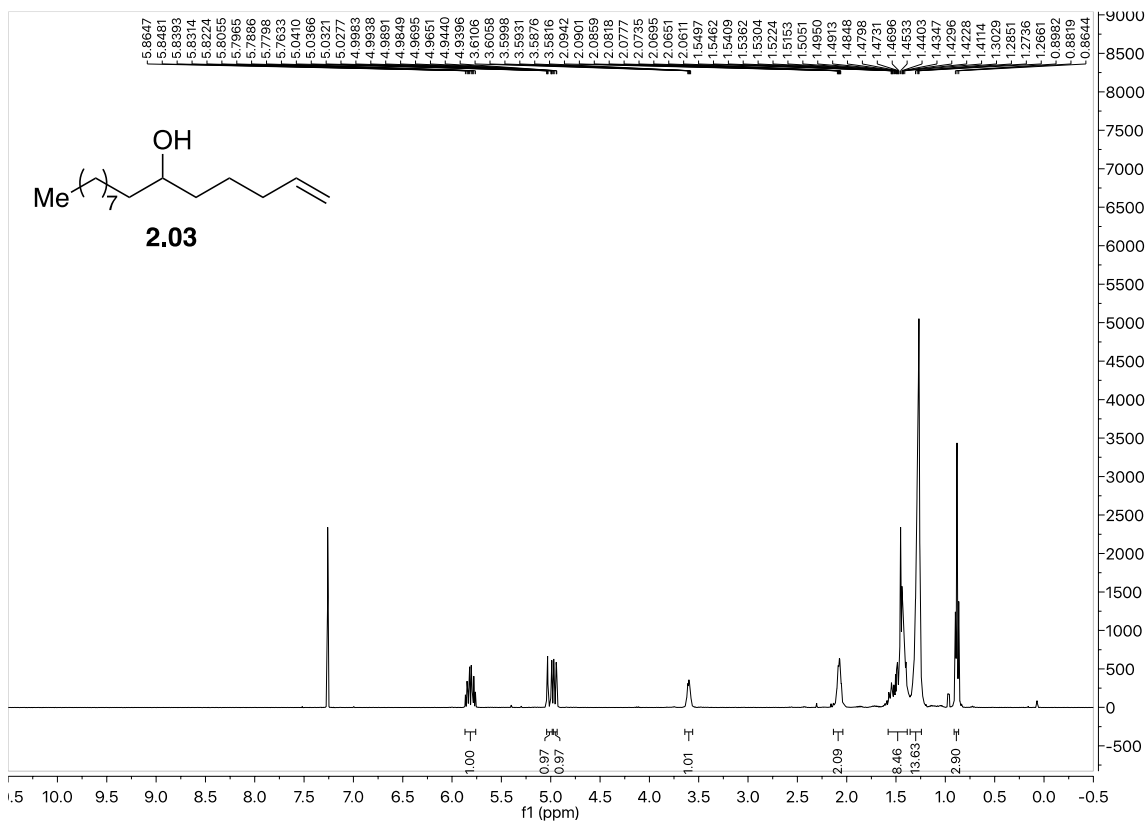
[α]²⁵_D = +21.9 (c 1.0, CHCl₃)

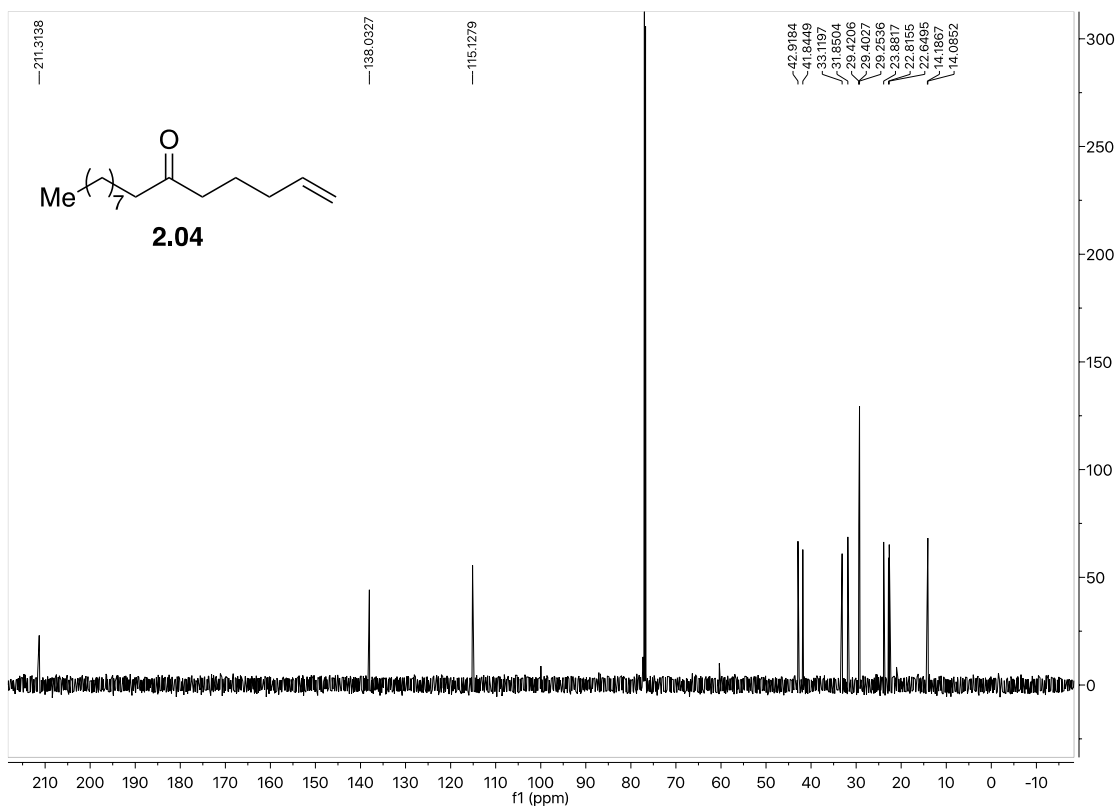
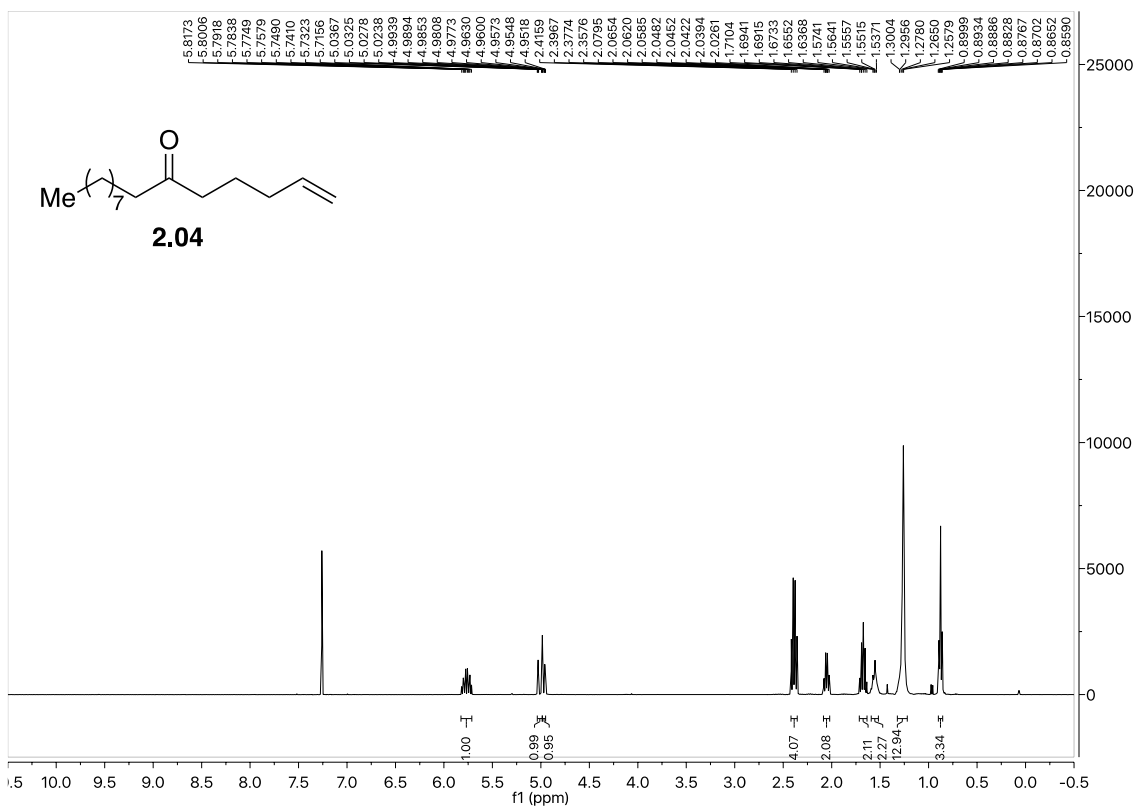
Appendix A. ^1H and ^{13}C NMR Spectra

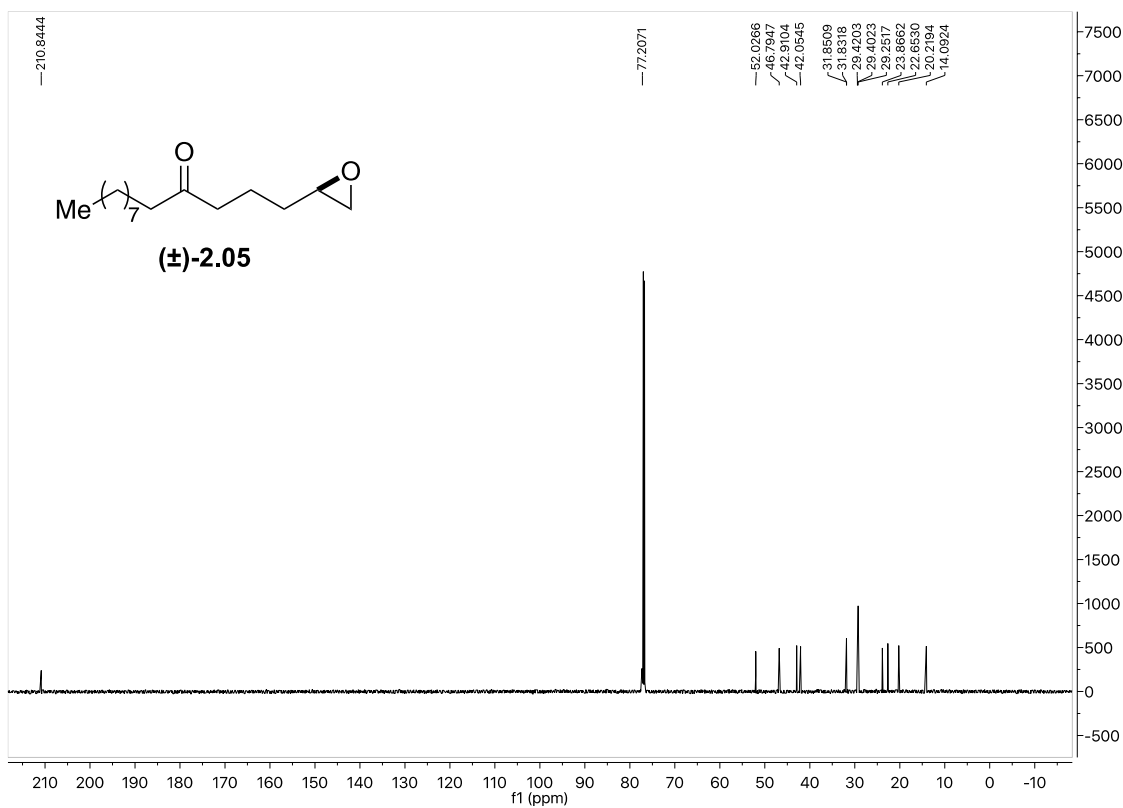
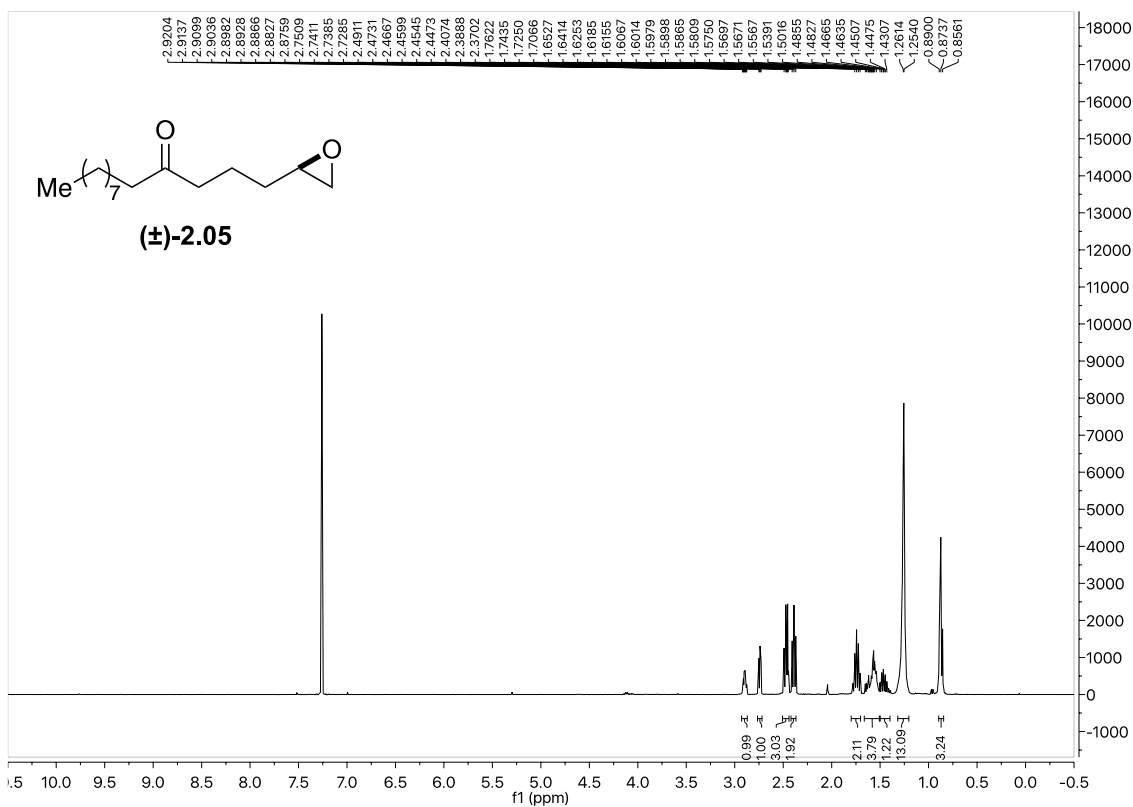


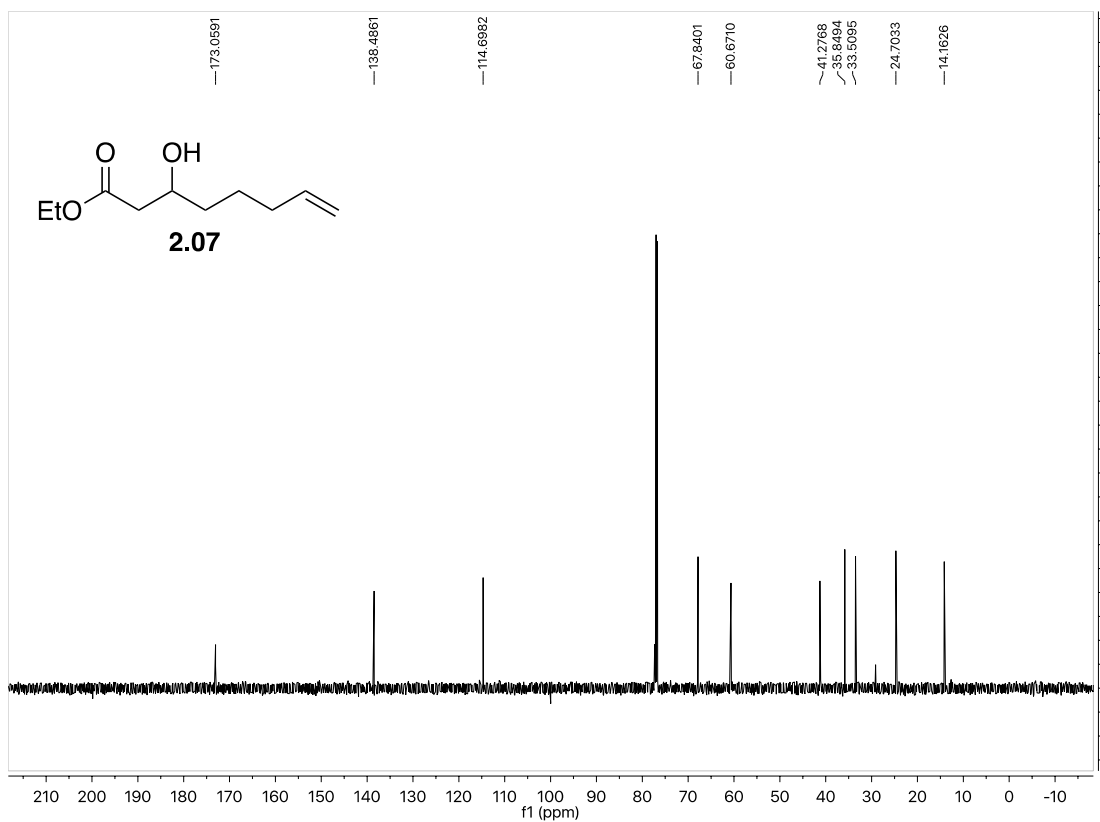
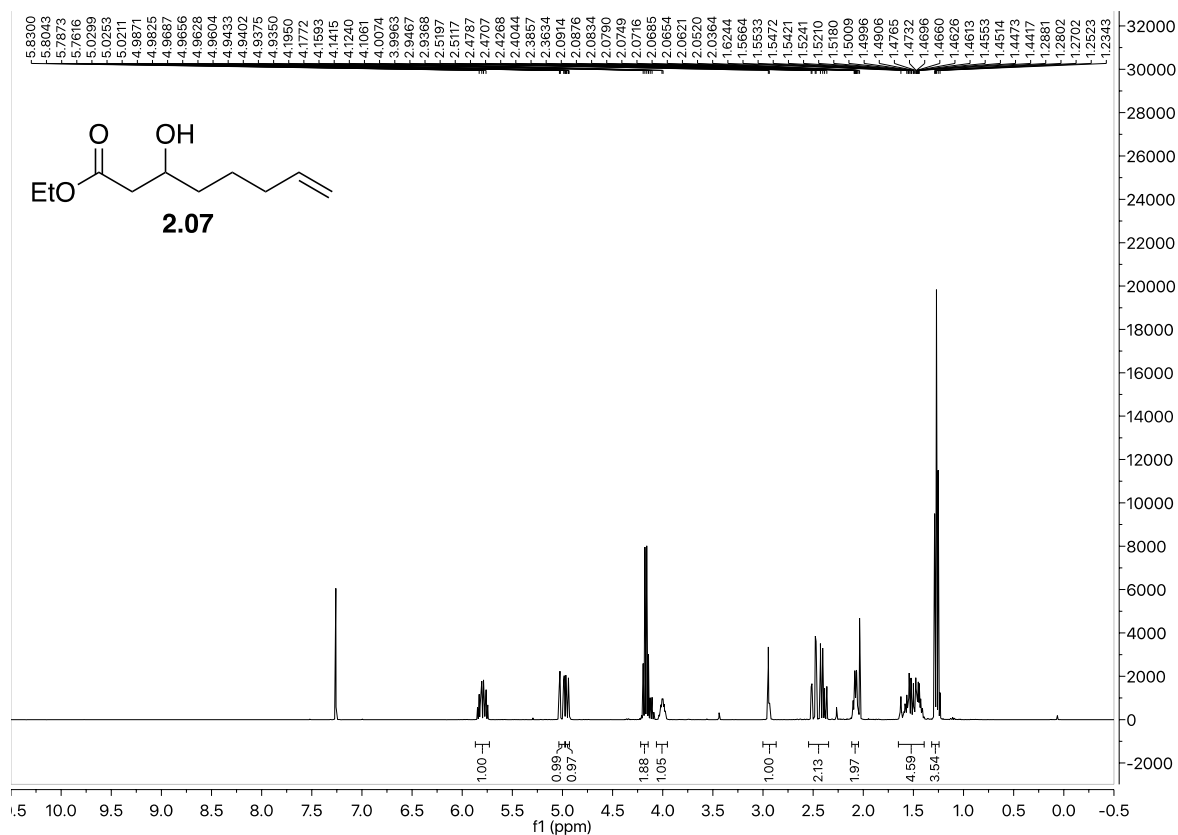


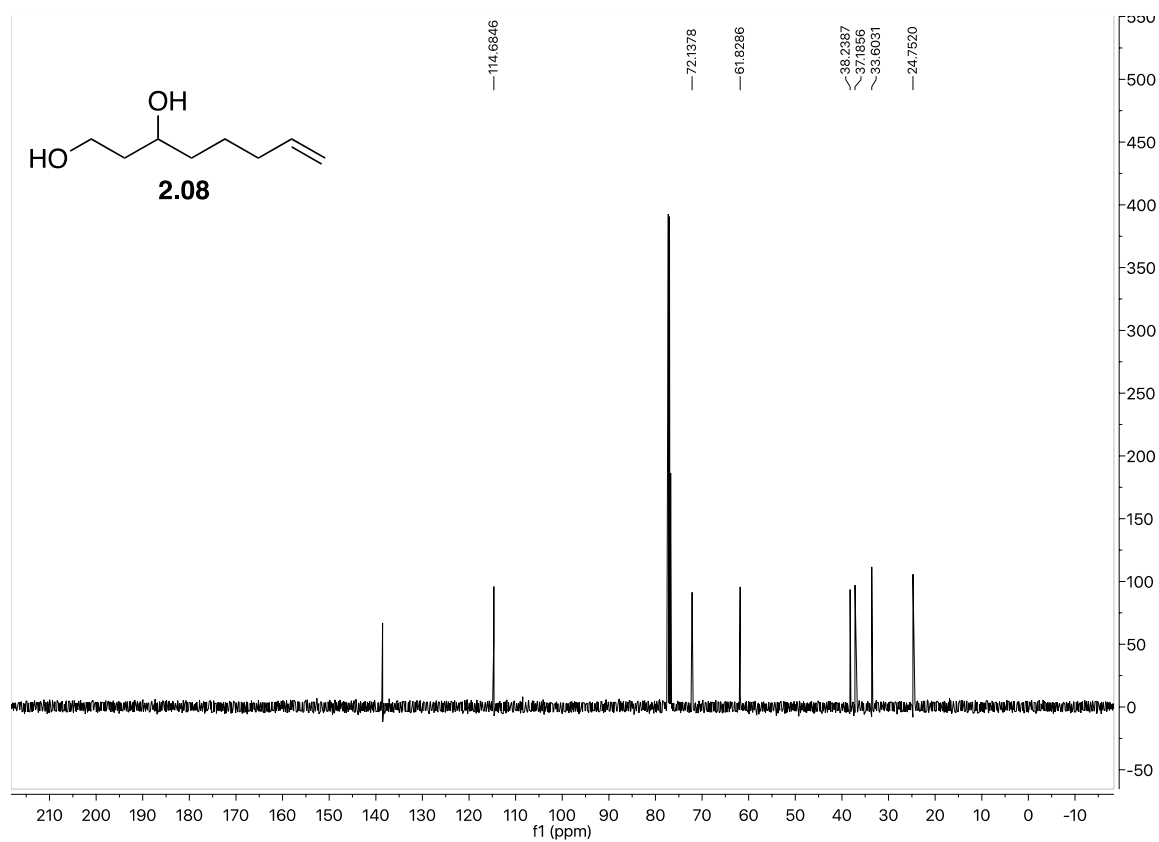
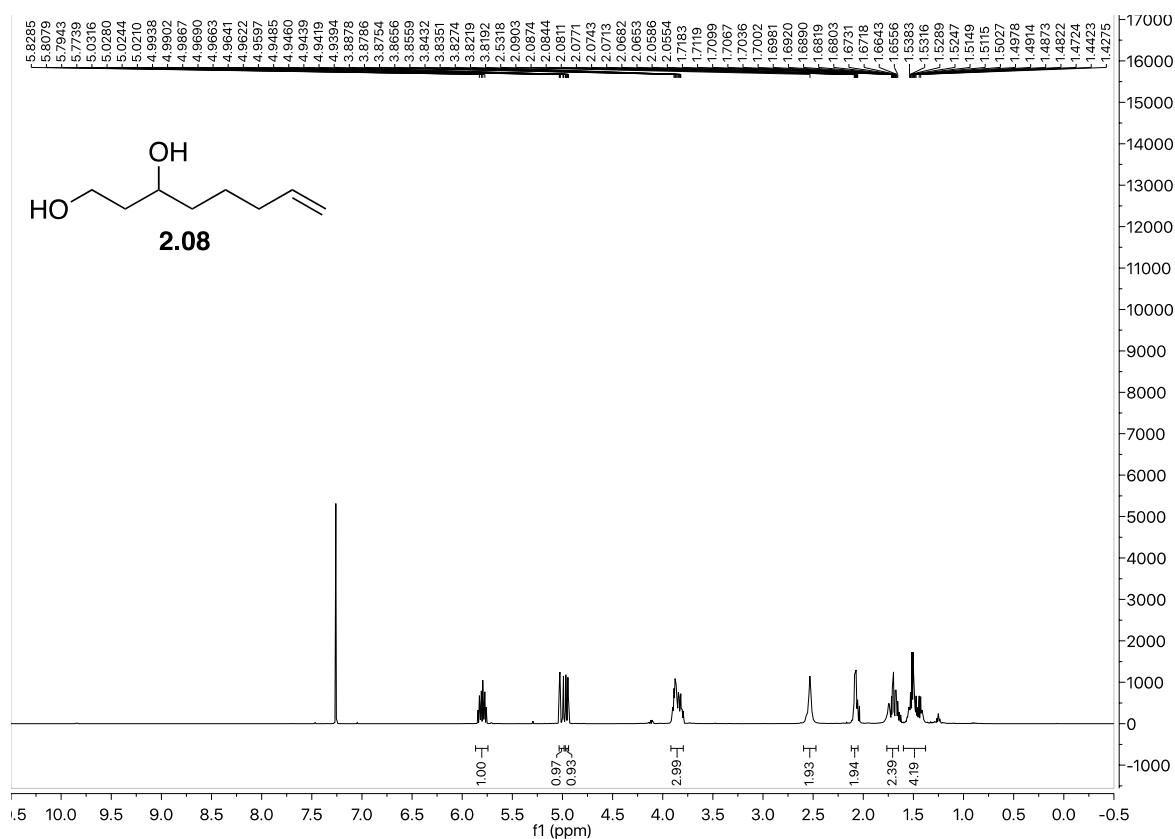


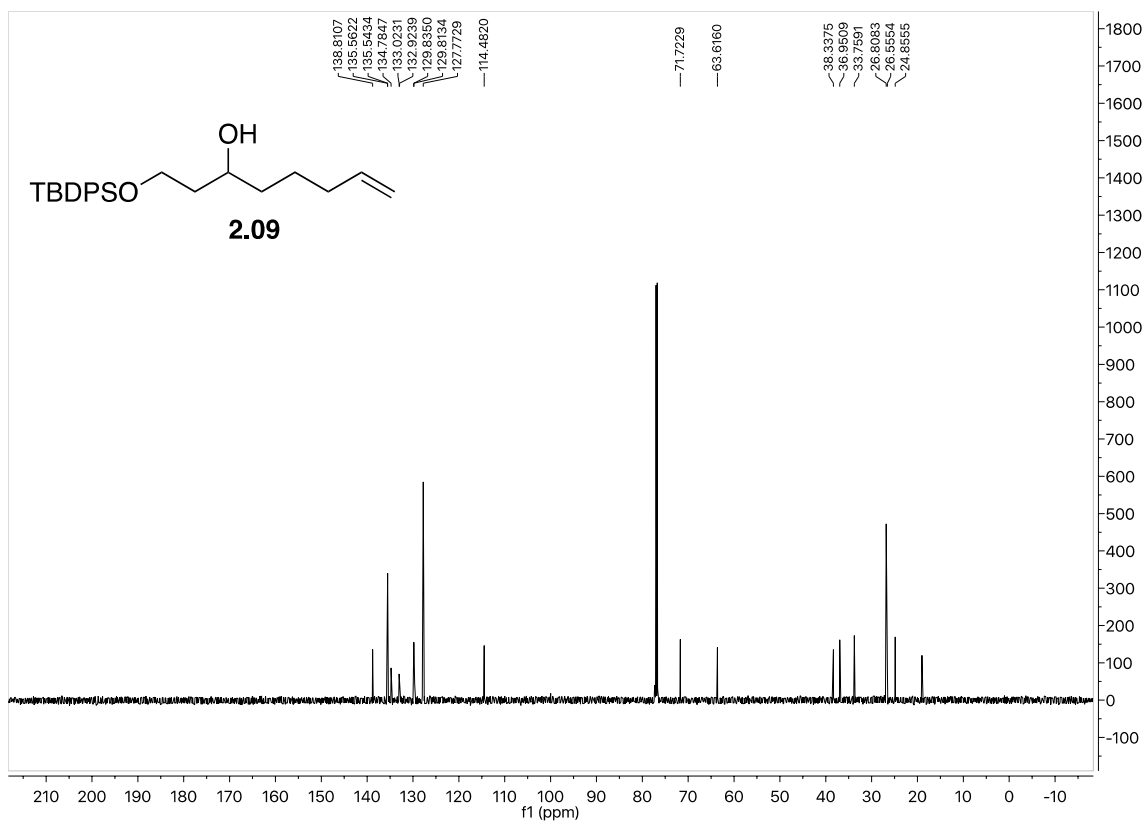
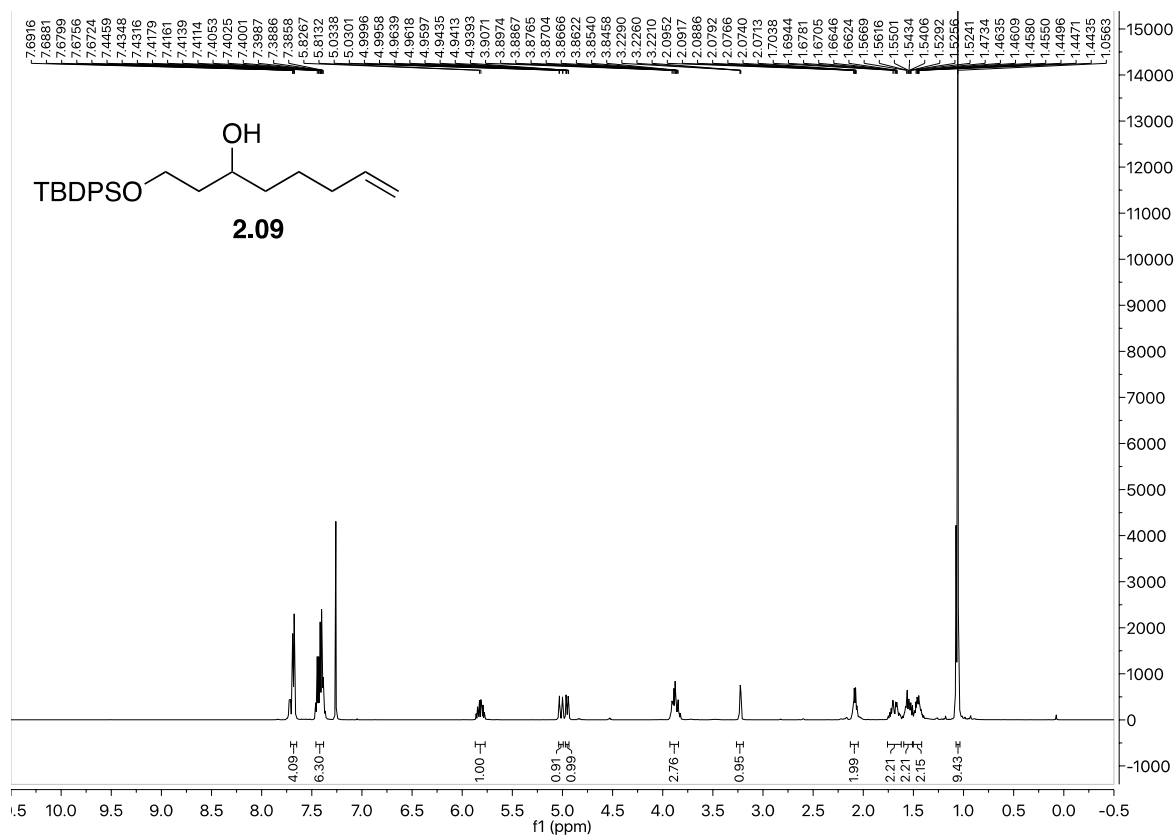


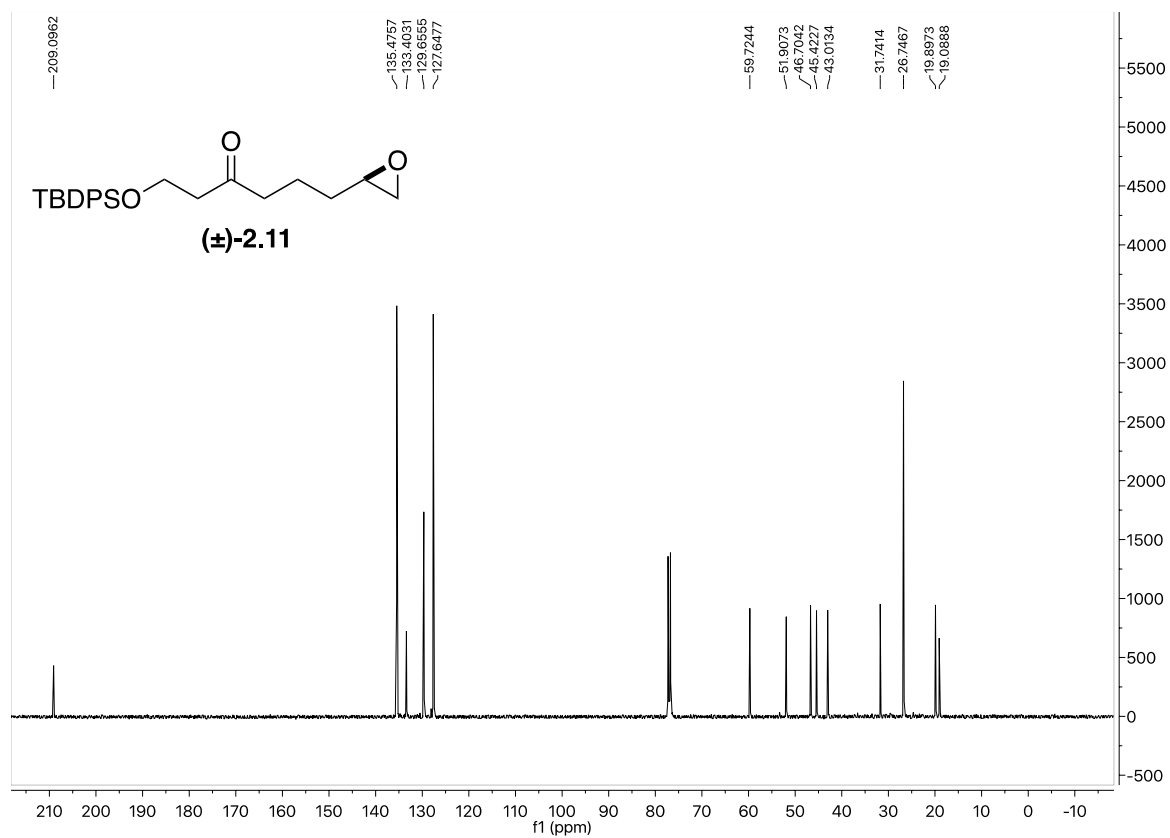
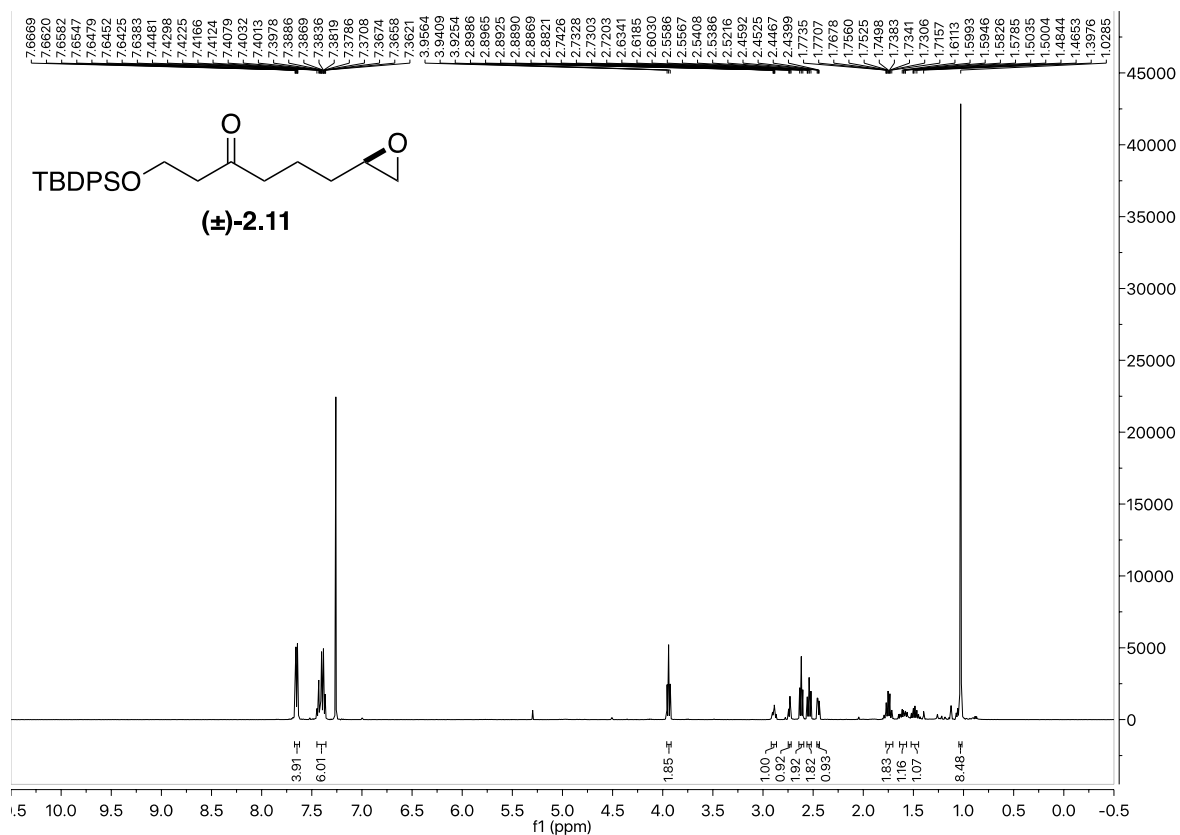


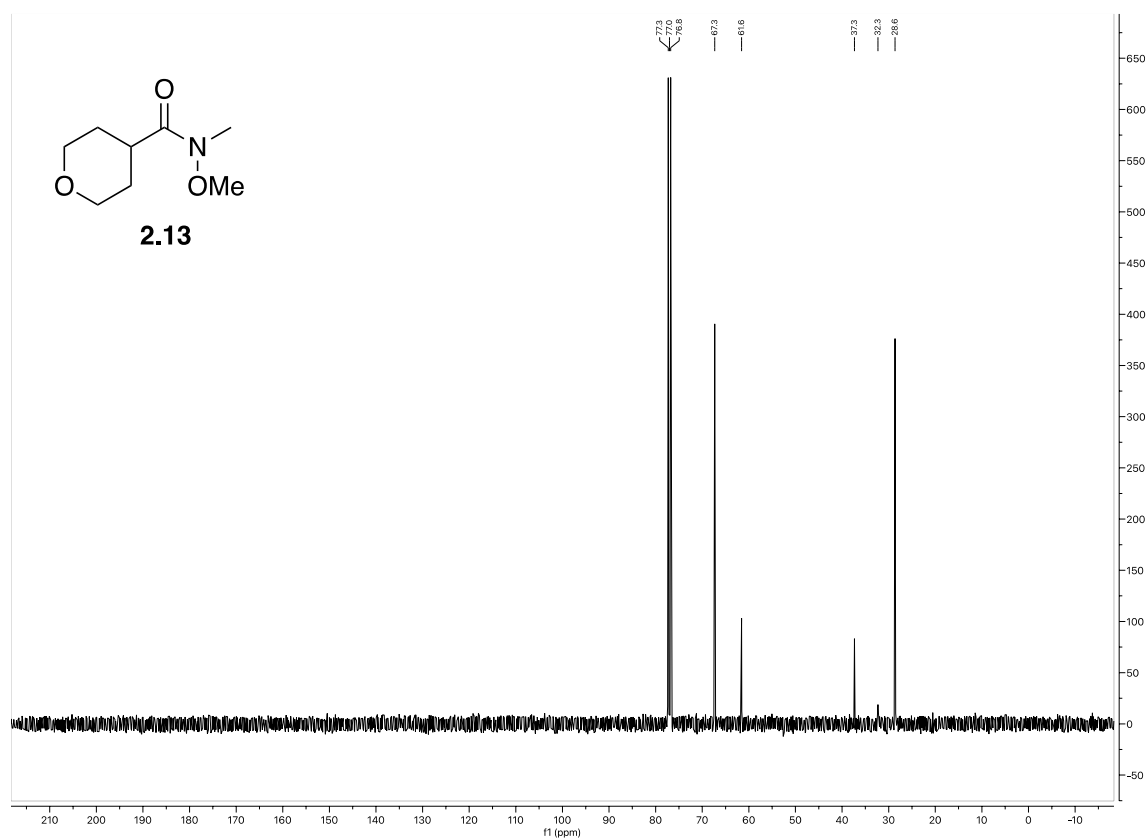
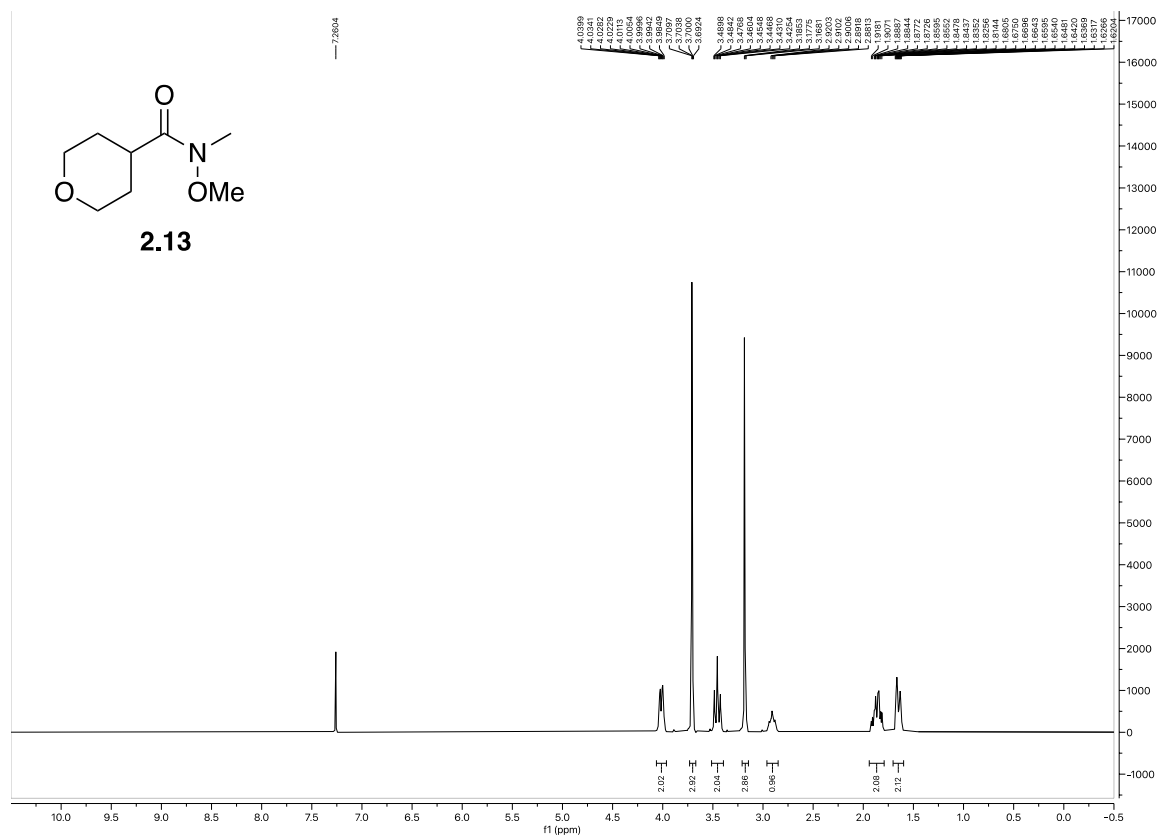


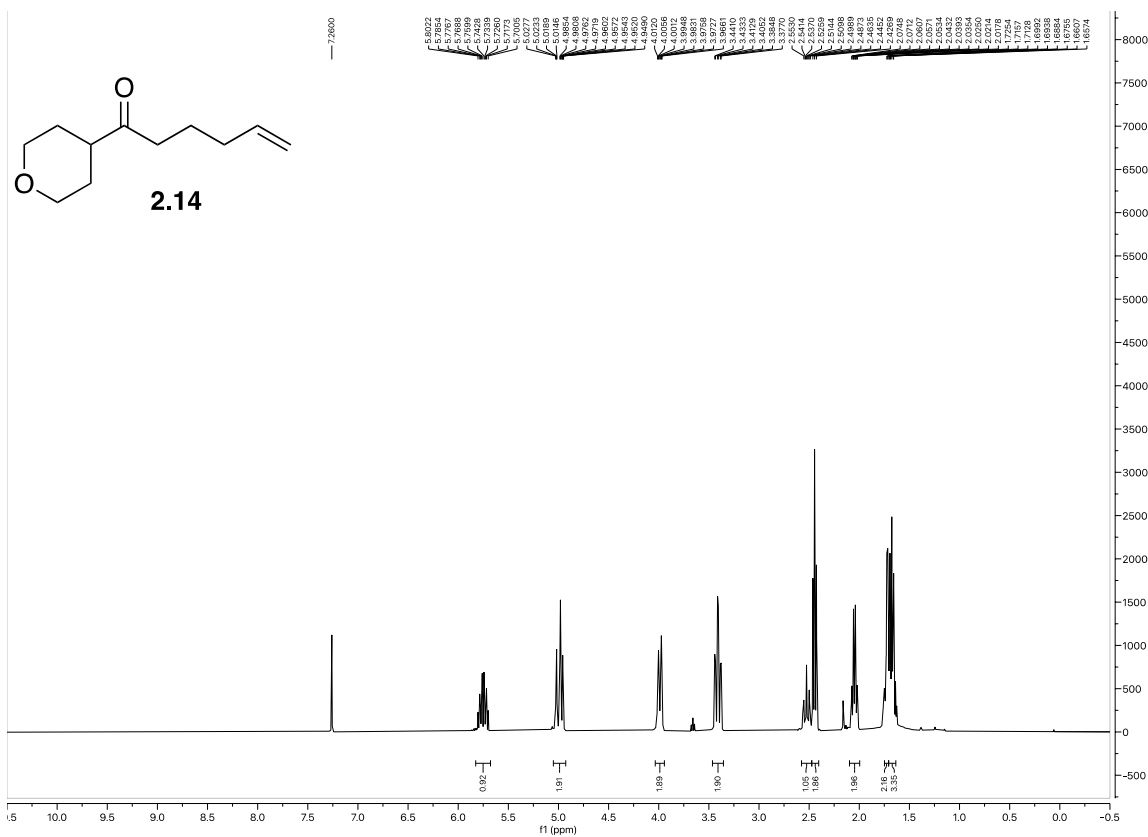


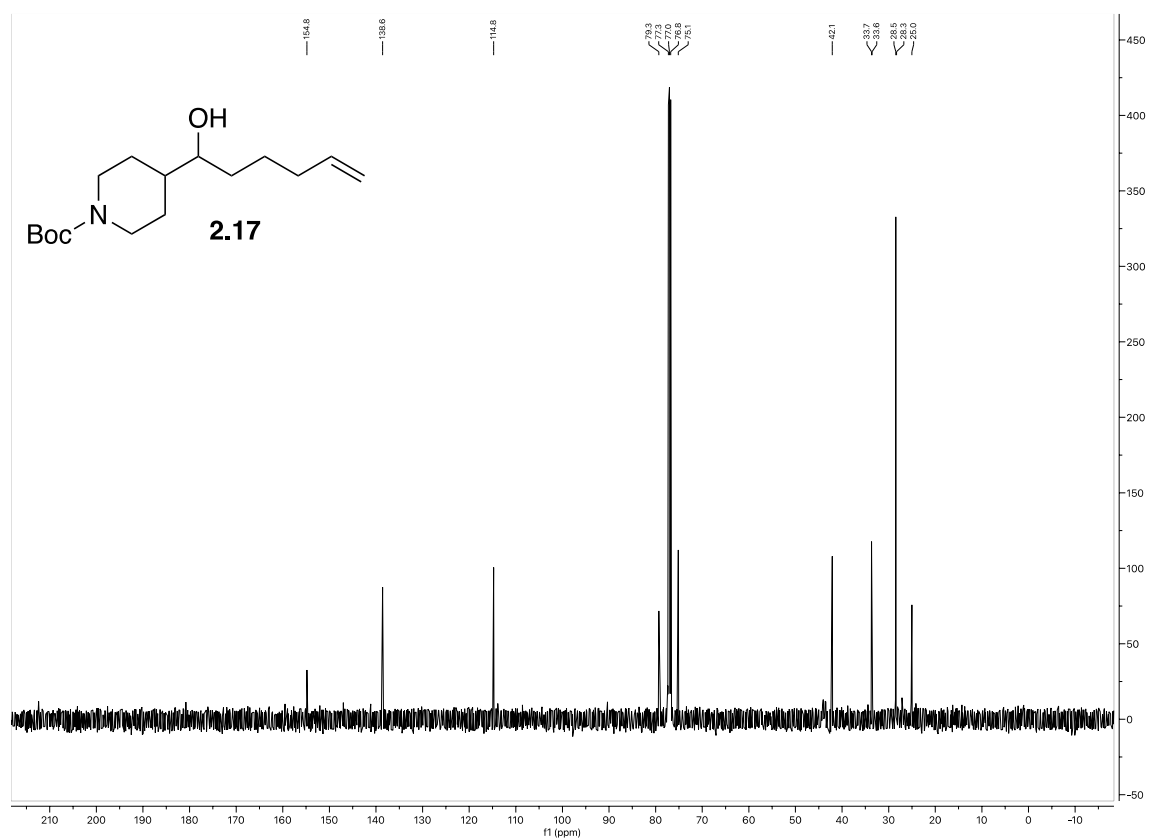
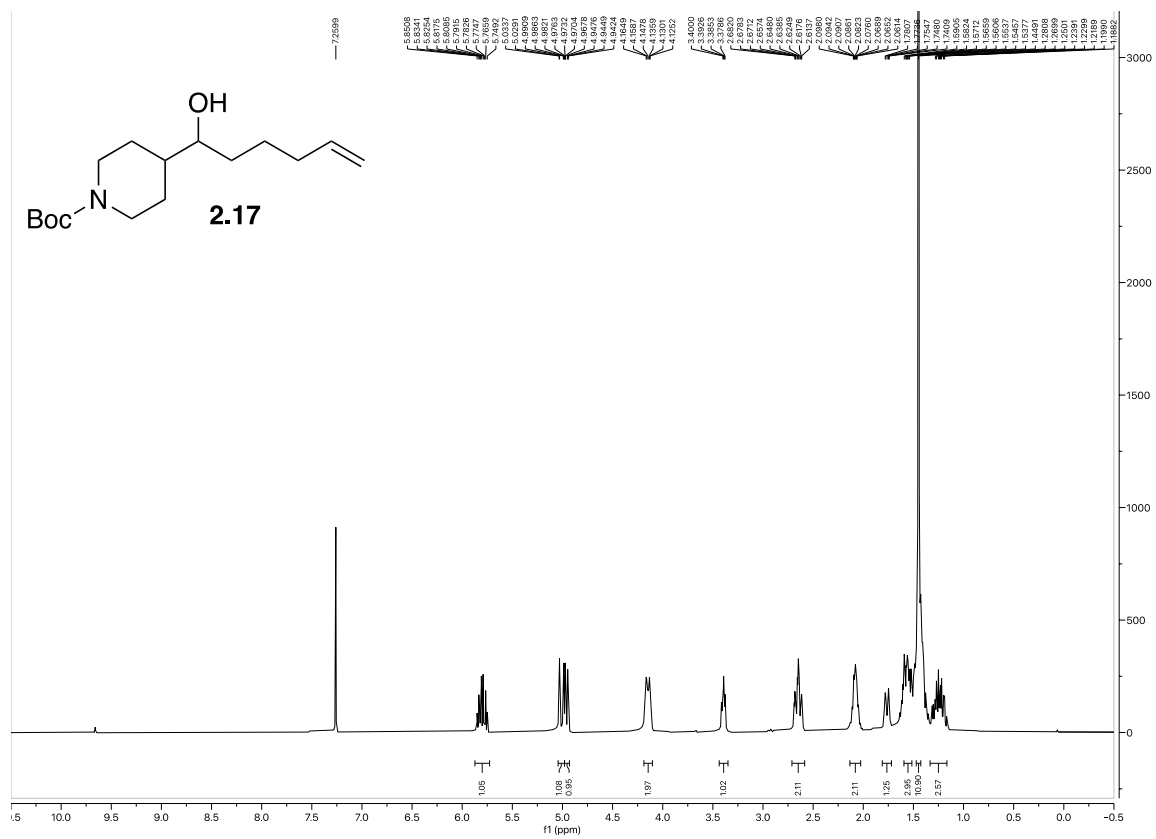


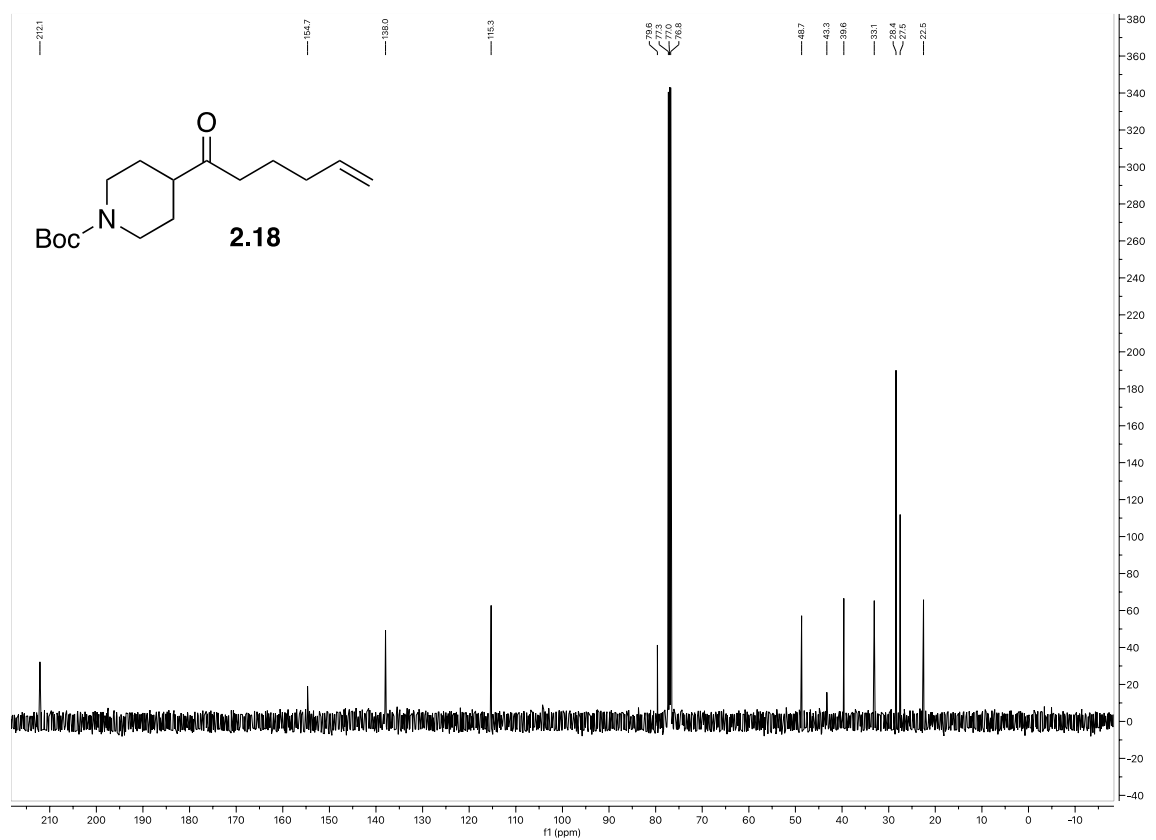
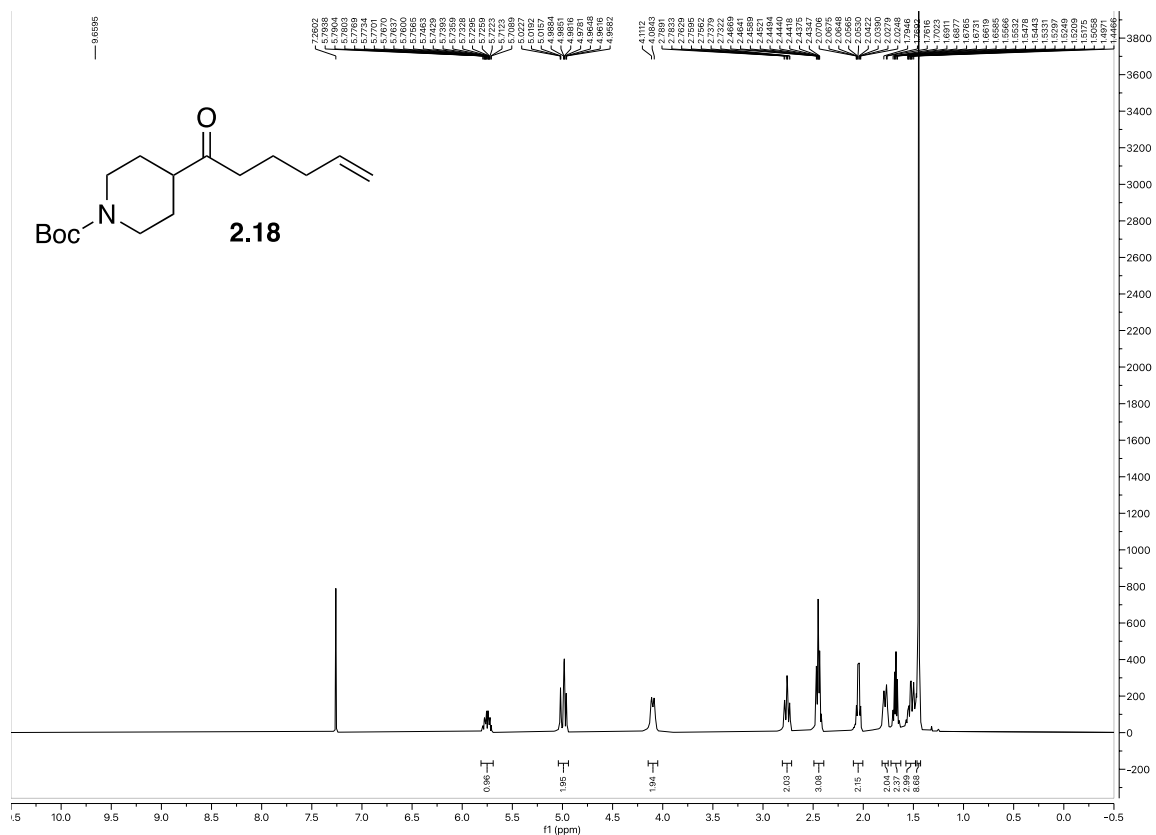


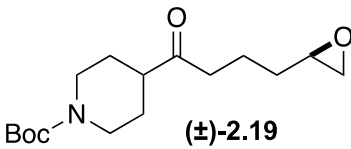
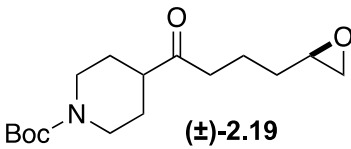


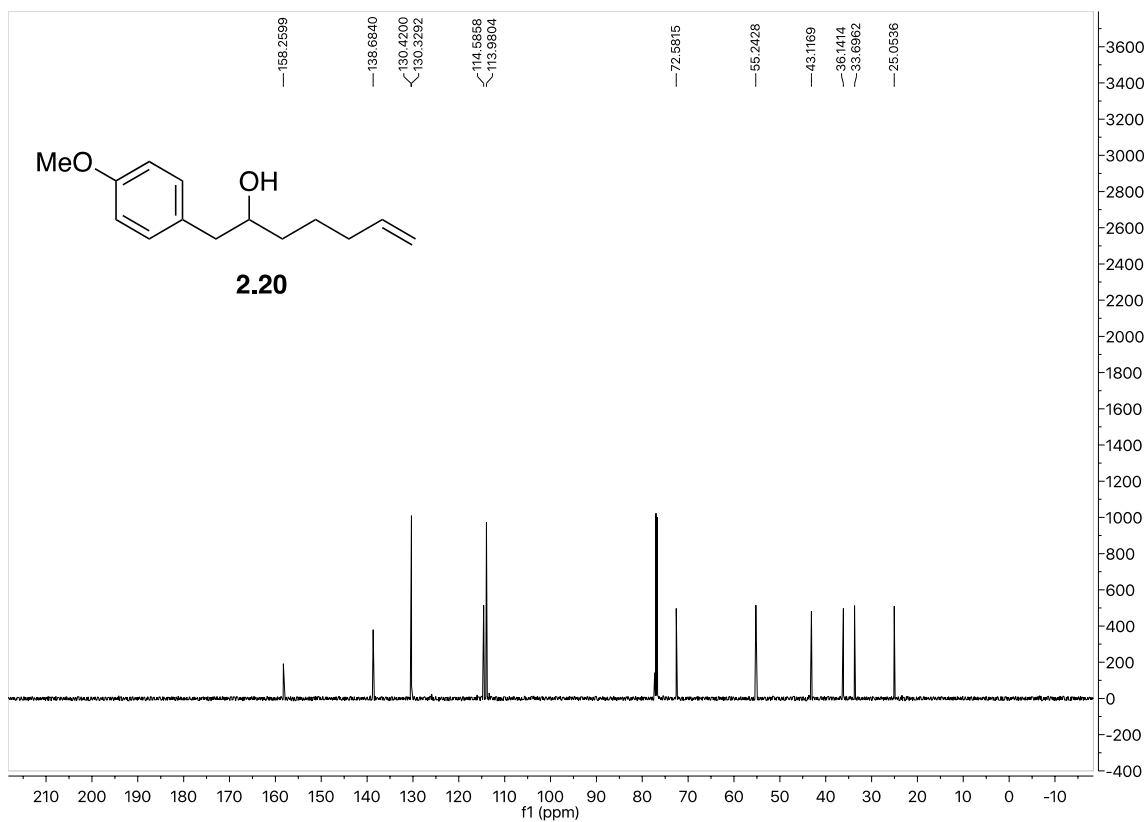
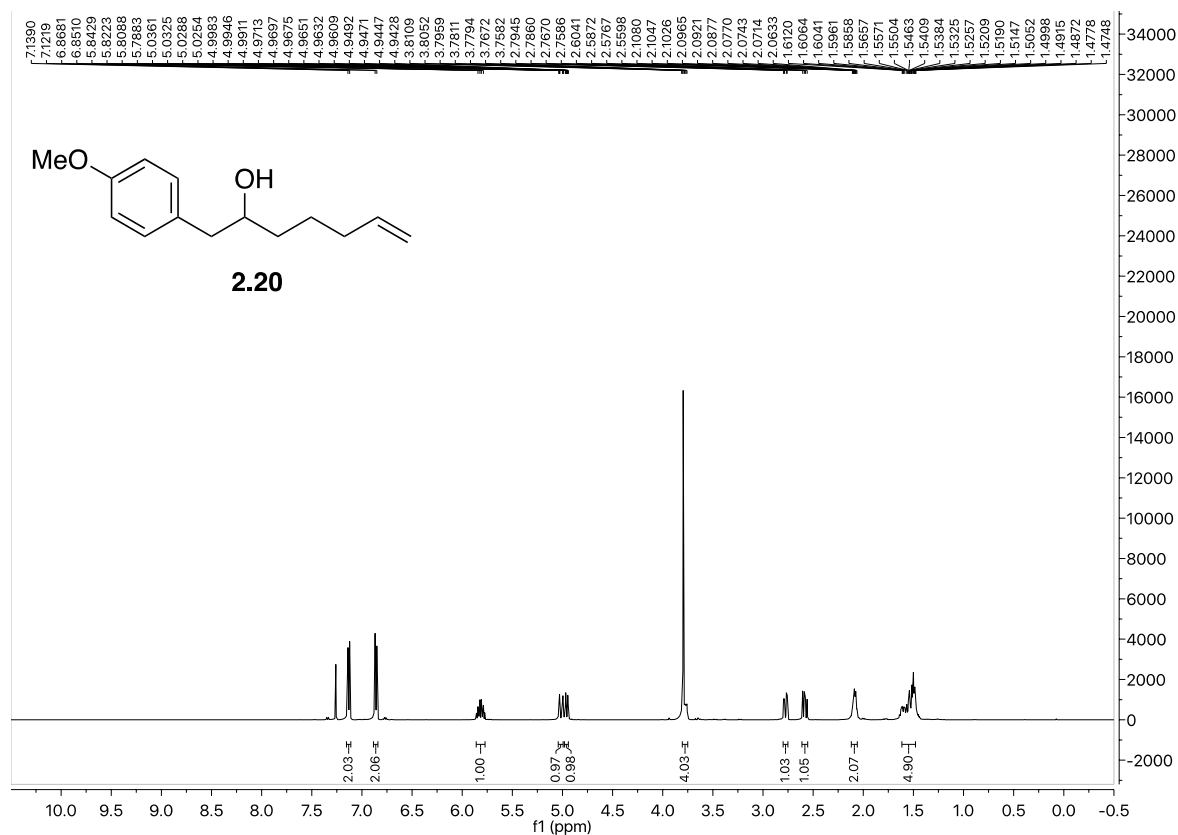


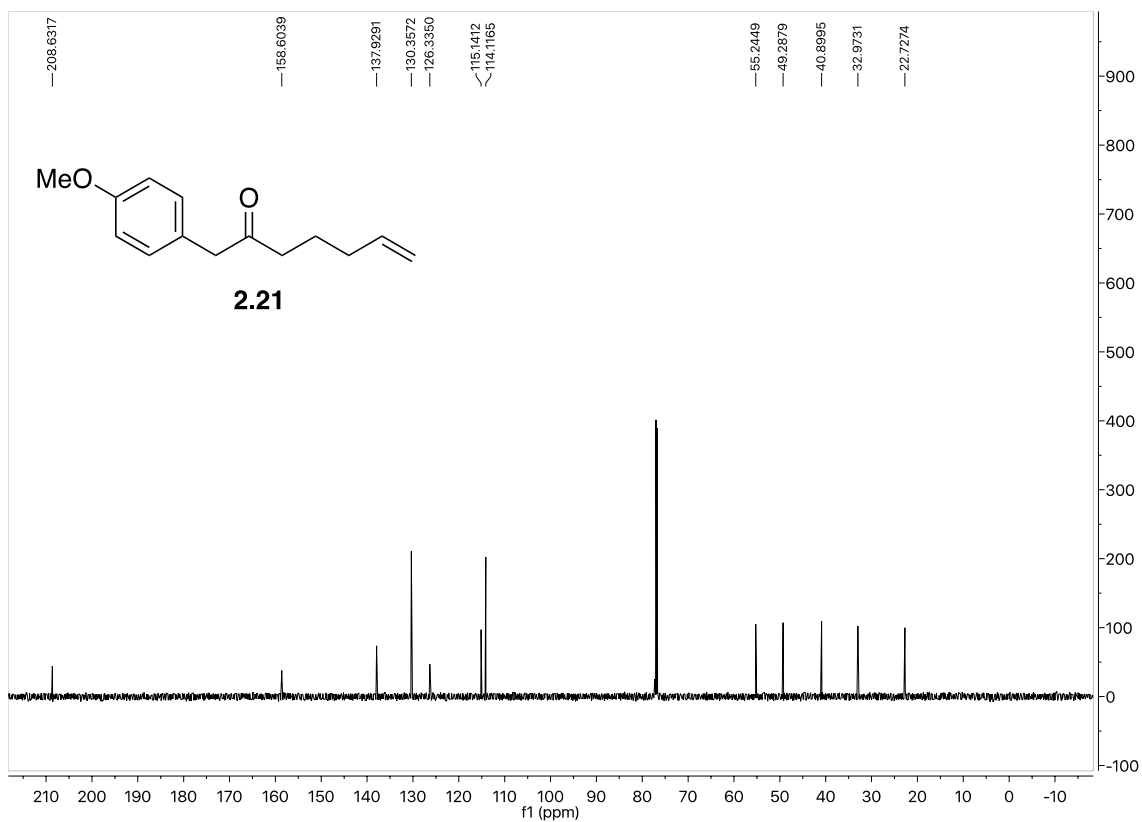
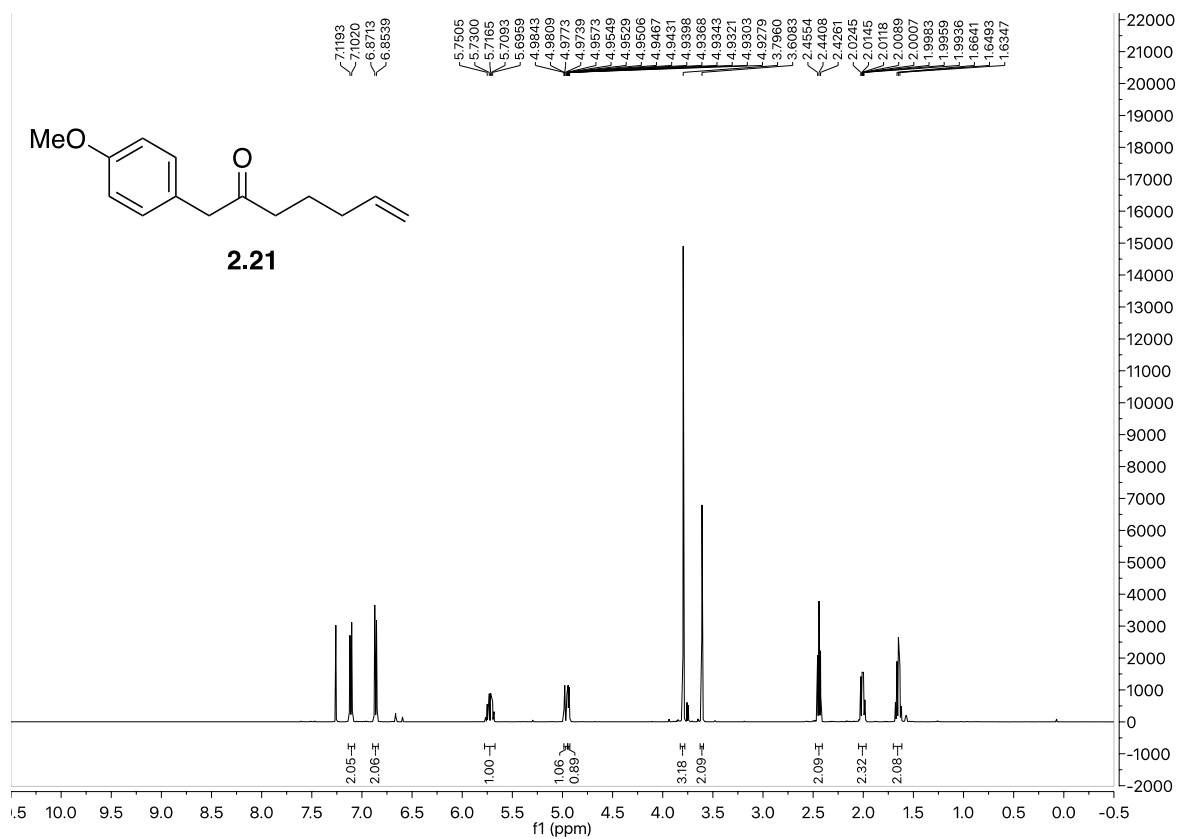


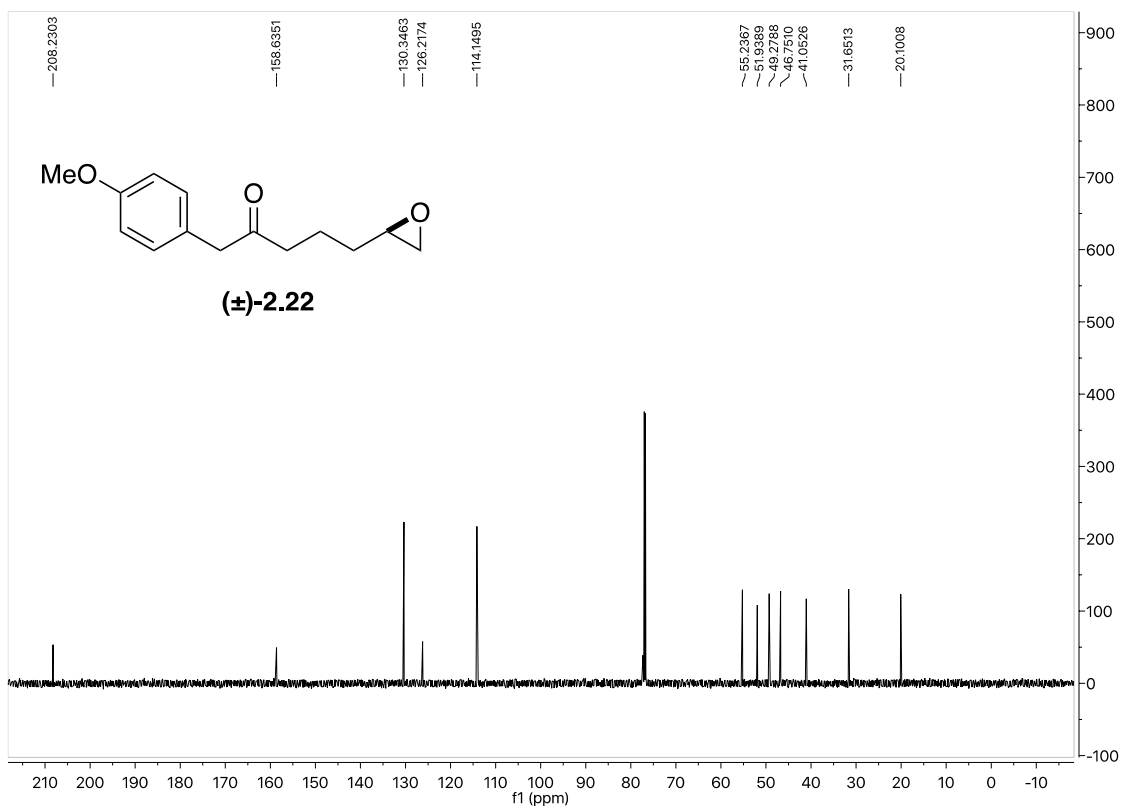
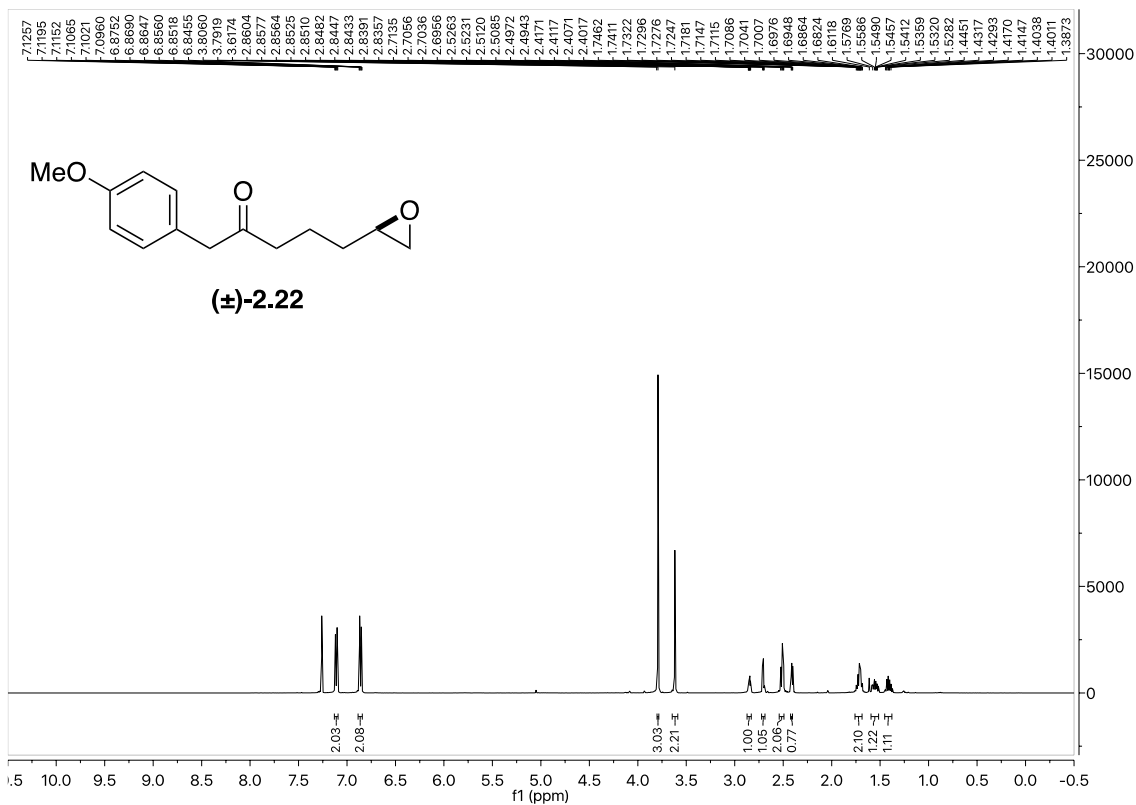


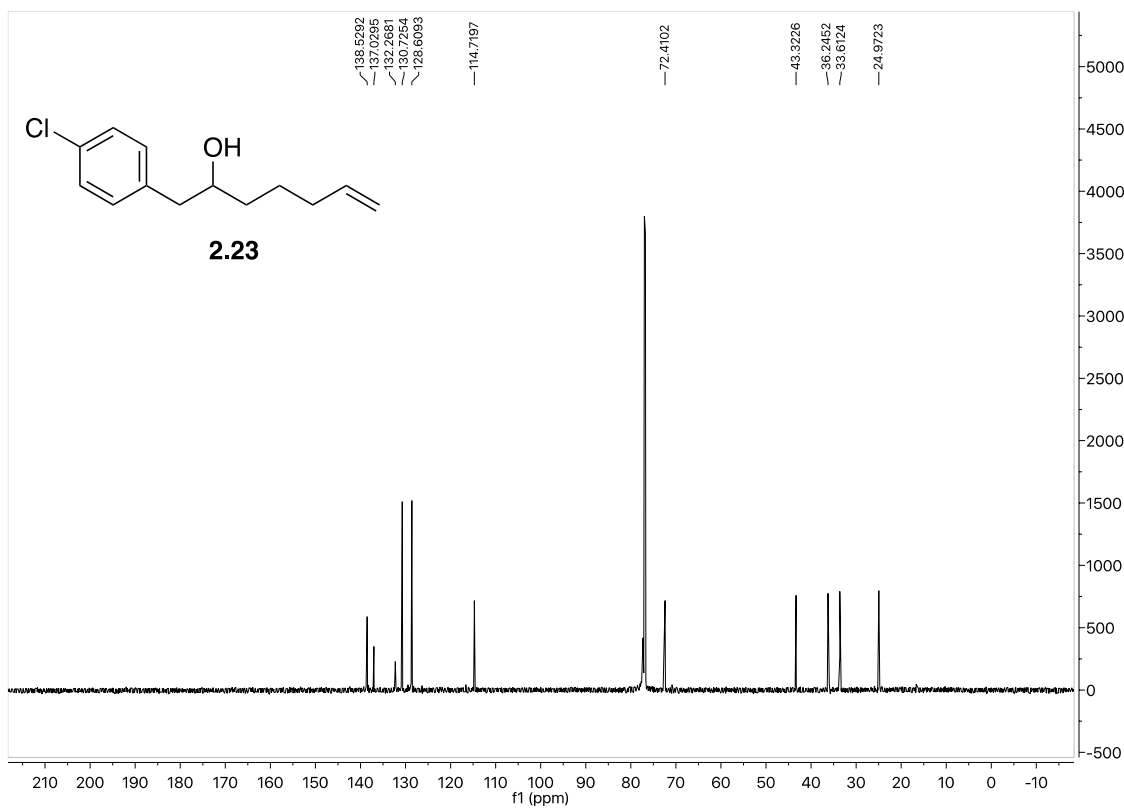
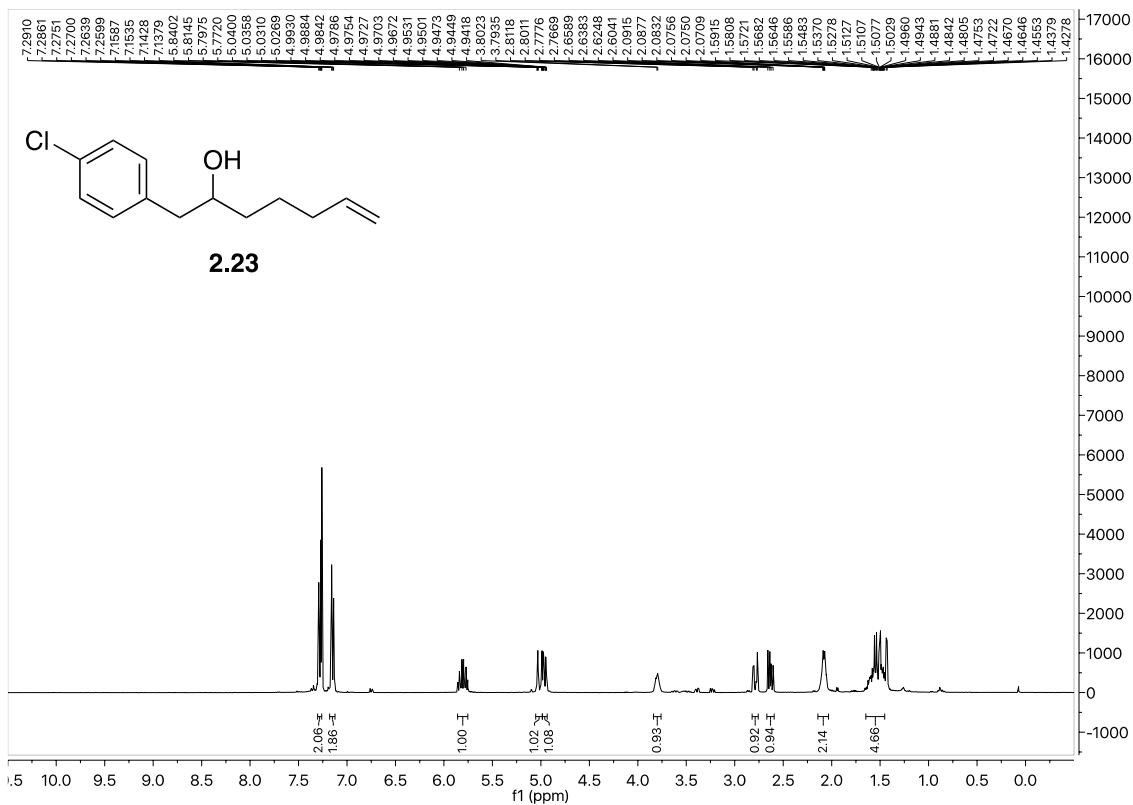


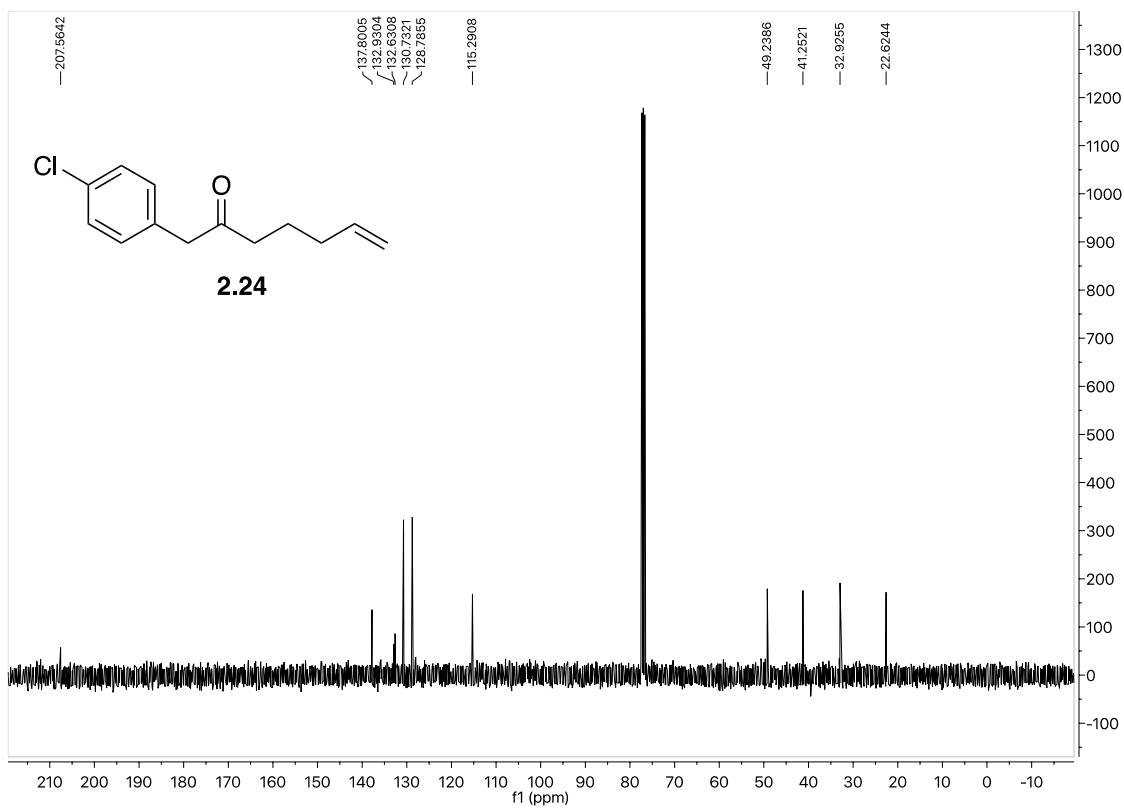
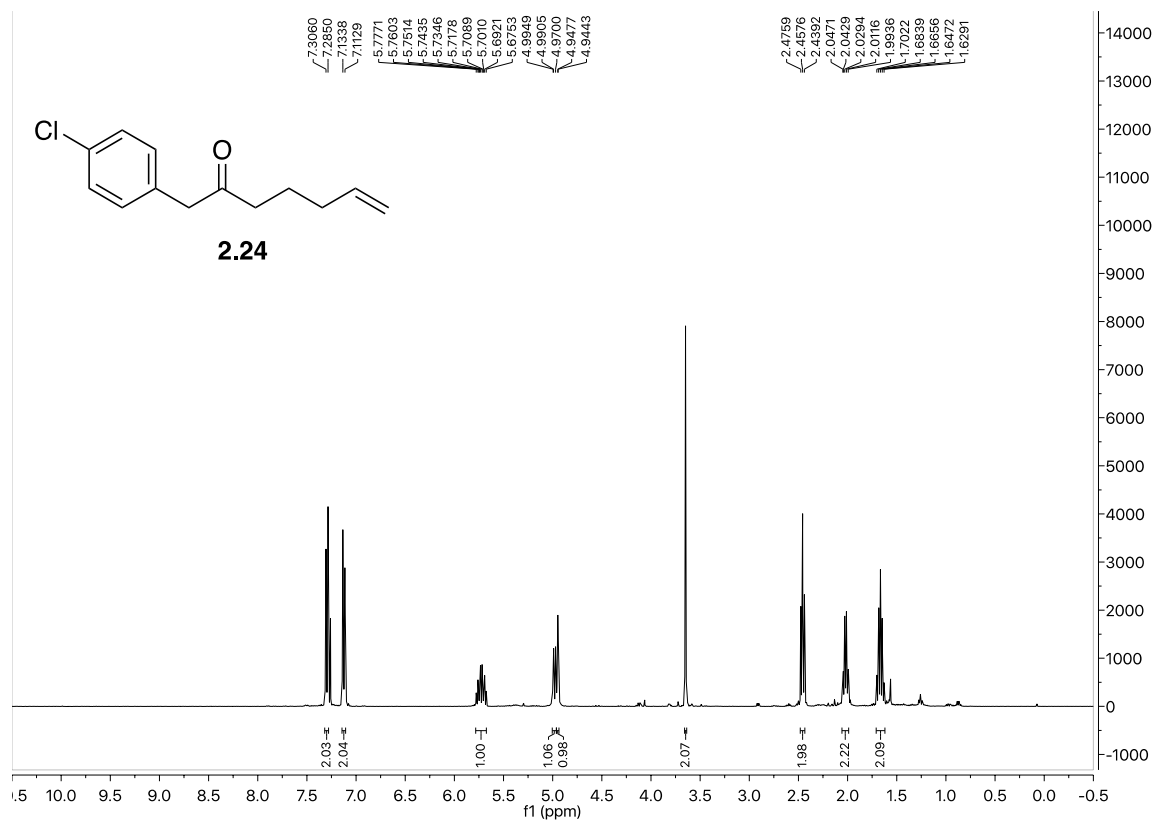


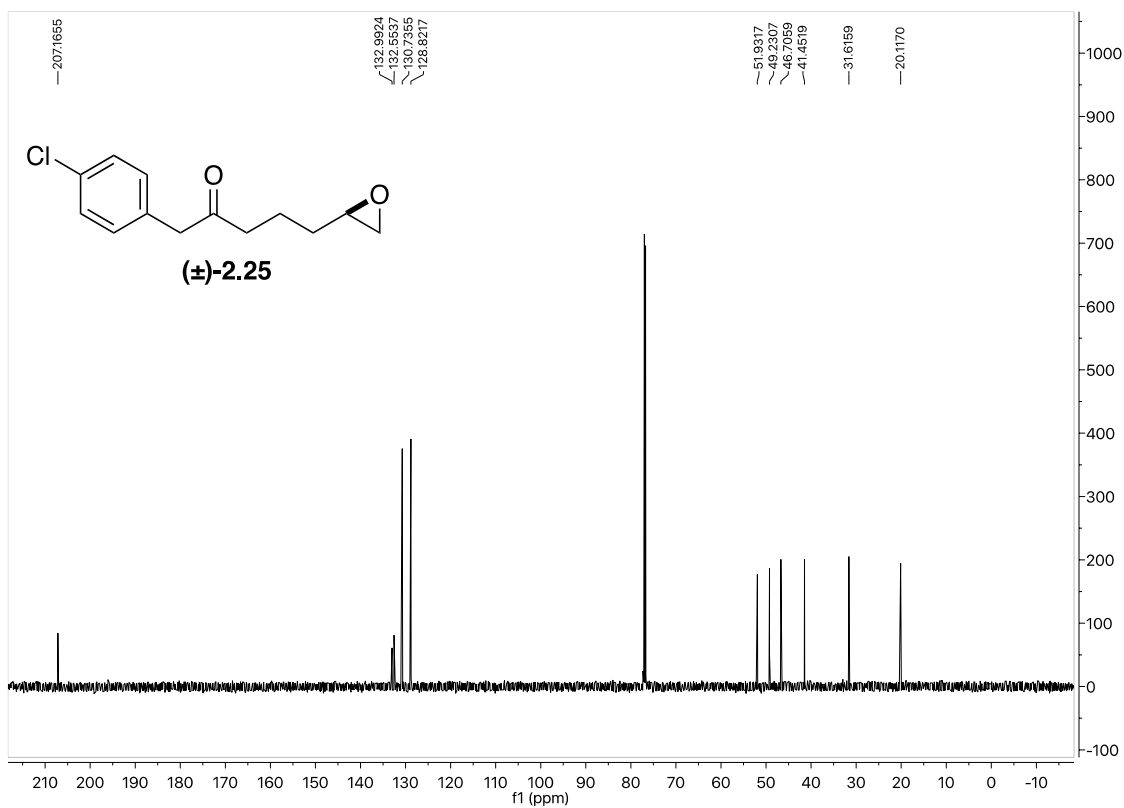
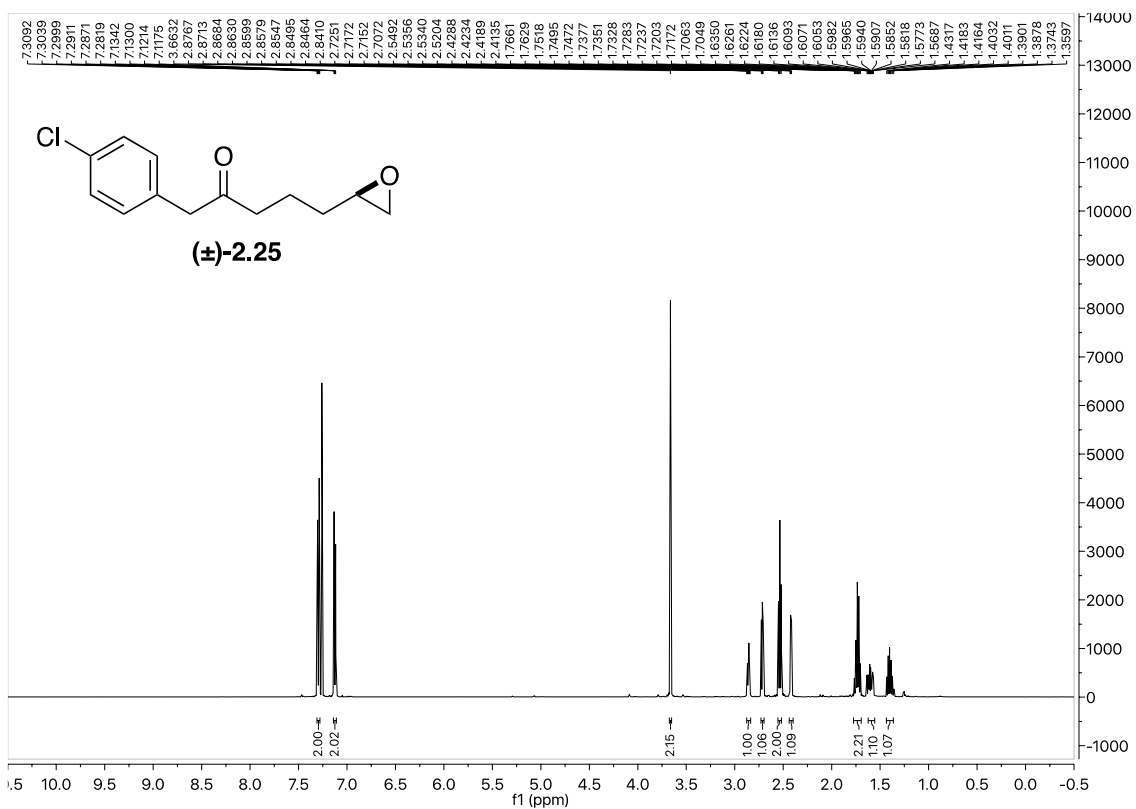


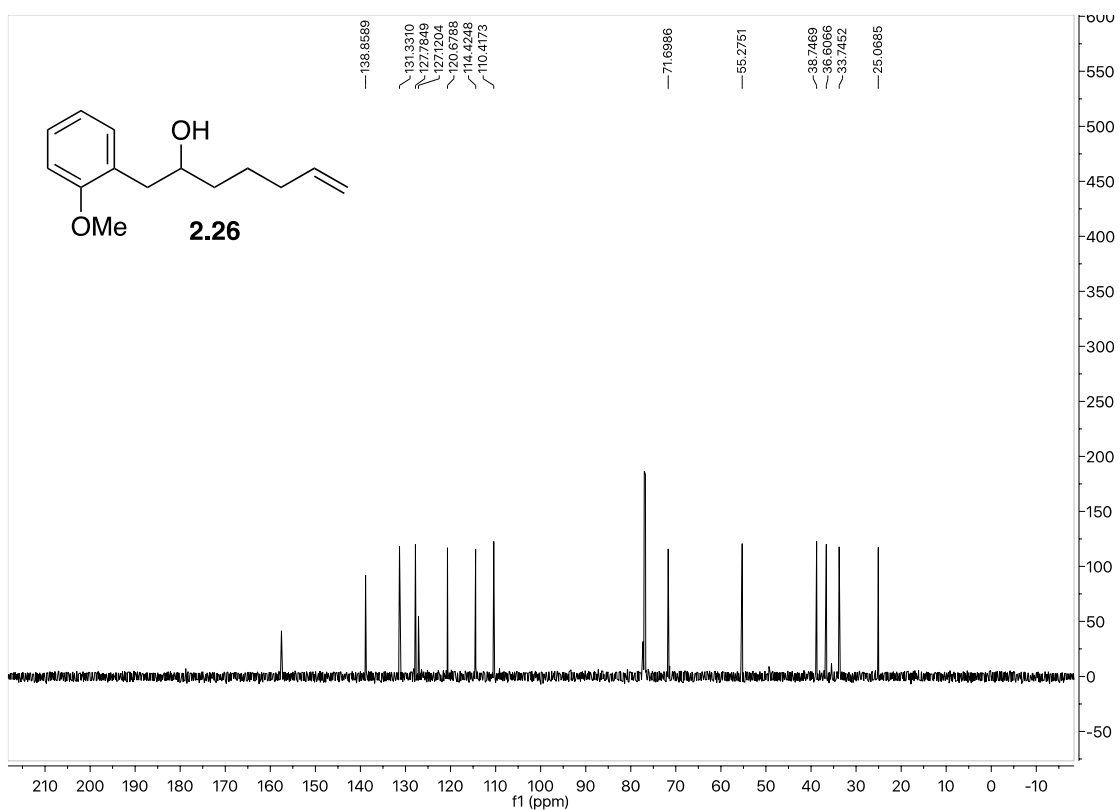
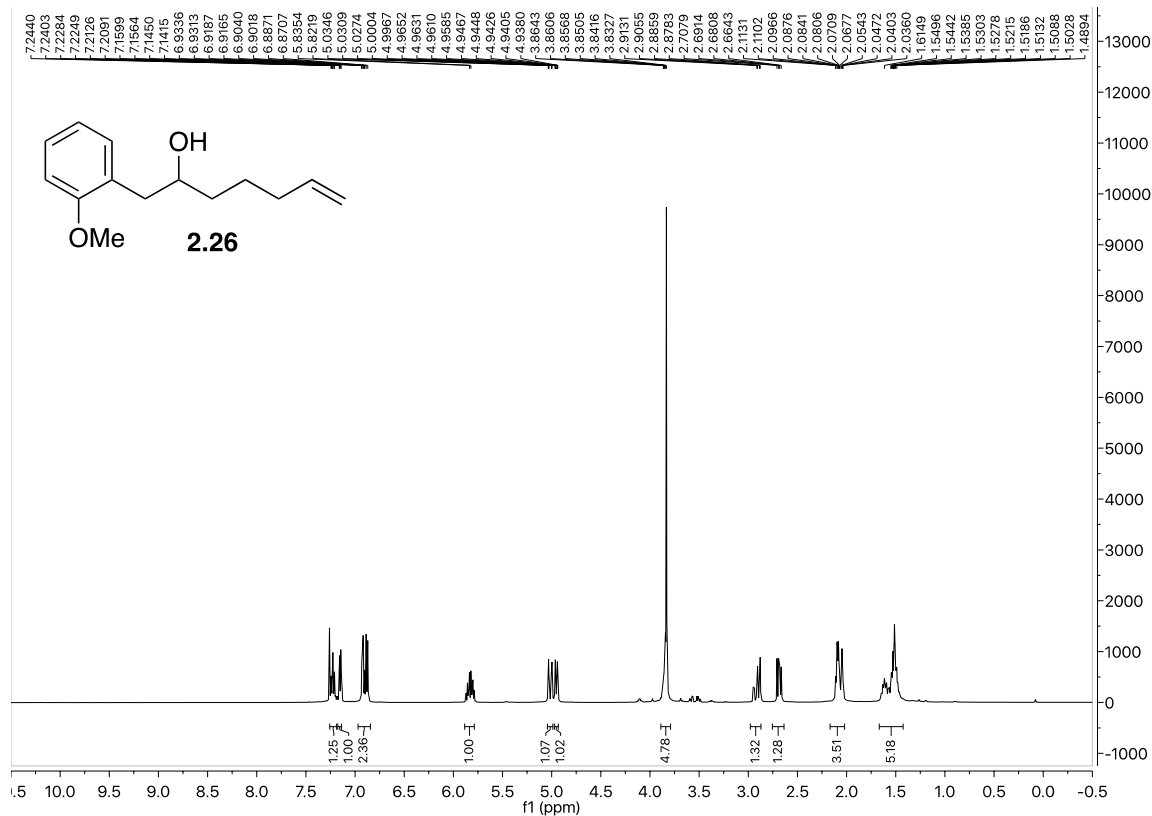


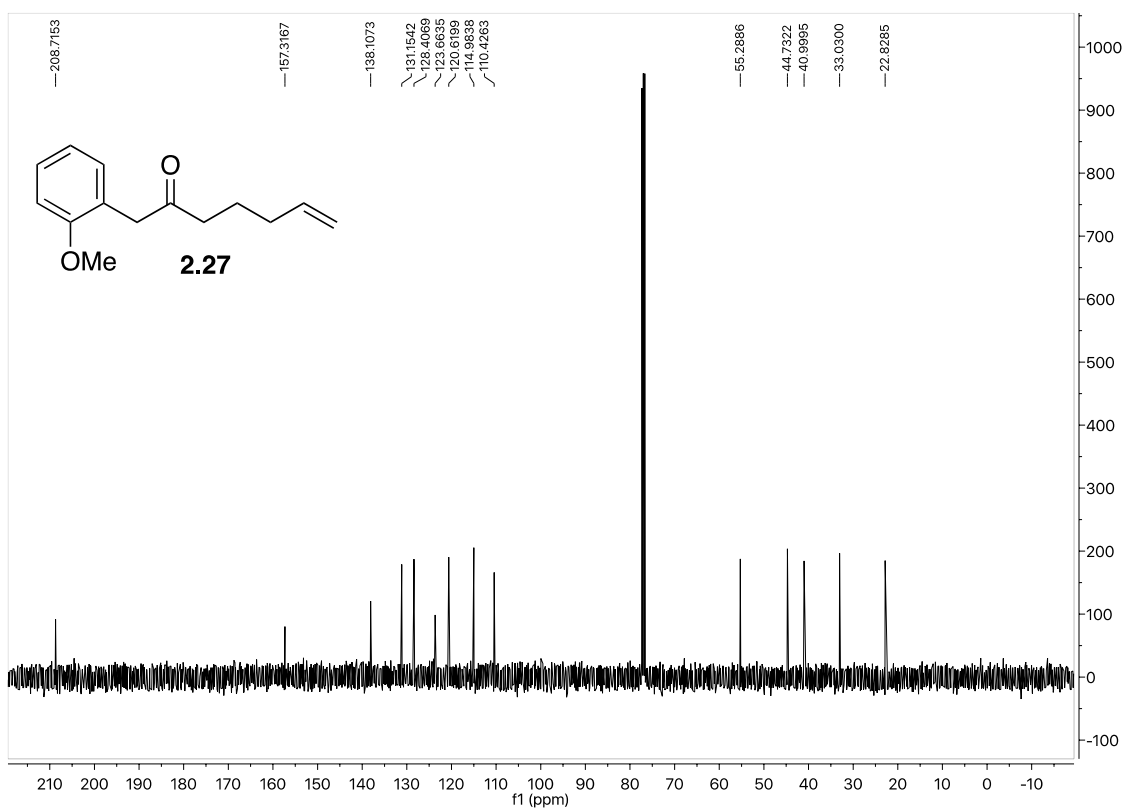
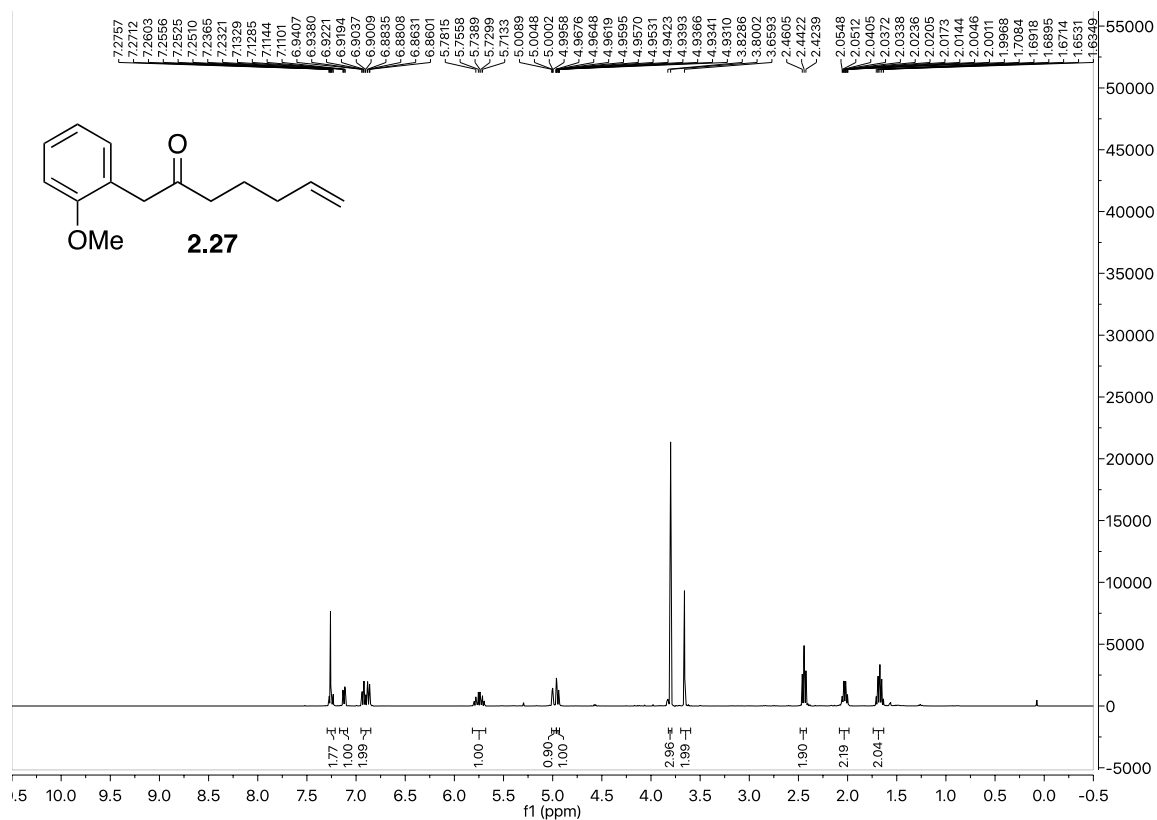


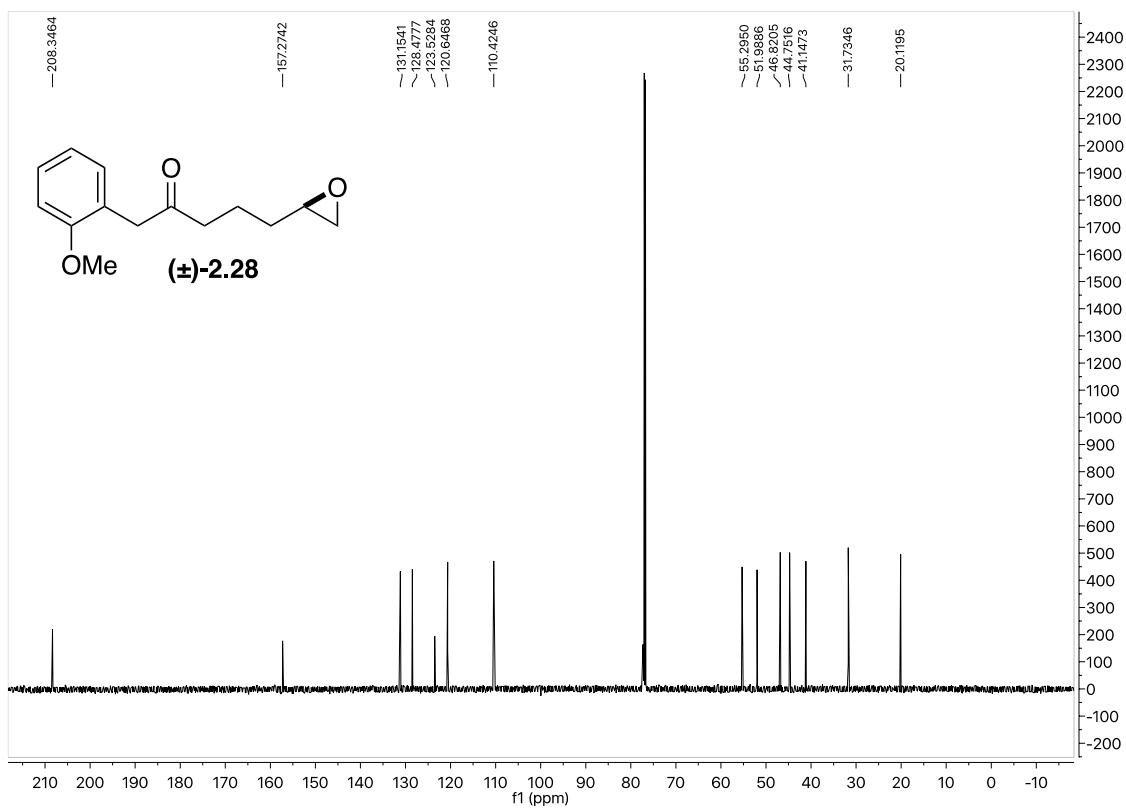
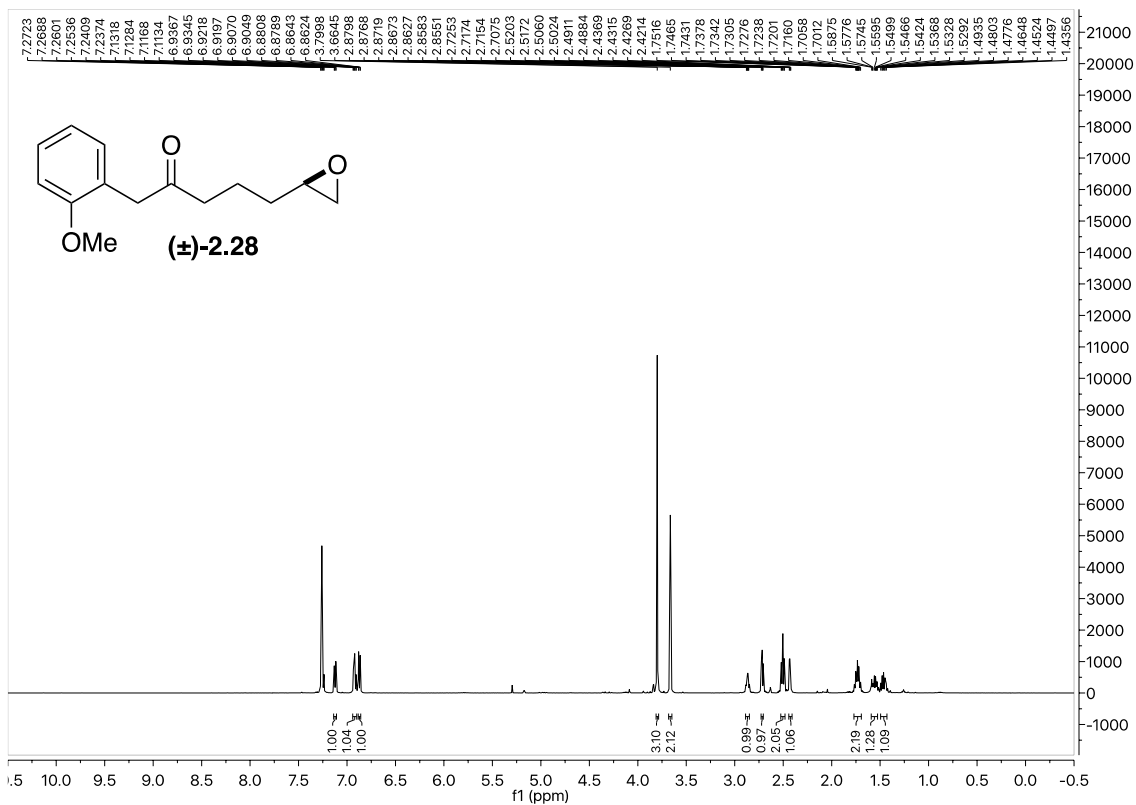


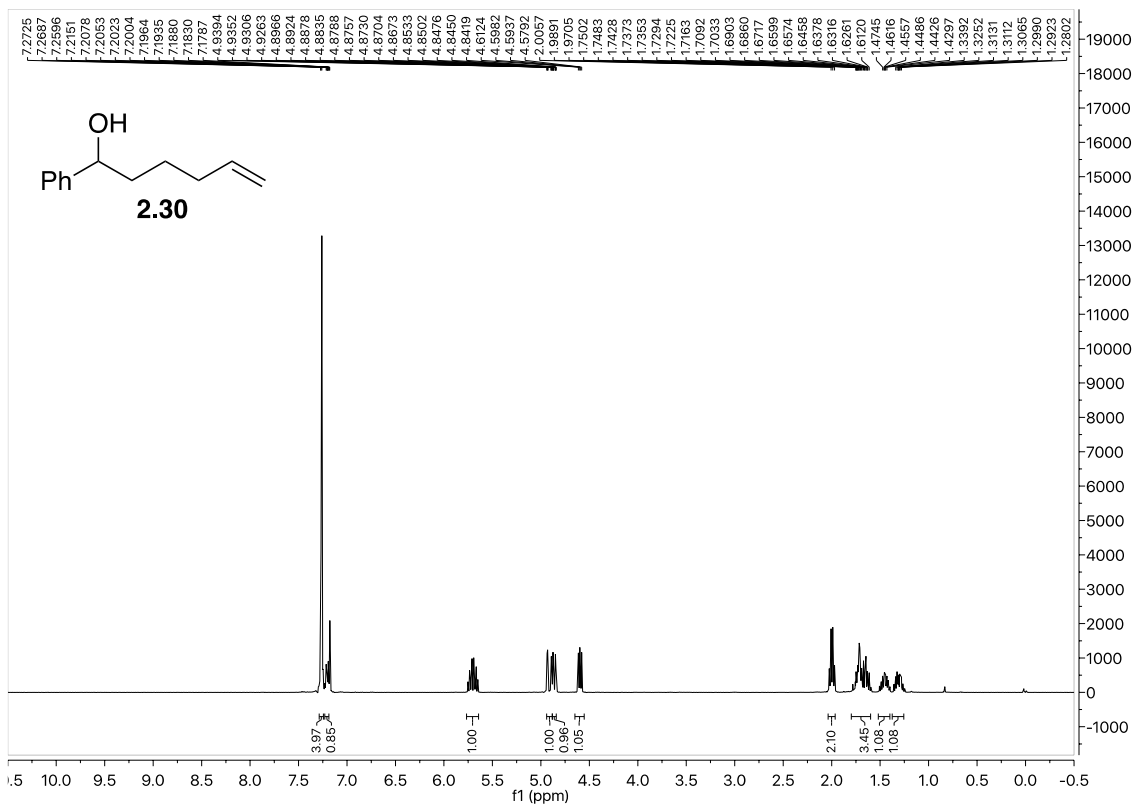


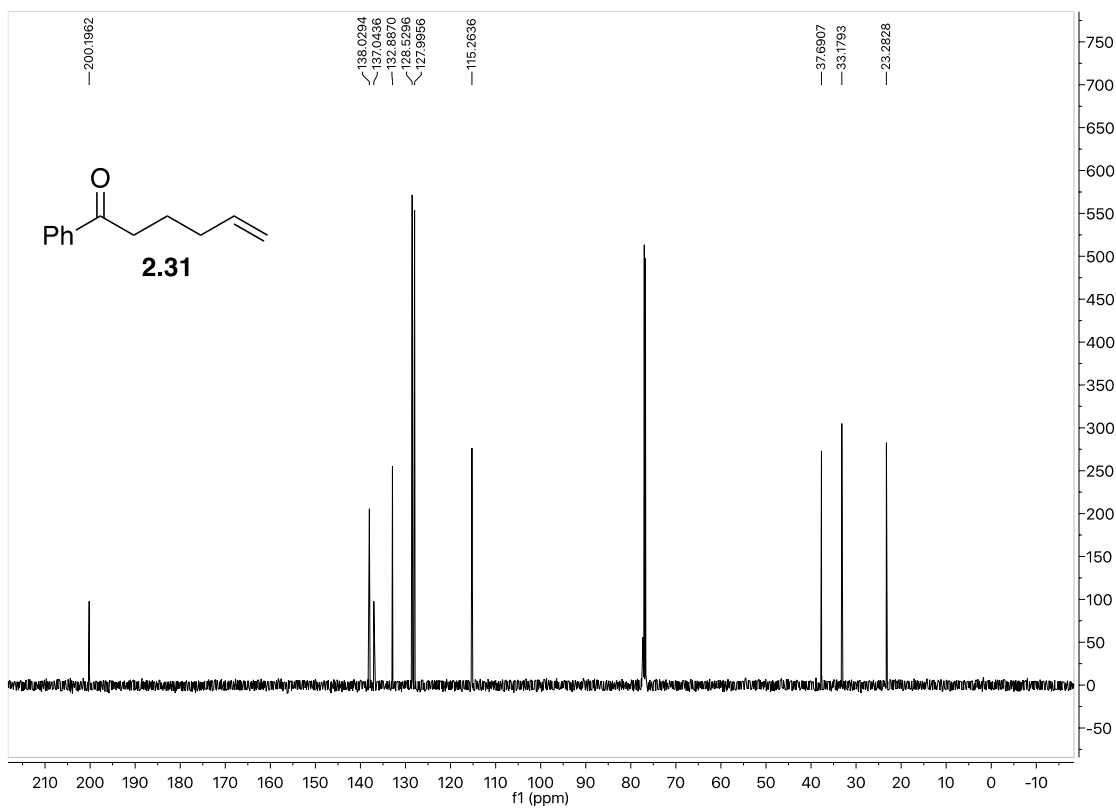
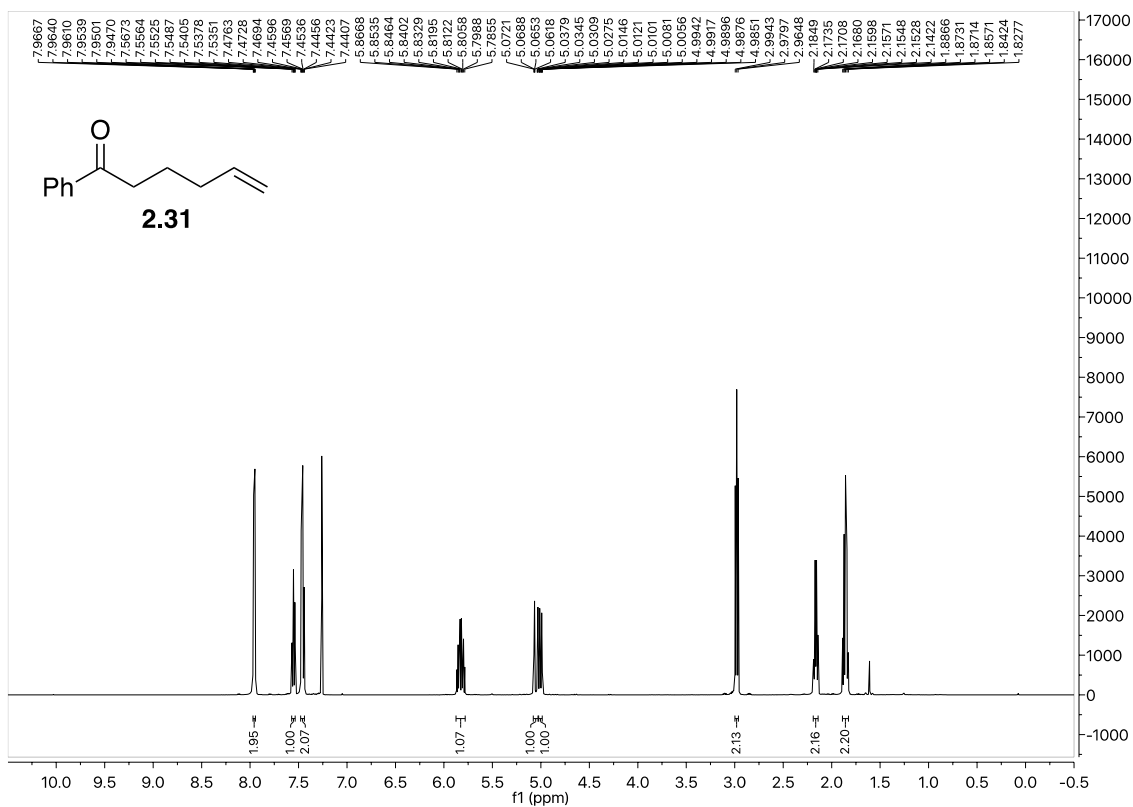


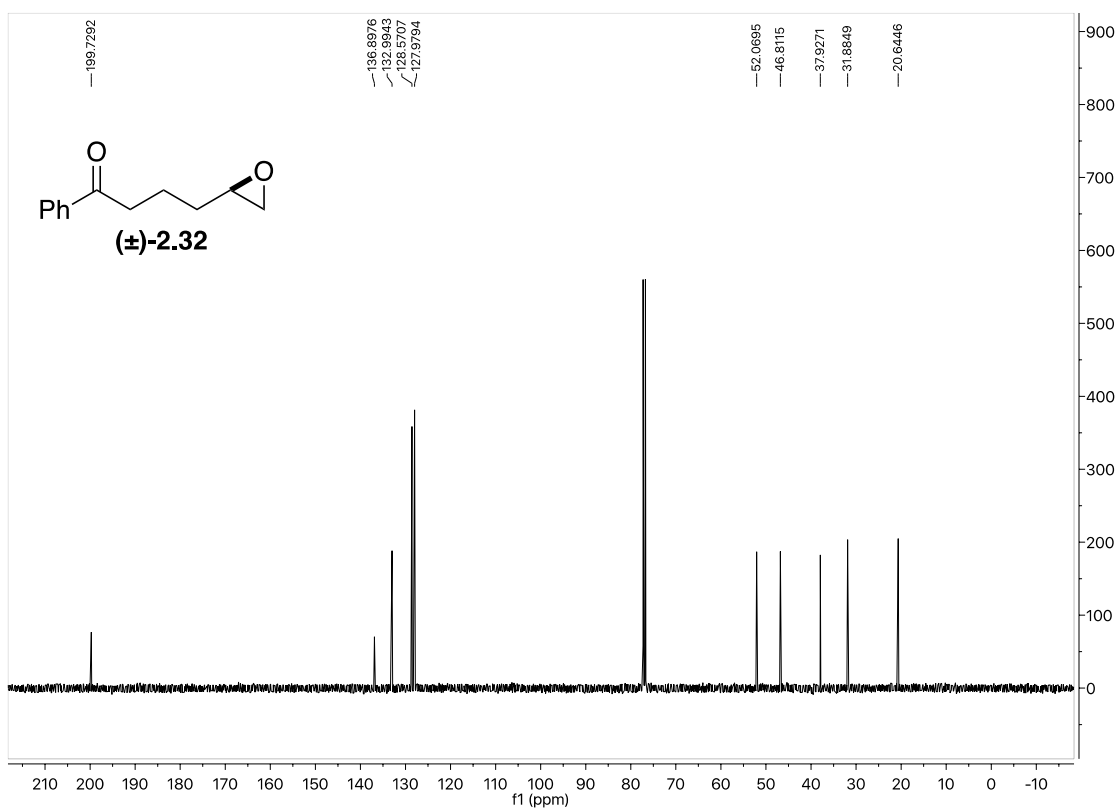
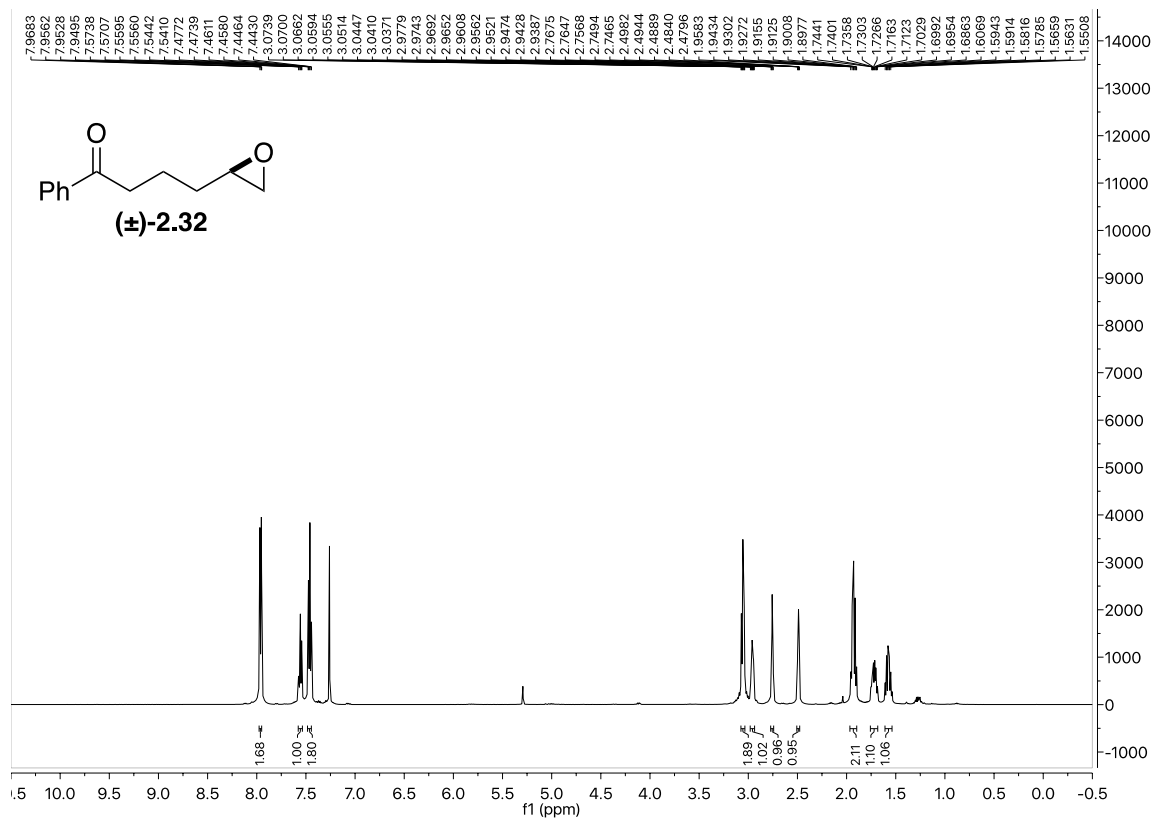


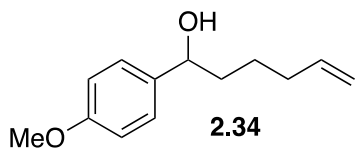
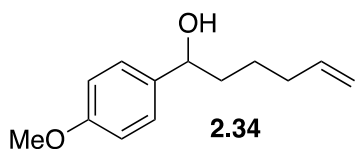


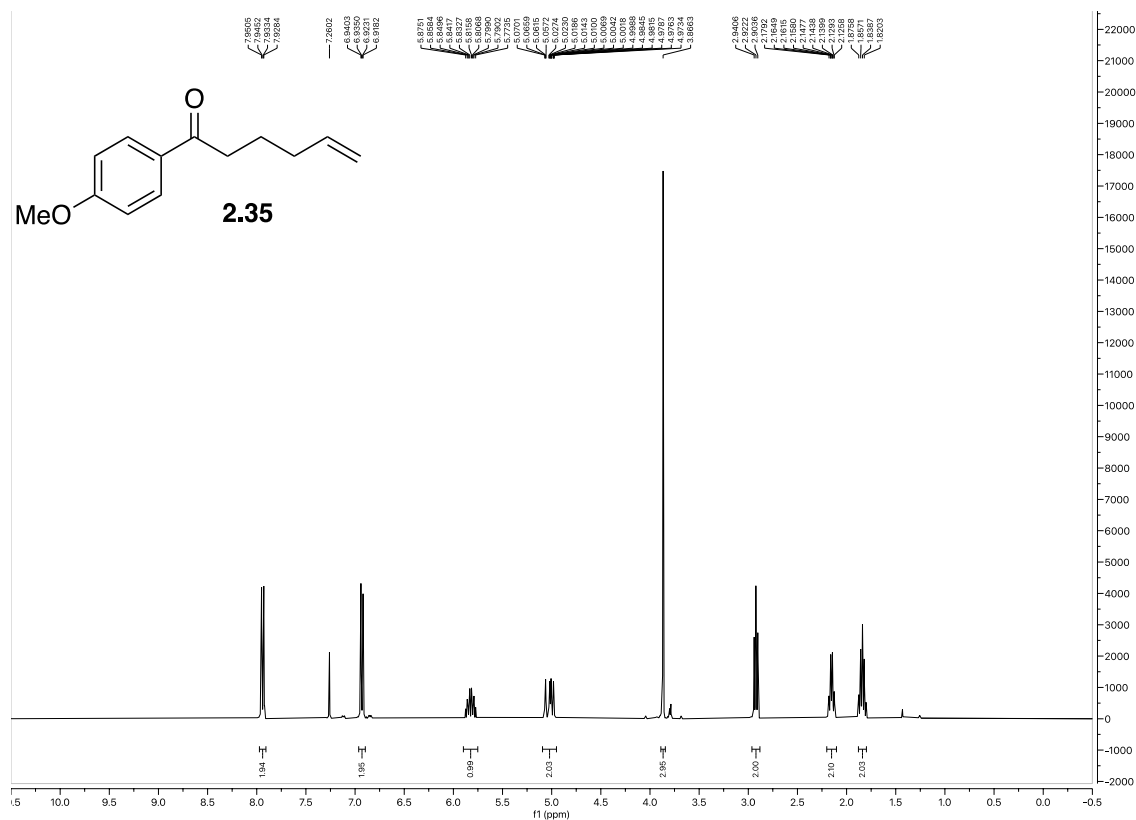


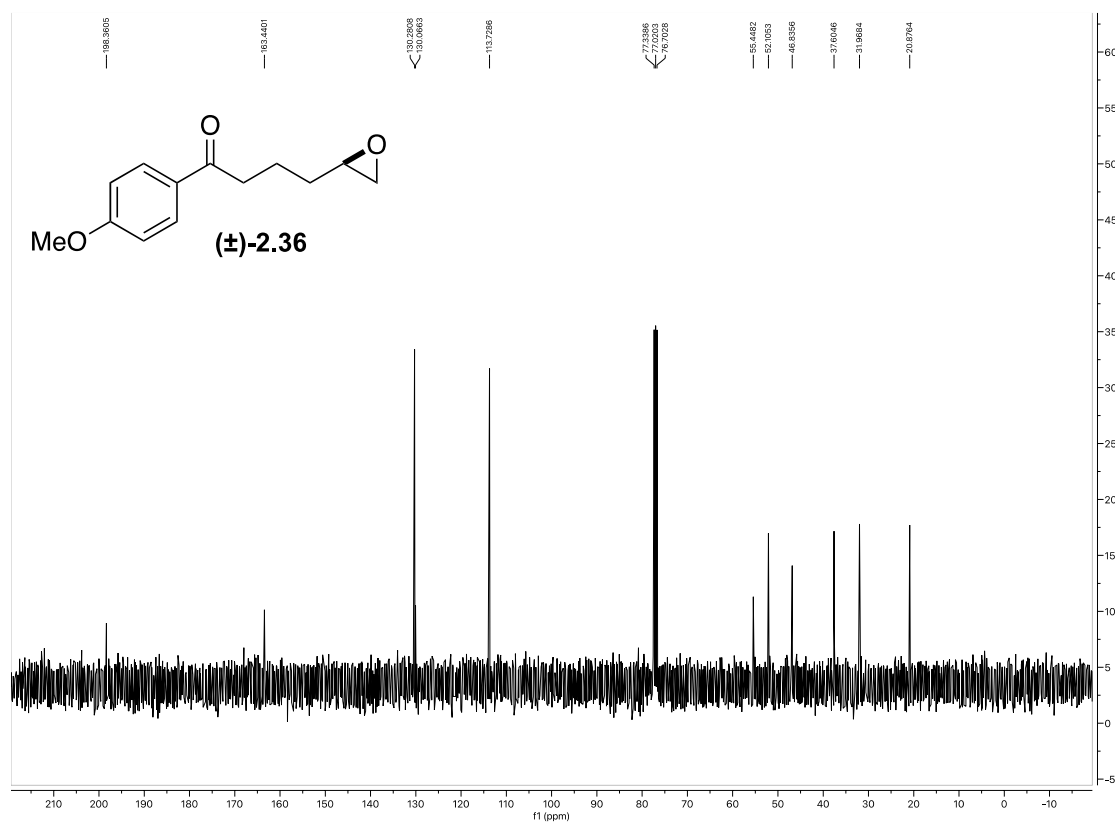


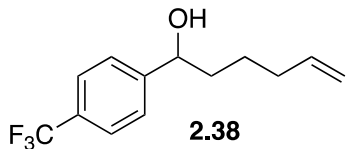
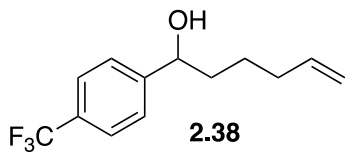


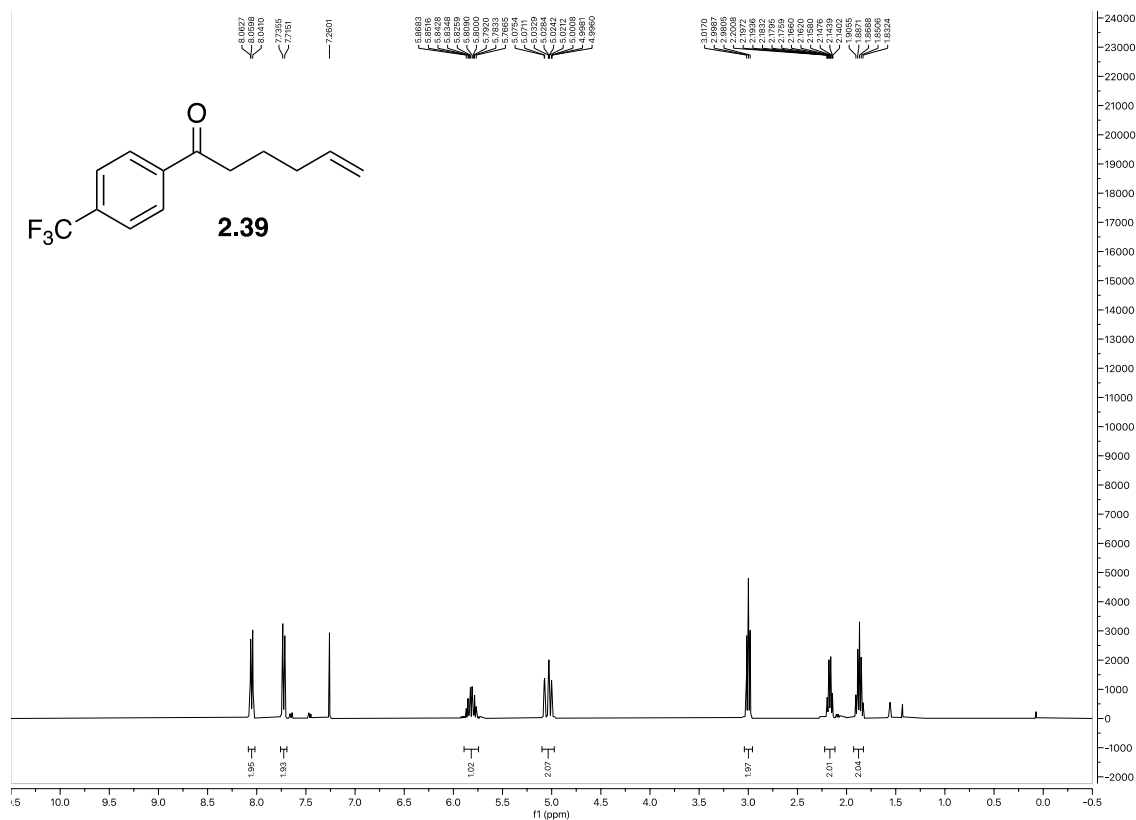


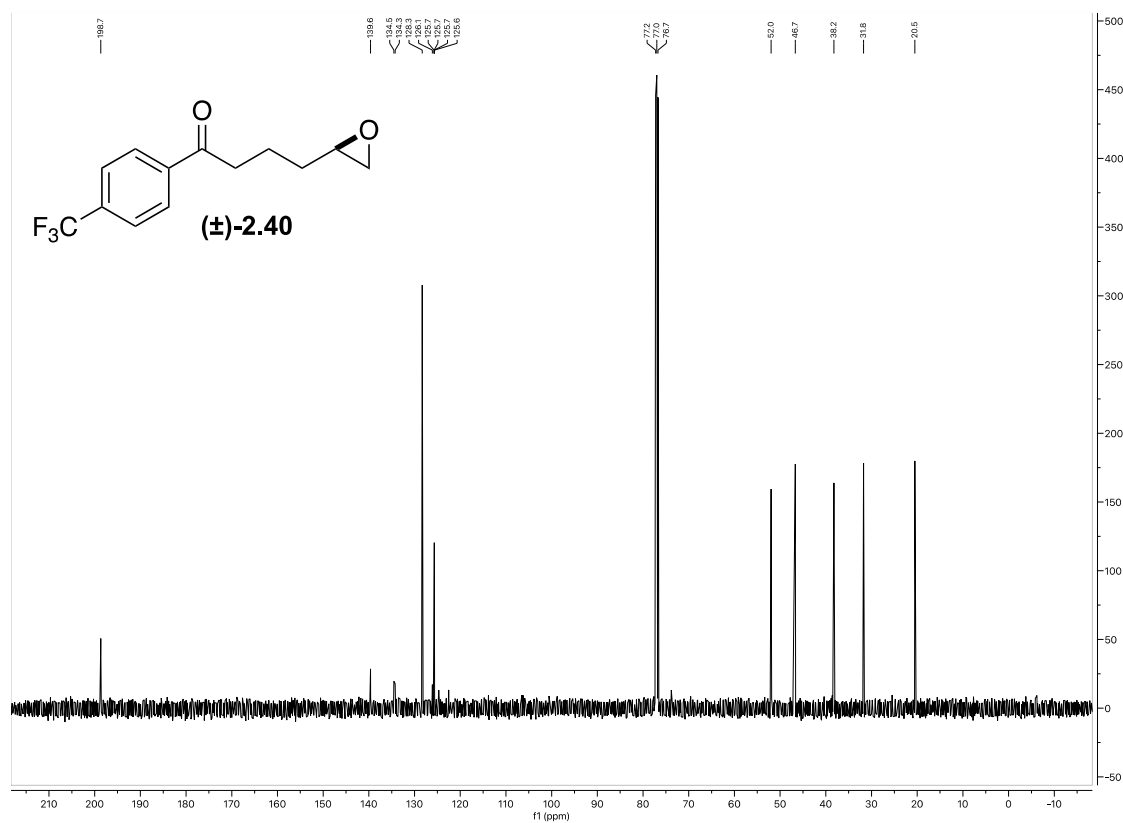


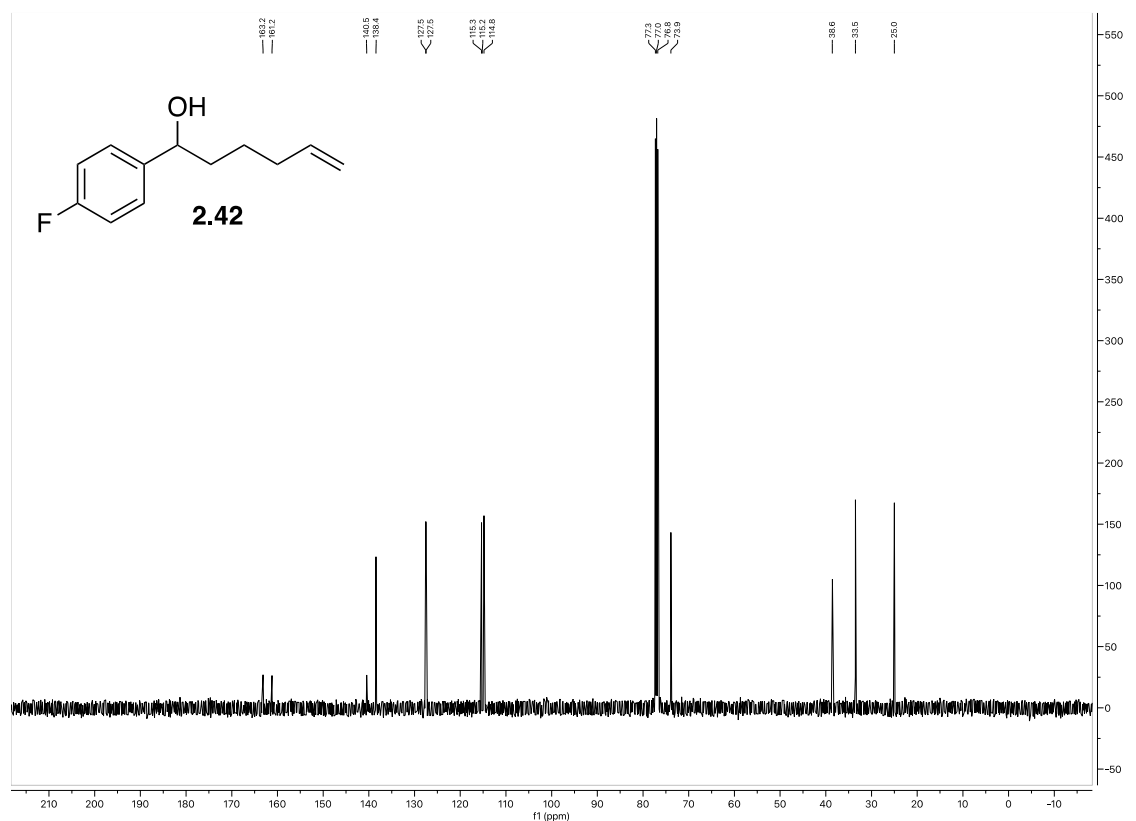


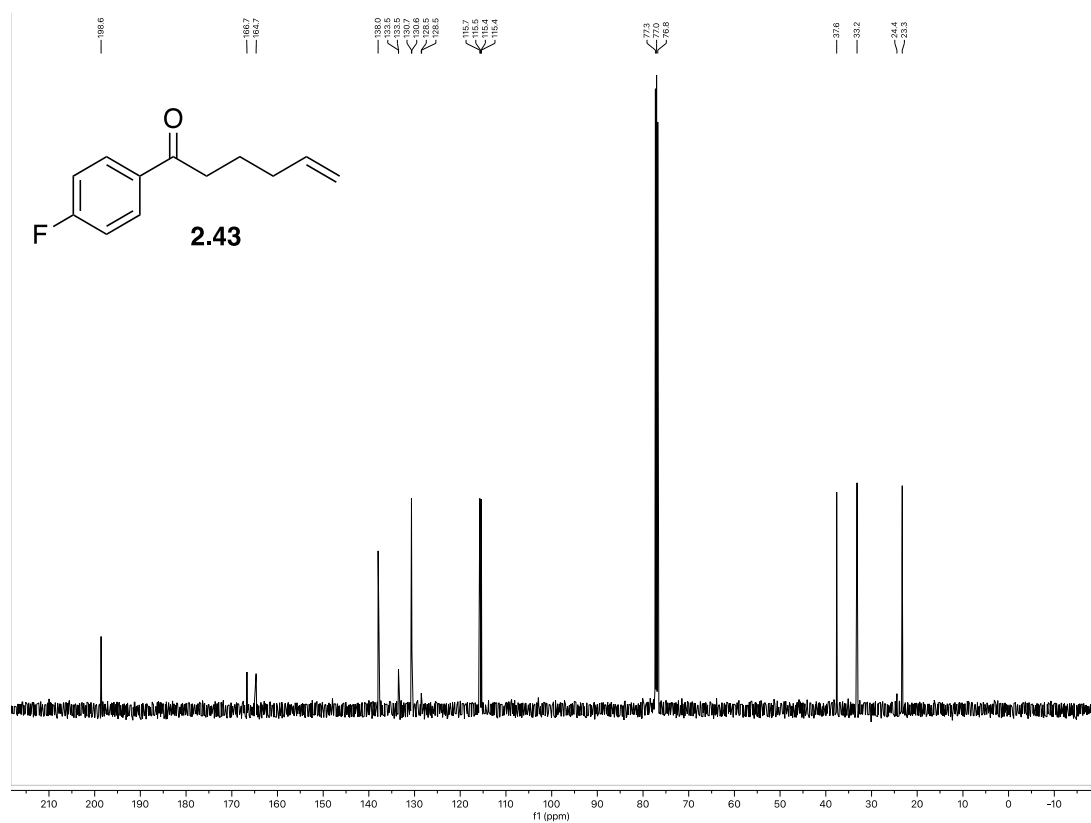
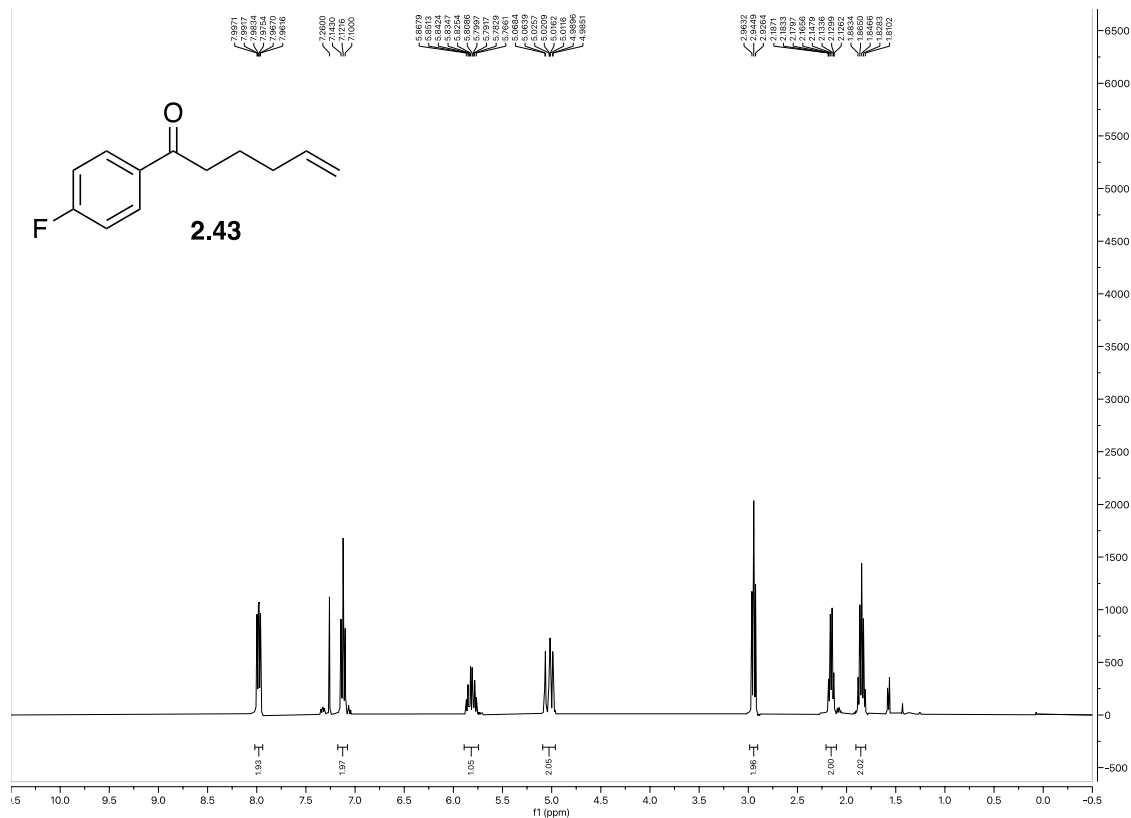


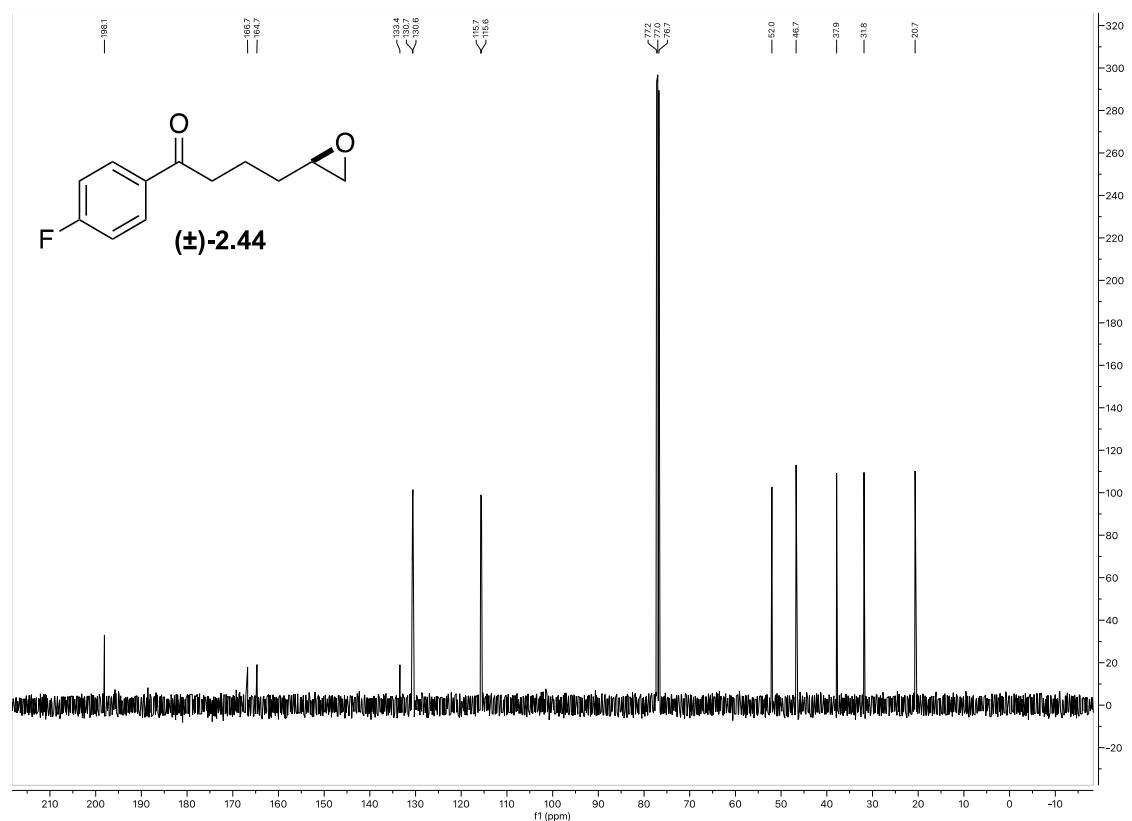


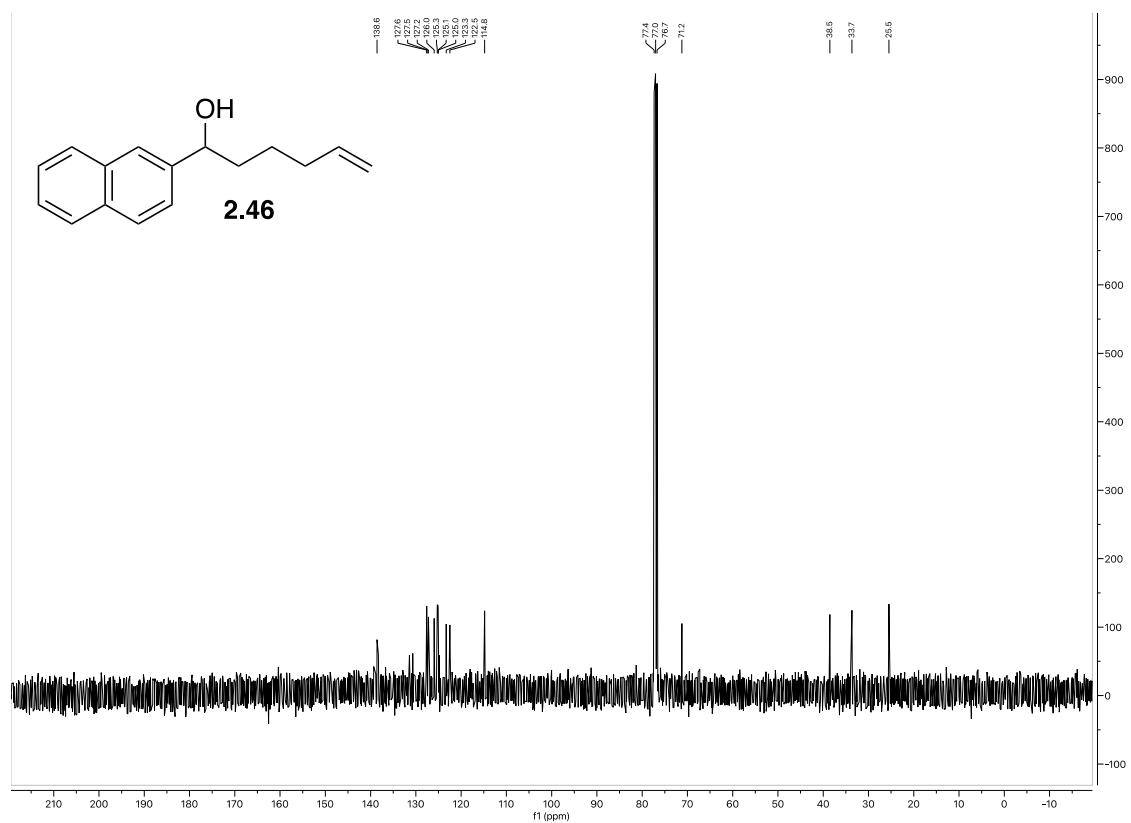
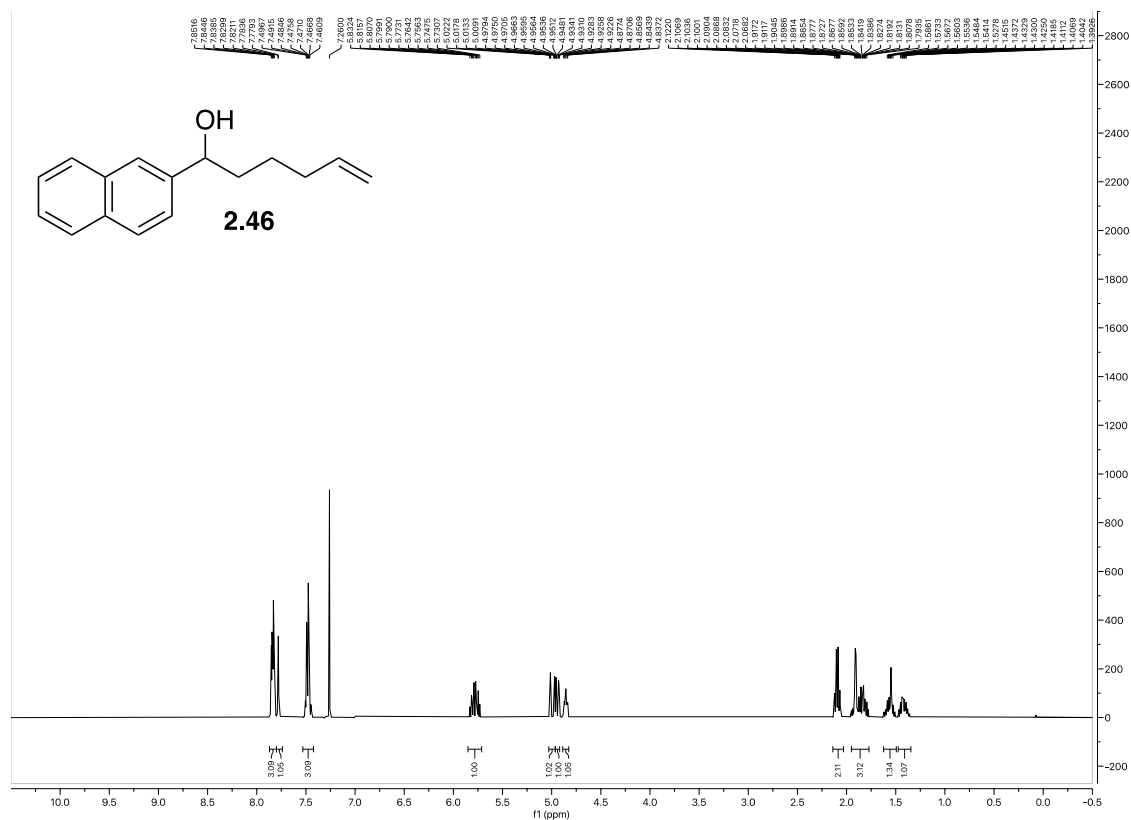


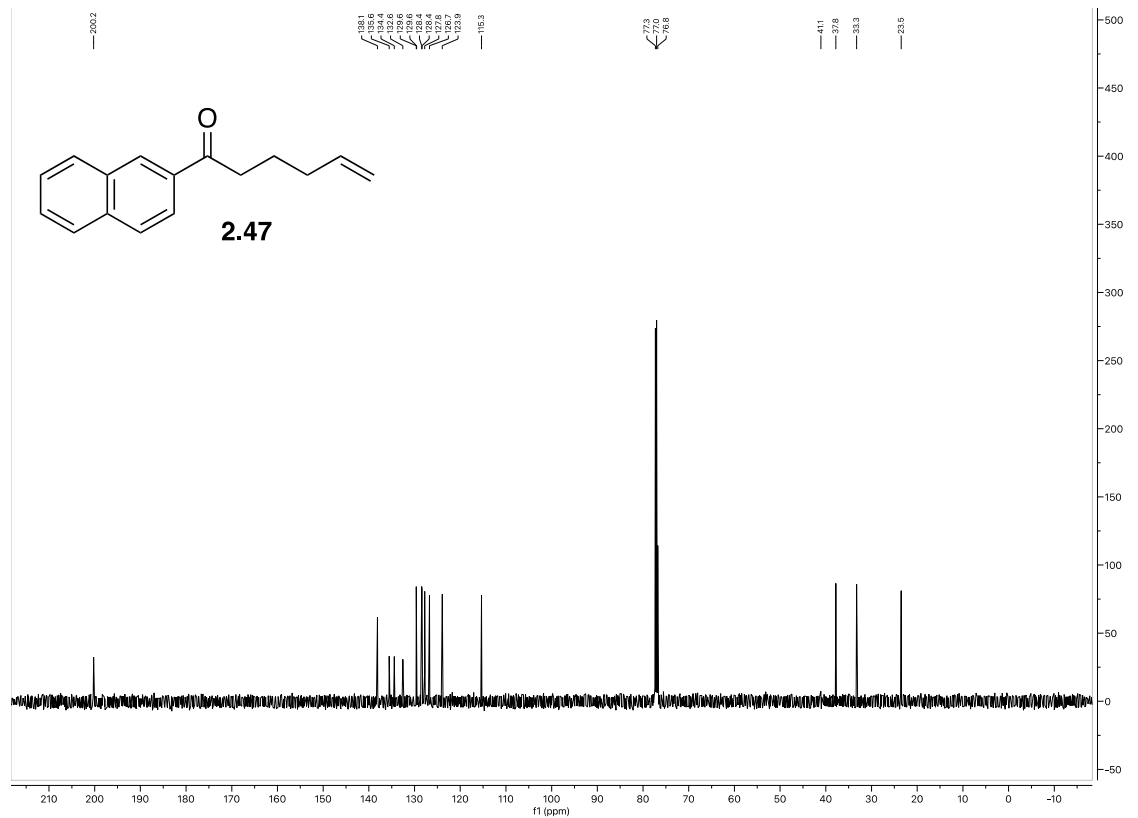


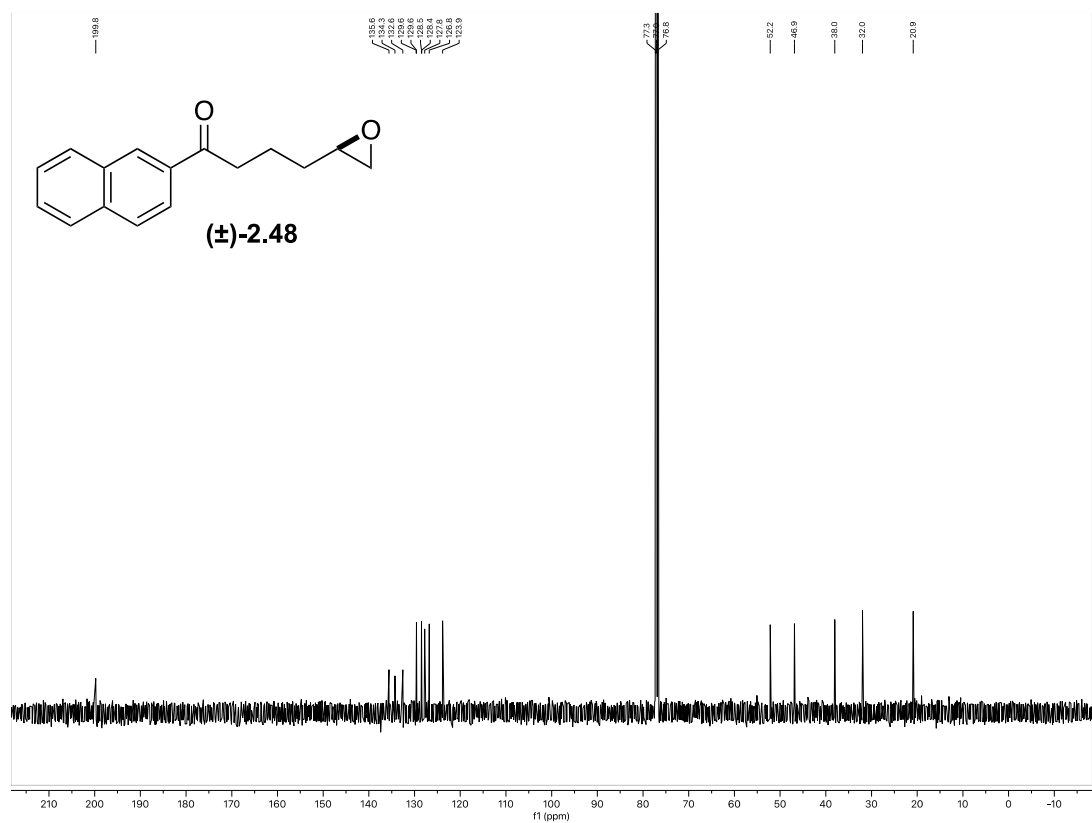
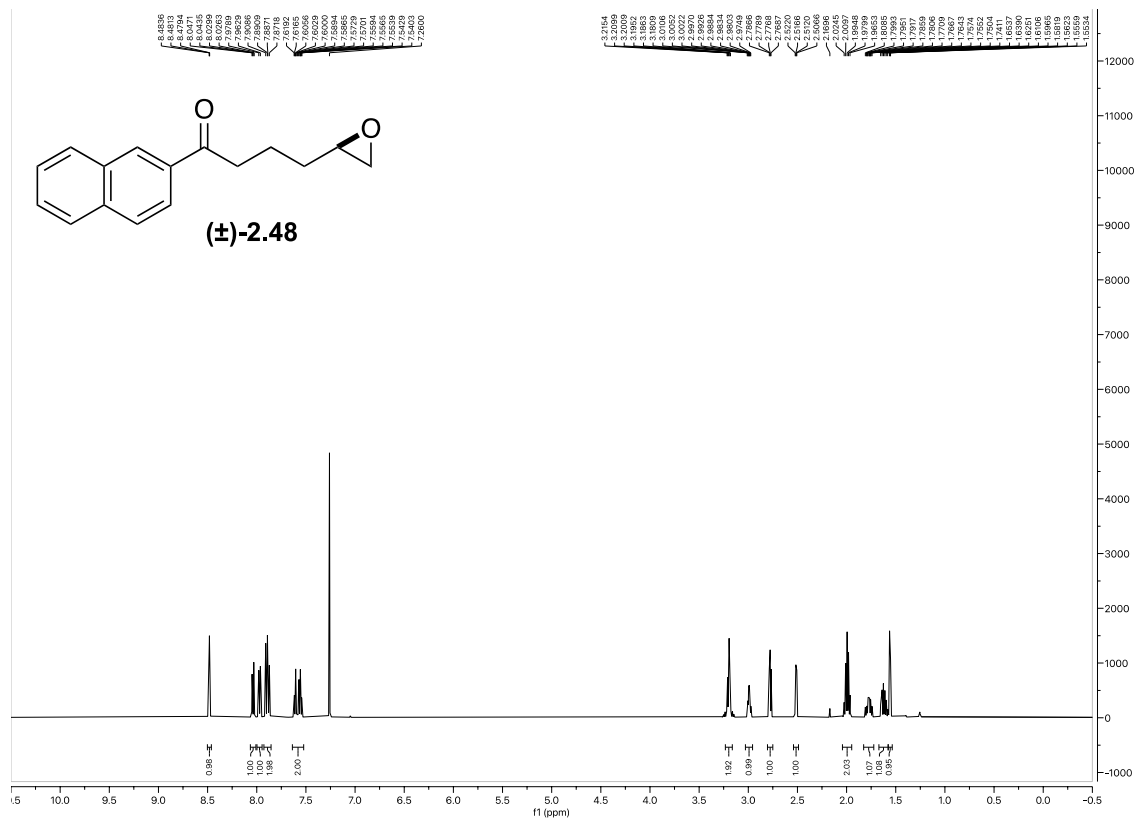


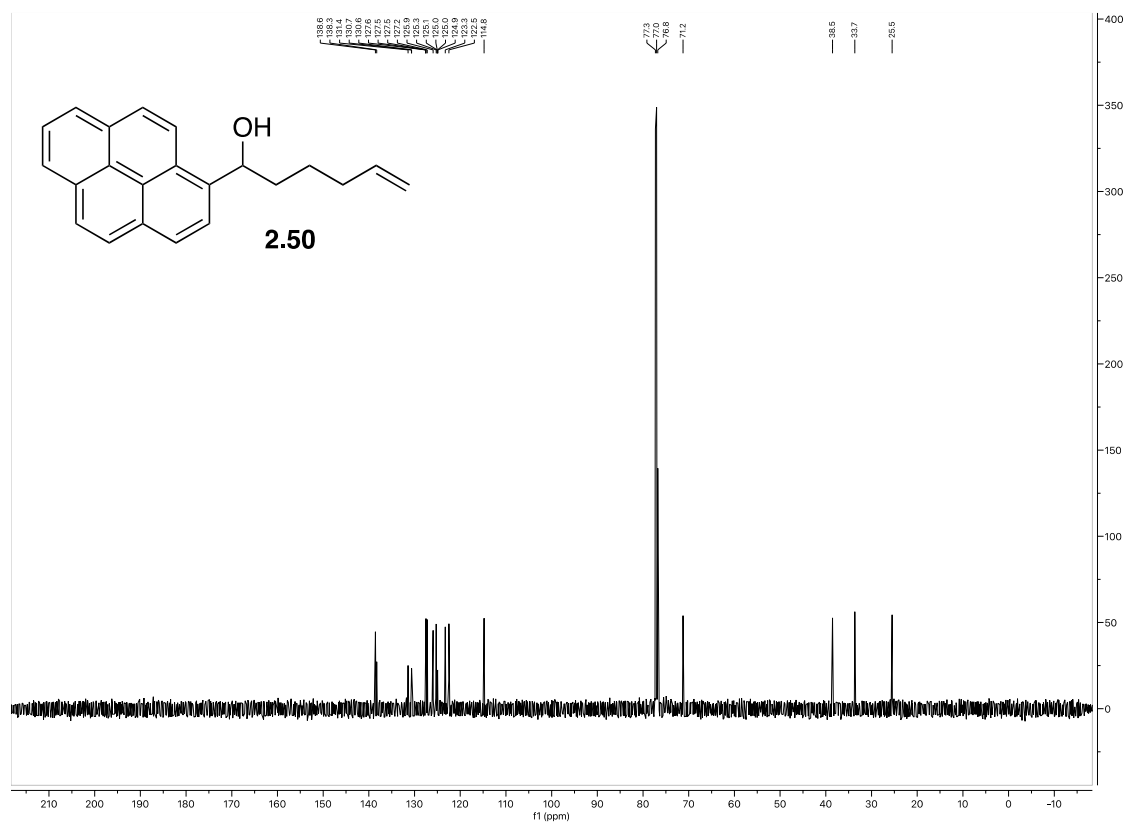
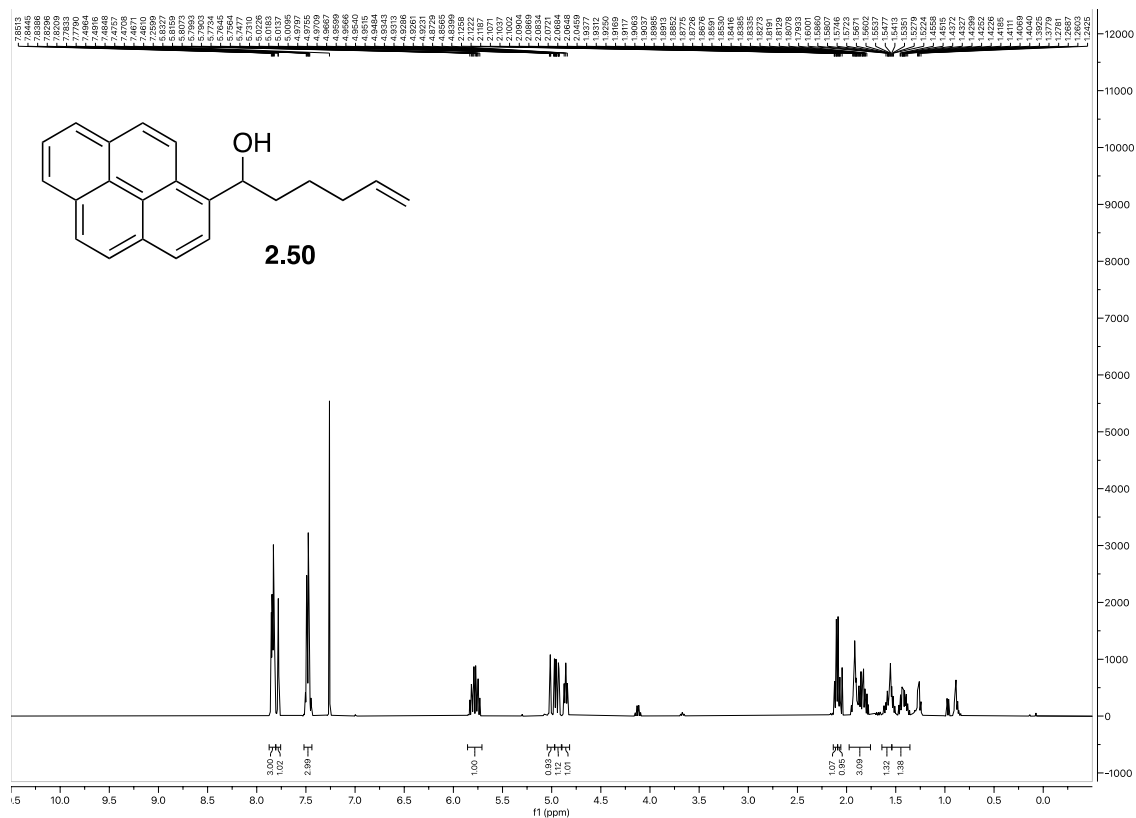


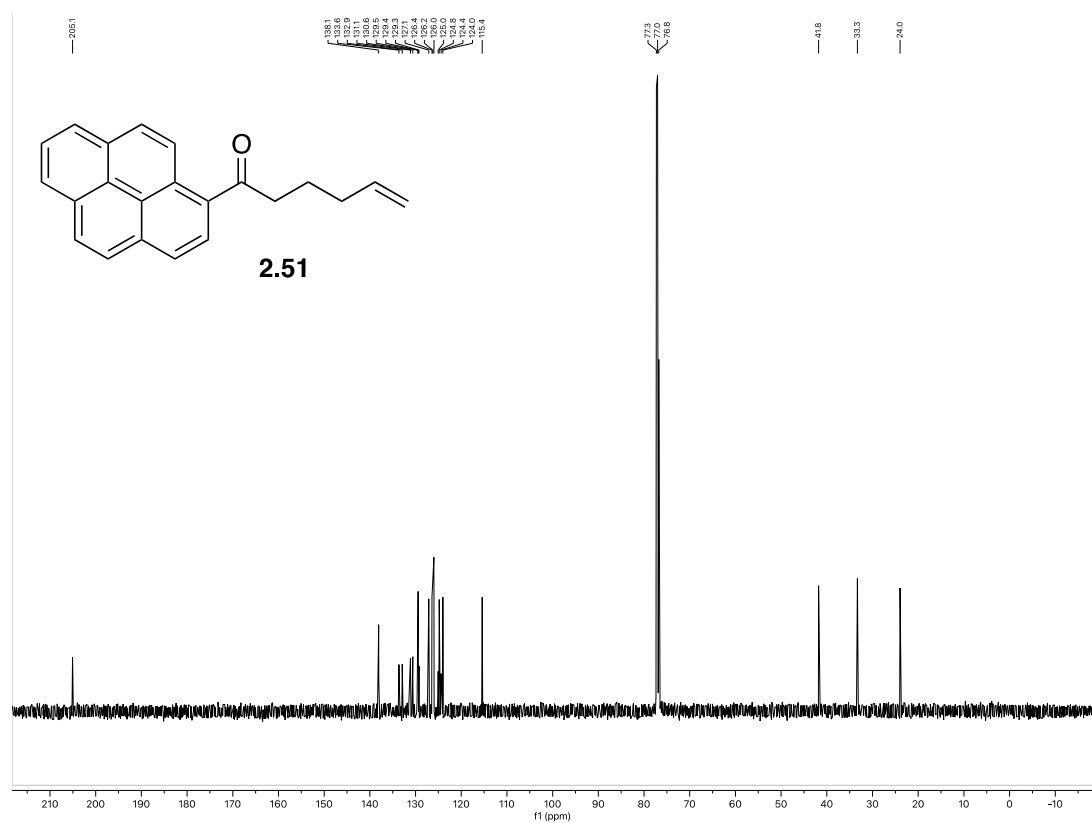
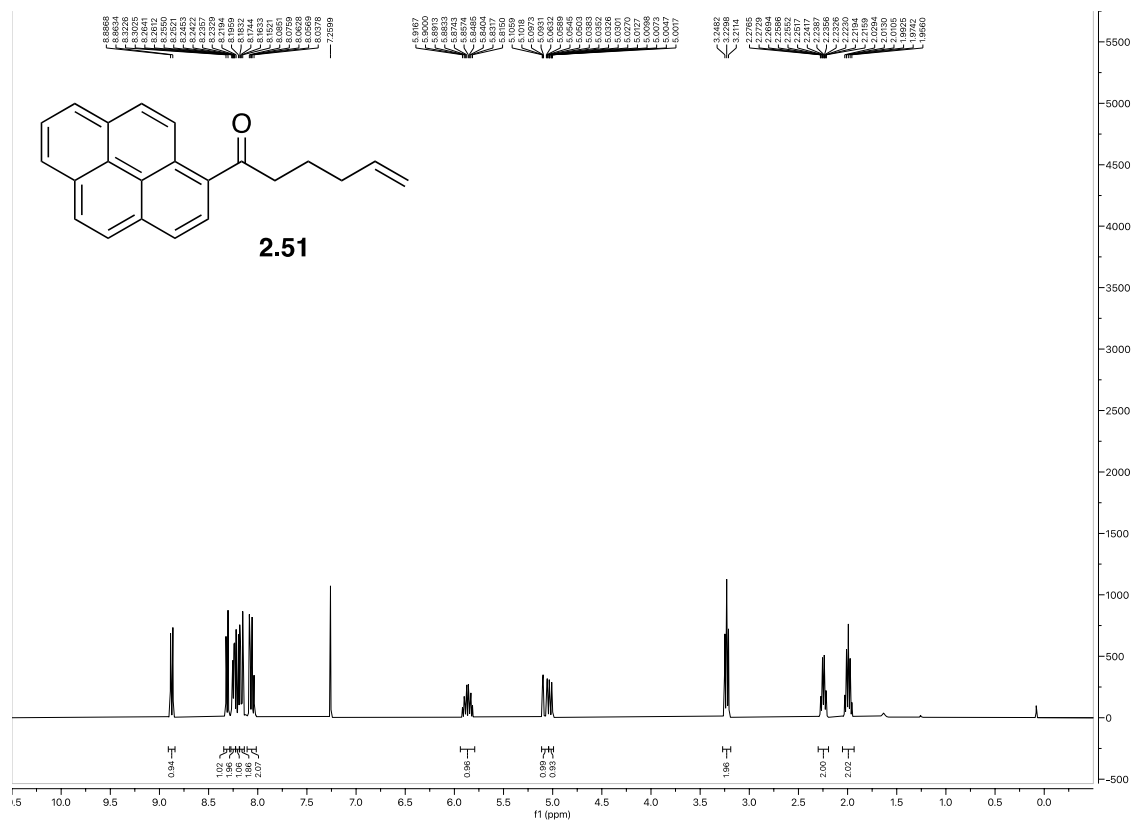


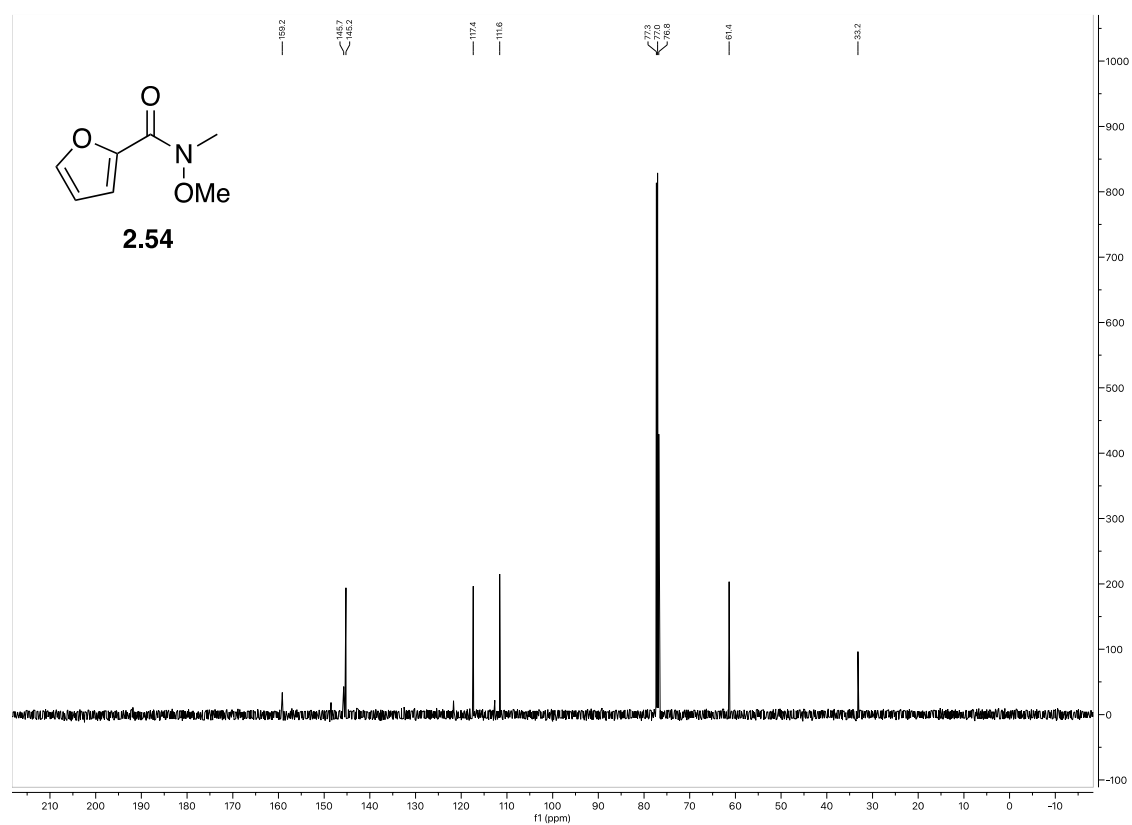
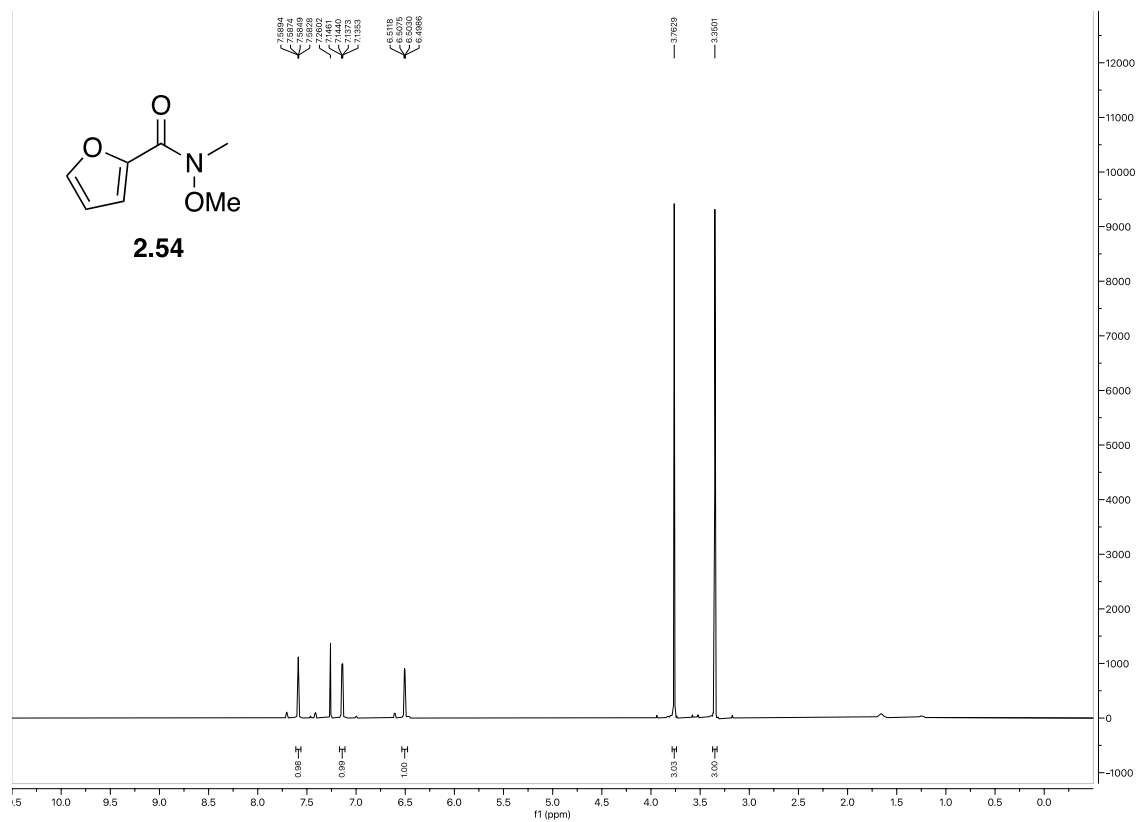


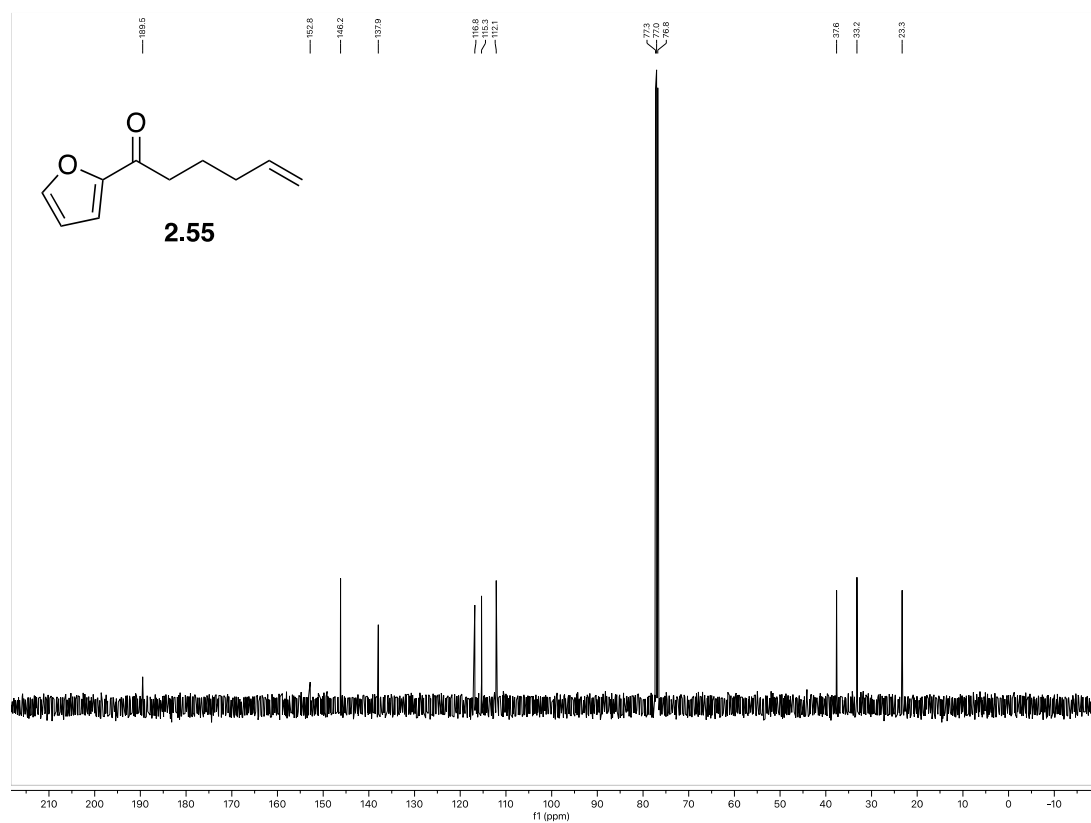
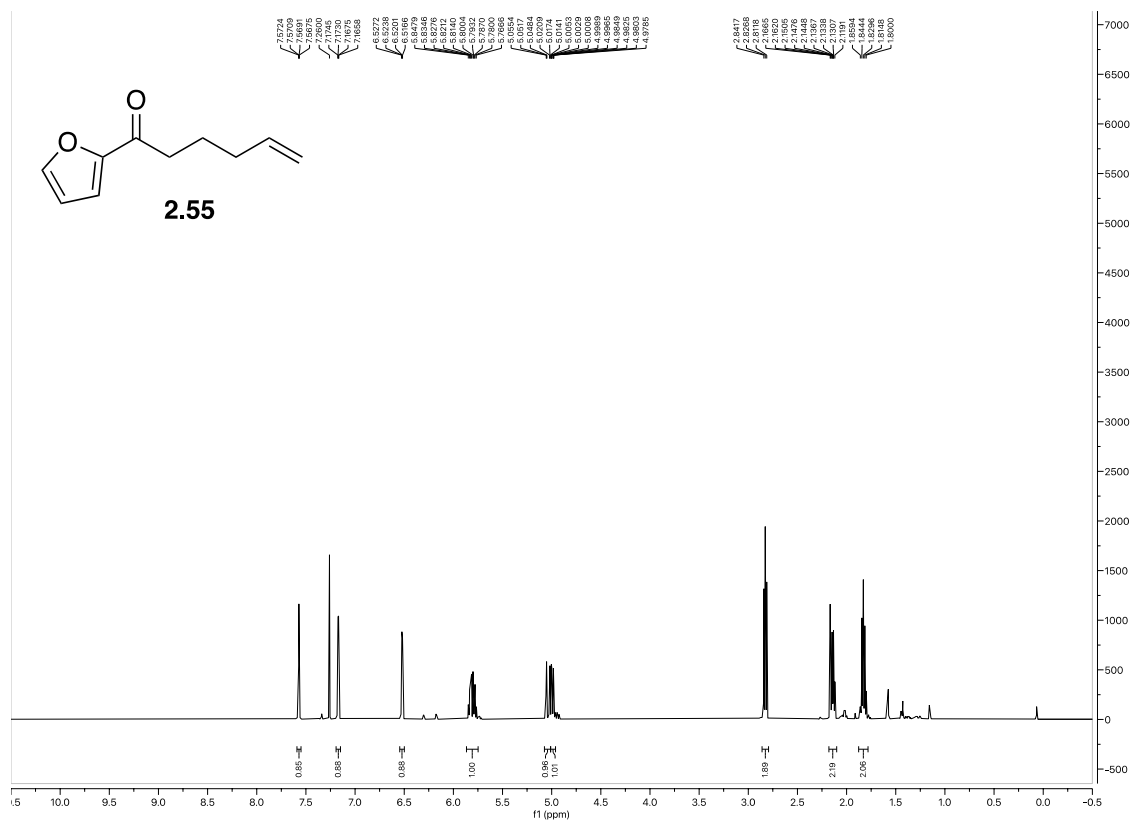


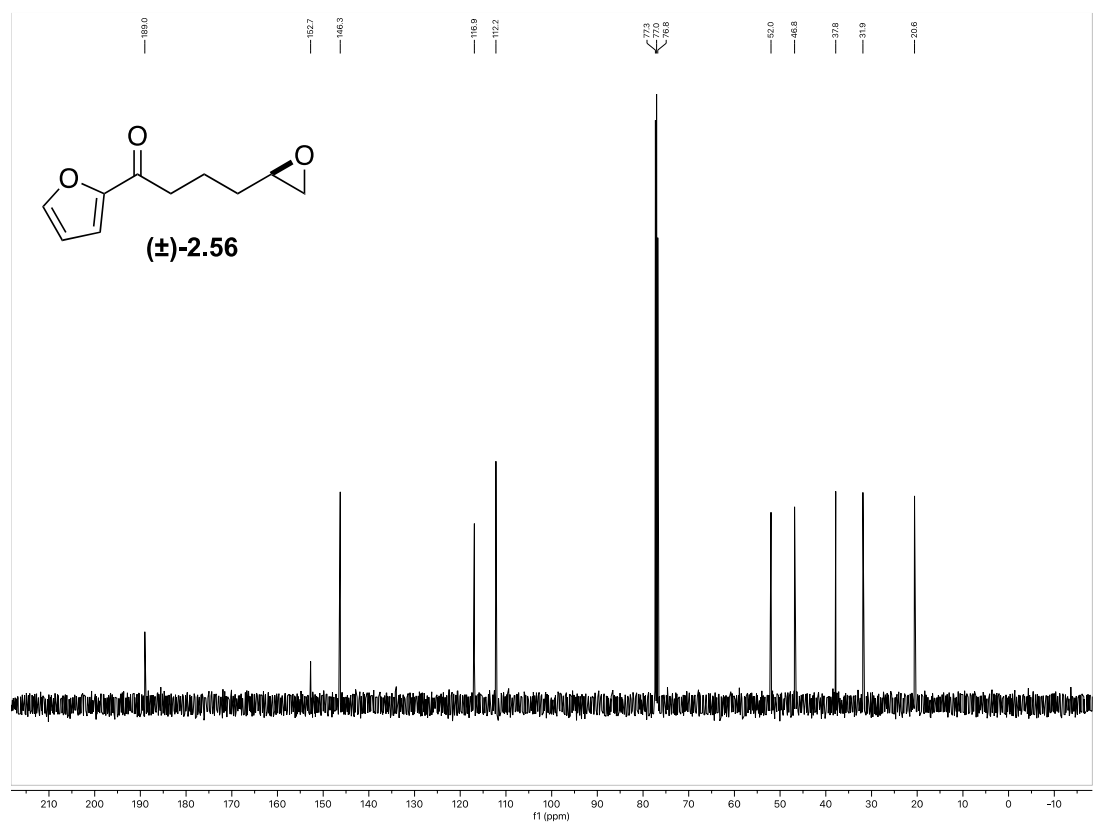
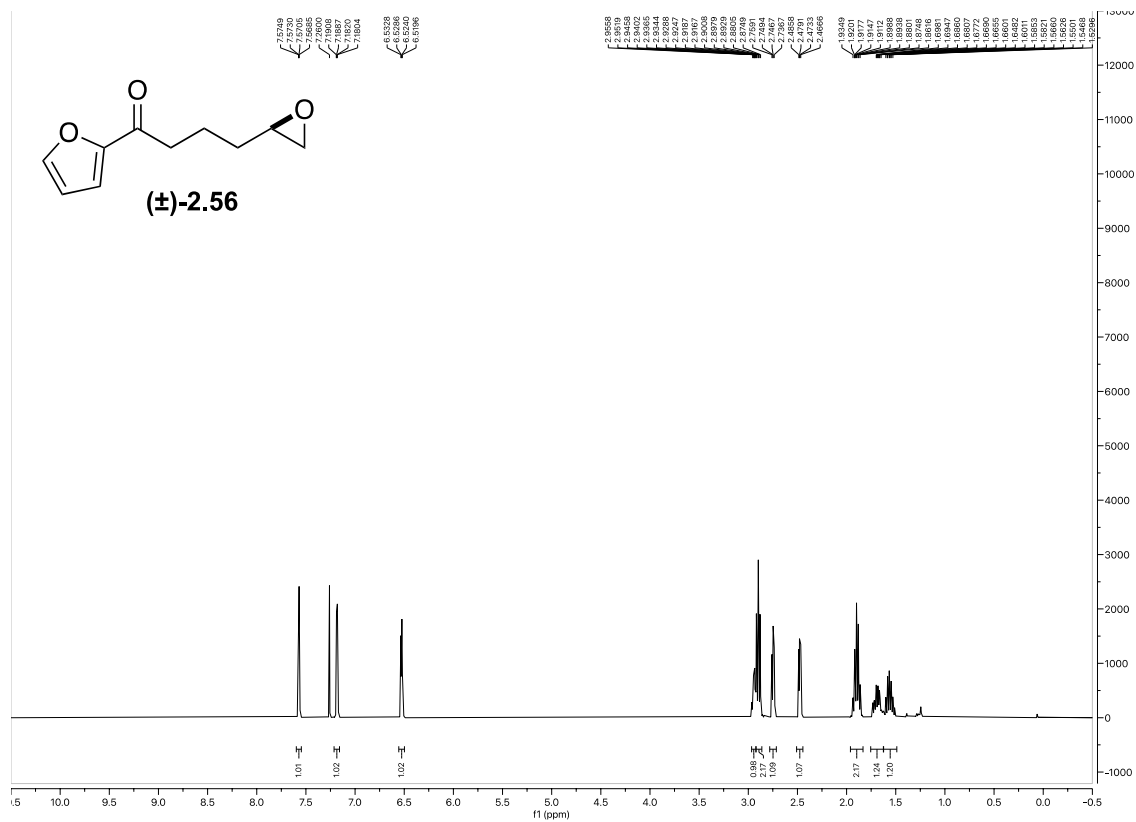


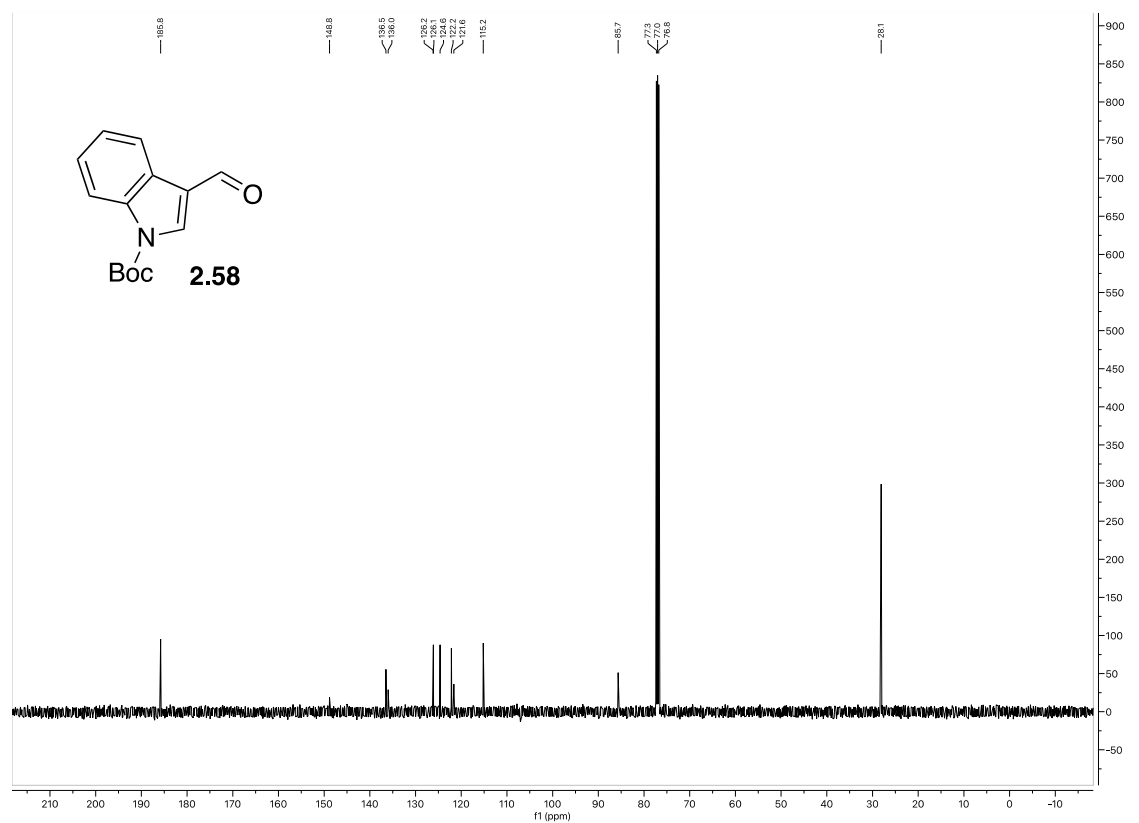
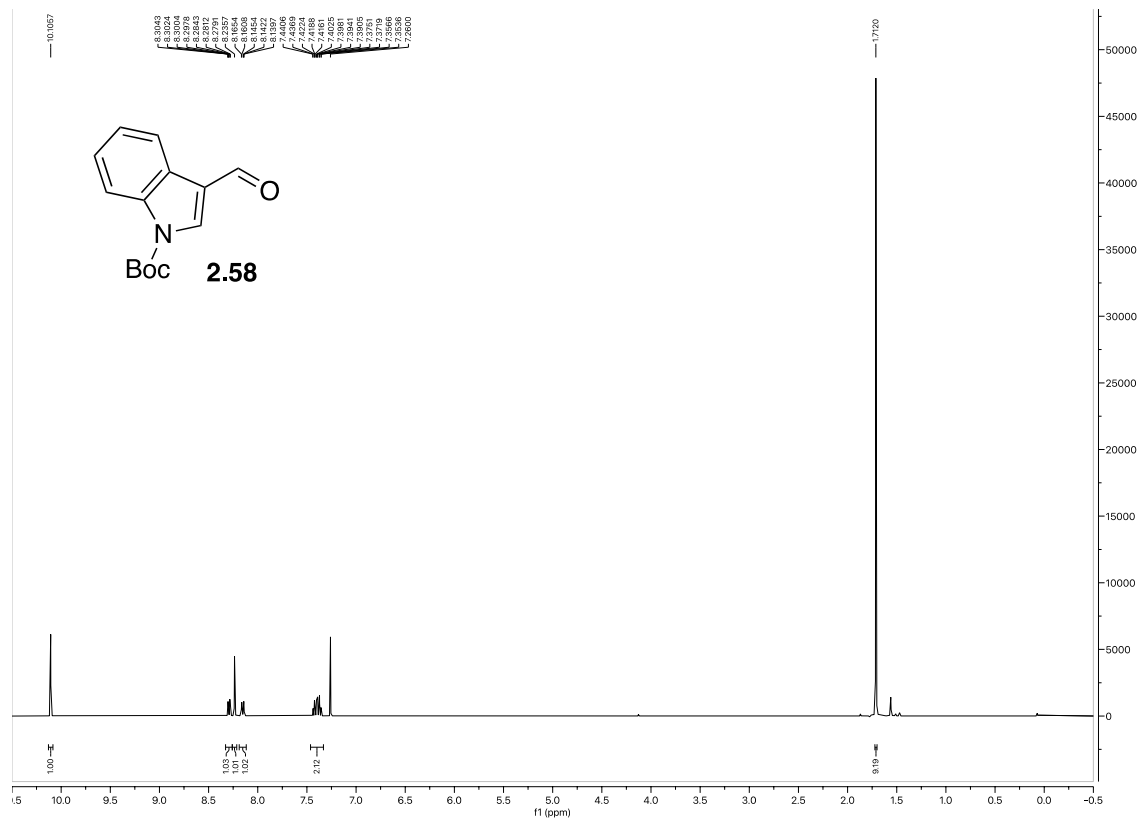


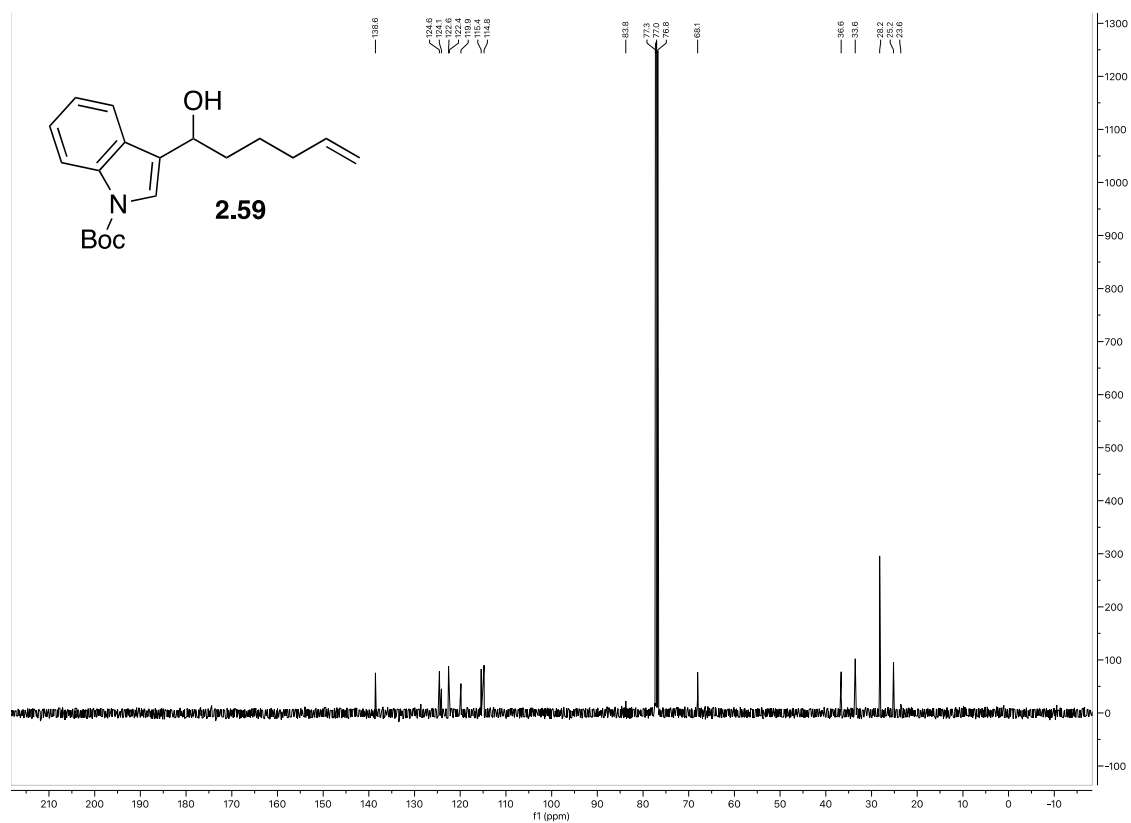
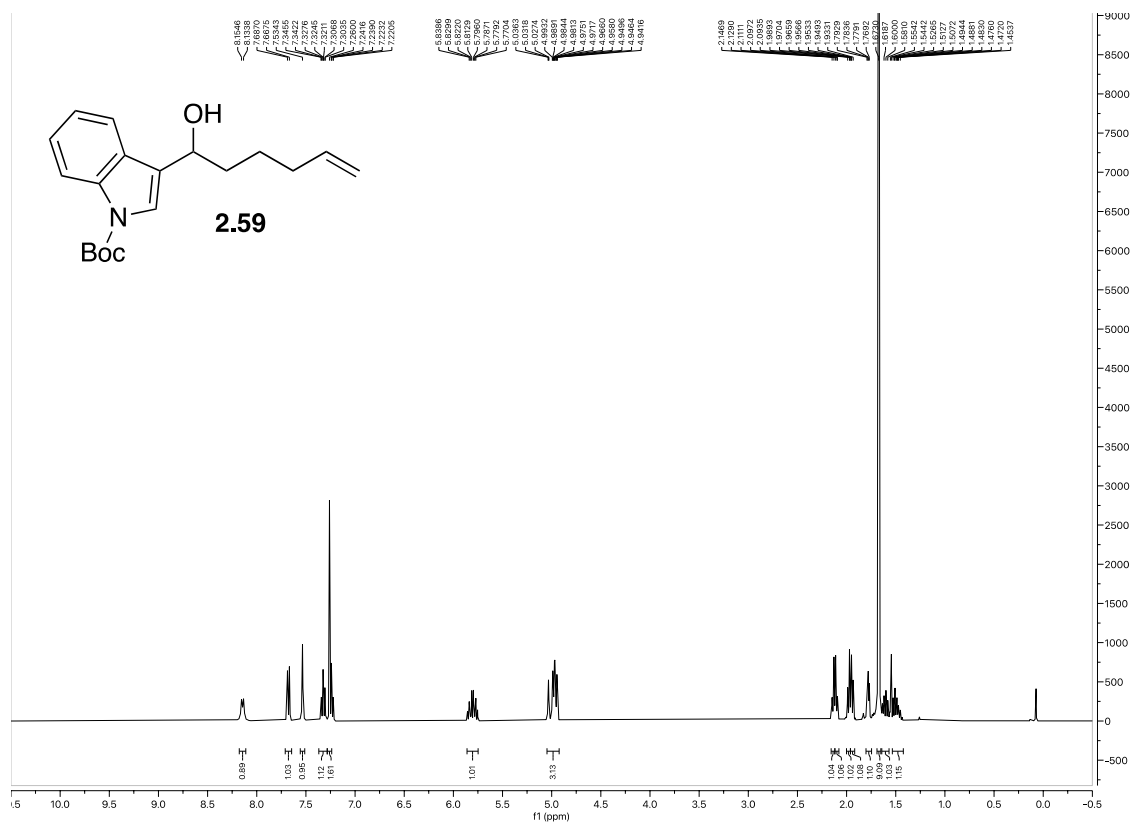


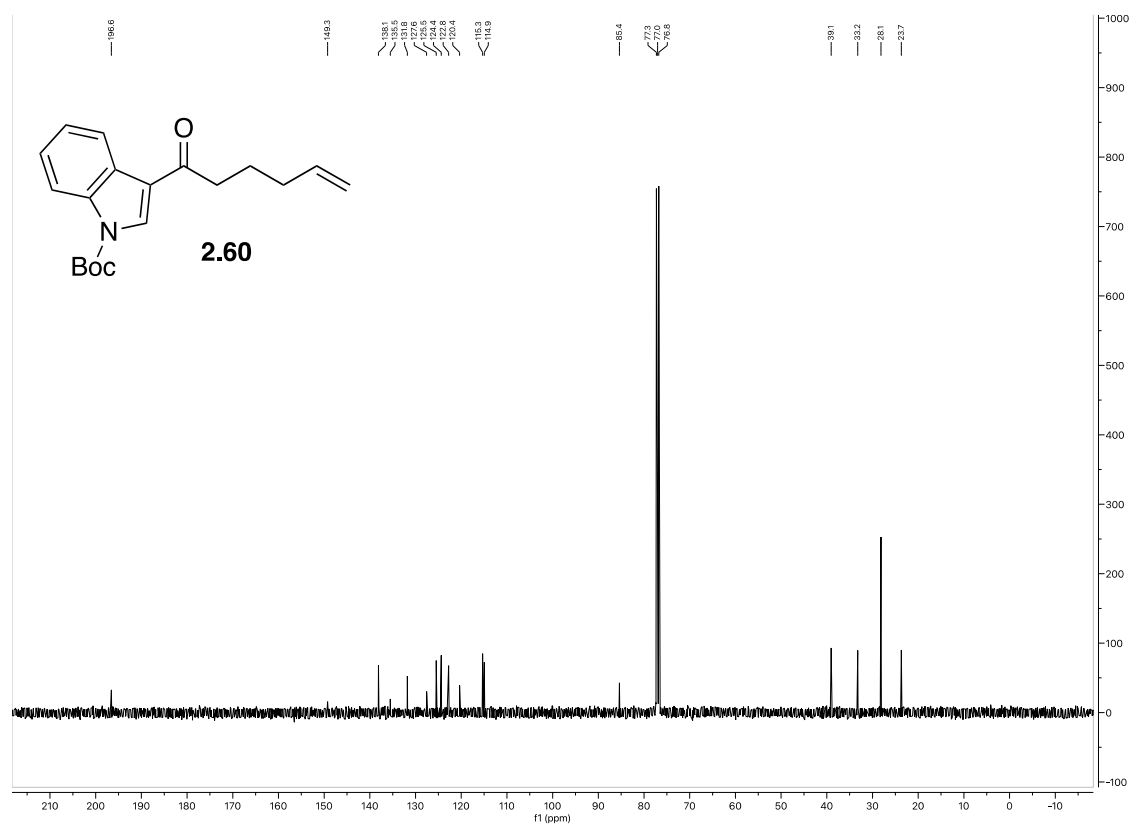
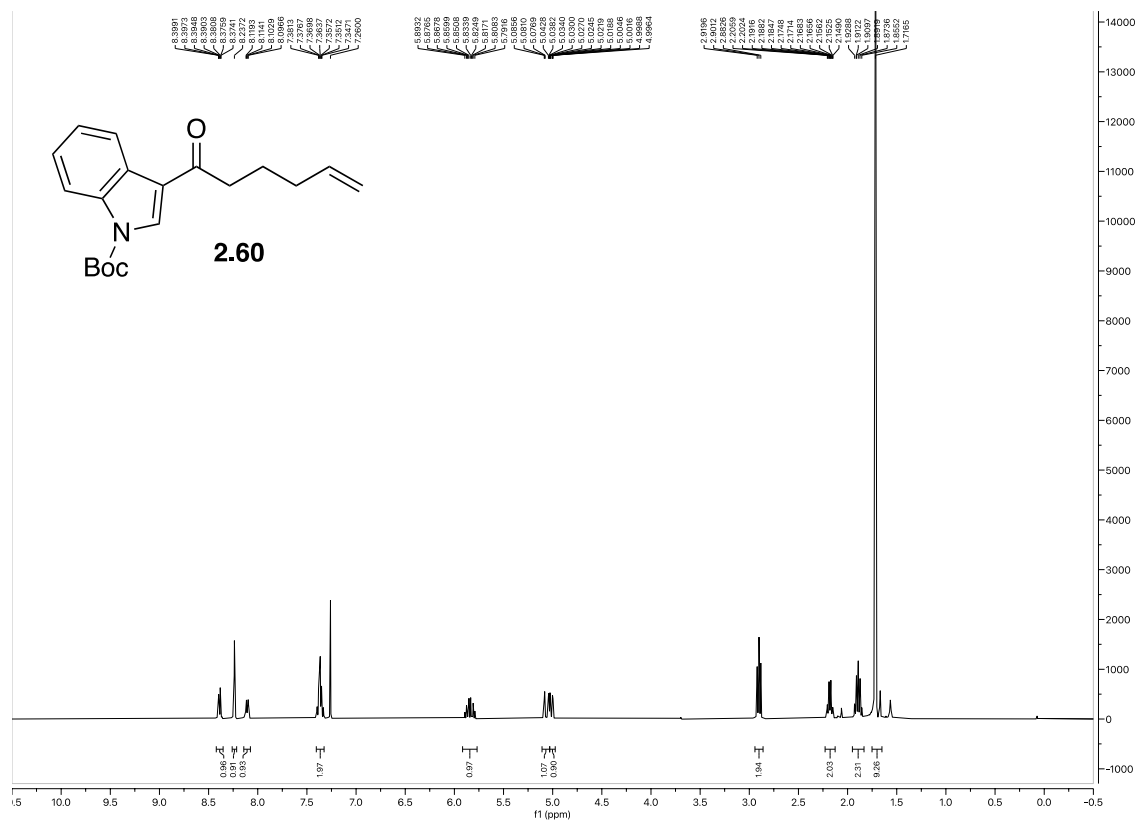


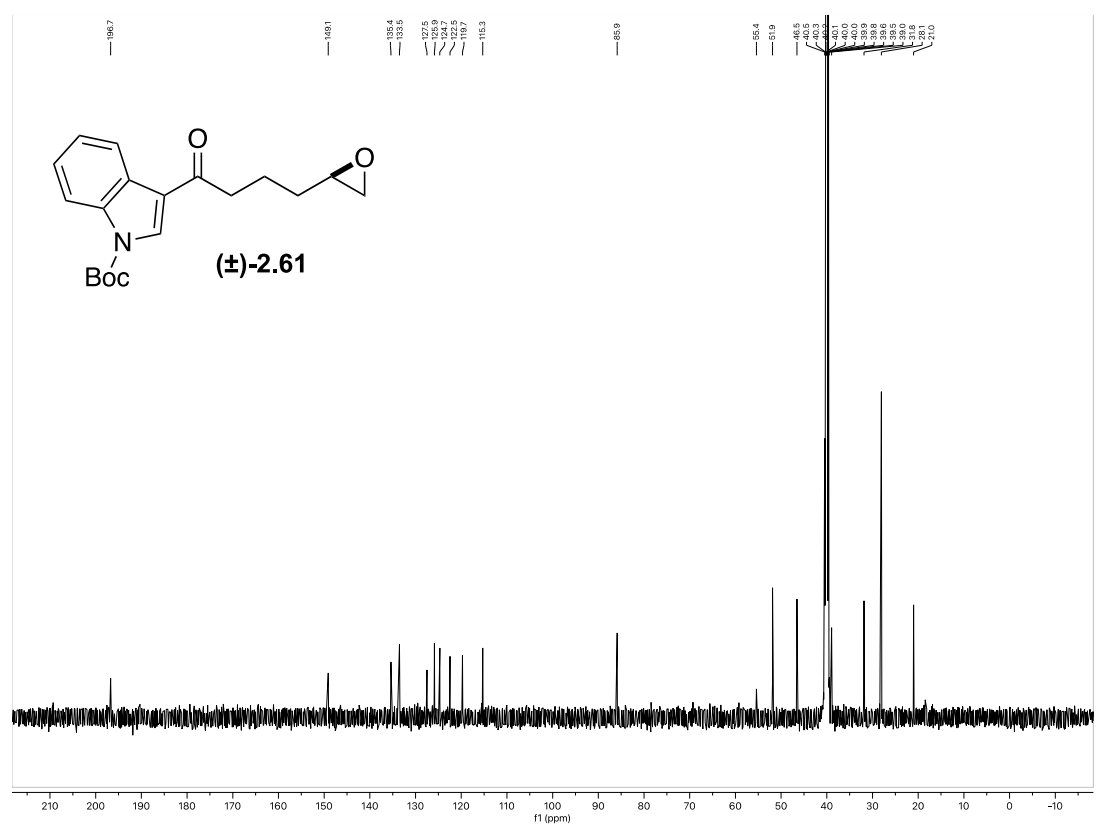
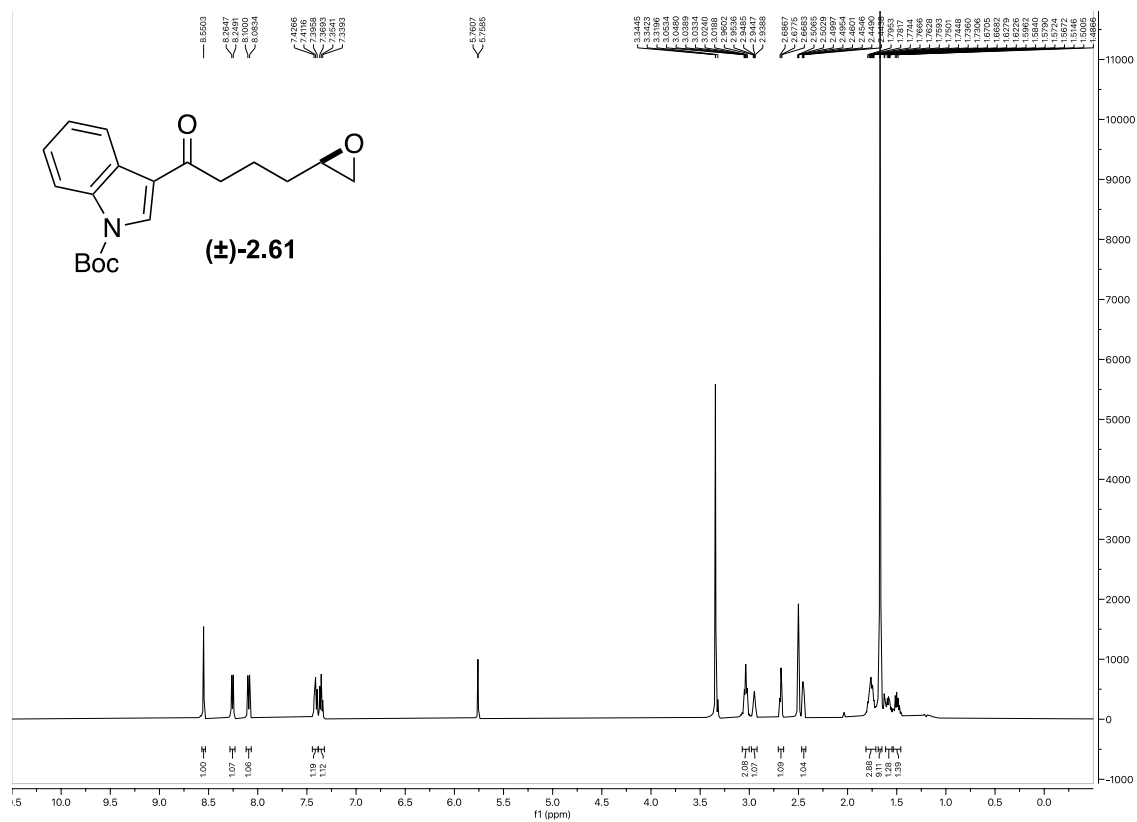


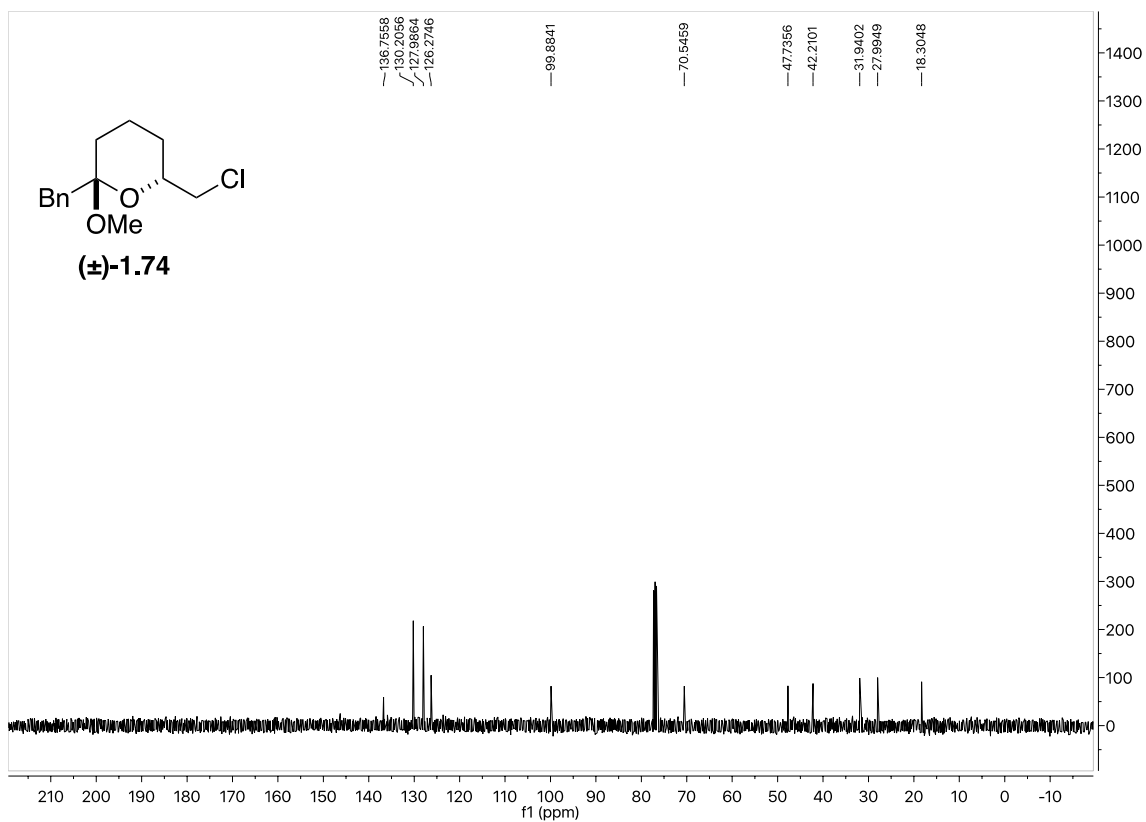
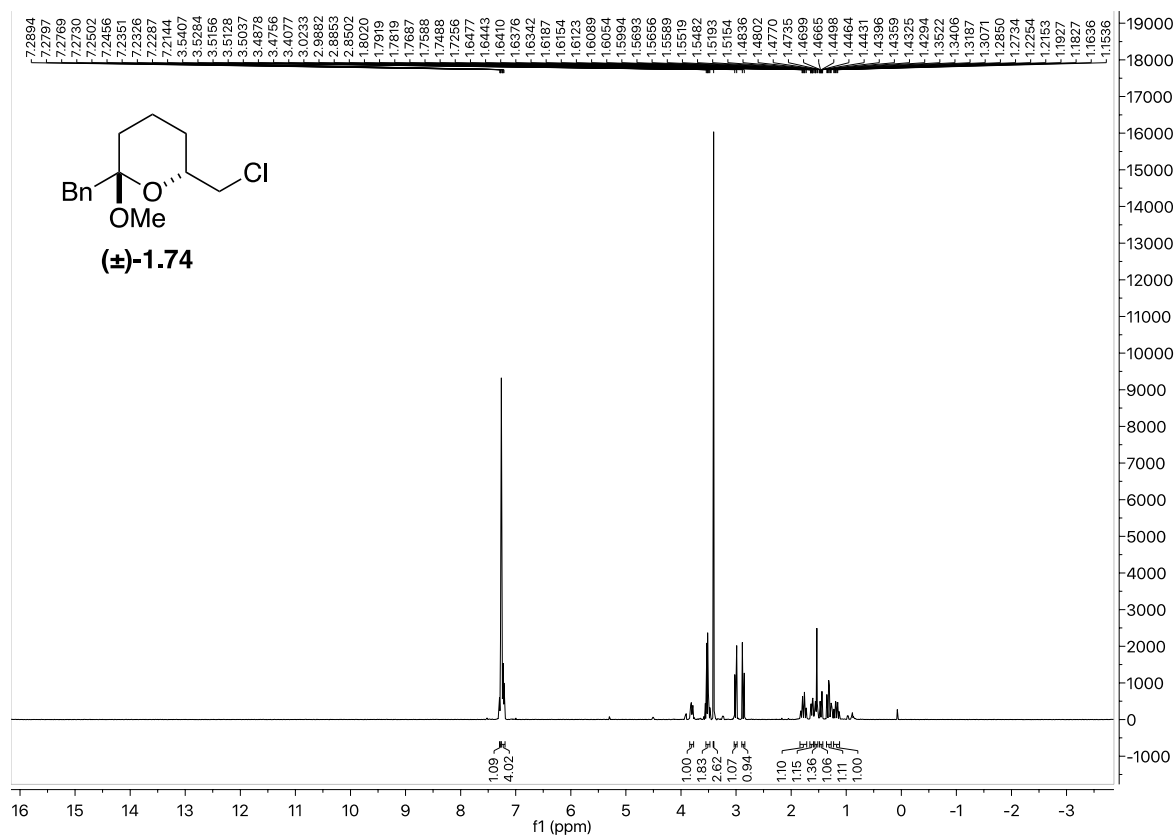


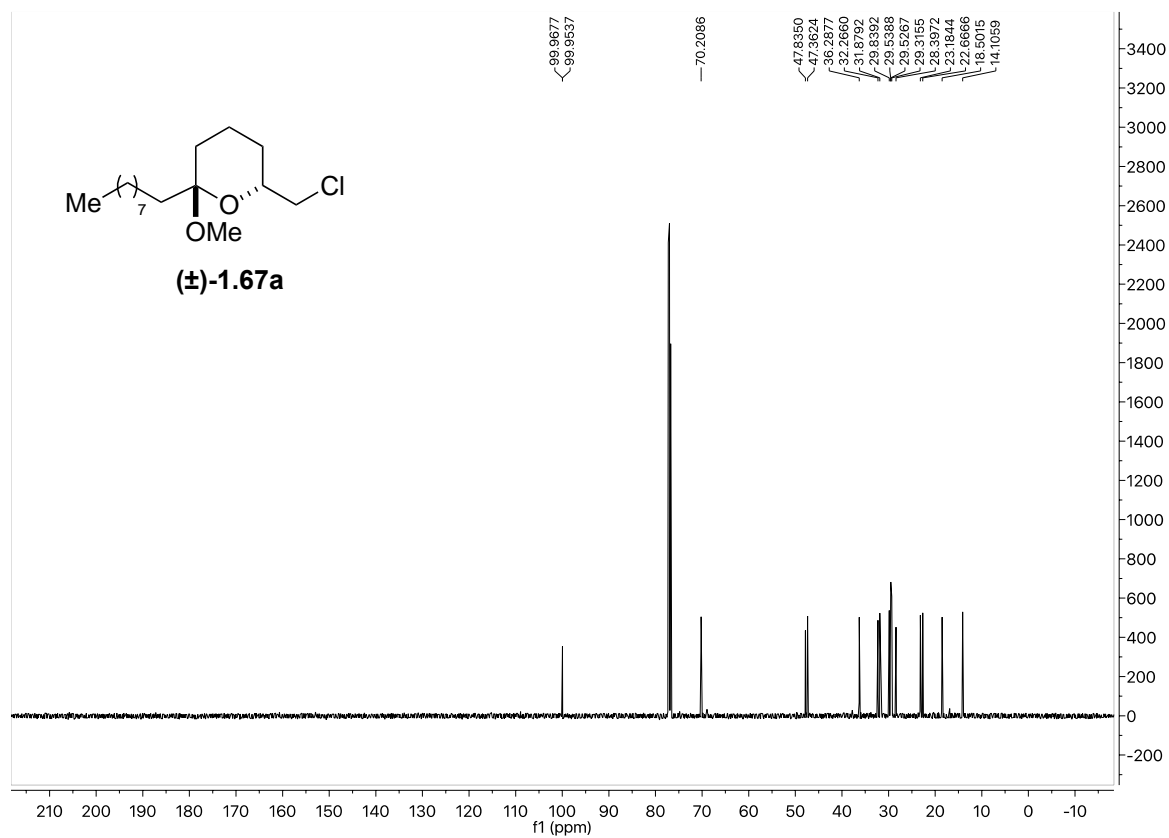
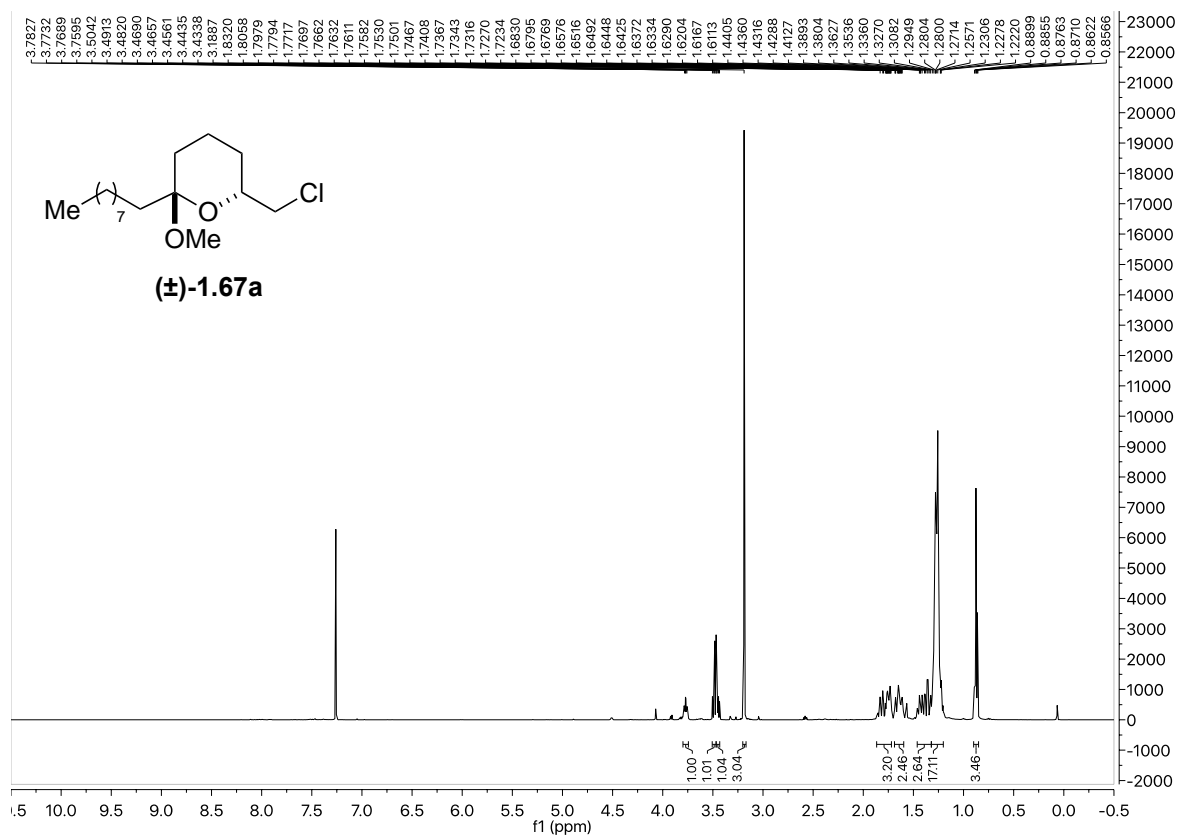


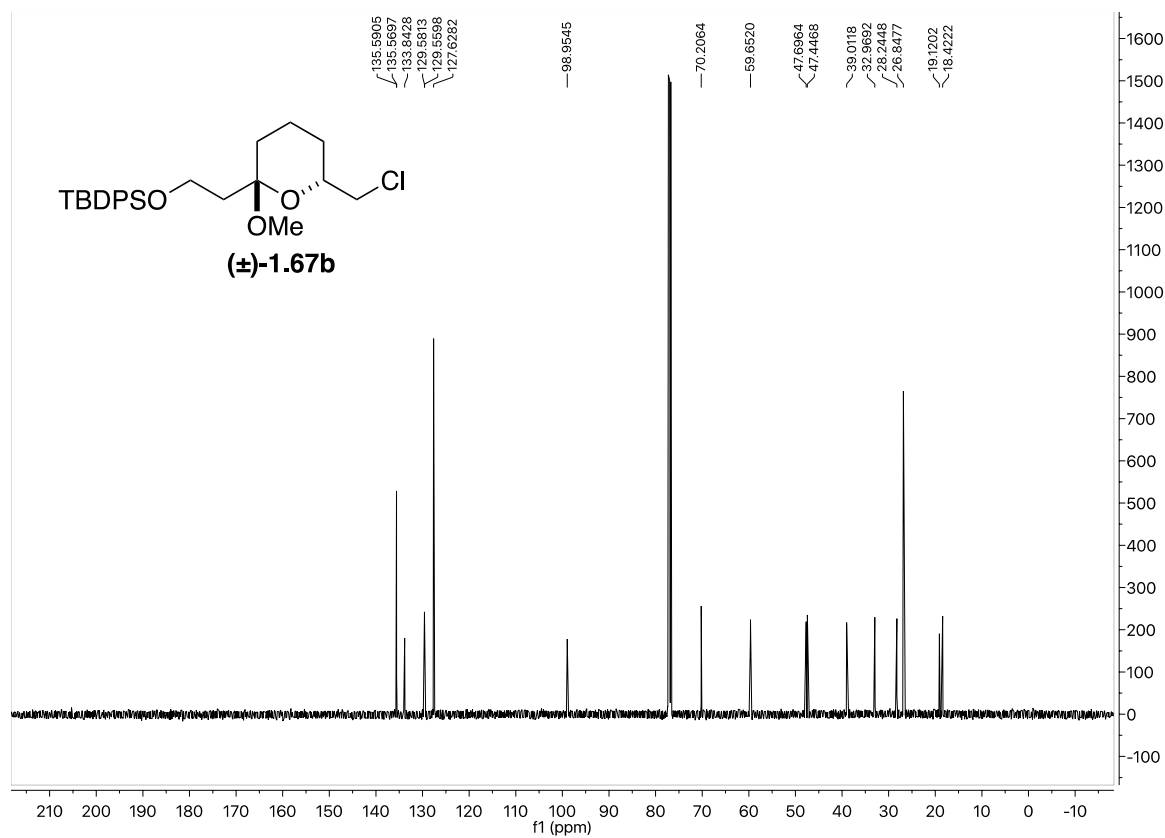
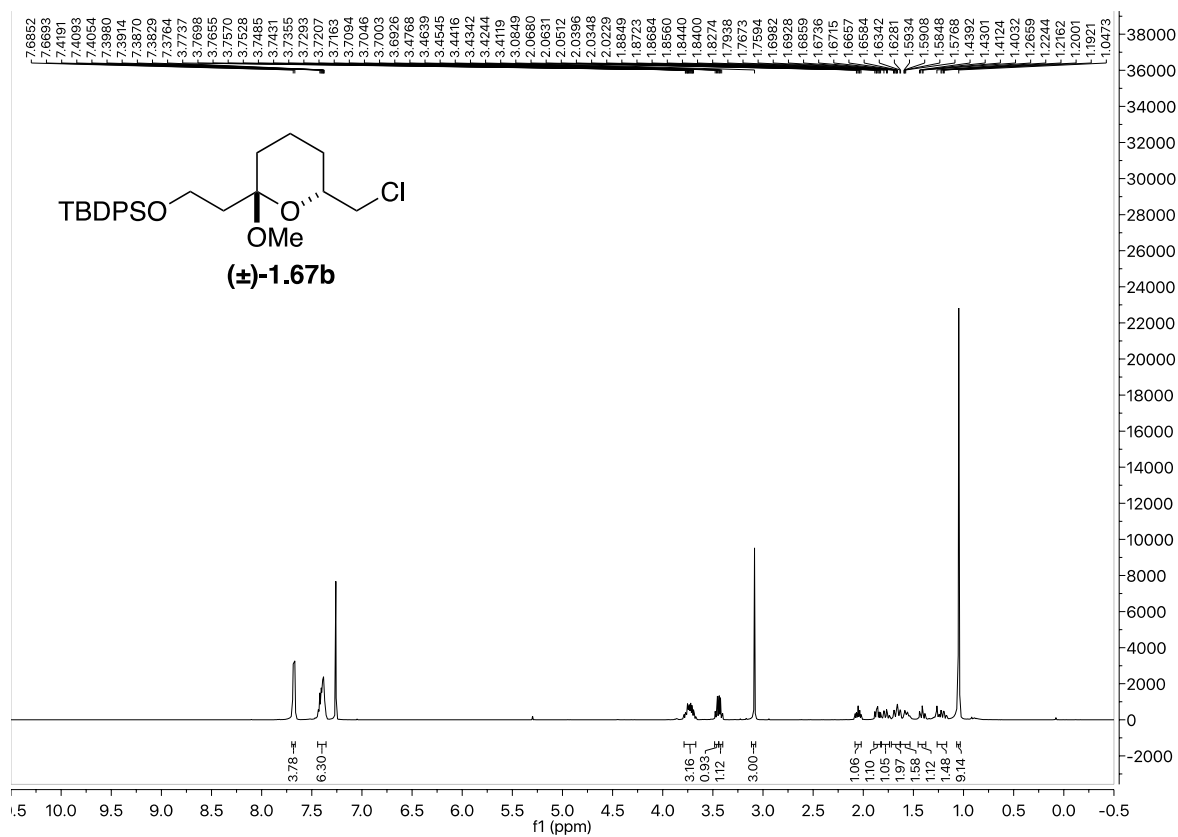


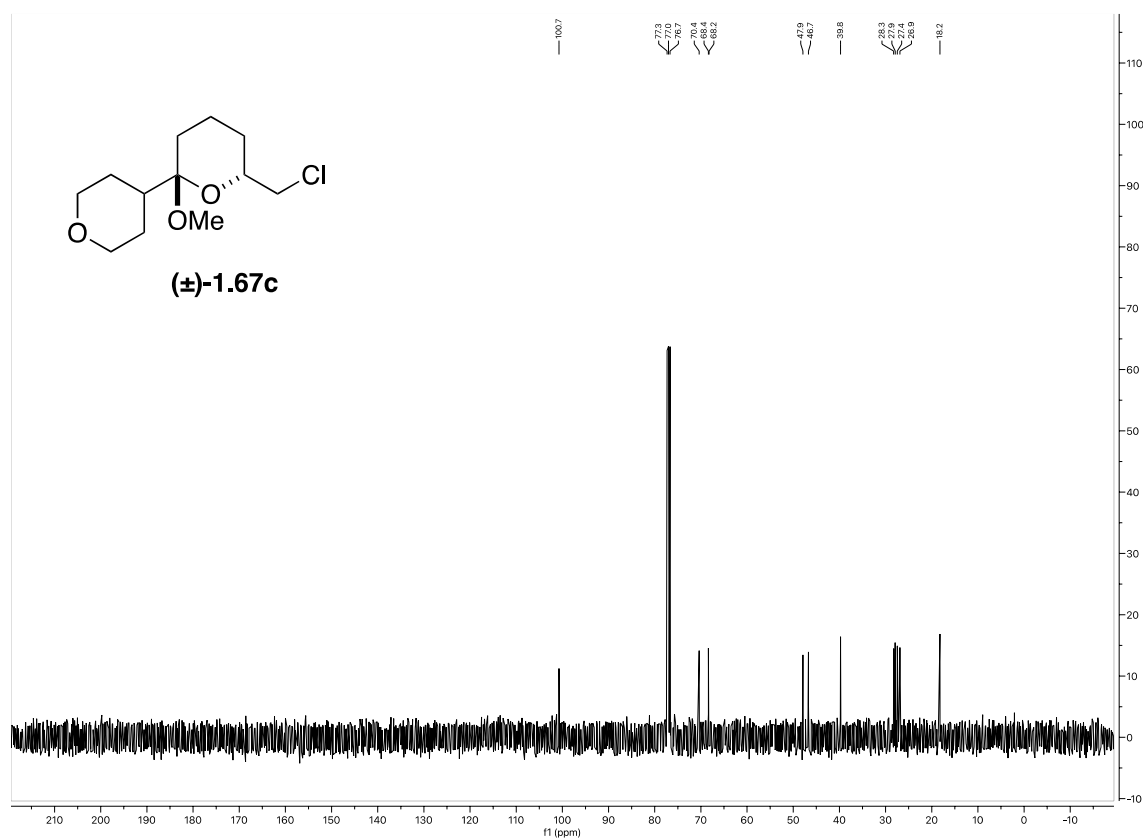
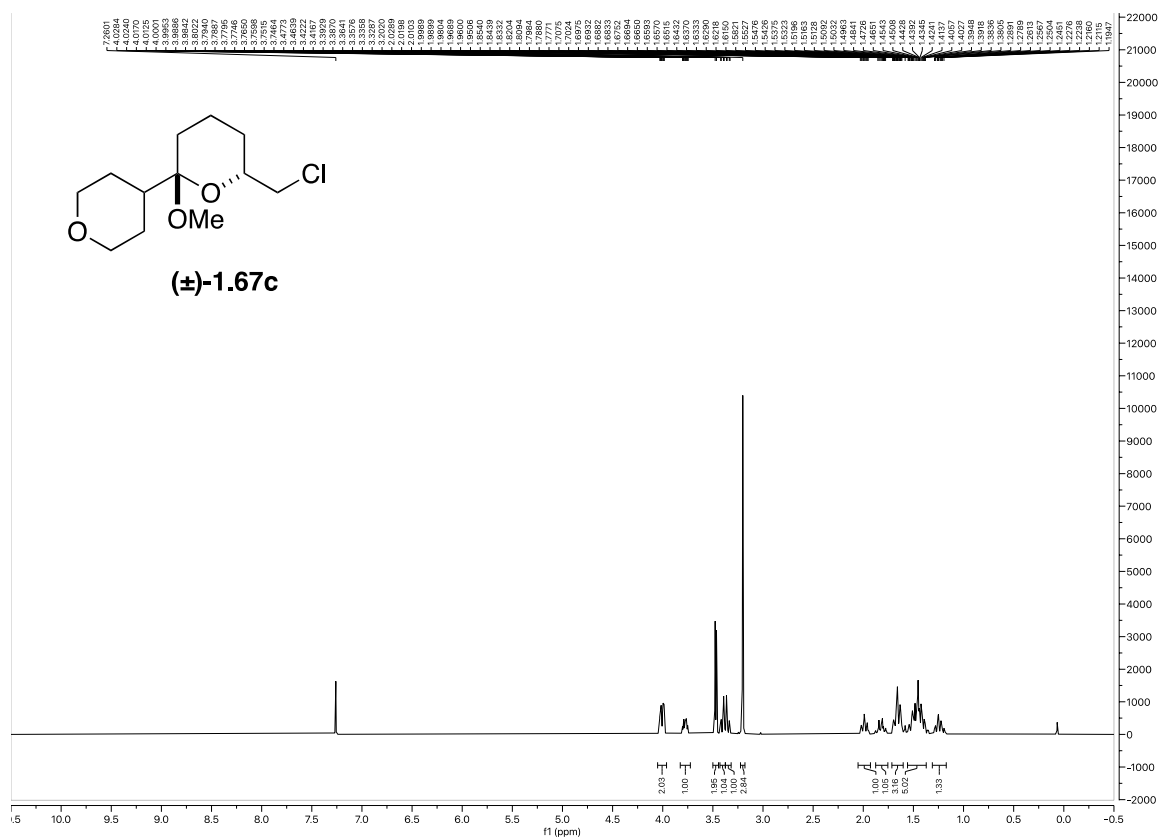


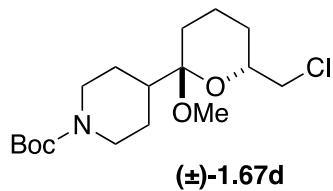
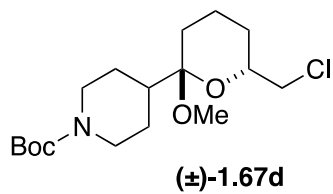


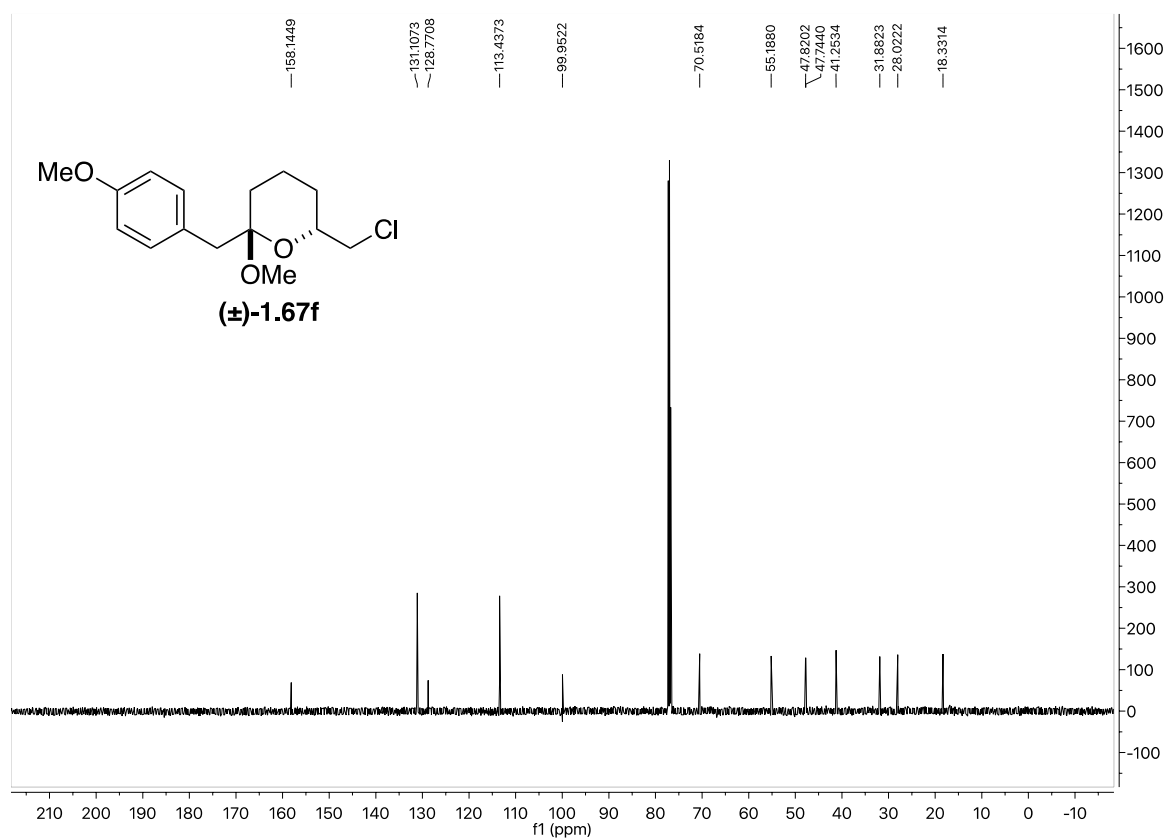
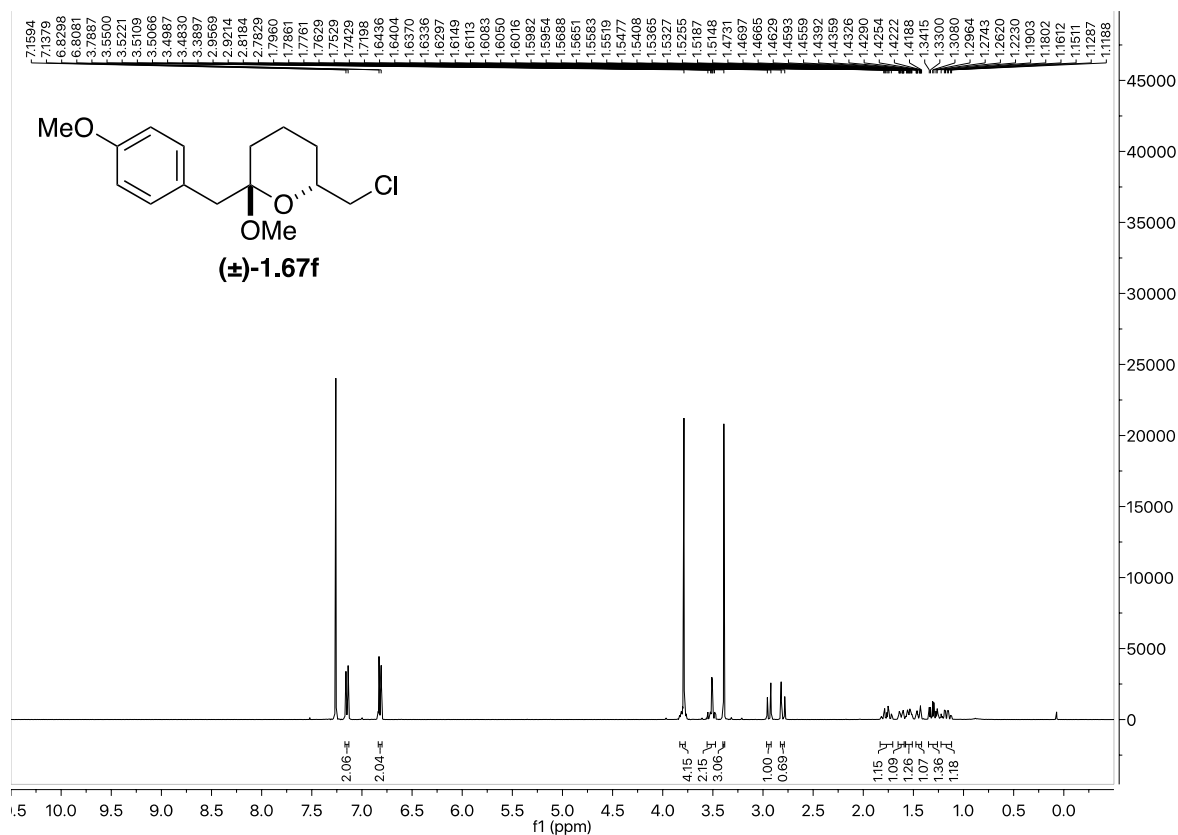


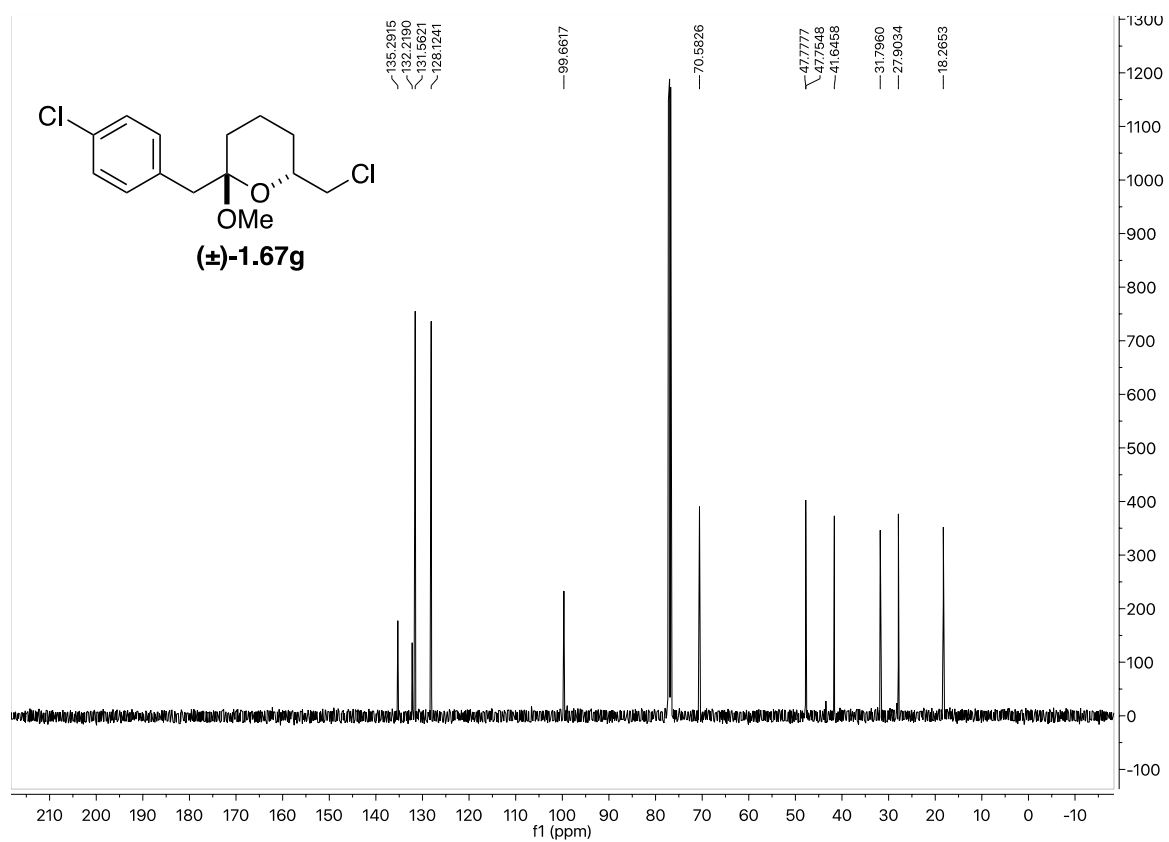
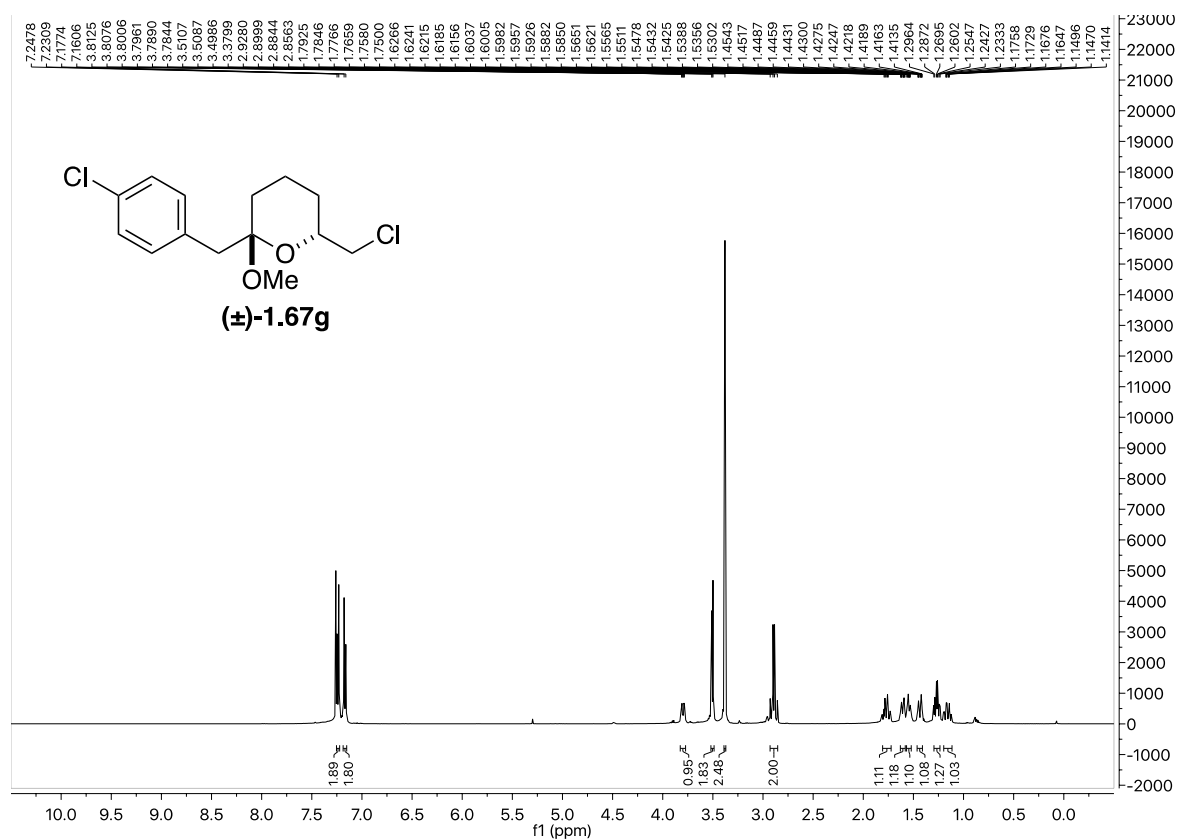


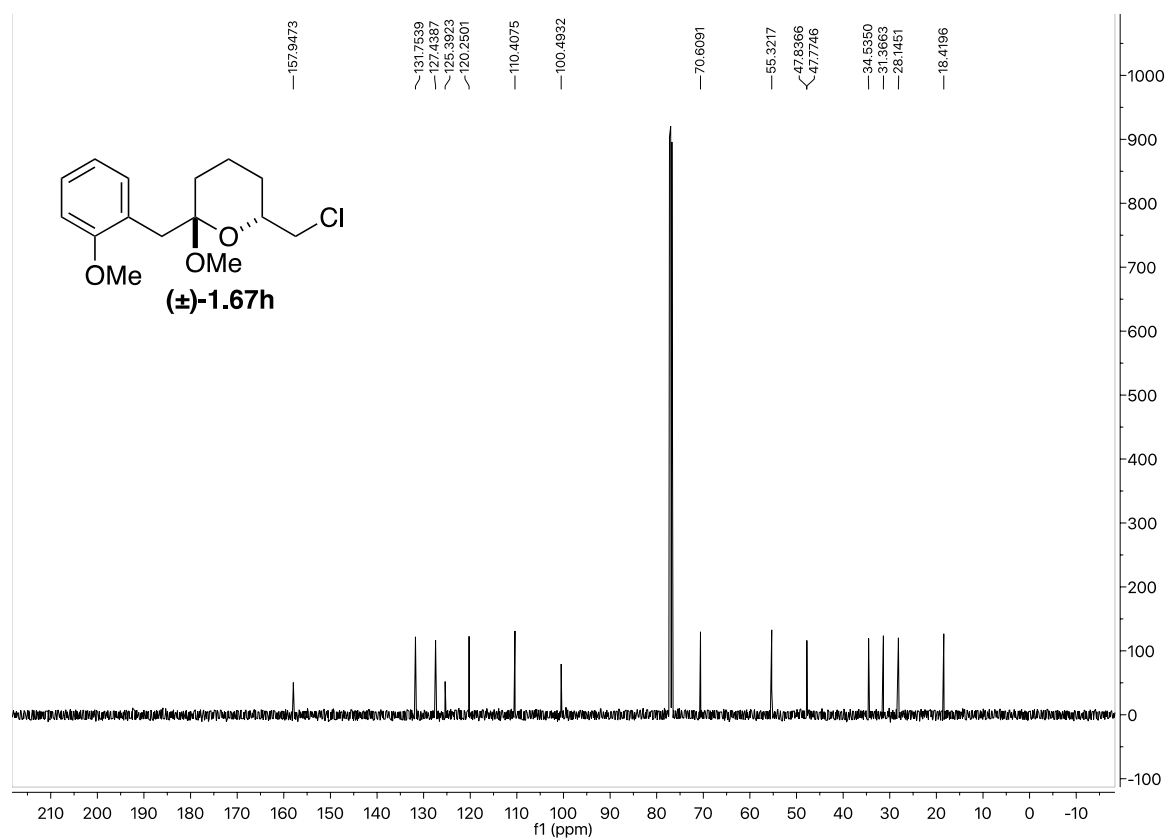
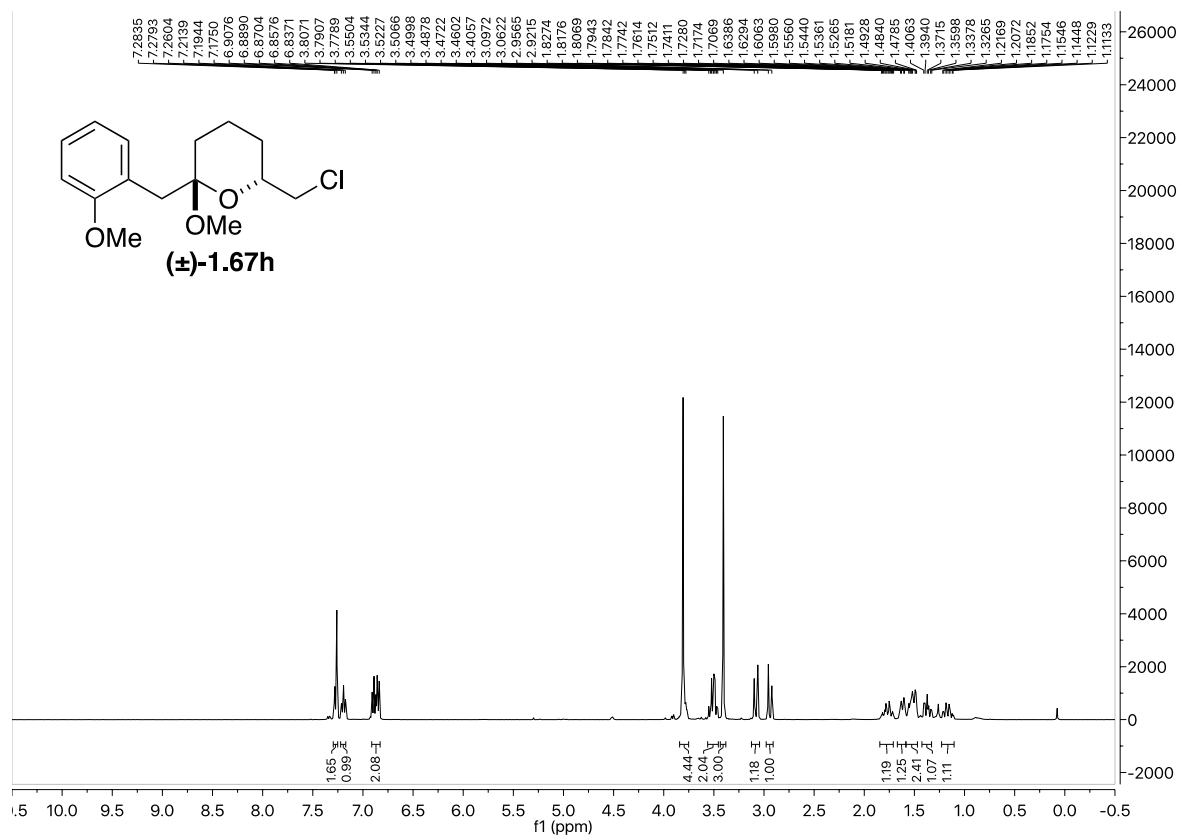


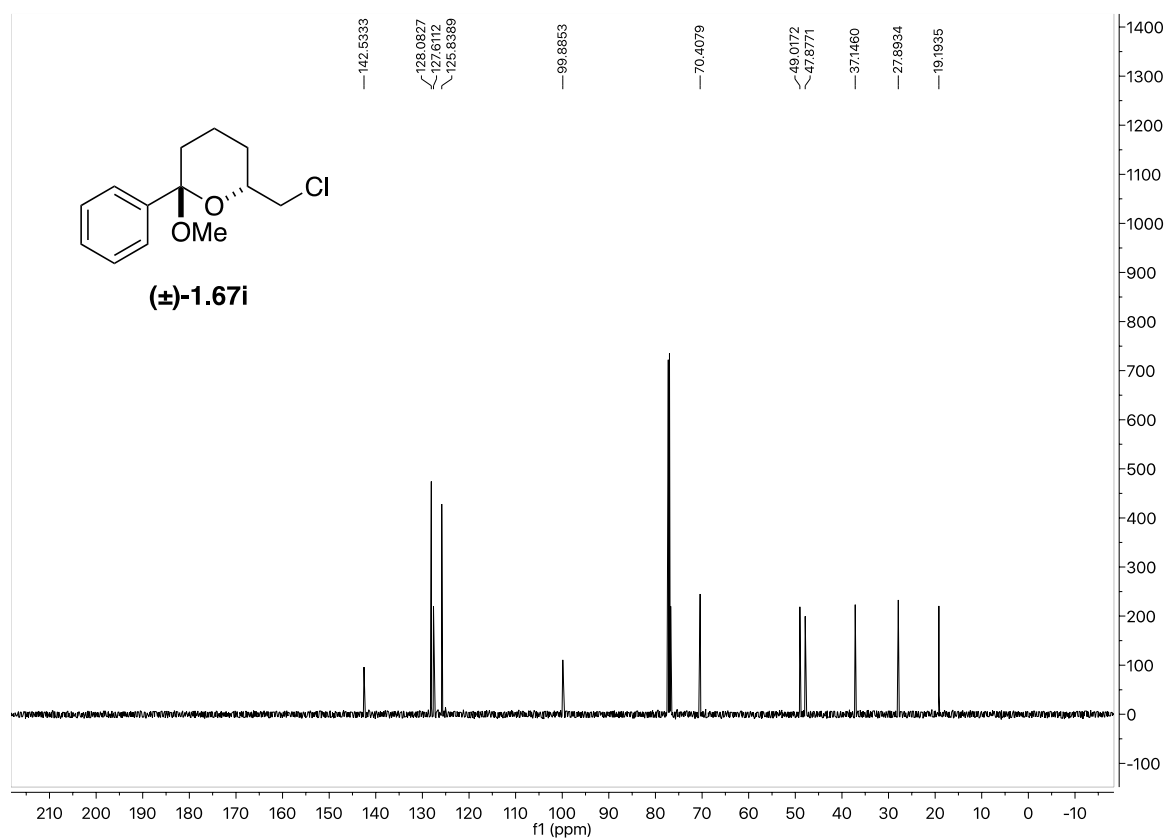
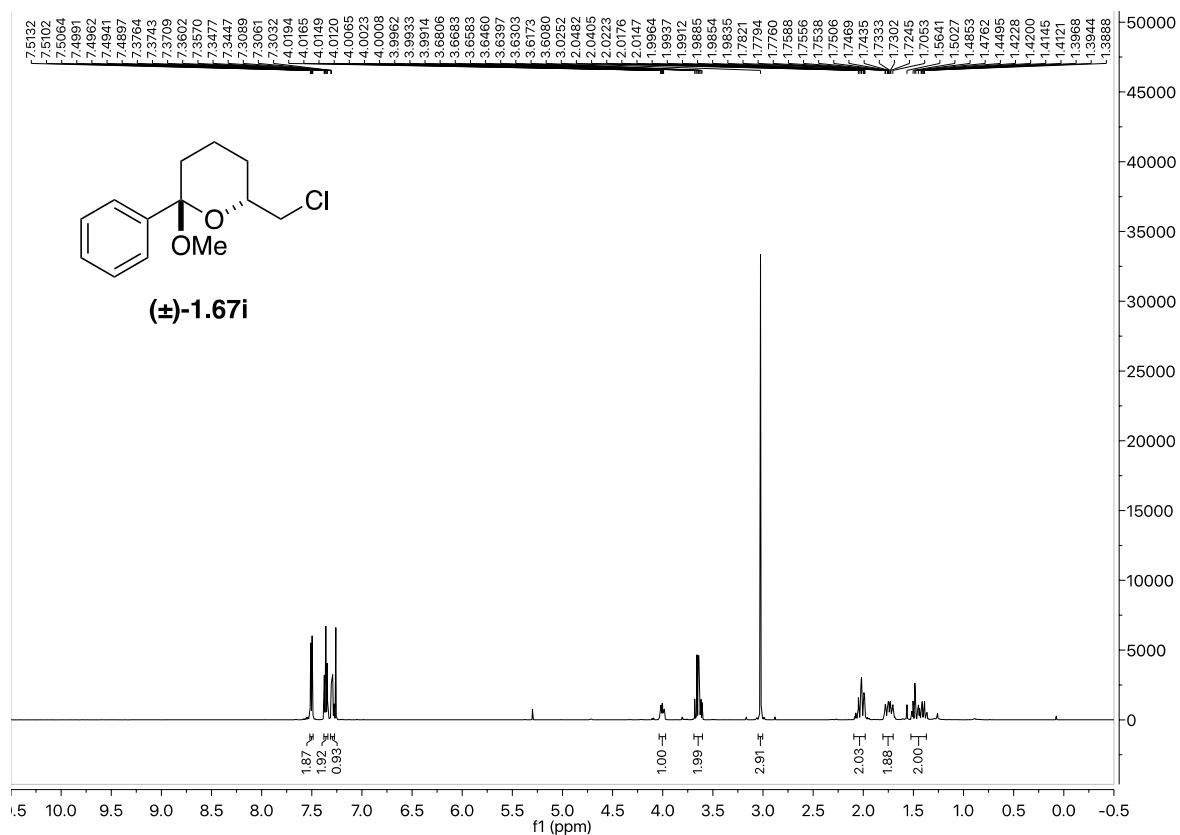


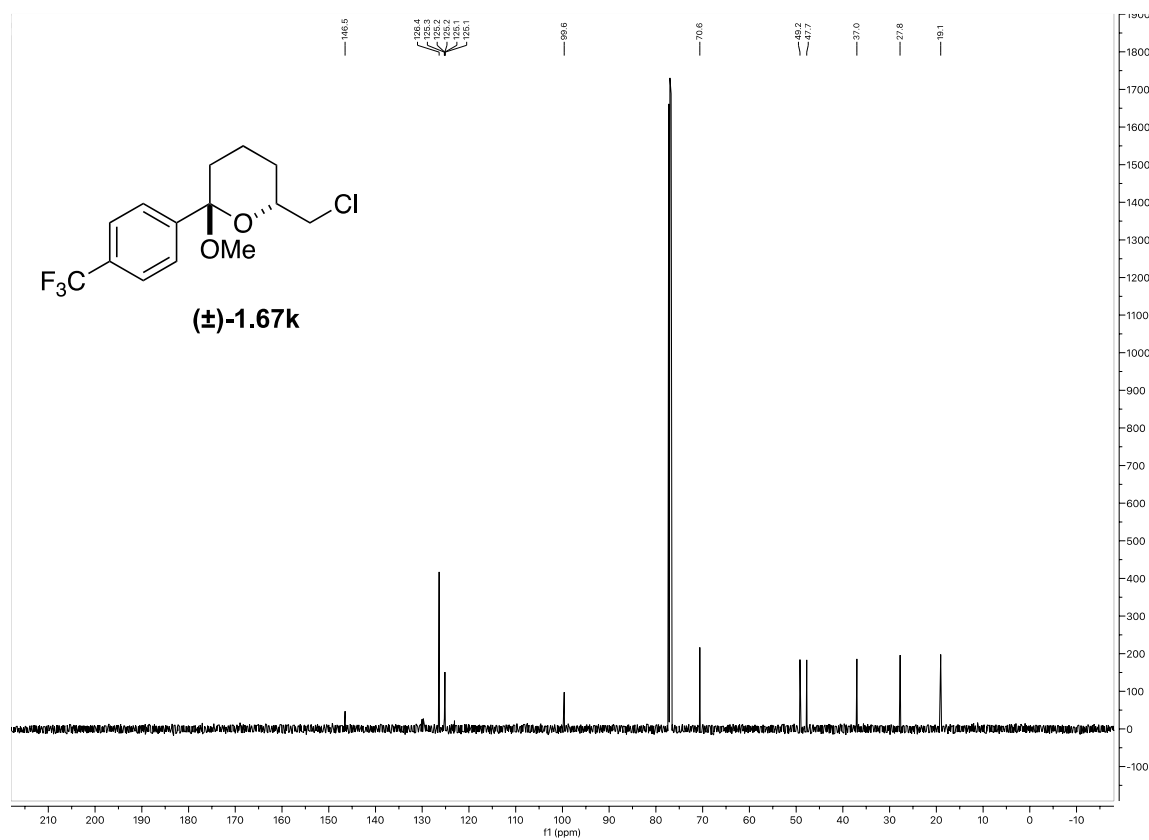


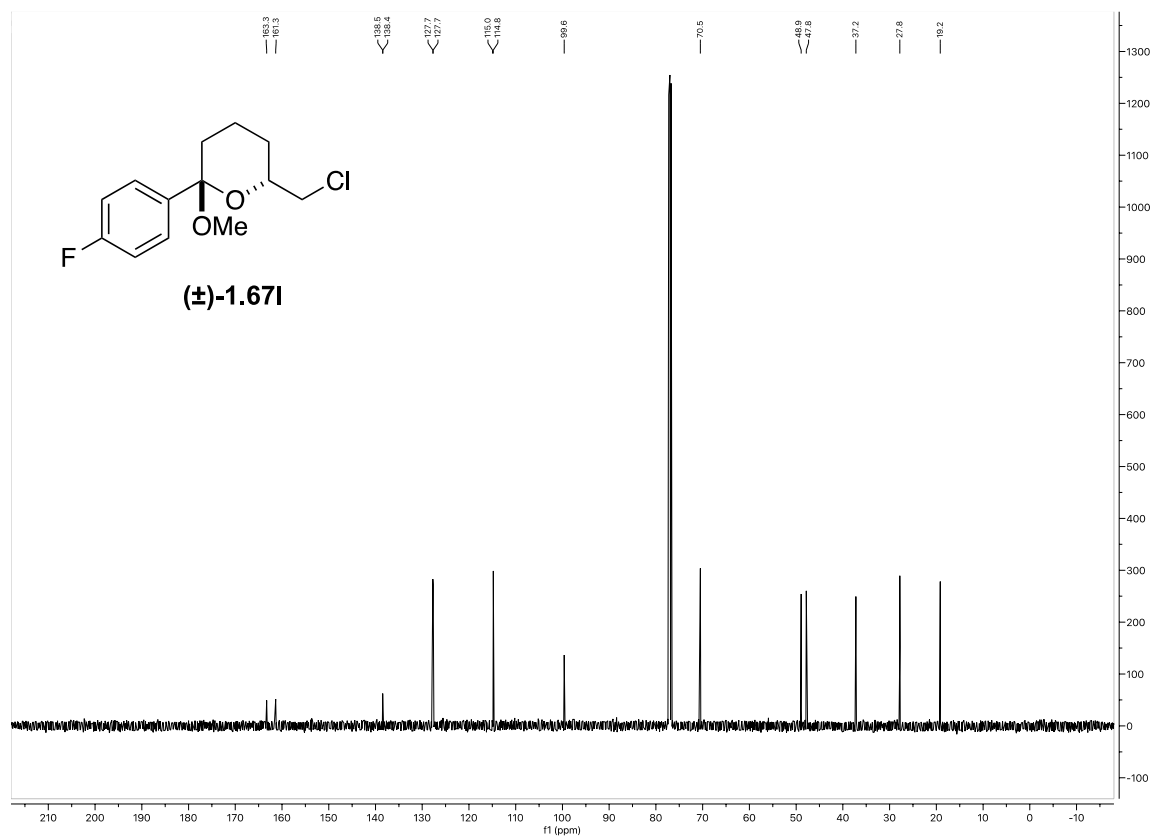
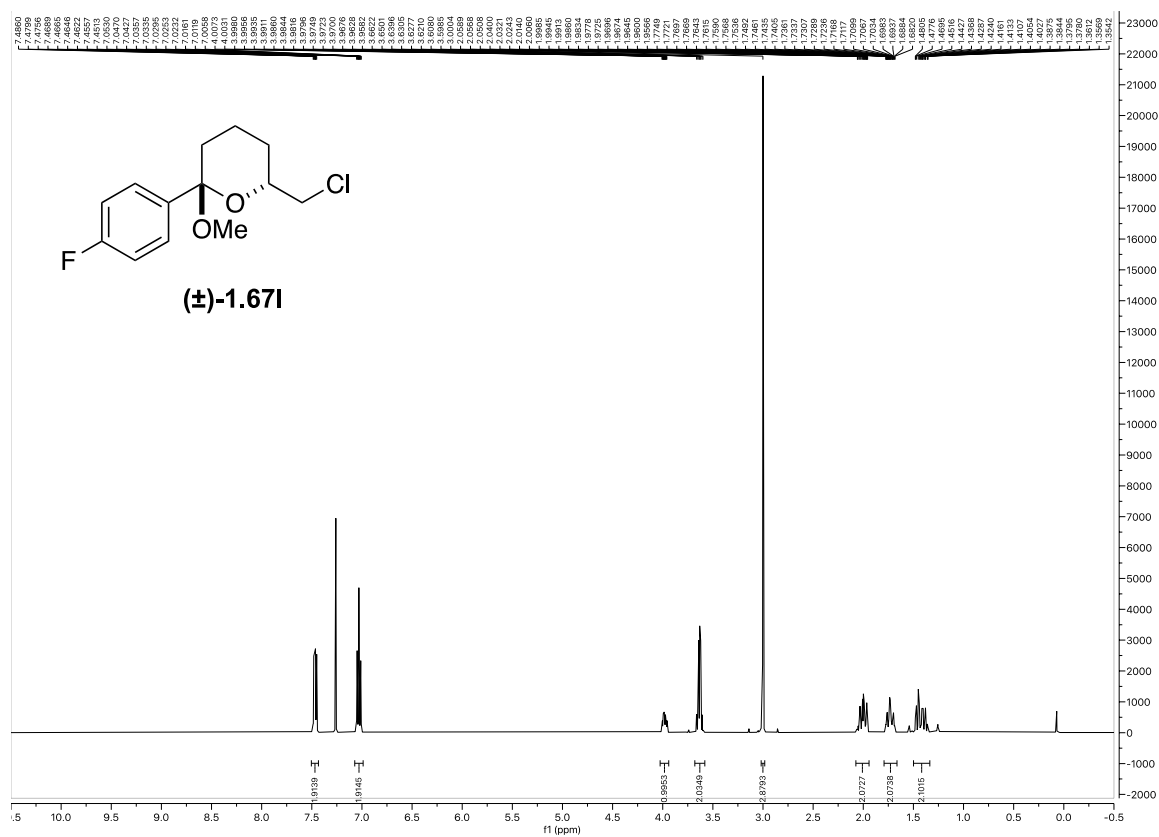


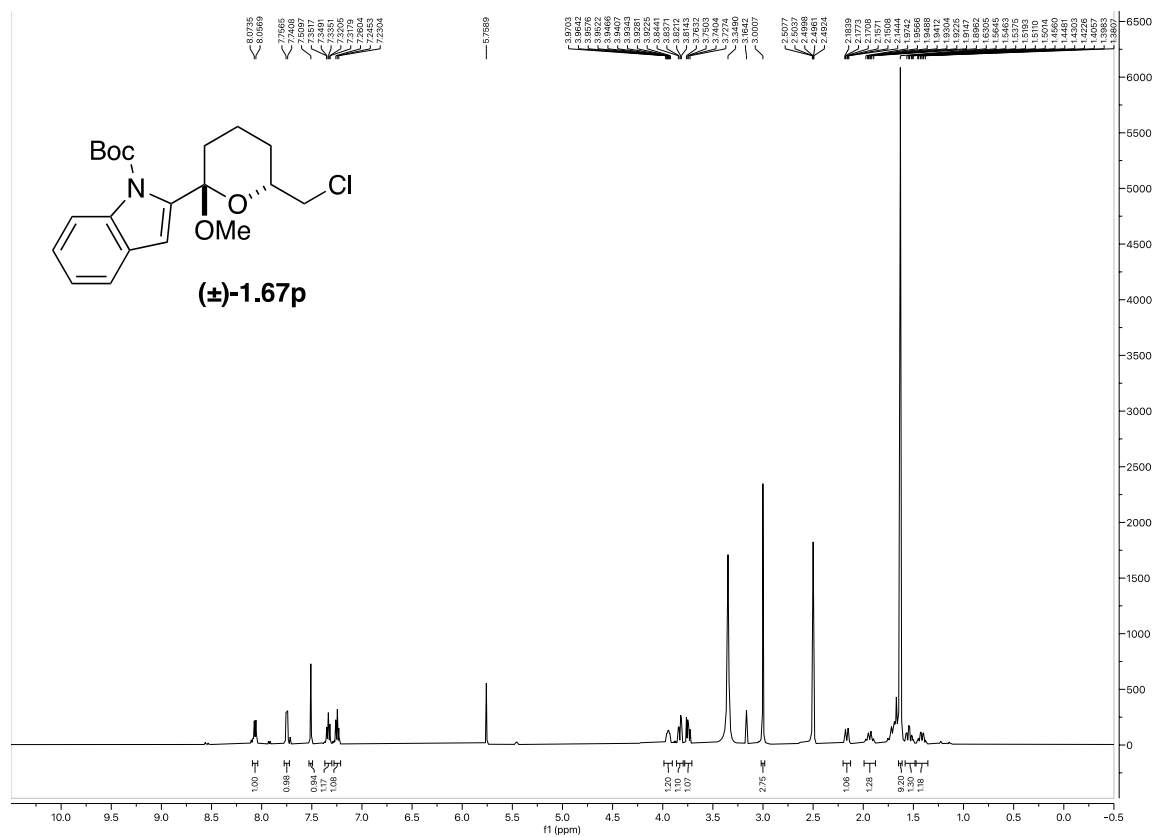


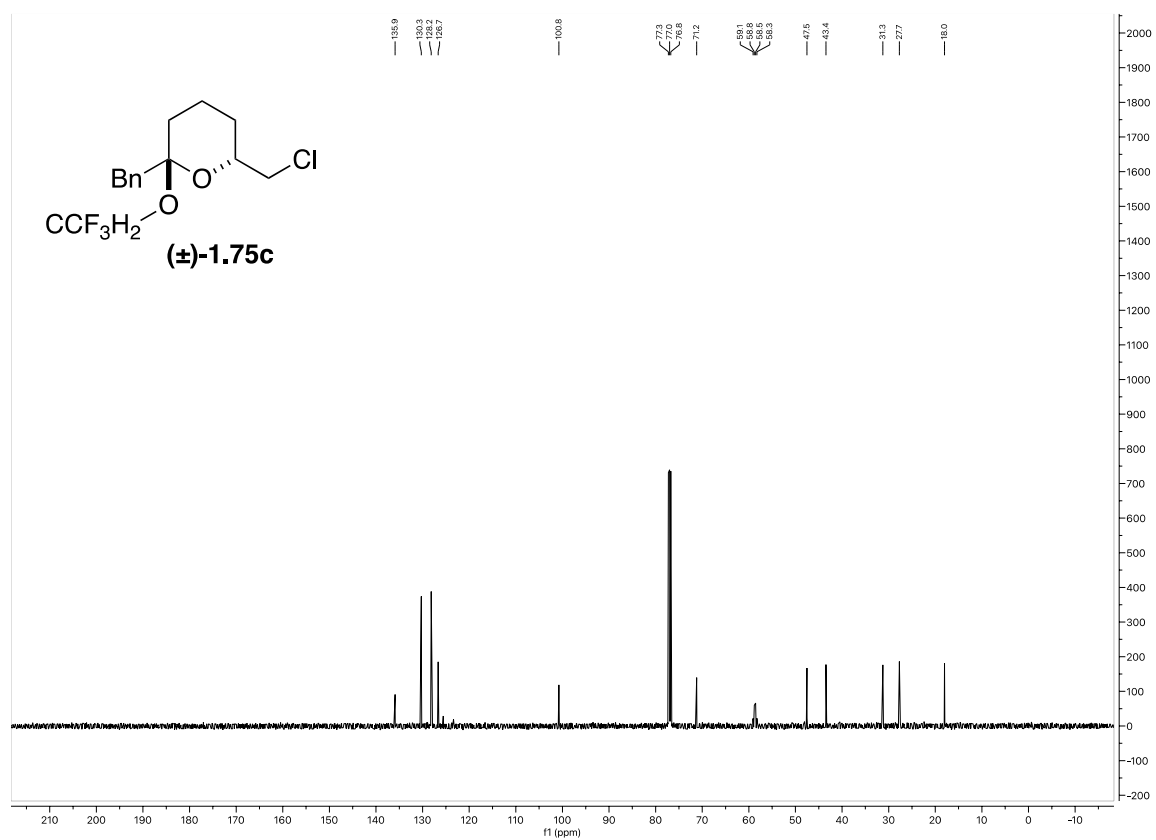
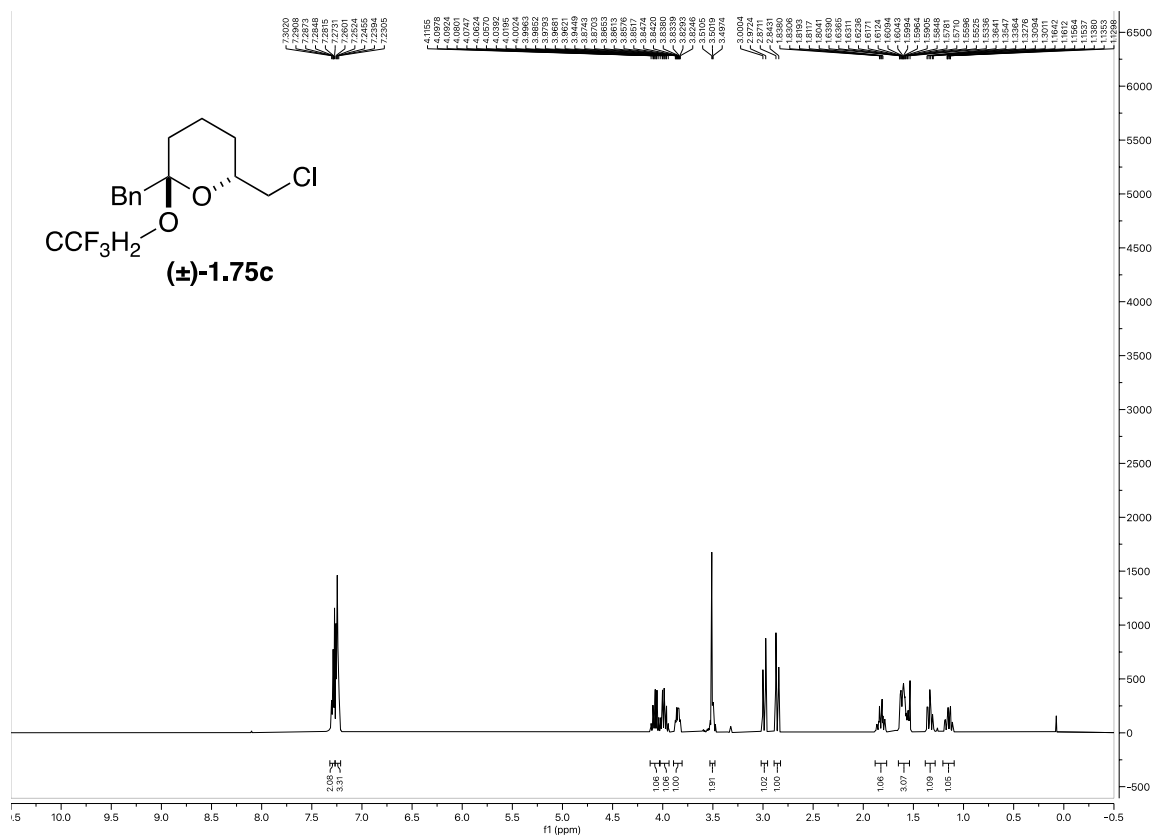


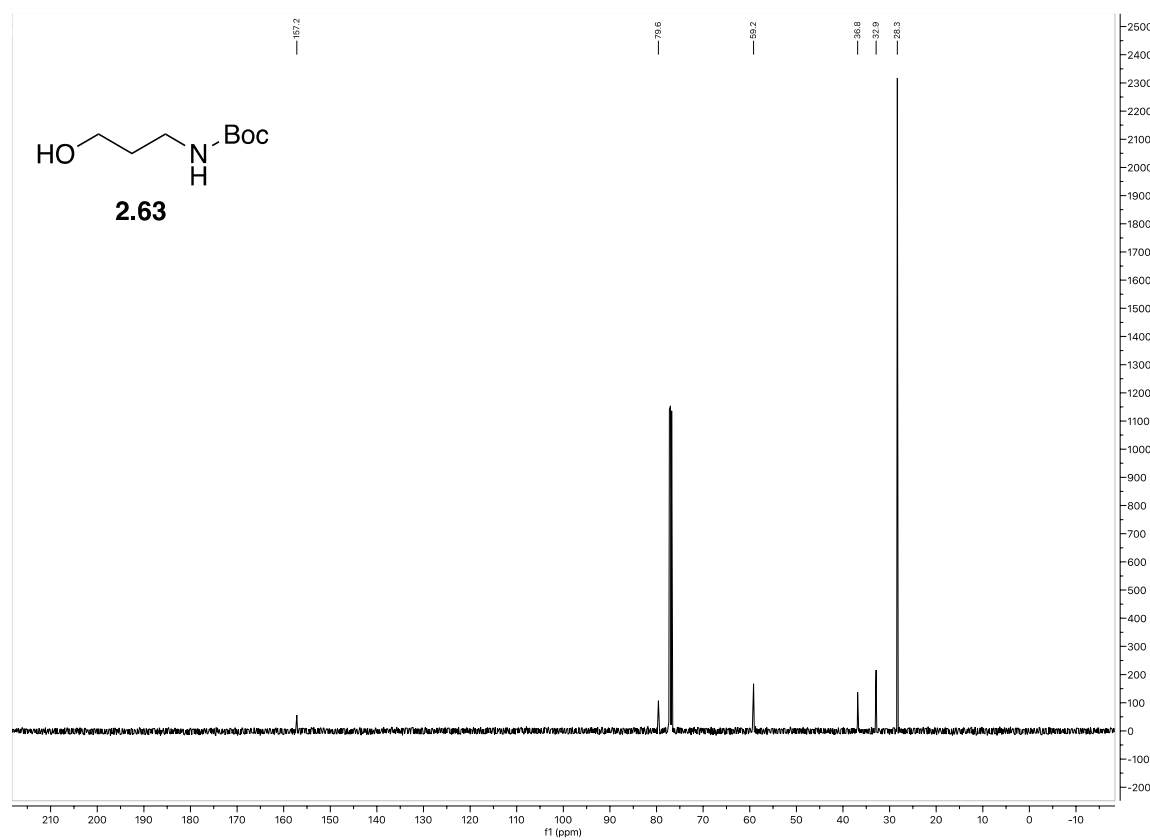
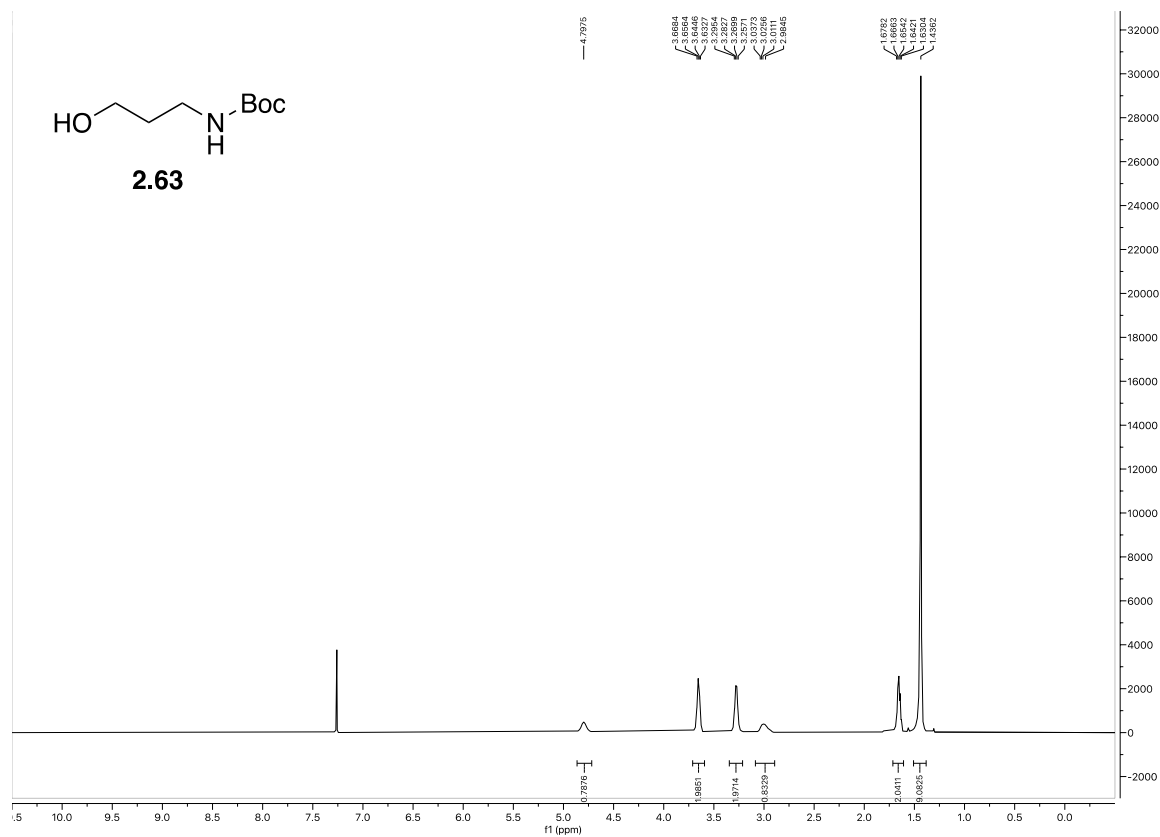


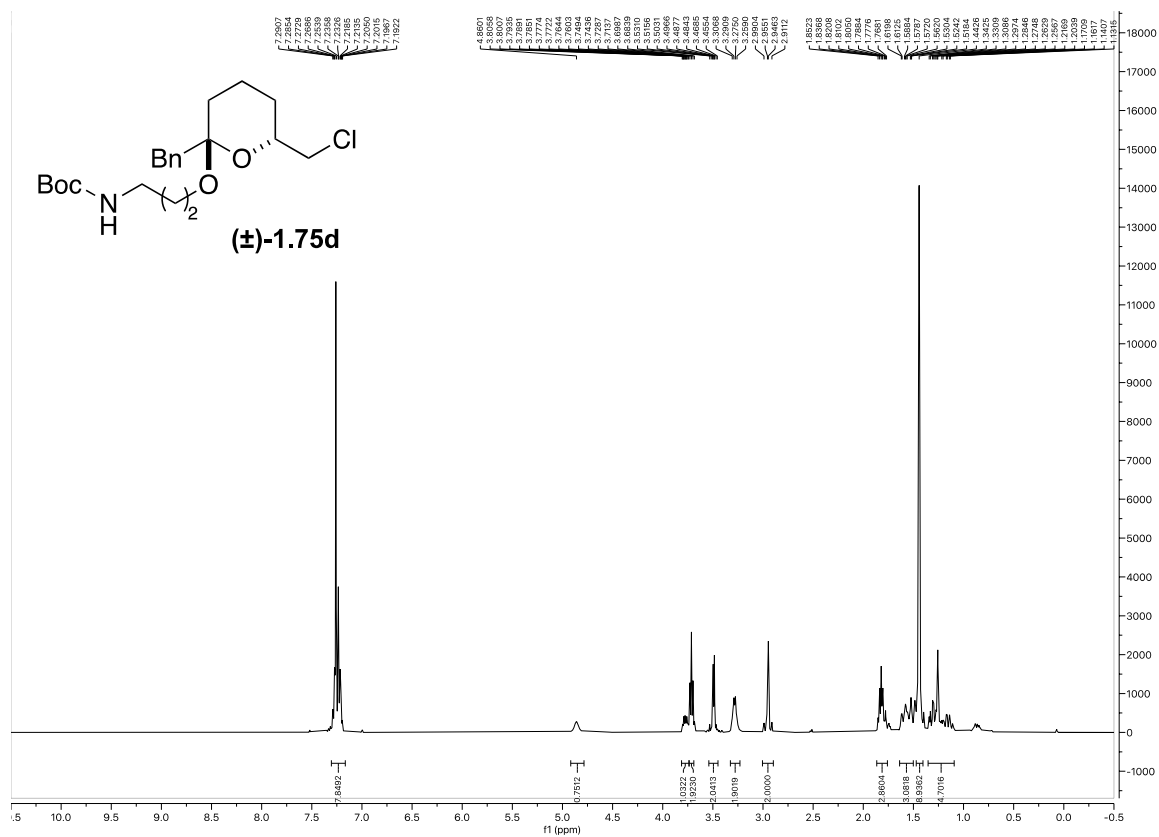


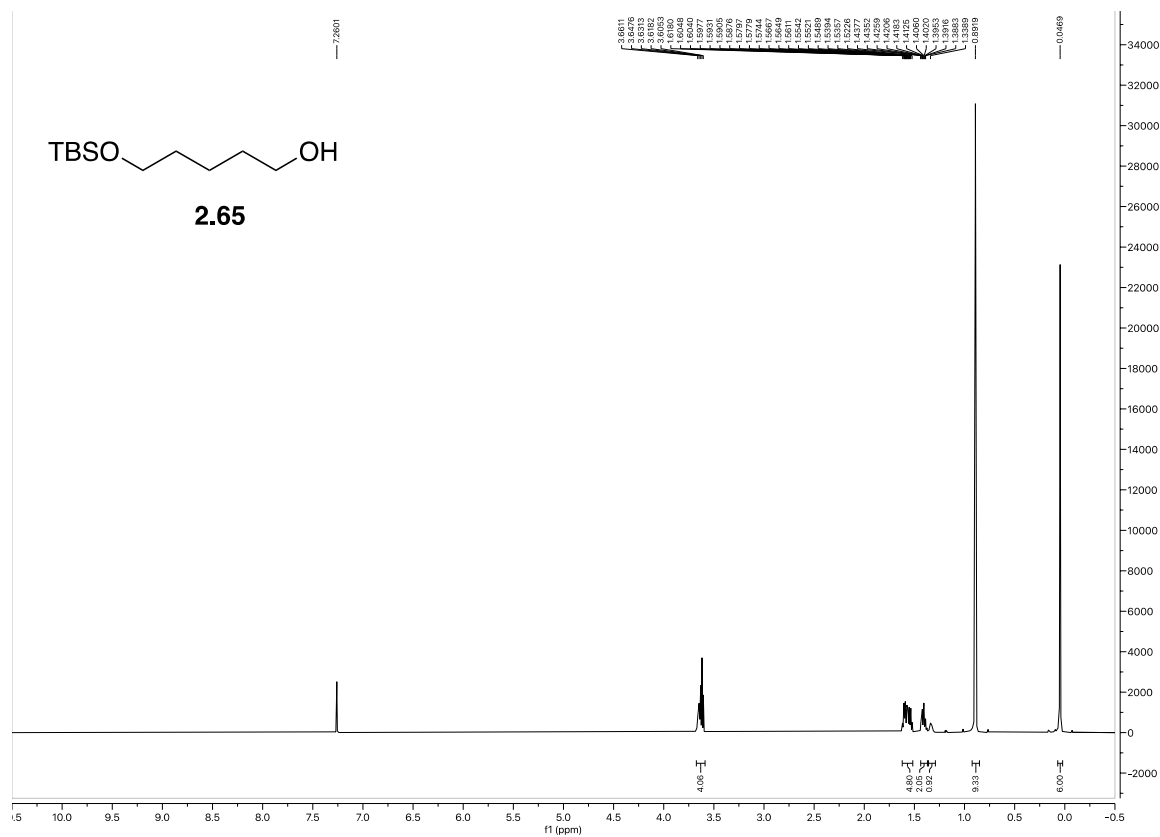


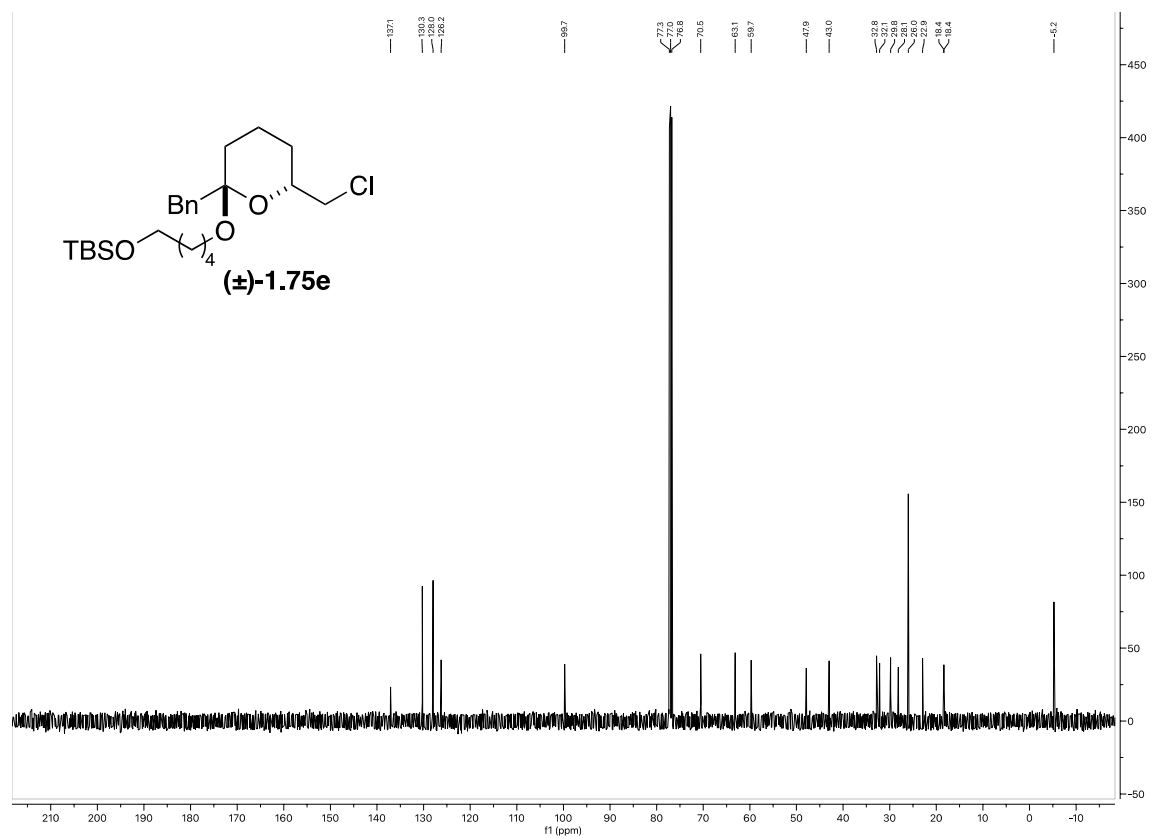
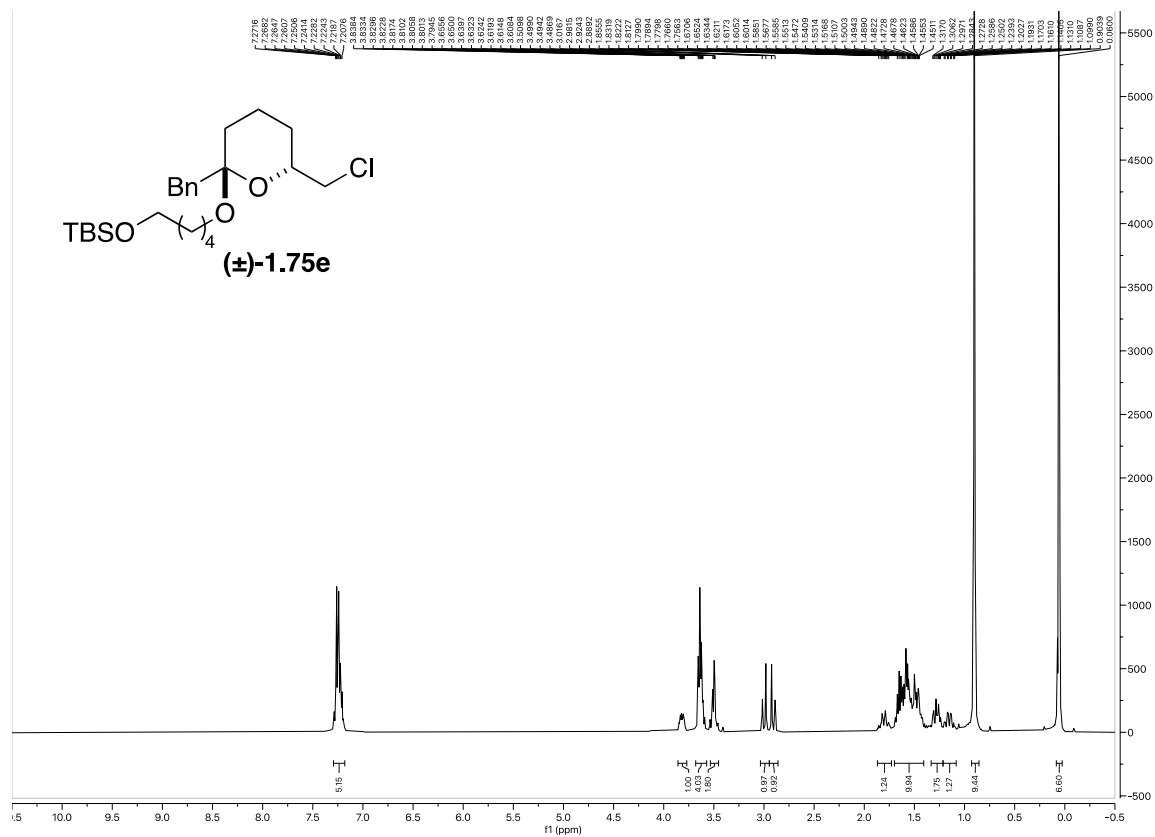


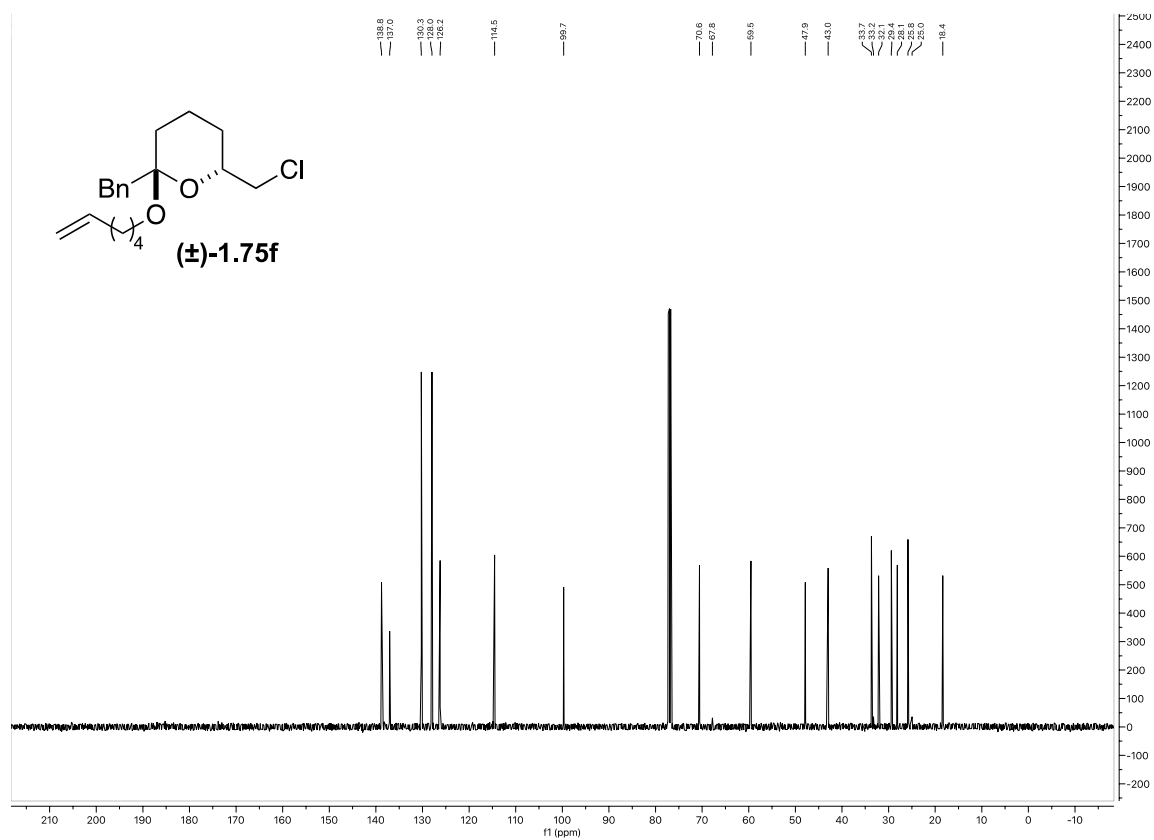
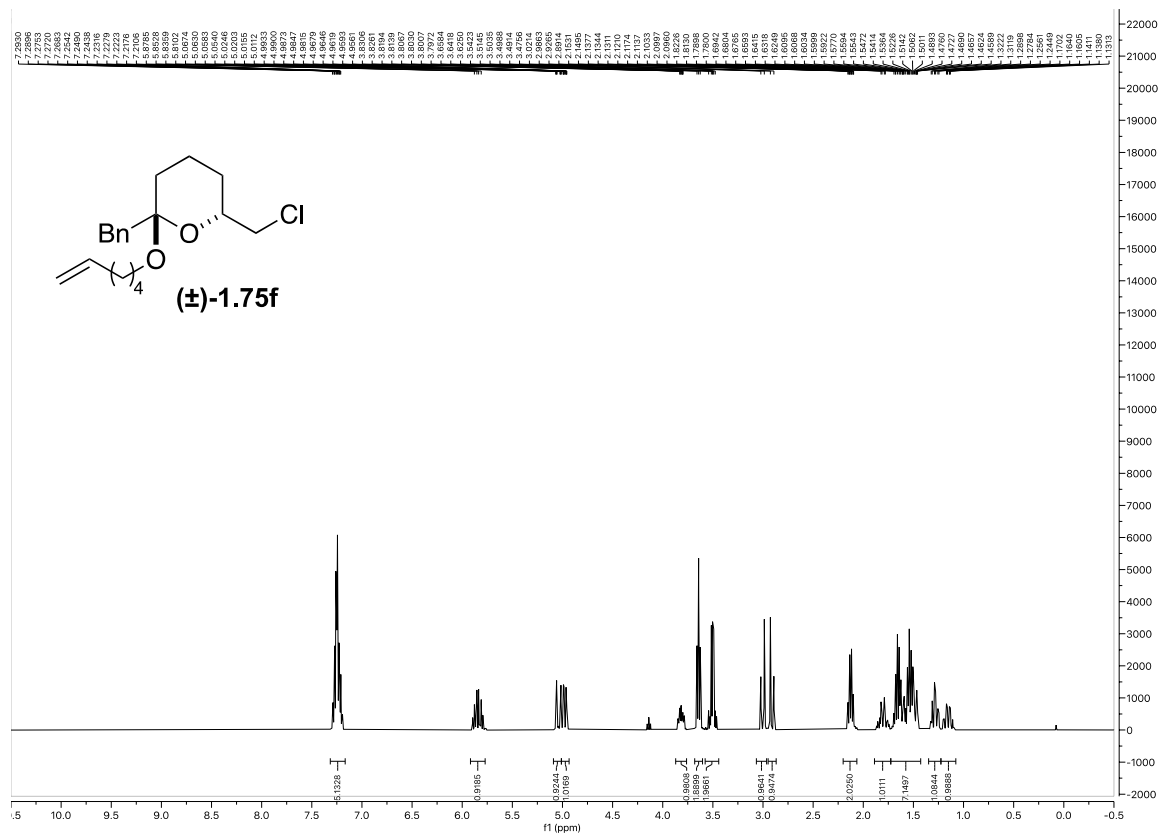


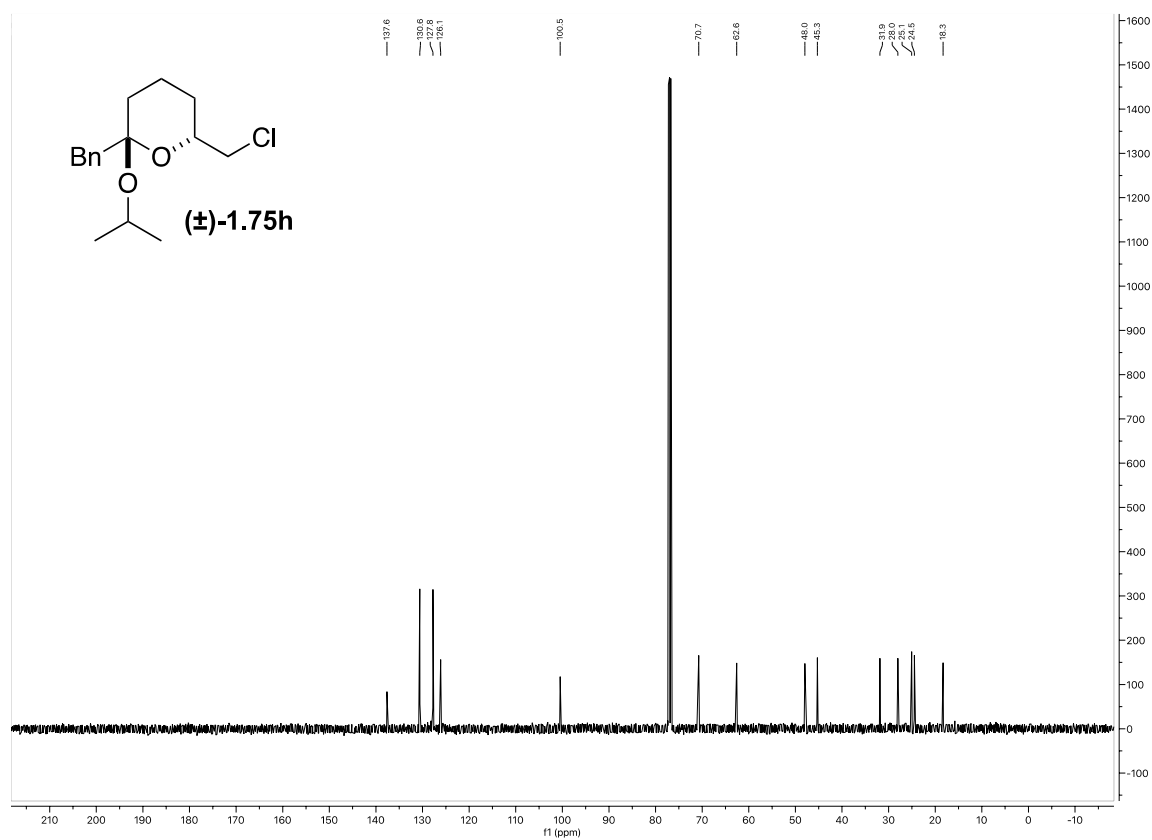
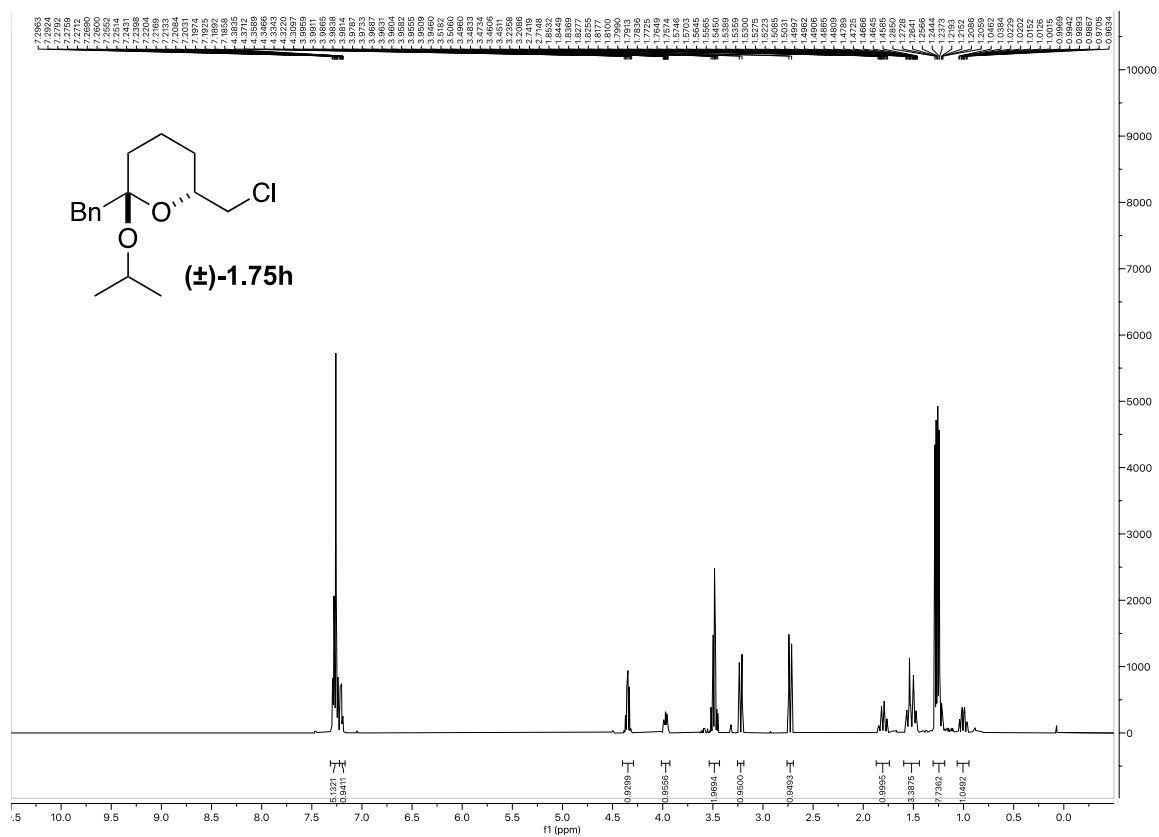


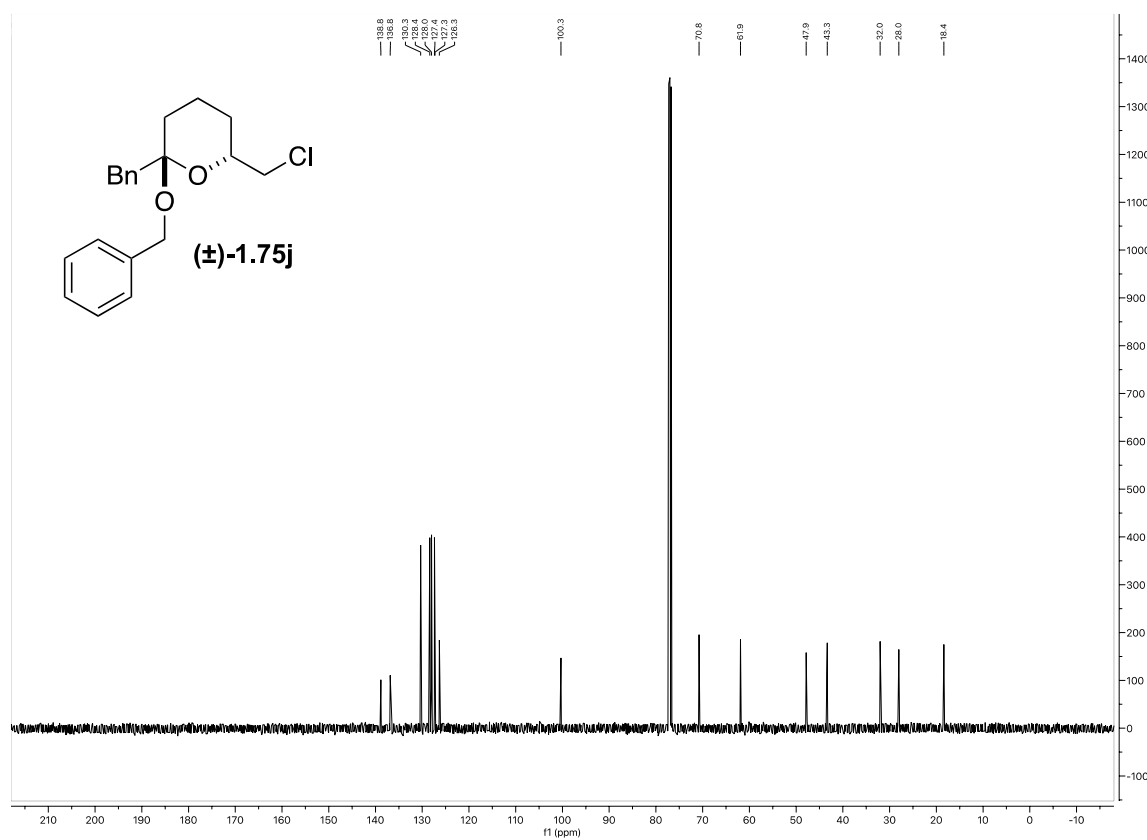
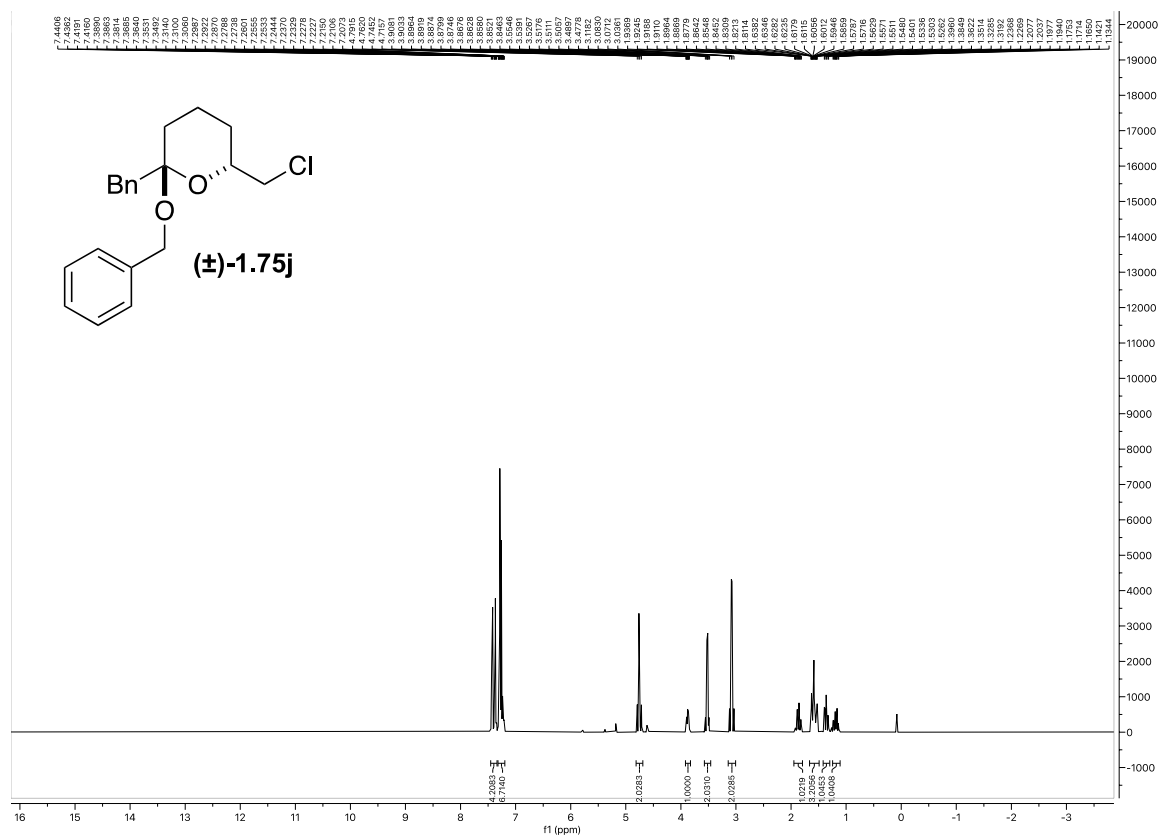


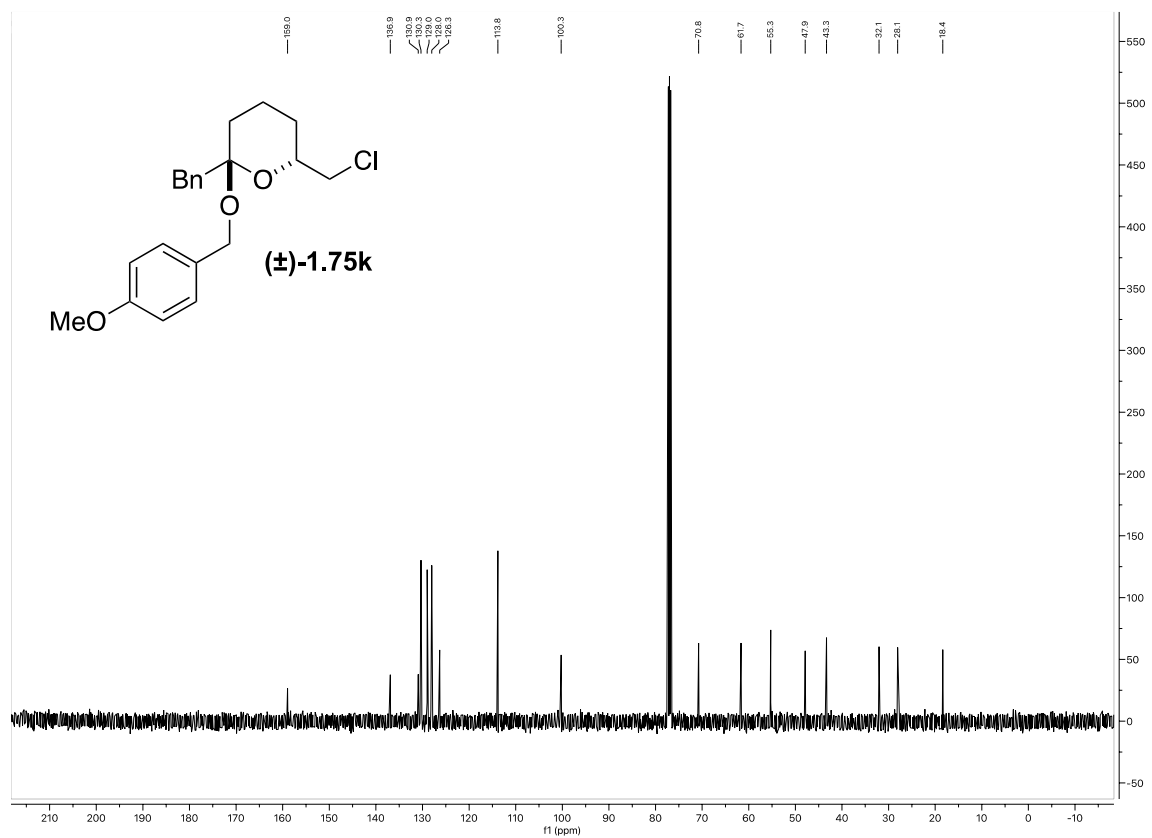
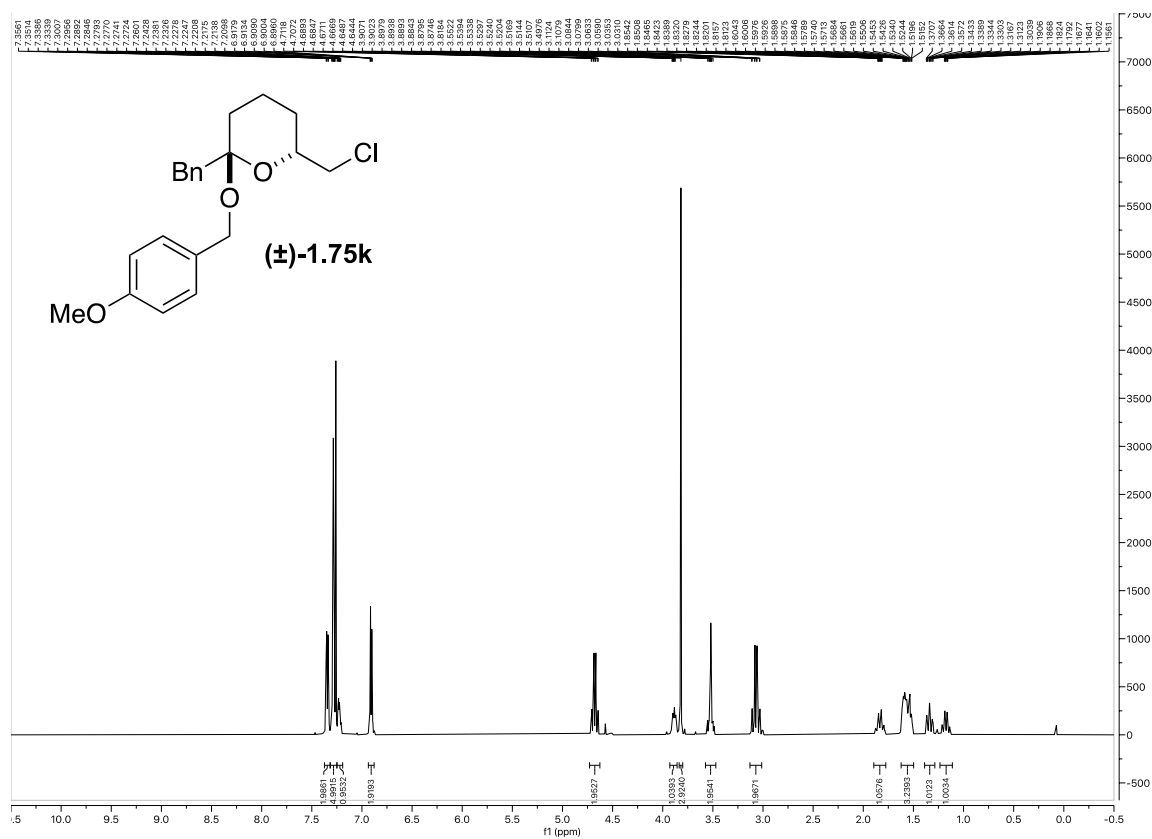


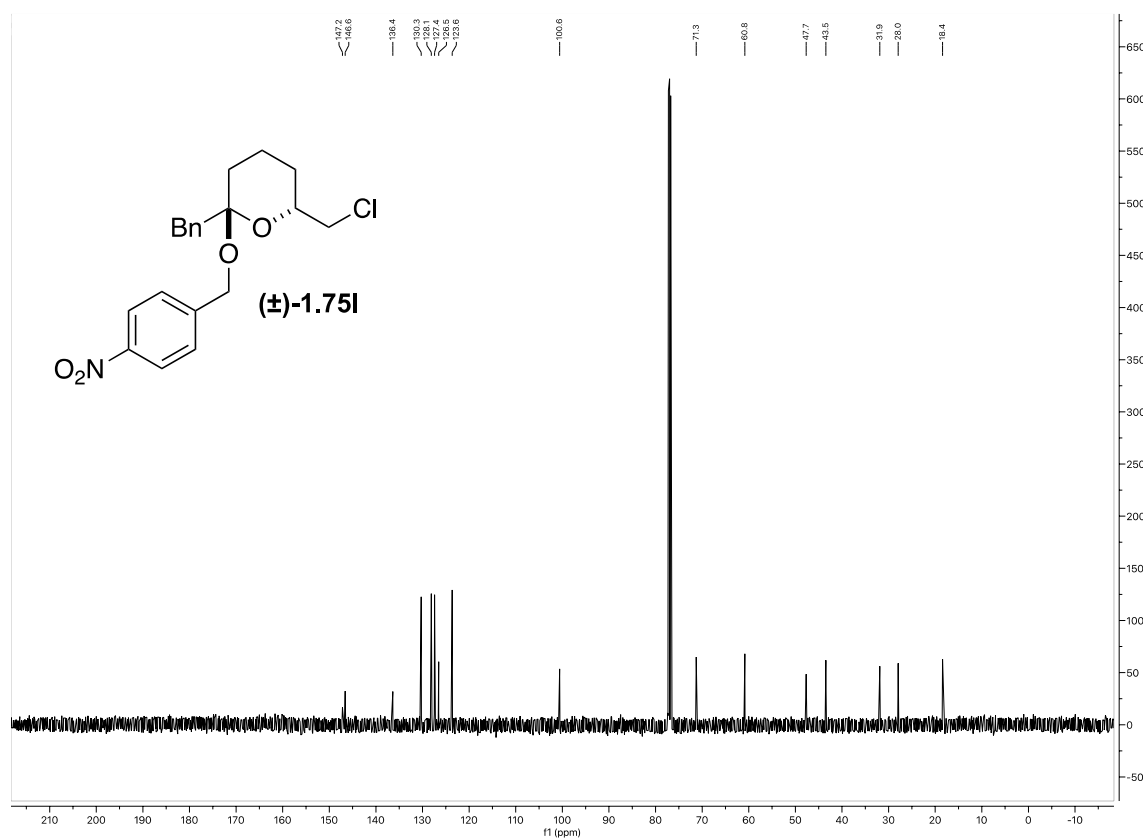
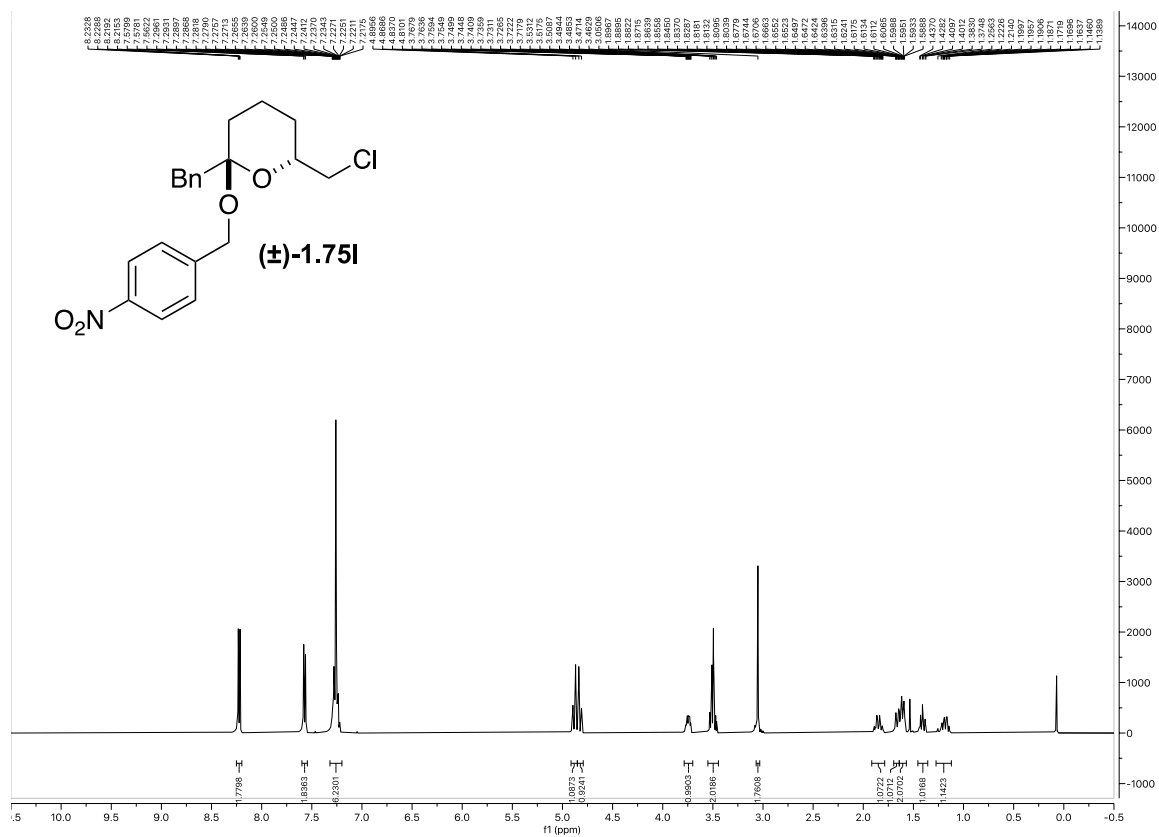


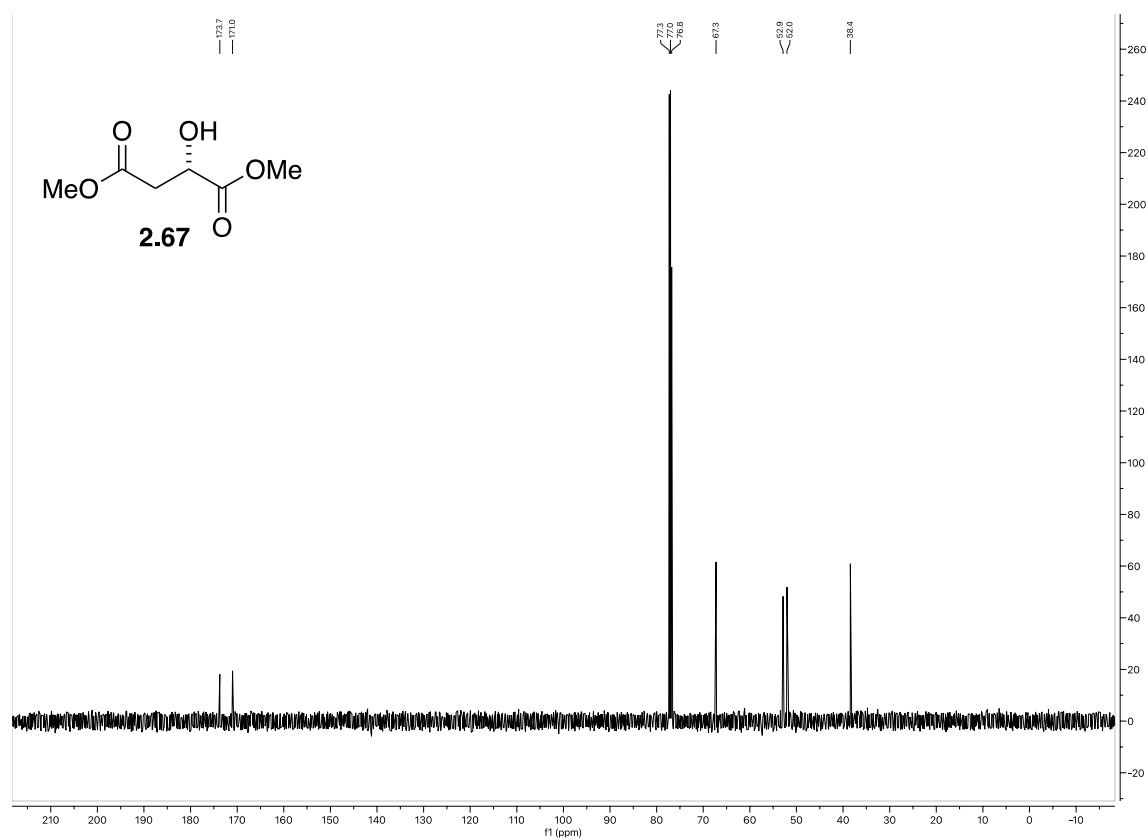
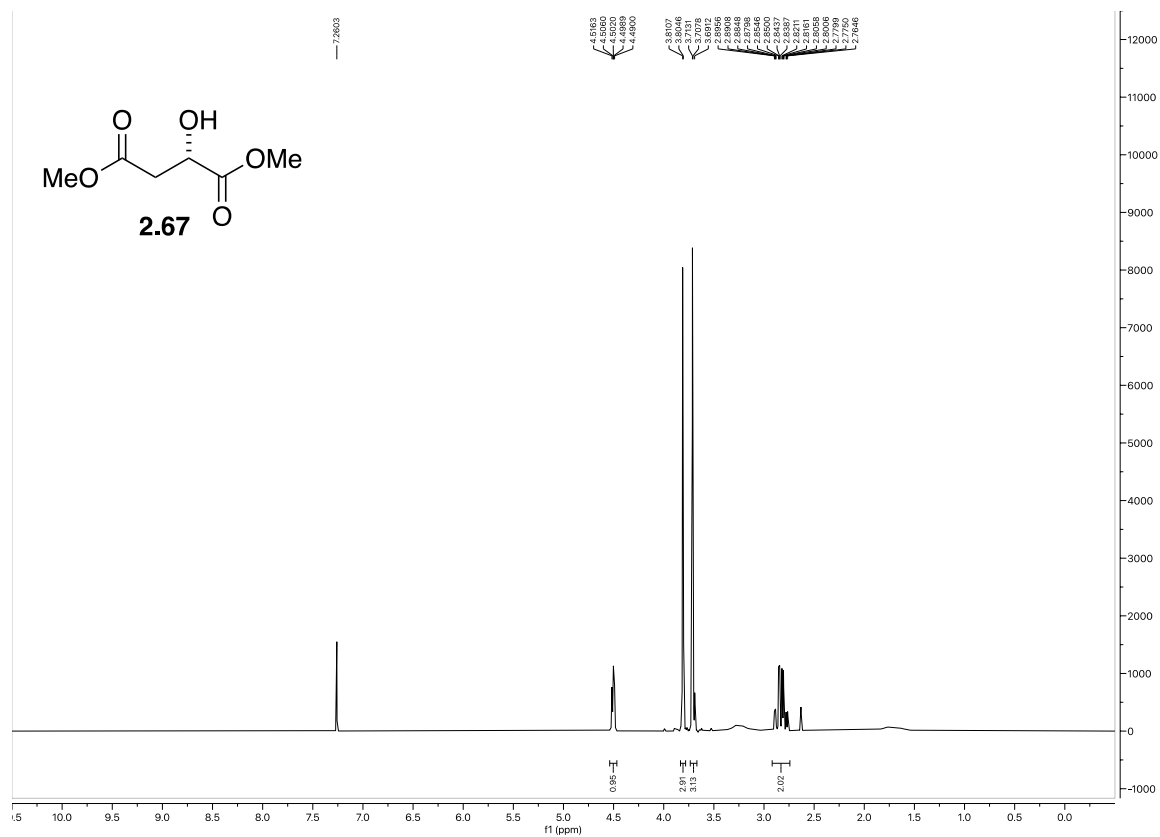


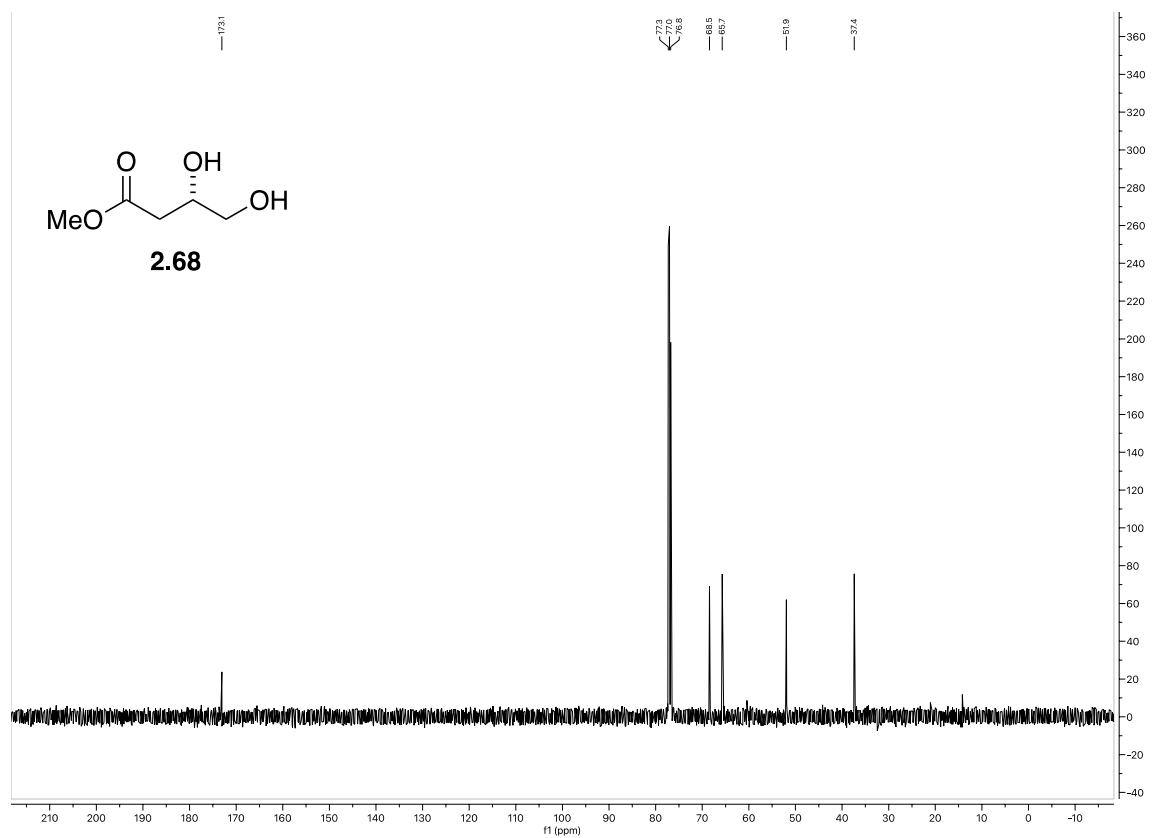
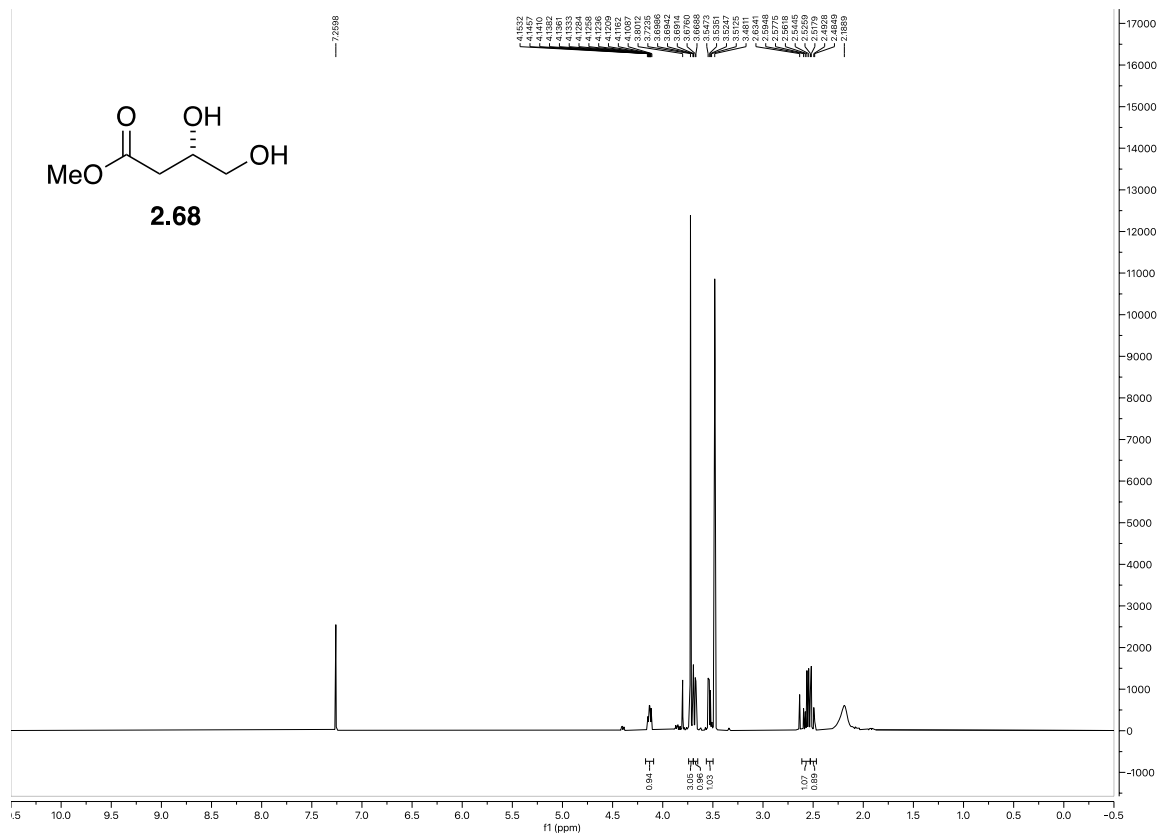


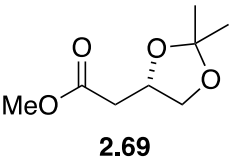
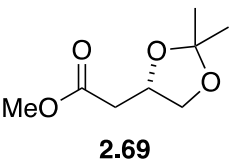


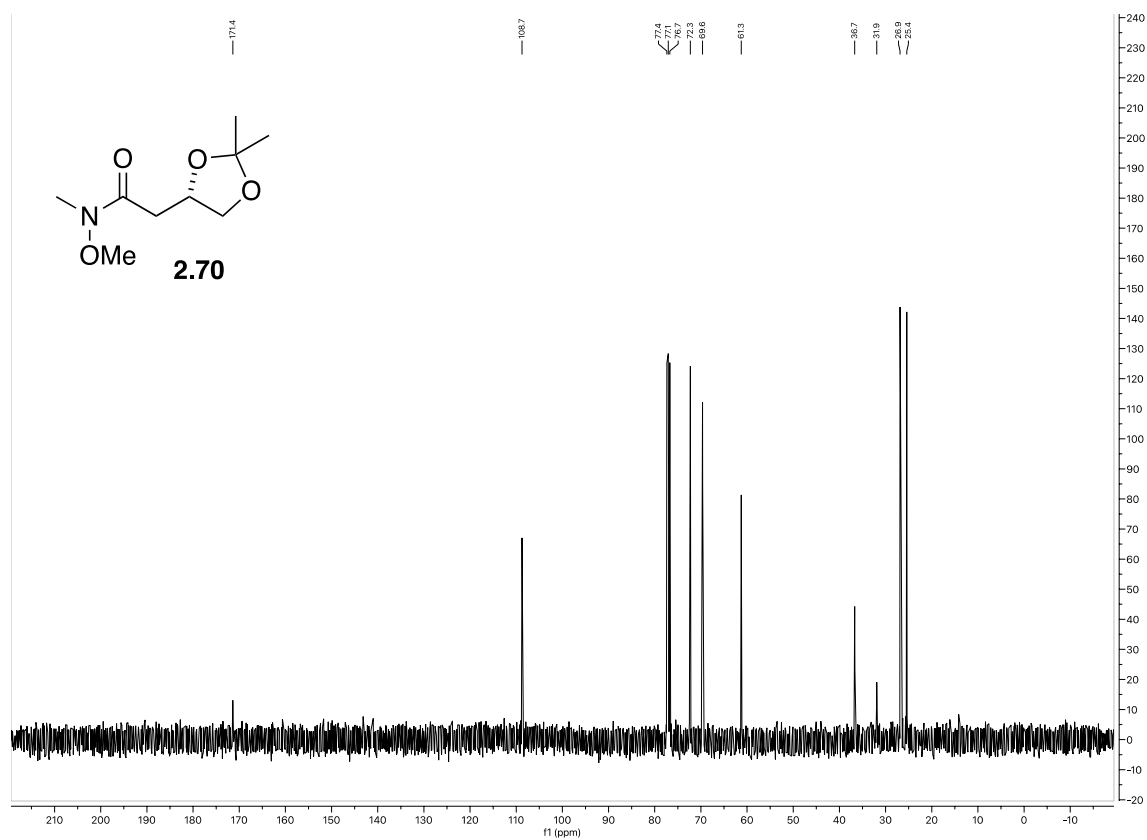
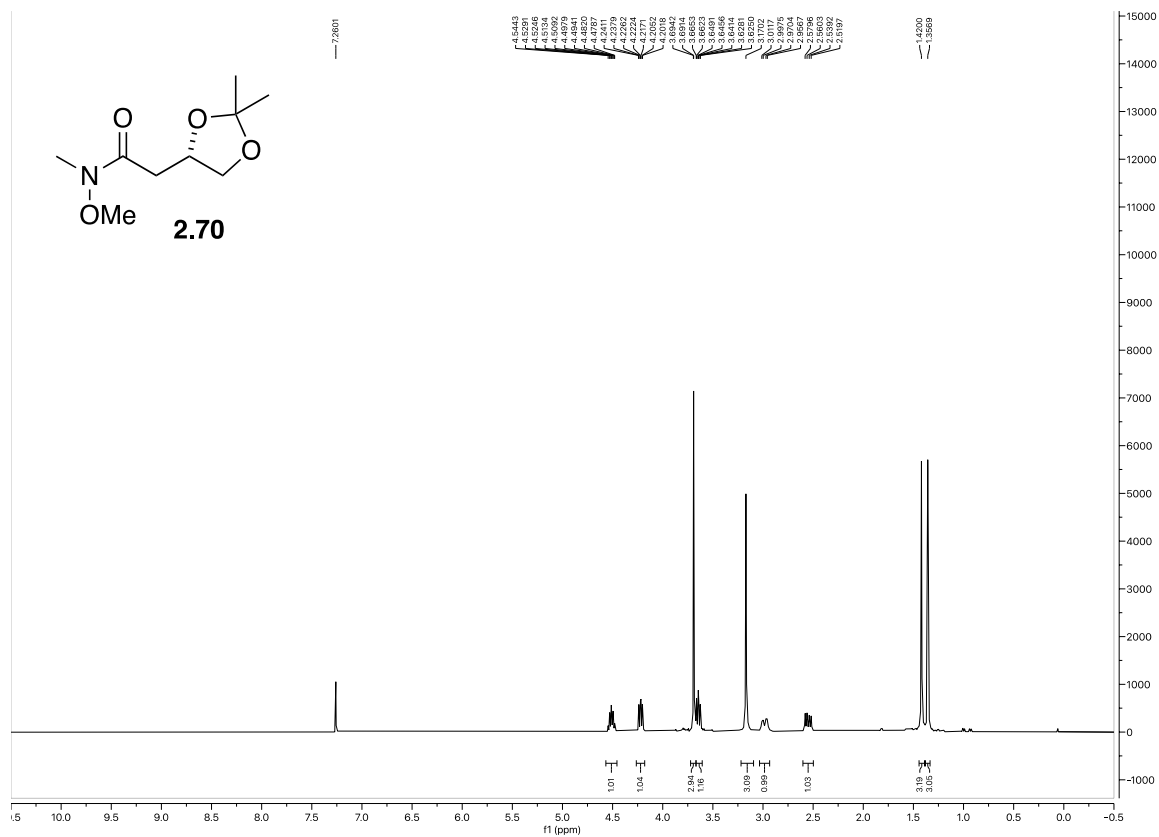


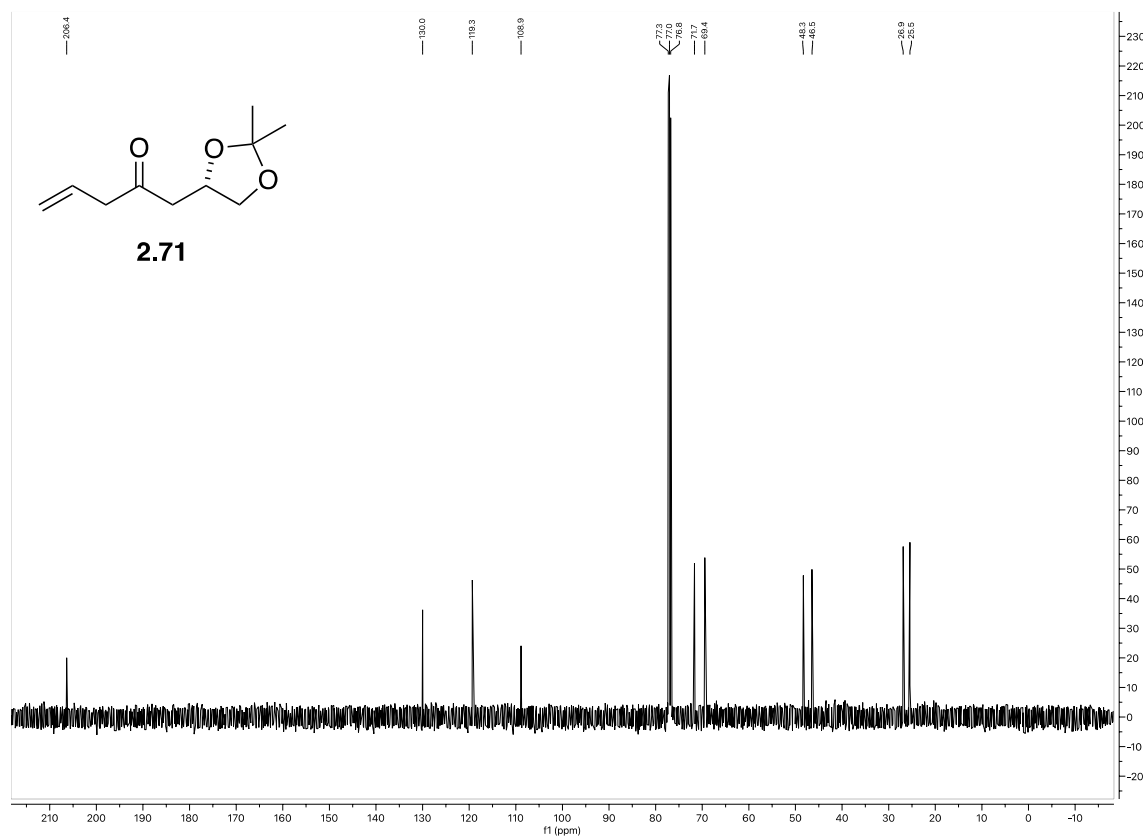
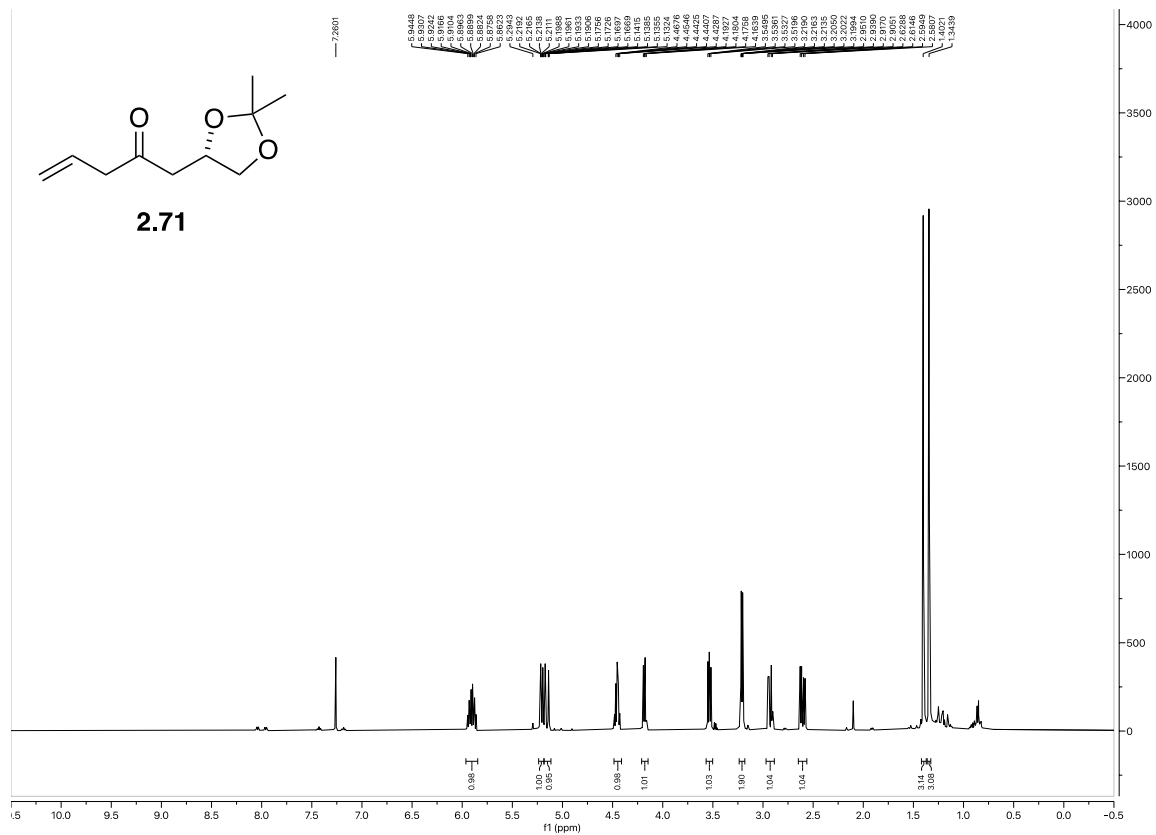


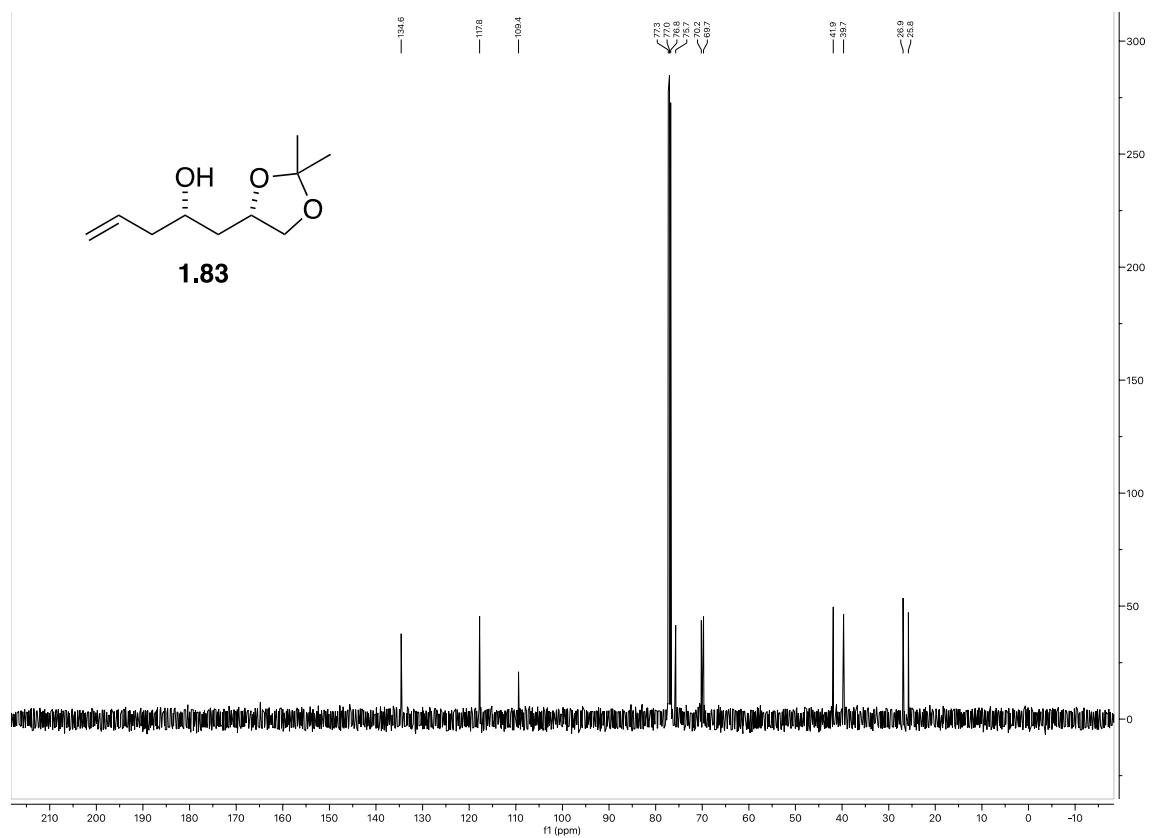
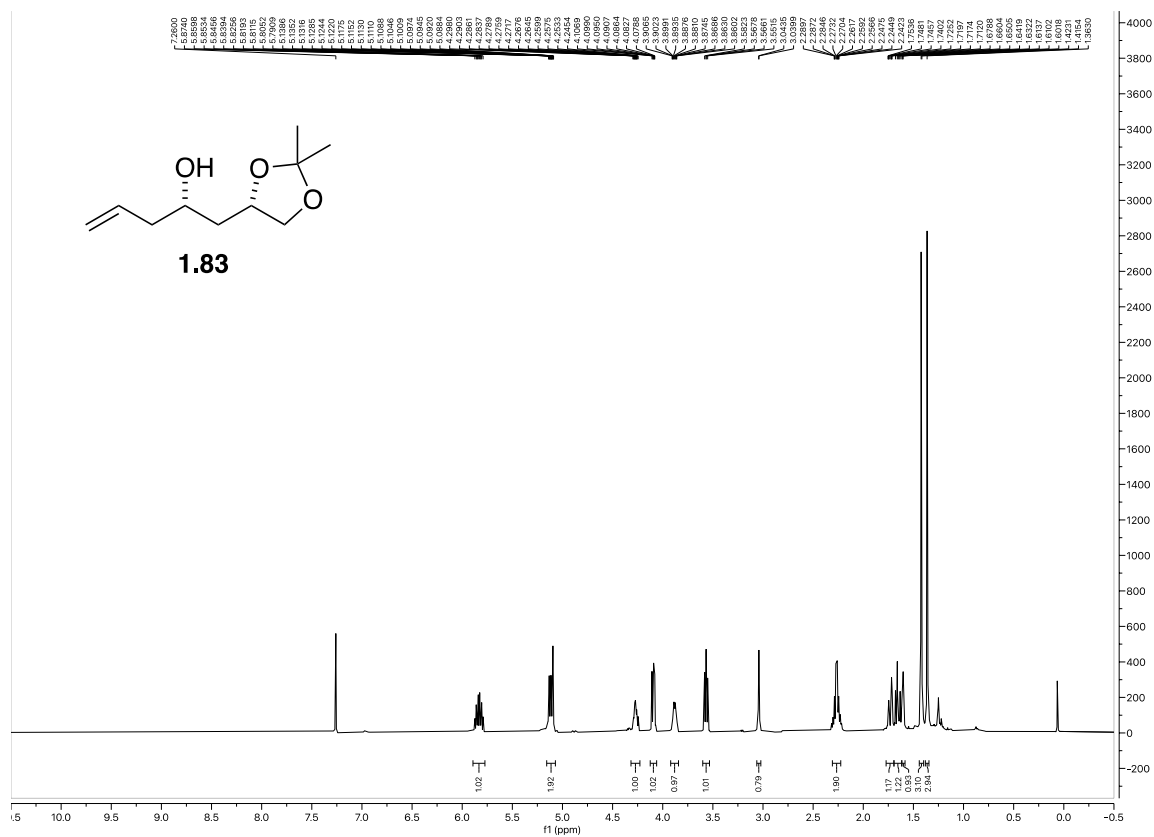


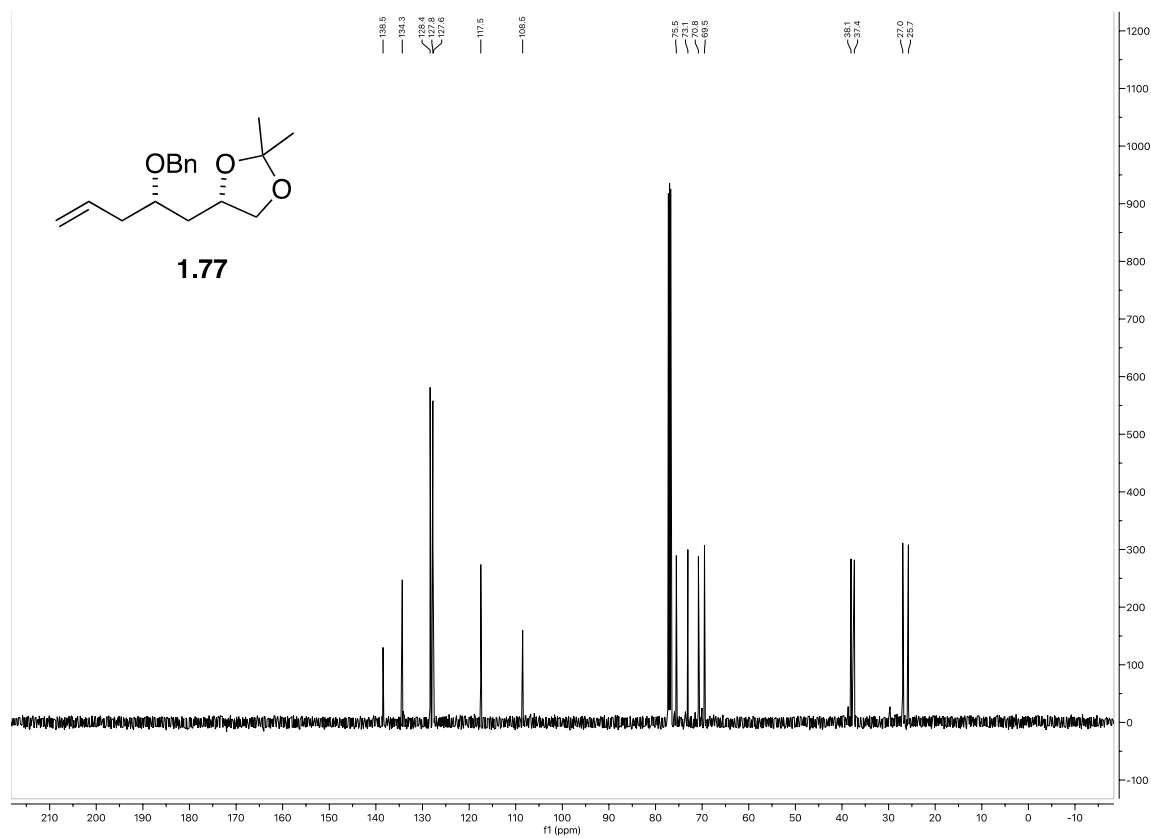
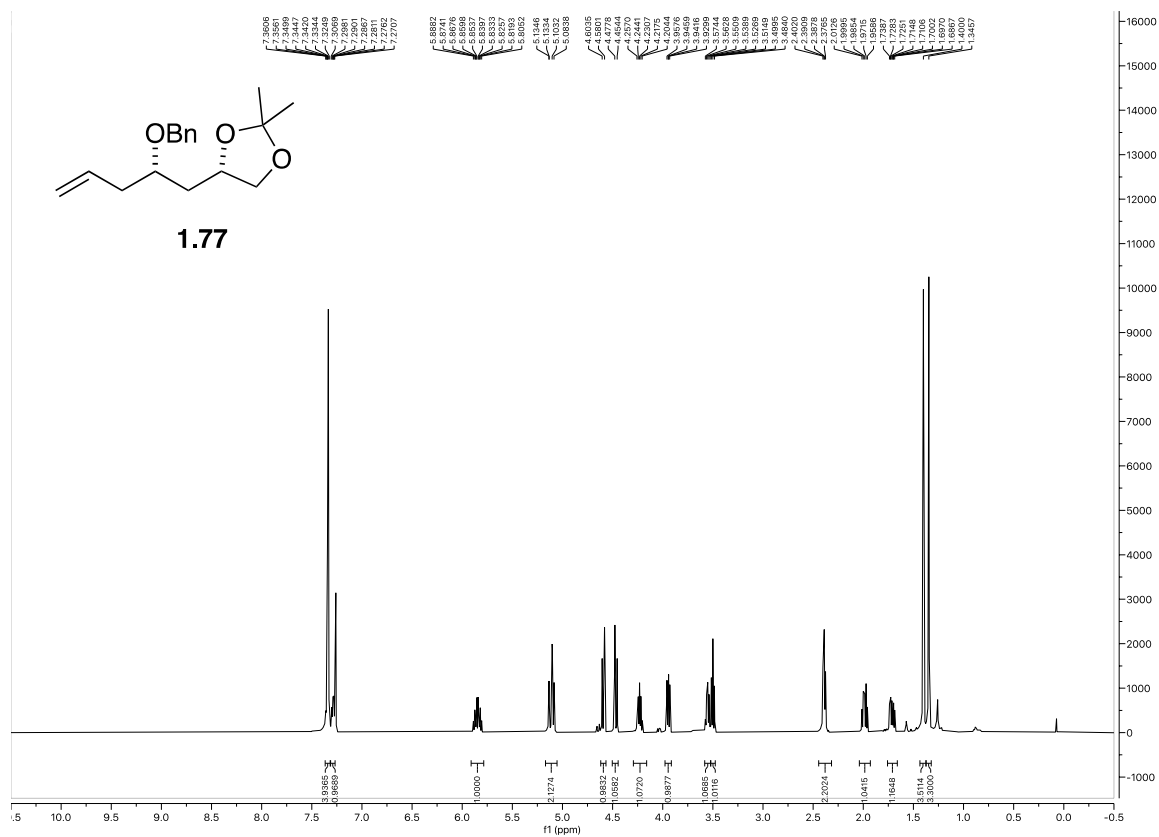


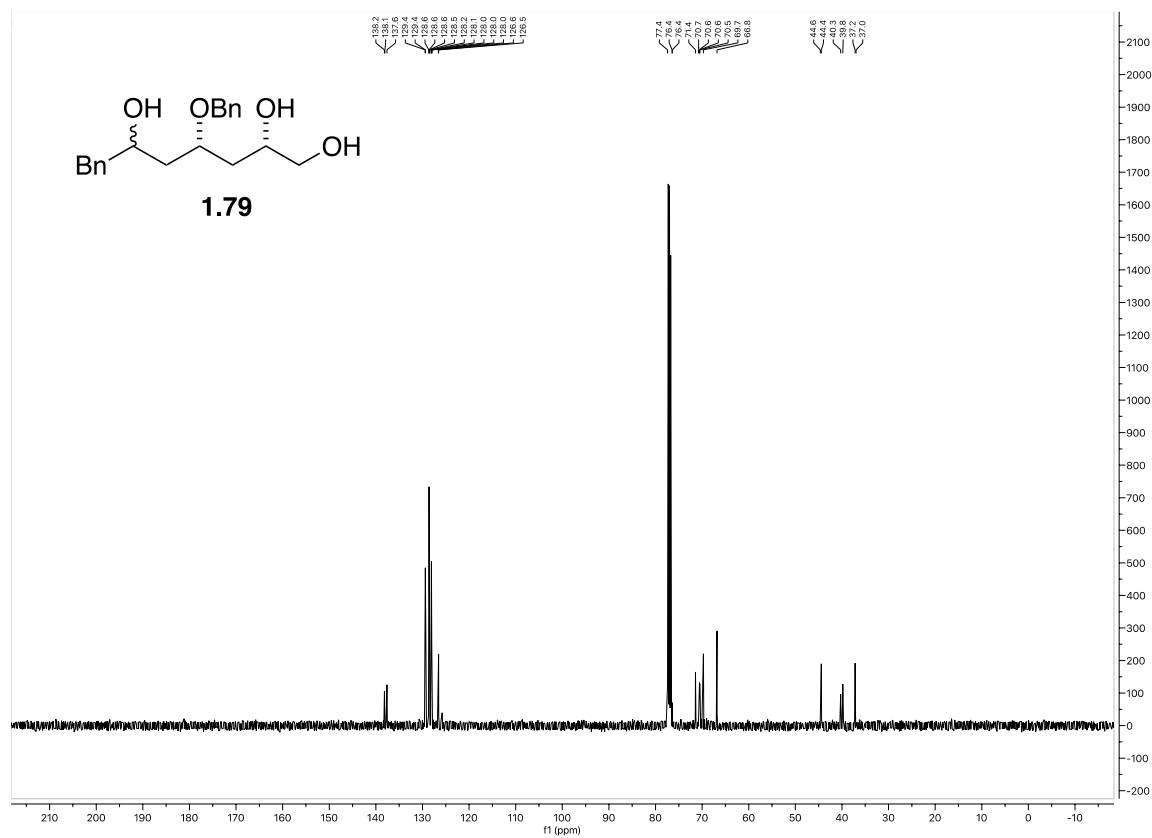
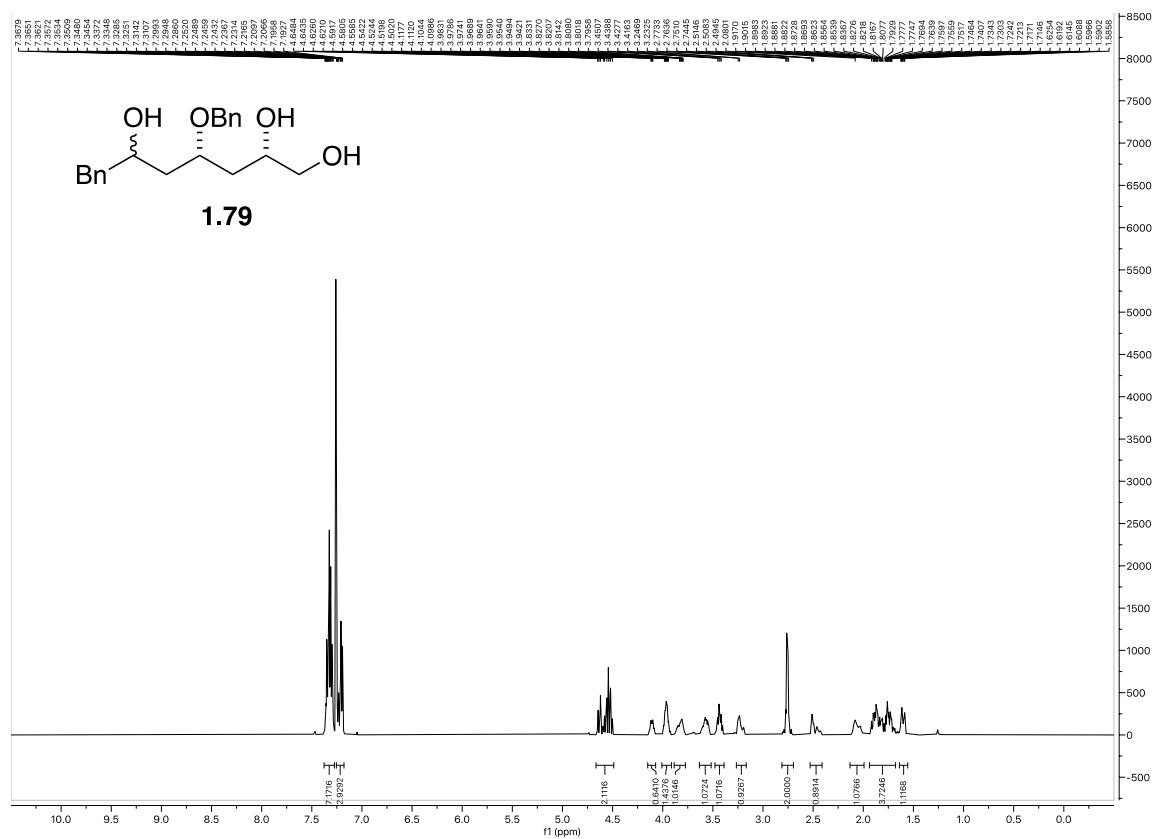


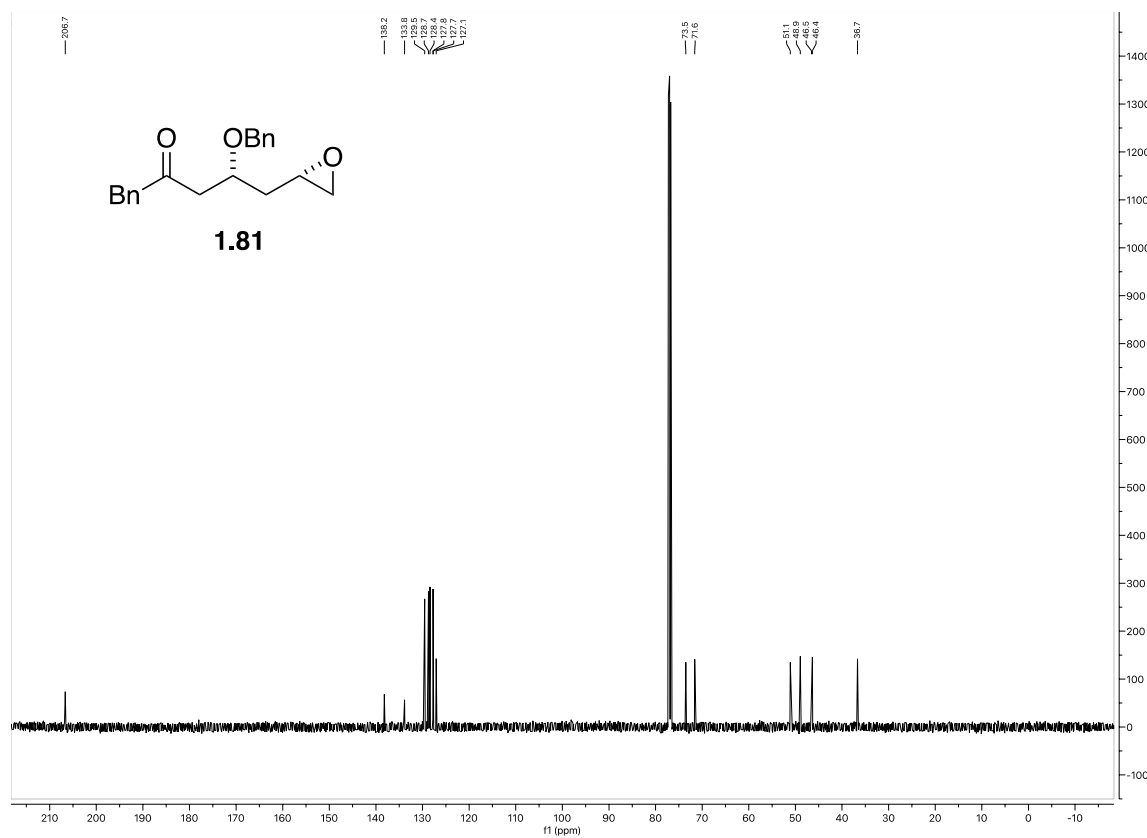
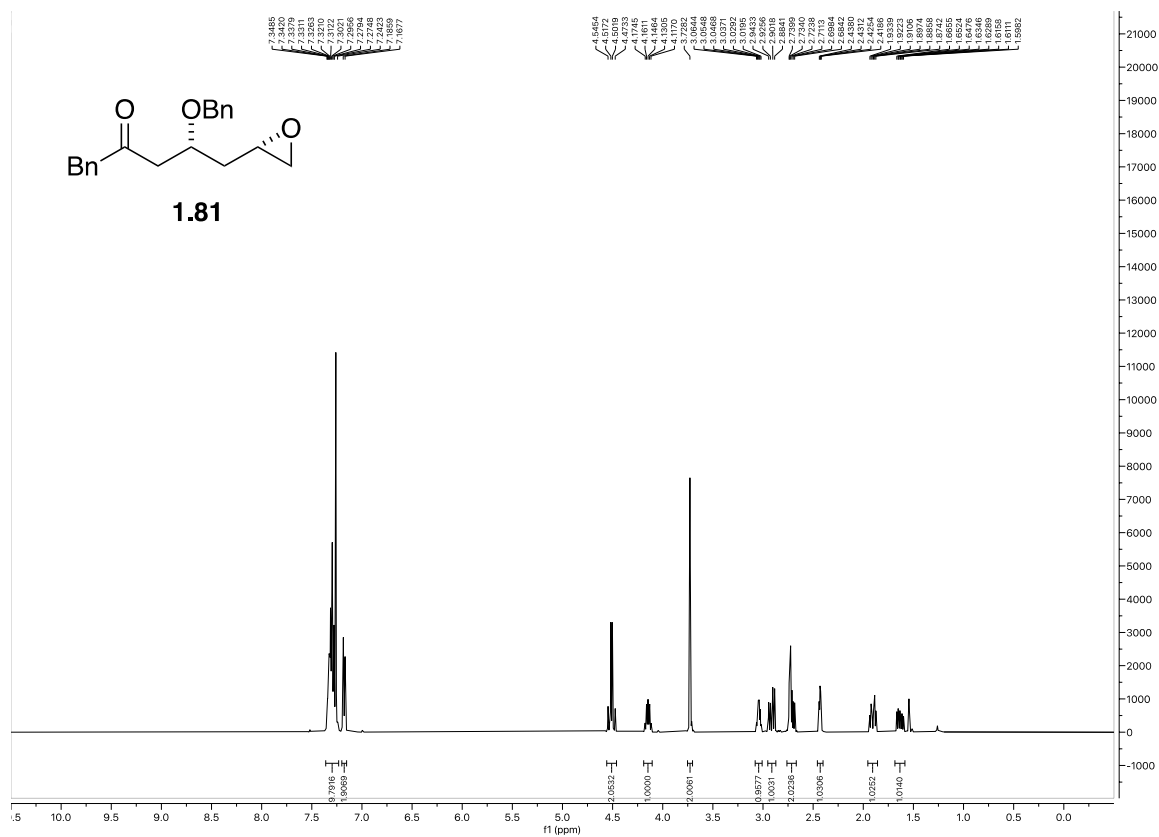


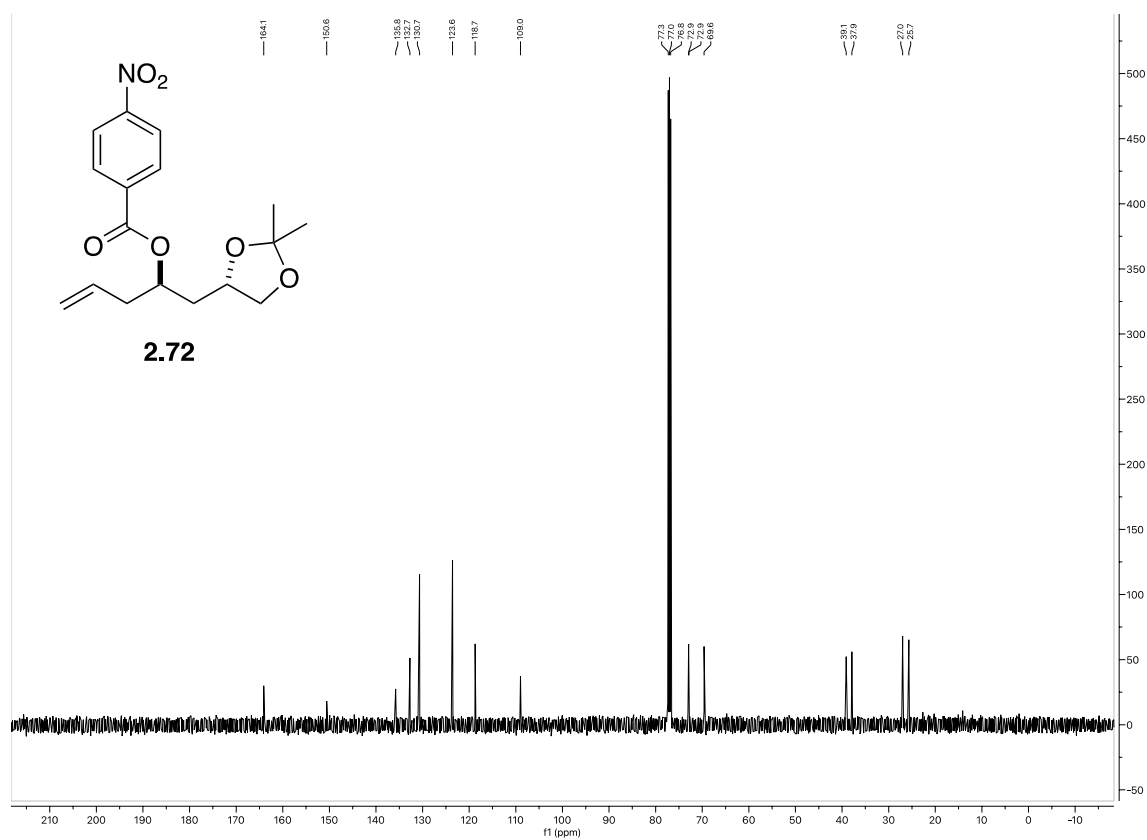
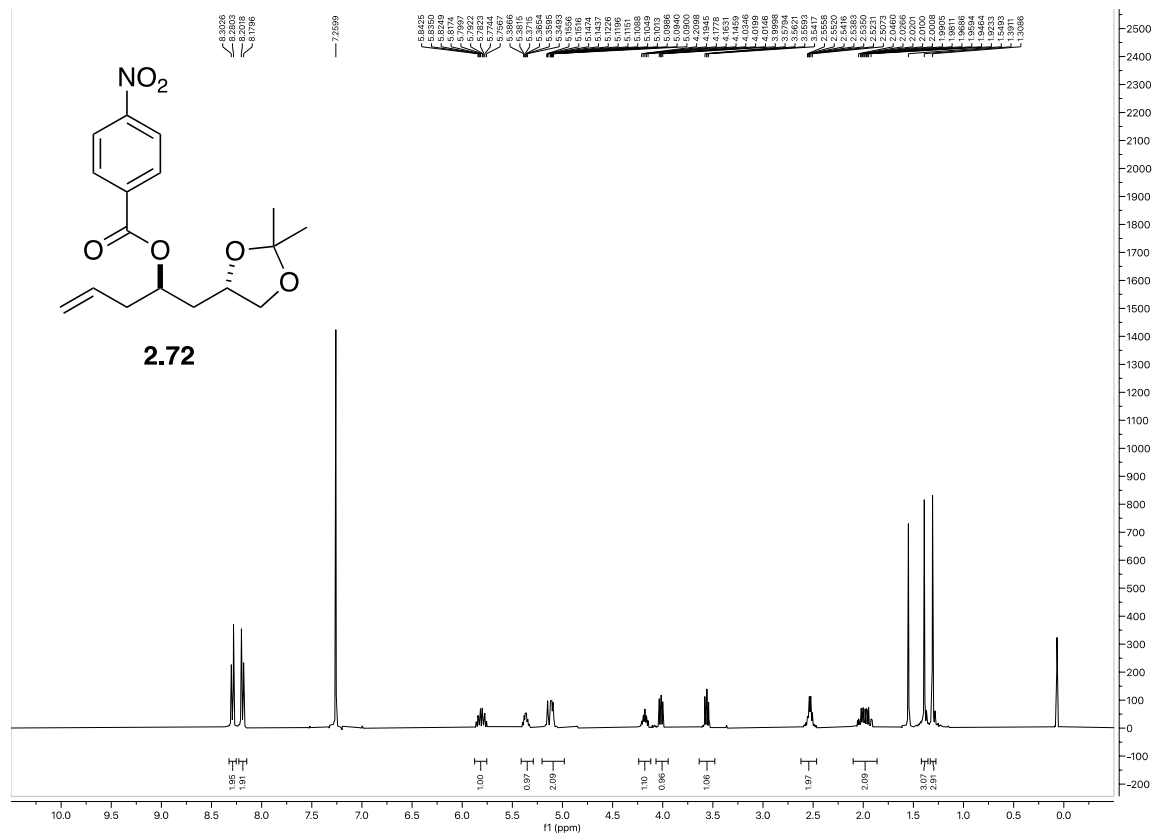


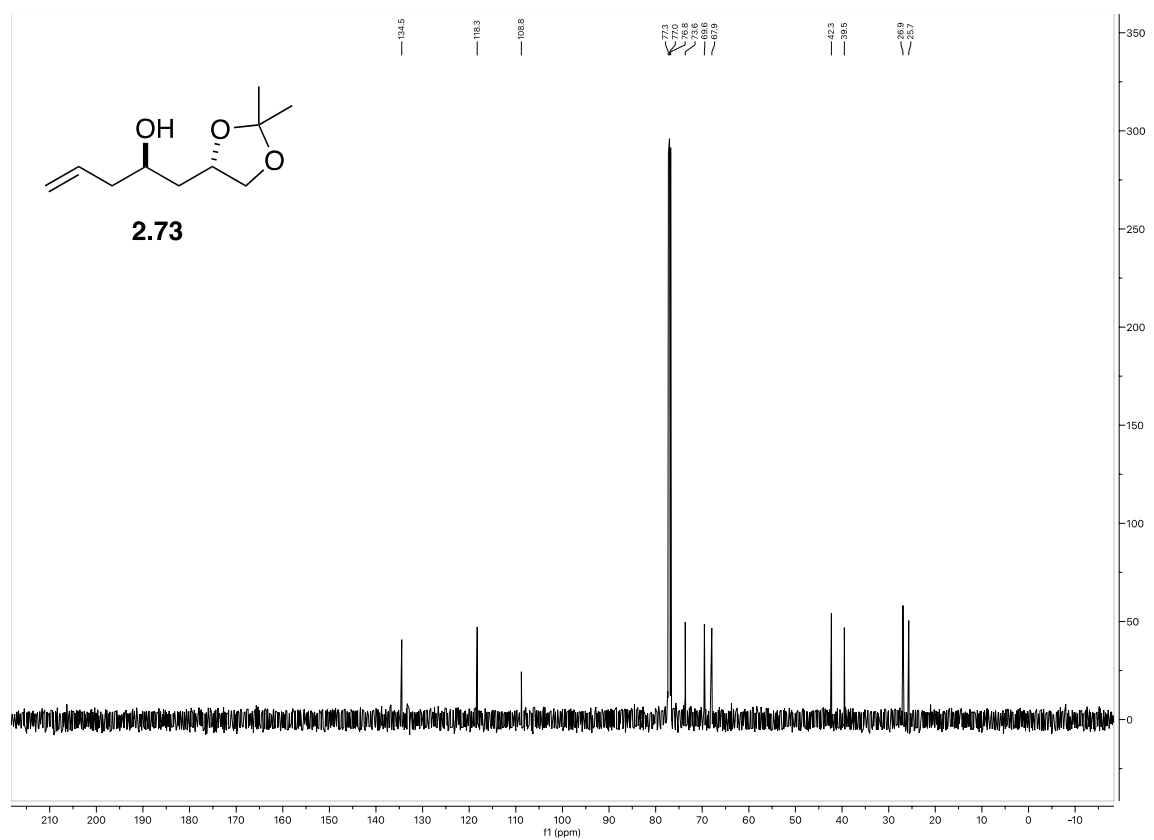
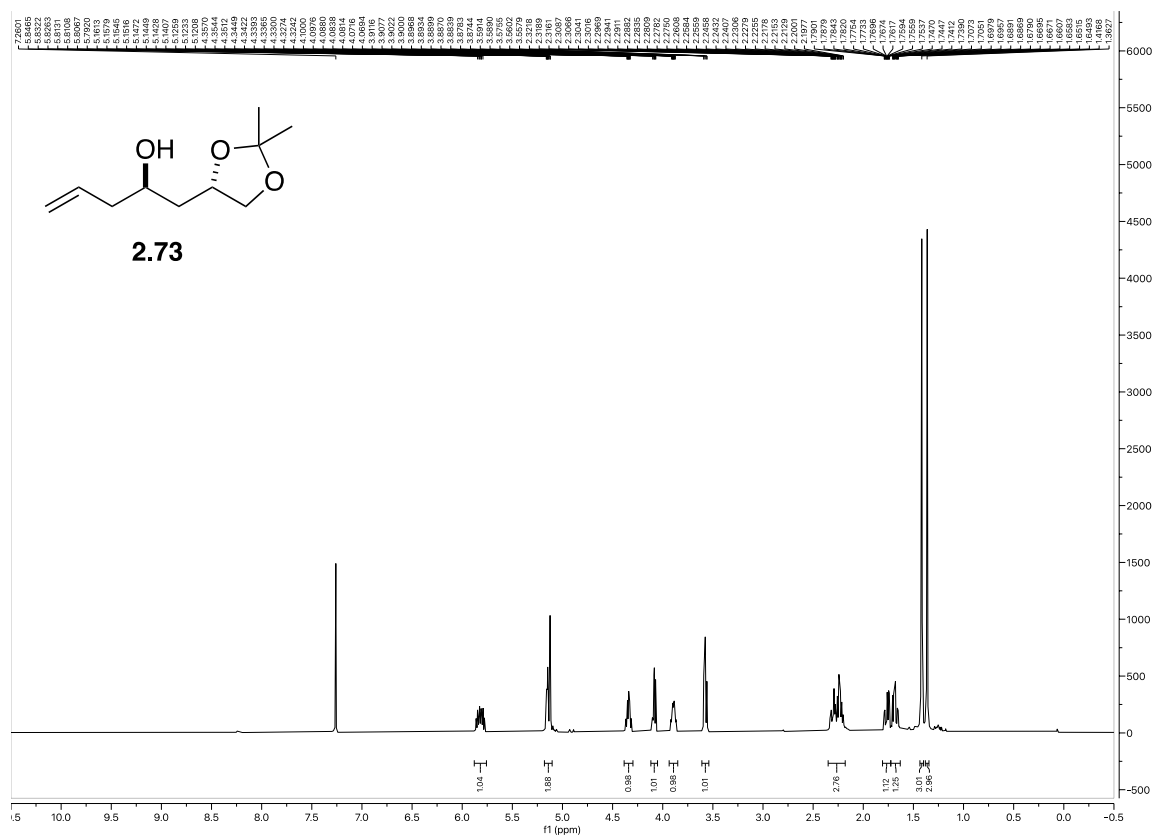


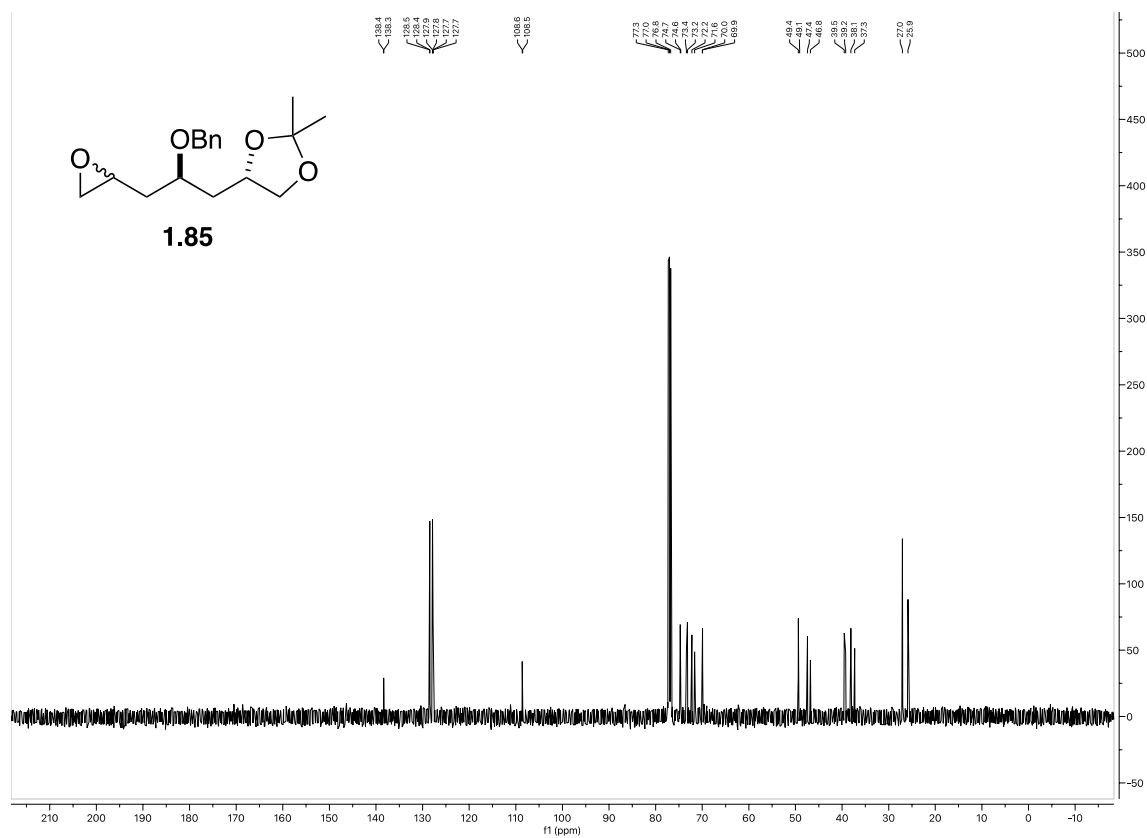
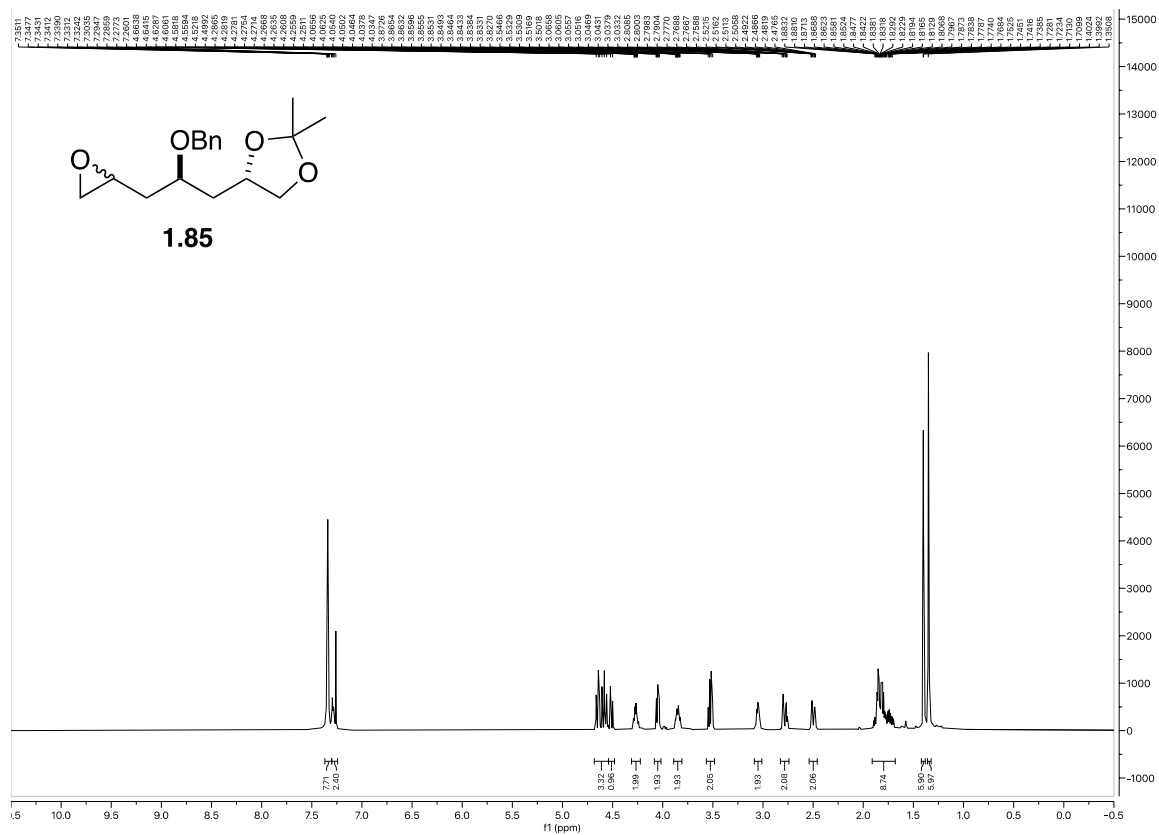


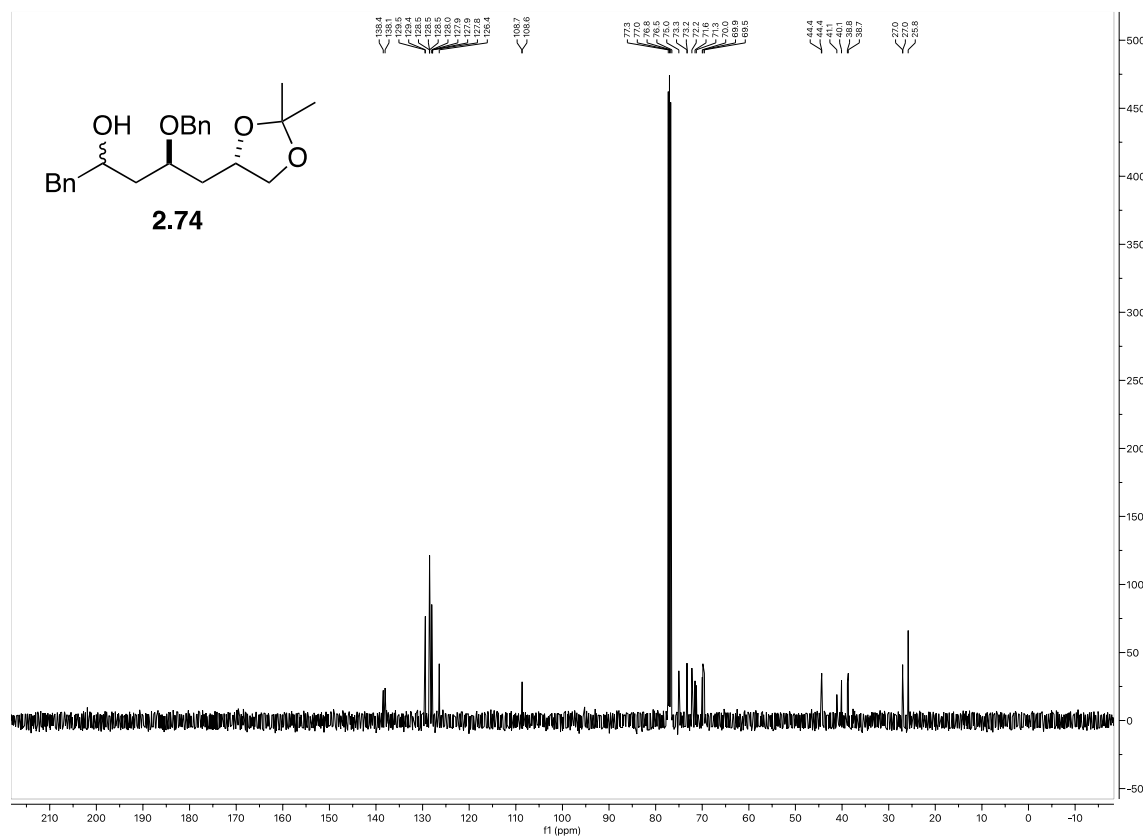
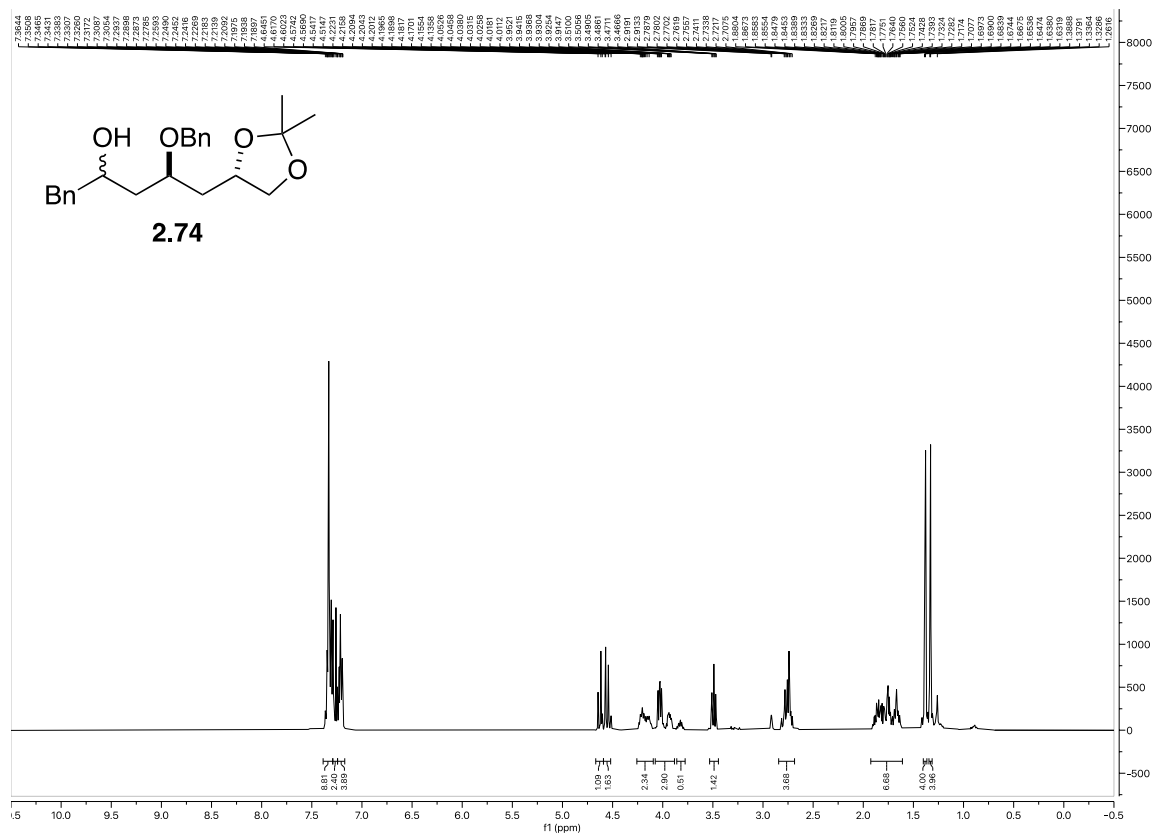


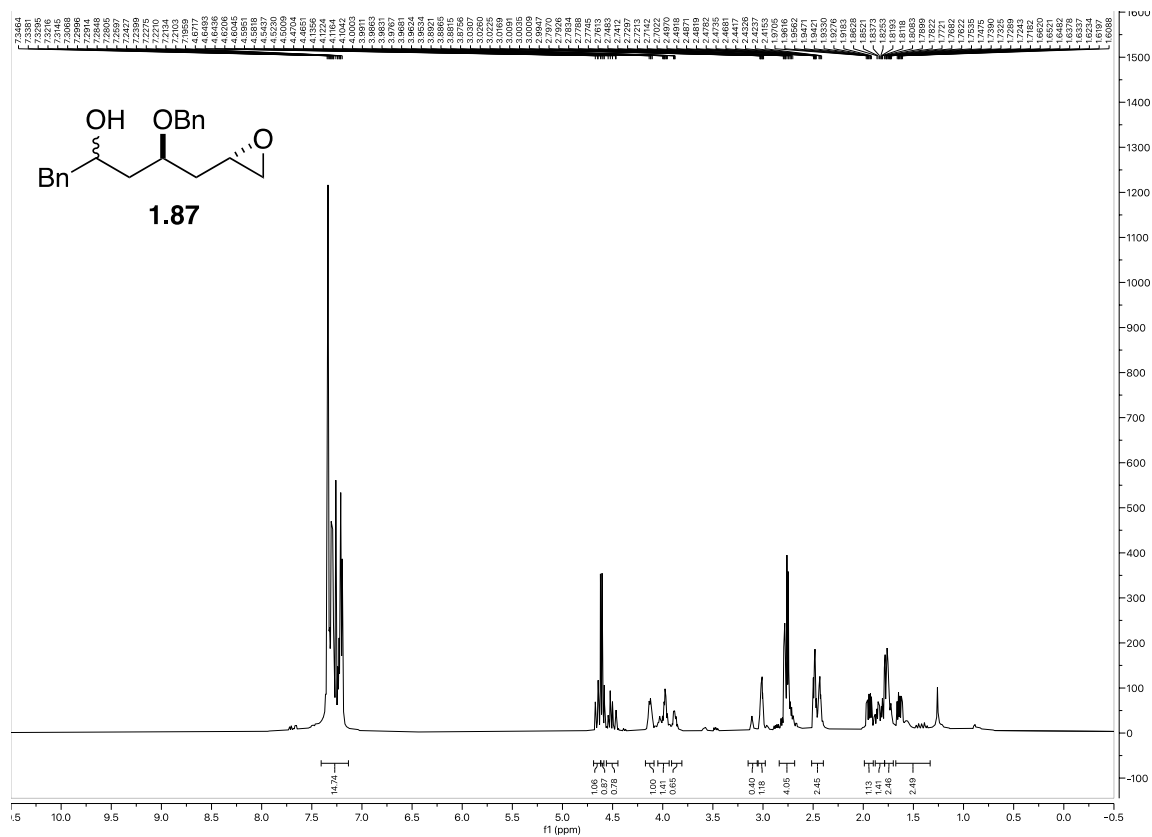


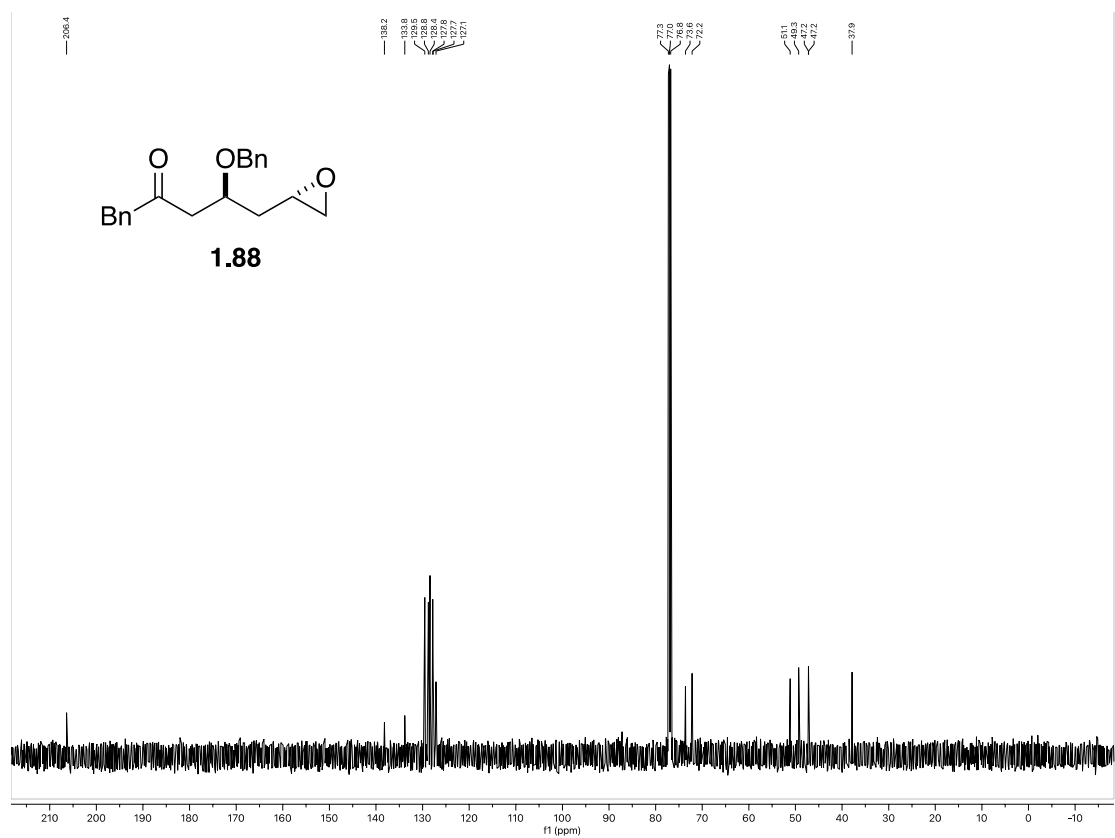
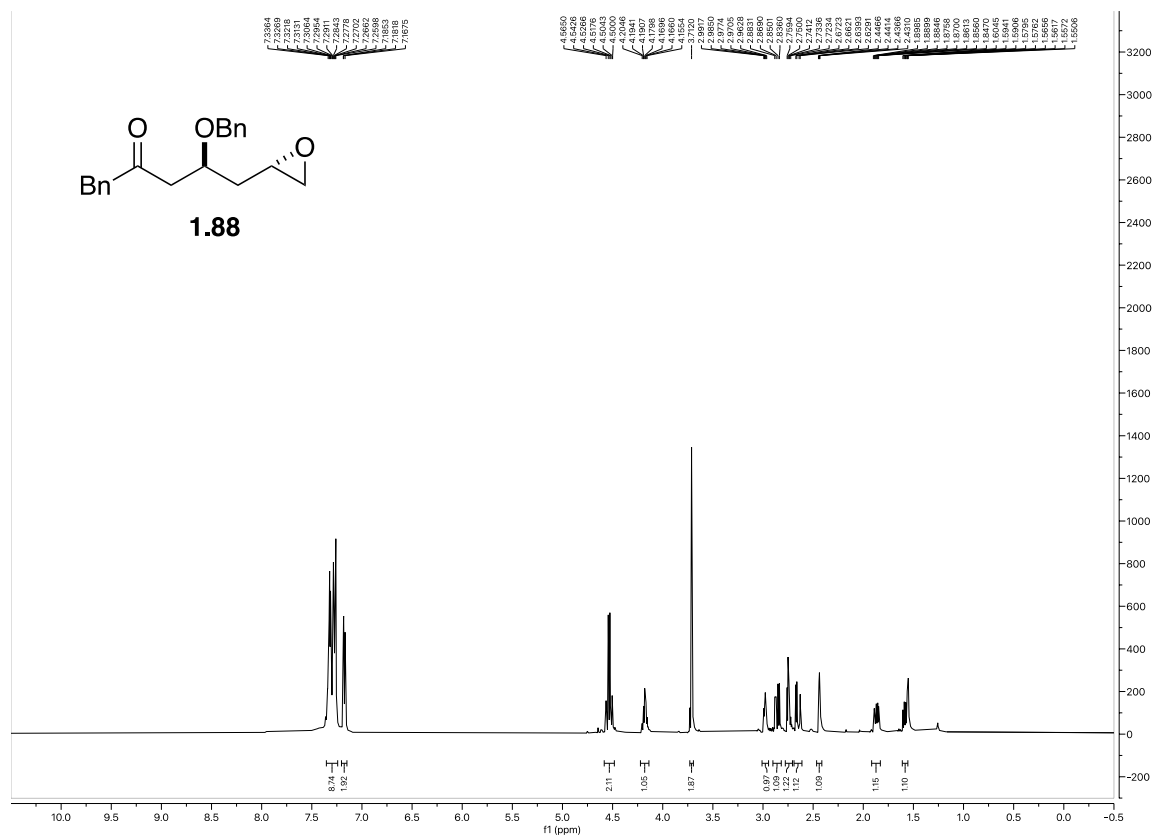












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Vita

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